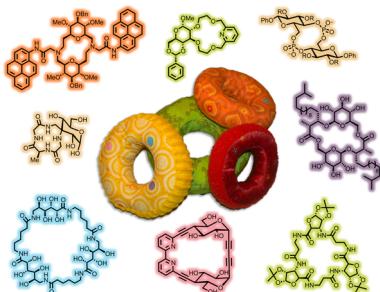


Synthesis and Applications of Carbohydrate-Derived Macrocyclic Compounds

Juan Xie* and Nicolas Bogliotti

PPSM, Institut d'Alembert, ENS Cachan, CNRS, UMR 8531, 61 av. Président Wilson, F-94235 Cachan Cedex, France



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1. INTRODUCTION

Macrocyclic compounds are of growing interest because of their natural existence, their interesting biological, physicochemical properties, and potential applications in medicine.^{1–5} Various natural as well as non-natural macrocycles have been synthesized, and synthetic methodologies aiming to access macrocycles containing or derived from carbohydrates have blossomed over the last decades. Such macrocycles, naturally present in a number of biologically active products from plant and microorganism, have attracted great interest due to their structural complexity and the synthetic challenges associated with their total synthesis.^{6–8} More recently, an increasing number of studies have been devoted to the preparation of structurally simpler unnatural structures for biological, chemical, or analytical applications.

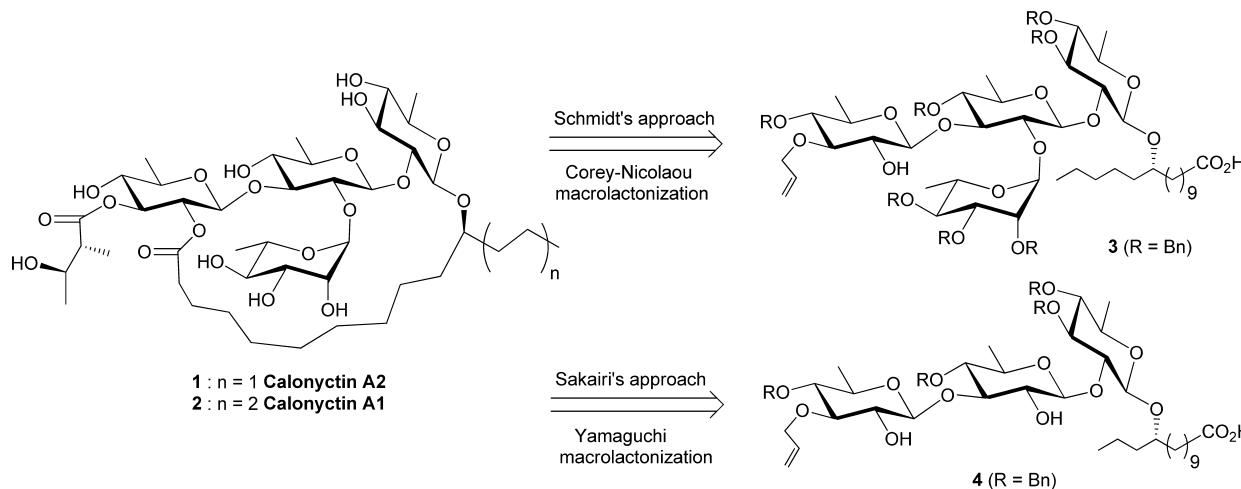
Many advantages are associated with carbohydrate-derived structures. First, carbohydrates are readily accessible from natural source; the existence of several stereoisomers allows the design

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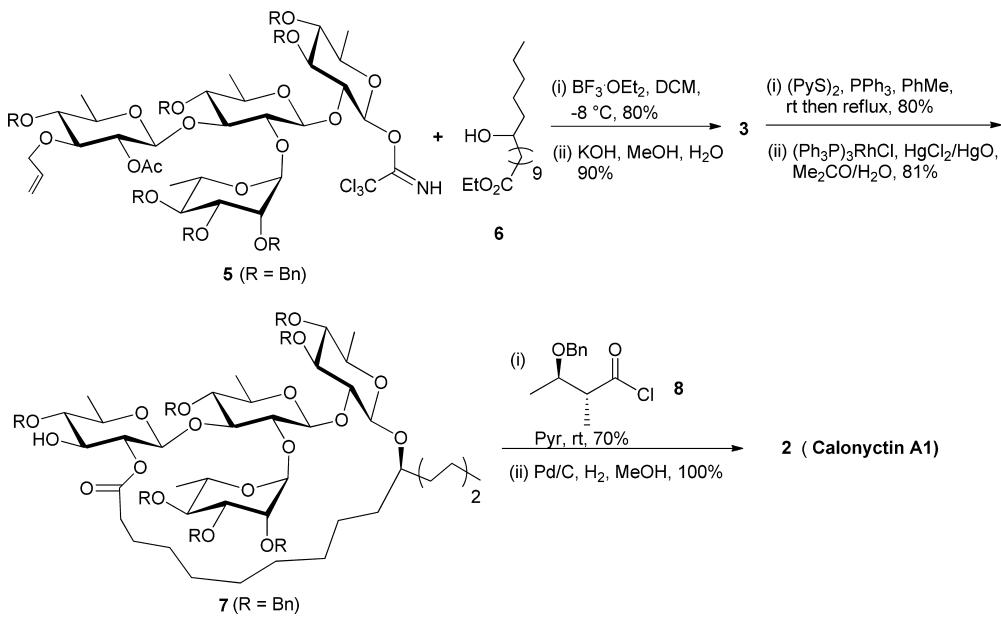
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Scheme 1. Retrosynthesis of Calonyctin A



Scheme 2. Total Synthesis of Calonyctin A1 by Schmidt's Group



and synthesis of a large variety of macrocycles. Second, the multifunctionality of carbohydrate not only provides the possibility of linkage through the different positions of sugar ring so as to enlarge the structure diversity, but also allows a modulation of the physicochemical properties (like solubility, hydrophilic/lipophilic balance, biodisponibility, etc.). Third, the presence of a furanoid or pyranoid cycle imposes geometric constraints, which is highly desirable for the design of conformationally restricted molecular platforms. Furthermore, the chiral nature of carbohydrates allows the preparation of chiral cavities, which can be useful in the field of asymmetric catalysis and chiral recognition. Finally, synthesis of carbohydrate-derived macrocycles using sugar building blocks such as sugar amino acids (sugars containing both an amino and a carboxylic acid group) offers the possibility to access a variety of compounds in a modular way.

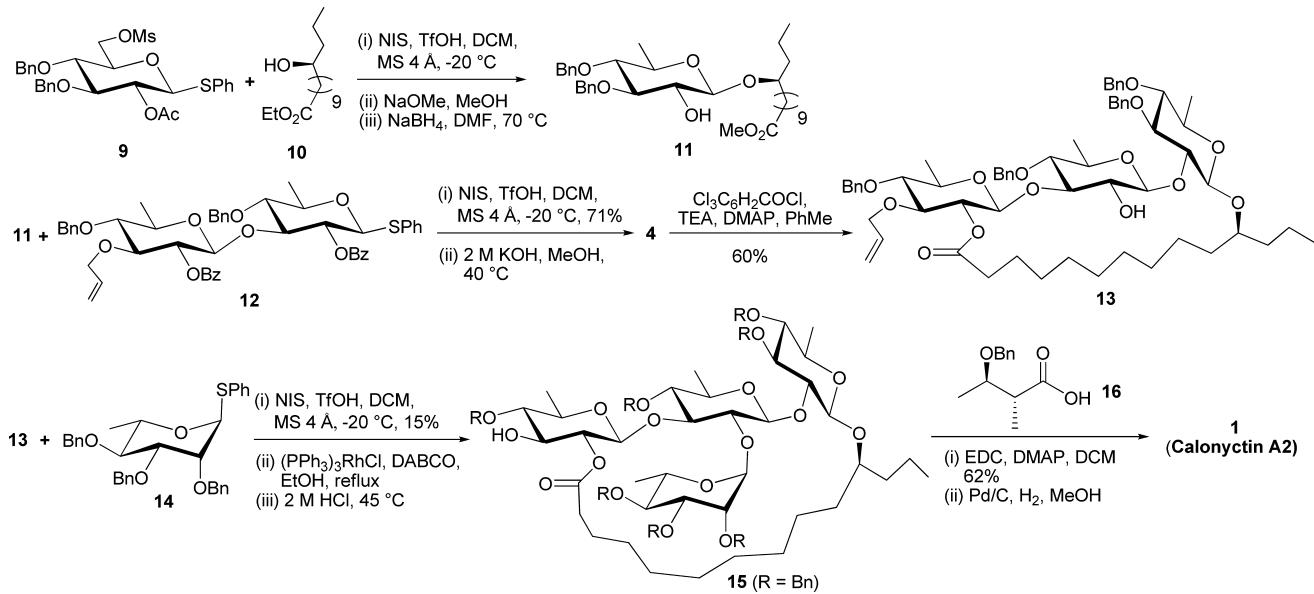
The aim of this Review, which covers the literature until July 2012, is to provide an overview of the structural diversity of carbohydrate-containing natural and synthetic macrocycles, the methodologies used to access these structures, as well as some of

their applications, based on a classification according to the chemical functions involved in the macrocyclization step. A number of natural carbohydrate-containing macrocycles have been synthesized using alkene/alkyne metathesis as a key step, and such strategies have been extensively reviewed until recently.^{9–15} Therefore, this aspect will not be included in this Review. Synthesis of ellagitannin natural products has been recently reviewed and thus will not be covered.^{8,16,17} Also outside the scope of this Review is the synthesis of cyclic oligosaccharides. Sugar-derived crown ethers have also attracted a great interest,^{18–22} and the recent most significant research in this field will be highlighted in section 5.

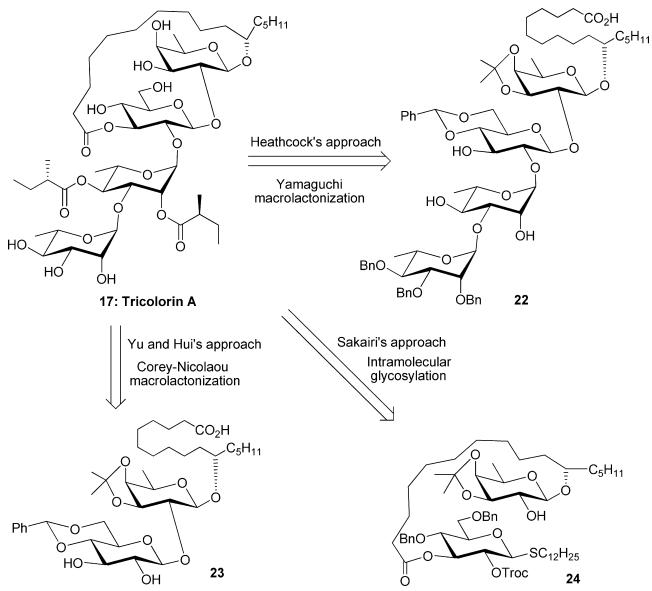
2. NATURAL CARBOHYDRATE-CONTAINING MACROCYCLES

Complex carbohydrate-containing macrocycles, isolated from plants or microorganisms, have usually several monosaccharides or an oligosaccharide flanked on a hydroxylated fatty acid (for complex glycolipids including resin glycosides) or benzoic acid (for cyclic dimers of 4-glycosyloxybenzoates) arranged in an 18–

Scheme 3. Total Synthesis of Calonyctin A2 by Sakairi's Group



Scheme 4. Retrosynthesis of Tricolorin A



46-membered macrolactone ring. This kind of macrolactone structure is also present in the triterpene saponins named cyclic bisdesmosides, which are composed of two oligosaccharides and a pentacyclic triterpene bridged with 3-hydroxy-3-methyl glutarate. These amphiphilic metabolites display various biological activities such as plant growth regulation, cytotoxicity against human breast cancer cell lines, antiviral, as well as ionophoretic activities. The intact macrolactone ring is essential for their bioactivity.^{23,24}

Total synthesis of complex carbohydrate-containing macrocycles has been motivated by absolute structure determination and synthetic challenge to construct these complex glycoconjugates, especially the elaboration of the macrocyclic core structure. Corey–Nicolaou protocol (2,2'-pyridyl disulfide, PPh₃),²⁵ Yamaguchi conditions (2,4,6-trichlorobenzoyl chloride, Et₃N, DMAP),²⁶ DMC (2-chloro-1,3-dimethylimidazolinium chloride)-mediated template-directed macrodimerization,²⁷ DCC/

DMAP, and intramolecular glycosylation are among the five most employed methods for the critical macrocyclization.

2.1. Glycolipids from Plants

2.1.1. Calonyctin A. Calonyctin A, extracted from the leaves of *Calonyction aculeatum* L. House, is a plant growth regulator promoting the growth and yield of various crops. Calonyctin A is a 22-membered macrolactone composed of a 6-deoxygenated tetrasaccharide residue and 11-hydroxy fatty acid, which exists as Calonyctin A1 (2) and A2 (1) (Scheme 1). Two total syntheses of Calonyctin A have been reported, through the macrocyclization of either tri- (4) or tetrasaccharide intermediates (3).

The first synthesis was reported by Schmidt's group in 1995, as resumed in Scheme 2.²⁸ Configuration of the aglycons 3-hydroxy-2-methylbutyric acid and 11-hydroxyhexadecanoic acid (jalapinolic acid) was unknown. To determine the absolute configuration of the natural product, a racemic jalapinolic ester 6 was glycosylated with the tetrasaccharide intermediate 5 using the trichloroacetimidate method, affording a 1:1 mixture of two diastereomeric β -glycosides in 80% yield. Subsequent saponification allowed the separation of the two diastereomers by column chromatography. The (S) configuration of the natural jalapinolic acid was assigned after hydrogenolytic debenzylation and total acidic hydrolysis, by comparison of optical rotations with the literature data. The desired (S) isomer of 3 was then cyclized by redox condensation with 2-pyridyl disulfide and Ph₃P (Corey–Nicolaou protocol) under high dilution conditions (0.4 mM in toluene) to afford the corresponding macrolactone in 80% yield. Removal of the allyl protecting group with Wilkinson's catalyst led to the hydroxy derivative 7, which was acylated with the (R,R) or (S,S) 3-benzyloxy-2-methylbutyric acid chloride 8. Final hydrogenolytic debenzylation and comparison of optical rotations and NMR data with those of isolated natural compound allowed one to assign the (R,R) configuration for the 3-hydroxy-2-methylbutyric acid aglycon and accomplished the total synthesis of Calonyctin A1 (2).

In 2000, Sakairi's group reported the total synthesis of Calonyctin A2 (1) through the macrocyclization of the trisaccharide intermediate 4 (Scheme 3).²⁹ Phenyl thioglycosides have been chosen as glycosyl donors for successive glycosyla-

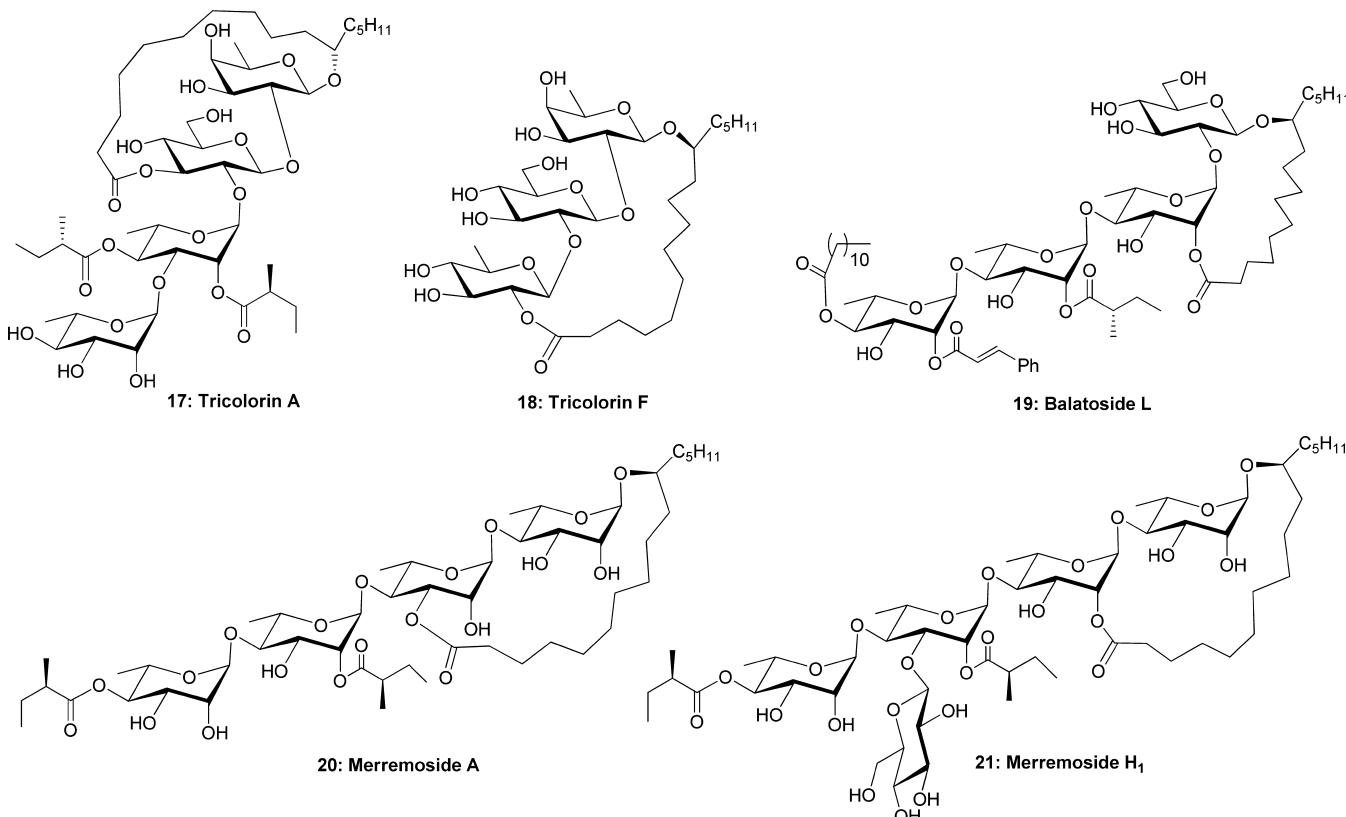
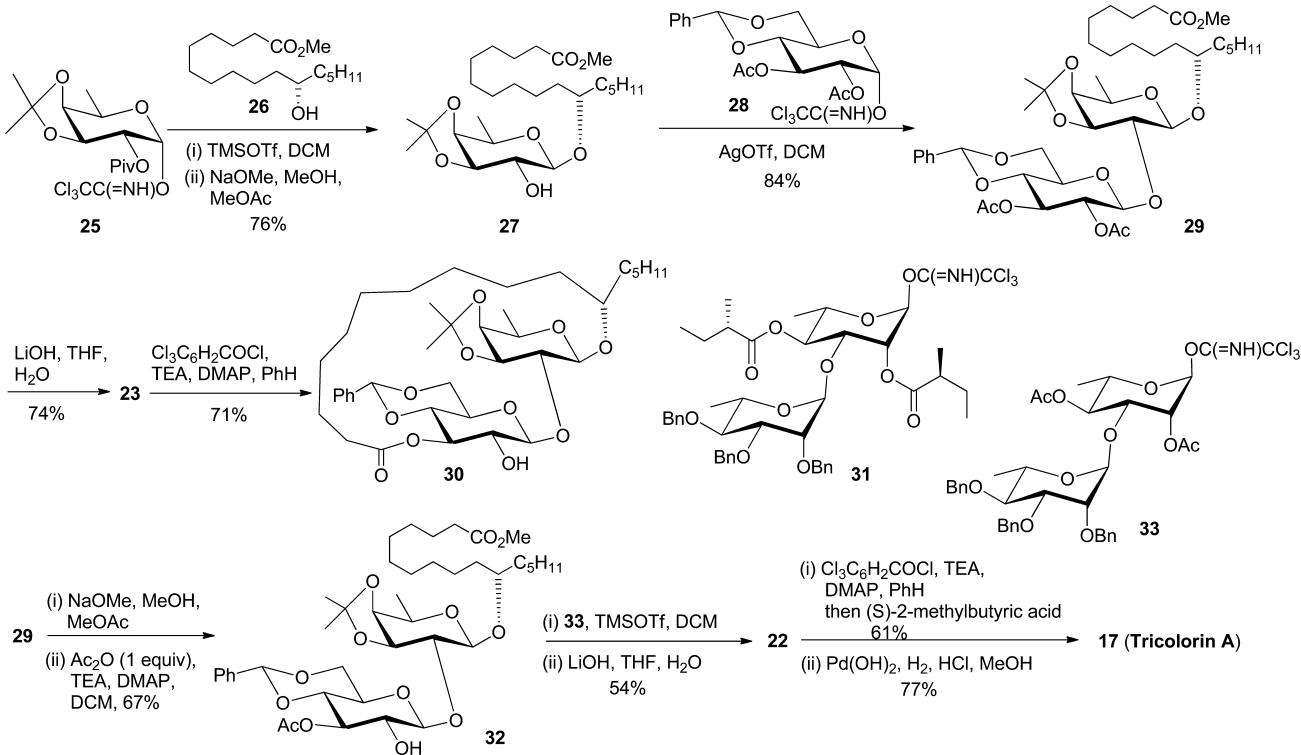


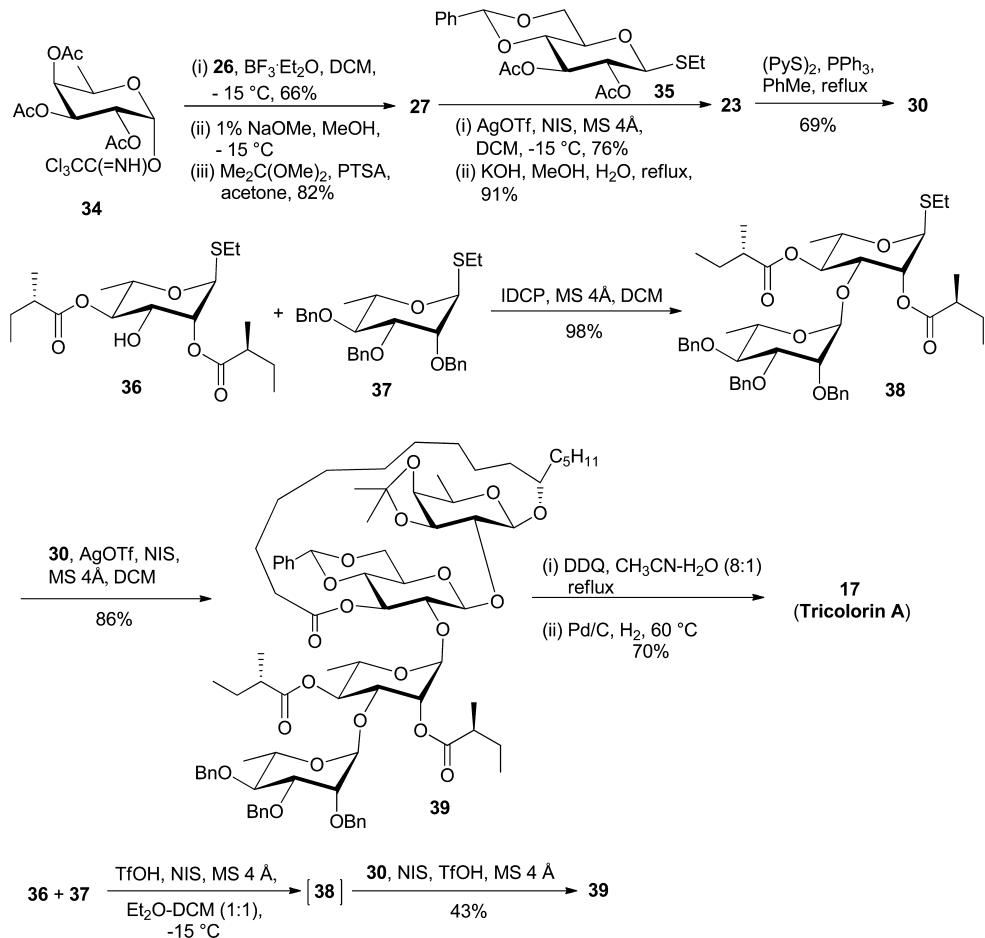
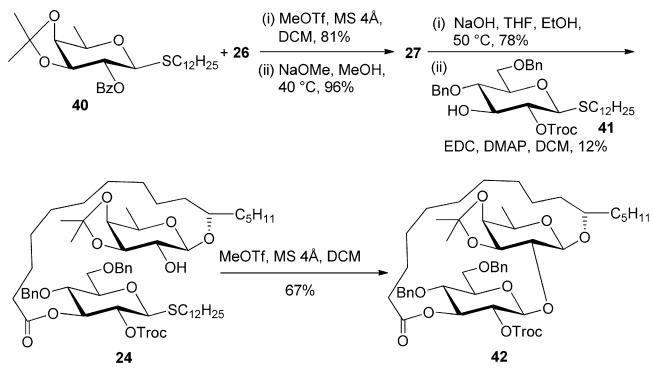
Figure 1. Structure of some resin glycosides from the morning glory family.

Scheme 5. Total Synthesis of Tricolorin A by Heathcock's Group



tions. Glycosylation of thioglucoside 9 with the 11(S)-hydroxymyristic ester 10 followed by Zemplen deacetylation and mesylate reduction gave the 6-deoxy- β -glucoside 11. Further glycosylation of 11 with the thiodisaccharide 12 and removal of

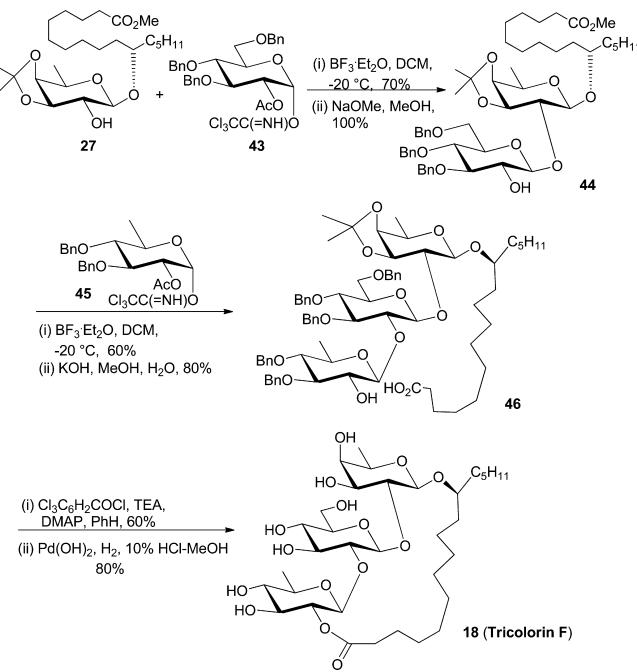
two benzoyl protecting groups afforded the carboxylic acid 4, which was subjected to macrolactonization by a mixed anhydride procedure (Yamaguchi's conditions) under high-dilution conditions (0.17 mM in toluene). Although two 2-hydroxyl groups

Scheme 6. Total Synthesis of Tricolorin A by Yu and Hui's Group**Scheme 7.** Synthesis of the Macrolactone Core of Tricolorin A by Sakurai's Group

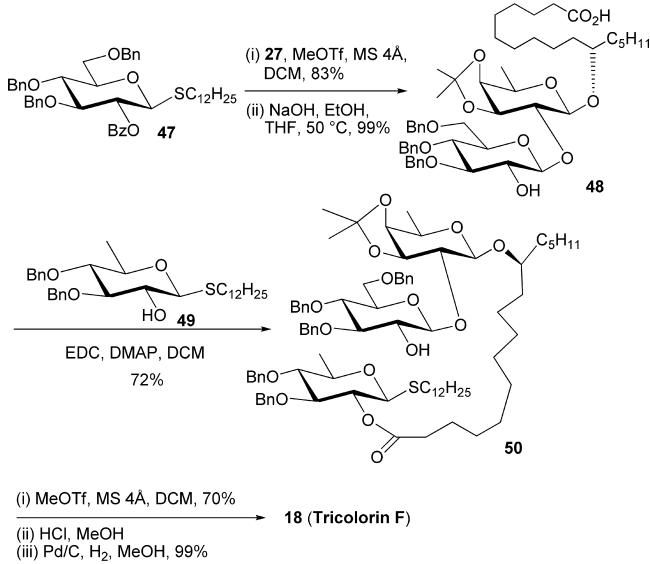
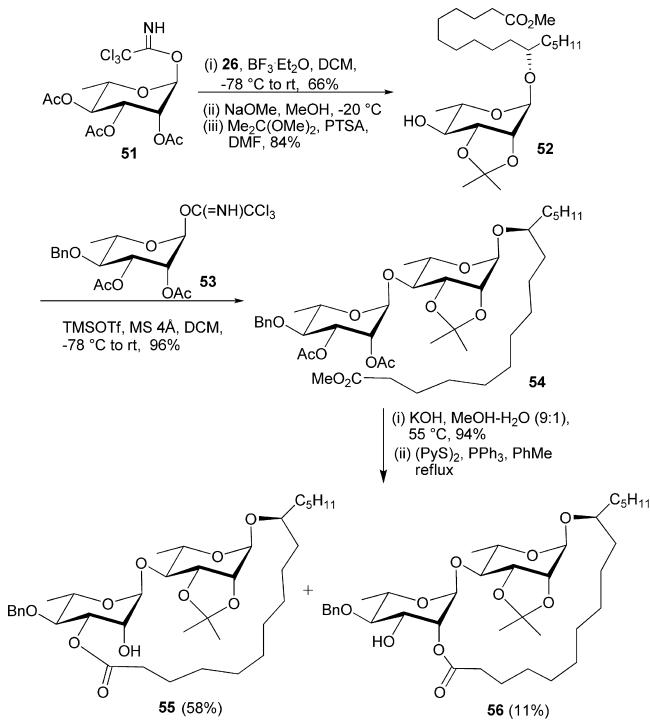
are present on the trisaccharide intermediate 4, the desired 22-membered macrolactone 13 was obtained as a single product in 60% yield. However, the yield of subsequent glycosylation with the thioglycoside 14 was poor (15%). Allyl group deprotection followed by coupling with (*R,R*) 3-benzyloxy-2-methylbutyric acid 16 and debenzylation achieved the total synthesis of Calonyctin A2 (1).

2.1.2. Resin Glycosides from the Morning Glory Family.

Like Calonyctin A, resin glycosides from the morning glory family (Convolvulaceae) of plants are a class of amphiphilic glycolipids bearing a macrolactone skeleton. These glycoconjugates are constituted by an oligosaccharide and a mono- or

Scheme 8. Total Synthesis of Tricolorin F by Heathcock's Group

dihydroxy C_{14} or C_{16} fatty acid (Figure 1). These resin glycosides, used in folk medicine around the world, have various promising

Scheme 9. Total Synthesis of Tricolorin F by Sakairi's Group**Scheme 10. Synthesis of the Macrolactone Core of Merrimosides by Yang's Group**

biological effects such as antibacterial, antifungal, cytotoxic, and plant growth controlling effects.

2.1.2.1. Tricolorin A. Tricolorin A, isolated in 1993 from *Ipomoea tricolor* cav. (convolvulaceae), a plant used in traditional Mexican agriculture to inhibit the growth of invasive weeds, is a 19-membered macrolactone. Several syntheses have been reported since 1996, involving either macrolactonization or intramolecular glycosylation strategy as shown in the retro-synthetic Scheme 4.

The glycosyl carboxylic acid 23 has been chosen as a key intermediate by two research groups, Heathcock,^{30,31} and Yu and Hui,^{32,33} for the total synthesis of tricolorin A. Using the trichloroacetimidate glycosylation, Heathcock's group synthe-

sized the disaccharide 23 by coupling the hydroxy ester 26 with D-fucosyl trichloroacetimidate 25, followed by removal of the 2-O-pivaloyl group, glycosylation with D-glucosyl trichloroacetimidate 28, and saponification of the three ester groups (Scheme 5). Yamaguchi's macrocyclization of 23 (0.19 mM in benzene) underwent selectively at the C-3 hydroxy position of the D-glucose, leading to the desired lactone 30 in 71% yield. The observed C-3 over C-2 selectivity in this intramolecular acylation was explained by the steric bulk of the glucose anomeric substituent.³¹ However, glycosylation of the lactone 30 with the glycosyl trichloroacetimidate 31 failed to give the corresponding macrolactone tetrasaccharide. Consequently, an alternative plan has been installed, consisting of the preparation of the tetrasaccharide intermediate 22 before macrocyclization. To favor the glycosylation on the C-2 position of the glucose unit of 23, the 3-hydroxy group was selectively acetylated by a two-step procedure: Zemplen deacetylation of 29, followed by selective acetylation with 1 equiv of Ac₂O. Reaction of the resulting compound 32 with the glycosyl trichloroacetimidate 33 followed by saponification gave the tetrasaccharide 22. One-pot macro-lactonization and esterification with (S)-2-methylbutyric acid using Yamaguchi's protocol (0.2 mM in benzene) and final deprotection accomplished the total synthesis of tricolorin A (17) in 47% yield from 22.

In a similar way, Yu and Hui's group started the synthesis of the disaccharide 23 by reaction of peracetylated D-fucosyl trichloroacetimidate 34 with the hydroxy ester 26 (Scheme 6). Removal of acetyl groups and isopropylideneation afforded the glycoside 27, which was then transformed into the disaccharide 23 by glycosylation with the thioglucoside 35 followed by saponification. Macrolactonization of 23 under the Corey–Nicolaou conditions (0.7 mM in toluene) led to the target macrolactone 30 in 69% yield, together with 11% of the 2''-OH macro-lactonized product. Glycosylation of the macrolactone disaccharide 30 with the thioldisaccharide 38, obtained from thioglycosides 36 and 37, led successfully to the macrolactone tetrasaccharide 39 in 86% yield. Final deprotection provided the tricolorin A (17) in 70% yield. An alternative “one-pot two-step” glycosylation procedure between thioglycosides 36, 37, and 30 has also been realized for assembling the tetrasaccharide block 39.

Sakairi's group studied an intramolecular glycosylation approach to construct the disaccharide macrolactone skeleton (Scheme 7).³⁴ Glycosylation of dodecyl thiofucoside 40 with methyl 11(S)-jalapionate 26, followed by Zemplen trans-esterification, gave the fucosyl ester 27. Subsequent saponification and coupling with the thioglucoside 41 gave the disaccharide 24 in only 12% yield, due probably to the migration of C-2 Troc protecting group in 41. MeOTf-promoted intramolecular glycosylation of 24 (2.4 mM in dichloromethane) provided the disaccharide macrolactone 42 in 67% yield.

2.1.2.2. Tricolorin F. Tricolorin F is a 21-membered trisaccharide macrolactone. The first total synthesis was reported by Heathcock's group in 2004, by using a similar strategy as for their synthesis of tricolorin A.³⁵ Glycosylation of the fucoside 27 with D-glucosyl trichloroacetimidate 43 followed by deacetylation led to the disaccharide 44, which was further glycosylated with the quinovosyl trichloroacetimidate 45 (Scheme 8). After saponification, the resulting carboxylic acid 46 (2.4 mM in benzene) was macrolactonized with Yamaguchi's procedure to give the target tricolorin F after debenzylation.

Sakairi's group applied also the intramolecular glycosylation strategy for the total synthesis of tricolorin F (Scheme 9).³⁴

Scheme 11. Total Synthesis of Batatoside L by Yang's Group

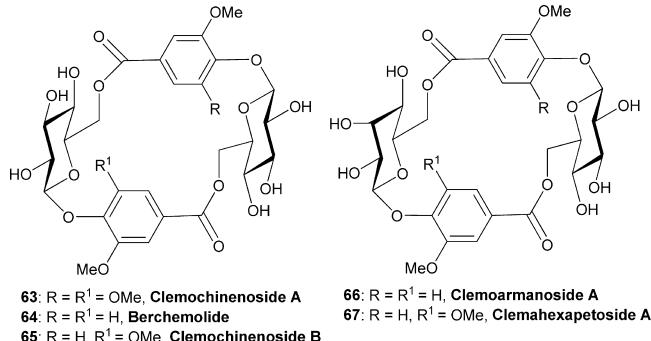
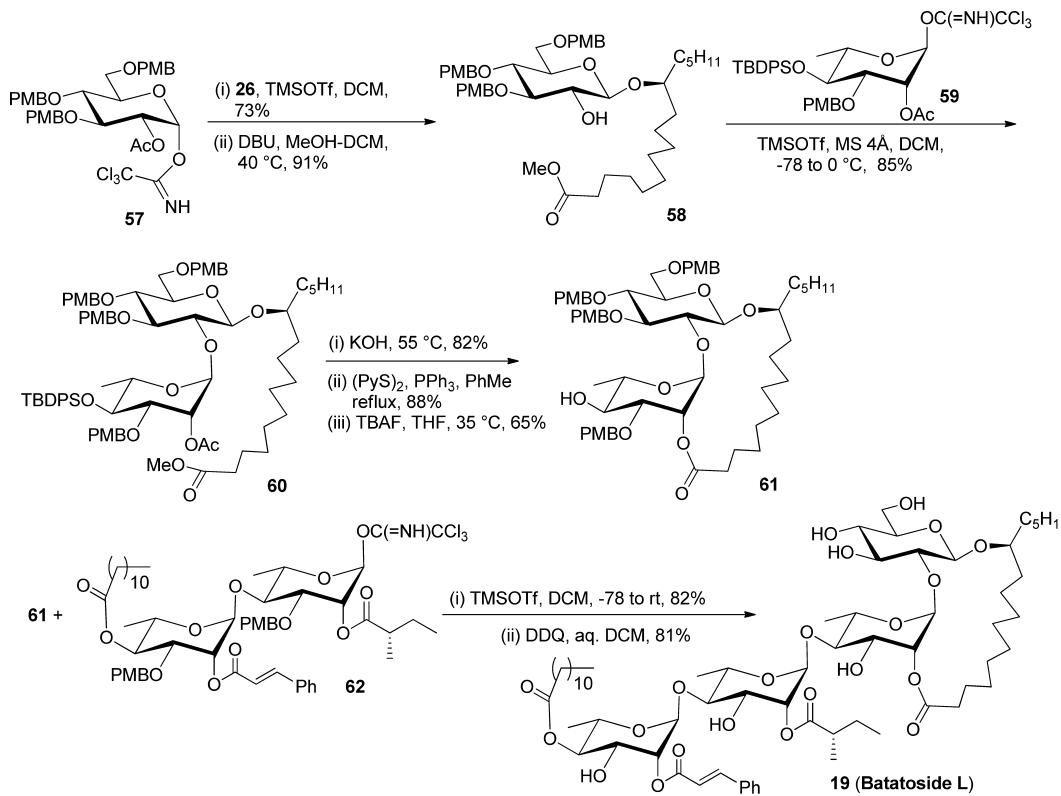
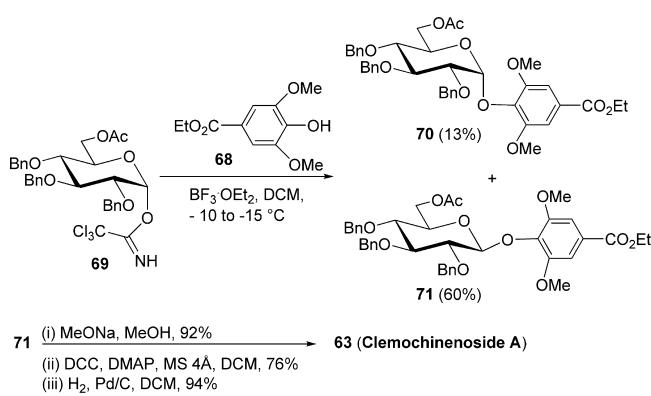


Figure 2. Structure of cyclic dimers of 4-(glycosyloxy)benzoates.

Scheme 12. Total Synthesis of Clemochinenoside A by Wang's Group

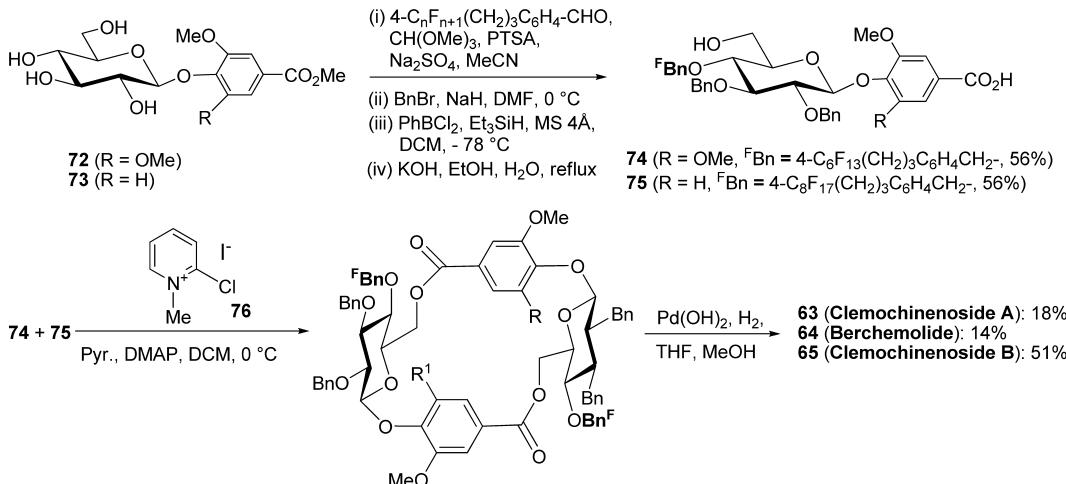
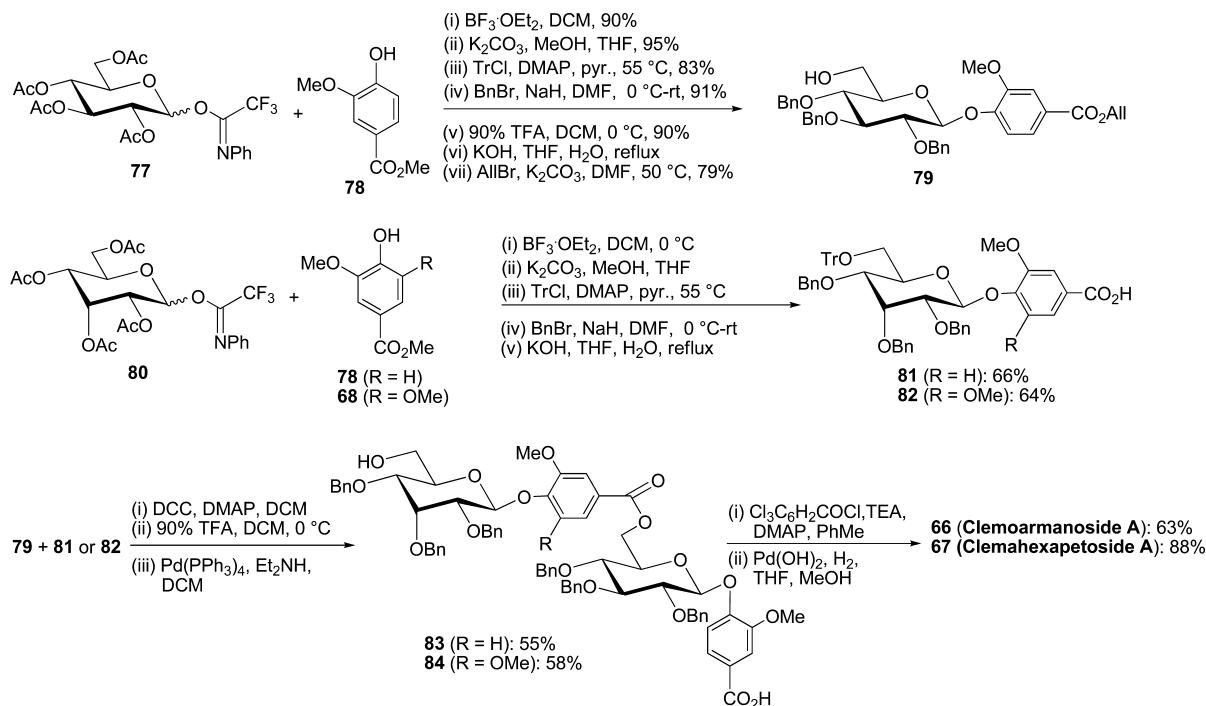


Reaction of the fucosyl ester 27 with the dodecyl thioglucoside 47 followed by saponification and coupling with thioquinovoside

49 provided the trisaccharide 50. Intramolecular glycosylation followed by deprotections accomplished the total synthesis of tricolorin F in 69%.

2.1.2.3. Merremosides. Merremosides (Figure 1) were isolated from the fresh tuber of *Merremia mammosa* (Lour.) Hall. f. (Convolvulaceae), a plant used in Indonesia for treating diabetes and illnesses involving the throat and respiratory system. These 20- and 21-membered macrolactones displayed ionophoretic activity capable of transporting Na^+ , K^+ , and Ca^{2+} across human erythrocyte membranes. Up to date, only the synthesis of the 20- and 21-membered macrolactone skeletons has been reported by Yang's group in 2006.³⁶ The disaccharide precursor 54 was prepared by glycosylation of methyl 11(S)-jalapionate 26 with the L-rhamnopyranosyl trichloroacetimidate 51 followed by removal of acetyl groups and isopropylidination of 2- and 3-hydroxy functions (Scheme 10). The resulting glycoside 52 was further glycosylated with the L-rhamnopyranosyl trichloroacetimidate 53. Macrocyclization of 54 under Yamaguchi's conditions failed, while the Corey–Nicolaou protocol under high-dilution condition (0.72 mM in toluene) afforded the 2'- and 3'-hydroxy lactones 55 and 56 in 58% and 11% yields, respectively.

2.1.2.4. Batatoside L. Batatoside-type resin glycosides were isolated from the tuber of *Ipomoea batatas* (L.) Lam. (Convolvulaceae), which has been used as a medicinal herb for promoting hemostasis and eliminating abnormal secretions in Chinese traditional medicine. It has also been shown that Batatoside L exhibited significant cytotoxic activity against laryngeal carcinoma (Hep-2) cells. Total synthesis of batatoside L, an 18-membered disaccharide macrolactone, has been achieved by Yang's group very recently, by construction of the disaccharide macrolactone core 61 followed by introduction of the exocyclic dirhamnoside unit 62 (Scheme 11).³⁷ Methyl 11(S)-jalapionate 26 was glycosylated with glucosyl trichlor-

Scheme 13. Total Synthesis of Clemochinenosides A and B, and Berchemolide by Takeuchi's Group**Scheme 14.** Total Synthesis of Clemoarmanoside A and Clemahexapetoside A by Yu's Group

oacetimidate 57 followed by selective deacetylation with DBU at 40 °C because of failure of deprotection with MeONa. Reaction of 58 with the L-rhamnopyranosyl trichloroacetimidate 59, followed by saponification, cyclization with the Corey–Nicolaou protocol in high dilute toluene (0.75 mM), and desilylation, led efficiently to the target macrolactone 61. The achievement of the total synthesis was realized by the glycosylation of 61 with the dirhamnoside trichloroacetimidate 62 and subsequent removal of PMB groups with DDQ.

