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VOLUME 26

**Monosaccharides, Disaccharides, and
Specific Oligosaccharides**

**A Review of the Literature
Published in 1992**

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Carbohydrate Chemistry

Volume 26

A Specialist Periodical Report

Carbohydrate Chemistry

Monosaccharides, Disaccharides,
and Specific Oligosaccharides

Volume 26

A Review of the Literature Published
during 1992

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Preface

The literature of 1992 again vividly illustrates the increasing complexity of the chemistry of the smaller members of the carbohydrate family, and while this increases the difficulty of the reporting task, it concurrently adds to the interest and benefit of the job from the reviewers' point of view. No longer are members of our team confined to reading "standard" carbohydrate chemistry; their duties introduce them to a vast range of reactions and methods which have applicability in general organic chemistry, and many natural products other than sugars and a range of biochemical phenomena must be surveyed in the course of abstracting.

One worrying issue directly related to the increasing complexity of the reactions now used with carbohydrates relates to the abbreviations employed for ever-more-complex reagents and substituent groups. Unhappily it is becoming not unusual for us to encounter abbreviations/acronyms which are not even explained in the texts of papers, and in such cases we must retain them in our abstracts, and thus be less helpful to readers than we would wish. Our lists of abbreviations given at the beginning of each volume are therefore becoming deficient, and this we of course regret. The time has come, one might speculate, for a standardisation in the use of abbreviated names and for an approval system. Such developments certainly would allow us to improve our product.

This volume sees the introduction of computer-drawn structural formulae. We trust that the inevitable minor problems caused by the transition will resolve readily and that we will be able to bring forward the publication dates. While this remains a continuing objective a necessary increase in the size of the team brings with it increasing possibility of delays.

This year Dr Tim Gallager, University of Bristol, is welcomed as a reporter, and the help of the staff of the Royal Society of Chemistry, especially Mr. A G. Cubitt and the artwork staff, is acknowledged with warm thanks.

R J Ferrier
April 1994

Contents

Chapter 1	Introduction and General Aspects	1
Chapter 2	Free Sugars	3
1	Theoretical Aspects	3
2	Synthesis	3
	Trioses to Hexoses	3
	Chain-extended Compounds	7
3	Physical Measurements	10
4	Isomerisation	11
5	Oxidation	11
6	Other Aspects	12
	References	12
Chapter 3	Glycosides	15
1	O-Glycosides	15
1.1	Synthesis of Monosaccharide Glycosides	15
1.2	Synthesis of Glycosylated Natural Products	22
1.3	O-Glycosides Isolated from Natural Products	24
1.4	Synthesis of Disaccharides and their Derivatives	25
1.5	Hydrolysis and Other Features	38
2	S- and Se-Glycosides	40
3	C-Glycosides	43
3.1	Pyranoid Compounds	43
3.2	Furanoid Compounds	50
	References	52

Chapter 4	Oligosaccharides	59
1	General	59
2	Trisaccharides	61
2.1	Linear Homotrisaccharides	61
2.2	Linear Heterotrisaccharides	62
2.3	Branched Homotrisaccharides	63
2.4	Branched Heterotrisaccharides	63
2.5	Analogues of Trisaccharides	64
3	Tetrasaccharides	66
3.1	Linear Homotetrasaccharides	66
3.2	Linear Heterotetrasaccharides	66
3.3	Branched Homotetrasaccharides	67
3.4	Tetrasaccharide Analogues	67
4	Pentasaccharides	68
4.1	Linear Pentasaccharides	68
4.2	Branched Pentasaccharides	68
5	Hexasaccharides	68
5.1	Linear Hexasaccharides	69
5.2	Branched Hexasaccharides	69
6	Heptasaccharides	70
7	Octasaccharides	70
8	Higher Saccharides	71
9	Cyclodextrins	72
	References	73
Chapter 5	Ethers and Anhydro-sugars	79
1	Ethers	79
1.1	Methyl Ethers	79
1.2	Other Alkyl and Aryl Ethers	79
1.3	Silyl Ethers	80
2	Intramolecular Ethers (Anhydro-sugars)	80
2.1	Oxirans	80
2.2	Other Anhydrides	81
	References	82

<i>Contents</i>	ix
Chapter 6 Acetals	84
1 Methylene, Ethyldene, Isopropylidene, and Benzylidene Acetals	84
2 Other Acetals	85
3 Reactions of Acetals	86
References	87
Chapter 7 Esters	88
1 Carboxylic Esters	88
1.1 Synthesis and Reactions	88
1.2 Isolation from Natural Sources	94
2 Phosphates and Related Esters	94
3 Sulfonates	97
4 Other Esters	98
References	100
Chapter 8 Halogeno-sugars	103
1 Fluoro-sugars	103
2 Chloro-, Bromo-, and Iodo-sugars	105
References	106
Chapter 9 Amino-sugars	108
1 Natural Products	108
2 Synthesis	108
2.1 Chain Extension	108
2.2 Amadori Reaction	108
2.3 Epoxide Opening	109
2.4 Radical Amination	110
2.5 Nucleophilic Displacement	110
2.6 From Nitro-sugars	112
2.7 From Unsaturated Sugars	113
2.8 Curtius Reaction	113
2.9 Reductive Amination	114

2.10	From Chiral Non-carbohydrates	114
3	Reactions, Properties, and Synthesis of Derivatives	116
4	Diamino-sugars	119
	References	120
Chapter 10	Miscellaneous Nitrogen Derivatives	123
1	Glycosylamines and Related Glycosyl- <i>N</i> -Bonded Compounds	123
2	Azido- and Diazirino-sugars	127
3	Nitro- and Nitroso-sugars	129
4	Nitriles, Oximes, Hydroxylamines, Nitrones, and Imines	130
5	Hydrazones, Osazones, and Related Heterocycles	132
6	Other Heterocycles	133
	References	135
Chapter 11	Thio-sugars	138
	References	142
Chapter 12	Deoxy-sugars	143
	References	147
Chapter 13	Unsaturated Derivatives	148
1	Glycals	148
2	Other Unsaturated Derivatives	149
	References	152

<i>Contents</i>	xi
Chapter 14 Branched-chain Sugars	154
1 Compounds with an R-C-O Branch	154
2 Compounds with an R-C-N Branch	156
3 Compounds with an R-C-H Branch	156
4 Compounds with an R-C-R or C=R Branch	162
References	163
Chapter 15 Aldosuloses and Other Dicarbonyl Compounds	165
1 Aldosuloses	165
2 Other Dicarbonyl Compounds	165
References	166
Chapter 16 Sugar Acids and Lactones	167
1 Aldonic Acids and Aldonolactones	167
2 Anhydroaldonic Acids and Lactones	169
3 Ulosonic Acids	170
4 Uronic Acids	174
5 Ascorbic Acids	176
References	178
Chapter 17 Inorganic Derivatives	181
1 Carbon-bonded Phosphorus Derivatives	181
2 Other Carbon-bonded Derivatives	181
3 Oxygen-bonded Derivatives	182
4 Nitrogen-bonded Derivatives	184
References	184

Chapter 18	Alditols and Cyclitols	186
1	Alditols	186
1.1	Acyclic Alditols	186
1.2	Anhydro-Alditols	190
1.3	Amino- and Imino-Alditols	191
2	Cyclitols	197
	References	207
Chapter 19	Antibiotics	211
1	Amino-Glycoside Antibiotics	211
2	Macrolide Antibiotics	212
3	Anthracycline and Related Polycyclic Antibiotics	213
4	Nucleoside Antibiotics	215
5	Miscellaneous Antibiotics	217
	References	220
Chapter 20	Nucleosides	224
1	General	224
2	Synthesis	224
3	Anhydro- and Cyclo-nucleosides	226
4	Deoxynucleosides	228
5	Halogenonucleosides	232
6	Nucleosides with Nitrogen-substituted Sugars	233
7	Thio- and Seleno-nucleosides	237
8	Nucleosides with Branched-chain Sugars	239
9	Nucleosides of Unsaturated Sugars, Keto-sugars, and Uronic Acids	244
10	C-Nucleosides	245

11	Carbocyclic Nucleoside Analogues	246
12	Nucleoside Phosphates and Phosphonates	248
13	Ethers, Esters, and Acetals of Nucleosides	253
14	Miscellaneous Nucleoside Analogues	255
15	Reactions	257
	References	259
Chapter 21	N.M.R. Spectroscopy and Conformational Features	266
1	General Aspects	266
2	Acyclic Systems	267
3	Furanose Systems	267
4	Pyranose Systems	269
5	Disaccharides	269
6	Oligosaccharides and Related Compounds	271
7	^{17}O N.M.R. Spectroscopy	273
	References	274
Chapter 22	Other Physical Methods	276
1	I.R. Spectroscopy	276
2	Mass Spectrometry	276
3	X-Ray and Neutron Diffraction Crystallography	278
4	E.S.R. Spectroscopy	283
5	Polarimetry, Circular Dichroism, and Related Studies	283
	References	284

Chapter 23 Separatory and Analytical Methods	288
1 Chromatographic Methods	288
1.1 General	288
1.2 Gas-Liquid Chromatography	288
1.3 Thin-Layer Chromatography	290
1.4 High-Pressure Liquid Chromatography	290
1.5 Column Chromatography	297
2 Electrophoresis	297
3 Other Analytical Methods	298
References	299
Chapter 24 Synthesis of Enantiomerically Pure Non-carbohydrate Compounds	302
1 Carbocyclic Compounds	302
2 γ - and δ -Lactones	305
3 Macrolides, Macroyclic Lactams, and Their Constituent Segments	308
4 Other Oxygen Heterocycles, including Polyether Ionophores	309
5 Nitrogen Heterocycles	313
6 Acyclic Compounds	315
7 Carbohydrates as Chiral Auxiliaries	319
References	321
Author Index	325

Abbreviations

The following abbreviations have been used:

Ac	acetyl
Ad	adenin-9-yl
AIBN	2,2'-azobisisobutyronitrile
All	allyl
BBN	9-borabicyclo[3.3.1]nonane
Bn	benzyl
Boc	t-butoxycarbonyl
Bz	benzoyl
Cbz	benzyloxycarbonyl
c.d.	circular dichroism
CI	chemical ionization
DAST	diethylaminosulphur trifluoride
DBU	1,5-diazabicyclo[5.4.0]undec-5-ene
DCC	dicyclohexylcarbodi-imide
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DEAD	diethyl azodicarboxylate
DIBAL	di-isobutylaluminium hydride
DMAP	4-dimethylaminopyridine
DMF	N,N-dimethylformamide
DMSO	dimethyl sulphoxide
EE	1-ethoxyethyl
e.s.r.	electron spin resonance
FAB	fast-atom bombardment
GC	gas chromatography
HMPT	hexamethylphosphorous triamide
i.r.	infrared
LAH	lithium aluminium hydride
LDA	lithium di-isopropylamide
LTBH	lithium triethylborohydride
MCPBA	m-chloroperbenzoic acid
MEM	methoxyethoxymethyl
MOM	methoxymethyl
m.s.	mass spectrometry
Ms	methanesulphonyl
NBS	N-bromosuccinimide
NIS	N-iodosuccinimide
n.m.r.	nuclear magnetic resonance
o.r.d.	optical rotatory dispersion
PCC	pyridinium chlorochromate
PDC	pyridinium dichromate
PTC	phase transfer catalysis
Py	pyridine

SIMS	secondary-ion mass spectrometry
TASF	tris(dimethylamino)sulphonium difluorotrimethyl silicate
TBDMS	t-butyl(dimethylsilyl)
Tf	trifluoromethanesulphonyl
Tfa	trifluoroacetyl
TFA	trifluoracetic acid
THF	tetrahydrofuran
Thp	tetrahydropyranyl
TMS	trimethylsilyl
TPP	triphenylphosphine
TPS	tri-isopropylbenzenesulphonyl
Tr	triphenylmethyl
Ts	toluene p-sulphonyl
U	uracil-1-yl

1

Introduction and General Aspects

Tributes to the life and work of Professors R. Bognár¹ and J. E. Courtois² have appeared in *Advances in Carbohydrate Chemistry and Biochemistry*.

A survey of major historical significance has been presented by F. W. Lichtenthaler on Emil Fischer's monumental work on the proof of the configuration of the sugars. A century on, it gives an in-depth insight into the story in which the reasoning and creative processes as well as elements of serendipity involved in the work are featured.³

In the area of synthesis Garegg has surveyed various regioselective reactions which are applied in oligosaccharide synthesis under the title "Challenges and opportunities for organic synthesis with saccharides of biological importance."⁴ More specifically a substantial review has dealt with basic aspects of the major issue of the methods available for the preparation of 1,2-asymmetric centres with defined relative stereochemistry, and 1,3-difunctional compounds in which 1,2-difunctional stereorelationships may also be established. A later publication which builds on this will be of more specific relevance in carbohydrate chemistry.⁵ More specific topics to have been surveyed are cycloaddition reactions in carbohydrate chemistry⁶ and noble metal-catalysed oxidations of carbohydrates.⁷

Enzymes continue to gain hold as specific synthetic tools in the field, and four major reviews on the topic have been published. One deals with their use in the field generally,⁸ while the others focus on the enzymic production of unusual sugars,⁹ glycosides,^{9,10} oligosaccharides⁹⁻¹¹ and complex carbohydrates e.g. glycoconjugates.¹¹

The topic of hydrogen bonding of carbohydrates and hydrate inclusion compounds has been surveyed¹² as have the topics of intramolecular hydrogen bonding and molecular association in monosaccharides and natural cellulose.¹³ Other reviews on physical aspects of carbohydrates have dealt with liquid crystal compounds¹⁴ and with molecular dynamics simulations in the field.¹⁵

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2

Free Sugars

1 Theoretical Aspects

The compositions of reducing sugars (aldoses, ketoses, mono- and di-saccharides) in solution (76 refs.)¹ and the hydrophobic behaviour of sugar molecules in aqueous media (33 refs.)² have been reviewed.

The interactions of D-glucopyranose, D-fructopyranose, and sucrose with a proteinaceous receptor have been examined by use of CPK models to validate the stereomolecular interpretation of sweet taste proposed for these sugars.³ In continuation of earlier studies (see Vol. 24, Chapter 2, ref. 7) the kinetic effects of 17 free sugars on the hydrolysis of 1-benzoyl-3-phenyl-1,2,4-triazole have been measured. Analysis of the results in terms of hydration and stereochemical features led to the conclusion that the relative positions of 2-OH and 4-OH in the sugars are critical.⁴

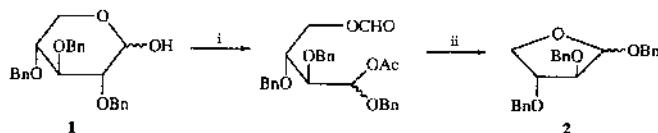
2 Synthesis

Reviews have been published on the synthesis of monosaccharides by use of enzyme mediated aldol condensations (127 refs.),⁵ on Dondoni's work on the acyclic synthesis of carbohydrates and related natural products by use of functionalized thiiazoles as formyl equivalents,⁶ and on Shiozaki's research on the conversion of D-glucose to L-glucose.⁷

2.1 Trioses to Hexoses. - It has been shown that atomic carbon (generated by vaporizing in an arc under high pressure) reacts with water at 77 K to form low yields of straight-chain aldoses with up to five carbon atoms. A mechanism involving the hydroxymethylene species was proposed.⁸ The production of a mixture of hexoses [sorbose (15%), fructose (12%), psicose (6%), tagatose (6%)] from glyceraldehyde under prebiotic conditions, *i.e.*, at 15 °C, pH 5-6, in the presence of iron (III) hydroxide as catalyst, has been reported.⁹

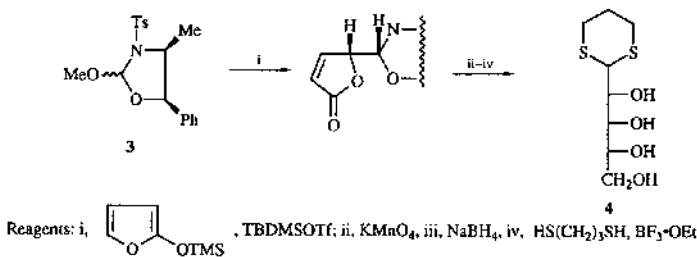
Polymer-supported thiiazolium salts have been found to have high catalytic activity in the formose reaction, the main product being hydroxyacetone.¹⁰ Use of synthetic α -ketols as catalysts in the formose reaction led to selective formation of trioses, especially with α -ketols bearing electronegative substituents.¹¹ Incubation of D-glucose with bakers' yeast in the presence of benzyl mercaptan gave S-benzyl thioglycerate in preparatively useful yields; fermentation experiments with

¹³C- and ¹H-labelled D-glucose were carried out to confirm the hypothesis that the thiol acts as a nucleophile in the glycolytic pathway and also to evaluate the potential of the process for the preparation of specifically labelled D-glycerols.¹²

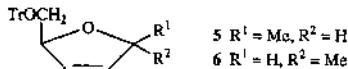


Reagents: i, $\text{PhI}(\text{OAc})_2$, I_2 (cat.); ii, HClO_4 , EtOH
Scheme 1

One-carbon-extrusion by way of C-1-alkoxy radical fragmentation gave tetro- and pento-furanose derivatives from pentose and hexose starting materials, respectively. As an example, the formation of benzyl 2,3-di-O-benzyl-D-threoside (**2**) from 2,3,4-tri-O-benzyl-D-xylose (**1**) is given in Scheme 1.¹³ The utility of norephedrine-derived 2-methoxyoxazolidines **3** as asymmetric formylating agents has been demonstrated by the synthesis of D-ribose (as its dithioacetal **4**), as shown in Scheme 2. The key-step was the trapping of the carbonium ion, formed from **3** on



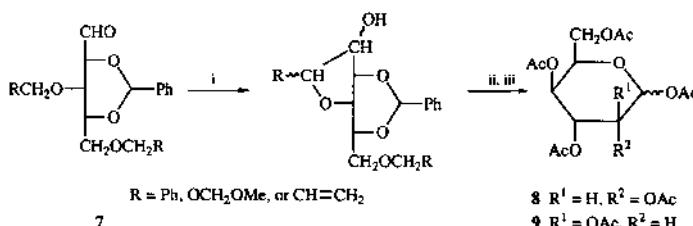
Scheme 2



5 $\text{R}^1 = \text{Me}, \text{R}^2 = \text{H}$
6 $\text{R}^1 = \text{H}, \text{R}^2 = \text{Me}$

treatment with a Lewis acid, by trimethylsilyloxyfuran.¹⁴ D-Xylose was converted to D-ribose and D-lyxose via the separable alkenes **5** and **6** which were *cis*-hydroxylated selectively from the faces opposite to the anomeric methoxy groups.¹⁵ Irradiation of the xylose derivative **7** led to a Norrish II rearrangement involving bond formation between C-1 and the methylene carbon of the protecting group at C-3, as indicated in Scheme 3. Hydrolysis furnished a mixture of D-gulose and D-idose which were isolated as the pentaacetates **8** and **9**, respectively.¹⁶

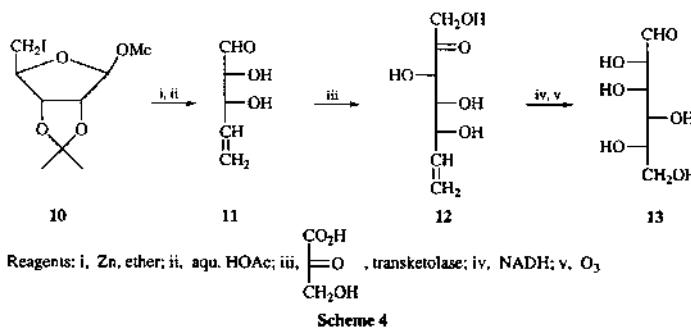
The biomimetic transformation of starch to D-fructose in a reactor containing inorganic phosphate and five enzymes has been described.¹⁷ Transketolase-catalysed stereospecific



Reagents: i. hv; ii. HCl, THF; iii. As₂O₃, HClO₄

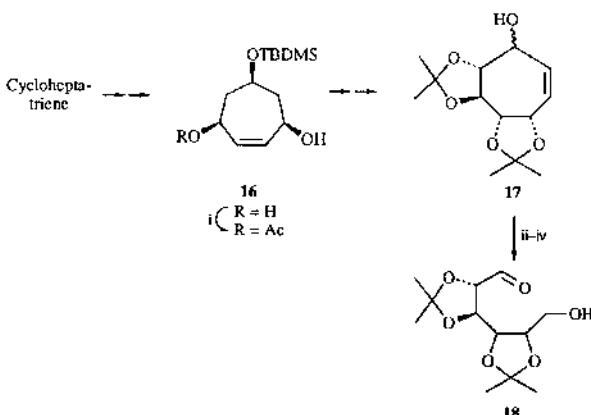
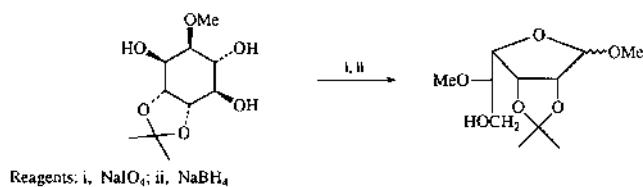
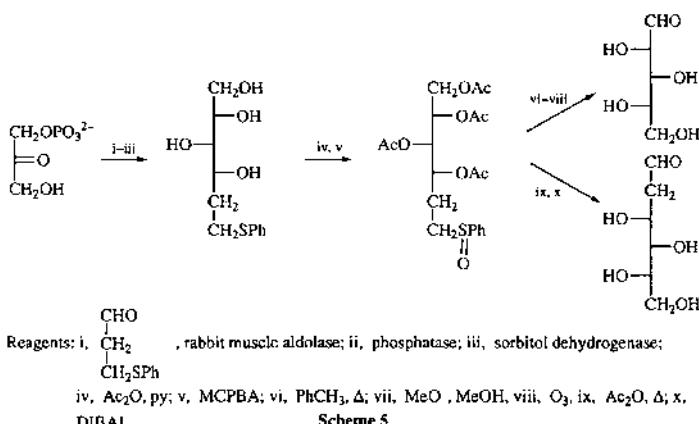
Scheme 3

condensation of hydroxypyruvic acid, under loss of CO₂ (see Vol. 25, Chapter 2, ref. 9), with enal 11, obtained from iodide 10 as shown in Scheme 4, furnished enone 12. Reduction of the carbonyl group with NADH and subsequent ozonolysis of the double bond gave L-gulose (13). L-Idose, 2-deoxy-L-xylo-hexose and L-xylose were similarly prepared by use of the appropriate enals.¹⁸ 2-Deoxy-L-xylo-hexose and L-xylose were also obtained by aldolase-catalysed reaction of dihydroxyacetone phosphate (see Vol. 25, Chapter 2, ref. 19; Vol. 24, Chapter 2, ref. 11) with 3-phenylthiopropanal followed by enzymic reduction and dephosphorylation to furnish intermediate 14. The syntheses were completed by several chemical steps, as shown in Scheme 5.¹⁹ The use of enzyme-mediated aldol condensations in the preparation of rare ketose 1-phosphates and of fagomine are covered in Chapters 7 and 18, respectively.

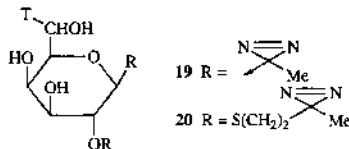


Scheme 4

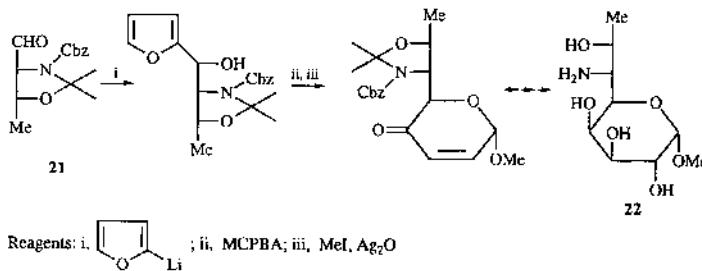
The key-step in the synthesis of 5-*O*-methyl-D-mannose from L-quebrachitol was the glycol cleavage of the isopropylidene derivative 15 (Scheme 6). L-Tagatose was prepared by a similar, but extended reaction sequence incorporating a Mitsunobu inversion at the future C-4.²⁰ L-Glucose has been synthesized in many steps from cycloheptatriene (Scheme 7) via the *meso*-intermediate 16 which was desymmetrized by enzymic monoacetylation. Transformation to the allylic alcohol 17 involved *inter alia* stereoselective oxygenation and *cis*-hydroxylation. Ozonolysis, followed by



reduction and glycol cleavage, gave the target compound as its di-isopropylidene derivative **18**.²¹ Alternative preparations of L-glucose and L-mannose are mentioned in Part 2.2 below.



The syntheses of D-[2-³H]- and D-[5-³H]-glucose involved, respectively, NaOD treatment of 2,3,4,6-tetra-O-benzyl-D-glucose and NaBD₄ reduction of an α-D-xylo-hexofuranose-2-ulose derivative,²² and D-[6-³H]galactose resulted from the NaBD₄ reduction of 1,2:3,4-di-O-isopropylidene-α-D-galacto-hexodialdo-1,5-pyranose, followed by deprotection.²³ The [8-³H]-labelled photoaffinity reagents **19** and **20** were accessible from the unlabelled compounds by oxidation with D-galactose oxidase/catalase and subsequent treatment with NaBT₄,²⁴ D-[1-¹¹C]Glucose and D-[1-¹¹C]mannose with radiochemical purities >97% have been obtained by addition of [¹¹C]niromethane to D-arabinose, followed by classical Nef reaction. The two products were separated by semipreparative h.p.l.c.²⁵ A multi-step enzymic procedure has been devised for



Scheme 8

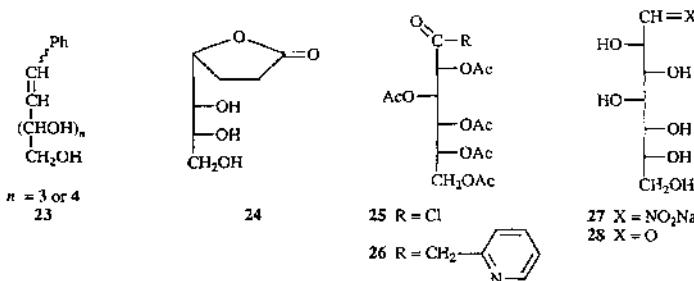
the synthesis of D-[1-¹⁴C,1-³H]glucose and D-[U-¹⁴C,1-²H]glucose from appropriately ¹⁴C-labelled D-fructose and D₂O.²⁶ D-[1,2-¹³C₂]Mannose has been converted in five steps, involving oxidation at C-6, reduction at C-1, and Ruff degradation, to D-[4,5-¹³C₂]arabinose. Reaction with K¹³CN and subsequent hydrogenation over Pt/BaSO₄ gave a mixture of D-[1,5,6-¹³C₃]-glucose and -mannose.²⁷

2.2 Chain-extended Compounds.-

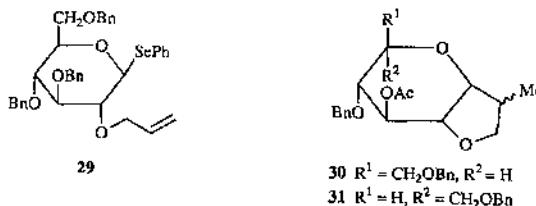
A review with 200 references on recent advances in the synthesis of C₇-C₉ sugars, including neuraminic acid analogues, has been published.²⁸

A new route to D- and L-aminooses by application of the method of Achmatowicz (see Vol. 19, Chapter 2, ref. 18) has been developed. As an example, the synthesis of methyl α-

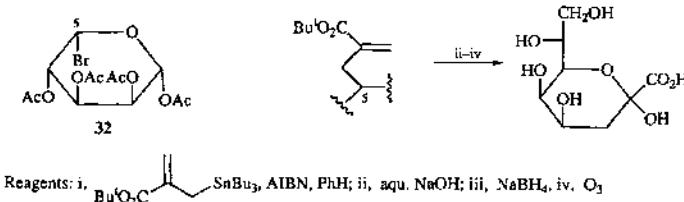
D-lincosaminide (**22**) starting from aldehyde **21**, prepared in 6 steps from D-threonine and furanyl lithium is outlined in Scheme 8.²⁹ Several unprotected aldoses (D-glucose, D-galactose, D-arabinose,



D-xylose) reacted with the semistabilized ylide $\text{Ph}_3\text{P}=\text{CHPh}$ in dioxane to give good yields of products **23**,²³ and reaction of D-arabinose with $\text{Ph}_3\text{P}=\text{CHCO}_2\text{Et}$ in the same solvent afforded, after hydrogenation and saponification, 2,3-dideoxy-D-*arabino*-heptono-1,4-lactone (**24**) in 60% overall yield.³¹ 1-C-Heteroaryl-substituted, linear uloses have been obtained from peracetylated glyconoyl chlorides (e.g., **25** \rightarrow **26**) on exposure to organoaluminium reagents *in situ* from

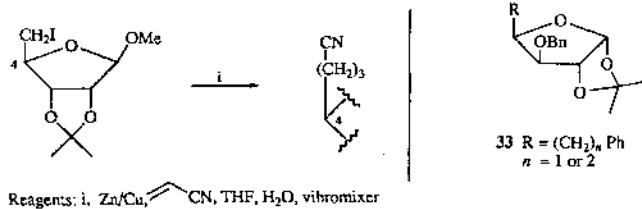


diethylaluminium chloride and the appropriate organolithium derivatives.³² Treatment of the sodium salt **27** of 1-deoxy-1-nitro-D-glycero-D-ido-heptitol with ozone furnished heptose **28**. D-glycero-D-gulo- and D-glycero-D-manno-heptose as well as L-glucose and L-mannose have been analogously prepared.³³ Condensation of 2,6-anhydro-7-deoxy-7-nitro-L-glycero-L-galacto-heptitol with formaldehyde, followed by ozonolysis of the adduct, gave as the major product 3,7-anhydro-D-glycero-L-manno-octose.³⁴ The 5-exocyclization of phenyl selenoglycoside **29** under radical conditions gave the expected product **30** together with **31** resulting from epimerization at C-5.³⁵



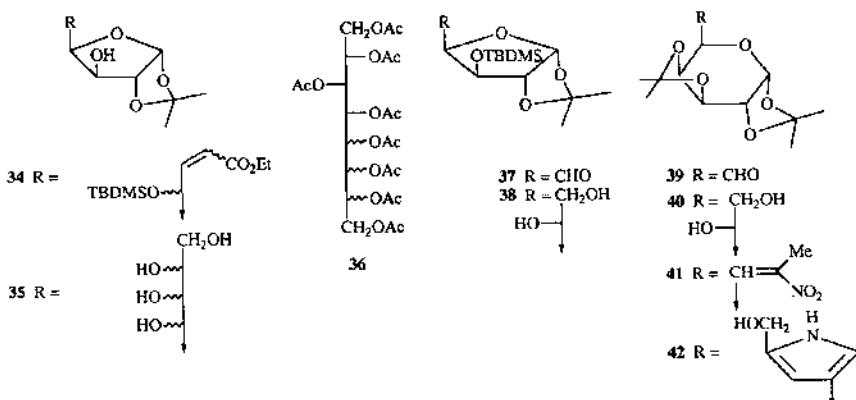
Scheme 9

Addition of the radical generated from bromide 32, obtained in mediocre yield by photobromination of L-lyxose peracetate, to *t*-butyl 2-(tributylstannylmethyl) propenoate (Scheme 9) was the crucial step in a new synthesis of 3-deoxy-D-manno-octulosonic acid (KDO).³⁶ Zinc/copper-induced addition of carbohydrate residues, derived from deoxy-iodo sugars, to activated alkenes has been achieved under vigorous stirring, without sonication. An example is shown in Scheme 10.³⁷ 3-O-Benzyl-1,2-O-isopropylidene- α -D-xylo-pentodialdo-1,5-furanose has been extended by use of Wittig methodology to give deoxy sugars 33.³⁸



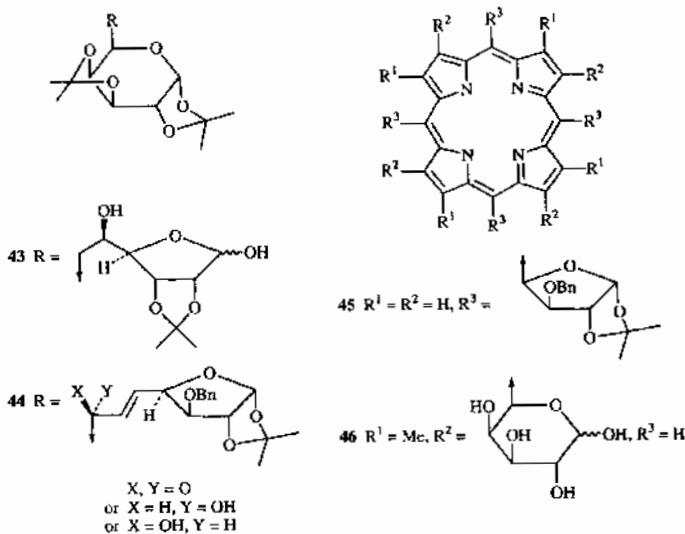
Scheme 10

The four isomeric 6,7-unsaturated octuronate derivatives 34 (see Vol. 25, Chapter 2, ref. 25 for their preparation) have been transformed to the octose monoacetonides 35 and octitol octaacetates 36, some of which are new compounds.³⁹ Vanadium (II)-catalysed pinacol cross condensation of the D-xylo- and D-galacto-dialdehyde derivatives 37 and 39 with paraformaldehyde furnished the D-configured products 38 and 40, respectively, in a non-chelation controlled process, together with very minor proportions of the corresponding L-sugars.⁴⁰



Dialdehyde 39 has also been used in the construction of the 11-carbon skeleton of the tunicamycin analogue 43⁴¹ and the 15-carbon linear monosaccharide 1,3-bis-D-galactopyranos-6-yl) glycerol.⁴² Dialdehyde 39 as well as some protected D-pentofuranose-5-aldehydes have been

condensed with pyrrole to give, after oxidation with chloranil, porphyrins, such as compound 45, with sugar residues at the *meso*-positions.⁴³ Alternatively, these dialdehydes were condensed with nitroethane to furnish nitroalkenes, e.g., compound 41, which were converted to pyrroles, e.g., compound 42. Tetramerization under acidic conditions, followed by oxidation and deprotection, gave water-soluble porphyrins, e.g., compound 46.⁴⁴



The steric course of the osmylation of five higher sugar olefins, such as compounds 44 has been examined. Kishi's rule was found to be obeyed in all but one case (44, X,Y = O).⁴⁵

3 Physical Measurements

The physical and chemical properties of some L-hexoses, especially those related to their use as alternative sweeteners, have been discussed.⁴⁶

The standard enthalpies of formation and combustion of D-ribose and D-ribono-1,4-lactone have been determined by calorimetric combustion in air.⁴⁷ Differential scanning calorimetry on an aqueous sucrose solution revealed two glass transitions, at -63 °C and -43 °C, upon cooling and warming, respectively, the bulk of the water freezing at -18 °C.⁴⁸

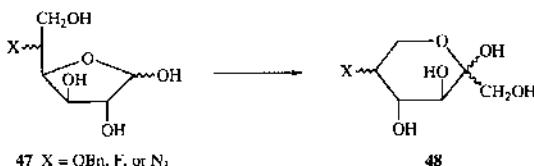
Studies have been published on the effect of pressure on the acoustic and thermal properties of dilute aqueous mannose solutions,⁴⁹ on the influence of structure and concentration of mono- and disaccharides on the ultrasonic absorption of their aqueous solutions,⁵⁰ on the stabilities of hydrogen

bonds in aqueous sucrose as evaluated from i.r. data,⁵¹ and on the thermodynamics of viscous flow of sucrose solutions.⁵²

The effect of temperature on the concentration of the open-chain form of D-fructose in D₂O and water has been determined by FT-IR spectroscopy.⁵³ Measurements by ¹H-n.m.r. spectroscopy of the temperature coefficients of chemical shifts, scalar coupling constants, and exchange rates for hydroxyl protons in sucrose have provided no evidence for persistent hydrogen bonds in aqueous solution.⁵⁴

4 Isomerization

The C-2 epimerization of aldoses promoted by Co(II) N,N,N'-trimethylethylenediamine complexes has been shown, by use of ¹³C-labelled substrates, to involve a skeletal rearrangement. D-[1-¹³C]glucose, for example, gave D-[2-¹³C]mannose.⁵⁵ D-Fructose was isomerized to hamamelose [2-C-(hydroxymethyl)-D-ribose] by Ni(II) N,N'-diethylethylene-diamine. The equilibrium mixture contained 29% of the branched component.⁵⁶



Reagents: i. immobilized glucose isomerase

Scheme 11

Glucose isomerase has been employed to convert D-glucos- and L-ido-furanose derivatives 47 into D-fructo- and L-sorbo-pyranose derivatives 48, respectively, in 70 - 80% yield, as shown in Scheme 11.⁵⁷ β -D-Fructofuranose has been found to bind to DNA preferentially, allegedly by three hydrogen bonds to phosphate. DNA thus moves the equilibrium β -D-fructofuranose \rightleftharpoons α -D-fructofuranose to the right.⁵⁸

5 Oxidation

The role of the crystalline surface structure, and in particular long range surface order, of platinum electrodes in the electrooxidation of D-glucose in acidic media has been discussed.^{59,60} Papers have been published on the effects of adsorbed anions on the oxidation of D-glucose on gold single crystal electrodes,⁶¹ and on the oxidation of D-sorbitose and 2,3:4,6-di-O-isopropylidene- α -L-sorbitose by air over supported platinum and palladium catalysts.⁶²

A voltammetric investigation of the direct electrooxidative decarboxylation of D-gluconate ion to D-arabinose on a graphite electrode has been described.⁶³ An "on line" chromatographic analysis of the products of electrocatalytic oxidation of D-glucose is referred to in Chapter 16.

The kinetics and mechanism of the oxidation of D-mannitol to D-mannose by Tl(III) and catalytic amounts of Ru(II) in aqueous acetic acid have been studied; [Tl(OAc)₃] is thought to be the reactive Tl species, and no evidence was found for free radical intermediates.⁶⁴ Further kinetic studies were concerned with the oxidation of L-sorbose by Mn(III) in aqueous H₂SO₄,⁶⁵ and of D-mannose and L-rhamnose by Cr(VI) in perchloric acid.⁶⁶ Kinetic data obtained in the oxidations of monosaccharides with acidic bromate and NBS, separately, in the presence of Hg(OAc)₂ have been compared with the results of earlier experiments using V(V) or Ce(IV) as oxidizing agents. It is surmised that the reacting monosaccharide species are the open-chain forms with V(V) and the ring forms with BrO³⁻ and Ce(IV), whereas with NBS the mechanism is complex.⁶⁷

Two papers on the kinetics of oxidation of D-glucose by pyridinium chlorochromate (PCC) have appeared,^{68,69} and the oxidation of L-arabinose, D-lyxose, D-ribose, and D-xylose by sodium N-bromo-p-toluene (bromamine T) in alkaline media has been examined.⁷⁰ An investigation of the RuO₄-catalysed oxidation of aldoses by alkaline N-bromoacetamide is referred to in Chapter 16.

H.p.l.c. analysis of the products formed in the degradation of cellobiose under Fenton's conditions showed that D-glucose and organic acids were the main products.⁷¹

6 Other Aspects

Kinetic studies on the Maillard reaction observed when L-ascorbic acid is incubated with protein indicated interaction of amino groups with threose which is formed from ascorbic acid directly as well as via dehydro-L-ascorbic acid and 2,3-keto-L-gulonic acid.⁷²

The complexation of a resorcinol-dodecanal cyclotetramer as achiral host with sugars as guest compounds has been reported.⁷³ Evidence has been presented of a biological radical deoxygenation step in the biosynthesis of ascarylose (3,6-dideoxy-L-arabino-hexose).⁷⁴ The role of transketolase catalysis in the conversion of D-glucose to aromatic amino acids has been investigated with a view to its application to a commercial process.⁷⁵

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3 Glycosides

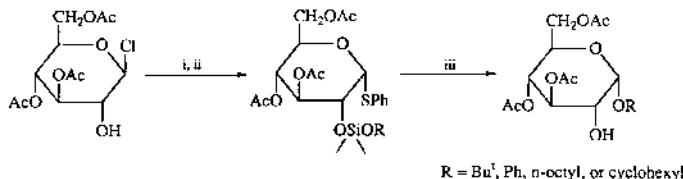
1 O-Glycosides

1.1 Synthesis of Monosaccharide Glycosides.—A further review on recent progress in methodological aspects of glycoside synthesis has appeared.¹

Fraser-Reid and coworkers have reviewed the group's work on the use of pentenyl glycosides and have included some useful experimental details.² In a related paper issues associated with matched and mis-matched glycosyl donors and acceptors and consequent effects on α , β -product ratios are considered.³

The isopropenyl group has been employed ingeniously to act as a leaving group in glycosyl donors, and also to activate hydroxyl groups as glycosyl acceptors (see section 1.4).⁴

A further extremely useful-looking development, which employs an intramolecular strategy and is applicable to the synthesis of α -D-glucopyranosides, is illustrated in Scheme 1.⁵



Reagents: i, PhSK ; ii, ROSiMe_2Cl ; iii, NIS, TiOH

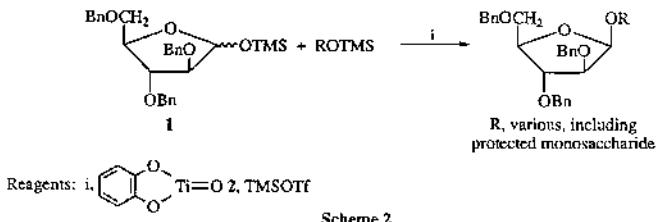
Scheme 1

Vasella has reported further on the use of glycosyl carbenes, derivable from diazirines. Mechanistic aspects and solvent effects on anomeric ratios of glycoside products are discussed.⁶ While carbenes derived from D-glucopyranosyl diazirines give β -glycosides with reasonable selectivity, 2-deoxy analogues show little or no selectivity. This observation has led to the suggestion that the benzyloxy groups at C-2 participate in the substitution processes.^{6a}

Tetra-O-acetyl- α -D-glucosyl trifluoroacetate in the presence of boron trifluoride or trimethylsilyl triflate, gives β -glucosides as expected.⁷ A related method of preparing β -glucosides with high stereoselectivity involves the use of 2,3,4,6-tetra-O-pivaloyl- β -D-

glucopyranosyl acetate and methyltrichlorosilane and silver perchlorate at catalysts. This method was applied in satisfactory syntheses of glucose-containing disaccharides.⁸

Using fully benzylated sugars having trimethylsilyl groups at O-1 Mukaiyama has reported conditions under which such compounds can be used to make α - and β -D-ribofuranosides and α -D-glucopyranosides each with good selectivity.⁹ In related work he has used the D-arabinofuranosyl ether 1 and catalyst 2 in the synthesis of β -D-arabinofuranosides (Scheme 2).¹⁰

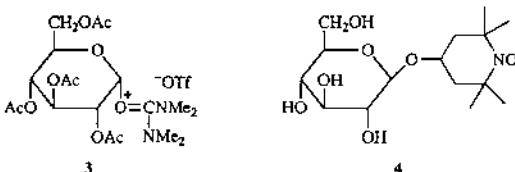


Scheme 2

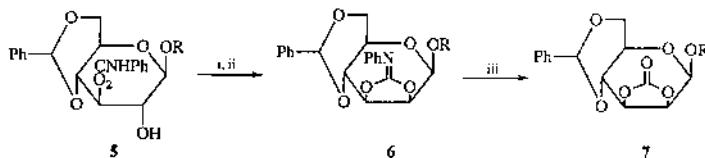
1,3,4,6-Tetra-O-benzoyl- α -D-fructofuranose, on treatment with DEAD, triphenylphosphine and alcohols, phenols and arylamines, gives access to the corresponding α -furanosyl products, the stereo-chemistry, it is presumed, being controlled by the intermediacy of a benzoxonium ion at C-2, C-3.^{10a}

Fischer glycosidation of L-arabinose using 2-chloroethanol, 2-bromoethanol or 2-iodoethanol gave the crystalline β -pyranosides directly in 20, 86 and 23% yield, respectively, and these products offered a means of obtaining a variety of analogues substituted in the 2-position of the aglycon.¹¹ Trifluoromethyl glycosides and sugar trifluoromethyl ethers have been discussed in an extensive review of trifluoromethyl derivatives.¹²

Salt 3 is obtainable crystalline in 56% yield from tetra-O-acetyl- α -D-glucopyranosyl bromide, tetra-N-methylurea and silver triflate. In methanol it afforded the β -glycoside, and in dichloromethane it condensed with methyl 2,4,6-tri-O-benzyl- β -D-glucopyranoside to give the 3- β -linked disaccharide in good yield.¹³



A potentially valuable new method of inverting configuration at C-2 in β -glucosides to give corresponding mannosides as been reported by Kunz. It involves the use of the 3-*O*-(*N*-phenyl)carbamoyl glucoside **5** which, after activation by triflation at C-2, can be converted into the cyclic intermediate **6** hydrolysis of which gives the products **7** (Scheme 3).¹⁴ An extensive range of examples was provided.



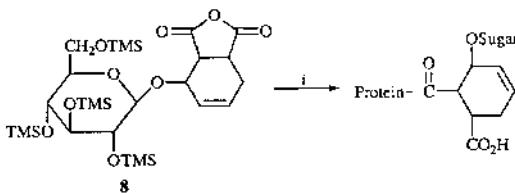
Reagents: i, Tf₂O, py; ii, evaporate; iii, DMF, py, 75 °C

Scheme 3

By use of the acylated glycal method long chain alkyl unsaturated glycosides have been produced from glucose, xylose and rhamnose, and the products were hydrogenated to give 2,3-dideoxy analogues which were examined as thermotropic non-amphiphilic chiral liquid crystals.¹⁵

An improved synthesis of "tempol" **4** involved the use of acetobromoglucose with silver triflate as activator in dichloromethane at -20°C.¹⁶

Diels Alder methods have been used to produce compound **8** which is proposed for use in the chemical stabilization of proteins (Scheme 4).¹⁷

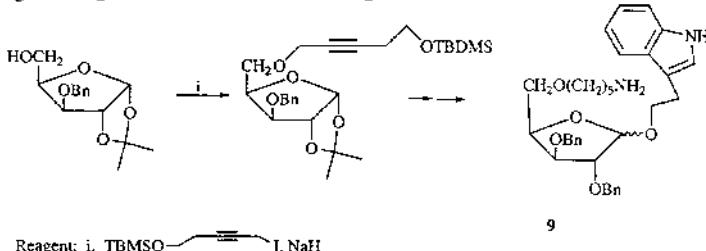


Reagent: Protein nucleophile

Scheme 4

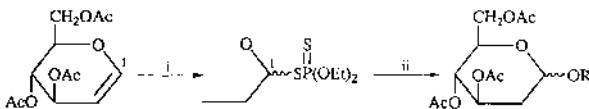
Two papers have appeared on the synthesis of non-peptide mimics of somatostatin. A 3-ethylindole-2'-yl glucoside carrying a 5-aminopentyl group at *O*-6 has a high affinity for substance P receptor and is also reported to be a somatostatin agonist.¹⁸ The xylofuranose analogue **9** has been prepared as indicated in Scheme 5, following conformational analysis of

the endogenous ligand and molecular modelling studies.¹⁹



Scheme 5

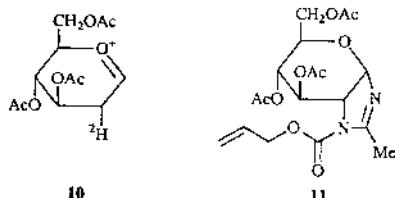
The long known addition of alcohol to glycals under acid conditions does not proceed by a diaxial process. Isotopic studies have shown that the intermediate **10** is involved in the addition of labelled alcohols to tri-*O*-acetyl- α -D-glucal to give α -glycosides.²⁰ A further method for making 2-deoxyglycosides, based on additions to glycals, is illustrated in Scheme 6.²¹



Reagent i, HSPS(OEt)₂; ii, NIS, ROH

Scheme 6

1,3,4,6-Tetra-*O*-acetyl-2-allyloxycarbonylamino-2-deoxy- β -D-glucose has shown itself to be a good β -glycosylating agent when used in nitromethane solvent with TMSOTf. It proved efficient with simple primary and secondary alcohols and with a monosaccharide derivative. When acetonitrile is used, especially in the absence of alcohol, imidazoline **11**, incorporating a molecule of solvent, was formed.²² In Chapter 9 further reference is made to the use of *N*-acyloxy carbonyl- and *N*-allyloxy carbonyl-amino derivatives in the synthesis of glycosides and disaccharides of 2-amino-2-deoxy sugars.²³



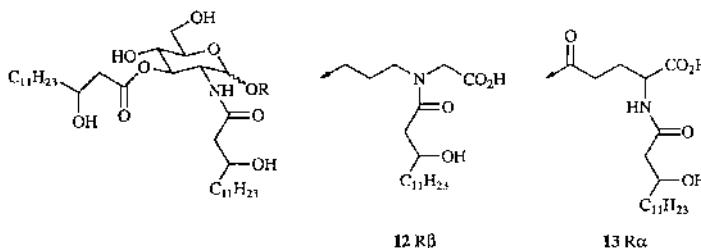
In closely related studies Mukaiyama has used the (trichloromethyloxycarbonyl)amino group, and with the analogous β -tetra-acetate and silylated alcohols in the presence of tin triflate has made β -glycosides in the *gluco-* and the *galacto-* series.²⁴ When they used *O*-

benzyl protected *N*-(2,2,2-trichloroethoxycarbonyl)amino-2-deoxy- α -gluco- and galactosyl acetates with trimethylsilyl chloride or bromide and with zinc triflate at activator, Iijigashi and Susaki were able to make α -glycosides, in one case almost exclusively.²⁵ The same group of workers have shown that glycosidic analogues of these glycosylacetates, for example benzyl, methyl, isopropyl compounds, can be used in transglycosidation reactions, α - or β - compounds being transformed into α -derivatives with good selectivity.²⁶

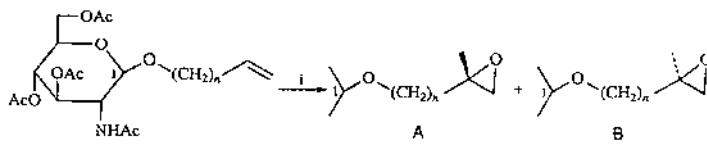
Trimethylsilyl bromide and zinc bromide were used as activators.

The peracetylated glycosyl chloride of glucosamine, used without solvent but with tetramethylurea as acid scavenger, gives good yields of the cholesteryl glycosides with α , β ratio 5:95. When the temperature was increased from 60 to 180°, however, the ratio changed to 83:17. Similar results were obtained with methyl 2,3,4-tri-*O*-benzyl- β -D-glucopyranoside as glycosyl acceptor.²⁷

The acyclic analogue of Lipid A 12 and corresponding ester 13 have been prepared.²⁸



As would be expected, asymmetric induction decreased with distance from the sugar ring in epoxidation of the amino sugar unsaturated glycosides shown in Scheme 7.²⁹



Reagent: MCPBA

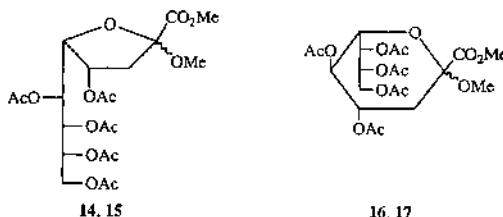
<i>n</i>	% d.e. of A
1	68
2	20
3	7

Scheme 7

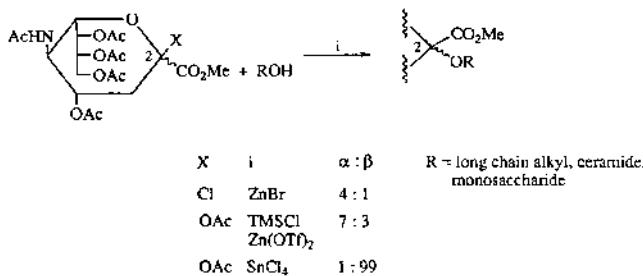
Related work has been carried out on the osmium tetroxide oxidation of allyl glycosides.^{29a}

In the area of sugar acids Fischer glycosidation of methyl 3-deoxy-D-glycero-D-galacto-2-nonulosonate led initially to the α,β -furanosides and then to the α,β -pyranosides (mainly the

β -pyranoside). All were crystallized as their acetates **14-17** and the crystal structures of all four compounds were reported. Acetylation of the acid in pyridine gave the pyranosyl analogues of **16, 17** (X-ray structures also reported).³⁰

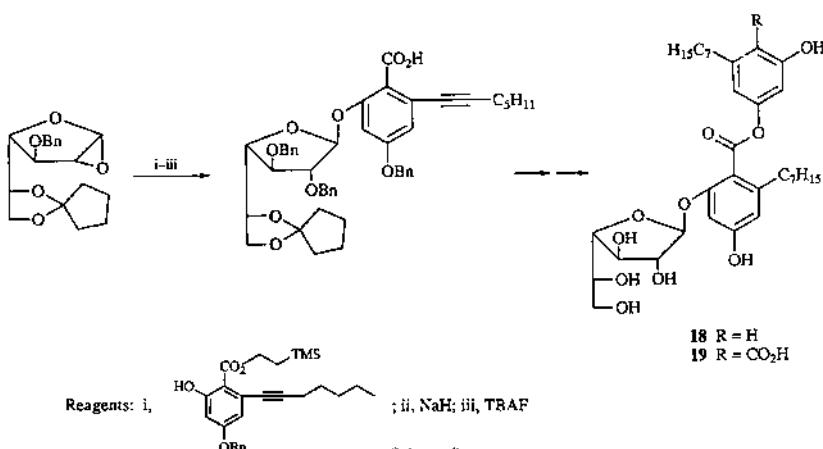


Details of methods which should be suitable for the large scale synthesis of α - and β -sialoglycosides are given in Scheme 8.³¹ The corresponding glycoside bromide was used in a simple procedure for the synthesis of the methyl and benzyl glycosides of *N*-acetyl-neuraminic acid and its 4-epimer.³²

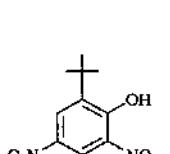


Scheme 8

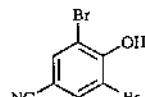
The total synthesis of KS-501 (**18**) and KS-502 (**19**), which are based on aromatic glycosides, are illustrated in Scheme 9.³³ As always, considerable interest has been taken in the field of aryl glycosides and a number have been synthesized. Structures of phenols which have been glycosylated are given (**20-27**) together with the references 34-38 to the papers in which the work appears. The aglycons of more complex aromatic compounds to have been glucuronosylated are shown in structures **28**.³⁹



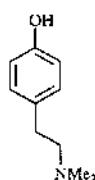
Scheme 9



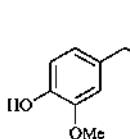
20 ref. 34



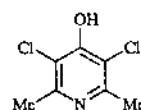
21 ref. 34



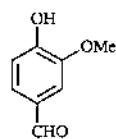
22 ref. 35



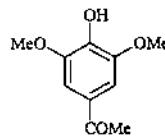
23 ref. 36



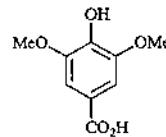
24 ref. 37



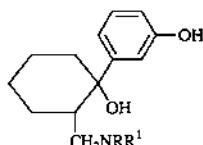
25 ref. 38



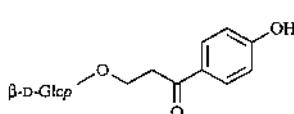
26 ref. 38



27 ref. 38

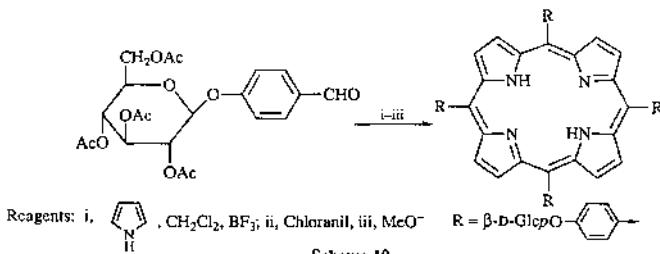


28

 $R, R' = H, Me$ 

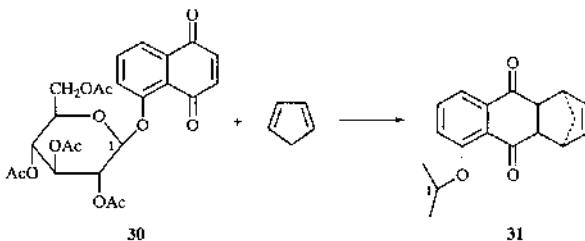
29

In Scheme 10 a very interesting compound which is a water soluble glycosylated porphin in illustrated.⁴⁰ Reaction of the aromatic glycoside **30** with cyclopentadiene gives



Scheme 10

the Diels-Alder product **31** as indicated in Scheme 11. Removal of the carbohydrate from the product provides means of obtaining the chiral (1*R*, 4*S*)-1,4-dihydro-5-hydroxy-1,4-methano-9,10-anthroquinone.⁴¹



Scheme 11

Appreciable use continues to be made of enzymes in the synthesis of glycosides. The use of almond β -D-glucosidase in 90% acetonitrile, which gives β -glucosides, can be employed at the concentration of 5g per litre.⁴² In a further example a lactase has been employed to synthesis the gypsy moth antifeedant substance **29** by use of 2-nitrophenyl β -D-glucopyranoside as donor.⁴³

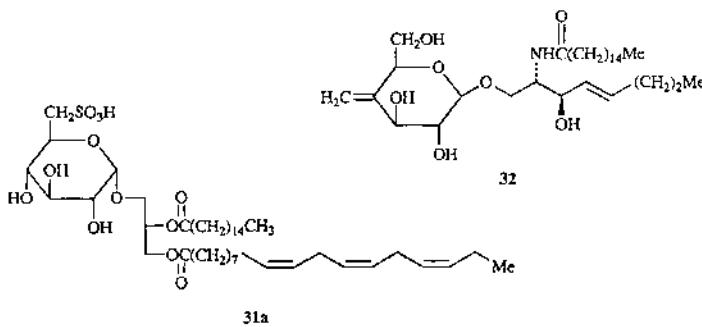
1.2 Synthesis of Glycosylated Natural Products.—A glucoside of dimethyl malate has been prepared for comparison with a degradation product of macrolactin B.⁴⁴ Interest continues in glycosylated glycerol derivatives, and compounds containing glucose⁴⁵ and galactose⁴⁶ β -linked to C-1 of glycerol otherwise substituted with long chain fatty acid ester residues at positions 2 and 3, have been described as has cyanobacterial sulfolipid **31a**.⁴⁷ A solid phase synthesis of a fragment of polyribosyl ribitol phosphate, a capsular polysaccharide of

Haemophilus influenzae type B, has been reported. The essential carbohydrate component has β -D-ribofuranosyl units linked to C-1 of ribitol.⁴⁸

General methods have been developed for the preparation of α - and β -O-glycosylated serine and threonine. For the α -linked compounds, the bromide-catalysed reaction of tetra-O-benzylglycosyl bromide was employed, whereas for β -anomers acetobromoglucose and silver triflate were used.⁴⁹ An extensive report of solid-phase syntheses of glycopeptides from human intestinal mucin which contain glucosamine and galactosamine linked to serine and threonine has been published.⁵⁰ A glycotetrapeptide involving an L-rhamnose linkage to serine, which is a component of a *Mycobacterium* glycopeptide, has been synthesized.⁵¹ Two reports have described the enzymic transfer of sugar units to serine: one reports β -galactosidase as a catalyst⁵² while the other utilizes α - and β -galactosidase and glucosidase.⁵³

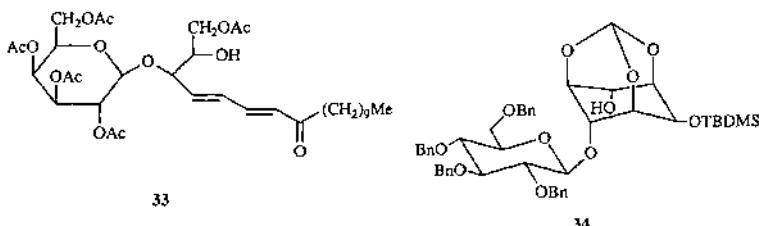
In a study of the role of the sugar moiety in bleomycin, glycosylated erythro- β -hydroxy-L-histidine compounds have been made by the trichloroacetimidate approach.⁵⁴ In work related to glycosylated amino acids, 2-azidoethyl glycosides have been prepared and reduced to the amino compounds for use in the preparation of neoglycoproteins.⁵⁵

A review has appeared on chemical and enzymic glycoslations of sphingolipid compounds.⁵⁶ A galactocerebroside, which was made using glucosamine as the source of the ceramide component has been reported,⁵⁷ as has a palmitoyl analogue of Gaucher spleen glucocerebroside.⁵⁸ Schmidt's group has focused attention on modified compounds of this series having branched methylene groups at C-4, for example, compound 32.^{59,60}



Further reference to this work is included in Chapter 14. The unsaturated ring of fully acetalated lactal has been opened to give access to the modified galactocerebroside 33.⁶¹

In the area of glycosylated inositols Vasella has reported compound 34 in connection with studies of activation of hydroxyl groups for substitution.⁶² Compound 35 has been



prepared and found to stimulate lipogenesis in rats to the extent of 40% of that induced by insulin; that is, it is an insulin-mimetic-*quasi*-disaccharide.⁶³ Several glycosylated inositol derivatives are reported in Chapter 18.

In the area of glycoslated steroids the α -L-rhamnosyl derivative of cholesterol has been made by a modified Lewis acid-catalysed route,⁶⁴ and several standard syntheses of 17-glycosylated androstanone and estradiol derivatives have been reported.⁶⁵ Likewise, 3- β -hydroxy-5 α -pregnan-20-one has been β -glucosylated.⁶⁶

In other areas of medicinal chemistry the synthesis of the anthracycline oxaunomycin and analogues have been completed by glycosylations,⁶⁷ and glucosylation of 11-deoxyprostaglandin E has been reported.⁶⁸ The anti-tumour etoposide⁶⁹ and the triterpene glycyrrhetic acid⁷⁰ are other compounds to have been subject to glucosylation and glucuronosylation, respectively.

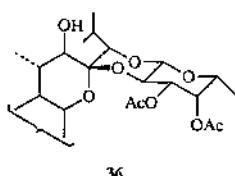
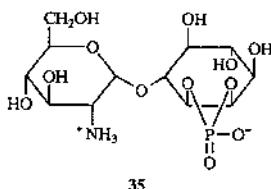
In the area of nitrogen-containing natural products the following have been glycosylated: the antitumor alkaloid 20(S)-camptothecin,⁷¹ the ergot alkaloids elymoclavine, chanoclavine, lysergol (enzymic reaction),⁷² and castanospermine.⁷³

Reports have also appeared on introduction of sugars to 4-methyl- and 4-(trifluoromethyl)umbelliferone,⁷⁴ and 6- and 8-acylamino-4-methylumbelliferone.⁷⁵

1.3 O-Glycosides Isolated from Natural Products.—As is the custom, only compounds showing special features (usually within the sugar moiety) are dealt with.

A set of aryl α -L-rhamnosides (some 4-O-acetylated) isolated from *Moringa oleifera* have various (alkyloxythiocarbonylamino)methyl substituents at the *para*-position of the aromatic rings.⁷⁶

In the terpene area new clerodane-like alcohol glycosides carrying various 6-deoxyhexoses have been extracted from *Dicranopteris pedata*,⁷⁷ and a triterpene from *Heloniopsis japonica* has a D-fucose-containing feature which exists in the acetal form 36.⁷⁸



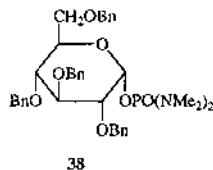
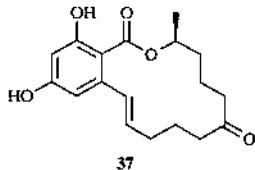
Zearalenone **37** has been found as a toxin masked by glucosylation which undergoes deglucosylation during digestion in the pig. The glycosylation has been repeated chemically; likewise for ochratoxin which carries phenylalanine amide-attached to an aryl system.⁷⁹

(3R, 25R)-Hexacosane-1,3,25-triol and its 3-epimer and the 3-keto derivative have been found as α -D-glucopyranosides in the cyanobacterium *Nodularia harveyana*, and are novel glycolipids involved in nitrogen-fixing cells.⁸⁰

A product from the shrub *Cestrum parqui*, thought to be responsible for poisoning grazing animals in South America and Australia, is a diterpene glycoside of 2-O-isopentanoyl-3-C-carboxy-D-allose carrying a 3,4-diketo furanoid substituent at O-4.⁸¹

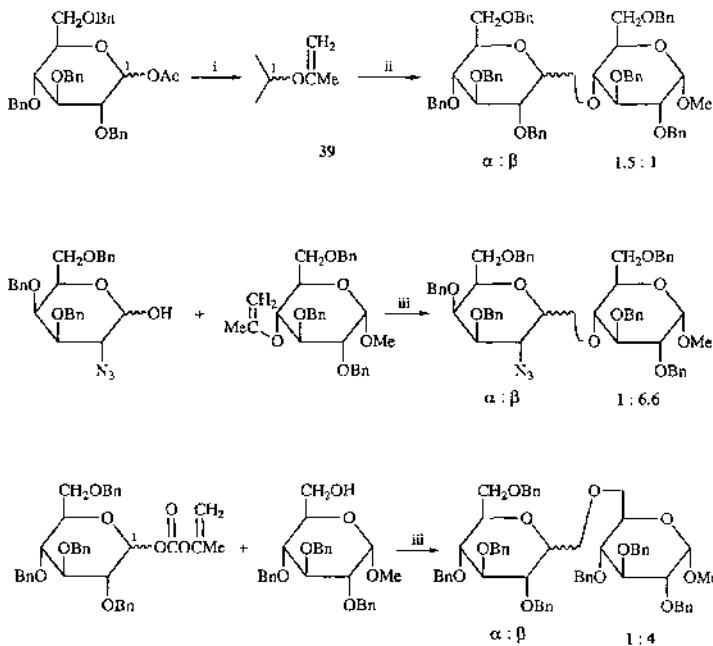
1.4 Synthesis of Disaccharides and their Derivatives.— In the area of non-reducing disaccharides Barrett's very elegant synthesis of sucrose, which depends on an intramolecular redox cyclization process, has been published in detail.⁸² See Vol. 24, p. 29 for a preliminary report. Enzymic transfer from UDP-Gal can be used to obtain β -D-galactopyranosyl 3-acetamido-3-deoxy- β -D-xylopyranoside.⁸³

In the field of reducing disaccharides, as usually, very considerable attention has been given to their syntheses and those of many derivatives. The shelf-stable glycosyl tetra-N-methylphosphoroamidates appear to be attractive glycosylating agents for the formation of 1,2-trans-linked products. Thus compound **38**, condensed with methyl 2,3,4-tri-O-benzyl- α -D-glucopyranoside in propionitrile at -78° in the presence of trimethylsilyl triflate, gives the



β -1,6-linked product in 93% yield, the α,β ratio being 4:96. The same agent condensed with

carbohydrate secondary alcohols gave products in high yield and with α,β ratios approximately 10:90. This latter selectivity falls when dichloromethane is used as solvent with secondary alcohol acceptors.⁸⁴ Isopropenyl glycosides which can be made by Tebbe methylenation of glycosyl acetates, are a further novel set of glycosylating agents. The anomers **39**, for example, with methyl 2,3,6-tri-*b*-benzyl- α -D-glucopyranoside in acetonitrile at -25°C in the presence of boron trifluoride as catalyst, give the α,β -1,4-linked glycosides in the ratio 1.5:1. This approach can ingeniously be used in the reverse sense; that is, with an isopropenyl ether acting as glycosyl acceptor and a free sugar, unsubstituted at O-1, as the donor. See Scheme 12 for examples of these and related reactions.⁸⁴ A further group of



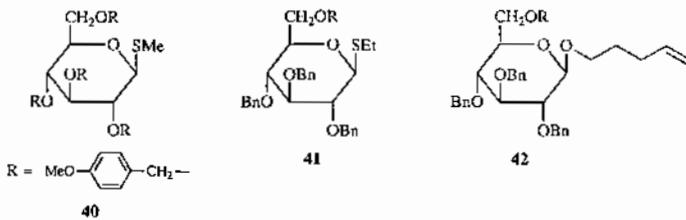
Reagents: i. Tebbe reagent; ii. methyl tri-*b*-benzylglucoside, MeCN, BF_3 , Et_2O
iii. MeCN, TMSOTf

Scheme 12

potentially interesting looking glycosylating agents are the glycosyl thiocyanates, 3,4,6-tri-*O*-acetyl-2-*O*-benzyl- β -D-glucopyranosyl thiocyanate in dichloromethane with trimethylsilyl triflate as catalyst, giving disaccharides of secondary alcohols in yields up to 75% (cf. Vol.

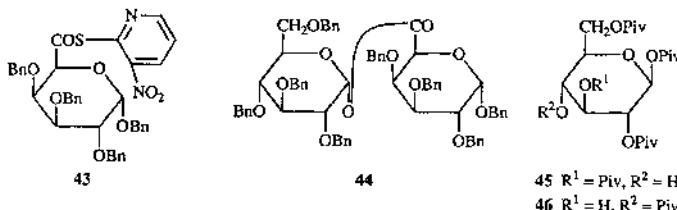
24, p. 30).⁸⁵

Phenylseleno glycosides, either O-benzylated or O-benzylolated, can be converted to 1,2-cis or 1,2-trans-related disaccharide products by way of iodonium intermediates. Iodonium-di-sym-collidine perchlorate (IDCP) or NIS and catalytic acid may be used for activation.⁸⁶ Several further reports of activation of thioglycosides as donors in disaccharide synthesis have appeared. Methyl tetrabenzyl-1-thio- β -D-glucopyranoside, activated with iodosobenzene and triflic anhydride, gives disaccharides without strong α,β preference. The less reactive acylated analogues, however, give β -products with good selectivity.⁸⁷ Activation of such benzylated starting materials with triflic anhydride by itself gives 95% yield of disaccharide with α,β ratio close to 2:1. Yields are not always as high as this and can be, in some cases, rather low.⁸⁸ For enhanced "arming" of thioglycosides as glycosylating agents *p*-methoxybenzyl *O*-protection has been used, and compound **40** gave over 80% of α -(1 \rightarrow 2) and α -(1 \rightarrow 3)-linked disaccharides when coupled with *p*-nitrophenyl 4,6-*O*-isopropylidene- α -D-glucopyranoside (CuBr₂/Bu₄NBr activation).⁸⁹ The bulk of the substituents at O-6 of the thioglycosides **41** and the pent-4-enyl analogues **42** has been shown to affect these compounds as glycosylating agents. The yields of products formed on 1⁺ promoted glycosidations of 1,2:5,6-di-*O*-isopropylidene-D-glucose with **41** and **42** decreased from 84% in the case of the 6-benzyl ether to 53% in the case of the trityl ether, and concurrently the α,β -ratio of products rose from 3:1 to 13:1.⁹⁰



Further work has been published on the use of the oxyanion derived from 2,3,4,6-tetra-benzyl-D-glucose which is now shown to be effective as a nucleophile in displacing triflate esters from secondary positions of carbohydrates. In DMF, HMPT as solvent at -10° quantitative yields of products with inversion of stereochemistry were produced with α,β ratios of approximately 2:1.⁹¹ The same anion, coupled with the thiouronate derivative **43**, gave 80% of the ester **44** ($\alpha:\beta$ ratio 100:1) which was reduced to the 1,6-linked disaccharide by way of the thiono analogue.⁹² 2-(Trimethylsilyl)ethyl glycosides are useful for making 1-hydroxy compounds.⁹³ Otherwise they may be obtained from 1 pivaloates. For example, compound **45**, produced in 63% yield by direct pivaloylation of glucose, is cleavable at the

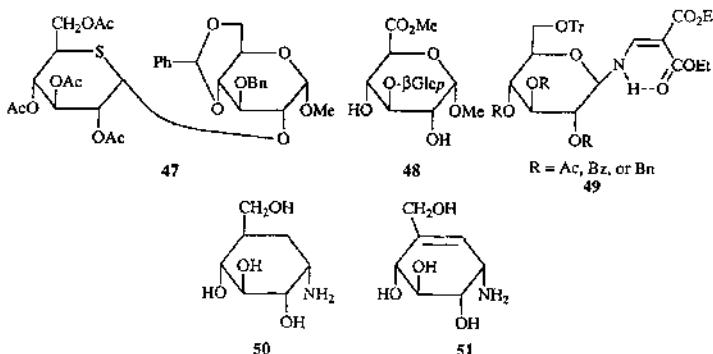
anomeric centre by use of hydrazine and acetic acid. From the product the trichloroacetimidate may be produced and used in glycoside syntheses. Together with compound **45** the isomeric **46** is produced in 24% yield, and by standard glycosylation this may be converted to laminaribiose derivatives.⁹⁴ The trichloroacetimidate method has been used to produce the disaccharide **47** containing sulfur in the ring.⁹⁵



Whereas glycosylations of methyl 4,6-*O*-benzylidene- α -D-altropyranoside with tetra-*O*-benzyl- α -D-glucopyranosyl bromide or trichloroacetimidate give mainly the β -(1 \rightarrow 3)-linked disaccharide, the corresponding diazirine reacts mainly at O-2. A rationalization is provided.⁹⁶

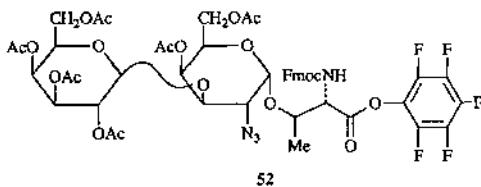
Baiyunoside is a sweet disaccharide-containing diterpene glycoside with 2-*O*- β -D-xylopyranosyl-D-glucose as the carbohydrate (Vol. 21, p. 24). Twenty three analogues have now been prepared and assessed for sweetness with 3-*O*-[β -D-Glc(1 \rightarrow 2) α -D-Glc]-(+)-baiyunol proving to be intensely sweet.⁹⁷ Several disaccharides including β -D-Glc(1 \rightarrow 2) α -D-Galp have been attached to the saponin sarasapogenin.⁹⁸ Enzymic glucosyl transfer has been used to make the uronic acid disaccharide **48**.⁹⁹ In the area of 1,4-linked glucobioses, cellobiose has been bonded to gibberellin A3¹⁰⁰ and diosgenin.¹⁰¹ In the latter paper several other disaccharides were similarly bonded and the antifungal and haemolytic properties of the products were compared. All except the lactosyl compound were found to be active. The preferred conformations of eight 1,4-C-linked disaccharides, i.e. the analogues of methyl α -D-maltoside and cellobioside, and their epimers at C-2 in the "reducing" units and 1,6-anhydro derivatives have been analyzed. Considerable similarity is noted between the conformation of C- and O-linked analogues.¹⁰² Glycosylation of the trityl ethers **49**, using acetobromoglucone with silver perchlorate activation in nitromethane, gave moderate yields of the 6-*O*-substituted product.¹⁰³ Validamycin H, the synthesis of which is referred to in Chapters 18 and 19, contains the β -(1 \rightarrow 6)-glucobiose disaccharide unit. In related work several glycosides including disaccharide glycosides of validamine **50** and valienamine **51** have been produced by enzymic synthesis. These include the 7- α -

isomaltoside of validamine and valienamine, and also the 4- α -isomaltoside of the latter.¹⁰⁴ The peracetyl derivatives of (E)-O-(6-O-cinnamoyl- β -D-glucopyranosyl)-(1 \rightarrow 2), (1 \rightarrow 3), and (1 \rightarrow 4)- α -L-rhamnopyranoses have been prepared.¹⁰⁵



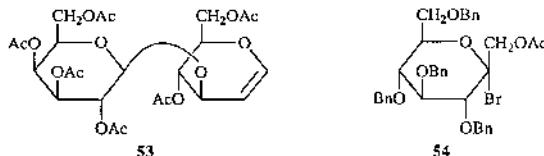
Several galactosyl disaccharides have been made by chemical procedures. 3,4,6-Tri-O-acetyl-1,2-O-cyanobenzylidene galactose has given access to the 1,6- and 1,3-linked galactobioses. In the main the glycosidic bonds of the products were β -linked.¹⁰⁶ Galactobioses containing 3,6-anhydro rings are referred to in Chapter 5.

Acetobromolactose has been used to make a *p*-(acryloyl-amino)-phenyl β -D-lactoside, and from it an antigenic water-soluble polymer.¹⁰⁷ References are made to the syntheses of α -(1 \rightarrow 6)-galactosylglucose in Chapter 6. Allyl β -N-acetyl lactosaminide has been produced by chemical procedures and used in trisaccharide syntheses.¹⁰⁸ Various (1 \rightarrow 3)-linked galactosylgalactosamine derivatives have been reported,^{109,110} and β -Gal(1 \rightarrow 3)- α -GalNAc has been used to make glycosylated peptides, e.g. 52, by solid phase procedures¹¹¹ and chemical methods have resulted in 1,6-anhydro-2-azido-2-deoxy- β -D glucose having 3-O-allyl-2,4-di-O-henethyl-6-O-trityl- β -D-glucose linked to O-4.¹¹² 4-O- β -D-Galactopyranosyl-D-xylose has been made by standard procedures for use in the evaluation of intestinal lactase.¹¹³

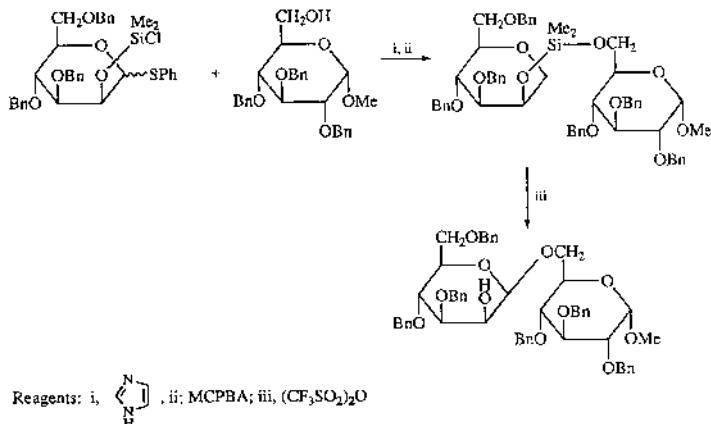


Considerable attention has been paid to the use of enzymes for galactosylation purposes. The procedure has been used to make α -(1 \rightarrow 3)-linked galactobiose derivatives¹¹⁴

and β -(1 \rightarrow 3)- together with β -(1 \rightarrow 6)-galactobioses linked to serine.^{115, 116} In the latter paper 1,2- and 1,6-linked glucopyranosyl galactoses were also reported. *N*-Acyllectosamine derivatives have also been produced in like fashion, and isomers,¹¹⁷ long chain alkyl¹¹⁸ and peptido¹¹⁹ glycosides and 2-deoxy analogues and 2-amino-2-deoxy analogues are amongst the compounds reported.¹²⁰ In addition, an analogue with sulfur as the ring atom in the non-reducing moiety has been made.¹²¹ Galactosylation of α -glucal using *p*-nitrophenyl β -D-galactopyranoside and β -galactosidase, followed by acetylation of the products, gave compound 53 in 50% yield. Small proportions of the 1,6-linked compound were also produced, and with 6-*O*-acetyl- α -glucal the 1,3-linked product was produced specifically in 42% yield.¹²² Similar galactosylation of β -D-xylopyranosides afforded 3- and 4-linked disaccharide products, the ratios being dependent on the nature of the aglycons.¹²³



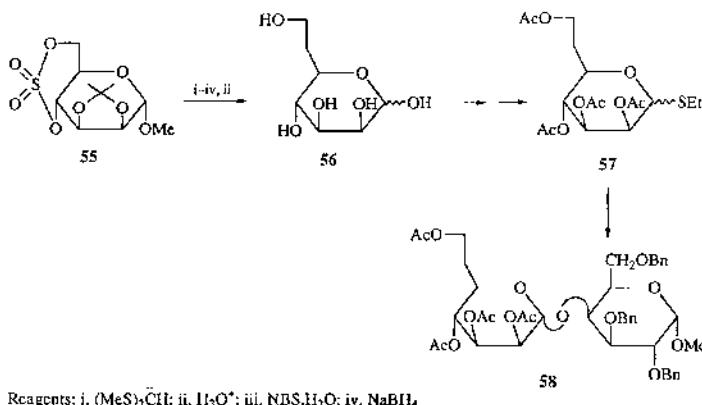
Barresi and Hindsgaul have published an improvement on their intramolecular preparation of β -D-mannopyranosyl disaccharides (see Vol. 25, p. 38).¹²⁴ In closely parallel work which uses a silicon bridging atom rather than carbon, Stork and Kim have published a further intramolecular method for preparing β -mannosyl compounds (Scheme 13).¹²⁵



Scheme 13

8-(Methoxycarbonyl)octyl glycosides have been produced for a range of disaccharides

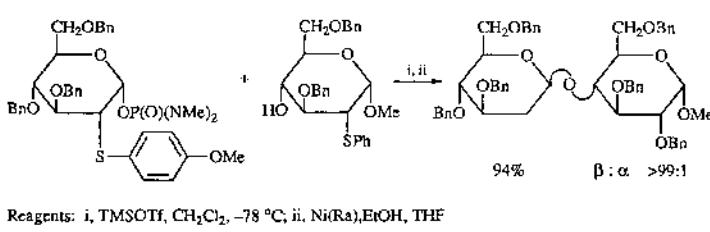
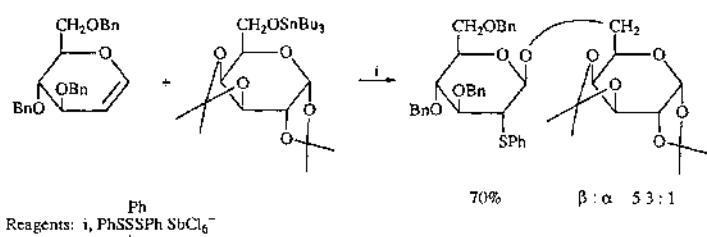
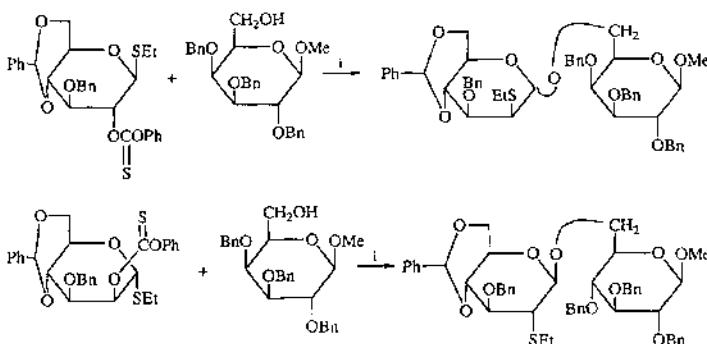
containing mannose. Mannobioses were involved as well as mannosamine-linked to mannose, glucosamine-linked to mannose by α - or β -linkages through the 2- and the 6-positions.¹²⁶ More specifically, syntheses of α -(1 \rightarrow 2)-mannopyranosyl- α -mannose and β -D-glucosaminyl- α -mannose have been reported,¹²⁷ as well as β -(1 \rightarrow 4)-N-acetyl-mannopyranosyl-D-glucosamine¹²⁸ and two separate papers have described the former disaccharide glycosidically linked to L-serine and L-threonine.¹²⁹ The glycosyl thiocyanate method has been utilized in the preparation of α - and β -(1 \rightarrow 4)-linked-mannopyranosyl-L-rhamnoses.¹³⁰ The 6-deoxy-D-manno-heptose compound 56, made from the 4,6-cyclic sulfate 55, has been converted to 57 and used in the synthesis of 58 (Scheme 14).¹³¹ α -Linked disaccharides are obtainable by use of the D-glucoheptulose derivative 54, but if participating groups are present at C-3, α,β -mixtures are produced.¹³²



Reagents: i. $(\text{MeS})_2\text{CHI}$; ii. H_3O^+ ; iii. $\text{NBS}, \text{H}_2\text{O}$; iv. NaBH_4

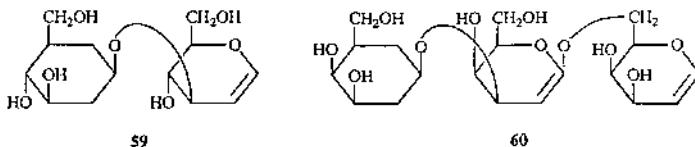
Scheme 14

As always, considerable attention has been given to the preparation of disaccharides involving deoxy sugars. In Scheme 15, two ingenious methods of synthesizing 2-deoxy α - and β -disaccharides specifically are indicated; the final products being obtained by reductive desulfurization.¹³³ In Scheme 16, a further method by which β -linked compounds can be made with good stereoselectivity is illustrated. A range of factors bearing on the chemistry of this process are described in this important paper.¹³⁴ A related process is illustrated in Scheme 17 (cf. Vol. 22, p. 28).¹³⁵ A different approach uses enzymes as catalysts, a β -glycosidase from almonds being found to cause the addition dimerization of D-glucal, the 1,3- β -linked dimer 59 being produced in 55% yield with small amounts of the 1,6- β -linked compound as a side product. Similar products were obtained from D-galactal

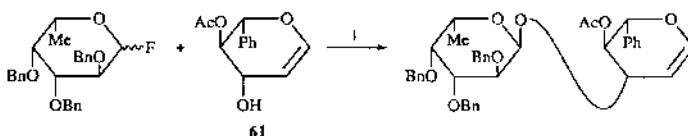


using an *E. coli* β -galactosidase, but in this case the selectivity was not so high and furthermore the trisaccharide **60** was obtained (29%).¹³⁶ In the area of 4-deoxy compounds,

the β -(1 \rightarrow 2)-linked disaccharide of 4-deoxy- α -arabino-hexopyranose has been produced by the trichloroacetimidate method.¹³⁷ Various 3-, 4- and 6-mono-deoxy disaccharides were synthesized as analogues of β -D-Galp-(1 \rightarrow 3)- α -D-GalpNAc-Bn in biosynthesis studies of O-glycopeptide compounds.¹³⁸



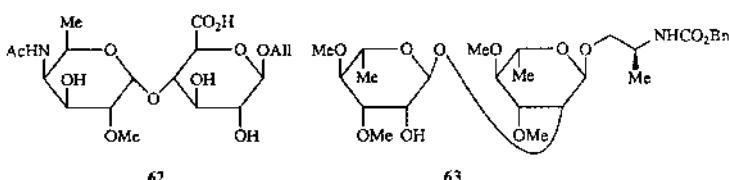
L-Fucose containing compounds have, as always, been of interest and L-Fucp-(1 \rightarrow 2)-DD-Gal¹³⁹ has been made by chemical methods (α,β 11:1) whereas fucosidases had been employed in the preparation of (1 \rightarrow 2)-, (1 \rightarrow 3)- and (1 \rightarrow 6)-linked disaccharides involving methyl β -D-galactopyranoside, D-glucose and N-acetylgucosamine as receptors, respectively.¹⁴⁰ Fucosylation of glycal **61**, obtained by selective enzymic deacetylation of the racemic diacetate, is illustrated in Scheme 18.¹⁴¹ Disaccharide **62**, the repeating unit of the glycolipid antigen of *Mycobacterium avium* serovar 26 and related compounds have been prepared.¹⁴²



Reagents: i. AgClO_4 , SnCl_2

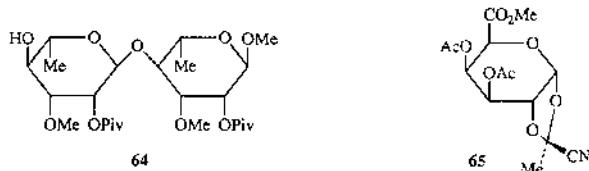
Scheme 18

In the L-rhamnose set, methyl 2-*O*- α -L-rhamnopyranosyl- α -L-rhamnopyranosides and the D-mannosyl rhamnoside analogue have been reported,¹⁴³ as has the unusual glycopeptide **63** which is a part of the glycolipid of *Mycobacterium fortuitum*.¹⁴⁴

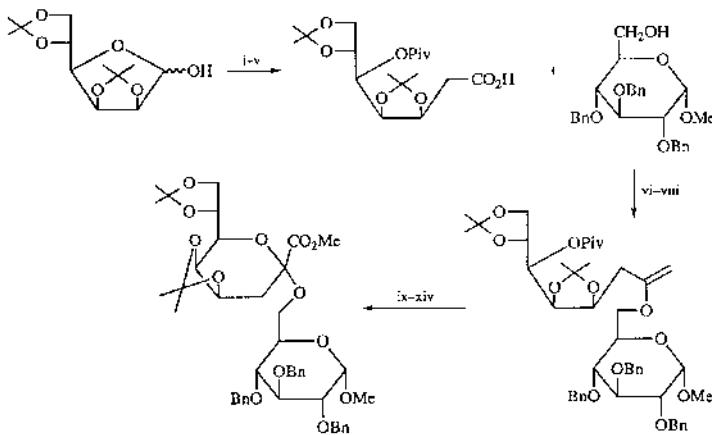


A new synthesis of methyl 4-*O*- α -L-oleandrosyl- α -L-oleandropyranosides, the tetraoxysugars of avermectins, has elegantly been produced by photolysis of the

relevant 2-*O*-pivaloyl compound **64** in aqueous HMPT.¹⁴⁵



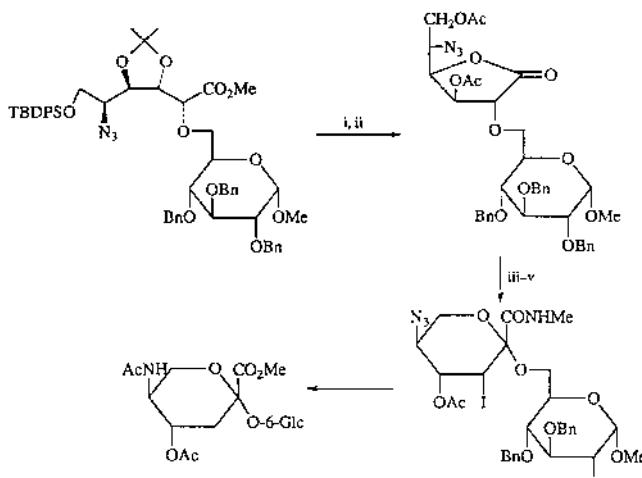
Considerable interest continues to be taken in disaccharides comprising uronic acid components. α -Galacturonic acid glycosylating agent **65** has been used in the preparation of 1,2-, 1,3- and 1,4- β -linked dimers of galacturonic acid.¹⁴⁶ A similar set of dimers of α -mannuronic acid have been made in like manner, and similarly mannuronic acid has been linked to the 4-position of α -rhamnose. The stereoselectivity in these reactions was not high, but when the condensations were conducted under high pressure (14 Kbar) better proportions of α -linked products were obtained.¹⁴⁷ Special attention as always has been given to disaccharides containing ulosonic acids, and in Scheme 19 a novel and ingenious



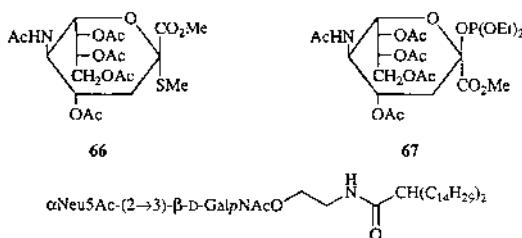
Reagent: i, $\text{Ph}_3\text{P}=\text{CH}_2$; ii, PivCl; iii, BH_3 ; iv, H_2O_2 , NaOH ; v, RuCl_3 , NaIO_4 ; vi, DCC; vii, DMAP; viii, Tebbe reagent; ix, LiAlH_4 ; x, $\text{Bu}^{\prime}\text{OK}$, I_2 ; xi, CsOAc ; xii, NaOMe ; xiii, $(\text{COCl})_2$, DMSO ; xiv, CH_2N_2

Scheme 19

synthesis of KDO-containing disaccharides is illustrated. This paper also describes the synthesis of α - α -KDO-(2 \rightarrow 3)- α -Glc¹⁴⁸ and the α - and β - α -KDO-(2 \rightarrow 6)- α -glucosamine derivatives have also been reported.¹⁴⁹ A somewhat related approach to the synthesis of α -glycosides of neuraminic acid analogues is illustrated in Scheme 20. Various disaccharides

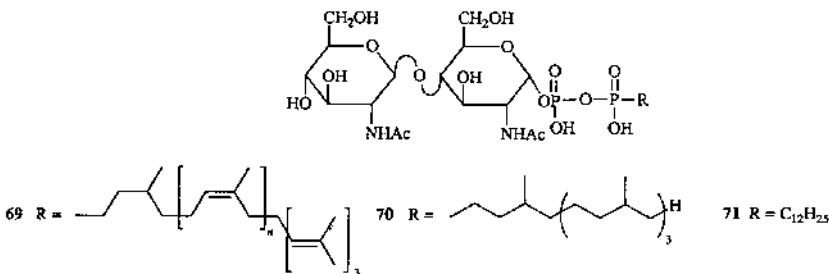


were made which are analogues of neuraminic acid compounds lacking the three-carbon terminating chain.¹⁵⁰ Thiophilic activation of compound **66** has resulted in about 45% yields of α -linked neuraminic acid bonded to O-2 of D-glucopyranosyl and D-galactopyranosyl compounds and to O-3 of 2-acetamido-2-deoxy analogues.¹⁵¹ The corresponding phosphite **67** can also be used to produce α -bonded disaccharides, and neuraminic acid has been linked in this way to O-6 of methyl α -D-glucopyranoside in 70% yield.¹⁵² Compound **68** and the 2 \rightarrow 6 linked isomer and related compounds have been prepared by established procedures, the last two then being converted into the N-terminal glycopentapeptides of human glycophorin A_M and A_N.^{153, 154}

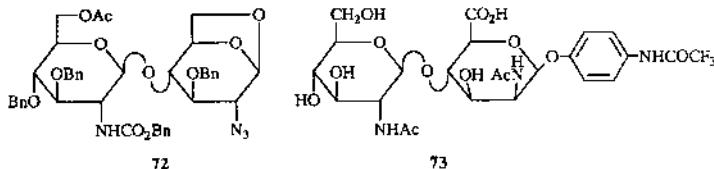


CMP-N-Acetylneuraminic acid has been produced by enzymic methods and used as a source of sialic acid in glycosylation reactions.¹⁵⁵

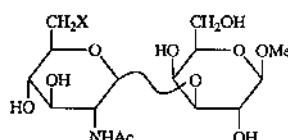
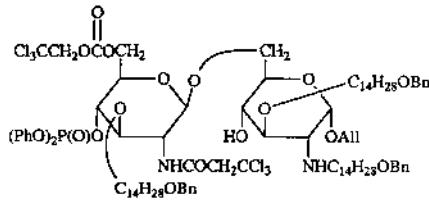
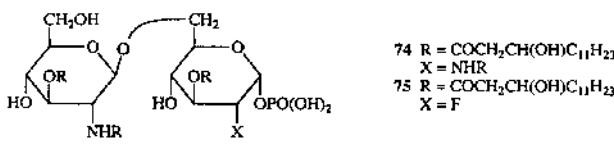
Considerable attention continues to be given to disaccharides containing amino sugars. Compound **69**, which comprises chitobiose linked to dolichol via an α -1-pyrophosphate bridge, has been prepared chemically as a substrate for enzymic glycosylation of peptides, and the chitobiose component was found to be transferable to a peptide.¹⁵⁶ In related work, compounds **70** and **71** were prepared starting from chitobiose octacetate, and the former acts as an efficient acceptor for mannosyl transferases.¹⁵⁷ The anhydrochitobiose



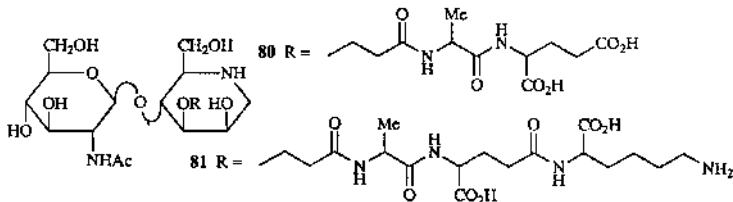
derivative **72**¹⁵⁸ and the uronic acid analogue **73**¹⁵⁹ have been made, the latter being the repeating unit of the *Haemophilus influenzae* type e capsular antigen.



Lipid A analogues **74**-**76** have been reported¹⁶⁰⁻¹⁶² as has a further analogue.¹⁶³ The preparation of analogues **78** and **79** of the acceptor **77** of bovine (1 \rightarrow 4)- β -D-galactosyltransferase has been described. Compound **79** was found to inhibit the enzyme.¹⁶⁴ The KDO-containing glycoside α -D-GlcNAcp-(1 \rightarrow 5)- β -KDO-2-OCH₂CH₂CH₂NH₂, which contains the repeating unit of the capsular *Pleuropneumoniae* serotype 5, has been prepared.¹⁶⁵ Compounds **80**, **81**, containing 1,5-dideoxy-1,5-imino-D-mannitol, have been made as potential inhibitors of peptidoglycan synthesis.¹⁶⁶



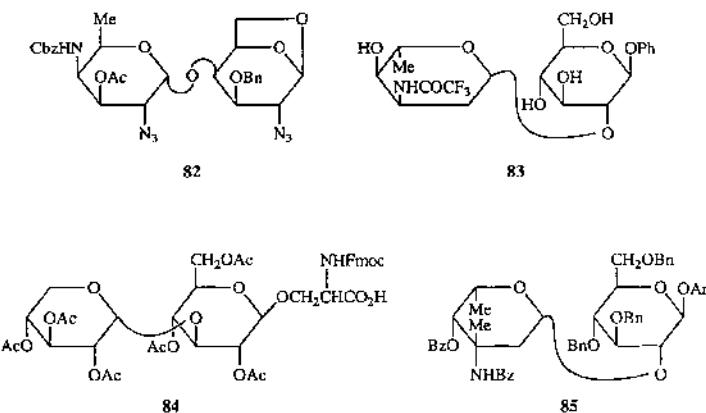
77 X = OH
 78 X = F
 79 X = SiI



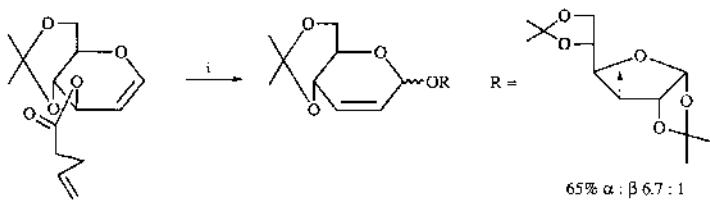
In the area of D-mannosamine-containing compounds an appropriate disaccharide monomer has been polymerised to give a product composed of β -D-ManNAc-(1 \rightarrow 4)- α -L-Rha(1 \rightarrow 3) units.¹⁶⁷

In the galactosamine series α -(1 \rightarrow 4) linked dimer derivatives having a further aminodeoxy group at C-4 of the non-reducing moiety have been described,¹⁶⁸ and N-acetyl-D-galactosamine has been linked α -(1 \rightarrow 4) to methyl 2-acetamido-2-deoxy- α -D-glucopyranoside by enzymic transfer, some of the β -(1 \rightarrow 6)-linked compound also being obtained. However, when methyl 2-acetamido-2-deoxy- β -D-glucopyranoside was used as acceptor, only the β -(1 \rightarrow 4)-linked dimer was produced.¹⁶⁹ A report of the preparation of disaccharides based on N-acetylallosamine has appeared¹⁷⁰ in connection with the synthesis of the naturally occurring chitinase inhibitor allosamidin (Vol. 25, p. 224). Further total

synthesis of this compound has also been reported.¹⁷¹ This paper neatly reports the dual inversion of a chitobiose derivative to an allosamine dimer and its coupling to the appropriate cyclopentane derivative.¹⁷¹ Compound **82**¹⁷² and **83**¹⁷³ are two disaccharides to have been prepared which contain modified amino-sugars. The latter is a derivative of avobiose, a disaccharide fragment of the vancomycin-related antibiotic avoparcin. The xylosylglucose glycoside **84** has been prepared for use in the solid phase glycoside synthesis.¹⁷⁴ The disaccharide **85**, which approximates to the aryloxy carbohydrate



component of vancomycin, has been prepared by addition technology applied to a glycal of the appropriate branched-chain sugar. The highly specific addition was catalysed by



Reagents: i, ROH, I(collidine)₂ClO₄, mol. sieve

Scheme 21

camphorsulfonic acid.¹⁷⁵ Disaccharides containing 2,3-unsaturated glycosyl non-reducing moieties can be prepared as indicated in Scheme 21. This represents a means of inducing coupling under non-acidic conditions.¹⁷⁶

1.5 Hydrolysis and Other Features.—Allyl glycosides can be converted to the free sugars by

reaction with tetrakis(triphenylphosphine)palladium in acetic acid. The reactions involve formation and cleavage of π -allyl complexes rather than formation of propenyl glycosides followed by hydrolysis.¹⁷⁷ The 3-but enyl group as aglycon, which is usefully stable, may be removed by ozonolysis followed by treatment of the 3-oxopropyl products with potassium carbonate in acetone; β -eliminations give the 1-hydroxy compounds in very efficient processes.¹⁷⁸ The Claisen rearrangement of 4-oxahexa-1,5-dienyl glycosides is discussed in Chapter 24.

Studies of the chemical hydrolysis of aryl α -glucosides of *N*-acetylneurameric acid have shown that four pathways are involved.¹⁷⁹ The aqueous hydrolysis of α -D-UDPG, studied under different conditions, has led to the conclusion that the compound is a glycosylating agent only in the pH range 1-3.¹⁸⁰ Glycosidic bonds between reducing end glucose and ceramide in glycosphingolipids is more stable to acid-catalysed hydrolysis than inter-hexoside bonds.¹⁸¹

Alkyl β -D-glucopyranoside tetra-acetates are anomerized in dichloromethane in the presence of iron(III)-chloride and lead to mixtures with α , β -ratios of appropriately 9:1. In the case of 2-deoxy analogues this ratio goes up to 94:6. Acetal protecting groups cannot be used during a reaction of this type.¹⁸² Detailed examination of the acetolyses in acetic anhydride containing sulfuric acid and iron(III)-chloride of methyl α -D-glucopyranoside, its β -anomer, the peracetylated dimethyl acetyl and acyclic analogues having acetoxy and methoxy groups bonded to C-1, give rise to mixed products including furanosyl derivatives. It was concluded that acetolyses of the pyranosides that give rise to both cyclic and acyclic products involve reaction from the β -rather than the α -anomer.¹⁸³ Attempts to glycosylate glycosides of polyethyleneglycol monomethyl ether did not lead to disaccharide products but rather to products of glycosyl exchange on the ether.¹⁸⁴

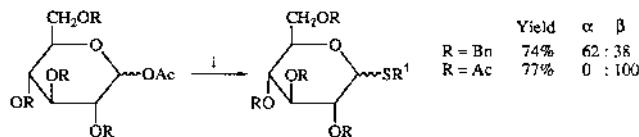
The degradations of methyl β -D-ribopyranoside and methyl β -D-xylopyranoside in oxygen in 1.25M sodium hydroxide at 120°C exhibited complex kinetics indicating auto-inhibited reactions. Both hydrogen peroxide and stable organic peroxides were detected. However, decomposition of the glycosides by way of C-1 radicals is not believed to constitute a major pathway. The products of reaction included small acidic fragments but also, interestingly, methyl furanosides having carboxy branch groups at C-2 or C-3.¹⁸⁵ Studies of the alkaline hydrolysis of *p*-nitrophenyl rhamnoside and arabinoside have been reported,¹⁸⁶ and the base-catalysed epimerizations at C-2 in several glucose- and mannose-containing disaccharides have been reported.¹⁸⁷

2-Deoxyglycosidic bonds are selectively cleaved under mild conditions (100°C) during

the hydrothermolysis of cardenolides.¹⁸⁸ Related hydrothermolytic degradative studies of triterpenoid and steroid glycosides, involving heating in dioxane and water at 140°C for half an hour and which lead to various fragments, have been reported.¹⁸⁹ Hydrolysis studies of the iridoid geniposide at temperatures up to 100°C, at pH values 2-12 have led to the determination of thermodynamic parameters.¹⁹⁰ Various physical and biological characteristics of glycosides have been reported as follows: the amphiphilic properties of several octyl glycosides,¹⁹¹ the surface activity, foam suppression action and biodegradability of alkyl thioglycosides,¹⁹² the effects of mono- and di-saccharides and polyols in their cryoprotective effects on liposomes during freeze drying,¹⁹³ and the haemolytic activities of methyl oleanolate diglycosides and monoglycosides.¹⁹⁴

2 S- and Se-Glycosides

A new approach to the synthesis of S-glycosides from glycosyl acetates is illustrated in Scheme 22.¹⁹⁵ A long paper has been published on many aspects of thioglycosyl compounds in which the preparation of thioglycosides by the addition of various sulfenyl halides to alkenes is described, and several descriptions of the preparation of glycosyl alkyl disulfides from glycosyl thiosulfenyl halides are included.¹⁹⁶ Reaction of glycosyl aryl sulfenates with triethyl phosphite gives the corresponding aryl thioglycosides, and thus the thiophilic reagent has removed oxygen rather than sulphur.¹⁹⁷ This is consistent with an earlier report (*Carbohydr. Rev.*, 1977, **58**, 397).

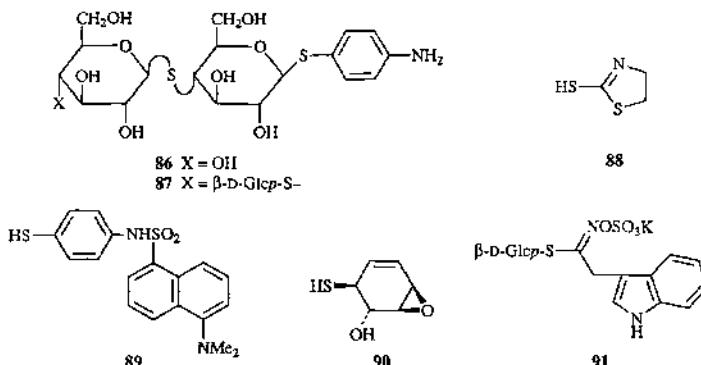


Reagents: i. $Bu_2Sn(OTf)_2$ (cat.), $Bu_2Sn(SR')_2$

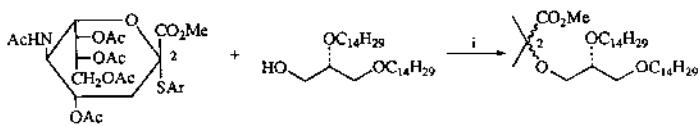
Scheme 22

Considerable attention has been given to the preparation of specific thioglycosides. Thus the three disaccharides comprising D-xylopyranose units connected by sulphur and β -(1 \rightarrow 2), (1 \rightarrow 3) and (1 \rightarrow 4)-links have been produced.¹⁹⁸ The related S-linked analogue of β -Neu5Ac-(2 \rightarrow 6)- β -D-GlcNAcp¹⁹⁹ has been synthesized as well as the galactosamine-containing analogue, and they have been linked to ceramide.¹⁹⁹ The sulfur-containing disaccharide **86** and a trimer analogue **87** have been coupled to Sepharose for use in affinity gels and the

products were used for the purification of cellobiohydrolases.²⁰⁰ *p*-Nitrophenyl thioglycosides of lactose, maltose, cellobiose and gentiobiose have been reported.²⁰¹ Various glycosides containing thiols **88-90** as aglycons have been reported.²⁰²⁻²⁰⁴ The *N*-acetyl-glucosaminyl derivative of the last of these is an irreversible inhibitor of human β -hexosaminidase. The first syntheses of glucobrassicin the indole glucosinolate **91** has been reported.²⁰⁵



The use of thioglycosides in the preparation of *O*-glycosides and disaccharides is now well developed as is illustrated in several instances earlier in this Chapter. Very interestingly and importantly, the potential of arylthio groups as leaving groups in glycosylating agents can be affected considerably by substitution in the aromatic rings as illustrated in Scheme 23. That is, electron-donating groups activate leaving potential and,



Ar = C_6H_4-p -NO₂, no reaction;
 = C_6H_4-p -NHAc or C_6H_4-p -ONa, rapid reaction

Reagents: i, DMTST

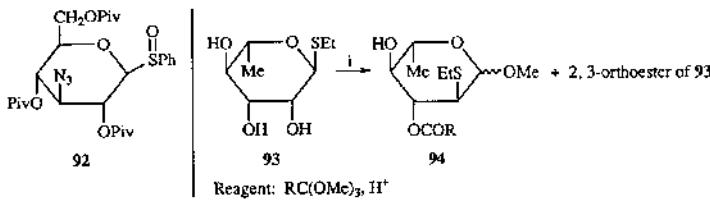
Scheme 23

conversely, electron-withdrawing groups deactivate. An illustration of the use of this approach is given.²⁰⁶ Further examples of the use of 2-pyridyl 2-deoxy-1-thioglycosides as glycosyl donors, used with methyl iodide activation, have been illustrated by the synthesis of several 2-deoxy di- and tri-saccharides.²⁰⁷ 2',3'-Dideoxynucleosides have been prepared by

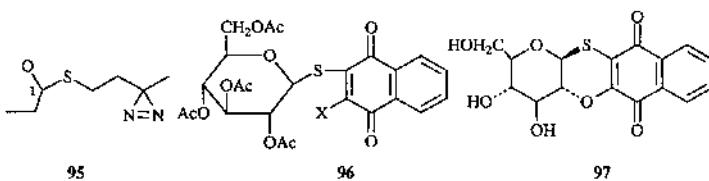
use of phenyl 2,3-dideoxy-1-thio-D-ribofuranose compounds activated by NBS.²⁰⁸

The use of sulfoxides as leaving groups in glycoside synthesis is less common, but compound **92** has been employed to couple with a secondary alcohol in the synthesis of hikizimycin (See Chapter 20).

In the field of reactions of thioglycosides the photobromination of phenylthio compounds has been covered in a review.²⁰⁹ As has been noted before, and has been used usefully in synthesis of 2-deoxy compounds, the alkylthio group of thioglycosides may migrate to C-2 under certain conditions. Thus, as well as compound **93** giving the expected 2,3-orthoester on treatment with alkyl orthoesters in acid conditions, it gave compound **94**



(Scheme 24). The problem was overcome by use of trimethyl orthobenzoate in DMF with camphorsulfonic acid as catalyst.²¹⁰ Thioglycosides with the general structure **95** are photolabile.²¹¹ Saponification of compound **96** led to the tetracyclic **97**.²¹² Treatment of

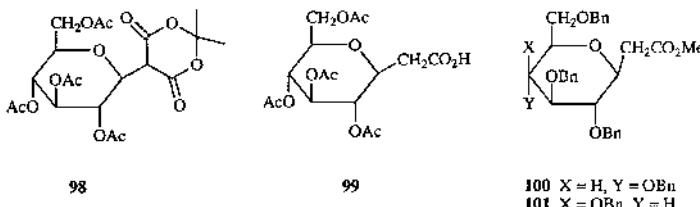


penta-*O*-acetyl- β -D-glucopyranose with phenylselenotrimethylsilane in the presence of trimethylsilyl triflate gave 17% of the β -linked phenylseleno glycoside together with 14% of the α -anomer.²¹³ In related work tetra-*O*-benzyl- α -D-glucopyranosyl chloride, condensed with dialkyl or aryl diselenide in the presence of potassium borohydride, afforded the β -linked alkyl or aryl selenoglycosides, whereas selenourea, under alkaline conditions followed by potassium borohydride treatment, gave primarily the α -compounds.²¹⁴

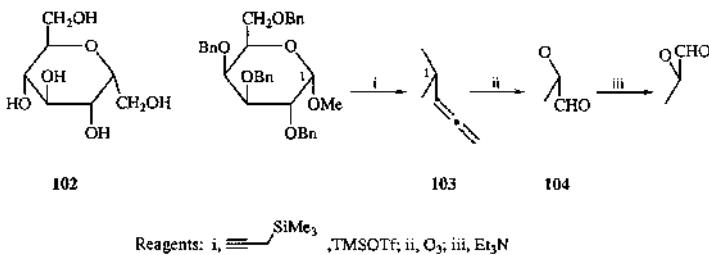
3 C-Glycosides

Developments reported over the period 1983 - 1991 in this synthesis of C-glycosides have been reviewed, methods utilized being covered under the topics a) concerted reactions, b) Wittig approaches, c) palladium-mediated reactions, d) sugar electrophiles, e) nucleophilic glycosides, and f) free radical approaches.²¹⁵

3.1 Pyranoid Compounds.—Reaction of 2,3,4,6-tetra-*O*-acetyl-*D*-glucose with the active methylene compound Meldrum's acid gives the *C*-glycoside **98** in 59% yield; on acid-catalysed hydrolysis this affords the acetic acid derivative **99**. The same condensation reaction applied to *L*-arabinose and *D*-mannose gives furanosyl compounds directly (see next section).²¹⁶ β -Linked glycosyl acetic acids **100**, **101** are produced on treatment of

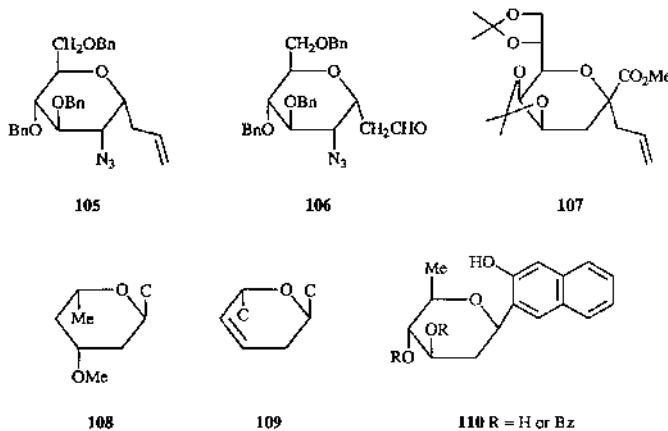


tetrabenzyl- α -D-glucose and D-galactose, respectively, with tributylphosphine and zinc with methyl bromoacetate in refluxing benzene. Yields are about 70%, and with the mannose analogue α - and β - compounds are produced in equal proportions, the yield being 50%.²¹⁷ α -Compounds related to 102 have been examined as inhibitors of glycogen phosphorylase.²¹⁸ Methyl tetra-O-benzyl- α -D-galactopyranoside, treated with propargyltrimethylsilane and

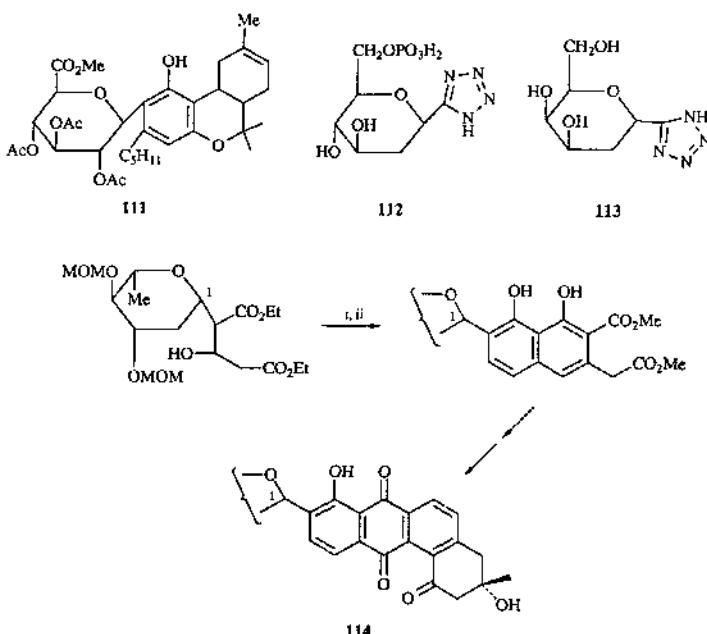


Scheme 25

trimethylsilyl triflate, gives the α -allene **103** ozonolysis of which affords the aldehyde **104**. With triethylamine this epimerizes to a 1:10 mixture of the α - and β - compounds (Scheme 25). Similar results were obtained in the α -glucose and α -mannose series, the equilibrium ratios of aldehydes being 20:1 and 8:1 respectively.²¹⁹ In extensions of this work a glycosyl nitrate was treated with allyltrimethylsilane and boron trifluoride etherate to give the allyl *C*-glycoside **105** from which **106** was made in work related to *C*-glycosides corresponding to parts of glycoproteins.²²⁰ The *C*-allyl glycosidic derivative of KDO **107** was prepared using allyltributyltin and the corresponding β -thiophenyl glycoside under radical conditions; the α,β -ratio of products was 9:1.²²¹ Tetra-*O*-benzyl- α -D-glycopyranosyl bromide, together with organoaluminium compounds, gave rise to *C*-glycosides in 40-80% yield, the highest stereoselectivity (α,β -ratio 90:10) occurring with triethylaluminium.²²² Related work has been carried out using benzylated glucopyranolactone with vinylaluminium.²²³ Structural units **108** and **109** have been found as constituents of sponge components.²²⁴ The β -



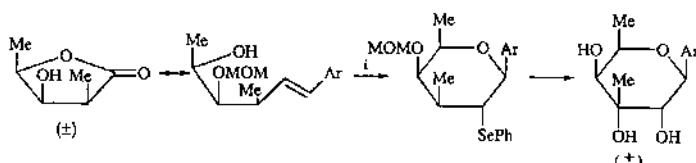
compounds **110** are produced in good yield and with good selectivity from precursors, which may be *O*-protected or unprotected, by use of trimethylsilyl triflate and silver perchlorate in acetonitrile or dichloromethane.²²⁵ Initially, β -naphthyl *O*-glycosides are formed and these rearrange to the *C*-linked compounds illustrated.²²⁶ A *C*-linked glucuronide of tetrahydrocannabinol (presumably with structure **111**) has been produced by use of Lewis acid catalysts, and the corresponding glycosyl trichloroacetimidate.²²⁷ (-)-Urdamycinone B **114**, the enantiomer of a natural antitumour antibiotic, has been prepared as illustrated in Scheme 26.²²⁸ The preparation of the virenose analogue (racemic) is illustrated in Scheme



Reagents: i, $\bar{\text{CH}_2\text{COCHCO}_2\text{Et}}$, ii, $\text{Ca}(\text{OAc})_2$, Δ

Scheme 26

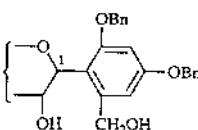
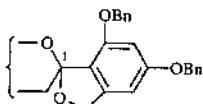
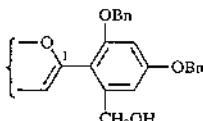
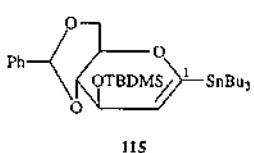
^{27,229} and a range of *C*-glycosyltetrazoles, for example 112 and 113, have been described starting from glycosyl nitriles. These were produced as analogues of 3-deoxy-*D*-arabinohexitulosonic acid.²³⁰ Palladium(0)-catalysed coupling of the glycal derivative 115 with 3,5-dibenzylxy-2-bromobenzyl alcohol afforded 116, MCPBA-oxidation of which gave the *spiro*-



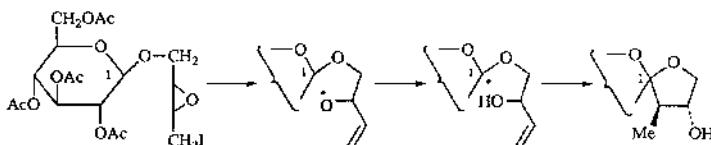
Reagents: i, PhSeCl; ii, H₂O, py; iii, OsO₄, NMNO; iv, HCl

Scheme 27

compound 117 which has the tricyclic structure of the papulacandins. Hydroboration of 116 afforded the aryl compound 118.²³¹ Spiroketal analogues of compound 117 were produced according to Scheme 28.²³² While one of the *erythro*-epoxides reacted very favourably to



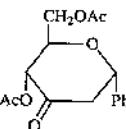
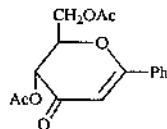
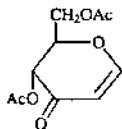
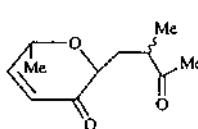
give the illustrated *spiro*-product in 68% yield, the other gave mixed isomers.



