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The collage consists of nine panels, each featuring a different research topic:

- Top Left:** A schematic diagram of a flow reactor system for the conversion of CO₂ and CO to O₂ over a molten salt catalyst. The reactor has two Ar ports at the top and a central vertical tube for gas flow. The reaction is driven by an external power source. (p 2863)
- Top Middle:** A graph showing a single sharp peak, followed by a text box describing the "Catalyst Economy" of CCTP (Coordinative Chain Transfer Polymerization). It shows the reaction scheme: Active [Catalyst Metal] + Polymer₁ + Polymer₂ → Dormant [Chain Transfer Metal]. Monomer(s) react with the active catalyst to form dormant species. (p 3836)
- Top Right:** A diagram of a protein complex involved in dopamine receptor signaling. It shows a membrane protein with various domains labeled: EL1, EL2, EL3, TMD, IL1, IL2, and IL3. NH₂ and COOH termini are indicated. Dopamine Receptors are shown interacting with the protein. (p PR123-PR178)
- Middle Left:** A sequence of three circles (green, yellow, red) connected by arrows, followed by a flask icon. (p 3686)
- Middle Center:** A chemical reaction scheme for a Mannich base: R¹-CH=NO₂ + R³-N=C(R²)-CH=O → R¹-CH(R²)-NH-CH(R³)-NO₂. Below it is a text box: "A forgotten classic" (p 2887).
- Middle Right:** A diagram illustrating "Stem Cell Fate in Differentiation". It shows stem cells differentiating into various cell types (represented by icons like a star, square, circle, etc.) under different conditions (Micro-patterned surface, Elasticity of matrix). (p 3297)
- Bottom Left:** A circular diagram showing the synthesis of various molecules from a core Perl's aldehyde scaffold. The scaffold is a 3D structure with an OH group, an OR₁ group, and a CHO group. Arrows point to: β-Lactams, Unprotected hydroxyl group, Natural product like molecules, Handle can be elaborated to amino functionality, Bioactive molecules, Enantiopure tetrahydropyrans, and Enantiopure tetrahydrofurans. (p 3605)
- Bottom Right:** A circular graphic titled "Toxic or not? Alerts Prediction" showing a workflow for predicting toxicity. (p 2940)
- Bottom Center:** A circular graphic titled "Enantiomerically pure natural products" showing a collection of various organic molecules, likely natural products, arranged in a circular pattern. (p 2958)



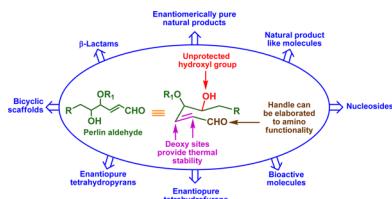
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Glycal-Derived δ -Hydroxy α,β -Unsaturated Aldehydes (Perlin Aldehydes): Versatile Building Blocks in Organic Synthesis

L. Vijaya Raghava Reddy,^{‡,§} Vikas Kumar,^{‡,§} Ram Sagar,[§] and Arun K. Shaw*

Division of Medicinal and Process Chemistry, CSIR-Central Drug Research Institute, Lucknow, India-226001



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1. INTRODUCTION

The presence of hydroxyl functionalities and well-defined chiral centers in carbohydrates as well as their natural abundance have

attracted chemists worldwide to exploit this class of molecules as precursors for synthesis of a large number of natural products and biologically active molecules during recent decades. Apart from that, various types of molecules have also been synthesized from carbohydrates with a view to using them to study biological phenomena taking place in living systems. Thus, both the diversity and easy availability of these relatively cheap chiral compounds led to a plethora of applications in the design and syntheses of natural and synthetic molecules of biological importance.¹ Among the many carbohydrate derivatives, unsaturated sugars occupy a significant place as starting materials for the syntheses of various types of organic compounds due to the wealth of functional, conformational, and stereochemical information associated with them.

For the last several years we have been working on various monosaccharide-derived enantiomerically pure δ -hydroxy α,β -unsaturated sugar aldehydes (carbohydrate enals) of the general structure I (Figure 1). The first synthesis of this class of enantiomerically pure unsaturated aldehydes was reported by A. S. Perlin in 1975.² Here in this review, the terms “Perlin aldehyde” and “Perlin hydrolysis” are used for δ -hydroxy α,β -unsaturated aldehydes of the general structure I and their synthesis from glycal, respectively. The inherent advantages of these Perlin aldehydes are (a) their high degree of functionality (free and protected hydroxyl groups, unsaturation (*E*) and aldehydic group); (b) the facility to selectively manipulate each position; (c) the extensive stereodiversity of two predefined chiral centers; (d) the deoxy sites, which provide thermal stability; and (e) most importantly, their optical purity. Given this, it is logical that these monosaccharide derivatives, since their discovery by A. S. Perlin,² have been utilized as chiral pool compounds by various research groups for the synthesis of a variety of natural products and molecules of biological importance as well. With our own experience and looking toward its importance as mentioned above, we felt that it was worth compiling the substantial amount of work centered around Perlin aldehydes since their discovery in the form of a review. Here, in this review on Perlin aldehydes, efforts are made to present a historical overview on the synthesis and utility of glycal (glucal, galactal, rhamnal, and arabinal) derived δ -hydroxy α,β -unsaturated aldehydes I. Attention has also been focused on the use of these unsaturated aldehydes toward the synthesis of natural and unnatural products of biological importance. Apart from that, efforts are also devoted to covering the significant applications of these unsaturated sugar aldehydes for stereoselective synthesis of various cyclic and acyclic building blocks of significant interest.

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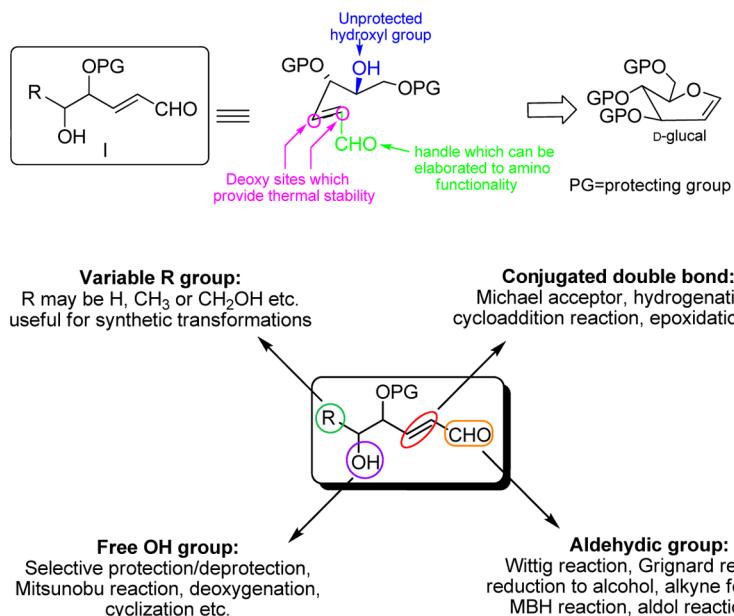
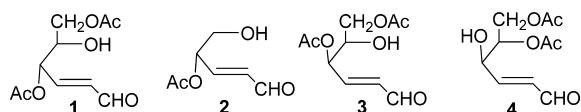


Figure 1. Typical reactivity sites of Perlin aldehydes.

2. SYNTHESIS OF PERLIN ALDEHYDES

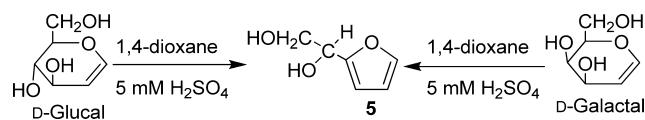
2.1. Mercurial Approach

A. S. Perlin noted that in the presence of mercuric sulfate (0.02 mol equiv), the acetyl-protected glycals (glucal and arabinal) dissolved in 1,4-dioxane and 5 mM sulfuric acid at room temperature were converted rapidly and quantitatively into their corresponding δ -hydroxy α,β -unsaturated aldehydes (**1** from acetylated glucal and **2** from acetylated arabinal). However, an oily product obtained in the case of 3,4,6-tri-O-acetyl-D-galactal was found to be a mixture of 4,6- and 5,6-diacetates **3** and **4** (Figure 2). Surprisingly, the

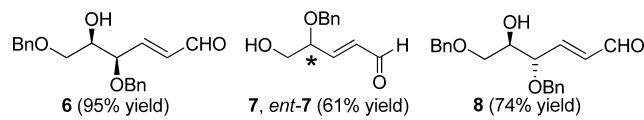
Figure 2. Structures of Perlin aldehydes **1**–**4**.

unprotected D-glucal and D-galactal underwent elimination instead of hydration and yielded 2-substituted furan **5** as the sole product under similar conditions (Scheme 1).²

Scheme 1. Hydration Reaction of Unprotected D-Glucal and D-Galactal

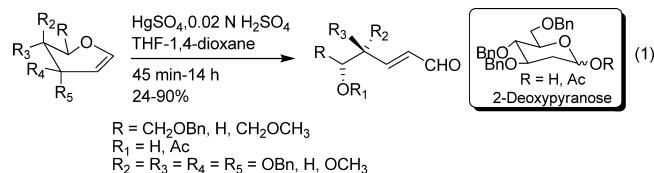


Prior to our studies on alkylated glycals in 2004,³ Hirata et al. reported the hydrolysis of 3,4,6-tri-O-benzyl-D-galactal in THF in 1 h to hydroxy-trans-enal **6** at room temperature in the presence of 10 mM sulfuric acid and a catalytic amount of mercuric sulfate.⁴ Tolstikov et al. reported the acidic opening of the O-benzyl ethers of D- and L-arabinal by $HgSO_4$ and 5 mM H_2SO_4 in dioxane at room temperature for 24 h to obtain (*E*)-(4*S*)-4-benzyloxy-5-hydroxy-2-pentenal **7** and its enantiomer *ent*-**7** (Figure 3) and utilized them in the preparation of chiral synthons with selectively substituted hydroxyl groups.⁵ Lellouche

Figure 3. Structures of Perlin aldehydes **6**–**8**.

and Quinton in 1994 disclosed the exclusive formation of (*E*)-4,6-di-O-benzyl-2,3-dideoxy-aldehydo-D-*erythro*-hex-2-enose **8** by mercuric sulfate-catalyzed hydrolysis of 3,4,6-tri-O-benzyl-D-glucal at room temperature in 68 h with 0.25 M aqueous sulfuric acid in dioxane.⁶ Unfortunately, under analogous conditions we failed to complete the reaction of benzyl-protected glucal even after stirring for a prolonged time period.

During our reinvestigation of the mercuration–demercuration reaction³ (eq 1), we found that refluxing a 1,4-dioxane solution of

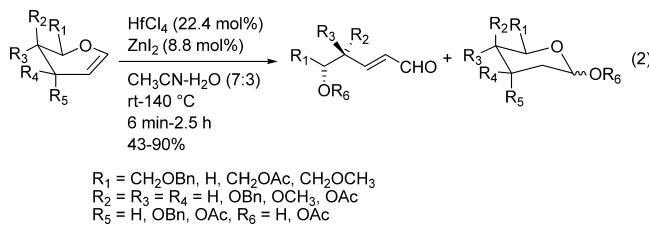


benzyl-protected glucal in aqueous acidic medium (10 mM H_2SO_4) in the presence of a catalytic amount of mercuric sulfate afforded 48% of its corresponding α,β -unsaturated aldehyde along with 24% of 2-deoxy product, which were isolated as their acetate derivatives, whereas the usage of THF as a solvent instead of 1,4-dioxane, for the same transformation, furnished the 2-deoxy product as major (52%) along with some α,β -unsaturated aldehyde (24%). On the contrary, the benzyl-protected arabinal, either in THF or 1,4-dioxane under refluxing conditions, furnished α,β -unsaturated aldehyde exclusively and the benzyl-protected galactal and methyl-protected glucal, galactal, and arabinal afforded their corresponding δ -hydroxy α,β -unsaturated aldehydes only at room temperature under similar reaction conditions.

2.2. Nonmercurial Approach

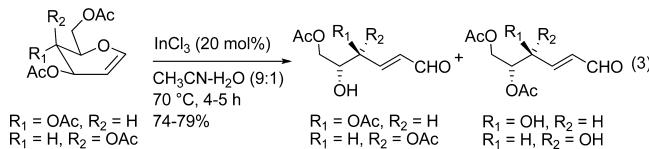
Since the use of Hg^{2+} is not recommended in the pharmaceutical industry owing to its toxicity, alternative methods to obtain

2,3-dideoxy- α,β -unsaturated carbohydrate enals from various protected glycals have been recently developed. We developed an efficient and alternative method to obtain 2,3-dideoxy- α,β -unsaturated carbohydrate enals from acyl-, arylalkyl-, and alkyl-protected glycals (eq 2).⁷ Here we utilized *in situ* generated push–



pull effect resulting from the synergistic combination of HfCl_4 and ZnI_2 . While the benzylated glucal produced corresponding δ -hydroxy α,β -unsaturated aldehyde along with its 2-deoxy product in a 4:1 ratio, benzylated and methylated galactal furnished a mixture of corresponding δ -hydroxy α,β -unsaturated aldehyde and 2-deoxy product in 1:1 and 3:2 ratios, respectively. This method also circumvents the problem of acyl group migration in the case of acyl-protected glycals as observed in the Hg^{2+} -catalyzed Perlin hydrolysis.²

Ramesh and co-workers reported the nonmercurial approach toward the synthesis of Perlin aldehydes from various glycals by utilizing InCl_3 as catalyst in the $\text{CH}_3\text{CN}-\text{H}_2\text{O}$ solvent system.⁸ InCl_3 -catalyzed Perlin hydrolysis of triacetylated D-glucal and D-galactal furnished Perlin aldehydes along with another isomer resulting from the acetyl group migration from the C-4 carbon to C-5 carbon (eq 3). On the other hand, the tribenzylated



glycals furnished the corresponding hemiacetal as the major products along with Perlin aldehydes in very low yields.

3. MECHANISM FOR THE FORMATION OF PERLIN ALDEHYDES FROM 3,4,6-TRI-O-ACETYL-D-GLUCAL

According to Perlin et al., the 1,2 π -bond in glucal peracetate is first attacked by a mercuric ion and subsequently by water at C-1 (Scheme 2).² The hydration products (**10** and **11**) were then converted to **1** presumably via elimination at C-2 and C-3. In order to account for formation of *trans*-alkene **1**, they prepared **14**, due to its close resemblance to the proposed intermediate **10**, and exposed this to the conditions as described above. The aldehyde **1** was indeed formed from **14**, although more slowly than directly from the glycal, confirming that D-*gluco* isomer **10** must undergo *cis* elimination via **12**.

4. APPLICATIONS OF PERLIN ALDEHYDES

4.1. Synthesis of Natural Products and Related Compounds

The use of monosaccharides and their derivatives as chiral templates for the synthesis of biologically active compounds is well established in the literature.⁹ Given their inherent advantages, it is logical that these Perlin aldehydes obtained from various monosaccharide-derived glycals have been utilized as chiral pool material by various groups for the synthesis of a variety of natural products, which are discussed below.

Fraser-Reid and co-workers established the structural details of the pendant C4 esters of the trichothecenes **15**–**17** (Figure 4) involving a simple synthetic strategy where they utilized Perlin aldehydes **19** and **20**, prepared from 6-deoxy analogues of triacetyl-D-glucal and galactal, respectively.¹⁰ The aldehydes **19** and **20** were converted into their respective isomers **21a** and **22a**, respectively, by adopting Peterson's reported procedure,¹¹ which were deacetylated to **21b** and **22b** with sodium methoxide (Scheme 3). The relative stereochemistries as well as configurations of six dienic esters, generated through transesterification of six trichothecenes **15**–**17** using catalytic amounts of sodium methoxide in methanol, were assigned by comparing their NMR parameters and optical rotations with those of **21b** and **22b**. From this analysis they concluded that the esters **15**, **16**, and **17** from B group possessed D-*erythro* stereochemistries, while those from A group had L-*threo* stereochemistries. Utilizing the intermediate **21a**, they also established the absolute configuration of the epoxy ester from trichodermadiene **18**.

Tolstikov et al. utilized Perlin aldehydes, prepared from glycals, as chiral templates in various types of natural products synthesis.¹² His group achieved the stereospecific synthesis of the optically pure sex pheromone of gypsy moth *Lymantria dispar* L-(+)-*cis*-disparlure (**30**) starting from Perlin aldehyde **3**, derived from 3,4,6-tri-O-acetyl-D-galactal (Scheme 4).^{13,14} The triacetoxy hexenal **24**, prepared by acetylation of the aldehyde **3**, on Wittig olefination furnished triacetoxydiene **25**. Its transformation to monotosylate **27** was carried out in four steps via **26**. After the deprotection of acetonide group, the resulting diol was converted to epoxide **28**. Its oxidation with Collins reagent followed by Wittig olefination of the resulting aldehyde with appropriate phosphonium salt yielded **29**, which on catalytic hydrogenation afforded optically pure (+)-*cis*-disparlure (**30**). In this synthesis, the chirality of building block **3** was incorporated into product **30** with retention of configuration at C5 and inversion of configuration at C4 of the enal. Synthesis of optical antipode, (−)-*cis*-disparlure, (7S,8R)-*cis*-2-methyl-7,8-epoxyoctadecane (**36**) was reported by the same group (Scheme 5) starting from galactose-derived aldehyde **31**.¹⁵ Wittig olefination of enal **33**, obtained by hydrolysis of galactal derivative (**32**), with n-heptyltriphenylphosphonium bromide gave **34**. Compound **34** was then converted into target compound **36** via **35** by hydrogenation followed by tosylation and then treatment with K_2CO_3 in methanol.

In early 1990s, the same group completed the enantiospecific synthesis of (9S,10R,3Z,6Z)-*cis*-9,10-epoxy-3,6-heneicosadiene (**42**), the basic component of sex pheromone of the American white moth *Hyphantria cunea drury* by utilizing the designed chiral enal **24** (Scheme 6).¹⁶ While the R configuration at C10 of the target molecule **42** was exploited with retention of the stereocenter at C4 of the enal **24**, the S configuration at C9 was obtained by inversion of C5 of this enal. The triacetoxydiene **37**, obtained from **24**, on catalytic hydrogenation and hydrolysis of acetyl groups furnished triol **38**. Selective tosylation of **38** afforded monotosylate **39**, whose alkaline treatment and subsequent benzoylation afforded the key epoxide **40**. Its reaction with 1,4-heptadiyne using n-butyl lithium and a catalytic amount of $\text{BF}_3\text{-Et}_2\text{O}$ followed by tosylation gave diacetylene precursor **41**, which on alkali treatment and Pd/ BaSO_4 -catalyzed selective hydrogenation in the presence of quinoline led to the formation of optically pure **42**.

