Modern Methods of Monosaccharide Synthesis from Non-Carbohydrate Sources

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I. Introduction

1. Overview

Humans have utilized carbohydrates in natural forms such as cellulose in cotton, sucrose in cane sugar, and sucrose, D-fructose, and D-glucose in honey from the dawn of civilization. However, the first documented synthesis of a sugar-like syrup presented in the chemical literature was the preparation of formose from formaldehyde reported in 1861 by Boutlerow.[1] Formose was subsequently shown by Fischer and Tafel to consist of a mixture of carbohydrates, two of which were identified as DL-*arabino*-hexulose and DL-*xylo*-hexulose by preparation of the phenylosazones **1** and **2**, respectively (Figure 1).[2] Osazone **1** was subsequently transformed to D-glucose, D- and L-mannose, and also D- and L-fructose by chemical and enzymatic (yeast fermentation) manipulation.[2]

The first documented enzymatic transformation of one carbohydrate to another was the oxidation of mannitol **3** to D-fructose **4** by means of *Bacterium aceticum* by Brown in 1886 (Figure 2).[3]

This author also made a rather prophetic statement that was to gain significance in the era of biocatalysis, at a time some hundred years distant:

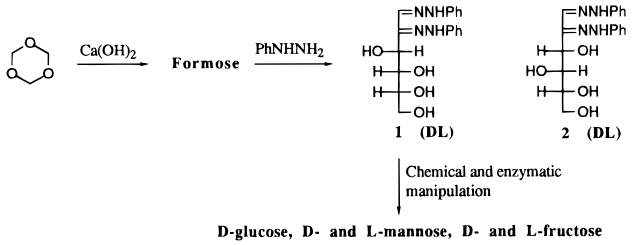

Figure 1. Fischer and Tafel's synthesis of nonracemic sugars from formose.

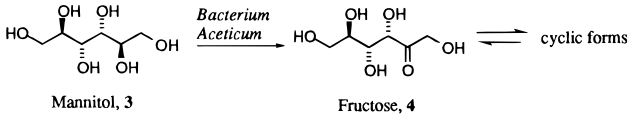

Figure 2. The first enzymatic carbohydrate-to-carbohydrate interconversion.

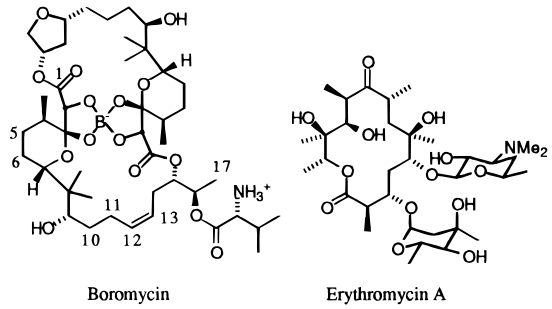

Figure 3. Examples of targets synthesized from carbohydrates.

"...I think the experiments just described will be of interest to biologists as well as chemists, as they help to show that the vital functions of certain organized ferments are most intimately connected with the molecular constitution of bodies on which they act..."

The union of chemistry and biology witnessed in the endeavors of the latter part of the twentieth century accords this visionary statement complete credibility.

For almost one hundred years the chemistry of sugars was dominated by structural and later stereochemical investigations. With the advent of complex synthetic ventures after World War II, sugars were viewed as convenient sources of chirality for asymmetric synthesis.[4] This discipline, made popular by Hanessian (see for example the synthesis of C3−C17 segment of boromycin, Figure 3),[5] Fraser-Reid,[6] and Fleet[7,8] among others, has stood as an inspiration to chemists working in asymmetric synthesis and in learning to manage asymmetry, its transfer, and propagation.

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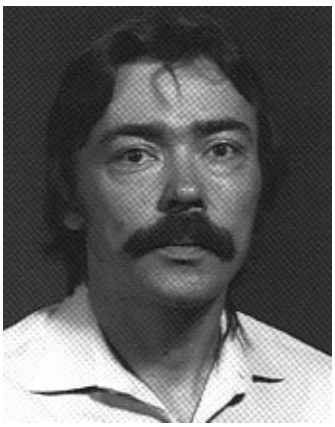
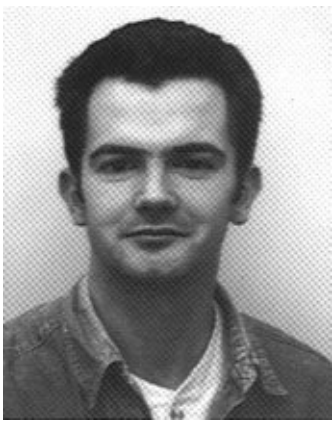


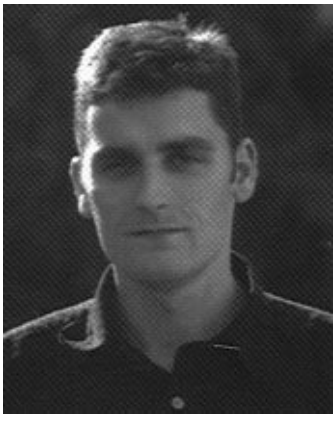
Tomas Hudlicky was born in 1949 in Prague, Czechoslovakia, and, following his arrival in the United States in 1968, he received his B.S. in chemistry at Virginia Tech in 1973. He studied with Prof. E. Wenkert at Rice University, where he received his Ph.D. in 1977. After a postdoctoral fellowship with Prof. W. Oppolzer at the University of Geneva, he joined the faculty at Illinois Institute of Technology in Chicago. In 1982 he moved to Virginia Tech, where he was promoted to Professor of Chemistry in 1988, a position he held until moving to the University of Florida as Professor of Chemistry in January 1995. Among the awards he has received are the A. P. Sloan Fellowship (1981), the NIH Research Career Development Award (1984), a Fulbright Fellowship at the University of Montevideo, Uruguay, for a lectureship (1984–1985) and for research (1985–1986), and the American Cyanamid Faculty Research Award (1992). The research interests of the Hudlicky group include the development of enantioselective synthetic methodologies, the design of practical syntheses of natural products, enzymatic methods of synthesis, and microbial degradation of aromatic hydrocarbons with prokaryotic dioxygenases. The group has devoted considerable effort to the implementation of general synthetic methodology for triquinane sesquiterpenes (1978–1988) and, more recently, for carbohydrates and derivatives.

Dr. Kevin K. Pitzer was born on November 9, 1969, in New Castle, PA. In 1991, he was commissioned a 2nd Lieutenant in the United States Army and was graduated Magna Cum Laude from Gannon University with a B.S. degree in Chemistry. In 1995, he earned a Ph.D. in Organic Chemistry from Virginia Polytechnic Institute and State University under the supervision of Dr. Hudlicky. Captain Pitzer is currently the Assistant Chief, Organic Synthesis Division at the Walter Reed Army Institute of Research. His current interests lie in the synthetic realm of medicinal chemistry.

One of the disadvantages of sugars as chiral pool reagents must surely be the number of protective and deprotective manipulations required to manage the fate of the asymmetric centers. As the regulatory pressures on chemical manufacturing mounted in the mid-1980s it became evident that synthetic ventures of 20−30 steps in length would have diminished practical or industrial credibility because of the amount of waste mass which would accumulate



David Entwistle was born in 1969, in Chelmsford, England. He studied chemistry at Imperial College of Science, Technology and Medicine, The University of London, where he gained his B.Sc. (hons) in 1990. Postgraduate research on the applications of dispiroketals in synthesis under Professor Steven V. Ley F.R.S. at Imperial College of Science, Technology and Medicine and The University of Cambridge resulted in his Ph.D. from the former, in 1994. From 1994 to late 1995 he worked with Professor Tomas Hudlicky at both Virginia Polytechnic Institute and State University and The University of Florida on the synthesis of pseudosugar monosaccharides and pseudosugar–inositol conjugates. He is presently engaged as a postdoctoral teaching fellow at The University of Nottingham under Professor Gerald Pattenden F.R.S. His research interests include the development of new synthetic methods for the synthesis of natural products.



Andrew Thorpe was born in Bolton, England, on December 3, 1968. He received his B.Sc. in Medicinal Chemistry from University College London, University of London, in 1990. He then joined Professor Stanley Robert's group at the University of Exeter where he studied synthetic approaches to carbocyclic nucleosides and was awarded his Ph.D. in 1993. From there he joined the Hudlicky research group developing novel routes to disaccharide mimics. He is currently a postdoctoral research associate with Eli Lilly and Company in Indianapolis.

during such operations. Consequently new methods of synthesis for carbohydrates began to emerge. Synthesis of sugars from non-carbohydrate precursors by means of clever chemical design and the use of chiral auxiliaries such as those used by Vogel[9] materialized in the 1980s. Parallel to these developments was the assembly of simple sugars by the exploitation of natural enzymatic pathways as exemplified by the work of Wong.[10,11] Finally, a systematic design of carbohydrates and derivatives from *cis*-cyclohexadienediols, derived from biological oxidation of aromatics, pursued by Hudlicky, further illustrated the power of biocatalysis in synthetic chemistry.[12] The latter two methods, comprised of the use of enzymes or whole cell fermentations, also reflected the response to waste management and

regulation. Synthetic sequences were shorter, and consequently their overall useful mass output greater. See a recent survey of enzymatic methods in synthesis.[12e,13d]

It is clear that the synthetic chemist must join forces with the biologist as the carbohydrate targets desired by the pharmaceutical and medicinal community increase in complexity. It is unimaginable that a chemical synthesis of a pentasaccharide containing all unnatural sugars and utilizing natural aldohexose sugars as starting materials would have any value, given the astronomical number of steps required to complete it.

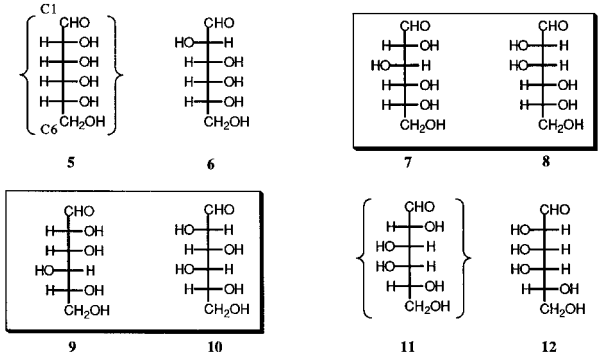
This review intends to summarize those modern methods of monosaccharide synthesis not directly based on sugar-derived starting materials. (The authors wish to direct the reader to an earlier review of a similar type concentrating on sugar synthesis from mainly acyclic precursors.)[13] A brief summary and reference guide is provided for those methods that do employ sugars as starting materials as homage to the pioneering efforts of researchers in their area. Excluded from this review are glycosidation methods,[14] higher sugar synthesis,[15] and glycoprotein preparations.[16] The literature is covered through December 1995.

2. Development of Sugar-Based Synthetic Methods

None of the work presented in this review would have been possible without the elegant work published in 1891 by Emil Fischer.[17] As a tribute to his landmark achievement a synopsis of his work is presented.

Aware of the basic topology of the carbohydrate framework, Fischer performed a series of reactions that elucidated the relative stereochemistry of D-glucose, which continues to stand as an excellent example of deductive reasoning. At the time the absolute stereochemistry of glucose was unknown, and Fischer arbitrarily assigned the configuration shown. Later, X-ray crystallographic techniques showed that his assignment was correct.

(a) The initial finding that D-glucose and D-mannose formed the same oxazone, **1**, Figure 1, meant that these compounds had the same C3, C4, and C5 stereochemistry. This implied that D-glucose and D-mannose must be a pairing of either **5** and **6**, **7** and **8**, **9** and **10**, or **11** and **12** (Figure 4).

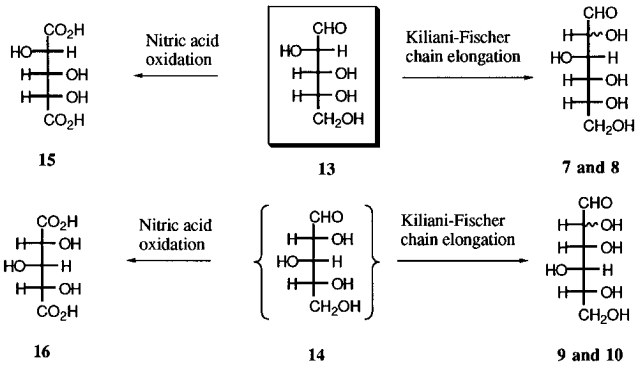


Sugars **5** an **11** in parentheses will give meso diacids on nitric acid oxidation. This excludes them (and as a corollary of point (a) their C2 epimer's **6** and **12**) from being D-glucose or D-mannose. The boxed two pairs of sugars are the only remaining canditates for the structure of D-glucose or D-mannose.

Figure 4. Part of the Fischer proof of glucose.

(b) Both D-glucose and D-mannose were oxidized to optically active diacids upon treatment with nitric acid. This eliminated structures **5** and **11** as these would give *meso* diacids and, because of the necessary pairings, **6** and **12**. This meant that D-glucose and D-mannose were either **7** or **8** or **9** or **10** (Figure 4).

(c) Kiliani−Fischer chain extension of D-arabinose gave D-glucose and D-mannose. This therefore requires arabinose to have either the structure **13** or **14** (Figure 5).



Sugar **14** in parentheses will give a meso diacid **16** on nitric acid oxidation. As this oxidation gives an optically active diacid structure **9** must be that of D-arabinose.

Figure 5. Fischer's deduction of the relative stereochemistry of arabinose.

(d) Arabinose was assigned the structure **13** because when it was oxidized with nitric acid it produced an optically active diacid (structure **14** would have necessarily given a *meso* diacid **16**). This, when combined with (b), meant that D-glucose and D-mannose were either **7** or **8**.

(e) Finally it had to be decided whether structure **7** or **8** was that of glucose. Fischer devised a series of reactions that exchanged the aldehyde and primary alcohol termini. When D-glucose was subjected to that series, a new sugar was produced which Fischer named L-gulose. When the termini of structure **7** are exchanged in this manner a new sugar **17** is formed, but when the termini of structure **8** are exchanged structure **8** is regenerated (Figure 6). This meant that the structure of D-glucose had to be as depicted in sugar **7**.

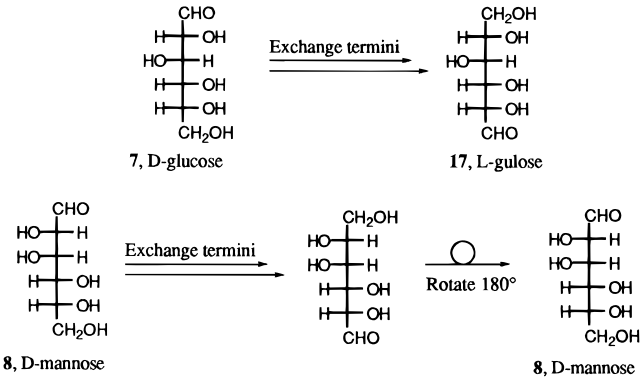
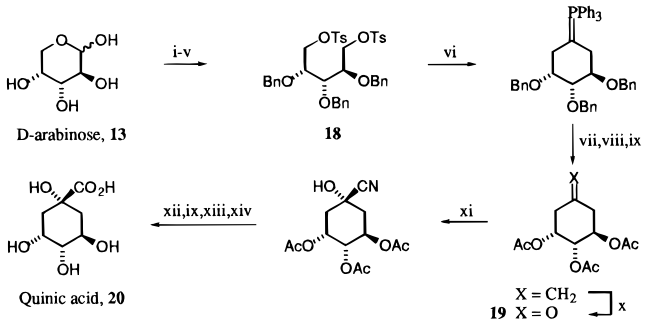


Figure 6. The final proof of the relative stereochemistry of glucose.