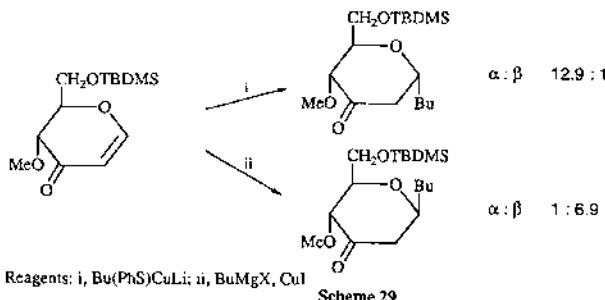
Reagent: i, Bu_3SnH , AIBN

Scheme 28

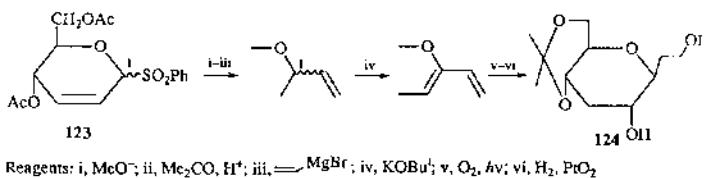
Many acylated glycals have been converted to 2,3-unsaturated *C*-glycosides, and now reports have appeared on the preparation of *C*-allyl compounds from lactose, α,β ratio 5:1.²³³ While tri-*O*-acetyl-*D*-glucal gives quantitative yields of the 2-trimethylsilylalkynyl unsaturated α -*C*-glycoside on treatment with 1,2-bis-trimethylsilyl ethyne in the presence of tin tetrachloride,²³⁴ *p*-cresol gives 2-hydroxy-4-methylphenyl compounds.²³⁵ In the latter case, the initially formed *O*-glycosides were converted to the *C*-glycosidic products on treatment with boron trifluoride in dichloromethane. 2,3-Unsaturated *C* glycosides may be produced by palladium(0)-catalysed reaction with compounds having activated methylene groups (see also Vol. 23, p. 40).²³⁶ Hydroxyglycal esters react with silylated allyl alcohols to give dicarbonyl products. For example, tri-*O*-acetyl-2-hydroxy-*D*-fucal can be converted into the dicarbonyl compound 119.²³⁷ *C*-Glycosides may also be prepared from carbohydrate-based enones such as 120 which, with benzene in the presence of palladium diacetate in acetic acid, gives the *C*-phenyl compounds 121 and 122 in 70% yield. The substitution and addition processes were rationalized.²³⁸ Similar adducts have been made by Michael-like



additions using organocuprates (Scheme 29). The markedly different anomeric ratios were

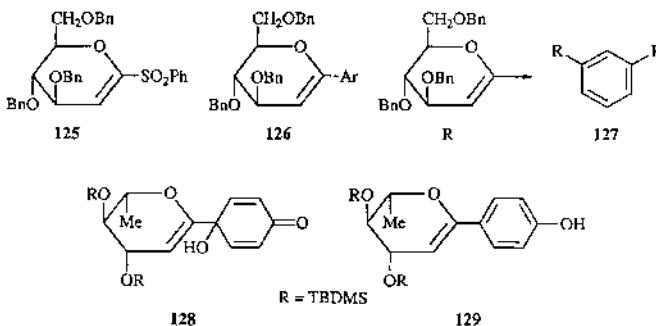


rationalized in terms of preferred conformations of enolate intermediates.²¹⁹ The use of the unsaturated glycosyl phenylsulfone **123** in the preparation of 2-hydroxyethyl 3-deoxy-C-glycoside **124** is illustrated in Scheme 30.²⁴⁰ The related glycal sulfone **125** can be converted

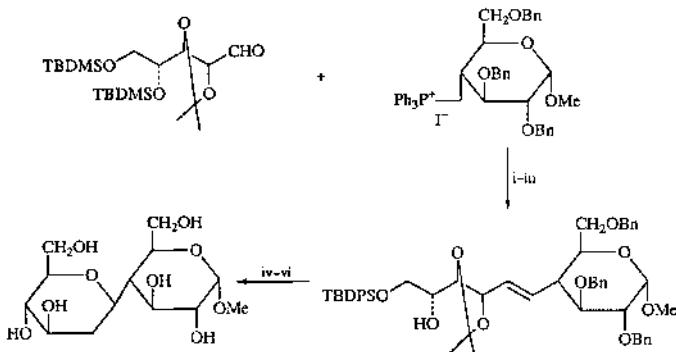


into the 1-tributylstannyl analogue and hence, using tetra-kis-(triphenylphosphinyl)palladium and aryl bromide into aryl glycosides **126**.²⁴¹ With *m*-dibromobenzene the symmetrical diglycoside **127** is obtainable. Reaction of benzoquinone with the appropriate glycal derivative in the presence of *t*-butyllithium gives the adduct **128** and hence the *p*-hydroxyphenyl compound **129**.²⁴²

Considerable interest continues to be shown in disaccharides linked by carbon



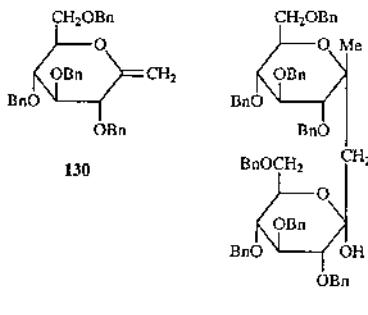
bonding. The synthesis of a cellobiose analogue having no inter-unit atom is illustrated in



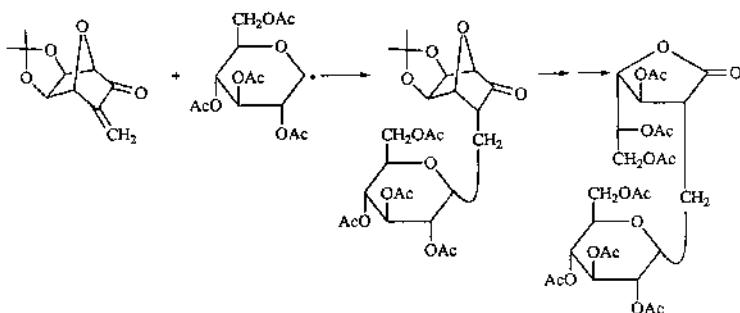
Reagents: i, KH; ii, Bu₄NF; iii, TBDPSiCl; iv, *h*_v to give *E*-isomer; v, Br₂, NBS; vi, TsOH

Scheme 31

Scheme 31.²⁴³ As reported previously, see Vol. 23, p. 43, 1-deoxyketoses or analogues having exocyclic methylene groups at C-1, on treatment with acids, form C-C-linked products. For example, from compound 130 the dimer 131 has been produced in 66%

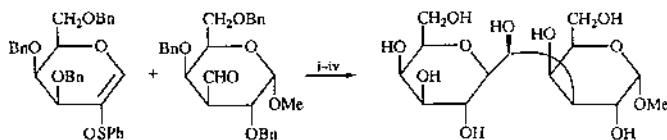


yield.²⁴⁴ A set of carba-linked disaccharides formed by radical addition to exo-alkenes of 'naked' sugars have been reported as outlined in Scheme 32.²⁴⁵ Thirty galactobiose analogue have been produced as indicated in Scheme 33 (see also Vol. 23, p. 40).²⁴⁶ Details of the synthesis of 1,4-C-linked disaccharides, using acyclic aldehyde derivatives of sugars and phosphonium salts on C-4-branches (see Vol. 25, p. 55), have been reported.²⁴⁷ Reaction of the lithio derivative 132 with tetrabenzylgluconolactone gave compound 133 in



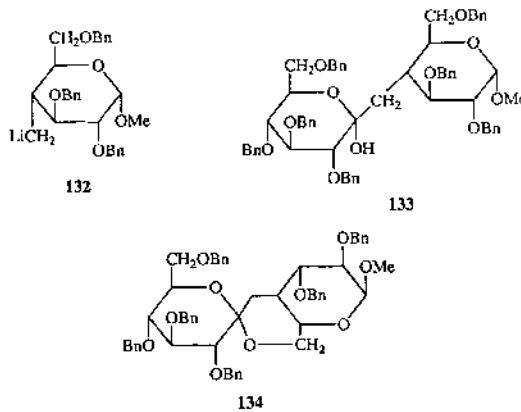
Scheme 32

60% yield. Attempts at deoxygenation at the anomeric centre gave rise to the *spiro*-linked disaccharide **134**.²⁴⁸



Reagents: i, LDA; ii, Ni(Ra); iii, $\text{BH}_3\text{-Me}_2\text{S}$, $\text{NaOH}, \text{H}_2\text{O}_2$; iv, H_2 , Pd/C

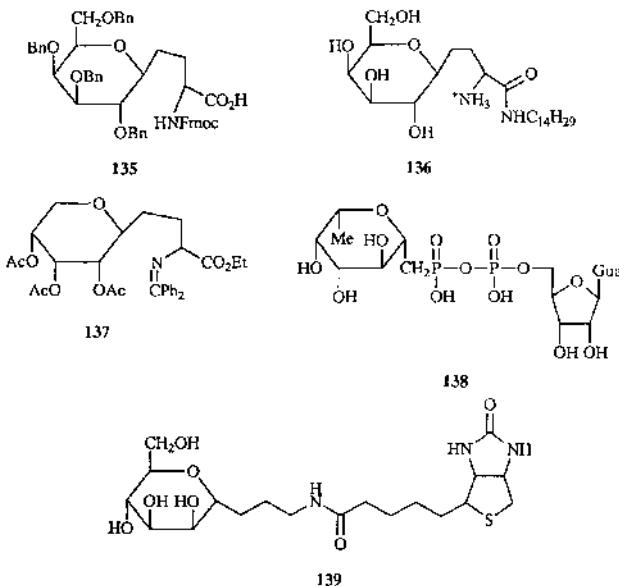
Scheme 33



Several compounds have been reported which involve *C*-glycosidation to biologically important compounds. Thus *C*-linked analogues of glucosylserine, for example, have been made and built into the glycopeptide compound **135**.²⁴⁹ The starting material for compound

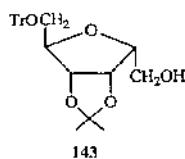
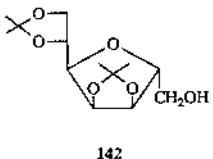
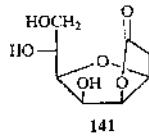
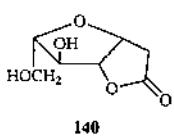
135 was the corresponding *C*-glycosyl 1-aldehyde and the same compound has been used for the preparation of *C*-linked galactosphingolipids **136** as potential inhibitors of HIV.²⁵⁰ In related work the β -D-xylopyranosyl *C*-glycoside **137** has been produced as a precursor of the analogue of β -D-xylopyranosyl-L-serine.²⁵¹ Radical addition has allowed the preparation of the analogous α -compound in the D-glucose series.²⁵² Elaboration of simple *C*-glycosides has allowed the preparation of *C*-fucopyranosyl analogues of GDP-L-fucose, for example, compound **138**.²⁵³ Reference is made in chapter 18 to a complex *C*-glycoside of neuraminic acid which is neuraminidase-resistant.

The *C*-glycosyl conjugate **139**, containing biotin, and several related compounds were prepared and their inhibitory activity towards the receptor-mediated adhesion of *E. coli* to yeast cells was tested.²⁵⁴

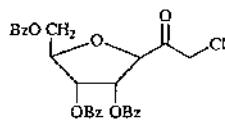
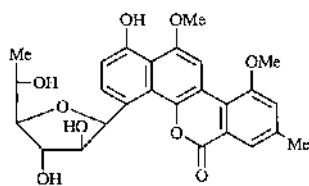
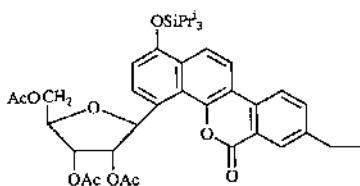
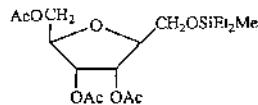
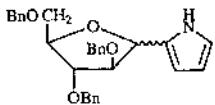


3.2 Furanoid Compounds.—Reaction of Meldrum's acid, which was mentioned at the beginning of the last section, with L-arabinose and D-mannose gives, in DMF in the presence of triethylamine, compounds **140** and **141** in 47% and 39%, respectively. In the case of the latter compound the *manno*-isomer, formed without epimerization, was produced in 11% yield.²¹⁶ Treatment of the corresponding free sugars with methylenesulphinyll ylid

(MeS(O)=CH₂) gives compounds **142** and **143** in good yield but not stereospecifically.²⁵⁵



Acid catalysed cyclization of the alditol derivative, formed on treatment of 2,3,5-tri-*O*-benzyl-d-arabinose with pyrrolyl magnesium bromide gave the furanosyl *C* nucleosides **144** with an α,β ratio of 51:29.²⁵⁶ Corresponding glycofuranosyl acetates with



HSiMeEt₂-CO-Co₂(CO)₈,²⁵⁷ the appropriate silylated phenol and tin tetrachloride²⁵⁸ and the appropriate phenol and silver perchlorate, Cp₂HfCl₂²⁵⁹ resulted in the synthesis of

compounds 145-147, the last being the antibiotic(+) -gilvocarcin M. The ribofuranosyl acidchloride 148 has been prepared from the corresponding glycosyl carboxylic acid and is of potential value for C-nucleoside synthesis.²⁶⁰

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4 Oligosaccharides

1 General

As previously, this Chapter deals with specific tri- and higher oligosaccharides, most references relating to their synthesis by specific chemical and, increasingly, enzymic or combined methods. Chemical features of the cyclodextrins are noted separately.

The synthesis of e.g. pentasaccharides is dealt with under that heading, and the required preparations of constituent parts are assumed and are not dealt with in their respective sections. Frequently, specific derivatives, e.g. glycosides, of the named compounds are involved, and this fact is often not recorded in the formulae used or the names listed.

Reviews have appeared on the synthesis of oligosaccharides of 2-amino-2-deoxy sugars,¹ the synthesis of β -glucans and dodecagalacturonic acids that elicit phytoalexin accumulation in soybean,² sialyl Lewis X,³ the use of 1D and 2D n.m.r. spectroscopy to establish the structures and substitution sites of naturally occurring glycosides and oligosaccharides has been reviewed,⁴ and the CASPER programme has been successfully applied to determine the correct structures of five linear or branched hexasaccharides.⁵ The question of internal mobility of oligosaccharides has been raised and the need for methods to generate realistic representations of three dimensional structure has been emphasised and new approaches offered.⁶

N.m.r. and mass spectrometric methods have been used to determine structures of 22 neutral oligosaccharides up to octasaccharides obtained from bovine submaxillary-gland mucin glycoprotein.⁷

2-Pyridyl 2-deoxy-1-thiohexopyranosides have been successfully applied with methyl iodide activation to produce a range of di- and tri-saccharides containing 2-deoxy-linked sugars. The linkages formed were mainly of the α -type. Similarly, the 2-pyridyl 1-thio-glycosides in the ribo- and manno-furanoside series led to α -linked products.⁸ The maltose oligosaccharides up to the pentasaccharide, each having a 4,6-ethylidene acetal on the non-reducing terminal unit, have been made for measuring K_D values with a maltose-binding protein of *E. coli*, and the same binding has been further examined by use of maltose-

oligomers having a photoaffinity label in the aglycon and a tritium atom in the reducing unit.⁹ The α -1,3-linked glucose oligomers up to the tetrasaccharide have been synthesized,¹⁰ as have the β -1,4-linked xylose oligomers up to the hexamer.¹¹

Interest remains in the use of carbohydrate monomers for the synthesis of polymeric materials and the subject has been reviewed.¹² A polymer comprising on average ten of the disaccharide units Glcp-(1 \rightarrow 3)- α , β -D-GlcAp-(1 \rightarrow 4), which is a synthetic model of the capsular polysaccharide from *Spreptococcus pneumoniae* type 3, has been prepared¹³ by condensation methods starting from a substituted disaccharide.¹³ A related approach, but using glycosylation with thiocyanate as the leaving group has led to a polymer comprising α -1,6-linked glucoses.¹⁴ A polymer derived from D-mannopyranose 1-phosphate, which involves linking between the phosphate residue and O-6 of neighbouring sugar unit, and containing 3-7 sugar units has been produced and, in addition, cyclic products were identified.¹⁵

Various fructosylated sucroses have been isolated from *Lolium temulentum*.¹⁶ N.m.r. work on related inulin oligomers up to the decasaccharide indicates that a conformational change occurs in compounds larger than the octamer.¹⁷ Extensive n.m.r. studies have identified a specific disaccharide unit responsible for the binding of histamine to heparin.¹⁸

Conversion of chito-oligosaccharides to the corresponding alditols significantly increases the chemicals stability of the compounds.¹⁹

Increasing use of enzymic methods in the field is evident, and the topic of enzymic *in vitro* synthesis of mammalian glycoconjugate compounds has been reviewed.²⁰ Organoboronic acids have been used in organic solvents to promote solubilization of glucose and thereby its enzymic self-condensation.²¹ α -Amylase-promoted condensation of α -maltosyl fluoride offers a new approach to the preparation of malto-oligosaccharides.²² Transfer of the D-glucosyl unit of sucrose onto maltose acceptors has led to the development of α -1,6-linked chains some also containing α -glucoses substituted at O-3. Products having approximately eight sugar units were examined.²³ In related studies, fucosyl oligosaccharides were prepared on a 15-30 mg scale using a cloned α -1,3-fucosyl transferase. The enzyme accepts a number of galactosides and sialosides as substrates, and it is useful for the preparation of sialyl Lewis X.²⁴ This compound has also been made by enzymic procedures using β -1,4-D-galactosyl transferase, a recombinant α -2,3-sialyl transferase and a α -1,3-fucosyl transferase. During the course of this work, substrate specificity and inhibition of the transferases were studied and a conformational analysis was undertaken using ^{13}C n.m.r. and molecular energetic calculations.²⁵

Galactose transferase has also been used to prepare oligosaccharides with 2-acetamido-2-

deoxyglucose and glucose as acceptors, and UDP-2-deoxygalactose also serves as a donor for transfer to the first of these two sugars.²⁶

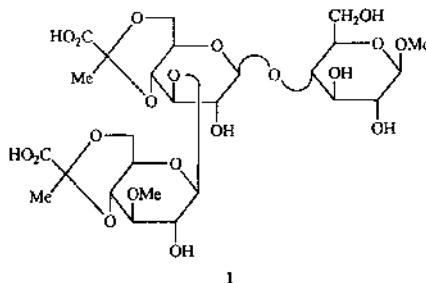
A paper has been given at a workshop on the oxidation of sucrose and isomaltulose to the 3-keto-derivatives by *Agrobacterium tumefaciens*, and the synthesis of oligosaccharides using dextran sucrase was described.²⁷

2 Trisaccharides

Compounds in sections 2.1 - 2.3 are categorized according to their non-reducing end sugars.

2.1 Linear Homotrisaccharides.—Dehydrative glycosylations of various glucose derivatives having 2,3,4 or 6-hydroxyl groups free with heptabenzyl glucobioses in the presence of *p*-nitrobenzenesulfonyl chloride, silver triflate and triethylamine in dichloromethane gave 60-85% yields of glucotrioses. Very high α -selectivity was observed when DMF was used in the reaction mixtures.²⁸

The trisaccharide derivative **1**, which is a segment of glycolipids of *Mycobacterium smegmatis*, has been completed using glycosyl fluoride methodology.²⁹ Two groups have described the synthesis of nephritogenoside which comprises α -D-Glc β -(1 \rightarrow 6)- β -D-Glc β -(1 \rightarrow 6)-O- α -D-Glc linked to a peptide.^{30, 31} The α -1,6-linked glucotriose has been made without specific hydroxyl groups in the reducing moiety as its methyl glycoside, and higher oligomers of this type have likewise been prepared for studying binding with monoclonal antibodies.³² Related work has produced β -D-Glc β -(1 \rightarrow 6)- β -D-Gal β -(1 \rightarrow 6)- β -D-Glc and β -D-Glc β -(1 \rightarrow 6)- β -D-Glc β -(1 \rightarrow 6)- β -D-Gal with 4-deoxy groups in the reducing and central moieties, respectively.³³



α -L-Rhap-(1 \rightarrow 3)- α -L-Rhap-(1 \rightarrow 3)- α -L-Rhap has been made as a trimethyl ether methyl glycoside as the outer trisaccharide of *Mycobacterium Xenopi* glycolipid.³⁴ The α -1,7 α -1,3-

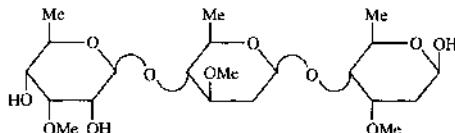
linked trimer of L-glycero-D-manno-heptopyranose, which is part of the *Salmonella* Ra core structure, has also been made as an aryl substituted ethyl glycoside.³⁵

2.2 Linear Heterosaccharides.—D-Galactose units have been transferred to several disaccharide acceptors by appropriate enzymes. In this way lactose has given rise to the trimers having α -D-galactopyranose linked to the 4- and 3-positions of the galactose units.³⁶ β -Galactosidase applied with lactitol as acceptor was also non-specific and gave trimer products with the galactose linked to position 3 or position 4 or 6.³⁷ Several other trisaccharides produced by use of β -galactose transferase and cellobiose, laminaribiose, gentiobiose and maltose have been described.³⁸ Several trimers containing galactopyranose as the non-reducing terminal unit have been prepared by chemical synthetic methods. These include: α -D-Galp-(1 \rightarrow 3)- β -D-Galp-(1 \rightarrow 4)-D-GlcP, α -D-Galp-(1 \rightarrow 4)- β -D-Galp-(1 \rightarrow 4)-D-GlcP,³⁹ β -D-Galp-(1 \rightarrow 4)- α -D-GlcP-(1 \rightarrow 3)- α -L-Rhap,⁴⁰ β -D-Galp-(1 \rightarrow 4)- β -D-GlcNAcp-(1 \rightarrow 3)- α - and β -D-GalNAc⁴¹ and β -D-Gal-(1 \rightarrow 4)- β -D-GlcNAc-(1 \rightarrow 6)- α -D-GalNAc.⁴²

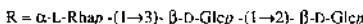
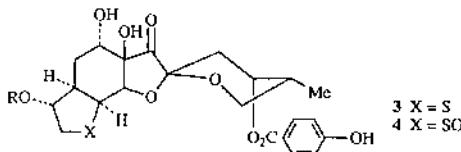
Several trisaccharides of this series having N-acetylhexosamine units at the non-reducing termini are as follows: β -D-GlcNAc-(1 \rightarrow 2)- α -D-Manp-(1 \rightarrow 6)-D-Man,⁴³ β -D-ManpNAc-(1 \rightarrow 4)- α -D-GlcP-(1 \rightarrow 2)-L-Rhap⁴⁴ and β -D-GalpNAc-(1 \rightarrow 4)- β -D-GlcPNAc-(1 \rightarrow 2)-D-Man.⁴⁵

Considerable interest continues in compounds having 6-deoxyhexoses as non-reducing terminal units: special interest has been shown in trisaccharide α -L-Fucp-(1 \rightarrow 2)- β -D-Galp-(1 \rightarrow 4)- β -D-GlcNAc, the H-type 2 human blood group trisaccharide.⁴⁶⁻⁵⁰ These papers also describe several derivatives of the trimer. The 1 \rightarrow 2, 1 \rightarrow 3 isomer has also been made.⁵¹ α -L-Fucp-(1 \rightarrow 3)- β -D-GlcNAc-(1 \rightarrow 6)- β -D-GalNAc,⁵² 4-O-Ac-2-O-Me- α -L-Fucp-(1 \rightarrow 3)-2-O-Me- α -L-Rhap-(1 \rightarrow 3)-2,4-di-O-Me-L-Rhap⁵³ and its O-deacetylated analogue^{53a} have also been synthesized, the latter pair being components of the cell wall of *Mycobacterium kansasii*.⁵³ Compounds β -L-Rhap-(1 \rightarrow 4)- β -D-GlcP-(1 \rightarrow 3)- α -L-Rha, β -L-Rhap-(1 \rightarrow 4)- β -D-GlcP-(1 \rightarrow 3)- β -D-GalpNAc, β -L-Rhap-(1 \rightarrow 4)- α -D-GlcP-(1 \rightarrow 3)- α -D-Gal, and β -L-Rhap-(1 \rightarrow 4)- β -D-GlcP-(1 \rightarrow 4)- β -D-Gal have been synthesized. They represent fragments of capsular polysaccharides of *Streptococcus pneumoniae* types 2, 2F, 22F, 23T.⁵⁴

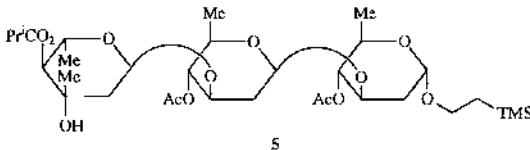
Two groups have isolated pregnane glycosides which contain the trisaccharide **2** and its



C-3' epimer as the glycosyl units.^{55,56} As always, several rhamnose-containing oligosaccharides have been found as aglycons in complex glycosides of plants. Compounds 3 and 4, that is brevian A and B, have been characterized.⁵⁷



Synthesis of the following trisaccharides have also been reported: O - α -D-Xylp-(1 \rightarrow 3)- O - α -D-Xylp-(1 \rightarrow 3)-D-Glc,⁵⁸ β -D-GalpA-(1 \rightarrow 4)- α -L-Rhap-(1 \rightarrow 3)-D-GalpA,⁵⁹ β -L,D-Hipp-(1 \rightarrow 6)- α -D-GlcP-(1 \rightarrow 2)-D-GlcP⁶⁰ and the substituted compound **5**, which is a synthetic precursor of olivomycin A.⁶¹



Considerable continued interest has been taken in trimers which are sialyl galactosyl glucoses (or glucosamines), and reports have appeared on the α -2,3 β -1,4,⁶²⁻⁶⁵ α -2,3 β -1,3⁶⁶ and α -2,6 β -1,4⁶⁷⁻⁶⁹ linked compounds.

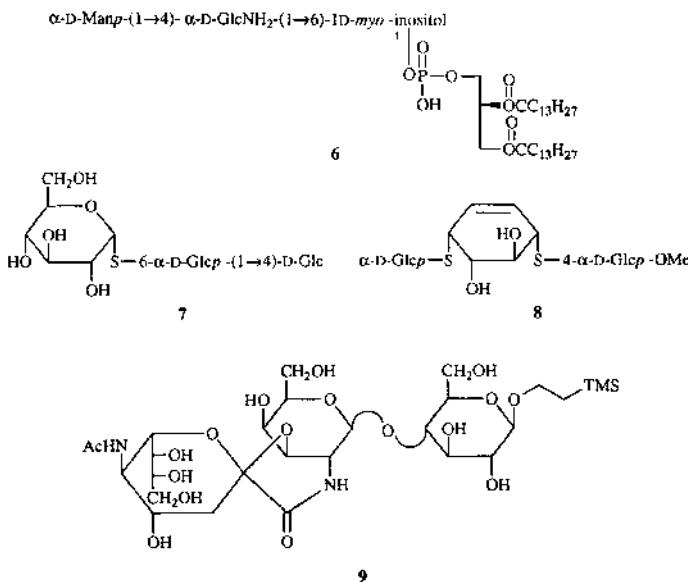
2.3 Branched Heterotrisaccharides.—Ogawa has published on several compounds related to 2,3-di- α -D-mannopyranosyl-D-mannose,⁷⁰ while Paulsen⁷¹ and Sinay⁷² have reported preparations of 3,6-disubstituted analogues.

2.4 Branched Heterotrisaccharides. Compounds in this section are categorized according to their reducing end sugars.

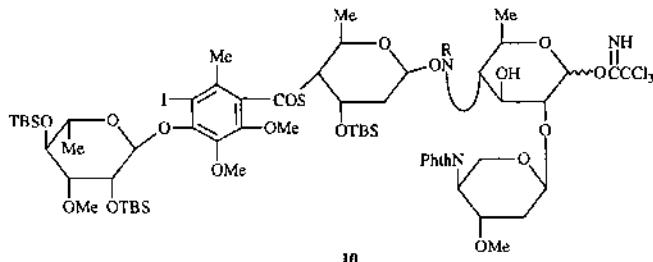
Enzymic galactosylation of lactitol has given mixed products which include compounds carrying galactose at positions 1, 5 or 6 of the alditol unit.³⁷ Chemical fucosylation of α -lactal carrying substituents at both primary positions favoured production of the trimer involving fucose bonding to the allylic oxygen. On the other hand, enzymic sialylation occurs specifically at the C3 position of the galactose unit.³⁸ Synthesis of α -D-GalpNAc-

(1→3)-[α -L-Fuc-(1→2)]-D-Gal and the galactosyl fucosyl galactose analogue⁷⁴ and α -D-Glcp-(1→2)-[β -D-GlcP-(1→4)]-D-Gal⁴⁰ have also been reported. Kochetkov's group has described the preparation of a range of 2,3-di-glycosylated mannoses,^{75,76} and Paulsen and co-workers have reported β -D-GlcNAc-(1→2)-[β -D-GlcNAc-(1→6)]-D-Man and the 1,2-, 1,4-linked isomer.⁴³ Kochetkov and collaborators have synthesized many 2,3-di-glycosyl-L-rhamnose derivatives.^{75,78} The branched trisaccharide α -D-GlcP-(1→3)-[α -Hepp-(1→7)]-Hep has been prepared where the abbreviation Hep is for L-glycero-D-manno-heptose.⁷⁹ Trisaccharides based on N-acetyl-D-hexosamines to have been prepared are: α -L-FucP-(1→4)-[β -D-GalP-(1→3)]-D-GlcNAc⁸⁰ and β -D-GalP-(1→3)-[α -Neu5Ac-(2→6)]-D-GalNAc.⁸¹

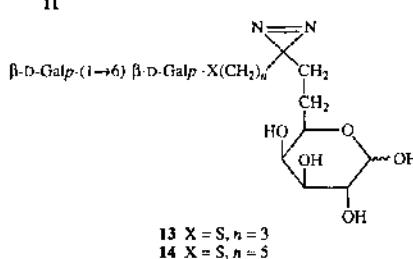
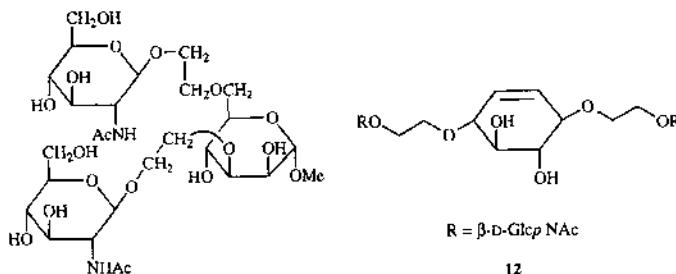
2.5 Analogues of Trisaccharides.—This section has been introduced for the first time to report several compounds which, while not being themselves trisaccharides, have structures very closely related to them. For example, thio-derivatives and compounds having carbon in place of oxygen atoms as inter-unit bridges and as ring atoms are dealt with. Compound α -L-FucP-(1→2)-C- β -D-GalP-(1→4)- α -D-GlcP-OMe, which is a C-linked trisaccharide analogue related to the type II blood group determinant has been described, and conformational analysis has been performed on it.⁸² Synthesis of the inositol compounds **6**⁸³ and β -D-GalP-(1→4)- α -D-GlcNAc-(1→4)-1D-myoinositol^{83a} have been described as have the thio compounds **7**⁸⁴ and **8**.⁸⁵

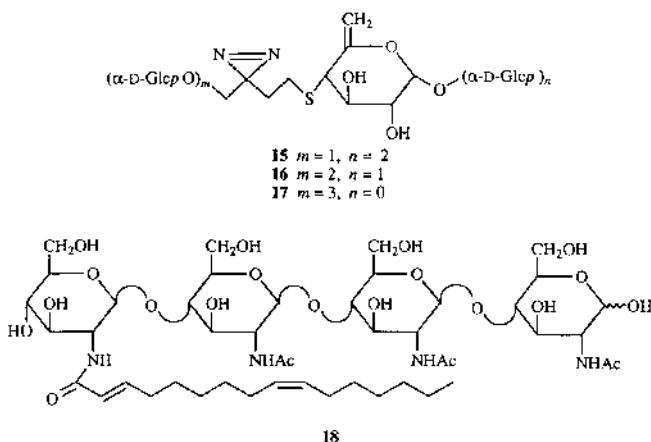


Synthetic work has been reported on compound **9** which is a hydrolytically stable analogue of GM₃ ganglioside lactone.⁸⁶ Compound **10**, which contains a trisaccharide having a hydroxylamine linking unit, and which is a derivative of the carbohydrate domain of calicheamicin, has been reported,⁸⁷ and carbohydrate fragments of esperamicin A₁, which also contain this type of bonding, have likewise been described.⁸⁸



Several compounds have been described by Lehmann's group which have three sugar (or similar) units separated by spacer groupings. For example, compounds **11**⁸⁹ and **12**⁹⁰ are both acceptors substrates for 1,4- β -galactosyl transferase comparable to the biantennary core heptasaccharide of *N*-glycoproteins. Compounds **13** and **14**⁹¹ and **15-17**⁹² which are trisaccharides which mimic galactotetraose and maltopentaose, respectively, have been prepared.





3 Tetrasaccharides

Compounds of this set are classified according to whether they have linear or branched structures and then by the nature of the sugars at the reducing termini.

3.1 Linear Homotetrasaccharides.—The total synthesis of the rhizobium nodulation factor 18 and related compounds, which are critical in rhizobium-legume symbiosis, have been completed by use of the glycosyl fluoride procedure.⁹³

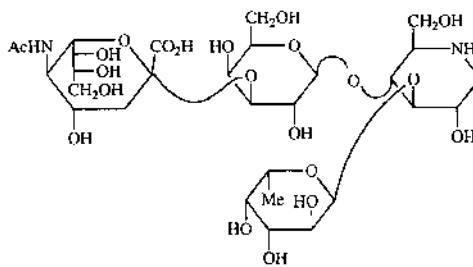
3.2 Linear Heterotetrasaccharides.—A report on a ¹³C relaxation study of $\beta\text{-D-Galp-(1\rightarrow4)\text{-}\beta\text{-D-GlcNAc-(1\rightarrow3)\text{-}\beta\text{-D-Galp-(1\rightarrow4)\text{-D-Glc}}$ has appeared.⁹⁴

The following heterotetrasaccharides have been synthesized: $\beta\text{-D-Galp-(1\rightarrow4)\text{-}\beta\text{-D-Glcp-(1\rightarrow6)\text{-}\beta\text{-D-Galp-(1\rightarrow4)\text{-D-Glc}}$,⁹⁵ $\alpha\text{-Neup5Ac-(2\rightarrow9)\text{-}\alpha\text{-Neup5Ac-(2\rightarrow3)\text{-}\beta\text{-D-Galp-(1\rightarrow4)\text{-D-Glc}}$,⁹⁶ the analogue of this with a sulfur atom linking the sialic acid units,⁹⁷ $\alpha\text{-D-GlcNAc-(1\rightarrow3)\text{-}\alpha\text{-L-Rhap-(1\rightarrow3)\text{-}\alpha\text{-L-Rhap-(1\rightarrow2)\text{-}\alpha\text{-D-Galp}}$,⁹⁸ $\alpha\text{-D-GlcNAc-(1\rightarrow3)\text{-}\alpha\text{-L-Rhap-(1\rightarrow3)\text{-}\alpha\text{-L-Rhap-(1\rightarrow2)\text{-D-Gal}}$,⁹⁹ $\alpha\text{-L-Rhap-(1\rightarrow3)\text{-}\alpha\text{-L-Rhap-(1\rightarrow2)\text{-}\alpha\text{-D-Galp-(1\rightarrow3)\text{-D-GlcNAc}}$,¹⁰⁰ $\beta\text{-D-GlcNAc-A}$.

(1→3)- β -D-GlcNAc-(1→4)- β -D-GlcPA-(1→3)- β -D-GlcNAc,¹⁰¹ β -D-GlcNAc-(1→4)- β -MurNAc-(1→4)- β -D-GlcNAc-(1→4)-MurNAc,¹⁰² α -D-Galp-(1→3)- α -D-GlcNAc-(1→3)- α -L-Rhap,¹⁰³ β -D-GlcPA-(1→3)- β -D-GalpSO₄-(1→3)- β -D-Galp-(1→4)- β -D-Xyl,¹⁰⁴ β -D-Galp-(1→4)- β -D-GlcP-(1→4)- α -D-Hepp-(1→5)- α -KDO.¹⁰⁵

3.3 Branched Heterotetrasaccharides.—The following compounds have been described mainly following synthesis, but the occasional compound is a natural product and that is indicated: α -D-GalpNAc-(1→3)- β -D-Galp-(1→4)-[α -L-Fucp-(1→3)]- β -D-GlcP,¹⁰⁶ α -Neu5Ac-(2→3)-[β -D-GalpNAc-(1→4)]- β -D-Galp-(1→4)- β -D-Glc,¹⁰⁷ α -D-Manp-(1→3)-[β -D-Xylp-(1→2)]-D-Manp-(1→4)-D-Glc,¹⁰⁸ β -D-GlcNAc-(1→2)- α -D-Manp-(1→3)-[α -D-Manp-(1→6)]-D-Man,¹⁰⁹ α -Neu5Ac-(2→8)- α -Neu5Ac-(2→3)-[β -D-GalpNAc-(1→4)]-D-Gal (a ganglioside component),¹¹⁰ α -Neu5Ac-(2→3)- β -D-Galp-(1→4)-[α -L-Fucp-(1→3)]-D-GlcNAc (a conformational study),¹¹¹ α -Neu5Ac-(2→3)- β -D-Galp-(1→4)-[α -L-Fucp-(1→3)]-GlcNH₂,^{112, 113} α -D-Galp-(1→3)-[α -L-Fucp-(1→2)]- β -D-Galp-(1→3)-D-GlcNAc,¹¹⁴ α -L-Fuc-(1→2)- β -D-Gal-(1→3)-[α -L-Fuc-(1→4)]-D-GlcNAc,¹¹⁵ β -D-Galp-(1→3)- β -D-GlcNAc-(1→6)-[β -D-Galp-(1→4)]-D-GalNAc,¹¹⁶ β -D-GlcP-(1→3)- α -L-Rhap(1→2)-[β -D-GlcP-(1→4)]-L-Ara (natural product)¹¹⁷ and β -D-Quip-(1→3)-[β -L-Rhap-(1→2)]- α -D-Quip-(1→2)-D-Qui (natural product).¹¹⁸

3.4 Tetrasaccharide Analogues.—An oligomer comprising four N-acetyl-glucosamine units separated by phosphate diester linkages between positions 1 and 3 has been reported,¹¹⁹ and compound **19** having deoxynojirimycin at the 'reducing end' has been reported.¹²⁰



4 Pentasaccharides

Again considerable interest has been shown in this category of oligosaccharides.

4.1 Linear Pentasaccharides.—The effect of different bulky substituents at C-6 of the non-reducing terminal unit of a glycoside of maltopentaose on the rates of hydrolysis by human salivary and pancreatic α -amylases has been studied.¹²¹ Several methyl ethers of the pentasaccharide unit of heparin responsible for antithrombin binding have been reported.¹²²⁻¹²⁴

Syntheses of pentasaccharides β -D-GlcNAc-(1 \rightarrow 3)- β -D-Galp-(1 \rightarrow 4)- β -D-GlcNAc-(1 \rightarrow 6)- α -D-Manp-(1 \rightarrow 6)- β -D-Manp¹²⁵ and β -D-Galp-(1 \rightarrow 3)- β -D-GalpNAc-(1 \rightarrow 4)-[α -NeuAc-(2 \rightarrow 3)]- β -D-Galp-(1 \rightarrow 4)-Glc¹²⁶ have been reported.

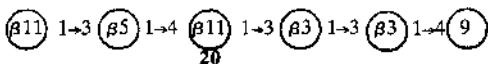
4.2 Branched Pentasaccharides.—Syntheses have been described of the following members of this category: α -Neu5Ac-(2 \rightarrow 3)- β -D-Galp-[α -L-Fucp-(1 \rightarrow 3)]- β -D-GlcNAc-(1 \rightarrow 3)-D-Gal,^{127,128} 3,6-bis-[β -D-GlcNAc-(1 \rightarrow 2)- α -D-Manp]-D-Man,^{129,130} (several specific deoxy derivatives of this compound were also described), β -D-GlcNAc-(1 \rightarrow 2)- α -D-Manp-(1 \rightarrow 3)-[α -D-Manp-(1 \rightarrow 6)]-4-O-Me- β -D-Manp-(1 \rightarrow 4)-D-GlcNAc,¹³¹ β -D-Galp-(1 \rightarrow 4)- β -D-GlcNAc-(1 \rightarrow 3)-[β -D-GlcNAc-(1 \rightarrow 6)]-D-Galp-(1 \rightarrow 4)-GlcNAc,¹³² β -D-Galp-(1 \rightarrow 4)-[α -L-Fucp-(1 \rightarrow 3)]- β -D-GlcNAc-(1 \rightarrow 6)-[β -D-Galp-(1 \rightarrow 3)]-D-GalpNAc,¹³³ β -D-GlcP-(1 \rightarrow 4)-[α -D-GlcP-(1 \rightarrow 2)]- β -D-Galp-(1 \rightarrow 4)- α -D-GlcP-(1 \rightarrow 3)-L-Rha¹³⁴ and β -D-Quip-(1 \rightarrow 2)- β -D-Galp-(1 \rightarrow 4)-[β -D-Quip-(1 \rightarrow 3)]- β -D-Xylp-(1 \rightarrow 3)-D-Quip.¹³⁵

5 Hexasaccharides

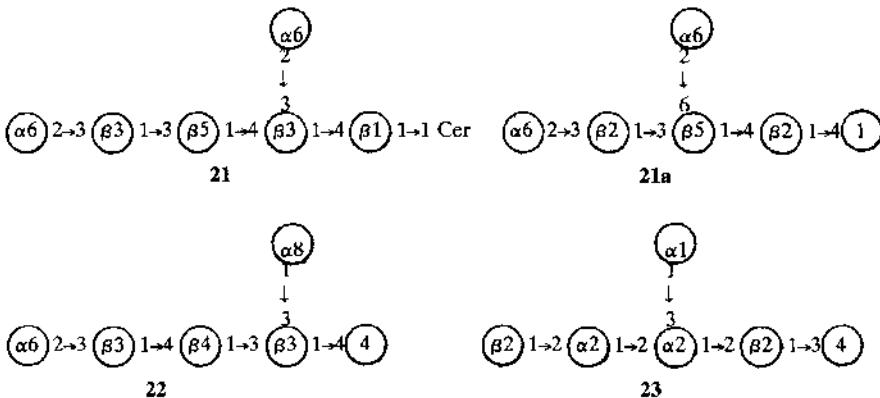
As has become customary in these volumes, an abbreviated method is now used for representing higher saccharides. Sugars will be numbered as follows, and linkages will be indicated in the usual way:

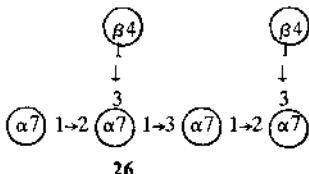
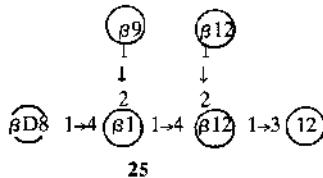
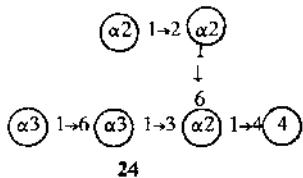
(1) D-GlcP	(2) D-Manp	(3) D-Galp
(4) D-GlcNAc	(5) D-GalpNAc	(6) NeupAc
(7) L-Rhap	(8) L-Fucp	(9) D-Xylp
(10) D-GlcNH ₂	(11) D-GlcPA	(12) D-Qui (6-deoxy D-glucose)

5.1 Linear Hexasaccharides.—Maltohexaose bearing a 6-deoxy-6-iodo group at the non-reducing end and a 6-amino-6-deoxy group in the unit next to the reducing moiety has been prepared by use of cyclodextrin glucanotransferase for the purpose of study of the active site of human α -amylase.¹³⁶ Compound **20**, which is the linkage region of chondroitin sulphate, has been prepared together with an ester carrying a sulphate group at *O*-4 of the *N*-acetylgalactosamine unit.¹³⁷



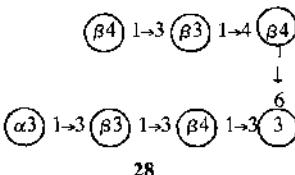
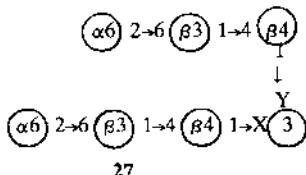
5.2 Branched Hexasaccharides.—Hasagawa's group has reported compounds **21** and **21a** which are isomers of previously described hexamers.¹³⁸ Compound **22** has been made by chemical/enzymic procedures as a specific epitope,¹³⁹ and hexamer **23**, which is the repeating unit of *Salmonella Thompson* serogroup C, *O*-antigen lipopolysaccharide, has also been prepared.¹⁴⁰ Compound **24** has been synthesized and linked to a *myo*-inositol phosphate derivative and also specifically phosphorylated to give the glycosyl phosphatidylinositol anchor of *Trypanosoma brucei*,¹⁴¹ and **25** has been prepared; it is the hexasaccharide moiety of Pectinioside E (isolated from starfish).¹⁴² The high-rhamnose oligomer **26**, a cell wall polysaccharide components of the β -haemolytic *Streptococci* Group A, has also been reported.¹⁴³



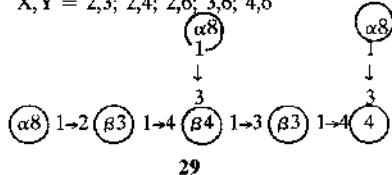


6 Heptasaccharides

The five compounds represented by structure **27**¹⁴⁴ have been made by chemo-enzymic methods, and **28**¹⁴⁵ and **29**¹⁴⁶ have also been reported.

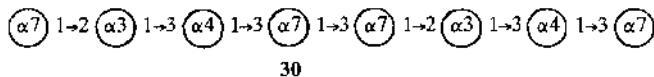


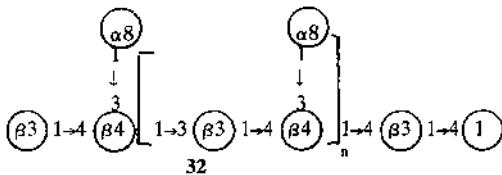
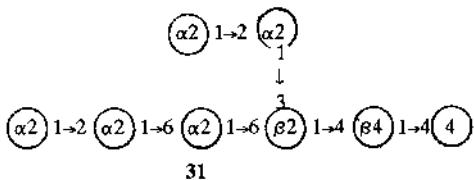
X, Y = 2,3; 2,4; 2,6; 3,6; 4,6



7 Octasaccharides

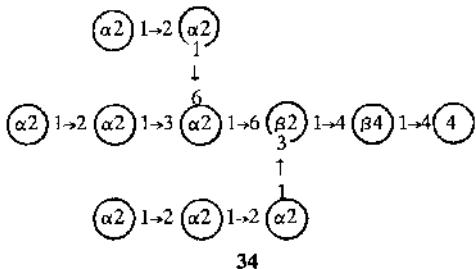
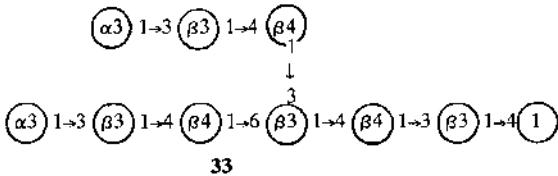
Compounds **30**,¹⁴⁷ **31**¹⁴⁸ and **32** ($n=1$)¹⁴⁹ have been synthesized.

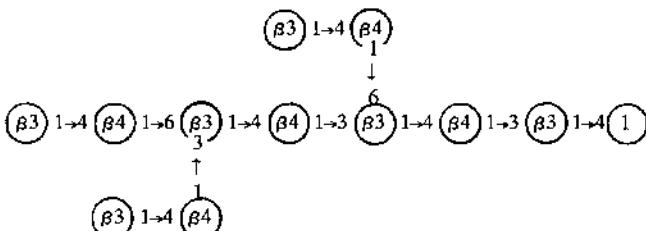




8 Higher Saccharides

Chemo-enzymic methods have been used to prepare a decasaccharide comprising two repeating units of the capsular polysaccharide of the human pathogenic type III group B *Streptococcus*,¹⁵⁰ and the further decasaccharide **33** has been described.¹⁵¹ In the area of undecasaccharides compound **32** ($n=2$)¹⁴⁹ and compound **34**¹⁵² have been described. The largest specific saccharides to have been reported apparently are the dodecamer **35**¹⁵³ and the tetradecamer **32** ($n=3$).¹⁴⁹





9 Cyclodextrins

Details of the solubilities of various cyclodextrins have been given, the β -compound having much lower solubilities than the others and therefore being more readily isolated by crystallization.¹⁵⁴

Cyclodextrin glucanosyltransferase, which cleaves cyclomaltohexaose and glycosidates at *O*-4 of acceptors, provides a means of making long-chain maltooligosaccharides.¹⁵⁵

Studies have been carried out on the interactions between cyclodextrins and hydrophobic fluorescence probes in water in connection with research on cell adhesion following oligosaccharide/oligosaccharide hydrophobic interactions. While linear oligomers bind 8-anilino-1-naphthalenesulfonate and 6-toluidino-2-naphthalenesulfonate in 1:1 proportions, the binding constants are smaller than for the corresponding cyclodextrins.¹⁵⁶ A review has appeared on the synthesis of cyclo- α -rhamnoglucohexaoses,¹⁵⁷ and a symposium paper has been given on 3,6-anhydro- α -D-glucose cyclodextrins.¹⁵⁸ Maltose and panose have been bonded to β -cyclodextrin by enzymic procedures and the enzymolytic reactions of the products were investigated.¹⁵⁹ Various isomeric di- α -D-glucopyranosyl cyclodextrins have been made by chemical procedures.¹⁶⁰ Bromine or iodine, together with triphenylphosphine in DMF, have given high yields of per-bromo- or per-iodo-6-deoxy compounds and hence per(6-deoxy)cyclodextrins have been produced in high yields.¹⁶¹ 6-Thiocyclodextrins carrying glucose units on the sulphur atoms have been studied,¹⁶² and the heptakis(6-*O*-dimethylhexylsilyl)- β -cyclodextrin has been obtained as a pure solid without chromatography.¹⁶³ A study of di-tritylated α - and β -cyclodextrins has produced mixed isomers which were investigated by halogenation of remaining primary hydroxyl groups and

elimination reactions applied to them.¹⁶⁴ Further work has led to isomeric tetra-trityl ethers.¹⁶⁵ Reaction of β -cyclodextrin with epichlorohydrin gave chlorine-containing ethers the chlorine atoms of which could be displaced by various nucleophiles.¹⁶⁶ In related work excess of (S)-propylene oxide was used to produce 2-hydroxypropyl derivatives.¹⁶⁷ Octylation of α - and β -cyclodextrins has led to products carrying the alkyl groups at O-2 and 6 and 2, 3 and 6. These were used in potentiometric electrodes to measure the enantiomeric purity of ephedrine in the presence of serum cations.¹⁶⁸ A symposium has been held on related alkyl and alkylacyl cyclodextrin derivatives.¹⁶⁹

A further symposium paper has been given on the synthesis of monofunctionalized cyclodextrins formed during cycloamylose-catalysed ester hydrolysis. *p*-Nitrophenyl esters derived from N-protected amino acid derivatives were in the main considered.¹⁷⁰

Naphthalene-2-sulfonyl derivatives carrying substituents at all of the primary groups have been prepared from α - and β -cyclodextrins by use of tin intermediates.¹⁷¹ Such intermediates permit the formation of 2-mesitylsulphonyl ester from β -cyclodextrin. From these a mixture of all possible 2,6-disulfonates was produced.¹⁷² Secondary mono-naphthalene sulfonates have also been described.^{172a} Denitration of cyclodextrin pernitrates occurs regio-specifically at the 2 positions and gives rise to the 3,6-di-*O*-nitro-products.¹⁷³ A symposium report has been given on the synthesis of a β -cyclodextrin derivative carrying one primary amino group and methyl ether groups at all other positions. This compound was coupled with amino acids and peptides.¹⁷⁴ By use of per-6-deoxy-6-iodo derivatives nitrile groups have been introduced at C-6; products based on 7-amino-6,7-dideoxyheptose have been obtained.¹⁷⁵ The same iodo starting materials with 1-thio-sugars has led to cyclodextrins having sugars bonded by way of sulfur atoms. In the same work 6-amino-6-deoxy compounds were converted into various amides.¹⁷⁶ Cyclodextrin derivatives bearing aminoalkylimino groups have been found to catalyse adol condensations.¹⁷⁷ Three isomeric dihistamine derivatives of β -cyclodextrin were prepared by use of different disulfonyl chlorides, for example, *m*-di(chlorosulfonylbenzene), di(chlorosulfonylbenzophenone) and di(chlorosulfonylbiphenyl). The sulfonyl groups were replaced by iodide and then by histamine in DMF.¹⁷⁸

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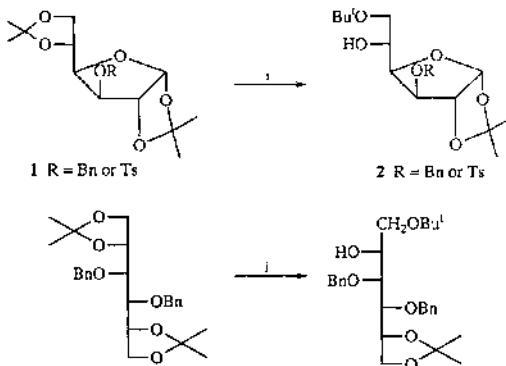
5

Ethers and Anhydro-sugars

1 Ethers

1.1 Methyl Ethers. - A number of mono-*O*-methyl derivatives of a tetrasaccharide have been prepared and their relative binding characteristics to a lectin studied.¹ 3-*O*-Methyl-6-deoxy-L-talose has been prepared and glycosyl-bonded to a tetrapeptide,² and the methylation of some nucleoside derivatives is mentioned in Chapter 20.

1.2 Other Alkyl and Aryl Ethers. - The syntheses of sugar trifluoromethyl ethers has been covered in a review of trifluoromethylation reactions.³ The (3-butenyl) ether group has been used as a base-stable protecting group removable by ozonolysis followed by mild base treatment.⁴ Isopropylidene groups have been converted to mono-*tert*-butyl ethers (Scheme 1) thus effecting an overall selective protection of terminal α -diol moieties. When the reaction was applied to the ester **1** R=Ac, the product was the corresponding deacetylated derivative **2** R=H.⁵ The *O*-tritylation of some monosaccharide derivatives under phase transfer conditions has been described,⁶ and the synthesis of some sugar polyfluoroalkyl ethers has been achieved.⁷



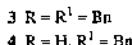
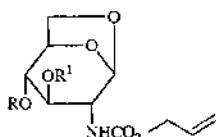
Reagents: *i*, $\text{AlMe}_3\text{-CH}_2\text{Cl}_2$

Scheme 1

A facile new synthesis of 4-*O*-allyl-D-xylopyranose has been reported,⁸ and 1,2,4-tri-*O*-acetyl-3-*O*-allyl-L-fucopyranose has been prepared in a number of steps from D-arabinose.⁹ A number of 2-,3-,4- and 6-*O*-(*n*-alkyl)-D-glucoses have been prepared by standard means (*via* alkylation of

otherwise protected methyl glucoside derivatives), and their behaviour as liquid crystalline materials has been investigated.¹⁰ The use of D-mannitol for the synthesis of some O-alkylated glycerol derivatives is covered in Chapter 18. The synthesis of all O-alkyl D-tetrose and D-pentose stereoisomers derivable from 2,3-O-isopropylidene-D-glyceraldehyde has been achieved using 2-trimethylsilylthiazole as a formyl anion equivalent,¹¹ and the complete assignments of the ¹H-n.m.r. spectra of a number of O-carboxymethyl derivatives of D-glucose have been reported.¹² Both 2,6-di-O-octyl- and 2,3,6-tri-O-octyl-cyclodextrins have been prepared.¹³ (See Chapter 4 for other cyclodextrin derivatives.)

Selective debenzylation of the dibenzyl ether **3** with titanium tetrachloride has afforded the 3-ether **4**.¹⁴ Catalytic transfer hydrogenolysis has been proposed as an excellent method for the selective cleavage of benzyl ethers in pyranoid monosaccharides. An order of reactivity of O-1 > O-2 > O-3 > O-4 > O-6 is given.¹⁵ Carbohydrate benzyl ethers have been oxidized to benzoate esters using catalytic ruthenium tetroxide.¹⁶



1.3 Silyl Ethers. - The selective cleavage of silyl ethers has been achieved using silicon tetrafluoride in dichloromethane or acetonitrile,¹⁷ and the use of methanol as solvent for the tetra-n-butylammonium fluoride-mediated desilylation of silyl ethers in the presence of base-sensitive groups has been described.¹⁸

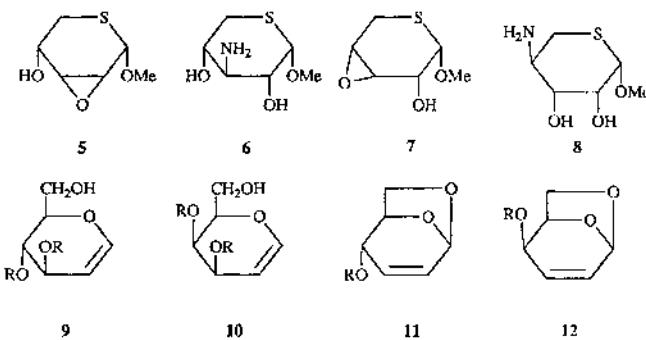
2 Intramolecular Ethers (Anhydro-Sugars)

2.1 Oxirans. - The synthesis of 1,2-anhydro-3,4-di-O-benzyl-6-deoxy- α -D-glucopyranose and its conformational analysis have been reported.¹⁹ A range of epoxides have been prepared by base treatment of bromohydrins, which were made by reaction of hydrogen bromide with aldonolactones.²⁰ A 'one-pot' conversion of vicinal diols into epoxides employs halohydrin ester intermediates generated from cyclic orthoacetates and either acetyl bromide or trimethylsilyl chloride.²¹ Levoglucosenone has been transformed into 1,6:3,4-dianhydro- β -D-talopyranose by way of a *trans*-iodo-acetoxylation of the alkene moiety.²²

Treatment of epoxide **5** with ammonia in methanol has afforded mainly the D-*xylo*-derivative **6**,

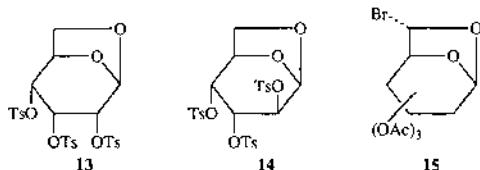
whereas epoxide **7**, under the same conditions, gave only the L-lyxo-derivative **8**.²³ The ring opening of some 2,3-anhydro sugars with *N,N*-diethyl- or dimethyl(trimethylsilyl)amine in the presence of aluminium chloride has afforded *N,N*-dialkylamino sugars.²⁴

2.2 Other Anhydrides. - Syntheses of 1,3-anhydro-2,4-di-*O*-benzyl- β -D-fucopyranose²⁵ and 1,3-anhydro-2,4-di-*O*-benzyl-6-deoxy- β -D-glucopyranose²⁶ by base treatment of the corresponding 3-*O*-acetyl glycosyl chlorides have been achieved. *N*-Acetyl-2,7-anhydroneuraminic acid has been synthesized by intramolecular glycosidation of a thioglycoside derivative using dimethyl(methylthio)sulphonium triflate as sulphur activator.²⁷ The synthesis of per-3,6-anhydro- α - and β -cyclodextrins is covered in Chapter 4.



R = Ac, Bz, or Bn for all of 9 – 12

The thermal decomposition of D-glucose catalysed by H₂SO₄ in aprotic solvents (DMF, DMSO) at 120°C has afforded good yields of levoglucosenone,²⁸ while treatment of partially protected glycol derivatives **9** and **10** with boron trifluoride diethyletherate gave the unsaturated 1,6-anhydro-sugars **11** and **12** respectively.²⁹ Pyrolysis of cellulose in the presence of Cu powder followed by tosylation has produced, as well as the usual products, low yields of the previously unreported anhydrides **13** and **14**.³⁰



The c.i. mass spectra of stereoisomeric 1,5-anhydropentofuranoses, 1,6-anhydrohexofuranoses and 1,6:3,5-dianhydrohexofuranoses are discussed in Chapter 22, and the synthesis of methyl 3-*O*(3,6-anhydro- β -D-galactopyranosyl)- α -D-galactopyranoside and methyl 3,6-anhydro-4-*O*- β -D-

galactopyranosyl- α -D-galactopyranoside are covered in Chapter 3.

The photobromination products **15** of acetylated 1,6-anhydro-D-hexoses with D-glucos-, D-manno- and D-galacto- configurations have been hydrolysed and oxidized to the corresponding carbonyl-containing derivatives which are 6,1-lactones of the corresponding uronic acids.³¹ The synthesis of 1,6-anhydro-2,4-dideoxy- β -D-*threo*-hexopyranose from 1,6-anhydro- β -D-glucopyranose is covered in Chapter 12. Lewis acid catalysed ring opening of 3,5-anhydro-1,2-O-isopropylidene- α -D-xylofuranose with a variety of nucleophiles has generated the corresponding 5-substituted xylofuranose compounds.³²

The ring opening polymerisations of 1,6-anhydro-2,3-di-O-benzyl-4-deoxy- β -D-xylohexopyranose and 1,6-anhydro-2-O-benzyl-3,4-dideoxy- β -D-*erythro*-hexopyranose have generated the corresponding (1 \rightarrow 6)- α -linked hexopyranans,³³ while the copolymerisation of 1,4-anhydro-2,3-O-benzylidene- α -D-ribopyranose with 1,4-anhydro-2,3-di-O-benzyl- α -D-ribopyranose in the presence of antimony pentachloride has been carried out and the structure of the pyranose copolymer was evaluated by ¹³C n.m.r. and polarimetry methods.³⁴

Treatment of 1-O-(α -D-glucopyranosyl)-D-fructose with hydrogen fluoride in pyridine has afforded a 1,1':2,2' dianhydride mixture with the fructose moiety in either the pyranose or furanose form.³⁵ Some novel 1,6-anhydro-lactose derivatives for the synthesis of oligosaccharides containing N-acetyl-lactosamine residues are mentioned in Chapter 4, and a 3,6-anhydroglucofuranose derivative resulting from an unusual molecular rearrangement of a xanthate is described in Chapter 7.

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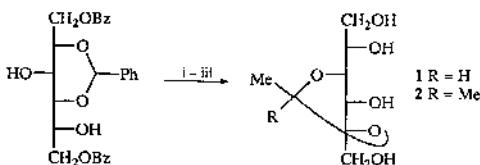
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6 Acetals

1 Methylene, Ethylidene, Isopropylidene, and Benzylidene Acetals

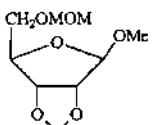
An efficient conversion of L-threitol to its 1,3:2,4-di-O-methylene derivative by use of formaldehyde and HBr, followed by Amberlyst 15 and 4 Å molecular sieves, has been reported.¹ 3,5-O-Ethylidene-**1** and 3,5-O-isopropylidene-D-glucitol (**2**) have been prepared, as shown in Scheme 1, in mediocre and good yield, respectively; both compounds were thermodynamically unstable and very sensitive to hydrolysis.² Improved yields have been claimed in the syntheses of isopropylidene saccharides with acetone in the presence of molecular sieves and toluenesulfonic³ or methanesulfonic⁴ acid.



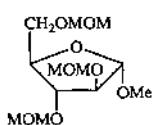
Reagents: i, MeCH(OEt)₂ or Me₂C(OMe)₂, H⁺; ii, MeO⁻, MeOH; iii, Pd/C, H₂

Scheme 1

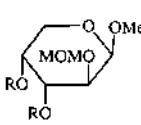
Acetalation of the methyl β -furanoside of D-ribose with dimethoxymethane gave the new methylene derivative **3**, whereas α -arabinose furnished the tri-O-methoxymethyl ether **4** under the same conditions; methyl β -D-arabinoside afforded a mixture of the two products **5** and **6**.⁵ Treatment of L-sorbose with acetone and catalytic quantities of heteropolyacids H₃PW₁₂O₄₀ or H₄SiW₁₂O₄₀ (0.1–0.35%) gave diacetonesorbose in 85% yield.⁶ The methyl β -glycoside monoacetetonides **7** and **8** were obtained in the ratio 7:2 (90% combined yield) on exposure of 2-acetamido-2-deoxy-D-galactose to 2,2-dimethoxypropane and *p*-TsOH in dioxane at 60 °C.⁷ When sucrose was heated in acetone



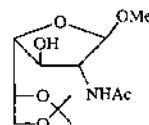
3



4



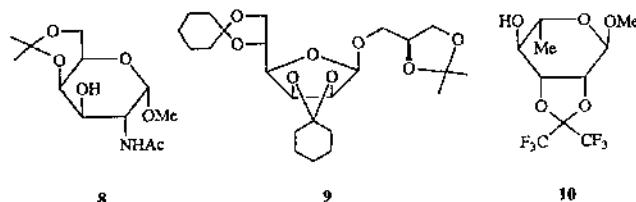
5 R = MOM
6 RR' = CH₂



7

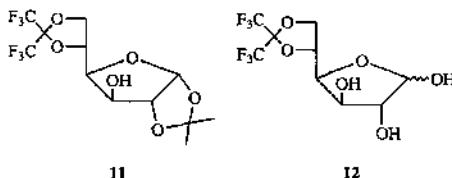
containing iodine, 1,2:5,6-di-O-isopropylidene- α -D-glucofuranose and 2,3:4,5-di-O-isopropylidene- α - and - β -D-fructopyranose were produced in 47, 11, and 37% yield, respectively. Other oligosaccharides gave similarly the stable diacetones of their constituent monosaccharides.⁶

A procedure suitable for the large scale (86 g) preparation of methyl 2,3:4,6-di-O-benzylidene- α -D-mannopyranoside has been published.⁹

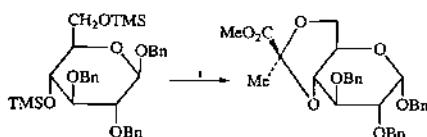


2 Other Acetals

The glycoside 9 of 2,3:5,6-di-O-cyclohexylidene- α -D-mannofuranose has been designed and synthesized for observing enantioselectivity towards asymmetric organic cations in FAB m.s. analysis.¹⁰



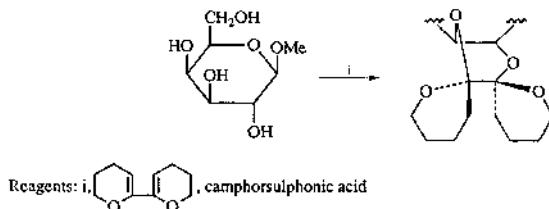
The 2,3-O-hexafluoroisopropylidene acetal 10 was formed almost quantitatively on treatment of methyl α -L-rhamnopyranoside with hexafluoroacetone in the presence of DCC, and the mixed diacetal 11 was similarly obtained from 1,2-O-isopropylidene- α -D-glucofuranose, although in moderate yield only. Compound 11 was selectively hydrolysed to the monoacetal 12, since hexafluoroacetonide groups are more stable towards acid than non-fluorinated ones.¹¹



Reagents: i, MeCOCO₂Me, TMSOTf

Scheme 2

The Lewis acid-catalysed acetalations of alkyl D-gluco- and D-galactopyranoside-4,6-diols and their 4,6-bis(trimethylsilyl) ethers with methyl 2,2-(diphenylthio)propanoate or methyl pyruvate, respectively, have been studied in detail. It was observed that these reactions are often accompanied by anomeration and by isomerization of the initial, kinetic acetal to the thermodynamically stable diastereomer with an axial CO₂Me group. An example is given in Scheme 2.^{12,13} The 4,6-O-methyl pyruvate-based acetal 14 has been synthesized from benzyl α-D-mannopyranoside via the 4,6-O-(1,1,3,3-tetraisopropyldisiloxane-1,3-diy)-protected derivative 13; this procedure requires fewer protection/deprotection steps than use of the more common 4,6-bis(trimethylsilyl) ether as intermediate.¹⁴

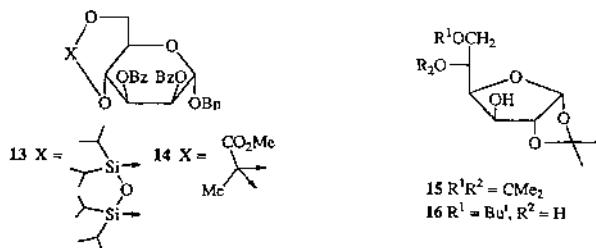


Scheme 3

Bis-dihydropyran has been employed for the selective protection of diequatorial vicinal diols, as shown in Scheme 3.¹⁵

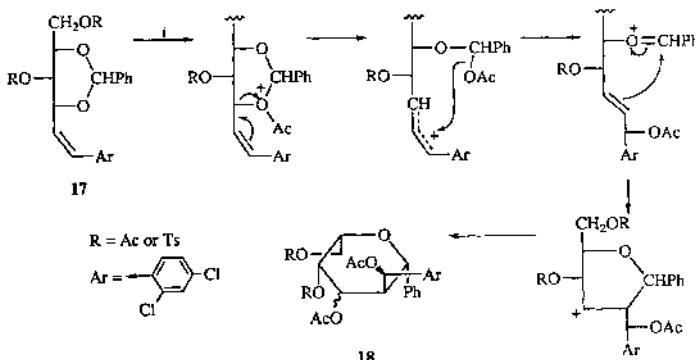
3 Reactions of Acetals

A non-aqueous method for the deprotection of isopropylidene and benzylidene acetals by transacetalation with a glycol (*e.g.*, propylene glycol) and catalytic TsOH in dichloromethane has been published.¹⁶ Regioselective mono-protection of terminal diols has been achieved by treatment of the appropriate isopropylidene derivatives with trimethylaluminium, thus converting them to primary mono-*tert*-butyl ethers (*e.g.*, 15 → 16).¹⁷ Under acetolysis conditions, certain unsaturated 2,4-O-benzylidenehexitols, for example compounds 17, rearranged to C-glycosylbenzene derivatives



18. A complex mechanism involving participation of the benzylidene group and acetyl migration, as shown in Scheme 4, has been proposed.¹⁸

Diacetoneglucose has been used in a study of the mechanism of the Mitsunobu reaction with tributylphosphine in place of the usual triphenylphosphine.¹⁹



Reagents: i. Ac₂O, H₂SO₄

Scheme 4

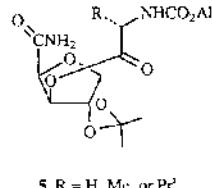
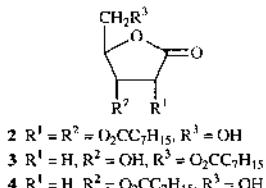
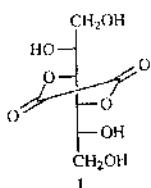
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7 Esters

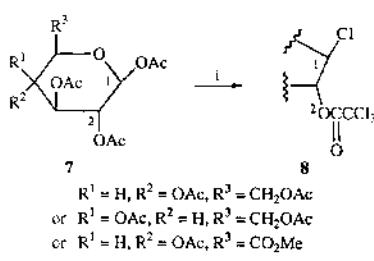
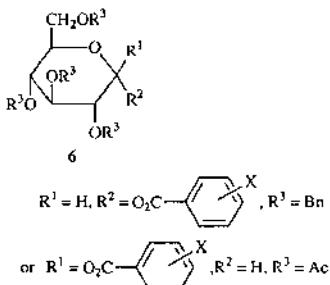
1 Carboxylic Esters

1.1 Synthesis and Reactions.— The high sensitivity of Raman spectroscopy to the stereochemistry of monosaccharide acetates is referred to in Chapter 2, and the reduction of propionates to propyl ethers by Et₃SiH in the presence of both trimethylsilyl triflate and boron trifluoride etherate is covered in Chapters 5 and 18.



Cyclic oxalate has been introduced as a new, acid-stable, base-labile cyclic protecting group for diols. Compound 1, for example, was prepared from 1,2:5,6-di-*O*-isopropylidene-D-mannitol by treatment with Et₂OCCOCl in the presence of triethylamine, followed by *p*-TsOH in wet ether.¹

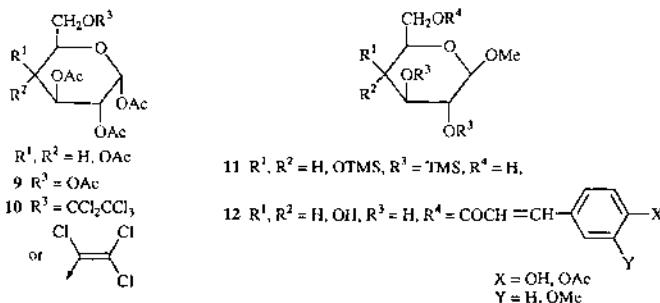
An efficient, facile preparation of an anomeric mixture of 1,2-di-*O*-acetyl-3,5-di-*O*-benzoyl-D-xylofuranose, a versatile intermediate for the synthesis of β -D-pentofuranosyl nucleosides, from commercial D-xylose has been described.² The D-ribonolactone diacetate 2 and the derivatives 3 and 4 of 2-deoxy-D-*erythro*-1,4-pentonolactone have been prepared as conformationally restricted analogues of diacyl glycerol by conventional procedures.³ Further, similar monoesters of 2-deoxy-D-*erythro*-1,4-pentonolactone and their *threo*-isomers, as well as some of their enantiomers, have been



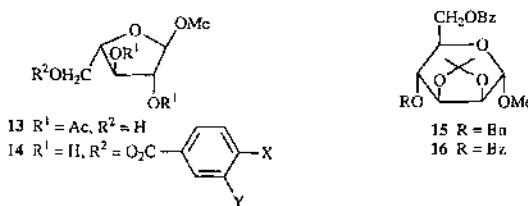
Scheme 1

synthesized from L-ascorbic- and D-isoascorbic-acid, respectively.⁴ The N-protected amino acid esters **5** of 1,2-O-isopropylidene- α -D-xyluronamide have been employed as acylating agents in the synthesis of peptides.⁵

Standard methodology was used to synthesize the tetra-O-benzyl- and tetra-O-acetyl-D-glucosyl esters **6** of substituted benzoic acids ("D-glucopyranosyl aspirin esters").⁶ The 2-O-trichloroacetyl- β -D-glycopyranosyl chlorides **8** were obtained as the major products from the corresponding β -peracetates **7** following the method of Lemieux and Huber (1953) as shown in Scheme 1. Under the same conditions, the α -anomeric peracetates **9** gave 6-O-modified products **10**. The use of compounds **8** in the preparation of (1 \rightarrow 2)-linked disaccharide glycosides is covered in Chapter 3.⁷



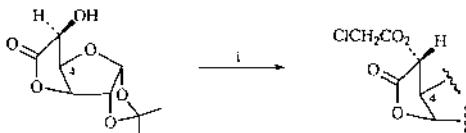
The 6-O-(substituted cinnamoyl) esters **12** of methyl β -D-gluco- and -galacto-pyranoside were obtained via the tri-O-trimethylsilyl ethers **11**. In the preparation of the corresponding primary monoesters **14** of methyl α -L-arabinofuranoside, on the other hand, acetyl protecting groups were employed, and the required selective hydrolysis of acetates in the presence of aromatic esters (**13** \rightarrow **14**) was achieved with 10% pyrrolidine in 95% ethanol.⁸ The preparation of mono- and di-formates, -acetates, and -benzoates of etoposide is covered in Chapter 19.



Carbohydrate monobenzyl ethers have been oxidized to the corresponding benzoates (e.g., **15** \rightarrow **16**) by $\text{RuCl}_3/\text{NaIO}_4$ in $\text{CCl}_4/\text{CH}_3\text{CN}/\text{H}_2\text{O}$ in 40-80% yield. Debenylation was minimal in this solvent system and protecting groups, apart from allyl ethers, were stable.⁹ Chloroacetic acid was found to be an excellent reagent for the esterification of sterically congested alcohols under Mitsunobu conditions. One of the two carbohydrate examples given is shown in Scheme 2.¹⁰ Iodine

has been recommended as catalyst for the mild acetolysis of 1,6-anhydroglucopyranose derivatives.¹¹

Stereospecific conversion of peracetylated hexopyranosyl halides to 1-esters of complex carboxylic acids has been achieved in excellent yields by use of cesium salts (e.g., cesium salts of amino acids), a method borrowed from peptide chemistry, the "cesium effect" ensuring a strictly S_N2 process.¹²



Reagents: i. ClCH₂CO₂H, DEAD, PPh₃

Scheme 2

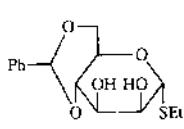
The syntheses and thermal properties of cellobiose octaalkanoates (C₇-C₁₄),^{13,14} chitobiose octaalkanoates and chitotriose undecaalkanoates,¹⁵ and of cello- and chito-oligosaccharide peralkanoates¹⁶ have been described. The emulsifying properties of a series of perfluoroalkylated fatty acid monoesters of α,α -trehalose and sucrose have been evaluated.¹⁷

α -D-Fructofuranose 1,3,4,6-tetrabenzoate was obtained selectively, in 62% crystalline yield, by conventional benzoylation (5 molar equiv. BzCl in pyridine) of D-fructose. Its use in a study of the anomeric reactions of D-fructofuranose is covered in Chapters 3 and 10.¹⁸ Benzyl 2,3-O-isopropylidene- α -D-manno- and - α -D-gluco-furanoside have been regioselectively acetylated or benzoylated at the primary positions either directly or via tin intermediates.¹⁹⁻²¹

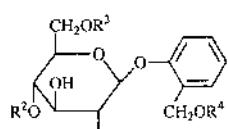
Further examples of 1,2-alkylthio group migration in the attempted selective 2-benzoylation of alkyl 1-thioglycopyranoside 2,3-diols, such as compound 17, via hydrolysis of their 2,3-orthoesters have been reported (see Vol.25, Chapter 7, ref.4).^{22,23} The problem was, however, avoided either by use of very low concentrations of *p*-TsOH²⁴ or by thorough removal of the alcohol released²² in the orthoester formation, or by performing the hydrolysis of the orthoester in acetonitrile instead of DMF.²³

The natural product tremuloidin (20) has been synthesized from salicin (18) by selective benzoylation of the partly protected intermediate 19 by use of benzoyl cyanide, followed by deprotection.²⁵ A practical one-pot technique for the conversion of methyl α -D-gluco- and -mannopyranoside to their 2,3,4-tri-O-(4-methylbenzoates) has been described.²⁶

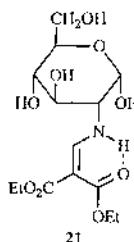
Some factors influencing the selectivity of the acetylation of 1,6-anhydro- β -D-glucopyranose have been discussed in a theoretical paper.²⁷ The expected mixture of mono- and di-benzoates was formed when methyl β -D-arabinopyranoside was exposed to 1 or 2 molar equiv. of benzoyl chloride in pyridine at -40 °C. The order of reactivity was concluded to be OH-2>OH-4>OH-3 for mono- and OH-2>OH-3>OH-4 for di-benzoylation.²⁸ For the 2-deoxy-2-amino- α -D-glucose derivative 21,



17



18 $R^1 = R^2 = R^3 = R^4 = H$
 $R^1 = H, R^2, R^3 = \text{PhCH} \leftarrow, R^4 = \text{Tr}$
 $R^1 = \text{Bz}, R^2 = R^3 = R^4 = H$

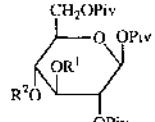
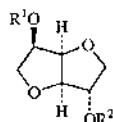
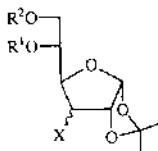
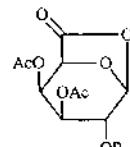


21

the order of reactivity in the conventional benzoylation ($\text{BzCl}/\text{pyridine}$) was $\text{OH-6} > \text{OH-3} > \text{OH-1} = \text{OH-4}$; with 3 molar equiv. of reagent at -15°C , a 37% yield of the primary monobenzoate was obtained.²⁹ Pivaloylation of D-glucose with excess of PivCl in pyridine gave the tetraesters **22** and **23** in 63 and 24% yield, respectively, and only 13% of the pentapivaloate **24**. The main product **22** was selectively deprotected at the anomeric centre by treatment with hydrazine acetate for use in disaccharide synthesis (see Chapter 3).³⁰ In a different pivaloylation study of D-glucose under similar conditions two pathways, a major and a minor one, were found with successive esterification at O-6, -1, -3, -4, and -2, and at O-6, -2, -1, -4, and -3, respectively.³¹

The lipase-catalyzed esterification of glucitol, glucose, and fructose with oleic acid in buffered 2-pyrrolidone has been discussed in a symposium report.³²

The isomerically pure 1,4:3,6-dianhydro-D-glucitol monoacetates **27** and **28** were available by selective esterification of the diol **25** or selective hydrolysis of the diacetate **26**, respectively, with SAM II lipase (a highly selective lipase from *Pseudomonas* sp.).³³

**22** $R^1 = \text{Piv}, R^2 = H$ **23** $R^1 = H, R^2 = \text{Piv}$ **24** $R^1 = R^2 = \text{Piv}$ **25** $R^1 = R^2 = H$ **26** $R^1 = R^2 = Ac$ **27** $R^1 = Ac, R^2 = H$ **28** $R^1 = H, R^2 = Ac$ **29** $R^1 = R^2 = Ac$ **30** $R^1 = Ac, R^2 = H$ **31** $R^1 = H, R^2 = Ac$ $X = H, \text{OMe}, \text{OAc},$
or NHAc **32** $R = Ac$ **33** $R = H$

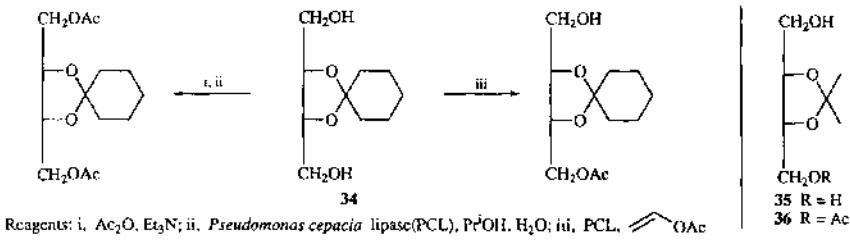
The selective deacetylation of methyl 2,3-di-O-acetyl- α -D-threoside by use of porcine liver esterase afforded the 3-O-acetate exclusively. The β -anomer gave a mixture of the 2- and 3-monoacetates without any trace of fully deacetylated product.³⁴ Hydrolysis of a series of 1,2-isopropylidene- α -D-hexofuranose 5,6-diacetates **29** by the same enzyme gave initially the 5-acetates **30**, which quickly isomerized to the 6-acetates **31**.³⁵ Selective secondary acylation of 2-deoxynucleosides was achieved with Amano PS lipase and oxime esters in pyridine at 60°C ,³⁶ and

numerous new examples of selective primary acylation of hexoses and pentoses by acyl transfer from oxime esters under lipase-catalysis have been reported (see Vol.25, Chapter 7, ref.17).³⁷

Monoacetylation by use of lipase/trifluoroethyl butanoate systems occurred predominantly at the 2-position of methyl 6-O-butanoyl- α -D-glucopyranoside and at the 4-position of methyl 6-deoxy- α -L-glucopyranoside.³⁸ Methyl 4,6-O-benzylidene- α - and - β -D-glucopyranoside were preferentially acetylated at O-2 and O-3, respectively, by lipase/vinyl acetate.³⁹ Exposure of the galacturon-6,1-lactone triacetate **32** (see Chapter 16 for its synthesis) to wheat germ lipase gave the diacetate **33** in modest yield.³⁸

6-O-Butanoyl-D-glucose was produced from the unprotected free sugar and butanoic acid by a *Nicotiana plumbaginifolia* suspension cell culture.⁴¹ A neural network has been trained to predict and optimize the enzymic preparation of surface active ethyl 6-O-acyl- α -D-glucopyranosides (see structure **21**, Vol.24, p.88).⁴² Selective primary deacetylation by yeast esterase and subsequent acetyl migration were important steps in a transformation of GlcNAc to GalNAc which is covered in Chapter 2.

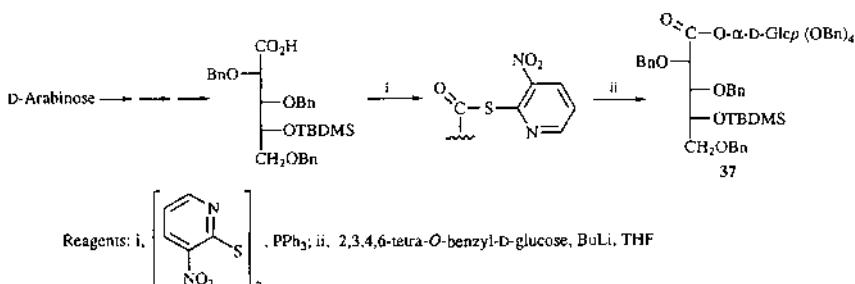
The 6'-monobutanoate of methyl β -lactoside was prepared by subtilisin-catalyzed ester transfer from 2,2,2-trichloroethyl butanoate. Mesitylation gave the hexaester which was converted to the 6'-fluoride (see Chapter 8).⁴³ 2,3,6,3',4'-Penta-O-acetylsucrose, the precursor of sucralose, was available from the octaacetate by selective hydrolysis first with alcalase, then with AP-6 lipase. The main by-product, the 2,3,4,3',4'-pentaacetate, was readily converted to the required isomer by acetyl migration on treatment with phosphate buffer.⁴⁴ An enzymatic acylation of cyclodextrin is referred to in Chapter 3.



Scheme 3

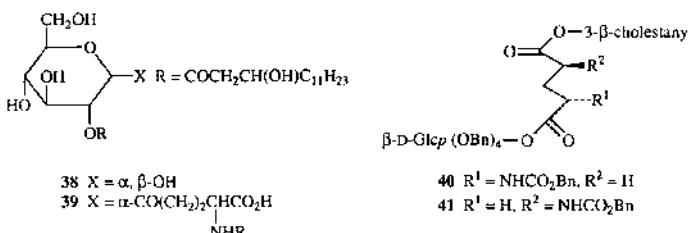
High yields and >99% ee were achieved in the lipase-mediated desymmetrization of 2,3-O-cyclohexylidene-erythritol **34**, as shown in Scheme 3.⁴⁵ The acetonide **35** was similarly asymmetrically acetylated to give the monoacetate **36**, which was employed in a synthesis of (+)-*endo*-brevicomitin (see Chapter 24).⁴⁶ The enzymatic kinetic resolution of racemic synthetic glycals is referred to in Chapter 13.

The 1-O-acyl-tetra-O-benzyl- β -D-glucopyranose derivative **37**, an intermediate in the synthesis of sucrose by redox glycosidation (see Chapter 3), was obtained from D-arabinose and 2,3,4,6-tetra-



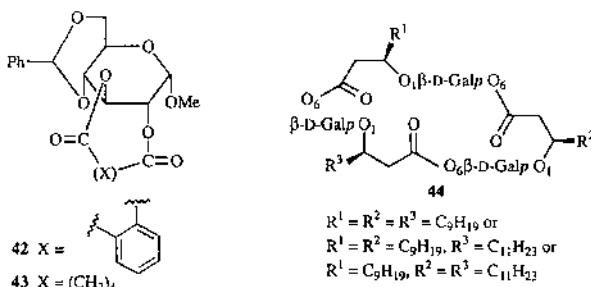
Scheme 4

O-benzyl-D-glucose, as shown in Scheme 4,⁴⁷ DCC-Promoted coupling was used to prepare the aminoglycosyl ester **39**, an acyclic analogue of lipid A, from the free sugar derivative **38**.⁴⁸ 1-(Cholestan-3 β -yl)-5-D-glucopyranosyl-L-glutamate, as an anomeric mixture of the perbenzyl ethers **40**, and their isomers **41** were obtained by acetylation of 2,3,4,6-tetra-*O*-benzyl-D-glucose with the appropriate acyl chlorides.⁴⁹ The ester glycosidic linkages of terpenoid 3,28-*O*-bisglycosides were selectively cleaved by hydrothermolysis.⁵⁰

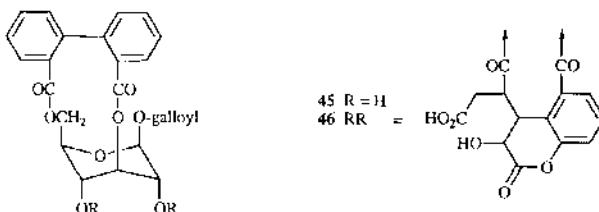


Dibutylstannylene-mediated condensation of methyl 4,6-*O*-benzylidene- α -D-glucopyranoside with phthaloyl or glutaryl dichloride gave dilactones **42** and **43**, respectively, and as by-products tetralactones (see structure **22**, Vol.23, p.78).⁵¹

Primary AZT esters of lipidic amino acid oligomers are covered in Chapter 20.



1.2 Isolation from Natural Sources.— Koelzioside, an iridoid glycoside from the plant *Scrophularia Koelzii*, contains a 4-*O*-acetyl-2,3-di-*O*-cinnamoyl- α -L-rhamnopyranosyl residue.⁵² Berchemolide, a novel, vanillic acid-bridged diglucofuranose, was isolated from the stems of *Berchemia racemosa*.⁵³ The fatty acid-bridged triglycosides Arthrobacilins A, B, and C (**44**) are new cell-growth inhibitors produced by *Arthrobacter*.⁵⁴ The structure of a component of the plant constituent calonyctin A which contains ester-linked sugar residues, is referred to in Chapter 19.



A symposium report on the convenient and generally applicable determination of acyl group orientation in hydrolyzable tannin oligomers has appeared.⁵⁵ The *O*-2,*O*-4-cyclic diesters **45** and **46** of glucosyl β -D-galactoate, termed corilagin and chebulagic acid, respectively, were extracted from the Chinese plant *Erodium stephanianum*.⁵⁶ 1,2,3,4,6-Penta-*O*-galloyl- β -D-glucopyranose was found to be a potent inhibitor of certain NADH dehydrogenases.⁵⁷ Three new hydrolyzable tannins from *Coriaria japonica*, coriarins G, H, and I, have sedoheptulose residues ester-linked through C-1; they are present as mixtures of anomeric and ring-size isomers.⁵⁸ Tannins with gluconic acid cores are covered in Chapter 16.

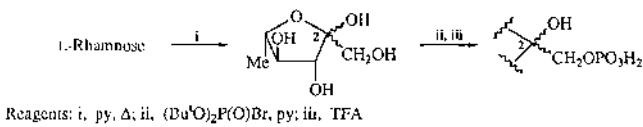
2 Phosphates and Related Esters

¹H-N.m.r. spectroscopic studies on the phosphoglucoisomerase-catalyzed interconversion of hexose phosphates are covered in Chapter 21.

In continuation of earlier work with over-expressed enzymes from *E. coli* (see Vol.25, Chapter 7, ref.44), D-tagatose 1,6-diphosphate has been synthesized from dihydroxyacetone by use of a combination of several enzymes including a newly isolated tagatose 1,6-bisphosphate aldolase.⁵⁹ An efficient synthesis of D-fructose 1,6-diphosphate by use of four enzymes in a one pot operation has been described.⁶⁰ D-[1-¹³C] Fructose 6-phosphate has been prepared from ¹³C-enriched formaldehyde and D-ribose 5-phosphate by a formaldehyde fixing enzyme system from *Methylomonas aminofaciens*,⁶¹ and various ¹³C-substituted D-fructose phosphates have been obtained by enzymic methods from ¹³C-substituted pyruvate or L-alanine.⁶²

D-Glucose-, D-galactose-, D-mannose-, and L-rhamnose-1-phosphate have been prepared from suitably protected free sugars by phosphorylation with diphenylchlorophosphate/DMAP, a method

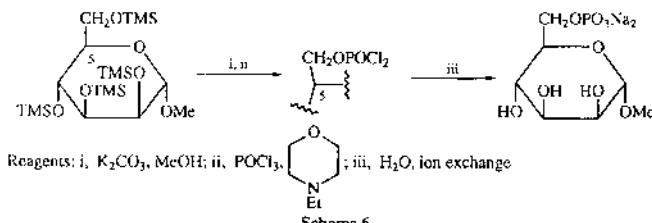
which furnishes in the first instance β -products. Whereas the manno- and rhamno-configurated β -glycosyl phosphate triesters were stable, the β -glucosyl- and β -galactosyl-diphenylphosphates isomerized quickly to the α -anomers. The diphenylphosphate groups were readily displaced by azide to give the glycosyl azides of opposite anomeric configuration.⁶³ The preparations of 2-deoxy-, 4-deoxy-, and 6-deoxy- α -D-mannosyl phosphate have been carried out from appropriate methyl deoxy- α -D-mannoside precursors via the 1-chlorides from which the halide was displaced with silver dibenzyl phosphate.⁶⁴



Scheme 5

Several rare ketose 1-phosphates have been obtained by use of L-rhamnulose kinase on the corresponding ketoses which were, in turn, available by isomerization of the appropriate 2R- or 2S-aldooses (D-ribose, L-lyxose, L-mannose, L-talose, D-glucose, D-allose, L-rhamnose, L-fucose) with L-rhamnose- or L-fucose-isomerase, respectively.⁶⁵ β -L-Fucose 1-phosphate and the thermodynamically less stable β -anomer of GDP fucose were accessible by use of enzymatic processes.⁶⁶ A new, simple, chemical preparation of rhamnulose 1-phosphate from L-rhamnose is outlined in Scheme 5.⁶⁷

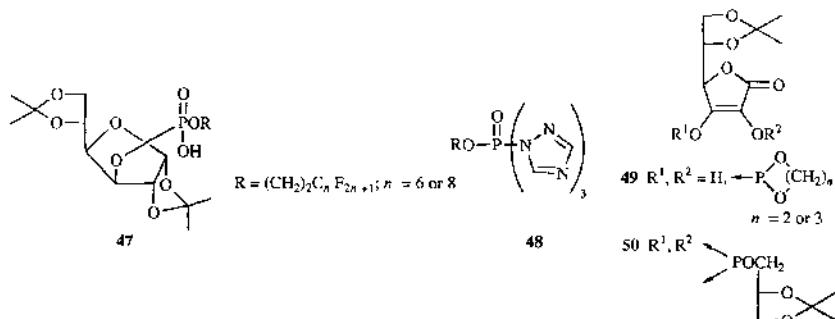
The synthesis of methyl D-mannoside 6-phosphate, shown in Scheme 6, has been executed on a 35 g scale. The method has also been applied, on a smaller scale, to the preparation of several other alkyl hexoside 6-phosphates and, with minor changes, to that of D-mannose 6-phosphate.⁶⁸ Several monosaccharide phosphates have been converted to their phosphofluoridates by use of 2,4-dinitrofluorobenzene, and the mechanism of the reaction has been discussed.⁶⁹



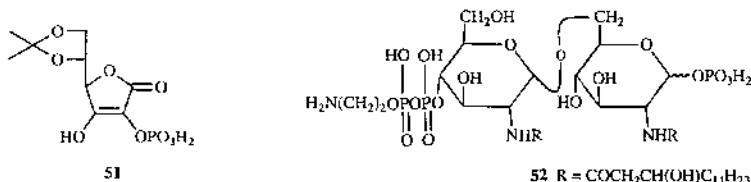
Scheme 6

The diacetone-D-glucosyl-3-O-(N,N-diethylamido)thiophosphates of the lipid-soluble vitamins D₂, D₃, and E have been obtained in a one-pot procedure by sequential addition of the vitamin, the sugar, and sulfur to phosphorous acid tris(N,N-diethyl)amide in the presence of catalytic iodine.⁷⁰ In the preparation of the 3-[sodium-2-(perfluoroalkyl)ethyl phosphates] 47 of diacetone glucose,

symmetrical phosphorylation to give phosphorodiesters was avoided by use of ditriazolides 48.⁷¹ The stereochemistry of the epoxide-induced oxidative rearrangement of ribonucleoside 2',3'-cyclic phosphorothioates to the corresponding 2',3'-phosphates has been investigated,⁷² and the synthesis and properties of 2'-deoxyribonucleoside 5'-phosphites labelled with tritium in the phosphate group have been reported.⁷³ Several hydroxoaqua tetramine cobalt(III) complexes were found to effect selective 5'-hydrolysis of adenosine cyclic 3',5'-monophosphate.⁷⁴



L-Ascorbic acid has been converted to the cyclic alkyleneephosphites **49** by reaction with alkylene chlorophosphites, and to the 2',3'-cyclic phosphites **50** by treatment with phosphinidyne triimidazole followed by isopropylideneglycerol. Compounds **49** and **50** were treated with sulfur or selenium to give the corresponding thio- or seleno-phosphates.^{75,76} The 2-phosphate **51** of 5,6-O-isopropylidene-D-*erythro*-ascorbic acid was prepared by use of POCl_3 under basic conditions. As minor by-products, the 2-diphosphate and the 2,2'-phosphodiester were formed.⁷⁷



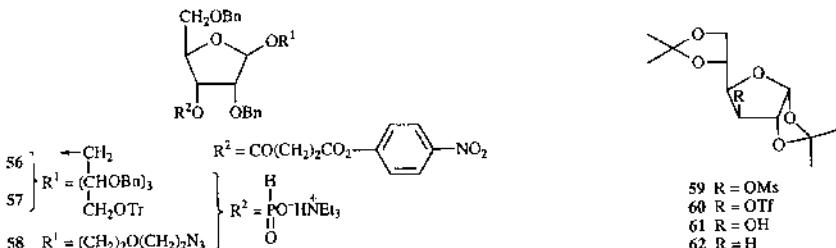
The structure of a lipid A sugar phosphate moiety has been established as **52** on the basis of chemical and n.m.r. data.⁷⁸ The hydrogenphosphonate approach was used in the synthesis of sucrose 6'-(D-glucos-2-yl)phosphate, thought to be agrocinopine C,⁷⁹ the dimeric biopolymer fragments **53**-**55**,⁸⁰ a similarly (1→3)-phosphate linked tetrameric fragment,⁸¹ and cyclic as well as linear oligo(mannosyl phosphates).⁸²

53 α-D-Gluc-P-6-D-Man

54 α -D-GlcNAc-P-6-D-Man

55 α -D-GlcNAc-P- α -D-GlcNAc ($n = 3$ or 4)

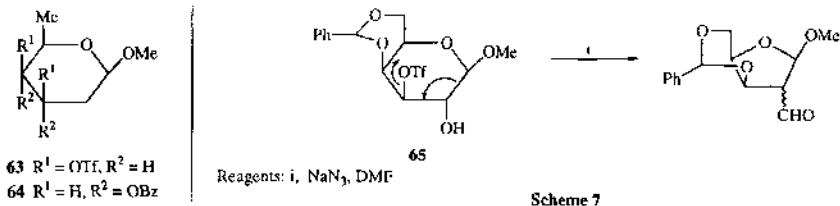
The solid-phase synthesis of a hexameric polyribosyl ribitol phosphate fragment has been achieved with compounds **56**, **57**, and **58**, respectively, as chain-initiation-, chain-propagation-, and chain-terminating-linker-monomers.⁵³



3 Sulfonates and Related Esters

Tosylation of the four D-pentono-1,4-lactones with 2.0–2.3 equiv. TsCl in pyridine gave as the main products, the 2,5-ditosylates. On similar treatment, the eight D-hexono-1,4-lactones furnished mainly the 2,6-ditosylates, and D-glycero-D-gulo-heptonolactone yielded the 2,7-ditosylate. Monotosylation of D-erythro- and L-rhamnono-lactone took place at O-2.⁵⁴

On irradiation in methanolic solutions containing KI and NaHCO₃, carbohydrate mesylates, e.g., compound **59**, were hydrolyzed to the corresponding alcohols without concomitant reduction⁵⁵ in contrast to triflates, such as compound **60**, which furnished hydrolysis **61** and deoxygenation **62** products in roughly equal proportions.⁵⁶ The vicinal ditriflate **63** was transformed cleanly to the dibenzoate **64** on treatment with Bu₄NBOB2; more often, however, such double displacements were accompanied by elimination and/or hydrolysis due to neighbouring group participation (see Vol.25, Chapter 7, ref.72).⁵⁷ Diequatorial, vicinal diol monotriflates underwent, in the main, S_N2 displacement and epoxide formation, respectively, on exposure to soft, non-basic (SMe, N₃) and basic (F, t-Bu) nucleophiles. The methyl α -D-galactoside derivative **65**, however,⁵⁸ and several diol monotriflates with axial/equatorial arrangements⁵⁹ suffered ring contraction under these conditions, as illustrated in Scheme 7.



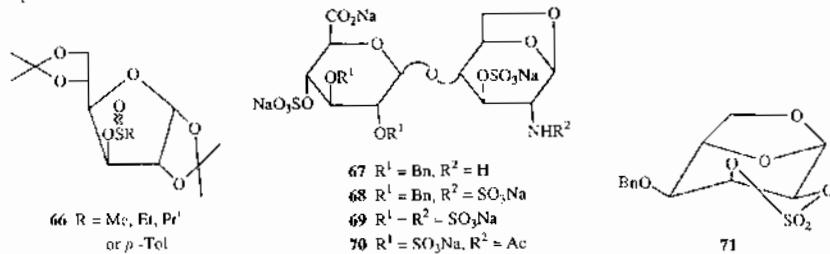
Scheme 7

A rationale has been provided for the formation of the *S_s* and *R_s* diastereomers of sulfonates **66** on reaction of diacetone glucose with alkane- (or arene)-sulfinyl chlorides in ethyldiisopropylamine and pyridine, respectively (see Vol.25, Chapter 7, ref.67).⁹⁰

4 Other Esters

A review on the use of cyclic sulfites and cyclic sulfates as epoxide equivalents contained a number of applications to carbohydrate chemistry.⁹¹

A study on regioselectivity in the sulfation of galactosides with sulfuric acid/DCC led to the conclusion that reaction at the primary position is predominant.⁹² In the course of liquid crystal studies, the 6-sulfates of dodecyl α - and β -D-glucopyranoside and a mixture of tetradecyl β -maltose 6- and 6'-sulfate were prepared by use of SO₃/pyridine.⁹³ Methyl 2-deoxy-2-sulfamino- α -D-glucopyranoside 3-sulfate has been synthesized and subjected to acid and base conditions as a model for anticoagulant activity of heparin under these conditions.⁹⁴ The syntheses and conformations of sulfated derivatives **67-70** of 1,6-anhydro-4-O-(β -D-glucopyranosyluronate)- β -D-glucose have been described. The monocyclic pyranose rings of the two most highly sulfated compounds **69** and **70** were found to assume ^{3,0}B conformations to achieve maximal charge separation.⁹⁵



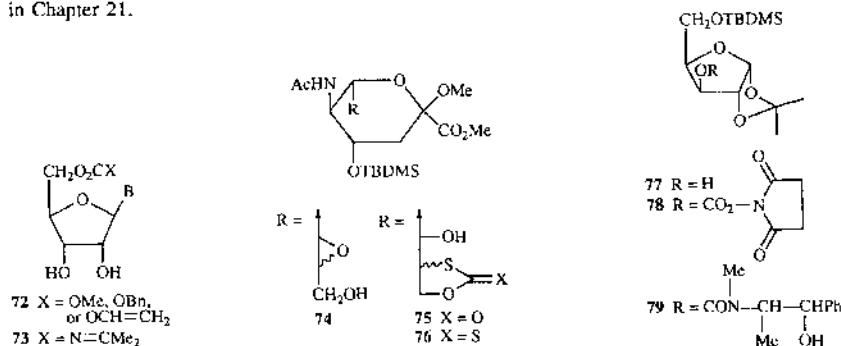
A series of five-membered cyclic sulfates have been synthesized by treatment of pyranoid diols with SOCl₂, followed by oxidation with RuCl₃/NaIO₄; they were opened with LiN₃ with good selectivity, generally by attack at the equatorially substituted centre, to give, after hydrolysis of the monosulfates, azidodeoxy compounds. Surprisingly, however, the cyclic ester **71** gave 1,6-anhydro-3-azido-4-O-benzyl-3-deoxy- β -D-idose, the product of diequatorial opening, in high yield.⁹⁶ The use of a cyclic sulfate in chain-extension reactions is covered in Chapter 2. Selective primary desulfation of methyl α -D-galactopyranoside 1,6-disulfate has been achieved on a preparative scale by treatment of the pyridinium salt with *N,O*-bis-(trimethylsilyl)-acetamide or -trifluoroacetamide.⁹⁷

Benzyl β -D-glucopyranoside 2-sulfate has been isolated from the plant *Salvadora persica*.⁹⁸

The nitrations of cyclodextrins and of meso-erythritol are referred to in Chapters 4 and 18,

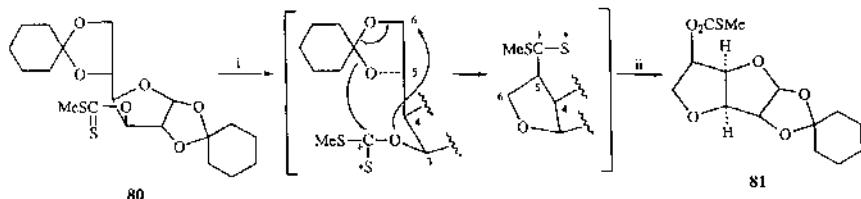
respectively, the denitrations of 2-azido-monosaccharide 1-nitrates in Chapter 10, and i.r. studies on monosaccharide nitrates in Chapter 22.

Diphenyl-3,3'-diboronic acid complexes of disaccharides are covered in Chapter 22, and a reference to n.m.r. spectroscopic studies on 1,2-orthoesters in the gluco- and galacto-series is found in Chapter 21.



Ribo- and deoxyribo-nucleosides were alkoxycarbonylated under catalysis by a *Candida antarctica* sp. lipase, using alkoxycarbonyloximes as donors. Adenosine and uridine, for example, afforded products **72** and **73**.⁹⁹ Cyclic thionocarbonates have been prepared from sugar diols by use of CS₂ under phase transfer conditions,¹⁰⁰ and from sugar tetrols by use of thiophosgene and dibutyltin oxide.¹⁰¹ On heating in toluene in the presence of dibutyltin oxide or bis(tributyltin) oxide, cyclic thionocarbonates gave the corresponding carbonates in satisfactory yields.¹⁰² The *N*-acetylneuraminic acid epoxides **74** were transformed into mixtures of the cyclic mono-**75** and di-thiocarbonates **76** on treatment with diimidazolyl thiocarbonate.¹⁰³

N,N'-Disuccinimidyl carbonate reacted with the ribose derivative **77** to give the mixed active carbonate **78**, which was used to alkoxycarbonylate amines. The resulting carbamates, e.g., compound **79** from ephedrine, are of interest in medicinal chemistry.¹⁰⁴ The xanthate **80** underwent an unusual radical rearrangement, as outlined in Scheme 8, as the result of an electron transfer process induced by (p-BrC₆H₄)₂NSbCl₆ in the presence of light. The end product was the 3,6-anhydrofuranose derivative **81**.¹⁰⁵



Reagents: i. (p-BrC₆H₄)₂NSbCl₆, h v; ii. H₂O

Scheme 8

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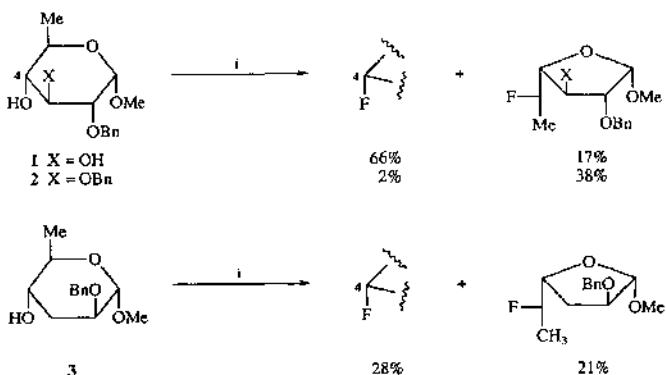
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1 Fluoro-sugars

Protected β -thioglycosides have been converted rapidly and efficiently by dimethyl (methylthio)sulfonium tetrafluoroborate into the corresponding α -glycosyl fluorides,¹ while tetra-*O*-acetyl- α -D-glucopyranosyl fluoride has been rearranged in anhydrous HF to the 2,3:5,6-diacetoxonium ion of α -D-mannofuranosyl fluoride.² The synthesis of 3,4,5-tri-*O*-benzyl-7-*O*-*t*-butyldiphenylsilyl-1-*O*-(2,2,2-triphenyl)ethyl-D-*gluco*-2-heptulopyranosyl fluoride has been described.³

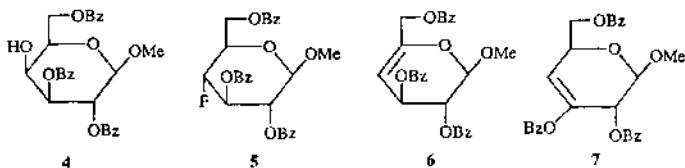
An extensive review on trifluoromethylation reactions has covered syntheses of trifluoromethyl glycosides, sugar trifluoromethyl ethers and 6-deoxy-6,6,6-trifluorohexoses.⁴ Another synthesis of a 2,3,6-trideoxy-6,6,6-trifluoro-hexose featured an enzymic resolution step.⁵ Glucosidase has been used to convert 5-deoxy-5-fluoro-D-glucofuranose into 5-deoxy-5-fluoro-D-fructopyranose in high yield,⁶ and further uses of deoxyribose-5-phosphate aldolase employing fluoroacetone as a substrate has given rise to deoxyfluoro sugars.⁷ Treatment of tri-*O*-acetyl-D-galactal with XeF_2 followed by hydrolysis has afforded 2-deoxy-2-fluoro-D-galactose,⁸ and the synthesis of 5-azido-3,5-dideoxy-3-fluoro-1,2-*O*-isopropylidene- α -D-glucofuranose by standard methods has been reported.⁹ Benzyl 3-*O*-benzyl-4,6-*O*-benzylidene- β -D-*arabino*-hexopyranosid-2-ulose, when treated with DAST, gave the corresponding 2,2-difluoride, which on hydrogenolytic deprotection afforded 2-deoxy-2,2-difluoro-D-*arabino*-hexose. This is a rapid synthesis, said to be suitable for ¹⁸F work.¹⁰ When alcohols **1-3** (Scheme 1) were allowed to react with DAST, participation by the ring oxygen atom was observed so that both the 4-fluorides with retained configuration and ring contracted 5-fluorofuranosides were obtained.¹¹ On the other hand the alcohol **4** with DAST afforded the product of displacement with inversion **5** along with lesser amounts of the two elimination products **6** and **7**.¹² Treatment of 3-*O*-benzyl-4-*O*-*t*-butyldimethylsilyl-1,2-*O*-isopropylidene- β -D-fructopyranose with DAST gave the corresponding 5-deoxy-5-fluorosorbose derivative which was converted into 2,6-dideoxy-2-fluoro- α -L-talopyranose via a head-to-tail inversion.¹³

Epoxide **8** (Scheme 2) has been opened by fluoride ion with good regioselectivity affording mostly (25:1) fluoride **9** which was converted into 3'-deoxy-3'-fluoro-thymidine.¹⁴ The very similar epoxide **10** has been treated with titanium reagents (*e.g.* $(\text{PrO})_2\text{TiF}_2$) to get the fluorinated product analogous to **9**, but in lower yield.¹⁵ A number of conditions have been evaluated for opening

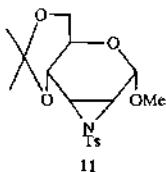
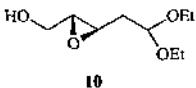


Reagents: i, DAST

Scheme 1

Reagents: i, $\text{Bu}_4\text{NH}_2\text{F}_3$, 150 °C

Scheme 2



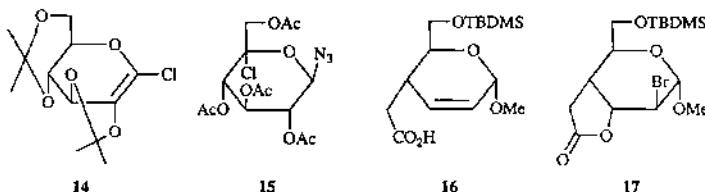
methyl 2,3-anhydro- α -D-allopyranoside with fluoride to get the 3-deoxy-3-fluoro-glucoside rather than the 2-deoxy-2-fluoro-altroside. Using KHF_2 in ethylene glycol at 160°C a 48% yield of methyl 3-deoxy-3-fluoro- α -D-glucopyranoside was obtained. These conditions were then applied to an analogous kanamycin A derivative and provided 3'-deoxy-3'-fluorokanamycin A.¹⁶

When the *N*-tosylaziridine **11** was opened with fluoride (KHF_2 , DMF, 150°C) initially the 2-fluoride **12** was produced, but over time the thermodynamic product **13** formed, presumably by reversal back to **11**. This reaction was also utilized in the synthesis of fluorinated kanamycin derivatives.¹⁷ These and other syntheses of 4'-deoxy-4'-fluorokanamycins A and B are covered in Chapter 19. The synthesis of a fluorinated analogue of the acceptor of bovine (1→4)- β -D-galactosyl transferase is mentioned in Chapter 3, and the conformational analysis of some deoxyfluoro sugars by ^1H -n.m.r. spectroscopy is detailed in Chapter 21. The use of e.i. and c.i. mass spectrometry to determine the location of a fluorine atom in deoxyfluoro glucosides is outlined in Chapter 22.

A robot-performed synthesis of 2-deoxy-2-[^{18}F]fluoro-D-glucose has been described,¹⁸ and the synthesis and biodistributions in the rat of both 2-deoxy-2-[^{18}F]fluoro-D-galactose¹⁹ and 2-deoxy-2-[^{18}F]fluoro-D-talose²⁰ have been reported.

2 Chloro-, Bromo-, and Iodo-sugars

The radical-mediated bromination of carbohydrate derivatives has been reviewed,²¹ as has the photobromination of C-1 substituted sugars.²² 3,4,6-Tri-*O*-acetyl-2-*O*-trichloroacetyl- β -D-glucopyranosyl chloride has been employed in glycosidation reactions, deprotected at O-2 and then glycosylated at this site.²³ Samarium iodide has been allowed to react with some glycosyl halide derivatives affording glycal products and/or C-glycosides upon addition of cyclopentanone.²⁴ Treatment of 2,3:4,6-di-*O*-isopropylidene-D-mannono-1,5-lactone with tris-(dimethylamino)phosphine in carbon tetrachloride has afforded the unsaturated glycosyl chloride **14** in good yield.²⁵

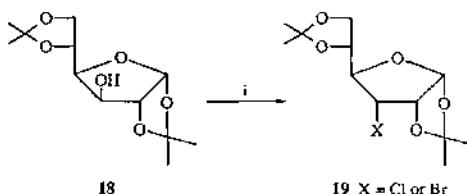


Treatment of suitable free sugars with triphenylphosphite and bromine has afforded the corresponding glycosyl bromides in good yield,²⁶ and hexopyranos-2-ulosyl bromides have been prepared from 2-hydroxyglucal derivatives using NBS. These products have been employed in glycosidation reactions and other nucleophilic displacements at C-1.²⁷

Radical chlorination (SO_2Cl_2 , AIBN) of tetra-*O*-acetyl- β -D-glucopyranosyl azide produced the 5-chloro compound **15**, whereas use of NBS in place of SO_2Cl_2 gave a product *via* bromination at C-1.²⁸ The reaction of a 1-bromo-1-chloroglucopyranosyl derivative with tributyltin hydride in the presence of acrylonitrile is discussed in Chapter 2, and use of the 6-bromo compound, that results from photobromination of tri-*O*-acetyl-1,6-anhydro- β -D-glucopyranose, in substitution and oxidation reactions is mentioned in Chapters 5, 7, and 16.

The synthesis of a new sweetener, 1'4,6'-trichloro-1',4,6'-trideoxygalactosucrose has been reported,²⁹ and bromolactonisation of some 4-C-branched hex-2-enopyranosides such as **16** has afforded 2-bromo compounds, e.g. **17**.³⁰ A synthesis of 3-bromo-3-deoxy-5-*O*-methyl-L-arabinono-1,4-lactone has been described³¹ and 2-deoxy-2-iodo-D-mannopyranose derivatives have been produced from tri-*O*-acetyl-D-glucal by treating with iodine in an appropriate solvent.³² Some unprotected glycals have been enzymically hydroxyhalogenated to 2-deoxy-2-halogeno sugars using a chloroperoxidase.^{33,34} The reaction of a 3,5-anhydro-pentofuranose derivative with halide ions is covered in Chapter 5 and the chlorination of some 3-(pentitol-1-yl) pyrazoles is discussed in Chapter 10.

Anion exchange resin in the chloride form has been reported as an effective and selective reagent for the nucleophilic displacement of primary sulfonyloxy groups by chloride ion.³⁵ Conditions have been found that will effect the conversion of alcohol **18** into halides **19** (Scheme 3) without affording the corresponding isomerised 6-deoxy-6-halo-compounds,³⁶ and the bromination of some cyclodextrins is discussed in Chapter 4. Some unprotected hexitols have undergone direct regioselective chlorination using Viehe's salt ($\text{Me}_2^+\text{N} = \text{CCl}_2\text{Cl}$) affording 1,6-dichloro-1,6-dideoxy derivatives.^{37,38}



Reagents: i, Ph_3P , imidazole, toluene, reflux, slow addition of NBS or NCS

Scheme 3

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9

Amino-sugars

1 Natural Products

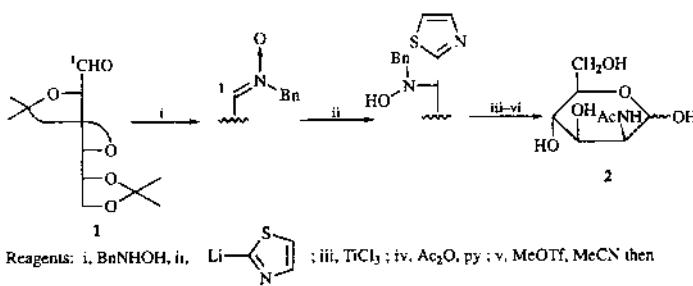
A 2-acetamido-2-deoxy- β -D-glucopyranosyl moiety, rarely found as a plant component, is a constituent of a saponin from *Albizia julibrissin* stem bark.¹ Kedarcidin, a new chromoprotein anti-tumour fermentation product of the enediyne class contains the novel amino sugar kedarosamine (2,4,6-trideoxy-4-dimethylamino-L-arabino-hexopyranose), isolated as its methyl glycoside.^{2,3} A microscale chromatographic analytical method for *N*-acetylneurameric acid in glycoproteins is covered in Chapter 23.

2 Synthesis

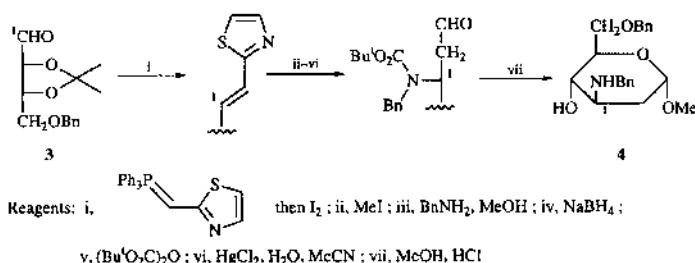
Syntheses covered in this section are grouped according to the method used to introduce the amino-functionality.

2.1 Chain extension. - Dondoni and co-workers have further exemplified the utility of thiazole chain-extension chemistry with the synthesis of 2-acetamido-2-deoxy-D-mannose (**2**) from the D-arabinose diacetone **1** (Scheme 1),⁴ and the kanosamine derivative **4** from the D-erythrose derivative **3** (Scheme 2),⁵ itself prepared from 2,3-*O*-isopropylidene-D-glyceraldehyde by a one carbon extension via thiazole anion addition. The methodology in Scheme 1, which features an improved thiazole to aldehyde deprotection sequence (step v), was also used to synthesize 2-amino-2-deoxy-D-mannose and, in addition, 2-amino-2-deoxy-D-erythrose from 2,3-*O*-isopropylidene-D-glyceraldehyde.