In their next communication, they showed another application of 3,4,6-tri-O-acetyl-D-galactal-derived Perlin aldehyde **3** to obtain the pheromone of the egg-laying yellow fever mosquito *Culex pipiens fatigans* (Scheme 7).¹⁷ The Grignard reaction of terminal epoxide **43**, obtained from previously

Scheme 2. Mechanism of Perlin Hydrolysis

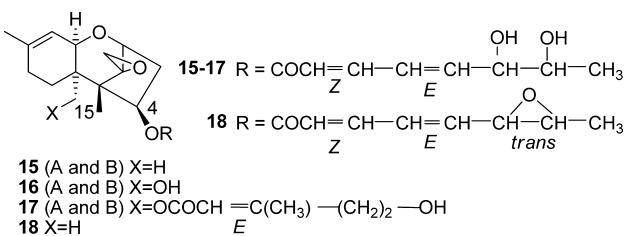
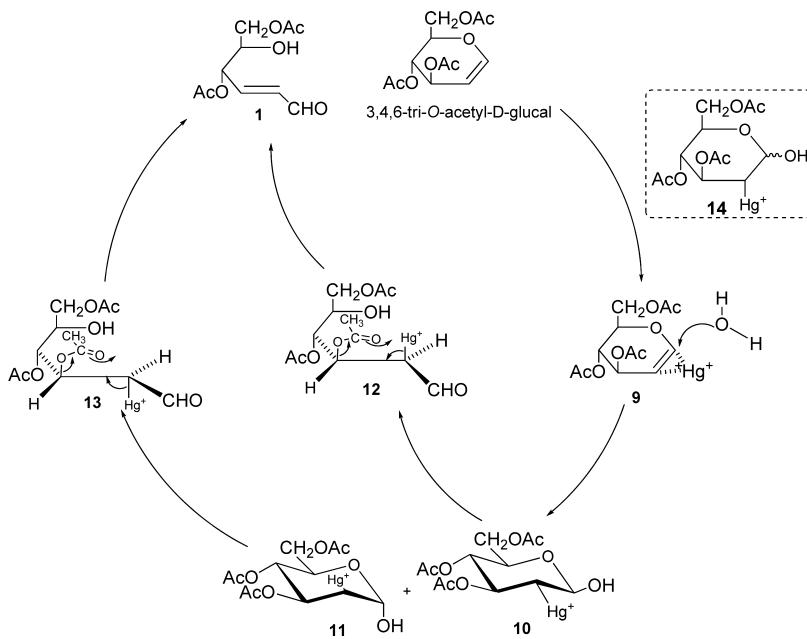


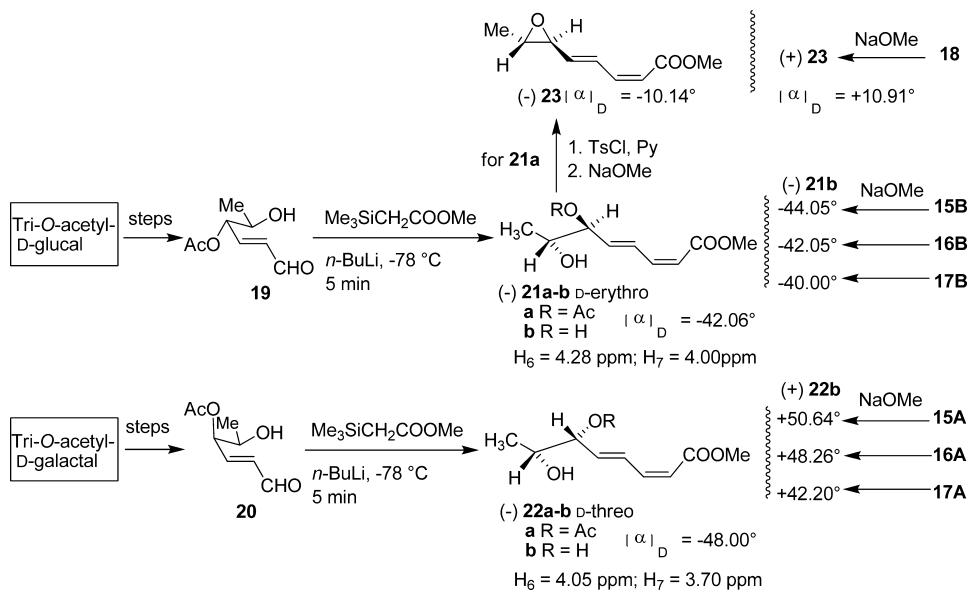
Figure 4. Structures of trichothecenes 15–17 and trichodermadiene 18.

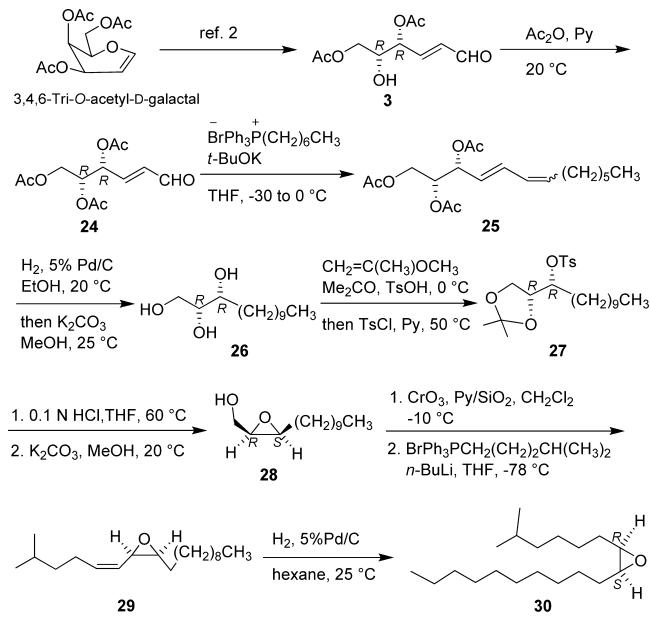
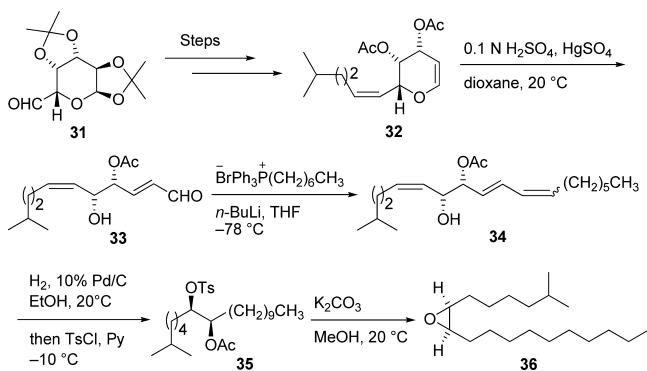
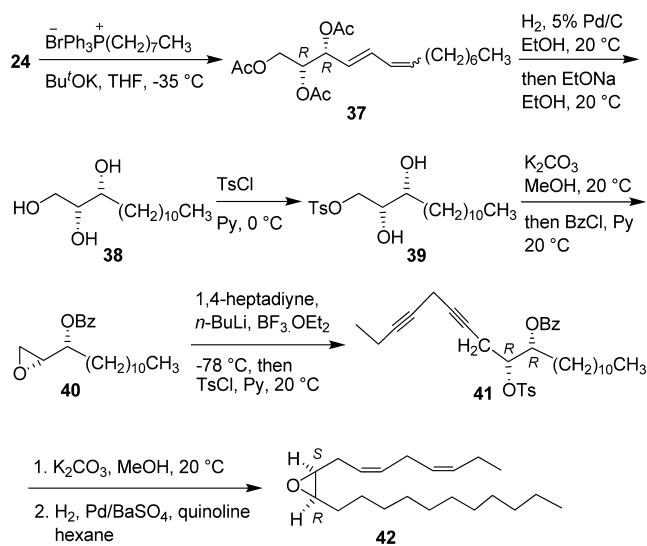
synthesized triol **26**, followed by protection of the resulting *cis* diol furnished the acetonide **44**. The ozonolysis of **44** and the hydrogenation of the peroxide products on Pd/CaCO₃ furnished the aldehyde **45**. Oxidation of the aldehyde and

subsequent hydrolysis of the acetonide protection, lactonization of the resulting hydrolyzed product and acetylation of the remaining hydroxyl functionality in succession provided (*S*₆*R*)-6-acetoxy-5-hexadecanolide **47**, a stereoisomer of the native pheromone with 98% optical purity. This demonstrates the possibility of the use of Perlin aldehydes for the synthesis of all the probable pheromone stereoisomers.

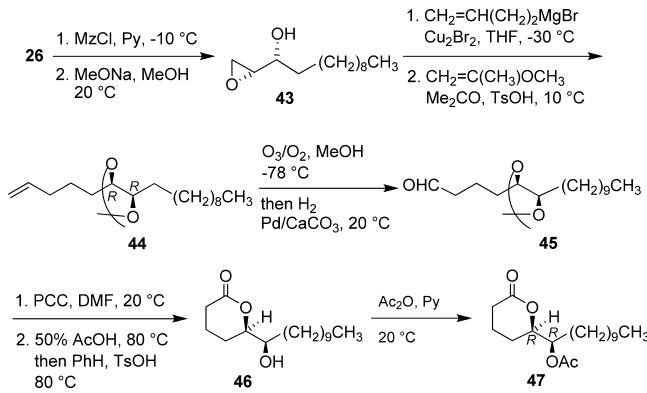
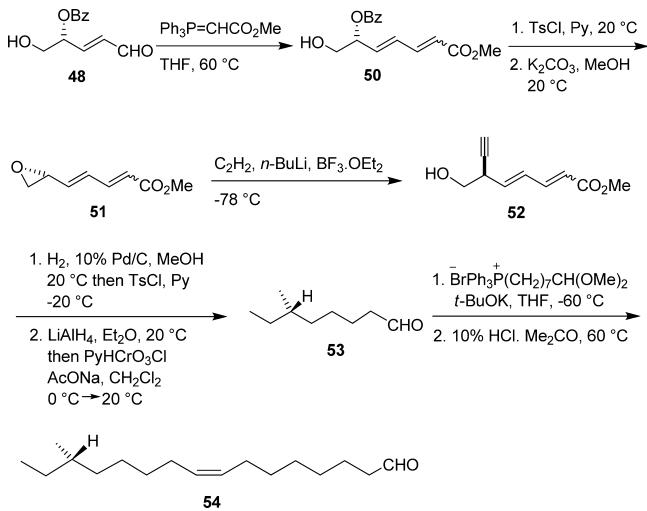
Tolstikov and co-workers also reported an elegant method for the synthesis of the stereoisomer of native pheromone (14*S*,8*Z*)-trogodermal **54**, utilizing L-arabinal dibenzoate-derived Perlin aldehyde **48** (Scheme 8). They exploited the C-4 stereocenter of the enal **48** in this chiral pool synthesis to provide the target molecule **54**. The enal on Wittig olefination furnished dienoic ester **50**, which on tosylation, followed by

Scheme 3. Synthesis of Esters 21–23 and Determination of Relative and Absolute Configuration of the Pendant C4 Esters of the Trichothecenes 15–18

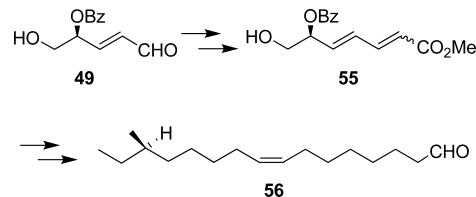


Scheme 4. Synthesis of (+)-*cis*-Disparlure 30**Scheme 5. Synthesis of (-)-*cis*-Disparlure 36****Scheme 6. Synthesis of (9S,10R,3Z,6Z)-*cis*-9,10-Epoxy-3,6-heneicosadiene 42**

treatment with K_2CO_3 in methanol, produced epoxyester 51. The reaction of lithium acetylide with epoxyester 51 proceeded regiospecifically with the formation of primary

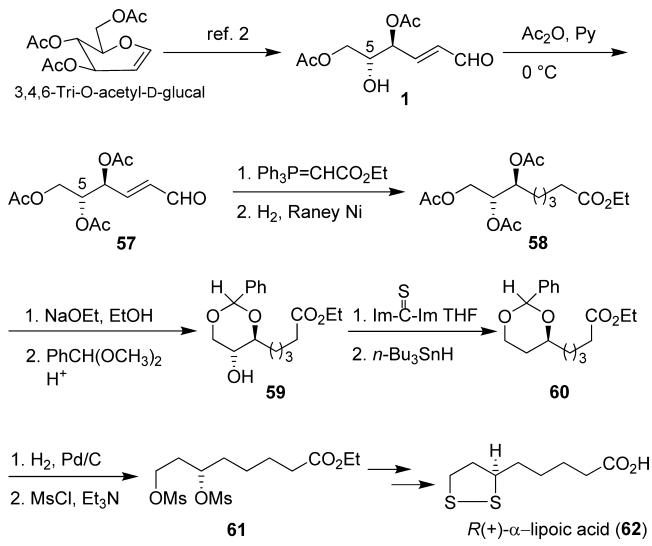
Scheme 7. Synthesis of (5*R*,6*R*)-6-Acetoxy-5-hexadecanolide 47**Scheme 8. Synthesis of (14*S*,8*Z*)-Trogodermal 54**

acylenic hydroxyester 52. Exhaustive hydrogenation, tosylation, LAH reduction, and oxidation with pyridinium chlorochromate complex in succession furnished the key aldehyde intermediate 53. Its Wittig reaction with (8,8-dimethoxyoctyl)-triphenylphosphonium bromide, followed by acidic hydrolysis, afforded (14*S*,8*Z*)-trogodermal 54 (a stereoisomer of the native pheromone) in 98% ee. By applying the same methodology, they successfully synthesized the natural (14*R*,8*Z*)-*cis*-trogodermal 56 starting from D-arabinal dibenzoate-derived unsaturated enal 49 via the dienoic ester 55 (Scheme 9).¹⁸

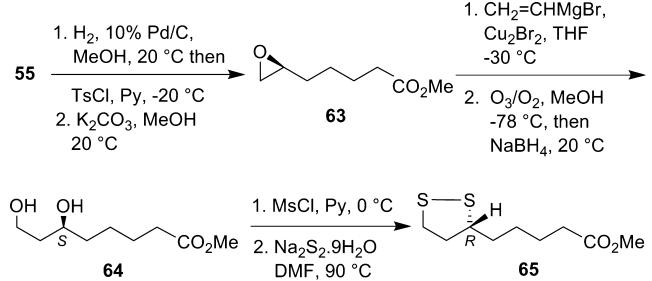
Scheme 9. Synthesis of (14*R*,8*Z*)-*cis*-Trogodermal 56

In 1987, Rao et al. used 4,5,6-tri-O-acetyl- α,β -unsaturated aldehyde 57, prepared from Perlin aldehyde 1 by acetylation of its 5-OH group, for enantiospecific synthesis of *R*-(+)- α -lipoic acid 62, which is a prosthetic group and a vital cofactor in α -keto acid decarboxylation (Scheme 10).¹⁹ Wittig olefination of aldehyde 57 followed by hydrogenation afforded triacetoxy ester 58, which was converted to deoxygenated compound 60

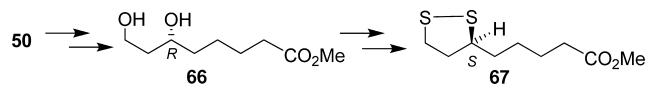
Scheme 10. Synthesis of *R*(+)- α -Lipoic Acid 62



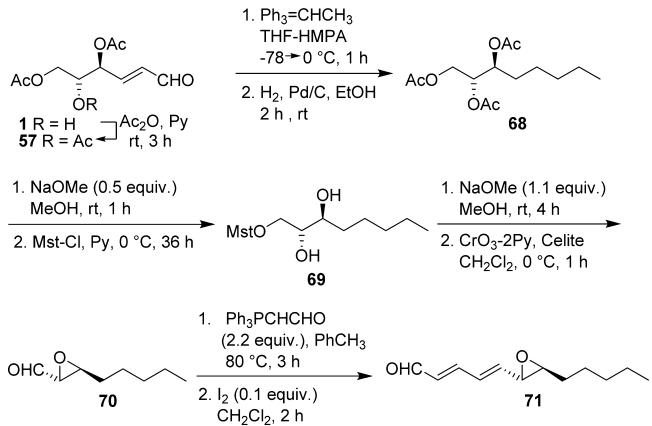
Scheme 11. Synthesis of R(+)-Lipoic Acid Methyl Esters 65



Scheme 12. Synthesis of (S)-(-)-Lipoic Acid Methyl Esters



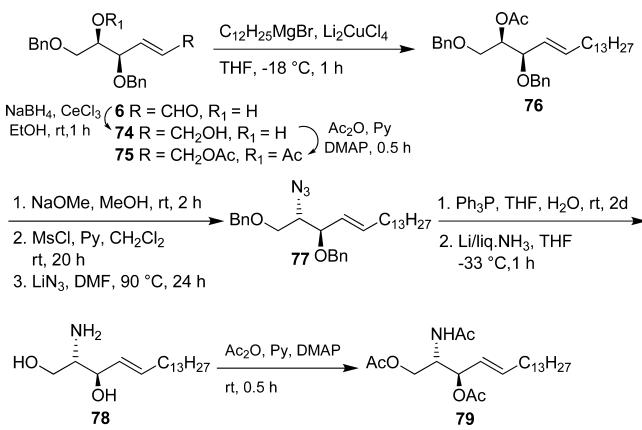
Scheme 13. Synthesis of Diene Epoxy Aldehyde 71



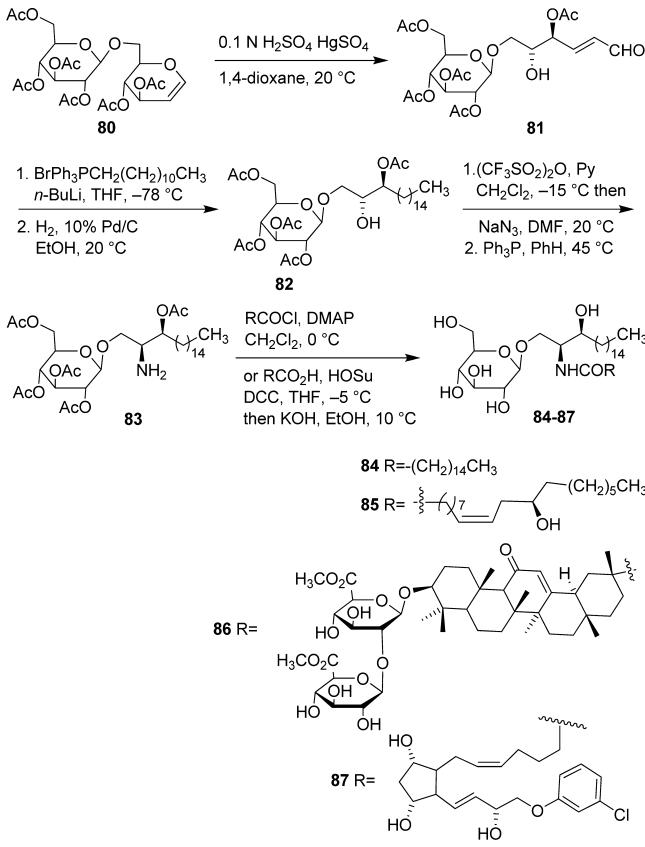
in four steps via compound **59**. Deprotection of benzylidene in **60**, followed by mesylation furnished dimesylated product **61**, which was finally converted to *R*-(+)- α -lipoic acid **62**.