Carbohydrate chemistry grew quickly since Fischer's publication. Initially structural elucidation

studies were explored, and then more involved chemical syntheses such as those of Lemieux were pursued.[18] With the development of spectroscopic analysis and the ease of identification, the synthesis of other rare or unnatural sugars ensued. The recognition of the value of sugars as part of a "chiral pool" also brought about the development of asymmetric synthesis of non-carbohydrate natural products from homochiral carbohydrate sources as well as the concepts of "chiral templates" and "chirons" as extolled by Hannesian.[4] These syntheses related the sugar stereochemistry to the target natural product as can be seen in the example of the 14-step synthesis of quinic acid **20** from D-arabinose **13** (Scheme 1).[19]

Scheme 1[a]



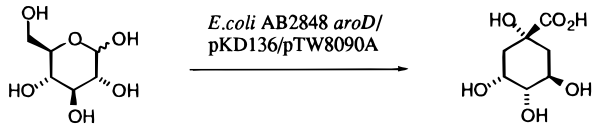
[a] Reagents: (i) Ni(R), H_2; (ii) TrCl, Py. (iii) BnCl, KOH; (iv) AcOH(aq); (v) TsCl, py; (vi) PPh_3CH_2; (vii) CH_2O; (viii) Na, NH_3; (ix) Ac_2O, py; (x) OsO_4, $NaIO_4$; (xi) HCN; (xii) HBr, AcOH; (xiii) N_2O_3; (xiv) AcOH(aq).

The two key steps in the synthesis are the introduction of the endocyclic and exocyclic carbon atoms.

Even though these chiron approaches have great merit, they in general require many steps, the largest proportion being protection−deprotection sequences. The use of carbohydrates as a chiral pool resource in organic synthesis continues; however, before committing to these lengthy sequences more notice should be given to alternative synthetic methods.

A more recent example of the use of natural sugars in the synthesis of carbocyclic natural products is the "one-step" biocatalytic conversion of D-glucose **7** into quinic acid **20** by means of genetically engineered *Escherichia coli* (Scheme 2).[20]

Scheme 2



One important role sugars have played in more recent years is in the preparation of chiral auxiliaries.[21] Carbohydrate-derived chiral auxiliaries have been used to introduce asymmetry into a host of organic reactions. The chiral allyl titanate **21** has been reacted with aldehydes yielding optically active homoallylic alcohols.[22] The simple allyl glucose derivative **22** has successfully been used in asymmetric Simmons−Smith cyclopropanations,[23] and derivative **23** has been used as a dieneophile in asymmetric Diels−Alder reactions (Figure 7).[24]

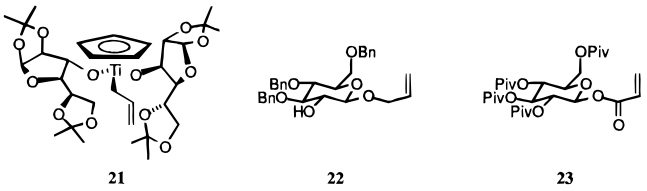


Figure 7.

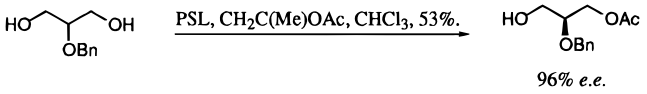
3. Review of Enzymatic Manipulations Leading to Carbohydrates

With the heightened biological and medicinal interest in carbohydrates in recent years, many new methods for their construction have been developed. Highly efficient and environmentally benign ways have involved the use of enzymatic reactions in either isolated or whole organism form.[25−30]

There are three main areas where enzymes have been used in carbohydrate chemistry:[30]

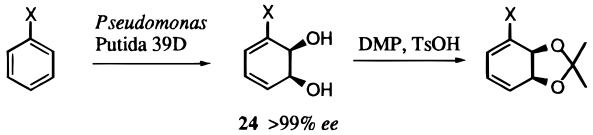
(i) The synthesis of enantiomerically pure starting materials for sugar synthesis. An example of this strategy is the desymmetrization of glycerol derivatives catalyzed by *Pseudomonas* sp. lipase (PSL) (Scheme 3).[31]

Scheme 3



Another example is the whole-cell use of the dioxygenases present in the blocked mutants of *Pseudomonas putida*, a soil bacterium that degrades benzenes to substituted cyclohexadienediols **24** (Scheme 4). These dienediols have been shown to be versatile starting materials in the synthesis of a wide variety of carbohydrates.

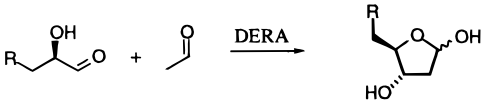
Scheme 4



X = H, Cl, Br, I, CN, Me and many others[40]

(ii) The direct formation of sugars by the use of aldolases and also to a lesser extent transketolases.[25−30] The example below shows where 2-deoxyribose-5-phosphate aldolase (DERA) has been used to prepare unnatural 2-deoxyribose derivatives **25** (Scheme 5).[32a,32b]

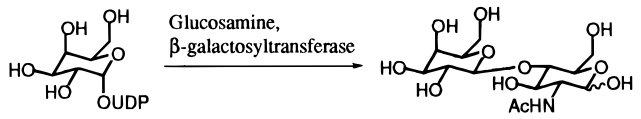
Scheme 5



R = H, F, OH, N_3, OPO_3^{2-}

(iii) Selective glycosidation reactions. Glycosidases have been used for the synthesis of oligosaccharides to a minor extent. Glycosyltranferases have had more widespread use as exemplified in Scheme 6.[33]

Scheme 6



UDP = uridinediphosphate

This review will highlight only some of the most commonly used methods in areas (i) and (ii) as some of these catagories have been recently reviewed elsewhere.[25−30]

4. Future Prospects of the Chemistry of Mono- and Oligosaccharides

Although not covered in this review, today's highly efficient glycosidation technologies[11,14,30] and enormously powerful spectroscopic structural determination techniques have brought about the syntheses of many highly complex oligo- and polysaccharides. Some of the most recently notable being those of Nicolaou and Wong (sialyl Le_x),[34] Danishefsky (GM_3),[35] Paulson (GM_3 synthesis),[36] and Ogawa (GM_3 and partial GPI syntheses) (Figure 8).[37,38]

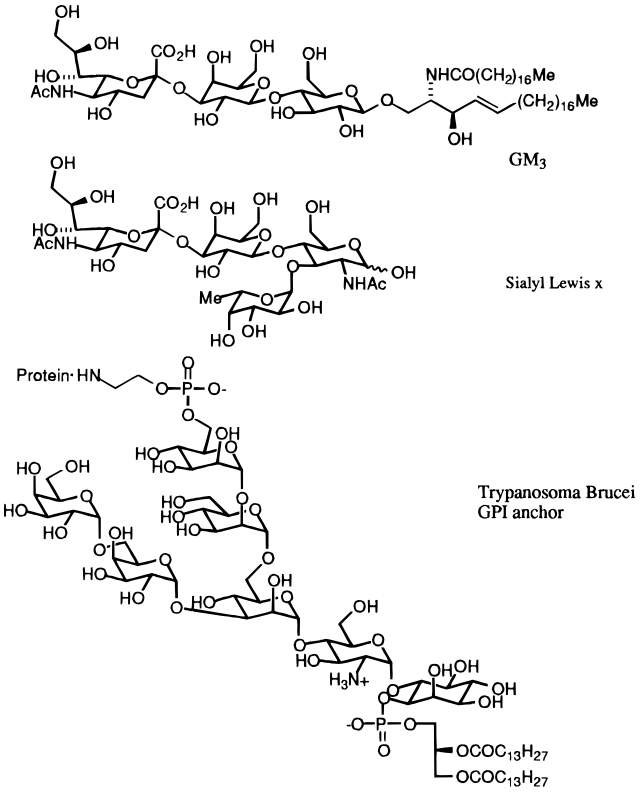


Figure 8.

The union of chemical and enzymatic glycosidation technologies, as witnessed by the aforementioned syntheses, bodes well for the synthesis of many rare natural or unnatural oligo- and polysaccharides. This, combined with automated combinatorial synthetic methods and high-input screening technologies, will in the future be of vital importance for the invention and discovery of new therapeutic drugs for the treatment for a variety of diseases. Among future endeavors will no doubt be the synthesis of unnatural derivatives of carbohydrates and oligosaccharides, by either direct or combinatorial methods.

II. Synthesis of Monosaccharides

1. Tetroses

(i) Metabolites of type **24**[12,39,40] (Scheme 4) have had widespread use in the synthesis of carbohydrates[41] and many other heterocyclic[42−44] and carbocyclic molecules.[45−48] This unique enantioselective oxidative transformation, with no known equivalent in chemical organic synthesis until 1995,[49] was discovered by Gibson in the late 1960s.[40] The large and ever growing number of structurally diverse microbial metabolites[50] have added considerably to the "chiral pool". As of this writing, only a small fraction of the reported metabolites have been used in organic synthesis. This means that other, more complex, natural product syntheses stand to profit from the use of these microbial metabolites as homochiral starting materials.

The highly functionalized ring and homochiral nature of the diol make these metabolites excellent synthetic starting materials. Ozonolysis of the acetonide-protected chlorocyclohexadiene-*cis*-diol **26** gave erythruronolactone **27** (Scheme 7).[41a] Reduction of the lactol **27** with sodium borohydride gave the lactone **28**, which is further reduced with Dibal-H to give the tetrose, L-erythrose acetonide **29**.[41b]

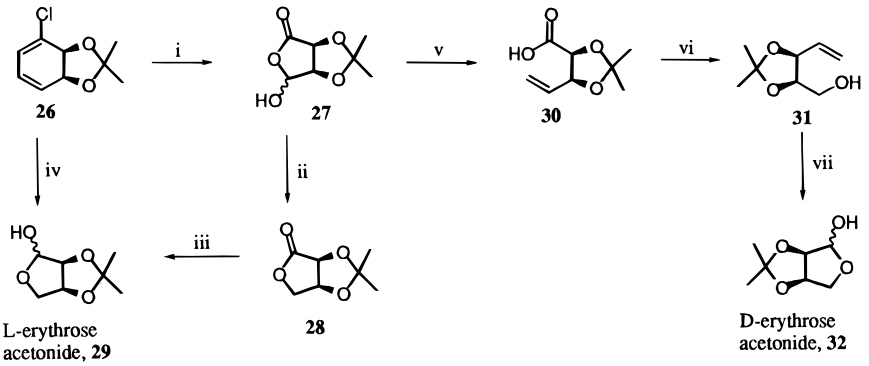
Alternatively, acetonide **26** can be converted to protected L-erythrose **29** in 54% yield in just one ozonolytic step with sodium borohydride workup.[41b] A key point to note is that this synthesis is enantiodivergent from erythruronolactone **27**. When the lactol is first treated with triphenylmethylenephosphorane it gives the δ,γ-unsaturated acid **30** whose reduction to alcohol **31** followed by ozonolysis yields the opposite carbohydrate enantiomer, D-erythrose acetonide **32**.[41b]

(ii) The use of D-glyceraldehyde acetonide **33** in sugar synthesis is widespread and has been reviewed fairly recently.[13a,51] Although aldehyde **33** is itself a carbohydrate and therefore excluded from this review as a starting material, the example below and those in future sections stand to give the reader the general pattern of usage.

2-Benzyl-3-*O*,4-*O*-isopropylidene-D-erythose (**35**) was made by the hydrolysis of the thiazole **34**, formed from the homologation of **33** by means of 2-(trimethylsilyl)thiazole (ThTMS) (Scheme 8).[52] This method is particularly attractive in that the thiazole addition is highly stereoselective (giving the *anti* isomer shown) and that it is an iterative process which has been used to make an octahydroxy compound.[53]

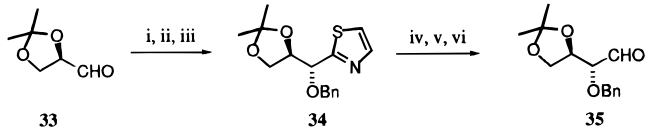
(iii) Another very common method used in the construction of sugars entails the Sharpless asymmetric epoxidation of allylic alcohols.[13a,54] This method has general utility in most of the sugar areas listed below as it can be used to introduce asymmetry into prochiral substrates, to kinetically resolve racemic substrates, and to desymmetrize *meso* substrates. Asymmetric epoxidation of the prochiral allylic alcohol **36** and treatment with benzene isocyanate gave the amidate **37** (Scheme 9).[55] Exposure to 5% aqueous hydrogen perchlorate gave the carbonate **38**, which on exhaustive deprotection and peracetylationgave L-threitol tetraacetate **39** The appeal of this

Scheme 7[a]



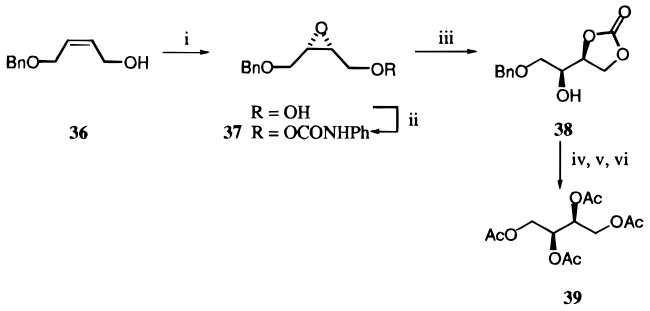
[a] Reagents: (i) O_3, EtOAc; then DMS; (ii) $NaBH_4$, MeOH; (iii) Dibal-H, DCM; (iv) O_3, EtOAc; then $NaBH_4$; (v) Ph_3PBrMe, BuLi, DCM; (vi) LAH, Et_2O; (vii) O_3, DCM; then DMS.

Scheme 8[a]



[a] Reagents: (i) ThTMS, DCM, 0 °C; (ii) TBAF, THF; (iii) NaH, BnBr, THF; (iv) MeI, MeCN, Δ; (v) $NaBH_4$, MeOH; (vi) $HgCl_2$, MeCN, H_2O.

Scheme 9[a]



[a] Reagents: (i) (−)-DET, TBHP, $Ti(O^iPr)_4$, DCM, 0 °C; (ii) PhNCO, Et_3N, DCM; (iii) 5% aqueous $HClO_4$, MeCN; (iv) NaOH, H_2O, MeOH; (v) Pd/C, MeOH, pTSA; (vi) Ac_2O.

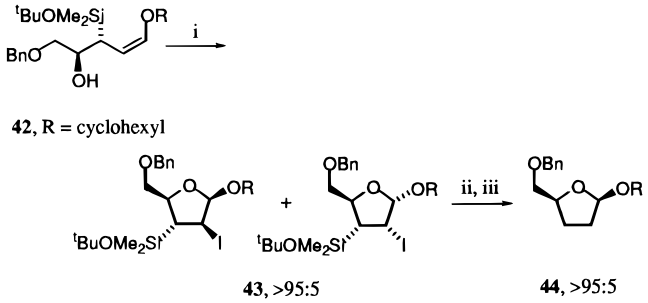
method lies in the ready syntheses of both enantiomeric series, in high enantiomeric excess using either the (−) or (+) enantiomer of diethyl tartrate (DET) in the asymmetric epoxidation.

2. Pentoses

(i) The δ,γ-unsaturated acid **30** derived from the microbial metabolite **26** (Scheme 4) has also been used by Hudlicky in the synthesis of the pentose sugar L-ribonic γ-lactone acetonide **41** (Scheme 10).[41c] Osmylation of this alkene selectively gave diol **40**, which spontaneously cyclizes to the L-ribonic γ-lactone acetonide **41**.

(ii) The conceptually very different method of Lipshutz originates with the use of an acyclic precursor and leads to dideoxyriboses.[56] Cyclization in a 5-*endo-trig* manner of the enolether **42** in the presence of potassium hydride and iodine gave the tetrahydrofuran **43** in over 90% de (Scheme 11). Dehalogenation followed by desilylation gave the 3,4-dideoxyribose **44**.