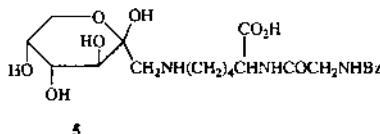
2.2 Amadori reaction. - The 1-amino-1-deoxy-D-fructose derivative **5** was synthesized by condensation of D-glucose with hippuryl-lysine in methanol; it was intended for use as a standard in the analysis of 'protein-fructosamines' by reaction with nitro blue tetrazolium (NBT) under alkaline conditions, but it and related 'peptide-fructosamines' gave much lower relative responses than the 'protein-fructosamines' in this assay.⁶



Scheme 1

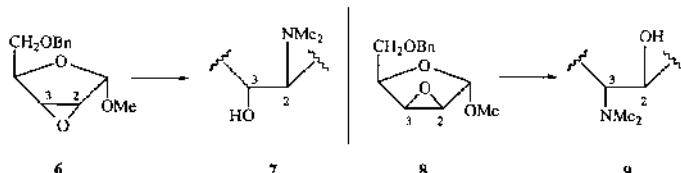


Scheme 2

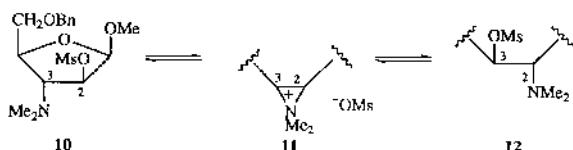


2.3 Epoxide opening. - The regioselectivity of epoxide ring opening in anomeric 2,3-anhydropentofuranosides by dimethylamine or ammonia has been determined. The α -glycosides **6** and **8** gave almost exclusively the 2- and 3-dimethylamino-products **7** and **9**, respectively (Scheme 3). An equilibrium is established between isomeric mesylate derivatives of such 1,2-*trans*-dimethylaminoalcohols, as for **10** and **12** in Scheme 4. The intermediate aziridinium ion **11** was observed at 75°C in CD_3CN , in which the ratios of **10** : **11** : **12** were $20 : 70 : 10$. Similar equilibria are established between isomeric 1,2-*trans*-chlorodimethylamino-derivatives on reaction of the mesylates **10** and **12** with triethylamine hydrochloride.⁷ 6-Deoxy-1,2-*O*-isopropylidene-3-*O*-methyl-6-[tris(hydroxymethyl)amino]-D-glucofuranoside, a new 'azapodand' that readily complexes Cu^{2+} in alkaline media, was obtained by reaction of tris(hydroxymethyl)amine with the corresponding carbohydrate **5,6**-epoxide. Related *N*-[tris(hydroxymethyl)]-derivatives of 2,3:5,6-di-*O*-cyclohexylidene-D-mannose and carboxamidomethyl 2,3:5,6-di-*O*-cyclohexylidene- α -D-

glucofuranoside were also prepared.⁸ Full details on the synthesis of *N,N*-dialkylaminosugars by aluminium trichloride-catalysed opening of epoxides with dialkylaminosilanes have been published.⁹ Synthesis of various analogues of the amino-linked *pseudo*-disaccharide acarviosin are detailed in Chapter 18; they involve coupling carbocyclic sugar epoxides with 4-amino-sugar derivatives.^{10,11} 4-Amino-4-deoxy-1,2-*O*-ethylene- α -D-xylopyranoside was obtained following opening of the corresponding 3,4-anhydro- β -L-arabinopyranoside with azide.¹²

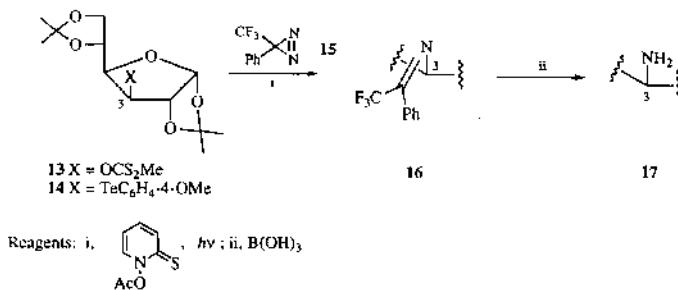


Scheme 3



Scheme 4

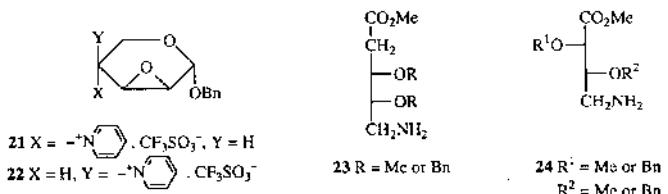
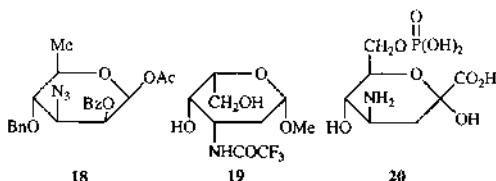
2.4 Radical amination. - A radical reaction has been developed to effect the replacement of a hydroxy-group by an amino-group. For example, the carbon radicals generated from either the xanthate **13** or anisyltelluride **14** can be trapped by the diazirine **15** (Scheme 5). The resulting imine **16** was hydrolysed to the amine **17**.¹³



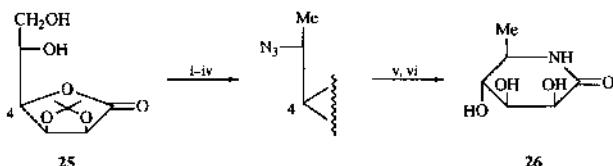
Scheme 5

2.5 Nucleophilic displacement. - Sulphonate ester displacement reactions continue to be widely applied in amino-sugar syntheses. The precursor **18** of 3-amino-3,6-dideoxy-D-mannose was obtained from 1,2:5,6-di-*O*-isopropylidene-D-glucofuranose in a multi-step procedure. The procedure

employed three nucleophilic displacements of (1-imidazolyl)sulphonate esters, two to effect a double inversion at C-3 with introduction of azide, and one to invert stereochemistry at C-2 in a pyranoside derivative.¹⁴ The L-daunosamine derivative **19** was also obtained from the same starting material in 13 steps, 10% overall yield. Introduction of azide at C-3 by displacement of triflate with inversion was accompanied by competitive elimination to give the 3-alkene as a byproduct. Remaining key steps were inversion at C-5 (mesylate displacement with cesium propionate) and C-2 deoxygenation (Barton radical reaction).¹⁵ 4-Amino-3,4-dideoxy-D-*arabino*-heptulosonic acid 7-phosphate (**20**), required for studies of a new variant of the shikimic acid pathway leading to 3-amino-5-hydroxybenzoic acid, a proposed precursor of the mC₂N units in ansamycin antibiotics, was obtained from the known methyl (methyl 3-deoxy- α -D-*arabino*-heptulosonate) (Vol. 14, p.152). Key steps were 5,7-O-benzylidenation, and double inversion at C-4 by oxidation-reduction and triflate displacement by azide.¹⁶ The benzyl 2,3-anhydro-4-deoxy-4-(N-pyridinium)- α -D-*lyxo*- and β -L-*ribo*-pentopyranoside salts, **21** and **22**, were synthesized by reaction of the corresponding *ribo*- and *lyxo*-4-triflates, respectively, with pyridine. The *lyxo*-product **21** is stable, but the *ribo*-product **22** decomposes in a few hours.¹⁷ Analogues of the H-type 2 human blood group trisaccharide glycoside, α -L-Fucp-(1 \rightarrow 2)- β -D-Galp-(1 \rightarrow 4)- β -D-GlcNAc-OMe, synthesized to test bonding with a lectin, included analogues with 6-NH₂, 6-NHAc-, and 6-NHCOCMe₃-GlcNAc residues prepared via displacement of a 6-mesylate by azide.¹⁸ A general strategy for the synthesis of δ - and γ -amino-acids from pentofuranose derivatives involved introduction of the amino-function by displacement of a primary tosylate with azide. The δ -amino-derivatives **23** were thus obtained from methyl 2-deoxy- α , β -D-*erythro*-pentofuranoside, while the δ -amino-derivatives **24** were obtained from 1,2-O-isopropylidene- α -D-*xylo*furanose, chain cleavage between C-1 and C-2 being effected by periodate oxidation.¹⁹

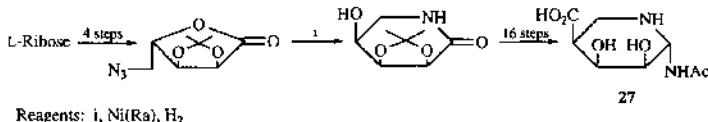


D-Rhamnonolactam (**26**) was synthesized from L-gulono-1,4-lactone via its monoacetonide **25** (Scheme 6), as also was 1-deoxy-D-rhamnojirimycin (see Chapter 18). Their L-enantiomers were synthesized from D-gulonolactone in the same way. None proved to be inhibitors of the enzyme naringinase, an α -L-rhamnosidase.²⁰ The total synthesis of (+) and (-)-nojirimycin from *myo*-inositol (cf Vol. 23, p.100) has been reviewed.²¹ Siastatin B, a *Streptomyces* metabolite and inhibitor of neuraminidase, was shown to have structure **27** by total synthesis from L-ribose, available from D-ribono-1,4-lactone, as outlined in Scheme 7. Key steps were (i) introduction of nitrogen at C-5 by reaction of 1,2-O-isopropylidene-5-O-mesyl-L-ribose with azide ion; (ii) introduction of an N-phthalimido-group at the anomeric position of a free sugar by Mitsunobu reaction; and (iii) introduction of the C-4 carboxy-group by reaction of a 4-ketone with nitromethane, followed by dehydration and reduction. The enantiomer was also made (from D-ribonolactone).²²



Reagents: i, Ph₃P, CBr₄; ii, H₂, Pd/C, Et₃N; iii, Tf₂O, py; iv, NaN₃, DMF; v, H₂, Pd/C; vi, CF₃CO₂H, H₂O

Scheme 6

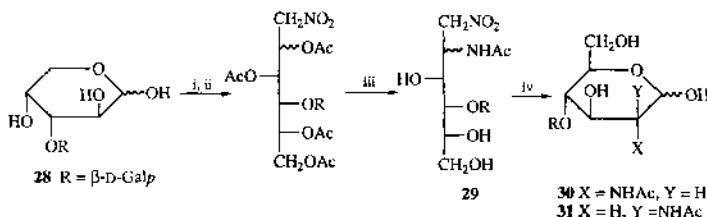


Reagents: i, Ni(Ra), H₂

Scheme 7

The utility in the analysis of amylases of maltopenta- and hexa-ose derivatives bearing an amino- or phthalimido-function on C-6 of one of their sugar residues is covered in Chapter 4, as is the synthesis of mono(6-amino-6-deoxy-2,3-di-O-methyl)-hexakis(2,3,6-tri-O-methyl)- β -cyclodextrin and its amino-acid and peptide coupling products.

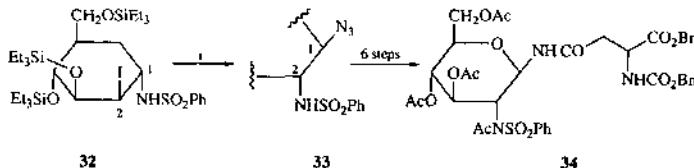
2.6 From nitro-sugars. -N-Acetyl-lactosamine **30** and *N*-acetyl-*epi*-lactosamine **31** were obtained as a *manno*-rich epimeric mixture on ozonolysis of the 2-acetamido-1-nitro-derivatives **29**, obtained from 3-*O*-(β -D-galactosyl)-D-arabinose **28** (Scheme 8). The *manno*-isomer **32** could be obtained in 15% yield from **28**, by direct crystallization. Treatment of the product mixture with aqueous ammonia gave a *gluco*-rich mixture from which the *gluco*-isomer **30** could be crystallized (32% yield from **28**). Similar procedures applied to L-arabinose led to 2-acetamido-2-deoxy-L-mannose and -glucose.²³



Reagents: i, MeNO_2 , MeONa ; ii, Ac_2O , H_2SO_4 ; iii, NII_3 , MeOH ; iv, O_3 , NaOH , H_2O

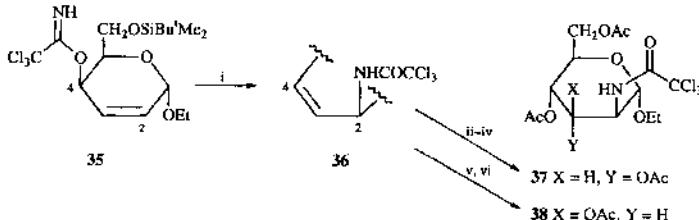
Scheme 8

2.7 From unsaturated sugars. - A general route to glycopeptides in which a 2-acetamido-2-deoxy-D-glucopyranosyl unit is β -linked to an asparagine residue and which is based on methodology developed earlier for the synthesis of 2-amino-2-deoxy- β -D-glycosides from D-glycals (Vol. 24, p.111) has been developed. 2-Iodo-glycosyl sulphonamide 32, available from D-glucal, gave azide 33 on reaction with sodium azide, and this was elaborated to, for example, the glycosylamide 34 (Scheme 9).²⁴ [3,3]-Rearrangement of the unsaturated trichloroacetimidate ester 35 derived from tri-O-acetyl-D-glucal, led to the 2-amino-hex-3-enoside 36 which was separately converted to the D-*altro*-37 and D-*manno*-38 amino-sugar glycosides as major products (Scheme 10). The C-4 epimer of 35 did not undergo an analogous rearrangement.²⁵



Reagents : i, NaN_3 , DMF

Scheme 9

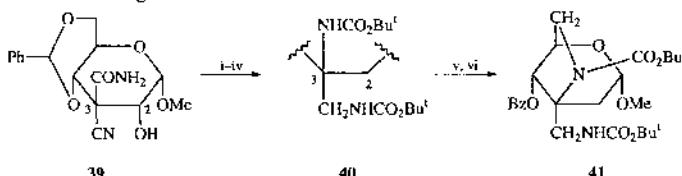


Reagents : i, xylene, Δ ; ii, OsO_4 , py then NaHSO_3 ; iii, Bu_4NF ; iv, Ac_2O , py; v, MCPBA ; vi, Au_2O , AcOH , BF_3OEt_2

Scheme 10

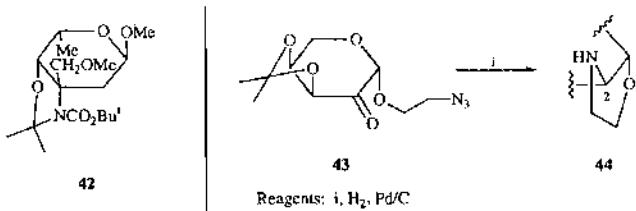
2.8 Curtius reaction. - The C-3-branched 3-amino-2,3,6-trideoxy-sugar analogue 40 of daunosamine has been synthesized from the di-C-branched derivative 39, and converted to the bicyclic derivative 41 (Scheme 11). Preparation of an analogous derivative 42 from a known

branched-chain amino-sugar was also detailed.²⁶

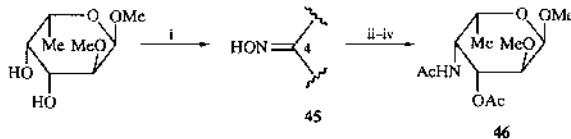


Scheme 11

2.9 Reductive amination. - Reductive amination of the 2-ketone **43** led to the *trans*-fused 2-amino-2-deoxy-1,2-*O,N*-ethylene- β -L-riboside **44** in modest yield (Scheme 12).¹² Methyl 4-amino-4-deoxy- α -L-lyxopyranoside was obtained by reduction of the oxime derivative of methyl 2,3-*O*-benzylidene- α -D-*erythro*-pent-4-uloside.²⁷ Methyl 4-acetamido-3-*O*-acetyl-4,6-dideoxy-2-*O*-methyl- α -L-galactopyranoside **46** was synthesized as shown in Scheme 13; catalytic reduction of the oxime **45** over platinum yielded mainly the desired *galacto*-isomer. Its enantiomer was similarly prepared, and it was demonstrated that it is the L-enantiomer that is present as a terminal residue on the glycoprophospholipid of *Mycobacterium avium* serovar 26. Compound **46** was used in the construction of disaccharides (see Chapter 3).²⁸



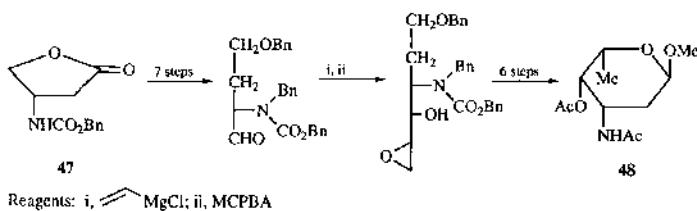
Scheme 12



Scheme 13

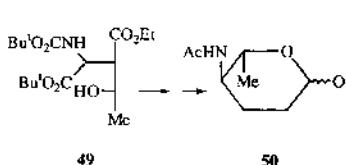
2.10 From chiral non-carbohydrates. - Several syntheses of amino-sugars from chiral non-carbohydrate starting materials have been reported. The α -L-daunosamine derivative **48** was obtained from L-aspartic acid *via* the known lactone **47**, which was prepared in 2 steps. Key reactions were the *anti*-selective Grignard addition and *syn*-selective epoxidation (steps i and ii),

respectively, in Scheme 14.²⁹ *N*-Acetyl-L-tolylposamine **50** was synthesized in 13 steps, 16% overall yield, via the known L-*allo*-threonine derivative **49** (Scheme 15), available in one step from ethyl (*S*)- β -hydroxybutyrate.³⁰ Full details of the synthesis of D-lividonamine from a chiral bicyclic adduct of furan with cyanovinyl camphanate have been published, along with the synthesis of the derivative **52** of its C-2 epimer from adduct **51** (Scheme 16).³¹ A new route to enantiomerically pure 6-amino-6-deoxy-D-and L-octoses is exemplified in Scheme 17 by the synthesis of methyl α -D-lincosaminide **55** from aldehyde **53**, prepared in 6 steps from D-threonine. Addition of furyllithium to **53** gave mixtures of *syn*- and *anti*-addition products, the ratio depending upon the conditions employed. The C-3 epimer of **53**, available in 4 steps from D-threonine, was elaborated to isomers of enone **54** in the same way.³² The lactam **56**, a chiral intermediate in the preparation of calyculins, was synthesized from (*S*)-pyroglutaminol.³³

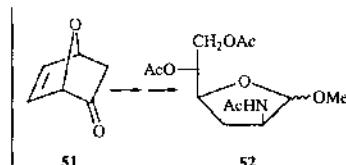


Reagents: i, $\text{CH}_2=\text{CHMgCl}$; ii, MCPBA

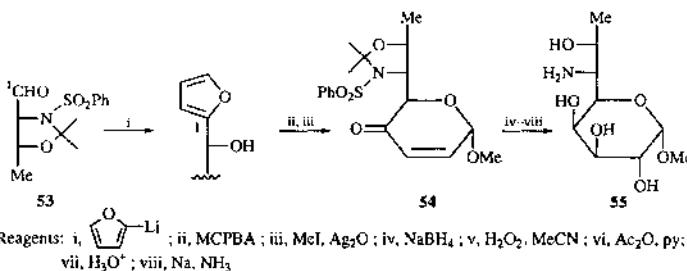
Scheme 14



Scheme 15



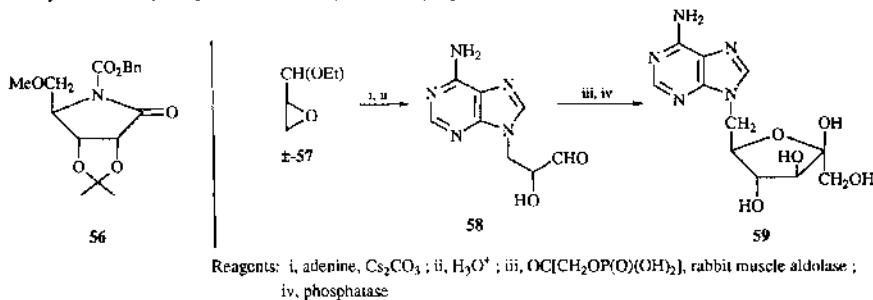
Scheme 16



Scheme 17

The nucleoside analogue 6-adenyl-6-deoxy-D-fructose **59** was made by combined use of chemical and enzymic methods (Scheme 18). The racemic epoxide **57** was available from acrolein

diethyl acetal and was condensed with adenine to give, after hydrolysis, the aldehyde **58**. Enzyme catalysed aldol coupling of an excess of **58** with dihydroxyacetone bisphosphate gave the kinetically preferred product **59** in 20% yield. The L-sorbose analogue of **59** could be made similarly in 33% yield by using the (*S*)-enantiomer of **57**, prepared by a route involving enantioselective lipase catalysed ester hydrolysis of 2-acetoxy-3-chloropropanol diethyl acetal.³⁴



Scheme 18

Syntheses of amino-derivatives of branched-chain sugars, cyclitols and nucleosides are covered in Chapters 14, 18 and 20, respectively.

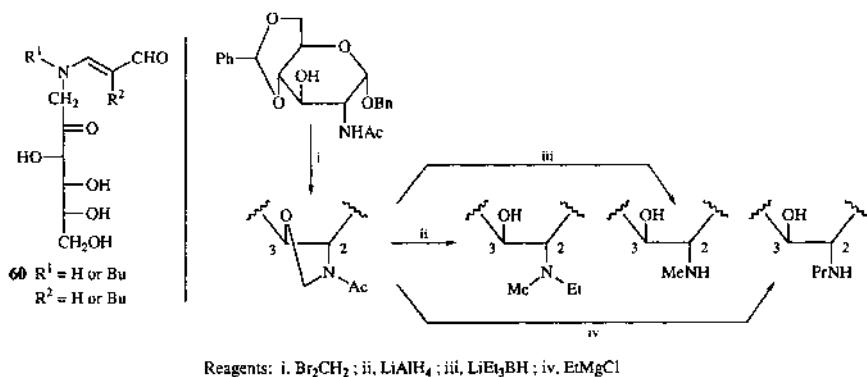
3 Reactions, Properties and Synthesis of Derivatives

The reactions of malondialdehyde and methyl malondialdehyde with 1-amino-1-deoxy-D-fructose and its *N*-butyl derivative have been studied as part of an investigation of the Maillard reaction. The initial enamine adducts **60** cyclised readily to mixtures of pyrrole and pyridinone derivatives (see Chapter 10).³⁵

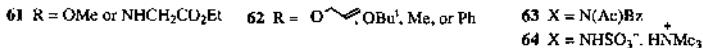
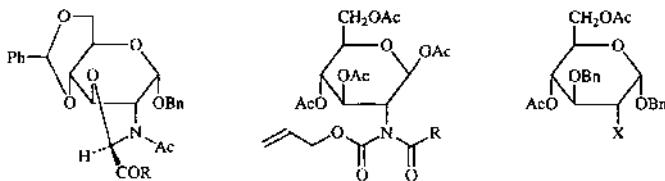
Syntheses of amino-sugar glycosides and disaccharides are covered in Chapter 3.

A new method for synthesis of *N*-alkyl- and *N,N*-dialkyl-derivatives of 2-amino-2-deoxy-D-glucose is shown in Scheme 19.³⁶ Oxazolidine derivatives such as **61** related to muramic acids, but with conformational restrictions, were synthesized by alkylation of the corresponding 2-acylamino-2-deoxy-3-hydroxy-sugars with dichloroacetic acid.³⁷

N-Acyl-2-amino-2-deoxy-[¹⁴C]-D-glucoses were synthesized as precursors for the biosynthesis of novel *N*-acylneuraminic acids, by reaction of [¹⁴C]-D-glucosamine with C₃-C₇ fatty acid anhydrides.³⁸ ¹²³I-Labelled 2-deoxy-2-(*m*- and *p*-iodobenzamido)-D-glucose have been synthesized for use as radioligands in monitoring the biodistribution of hexokinase, for which they are non-competitive inhibitors.³⁹ 2-Amino-2-deoxy-*N*-(methacryloylglycylglycyl)-D-galactose, -mannose and -glucose, and the *N*-fucosylamine analogue, were synthesized by *N*-acylation of the free amino-sugars and used as a monomers in the synthesis of *N*-(2-hydroxypropyl) methacrylamide co-



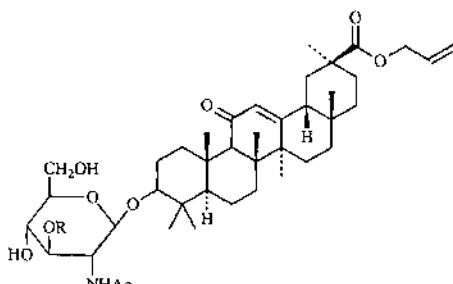
Scheme 19



polymers with pendant saccharide moieties. Of these copolymers, the fucosylamine derivative adhered selectively to colonic tissue and thus has potential as a drug carrier.⁴⁰ The synthesis and cysteine protease inhibitory properties of *N*-peptidyl derivatives of 2-amino-2-deoxy-D-glucose have been reported.⁴¹ *N*-Acyl- and *N*-alkoxycarbonyl-derivatives of tetra-O-acetyl-2-allyloxycarbonylamino-2-deoxy- β -D-glucopyranose, **62**, have been synthesised by *N*-acylation reactions, and their use in 1,2-trans-glycosylations studied.⁴² Syntheses of the *N,N*-diacyl derivative **63** and the *N*-sulphate **64** have been reported.⁴³

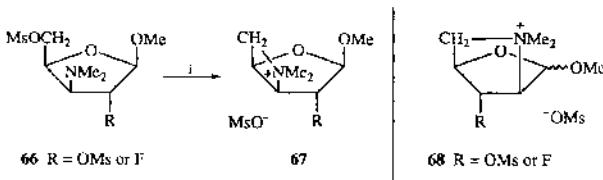
Aqueous hydrolysis of a 3-O-acetyl group in a 2-amino-2-deoxy-D-glucoside derivative is sixty times faster than that of ethyl acetate, evidently being catalyzed by the adjacent free 2-amino-group.⁴⁴

The glycyrrhetic acid glycosides **65** are representatives of a new class of potent antiproliferative glycolipids; the conventional synthesis and biological activity of such compounds has been reported.⁴⁵ 2-Deoxy-2-[(2S,3R)- and (2R,3S)-(2-fluoro-3-hydroxytetradecanoyl)aminol-3-O-[(3R)-3-tetradecanoyloxytetradecanoyl]-D-glucopyranose 4-(dihydrogen phosphate) were synthesized by conventional means as analogues of GLA-60, a lipid A analogue with therapeutic



properties. The (*2S,3R*)-isomer was a little more active than GLA-60 in a prostaglandin D₂ releasing test on macrophages, while the (*2R,3S*)-isomer was inactive. The fluorine was introduced in an unsuccessful attempt to stabilise the amide linkage towards metabolic degradation.⁴⁶ One synthetic approach to lipid A analogues involved regioselective construction of the β -(1 \rightarrow 6)-linked disaccharide core using *N*-allyloxycarbonyl protected 2-amino-2-deoxy-D-glucose derivatives,⁴⁷ while another utilized Koenigs-Knorr glycosidation.⁴⁸

The bicyclic azetidinium salts **67** were formed by intramolecular ring closure of 5-mesylates **66**, even when competitive aziridinium salt formation could have occurred (Scheme 20). The pyrrolidinium salts **68** were obtained similarly. Compounds **67** and **68**, with X=F or OMs, were isolable solids.⁴⁹ Synthesis of amino-fluoro-sugar derivatives from *N*-tosyl-aziridine derivatives is covered in Chapter 8 and 19.



Reagents: *i*, Δ , CD₃CN

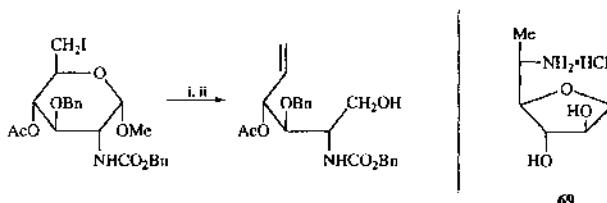
Scheme 20

A six step conversion of 2-acetamido-2-deoxy-D-glucose into 2-acetamido-2-deoxy-D-galactose involved as key steps a selective 6-*O*-deacetylation with yeast esterase, acid-catalysed acetate migration from O-6 to O-4 under acidic catalytic, and inversion at C-4 via triflate displacement.⁵⁰ 2-Acetamido-2-deoxy-3-[³H]-D-galactose was obtained via borodeuteride reduction of benzyl 2-acetamido-4,6-*O*-benzylidene- α -D-glucopyranosid-3-ulose, a reaction in which only a trace of the C-3 epimeric D-*gulo*-derivative was formed.⁵¹

Methyl 3-amino-3-deoxy-D-alluronate was synthesized from 3-azido-3-deoxy-1,2:5,6-di-*O*-isopropylidene-D-glucofuranose, oxidation at C-6 being achieved by reaction of a 6-trityl ether

derivative with Jones' reagent; it was obtained as a solid mixture of anomeric pyranose and furanose isomers.⁵² A new convenient synthesis of 6-amino-6-deoxy-2,3,4,5-tetra-*O*-methyl-D-gluconic acid, required for making polyamides, from methyl α -D-glucoside, involved oxidation ($\text{Ac}_2\text{O}\text{-Me}_2\text{SO}$) of 6-azido-6-deoxy-2,3,4-tri-*O*-methyl-D-glucose to the 1,5-lactone, followed by methylation and catalytic reduction.⁵³

A route suitable for accessing differently protected 4-amino-4-deoxypentoses required for the synthesis of azinomycins A and B is shown in Scheme 21.⁵⁴ 2-Aminol-1,2-dideoxy-D-galactitol hydrochloride was obtained following desulphurization of the peracetylated diethyl dithioacetal derivative of 2-amino-2-deoxy-D-galactose, and cyclized to the 3,6-anhydride **69** (correctly named as a 1,4-anhydro-L-galactitol derivative) on treatment with conc. hydrochloric acid.⁵⁵ The synthesis of 2-C-acylated 3-trifluoroacetamido-1-glucal derivatives is covered in Chapters 13 and 14.



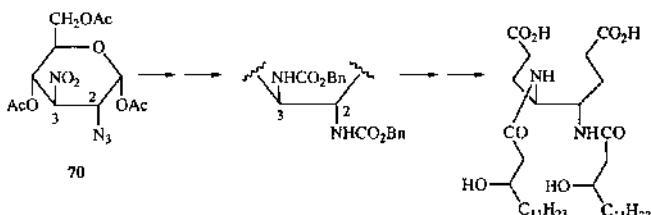
Reagents: i, Zn, EtOH ; ii, NaBH₄

Scheme 21

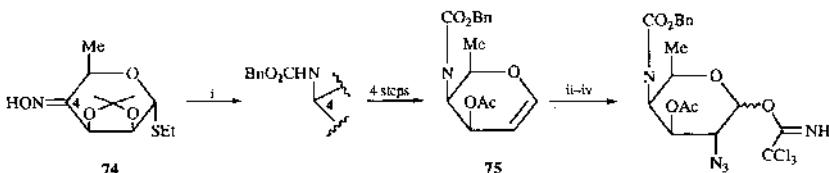
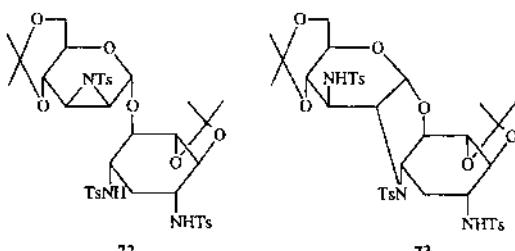
4 Diamino-sugars

¹H- and ¹³C-N.m.r. assignments for 2,3-diacetamido-2,3-dideoxy-D-glucopyranose have been reported.⁵⁶ The potential lipopolysaccharide antagonist **71** was synthesized from the known 2-azido-3-nitro-sugar **70** (Scheme 22), the $\text{CH}_2\text{CO}_2\text{H}$ groups being introduced first at C-1 then at C-4 after liberation of the C-5,6 diol and periodate oxidation.⁵⁷ In an attempt to obtain a 3-amino-2-fluoro-D-glucopyranosyl moiety as an analogue of a component of kanamycin, the aziridine **72** was treated with KHF_2 in DMF at 150°C, but the intramolecular cyclisation product **73** predominated.⁵⁸

2-Acetamido-4-amino-2,4,6-trideoxy-D-galactopyranosyl precursors such as trichloroacetimidate **76**, were prepared from ethyl 1-thio- α -D-mannopyranoside. Key steps were stereoselective reduction of oxime **74** (available in 5 steps), and azidonitration of glycal **75** (Scheme 23).⁵⁹ Their application in the synthesis of disaccharides is covered in Chapter 3. Benzyl 2,4-diacetamido-3-*O*-benzyl-2,4,6-trideoxy- β -D-galactopyranoside has been synthesized in 5 steps from benzyl 2-acetamido-3-*O*-benzyl-2-deoxy- β -D-galactopyranoside.⁶⁰



Scheme 22



Reagents: i, NaBH_4 , NaOAc , TiCl_3 , H^+ , MeOH then BnO_2CCl_2 , NaHCO_3 ; ii, NaN_3 , $\text{Ce}(\text{NH}_4)_2(\text{NO}_3)_6$; iii, PhSH , EtNPr_2^1 ; iv, Cl_3CCN , K_2CO_3

Scheme 23

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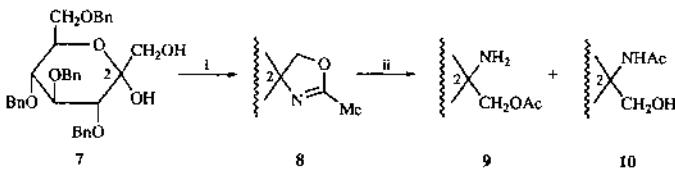
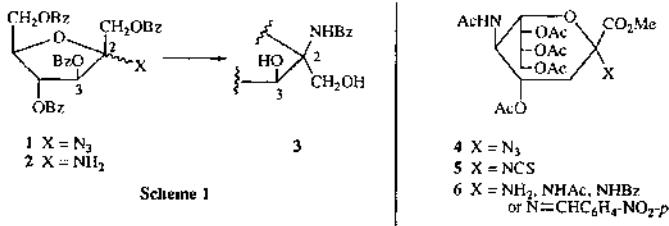
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10

Miscellaneous Nitrogen Derivatives

1 Glycosylamines and Related Glycosyl-N-bonded Compounds

1,3,4,6-Tetra-*O*-benzoyl- α -D-fructofuranose, which has a free anomeric hydroxyl group, has been converted into the corresponding *N*-(4-methoxyphenyl)-fructosylamine derivative under Mitsunobu conditions, and into the fructosyl azide **1** (*i*, Ac_2O -NaOAc; *a*, Me_3SiN_3 - TiCl_4) and thence the fructosylamine derivative **2**. On standing in tetrahydrofuran solution, **2** underwent O \rightarrow N benzoyl migration to yield the β -anomer **3** (Scheme 1).¹ A phase transfer catalysis method has been used to synthesize the α -*N*-acetylneuraminyll azide **4** and isothiocyanate **5** from the corresponding β -glycosyl chloride. Azide **4** was converted to the glycosylamine and glycosylamide derivatives **6**.² Ritter reaction of the heptulose **7** gave oxazoline **8**, which on acid-catalysed hydrolysis was converted mainly to the *O*-acetate **9**, accompanied by a small amount of the *N*-acetate **10** (Scheme 2).³

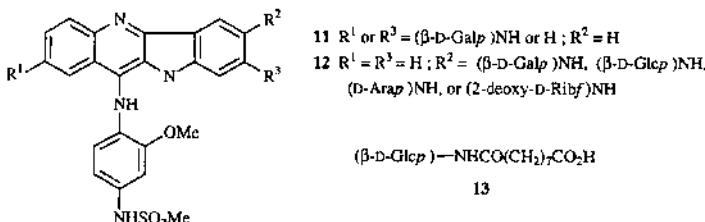


Reagents: *i*, MeCN , BF_3OEt_2 ; *ii*, H_3O^+

Scheme 2

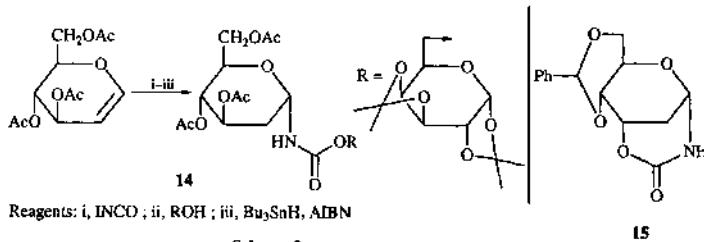
The glycosylamino-indolo[3,2-*b*]quinolines **11** and **12** were synthesized by coupling aglyconic amines with a protected glycosyl bromide in pyridine-DMF. The 7- β -D-galactosyl derivative **12** had improved antitumour activity and better solubility and bioavailability than the aglycon itself.⁴ The *N*-arabinosyl, *N*-xylosyl and *N*-lyxosyl derivatives of tryptamine and tyramine, produced by

condensation of the free sugars with these amines, have been characterized.⁵ Radical halogenation of *N*-aryl- β -D-glucopyranosylamine tetraacetate occurred exclusively on the aromatic ring, rather than at C-1 or C-5 of the carbohydrate moiety.⁶ The conversion of *N*-(2-pyridyl)-glycosylamines to 1-amino-1-deoxy-alditols is covered in Chapter 18, and the NMR examination of *N*-alkyl-lactosylamines in Chapter 21.



A β -cyclodextrin with a pendant glucosylamine attached by a spacer arm has been prepared by sequential condensation of tetra- O -acetyl- β -D-glucopyranosyl isothiocyanate with nonanedioic acid mono-methyl ester, hydrolysis and condensation of the product 13 with mono-6-amino-6-deoxy- β -cyclodextrin. It is much more soluble in water than β -cyclodextrin, and retains the capacity to include and enhance the solubility of pharmacologically active substances.⁷ *N*-(Methacryloylglycylglycyl)- α -L-fucopyranosylamine and related amino-sugar derivatives were synthesised as monomers for preparing *N*-(2-hydroxypropyl)methacrylamide copolymers with pendant saccharide residues. The water soluble fucosylamine-substituted polymer bound selectively to colonic tissue. Such materials have the potential to be drug carriers targeted to particular tissues.⁸ The preparation and use of neoglycolipids from neutral *N*-linked oligosaccharides as probes in elucidating the function of glycoprotein oligosaccharide chains have been discussed.⁹

A series of 2-deoxyglycosyl carbamates such as **14** were synthesized from glycals (Scheme 3). The intramolecular carbamate **15** was formed from 4,6-*O*-benzylidene-D-allal.¹⁰ The use of *N*-glycosylimines as chiral auxiliaries is covered in Chapter 24.

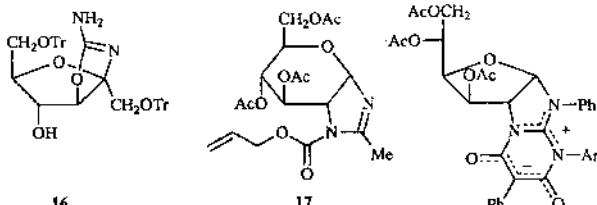


Scheme 3

The construction of *N*-linked glycopeptides and related model compounds continues to be

investigated. Fmoc-Protected 4-N-glycosyl-asparagines were prepared by coupling glycosylamines with a pentafluorophenyl aspartate derivative as potential reagents for the solid-phase synthesis of glycopeptides. The preparation of the glycosylamines by reaction of free sugars with ammonium carbonate (Vol. 20, p.106) worked well for galactose, lactose, fucose and mannose, but not so well for 2-acetamido-2-deoxy-D-mannose or 2-deoxy-glucose.¹¹ [D-Met², Pro³]-Enkephalin-*N*-(β-D-galactopyranosyl)amide, a glycopeptide with a galactose residue at the C-terminal position, was synthesised and shown to have greater antinociceptive potency than the parent peptide or its *N*-glucosylamide analogue. Derivatives bearing up to three galactose residues linked to the oligopeptide backbone by a hydrophobic spacer arm were also prepared.¹² *N*-Glycosylation of a dodeca- and trideca-peptide on a central asparagine residue with one or two 2-acetamido-2-deoxy D-glucose or glucose residues has been shown to alter the peptide conformation, indicating that glycosylation might be an important element in determining peptide antigen structure and function.¹³ Nephritogenoside, a 21 amino acid peptide with a C-terminal 4-*N*-(α-D-GlcP(1→6)-β-D-GlcP-(1→6)-α-D-GlcP)-asparagine residue, was synthesized by coupling a trisaccharide αβ-glycosylamine with a depeptide, separating the 5:1 mixture of α- and β-anomers and solid phase peptide synthesis.¹⁴ A highly selective route to 4-*N*-(2-acetamido-2-deoxy-β-D-glucopyranosyl)asparagine glycopeptides from D-glucal is covered in Chapter 9, and the use of partially protected *N*-(β-D-glucopyranosyl)-enamines as glycosyl acceptors in Chapter 3.

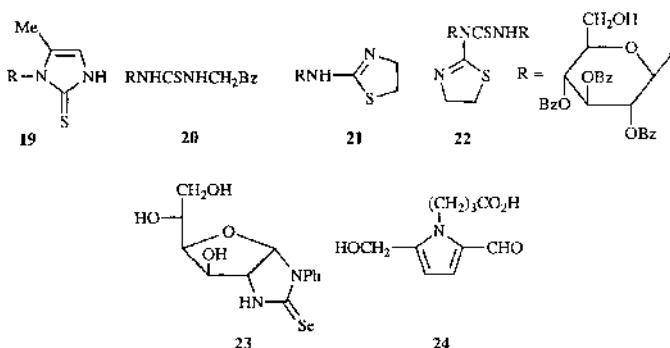
The fructofurano-oxazoline **16** was obtained by reaction of 1,6-di-*O*-trityl-D-fructose with cyanamide, and used in the construction of nucleoside analogues (see Chapter 20).¹⁵ The imidazoline **17** formed through solvent incorporation when 1,3,4,6-tetra-*O*-acetyl-2-allyloxycarbonylamino-2-deoxy-β-D-glucose was used as a glycosylating agent in acetonitrile.¹⁶ Synthesis of the cross-conjugated betaines **18** from glucosylamine has been reported.¹⁷



18 Ar = e.g. 4-MeO-C₆H₄

A facile synthesis of 2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl isothiocyanate from the corresponding ribosyl chloride has been detailed.¹⁸ 2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl isothiocyanate continues to be a popular reagent for preparing diastereomeric thiourea or dithiocarbamate derivatives in the reversed-phase resolution of enantiomeric amine- or thiol-

containing drugs.^{19,20} Both commercial and in-house synthesized samples of this reagent, however, were found to contain a minor, reactive, as yet unidentified impurity. When the reagent was used in large excess (250-fold) for the preparation of derivatives from amino-alcohol drugs such as propranolol, up to 50% of an undesired derivative was formed from this impurity. The problem could be minimized by use of less reagent, or pretreatment of the reagent with a limited amount of another amine.²¹ 2,3,4-Tri-O-acetyl- and benzoyl- β -D-glucopyranosyl isothiocyanates were synthesized from the corresponding glycosylamines (Cl_2CS , CaCO_3 , H_2O , CH_2Cl_2), and converted to derivatives such as 19 - 22 by reaction with various amines.²²



Glucofuranos-imidazoline-2-selenones such as 23 were obtained on condensation of 2-amino-2-deoxy-D-glucose with aryl isoselenocyanates.²³

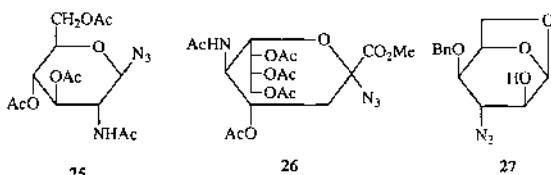
Maillard reaction products have been extensively investigated. About 70 products from reaction of D-glucose and L-methionine were separated by semi-preparative h.p.l.c. and characterised by ¹³C-n.m.r. and FAB-m.s.²⁴ α -Dicarbonyl fragmentation products from reactions of glucose or xylose with β -alanine were trapped as quinoxalines by reaction with σ -phenylenediamine; 5-hydroxymethyl-2-methyl-3(2H)-furanone was also detected.²⁵ The reaction of D-glucose with γ -aminobutyric acid generated more reducing substances than its reaction with α -amino-acids; the pyrrole 24 was isolated and characterized.²⁶ Products from reaction of D-glucose with diglycine, triglycine, tetraglycine, glycylleucine, leucylglycine and a mixture of leucine and glycine were compared. A number of 2(1*H*)-pyrazinones were identified as dipeptide-derived products²⁷ 1,4-Disubstituted-2,5-piperazinediones were identified by e.s.r. and ¹³C-n.m.r. spectroscopic examinations of the products of reaction of "sugar" with amino-acids.²⁸ 2-Furaldehyde was >99% of the total volatiles formed on reaction of D-xylose and lysine hydrochloride, at pH 5, although 68 other compounds were identified. Without pH control, the amounts of 2-furaldehyde and other mono- and bi-cyclic furans increased, and the amounts of *N*-containing heterocyclic and pyrazines decreased. Four 2,3-dihydro-1*H*-pyrrolizines and 3-methyl-2-(1-pyrrolylcyclopent-2-en-1-one were also

identified.²⁹ The alkylpyrazines formed in model reactions of glucose with ammonia and amino-acids in wet glycerol were studied by g.c.-m.s., the numbers identified (10-23) depending upon the natures of the amino-acids.³⁰

1-Deoxy-1-(*N*-nitrosyl-*N*-glycanyl and *N*-alanyl)-D-fructose have been synthesized as standards for the h.p.l.c. analysis of nitrosated Amadori compounds in browned food.³¹

2 Azido- and Diazirino-sugars

The conditions for converting 2,3,5-tri-*O*-acetyl- or benzoyl- β -D-ribofuranosyl acetate into the corresponding β -ribosyl azide (with $\text{Me}_3\text{SiN}_3\text{-SnCl}_4$) have been optimized.³² Phase transfer catalysis conditions ($\text{Bu}_4\text{N}^+\text{HSO}_4^-$, NaN_3 , CH_2Cl_2 , aq. NaHCO_3) have been used to synthesize, in 93-98% yields, 1,2-*trans*-glycosyl azides [e.g. 25] from the corresponding 1,2-*cis*-glycosyl chlorides and the α -sialic acid azide 26 from the corresponding β -chloride.³³ Glycosyl azides can also be synthesized by displacement of an anomeric diphenylphosphate group with azide ion.³⁴

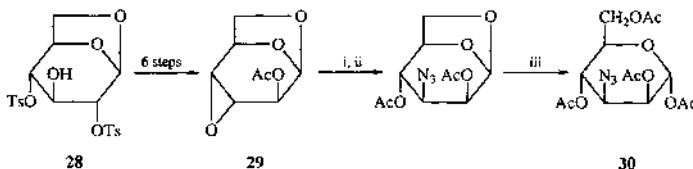


Hydrazine has been used to produce free 2-azido-2-deoxy-sugars from the corresponding glycosyl nitrates that are formed on azido-nitration of glycals.³⁵ 1,6-Anhydro-2-azido-2-deoxy- β -D-glucopyranose was synthesized from D-glucal [i, $\text{I}_2\text{-}(\text{Bu}_3\text{Sn})_2\text{O}$; ii, NaN_3], converted into its 2-*O*-benzyl ether, and 4-*O*-glycosylated with a protected 2-amino-2-deoxy- β -D-glucopyranosyl residue.³⁶ 1,6-Anhydro-6'-*O*-trityl-lactose was converted into related 2-azido-derivatives useful for the synthesis of oligosaccharides containing *N*-acetyl-lactosamine, via 2-*O*-(trisopropylbenzenesulphonylation), 2,3-*manno*-epoxide formation and azide ring opening reactions.³⁷

Various azides were obtained by opening cyclic sulphates obtained from *cis*-diols with azide ion. The cyclic sulphates from 1,6-anhydro-4-*O*-benzyl- β -D-mannopyranose and 1,6-anhydro-2-*O*-benzyl- β -D-galactopyranose yielded mainly the *trans*-dixial products 1,6-anhydro-2-azido-4-*O*-benzyl- and 4-azido-2-*O*-benzyl- β -D-glucopyranose, respectively. The cyclic sulphate from 1,6-anhydro-4-*O*-benzyl- β -D-talopyranose, however, unexpectedly gave the *trans*-diequatorial product 27. Cyclic sulphates derived from monocyclic diols sometimes gave one, sometimes two products. Thus methyl 2,6-di-*O*-benzoyl- β -D-galactopyranoside gave a mixture of 3-azido-3-deoxy-D-guloside and 4-azido-4-deoxy-D-glucoside derivatives in a 6:1 ratio.³⁸

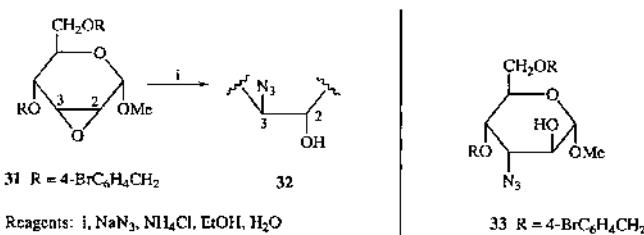
Two syntheses of 3-azido-3-deoxy-D-mannose tetraacetate 30 have been reported. In one, the

levoglucosan ditosylate **28** was converted into epoxide **29**, which was opened with azide ion (Scheme 4). In the second, the stereochemistry at C-2 of 2,4-di-*O*-acetyl-1,6-anhydro-3-azido-3-deoxy- β -D-glucopyranose was inverted by triflate displacement with acetate ion, selective *O*-2 deprotection having been effected by enzymic hydrolysis with Alcalase.³⁹ Azide opening of the D-*allo*-epoxide **31** gave the 3-azido-3-deoxy-D-glucoside **32** by *trans*-diequatorial ring opening in 70% yield (Scheme 5) whereas the corresponding 4,6-*O*-benzylidene derivative had given the *trans*-dixial ring opened product. The isomeric D-*manno*-2,3-epoxide gave the 3-azido-3-deoxy-D-alatoside **33** just as the 4,6-*O*-benzylidene analogue had done.⁴⁰



Reagents: i, NaN_3 ; ii, Ac_2O , py; iii, Ac_2O , H^+

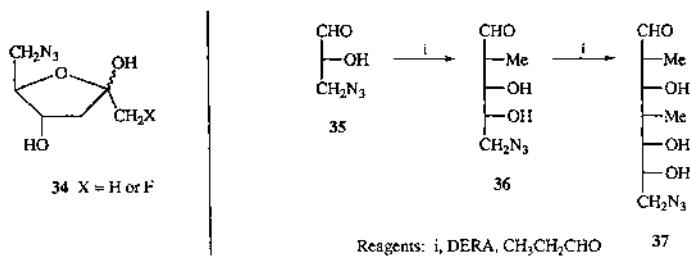
Scheme 4



Scheme 5

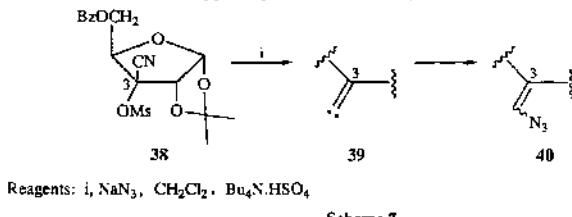
5-Azido-3,5-dideoxy-3-fluoro-1,2-*O*-isopropylidene- α -D-glucopyranose has been synthesized from a glucofuranose derivative via a 5-bromo-5-deoxy-L-mannofuranose derivative (see Chapter 8 for details).⁴¹ Treatment of 5-azido-5-deoxy-D-glucose or -L-idose with immobilized glucose isomerase gave 5-azido-5-deoxy-D-fructose and -L-sorbose, respectively, in high yield.⁴² 5-Azido-5-deoxy-1,2-*O*-isopropylidene- α -D-xylofuranose was obtained on reaction of the corresponding 3,5-anhydride with trimethylsilyl azide under Lewis acid catalysis.⁴³

DERA (deoxyribose-5-phosphate aldolase) has been used to catalyse the condensation of 3-azido-3-deoxy-D-glyceraldehyde **35** with acetone or fluoroacetone to give 6-azides **34**, and with propanal to give the branched-chain sugar azides **36** and **37** which adopt furanosyl and pyranosyl ring forms, respectively (Scheme 6). Reductive amination of **36** and **37** gave novel 1,5-imino-adducts (see Chapter 18).⁴⁴



Scheme 6

Reaction of the cyanohydrin mesylate **38** with azide ($\text{NaN}_3 \cdot \text{CH}_2\text{Cl}_2$) led not to the product of simple displacement, but to the vinyl azide **40** in 30% yield, through the alkylidene carbene **39** (Scheme 7), which could be trapped by insertion into cyclohexene or triethylsilane.⁴⁵

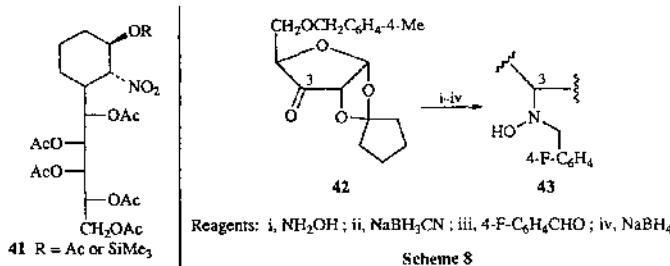


Scheme 7

The work of Lehmann and co-workers on synthesis of oligosaccharide mimics bearing diaziridine groups for use in photoaffinity labelling of the binding sites of enzymes, is covered in Chapters 3 and 4, and glycosylation using a glycosylidene diaziridine in Chapter 3.

3 Nitro- and Nitroso-sugars

A review (37 refs.) on the application of molecular orbital calculations to the stereoselectivity of addition reactions of nitro-enitol derivatives has been published in Japanese.⁴⁶ Cycloaddition of 1-acetoxy- or 1-trimethylsilyloxy-butadiene to 1,2-dideoxy-1-nitro-D-glucoshept-1-enitol tetraacetate gave mainly the cyclohexane derivatives **41**.⁴⁷ Additions of alcohols, carbon radicals and phosphoryl



Scheme 8

groups to nitroalkenes are covered in Chapters 5, 14 and 17, respectively.

The production of free sugars by ozonolysis of the sodium salts of 1-deoxy-1-nitro-adducts is covered in Chapter 2. A naturally occurring branched-chain C-nitroso-sugar moiety is mentioned in Chapter 19.

4 Nitriles, Oximes, Hydroxylamines, Nitrones and Imines

A one flask synthesis of 2,3,5-tri-*O*-benzoyl- β -D-ribofuranosyl cyanide from the corresponding β -ribosyl acetate (with Me₃SiCN, SnCl₄, MeCN) has been detailed.⁴⁸

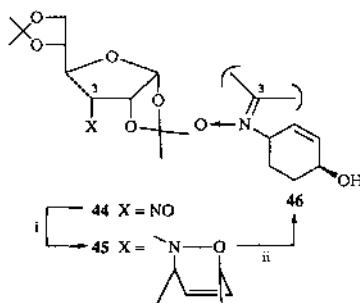
The preparation of the *O*-benzoyloxime derivative of 2,3,6-tri-*O*-benzoyl α -D-*arabino*-hex-2-ulopyranosyl bromide and its reactions with nucleophiles at the anomeric centre are covered in Chapter 8.

Approaches to the preparation of 3'-deoxy-3'-(*N*-hydroxyamino)-analogues of nucleosides are covered in Chapter 20. They are based on reductive hydroxyaminations of ketone derivatives, as shown for the conversion of the D-*erythro*-pentos-3-ulose derivative **42** to the hydroxylamine derivative **43** (Scheme 8). E.s.r. spectra of the free radicals formed spontaneously from these materials have been studied.⁴⁹

Hetero-Diels-Alder reactions of deoxy-C-nitroso-compounds gave deoxy-C-hydroxylamino-derivatives. The 3-C-nitroso-compound **44** gave a single isomeric product **45**, whereas primary nitroso-compounds gave stereoisomeric mixtures (Scheme 9). Periodate oxidation of **45** gave the nitrone **46**.⁵⁰ The related nitrone **47**, derived by condensation of the corresponding 3-keto-sugar with an *N*-substituted hydroxylamine, cyclized to the spiro-cyclic derivative **48** (Scheme 10), which gives an aminoxy radical by spontaneous air oxidation.⁵¹

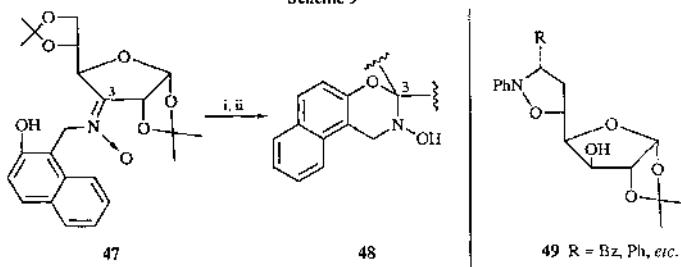
Cycloaddition of nitrones to 5,6-dideoxy-1,2-*O*-isopropylidene- α -D-*xylo*-hex-5-enofuranose gave mainly or exclusively the *cis*-substituted isoxazolines **49**.⁵² The hydroxylamine-linkage of the esperamicin trisaccharide **51** was constructed by *O*-glycosylation of the nitrone **50** followed by deprotection (Scheme 11).⁵³

Photobromination of either 2,3,4,6-tetra-*O*-acetyl- α - or β -D-glucopyranosyl azide gave the bromiminolactone **52**, the β -anomer reacting much the faster.^{54,55} 1,2:5,6-Di-*O*-isopropylidene- β -D-mannofuranosyl azide similarly gave a bromiminolactone.⁵⁶ The crystalline branched-chain imine **54** was obtained on reaction of enone **53** with *p*-toluidine or *p*-anisidine in boiling ethanol (Scheme 12), rather than the desired product in which one methylthio-group would have been replaced by an arylamino-group.⁵⁵



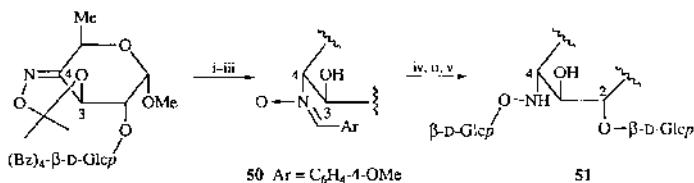
Reagents: i, cyclohexa-1, 3-diene; ii, NaIO₄

Scheme 9



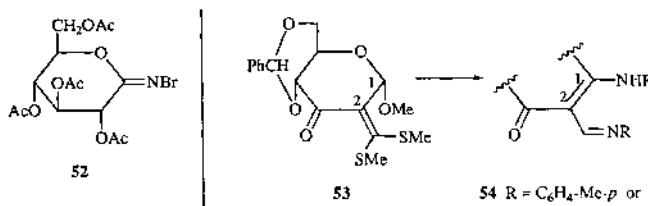
Reagents: i, Ac₂O ; ii, NaOMe, MeOH

Scheme 10



Reagents: i, NaBH₃CN, HCl ; ii, H₃O⁺ ; iii, ArCHO ; iv, (Ac)₄- α -D-Glcp-Br ; v, MeONa, MeOH

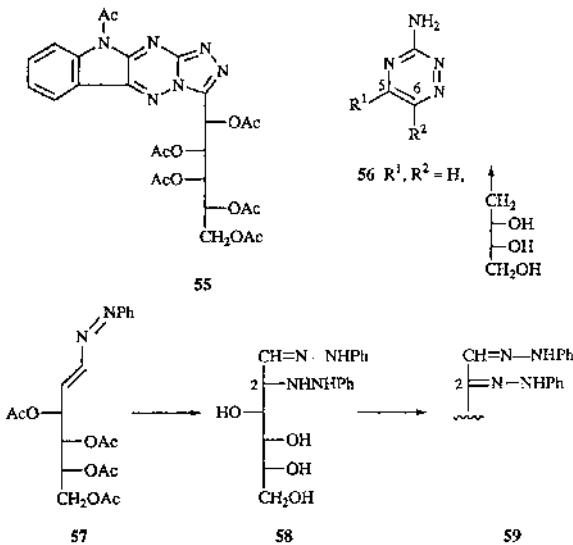
Scheme 11



Scheme 12

5 Hydrazones, Osazones and Related Heterocycles

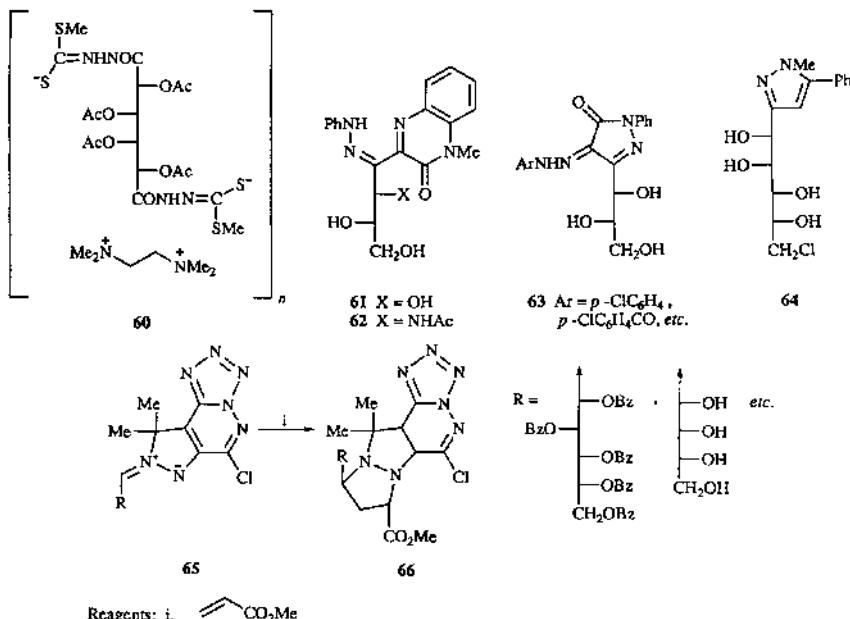
The hydrazone derivatives of 1,2:5,6-di-*O*-isopropylidene- α -D-*ribo*-hexofuranos-3-ulose and its *N*-methyl, *N*-phenyl, and *N*-trityl analogues have been synthesized and characterised.⁵⁶ Tetracyclic derivatives such as 55 were obtained on condensation of six aldoses with a tricyclic heteroaromatic hydrazine, followed by dehydrogenation and acetylation.⁵⁷ Isomeric 5- or 6-substituted 3-amino-1,2,4-triazine derivatives, e.g. 56, were produced by reaction of 3-deoxy-D-*erythro*-hexos-2-ulose or 3-deoxy-D-*erythro*-pentos-2-ulose with aminoguanidine. Analogous reactions of D-*arabino*-hexos-2-ulose and D-*threo*-hexos-2-ulose gave only 5-substituted triazines.^{58,59} The azoalkene 57 on addition of phenylhydrazine gave hydrazone 58 which suffered spontaneous oxidation to osazone 59 (Scheme 13).⁶⁰



Scheme 13

The formation and isomeric composition of fructose (4-substituted)-thiosemicarbazones have been investigated.⁶¹ Reaction of tetra-*O*-acetyl-galactaryl bis-4-*S*-alkyl semicarbazide with diamines such as tetra-*N*-methyl-ethylenediamine gave either monomeric amine salts, or polymeric amine salts, e.g. 60, depending on the molar ratio of amine to semicarbazide.⁶² Acetylation of hydrazones such as 61 followed by treatment with methanolic ammonia gave acetamido-derivatives such as 62 of undefined configuration at C-2.⁶³ The synthesis of pyrazolinones 63 and some of their reactions have been investigated.⁶⁴ The 3-(5-chloro-5-deoxy-D-*manno*-pentitol-1-yl)pyrazole 64 was obtained by reaction of the corresponding pentitol-1-yl pentaacetate with boron trichloride followed by

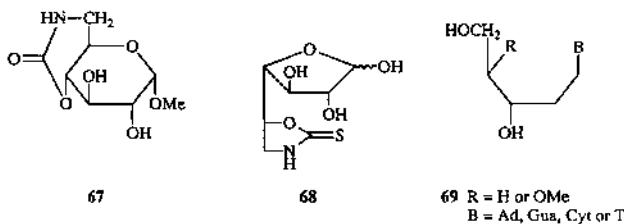
methanol.⁶⁵ Azomethine imines **65** were obtained from aldehydo-sugar derivatives, and underwent dipolar cycloaddition with methyl acrylate to "C-nucleosides" **66** (Scheme 14).⁶⁶



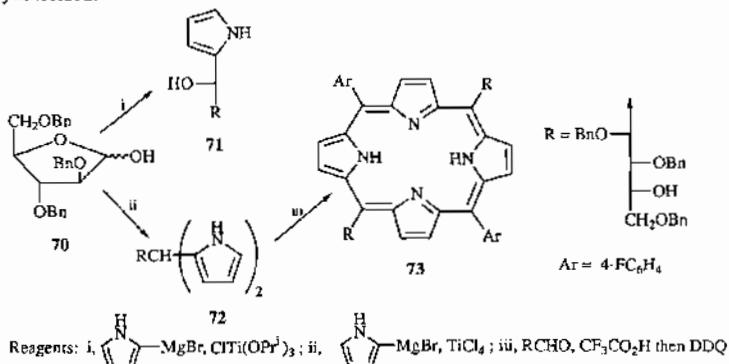
Scheme 14

6 Other Heterocycles

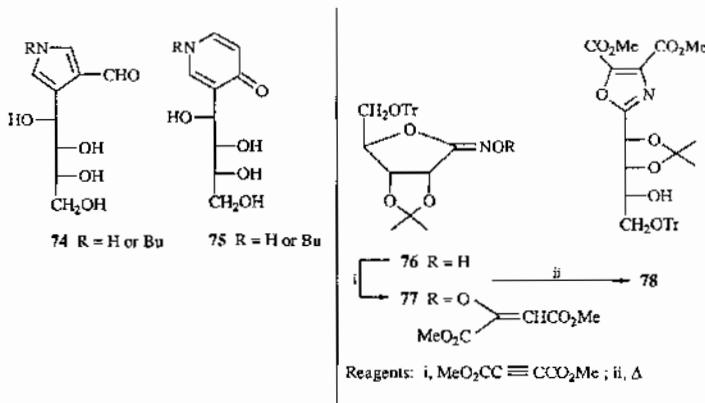
The oxazolinethione **67** was obtained from methyl 6-deoxy-6-isothiocyanato-D-glucopyranoside on treatment with triethylamine, and the oxazolinethione **68** from 6-deoxy-6-isothiocyanato-D-galactopyranose diacetone on hydrolysis.⁶⁷ Cyclonucleosides (**69**) were synthesized from methyl 3,5-di-O-benzyl-2-deoxy-D-*erythro*-pentofuranoside, via 5-deoxygenated or 5-O-methylated 1-O-mesylalditol derivatives which were condensed with various bases.⁶⁸ Several 3-(alditol-1-yl)glutarimide derivatives are covered in Chapter 24.



The mono- and di-pyrrole-substituted alditols **71** and **72** were synthesized by condensing the free sugar **70** with organomagnesium - titanium(IV) reagents (Scheme 15). Dehydration of **71** led to anomeric C-pyrrole D-arabinofuranosides (see also Chapter 3), while a further condensation reaction involving **72** led to the porphyrin C-glycoconjugate **73**.⁶⁹ Mixtures of pyrrole **74** and pyridone **75** derivatives were isolated from the condensation and cyclisation of 1-amino-1-deoxy-D-fructose and its *N*-butyl derivative with malondialdehyde.⁷⁰ Various hydrazone, thiosemicarbazone and imino derivatives of 6,6-dimethyl-4-oxo-4,5,6,7-tetrahydro-2-(D-*arabino*-tetritol-1-yl)indole have been synthesized.⁷¹



Scheme 15

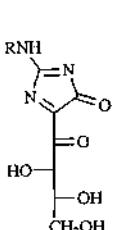


Scheme 16

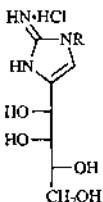
Various 2-(alditol-1-yl)oxazole derivatives, e.g. **78**, have been obtained in modest yields from sugar lactone oximes via their *O*-vinyl ethers, e.g. **76**→**77** (Scheme 16).⁷²

Addition of guanidine or its *N*-isopropyl-derivative to ascorbic or dehydroascorbic acid

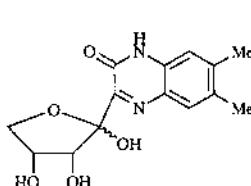
afforded the 2-amino-imidazole derivatives **79**.⁷³ Addition of cyanamide to 1-amino- or 1-alkylamino-1-deoxy-D-lyxo-hex-2-ulose, precipitation with picroic acid, and treatment with acid yielded the imidazolin-2-ylideneammonium salts **80**.⁷⁴



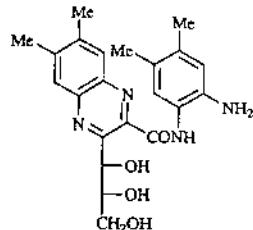
79 R = H or Pr²



80 R = H, Me, etc.



81



82

Condensation of dehydro-D-isoascorbic acid (dehydro-D-erythorbic acid) with one or two equivalents of 1,2-diamino-4,5-dimethyl-benzene afforded a quinoxalinone, e.g. **81** or a quinoxaline, e.g. **82**, respectively.⁷⁵ An isomer of flavin adenine dinucleotide containing a D-*arabinitol*-1-yl rather than a D-*ribitol*-1-yl moiety, has been identified as a naturally occurring co-factor of the alcohol oxidase of methanol utilizing yeasts.⁷⁶

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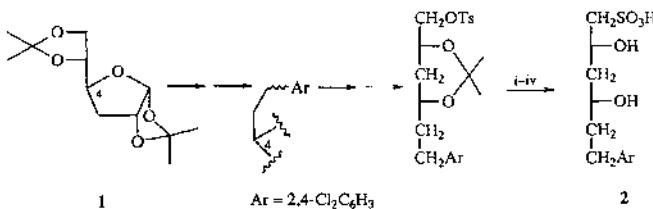
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11

Thio-sugars

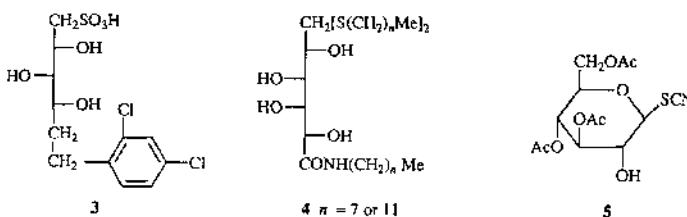
The mevalonic acid model **2** has been synthesized from diacetone 3-deoxy-D-glucose (**1**) in many steps, as outlined in Scheme 1,¹ and its analogue **3** with an additional hydroxyl group was made available by a similar reaction sequence starting from 2,4-O-benzylidene-D-glucitol.² The preparation and liquid crystalline properties of dithioacetals **4**, obtained from D-galacturonic acid *n*-alkylamides by treatment with *n*-alkyl thiols in the presence of trimethylsilyl chloride have been described.³



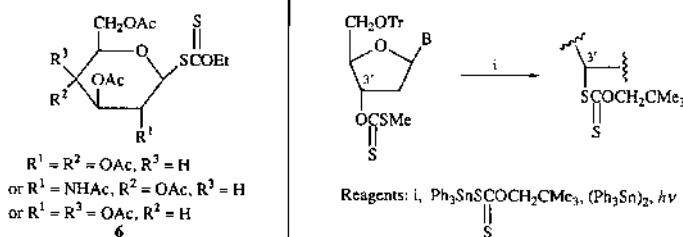
Reagents: i, KSBz; ii, MeO⁻, MeOH; iii, KMnO₄; iv, H⁺

Scheme 1

A new route to 1,2-*trans*-glycosyl thiocyanates, such as the glucose derivative **5**, involved opening of 1,2-anhydrosugars with ammonium thiocyanate⁴ and phase transfer catalyzed reaction of glycosyl halides with *O*-ethyl-*S*-potassium dithiocarbonate proved to be an efficient new method for the preparation of the known *S*-glycosyl xanthates **6**.⁵

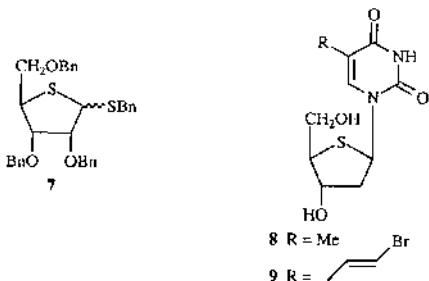


A novel radical chain reaction based on *O*-alkyl tin dithiocarbonate reagents which allows transformation of sugar xanthates to thiosugar dithiocarbonates with retention of configuration has been developed. Its application to the preparation of a thionucleoside derivative is shown in Scheme 2.⁶ The tribenzyl ether **7** of benzyl 1,4-dithio-D-ribofuranoside has been obtained from L-

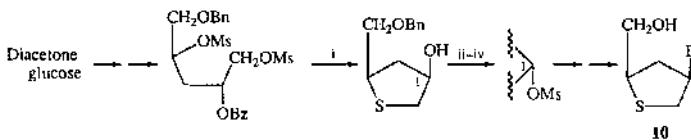


Scheme 2

lyxose by a known procedure (see Vol. 25, Chapter 11, Scheme 4). Further conversion of compound 7 to 4'-thionucleosides is covered in Chapter 20.⁷ A conformational study by ¹H-n.m.r. spectroscopy of the known 2'-deoxy-4'-thionucleoside analogues 8 and 9 has been published.⁸



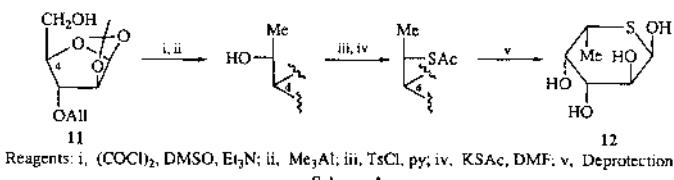
Tetrahydrothiophen-based nucleosides 10 have been produced from diacetone glucose in a multi-step synthesis, as outlined in Scheme 3.⁹



Reagents: i, Na_2S , DMF; ii, BzOH , PPh_3 , DEAD ; iii, K_2CO_3 , MeOH ; iv, MsCl , py

Scheme 3

Two independent preparations of 5-thio-L-fucopyranose (12) have been reported, both involving stereoselective chain-extension at C-5 of an arabinose derivative (e.g., compound 11) and



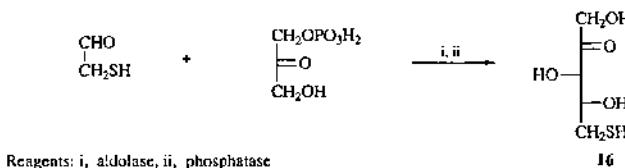
Reagents: i, $(\text{COCl})_2$, DMSO , Et_3N ; ii, Me_3Al ; iii, TsCl , py; iv, KSAc , DMF ; v, Deprotection

Scheme 4

displacement of a sulfonate group at C-4 by potassium thioacetate, followed by deprotection, as illustrated in Scheme 4.^{10,11} Methyl 3-acetamido-3-deoxy-5-thio- α -D-xylopyranoside (**14**) and methyl 4-acetamido-4-deoxy-5-thio- β -L-lyxopyranoside (**15**) were obtained from the known 5-thio-D-xylose derivative **13** by sulfonate displacement with azide or ammonia accompanied by formation and opening of epoxide intermediates (see Chapter 5).¹²

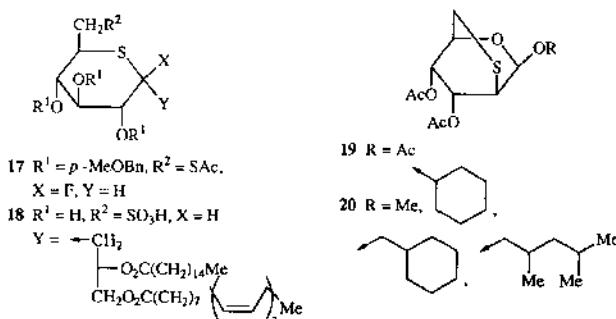


S-Thio-D-threo-pentulose (**16**) has been produced by stereospecific aldolase-catalyzed condensation of thioglycolaldehyde with hydroxyacetone monophosphate and subsequent treatment with phosphatase, as shown in Scheme 5, and 6-thio-D-fructose has been similarly obtained by use of racemic 3-thioglyceraldehyde.¹³ The preparation of an AZT 5'-lipidic sulfide is referred to in Chapter 20.

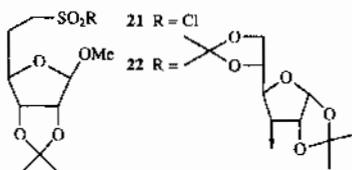


Scheme 5

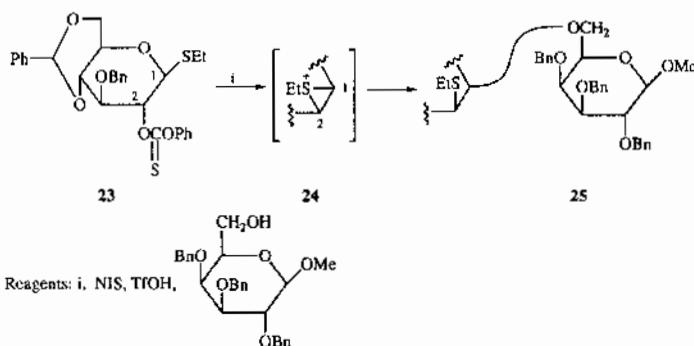
The 5,6-dithio-glucosyl donor **17** was synthesized in eight conventional reaction steps from tri-*O*-acetyl-D-glucal and converted in six further standard steps to the cyanobacterial sulfolipid **18**.¹⁴ By reaction with the corresponding alcohols under Lewis acid catalysis, the 2,6-anhydro-2 thio-D-altrose derivative **19** has been converted, almost quantitatively, to alkyl glycosides **20** which on desulfuration should give easy access to alkyl 2,6-dideoxy- β -D-ribo-hexopyranosides.¹⁵



Monosaccharide sulfonyl chlorides, e.g., compound 21, are available by treatment of quaternary ammonium salts of the corresponding sulfonates with sulfonyl chloride in the presence of triphenyl phosphine. Reaction of compound 21 with diacetoneallose represents a simple, new route to the sulfonyl-linked desaccharide 22 (see Vol. 25, Chapter 11, ref. 21).¹⁶ UDP-5'-Thiogalactose, prepared by established procedures, has been used as the donor substrate for galactosyl transferase in the preparation of *N*-acetyl-5'-thioglactosamine from β -D-GlcNAc-O(CH₂)₆CO₂Me.¹⁷ 2'-Thiodisaccharides such as compound 25, obtained by use of ethyl 1,2-*trans*-thiocarbonatothioglycoside 23 as glycosyl donor, are a potential source of 2'-deoxyglycosides. The reaction is assumed to proceed *via* an epiminium intermediate 24, as indicated in Scheme 6 (see also Chapter 7, refs. 21,22).¹⁸ Nicolaou's method for stereospecific formation of 2-deoxyglycosides with the help of an auxiliary phenylthio group adjacent to the anomeric centre of the glycosyl donor (see Vol. 20, Chapter 3, Scheme 5) has been applied to the total synthesis of sialyl dimeric Le^x.¹⁹

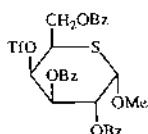


The use of 2,3,4,6-tetra-*O*-acetyl-5-thio- α -D-glucopyranosyl trichloroacetimidate as glycosyl donor is covered in Chapter 3. The key-steps in the syntheses of the sulfur-linked di- and tri-saccharides 27 and 28 were the substitution of the triflate group of compound 26 by the anions of 1-thio- β -D-glucose and 1,4-dithio- β -cellobiose, respectively.²⁰ Various photolabile (3-azibutyl)thioethers of maltose and maltotriose have been prepared by displacement of the appropriate sugar triflates by KSAc, followed by *S*-deacetylation and alkylation with 3-azibutyl-1-

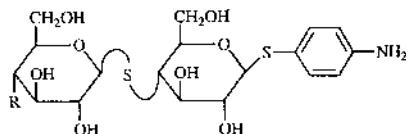


Scheme 6

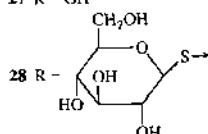
tosyloxybutane.²¹ Sulfur-containing derivatives of β -D-GlcNAc-(1 \rightarrow 3)- β -D-Galp-OMe and of linear and cyclic malto-oligosaccharides are referred to in Chapters 3 and 4, respectively.



26



27 R - OH

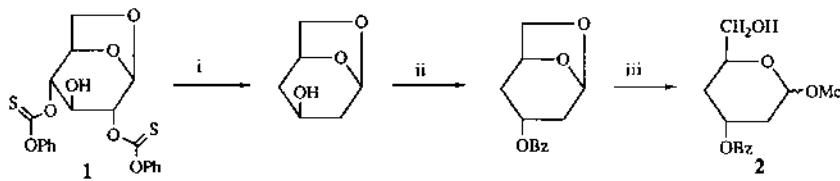


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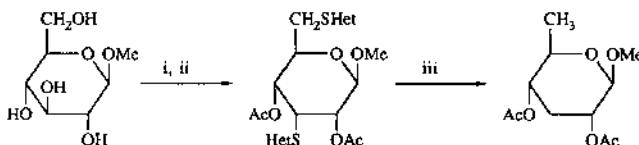
12 Deoxy-sugars

There continue to be developments and refinements in methods for free-radical deoxygenation. Cheap dialkyl phosphites (with dibenzoyl peroxide)¹ and hypophosphorous acid (with AIBN)² have been used as hydrogen atom sources in high-yielding deoxygenations of a number of fairly standard carbohydrate substrates. A double deoxygenation of the levoglucosan derivative **1** was used in a route to a precursor (**2**) of the lactone unit of the mevinic acids (Scheme 1). In this work, tris(trimethylsilyl)silane proved the best hydrogen donor,³ but the Texas group have pointed out that the much more economical diphenylsilane can also be used with equally good results if the free hydroxyl group of **1** is protected by silylation with TMSCl before the deoxygenation, presumably to stop partial silylation by the diphenylsilane.⁴ Other workers have reported an alternative route from D-glucose to the *p*-nitrobenzoyl analogue of **2**, where again free-radical deoxygenation was involved at C-4.⁵ Mitsunobu reactions with thiols, followed by tributylstannane reduction, can be carried out on unprotected glycosides to give deoxy- and dideoxy-derivatives, as illustrated by the case in Scheme 2 (HetSH = 2-mercaptopbenzothiazole).⁶ A polymer-bound tin hydride reagent has been developed and used in Barton-McCombie deoxygenations, including on diisopropylidene glucose, and on methyl 4,6-*O*-benzylidene- α -D-glucopyranoside, where the 2,3-ene was formed.⁷



Reagents: i, $(\text{TMSS})_3\text{SiH}$, AIBN; ii, Ph_3P , DEAD, PhCO_2H ; iii, MeOH , Amberlite H^+

Scheme 1

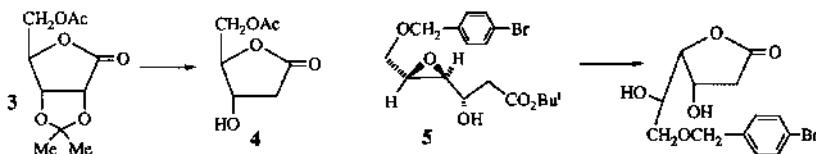


Reagents: i, HetSH, Ph_3P , DEAD; ii, Ac_2O ; iii, Bu_3SnH , AIBN.

Scheme 2

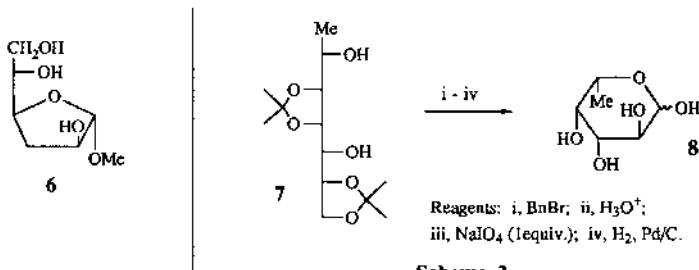
Other advances in methodology for synthesis of deoxysugars include the reduction of triflate esters with tetrabutylammonium borohydride, and the same reagent was also used for reductive

openings of epoxides.⁸ Direct reduction of 2-hydroxy-lactones to 2-deoxy-lactones can be accomplished using SmI_2 , and 2,3-acetals of aldonolactones react similarly, as in the conversion of **3** to **4**.⁹ Another route to 2-deoxy-lactones involves the cyclization of epoxyesters such as **5**, produced by *erythro*-selective addition of *t*-butyl lithioacetate to the epoxyaldehyde, when treated with either zinc metal and TMSCl , or with ZnCl_2 .¹⁰ A potential stereospecific route to 2-deoxyglycosides is mentioned in Chapters 3 and 11.



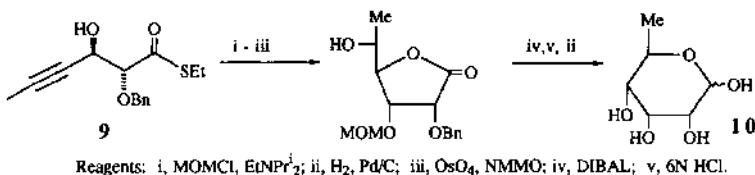
Further evidence has been accumulated to support the theory that the key reductive step in the deoxygenation at C-3 during the biosynthesis of ascaryllose (3,6-dideoxy-L-*arabino*-hexose) proceeds via a radical mechanism (see Vol. 22, p. 126).¹¹

Full details have appeared of the preparation by Vogel's group of methyl 3-deoxy- α -D-*arabino*-hexofuranoside and methyl 4-deoxy- α -D-*lyxo*-hexopyranoside (see Vol. 23, p. 132), and a stereochemical modification permitted the synthesis of the 3-deoxy- β -L-*xylo*-hexofuranoside **6**.¹² The same group has also used the 'naked sugar' approach to make 2-deoxy-L-fucose (2,6-dideoxy-L-*lyxo*-hexose).¹³ Two new syntheses of L-fucose itself (**8**) have been described. One of these



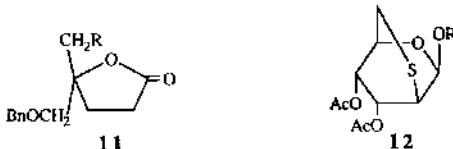
Scheme 3

involves the synthesis of **7** by stereospecific addition of methyl lithium to di-*O*-isopropylidene-D-mannose, followed by the reactions of Scheme 3; use of other alkylolithium reagents permitted the synthesis of chain-extended variants.¹⁴ In another approach, stereoselective addition of Me_2CuLi to an aldehyde function at C-5 of a D-*arabinofuranoside* gave mainly the product of L-*fuco*-configuration.¹⁵ A route to 6-deoxy-D-allose (**10**) involves the acyclic intermediate **9** (Scheme 4), which was produced enantiospecifically by an aldol condensation in the presence of a chiral catalyst; the two other chiral centres were introduced by a diastereoselective dihydroxylation, although the degree of *erythro*-selectivity depended on the protecting group at O-3.¹⁶ When several methyl 6-deoxy-5-enopyranosides, with C-methyl branches at C-2, C-3, and C-4 were reduced catalytically, the 6-deoxy- β -L-hexopyranoside was the major product in each case.¹⁷



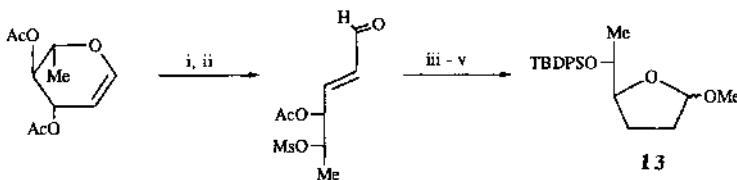
Scheme 4

In a route to 2,3-dideoxy pentofuranosides with alkyl branches at C-4 (**11**), the chiral centre was established by asymmetric epoxidation of an appropriate allylic alcohol.¹⁸ Desulfurization of glycosides of type **12** gives a route to 2,6-dideoxy- β -D-*ribo*-hexopyranosides. Since it is possible to obtain the α -anomers of **12** by modification of the conditions of the glycosidation, the α -anomers of the 2,6-dideoxyhexopyranosides can also be obtained.¹⁹ Methyl 2,6-dideoxy- β -D-*arabino*-, 3,6-dideoxy β -D-*ribo*-, and 4,6-dideoxy- β -D-*xylo*-hexopyranosides have been made by partial photochemical deoxygenation of methyl β -D-quinovoside and subsequent separation of the products by g.c.²⁰



In order to resolve synthetic racemic lomatin, a hydroxylated dihydropyranocoumarin, the racemate was converted into its diastereomeric α -L-glycosides by reaction with 3,4-di-O-acetyl-2,6-dideoxy- α -L-arabino-hexopyranosyl bromide; the separable isomers were subsequently hydrolysed, and a 2-deoxy-sugar was used to facilitate this acidic hydrolysis, since lomatin itself is sensitive to acid.²¹

L-Rhamnose was used as a starting material to prepare the trideoxyhexofuranose **13**, a subunit

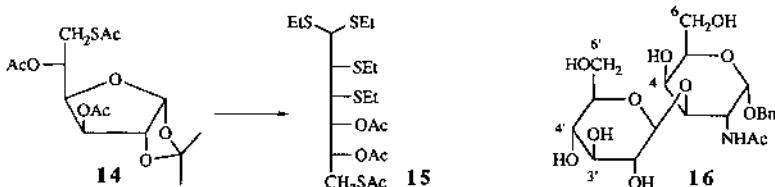


Reagents: i, HgSO_4 , H^+ ; ii, MsCl ; iii, H_2 , Pd/C ; iv, NaOMe ; v, TBDPSCl

Scheme 5

of the ionophoric antibiotic tetracycline. The route (Scheme 5) involved inversion of configuration at both C-4 and C-5 of the sugar, via an intermediate epoxide.²² An improved synthesis of D-amicetose (2,3,6-trideoxy-D-*erythro*-hexose) has been described, in which the glucofuranose derivative 14 is converted into the product 15 of D-*allo*-configuration on treatment with ethanethiol and acid (see Vol.

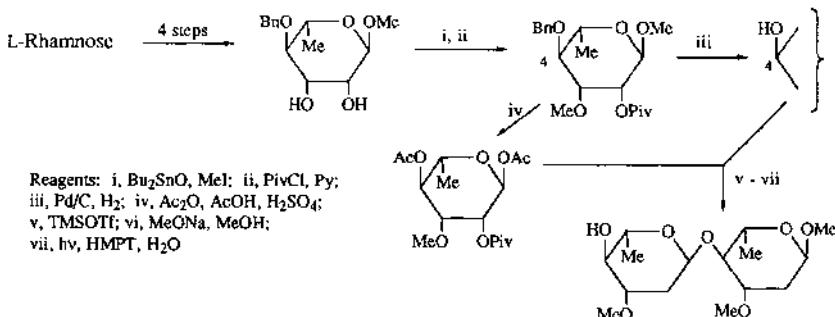
7, p. 94).²³ The 4-*O*-methyl ether of D-amicetose has been found, as its α -pyranoside, as a unit in the polyether antibiotic CP-82009,²⁴ and the synthesis of the trifluoromethyl analogue of D-amicetose is mentioned in Chapter 8.



A chemicoenzymatic synthesis of 2-deoxy-D-xylo-hexose is discussed in Chapter 2, and the occurrence of 2-*O*-methyl-6-deoxy-L-talose in an *O*-linked glycopeptide in Chapters 3 and 5. Syntheses of 2-deoxykanosamine and methyl α -D-*evalopyranoside are mentioned in Chapters 9 and 14 respectively, and deoxyanalogues of ulosonic acids are covered in Chapter 16.*

Free-radical deoxygenation of appropriately protected derivatives was used to prepare the 3-, 4-, and 6-deoxy-analogues of benzyl 2-acetamido-2-deoxy- α -D-galacto-pyranoside,²⁵ and two of these compounds were then employed to make the 4- and 6-deoxy-derivatives of β -D-Galp-(1 \rightarrow 3)- α -D-GalpNAc-OBn (**16**). The 3', 4', and 6'-deoxy- analogues of **16** were also prepared, all these compounds being of interest as model substrates for studies of the biosynthesis of *O*-glycopptides.²⁶

There has been further work reported on deoxyderivatives of lactose (see Vol. 24, p. 147 for earlier work). Deoxygenation reactions on suitable partially-protected derivatives were used to make the 2-, 3-, 6-, 2'- 3', 4'-, and 6'-deoxy-analogues of methyl β -lactoside, and these compounds were used to study binding to the galactose-specific agglutinin from *Ricinus communis*, with the conclusion that the 3-, 4-, and 6-hydroxy functions of the β -D-galactopyranosyl unit are the key polar groups for recognition.²⁷ Other workers have reported routes to methyl 2-deoxy- α -lactoside and methyl 3-deoxy- β -lactoside, together with 1,5-anhydro-4-*O*- β -D-galactopyranosyl-D-glucitol (1-deoxy-lactopyranose) and its 2-deoxy- and 2,3-dideoxy-derivatives. All of these were substrates for the β -galactosidase from *E. coli*, though the rates of hydrolysis varied.²⁸



Scheme 6

The di-oleandrosyl unit found in the avermectins has been prepared from L-rhamnose as indicated in Scheme 6. The α -linkage was secured by having a directing pivaloyloxy group present at C-2 of the glycosyl donor, and subsequently removing it, together with an equivalent group in the acceptor, photochemically.²⁹ A new route to L-oleandrose itself from L-rhamnal involves stannylene-mediated selective methylation at O-3 as a key step.³⁰

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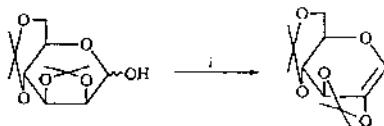
13 Unsaturated Derivatives

1 Glycals

A more detailed paper on the kinetic resolution of synthetic racemic glycals containing an unprojected C-3 hydroxyl group, using vinyl acetate and lipase PS-30 has appeared.¹ (See Vol. 25, p. 152, Scheme 3 for previous report). Glycals prepared by this method which have shown inhibition of the bovine α -L-fucosidase have been used to help map the active site of this enzyme.²

A reductive elimination strategy using samarium diiodide in THF-HMPA has been developed for converting glycosyl phenyl sulfones containing a 2-O-acyl group into glycals.³ With analogues possessing 2-O-alkyl groups the reaction fails.

The preparation of 2-O-alkyl protected oxyglycals by a two step dehydration process involving preparation of an anomeric mesylate followed by oxidative addition of Pd⁰ and subsequent β -hydride elimination has been reported.⁴ By this method a new class of acetal-protected oxyglycals can be prepared (Scheme 1).



Scheme 1

The preparation of 3-deoxy-3-trifluoroacetamido-substituted C-2-acyl glycals such as **1** has been achieved by treating either 1-*O*-*t*-butyldimethylsilyl ethers of appropriate 2-deoxy pyranoses or glycals with acyl chlorides in the presence of aluminium trichloride or ferric chloride.⁵

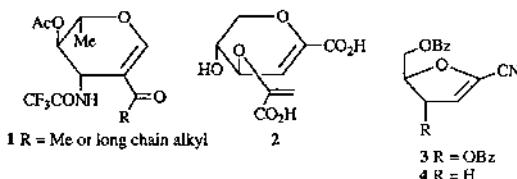
The synthesis of the glycal acid **2** from D-xylose has been reported and its thermal- and chorismate mutase-catalyzed Claisen reaction studied.⁶

O-Silylated glycals react with benzoquinone in the presence of *t*-butyllithium to produce C-1-benzo-quinol glycals which can be reduced with sodium dithionite to C-1-*p*-hydroxyaryl glycals.⁷

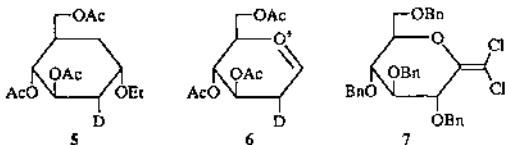
An unexpected preparation of C-3-aryl-3-deoxy-glycals has been discovered during an attempt to add phenols by acid-catalyzed Michael reaction applied to C-2-formyl glycals.⁸

The preparation of nitrile **4** (as an intermediate for nucleoside synthesis) by a Pd⁰ catalyzed sodium borohydride reduction of the previously reported (Vol. 24, p. 132, Scheme 14) nitrile **3** has appeared.⁹

Treatment of 2-benzothiazolyl 2,3-dideoxy-4,6-O-isopropylidene-1-thio- α -D-*erythro*-hex-2-enopyranoside with MeMgBr or PhMgBr in the presence of copper(I) iodide led with allylic rearrangement to the formation of 1,5-anhydro-4,6-O-isopropylidene 2,3-dideoxy-3-C-methyl- or phenyl-D-*ribo*-hex-1-enitol.¹⁰ This paper is an extension of earlier work (*J. Org. Chem.*, 1990, 55, 2294.) and reports similar results to those described in Vol. 24, p. 159, ref. 27.



Addition of triphenylphosphine-deuterochloride to tri-O-acetyl-D-glucal followed by addition of deuterioethanol afforded **5** as the main product (α : β ratio was 3:1 and equatorial:axial deuterium ratio was 2:1). The former ratio may result from the influence of the kinetic anomeric effect applying during the trapping of the intermediate oxonium ion **6**. The results from this reaction and several other examples were used as evidence that the addition of alcohols to glycals under acid catalysis does not proceed by a trans diaxial process.¹¹



For reference to the use of glycals as starting materials for the preparation of 2-deoxy- α - or β -glycosides, sialyl Lewis X antigen or 2-bromo-2-deoxy sugars, see Chapter 3. Also mentioned in Chapter 3 is a method for producing glycosides from glycals by a non-acidic Ferrier rearrangement, as well as the conversion of glycals into diketo-C-glycosides. The identification of (Z)-5,6,7,9-tetra-O-acetyl-4,8-anhydro-2,3-dideoxy-D-glucosone and (E)-5,6,7,9-tetra-O-acetyl-4,8-anhydro-2,3-dideoxy-D-arabinosone amongst other products is covered in Chapter 2 and the addition of trichloroacetyl isocyanate to glycals is referred to in Chapter 14.

2 Other Unsaturated Derivatives

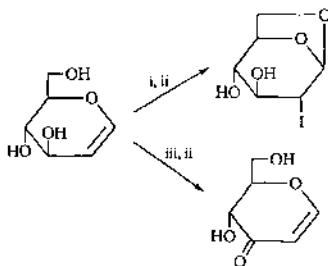
The preparation of dichloro enitol **7** by treatment of tetra-O-benzyl-D-glucono- δ -lactone with tris (dimethylamino) phosphine-carbon tetrachloride has been reported.¹² (See Vol. 25, p. 155 Scheme 10 for similar work.)

Heating D-glucose at between 50°-120° in aprotic solvents in the presence of catalytic sulfuric

acid afforded a moderate yield of levoglucosenone¹³ and the predominant preparation of the related α -C, S or O-glycosides of 4-enopyran-2-uloses by a similar route to that previously described (Vol. 25, p. 156, Scheme 12) has been reported.¹⁴ In a similar way C-glycosides such as allyl and phenacyl have also been prepared starting from hexa-O-acetyl-D-lactal.¹⁵

The preparation of branched-chain 4-eno-pyran-2-uloses derived from levoglucosenone is mentioned in Chapter 14. Studies on the addition of methanol to 2-C- and 3-C-nitro- α - and β -D-*erythro*-hex-2-enopyranosides as well as the preparation of C-1 glycosides by the addition of organometallic agents to 2,3-dihydro-4H-pyran-4-ones can be found in Chapter 3.

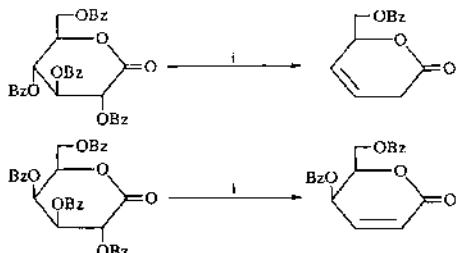
Treatment of D-glucal with bis(tributyltin) oxide then N-iodosuccinimide gives rise to solvent dependent products as shown in Scheme 2.¹⁶ The use of molecular bromine or iodine gave only products of halocyclization regardless of the solvent used.



Reagents: i, $(Bu_3Sn)_2O$, CH_3CN ; ii, NIS; iii, $(Bu_3Sn)_2O$, PhH

Scheme 2

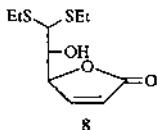
Per-benzoylated aldonolactones undergo a reductive elimination reaction with samarium diiodide leading to unsaturated derivatives (Scheme 3).¹⁷ Deoxygenation at the 2-position can also take place. The difference in the reductive elimination patterns between the D-*gluco* and D-*galacto* isomers may be due to the axial disposition of the OBz in the *galacto* isomer.



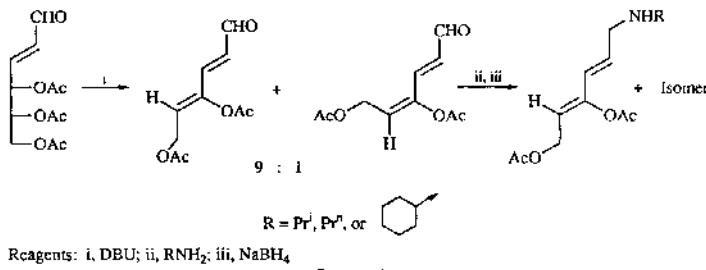
Reagents: i, SmI_2 (3 equivs)

Scheme 3

The apparent conversion of D-glucurono-6,3-lactone diethyl dithioacetal into unsaturated lactone **8** has been reported.¹⁸



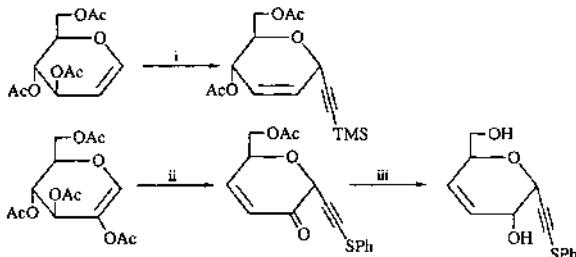
The conversion of acetylated 2,3-dideoxy-hex-2-enoses into acyclic allylamines via acetoxydienal mixtures has been reported (Scheme 4).¹⁹ In a similar way (2E)-4,5,6,7-tetra-O-acetyl-2,3-dideoxy-aldehydo-D-arabino-hept-2-enose was also used as starting material.



Scheme 4

The preparation of 3-*O*-benzyl-5,6-dideoxy-1,2-*O*-isopropylidene- α -D-xylo-hex-5-enofuranose from 3-*O*-benzyl-5,6-di-*O*-methanesulfonyl-1,2-*O*-isopropylidene- α -D-glucofuranose has been reported.²⁰ (See Vol.25, p. 159, ref. 26 for a similar preparation of the 3-*O*-tosyl derivative).

Glycal or hydroxyglycal esters can be converted into the unsaturated C-glycosides as shown in Scheme 5.²¹

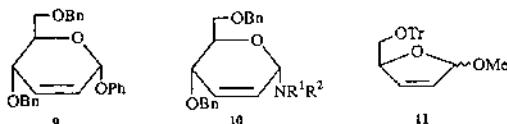


Reagents: i, TMS-C≡C-TMS, SnCl₄; ii, TMS-C≡C-SPh, BF₃•OEt₂, then H⁺ or OH⁻; iii, NaBH₄, CeCl₃ or LiAlH₄

Scheme 5

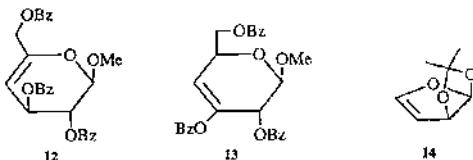
The conversion of the 2,3-unsaturated hexopyranoside **9** into the amino glycoside **10** by reaction of an amine (morpholine, imidazole or adenine) and a catalytic amount of bis-1,4-(diphenylphosphino)butane palladium has been reported.²²

The synthesis of dideoxypentene furanoside **11** has been achieved by Zn-Cu reductive elimination of methyl 2,3-di-*O*-mesyl-5-*O*-trityl-D-xylofuranoside.²³

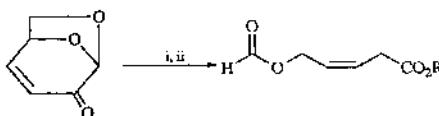


Treatment of methyl 2,3,6-tri-*O*-benzoyl- β -D-galactopyranoside with DAST led to the formation of **12** and **13** in addition to methyl 2,3,6-tri-*O*-benzoyl-4-fluoro- β -D-glucopyranoside.²⁴

The synthesis of (-)-**14** in six steps from D-glucose using conventional chemistry has been disclosed.²⁵



The photochemical α -cleavage of levoglucosenone to afford (*Z*)- β,γ -unsaturated acid derivatives has been reported (Scheme 6).²⁶



Reagents: i, $h\nu$, Hg or pyrex filter; ii, ROH

Scheme 6

The mass spectra of some unsaturated C-glycosides are reported in Chapter 22. The preparation of unsaturated derivatives by radical deoxygenation processes is covered in Chapter 12. Unsaturated sugar acids and nucleosides are mentioned in Chapter 16 and 20 respectively. The preparation of acyclic α,β -unsaturated aldehydes via stannylenes is covered in Chapter 17 and 6,7-unsaturated octuronates in Chapters 2 and 18.

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14

Branched-chain Sugars

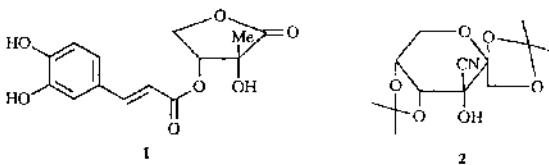
1 Compounds with an R-C-O Branch

A symposium on the synthesis of L-arcanose and L-olivomycose by a Lewis acid mediated reaction of allenylmethyltrimethylsilane with aldehydes and acetals has been reported.¹ (See Vol. 25, p.163, Scheme 4 for similar work).

A new anti-tumor fermentation product of the enediyne class, named kedarsidin, has been shown to be a glycoside of α -L-inycarose.²

The isolation of the branched-chain D-erythro-1,4-lactone ester **1** and its corresponding hydroxy acid hydrolysis product from the leaves of *Bidens pilosa* have been described.³

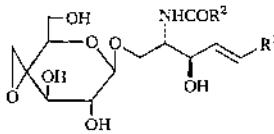
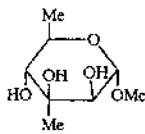
A report on the stereoselective preparation of the cyanohydrin **2** from the corresponding ketone by phase transfer catalysis has appeared.⁴



The synthesis of 4-C-methyl-D-ribofuranose derivatives as key intermediates for 4'C-methyl nucleosides from D-glucose has been reported.⁵

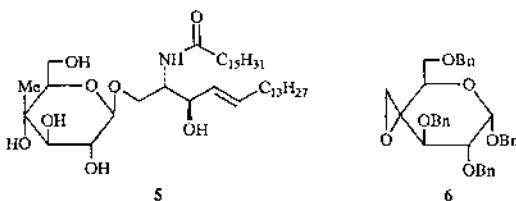
The synthesis of methyl α -D-avalopyranoside **3** in eleven steps by conventional chemistry from the known methyl 2,3-anhydro-4,6-O-benzylidene- α -D-allopyranoside has been disclosed.⁶

The synthesis of 4-epoxy-4-C-methyleneglycosyl ceramides such as **4** as potential glycosyl transferase inhibitors has been reported.⁷ Also reported by the same authors is the synthesis of the 4-C-methyl analogue of glucosyl ceramide **5** by way of hydrogenolysis of epoxide **6**.⁸ (See also ref. 45 this Chapter for related work)

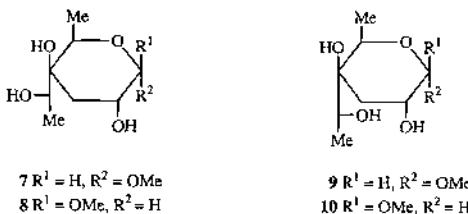


3

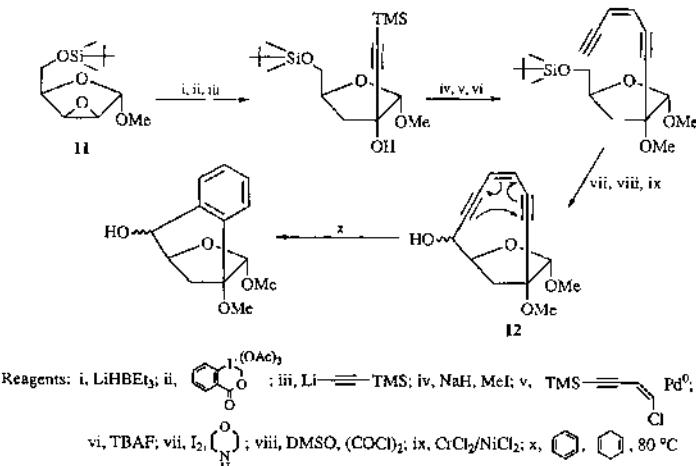
4 R¹ = C₁₃H₂₇, R² = C₁₅H₃₁



The synthesis of methyl 3,6-dideoxy-4-C-(L-glycero-1'-hydroxyethyl)- α - and β -D-xylo-hexopyranoside **7** and **8** and of methyl 3,6-dideoxy-4-C-(D-glycero-1'-hydroxyethyl)- α and β -D-xylo-hexopyranoside **9** and **10** from levoglucosan has been achieved.⁹ These structures permitted the stereochemical assignment of the naturally occurring yersiniloses to be established.



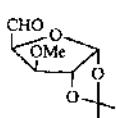
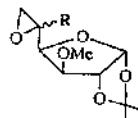
The preparation of oxabicyclo[7.2.1]enediyne **12** starting from the anhydro sugar **11** has been reported (Scheme I).¹⁰ Heating **12** in benzene containing 1,4-cyclohexadiene gave the benzenoid product of thermal rearrangement as shown.



Scheme I

The addition of Grignard reagents to *3,4-O*-isopropylidene-*1-O*-triphenylmethyl-L-glycero-2-tetrolose and *1-O*-benzoyl-*3,4-O*-isopropylidene-L-glycero-2-tetrolose gave product ratios that depended greatly upon solvent, temperature and the nature of the Grignard reagent.¹¹ In a similar way the diastereoselectivity of the addition of various organometallic reagents (including Grignards) to various L-erythulose derivatives was also shown to be dependent on the solvent, temperature and nature of the organometallic, with the best selectivity being observed with dimethylcopper lithium (mainly L-*erythro* product) and MeTi(O*i*Pr)₃ (mainly L-*threo* product).¹²

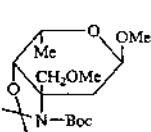
Aldehyde **13** has been used as starting material for the preparation of branched-chain sugars like **14** by the addition of Grignard reagents followed by oxidation to the ketone and addition of diazomethane. The selectivity of the last reaction was investigated as well as the selectivity of the addition of dimethylsulfonium methyllylide.¹³

**13****14** R = H, Me or Ph

The preparation of branched-chain 2-deoxyfuranolactones and of C-4-alkyl-2,3-dideoxyribosides is mentioned in Chapter 12.

2 Compounds with an R-C-N Branch

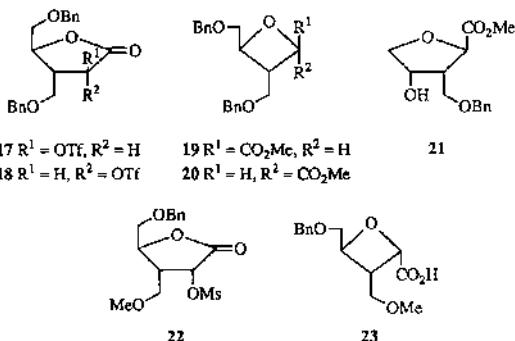
The preparations of C-3 branched amino-sugars of the 2,3,6-trideoxy-L-hexopyranose type related to daunosamine, for example **15** and **16**, have been reported.¹⁴ (See Vol. 25, Chapter 14, ref. 16 and 49 and Vol. 24, Chapter 14, ref. 28 for related work).

**15****16**

3 Compounds with an R-C-H Branch

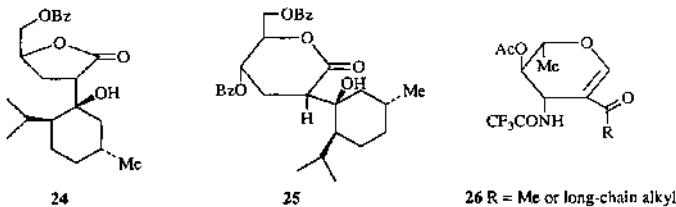
Treatment of the *arabino*-pentolactone triflate **17** with potassium carbonate in methanol afforded oxetane ester **19** together with the tetrahydrofuran **21**, the ratio of which depended on the temperature.¹⁵ This result is inconsistent with a previous report (See Vol. 24, p. 176, Scheme 4). On the other hand lactone triflate **18** gave oxetane **20** with no THF product.

In a similar way it has been shown that reaction of mesylate **22**, under aqueous basic conditions, affords the oxetane acid **23**. This latter compound was used for a formal synthesis of the anti-viral oxetanocin.¹⁶ (See also Vol. 24, p. 217 and p. 176 for similar work.) The synthesis of other branched-chain nucleosides is covered in Chapter 20.



Methyl 3-*O*-benzyl-4,6-*O*-benzylidene- α -D- and β -D-*arabin*-hexopyranosid-2-ulose have been used as starting materials for the preparation of methyl 2-C-acetamidomethyl-2-deoxy- α -D-glucos- and *manno*-pyranosides as well as for methyl 3-*O*-benzyl-4,6-*O*-benzylidene-2-deoxy-2-C-hydroxymethyl- α -D-glucos- and *manno*-pyranosides.¹⁷

The diastereoselective transformation of various 3-deoxy-aldonolactones by reaction with terpene ketones in the presence of samarium diiodide into derivatives such as **24** or **25** has been reported.¹⁸ The same authors have also reported similar work using simpler ketones.¹⁹



The conversion of several *O*-substituted 2-bromo-2-deoxy-D-*arabin*ono-1,4-lactones into 2-C-allyl lactones on treatment with allyltributylstannane has been disclosed.²⁰ The stereochemistry of the products appeared dependent on the orientation and nature of the *O*-substituents as well as on polar effects.

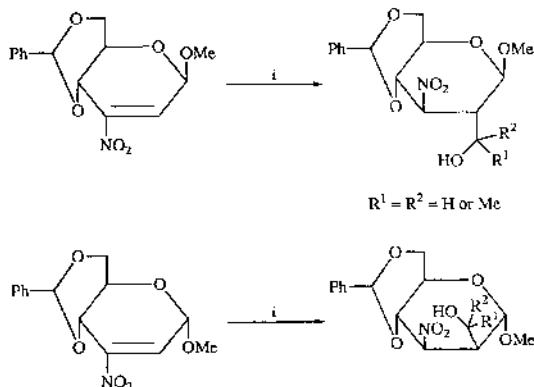
3-Deoxy-3-iodo-1,2:5,6-di-*O*-isopropylidene- α -D-allo- or -gluco-furanose reacted with acrylonitrile, methyl vinyl ketone and methyl acrylate in the presence of a zinc-copper couple to give the corresponding C-3 conjugate addition products *via* radical mechanisms.²¹

Treatment of 2-benzothiazolyl 2,3-dideoxy-4,6-O-isopropylidene-1-thio- α -D-erythro-hex-2-enopyranoside with MeMgBr or PhMgBr in the presence of copper (I) iodide afforded 1,5-anhydro-4,6-O-isopropylidene 2,3-dideoxy-3-C-methyl or phenyl-D-ribo-hex-1-enitol.²¹ This paper is an extension of earlier work (*J. Org. Chem.*, 1990, **55**, 2294) and similar to that reported in Vol. 24, p. 159, ref. 27).

An unexpected direct displacement of a C-3 methoxy group to give C-3-aryl-3-deoxy glycals occurred during an attempt to add phenols in an acid-catalyzed Michael reaction to 2-C-formyl glycal ethers.²³

The preparation of C-2 acyl glycals like **26** has been achieved by treating either 1-O-t-butylidemethylsilyl ethers of 2,3-dideoxy-3-trifluoroacetamido-pyranoses or glycals with acyl chlorides in the presence of aluminium trichloride or ferric chloride.²⁴

The photoaddition of alcohols to nitroalkenes has been described (Scheme 2).²⁵ Three of the same authors have reported similar work on the photolysis of 3-nitro 2-enopyranosides in 1,3-dioxolane to give the corresponding 2-C-(dioxolan-2-yl)-3-nitro derivatives.²⁶



Reagents: i, $R^1R^2\text{CHOH}$, $h\nu$, Ph_2CO

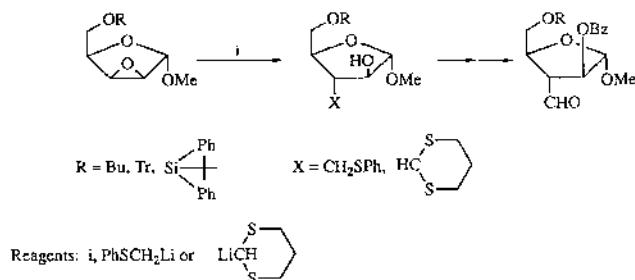
Scheme 2

The preparation of the branched C-formyl furanoside derivatives by opening of an epoxide with phenylthiomethyl lithium or 2-lithio-1,3-dithiane has been described (Scheme 3).²⁷

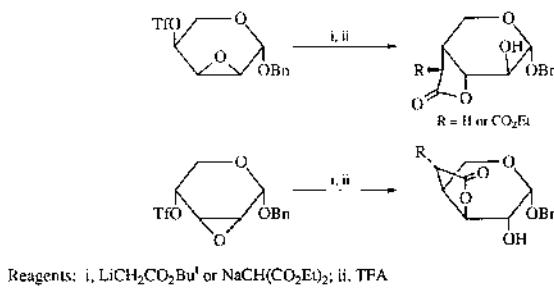
A synthesis of the C-5 homologue of *N*-acetylneurameric acid has been described in which the addition of nitromethane anion to methyl 4,6-O-benzylidene-3-O-benzyl- β -D-arabino-hexopyranosid-2-ulose provided the appropriate branching point.²⁸

An efficient synthesis of chiral butenofides has been reported. (Scheme 4).²⁹

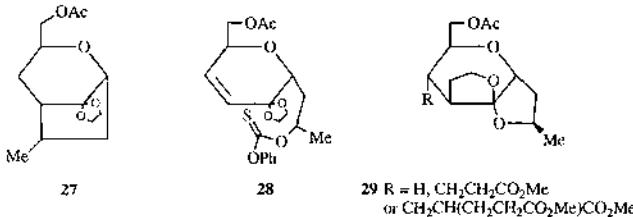
The preparation of the branched C-pyranoside **27**, which is structurally related to trichothecenes, has been carried out by treatment of the thionoformate **28** (prepared in several steps from 2,3,4,6-tetra-O-acetyl-2-hydroxy-D-glucal) with tributyltin hydride.³⁰ Also described are the tricyclic compounds **29**, prepared from an intermediate used for the synthesis of **27**.



Scheme 3



Scheme 4

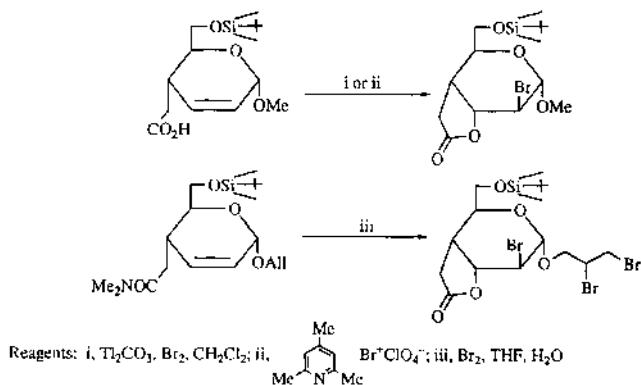


A halolactonization strategy has been developed for the preparation of 4-C-branched hex-2-enopyranosides (Scheme 5).³¹ Several examples are given.

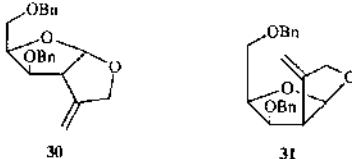
A full account of earlier work (see Vol. 25, p. 171, Scheme 17) concerning the synthesis of homochiral trisubstituted γ -butyrolactones has appeared.³²

Two further papers with full details and extensions on the preparation of hexopyranosido[4,3-*b*] and [1,2-*b*] furans by radical cyclization of propargyl ethers, acetals or ethoxy-iodoethyl groupings on a hexenopyranoside derivative have appeared.^{11,14} (See Vol. 25, p. 172, Scheme 20.)

The synthesis of the chiral furo[2,3-*b*]furans 30 and 31 by radical induced cyclization of the 2-(*S*-methylthio)thiocarbonyl derivatives of the 1-*O*-propargyl-3,5-di-*O*-benzyl α - and β -D-xylose respectively has been disclosed.³³

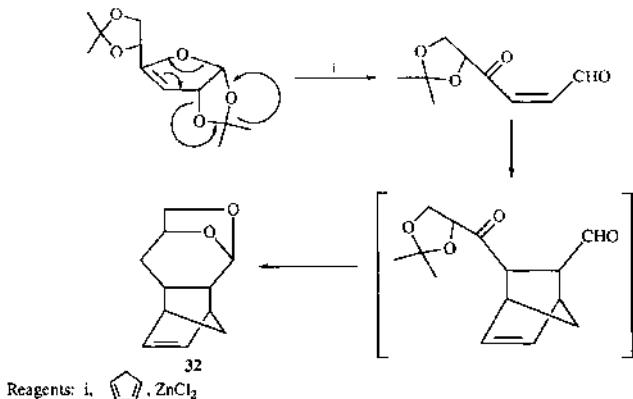


Scheme 5



The 2+2 cycloaddition (together with some 4+2 additions) of trichloroacetyl isocyanate to various benzylated glycals affording *cis* products has been reported.³⁶

Treatment of a D-glucose derived hex-3-enose derivative provides cycloadduct 32 as the main product together with three isomeric derivatives (Scheme 6).³⁷ This unusual and novel reaction is thought to proceed through an initially rearranged acyclic sugar as shown.