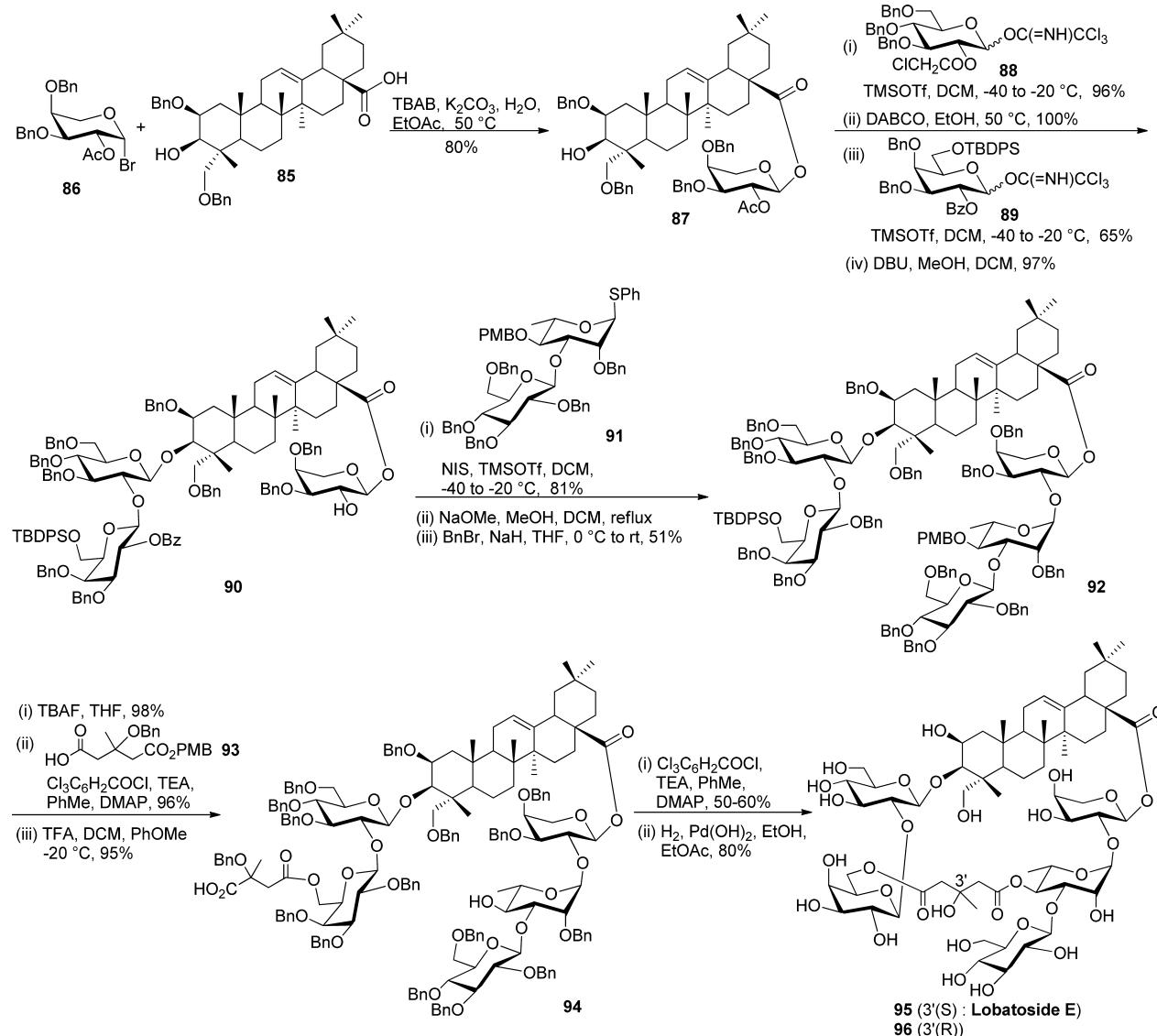
2.2. Macrolactones from Plants

2.2.1. Cyclic Dimers of 4-(Glycosyloxy)benzoates. Eight cyclic dimers of 4-(glycosyloxy)benzoates have been identified from a variety of folk medicinal plants.³⁸ Five of these 22-membered macrodilactones, including clemochinenosides A and B, berchemolide, clemoarmanoside A, and clemahexapetoside A (Figure 2), have been totally synthesized. Two D-glucopyranose units are found in clemochinenosides A, B, and berchemolide,

while clemoarmanoside A and clemahexapetoside A are composed of one D-glucopyranose and one unusual D-allopyranose as sugar units. Clemochinenosides A and B were isolated from the roots and rhizomes of *Clematis chinensis*, *C. armandii*, *C. mandshurica*, *C. hexapetala*, and *Capparis tenera*; berchemolide from the stems of *Berchemia racemosa* and *C. armandii*; clemoarmanoside A from *C. armandii* and *C. hexapetala*; and clemahexapetoside A from *C. hexapetala*. The roots and rhizomes of *Clematis* species have been used as anti-inflammatory, antitumor, and analgesic agents or for the treatment of headache in the Chinese Pharmacopoeia, while the stems of *B. racemosa* have been used to treat gall stones and stomach ache in Japan.

Wang and colleagues first described the synthesis of clemochinenoside A by cyclodimerization of aryl β-glucoside (Scheme 12).³⁹ Glycosylation of ethyl syringate 68 with the glucosyl trichloroacetimidate 69 gave predominantly the aryl β-

Scheme 15. Total Synthesis of Lobatoside E by Yu's Group



glucoside 71. Cyclodilactonization of 71 was accomplished by DCC/DMAP coupling method in 76% yield after deprotection with MeONa . Final hydrogenolysis provided the target clemochinenoside A (**63**).

A one-pot procedure via homo- and heterocyclodimerization of two different aryl β -glucosides has been reported by Takeuchi's group for the simultaneous synthesis of clemochinenosides A, B, and berchemolide by a fluorous mixture synthetic method (Scheme 13).⁴⁰ Fluorous benzylidene was used to protect the 4,6-hydroxyl groups of glucosides 72 and 73. After benzylidation, regioselective benzylidene ring-opening followed by saponification led to the corresponding 4- $O^{\text{F}}\text{Bn}$ protected compounds 74 and 75. Cyclodimerization of a 1:1 mixture of 74 and 75 with Mukaiyama's reagent 76 afforded a mixture of three cyclic dimers of 4-(glucosyloxy)benzoates, which were easily separated by column chromatography with a Fluoro Flash silica gel.⁴¹ Subsequent debenzylation afforded clemochinenosides A and B, and berchemolide in 18%, 51%, and 14% yields, respectively.

Very recently, clemoarmanoside A and clemahexapetoside A, containing one D-glucose and one D-allopyranose, have been

prepared by Yu's group.³⁸ Synthesis of three key aryl β -glucosides 79, 81, and 82 was realized by glycosylation with trifluorooacetimides 77 and 80 as glycosyl donors, followed by successive protection/deprotection steps (Scheme 14). The 4-(glucosyloxy)benzoate 79 was then coupled with 81 or 82 via DCC/DMAP. Detritylation with TFA, followed by cleavage of allyl ester and intramolecular esterification under Yamaguchi conditions in a diluted toluene solution (2.5 mM), led smoothly to the desired cyclic dilactones, which were debenzylated to give clemoarmanoside A (**66**) and clemahexapetoside A (**67**) in good yields.

2.2.2. Cyclic Triterpene Saponin. Cyclic triterpene saponins, named cyclic bisdesmosides, are glutarate bridged macrolactones isolated from Chinese medicinal plants *Bolbotrema paniculatum* and *Actinostemma lobatum* (Cucurbitaceae). These saponins display antitumor activity due to their cyclic structure. Lobatoside E, a 34-membered macrocycle (Scheme 15), shows the highest potency among its congeners against the growth of tumor cells. Its first total synthesis has been achieved by Yu's group in 2008.⁴² Coupling of the pentacyclic triterpene 85 with the β -arabinosyl bromide 86 under phase

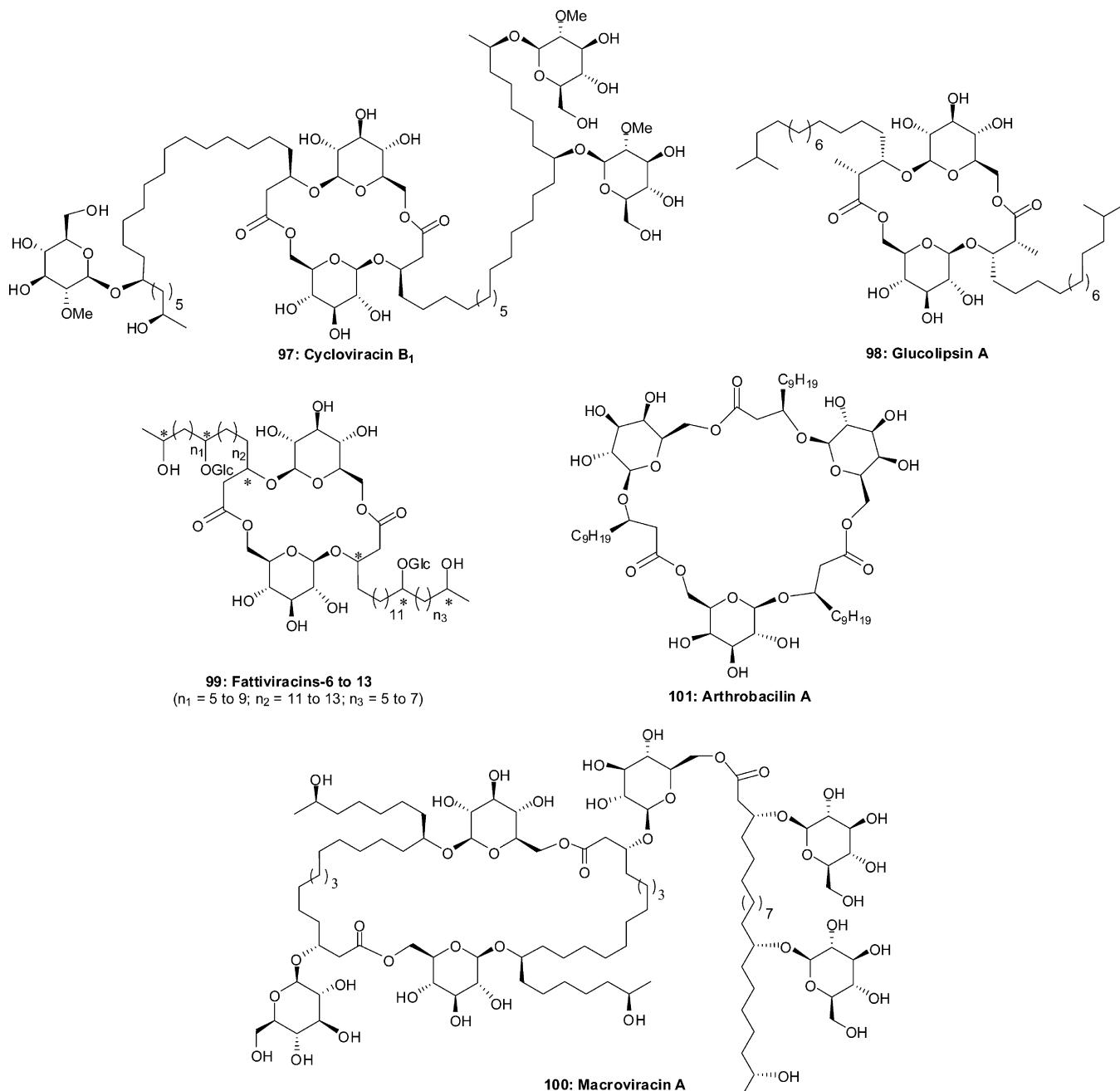


Figure 3. Structure of glycolipids from microorganisms.

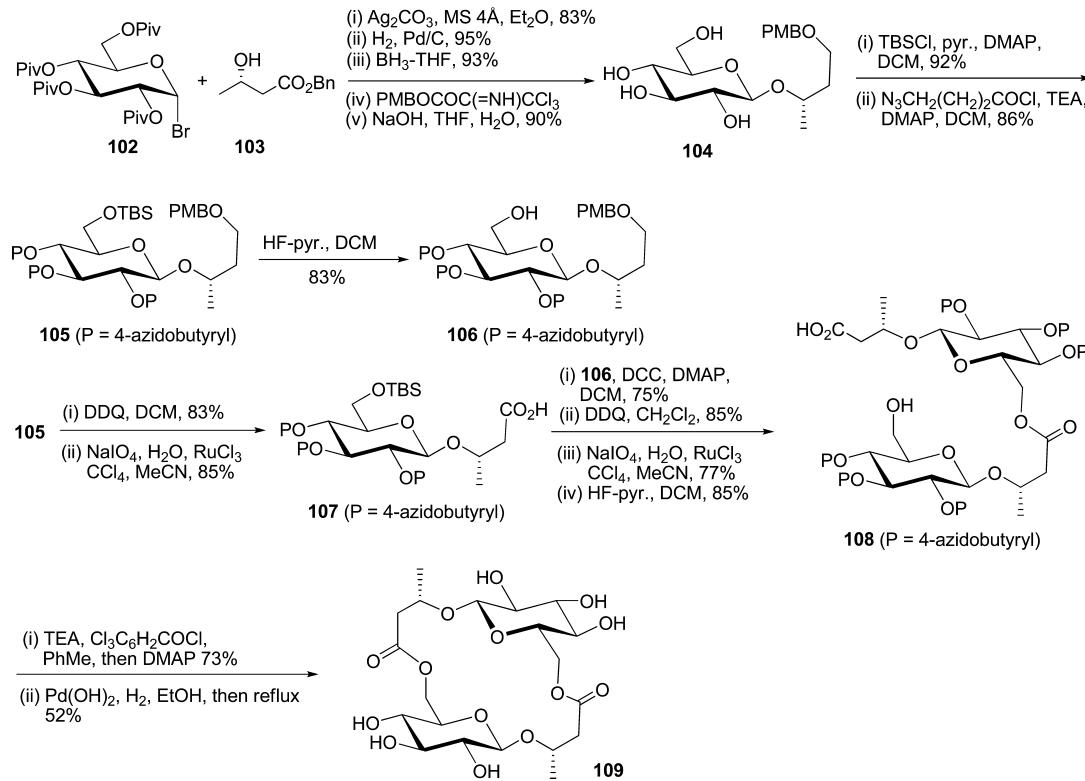
transfer conditions afforded the α -arabinoside 87. Subsequent glycosylation of the 3-OH in 87 with the glucosyl trichloroacetimidate 88 and selective removal of chloroacetyl group with DABCO allowed the further glycosylation with the galactosyl trichloroacetimidate 89 to give 90 after selective deprotection of Ac group on the arabinose unit with DBU. Reaction of the thiodisaccharide 91 with 90 provided stereoselectively the corresponding α -rhamnosyl-linked pentasaccharide where the Bz group on the galactose unit was then converted into the Bn group in 92. The silyl group on the galactose unit was removed with TBAF, and the resulting primary alcohol was esterified with carboxylic acid 93 under the Yamaguchi conditions. Removal of the two PMB groups with TFA led to the lobatoside E precursor 94. The macrocyclization was achieved by Yamaguchi's protocol,

affording two separable diastereomers (about 1:1) in 50–60% yield. Final debenzylation provided the target lobatoside E (95).

2.3. Glycolipids from Microorganisms

Glycolipids containing C₂- or C₃-symmetrical (di- or trilactones, respectively) core structures have been isolated from microorganisms (Figure 3). Cycloviracins and fattiviracins, isolated from the soil microorganisms *Kibdelosporangium albatum* so. nov. (R761-7) and *Streptomyces microflavus* no. 2445, respectively, own an 18-membered dilactone core and exhibit antiviral activity against herpes simplex virus type 1 (HSV-1), varicella-zoster virus (VZV), influenza virus A and B, and human immunodeficiency virus type 1 (HIV-1). Glucokinase inhibitors, glucolipsin A and B, isolated from the culture broth of *Streptomyces purpurogeniscleroticus* and *Nocardia vaccinii*, respectively, have a core structure similar to that of cycloviracins and

Scheme 16. Synthesis of Cycloviracin Lactide Core by Peña's Group



fattiviracins, composed of two molecules of D-glucose and two fatty acids. Glucokinase, responsible for glucose phosphorylation, remains a potential therapeutic target in diabetes. The 42–46-membered macrodilactones from the mycelium extracts of *Streptomyces* sp. BA-2836, macroviracins, exhibit powerful antiviral activity against HSV-1 and VZV. Arthrobacilin A, a C₃-symmetrical 27-membered macrotrilactone bearing galactose as sugar unit, was isolated from the culture broth of *Arthrobacter* sp. NR2967 as a cell growth inhibitor.

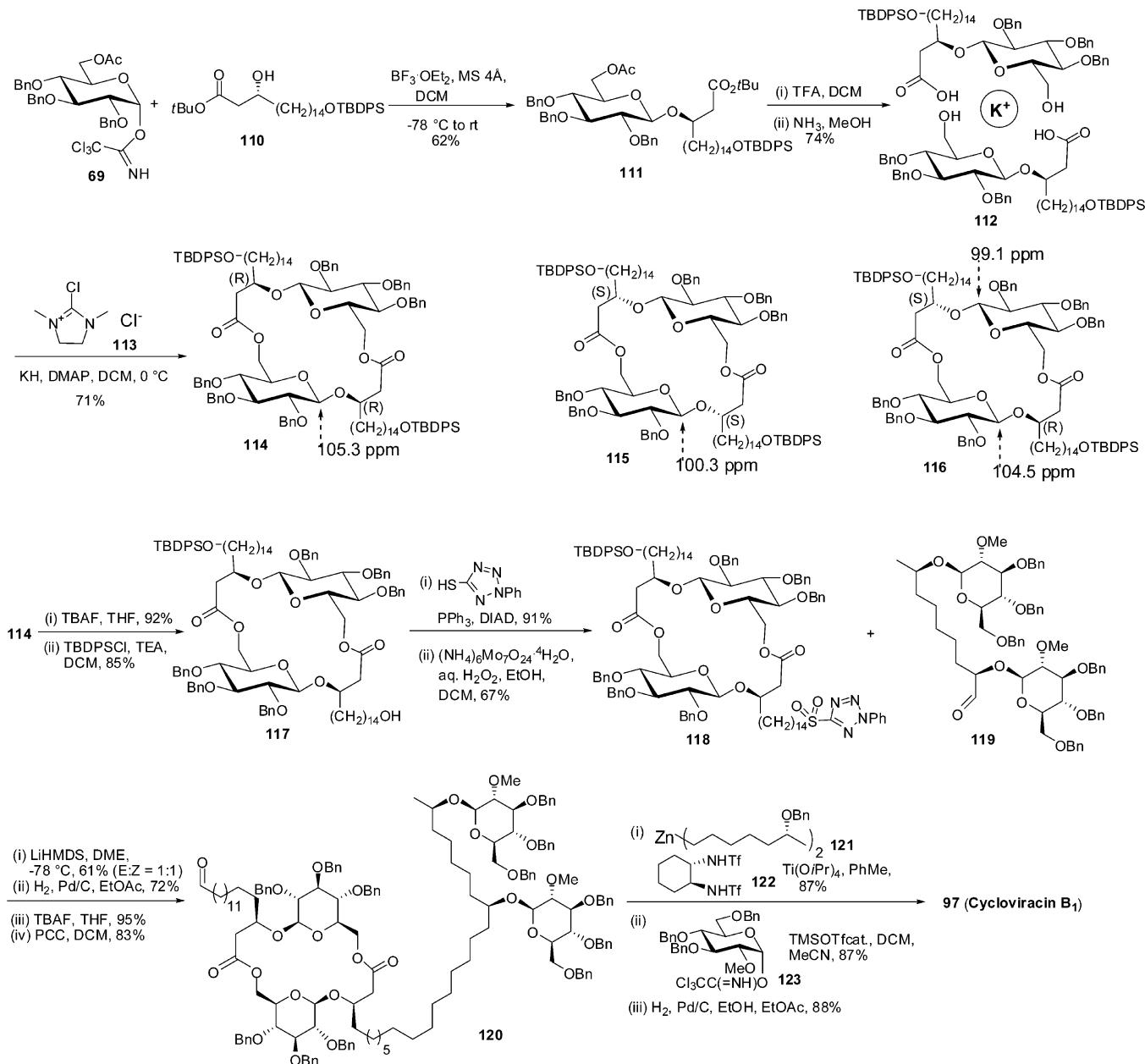
2.3.1. Cycloviracin B₁. The C₂-symmetrical lactide core structure of cycloviracins has been investigated by several groups. After miscarriage of attempted cyclodimerization of a model glucopyranoside with porcine pancreatic lipase, the group of Peña synthesized, in 1996, the truncated cycloviracin core structure by a stepwise procedure as illustrated in Scheme 16.⁴³ Koenigs–Knorr glycosylation method was used to introduce stereoselectively the β-hydroxyl ester 103 on the glucosyl bromide 102. Subsequent debenzylation, carboxylic acid reduction to alcohol, PMB protection, and saponification led to β-glucoside 104. The hydroxyl functions of 104 were then orthogonally protected by silyl and 4-azidobutyryl groups. The two building blocks 106 and 107 for the synthesis of disaccharide intermediate 108 were derived from 105 after desilylation or oxidation preceded by oxidative removal of PMB group. The disaccharide 108 was obtained by DCC-promoted coupling of 106 and 107 followed by deprotection and oxidation to carboxylic acid. Once again, Yamaguchi's macrolactonization proved to be successful for the synthesis of dilactone under high dilution (0.2 mM in toluene). Final deprotection afforded the macrodilactone 109 in 52% yield.

The structure assignment of cycloviracin B₁ was achieved by Fürstner's group,^{24,44,45} by preparing three stereoisomers of cycloviracin lactides 114 (3R,3'R), 115 (3S,3'S), and 116 (3R,3'S) (Scheme 17). For the synthesis of lactide 114, the β-

glucoside 111 was first prepared by careful selection of the promoter and solvent (BF₃·Et₂O in CH₂Cl₂) so as to glycosylate stereoselectively the benzyl protected trichloroacetimidate 69. After treatment with TFA and deacetylation, the hydroxy acid 112 was cyclodimerized through a template-directed macrodilactonization approach, promoted by 2-chloro-1,3-dimethylimidazolinium chloride 113 (DMC) to afford the macrodilactone 114 in 71% yield. Examination of ¹³C NMR data of the three diastereoisomers 114–116 and the natural product has allowed one to establish the stereochemistry at the branching points in the cycloviracin core as (3R,3'R). To achieve the total synthesis of cycloviracin B₁, compound 114 was then desymmetrized into monosilylated alcohol 117, which was then transformed into sulfone 118. Subsequent Julia–Kocienski olefination with the aldehyde 119, reduction of the obtained alkene function, desilylation, and PCC oxidation afforded the aldehyde 120. Reaction of 120 with the diorganozinc reagent 121 under stereocontrolled conditions, followed by β-stereoselective glycosylation with trichloroaceimide 123 and final debenzylation, accomplished the total synthesis of cycloviracin B₁ (97). Biological study of the synthetic cycloviracin B₁ and some of key intermediates showed that the entire structure of cycloviracin is necessary for antiviral activity.

Fürstner's template-directed macrodilactonization approach has been successfully applied by Cleophax's group for the synthesis of the macrocyclic core structure of cycloviracin.⁴⁶

2.3.2. Glucolipsin A. By synthesizing all conceivable C₂-symmetric stereoisomers and comparing their spectroscopic and analytical data with the natural product, Fürstner's group has elucidated the configuration of all four asymmetric carbons in glucolipsin A.⁴⁷ First, *syn*- and *anti*-aldols 124–127 were prepared by oxazolidinone- or norephedrine-derived auxiliary-based aldol methodology (Scheme 18). Glycosylation with trichloroacetimidate 69 followed by cleavage of chiral auxiliary

Scheme 17. Total Synthesis of Cycloviracin B₁ by Fürstner's Group

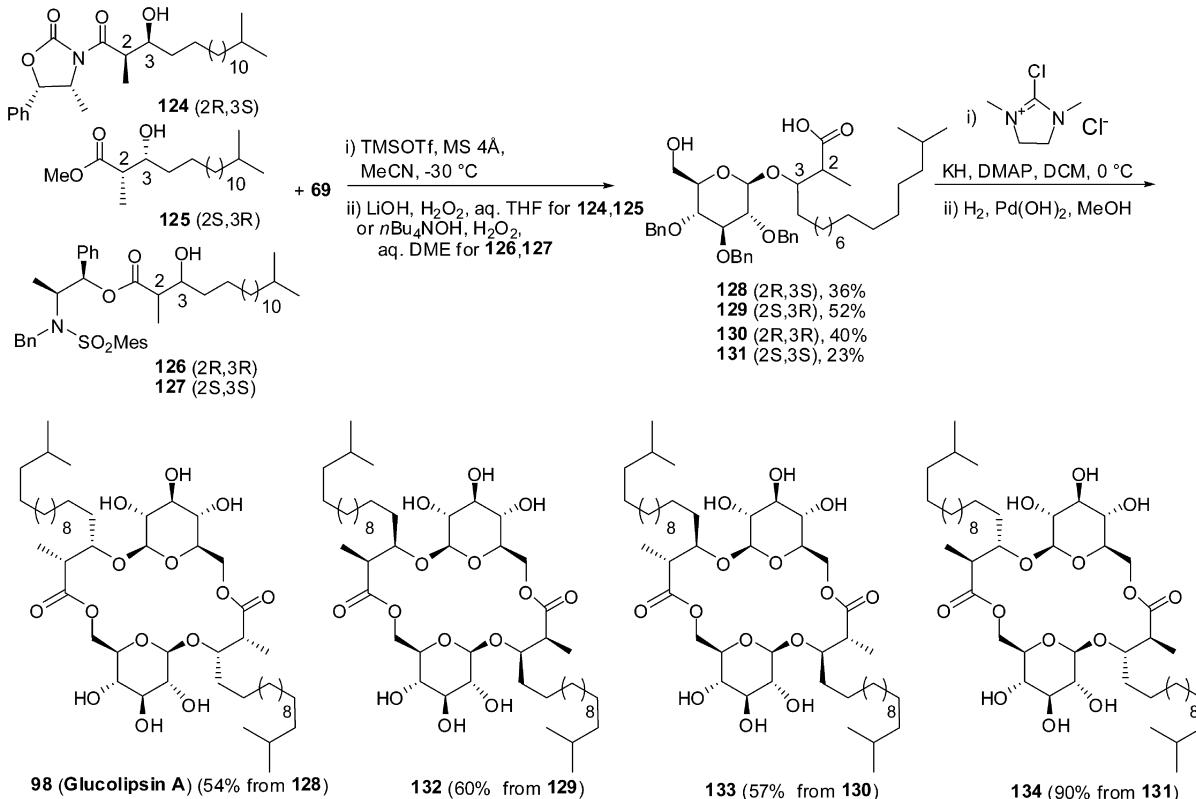
and acetyl group afforded the corresponding glucosyl acids 128–131, which were subjected to a macrodilactonization reaction in the presence of admixed potassium cations as templates, mediated by DMC. Subsequent debenzylation afforded the glucolipsin A. The diastereoisomers 132–134 were prepared in a similar way. All of these diastereomeric dilactones inhibit the dual specific phosphatase Cdc25A with IC_{50} in the micromolar range, with no activity against the protein tyrosine phosphatase PTP1B *in vitro*.

2.3.3. Fattiviracins. The configuration of fattiviracins *C*₂-symmetric core structure has yet to be elucidated. The core lactide synthesis has been recently investigated by Kaji's group.⁴⁸ Glycosylation of (+)-hydroxy ester 136, obtained by enzymatic kinetic resolution, with trichloroacetimidate 135 followed by deacetylation provided the β -glucoside 137 (Scheme 19). The four hydroxy groups were then regioselectively protected by benzylidene and benzyl groups through intermediate TMS

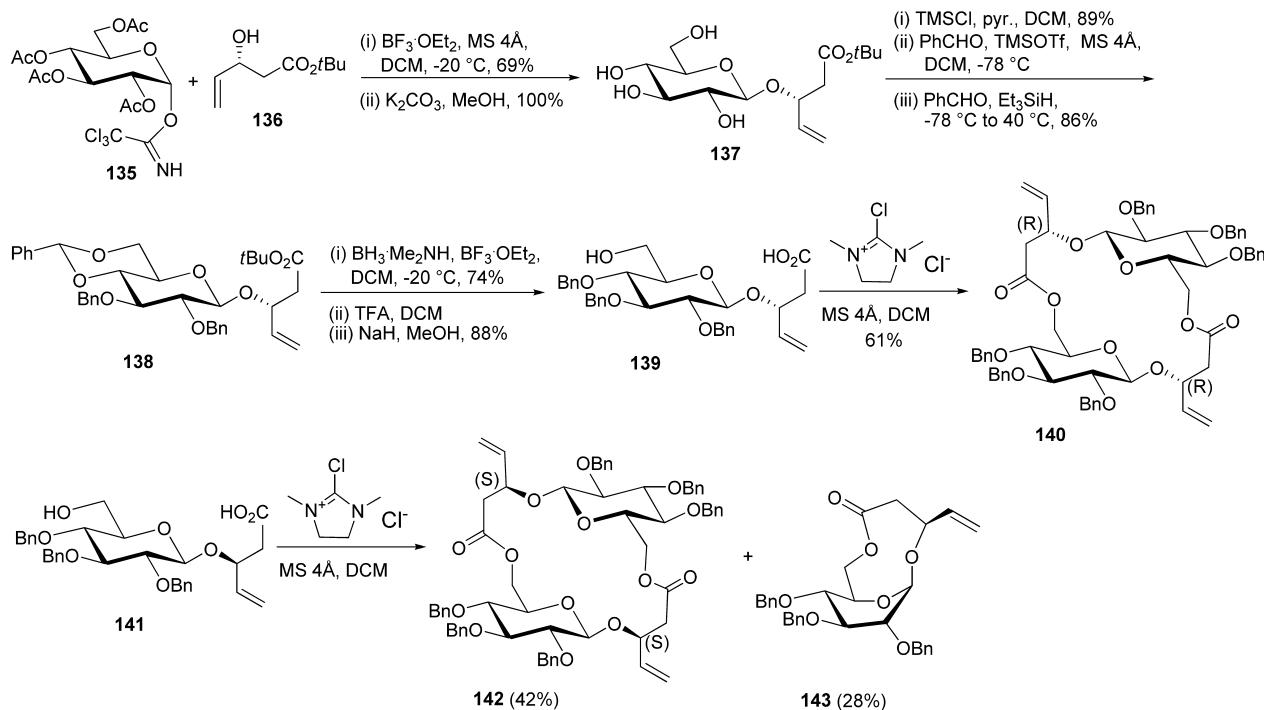
ethers under acidic conditions, which avoided the undesired β -elimination reaction of the aglycon. Regioselective opening of benzylidene group and hydrolysis of *t*-Bu ester, followed by methanolysis of resulting 6-trifluoroacetate, furnished the glucosyl seco acid 139. The best result of macrodilactonization (61%) was obtained with DMC in CH_2Cl_2 at 0.1 M concentration. Introduction of KH or DMAP led to a lower yield of 140. The seco acid 141 was prepared in a similar way from (-)-hydroxy ester 136. Its dimerization provided a mixture of the desired dilactone 142 and the intramolecular lactonization product 143, whatever the reaction conditions. The olefin function in 140 and 142 could be further used to introduce the side chains of fattiviracin derivatives by cross metathesis.

2.3.4. Macroviracin A. Macroviracin A is a 42-membered macrodilactone composed of a glucopyranosyl *C*₂₂ fatty acid dimer and a long side chain attached to the core (Figure 3). Its absolute structure has been established by Takahashi's group,

Scheme 18. Total Synthesis of Glucolipsin A by Fürstner's Group

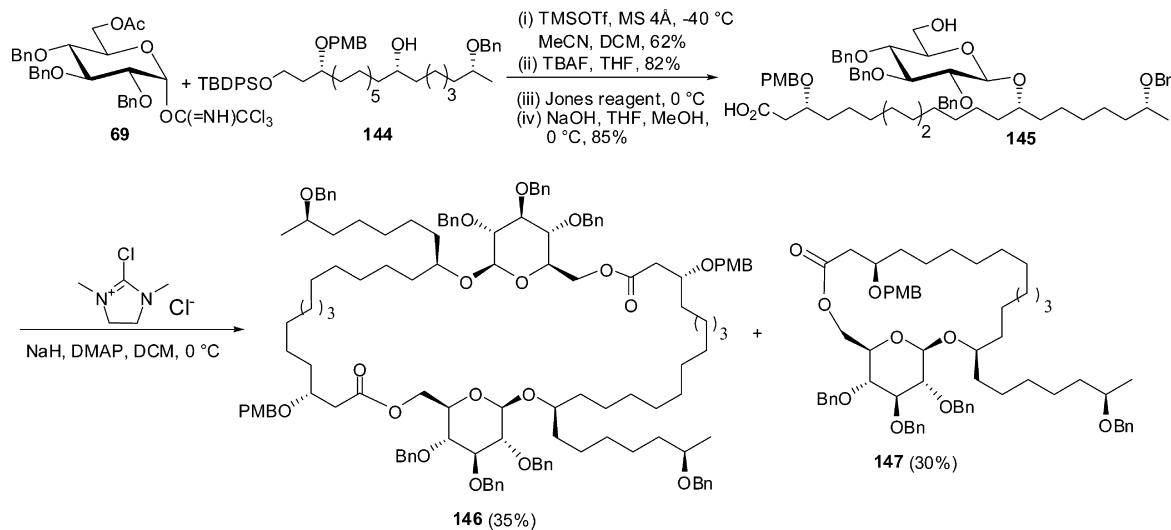
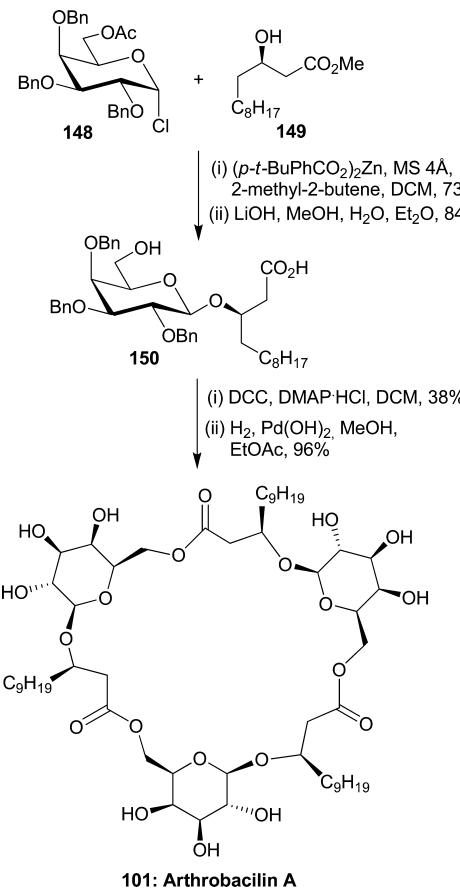


Scheme 19. Synthesis of Fattiviracins Core Lactides by Kaji's Group



through stereocontrolled synthesis of methyl ester of C₂₂ fatty acids and comparison with the natural one.⁴⁹ The C₄₂ macrolactone core was prepared one year later by the same group.⁵⁰ Glycosylation of the long chain alcohol 144 with the trichloroacetimidate 69, followed by silyl deprotection, Jones oxidation, and saponification afforded the glucosyl fatty acid 145

(Scheme 20). Cyclodimerization of this flexible C₂₂-hydroxy carboxylic acid appeared not to be trivial, because lactonization of 145 under Yamaguchi's condition led mainly to the monolactone 147, while Mitsunobu reaction afforded a 1:1 mixture of 146 and 147 in 20% total yield. The best result was obtained with DMC/

Scheme 20. Synthesis of Macroviracin A Macrolactone Core by Takahashi's Group**Scheme 21.** Total Synthesis of Arthrobacilin A by Nishizawa's Group

DMAP promoted system in the presence of NaH, leading to 35% of the target dimer 146, along with 30% of monomer 147.

2.3.5. Arthrobacilin A. The total synthesis of arthrobacilin A has been achieved by Nishizawa's group in 1994, by a cyclooligomerization approach.⁵¹ The key intermediate 150 was prepared through zinc *p*-*tert*-butylbenzoate-promoted glycosylation of the fatty acid 149 with 2-*O*-benzyl protected galactosyl chloride 148, leading to 73% β -galactoside along with 27% α -isomer, followed by saponification (Scheme 21).

Cyclooligomerization in the presence of DCC and DMAP·HCl in CH₂Cl₂ (0.01 M) led to the corresponding cyclotrimer (38%) along with cyclotetramer (19%), cyclodimer (21%), and a mixture of cyclopentamer and cyclohexamer (14%). Cyclization of 150 promoted by DMC and DMAP afforded only the cyclodimer in 70% yield, in accordance with previous results.^{24,44–48} The arthrobacilin A (101) was then obtained after debenzylation of the cyclotrimer.

3. MACROCYCLES CONTAINING ESTER, AMIDE, AMINE, ETHER, OR ACETAL LINKAGES

Macrocycles containing ester, amide, amine, ether, or acetal linkages have been designed and synthesized as glycolipid analogues, peptidomimetics, conformationally constrained oligosaccharides, carbohydrate ligands for carbohydrate–protein or carbohydrate–nucleic acid interaction, enzyme inhibitors, as well as artificial receptors.

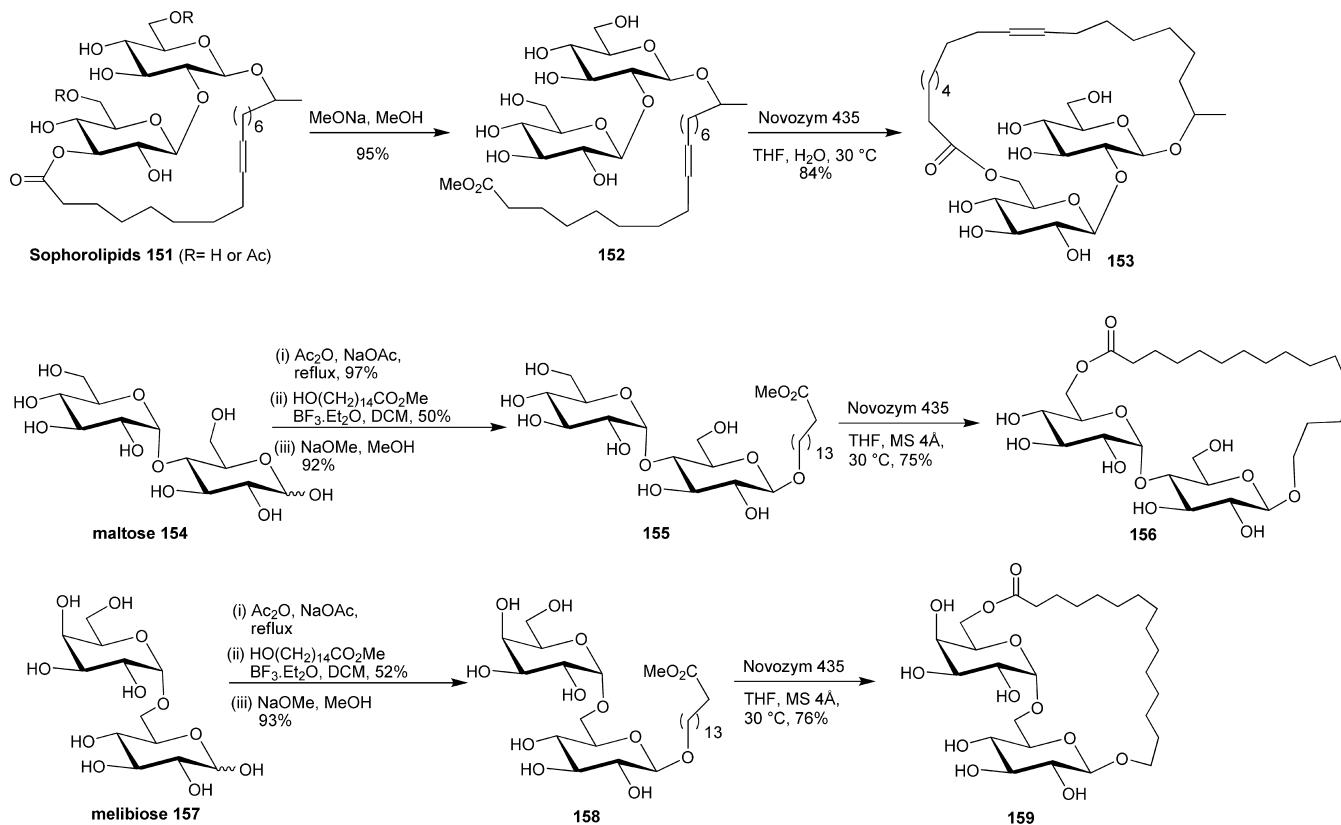
3.1. Glycolipid Analogues

Sophorolipids, existing as a mixture of macrolactone and free acid structures, are microbial extracellular surface-active glycolipids with promising activities for the treatment of cytokine-related immune disorders. Bisht et al. reported an enzymatic synthesis of sophorolactone 153 as analogue of microbially produced lactone (Scheme 22).⁵² Lipase Novozym 435 efficiently catalyzed the macrolactonization of sophorolipid ester 152, generated from crude sophorolipid mixture 151. This reaction was highly regioselective, leading to the acylation on the C-6'' position. It has been demonstrated that lipases are excellent biocatalysts, having the remarkable ability of assuming a variety of conformations to accommodate substrates of varying sizes and complexities. Such catalytic property has been confirmed by the synthesis of glycolipids 156 and 159.⁵³ Readily available maltose and melibiose peracetates were glycosylated with methyl 15-hydroxypentadecanoate. After Zemplan deacetylation, lipase-catalyzed macrocyclization of disaccharides 155 and 158 provided regioselectively the 1,6''-macrolactones 156 and 159 in good yields.

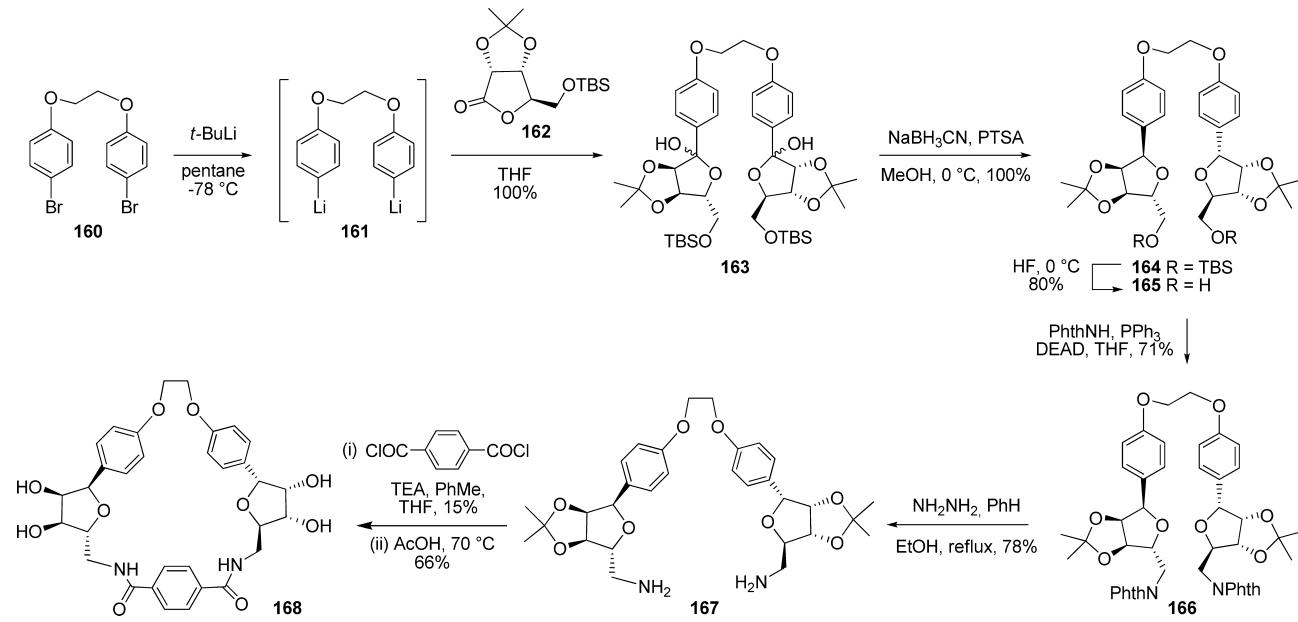
3.2. Glycophanes and Calixsugars

The term glycophane was first employed by Wilcox to name cyclodextrin–cyclophane hybrid receptors.⁵⁴ The water-soluble glycophane 168 was synthesized by C-arylation of ribofuranos-

Scheme 22. Synthesis of Glycolipid Analogues by Bisht's Group



Scheme 23. Synthesis of Glycophanes from Ribonolactone



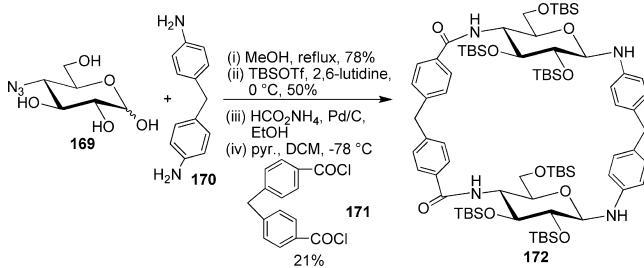
lactone **162** with diorganolithium derived from **160**, followed by stereoselective reduction of bis(hemiacetal), introduction of amino function on the ribofuranoside, macrocyclization with terephthaloyl chloride, and final deprotection (Scheme 23).⁵⁵

A symmetrical glycophane has been prepared from a glucose derivative.⁵⁶ β -N-Glycosylation of diamine **170** with 4-azido-4-deoxy-D-glucose **169**, followed by silylation, reduction of azido group, and amidation with the diacid dichloride **171** gave the macrocycle **172** (Scheme 24). Recently, Jarosz also reported the

synthesis of a macrocyclic diamide-linked sucrose derivative containing isophthalic or 2,6-pyridinedicarbonate amide moieties.⁵⁷

Further investigation on the glycophane has been realized by Penadés' group.^{58,59} Several glycophanes have been synthesized through nucleophilic substitution of α,α' -trehalose ditriflate **174** with 2,7-dihydroxynaphthalene **175** or 4,4'-isopropylidenediphenoxy **177** (Scheme 25). The hydrosoluble glycophane **176** is capable of complexing electron-deficient aromatic guests like di-

Scheme 24. Synthesis of Glycophane from 4-Azido-4-deoxy-D-glucose



or trinitrophenols in aqueous methanol (1:1) or borate buffer. Compound 176 displayed also chiral discrimination toward racemic 2,4-dinitrophenyl amino acid derivatives, with enantioselectivity ranging from 5% to 40%. A carbohydrate–carbohydrate interaction has been demonstrated between glycophane 176 and 4-nitrophenyl glycosides in water, which was found to be stereospecific for α -glycosides. ¹H NMR study, molecular mechanics, and dynamic calculations showed that lipophilic forces between carbohydrate surfaces mainly determine the stability of the association.⁶⁰

Ester-linked glycophane 182 has been prepared from maltose (Scheme 26).^{61,62} Trichloroacetimidate method has been employed to obtain the α -disaccharide 181 from the maltose 180, which was cyclodimerized with DCC, DMAP, and DMAP·HCl in 29% yield. TFA deprotection yielded the water-soluble glycophane 182, which was further transformed into the glycophane 183 through double transesterification from position 4' to 6' in water. No transacylation was observed in DMSO. NMR and molecular mechanics simulations showed that carbohydrate–arene stacking directed conformational equilibrium of the more flexible glycophane 183, which adopted a folded conformation in water as a result of intramolecular interactions between a glucose moiety and a phenyl ring.⁶³ This interaction was not observed in the more rigid glycophane 182, and its conformation resembled that of cyclodextrins. Like the

glycophane 176, glycophanes 182 and 183 formed complexes in water with a series of 4-nitrophenyl glycosides. ¹H NMR spectroscopy and molecular mechanics calculations showed the existence of stabilizing carbohydrate–carbohydrate interactions between host and guest lipophilic sugar surfaces. Despite the great flexibility of 183 related to 176 and 182, these three glycophanes displayed similar α / β selectivity on binding the 4-nitrophenyl glycosides.