Scheme 11[a]



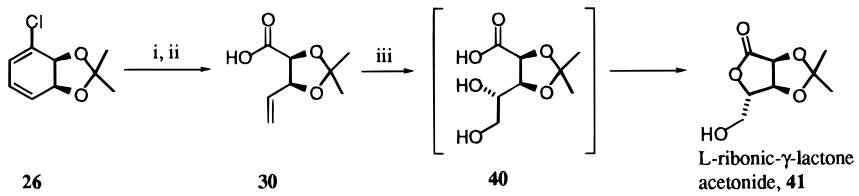
[a] Reagents: (i) KH, I_2, Et_2O, −78 °C; (ii) Bu_3SnH; (iii) CsF, TBAF, DMF.

(iii) Wong has also made use of acyclic methodology in his utilization of aldolase chemistry in the synthesis of many natural and unnatural sugars and derivatives in the pentose and hexose domains.[25−30] As mentioned earlier this particular area has been recently reviewed.[30]

2-Deoxyribose-5-phosphate aldolase (DERA) is unusual in that it is the only aldolase that accepts two aldehydes as the aldol substrates, the natural reaction being between acetaldehyde (the nucleophile) and D-glyceraldehyde-3-phosphate (the electrophile where R = OPO_3^{2-}, Scheme 12). This methodology has been especially useful for the synthesis of 2-deoxy-5-deoxy-5-substituted-furanoses **25**.[32]

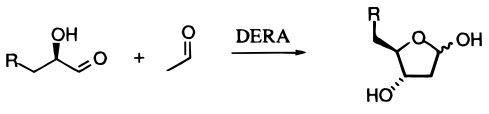
Unlike fructose-1,6-diphosphate aldolase (FDP aldolase) which can only tolerate 1,3-dihydroxyacetone phosphate (DHAP) as the nucleophilic donor (*vide infra*), DERA can tolerate changes in both donor and

Scheme 10[a]



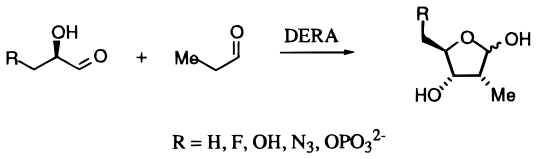
[a] Reagents: (i) O_3, EtOAc; then DMS; (ii) Ph_3PBrMe, BuLi, DCM; (iii) OsO_4, acetone, H_2O, 25 °C.

Scheme 12



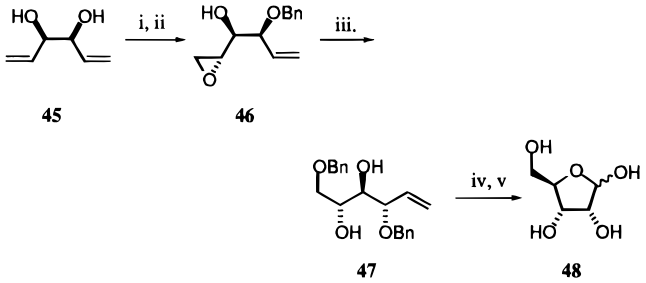
acceptor substrate such as in the propionaldehyde case shown in Scheme 13.

Scheme 13



(iv) The Sharpless asymmetric epoxidation has been used extensively in the synthesis of pentose sugars. The example in Scheme 14 exemplifies the method's utility in resolving a racemic substrate. Following monobenzylation of the diol **45**, Sharpless asymmetric epoxidation conditions give a kinetic resolution to yield the epoxide **46** (Scheme 14).[57] After epoxide opening with titanium tetrabenzoxide the alkene **47** is oxidatively cleaved and the protecting groups removed by hydrogenation to give the pentose sugar D-ribose **48**.

Scheme 14[a]



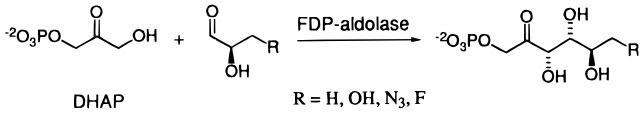
[a] Reagents: (i) BaO, $Ba(OH)_2$, DMF, BnBr; (ii) (−)-DET, TBHP; (iii) $Ti(OBn)_4$; (iv) O_3; (v) H_2, Pd/C.

3. Hexoses

(i) The biochemically derived chlorocyclohexadiene-*cis*-diol acetonide **26** has again been successfully used in the synthesis of a hexose sugar, D-mannono-γ-lactone **49**.[41d] Chemo- and regioselective *cis* hydroxylation of the most electron rich alkene gives diol **50** (Scheme 15). Upon ozonolysis, 2,3-isopropylidenyl-D-mannoso-δ-lactone acetonide **51** forms which rapidly isomerizes to the γ-lactone **52**. Acid-catalyzed deprotection of the acetonide gave D-mannono-γ-lactone **49**. This method has recently been applied to the syntheses of fully and partially per- and semideuterated mannoses **53** starting from perdeuterobromobenzene.[41e]

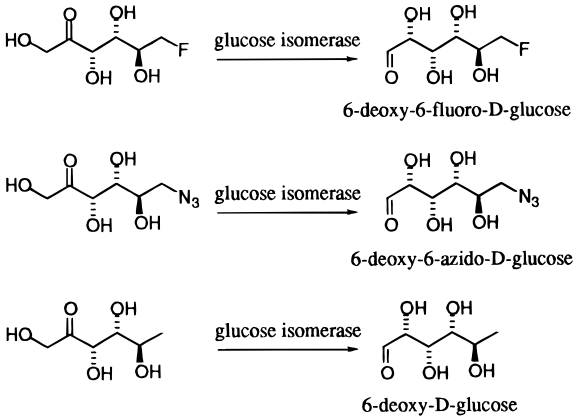
(ii) Most prominent in the field of synthesis of hexose sugars using aldolase chemistry have been Wong, Whitesides,[25−30] and Effenberger.[58] Fructose-1,6-diphosphate aldolase (FDP aldolase) has very broad aldehyde acceptor substrate tolerance but is highly donor-specific for dihydroxyacetone bisphosphate (DHAP).[29] Several ketose sugar derivatives such as the deoxy, fluoro, and azido sugars have been made (Scheme 16).[59,60]

Scheme 16



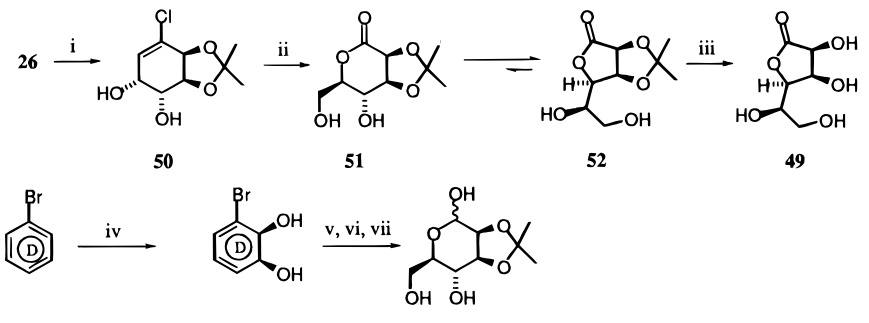
The dephosphorylated products of these FDP aldolase reactions have been used in a further enzymatic reaction where glucose isomerase (or glucose-6-phosphate isomerase) effects the isomerization of the ketose to the aldose sugar (Scheme 17).[60a, 61]

Scheme 17



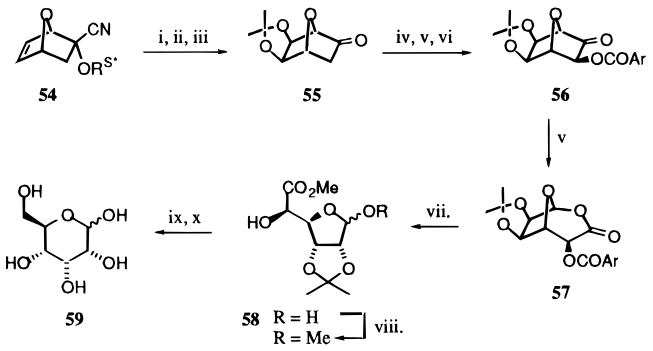
(iii) Methodology based on 7-oxabicyclo[2.2.1]hept-5-en-2-one derivatives has been developed for the synthesis of hexoaldose sugars by Vogel.[9] The 7-oxabicyclo[2.2.1]hept-5-ene derivative **54** made by the Diels−Alder reaction of furan and 1-(cyanovinyl)-

Scheme 15[a]



[a] Reagents: (i) $KMnO_4$, $MgSO_4$; (ii) O_3, $NaHCO_3$, MeOH; then H_2, Pd/C; (iii) TFA, H_2O; (iv) *P. pudita* 39D; (v) DMP, *p*-TsOH; (vi) O_3, MeOH; then $NaBH_4$ or $NaBD_4$; (vii) HCl/THF.

Scheme 18[a]



[a] Reagents: (i) OsO_4, NMO, BuOH, H_2O; (ii) DMP, $TsOH \cdot H_2O$; (iii) MeONa, MeOH; (iv) TBSOTf, Et_3N, DMF; (v) *m*CPBA, THF; (vi) 200 °C; (vii) MeOH, K_2CO_3; (viii) MeOH, CSA; (ix) LAH, THF; (x) 2% H_2SO_4.

(1*S* ′)-camphamate[62] is readily converted to the tricyclic ketone **55** by alkene osmylation, acetonide protection of the resultant diol, and sodium methoxide cleavage of the camphamate ester (Scheme 18). Treatment of the *tert*-butyldimethylsilyl enol ether of ketone **55** with *m*CPBA followed by heating at 200 °C gave the aryl ester **56**,[63] which upon Baeyer−Villiger oxidation gave lactone **57** in a highly selective fashion. Methanolysis in the presence of catalytic potassium carbonate isomerizes the lactone to the furanoside **58**. Acidic methanolysis, LAH reduction of the esters, and treatment with hydrochloric acid gave D-allose **59**.

Bromination of the *tert*-butyldimethylsilyl enol ether of ketone **55** gave a bromoketone which on further elaboration yields L-talose.[63b] The antipode of the 7-oxabicyclo[2.2.1]hept-5-ene derivative **54** is available from the Diels−Alder reaction of furan and 1-(cyanovinyl)-(1*R* ′)-camphamate and has been used to synthesize L-allose and D-talose. This methodology has also found use in the synthesis of aza sugars, amino sugars, and conduritols (*vide infra*).

(iv) Danishefsky adapted the hetero Diels−Alder reactions for the synthesis of sugars.[64] The key Diels−Alder reaction between the diene **60** and (benzyloxy)acetaldehyde used in the synthesis of *N*-acetylneuramic acid is shown in Scheme 19. This reaction catalyzed by boron trifluoride etherate at low temperature proceeded in good yield with 5:1 diastereoselectivity giving the *cis* adduct **61** as the major product. Luche-type reduction of the enone **61** followed by methanolysis and silylether formation gave the pyranoside **62**. Debenzylation, primary oxidation, and olefination gave the enone **63**, which was stereoselectively *cis* hydroxylated and the ester reduced. Conversion to the tetrabenzoate and ruthenium tetraoxide-mediated fragmentation of the furan followed by diazomethane treatment gave the methyl ester **64**. Desilylation of **64** with concomitant benzoyl migration gave the desired alcohol **65**. Mesylation of the free alcohol, displacement with azide, hydrogenolysis, and acetylation gave the methyl ester of (±)-neuraminic acid tetrabenzoate **66**.

III. Synthesis of Cyclitols

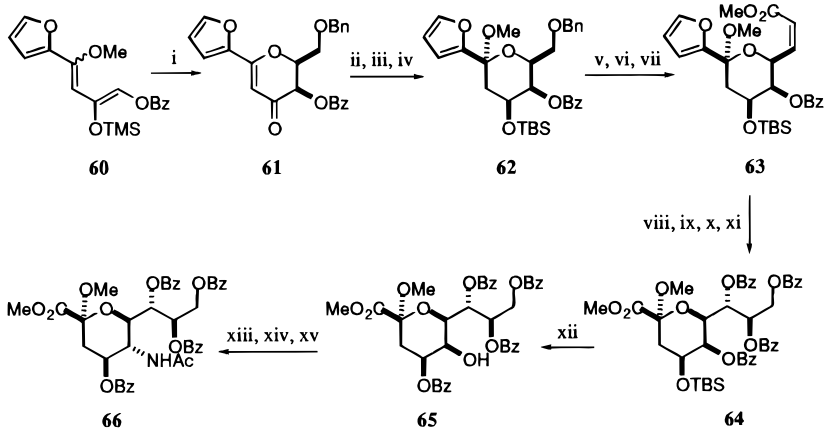
1. Inositols

The inositols and their phosphates constitute an extremely important class of compounds whose biological activities have been extensively reviewed.[65,80a] Of the nine inositol stereoisomers several are commercially available, and there are many reported syntheses in the literature. A great number of the documented syntheses rely heavily on long protection deprotection techniques starting from *myo*-inositol[65e,f] or the Ferrier reaction of sugar derivatives.[65e,f] In this section attention will be given only to those syntheses that arise from non-inositol or non-carbohydrate sources.

(i) As with the carbohydrates, the cyclohexadienediols of type **24** (Scheme 4) derived from aromatic precursors by microbial oxidation have been extensively used in the synthesis of inositols. That every carbon atom in these molecules is oxygenated or unsaturated makes them very attractive as inositol precursors, and to date most of the nine inositols have been synthesized from these metabolites.[12]

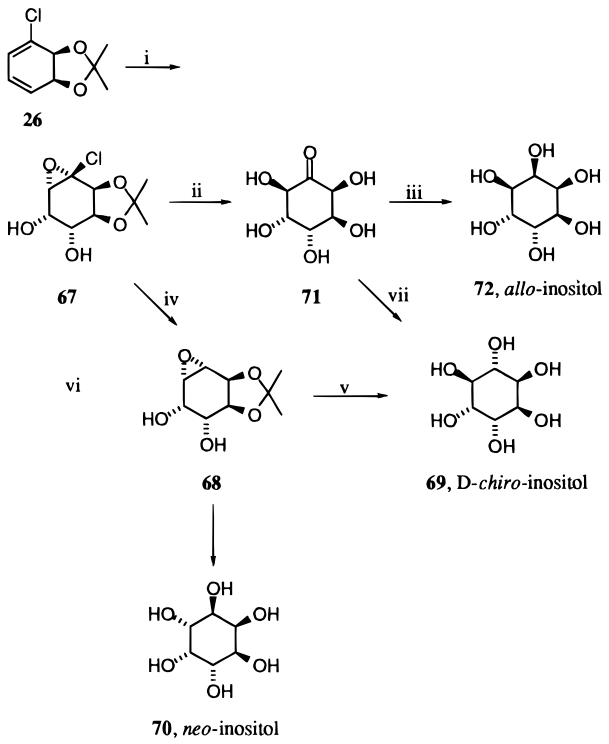
Three of the more rare or commercially unavailable inositols, D-*chiro*-, *neo*-, and *allo*-inositols, have been made from a common epoxide intermediate **67**

Scheme 19[a]



[a] Reagents: (i) benzyloxyacetaldehyde, $BF_3 \cdot Et_2O$, −78 °C, PhMe; (ii) $NaBH_4$, $CeCl_3$, EtOH, −78 °C; (iii) CSA, MeOH; (iv) TBSCl, imid, DCM; (v) H_2, $Pd(OH)_2$/C, EtOAc, MeOH; (vi) $CrO_3 \cdot Py$; (vii) $(CF_3CH_2O)_2P(O)CH_2CO_2Me$; (viii) OsO_4, py; (ix) $LiEt_3BH$, THF; (x) BzCl, DCM, DMAP; (xi) (a) RuO_2, $NaIO_4$, $NaHCO_3$, H_2O; (b) CH_2N_2; (xii) HF; (xiii) MsCl, DMAP, NaN_3, DMF; (xiv) H_2, $Pd(OH)_2$/C, EtOAc, MeOH; (xv) Ac_2O, py, DMAP.

Scheme 20[a]



[a] Reagents: (i) $KMnO_4$, $MgSO_4$, H_2O, acetone; (ii) Al_2O_3, H_2O, 80 °C; (iii) H_2, Ni(Ra), MeOH; (iv) TTMS, AIBN, PhMe, 110 °C; (v) NaOBz, H_2O, 100 °C; (vi) H_2O, 100 °C, 30% plus 60% **69**; (vii) $NaBH(OAc)_3$.