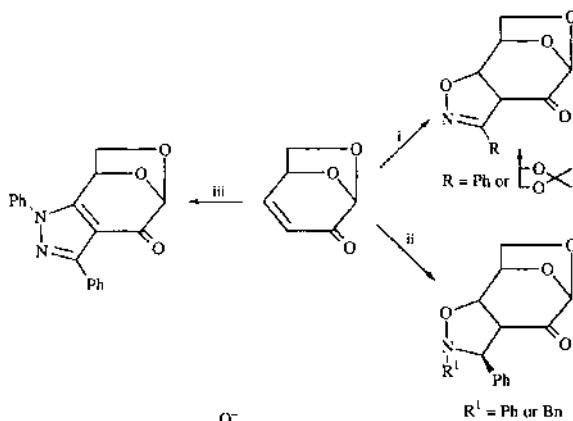


Scheme 6

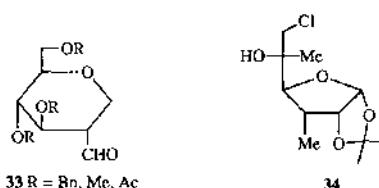
The cycloaddition of various 1,3-dipoles to levoglucosenone has been described (Scheme 7).³⁸

The rhodium catalyzed hydroformylation of glycals in the presence of tris(*ortho*-*tert*-butylphenyl) phosphite to afford 2-formyl derivatives such as 33 has appeared.³⁹

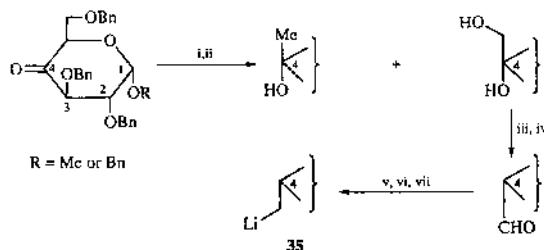
The preparation of the doubly C-branched derivative of D-allose **34** by the use of enantiomerically enriched (Z)-anti-3,5-dialkyl-4-hydroxy-1,5-alkadienyl *N,N*-diisopropylcarbamates, obtained by the homoaldol approach, in a similar way to that described in Vol. 25, Chapter 14, ref. 31, has been reported.⁴⁰ Other furanosides are also described.



Scheme 7



The preparation of the lithiated branched-chain sugar **35**, required for the preparation of C-glycosides, has been reported (Scheme 8).⁴¹

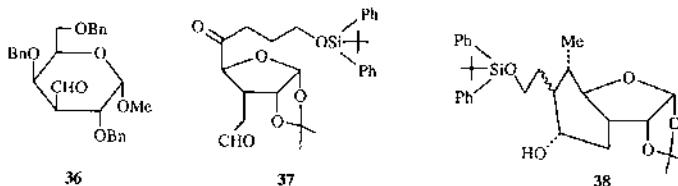


Reagents: i, $\text{Ph}_3\text{P}=\text{CH}_2$; ii, $\text{BH}_3\cdot\text{Me}_2\text{S}$; iii, $\text{DMSO}, \text{Ac}_2\text{O}$; iv, Et_3N ; v, NaBH_4 ; vi, $\text{Ph}_3\text{P}, \text{I}_2, \text{NH}_3$; vii, $\text{Bu}^{\text{t}}\text{Li}$

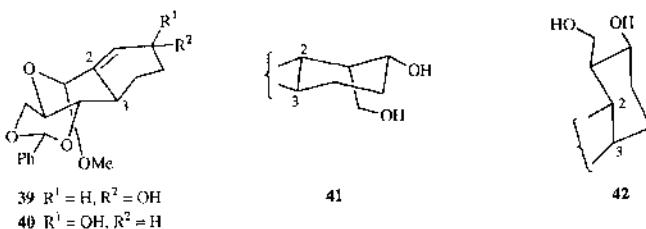
Scheme 8

The preparation of the *C*-3-formyl derivative **36** has been described starting from methyl 2,4,6-tri-*O*-benzyl- α -D-galactopyranoside *via* a sequence involving oxidation of the *C*-3 hydroxyl, Tebbe reaction, hydroboration and Swern oxidation.⁴²

The preparation of compound **38** has been achieved in five steps from the aldol condensation product of derivative **37**, which in turn is available in several steps from D-glucose.⁴³



The stereoselective reductive hydroxymethylation of annulated sugars **39** and **40** to give derivatives **41** and **42** has been described.⁴⁴



The preparation of C-2 branched deoxyheptitols and pentitols is covered in Chapter 18.

4 Compounds with an R-C-R or C=R Branch

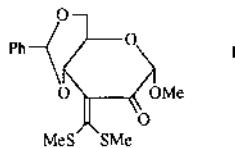
The transformation of 2,3:5,6-di-*O*-isopropylidene-D-xylo-hexos-4-ulose diethyldithioacetal into 4-deoxy-4-C-methylene- β -D-glucopyranosylceramide as a potential inhibitor of glycosyl transferases has been described.⁴⁵ (See also ref. 7 and 8, this Chapter for related work.)

The synthesis of 2,3-dideoxy 3-C methylene- α -glycero-pentofuranose has been achieved by Sharpless epoxidation of 5,5-diethoxy-3 methyl-2-pentenal followed by rearrangement of the product to 2,3-dideoxy-3-C-methylene-D-glycero-pentose diethylacetal and, finally, hydrolysis.⁴⁶

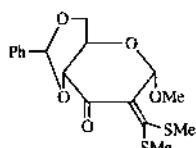
The treatment of 4,6-*O*-benzylidene-3-deoxy- α -D-*erythro* hexopyranosid-2-ulose and the corresponding 2-deoxy-3-ulose with carbon disulfide-methyl iodide and sodium hydride gives branched-chain derivatives **43** and **44** respectively.⁴⁷ Reaction of **43** with ethanol in *p*-toluidine or *p*-anisidine gave, unexpectedly, derivatives **45** and **46**.

The preparation of glycosyl tosylhydrazones and their reaction (*via* a glycosyl carbene) with acrylonitrile to afford all stereoisomers of the glycosyl cyanocyclopropane products has been reported.⁴⁸ Similar work has been reported by other workers (See Vol. 25, Chapter 14, Scheme 29).

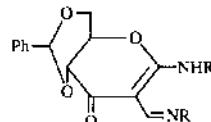
For the preparation of some branched-chain sugars from alkylidene carbenes see Chapter 10. The use of methylene branched acyclic sugars as Diels-Alder precursors is covered in Chapter 24.



43



44

45 R = *p*-MeC₆H₄46 R = *p*-MeOC₆H₄

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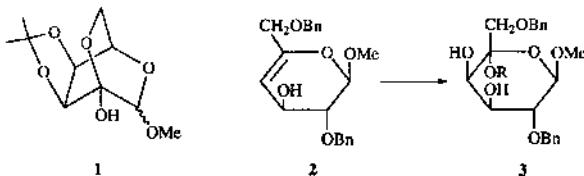
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15

Aldosuloses and Other Dicarbonyl Compounds

1 Aldosuloses

The preparation and use of 1,2:5,6-di-*O*-isopropylidene- α -D-ribo-hexos-3-ulose as a chiral template in organic synthesis has been reviewed.¹ Two saponins isolated from the leaves of *Gymnema sylvestre* contained *O*- β -D-arabino-hexos-2-ulopyranosyl moieties, present as a hemiacetal with an adjacent sugar moiety². The alkaline isomerisation in pyridine solution of methyl α - and β -D-arabino-hexos-2-ulopyranoside into the D-arabino-and then D-ribo-hexos-3-ulopyranosides has been monitored and shown to involve hydride shift and 2,3-enediol-containing mechanisms³. Methyl 3,4-*O*-isopropylidene- α and β -D-lyxo-hexos-2-ulopyranoside have been found to exist as the bicyclic hemiacetals **1**.⁴ Treatment of alkene **2** with MCPBA in an alcohol solvent (ROH) afforded the diglycoside **3** which, after hydrogenolysis and hydrolysis, was converted into L-arabino-hexos-5-ulose.⁵

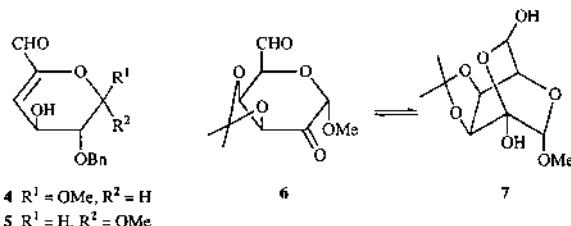


Methods have been described for the purification and h.p.l.c. analysis of 3-deoxy-D-erythro-hexos-2-ulose. Its reactivities in acid and base have also been studied.⁶ Another method for the detection of this aldulosulose in plasma and urine is mentioned in Chapter 23. Sucrose and isomaltulose have been oxidised using *Agrobacterium tumefaciens* to their 3-keto derivatives.⁷ The reaction of dicarbonyl sugars with aminoguanidine is discussed in Chapter 10, and the synthesis of the antibiotic cortalcerone is covered in Chapter 19.

2 Other Dicarbonyl Compounds

When sucrose is oxidised with sodium periodate in 50% aqueous DMF the reaction is selective for the glucose moiety producing a single dialdehyde.⁸ Attempted Swern oxidation of methyl 2-*O*-benzyl-3,4-*O*-isopropylidene- α , β -D-galactopyranoside afforded mostly the unsaturated product

4 for the β -glycoside and ca. 50% of 5 for the α -isomer, rather than the expected saturated aldehyde.⁹ The keto-aldehyde 6 has been found to exist in equilibrium with the cyclic hydrate 7.⁴



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16

Sugar Acids and Lactones

1 Aldonic Acids and Aldonolactones

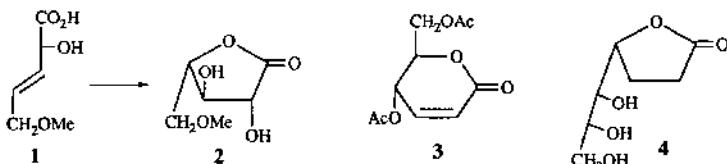
The structure of the first hydrolysable tannin with a gluconic acid 'core' (Vol. 20, p. 158) has been revised to the 2,5-di-*O*-galloyl ester.¹

A convenient, large-scale preparation of D-ribono-1,4-lactone has been described, involving oxidation of D-ribose with bromine in aqueous sodium carbonate solution.² When the allylic alcohol **1**, obtained by bioreduction of the α -ketoacid, was epoxidized with MCPBA, followed by acid hydrolysis, 5-*O*-methyl-L-arabinono-1,4-lactone (**2**) was the major product, with lesser amounts of the D-ribonolactone derivative. *Cis*-dihydroxylation of **1** with OsO₄-NMMO gave about equal amounts of the L-*lyxo*- and D-*xylo*-products.³ 2-Deoxy-D-*erythro*-pentono-1,4-lactone (2-deoxy-D-ribono-1,4-lactone) has been isolated following photosensitized oxidation of deoxyguanosine,⁴ and a novel synthesis of the racemic material has been described.⁵ Some acylated derivatives of pentonolactones and 2-deoxy-pentonolactones, made as rigid deacylglycerol analogues, are mentioned in Chapter 7, as are selective tosylation of aldonolactones.

There have been reports on the electro-chemical oxidation of glucose to give D-gluconic acid,⁶ and its zinc⁷ and magnesium salts.⁸ The kinetics and mechanism of the RuO₄-catalyzed oxidation of aldoses to aldonic acids by alkaline N-bromoacetamide have been studied, with the conclusion that hypobromite is the reactive oxidizing species.⁹

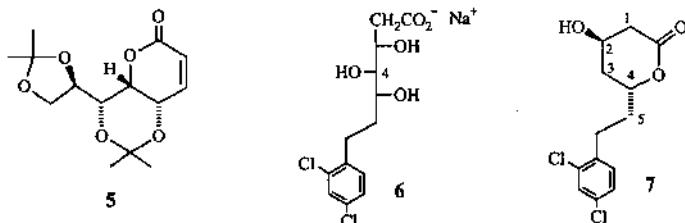
The vanadate analogue of NADP ('NADV') is accepted as a substrate by glucose-6-phosphate dehydrogenase, permitting the formation of 6-phosphogluconate and the reduced coenzyme ('NADVH').¹⁰

The enone **3** can be synthesized directly from tri-*O*-acetyl-D-glucal by treatment with MCPBA-FeCl₃.¹¹

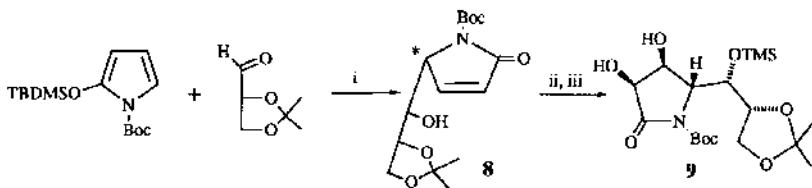


In the area of longer-chain systems, the dideoxy-heptonolactone **4** has been made using a Wittig reaction on unprotected D-arabinose,¹² and a *cis*-selective Wittig reaction was also used to prepare the unsaturated lactone **5**, potentially useful for the synthesis of sialic acids and analogues, from 2,4:5,6-di-*O*-isopropylidene-aldehydo-D-glucose.¹³ 2,4-*O*-Benzylidene-L-xylose was converted, by Wittig reaction and one-carbon chain extension at C-5, into the carboxylate **6**, which was

a weak inhibitor of HMG-CoA reductase.¹⁴ The same group also prepared the known inhibitor **7**, which corresponds in structure to **6**, but with the deletion of O-4, from D-glucose (sugar carbons numbered).¹⁵ The solution conformations of the two alditols obtained by borohydride reduction of *N*-acetyl-neuraminic acid have been studied by ¹H- and ¹³C-nmr,¹⁶



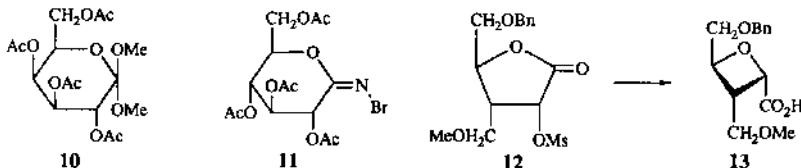
The chemistry of Scheme 1 has been used to prepare the D-glycero-D-talo-heptonolactam **9**. The initial aldol-type condensation was stereoselective for the D-arabino-product **8**, but it was found that treatment of **8** with Et₃N-DMAP caused smooth isomerization at the asterisked carbon to give the D-ribo-lactam.¹⁷ Similar work by the same group using 2-trimethylsilyloxyfuran has been mentioned in earlier Volumes (Vol. 24, p. 174-5, and earlier).



Reagents: i, SnCl₄; ii, TMSCl; iii, KMnO₄, crown ether, CH₂Cl₂

Scheme 1

Ortholactones such as **10** can be prepared from the corresponding 1-bromo-glycosyl cyanide by treatment with the alcohol in the presence of silver triflate and 2,6-lutidine,¹⁸ and bromoimino-lactones such as **11** are the products formed by treatment of *O*-protected glycosyl azides with NBS under photolytic or free-radical initiation.^{19,20}

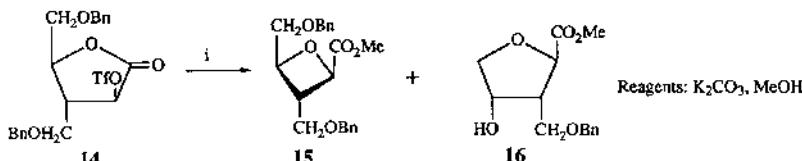


A method has been developed for determining the absolute configuration of aldonic acids, based on the magnitudes of ¹H-nmr shifts induced by a chiral Eu(III) reagent,²¹ and a theoretical

study of the hydrolysis of 1,5-gluconolactone using semiempirical (MNDO-PM3) methods has been reported.²²

2 Anhydroaldonic acids and Lactones

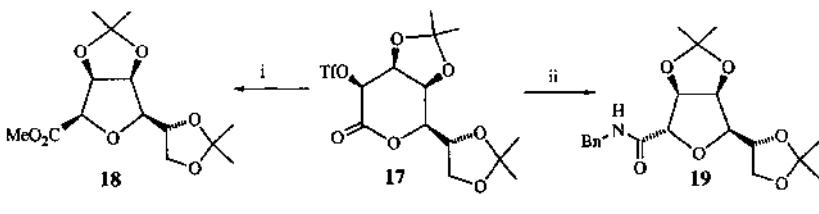
There have been further papers related to Fleet's report on the ring-contraction of carbohydrate γ -lactones to give oxetan derivatives (see Vol. 24, p.176 and 217). The mesylate **12** underwent ring contraction to give **13**, the product of inversion of configuration at C-2, on treatment with NaOH in aqueous methanol; the non-aqueous conditions used in the earlier work had proved unsuccessful with mesylates, and triflates were used instead. The tosylate analogue of **12** also underwent ring contraction to the *N*-benzylamide of **13** on treatment with benzylamine followed by sodium hydride.²³ Other workers have reported that the ring contraction of **14** gives the tetrahydrofuran **16** as well as the oxetan **15** (Scheme 2) (compare Vol. 24, p. 176), and the ratio of products is



Scheme 2

temperature-dependent. Other similar ring-contractions gave only oxetan products.²⁴

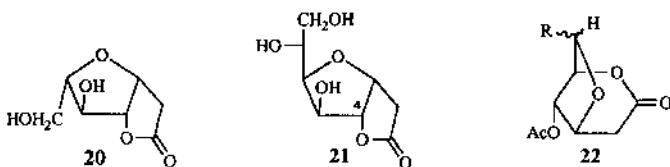
Meanwhile, the Oxford-Glaxo group have studied the analogous ring-contraction of δ -lactones, as exemplified by the conversion of the D-glycero-D-talo compound **17** (see Vol. 25, Chapter 16) to the tetra-hydrofuran **18** with inversion of configuration (Scheme 3). Alternative conditions, however, give the product **19** of retention of configuration as the major epimer (*ca.* 2:1 ratio).²⁵

Reagents: *i*, K₂CO₃, MeOH; *ii*, BnNH₂

Scheme 3

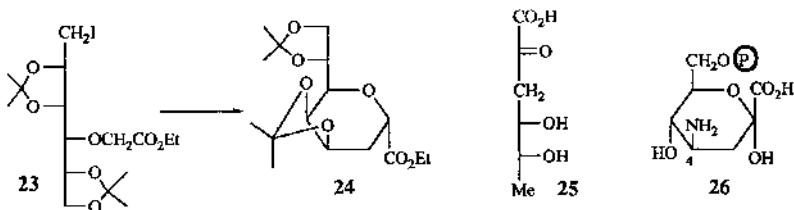
Reactions of free sugars with Meldrum's acid (see Vol. 24, p.175) have been further investigated. L-Arabinose gave the L-glucos- product **20** in reasonable yield, whilst the reaction with D-mannose gave mostly the D-glycero-D-ido-product **21**, probably due to isomerization at C-4 in the α,β -unsaturated lactone formed as an intermediate.²⁶ Intramolecular cyclizations of α,β -unsaturated lactones were also used to make bicycles of type **22**. The precursors were prepared by addition

of organometallics to a 2,3-ene-6-aldehyde, and the cyclizations proceeded faster when the substituent R occupied an *exo*-position.²⁷



In a new route to 2-deoxy- β -KDO, the key step was the intramolecular alkylation of 23, made from D-mannose, in the presence of LDA, to give 24 stereospecifically.²⁸

An unsaturated anhydroaldonic acid prepared during a study of the rearrangement of chorismic acid analogues is discussed in Chapter 13, and some epoxyaldonolactones are mentioned in Chapter 5.



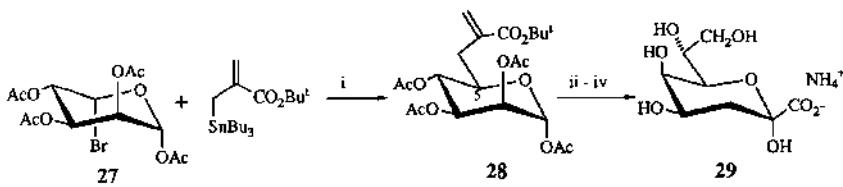
3 Ulosonic acids

The natural substrates for 2-keto-3-deoxy-6-phosphogluconate aldolase are D-glyceraldehyde-3-phosphate and pyruvate. It has now been shown that the enzyme will accept various other aldehydes as substrates, including D-glyceraldehyde itself, and D-lactaldehyde, from which the product is the didcoxyhexulosonate 25.²⁹

The production of 2-keto-D-gluconic acid by electrochemical oxidation of D-glucose has been monitored by 'on-line' chromatographic methods, and a reaction mechanism was proposed.³⁰

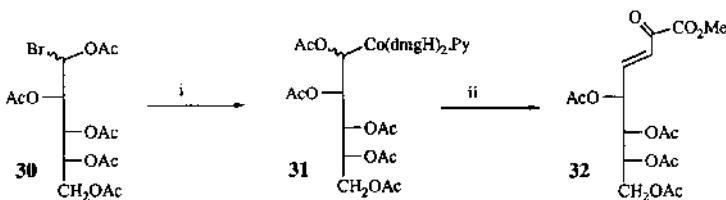
The amine 26 has been proposed as a putative intermediate in the biosynthesis of 3-amino-5-hydroxybenzoic acid and the *m*-C₇N unit in the ansamycin antibiotics, and it has been prepared from the methyl ester-methyl glycoside of 3-deoxy-D-*arabino*-heptulosonic acid by a double inversion at C-4.³¹

Giese's group have described two routes to KDO, both of which involve free-radical chemistry. In the first of these (Scheme 4) tetra-*O*-acetyl- α -D-lyxopyranose was brominated to give 27, which was then manipulated as indicated to give KDO as its ammonium salt (29). The adduct 28 was produced as a 3:1 mixture with its C-5 epimer.³² In an alternative approach (Scheme 5), the bromide 30, made by Barton-Hunsdiecker degradation of penta-*O*-acetyl-D-gluconic acid, was converted into an organocobalt compound 31 which underwent photochemical reaction with the TMS enol ether of methyl pyruvate to give the known KDO precursor 32.³³ For an alternative route



Reagents: i, AIBN, C₆H₆, Δ; ii, NaOH, H₂O; iii, NaBH₄; iv, O₃, then Me₂S; v, NH₄OH.

Scheme 4



Reagents: i, NaCo(dmgH)₂.Py; ii, CH₂=C(OTMS)CO₂Me, hν

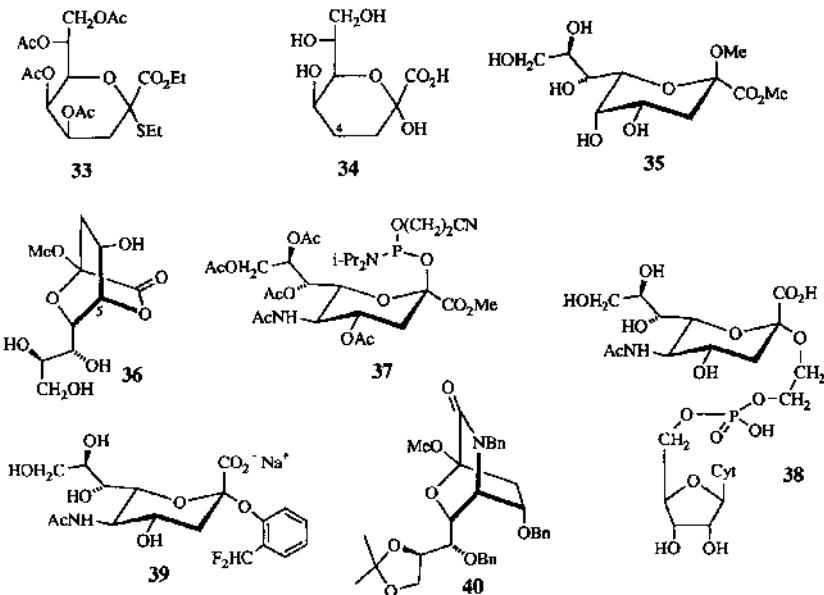
Scheme 5

to KDO involving organocobalt intermediates see Vol. 22, p.162. The thioglycoside 33 of KDO has been made by a variation on an earlier approach involving ring-opening of a cyclic sulfate derived from D-mannitol (Vol. 23, p.161-2), and used to prepare glycosides of KDO (Chapter 3).³⁴ The 4-deoxy-analogue (34) of KDO has been made by a sequence involving a Wittig reaction on 2,3,4,5-di-*O*-isopropylidene-aldehydo-D-arabinose using the ylid derived from Ph₃P and ethyl bromo-pyruvate, and the D-xylo-isomer of 34 was made in the same way.³⁵ A C-glycoside of KDO is discussed in Chapter 3.

A review has appeared dealing with biological diversity of sialic acids in oligosaccharides and sialoglycoproteins; sialic acid nomenclature is also discussed.³⁶ In a synthetic route to *N*-acetylneuraminic acid (Neu5Ac) from D-glucose, the β -D-pyranoside **35** was prepared, along with other isomers, by condensation of D-glucose with oxaloacetate followed by treatment with acidic methanol. The isomers were separated by h.p.l.c., and **35** was hydrolysed and then lactonized by DCC to **36**. After protection of the four hydroxyl groups, the lactone was reopened and nitrogen introduced at C-5 with inversion of configuration to give Neu5Ac.³⁷

There has been a further extended report from Wong's laboratory on the condensation of L-sugars with pyruvate, catalysed by Neu5Ac aldolase (see Vol. 25). In these reactions, the newly-created chiral centre has *R*-stereochemistry, as opposed to the *S*-chirality found with more normal substrates.³⁸ In an important paper from this group, they describe the production of two forms of CMP-sialic acid synthetase from *E.coli*, the native form and a modified form where the C-terminus is tagged with a decapeptide. The modified enzyme was used to make CMP-Neu5Ac from *N*-acetylmannosamine in the presence of Neu5Ac aldolase, the required CTP being generated enzymically *in situ* from CMP and phosphoenolpyruvate. Various analogues of Neu5Ac were also made using Neu5Ac aldolase, and these were used to probe the substrate specificities of the native and modified CMP-Neu5Ac synthetases. Both enzymes had high activity for modifications at C-9, but some

modifications at C-5 (hydroxy-, deoxy-, deoxyfluoro-) were not acceptable as substrates.³⁹ The same team have also prepared the phosphoramidite 37, and used it to make CMP-Neu5Ac.⁴⁰ A β -glycoside of Neu5Ac has been linked to Sepharose 4B to give an affinity ligand for the purification of CMP-Neu5Ac synthase.⁴¹ The sialate-nucleotide 38 has been reported, along with thymidine and AZT analogues.⁴²



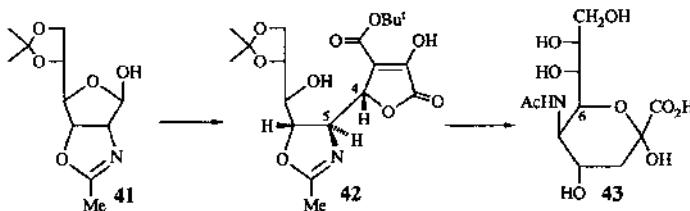
The α -(difluoromethyl)phenyl glycoside 39 of Neu5Ac has been made as a potential mechanism-based inhibitor of a bacterial neuraminidase.⁴³ An α -ketoside of Neu5Ac incorporating a dansyl group has been designed as a tightly-binding fluorescent ligand for influenza A hemagglutinin,⁴⁴ whilst in the same area other workers have designed and synthesized an α -glycoside of Neu5Ac with a long-chain acyclic aglycone designed to mimic the four saccharide units and the ceramide of ganglioside G₂, and again incorporating a fluorescent probe. Liposomes containing this species were good inhibitors of haemagglutination of erythrocytes by influenza virus, with the conclusion that relatively simple monosaccharides may prove effective in this area.⁴⁵

Kinetic studies have been reported on the chemical hydrolysis of aryl- α -glycosides of Neu5Ac, where four different pathways for hydrolysis of the neutral molecule and the anion were identified and investigated.⁴⁶ Various α - and β -glycosides of 3 β -hydroxy-neuraminic acid have been prepared (methods as in Vol. 21, p.161), and their calcium-binding ability and stability towards hydrolysis, both chemical and enzymic, was investigated and compared with the same properties of the corresponding glycosides of Neu5Ac. The hydroxylated species were more stable to hydrolysis, whilst the β -methyl glycosides of Neu5Ac and its 3 β -hydroxy-analogue both bound

calcium tightly implying a common conformation.⁴⁷ Other references to glycosides of Neu5Ac and sialyloligosaccharides can be found in Chapters 3 and 4.

There is continued interest in the chemical modification of Neu5Ac. The Vienna group have shown that the bicyclic lactam **40** can be formed from the α -methyl glycoside of 8,9-*O*-isopropylidene-Neu5Ac methyl ester by treatment with sodium hydride-benzyl bromide. The lactam can be reopened by base after structural modification, and selective *N*-debenzylation can be carried out using potassium *t*-butoxide in DMSO in the presence of oxygen. Similar reactions can be carried out on 2-deoxy- α -Neu5Ac.⁴⁸

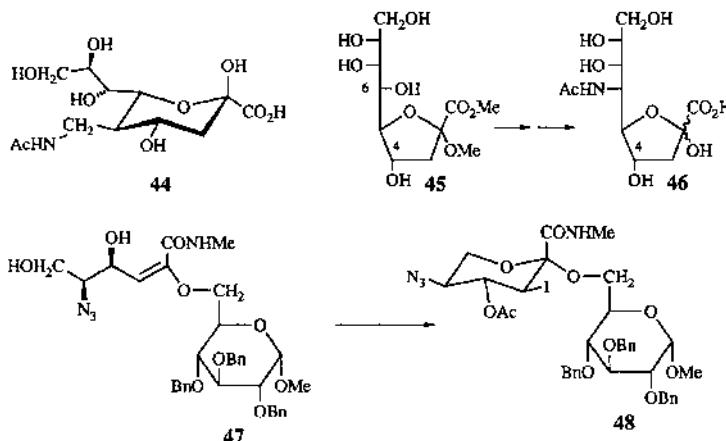
When the D-*allo*-oxazoline **41** (Scheme 6) was treated with di-*t*-butyl oxaloacetate under basic conditions, the lactone **42** was produced, together with its C-4 epimer. Both **42** and its epimer had undergone epimerisation at C-5 to give the *trans*-disubstituted oxazoline. Acidic hydrolysis and



Scheme 6

decarboxylation of **42** gave 6-*epi*-NeuAc (**43**), whilst the C-4 epimer of **42** gave 4,6-bis-*epi*-NeuAc.⁴⁵ The α -methyl glycoside of 8-oxo-NeuAc has been prepared,⁵⁰ and 4-*epi*-Neu5Ac α -methyl glycoside was made by a selective oxidation of 8,9-*O*-isopropylidene-Neu5Ac α -methyl ketoside methyl ester using RuO₄, followed by reduction with BH₃.NH₃. Selective formation of 4,8,9-tri-*O*-TBDMS-Neu5Ac methyl glycoside methyl ester permitted access to the α -methyl glycoside of 7-*epi*-Neu5Ac. The α -methyl glycosides of 8-*epi*- and 7,8-di-*epi*-Neu5Ac were also reported in the same paper.⁵¹ The 4-, 7-, 8-, and 9-deoxyderivatives of Neu5Ac have been prepared as peracetylated α -methylthioglycoside methyl esters,⁵² and used as glycosyl donors to make a series of ganglioside GM₃ analogues.⁵³

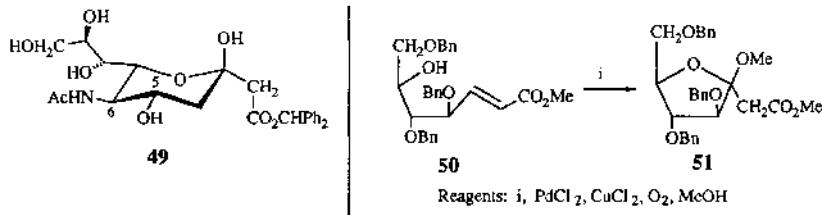
The C-5 homologue **44** of Neu5Ac was prepared by making the C-2 homologue of *N*-acetylmannosamine (Chapter 14), and converting it into **44** by reaction with pyruvate catalysed by NeuAc aldolase.⁵⁴ The α -furanose epimer **45** could be isolated from the products of reaction of D-glucose with oxaloacetate, followed by acidic methanol (see above); C-6 in **45** could be differentiated by lactonization with C-1, permitting the introduction of nitrogen at C-6 with inversion of configuration so as to give ultimately the sialic acid isomer **46**. The C-4 epimer of **45** was also isolated from the initial mixture, and gave the C-4 epimer of **46**. Both **46** and the epimer were strong inhibitors of the neuraminidase of influenza virus.⁵⁵ When the enol ether **47**, in which the acyclic unit was prepared from D-gluconolactone, was treated with NIS in propionitrile, cyclization to **48** occurred, and this was used as a route to various analogues of the Neu5Ac- α -glycoside, lacking the three-carbon side-chain.⁵⁶ Some 8,9-thiocarbonates of Neu5Ac are mentioned in Chapter 7, and some glycosylazides and glycosylamine derivatives in Chapter 10.



N-Acetyl- and *N*-glycolyl-2,7-anhydrononuramic acids have been made by cyclization of α - (methylthio)glycosides with DMTST (see also Vol. 25), after initial selective benzylation to the 4,9-dibenzoate.⁵⁷

In a study of the Fischer glycosidation of methyl 3-deoxy-D-glycero-D-galacto-2-nonulosonate (KDN methyl ester), the furanosides were initially formed, followed by pyranosides after longer times. All four compounds were isolated as their peracetates. Acetylation of KDN methyl ester in pyridine gave only the two peracetyl pyranoses.⁵⁸ Some nucleoside derivatives of KDN are mentioned in Chapter 20.

An extended NeuAc analogue **49** has been prepared by the reaction of 5,6-O-isopropylidene-*N*-acetylmannosamine with disodium acetone dicarboxylate in the presence of nickel acetate; the C-5 and C-6 epimers of **49** were also formed. Deprotection of **49** by hydrogenolysis gave the free acid which decarboxylated readily.⁵⁹ Treatment of the Wittig product **50** under Wacker-type conditions led to the glycoside **51** of a 3-ulosonic acid (Scheme 7).⁶⁰



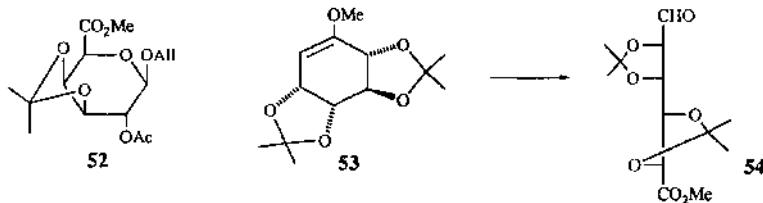
Scheme 7

4 Uronic Acids

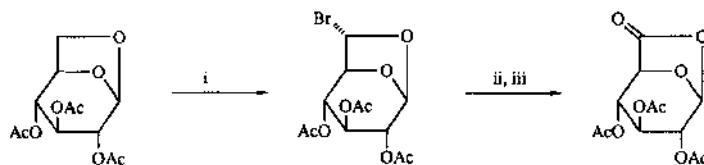
A review has been published on the oxidation of carbohydrates to carboxylic acids, with particular emphasis on catalytic oxidation of primary alcohol functions to uronic acids by use of molecular

oxygen.⁶⁰ The kinetics and mechanism of the selective oxidation of methyl α -D-glucopyranoside to the uronate on a carbon-supported platinum catalyst have been studied.⁶²

Improved preparations have been reported for the galacturonic acid derivative **52**, for use in making specific uronic acid-containing disaccharides (Chapter 3),⁶³ and for the diethyl dithioacetal of D-glucurono-6,3-lactone.⁶⁴ The mono-O-methylated cyclitol L-quebrachitol could be converted in three steps to the enol ether **53**, ozonolysis of which gave the acyclic L-guluronic acid derivative **54**.⁶⁵



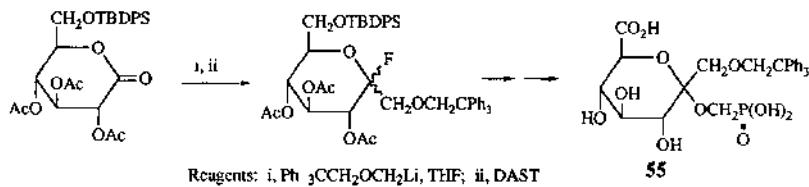
A new approach to 6,1-lactones of uronic acids is illustrated in Scheme 8 for the D-*glucosidase*, but was also applied to the D-*manno*- and D-*galacto*-configurations.⁶⁶



Reagents: i, Br₂, CCl₄, Δ; ii, Ag₂CO₃, acetone-water; iii, PDC

Scheme 8

The phosphonate **55**, designed as a transition-state analogue for the inhibition of UDP-glucuronosyltransferase, the enzyme involved in the detoxification of xenobiotics by glucuronidation, has been made as outlined in Scheme 9, the uronate function being introduced by Jones

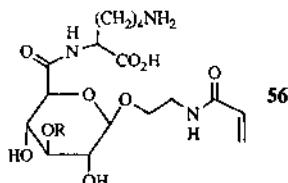


Reagents: i, Ph₃CCH₂OCH₂Li, THF; ii, DAST

Scheme 9

oxidation.⁶⁷ Both ether and ester glucuronides of the phenolic acid naproxen can be made enzymically from UDP-glucuronic acid and rabbit microsomal protein, the products being isolated by HPLC.⁶⁸

Lipidic aminoacids, and a dipeptide, have been conjugated via amide links to D-glucuronic acid, to improve their water solubility. The products were present as monomers in solution in non-aqueous solvents at low concentrations, but formed aggregates or inverted micelles at higher concentrations.⁶⁹ The acrylamide monomers **56** ($R=H$ or β -D-GlcNAc) have been prepared and

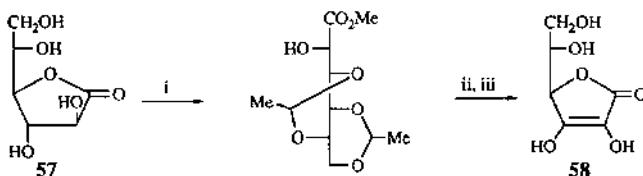


copolymerised with acrylamide to give high-molecular weight neoglycoconjugates.⁷⁰ Various long chain alcohols, thiols and amines have been linked as (thio)esters or amides to D-galacturonic acid, and the liquid crystalline properties of these compounds were studied. The bis-galacturonamide of dodeca-1,12-diamine and bis-galacturonate of dodeca-1,12-diol were also included in this study.⁷¹

A tributylstannyl ester of glucuronic acid is mentioned in Chapter 17, and nucleotides and nucleosides with uronic acid substructures are covered in Chapter 20.

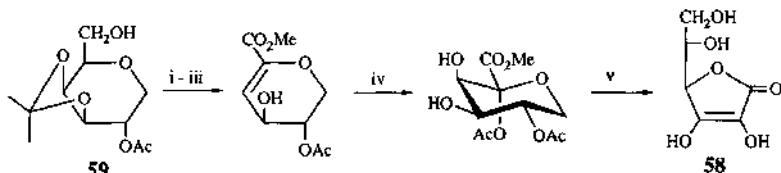
5 Ascorbic acids

Two new routes to L-ascorbic acid (**58**) have been described. In one of these, L-galactono-lactone (**57**) is the precursor, convertible in three steps (Scheme 10) into ascorbic acid,⁷² whilst in the other (Scheme 11), the 1,5-anhydro-D-galactitol **59**, accessible from D-galactose, was used as an intermediate.⁷³



Reagents: i, CH₃CHO, MeOH, HCl; ii, RuO₂, Ca(OCl)₂; iii, HCl, EtOH, CH₂Cl₂

Scheme 10



Reagents: i. COCl ; ii. DMSO , Et_2N ; iii. NaClO_2 ; iv. CH_3NO_2 ; v. MCPBA , HOAc ; vi. NaOMe , then HCl .

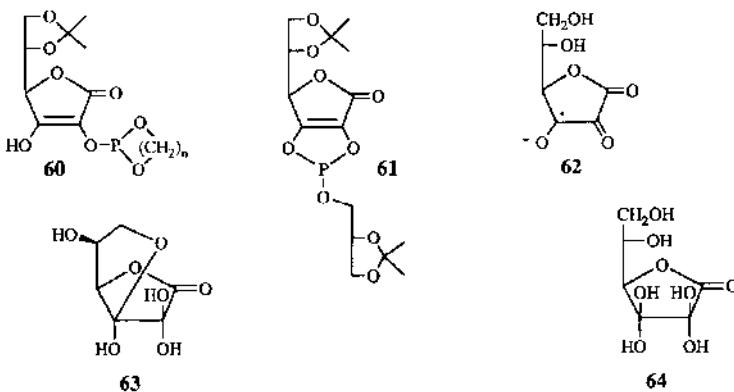
Schema 11

Displacement of a cyclic sulfate with labelled fluoride ion was used in a rapid (90 min) synthesis of 6-deoxy-6-[¹⁸F]-fluoro-L-ascorbic acid.⁷⁴

There have been reports on the phosphorylation of ascorbic acids. Phosphorylation of 5,6-O-isopropylidene-D-isoascorbic acid gave, after acid hydrolysis, mostly the 2-phosphate,⁷⁵ whilst treatment of 5,6-O-isopropylidene-L-ascorbic acid with alkylene chlorophosphites gave products of type **60** ($n=2,3$), together with the O-3 phosphites. These products were converted to thio- and selenophosphates, and the same paper also describes some 2,3-cyclic phosphites and phosphorothioates.⁷⁶ The same group has also prepared the cyclic phosphite **61**, convertible to a thiophosphate, which on treatment with $C_{17}H_{35}COCl \cdot ZnCl_2$ gave the tetra-O-acyl derivative, a lipid derivative of ascorbic acid.⁷⁷

Other lipophilic derivatives of L-ascorbic acid have been made by selective alkylation of the 5,6-O-isopropylidene derivative at O-3; the products after hydrolysis are inhibitors of lipid peroxidation, and of potential use in treating reperfusion injury.⁷⁸ Other fatty acid esters at O-5 and O-6 of ascorbic acid have been studied as antioxidants in liposomal membranes.⁷⁹

Molecular orbital calculations have been used to investigate the reaction of ascorbic acid (**58**) and its monoanion with the hydroxyl radical. The site of attack was found to be C-2, with a preference for the anion; dehydration was then predicted to lead to the anion-radical **62**.⁸⁰



Semi-empirical and *ab initio* approaches indicate that the bicyclic 3,6-hemiketal form of ascorbic acid is somewhat more stable than the 2,3-enediol (**58**), but because of its higher dipole moment, **58** gains in stability in polar solvents.⁸¹

The nature of the intermediates and products formed on oxidation of L-ascorbic acid and its 6-benzoate and 6-palmitate by iodine have been investigated by ¹³C-nmr in both D₂O and d₆-DMSO. In D₂O, there was evidence for the formation of the 3,6-hemiketal-hydrate **63** in equilibrium with the bis-hydrate **64** of dehydroascorbic acid. A similar bis-hydrate was formed from the 6-O-benzoyl derivative in D₂O, and this formed a bis-anhydrodimer on standing. In d₆-DMSO, the 6-O-acyl derivatives formed the 2,3-dione (dehydroascorbate), which formed the bis-hydrate on adding water.⁸² The hydrogen-ion dependence in the oxidation of L-ascorbic acid by hexacyanoferrate(III) in aqueous ethanol has been investigated; the rate law was derived and the

effects of ionic strength, solvent and temperature on reaction rate were analysed and interpreted.⁸³

Another worker has also reported on the dissociation constants and normal redox potentials for various ascorbic acids and determined second-order rate constants for ferricyanide reduction by these acids.⁸⁴ The kinetics of oxidation of L-ascorbate by Se(IV) in aqueous perchloric acid have been investigated.⁸⁵

In connection with studies of Maillard reactions involving ascorbate and proteins, the rates of formation of L-threose from L-ascorbate, dehydroascorbic acid, and 2,3-diketo-L-gulonate were measured in the presence and absence of oxygen. Ascorbate only gave threose in aerobic conditions, whilst the oxidised compounds also formed threose without oxygen, and the rate was faster from diketogulonate. Incubation of dehydroascorbate with N^{α} -acetyl-L-lysine in the presence of cyanoborohydride gave N^{α} -acetyl- N^{ϵ} -(1-deoxy-L-threitol-1-yl)-L-lysine. It thus appears that, in Maillard reactions of ascorbate, initial oxidation is necessary, but that further degradation of dehydroascorbate or diketogulonate can occur anaerobically.⁸⁶ It has been found that the degradation of aqueous solutions of ascorbic acid by ultrasound and ionising radiation was more extensive under aerobic conditions, and the products of such degradation have been identified.⁸⁷

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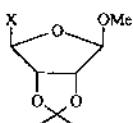
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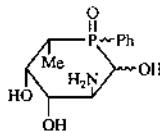
17 Inorganic Derivatives

1 Carbon-bonded Phosphorus Derivatives

The synthesis of the 1,3,5-tri-*O*-acetyl-2,4-dideoxy-4-methoxyphosphonyl-*D*-*erythro*- and *L*-*threo*-pentofuranoses has been described by way of a conjugate addition of dimethylphosphonate to an α,β -unsaturated nitro-compound.¹ Similarly, a number of 5,6-dideoxy-6-nitro-*D*-hex-5-enofuranoses, on treatment with dimethylphosphonate, have afforded predominantly either 5(R)- or 5(S)-5,6-dideoxy-6-nitro-5-dimethoxyphosphonyl adducts, depending on the conditions.² Full details of the photolysis of *N*-hydroxy-2-thiopyridone esters of uronic acids, e.g. 1, in the presence of diethyl vinylphosphonate to give phosphonates e.g. 2 have been published.³ (See SPR Vol. 23, p.172, 224.) The phosphorus-in-the-ring analogue 3 of L-fucosamine has been prepared in a multi-step procedure from D-glucose,⁴ and the synthesis of the 6-phosphono analogue of D-fructose-6-phosphate has been achieved.⁵ Methyl 2,5-dideoxy-5-diethylphosphonyl-3-*O*-pivaloyl- α,β -D-ribofuranose has been prepared and converted into a number of 2',5'-dideoxy-5'phosphonylnucleosides.⁶ A glycosyl phosphonate analogue of lipid A is mentioned in Chapter 3, and some recent topics of carbon-phosphorus compounds of bioorganic chemistry interest have been reviewed (in Japanese).⁷



1 X = CO₂H
2 X = CH₂CH₂PO(OEt)₂



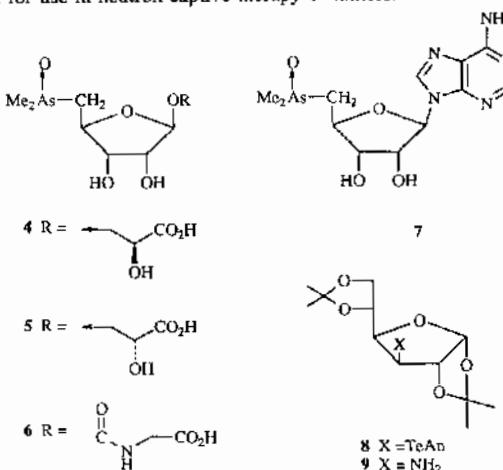
3

2 Other Carbon-bonded Derivatives

Palladium(0) catalysed coupling of 1-tributyltin-substituted glycals with aryl bromides has afforded 1,2-unsaturated aryl C-glycosides.^{8,9}

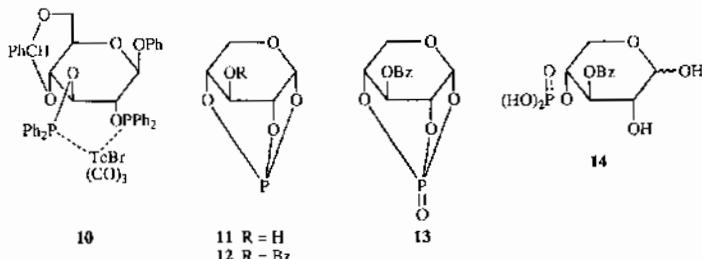
Three novel arsenic containing sugars 4-6 have been isolated from the kidneys of the giant clam *Tridacna maxima*, as well as the nucleoside derivative 7.¹⁰ The anisyl telluride moiety in the 3-deoxyglucose derivative 8 has been displaced by nitrogen in a radical amination procedure affording the 3-amino-3-deoxyglucose derivative 9. Further carbohydrate substituted carboranes

have been prepared for use in neutron captive therapy of tumors.^{12,13}

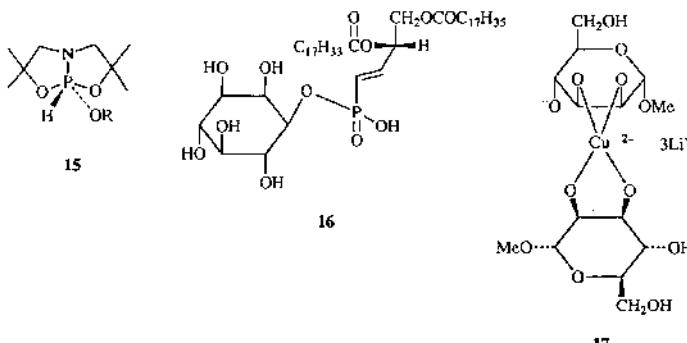


3 Oxygen-bonded Derivatives

The use of a variety of 1,2- and 1,3-diol phosphinites, prepared from readily available mono- and disaccharides, as ligands for asymmetric synthesis has been described¹⁴ as has the synthesis of 1,2-O-isopropylidene- α -D-glucofuranose 3,5-phenyl cyclophosphonate.¹⁵ The technetium complex tricarbonyl[phenyl 4,6-O-benzylidene-2,3-O-bis(diphenylphosphino)- β -D-glucopyranoside]-technetium(I) bromide **10** was prepared and characterized by i.r. and ⁹⁹Tc n.m.r. spectroscopy¹⁶. Reaction of D-xylose with tris (3,5-dimethylpyrazolyl) phosphite has afforded the 1,2,4-triphosphate **11**. Oxidation of the corresponding benzoate **12** gave phosphate **13** which on hydrolysis generated the 4-phosphate **14**¹⁷. Alkoxyphosphoranes **15** (R=protected monosaccharide derivatives) have been prepared¹⁸ as has the isosteric phosphonic acid analogue **16** of phosphatidylinositol.¹⁹



The 1,6-O-dibutylstannyles of some 2,3,4-tri-O-benzyl-D-hexopyranoses have been



prepared and their conformations analysed by n.m.r. spectroscopy.²⁰ Treatment of D-glucuronic acid with bis(tributyltin) oxide has afforded the corresponding tributyltin ester.²¹ Borate esters of D,L-threitol, xylitol, L-arabinitol, 1,2:5,6-di-O-isopropylidene-D-mannitol, D-mannitol, D-glucitol, D-galactitol, and 1-deoxy-1-methylamino-D-glucitol were prepared by treatment with aqueous boric acid in the presence of KOH. The structures were established by ¹¹B and ¹³C n.m.r. spectroscopy²².

The complexes formed between Cu(II) ions and a number of D-aldonic and D-alduronic acids in aqueous solution has been studied,²³ and the complex obtained from methyl α -D-mannopyranoside and copper(II) hydroxide in the presence of lithium hydroxide has been identified as the square planar structure 17.²⁴ The determination of stability constants of Ca²⁺ complexes with *myo*-inositol 1,4,5-trisphosphate is discussed in Chapter 18. The interaction of L-ascorbic acid with some metal ions has been studied in aqueous solution at pH 6-7, and the solid hydrated salts lithium, sodium, potassium, ammonium, rubidium and cesium ascorbate have been isolated and characterised by ¹³C n.m.r. and f.t.i.r. spectroscopy.²⁵

Studies of heavy metal binding to synthetic sulphated heparin disaccharides have implicated the idopyranosiduronic acid residue as the major metal binding site.^{26,27} Potassium chromate has been shown to be reduced by D-glucose and D-fructose to form Cr(III)-saccharide complexes via intermediate Cr(V) species. These saccharide complexes have been isolated and characterised.²⁸ Monosaccharide complexes with ammonium heptamolybdate and ammonium paratungstate have been studied by c.d. spectroscopy and their relationships to the C-2 epimerisation of aldoses have been discussed.²⁹ The formation and structures of dimolybdate complexes of ketoses of the *ribo*- and *lyxo*- series and of aldoses of the *lyxo*- series have been studied by ¹³C and ¹H n.m.r. spectroscopy.³⁰ The relative binding abilities of alditols, aldopentoses, aldohexoses and 2-ketohexoses to ion-exchange resin containing hexaammonium heptamolybdate have been studied. Alditols were bound most strongly.³¹

D-Glucose complexes involving Ti^{4+} , V^{4+} , Cr^{3+} and Mn^{2+} ions have been prepared in non-aqueous media and isolated crystalline. They were characterised by analytical and spectroscopic techniques.³² The binding of oxovanadium(IV) ions to simple sugars in aqueous solution has been studied by e.p.r. and electronic absorption spectroscopy. The results showed that complexation is favoured in basic media and involved coordination of the metal ion to a *cis* pair of adjacent deprotonated hydroxyl groups of the sugars.³³ A novel class of titanium complexes, cyclopentadienyl-dialkoxy-chlorotitanates, have been described including some examples where the alkoxy moieties were carbohydrate alcohols. These compounds have been used as highly enantioselective reagents in some carbon-carbon bond forming reactions³⁴. The cluster $Ru_3(CO)_{12}$ has been treated with 1,2-O-isopropylidene- α -D-glucofuranose or 1,2:5,6-di-O-isopropylidene- α -D-glucofuranose to give the clusters $Ru_3(CO)_8(L)$.³⁵

4 Nitrogen-bonded Derivatives

The structure of a rhenium(V) complex with 1,3,5-trideoxy-1,3,5-tris (2-hydroxybenzylamino)-*cis*-inositol has been described,³⁶ and the metal ion sequestering abilities of borate esters of 2-amino-2-deoxy-D-gluconate and 2-amino-2-deoxy-D-galactonate have been studied. The largest effects were measured upon adding Cd(II) or Ni(II) to the borate - 2-amino-2-deoxy-D-gluconate system.³⁷ A ribonucleoside technetium chelate prepared from 2',3'-diamino-2',3'-dideoxyadenosine is mentioned in Chapter 20.

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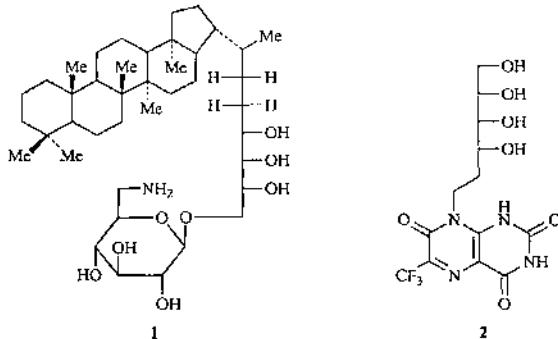
18

Alditols and Cyclitols

1.1 Acyclic Alditols. - The tritium labelling of mannitol and galactitol by solid state isotope exchange with gaseous tritium has been reported.¹ A high yielding preparation of partially methylated alditol acetates derived from glycoproteins has appeared.² The electrochemical reduction of glucose to glucitol at a lead cathode³ and the use of ruthenium and sulfur modified ruthenium in glycerol, erythritol, xylitol and glucitol hydrogenolysis⁴ have been reported. A study of the standard free energies of nitration of erythritol⁵ and of the kinetics and mechanism of the ruthenium (III) catalyzed oxidation of erythritol and galactitol to aldonic acids by *N*-bromoacetamide⁶ as well as the iridium (III) catalyzed oxidation of galactitol and ribitol by *N*-bromoacetamide⁷ have appeared.

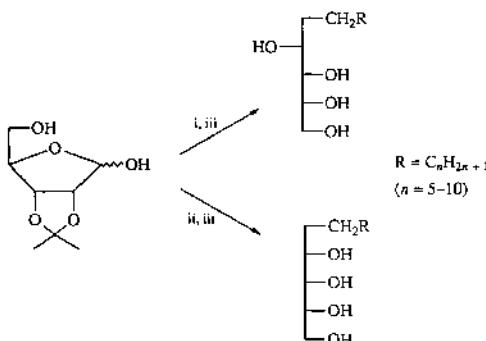
The preparation of chitoooligosaccharide-alditols by hydrogenation over a ruthenium catalyst is mentioned in Chapter 4.

The novel alditol **1** has been isolated from a cyanobacterium⁸ and the fluorolumazine **2** has been synthesized and used as a ¹⁹F probe for a bacterial riboflavin synthase.⁹



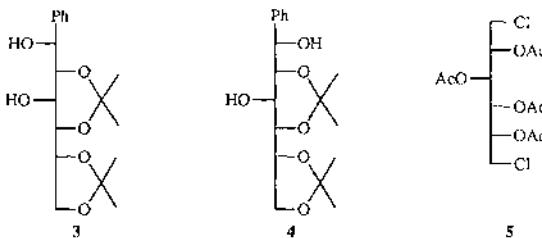
The synthesis of mesogenic alkanetetroses from D-ribose has been described (Scheme 1).¹⁰ The arabinitol product formed under the first conditions is thought to arise by base induced epimerization before the Wittig reaction occurs. (See Vol. 25, p. 201, Scheme 2 for other carbohydrate based mesogens.)

The synthesis of the D-glycero-D-ido-hexitol **3** and of the D-glycero-D-gulo-hexitol **4** as key intermediates in the synthesis of the naturally occurring goniofufurone and goniopyrpyrone (Chapter 24, this Volume) has been reported in four steps starting from D-glycero-D-gulo heptono-γ-lactone.¹¹



Reagents: i, $\text{RCI}=\text{PPh}_3$ (1 equiv.); ii, $\text{RCI}=\text{PPh}_3$ (2 equivs.); iii, $\text{Pd/C}, \text{H}_2, \text{H}_2\text{O}, \text{H}^+$

Scheme 1

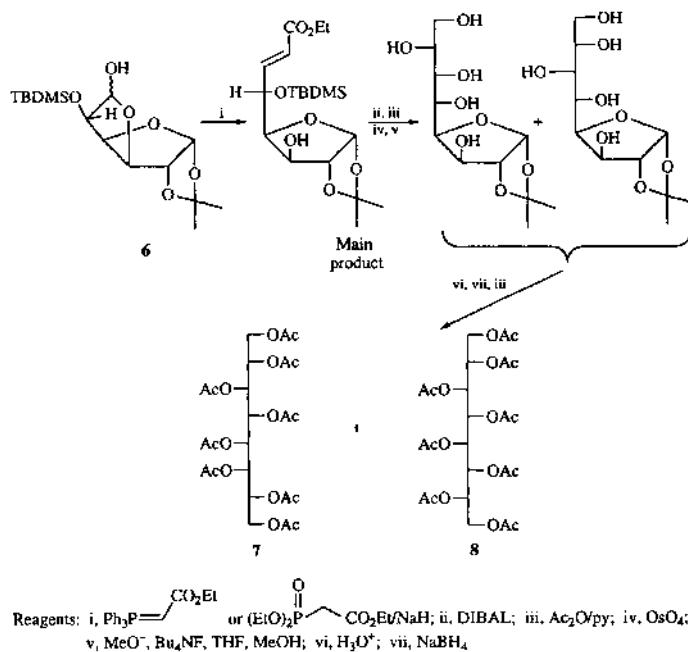


The direct regioselective chlorination of unprotected hexitols and pentitols by Vilsmeier-Haack reagent ($\text{Me}_2\text{N}^+=\text{CHCl}\text{Cl}^-$) has been described.¹² For example, D-glucitol was converted, (following acetylation) into 5. Some 2,3,5-tri-O-acetyl-1,4-anhydro-6-chloro-6-deoxy-D-glucitol was also formed.

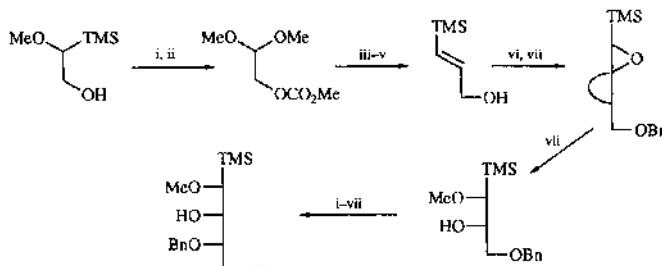
A short (six step) synthesis of 2-O-benzyl-1-O-hexadecyl glycerol in 11% overall yield from 3,4-isopropylidene mannitol has been reported.¹³

The syntheses of eight isomeric octitol octaacetates starting from 5-O-*tert* butyldimethylsilyl-1,2-O-isopropylidene- α -D-gluco- or β -L-*ido*-hexodialdose 6 have been described.¹⁴ For example 6 was converted into the L-*threo*-L-*galacto* (D-*threo*-L-*ido*) derivative 7 and the L-*threo*-L-*ido*-derivative 8 as shown in Scheme 2.

A new iterative route to enantio-pure polyols using α -alkoxysilanes has appeared (Scheme 3).¹⁵ Thus, electrochemical oxidation of the α -methoxysilane followed by protection of the hydroxyl gave the dimethyl acetal intermediate as shown. Subsequent olefination afforded the vinyl silane which was further converted as indicated into the homologated β -hydroxy- α -methoxysilane. Further chain extension can be obtained by repeating the cycle.



Scheme 2

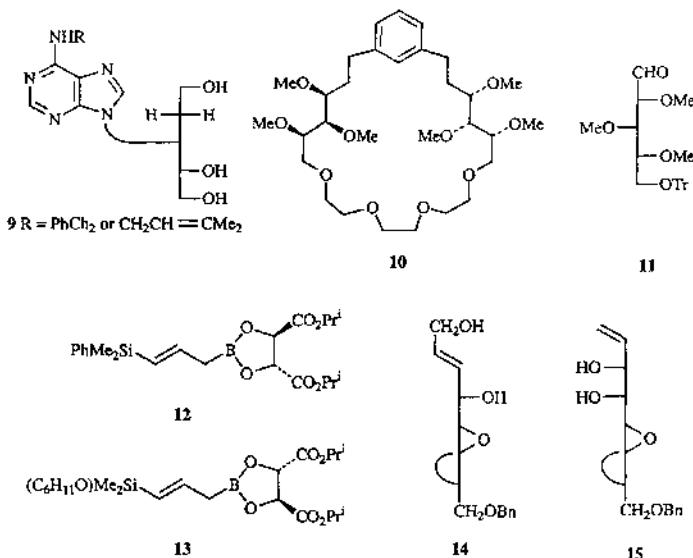


Scheme 3

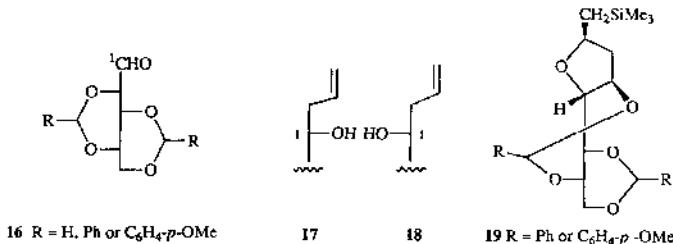
The reaction of 2-deoxy-D-ribose with N⁶ protected (benzyl or 3-methyl-2-butanyl) adenine in the presence of P₂O₅ and tributylamine gives the 3-(6-protected-aminopurin-9-yl)-2,3-dideoxy-D-threo-pentopyranoses which on reduction with NaBH₄ afford pentitols 9.¹⁶

The synthesis of carbohydrate-derived crown ethers such as 10 starting from the D-xylose derivative 11 has been reported.¹⁷

The preparation of 2-butene-1,4-diols and *anti*-1-butene-3,4-diols by the addition of chiral allylboronates **12** or **13** to various chiral aldehydes, followed by oxidation-Peterson elimination has been described.¹⁸ For example 2,3-anhydro-4-*O*-benzoyl-L-threose with **12** affords **14** and with **13** product **15** is obtained.



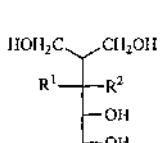
The Lewis acid-controlled addition of allyltrimethylsilane to various L-xylene derived acetals **16** afford chelation or non-chelation products **17** or **18**.¹⁹ In two cases in which **16** R=Ph or C₆H₄-*p*-OMe was used in the presence of BF₃OEt₂, the tetrahydrofuran derivative **19** was obtained. The synthesis of compounds **16** are effected by way of periodate oxidation of appropriate alkylidene D-glucitol.



The preparations of *C*-2-branched-2-deoxy pentitols²⁰ **20** or **21** and of *C*-2-branched-2-deoxy heptitols²¹ **22** and **23** have been achieved by the addition of di-*L*- or -*d*-menthyl malonate to isopropylidene-D-glyceraldehyde or 2,3:4,5-di-*O*-isopropylidene-L-arabinose respectively, followed

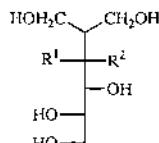
by reduction and deprotection.

See also Chapter 14 for other examples of *C*-branched alditols. The conversion of *O*-isopropylidene protected alditol derivatives into mono-*tert*-butyl ethers is mentioned in Chapters 5 and 6. The preparation and use of 1,3-di-*O*-acetyl-2,4:5,6-di-*O*-isopropylidene-1-*C*-phenyl-D-glycero-D-gulo-hexitol in the preparation of (-)-goniatriol is covered in Chapter 24.



20 R¹ = OH, R² = H

21 R¹ = H, R² = OH



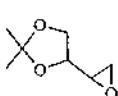
22 R¹ = OH, R² = H

23 R¹ = H, R² = OH

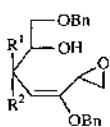
1.2 Anhydro-Alditols- An improved preparation of the four epoxybutanedio! acetonides **24** (RR,RS,SR or SS) from L-ascorbic acid or D-isoascorbic acid (cf. Vol. 24, p. 195, ref. 16) has been described.²² The conversion of these isomers into enantiomerically pure glyceraldehyde derivatives, threose/erythrose derivatives or 2,3-anhydro threose/erythrose derivatives by initial treatment of **24** with various organometallic reagents is also reported. These latter compounds are useful building blocks for the synthesis of acyclic oxygenated fatty acid metabolites.

The treatment of 2,3,4,6-tetra-*O*-benzyl ethers of glucose, mannose or galactose with dimethylsulfonium methyl ylide gives rise to anhydro derivatives **25**.²³

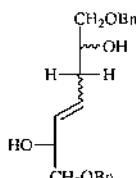
The asymmetric epoxidation of all four isomeric allylic-homoallylic alcohols of the type **26** and the subsequent hydride reduction of each epoxide to both possible dideoxyheptitols has been reported.²⁴ Only three isomers of **26** undergo a diastereoselective epoxidation and it was concluded that the direction of epoxidation for E-alkenes was controlled by the chirality of the allylic alcohol, whereas for Z-configurated olefins the relative stereochemistry between the two alcohols is important.



24



25 R¹ = H, R² = OBn
or R¹ = OBn, R² = H



26

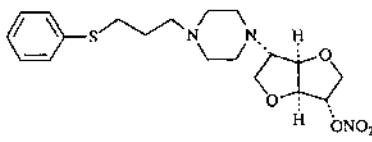
Exposure of the four regioisomeric methyl tri-*O*-methyl-*O*-propanoyl- α -D-glucopyranosides and

two of the corresponding β -derivatives to triethylsilane in the presence of trimethylsilyl triflate or boron trifluoride etherate affords in all cases the expected 1,5-anhydro-tri-*O*-methyl-*O*-propanoyl-D-glucitol.²⁵

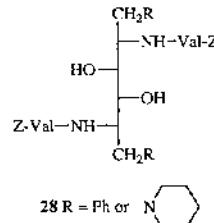
The preparation of 1,5-anhydro-4-*O*- β -D-galactopyranosyl-D-glucitol together with the 2-deoxy and 2,3-dideoxy derivatives from appropriate lactose based compounds by conventional chemistry has been reported.²⁶ All derivatives were substrates for *E.Coli* derived β -galactosidase.

The conversion of 2-amino-2-deoxy-D-galactose into 2-amino-1,2-dideoxy-D-galactitol in three steps has been described.²⁷ Attempts to convert the latter compound into 1,5-dideoxy-1,5-imino-L-fucitol using D-galactose:oxygen oxidoreductase, EC1.1.3.9 were unsuccessful but it could be selectively dehydrated with cHCl to 5-amino-1,4-anhydro-5,6-dideoxy-L-galactitol hydrochloride.

D-Glucitol is converted to a mixture of 1,4-anhydro-D-glucitol, 2,5-anhydro-L-iditol, 2,5-anhydro-D-mannitol and 1,4;3,6-dianhydro-D-glucitol on treatment with hydrogen in the presence of a Cu-Ru catalyst.²⁸ Reactions of other alditols with bimetallic catalysis are described. The preparations of three stereoisomers (exo, endo; endo, exo; endo, endo) of the known (*Chem. Abstr.*, 1991, 115, 136 644) dianhydro nitrate derivative 27 (exo, exo form) have been reported²⁹ and the enzymatic preparations of 1,4;3,6-dianhydro-D-glucitol mono acetates is mentioned in Chapter 7.



27

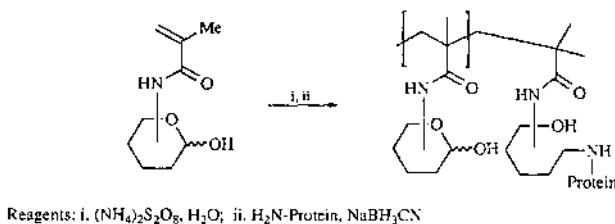


1.3 Amino- and Imino-Alditols - The synthesis of the C₂ symmetric compounds 28 as HIV protease inhibitors has been described.³⁰ (See also Vol. 25, p. 331 ref. 84, 85 and 86 for similar work.)

The conversion of unprotected lactose, cellobiose and maltose into 1-amino-1-deoxyalditols by reductive amination with benzylamine followed by hydrogenolysis of the *N*-benzyl group has been disclosed.³¹ In a similar manner the preparation of 1-alkylamino-1-deoxy alditols having *N*-linked 7-10 membered carbon side chains as non-ionic surfactants from unprotected lactose has been reported.³² The preparation of acyl or aryl amide derivatives of 1-amino-1-deoxyglucitol or 1-deoxy-1-methylaminoglucitol without protection as potential sweetners has been disclosed.³³ The conversion of pyridylamino lactose to 1-amino-1-deoxy-*N*-acetylglucosaminitol and 1-amino-1-deoxy-lactitol, respectively, by subsequent hydrogenation and hydrazinolysis as model compounds for oligosaccharides has been reported.³⁴ The synthesis of fluorine labelled polyamino dextran derivatives is mentioned in Chapter 4.

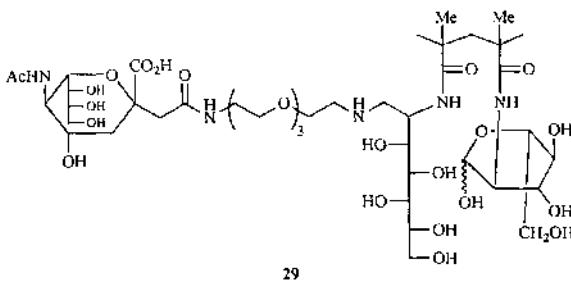
The reaction of 1,2-anhydro-3-*O*-(*o*-ethoxyphenyl)glycerol with 1-alkylamino-1-deoxyhexitols to give the corresponding amino glycerol derivatives has been reported.³⁵

The preparation of new carbohydrate-based materials for the stabilisation of proteins such as α -chymotrypsin, trypsin and subtilisin has been described (Scheme 4).³⁶



Scheme 4

The preparation of the complex aminoalditol **29** as a neuraminidase resistant derivative of sialic acid glycosides has been disclosed.³⁷



In the field of imino-alditols a further paper including corrections to a previous one (See Vol. 25, p. 203, ref 30) on the biosynthesis of 1-deoxynojirimycin (DNJ) and 1-deoxymannojirimycin (DMJ) has appeared.³⁸ See also Chapter 19 for other syntheses of DNJ and DMJ and Chapters 3 and 4 for DMJ glycosides and DNJ-containing oligosaccharides respectively.

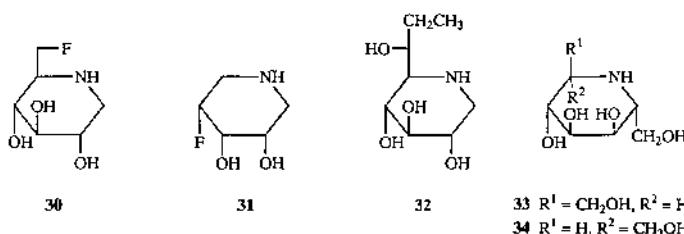
1-Deoxynojirimycin has been prepared from sucrose in 35% overall yield by successive treatment with triphenylphosphine-carbon tetrachloride, sodium azide and acid resin to give 6-azido-6-deoxy-D-glucose and 6-azido-6-deoxy-D-fructose in which the former could be converted to more of the latter by use of polymer supported glucose isomerase. Hydrogenation of the fructose derivative gave DNJ.³⁹

Sphingofungin D (a recently discovered antifungal agent) has been partly degraded and transformed into 1-deoxynojirimycin pentaacetate in order to establish its absolute stereochemistry.⁴⁰

The syntheses of the fluoro-1,5-imino-D-glucitol **30** and fluoro-1,5-imino-D-ribitol **31** by conventional chemistry from L-sorbose and 5-amino-5-deoxy-2,3-isopropylidene-D-ribonolactam respectively have been reported.⁴¹

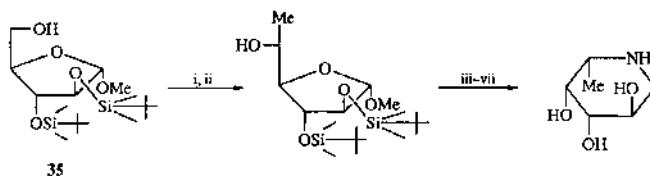
The preparation of (6S)-6-C-ethyl-1-deoxynojirimycin **32** has been effected in order to study the entropic part of the free energy of binding of castanospermine to α - and β -glucosidases.⁴²

Full details of an earlier paper (Vol. 23, p. 181, ref. 32) on the synthesis of α -homomannojirimycin 33 and its 6-epimer 34 have appeared.⁴³



1-Deoxy-D-rhamnojirimycin and its enantiomer have been prepared from L- or D-gulonolactone respectively.⁴⁴

The preparation of 1-deoxyfucojirimycin has been effected from the D-arabinose intermediate 35 according to Scheme 5.⁴⁵

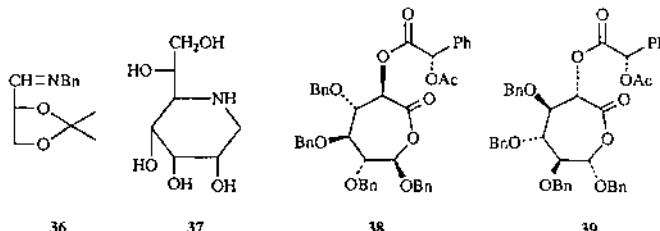


Reagents: i, $(\text{COCl})_2$, DMSO; ii, Me_3Al ; iii, MsCl , py; iv, NaN_3 , DMSO; v, Ac_2O , AcOH , H_2SO_4 ; vi, NaOMe ; vii, H_2 , Pd/C

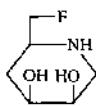
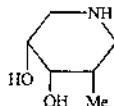
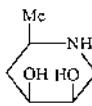
Scheme 5

The preparation of the 1,5-imino-heptitol 37 has been achieved in which the key step involved addition of TMS-furan to N-benzyl limine 36 to afford a D-*ribo*-butenolide followed by conventional chemistry.⁴⁶

A synthesis⁴⁷ of both enantiomers of DNJ from lactones 38 and 39, which are derived from *myo*-inositol (See Vol. 22, p. 165) as well as a symposium report⁴⁸ have appeared.



The preparation of the novel compounds **40-42** by a chemo-enzymatic approach similar to one reported earlier (See Vol. 25, p. 204, ref. 32) has appeared.⁵⁰

**40****41****42**

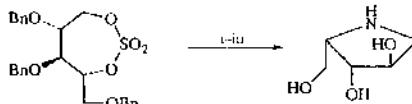
Reaction of (R)/(S)-3-cyano-2-hydroxypropanal with lithium hydroxypyruvate under trans ketolase control followed by a palladium catalyzed-reductive amination afforded 1,2,5-trideoxy-1,5-imino-D-*arabino*-hexitol (fagomine)⁵⁰

The uses of fuculose-1-phosphate aldolase in the preparation of 1,5-dideoxy-1,5-diamino-D-talitol and 1-deoxygalactostatin have been described.⁵¹

Various known aza-sugars (See Vol. 25, p. 204, ref. 32 and 33) have been used to study the active site of bovine kidney α -L-fucosidase.⁵²

The preparation of C₇-symmetric 2,5-dideoxy-2,5-imino-L-iditol by a route similar to that described earlier (Vol. 22, p. 181, ref. 35 and Vol. 21, p. 177) has been reported.⁵³

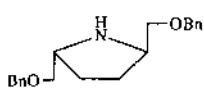
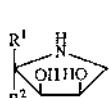
The preparations of 1,4-iminoalditol derivatives of L-xylitol, L-arabinitol and D-xylitol using cyclic sulfate intermediates have been reported (Scheme 6).⁵⁴



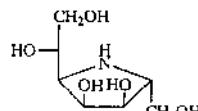
Reagents: i, PhCH₂NH₂/DMP; ii, BuⁿLi, 50 °C; iii, H₂, Pd/C

Scheme 6

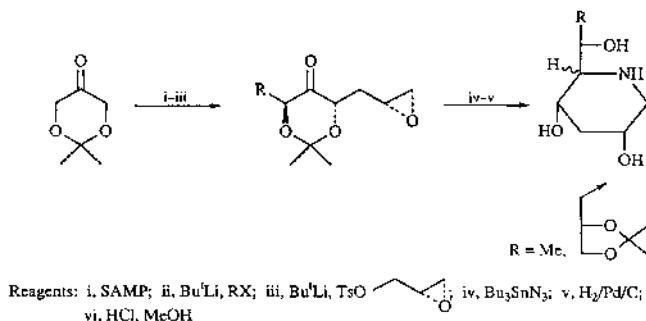
The synthesis of the 2,5-disubstituted pyrrolidine **43** from D-mannitol by standard chemistry⁵⁵ and the synthesis of pyrrolidines **44** by addition of azomethine ylides to vinylene carbonate^{56,57} as well as the synthesis of the imino-heptitol **45** from 2,3,5,6-di-O-isopropylidene- α -D-mannofuranose⁵⁸ have been reported.

**43**

44 R¹ = CH₂OH, R² = H
or R¹ = H, R² = CH₂OH

**45**

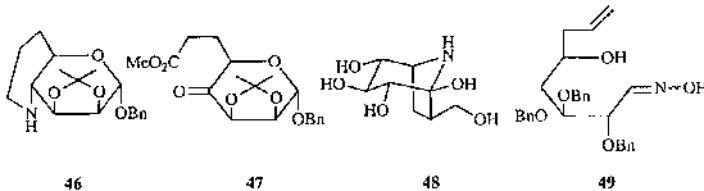
An example of the use of SAMP/RAMP methodology to prepare polyhydroxylated piperidines is illustrated in Scheme 7.⁵⁹ Other examples are also described.



Scheme 7

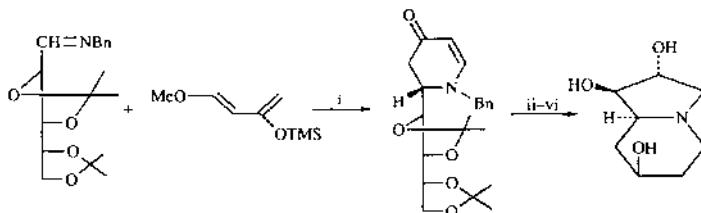
The preparation of the piperidine 46 from keto-ester 47 which in turn is derived from D-mannose has been reported as a valuable intermediate en route to (-)-swainsonine.⁶⁰

The synthesis of amine 48 as an analogue of the alkaloid calystegine B₂ has been achieved by successive treatment of oxime 49 (prepared from methyl- α -D-glucopyranoside in several steps) with NaOCl ; $\text{Zn}(\text{N}_3)_2$, Ph_3P , DIAD; then H_2/Pd black.⁶¹



A review on the synthetic approaches to stereoisomers and analogues of castanospermine, many of which involve carbohydrate precursors has appeared.⁶²

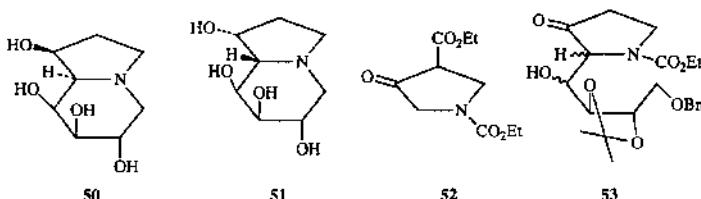
A new synthesis of swainsonine analogues has been reported (Scheme 8).⁶³ The enantiomer of the product in Scheme 8 has also been made starting from L-arabinose.



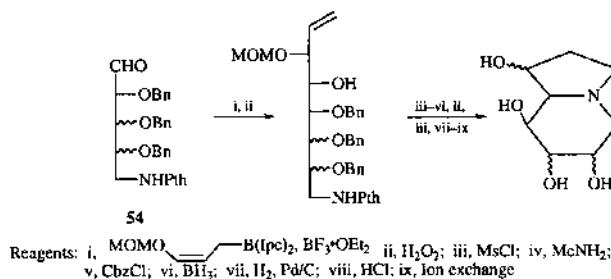
Reagents: i, ZnCl_2 ; ii, NaBH_4 ; iii, AcOH ; iv, $\text{Pb}(\text{OAc})_4$; v, TFA ; vi, $\text{H}_2/\text{Pd-C}$

Scheme 8

The syntheses of 8-epicastanospermine **50** and of 1,8,8a-triepicastanospermine **51** have been achieved by coupling of the dianion derived from **52** with 4-*O*-benzyl-2,3-di-*O*-isopropylidene-L-threose, which after ester cleavage-decarboxylation gave all four diastereomeric aldol adducts **53**. The two major forms were separated and individually converted into **50** and **51** by standard chemical transformations.⁶⁴



A strategy for preparing stereoisomers of castanospermine has appeared in which the key step involves asymmetric allylation of the D-ribo-, L-arabino- or D-xylo-aldehydes **54** as shown in Scheme 9.⁶⁵



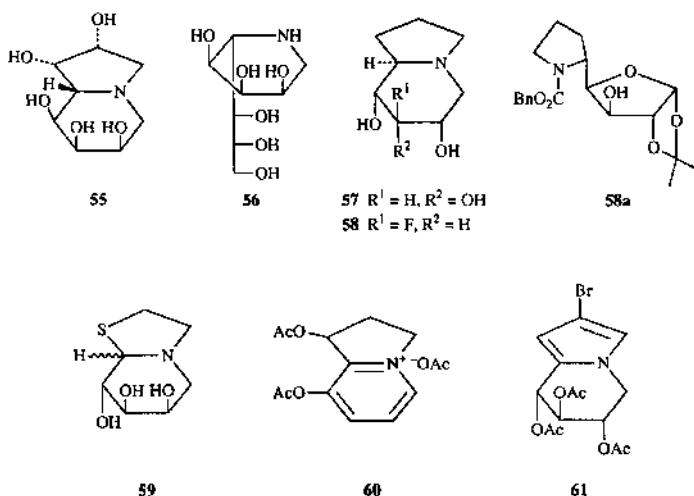
Scheme 9

The preparations of the unnatural enantiomers of castanospermine and 1-epicastanospermine, starting from D-xylose, by standard chemical transformations⁶⁶ and a non-carbohydrate approach to four stereoisomers of 1-deoxycastanospermine⁶⁷ have been achieved.

Application of Vogel's "naked" sugar approach has led to the preparation of **55** from intermediate imino-octitol **56**⁶⁸ and the deoxy-*epi*-castanospermine derivative **57** and fluoro derivative **58** have been achieved from known 5,8-imino- α -D-glucos-octose **58a** (see Vol. 21, p. 268, Scheme 21)⁶⁹

A synthesis of the thio-castanospermine derivative **59** from D-arabinose in several steps has been described.⁷⁰ The indolizinium acetate **60** resulted from application of the Polonovski reaction applied to the *N*-oxide of castanospermine acetate and a low yield of **61** was produced by photolysis of castanospermine acetate in the presence of NBS.⁷¹

The synthesis of glycosides of castanospermine are reported in Chapter 3.



2 Cyclitols

Reviews on the use of cyclohexa-3,5-diene-1,2-diols in the synthesis of cyclitols and conduritols⁷² and on the use of cyclopentadiene and benzene in the preparations of chiral cyclopentanols and chiral conduritol and conduramines⁷³ have appeared.

Use of a cloned quinic acid dehydrogenase has led to the successful conversion of D-glucose into quinic acid which was further transformed into benzoquinone.⁷⁴

The synthesis of the amine, 62, a portion of which is the herbicide "glyphosate" has been reported as a novel inhibitor of EPSP synthase.⁷⁵

A number of analogues that mimic the intermediate formed during the EPSP synthase conversion of shikimic-3-phosphate into EPSP (5-enolpyruvyl shikimate-3-phosphate) have been prepared and tested as inhibitors of the enzyme.⁷⁶ The best was shown to be 63. (Z)-3-Fluorophenoxyenolpyruvate functions as a pseudosubstrate for EPSP synthase producing in one step the same adduct 63, but as an isomeric mixture.⁷⁷

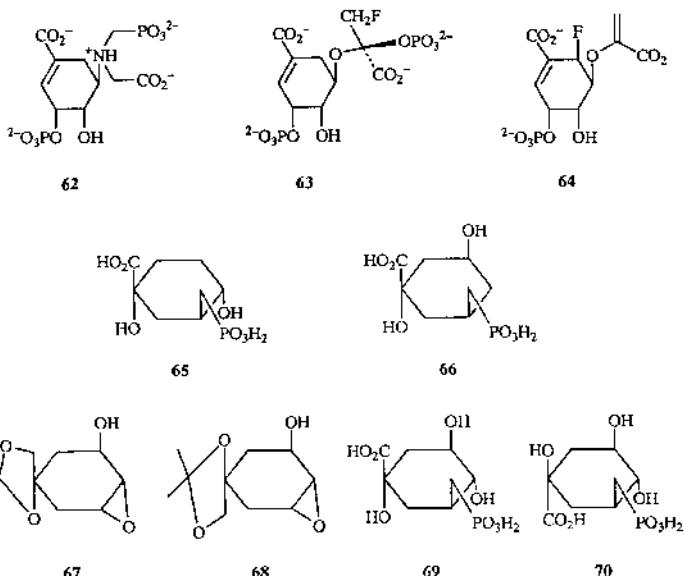
With fluoroshikimate derivative 64 the FMNH₂ cofactor of *E. Coli* chorismate synthase is quantitatively oxidized to a stable flavin semiquinone radical.⁷⁸

Kinetic evidence is presented that compounds 65 and 66 exhibit 3-dehydroquinate (DHQ) synthase inhibition as a consequence of selective destabilization of an activation barrier separating two enzyme internal sites.⁷⁹

The synthesis of epoxy alcohols 67 and 68 from quinic acid and their subsequent

transformation into phosphonates **69** and **70** respectively has been reported.⁴⁰ The latter two compounds were prepared as inhibitors of DHQ synthase.

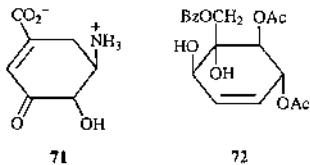
Both (-)-shikimate-3-phosphate and quinic acid 3-phosphate have been synthesized by standard chemical transformation from methyl shikimate and quinic acid respectively.⁴¹



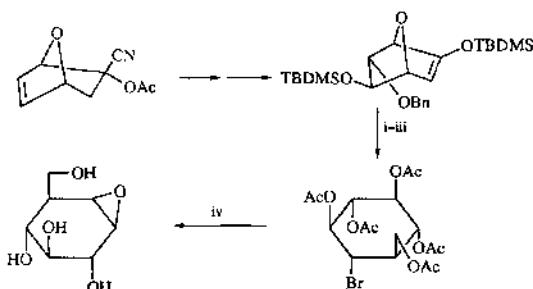
The amino derivative **71** has been synthesized from shikimic acid to explore a new variant of the shikimate pathway which, leads to 3-amino-5-hydroxybenzoic acid, a proposed precursor of part of the ansamycin antibiotics.⁴²

The synthesis of glycosyltetrazoles as analogues of 3-deoxy-D-arabino-heptulosonic acid 7-phosphate (DAHP) and 2-deoxy DAHP is mentioned in Chapter 3.

The isolation of the unsaturated compound **72**, from *Piper ribesoides* and named senediol, has been described.⁴³



The total synthesis of racemic cyclohelitol from furan has been reported (Scheme 10).⁴⁴ (See Vol. 24, p. 200, ref. 52 for an alternative synthesis.)



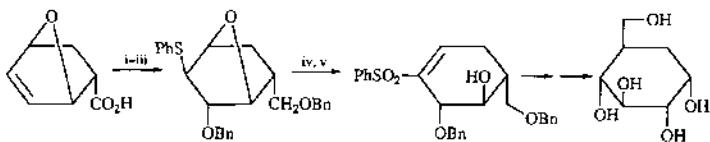
Reagents: i, CH₂O, TiCl₄; ii, NaBH₄; iii, HBr, AcOH; iv, NaOMe

Scheme 10

The use of bacterial oxidation of aryl halides to arene *cis*-diols and their subsequent transformation into (+) and (-) pinitols and other cyclitols⁸⁵ as well as (-)-conduritol C⁸⁶ and (+) and (-)-conduritol E epoxide,⁸⁷ have been disclosed. (-)-Conduramine C-1 has been prepared from benzene using similar bacterial oxidation methodology and asymmetry introduced by a *Pseudomonas cepacia* lipase (Amano P-30) catalyzed *O*-acetylation reaction.⁸⁸ The synthesis of (-)-conduritols C, E, F and other derivatives⁸⁹ as well as of carba- α -D-mannopyranose and unnatural shikimic acid analogues⁹⁰ starting from cyclohexadiene in which asymmetry is introduced by way of an esterase de-*O*-acetylation reaction have appeared. A synthesis of carba- α -D-glucopyranose using microbial oxidation of benzene and de-symmetrization by way of an intermediate (*R*)-methylbenzyl ether⁹¹ and a synthesis of conduritol C and E from *p*-benzoquinone⁹² have been reported.

Full details of an earlier paper (see Vol. 25, p. 209, ref. 62) on the synthesis of carba- α -D-gluco and manno-pyranoses from (-)-quinic acid have appeared.⁹³

The preparation of carba- α -D,L-glucopyranose by way of a strain-directed bridge cleavage of a phenylsulfonyl 7-oxabicyclo[2.2.1] heptane derivative has been described (Scheme 11).⁹⁴



Reagents: i, PhSCl; ii, LiAlH₄; iii, BnBr; iv, Mg peroxyphthalate; v, BuLi

Scheme 11

A synthesis of the carbocyclic analogue of *N*-acetylneuraminic acid starting with the Diels-Alder reaction of furan and acrylic acid has been achieved.⁹⁵

A new inositol, 1,2-di-*O*-methyl-*muco*-inositol termed "viscumitol" along with other known

inositols has been isolated from *Viscum album*.⁹⁶ The isolation of 1-*O*-methyl-*muco*-inositol, quebrachitol and L-inositol from *Croton cortesianus* has been described and low temperature NMR studies were carried out on the former.⁹⁷

The preparations of 5-deoxy-5-fluoro-*myo*-inositol, 1L-1-deoxy-1-fluoro-*myo*-inositol, 1D-4-deoxy-4-fluoro-*myo*-inositol, 1L-4-deoxy-4-fluoro-*myo*-inositol, and 2-deoxy-2-fluoro-*myo*-inositol by conventional chemistry from known racemic *myo*-inositol derivatives and resolution by use of (S)-(-)-camphamic acid have been described.⁹⁸ In a similar way the synthesis of 1-deoxy-1-fluoro-*scyllo*-inositol, 2-deoxy-2,2-difluoro-*myo*-inositol, D,L-2-deoxy-2-fluoro-*scyllo*-inositol 1,4,5-triphosphate and D,L-2-deoxy-2,2-difluoro-*myo*-inositol 1,4,5-triphosphate have been described.⁹⁹

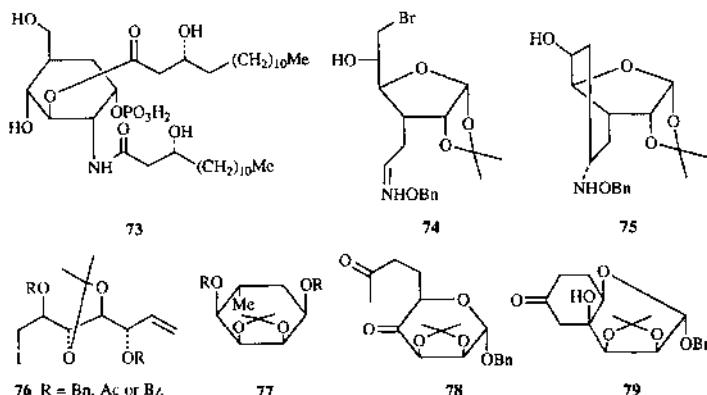
The synthesis of silyl protected *myo*-inositols with free hydroxyls at 1-, 5-, 6-, 1,4-, 4,5-, 5,6-, 1,4,5-, and 1,4,6-positions has been described.¹⁰⁰

A full account of an earlier report (Vol. 24, p. 202, ref. 63) on the Lewis-acid catalyzed rearrangements of *myo*-inositol orthoformate derivatives has appeared.¹⁰¹

As part of a biochemical study on the biosynthesis of 2-deoxystreptamine, the preparations of 2-deoxy-*scyllo*-inose and [2,2-²H₂]-2-deoxy-*scyllo*-inose have been described, the former by a multi-step synthesis from *myo*-inositol and the latter involving a modified Ferrier reaction.¹⁰² The Ferrier reaction has also been used to construct the carbocyclic framework of the carbocyclic analogue of Lipid X 73.¹⁰³ The stereochemistry of the Pd (II) catalyzed Ferrier reaction has also been studied and concluded to give the same products to that observed in the Hg²⁺ catalyzed reaction.¹⁰⁴ The synthesis of L-sugar derivatives from L-quebrachitol is mentioned in Chapter 2 and 16.

The 6-exo radical induced cyclization of bromo-oximes to produce aminocyclitols and carbahexopyranoses in a similar way to that reported in Vol. 25, p. 211, ref. 82 and 83 has been disclosed.¹⁰⁵

Treatment of bromo-oxime 74 with Bu₃SnH gave a low yield of cyclization product 75. Mixed products were obtained when nitrile and alkene groups were used in place of oxime.¹⁰⁶



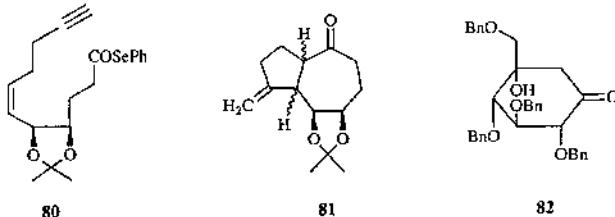
Treatment of iodo-hept-1-enitols like **76** with Bu_3SnH afford cyclitols **77**.¹⁰⁷ Several other examples are given in which seven-membered rings are observed. It appears the product ratios depend on the disposition and type of protecting group used.

Full details of an earlier report (see Vol. 23, p. 184, ref. 51) on the preparation of cyclopentane and cyclohexane derivatives by a radical mechanism have been described.¹⁰⁸

Treatment of the diketone **78** with pyrrolidine afforded cyclohexanone derivative **79** exclusively.¹⁰⁹ Other bases (piperidine, KOH) also led to the C-4 and C-5 epimer of **79**.

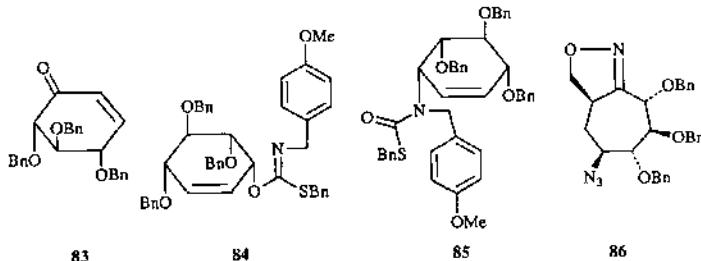
The preparation of optically pure cyclohexanones by radical-induced cyclization of phenylseleno esters onto a terminal double bond has been described.¹¹⁰ The method was also extended to the production of bicyclo derivatives such as **81** from seleno ester **80**.

Other carbocyclic preparations by radical cyclizations are mentioned in Chapter 24 and the rhodium (V) complex of 1,3,5-trideoxy-1,3,5-tris(2-hydroxybenzylamino)-*cis*-inositol is mentioned in Chapter 17.



The sequential opening of benzyl protected D-glucono-1,5-lactone with dithiane anion, LAH reduction, Swern oxidation, base cyclization and Raney Nickel reduction gave cyclitol derivative **82**¹¹¹ which was used in a synthesis of valiolamine.¹¹² Various *N*-substituted derivatives of valiolamine were prepared as α -glucosidase inhibitors and included validoxylamine G and validamycin G. The use of the well known enose **83** in a straightforward synthesis of valienamine has been described.¹¹³ Compound **83** was also used for the synthesis of 7-nor-valienamine and a related disaccharide in which the key step involved a [3,3]-sigmatropic rearrangement of a carbonimidothioate, *i.e.* **84** \rightarrow **85**.

The azido cyclitol **86** was formed by treatment of oxime **49** with sodium hypochlorite and treatment with azide under Mitsunobu conditions.⁶¹



A low yielding synthesis of 2-acetamido-5*a*-carba-2-deoxy- α -D,L-*allo*- and *gulo*-pyranose tetraacetates and some 3-acetamido-3-deoxy derivatives have been achieved starting from bicyclic acetate **87**.¹¹⁴ By use of the same intermediate the preparations of valienamine and valiolamine have also been achieved.¹¹⁵

The synthesis of homochiral C-methylamino and azido-inositol for example **88** and **89** by way of *Pseudomonas putida* oxidations of toluene and conventional chemical transformations has been reported.¹¹⁶

The preparation of amino cyclitols as building blocks for carba-oligosaccharides related to cell-surface glycans from intermediate **90** has been described.¹¹⁷

The total synthesis of the alkaloid (+)-lycoricidine from amino cyclitol **91**, prepared from bromobenzene by microbial oxidation has been reported.¹¹⁸

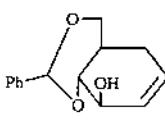
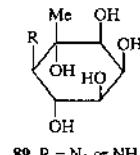
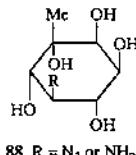
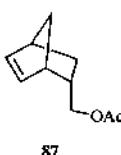
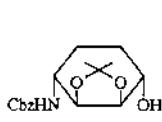
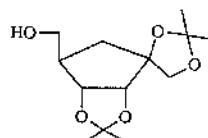
The synthesis of mesyl substituted purinyl-*muco*-inositol derivatives by coupling of a 6-chloropurine with 2,3-anhydro-1,5,6-tri-*O*-mesyl-*epi*-inositol has been disclosed.¹¹⁹

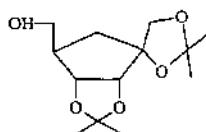
Studies on the conformational and stereochemical aspects of the Ferrier reaction leading to cyclitols and azido cyclitols as an extension of earlier work (Vol. 19, p. 173) have been reported.¹²⁰

The synthesis of racemic 6-acetamido-1,2-anhydro-6-deoxy-*myo*-inositol as a tight binding inhibitor and pseudosubstrate for *N*-acetyl- β -D-glucosaminidase has appeared starting from racemic tetra-*O*-acetylconduritol.¹²¹

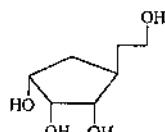
The synthesis of amino-cyclitols related to Hygromycin A are covered in Chapter 19.

The preparation of (-)-carba- β -ribofuranose and (+)-carba- α -ribofuranose by enzymatic resolution of racemic 3 *β* -acetoxy-5 *β* -(t-butylidemethylsilyloxymethyl)cyclopentene and racemic 4 *β* -(triphenylmethoxymethyl)cyclopent-2-en-1 *β* -ol, respectively, as the key step has been reported.¹²² The preparation of β - and α - carba-psicofuranose derivatives **92** and **93** has been described starting from norbornenol,¹²³ and the synthesis of the chain-extended carba-sugars **94** and **95** by a multistep process starting from D-allose derivatives has been reported.¹²⁴

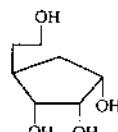
**90****91****92**



93



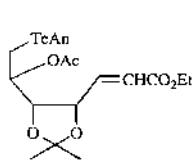
94



95

The p-anisyltelluride compound **96** underwent radical cyclization and with three subsequent chemical steps afforded cyclopentanone **97**.¹²⁵

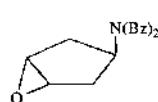
Treatment of the epoxide **98** with TMSCN led unexpectedly to compound **99**.¹²⁶ Epoxidation of cyclopentadiene yields a di-epoxide which on treatment with sodium azide gives a mixture of products from which cyclitol **100** can be obtained as a useful precursor to carbocyclic nucleosides and amino cyclitols.¹²⁷



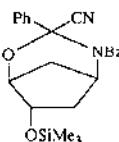
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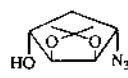
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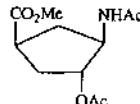
98



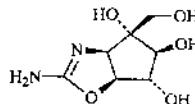
99



100



101



102

A new route to racemic *cis*-4-amino-2-cyclopentene-1-methanol as a key intermediate in the synthesis of carbanucleosides has been described.¹²⁸ An attempt to resolve the amino alcohol by way of its 10-camphorsulfonate failed.

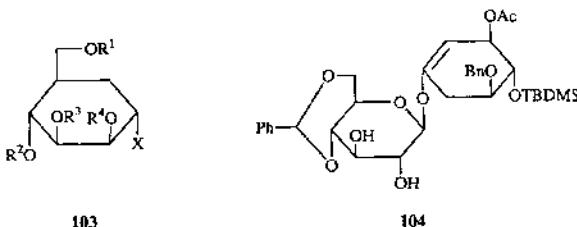
The preparation of cyclopentane derivative **101** as a carbacyclic nucleoside intermediate has been achieved from 2-(4'-methoxybenzyl)-2-azabicyclo[2.2.1]hept-5-en-3-one.¹²⁹ (See Vol. 25, p. 211, ref. 80 for similar work.)

The preparation of the carbanucleoside aristeromycin and carbacyclic precursors of neplanocin A are mentioned in Chapter 19. The preparation of intermediates for the synthesis of unsaturated carbocyclic nucleosides is covered in Chapter 20.

A preliminary report has appeared on the synthesis of allosamizoline, the aglycone of allosamidine¹³⁰ (See also Chapter 19, for a full account) as well as the synthesis of the amino oxazoline **102**¹³¹ from the known (*Helv. Chim. Acta.*, 1979, **62**, 1990) 2R,3S,4R-4-(benzoyloxy)-2,3-bis-[(methoxymethyl)oxy]-5-hexen which was shown to be identical with the aglycone of the naturally occurring trehalase inhibitor, trehzolin.

A full paper (for earlier work see Vol. 25, p. 213, ref. 92) on the preparation of the cyanoglycoside simmondsin has been reported.¹³²

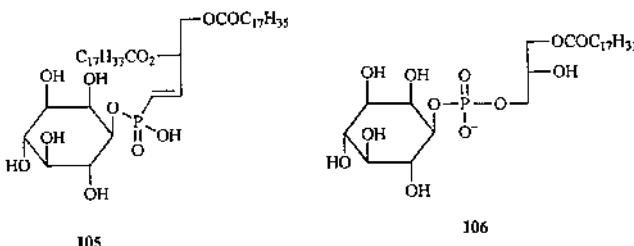
The synthesis of the carba di- and tri-saccharides **103** has been described.¹³³ and the preparation of carba-disaccharide **104** by a similar process to that reported earlier (Vol. 25, p. 214, ref. 95) has appeared.¹³⁴ For the preparation of glycosides of cyclitol derivatives see also Chapter 3. Carbocyclic analogues of GDP fucose have been made as potential inhibitors of fucosyl transferases.¹³⁵



- X = OH, R² = R⁴ = H, R¹ = R³ = α -D-Manp
- X = NHAc, R² = R⁴ = H, R¹ = R³ = α -D-Manp
- X = OH, R¹ = R² = R³ = H, R⁴ = α -D-Manp
- X = OH, R¹ = R² = R³ = H, R⁴ = β -D-Glc β NAc

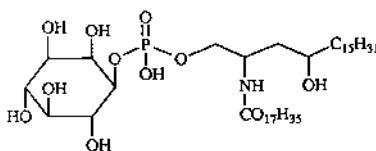
Inositol Phosphates and Derivatives. The isosteric phosphonic acid analogue **105** of phosphatidyl inositol in which the chiral glycerol moiety was prepared from D-mannitol¹³⁶ and the synthesis of the antifungal lysofungin **106**¹³⁷ have been described. The preparation of the related natural ceramide phospho-*myo*-inositol **107** by phosphoramidite methodology has also been reported.¹³⁸ The synthesis of 1-*O*-(1,2-dipalmitoyl-*Sn-glycero*-3-phosphinyl)-2,6-di-*O*- α -D-mannopyranosyl-D-*myo*-inositol of mycobacterial origin has been reported.¹³⁹ Mention is made in Chapter 4 to other glycosyl inositols including the part structure of the GPI anchor of *Trypanosoma brucei*.

The synthesis of the 2-deoxy phosphatidyl inositol analogue **108** in which the phosphorus-containing group is introduced using a novel coupling agent, bis(diisopropylamino)(2-trimethylsilyl ethoxy)phosphine has been described.¹⁴⁰

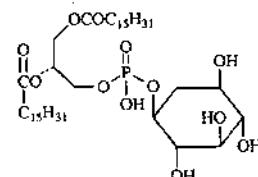


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107

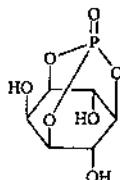


108

The preparation of phosphatidyl inositol derivatives with a thiophospho linkage has been reported,^{141,142} together with a synthesis of phosphatidylinositol 3-phosphate by diisopropyl carbodiimide-promoted migration of the 4-phosphate.¹⁴³

A fluorescent substrate, 2-naphthyl *myo*-inositol-1-phosphate has been prepared for monitoring PIP-specific phospholipase C.¹⁴⁴ New tetherable derivatives of *myo*-inositol-2,4,5- and 1,3,4-triphosphates have been made for use in affinity chromatography in a similar way to that reported earlier (Vol. 25, p. 216, ref. 115 and 116).¹⁴⁵ Other derivatives for affinity chromatography and photoaffinity labelling include 2-substituted ester (*p*-amino, *p*-azido-phenyl for example) derivatives of *myo*-inositol-1,4,5-triphosphate,¹⁴⁶ 1-[3-aminopropoxy(hydroxy)phosphinyl]-D-*myo*-inositol-4,5-bisphosphate (used for isolation of *myo*-inositol 1,4,5-triphosphate binding proteins),¹⁴⁷ and a fluorescent derivative prepared by coupling D,L-*myo*-inositol 1-phosphorothioate-4,5-phosphonate to 4-[*N*-(2-(iodoacetoxy)ethyl)-*N*-methylamino]-7-nitro-2,1,3-benzoxadiazole (IANBD).¹⁴⁸ Also described in the last report is a resolution via a 4,5-bis campharmate ester to produce D-*myo*-inositol-1-phosphorothioate-4,5-bisphosphate.

The preparation of 2-*O*-alkyl-*myo*-inositol-1-phosphates as competitive inhibitors of inositol monophosphatase¹⁴⁹ and the synthesis of *myo*-inositol-1,3,5-*O*-phosphate 109¹⁵⁰ as a new type of caged phosphate has been reported.



109

The preparation of *myo*-inositol 1,4,5-triphosphate by a process involving selective formation of diastereomeric methyl esters in a similar way¹⁵¹ to that described in Vol. 25, p. 209, ref. 59 or by resolution of racemic derivatives with R-mandelic acid¹⁵² or 1-*l*-menthoxyacetyl chloride¹⁵³ (which involves the use of a new phosphitylating agent, *o*-xylene *N,N*-diethylphosphoramidite) have been reported.

Full details of an earlier report (Vol. 25, p. 218, ref. 128 and 129) on the diastereoselective preparation of D-camphanate acetals by precipitation reaction to prepare homochiral *myo*-inositol phosphate derivatives have been disclosed.¹⁵⁴

Also reported is a full account of earlier work (Vol. 23, p. 186, ref. 66) on the chemo-enzymatic synthesis of D-*myo*-inositol 1,3,4-triphosphate and of D-*myo*-inositol 1,3,4,5-tetraphosphate.^{155,156}

The formation of camphanate esters for resolution of racemic inositol has led to the preparation of 1D-2,3,6-tri-, -2,4,5-tri-, -2,5,6-tri-, -1,2,3,4-tetra-, 1,2,3,6-tetra-, -1,2,4,5-tetra- and -2,3,5,6-tetra-O-benzyl-*myo*-inositols¹⁵⁷ and the subsequent use of some of these in the preparation of *myo*-inositol phosphates. The same group has also reported similar work involving the use of allyl, crotyl and isopropylidene protecting groups in addition to benzyl groups.^{158,159}

The syntheses of racemic *myo*-inositol 1,4,5-triphosphate and 1,4-bisphosphate by standard processes involving isopropylidene acetals¹⁶⁰ as well as the syntheses of [³H]-D-3-azido-3-deoxy-*myo*-inositol and D-3-azido-3-deoxy-*myo*-inositol 2,4,5-triphosphate¹⁶¹ have been reported.

A full account of an earlier paper (Vol. 25, p. 217, ref. 125) on the preparation of L-chiro-inositol 2,3,5-triphosphate from L-quebrachitol¹⁶² and the synthesis of L-chiro-inositol 1,4,6-triphosphate and the corresponding triphosphorothioate also from L-quebrachitol¹⁶³ has been reported. Also, a full account (Vol. 23, p. 186, ref. 70) on the preparation of racemic *myo*-inositol 1,4,5-triphosphate and 1,4-bisphosphate-5-phosphorothioate has been reported¹⁶⁴ as well as the preparation of phosphorylated intermediates for the synthesis of both chiral and racemic *myo*-inositol 1,4,5-triphosphate and its phosphorothioate analogue.¹⁶⁵

The preparation of D,L-*myo*-inositol-1-phosphate-4,5-pyrophosphate from *myo*-inositol 1-phosphate-4,5-bisphosphorothioate by treating the latter with NBS has appeared.¹⁶⁶

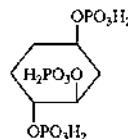
The synthesis of racemic 6-deoxy-6-fluoro-*chiro*-inositol 2,3,5-triphosphate starting from cyclohexa-1,4-diene has been achieved.¹⁶⁷

The preparation of 5-methylphosphonate and 5-(difluoromethyl)phosphonate analogues of *myo*-inositol 1,4,5-triphosphate and 1,3,4,5-tetraphosphate has been disclosed.¹⁶⁸ Other phosphonate derivatives to have been synthesized include D,L-*myo*-inositol 1,4,5-trimethylphosphonate, 4,5-bis and 5-mono methyl phosphonates.¹⁶⁹

The synthesis of analogues of *myo*-inositol 1,4,5-triphosphate with sulfonamide, sulfate, methylphosphonate and carboxymethyl groups have been reported.¹⁷⁰ (See Vol. 24, p. 206, ref. 99 for similar work.)

A number of carbamate derivatives as possible inhibitors of phospholipase C have been

made¹⁷¹ and the trideoxy analogue **110** of D-*myo*-inositol-1,4,5-triphosphate has been prepared from anisole.¹⁷²

**110**

The stability constants of the complexes formed from Ca^{2+} and *myo*-inositol-1,4,5-triphosphate in an attempt to assess the biological significance of the metal binding to this triester have been reported.¹⁷³

The mass spectra of some silylated 2-deoxy-*scyllo*-inoses is covered in Chapter 23.

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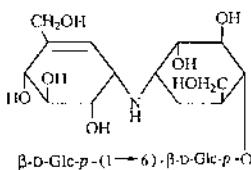
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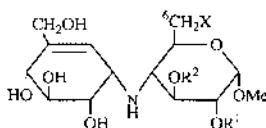
Antibiotics

1 Amino-Glycoside Antibiotics

A first total synthesis of validamycin II **1** has been described.¹ Ogawa's group has reported the syntheses of a series of analogues of methyl acarviosin **2**; compounds **3** have been prepared,² as well as analogues having an α -D-*manno*-configuration and a saturated cyclohexane ring.³ In addition, syntheses of methyl 1'-epiacarviosin and its 6-hydroxy derivative have been described.⁴



1



2 R¹ = R² = X = H

3 R¹, R² = H or Me, X = OH, N₃, NH₂, NHAc

Kanamycin precursors have been used to prepare 3'-deoxy-3'-fluorokanamycin B,⁵ 3'-deoxy-3'-fluorokanamycin A,⁶ 4'-deoxy-4'-fluorokanamycins A and B,⁷ 5-deoxy-5-fluoro-kanamycin B, 5,3'-dideoxy-5-fluorokanamycin B, and 5,4',3'-trideoxy-5-fluorokanamycin B.⁸ This last reference also reports syntheses of 5,5-difluoro analogues.

A total synthesis of allosamidin is mentioned in Chapter 3. Full details of the synthesis of allosamizoline, the aglycone of allosamidin, have been reported.⁹ Studies of allosamidin biosynthesis using labelled D-glucose and D-glucosamine indicate that the latter sugar is the precursor to each N-acetyl-D-allosamine and to the allosamizoline component.¹⁰

Different approaches to the selective protection of amino groups in the synthesis of kanamycin and ribostamycin have been reviewed.¹¹

The chemical structure of the pseudotrisaccharide nebmycin T has been studied by 1D and 2D n.m.r. techniques.¹²

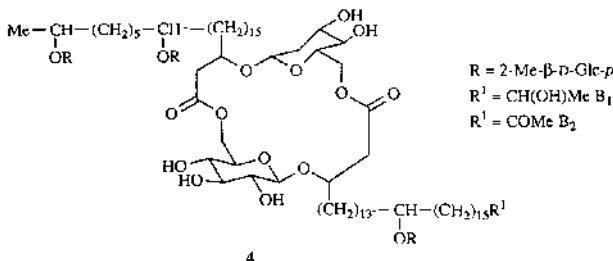
Studies on neomycin biosynthesis using labelled D-glucose and 6-deoxy-D-glucose derivatives investigated labelling in the streptamine ring. They have strengthened previous suggestions that the 6-hydroxy group is removed prior to cyclization, and showed that the C-4 and C-5 hydrogen atoms are removed, which is assumed to follow ketonization at C-4.¹³

The formation of 2-deoxy-*scyllo*-inosose as an intermediate in the biosynthesis of 2-deoxystreptamine has been confirmed with a cell-free preparation of *S. fradiae*.¹⁴

Solid-state properties of tobramycin have been investigated.¹⁵

2 Macrolide Antibiotics

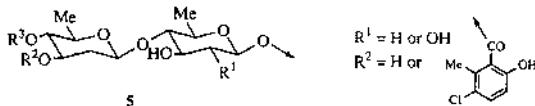
The structures of the novel antiviral antibiotics cycloviracin B₁, **4** and B₂ have been elucidated; they are macrocyclic diesters incorporating two molecules of D-glucose in the ring with 2-O-methyl-D-glucose residues attached to hydroxy-fatty acids.¹⁶



New 14-membered macrolide antibiotics, the sporeamicins, have been isolated from a *Saccharopolyspora* strain. They contain desosamine and cladinose or mycarose separately attached to the macrolide ring which contains an oxolone unit.¹⁷⁻¹⁹

New 14-membered macrolactam antifungal antibiotics isolated from the broth of a new species of *Actinomadura* contain either mycosamine or its 4-epimer, 3-amino-3,6-dideoxy-L-talopyranose, attached to the macrolide ring.^{20,21}

Cholesterol biosynthesis inhibitors isolated from *S. sp.* A7361 have been shown to be analogues of chlorothricin, containing the disaccharide units **5** attached to the macrolide ring.²²



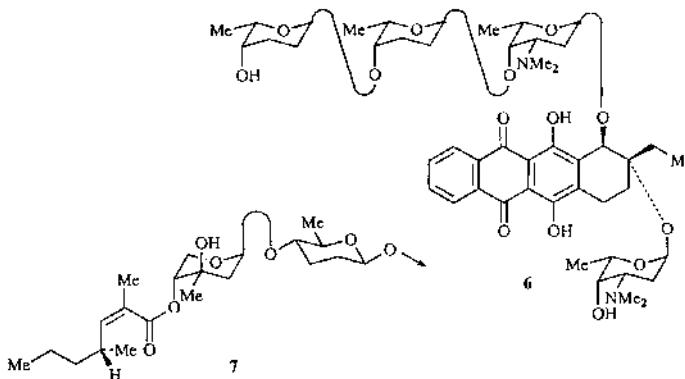
Minor components of the mycinamicin complex obtained from *Micromonospora griseorubida* have been isolated and characterized; they contain mycinose and/or desosamine separately attached to the 16-membered macrolide ring.²³ Some derivatives of angolamycin together with the parent compound have been identified in a broth of a *Streptomyces* strain (86-070); the same

sugars angulosamine, mycarose, and mycinose, are present in the analogues, attached to slightly variant macrolide rings.²⁴

3-Deoxy-5-O-(4-deoxymycaminosyl)-tylonolide is highly anti-bacterial.^{24a}

3 Anthracycline and Related Polycyclic Antibiotics

A new cytotoxic antibiotic cytorhodin X from a *Streptomyces* strain has been shown to be an unusual anthracyclinone 9 α -glycoside **6**.²⁵ Another new anthracycline antibiotic, dutomycin, also obtained from a *Streptomyces* strain, contains a disaccharide component **7** including the branched chain sugar L-axenose.²⁶

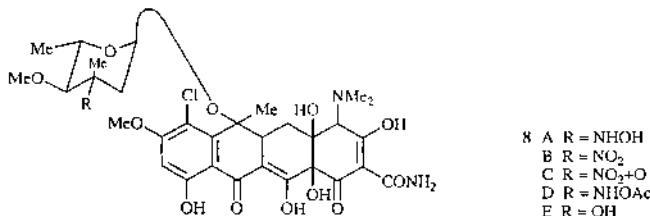


Cinerubin R, a new antibiotic isolated from a *S. eurythermus* strain, has been characterized as 4"-aculosyl-4'-rhodinosyl-7-rhodosaminyl- ϵ -pyromycinone.²⁷ Spartanamicins A and B obtained from a *Micromonospora* strain have a closely related structure, spartanamicin B being 4"-cinerulosyl-4'-deoxyfucose-4-rhodosaminyl-pyromycinone, with the A isomer containing a second ether bridge linking the 3' and 2" positions.²⁸

A new antitumour tetracycline antibiotic, SF 2575, isolated from the *Streptomyces* strain bearing this coding, contains 4-O-angeloyl-2,6-dideoxy-arabino-hexopyranose linked as a C-glycoside to the A ring of the aglycone.²⁹

Dactylocyclines A-E, novel tetracycline derivatives produced by *Dactylosporangium* sp. (ATCC 53693), have the structure summarized in **8**, variations being in the nitrogenous branched-chain sugar.³⁰ Protorubradirin, containing a C-nitroso sugar, has been shown to be the true secondary metabolite produced by *S. achromogenes* var. *rubradiridis*, the nitroso sugar being oxidized on exposure to light and air to the C-nitrosugar rubranitrose present in rubradirin; the

authors suggest an analogous change occurs in the conversion of viriplanin A to viriplanin O.³¹



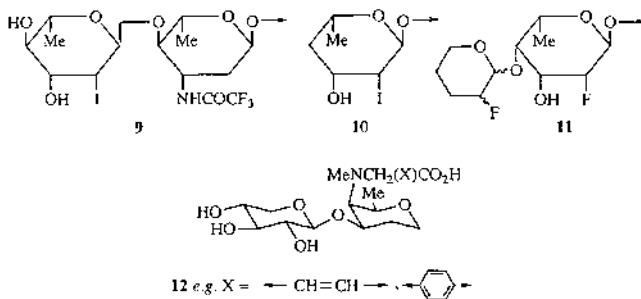
A new mutactimycin, SO-75RI, from *Nocardia brasiliensis*, contains 3,4-di-*O*-methyl-1-*D*-rhamnose rather than the 3-*O*-monomethyl ether present in mutactimycin A.³²

New anthracycline antibiotics rubomycins F and H, isolated from *S. coeruleorubidus* along with other daunomycinone derivatives, have been shown to be *N*-acylated derivatives of daunorubicin.³³ Rubomycin M and N are disaccharide derivatives of daunomycinone, having a daunosamine unit glycosylated at C-4' with either of two 2,6-dideoxy-*L*-hexopyranoses.³⁴

3"-Demethylchartreusin has been identified as a minor component of crude chartreusin from *S. chartreusis*.³⁵

Routine methods have been used to prepare glycosides of aranciamycinone with pentose and hexose sugars,³⁶ to prepare the disaccharide **9** derivative of daunomycinone using glycal intermediates,³⁷ and to prepare 3'-deamino-3'-hydroxy-2'-iodoerubixin containing the sugar **10** from 4,6-dideoxy-*L-threo*-hex-1-enitol.³⁸ 4'-*O*-Acylanthracyclines have been prepared from oxazoline intermediates,³⁹ and the fluorinated derivative **11** of daunomycinone has been synthesized from the 2'-fluoroglycoside precursor.⁴⁰

The 4'-amino group in the disaccharide unit of pradimicin has been converted to a variety of *N*-alkylcarboxylic acid derivatives to give compounds containing the units **12**, some of which are antifungal with improved water solubility.⁴¹



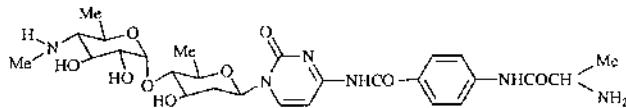
N-Demethyl derivatives of anthracyclines have been obtained photochemically, giving *N*-methyldaunosamine and daunosamine analogues from rhodosamine precursors; products were mostly less active than the parent antibiotics.⁴² Glycosylated prodrugs of daunorubicin involving D-galactose have been described, the galactose residue being attached through an *N*-acyl bridge; drug release involves enzymic glycoside hydrolysis leading to a carbamic acid intermediate.⁴³

Glycosides of the antitumour alkaloid camptothecin and an enantiomer of gilvocarcin M are mentioned in Chapter 3.

