Toward a Carbohydrate-Based Chemistry: Progress in the Development of General-Purpose Chiral Synthons from Carbohydrates

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I. Introduction and General Perspectives on Carbohydrates as a Chemical Resource

Petroleum is the most used organic resource in the organic chemistry industry, but in many ways, it is not the ideal chemical feedstock. It is an intractable substance, but thermal degradation or "cracking" has made it possible to liberate small usable fragments. These fragments which include methane, ethylene, benzene, and acetylene can then be separated and subjected to a myriad of simple reactions. These include processes such as halogenations, hydrations, and oxidations. This approach led to the generation of commodity industries for compounds that include phenols, acids, alcohols, ketones, aldehydes, and halo compounds. These are the stock-in-trade of the "old line" chemical companies. They formed the basis for the production of other derivatives which, in turn, led to other derivatives and the extensive spectrum of petroleum-derived organic molecules, from commodities to specialties, that we know today. This ever-expanding evolution in chemical output from the simplicity of commodity to the complexity of specialty chemicals is the typical path of evolution in this industry. Cracking is not necessarily an efficient process, but it provided a way into the important petroleum chemical resource. This evolution in scale and complexity is the essential paradigm in the generation of any substantial sector in the chemical industry.

Carbohydrates are very abundant molecules. Many of them are, in fact, much more accessible than petroleum. When one considers the cost of crude oil (over $30.00 per barrel or over $0.20 per kg), newspaper (largely cellulose) is a real bargain. Carbohydrates have many other advantages over petroleum also. Functionality, chirality, and structural variations are all features of carbohydrate feedstock that are not present or at a minimum in petroleum.

As we pointed out earlier, the essential feature of the typical evolution of an "industrial chemistry" seems to be the development of routes to a few flexible general-purpose molecules. In the case of the traditional petroleum-based industry, these are compounds such as benzene, ethylene, and acetylene. The challenge in the development of a truly industrially relevant carbohydrate-based chemistry is the development of routes to specific general-purpose molecules that have very wide areas of applicability. Ways of "cracking" carbohydrate to generate these molecules have to be developed. As the title might imply, one would hope that carbohydrates will eventually become the base for a substantial industrial chemistry. The question of chirality is one area in which carbohydrates have a special potential advantage among all naturally occurring molecules. Several adjuncts are required in order to address chirality using traditional petroleum-based chemistry. This is an area where the first inroads from a successful carbohydrate-based chemical technology might be made. The generation of a comprehensive series of general-purpose chiral intermediates is preferred to case-by-case transformations that cannot profit from the economies of scale. In this review, we will focus primarily on advances in the development of such general-purpose synthons.

A. Chirality and the Carbohydrate Chiral Pool

Chirality at the molecular level has emerged as one of the major issues in the development of chemical

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Rawle Hollingsworth received his Ph.D. degree from the University of the West Indies in 1983 in the area of synthetic organic chemistry with an emphasis on carbohydrate transformations with Earl Roberts and Vernon Box. He then spent four years as a Research Associate at Michigan State University studying the structures and conformations of complex bacterial carbohydrate surface antigens and developing synthetic methods for various substructures of these. After a year as a Visiting Professor in the Biochemistry Department at Michigan State University, he joined the faculty jointly in Chemistry and Biochemistry. He is now a Full Professor of Chemistry and Biochemistry at Michigan State University. His fields of interest include synthesis, structure determination, modeling of structure and phenomena, self-assembly and nanosystems, and mechanisms of adaptation of living systems to extreme environments. He is the author of over 100 papers and patents.

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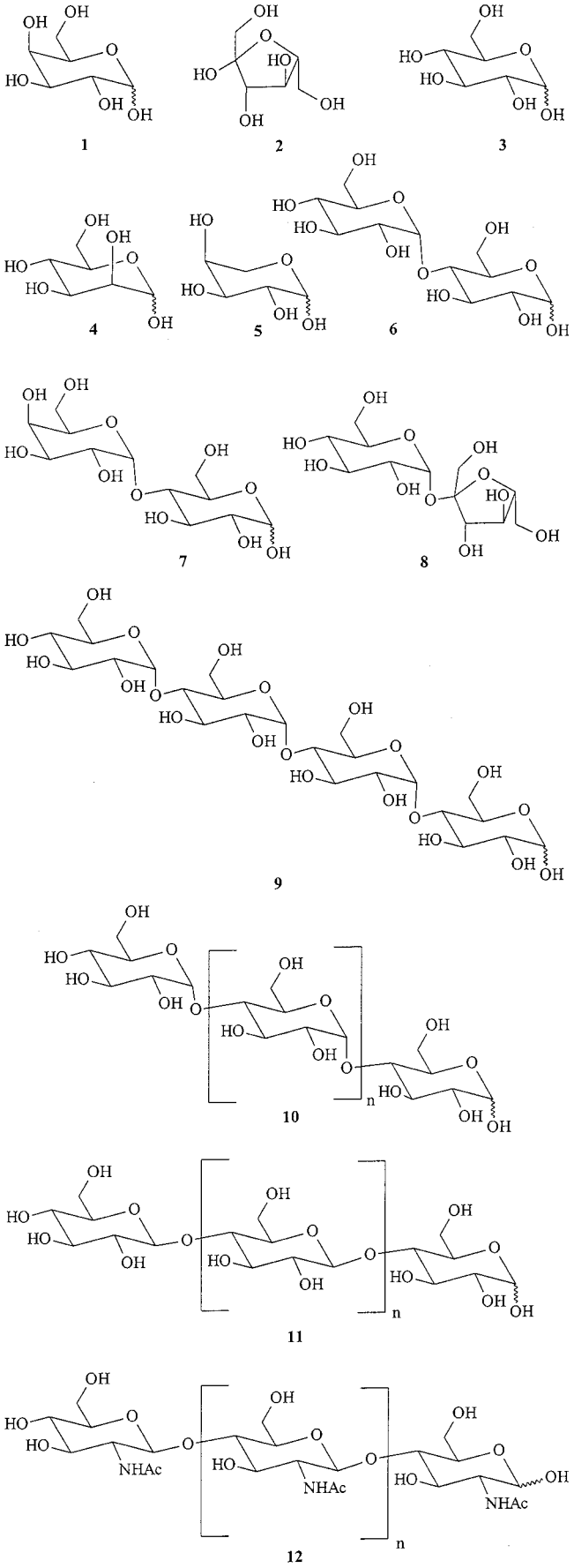
technology, especially in the areas of drug synthesis and advanced materials. Although chirality is not a prerequisitive for biological activity, great differences are usually observed between the two enantiomers of a compound. The push to use only optically pure intermediates in drugs and to conserve the integrity of chiral centers in subsequent transformations has placed very high technical and economical constraints on the development of new drug candidates. Optical purity is not only a requirement for drug synthesis but often also for the construction of other molecular systems such as biomembrane models and mimics, membrane probes, liquid-crystalline systems, drug delivery vehicles, and biosensors where asymmetric molecular species must fit together in register. Development of chemistry in these areas on a commercial scale is also plagued with technical and cost problems. The four common ways in which chirality is integrated into molecular targets are by carrying out transformations on a chiral core, integrating a preformed fragment or chiral synthon into the target, using a chiral catalyst, and using a chiral auxiliary. The first of these approaches is very well developed and is easily the most widely practiced. The others are not as popular, but interest in them has been soaring recently.

A general and yet selective chemical transformation method that generates a new chiral center and will work in any chemical context is difficult (if not impossible) to develop. Because of this, a "tool kit" approach toward chiral technology is often used. A different method is employed for each different functionality. A different method may also be used for the same functionality but in a different context.

Because there is a reasonably low number of molecular fragments between 3 and 5 carbon atoms in size, accessing a few of these on a grand scale by one chiral technology and transforming them to the others using standard chemical transformations is, in principle, a very valuable strategy. The "chiral pool" approach, where chiral substructures are carved or derived from readily available, cheap, renewable materials such as carbohydrates, amino acids, organic acids, and terpenes, is especially important from this perspective. Substructures obtained by this method can be used as synthons and integrated directly into target molecules or can be used in the synthesis of catalysts or auxiliaries. Thus far, the chiral pool approach has been dominated by methods involving amino acids and, to a lesser extent, organic acids. This despite the fact that only 20 or so amino acids occur naturally to any considerable extent in proteins, and D-lactic, L-tartaric, and L-malic acids are really the only optically active organic acids available in large enough quantities to be of significance. The main reason for the preference of amino acids as substrates for the chiral pool approach is because they are more simple in structure than most molecules and can be more readily manipulated. From a biotechnology standpoint, it is also an easier task to engineer the biosynthesis of amino acids and organic acids. The advances in molecular biology technology have been used to further this approach.

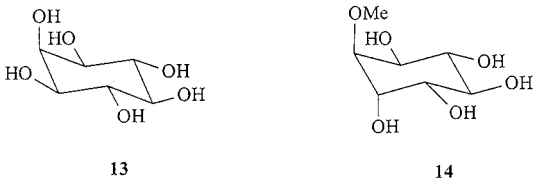
Carbohydrates are easily the most prominent members of the chiral pool. They are major constituents of all major structural molecules in living systems. They occur alone in polymers such as starch, pectin, cellulose, and chitin. They are also key components of DNA and RNA. Carbohydrates can form a large proportion of some glycoproteins and constitute much of the cell wall and extracellular slime of bacteria and other microorganisms. They also occur in combination with lipids to form gly-



colipids. In the plant kingdom, digalactosyl diacylglycerol and sulfoquinovosyl diacyglycerol are the two major membrane components. Some glycoconjugates such as cyclic adenosine monophosphate play a key role as so-called "messenger" molecules and an undeniably important role in energy storage in cells in the form of ATP, GTP, starch, and glycogen.