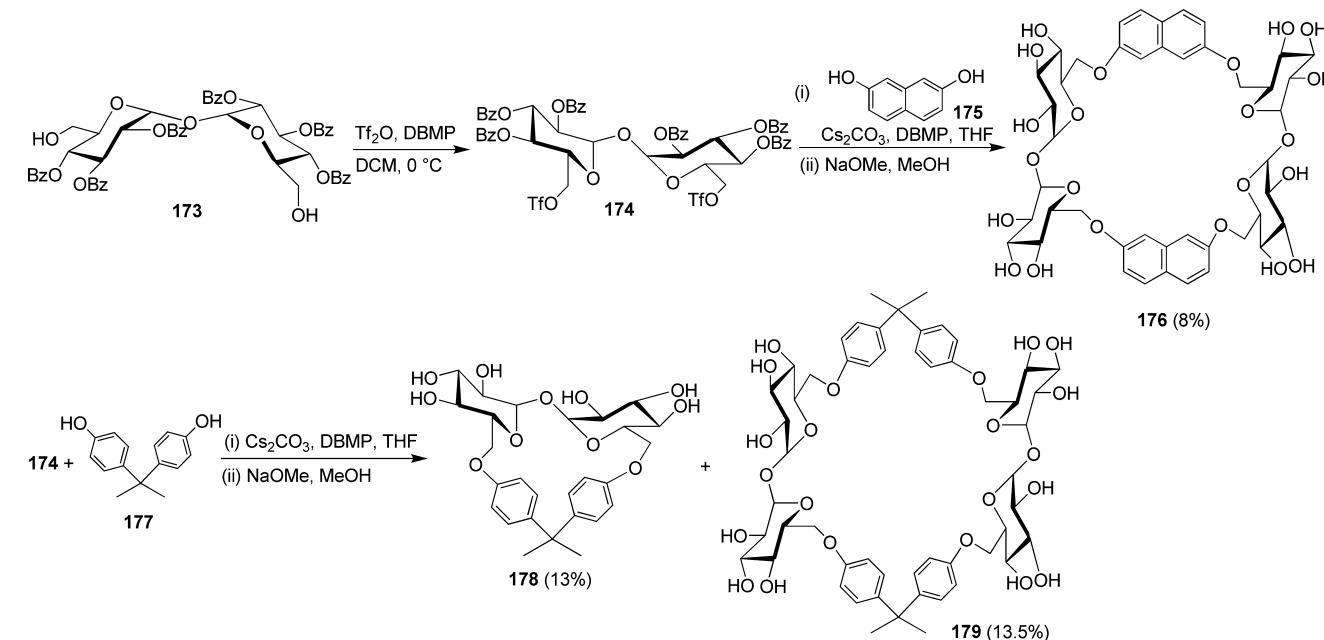
Natural cyclic dimers of 4-(glycosyloxy)benzoates like clemochinenosides A and B, berchemolide, clemoarmanoside A, and clemahexapetoside A (Figure 2) can be considered as glycophanes. By applying the strategy to access clemoarmanoside A and clemahexapetoside A (Scheme 14),³⁸ Yu's group has prepared cyclic trimer 187, tetramer 189, as well as pentamer 190 of 4-(glucosyloxy)benzoates, with yields varying from 50% to 64% for the intramolecular lactonization under Yamaguchi's conditions of the corresponding linear oligomers, which were obtained by stepwise coupling of monomers 184 and 185 (Scheme 27).

Sugar-calix[4]arenes conjugated macrocycles have been studied by Dondoni's group.⁶⁴ Bridged and double calixsugars have been prepared through ester and amide linkages between α,α' -trehalose diols 191, 195 or diamine 196 and calixarene diacid 1,3-dichloride 192 (Scheme 28). The receptor property of the synthesized bridged calixsugars 193, 194, 197–200 has been evaluated by ¹H NMR analysis. The double calixsugar 194 showed selective recognition toward imidazole.

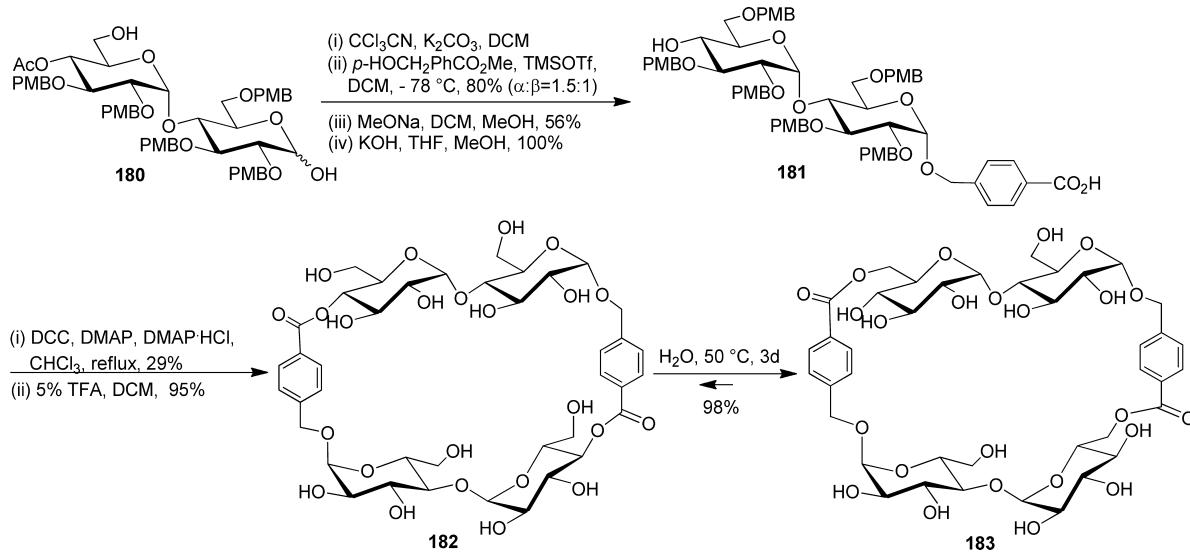
3.3. Macroaldonolactones

From D-galactono-1,4-lactone 201, Varela and colleagues have synthesized 14- and 21-membered macroaldonolactones 204 and 205 (Scheme 29).⁶⁵ D-Galactono-1,4-lactone 201 was first transformed into the open-chain diacetone ester 202, which is converted into carboxylic acid 203. Oligocyclomerization with DCC and DMAP provided an equimolar mixture of cyclic dimer 204 and trimer 205. Alternatively, ester 202 was transformed into carboxylic acid 206. Compound 203 was esterified with benzyl bromide and then coupled with 206 in the presence of

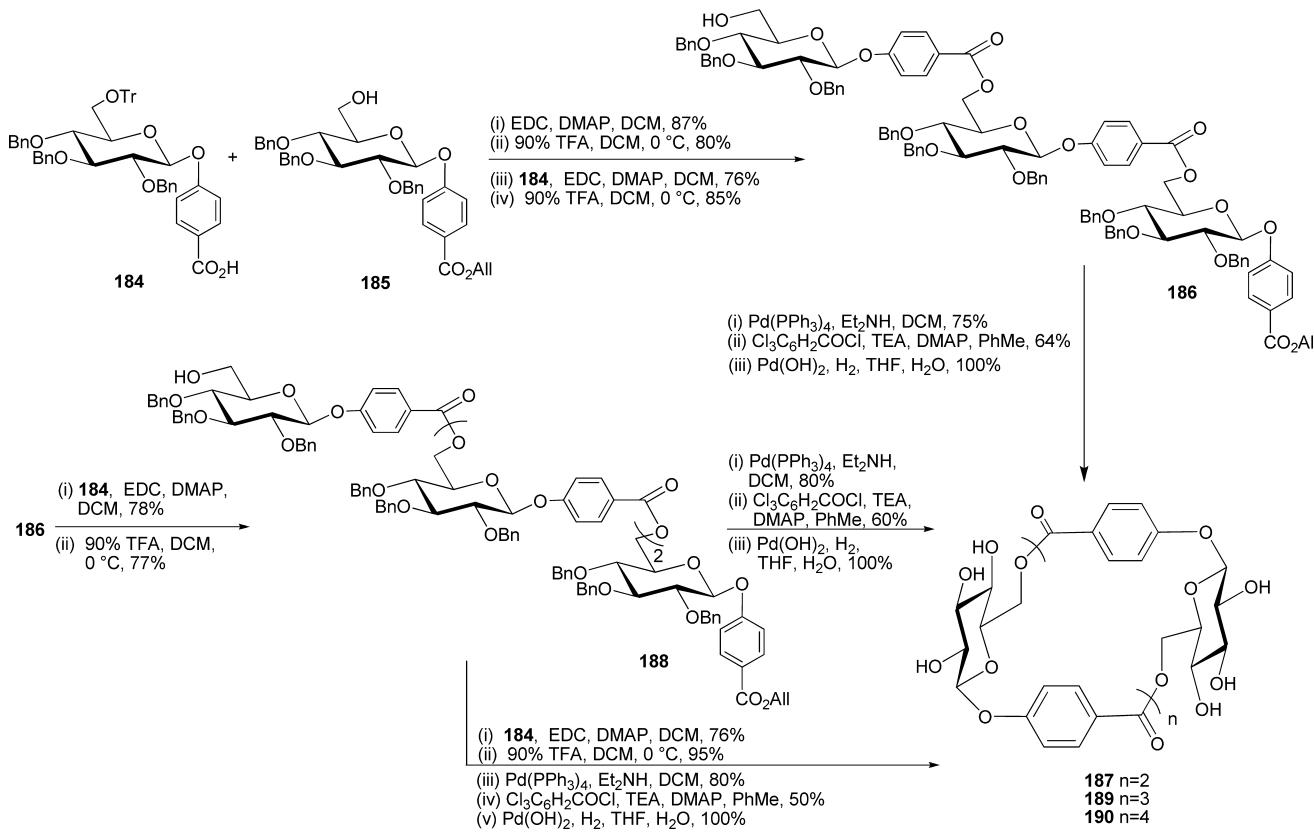
Scheme 25. Synthesis of Glycophanes from α,α' -Trehalose



Scheme 26. Synthesis of Glycophanes from Maltose



Scheme 27. Synthesis of Glycophanes from Glucose

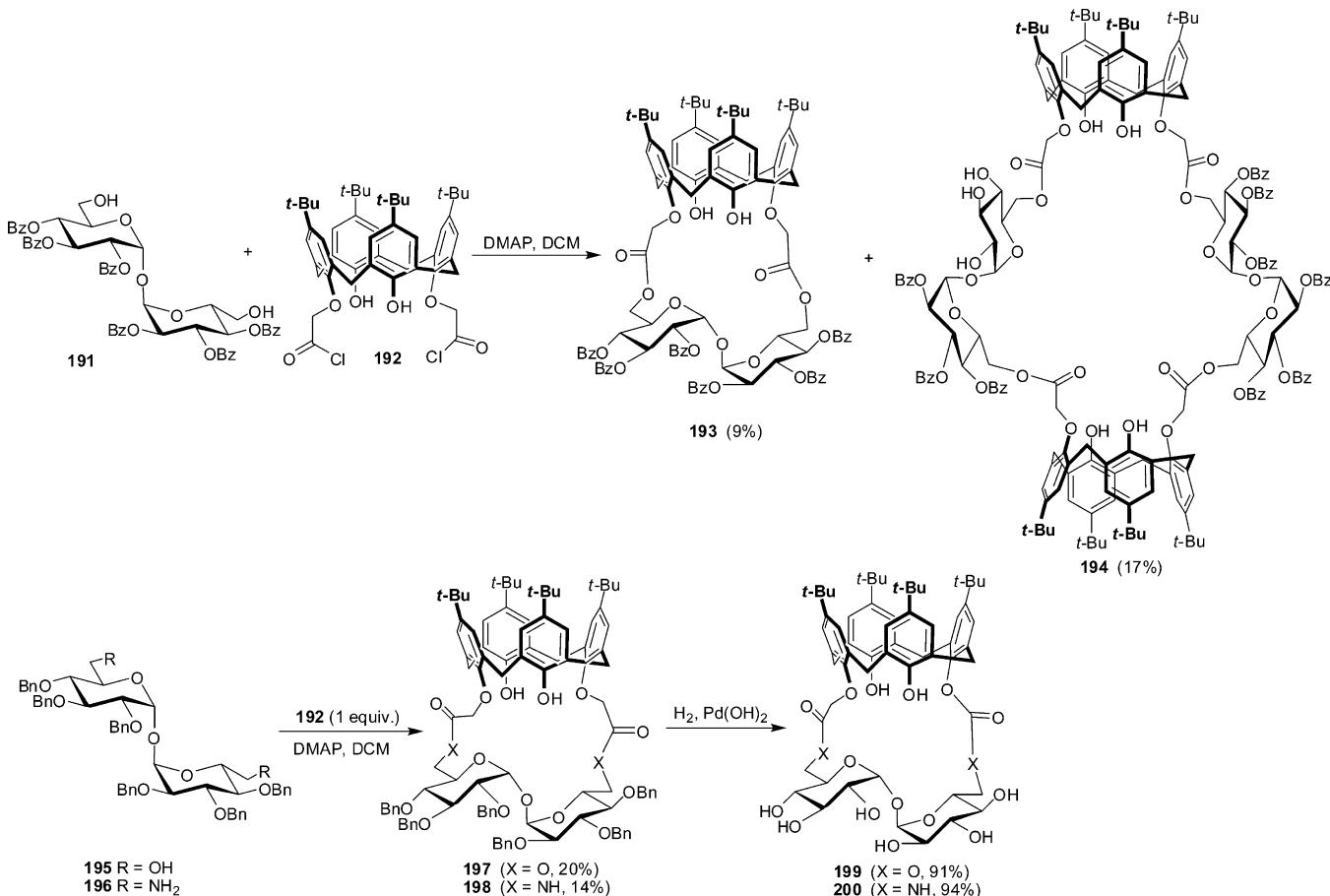


DCC/DMAP to afford, after removal of the silyl group, the dimer **207**. This compound is the key intermediate in the synthesis of both dimeric and trimeric macrocycles, because it can either be converted in two steps to lactone **204** or be coupled to carboxylic acid **206** to afford the corresponding linear trimer, which can be deprotected and further converted into the trimeric macro-lactone **205**. Better yields of cyclization were obtained with DCC/HOBt as compared to DCC/DMAP method. Synthesis of functionalized cyclic polyesters as biomaterials by ring-opening polymerization of sugar lactone has also been reported.⁶⁶

3.4. Conformationally Constrained Oligosaccharides

To study the conformational influence on carbohydrate–protein or carbohydrate–nucleic acid interactions, conformationally constrained oligosaccharides have been recently synthesized. Methylene-bridged galabiosides were synthesized by G. Magnusson and colleagues.⁶⁷ Glycosylation of thiogalactoside **208** with the galactoside **209** led to the corresponding galabioside ($\text{Gal}\alpha-1\text{-Gal}$), which, after debenzylation, was subjected to methylation with formaldehyde diphenylmercapto-NIS/TfOH to afford the compound **210**. Zemplan deacetylation gave the $O^6\text{-}O^{2'}\text{-methylene}$ bridged galabioside

Scheme 28. Synthesis of Bridged and Double Calixsugars

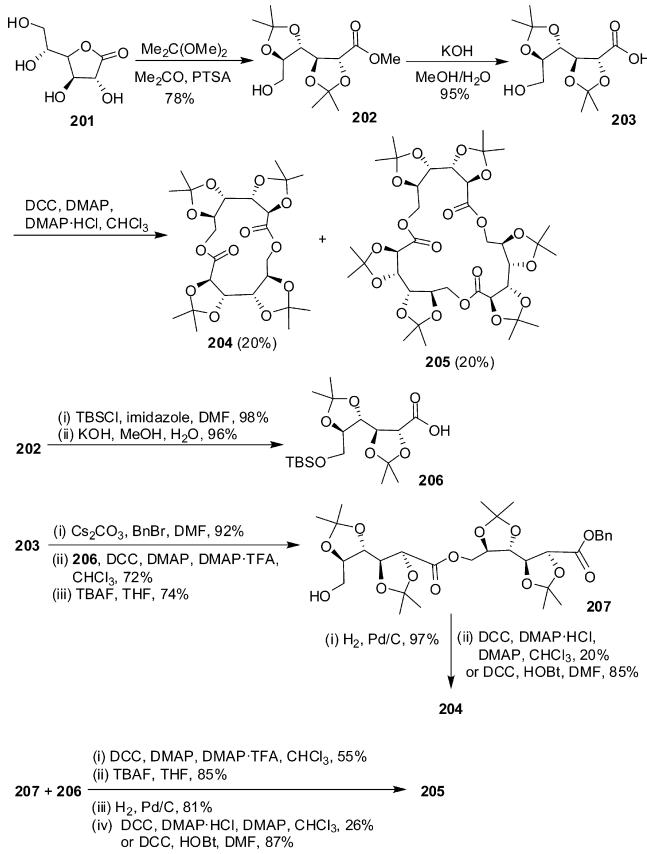


211 possessing conformation similar to that of the nonacetylated glycoside (Scheme 30). The neoglycolipid analogue **213** was obtained by nucleophilic substitution of 2-bromoethyl glycoside **212** with octadecanethiol. Trichloroacetimidate method was employed to synthesize the β -glycoside **212**.

G.-J. Boons and colleagues have first synthesized conformationally constrained trisaccharides to study their interactions with α -D-Man-specific lectins like concanavalin A (Scheme 31).^{68,69} The design of trisaccharide **217** is based on mimicking an intramolecular hydrogen bond O-2…O-6'', which was present in the crystalline lectin–oligosaccharide complex by a methylene acetal. The trisaccharide **211** containing a methylene acetal linking O-4 with O-6'' was designed to mimic O-4…O-6'' intramolecular hydrogen bond predicted in a possible docking mode of GlcNAc β (1–2)Man α (1–3)Man with ConA. Methylene-linked trisaccharides **216** and **220** were obtained by coupling of methylthiomethyl protected glycosides **215** or **218** with **214** or **219**, respectively, in the presence of NIS/triflic acid, followed by deacetylation and conversion into thioglycoside or trichloroacetimidate suitable for an intramolecular glycosylation. Macrocyclization worked better for the trisaccharide **220** compared to **216**. Subsequent hydrazinolysis, acetylation, and debenzylation provided the target conformationally constrained trisaccharides **217** and **221**. NMR spectroscopic and molecular modeling studies showed that these cyclic compounds were indeed considerably less flexible than the linear one.

Later, Boons's group synthesized conformationally constrained *N*-acetyl lactosamine (Gal β (1–4)GlcNAc) derivatives to study the effect of inter-residual flexibility of glycosyl acceptors

on kinetic parameters of glycosyl transfer as well as the conformation of glycosyl acceptor recognized by glycosyltransferase.^{70,71} The key disaccharide **224** was prepared by glycosylation of **223** with the trichloroacetimidate **222** followed by desilylation (Scheme 32). Subsequent mesylation, deacetylation, cyclization through nucleophilic substitution assisted by NaH, and debenzylation afforded the disaccharide **226** with a rigid seven-membered ring. The ethylene-bridged derivative **228** was obtained by deacetylation of **224**, followed by regioselective etherification with MsOCH₂CH₂OTBS, transformation of silyl group to mesylate, intramolecular cyclization, and hydrogenolysis. Synthesis of methylene-bridged disaccharide **230** with (PhS)₂CH₂ in the presence of NIS/TfOH for intramolecular methylene acetal formation required the replacement of the acetamido group by an azido, which was transformed into the acetamido moiety after cyclization via reduction with propanedithiol and acetylation. Correlation of the conformational properties of *N*-acetyl lactosamine and its derivatives with the corresponding apparent kinetic parameters of rat liver α -2,6-sialyltransferase-catalyzed sialylations revealed that this enzyme recognized LacNAc in a low energy conformation. The anhydro derivative **226** is not a substrate, whereas the ethylene-bridged LacNAc proved to be the best substrate tested, indicating that **228** is preorganized in a conformation that is favorable for the transferase.⁷⁰ On the basis of this result, a more rigid analogue of **228**, the amide linked conformationally constrained LacNAc **232**, was synthesized.⁷¹ Reaction of the mesylated disaccharide **231** with NaN₃, followed by removal of acetyl group, reduction of azido function and chloroacetylation, macrocyclization with

Scheme 29. Synthesis of Macroaldonolactones

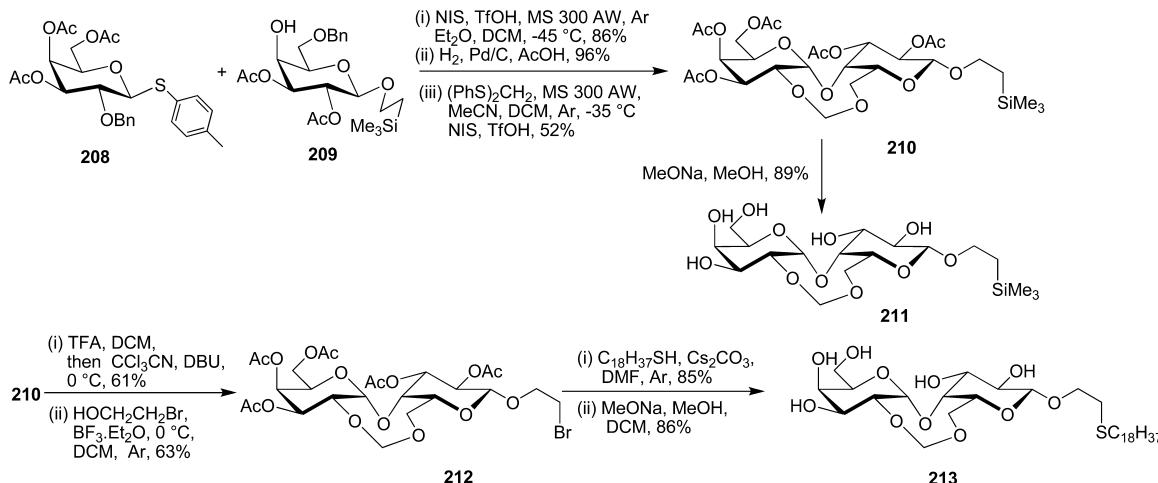
NaH , and debenzylation, provided the target compound 232. This methylene amide bridged LacNAc proved to be a substrate for rat liver α -2,6-sialyltransferase and fucosyltransferase V. Its enzymatic glycosylation gave conformationally constrained trisaccharides 233 and 234. Furthermore, the apparent kinetic parameters for the α -2,6-sialyltransferase and fucosyltransferase V-catalyzed transformations indicated that these two enzymes responded differently to imposed conformational constraints of the substrate.

Bundle's group has prepared tethered trisaccharides to mimic the bound state of the trisaccharide epitope α -D-Galp(1 \rightarrow 2)[α -

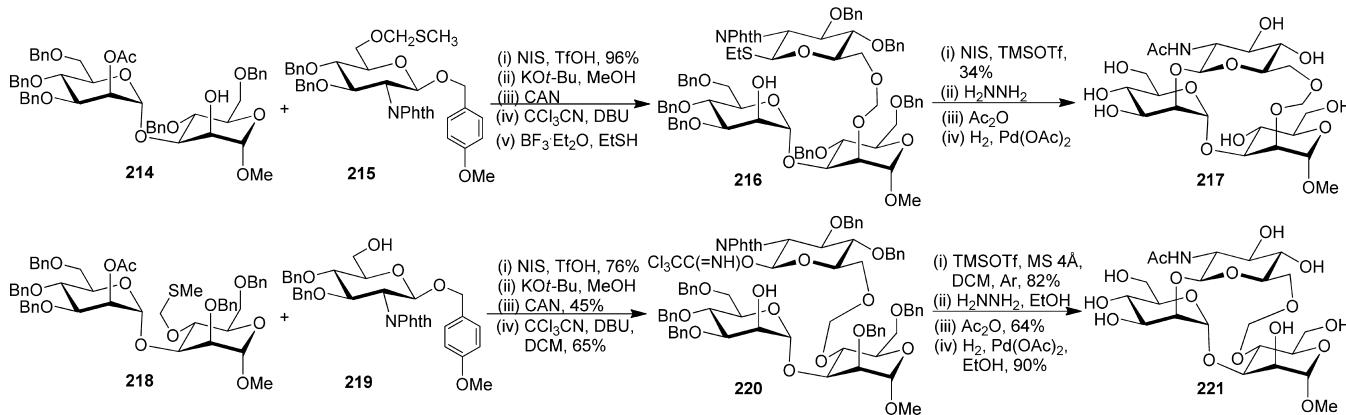
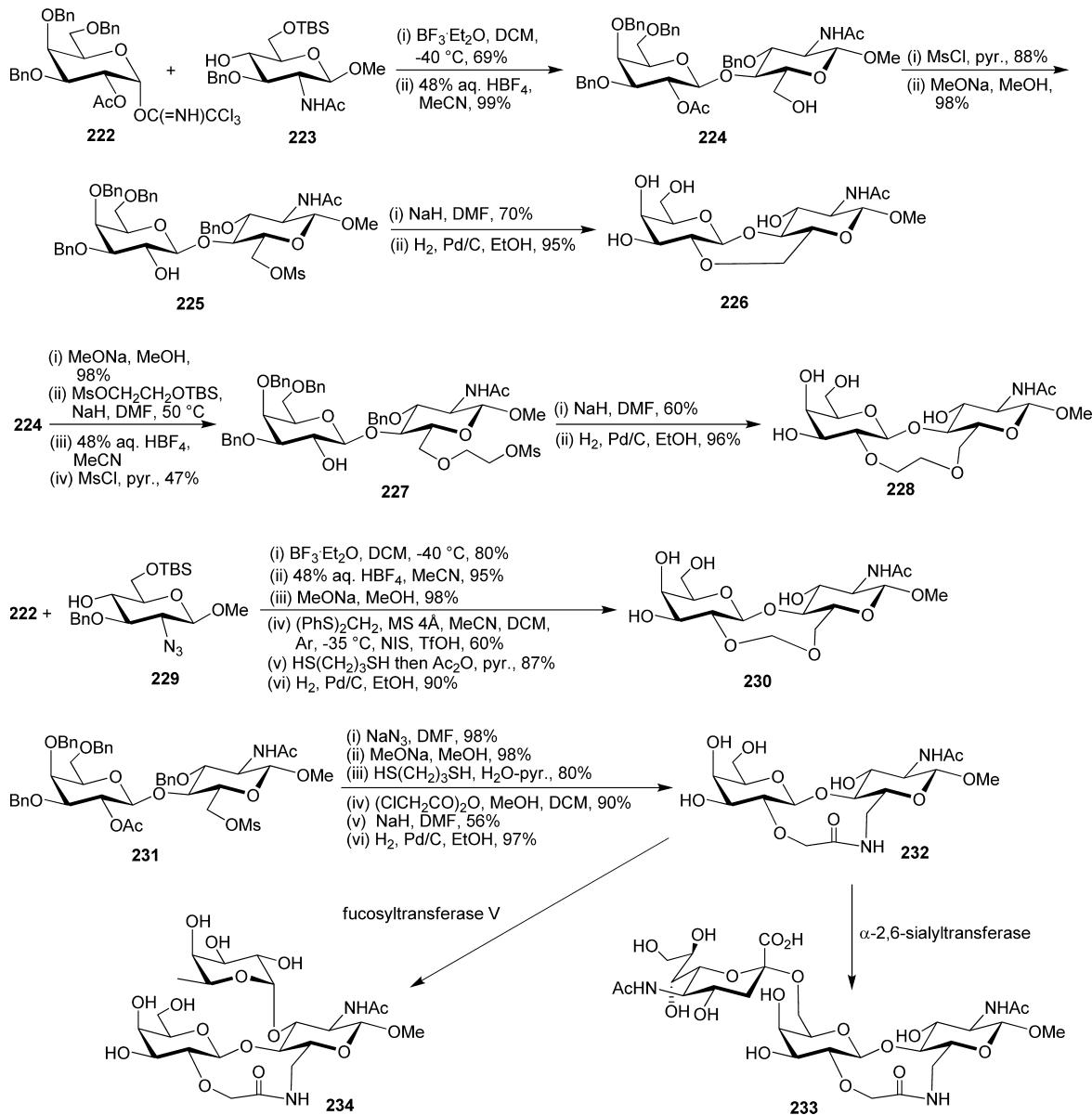
D-Abep(1 \rightarrow 3) α -D-Manp(1 \rightarrow OMe] to antibody Fab and single-strain Fv fragments.^{72,73} Two synthetic strategies were employed (Scheme 33). Glycosylation of the mesylated mannose 235 with the thiogalactosides 236–238 each bearing a different sized tether attached at O-6, cleavage of the trityl ether, followed by intramolecular nucleophilic substitution led to the corresponding tethered disaccharides 239–241. A more efficient synthesis of the cyclic disaccharide 241 was achieved by placing the mesylate leaving group on the tether attached to the mannose residue 246 and displacing it with the alkoxide generated at C-6 of the galactose moiety from 247. Selective allyl ether removal in 239–241 followed by glycosylation with the thioglycoside 242 and hydrogenolytic debenzylation afforded the tethered trisaccharides 243–245. Solid-phase enzyme immunoassays showed that the tethered trisaccharides 243–245 were weaker inhibitors than the native trisaccharide toward the monoclonal Se-155.4 antibody.

Through intramolecular aglycon delivery strategy, Bundle's group has designed and synthesized the constrained H-type blood group trisaccharide 252 in the search for high affinity lectin ligands (Scheme 33).⁷⁴ The tethered disaccharide 250 was first prepared by nucleophilic substitution of the glycoside 249 with the mesylated thiogalactoside 248 in the presence of NaH , followed by regioselective benzylidene ring-opening, intramolecular glycosylation, and cleavage of PMB ether. Further glycosylation with the thiofucoside 251 and subsequent deprotections accomplished the synthesis of the target trisaccharide 252. Solid-phase binding assays showed that the tethered trisaccharide 252 was less active than native H-type 2 trisaccharide against *Ulex* lectins, suggesting once again that reduction of oligosaccharide flexibility by intramolecular tethering provided no significant gain in binding energy.

To understand aminoglycoside antibiotics interaction with RNA and resistance enzymes, conformationally constrained neomycin and paromomycin analogues have been designed, synthesized, and evaluated. Tor's group synthesized constrained neomycin and paromomycin analogues 256 and 263 from 5'-O-TIBS (2,4,6-triisopropylbenzenesulfonyl)-activated Boc-protected aminoglycosides 254 and 262 (Scheme 34).⁷⁵ TFA-mediated Boc deprotection, followed by dilution and neutralization with TEA, allowed a slow (10 days) intramolecular cyclization. The obtained macrocycles were reprotected with Boc_2O to facilitate the purification. Final acidic deprotection

Scheme 30. Synthesis of Methylene-Bridged Galabiosides

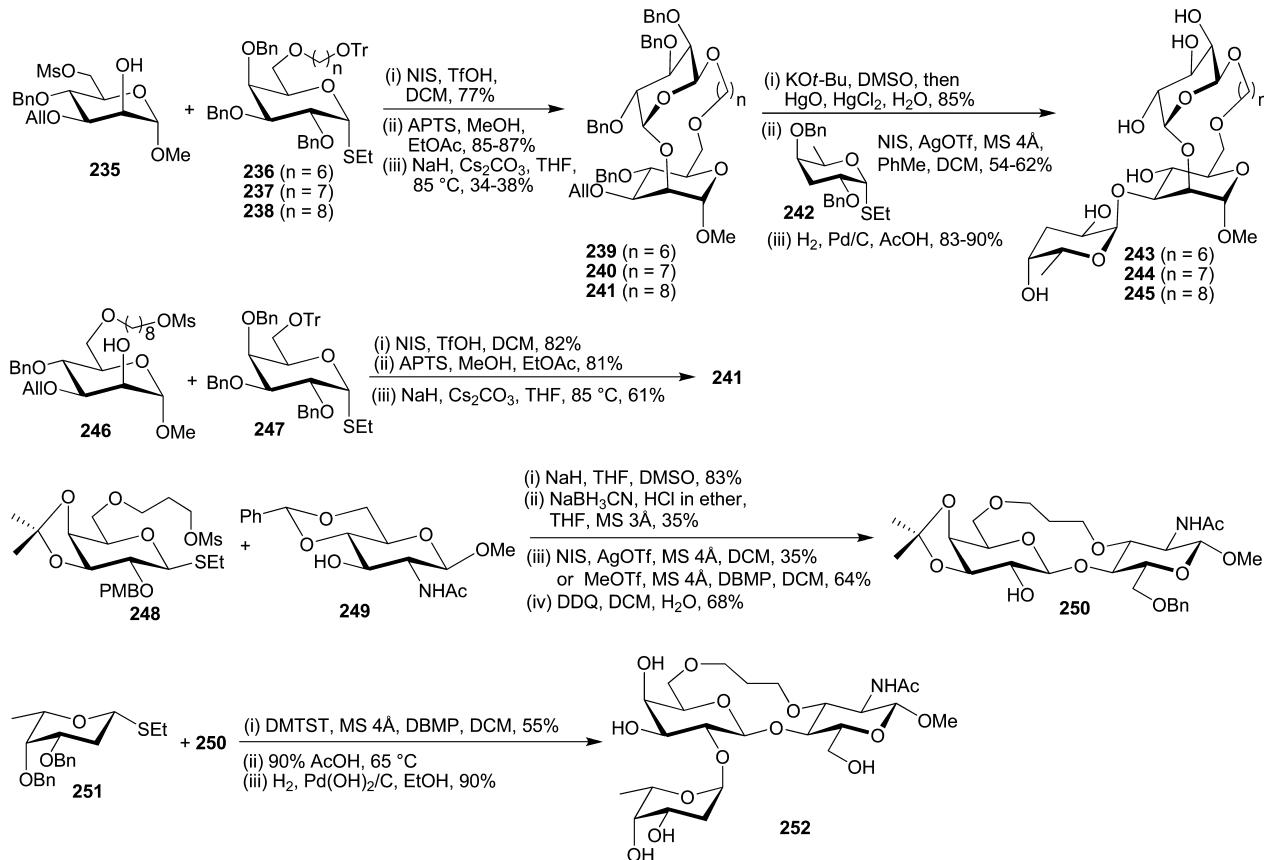
Scheme 31. Synthesis of Methylen Bridge Trisaccharides

Scheme 32. Synthesis of Conformationally Constrained *N*-Acetyllactosamine Derivatives

provided 256 and 263 in 12% and 20% yields, respectively. Examination of the binding affinity of neomycin, paromomycin, and their constraint analogues 256 and 263 to two different RNA targets, the A-site and the HIV-1 TAR, showed that conformational constraint had no deleterious effect on binding to the HIV-1 RNA sequence, while the deeply encapsulating A-site was a

target, the A-site and the HIV-1 TAR, showed that conformational constraint had no deleterious effect on binding to the HIV-1 RNA sequence, while the deeply encapsulating A-site was a

Scheme 33. Synthesis of Conformationally Constrained Trisaccharides



more discriminating RNA target, where a minimal deleterious effect on binding was observed.

Asensio and colleagues have exploited the conformational differences exhibited by aminoglycosides within the binding pockets of the ribosome and of those enzymes involved in bacterial resistance for designing new antibiotic derivatives.^{76,77} Neomycin-B locked derivatives 256 and 261 (Scheme 34) have been designed to mimic the bioactive RNA-bound structure of the drug. Compound 256 was obtained through Cbz-protected neomycin 255, by employing a strategy similar to that of Tor's group.⁷⁵ The synthesis of 261 started with regioselective silylation of 257, followed by acetylation of secondary hydroxyl groups, desilylation, and Dess–Martin oxidation to the aldehyde 258. Side-chain elongation through Wittig reaction of 258 with Ph₃P=CHCO₂Me, followed by reduction with NaBH₄ in the presence of catalytic LiCl, led to the alcohol 259. After regioselective silylation and acetylation of secondary hydroxyl functions, the silyl group was converted into tosylate 260, which was deacetylated by mild KCN-catalyzed methanolysis. Removal of carbamate group allowed the regioselective cyclization at 40 °C and pH 7.0 in water to give the target 261 as the only macrocyclic derivative in 62% yield. The constrained aminoglycosides 256 and 261 maintained a reasonable affinity for the target A-site RNA and exhibited significant antibiotic activities, while displaying a large impact on their enzymatic inactivation. These studies open the way for designing new antibiotic derivatives with improved activity in resistant strains.

More recently, the constrained tricyclic aminoglycoside 265 has been prepared from neamine 264, which was obtained by methanolysis of neomycin (Scheme 34).⁷⁸ The 3- and 6'-amino groups were selectively protected by Boc₂O in the presence of

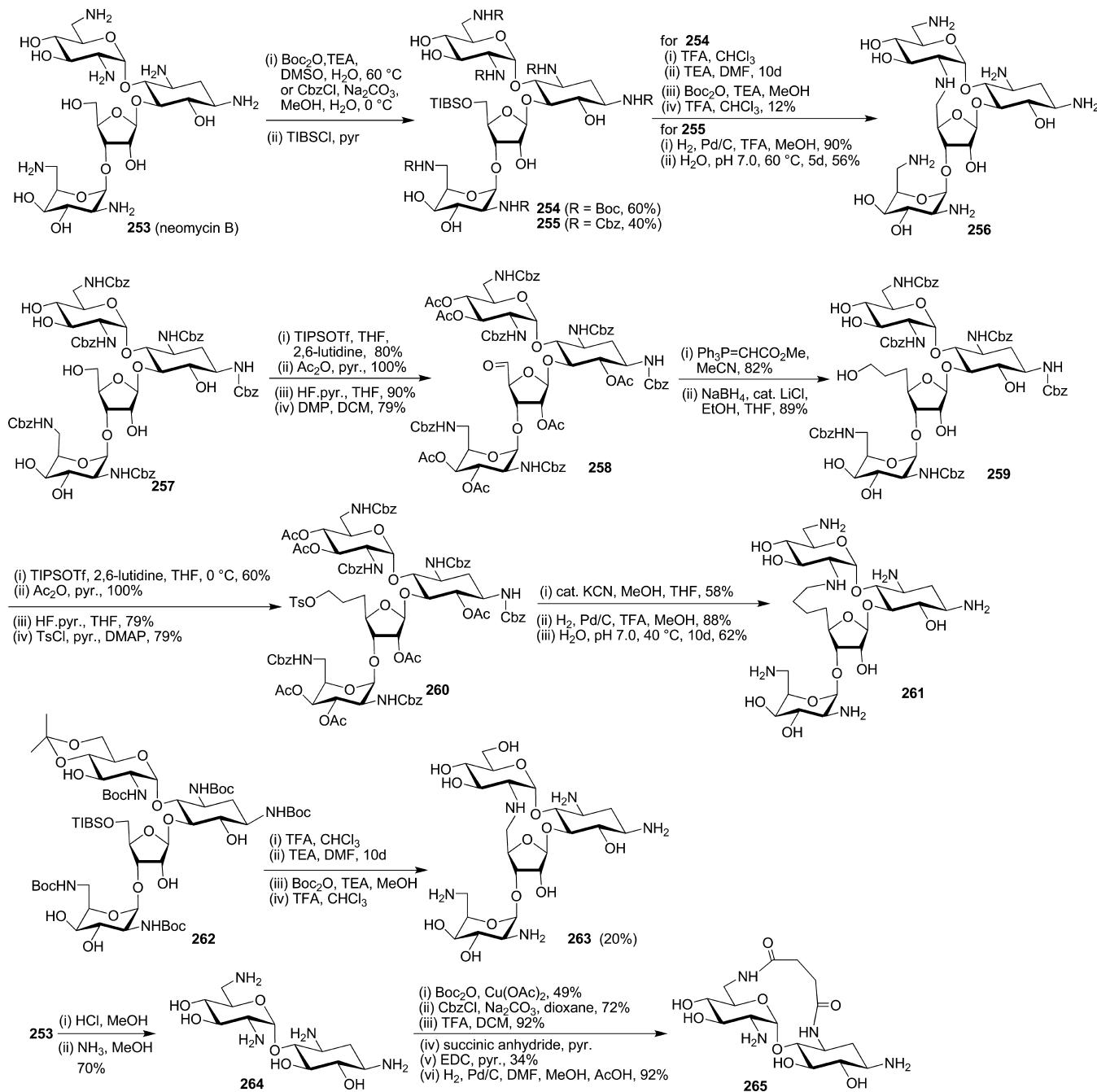
Cu²⁺. Subsequent treatment with CbzCl, removal of Boc group, regioselective acylation with succinic anhydride and macrocyclization promoted by EDC, followed by hydrogenolysis led to the cyclic compound 265 in 8% overall yield.

3.5. Cyclic Glycopeptides

Carbohydrate-peptide containing macrocycles have been designed and synthesized as protein ligands, enzyme inhibitors, or quadruplex DNA binders. On the basis of the crystal structures of a monoclonal antibody SYA/J6, which detailed the position of the native trisaccharide epitope Rha-Rha-GlcNAc, Bundle and colleagues have synthesized tethered trisaccharides 272 and 273 as tighter binding ligands of SYA/J6 (Scheme 35).⁷⁹ The core trisaccharide 269 was obtained by glycosylation of aminoglucoside 266 with rhamnosyl thioglycoside 267, followed by deacetylation and glycosylation with L-thiomannoside 268. After treatment with ethylene diamine and desilylation, the free amine group was linked with N-Fmoc protected glycine or β-alanine to afford compounds 270 and 271. Subsequent oxidation of primary alcohol to carboxylic acid, removal of Fmoc group, macrolactamization promoted by TBTU/HOBt, and hydrogenolysis led to the target compounds 272 and 273. Binding measurements indicated that the glycanyl tethered trisaccharide 272 was inactive, while the β-alaninyl tethered trisaccharide 273 displayed a 15-fold increase in affinity for SYA/J6. Potential energy and dynamics calculations indicated that trisaccharide 273 adopted a rigid conformation similar to that of the bound conformation of the native trisaccharide epitope.

Two rigid macrocyclic glycopeptides have been designed to mimic the tetrasaccharide sialyl Lewis X as inhibitors of P-selectin.⁸⁰ L-Galactoside 274 was converted into the acid

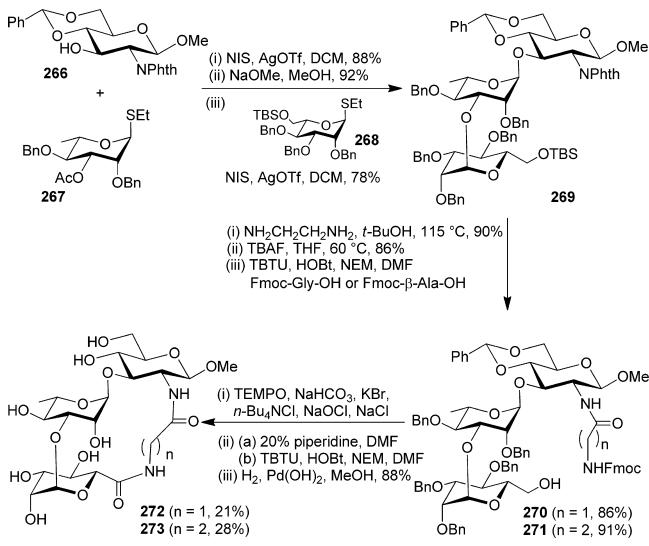
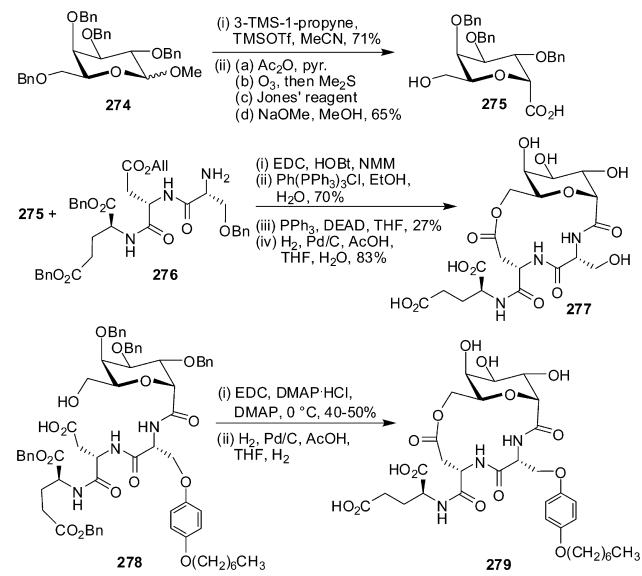
Scheme 34. Synthesis of Conformationally Constrained Aminoglycosides



derivative 275 through α -C-allenylation with 3-TMS-1-propyne and TMSOTf with concomitant removal of 6-O-benzyl group, followed by temporary acetylation of 6-hydroxyl group, ozonolysis, Jones oxidation, and deacetylation (Scheme 36). Coupling of 275 with tripeptide 276, followed by removal of allyl protecting group, macrolactonization under Mitsunobu conditions, and debenzylation accomplished the synthesis of the target cyclic glycopeptide 277. Glycopeptide 278, prepared in a similar way, was subjected to the macrocyclization using EDC, DMAP, and DMAP-HCl in 40–50% yield. However, the deprotected cyclic glycopeptide 279 was not soluble in usual solvents. Cyclic glycopeptide 277 was found to be 1000-fold more potent than SLE^x with $\text{IC}_{50} = 1 \mu\text{M}$ in inhibiting P-selectin.

Cyclic glycopeptides have also been synthesized to act as mimetics of loop 2 of the proangiogenic molecule vascular

endothelial growth factor D (VEGF-D) to inhibit angiogenesis via blocking dimerization of the receptors (VEGFR-2 and VEGFR-3) by VEGF-D.⁸¹ Synthesis of cyclic glycopeptide 284 was realized by coupling of tripeptide 281 with Glc β (1 → 4)Glc disaccharide 280 to give the glycopeptide 282, which was deprotected with piperidine, and coupled with Boc-Cys(Tr)-OH 283 (Scheme 37). Further treatment with iodine led to loss of the S-trityl groups and to disulfide bond formation. The target compound 284 was obtained after deprotection with TFA in the presence of triethylsilane in 51% yield. Cyclic glycopeptides 285 and 286 bearing an isoleucine or valine residue in place of leucine in 284 have been obtained in a similar way. The bigger macrocycle 288 was prepared by coupling of glycopeptide 282 with dipeptide 287 in 45% overall yield. Diastereomeric cyclic glycopeptides 290 and 291 containing an *allo*-configured sugar

Scheme 35. Synthesis of Cyclic Trisaccharides**Scheme 36. Synthesis of Cyclic Sialyl Lewis X Mimetics**

moiety were synthesized from the disaccharide 289 in good yield. Among the synthesized cyclic glycopeptides, only the bigger macrocycles 288 and 291 showed moderate ability to inhibit the biological activity of VEGF-D through VEGFR-2 in cell-based assays.

By bis-tethering neomycin on three aromatic platforms (phenanthroline, acridine, quinacridine), Teulade-Fichou and colleagues have prepared four aminoglycoside-capped macrocycles for quadruplex DNA recognition and telomerase inhibition.⁸² Partially protected neomycin 292 was first coupled to lysine or capronic acid to afford the compounds 293 and 294 after hydrogenolysis (Scheme 38). Subsequent reductive amination with dialdehydes 295–297 and deprotection led to neomycin-capped macrocycles 298–301. NMR studies showed that these cyclic compounds adopted a highly flexible structure without conformational restriction of the aminoglycoside moiety. These macrocycles exhibited a good to high affinity for intramolecular quadruplexes and a good selectivity for DNA quadruplexes versus duplexes. Moreover, the best quadruplex-

binder 300 is also a potent and selective telomerase inhibitor with IC₅₀ in the submicromolar range.

To examine the utility of ester-linked carbohydrate-peptide conjugates as peptide prodrugs, peptides containing D-glucose at C-terminal were synthesized.⁸³ Esterification of free D-glucose with active ester 303 followed by peptide chain elongation gave the corresponding glycopeptide 305, which underwent intramolecular condensation reaction between the N-terminal free amine group and glucose hemiacetal function in pyridine/acetic acid, leading to macrocycle 307 after Amadori rearrangement of the resulting imine 306 (Scheme 39). In the case of shorter glycopeptide 308, the cyclic glycosylamine 310 was isolated after treatment at 37 °C in pyridine/acetic acid. These results demonstrated the instability of glycopeptides containing free amino group(s) in the peptide part and a reducing sugar moiety as in 305 and 308.