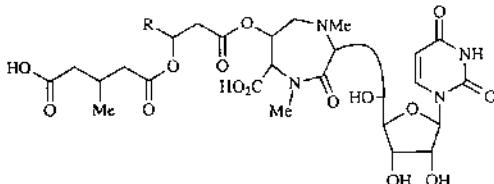
4 Nucleoside Antibiotics

Current progress in the chemistry of nucleoside antibiotics⁴⁴ and recent developments in the synthesis of anti-HIV dideoxy nucleosides⁴⁵ have been reviewed. A further review on the use of radical reactions for synthesizing nucleosides including antibiotics is mentioned in Chapter 20.

Anti-cancer 1- β -D-arabinofuranosylcytosine has been isolated from the mushroom *Xerocomus nigromaculatus*.⁴⁶ The broth of *Nocardia brasiliensis* SF2457 has yielded the antibiotic SF2457 13, a close relative of amicetin.⁴⁷ Liposidomycins A-C 14 have been isolated from *S. griseosporeus*,⁴⁸ and a stereospecific synthesis of a stereoisomer of the ribosyl-diazepanone unit has been described in an attempt to elucidate the stereochemistry of the B component.^{48a}



13

[4 R = C₁₁ alkyl or C₁₃ diaryl]

An improved preparation of pentostatin has been reported.⁴⁹ Uracil analogues of sinefungin have been synthesized using the route applied to sinefungin itself which involves a radical coupling reaction.⁵⁰ (See Vol. 25, Chap. 19, ref. 62.) An efficient microbial alternative to

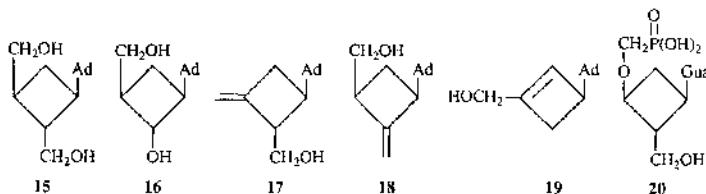
chemical synthesis of 4-thiouridine has been described.⁵¹

The total synthesis of hikizimycin has been reported, which involves the use of nitrobenzene as solvent in an improved Vorbrüggen reaction.⁵²

Some intermediates involved in the biosynthesis of nikkomycins by *S. tendae*, analogues of octenyl acids, have been reported.⁵³ A study of the biosynthesis of griseolic acids by *S. grisea-aurantiacus* using ¹³C and ¹⁵N labelled substrates suggests that glucose and ribose contribute to the adenine and ribose moieties in griseolic acid A.⁵⁴

Ring contraction of mesylates of α -hydroxy- γ -lactones provides a route to 3'-O-methyloxetanocins.⁵⁵ The synthesis of oxetanocin and oxetanose chemistry has been reviewed (in Japanese).⁵⁶

The carbocyclic analogue of oxetanocin A 15 has been synthesized from cyclobutane precursors,⁵⁷ and the further analogues 16 (both enantiomers)⁵⁸ and 17 - 19⁵⁹ have been prepared. Likewise the guanosine analogue of 15⁶⁰ and the phosphonate 20,⁶¹ 5-vinyluracil analogues of 15 and 16,⁶² and the adenine and 7-deazaguanosine derivatives of 3-hydroxymethyl cyclobutane have been synthesized.⁶³



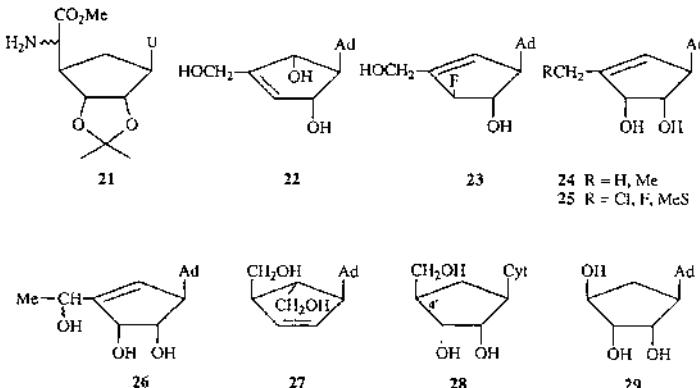
The nucleoside portion 21 of a carbocyclic analogue of nikkomycin Z has been synthesized.⁶⁴

(-) Neplanocin A has been synthesized from a chiral cyclopentenone precursor,⁶⁵ and the precursor cyclopentylamine has been made from a *meso*-cyclopentane dicarboxylate using enzymic resolution.⁶⁶

6'-Modified neplanocin A analogues have been prepared,⁶⁷ as well as anti-tumour 6'-phosphatidyl derivatives, using an enzymic coupling procedure.⁶⁸

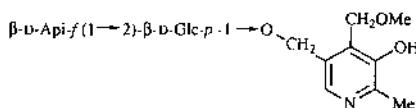
Syntheses have been described for (\pm)-neplanocin F 22,⁶⁹ the 3'-deoxy-3'-fluoro-*L-threo*-analogue 23 of neplanocin,⁷⁰ 4'-modified analogues of neplanocin A and aristeromycin, e.g., 24, from D-ribonolactone,⁷¹ and derivatives 25 and 26 from neplanocin A, one epimer of (26) being a very active SAII-hydrolase inhibitor.⁷² Other papers report the preparation of the neplanocin analogue incorporating 5-azacytidine instead of adenine, which is anti-leukaemic,⁷³ and the anti-HIV analogue 27 of carbovir.^{74,75}

Asymmetric enzymic hydrolysis of cyclopentane diester derivatives has been used in three routes to both (-) and (+) aristeromycin.⁷⁶⁻⁷⁸ Reactions of aristeromycin are also mentioned in Chapter 20. The cytidine analogue of neplanocin has been selectively reduced to carbodine **28** (using diimide) or its 4'-epimer, isocarbodine (using hydrogen with palladium catalyst).⁷⁹ (-)-5'-Noraristeromycin **29** has also been synthesized.⁸⁰



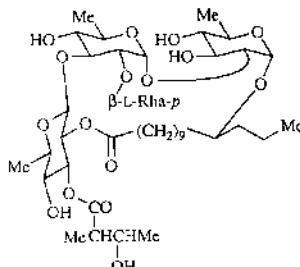
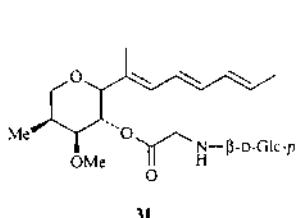
5 Miscellaneous Antibiotics

Julibrin II, an arrhythmia-inducing heart drug isolated from the bark of *Albizzia julibrissin*, has been shown to be the apiosyl-glucosyl disaccharide derivative **30**.⁸¹ KS-505a, an enzyme inhibitor from *S. argenteolus*, contains 2-O-methyl-β-D-glucuronic acid β-linked to a steroid-like aglycone.⁸² β-D-Glucopyranoside units occur in a fungal tetracyclic triterpene antagonist of leucotriene B₄ WF11605,⁸³ and as a glycosylamine residue in the antifungal glucolanomycin **31** obtained from *Pycnidiphora dispersa*.⁸⁴



30

A paper (in Chinese) reports the structure of one component, DC-2b **32**, of calonyctin A obtained from the leaves of *calonyction aculeatum*. Evidence from various n.m.r. techniques was used to establish the structure.⁸⁵



Galacardins A and B, new glycopeptide antibiotics from *Saccharothrix* sp. SANK64289, are related to β -avoparcin, but with differing sugar composition. Besides the ristosamine, glucose, rhamnose, and mannose present in β -avoparcin, galacardin B has one molecule of galactose, and the A component two molecules separately attached to the peptide core.⁸⁶

A new polyether antibiotic, octacyclomycin, differs from the close relative UK-58852 only by an additional hydroxyl in the polyether aglycone.⁸⁷ Another new polyether antibiotic, CP-82,009, a potent anticoccidial related to septamycin, produced by *Actinomadura* sp. ATCC 53676, contains the same 2,3,6-trideoxy-4-O-methyl- α -D-*erythro*-hexopyranose as UK-58,852.⁸⁸

A new indolocarbazole antibiotic, RK-286D, obtained from *S.* sp RK-286, is a β -glycosylamine derivative of digitoxose.⁸⁹ Reference to kedarenidin, an antitumour antibiotic containing a new amino sugar, kedarosamine, and L-mycarose, is made in Chapters 9 and 14. The potent NADH inhibitor, penta-O-galloyl- β -D-glucopyranose, is referred to in Chapter 17.

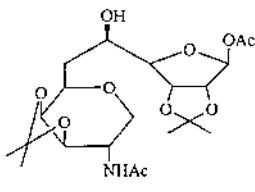
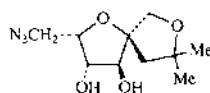
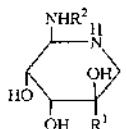
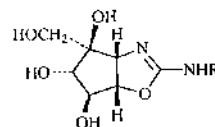
A total synthesis of calicheamycin γ_1^1 has been reported.⁹⁰ Degradation studies on this and other calicheamycins have allowed their structures to be assigned by comparative ^1H and ^{13}C n.m.r. studies.¹⁹ Specific bindings of calicheamycin γ_1^1 with DNA have been examined by use of oligosaccharide fragments of the antibiotic.^{92,93}

The tunicamine derivative **33** has been synthesized from 2-azido-2-deoxy-D-galactose.⁹⁴

L-Sorbose has been used as a substrate for synthesizing 1-deoxyojirimycin via the azide **34**, which was converted to the antibiotic in a one-pot reaction.⁹⁵ Another synthesis employs methyl

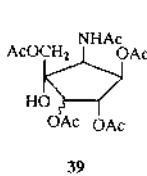
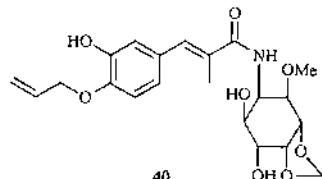
D-mannofuranoside as a starting material, and involves a reductive amination of a D-lyxo-hexos-5-ulose derivative.⁹⁶

D-Ribono- γ -lactone is a convenient substrate for the synthesis of siastatin B analogues **35**, including their enantiomers.⁹⁷ Other analogues **36** have also been prepared,⁹⁸ including ring nitrogen N-alkyl analogues.⁹⁹

**33****34****35** $R^1 = CH_2NO_2, CH_2NHI_2, CO_2H$
 $R^2 = Ac$ **36** $R^1 = CH_2NO_2, CH_2NH_2, CO_2H$
 $R^2 = TFA$ or CH_2OH **37** $R = H$
38 $R = \alpha\text{-D-Glc-}p$

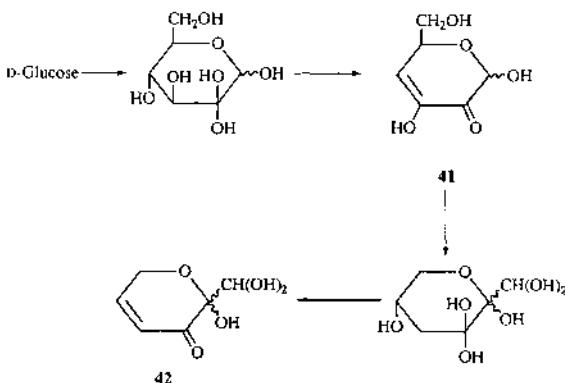
The amino-oxazoline **37**, and hence the trehalose inhibitor trehzolin **38**, have been prepared by nitrone addition to a hexenal derivative obtained from D-glucose.¹⁰⁰ Compound **38** has also been synthesized together with analogues **39** (both epimers) from *myo*-inositol to establish the correct structures of trehzolin and its epimer trehalostatin.^{101,102}

A series of analogues of hygromycin A have been prepared by varying the acyl unit on the amino-cyclitol moiety, e.g., **40**, and varying the substitution pattern or stereochemistry in the aminocyclitol ring. Although **40** was active, most variations destroyed biological activity.¹⁰³⁻¹⁰⁵

**39****40**

2"-And 3"-mono-*O*- and 2".3"-di-*O*-substituted derivatives of etoposide have been synthesized, by methods which involved standard ester groups on the glucose moiety.¹⁰⁶

The antibiotic cortalcerone **42**, a metabolite of the fungus *corticium caeruleum*, has been prepared from D-glucose using a pyranose 2-oxidase and an aldose-2-ulose dehydratase to prepare the unstable tricarbonyl derivative **41** and hence the product, as shown in Scheme 1.¹⁰⁷



Scheme 1

Glycosylated *erythro*-β-hydroxy-L-histidine compounds have been prepared (from D-Glc, D-Man, D-Gal) in the study of the role of the sugar in bleomycin; they show excellent dioxygen activating capability.¹⁰⁸

The biosynthesis of streptothricin F has been studied using ²H-labelled arginine substrates; the results suggest that hydroxylation occurs with retention of configuration at C-4.¹⁰⁹

Amides of streptonigrin have been synthesized using amino-dicarboxylic acids or aminosugars, and coupling via the *N*-hydroxysuccinimido ester group.¹¹⁰

Spectroscopic data suggest that the *N*-methylamino group of the aminosugars present in neocarzinostatin acts as an internal base in organic solvents.¹¹¹

The synthesis of the avobiose unit in avoparcin, of bioactive methyl oleonolate diglycosides, and of antifungal diosgenyl glycosides is mentioned in Chapter 3. The synthesis of antitumour glycosylamino-indoloquinolines is covered in Chapter 10, and the preparation of methyl α-D-evalopyranoside, present in orthosomycin antibiotics, is referred to in Chapter 14.

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20 Nucleosides

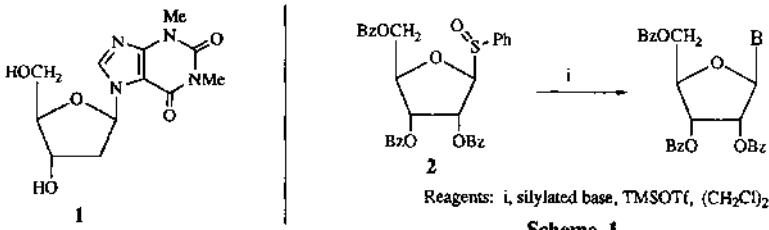
1 General

The 5'-O-acetyl derivative of 3'-deoxyadenosine (cordycepin) has been isolated from the fungus *Emericella nidulans*, along with cordycepin itself,¹ and the N⁷-linked purine nucleoside aplysidine (**1**) has been found in an Okinawan marine sponge, and synthesized by glycosylation of the sodium salt of the base. The same sponge was also found to contain 2',3'-didehydro-2',3'-dideoxyuridine (d4U), the first report of the natural occurrence of this sugar moiety.² An efficient microbiological preparation of 4-thiouridine, using a strain of *Streptomyces libani*, has been advocated as an alternative to chemical synthesis.³

The synthesis and chemistry of heterocyclic analogues of purine nucleosides and nucleotides have been comprehensively reviewed,⁴ as have the synthesis and properties of various disaccharide nucleosides.⁵ Other reviews have discussed the importance of nucleoside analogues in chemotherapy and in other potential therapeutic applications such as immunomodulation or the regulation of gene expression,⁶ recent developments in the synthesis of nucleoside analogues with anti-HIV activity,⁷ and the synthesis of 2',3'-dideoxynucleosides, with or without substituents at C-2' or C-3', by methods which involve condensations of modified sugars with heterocyclic bases.⁸ In a review on progress in free radical chemistry in his laboratories, Barton has discussed applications to the synthesis of C-nucleosides, chain-extended nucleosides and nucleoside phosphonates.⁹

2 Synthesis

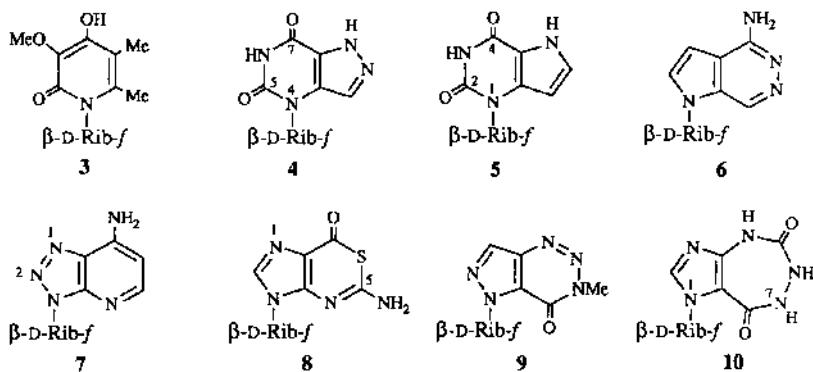
As regards novel methodology for making β-D-ribofuranosyl nucleosides, the sulfoxide **2** has been employed (Scheme 1) for preparing protected nucleosides with all the normal nucleobases; the



method was used to make [1'-¹³C]-nucleosides from [1-¹³C]-D-ribose, and hence, by standard deoxygenation, the [1'-¹³C]-2'-deoxynucleosides.¹⁰ The use of Cp₂MC₂ (M = Hf or Zr) and a

silver salt has been applied to the coupling of 2,3,5-tri-*O*-benzyl- β -D-ribofuranosyl fluoride and silylated uracil; the combination of Cp₂HfCl₂ and AgOTf gave 95:5 selectivity for formation of the β -nucleoside.¹¹ Trifluoro- and trichloro-acetoxy leaving groups have been used in the synthesis of β -D-ribofuranosyl derivatives of substituted uracils from the silylated heterocycle in the presence of SnCl₄.¹²

Standard procedures have been used to prepare β -D-ribofuranosyl nucleosides of some pyridine 2,4-diones (e.g. 3),¹³ 5-hydroxy-6-methyluracil (ribosylation at N³),¹⁴ some 5-substituted uracils,¹⁵ and some furfurylidene derivatives of barbituric acid.¹⁶ Also reported have been 4- β -D-ribofuranosyl-5,7-disubstituted pyrazolo[4,3-*d*]pyrimidines such as 4 and 1-ribosylated-2,4-disubstituted pyrrolo[3,2-*d*]pyrimidines (e.g. 5),¹⁷ the 4-aminopyrrolo[2,3-*d*]pyridazine nucleoside 6 and its β -D-arabinofuranosyl analogue, made by sodium-salt ribosylation of a 2,3-disubstituted pyrrole and subsequent annulation of the pyridazine ring,¹⁸ 8-aza-1-deazaadenosine (7) and its 2'-deoxy analogues, where the sodium salt glycosylation also gave comparable amounts of N¹- and N²-ribosylated products,¹⁹ nucleosides of 5-substituted imidazo[4,5-*d*][1,3]-thiazines (e.g. 8, and N¹-ribosylated compounds),²⁰ pyrazolo[4,3-*d*]-1,2,3-triazin-4-one nucleosides such as 9, where substituted pyrazole nucleosides were employed as precursors,²¹ the imidazo[4,5-*e*][1,2,4]-triazepine nucleoside 10, where the N⁷- regioisomer could be obtained under different conditions of condensation,²² and some naphthimidazole nucleosides.²³

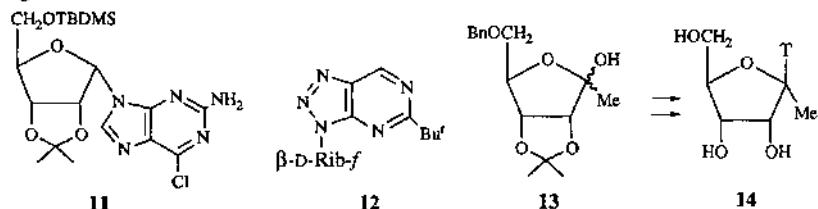


The α -linked product 11 was the major isomer produced by condensation of the ribofuranosyl chloride and the heterocycle in the presence of cesium carbonate and *N*-methylpyrrolidone, thus giving an expeditious route to α -guanosine.²⁴

The triazolo[4,5-*d*]pyrimidine nucleoside 12 was obtained, albeit in low yield, by cyclization of tri-*O*-benzoyl- β -D-ribofuranosyl azide with 2-*t*-butyl-4-pyridyne generated *in situ*.²⁵

Exposure of methyl α,β -D-ribofuranoside to Raney nickel and D₂O for prolonged periods gave high levels of deuterium incorporation at C-2, -3, -4, and -5, with relatively low amounts at C-1. This deuterated material was then used to prepare ribonucleosides highly enriched with deuterium, and, by free radical reduction using Bu₃SnD, 2'-deoxyribonucleosides. These deuterated materials and their natural counterparts were combined to form partially deuteriated DNA and RNA.

dinucleotides which were examined by nmr to evaluate the simplification achieved, and the potential use of this technique to provide a spectral window for observing selected residues in oligonucleotides.²⁶

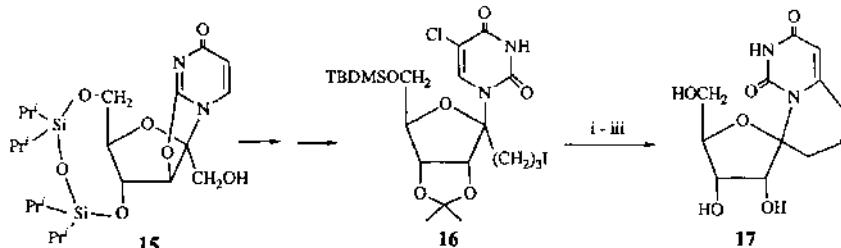


Various 5-substituted α -D-arabinofuranosyluracils have been prepared conventionally,²⁷ and a full account has been given of a route to L-threo-furanosyl nucleosides by ring-expansion of oxetane derivatives (see Vol. 24, p. 226).²⁸

The hemiketal 13, made by addition of McLi to the lactone, has been converted into 1'-deoxy-D-psicofuranosylthymine, and under certain conditions the β -anomer 14 was the major product.²⁹ A synthesis of psicofuranosyluracil is mentioned in Section 3 below.

In the area of hexopyranosyl nucleosides, it has been shown that the Vorbrüggen-type coupling between penta-O-acetyl- β -D-glucopyranose and silylated cytosine proceeds in higher yield and at lower temperatures if nitrobenzene is used as solvent, a result which was then applied in the synthesis of the nucleoside antibiotic hikizimycin (see Chapter 19).³⁰ Standard methods have been used to make β -D-glucopyranosyl and 6'-amino-6'-deoxy- β -D-glucopyranosyl derivatives of 2-aminopurine,³¹ and the Traube synthesis has been employed to prepare 9- β -D-xylopyranosyl- and 9- β -D-glucopyranosyl-2-substituted purines from the corresponding glycosylamine derivatives.³² The N - β -D-galactopyranoside of 5-fluorouracil has been prepared in a standard manner.³³

3 Anhydro- and Cyclo-nucleosides



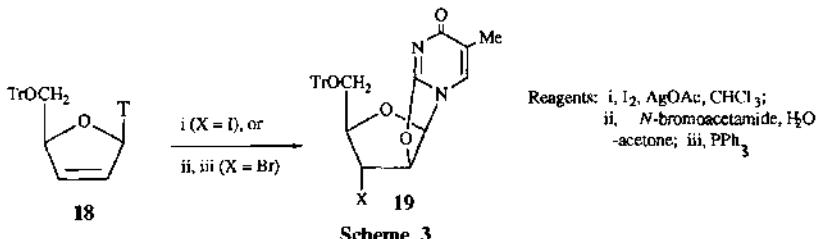
Reagents: i, Bu_3SnH , AIBN; ii, DBU; iii, H_3O^+

Scheme 2

6,1'-Propanouridine (17), a carbon-bridged cyclonucleoside fixed in the *syn*- conformation, has been prepared from D-fructose with the intermediacy of the known 2,3'-anhydronucleoside 15 (see Vol. 20, p. 215-6). This was converted (Scheme 2) in a multistep process to 16, and the propano-bridge

was introduced by radical chemistry. Intermediates in this work were also used to make β -D-psico-furanosyluracil.³⁴

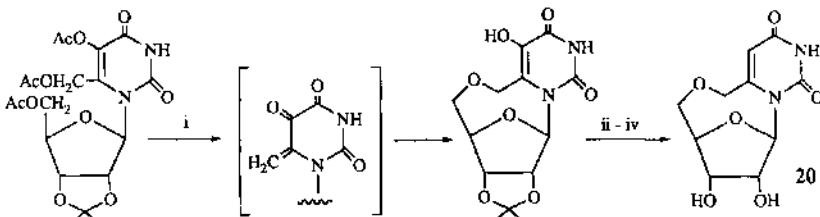
The d4T derivative **18** could be converted into the 2,2'-anhydronucleoside **19**, X=I, as indicated in Scheme 3, iodide **19** (X=I) being of use for making various other 3'-deoxy-3'-substituted arabinofuranosylthymines via the 2',3'-lyxo-epoxide.³⁵ The corresponding bromo-compound **19**, X=Br, is however more reliable in such processes since the iodocompound can undergo deiodination processes in some cases. Reaction of **18** with *N*-bromoacetamide leads to addition of the elements of HOBr across the 5,6-positions of the pyrimidine ring, as well as to cyclonucleoside formation, but this side reaction can be reversed by treatment with triphenylphosphine.³⁶



Scheme 3

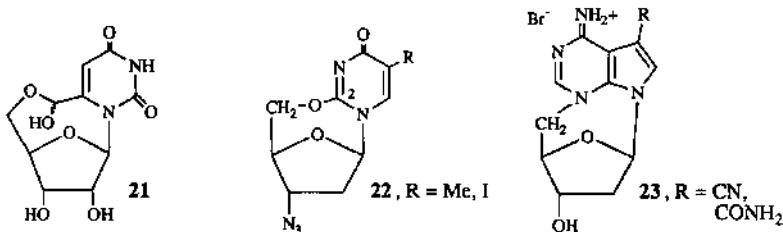
The solution conformations of 2'-deoxy-8, 2'-methano- and -ethano-adenosine have been studied by 1H -nmr spectroscopy, and by X-ray crystallography.³⁷

A full account has been given of the formation of 5'-*O*, 8-cycloadenosine derivatives by oxidation of the parent compounds with lead tetraacetate (see Vol. 18 p. 195),³⁸ and 5'-*O*, 6-methanouridine (**20**), a new type of pyrimidine cyclonucleoside, has been prepared as outlined in Scheme 4; conformational studies were also carried out on this system.³⁹ The previously-reported 'instability' of uridine 6-carbaldehyde has been reinvestigated, and it has been found that the compound and its derivatives have a propensity to hydrate to *gem*-diols, and, in the case of the parent compound, form the cyclic hemiacetal **21**.⁴⁰



Scheme 4

Efficient routes have been described for the preparation of the 2,5'-anhydropyrimidines 22, labelled with ^{14}C at C-2,⁴¹ and the cyclic pyrrolopyrimidine nucleosides 23 have been prepared, with 5'-deoxy-5'-halogenonucleosides as intermediates.⁴²



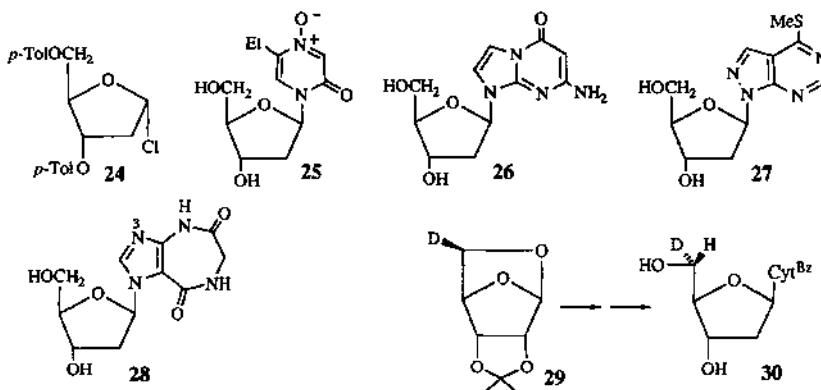
A number of applications of anhydronucleosides in syntheses of other types of nucleoside derivatives are mentioned in subsequent sections.

4 Deoxynucleosides

A review has been published, in Japanese, on the stereoselective synthesis of nucleosides by condensations between nucleobases and 2-deoxysugar derivatives, together with transformations to 2',3'-dideoxy- and 2'-3'-dihydro-2',3'-dideoxyderivatives.⁴³

A systematic study has been reported on the isomer distribution in condensations between 2-deoxy-3,5-di-O-p-toloyl- α -D-*erythro*-pentofuranosyl chloride (24) and the sodium salts of various 2-substituted and 2,6-disubstituted purines. Typically 9- β - and 7- β -products were obtained in ratios of *ca.* 4:1, with smaller amounts of α -nucleosides, with 2-bromo-6-(methylthio)purine giving the highest amount of 9- β -linked product. 2,6-Dibromopurine, however, gave only N-9 linked products (β : α , 4:1).⁴⁴ Other workers have reported that if the α -chloride 24 is allowed to stand in acetonitrile-THF for periods of 30-40 min, followed by the addition of the sodium salt of a purine, or of 2,4-bis-O-trisylthymine, then α -2'-deoxynucleosides can be obtained (α : β *ca.* 3:1), a result which is attributed to epimerization of the glycosyl halide before coupling.⁴⁵

The synthon 24 has also been used in conventional syntheses of 3-deazathymidine,⁴⁶ 2'-deoxyuridines substituted at C-5 with alkoxyethyl groups,⁴⁷ cyclopropyl and various aryl groups,⁴⁸ 2-nitrovinyl (the ribonucleoside was also reported),⁴⁹ trifluoromethylthio- and trifluoromethylselenyl-groups,⁵⁰ and 2'-deoxy- β -D-ribofuranosyl derivatives of a pyrazinone-4-oxide (25),⁵¹ imidazo[1,2-*a*] pyrimidines such as 26 (2',3'-dideoxynucleosides were also prepared),⁵² methylthiopyrazolo[3,4-*d*]pyrimidines such as 27 (*N*-2 regioisomers also being formed),⁵³ and the imidazo[4,5-*e*][1,4]diazepine 28, where condensation using a nitroimidazole, followed by a formation of the 7-membered ring, gave access also to the *N*-3 regioisomers.⁵⁴ The enantiomer of 24 has also been used to make 2'-deoxy- β -L-nucleosides,^{55,56} the purine nucleosides also being accessible by chemical transglycosidation from 3',5'-di-O-benzoyl- β -L-*erythro*-pentofuranosyl-uracil. It was found that L-thymidine is phosphorylated by HSV-1 thymidine kinase almost as well as the D-enantiomer.⁵⁶

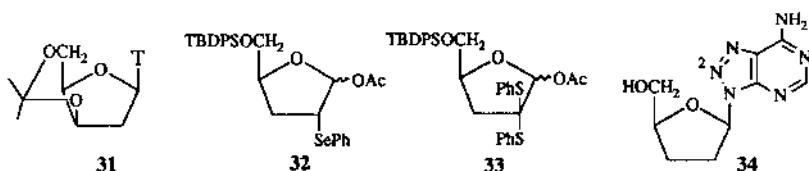


Deoxygenation of ribonucleosides via their 3',5'-TIPDS derivatives has been used to make the 2'-deoxyderivative of zebularine [1-(β -D-ribofuranosyl)-1,2-dihydropyrimidine-2-one],⁵⁷ 2'-deoxy-6-azacytidine,⁵⁸ 2'-deoxyribosides of some 2,4-quinazolininediones (3'-deoxy- and 2',3'-dideoxynucleosides also being reported),⁵⁹ and in the preparation of the 2'-deoxycytidine derivative **30** from the known anhydrosugar **29** (Vol. 18, p. 85), where Mitsunobu inversion gave also the 5'-epimer of **30**.⁶⁰

A crude nucleoside *N*-deoxyribosyltransferase preparation from *Lactobacillus leichmannii* has been used to prepare 9- β -D-2'-deoxy- and 2',3'-dideoxy-nucleosides of 2-aminopurine.⁶¹

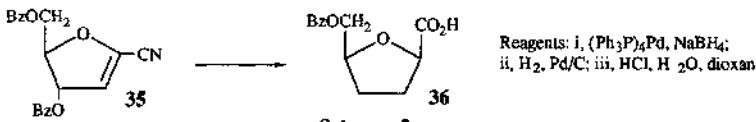
The 2'-deoxy-D-*threo*-pentofuranosylthymine derivative **31** was prepared with good yield and β -selectivity by reaction of silylated thymine with the phenylthio α -glycoside, activated by NBS; the α/β ratio was found to be dependent on the nature of the 3', 5'-protection.⁶²

The same group have also used phenylthio glycosides to make 2',3'-dideoxynucleosides. Various bases and activators were investigated, and moderate β -selectivity could be obtained in some cases.⁶³ The area of 2',3'-dideoxynucleosides and the related d4 systems continues to be an active field. A full account has been given of the use of the phenylselenyl substituent in **32**, introduced through phenylselenylation of the 1,4-lactone, to direct nucleoside formation in a β -sense, the selenyl group subsequently being removable either oxidatively to give d4 systems, or reductively to give dideoxynucleosides (see Vols. 24 and 25).⁶⁴ The related bis(phenylthio) compound **33**, also made by functionalization of the 1,4-lactone, similarly gives reasonable β -selectivity in reactions with silylated nucleobases, and the phenylsulfenyl groups can again be

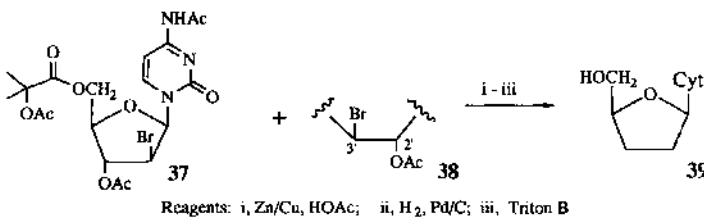


removed by reduction with tributylstannane.⁶⁵ 2',3'-Dideoxy-8-azaadenosine (**34**) has been prepared by direct coupling, in which *N*-2 regioisomers were also obtained. The 5'-triphosphate of **34** showed moderate levels of inhibition of HIV-1 reverse transcriptase.⁶⁶

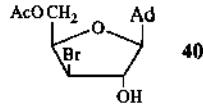
In a route to dideoxuryidine, the unsaturated nitrile **35**, made from D-glucosamine (Vol. 24, p. 132), was converted as outlined in Scheme 5 into the carboxylic acid **36**. This was converted into



the glycosyl isocyanate by a Curtius reaction, and the uracil ring was then elaborated.⁶⁷ Workers at Hoffmann-la Roche have developed two routes for conversion of cytidine into ddC, through 2',3'-unsaturated intermediates. In one method, the 2',3'-thionocarbonate of *N*⁴-acetyl-5'-*O*-TBDMS-cytidine was converted to the 2',3'-ene on treatment with 1,3-dimethyl-2-phenyl-1,3-diazaphospholidine (the Corey-Hopkins procedure), whilst in the alternative (Scheme 6), treatment of cytidine with α -acetoxyisobutyryl bromide gave the mixed acetoxybromides **37** and **38**, convertible as indicated to ddC (**39**). This latter procedure gave an overall yield of 40% from cytidine to ddC,⁶⁸ and other workers have used a very similar method to make ddI from inosine in 51% overall yield with no chromatography involved.⁶⁹ In another related conversion of cytidine to ddC (**39**), the 5'-*O*-acetates analogous to **37** and **38** underwent reductive elimination when treated with potassium bicarbonate in methanol, in the presence of hydrogen gas and Pd/C catalyst, but considerable



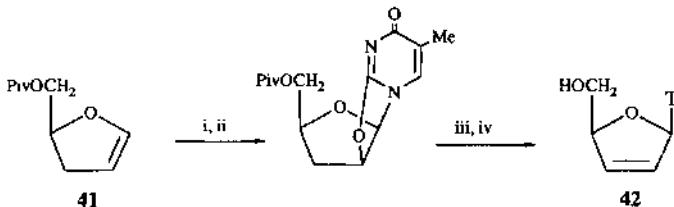
Scheme 6



amounts of 3'-deoxycytidine were also produced.⁷⁰ In a route to dideoxyadenosine, the bromo-alcohol **40** was made by selective hydrolysis of the 2',5'-di-*O*-acetyl derivative in the presence of β -cyclodextrin; after mesylation, the bromomesylate underwent elimination - reduction when treated under basic conditions with hydrogen gas and Pd/C catalyst.⁷¹ Generation of a 2',3'-ene in the purine series could be accomplished by treatment of adenosine, inosine and 7-deazaadenosine with α -acetoxyisobutyryl bromide to make the acetoxybromides analogous to **37** and **38**; selective

deacetylation at $O\text{-}2'$ / $3'$ could then be carried out, and on formation of the phenoxythiocarbonyl derivatives, treatment with tributylstannane gave, after $5'$ -O-deacylation, d4A, d4I, and 7-deaza-d4A.⁷²

A number of syntheses of d4T (42) have been described. One of these is a development of a method for making AZT reported last year (Vol. 25, p. 252) involving a chiral epoxyalcohol; regioselective opening of this with phenylselenyl anion and oxidative elimination were used to generate the $2',3'$ -ene.⁷³ In another approach, the enol ether 41 (Scheme 7), prepared from L-glutamic acid, could be coupled directly with thymine as indicated, and a modification of this gave

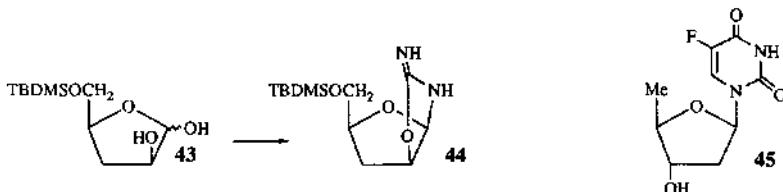


Reagents: i, NIS, $(\text{TMS})_2\text{thymine}$, THF; ii, DBU; iii, KOBu^4 ; iv, NaOMe , MeOH

Scheme 7

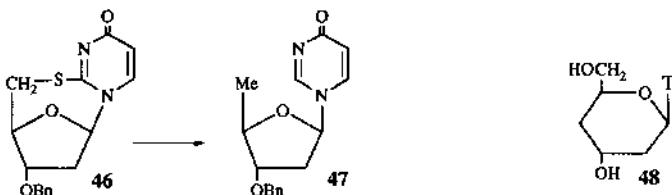
rise to ddA.⁷⁴ In a third synthesis, the 3-deoxysugar 43 was made from D-arabino-1,4-lactone, and treated with cyanamide to give the oxazoline 44. This was then converted to the 2,2'-anhydro-thymidine, which was opened with phenylselenide anion; oxidative elimination then gave d4T (42).⁷⁵ Reese's group have described various ways for the conversion of pyrimidine 2'-deoxy-nucleosides into didehydrodeoxy systems; the d4 analogues of trifluridine and 5-iodouridine were made by opening 2,3'-anhydronucleosides with phenylselenide and oxidative elimination, whilst sodium hydride-induced eliminations from 2,3'-anhydrosystems (made as in Vol. 23, p. 215) or 3',5'-anhydro-derivatives were used to make d4U, d4T, and the didehydrodeoxyderivatives of 5-ethyl- and 5-fluorouridine.⁷⁶

$2',3'$ -Didehydrodeoxy derivatives of 5-(2,2,2-trifluoroethoxymethyl)- and 5-bis(2,2,2-trifluoroethoxy)methyluridine,⁷⁷ 5-styryluridine,⁷⁸ and doridosine (1-methyl-isoguanosine)⁷⁹ have also been described.



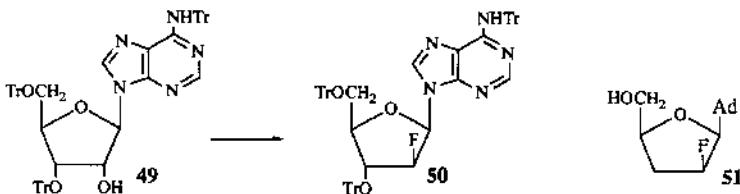
The 1-deoxypicofuranosyl nucleoside 14 has been converted to the 1,3,4-trideoxy-derivative by stepwise deoxygenations,⁸⁰ and $2',5'$ -dideoxy-5-fluorouridine (45) has been made by trans-glycosylation of 5'-deoxythymidine using thymidine phosphorylase.⁸¹ The anhydro-thionucleoside 46 was prepared by intramolecular glycosidation (see Vol. 8, p. 149 for a similar case), and on treatment with Raney nickel gave the $2',5'$ -dideoxynucleoside 47.⁸²

Two routes have been developed, both from D-glucose, to the 2,4-dideoxyhexopyranosyl derivative **48** of thymine, and this ring-expanded thymidine analogue was incorporated into some oligonucleotides.⁸³



5 Halogenonucleosides

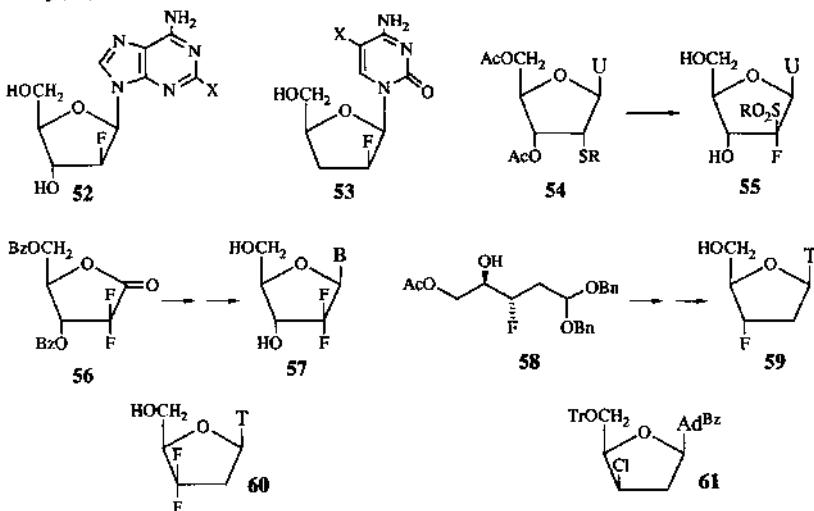
A new route to 2'-deoxy-2'-fluoroguanosine involves a double inversion at C-2 of 3',5'-O-TIPDS-guanosine, the fluorine being introduced by the use of DAST.⁸⁴ Following from the first successful introduction of a 2'- β -fluorosubstituent into a preformed purine nucleoside (Vol. 25, p. 249), the Sloan-Keuttering group have shown that treatment of the adenosine derivative **49** with DAST gives the 2'-deoxy-2'-fluoro-arabinofuranosyl system **50** in good yield. It was essential to have O-3' and -5' blocked as trityl ethers; O-benzyl compounds gave mostly the 2',3'-ene, and this difference was ascribed to the bulk of the trityl group shifting the conformational preference of the sugar ring towards the C-2'-*endo*- arrangement, in which elimination is less favourable for stereoelectronic reasons. Analogous chemistry was also carried out on hypoxanthine,⁸⁵ and extended to the preparation of 9-(2-deoxy-3'-fluoroguanosyl)guanine. DAST was also used for the preparation of 3'-deoxy-3'-fluoroguanosine.⁸⁶ Bromhydrin **40** could be debrominated by hydrogenolysis; use of DAST then led to the dideoxy-fluoroadenosine **51** (see also Vol. 24, p. 231).⁷¹ Adenosine analogues of type **52** (X=F, Cl, Br) have been prepared by base-sugar coupling procedures,⁸⁷ as have the 3'-deoxycytidines **53** (X=H, F), which have anti-HIV activity, and some related 2',3'-dideoxy-2'-fluoro-arabinofuranosyluracils (see also Vol. 24, p. 231).⁸⁸



When the 2'-thionucleoside derivatives **54** (R = Me, *p*-methoxyphenyl), made by opening of the 2,2'-anhydronucleoside with thiolate anion, were treated with xenon difluoride or with DAST in the presence of SbCl₃, the 2'-disubstituted compounds **55** could be obtained after deacetylation.⁸⁹

In work reminiscent of an earlier report (Vol. 22, p. 210), the difluorolactone **56** was obtained by means of a sequence involving a Reformatsky reaction between isopropylidene-D-glyceraldehyde and ethyl bromodifluoroacetate. The D-*threo*-epimer of **56** was removed by

crystallization (on a 2000-gallon scale), and **56** was used to make the *gem*-difluoronucleosides **57** ($B = \text{Cyt}, \text{U}$).⁹⁰



In a synthesis of 3'-deoxy-3'-fluorothymidine (**59**), the fluoride **58** was a key intermediate, being made by regioselective opening of the homochiral epoxide with $\text{Bu}_4\text{N}^+ \text{H}_2\text{F}_3^-$, in a procedure similar to that used for a synthesis of AZT (see Vol. 25, p. 252).⁹¹ A synthesis of **59** labelled with ^{18}F has been reported, the isotope being introduced by displacement of an 'up' mesyloxy group with K^{18}F in the presence of 18-crown-6.⁹² N.m.r. studies of 3'-deoxy-3'-fluoro- and 2',3'-dideoxy-3'-fluoro-nucleosides have indicated that the 3'-fluorosubstituent stabilises the S-conformation of the furanose ring.⁹³

3'-Deoxy-3',3'-difluorothymidine (**60**) has been prepared from the 3'-ketonucleoside by the use of DAST (see Vol. 23, p. 213 for earlier similar work). This difluorocompound was shown also to have a 2'-*endo* (southern) conformation, but it was not active against HIV-1.⁹⁴

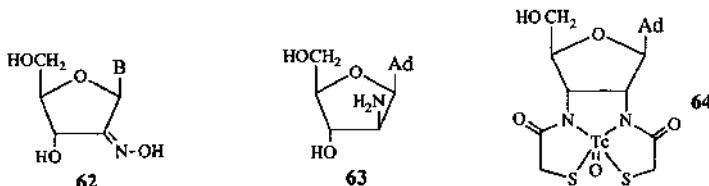
5-Fluorouridine has been converted into 5'-deoxy-5,5'-difluorouridine in a four-step process.⁹⁵

Tris-(2,4,6-tribromophenoxy)dichlorophosphane has been used for the rapid conversion of hydroxy groups of nucleosides into chloro-functions. 3'-Chlorocompound **61** was thus prepared from the 2'-deoxyadenosine derivative, and cases of 5'-chlorination were also reported.⁹⁶ Some 2'-chloro- and -bromo-2'-deoxyderivatives of uridine, *N*-linked to amino-acids at the 5'-position, have been described, with the halide being introduced through 2,2'-anhydronucleosides.⁹⁷

6 Nucleosides with Nitrogen-substituted Sugars

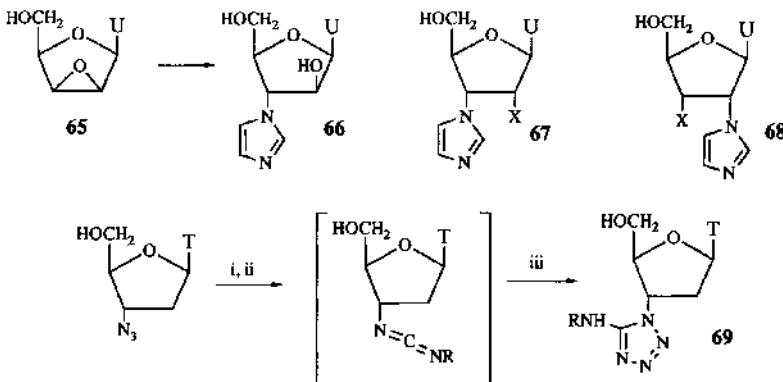
A method described earlier for the synthesis of 2'-azido-2',3'-dideoxyadenosine involving 2'-keto intermediates (see Vol. 21, p. 208 and Vol. 23, p. 215) has been extended to the preparation of a range of other 2'-azido-2',3'-dideoxynucleosides.⁹⁸ 2'-Ketonucleosides have been converted into the

2'-deoxy-2'-oximinocompounds **62** ($B = T, Cyt$), and the analogous *O*-methyloximes were also reported.⁹⁹ M.J. Robins' group have described efficient routes to convert adenosine into 2'-amino-2'-deoxyadenosine and its arabinofuranosylanalogue **63**, both sequences involving displacements of triflates at C-2' with azide ion; a route to 3'-amino-3'-deoxyadenosine was also described.¹⁰⁰



2'-3'-Diamino-2',3'-dideoxyadenosine has been converted into the water-stable technetium complex **64**, as a model for the transition state in ribonuclease-catalysed hydrolysis of inter-nucleotidic links.¹⁰¹

There have been a number of further reports on nucleosides substituted, mostly at C-3', with nitrogen heterocycles. Treatment of the D-*lyxo*-epoxide **65** with imidazole in DMF at 120°C gave predominantly the product **66** of ring-opening at C-3'; however, when the 5'-*O*-trityl ether of **65** was treated with imidazolidine anion, predominant attack at C-2' was observed. Similarly, conditions for regioselective opening of the epoxide with pyrazole and 1,2,4-triazole were determined. In the imidazole series, appropriate inversions gave the compounds **67** and **68** ($X = N_3$ or F).¹⁰² AZT has been converted into tetrazolyl-substituted thymidines of type **69** by the chemistry indicated in



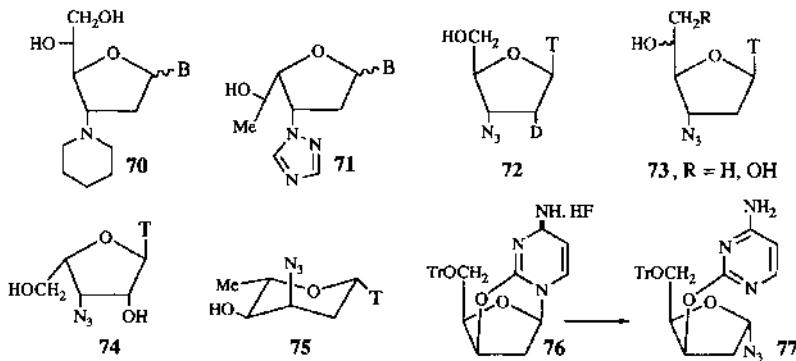
Reagents: i, Ph_3P , THF, Δ ; ii, RNCO ; iii, HN_3 , toluene, Δ

Scheme 8

Scheme 8.¹⁰³ Pedersen's group have made 2',3'-dideoxy-3'-piperidino-D-ribohexofuranosyl nucleosides **70** ($B = U, T$, both anomers), and the pyrrolidino-analogues, using the synthetic approach developed earlier for other nitrogen substituents at C-3' (see Vol. 25, p. 253),¹⁰⁴ and

starting from L-rhamnal, this approach was used to make the triazolyl-substituted systems **71** ($B = U, T$, both anomers).¹⁰⁵

There has been a further report on the synthesis of AZT from D-xylose,¹⁰⁶ and derivatives of β -D-xylofuranosylthymine were used in a synthesis of the stereospecifically-deuteriated AZT **72**, used for n.m.r. studies.¹⁰⁷ A paper on the conformational analysis of AZT is discussed in Chapter 21. Analogues of AZT with 5'-substituted-2-thiouracils,¹⁰⁸ 5-hydroxymethyl- and 5-benzyl-oxymethyl-uracil,¹⁰⁹ and 5-trimethylsilyluracil¹¹⁰ replacing thymine have been described. A full account has been given of the synthesis of a homologue of AZT from di-O-isopropylidene-D-glucose (see Vol. 24, p. 232) and this work was extended to the synthesis of the analogues **73** (both epimers at C-5').¹¹¹ Various 1-(3-deoxy-3-substituted- α -L-lyxofuranosyl)thymines, such as the AZT analogue **74**, have been prepared using nucleophilic substitutions on 3'-O-triflates of L-arabino-configuration, but they did not show significant antiviral activity.¹¹² The β -L-ribopyranosyl analogue **75** of AZT has also been reported.¹¹³

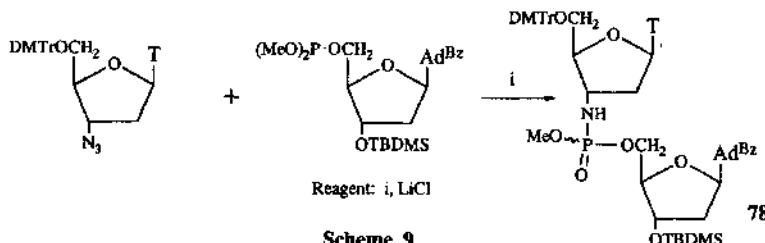


During an investigation into a route to AZC, treatment of the cyclonucleoside **76** with LiN₃ in DMF gave the unexpected product **77** in about 1:1 ratio with the predicted azidonucleoside.¹¹⁴

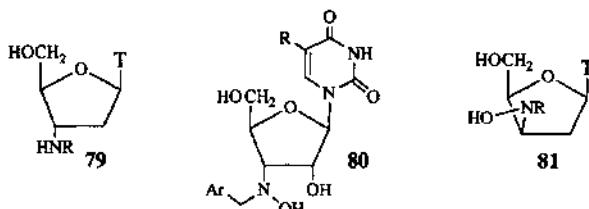
A study has been reported on the electrochemical reduction of 3'- and 5'-azido derivatives of thymidine, uridine and 5'-halogenouridines, and this method was advocated for preparative purposes, and also for monitoring chemotherapeutically-active compounds in physiological fluids.¹¹⁵ A Staudinger-type reaction on an AZT derivative was used to prepare the dinucleotide **78** (Scheme 9) with a 3'-phosphoramidate linkage. The Michaelis-Arbusov step was facilitated by the presence of LiCl, and **78** was used in oligonucleotide synthesis.¹¹⁶ The alkylation of a phosphine imine was used to prepare the *N*-methyl derivative **79** ($R=Me$) of 3'-amino-3'-deoxythymidine, and reductive amination was also used to make the same compound, and the *N,N*-dimethyl analogue.¹¹⁷ Other workers have prepared a series of *N*-substituted derivatives of 3'-amino-3'-deoxythymidine **79**, $R = CN, CH_2CN, CHO, CONH_2, CO_2Me, C(=NH)NH_2$.¹¹⁸

Some 3'-deoxy-3'-hydroxylamino-analogues of nucleosides of type **80** ($R = H, Br, I$), have been made by condensation procedures with a substituted sugar derivative (see Chapter 10).

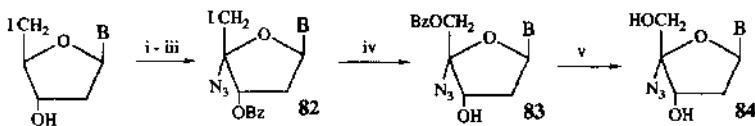
Structures **81** ($R = Me, Bn$) were made from a 3'-ketonucleoside by formation of the nitrone and stereoselective reduction. The esr spectra of some of the free radicals spontaneously formed from the hydroxylamines were also studied.¹¹⁹



Scheme 9



A route has been developed (Scheme 10) for the synthesis of the 4'-azido-2'-deoxynucleosides of type **84** ($B = U, T, Ad, Gua$). In the conversion of **82** into **83**, a 3',5'-oxonium ion is assumed as an intermediate. Similar chemistry was used to make the uridine analogue in the D-*ribo*-series, and the 2'-deoxy compounds **84** proved to have good anti-HIV activity.¹²⁰



Reagents: i, DBN or NaOMe; ii, IN₃, DMF; iii, BzCl; iv, MCPBA, CH₂Cl₂, H₂O; v, NaOMe

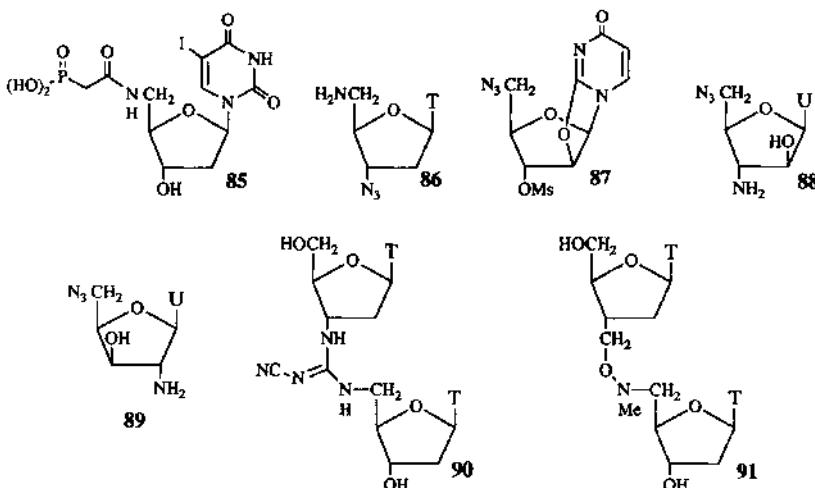
Scheme 10

The *N*-phosphonoacetyl derivative **85** has been prepared as an analogue of 5-iodo-deoxyuridine 5'-diphosphate,¹²¹ and 5'-amino-5'-deoxythymidine has been linked via an amide bond to D- and L-cysteine and D- and L-penicillamine.¹²²

3',5'-Di-*O*-mesylthymidine was used as a precursor of 5'-amino-3'-azido-3',5'-dideoxythymidine (**86**), the synthetic route involving selective displacement of the 5'-*O*-mesyl group by azide ion.¹²³ The 2',3',5'-tri-*O*-mesyl derivative of uridine gave the anhydro-azidoneucleoside **87** when treated with sodium azide, and this could be converted, via the 2',3'-lyxo-epoxide, into a mixture of amino-azido nucleosides **88** and **89**.¹²⁴

Novel nitrogen-containing internucleotidic links have been reported. 3'-Amino-3'-deoxythymidine and 5'-amino-5'-deoxythymidine have been linked as the cyanoguanidine **90**,¹²⁵ and the *N*-methylhydroxylarnino-linked dithymidine **91** was made by joining a 5'-aldehyde

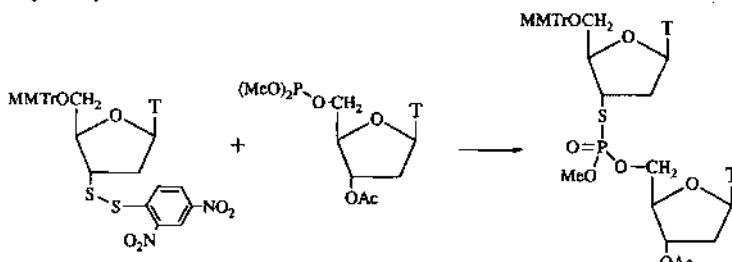
corresponding to the 'bottom' unit with an *O*-alkyl-hydroxylamine derivative (see Section 8) by reductive amination.¹²⁶



Some other nucleosides with amino- and azido-substituents are also discussed more appropriately in later sections.

7 Thio- and Seleno-nucleosides

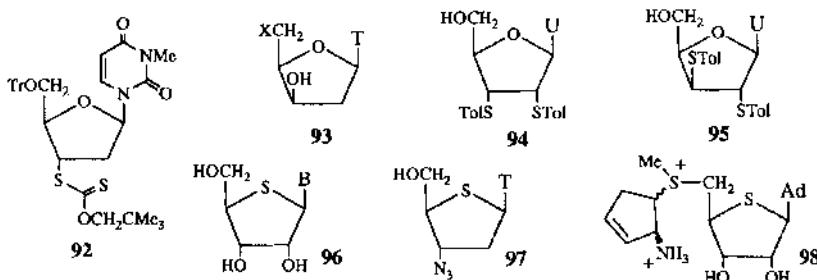
The synthesis of a protected form of 2'-deoxy-3'-thioadenosine has been reported, sulfur being introduced by displacement of a 3'-*'up'*-mesylate. The product was incorporated into a dinucleoside 3'-5'-phosphorothiolate using a phosphoramidite approach,¹²⁷ and the same group have also made the same linkage, in the case of a bis(thymidinyl) system, using either a Michaelis-Arbusov reaction as indicated in Scheme 11, or by a phosphotriester approach.¹²⁸ The 2'-deoxy-3'-thionucleoside derivative 92 has been prepared by the interaction of a xanthate-derived radical at C-3' with the *S*-triphenylstannylxanthate.¹²⁹



Scheme 11

When 2,3'-anhydrothymidine was treated with isopropylthiolate anion or with phenyl-selenide anion, in addition to the expected products of ring-opening by nucleophilic attack at C-3', the 5'-thio- and seleno-species **93** ($X = \text{SPri}^+$ or SePh) were also produced, and it was surmised that the 2,5'-anhydronucleoside was involved as an intermediate.¹³⁰ The 2',3'-dithiouridine derivative **94** can be obtained by treatment of 2',3'-di-O-mesyl-5'-O-trityl- β -D-lyxofuranosyluracil with *p*-tolylthiolate anion, followed by detritylation. The same product was also obtained in good yields from starting materials of D-*arabino*- and D-*xylo*-configurations, presumably involving anhydronucleoside intermediates, but the relative accessibility of the D-*lyxo*-configured compound made it the preferred precursor. The same reaction sequence, when applied to 2',3'-di-O-mesyl-5'-O-trityl uridine (i.e. precursor of D-*ribo*-configuration) gave the D-*xylo*-product **95**.¹³¹

The regrowth of interest in 4'-thionucleosides has led to the development of an efficient route to 4-thio-D-ribufuranose derivatives (see Chapter 11), and their use in making 4'-thionucleosides in the pyrimidine series, **96** ($B = \text{U}, \text{T}$).¹³² The group at Southern Research Institute have made a series of 4'-thio-2',3'-dideoxynucleosides, using L-glutamic acid as precursor for the furanose building block, and extended their synthesis of 4'-thiothymidine (Vol. 25, p. 254) to the preparation of the AZT analogue **97**, by means of a 2,3'-cyclonucleoside.¹³³

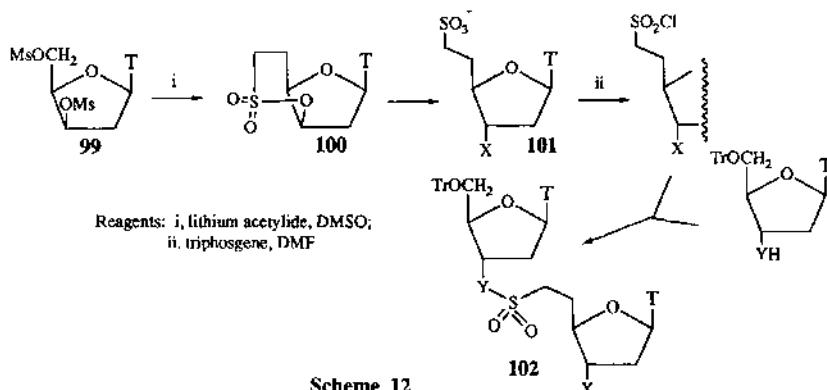


5'-Methylthioguanosine has been identified in human urine by g.c. - m.s.¹³⁴ Various new analogues of S-adenosylhomocysteine have been described, including one with 7-deazaadenine as base, and the 3'-deoxy-3-deazaadenosine and 3'-deoxyformycin analogues,¹³⁵ whilst the S-adenosylmethionine (SAM) analogue **98** has been made as an enzyme-activated irreversible inhibitor of SAM decarboxylase (see also Vol. 25, p. 255).¹³⁶ Some 9-[5'-deoxy-5'-(alkylthio)- β -D-xylofuranosyl]adenines have been made as potential antiviral agents, but proved inactive,¹³⁷ and an AZT analogue has been reported in which an *n*-octadecylthio-group replaces the 5'-hydroxy function.¹³⁸

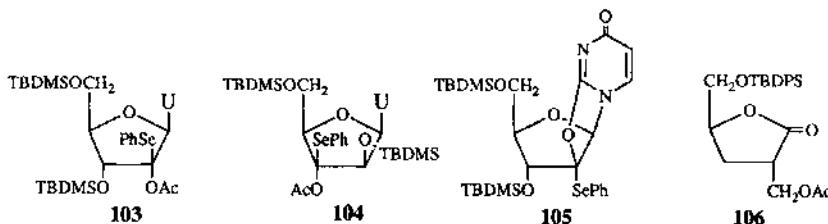
Interesting work has been reported on the formation and reactions of nucleoside sulfones. Dimesylate **99** could be converted as indicated in Scheme 12 into sultone **100**, which underwent nucleophilic attack to give sulfonates of type **101** [$X = \text{N}_3, \text{OH}, \text{OAc}, \text{H}$ (from NaBH_4)]. The epimeric sultone in the D-*erythro*-series was formed similarly, but reacted less cleanly with nucleophiles.¹³⁹ Compounds **101** ($X = \text{N}_3, \text{OAc}$) could then be used to make dinucleotide

analogues of type **102** ($Y = O, NH$) with a sulfonate or sulfonamide link replacing the phosphodiester.¹⁴⁰

A full account has been given of the work from Barton's laboratory on the preparation of chain-extended nucleoside sulfones from uronic acid nucleosides (see Vol. 22, p. 141).¹⁴¹

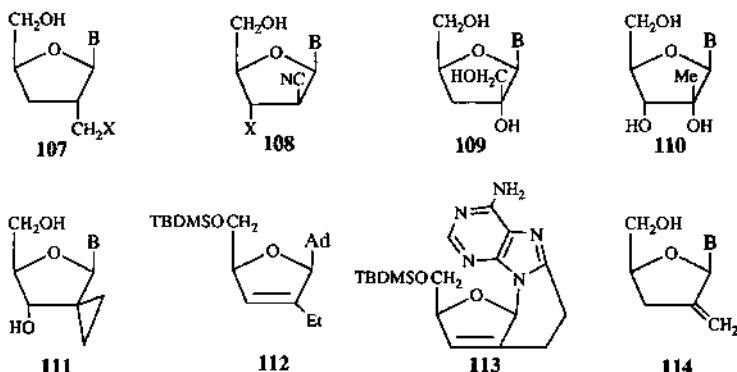


Pummerer rearrangements of selenium-containing uracil nucleosides have been investigated. The α -acetoxyselenides **103** and **104** could be obtained from phenylselenides of D-ribo- and D-arabino-configuration, respectively, and a similar reaction was carried out on a 5'-deoxy-5'-phenylselenyl compound. Treatment of the 2'-deoxy-2'-phenylselenyl nucleoside with NBS gave the cyclonucleoside **105**, as well as the product of bromination at C-5.¹⁴²



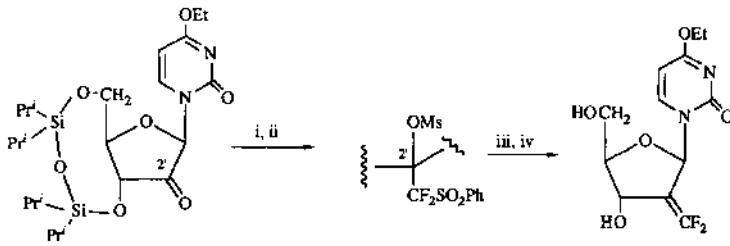
8 Nucleosides with Branched-chain Sugars

Synthon **106** can be made stereoselectively by formylation of the γ -lactone, borohydride reduction, and acetylation, and can then be used to synthesise C-2-branched dideoxynucleosides of type **107** ($X = H, OH, N_3$).¹⁴³ There has been a further paper describing the synthesis of 2'-C-cyano-2'-deoxynucleosides **108** ($X = H, OH; B = U, Ade, Cyt$) by deoxygenation of cyanohydrins (see Vol. 25, p. 256).¹⁴⁴ Use of α -D-isosaccharinolactone and α -D-glucosaccharinolactone, respectively, as starting materials led to the synthesis of 2'-C-substituted nucleosides of type **109** and **110** ($B = Ad, T$).¹⁴⁵



The novel *spiro*-cyclopropyl nucleosides **111** ($B = Ad, U$) were made by cyclo-addition of diazomethane to a 2'-deoxy-2'-methylene nucleoside. These compounds were made to probe the mechanism of ribonucleotide diphosphate reductase, and in initial biomimetic work it was found that when the 3'-*O*-phenylthionocarbonyl-5'-*O*-TBDMS-derivative of **111** ($B = Ad$) was treated with Bu_3SnH , the initial cyclopropylcarbinyl radical fragmented to give the two products **112** and **113**; analogous results were obtained from the uridine analogue.¹⁴⁶ The same group have extended their earlier work on the synthesis of 2'-deoxy-2'-methylene- and 3'-deoxy-3'-methylene-nucleosides by Wittig reactions to the synthesis of the guanosine analogues and of 2'-deoxy-2'-methylene-7-deazaadenosine.¹⁴⁷ The 2',3'-dideoxy-2'-methylene nucleosides **114** ($B = U, T$) were also made using Wittig methylenations, with $O-3'$ being removed at an earlier stage in a 2,2'-cyclonucleoside.¹⁴⁸ Matsuda has given a full account of the work of the Hokkaido group on the synthesis of **114** ($B = U, T, Cyt$), the 2',3'-dideoxy-3'-methylene systems, and the isomeric 2',3'-dihydro-2',3'-dideoxy-2'- and -3'-methyl-compounds (see Vol. 23, p. 217, and earlier).¹⁴⁹

2'-Deoxy-2'-difluoromethylene nucleosides, also of interest in connection with the inhibition of ribonucleotide diphosphate reductase, have been made by a modified Julia synthesis as outlined in Scheme 13; the cytosine analogue was also reported.¹⁵⁰



Reagents: i, $PhSO_2CF_2H$, $LiN(TMS)_2$; ii, $LiN(TMS)_2$, $MsCl$; iii, SmI_2 ; iv, Bu_4NF

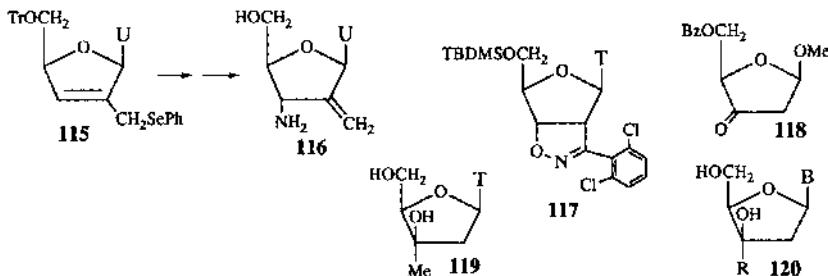
Scheme 13

The selenide **115** has been prepared by displacement, with allylic rearrangement, of a 2'-methylene-3'-*O*-mesyl system; when **115** was treated with NCS and *t*-butyl carbamate in the

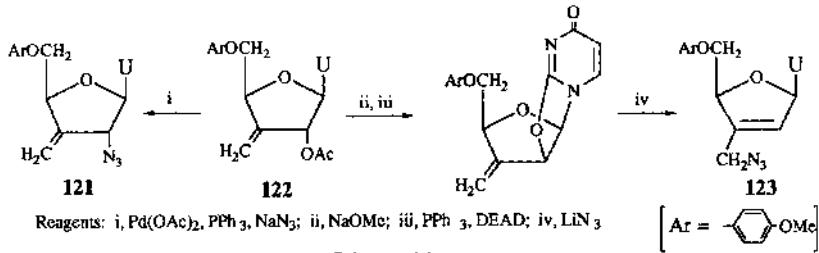
presence of triethylamine, it underwent [2,3]-sigmatropic rearrangement, via the *N*-Boc-selenimine, to give after deprotection the 3-amino-2',3'-dideoxy-2'-methylene compound **116**.¹⁵¹

Cycloaddition of 2,6-dichlorobenzonitrile oxide to the 5'-O-TBDMS-derivative of d4T gave predominantly (3:1) the regioisomer **117**; exclusively *anti*-adducts were obtained, the reaction was less regioselective with d4T itself, and failed with carboethoxyformonitrile oxide.¹⁵²

There have been a number of reports on different approaches to systems branched at C-3'. Grignard addition to **118** proceeded selectively from the α -face, thus giving a route to 3'-C-methyl-thymidine **119** (see also Vol. 22, p. 213). Use of the α -anomer of **118** gave access to the 3'-epimer of **119**. The 3',5'-anhydroderivative (oxetan) was prepared from **119**, and elimination of water gave a mixture of 3'-deoxy-3'-methylthymidine and 3'-methyl-d4T.¹⁵³ Nucleophilic attack of organocerium reagents on 2'-deoxy-3'-ketonucleosides provides a good route to a range of compounds of type **120** ($R = Me, -CH=CH_2, -C\equiv CH, B=Ad, T, Cyt$).¹⁵⁴



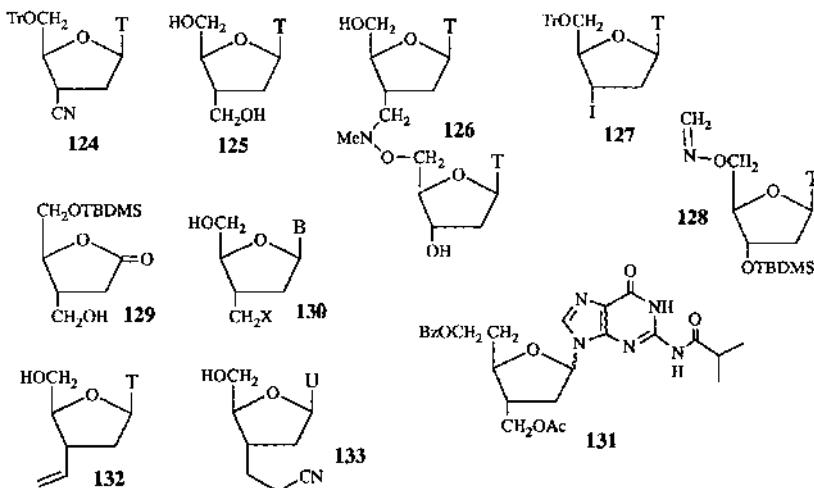
The 3'-methylene compound **122** has been made by direct sugar-base condensation, and could be converted into the two isomeric alkenyl azides **121** and **123** as outlined in Scheme 14. The 3'-methyl analogue of d4U was also prepared, as reported earlier in the thymidine series by the same group (Vol. 24, p. 234).¹⁵⁵



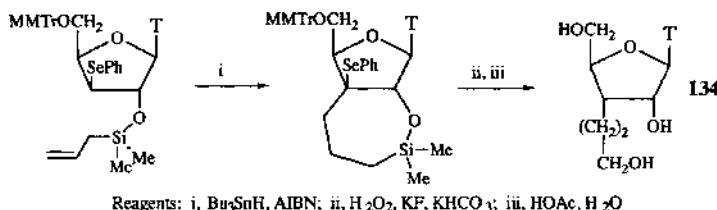
Scheme 14

It has been shown that during the synthesis of the nitrile **124** by free radical chemistry (Vol. 22, p. 214), some of the C-3' epimer is also formed.¹⁵⁶ Nitrile **124** was used in an alternative route to 3'-deoxy-3'-C-hydroxymethylthymidine **125** (see Vol. 25, p. 257); Mitsunobu reaction with *N*-hydroxyphthalimide at the branched hydroxymethyl group gave an *O*-alkyl hydroxylamine used to make the dinucleotide analogue **91** (see Section 6).¹²⁶ The 3'-aldehyde formed as an intermediate in

the conversion of **124** to **125** was linked with an *O*-(5'-nucleosidyl)hydroxylamine to give the alternative dinucleotide analogue **126**,¹⁵⁷ and the same team have developed another ingenious approach to **126**, the key step involving addition of a C-3' radical derived from **127** to the oxime ether **128**.¹⁵⁸ The synthon **129** has been prepared by stereoselective photochemical addition of methanol to the α,β -unsaturated lactone, and used to make 2',3'-dideoxy-3'-hydroxymethylcytosine, which displays anti-HIV activity.¹⁵⁹ Other workers have also described routes to carbohydrate precursors of **125** and related compounds, and earlier work in this area (Vol. 25, p. 257) has been extended to fluoromethyl- and azidomethyl systems **130** (X = F, N₃; B = T, Cyt, Ad).¹⁶¹ This approach, involving asymmetric epoxidation, has also been used to make the enantiomer of **125** and the equivalent cytidine and adenosine analogues.¹⁶² Regioselective glycosylation at *N*⁹ of *N*²-isobutyryl-*O*⁶-[2(*p*-nitrophenyl)ethyl]guanine was used to make the branched and homologated compound **131**,¹⁶³ whilst conjugate Cu^I-catalysed addition of vinyl Grignard reagent to an α,β -unsaturated -1,4-lactone, followed by DIBAL reduction and nucleoside formation, led to **132**, the related ethynyl and α -bromovinyl compounds being made also by modification of the route (compare Vol. 22, p. 214).¹⁶⁴ Free-radical coupling to acrylonitrile was used to make a branched deoxyglycoside, convertible into **133**, and other related cases were reported.¹⁶⁵



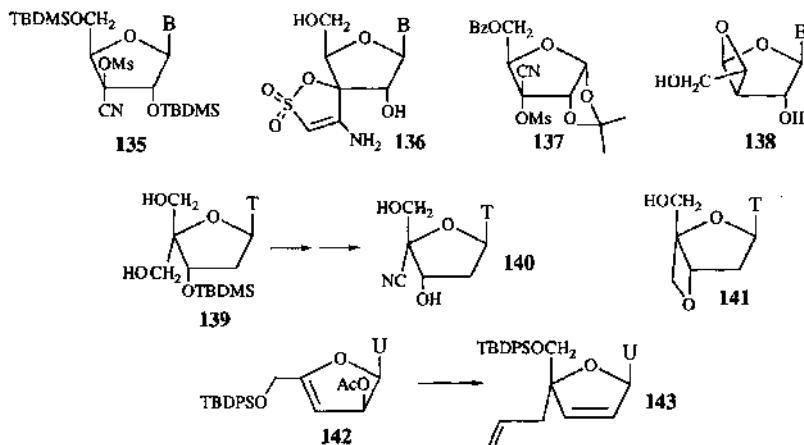
Detailed n.m.r. studies have been reported on some bicyclic uridine analogues reported last year by Chattopadhyaya's group, formed by intramolecular addition of free radicals to allyl ethers (see Vol. 25, p. 258).¹⁶⁶ The same group have described the preparation of the thymine nucleoside **134** by means of intramolecular free radical trapping by an allyl group tethered by a temporary silicon connection (Scheme 15). Similar sequences were used to make analogous compounds with the three-carbon branch at C-2' in a 'down' position (*D-ribo-*), and at C-3' in the 'up' orientation, but an attempt to make the compound with the C-2' 'up' stereochemistry led to a tricyclic product after oxidation in which the intermediate bicyclic radical had attacked C-6 of the thymine ring.¹⁶⁷



Scheme 15

The mesylated cyanohydrins **135** ($B = \text{pyrimidine}$) were the major epimers obtained from cyanide attack on the 3'-ketonucleosides; these compounds could be cyclized in base and deprotected to give the spiro-systems **136**. The 3'-epimers could also be obtained as minor products from this chemistry,^{168,169} but were better obtained by making nitrile-mesylate **137** stereospecifically, followed by base-sugar condensation and cyclization.¹⁷⁰

Racemic oxetan-fused nucleoside analogues of type **138** have been made by the Paterno-Büchi reaction of furan and benzyloxyacetaldehyde, epoxidation, and reaction with silylated base.¹⁷¹



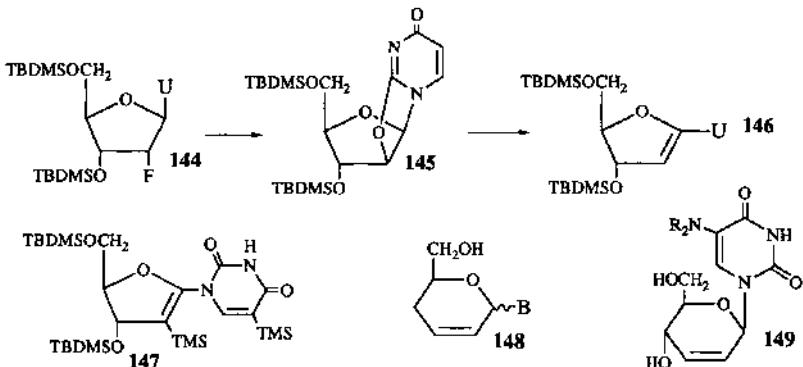
There have been reports on compounds branched at C-4', some with interesting bioactivity. Hydroxymethyl nucleoside **139**, made using a Cannizzaro reaction, could be selectively oxidized under Swern conditions, to give, via the oxime, 4'-cyanothymidine **140**, which showed good anti-HIV activity. 3'-Deoxyanalogue and compounds with other pyrimidine bases were also made.¹⁷² 4'-Azidomethylthymidine and the oxetane **141** were also prepared, and displayed anti-HIV activity, in the case of **141** with low bone marrow toxicity. It was found that, surprisingly, reaction of **139** with 1 equivalent of DMTrCl formed selectively the mono-DMTr ether on the 4'-hydroxymethyl group.¹⁷³ Alkene **142** could be made by selenoxide elimination, and on treatment with allyltrimethylsilane and SnCl_4 it gave stereoselectively the 4'-C-allyl derivative **143**; similar reactions also took place with silyl enol ethers and TMSCN .¹⁷⁴

9 Nucleosides of Unsaturated Sugars, Ketosugars and Uronic Acids

Papers dealing with 2',3'-didehydro-2',3'-dideoxy-derivatives are discussed along with their saturated analogues in Section 4.

Treatment of either **144** or **145** with LDA gave, after quenching the reaction, the 1',2'-ene **146**. If MeOD was used to quench the reaction, deuterium was incorporated at C-6 of the uracil ring. When anhydronucleoside **145** was treated with lithium 2,2,6,6-tetramethylpiperidine, followed by quenching with TMSCl, the bis-TMS compound **147** was formed; the mechanism of this process is unclear, but the structure of **147** was established by X-ray crystallography of a derivative.¹⁷⁵

Pyranoid analogues **148** ($B = U, T$) of d4 systems have been prepared by standard procedures, as have the related 3'-enes.¹⁷⁶ The same group have also reported 5-aminouracil nucleosides of type **149**, the base-sugar link being made by Ferrier-type condensation with triacetyl-D-glucal.¹⁷⁷ Some α -nucleosides similar to **149**, with various bases, have been made by Pd0-catalysed condensation of the base with phenyl 3,5-di-O-benzyl- α -D-erythro-hex-2-enopyranoside.¹⁷⁸



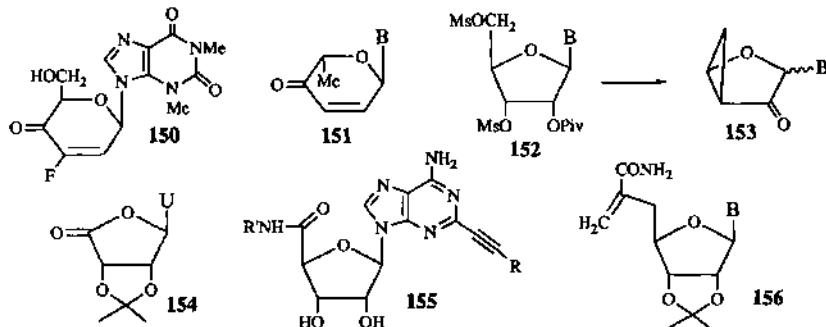
The theophylline ketonucleoside **150** has been reported,¹⁷⁹ as have pyrimidine nucleosides of type **151**, as well as the regiosomeric 3'-ene-2'-ones.¹⁸⁰

When dimesylates **152** ($B = U, \text{Cyt, Gua}$) were treated with KOH in MeOH-TMF, the unusual cyclopropane-containing ketonucleosides **153** were produced by a mechanism involving a 2',3'-hydride shift. The products were predominantly of α -configuration.¹⁸¹

Sharpless' oxidation method ($\text{RuCl}_3, \text{NaIO}_4$ in $\text{CH}_3\text{CN}\text{-CCl}_4\text{-water}$) has been shown to oxidise 2',3'-*O*-isopropylidene derivatives of ribonucleosides to the uronic acid nucleosides in very high yield under mild, neutral conditions,¹⁸² and potassium persulfate is also effective for recycling the ruthenium reagent in such oxidations; the latter procedure was used to make, *inter alia*, the uronic acid analogue of AZT.¹⁸³ Oxidation of isopropylidene uridine with CrO_3 , PCC or PDC in the presence of acetic anhydride leads to the formation of lactone nucleoside **154** in 50% yield, and several similar cases were reported.¹⁸⁴

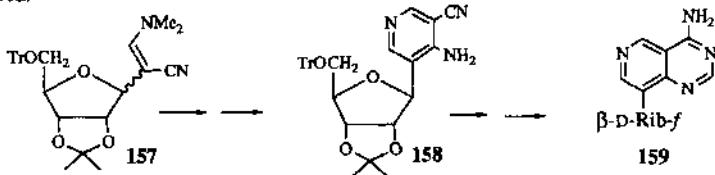
Two groups have described the synthesis of uronamides of type 155 as A₂-selective adenosine receptor agonists.^{185,186}

Trapping of a free radical at C-4', generated by fragmentation of the *N*-acyloxy pyridine-2-thione (see Vol. 22, p. 141), by α -(phenylthiomethyl)acrylamide led to the unsaturated uronamide 156 (B = U, Ad^{N-Bz}).¹⁴¹



10 C-Nucleosides

The well-known intermediate 157 has been elaborated into the pyridine derivative 158, separable from the α -anomer, using a Thorpe-Ziegler cyclization followed by dehydrogenation; hence the pyrido[4,3-*d*]pyrimidine *C*-nucleoside 159 and the corresponding inosine analogue were prepared.¹⁸⁷

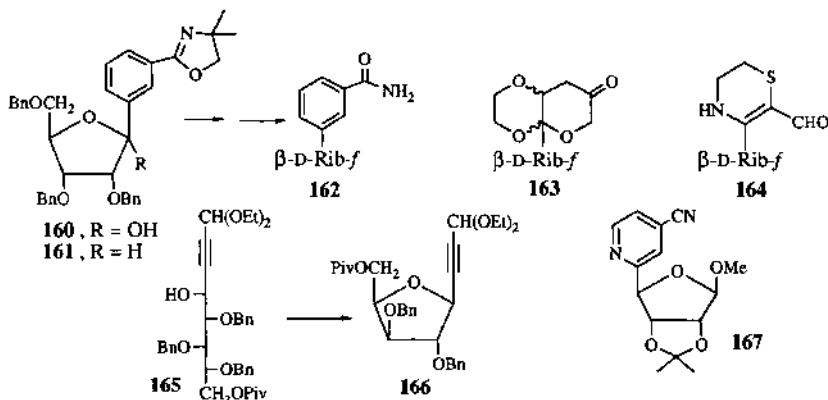


Addition of an aryl Grignard reagent to the γ -lactone led to 160. Subsequent treatment with triethylsilane and SnCl₄ led stereoselectively to the β -C-glycoside 161, convertible to the analogue 162 of nicotinamide riboside.¹⁸⁸ Macba's group have extended their previous work (see Vol. 25, p. 260, and earlier) to the synthesis of the bicyclic structures 163 (both *cis*-fused isomers),¹⁸⁹ the 1,4-thiazine 164, and related compounds.¹⁹⁰

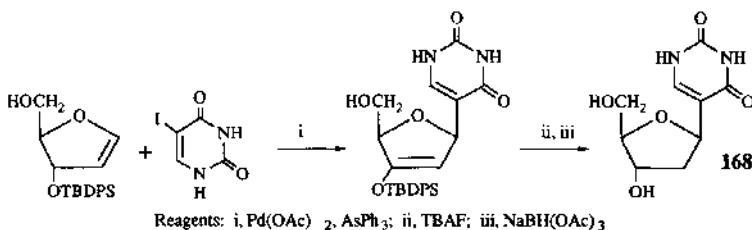
In an improved route to 3-(β -D-xylofuranosyl)pyrazole, the key steps involved stereoselective addition of an acetylenic Grignard to tri-*O*-benzyl-D-xylopyranose to give, after pivaloylation, 165, which cyclized to 166 on treatment with TsCl in warm pyridine.¹⁹¹

Photochemical decarboxylation in the presence of diacetoxymidobenzene and the appropriate heterocycle has been used to make some compounds related to C-nucleosides, such as 167.¹⁹²

The preparation of a chloromethyl ketone related to 2,5-anhydro-D-allonic acid, and of potential use in C-nucleoside synthesis, is discussed in Chapter 3.



A review has appeared discussing the chemistry, in particular the synthesis, of 2'-deoxyribo-C-nucleosides.¹⁹³ A route to 2'-deoxy-pseudouridine **168** is outlined in Scheme 16, and use of a 3-iodo-pyrazolo[4,3-d]pyrimidine in a similar sequence led to 2'-deoxyformycin B.¹⁹⁴ The carboxylic acid **36** (Scheme 5), also made using organopalladium chemistry was used to prepare 2',3'-dideoxyformycin B and 2',3'-dideoxyshowdomycin.⁶⁷ Photolysis of an *N*-acyloxy pyridine-2-thione, and reaction of the resultant anomeric free radical with a heterocycle, has been applied to the synthesis of 2'-deoxy-C-nucleosides, with α -selectivity (see Vol. 25, p. 260 for similar chemistry in the ribo-C-nucleoside series).¹⁹⁵ Modifications of Vogel's 'naked sugar' methods for nucleoside synthesis (Vol. 24, p. 238-239) have led to the fluoro-C-nucleoside **169**,¹⁹⁶ and the azidocompound **170**.¹⁹⁷



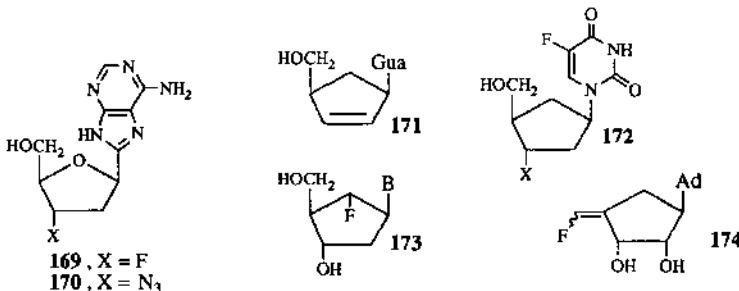
Scheme 16

11 Carbocyclic Nucleoside Analogues

Two members of the Glaxo team have produced a comprehensive review on the synthesis of chiral carbocyclic nucleosides.¹⁹⁸

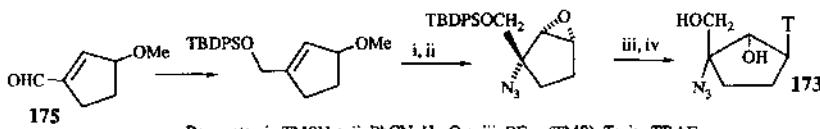
There have been further papers on the synthesis of carbovir. Roberts and coworkers have described in full their routes both to the bioactive (-)-isomer **171** and to its enantiomer using enzymic resolutions (see Vol. 24, p. 239-40 and Vol. 25, p. 261).¹⁹⁹ One of their routes relied upon π -allyl palladium intermediates, and other workers have described a similar approach for making

racemic carbovir,²⁰⁰ whilst Trost's group have also used organopalladium chemistry to prepare (-)-carbovir (171), where an ingenious desymmetrization of a *meso*-intermediate was used.²⁰¹ The 7-deaza-analogue of carbovir has been synthesised in racemic form, the pyrrolopyrimidine ring being built up on the amino group of an allylic amine.²⁰²



The carbocyclic nucleosides 172 (X = Cl, Br, N₃) of 5-fluorouracil have been made as racemates, the group X being introduced by displacement of a 3'-*up*' mesylate,²⁰³ and the 6'-fluorospecies 173 (B = T, Ad) have been prepared by modification of earlier work in which a chiral bicyclic ketone was manipulated via strained tricyclic intermediates (see Vol. 23, p. 222 and Vol. 25, p. 262).²⁰⁴ The fluoroalkenes 174 (both isomers) have been made as potential inhibitors of adenosylhomocysteine hydrolase, by the same method as was reported last year in the ribonucleoside case (see Vol. 25, p. 250-251).²⁰⁵

The 4'-azido-carbocyclic nucleoside 176, related to the furanoside 84 (Section 6), has been prepared as a racemate by the chemistry outlined in Scheme 17; the cyclopentene 175 was prepared from 3-methoxycyclohexene by oxidative cleavage and subsequent aldol condensation.²⁰⁶



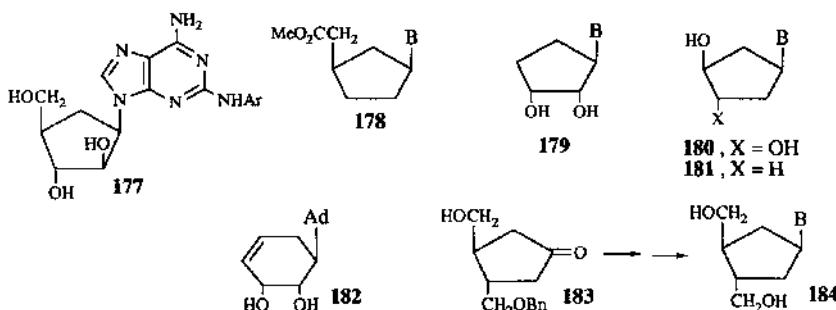
Reagents: i, TMSN₃; ii, PhCN, H₂O₂; iii, BF₃, (TMS)₂T; iv, TBAF

Scheme 17

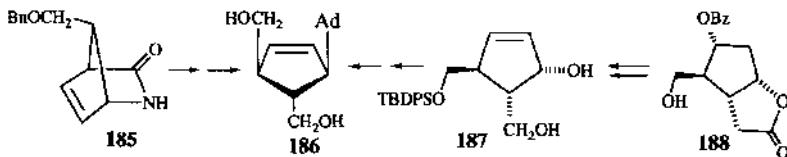
Various 5'-*O*-sulphamoylated purine carbocyclic nucleosides, including those derived from aristeromycin and 8-aza-aristeromycin, have been prepared as analogues of nucleocidin.²⁰⁷ A number of 2'-arylamino-purine *ara*-carbocyclic nucleosides of type 177 have been reported as potential anti-cytomegalovirus agents,²⁰⁸ and 5'-extended analogues of type 178 have been prepared using Mitsunobu reactions to link the bases and the cyclopentane unit,²⁰⁹ as have truncated systems 179 (B = U, Ad, Gua) using π -allyl palladium chemistry.²¹⁰ Racemic *nor*-nucleosides 180 (B = Ad, Gua) have been reported on in full (see Vol. 24, p. 241),²¹¹ and 181 (B = Gua) and its stereoisomer (both racemates) have been made by conjugate addition of 2-amino-6-chloropurine to cyclopentenone. This paper also describes a cyclohexane analogue of 181,²¹² and other workers have

also described a range of racemic cyclohexenyl nucleobases such as **182** and its dihydro-derivative.²¹³

Two groups have reported on the synthesis of the hydroxymethyl-branched carbocyclic systems **184** ($B = Ad, Gua$), which can be regarded as ring-enlarged oxetanocin analogues or as carbocyclic analogues of important anti-HIV agents. In one approach, the racemic unit **183** was produced by photochemical addition of methanol to the enone,²¹⁴ whilst other workers reported routes to both **184** and its enantiomer.²¹⁵



Bicyclic adduct **185**, derived by the cycloaddition of tosyl cyanide to 5-benzyloxymethyl-cyclopentadiene, was converted into the *racemic* branched carbocyclic nucleoside **186** ('BCA'), which was found to protect MT-4 cells from the cytopathic effects of HIV-1.²¹⁶ Resolution of the racemate showed that the bioactivity was due to the (-)-enantiomer.²¹⁷ It was shown that formula



186 represents (-)-BCA by means of an enantiospecific synthesis from the (-)-Corey lactone derivative **188**, via the key intermediate **187**, a Mitsunobu reaction being used to introduce 6-chloropurine with regioselectivity for the N^9 -linked product. It is interesting that (-)-BCA has the 'unnatural' absolute configuration for the 'sugar' unit.²¹⁸

Some references to phosphonates of carbocyclic nucleosides are discussed in the next Section.

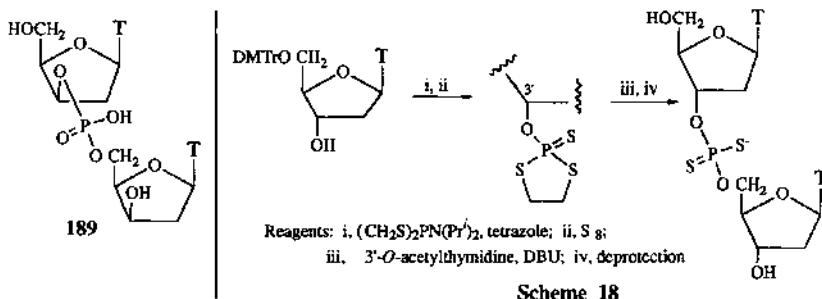
12 Nucleoside Phosphates and Phosphonates

The synthesis, reactions and properties of nucleoside mono-, di-, tri-, and tetraphosphates and nucleotides with changes in the phosphoryl residue are the subject of a major review.²¹⁹

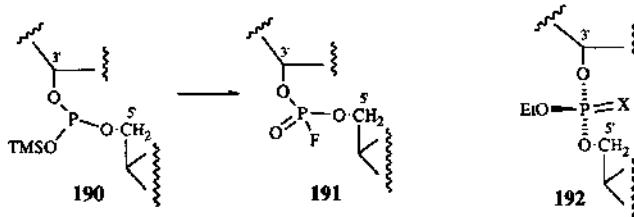
2'-Deoxy- 3'-phosphoramidites, for use in oligonucleotide synthesis, have been reported for 5-hydroxymethyluridine²²⁰ and 5-methyl 1-β-D-ribofuranosyl-4-pyrimidinone,²²¹ whilst 3'-deoxy-2'-phosphoramidites of adenosine and 5-methyluridine have been made as intermediates in 2'→5'-linked oligodeoxyribonucleotide synthesis.²²² Improved routes have been described for making 2'-O-(2-chlorobenzoyl)-3'-H-phosphonate building blocks for oligoribonucleotide synthesis.²²³

Di(deoxynucleoside) phosphates have been prepared with 4-thiouracil and 6-thiohypoxanthine as bases,²²⁴ whilst a series of base-modified uridine dinucleoside phosphates have been made as models for the investigation of conformation and structure of 'wobble position' 5'-modified uridine units.²²⁵ The doubly-isomerised TpT dimer **189** has been prepared by the H-phosphonate method, and its conformation studies.²²⁶

There has been a further report (see Vol. 25, p. 265) on the use of nucleoside -3'-O-bis(1,1,1,3,3,3-hexafluoro-2-propyl)phosphites as precursors for other analogues, including H-phosphonothioates and dinucleoside phosphorothioates,²²⁷ and the method outlined in Scheme 18 has been used to make di- and oligo-deoxynucleotide phosphordithioates, with best results in the pyrimidine series.²²⁸ The (*Rp*, *Rp*) and (*S_p*, *S_p*)-diastereomers of the bis-(phosphorothioate) of UpUpU have been prepared in a stereocontrolled manner.²²⁹

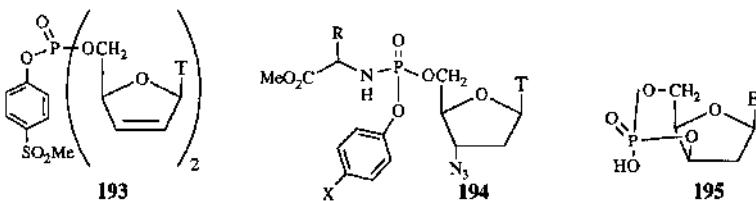


As regards the modification of internucleosidic links, bis(deoxynucleosidyl)-trimethylsilyl phosphites **190** can be converted to phosphorofluorides **191** by the use of SO_2ClF ,²³⁰ and dibenzoyltetrasulfide has been advocated as a rapid sulfur transfer agent in the synthesis of nucleoside phosphorothioates, being used to prepare a phosphorothioate after each cycle of a phosphoramidite synthesis.²³¹ Oxidation of internucleosidic H-phosphonothioates (2'-deoxy series) with iodine in aqueous acetonitrile in the presence of trimethylamine gives



phosphorothioates with inversion of configuration; carrying out this oxidation on either H-phosphonates or H-phosphonothioates in the presence of ethanol gives the stereochemically-pure triesters **192** ($X = O, S$) or their diastereomers.²³² Oxidation of diastereomerically-pure H-phosphonothioates (ribonucleoside series) with 3-H-2,1-benzoxathiol-3-one-1-oxide gives the phosphorothioates with retention of configuration.²³³ Oxidation of internucleosidic H-phosphonates with elemental sulfur also gives diribonucleoside phosphorothioates with retention of configuration,²³⁴ whilst use of the new selenium-transferring reagent 3-H-1,2-benzothiaselenol-3-one on either di(deoxyribonucleoside) H-phosphonates or H-phosphonothioates gives the phosphoroselenoates or phosphorothioselenoates respectively, and on mechanistic grounds these stereospecific processes are also assumed to occur with retention of configuration.²³⁵ When 5-aryl dinucleoside phosphorothioates (2'-deoxy series, racemic at phosphorus) were treated with tributyltin alkoxides, the alkyl dinucleosidyl phosphotriesters were formed,²³⁶ and the same triester products could also be obtained by treating a dinucleosidyl phosphate with tributyltin methoxide, and alkylation of the tributylstannyl ester thus formed with an alkyl halide.²³⁷

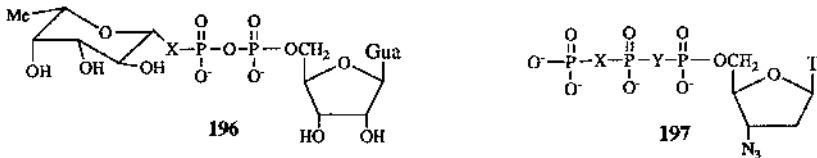
Various 5'-phosphates and phosphonates of d4A and d4C, as well as dinucleoside phosphates with thymidine, have been prepared as potential prodrugs; some of the phosphates displayed anti-HIV activity.²³⁸ 5'-Triphosphates of various 3-alkyl derivatives of AZT have been described,²³⁹ as have *O*-aryl-5,5'-dinucleoside phosphates of dideoxy- and didehydrodideoxy-systems, such as **193**, which showed some anti-HIV activity.²⁴⁰ Similar triesters, incorporating an AZT unit, a cordycepin (3'-deoxyadenosine) unit and a long-chain aliphatic residue, have also been made as potential prodrugs.²⁴¹ 5'-Bis(haloalkyl) phosphotriesters of ara-A and ara-C have proved in some cases to display better bioactivity than the parent systems.²⁴² A range of phosphoramidates of type **194**, derived from AZT and a range of amino acids have been synthesised,²⁴³ and AMP has been linked as a phosphoramidate to the ε-amino group of the dipeptide Thr-Lys to give a model for the RNA ligase active centre.²⁴⁴



In the area of 3',5'-cyclic nucleotides, it has been found that attempted 5'-phosphorylation of the 3'-epimers of thymidine and deoxyadenosine with phosphoryl chloride gave the cyclic phosphates **195** ($B = Ad, T$); the 5'-phosphates could be obtained by phosphorylation of the 3'-*O*-benzoyl derivatives.²⁴⁵ Two groups have reported the synthesis of base-modified derivatives of cAMP (e.g. benzimidazoles, benzotriazoles, indazoles), for evaluation as activators of cAMP-dependent protein kinase I.^{246,247} There have been syntheses described of ribonucleoside 3',5'-cyclic methyl- and phenyl-phosphonates^{248,249} and -phosphonothioates, one of the procedures giving both the cyclic phosphonates and phosphonothioates as the Sp-epimer only.²⁴⁹ A paper

discussing conformational aspects of cTMP methyl ester and the phenyl phosphonite is mentioned in Chapter 21, and some papers on the reactions of cyclic phosphates are discussed in Section 15.

Whitesides' group have continued their work on large-scale enzymic routes to nucleoside diphosphosugars, reporting gram-scale routes to UDPGlcNAc,²⁵⁰ UDP-Gal, and UDP-GalNAc.²⁵¹ Others have reported enzymic routes for the conversion of TDP-glucose to TDP-*6*-deoxy-D-*xylo*-4-hexulose and TDP-L-rhamnose.²⁵² An efficient chemical synthesis of GDP- β -L-fucose has been developed, dependent on two new routes for making L-fucose-1-phosphate with high anomeric excess of the β -L-isomer.²⁵³ The analogue of GDP- β -L-fucose containing a carbocyclic hexose unit has been prepared as a potential inhibitor of fucosyl transferases (for the route to carba-L-fucose, see Chapter 18),²⁵⁴ and routes have been developed for the synthesis of C-fucopyranosyl analogues of GDP-fucose, including the 'stretched' phosphates **196** ($X = -CH_2O-$ and $-CH_2CH_2O-$), and the isosteric phosphonate **196** ($X = -CH_2-$) (for the synthesis of the relevant C-glycosides, see Chapter 3).²⁵⁵ Both anomers of GMP-L-fucose have been produced by interaction of the 1-*O*-trichloroacetamidate of 2,3,4-tri-*O*-acetyl- α -L-fucopyranose with 2',3'-di-*O*-acetyl-GMP, and the analogous adenosine- and uridine-monophosphate-L-fucoses were also synthesised.²⁵⁶ The analogue of UDP- α -D-glucuronic acid in which the phosphate unit adjacent to the glucuronate is present as a phosphorothioate has been prepared by a synthesis involving enzymic oxidation of the UDP-glucose analogue as the last step.²⁵⁷ Compounds in which sialic acid is linked to nucleoside 5'-monophosphates via a spacer are mentioned in Chapter 16.

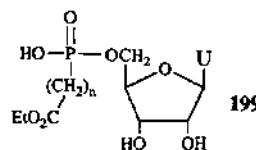
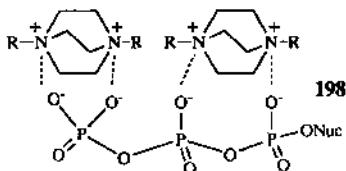


A chemico-enzymatic approach has been used for the synthesis of Coenzyme A analogues, modified in the thioethanolamine unit, using ATP as one starting material.²⁵⁸ Pyrophosphate bond formation from a nucleoside 5'-phosphorimidazolidine catalysed by divalent metal ions (Mn^{2+} , Cd^{2+} or Mg^{2+}) has been used to make dinucleoside di- and tri-phosphates such as CppC and GpppG.²⁵⁹ A vanadate analogue of NADP is mentioned in Chapter 16, in connection with its ability to function as a redox cofactor.

The 5'-triphosphates and α -thio-triphosphates of 2'-*O*-methylribonucleosides have been synthesized with the nucleoside attached via *O*-3' to the surface of controlled pore glass.²⁶⁰ A range of imido-analogues of AZT triphosphate, **197** ($X, Y = O, NH$) have been prepared, together with similar derivatives of TTP itself; the TTP analogue with $X = O$, $Y = NH$ proved the best inhibitor of HIV 1 reverse transcriptase.²⁶¹

An interesting study has been described concerning the transport of nucleoside triphosphates (ATP, CTP, dideoxy-TTP, and AZTTP) across liquid organic membranes, mediated by DABCO-derived cationic carriers. The best carrier was found to be a bisquaternary type which formed a 2:1 complex with the nucleoside triphosphate; tetraquaternary carriers in which two DABCO units are

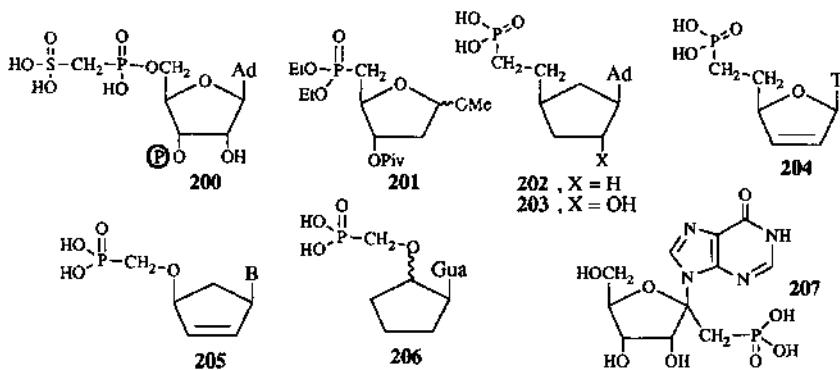
linked by a spacer proved less effective. A structure of type **198** was proposed for the 2:1 complex.²⁶²



Phosphonate analogues of nucleotides continue to attract attention. 5'-Hydrogen-phosphonates and 5'-methylphosphonates of various anti-HIV nucleosides have been made, and the H-phosphonates from AZT and 3'-deoxy-3'-fluorothymidine were highly active.²⁶³ 5'-Fluoromethyl- and -difluoromethyl-phosphonates have been prepared from d4T,²⁶⁴ AZT,^{264,265} and various other nucleosides and deoxynucleosides,²⁶⁵ and phosphonates **199** ($n = 1, 2$) were prepared from the 5'-bis(TMS)phosphite by Arbusov or Michael reaction.²⁶⁶ The non-hydrolysable analogue **200** of phosphoadenosine phosphosulfate ('active sulfate') has been described. The 3'-phosphate was put on in the last step using trimetaphosphate, and the desired product was separated from the 2'-phosphate by hplc.²⁶⁷

A new route to non-isosteric 5'-deoxy-5'-phosphonates of deoxynucleosides involves the synthesis of **201** by Arbusov reaction applied to the 5'-deoxy-5'-iodocompound, followed by making the base-sugar link.²⁶⁸ Some 5'-deoxy-5'-phosphonates, including that of 2-O-methyluridine, have been described for the first time.²⁶⁹

The Gif group have given a full account of their route to isosteric phosphonate analogues of nucleoside 5'-phosphates by the photolysis of *N*-hydroxy-2-thiopyridone esters of uronic acids, and trapping of the resultant radicals with vinyl phosphonates (see Vol. 23, p. 224-225).²⁷⁰ The phosphonate analogue of AZT monophosphate has been made by a Wittig synthesis, and converted to the diphosphoryl phosphonate (AZTTP isostere).²⁷¹ The Wittig route to isosteric phosphonate analogues of dideoxynucleoside monophosphates has been described in full (see Vol. 23, p. 225),²⁷² and the enzymic pyrophosphorylation of carbocycle **202** and some related phosphonates (Vol. 25, p. 263), including **203** which is newly described, has been carried out by transfer of pyrophosphate from phosphoribosyl pyrophosphate (PRPP) using PRPP synthetase.²⁷³ Workers at Bristol-Myers have made the isosteric phosphonate **204** of d4T monophosphate by elimination from an intermediate previously described by Tanaka *et al* (Vol. 23, p. 225). This paper also describes a route to the carbocyclic phosphonate **205** ($B = T$),²⁷⁴ and the related guanine compound **205** ($B = \text{Gua}$), an analogue of carbovir monophosphate, has also been reported by the same team. The cyclopentanes **206** (both isomers, as racemates) were also made by opening cyclopentene epoxide by the anion of 6-O-benzylguanine, followed by Mitsunobu inversion in the case of the *cis*-product, which displayed modest anti-HIV activity.²⁷⁵ Compounds **205** ($B = \text{Gua}, T$) and their dihydroderivatives, have previously been reported by the Exeter-Glaxo group, who also made some diphosphoryl phosphonates (triposphate analogues), and a full account of this work has appeared.²⁷⁶



Full details have also been given of the synthesis of 207, designed as an inhibitor of purine nucleoside phosphorylase, from D-fructose.²⁷⁷

13 Ethers, Esters and Acetals of Nucleosides

A review on the synthesis of oligonucleotides by the phosphoramidite approach contains sections on O-2' and O-5' protecting group chemistry.²⁷⁸

A convenient preparation of 2'-O-methylguanosine involves the interaction of *N*²-isobutyryl-5'-O-dimethoxytritylguanosine with trimethylsilyldiazomethane, followed by deprotection.²⁷⁹ Allylation of uridine and cytidine at O-2' can be achieved with some regioselectivity by use of either allyl ethyl carbonate and a Pd⁰ catalyst, in which case protection of *N*³- of the uracil unit was necessary,²⁸⁰ or by allylation of a stannylene derivative.²⁸¹ Alkylation of UMP also has some selectivity towards O-2'.²⁸²

There have been further reports on carboranyl derivatives of nucleosides (see Vol. 24, p.245), for use in neutron-capture therapy of cancer. Carboranyl nucleosides have been prepared by addition of B₁₀H₁₄ to propargyl ethers at O-2', O-3', and O-5' of uridine,²⁸³ and the 2'-O-derivative 208 has been made by an improved procedure in which B₁₀H₁₄ was added to 1,2,5,6-di-O-isopropylidene-3-O-propargyl- α -D-allofuranose, followed by oxidative removal of C-1 to give a ribofuranose derivative which was then coupled to uracil under Vorbrüggen-type conditions.²⁸⁴

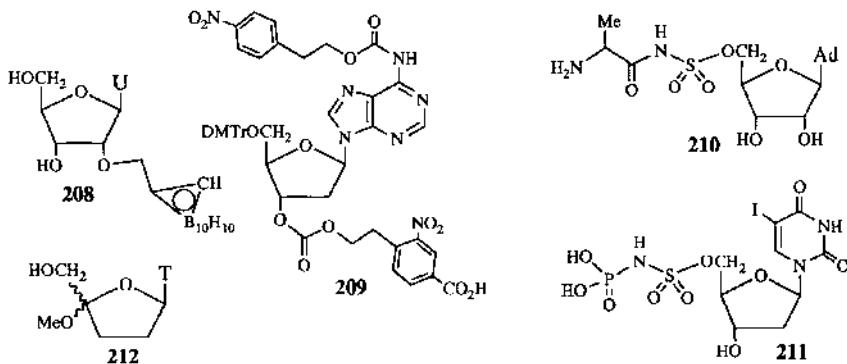
The 2',3'-bis-TBDSM ether of adenosine can be made by firstly preparing the 2',3',5'-trisilylated material, followed by partial acid hydrolysis,²⁸⁵ and an improved synthesis of 3',5'-O-(di-*t*-butylsilanediyl)cytidine has been described, avoiding problems of silylation of the heterocycle.²⁸⁶

Lipase enzymes have been used for further regioselective acylations of nucleosides (see also Vols. 24 and 25). Amano PS lipase effects selective acylations of 2'-deoxynucleosides at O-3', using oxime esters as acyl donors,²⁸⁷ and use of acetone oxime carbonates with the same lipase gives 3'-O-alkoxycarbonyl-2'-deoxynucleosides.²⁸⁸ If the lipase used was that from *Candida antarctica*, then alkoxycarbonylation of thymidine occurred mostly at O-5'; similar regioselectivity was found for ribonucleosides (adenosine and uridine), but in addition to 5'-O-alkoxycarbonyl derivatives, 5'-O-(acetoneoximecarbonyl)-derivatives were also formed.²⁸⁹

3'-*O*-Formyl derivatives of thymidine and 2'-deoxyuridine have been made by interaction of the Vilsmaier reagent with the 5'-*O*-TBDMS ethers; the thymidine derivative had moderate anti-HIV activity.²⁹⁰ 3'-*O*-(Methylthio-thiocarbonyl)- and 3'-*O*-(thiocarbamoyl)- derivatives of thymidine have also been made.²⁹¹

As regards the synthesis of esters as potential prodrugs, five 5'-*O*-esters of 2',3'-dideoxyadenosine have been prepared, and their bioavailability assessed in rats,²⁹² and AZT has been linked at *O*-5' to various lipidic amine acid oligomers.¹³⁸ The antiviral agent 9-(β -D-arabinofuranosyl)-6-methoxypurine has been converted into 5'-*O*-acyl derivatives,²⁹³ and into di- and triesters,²⁹⁴ and esters of 2'-deoxy-2'-methylene cytosine, an antitumour agent, have also been described.²⁹⁵

The 2'-deoxynucleoside derivative **209** has been synthesised and coupled to controlled pore glass for use as a primer in oligonucleotide synthesis. It can be cleaved without recourse to ammonia using 0.5 M DBU in dioxan, and hence the oligonucleotides could include units that are ammonia sensitive.²⁹⁶

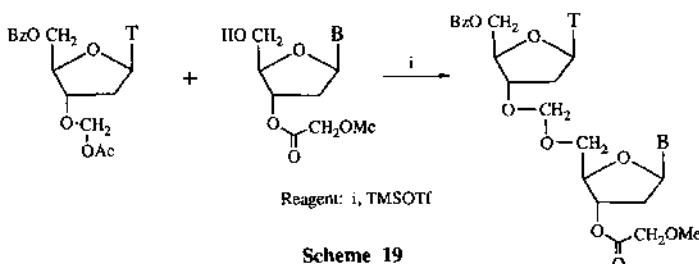


The sulphamate **210** has been made as an analogue of alanyl-AMP, in order to probe the substrate specificity of alanyl-tRNA synthetase,²⁹⁷ and **211** and some related structures have been synthesized as analogues of IdU diphosphate.¹²¹

Treatment of the 4'-ene with MCPBA in methanol led to the 4'-methoxy-derivative **212** of d4T, and 4'-methoxy-2'-deoxyadenosine was made in a similar way.¹²⁰

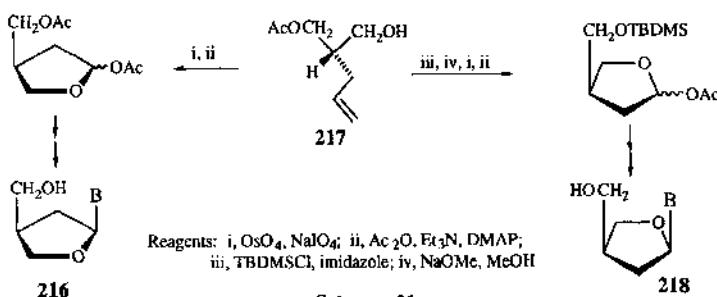
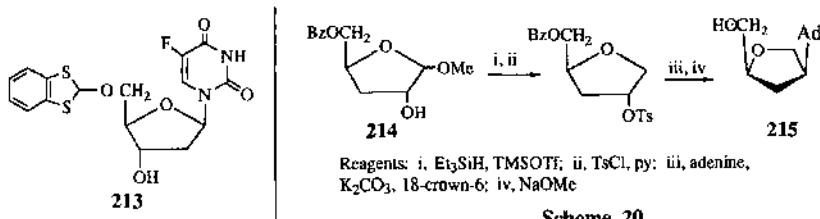
There have been further reports from the Leiden group on the synthesis of dinucleosides linked by a (3' → 5') methylene acetal (see Vol. 25, p. 270). A cytosine-(3' → 5')-uridine unit with this type of link has been made, using activation of a 3'-*O*-methylthiomethyl ether with NIS and triflic acid to form the internucleosidic acetal, and the product was converted to a 3'-phosphoramidite.²⁹⁸ An alternative way of establishing the link, using 3'-*O*-acetoxymethyl ethers, is illustrated in Scheme 19.²⁹⁹

There has been a further report on the introduction of the [[2-(methylthio)phenyl]thio]methyl (MPTM) protecting group into the 2'-position of adenosine, guanosine and cytidine building blocks for oligonucleotide synthesis (See Vol. 25, p. 270).³⁰⁰ Some thioacetals and dithioorthoesters at *O*-5' of FdU, such as **213** have been prepared and subjected to γ -radiolysis.³⁰¹

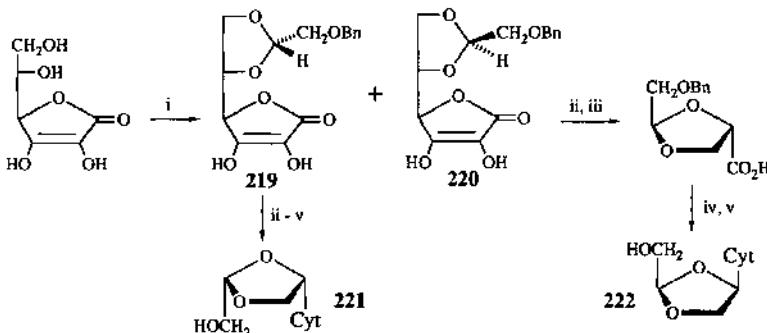


14 Miscellaneous Nucleoside Analogues

There continues to be considerable activity in the synthesis of nucleoside analogues with major modifications in the ribofuranose ring, and interesting observations concerning bioactivity have been found. A fuller account has been given of the synthesis of 'iso-ddA' (see Vol. 23, p. 227), and other bases have been introduced into this system.³⁰² Workers at Glaxo have also reported a route to iso-ddA and other base analogues starting from L-glucose, together with a full account of their work on the sulfur analogues (Vol. 25, p. 271).³⁰³ Meanwhile, Nair's group have used the pentose 214 derived from D-xylose, to make the enantiomer 215 of iso-ddA (Scheme 20) and again compounds containing the other nucleobases were also prepared.³⁰⁴ The same group have also prepared both of the enantiomeric structures 216 and 218 (B = Ad, Gua, U, T, Cyt) (Scheme 21) from the same chiral precursor, which was obtained by lipase-catalysed hydrolysis of the *meso*-diacetate.³⁰⁵

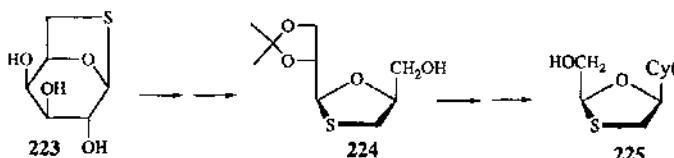


L-Ascorbic acid can be converted to the separable epimers 219 and 220 (Scheme 22); sequential oxidative degradation of each of them then gave routes to both the L-(-)- and D-(+)-enantiomers, 221 and 222 respectively, of dioxolane-C, together with the α -anomers.³⁰⁶ Other workers have also described fully the synthesis of 222 and its thymidine analogue from 1,6-anhydro-D-mannose (see Vol. 25, p. 271),³⁰⁷ and have used a similar approach, with 1,6-anhydro-L-gulose as precursor, to L-(-)-dioxolane-C 221, and to L-(+)-dioxolane-T. The L-(-)-isomer 221 of dioxolane-C was found to have higher antiviral activity against HIV and hepatitis B virus than the enantiomer 222.³⁰⁸

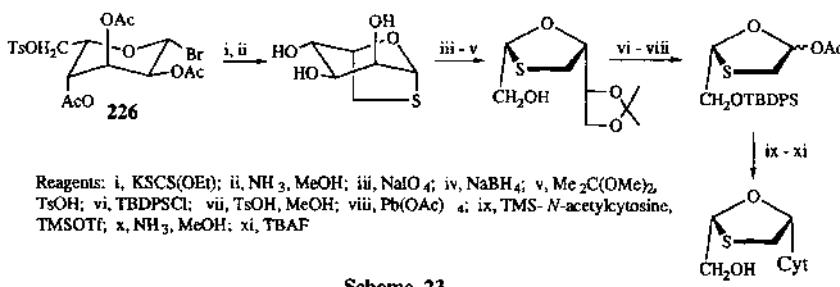


Reagents: i, $\text{BnOCH}_2\text{CH}(\text{OMe})_2$, TsOH ; ii, H_2O_2 , K_2CO_3 ; iii, RuCl_3 , NaOCl ,
iv, $\text{Pb}(\text{OAc})_4$; v, $\text{TMS-N-acetylcytosine}$, TMSOTf

Scheme 22

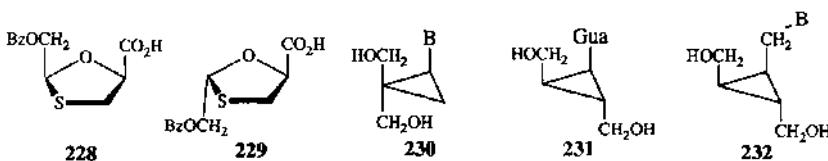


In the oxathiolane series, controlled periodate-borohydride cleavage of the C3-C4 bond in 223 led to 224, convertible to the (+)-isomer 225 of BCH-189 (4TC),³⁰⁹ whilst L-gulose could be



Scheme 23

converted into 226 (Scheme 23) and hence into the (-)-isomer 227. Again, the (-)-isomer 227 proved to be more active against HIV and hepatitis B virus than the 'natural' enantiomer 225 by an order of magnitude.³¹⁰ The enantiomers of BCH-189 (225 and 227) and of its 5-fluoroanalogue (FTC) have been resolved by selective enzymic hydrolysis of butyrate esters,³¹¹ and reaction of the (S)-isomer of 2-hydroxy-3-mercaptopropionic acid with benzoyloxacetaldehyde gave the separable isomers 228 and 229, and the major product 229 could be converted to 227 using methods similar to Scheme 23.³¹² Both groups of workers^{310,312} found that the Lewis acid catalyst used in the nucleoside formation was important; SnCl₄ gave high β-selectivity, but the product was racemic, due presumably to reversible opening-closing of the oxathiolane. Some tetrazole oxathiolane nucleosides have also been reported.³¹³



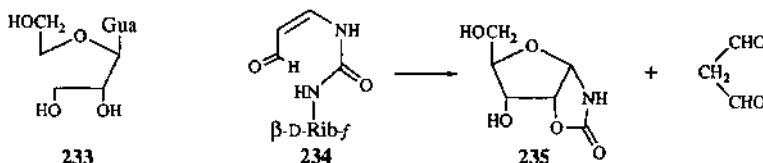
There have been reports of racemic cyclopropane nucleosides of type 230,³¹⁴ of the guanosine analogue 231,³¹⁵ and of homonucleosides of type 232 and the all-cis-epimers.³¹⁶

The seconucleoside 233 has been made by periodate-borohydride cleavage of an α-L-arabinopyranosyl nucleoside, and a number of related compounds were also described.³¹⁷ 5'-Modified-2',3'-secoribavirins have been reported,³¹⁸ and 6,5'-cyclo-5'-deoxy-5-methyluridine has been cleaved and reduced to the 2',3'-secoderivative.³¹⁹

Various 5'-O-sulfonylamino- and -thiocarbonylamino- derivatives of 2'-deoxy-5-fluorouridine have been made from the 5'-O-aminonucleoside, and subjected to γ-radiolysis.³²⁰

15 Reactions

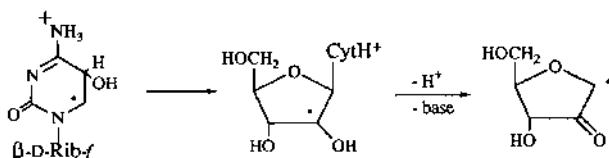
The base hydrolysis of zebularine [1-(β-D-ribofuranosyl)-1,2-dihydropyrimidin-2-one] has been investigated; ring opening to give 234 is followed by formation of the oxazolidinone 235 and malondialdehyde, and it was theorised that the production of malondialdehyde, a known mutagen, may account in part for the antitumour activity of the nucleoside.³²¹



Some empirical M.O. studies have been used to help rationalise the experimental findings concerning repair mechanisms of alkylated nucleosides, namely that *N*⁷-alkylation of

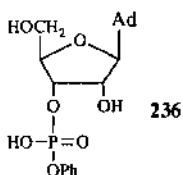
guanine residues is repaired by spontaneous depurination or glycosylase-induced hydrolysis, whilst O^6 -guanine and O^4 -thymine ethers undergo dealkylation.³²²

In an ESR study of the reactions of hydroxyl radicals and sulfate anion radicals with pyrimidine nucleosides, it was concluded that the formation of base-centred radicals is followed both by hydration and, in the case of ribonucleosides, by loss of H-2' followed by further fragmentation. The case of the interaction of cytidine with HO[·] at low pH is illustrated in Scheme 24.³²³



The regiochemistry of glycosylation of certain 1- β -D-ribofuranosyl-2,3-disubstituted imidazoles can be determined by a sequence of quaternization with Me₂SO₄, hydrolysis, and identification of the *N*-methylimidazole with reversed orientation of the substituents at C-4 and C-5.³²⁴

In order to probe the rate-limiting steps in RNA hydrolysis, the phenyl ester 236 was prepared, along with the 2'-phosphate, by reaction of adenosine 2',3'-cyclic phosphate with phenol. This ester hydrolyses about 10⁵ times faster than ApA at the same pH, to give the cyclic phosphate and phenol; thus the hydrolysis rate is governed by the basicity of the leaving group and decomposition of the pentacoordinated intermediate is rate-limiting in the alkaline hydrolysis of ApA.³²⁵ The 2',3'-cyclic phosphates of 2'- and 3'-C-methyl uridine were made, and, on hydrolysis, gave firstly the products where the tertiary alcohol was phosphorylated. Phosphate migration to the secondary positions then took place together with hydrolysis, and the kinetic analyses were compared with uridine 2',3'-cyclic phosphate.³²⁶ A paper on the hydrolysis of cAMP in the presence of cobalt (III) complexes is mentioned in Chapter 7.