Later, Tolstikov and Tolstikov exploited dienoic esters **55** and **50**, derived from Perlin aldehydes **49** and **48**, respectively, for the synthesis of (*R*)-(+)- and (*S*)-(−)-lipoic acid methyl esters

Scheme 14. Synthesis of Sphingosine 78 and Acetyl Derivative 79

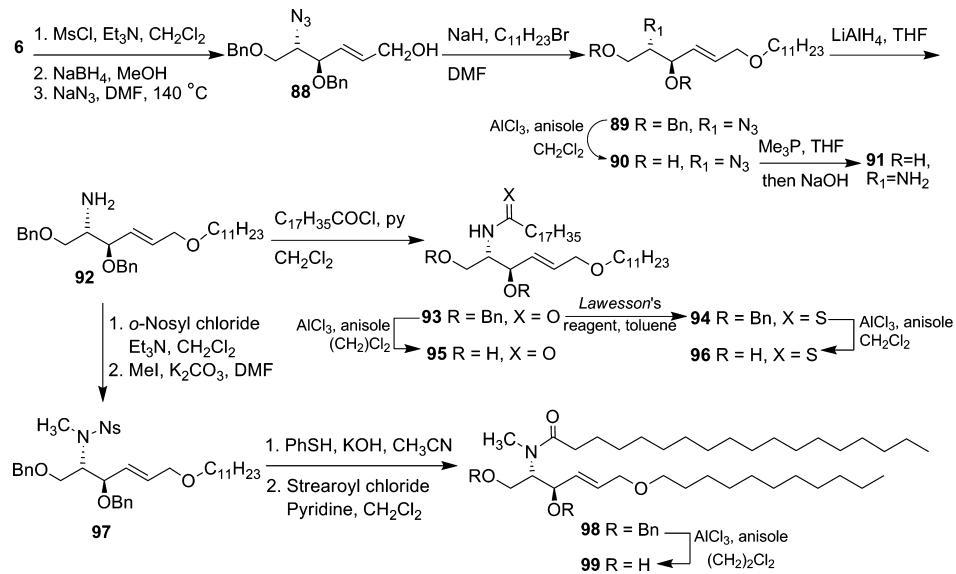
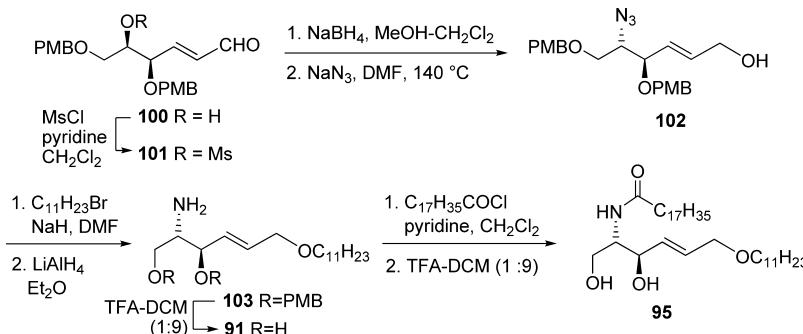
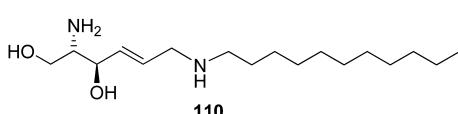
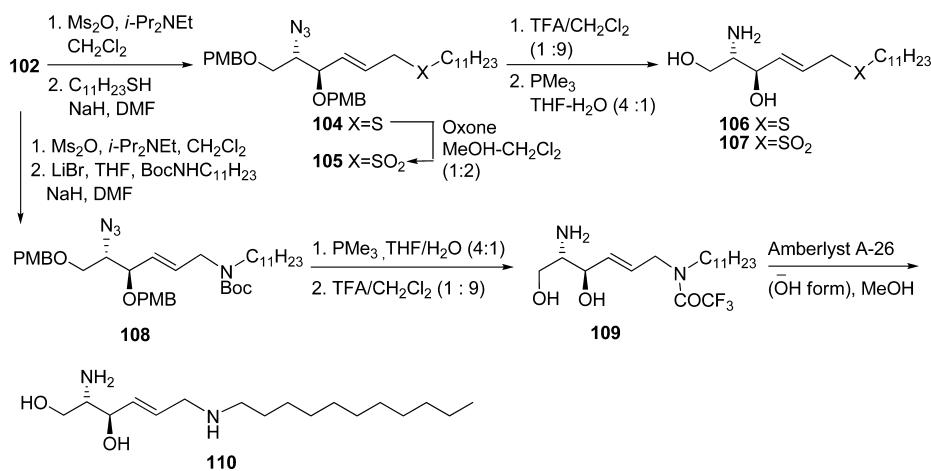


Scheme 15. Synthesis of Glucocerebrosides 84–87



65 (Scheme 11) and **67** (Scheme 12), respectively.²⁰ The C-4 stereogenic center in each of the Perlin aldehydes **48** and **49** was translated to their respective target molecules with inversion of configuration. The synthesis of **65** began from the dienoic ester **55**, which was transformed into methyl-(*S*)-6,7-epoxyheptanoate **63** after three steps. Its Grignard reaction, followed by ozonolysis and reduction of peroxide products, led to the formation of dihydroxy ester **64**. It was then successfully transformed into natural (*R*)-(+)- α -lipoic acid methyl ester **65** via dimesylation followed by reaction with sodium disulfide. Analogously, the (*S*)-(-) optical antipode **67** was synthesized from dienoic ester **50** via diol **66**.

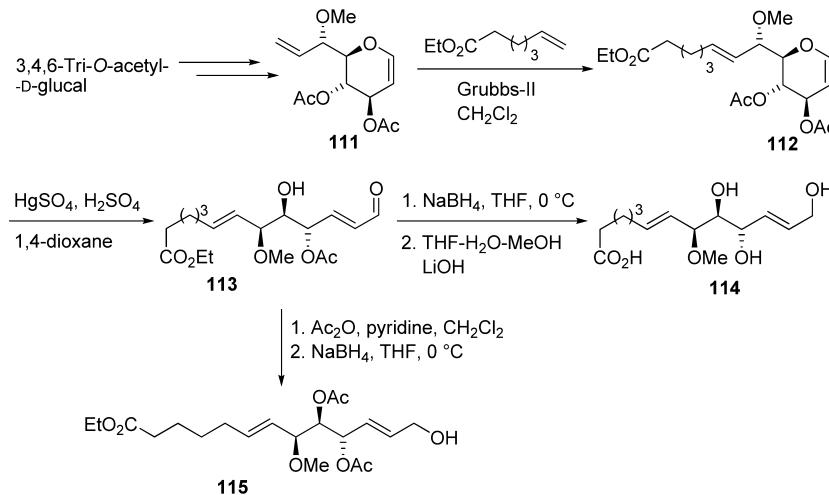
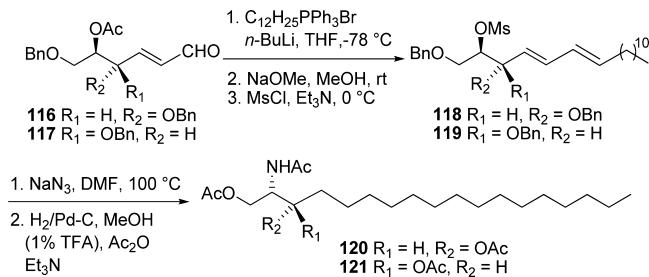
Rao et al. reported an efficient and enantiospecific synthetic approach toward 14*S*, 15*S* LTA₄ methyl ester, which could be adaptable for a large scale preparation (Scheme 13).²¹

Scheme 16. Syntheses of 7-Oxasphingosine 91, 7-Oxaceramide 95, Thio-oxaceramide 96, and N-Methyloxaceramide 99**Scheme 17. Improved Synthesis of 7-Oxasphingosine 91 and 7-Oxaceramide 95****Scheme 18. Synthesis of Sphingosine Analogues 106, 107, 109, and 110****Figure 5. Structure of Dorrigocin A.**

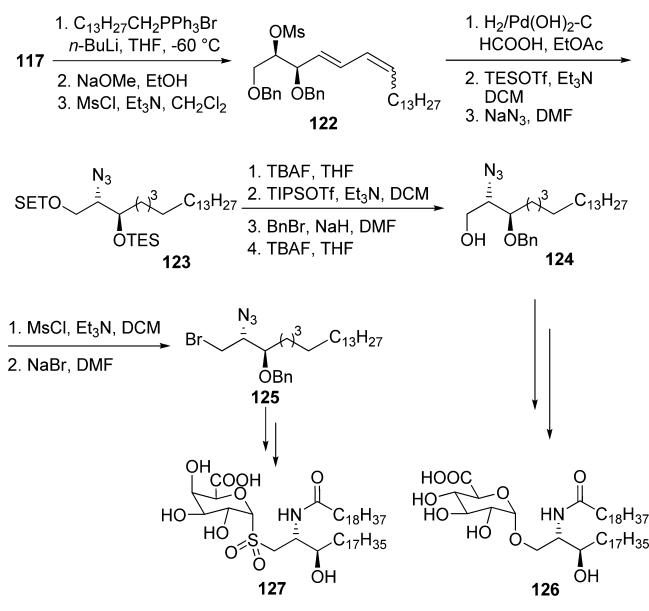
Commencing from Perlin aldehyde 1, the key diene epoxy aldehyde 71 was prepared stereoselectively. Two-carbon

homologation of enal 57 was achieved by Wittig olefination followed by hydrogenation to furnish triacetate 68. Its saponification, followed by selective mesylation of the resulting triol afforded diol 69. It was then converted to epoxaldehyde 70 in two steps involving formation of the terminal epoxide, its *in situ* rearrangement under basic conditions, and subsequent oxidation. Coupling of aldehyde 70 with 2 equiv of formylmethylenetriphenylphosphorane, followed by iodine-catalyzed isomerization,

Scheme 19. Synthesis of Analogs of Dorrigocin A 114 and 115

Scheme 20. Stereoselective Synthesis of Acetylated (*2S,3S*)-Safingol 120 and Acetylated (*2S,3R*)-Safingol 121

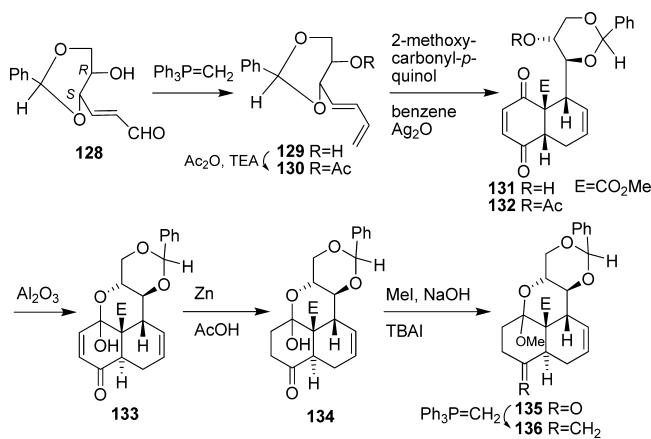
Scheme 21. Synthesis of Glycolipid 126 and Its Mimetic 127



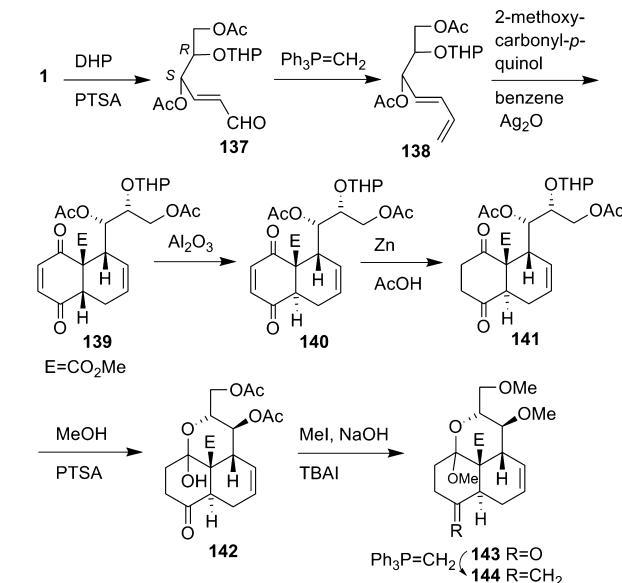
afforded all-*trans* isomer 71. Its coupling with the phosphonium salt 72, prepared from tetrahydropyranyl chloride, using LHMDS as the base for phosphorane generation in THF-HMPA (4:1) afforded a *cis:trans* mixture of target compound 73 in an 80:20 ratio (eq 4).

Hirata et al. successfully utilized the 3,4,6-tri-O-benzyl-D-galactal-derived Perlin aldehyde 6 for the synthesis of D-*erythro*-C₁₈-sphingosine 78 (Scheme 14).⁴ Luche reduction of 6

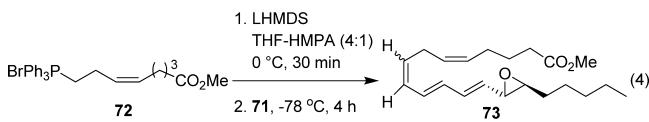
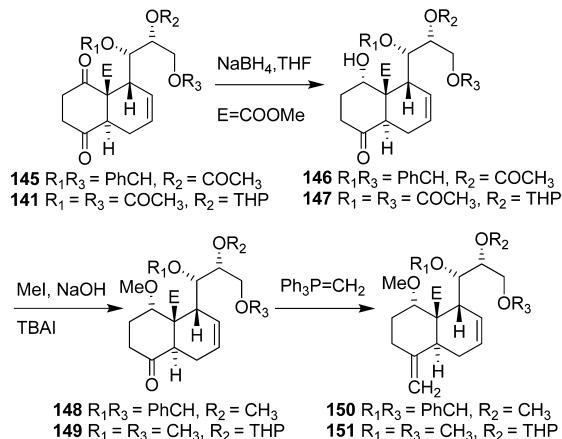
Scheme 22. Synthesis of Olefin 136



Scheme 23. Synthesis of Olefin 144

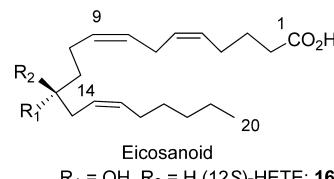
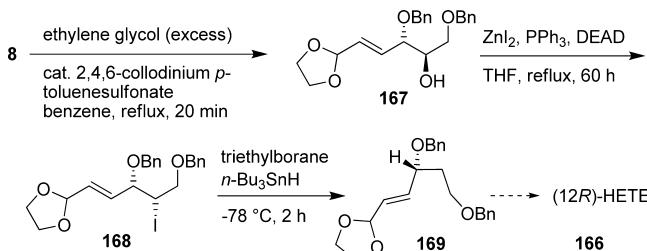
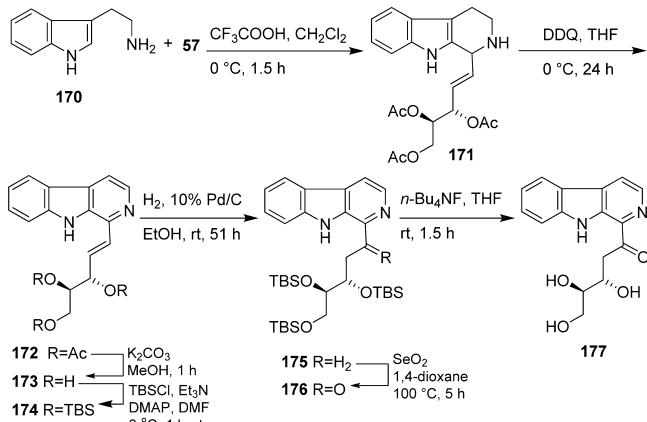
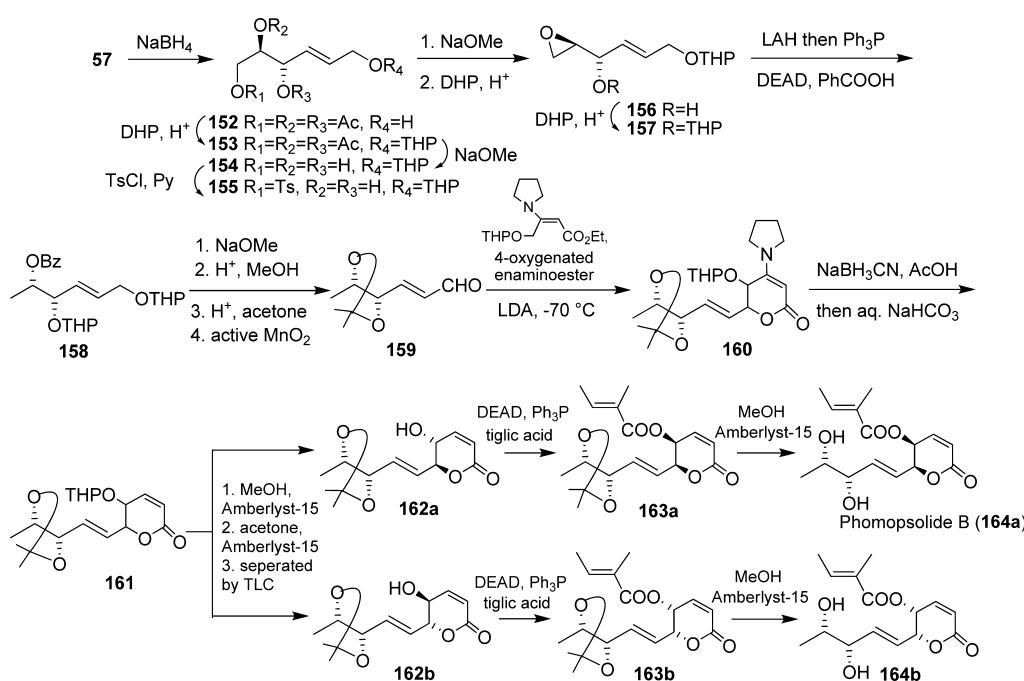


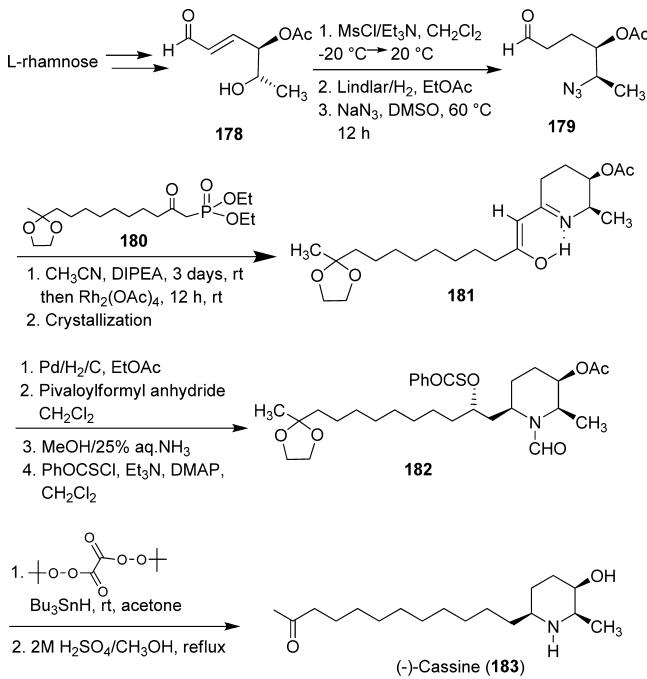
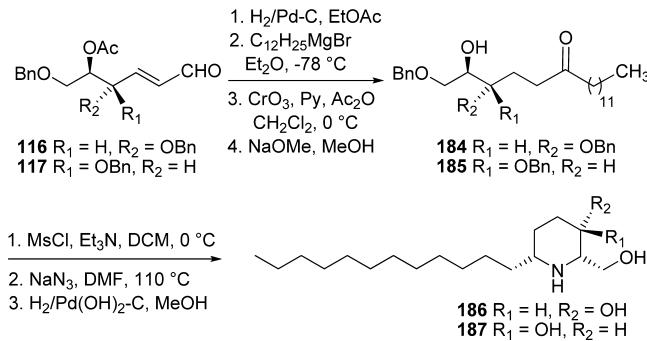
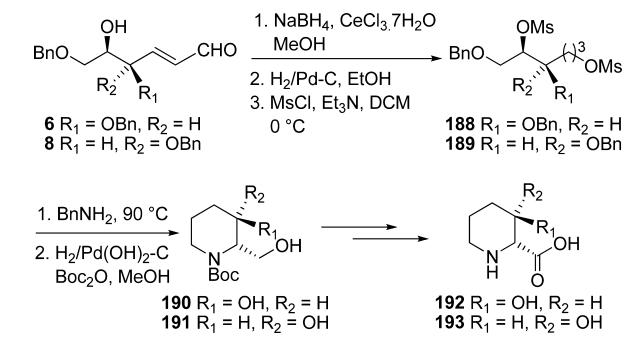
followed by acetylation and then key coupling with dodecyl magnesium bromide furnished 76. Here the role of acetate as a leaving group was crucial compared to other leaving groups (such as OMs or OTf) that gave disappointing results.