Two cyclic pseudotetrapeptides have been obtained during the investigation of sugar-derived α -amido nitriles for accessing restricted disubstituted glycine like compounds.⁸⁴ Aminocyanation of ulose 311 with Gly-OMe followed by reduction of nitrile group gave 312, which was further transformed into the glycopeptide 313 (Scheme 40). Macrocyclization promoted by DPPA was realized after saponification and hydrogenolysis, to provide the cyclic furanose derivative 314. Removal of isopropylidene groups gave the corresponding pyranose derivative 315.

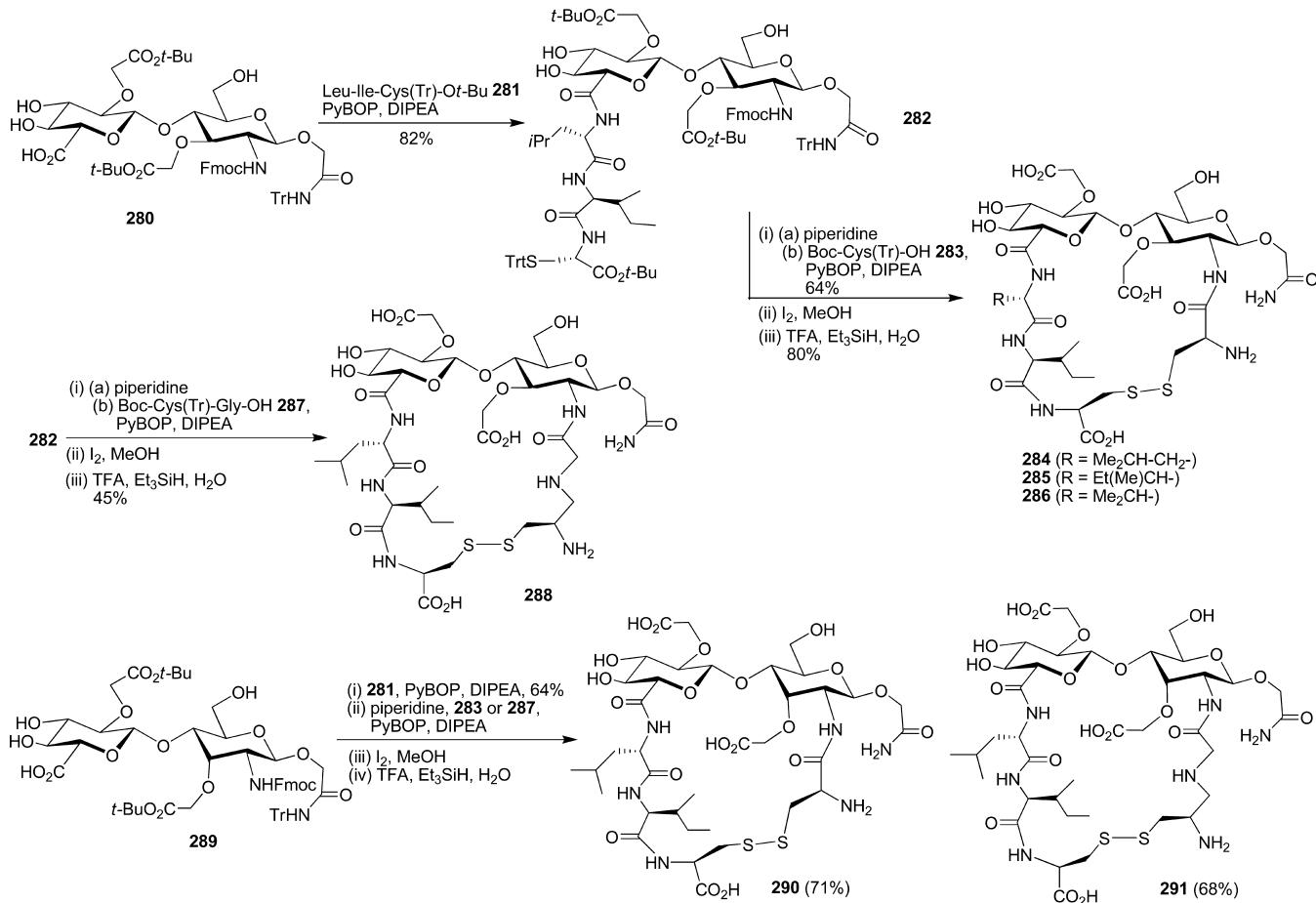
3.6. Macrocycles Containing Sugar Amino Acid

Sugar amino acids (SAAs) are multifunctional carbohydrate building blocks containing amino and carboxylic groups on a furanoid or pyranoid ring. α , β , γ , δ , and ϵ -SAAs have been employed in the design and synthesis of peptidomimetics, enzyme inhibitors, oligomers, and polymers, or for conformation and secondary structures investigations.^{85–89} Cyclic homooligomers of SAAs as well as cyclic SAA/AA hybrid molecules have been reported since 1994.

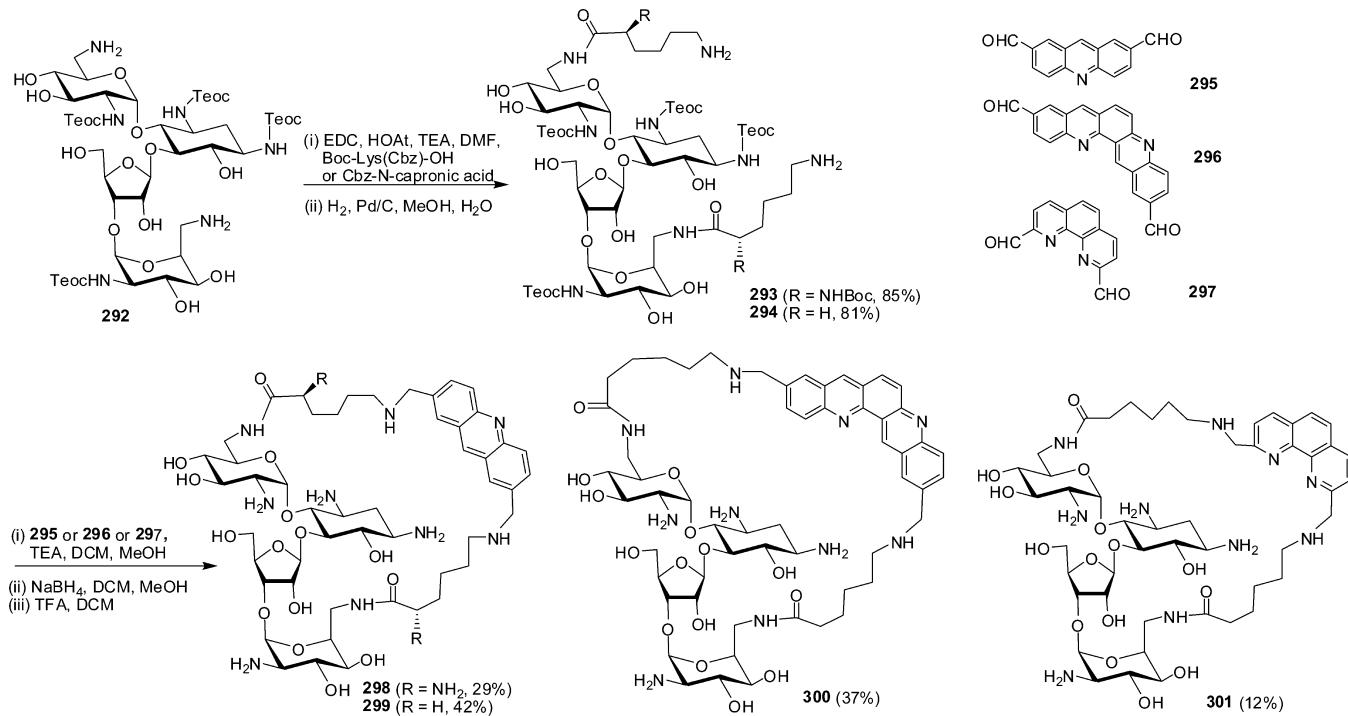
3.6.1. Macrocycles Containing Sugar Amino Acid and Amino Acid. Kessler and colleagues have pioneered in the use of SAA as a new type of dipeptide isostere.⁹⁰ Pyranoid δ -SAA H-Gum-OH 318 has been designed as dipeptide isostere of Gly-Ser/Thr with a flexible β -turn conformation (Scheme 41). The first synthesis of H-Gum-OH was realized from glucose through nitroaldol reaction in 12% overall yield. A more efficient synthesis has been achieved by reacting per-acetylated glucosyl bromide 319 with Hg(CN)₂ followed by LiAlH₄ reduction to afford the β -glucosylmethylamine 320.⁹¹ Subsequent protection/deprotection and TEMPO oxidation led to Fmoc-Gum-(Bn)₃-OH 322 in 22% overall yield. The H-Gum-OH was then used to replace the amino acids Pro-Phe in the highly active somatostatin cyclic hexapeptide *cyclo*(Phe-Pro-Phe-D-Trp-Lys-Thr) 325.^{90,92} The linear oligopeptide 323 was prepared from Z-Gum-OMe 317, by successive saponification, coupling with Phe-D-Trp-OMe, hydrogenolysis, and recoupling with Boc-Lys(Cbz)-Thr-OH promoted by EDC/HOBt. After deprotection, the intramolecular cyclization was realized with TBTU/HOBt as coupling reagent under high dilution (1 mM in DMF) in 56% yield. Synthesis of target cyclopeptide 324 was accomplished after hydrogenolysis. The cyclopeptide 324 inhibits the release of growth hormone with an IC₅₀ of 0.15 μ M, only 75 times less active than the highly potent somatostatin peptide analogue 325.

In a similar way, pyranoid γ -SAA 326 and β -SAA 327 have been incorporated into the cyclopeptides 328 and 329 (Figure 4).⁹² Conformational analysis of cyclopeptides 324, 328, and

Scheme 37. Synthesis of VEGF Inhibitors

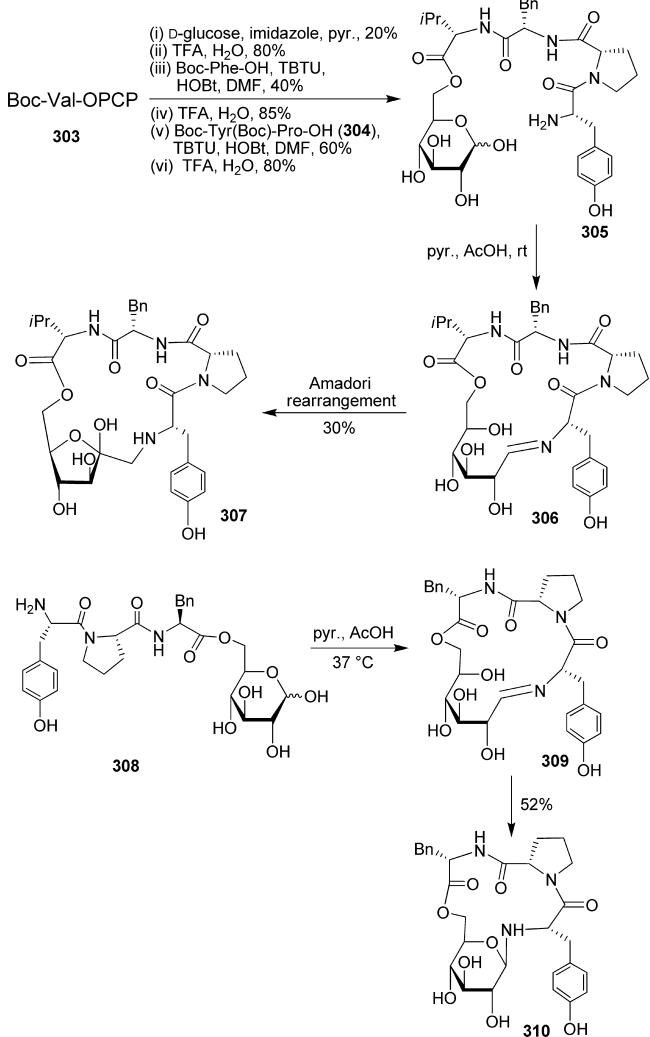


Scheme 38. Synthesis of Neomycin-Capped Macrocycles

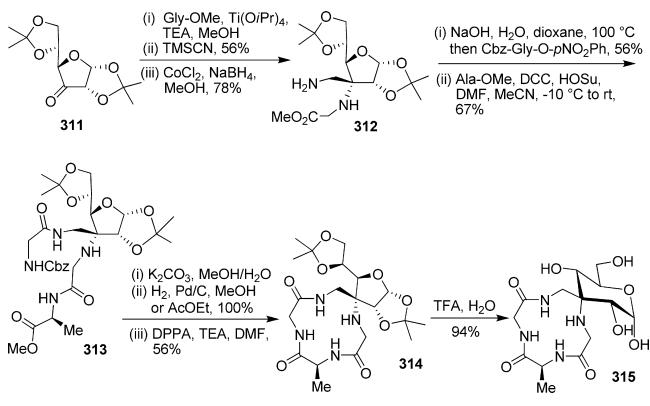


329 by various NMR techniques in combination with distance geometry calculations and subsequent dynamic simulations

Scheme 39. Synthesis of Ester-Linked Carbohydrate–Peptide Adducts



Scheme 40. Synthesis of Cyclic Pseudotetrapeptides



shows that SAAs 318 and 326 induce a β -turn structure, while SAA 327 mimics a γ -turn. The carbohydrate ring remains in a ${}^4\text{C}_1$ conformation.

To improve the pharmacokinetic and dynamic properties of cyclic RGD peptides, Kessler and colleagues have synthesized *cyclo*(β -SAA(Bn)₃-RGD) 330 and *cyclo*(α -SAA(Bn)₃-RGD) 331 by replacement of two amino acids D-Phe-Val in the lead RGD cyclopentapeptide *cyclo*(Arg-Gly-Asp-D-Phe-Val) by δ -SAA H-

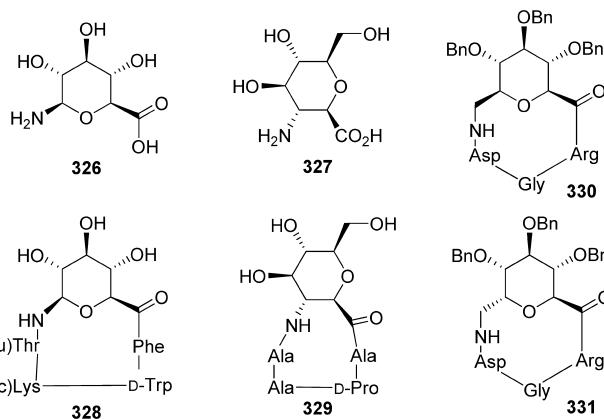


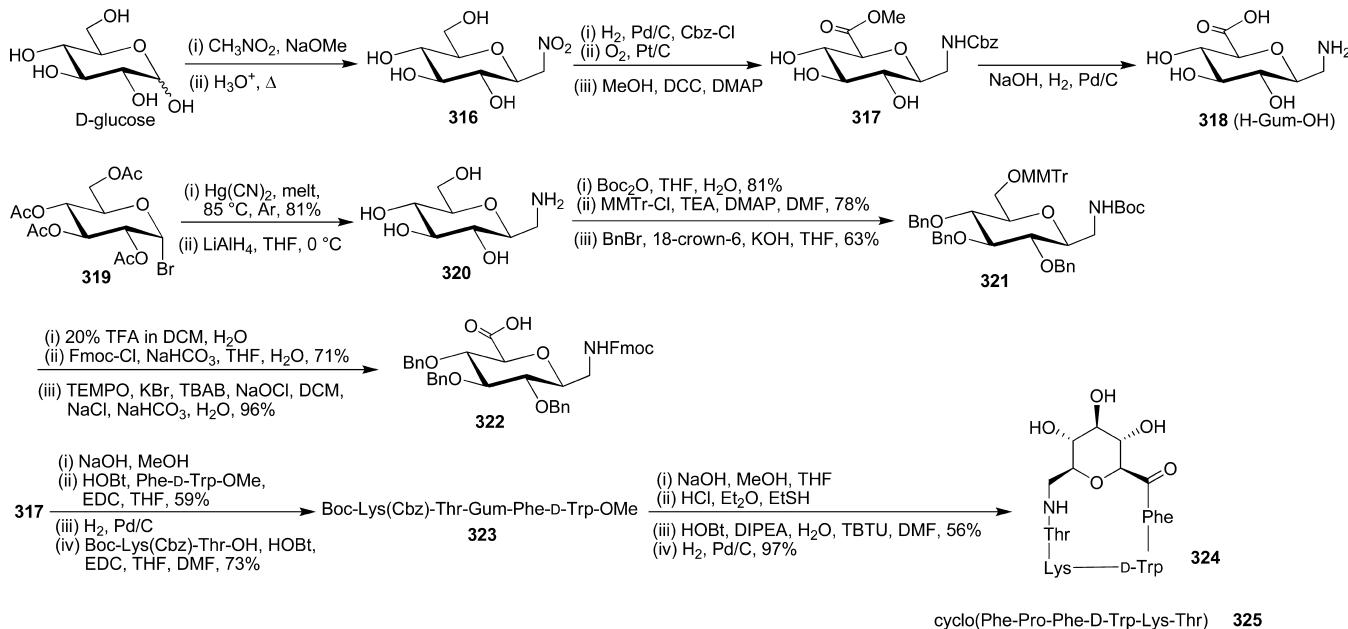
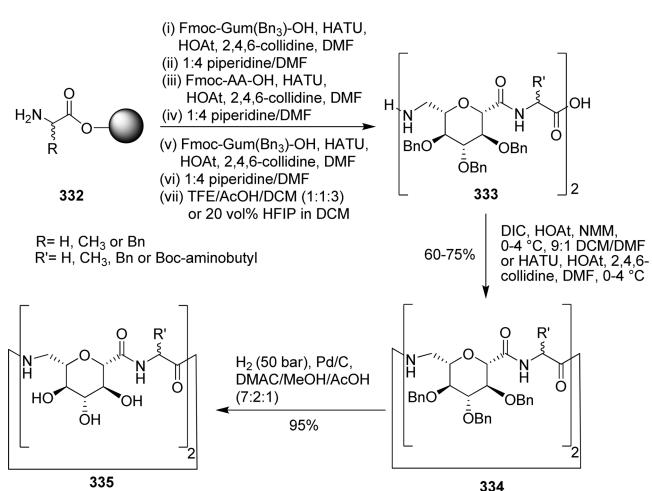
Figure 4. Structure of cyclopeptides containing pyranoid β - and γ -SAAs as well as cyclic α -selective RGD peptides.

Gum-OH 317 and its diastereomer (Figure 4).⁹³ Both compounds have a high α β_3 activity ($\text{IC}_{50} = 25 \text{ nM}$ for 330 and 150 nM for 331). In addition, the more flexible β -SAA peptide 330 exhibited an unexpected high activity against the $\alpha_{\text{Hb}}\beta_3$ receptor ($\text{IC}_{50} = 13.4 \text{ nM}$).

Kessler's group has also synthesized cyclopeptides containing SAA H-Gum-OH alternating with Gly, L-Ala, D-Ala, L-Phe, D-Phe, L-Lys, or D-Lys by a combination of solid-phase and solution synthesis (Scheme 42).⁹¹ Linear oligomers were first synthesized by solid-phase synthesis with Fmoc strategy using TentaGel S-Tr resin. With HATU and HOAt as coupling reagents and 2,4,6-collidine as a base in DMF, high coupling yields and low racemization were obtained. After resin cleavage, cyclization of linear oligomers 333 was realized with DIC/HOAt/NMM or HATU/HOAt/2,4,6-collidine under high dilution conditions (0.2 mM). Final debenzylation furnished the deprotected macrocycles 335 in excellent yields (95%). Structure of *cyclo*(Gum-L-Lys-Gum-D-Phe) has been solved by NMR.

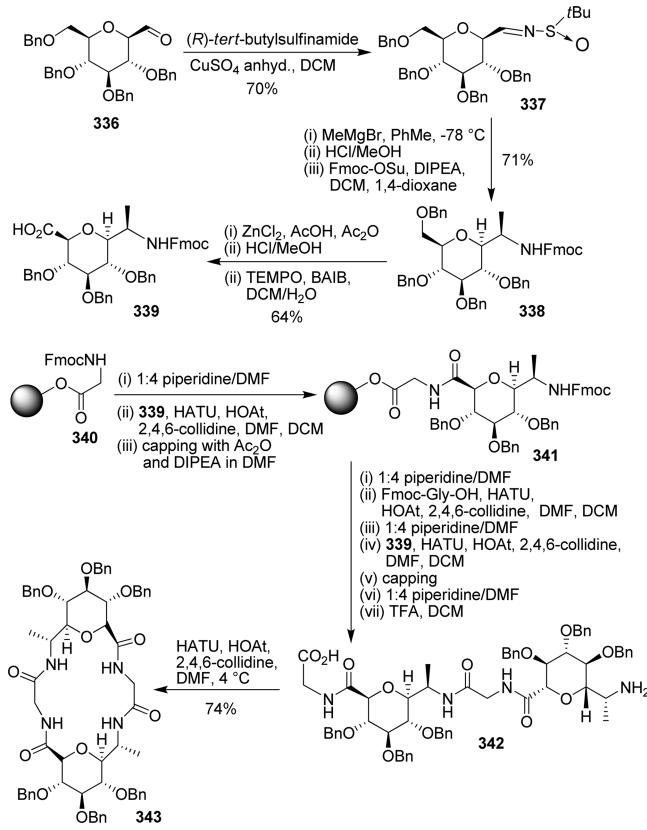
Overhand's group has designed and synthesized alkylated δ -SAAs as highly functionalized dipeptide isostere via a diastereoselective alkyl/arylation of a glucose-derived sulfinylimine.⁹⁴ As shown in Scheme 43, condensation of C-glucoside 336 with (R)-*tert*-butylsulfinamide afforded the corresponding sulfinimine 337, which reacted stereoselectively with MeMgBr to provide the amine 338 after removal of the sulfonyl auxiliary and Fmoc protection. Acetylisis of primary benzyl ether allowed its selective deprotection and oxidation into the methylated δ -SAA 339 as D-Ala-Ser/Thr isostere. This SAA was then condensed with glycine-functionalized Wang resin 340 to prepare the linear oligomer 341 with Fmoc strategy. Intramolecular cyclization was accomplished with HATU/HOAt/2,4,6-collidine under high dilution conditions (1 mM in DMF) to provide benzylated cyclic tetramer 343 in 74% yield.

Kessler and colleagues have also employed furanoid SAA to prepare somatostatin analogues to fight against resistance to cancer chemotherapy.⁹⁵ The furanoid β -SAA 346 is easily synthesized from diacetone D-glucose by introducing azido group on 3-position via triflate, followed by selective deprotection to generate exocyclic hydroxyl groups, oxidative diol cleavage, KMnO₄ oxidation, and one-pot transformation of azide to Fmoc-protected SAA 346 in 44% overall yield (Scheme 44). Eight cyclopeptides incorporating SAA 346 have been prepared by assembling linear peptides by solid-phase synthesis on trityl chloro-polystyrene (TCP) resin using Fmoc-strategy with HATU/HOAt/2,4,6-collidine as coupling conditions, followed

Scheme 41. Synthesis of Somatostatin Analogue Containing Pyranoid SAA Gum**Scheme 42.** Synthesis of Cyclopeptides Containing Two SAAs

by resin cleavage with hexafluoro 2-propanol, final cyclization with DPPA/NaHCO₃ in DMF (0.1 mM), and deprotection with 3% hydrazine in DMF. Four of them (compounds 351–354, Scheme 44) possess strong antiproliferative and apoptotic activity against both multidrug-resistant and drug-sensitive hepatoma carcinoma cells, with IC₅₀ values in the low micromolar range, making them promising leads for chemotherapeutic drugs against multidrug resistant carcinoma.

van Boom's group reported a parallel synthesis of cyclic furanoid SAA/AA hybrid molecules via robot-assisted solid-phase synthesis using an oxime resin, which allowed cyclization of peptides with concomitant release from the solid support with Boc-strategy.⁹⁶ The furanoid ε-SAA 356 was obtained from 2,3-O-isopropylidene-D-ribose 355, through C-glycosylation using Wittig reaction, azidation via mesylate, azide reduction and removal of O-isopropylidene group, and subsequent Boc protection and saponification (Scheme 45). The first AA was anchored to the oxime resin with DIC/HOBt. After each Boc-deprotection, stepwise couplings were promoted by BOP/HOBt

Scheme 43. Synthesis of Alkylated δ-SAA and Cyclic Tetramer

in the presence of DIPEA. Acid-catalyzed cyclization of linear peptides released the target cyclopeptides 361 and 362 in 10–30% yields. This synthetic procedure has then been applied to prepare cyclic RGD-furanoid SAA peptides 363–367 as integrin inhibitors, with the cyclic tetrapeptide 363 being the most promising with an IC₅₀ of 1.49 μM for the α₁β₃ receptor and 384 nM for the α_{Hb}β₃ receptor.⁹⁷ Conformational study has been realized on cyclopeptides 362 (with R₁ = Me, R₂ = Bn), 363 and

Scheme 44. Synthesis of Furanoid β -SAA 346 and Structures of Furanoid β -SAA Containing Somatostatin Analogues

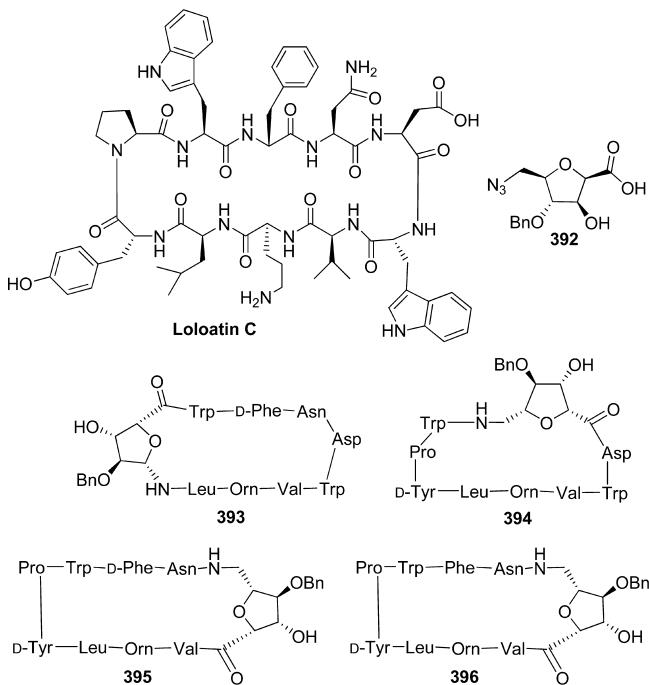
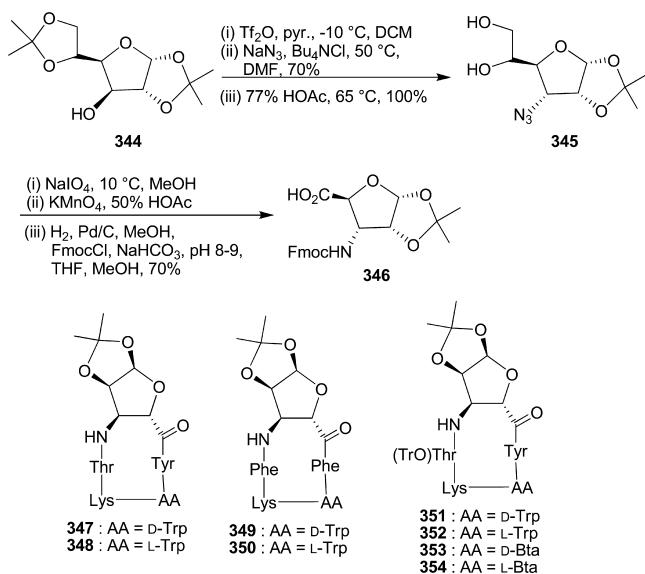
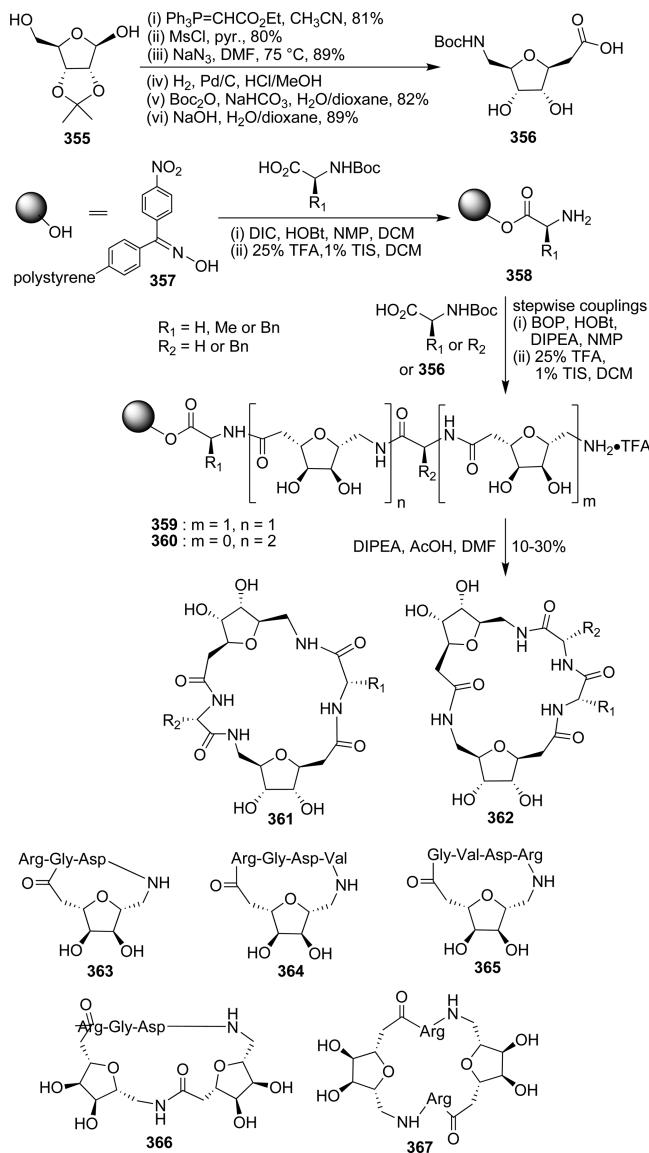


Figure 5. Structures of loloatin C and analogues.

364 using molecular dynamics calculations in combination with NMR analysis, demonstrating that furanoid ϵ -SAA 356 is able to introduce an unusual intraresidual hydrogen bond-stabilized β -turn-like conformation in compounds 362 and 363.⁹⁸ On the other hand, compound 364 remains conformationally flexible.

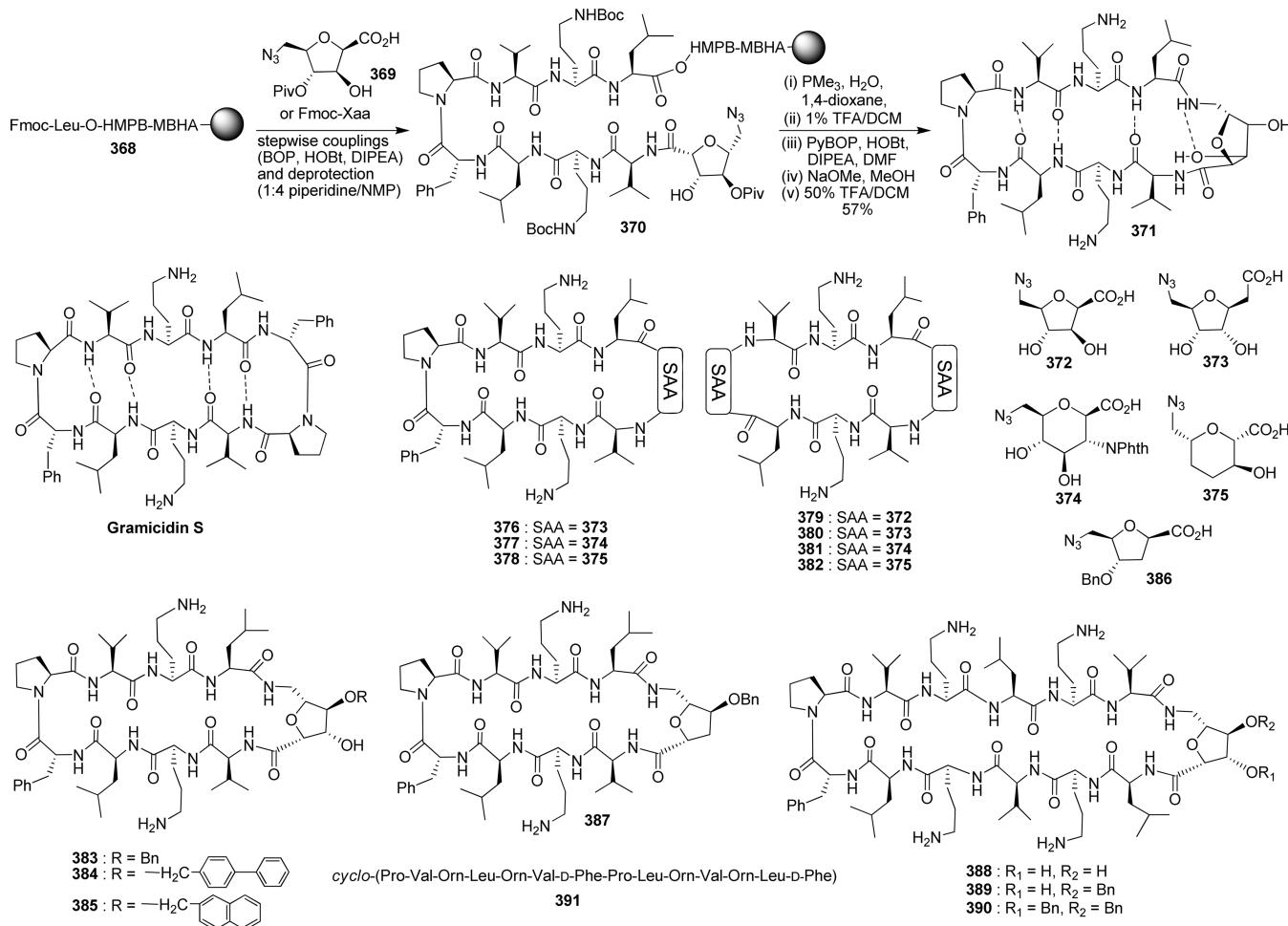
Gramicidin S (GS), a cationic antimicrobial cyclodecapeptide with the primary sequence *cyclo-(Pro-Val-Orn-Leu-d-Phe)*₂, kills several Gram-positive bacteria by disrupting the bacterial lipid bilayer thanks to its amphiphilic nature (with the hydrophobic Val and Leu residues on one side of the molecule and the hydrophilic Orn side chains on the other). However, because of its hemolytic activity toward human blood cells, GS cannot be used to treat systemic infections.⁹⁹ GS adopts an antiparallel β -sheet structure with the two Val-Orn-Leu stretches aligning as

Scheme 45. Parallel Solid-Phase Synthesis of Cyclic SAA/AA Hybrid Molecules



two β -strands and the two d-Phe-Pro dipeptides as two type II' β -turn. This rigid β -hairpin conformation is stabilized by four intramolecular hydrogen bonds (Scheme 46). Overhand and colleagues have replaced one or both d-Phe-Pro dipeptide by different furanoid SAA to investigate its influence on the structure as well as biological activities of furanoid SAA containing GS.^{100–104} Synthesis of GS analogues has been realized by stepwise solid-phase chemistry with the highly acid-sensitive HMPB-MBHA resin, followed by mild acidic cleavage of linear peptides and cyclization under high dilution conditions. As shown in Scheme 46, standard Fmoc-based solid-phase peptide synthesis using the appropriate amino acid building blocks furnished immobilized nonapeptide 370. The azido function was then reduced by Staudinger reduction conditions to the corresponding amine. After mild acidic cleavage from the resin, the partially protected linear peptide was then cyclized using PyBOP/HOBt/DIPEA under diluted DMF (1.3 mM). Subsequent deprotections afforded the target cyclopeptide 371 in 57% yield.¹⁰⁰ Conformational study by NMR and X-ray analysis showed that the C3-hydroxy group of SAA is involved in

Scheme 46. Structures and Synthesis of SAA Containing Gramicidin Analogues



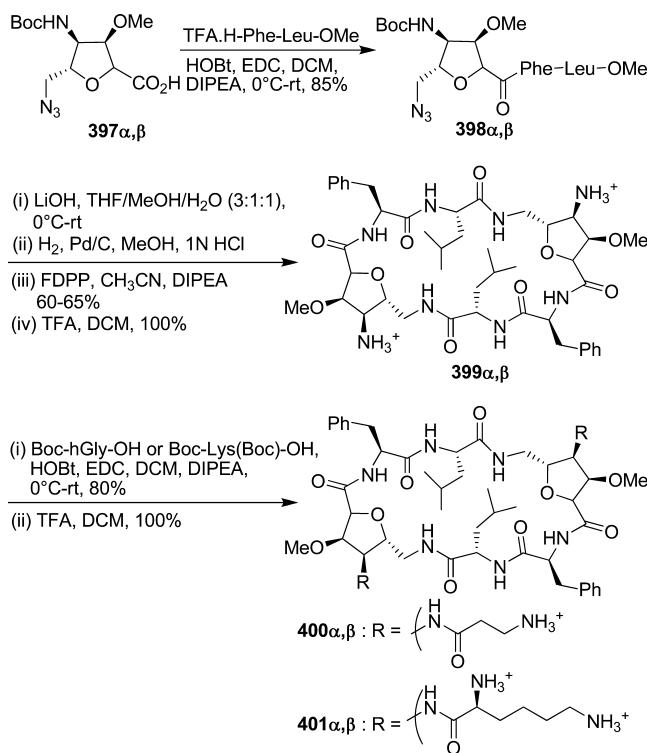
an intraresidual hydrogen bond leading to a distortion of the β -sheet structure, as compared to GS. Its X-ray structure revealed a hexameric β -barrel-like pore structure composed of six crystallographically equivalent units of 371. This method has been successfully applied to the synthesis of GS analogues 376–382 containing one or two SAA 372–375.¹⁰¹ However, compounds 371, 376–382 showed a deleterious effect on the antimicrobial activity with a similar decrease in toxicity toward human erythrocytes. To investigate if the strongly reduced antibacterial activity displayed by 371 is caused by the altered β -hairpin structure or by the hydrophilic character of the SAA moiety as compared to the hydrophobic D-Phe-Pro sequence, O-arylated SAA-containing GS analogues 383–385 have then been synthesized.¹⁰² Conformational studies show that arylated compounds 383–385 adopt a β -sheet structure with the SAAs occupying a distinctive reverse turn analogous to the nonarylated GS analogue 371. Interestingly, compounds 383–385 proved to be as active as the parent GS as antibacterial agents with, however, higher hemolytic activity, suggesting that the presence of aromaticity in the turn regions of GS derivatives is required for biological activity, whereas the native β -hairpin conformation is not. Further replacement of D-Phe-Pro sequence with 3-deoxy SAA 386 or flexible linear aminoethoxy acetic acid led to the corresponding GS analogues active against the Gram-positive bacterial strains.¹⁰⁴ Compound 387 displayed a conformation similar to that of compounds 371 and 383. Extended GS derivatives 388–390 have also been prepared (Scheme 46).¹⁰³

As compared to the tetradecameric GS derivative 391, replacement of one of its turn D-Phe-Pro sequence by SAA in compounds 388–390 induces slight distortion of the cyclic β -hairpin structure. Hemolytic and antimicrobial activity measurements show that compounds 388–390 have an improved antibacterial activity against a small series of Gram-positive and negative bacteria and a decreased toxicity.

Cyclic cationic antimicrobial decapeptide loloatin C, active against Gram positive as well as certain Gram negative bacteria, is an interesting lead compound for further development toward broad spectrum antibiotics. Loloatin C, which shares 4 out of 10 AAs with GS, has a zwitterionic character because of the presence of Orn and Asp (Figure 5). By employing the previously developed solid-phase Fmoc-chemistry with the highly acid-sensitive HMPB-MBHA resin, Overhand and colleagues have synthesized several loloatin C analogues by replacing the Pro-D-Tyr (compound 393), the Asp-D-Phe (compound 394), or the Trp-Asp motif (compounds 395 and 396, with L-Phe instead of D-Phe in 396) of loloatin C by furanoid SAA 392.¹⁰⁵ However, both the antimicrobial and the hemolytic activities of compounds 393–396 are rather low as compared to loloatin C.

Nevertheless, furanoid SAA-based 24-membered macrocyclic C₂-symmetric cationic peptides (Scheme 47) showed encouraging good activity against Gram positive and Gram negative bacteria and exhibited low hemolytic activity.¹⁰⁶ Their synthesis is exemplified in Scheme 47, starting by coupling of α - or β -anomers of furanoid SAA 397 with Phe-Leu-OMe to provide the

Scheme 47. Synthesis of Furanoid δ-SAA Containing Cyclic Cationic Antimicrobial Peptides

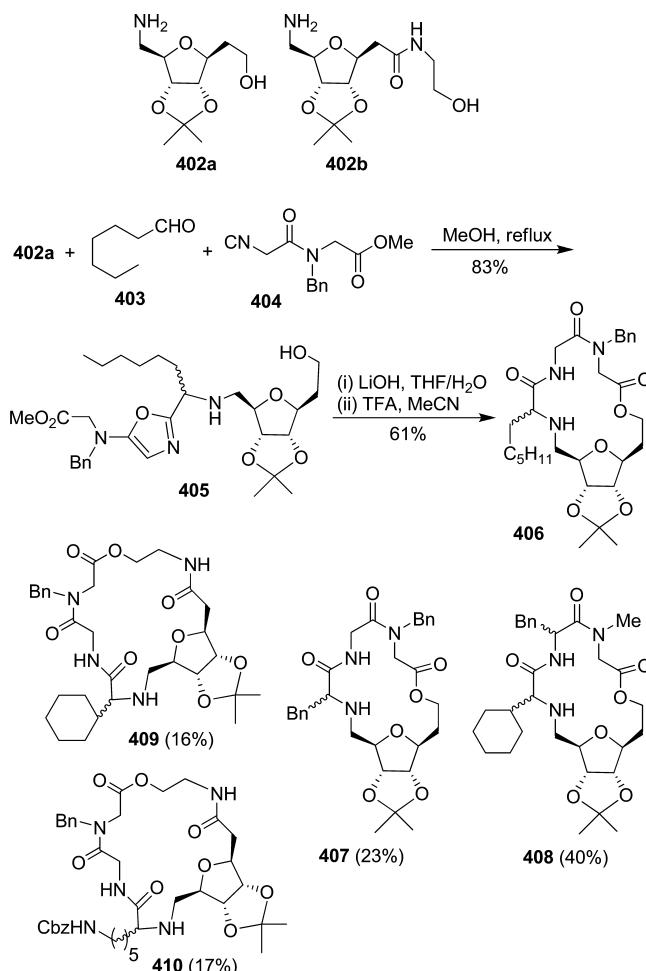


tripeptides **398 α,β** . After saponification and azide reduction, the resulting crude peptides cyclodimerized in the presence of pentafluorophenyl diphenylphosphinate (FDPP) in CH_3CN under dilute condition (2 mM) in 60–65% yield. The target cyclodimers **399 α,β** were then obtained after Boc-deprotection. Further coupling of **399 α** and **399 β** with Boc-hGly-OH or Boc-Lys(Boc)-OH followed by TFA treatment afforded compounds **400** and **401**. Conformational analysis by NMR and circular dichroism of cyclopeptides **399–401** showed that these peptides resemble more the dumbbell-shaped loloatin than the typical β -sheet structure of GS.

A two-step process has been recently developed for rapid synthesis of cyclodepsipeptides containing a SAA or a sugar amino alcohol.¹⁰⁷ A three-component reaction of a SAA or a sugar amino alcohol derivative **402**, an aldehyde **403**, and a dipeptide isonitrile **404** in refluxing methanol afforded the corresponding 5-aminooxazole **405**, which, after saponification, underwent a TFA-catalyzed macrocyclization in diluted CH_3CN (1 mM) to furnish the cyclic depsipeptides **406–410** (Scheme 48).

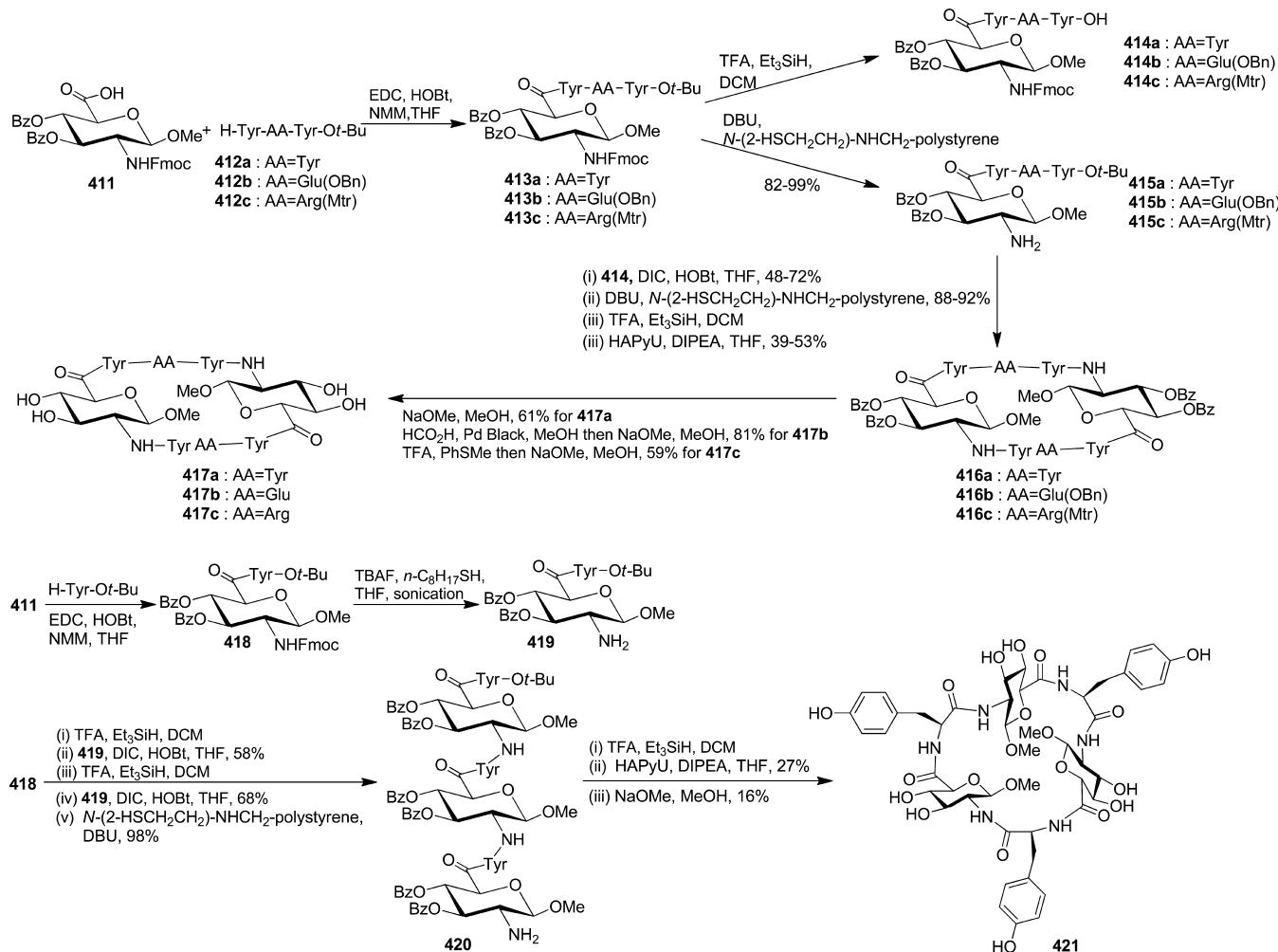
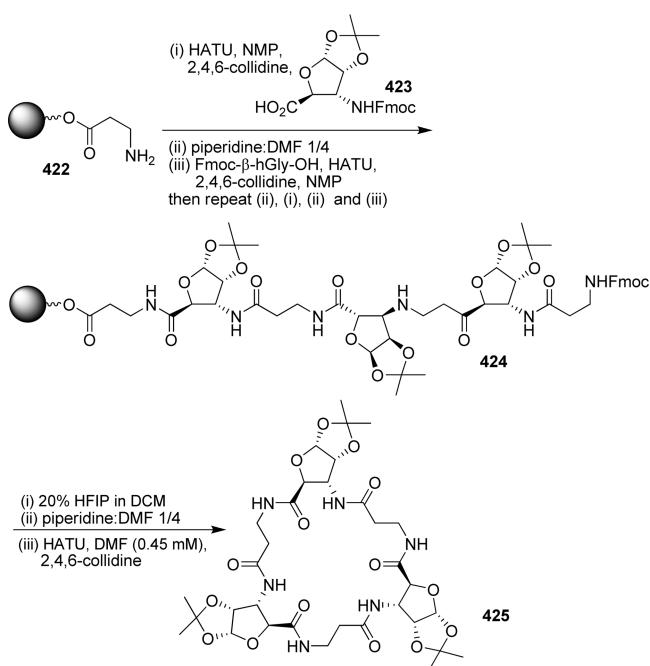
Nilsson and colleagues have explored the use of SAA as polar structural elements combined with nonpolar aromatic AAs for the construction of amphiphilic macrocycles as biomimetic receptors.^{108,109} The C_2 -symmetric macrocycles **417a,b,c** were then prepared from the pyranoid δ-SAA **411** and tripeptides **412a,b,c** (Scheme 49).¹⁰⁹ Reaction of SAA **411** with tripeptides furnished the compounds **413a,b,c**, which were selectively deprotected to amines **415a,b,c** by Fmoc deprotection using DBU in the presence of a supported thiol scavenger or transformed into acids **414a,b,c** by action of TFA in the presence of Et_3SiH . Coupling of **414** with **415** using DIC/HOBt/NMM protocol results in excessive epimerization. After deprotections, macrolactamization under high dilution con-

Scheme 48. Synthesis of Cyclodepsipeptides Containing SAA or Sugar Amino Alcohol



ditions of 1 mM was efficient using TBTU, HATU, and HAPyU, providing the protected macrocycles **416a,b,c**. The HATU and HAPyU reagents proved to induce less epimerization than TBTU in the cyclization. Final amino acid side-chains deprotection under standard conditions led to the macrocycles **417a,b,c**. Examination of their binding properties toward *p*-nitrophenyl glycosides, nucleotides, and purines in phosphate buffer showed weak but significant interaction between **417b** with caffeine and **417c** with purine nucleotides dAMP and dGMP, with $K_a \approx 10 \text{ M}^{-1}$. A C_3 -symmetric macrocycle **421** with alternating SAA and tyrosine residues has also been prepared by coupling the pyranoid δ-SAA **411** with Tyr-Ot-Bu to provide compound **418**, followed by successive deprotections, coupling with amine **419**, and intramolecular cyclization with HAPyU/DIPEA in THF (Scheme 49).¹⁰⁸ However, no binding property has been reported for **421**.