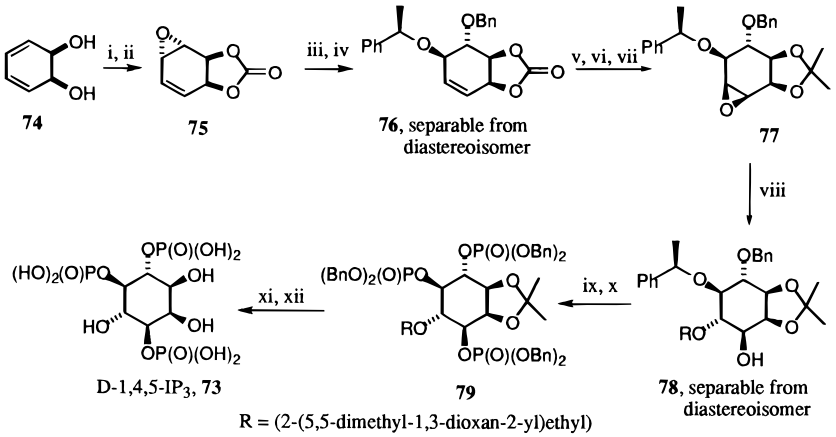
derived from the novel potassium permanganate oxidation of chlorocyclohexadiene-*cis*-diol acetonide **26** (Scheme 20).[41d,45a,b] Treatment of diene **26** with potassium permanganate gave the chloro epoxide **67** in 80% yield. Dehalogenation with tris(trimethylsilyl)silane and AIBN in toluene at reflux yielded epoxide **68**, whose base-catalyzed hydrolysis with concomitant acetonide deprotection when sodium benzoate in boiling water was used gave D-*chiro*-inositol **69** in excellent yield. *neo*-Inositol **70** is readily made from epoxide **68** by acid-catalyzed hydrolysis. In this reaction the major product is in fact D-*chiro*-inositol **69** (60%), but fortunately the *neo*-inositol **70** (30%) is readily isolated with one crystallization. Basic hydrolysis of the chloro epoxide **68** gave inososе **71** which when hydrogenated over Raney nickel yields *allo*-inositol in excellent yield. The inososе **71** has also been converted to D-*chiro*-inositol **69** by the chelation-controlled reduction with sodium triacetoxyborohydride.

(ii) Another ambitious inositol synthesis using the microbial metabolites was that of D-*myo*-inositol-1,4,5-triphosphate **73** from the simplest metabolite, cyclohexa-1,3-diene-5,6-diol **74** (Scheme 21).[47] The *meso* diol **74** was protected as a carbonate and epoxidized to give the racemic epoxide **75**, which was then opened with (*R*)-α-methylbenzyl alcohol to give the separable 1:1 diastereomeric mixture of homochiral alcohols **76** and diastereoisomer (not shown). The required alcohol **76** was benzylated and the carbonate cleaved to reveal the free diol. Stereoselective hydroxyl-group-directed *m*CPBA oxidation and diol reprotection gave the epoxide **77**, which was opened with alcohol to give the alcohol **78** and a minor diastereoisomer (not shown). Hydrogenation of the both benzyl ethers of **78** and triphosphorylation gave the triphosphate **79**. Hydrogenation revealing the free phosphoric acids and TFA cleavage of the remaining protecting groups gave D-IP_3 **73**.

Although there is a formal resolution, which doubles as protection, during this synthesis the strategy of it is such that it allows the production of analogs by opening epoxide **77** with different nucleophiles such as hydride, fluoride, and methyl cuprate.

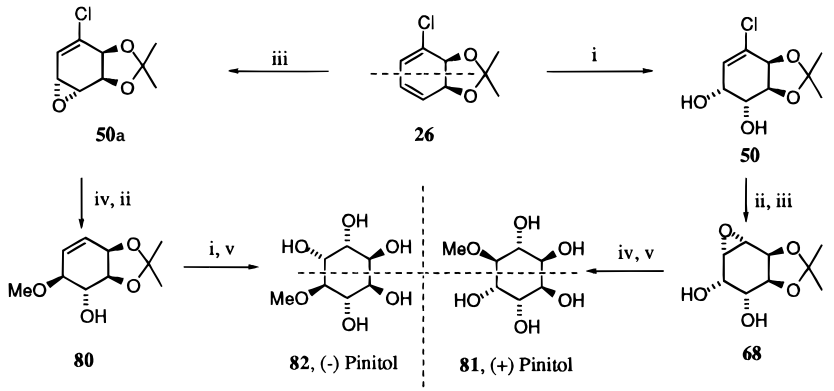
(iii) One of the most desirable features of using the non-*meso* cyclohexadienediols is the ability to make many targets in either enantiomeric form from the same common starting material. Such an example is the synthesis of the inositol ether, pinitol. The first synthesis of (±)-pinitol using arene-derived dienediols appeared in 1987[66a] and was subsequently adapted to produce both the (+) and (−) forms.[66b] This was the first such synthesis[66] to use a cyclohexadienediol as starting material. Although the preparation was concise, a resolution was required for the homochiral syntheses[47,66] of enantiomerically pure pinitols. In 1990 a enantiodivergent synthesis of both pinitol enantiomers was completed that was highly concise and required no resolution step (Scheme 22).[45c−e] The diene **26** was converted into epoxide **68** in several steps. The epoxide was then regioselectively opened

Scheme 21[a]



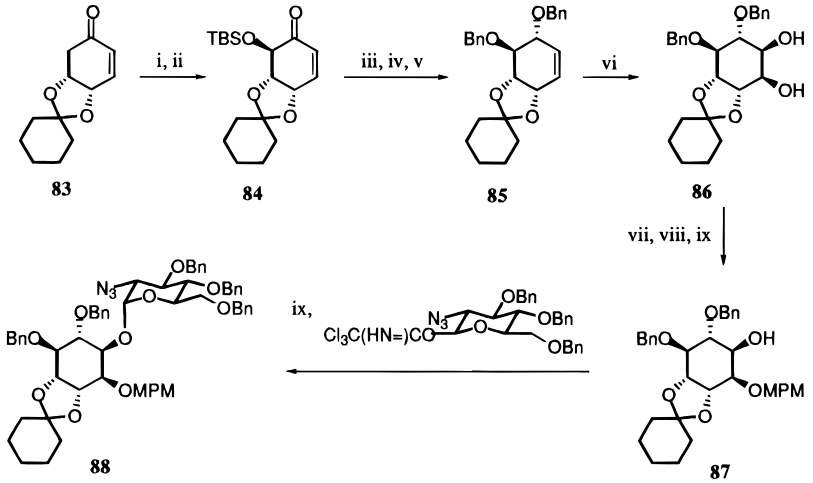
[a] Reagents: (i) $(MeO)_2CO$, MeONa; (ii) *m*CPBA, DCM; (iii) (*R*)-(+)-*sec*-phenethyl alcohol, $HBF_4{\cdot}OEt_2$, cat; (iv) BnBr, Ag_2O, DMF, 72 h; (v) Et_3N, MeOH, H_2O, 72 h; (vi) *m*CPBA, DCM; (vii) DMP, CSA, DCM; (viii) NaH, 5,5-dimethyl-1,3-dioxane-2-ethanol, TMEDA, 110 °C; (ix) H_2, Pd/C, EtOH; (x) LDA, THF, tetrabenzylpyrophosphate, −30 °C to room temperature; (xi) H_2, Pd/C, EtOH; (xii) 80% aqueous TFA.

Scheme 22[a]



[a] Reagents: (i) OsO_4, NMO, H_2O, Me_2CO; (ii) LAH, THF; (iii) *m*CPBA, DCM; (iv) MeOH, Al_2O_3; (v) HCl, H_2O, Me_2CO.

Scheme 23[a]



[a] Reagents: (i) TBSOTf, Et_3N, DCM, 0 °C; (ii) *m*CPBA, hexane, −16 °C; (iii) $NaBH_4$, $CeCl_3$, MeOH, 0 °C; (iv) TBAF, THF, 0 °C; (v) NaH, BnBr, DMF; (vi) OsO_4, NMO, Me_2CO/H_2O (9:1); (vii) Bu_2SnO, $PhCH_3$; BzCl, 4A sieves, PhH; (viii) *p*-$(NO_2)(C_6H_4)CH_2OC(NH)CCl_3$, Ph_3CBF_4, Et_2O, 40 °C; (ix) K_2CO_3, MeOH.

with methanol in the presence of alumina and then deprotected with acid to give (+)-pinitol **81**.

If one simply changes the order of synthetic steps and hence functionalizes the opposite side of the proenantiotopic plane of the diene, (−)-pinitol **82** can be readily made. A detailed analysis of the commutative principles of enantiodivergent synthesis has been published.[12a,45f]

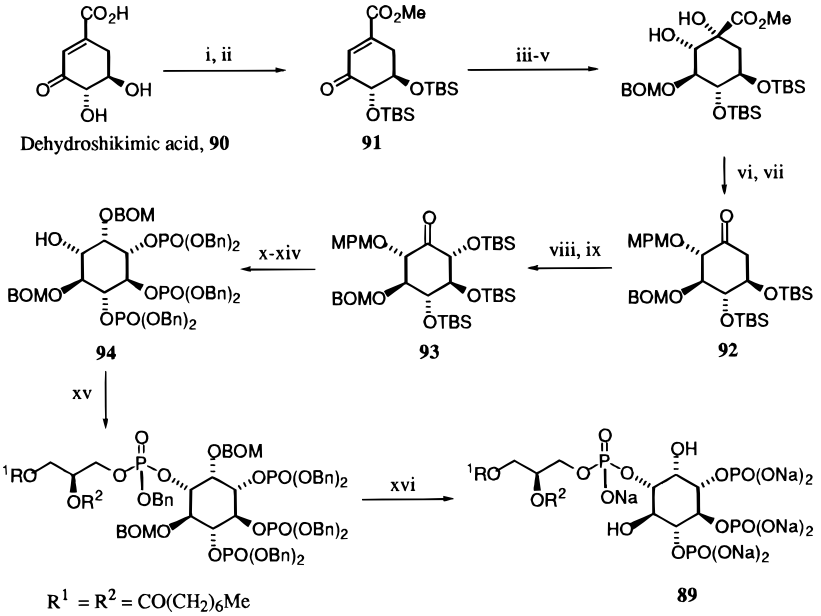
More recently *muco*-, *allo*-, *epi*-, and (±)-*chiro*-inositols have also been made from the benzene-derived diol **74**, the key step being the Diels−Alder reaction of the diene with singlet oxygen.[67] The use of the dienes **26** and **74** in the stereodivergent syntheses of D-*chiro*-, *allo*-, *neo*-, *muco*-, and *epi*-inositols, (+)- and (−)-pinitol, and IP_3 respectively exemplifies the suitability and importance of microbial oxidation in inositol synthesis.

(iv) Falck has used quinic acid and other shikimic metabolites in his recent syntheses of important intracellular messengers.[68,69] Quinic acid was transformed to the known enone **83**.[70] The *tert*-butyldimethylsilyl enol ether of ketone **83** was oxidized to give the silyl ether **84** (Scheme 23).[68] Reduction of the ketone followed by desilylation and benzylation gave the dibenzyl ether **85**. Selective *cis*-hydroxylation of the alkene *anti* to the cyclohexylidene gave the diol **86**. Protecting group manipulation of diol **86** gave the required protected inositol **87** which was then successfully coupled to 3-deoxy-3-azidoglucosyl trichloroacetimidate to give protected 6-*O*-(2-amino-2-deoxy-α-D-glucopyranosyl)-D-*chiro*-inositol (**88**).

In a related synthesis the biologically important phosphatidyl-D-*myo*-inositol 3,4,5-triphosphate **89** was synthesized from dehydroshikimic acid **90** (Scheme 24).[69] Both quinic acid and dehydroshikimic acid are readily available from glucose from genetically engineered *E.coli*'s shikimate pathway[20] and both have had increasing popularity as homochiral starting materials.[72,73,74,75a,76] Dehydroshikimic acid was converted to the known ester **91**[71] which was selectively reduced, protected and *cis*-hydroxylated. Protection of the secondary hydroxyl group followed by oxidative cleavage gave ketone **92**, the *tert*-butyldimethylsilyl ether of which was oxidized to give ketone **93**. Reduction of this substrate and subsequent protection, phosphorylation and removal of the paramethoxybenzyl ether gave the alcohol **94**. Attachment of the glycidic side chain and exhaustive hydrogenation in the presence of sodium carbonate gave the target compound **89**.

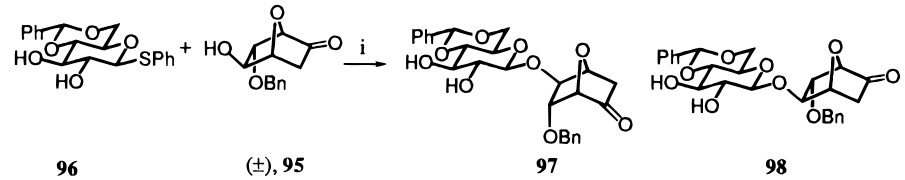
(vi) The oxanorbornene methodology developed by Vogel has been used in a stereodivergent manner by Pradilla and Plumet to synthesize two inositol glucose glycoconjugates.[77] Glycosidation of the bicyclic alcohol **95** with phenyl 6-*O*,4-*O*-benzylidene-1-thio-β-D-glucopyranoside (**96**) gave two diastereoisomers

Scheme 24[a]



[a] Reagents: (i) CH_2N_2, −40 °C, Et_2O; (ii) TBSCl, imidazole, DMF; (iii) LiAlH(O^tBu)3, −78 °C; (iv) BOM-Cl, $^iPr_2NEt$; (v) OsO_4, NMO; (vi) MPM-OC(NH)CCl_3, Ph_3CBF_4; (vii) $NaBH_4$, EtOH; $NaIO_4$, THF, H_2O; (viii) TBSOTf, Et_3N; (ix) dimethyldioxirane, CSA; (x) $NaBH_4$; (xi) BOMCl, $^iPr_2NEt$; (xii) TBAF; (xiii) $^iPr_2NP(OBn)_2$, 1*H*-tetrazole; *m*CPBA; (xiv) DDQ, DCM, H_2O; (xv) $^iPr_2NP$-(OBn)$OCH_2CH(OCO(CH_2)_6Me)CH_2OCO(CH_2)_6Me$, 1*H*-tetrazole; *m*PBCA; (xvi) H_2 50 psi, Pd/C; BuOH/H_2O, $NaHCO_3$.

Scheme 25[a]

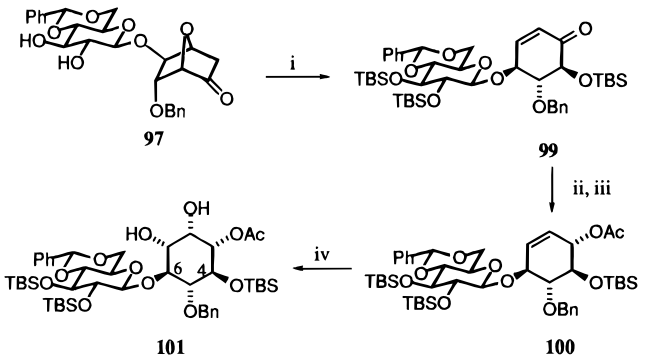


[a] Reagents: (i) PhSeOTf.

97 and **98**, which were readily separable by tituration with chloroform (Scheme 25).[78]

tert-Butyldimethylsilyl hydroxyl group protection and *tert*-butyldimethylsilyltriflate-mediated oxabridge fragmentation of diastereoisomer **97** gave enone **99**, which was reduced with lithium aluminum tri-*tert*-butoxyhydride (Scheme 26).[77] Highly selective (91:9) *cis* hydroxylation of the allylic acetate **100** with osmium tetroxide proceeded cleanly to give the desired 1-glucosyl-*myo*-6-inositol **101**.