**Scheme 24. Synthesis of Olefins 150 and 151**

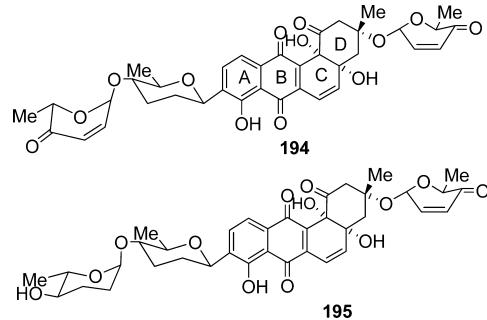
Replacement of the acetyl group by azide was carried out via methanolysis and mesylation, followed by azidation to obtain the azide 77. Its reduction, followed by benzyl deprotection, provided the required D-*erythro*-C₁₈-sphingosine 78, which was acetylated to furnish 79.

Tolstikov et al. reported an application of disaccharide-derived enal 81 for the synthesis of a new group of modified glucocerebrosides (Scheme 15).¹² Wittig olefination of 81 with dodecyltriphenylphosphonium bromide followed by exhaustive hydrogenation furnished the saturated O-glycoside 82. Its reaction with trifluoromethanesulfonic anhydride and displacement of the resulting triflate with sodium azide gave an azide intermediate, whose reduction with PPh₃ furnished the aminoacetate 83. This aminoacetate was ultimately converted

**Figure 6. Structures of (12S)- and (12R)-HETE.****Scheme 26. Synthesis of Chiral Synthon 166****Scheme 27. Synthesis of β-Carboline Derivative 177****Scheme 25. First Total Synthesis of Phomopsolide B 164a and Its Diastereoisomer 164b**

Scheme 28. Synthesis of Natural (−)-Cassine 183**Scheme 29. Synthesis of (−)-Deoxoprosophylline, (+)-2-*epi*-Deoxoprosopinine****Scheme 30. Synthesis of (2*R*,3*R*)- and (2*R*,3*S*)-3-Hydroxypipeolic Acids**

to the desired target compounds on coupling with required acid chlorides or acids. Thus, the treatment of palmitic and (11*R*)-ricinoleic chlorides with the aminoacetate 83, followed by deacetylation led to the formation of compounds 84 and 85, respectively, while coupling of the pentaacetate of 18*B*H-glycyrhristic acid trichloride with 83 followed by deacetylation and reaction with diazomethane solution gave compound 86.

**Figure 7. Structures of Sch 47554 (194) and Sch 47555 (195).**

Conjugate 87 was obtained by the reaction of amine 83 with (*5Z,13E*)-16-(2-chlorophenoxy)-9*α*,11*α*,15*α*-trihydroxy-17,18,19,20-tetranor-5,13-prostadienoic acid and *N*-hydroxy-succinimide in the presence of DCC.

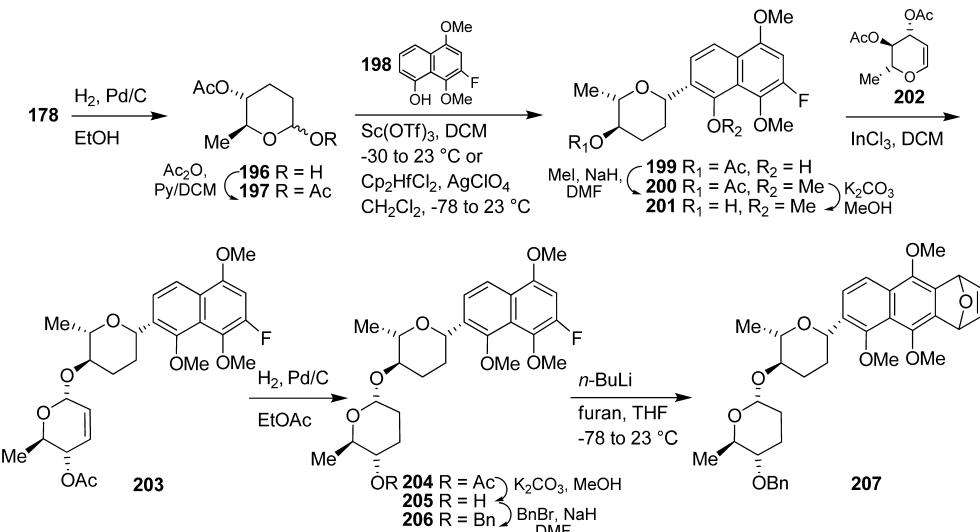
The chiral building block 6 was also exploited by Vasella et al. for the syntheses of 7-oxasphingosine 91, 7-oxaceramide 95, thio-oxaceramide 96, and *N*-methyloxaceramide 99 (Scheme 16).²² By using a human neuroblastoma (SK-N-BE) and a murine promyelocyte derived (32d) cell line, the apoptosis-inducing properties of the synthesized compounds were compared with those of sphingosine and ceramide. Here, the enal 6 was converted to azido alcohol 88 in three steps via mesylation, borohydride reduction, and S_N2 replacement of OMs with azide. *O*-Alkylation of alcohol 88 followed by debenzylation with AlCl₃ and reduction of the azide functionality with trimethylphosphine furnished 7-oxasphingosine 91 via intermediate 89. To synthesize 7-oxaceramide 95, azido compound 89 was reduced with LAH to furnish amine 92. Its *N*-acylation with stearoyl chloride, followed by debenzylation with AlCl₃, provided 7-oxaceramide 95. Thio-oxaceramide 96 was synthesized from intermediate 93 by its treatment with Lawesson's reagent followed by debenzylation. In order to synthesize *N*-methyloxaceramide 99, amine 92 was converted to nosylated compound 97 via nosylation followed by *N*-methylation. Removal of the nosyl group followed by *N*-acylation with stearoyl chloride and debenzylation afforded *N*-methyloxaceramide 99.

In 2009, the same group explored the applicability of Perlin aldehyde 100 for the improved synthesis of 7-oxasphingosine 91 and 7-oxaceramide 95 via azido alcohol 102 (Scheme 17).²³ This azido alcohol was also utilized for the construction of sphingosine analogues 106, 107, 109, and 110 (Scheme 18), which were evaluated as substrates for sphingosine kinases (SPHK), CD1d ligands, and activators of iNKT cells.

Dorrigoxin A (Figure 5) is known to display various biological activities. It inhibits carboxymethyltransferase involved in Ras processing and causes reversal of the morphology of Ras-transformed NIH/3T3 cells. The synthesis of its analogues 114 and 115 was reported by Murphy and co-workers from 3,4,6-tri-*O*-acetyl-D-glucal-derived enantiomerically pure α,β -unsaturated aldehyde 113, which was prepared by Perlin hydrolysis of 112, obtained from 3,4,6-tri-*O*-acetylglucal via 111 (Scheme 19).²⁴ Sodium borohydride reduction of aldehyde 113 followed by saponification of the ester groups furnished dorrigoxin A analogue 114. Alternatively, aldehyde 113 was converted to compound 115 via acetylation and subsequent reduction.

Vankar and his group disclosed the stereoselective synthesis of acetylated derivatives 120 and 121 of antineoplastic, antipsoriatic, and protein kinase inhibitor (2*S,3S*)-safingol and its natural (2*S,3R*) isomer, by taking advantage of the carbohydrate (Scheme 20).²⁵ The two *trans*-enals 116 and

Scheme 31. Synthesis of an Oxa-Bridged 1,4-Dihydroanthracenyl C,O-Disaccharide 207



Scheme 32. Synthesis of (-)-Pyriculariol 212

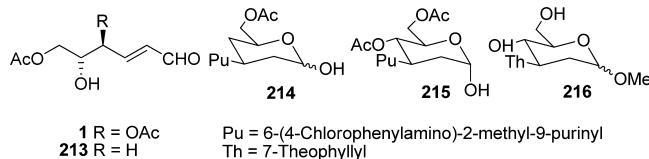
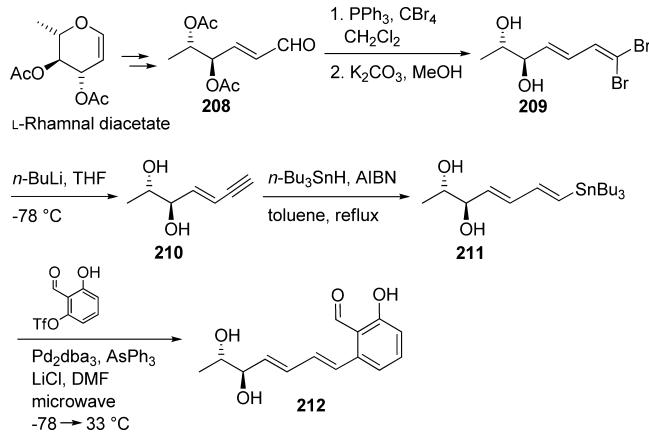
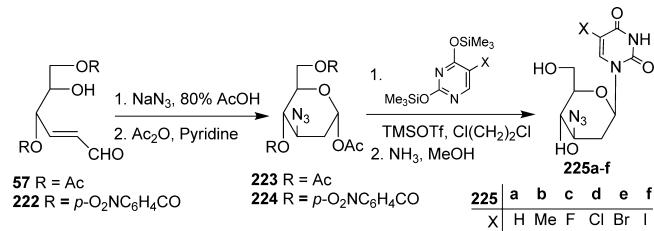


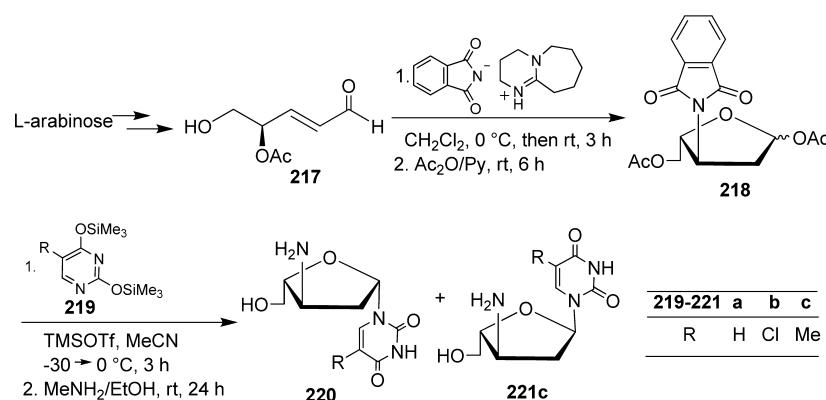
Figure 8. Structures of aldehydes 1, 213, and isonucleosides 214–216.

Scheme 34. Synthesis of 3'-Azido-2',3'-dideoxy- β -D-arabinohexapyranosyl Nucleosides 225a–f

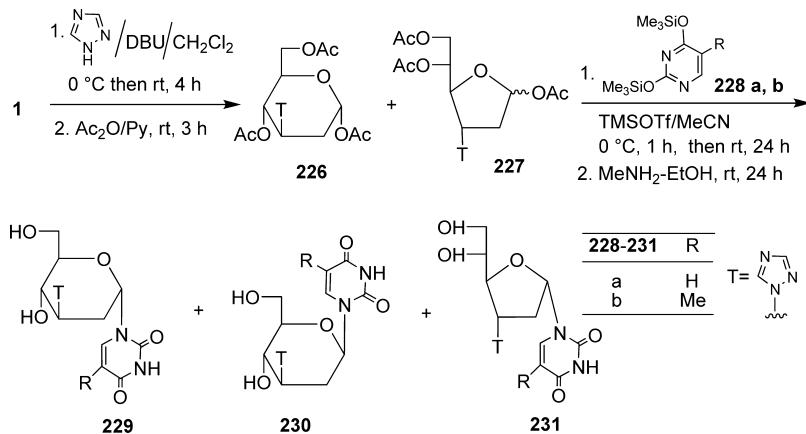
117 were prepared by Perlin hydrolysis of their respective 3,4,6-tri-O-benzyl-D-glycals (globally benzyl-protected D-glucal and D-galactal) followed by acetylation of their 5-OH groups. The two *trans* dienes 118 and 119 were obtained from enals 116 and 117, respectively, by Wittig olefination, deacetylation, and mesylation in succession. The S_N2 displacement of OMs with azide furnished azido *trans*-dienes with complete inversion at C-2, with the required *threo* and *erythro* configurations. The key step involved in the synthesis of target molecules 120 and 121 was Pd-C-catalyzed hydrogenation of the resulting azido *trans*-diene intermediates followed by acetylation in a one-pot procedure.

In 2009, Murphy and co-workers employed a building block enal 117 for the synthesis of dihydroceramide derivative 124 and its bromo derivative 125, which were further utilized for the

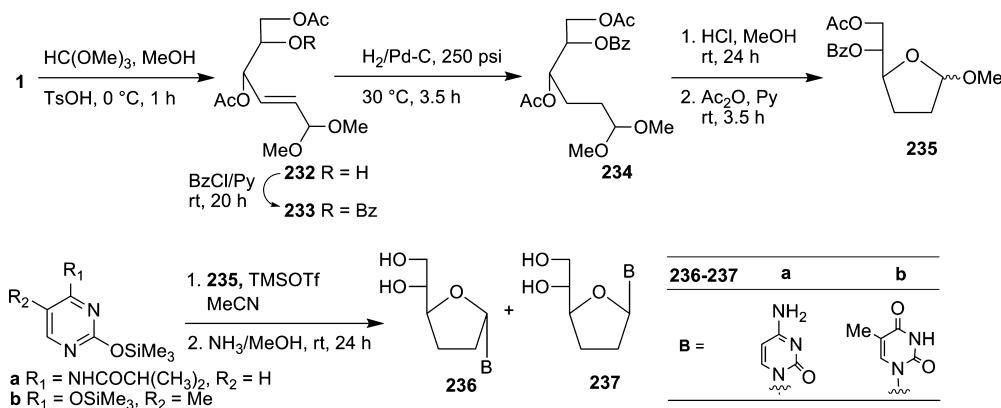
Scheme 33. Synthesis of L-3'-Amino-2',3'-dideoxyuridines



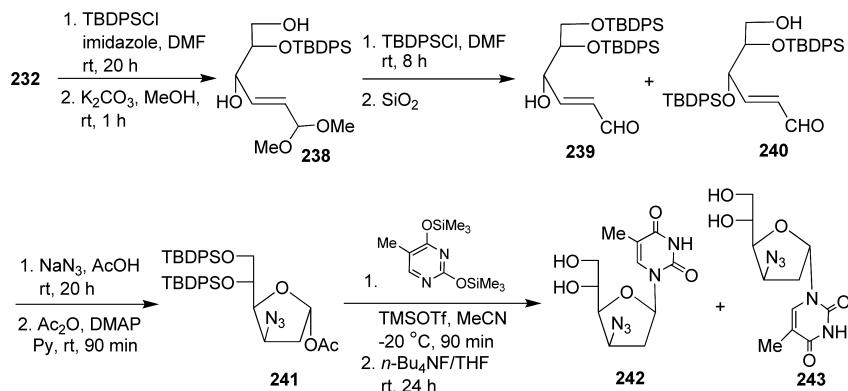
Scheme 35. Synthesis of Pyranose and Furanose Pyrimidine Nucleosides 229–231



Scheme 36. Synthesis of 2',3'-Dideoxy-D-erythro-hexafuranosyl Nucleosides 236 and 237



Scheme 37. Synthesis of 3'-azido-2',3'-dideoxy-D-arabino-hexafuranosyl nucleosides 242 and 243

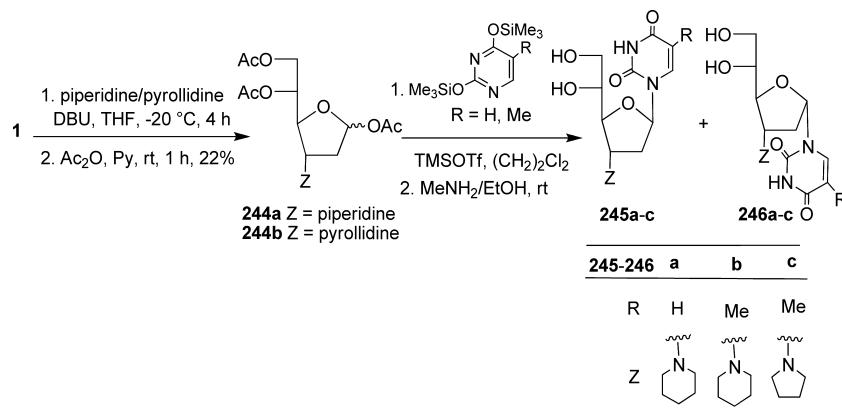


synthesis of glycolipid 126 and its mimetic 127, respectively (Scheme 21).²⁶ Aldehyde 117 was converted to mesyl derivative 122 via Wittig olefination, deacetylation, and mesylation. This mesyl derivative on exhaustive hydrogenation, followed by silyl protection and subsequent displacement of mesylate with azide, afforded azido compound 123. It was then transformed to dihydroceramide derivative 124 in four steps. Conversion of compound 124 to bromide 125 was achieved via mesylate intermediate. Ceramides 124 and 125 were utilized as precursors in the synthesis of glycolipids 126 and 127, respectively, by exploiting chelation-controlled anomeration as the key step.

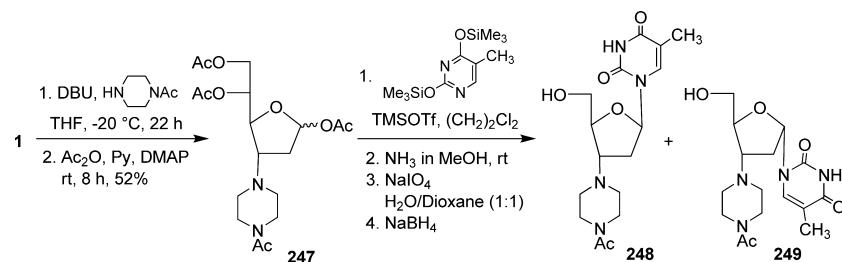
Bhakuni and his colleagues, in their attempt toward an alternative approach for the proposed synthesis of highly

oxygenated labdane diterpenoid, forskolin, reported a convenient route for the synthesis of key compounds 136 (Scheme 22), 144 (Scheme 23), 150, and 151 (Scheme 24).^{27,28} Perlin aldehyde 128, obtained by Perlin hydrolysis of 3-O-acetyl-4,6-O-benzylidene-D-allal, was subjected to a series of chemical transformations in a sequence involving Wittig olefination, Diels–Alder reaction, epimerization, and reduction to furnish hemiketal 134. Since Wittig olefination of the keto group at C4 of this hemiketal did not give the desired product, the hemiketal functionality of compound 134 was then protected. Its protection by alkaline methyl iodide in the presence of a catalytic amount of TBAI, followed by base-free Wittig olefination with methylenetriphenylphosphorane, delivered the required olefin 136.