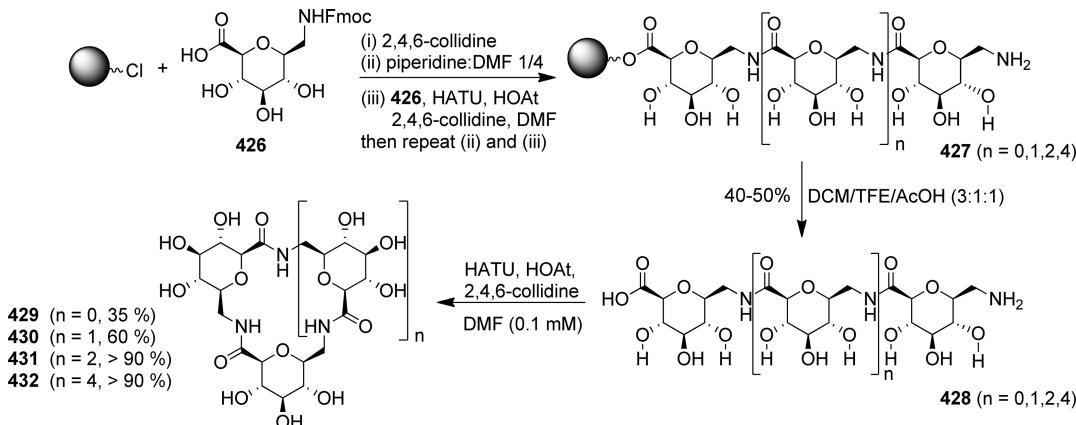
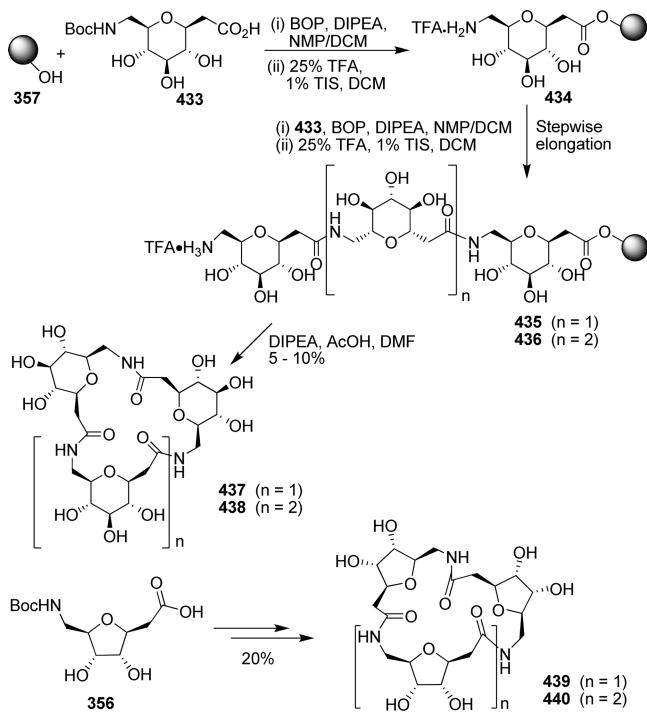
A C_3 -symmetric macrocycle with alternating furanoid β-SAA and homoglycine (hGly) residues was synthesized by solid-phase Fmoc-chemistry using tritylchloropolystyrene (TCP) resin combined with solution cyclization.¹¹⁰ As shown in Scheme 50, HATU was used as coupling reagent to prepare the linear peptide **424** on solid phase and macrocyclization in diluted DMF after resin cleavage to furnish the macrocycle **425** (41% overall yield), which exhibits a C_3 -symmetric conformation on the NMR time scale.

Scheme 49. Synthesis of Symmetrical Macrocycles Containing Pyranoid δ -SAA as Artificial ReceptorsScheme 50. Synthesis of Furanoid β -SAA Containing C_3 -Symmetric Macrocycles

3.6.2. Cyclic Homooligomers of Sugar Amino Acid.

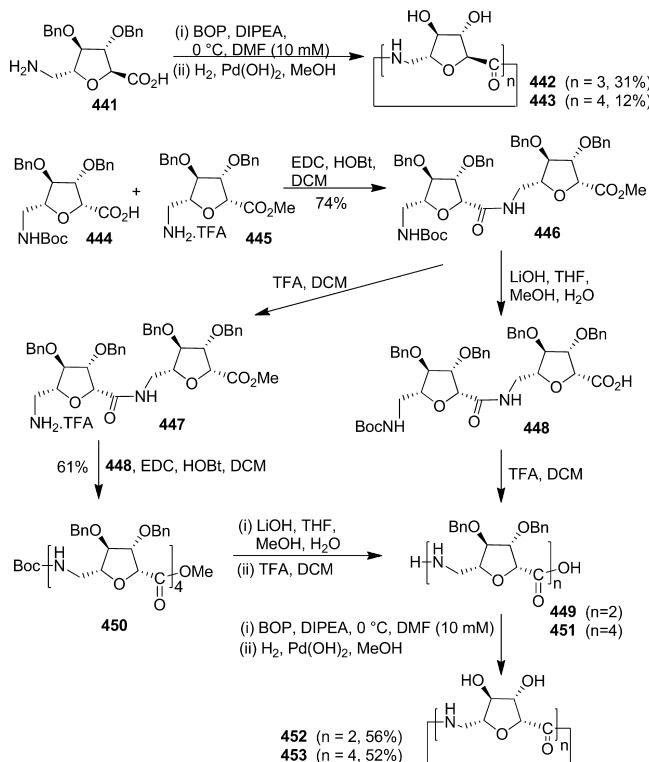
Cyclic homooligomers of SAAs have been designed, synthesized, and investigated on conformation, host property, and assembly formation. Using TCP resin, Kessler and colleagues have synthesized different oligomers of pyranoid δ -SAA H-Gum-OH 426 with HATU/HOAt as coupling reagent and 2,4,6-collidine as base (Scheme 51).¹¹¹ Use of the stronger base DIPEA is to be avoided due to the induced epimerization on the α -position of sugar carbonyl group. After resin cleavage with trifluoroethanol and AcOH in CH₂Cl₂, final macrolactamization is carried out under high dilution in DMF to afford water-soluble cyclic dimer 429, trimer 430, tetramer 431, and hexamer 432. NMR titration studies revealed that cyclic hexamer 432 acts as a mimetic of cyclodextrins in its ability to form inclusion complexes with benzoic acid.

Cyclic homooligomers of ϵ -SAAs were synthesized using oxime resin through a cyclization/cleavage approach.¹¹² The pyranoid ϵ -SAA 433 was first loaded on the oxime resin 357 with BOP/DIPEA (Scheme S2). Stepwise elongation by repeated Boc-deprotection and BOP-promoted coupling led to the linear trimer 435 and tetramer 436. Cyclization was accomplished by treatment of the resin with a 1:1 mixture of DIPEA and acetic acid in DMF to afford the cyclic trimer 437 and tetramer 438. The furanoid ϵ -SAA 356 was converted into the cyclic trimer 439 and tetramer 440 in a similar way. Conformational analysis by an

Scheme 51. Synthesis of Cyclic Pyranoid δ -SAA Homooligomers**Scheme 52.** Synthesis of Cyclic ϵ -SAA Homooligomers

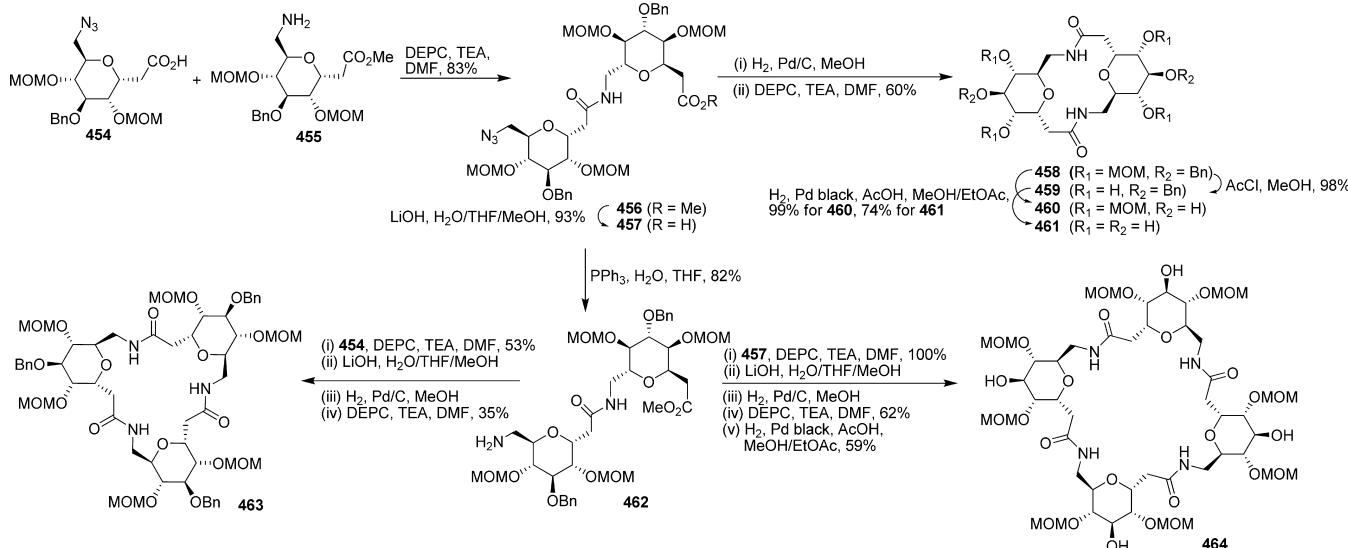
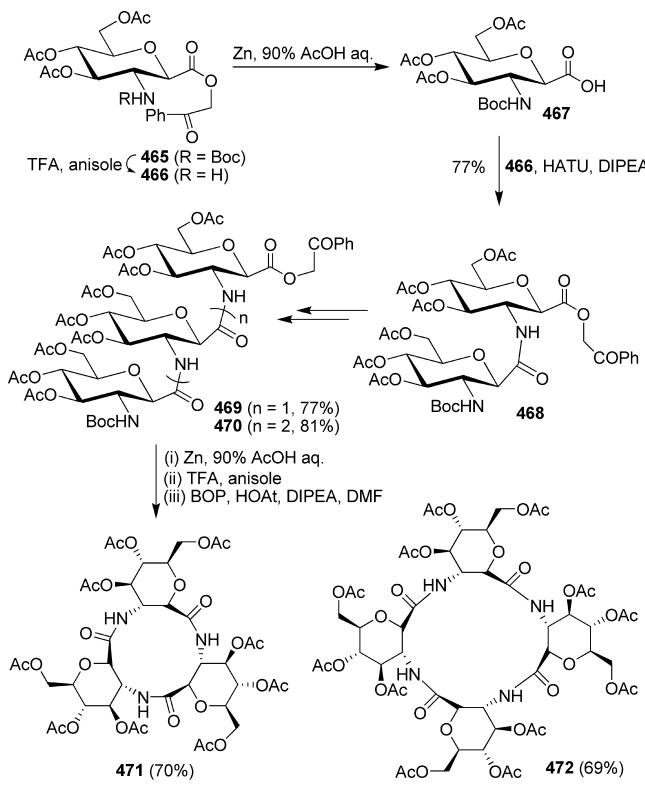
unrestrained simulated annealing technique showed that cyclic trimers **437** and **439** have a flat structure.

Chakraborty and colleagues succeeded in cyclohomooligomerization of the mannose-derived furanoid δ -SAA **441**, to afford, in one-step, the cyclic trimer and tetramer in 31% and 12% yields, respectively, which were debenzylated quantitatively to **442** and **443** (Scheme 53).¹¹³ Because of failure of cyclohomooligomerization as the *manno* SAA **441**, the glucose-based homooligomers **452** and **453** were prepared by intramolecular cyclization of corresponding linear dimer **449** and tetramer **451**. Conformational analysis by NMR and constrained MD studies revealed that all of the cyclic compounds had symmetrical structures. In the cyclic trimer **442**, the C₂-H and CO groups are placed on one side of the ring, while the NHs point to the opposite side, with both CO and NH groups being perpendicular to the ring. The NHs point into the ring while the carbonyls are positioned outside in the cyclic tetramer **443**. The cyclic dimer **452** displayed an unusual six-membered intramolecular hydrogen bond between NH_i → C₃-O_{i-1} and a syn orientation

Scheme 53. Synthesis of Cyclic Furanoid δ -SAA Homooligomers

between the C₂-H and CO. Note that the same group had previously synthesized and studied cyclic homooligomers derived from a thymidine-based nucleoside amino acid.¹¹⁴

Xie and colleagues have synthesized orthogonally protected cyclic homooligomers with two to four sugar units from pyranoid ϵ -SAA (Scheme 54).¹¹⁵ The cyclic dimer **458** was obtained by coupling of azido acid **454** with amino ester **455** promoted by DEPC, followed by saponification, reduction of azido group, and intramolecular cyclization in diluted DMF (2.2 mM). The MOM or benzyl group in cyclodimer **458** can be selectively or fully deprotected, affording the macrocycles **459–461** ready for further functionalization. Cyclotrimer **463** and cyclotetramer **464** were synthesized in a similar way. Better cyclization yields (60–62%) were obtained for cyclodimer **458** and cyclotetramer **464** as compared to cyclotrimer **463**.

Scheme 54. Synthesis of Orthogonally Protected Cyclic Pyranoid ϵ -SAA Homooligomers**Scheme 55.** Synthesis of Cyclic Pyranoid β -SAA Homooligomers

Fujimura et al. have synthesized cyclic trimer and cyclic tetramer of pyranoid β -SAA to investigate their molecular assembling properties.¹¹⁶ Compounds 471 and 472 were obtained by macrolactamization of linear compounds 469 and 470 with BOP/HOAt as coupling reagents (Scheme 55). The cyclic trimer 471 and tetramer 472 showed remarkable improvement of solubility in comparison with other cyclic β -peptides. FT-IR and NMR measurements and geometry optimization revealed a highly symmetric and planar conformation for both compounds with all-trans-amide groups, which took a vertical orientation against cyclic skeleton. Their

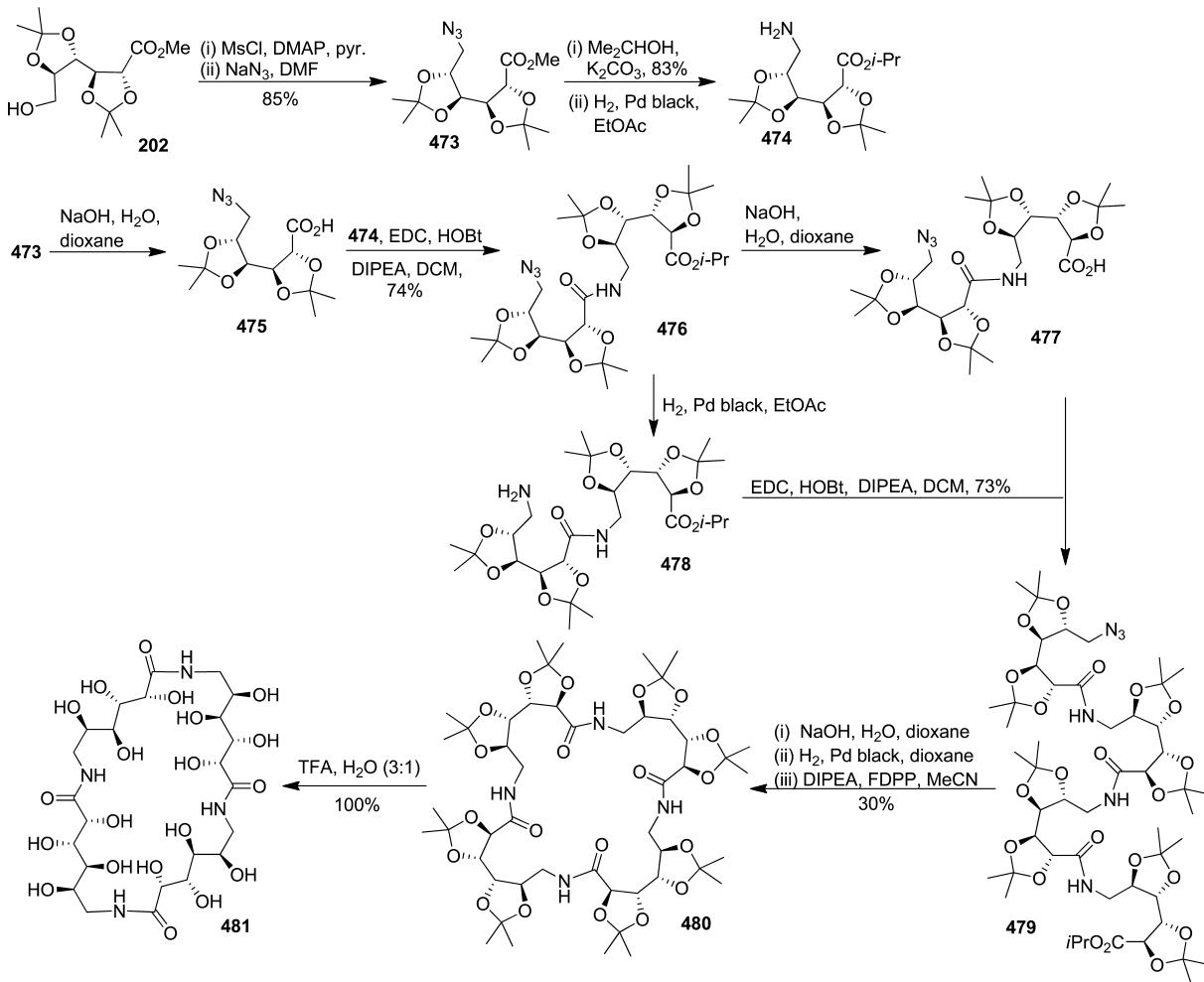
recrystallization in TFE/EtOH (2:1) for 471 or pyridine/MeOH (3:1) for 472 led to nanometric rod-shaped molecular assemblies.

3.6.3. Macrocycles Containing Open-Chain Sugar Amino Acid.

Fleet and colleagues have prepared several cyclic oligomers of 6-amino-6-deoxy-D-galactonate as a new class of biomaterial.^{117–120} The building block 473 (Scheme 56) for acceding cyclooligomers was obtained from D-galactonolactone-derived hydroxy ester 202 (Scheme 29). The methyl ester 473 was then exchanged to isopropyl ester before reduction of azido group to the amine 474 so as to prevent the possible self-condensation of the amino methyl ester. Saponification of 473 followed by coupling with amine 474 provided the dimer 476 in 74% yield. This dimer was then reduced to the amine 478 and separately hydrolyzed to the acid 477. Subsequent coupling with EDC/HOBt led to the linear tetramer 479 in 73% yield. Saponification, followed by azide reduction and activation as pentafluorophenyl ester in acetonitrile (\sim 20 mM concentration) formed the cyclic tetramer 480 in 30% yield. The isopropylidene protecting groups were then removed quantitatively by treatment with TFA, providing the 28-membered macrolactame 481, which was not stable under strongly acidic conditions.¹¹⁸ The ¹H NMR showed a symmetrical structure for 481.

Fleet and colleagues have also exploited the intramolecular macrolactamization of linear ω -azido-pentafluorophenyl esters through hydrogenation to prepare huge macrocyclic lactams (Scheme 57).¹¹⁹ For example, the azido dimer 482 was first converted to the pentafluorophenyl ester 483.¹¹⁷ Hydrogenation with Pd black at a concentration of 13.8 mM in dioxane gave 30% of 14-membered cyclic dimer 484 and 30% of cyclic tetramer 480. Reaction in more diluted solution (1.38 mM) gave 75–87% of cyclic dimer 489, along with about 10% of cyclic tetramer 480. Hydrogenation of tetramer 486 at a concentration of 8.0 mM furnished 80% of 480 and 17% of 56-membered cyclic octamer 487, while 57% of 480 and 31% of 487 were obtained at 4.0 mM concentration. This method provided a better yield of cyclic tetramer 480 as compared to the previous in situ activation of the preformed linear amino acid (Scheme 56). Both cyclic dimer and tetramer can be fully deprotected under acidic conditions, while complete deprotection of cyclic octamer 487 failed. Cyclization of linear trimer 488 at 1 mM concentration afforded the 21-

Scheme 56. Synthesis of Cyclic Tetramer of 6-Amino-6-deoxy-D-galactonate



membered cyclic trimer in 75% yield, without detection of significant amount of cyclic hexamer. In contrast, reduction of azido group of the pentamer **490** at 0.67 mM concentration afforded 71% of 35-membered cyclic pentamer **491**, together with 9% of 70-membered cyclic decamer **492**. All of these cyclizations were realized without epimerization.

In a similar way, Fleet and colleagues have prepared mixed sugar-nylon macrocyclic lactams (Schemes 58 and 59).¹²⁰ The azidoester **475** was coupled with 6-aminohexanoic acid so as to prepare the linear *gal-hex* monomer **495** and dimer **500** pentafluorophenyl esters (Scheme 58). Hydrogenation of **495** at 31 mM concentration in dioxane furnished a separable mixture of the cyclic monomer **496**, dimer **497**, and trimer **498** in a ratio of 1:2:1 with a combined yield of 91%. Reduction of dimer **500** gave the cyclic dimer **497**, without observing a catenane structure. The cyclic monomer **496** could be deprotected with Amberlyst-15 to the lactame **501**. Similarly, the azido-*mannono-lactone* **502** was converted into the linear *manno-hex* pentafluorophenyl ester **504**, which, after hydrogenation, afforded the cyclic monomer **505**, dimer **506**, and trimer **507** in 21%, 37%, and 15% yield, respectively (Scheme 59). Acidic hydrolysis of **505** gave the fully deprotected lactam **515** in quantitative yield. Interestingly, cyclooligomerization of the fully protected *manno-hex* pentafluorophenyl ester **510** favored the formation of cyclic dimer **512**, with the cyclic monomer **511**,

dimer **512**, and trimer **513** in a ratio of 1:3:1. The cyclic dimer **512** was also prepared from the linear dimer **514** in 79% yield.

4. MACROCYCLES CONTAINING TRIAZOLE LINKAGES

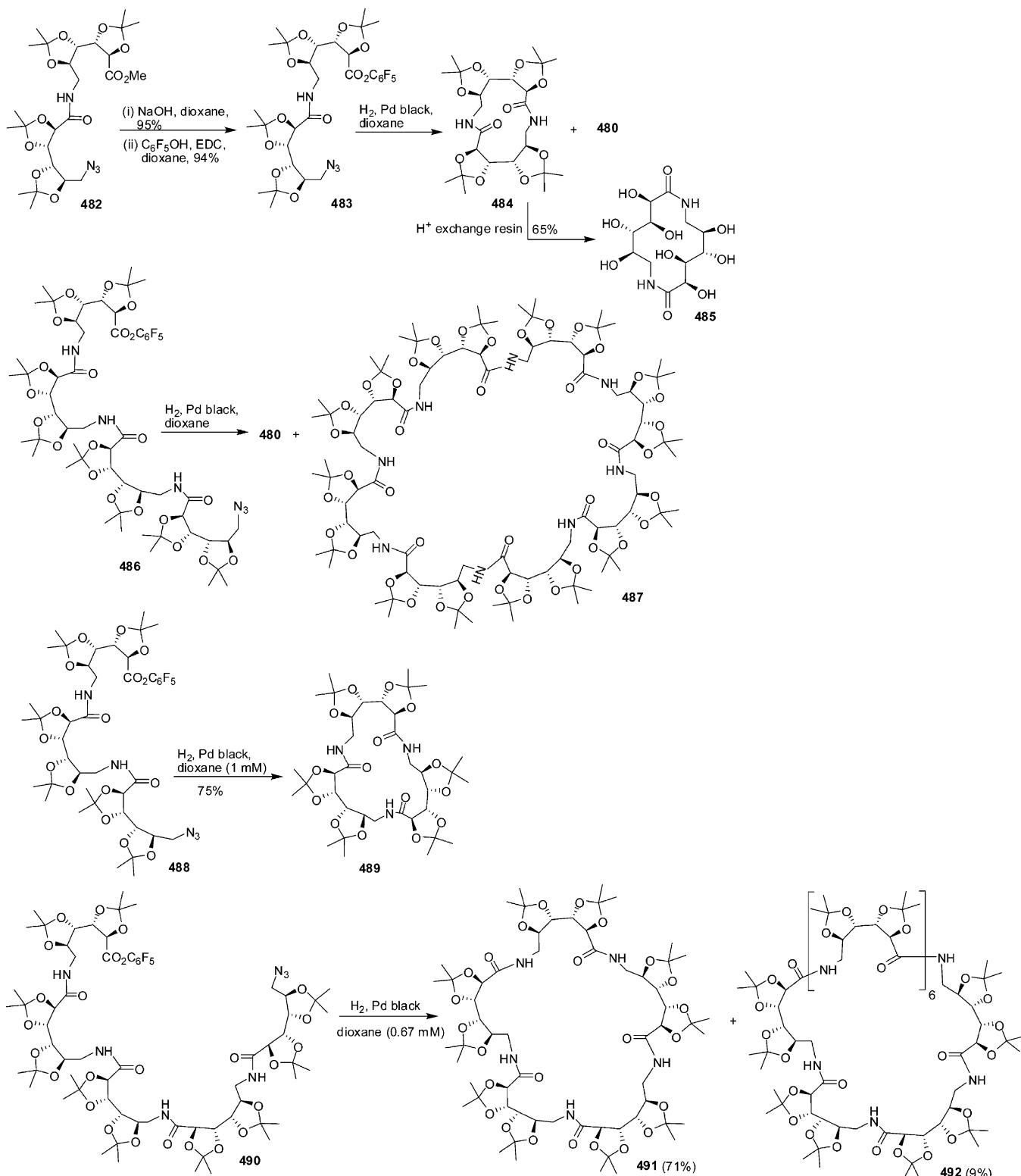
The copper-catalyzed Huisgen [3 + 2] cycloaddition (CuAAC) between an alkyne and an azido group, the archetypal “click” reaction, has found applications in many fields ranging from material science to chemical biology and drug discovery.^{121,122} Over the years, the 1,2,3-triazole moiety formed during this process has emerged as more than just a passive linker; it is indeed able to form complexes with both ions and cations, readily associate with biological targets through hydrogen-bonding and dipole interactions, and has been proven to act as pharmacophore.^{123–125} These interesting properties have stimulated the incorporation of triazoles in carbohydrate-derived macrocycles.

4.1. C_n-Symmetric Macrocycles

Triazole formation by CuAAC has been used to produce C_n-symmetric carbohydrate-containing macrocycles, often in the aim of producing CD analogues that could be easily modified with functional groups in specific positions of the macrocycle. Note that Vasella and colleagues have reported the synthesis of non C_n-symmetric CD analogues containing a 1,2,3-triazole unit by thermal azide-alkyne [3 + 2] cycloaddition for structural studies.¹²⁶

Gin and co-workers have investigated the synthesis of CD analogues by cyclodimerization of appropriately substituted

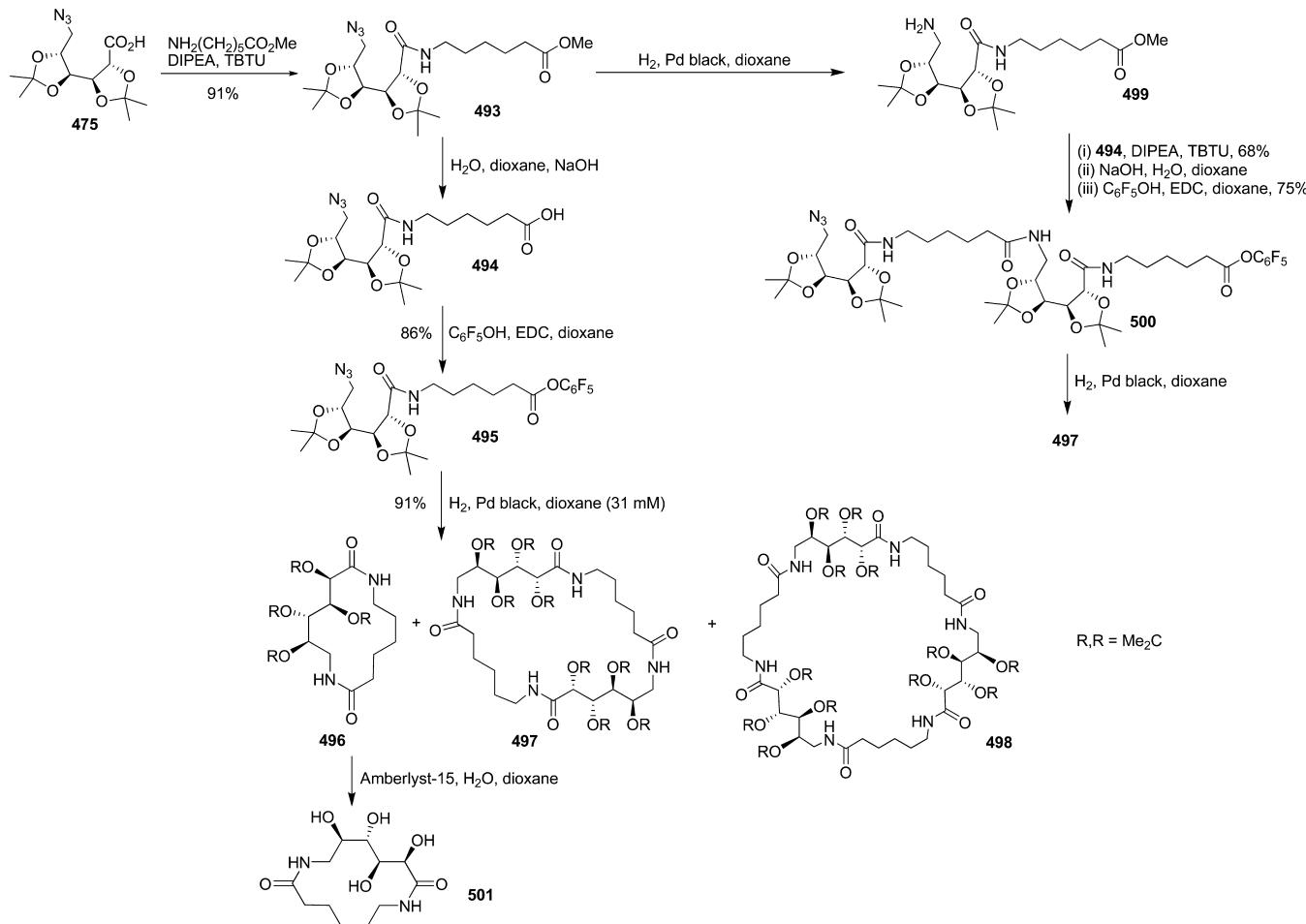
Scheme 57. Synthesis of Macroyclic Lactams of 6-Amino-6-deoxy-D-galactonate



trisaccharides.¹²⁷ The mannoside **516** was propargylated at C-4,¹²⁸ then anomeric deprotection with CAN afforded hemiacetal **517** as a 9:1 $\alpha:\beta$ mixture. This compound served as a donor for glycosylation with **516** performed in the presence of Ph_2SO and Tf_2O , leading to trisaccharide **518** after deprotection of the *p*-methoxyphenyl group and further glycosylation with **516**. Azide **519**, obtained by treatment of **518** with Ph_2SO , Tf_2O , $TMSN_3$,

and TEA, was reacted with CuI and DBU at a concentration of 2.3 mM in toluene to give, after hydrogenolysis of the benzyl groups, the desired cyclodimer **520** in 80% yield (Scheme 60). This compound associates with 8-anilino-1-naphthalenesulfonate (ANS) in water with a binding constant of $38 \pm 10 M^{-1}$, presumably through formation of an inclusion complex although the precise mode of interaction remained to be clarified.

Scheme 58. Synthesis of Mixed [Gal–Hex] Cyclooligomers



Using a similar strategy, the smaller C_2 - and C_3 -symmetric mannose-derived macrocycles **521** and **522** were synthesized (Figure 6).¹²⁹ Like cyclodextrins, they formed host–guest complexes in the presence of 2,4-hexadiyne-1,6-diol **523** in D_2O , with association constants ranging from $8.8 \pm 1.5 \text{ M}^{-1}$ for **522** to $10.4 \pm 1.1 \text{ M}^{-1}$ for **521**, comparable to β -CD ($18 \pm 2 \text{ M}^{-1}$). In contrast, five- or six-membered aromatic rings such as pyrrole and benzoic acid did not bind to these macrocycles, which was explained by the distorted toroidal cavity adopted by these compounds, making guest binding difficult.

Chandrasekhar et al. reported interesting observations concerning the influence of minor structural modifications on the outcome of furanose azido-alkyne cyclization (Scheme 61).¹³⁰ Indeed, treatment of propargyl ester **524** with copper turnings and CuSO_4 in refluxing EtOH (at a concentration of 36 mM) yielded 70% of the C_2 -symmetric 16-membered macrocycle **525**. In contrast, use of propargyl ether **526** under similar conditions gave the tricyclic 1,5-triazole **527** in 85% yield, while propargyl amide **528** resulted in the formation of the 24-membered ring of C_3 -symmetry **529** in 48% yield, with less than 5% of the corresponding cyclodimer.

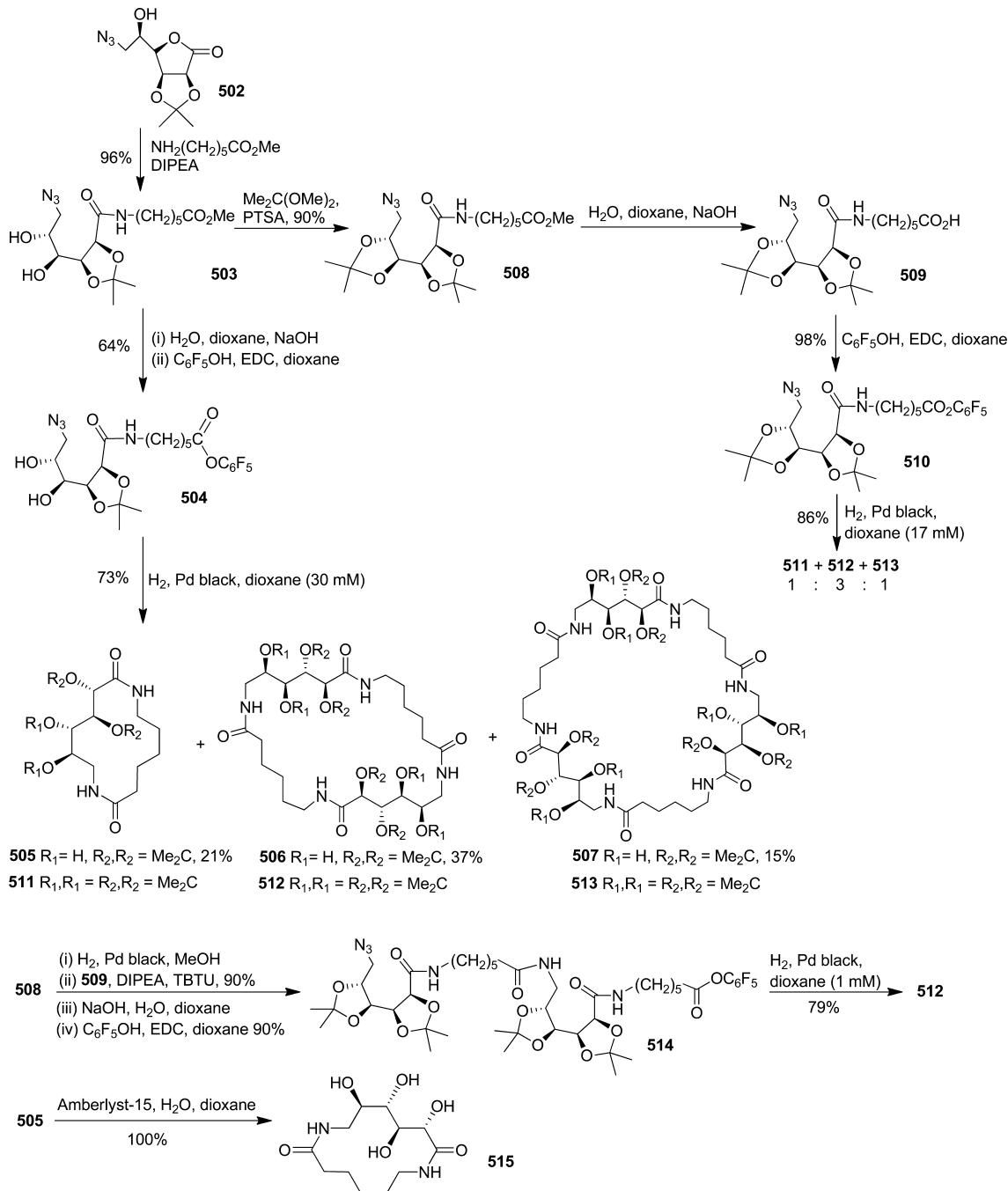
The group of Jarosz also experienced competitions between intramolecular cyclization and cyclodimerization of azido-alkyne sugar **531** (Scheme 62).^{131,132} Hexa-O-benzylsucrose **530** was preferentially silylated at the 6'-OH by action of TBDPSCl, DIPEA, and DMAP in DCM,¹³³ and then the remaining hydroxy group at C-6 was converted to the corresponding mesylate and substituted by NaN_3 . Deprotection of the silyl group followed by

propargylation gave the sucrose-derived azido alkyne **531**. After a number of reaction conditions were tested, the best results for cyclodimerization of **531** were obtained by copper-free [3 + 2] cycloaddition in toluene (at a concentration of 3.8 mM) at 80°C , yielding 45% of the C_2 -symmetric macrocycle **532**.

Field and colleagues synthesized several C_n -symmetric *pseudo*-galactooligosaccharides by cyclooligomerization of galactosyl azido alkyne **535** followed by enzymatic glycosylation (Scheme 63).¹³⁴ Diacetone D-galactose **533** was converted into alkyne **534** (obtained as a 2:5 mixture of α - and β -anomers) by O-6 alkylation with propargyl bromide, acidic deprotection of the isopropylidene groups, and per-acetylation. Treatment with HBr/AcOH led to the α -galactosyl bromide, which was converted to the β -galactosyl azide **535** by reaction with NaN_3 under phase transfer conditions followed by deacetylation. Reaction in the presence of copper and copper sulfate under microwave irradiation in DMF at a concentration of 0.18 M resulted in a mixture of cyclic di-, tri-, and tetramers **536**, **537**, and **538** in 29%, 13%, and 4% yield, respectively. Interestingly, applying the same conditions at higher concentration (1.0 M) resulted in the formation of the same di-, tri-, and tetramers in 10%, 35%, and 3% yield, respectively. Compounds **536** and **537** were efficiently sialylated to the corresponding **539** and **540** in the presence of recombinant *Trypanosoma cruzi trans-sialidase* (TcTS), while no similar compound could be detected upon reaction with **538**.

Other symmetric triazole-linked cycloglucopyranosides were obtained by the group of Marra.¹³⁵ The C -glycoside building

Scheme 59. Synthesis of Mixed [Manno-Hex] Cyclooligomers



blocks 542 and 543, both derived from glucopyranosyl acetate, were assembled by “click” chemistry into triazole 544 (Scheme 64). This compound was transformed into azido-alkyne dimer 545, tetramer 547, and hexamer 549, once again using CuAAC. The corresponding cyclooligomers 550–552 were finally obtained after TBS deprotection, intramolecular CuAAC in dilute toluene solution (6.3 mM), and hydrogenolysis of the benzyl groups. Various experiments based on fluorescence and ^1H NMR spectroscopy revealed that cyclohexamer 552 formed inclusion complexes with fluorescent ANS in water, with an association constant of $22.5 \pm 1.3 \text{ M}^{-1}$, while cyclotetramer 551 formed host–guest complexes in the presence of phenylalanine hydrochloride.

4.2. Amide Derivatives

Billing and Nilsson developed a method for the preparation of macrocyclic carbohydrate/peptide hybrids by CuAAC.¹³⁶ This straightforward synthesis is based on the coupling of azido aminoglucopyranoside 553 to the Tyr-Tyr propiolamide 554, leading to azido-alkyne glucopyranoside 555 (Scheme 65). Cyclodimerization by “click” chemistry (CuI, DIPEA, 0.2 mM in MeCN), followed by debenzoylation, yielded the expected macrocycle 556. Macrocycle containing Tyr-Arg dipeptide has also been prepared.

The group of Bhattacharjya synthesized triazolophanes with furanoside and peptidic tethers.¹³⁷ Azido-furanose 557 was transformed into peptide-linked azido-alkyne 558, which underwent intramolecular CuAAC under standard conditions

Scheme 60. Gin's CD Analogues Obtained by Cyclodimerization of a Trimannoside

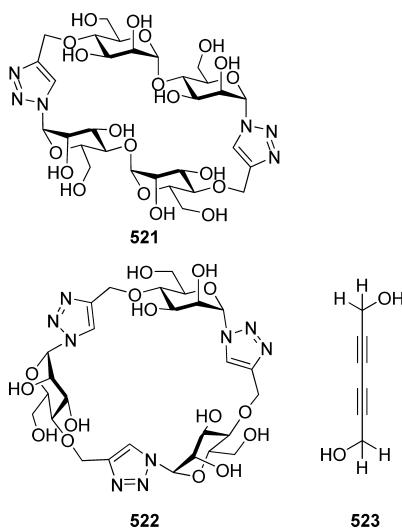
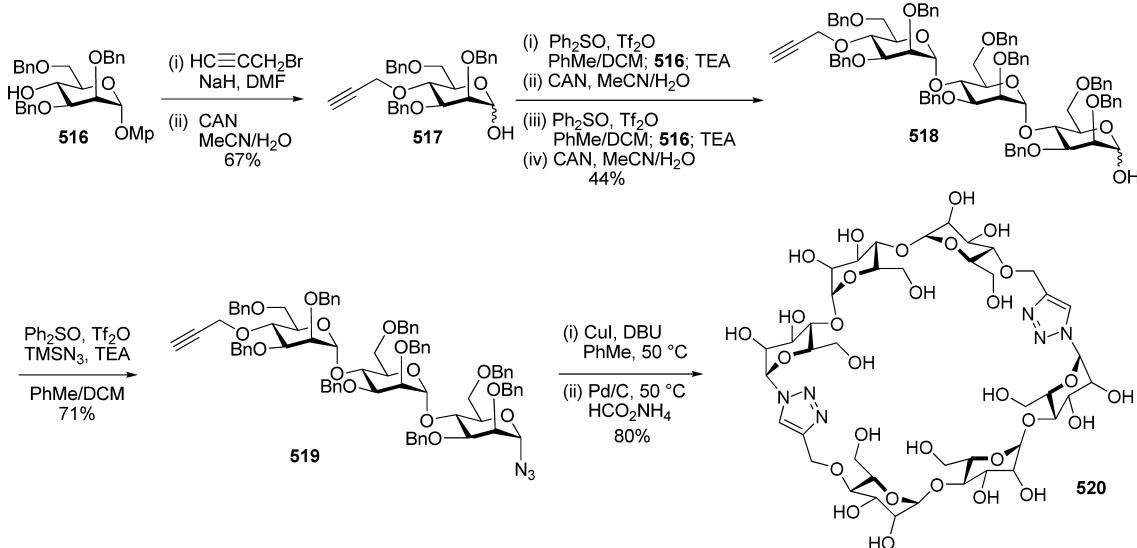
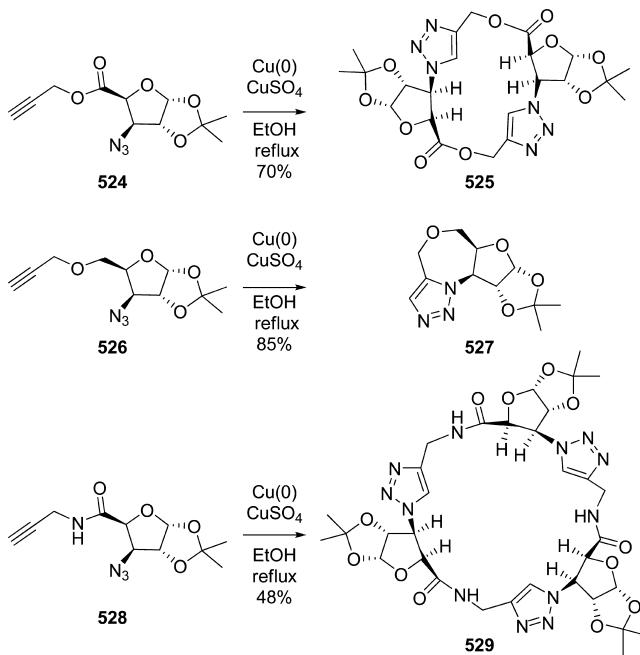


Figure 6. Structure of mannose-derived cyclic macrocycles.