There are two main strategies for the use of carbohydrates in asymmetric synthesis. The first is to employ them as scaffolds, cores, or templates on which structural transformations are wrought transforming them into new entities that share reasonably close structural similarity with the starting species. Many of these new entities may actually be carbohydrate analogues. In the second strategy, carbohydrates are totally transformed to often unrelated compounds that are then used in a much broader variety of synthetic applications. These new compounds may also be used in the preparation of catalysts or as chiral auxiliaries.

The carbohydrate chiral pool is extremely extensive ranging from simple molecules such as D-galactose **(1)**, D-fructose **(2)**, D-glucose **(3)**, D-mannose **(4)**, and L-arabinose **(5)** through disaccharides such as maltose **(6)**, lactose **(7)**, and sucrose **(8)** to oligosaccharides such as maltodextrins **9** and polysaccharides such as starch **(10)**, cellulose **(11)**, hemi-celluloses, and chitin **(12)**. The inositols and their derivatives are also important members of the carbohydrate chiral pool. These are hexahydroxycyclohexanes of which *myo*-inositol **(13)** and L-quebrachitol **(14)** are the most abundant. *myo*-Inositol is an achiral mol-



ecule (meso) that is obtained commercially from corn steep liquors. Quebrachitol (1-L-2-*O*-methyl-*chiro*-inositol) is optically active and obtained from the sap of the rubber tree. Glucose is obtained from the hydrolysis of starch, lactose, maltose, or sucrose. Galactose is obtained from lactose, and fructose is obtained from the hydrolysis of sucrose, the isomerization of glucose, or the hydrolysis of inulin, a plant polysaccharide that contains fructose only. Arabinose is a component of plant cell wall polysaccharides, and some polysaccharidess such as mesquite gum are composed largely of L-arabinose. Maltose can be obtained by the enzymatic degradation of cellulose. Lactose is a major component of whey from cheese processing. Maltodextrins are obtained from the enzymatic or acid-catalyzed hydrolysis of starch. These carbohydrate substrates can all be obtained as crystalline materials in a very pure state in high volume at low cost.

B. Potential and Limitations of the Use of Carbohydrates in Chiral Synthesis

Their low cost, abundance, and ease with which they can be obtained in a pure state are among the most important features that make carbohydrates prime chiral pool candidates from a raw materials standpoint. Some lower molecular weight carbohy-

drates such as maltose, lactose, sucrose, and glucose can be obtained in a very pure state in extremely large commercial quantities. Carbohydrates are also a renewable resource and contain the highest density of functional groups of any naturally occurring materials. The high solubility of most carbohydrates in water, the most environmentally benign solvent, is a decided plus from a "green chemistry" perspective. An important factor in the use of carbohydrates over most potential chiral pool materials is price. Many carbohydrates such as starch, cellulose, lactose, and sucrose are extremely cheap, some of them literally pennies per pound. Lactose, for instance, costs ~$0.10 (U.S.) per pound on commercial scale. This amounts to only 1 penny per mole for each of the 10 chiral centers. These factors are all key advantages carbohydrates offer for the development of a commercially relevant chiral chemistry. Their abundance of functionality is another advantage of carbohydrates over other chiral pool materials. When several chiral centers are needed, especially on contiguous carbon atoms, carbohydrates are the obvious low-priced, high-volume chiral pool source.

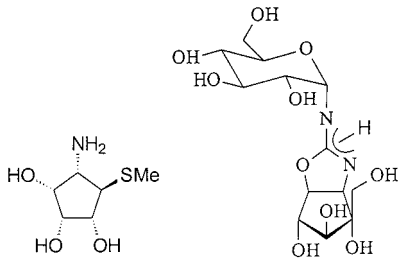
There are several obstacles to the use of carbohydrates in general chiral chemistry synthesis. For one, their very limited solubility in all but the most polar, protic solvents seriously restricts the spectrum of chemical transformations that can be performed on them. Most of the typical oxidation reactions used in organic chemistry, for instance, are not possible in protic solvents. The high density and redundancy of the functional groups can also be a disadvantage. Almost every ring carbon in the typical carbohydrate molecule is an asymmetric center. All but a few of the functional groups are hydroxyl groups. Because of this, specificity and selectivity of reaction are very difficult to achieve. Very subtle differences in reactivity of the various hydroxyl groups and other functions have to be exploited. The sheer density of functionality also leads to several unusual and unexpected processes ranging from isomerizations through rearrangements. These rearrangements are not limited to ring expansions, contractions, and functional group migrations. Very often elaborate series of protection and deprotection schemes have to be utilized to control these unwanted processes. These nuances coupled with an extremely onerous system of nomenclature present real challenges for the development of a carbohydrate-based chiral chemistry.

The challenges outlined above notwithstanding, real progress has been made. Although the applications in which they are used as chiral scaffolds, cores, or templates have dominated the uses of carbohydrates in synthesis, applications in which enantiomerically pure fragments are carved out of carbohydrate molecules and then used in the synthesis of optically active molecules have the greatest general potential. Such applications are the primary focus of this review.

C. Carbohydrates as Chiral Scaffolds, Cores, or Templates

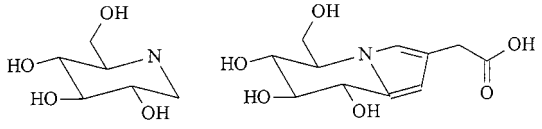
This is the most common application of carbohydrates in organic synthesis. There have been several authoritative treatments of this general area over the years.[1−3] Because this area is so broad, only a few aspects of high current interest will be singled out here. The transformation of simple carbohydrates to cyclopentanes and cyclohexanes is one such area, and several reviews or comprehensive works describing it have been published.[4−6] This is also true for the area of nitrogen heterocycles.[7,8] Although simple monosaccharide derivatives of glucose and other aldoses are usually the starting materials for these syntheses, a significant amount of work has been accomplished using other raw materials. The growing body of results in which the unusual but relatively abundant inositol L-quebrachitol was employed[9−11] deserves special mention.

Cyclopentanes are of special interest because this ring system is the basic skeleton of important "carbasugar" analogues of pentoses such as mannostatin **(15)** and trehazolin **(16)**. In addition to their use in



15 16

the control of carbohydrate and nucleic acid processing, they are also key building blocks for the synthesis of prostaglandins and their analogues, some of which also have uses as inhibitors for therapeutic purposes. A tremendous amount of work has been done recently in this area.[12] Carbohydrate-derived nitrogen heterocycles also deserve special mention. Tremendous advances have also been made in this area as well.[13] The imino sugars (or aza sugars as they are commonly called) are especially important because of their potential as drugs for the treatment of a wide spectrum of diseases ranging from cancer through diabetes and viral infections.[7,8] Compounds in this class include deoxynojirimycin **(17)** and nagstatin **(18)**.



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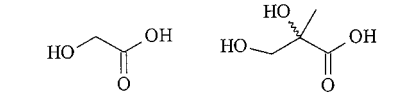
II. Carbohydrate-Derived Optically Active General-Purpose Synthons

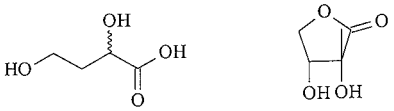
The most abundant and generally accessible monosaccharides are hexose (six carbon) sugars such as glucosamine, glucose, galactose, and mannose. Unfortunately, the optimum size for a general-purpose chiral synthon is 3−4 carbons. Selective methods for cleaving or paring down the carbohydrate skeleton have to be developed. This is a nontrivial operation and represents the greatest challenge in the use of

carbohydrates as chiral pool materials. The most obvious strategies would involve the selective protection of some hydroxyl groups leaving others available for reaction. The protection methods must be ones in which essentially only one product can be formed and a sufficiently high level of protection is obtained. The perfect strategy would, of course, involve no prior protection. The question of protection is an especially acute one because of the zero or poor solubility of carbohydrates in most solvents that are nonaqueous. Even if aqueous conditions in which to carry out chemical transformations can be found, the pH of the solution is still an important factor. Free sugars are unstable both in acidic and basic media.

The transformation of free sugars to furfuraldehyde, formic acid, catechols, and a myriad of other compounds in mild to moderately acidic solutions is well documented.[14] Free sugars are extremely base labile, even in mildly to moderately alkaline solutions. Several classic studies have been carried out in this area, and the various elminations, tautomerizations, and the interesting rearrangements that occur under basic conditions and that eventually lead to the formation of unusual compounds such as isosaccharinic acids have been elucidated.[15] In one study, it was observed that D-glucose was completely degraded in 30 min at 100 °C in 0.1 M calcium hydroxide yielding a complex mixture of over 50 compounds.[16] Products formed included lactic acid, glycolic acid **(19)**, 2-*C*-methyl glyceric acid **(20)**, 2,4-dihydroxybutanoic acid **(21)**, 2-*C*-methyl ribono-1,4-lactone **(22)**, acetic acid, and formic acid. Similar products were formed in the alkaline degradation of fructose.[17]



19 **20**



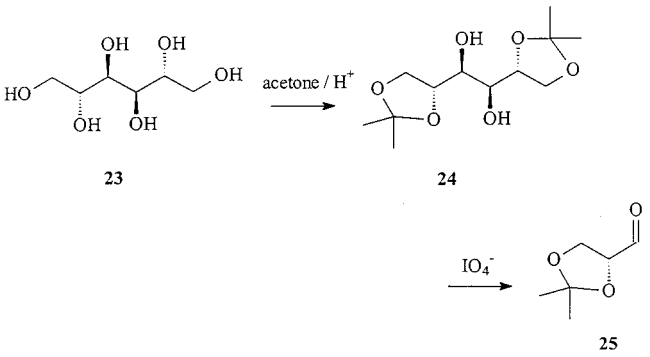
21 **22**

There are three major classes of compounds that are used as carbohydrate-derived building blocks and that serve as general intermediates from which more elaborate building blocks for general use in synthetic chemistry are derived.