5'-Deoxy-5-fluoro-*N*⁴-(3,4,5-trimethoxybenzoyl)cytidine has been prepared as a prodrug of the antitumour agent 5'-deoxy-5-fluorouridine, and its stability and degradation were examined at different pH values.³²⁷

Crystalline bis(cytidinium) sulfate and bis(2'-deoxycytidinium)sulfate have been prepared, and an unusual ion-exchange reaction in the solid state was observed when the latter was finely ground in the solid state with NaCl, KCl or KBr, to give 2'-deoxycytidinium bromide or chloride quantitatively.³²⁸

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N.M.R. Spectroscopy and Conformational Features

1 General Aspects

Recent studies on the origins and consequences of the *exo*- and *endo*-anomeric effects, including second and lower row anomeric interactions, have been reviewed (213 refs.).¹ A review with 12 refs. on applications of molecular modelling in glycotechnology, using a ganglioside and sucrose in water as examples, has been published.²

Quantum mechanical and force field calculations for representative torsion angles in a series of tetrahydropyran derivatives have been carried out in a study on conformational preferences for hydroxyl groups.³ The enthalpy and entropy factors governing the conformational equilibria in 2-methoxy- and 2-(2,2,2-trifluoroethoxy)-tetrahydropyran have been measured in several solvents by variable temperature ¹H- and ¹³C-n.m.r. spectroscopy; evidence has been obtained for preferential bonding of methanol to axial alkoxy groups.⁴ These studies have been extended to 2-cyano- and 2-carbomethoxy-tetrahydropyran, and to the corresponding piperidine and cyclohexane derivatives; the increasing stability of the axial conformation along the series cyanocyclohexane / 2-cyanotetrahydropyran / 2-cyanopiperidine is attributed to an increasing *endo*-anomeric effect.⁵ The conformations and reactivities of glycosyl radicals have been determined by *ab initio* calculations, using the 2-tetrahydropyranyl- and the 3-fluoro-tetrahydropyranyl-radical as models.⁶

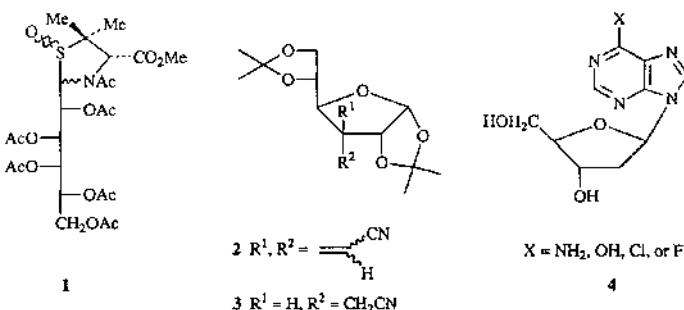
Three isotope-edited n.m.r. methods have been applied to selectively ¹³C-substituted monosaccharides and nucleosides in an attempt to simplify their spectra, and the implications of these new approaches for the structural analysis of more complex systems have been briefly discussed.⁷ The 1-, 2-, and 3-bond ¹³C-¹³C spin-spin coupling constants involving the terminal carbon atoms of all aldo-hexoses, -pentoses, and -tetroses have been measured in D₂O by use of extensive high resolution ¹H-decoupled ¹³C-n.m.r. techniques on substrates with ¹³C-enrichment at the terminal hydroxymethyl carbons.⁸ Natural-abundance ¹³C-chemical shift editing of homonuclear correlated data for carbohydrates *via* the heteronuclear 3D n.m.r. sequence TOCSY-HECTOR (total correlation spectroscopy-heteronuclear correlated), involving direct ¹³C-detection, has been reported to give optimal resolution and sensitivity; it has been illustrated by use of sucrose as example.⁹ In an application of water-eliminated Fourier-transform (WEFT) ¹H-n.m.r. spectroscopy to the study of optical rotation phenomena, the optical rotation changes in aqueous solutions of α - and β -D-glucose, -D-galactose, and -lactose were correlated with the integral values of the n.m.r. signals for the

corresponding anomeric protons.¹⁰ The water association in solutions of glucose, fructose, sucrose, and lactose has been investigated by an examination of the dependence of the low-field ¹H-longitudinal relaxation rate on concentration.¹¹

The complete assignment of the ¹H-n.m.r. spectra of 2-, 3-, 2,3-di-, 2,6-di-, and 2,3,6-tri-O-carboxymethylglucose have been reported.¹² The distinction of the 1-monodeutero-isotopomers of D-fructose 6-phosphate by ¹H-n.m.r. spectroscopic means provided a new tool for assessing the relative extent of interconversion of hexose phosphates in the reactions catalysed by phosphoglucoisomerase and phosphomannoisomerase, respectively.¹³ Vibrational spectra and force field calculations on crystalline α - and β -D-galactose are thought to provide an interesting approach to spectroscopic studies on carrageenans and other galactans.¹⁴ The determination of the absolute configurations of aldonic acids by use of shift reagents is referred to in Chapter 16.

2 Acyclic Systems

A review with 190 refs. on conformations and absolute configurations of acyclic diols and polyols and their benzoates in solution, as determined by chiroptical methods including the exciton chirality concept, has been published.¹⁵ The conformations of aqueous erythritol and L-threitol in relation to their sweetness properties have been analysed by molecular dynamics simulation.¹⁶ ¹H- And ¹³C-n.m.r. experiments have been performed to analyse the conformations and stereochemistry of the four diastereomeric thiazolidine sulfoxides **1**.¹⁷

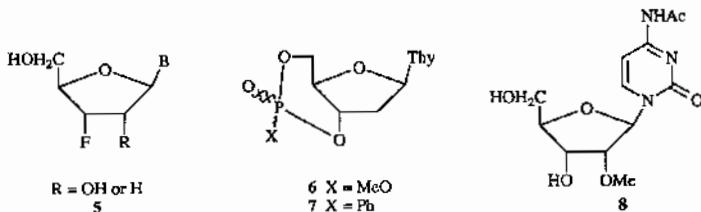


3 Furanose Systems

N.m.r. spectroscopy and molecular modelling allowed the unequivocal structural assignments of the diacetoneglucose-derived, branched derivatives **2** and **3**.¹⁸ Conformational analysis on a number of tetro- and pento-furanosides, based on ³J_{H,H} values expressed as a function of the pseudorotation parameters, has been reported.¹⁹

Whereas the anomeric protons of 2'-deoxypyrimidine nucleosides **4** have long been known to appear as triplets in ^1H -n.m.r. spectra recorded in polar solvents, it has only now been found that they resonate as doublets of doublets in non-polar solvents, due to intramolecular H-bonding between O-5' and N-3. Careful attention to solvent polarity in interpreting such splitting patterns has therefore been recommended; appearance of H-1' as doublets of doublets has previously been associated with α -stereochemistry.²⁰

Conformational studies have been undertaken on the four D-erythonucleosides corresponding to the main ribonucleosides of RNA by 75 MHz ^{13}C - and 620 MHz ^1H -n.m.r. spectroscopy, with a view to assessing the effects of the CH_2OH groups in the D-ribonucleosides.²¹ Extensive conformational analysis of AZT at the semiempirical AM1 level furnished optimized geometries agreeing more with n.m.r. than with crystallographic data and bearing little resemblance to molecular mechanics results; no evidence of a single dominant conformation or single conformation-determining parameter was revealed.²²



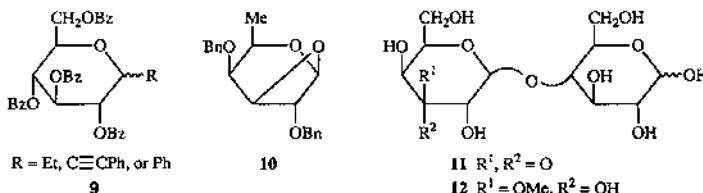
The conformations of the 3'-deoxy-3'-fluoro- and 2',3'-dideoxy-3'-fluoro-ribonucleosides **5**, determined from their ^1H -n.m.r. spectra, indicated that introduction of a highly electronegative substituent at C-3' stabilizes the $^2\text{S}_1$ -form of the furanose rings.²³ The solution conformation of adenosine 5'-phosphate has been deduced from experimental and simulated T_1 -values to be an equilibrium between the 2'-*endo-anti*-, 3'-*endo-anti*-, and 2'-*endo-syn*-forms.²⁴ The chair-twist equilibria of the phosphorus-containing, six-membered rings of *cis*- and *trans*-thymidine methyl cyclic 3',5'-phosphates (**6**) and of the corresponding phenylphosphonates **7** have been investigated by ^1H -n.m.r. techniques.²⁵ The high conformational rigidity of N^4 -acetyl-2'-*O*-methylcytidine (**8**) has been investigated by ^1H -n.m.r. spectroscopy.²⁶ Selective INEPT experiments have been employed to distinguish between the imino hydrogen atoms of uridine and thymidine, which is not possible on the basis of chemical shifts.²⁷

AM1 calculations on 3 conformers each of 4 tautomeric forms of ascorbic acid have been reported.²⁸

4 Pyranose Systems

A review with 40 refs. on molecular dynamics simulations of the pyranoid ring of glucose has been published.²⁹ A new molecular mechanics software package called REFINE has been designed especially for work on pyranose rings.³⁰

The ¹H- and ¹³C-n.m.r. spectra of the lipid A constituent 2,3-diacetamido-2,3-dideoxy-D-glucopyranose have been fully assigned by use of 2D methods.³¹ Application of 2D n.m.r. techniques to alkyl-, alkynyl-, and aryl-C-glucopyranoside perbenzoates **9** confirmed a diastereomeric effect in the chemical shifts related to the anomeric configuration.³² A Karplus-type equation based on empirical data has been proposed for ¹³C-¹H coupling in the C-S-C-H fragment in 1-thioglycosides.³³ Virtual long-range coupling has been observed in the ¹H-n.m.r. spectra of some tetra-O-acetyl-1-O-aryl- β -D-hexopyranoses.³⁴



Conformational studies by ¹H-n.m.r. spectroscopy have been performed on 4-deoxy-4-fluoro-D-glucopyranose, 6-deoxy-6-fluoro-D-glucopyranose, and 6-deoxy-6-fluoro-D-galactopyranose in several solvents,³⁵ on 1,3-anhydro-2,4-di-O-benzyl- β -D-fucopyranose (**10**),³⁶ and on three 1,2:3,4-di-O-methylenepyranoses.³⁷ [6-¹³C]-Labelled tetradecyl 2-deoxy- α - and - β -D-glucoside and a number of similar, labelled, long-chain alkyl hexopyranosides have been subjected to ¹³C-n.m.r. spectroscopic analysis to determine the conformations of their head groups in detergents such as 1,2-dimyristoyl *sn*-3-glycerophosphocholine (DMPC).³⁸ Structural and conformational studies on the *N*-D-pentopyranosylamines of tryptamine and tyramine are referred to in Chapter 10.

5 Disaccharides

In a workshop report, the evolution of the structural representation of sucrose from the establishment of its constitutional formula and conformational features to the present-day possibilities for interactive graphic display of its molecular geometry and for the computation of contact surface properties relevant for structure-sweetness relationship considerations has been presented.³⁹

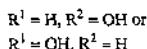
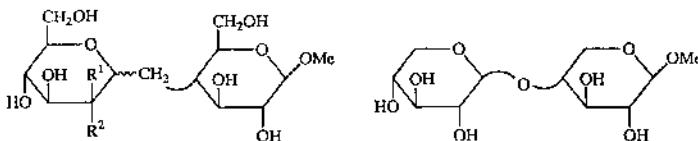
The ¹H- and ¹³C-n.m.r. spectra of α -D-galactopyranosyl-(1→3)-L-arabinose in D₂O have been fully assigned by use of COSY and HECTOR techniques,⁴⁰ and complete ¹H- and ¹³C-n.m.r. analysis

(1D and 2D) of long-chain *N*-alkyl lactosylamines has been reported.⁴¹ All ¹H- and ¹³C-resonances of potassium sucrose octasulfate have been assigned with the help of 2D and deuterium-induced differential-isotope-shift (DIDIS) n.m.r. methods.⁴² A ¹H-n.m.r. study in D₂O showed that 3'-ketolactose (**11**) crystallized from methanol as the hemiacetal **12** with an equatorial methoxy group.⁴³ A 500 MHz ¹H-n.m.r. investigation of methyl β -cellobioside confirmed the presence of an intramolecular hydrogen bond between HO-3 and O-5' in DMSO, but not in D₂O or CD₃OD.⁴⁴

Anomeric ¹J_{C,H} values have been used for detecting the formation of 1,2-orthoesters during disaccharide synthesis⁴⁵.

In continuation of earlier studies on α,α -trehalose polypivaloates (Vol. 24, p. 87, ref. 26), the ¹H- and ¹³C-n.m.r. spectra of unsymmetrical hexa- and hepta-pivaloyl derivatives have been investigated.⁴⁶ Conformational studies by n.m.r. spectroscopy and/or theoretical methods have been reported for the following compounds and groups of compounds: sucrose,⁴⁷ gentiobiose,⁴⁸ methyl 4-thio- α -maltose,⁴⁹ β -D-fructofuranosyl-(2 \rightarrow 6)-fructofuranose (levanose),⁵⁰ β -D-fructofuranosyl-(2 \rightarrow 6)-fructopyranose,⁵¹ methyl α -L-rhamnopyranosyl-(1 \rightarrow 2)- α -L-rhamnopyranoside,⁵² the CD₃ glycoside of β -D-mannopyranosyl-(1 \rightarrow 4)-2-acetamido-2-deoxy- β -D-glucose,⁵³ lactal in D₂O and DMSO-d₆ and lactal hexaacetate in CDCl₃,⁵⁴ both anomers of kojibiose, nigerose, and maltose,⁵⁵ both anomers of sophorose, laminarabiose, and cellobiose,⁵⁶ 4-thiomaltose, 4-O-(α -D-glucopyranosyl)-N-methyl-deoxynojirimycin, and acarviosine (the *pseudo*-disaccharide moiety of acarbose),⁵⁷ eight (1 \rightarrow 2)- and (1 \rightarrow 3)-linked disaccharides in which the glycosidic linkages were in different environments,⁵⁸ and eight isomeric *pseudo*-trehalose derivatives with α -D-, β -D-, α -L-, and β -L-5a-carba-glucopyranoside moieties, respectively, connected to either an α - or β -D-glucopyranosyl residue.⁵⁹

In a further molecular mechanics study (MM3), the energy surfaces of α,α -, α,β -, and β,β -trehalose were compared with those of the corresponding 2-(6-methyltetrahydropyran-2-yloxy)-6-methyltetrahydropyran and 5a-carba trehaloses; it was concluded that the *exo*-anomeric effect plays an important role and that linkage-type (α or β) is more important than the presence or absence of exocyclic substituents in determining disaccharide conformations.⁶⁰ The preferred solution conformations of eight (1 \rightarrow 4)-C-linked disaccharides, such as compounds **13**, have been determined on the basis of vicinal ¹H-¹H coupling constants, and conformational similarities between



corresponding *C*- and *O*-linked derivatives have been demonstrated by a comparison of NOE and T_1 data.⁶¹

A newly developed, two-dimensional inverse-detected n.m.r. method for the measurement of long-range heteronuclear coupling constants has been illustrated by use of disaccharide 14.⁶² The ^{13}C chemical shift pH titration curves of the aminoalditols derived from cellobiose, maltose, and lactose have been recorded.⁶³ The force field previously determined for both anomeric forms of glucopyranose has been applied to several disaccharides of glucose (trehalose, sophorose, laminarabiose, maltose, cellobiose, and gentiobiose); specific parameters have been obtained for the different types of glycosidic linkage.⁶⁴

6 Oligosaccharides and Related Compounds

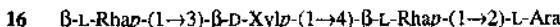
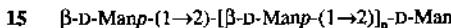
The use of 1D and 2D n.m.r. spectroscopy for establishing the structures and substitution sites of naturally occurring oligosaccharides and glycosides has been reviewed (237 refs.),⁶⁵ and a 144-page review on high resolution ^1H -n.m.r. spectroscopy of oligosaccharide alditols released from mucin-type *O*-glycoproteins has been published.⁶⁶

Homo- and heteronuclear correlation spectroscopy techniques have been employed to completely assign the resonances of the pyranose ring protons, the acetyl methyl protons, and the acetyl carbonyl carbon atoms of various peracetylated α -D-mannosyl- and 2-acetamido-2-deoxy- β -D-glucosyl-containing oligosaccharides; by application of SIMCA class modelling algorithm and PC (principal-component) analysis, subsets of chemical shifts and coupling constants characteristic for certain residue types have been selected from these data.⁶⁷ New techniques involving 2D RELAY-HOHAHA and either differential NOE⁶⁸ or 1D multiple relay COSY⁶⁹ have been recommended for the extraction of subspectra corresponding to individual sugar components in complex systems from overlapping signals allowing, for example, assignment of all sugar ^1H -resonances in the spectra of intact natural glycosides.

The computer program CASPER, which predicts the structures of linear or branched oligosaccharides on the basis of information on components, linkages, and n.m.r. chemical shifts, has been tested on five reducing tri- to hexa-saccharides or their methyl glycosides.⁷⁰ It has also been used in the structural analysis of several oligosaccharides from human milk, containing vicinally branched residues.⁷¹

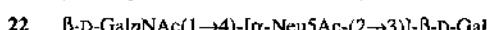
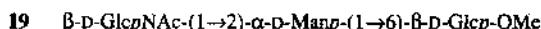
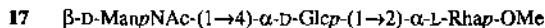
A structural investigation, by ^1H -n.m.r. spectroscopy, of manno-oligosaccharides released by mild acid hydrolysis from the phosphopeptidomannan of a *Candida albicans* strain and ranging from biose to heptaose, showed them to be of the β -(1 \rightarrow 2)-linked type. Some general rules pertaining to

the ^1H -n.m.r. spectroscopic analysis of linear manno-oligosaccharides of structure **15** have been formulated.⁷²

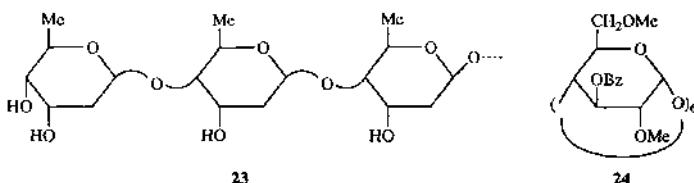


The ^1H -n.m.r. spectra of various carrageenan-derived oligosaccharides have been analysed by means of DQ COSY and ^1H - ^{13}C -correlated methods.⁷³ ^1H - and ^{13}C -assignments have been reported for sialylated oligosaccharide alditols related to mucins,⁷⁴ and for the pentasaccharide of the genus-specific epitope of *Chlamydia* lipopolysaccharide.⁷⁵ The structure of the fully methylated alditol acetate of **16** has been determined solely on the basis of n.m.r. data.⁷⁶ A ^1H - ^{13}C natural abundance heteronuclear-multiple-quantum-coherence (HMQC) experiment has been illustrated by use of trisaccharide Lewis^X glucat.⁷⁷ The solid state n.m.r. spectra of *N*-acetylurea derivatives obtained by reaction of hyaluronic acid with isotopically-labelled carbodiimides have been recorded.⁷⁸

Recent advances in resolving seemingly intractable problems concerning oligosaccharide conformational structure by molecular dynamics modelling of carbohydrate flexibility and solvation have been discussed.⁷⁹ Application of various 2D and 3D n.m.r. techniques to the conformational study of a diantennary oligosaccharide confirmed the flexibility of the α -D-Manp-(1 \rightarrow 3)-D-Man linkage,⁸⁰ whereas MM2 and HESA studies on the trisaccharides **17** and **18** indicated rather rigid conformations at the Glcp-(1 \rightarrow 2)- and -(1 \rightarrow 3)- α -L-Rhap junctions.⁸¹ A comprehensive strategy for detailed characterization of the solution conformation of the trisaccharide sialyl- α -(2 \rightarrow 6)-lactose by n.m.r. spectroscopy and force field calculations based on Metropolis Monte Carlo simulations has been presented.⁸²



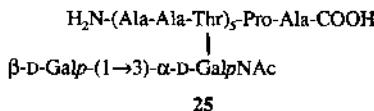
Further conformational studies have been carried out on trisaccharide **19**,⁸² on lacto-*N*-neotetraose (**20**),⁸⁴ on the tetra- and tri-saccharide moieties **21** and **22** of the gangliosides GD1b and GD1b-monolactone, respectively,⁸⁵ and on the trisaccharide portion **23** of digoxin.⁸⁶ Evidence has been obtained, by use of ^1H -n.m.r. spectroscopy, that the preferred conformation of GM2 ganglioside is stabilized by an inter-residue amide-carboxyl hydrogen bond.⁸⁷



The conformational mobility of α -cyclodextrin derivative 24 and some related compounds in solvents such as benzene, dichloromethane, and chloroform has been thoroughly investigated by dynamic n.m.r. spectroscopy,⁶⁸ and the ^1H -n.m.r. chemical shifts and coupling constants for α - and β -cyclodextrin and their permethyl ethers in neutral aqueous media have been assigned; to obtain accurate data, the experimental spectra were analysed with the Raccoon spin simulation program.⁶⁹

The structure of the copolymer obtained by treatment of 1,4-anhydro-2,3- O -benzylidene- α -D-ribopyranose and 1,4-anhydro-2,3-di- O -benzyl- α -D-ribopyranose with SbCl_5 (see Chapter 5) has been determined from its ^{13}C -n.m.r. spectrum and its optical rotation.⁷⁰

The conformational behaviour of the glycopeptides *N*-acetylmuramoyl-L-alanyl-D-isoglutamine (MDP) and *N*-acetylmuramoyl-L-alanyl-3-carboxymethyl-D-proline methyl ester (MAP) in DMSO has been studied by computer modelling assisted by 1D and 2D ^1H -n.m.r. experiments; dihedral angles, inter-proton distance constants, and the shapes of the peptide chains have been determined.⁷⁰ Eight closely related glycoproteins with structures such as 25 (antifreeze glycoproteins) have been subjected to 2D n.m.r. spectroscopy aided by MM2 calculations.⁷²



7 ^{17}O -N.m.r. Spectroscopy

Well resolved natural abundance ^{17}O -n.m.r. spectra of eight 1,6-anhydro- β -D-hexopyranoses and three deoxy model compounds have been recorded in aqueous solution at 90 °C. Resonances were assigned with the help of O -acetylation, lanthanide shift reagents, and computational methods. The ^{17}O chemical shifts were evaluated in terms of relative orientation of ring oxygen atoms and hydroxyl groups. A new type of interaction (δ -effect) between equatorial hydroxyl oxygens in a planar zig-zag arrangement has been discovered in the course of the work.⁷³

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22

Other Physical Methods

1 I.r. Spectroscopy

The hydrogen bond network in crystalline sugars has been studied by variable low temperature i.r. spectroscopy. β -L-Arabinose, methyl α -D-glucopyranoside and di- β -D-fructopyranose 1,2:2,1'-dianhydride were studied and the influence of low temperature on band density, band shape and band maxima has been reported. Most surprising is the contradictive behaviour of the shift of the band frequency maxima of methyl α -D-glucopyranoside; an increase was observed for the free hydroxyl group while those involved in hydrogen bonding were red shifted. In addition, deuterium exchange experiments showed the presence of vibrational coupling in the gluco series but not in the fructose structure that was examined.¹ A similar variable temperature study has also been conducted on β -D-fructopyranose in the range from 300 K to 110 K. Deuterium exchange was used to establish the presence of vibrational coupling between some of the hydrogen bonded hydroxyl groups and a tentative assignment of the O-H stretching region has been offered.² I.r. and Raman spectra of crystalline α - and β -D-galactose in both the mid (500-4000 cm^{-1}) and far (50-500 cm^{-1}) range have been obtained and used to contribute to a force field to describe the crystalline state.³

The carbonyl absorption band at 1728 cm^{-1} (in ${}^2\text{H}_2\text{O}$ or H_2O) has been assigned to the open (keto) form of D-fructose, and the concentration of the open form (at different temperatures and pH values) may be monitored by observing changes in the intensity of this band. The concentration of the open form was found to be an order of magnitude higher at 80 °C than at 30 °C.⁴ Low frequency i.r. spectra of a series of monosaccharide nitrates have been shown to be dependent on both the position of substitution and conformation of the nitrate moiety.⁵ Carbonyl and N-H i.r. stretching regions have been examined in the case of lactams derived from 6-amino-6-deoxyhexonic acids and the corresponding tetra-O-acetyl derivatives.⁶

Raman spectra of monosaccharide-derived acetates are highly sensitive to substrate stereochemistry, and have proven useful in the study of specific conformational properties.⁷ The f.t. Raman spectrum of α -D-glucose monohydrate has been recorded for the first time and, by incorporating crystallographic and vibrational spectroscopy data, band assignments have been made.⁸

2 Mass Spectrometry

Recent advances in mass spectrometric instrumentation and methodology have been reviewed within the context of the structural analysis of carbohydrates.⁹ A review (16 refs, in Chinese) on the application of fast atom bombardment (FAB)-m.s. to the analysis of *O*-glycosides has appeared.¹⁰

$^1\text{H}/^2\text{H}$ Exchange reactions can be conducted in conjunction with either FAB-m.s. or desorption chemical ionization (DCI)-m.s. to quantify the number of mobile hydrogen atoms in a range of biomolecules, including saccharides. Experimental parameters that influence the efficiency of $^1\text{H}/^2\text{H}$ exchange have been discussed in detail.¹¹ M.s. studies of various monosaccharides and their derivatives have been described. These include di-D-fructose dianhydrides,¹² and, in a separate study,¹³ a series of stereoisomeric 1,5-anhydropentofuranoses, 1,6-anhydrohexofuranoses and 1,6:3,5-dianhydrohexofuranoses. The reaction of glycosidic oxocarbenium ions with ammonia has been studied by f.t. ion-cyclotron resonance. This involved chemical ionisation (using isobutane) of permethylated derivatives of methyl β -D-mannopyranoside, β -D-glucopyranoside and β -D-galactopyranoside and the efficiency of adduct formation (between NH_3 and oxocarbenium ion) was shown to depend on the stereochemistry of the pyranosyl component.¹⁴

Both c.i.-m.s. and c.i.-m.s. have been used to establish the location of the fluoro substituents in all the fully acetylated methyl deoxymonofluoro- α -D-glucopyranosides.¹⁵ The interaction of both peracetylated aldopyranosides and N-butylglycosylamines with organic ($n\text{-C}_8\text{H}_{17}\text{N}^+\text{H}_3$) and metal (K^+ , Li^+) cations, to give 1:1 adducts, has been studied by quantitative FAB-m.s.¹⁶ The fragmentation of tetrahydrofuran-2-methanol and tetrahydropyran-2-methanol (as simple models for monosaccharides) has been studied using negative ion m.s.-m.s. Under these conditions, deprotonation of the hydroxyl group occurs and major fragmentation pathways involve competitive losses of H_2O and CH_2O .¹⁷

The use of mass spectrometric methods in the structural elucidation of oligosaccharides continues to develop. Metal-ion co-ordination to promote specific dissociation pathways has been used to differentiate the linkage position of three isomeric disaccharides (sophorose, lactose and laminaribose). This was achieved by a combination of FAB and tandem m.s. on the ^2H and ^{18}O -labelled dilithiated disaccharide. Semi-empirical calculations support the experimental data that one lithium ion is tetraco-ordinate between the two sugar-rings, with the other ion being dico-ordinate with one ligand being the anomeric alkoxide at the reducing end.¹⁸ Unambiguous assignment of linkage position has also been achieved for a series of peracetylated disaccharides using desorption electron ionisation and ammonia desorption chemical ionisation.¹⁹ FAB-m.s. and c.i.-m.s. of disaccharide fragments derived from periodate oxidation followed by reduction showed highly characteristic ions from which both glycosidic linkage patterns and ring size were determined.²⁰ The fragmentation behaviour of lactosides during desorption ionisation has also been reported.²¹ Ammonia desorption c.i.-m.s. of peracetylated gentiobiose together with two isotopically labelled variants has been examined and the structures of ions inferred by comparison of mass-analysed ion kinetic energy (MIKE) spectra with those derived from compounds of established structure.²² FAB-m.s., using a B/E link, provides a valuable method for the sequence analysis of oligosaccharides that does not require prior derivatisation of the sample.²³ The structure determination of underivatised branched oligosaccharides (containing a 3-O-glycosidic linkage) has also been achieved using negative ion FAB-m.s.²⁴ Glucosamine and

N-acetylglucosamine oligomers have been characterised by FAB-m.s.²⁵ The FAB-m.s. of oligomers of galacturonic acids have been described.²⁶

The characterisation of a series of isomeric ribofuranosylimidazole nucleosides and 2'-deoxy analogues has been conducted using positive ion FAB-m.s.. The use of m.s.-m.s. then allowed full stereo- and regiochemical assignment.²⁷ Negative ion FAB-m.s. has been successfully used to characterise a series of nucleosides linked, via a phosphodiester at C-5', to oxysterols. This approach solved the problems of lability and lack of volatility associated with such phosphodiesters.²⁸

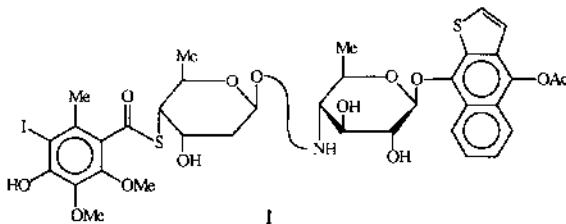
The "anomeric" configuration of saturated and unsaturated C-glycosides may be assigned using MIKE spectra and collision-activated dissociation.²⁹ Mass spectroscopic methods have been utilised to identify a dephosphorylated derivative of prostaglandinylinositol cyclic phosphate, generated as a metabolic product from rat liver.³⁰

The applications of coupled h.p.l.c.-m.s. and related systems continue to stimulate activity. The separation and analysis of mono- and di-saccharides by h.p.l.c.-atmospheric-pressure c.i.-m.s. allows characterisation by fragmentation pattern with a detection limit of 3-5 ng for glucose and fructose.³¹ H.p.l.c.-thermospray-m.s. has been used to characterise homologous α -1,4-gluco-, α -1,5-arabino-, β -1,4-xylo-oligosaccharides, as well as heterogeneous oligomers that are produced by enzymatic degradation of plant cell walls.³² H.p.l.c.-continuous flow FAB-m.s. has been established as a method for the detection of glucuronic acid conjugates of the carcinogenic polycyclic aromatic, benzo[a]pyrene.³³

Other analytical procedures based on h.p.l.c.-m.s. or g.c.-m.s. include the monitoring of dermatan sulphate and heparin,³⁴ analysis of complex mixtures of carbohydrate-derived urinary acids,³⁵ analysis of 2,3'-dideoxycytidine in plasma,³⁶ and the characterisation of the radiation-induced decomposition of thymine and thymidine.³⁷

3 X-ray and Neutron Diffraction Crystallography

Analysis of the geometrical properties of C-H--O hydrogen bonds in carbohydrates has been carried out by neutron diffraction.³⁸ Degradation of the potent anti-tumour antibiotic calicheamicin produced the disaccharide 1 incorporating the unusual N-O glycosidic linkage.³⁹



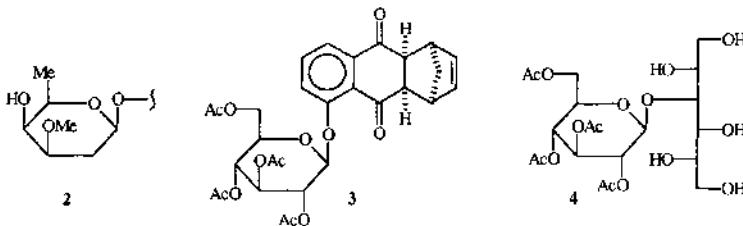
A combination of X-ray diffraction and differential scanning calorimetry has been used to probe the properties of a homologous series of saturated 1,2-di-*O*-acyl-2-*O*-(β -D-galactopyranasyl)-*sn*-

glycerols.⁴⁰ Three types of crystalline lactose hydrates have been prepared and characterized by X-ray powder diffraction, together with optical rotation and phase transition. The nature of the lactose hydrate isolated was dependent on both the lactose/solvent ratio used and the pH.⁴¹ Minutes of the 5th International Symposium on Cyclodextrins (1990) have been published and crystal structures of inclusion complexes of β -cyclodextrin with 4-tert-butyltoluene⁴², 4-tert-butylbenzyl alcohol,⁴³ dimethylformamide,⁴⁴ and potassium⁴⁵ have been reported.

Specific X-ray crystal structures have been reported as follows (solvent molecules of crystallization are frequently not noted):

3.1 Free Sugars and Simple Derivatives Thereof. - α -D-Glucopyranosyl potassium hydrogenphosphate,⁴⁶ lithium L-ascorbate dihydrate,⁴⁷ D-, L-iditol,⁴⁸ D- and L-threitol (determined at 119 K and 298 K),⁴⁹ 1-O-acetyl-2,3,5-tri-O-benzoyl- β -D-ribofuranose,⁵⁰ 1,3,4,6-tetra-O-acetyl- β -D-allopyranose,⁵¹ and β -D-fructopyranose 1-phosphate (as disodium salt).⁵²

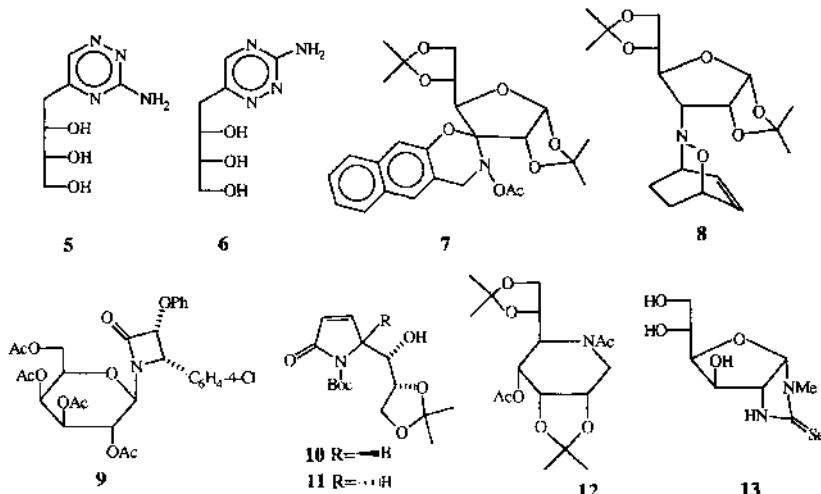
3.2 Glycosides, Disaccharides and Derivatives Thereof. - 2-O- α -D-Glucopyranosyl-L-ascorbic acid,⁵³ n-octyl α - and β -glucopyranoside (as a 1:1 complex),⁵⁴ amaloside A (a cis-B/C steroid incorporating pyranoside 2),⁵⁵ the cyclopentadiene-juglon glucoside cycloadduct 3,⁵⁶ D-glycero- α -D-glucopyranoside-3-ulose,⁵⁷ methyl β -D-laminarabioside [β -D-GlcP-(1 \rightarrow 3)- β -D-GlcPOMe],⁵⁸ lactulose (as trihydrate),⁵⁹ lacritol (β -D-Gal(1 \rightarrow 4)-D-glucitol) 4,⁶⁰ lactitol dihydrate,⁶¹ lactitol trihydrate.⁶²



3.3 Anhydru-sugars. - Methyl 2,3-anhydro 4,6-di-O-p-bromobenzyl- α -D-allopyranoside and methyl 2,3-anhydro-4,6-di-O-p-bromobenzyl- α -D-mannopyranoside,⁶³ benzyl 3,4-anhydro-2-O-mesyl-6-O-trityl- α -D-altropyranoside,⁶⁴ 2,3'-anhydrosucrose.⁶⁵

3.4 Nitrogen, Sulphur and Selenium-containing Compounds. - The 5- and 6-substituted 3-amino-1,2,4-triazines 5 and 6,⁶⁶ the spiro-naphthoxazine 7,⁶⁷ the hetero Diels-Alder cycloadduct 8,⁶⁸ 5-azido-3-O-benzyl-6-O-tert-butyldiphenylsilyl-5-deoxy-1,2-O-isopropylidene- β -L-talofuranose,⁶⁹ 5-azido-6-O-benzoyl-3,5-dideoxy-3-fluoro-1,2-O-isopropylidine- α -D-glucofuranose,⁷⁰ kedarosamine (2,4-dideoxy-4-dimethylamino-L-fucopyranose) as the 3-O-(4-bromobenzoyl) derivative,⁷¹ 1,2:5,6-Di-O-isopropylidene- α -D-ribohexos-3-ulose phenylhydrazone,⁷² β -lactam 9 (from a diastereoselective [2+2] cycloaddition to a carbohydrate-based arylimine),⁷³ the D-arabino and D-ribo lactam derivatives 10 and 11,⁷⁴ the fully-protected iminosugar 12,⁷⁵ 2,3,4,5-tetra-O-acetyl-6-amino-6-deoxy-D-mannolactam,⁷⁶ 4,8-anhydro-3-

deoxy-3-nitro-D-lyxo-D-gluco-nonitol,⁷⁷ 4,6-di-O-acetyl-S-acetyl-2,3-di-S-ethyl-2,3,6-trithio-D-allose diethyldithioacetal,⁷⁸ 2,3,4,6-tetra-O-acetyl-1-S-benzhydroximoyl- α -D-glucopyranose,⁷⁹ 1-p-bromophenyl-(1,2-dideoxy- α -D-glucofuranosyl)2,1-d]imidazoline-2-selone **13**.⁸⁰



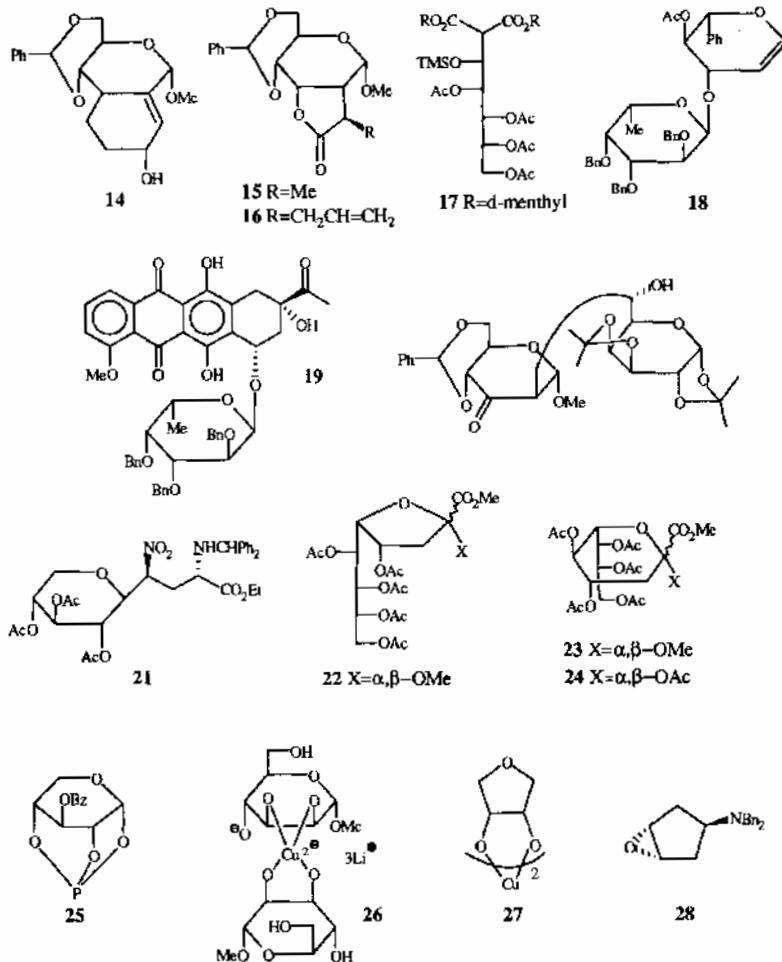
3.5 Unsaturated Sugars. -Methyl 3,6-di-O-benzoyl-2-deoxy- α -D-glycero-hex-2-enopyranoside-4-ulose.⁸¹

3.6 Branched-chain Sugars. The silicon-tethered radical cyclisation adduct **14**,⁸² 1-O-acetyl-2,4,5,6-di-O-isopropylidene-1-C-phenyl-D-glycero-D-ido-hexitol,⁸³ the butyrolactones **15** and **16**,⁸⁴ the D-arabinose derived **17**,⁸⁵ the diastereomerically pure disaccharide **18**,⁸⁶ and the α - and β -5'-phenyl analogues of daunomycin **19**,⁸⁶ and the C-linked disaccharide **20**.⁸⁷

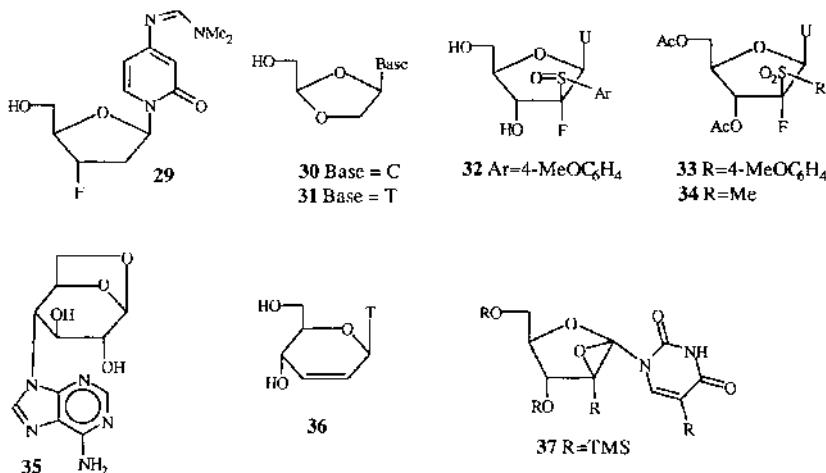
3.7 Sugar Acids and their Derivatives. - The C-glycosyl amino acid analogue **21**,⁸⁸ 2-deoxy-4,6-O-isopropylidene-3-O-methyl-7-C-phenyl-D-glycero-1-ido-heptono- γ -lactam,⁸⁹ methyl 5-acetamido-2,7-anhydro-3,5-didexy- α -D-glycero-D-galacto-2-nonulopyranosonate,⁹⁰ * Fischer methyl glycosidation of KDO was nonselective giving, after acetylation, α - and β -**22** and α - and β -**23**; direct acetylation of KDO gave, however, only pyranosides **24**.⁹¹ 3-O-Benzyl-6,7-dideoxy-1,2-O-isopropylidene-7-C-methylene- β -D-ido-octofuranuron-8,5-lactone,⁹² *N*-(n-octyl)-D-gluconamide.⁹³

3.8 Inorganic Derivatives. - Methyl 4,6-O-benzylidene-2,3-O-dibutylstannylene- α -D-glucopyranoside (improved R value),⁹⁴ 1,2,4-triphosphite **25**,⁹⁵ copper(II)-methyl α -D-mannopyranoside complex **26**,⁹⁶ copper(II)-1,4-anhydroerythritol complex **27** (in which the two sugar rings adopt an *anti*-relationship),⁹⁶ Ru₃(CO)₈(L) (L = 1,2-O-isopropylidene- α -D-glucofuranose or 1,2:5,6-di-O-isopropylidene- α -D-glucofuranose).⁹⁷

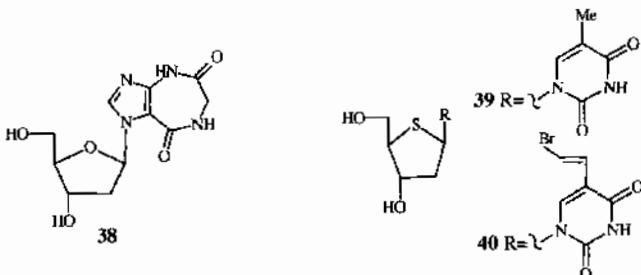
3.9 Alditols, Cyclitols and Derivatives Thereof. - 2,5:3,4-Dianhydro-D-altritol,⁹⁸ 2,5-anhydro-3,4-*O*-(1,2-ethanediyl)-D-mannitol,⁹⁹ pentaerythritol tetraacetate,¹⁰⁰ ribitol tetraacetate,¹⁰¹ xylitol tetraacetate,¹⁰¹ D-arabinitol tetraacetate,¹⁰¹ D, L-arabinitol tetraacetate,¹⁰¹ 2,4:3,5-di-*O*-isopropylidene-D-mannitol,¹⁰² hexa-*O*-acetyl-D-mannitol,¹⁰³ allitol hexaacetate,¹⁰⁴ D-mannitol hexaacetate,¹⁰⁴ D, L-mannitol hexaacetate,¹⁰⁴ D-iditol hexaacetate,¹⁰⁴ D, L-iditol hexaacetate,¹⁰⁴ D, L-glucitol hexaacetate,¹⁰⁴ D, L-altritol hexaacetate,¹⁰⁴ L-galacto-D-galacto-decitol (which is C₂-symmetric),¹⁰⁵ 6-*O*-benzyl-2,3-*O*-[(S)-camphanyliden]-1,4,5-tris-*O*-pivaloyl-D-*myo*-inositol,¹⁰⁶ D-3,6-di-*O*-benzyl-1-*O*-(S)-camphanyl-2-deoxy-2,2-difluoro-4,5-*O*-isopropylidene-*myo*-inositol,¹⁰⁷ cyclopentane 28.¹⁰⁸



3.10 Nucleosides and their Analogues and Derivatives Thereof. - 1-(β -D-Arabinofuranosyl)-6-methylcytosine,¹⁰⁹ 2'-deoxy-2'-methylene-cytidine,¹¹⁰ 2',3'-dideoxy-3'-fluorocytidine and the N^4 -dimethylaminomethylene analogue **29**,¹¹¹ the dioxolan-C and dioxolan-T variants **30** and **31**, both of which have O^3 -*endo* conformations,¹¹² 1-(3-deoxy-3-phenylseleno-2,5-di-*O*-pivaloyl- β -D-xylofuranosyl)uracil,¹¹³ 2',3'-dideoxy-3',5-difluorouridine,¹¹⁴ 5'-O-acetyl-4'-cyano-2',3'-didehydro-2',3'-dideoxyuridine¹¹⁵ the 2'-fluoro-2'-aryl sulfinyl and corresponding aryl and alkyl sulfonyl uridines **32**-**34**,¹¹⁶ 2,3'-didehydro-2',3'-dideoxyguanosine (complex with pyridine),¹¹⁷ guanosine 5'-phosphate (Ba salt),¹¹⁸ 2',3'-*O*-isopropylidene inosine,¹¹⁹ 8-bromo-2',3',5'-tri-*O*-acetyl adenosine and the guanosine analogue,¹²⁰ deoxyinosine 5'-phosphate (Na salt),¹²¹ the β -D-glucopyranose adenyl derivative **35** (as dihydrate),¹²² 2',3'-anhydroadenosine,¹²³ 5'-*O*-[*N*-(L-alanyl)-sulfamoyl]adenosine (a substrate analogue for alanyl-tRNA synthetase),¹²⁴ 2'-deoxy-8,2'-methanoadenosine and 2'-deoxy-8, 2'-ethanoadenosine.¹²⁵



The structures of two new anti-HIV analogues, 9-(2',3'-dideoxy-2'-fluoro- β -D-threopentofuranosyl)adenine and the corresponding hypoxanthine derivative, have been described.¹²⁶ The structure of the pyranosyl thymine analogue **36** has been reported and the structural comparison to AZT has been made; **36** is not, however, active against HIV 1 *in vitro*.¹²⁷ 9- β -D-Xylofuranosyltheophylline,¹²⁸ the unusual epoxysilane **37**,¹²⁹ the imidazo[4,5-e]diazepine **38**,¹³⁰ 1-(3'-deoxy-3'-C,2'-*O*-(1-methylethylene)- β -D-ribo-furanosyl)uracil,¹³¹ and the 4'-thio-2'-deoxynucleoside analogues **39** and **40**,¹³²



4 E.s.r. Spectroscopy

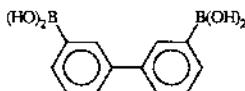
Crystalline rhamnose has been examined by e.s.r. and related techniques and the fate of the radicals produced by X-ray irradiation has been studied.¹³³ Gamma irradiation of glucose oligomers gave radical intermediates which were also trapped by 2-methyl-2-nitrosopropane. The results of this study provide the first step towards the elucidation of the radiolysis mechanism of starch.¹³⁴ E.s.r. has also been used to examine the degradation of a series of deoxy sugars and disaccharides in DMSO/Bu₄NOH. The nature of the radicals produced is dependent on both the anomeric configuration of the non-reducing moiety and on the position of linkages and deoxy sites.¹³⁵ Gamma radiolysis of sucrose in the solid state and in aqueous solution at 0 °C has been studied.¹³⁶

5 Polarimetry, Circular Dichroism and Related Studies

The chiroptical properties of benzoylated acyclic polyols have been reviewed (190 refs).¹³⁷ The violations of parity by weak interaction ensures that enantiomeric chiral molecules have different energies. These energy differences have been calculated for a variety of sugars and implications of this for the transition from a prebiotic racemic geochemistry to a homochiral biochemistry on terrestrial evolution have been discussed.¹³⁸ An empirical polarimetric method for determining the anomeric configuration of nucleosides has been described but the method is limited to nucleosides having a carbohydrate ring capable of undergoing periodate cleavage.¹³⁹

Vibrational Raman optical activity of biomolecules, including carbohydrates, has been reviewed (23 refs).¹⁴⁰ A general procedure for assigning both relative and absolute configuration to multiple stereocentres in acyclic aminopolyols based on application of the exiton chirality method is presented. The method has been applied to the side chain aminopolyol of a natural bacterial-derived terpenoid derivative.¹⁴¹

Diphenyl-3,3'-boronic acid **41** forms 1:1 complexes with cellobiose, maltose and lactose (but not sucrose), giving exiton coupling in c.d. spectroscopy owing to the immobilisation of the two phenyl rings of **41** in a chiral form.¹⁴²



41

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23

Separatory and Analytical Methods

1 Chromatographic Methods

1.1 General. - Reviews have appeared on: liquid, supercritical fluid, gas and thin layer chromatography and electrophoresis of carbohydrates (360 refs.);¹ supercritical fluid chromatography for the analysis of natural products, including sugars;² and diagnostic microscale reactions of carbohydrate derivatives as a complement to ordinary capillary g.c.-m.s. and h.p.l.c.-m.s. analyses.³

1.2 Gas-Liquid Chromatography. - All the following analyses were performed on capillary g.c. columns.

Incomplete esterification is a problem in the g.c. detection and quantification of apiose as its alditol acetate. A method has therefore been developed to quantify concurrently both the tetraacetate, i.e. with the tertiary hydroxy group unprotected, and the pentaacetate⁴. A sensitive, specific assay for 3-deoxyglucosone (3-deoxy-D-*erythro*-hexos-2-ulose) and 3-deoxyfructose in human urine and plasma involved reduction to the 3-deoxyhexitol derivatives (separately with NaBH₄ and NaBD₄), acetylation and g.c.-m.s. with selected ion monitoring. The proportions of these two compounds could be obtained from the data. 3-Deoxyglucosone is a reactive intermediate in the reaction of glucose with proteins; several milligrams are formed in the body per day and detoxified by reduction to 3-deoxyfructose.⁵ The application of conventional constituent sugar and methylation analyses (with g.c. detection of derived alditol acetates) to anthocyanin and flavonol glycosides has been reported.⁶

A method for determining the reducing end groups of oligosaccharides involved reduction (NaBD₄), hydrolysis, acetylation, and g.c.-m.s. analysis with selected ion monitoring for ions with *m/z* 188 and 218 that are characteristic of deuterated pentitol and hexitol acetates and not peracetylated aldoses. The DP of the oligosaccharide was determined using ratios of aldose- and alditol-derived peaks.⁷

A relationship between chemical structure and g.c. retention index has been developed for permethylated, peracetylated or pertrimethylsilylated alditols, so that a tentative identification of monosaccharides present at trace levels can be made.⁸

The relative stability of various pyruvate ketal substituents in polysaccharides to either permethylation-methanolysis or permethylation-reductive cleavage (Et₃SiH - Me₃SiOTf) has been

established. Generally the reductive cleavage procedure resulted in greater loss of pyruvate substituents. The mass spectra of the permethylated methyl 4,6-O-(β -carbomethoxyethylidene)-D-hexopyranoside and 1,5-anhydro-D-hexitol derivatives of glucose, galactose and mannose, and permethylated methyl 5,6-O-(β -carbomethoxyethylidene)-D-galactofuranoside and 1,4-anhydro-D-galactitol, were reported.⁹ The degree of substitution of partially acetylated or butanoylated, partially pentylated cyclodextrins was determined by the reductive cleavage method, a new work up procedure being employed that avoids loss of ester substituents as occurs with a methanol quench.¹⁰

The turnover rate for glucose in humans has been evaluated by infusion of [6,6- $^2\text{H}_2$]glucose and analysis as its aldononitrile acetate derivative by g.c.-m.s. with selected ion monitoring.¹¹ The products of partial acetylation of 1,2-O-isopropylidene- α -D-glucofuranose were identified by g.c.-m.s.¹²

The usefulness of measuring the ratios of D- and L-arabinitol, determined by g.c.-negative ion c.i.m.s. of the pertrifluoroacetylated derivatives on a chiral-phase capillary column, for detection of disseminated candidiasis, has been evaluated.¹³

A method for determining monoterpene and aromatic glycosides in grapes and wine was developed using synthetic β -D-glucosides, β -rutinosides and 6-O-(α -L-arabinofuranosyl)- β -D-glucopyranosides, and their aglycons, diluted into synthetic imitation wines. After isolation onto Amberlite XAD-2, analyses were conducted by g.c.-m.s. of the pertrifluoroacetate or pertrimethylsilyl derivatives.¹⁴ An application of this method to monoterpene glycosides in grapes utilized g.c. with both e.i. - and c.i.(NH₃) - m.s. detection.¹⁵ The legume oligosaccharides sucrose, raffinose, stachyose and verbascose were determined as their pertrimethylsilyl ether or pertrifluoroacetyl ester derivatives. The more volatile pertrifluoroacetates were subject to discrimination during split injection, leading to poorer reproducibility.¹⁶

5-Fluoro-2'-deoxyuridine in plasma was determined by g.c. - negative ion c.i. m.s. of the 3',5',N-tris(pentafluoropropionate) derivative with selected ion monitoring, using the [$1,3-^{15}\text{N}_2$] labelled derivative as internal standard.¹⁷

The retention times of the pertrimethylsilyl ether derivatives of seventeen disaccharides were determined for two liquid phases, and an attempt was made to relate these to structural features.¹⁸ A quantitative analysis of 2-deoxy-scyllo-inosose by g.c.-m.s. with selected ion monitoring was used to study its enzymatic synthesis, and its m.s. fragmentation was studied using the [$2,2-^{2}\text{H}_2$]-labelled derivative.¹⁹

Complex mixtures of urinary organic acids including many sugar acids, have been examined by g.c.-m.s. of their pertrimethylsilyl ether derivatives by use of a beam deflection time-of-flight spectrometer.²⁰

1.3 Thin-Layer Chromatography. - Diacetone ketogulonic acid (2,3:4,6-di-O-isopropylidene- α -L-xylo-hex-2-ulosonic acid), an intermediate in ascorbic acid manufacture, could be determined in aqueous samples by concentration on to a polymeric C₁₈ adsorbent and separation by 1D- or 2D-h.p.t.l.c.²¹

1.4 High-Pressure Liquid Chromatography. - References are grouped according to the class of sugar being analysed. Sometimes more than one class is analysed simultaneously, so that the section on neutral sugars etc., contains references to di- and oligo-saccharides, and that on oligosaccharides etc., includes references to oligomers containing acidic sugar residues.

H.p.l.c. on pellicular anion exchange packings with a strongly alkaline eluant and pulsed-amperometric detection (the Dionex system) has gained sufficient prominence to be given its own abbreviation (HPAEC), which is used herein.

1.4.1 General reviews. - A critical review (264 refs.) on h.p.l.c. methods for sugar analysis,²² and one on procedures for the analysis of mono- and oligo-saccharides²³ have been published.

1.4.2 Detection methods. - Various metallic wires were investigated for use in constant-potential amperometric detection of carbohydrates in HPAEC eluates. Copper proved best, and when conditions were optimized, picomole amounts of various sugars could be detected.²⁴ Conditions for post-column generation of fluorescence by reaction of mono- to tri-saccharides with an ethanolamine-boric acid reagent were optimized, and applied to the h.p.l.c. analysis (anion-exchanger, alkaline aq. borate eluant) of mono- and di-saccharides in wine. The detection of disaccharides was markedly improved if a post-column acid-catalysed hydrolysis reactor was added prior to detection.²⁵

1.4.3 Neutral sugars, amino-sugars, alditols and derivatives thereof. - The retention behaviour on both h.p.l.c and supercritical fluid chromatography of nine monosaccharides and three alditols on silica or bonded-phase nitrile, diol, nitro or phenyl silica columns (with evaporative light scattering detection) has been statistically analysed. Retention in both chromatographic systems was shown to be the sum of two mathematically independent physico-chemical phenomena, one related to the number of accessible hydroxy-groups, the other well quantified but not physico-chemically interpreted.²⁶

Reversed-phase h.p.l.c. with appropriate on-line immobilized oxidase enzyme reactors and an electrochemical detector to determine the hydrogen peroxide generated, proved sensitive (nM to pM detection limits), selective and rapid, and was applicable to the analysis of sugars in foodstuffs or

biological extracts. Example analyses were of: i) glucose and sucrose in pear juice using a reactor combining invertase, mutarotase and glucose oxidase enzymes; ii) galactose and lactose in soft cheese using a galactose oxidase reactor; iii) glucose and malto-oligosaccharides in beer using a reactor combining amyloglucosidase and glucose oxidase; and iv) fructose using a reactor combining glucose isomerase and glucose oxidase.²⁷

Mono-, di- and tri-saccharides were eluted from an Asahipak NH2P-50 column (a polyamine-bonded vinyl alcohol co-polymer gel formed by reaction of the gel with epichlorohydrin then reaction with pentaethylenehexamine) in a very similar order to that observed with an amine-bonded silica column but the peak shapes were better with the gel column. The recovery of aldoses was incomplete in both cases (as low as 20% for some sugars), but the gel column retained its efficiency during prolonged use and tolerated a wider range of eluent pH values.²⁸ The performance of the same gel column and a Zn²⁺-form polystyrene-based sulphonic acid resin column in separating a range of reducing and non-reducing sugars and malto-oligosaccharides (up to DP 7) was studied, and applied to the determination of carbohydrates in beer. Post-column addition of lithium hydroxide permitted pulsed amperometric detection down to 0.7-2.7 ng of analyte at a signal to noise ratio of 3.²⁹ The separation of a selection of nine mono- to oligo-saccharides and arabinitol on a newly developed 3-morpholinopropylsilyl-modified silica column using a borate containing eluent has been investigated. The new packing was chemically stable, unlike aminopropyl-bonded silica. The system was applied to determining glucose and/or sucrose in an infusion and in soft drinks.³⁰

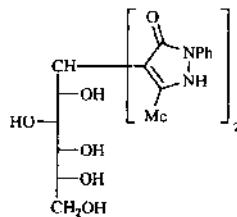
HPAEC has been used to separate [$1\text{-}^2\text{H}$]- and [$2\text{-}^2\text{H}$]-D-glucose on the basis of their differing pK_a values,³¹ nanomole quantities of neutral and amino-sugars and *N*-acetylneuraminic acid released by hydrolysis of glycoproteins,³² sets of all isomeric mono-*O*-methyl-D-glucoses and D-glucobioses, as well as three isomeric D-glucose monophosphates,³³ and glucose and mono-, di- and tri-*O*-(carboxymethylated)-glucoses released from three commercial carboxymethylcelluloses on hydrolysis.³⁴ In the last case, components were isolated, identified by permethylsilylation-g.l.c.-m.s., and used to determine response factors.

H.p.l.c. on an H⁺-form cation exchange resin with an acidic eluant was used to determine glucose and fructose, carboxylic acids, glycerol and ethanol in wine and grape musts.^{35,36}

Muramic acid [2-amino-2-deoxy-3-*O*-(1-carboxyethyl)-D-glucose], released from bacterial samples on hydrolysis, was determined by h.p.l.c.-plasma spray m.s. with selected ion monitoring, the chromatography being on a silica-based strong cation exchanger.³⁷ H.p.l.c. coupled with atmospheric pressure c.i.-m.s. gave the same molecular ion (*m/z* 179) for all hexoses, but their fragmentation patterns differed. The limit of detection was 3-5 ng for glucose and fructose.³⁸

Per-2-naphthoate derivatives of alditols from neutral and amino-sugars were best synthesized using (2-naphthoyl)-imidazole as reagent. They separated well by h.p.l.c. on silica and were detected fluorimetrically at the sub-picomole level.³⁹

A novel derivatization procedure for neutral and amino-sugars was omitted from the review of 1989 literature. It involves reaction with 3-methyl-1-phenyl-2-pyrazolin-5-one in alkaline conditions. Single products were formed from each sugar. The compound formed from D-glucose was shown to be 1 by n.m.r. and m.s. These derivatives were well separated by reversed-phase h.p.l.c. and were readily detected by u.v. or electrochemical methods.⁴⁰



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1.4.4 Glycosides. – A review on the chromatographic analysis of tea constituents focused particularly on h.p.l.c. methods and included sections on flavonoid glycosides and on caffeoyl, *p*-coumaroyl and galloyl quinic acids.⁴¹ Twenty two flavonol glycosides were identified by reversed-phase h.p.l.c. of the herbal medicine from *Ginkgo biloba*,⁴² while flavonol 2-*O*-glycosides from *Calendula officinalis* and *Sambucus nigra* flowers were separated by both reversed-phase h.p.l.c. and micellar electrokinetic capillary electrophoresis.⁴³ Potato glycoalkaloids in serum were concentrated on a cyanopropylsilica column then separated on a silica column.⁴⁴ The amphiphilic properties of a range of hexyl, octyl, decyl and dodecyl glycosides, disaccharide glycosides and 1-thioglycosides have been assessed from their reversed-phase h.p.l.c. retention behaviour.⁴⁵

1.4.5 Oligosaccharides and glycopeptides. – Oligosaccharide-alditols prepared from mono- to hexasaccharides containing acetamido-sugar and sialic acid residues were separated on a relatively newly introduced porous graphitized carbon column with a volatile eluant (H_2O -MeCN-CF₃CO₂H) that permitted preparative isolation of components. Isomers differing only by having either a (1→3)- or a (1→4)-linkage were separated.⁴⁶ The chromatography of malto-oligosaccharides (DP up to 10) and a range of mono- and di-saccharides on three size exclusion columns has been examined. Post-column addition of sodium hydroxide and pulsed amperometric detection were employed. Separation was by size exclusion with 0-40% aq. acetonitrile but by partition chromatography with ≥50% aq. acetonitrile, with the order of elution being reversed. A good separation of malto-oligosaccharides up to DP 19 was attained on a Waters Protein-Pak 60 with gradient elution (70 to

50% aq. acetonitrile.⁴⁷ Potential impurities in α -cyclodextrin used in pharmaceutical formulations, namely α - and β -cyclodextrin, glucose and malto-oligosaccharides up to DP7, were detected at the 0.1-1.2% w/w level by normal phase h.p.l.c. on an amino-cyano-alkyl-silica column with a refractive index detector.⁴⁸ Sucrose, raffinose, stachyose and verbascose were determined by h.p.l.c. on an amino-bonded silica column in connection with the monitoring of raffinose-family oligosaccharide levels during germination of lupin seeds.⁴⁹ Synthetic glycopeptides of 6-19 amino-acid residues bearing one of a number of different mono- and di-saccharides *N*-linked to an asparagine or *O*-linked to a serine residue were examined by reversed-phase h.p.l.c., the influence of the sugar residues on retention being studied.⁵⁰

HPAEC was used to separate *N*-linked oligosaccharides released from human serum glycoprotein by enzymic hydrolysis, and also products derived from them by degradation with specific glycosidases or acid hydrolysis.⁵¹ Neutral reduced di-to tetra-saccharides liberated from mucins by alkaline borohydride treatment were poorly retained on HPAEC, but a variety of sialylated reduced oligosaccharides were efficiently separated, and *N*-glycolylneuraminic acid containing compounds had strikingly delayed elution times in comparison with the corresponding *N*-acetyl-neuraminic acid containing analogues.⁵² Neutral oligosaccharides from human milk were separated by HPAEC with a strongly alkaline eluant (>100 mM aq. NaOH). A much lower base concentration (15 mM) was necessary for chromatography of oligosaccharide alditols released from glycoproteins by alkaline borohydride treatment, and even then this was ineffective for fractionating hexitols. Both free and reduced oligosaccharides could be detected at the picomole level. On-line desalting by an ion exchange membrane was found to be effective for preparative isolation of components for n.m.r. and m.s. analysis.⁵³ HPAEC coupled with thermospray m.s. via on-line desalting with an anion micromembrane suppressor (*cf* Vol. 24, p. 278) has been used for characterizing homologous 1,4- α -gluco-, 1,5- α -arabino- and 1,4- β -xylo-oligosaccharides of DP up to 6, 11 and 25, respectively.⁵⁴

The h.p.l.c. and h.p.l.c.-m.s. analysis of complex oligosaccharides as their *N*-(2-pyridyl)-1-amino-1-deoxy-alditol derivatives has been reviewed (in Japanese).^{55,56}

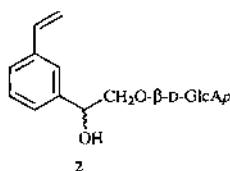
1.4.6 Disaccharides from glycosaminoglycans. — Unsaturated disaccharides released by enzymic hydrolysis of chondroitin sulphate have been separated on a primary amino-containing gel column,⁵⁷ those from hyaluronic acid, chondroitin sulphate and dermatan sulphate by reversed-phase h.p.l.c. on an amido-phase as their dansyl hydrazone derivatives with chemiluminescence detection,⁵⁸ and those from dermatan sulphate and heparin by ion-pair reversed-phase microbore h.p.l.c. coupled with ion-spray m.s. for use in monitoring their presence in patients treated with these polysaccharides intravenously.⁵⁹

1.4.7 Amadori and Maillard products. – The separation of synthetic 1-deoxy-1-(*N*-nitroso-*N*-glyciny) and -*N*-L-alanyl)-D-fructose and the results obtained using a thermal energy analyzer as a detector have been reported as a contribution towards the analysis of polar nonvolatile nitrosamines in food.⁶⁰ Chromatographic methods, predominantly h.p.l.c., for the analysis of Maillard reaction products, particularly ϵ -*N*-2-furanyl methyl-L-lysine, ϵ -pyrrolelysine, browning pigments and *N*-acetylmethionine, have been reviewed.⁶¹

1.4.8 Sugar acids. – A combination of enzymic hydrolysis (with Driselase, a commercial mixture of enzymes) and h.p.l.c. on an H⁺-form strong anion exchanger with an acidic eluant has been developed for the analysis of pectic substances. The neutral sugars elute as one peak, well ahead of galacturonic acid.⁶² Oligogalacturonic acids of DP 2-19 were separated on an h.p.l.c. gel filtration column with a diol-bonded silica packing.⁶³

A microscale method for detection and quantification of *N*-acetylneuraminic acid in glycoproteins used acid hydrolysis and HPAEC.⁶⁴ Alternatively *N*-acetylneuraminic acid released by hydrolysis of serum could be converted into fluorescent compounds (unspecified structures) by reaction with malononitrile, and determined by reversed-phase h.p.l.c. with fluorescence detection.⁶⁵

The following compounds were analysed in biological samples by reversed-phase h.p.l.c. with ion-suppression (i.e. an acidic eluant): paracetamol and four major metabolites, including a glucuronide with an ion-pair reagent in the eluant),⁶⁶ 1,3-divinylbenzene and its urinary metabolite **2**,⁶⁷ phenolphthalein and its glucuronide,⁶⁸ naproxen, its 6-O-demethyl-derivative and their ester and ether glucuronides,⁶⁹ and racemic flumequine and its acyl glucuronide.⁷⁰ H.p.l.c. on a silica column dynamically modified with cetyl trimethyl ammonium salt in the eluant was also used to determine naproxen and its glucuronide metabolites.⁷¹ An h.p.l.c.-continuous flow negative ion FAB-high resolution m.s. system, in which glycerol is pumped into the ion source, was used to detect the 3-sulphate and 1- and 3-glucuronide conjugates of benzo[a]pyrene in cell culture medium.⁷²



A review on the chromatographic determination of vitamins in food has a section on h.p.l.c. methods for ascorbic acid (vitamin C).⁷³ Ascorbic acid in artificial diets has been determined by reversed-phase h.p.l.c. with electrochemical detection,⁷⁴ and in potatoes and strawberries by ion exclusion h.p.l.c. (H⁺-form cation exchanger, acid eluant) with u.v. detection at 254 nm, with the

dehydroascorbic acid content being determined by the increase in ascorbic acid after reduction.⁷⁵

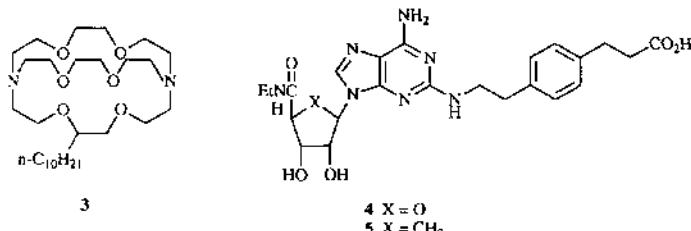
1.4.9 Inositol phosphates. — Separations have been achieved on strong anion exchange columns. Inositol mono- to hexakis-phosphates were eluted with ionic gradients, and detected by conductivity,⁷⁶ a phosphorus specific u.v. oxidizing reactor (using flow injection of an ascorbic acid/molybdate reagent and high intensity u.v. radiation) followed by spectrophotometry,⁷⁷ or, in the case of radiolabelled material, off-line liquid scintillation counting.⁷⁸ Inositol tris- to hexakis-phosphates were similarly separated and detected using a post-column dye detection system in which the complex between 2-(4-pyridylazo)resorcinol and Y³⁺ is disrupted by eluting anions which complex with the Y³⁺, lowering the absorption at 520 nm.⁷⁹ Simple methods for removal of extraneous material from tissue extracts prior to h.p.l.c. analysis of inositol phosphates on anion exchange columns employed acid precipitation followed by treatment with a cation exchange sorbent to remove unwanted material.⁸⁰

1.4.10 Antibiotics. — Reversed-phase h.p.l.c. analyses have been reported for the following dialkylamino-sugar-containing antibiotics: the anthracycline glycoside 3'-deamino-3'-(2(S)-methoxy-4-morpholinyl)doxorubicin and its possible 13-dehydro-metabolite,⁸¹ the macrolide antibiotics rokitamycin and josamycin as their dansylhydrazone derivatives.⁸² In addition, erythromycin ethyl succinate and its process impurities erythromycin A, the ethyl succinate esters of erythromycin B and C and *N*-(ethyl succinyl)-*N*-demethylerythromycin A were analyzed by ion-pair reversed-phase h.p.l.c.⁸³

Automated pre-column derivatization and h.p.l.c. analyses of aminoglycoside antibiotics have been reported, in an attempt to overcome problems associated with the instability of the derivatives. Reaction of amikacin with σ -phthalaldehyde and mercaptoethanol in a borate buffer, reversed-phase separation, and u.v. detection at 340 nm produced two peaks, one from incomplete derivatization. It was claimed that the method was successfully applied to other aminoglycoside antibiotics containing a primary amino-group, *i.e.* gentamycin, tobramycin and kanamycin.⁸⁴ Other workers have reported related derivatization and analysis conditions for tobramycin wherein mainly one peak was observed, though of unknown identify.⁸⁵

Amikacin can also be determined by reversed-phase h.p.l.c. following derivatization with 1-fluoro-2,4-dinitrobenzene.⁸⁶ The aminoglycoside antibiotics spectinomycin, hygromycin, streptomycin and dihydrostreptomycin were determined in bovine tissues by ion-pair reversed-phase h.p.l.c. using volatile ion-pair reagents, and by HPAEC.⁸⁷

1.4.11 Nucleosides. – Nine nucleotides and six nucleosides were simultaneously separated by h.p.l.c. on a polystyrene packing loaded with D2.2.2 (**3**), a hydrophobic cryptand. This cryptand binds metal ions in the eluant to form ion-exchange sites, so that both ionic and hydrophobic interactions occur. Excellent separations were observed.⁸⁸



The following compounds were analyzed by reversed-phase h.p.l.c.: adenosine and other purine nucleosides and bases in placenta,⁸⁹ methylated purine and pyrimidine nucleosides (concentrated on a phenylboronate sorbent) that were derived from degraded t-RNA and shown to be excreted in abnormal amounts in the urine of cancer patients,⁹⁰ *S*-adenosyl-L-methionine (concentrated on a strong cation exchange sorbent) in erythrocytes with *S*-adenosyl-L-ethionine as internal standard,⁹¹ 2',3'-didehydro-3'-deoxythymidine with either 2',3'-dideoxynosine⁹² or 3',5'-anhydrothymidine⁹³ as internal standard, and 2',3'-dideoxy-inosine and -adenosine in rat plasma after esterification with 2-(5-chlorocarbonyl-2-oxazolyl)-5,6-methylenedioxobenzofuran, using 3'-deoxythymidine as internal standard and fluorescence detection.⁹⁴ A variety of reversed-phase columns and eluants were evaluated for the analysis of five 2',3'-dideoxynucleosides (including 3'-azido-3'-deoxythymidine, AZT) and 5'-*O*-glucuronosyl-AZT, the behaviour of common and base methylated 2'-deoxynucleosides under the favoured separation conditions being recorded.⁹⁵ Preparative reversed-phase purifications of the liponucleotides AZT monophosphate diglyceride and 2',3'-dideoxycytidine monophosphate diglyceride have been reported.⁹⁶

The following compounds were analyzed by ion-pair reversed-phase h.p.l.c.: heart tissue nucleosides, nucleotides and their metabolites as well as creatine phosphate related compounds in a single run,⁹⁷ adenosine and its metabolites and nucleotides as well as creatine phosphate related compounds in biological samples, and in addition 2-chloro- and 2'-*O*-methyladenosine as potential internal standards,⁹⁸ adenosine in blood plasma using a blank generated by adenosine deaminase treatment of part of the sample,⁹⁹ AZT and its mono-, di- and tri-phosphates,¹⁰⁰ and 5-fluorouracil and its main metabolites 5-fluorouridine and 2'-deoxy-5-fluorouridine and its monophosphate in human plasma.¹⁰¹ In an automated extraction (onto a C₁₈-cartridge) and ion-pair reversed-phase h.p.l.c. analysis of the adenosine antagonist **4** in biological matrices, its carbocyclic analogue **5** was used as an internal standard.¹⁰²

Reversed-phase h.p.l.c. - thermospray m.s. analyses of radiation induced decomposition products of thymine and thymidine, which are modified in the base moiety,¹⁰³ and of 2',3'-dideoxycytidine in plasma¹⁰⁴ have been reported.

1.5 Column Chromatography. - A mathematical model had been developed for the effect of mutarotation on the separation of glucose and fructose on a Ca²⁺-form cation exchange resin at different temperatures. The model successfully predicted chromatographic behaviour and identified the equilibrium and rate constants for the interconversions of the various isomeric forms.¹⁰⁵ The adsorptive properties of the Ca²⁺-form of a cation exchange resin for glucose and fructose under conditions of high concentration have been measured, and used to model the continuous simulated moving bed separation used in industry.¹⁰⁶

The influence of cross-linking and bead size on the resolution of mannitol/sorbitol and arabinitol/xylitol mixtures on seven Ca²⁺-form cation exchange resins has been studied.¹⁰⁷ Alditols with at least four vicinal hydroxy-groups are retained more strongly than aldoses and ketoses when applied to anion exchange resins as their complexes with hexaammonium heptamolybdate. While the free sugars can be eluted with water, the alditols require 0.1 M aq. ammonia. Oxalic, citric and α-hydroxycarboxylic acids afford stable complexes with molybdate ions, so that they need to be removed from mixtures, if the separation of aldoses and alditols is to be achieved.¹⁰⁸

Radiolabelled inositol mono- to tris-phosphates in cancer cells were rapidly determined by concentration on a minicolumn of strong anion exchanger, and selective elution with an increasing concentration of buffer.¹⁰⁹ [³H]-Labelled phosphatidyl inositol and its 4-mono- and 4,5-bis-phosphates were isolated directly by DEAE-cellulose chromatography, or after alkaline hydrolysis, as the corresponding inositol phosphates by ion-pair elution from a reversed-phase minicolumn, the fractions being analysed by scintillation counting and determination of inorganic phosphate.¹¹⁰

2 Electrophoresis

Capillary zone electrophoresis (c.z.e.) separation of anions including carboxylates of sugar acids was achieved in a 3 minute run with indirect u.v. detection using a complex co-ion as an electroosmotic flow modifier that dynamically coats the capillary walls.¹¹¹ Inositol mono-, bis-, tris- and hexakis-phosphates were similarly separated using a tetradecylammonium bromide - borate buffer combination. Inositol 1- and 2-phosphate were easily separated.¹¹²

Heparin oligosaccharides (MW ≤ 3,500) prepared by heparinase digestion and synthetic heparin oligosaccharides and their analogues have been separated by c.z.e. at low pH values with u.v. detection. Optimum conditions were established using sialyloligosaccharides and unsaturated

heparin disaccharides as reference compounds. Capillary electrophoresis proved to be a 1000-fold more sensitive for the detection of these oligosaccharides than h.p.l.c. on an anion exchange resin.¹¹³ Unsaturated disaccharides released from different glycosaminoglycans by chondroitinase ABC digestion were simultaneously analysed by c.z.e. with u.v. detection after derivatization with 3-methyl-1-phenyl-2-pyrazoline-5-one (see reference 40 for the type of structure formed).¹¹⁴ Earlier reference to related work on aldoses and oligosaccharides (Vol. 25, p. 314, ref. 108) incorrectly referred to these derivatives as glycosylamines. The separation by c.z.e. of eight commercially available unsaturated disaccharides derived from heparin, heparan sulphate and derivatized heparins, was optimized, and the method was applied to enzymic digests of these polymers. As little as 50 fmol of a disaccharide could be detected by u.v. absorbance in this way.¹¹⁵

Linear and branched oligosaccharides were reductively aminated (NaBH_4CN) with 2-aminopyridine or 6-aminoquinoline, separated by c.z.e. on polyether coated fused silica capillaries, and detected by u.v. absorbance. The latter derivatives were detected with 8-fold greater sensitivity. Linear plots of DP vs log(electrophoretic mobility) were observed for *N*-acetylchitooligosaccharides. The other samples examined were high-mannose branched oligosaccharides from bovine ribonuclease B, and xyloglucan oligosaccharides from cotton cell walls.¹¹⁶ Thirteen aminoglycoside antibiotics were analyzed by c.z.e. in the anionic mode with indirect u.v. detection, by addition of the fluoro-surfactant FC135 to create reversed electroosmotic flow. FC135 bonds to the negatively charged capillary walls, reversing the wall charge and thereby permitting the otherwise difficult separation of the positively charged aminoglycosides. To enable neutral compounds to be determined as well, the cationic surfactant cetyl trimethylammonium bromide was added to form positively charged micelles that then migrated (i.e. micellar electrokinetic capillary chromatography or m.e.c.c.)¹¹⁷

M.e.c.c. has been applied to the qualitative and quantitative analysis of intact glucosinolates and desulphoglucosinolates in plant extracts,¹¹⁸ and flavonol 2-*O*-glycosides in flowers.⁴³ Addition of glucose to the micellar solution used for m.e.c.c. significantly improved the separation of nine nucleosides by extending the elution range and changing the selectivity. The mechanism for this altered separation is not yet understood.¹¹⁹

3 Other Analytical Methods

A simple, rapid fluorimetric assay for reducing sugars involved condensation with hydrazine then fluorescamine, and measurement of fluorescence intensity (excitation at 400 nm, emission at 490 nm).¹²⁰ Glucuronic, galacturonic and gluconic acids, as well as glucono-1,5-lactone and mannono-1,4-lactone were separately determined by measurement of fluorescence intensity of the

amide derivative formed by activation with a water-soluble carbodiimide, coupling with *N*-(1-naphthyl)ethylenediamine, and isolation from the reaction mixture by size exclusion gel chromatography.¹²¹

A flow injection analysis of serum glucose used an immobilized enzyme reactor containing glucose oxidase, and chemiluminescence detection of the hydrogen peroxide produced.¹²²

The structures of disaccharides and disaccharide alditols were revealed by periodate oxidation, reduction and analysis of the products by e.i.- and FAB-m.s. as their peracetyl or permethyl derivatives. The compounds gave simple m.s. with intense and characteristic ions from which the glycosidic linkage positions and ring size could be determined.¹²³

Polarographic studies of 2,3-diketo-L-gulonic acid (i.e. L-*threo*-hex-2,3-dulosonic acid, the hydrolysis product of dehydroascorbic acid) and the 2,3- and 3,4-endiol forms of its 1,5-lactone have been reported. On condensation with σ -phenylenediamine, these compounds form a single product, 2-(2-aminophenyl)-3-(L-*threo*-tritol-1-yl)quinoxaline, that gives a well defined cathodic wave suitable for analytical purposes.¹²⁴

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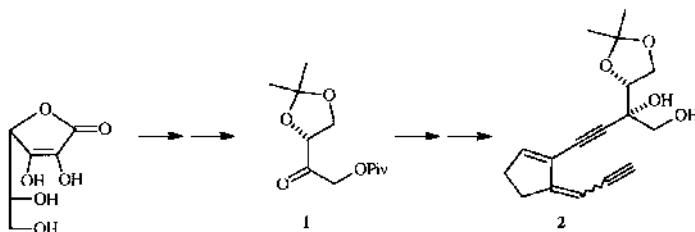
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Synthesis of Enantiomerically Pure Non-carbohydrate Compounds

A review has appeared on the use of 1,2:5,6-di-*O*-isopropylidene- α -D-*ribo*-hexos-3-ulose as a chiral template for synthesis¹ and the potential of cyclitols in the synthesis of a range of natural products has been summarized.² "Novel reactions of carbohydrates discovered *en route* to natural products" is the intriguing title of a paper describing approaches to tetrodotoxin from 1,6-anhydro-D-mannose.³

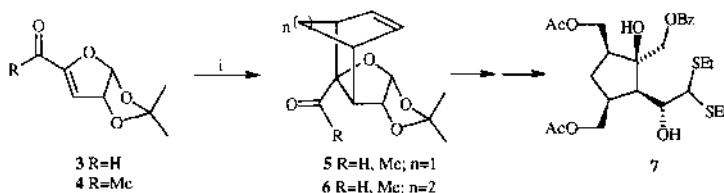
1 Carboyclic Compounds

D-Isoascorbic acid has been used, with ketone **1** as an intermediate, in the synthesis of (E)- and (Z)-**2**, structural analogues of the cyclopentyl core of neocarzinostatin (Scheme 1).⁴



Scheme 1

The furanoside-based dienophiles **3** and **4** undergo stereoselective Diels-Alder cycloaddition with cyclopentadiene and 1,3-cyclohexadiene to give exclusively the *exo*-adducts **5** and **6** respectively; adduct **5** ($n=1$) has been converted to the complex cyclopentane **7** (Scheme 2).⁵ A lengthy synthesis of PGF₂ α from D-mannitol has been described with the carbohydrate unit contributing stereochemical centres in both the cyclopentane ring and the side chain.⁶

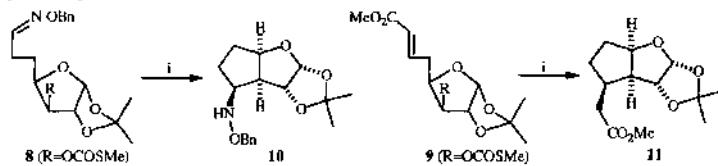


Reagents. i, cyclopentadiene or cyclohexadiene

Scheme 2

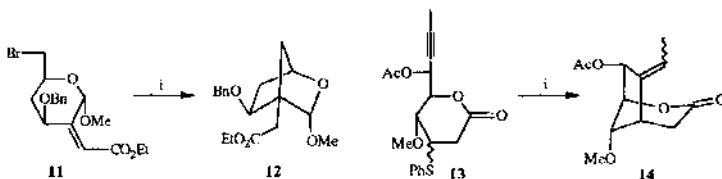
This year sees a number of examples of the use of free radical cyclisations in the synthesis of complex carbocycles. Oxime ether **8** and acrylate **9**, both derived from D-glucose, undergo

5-*exo* cyclisation to give **10** and **11** with the stereochemistry as shown in Scheme 3 predominating. Use of either a simple alkene or an enol ether as a radical acceptor proved to be less efficient.⁷ 5-*Exo* cyclisation across a sugar ring has been used to generate cyclopentyl derivatives **12**⁸ and **14**⁹ (Scheme 4). The nucleophilicity of the C-3 radical derived from **13** corresponds to a reversal of the reactivity normally associated with this electrophilic site (β to a carbonyl moiety).



Reagents: i, Bu_3SnH , AIBN

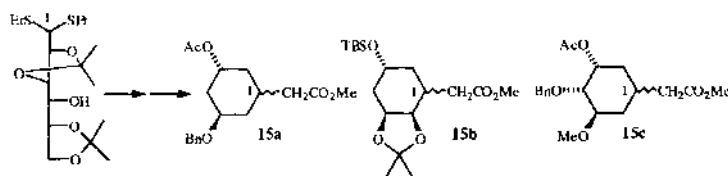
Scheme 3



Reagents: i, Bu_3SnH , AIBN

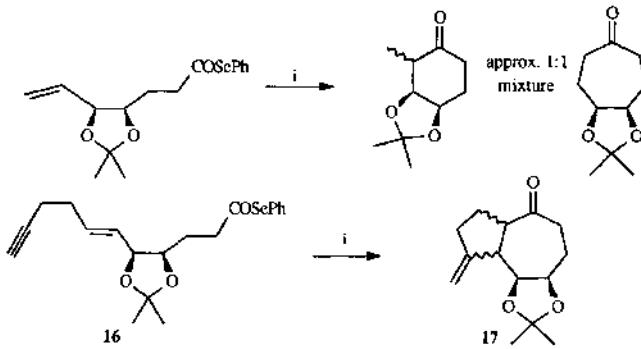
Scheme 4

6-*Exo* cyclisations involving derivatives of 2,3:5,6-di-*O*-isopropylidene-D-glucose diethyl dithioacetal provides a versatile strategy for the construction of the range of cyclohexanes **15a-c** (sugar numbering shown), molecules that may also be viewed as branched chain cyclitols.¹⁰



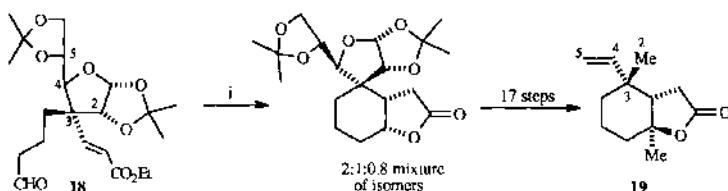
Acyl radicals, produced by fragmentation of acyl selenides, such as **16**, derived from 2,3-*O*-isopropylidene-*L*-*erythro*-furanose, undergo 6-*exo* and 7-*endo* cyclisation leading to cyclohexanones and cycloheptanones respectively. Selenide **16**, incorporating an alkynyl chain extension, leads to bicycle **17** (as a mixture of four diastereomers) *via* a 7-*endo*-5-*exo* tandem cyclization (Scheme 5).¹¹ Reductive cyclization of aldehyde **18** (prepared from D-glucose), which proceeds formally *via* a Sm-complexed alkoxy-stabilized radical, has been exploited in a

synthesis of (-)-anastrephin 19 (showing sugar numbering), although only modest selectivity was observed in the key step illustrated (Scheme 6). 7a-Epianastrephrin was also been prepared.¹²



Reagen. i, Bu₃SnH, AIBN

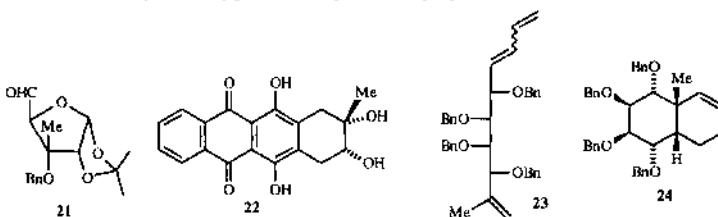
Scheme 5



Reagen. i, SmI₂, iso-PrOH, HMPA, THF

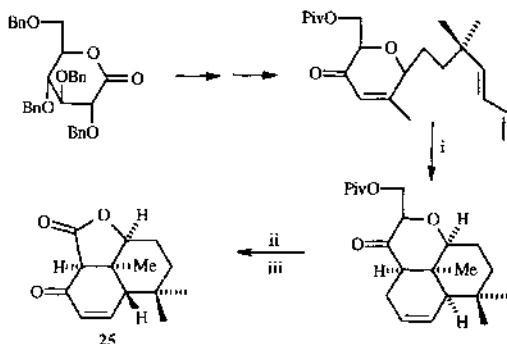
Scheme 6

Stereoelectronic and conformational aspects of the Ferrier rearrangement route leading to polysubstituted cyclohexanones have been studied¹³ and the cyclohexyl-fused anthracyclinone 22 has been synthesized using the branched sugar 21 (from D-glucose). A sequence involving two condensation/benzylic deoxygenation steps was employed.¹⁴



Intramolecular Diels-Alder reactions continue to be of value in carbocycle synthesis. Thermolysis (200°C, PhMe) of 23, prepared from D-galactose, gave octahydronaphthalene 24.¹⁵

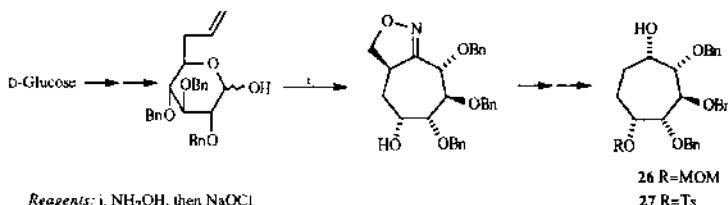
and Fraser-Reid has described the use of an intramolecular Diels-Alder reaction as a key step in the synthesis of **25** in work directed towards forskolin (Scheme 7).¹⁶



Reagents: i, heat; ii, Cr(VI), AcOH; iii, NaOMe

Scheme 7

Intramolecular nitrile oxide cycloaddition combined with differential hydroxyl manipulation has provided the cornerstone of an approach to both of the functionalized cycloheptanols **26** and **27** which have been converted to (+)- and (-)-calstegine B2, respectively (see Section 5) (Scheme 8).¹⁷

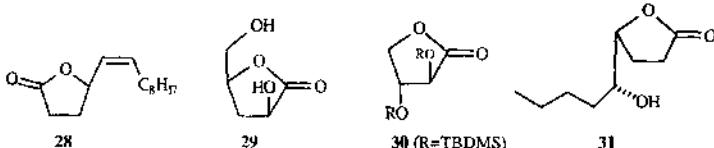


Reagents: i, NH_2OH , then NaOCl

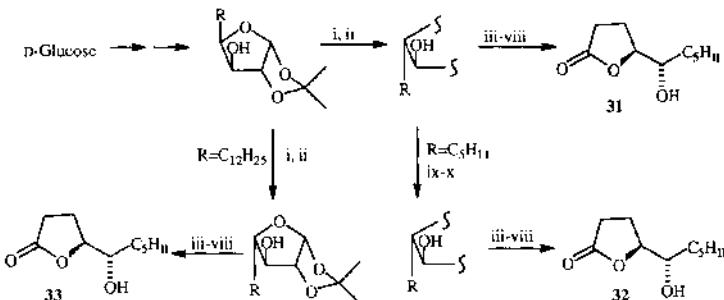
Scheme 8

2 γ - and δ -Lactones

A synthesis of the Japanese beetle pheromone, japonilure **28**, from D-ribose has been described,¹⁸ and the same group have synthesized (2*S*, 4*S*)-2-hydroxy-4-hydroxymethyl-4-butanolide **29** (3-deoxy-D-threo-penteno- γ -lactone), a hunger substance, from D-ribono-1,4-lactone.¹⁹



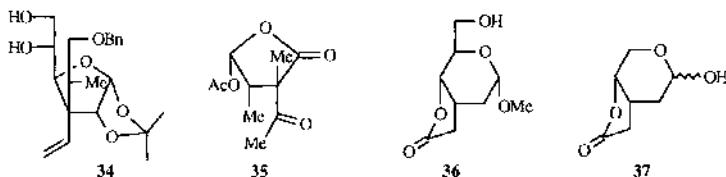
(+)-L-Factor **31** has been synthesized from both butanolide **30**²⁰ and D-glucose.²¹ The glucose-based route has been adapted to provide the (4R, 5S) diastereomer **32** as well as the structurally related butanoide, muricatacin **33** (Scheme 9).



Reagents: i, Tf₂O, py; ii, diisoamylborane, H₂O₂, NaOH; iii, NaH, BaCl; H₃O⁺; v, NaIO₄; vi, (EtO)₂POCH₂CO₂Et, NaH; vii, TFA, H₂O; ix, (COCl)₂, DMSO; x, NaH

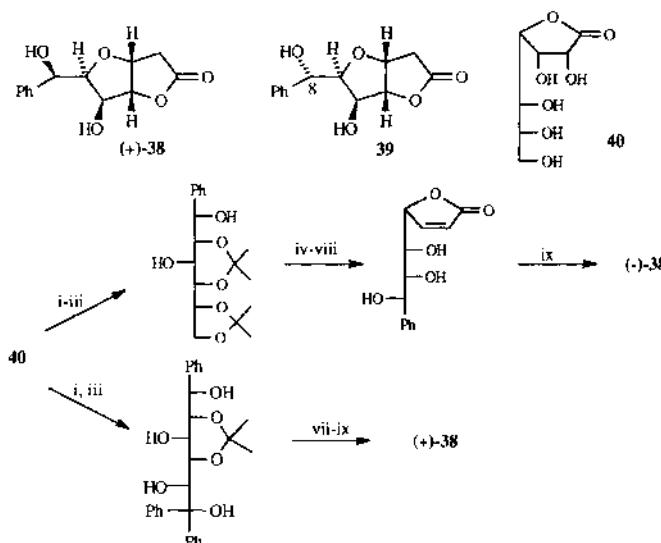
Scheme 9

A synthesis of acetomyein **35**, together with three stereoisomers, has been achieved using the D-glucose based precursor **34**.²² The known branched glycoside **36** has been used in the synthesis of lactone **37** which has then been used, *via* a Pictet-Spengler cyclocondensation with tryptamine, in a new approach to the corynantheine and heteroyohimbine classes of indole alkaloids.²³



Both the elucidation of the structure and the synthesis of goniofufurone are tasks that have attracted widespread interest this year. The absolute configuration of both (+)-goniofufurone **38** and 8-epi-goniofufurone **39** was established by Shing²⁴ by unambiguous syntheses of the **unnatural** enantiomers of **38** and **39**, starting from D-glycero-D-gulo-heptono-γ-lactone **40**.^{24,25}

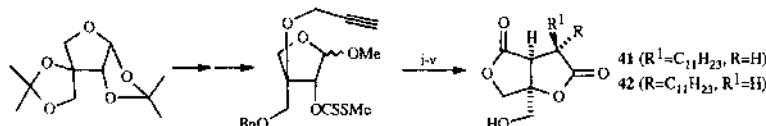
Shing has used this same commercially available starting material and, by clever juxtaposition of the key functional groups, has synthesized naturally occurring (+)-**38** in 12.7% overall yield (Scheme 10, also showing route used to synthesize (-)-**38**).²⁶



Reagents: i, Me₂CO, ZnCl₂, H₃PO₄; ii, NaBH₄; iii, NaIO₄ then PhMgBr; iv, PCC, then NaBH₄, CeCl₃; v, Ac₂O, py, then HOAc-H₂O; vi, MeONa, MeOH; vii, NaIO₄; viii, Ph₃P=CHCO₂Me; ix, DBU

Scheme 10

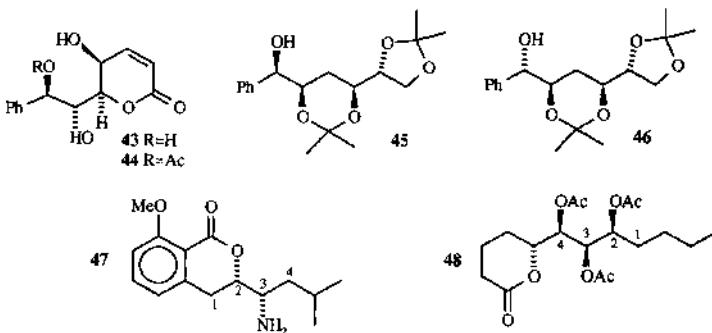
Similar work - a synthesis of (-)-38 to establish the configuration of the natural product - based on 1,2-O-isopropylidene-D-glucose has been described by Jäger; this latter sequence requires 6 steps (11% overall yield).²⁷ D-Glucose has, more recently, been used by Murphy to synthesize (+)-39 (13 steps) with key steps being the use of a redox process to correct the stereochemistry at C-8 of 39 and an intramolecular Wittig reaction to construct the lactone ring.²⁸ The synthesis of two rigid diacylglycerol analogues 41 and 42 as protein kinase C inhibitors has been achieved starting from 1,2,3,5-di-O-isopropylidine- α -D-threo-apiofuranose using a 5-exo radical cyclisation to construct the bicyclic framework. Cuprate-mediated addition to introduce the C₁₁-side chain was nonselective (Scheme 11).²⁹



Reagents: i, Bu₃SnH, AIBN; ii, SnO₂ then MnO₂; iii, C₁₀H₂₁MgBr, CuCl; iv, HCl; v, PCC then H₂, Pd/C

Scheme 11

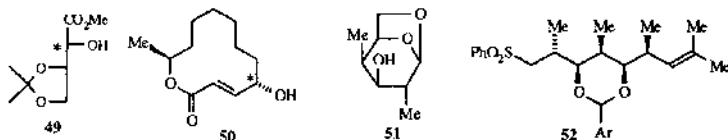
The absolute configurations of the δ -lactones, goniotriol **43** and 8-acetylgoniotriol **44** have been assigned by Shing *via* unambiguous syntheses of their enantiomers, again based on D-glycero-D-gulo-heptono- γ -lactone **40**.³⁰ The synthesis of the partially-protected polyols **45** and **46** as intermediates in the construction of goniofufurone and goniopyrpyrone has also been described.³¹ The synthesis of the aminodihydrocoumarin **47** (sugar numbering shown), the amino component of A1-77-B, has been synthesized from D-ribose³² and perbenzylated D-glucose has been utilized in a synthesis of (+)-boronolide **48** (sugar numbering shown).³³



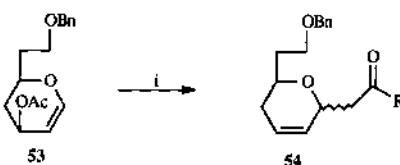
3 Macrolides, Macrocyclic Lactams and their Constituent Segments

Patuloide C **50**, an antifungal macrolide, has been synthesized from ascorbic acid *via* ester **49**; the key stereocentre is marked (*).³⁴ The C(1)-C(7) fragment **52** ($\text{Ar}=4\text{-MeOC}_6\text{H}_4$) relating to oleandomonolide and lankanolide has been synthesized from the anhydrogalactose derivative **51**.³⁵

The synthesis of a C(1)-C(15) fragment for swinholide A and scytophyycin C has



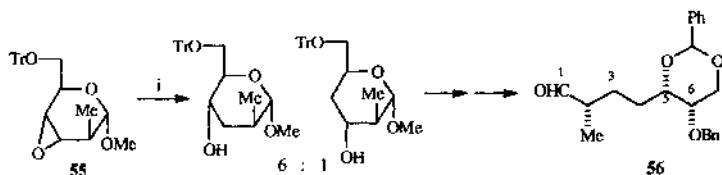
employed a vinylogous Mukaiyama aldol reaction for the conversion of **53** to **54** (Scheme 12). This reaction may be classified as a 'carbon-Ferrier' rearrangement, though **53** is of non-carbohydrate origin.³⁶



Reagents: i, $ZnBz_2$ or $TiCl_4(OPr)_2$, $H_2C=(OTMS)R$, where R=OMe, H

Scheme 12

The first total synthesis of the benzoquinonoid ansamycin antibiotic herbimycin A has been reported.³⁷ Methyl α-D-mannopyranoside played a key role in the synthesis of the C(9)-C(15) segment 56 (mannose numbering) which required regioselective reduction of the C(2)-branched epoxide 55 followed by homologation at C(6) (sugar numbering) (Scheme 13).

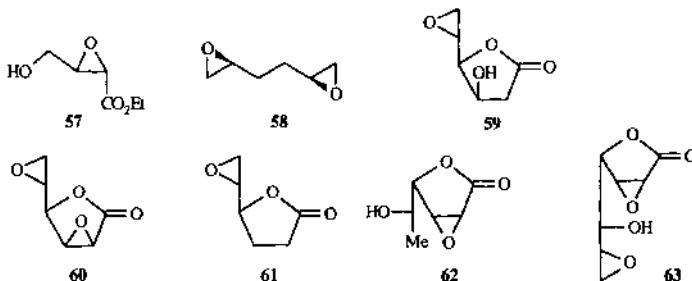


Reagents i, Diisoamyl borane, $NaBH_4$

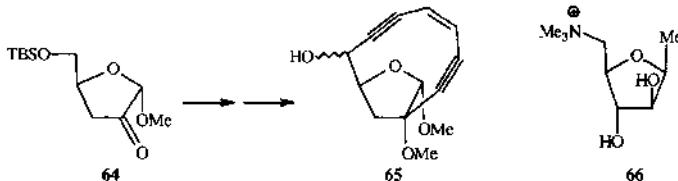
Scheme 13

4 Other Oxygen Heterocycles, including Polyether Ionophores

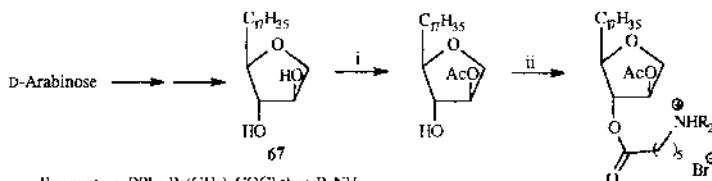
Isoascorbic acid (Na salt) has been converted to oxirane 57 which has been utilized in a cephalosporin synthesis.³⁸ An improved synthesis of the versatile C_2 -symmetric bis(oxirane) 58 has been described from D-mannose³⁹ and a series of useful mono and bis(oxiranes) 59–63 has been generated from either D-glucono- δ -lactone or L-rhamnonolactone.⁴⁰



Ketone **64** has been synthesized from D-xylose and used to construct the tetrahydrofuranyl calicheamicin analogue **65**.⁴¹ Last year, Fleet described a synthesis of muscarine from L-rhamnose and this has now been extended to (3R)-hydroxymuscarine **66** (tosylate salt).⁴² Both syntheses (and full details of the muscarine work have also appeared) proceed without the necessity of functional group protection.



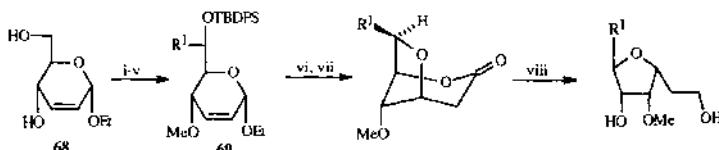
Seven cyclic analogues of platelet-activating factor (PAF) have been obtained using a chemoenzymatic strategy starting from D-arabinose. This is illustrated in Scheme 14 for the C(2)-acetylated series where porcine pancreatic lipase (PPL) has been used to achieve regioselective functionalisation of diol **67**.⁴⁴



Reagents. i, PPL; Br(CH₂)₅COCl then R₂NH

Scheme 14

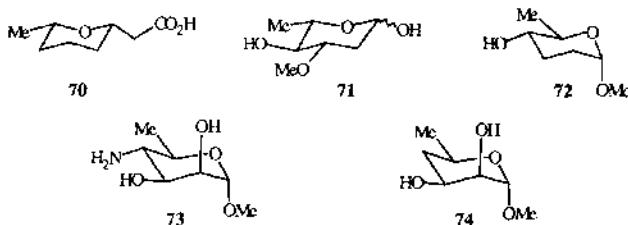
The known hex-2-enopyranoside **68** provides a stereoselective entry to substituted tetrahydrofurans based on an intramolecular 1,4-addition to establish the new oxygen heterocycle followed by manipulation of the lactone moiety (Scheme 15). Both stereoisomers [at C(6)] of **69** were available, but the *exo*-isomer shown underwent more rapid cyclisation, presumably for steric reasons.⁴⁵



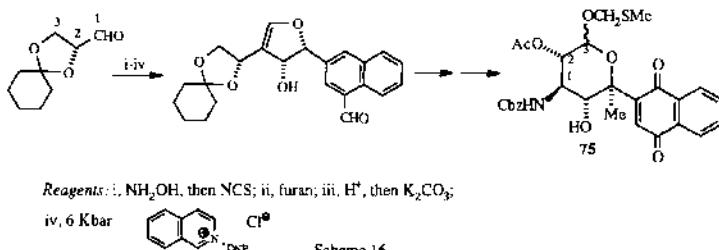
Reagents: i, TBDMSCl, NEt₃; ii, MeI, NaH then Bu₄NF; iii, (COCl)₂, DMSO then R¹Li or R¹MgX; iv, Ac₂O, py; v, Na₂CO₃, MeOH then t-BuPh₂SiCl (TBDPSCl), imidazole; vi, mCPBA; vii, Bu₄NF; viii, i-Bu₂AICl

Scheme 15

Last year saw the application of D-xylose to the synthesis of sesbanimide and this strategy has been extended to encompass ring C variants.⁴⁶ A new synthesis of the cosmetic component **70** (a well-studied synthetic target that is derived from the civit cat) from 3,4-di-O-acetyl-L-rhamnal has been developed⁴⁷ and the same group have described the use of L-rhamnal for synthesis of L-oleandrose **71**.⁴⁸ Methyl 6-deoxy-2,3-O-isopropylidene- α -D-mannopyranoside provides a flexible precursor to a series of deoxysugars (tetrahydropyrans), α -D-amicetoside **72**, α -D-perosaminoside **73** and α -D-janoside **74**.⁴⁹

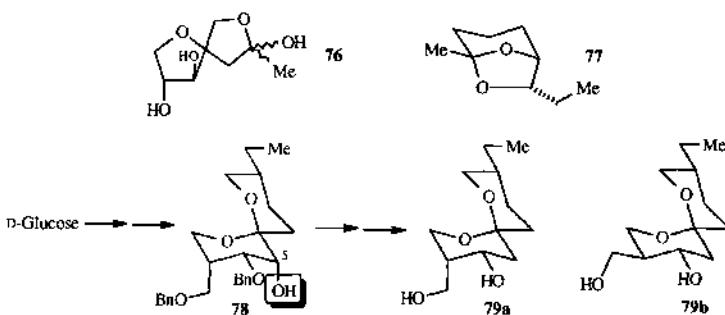


The CDEF fragment **75** of the anthracycline antibiotic nogalamycin has been described, with D-glyceraldehyde providing the three stereocentres marked.⁵⁰ An interesting feature of this sequence was the use of a high pressure (6 Kbar) Bradsher cycloaddition to establish the arene-sugar linkage (Scheme 16).

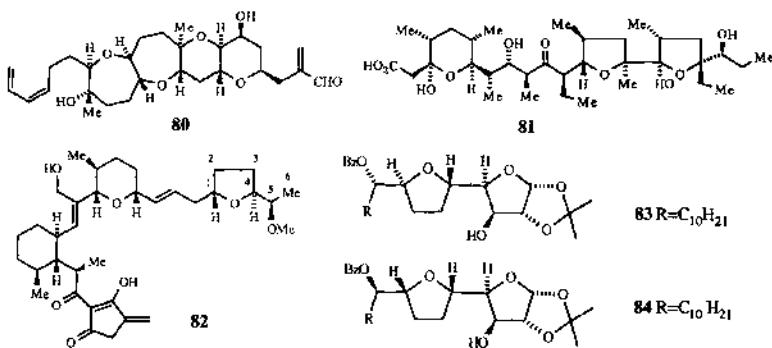


Scheme 16

Rabbit muscle aldolase is proving to be a synthetically important tool and this methodology has now been used to synthesize the structurally unusual spiroketal, sphydrofuran **76**,⁵¹ and a synthesis of (+)-endobrevicomine **77** has been achieved using erythritol.⁵² A very clever application of the A2 effect (the preference for a trans-dixial arrangement between C(1)-OH and C(2)-OH on a pyranose ring) to control spiroketal stereochemistry has allowed synthesis of (-)-talaromycin A **79a** from D-glucose.⁵³ The key here was retention of the C(5)-OH in **78** until the spiroketal centre had been established. Deoxygenation was then carried out under very mild conditions to avoid compromising this thermodynamically less stable spiroketal configuration towards equilibration that would lead to talaromycin B **79b**.