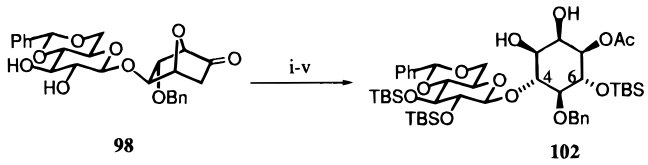
Scheme 26[a]



[a] Reagents: (i) TBSOTf, Et_3N, −23 °C, PhMe; (ii) LiAl(^tOBu)H, THF, −78 °C; (iii) Ac_2O, Et_3N, DMAP, DCM; (iv) OsO_4, Me_3NO, Me_2CO, H_2O.

Synthesis of 1-glucosyl-*myo*-4-inositol (**102**) was achieved by a similar synthetic sequence of reactions on the other glucosyloxanorbonene diastereoisomer **98** (Scheme 27).[78]

Scheme 27[a]



[a] Reagents: (i) TBSOTf, Et_3N, −23 °C, PhMe, DMF; (ii) TBSOTf, Et_3N, −23 °C, PhH; (iii) LiAl(^tOBu)H, THF, −78 °C; (iv) Ac_2O, Et_3N, DMAP, DCM; (v) OsO_4, Me_3NO, Me_2CO, H_2O.

2. Conduritols

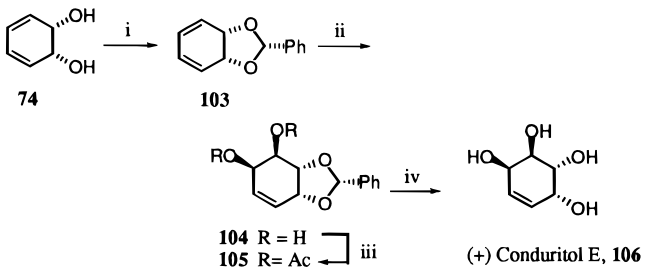
Conduritols and their derivatives act as glycosidase inhibitors,[79] and therefore considerable effort has been focused on their syntheses.[80] Many of the syntheses of inositols listed in the previous section originate from conduritol intermediates and will not be repeated here.

(i) The dienediol microbial metabolites **24** (Scheme 4) have played a major role in the synthesis of optically active conduritols.[81] As in the synthesis of inositols, their applicability lies in the absence of any need to form any new carbon−carbon bonds, in the homochiral nature of the starting diol, and the

unsaturation around the ring allows selective polyhydroxylation. There are many conduritol syntheses using these metabolites,[80,81] all of which are too numerous to elaborate on but in general follow many of the principles outlined in the pinitol syntheses, such as facially selective *cis* hydroxylation or epoxidation and regioselective epoxide opening.

The *meso*-benzene-derived dienediol **74** has been desymmetrized by means of Sharpless' asymmetric *cis* hydroxylation technology to successfully make (+)-conduritol E, **106** (Scheme 28).[82] The initial asymmetric hydroxylation of **103** gave the diol **104** with 85% enantiomeric excess and resulted in an enantiomerically pure compound by a single recrystallization of the diacetate **105**.

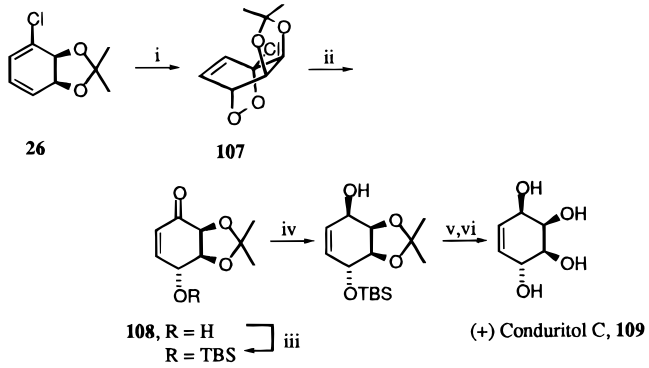
Scheme 28[a]



[a] Reagents: (i) $PhCH(OMe)_2$, TsOH; (ii) AD-mix-β; (iii) Ac_2O, Et_3N, DMAP, DCM; (iv) acidic resin.

Other syntheses have utilized the Diels−Alder reaction between diene and singlet oxygen such as that of (+)-conduritol C, **109** (Scheme 29).[45e,f] The product of the Diels−Alder reaction between diene **26** and singlet oxygen was the bicyclic *endo*-peroxide **107**, which when treated with thiourea gave the hydroxy enone **108**. *tert*-Butyldimethylsilyl hydroxyl protection, L-Selectride (Aldrich) reduction, and exhaustive acidic deprotection gave conduritol C, **109**, in good overall yield.

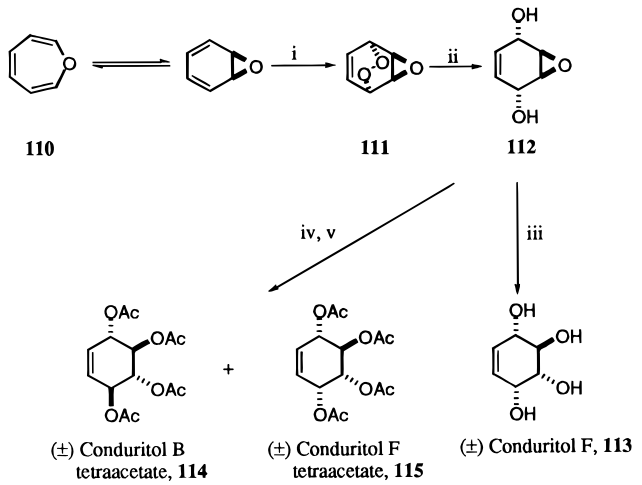
Scheme 29[a]



[a] Reagents. (i) O_2, Tpp, $CHCl_3$, *hν*; (ii) Thiourea, MeOH; (iii) TBSCl, DMF; (iv) L-Selectride, THF; (v) HCl, H_2O; (vi) Pd/C, H_2, MeOH.

(ii) Another novel Diels−Alder approach to conduritols was the singlet-oxygen addition to oxacylcooctatriene **110** selectively giving the endoperoxide **111** (Scheme 30).[83] Acidic treatment of the reduction product **112** gave (±)-conduritol F, **113**, whereas acetylation and acid treatment gave (±)-conduritol F tetraacetate, **114**, and (±)-conduritol B tetraacetate, **115**.

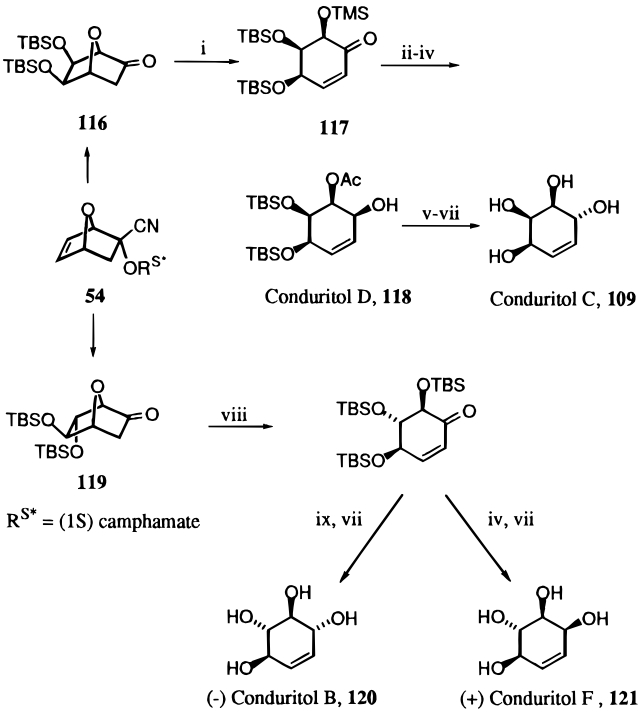
Scheme 30[a]



[a] Reagents: (i) O_2, Tpp, $CHCl_3$, *hν*; (ii) thiourea, MeOH; (iii) H_2SO_4, H_2O; (iv) Ac_2O, Py, DMAP; (v) H_2SO_4, Ac_2O.

(iii) A Diels−Alder approach to conduritols has been reported by Vogel again using the furan-derived norbornene derivatives. Trimethylsilyl triflate-promoted opening of the cyclic ether **116** gave the enone **117** (Scheme 31).[84a] Selective hydrolysis of the trimethylsilyl group, reprotection as an acetate and Luche-type reduction gave the protected conduritol D **118**. Inversion of the free hydroxyl group and silyl ether hydrolysis led to the formation of (−)-conduritol C, **109**. Similar reactions were carried out on the *trans*-diacetate **119** to give (−)-conduritol B, **120**, and (+)-conduritol F, **121**.[84b]

Scheme 31[a]



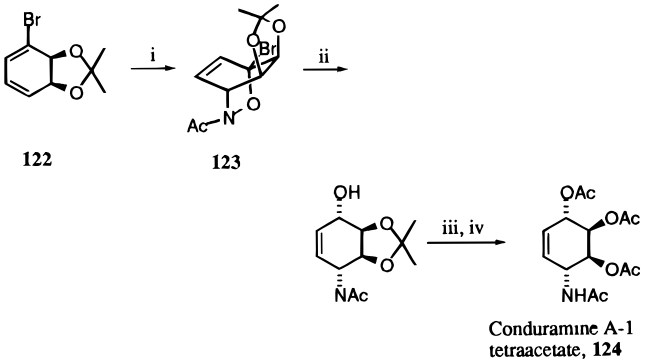
[a] Reagents: (i) TMS−OTf, Et_3N; (ii) HF, MeOH, H_2O; (iii) Ac_2O, py, DMAP; (iv) $NaBH_4$, $CeCl_3$, MeOH; (v) DEAD, PPh_3, BzOH, THF; (vi) MeOH, KOH; (vii) HF, MeCN; (viii) TBSOTf, Et_3N; (ix) Dibal-H, THF, −78 °C.

3. Aminoconduritols

(i) As with the purely hydroxyl group substituted conduritols and inositols, amino-substituted cyclitols

have recently been prepared from microbially derived cyclohexadiene-*cis*-diols. A direct way of incorporating nitrogen into the molecule is by the Diels−Alder reaction of a nitrosyl compound derived *in situ* from the corresponding hydroxamic acid with the bromo diene **122** (Scheme 32).[43b] The oxazine **123,** formed with total regioselectivity and facial selectivity, was treated with aluminum amalgam to give, after acetonide removal and peracetylation, conduramine A-1 tetraacetate, **124**.

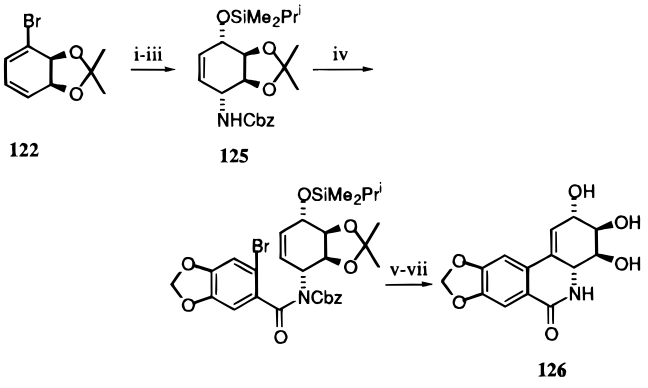
Scheme 32[a]



[a] Reagents: (i) AcNHOH, Bu_4NIO_4; (ii) Al(Hg); (iii) AcOH, THF, H_2O; (iv) Ac_2O, py, DMAP.

This method has also been used successfully in the synthesis of (+)-lycoricidine, **126** (Scheme 33).[45j] The benzyl carbamate **125** was obtained from bromobenzene cyclohexadiene-*cis*-diol **122** by a set of reactions similar to those described in Scheme 32. Lactamization gave an intermediate that was subjected to an intramolecular Heck reaction. Functional group deprotection with trifluroacetic acid furnished (+)-lycoricidine **126**.

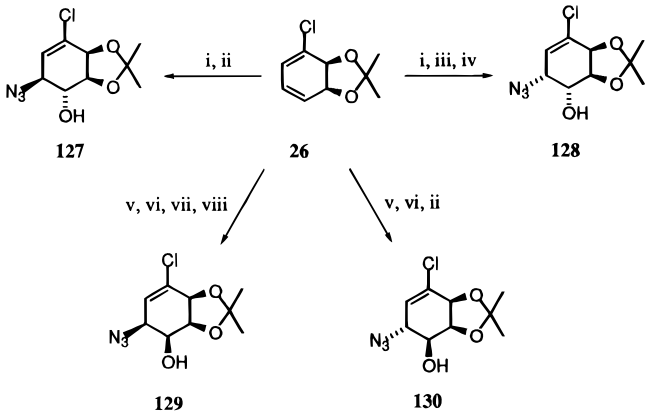
Scheme 33[a]



[a] Reagents: (i) BnOC(O)NHOH, Bu_4IO_4, DCM; (ii) Al(Hg), THF; (iii) $^iPrMe_2SiCl$, imidazole, DCM; (iv) BuLi, THF, −78 °C then 2-bromopiperonyloyl chloride; (v) $Pd(OAc)_2$, Tl(OAc), DIPHOS, anisole; (vi) Pd/C, cyclohexene, EtOH; (vii) TFA.

Nitrogenous functionality has been added to the dienediol framework in other ways. The haloconduramine precursors **127**,[43b] **128**,[45g] **129**,[45h] and **130**[45i] have all been synthesized from the chloro *cis*-diol acetonide **26** by the opening of derived epoxides or displacement of halide from halohydrins with azide anion (Scheme 34).

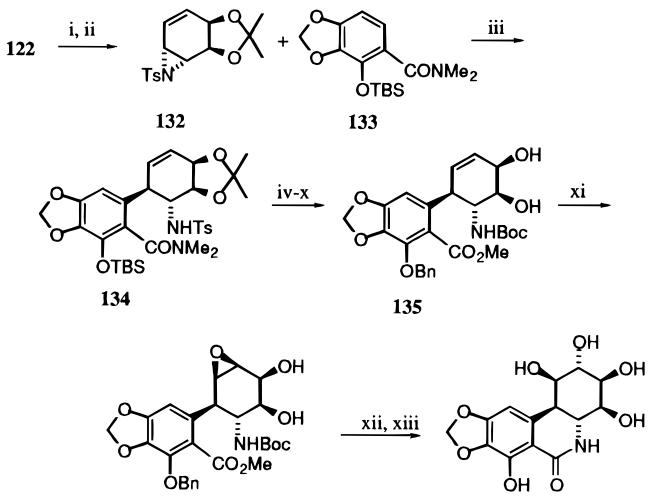
Scheme 34[a]



[a] Reagents: (i) *m*CPBA, DCM; (ii) NaN_3, NH_4Cl, DME, EtOH, H_2O, 65 °C; (iii) LiCl, EtO_2CCH_2COMe, THF, 45 °C; (iv) NaN_3, DMF; (v) NBS, DME, H_2O, O °C; (vi) NaOH, Bu_4NHSO_4, DCM, reflux; (vii) LiBr, EtO_2CCH_2COMe, THF, 35 °C; (viii) NaN_3, DMSO.

A recent syntheses of (+)-pancratistatin **131** utilized the ring opening of the aziridine **132** derived from acetonide **122** with a metalated aromatic fragment **133** to give amide **134** (Scheme 35).[85] Extensive protecting group manipulation gave the diol **135** which was converted to (+)-pancratistatin **131** by selective hydrolysis of the epoxide **136** and final protecting group hydrolysis and hydrogenation.