A. 2,3-*O*-Alkylidene Acetals of Glyceraldehyde or Glyceric Acid

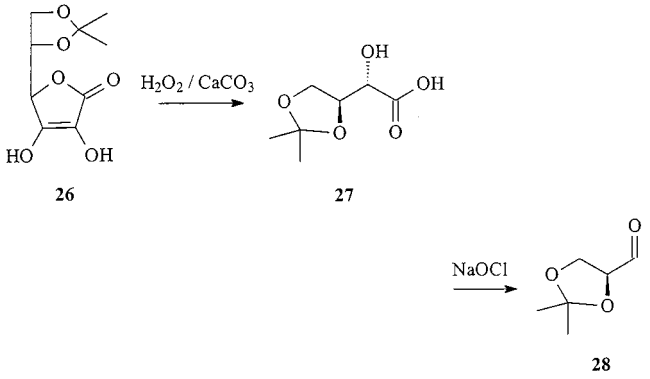
Optically active 2,3-*O*-alkylidene glyceraldehydes are easily the most used carbohydrate-derived optically active fragments in synthetic organic chemistry. Of these, the isopropylidene derivatives are the most used. The (*R*)-enantiomer **25** is usually obtained by the periodate or lead tetraacetate oxidation of 1,2−5,6-di-*O*-isopropylidene-D-mannitol **(24)** (Scheme 1).[18] Because of the unavailability of L-mannitol, the (*S*)-enantiomer **28** is obtained by the similar oxidation of the 5,6-*O*-isopropylidene acetal of L-ascorbic acid

Scheme 1



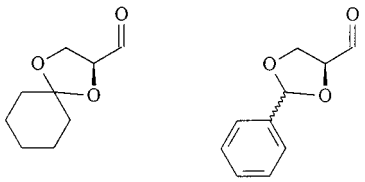
23 **24** **25**

Scheme 2



26 **27** **28**

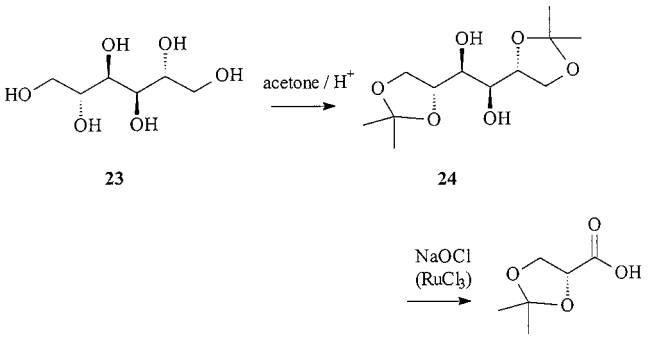
(Scheme 2).[19] The oxidation of the 1,2−5,6-di-*O*-isopropylidene-D-mannitol is a good example of a method where all of the chiral pool material is used in the final product. The corresponding cyclohexylidene **29** and benzylidene **30** acetals are two related derivatives that have also found much use. A related



29 **30**

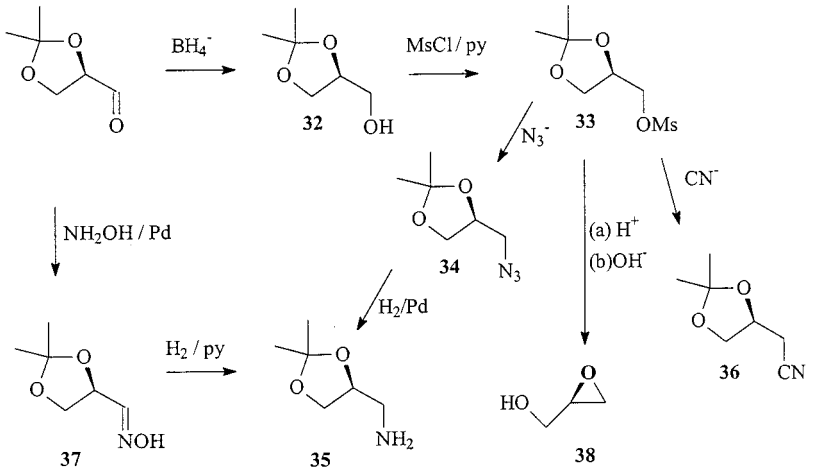
carbohydrate-derived synthon is (*R*)-2,3-*O*-isopropylidene glyceric acid **(31)**. This can be obtained in good yield by the oxidation of 1,2−5,6-di-*O*-isopropylidene-D-mannitol **(24)** with ruthenium and sodium hypochlorite (Scheme 3).[20] Acetals and ketals of L-ascorbic acid were oxidized with sodium hypochlo-

Scheme 3



23 **24** **31**

Scheme 4



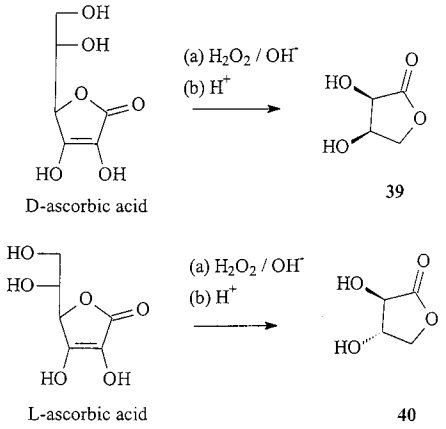
rite using a perruthenate catalyst to form acetals and ketals of (*S*)-glyceric acid. D-Isoascorbic acid gave the (*R*)-glyceric acid derivatives by a similar process.[21]

The optically active 2,3-*O*-alkylidene glyceraldehydes are very flexible synthons. One of their limitations, however, is the ease with which stereochemical integrity can be lost, especially under mildly basic conditions, because of their ease of enolization. The acetal group is, of course, unstable in acidic media in protic solvents. 2,3-*O*-Alkylidene glyceraldehydes can be converted into several other useful chiral intermediates using very common methods. Some of these transformations, which can be made by very standard methods, are illustrated in Scheme 4 and allow access to intermediates such as the isopropylidene glycerol **(32)**, mesylate **(33)**, azide **(34)**, amine **(35)**, nitrile **(36)**, oxime **(37)**, and glycidol **(38)**.

B. D-Threonic and L-Erythronic Acid-γ-lactones

D-Erythronic acid-γ-lactone **(39)** can be prepared by the oxidation of D-ascorbic acid with hydrogen peroxide and base (Scheme 5).[22] The isomeric L-

Scheme 5

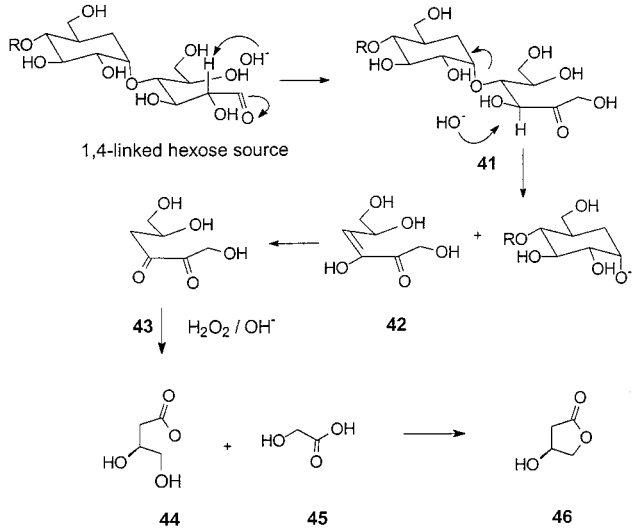


threonic acid lactone **(40)** can be prepared from L-ascorbic acid by a similar method. This is one of the few examples where useful products can be obtained from a carbohydrate without prior protection or derivitization.

C. (*S*)- and (*R*)-3-Hydroxy-γ-butyrolactone

(*S*)- and (*R*)-3-Hydroxy-γ-butyrolactone (**46** and **52**, respectively) are two extremely flexible chiral synthons. Earlier synthetic routes to these compounds all relied on involved structural transformations or selective reductions of malic acid.[23−27] They can now be obtained in high yield from several carbohydrate raw materials. The (*S*)-lactone **46** can readily be prepared by the oxidation of 4-linked D-hexose sources such as cellobiose, lactose, maltose, maltodextrins, starch, etc., with hydrogen peroxide and an alkaline or alkaline-earth hydroxide.[28,29] The mechanism is shown in Scheme 6. Treatment of a 4-linked hexose

Scheme 6

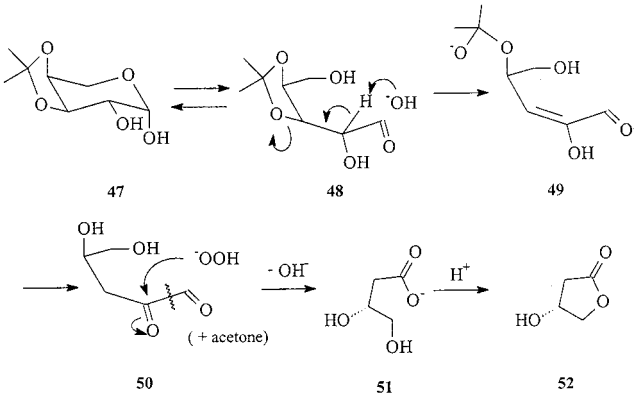


with base leads to an isomerization to the 4-linked ketose **41**, which readily undergoes β-elimination to form enone **42** which then tautomerises to the diketone **43**. The diketone is readily cleaved with hydrogen peroxide to give the salt of (*S*)-3,4-dihydroxybutyric acid **44** and glycolic acid **45**. Acidification and concentration yields the lactone **46**. This is another of the very few instances where a carbohydrate molecule can be converted into a useful chiral molecule without prior protection or functionalization.