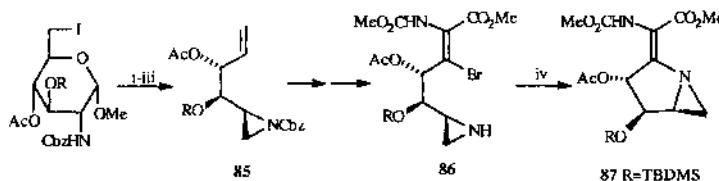


This year has seen a number of very significant achievements in the polyether area. Nicolaou has described the total synthesis (from D-mannose) of hemibrevitoxin **80**⁵⁴ - a major advance in this field - and studies culminating in the synthesis of lysocellin **81** have also been reported.⁵⁵ In a series of three papers, Kishi has described synthetic efforts directed towards the halichondrin class of polyether antitumour agents. Fragments of these complex molecules have been prepared by the Harvard group using a variety of modern synthetic tools.⁵⁶ This year has also seen full details published of the first total synthesis of tetrodomyycin **82**. L-Rhamnal diacetate was the only carbohydrate unit used and this was incorporated into the tetrahydrofuran component of **82**; the L-rhamnal carbon atoms are shown (sugar numbering).⁵⁷ D Glucose has been used to synthesize the two carbohydrate-derived units **83** and **84** as part of a projected synthesis of the tetrahydrofuran acetogenins.⁵⁸



5 Nitrogen Heterocycles

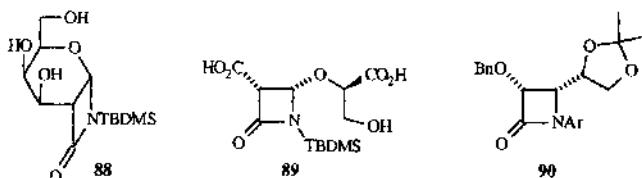
The synthesis of the aziridinyl-based core **87** of azinomycin A and B has been described (Scheme 17). The illustrated 6-iodo-6-deoxy-D-glucosamine derivative underwent fragmentation and ring-closure to provide aziridine **85**. Oxidative cleavage of **85**, followed by Wadsworth-Horner elaboration and bromination, afforded **86** which underwent an intramolecular addition-elimination to generate **87**.⁵⁹



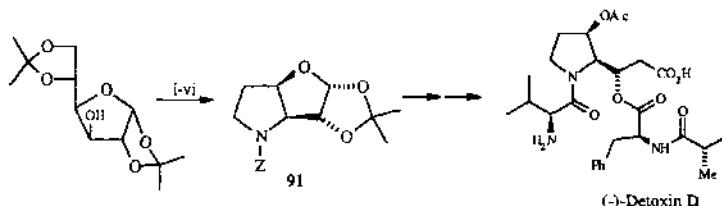
Reagents: i, Zn, EtOH; ii, NaBH₄; iii, DEAD, PPh₃; iv, DABCO

Scheme 17

Cycloadducts **88** (from glycals and isocyanates) undergo a two-stage oxidation (NaIO₄ followed by NaOCl) to provide β -lactams **89**⁶⁰ and this chemistry has been used in clavam synthesis.⁶¹ Full details of synthesis of carbapenem precursors from aldono-1,5-lactones have also appeared.⁶² N-Aryl Schiff bases (derived from D-glyceraldehyde) undergo efficient [2+2] cycloaddition to ketenes (e.g. BnOCH=C=O) to afford β -lactams **90**. This process, which has been carried out on 100–500 g scale, was shown to benefit greatly from exposure to microwave radiation.⁶³



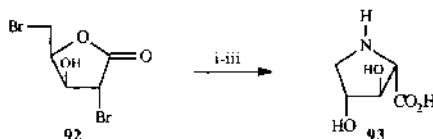
Diacetone D-glucose has been used to construct the pyrrolidine unit **91** (Scheme 18) which was then converted to (–)-detoxin D₁, the most active component of the detoxin complex.⁶⁴



Reagents: i, PCC; ii, NaBH₄, then MsCl; iii, H₃O⁺; iv, PPh₃, CBr₄, then NaN₃; v, RaNi then NaOAc; vi, CbzCl; vii, PPh₃, I₂, imidazole, then Bu₃SnH, AIBN

Scheme 18

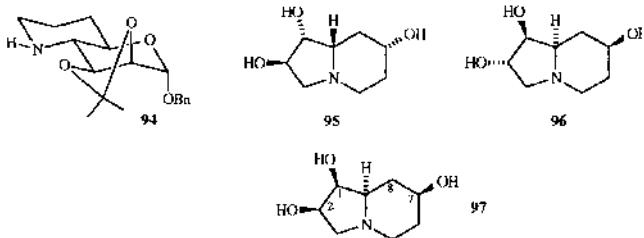
2,5-Dibromo-2,5-dideoxy-D-*xylono*-1,4-lactone **92** has been converted (in three steps) to (2S,3R,4R)-3,4-dihydroxyproline **93** (Scheme 19).⁶⁵



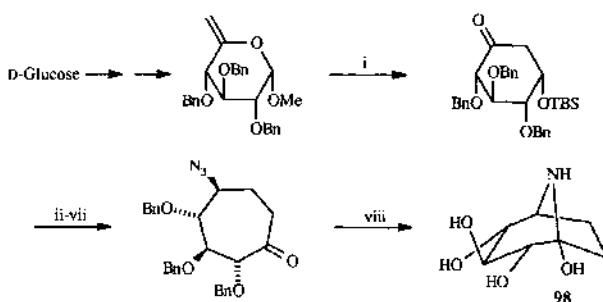
Reagents: i, NaN_3 ; ii, H_2 , 5% Pd on C; iii, Ba(OH)_2

Scheme 19

This year has also seen a significant level of activity in the castanospermine and nojirimycin area. Synthetic developments in the polyhydroxylated indolizidine field (castanospermine) have been reviewed (94 refs)⁶⁶ and Burgess has also described synthesis of 1,6-diepicastanospermine, 1,6,8-trepicastanospermine, 1,6,7,8-tetraepicastanospermine.⁶⁸ An efficient (15 steps, 20% overall yield) route to **94**, an intermediate in the synthesis of (-)-swainsonine has been described.⁶⁹ Swainsonine analogues have also been reported this year and D- and L-arabinose have been used to synthesize the novel C-7 hydroxylated derivatives **95** and **96** and their enantiomers.⁷⁰ The 8-deoxy-7-hydroxy analogue **97** of swansonine has been synthesized⁷¹ from D-isoascorbic acid and the same paper also details a synthesis of racemic 6,8-dideoxycastanospermine.



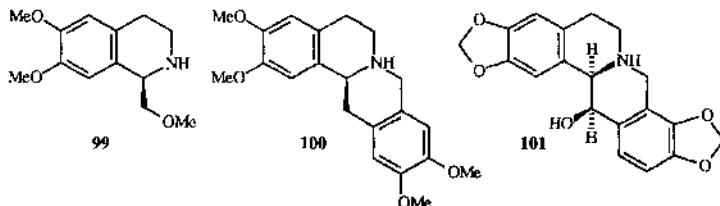
Myo-inositol has been used as the basis of a synthesis of both (+)- and (-)-nojirimycin and the corresponding 1-deoxy variants.⁷² The unnatural isomers [(-)-nojirimycin and (-)-1-deoxynojirimycin] possess moderate-to-high inhibitory glycosidase activity. The polyhydroxylated nortriapane alkaloid (-)-calystegine B₂ **98** has been synthesized from D-glucose (Scheme 20).⁷³ Key reactions include a Ferrier reaction to establish the cyclohexanone ring and cyclopropanation of a silyl enol ether to affect ring expansion. D-Glucose has been used, in a quite different approach, to prepare both (+)- and (-)-calystegine B₂.¹⁷



Reagents: i, $\text{Hg}(\text{OCOCH}_3)_2$, AcOH , H_2O ; ii, LDA, TMSCl; iii, $\text{Et}_2\text{Zn}, \text{CH}_2\text{I}_2$; iv, FeCl_3 then NaOAc , MeOH ; v, H_2 , Pd/C ; vi, MsCl , py then NaN_3 ; vii, Bu_4NF then PCC; viii, H_2 , Pd on C

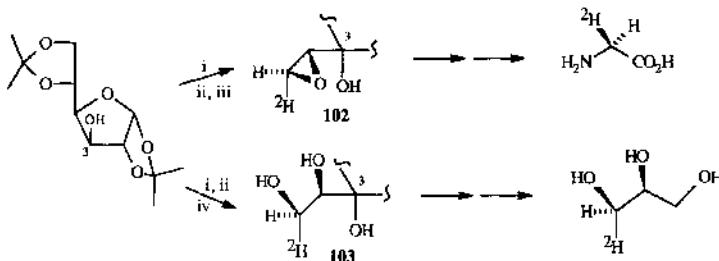
Scheme 20

Finally, D-ribonolactone has been used to synthesize (R)-calycotamine **99**⁷⁴, (S)-xylopinine **100**⁷⁴ and epi- α -decumbensine **101**.⁷⁵ The synthesis of other tryptamine-based indole alkaloids has been mentioned earlier.²³



6 Acyclic Compounds

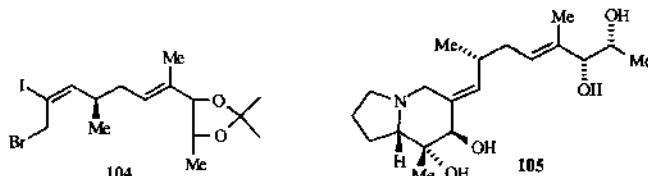
This year has seen the application of carbohydrates in the synthesis of enantiomerically pure acids, amino acids and diols, including those containing isotopic labels. 1,2:5,6-Di-*O*-isopropylidene- α -D-glucofuranose has been converted to diastereomerically pure epoxide **102** and diol **103** and the reactivity of these units has been exploited for the synthesis of enantiomerically pure labelled glycine and acetic acid, as well as 1,2-diols (Scheme 21).⁷⁶



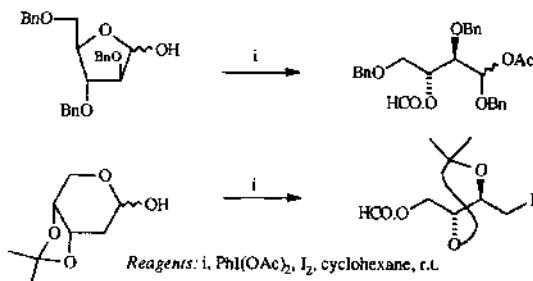
Reagents: i, PCC, then $\text{HC}\equiv\text{CMgBr}$ then H_2O ; ii, LiAl^2H_4 ; iii, mCPBA; iv, OsO_4 , NMMNO

Scheme 21

4-Deoxy-D-threose provides the backbone of diol unit **104** which forms the side chain of (+)-allopumiliotoxin **105**.⁷⁷

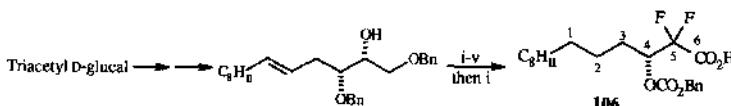


The generation and subsequent fragmentation [by cleavage of C(1)-C(2) bond] of anomeric alkoxy radicals provides a flexible entry into a range of acyclic polyhydroxylated derivatives.⁷⁸ This is illustrated in Scheme 22 and noteworthy is the formation of primary iodides in fragmentations involving 2-deoxy sugars; protected 2-hydroxy sugars lead to hemiacetal derivatives.



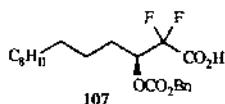
Scheme 22

The fluoro-containing β -hydroxy acid derivatives **106** and **107** have been synthesized from triacetyl D-glucal and methyl α -D-galactoside respectively. The strategy used is illustrated in Scheme 23 for **106** with the key fluorination step being carried out on the corresponding ketone using DAST.⁷⁹

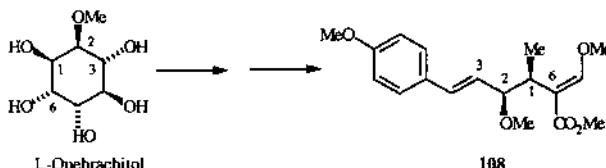


Reagents: i, Jones reagent; ii, Et_2NSF_3 ; iii, H_2 , Pd/C ; iv, TBDMSCl , DMAP; v, BnOCOCl , then H_3O^+

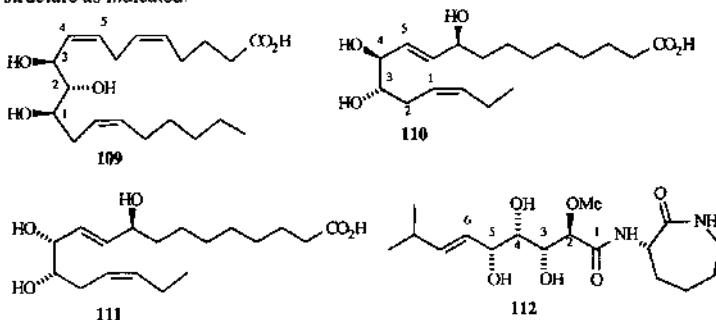
Scheme 23



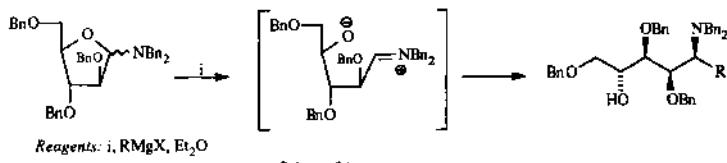
The first total synthesis of (-)-oudemansin **108** has been achieved using, as a chiral pool starting material, L-quebrachitol.⁸⁰ This chemistry not only illustrates the synthetic versatility of cyclitols, but also served to establish the absolute stereochemistry of **108** (sugar numbering shown).



Trioxilin B3 (10(S)-diastereomer) **109**, a putative metabolite in the arachidonate pathway, has been synthesized from D-mannose (sugar numbering shown),⁸¹ and stereoselective syntheses of the structurally related fatty acids **110** and **111** have been achieved from 1,2:5,6-di-O-isopropylidene- α -D-glucofuranose (again the relevant sugar carbons are indicated).⁸² 1,2:5,6-Di-O-isopropylidene- α -D-glucofuranose has also been utilized in a synthesis of benganside E **112** and noteworthy is the complete incorporation of all the carbon atoms of D-glucose into the target structure as indicated.⁸³



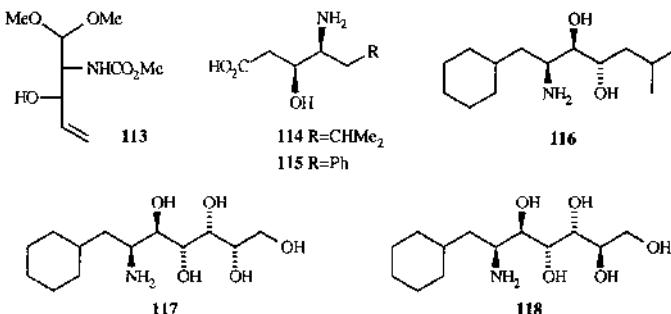
Pentose-derived α -alkoxyiminium ions undergo stereoselective addition of Grignard reagents to give, ultimately, polyhydroxyamine derivatives (Scheme 24).⁸⁴ The rate of reaction is highly dependent on the nature (and co-ordinating ability) of the residue at C(5) - S-deoxy derivatives react slowly - and the face selectivity observed in the nucleophilic addition is opposite to that observed with the corresponding aldehydes. A mechanistic rationale for this observation (based on A_{1,3} interactions) is presented.



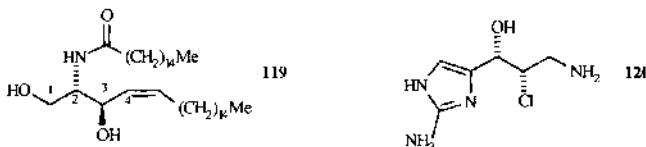
Reagents: i, RMgX , Et_2O

Scheme 24

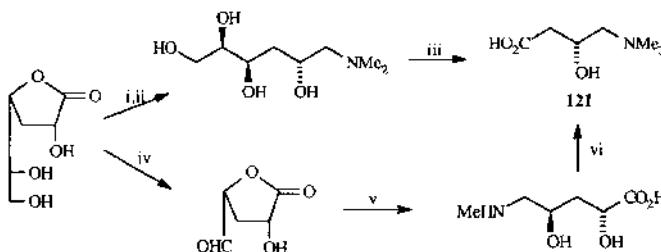
This year has also seen activity in the synthesis of amino acids and peptide mimetics. (3S,4R)-Statine **114** (together with analogue **115**) has been obtained from D-glucosamine via acetal **113**.⁸⁵ Two groups have described syntheses of the dipeptide isostere **116** (incorporating a dihydroxyethylene unit as an equivalent of a peptide linkage), a component of several renin inhibitors, from D-ribose⁸⁶ and D-isoascorbic acid,⁸⁷ and two structurally related renin inhibitors **117** and **118** have been synthesized from L-glucose and D-mannose respectively.⁸⁸



D-Glucose has been used to prepare 3-O-benzoyl derivative of ceramide **119**⁸⁹ (sugar numbering shown) and, starting from D-arabinose, a synthesis of giroline **120** has been accomplished.⁹⁰



Finally, (R)-carnitine **121** has been synthesized by two simple and efficient routes starting from D-galacto-1,4-lactone. (Scheme 25).⁹¹

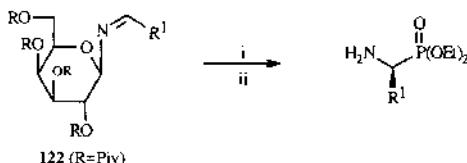


Reagents: i, Me₂NH; ii, BH₃-SMe₂; iii, MeI, then KMnO₄; iv, NaIO₄; v, MeCNH₂, H₂, Pd on C, then KOH, H₂O; vi, Me₂SO₄, then KMnO₄

Scheme 25

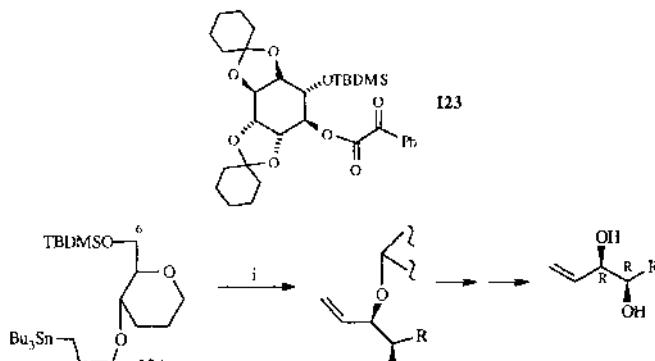
7 Carbohydrates as Chiral Auxiliaries

The galactosyl amine derivative **122** undergoes stereoselective addition (up to 86% d.e.) of diethyl phosphite to provide, after acidic cleavage of the auxiliary, (S)- α -amino phosphonic acids (Scheme 26).⁹²



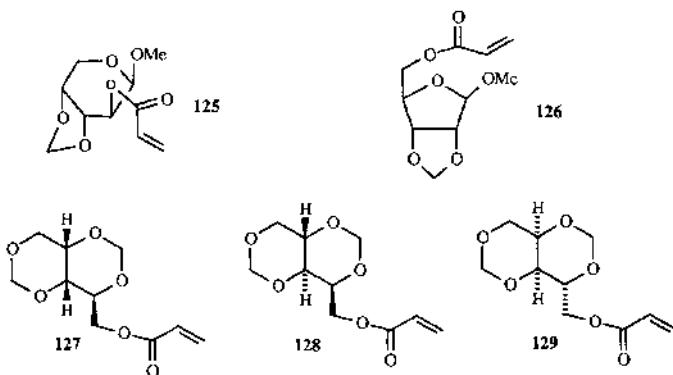
Scheme 26

Auxiliaries based on either D-arabinose or L-fucose provide access to the corresponding (R)- α -amino phosphonic acids. The ketone function of **123**, incorporating a *chiro*-inositol auxiliary, undergoes stereoselective addition of RLi , RMgX and allylsilanes under both chelation and non-chelation controlled conditions to give, ultimately, α -hydroxyacids.⁹³ Allylstannane **124** (derived from tri-*O*-acetyl-D-glucal) undergoes stereoselective addition to aldehydes to provide syn 1,2-diols in up to 95 % d.e. Cleavage of the carbohydrate auxiliary requires 5 steps and involves, in essence, oxidation of the silyl-protected alcohol [at C(6)], followed by β -elimination to release the diol unit (Scheme 27).⁹⁴

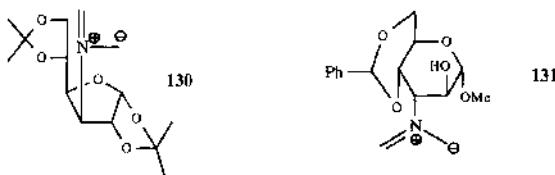


Scheme 27

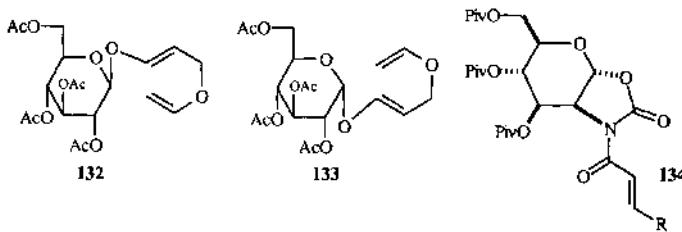
This year has seen several studies directed towards the use of carbohydrates as auxiliaries for Diels-Alder, 1,3-dipolar cycloadditions and related pericyclic processes. The *arabino* and *ribo* derivatives **125** and **126** have both been evaluated as dieneophiles in the Diels-Alder reaction and shown to provide efficient asymmetric induction.⁹⁵ The xylitol, ribitol and arabinitol-based auxiliaries **127-129** also provide good levels of induction by a mechanism that requires chelation involving the oxygen centres of the dioxane rings.⁹⁶



Cyclitols have been used as chiral auxiliaries for nitrile oxide additions to acrylates,⁹⁷ and chiral azomethine ylides, for example 130 and 131, have been used for the asymmetric synthesis of pyrrolidines; ylide generation involves treatment of a tertiary amine N-oxide with LDA.⁹⁸

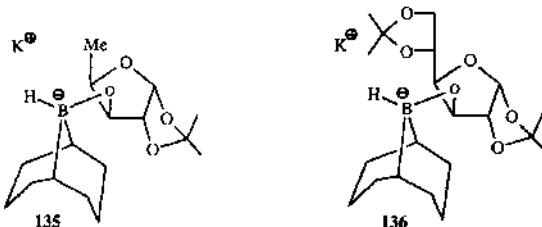


The Claisen rearrangements of enol ethers 132 and 133 proceed with a very modest (20 % d.e.) levels of selectivity at the newly-created allylic centre.⁹⁹ Photodeconjugation of acrylates is a synthetically useful process that can be effectively controlled by use of 1,2:5,6-di-*O*-isopropylidene- α -D-glucofuranose as an auxiliary using C(3) hydroxyl as the point of attachment.¹⁰⁰ The carbohydrate-based oxazolidinone 134 undergoes highly selective 1,4-addition of dialkylaluminium chlorides under either ionic or radical conditions.¹⁰¹

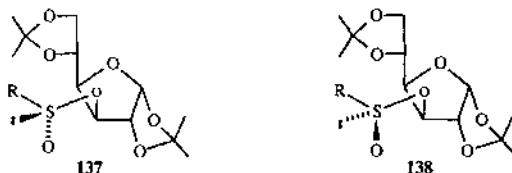


Two new borane reducing agents 135 and 136 have been applied to the reduction of cycloalkanones, α -haloketones, α -amino ketones and aryl alkyl ketones.¹⁰² The effect of

6-amino-6-deoxy- β -cyclodextrin on the reduction of arylol formic acid with NaBH₄ has been reported.¹⁰³



Enantiomerically pure sulfoxides have been prepared by displacement reaction of sulfonates 137 and 138 with Grignard reagents. Interestingly, both sulfonates 137 and 138 were prepared from 1,2:5,6-di-O-isopropylidene- α -D-glucofuranose and an alkyl or arylsulfinyl chloride with the diastereoselectivity observed being conditional on the nature of the base used.¹⁰⁴



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Author Index

In this index the number in parenthesis is the Chapter number of the citation and this is followed by the reference number or numbers of the relevant citations within that Chapter.

- Abass, T.M. (10) 62
Abbaci, B. (19) 37
Abbas, M.M. (20) 42
Abdelal, A.M. (20) 23
Abdel-Megied, A.E.-S. (17) 6; (20) 268
Abe, Y. (16) 80
Abell, C. (18) 78
Abeln, D. (22) 88
Abiru, T. (20) 186
Abouhilale, S. (7) 17
Abraham, R.J. (21) 35
Abushanab, E. (7) 4; (20) 75, 82
Acena, J.L. (18) 94
Achiwa, K. (16) 42
Achmatowicz, O. (2) 29; (9) 32
Ackermans, M.T. (23) 117
Acquotti, D. (4) 110; (21) 85
Adachi, H. (7) 57
Adaciu, K. (4) 62, 63; (16) 52, 53
Adam, S. (9) 45
Adams, B. (2) 54
Adams, D.M. (17) 13; (20) 283
Adams, J.P. (18) 73, 88
Adelhorst, K. (9) 55; (12) 28; (18) 26, 27
Adovasio, A. (18) 21
Adovasio, V. (22) 85
Adzic, R.R. (2) 61
Afans'eva, S.V. (3) 74
Aftab, K. (3) 76
Aghack, P. (20) 167
Ager, D.J. (1) 5
Agnel, J.P.L. (22) 134, 136
Agrawal, A. (16) 83
Agrawal, G.L. (2) 68
Agrawal, P.K. (4) 4; (9) 56; (21) 31, 65
Agris, P.F. (20) 225
Aguilar, G.J. (18) 119
Aguiló, A. (18) 151
Ahmad, V.U. (20) 282
Ahmad, Z. (9) 9
Ahmed, A.F.S. (20) 97
Ahmed, S. (9) 27
Ahmed, S.N. (2) 8
Ahmed, Z. (5) 24
Ahn, S.K. (20) 64, 307; (22) 112
Ahn, Y. (9) 16; (16) 31; (18) 82
Ahnoff, M. (10) 21
Ahond, A. (24) 90
Aicher, T.D. (24) 56
Aiyar, J. (19) 92
Ajisaka, K. (3) 140
Akama, T. (19) 22
Akamatsu, Y. (9) 46
Akao, E. (23) 40
Akao, M. (19) 32
Akgün, E. (22) 73
Akilar, M. (19) 13; (20) 139, 140
Akiyama, A. (9) 25
Akiyama, H. (23) 58
Akiyama, S. (23) 30
Akiyama, T. (24) 93, 97
Akulov, G.P. (18) 1
Al-Abed, Y. (14) 29
Alagbek, T. (4) 101
Alais, J. (9) 14
Alberg, D.G. (18) 76
Albericio, F. (20) 296
Alberto, R. (17) 36
Alcudia, F. (7) 90; (9) 36, 37; (24) 104
Al-Daher, S.S. (9) 20; (18) 44, 58
Aldaz, A. (2) 59, 60
Alejska, M. (20) 328
Alekseev, V.V. (10) 61
Alekseev, Yu.E. (5) 6; (9) 8
Ali, A.A. (7) 98
Ali, S.M. (20) 205
Alisi, M.A. (18) 141, 142
Al-Kadir, A.J. (6) 2
Alker, D. (6) 9; (14) 32; (22) 84
Allen, S.T. (16) 29
Allevi, P. (3) 69
Allison, J. (22) 35; (23) 20
Al-Masoudi, N.A.L. (5) 23; (11) 12
Almer, H. (20) 234
Almond, M.R. (18) 128; (20) 156
Al Mourabit, A. (24) 90
Alonso, R.A. (18) 108; (24) 3
Alpegiani, M. (14) 20
Al-Timari, U.A.R. (10) 52
Alton, G.R. (4) 139
Alvarez, E. (3) 240
Alvarez, R.B. (2) 52
Alves, A.J. (20) 307-310; (22) 112
Alvi, K.A. (3) 224
Aly, Y.L. (17) 6; (20) 268
Amari, J.V. (23) 96
Ames, J.M. (10) 29
Ampofo, S.A. (23) 115
Anastasia, M. (3) 69
Anderson, C. (18) 85
Andersen, J.V. (16) 68; (23) 71
Andersen, N.H. (19) 30
Anderson, B.D. (20) 302
Anderson, G.J. (16) 69
Anderson, L. (23) 109

- Andersson, F.O. (3) 201, 206; (10) 33; (11) 5
 Ando, T. (4) 127, 128
 Andre, C. (22) 93
 Andre, F. (20) 241
 Andrei, G. (19) 72, 80
 Andrews, D.M. (20) 127
 Andrews, M.A. (6) 16
 Andrianomenjanahary, S. (19) 43
 Andrienko, L.P. (18) 5
 Andriollo, N. (22) 11
 Angel, A.S. (22) 20; (23) 123
 Angyal, S.J. (2) 1
 Anikin, M.V. (3) 45
 Anisuzzaman, A.K.M. (17) 12, 13; (20) 283, 284
 Anker, D. (9) 7, 49
 Annette, D. (23) 75
 Anraku, Y. (19) 87
 Anteunis, M. (5) 30
 Anthonsen, T. (14) 13
 Antoniu, A. (23) 25
 Antonakis, K. (3) 237; (7) 10; (20) 179
 Anumula, K.R. (18) 2
 Aoyagi, S. (24) 77
 Aoyama, Y. (2) 73; (4) 156; (19) 35
 Apriyantono, A. (10) 29
 Aragon, J.J. (3) 113
 Arahire, M. (4) 159
 Arai, K. (24) 4
 Arai, M. (9) 46
 Arni, S. (19) 75
 Araki, K. (9) 1
 Arcamone, F. (20) 56
 Arechka, V. (20) 25
 Arstoff, P. (3) 242; (13) 7
 Ariza, X. (20) 102
 Arjona, O. (18) 94, 134
 Armour, M.-A. (17) 1, 4
 Armstrong, R.W. (3) 243
 Arshman, B.M. (8) 15; (14) 46
 Arzumanov, A.A. (20) 264
 Ashida, N. (20) 295
 Ashizawa, T. (20) 320
 Ashwell, M. (3) 179; (16) 46
 Asman, M. (2) 50
 Aspinall, G.O. (3) 142; (9) 28
 Assat, M.H. (7) 98
 Atallah, A.F. (7) 55
 Atrazhev, A.M. (20) 117
 Ats, S.-C. (4) 89, 90
 Atta, K. (10) 64
 Attal, S. (3) 53, 115
 Aubertin, A.M. (20) 112
 Auclair, S.X. (16) 60
 Augé, C. (1) 8, (4) 66, 81
 Augé, J. (24) 99
 August, E.M. (20) 41
 Augustyns, K. (20) 83
 Auzanneau, F.I. (3) 149
 Avalos, M. (10) 17
 Avino, A. (20) 296
 Avizonis, D. (20) 220
 Awabaugh, A.E. (21) 86
 Ax, H.A. (19) 30
 Axenrod, T. (4) 173
 Ayukawa, H. (20) 236
 Baba, M. (20) 239
 Babain, V.A. (7) 73
 Babiano, R. (10) 17
 Babirad, S.A. (3) 102, 247; (21) 61
 Babu, J.R. (20) 64
 Bacher, A. (18) 9
 Bachmann, F. (3) 15
 Badet, B. (17) 5
 Bader-Denisot, M.-A. (17) 5
 Badia, J. (7) 65
 Baecker, T. (21) 28
 Back, S.H. (3) 226
 Baer, H.H. (4) 161, 175; (9) 26; (14) 14
 Baggett, N. (6) 2
 Bagley, S. (4) 94; (21) 84
 Baikova, I.P. (2) 32
 Bailey, L.C. (23) 68
 Baiocchi, C. (22) 34; (23) 59
 Baird, W.M. (22) 33; (23) 72
 Bajpai, S. (18) 6, 7
 Baker, M.L. (18) 103
 Baker, R. (18) 149
 Baker, W.R. (24) 87
 Bakhtmedova, A.A. (20) 47, 109, 110
 Bakinovskii, L.V. (3) 167
 Bakker, A.R. (7) 75; (16) 76
 Bakshi, P.K. (22) 94
 Balasubramanian, K.K. (3) 235; (13) 8; (14) 23
 Balasubramanian, S. (18) 78
 Balci, M. (18) 92
 Ball, G.E. (3) 108
 Ballou, C.E. (18) 147
 Balmer, K. (10) 21
 Baltas, M. (12) 10; (18) 81
 Balzarini, J. (19) 72, 80, 110; (20) 94, 122, 135, 147, 153, 168-170, 238, 240
 Banhaoud, T. (10) 53
 Banaszek, A. (3) 137; (22) 64
 Bandgar, B.P. (16) 51
 Baudouzi, A. (8) 25; (13) 12
 Banfi, L. (9) 30
 Banik, B.K. (24) 63
 Bankston, D.D. (20) 156
 Bannister, B. (19) 31
 Banno, A. (5) 33
 Banoub, J.H. (4) 1; (22) 27, 29
 Bar, N. (7) 33
 Barakat, K.J. (24) 63
 Baraldi, P.G. (20) 21
 Baran, J. (22) 1, 2
 Barascut, J.-L. (11) 7; (20) 132
 Barba, A.P. (18) 60; (24) 69
 Barbalat-Roy, F. (10) 50; (22) 68
 Barber-Heyob, M. (23) 101
 Barbhaiya, R.H. (23) 86, 93
 Barbier, J. (18) 4, 28
 Barchi, J.J., Jr. (7) 4; (19) 79; (20) 57, 88, 321
 Bardos, T.J. (20) 51
 Barfoed, M. (7) 42
 Bardt, P.L. (15) 4, 5, 9; (16) 73
 Barnes, C.L. (10) 58; (22) 66
 Baron, P. (20) 263
 Barr, P.J. (20) 261
 Barragan, M.A. (10) 74
 Barrere, B. (16) 43
 Barresi, F. (3) 124
 Barrett, A.G.M. (3) 82, 92; (7) 47
 Barroa, L.D. (22) 140
 Barth, R.F. (17) 13; (20) 283
 Bartlett, P.A. (18) 76
 Bartlett, W.J. (19) 71
 Barton, D.H.R. (5) 5; (6) 17; (7) 105; (9) 13; (12) 1, 2, 4; (17) 3, 11; (18) 125; (19) 50; (20) 9, 141, 270
 Barzi, A. (20) 19
 Baschang, G. (19) 58
 Baston, J. (4) 122-124
 Batelaan, J.G. (17) 37
 Bates, P.S. (4) 168; (5) 13
 Bathurst, I.C. (20) 261
 Batley, M. (23) 51
 Batta, G. (8) 30; (14) 31; (20) 113
 Battesti, C.M. (22) 134, 136
 Battina, L.A. (20) 14
 Batty, D. (18) 110; (24) 11
 Baudendistel, L.J. (23) 98
 Bauer, C.J. (4) 7
 Bauer, F. (18) 13
 Bauman, J.G. (20) 106
 Baumes, R.L. (23) 14, 15
 Baumgartner, H. (19) 64
 Bause, E. (18) 42
 Baust, J.G. (2) 48
 Baxter, E.W. (19) 96
 Bay, S. (3) 53, 136
 Bayer, R. (4) 25
 Bayle, C. (3) 178; (5) 4
 Baynes, J.W. (23) 5
 Bayonove, C.L. (23) 14

- Bazzanini, R. (20) 21
 Beach, J.W. (20) 64, 307-310;
 (22) 112
 Beagley, B. (3) 41; (22) 56
 Bearden, D.W. (21) 92
 Beau, J.-M. (3) 158, 231, 241;
 (10) 36, 53; (17) 8, 9; (20) 10
 Beauchage, S.L. (20) 278
 Beaupère, D. (3) 217, 255; (5) 15;
 (8) 37, 38; (18) 12, 23
 Beechi, M. (22) 27, 29
 Becker, A. (3) 203
 Becker, D. (3) 94; (7) 30
 Beckers, J.L. (23) 117
 Beden, B. (16) 30
 Bedford, C.T. (3) 180
 Bednarik, K. (3) 160, 161
 Bednarski, M.D. (2) 5; (3) 108,
 219, 220, 249, 250, 254; (18)
 36, 37
 Bedoya-Zurita, M. (24) 90
 Bebling, J.R. (12) 18; (19) 95
 Beierbeck, H. (4) 115; (5) 1
 Beijnen, J.H. (23) 92
 Bekker, A.R. (17) 17; (22) 95
 Belcher, L.M. (3) 82; (7) 47
 Belica, P.S. (20) 68
 Bella, L. (20) 132
 Bellamy, F. (12) 3
 Bellanger, N. (24) 99
 Belleau, B.R. (20) 306
 Bellon, L. (11) 7
 Bel'skii, V.K. (17) 15
 Belton, A.M. (12) 24; (19) 88
 Belyakov, S. (9) 52
 Belzecki, C. (14) 36; (24) 62
 BeMiller, J.N. (3) 251; (18) 33;
 (22) 88
 Benazza, M. (8) 37, 38; (18) 12
 Bender, S.L. (20) 154
 Benefice-Malouet, S. (14) 27
 Bengtsson, M. (3) 48; (7) 83
 Bentaddou, R. (3) 214, 238
 Bennani-Baiti, M.I. (20) 179
 Benneche, T. (20) 200
 Benner, S.A. (2) 17; (20) 163,
 209
 Bennett, S.M. (22) 36; (23) 104
 Benseler, F. (20) 84
 Benson, T.J. (20) 324
 Bentrud, W.G. (20) 238; (21) 25
 Berchtold, G.A. (13) 7
 Berenguel, A.V. (4) 161, 175; (9)
 26; (14) 14
 Berg, A.A. (3) 233; (13) 15
 Berger, A. (2) 39, 57; (8) 6; (10)
 42; (18) 14, 42
 Berger, E.G. (3) 118
 Berger, M. (22) 37; (23) 103
 Berger, S. (16) 82
 Bergmann, R. (8) 19
 Bergogne, M.C. (7) 2
 Bergon, P. (9) 16, (16) 31; (18) 82
 Bergstrom, D.E. (20) 94
 Berkowitz, D.B. (3) 141; (13) 1,
 2; (18) 52; (22) 86
 Bernabé, M. (13) 10, (14) 22
 Bernat, J.L. (23) 25
 Bernardi, A. (2) 14
 Bernardinelli, G. (10) 50, 51; (22)
 67, 68
 Bernet, B. (3) 196
 Berova, N. (22) 141
 Berry, D.E. (7) 56
 Berry, J.W. (2) 75
 Bert, G. (15) 4, 5, 9, (16) 73
 Bertoli, V.I. (3) 106, 146, 147;
 (4) 13, 59; (16) 63
 Beyer, E.M. (3) 75
 Beyer, G.J. (8) 19
 Beyerbach, A. (3) 246; (14) 42
 Bhadri, V.S. (20) 22
 Bhaduri, S. (17) 35; (22) 97
 Bhakuni, D.S. (20) 137
 Bhan, A. (20) 22, 54; (22) 130
 Bhan, P. (20) 279
 Bhandari, S.P.S. (7) 52
 Bhat, V. (20) 69
 Biarez, O. (23) 82
 Bichard, C.J.F. (16) 25
 Bielawska, H. (3) 20, (13) 11
 Bielfeldt, T. (3) 50, 111
 Biely, P. (3) 198
 Biggadike, K. (19) 70; (20) 198
 Bilik, V. (17) 31; (23) 108
 Billington, D.C. (18) 149
 Bimwala, R.M. (3) 245
 Binderup, L. (19) 36
 Bing, H.X. (4) 135
 Binkley, R.W. (7) 85-87, 89
 Birault, V. (6) 14
 Bis, S.J. (18) 73
 Bisacchi, G.S. (19) 62
 Bisagni, E. (18) 126; (19) 63; (22)
 108
 Bischoff, M. (22) 48, 104
 Bitur, S.M. (23) 14
 Bizdene, E. (20) 223
 Bjorkling, F. (7) 42
 Blake, A.J. (14) 38
 Blakeney, A.B. (23) 4
 Blanchard, J.S. (16) 10
 Blanchard, P. (2) 37; (14) 21
 Blanc-Muesser, M. (3) 211; (4)
 85; (11) 21; (21) 33
 Blandamer, M.J. (2) 4
 Blankacrt, N. (8) 3; (16) 67
 Blatou, N.M. (22) 114
 Bliard, C. (8) 10
 Blomberg, L. (8) 1
 Blumberg, P.M. (7) 4
 Blumenstein, M. (3) 20; (13) 11
 Bochkarev, A.V. (20) 153; (22)
 123, 128
 Bock, K. (3) 13, 50, 111, 129; (4)
 144; (7) 68; (12) 28; (18) 26,
 31; (21) 59, 63, 75, 83
 Bocker, T. (7) 93
 Bockovich, N.J. (4) 93
 Bodenteich, M. (18) 123; (19) 69
 Böckers, W. (3) 79
 Boelens, R. (21) 80
 Boghai, D.M. (17) 25
 Boitiaux, J.P. (18) 28
 Boivin, J. (11) 6; (20) 129
 Boldt, P.-C. (3) 29
 Bolgar, M.S. (19) 30, 84
 Bolitt, V. (3) 236; (13) 22; (20)
 178
 Bollhagen, R. (18) 121
 Bols, M. (3) 5; (19) 36; (24) 65,
 91
 Bon, M. (21) 41
 Bondo, P.B. (2) 27; (21) 8
 Boniface, C. (10) 24
 Bonnaffè, D. (3) 17; (8) 31; (16) 3
 Bonnett, R.V. (14) 44; (22) 82
 Booma, C. (13) 8; (14) 23
 Boons, G.J.P.H. (3) 165, 168,
 172; (4) 79, 105; (8) 3; (9) 59;
 (16) 34, 67
 Booth, H. (21) 4, 5
 Boppana, V.K. (10) 19
 Boquel, P. (12) 3
 Borchardt, R.T. (19) 71; (20) 147,
 205, 213
 Borchering, D.R. (19) 71
 Borders, D.B. (19) 91; (22) 39
 Bordner, J. (12) 24; (19) 88
 Borisov, E.V. (20) 93; (21) 23
 Bornemann, S. (9) 50
 Borrull, F. (23) 35, 36
 Berthwick, A.D. (19) 70; (20) 198
 Bose, A.K. (24) 63
 Bosso, C. (22) 25
 Bossuyt, X. (8) 3; (16) 67
 Bou, V. (20) 49
 Bouali, A. (3) 10; (5) 14; (7) 18;
 (10) 1
 Bougauchi, M. (2) 44
 Bougandjioua, N. (3) 35, 105

- Boulanger, Y. (21) 91
 Boullanger, P. (3) 23, 163; (4) 1, (5) 14; (9) 42, 47
 Boumaiza, L. (3) 237
 Bounja, Z. (17) 18
 Boutaiba, L. (5) 15
 Bouxon, B. (4) 81
 Bouyssou, P. (7) 25
 Bovin, N.V. (3) 32; (4) 74
 Bowie, J.H. (22) 17
 Boyd, J. (21) 62
 Boye, H. (4) 59
 Boyer, F.-D. (24) 73
 Boyer, S.H. (4) 87
 Bozó, E. (3) 96
 Brade, H. (4) 60; (21) 75
 Brady, J. W. (21) 29, 79
 Brakta, M. (3) 236; (22) 29
 Bramibilla, P. (23) 11
 Branca, M. (17) 33
 Brandenburg, A. (17) 20
 Brandstetter, H.H. (7) 103
 Brandstetter, T. (14) 10; (24) 41
 Bratcz-Wiewiorowska, M.D. (20) 328
 Bratt, P. (4) 18
 Braun, F.O. (10) 33
 Braun, H. (20) 256
 Brazier, M. (7) 41
 Breda, M. (23) 81
 Bredenkamp, M.W. (7) 51, 101; (12) 30; (24) 47, 48
 Brennan, P.J. (3) 142; (9) 28
 Brennan, S.O. (23) 51
 Breslow, R. (20) 222
 Briggs, J.C. (7) 3
 Briks, E.M. (20) 41
 Brimacombe, J.S. (22) 105
 Briner, K. (3) 6, 160
 Brisson, J.-R. (3) 129
 Brockhausen, I. (3) 138; (4) 43, 71, 131; (12) 25, 26
 Broder, S. (20) 302
 Bronson, J.J. (20) 274, 275
 Brossmer, R. (14) 28; (16) 49, 54, 59; (22) 57
 Brown, D. (16) 25; (24) 42, 43
 Brown, E.G. (3) 108
 Brown, P.R. (23) 96
 Brown, R.F.C. (18) 71
 Browne, P. (22) 51
 Brownell, J. (20) 207
 Browning, L.M. (18) 33
 Browne, R.T.C. (23) 4
 Broxterman, H.J.G. (18) 54
 Bruce, J. (3) 218; (18) 43, 58
 Brufani, M. (18) 141, 142, 171
 Bruggink, C. (22) 32; (23) 54
 Brunner, H. (4) 155
 Bruno, A. (23) 43
 Bruns, C. (3) 19
 Bruzik, K.S. (18) 100, 152, 154; (22) 106
 Bryamova, N.E. (3) 32
 Bryukhanova, O.V. (3) 147
 Buch, C. (20) 165
 Buchanan, J.G. (3) 230; (16) 18; (20) 191
 Buchholz, K. (4) 27; (15) 7
 Buchko, G.W. (16) 4
 Buegner, G.S. (20) 214
 Bueno Martinez, M. (3) 216; (9) 53; (16) 26
 Buisson, G. (22) 79
 Buleon, A. (21) 57
 Bulusu, M.A.R.C. (3) 28; (7) 48; (9) 57
 Bulusu, S. (4) 173
 Bunge, R.H. (19) 49
 Bur, D. (18) 127
 Burger, D.M. (23) 92
 Burgess, K. (18) 62, 65; (24) 66-68
 Burns, C.L. (20) 294, 311
 Buschman, J. (18) 66
 Bush, C.A. (9) 56; (21) 31; (23) 53
 Bushnev, A.S. (18) 138
 Busia, K. (18) 167
 Busson, R. (19) 11
 Buszek, K.R. (24) 56
 Butt, E. (20) 247
 Byers, C.H. (23) 105
 Byrd, R.A. (21) 52
 Bystrykh, L.V. (10) 76
 Cáceres, L.E. (10) 47
 Cachet, Th. (23) 83
 Cadena, R.A. (18) 119
 Cadet, J. (16) 4; (22) 37; (23) 103
 Cai, L.-N. (3) 7
 Cai, M. (20) 12; (21) 34
 Cai, M.-S. (3) 7; (6) 3, 4
 Cai, S. (7) 43; (10) 35; (18) 135; (20) 254
 Cai, Y. (16) 7
 Caillebourdin, S. (24) 99
 Calabrese, J.C. (18) 140
 Caldwell, K.K. (18) 143
 Calhull, M. (23) 35, 36
 Callahan, L. (20) 267
 Calle, P. (22) 135
 Callstrom, M.R. (18) 36, 37
 Calvo, M.M. (23) 18
 Camara, J. (11) 6; (18) 125; (20) 129
 Camarasa, M.-J. (10) 18, 45; (20)
- 144, 168-170
 Cameron, T.S. (22) 94
 Camp, D.A. (6) 19
 Campi, M. (20) 313
 Candelore, M.R. (3) 18
 Candilejo, A. (18) 134
 Caneva, E. (3) 244
 Cano, H. (18) 106
 Cantacuzene, D. (3) 53, 115, 136
 Cao, L. (5) 25; (21) 36
 Cao, S. (11) 5
 Capek, K. (10) 49; (20) 119; (22) 65
 Capobianco, F. (20) 56
 Cappelacci, L. (20) 19
 Carboni, B. (16) 33
 Carcanague, D.R. (4) 93
 Carcuro, A. (20) 56
 Carda, M. (14) 12
 Caris, B.M.G. (6) 8
 Carless, H.A.J. (18) 72, 86, 87, 116, 167
 Carpenter, A.J. (9) 54; (24) 59
 Carpenter, N.C. (9) 20; (18) 44
 Carper, W.R. (16) 22
 Carrigan, S.W. (20) 309
 Carroll, J.A. (22) 21
 Carrondo, M.A.A.F.de C.T. (22) 92
 Carta, G. (23) 105
 Caruel, H. (23) 107
 Carver, J.P. (4) 6
 Casalnuovo, A.L. (17) 14
 Casara, P.J. (20) 265
 Cascieri, M.A. (3) 18
 Cashman, J.R. (23) 8
 Cashmore, G.C. (4) 7
 Casiragli, G. (3) 256; (10) 69; (16) 17; (18) 46; (22) 74, 75
 Castillon, S. (8) 10; (14) 39; (20) 11
 Castro-Pichel, J. (20) 122
 Catelani, G. (15) 5
 Catterall, H. (20) 323
 Caturla, M.C. (23) 84
 Cauchon, N.S. (20) 81
 Cazalet, C.L. (12) 3
 Celeddu, N. (22) 75
 Cenci de Bello, I. (9) 20; (18) 43, 44, 58
 Cerny, I. (3) 65
 Cerny, M. (21) 93
 Cert-Ventula, A. (10) 65
 Cesta, M.C. (18) 141, 142, 171
 Cetovic, G. (12) 23
 Chae, W.-G. (20) 81
 Chaguir, B. (3) 236; (13) 22; (20) 178; (22) 29
 Chahoua, L. (18) 81

- Chai, W. (4) 7
 Chamberlain, S.D. (20) 293, 294
 Chamberlin, B.A. (22) 35; (23) 20
 Chambers, E.J. (21) 35
 Chan, M.F. (24) 86
 Chan, T.A. (7) 56
 Chandler, M.C. (24) 81
 Chandrasekaran, E.V. (4) 49
 Chang, C.C. (19) 91; (22) 39
 Chang, C.-j. (20) 81
 Chang, C.-N. (20) 308, 310
 Chang, M. (3) 182; (10) 4
 Chang, Y.T. (18) 160
 Chantegrel, B. (16) 43
 Chanteloup, L. (20) 10
 Chao, L.R. (3) 35, 105
 Chapelle, S. (17) 30
 Chapleur, Y. (8) 25; (12) 3; (13) 12; (14) 33, 34
 Chaplin, D.A. (9) 50; (18) 65; (24) 67, 68
 Charon, D. (3) 149
 Charpin, P. (22) 45
 Charvet, A.-S. (20) 313
 Chastanet, J. (24) 98
 Chatani, N. (3) 257
 Chatterjee, D. (3) 142; (9) 28
 Chatterjee, S. (20) 92
 Chattopadhyaya, J. (11) 8; (20) 26, 166, 167; (22) 131, 132
 Chekunova, E.V. (20) 47
 Chen, C.F. (3) 190
 Chen, C.M. (22) 10
 Chen, C.-S. (18) 155, 156; (20) 79
 Chen, F.L. (2) 38; (23) 120
 Chen, G.L. (3) 190
 Chen, G.X. (4) 56
 Chen, L. (1) 9; (8) 7; (10) 44; (18) 49
 Chen, M.-Q. (19) 26
 Chen, S. (4) 118; (19) 85
 Chen, S.G. (18) 3
 Chen, S.-L. (24) 50
 Chen, T.-H. (18) 67
 Chen, W. (8) 29
 Chen, X. (19) 60; (20) 202
 Chen, Y. (10) 28; (18) 68; (20) 95, 106
 Chen, Y.-T. (14) 16; (16) 23; (19) 55
 Chen, Z. (3) 37; (20) 33
 Chenault, J. (7) 25
 Chénédé, A. (13) 3
 Cheng, X. (18) 125
 Cheng, Y.-C. (20) 51, 308, 310
 Chermann, J.-C. (20) 313
 Chern, J.W. (20) 79
 Chernyak, A.Y. (3) 55; (16) 70
 Chi, D.Y. (3) 260
 Chiara, J.L. (12) 9; (13) 17
 Chiaronti, A. (18) 70
 Chida, N. (2) 20; (9) 21; (16) 65, (18) 47, 48, 132; (24) 2, 72, 80
 Chin, P.C. (4) 154
 Chin, M.J. (7) 39
 Chittenden, G.J.F. (6) 8
 Chiu, E. (23) 32
 Chmielewski, M. (14) 36; (24) 60-62
 Cho, B.T. (24) 102
 Cho, H.-S. (24) 21
 Cho, I.H. (24) 5
 Choay, J. (9) 43; (17) 26
 Choi, B.G. (20) 307; (22) 112
 Choi, H.S. (21) 89
 Choi, S.S. (16) 25; (18) 58
 Chou, T. (7) 55
 Chou, T.-C. (20) 263
 Chou, T.S. (20) 90
 Chovan, J.P. (23) 102
 Christensen, M.K. (7) 68
 Christian, R. (16) 16; (21) 75
 Christiansen-Brams, I. (18) 31; (21) 63
 Chu, C.K. (20) 64, 106, 291, 307-310; (22) 112, 117
 Chu, T. (17) 19; (18) 136
 Chun, M.W. (20) 318
 Chun, Y.S. (24) 102
 Chung, D.I. (7) 1
 Chung, J. (21) 77
 Chung, K.H. (20) 13
 Chung, S.K. (18) 160
 Chung, W.K. (23) 318
 Churchill, M.E.A. (22) 118
 Churms, S.C. (23) 1
 Ciarrocchi, G. (20) 56
 Cinget, F. (3) 16
 Ciuffreda, P. (3) 69
 Ciunik, Z. (22) 57, 87
 Cizeau, J. (3) 38
 Claes, P. (19) 11
 Claesson, A. (3) 221
 Clardy, J. (9) 2; (22) 71
 Clark, D. (4) 88
 Clarke, S.J. (23) 106
 Classon, B. (20) 143, 161, 162, 215
 Clauss, A. (20) 265
 Claver, C. (14) 39
 Claviller, J. (2) 59
 Clayton, S.D. (20) 87
 Clelland, A.P.W. (3) 230; (16) 18
 Cleophas, J. (16) 72; (18) 120; (24) 13
 Clivio, P. (20) 224
 Coburn, C.A. (3) 242; (13) 7
 Cody, V. (22) 111
 Coe, D.M. (20) 276
 Coe, P.L. (11) 8; (14) 27; (20) 15, 49; (22) 132
 Coggins, J.R. (18) 78
 Cohen, L.M. (23) 105
 Coleman, A.W. (4) 163, 167, 174; (10) 7; (22) 45
 Coleman, R.S. (9) 54; (24) 59
 Coleman, W.M., III (17) 21
 Collins, D.J. (18) 71
 Colombo, D. (7) 38; (21) 81
 Colomer, J. (20) 25
 Colonna, F. (20) 56
 Colson, K.L. (9) 3; (14) 2
 Comber, R.N. (20) 272
 Combs, B.S. (16) 22
 Condon, S.L. (24) 87
 Congson, L.N. (3) 128; (21) 53
 Conley, D.L. (2) 75
 Consalvi, V. (9) 41
 Conti, M.R. (20) 220
 Cook, D.G. (3) 250
 Cook, P.D. (20) 126, 157, 158
 Cook, T.A. (14) 38
 Cooke, A.M. (18) 164
 Cooke, N.G. (5) 32; (10) 43
 Cooney, D.A. (19) 73
 Cooper, R. (19) 21
 Corbett, E.C. (22) 8
 Corey, E.J. (5) 17
 Corizzi, V. (17) 5
 Cornia, M. (3) 256; (10) 69
 Cortés García, R. (21) 46
 Cosstick, R. (20) 127, 128
 Coste-Sarguet, A. (4) 162
 Coszewski, L.A. (20) 85
 Cottaz, S. (4) 84
 Cotterill, I.C. (19) 57
 Cottier, L. (3) 202
 Couder, C. (9) 43
 Coward, J.K. (3) 156
 Cramer, F. (20) 230
 Crans, D.C. (16) 10
 Crawford-Ruth, D. (20) 120
 Crews, F.T. (18) 161
 Crews, P. (3) 224
 Crich, C. (18) 110
 Crich, D. (24) 11
 Cristalli, G. (20) 185
 Critchley, P. (3) 169
 Cromer, R. (4) 48
 Crooks, P.A. (20) 123, 139, 140
 Crossman, A., Jr. (10) 60
 Crothers, D.M. (19) 92
 Crouch, R.C. (21) 86
 Crout, D.H.G. (3) 169; (9) 50
 Crow, J.A. (23) 2
 Cruz-Sánchez, S. (21) 46
 Csanádi, J. (8) 32

- Cuadrado, C. (23) 49
 Cucinotta, V. (4) 178
 Cuellar, M.E. (13) 19
 Cuevas, G. (21) 1
 Cuevas, T. (7) 29
 Cui, Y. (18) 93
 Culeddut, N. (18) 46
 Cullen, W.P. (12) 24; (19) 88
 Cummings, J. (23) 109
 Cunningham, D. (22) 51
 Cuny, E. (10) 55; (14) 47
 Curtis, A.D.M. (3) 41; (22) 56
 Cushman, M. (18) 9
 Cusido, E. (23) 84
 Cuvillier, O. (21) 74
 Cyronak, M.J. (10) 19
 Czamiecki, M. (9) 19
 Czarnocki, Z. (24) 74, 75
 Czernecki, S. (3) 214, 238; (13) 16; (20) 155
 Cziba, M. (16) 72
 Czechalski, B. (20) 115
- Dabrowski, W. (20) 230
 Da Col, R. (22) 34; (23) 59
 Dahlhoff, W.H. (18) 10
 Dahms, T.E. (23) 98
 d'Alarcão, M. (3) 63
 D'Alcessandro, F. (4) 178
 Daley, L. (9) 15
 Dalko, P.J. (7) 105
 Dalley, N.K. (20) 89; (22) 116
 Dalvoy, V.S. (5) 29
 Damini, J.B.L. (23) 113
 Dancy, I. (12) 6
 Dandekar, K.A. (23) 93
 D'Andrea, F. (15) 4, 5, 9; (16) 73
 Daniel, J.R. (18) 33
 Danishefsky, S.J. (3) 33, 47, 141, 175; (4) 24, 73, 87, 113; (9) 24; (11) 14; (13) 1, 2; (18) 52; (19) 92; (22) 86
 Darcy, R. (4) 162
 Dash, A.K. (19) 15
 Dashevskaya, T.A. (20) 58
 DaSilva, A.D. (14) 21
 Dauchez, M. (21) 14, 64; (22) 3
 Daves, G.D. (3) 258; (20) 194
 David, S. (1) 8; (3) 3; (9) 14
 Davies, M.J. (14) 44; (20) 323; (22) 82; (23) 46
 Davis, G.M. (18) 78
 Dawson, A.P. (7) 3
 Dux, K. (2) 39; (18) 14, 42
 Dean, B. (10) 35
 de Armas, P. (24) 78
 Debart, F. (20) 126, 157, 158
 de Boer, R.F. (20) 285
- De Bruyn, A. (5) 30; (21) 43
 De Clercq, E. (10) 68; (19) 67, 72, 73, 80, 110; (20) 94, 111, 122, 135, 147, 153, 168-170, 211, 238, 240
 Defayé, J. (3) 178, 198, 200; (4) 161, 162; (5) 4, 35; (11) 20
 De Goede, A.T.J.W. (1) 7
 de Guchteneire, E. (9) 31
 Deguin, B. (24) 14
 Dehalow, H. (18) 66
 De Jong, R.L. (18) 73
 Delany, J.J., III (13) 6
 de la Pradilla, R.F. (18) 94, 134
 De las Heras, F.G. (10) 18, 48
 Delay, D. (3) 38
 Delmotte, F. (3) 38
 Del Nozal, M.J. (23) 25
 del Olmo Fernandez, E. (16) 69
 Del Sante, C. (3) 256; (10) 69
 Demainly, G. (3) 217, 255; (5) 15; (8) 37, 38; (18) 12, 23
 DeMarco, A. (21) 76
 Demchenko, A.V. (3) 85, 130; (4) 14; (11) 4
 De Mesmacker, A. (2) 35
 de Miranda, P. (20) 293, 294
 Dennis, J.W. (4) 116
 Depew, W.T. (4) 95
 Depczay, J.C. (18) 22, 61; (24) 17
 de Pouilly, P. (8) 24; (13) 3
 de Raadt, A. (2) 57; (8) 6; (10) 42; (18) 39
 De Rango, C. (22) 43, 45
 De Ranter, C.J. (22) 114
 Deralani, A. (4) 165
 de Rios, A. (18) 134
 Desai, T. (18) 157-159, 165
 Descotes, G. (3) 10, 202, 209; (7) 18; (8) 22, 28; (10) 1, 5, 6, 54, (14) 48; (16) 19, 20; (20) 29, 80; (22) 27
 Deshayes, C. (16) 43
 Desmet, G. (7) 41
 Dessim, A. (17) 33
 de Villegas de Naide, F. (10) 49; (20) 119
 De Voss, J.J. (20) 60
 de Vroom, E. (20) 249
 De Waard, P. (21) 80
 De Wit, D. (1) 7; (10) 56, (15) 8; (22) 72
 Deya, E. (4) 37
 Dhar, R.K. (2) 69
 Dhar, T.G.M. (18) 113
 Dheilly, L. (3) 217, 255; (18) 23
 Di, J. (18) 41
 Diánzec-Millan, M.J. (10) 17, 23; (22) 80
- Diaz-Maurino, T. (12) 27
 Di Bussolo, V. (15) 4, 9; (16) 73
 Diederich, F. (20) 262
 Dijkhuizen, L. (10) 76
 Dill, K. (21) 92
 Dimock, S.H. (12) 18
 Ding, W.P. (4) 56
 Dinya, Z. (20) 113
 Dirlam, J.P. (12) 24; (19) 88
 Dirlikov, S.K. (4) 12
 Disbrow, G.L. (2) 75
 Di Stefano, C. (10) 54; (16) 19
 Divjakovic, V. (22) 78
 Dixit, D.M. (20) 306
 Dixon, J.M. (21) 4, 5
 Djurendic, E. (8) 32
 Dobro-Rodriguez, A. (3) 88
 Dobbelaere, S. (18) 89
 Dobyns, K.A. (19) 73
 Doi, M. (20) 297; (22) 124
 Domaille, P. (4) 144
 Donard, A. (22) 25
 Dominguez, X.A. (18) 97
 Donaldson, C. (3) 18
 Dondoni, A. (2) 6; (5) 11; (9) 4, 5
 Dong, X. (3) 173; (19) 43
 Dong, Y. (9) 54
 Donnarumma, L. (18) 171
 Donosa, M.T.U. (9) 53
 Doong, S.-L. (20) 310
 Dorland, E. (20) 72, 135
 Dormer, P.G. (4) 57
 Doskeland, S.O. (20) 247
 Dougherty, J.P. (20) 222
 Douglas, S.P. (3) 184
 Doutheau, A. (16) 43
 Dowd, M.K. (21) 55, 56, 60
 Doyle, T.W. (9) 3; (14) 2
 Drach, J.C. (20) 18, 319
 Drasar, P. (3) 65
 Draths, K.M. (2) 75; (18) 74
 Dreux, M. (23) 45
 Dreef, C.E. (18) 139, 168
 Dreux, M. (3) 191
 Driguz, H. (3) 200, 211; (4) 84, 85, 176; (11) 20, 21; (21) 33
 Driguez, P.-A. (16) 43
 Driscoll, J.S. (20) 88
 Drueckhammer, D.G. (20) 258
 D'Souza, M. (20) 267
 Dua, S. (22) 17
 Dubois, E. (3) 231, 241; (17) 8, 9
 Dubreuil, D. (18) 120, 166; (24) 13
 Duchaussoy, P. (4) 124
 Duclos, O. (18) 61; (24) 17
 Dudley, R.L. (22) 59
 Dudon, A. (18) 104
 Duee, E. (22) 79

- Dueholm, K.L. (20) 8
 Dufresne, C. (18) 40
 Dulworth, J. (20) 212
 Dumas, D.P. (1) 9; (4) 24, 25, 73;
 (8) 7; (10) 44; (13) 2; (18) 49,
 52
 Dumas, J. (18) 22
 Dumortier, L. (18) 89, 90
 Dunkel, M. (20) 59
 Dunne, T.S. (19) 91; (22) 39
 Duong, T.T. (7) 104
 Dupas, S. (4) 174
 Duréault, A. (18) 61; (24) 17
 Durgnat, J.-M. (12) 13
 Durier, V. (22) 79
 Dushin, R.G. (3) 33, 175
 Duthaler, R.O. (17) 34
 Dutta, B. (13) 20
 Dutta, P. (7) 19
 Dutton, G.G.S. (23) 9
 Duus, J.O. (4) 144; (21) 59, 83
 Dwck, R.A. (21) 62
 Dyakkina, N.B. (20) 264
 Dybusch, M. (14) 40
 Dyson, M.R. (11) 8; (22) 132
- Eakins, M.N. (23) 48
 East, M.B. (1) 5
 Eaton, G. (2) 58
 Ebata, T. (5) 22; (20) 43, 65; (24)
 18, 19
 Echarri, R. (20) 11
 Eckert-Maksic, M. (16) 81; (21)
 28
 Eckhardt, E. (4) 29; (6) 12-14
 Eckstein, F. (20) 84
 Edgar, K.J. (4) 100
 Edison, A.M. (18) 137
 Edmonds, J.S. (17) 10
 Edmunds, C.R. (19) 49
 Effenberger, F. (11) 13
 Efimova, V.L. (18) 1
 Efremov, A.A. (5) 28; (13) 13
 Egan, W. (21) 52
 Egashira, Y. (4) 172
 Eggenspiller, A. (20) 212
 Egli, A. (17) 36
 Egron, M.-J. (20) 179
 Eguchi, S. (20) 35
 Eguchi, T. (15) 1; (24) 1
 Ehn, G. (3) 160
 Eisenbeiss, A. (23) 21
 El Ashry, E.S.H. (10) 57, 75
 El-Badawi, M. (20) 16
 Elbeci, A.D. (18) 65; (24) 68
 El-Eman, A.A. (20) 23
 Eleuteri, A. (20) 185
 Elie, C.J.J. (18) 139, 168
- Eliseeva, G.I. (7) 80
 El Khadem, H.S. (10) 60
 El Kharraf, Z. (8) 28; (10) 6; (16)
 20
 El Kilany, Y. (10) 75
 El Kortbi, M.S. (2) 37
 El-Laghdach, A. (8) 10
 Ellestad, G.A. (19) 91; (22) 39
 Elliott, R.D. (20) 277
 Ellis, J.W. (18) 33
 Ellwood, P. (4) 158; (21) 88
 Elmes, B.C. (20) 70
 Elmroth, I. (23) 37
 El Nemr, A. (10) 57
 El Rassi, Z. (23) 116
 El Sadek, M.M. (10) 71
 El-Sekily, M.A. (10) 64
 El-Shanawani, M.A. (7) 98
 El Subbagh, H.I. (20) 82
 El-Torgoman, A.M. (20) 108
 El-Toukhy, A.A. (10) 62
 Elwood, J.W. (23) 77
 Elyakova, L.A. (3) 99
 Emmerling, M. (23) 6
 Ermrich, F. (23) 79
 Enders, D. (18) 59
 Endo, J. (23) 122
 Endo, T. (19) 46; (20) 248
 Engberts, J.B.F.N. (2) 4
 Engel, R. (17) 19; (18) 136
 Engelhardt, U.H. (23) 41
 Engels, J.W. (20) 116
 Enholm, E.J. (14) 18, 19
 Enokita, R. (19) 86
 Eremenko, L.T. (18) 5
 Eremin, O. (20) 264
 Erntz, R. (20) 296
 Ernst, B. (3) 118
 Erl, P. (10) 52
 Esaki, S. (3) 143
 Escandar, G.M. (17) 23
 Eschenhof, H. (20) 46
 Escudier, J.-M. (12) 10
 Esnault, J. (3) 4
 Espartero, J.L. (9) 36, 37
 Espina, M.R. (18) 60, 109; (24)
 69
 Espinosa, J. (10) 17
 Esteban, A. (23) 66
 Estevez, V.A. (18) 145
 Estrada de Oya, M.D. (10) 17, 23;
 (22) 80
 Esuimi, Y. (24) 76
 Eugui, E.M. (20) 173
 Evans, C.A. (20) 306, 312
 Evans, C.T. (20) 199
 Evans, F.E. (3) 239
 Evans, J.C. (22) 134
 Evans, L. (23) 90
- Even, L.F. (4) 93
 Everaert, D.H. (22) 114
 Everaerts, F.M. (23) 117
 Evtushenko, E.V. (3) 99; (12) 20
 Ewing, D.F. (3) 10; (7) 18; (10) 1
 Eyrisch, O. (7) 59, 65
 Ezawa, T. (20) 327
 Ezzitouni, A. (20) 155
- Faessler, A. (18) 76
 Faillard, H. (3) 203; (10) 2
 Faillé, C. (21) 72
 Fairbanks, A.J. (9) 20; (16) 25;
 (18) 44, 58
 Faivre-Buet, V. (20) 29, 80
 Faizi, S. (3) 76
 Fang, F.G. (24) 56
 Fang, Y. (4) 118; (19) 85
 Faraj, A. (20) 118
 Farid, P. (19) 95
 Farkas, F. (18) 127
 Farkas, I. (8) 28; (10) 6; (16) 20
 Farnsworth, N.R. (4) 55
 Farr, R.N. (3) 258
 Farrant, R.D. (21) 86
 Fathallah, H. (24) 98
 Fatima, A. (14) 29
 Fattori, D. (9) 31; (12) 12
 Fatykhov, A.A. (21) 32
 Fauq, A.H. (18) 161
 Faury, P. (20) 313
 Fava, G.G. (16) 17; (18) 46; (22)
 74, 75
 Favre, A. (20) 224
 Feather, M.S. (2) 72; (10) 58, 59;
 (16) 86; (22) 66; (23) 5
 Fedorov, I.I. (20) 117, 153; (22)
 128
 Fedorova, G.B. (19) 33
 Feeney, J. (4) 7
 Feeney, R.E. (21) 92
 Fehlhaber, H.-W. (19) 25
 Feigl, E.O. (23) 99
 Feist, H. (10) 55; (14) 47
 Feizi, T. (4) 7
 Felin, J.M. (2) 59
 Felix, V. (22) 92
 Fenet, B. (5) 14
 Feng, R. (21) 68, 69
 Fenical, W. (3) 44
 Fenwick, G.R. (23) 49
 Fernández, E. (14) 39
 Fernandez, I. (7) 90; (24) 104
 Fernández-Bolaños Guzmán, J.
 (3) 13, 103; (10) 23, 74; (21)
 59; (22) 80
 Fernández de la Pradilla, R. (18)
 94, 134

- Fernandez-Mayoralas, A. (3) 113, 114, 123; (4) 106; (18) 165
 Fernandez-Rosa, P. (10) 48
 Fernandez-Vega, A. (2) 60
 Ferrara, L.M. (20) 274, 275
 Ferrari, E. (18) 141, 142, 171
 Ferrari, M.B. (16) 17; (18) 46; (22) 74, 75
 Ferrier, R.J. (3) 232; (8) 21; (14) 30
 Ferro, D.R. (21) 30
 Fessner, W.-D. (7) 59, 65
 Feste, A.S. (23) 47
 Fialkov, Yu.Ya. (2) 52
 Fiedler, H.-P. (19) 53
 Field, A.K. (19) 62
 Figlerowicz, M. (20) 328
 Filemon, W. (3) 165; (7) 96; (10) 38; (16) 34; (18) 54
 Filocamo, L. (18) 141, 142, 171
 Findeisen, M. (17) 16
 Finger, A. (23) 41
 Firsov, S.P. (22) 7
 Fischer, H. (11) 3; (16) 71
 Fischer, P. (10) 25
 Fisera, L. (10) 52
 Fiserová, A. (3) 72
 Fizza, K. (20) 282
 Flanagan, G. (2) 8
 Fleet, G.W.J. (3) 218; (9) 20; (16) 25; (18) 43, 44, 58; (24) 42, 43
 Fleming, I. (16) 5
 Flinioux, M.-A. (7) 41
 Flitsch, S.L. (3) 157; (4) 69
 Florcet, J.-C. (19) 37, 43; (20) 118, 145; (24) 14
 Floss, H.G. (9) 16; (16) 31; (18) 82
 Flowers, H.M. (7) 51
 Fluitsma, C.F. (23) 113
 Foces-Foces, C. (18) 106
 Focher, F. (20) 56
 Fodor, G. (16) 81
 Fölsedi, A. (20) 26
 Fokt, I. (3) 197
 Foley, J.P. (23) 2
 Fomicheva, E.V. (19) 33, 34
 Font, J.L. (18) 75
 Fontaine, T. (23) 9
 Ford, P.S. (24) 42
 Foro, E. (8) 35
 Forsyth, A.C. (14) 38
 Forsyth, C.J. (24) 56
 Fournet, B. (23) 9
 Fournier, J.-P. (9) 43
 Fourrey, J.-L. (2) 37; (14) 21; (20) 224
 Fraisse, D. (22) 27
 Francesconi, K.A. (17) 10
 Franchetti, P. (20) 19
 Francisco, C.G. (24) 78
 Franck, R.W. (3) 20, 134; (13) 11; (24) 50
 Francois, P. (4) 66
 Franke, M. (3) 39
 Franssen, M.C.R. (7) 32
 Frantova, A.Y. (18) 138
 Frappier, F. (20) 118
 Frascaroli, M.I. (2) 66
 Fraser-Reid, B. (3) 2, 176, 183; (4) 114, 152; (18) 108; (24) 3, 16
 Fraser-Smith, E.B. (20) 172
 Frayssinet, C. (20) 179
 Fraizer, J.W. (24) 38
 Fréchou, C. (3) 217, 255; (5) 15; (18) 23
 Freeman, G.A. (20) 271
 Freimanis, J. (3) 68
 French, A.D. (21) 55, 56, 60
 French, J.C. (19) 49
 Friesen, M. (10) 5
 Fronczeck, F.R. (22) 98, 99
 Fronza, G. (2) 12; (4) 110; (21) 85
 Frost, J.W. (2) 75; (18) 74, 79, 80
 Fu, H. (8) 34
 Fuchita, Y. (22) 100
 Fudong, W. (24) 60
 Fuentes, J. (3) 103; (7) 29; (10) 22, 67
 Fuganti, C. (2) 12
 Fugimoto, Y. (24) 1
 Fuhrhop, J.-H. (22) 93
 Fujibashi, T. (20) 248
 Fujii, A. (20) 295
 Fujii, K. (3) 193
 Fujii, Y. (3) 67
 Fujimori, S. (20) 55
 Fujimoto, K. (13) 25
 Fujimoto, Y. (15) 1
 Fujioka, H. (3) 67
 Fujita, K. (4) 171, 172
 Fujita, S. (4) 67
 Fujita, Y. (3) 195
 Fukase, H. (18) 111, 112
 Fukase, K. (3) 87; (4) 3, 58
 Fukuda, M. (23) 33
 Fukuda, T. (7) 13-16
 Fukui, K. (9) 1
 Funabashi, M. (10) 72
 Funakoshi, H. (20) 227
 Funayama, S. (19) 87
 Furst, G.T. (3) 18; (4) 57
 Furst, W. (23) 97
 Furuhata, K. (3) 30; (5) 27; (16) 57, 58; (22) 90, 91
 Furui, H. (4) 120
 Furumoto, T. (3) 104
 Furuno, Y. (9) 21; (18) 47, 48; (24) 2, 72
 Furusawa, K. (20) 286
 Furuta, T. (3) 71
 Gabrielson, J. (23) 44
 Gadelle, A. (4) 161, 162
 Gagnaire, D. (3) 16
 Gais, H.-J. (7) 45
 Galambos, G. (11) 1; (16) 15
 Galbis Perez, J.A. (3) 216; (9) 53; (13) 19; (16) 26
 Galema, S.A. (2) 4
 Galensa, R. (23) 27
 Galeone, A. (20) 220
 Galili, N. (3) 94; (7) 30
 Gallagher, R.T. (4) 57
 Gallagher, T. (18) 64
 Galli Kienle, M. (23) 11
 Gallina, C. (9) 41
 Galons, H. (4) 163, 174; (10) 7
 Galoyan, A.A. (3) 74
 Gambacorta, A. (3) 80
 Gammon, D.W. (3) 142; (9) 28
 Gandolfo, F. (2) 66
 Ganesh, K.N. (20) 280, 281
 Ganguly, A.K. (14) 16; (16) 23; (19) 55
 Gao, Y.G. (22) 126
 Garbesi, A. (20) 56
 Garcés, J. (20) 102
 Garcia, D.M. (3) 64
 Garcia, J.G. (22) 98
 Garcia, J.I. (4) 175
 Garcia-Anton, J.M. (10) 12
 Garcia Fernandez, J.M. (3) 103; (5) 35; (10) 67
 Garcia-Junceda, E. (4) 25
 Garcia-Lopez, M.T. (10) 18; (20) 122
 Garcia-Ochoa, S. (12) 5; (16) 13
 Garcia-Raso, A. (23) 18
 Gardiner, J.M. (20) 73
 Gardrat, C. (3) 205
 Garegg, P.J. (1) 4; (3) 159; (4) 35, 98, 140; (7) 22, 24
 Gareis, M. (3) 79
 Garelli, R. (18) 32
 Garg, H.S. (7) 52
 Gargaro, A.R. (22) 140
 Gariboldi, P. (21) 76
 Garner, P. (20) 31
 Garozzo, D. (22) 24
 Gasche, J. (20) 224
 Gaset, A. (23) 107
 Gasi, K. (8) 32
 Gasparini, F. (20) 196, 197
 Gaudel, G. (12) 21; (19) 43; (24)

- 14
 Gaudino, J.J. (4) 150; (24) 84
 Gaudiosi, A. (15) 4
 Gaur, R.K. (20) 260
 Gautheron, C. (1) 8; (4) 81
 Gautier, C. (3) 200; (9) 15; (11) 20
 Gavars, M. (3) 68
 Gawronska, K. (21) 15; (22) 137
 Geerlings, P. (20) 25
 Gehurke, C.W. (23) 90
 Geilen, C.C. (8) 8
 Geller, D.H. (20) 267
 Gelpi, M.E. (18) 119
 Genieser, H.-G. (20) 247
 Gentile, F. (19) 20
 Genu-Dellac, C. (20) 112
 Georg, G.L. (22) 73
 Gerasimov, P.A. (2) 47
 Gergely, L. (20) 113
 Géro, S.D. (7) 105; (16) 72; (17) 3; (18) 120, 125; (19) 50; (20) 270; (24) 13
 Gervay, J. (4) 73, 113
 Geschwindt, L. (10) 19
 Gesson, J.-P. (12) 14; (19) 43; (24) 58
 Ghosh, S.K. (16) 5
 Giannis, A. (2) 30
 Gibbons, W.A. (16) 69; (20) 138
 Gibson, I. (7) 3
 Gibson, W.T. (3) 169
 Giese, B. (2) 36; (16) 32, 33
 Gigg, J. (18) 157-159, 165
 Gigg, R. (18) 157-159, 165
 Gilani, A.-Ul-H. (3) 76
 Gilbert, B.C. (20) 323
 Gilbert, L.I. (18) 37, 101
 Giles, M. (18) 64
 Giocli, C. (20) 26
 Giordano, C. (9) 41
 Girard, B. (6) 5
 Girard, C. (12) 9; (13) 17
 Giraud, B. (24) 95
 Girjavallabhan, V.M. (14) 16; (16) 23; (19) 55
 Giudicelli, M.-B. (9) 7, 49
 Giuffreda, P. (21) 81
 Glassgen, W.E. (23) 6
 Glaudemans, C.P.J. (4) 32, 33, 99, 103, 147; (8) 12; (13) 24
 Gleason, J.G. (3) 253, (20) 255
 Glemarec, C. (20) 26
 Glazinski, P. (22) 64
 Gmeiner, W.H. (21) 27
 Goda, S.K. (19) 13
 Göbel, T. (16) 33
 Goekjian, P.G. (3) 102; (4) 82; (21) 61
 Goenechea, S. (3) 39
 Golavnya, R.V. (10) 30
 Goldberg, I. (22) 103
 Goldstein, B.M. (19) 69
 Golebiowski, A. (2) 21; (9) 29; (18) 73
 Golik, J. (9) 2, 3; (14) 2; (22) 71
 Goljer, I. (10) 52
 Gomez, A.M. (12) 5; (13) 10; (14) 22; (16) 13, 27; (24) 9, 45
 Gomez, F.J. (23) 25
 Gomez-Guillem, M. (10) 65
 Gomez-Sanchez, A. (9) 35; (10) 70
 Gomi, S. (19) 29
 Gomtsyan, A. (9) 52
 Gong, M.L. (2) 38
 Gonzalez, F. (14) 12
 Gonzalez, F.B. (18) 60, 109; (24) 69
 Gonzalez, F.S. (4) 161, 175; (9) 26; (14) 14
 Gonzalez-Scarano, F. (3) 250
 Goodwin, T.E. (3) 239
 Gopalakrishnan, V. (20) 280, 281
 Goral, J. (22) 8
 Gordon, D.M. (3) 47; (11) 14
 Gorrichon, L. (12) 10; (18) 81
 Gorshkova, R.P. (14) 9
 Gosh, A.K. (7) 104
 Gosh, R. (3) 110; (6) 7
 Gosselin, G. (7) 2; (20) 6, 112, 317
 Gostoli, B. (18) 142
 Gostoli, G. (18) 171
 Gostoli, L. (18) 141
 Goto, F. (4) 104, 138
 Gotor, V. (7) 36, 37, 99; (20) 287-289
 Gottlieb, M. (4) 169
 Gou, D.-M. (18) 155, 156
 Gould, G.L. (6) 16
 Gould, R.O. (14) 38
 Gould, S.J. (19) 109
 Goux, W.J. (7) 62; (21) 67
 Grabley, S. (3) 79
 Gracza, T. (24) 27
 Gradaing, G. (2) 39, 57; (8) 6; (10) 42; (18) 14, 42
 Graells, M. (23) 66
 Graham, W.D. (23) 75
 Grand-Maitre, C. (3) 201
 Granucci, I. (15) 9; (16) 73
 Gras, J.-L. (6) 1, 5; (24) 95, 96
 Grasdalen, H. (21) 73
 Grassberger, V. (2) 39; (18) 14, 42
 Grasser, M. (2) 57; (8) 6; (10) 42
 Gravier-Pelletier, C. (18) 22
 Gray, G.R. (18) 25
 Green, D. (22) 103
 Greenberg, G.E. (23) 102
 Gregson, J.M. (19) 48
 Greiner, J. (7) 17, 71
 Grewal, G. (3) 134
 Grey, A.A. (4) 43, 116
 Griengl, H. (19) 64
 Grierson, D.S. (18) 70; (20) 118, 145
 Griffantini, M. (20) 19
 Griffith, D.A. (4) 73, 113
 Griffith, O.H. (18) 144
 Grigera, J.R. (21) 16
 Grignon-Dubois, M. (2) 15; (13) 23
 Grignau, H. (22) 79
 Grindley, T.B. (22) 94
 Grodner, J. (14) 36; (24) 60, 61
 Gronowitz, S. (7) 70; (20) 48
 Grouiller, A. (3) 10; (7) 18; (10) 1, (20) 29, 80
 Grover, P.T. (18) 18
 Groziak, M.P. (20) 40
 Grützmacher, H.-F. (22) 14, 15
 Gruys, K.J. (18) 75
 Grynkiewicz, G. (13) 5; (14) 24
 Guanti, G. (9) 30
 Guard, H.E. (17) 21
 Guarini, A. (22) 11
 Guarneri, M. (20) 21
 Gubareva, A.L. (2) 47
 Guenther, K. (8) 19
 Guga, P. (7) 72
 Guglielmetti, G. (22) 11
 Guidelli, R. (2) 63
 Guilbert, B. (4) 69
 Guile, S.D. (19) 78; (20) 201
 Guilhem, J. (18) 126; (22) 108
 Guillet, J.M. (3) 198
 Gulati, D. (20) 137
 Gulayi, I.S. (2) 51
 Gullo, V. (19) 20, 21
 Gumbowski, R. (20) 52
 Gunata, Z.Y. (23) 14
 Gundersen, L.-L. (20) 200
 Gundes, A.F. (9) 19
 Gunnarsson, I. (19) 20
 Gunther, W. (3) 14
 Guo, J. (17) 29
 Guo, W. (4) 18
 Guo, X. (3) 179; (16) 46
 Gupta, D. (2) 23; (9) 51
 Gupta, R. (16) 9
 Gurjar, M.K. (3) 29, 51, 144; (4) 34, 53; (5) 2; (20) 107
 Gurskaya, G.V. (20) 153; (22) 123, 128
 Guse, A.H. (23) 79

- Guzmán, J.F.-B. (3) 13, 103; (10) 23, 74; (21) 59; (22) 80
 Gyorgydeak, Z. (21) 17
- Ha, E.Y. (20) 318
 Ha, S.N. (21) 29
 Haas, A. (20) 50
 Habermann, N. (17) 24; (22) 96
 Haces, A. (20) 57
 Hada, N. (4) 108
 Hadjoudis, E. (22) 42
 Hudley, M.S. (18) 64
 Haebich, D. (20) 103
 Häggren, C. (4) 98, 140; (7) 22, 24, (21) 45
 Hafner, A. (17) 34
 Hagedorn, H.-W. (16) 59; (22) 57
 Hager, M.W. (8) 14; (20) 91
 Haigom, H. (4) 28
 Haines, A.H. (7) 3
 Hakimclahi, G.H. (20) 269
 Hakomori, S. (7) 43; (18) 135; (20) 254
 Halazy, S. (20) 212, 273
 Halcomb, R.L. (4) 87; (16) 38
 Halenbeck, R. (19) 107
 Hall, D.W. (3) 232
 Halldin, C. (2) 25
 Hallows, W.H. (19) 69
 Hallstrom, S. (23) 97
 Haltiner, R. (3) 19
 Hamano, Y. (20) 35
 Hambalek, R.J. (20) 171
 Hamid, H.A. (10) 57, 75
 Hamid-ul-Qadir, M. (3) 186
 Hammargren, W.M. (20) 134
 Hammerschmidt, F. (18) 50
 Han, H.K. (3) 260
 Han, S.-Y. (24) 64
 Hanada, K. (19) 22
 Hanafusa, T. (6) 10; (22) 16
 Hanagata, G. (4) 37
 Hanai, Y. (19) 59
 Hanamoto, T. (2) 13
 Hanaya, T. (17) 1, 2, 4, 7
 Haneda, T. (4) 82
 Hanessian, S. (12) 9; (13) 17; (14) 20; (21) 91
 Hangland, J.J. (20) 60
 Hansen, H.B. (18) 16; (20) 176
 Hansen, J. (19) 36
 Hansen, S.H. (16) 68; (23) 71
 Haque, M.E. (7) 19-21; (9) 27, (13) 20
 Hara, K. (4) 41
 Hara, S. (7) 92, 97; (20) 20
 Harada, H. (3) 84
 Harada, T. (22) 142
- Haradahira, T. (8) 20
 Haraguchi, K. (20) 142, 174; (22) 113, 115
 Haratake, M. (3) 78
 Harbin, A.-M. (23) 46
 Harbison, G.S. (21) 78
 Harder, W. (10) 76
 Hardwick, D.J. (2) 22; (18) 38
 Hardy, G.W. (11) 8; (22) 132
 Harigaya, Y. (9) 25
 Harlicek, V. (3) 72
 Haro, I. (10) 12
 Harrap, K.R. (20) 135
 Harrington, P.H. (19) 111
 Harris, P.J. (23) 4
 Harris, S.L. (4) 143
 Harris-Brands, M. (4) 116
 Harrold, M.P. (23) 112
 Hart, D.J. (3) 229
 Hartgers, W.A. (20) 285
 Hartmann, M. (16) 50
 Haruyama, H. (19) 54, 86
 Hase, S. (4) 58, 136; (18) 34; (23) 56
 Hasegawa, A. (3) 151, 153, 199; (4) 62, 63, 96, 97, 107, 120, 127, 128, 137; (16) 52, 53
 Hasegawa, T. (16) 47; (20) 292
 Hashigaki, K. (10) 4
 Hashimoto, H. (3) 84, 164; (5) 9, (11) 11; (12) 17
 Hashimoto, S. (3) 135
 Hashimoto, Y. (4) 28; (20) 55
 Hashizume, T. (21) 26
 Hasler, A. (23) 42
 Hassan, A.A.A. (20) 151
 Hassan, M.E. (18) 56, 57
 Hassan, R.M. (16) 85
 Hasuoka, A. (3) 87
 Hata, T. (20) 96, 236, 237
 Hatanaka, C. (23) 62
 Hatanaka, K. (5) 34; (21) 90
 Hatano, T. (7) 55, 58
 Hatfield, R.D. (7) 8
 Hato, M. (3) 57, (24) 89
 Hatokeyama, S. (14) 1
 Hatsu, M. (19) 29
 Hattori, K. (24) 103
 Hattori, S. (7) 58
 Hau, W.H. (3) 190
 Haudrechy, A. (3) 148
 Hoang, S. (14) 2
 Havel, M. (3) 65
 Havlicek, J. (22) 6, 76
 Hawkes, T.R. (18) 78
 Hawrelak, S.D. (20) 100
 Hay, A.J. (20) 61, 243
 Hay, G.W. (4) 95
 Hayashi, H. (18) 29
- Hayashi, M. (19) 17, 23
 Hayashi, N. (20) 297; (22) 124
 Hayes, R.N. (22) 17
 Haynes, P.A. (23) 51
 He, D.Y. (6) 3, 4
 He, Y. (4) 173
 Hearne, D.O. (3) 185
 Heath, J.A. (20) 60
 Heath, P.C. (20) 90
 Hecht, L. (22) 140
 Hecht, S.M. (7) 56
 Hecker, S.J. (19) 103-105
 Hedtmann, V. (19) 25
 Heeg, M.J. (18) 88
 Hegde, V. (19) 20
 Hegedus, L. (19) 79
 Hegeschweiler, K. (17) 36
 Heidas, J.E. (2) 19; (20) 250, 251
 Heikkilä, H. (22) 60
 Heinemann, F. (3) 22; (10) 16
 Heins, H. (20) 188
 Heintzelman, G.R. (16) 29
 Heitschmidt, T.A. (18) 33
 Heitsch, H. (24) 88
 Helander, A. (3) 129
 Helin, J. (4) 132
 Helland, A.-C. (4) 146
 Hellenas, K.-E. (23) 44
 Hellwell, M. (22) 118
 Helm, R.F. (7) 8
 Hemmerle, H. (7) 45
 Henderson, J. (18) 62, 65; (24) 66, 68
 Hendry, P. (7) 74
 Heng, R. (24) 90
 Henin, Y. (20) 241
 Henk, T. (2) 30
 Henning, R. (24) 88
 Henshall, A. (23) 112
 Henton, J.D. (23) 87
 Herald, G. (6) 12, 13
 Herbreteau, B. (23) 22, 26
 Herczegh, P. (18) 63; (24) 70
 Herdewijn, P. (10) 68; (20) 83, 125; (22) 114
 Hermansson, K. (21) 71
 Hermosin, I. (9) 35; (10) 70
 Hernandez, A.E. (20) 100
 Herranz, R. (20) 122
 Herrin, T. (19) 61; (20) 315
 Herrmann, S.C. (23) 99
 Herscovici, J. (3) 237
 Heskamp, B.M. (3) 132
 Heusinger, H. (16) 87
 Hickman, C.T. (3) 180
 Hicks, K.B. (22) 59
 Hicks, N. (20) 61
 Hidai, M. (2) 55
 Hidaka, Y. (22) 16

- Hiebl, J. (20) 111
 Hiegemann, M. (3) 22; (10) 16
 Higashi, K. (3) 25, 26, 31, 162,
 177; (9) 48
 Higashio, H. (3) 40
 Higgins, E. (4) 116
 ghcock, R.M. (11) 9; (20) 303
 Iguchi, H. (9) 1; (19) 81
 Iguchi, R. (3) 188, 189, (7) 50
 Higuchi, T. (4) 28
 Hikage, N. (12) 22; (24) 57
 Hildebrand, C. (20) 44
 Hildebrandt, J. (3) 28; (7) 48
 Hill, T.G. (18) 36, 37
 Hindsgaul, O. (3) 121, 124, (4)
 45, 125, 130; (11) 17; (21) 83
 Hiraoaka, K. (3) 36
 Hiraoaka, T. (9) 46
 Hirase, S. (7) 92, 97
 Hirata, M. (18) 146
 Hirata, N. (23) 28
 Hirayama, N. (24) 4
 Hirooka, M. (4) 28
 Hirota, K. (20) 38, 239, 291
 Hirota, T. (20) 35
 Hirota, Y. (20) 45
 Hirsch, J. (10) 58, 59; (22) 14, 66
 Hirschmann, R. (3) 18
 Hiruma, S. (19) 51; (20) 3
 Hisamichi, K. (3) 187
 Hisamura, K. (20) 301, 320
 Hjelde-Nielsen, H.P. (18) 16
 Ho, C.T. (10) 27
 Hoang, L.C. (18) 4, 28
 Hobbs, C.J. (3) 108
 Hockstein, D.R. (19) 62
 Hodoseck, M. (16) 81
 Hodosi, G. (8) 36; (11) 1; (16) 15
 Hoeprich, P.D., Jr. (3) 249
 Hornfeld, A.-B. (20) 48
 Hoeweler, U. (21) 28
 Hoffmann, D. (19) 25
 Hoffmann, P. (2) 35
 Hofmann, R. (23) 6
 Hofstead, S.J. (9) 2, 3; (14) 2; (22)
 71
 Hogan, M.E. (20) 183
 Hogg, A.M. (17) 1, 4
 Holan, G. (20) 70
 Holla, E.W. (3) 52; (10) 39
 Hollosi, M. (10) 11, 13
 Holman, M.J. (20) 68
 Holmes, A.B. (18) 101
 Holpe-Kozlova, N.V. (19) 110
 Holst, O. (4) 60; (21) 75
 Holtz, J. (5) 10
 Holzapfel, C.W. (7) 51, 101; (12)
 30; (24) 47, 48
 Homma, H. (20) 186
- Hon, Y.S. (2) 38
 Honda, S. (23) 40, 114
 Honda, T. (3) 84, 135
 Honek, J.F. (7) 67
 Hong, N. (4) 2
 Honmi, S. (20) 189
 Hoogmartens, J. (10) 68; (23) 83
 Hook, J. (7) 3
 Hoong, L.K. (20) 311
 Hoppe, B. (9) 38
 Hoppe, D. (14) 40
 Horakova, I. (7) 35
 Horan, A. (19) 20, 21
 Horgan, R. (4) 16
 Hori, K. (12) 22; (24) 57
 Horie, R. (4) 41
 Horiguchi, A. (3) 228
 Horii, S. (18) 111, 112
 Horii, T. (16) 80
 Horikoshi, I. (7) 57
 Horita, K. (24) 55
 Horlacher, J. (20) 209
 Horton, D. (3) 178; (5) 4; (14) 37
 Horváth, G. (3) 173; (19) 24
 Horváth, K. (21) 51
 Hosaka, H. (20) 227
 Hoshi, H. (19) 41
 Hoshi, T. (12) 8
 Hosmane, R.S. (20) 22, 54; (22)
 130
 Hosono, H. (20) 291
 Hosoya, M. (19) 72, 80
 Hosoya, T. (3) 259
 Houalla, D. (17) 18
 Houdier, S. (3) 90
 Hough, L. (2) 3; (3) 11; (9) 12
 Houssell, E.F. (4) 7; (23) 46
 Howard, E. (21) 16
 Howarth, J. (14) 44; (22) 82
 Hronowski, L.J.J. (4) 95; (20) 203
 Hruby, V.J. (3) 49
 Hsiao, M.W. (2) 61
 Hsiao, C.-N. (24) 86
 Hsu, L.Y. (20) 319
 Hsu, V.L. (20) 220
 Hu, W. (3) 37
 Huang, D.-B. (22) 49, 59
 Huang, D.-H. (4) 111
 Huang, J. (11) 16
 Huang, L.H. (12) 24; (19) 88; (21)
 92
 Huang, S. (9) 3
 Huang, T.-N. (20) 68
 Huang, W. (5) 7
 Huang, Y.P. (2) 38
 Hudlicky, T. (18) 85, 118
 Hudson, B.D. (21) 86
 Huel, C. (2) 43; (18) 126; (22)
 108
- Hürzeler, M. (3) 196
 Huet, F. (19) 63
 Hug, P. (2) 35
 Hug, W. (22) 140
 Hughbanks, D. (23) 95
 Humber, D.C. (20) 312
 Humble, R.W. (22) 27
 Hummel, C.W. (4) 93, 111, 112;
 (11) 19; (19) 90
 Hunt, A.H. (20) 90
 Hurley, T.R. (19) 49
 Huryn, D.M. (19) 45; (20) 7, 302
 Huser, H. (16) 30
 Hussain, R. (16) 69; (20) 138
 Huston, M.E. (18) 36
 Hutchinson, D.W. (2) 22; (9) 50;
 (18) 38; (20) 61, 219
 Hutchinson, E.J. (19) 66
 Huynh-Dinh, T. (20) 241
 Hwang, C.H. (20) 13
 Hwang, K.J. (23) 120
 Hwh, E.Y. (7) 1
- Ichikawa, Y. (1) 9; (3) 120, 155;
 (4) 24, 25, 68, 111; (8) 34; (16)
 38-40; (20) 253
 Ichinose, K. (3) 98; (7) 7; (8) 23
 Ichishima, E. (23) 121
 Ichiya, Y. (8) 20
 Ida, Y. (9) 1
 Ignatenkov, A.V. (4) 15; (7) 78,
 82
 Iida, Y. (3) 8
 Iihana, Y. (15) 1; (24) 1, 76
 Iijima, H. (3) 154
 Iimura, S. (19) 41
 Ikeda, K. (16) 42; (20) 20
 Ikeda, M. (3) 59
 Ikeda, T. (3) 257; (9) 1
 Ikegaki, T. (4) 28
 Ikegami, S. (3) 84, 135
 Ikemoto, H. (18) 47; (24) 72
 Ikemoto, N. (3) 182, (19) 52; (20)
 30; (23) 39
 Ikenaga, T. (4) 58
 Ikenaka, T. (4) 136
 Ikeuchi, Y. (4) 37
 Ikeura, C. (3) 228
 Ikota, N. (9) 33
 Ilyina, G.S. (3) 75
 Imada, T. (20) 237
 Imagawa, H. (4) 157
 Imai, K. (3) 192
 Imamura, N. (24) 76
 Imanari, T. (23) 57, 58
 Imbach, J.-L. (7) 2, (11) 7; (20) 6,
 112, 132, 317
 Immel, S. (21) 39

- Imoto, T. (4) 172
 Impallomeni, G. (22) 24
 Impellizzeri, G. (4) 178
 In, Y. (20) 297; (22) 124
 Inagaki, A. (12) 22; (24) 57
 Inami, K. (16) 37, 55
 Inanaga, J. (2) 13
 Inderbitzin, W. (19) 58
 Inoue, H. (16) 80
 Inoue, M. (20) 297; (22) 124
 Inoue, S. (23) 62
 Inoue, T. (7) 53; (24) 55
 Inoue, Y. (23) 29
 Inouye, S. (19) 29
 Inouye, Y. (19) 27
 Inukai, M. (19) 86
 Ioannidis, P. (20) 143
 Iotti, S. (20) 56
 Iqbal, K. (23) 106
 Irie, H. (24) 34
 Irie, K. (3) 126
 Irie, M. (10) 72
 Irisawa, T. (4) 28
 Ishibashi, M. (19) 32; (20) 2
 Ishida, H. (4) 97
 Ishida, N. (9) 46
 Ishida, T. (20) 297; (22) 124
 Ishido, Y. (3) 117
 Ishigami, S. (20) 195
 Ishihara, J. (24) 22
 Ishii, H. (3) 40
 Ishikawa, K. (24) 93
 Ishimaru, K. (16) 1
 Ishizawa, A. (19) 17
 Ishizawa, K. (19) 18, 19
 Ishizu, T. (4) 172
 Ishizuka, T. (3) 225
 Islam, L.E. (20) 42
 Islam, Q. (20) 64
 Ismail, A.A. (2) 53; (22) 4
 Ismail, E.S. (20) 42
 Isobe, M. (3) 234; (13) 21
 Isoc, S. (18) 15
 Isono, K. (19) 44, 48, 89
 Isshiki, Y. (24) 12
 Ittczono, Y. (7) 54
 Ito, C. (20) 189, 190
 Ito, S. (10) 20
 Ito, Y. (3) 31, 57, 126; (4) 126,
 151, 153; (20) 190
 Itoh, A. (18) 53
 Itoh, H. (19) 68
 Itoh, J. (19) 47
 Itoh, T. (7) 13, 16
 Itoh, Y. (20) 174; (22) 113, 115
 Ivanova, I.A. (4) 119; (7) 80, 81
 Iwabuchi, Y. (4) 112; (11) 19
 Iwagami, H. (20) 71
 Iwanami, N. (20) 55
 Iwasawa, H. (3) 126
 Iwase, H. (23) 74
 Iwashita, T. (4) 17
 Iwitzki, F. (20) 247
 Iyengar, T.A. (2) 70
 Iyer, R.P. (20) 278
 Izawa, K. (20) 71
 Izawa, T. (14) 15; (16) 24; (20)
 314
 Izumi, A. (16) 78
 Izumi, M. (4) 19; (5) 9; (11) 11
 Jack, Y.-C. (20) 101
 Jackson, G.E. (21) 40
 Jacobs, G.A. (19) 62
 Jacquesy, J.-C. (12) 14; (19) 43
 Jacquin-Dubreuil, A. (7) 41
 Jacquinet, J.-C. (3) 158; (10) 36
 Jadan, P.K. (18) 30
 Jäger, V. (24) 27
 Jackel, F. (24) 15
 Jagannadham, V. (2) 64
 Jaime, C. (21) 37
 Jain, R.K. (3) 89; (4) 42, 49, 50,
 52, 133
 Jajoo, H.K. (22) 36; (23) 104
 Jakobsons, J. (7) 27
 Jaksic, M.M. (16) 6
 Jakupovic, J. (18) 97
 Janado, M. (2) 2
 Janda, K.D. (20) 101
 Jandik, P. (23) 111
 Jang, D.O. (12) 1, 2, 4
 Janiszewski, J.S. (23) 93
 Janson, R.W. (23) 100
 Janson, M. (20) 215
 Janssen, A.E.M. (7) 32
 Janssen, G. (10) 68; (23) 83
 Jansson, A.M. (3) 129
 Jansson, P.-E. (4) 5; (21) 58, 70,
 71
 Jansze, J.-P. (18) 168
 Janzek, E. (3) 160
 Jaramillo, C. (7) 88
 Jarosz, S. (2) 28, 42, 45
 Jarrig, J.-M. (20) 145
 Jary, J. (7) 34, 35
 Jasko, M.V. (20) 153
 Jaskolski, M. (20) 328
 Jastorff, B. (20) 247
 Jaszberenyi, J.C. (9) 13; (12) 1, 2,
 4; (17) 11; (18) 125
 Jaurand, G. (4) 122-124
 Jean, E. (10) 50; (22) 68
 Jeanneret, V. (20) 197
 Jeffrey, G.A. (1) 12, 14; (22) 49,
 54, 59
 Jegeika, U. (18) 59
 Jelicks, L.A. (20) 39
 Jenkins, I.D. (6) 19
 Jenkins, P.R. (14) 44; (22) 82
 Jennings, H.J. (4) 150
 Jennings, L.J. (20) 121
 Jenny, T.F. (20) 163, 209
 Jensen, P.R. (3) 44
 Jeong, L.S. (20) 64, 307-310; (22)
 112
 Jerkovich, G. (6) 18
 Jeschke, U. (11) 3; (16) 71
 Jha, D.D. (2) 65
 Jiang, C. (4) 139
 Jiang, H. (8) 9; (10) 41; (22) 69,
 70
 Jiang, S. (14) 18, 19
 Jiang, T. (21) 34
 Jiang, X. (21) 10
 Jiang, X.-J. (20) 263
 Jiang, Z.-H. (4) 142
 Jian, X. (6) 4; (20) 12
 Jimenez, J.L. (10) 17
 Jimenez-Barbero, J. (3) 113; (12)
 27, (21) 54
 Jimeno, M.L. (18) 105; (24) 7
 Jin, H. (20) 306, 312
 Joerdening, H.J. (4) 27; (15) 7
 Jörnig, W.P.A. (3) 168, 172; (9)
 59
 Johansson, L.A.M. (15) 8
 Johansson, N.G. (20) 48
 Johdo, O. (19) 42
 Johnson, C.R. (2) 21; (18) 73, 88
 Johnson, L.N. (3) 218
 Johnson, P.D. (3) 242; (13) 7
 Johnson, R. (20) 131
 Johnson, T. (3) 230; (16) 18
 Johnston, J.H. (19) 84
 Jokic, A. (16) 6
 Jones, A.H. (18) 58
 Jones, B.C.N.M. (20) 242
 Jones, C.R. (18) 77
 Jones, D.A. (5) 32; (10) 43
 Jones, D.N. (6) 9; (13) 18; (14)
 32; (16) 64; (22) 84
 Jones, G.S. (13) 4
 Jones, L.A. (20) 293, 294
 Jones, M.F. (11) 9; (20) 303, 312
 Jones, P.G. (17) 35; (22) 97
 Jones, W.R. (20) 180; (23) 181
 Joo, Y.H. (24) 5
 Jorgensen, P.T. (20) 27
 Joseph, B. (3) 191; (23) 45
 Joseph-Nathan, P. (21) 46
 Joshi, B.V. (20) 76, 130, 131
 Joullié, M.M. (24) 64
 Joyce, G.F. (19) 93
 Juari, E. (21) 1
 Jürgens, U.J. (18) 8

- Jund, K.C. (20) 265
 Jung, G. (2) 24; (17) 24; (22) 96
 Jung, K.-H. (3) 248; (14) 41; (20) 256
 Jung, M.E. (13) 9; (20) 67, 73
 Jung, S.H. (24) 56
 Junguera, F. (9) 4
 Juni, K. (20) 292
 Juodka, B. (20) 244
 Jurczak, J. (9) 29
 Just, G. (20) 171
- Kabir, A.K.M.S. (7) 19-21; (13) 20
 Kabuto, K. (16) 21
 Kádár-Paunz, J. (19) 24
 Kadém, L. (17) 16
 Kadota, I. (24) 94
 Kählig, H. (18) 50
 Kähling, H. (18) 50
 Kagemoto, T. (10) 72
 Kageyama, S. (19) 24
 Kahle, A.D. (19) 30, 84
 Kaila, N. (3) 20, 134; (13) 11
 Kaiwaz, S.P. (17) 28, 32
 Kajii, A. (20) 248
 Kajii, E. (4) 44; (9) 25
 Kajihara, Y. (3) 164; (12) 8
 Kajikawa, Y. (3) 257
 Kajima, Y. (3) 153
 Kajimoto, T. (1) 9; (13) 2, (18) 52
 Kajiwara, M. (24) 6
 Kakefuda, A. (20) 149
 Kakehi, A. (20) 36
 Kakuchi, K. (23) 40, 114
 Kakiimoto, K. (7) 102
 Kakinuma, K. (15) 1; (18) 102; (19) 14; (23) 19; (24) 1, 76
 Kal, U.E. (20) 299
 Kalicheva, I.S. (3) 74
 Kalman, T.I. (22) 111
 Kalteneb, R.F., III (18) 140
 Kaluza, Z. (24) 63
 Kalvinsh, I. (9) 52
 Kamachi, H. (19) 41
 Kamazawa, H. (23) 38
 Kameda, W. (3) 36
 Kameda, Y. (3) 104
 Kamei, H. (19) 106
 Kamei-Hayashi, K. (7) 92, 97
 Kamel, M.S. (7) 41, 98
 Kamerling, J.P. (4) 40, 54, 134; (5) 12; (21) 12, 66; (23) 34
 Kameyama, A. (4) 127, 128
 Kaniinskii, Yu.L. (7) 73; (18) 1
 Kamiya, S. (3) 143
 Kamori, T. (7) 50
 Kan, Y. (4) 157
 Kanaan, R. (3) 81
 Kanakamma, P.P. (8) 26
 Kanazawa, H. (22) 31
 Kanazawa, S. (14) 43
 Kanda, Y. (3) 70
 Kane, R.W. (2) 71
 Kaneda, J. (6) 10
 Kaneda, N. (4) 55
 Kaneko, C. (19) 74, 75; (20) 20, 216-218, 316
 Kanematsu, T. (18) 146
 Kanemitsu, K. (7) 102
 Kaneta, T. (23) 119
 Kang, S.-K. (24) 21
 Kang, Y.H. (3) 260
 Kanters, J.A. (22) 1, 2
 Kaptein, R. (21) 80
 Karoutis, A.I. (23) 16
 Kasai, M. (23) 28
 Kasai, R. (7) 98
 Kase, H. (19) 82
 Kashem, M.A. (4) 116, 139
 Kashino, S. (22) 50
 Kashiwa, K. (4) 22
 Kasmi, S.N. (9) 9
 Kassem, A.A. (10) 62
 Katagiri, N. (19) 74, 75; (20) 216-218, 316
 Kataky, R. (4) 168; (5) 13
 Katalenic, D. (20) 124
 Katayama, T. (19) 35, 86
 Kato, A. (8) 20
 Kato, I. (23) 55
 Kato, K. (14) 15; (16) 24; (20) 28, 314
 Kato, N. (7) 61
 Kato, T. (3) 126
 Katona, T. (23) 48
 Katrukh, G.S. (19) 33
 Katrusiak, A. (22) 102
 Katsunata, K. (3) 213
 Katsunata, R. (3) 117
 Katsunata, A. (3) 143
 Katsurada, M. (3) 8
 Katz, R.N. (23) 13
 Kaufmann, F. (9) 45
 Kaufmann, R. (22) 30
 Kaul, S. (23) 93
 Kaula, I. (3) 68
 Kaur, K.J. (4) 130
 Kawada, K. (3) 192
 Kawagishi, H. (4) 19
 Kawaguchi, T. (20) 292
 Kawahara, N. (20) 1
 Kawai, G. (21) 26
 Kawai, H. (19) 39
 Kawakami, H. (5) 22; (20) 43, 65; (24) 18, 19
 Kawamoto, H. (17) 4
 Kawamoto, I. (19) 82
 Kawamura, M. (14) 1
 Kawana, M. (20) 98, 181
 Kawasaki, H. (4) 28
 Kawasaki, T. (3) 78
 Kawashima, A. (19) 22
 Kawashima, K. (3) 46, 58
 Kawashima, Y. (10) 20
 Kawczyński, W. (20) 115
 Kayakiri, N. (19) 83
 Kayser, H. (9) 38
 Kazakov, A.I. (18) 5
 Kazanietz, M.G. (7) 4
 Kazimierczuk, Z. (20) 53
 Kazmi, S.N.H. (5) 24
 Kaz'mina, E.M. (20) 153; (22) 128
 Kazuhara, H. (12) 15
 Kazuta, K. (18) 53
 Keuna, J.F.W. (18) 144
 Kearns, A.E. (20) 267
 Kearns, D.R. (20) 220
 Koenan, T.P. (4) 57
 Kefurt, K. (7) 34, 35; (22) 6, 76
 Kefurtova, Z. (7) 35
 Kelland, J. (3) 81
 Kelley, J.A. (19) 79; (20) 88
 Kellogg, R.M. (10) 76
 Kelm, S. (4) 144
 Kenne, L. (3) 129, (4) 5; (21) 70, 71
 Kenny, M. (20) 212
 Kenyon, G.L. (20) 261
 Kern, M. (3) 161
 Kervagoret, J. (24) 23
 Kessler, H. (3) 252
 Ketcham, C. (4) 25
 Khalilov, L.M. (20) 14
 Khair, N. (7) 90
 Khakhalina, N.V. (24) 20
 Khalaf-Nezhad, A. (20) 269
 Khalilov, L.M. (3) 222; (21) 32
 Khan, I. (23) 47
 Khan, K.A. (20) 282
 Khan, R. (9) 50
 Khan, S.H. (4) 43
 Khan, S.I. (20) 137
 Khan, T.H. (4) 69
 Khanna, I. (19) 95
 Khare, D.P. (4) 48
 Khedhair, K.A. (21) 5
 Khiar, N. (24) 104
 Khrpach, N.B. (20) 93; (21) 23
 Khuong-Huu, Q. (24) 23
 Khwaja, H. (17) 35; (22) 97
 Kibayashi, C. (24) 39, 77
 Kieboom, A.P.G. (10) 56; (15) 8; (17) 37
 Kikuchi, Y. (2) 73
 Kilaas, L. (14) 13

- Kim, B.K. (24) 21
 Kim, C.-G. (9) 16; (16) 31; (18) 82
 Kim, C.U. (20) 73, 274
 Kim, G. (3) 125
 Kim, H.O. (20) 64, 307-310; (22) 112
 Kim, J.-H. (3) 260
 Kim, J.N. (20) 152, 184
 Kim, J.Y. (7) 60
 Kim, K.E. (7) 1
 Kim, K.S. (24) 5
 Kim, M.J. (7) 60
 Kim, O.K. (3) 182
 Kim, S. (23) 77
 Kim, S.H. (4) 82
 Kim, V.I. (2) 62
 Kim, Y.C. (3) 188, 189; (7) 50
 Kimura, K.-i. (19) 48
 Kimura, T. (24) 37
 King, A. (19) 20
 King, C.R. (3) 73; (23) 89
 Kingery-Wood, J.E. (16) 45
 Kingsford-Adaboh, R. (22) 50
 Kinjo, J. (9) 1; (19) 81
 Kinoshita, I. (3) 87
 Kinoshita, K. (19) 23
 Kinoshita, M. (3) 225
 Kirihara, M. (3) 67
 Kirk, O. (7) 42
 Kim, A. (20) 112
 Kirschning, A. (9) 16; (16) 31; (18) 82
 Kislev, M.Yu. (8) 18
 Kishi, Y. (3) 102, 247; (4) 82; (21) 61; (24) 56
 Kishimoto, H. (24) 83
 Kiso, M. (3) 151, 153, 199; (4) 62, 63, 96, 97, 107, 120, 127, 128, 137; (16) 52, 53
 Kita, K. (7) 61
 Kita, Y. (3) 67, (16) 11
 Kitade, Y. (20) 38, 239, 291
 Kitagawa, I. (3) 46, 59, 66
 Kitajima, T. (4) 148
 Kitamura, F. (23) 24
 Kitamura, S. (4) 10, 11; (5) 8; (22) 58
 Kitazume, T. (8) 5
 Kitaka, A. (20) 175; (22) 129
 Kiuchi, F. (15) 2
 Kivikoski, J. (22) 60-62
 Kivimaki, A.-M. (2) 67
 Kiyota, H. (24) 52
 Kiyoto, H. (7) 46
 Kjaersgaard, U. (20) 108
 Kjolberg, O. (24) 49
 Klaasen, M. (17) 24; (22) 96
 Klabbers, C. (7) 32
 Klärkes, U. (8) 27
 Kläfke, W. (10) 39
 Kleemann, H.-W. (24) 88
 Klein, R.S. (20) 39, 187
 Klement, U. (22) 78
 Klessinger, M. (21) 28
 Klimov, E.M. (3) 85, 130; (4) 14; (11) 4
 Klimovich, V.M. (2) 51
 Kline, P.C. (21) 21
 Klinger, M.M. (20) 257
 Klinghorn, A.D. (4) 55
 Klohr, S.E. (9) 3; (14) 2
 Klotz, K.-N. (20) 185
 Klotz, W. (3) 91
 Klüfers, P. (17) 24; (22) 96
 Knapp, S. (7) 88; (18) 113
 Knaus, E.E. (20) 290
 Knecht, K.J. (23) 5
 Knezeck, L. (17) 31; (23) 108
 Knowles, J.R. (16) 44
 Knupp, C.A. (23) 86
 Knutsen, I.J.S. (20) 193
 Knutsen, S.H. (21) 73
 Ko, C.H. (4) 154
 Ko, J.H. (24) 5
 Kobayashi, H. (3) 187
 Kobayashi, J. (19) 32; (20) 2
 Kobayashi, K. (2) 73; (4) 156; (24) 94
 Kobayashi, M. (7) 53; (23) 121
 Kobayashi, S. (3) 10, 54; (4) 22, 159; (12) 16; (19) 108
 Kobayashi, Y. (8) 16, 17; (9) 46, 58; (18) 131; (19) 5, 6, 8, 100; (24) 79
 Kobe, J. (10) 32
 Koberitz, W.R. (3) 219, 250
 Kobori, Y. (2) 18
 Koch, M. (3) 35, 105; (12) 21, (19) 43
 Kocher, W. (24) 88
 Kochetkov, N.K. (3) 55, 85, 106, 130, 147, 167; (4) 14, 51, 59, 75-78; (11) 4; (16) 70; (24) 8, 35
 Kochetkova, M.V. (20) 47
 Kodama, H. (3) 164
 Kodama, Y. (19) 29
 Koeck, M. (3) 252
 Koehler, J. (1) 15
 Köll, P. (5) 30; (22) 13, 48, 77, 88, 101, 104, 105
 König, W.A. (19) 53
 Köpfer, S. (17) 20
 Koga, K. (9) 58
 Koga, M. (20) 208, 211
 Koga, T. (4) 172
 Koh, L.L. (8) 9; (10) 41; (22) 69, 70, 81
 Kohata, K. (3) 40
 Kohdoh, K. (20) 295
 Koike, S. (5) 16; (7) 9
 Koike, Y. (7) 61
 Koizumi, K. (4) 160, 164; (23) 33
 Kojima, K. (4) 31; (10) 14
 Kojima, Y. (3) 151; (12) 24; (19) 88
 Kokom, K.B. (16) 30
 Kolb, H.C. (5) 21
 Kollat, E. (10) 13
 Kolosova, T.E. (22) 5
 Kolotyrkina, N.G. (11) 4
 Komeshima, N. (19) 39
 Komiyama, K. (19) 87
 Komiyama, M. (20) 325
 Komori, T. (3) 188, 189
 Komura, H. (4) 17
 Komuro, E. (16) 79
 Kou, K. (19) 35
 Konda, Y. (9) 25
 Kondo, A. (23) 55
 Kondo, D. (19) 97
 Kondo, H. (4) 68; (8) 34; (16) 40
 Kondo, K. (20) 2; (22) 142
 Kondo, S. (9) 22; (19) 29, 98, 99
 Kondo, Y. (7) 28; (18) 153
 Kong, F. (5) 19, 25, 26, (10) 40; (21) 36; (22) 63
 Konig, W.A. (4) 155
 Konishi, J. (9) 39
 Konishi, K. (7) 57
 Konishi, M. (19) 16, 41
 Konno, S. (3) 187
 Kononov, L.O. (3) 55; (16) 70
 Koohang, A. (20) 40
 Koole, L.H. (11) 8; (20) 166; (22) 131, 132
 Koomen, G.-J. (18) 19; (20) 285; (24) 46
 Kopeck, J. (9) 40; (10) 8
 Kopeckova, P. (9) 40; (10) 8
 Kopf, J. (22) 48, 77, 101, 104, 105
 Koppert, K. (14) 28; (16) 54
 Korchagina, E.Yu. (4) 74
 Korf, J. (22) 88
 Kornhauser, D.M. (22) 36; (23) 104
 Korol, E.L. (5) 6; (9) 8
 Korolev, A.M. (18) 5
 Koroteev, M.P. (17) 15, 17; (22) 95
 Korsakov, M.V. (8) 18
 Koseki, K. (4) 24, 73, 113; (5) 22; (20) 65; (24) 18, 19
 Koshiishi, I. (23) 57
 Koshino, H. (19) 89
 Kosma, P. (21) 75