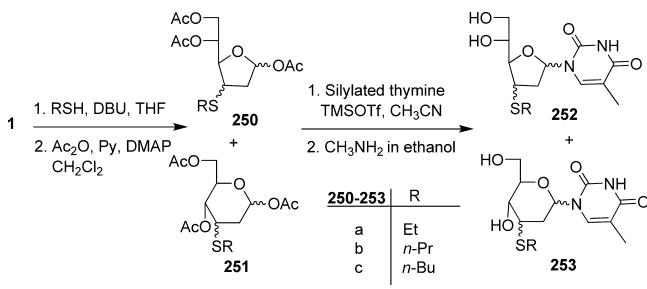
Scheme 38. Synthesis of 2',3'-Dideoxy-3'-piperidino- and 2',3'-Dideoxy-3'-pyrrolidine-d-ribo-hexafuranosyl Nucleosides (245a–c and 246a–c)



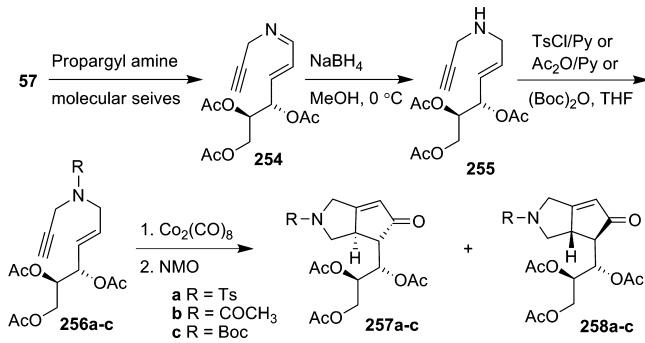
Scheme 39. Synthesis of 3'-Substituted-2',3'-dideoxynucleosides with Pentafurano Skeletons



Scheme 40. Synthesis of 3'-Alkylthio-2',3'-dideoxynucleoside (252 and 253)

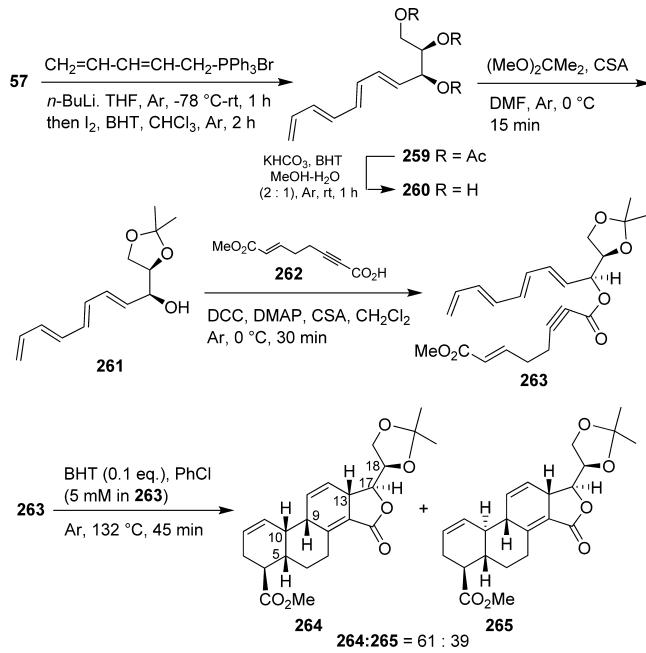


Scheme 41. Synthesis of Enantiomerically Pure N-Substituted-3-azabicyclo[3.3.0]octen-7-one Derivatives



In order to circumvent the circuitous synthesis of hemiketal 135, they simultaneously investigated the synthesis of 144 starting from Perlin aldehyde 1 just by changing the protecting groups as shown in Scheme 23. The key exomethylene compounds 150 and 151 were made available from 145 and

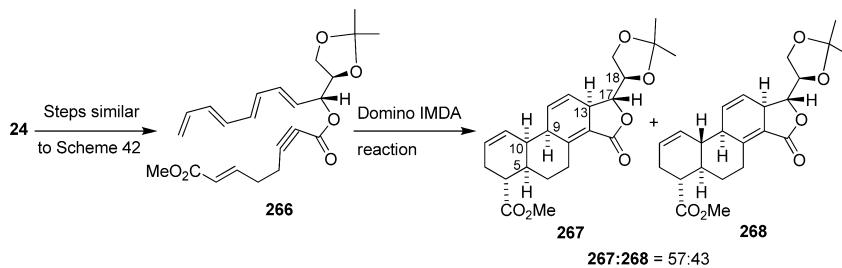
Scheme 42. Synthesis of Tetracyclic Products 264 and 265 via Zipper-Mode Domino Intramolecular Diels–Alder (IMDA) Strategy



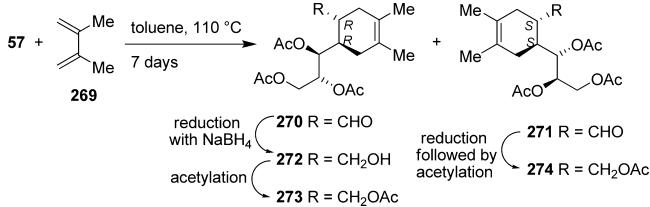
141, respectively (Scheme 24), in three steps: selective reduction, protection of alcohol, and Wittig olefination.

Noshita et al., by utilizing the enal 57, successfully completed the first total synthesis of optically active phomopsolide B (164 a), one of the major metabolites of the fungus *Phomopsis oblonga* cohabiting the elm tree (Scheme 25).^{29,30} The highlight of their synthetic protocol was the coupling of the unsaturated aldehyde

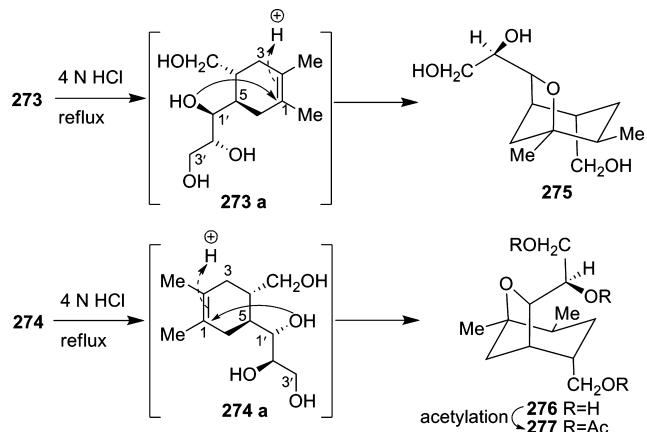
Scheme 43. Synthesis of Cycloadducts 267 and 268



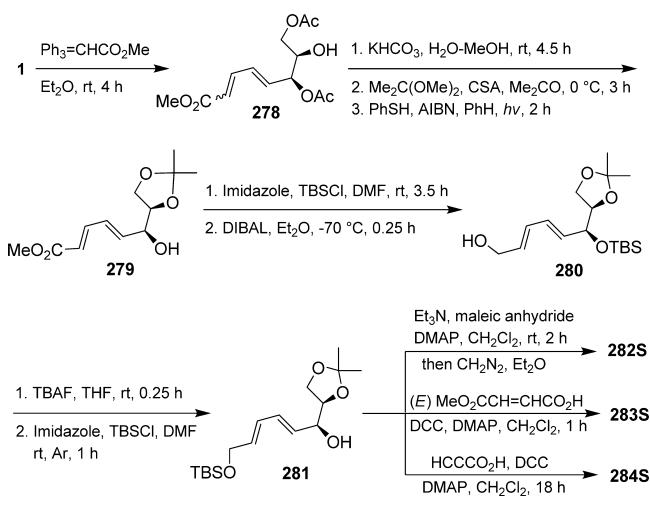
Scheme 44. Synthesis of Intermediates 273 and 274



Scheme 45. Synthesis of 6-Oxabicyclo[3.2.1]octanes



Scheme 46. Synthesis of C-9 Substituted 1,3,8-Nonatrienes 282S, 283S, and Nonadiyne 284S



159 and 4-oxygenated enaminoester by Schlessinger's method.³¹ To synthesize aldehyde **159**, 3,4-O-diacetyl-6-deoxy-D-glucal (diacetyl-D-rhamnal) was used as the chiral starting material. But the aldehyde **159** obtained from diacetyl-D-rhamnal showed low

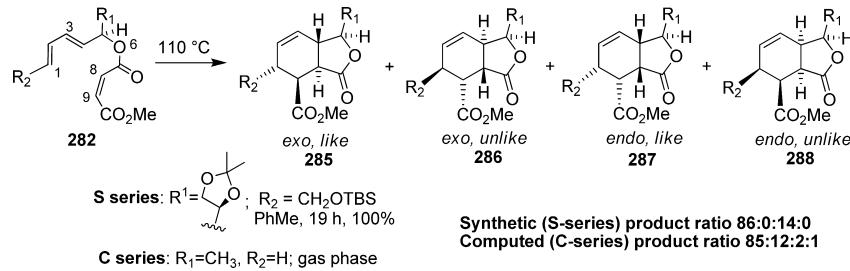
optical purity (ca. 25%), which was attributed to possible migration during the synthetic and/or purification process. Therefore, unsaturated aldehyde **159** was prepared from peracetyl Perlin aldehyde **57** by a simple and efficient set of reactions: reduction, protection–deprotection manipulations, and Mitsunobu reaction. In the next step, aldehyde **159** was coupled with 4-oxygenated enaminoester using LDA to give a 5,6-*trans* and 5,6-*cis* diastereomeric mixture of dihydropyranones **160** in a 4:1 ratio. Its 5,6-*trans* isomer was converted into dihydropyranone **161** by sodium cyanoborohydride reduction and subsequent treatment with aq. NaHCO₃. Removal of acid-sensitive protecting groups (acetone and THP) and re-protection of the resulting vicinal dihydroxyl groups as their acetonide furnished a separable diastereomeric mixture of 5-hydroxy dihydropyranones **162a** and **162b**, which were then ultimately converted to phomopsolide B (**164a**) and its (5*R*,6*R*) diastereoisomer **164b**, respectively, involving a Mitsunobu reaction (Ph₃P, DEAD, and tiglic acid) followed by acetonide deprotection.

It is known from the literature that compound **165** (12*S*-HETE (Figure 6)) is the major lipoxygenation product found in human platelets, while its optical antipode (12*R*-HETE **166**) is found in large amounts in psoriatic scales. In view of their importance, Lellouche and Quinton identified the 3,4,6-tri-O-benzyl-D-glucal-derived Perlin aldehyde **8** as the precursor of choice for the synthesis of a new six-carbon multifunctionalized chiral synthon **169**,⁶ a useful intermediate for eicosanoid (**166**) synthesis (Scheme 26). The crucial deoxygenation of **167** was done by its modified Mitsunobu reaction to give iodide **168**, whose triethyl borane (Et₃B)-catalyzed reduction by *n*-tributyltin hydride (*n*-Bu₃SnH) furnished **169** in good yield.

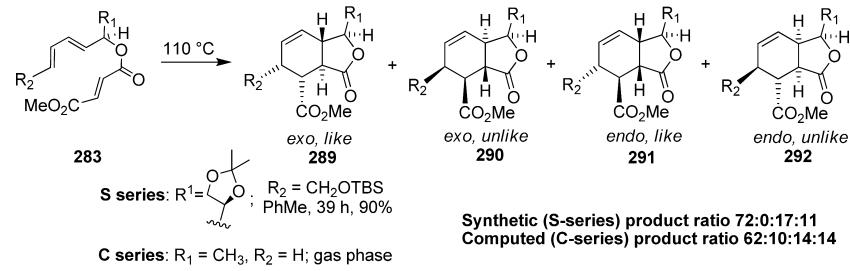
Aimi and co-workers isolated a new chiral β-carboline derivative **177** during the chemical investigation of the metabolites formed by cultured hybrid cells of two Apocynaceae plants, *Rauvolfia serpentina* Benth and *Rhazya Stricta* Decaisne (Scheme 27).³² The structure of **177** was confirmed by its chemical synthesis starting from tryptamine **170** and the enal **57**. Acid-catalyzed condensation of aldehyde **57** with tryptamine **170** afforded tetrahydro-β-carboline **171**, which was converted to **174** using DDQ-mediated aromatization and deprotection–protection sequences. Hydrogenation, followed by arylidic oxidation and subsequent desilylation of compound **174**, gave alkaloid **177**.

L-Rhamnose-derived Perlin aldehyde **178** was exploited by Herdeis et al. for the synthesis of natural (−)-cassine **183** (Scheme 28).³³ Enal **178** was transformed to azido derivative **179** in three steps that involved mesylation, hydrogenation, and displacement of mesylate with azide. Horner–Wadsworth–Emmons (HWE) reaction and concomitant cycloaddition with ketophosphonate **180**, followed by crystallization, provided compound **181**. It was converted to the thiocarbonate **182** in four steps. Its deoxygenation with di-*tert*-butyl peroxyoxalate

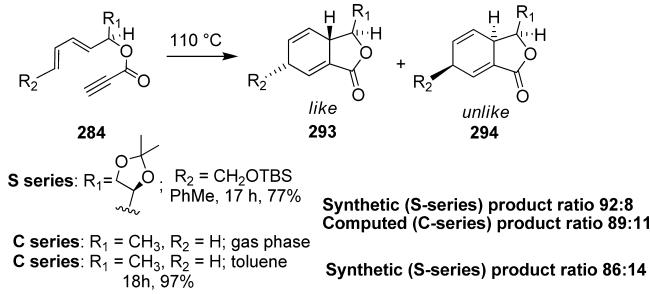
Scheme 47. IMDA Reactions of Triene 282



Scheme 48. IMDA Reactions of Triene 283



Scheme 49. IMDA Reactions of Dienyne 284



and $n\text{-Bu}_3\text{SnH}$, followed by acid hydrolysis, furnished the title molecule (*-*)-cassine **183**.

The applicability of glycal-derived α,β -unsaturated Perlin aldehydes for the synthesis of naturally occurring bioactive piperidine alkaloids and their derivatives was also explored by Vankar and his group.³⁴ They synthesized (*-*)-deoxoprosophylline and (+)-*2-epi*-deoxoprosopinine from unsaturated aldehydes **116** and **117**, respectively, as outlined in Scheme 29. Unsaturated aldehyde **116** was transformed to ketone **184** in four steps involving hydrogenation of the *E*-double bond, Grignard reaction using dodecylmagnesium bromide, oxidation of the newly generated hydroxyl group and deacetylation. Its mesylation followed by S_N2 displacement of mesylate with azide and subsequent hydrogenation afforded (+)-*2-epi*-deoxoprosopinine **186**. Similarly, (*-*)-deoxoprosophylline **187** was synthesized from unsaturated aldehyde **117**.

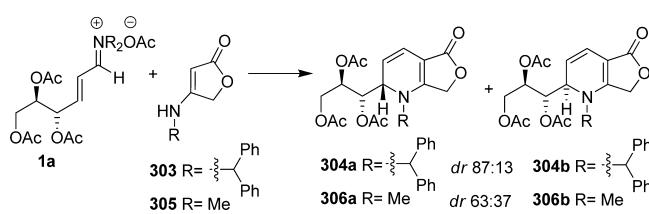
In the same communication, they also reported the syntheses of (*2R,3R*)- and (*2R,3S*)-3-hydroxypipeolic acids **192** and **193** from aldehydes **6** and **8**, respectively (Scheme 30). Luche reduction of Perlin aldehyde **6** followed by hydrogenation and subsequent mesylation afforded dimesylate **188**. The Boc-protected piperidine **190** was obtained by cyclization of **188** with benzylamine, followed by debenzylation and *in situ* Boc protection, which was finally converted to isomeric 3-hydroxypipeolic acid **192** by using literature methods. Analogously, Perlin aldehyde **8** was converted to another isomeric target molecule 3-hydroxypipeolic acid **193**.

Table 1. Aza-[3 + 3] Annulation Reactions of Perlin Aldehyde with Different Amides

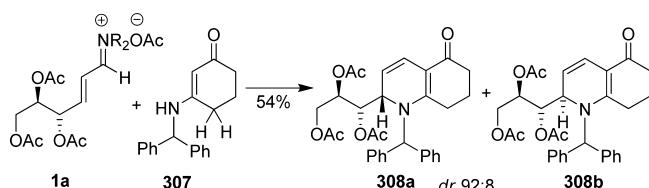
Entry	Amide	Cycloadduct	T (°C)	Yield (%)	dr
1	295	299	150	64	75:25
2	296	300	130	49	77:23
3	297	301	170	61	69:31
4	298	302	150	76	83:17

Barrett and co-workers³⁵ disclosed the synthesis of an oxabridged 1,4-dihydroanthracenyl *C,O*-disaccharide **207**, a model compound relevant to the total synthesis of Sch 47555 (**195**, Figure 7), by utilizing aldehyde **178** (Scheme 31). Enal **178** was converted to **197** by hydrogenation followed by acetylation. Condensation of **197** with aryl fluoride **198** was catalyzed by scandium triflate or hafnocene dichloride and silver perchlorate to afford required C-aryl glycoside **199** as a single

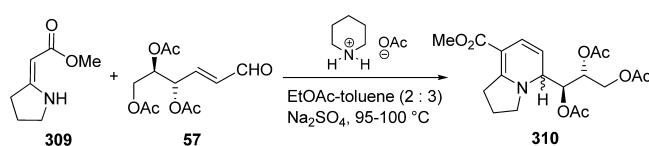
Scheme 50. Torquoselective 6π -Electron Electrocyclic Ring Closure of 1-Azatrienes



Scheme 51. Electrocyclic Ring Closure of 1-Azatrienes with Amide 307



Scheme 52. Synthesis of Tetrahydroindolizidine 310



diastereoisomer. Methylation of free hydroxyl in 199 followed by deprotection of acetyl group delivered 201. Indium trichloride-catalyzed Ferrier-type rearrangement of 201 with di-O-acetyl-D-rhamnal 202 produced disaccharide 203. Hydrogenation of the double bond in 203 followed by deacetylation gave the A–C ring unit of *ent*-Sch 47555 205. Protection of free hydroxyl group in 205 as a benzyl ether furnished 206, which on reaction with *n*-BuLi and furan afforded cycloadduct 207 as a 1:1 mixture of diastereoisomers. In compound 207, it was found that the disaccharide unit under acidic conditions was more prone to cleavage than the oxa-bridged 1,4-dihydroanthracenyl unit.