Scheme 35[a]

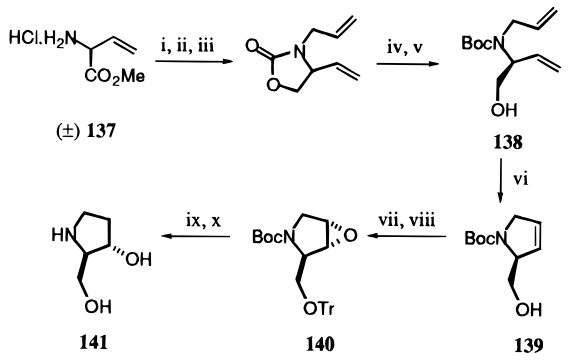


[a] Reagents: (i) PhI=NTs, $Cu(acac)_2$, MeCN; (ii) Bu_3SnH, AIBN, THF; (iii) (a) **133**, ^{s}BuLi, TMEDA, THF, −90 °C; (b) CuCN, −90 to −20 °C; (c) **132**, −78 °C to rt; (iv) (a) ^{s}BuLi, THF; (b) $(Boc)_2O$; (v) Na, anthracene, DME, −78 °C; (vi) SMEAH, morpholine, THF, −45 °C; (vii) K_2CO_3, BnBr, DMF; (viii) $NaClO_2$, KH_2PO_4, 2-methyl-2-butene, ^{t}BuOH, H_2O; (ix) CH_2N_2; (x) AcOH, THF, H_2O, 60 °C; (xi) ^{t}BuOH, $VO(acac)_2$, PhH, 60 °C; (xii) BzONa(cat.), H_2O, 100 °C; (xiii) H_2, $Pd(OH)_2$/C, EtOAc.

IV. Synthesis of Azasugars

The term azasugar has been used in the literature to describe compounds in which the endocyclic oxygen atom has been replaced with nitrogen, although in broad usage, this term is incorrect. (The authors are grateful to Professor S. Hanessian for pointing this out.) "Azahexose" would imply a nitrogen atom replacing a carbon atom; thus the term implies a molecule with endocyclic oxygen and nitrogen atoms.

Scheme 36[a]



[a] Reagents: BnOCOCl, $NaHCO_3$, H_2O, DCM; (ii) $LiBH_4$, MeOH, Et_2O; (iii) NaH, DME, allyl bromide; (iv) NaOH, H_2O, EtOH; (v) Boc_2O, Et_3N, DCM; (vi) $(Cl_2(Cy_3P)_2Ru{=}CHCH{=}CPh_2)$ 4%, PhH; (vii) Ph_3CCl, Et_3N, DCM, DMAP; (viii) *m*CPBA, Et_2O; (ix) $LiBH_4$, MeOH, diglyme, 150 °C; (x) HCl, MeOH.

The technically correct terms are "hydroxylated piperidines" for hexo- and pentopyranoses and "hydroxylated pyrrolidines" for pento- and tetrofuranoses.

Azasugars are a very important class of compounds that act as potent glycosidase inhibitors.[88] 1-Deoxynorjirimycin and some simple derivatives, for example, have a host of uses[89] ranging from a therapeutic agent in the treatment of cancer to activity against HIV-infected cells.[90]

1. Hydroxylated Pyrrolidines

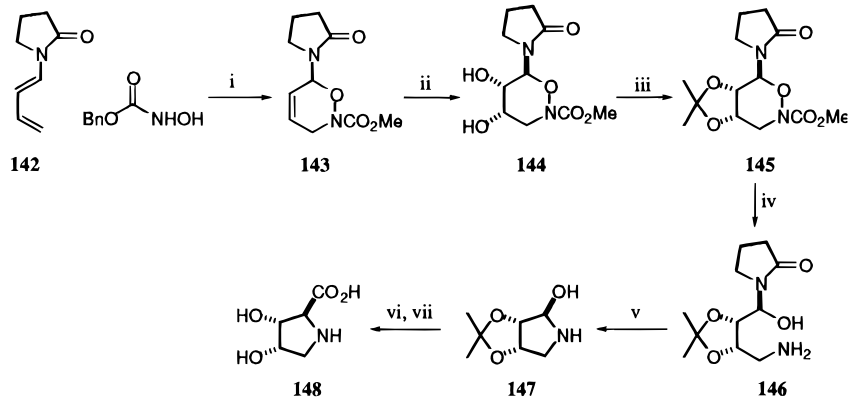
(i) A recent novel synthesis of a hydroxylated pyrrolidine involved the use of a ruthenium catalyst to bring about alkene metathesis.[86] (±)-Vinylglycine methyl ester hydrochloride **137** was converted to the bis-allyl amine **138** by conventional methods (Scheme 36). Treatment of **138** with Grubbs' catalyst $(Cl_2(Cy_3P)_2Ru{=}CHCH{=}CPh_2)$ brought about smooth metathesis that yielded the didehydropyrrolidine, **139**. Primary hydroxyl group protection and epoxidation gave epoxide **140**. Regioselective epoxide opening with lithium borohydride and protecting group removal gave the target 2-(hydroxymethyl)-3-hydroxypyrrolidine (**141**).

Use of optically active vinylglycine starting material and careful reduction of the ester functionality promises to make the synthesis above enantiospecific.

(ii) A hetero Diels−Alder approach has been used for the synthesis of racemic 4-amino-4-deoxyerythrose and dihydroxyproline derivatives.[87] Diels−Alder reaction of pyrrolidinone-substituted diene **142** with an acylnitroso compound formed by *in situ* oxidation of benzylhydroxamic acid gave adduct **143** in a highly regioselective manner (Scheme 37). Osmylation of the alkene proceeded in a totally selective fashion to give diol **144** which was protected as the acetonide **145**. Reduction of the nitrogen−oxygen bond by hydrogenolysis gave the amino alcohol **146**, which on treatment with barium hydroxide cyclized to give 4-amino-4-deoxy-2-*O*,3-*O*-isopropylideneerythrose, **147**. Treatment of **147** with hydrogen cyanide and acid hydrolysis gave the proline derivative **148**.

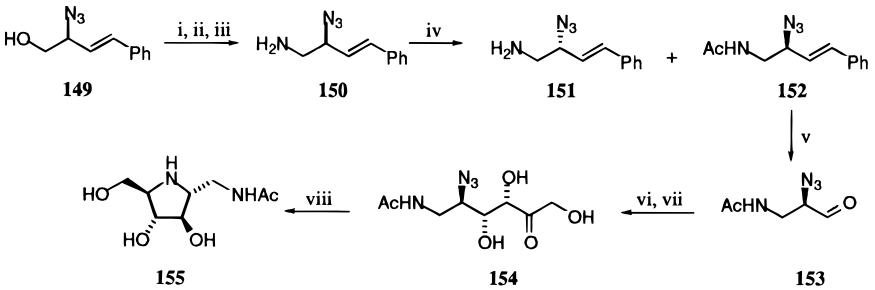
(iii) Wong has used aldolase chemistry to construct new hydroxylated pyrrolidines for the study of inhibition of *N*-acetylglucosaminyltransferases. Mesylation of the racemic alcohol **149,** displacement with iodide and hexamethylene tetramine, and hydrolysis of the resultant salt gave azido amine **150** (Scheme 38).[58b] Resolution of **150** with *Pseudomonas* lipase (Amano PS) gave the amide **152** in 80% ee, ozonolysis

Scheme 37[a]



[a] Reagents: (i) Bu_4IO_4; (ii) OsO_4, NMO; (iii) DMP, TsOH; (iv) H_2, Pd/C, MeOH; (v) $Ba(OH)_2$; (vi) HCN; (vii) 6 N HCl.

Scheme 38[a]

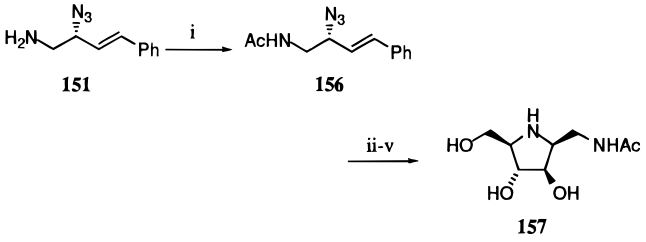


[a] Reagents: (i) MsCl, py; (ii) hexamethylenetetramine, NaI, EtOH, 4 days; (iii) HCl, EtOH; (iv) Amano PS, EtOAc; (v) O_3; (vi) DHAP, FTP aldolase; (vii) acid pase; (viii) H_2, Pd/C.

of which furnished the azido aldehyde **153**. Treatment of **153** with FTP aldolase and dihydroxyacetone monophosphate (DHAP) gave, after dephosphorylation, the keto azide **154**. Hydrogenation yielded desired azasugar **155** in good yield.

The same set of reactions was also carried out on the enantiomeric azide **156** previousy derived from amine **151** to yield the diastereomeric product **157** (Scheme 39).

Scheme 39[a]



151 156 157

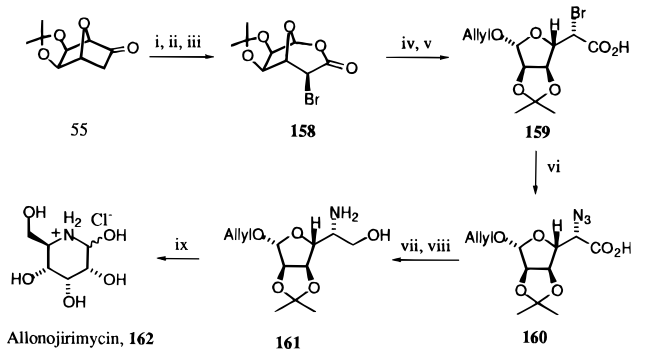
[a] Reagents: (i) Ac_2O, py; (ii) O_3; (iii) DHAP, FTP aldolase; (iv) acid pase; (v) H_2, Pd/C.

2. Hydroxylated Piperidines (alias Azasugars)

(i) Many hydroxylated piperidines have been made conveniently from the carbohydrate chiral pool, D-glucose, D-mannose, and D- and L-gulonolactone being the most notable.[7,8,91]

(ii) Again Vogel's norbornene derivatives have found use in this particular area of carbohydrate synthesis.[9,92] Opening of the bicyclic acetal and esterification of bromide **158** with allyl alcohol and mesic acid gave the allyl ester of acid **159** (Scheme 40). This was selectively hydrolyzed to give acid **159**,

Scheme 40[a]



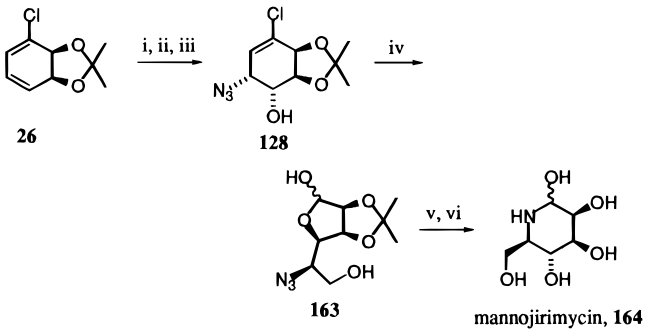
55 158 159 160 161 Allonojirimycin, 162

[a] Reagents: (i) TBS−OTf, Et_3N; (ii) Br_2, DCM, 50 °C; (iii) CF_3CO_3H, Na_2HPO_4, DCM; (iv) allyl alcohol, MsOH; (v) $Rh(PPh_3)_3Cl$, EtOH, H_2O, DBO; (vi) CsN_3; (vii) BnBr, DMF; (viii) LAH, THF, 61%; (ix) 1 N HCl.

which was treated with cesium azide resulting in the azide **160**. Stereochemistry was retained because of the neighboring group participation of the cesium carboxylate. Reduction of the benzyl ester of acid **160** to the primary alcohol **161** followed by hydrolysis gave allonojirimycin hydrochloride **162**.

(iii) The aforementioned azido alcohol **128** has also been used in azasugar synthesis[42] (Scheme 41). Ozonolysis of azide **128** with sodium borohydride

Scheme 41[a]



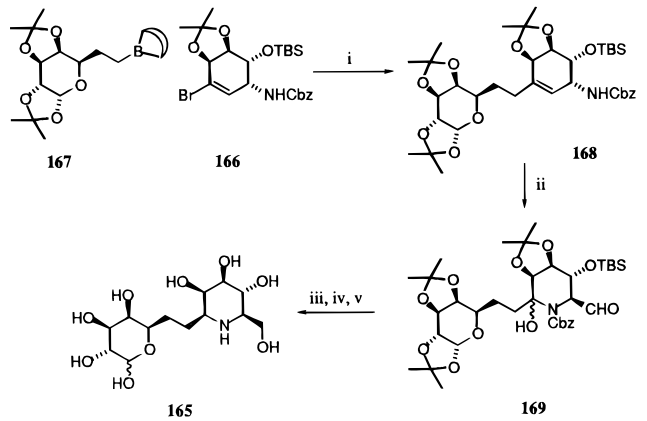
26 128 163 mannojirimycin, 164

[a] Reagents: (i) *m*CPBA, DCM; (ii) LiCl, $MeCOCH_2CO_2Me$; (iii) NaN_3, DMF; (iv) O_3, MeOH, −78 °C then $NaBH_4$; (v) PMe_3, THF, H_2O; (vi) 90% aqueous TFA.

workup gave 5-deoxy-5-azido-D-mannose 2-*O*,3-*O*-acetonide (**163**) which upon azide reduction and acidic acetonide removal yielded mannojirimycin (**164**).[45g]

Johnson has also made use of benzene- and bromobenzene-derived metabolites in his syntheses of (+)-deoxygalactonojirimycin[93] and aza-C-disaccharide **165**,[94] the latter of which is depicted in Scheme 42.

Scheme 42[a]



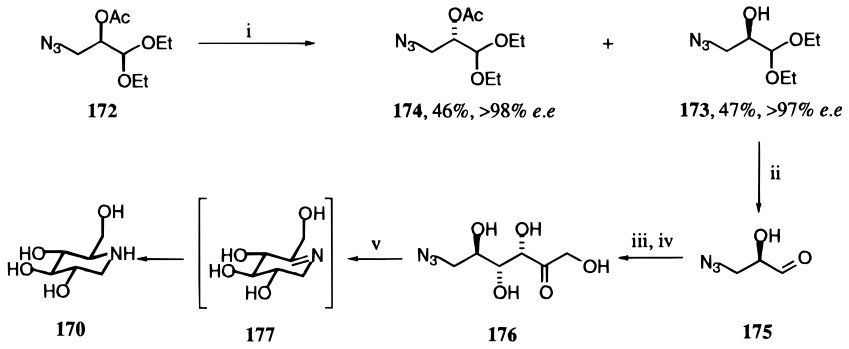
167 166 168 169 165

[a] Reagents: (i) $PdCl_2(dppf)$, DMF, K_3PO_4; (ii) O_3, MeOH, DCM, −78 °C then DMS; (iii) $NaBH_3CN$, MeOH, pH 4; (iv) H_2, Pd/C, MeOH; (v) 1 N HCl.

The known vinyl bromide **166** derived from bromobenzene[42] was coupled to the homogalactosyl borane **167** to yield the alkene **168** the ozonolysis of which gave the aminal aldehyde **169**. Reduction of the aldehyde moiety with sodium cyanoborohydride, hydrogenolysis of the aminal, and nitrogen protecting groups followed by acidic removal of the remaining protecting groups gave the desired aza-C-disaccharide **165**.

(iv) Almost simultaneously Wong[59a] and Effenberger[58] published syntheses of the azasugars deoxynorjirimycin (**170**). and deoxymannojirimycin (**171**), both involving enzymatic aldol reactions. Wong's first step was the lipase LP-80-catalyzed resolution of the azido acetate **172** to give azido tetraol **174** and azido acetate **173** both with very high enantiomeric excess. (Scheme 43). Aldol reaction of aldehyde **175** with dihydroxyacetone monophosphate (DHAP) catalyzed by recombinant bacterial fructose-1,6-diphosphate aldolase (FDP aldolase) gave, after dephospho-

Scheme 43[a]

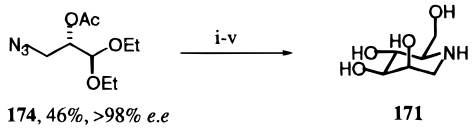


[a] Reagents: (i) LP-80, 51% conversion; (ii) 0.1 N HCl; (iii) DHAP, FDP aldolase; (iv) pase; (v) H_2, Pd/C.

rylation using a phosphatase enzyme, the azido alcohol **176**. Hydrogenation of azide **176** gave an intermediate imine **177**, which was selectively hydrogenated *in situ* to give deoxynorjirimycin **170**.