- Kossek, S. (7) 45
 Kosuge, Y. (19) 2
 Koszalka, G.W. (20) 311
 Kotake, C. (19) 16
 Kotani, K. (4) 121
 Koths, K. (19) 107
 Koto, S. (4) 28
 Kotsuki, H. (24) 32
 Kottenthalm, M. (3) 252
 Koudate, T. (15) 1; (24) 1
 Koufaki, M. (10) 51; (22) 67
 Kovac, J.P. (22) 15, 23
 Kovacic, P. (3) 109; (4) 32, 99, 100,
 (7) 11; (8) 12; (13) 24
 Kováčik, V. (22) 14, 15, 22
 Kovacs, H. (4) 94; (21) 84
 Kovács, I. (18) 63; (24) 70
 Kover, K.E. (21) 17
 Kowalewski, J. (4) 94; (21) 84
 Kowollik, W. (9) 17
 Koyama, Y. (8) 17; (19) 5, 7
 Kozak, J. (9) 29; (20) 210
 Kozhevnikov, I.V. (2) 62; (6) 6
 Kozikowski, A.P. (18) 161
 Kozioł, A.E. (22) 47
 Kozlova, I.K. (3) 75
 Kozłowski, J.F. (20) 81
 Kozyreva, O.I. (7) 73
 Kraemer, H.P. (19) 25
 Kraevskii, A.A. (20) 117, 264
 Krugten, E.A. (5) 12; (21) 12; (23)
 34
 Kraicovits, F. (9) 44
 Krajewski, J.W. (22) 64
 Kramer, W. (24) 88
 Kratochvil, B. (22) 65
 Kraus, G.A. (2) 16
 Kraus, J.-L. (20) 313
 Krayevsky, A.A. (20) 153, 263;
 (22) 123
 Krebs, A. (4) 95
 Krecmerova, M. (20) 245
 Kreis, U. (21) 39
 Kren, V. (3) 72
 Krenitsky, T.A. (20) 293, 294
 Krepinsky, J.J. (3) 128, 184; (21)
 53
 Kresteleva, J.V. (2) 32
 Krishna, P.R. (3) 55; (16) 70
 Krishnan, R. (22) 121
 Kristen, H. (4) 59; (5) 31; (7) 40;
 (16) 66; (18) 35
 Krivoichenko, I.N. (3) 45
 Krohn, K. (20) 188
 Kroon, J. (21) 44
 Kroon-Batenburg, L.M.J. (21) 44
 Krstajic, N. (16) 6
 Kruizinga, W. (10) 76
 Krupp, G. (20) 260
 Kryazhevskikh, I.A. (3) 106
 Krzeminski, J. (20) 85, 86
 Ksandr, Z. (22) 6
 Kuan, K.T. (7) 62
 Kubo, K. (4) 157
 Kubota, Y. (23) 33
 Kudelin, B.K. (18) 1
 Kudelska, W. (3) 202
 Kudo, K. (4) 28
 Kudo, T. (9) 22; (19) 97-99
 Kuge, S. (9) 46
 Kuhn, C.-S. (2) 24; (3) 204
 Kuhr, S. (23) 41
 Kukhanova, M.K. (20) 153
 Kulikarni, V.R. (3) 207; (4) 8
 Kullmann, R. (7) 5, 12
 Kumar, A. (18) 6
 Kumar, P. (20) 77
 Kumar, R. (20) 290
 Kumar, V. (20) 280, 281
 Kumazawa, H. (16) 55
 Kumpins, V. (20) 223
 Kunderenko, V.M. (2) 47
 Kuno, Y. (14) 11
 Kunz, H. (3) 14, 119; (4) 80; (7)
 5, 12; (24) 92, 101
 Kuo, J.-W. (21) 78
 Kuo, K. (23) 90
 Kurano, M. (7) 54
 Kurian, P. (18) 161
 Kurimoto, A. (19) 75
 Kurita, K. (3) 112; (10) 37
 Kuroda, H. (24) 34
 Kuroda, K. (19) 82
 Kuroda, T. (20) 301, 320
 Kurokawa, T. (19) 51; (20) 3
 Kuron, B.-M. (19) 111
 Kurz, L.J. (20) 173
 Kurz, W. (20) 173
 Kus, J. (16) 8
 Kusama, T. (3) 26, 162, 177; (9)
 48
 Kuster, B.F.M. (16) 62
 Kusumoto, S. (3) 87; (4) 3, 58
 Kuszmann, J. (6) 18; (11) 1, 2;
 (16) 14, 15
 Kuwajima, T. (7) 55
 Kyul-Ycheskiy, E. (20) 298, 299
 Kuzmann, J. (8) 36
 Kuz'min, A.S. (24) 35
 Kuzuhara, H. (3) 112, 171; (10)
 37; (11) 10; (18) 45; (20) 98,
 181
 Kvarnström, I. (20) 143, 161, 162,
 215
 Kwok, D.-I. (3) 258
 Laangstroem, B. (2) 25
 Lacazio, G. (7) 39
 La Colla, P. (20) 21
 Lacourt-Gadras, B. (2) 15; (13) 23
 Laczko, I. (10) 11
 Lafont, D. (3) 23, 163; (4) 1; (5)
 14; (9) 42, 47
 Lafosse, M. (3) 191; (23) 45
 Lagendijk, J. (23) 91
 Lagunita, L.M. (18) 71
 Lagodzin'skaya, G.V. (18) 5
 Lai, F. (23) 85
 Laine, R.A. (4) 38
 Lajoie, G. (7) 67
 Lajcic, S. (12) 23; (22) 78
 Lakhrissi, M. (8) 25; (13) 12
 Lakin, R.E. (20) 90
 Lakshman, M.K. (21) 20
 Lalitha, H.N. (22) 120
 Lalitha, S.V.S. (20) 107
 Lallmand, J.-Y. (24) 73
 Lamb, J.D. (23) 88
 Lamonde, L. (17) 22
 Lamont, R.B. (11) 9; (20) 303
 Lampe, D. (18) 148
 Lamy, C. (16) 30
 Lancelin, J.-M. (10) 53
 Lancelon-Pin, C. (4) 176
 Lang, E. (10) 11
 Lang, S.A., Jr. (8) 15
 Lange, G.L. (18) 83
 Langeneker, W. (20) 25
 Langlois, R. (22) 37; (23) 103
 Lankin, D.C. (21) 18
 Lannoo, P. (23) 83
 Lanotte, M. (20) 247
 Lappa, S. (18) 141, 142, 171
 Larice, J.-L. (10) 24
 Larsson, L. (23) 37
 Laschat, S. (24) 92
 Lassalleta, J.M. (10) 65
 László, P. (18) 104
 Latgé, P. (18) 32; (21) 41
 Lattes, A. (18) 32; (21) 41
 Lattová, E. (2) 33, 34; (9) 23
 Latxague, L. (3) 205
 Lau, J. (20) 165
 Lauhon, G.T. (18) 76
 Laupichler, L. (3) 21; (10) 10;
 (12) 6
 Lauterwein, J. (21) 93
 Lavaitte, S. (21) 33
 Lawrence, F. (19) 50
 Lawrence, N.J. (14) 44; (22) 82
 Lawson, A.M. (4) 7
 Lay, L. (3) 244
 Lazhko, E.I. (19) 34
 Leahy, E.M. (3) 18
 Leary, J.A. (22) 18
 Le Bas, G. (22) 43, 44

- Lebrilla, C.B. (22) 21
 Leclercq, F. (20) 179
 Lederman, J. (4) 122
 Ledl, F. (10) 25
 Lee, A.C. (3) 92
 Lee, A.Y. (9) 2; (22) 71
 Lee, C.-K. (10) 41; (18) 69; (22) 69, 70, 81
 Lee, C.R. (8) 9
 Lee, D.S. (4) 21
 Lee, E. (22) 51
 Lee, H.H. (3) 128; (21) 53
 Lee, J.Y. (20) 152
 Lee, J. (3) 156; (19) 109; (24) 29
 Lee, J.C. (3) 260
 Lee, J.K. (20) 13
 Lee, J.R. (3) 183
 Lee, M.D. (19) 91; (22) 39
 Lee, V.H.L. (23) 120
 Lee, V.J. (8) 15
 Lee, Y. (19) 71; (20) 147, 213
 Leeds, R.L. (19) 49
 Leeflang, B.R. (5) 12; (21) 12, 44, 80
 Lees, W.J. (18) 51; (20) 250, 251
 Leet, J.E. (9) 2, 3; (14) 2; (22) 71
 Lefkadiou, J. (3) 10; (7) 18; (10) 1
 Leger, J.M. (16) 30
 Leger, R. (14) 20
 Legler, G. (18) 42, 121
 Le Grand, D.M. (19) 76
 Legrand, P. (21) 14; (22) 3
 Le Grand, S.M. (21) 3
 Legraverend, M. (18) 126; (19) 63; (22) 108
 Lehmann, J. (2) 24; (3) 178, 204, 211; (4) 9, 85, 89-92; (5) 4; (11) 21
 Lehr, R.E. (21) 20
 Leja, B. (19) 49
 Lemaitre, M. (20) 118
 Le Merrer, Y. (18) 22
 Lemieux, R.U. (4) 46-48, 115; (5) 1; (9) 18
 Lemoine, H. (22) 30
 Lemon, T. (20) 180
 Lenfers, J.B. (24) 53
 Leonard, T.E. (20) 279
 Lepage, G. (21) 72
 Lepage, T.J. (21) 6
 Lepannen, A. (4) 132
 LePendu, J. (4) 48
 Lerch, U. (24) 88
 Lergenmüller, M. (8) 27
 Lermer, L.M. (2) 54; (20) 5; (22) 139
 Leroy, V. (3) 229
 Leslie, R. (6) 15
 Lesnikowski, Z.J. (20) 229
 Lespinasse, A.-D. (3) 10; (7) 18; (10) 1
 Letellier, M. (3) 206
 Letellier, S. (20) 118
 Leteux, C. (13) 16
 Level, M. (9) 43
 Levery, S.B. (21) 87
 Levin, G.V. (2) 46
 Levinsky, A.B. (3) 55
 Lewis, M.D. (18) 103
 Ley, S.V. (6) 15; (18) 91
 Li, C. (7) 6
 Li, H.Y. (15) 1; (24) 1
 Li, K. (23) 65
 Li, L. (19) 12, 78; (20) 201
 Li, T. (20) 262
 Li, W. (23) 78
 Li, W.-R. (24) 64
 Li, X. (20) 127, 128
 Li, Y. (3) 49; (18) 150
 Li, Y.-F. (16) 48
 Li, Z.-J. (3) 7
 Li, Za.J. (6) 3, 4
 Li, Zo.J. (6) 3, 4
 Liang, B. (4) 173
 Liaw, Y.C. (22) 126
 Libbey, L.M. (10) 31; (23) 60
 Lichtenhaler, F.W. (1) 3; (4) 44; (8) 27; (21) 39
 Lieb, M. (20) 50
 Liebelt, B. (5) 31; (7) 40; (16) 66
 Lieflander, M. (18) 13
 Lievense, J.C. (2) 75
 Lilley, S.C. (19) 104, 105
 Lim, B.B. (19) 73
 Lim, G.-J. (8) 13
 Lim, I.M. (19) 65
 Lin, C.-H. (16) 38
 Lin, F. (10) 28
 Lin, G. (19) 12
 Lin, G.S. (20) 79
 Lin, T.-S. (20) 41, 148
 Lin, Y.-C. (4) 25, 111
 Lindberg, A.A. (20) 252
 Lindberg, B. (4) 166
 Lindberg, J. (4) 166
 Lindberg, M. (7) 79
 Lindgren, M. (22) 133
 Lindh, F. (21) 71
 Lindh, I. (21) 83
 Lindhorst, T.K. (7) 93; (8) 30; (14) 31
 Lindman, Y. (10) 21
 Lindon, J.C. (21) 86
 Lindqvist, L. (20) 252
 Ling, C.-C. (4) 163, 167
 Linhardt, R.J. (23) 115
 Linhart, I. (23) 67
 Linker, T. (2) 36; (16) 32
 Linz, W. (24) 88
 Liotta, D.C. (8) 14; (20) 91, 311
 Liotta, F. (20) 210
 Lipkind, G.M. (4) 75-78
 Lipschutz, B.H. (12) 18
 Lipták, A. (1) 2; (5) 10
 Lis, T. (22) 46, 47, 52
 Liu, B.J. (22) 10
 Liu, C. (18) 162, 163
 Liu, C.S. (23) 32
 Liu, H. (22) 132
 Liu, H.-M. (15) 2, 3
 Liu, H.-W. (2) 74; (12) 11
 Liu, J. (21) 50, 51
 Liu, J.L.-C. (1) 9; (3) 155; (16) 39
 Liu, K.K.-C. (1) 9; (8) 33; (9) 34; (13) 2; (18) 52
 Liu, L. (17) 13; (20) 283
 Liu, M. (11) 8
 Liu, M.-C. (20) 41, 148
 Liu, P. (18) 89
 Liu, P.S. (3) 73
 Liu, S. (20) 205
 Liu, X.-G. (7) 85, 86
 Liu, Y. (14) 4; (17) 19; (18) 136; (23) 120
 Liu, Y.-C. (18) 155
 Liu, Y.Q. (6) 3, 4
 Liu, Z. (7) 94
 Ljevakovic, D. (7) 31
 Llera, J.M. (7) 90; (24) 104
 Llorca, M.J. (2) 59, 60
 Lloyd, K.O. (23) 52
 Lo, J.M. (22) 10
 Lo, L.-C. (3) 182; (23) 39
 Lo, T.B. (23) 32
 Loch, N. (8) 8
 Locke, R.D. (4) 49, 50
 Locenberg, D. (19) 20, 21
 Lönn, H. (4) 64
 Lönnberg, H. (20) 326
 Löw, H. (2) 57; (10) 42
 Logan, C.J. (3) 180
 Lohray, B.B. (7) 91
 Lohse, M.J. (20) 185
 Lohste, P. (3) 236
 Loibner, H. (3) 160, 161
 Loof, L. (23) 44
 Look, G.C. (3) 122; (8) 34
 López, E. (23) 35
 López, J.C. (3) 176; (12) 5; (16) 27; (24) 9, 45
 López, M.G. (2) 72; (16) 86; (18) 137
 Lopez, R. (3) 123
 López-Castro, A. (10) 17, 23; (22) 80
 Lopez-Munguia, A. (4) 23
 Lorenz, B. (17) 16

- Lorneau, J.-C. (9) 43
 Lourde, R. (3) 63
 Low, H. (8) 6
 Lowe, D.J. (18) 78
 Lowe, J.B. (3) 108; (4) 24
 Lown, J.W. (21) 27
 Lu, D. (5) 26; (10) 40; (22) 63
 Lu, G. (10) 40; (22) 63
 Lu, J. (23) 120
 Lu, T.L. (2) 38
 Lubineau, A. (3) 3, 17, 34; (4) 66, 81; (24) 99
 Luecke, L. (18) 35
 Luengo, J.I. (3) 253; (20) 255
 Lüning, B. (3) 174
 Luessmann, J. (14) 40
 Lüftler, D.R. (20) 134
 Luger, P. (18) 66; (22) 57, 87, 93, 122
 Luinge, H.J. (22) 2
 Lukacs, G. (8) 10; (14) 17; (24) 15
 Luna, H. (18) 85
 Lund, A. (22) 133
 Lund, I. (5) 20; (7) 84; (24) 40, 65, 91
 Luo, M.-Z. (20) 148
 Lupidi, G. (20) 19
 Lutz, E.T.G. (22) 1, 2
 Luu, B. (22) 28
 Lvov, V.L. (7) 78
 Lyga, J.W. (2) 31; (16) 12
 Lyle, S. (20) 267
 Lyman, N. (4) 162
 Lyngdoh, R.H.D. (20) 322
- Ma, L. (19) 12
 Ma, Q.-F. (20) 261
 Ma, V. (7) 16
 Maag, H. (20) 120, 206
 Maahimo, H. (4) 132
 Maat, L. (10) 56; (15) 8; (22) 72
 McArdle, P. (22) 51
 McCarthy, D.J. (20) 257
 McCarthy, J.R. (20) 150
 McCarthy, K.C. (3) 11; (4) 162, (9) 12
 Macchia, M. (20) 121
 McClinton, D.A. (3) 12; (5) 3; (8) 4
 McClinton, M.A. (3) 12; (5) 3; (8) 4
 McCloskey, J.A. (19) 48; (21) 26
 McCormack, J.J. (20) 57
 MacDermot, A.J. (22) 138
 McDevitt, R.E. (18) 108; (24) 3
 MacDiarmid, J.E. (20) 51
 McDonald, F.E. (4) 73, 113, (9) 24
 MacDonald, P. (3) 69
 McDonnell, P.D. (19) 49
 McElhaney, R.N. (22) 40
 McGahren, W.J. (19) 91; (22) 39
 McGeever-Rubin, B. (19) 62
 McGuigan, C. (20) 242, 243
 Machado, A.S. (18) 120; (24) 13
 Machida, H. (20) 295
 Machinaga, N. (24) 39
 Maciejewski, S. (24) 62
 Mack, H. (16) 49
 McKee, S.P. (7) 104
 Mackenzie, G. (3) 10; (7) 18; (10) 1; (22) 27
 MacKenzie, L. (7) 56
 McLaughlin, L.G. (23) 87
 McLaughlin, L.W. (20) 221
 MacLean, D.B. (22) 19, 22
 McPhail, D.R. (3) 183
 Macrae, R. (23) 23
 McRoberts, M.J. (20) 120, 173
 Mada, A. (23) 58
 Maddry, J.A. (20) 123, 139, 140
 Madson, R. (3) 2; (7) 84; (23) 90
 Maeba, I. (20) 189, 190
 Maeda, A. (19) 32
 Maeda, H. (3) 67; (12) 24; (19) 88
 Maeda, K. (3) 54; (19) 108
 Maeda, M. (8) 20; (16) 74
 Maehr, H. (20) 68
 Mackawa, T. (18) 15
 März, J. (4) 80
 Mag, M. (20) 116
 Maga, G. (20) 56
 Magata, Y. (9) 39
 Maggini, M. (24) 71
 Magni, F. (23) 11
 Magnusson, G. (3) 93; (4) 86
 Magomedova, N.S. (17) 15
 Maguire, M.H. (23) 89
 Mahadevappa, D.S. (2) 70
 Mahajan, A.J. (23) 105
 Mahmood, N. (20) 61, 243
 Mahmoud, S.H. (8) 28; (10) 6; (16) 20
 Mahuteau, J. (10) 7
 Maier, M.E. (14) 10; (24) 41
 Maillard, M. (20) 118
 Maillard, P. (2) 43
 Mainkar, A.S. (3) 29; (4) 34
 Maiorana, S. (18) 141, 142
 Majerus, P.W. (18) 143
 Mak, T.C.W. (18) 11; (22) 83, 89; (24) 30, 31
 Makaiyama, T. (3) 8
 Makarova, Z.G. (3) 147
 Maki, Y. (20) 38, 239, 291
 Makino, T. (20) 38
 Makita, T. (23) 17
 Maksic, Z.B. (21) 28
 Maksimochkin, G.I. (2) 49
 Malaisse, W.J. (2) 26; (21) 13
 Malaisse-Lagae, F. (2) 26; (21) 13
 Malchorn, S.H. (18) 33
 Malenkovskaya, M.A. (7) 75, 76; (16) 76, 77
 Malickel, B.P. (24) 51
 Malickel, M.P. (16) 48
 Malik, A. (5) 24; (9) 9
 Malik, S.S. (18) 116
 Malinowska, N. (20) 328
 Malkiewicz, A. (20) 225
 Mallet, J.-M. (4) 72; (8) 24; (13) 3
 Maloisel, J.-L. (3) 170
 Malysheva, N.N. (3) 85, 130; (4) 14; (11) 4
 Mamaev, V.P. (20) 110
 Manabe, M. (22) 26; (23) 63
 Manchand, P.S. (20) 68
 Mancy, S. (10) 64
 Mandai, T. (22) 53
 Mande, S.S. (22) 119, 120
 Mancis, G.B. (18) 5
 Manfredini, S. (20) 21
 Manhas, M.S. (24) 63
 Mani, N.S. (8) 26
 Manley-Harris, M. (22) 12
 Mann, J. (20) 159
 Mannock, D.A. (22) 40
 Manservigi, R. (20) 56
 Mansour, E.-S.M.E. (10) 62
 Mansour, T.S. (20) 306, 312
 Mansuri, M.M. (20) 275
 Mantell, S.J. (16) 25; (24) 42, 43
 Mantsch, H.M. (10) 13
 Mantzos, D. (22) 43
 Maracek, J.F. (18) 145
 Maras, A. (18) 92
 Marcé, R.M. (23) 35, 36
 Marchado, A.S. (14) 21
 Marchenko, G.N. (22) 5
 Marchiandi, M. (20) 192
 Marco, J.A. (14) 12
 Marco-Contelles, J. (18) 105, 106; (24) 7, 10
 Marcuccio, S.M. (20) 70
 Marck, M. (7) 34, 35
 Marfil, A. (13) 19
 Marin, G.B. (16) 62
 Marinier, P. (3) 191; (23) 45
 Markovac, A. (19) 65
 Marongiu, M.E. (20) 21
 Marques Braga, R. (24) 90
 Marquez, J. (19) 20, 21
 Marquez, V.E. (7) 4; (18) 123; (19) 65, 69, 73, 79; (20) 57, 88, 214, 321; (22) 126; (24) 29

- Marra, A. (3) 4
 Marschner, C. (19) 64
 Martin, D.P. (20) 258
 Martin, G.E. (21) 86
 Martin, J.C. (20) 274, 275
 Martin, J.D. (3) 240
 Martin, J.L. (3) 218
 Martin, T.J. (3) 152; (4) 65
 Martinez, L. (18) 105
 Martinez, M.B. (3) 216; (9) 53; (16) 26
 Martinez-Castro, I. (23) 18
 Martinez-Grau, A. (18) 105, 106
 Martinez-Ripoll, M. (18) 106
 Martín-Lomas, M. (3) 113; (4) 83, 106; (12) 27; (18) 151
 Martín-Zamora, M.E. (10) 65
 Martynov, B.I. (20) 264
 Marubayashi, N. (3) 78; (22) 110
 Marumo, K. (20) 252
 Maruyama, K. (2) 44
 Maruyama, T. (19) 59
 Marzabadi, M.R. (18) 75
 Marzi, M. (18) 55
 Masaki, Y. (18) 53; (24) 85
 Mashava, P.M. (22) 73
 Maslowska, J. (16) 8
 Masuda, A. (20) 149
 Masuda, K. (8) 20
 Masunari, K. (4) 171
 Mata, F.Z. (3) 216; (9) 53; (16) 26
 Matalla, K. (4) 27; (15) 7
 Matelich, M.C. (24) 56
 Mateo, F.H. (9) 26; (14) 14
 Matheu, I. (20) 11
 Matheu, M.I. (8) 10
 Mathias, J.P. (2) 19
 Matschulat, P. (16) 41
 Maison, J.A. (9) 2, 3; (14) 2; (22) 71
 Matsubara, K. (3) 9, 24
 Matsuda, A. (19) 68; (20) 34, 37, 39, 99, 149, 151, 186, 295; (22) 110, 125
 Matsuda, F. (24) 4
 Matsuhashi, S. (23) 62
 Matsui, E. (4) 44
 Matsui, K. (3) 104
 Matsui, T. (16) 11
 Matsukuma, I. (20) 320
 Matsumoto, H. (16) 78; (20) 20
 Matsumoto, K. (5) 22; (20) 65; (24) 18, 19
 Matsumoto, M. (13) 26
 Matsumoto, T. (3) 259
 Matsumura, G. (22) 109, 113
 Matsumura, S. (3) 192
 Matsuo, G. (3) 225, 226
 Matsuo, M. (7) 97
 Matsuo, Y. (20) 35
 Matsushita, H. (5) 22; (20) 43, 65, (24) 18, 19
 Matsushita, Y. (16) 11
 Matsuzaki, K. (7) 61
 Matsuzaki, T. (10) 26
 Matsuzaki, Y. (4) 151, 153
 Matsuzawa, T. (15) 1; (24) 1
 Matta, K.L. (3) 89; (4) 39, 42, 43, 49, 50, 52, 133
 Matulic-Adamic, J. (20) 263
 Matulova, M. (2) 34; (17) 31; (23) 108
 Matuo, I. (14) 25
 Mauri, P. (23) 43
 Mavridis, I.M. (22) 42, 43
 Maya, I. (9) 35; (10) 70
 Mayoi, L. (20) 220
 Mayon, P. (14) 33, 34
 Mazeau, K. (21) 33, 49
 Meachler, L. (3) 18
 Mcade, E.A. (20) 18
 Medich, J.R. (18) 73; (19) 95
 Meenhorst, P.L. (23) 92
 Meguro, H. (14) 5; (16) 28; (24) 83
 Mehta, S. (3) 95
 Meier, B. (23) 42
 Meier, C. (20) 241
 Meier, D.K.F. (23) 100
 Meinjohanns, E. (4) 109, 129
 Meldal, M. (3) 50, 111, 129; (7) 68; (18) 31; (21) 63
 Mele, A. (2) 12; (21) 62
 Melguizo, M. (20) 32
 Melkoumian, K. (17) 19; (18) 136
 Melnik, S.Ya. (20) 47, 109, 110
 Mendez, M.M. (10) 17
 Méndez, R. (21) 46
 Mendoza, P.G. (9) 26; (14) 14
 Menezo, J.C. (18) 4, 28
 Merchan, F.L. (9) 4
 Mercayala, H.B. (3) 207; (4) 8; (5) 29
 Merino, P. (5) 11; (9) 4, 5
 Merlin, J.L. (23) 101
 Mermenlin, P. (23) 64
 Merriman, G.H. (3) 229
 Merrill, J.R. (3) 2; (4) 152
 Mermann, K. (20) 66
 Merten, H. (16) 59
 Merz, K.M., Jr (21) 3
 Metcalfe, J.C. (18) 98
 Metzger, J. (10) 24; (22) 13; (23) 12
 Metzner, H. (4) 170
 Meyer, B. (21) 82
 Meyer, E. (3) 34
 Meyers, A.G. (19) 111
 Miao, Z. (21) 68, 69
 Micera, G. (17) 33
 Michaelsen, S. (23) 118
 Michalski, J.C. (20) 230; (21) 72, 74
 Michel, S. (19) 43
 Middleton, E.J. (20) 70
 Miethchen, R. (5) 10; (6) 11, (8) 2
 Mihara, S. (3) 36
 Mikami, Y. (19) 32
 Mikerin, I.E. (8) 15; (14) 46
 Mikhailopulo, I.A. (20) 114
 Mikhailov, S.N. (20) 326
 Mikhaylova, M.A. (3) 75
 Miki, T. (16) 78
 Milius, A. (7) 71
 Miščović, D. (8) 32, 35; (12) 23; (22) 78
 Miller, P.S. (20) 279
 Miller, V.P. (2) 74; (12) 11
 Miller, W.H. (3) 102; (20) 271; (21) 61
 Mills, S.J. (18) 148
 Milne, G.W.A. (7) 4
 Milstead, M. (22) 73
 Minami, M. (24) 12
 Minami, T. (3) 228
 Minamikawa, H. (3) 57; (24) 89
 Minamiura, N. (4) 172
 Minamoto, K. (20) 35, 36
 Minear, R.A. (23) 77
 Minetti, P. (18) 55
 Minich, M.L. (19) 103, 104
 Mino, Y. (4) 17
 Minoda, M. (7) 15, 16
 Miocque, M. (4) 167, 174; (10) 7
 Mischnick, P. (23) 10
 Misco, P.F. (20) 73
 Misharina, T.A. (10) 30
 Mishimura, Y. (19) 98
 Mishra, A. (7) 52; (20) 137
 Mishra, S.K. (16) 83; (19) 28
 Misiti, D. (18) 55
 Mitaki, S. (12) 21
 Mitchell, E.P. (23) 90
 Mitchell, R. (23) 24
 Mitera, J. (23) 67
 Mito, K. (3) 78
 Mitsunaga, J. (20) 297; (22) 124
 Mitsuya, H. (20) 88, 302
 Miya, N. (9) 25
 Miyadoh, S. (19) 47
 Miyajima, K. (3) 193
 Miyakawa, A. (20) 292
 Miyakoshi, M. (9) 1
 Miyakoshi, S. (19) 54
 Miyamae, Y. (14) 11
 Miyamoto, M. (18) 103
 Miyamoto, T. (7) 13-16

- Miyamoto, Y. (19) 1
 Miyasaka, T. (20) 142, 174, 175;
 (22) 109, 113, 115, 129
 Miyasaka, T. (3) 71
 Miyashita, M. (24) 34
 Miyashita, T. (20) 295
 Miyazaki, A. (24) 32
 Miyazaki, H. (18) 131; (19) 100
 Miyazawa, M. (24) 6
 Miyazawa, T. (21) 26
 Miyoshi, S. (3) 31
 Mizukoshi, T. (19) 2
 Mizuno, K. (24) 85
 Mizuno, Y. (20) 20
 Mizuchi, T. (10) 9
 Mizutani, K. (8) 5
 Mögeli, R. (23) 27
 Moeller, G. (4) 43
 Moffett, K.K. (20) 154
 Molena, G. (23) 100
 Molinari, H. (21) 76
 Moller, P. (23) 118
 Momentteau, M. (2) 43
 Momii, F. (3) 27
 Mondage, M. (3) 149; (24) 17
 Mondon, M. (12) 14; (19) 43
 Moncrel, C. (3) 173; (9) 15; (19)
 37, 43; (20) 118, 145; (24) 14
 Monsan, P. (4) 23
 Montassier, C. (18) 4, 28
 Montaudo, G. (22) 24
 Montchamp, J.-L. (18) 79, 80
 Montgomery, J.A. (20) 87, 123,
 133, 139, 140, 272, 277
 Monti, L. (23) 11
 Montreuil, J. (21) 74
 Moon, H.R. (20) 318
 Moon, S.H. (18) 160
 Moorman, A.R. (20) 134, 293,
 294
 Moradim, A. (2) 17
 Moreda, W. (3) 103; (10) 22
 Moreland, M. (19) 107
 Morf, M. (22) 48, 77, 101, 104,
 105
 Mori, K. (3) 43; (7) 46; (24) 52
 Mori, S. (12) 22; (24) 57
 Mori, T. (20) 20
 Mori, Y. (4) 28; (8) 11
 Morimoto, M. (20) 320
 Morimoto, Y. (20) 292
 Morin-Allory, L. (23) 26
 Moris, F. (7) 36, 99; (20) 287-289
 Morishima, N. (4) 28, 47; (8) 11
 Morishita, A. (19) 17-19
 Morishita, N. (20) 189
 Morita, M. (16) 28
 Morita, N. (23) 124
 Morita, T. (20) 45
 Morita, Y. (18) 15
 Moritz, V. (18) 84
 Moriyama, T. (19) 16
 Morizane, A. (9) 25
 Morohoshi, T. (19) 23
 Morozov, A.A. (2) 11
 Morozova, N.G. (3) 45
 Morris, M. (16) 60
 Morton, G.O. (19) 91; (22) 39
 Mosley, R.T. (18) 40
 Moss, S.F. (3) 166
 Motavavi, M.S. (20) 108
 Mott, A.W. (20) 94
 Moufid, N. (14) 33, 34
 Moukolo, J. (18) 28
 Mousaad, A. (10) 57, 75
 Moustafa, M.A. (20) 23
 Mozherin, D.Yu. (20) 117
 Muhs, R. (16) 33
 Mukaiyama, S. (11) 15; (12) 19
 Mukaiyama, T. (3) 9, 10, 24; (12)
 16
 Mukhamadeeva, R.M. (22) 5
 Mulder, G.J. (8) 3; (10) 3; (16) 67
 Mullah, K.B. (20) 89, 238; (22)
 116
 Mulvaney, D.E. (23) 93
 Mulzer, J. (18) 66
 Munesada, K. (3) 77
 Munoz, A. (17) 22
 Murachi, T. (23) 122
 Murai, S. (3) 257
 Murai, T. (3) 257
 Murakami, N. (3) 66
 Murakami, T. (3) 57; (24) 89
 Murakata, C. (4) 83, 141
 Muraoka, O. (20) 291
 Murata, Y. (4) 10, 11; (5) 8
 Murayama, S. (3) 112; (10) 37
 Murayama, T. (20) 186
 Murello, M.H. (10) 24
 Murofushi, S. (19) 18, 19
 Murphy, P.J. (24) 28
 Musina, L.Yu. (7) 78
 Musser, S. (20) 321
 Muto, N. (22) 53
 Mutoh, N. (19) 17-19
 Muzquiz, M. (23) 49
 Myers, J. (18) 152
 Myerscough, P.M. (16) 25; (18)
 58
 Myles, D.C. (2) 18
 Na, K. (7) 1
 Nagae, S. (4) 19
 Nagahama, T. (4) 107, 137
 Nagashashi, G. (9) 20
 Nagai, M. (24) 84
 Nagai, Y. (4) 156
 Nagamawa, H. (19) 42
 Nagano, H. (14) 11; (24) 33
 Nagao, Y. (16) 42
 Nagaoka, H. (23) 94
 Nagasawa, T. (3) 1
 Naggi, A. (22) 34; (23) 59
 Nagy, J.O. (3) 108; (18) 37
 Nahorski, S.R. (18) 162, 163
 Nair, M.G. (19) 28
 Nair, V. (20) 304, 305
 Naito, T. (19) 106
 Naja, J. (18) 28
 Nakabayashi, S. (3) 31
 Nakada, M. (19) 90
 Nakada, N. (7) 54
 Nakagami, K. (19) 68
 Nakagawa, K. (3) 26
 Nakahara, Y. (3) 154; (4) 2, 101,
 148
 Nakai, S. (20) 327
 Nakajima, K. (4) 30
 Nakajima, S. (19) 39
 Nakajima, T. (3) 67
 Nakajima, Y. (20) 99
 Nakamizo, N. (20) 301, 320
 Nakamoto, A. (23) 24
 Nakamura, H. (9) 25; (20) 227
 Nakamura, J. (23) 40
 Nakamura, M. (3) 30; (16) 58;
 (22) 91
 Nakamura, S. (19) 27
 Nakamura, T. (14) 25; (19) 86
 Nakamura, Y. (9) 11; (19) 3, 22
 Nakane, H. (20) 239
 Nakanishi, K. (3) 182; (22) 141;
 (23) 39
 Nakanishi, S. (19) 82
 Nakanishi, T. (20) 300
 Nakano, K. (3) 78; (4) 4; (20)
 134
 Nakao, R. (16) 80
 Nakashima, K. (4) 159; (23) 30
 Nakata, K. (23) 124
 Nakata, M. (3) 225; (19) 27; (24)
 37
 Nakatani, K. (24) 4
 Nakayama, K. (3) 162, 177; (9)
 48; (14) 15; (16) 24
 Nakayama, M. (16) 11
 Nakayama, N. (7) 54
 Nakazawa, M. (24) 6
 Namba, O. (7) 55
 Namibar, P.T.C. (7) 67
 Nampalli, S. (20) 64
 Nánási, P. (1) 2
 Nango, M. (2) 10
 Naohara, J. (22) 26; (23) 63
 Nardelli, M. (18) 21; (22) 85

- Narisano, E. (9) 30
 Narita, N. (3) 46, 58
 Nashabeen, W. (23) 316
 Nassr, A.M. (10) 62
 Naughton, A.B.J. (7) 88; (18) 113
 Navé, J.-F. (20) 265, 273
 Naylor, S. (3) 81
 Neamati, N. (13) 5, (14) 24; (19) 38
 Nedvický, W. (10) 25
 Negron, G. (24) 98
 Neidle, S. (20) 131, 166; (22) 131
 Neira, S. (4) 144, (7) 63; (10) 34
 Nelson, C.C. (19) 48
 Nelson, K.A. (21) 25
 Nemlin, J. (24) 23
 Nepogodov, S.A. (4) 60
 Neruda, W. (3) 160
 Neumann, G.D. (23) 6
 Neumann, J.-M. (20) 241
 Neumann, K. (6) 14; (7) 100; (24) 49
 Neumann, W.P. (12) 7
 Nevskii, N.N. (17) 17; (22) 95
 Ng, K. (20) 267
 Nickel, W.-U. (24) 88
 Nicolaou, K.C. (3) 18; (4) 88, 93, 111, 112; (11) 19; (19) 90, 93; (24) 54
 Nicolas, P. (23) 82
 Nicolis, I. (22) 45
 Nicotra, F. (3) 139, 244; (24) 44
 Nielsen, C. (17) 6; (20) 27, 165, 177, 268
 Nicmala, R. (4) 132
 Niessen, W.M.A. (22) 32; (23) 54
 Nifant'ev, E.E. (4) 51, 75-78; (7) 75, 76; (16) 76, 77; (17) 15, 17; (22) 95
 Niggemann, J. (7) 64
 Nihro, Y. (16) 78
 Niki, E. (16) 79
 Nikitenko, A.A. (8) 15; (14) 46
 Nikolaev, A.V. (4) 15, 119; (7) 80-82
 Nikrad, P.V. (4) 115; (5) 1
 Nilson, F.P.R. (20) 26
 Nilsson, S. (3) 48; (7) 83
 Nilsson, B. (22) 20; (23) 123
 Nilsson, K.G.I. (1) 11; (3) 114; (4) 20
 Nilsson, M. (4) 146
 Nilsson, V. (4) 86
 Ninomiya, M. (10) 26
 Nioto-Sampedro, M. (4) 106
 Nishi, K. (3) 127; (4) 70; (18) 117, 133
 Nishida, Y. (3) 83
 Nishijima, M. (9) 46
 Nishikawa, H. (20) 320
 Nishikiori, T. (19) 51; (20) 3
 Nishimoto, H. (24) 93
 Nishimura, S.-I. (3) 112; (4) 19; (10) 37
 Nishimura, Y. (9) 22; (19) 97, 99
 Nishino, T. (20) 20
 Nishio, T. (3) 54; (19) 108
 Nishioka, I. (16) 1
 Nishiyama, S. (12) 24; (14) 15; (16) 24; (19) 56, 88; (20) 28, 314
 Nishiyama, Y. (19) 106
 Nishizaki, T. (14) 5
 Nishizawa, M. (3) 27, 64, 97; (4) 157
 Nitsch, E. (22) 59
 Niwas, S. (20) 277
 No, Z. (20) 152
 Noble, N.J. (18) 164, 166
 Noble, S.A. (11) 9; (20) 303
 Nocentini, G. (20) 19
 Noguchi, A. (17) 1
 Noguchi, K. (22) 58; (23) 28
 Nogueras, M. (20) 32
 Nohara, T. (3) 78; (9) 1; (19) 81
 Nobia, H. (23) 94
 Noiro, A.-M. (3) 158; (10) 36
 Nokata, K. (3) 71
 Nomura, K. (12) 22; (24) 57
 Nomura, M. (19) 75; (20) 216
 Nomura, Y. (20) 186
 Nonaka, G. (16) 1
 Nongaillard, B. (2) 50
 Noort, D. (3) 132; (8) 3; (10) 3; (16) 67
 Norbeck, D.W. (19) 61; (20) 315
 Norberg, T. (3) 48, 174; (4) 146; (7) 79, 83; (8) 1
 Norin, T. (20) 210
 Norman, M.H. (18) 128
 Nouguier, R. (6) 5; (21) 37; (24) 95, 96
 Nouws, J.F.M. (23) 70
 Novicov, N.I. (20) 153
 Novikov, N.A. (20) 117
 Novotny, J. (22) 65, 76
 Nozaki, H. (3) 195
 Nozaki, Y. (11) 15; (12) 19
 Nozdrev, V.F. (2) 49
 Nozoe, S. (19) 46, 87
 Nuesca, Z.M. (20) 304
 Nugent, S.T. (21) 18
 Nukada, T. (4) 148
 Null, V. (11) 13
 Numata, N. (4) 67
 Nunomura, S. (4) 126
 Nunozawa, T. (19) 46
 Nurmi, J. (22) 61, 62
 Obara, T. (19) 67, 68, 72
 Obata, R. (19) 106
 Obe, K.-i. (4) 171, 172
 Oberdorfer, F. (8) 8
 Obert, G. (20) 112
 Ochi, M. (24) 32
 O'Connor, J. (23) 7
 Oda, H. (18) 53; (24) 85
 Odashima, T. (3) 40
 Odham, G. (23) 37
 Oehler, L.M. (18) 36
 Öhrlein, R. (3) 118
 Oelrichs, P.B. (3) 81
 Oertel, F. (20) 53
 Ötvös, L., Jr. (9) 44; (10) 11, 13; (20) 246; (23) 50
 Offer, J.L. (18) 98
 Ogasawara, K. (18) 24
 Ogasawara, T. (18) 146, 153
 Ogata, T. (20) 248
 Ogawa, H. (3) 199; (4) 96, 97
 Ogawa, K. (14) 3
 Ogawa, M. (3) 151, 153
 Ogawa, S. (2) 20; (3) 127; (4) 70; (9) 10, 11, 21; (14) 43; (16) 65; (18) 47, 48, 95, 114, 115, 117, 132, 133; (19) 1-4, 101, 102; (21) 59; (24) 2, 12, 22, 72, 80
 Ogawa, T. (3) 154; (4) 2, 67, 83, 101, 104, 126, 138, 141, 148, 151, 153
 Ogihara, Y. (4) 31, 108; (10) 14
 Ogonski, T. (16) 84
 Ogreid, D. (20) 247
 Oguma, T. (23) 57
 Ogura, H. (3) 30; (5) 27; (16) 57, 58; (22) 90, 91
 Oh, Y.C. (10) 27
 O'Hair, R.A.J. (22) 17
 Okashi, S. (19) 32
 Ohe, K. (3) 257
 Ohgi, T. (8) 17; (19) 5
 Ohgiya, T. (20) 28
 Ohhara, O. (19) 74; (20) 217
 Ohi, H. (3) 117
 Ohkama, T. (20) 248
 Ohki, H. (4) 107
 Ohkura, Y. (23) 94
 Ohnomo, Y. (9) 39
 Ohno, M. (3) 54; (14) 11; (19) 108
 Ohnuma, T. (19) 106
 Ohrai, H. (14) 5; (16) 28; (24) 83
 Ohta, K. (4) 171
 Ohta, Y. (19) 22

- Ohtakara, A. (4) 19
 Ohtani, K. (7) 98
 Ohlsuka, T. (7) 54
 Ohuchi, S. (20) 96, 236, 237
 Oikonomakis, N.G. (3) 218
 Oishi, M. (20) 36
 Oivanen, M. (20) 326
 Oka, M. (4) 17
 Okabe, M. (19) 45; (20) 7
 Okada, K. (24) 97
 Okada, M. (5) 33
 Okada, S. (16) 80
 Okajima, H. (20) 149
 Okamoto, K. (16) 47
 Okamoto, M. (4) 28
 Okamoto, R. (19) 42
 Okano, H. (24) 94
 Okano, K. (5) 22; (20) 65; (24) 19
 Oki, T. (19) 16, 41, 106
 Okide, G. (21) 67
 Okonogi, A. (7) 55
 Okruszak, A. (7) 72; (20) 228
 Oksman, P. (20) 326
 Oku, M. (3) 181
 Okuda, M. (23) 40
 Okuda, T. (7) 55, 58
 Okukado, N. (16) 47
 Okuma, T. (3) 228
 Okumura, Y. (22) 16
 Okuno, S. (3) 126
 Okuyama, K. (22) 58
 Okuyama, S. (19) 41
 Olde-Hanter, B. (4) 123, 124
 Olechno, J.D. (23) 31, 76
 Olesker, A. (8) 10; (14) 17; (24) 15
 Olivo, H.F. (18) 118
 Ollapally, A.P. (20) 180
 Olucha, J.C. (23) 35
 Omichi, K. (4) 136
 Omura, S. (19) 87
 Ondracek, J. (22) 65, 76
 O'Neill, R.A. (3) 108
 Ong, G.-T. (7) 44
 Ongeret, C. (11) 20
 Ono, K. (20) 239
 Ono, M. (3) 78
 Ono, N. (2) 44
 Onose, R. (19) 89
 Onozawa, S. (12) 16
 Orchard, M.G. (3) 218
 Orduna, J. (5) 11
 Oreshkina, T.D. (19) 110
 Organ, M.G. (18) 83
 Orgeret, C. (3) 200
 Orihara, M. (18) 114
 Orita, M. (19) 24
 Oriyama, T. (4) 73, 113
 Ortez Mellet, C. (10) 67
 Ortiz, C. (3) 103; (10) 22
 Ortiz, F.L. (7) 37
 Osa, Y. (4) 44
 Osada, H. (19) 89
 Osanai, S. (2) 56
 Osawa, E. (21) 2
 Osawa, K. (19) 82
 Oscarson, J.R. (12) 24; (19) 88
 Oscarson, S. (3) 129, 159; (4) 35; (7) 79
 Oshitari, T. (3) 54; (19) 108
 Osipova, T.V. (19) 110
 Osman, S.F. (23) 7
 O'Sullivan, J. (19) 84
 Osumi, K. (20) 62
 Osumi, T. (24) 37
 Ota, A. (10) 20
 Ota, N. (4) 17
 Otake, N. (19) 39
 Otera, J. (3) 195
 Otsubi, Y. (20) 301
 Otsuka, M. (3) 54; (19) 108
 Otsuka, T. (9) 46
 Otsuki, J.-I. (4) 156
 Ott, A.Y. (3) 146, 147; (4) 13, 59; (16) 63
 Otten, M.G. (16) 82
 Otter, B.A. (20) 34, 39, 187
 Ottosson, H. (3) 2
 Ourak, M. (2) 50
 Overhand, M. (4) 79
 Overill, R.E. (22) 138
 Overlift, G.T. (23) 113
 Ovodov, Y.S. (14) 9
 Owa, T. (3) 54; (19) 108
 O-Yang, C. (20) 172, 173
 Ozaki, H. (23) 33
 Ozaki, S. (18) 146, 153; (24) 93, 97
 Ozawa, K. (15) 1; (24) 1, 76
 Pabel, B. (23) 27
 Pacic, M.M. (3) 121; (11) 17
 Padua, G.W. (21) 11
 Padykula, R.E. (13) 7
 Paesen, J. (23) 83
 Pacz, M.I. (23) 18
 Pagella, P.G. (18) 141, 142, 171
 Pakulski, Z. (4) 60
 Palacios, J.C. (10) 17
 Pale, P. (20) 250
 Palic, M.M. (4) 45
 Palmer, C.F. (18) 129
 Pan, J. (7) 6
 Pan, Y.T. (18) 65; (24) 68
 Pancrazi, A. (24) 23
 Pandey, R.C. (19) 28
 Pandit, U.K. (18) 17; (24) 46
 Panfil, I. (24) 62
 Pani, A. (20) 21
 Pankiewicz, K.W. (20) 85, 86
 Pannecoucke, X. (22) 28
 Pannecouque, C. (20) 125
 Pannell, L.K. (22) 23
 Panscgrau, P.D. (18) 75
 Panza, L. (3) 139, 244; (24) 44
 Papageorgiou, C. (3) 19
 Papchikhin, A. (22) 123
 Papp, E.A. (23) 86
 Parente, A. (10) 12
 Park, H.O. (4) 21
 Park, J.S. (2) 40; (20) 13
 Parkanyi, C. (10) 24
 Parker, D. (4) 168; (5) 13
 Parker, K.A. (3) 242; (13) 7
 Parker, W.B. (20) 123
 Parkin, A. (20) 121
 Parrot-Lopez, H. (4) 163, 174; (10) 7
 Parry, K.P. (18) 129
 Passingham, C. (22) 8
 Pastori, N. (20) 192
 Paszkiewicz-Hnatow, E. (4) 47
 Patel, H.H. (18) 9
 Patel, M. (19) 20, 21
 Paterson, I. (24) 36
 Pathirana, C. (3) 44
 Pathirana, R.N. (20) 243
 Patil, S.D. (19) 80; (20) 39, 211
 Paton, R.M. (14) 38
 Patterson, L.E. (20) 90
 Paul, F. (4) 23
 Paulson, H. (3) 50, 111, 138; (4) 43, 71, 109, 129, 131; (12) 25, 26; (16) 41
 Paulson, J.C. (4) 25, 144, 150
 Pavlik, V. (4) 99
 Payne, A.N. (20) 204
 Payne, J.J. (20) 312
 Payne, S. (18) 157, 158, 165
 Peach, R.J. (23) 51
 Pearce, C.M. (3) 81
 Pechennikov, V.M. (22) 128
 Pechy, P. (20) 196, 197
 Pequet, P. (19) 63
 Pedersen, C. (5) 20; (8) 2; (24) 40, 91
 Pedersen, E.B. (17) 6; (18) 16; (20) 8, 27, 104, 105, 108, 165, 176, 177, 268
 Pedersen, H. (18) 16; (20) 177
 Pedersen, S.F. (2) 40
 Pedrocchi-Fantoni, G. (2) 12
 Pedroso, E. (20) 296
 Peeters, O.M. (22) 114
 Pelmore, H. (2) 58
 Pelosi, G. (18) 17; (18) 46; (22)

- 74, 75
 Pellicer, J.M. (22) 19, 22
 Pelyvas, I.F. (3) 15; (8) 30; (14)
 31
 Penadés, S. (18) 151, 159
 Penning, T.D. (18) 73
 Penttilä, L. (4) 132
 Peoples, M.E. (20) 293
 Percheron, F. (1) 1
 Percival, M.D. (7) 69
 Perez, C. (20) 122
 Perez, J.A.G. (3) 216; (9) 53; (13)
 19; (16) 26
 Perez, S. (21) 57
 Perez-Matco, M. (23) 66
 Pérez-Pérez, M.-J. (10) 45; (20)
 168-170
 Perez-Soler, R. (19) 38
 Pergola, F. (2) 63
 Périgaud, C. (20) 6, 317
 Perkins, D.J. (17) 13; (20) 283
 Perlín, A.S. (7) 94
 Perly, B. (4) 174
 Pernikis, R. (7) 27
 Perrella, F.W. (18) 140
 Peschke, B. (14) 40
 Peseke, K. (10) 55; (14) 47
 Pestchanker, M.J. (18) 101
 Petazzini, G. (2) 63
 Pitcher, T.J. (3) 19
 Pete, J.-P. (24) 100
 Peter, M.G. (3) 29
 Peters, D. (8) 2; (20) 48
 Peters, J.A. (17) 37
 Peters, S. (3) 50, 111
 Peters, T. (3) 129
 Peterseim, M. (12) 7
 Petersen, P.M. (14) 30
 Petersen, S. (3) 29
 Peterson, E.M. (20) 207
 Peterson, J.M. (4) 73, 113
 Petit, P. (12) 14; (19) 43
 Petit, S. (16) 72
 Petitjean, O. (23) 82
 Petitou, M. (4) 122-124; (9) 43
 Petrušnaitė, R. (20) 244
 Petráková, E. (4) 32, 46; (8) 12;
 (9) 18; (10) 59; (13) 24
 Petrova, M. (20) 223
 Petrus, L. (2) 33, 34; (3) 251; (9)
 23; (22) 77, 88
 Petrusova, M. (2) 33, 34; (22) 77
 Petry, S. (4) 89, 90
 Pfleiderer, P.E. (22) 59
 Pfleiderer, W. (20) 59
 Phemius, P. (23) 107
 Phillipson, D.W. (19) 84
 Pianezzola, E. (23) 81
 Piarulli, U. (2) 14
 Picard, S. (7) 25
 Pieq, D. (9) 7, 49
 Piebler, L.T. (18) 79, 80
 Pietranico, S. (3) 18
 Pietrusiewicz, K.M. (18) 154; (22)
 106
 Pieta, P. (23) 43
 Pike, R.E. (14) 16; (16) 23; (19)
 55
 Pinches, H.L. (3) 157
 Ping, H. (22) 73
 Ping, L.-J. (20) 82
 Pinna, L. (16) 17; (18) 46; (22)
 74, 75
 Pinto, B.M. (3) 95; (4) 143
 Pipik, B. (7) 88
 Piszkorska, D. (10) 5
 Piskorz, C.F. (4) 42, 50, 52
 Pitha, J. (4) 166
 Pitkänen, I. (22) 60, 62
 Pitsinos, E.N. (19) 90
 Piva, O. (24) 100
 Pivarník, P.E. (23) 96
 Place, P. (3) 34
 Plattner, J.J. (19) 61; (20) 315
 Plavec, J. (11) 8; (20) 167; (22)
 132
 Ple, P.A. (18) 88
 Plepis, E. (7) 27
 Plewe, M. (3) 59, 60; (14) 7, 8, 45
 Plumet, J. (18) 94, 134
 Podányi, B. (6) 18; (8) 36; (11) 1,
 2; (16) 14, 15; (19) 24
 Pohl, D. (20) 310
 Polcseli, S. (23) 73
 Poli, G. (2) 14
 Pollock, C.J. (4) 16
 Polo, A. (14) 39
 Polomík, S.G. (3) 212
 Polsky, B. (20) 263
 Polt, R. (3) 49
 Poma, R. (23) 11
 Pompliano, D.L. (2) 75
 Poni, A. (6) 1
 Poncet, A. (24) 96
 Popelis, J. (20) 223
 Poppe, L. (21) 47, 48, 82
 Popping, B. (4) 165
 Popsavín, M. (8) 35
 Porcella, S. (23) 61
 Portenlaeger, G. (16) 87
 Porubcan, M.A. (19) 30
 Postema, M.D.G. (3) 215
 Potapova, N.P. (19) 33, 34
 Potier, L.M. (20) 90
 Potier, P. (24) 90
 Potter, B.V.L. (18) 99, 148, 162-
 164, 166; (22) 107
 Poukain, D. (21) 72
 Poupat, C. (24) 90
 Pouyani, T. (21) 78
 Pouzar, V. (3) 65
 Powers, J.P. (21) 6
 Powis, G. (18) 161
 Pozsgay, V. (3) 210; (4) 103, 147,
 150; (7) 23
 Pozuelo, C. (18) 105; (24) 10
 Pozza, G. (23) 11
 Prade, H. (5) 10
 Pradera, M.A. (3) 103; (7) 29
 Praly, J.-P. (3) 209; (8) 22, 28;
 (10) 6, 54; (14) 48; (16) 19, 20
 Pramanik, B. (19) 20, 21
 Pratap, R. (20) 137
 Prathanturarug, S. (18) 83
 Prato, M. (24) 71
 Pratt, C. (17) 19; (18) 136
 Predvoditelev, D.A. (7) 75, 76;
 (16) 76, 77
 Preobrazhenskaya, M.N. (19) 110;
 (20) 110
 Prestegard, J.H. (21) 38, 77
 Prestwich, G.D. (18) 145; (21) 78
 Preuss, R. (3) 248; (14) 41
 Previsani, N. (20) 209
 Price, J.D. (18) 85
 Priebe, W. (13) 5; (14) 24; (19) 38
 Priest, M.A. (19) 65
 Prikhodchenko, L.K. (22) 5
 Prisbe, E.J. (20) 120
 Pritchard, R.G. (3) 41; (22) 56,
 118
 Prokhorova, N.A. (3) 222, 223;
 (21) 32
 Prokopenko, O.F. (3) 61, 233;
 (13) 15
 Promel, R. (20) 25
 Provasoli, A. (21) 30
 Prunier, M.L. (19) 95
 Prusoff, W.H. (20) 41
 Puar, M. (19) 20, 21
 Puar, M.S. (14) 16; (16) 23; (19)
 55
 Pucker, R. (19) 64
 Pudio, J.S. (16) 2; (20) 160
 Pudio, P. (3) 15
 Puebla, P. (13) 10, (14) 22
 Pugasheva, N.M. (17) 15
 Pulido, R. (7) 37
 Pupeiko, N.E. (20) 93; (21) 23
 Pupok, K. (20) 165
 Purisima, E. (21) 91
 Putnam, A.R. (19) 28
 Qan-Zhang, M. (22) 55
 Qian, Z.-H. (3) 43
 Qing, C.Y. (10) 56; (22) 72

- Qiu, D.X. (4) 36; (6) 3, 4
 Quadflieg, P.J.L.M. (20) 298,
 299
 Quash, G. (16) 43
 Qudrat-e-Khuda, M. (20) 282
 Quiclet-Sire, B. (17) 3; (18) 125;
 (19) 50; (20) 270
 Quigley, G.J. (24) 50
 Quijano, M.L. (20) 191
 Quirosa-Guillou, C. (10) 73
 Qui-Tai, Z. (22) 55
- Rabenstein, D.L. (4) 18
 Rabius, E. (22) 122
 Radics, L.R. (3) 128; (21) 53
 Radziszewski, E. (2) 50
 Raffi, J.J. (22) 134, 136
 Ragazzi, M. (21) 30
 Ragg, E. (4) 110; (21) 85
 Ragouzeos, A. (21) 86
 Rahim, S.G. (11) 8; (18) 128; (22)
 132
 Rahman, K.M.M. (7) 19-21; (9)
 27, 60; (13) 20
 Rahman, Z. (7) 20, 21
 Raich, I. (7) 34
 Raifeld, Y.E. (8) 15; (14) 46
 Raimbaud, E. (21) 57
 Rainer, H. (3) 145; (12) 29
 Rajanbabu, T.V. (17) 14
 Rajanikanth, B. (18) 41
 Rajur, S.B. (20) 221
 Ralph, J. (7) 8
 Ramachandran, R. (21) 9
 Ramakumar, S. (22) 120
 Ramesh, K. (20) 213
 Ramesh, N.G. (3) 235
 Ranjee, M.N. (18) 78
 Ramsay, M.V.J. (20) 312
 Ransden, N.G. (3) 218; (9) 20;
 (18) 44
 Ranuza, J. (2) 41; (19) 94
 Randriamandimby, D. (3) 214
 Ranelli, M. (24) 71
 Rao, A.V.R. (3) 55; (16) 70; (20)
 107
 Rao, B.V. (3) 207; (4) 8; (24) 3
 Rao, C.P. (17) 28, 32
 Rao, C.S. (3) 2; (4) 114
 Rao, C.T. (4) 166
 Rao, K.V.B. (20) 187
 Rao, M.V. (20) 231
 Rao, S.M. (24) 82
 Rao, S.N. (21) 18
 Rao, T.S. (20) 17, 76, 238
 Rabro, J.W. (23) 90
 Rashed, N. (10) 75
 Rasmussen, P. (19) 36
- Rasoanaivo, P. (4) 55
 Rassu, G. (3) 256; (10) 69; (16)
 17; (18) 46; (22) 74, 75
 Ratajczak, H. (22) 1, 2
 Rathi, R.C. (9) 40; (10) 8
 Rathore, A. (20) 139
 Ratovelomanana, V. (21) 91
 Rauter, A.P. (22) 92
 Rava, A. (23) 43
 Ravi, D. (3) 207; (4) 8
 Ray, A.K. (4) 86
 Ray, R. (3) 107, 206
 Raza, Z. (17) 29
 Readshaw, S.A. (21) 4
 Reardon, J.E. (20) 271
 Rebarchak, M.C. (20) 24
 Reck, F. (4) 71, 109, 131
 Reddy, G.B. (3) 207, (4) 8, (23)
 53
 Reddy, K.K. (24) 81
 Reddy, K.R. (4) 53; (24) 54
 Redlich, H. (18) 107; (24) 53
 Redmond, J.W. (23) 51
 Reese, C.B. (20) 76, 130, 131,
 231
 Reeves, P.R. (20) 252
 Refn, S. (3) 13
 Reh, K.D. (4) 27; (15) 7
 Rchel, B. (3) 163; (9) 47
 Reig, F. (10) 12
 Reilly, P.J. (21) 55, 56, 60
 Reimer, K.B. (4) 143
 Reimer, M.L.J. (20) 134
 Reinhard, B. (3) 203
 Reitter, B.E. (18) 128
 Reitz, A.B. (19) 96; (20) 24
 Renaud, M. (4) 23
 Rémy, S. (24) 15
 Ren, W.-Y. (20) 85
 Renaud, C. (18) 4
 Renhofa, R. (20) 223
 Renko, D.Z. (10) 73
 Renkonen, O. (4) 132
 Rennie, R.A.C. (3) 230; (16) 18
 Renoux, B. (19) 43
 Rentsch, D. (6) 11
 Reuke, S. (23) 21
 Reuss, K.-P. (18) 13
 Reutter, W. (8) 8; (9) 38
 Revankar, G.R. (20) 4, 17
 Revel, M. (17) 18
 Rey, C. (23) 49
 Reyes, F.G.R. (10) 31; (23) 60
 Reynolds, D.J. (20) 293, 294
 Reynolds, R.C. (20) 123, 139, 140
 Rezzonico, B. (2) 15
 Rhodes, G. (10) 19
 Richards, G.N. (22) 12
 Richardson, A.C. (3) 11; (9) 12
- Riche, C. (18) 70
 Richter, A. (18) 96
 Richter, P. (20) 53
 Ricketts, A.P. (12) 24, (19) 88
 Rico, I. (18) 32; (21) 41
 Rico, M. (3) 240
 Rideout, J.L. (20) 271
 Rieck, M. (19) 53
 Riediker, M. (17) 34
 Riess, J.G. (7) 17, 71
 Rigal, L. (23) 107
 Riggs, R.M. (20) 133, 272
 Rihova, B. (9) 40; (10) 8
 Riley, P.A. (20) 242
 Riordan, J.M. (20) 87, 277
 Ristic, N. (16) 6
 Ritzen, H. (4) 35
 Riva, R. (9) 30
 Rivera-Sagredo, A. (3) 113; (12)
 27; (21) 54
 Rivoire, B. (3) 142; (9) 28
 Rizzo, C.J. (20) 222
 Rizzolo, A. (23) 73
 Rizzotto, M. (2) 66
 Robbins, J.B. (4) 103, 147
 Robert, J.M. (4) 18
 Robert-Gero, M. (2) 37; (14) 21;
 (19) 50
 Roberts, C. (3) 2
 Roberts, S.M. (7) 39; (18) 122,
 124, 129; (19) 57, 66, 76; (20)
 199, 204, 276
 Robertson, C.A. (11) 9; (20) 303
 Robina, I. (3) 103; (10) 22, 65
 Robins, M.J. (5) 18, (20) 89, 100,
 146, 147, 266; (22) 116
 Robins, R.K. (10) 15; (20) 4, 17
 Robinson, B. (20) 324
 Robles, J. (20) 296
 Roboz, J. (23) 13
 Rodes, A. (2) 59
 Rodionov, A.V. (7) 78
 Rodriguez, R.M. (3) 240
 Rodriguez, S. (14) 12
 Roelen, H.C.P.F. (20) 249
 Roger, P. (9) 15
 Rohmer, M. (18) 8; (22) 141
 Rohrer, J.S. (23) 31, 76
 Rollin, P. (3) 205; (12) 6; (22) 79
 Román, E. (10) 47; (13) 19
 Romano, A. (3) 139
 Romanowska, A. (3) 107; (4) 42
 Ronchetti, F. (7) 38; (21) 81
 Rosankiewicz, J.R. (4) 7
 Rosemeyer, H. (20) 114, 226
 Rosenberg, I. (20) 263
 Rosenbrook, W. (19) 61; (20) 315
 Rosing, H. (23) 92
 Roski, J.P. (14) 37

- Ross, K. (3) 218
 Ross, M.M. (17) 21
 Rossi, G. (24) 98
 Roth, J.S. (20) 88
 Rothenmel, J. (3) 203; (10) 2
 Rothman, N.M. (3) 239
 Roush, W.R. (4) 61; (18) 18
 Rouwenhorst, I.M. (7) 34
 Roy, N. (3) 110; (6) 7
 Roy, R. (3) 201; (4) 42; (7) 52;
 (10) 33; (11) 5
 Rosenberg, S.G. (7) 73
 Rozners, E. (20) 223
 Rozynov, B.N. (4) 15; (7) 82
 Ruan, J.L. (4) 56
 Ruangrungsi, N. (18) 83
 Rubtsov, Yu.I. (18) 5
 Ruchaud, S. (20) 247
 Rück, K. (24) 101
 Ruecker, G. (3) 39
 Ruiz, F.J. (9) 37
 Ruiz, P. (24) 7
 Rulin, F. (18) 85
 Runsink, J. (3) 145; (12) 29
 Ruppert, D. (24) 88
 Russ, P.L. (19) 79
 Russell, M.G.N. (18) 149
 Russo, G. (3) 139, 244; (24) 44
 Rutan, J.F. (3) 155; (16) 39
 Rutz, V. (3) 138; (12) 25, 26
 Rychnovsky, S.D. (3) 44; (21) 6
 Ryckman, D.M. (3) 102; (21) 61
 Rydzewski, R.M. (20) 120, 206
 Rysanek, N. (22) 44
 Ryu, E.K. (20) 13, 152, 184
 Ryu, Y. (18) 160
- Saba, A. (18) 20, 21; (22) 85
 Sabesan, S. (4) 144; (7) 63; (10)
 34
 Sabio, M. (21) 22
 Sabol, J.S. (20) 150
 Saburova, T.P. (19) 34
 Sadek, M. (23) 4
 Saenger, W. (22) 38
 Safrany, S.T. (18) 163
 Sagi, G. (20) 246
 Sagstuen, E. (22) 133
 Saha, U.K. (3) 51, 144; (5) 2
 Sahlgberg, C. (20) 164
 Satäh, M. (7) 10
 Samoto, H. (19) 90
 St.-Denis, Y. (18) 67
 Saisho, M. (22) 142
 Saito, K. (4) 121
 Saito, M. (19) 27; (23) 94
 Saito, S. (3) 70, 98; (7) 7; (8) 23;
 (19) 51; (20) 3, 142, 174
- Saito, T. (19) 68
 Saito, Y. (19) 82
 Saitoh, K. (19) 41
 Saji, H. (9) 39
 Sajus, H. (3) 21
 Sakai, K. (3) 117; (19) 77
 Sakai, N. (24) 103
 Sakai, S. (22) 53
 Sakaida, Y. (19) 86
 Sakakibara, M. (3) 213; (19) 39
 Sakakibara, T. (10) 46; (12) 24;
 (14) 25, 26; (19) 88
 Sakata, S. (20) 295; (22) 110
 Saksena, A.K. (14) 16; (16) 23;
 (19) 55
 Sakuda, S. (19) 10
 Sakurza, S. (12) 17
 Sakurai, N. (7) 53
 Sala, L.F. (2) 66; (17) 23
 Salamonczyk, G.M. (18) 154; (22)
 106
 Salavar, K.L. (3) 239
 Saleem, R. (3) 76
 Salitzky, D.J. (3) 44
 Saltiel, A.R. (3) 63
 Salvino, J. (3) 18
 Samadi, M. (17) 3, (19) 50; (20)
 141, 270
 Samano, V. (20) 146, 147
 Samreth, S. (12) 3
 Samuelsson, B. (20) 143, 161,
 162, 215
 Sánchez, A. (20) 32; (22) 135
 Sánchez, B. (24) 7, 10
 Sanders, C.R., II (21) 38
 Sandhoff, K. (2) 30; (3) 59, 60,
 204; (14) 7, 8, 45
 Sandström, A. (20) 167
 Saneyoshi, M. (20) 78, 292
 San-Félix, A. (20) 168, 169, 170
 Sanghvi, Y.S. (20) 126, 157, 158
 Sanna, D. (17) 33
 Sano, T. (3) 257
 Santas-Benito, F.F. (4) 106
 Sanvito, A.M. (3) 69
 Sanz, J. (23) 18
 Sapis, J.-C. (23) 15
 Sapre, N. (17) 35; (22) 97
 Sarabu, R. (20) 31
 Sarda, P. (14) 17
 Sargeon, A.M. (7) 74
 Sarkar, A.K. (4) 39
 Sarkar, B. (17) 26, 27
 Sacra, M.S.P. (20) 187
 Sarzynska, J. (20) 328
 Sasai, K. (20) 327
 Sasaki, K. (16) 21
 Sasaki, S. (16) 74
 Sasaki, T. (19) 29; (20) 99
- Sasaki, Y. (3) 70, 98; (7) 7; (8)
 23; (16) 21
 Sasamori, A. (16) 78
 Sashida, Y. (14) 3
 Saska, M. (23) 106
 Sasnauskienė, S. (20) 244
 Satake, M. (19) 89; (20) 1
 Sato, F. (24) 54
 Sato, H. (19) 74, 75; (20) 216,
 218, 316
 Sato, J. (23) 17
 Sato, K. (12) 8, 17
 Sato, N. (9) 25
 Sato, T. (3) 195
 Sato, Y. (7) 61, 102; (19) 59
 Satoh, T. (16) 78
 Satorre, J. (23) 66
 Sauerbri, B. (3) 116
 Saunders, J.K.M. (3) 81; (16) 25
 Sauvage, J.-P. (17) 30
 Savage, A. (23) 52
 Savateeva, E.E. (13) 14; (24) 20
 Savelyeva, I. (9) 52
 Sawa, T. (19) 42
 Sawada, M. (6) 10; (22) 16
 Sawada, S. (3) 71; (23) 124
 Sawai, H. (20) 45, 259
 Sawairi, S. (7) 54
 Sawyer, D.A. (18) 99; (22) 107
 Saxena, M. (16) 9
 Scala, A. (7) 38
 Scandura, R. (9) 41
 Scanlan, R.A. (10) 31, (23) 60
 Scaros, M.G. (19) 95
 Schacht, E. (10) 12
 Schachter, H. (4) 43
 Schaefer, M.E. (18) 37
 Schallier, H. (3) 161
 Scharf, H.-D. (3) 145; (12) 29;
 (14) 6
 Schenkel, E.P. (4) 117
 Scheuring, M. (3) 178; (4) 91; (5)
 4
 Schiering, T.D. (4) 18
 Schiltz, E. (4) 9
 Schinazi, R.F. (20) 291, 307, 308,
 310, 311; (22) 112
 Schleiden-Schmid, I. (3) 39
 Schlewer, G. (18) 172, 173
 Schliemann, W. (3) 100
 Schmalie, H.W. (17) 36
 Schmid, W. (2) 19; (24) 51
 Schmidt, K. (17) 16
 Schmidt, R. (20) 116
 Schmidt, R.R. (3) 59, 60, 91, 150,
 152, 246, 248, (4) 36, 65, 102,
 135, 142, 149; (14) 7, 8, 41,
 42, 45; (16) 56; (20) 256
 Schmitt, L. (18) 172, 173

- Schnaccerson, R. (4) 103, 147
 Schneider, A. (7) 65
 Schneider, M.P. (7) 33
 Schneller, S.W. (19) 60, 80; (20) 202, 208, 211
 Schoops, K.O. (2) 25
 Schols, H.A. (22) 32; (23) 54
 Scholz, D. (3) 160, 161
 Schram, K.H. (20) 134
 Schreiber, S.L. (19) 52; (20) 30
 Schroeder, D.R. (9) 3; (14) 2
 Schroeder, L.R. (3) 185
 Schudok, M. (3) 52
 Schütz, T.C. (19) 53
 Schütze, E. (3) 28; (7) 48
 Schulte, G.K. (3) 141; (13) 1
 Schulte, J. (21) 93
 Schulte, K.E. (4) 117
 Schultz, G.A. (22) 35; (23) 20
 Schultz, G.K. (22) 86
 Schultz, J.E. (3) 108
 Schultz, M. (3) 119
 Schultz, P. (23) 90
 Schulz, G. (3) 28; (7) 48; (16) 16
 Schulz, S. (20) 247
 Schumacher, M. (21) 93
 Schuurman, Y. (16) 62
 Schwarting, W. (22) 13
 Schwartz, N.B. (20) 267
 Schwidetzky, S. (8) 27
 Schwinden, M.D. (2) 16
 Scola, P.M. (24) 56
 Scolastico, C. (2) 14
 Scorrano, G. (24) 71
 Scott, I.L. (13) 18; (16) 64
 Scott, M.D. (23) 98
 Scott, W.J. (13) 4
 Sebesta, D.P. (4) 61
 Secco, A.S. (22) 127
 Sezen, H. (18) 92
 Sechrist, J.A., III (20) 87, 123, 133, 139, 140, 272, 277
 Sedmora, P. (3) 72
 Seela, F. (20) 52, 53, 66, 114, 226, 245
 Seemayer, R. (7) 33
 Seguin, E. (3) 35, 105
 Sehgal, R.K. (23) 96
 Seib, P.A. (7) 77; (16) 75
 Seidat, J. (23) 64
 Seillier, E. (3) 200; (11) 20
 Seitz, H.U. (23) 6
 Seitz, S.P. (18) 140
 Seki, T. (20) 292
 Sekine, M. (20) 300
 Sekita, S. (20) 1
 Sekkal, M. (21) 14; (22) 3
 Sells, T.B. (20) 305
 Semchenko, F.M. (20) 264
 Senanayake, C.H. (18) 73
 Seppelt, K. (8) 8
 Seppo, A. (4) 132
 Sequin, U. (18) 127
 Serafinowski, P. (20) 72, 135
 Sercbrennikova, G.A. (3) 45
 Serianu, A.S. (2) 27; (21) 7, 21
 Serrano, J.A. (10) 47; (13) 19
 Serriani, A.S. (21) 8
 Servi, S. (2) 12
 Seshadri, T.P. (22) 119, 121
 Seta, A. (14) 25, 26
 Seto, H. (7) 54
 Setoh, M. (18) 24
 Sezaki, M. (19) 29
 Shah, B.B. (22) 41
 Shah, R.N. (4) 43
 Shafullah, A.Z. (9) 60
 Shalamai, A.S. (20) 58
 Sham, H.L. (19) 61; (20) 315
 Shamala, N. (22) 119
 Shanmuganathan, K. (20) 308
 Sharma, A.P. (20) 180
 Sharma, G.V.M. (3) 55, 207; (4) 8; (14) 35; (24) 82
 Sharma, N. (16) 83
 Sharma, P.A. (20) 107
 Sharma, P.D. (16) 83
 Sharma, S. (12) 18
 Sharpless, K.B. (5) 21
 Sharshidhar, M.S. (18) 144
 Shashkov, A.S. (4) 51, 75, 76, 78; (7) 78; (14) 9
 Shashkov, N.K. (4) 77
 Sheehan, T. (23) 85
 Shekhan, M.S. (14) 29
 Shen, G.-J. (1) 9; (3) 155; (4) 25; (16) 39
 Shen, Y. (4) 175
 Shepard, T.A. (23) 68
 Sherman, J.S. (18) 25
 Sheuring, J. (18) 9
 Shevin, P.B. (2) 8
 Shiba, T. (4) 30; (16) 37, 55
 Shibaev, V.N. (4) 15, 119; (7) 80-82
 Shibata, N. (3) 187
 Shibata, S. (21) 24
 Shibata, Y. (9) 10; (19) 2, 4
 Shibayama, K. (19) 90
 Shibayama, S. (4) 126
 Shibukawa, M. (3) 126
 Shibuya, H. (3) 46, 58, 66
 Shibuya, M. (9) 16; (16) 31; (18) 82
 Shichi, S. (4) 28
 Shidawara, S. (23) 58
 Shigematsu, H. (10) 26
 Shigematsu, N. (19) 83
 Shigemori, H. (20) 2
 Shigenobu, K. (23) 33
 Shigeta, S. (20) 239
 Shigihara, A. (7) 53
 Shiba, T. (20) 325
 Shim, S.C. (4) 21
 Shimada, F. (3) 66
 Shimada, J. (4) 22
 Shimada, N. (19) 51; (20) 3
 Shimada, S. (3) 101
 Shimadate, T. (5) 16; (7) 9
 Shimanura, M. (3) 181
 Shimayama, T. (24) 6
 Shimizu, K. (4) 28
 Shimizu, M. (20) 259; (22) 109
 Shimizu, S.I. (20) 240
 Shimomoto, W. (3) 27
 Shing, T.K.M. (16) 35; (18) 11, 93; (22) 83, 89; (24) 24-26, 30, 31
 Shingu, K. (3) 78
 Shingu, T. (7) 58
 Shirakai, S. (22) 142
 Shinoda, M. (19) 41
 Shinomiya, K. (23) 57
 Shinozaki, K. (24) 85
 Shinozuka, K. (20) 45, 259
 Shiomi, Y. (22) 142
 Shiori, T. (19) 54
 Shiotani, N. (18) 153
 Shioya, E. (3) 26
 Shiozaki, M. (9) 46; (18) 131; (19) 100; (24) 79
 Shiragami, H. (20) 71
 Shiraishi, J. (20) 217
 Shiraishi, T. (19) 74; (20) 218
 Shirakabe, M. (3) 140
 Shirasaka, T. (20) 88
 Shitara, T. (19) 8
 Shizuma, M. (6) 10; (22) 15
 Shklyacv, Yu.V. (2) 32
 Shoberu, K.A. (18) 122, 124; (20) 199
 Shockcor, J.P. (21) 86
 Shoda, S. (4) 22
 Shoji, J. (9) 1
 Shoku, Y. (20) 297; (22) 124
 Shortnacy-Fowler, A.T. (20) 87
 Showalter, H.D.H. (19) 49
 Shu, C.K. (10) 27
 Shu, Y.T. (4) 161
 Shudo, K. (20) 55
 Shugar, D. (20) 115
 Shultis, E.A. (7) 56
 Shuto, S. (19) 67, 72
 Shuu, S. (19) 68
 Shvets, V.I. (18) 138
 Siddiqi, S.M. (19) 60; (20) 202
 Siddiqui, A. (20) 312

- Siddiqui, B.S. (3) 76
 Siddiqui, H.L. (3) 77
 Siddiqui, M.A. (20) 88
 Siegel, M.M. (19) 91; (22) 39
 Siciro, C. (22) 135
 Siems, K. (18) 97
 Sierzchala, A. (20) 228
 Sierzputowska-Gracz, H. (20) 225
 Sigal, G.B. (16) 45
 Sigimura, H. (3) 208
 Signorella, S.R. (2) 66
 Sik, V. (18) 129
 Sikorski, J.A. (18) 75, 77
 Silvestro, L. (22) 34; (23) 59
 Silvey, G.L. (21) 42
 Sim, H.-S. (24) 21
 Sim, I. (20) 302
 Sim, K.Y. (18) 69
 Sim, M.M. (20) 253
 Simenel, C. (9) 43
 Simkins, N.S. (18) 130
 Simon, H. (8) 31; (16) 3
 Simone, C.M. (16) 10
 Simoni, D. (20) 21
 Simonin, P. (18) 8
 Simpkins, N.S. (19) 9
 Simis, I.M. (4) 16
 Sinay, P. (3) 4, 148; (4) 72; (8) 24; (13) 3
 Sinerius, G. (7) 65
 Singer, M. (19) 64
 Singh, A. (16) 9
 Singh, A.K. (16) 9; (18) 7; (20) 182; (23) 110
 Singh, B. (16) 9; (18) 6, 7
 Singh, D. (18) 6
 Singh, R.K. (20) 96; (22) 41
 Singh, S. (3) 169
 Singhal, R.P. (23) 95
 Sianott, M.L. (3) 179; (16) 46
 Sinnwell, V. (10) 39
 Sinou, D. (3) 236; (13) 22; (20) 178; (22) 29
 Siouffi, A. (10) 24
 Siriwardena, A.H. (18) 70
 Skalskounis, A.-L. (3) 35, 105; (12) 21
 Skaric, V. (20) 124
 Skread, B.M. (16) 25
 Skelton, N.J. (3) 81
 Skokotas, G. (24) 54
 Skorupowa, E. (23) 12
 Skorynin, I.Yu. (20) 93; (21) 23
 Skrydstrup, T. (10) 23; (22) 80
 Slanina, P. (23) 44
 Slashchinin, G.A. (5) 28; (13) 13
 Slater, G.P. (23) 16
 Slęzak, P. (23) 89
 Sluboski, B.C. (20) 302
 Sluzarchyk, W.A. (19) 62
 Smejkal, J. (23) 67
 Smid, P. (3) 168, 172; (9) 59
 Smith, A.B., III (3) 18; (4) 57; (13) 25
 Smith, A.L. (19) 90
 Smith, D.L. (22) 33; (23) 72
 Smith, G.A. (18) 98
 Smith, J.D. (24) 36
 Smith, K.D. (23) 46
 Smith, M.B. (18) 36
 Smith, P.R. (9) 6
 Smith, R.J. (18) 71
 Smith, R.W. (22) 22
 Smith, W.S. (20) 225
 Smyth, J.F. (23) 109
 Snatzke, G. (17) 29
 Sneklova, E.V. (18) 1
 Snoeck, R. (10) 68; (19) 72, 80; (20) 211
 Snook, C.F. (20) 131
 Snyder, R.D. (20) 265
 Sobolev, A.N. (17) 15
 Sochacka, E. (20) 225
 Sochacki, M. (20) 228
 Sodaño, G. (3) 80
 Soga, T. (3) 162, 177; (9) 48; (23) 29
 Sogawa, S. (16) 78
 Sohioine, H. (19) 40
 Sokolov, G.P. (3) 68
 Sokolowski, J. (10) 5; (23) 12
 Solis, D. (12) 27
 Solov'ev, D.V. (8) 18
 Soloway, A.H. (17) 12, 13; (20) 283, 284
 Somerville, R.L. (18) 77
 Somogyi, L. (10) 63
 Somáék, L. (8) 21, 28; (10) 6, 54; (14) 48; (16) 19, 20
 Son, J.C. (16) 25
 Soner, A. (2) 26
 Song, Y.H. (24) 5
 Sonnino, S. (4) 110; (21) 85
 Sood, R.K. (3) 142; (9) 28
 Sorensen, H. (23) 118
 Soriente, A. (3) 80
 Sorrels, S.L. (3) 239
 Sottile, L. (7) 62
 Spackman, D.G. (7) 39
 Spada, M.R. (19) 48; (20) 39
 Spadari, S. (20) 56
 Spanu, P. (3) 256; (10) 69; (16) 17; (18) 46; (22) 74, 75
 Spasojević, S. (16) 6
 Speers, P.J. (22) 138
 Spencer, C.M. (21) 88
 Spencer, N. (21) 88
 Spiess, B. (18) 172, 173
 Spijker, N.M. (4) 145
 Spina, E. (22) 24
 Spirikhin, L.V. (3) 233; (13) 14; 15; (20) 14; (24) 20
 Spitzer, T.D. (21) 86
 Spivak, A.Yu. (2) 32; (3) 222, 223; (21) 32
 Spohr, U. (4) 46-48; (9) 18
 Sprengeler, P.A. (3) 18
 Sproat, B.S. (20) 260
 Srivastava, G. (4) 125
 Staemli, A. (22) 18
 Stamatov, S. (7) 70
 Stangier, P. (16) 41
 Stanovnik, B. (10) 66
 Staszak, M.A. (24) 38
 Stawersky, R.J. (2) 75
 Stawinski, J. (20) 232-235
 Stayanarayana, V. (3) 182
 Stec, W.J. (7) 72; (20) 228
 Steck, J. (3) 211; (4) 9, 85; (11) 21
 Steensma, D.H. (2) 21; (18) 73
 Steffan, W. (3) 146; (4) 59; (5) 31; (7) 40; (16) 63, 66
 Steffens, B. (20) 50
 Stein, Z. (22) 103
 Steinbach, J. (8) 19
 Steinbach, K. (16) 82
 Steiner, T. (22) 38
 Stenvall, K. (4) 64
 Stepanov, A.E. (18) 138
 Stephen, A.M. (21) 40
 Stepiak, K. (22) 47
 Stevanovic, S. (2) 24
 Stewart, J.J.P. (16) 22
 Stipak, J.K. (2) 65
 Sticher, O. (23) 42
 Stick, R.V. (17) 10
 Stiller, R. (7) 66
 Stimac, A. (10) 32
 Stocker, E. (20) 69
 Stoddart, J.F. (4) 158; (21) 88
 Störmann, R. (20) 247
 Stokes, S. (18) 130; (19) 9
 Stoll, G. (4) 170
 Stoll, N. (6) 11
 Stone, B.A. (23) 4
 Stone-Elander, S. (2) 25
 Stoodley, R.J. (3) 41; (22) 56
 Stoppok, E. (4) 27; (15) 7
 Storer, R. (11) 9; (20) 276, 303
 Stork, G. (3) 125
 Strader, C.D. (3) 18
 Strange, L.E. (20) 311
 Straub, A. (11) 13
 Strazewski, P. (20) 46
 Strecker, G. (21) 72, 74
 Strömborg, R. (20) 232, 234

- Stroholz, I. (20) 226
 Strolin Benedetti, M. (23) 81
 Stroud, M.R. (18) 135; (20) 254
 Struik-Prill, R. (21) 82
 Stütz, A.E. (2) 39, 57; (8) 6; (10)
 42; (18) 14, 39, 42
 Sturgess, M.A. (16) 60
 Suami, T. (2) 3
 Suarez, E. (24) 78
 Subramanian, R.S. (18) 64
 Suda, S. (3) 10
 Sudan, W. (18) 107
 Sudarceva, T.P. (5) 6; (9) 8
 Sudo, T. (16) 78
 Süthecay, Y. (18) 92
 Suga, T. (3) 77
 Sugai, T. (16) 38
 Sugawara, K. (14) 1
 Sugawara, T. (3) 126
 Sugimoto, M. (4) 67
 Sugimoto, Y. (2) 13
 Sugimura, H. (20) 62, 63
 Sugiura, M. (7) 15, 16
 Sugiura, Y. (3) 54; (19) 108
 Sugiyama, N. (3) 143
 Suguri, T. (4) 37
 Sujino, K. (3) 208; (10) 72; (20)
 62, 63
 Sukatsch, D.A. (19) 25
 Sulikowski, G.A. (13) 25, 25
 Sultanpuratova, V.R. (3) 222,
 233; (13) 15
 Sumita, S. (3) 70, 98; (7) 7; (8) 23
 Sunimoto, H. (5) 33
 Sun, C. (3) 37; (20) 33
 Sun, G. (16) 7
 Sunjic, V. (17) 29
 Suopanki, J. (4) 132
 Surolia, A. (2) 23; (9) 51
 Suryanarayanan, R. (19) 15
 Susaki, H. (3) 25
 Sutherland, A.G. (20) 199
 Sutoris, H. (4) 33
 Suzuki, A. (20) 239
 Suzuki, F. (18) 29
 Suzuki, H. (19) 23
 Suzuki, K. (3) 1, 259
 Suzuki, M. (2) 20; (16) 65
 Suzuki, S. (3) 187; (4) 28, (23) 40
 Suzuki, T. (19) 93
 Svansson, L. (20) 161, 162, 215
 Svenson, S. (22) 93
 Svensson, B. (4) 84
 Svensson, C. (20) 162
 Svensson, S.C.T. (20) 162, 215
 Sviridov, A.F. (14) 9; (24) 8, 35
 Swarna, G.V.T. (21) 9
 Swartling, D.J. (20) 94
 Sweeley, C.C. (22) 35; (23) 20
 Swoboda, B.E.P. (3) 169
 Sychev, V.A. (17) 17; (22) 95
 Symons, M.C.R. (2) 58
 Szabó, B. (20) 113
 Szabo, I. (23) 89
 Szabó, L. (3) 49, 149
 Szardenings, A.K. (18) 107
 Szarek, W.A. (4) 95; (18) 41; (22)
 19, 22
 Szarek, W.D. (20) 203
 Szechner, B. (2) 29; (9) 32
 Szeja, W. (3) 197
 Szilágyi, L. (18) 63; (24) 70
 Szonyi, M. (4) 35
 Szaricskai, F. (1) 2; (3) 173; (18)
 63; (19) 110, (20) 113; (24) 70
 Szucs, K. (20) 246
 Tabata, M. (23) 122
 Tada, T. (19) 83
 Tadano, K. (14) 43; (24) 12, 22
 Taga, M. (23) 119
 Tahara, T. (4) 172
 Tailor, D. (3) 158; (10) 36
 Tajmir-Riahi, H.A. (17) 25
 Takada, A. (7) 13, 14, 16
 Takagi, M. (23) 124
 Takagi, Y. (8) 13; (19) 40
 Takahata, S. (23) 17
 Takahashi, A. (19) 46
 Takahashi, K. (4) 44; (12) 17;
 (24) 103
 Takahashi, M. (4) 30; (16) 79;
 (18) 24
 Takahashi, S. (3) 171; (11) 10;
 (12) 15; (19) 54, 86; (22) 16
 Takahashi, T. (24) 6
 Takahashi, Y. (3) 6; (4) 28; (19) 7
 Takai, N. (22) 31; (23) 38
 Takai, V. (6) 10
 Takai, Y. (22) 16
 Takaide, A. (14) 25, 26
 Takaka, H. (20) 227
 Takano, E. (7) 49
 Takano, R. (7) 92, 97
 Takano, S. (14) 1; (18) 24
 Takao, K. (14) 43
 Takarashi, S. (18) 45
 Takase, S. (19) 83
 Takatori, K. (24) 6
 Takayanagi, H. (3) 30; (16) 58;
 (22) 91
 Takechi, M. (3) 101, 194
 Takeda, K. (9) 25
 Takeda, M. (8) 5
 Takeda, T. (3) 193; (4) 31, 108;
 (10) 14
 Takei, T. (2) 55
 Takemoto, N. (9) 1
 Takenaka, S. (19) 23
 Takenuki, K. (22) 110
 Takeo, K. (4) 10, 11, (5) 8; (22)
 58
 Takeuchi, M. (19) 86
 Takeuchi, T. (19) 40, 42, 97-99;
 (20) 20, 36
 Takeuchi, Y. (10) 4
 Taki, T. (18) 95
 Takita, T. (14) 15; (16) 24; (20)
 28, 314
 Takusagawa, F. (22) 73
 Talmont, F. (23) 9
 Tam, S.Y. (20) 68, 302
 Tamai, M. (22) 31; (23) 38
 Tamai, T. (24) 37
 Tameda, C. (19) 75
 Tameichi, N. (8) 17; (19) 5
 Tanii, C. (20) 46
 Tamura, J. (5) 16; (7) 9
 Tamura, S. (19) 41
 Tamura, Y. (3) 67; (23) 28
 Tanaka, C. (9) 39
 Tanaka, H. (7) 54; (19) 35, 83;
 (20) 142, 174, 175; (22) 109,
 113, 115, 129
 Tanaka, K. (3) 193; (8) 16; (16)
 79, (19) 6; (24) 55
 Tanaka, M. (4) 164; (19) 77
 Tanaka, O. (7) 98
 Tanaka, S. (23) 119
 Tanaka, T. (16) 1; (22) 16
 Tanaka, Y. (3) 101, 194; (20) 71
 Tanase, T. (2) 55
 Taneichi, N. (9) 58
 Tang, Y. (18) 93
 Taniguchi, S. (16) 80
 Tanimoto, T. (4) 160, 164; (23) 33
 Tanner, J.K. (23) 80
 Tao, L. (23) 78
 Tapiero, C. (23) 14
 Taravel, F.R. (21) 33
 Tari, L.W. (22) 127
 Tarusova, N.B. (7) 73; (20) 263
 Tashiro, T. (10) 4
 Tatsuta, K. (3) 226; (11) 15; (12)
 19; (19) 39; (24) 37
 Taylor, G.M. (6) 9; (14) 32; (22)
 84
 Taylor, J.P. (3) 157
 Taylor, P.B. (18) 2
 Taylor, R.J.K. (7) 3
 Teegarden, B.R. (3) 243
 Teffera, Y. (22) 33; (23) 72
 Tegge, W. (18) 147
 Teibrant, J. (3) 174
 Tejero, T. (9) 4
 Teng, K. (7) 4; (24) 29

- Terada, T. (3) 199
 Terasawa, H. (15) 1; (24) 1
 Terashima, S. (24) 4
 Terayama, H. (3) 171
 Termin, A. (4) 102
 Teshima, T. (4) 30; (16) 37, 55
 Thal, C. (10) 73
 Thangarasa, R. (22) 94
 Thelin, M. (20) 233-235
 Theodorakis, E.A. (9) 13; (17) 11
 Thérissod, M. (3) 17
 Thiem, J. (1) 10; (3) 15, 79, 83,
 116; (4) 26; (7) 64, 66, 93; (8)
 30, (10) 10; (12) 6; (14) 31;
 (16) 41
 Thiem, T. (3) 21
 Thiery, C.L. (22) 134, 136
 Thiery, J.M. (22) 134
 Thoelmann, D. (22) 14
 Thomas, D. (3) 42
 Thomas, N.F. (18) 120; (24) 13
 Thomas, W.A. (21) 35
 Thomé, M.-A. (9) 7
 Thompson, N.S. (3) 185
 Thompson, W.J. (7) 104
 Thomsen, J.U. (21) 75
 Thormählen, S. (24) 53
 Thorn, W. (4) 155
 Thornalley, P.J. (9) 6
 Thorncley, R.N.F. (18) 78
 Thorpe, A.J. (19) 66
 Thurin, J. (10) 13; (23) 50
 Tiden, A.-K. (3) 159
 Tielemans, M. (20) 25
 Tiffin, P.D. (6) 15
 Tillequin, F. (3) 35, 105, 173; (12)
 21; (19) 43
 Timmers, C.M. (20) 299
 Tampa, J.D. (2) 71
 Tino, J.A. (19) 62
 Trisler, M. (10) 66
 Tisnes, P. (18) 81
 Tiwari, K.N. (20) 133
 Tiwari, S. (2) 68
 Tjan, S.B. (15) 6
 Tjarks, W. (17) 12, 13; (20) 283,
 284
 Tobe, T. (9) 21; (18) 48; (24) 2
 Tod, M. (23) 82
 Todaro, L. (24) 50
 Todd, J.S. (3) 224
 Toemen, F. (12) 30
 Toepfer, A. (4) 149
 Toerien, F. (7) 101; (24) 47, 48
 Togo, H. (10) 72; (20) 195
 Toi, H. (4) 156
 Toida, T. (23) 58
 Tokutake, S. (4) 121
 Tolbert, T.J. (18) 79
 Tolkach, A.M. (3) 212
 Tollerfield, S.M. (20) 242
 Tolman, J.R. (21) 77
 Tolman, R.L. (10) 15
 Tolstikov, A.G. (3) 61, 233, (13)
 14, 15; (24) 20
 Tolstikov, G.A. (2) 32; (3) 61,
 222, 223, 233; (13) 14, 15,
 (20) 14; (21) 32; (24) 20
 Tolstikov, V.V. (19) 110
 Toma, L. (7) 38; (21) 81
 Tomasic, J. (7) 31
 Tomic, S. (7) 31
 Tomimatsu, T. (3) 78
 Tomita, K. (4) 67; (20) 37; (22)
 110, 125, (24) 22
 Tone, H. (19) 42
 Tone, J. (12) 24; (19) 88
 Tonegawa, T. (18) 117
 Tong, H.-H. (16) 1
 Toone, E.J. (16) 29
 Topiol, S. (21) 22
 Topper, F.D. (11) 5
 Toribio, L. (23) 25
 Torii, Y. (8) 20
 Torikata, A. (19) 5
 Toriya, M. (19) 72
 Torri, G. (20) 192; (22) 34; (23)
 59
 Toru, T. (3) 213
 Toshima, K. (3) 225, 226; (11) 15;
 (12) 19
 Totani, M. (23) 122
 Toth, I. (16) 69; (20) 138
 Toubal, M. (2) 50
 Tovar-Miranda, R. (21) 46
 Townsend, C.A. (20) 60
 Townsend, L.B. (16) 2; (20) 18,
 160, 319
 Toyoda, H. (23) 57, 58
 Toyokuni, T. (7) 43; (10) 35; (18)
 135; (20) 254
 Toyomaki, Y. (16) 47
 Toyota, A. (19) 74, 75; (20) 217,
 218
 Tramontano, E. (20) 21
 Tranter, G.E. (22) 138
 Trchan, S.B. (20) 51
 Treiberg, J. (3) 49
 Trew, S.J. (2) 22; (18) 38
 Trifunovic, I.D. (13) 9; (20) 67
 Trinccone, A. (3) 80
 Triolet, J. (22) 136
 Tronchet, J.M.J. (7) 26; (10) 49-
 51; (20) 119; (22) 67, 68
 Trouquet, C. (19) 87
 Tropp, B.E. (17) 19; (18) 136
 Tropper, F.D. (3) 107, 201; (4)
 42; (10) 33
 Trost, B.M. (19) 78; (20) 201
 Trumtel, M. (3) 88
 Truymeees, I. (19) 21
 Tsai, M.-D. (18) 100, 152
 Tsang, R. (24) 16
 Tsay, S.-C. (19) 93
 Tse, H.L.A. (20) 306, 312
 Tsetsokho, T.A. (22) 7
 Tso, J.M.Y. (23) 112
 Tsoucaris, G. (4) 174; (22) 42, 44
 Tsuchiya, T. (8) 16, 17; (9) 58;
 (19) 5-8, 24, 40
 Tsuda, K. (2) 10
 Tsuda, Y. (7) 102; (15) 2, 3
 Tsui, H.-C. (18) 11; (22) 83; (24)
 24-26, 31
 Tsujii, E. (19) 83
 Tsujikawa, J. (4) 160
 Tsujino, M. (19) 68
 Tsukagoshi, S. (10) 4
 Tsukiyama, T. (3) 234; (13) 21
 Tsukuda, K. (12) 24; (19) 88
 Tsunakawa, M. (19) 16
 Tsuneda, S. (19) 7
 Tsunoda, H. (18) 114, 115
 Tsunoda, T. (18) 85
 Tsuruo, T. (10) 4; (19) 74; (20)
 216, 217
 Tsutsumi, T. (8) 13
 Tsvetkov, Yu.E. (3) 91, 167
 Tu, G. (19) 12
 Tu, Y. (21) 91
 Turek, M. (23) 21
 Tulshian, D.B. (9) 19
 Tuomari, A.V. (19) 62
 Turcotte, J.G. (23) 96
 Turner, N.J. (3) 157; (7) 39
 Turovskis, I. (3) 68
 Tuzikov, A.B. (3) 32
 Tvaroska, I. (21) 33, 49
 Tyler, R.T. (23) 16
 Tymiak, A.A. (19) 30
 Uakagi, I. (24) 76
 Ubbink, J.B. (23) 91
 Ubukata, M. (19) 48
 Uchibori, T. (3) 192
 Uchida, C. (9) 10; (19) 4, 101,
 102
 Uchida, Y. (20) 71
 Uchiyama, H. (22) 31; (23) 38
 Udagawa, S.-i. (20) 1
 Udonong, U.E. (3) 2; (4) 114
 Uechi, T. (22) 100
 Ueda, H. (20) 297; (22) 124
 Ueda, I. (3) 78; (22) 110
 Ueda, T. (7) 92; (19) 68; (20) 34,
 37, 99, 149, 295; (22) 110,

- 125; (23) 24
 Uejima, Y. (7) 92
 Uemura, M. (18) 114
 Ueno, A. (24) 37
 Ueno, T. (23) 114
 Ueno, Y. (3) 213
 Ugarkar, B.G. (20) 69
 Uhmann, P. (3) 62
 Uhrin, D. (21) 62
 Umemura, E. (8) 16; (19) 6
 Umezawa, H. (19) 39
 Umezawa, S. (8) 13; (19) 7, 8, 24,
 40
 Undheim, K. (20) 200
 Unelius, C.R. (20) 210
 Ungerank, M. (18) 42
 Uoto, K. (3) 162, 177; (9) 48
 Uramoto, M. (24) 76
 Urbach, H. (24) 88
 Urbahns, K. (4) 85
 Urbanczyk-Lipowska, Z. (24) 60
 Urbanski, R. (14) 36
 Urge, L. (10) 11, 13; (23) 50
 Uryu, T. (5) 34; (21) 90
 Usui, H. (20) 37; (22) 125
 Usui, T. (3) 117
 Utikina, N.S. (4) 15; (7) 82
 Utley, J.H.P. (18) 3
 Utz, R. (24) 88
 Utzig, E. (20) 328
 Uvarova, N.I. (3) 212
 Uzan, R. (3) 217, 255; (5) 15; (8)
 37, 38; (18) 12, 23
- Vaaks, E.V. (20) 114
 Vale, W. (3) 18
 Valkonen, J. (22) 60, 61
 Vallance, S.L. (3) 166
 Valverde, S. (12) 5; (13) 10, (14)
 22; (16) 13, 27; (24) 9, 45
 Van Aerschot, A. (10) 68; (20) 83,
 125; (22) 114
 van Beem, J.H. (9) 59
 Van Beeumten, J. (21) 43
 Van Bekkum, H. (1) 7; (16) 61;
 (17) 37
 Van Boeckel, C.A.A. (4) 122-124,
 145; (18) 170
 Van Boom, J.H. (3) 86, 131-133,
 165, 168, 172; (4) 53, 79, 105,
 (7) 96; (8) 3; (10) 3, 38; (11)
 18; (16) 34, 67; (18) 54, 139,
 168; (20) 249, 298, 299
 van Dedem, G.W.K. (23) 113
 Van Delft, F.L. (4) 105
 van den Berg, R. (15) 8
 van den Bos, J.C. (24) 46
 Vandendriessche, F. (10) 68
 van der Biggelaar-Martea, M. (23)
 69
 van der Eycken, J. (18) 89, 90
 van der Greef, J. (22) 32; (23) 54
 van der Hoeven, R.A.M. (22) 32;
 (23) 54
 van der Klein, P.A.M. (3) 86,
 131, 133, 165; (4) 105; (7) 96;
 (10) 38; (11) 18; (16) 34; (18)
 54
 van der Maas, J.H. (22) 1, 2
 van der Marel, G.A. (3) 86, 132,
 133, 163, 168, 172; (4) 53, 79,
 105; (7) 96; (8) 3; (9) 59; (10)
 3, 38; (11) 18; (16) 34, 67; (18)
 54, 139, 168; (20) 249, 298,
 299
 van der Meer, P.H. (3) 86
 Vander Velde, D. (22) 73
 van der Ven, J.G.M. (4) 134
 Vanderwalle, M. (18) 89, 90
 van der Wiele, K. (16) 62
 van Dorsselaer, A. (22) 28
 van Dorst, J.A.L.M. (4) 109
 van Duijneveldt, F.B. (22) 1
 van Duuren, A.M.G. (3) 168,
 172; (9) 59
 van Ejck, B.P. (21) 44
 van Ewijk-Beneken Kolmer,
 E.W.J. (23) 70
 van Gijn, R. (23) 92
 van Halbeek, H. (21) 47, 48, 82
 van Haveren, J. (17) 37
 van Koningsveld, H. (22) 72
 van Lier, J.E. (22) 37
 van Lier, J.G. (23) 103
 van Maarschalkervaart, D.A.H.
 (18) 17
 van Middlesworth, F. (18) 40, 137
 van Nuffelen, W.F. (3) 155; (16) 39
 van Rantwijk, F. (10) 56; (15) 8;
 (22) 72
 van Rijsberg, R. (5) 30
 van Roey, P. (20) 307; (22) 112,
 117
 van Schepdael, A. (19) 11
 van Seestevens, P. (4) 134
 van Steenkiste, S. (10) 12
 van Sicijen, A.M.P. (4) 40, 54, 134
 van Straten, N.C.R. (8) 3; (16) 67
 van Tellingen, O. (23) 92
 van't Riet, K. (7) 32
 van Zandt, M.C. (18) 73
 Varela, D. (21) 19
 Vargas, D. (22) 99
 Vargeese, C. (20) 75
 Varki, A. (16) 36
 Varma, R.S. (20) 182, 183
 Varma, V. (4) 143
 Vasella, A. (3) 6, 62, 96, 160,
 170, 196
 Vasil'eva, E.V. (21) 32
 Vasil'eva, I.B. (6) 6
 Vasseur, J.-J. (20) 126, 157, 158
 Vasyanina, L.K. (7) 75; (16) 76;
 (17) 17; (22) 95
 Vauzeilles, B. (8) 24
 Vayonne, C.L. (23) 15
 Vecchio, G. (4) 178
 Veeneman, G.H. (3) 165; (7) 96;
 (10) 38; (16) 34; (18) 169
 Vega-Pérez, J.M. (9) 36, 37
 Velázquez, S. (20) 144
 Velde, D.V. (20) 213
 Veldhuizen, Y.S.J. (22) 2
 Veluraja, K. (3) 218
 Venkataramanaiyah, K.C. (5) 29
 Veno, H. (18) 29
 Venot, A.P. (4) 139
 Venturella, V.S. (23) 68
 Vepachedu, S.R. (14) 35
 Vercière, J.-F. (17) 30
 Verduyn, R. (18) 139
 Vereb, G. (20) 246
 Vergoten, G. (21) 14, 64; (22) 3
 Verhart, C.G.J. (6) 8
 Verheyden, J.P.H. (20) 120, 173
 Verloo, R.A. (18) 19
 Verma, N. (20) 252
 Vermaak, W.J.H. (23) 91
 Vermulen, B.W.M. (23) 113
 Vermin, G. (10) 24
 Verner, I.K. (7) 78
 Verotta, L. (21) 76
 Verwey-van Wissen, C.P.M.G.M.
 (23) 69
 Vestergaard, B.F. (20) 104, 176
 Vetter, D. (4) 155
 Veyrières, A. (3) 4; (13) 16
 Viano, I. (22) 34; (23) 59
 Viaud, M.-C. (3) 205
 Vic, G. (3) 42
 Victorova, L.S. (20) 153
 Vid, G.Ya. (14) 46
 Vidal, P. (20) 263
 Vigne, L. (4) 85
 Vignon, M. (4) 23
 Villarrasa, J. (20) 102
 Vilkman, A. (4) 132
 Vill, V. (3) 15; (7) 93; (11) 3; (16)
 71
 Villa, R. (2) 14
 Villain, F. (22) 44, 45
 Villanueva, D. (3) 113
 Ville, G. (3) 238
 Vilpo, J.A. (20) 53
 Vinavak, R.S. (20) 17
 Vince, R. (20) 207

- Vincent, B.R. (11) 8; (22) 132
 Vincent, P.B. (22) 134, 136
 Vincenti, M. (22) 11
 Vinke, P. (1) 7
 Virgili, A. (6) 5; (21) 37; (24) 95
 Virtanen, P.O.I. (2) 67
 Vismara, E. (20) 192
 Viso, A. (18) 94
 Visser, J. (23) 100
 Viswantha, M.A. (22) 44, 119, 120
 Vite, G.D. (18) 108; (24) 3
 Vit, S. (10) 30
 Vittori, S. (20) 185
 Vlahov, I.R. (3) 150; (16) 56
 Vlahova, P.I. (3) 150; (16) 56
 Vliegenthart, J.F.G. (4) 40, 54, 134; (5) 12; (21) 12, 44, 66, 80; (23) 34
 Vloon, W.J. (24) 46
 Voelker, W. (9) 17; (14) 29
 Vogel, C. (3) 146; (4) 59; (5) 31; (7) 40; (11) 3; (16) 63, 66, 71
 Vogel, P. (3) 245; (9) 31; (12) 12, 13; (18) 68, 84; (20) 196, 197
 Vogt, D.C. (21) 40
 Vorin, S.G. (23) 14, 15
 Volka, K. (22) 6
 Voll, R.J. (22) 98, 99
 Vollerthum, R. (18) 107
 Volosyuk, T.P. (20) 109
 Volpin, R. (20) 185
 Volwerk, J.J. (18) 144
 Von der Bey, E. (4) 169
 Voorheis, H.P. (18) 98
 Voragen, A.G.J. (22) 32; (23) 54
 Vosmanska, M. (23) 67
 Vottero, P.J.A. (3) 16, 90
 Voznyi, Y.V. (3) 74
 Vrantska, M. (3) 198
 Vrath, R.V. (2) 64
 Vree, T.B. (23) 69, 70
 Vreckamp, R.H. (18) 140
 Vsui, A. (18) 53
 Vuister, G.W. (21) 80
 Vukojevic, N. (8) 32, 35
 Vuorinen, T. (21) 8
 Vyle, J.S. (20) 128
 Vyplc, H. (3) 161
- Wada, T. (20) 96
 Wadouachi, A. (5) 15
 Waga, T. (14) 5
 Waglund, J. (3) 221
 Wagner, A. (24) 88
 Wahren, M. (17) 16
 Wait, R. (22) 9
 Wakabayashi, H. (20) 259
 Wakai, H. (20) 259
 Wakao, N. (2) 10
 Wakimura, M. (20) 190
 Walczak, K. (20) 105, 165
 Waldner, A. (2) 35
 Waldstätten, P. (3) 28; (7) 48; (9) 57
 Walker, K.A.M. (20) 172, 173
 Walker, L.E. (4) 25
 Walker, M.C. (18) 77
 Walker, R.T. (11) 8; (14) 27; (20) 15, 49, 240; (22) 132
 Walsh, J.P. (18) 143
 Wan, Y.W. (4) 56
 Wang, A.H.-J. (20) 249
 Wang, H.J. (3) 190
 Wang, H.M. (23) 115
 Wang, I.F. (4) 154
 Wang, J.J. (9) 16; (16) 31; (18) 82
 Wang, K.-T. (7) 44
 Wang, P. (18) 36, 37
 Wang, R. (3) 120
 Wang, S. (7) 6; (18) 150
 Wang, T.-C. (24) 77
 Wang, W.-M. (9) 22
 Wang, Y. (3) 102, 247; (20) 33; (21) 61
 Wanner, M.J. (18) 19; (20) 285
 Ward, O.P. (7) 67
 Ward, P. (16) 69
 Ward, T.L. (18) 74
 Wartchow, C.A. (18) 36
 Wasner, H.K. (22) 30
 Wasylky, J.M. (2) 48
 Watanabe, H.K. (3) 126
 Watanabe, J. (7) 14, 15
 Watanabe, K. (20) 35, 36; (23) 17
 Watanabe, K.A. (20) 85, 86, 263
 Watanabe, S. (3) 43
 Watanabe, Y. (3) 213; (18) 146, 153; (20) 186
 Waterhouse, A.L. (21) 50, 51
 Watkin, D.J. (24) 42
 Watson, J.T. (22) 35; (23) 20
 Webster, J.M. (6) 2
 Weber, A. (3) 52
 Weber, A.L. (2) 9
 Weber, B. (10) 2; (23) 101
 Weber, D.S. (7) 62; (21) 67
 Weber, M. (19) 25
 Weck, R. (24) 88
 Weenen, H. (15) 6
 Wei, H. (2) 63
 Wei, Y. (8) 29
 Weichsel, A. (22) 52
 Weier, R.M. (19) 95
 Weigel, L.O. (24) 38
 Weigle, M. (20) 302
 Weinhold, E.G. (16) 44
 Weintraub, A. (20) 252
 Wellington, E.M.H. (2) 22; (18) 38
 Welsh, C. (3) 103; (10) 22
 Welzel, P. (3) 22; (10) 16
 Wen, T. (18) 3
 Wen, Z.Q. (22) 140
 Wengel, J. (20) 104, 105
 Wenz, G. (4) 169
 Werner, K.M. (19) 103-105
 Wernes, W. (4) 117
 Wernig, P. (7) 12
 Wessel, H.P. (3) 88; (7) 95
 Westerdahl, G. (23) 37
 Westerduin, P. (4) 145; (18) 169, 170
 Westerlund, D. (23) 84
 Weston, B.W. (3) 108; (4) 24
 Wetterich, F. (16) 33
 Weymouth-Wilson, A. (20) 159
 Whale, R.F. (20) 15, 49
 White, G. (23) 48
 Whitesides, G.M. (2) 18, 19; (9) 55; (16) 45; (18) 27, 51; (20) 250, 251
 Whitfield, D.M. (3) 128, 184; (17) 26, 27; (21) 53
 Whiting, A. (5) 32; (10) 43
 Whittle, A.J. (18) 130; (19) 9
 Widlanski, T.S. (11) 16
 Widmalm, G. (4) 5, 94; (21) 52, 58, 70, 71, 84
 Wiebe, L.I. (20) 77, 290
 Wiczorek, W. (22) 106
 Wiederschain, G.Y. (3) 75
 Wiegand, F. (24) 88
 Wielckens, K. (20) 188
 Wiemann, T. (3) 83; (4) 26
 Wierczorek, W. (18) 154
 Wierszeski, J.M. (21) 72, 74
 Wiewiorowski, M. (20) 328
 Wigerinck, P. (20) 125
 Wightman, R.H. (3) 230; (16) 18; (20) 191
 Wijesekera, R. (7) 74
 Wilcox, C.S. (24) 84
 Wilhelm, J.A. (23) 68
 Wilkens, R. (4) 131
 Willard, N.P. (18) 17
 Willem, R. (21) 13
 Willems, H.A.M. (18) 169, 170
 Williams, D.H. (3) 81
 Williams, D.M. (20) 84
 Williams, K.W. (16) 45
 Williams, M.A. (4) 25
 Wilson, I.K. (20) 92
 Wilson, K.E. (18) 40, 137
 Winchester, B.G. (9) 20; (18) 43, 44, 58

- Wincoff, F.E. (18) 40
 Wingert, L.M. (1) 14
 Winkler, E. (20) 247
 Winkler, F.J. (22) 13
 Winkler, T. (2) 35
 Winter, H. (20) 53
 Wise, D.S. (20) 319
 Wisniewski, A. (23) 3, 12
 Withers, S.G. (7) 69
 Wittmann, V. (3) 252
 Witnyk, J. (19) 109
 Wnuk, S.F. (20) 89, 100, 266;
 (22) 116
 Woerner, F.J. (18) 30
 Wolf, J. (20) 145
 Wolf, R. (17) 18
 Wolf, W. (20) 92
 Wolfe, M.S. (19) 71; (20) 205,
 213
 Wolff-Kugel, D. (20) 273
 Won, J.H. (20) 13
 Wong, A.H.J. (22) 126
 Wong, C.-H. (1) 9; (3) 120, 122,
 155; (4) 24, 25, 68, 73, 111;
 (8) 7, 33, 34; (9) 34; (10) 44;
 (13) 2; (16) 38-40; (18) 49, 52;
 (20) 253
 Wong, N.R. (18) 71
 Wood, I.P. (16) 69
 Wood, W.W. (6) 9; (13) 18; (14)
 32; (16) 64; (22) 84
 Woodcock, E.A. (23) 80
 Woods, M. (6) 15
 Worm, A. (12) 13
 Wormald, M.R. (21) 62
 Woster, P.M. (20) 136
 Wotring, L.L. (20) 18
 Wright, G.E. (20) 44
 Wróblewski, K. (10) 11
 Wrubel, F. (18) 35
 Wu, H.Y. (20) 172
 Wu, J. (2) 27; (21) 7, 8
 Wu, J.-C. (20) 166, (22) 131
 Wu, M.D. (23) 106
 Wu, S.-H. (7) 44
 Wu, X. (5) 26; (10) 40; (22) 63
 Wu, Y. (20) 136
 Wu, Z. (3) 2
 Wu, Z.J. (22) 73
- Xi, Z. (20) 167
 Xian, J. (23) 95
 Xiao, X.-Y. (24) 54
 Xiao-Ling, S. (22) 55
 Xie, R. (4) 177
 Xie, Y. (5) 7
 Xu, F. (18) 53
 Xu, S.-H. (19) 26
- Xu, Y.-M. (16) 1; (19) 26
 Xuan, L.-J. (19) 26
- Yadav, J.S. (24) 81
 Yaegashi, T. (3) 71
 Yaginuma, S. (19) 17-19, 68
 Yahara, S. (3) 78
 Yakabe, T. (4) 37
 Yakoh, Y. (7) 14
 Yakovleva, L.A. (7) 73
 Yakovleva, V.N. (10) 30
 Yamabe, S. (16) 80
 Yamada, H. (3) 27, 31, 64, 97, (4)
 157; (22) 16; (24) 6
 Yamada, K. (2) 20; (16) 65; (18)
 132; (23) 30; (24) 80
 Yamada, M. (3) 10; (12) 24; (19)
 88
 Yamada, S. (13) 26
 Yamada, Y. (19) 10
 Yamagata, T. (3) 181
 Yamagata, Y. (20) 37, (22) 110,
 125
 Yamagihara, Y. (23) 28
 Yamaguchi, M. (19) 22
 Yamaguchi, K. (20) 175; (22)
 109, 113, 115, 129, (23) 29
 Yamaguchi, M. (3) 228
 Yamaguchi, N. (23) 19
 Yamaguchi, T. (20) 78
 Yamaguchi, Y. (3) 40
 Yamaji, N. (4) 121
 Yamakawa, M. (16) 47
 Yamamoto, F. (16) 74
 Yamamoto, H. (3) 67; (17) 1, 2, 4,
 7
 Yamamoto, I. (22) 53
 Yamamoto, K. (10) 20
 Yamamoto, M. (19) 35
 Yamamoto, T. (4) 172; (16) 37,
 55; (19) 17
 Yamamoto, Y. (24) 94
 Yamamura, H. (4) 171
 Yamamura, S. (14) 15, (16) 24;
 (19) 56; (20) 28, 314
 Yamashita, G.A. (19) 62
 Yamanishi, S. (23) 57
 Yamao, H. (6) 10
 Yamasaki, K. (7) 98
 Yamasaki, T. (19) 16, 106
 Yamash, H. (7) 61
 Yamashita, K. (2) 10
 Yamauchi, N. (18) 102; (19) 14;
 (24) 76
 Yamazaki, C. (19) 32
 Yamazaki, M. (4) 28; (19) 54
 Yamazaki, T. (8) 5
 Yamilov, R.Kh. (3) 61; (24) 20
- Yamamoto, M. (10) 4
 Yanagihara, R. (2) 56
 Yanagisawa, Y. (9) 25
 Yanagiya, Y. (3) 84, 135
 Yanahira, S. (4) 37
 Yang, C. (5) 25; (21) 36
 Yang, G. (5) 19
 Yang, H. (7) 77; (16) 75; (24) 34
 Yang, J.-M. (4) 43
 Yang, J.W. (20) 318
 Yang, L. (22) 55
 Yang, R.T. (20) 68
 Yang, Z.C. (23) 8
 Yano, S. (2) 55
 Yano, Y. (2) 2
 Yarborough, R. (19) 21
 Yartseva, I.V. (20) 47, 109, 110
 Yasaka, T. (20) 134
 Yashunskii, D.V. (24) 35
 Yas'ko, M.V. (7) 73; (20) 117,
 264
 Yaso, M. (19) 68
 Yasuda, M. (21) 26
 Yasui, H. (24) 33
 Yaylayan, V.A. (2) 53; (22) 4
 Yazawa, K. (19) 32
 Ye, Y.K. (23) 88
 Yeager, E.B. (2) 61
 Yeh, H.J.C. (8) 12; (13) 24
 Yeh, P. (7) 86
 Yeon, Y. (22) 54
 Yeung, L.L. (18) 91
 Yi, K.Y. (5) 17
 Yin, H. (24) 50
 Ying-Jie, H. (22) 55
 Yogyaraj, (2) 64
 Yokai, S. (21) 59
 Yokomizo, Y. (3) 10
 Yokoyama, A. (9) 39
 Yokoyama, J. (18) 117
 Yokoyama, M. (10) 72; (20) 195
 Yokoyama, S. (21) 26
 Yokoyama, Y. (2) 13
 Yokoyura, T. (3) 71
 Yonemitsu, O. (24) 55
 Yoneyama, M. (22) 53
 Yong, S.F. (22) 81
 Yoo, I.Y. (24) 5
 Yoo, J.U. (20) 31
 Yoon, E. (4) 38
 Yoon, S.K. (24) 56
 Yoshida, H. (23) 119
 Yoshida, J.-i. (18) 15
 Yoshida, M. (4) 62, 63, (16) 52,
 53
 Yoshida, T. (7) 55
 Yoshihara, R. (7) 58
 Yoshii, E. (12) 22; (24) 57
 Yoshikawa, M. (3) 66; (18) 95.

- 114
 Yoshikawa, S. (2) 56; (3) 192
 Yoshikawa, T. (3) 126
 Yoshimoto, A. (19) 42
 Yoshimura, Y. (20) 34, 39, 149
 Yoshioka, M. (19) 77
 Yoshizaki, M. (7) 58
 Younathan, E.S. (22) 98, 99
 Young, D.G.J. (3) 229
 Young, M.G. (19) 62
 Young, R.C. (18) 101
 Yu, C. (21) 34
 Yu, J. (14) 4
 Yu, K.-L. (22) 87
 Yu, L. (10) 28
 Yu, X. (10) 28
 Yuan, C. (18) 150; (20) 205
 Yuan, C.-S. (20) 147
 Yuan, D. (4) 177
 Yuan, J. (21) 10
 Yuan, L. (4) 173
 Yuasa, H. (3) 121; (11) 17
 Yukawa, T. (20) 71
 Yukose, K. (7) 54
 Yunling, Y. (19) 102
 Yunda, N.G. (18) 5
 Yuno, T. (4) 164
 Yurkevich, A.M. (20) 109
 Yusa, K. (19) 74; (20) 216, 217
- Zabelin, L.V. (22) 5
 Zacharie, B. (20) 312
 Zahn, H. (19) 53
 Zagur, C. (14) 6
 Zagulyaeva, O.A. (20) 110
 Zahler, R. (19) 62
 Zahner, D. (2) 26
 Zain, R. (20) 232
 Zaitseva, I.A. (20) 114
 Zakharova, E.V. (2) 62
- Zaman, F. (14) 29
 Zamyski, A. (2) 7, 28, 41, 42; (4) 60; (19) 94
 Zamora Mata, F. (3) 216; (9) 53; (16) 26
 Zane, P.A. (23) 102
 Zapata, A. (4) 83
 Zapata, G. (3) 155; (16) 39
 Zapotocky, B.A. (19) 31
 Zard, S.Z. (11) 6; (20) 129
 Zarotskii, V.V. (6) 6
 Zarzycki, R. (21) 88
 Zbiral, E. (7) 103; (16) 16, 48, 50, 51; (20) 111
 Zdanov, A. (22) 123
 Zedde, C. (18) 81
 Zegeelaar-Jaarsveld, K. (4) 53
 Zehnder, M. (18) 127
 Zehner, L.R. (2) 46
 Zeitler, R. (9) 38
 Zelenin, K.N. (10) 61
 Zen, S. (4) 28, 44; (9) 25
 Zeng, F. (20) 95
 Zeng, Z. (21) 55
 Zerial, A. (20) 118
 Zhang, C. (20) 33
 Zhang, H.-C. (20) 194
 Zhang, H.-L. (19) 26
 Zhang, L. (21) 10
 Zhang, P. (4) 163; (5) 26
 Zhang, W. (5) 18; (20) 147
 Zhang, Y. (20) 33
 Zhang, Y.-M. (4) 72
 Zhang, Z. (21) 34
 Zhao, H. (4) 177
 Zharskii, V.B. (19) 34
 Zhbankov, R.G. (1) 13; (22) 5, 7
 Zhdanov, A.S. (22) 128
 Zhdanov, Yu.A. (5) 6; (9) 8
 Zheng, D. (21) 10
- Zheng, Y.A.J. (21) 3
 Zhengyun, Z. (20) 231
 Zhitomirskii, A.N. (2) 52
 Zhong, Z. (1) 9
 Zhou, P. (7) 67; (22) 141
 Zhou, Z. (22) 18
 Zhou, Z.-H. (18) 11; (22) 83, 89; (24) 25, 26, 30, 31
 Zhou, Z.-Y. (19) 10
 Zhov, J. (20) 95
 Zhu, J. (5) 5; (6) 17; (18) 69
 Zhu, Q.-Y. (20) 263
 Zhuang, D. (4) 116
 Zhukova, O.S. (20) 109
 Zichy, V. (22) 8
 Ziegler, T. (4) 29, 33; (6) 12-14
 Zielenkiewicz, W. (20) 328
 Zimmer, B. (22) 48, 77, 101, 104, 105
 Zimmer, J. (7) 12
 Ziser, L. (4) 92
 Zlicar, M. (10) 66
 Zmai, H. (18) 150
 Zodda, J.P. (23) 48
 Zorn, M. (20) 247
 Zosimo-Landolfo, G. (7) 26; (10) 51; (22) 67
 Zottola, M.A. (24) 3
 Zsély, M. (10) 49; (18) 63; (20) 119; (24) 70
 Zuber, M. (9) 43
 Zubkov, V.A. (14) 9
 Zucchelli, L. (24) 44
 Zulauf, M. (3) 52
 Zurita, D. (3) 240
 Zuurmond, H.M. (3) 86, 133; (11) 18
 Zvonkova, E.N. (18) 138
 Zwanenburg, C. (6) 8
 Zweerink, M. (18) 137

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