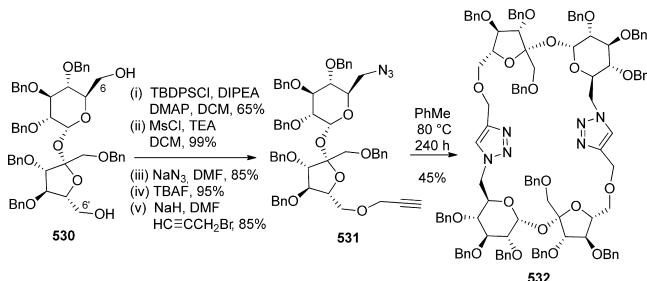
(CuSO_4 , Na-ascorbate in aqueous $t\text{-BuOH}$), yielding 31% of 559, while reaction catalyzed by CuI/DIPEA in THF led to 20% of 559 (Scheme 66).

Other structurally related macrocycles derived from galacturonic acid, containing an amide function and a triazole ring, were synthesized by the group of Plantier-Royon.¹³⁸ The synthesis began with reaction of D-galacturonic acid with methanol in the presence of acidic Amberlite IR 120-H resin, to give furanoside 560. Subsequent acetylation, $\text{BF}_3\cdot\text{OEt}_2$ -mediated glycosylation with propargyl alcohol, and deprotection afforded alkyne 561 in good overall yield, which underwent transacylation with azido amine 562 to give azido-alkyne 563 (Scheme 67). Interestingly, the outcome of the CuAAC was greatly dependent on the reaction conditions. For example, CuSO_4 in the presence of Na-ascorbate yielded monomeric macrocycle 564 as the major product, while cyclodimer 565 was exclusively formed when CuI/DIPEA was used in water (Table 1). It is to be noticed that click reaction between 561 and 562 before amidation failed to give the macrocyclic compound 564. Investigation of the complexation of Cu(II) by glycocryptand 564 by EPR, UV/vis

Scheme 61. Structural Effects in Furanose Azido-Alkyne Cyclization

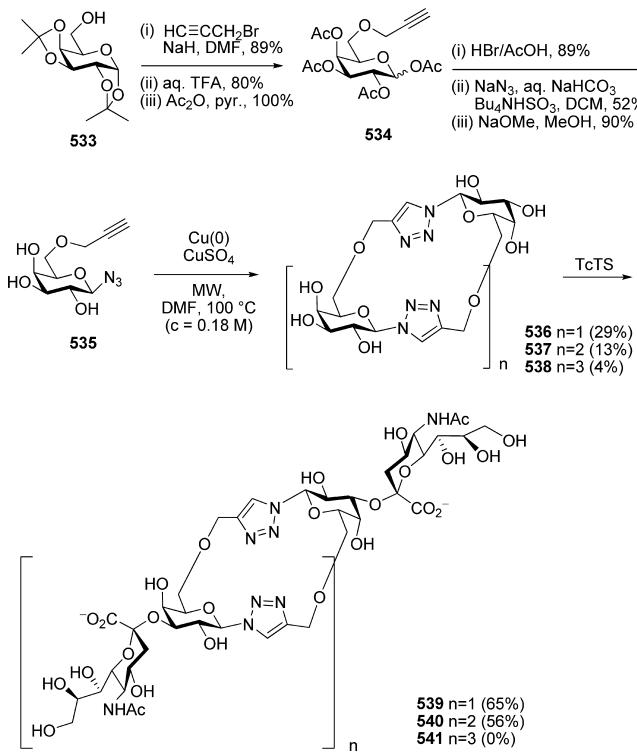


Scheme 62. Cyclodimerization of an Azido-Alkyne Derived from Sucrose



spectroscopy, and mass spectrometry suggested the formation of species [564·Cu], involving a penta-coordinated copper center.

Scheme 63. Cyclooligomerization of Galactosyl Azido Alkyne Followed by Chemoenzymatic Sialylation



Chen et al. reported a chemoenzymatic method for obtaining structurally defined macrocyclic oligosaccharides of varied sizes (Scheme 68).¹³⁹ The synthesis began with aldolase-mediated conversion of azide 566 to azido-containing sialic acid 567, which was activated in situ as the cytidine-5'-monophosphate (CMP) derivative 568. Reaction with various oligosaccharides containing a galactose at nonreducing end and a propargyl group at reducing end as sialyltransferase acceptors, followed by intramolecular CuAAC-macrocyclization, afforded a variety of macrocyclic oligosaccharides (571–577, up to 78-membered ring) in 30–91% yields. For example, enzymatic reaction of 569 with 568 afforded trisaccharide 570. Intramolecular CuAAC ([570] = 1 mM) yielded 91% of macrocycle 571. These compounds have high solubility in water and interact with small hydrophobic molecules such as *para*-toluene sulfonate or *para*-methyl benzoate in a size-dependent manner.

4.3. Macrocycles Containing Aromatic Rings

As an extension of their work on carbohydrate/peptide hybrids (see Scheme 65), Nillson and co-workers developed a modular approach to fluorescent macrocycles.¹⁴⁰ The suitably functionalized glutamic acid derivatives 578 and 579 were easily obtained through classical protecting group manipulation and amide bond formation procedures. Amine 578 was coupled to the SAA 581 with EDC and HOBr,¹⁴¹ followed by Fmoc deprotection and coupling with 579 (DIC, HOBr) to afford 582. Macrocyclization with diazide 580 in the presence of Cu(I) and DIPEA in acetonitrile under high-dilution (0.22 mM) yielded 22% of the desired 583 after 3 days at 45°C (Scheme 69).

In a similar approach, Leyden and Murphy prepared bisazide 585 in three steps from 584 and reacted it with bis-(propargyloxy)benzene 586 in the presence of CuSO_4 and Na-ascorbate in $\text{MeCN}/\text{H}_2\text{O}$ (final concentration 22 mM),¹⁴² to obtain glucotriazolophane 587 (Scheme 70).¹⁴³

A more recent example was reported by the group of Chattopadhyay, who obtained a dimeric macrocycle byproduct in the course of the synthesis of medium-ring-benzo-heterocycles.¹⁴⁴ Diacetone D-allofuranose 588 was converted to its triflate derivative and underwent nucleophilic substitution with 2-azidophenol to afford 589 (Scheme 71). After selective isopropylidene deprotection, oxidative cleavage, and treatment of the resulting aldehyde with Bestmann–Ohira’s reagent,^{145,146} alkyne 590 was isolated. Heating in DMF (120°C) under inert atmosphere at a concentration of 33 mM led to a mixture of monomeric and dimeric 1,5-disubstituted triazoles 591 and 592 in 36% and 24% yields, respectively.

In the course of the reviewing of this work, the group of Xie reported the synthesis of a series of fluorescent 23–27-membered macrocycles containing an embedded BODIPY core, various C-glucosyl amino acid units, and a triazole ring, using CuAAC for the macrocyclization.¹⁴⁷ These compounds showed a quenching of fluorescence in the presence of both cations (Cu^{2+} and Fe^{3+}) and anions (F^- and CN^-) in MeCN.

4.4. “Click” Chemistry-Assisted Macrocyclization

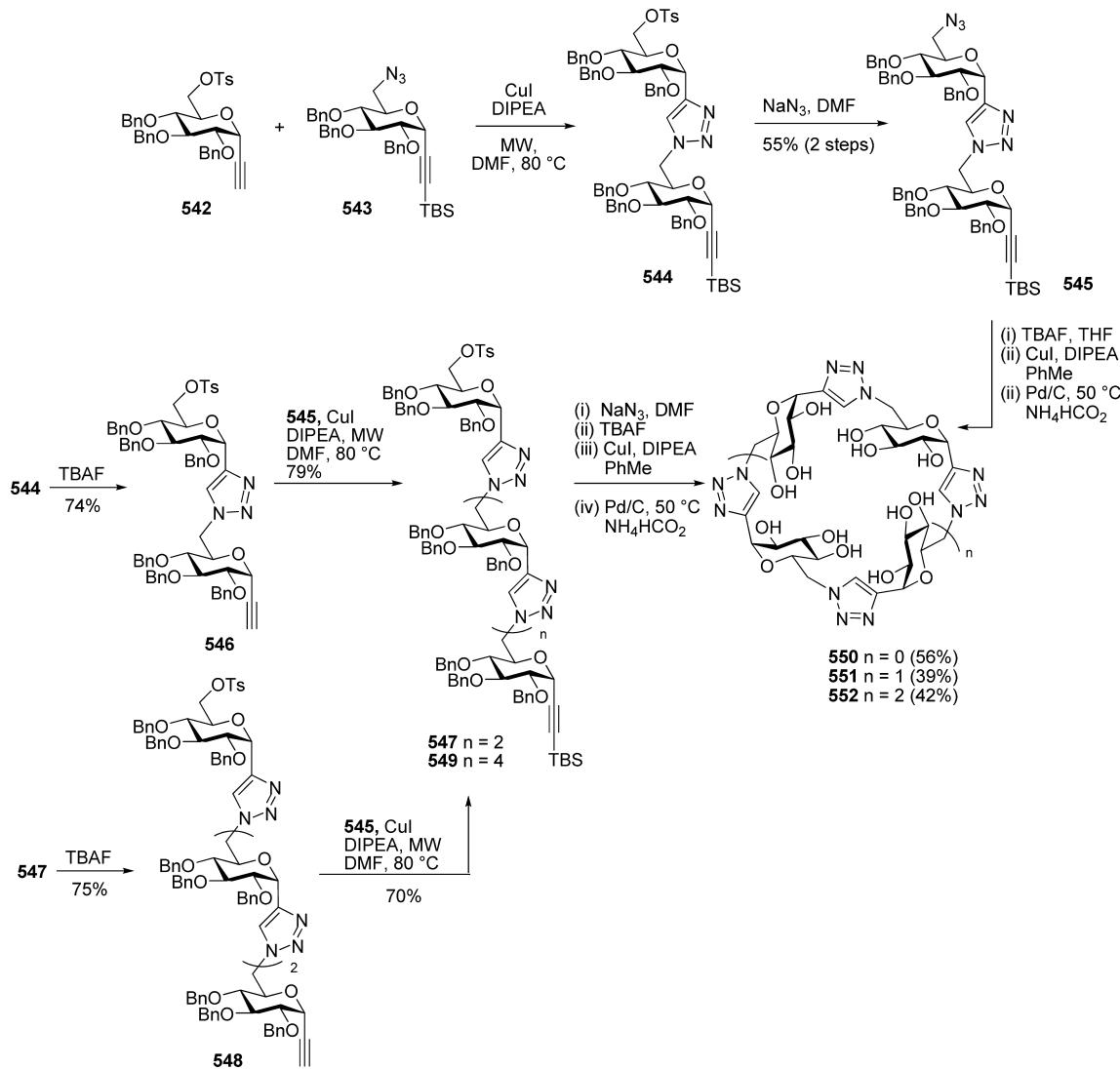
In several cases, CuAAC was used in combination with another reaction to perform the macrocyclization. For example, in 2005 Dörner and Westermann used a “click”-dimerization/ring-closing metathesis cascade for the synthesis of macrocycles 597–600 from the corresponding 6-azido glycosides 593–596 and 1,7-octadiyne (Scheme 72).¹⁴⁸

Very recently, the group of Schmidt developed a method for the preparation of disaccharide-containing macrocycles by “click” connection followed by intramolecular glycosylation.¹⁴⁹ First, orthoester 602 was obtained in three steps from glucosyl bromide 601, then deprotection, acetylation, glycosylation with thiophenol, and separation of anomers by column chromatography afforded α - and β -thioglucosides 603, which were easily converted to the corresponding 2-O-propargyl thioglucosides 604 (Scheme 73). Azido-furanose 606, synthesized in five steps from diacetone D-glucose 344, was reacted with 604β in the presence of CuI and DIPEA to give the corresponding 1,2,3-triazole 607, which, after oxidative PMB deprotection, underwent β -selective intramolecular glycosylation leading to 15-membered macrocycle 608 in 58% yield. It has been observed that the yield of macrocyclization was practically independent of the concentration of PMB-deprotected 607 in the 0.01–0.1 molar range, and reaction with 603α led also to the macrocycle 608 with the β -anomeric configuration. However, intramolecular glycosylation of *m*-xylene counterpart 609 furnished the 16-membered macrocycle 610 as a separable mixture of α - and β -anomers in a ratio of 1:3. Intramolecular glycosylation with the secondary alcohol in the case of 611 and 613 gave also the corresponding 15- or 16-membered macrocycles 612 and 614 with an α/β ratio of 3:2 and 2:1, respectively. With the conformationally more restricted glycosyl acceptor 615, glycosylation led selectively to the α (1–5)-linked disaccharide as part of 16-membered macrocycle 616 in 20% yield. In a similar way, 16- and 17-membered macrocycles containing two glucopyranosides units 617–620 have been prepared as a mixture of α/β isomers in good yield. Reducing ring size exclusively afforded the α (1–4)-linked 15-membered macrocycle 621.

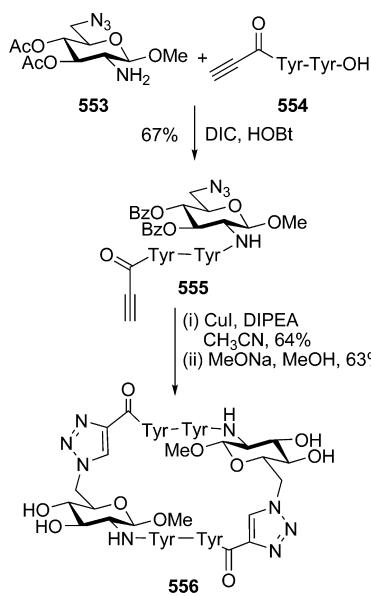
5. GLYCO-CROWN ETHER DERIVATIVES

The field of sugar-derived crown ethers has attracted considerable interest, essentially since their ion complexing

Scheme 64. Marra's Approach to Triazole-Linked Cycloglucopyranosides



Scheme 65. Billing and Nilsson's Macrocyclic Carbohydrate/Peptide Hybrids



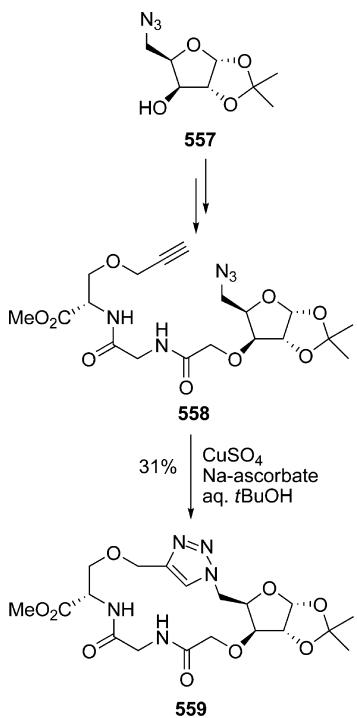
ability found applications in catalysis and enantiomeric differentiation.^{18–22} The main strategies to access these crown ether derivatives are based on intramolecular nucleophilic substitution (with cation templating), domino Staudinger aza-Wittig reaction, reductive amination, and reduction of amide-linked macrocycles. Literature from 2006 will be reviewed in this section.

5.1. Macrocycles by Intramolecular Nucleophilic Substitution

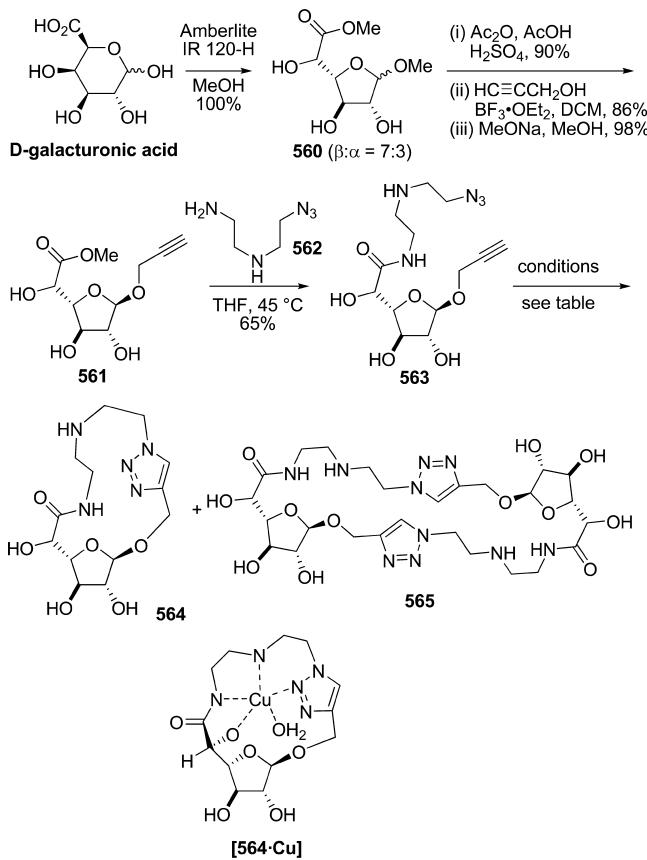
As a continuation of their extensive work in the field of chiral crown ethers based on carbohydrates, Bakó and co-workers investigated systematically the properties of sugar-based azacrown ethers such as 622–628 (Figure 7) as liquid–liquid phase transfer catalysts, focusing on the reactivity of chalcones and their analogues in asymmetric Michael addition, Darzens condensation, and epoxidation.

The synthesis of pyridino-crown ether 628 is representative of the strategy used to prepare other catalysts 622–627 and illustrates the importance of template effect in macrocyclization reactions (Scheme 74).¹⁵⁰ The authors investigated a possible correlation between the complexing ability of the two reaction partners, quantified by the relative peak intensity (PI) observed by mass spectrometry (see Table 2) and the yield of aza-crown

Scheme 66. Triazolophane with Furanoside and Peptidic Tether



Scheme 67. Plantier-Royon's "Click" Reactions of Galacturonic Acid-Derived Azido-Alkyne



ether formation. From this study, it appeared that reacting 629 (PI = 900, very strongly complexing Na⁺) with 630 (PI = 2.8,

Table 1. Conditions for the Synthesis of Macrocycles 564 and 565

conditions ^a	ratio 564/565	overall yield
CuSO ₄ , Na-ascorbate H ₂ O, rt	80:20	84%
CuI, THF/MeCN, DIPEA, rt	70:30	90%
CuI, H ₂ O, DIPEA, rt	0:100	55%

^aAll reactions were performed with [563] = 2.9 mM.

very weakly complexing Na⁺) yielded only 8% of the desired crown-ether, while reacting 631 (PI = 410, strongly complexing Na⁺) with 632 (PI = 44, weakly complexing Na⁺) led to the desired 628 in 40% yield. However, the excellent complexation activity of 634 (PI = 1450) is not enough because the secondary hydroxy groups of 633 are of low reactivity, leading to only 12% of 628. As mentioned by the authors, besides the template effect, other factors such as possible elimination of tosylates could also play a role in the outcome of the reaction.

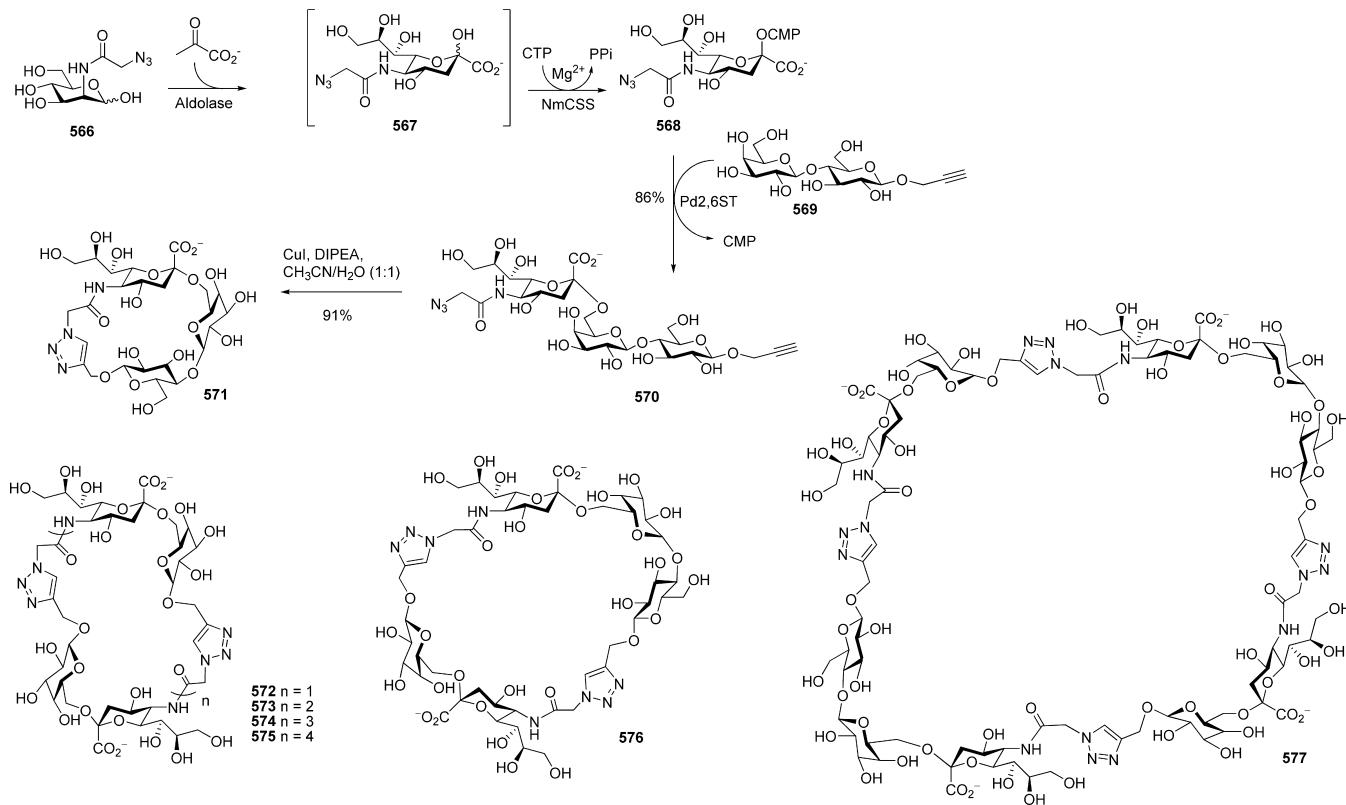
The structure–activity relations of catalysts 622–628, with various substitution patterns at 4- and 6-positions of methyl- α -D-glucopyranoside (622–625), sugar configuration (gluco- 622, manno- 626, and altro- 627), or crown ether structure (622 and 628), were compared for three model reactions: Michael addition of chalcone with 2-nitropropane, Darzens condensation of phenacyl chloride with benzaldehyde, and epoxidation of chalcone (Table 3).^{150–152} Among the catalysts tested, benzylidene protected glucopyranoside-based aza-crown 622 proved the most efficient for epoxidation and Darzens condensation (entry 1), while the best enantioselectivity for Michael addition (90%) was obtained with the naphthyl derivative 623 (Table 3, entry 2). For the epoxidation, the use of glucopyranoside-based catalysts (622–625, 628) and mannopyranoside-based crown-ether 626 results in the preferred formation of the optical antipodes of the corresponding epoxides (configuration 2R,3S for 622–625, 628 and 2S,3R for 626), while practically no asymmetric induction was observed for the altropyranoside 627.

Structural factors affecting the efficiency of epoxidation catalyzed by 622 and 627 were investigated by modifying the position of substituents on chalcone and chalcone analogues.¹⁵³ The general trends exhibited by most substituents on the aryl groups in R¹ or R² are an increase in enantioselectivity when displacing the substituents from position ortho to meta and para (Table 4). Also, the presence of a methyl group in R¹ results in no reaction, while 55% ee was obtained when a methyl group is in R².

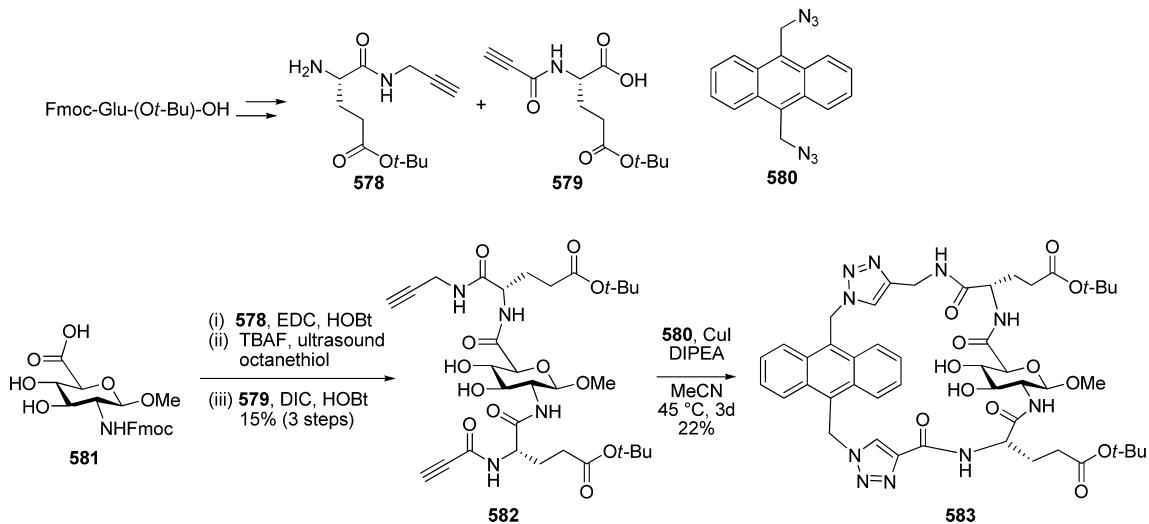
Epoxides functionalized with aromatic heterocycles were recently obtained through Darzens condensation catalyzed by 622, leading to furyl, thiienyl, or methyl pyrrolyl epoxyketones with moderate to good enantioselectivity, and poor enantioselectivity for pyrrole derivatives (Table 5).^{154,155}

This reaction was finally extended to chloro-tetralone and -indanone, affording the corresponding epoxyketones with variable yield and enantioselectivity depending on the structure of the reagents (Table 6).¹⁵⁶ Under similar reaction conditions, tetralones usually gave higher yields than their corresponding indanone; the influence of structure on enantioselectivity is however more difficult to rationalize. Nevertheless, the D-glucose-based catalyst 622 gave the best results as compared to the D-mannose-based counterpart 626, with opposite enantioselective induction.

Scheme 68. Chemoenzymatic Synthesis of Sialic Acid-Containing Macrocycles



Scheme 69. Nilsson's Fluorescent SAA/Peptide Hybrid

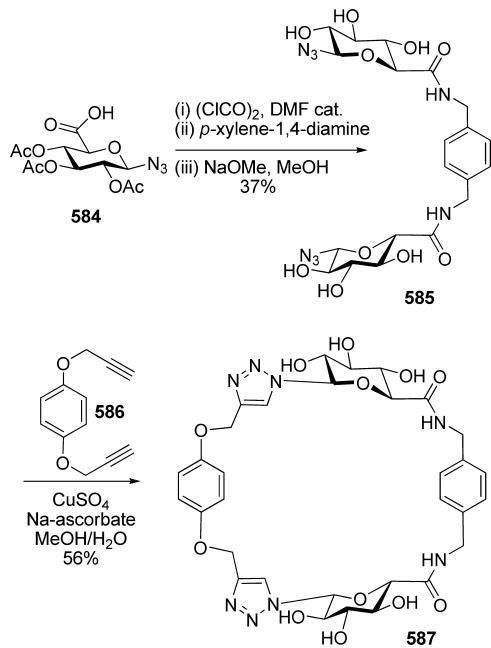
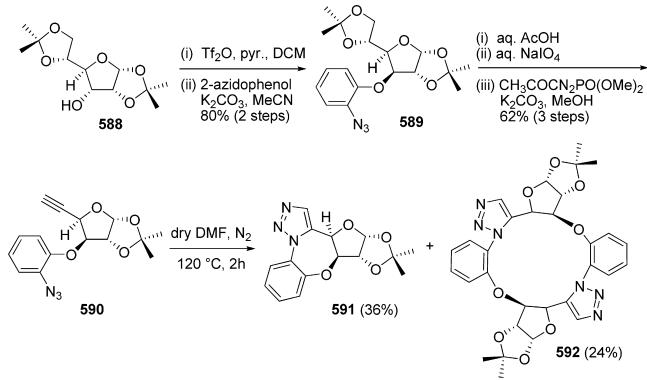
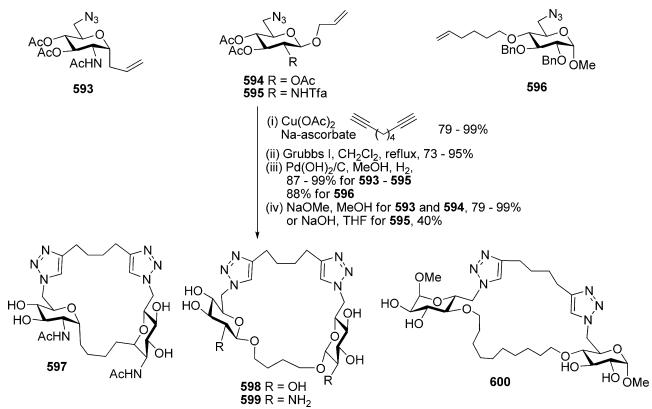


The structurally related glucose-derived crown-ether **635** catalyzed the enantioselective Michael addition of phosphonate **636** to cyano-methacrylate **637**, leading to a 6:1 diastereomeric mixture of substituted iminophosphonate **638**, obtained in 76% overall yield with 86 and 60% ee, respectively (Scheme 75).¹⁵⁷

Crown ethers containing glycolipids have also been synthesized by cation templating based on hydroxyethylated alkyl glucosides and oligoethylene glycol ditosylates.¹⁵⁸ The assembly behavior in water of a series of macrocyclic glycolipids **639–643** was studied (Figure 8). The results indicated that only **642** and **643** (with crown ether attached to the 4- and 6-positions) formed a columnar phase, while **639–641** (with crown ether attached to the 2- and 3-positions of glucose) did not

exhibit any liquid crystalline behavior. Furthermore, the presence of the macrocycle only induced a moderate increase in critical micelle concentration, as compared to the corresponding dodecyl β -glucopyranoside. The 15-crown-5 **639** and 16-crown-5 **642** showed higher affinity for Na^+ than for K^+ , while more effective K^+ -complexation was found for 21-crown-7 **641**.

Montesarchio and colleagues reported the synthesis of crown ether with a ring-fused uridine (Scheme 76).¹⁵⁹ Diacetylation of 5'-O-DMT-uridine **644** followed by Mitsunobu reaction with 2-(phenylthio)ethanol and alkaline 2',3'-O-deacetylation afforded **645** in 86% yield. Macrocyclization with penta(ethylene glycol) ditosylate in the presence of NaH in THF ($c = 47 \text{ mM}$), thioether oxidation to sulfone, and deprotection of the resulting

Scheme 70. Murphy's Glycotriazolophane**Scheme 71.** Synthesis of 1,2,3-Triazole-Fused Furobenzoxazepine Derivative and Macrocycle**Scheme 72.** Westermann's "Click"-Dimerization/Ring-Closing Metathesis Cascade

(phenylsulfonyl)ethyl and DMT groups yielded 53% of uridine-fused crown-ether 646. ^1H NMR and ESI-MS experiments supported coordination of the crown ether with a sodium ion, presumably incorporated during the NaH -promoted cyclization.

Preliminary biological evaluation of 646 showed no relevant antiviral activity.

Jarosz and co-workers synthesized di-, tri-, and tetra-aza-coronand sucrose "crowns" 649–651 and 653 from hexa-O-benzyl sucrose 530 (Scheme 77).^{160,161} Double mesylation followed by substitution with benzyl amine afforded diamine 647, which was converted into diol 648 by alkylation with bromoacetate followed by LAH reduction. Macrocyclization to 649 was performed by mesylation followed by double substitution with 1.2 equiv of benzylamine in acetonitrile under dilute conditions (3.85 mM).¹⁶⁰ Using a similar route, the authors also synthesized the macrocyclic receptors 650 and 651.¹⁶¹ Finally, double allylation of 530 followed by OsO_4 -mediated oxidative cleavage to aldehyde and NaBH_4 reduction yielded diol 652, which was converted to the desired macrocycle 653 by mesylation, benzylamine substitution, and ring closing in the presence of ethylene glycol ditosylate, under dilute conditions (3.45 mM).

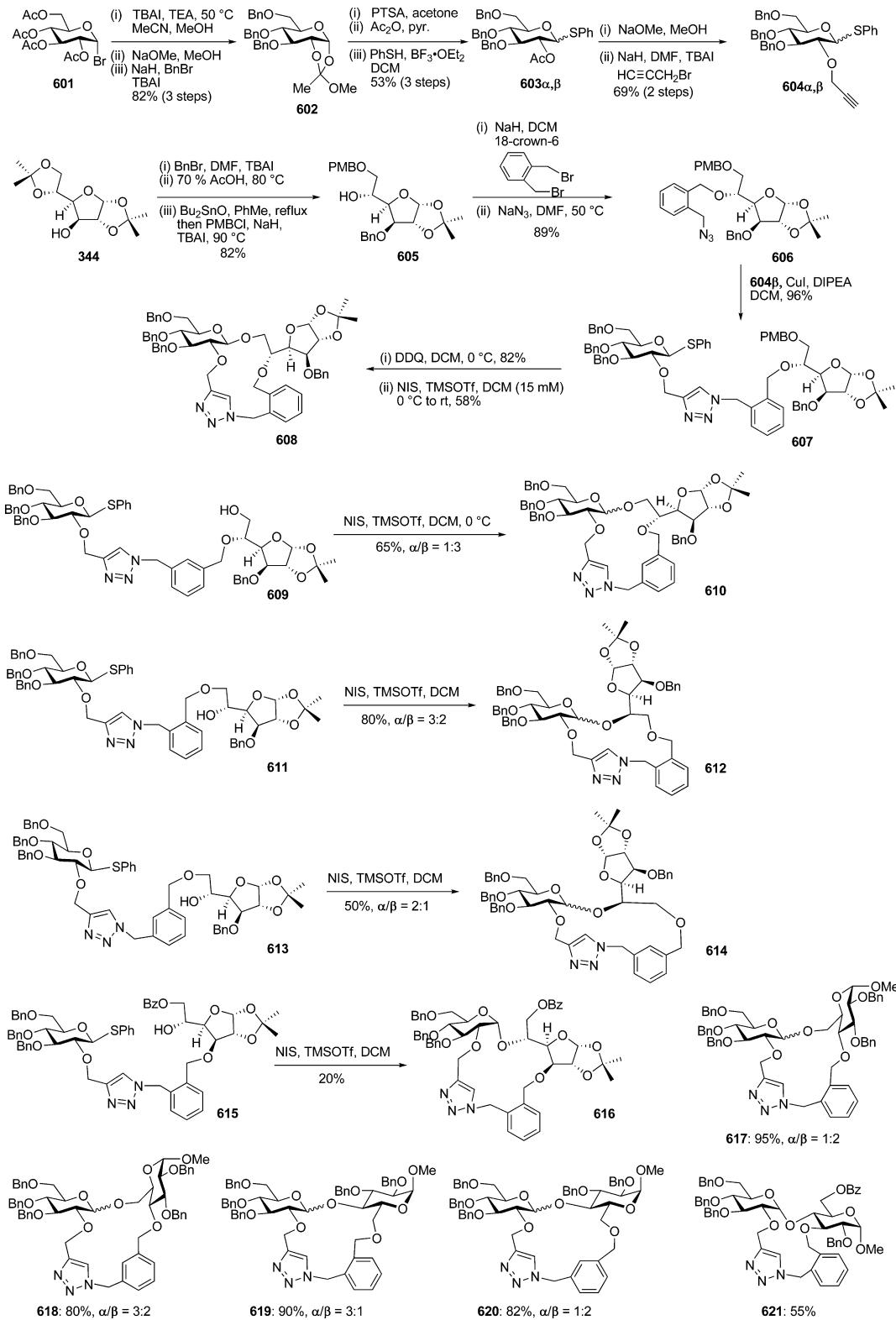
These aza-crown ethers were investigated by ^1H NMR for their ability to complex simple ammonium cations, as well as both enantiomers of α -phenylethylammonium chloride (Table 7).¹⁶¹ Receptor 649 showed higher K_a values toward all ammonium ions tested than the bigger macrocycles 650, 651, and 653. A majority of receptors showed a preferential complexation of the (*S*)-amine, but aza-crowns 650 and 653 showed remarkable complexation selectivity, because no interaction with the (*R*)-enantiomer could be observed.

Sucrose-derived C_2 -symmetrical chiral macrocycles were also synthesized by amino acid templated cyclization.¹⁶² The CuAAC between azido-sucrose 654 and dialkyne 655 afforded the C_2 -symmetrical 656, which was converted to the corresponding mesylate 657 and then reacted with ethylenediamine and Na_2CO_3 in refluxing acetonitrile ([657] = 10 mM) (Scheme 78). Interestingly, no trace of the desired product could be observed until L-phenylglycine methyl ester was added as a template, yielding 20% of 658. Noteworthy is the fact that the corresponding D-amino ester, metal cations, or simple organic compounds (aromatic molecules and H-bond donors and acceptors) were not effective as templates. The yield of macrocycle 659 increased also from 5% to 25% in the presence of this L-amino acid template.

Rathjens and Thiem disclosed a general synthetic approach for the selective construction of aza-macrocycles from monosaccharides.¹⁶³ For example, dialkylation of diethylene glycol ditosylate with glucoside 660 under phase transfer conditions gave diazide 661, which was converted into the corresponding ditosylamine by hydrogenation (without cleavage of benzyl ethers) followed by tosylation (Scheme 79). Finally, Richard-Atkins cyclization with diethylene glycol ditosylate afforded the macrocycle 663 in 54% yield.¹⁶⁴ The strength of this approach lies in its highly modular character, providing access to a variety of aza-macrocycles functionalized with various alkyl or aryl tethers in average yield above 50%. Symmetrical macrocycles containing four glucose units such as 665 have also been readily obtained by Richard-Atkins macrocyclization.

In 2011, the group of Lee reported the synthesis of new macrocyclic C-aryl glucosides as inhibitors of SGLT2, a sodium-dependent glucose transporter, recognized of therapeutic interest in the treatment of diabetes.¹⁶⁵ The rationale behind these novel cyclic structures was to obtain ring-closed analogues of Bristol-Myers Squibb's dapagliflozin (at that time in clinical trials), to modulate their physicochemical properties and possibly improve biological activity (Figure 9).

Scheme 73. Synthesis of Disaccharide-Containing Macrocycles by “Click” Chemistry and Intramolecular Glycosylation



The core of the molecule was assembled by selective lithiation of aglycone **667** followed by reaction with gluconolactone **666**, to afford an anomeric mixture of C-aryl glucoside **668** after methyl glycosylation and concomitant desilylation (Scheme 80). The pure β -anomer **669** was obtained after reduction in the presence of Et₃SiH and BF₃•OEt₂, followed by temporary peracetylation, crystallization, and deprotection. Several steps of

protecting groups manipulation led to **670**, then 6-O-alkylation with Br(CH₂)₅OTBDPS, TBDPS, and O-allyl deprotection, and iodination of the resulting primary alcohol gave iodide **671**. This compound was submitted to intramolecular O-alkylation in DMF, at a concentration of 10 mM, in the presence of K₂CO₃ and 18-crown-6, to afford macrocycle **672** after deprotection of the benzyl groups. The analogue **673**, with a shorter linker, was

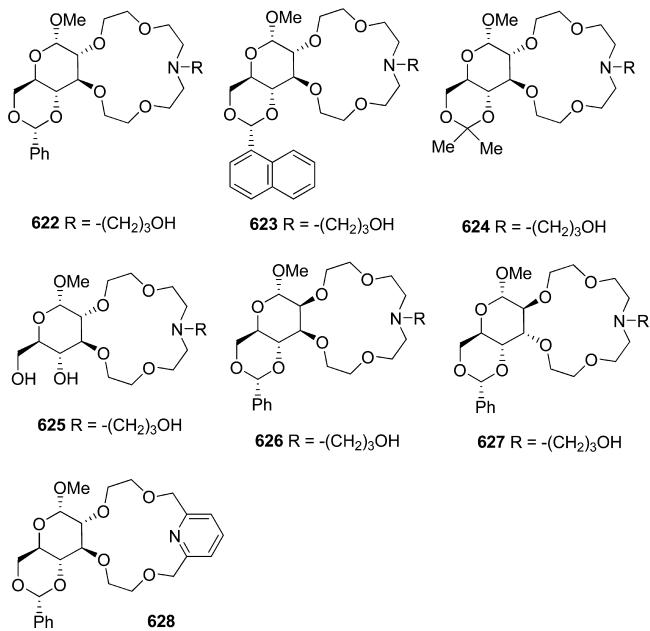


Figure 7. Bakó's monosaccharide-based chiral aza-crown ether catalysts.

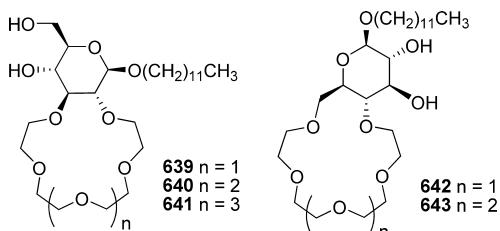


Figure 8. Heidelberg's glycolipid crown ethers.

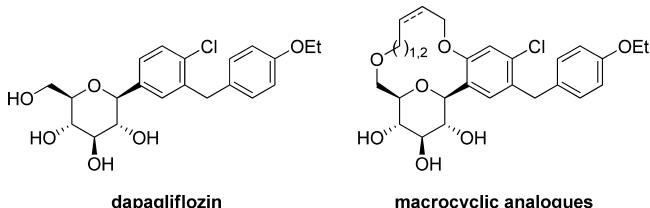
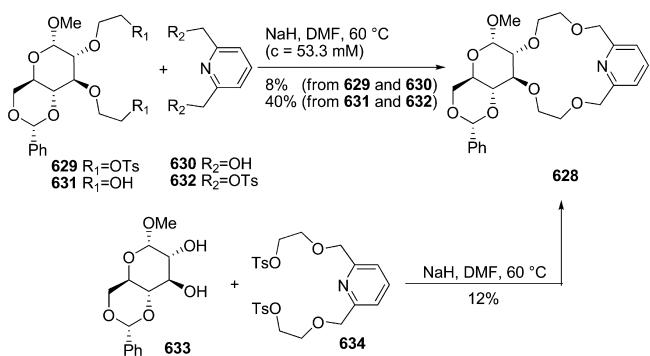


Figure 9. Structures of dapagliflozin and Lee's macrocyclic analogues.

Scheme 74. Template Effect-Mediated Synthesis of Pyridino-Crown Ether 628



obtained from the same intermediate 670 by 6-O-allylation, followed by Grubbs-II catalyzed RCM and hydrogenation of the

Table 2. Sodium Ion Binding Ability of Compounds 629–634 Deduced from the Relative Peak Intensity (PI) As Determined by FAB-MS

compounds	629	630	631	632	634
PI ^a = [M + Na] ⁺ /[M + H] ⁺	900	2.8	410	44	1450

^aRelative peak intensity as deduced from FAB-MS in the presence of sodium picrate in 3-nitrobenzyl alcohol matrix.

resulting double bond. The macrocyclic alkene 675 was synthesized from the per-acetylated C-glucoside 674.

Compounds 672 and 675 showed a slightly better inhibitory activity against hSGLT2 as compared to dapagliflozin, whereas the activity of 673 was inferior (Table 8). Encouraged by these results, the authors investigated the potential of their most active candidate to induce urine glucose excretion *in vivo*; however, 672 revealed a decreased efficacy as compared to dapagliflozin, presumably because of poor pharmacokinetic properties.

A D-glucose-conjugated 15-crown-5 ether with a spiro ketal structure 678 has been prepared from 1-C-vinyl hemiketal 676, through successive glycosylation, oxidation of vinyl group to carboxylic acid, debenzylation, and macrolactonization (Scheme 81).¹⁶⁶

5.2. Sugar-Aza-Crown Ethers by Reduction of Cyclic SAA

Xie and colleagues have obtained sugar-aza-crown (SAC) ethers 679–681 by reduction of amide bonds of the cyclic pyranoid SAA homooligomers (see Scheme 54). BH₃·THF-mediated amide reduction of cyclodimer 458 yielded 91% of the benzyl- and MOM-protected SAC 679 (Scheme 82). When the same reaction was performed on cyclotrimer 463 and cyclotetramer 464, partial deprotection of MOM groups was observed. Consequently, the corresponding SAC ethers 680 and 681 were isolated after removal of all MOM groups under acidic conditions.

5.3. Sugar-Aza-Crown Ethers by Domino Staudinger Aza-Wittig reaction

A one-pot cyclodimerization of C-glycosyl azido aldehydes via a domino Staudinger aza-Wittig reaction has been developed by Xie and co-workers to synthesize SAC ethers (Scheme 83).¹⁶⁷ Oxidative cleavage of α -C-allyl glucoside 682¹⁶⁸ with OsO₄, NaIO₄, and 2,6-lutidine afforded the azido aldehyde 683, which was first submitted to hydrogenation conditions affording almost quantitatively the cyclodiimine 684, while the desired cyclodiimine 685 was obtained only in trace amount. Treatment of 683 with polymer-bound diphenylphosphine in THF (0.1 M) yielded also efficiently the cyclic diimine 684 by inter- and intramolecular Staudinger/aza-Wittig reaction between azide and aldehyde in the presence of phosphine. Purification of cyclodiimine by simple filtration followed by reduction with NaBH(OAc)₃ and cleavage of the boron-amine adducts using Pd/C in methanol afforded the desired α -C-glucosyl-aza-crown ether 685 in 69% yield over the three steps. Using a similar procedure, glyco-aza-crown ethers 679 and 686, containing Bn or MOM/Bn protecting groups, were also synthesized. An efficient access to the β -C-glucosyl-aza-crown ether 689 was also developed from 683 by anomerization with Zn(OAc)₂/NaOMe, leading to 687, followed by the one-pot Staudinger/aza-Wittig reaction and imine reduction.

Investigation by positive-ion electrospray mass spectrometry of the affinity of SAC ethers 685, 686, and 689 toward various transition metal cations (including Cu²⁺, Ni²⁺, Co²⁺, Fe²⁺, and Zn²⁺) revealed a selective complexation of Cu²⁺ with a 1:1 stoichiometry for the three macrocycles.¹⁶⁹ This study also

Table 3. Yields and Enantioselectivities Induced by Chiral Aza-Crown Ether Catalysts 622–628

Michael addition: Ph-CH=CH-C(=O)-Ph reacts with 2-nitropropane (2.3 equiv) in the presence of 7 mol% catalyst 622, t-BuONa (0.35 equiv), PhMe, rt, to yield a product with ee %.

Darzens condensation: Ph-CH=CH-C(=O)-Cl reacts with PhCHO (1.5 equiv) in the presence of 7.7 mol% catalyst 623, 30% aq. NaOH (5.8 equiv), PhMe, rt, to yield a product with ee %.

Epoxidation: Ph-CH=CH-C(=O)-Ph reacts with t-BuOOH (2 equiv) in the presence of 7 mol% catalyst 628, 20% aq. NaOH (3.5 equiv), 0 to 4 °C, to yield an epoxide product with ee %.

entry	catalyst	Michael addition		Darzens condensation		epoxidation ^a	
		yield %	ee %	yield %	ee %	yield %	ee %
1	622	53	85	74	62	50, ¹⁵¹ 82 ¹⁵²	92, ¹⁵¹ 94 ¹⁵²
2	623	49	90	75	48	46	89
3	624	34	80	61	42	59	67
4	625	35	24	76	31	21	18
5	626					67 ^b	82 ^b
6	627					51	3
7	628	48	72 ^c			38	54

^aAbsolute configuration: 2R,3S. ^bAbsolute configuration: 2S,3R. ^cAbsolute configuration: S.