In principle, the (*R*)-lactone **52** can be synthesized by a similar route using a 4-linked L-hexose source

since the chiral center in the product is derived from the 5-carbon of the hexose. Unfortunately, L-isomers of hexose sugars are quite rare and simple 4-linked L-hexoses are not known. Some L-sugars such as arabinose and xylose are readily available. L-Arabinose is a major component of some plant cell wall materials and plant gums. It is easily the major component of sugar beet pulp and mesquite gum.[30,31] It can be recovered from the latter material in high yield by simple mild acid hydrolysis and crystallization of the syrup.[31] The (*R*)-lactone was obtained in high yield from L-arabinose **(5)** by the simple strategy of functionalizing the 3-position by forming a 3,4-acetal **47** and oxidizing it under similar conditions as those used for the preparation of the other isomer.[32] This oxidation yields the dihydroxy acid **51** and formic acid via the unsaturated aldehyde **49** which tautomerises to the α-dicarbonyl compound **50**. The dihydroxy acid is then converted to the lactone **52** by acidification and concentration (Scheme 7). The

Scheme 7



optically active 3-hydroxy-γ-butyrolactones are extremely flexible chiral synthons. They can be converted to an extremely large number of useful and important intermediates with a wide range of applications.

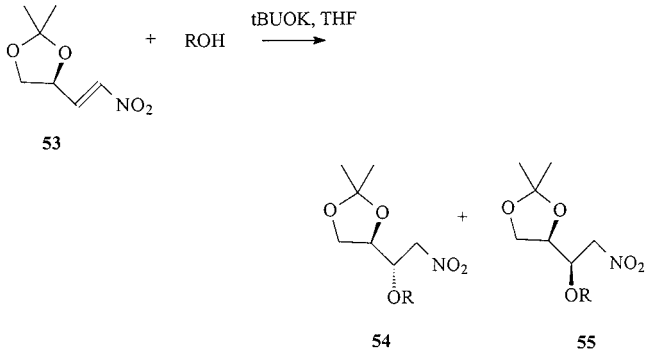
III. Applications of Carbohydrate-Derived General-Purpose Synthons

A. 2,3-*O*-Alkylidene Acetals of Glyceraldehyde or Glyceric Acid

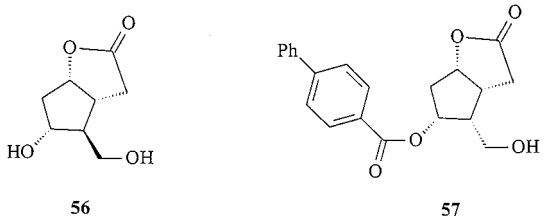
Optically active 2,3-*O*-alkylidene glyceraldehydes and glyceric acids have seen much use in asymmetric organic synthesis. Of these, the isopropylidene derivatives are by far the most used. The nitroalkane **53** has been synthesized from (*R*)-2,3-*O*-isopropylidene glyceraldehyde and used as a Michael acceptor for the preparation of various trialkyloxy functionalized butanes with general structure **54** and **55**.[33] These can be used in the synthesis of chiral carbocyclic and heterocyclic compounds (Scheme 8). This followed other work on the cyclopropanation and stereoselective conjugate addition of various organometallic nucleophiles to the same or related compounds.[34]

The Corey lactone alcohol **56** and its protected variant **57** are key intermediates in the synthesis of

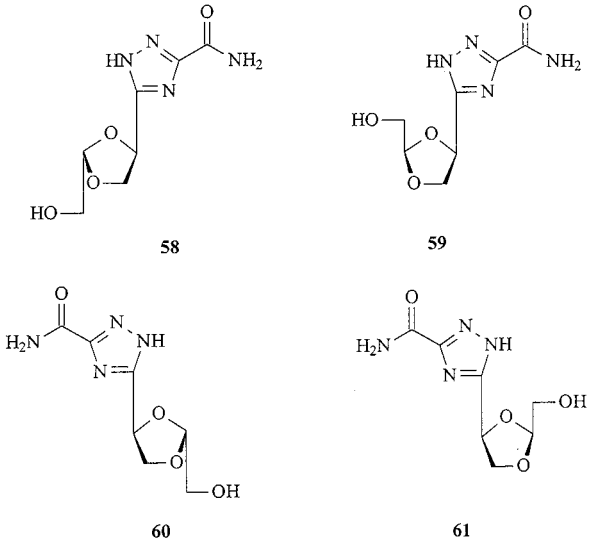
Scheme 8



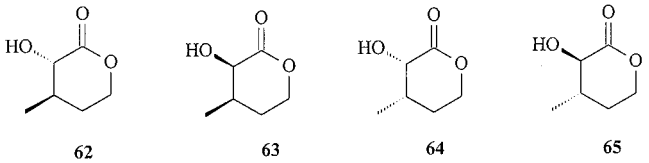
prostanoids and have always been important synthetic targets.[35] Asymmetric syntheses of *ent* Corey lactone derivatives and their various epimers were carried out using (*R*)-2,3-*O*-isopropylidene glyceraldehyde as the key source of chirality.[36]



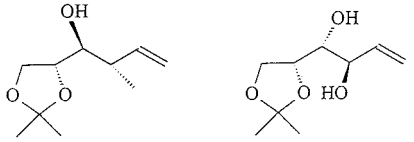
C-Nucleosides contain a C−C bond instead of a C−N bond between the sugar and the base. They are important candidates for anti-cancer drugs.[37] The *C*-nucleosides **58** and **59** were prepared from (*R*)-2,3-*O*-isopropylidene glyceraldehyde. The two isomeric compounds **60** and **61** were prepared from the (*S*) isomer.[38]



The four isomers (**62-65**) of the δ-lactone (−)-verrucarinolactone **62** were synthesized from the ene−triols derived from **66** and **67** which in turn were obtained from (*R*)-2,3-*O*-isopropylidene glyceraldehyde.[39] (*R*)-2,3-*O*-Isopropylidene glyceraldehyde has also been employed in the synthesis of the lactone (+)-roccellaric acid **68** and its enantiomer[40] and in the synthesis of rubrenolide **69**.[41] In this latter

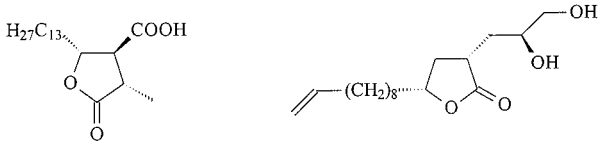


62 63 64 65



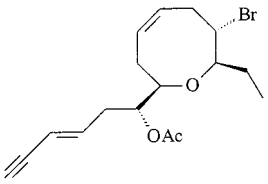
66 67

sequence, the diol side chain was derived from (*R*)-2,3-*O*-isopropylidene glyceraldehyde.



68 69

Other compound classes in the synthesis of which optically active isopropylidene glyceraldehydes were used include sphingosine chains,[42] 3-amino-2-azetidinones,[43] β,γ-unsaturated-α-amino acids,[44] fluorinated macrocyclic bis(indolyl) maleimides,[45] fluorocyclopropyl alcohols,[46] and large-ring cyclic ethers such as (+)-laurencin **70**.[47] Other examples of lipid



70

synthesis using these synthons are the preparation of enantiomerically pure 1-*O*-phosphocholine-2-*O*-acyl-octadecanes and 1-*O*-phosphocholine-2-*N*-acyloctadecane,[48] the synthesis of diacyl glycerols,[49−53] and the synthesis analogues of fragments of leukotriene-B4.[54]

Optically active isopropylidene glyceraldehyde prepared from both mannitol and ascorbic acids have also been used in the synthesis of 5-hydroxymethyloxazolidinones **71** and **72** by two routes, one involving the oxime of the aldehyde and another involving isopropylidene glycerol made by reduction of the aldehyde group.[55]

71 72

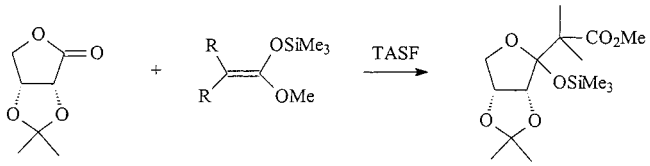
There are several studies of mechanistic and some synthetic significance that involve the use of optically active 2,3-*O*-isopropylidene glyceraldehydes. These include studies on the rearrangement of chiral allyl imidates,[56] the stereoselective synthesis of alcohols employing organotitanium and organozinc reagents,[57] the addition of alkyl radicals to chiral (*Z*)-α,β-unsaturated esters,[58] and studies on the effects of a phosphazene base on the selectivity of α-sulfonyl carbanion additions.[59]

Optically active isopropylidene glyceric acid and glyceric acid have seen much more limited use in asymmetric synthesis compared to the isopropylidene glyceraldehydes. D-Glyceric acid was used in the synthesis of (*R*)-3-methylbutane-1,2,3-triol-1-tosylate (**73**) a key intermediate in the synthesis of (24*R*)-24,-25-dihydroxyvitamin D_3.[60] Other uses have been also in the lipid area for the preparation of 1,2-dialkylglycerophosphorylcholines and for diacyl glycerols and phosphatidylcholines.[61] Two excellent reviews on the preparation and applications of (*R*)- and (*S*)-2,3-*O*-isopropylideneglyceraldehyde in stereoselective organic synthesis are available.[62]