The synthesis of deoxymannojirimycin (**171**) from azido acetate **174** followed exactly the same lines (Scheme 44).

Scheme 44[a]

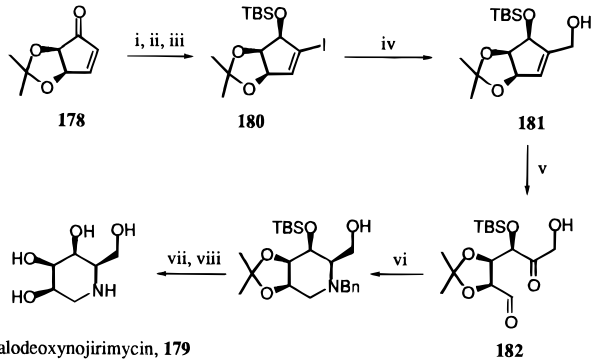


[a] Reagents: (i) MeONa, MeOH, 0 °C; (ii) 0.1 N HCl; (iii) DHAP, FDP aldolase; (iv) pase; (v) H_2, Pd/C.

Effenberger's simultaneous and essentially identical route used rabbit muscle aldolase (RAMA) for the key aldol step with racemic aldehyde **175** as acceptor, and the final reductive amination was performed over platinum instead of palladium.[58]

(v) Johnson has used the chemoenzymatically produced enone **178** in the syntheses of D-*talo*-deoxynojirimycin (**179**) and D-*manno*-deoxynojirimycin, the former of which is demonstrated in Scheme 45.[95] Conversion of the enone **178** to the vinyl iodide

Scheme 45[a]

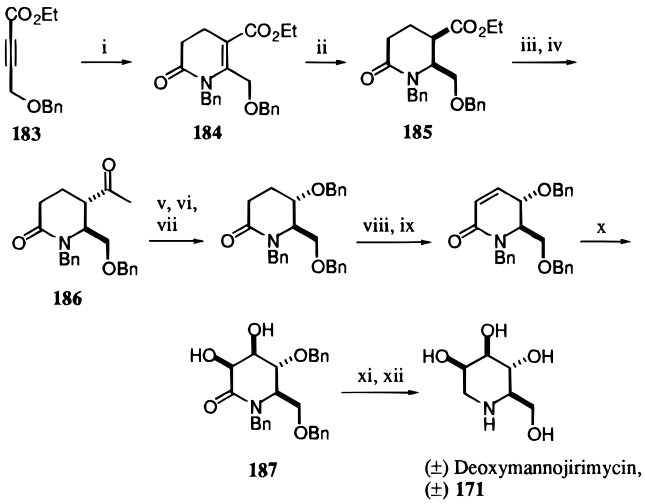


[a] Reagents: (i) I_2, Et_3N; (ii) $NaBH_4$, $CeCl_3 \cdot 7H_2O$, MeOH, −78 °C; (iii) TBSCl, Imid., DMF; (iv) CO (1 atm), Bu_3SnH, $Pd(Ph_3)_4$, THF, then $NaBH_4$, $CeCl_3 \cdot 7H_2O$, MeOH, −78 °C; (v) O_3, MeOH, −78 °C then DMS; (vi) $BnNH_3Cl$, $NaBH_3CN$, MeOH; (vii) 1 N HCl, MeOH; (viii) H_2 (2 atm), Pd/C, MeOH.

followed by Luche reduction and silyl ether formation gave vinyl iodide **180**. Treatment of **180** with tributyltin hydride in an atmosphere of carbon monoxide gave, after reduction, the primary alcohol **181**. Ozonolysis gave the dicarbonyl compound **182**, which upon reductive amination and full deprotection provided D-*talo*-deoxynorjirimycin **179**.

(vi) In Stille's synthesis of (±)-mannolactam and (±)-deoxymannojirimycin [(±)-**171**] the key step was the aza annulation of the alkyne **183** and acrylic anhydride to give the lactam **184** (Scheme 46).[96]

Scheme 46[a]



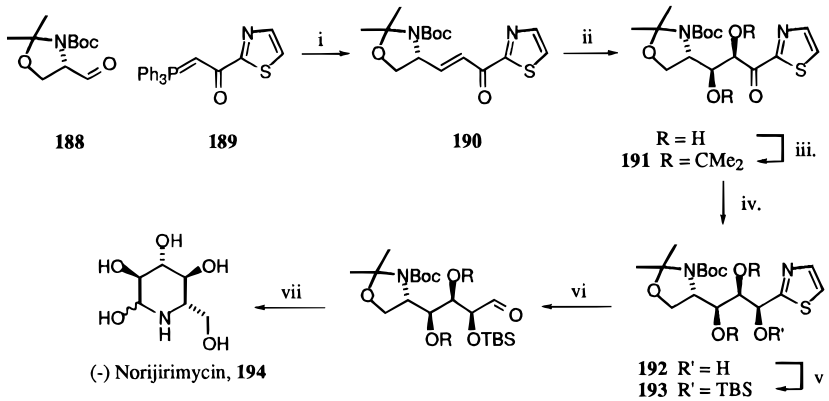
[a] Reagents: (i) (a) $BnNH_2$, THF; (b) acrylic anhydride; (ii) H_2, Pd/C, Na_2CO_3, EtOH; (iii) MeMgBr, Et_3N; (iv) DBU; (v) TFA, *m*CPBA; (vi) KOH, H_2O; (vii) BnBr, KOH; (viii) (a) LDA; (b) PhSeCl; (ix) $NaIO_4$; (x) OsO_4, NMO; (xi) LAH; (xii) H_2, Pd−C, MeOH.

After hydrogenation, the ester **185** was converted to the ketone, epimerized to the *trans* product **186**, and subjected to Baeyer−Villiger oxidation. Introduction of unsaturation, *cis*-hydroxylation gave diol **187** which, after debenzylation and lactam reduction, gave (±)-deoxymannojirimycin (**171**).

(vii) Surprisingly, naturally occurring amino acids have been used to a much lesser extent than carbohydrates in approaches to azasugars. Serine-derived aldehyde **188** has been used in the synthesis of galactonojirimycin[97a] and also more recently in the synthesis of (−)-nojirimycin and (-) mannojirimycin (Scheme 47).[97b]

Wittig reaction of phosphorane **189** with serinal derivative **188** gave the α,β-unsaturated ketone **190**,

Scheme 47[a]



[a] Reagents: (i) PhMe, 110 °C; (ii) OsO_4, NMO, ^{t}BuOH H_2O; (iii) DMP, TsOH, PhH; (iv) $NaBH_4$, MeOH, −60 °C; (v) TBSCl, imidazole, DMF, 80 °C; (vi) (a) MeI, MeCN, reflux; (b) $NaBH_4$, MeOH; (c) $HgCl_2$, MeCN, H_2O; (vii) TFA, H_2O.

which was selectively *cis*-hydroxylated and the diol protected as an acetonide **191** (Scheme 47). The saturated ketone **190** was reduced and the resultant alcohol **192** and protected as the *tert*-butyldimethylsilyl ether **193**. Hydrolysis of the thiazole and treatment with trifluoroacetic acid gave the target (−)-norjirimycin, **194**.

V. Synthesis of Amino Sugars

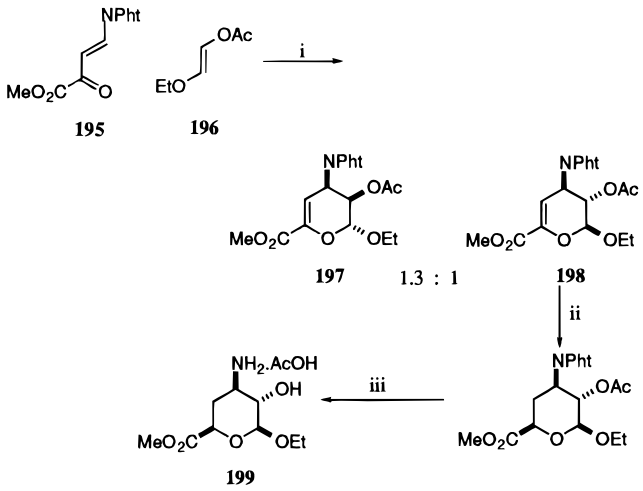
Amino sugars have been known of for approximately one hundred eighty years.[98] They are ubiquitous in nature, occurring in plants, mammals, invertebrates, and microorganisms.[99] However, intense interest in these compounds arose just a few decades ago when researchers determined that 2-deoxy-2-(methylamino)-L-glucosamine was found to be a component of the antibiotic streptomycin.[100] As a whole, amino sugars have been found to be constituents of blood and antigenic determinants[101,102] and glycolipids.[103] The aminoglycoside structures of the calicheamycins and the esperamycins have also been shown to play a crucial role in the recognition and binding to the DNA substrate.[104] For further information on the biological activities of amino sugars, the reader is encouraged to consult the cited references.[105]

Amino sugars have been made by four general methods: from 1,2-anhydro sugars; by Diels−Alder reactions; from amino acid derivatives, and from other chiral pool materials.

(i) Synthesis of 2-deoxy-2-amino sugars is most readily carried out by the conversion of the natural 2-hydroxy sugar to the 1,2-anhydro sugar (the glycal). The glycal can then be functionalized in a number of different ways to give the desired 2-deoxy-2-amino sugar.[106]

(ii) The most common type of Diels−Alder approach for the synthesis of amino sugars is the hetero Diels−Alder reaction between an unsaturated ketone and an activated alkene.[107] The synthesis of the methyl ester of (±)-ezoaminuroic acid, a component of the antifungal ezomycins A,[108] was readily carried out in three steps from enone **195** (Scheme 48). Heating

Scheme 48[a]

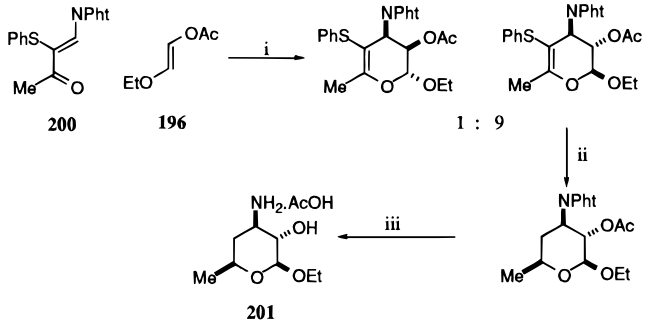


[a] Reagents: (i) PhMe, DCM; (ii) H_2 (40 bar), PtO_2, AcOH; (iii) (a) $NaBH_4$, IPA, H_2O; (b) AcOH, 90 °C.

enone **195** with alkene **196** in toluene gave a 1:1.3 mixture of dihydrofurans **198** and **197** in 97% yield. The required dihydrofuran **198** was then hydrogenated and the phthalimido protecting group cleaved to give (±)-ezoaminuronic acid methyl ester **199**.

In a similar set of reactions the acetic acid salt **201** of (±)-desosamine, a constituent of erythromycin[109] was made from the enone **200** (Scheme 49).

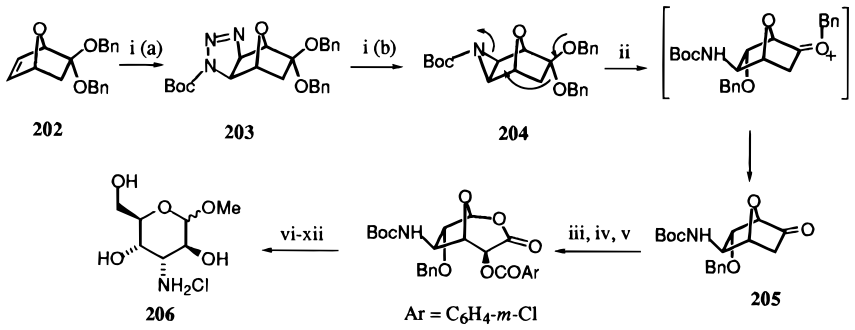
Scheme 49[a]



[a] Reagents: (i) PhMe, DCM; (ii) H_2, Ni (R), MeOH; (iii) (a) $NaBH_4$, IPA, H_2O; (b) AcOH.

Another Diels−Alder approach was published by Vogel who adapted the methodology used for the synthesis of hexoses, *vide supra*, to the synthesis of

Scheme 50[a]

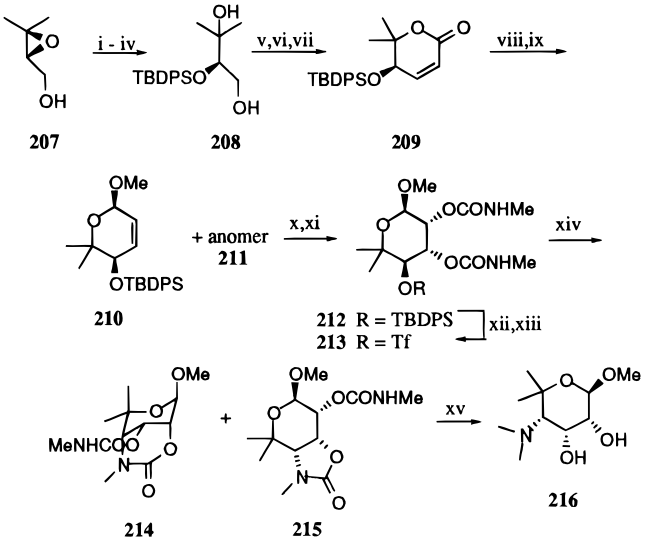


[a] Reagents: (i) (a) $N_3CO_2{}^tBu$, acetone, 50 °C; (b) irradiation; (ii) CF_3COOH, $CHCl_3$; (iii) (a) LiHMDS, THF; (b) TBSCl, THF; (iv) *m*CPBA, DCM, 0 °C; (v) *m*CPBA, $NaHCO_3$, $CHCl_3$; (vi) K_2CO_3, MeOH; (vii) TBSOTf, 2,6-dimethylpyridine, DCM, −10 °C; (viii) $LiBH_4$, THF; (ix) Pd/C; (10%) THF/H_2O (4:1); (x) TBAF, THF; (xi) Ac_2O, pyridine, DMAP, DCM; (xi) HCl, MeOH.

3-deoxy-3-amino sugars.[9,63a,110a] Aziridination of the alkene **202** was accomplished by formation of two diastereomeric triazenes, only one of which, **203**, is shown in Scheme 50. Photolytic ring contraction of **203** to the aziridine **204** followed by treatment with trifluoroacetic acid intramolecularly delivered the benzyloxy group to give the ring-opened product **205**. This ketone was then taken through a very similar series of elaborative steps as was ketone **55** in the synthesis of D-allose (Scheme 18), to eventually yield methyl D-3-amino-3-deoxyaltropyranoside hydrochloride, **206**.[110b]

(iii) The Sharpless asymmetric epoxidation has been used by Hirama as the key step for the introduction of asymmetry in the synthesis of an analog of a 4-deoxy-4-amino sugar.[111] Asymmetric epoxidation of the 3-methylbut-2-en-1-ol using (−)-diisopropyl tartate (DIPT) gave epoxide **207** in high enantiomeric excess (Scheme 51). Hydroxyl group benzylation of **207** and acidic hydrolysis of the epoxide gave, after selective secondary alcohol protection and hydrogenolysis, the *tert*-butyldiphenylsilyl ether **208** (Scheme 51). Selective primary oxidation, alkene formation, and PPTS-catalyzed lactonization gave the lactone **209** which was subsequently reduced and converted to a mixture of anomeric methyl acetals **210** and **211**. This mixture was oxidized with only the desired anomer, **210**, reacting and the resultant diol converted to a dicarbamate **212**. The unreacted anomer, **211**, was recycled by equilibrating under acidic methanolic conditions. Removal of the *tert*-butyldiphenylsilyl group followed by triflation gave the triflate **213**, exposure of which to potassium hydride at low temperature caused the pivotal cyclization to give the cyclic carbamates **214** and **215**, thus introducing nitrogenous functionality to the heterocyclic ring. Lithium aluminum hydride reduction revealed 4-deoxy-4-amino derivative **216** required.