Table 4. Asymmetric Epoxidation of Chalcone and Analogs with Different R¹ and R² Substituents

Chalcone (R¹-C(=O)-CH=CH-R²) reacts with 622 (7 mol%), t-BuOOH (2 equiv), 20% aq. NaOH (3.5 equiv), PhMe, 0–2 °C, to yield an epoxide product with ee %.

entry	R ¹	R ²	yield %	ee %
1	2-MeO-C ₆ H ₄	Ph	69	84
2	3-MeO-C ₆ H ₄	Ph	77	88
3	4-MeO-C ₆ H ₄	Ph	58	95
4	Ph	2-MeO-C ₆ H ₄	49	62
5	Ph	3-MeO-C ₆ H ₄	78	82
6	Ph	4-MeO-C ₆ H ₄	79	85
7	Me	Ph	no reaction	
8	Ph	Me	60	55

Table 5. Asymmetric Darzens Epoxidation of 2-Chloroacetyl Heterocycles with Aromatic Aldehydes

2-Chloroacetyl heterocycle (X-C(=O)-CH₂-Cl) + aromatic aldehyde (R-C(=O)-H) reacts with 622 (7.5 mol%), 30% aq. NaOH (4 equiv), PhMe, 0–5 °C, to yield an epoxide product with ee %.

entry	X	R	yield %	ee %
1	O	Ph	55	54
2	O	2-Cl-C ₆ H ₄	77	70 (91 ^a)
3	O	3-Cl-C ₆ H ₄	61	60
4	O	4-Cl-C ₆ H ₄	67	62
5	S	Ph	63	71 (84 ^a)
6	S	2-Cl-C ₆ H ₄	53	51
7	S	4-Cl-C ₆ H ₄	54	65 (79 ^a)
8	NH	Ph	33	36
9	NMe	Ph	80 ^b	79

^aAfter recrystallization. ^bReaction with 10% aq KOH in 96% EtOH at 22 °C.¹⁵⁴

evidenced a strong influence of the nature of the substituents at O-2 and O-4 on the complexation ability of the SAC ethers, with 685 (containing methoxy groups) being significantly more efficient than 686 (containing benzyloxy groups). Furthermore, the efficiency of Cu²⁺-complexation was also affected by the stereochemistry of the macrocycle, because the β-configured SAC ether 689 proved to be a better complexing agent than its corresponding α-anomer 685.

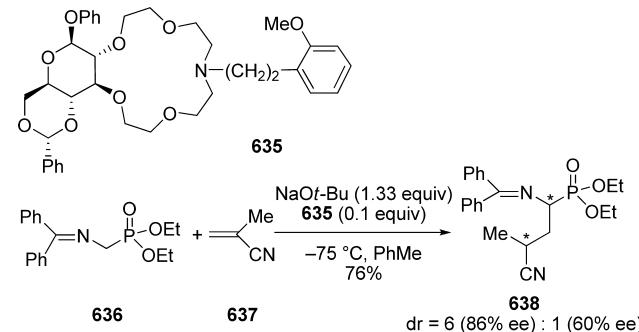
Table 6. Asymmetric Darzens Epoxidation of Chloro-indanone (*n* = 1) and Chloro-tetralone (*n* = 2) with Aromatic Aldehydes

Chloro-indanone (n=1) or chloro-tetralone (n=2) + aromatic aldehyde (R-C(=O)-H) reacts with 622 (7.5 mol%), 30% aq. NaOH (4 equiv), PhMe, -10–0 °C, to yield an epoxide product with ee %.

entry	n	R	yield %	ee %
1	1	Ph	59	65 (70 ^a)
2	1	2-Cl-C ₆ H ₄	52	85
3	1	4-NO ₂ -C ₆ H ₄	16	0
4	2	Ph	84	74
5	2	2-Cl-C ₆ H ₄	84	36
6	2	4-NO ₂ -C ₆ H ₄	51	75

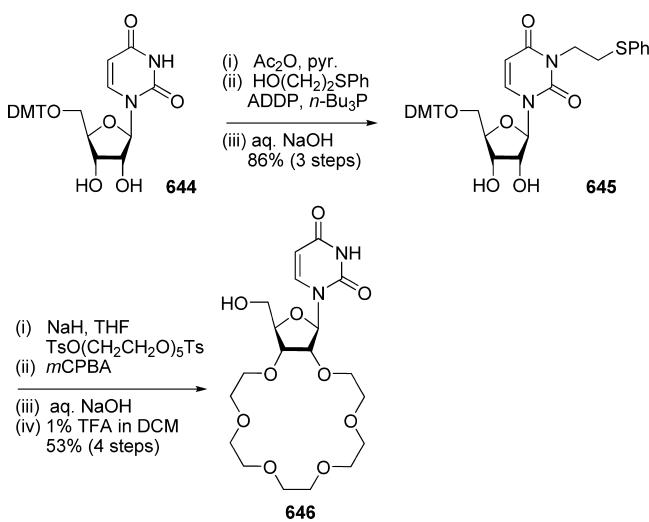
^aAfter recrystallization.

Scheme 75. Synthesis of Enantioenriched Phosphonate



The α- and β-C-glucosyl-aza-crown ethers 679 and 689 were converted to the fluorescent chemosensors 690 and 691, respectively, by treatment with *N*-(1-pyrenyl)chloroacetamide (Scheme 84).¹⁷⁰ Both 690 and 691 displayed a Cu²⁺-sensitive fluorescence quenching with a 1:1 stoichiometry and association constants of 5.0×10^6 and $6.3 \times 10^7 \text{ M}^{-1}$ in MeOH, respectively. Conformational analysis by DFT calculations indicated that in the absence of cation, both compounds are free to adopt many accessible conformations and are thus flexible enough to form pyrene excimers. However, in the presence of Cu²⁺, the cation is coordinated with the two carbonyl groups and the sugar-aza-crown ethers, which rigidified the complex and placed the two pyrene moieties far apart. The quenching effect was rationalized

Scheme 76. Synthesis of a Crown Ether Ring-Fused Uridine Analogue



on the basis of photoinduced electron transfer (PET) from the excited pyrene to the complexed Cu^{2+} cation.

5.4. Macrocycles by Reductive Amination

Wu and co-workers synthesized furanoid analogues of Xie's sugar-aza-crown ethers from C-ribosyl azido aldehyde by reductive amination.¹⁷¹ The azido β -C-riboside ester **692** was reduced to the corresponding aldehyde **693** using DIBAL-H, and epimerized to the α -anomer **694** with $\text{Zn(OAc)}_2/\text{MeONa}$ (Scheme 85). Reductive amination in MeOH (0.2 M) yielded 80% of the desired macrocyclic SAC ether **695**. Double N-alkylation with propargyl bromide afforded **696**, which was reacted with 9,10-di(azidomethyl)anthracene using $(\text{EtO})_3\text{P-CuI}$ as catalyst in toluene ($[696] = 52 \text{ mM}$) under microwave irradiation, to give fluorescent cavitand **697** in 35% yield.¹⁷² Using similar methods, dipyrone **698** and dianthracene **699** were also synthesized.^{173,174} Cavitand **697** selectively binds Cu^{2+} in MeOH (1:1 stoichiometry, $K_a = 2.5 \times 10^4 \text{ M}^{-1}$) resulting in an ca. 395% fluorescence enhancement as compared to the free

cavitand.¹⁷² Likewise, **698** exhibits selective recognition properties toward Hg^{2+} and Cu^{2+} and an increase in fluorescence emission (ca. 128% and 51%, respectively), although the association constant in MeOH was significantly lower than that reported for **697** ($K_a = 4.4 \times 10^3$ and $7.4 \times 10^1 \text{ M}^{-1}$, respectively).¹⁷³ The fluorescence enhancement exhibited by **697** and **698** was ascribed to a PET occurring upon complexation of the nitrogen atoms by metal ion. In contrast, the fluorescence of **699** was quenched upon addition of Hg^{2+} and Cu^{2+} (82% and 92% inhibition, respectively), presumably as a consequence of a reverse PET mechanism involving electron donation from the excited anthracene units to the triazole groups.¹⁷⁴ Reductive amination of β -glycosyl aldehyde **693** led however to the tricyclic lactam through intramolecular cyclization. Consequently, the corresponding SAC ether **701** was synthesized from furanoid SAA **692**, by stepwise preparation of a linear disaccharide, intramolecular cyclization to cyclic SAA **700**, and reduction by LAH under microwave irradiation conditions.

6. MACROCYCLES CONTAINING ALKyne LINKAGES

Oxidative coupling has been by far the most widely used method for the synthesis of macrocycles containing alkyne linkages, although several sugar-derived benzannulated chiral macrocycles have been recently synthesized by base-free Sonogashira reaction.¹⁷⁵

6.1. Oxidative Coupling

In a seminal work by Bürli and Vasella,¹⁷⁶ the C_3 -symmetrical cyclotrimer **707** was synthesized using orthogonal $C\text{-SiMe}_3$ and $C\text{-GeMe}_3$ alkyne protecting groups.^{177,178} Triol **702** was converted either to the bromoalkyne monomer **703** by acetylation and bromination using $\text{CBr}_4/\text{PPh}_3$ or to the (trimethylgermyl)alkyne **704** by methoxymethylation followed by alkyne-deprotonation with EtMgBr , treatment with Me_3GeCl , and TMS deprotection (Scheme 86). Heterodimer **705** was obtained by diyne coupling of **703** and **704** followed by desilylation. Further coupling with bromoalkyne **703**, followed by bromodegermylation with CuBr/NBS , afforded trimer **706**. Finally, the desired cyclotrimer **707** was isolated in five steps and 62% yield after deprotection of acetyl and TMS groups,

Scheme 77. Synthesis of Sucrose-Derived Coronands

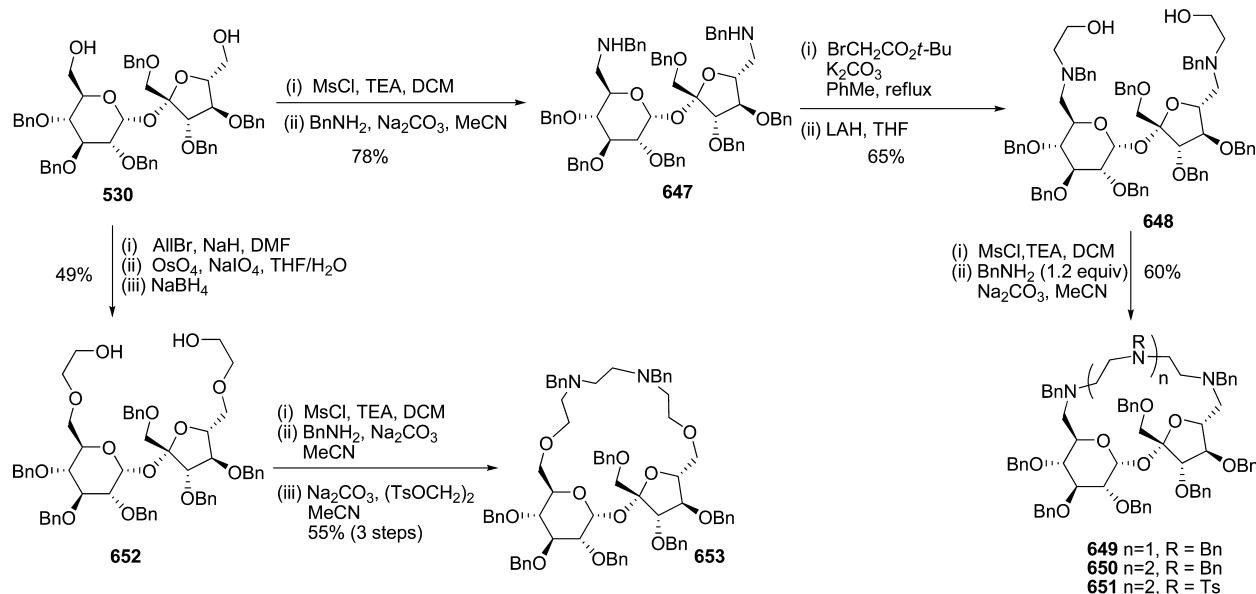
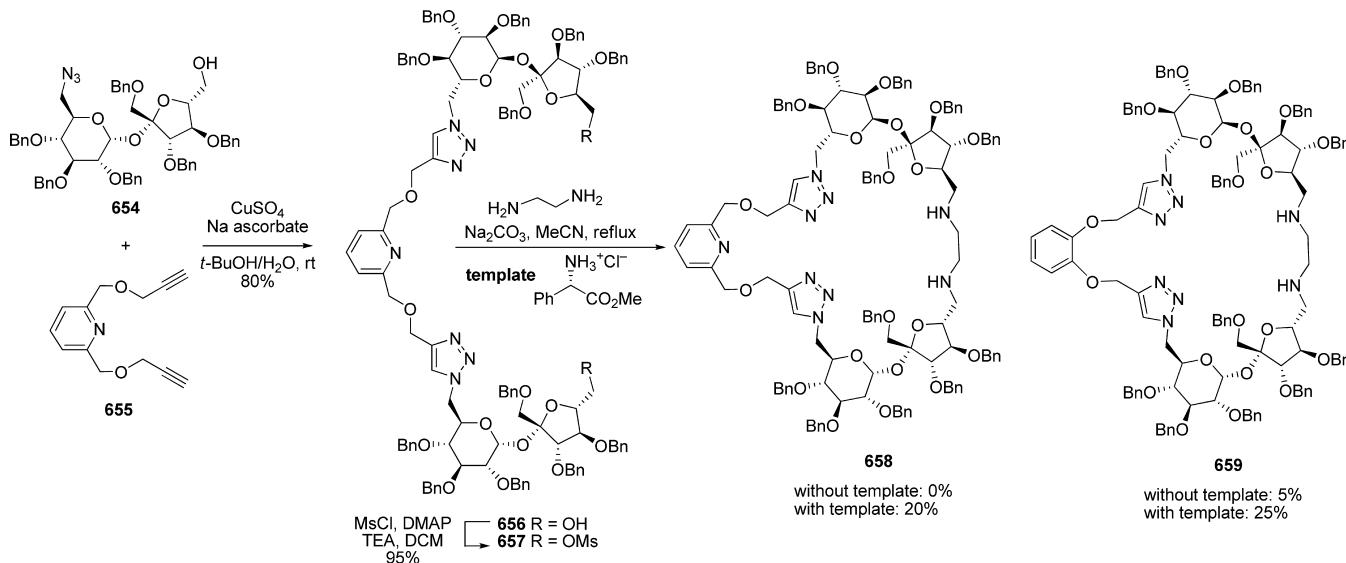


Table 7. Stability Constants for Complexes of Aza-Crowns with Various Ammonium Cations^a

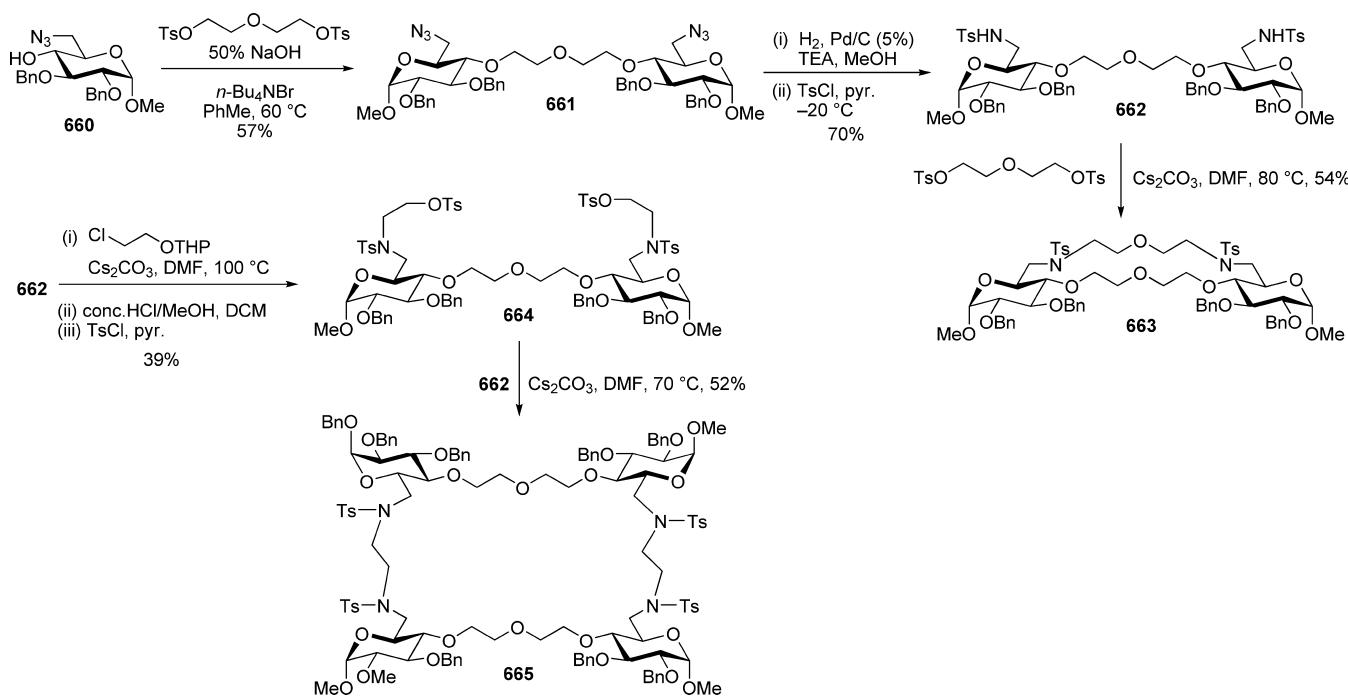
entry	receptor	$K_a (\text{NH}_4^+)^b$	$K_a (\text{S}(-)\text{-PhCHMeNH}_3^+)^c$	$K_a (\text{R}(+)\text{-PhCHMeNH}_3^+)^c$
1	649	560 ± 36	1244 ± 192	837 ± 104
2	650	129 ± 10	264 ± 36	^d
3	651	112 ± 18	^d	^d
4	653	230 ± 18	945 ± 221	^d

^aExpressed in M⁻¹. ^bCounteranion: SCN⁻, measured in acetone-d₆. ^cCounteranion: Cl⁻, measured in CDCl₃. ^dNo complex observed.

Scheme 78. Amino Acid Template-Assisted Macrocyclization of Triazolyl-Sucrose Derivatives



Scheme 79. Synthesis of Aza-Macrocycles by Richman–Atkins Cyclization



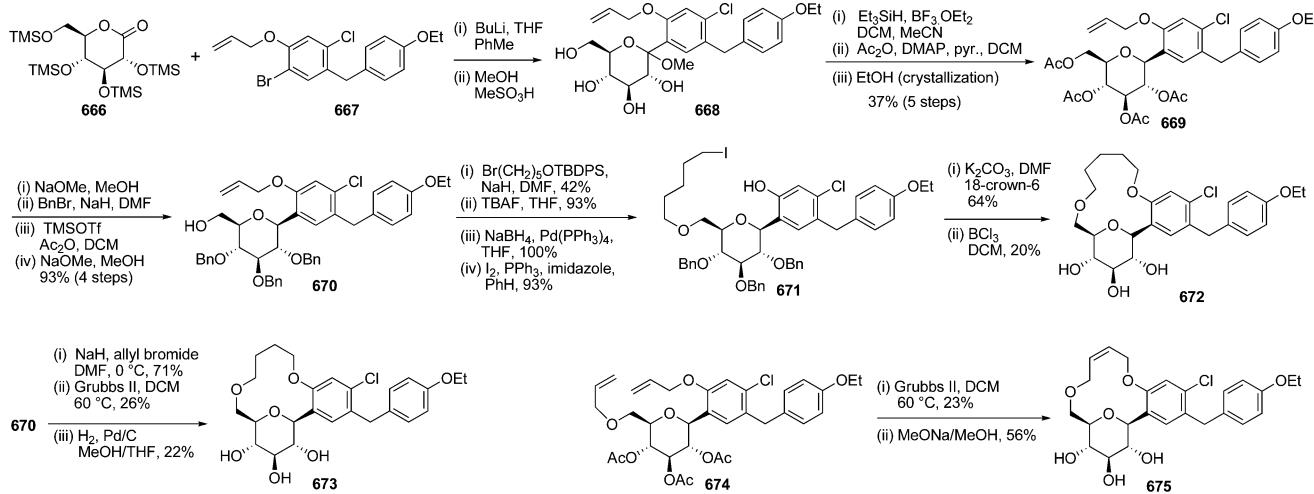
macrocyclization by diaryle coupling in dilute DMSO (0.59 mM), and protection/deprotection sequences. Extension of this work allowed the preparation of the structurally related 2-acetamido-2-deoxy-D-glucopyranose analogue 708 (Figure 10).¹⁷⁹

The *D*₂-symmetric cyclotetramer 709 (together with *D*₃-symmetric cyclohexamer 710 and *D*₄-symmetric cyclooctamer

711 as byproducts) and its *C*₁-, *C*₂-, and *C*₄-symmetric analogues 712, 713, and 714, respectively, were also synthesized (Figure 10).^{180,181}

Macrocycle 709 binds D- or L-adenosine in a 1:1 stoichiometry with a higher association constant than isomers 713 and 714 (Table 9).^{180,181} These results were explained by significant

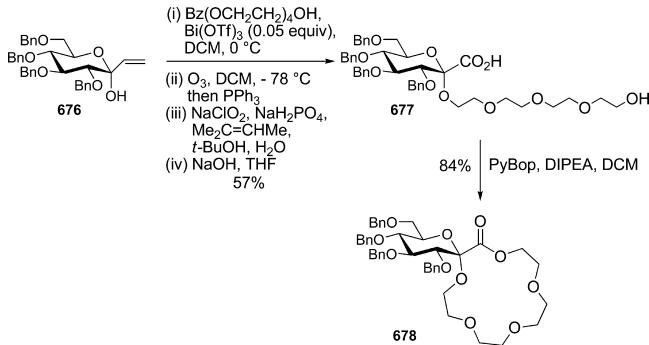
Scheme 80. Synthesis of Macrocyclic Analogues of Dapagliflozin

Table 8. In Vitro Inhibitory Activity Against *h*SGLT2 and in Vivo Urine Glucose Excretion (UGE)

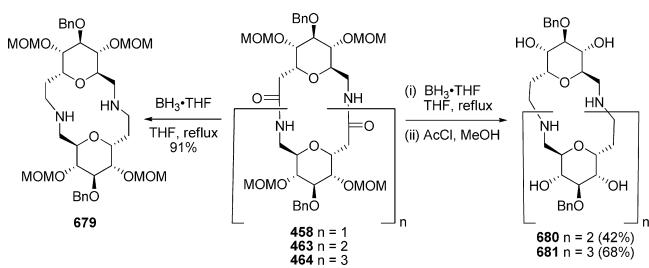
compound	<i>h</i> SGLT2 IC ₅₀ (nM)	UGE ^a
dapagliflozin	1.35	1648
672	0.899	226
673	2.27	nd
675	0.974	nd

^aValues determined in rats, expressed in mg/200 g body weight.

Scheme 81. Synthesis of D-Glucose-Conjugated 15-Crown-5 Ether with a Spiro Ketal Structure



Scheme 82. Synthesis of SAC Ethers by Reduction of Cyclic SAAs



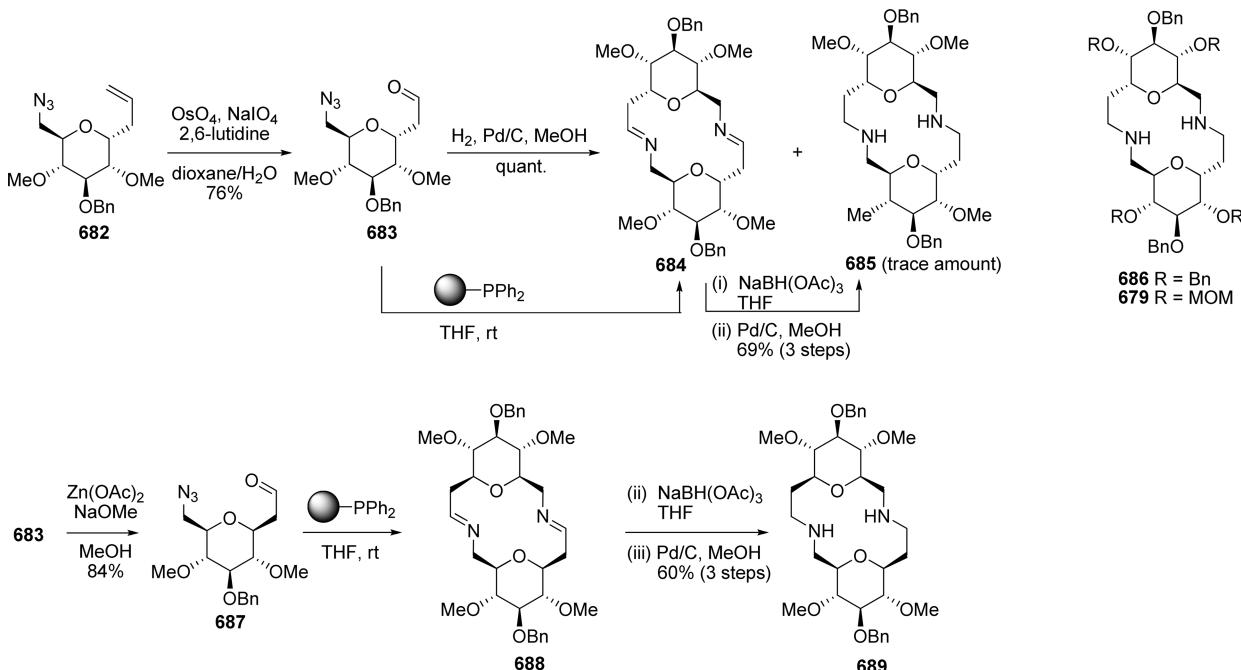
differences in the shape and size of the internal cavity. The *D*₂-symmetric 709 notably shows a shorter distance between two opposite buta-1,3-diyne-1,4-diyil groups (ca. 7.7 Å) as compared to other isomers (distances ranging from 8.4 to 11.0 Å), which may enhance the host/guest interaction and increase desolvation of the aromatic moiety of adenosine.

Cyclic hybrids of 2,2'-bipyridine and acetylenosaccharides such as 717 were also synthesized by coupling of 702 with dibromo-dipyridine 715 to afford 716, which underwent desilylation and Cu(OAc)₂-mediated oxidative cyclization in dilute pyridine (0.91 mM), followed by in situ acetylation to facilitate removal of copper salts and deacetylation (Scheme 87).¹⁸² These compounds were tested for ion complexation in H₂O. Among the various cations tested, Zn²⁺ and Ni²⁺ proved especially interesting because the former selectively induced a bathochromic shift in the UV spectrum of the cyclic disaccharide 717, while the latter was specific to the linear disaccharide 716, presumably forming 1:2 or 1:3 complexes with the bipyridine moiety.

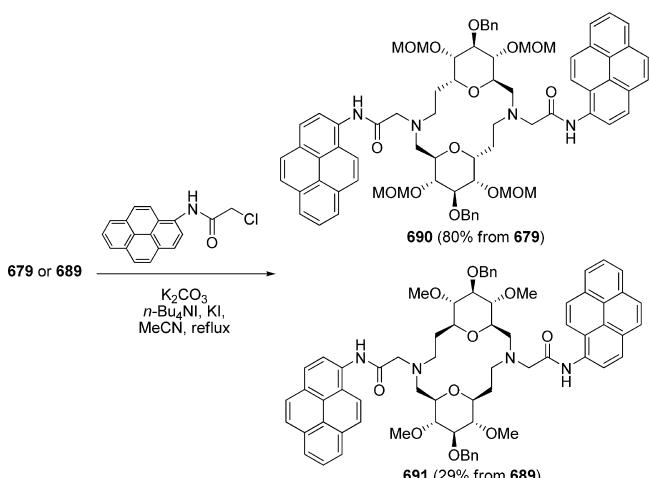
Stichler-Bonaparte and Vasella investigated the synthesis, structure, and properties of novel cyclodimeric α -mannopyranosyl-acetylenes (Scheme 88).¹⁸³ O-TIPS protection of 1,6-anhydro sugar 718 followed by *trans*-dialixal opening of epoxide with lithium (trimethylsilyl)acetylidyde (LiTMSA) in the presence of AlMe₃ and silylation of the resulting secondary alcohol afforded 719 as a single isomer. Further reaction with LiTMSA in the presence of AlCl₃ and TMS deprotection gave the desired α -D-mannopyranosyl-diacetylene 720. Oxidative treatment with Cu(OAc)₂ in pyridine at 23 °C yielded 77% of linear dimer 721, which underwent cyclization to 722 under the same conditions (1 mM) at 100 °C. Interestingly, this strained cyclic compound decomposed within several days at room temperature, and DSC analysis evidenced an irreversible exothermic transition of 63 kcal/mol in the temperature range of 185–205 °C, while precursor 722 showed only an endothermic transition (melting) at 118 °C. Reduction of the triple bonds by hydrogenation afforded 723, which was deprotected to 724 by TBAF. Both compounds were thermally stable, with melting points of 218–220 and 212–213 °C, respectively.

Analogues of γ -CD containing buta-1,3-diyne-1,4-diyil and butane-1,4-diyil units were also synthesized (Scheme 89).¹⁸⁴ Acetolytic ring cleavage of per-O-acetylated- α -CD gave the fully acetylated hexamaltosaccharide 726 ($\alpha/\beta > 9:1$), which was converted to the deprotected phenyl thioglycoside 727 in two steps. The 4,6-O-benzylidene acetal 728 was prepared by reaction with α,α -dibromotoluene in pyridine followed by per-O-4-chlorobenzylation. Glycosylation of the acceptor 729 was performed under standard conditions (NIS, TfOH, Et₂O) to yield 95% of the desired heptasaccharides ($\alpha_5\alpha$)-730 and ($\alpha_5\beta$)-

Scheme 83. Synthesis of SAC Ethers by Domino Staudinger Aza-Wittig Reaction



Scheme 84. Xie's Fluorescent SAC Ethers



731 in a 5:4 ratio, respectively. Debenzylidenation of 730 followed by tin-alkoxide-mediated regioselective 4-chlorobenzylation afforded alcohol 732 (Scheme 90). Subsequent glycosylation with 733 yielded 84% of octasaccharides ($\alpha\alpha_5\alpha$)-734 and ($\beta\alpha_5\alpha$)-735 (5:4 ratio), separable by column chromatography. Treatment of 734 and 735 with Cu(OAc)₂ in a pyridine-acetonitrile mixture (ca. 0.5 mM) gave, after FeCl₃-mediated de-4-chlorobenzylation, the isomeric cyclic diynes 736 and 737, respectively. Hydrogenation of benzyl protected ($\alpha\alpha_5\alpha$)- and ($\beta\alpha_5\alpha$)-octasaccharides afforded the CD analogues containing a butane-1,4-diyi unit 738 and 739. Molecular modeling indicated significantly different shapes between these compounds.

The group of Wilcox reported the stereoselective synthesis of the diyne glycophane 744 (Scheme 91).⁵⁴ The synthesis started with reduction of ribofuranolactone 162 with DIBAL-H, followed by lithioacetylene stereoselective addition leading to the open-sugar diol, and monotosylation, which induced the intramolecular nucleophilic substitution to the C-ribofuranoside

740. Subsequent desilylation, Mitsunobu reaction, hydrazinolysis, and tosylation of the resulting amine function led to the C-alkynyl sulfonamide 741. After alkylation with the bischloride 742, conversion of bis-C-glycosyl sulfonamide to trifluoroacetamide 743 was necessary for amine deprotection. The cyclization was realized by an oxidative alkyne coupling in pyridine (3 mM) using a thermal flow reactor in 28% yield. Removal of trifluoroacetyl group led to the target chiral glycophane 744.

In an effort to access cage-like molecules possessing electron-rich cavities, Belghiti et al. synthesized glycophanes 748 and 749 (Scheme 92).¹⁸⁵ The Ferrier rearrangement of tri-O-acetyl glucal 745 with BF₃·OEt₂ and 2-butyne-1,4-diol afforded dimer 746 (α -anomer exclusively), which was converted in three steps into bis-acetylene 747. Intramolecular cyclization by oxidative homocoupling was performed in the presence of Cu(OAc)₂, leading to compound 748 in 47% yield. Glycophane 749 was prepared in a similar way.

Very recently, Mukherjee and colleagues developed an intramolecular base-free Sonogashira reaction for the synthesis of benzannulated chiral macrocycles embedded in carbohydrate templates.¹⁷⁵ O-Propargyl-O-ortho(or para)bromobenzyl furanoses and pyranosides readily underwent intramolecular Sonogashira reaction in the presence of recyclable heterogeneous Pd catalyst (prepared by using basic alumina as the solid support) and CuI in THF to give 10–13-membered macrocycles 751–764 in good yields (Scheme 93).

6.2. Diyne Derivatization

Vasella's macrocycles such as 765, synthesized according to the methods described above, served as a precursor for the preparation of the thiophene-containing CD analogue 766, by treatment with Na₂S·9H₂O (Scheme 94).¹²⁶

Scheme 85. Wu's Synthesis of Fluorescent Furanoid SAC Ethers

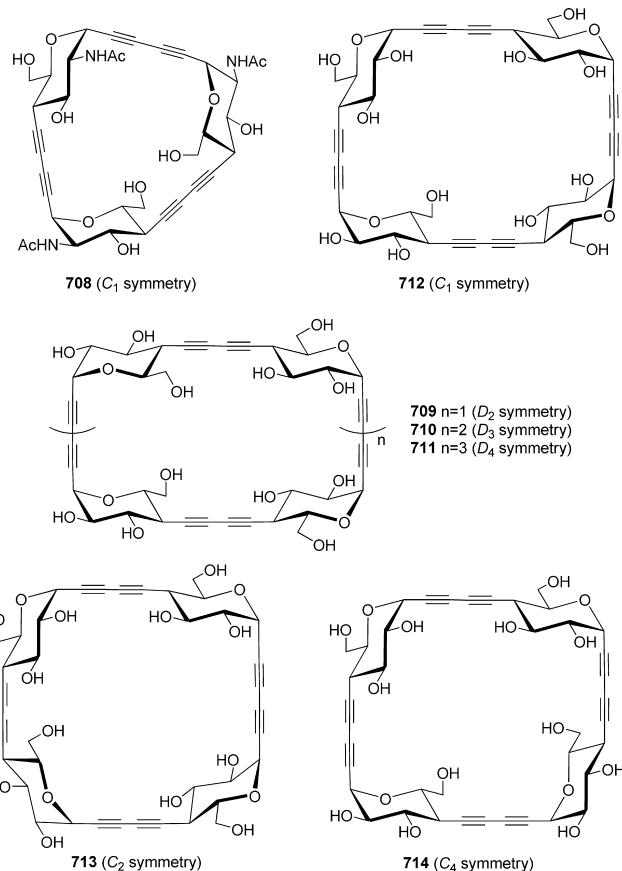
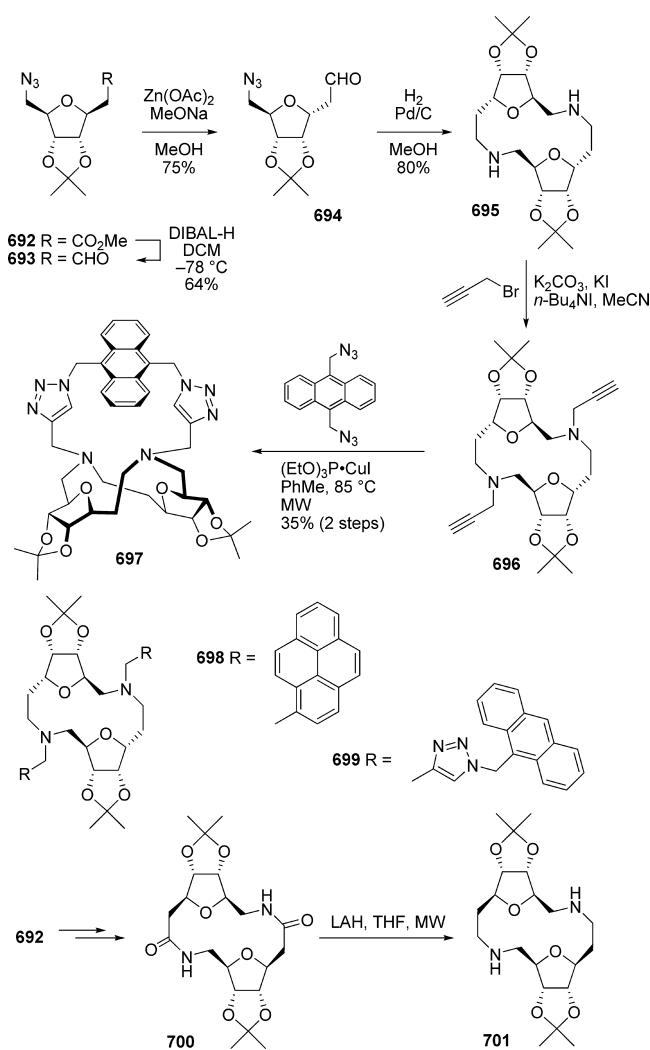


Figure 10. Acetyleno-saccharide-derived cyclodextrin analogues with various symmetry.

7. MACROCYCLES CONTAINING UREA, THIOUREA, CARBAMATE, AND GUANIDINE LINKAGES

7.1. Addition to Isocyanate/Isothiocyanate

Chong and Petillo reported the synthesis of symmetric carbamate-containing di-, tri-, and tetrameric macrocycles

Scheme 86. Synthesis of Acetyleno-Saccharide-Derived Cyclodextrin Analogues

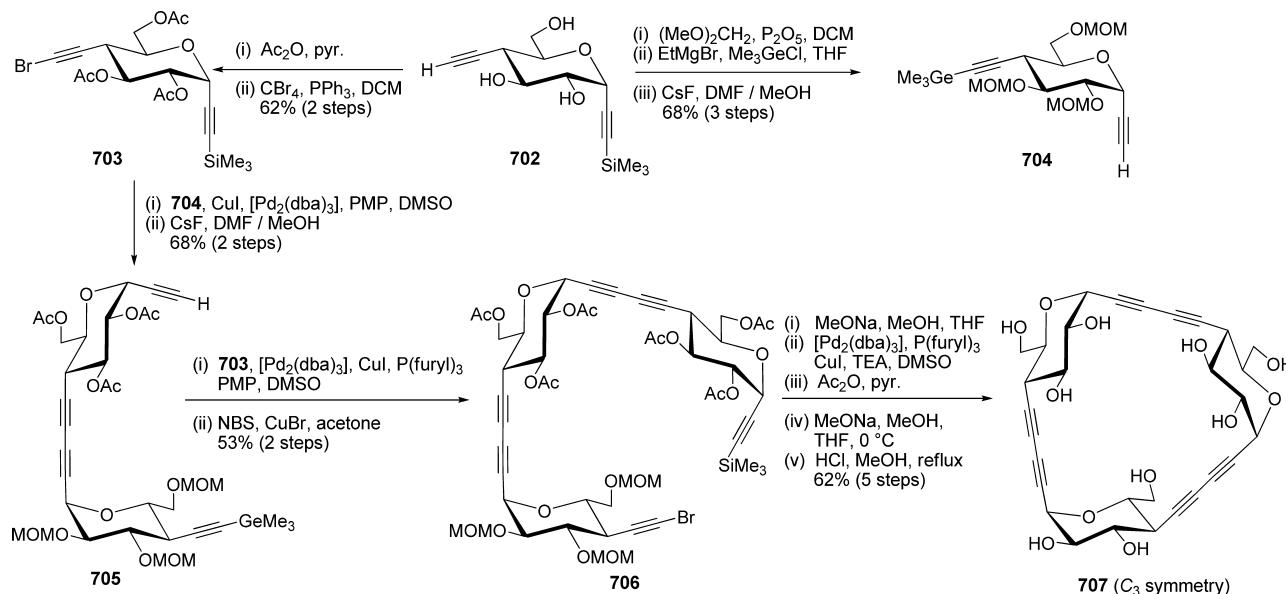
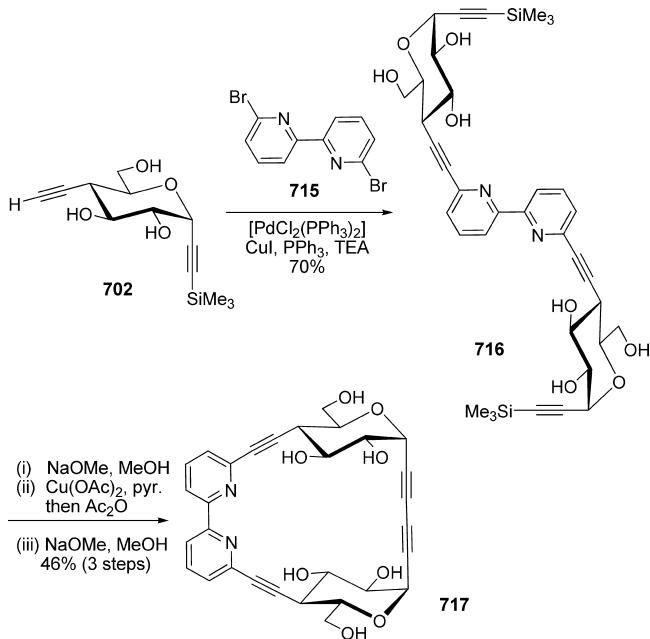


Table 9. Association Constants K_a for 1:1 Complexes of the Cyclotetramers with D- or L-Adenosine in D_2O at 23 °C

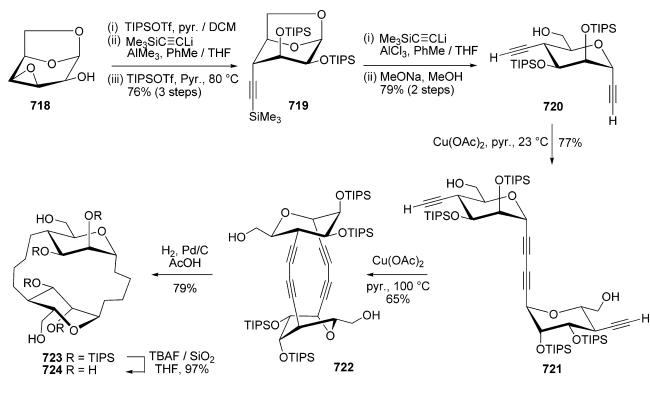
host	guest	K_a^a
D ₂ -709	D-adenosine	40
D ₂ -709	L-adenosine	32
C ₂ -713	D-adenosine	5
C ₄ -714	D-adenosine	9

^aExpressed in M⁻¹.

Scheme 87. Synthesis of a Cyclic Hybrid of 2,2'-Bipyridine and Acetylenosaccharide



Scheme 88. Synthesis of Cyclodimers Derived from α -D-Mannopyranosyl-Diacetylenes



(Scheme 95).¹⁸⁶ The azido- β -D-glucopyranoside 767, obtained in six steps from the fully acetylated glucopyranosyl trichloroacetimidate 135, was transformed into carbamate 768 by hydrogenation in the presence of Raney nickel, followed by treatment with sodium bicarbonate and *p*-nitrophenylchloroformate. These heterogeneous conditions allowed facile isolation and minimal base-induced decomposition of the desired compound. Cyclooligomerization of 768 was performed by treatment with both NaH and triethylamine in DCM (29 mM), affording a mixture of oligomeric macrocycles 770, 771, and 772 in 20%, 9%, and 3% yields, respectively. Na⁺ seems to be

important in promoting the cyclization process because only cyclized oligomers were observed in the presence of NaH. Dimer 770 and trimer 771 were fully deprotected to 773 and 774 in two steps by treatment with TFA followed by MeONa.

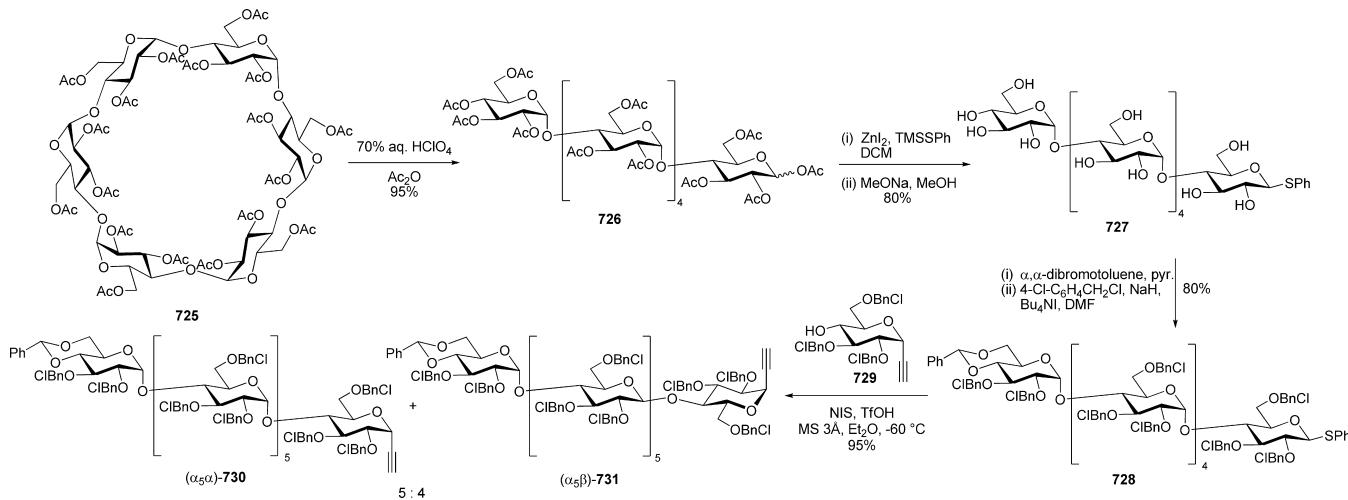
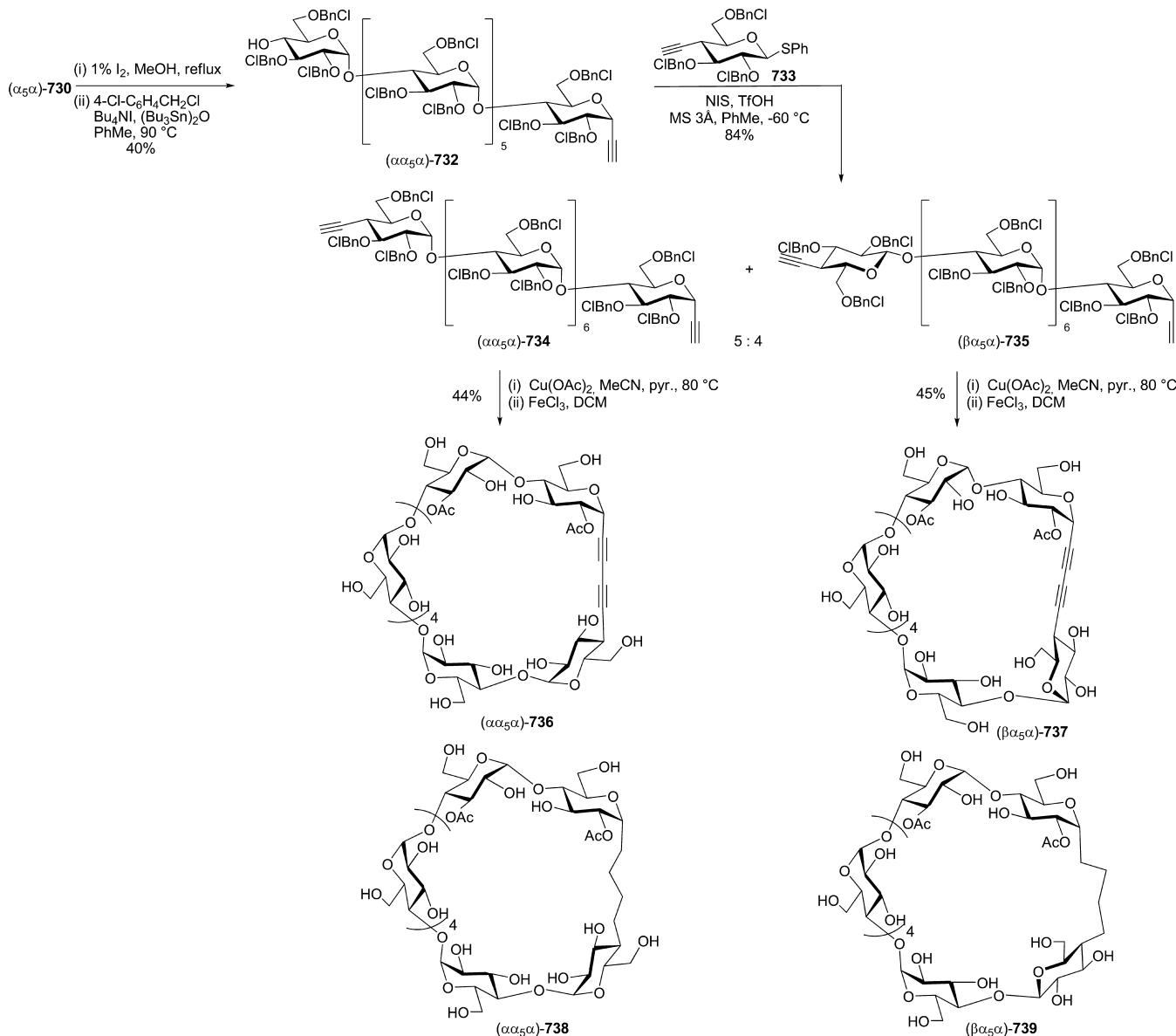
Porwanski and Marsura developed a one-pot template-directed macrocyclization between diazidocellobiose 775 and diazacrown 776 based on the Staudinger-aza-Wittig reaction (Scheme 96).¹⁸⁷ Interestingly, treatment of 775 with PPh₃ in DMF followed by 776 in the presence of Na₂CO₃ upon CO₂ bubbling ([775] = [776] = 20 mM) afforded 777 in 46% yield, whereas 778 was formed in 23% yield when Cs₂CO₃ was used. As a control experiment, the same conditions were applied without salt addition, yielding a mixture of 777 and 778. The mechanism of the reaction is supposed to involve the formation of a diisocyanatocellobiose followed by two nucleophilic additions of the preorganized sodium or cesium diazacoronates. Reaction of per-acetylated diazidocellobiose with diazacrown 776 templated with Na⁺ or Cs⁺ led to the corresponding peracetylated monocellobiosyl[(bis(ureido)] diazacrown cryptand analogue of 777 or bis (cellobiosyl)tetraureido[bis(diazacrown)] cryptand analogue of 778 in 47% and 40% yields, respectively.