B. D-Threonic and L-Erythronic Acid-γ-lactones

L-Threonolactone, D-erythronolactone, and 2,3-*O*-isopropylidene-D-erythronolactone have found much use in several spheres of interest in asymmetric synthesis. Addition and coupling reactions involving the carbonyl groups of these molecules have been of special interest. The reaction of silyl ketene acetals with 2,3-*O*-isopropylidene-D-erythronolactone has been studied and shown to proceed in good yield to give the C1 extended product **75** with the *endo* trimethylsiloxy group (Scheme 9).[63]

Scheme 9

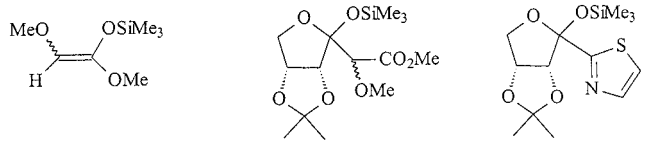


74a 75

(a) R=Me
(b) R=Et

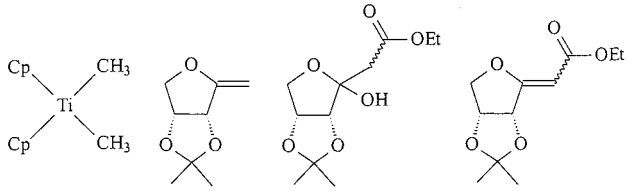
TASF = tris(dimethylamido)sulfonium difluorotrimethylsilicate

In a more detailed study, the reaction illustrated in Scheme 9 was re-explored using the catalyst tris-(dimethylamido)sulfonium difluorotrimethylsilicate (TAS−$TMSF_2$).[64] 2,3-*O*-Isopropylidene-D-erythronolactone reacted with 1-methoxy-2-methyl-1-trimethylsilyloxypropene **(74a)** in the presence of TAS−$TMSF_2$ to give the anomer of **75**. Reaction of the isopropylidene acetal with the silylketene acetal **76** gave a 31:19 mixture of the diastereomers **77** in a 50% total overall yield. The major product was not identified. When the reagent was switched to 2-(trimethylsilyl)thiazole, the C1 extended masked aldehyde **78** was obtained in 64% yield.



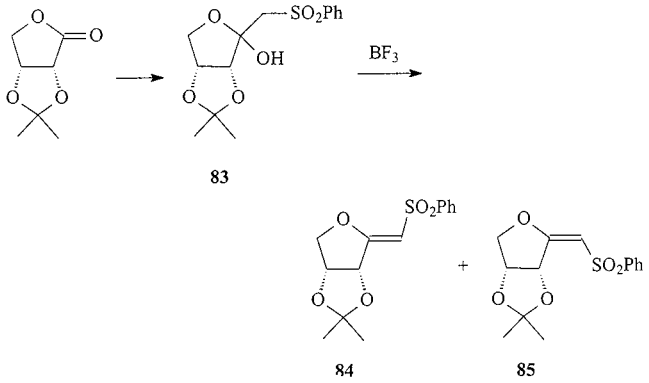
76 77 78

The methylenation of 2,3-*O*-isopropylidene-D-erythronolactone is another transformation of considerable interest. The reaction of this compound with dicyclopentadienyldimethyltitanium **(79)** yielded the 1-protected erythrose in 64% yield.[65] In the same study, 2,3-*O*-isopropylidene-D-erythronolactone was converted to to the lactol **81** in good yield via a Reformatsky-type reaction with ethylbromoacetate. This was readily dehydrated to a mixture of the isomeric α,β-unsaturated esters **82**.



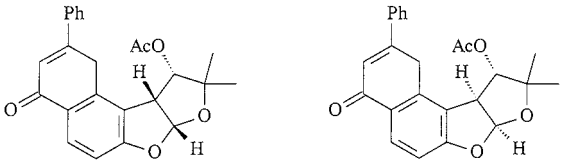
79 **80** **81** **82**

In another methylenation reaction,[66] 2,3-*O*-isopropylidene-D-erythronolactone was converted to a mixture of tetrahydrofuranylidene sulfones **84** and **85** by treatment with dilithiomethylphenyl sulfone to form the lactol **83** which was then dehydrated to give the final products.



83 **84** **85**

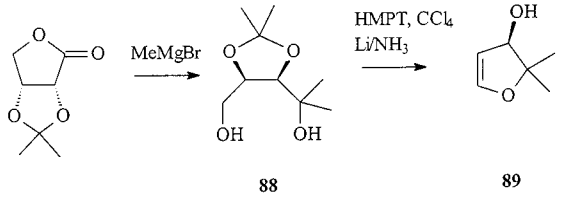
2,3-*O*-Isopropylidene-D-erythronolactone was used in the synthesis of the platelet aggregation antagonist pseudosemiglabrin **86** and its diastereomer semiglabrin **87**.[67] In the synthesis, the preparation



86 **87**

of the triisopropyl ether-protected dihydrofuran **89** and its subsequent rhodium-assisted coupling to 2-diazo-1,3-cyclohexadione were the critical steps in the formation of the enantiocenters. The synthesis of the dihydrofuran is outlined in Scheme 10.

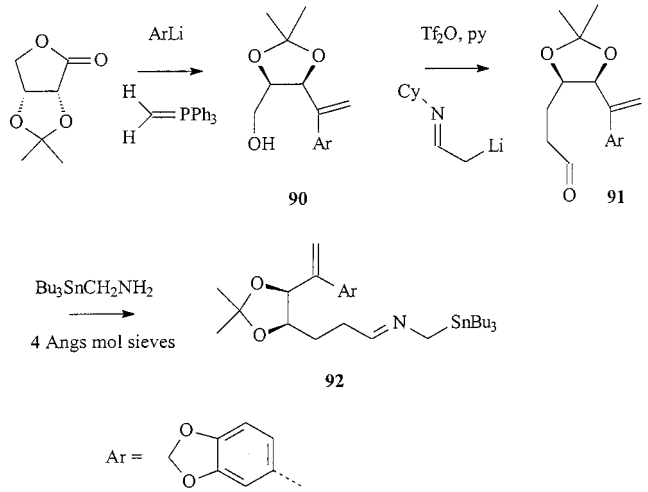
Scheme 10



88 **89**

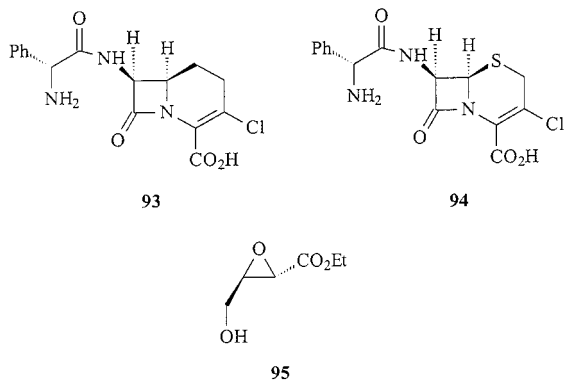
The (2-azaallyl)stannane **92**, a key intermediate in the synthesis of (−)amabiline, was prepared in excellent yield in three steps from 2,3-di-*O*-isopropylidene-D-erythronolactone (Scheme 11).[68]

Scheme 11



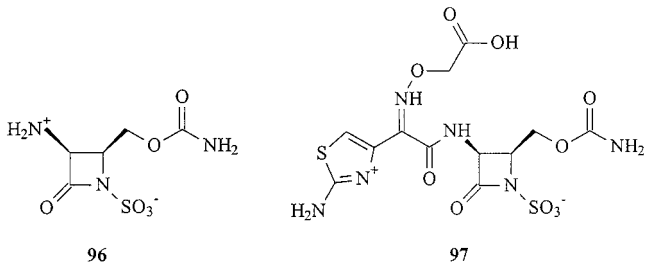
90 **91** **92**

The synthesis of optically active β-lactams is another area where D-erythronolactone and its 2,3-isopropylidene acetal have played an important role. β-Lactams have a well-known role in the pharmaceutical arena as antibacterial agents. Loracarber **(93)**, a 1-carba(1-dethia)-analogue of the cephalosporin cefaclor **94,** was prepared from D-erythronolactone via the intermediate ethyl-4-hydroxy-(2*S*,3*R*)-epoxybutyrate **(95)**.[69] The epoxide was formed from a 2-tosylate.[70]



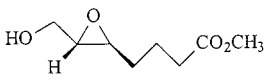
93 **94** **95**

Another example of the use of an optically active tetronic acid γ-lactone in the synthesis of a clinically important β-lactam is the preparation of the key intermediate **96** required for the preparation of RO17-2301 (**97**) via L-threonolactone.[71]

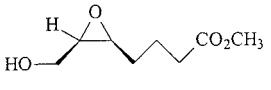


96 **97**

The preparation of analogues or key intermediates in prostaglandin synthesis is another area where tetronic acids, their lactones, and acetals have been employed.[72,73] In the first example,[72] a 5*S*,6*S*-epoxy alcohol **98** and its 6-epimer **99**, compounds used in the synthesis of leucotrienes, were prepared using 2,3-*O*-isopropylidene-D-erythronolactone as a key starting material. The key steps in the synthesis of **98**

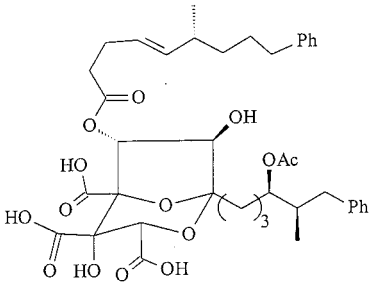


98



99

and **99** were the reduction of the lactone to a lactol (2,3-*O*-isopropylidene-D-erythrose) and extension of C1 by a Wittig reaction. A similar strategy was used in the syntheses of leucotrienes C_4, D_4, and E_4. The dioxobicyclooctane cores of (+)-zaragozic acid-C **(100)**[74] and both enantiomers of the insect pheromone *endo*-brevicomin (**101** and **102**)[75] were both derived from 2,3-*O*-isopropylidene-D-erythrolactone.