Sasaki et al. determined the absolute configuration of (*−*)-pyriculariol, a phytotoxin, by its total synthesis from L-rhamnal diacetate-derived α,β -unsaturated aldehyde 208 (Scheme 32).³⁶ Enal 208 was converted to dibromoolefin

Table 2. Synthesis of Enantiomerically Pure Trisubstituted Tetrahydrofurans

Entry	Epoxide	Product	Yield (%)
1	316	323	82
2	317	324	78
3	318	325	76
4	319	326	83
5	320	327	70
6	321	328	77
7	314	313	68
8	322	329	60

Scheme 53. Epoxidation Studies of Perlin Aldehyde-Derived Allylic Alcohol 311

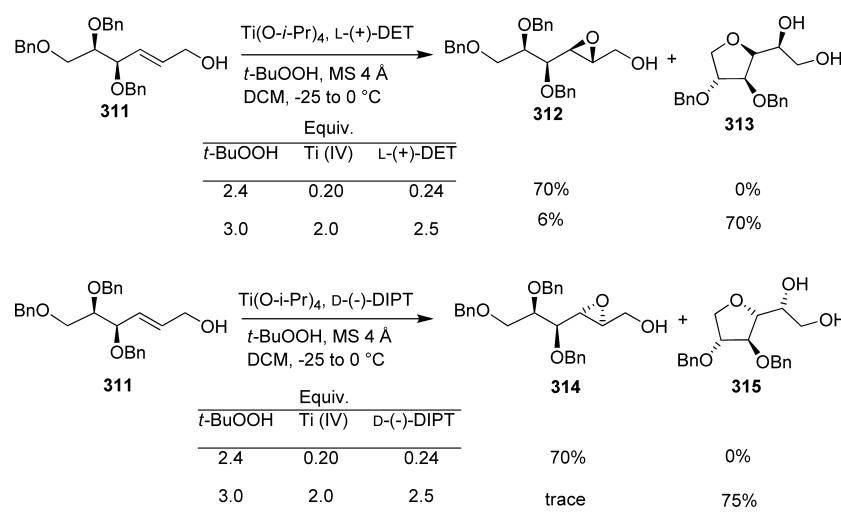


Table 3. Direct Conversion of Perlin Aldehyde-Derived Allylic Alcohols into Enantiomerically Pure THF Domains

Entry	Reactant	Major (yield)		Minor (yield)
		330	333 (48%)	
1 ^a	BnO ₂ CH(R ₂)CH(R ₁)CH=CHCO ₂ H			
2 ^a	BnO ₂ CH(OH)CH(R ₂)CH(R ₁)CH=CHCO ₂ H			
3 ^a	BnO ₂ CH(OBn)CH(R ₂)CH(R ₁)CH=CHCO ₂ H			
4 ^a	BnO ₂ CH(OBn)CH(R ₂)CH(R ₁)CH=CHCO ₂ H			
5 ^b	BnO ₂ CH(OH)CH(OBn)CH(R ₂)CH(R ₁)CH=CHCO ₂ H			
6 ^b	BnO ₂ CH(OH)CH(OBn)CH(R ₂)CH(R ₁)CH=CHCO ₂ H			
7 ^b	BnO ₂ CH(OH)CH(OBn)CH(R ₂)CH(R ₁)CH=CHCO ₂ H			

^aSharpless reagent (+)-DET. ^bSharpless reagent (-)-DET.

209 by Corey–Fuchs reaction followed by deacetylation. *n*-BuLi mediated elimination of both the bromines furnished enyne 210. Radical-mediated hydrostannylation of 210 with tributyltin hydride under reflux conditions gave stannane 211. Its key Stille coupling reaction with an aromatic triflate using microwave irradiation at –78 to 33 °C afforded the target natural product 212.

4.2. Synthesis of Nucleosides

Synthesis of 2',3'-dideoxynucleosides has been a topic of intense interest owing to their potential antiretroviral activity against human immunodeficiency virus (HIV) by inhibiting reverse transcriptase.^{37–39} Pedersen and Wengel have investigated the synthetic utility of the above-described α,β -unsaturated sugar aldehydes (Perlin aldehydes), derived from their appropriate glycals, as precursors for the synthesis of differentially substituted nucleosides.

Pedersen et al. in 1988 achieved the synthesis of isonucleosides 214, 215, and 216 by Michael-type addition of purines to Perlin aldehydes 1 and 213 in the presence of organic base, in DMF at 40 °C (Figure 8).⁴⁰ They observed a large increase in

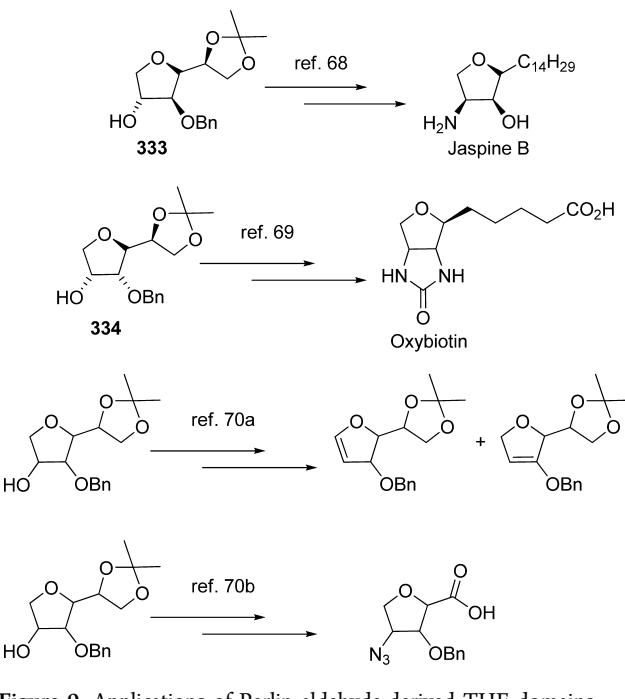
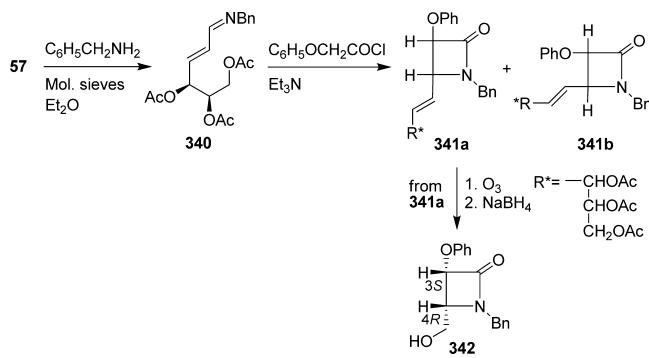
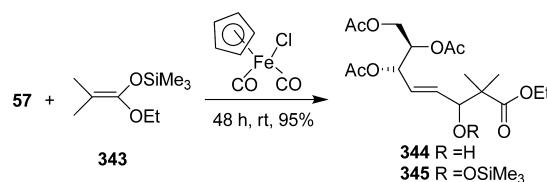


Figure 9. Applications of Perlin aldehyde-derived THF domains.

Scheme 54. Synthesis of Enantiomerically Pure β -Lactams



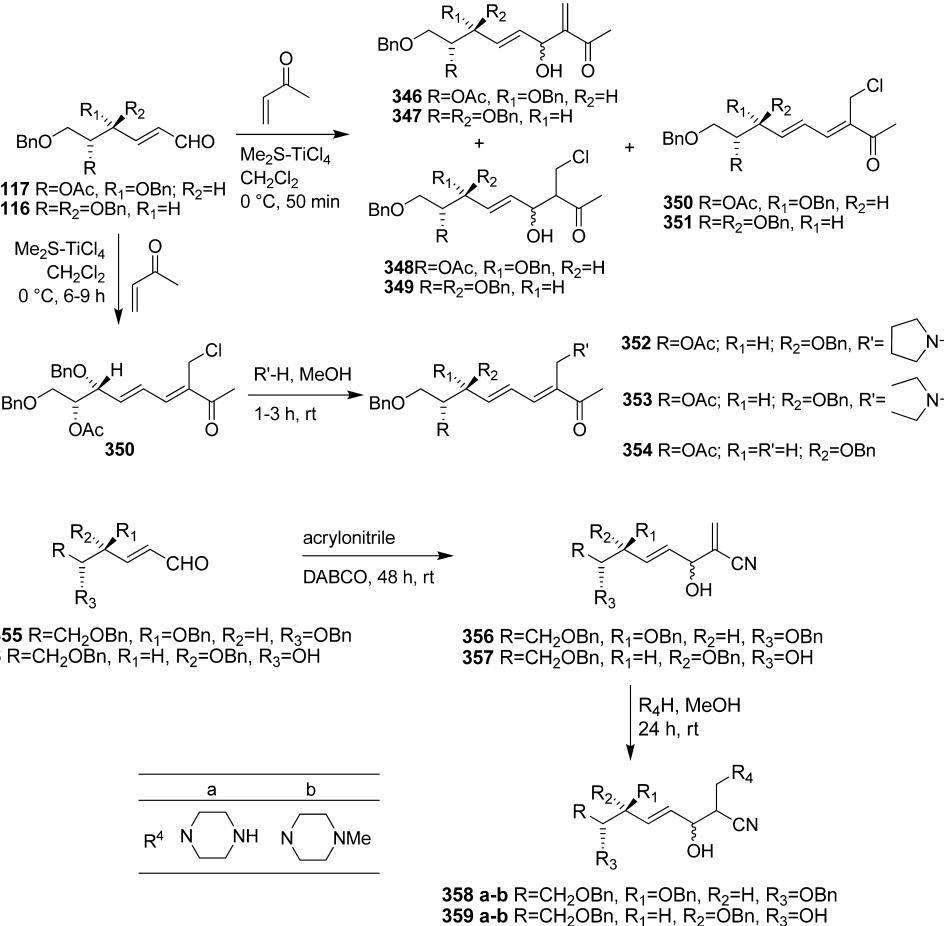
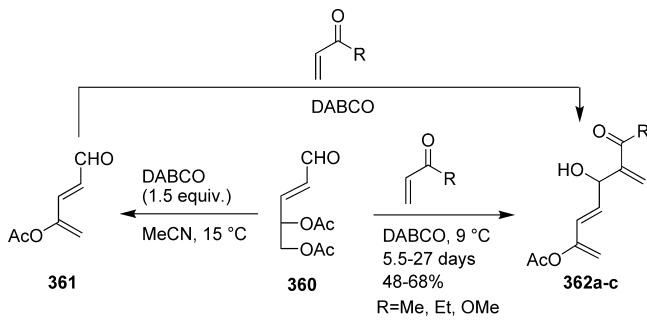
Scheme 55. Aldol Addition of Enolsilane to Perlin Aldehyde 57



reaction rate during the addition of theophylline to aldehyde 1 when DBU was used as a base instead of Et₃N.

The same group also reported an elegant method for the first synthesis of L-3'-amino-2',3'-dideoxyuridines starting from L-arabinal-derived Perlin aldehyde 217 (Scheme 33).⁴¹ Michael-type addition of phthalimide to enal 217 and subsequent acetylation delivered an anomeric mixture of 1,5-di-O-acetyl-2,3-dideoxy-3-phthalimido-L-*erythro*-pentofuranose 218. In this step only the furanose form was obtained by shifting of the acetyl group from 4-O to 5-O during an addition reaction. Trimethylsilyl triflate-catalyzed reaction of furanose 218 with silylated 2,4-dihydroxypyrimidines 219, followed by deprotection of amino and hydroxy groups with methylamine, afforded L-3'-amino-2',3'-dideoxynucleosides 220 and 221c.

Scheme 56. Studies of MBH Reactions of Perlin Aldehyde As Electrophilic Partner

Scheme 57. Tandem β -Elimination-Morita-Baylis-Hillman Reaction of Acetylated Perlin Aldehyde 360

Synthesis of 3'-azido-2',3'-dideoxy- β -D-arabino-hexopyranosyl nucleosides 225a-f utilizing the D-glucal derived Perlin aldehydes 57 and 222 was reported by Pedersen and co-workers (Scheme 34).⁴² Treatment of these enals with sodium azide in acetic acid and water followed by acetylation of the resulting azido compounds gave 3-azido-2,3-dideoxyhexopyranoses 223 and 224, respectively. Their TMSOTf-catalyzed reaction with 5-substituted 2,4-bis(trimethylsiloxy)pyrimidines and subsequent deprotection with a saturated solution of ammonia in methanol afforded β -arabino nucleosides 225 as the exclusive product.

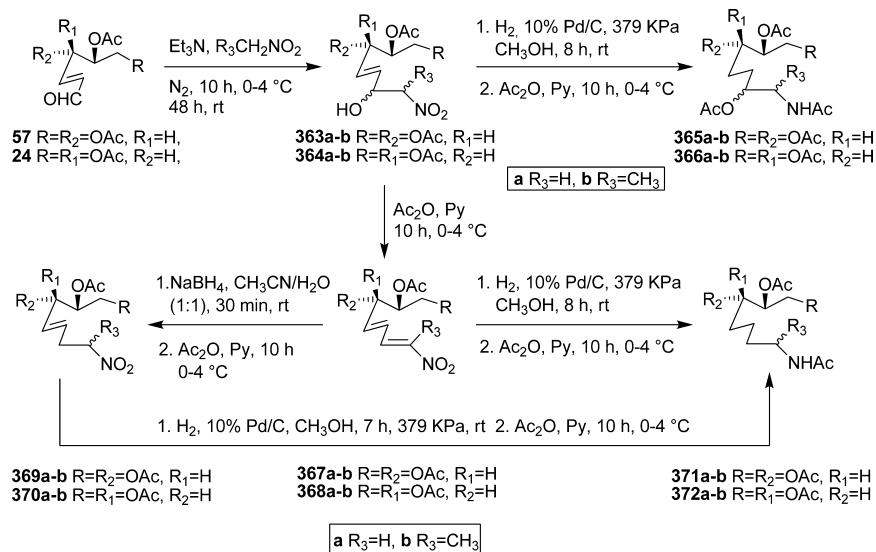
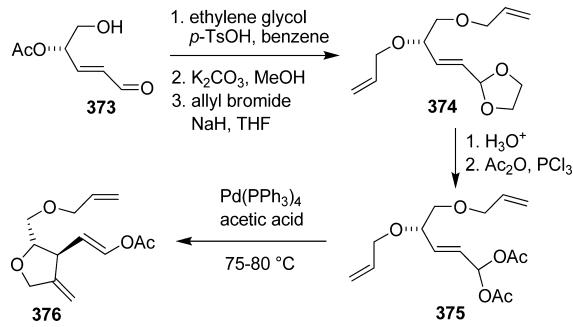
Pedersen and co-workers also demonstrated the synthesis of both pyranose and furanose pyrimidine nucleosides 229–231 starting from Perlin aldehyde 1 (Scheme 35).⁴³ Michael-type

addition reaction of 1,2,4-triazole to Perlin aldehyde 1 in the presence of DBU followed by acetylation produced an isomeric mixture of 1,4,6-tri-O-acetyl-2,3-dideoxy-3-(1,2,4-triazol-1-yl)- α -D-arabino-hexopyranoside 226 and 1,5,6-tri-O-acetyl-2,3-dideoxy-3-(1,2,4-triazol-1-yl)- α,β -D-ribo-hexofuranosides 227. Modified Freidel-Crafts catalyzed silyl-Hilbert-Johnson reaction⁴⁴ of this mixture with silylated bases 228 in the presence of TMSOTf, followed by deprotection of acetyl groups with methylamine, produced nucleosides 229–231.

In another report, Perlin aldehyde 1 was also exploited in the synthesis of 2',3'-dideoxy-D-erythro-hexofuranosyl nucleosides and 3'-azido-2',3'-dideoxy-D-arabino-hexofuranosyl nucleosides (Scheme 36).⁴⁵ The enal 1 was converted to unsaturated acetal 233 by acetalation followed by benzoylation. The synthetic strategy, involving a sequence of reactions to obtain the designed 2',3'-dideoxy-D-erythro-hexofuranosyl nucleosides 236 and 237, were as follows. Hydrogenation of the double bond in 233 provided saturated acetal 234. Its methanolysis followed by acetylation afforded methyl glycoside 235. Coupling of the furanoside 235 with silylated N⁶-iso-butyrylcytosine or silylated thymine in the presence of Lewis acid (TMSOTf), followed by deacetylation with methanolic ammonia, furnished 2',3'-dideoxy nucleosides 236 (α -isomer) and 237 (β -isomer).

Further, they also reported the synthesis of 3'-azido-2',3'-dideoxy-D-arabino-hexofuranosyl nucleosides 242 and 243 from unsaturated acetal 232, which was in turn prepared from carbohydrate enal 1 (Scheme 37). Acetal 232 was transformed to diol 238 involving silyl protection followed by deacetylation.

Scheme 58. Synthesis of Acyclic Nitro and Amino Deoxy Alditols

Scheme 59. Synthesis of Enantiopure *trans*-enolacetate 376

Its silyl protection with TBDPSCl followed by cleavage of acetal afforded a 1:1 mixture of aldehydes **239** and **240**. The 1,4-addition of hydrazoic acid to these α,β -unsaturated aldehydes and subsequent acetylation furnished β -D-*arabino* furanose **241**. Its coupling with silylated thymine in the presence of TMSOTf, followed by desilylation with TBAF, gave the designed nucleosides **242** (β -isomer) and **243** (α -isomer) in a 1:1 ratio.

Wengel et al. synthesized 2',3'-dideoxy-3'-piperidino- and 2',3'-dideoxy-3'-pyrrolidino-D-*ribo*-hexofuranosyl nucleosides (**245a–c** and **246a–c**) from Perlin aldehyde **1** (Scheme 38).⁴⁶ Michael-type addition of piperidine and pyrrolidine to **1** in the presence of DBU, followed by acetylation, afforded anomeric mixtures of 2,3-dideoxy-3-piperidino-D-*ribo*-hexofuranose (**244a**) and 2,3-dideoxy-3-pyrrolidino-D-*ribo*-hexofuranose (**244b**). Condensation of **244a** and **244b** with silylated uracil and silylated thymine using TMSOTf as catalyst, and subsequent deacetylation with methyl amine provided nucleosides **245a–c** and **246a–c**.

In another communication,⁴⁷ the same group reported an advantageous and general method for the synthesis of 3'-substituted-2',3'-dideoxynucleosides with pentafuranose skeletons from easily accessible Perlin aldehyde **1** in only six steps (Scheme 39). Addition of *N*-acetylpirperazine to **1** in the presence of DBU, followed by base-promoted acetyl shift from 4-O to 5-O and subsequent acetylation, produced furanose **247**. It was then converted to nucleosides **248** and **249** in four steps involving TMSOTf-catalyzed condensation with silylated thymine, deacetylation using ammonia in methanol, oxidative

cleavage of the resulting diol with $NaIO_4$, and reduction with sodium borohydride.

Subsequently, the same group⁴⁸ reported the synthesis of a small library of 17 novel 3'-alkylthio-2',3'-dideoxynucleosides **252** and **253** (Scheme 40). Michael-type addition of alkanethiols to **1**, followed by acetylation, afforded **250** and **251**. Their nucleoside coupling with silylated thymine under identical conditions and acetyl deprotection by methylamine gave nucleosides **252** and **253**.

4.3. Cycloaddition Reactions

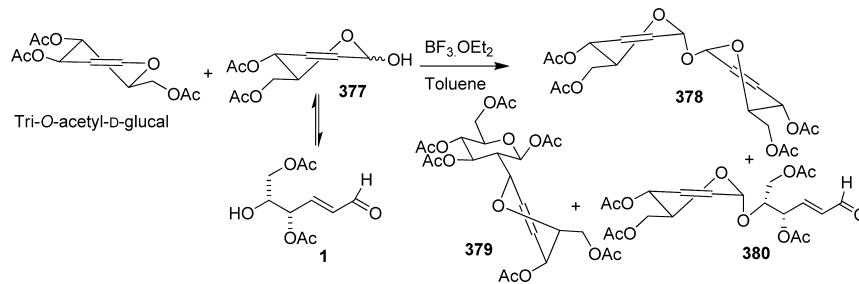
Use of cycloadditions in organic synthesis is ubiquitous, mostly because in one step multiple stereocenters can be generated in the desired molecule with high selectivities and usually good yields.⁴⁹

4.3.1. Intramolecular Pauson-Khand Cycloaddition. Enantiomerically pure *N*-substituted-3-azabicyclo[3.3.0]octen-7-one derivatives are important intermediates for the synthesis of (−)-Kainic acid. A convenient synthesis of this class of intermediates **257a–c** and **258a–c** was achieved from enal **57** by Areces and co-workers (Scheme 41).⁵⁰ Conversion of aldehyde **57** to azaenynes **256a–c** was performed in three steps. $Co_2(CO)_8$ -catalyzed intramolecular Pauson-Khand (IPK) cycloaddition of these azaenynes **256a–c**, followed by treatment with NMO, afforded diastereomeric cycloadducts **257a–c** and **258a–c**.