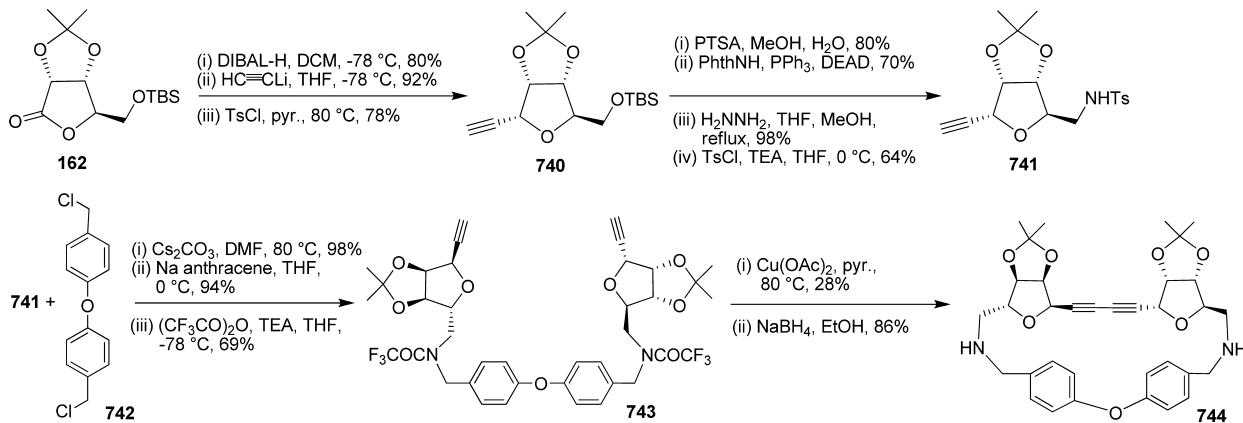
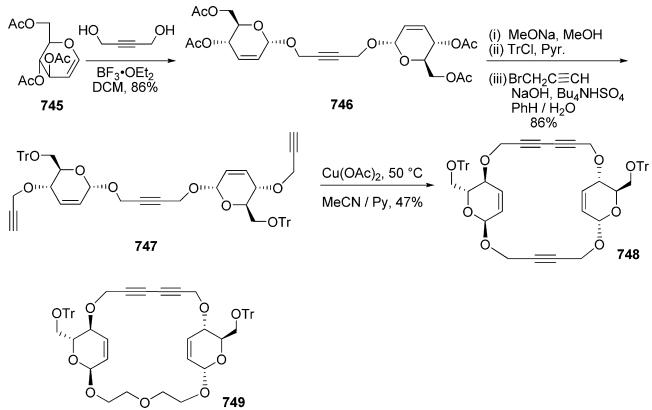
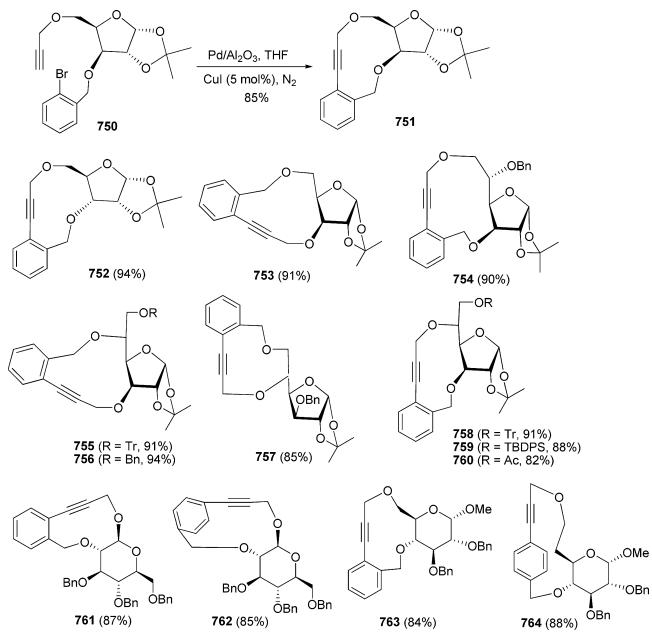
Important efforts by Fuentes, Fernández, and Ortiz Mellet were devoted to the development of novel trehalose-based CD analogues, named cyclotrehalans (CTs), as artificial receptors featuring a tronconic structure with a hydrophobic cavity.^{188–190} Macroyclic compounds containing two α,α' -trehalose subunits linked by 1,3-thiourea spacers such as 781, 786, and 787 were synthesized (Scheme 97). Reaction of diamine 779 with diisothiocyanate 780 generated from 779 and thiophosgene in the presence of CaCO₃ afforded CT2 781. Temperature-variable NMR spectra evidenced the existence of 781 as an equilibrating mixture of conformers 781-A and 781-B, both presumably involving hydrogen bonds with the two NH protons directed to the inside of the cavity. Cation-binding studies in water of the fully deprotected 782 indicated the following binding preference: Cs⁺ > K⁺ > Na⁺ and Cu²⁺ ≫ Zn²⁺, Ba²⁺, and Ca²⁺, although the association constant was not determined.¹⁸⁸ CT3 786 and 787 were prepared from diisothiocyanate 783 by water-promoted self-condensation, followed by reaction with unprotected diamine 785, deacetylation, and protection steps.¹⁹⁰

7.2. Derivatization of Thiourea

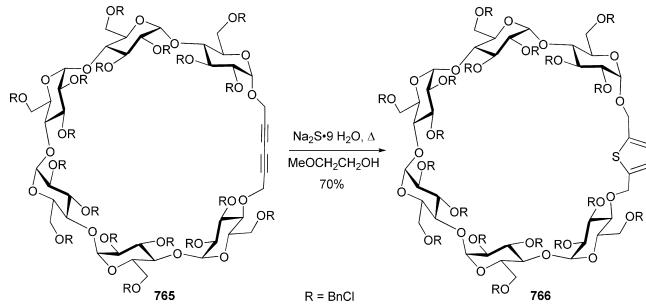
The dimeric and trimeric cyclotrehalans 788 (CT2) and 786 (CT3) proved to be versatile intermediates in the synthesis of various analogues (Scheme 98). HgO-promoted desulfurization converted dimeric 788 and trimeric 786 into the corresponding carbodiimide 790 and 791, then to ureas 792 and 793 by acidic treatment (TFA) in acetone–water mixture. Bis-guanidinium 795 was obtained in 91% from 790 in the presence of benzylamine hydrochloride and triethylamine in DMF at 100 °C.

Conformation of the fully deprotected water-soluble thioureas 782, 789 and urea 794 were studied in more details. On the basis of molecular mechanics, CT3 789 was found to exhibit a truncated-cone structure (with the hydroxy groups located at both rims, as in CDs) with a higher (though limited) flexibility than its corresponding CT2 782.¹⁸⁹ The dimensions of the cavity of 789 (7.1 Å internal medium diameter) are intermediate between those of α -CD (5.7 Å) and γ -CD (7.8 Å), but the capability of CT3 to orientate the N–H protons to the inside or the outside of the cavity and to modify the diameters of the rims was expected to result in a higher adaptability toward potential guests.

Scheme 89. Synthesis of Heptasaccharide Precursors of γ -CD AnaloguesScheme 90. Synthesis of γ -CD Analogues Containing a Buta-1,3-diyne-1,4-diyil or a Butane-1,4-diyil Unit

Scheme 91. Synthesis of Diyne Glycophanes from Ribonolactone**Scheme 92.** Synthesis of Strained Glycophanes by Oxidative Coupling of Bis-acetylene Derived from D-Glucal**Scheme 93.** Synthesis of Benzannulated Macrocycles by Intramolecular Sonogashira Reaction

Compound **789** was found to bind benzoate, naphthalenesulfonate, and adamantanone carboxylate anions in water with a 1:1 stoichiometry and association constants of 8 ± 2 , 235 ± 15 , and

Scheme 94. Thiophene-Containing CD Analogue by Diyne Derivatization

$4.6 \pm 0.4 \times 10^4 \text{ M}^{-1}$, respectively (Figure 11).^{189,190} These values compare well with those observed with α -CD and β -CD as hosts. Complexation-induced chemical shift modification as well as intermolecular ROE interactions for the **789**:benzoate complex were consistent with the aromatic ring of the benzoate moiety bound inside the cavity through hydrophobic interactions and the carboxylate anion solvated outside the cavity.

Further studies performed with the fluorescent probes ANS and TNS ($K_a = 839 \pm 25$ and $940 \pm 23 \text{ M}^{-1}$, respectively) revealed a modest fluorescence intensity enhancement upon addition of CT host to buffered aqueous solutions of guests (compared to CDs), thus revealing a probably less hydrophobic character of cyclotrehalans than cyclodextrins.¹⁹⁰

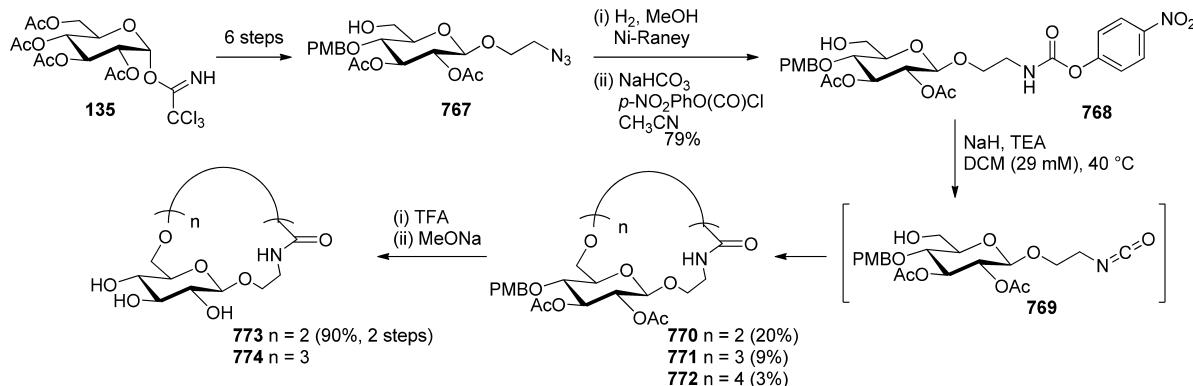
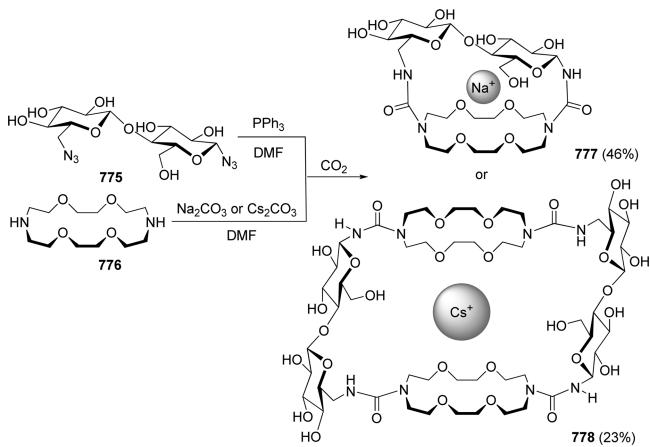
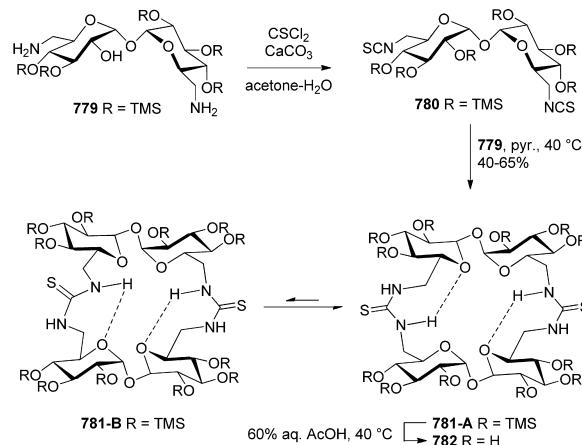
7.3. Rearrangement of Urea-oxazolidinone

The readily available glucosamine derivative **797** served as a precursor for the urea-linked cyclic dimer **800** (Scheme 99).¹⁹¹ Treatment of **797** with 4-nitrophenyl chloroformate followed by NaH yields the urea-linked dimer **798**. After selective oxazolidinone cleavage, the resulting alcohol **799** was treated with DBU, which induced rearrangement of the urea and oxazolidinone moieties to give the carbamate-linked disaccharide **800** and the water-soluble macrocycle **801** after benzylidene deprotection.

8. OTHER CARBOHYDRATE-DERIVED MACROCYCLES

8.1. Macrocycles Containing Phosphodiester Linkages

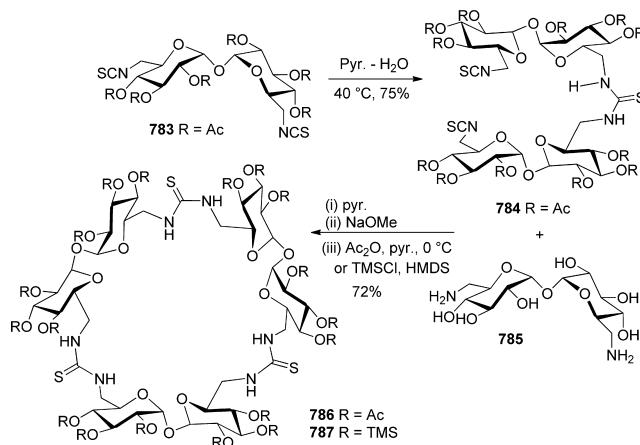
In 2007, the group of Montesarchio reported amphiphilic cyclic disaccharides connected through phosphodiester linkages, named CyPLOS (cyclic phosphate-linked oligosaccharides).¹⁹² Phenyl β -D-glucopyranoside **802** was converted in four steps into **803a** and **803b**, containing C11 alkyl and tetraethylene glycol

Scheme 95. Synthesis of Carbamate-Containing Oligomeric Macrocycles**Scheme 96. Tandem Staudinger-Aza-Wittig Templated Reaction for the Synthesis of Sugar-Ureido Cryptands****Scheme 97. Synthesis of Trehalose-Based Macrocycles Containing Thiourea Spacers**

(TEG) chains, respectively (Scheme 100). Both compounds were either treated with 2-chlorophenyl-dichlorophosphate followed by DMT deprotection to give **804a/b** or with 2-cyanoethyl-*N,N*-diisopropyl-chlorophosphoramidite to afford DMT-protected phosphoramidites **806a/b**. Coupling of **804** and **806** by activation with tetrazole followed by *t*-BuOOH-mediated oxidation yielded 75–80% of **807a/b**, which were cyclized by treatment with 1-mesitylsulfonyl-3-nitro-1,2,4-triazol (MSNT) in pyridine (1 mM), to give, after deprotection, the desired cyclic phosphate-linked oligosaccharides **809a/b** in ca. 75% yield for three steps.

Despite their ionic character, compounds **809a/b** proved to be very lipophilic (they easily dissolved in CHCl_3 and CH_2Cl_2), and NMR investigations clearly indicated a tendency for self-assembly into ordered superstructures.¹⁹² This propensity for aggregation proved beneficial in the context of ion-transport with synthetic ionophores. The TEG-containing CyPLOS **809b** indeed showed a significant ionophoric activity (while **809a** was inactive) with both group I alkali metal cations and anions such as halogens (except fluoride), nitrate, and perchlorate.¹⁹³

The dansyl-labeled CyPLOS **810**, a fluorescent analogue of **809b**, has been prepared to investigate in more detail the propensity to self-aggregate in solution (Figure 12).¹⁹⁴ The critical aggregate concentration was found to be around 0.2–0.3 mM in CDCl_3 . Studies performed in aqueous solution and pseudophysiological buffer revealed the formation of both large vesicles (hydrodynamic radius $R_h = 670 \pm 20; double layer thickness $\tau = 13.1 \pm 0.9) and micelles ($R_h = 44 \pm 20).$$$



Solvent-dependent fluorescence changes of **810** in liposome suspension were consistent with the TEG tentacles infiltrating the midpolar region of the membrane. Compound **810** was shown to be reasonable effective ionophore, with higher activity than **809b**. The search for other CyPLOS derivatives resulted in the synthesis of the bis-crown ether derivative **812**, but, unexpectedly, this compound could not be investigated in transmembrane ionic transport because it does not permeate lipid systems.¹⁹⁵ Furthermore, in an effort to access CyPLOS structures suitable for late-stage functionalization, the same group investigated in detail the compatibility of azide function in

Scheme 98. Synthesis of Ureido Cyclotrehalans

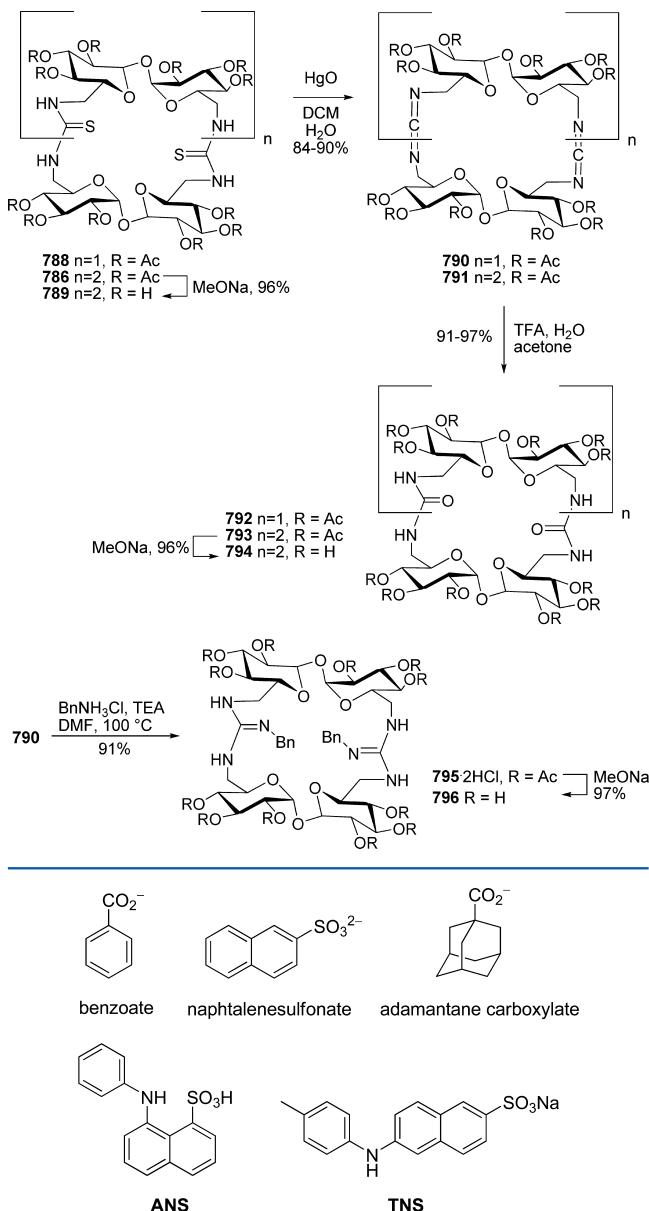


Figure 11. Structure of the guests forming 1:1 inclusion complexes with 789.

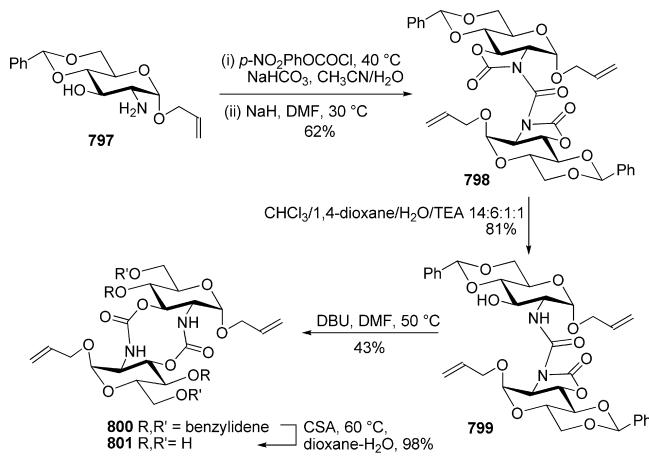
phosphoramidite-based couplings by synthesizing the azido-containing CyPLOS 811.¹⁹⁶

8.2. Isoxazoline Macroyclic Ethers

Shing and Zhong studied the intramolecular nitrile oxide-alkene cycloaddition of furanose derivatives with varying chain length (Scheme 101).¹⁹⁷ Alkylation of the diacetone-D-glucose 344 with dibromo-alkanes in the presence of NaH at reflux led to the corresponding O-alkenyl furanoses, which were further transformed into aldehydes 813–815 in 37–52% overall yield. Oximes 816–819, obtained by reaction with hydroxylamine, were treated with NaOCl under high dilution condition (1.2 mM) to generate in situ the corresponding nitrones, which underwent intramolecular cycloaddition to afford the *endo*-cyclized isoxazoline macrocycles 819–821 in 28–49% yields.

Bhattacharjya and co-workers developed a route to isoxazolines fused to 10–16-membered oxacycles (Scheme 102).¹⁹⁸

Scheme 99. Synthesis of a Carbamate-Linked Cyclic Disaccharide by Rearrangement of a Urea-Oxazolidinone Disaccharide



Mesylate 822 was transformed in four steps into disaccharide oxime 823, then reacted with NCS/DMAP in CH_2Cl_2 (72 mM) to afford nitrile oxide 824, which spontaneously underwent intramolecular [3 + 2] cycloaddition, yielding 50% of macrocycle 825. Using a similar strategy, compounds 827–831 were also synthesized. Reductive cleavage of isoxazoline by LAH (for 825 and 827) or by hydrogenation (for 828) afforded the macrocycles 826, 832, and 833.

These compounds were derivatized to the corresponding cyclic bis- and trisuracil nucleosides 834–836 by isopropylidene deprotection, acetylation, and *N*-glycosylation with uracil, in the presence of BSA and TMSOTf (Scheme 103).¹⁹⁹ These nucleoside-functionalized macrocycles exhibited interesting aggregation properties in water, as revealed by TEM, with various morphologies such as spheres, fibers, rods, or nanotubes depending on the concentration and on the presence of a complementary adenine nucleoside 837.¹⁹⁹

The same group recently reported the synthesis of a structurally related sulfoxide-oxazoline macrocycle with interesting self-association properties.²⁰⁰ The protected D-allofuranose 588 was first transformed into gluco derivative 838 through Mitsunobu reaction, S-alkylation, and selective isopropylidene cleavage (Scheme 104). Oxidative cleavage with NaIO_4 with concomitant sulfur oxidation to sulfoxide and oxime formation afforded 839 in good yield. Treatment with NCS and DMAP in benzene (66 mM) followed by intramolecular cycloaddition afforded the 11-membered macrocycle 840 in 63% yield. This compound formed organogels in hydrocarbon solvents such as pentane, hexane, and cyclohexane.

8.3. Macrocycles Containing Hydrazone Linkages

The group of Poulsen has investigated the formation of sugar-derived cyclic oligomers by dynamic combinatorial chemistry, based on reversible acylhydrazone formation (Scheme 105).²⁰¹ Treatment of a 5 mM solution of the furanoid SAA derivative 841 in $\text{H}_2\text{O}/\text{DMSO}$ (1/4, v/v) in the presence of a catalytic amount of TFA (5 μL) yielded after 6 h a mixture of cyclic oligomers 842, as revealed by ESI-MS. When the same reaction was performed with a higher amount of TFA (25 μL) and stirred for 72 h, the dominant product was by far the cyclic dimer 843, indicating its greater thermodynamic stability as compared to other potential library members.

Scheme 100. Synthesis of O-Alkyl or TEG-Containing CyPLOS

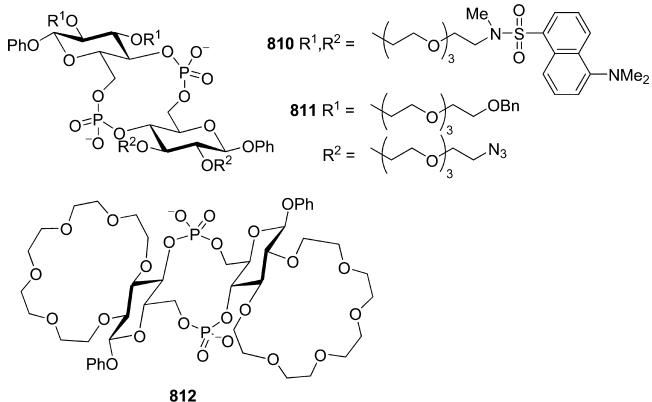
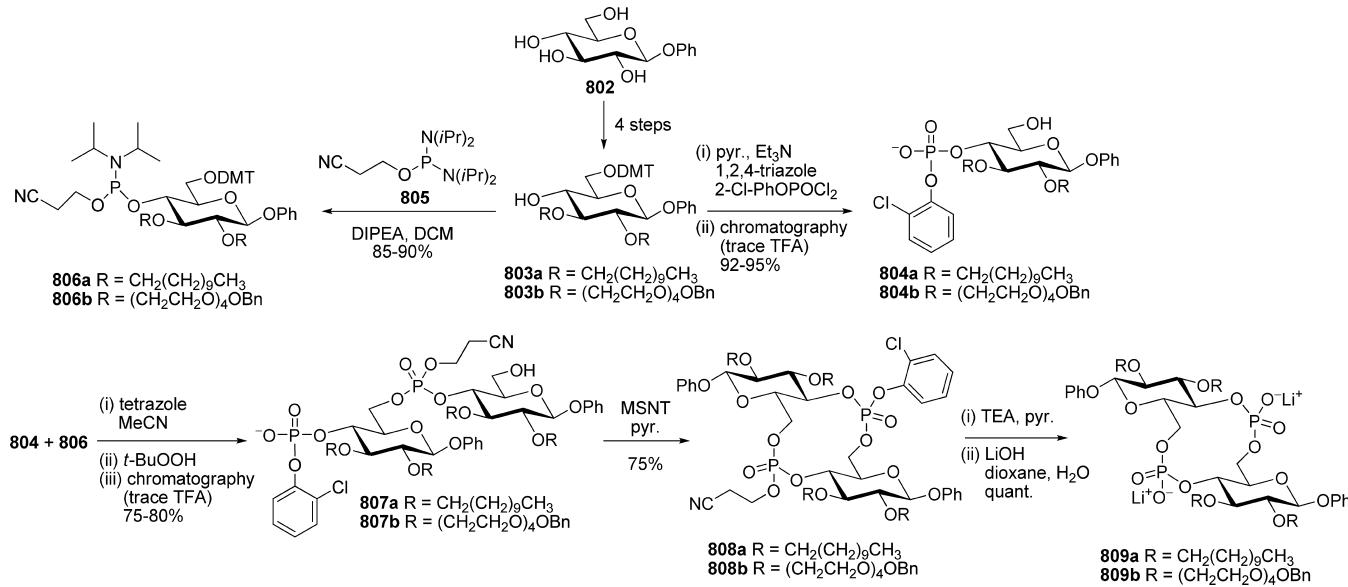
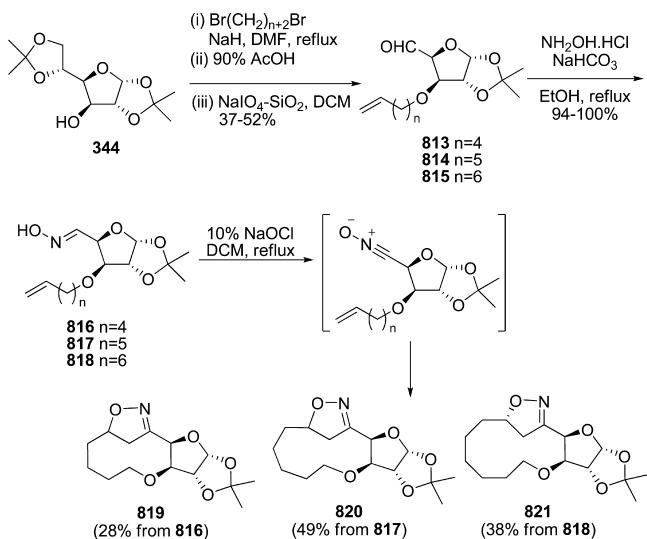
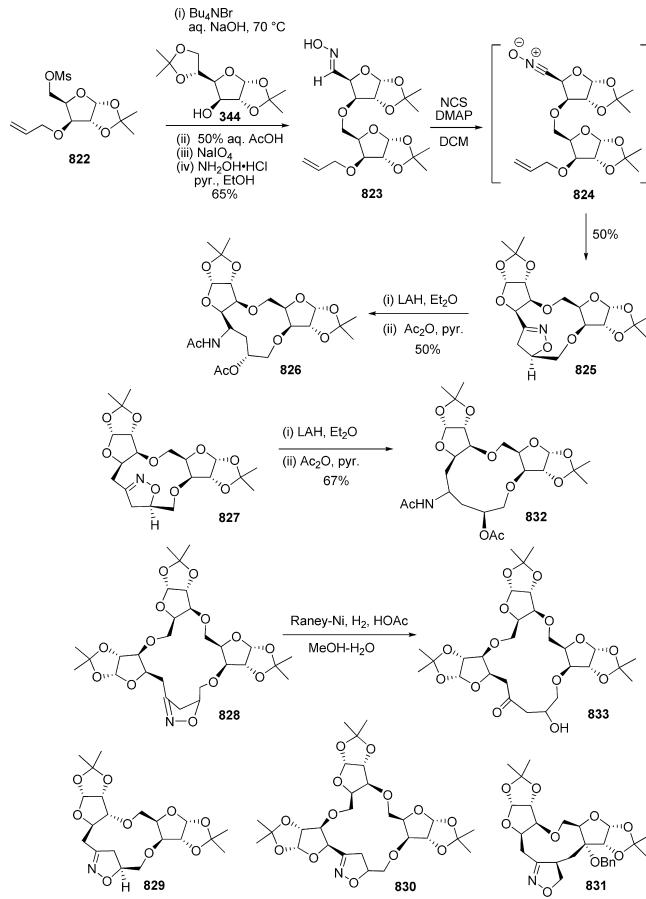


Figure 12. Various CyPLOS derivatives synthesized by the Montesarchio group.

Scheme 101. Synthesis of Isoxazoline-Macrocyclic Ethers by Nitrile Oxide-Alkene Cycloaddition

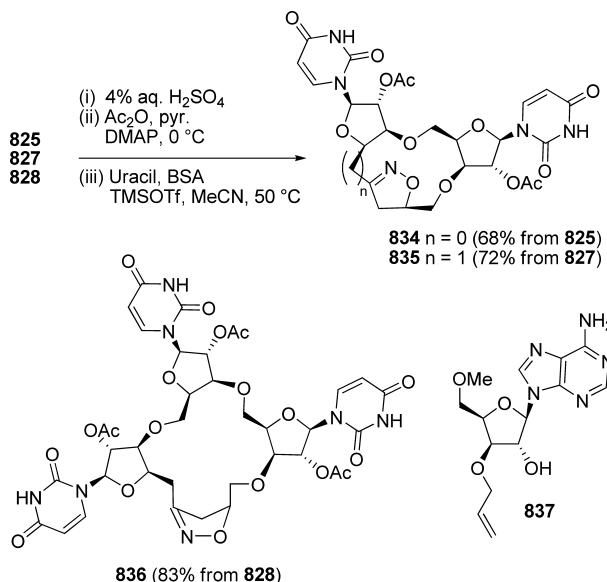
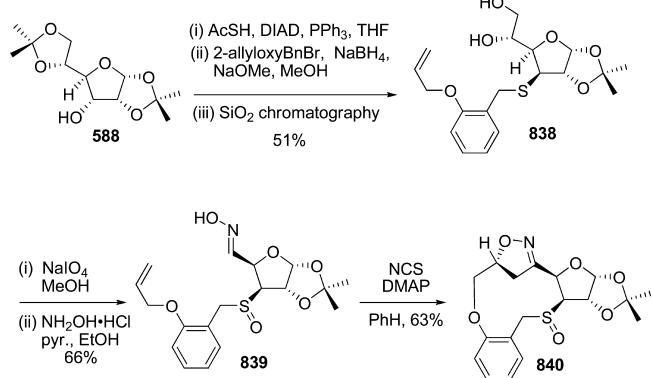
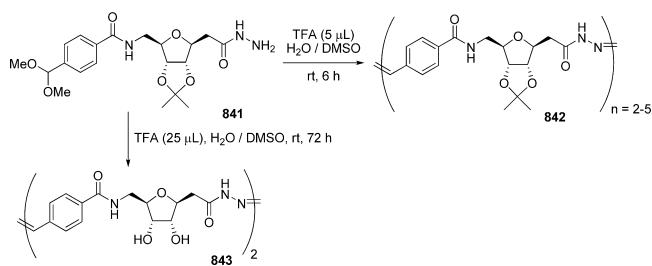


Scheme 102. Synthesis of Macrooxacycles from 3',S'-Linked Pseudooligosaccharides



9. CONCLUSION AND OUTLOOK

The syntheses and applications of natural and synthetic carbohydrate-containing macrocycles have been reviewed. Solution, solid-phase, and chemoenzymatic syntheses have been employed to obtain up to 78-membered macrocycles,

Scheme 103. Synthesis of Macroyclic Oxazoline Nucleosides**Scheme 104. Synthesis of Sulfoxide-Oxazoline Sugar-Derived Macrocycles****Scheme 105. Synthesis of a Small Library of Cyclic Oligomers of Modified SAA Utilizing Dynamic Combinatorial Library**

using different strategies for the cyclization step including macrolactonization, macrolactamization, metal ion, or amino acid template-assisted lactonization or nucleophilic substitution, intramolecular glycosylation, [3 + 2] cycloaddition between azide/alkyne or nitrile oxide/alkene, metathesis, oxidative coupling of bis-thiol or bis-acetylene, Sonogashira reaction, cyclooligomerization of hydroxyl- or amino-functionalized acid/activated ester, hydroxy-isocyanate and diisothiocyanate, cyclooligomerization through domino Staudinger/aza-Wittig reaction, as well as reductive amination. Concentration of the macrocyclization reaction is usually a key factor for controlling

the ring-size and yield of the formed macrocycles, with most macrocyclization achieved at milli- or submillimolar concentration. Total synthesis of a number of natural cyclic glycolipids and macrolactones has been achieved since 1990s; others still remained to be accomplished. These syntheses have not only allowed one to determine the absolute configurations of some natural compounds, but also established the role of cyclic structure for the bioactivities. Synthetic macrocycles have been designed and prepared for biological (as glycolipids analogues, bioactive cyclopeptides mimetics, protein ligands, enzyme inhibitors/substrates, quadruplex DNA binders), chemical (for chiral recognition, as catalysts for asymmetric synthesis), and supramolecular or analytical applications (as synthetic receptors for ions and organic compounds), or as biomaterials. These studies open the way for designing new antibiotics with improved activity in resistant strains, or new chemotherapeutic drugs against multiresistant carcinoma, although the biological activity of most synthetic macrocycles has not been tested. Generation of new organic or organometallic catalysts from supramolecular interactions with carbohydrate-based macrocycles remains to be explored. Because of the rich availability of natural carbohydrates with well-defined configurations and their easy transformations/functionalization, there is still plenty of room to design and synthesize carbohydrate-derived macrocyclic compounds as catalysts for asymmetrical synthesis or for various applications in biological, analytical, and material sciences.

AUTHOR INFORMATION

Corresponding Author

*Fax: +33 147402454. E-mail: joanne.xie@ens-cachan.fr.

Notes

The authors declare no competing financial interest.

Biographies



Juan Xie was born in China in 1964. After graduating from China Pharmaceutical University, she studied chemistry at University Paul Sabatier (Toulouse III) in France and obtained a "DEA" in 1985 and a Ph.D. at University Paris V in 1998 under the supervision of Professors M. C. Fournier-Zaluski and B. P. Roques. After postdoctoral study at CNRS in the group of Dr. M. Wakselman, she moved to University Paris VI as an Assistant Professor (1991). In 2004, she moved to the Department of Chemistry of Ecole Normale Supérieure de Cachan as a full Professor. Her current research is focused on the design, synthesis, and study of bio- or photoactive molecules, including stereocontrolled synthesis of carbohydrate derivatives and glycoconjugates for biological applications, synthesis of fluorescent amino acids/carbohydrates, or carbohydrate-based fluorescent macrocycles as molecular receptors for molecular and ionic recognition.



Nicolas Bogliotti was born in Cannes (France) in October 1980. He studied chemistry at Université Nice Sophia Antipolis, then at Université Pierre et Marie Curie (Paris), where he obtained a Ph.D. under the guidance of Prof. Janine Cossy and Dr. Peter Dalko, working in the field of Ru-catalyzed asymmetric ketone reduction and total synthesis of a natural product. In 2006, he joined the group of Prof. Andrea Vasella at ETH Zürich (Switzerland) where he studied the gelation properties of oligonucleotide analogues with integrated bases and backbones. Back to Paris in 2008, he worked for two years at Institut Curie toward the preparation of gold nanorods–protein conjugates for cancer imaging and therapy. In 2010, he was appointed assistant professor at Ecole Normale Supérieure de Cachan and joined the group of Prof. Juan Xie. His current research interest is the synthesis of photosensitive organic molecules for applications in biology, ion sensing, and catalysis.

ABBREVIATIONS

AA	amino acid
Abe	abequose
Ac	acetyl
ADDP	1'1'-(azodicarbonyl)dipiperidine
aq	aqueous
Ala	alanine
All	allyl
Anhyd	anhydrous
ANS	8-anilinilo-1-naphthalenesulfonate
Ar	argon
Arg	arginine
Asn	asparagine
Asp	aspartic acid
BAIB	bis(acetoxy)iodobenzene
Boc	<i>tert</i> -butoxycarbonyl
Bn	benzyl
BnCl	4-chlorobenzyl
BOP	benzotriazol-1-yloxytris(dimethylamino)-phosphonium hexafluorophosphate
BSA	<i>N,O</i> -bis(trimethylsilyl)acetamide
Bta	benzothienylalanine
Bz	benzoyl
<i>c</i>	concentration
CAN	ceric ammonium nitrate
Cbz	benzyloxycarbonyl
CD	cyclodextrin
Cdc25A	cell division cycle 25 homologue A
ConA	concanavalin A
CMC	critical micelle concentration
CMP	cytidine 5'-monophosphate
CSA	camphor-10-sulfonic acid
CT	cyclotrehalane
CTP	cytidine 5'-triphosphate
CuAAC	Cu(I)-catalyzed azide–alkyne cycloaddition
CyPLOS	cyclic phosphate-linked oligosaccharides
Cys	cysteine
d	day
DABCO	diazabicyclo[2.2.2]octane
dAMP	2'-deoxyadenosine 5'-monophosphate
dba	dibenzylideneacetone
DBMP	2,6-di- <i>tert</i> -butyl-4-methylpyridine
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	dicyclohexylcarbodiimide
DCM	dichloromethane
DDQ	2,3-dichloro-5,6-dicyano- <i>p</i> -benzoquinone
DEAD	diethylazodicarboxylate
DEPC	diethyl phosphoryl cyanide
DFT	density functional theory
dGMP	2'-deoxyguanosine 5'-monophosphate
DIAD	diisopropyl azodicarboxylate
DIBAL-H	diisobutylaluminum
DIC	diisopropylcarbodiimide
DIPEA	<i>N,N</i> -diisopropylethylamine
DMAC	<i>N,N</i> -dimethylacetamide
DMAP	4-dimethylaminopyridine
DMC	2-chloro-1,3-dimethylimidazolinium chloride
DME	1,2-dimethoxyethane
DMF	dimethylformamide
DMP	Dess–Martin periodinane
DMSO	dimethyl sulfoxide
DMT	4,4'-dimethoxytrityl
DMTST	dimethyl(methylthio)sulfonium triflate
DPPA	diphenyl phosphoryl azide
dr	diasteriomic ratio
DSC	differential scanning calorimetry
EDC	1-ethyl-3-(3-(dimethylamino)propyl)carbodiimide
ee	enantiomeric excess
EPR	electron paramagnetic resonance
ESI-MS	electrospray ionization mass spectrometry
equiv	equivalent
FAB-MS	fast atom bombardment mass spectrometry
Fab	fragment antigen binding
FDPP	pentafluorophenyl diphenylphosphinate
Fmoc	9-fluorenylmethoxycarbonyl
FSPE	fluorous solid-phase extraction
FT-IR	Fourier transform infrared spectroscopy
Fv	variable fragment
Glc	glucose
Glu	glutamic acid
Gly	glycine
Gal	galactose
GS	Gramicidin S
Gum	glucosyluronic acid methylamine
HAPyU	1-(1-pyrrolidinyl-1 <i>H</i> -1,2,3-triazolo[4,5- <i>b</i>]pyridinylmethylene)pyrrolidinium hexafluorophosphate 3-oxide
HATU	1-[bis(dimethylamino)methylene]-1 <i>H</i> -1,2,3-triazolo[4,5- <i>b</i>]pyridinium hexafluorophosphate 3-oxide
hex	hexyl
HFIP	hexafluoro 2-propanol
hGly	homoglycine
HIV-1	human immunodeficiency virus type 1
hLys	homolysine
HMDS	1,1,1,3,3-hexamethyldisilazane

HMPB	4-(4-hydroxymethyl-3-methoxyphenoxy)-butyric acid	R _h	hydrodynamic radius
HOAt	1-hydroxy-7-azabenzotriazole	Rha	rhamnose
HOBt	1-hydroxybenzotriazole	ROE	rotating-frame Overhauser enhancement
HOSu	N-hydroxysuccinimide	rt	room temperature
hSGLT2	human sodium-glucose linked transporter 2	SAA	sugar amino acid
HSV-1	herpes simplex virus type 1	SAC	sugar-aza-crown
IC ₅₀	half maximal inhibitory concentration	Ser	serine
IDCP	iodium di-sym-collidine perchlorate	SGLT2	sodium-glucose linked transporter 2
Ile	isoleucine	SLe ^x	sialyl Lewis X
i-Pr	iso-propyl	TAR	transactivation response
K _a	association constant	TBAB	tetrabutylammonium bromide
LacNAc	N-acetyllactosamine	TBAF	tetrabutylammonium fluoride
LAH	lithium aluminum hydride	TBAI	tetrabutylammonium iodide
Leu	leucine	TBDPS	tert-butyldiphenylsilyl
LiTMSA	lithium trimethylsilyl acetylide	TBS	tert-butyldimethylsilyl
Lys	lysine	TBTU	O-(benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium tetrafluoroborate
Man	mannose	t-Bu	tert-butyl
MBHA	4-methylbenzhydrylamine	TCP	tritylchloropolystyrene
mCPBA	meta-chloroperbenzoic acid	TcTS	<i>Trypanosoma cruzi trans-sialidase</i>
MD	molecular dynamics	TEA	triethylamine
Mes	mesityl (2,4,6-trimethylphenyl)	TEG	tetraethylene glycol
MMTr	4-methoxyphenyldiphenylmethyl	TEM	transmission electron microscopy
MOM	methoxymethyl	TEMPO	2,2,6,6-tetramethyl-1-piperidinyloxy
Mp	para-methoxy phenyl	TeOC	2-trimethylsilylethyl carbamate
Ms	methanesulfonyl	Tfa	trifluoroacetyl
MS	molecular sieves	TFA	trifluoroacetic acid
MSNT	1-mesitylsulfonyl-3-nitro-1,2,4-triazole	Tf	trifluoromethylsulfonyl
Mtr	4-methoxy-2,3,6-trimethylbenzenesulfonyl	TFE	trifluoroethanol
MW	microwave	TFOH	trifluoromethanesulfonic acid
nd	not determined	THF	tetrahydrofuran
NBS	N-bromosuccinimide	THP	tetrahydropyran-2-yl
NCS	N-chlorosuccinimide	Thr	threonine
NEM	N-ethyl morpholine	TIBS	2,4,6-triisopropylbenzenesulfonyl
NIS	N-iodosuccinimide	TIPS	triisopropylsilyl
NmCSS	<i>Neisseria meningitidis</i> CMP-sialic acid synthetase	TIS	triisopropylsilane
NMM	N-methylmorpholine	TMS	trimethylsilyl
NMP	N-methylpyrrolidinone	TNS	6-p-toluidino-2-naphthalenesulfonate
NMR	nuclear magnetic resonance	Tr	trityl
Orn	ornithine	Trp	tryptophan
PCC	pyridinium chlorochromate	Tyr	tyrosine
PCP	pentachlorophenyl	Troc	4-nitrophenyl 2-(trimethylsilyl)ethyl carbonate
Pd2,6ST	<i>Photobacterium damsela</i> α 2,6-sialyltransferase	Ts	p-toluenesulfonyl
PET	photoinduced electron transfer	UGE	urine glucose excretion
Ph	phenyl	Val	valine
Phe	phenylalanine	VEGF	vascular endothelial growth factor
Phth	phthaloyl	VEGFR	vascular endothelial growth factor receptor
PI	peak intensity	VZV	varicella-zoster virus
PMB	para-methoxybenzyl		
PMP	1,2,2,6,6-pentamethylpiperidine		
PPi	inorganic pyrophosphate		
Pro	proline		
PTSA	p-toluenesulfonic acid		
PTP1B	protein-tyrosine phosphatase 1B		
Piv	pivaloyl		
Py	pyridyl		
PyBOP	benzotriazol-1-yl-oxytritypyrrolidinophosphonium hexafluorophosphate		
Pyr	pyridine		
Quant	quantitative		
RCM	ring-closing metathesis		
RGD	Arg-Gly-Asp		
RNA	ribonucleic acid		

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