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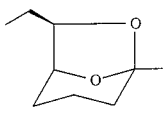

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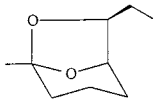
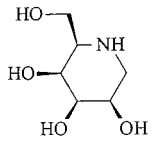


102

As discussed earlier, the imino sugars (also known as aza sugars) is a class of compounds of extremely high pharmacological significance. 1-Deoxy-talonojirimycin **(103)**, swainsonine **(104)**, and indolizidinediol **(105)** (a putative advanced intermediate in the biosynthesis of swainsonine)[76] were all prepared from 2,3-*O*-isopropylidene-D-erythronolactone,[77−79] respectively. There were no common themes in the ap-



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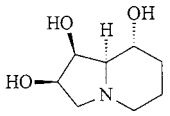

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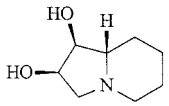
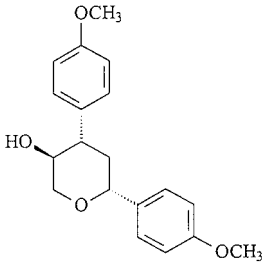


105

proaches used to these three compounds, attesting to the tremendous flexibility and value of these tetrose and tetronic acid derivatives in asymmetric synthesis.

One interesting use of D-erythronolactone is as a chiral auxiliary in [4 + 2] heterocycloadditions. This strategy was employed in the synthesis of (−)-*O*-dimethylsugiresinol **(106)**.[80,81] In this approach, a



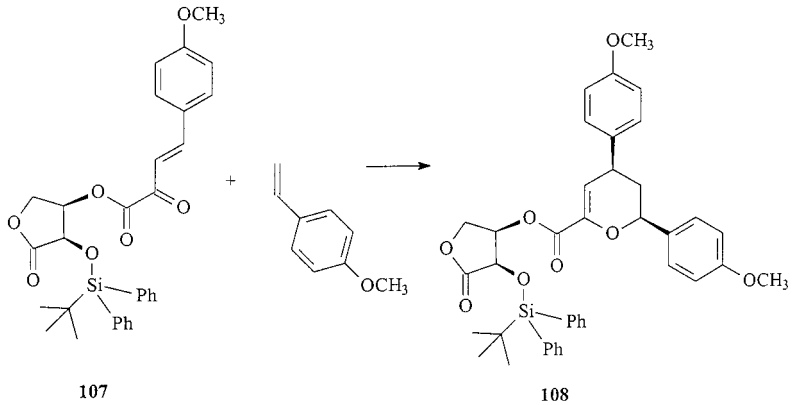
106

chiral benzylidene−pyruvic ester in which the alkoxy fragment is D-erythronolactone substituted at the 2-oxygen with a *tert*-butyldiphenylsilyl group **107** was coupled with 4-methoxystyrene (Scheme 12) to generate the chiral dihydropyran ring in the key intermediate **108**. The yield was 76% and the *endo*/*exo* selectivity >97:3.

C. (*S*)- and (*R*)-3-Hydroxy-γ-butyrolactone

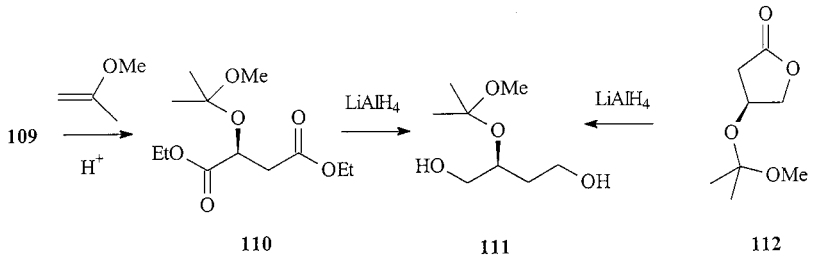
The 2-(2-methoxyisopropyl)ether of (*S*)-1,2,4-butanetriol was used as a key intermediate in the synthesis of (*S*)-12-hydroxy-5,8,14-*cis*-10-*trans*-eicosatetraenoic acid (Samuelson's HETE) **(116)**.[82] This was prepared from malic acid diethyl ester **109** as indicated in Scheme 13. The same intermediate can easily be obtained by a similar acetalization and

Scheme 12

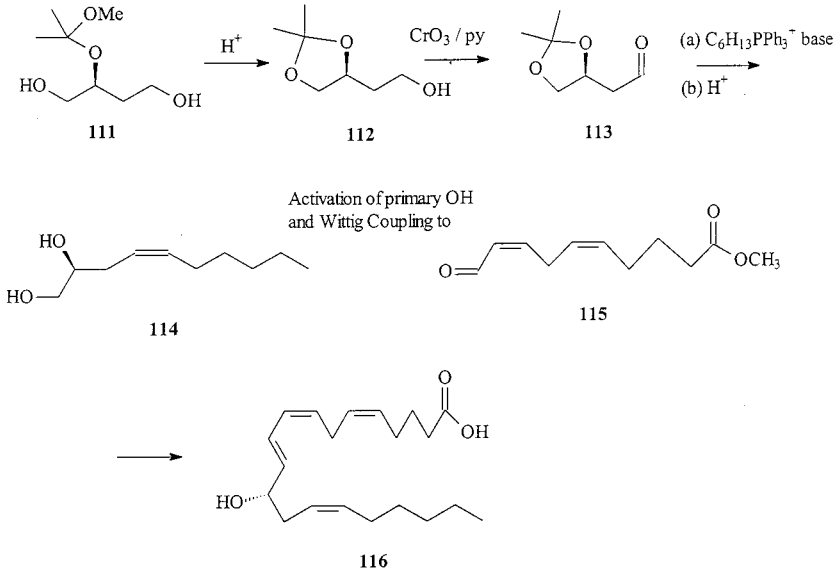


107 **108**

Scheme 13



Scheme 14

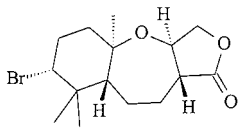


reduction of (*S*)-3-hydroxy-γ-butyrolactone as indicated in the same scheme. The partially protected triol readily lost methanol under acid catalysis to form 2,2-dimethyl-5-hydroxyethyl-1,3-dioxolane **(112)**, which was oxidized under the standard Collin's conditions (CrO_3) to the aldehyde **113**. This aldehyde was coupled to *n*-hexyltriphenylphosphorane to give the unsaturated diol **114**. The primary hydroxyl function of **114** was activated for Wittig coupling and combined with the diunsaturated aldehyde **115** to form the desired product **116** after hydrolysis of the carboxylic ester function (Scheme 14). Both enantiomers of the aldehyde **113** were used in the synthesis of (*R*)- and (*S*)-3-hydroxy-γ-butyrolactone for pharmacological testing on hunger and satiety responses.[83]

The unusual base (*S*)-(+)-5-(4′,5′-dihydroxypentyl)-uracil **(123)** which replaces thymidine in the DNA of the bacteriophage SP-15 was synthesized via the (*S*)-1,2,4-butane triol.[84] The strategy used in this case was to prepare the 1-carbon higher homologue of the aldehyde **113** via the creative strategy shown in Scheme 15. In this approach, the dioxolane **112**, this time prepared by acetonation of the butanetriol, was converted to the bromo compound **117** which was activated for Wittig coupling to phenyl acetaldehyde. Isomerization of the alkene thus formed with base yielded **120**. Ozonolysis of **120** yielded the protected 4,5-dihydroxypentanal **(121)**, which was coupled to the pyrimidine ring to give the intermediate alcohol **122**. Deoxygenation and deprotection of **122** gave the desired product **123**.