4.3.2. Diels–Alder Reaction. Sherburn et al. disclosed one-step construction of enantiomerically pure 6/6/6/5 steroid-type tetracyclic framework by utilizing zipper-mode domino intramolecular Diels–Alder (IMDA) strategy (Scheme 42).⁵¹ Enal **57** was converted to conjugated *E,E,E*-tetraene **259** by its Wittig olefination with a 2,4-pentadienyl triphenyl phosphonium bromide-derived semistabilized ylide and iodine-catalyzed equilibration. Deacetylation of **259** followed by selective acetal formation of the resulting triol and subsequent condensation with acid **262** provided enantiomerically pure domino Diels–Alder precursor **263** via **261**. Its domino IMDA reaction in refluxing chlorobenzene led to only two of the eight possible stereoisomeric tetracyclic products, **264** and **265** in a ratio of 1.56:1. Stereochemistries of these IMDA products were determined by NMR experiments and single crystal X-ray analysis.

Further, the α,β -unsaturated aldehyde **24**, prepared by acetylation of Perlin aldehyde **3**, was utilized as a chiral pool material for the synthesis of **267** and **268** (Scheme 43) via **266**.

Scheme 60. Synthesis of 4,6-Di-O-acetyl-5-O-(4,6-di-O-acetyl-2,3-dideoxy- α -D-erythro-hex-2-enopyranosyl)-aldehydo-2,3-dideoxy-D-erythro-E-hex-2-enose

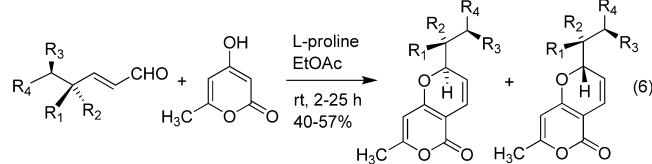


Here, the domino IMDA precursor **266**, a diastereoisomer of **263**, was subjected to a domino IMDA sequence to furnish two double cycloadducts, **267** and **268**, in a ratio of 1.34:1 by executing similar chemical transformations as shown in Scheme 42.

Serrano and co-workers disclosed a short approach to the synthesis of 6-oxabicyclo[3.2.1]octanes **275** and **276** from 4-formyl-5-glycyclohexenes **270** and **271**, which were in turn obtained by thermal and catalytic Diels–Alder reaction of acyl protected enal **57** with 2,3-dimethyl-1,3-butadiene **269** (Scheme 44).⁵² They reasoned that the protonation at C-2 in the nonisolated **273a** and **274a**, followed by intramolecular nucleophilic attack from the hydroxyl group at C-1' on the carbonium ion at C-1, gave cyclic products **275** and **276**, respectively (Scheme 45).

Another useful synthetic application of Perlin aldehyde **1** as chiral template was shown by Sherburn et al. in their synthetic and computational investigation of tether-induced stereocontrol in IMDA reactions. They examined IMDA reactions of C-9 substituted 1,3,8-nonatrienes **282S**, **283S**, and nonadienyne **284S**, which were prepared from aldehyde **1** as depicted in Scheme 46.⁵³ By carrying out density functional calculations (DFT) at the B3LYP/6-31G(d) level and their subsequent interpretation, the synthetic results were complemented by the calculation of the TSs for IMDA reactions of structures **282C**, **283C**, **284C** (Schemes 46, 47, 48, and 49).⁵⁴ Their studies revealed that in IMDA reactions of 1,3,8-nonatrienes and nonadienyne a tether dioxolanyl group invokes a strong *lk* π -diastereofacial preference.⁵⁵ They observed that *exo*-mode cycloadditions were predominant over *endo*-mode cycloadditions in the triene series with both *E*- and *Z*-dienophiles.

4.3.3. Annulation Reaction. With our growing interest in the δ -hydroxy α,β -unsaturated carbohydrate enals or Perlin aldehyde as a versatile building block, L-proline-catalyzed diastereoselective one-pot condensations of 4-hydroxypyran-2H-ones with glycal-derived Perlin aldehydes were reported (eqs 5 and 6) from our laboratory.⁵⁶ The significant features of



$R_1 = H, R_2 = R_3 = O\text{Bn}, R_4 = \text{CH}_2\text{OBn}$ (dr 1:1)
 $R_1 = \text{OBn}, R_2 = H, R_3 = OH, R_4 = \text{CH}_2\text{OBn}$ (dr 1:1)
 $R_1 = H, R_2 = R_3 = \text{OAc}, R_4 = \text{CH}_2\text{OAc}$ (dr 99:1)
 $R_1 = R_3 = \text{OAc}, R_2 = H, R_4 = \text{CH}_2\text{OAc}$ (dr 75:25)
 $R_1 = H, R_2 = \text{OpNB}, R_3 = \text{OAc}, R_4 = \text{CH}_2\text{OpNB}$ (dr 64:36)
 $R_1 = H, R_2 = \text{OAc}, R_3 = \text{OAc}, R_4 = H$ (dr 60:40)

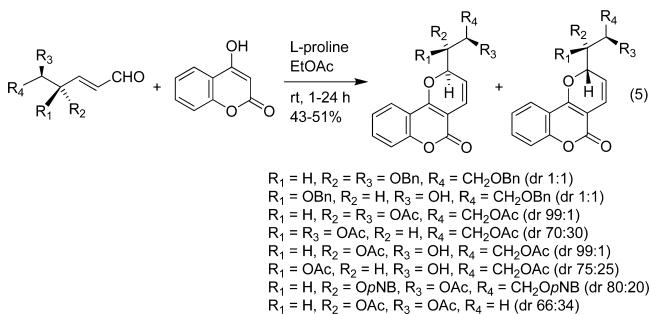
from tri-O-acyl protected glucal, underwent stereoselective annulation with 4-hydroxypyran-2H-ones in the presence of L-proline with more than 99% selectivity, Perlin aldehydes derived from tri-O-acyl-protected galactal underwented the same reaction with moderate selectivity under identical conditions. However, the one-pot condensation of 4-hydroxypyran-2H-ones with benzyl-protected δ -hydroxy enal or its globally benzyl-protected derivative derived from either tri-O-benzyl glucal or galactal furnished an inseparable diastereoisomeric mixture of annulated products in a ratio of 1:1. The poor selectivity was also noted in this condensation reaction with an acyl-protected enal, derived from 3,4-di-O-acetyl-D-arabinol, a pentose derivative. Thus the results (eqs 5 and 6) clearly indicate that the acyl protection in carbohydrate enals derived from pentose or hexose is an essential requirement for a moderate to high degree of stereoselectivity in their annulation with 4-hydroxypyran-2H-ones.

Hsung and co-workers reported a torque-selective 6π -electron electrocyclic cyclization of 1-azatrienes with acyclic chirality at the C-terminus.⁵⁷ They used Perlin aldehyde **1** as one of the precursors for generating 1-azatrienes bearing chirality at the C-terminus through aza-[3 + 3] annulation with different amides under standard reaction conditions (Table 1). A close examination revealed that the size of the nitrogen substituent influenced the rotational preference with the larger substituent providing higher diastereomeric ratio (Scheme 50). Their further reactions also confirmed that greater $A^{1,3}$ -strain interaction may also improve the diastereoselectivity (Scheme 51).

Ghosh et al. reported the synthesis of tetrahydroindolizidines by [3 + 3] annulation of exocyclic vinyllogous amides with vinyl iminium salts derived from several α,β -unsaturated aldehydes (Scheme 52).⁵⁸ They also utilized aldehyde **57** for a [3 + 3] annulation reaction with vinyllogous urethane **309** to give tetrahydroindolizidines **310**.

4.4. Stereoselective Synthesis of Tetrahydroquinolines, 1,5-Benzodiazepines and N-Aryltetrahydropyridines

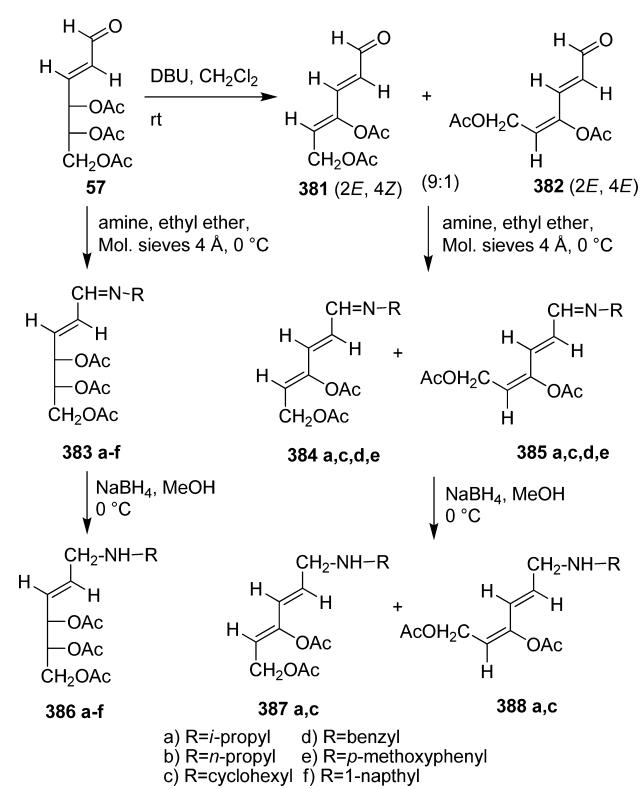
Yadav and his group reported a tandem Michael and intramolecular Friedel–Crafts-type cyclization of Perlin aldehyde with arylamines in the presence of mild Lewis acids such



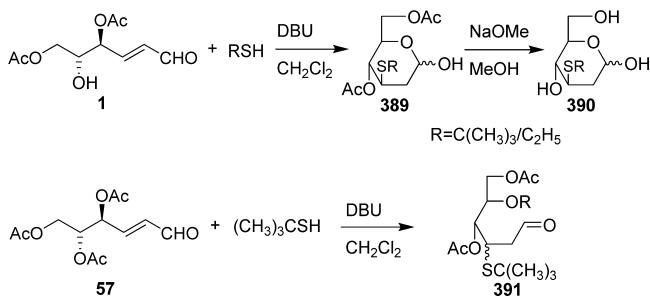
$R_1 = H, R_2 = R_3 = \text{OBn}, R_4 = \text{CH}_2\text{OBn}$ (dr 1:1)
 $R_1 = \text{OBn}, R_2 = H, R_3 = OH, R_4 = \text{CH}_2\text{OBn}$ (dr 1:1)
 $R_1 = H, R_2 = R_3 = \text{OAc}, R_4 = \text{CH}_2\text{OAc}$ (dr 99:1)
 $R_1 = R_3 = \text{OAc}, R_2 = H, R_4 = \text{CH}_2\text{OAc}$ (dr 70:30)
 $R_1 = H, R_2 = \text{OAc}, R_3 = OH, R_4 = \text{CH}_2\text{OAc}$ (dr 99:1)
 $R_1 = \text{OAc}, R_2 = H, R_3 = OH, R_4 = \text{CH}_2\text{OAc}$ (dr 75:25)
 $R_1 = H, R_2 = \text{OpNB}, R_3 = \text{OAc}, R_4 = \text{CH}_2\text{OpNB}$ (dr 80:20)
 $R_1 = H, R_2 = \text{OAc}, R_3 = \text{OAc}, R_4 = H$ (dr 66:34)

this condensation were 1,2-addition, dehydration, and ring closure via a 6π -electron electrocyclisation process. It was observed that while acyl protected δ -hydroxy enal (Perlin aldehyde) or its completely acyl-protected derivative, derived

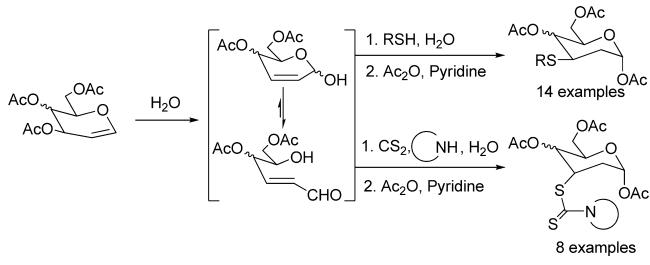
Scheme 61. Synthesis of Acyclic Unsaturated Sugar Derivatives



Scheme 62. Synthesis of 3-Alkylthio-2,3-dideoxy-arabino-hexopyranose

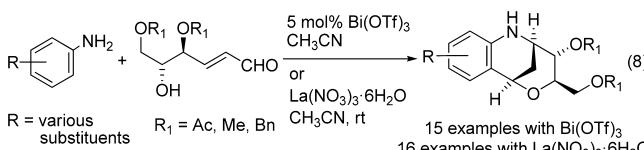
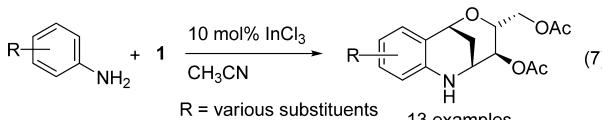
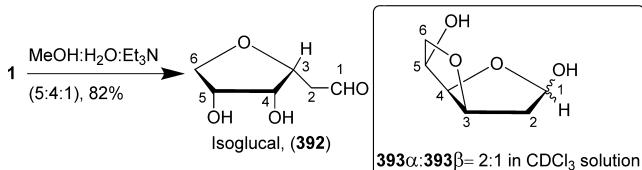


Scheme 63. Synthesis of 3-Thio- and 3-Dithiocarbamoyl-2-deoxy Glycosides



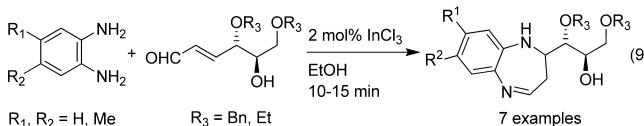
as InCl_3 ⁵⁹ and $\text{Bi}(\text{OTf})_3$ ⁶⁰ to obtain a new class of chiral tetrahydroquinolines in good yields with high stereoselectivity (eqs 7 and 8). Here, the δ -hydroxyl group was essential for this transformation, as simple α,β -unsaturated aldehydes without a δ -hydroxyl group did not produce bicyclic adducts. Later, Venkateswarlu and co-workers disclosed the synthesis of tetrahydroquinolino pyranose derivatives from sugar-derived

Scheme 64. Synthesis of Isoglucomannan

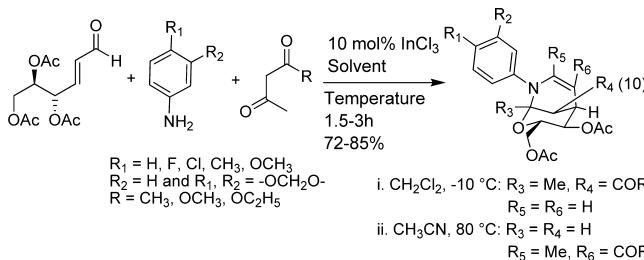


Perlin aldehydes and aryl amines using catalytic amounts of lanthanum(III) nitrate hexahydrate (eq 8).⁶¹

Subsequently, Yadav and co-workers also described indium(III)-chloride catalyzed novel and rapid approach for the synthesis of a new class of 1,5-benzodiazepines from *o*-phenylenediamines and glucal-derived δ -hydroxy- α,β -unsaturated aldehydes (Perlin aldehydes) (eq 9).^{62a}

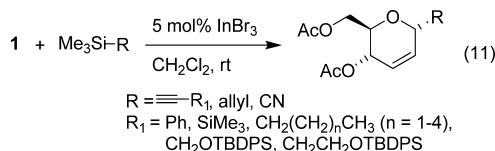


Similarly, Reddy et al. reported the synthesis of sugar-annulated *N*-aryltetrahydropyridines from the reaction of Perlin aldehyde **1** with various arylamines and 1,3-dicarbonyl compounds by using indium(III) chloride as catalyst. Varying the temperature and solvent furnished the isomeric products in good yields with high selectivity (eq 10).^{62b,c}



4.5. Stereoselective Synthesis of C-(Alkynyl)-, C-(Allyl)-, and C-(Cyano)-pseudoglycals

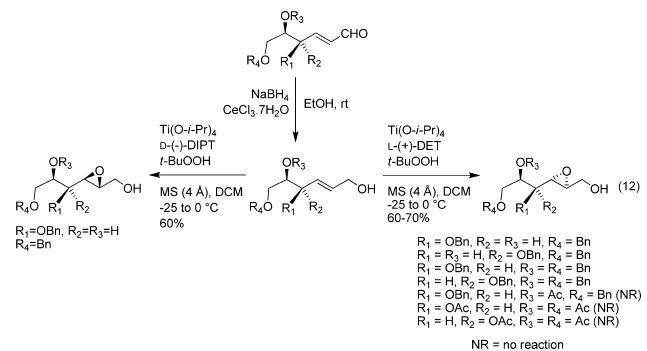
Yadav et al. reported an efficient strategy for synthesizing simple as well as complex C-(alkynyl)-, C-(allyl)-, and C-(cyano)-pseudoglycals from several alkynyl-, allyl-, and cyanosilanes, respectively, by treating each of them in a highly regio- and stereoselective manner with Perlin aldehyde **1** in the presence of InBr_3 (eq 11).^{63,64} This method worked both with sugar and nonsugar aldehydes. However, to their surprise, neither of the simple unprotected acetylenes such as phenyl acetylene nor α,β -unsaturated aldehydes without free hydroxyl groups delivered the desired products under the reaction conditions. They also observed that enals not possessing a δ -hydroxyl group did not give the expected products. The above methods will be very



useful for the synthesis of substituted dihydropyran ring-containing natural products. From these results it was evident that presence of δ -hydroxyl groups is essential for the synthesis of such class of cyclic compounds.

4.6. Synthesis of 2,3-Epoxy Alcohols, Trisubstituted Tetrahydrofurans and Their Derivatives

In 2006, our group reported the results of a detailed comparative study on the epoxidation of allylic alcohols, prepared from Perlin aldehydes, by Sharpless asymmetric epoxidation (SAE), *m*-CPBA, and *m*-CPBA/KF (Camp's reagent) reagents.⁶⁵ From the course of this study, it was found that *m*-CPBA- or *m*-CPBA/KF-mediated epoxidation of allylic alcohols, prepared from Luche's reduction of their respective Perlin aldehydes, as shown in eq 12, furnished the

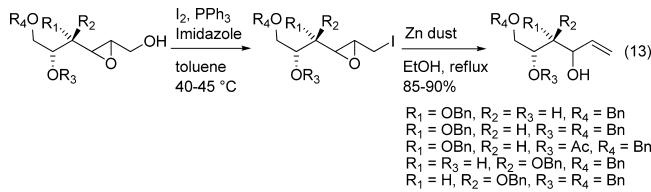


diastereomeric mixture of epoxy alcohols showing moderate diastereoselectivities. However, SAE of allylic alcohols derived from di-*O*-benzyl-protected δ -hydroxy α,β -unsaturated aldehydes by using 2.4 equiv of *t*-BuOOH and a substoichiometric amount of $Ti(O-i-Pr)_4$ (0.20 equiv) and *L*-(+)-DET or *D*-(-)-DIPT (0.24 equiv) at -25 to 0 °C was highly diastereoselective (>99%) in nature, giving epoxides in 60–70% yields (eq 12). Similar results were obtained when fully benzyl-protected allylic alcohols were used as substrates for the title reaction under the same reaction conditions. However, partially or globally acyl-protected allylic alcohols did not undergo SAE, even performing the reaction for a longer period of time.