The aldehyde **113** was again featured in the development of general synthetic methods for the preparation of *syn*-1,3-polyols.[85] The *syn*-polyol functionality is a common feature of some macrolide antibiotics. In this case, the 1,3-dithiane **124** derived from **113** was reacted with the protected epoxyalcohol **125** (obtainable from **112**) to form the intermediate dithiane **126**. Removal of the dithiane function from **126** yielded ketone **127**, which was reduced with $LiAlH_4$/LiI to give the partially protected *syn*-polyol **128** (Scheme 16). The syn:anti ratio was 95:5. The same group carried out a more comprehensive study on selective *syn*-diol formation using this method and a series of ketones derived from the 3,4-*O*-isopropylidene acetal of (*S*)-3,4-dihydroxybutyric acid.[86]

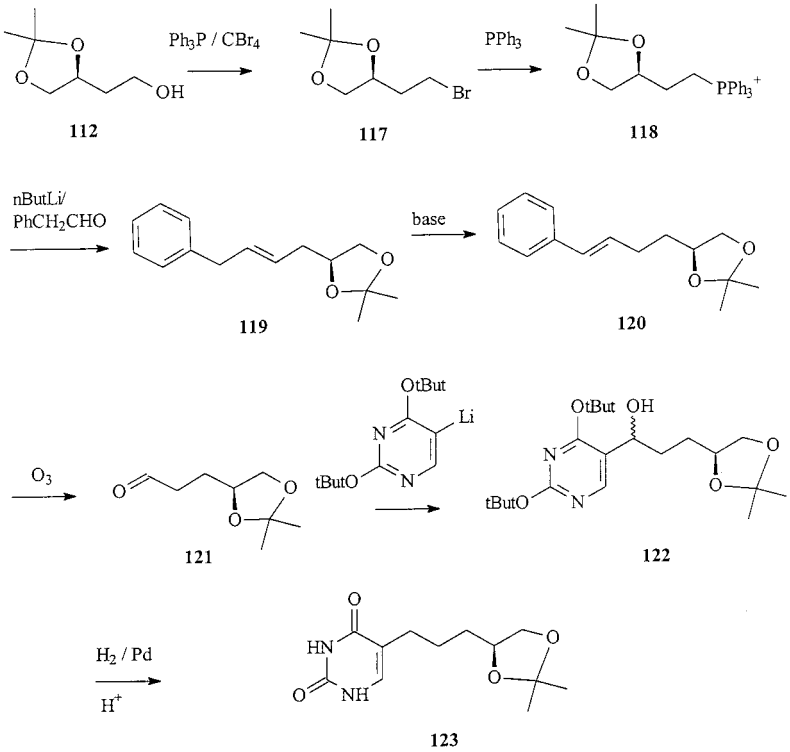
(−)-Aplysistatin **129**, an anti-cancer agent,[87] was synthesized from (*R*)-3-hydroxy-γ-butyrolactone, which provides the 2-pyrone substructure.



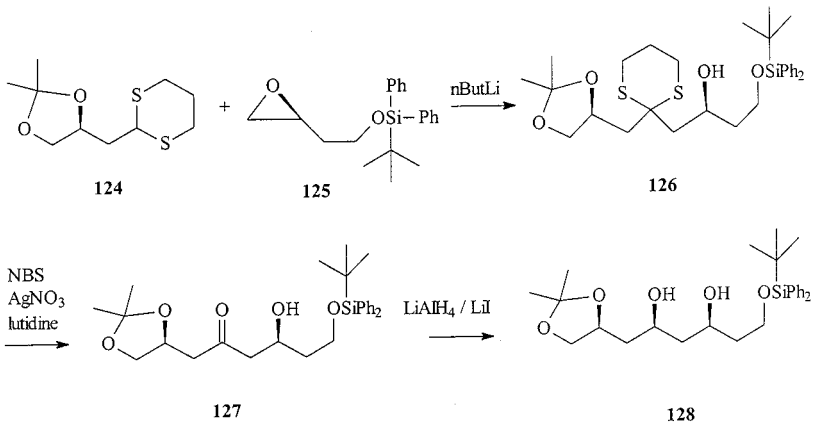
129

(*S*)-3-Hydroxy-γ-butyrolactone was recently used in the facile preparation of β-lactams (azetidinones) for use in the synthesis of cholesterol absorption inhibitors (Scheme 17).[88,89]

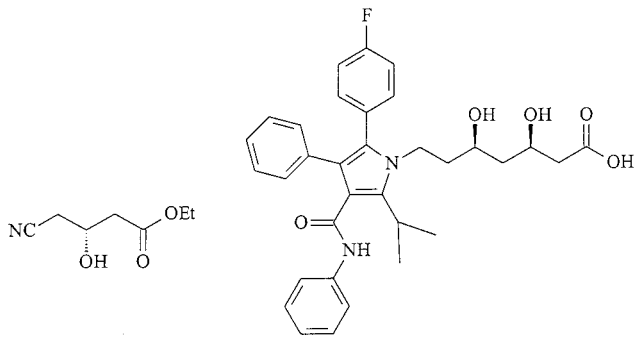
Scheme 15



Scheme 16



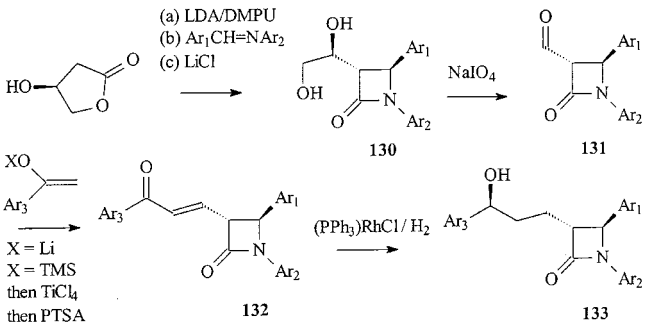
The hydroxycyanoester **134** is a key intermediate in the synthesis of the optically active 3,5-dihydroxy-heptanoic acid side chain of the cholesterol lowering drug CI-981 (**135**) and related compounds.[90] These



134 135

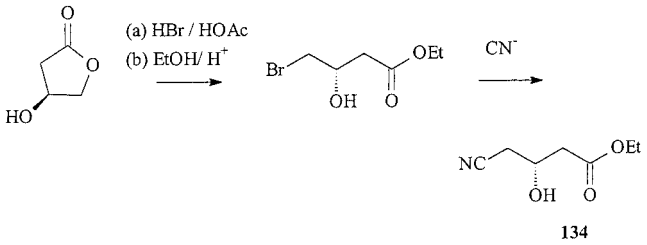
function as HMG-CoA reductase inhibitors. This side-chain component **134** can be readily prepared in a

Scheme 17

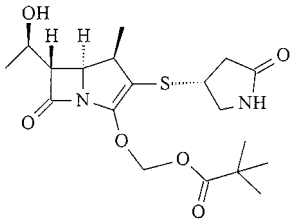


few steps from (*S*)-3-hydroxy-γ-butyrolactone via the (*S*)-4-bromo-3-hydroxybutyric acid ethyl ester formed by HBr treatment of the lactone followed by ethanolysis and treatment of the intermediate bromo−ethyl ester with cyanide as illustrated in Scheme 18.[91]

Scheme 18



Carbanenems are potent γ-lactam antibiotics with a broad activity spectrum against both Gram negatives and Gram positives.[92] The hydroxypyrrolidinone formed by treatment of the bromo−ethyl ester described above with ammonia was used as a key intermediate in the synthesis of the (*R*)-5-oxopyrrolidin-3-ylthio side chain of the carbapenem drug candidate CS-834 (**136**).[93] The preparation of the side



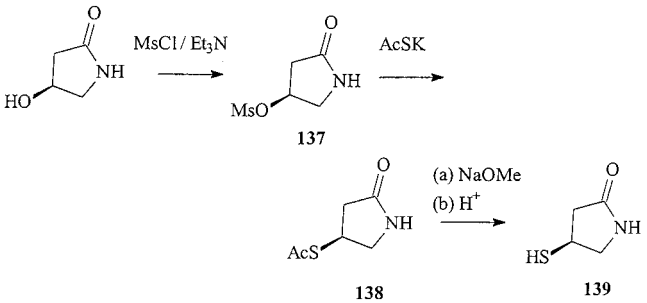
136

chain is described in Scheme 19. The hydroxypyrrolidinone was also used in the synthesis of a chiral bicyclic imidazole side chain of another carbapenem.[94] The pyrrolidinone can be easily prepared from (*S*)-3-hydroxy-butyrolactone by the method shown in Scheme 20.

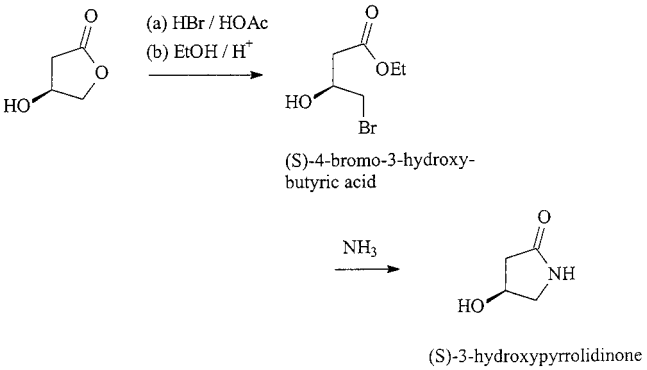
The preparation of optically active 3-hydroxyalkanoic acids is another area of considerable interest. The (*S*)-4-bromo-3-hydroxybutyric acid ethyl ester whose preparation is shown in Scheme 20 can be readily converted to (*S*)-3,4-epoxybutyric acid ethyl ester. The epoxyester can easily be alkylated with an alkyl Grignard to yield optically active 3-hydroxy esters. The synthesis of 3-hydroxy acids by this strategy was first demonstrated by Larcheveque and Henrot,[95] and the preparation of (*R*)-3-hydroxytetradecanoic acid was later demonstrated.[96]

In the examples given above of the use of the optically active 3-hydroxy-γ-butyrolactones, the chiral fragment that was integrated into the final structure was a 4-carbon fragment. There are several classes of drugs that contain chiral 3-carbon fragments

Scheme 19

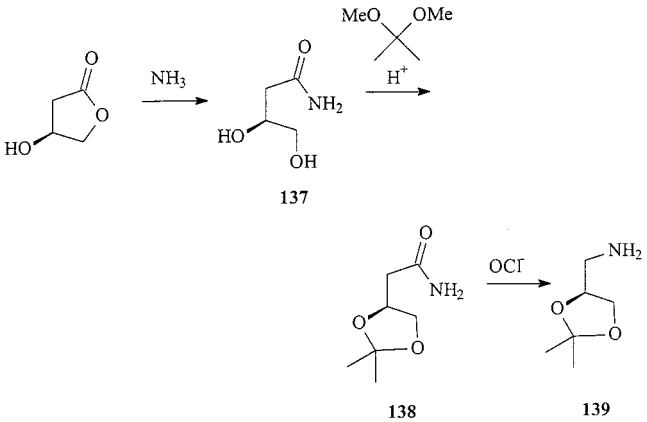


Scheme 20



(Figure 1). The common chiral substructure is an aminodiol. Many of these are accessible by synthetic routes employing free or protected optically active glyceraldehyde, glycerols, glyceric acids glycidols, or related 3-carbon synthons. A very significant breakthrough in the use of optically active 3-hydroxy-γ-butyrolactones in asymmetric synthesis came with the development of decarboxylation routes using Hofmann or Curtius degradations on functionalized butyramides or butyric acid hydrazides.[91,97,98] The main strategy for converting optically active 3-hydroxy-γ-butyrolactones to 3-carbon chiral synthons is illustrated in Scheme 21. This involved the conver-

Scheme 21



sion of the lactone to the 3,4-dihydroxybutyramide **137** and then to the isopropylidene acetal **138**.[97] Treatment of the amide with hypochlorite yielded the isopropylidene acetal of 3-amino-1,2-dihydroxypropane **139**. In the same study, the amine was converted to optically active 1-halo-2,3-dihydroxypropanes by deaminative halogenation with sodium nitrite in the presence of chloride or bromide ions. Both isomers of the 3-amino-1,2-dihydroxypropanes have been obtained from carbohydrates before, but in both cases, oxidation with lead tetraacetate or periodate was required.[55,99] The chemistry based on the hydroxybutyrolactones also allowed ready access to L-carnitine and related molecules from the (*S*)-lactone. It also affords very efficient access to the full range of 3-carbon intermediates shown in Scheme 4.

IV. Other Applications

In addition to the applications in the areas of pharmaceutical and medicinal chemistry and natural

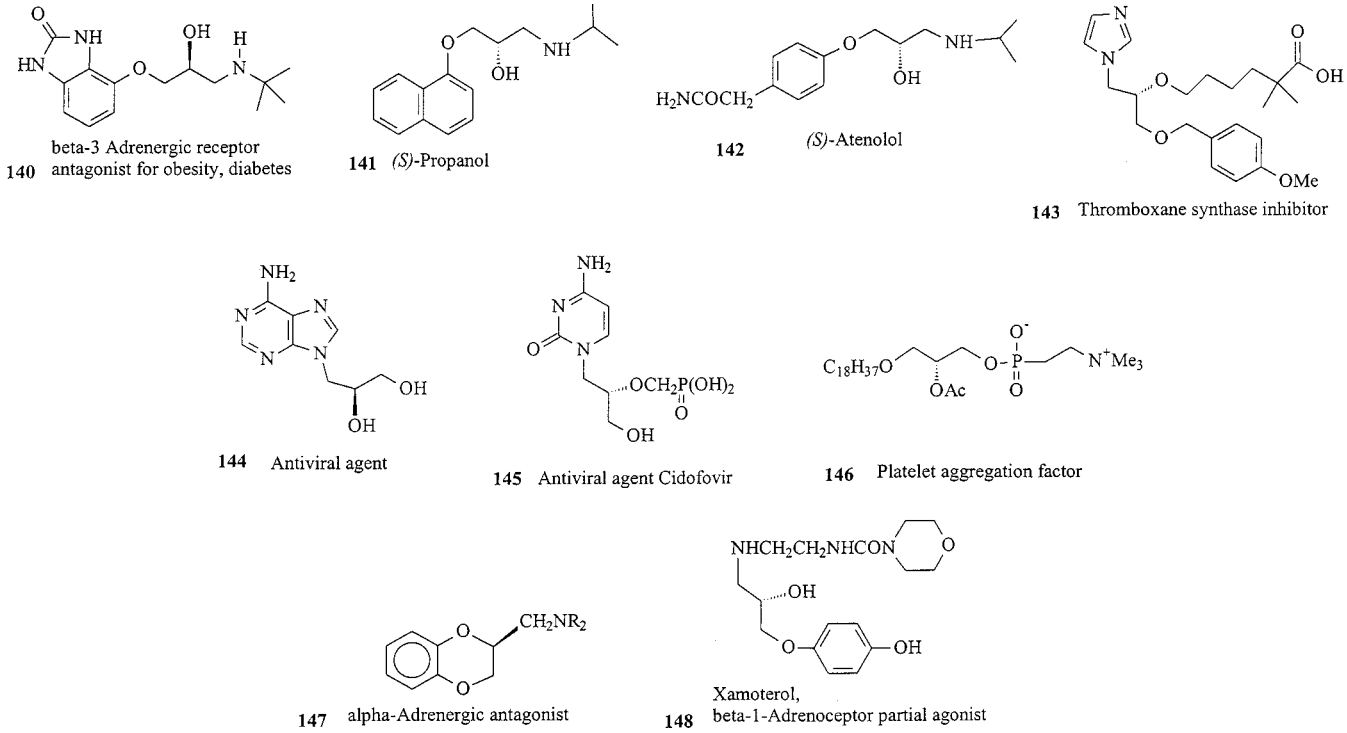
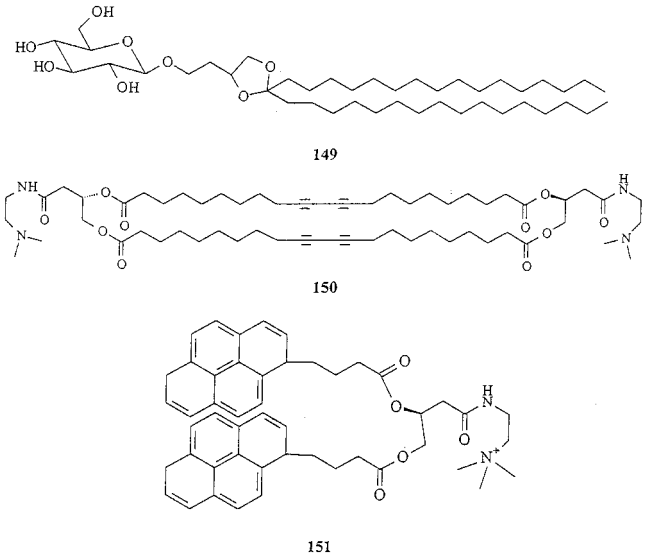


Figure 1.

products chemistry, (*S*)-3-hydroxy-γ-butyrolactone and its derivatives have been used in the synthesis and fabrication of several molecular systems that are of importance to the drug delivery, biomolecular probe, and biosensor areas. The approach to these systems is essentially the design and fabrication of lipid-based supramolecular ensembles. A lipid analogue that resembles monoglucosyl diacylglycerol but in which the alkyl chains are connected to the headgroup through an acetal linkage was synthesized, and the membrane vesicles formed from them were studied. This analogue **149** readily formed liposomes that can rupture in response to a drop in pH.[100] This was designed as a prototypical system for



the fabrication of pH-responsive "smart liposomes". A lipid analogue **150** based on the motif of a thermophilic membrane lipid component and that forms liposomes that are stable to temperatures in excess of 70 °C was also synthesized and studied.[101,102] (*S*)-3-Hydroxy-γ-butyrolactone was also used in the synthesis of a cationic lipid analogue **151** that can be used as a probe for the detection of phospholipase-A activity and for the analysis of biomembrane dynamics.[103] On the basis of these successes, the somewhat related areas of lipid analogues, biomembrane mimics, liquid crystals, and bio-based advanced materials should benefit greatly by the ready availability of these very flexible optically active building blocks.

V. Summary

There is a lot that can be said for an approach in which a few molecules with good scope of chemical reactivity can be obtained from some large reservoir of material which is otherwise intractable because of undesirable aspects of molecular weight, redundancy of functionality, composition, physical properties, or other attribute. This is in many ways the story of industrial organic chemistry as we know it. It was the liberation of very low molecular weight alkenes, benzene, and toluene from the chemically intractable reservoirs of oil and their conversion to basic oxidation products such as acetone, alcohols, and phenols that was responsible for the tremendous boom in industrial organic chemistry that we know. Very simple transformations such as hydrations, halogenations, nitrations, alkylations, acylations, and reductions carried out on these few simple structures to form alcohols, ketones, acids, phenols, and the like have led to the richness of the chemistry we know now. These industrial developments have resulted in the availability of a relative handful of extremely high-volume commodity chemicals. The availability of these has, in turn, spawned a large spectrum of

lower volume specialty and fine-chemistry industries and fueled the enormous growth that polymer, pharmaceutical, materials, and the many other areas of organic chemistry has enjoyed both in the lab and in the industrial environment.

Carbohydrates are much more abundant than fossil fuels. They are also a renewable resource. Until now carbohydrates have been used largely for their physical properties. Some progress has been made in "cracking" this vast reservoir of highly functionalized chirality, giving access to an impressive diversity of high-valued compounds. These compounds are much more functionalized than those obtained directly from fossil fuels. In fact, they cannot be obtained from fossil fuel-based intermediates without the exacting of an extreme price. They lend themselves to applications and uses across the chemical spectrum in areas and applications ranging from drug discovery, drug manufacture, drug delivery, and advanced materials. The current availability of optically active carbohydrate-derived chemical intermediates such as optically active 3-hydroxy-γ-butyrolactones, their parent acids, and several derivatives on the multi-ton scale represents a very important step forward in our quest to successfully address the formidable challenge of mastering, harnessing, and exploiting carbohydrate complexity. As new uses are found for carbohydrate-based intermediates and the demand fuels volume, the old paradigm in which a particular chemical commodity becomes the core around which new compounds and new applications are developed will be established. At this time, we will begin to realize the full potential of carbohydrates as the raw material of the new emerging renewable resource-driven chemical age.

VI. References

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