In this study, we observed an interesting result in that when a noncatalytic version of SAE was performed by increasing the equivalents of Sharpless epoxidizing reagents (2.4 equiv to 3.0 equiv of *t*-BuOOH, 0.20 to 2.0 equiv of $Ti(O-i-Pr)_4$ and 0.24 equiv to 2.5 equiv of DET), the allylic alcohols with unprotected 5-OH produced almost the same result, except for the allylic alcohols derived from globally O-benzyl protected Perlin aldehyde **311**, which was prepared from 3,4,6-tri-O-benzyl galactal (Scheme 53).³ In this case, the intramolecular S_N2 opening of the *in situ* generated 2,3-epoxy alcohols **312** or **314** by 6-OBn with concomitant debenzylation resulted in the formation of enantiomerically pure, highly functionalized, tetrahydrofuran derivative **313** or **315** as the major product.

In our next communication, the above-mentioned 2,3-epoxy alcohols were utilized for the synthesis of highly functionalized acyclic long-chain terminal alkenic alcohols, an important class of building block for syntheses of natural and bioactive compounds. Several 2,3-epoxy alcohols, prepared from various Perlin aldehydes,

were converted to 2,3-epoxy-1-iodides using the Garegg-Samuelsson method (eq 13).⁶⁶ These iodides, on further reduction with



commercial zinc dust in refluxing ethanol, produced the terminal alkenic alcohols in good yields.

In the same year, our group demonstrated the synthesis of densely *O*-functionalized enantiopure 2,3,4-trisubstituted tetrahydrofurans with three contiguous stereocenters (Table 2).⁶⁷ Here, the treatment of 2,3-epoxy alcohols, prepared from Perlin aldehydes, with phenylhydrazine hydrochloride in refluxing ethanol yielded enantiomerically pure trisubstituted tetrahydrofurans. The *O*-acyl-protected epoxy alcohol **320** was not stable under these reaction conditions and produced the deacetylated product **327** (entry 5, Table 2). It was argued that opening of the epoxide ring was highly regio- and stereoselective irrespective of the protected or unprotected nature of 5-OH.

In our next report, we disclosed a facile and mild strategy for stereoselective synthesis of highly substituted, enantiomerically pure, THF domains directly from allylic alcohols, derived from their respective Perlin aldehydes, under SAE conditions (Table 3).⁶⁸ Here, the use of a saturated solution of citric acid in acetone played an important role in the workup procedure for SAE of Perlin aldehyde-derived allylic alcohols and led directly to the formation of enantiopure trisubstituted tetrahydrofurans. Here, we suggested that the insoluble titanium citrate complex formed during workup probably induced the C3 selectivity, leading to *in situ* intramolecular nucleophilic asymmetric ring-opening (ARO) of the 2,3-epoxy alcohol at C3 to furnish the stereochemically pure trisubstituted THF by involving the participation of the C-(6)-benzyloxy oxygen atom and subsequent protection of the terminal vicinal diol by acetone.

Further, our group made use of the above-synthesized THF domains for the synthesis of natural products like pachastrissamine (jaspine B),⁶⁹ oxybiotin,⁷⁰ chiral building blocks such as furanoid glycals, highly functionalized 2,5-dihydrofurans^{71a} and γ -azido-tetrahydrofuran carboxylic acid monomers (Figure 9).^{71b} Thus, the synthesis of these natural products from their respective Perlin aldehydes further demonstrated their utility as versatile chiral building blocks in organic synthesis.

4.7. Synthesis of Optically Pure β -Lactams

The Perlin aldehyde 57, derived from tri-*O*-acetyl-D-glucal, has been used successfully as a tethered chiral auxiliary in the synthesis of enantiomerically pure 4-hydroxymethyl-3-phenoxy-2-azetidinone by Areces et al. (Scheme 54).⁷² Conversion of the enal 57 to imine 340, followed by its reaction with phenoxyacetyl chloride in the presence of triethylamine, afforded a 1.3:1 diastereomeric mixture of β -lactams 341a and 341b. Ozonolysis of 341a, followed by reduction with sodium borohydride, produced 4-hydroxymethyl β -lactam 342. The relative configuration of the β -lactam formed was confirmed by its X-ray analysis.

4.8. Aldol Addition Reaction

Colombo and co-workers studied aldol addition of enolsilane 343 to various aldehydes including the unsaturated aldehyde 57 in the presence of (*dicarbonyl*)(η^5 -cyclopentadienyl) iron halides as catalysts (Scheme 55).⁷³ In general, all the halides worked equally well and the reactions were high yielding.

4.9. Morita-Baylis-Hillman (MBH) Chemistry

Our research group for the first time demonstrated the application of Perlin aldehydes, as electrophiles, in the Morita–Baylis–Hillman reaction with methylvinyl ketone in the presence of $\text{Me}_2\text{S}-\text{TiCl}_4$ (Scheme 56).⁷⁴ To our surprise, the unsaturation in the enal did not affect either the electrophilicity of the electrophilic aldehydic carbon or the nature of products. During this study it was observed that distribution of products was dependent on the reaction time. While performing this reaction for 15 min led to the formation of chloro compound 348 as the major product, olefin 346 was the major isomer after 50 min. Conjugated diene 350 was the sole product when the reaction was continued for 6 h. The application of the resulting adduct 350 was exemplified by preparing chain-extended amino polyols (352–354) involving the nucleophilic substitution of chloride with amines and hydride. The reaction of enals 355 and 6 with acrylonitrile and the $\text{Me}_2\text{S}-\text{TiCl}_4$ system was not successful and it was replaced with DABCO. All the synthesized MBH adducts were tested for their *in vitro* antitubercular activity.⁷⁵

Later, Areces and co-workers reported the first tandem β -elimination-Morita–Baylis–Hillman reaction of acetylated Perlin aldehyde 360, prepared from 3,4-di-*O*-acetyl-*D*-arabinal, with activated alkenes (Scheme 57).⁷⁶ The direct transformation of the aldehyde 360 in the MBH reaction with activated alkenes to give adducts 362a–c could involve 4-acetoxypent-2,4-dienal 361, which was shown by its MBH reaction with the same alkene to give adducts similar to those obtained from aldehyde 360. For this study, the dienal 361 was prepared from unsaturated aldehyde 360 by DABCO-induced elimination of an δ -acetoxyl group.

4.10. Miscellaneous Applications of Perlin Aldehydes

Our research group reported certain acyclic nitro and amino deoxy alditoles,⁷⁷ involving a Henry reaction between different nitroalkanes and acetyl derivatives of Perlin aldehydes using triethylamine as base (Scheme 58), and studied their *in vitro* antimycobacterial activity against *Mycobacterium tuberculosis*.⁷⁸ It was observed that compounds that were chirally pure and had deoxy sites in succession and less restricted rotation were most active against tuberculosis.

Holzapfel et al. showed that the allylic geminal diacetate 375, prepared from *D*-xylal-derived Perlin aldehyde 373, in the presence of a palladium catalyst, underwent cyclization to produce enantiopure *trans*-enolacetate 376, which can be further elaborated to enable facile entry to natural product synthons (Scheme 59).⁷⁹ Here stereochemistry at C-4 of the substrate enal 373 controlled the absolute stereochemistry of the product and the cyclization presumably proceeded via a lower energy conformation, in which the nonparticipating C-4 substituent and the enolacetyl are in an anti orientation to give a 2,3-*trans* isomer.

Wessel and Englert, while reanalyzing the reaction of tri-*O*-acetyl-*D*-glucal and 4,6-di-*O*-acetyl-2,3-dideoxy-*D*-erythro-hex-2-enopyranose 377, which could be in equilibrium with Perlin aldehyde 1 in the presence of boron trifluoride etherate by replacing the solvent benzene with less toxic toluene, noticed the formation of the unreported 4,6-di-*O*-acetyl-5-*O*-(4,6-di-*O*-acetyl-2,3-dideoxy- α -*D*-erythro-hex-2-enopyranosyl)-aldehydo-2,3-dideoxy-*D*-erythro-*E*-hex-2-enose 380 (Scheme 60).⁸⁰ The formation of 380 was deemed responsible for the presence of 1 under the reaction conditions and explained that the attack of the C-5 hydroxyl group of 1 at the double bond of the glycal might have resulted in the disaccharide 380.

Serrano and co-workers synthesized acyclic unsaturated sugar derivatives 381 and 382 in a 9:1 ratio from enal 57 by a DBU-mediated elimination reaction (Scheme 61).⁸¹ In the same communication, they also described the synthesis of allylic amines

(386, 387, and 388) by the selective reduction of their corresponding unsaturated aldimines (383, 384, and 385), obtained from their respective unsaturated aldehydes 57, 381, and 382.

Lau et al. demonstrated the synthesis of 3-alkylthio-2,3-dideoxy-arabino-hexopyranose 390 that involved a thermodynamically controlled 1,4-addition of 2-methyl-2-propanethiol or ethanethiol to the Perlin aldehyde 1 in the presence of DBU to obtain 389, followed by deprotection of its acetyl groups with sodium methoxide (Scheme 62).⁸² They performed 1,4-addition of 2-methyl-2-propanethiol to enal 57 to ascertain whether the stereoselective formation of 389 was of thermodynamic origin. As expected, the 1,4-adduct of 57 did not undergo ring closure, and a nearly 1:1 mixture containing the *ribo* and *arabino* isomers of 391 was obtained, confirming that the stereoselective formation of 389 must be reversible and thermodynamically controlled.

Misra and his team designed and synthesized a series of 3-thio- and 3-dithiocarbamoyl-2-deoxy glycosides (Scheme 63).⁸³ The synthesis of the aforementioned class of compounds was initiated by the hydration of tri-*O*-acetyl-*D*-glycal at 80 °C. The resulting intermediate Perlin aldehyde, in equilibrium with 4,6-di-*O*-acetyl-2,3-dideoxy-*erythro/threo*-hex-2-eno-pyranose, was then treated with a series of thiols including carbohydrate-derived thiols or secondary amines with carbon disulfide at room temperature, followed by acetylation of the resulting pyranoses to obtain 1,4,6-tri-*O*-acetyl-2-deoxy-3-mercaptopalkyl/aryl-*D*-glycopyranose or 1,4,6-tri-*O*-acetyl-2-deoxy-3-dithiocarbamoyl-*D*-glycopyranose.

Roman et al. described a facile synthesis of 3,6-anhydro-2-deoxy-*D*-glucose 392 (isoglucal) starting from Perlin aldehyde 1 (Scheme 64).⁸⁴ They proposed that compound 392 could exist in equilibrium with its corresponding bicyclic form 393 and also determined their anomeric configurations and ring sizes. The cyclization through C-4 was consistent with the differences in the chemical shifts for C-5 and C-6 in the ^{13}C NMR spectra of each compound and its corresponding acetate.

5. CONCLUSION

In summary, the present review is an attempt to describe the useful and important applications of Perlin aldehydes in organic synthesis. As shown in section 4.5, the δ -hydroxyl group is essential for the synthesis of cyclic compounds, and in addition to this, we have also shown the utility of the C-6 benzyloxy group participation for the synthesis of trisubstituted tetrahydrofuran; the utilization of this synthon in the synthesis of macrolides is yet to be witnessed. This review presents an excellent example of the ability of an organic chemist to exploit this inexpensive and widely available chiral building block for broader applications both in synthetic as well as medicinal chemistry. Our brief experience in this area convinces us that these building blocks do not as yet boast many applications in organic synthesis; it is however rapidly gaining momentum, and the coming years will witness interesting achievements due to their functional and stereochemical wealth. We hope that this review can motivate synthetic and carbohydrate researchers all over the world to further exploit its utility.

AUTHOR INFORMATION

Corresponding Author

*Tel.: +919415403775; fax: +91 522 2623405; e-mail: akshaw55@yahoo.com

Present Address

[§](L.V.R.R.) Albany Molecular Research Hyderabad Research Centre, Hyderabad, India 500 078.

(V.K.) Department of Organic Chemistry, Indian Institute of Science, Bangalore, India 560012.

(R.S.) Department of Chemistry, Shiv Nadar University, Greater Noida, India 203207.

Author Contributions

[‡]These authors contributed equally to this work.

Notes

The authors declare no competing financial interest.

Biographies



Lingala Vijaya Raghava Reddy was born in 1979 at Kadapa, India. He received his B.Sc. degree in 2000 from Sri Venkateswara University, Tirupati, and M.Sc. degree (Organic Chemistry) in 2003 from Sri Krishnadevaraya University, Anantapur, India. He was awarded his doctoral degree (Ph.D.) in Chemistry in 2008 from Sri Krishnadevaraya University, Anantapur, for his work on the synthesis of carbohydrate molecules of biological importance at CSIR-Central Drug Research Institute, Lucknow, India, under the supervision of Dr. Arun Kumar Shaw and cosupervision of Professor G. Narayana Swamy. He then moved to National Tsing Hua University, Taiwan, in 2009 where he did postdoctoral work with Professor Chun-Cheng Lin. His research interests are in the synthesis of carbohydrate antigens, PEGlyated glycosides, functionalized metal nanoparticles, and carbohydrate-derived natural products. At present, he is a senior research scientist, Albany Molecular Research Hyderabad Research Centre, Hyderabad, India-500 078.



Vikas Kumar was born in Uttar Pradesh, India. After obtaining his B.Sc. (2002) and M.Sc. (2004) degrees from C. C. S. University, Meerut, India, he moved to CSIR-Central Drug Research Institute, Lucknow in 2005 to begin his Ph.D. programme under the supervision of Dr. Arun K. Shaw. He received his doctoral degree jointly from Jawaharlal Nehru University, New Delhi, India, and CSIR-Central Drug Research Institute, Lucknow, India, for his work on total synthesis of natural products and natural

product-like molecules starting from commercially available sugars. After working for a few months as a junior scientist in a company, he then moved to Indian Institute of Science (IISc), Bangalore, as a research associate with Dr. Santanu Mukherjee. His current research interests are centered around asymmetric organocatalysis.



Ram Sagar was born in 1977 in the state of Utter Pradesh, India. He obtained his B.Sc. and M.Sc. (2001, Organic Chemistry) degrees from University of Lucknow, India. He received his Ph.D. degree in 2006 jointly from CSIR-Central Drug Research Institute (CDRI), Lucknow, and Dr. B. R. A. University Agra, India, under the supervision of Dr. Arun K. Shaw and cosupervision of Prof. R. C. Sharma. In his predoctoral research he worked in the area of synthetic carbohydrate chemistry and natural product chemistry. After working as a research associate (2006–2007) at the Indian Institute of Technology Kanpur (IITK), India, with Prof. Y. D. Vankar and postdoctoral fellow (2007–2008) at Seoul National University, South Korea, with Prof. Seung Bum Park, he joined the Chemistry Research Laboratory, University of Oxford, as a postdoctoral fellow with Prof. Ben Davis. His current research interests are chemical biology, sugar signaling in biological systems, and glycoconjugate chemistry. At present, he is Assistant Professor at Department of Chemistry, Shiv Nadar University, Greater Noida, India-203207.



Arun K. Shaw was born in Raniganj, West Bengal. He received his B.Sc. (Hons.) degree in Chemistry from Scottish Church College, Calcutta University, in 1975, his M.Sc. degree in Chemistry from Calcutta University in 1977, and his Ph.D. in Natural Product Chemistry under the supervision of Professor S. N. Ganguly from Bose Institute, Calcutta University, in 1985. After his doctoral work, he worked with Professors S. K. Talapatra and B. Talapatra in the Department of Pure Chemistry, Calcutta University, during 1985–1986. In 1987 he joined as a Scientist Gr. IV (1) in the Department of Food Chemistry, CSIR-Central Food Technological Research Institute, Mysore. He moved in the same capacity to the Division of Medicinal Chemistry, CSIR-Central Drug Research Institute,

Lucknow, in 1991. At present, he is working as a Senior Principal Scientist in the same division. He visited the laboratories of Professor Ralf Miethchen, Department of Organic Chemistry, University of Rostock, for three months in 2000 under the CSIR-DAAD Exchange of Scientists programme and Professor Pavel Kočovský of the Department of Chemistry, University of Glasgow, Scotland, for four weeks in March 2012 under the INSA, (New Delhi) and RSE (Edinburgh, Scotland) International Exchange Programme. His main areas of research are natural products chemistry, medicinal chemistry, and the 'Chiron' Approach to the synthesis of biologically active natural products and natural product-like molecules.

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DEDICATION

Dedicated to Professor A. S. Perlin.

ABBREVIATIONS

Ac	acetyl
AIBN	2,2'-azobisisobutyronitrile
BHT	2,6-di- <i>tert</i> -butyl-4-methylphenol
Bn	benzyl
Boc	<i>tert</i> -butoxycarbonyl
Bz	benzoyl
<i>m</i> -CPBA	<i>meta</i> -chloroperbenzoic acid
CSA	camphorsulfonic acid
DABCO	1,4-diazabicyclo(2.2.2)octane
DBU	1,8-diazabicyclo(5.4.0)undec-7-ene
DCC	1,3-dicyclohexylcarbodiimide
DCM	dichloromethane
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DEAD	diethylazodicarboxylate
DET	diethyltartrate
DFT	density functional theory
DHP	3,4-dihydro-2 <i>H</i> -pyran
DIBAL	diisobutylaluminium hydride
DIPEA	diisopropylethylamine
DIPT	diisopropyltartrate
DMAP	4-(dimethylamino)pyridine
DMF	<i>N,N</i> -dimethylformamide
DMSO	dimethylsulfoxide
dr	diastereoisomeric ratio
HMPA	hexamethylphosphoramide
HWE	Horner-Wadsworth-Emmons
IMDA	intramolecular Diels-Alder
KPa	kilopascal
LAH	lithium aluminum hydride
LHMDS	lithium bis(trimethylsilyl)amide
LTA4	leukotriene A4
MBH	Moria-Baylis-Hillman
MS	molecular sieves
Ms	methanesulfonyl

Mst/Mz	mesitylenesulfonyl
NMO	<i>N</i> -methylmorpholine-N-oxide
Ns	O-nitrobenzenesulfonyl
OpNB	<i>para</i> -nitrobenzoate
Ph	phenyl
PCC	pyridinium chlorochromate
PMB	<i>p</i> -methoxybenzyl
Pnb	<i>p</i> -nitrobenzoyl
PTSA	<i>p</i> -toluenesulfonic acid
Pu	6-(4-chlorophenylamino)-2-amino-9-purinyl
Py	pyridine
Rt	room temperature
SAE	Sharpless asymmetric epoxidation
TBAF	tetra- <i>n</i> -butylammonium fluoride
TBAI	tetra- <i>n</i> -butylammonium iodide
TBDPS	<i>tert</i> -butyldiphenylsilyl
TBS/TBDMS	<i>tert</i> -butyldimethylsilyl
TEA	triethylamine
TES	triethylsilyl
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
Th	theophyllyl
THF	tetrahydrofuran
THP	tetrahydropyran
TIPS	triisopropylsilyl
TMS	trimethylsilyl
TMSOTf	trimethylsilyl trifluoromethanesulfonate
TS	transition state
Ts	<i>p</i> -toluenesulfonyl

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