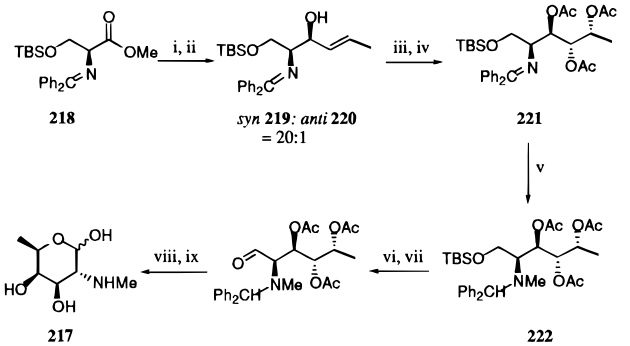
Scheme 51[a]



[a] Reagents: (i) KH, BnBr, THF; (ii) $HClO_4$(aq), ^tBuOH; (iii) TBDPSCl, imidazole, DMF; (iv) H_2, $Pd(OH)_2$, EtOH; (v) Dess−Matin periodinane; (vi) $(CF_3CH_2O)_2P(O)CH_2CO_2Me$, 18-crown-6, K_2CO_3, toluene; (vii) PPTS, PhH; (viii) Dibal-H, PhMe; (ix) TsOH, MeOH; (x) OsO_4, NMO, acetone, H_2O; (xi) MeNCO, Et_3N, dioxane; (xii) TBAF, THF; (xiii) Tf_2O, py, DCM; (xiv) KH, THF, −30 °C; (xv) $LiAlH_4$, Et_2O.

(iv) Amino sugars have also been synthesized from α-amino acids,[112] a typical example being that of Sames and Polt who have recently synthesized *N*-methyl-2-deoxy-2-aminofucose **217** from the serine derived imine **218** (Scheme 52).[113] Reduction of the

Scheme 52[a]



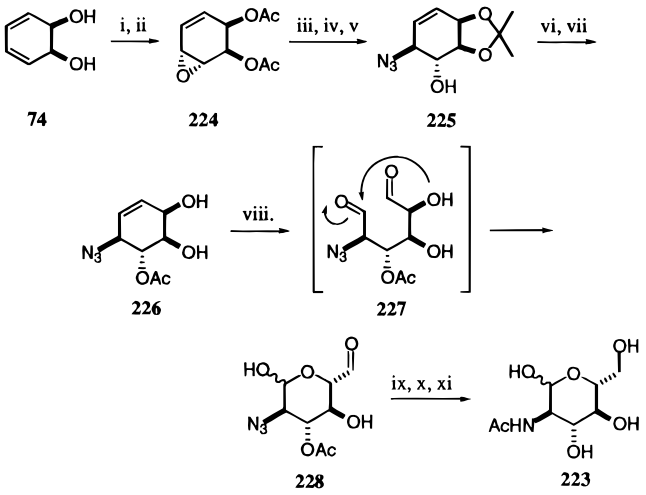
[a] Reagents: (i) Dibal-H, $^iBu_3Al$, DCM, −78 °C. (ii) *E* 1-lithiopropene, PhMe, −78 °C - r.t. (iii) $K_2Os_2(OH)_4$, K_2CO_3, $K_3Fe(CN)_6$, $^tBuOH/H_2O$ 1:1. (iv) Ac_2O, py. (v) $NaBH_3CN$, MeCN, CH_2O (37% aq.). (vi) HF (4% aq.), MeCN. (vii) DMSO, $(COCl)_2$, Et_3N. (viii) KCN (cat.), MeOH. (ix) H_2, Pd/C, MeOH.

ester to aldehyde with Dibal-H, followed by the addition of propenyllithium, afforded a mixture of *syn* and *anti* alcohols **219** and **220** in a ratio of 20:1. After separation, the major diastereomer **219** was subjected to oxidation, giving a 6:1 mixture of triols

hich were peracetylated. Reductive methylation of the major isomer **221** with sodium cyanoborohydride and formaldehyde gave the tertiary amine **222**. *N*-Methyl-2-deoxy-2-aminofucose **217** was obtained by desilylation, oxidation of primary alcohol to aldehyde, deacetylation, and hydrogenation.

(v) Lehmann and Moritz developed a synthesis of (±)-*N*-acetyl-2-amino-2-deoxyglucose (**223**) where *meso* diol **74** was protected as its diacetate and subjected to *m*CPBA oxidation to give epoxide **224** (Scheme 53).[114] Opening of the epoxide with sodium azide

Scheme 53[a]

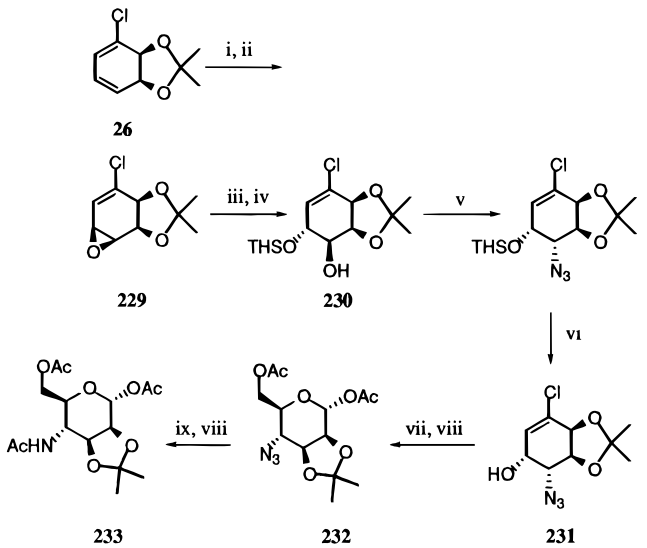


[a] Reagents: (i) Ac_2O, py; (ii) *m*CPBA, Na_2CO_3, DCM; (iii) NaN_3, AcOH (70%), 60 °C; (iv) NaOMe, MeOH; (v) acetone, $CuSO_4$, H_2SO_4 (cat.); (vi) Ac_2O, py; (vii) AcOH (70%); (viii) (a) O_3, MeOH, −78 °C; (b) DMS, −78 °C to room temperature; (ix) (a) $NaBH_3CN$, AcOH, MeOH; (b) Ac_2O, pyridine; (x) (a) Pd/C, H_2, room temperature; (b) Ac_2O, py; (xi) NaOMe, MeOH.

afforded azido alcohol **225**. Protecting group manipulations gave the diol **226**, which after ozonolysis to **227** spontaneously cyclized to form pyranose **228**. Sodium cyanoborohydride reduction of the aldehyde, peracetylation, hydrogenation of the azide and amine acetylation gave the pentaacetate which on treatment with sodium methoxide gave (±)-*N*-acetyl-2-amino-2-deoxyglucose (**223**).

A similar method has also been used by Hudlicky in a synthesis of a 4-deoxy-4-amino mannose.[115] Epoxide **229** was formed by treatment of the diene **26** with *N*-bromosuccinimide followed by sodium hydroxide (Scheme 54). Selective allylic epoxide opening with potassium hydroxide and highly selective protection of the least hindered allylic hydroxyl group yielded the dimethylthexylsilyl ether **230**. Activation and displacement of the hydroxyl group gave, after silyl group removal, alcohol **231**. Ozonolytic cleavage of the alkene with sodium borohydride workup gave, after acetylation, the azido diacetate **232**. Hydrogenation of the azide and acetylation gave the protected 4-deoxy-4-aminomannose **233**. This method has been extended to provide a general synthesis of 2-, 3-, and 4-deoxyamino hexopyranoses.

Scheme 54[a]



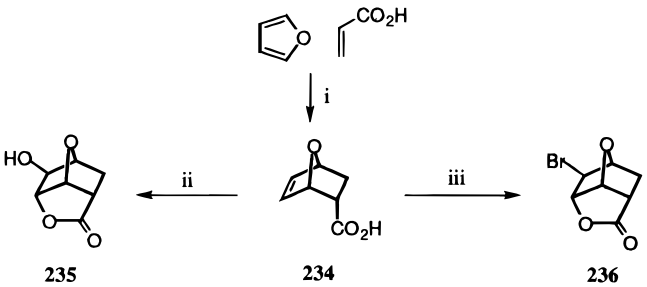
[a] Reagents: (i) NBS, DME/H_2O (4:1); (ii) NaOH, $^nBu_4NHSO_4$, CH_2Cl_2; (iii) KOH (10%), DMSO, 90 °C; (iv) THSCl, imidazole, CH_2Cl_2; (v) (a) Tf_2O, pyridine, CH_2Cl_2, 0 °C; (b) NaN_3, DMF, 53 °C; (vi) TBAF·H_2O, THF, 0 °C; (vii) (a) O_3, MeOH, $NaHCO_3$, −78 °C; (b) $NaBH_4$, 0 °C to room temperature; (viii) Ac_2O, pyridine, DMAP, CH_2Cl_2; (ix) H_2, Pd/C (10%), EtOH.

VI. Synthesis of Pseudosugars

In 1966 McCasland synthesized the first sugar where the endocyclic oxygen atom was replaced with methylene unit.[116] These so-called pseudosugars were postulated, and later some were found, to possess activity as enzyme inhibitors, the pseudosugar mimicking of the parent carbohydrate. Since that time there has been considerable interest in the field of pseudosugar synthesis, and all 16 of the racemic pseudoaldohexopyranoses[117] and the majority of the 32 optically active pseudoaldohexopyranoses have been made. In this section we review only the syntheses of pseudopyranoses.

Of the original sixteen racemic syntheses ten have made use of the furan acrylic acid Diels−Alder adduct **234**[118] as the key intermediate (Scheme 55).[117]

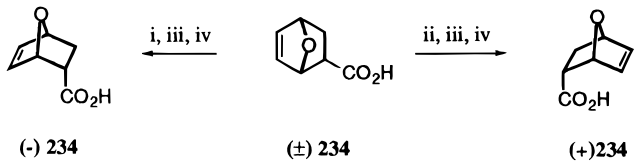
Scheme 55[a]



[a] Reagents: (i) hydroquninone, Δ, sealed tube; (ii) HCO_2H, H_2O_2; (iii) HOBr.

When acid **234** was treated with hydrogen peroxide and formic acid the hydroxy lactone **235** was formed (Scheme 56). The hydroxy lactone **235** was the intermediate for the synthesis of β-DL-*gluco*-,[118,119] α-DL-*galacto*-,[118,119] β-DL-*allo*-,[120] and α-DL-*gulo*-pseudohexopyranose.[120] The majority of remaining pseudo sugars, α-DL-*manno*-,[119] β-DL-*manno*-,[119] β-DL-*altro*-,[119] α-DL-*ido*-,[119] α-DL-*gluco*-,[120] and α-DL-*allo*-pseudohexopyranose,[120] were derived from the bromo

Scheme 56[a]



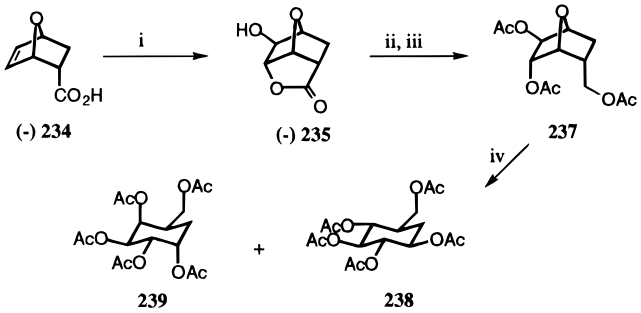
[a] Reagents: (i) (*R*)-phenethylamine, EtOH; (ii) (*S*)-phenethylamine, EtOH; (iii) fractional crystallization; (iv) Dowex 50W X2.

lactone **236** made by the action of hydrobromous acid on the acid **234** (Scheme 55).

The acid **234** has also be used in the synthesis of the optically active series of pseudohexopyranoses.[117] Acid **234** is readily resolved by the fractional crystallization of the mixture of salts formed between itself and optically active α-methylbenzylamine (Scheme 56).[121]

An example of the synthesis of pseudosugars made using this methodology is shown in Scheme 57. Acid

Scheme 57[a]



[a] Reagents: (i) H_2O_2, HCO_2H; (ii) LAH; (iii) Ac_2O, Py, DMAP; (iv) AcOH, Ac_2O, H_2SO_4.

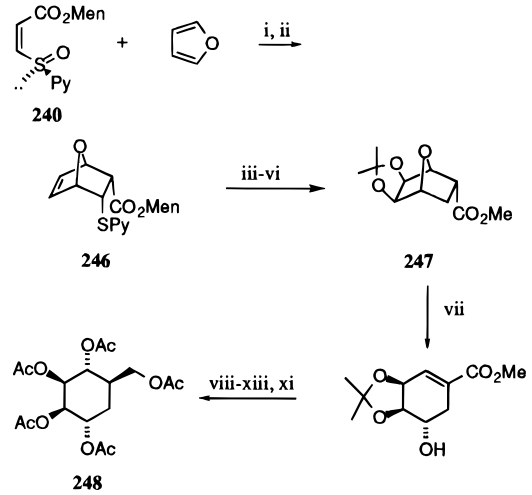
(−)-**234** was hydroxylactonized with hydrogen peroxide in formic acid. Reduction of the lactone (−)-**235** with LAH and peracetylation gave the triacetate **237**. Opening of the 1,4-epoxide under acidic conditions gave a mixture of two products, pseudo-β-D-glucopyranose pentaacetate **238** and pseudo-α-D-galactopyranose pentaacetate **239**, in 34% and 27% yield, respectively.[122]

This synthetic route highlights the main drawback of an otherwise very attractive method of pseudosugar synthesis. As the key step, the opening of the 1,4-epoxide under acidic conditions is not regioselective, and a mixture of two products results.

A more recent and conceptually similar chiral auxiliary approach has overcome this problem. The use of (−)-menthyl (S)$_s$-(2E)-3-(2-pyridylsulfinyl)propenoate, **240**, instead of acrylic acid in the Diels−Alder reaction with 3,4-bis(benzyloxy)furan gave the bicyclic ether **241** in 50% yield (plus 29% exo isomer) and excellent 92% de (Scheme 58).[123] Reduction and desulfurization of the sulfoxide with concomitant alkene hydrogenation yielded the saturated bicyclic alcohol **242**, which was oxidized and treated with diazomethane to give the bicylic ester **243**. Exposure of **243** to lithium hexamethyldisilazide regiospecifically opened the 1,4-epoxide to give a shikimate ester, which was protected as its TBDPS ether **244**. Reduction of the ester followed by stereoselective hydroboration of the alkene gave, after exhaustive deprotection and peracetylation, pseudo-α-L-mannopyranose pentaacetate **245**.

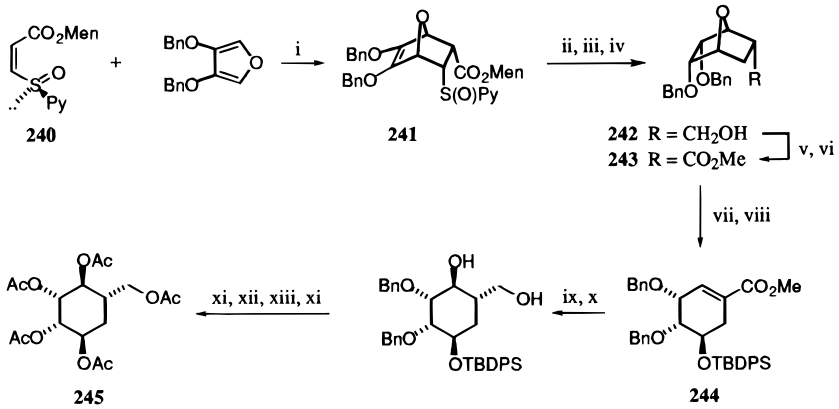
Stereoselective osmylation and acetonide protection of the reduced Diels−Alder adduct **246** derived from sulfoxide **240** and furan gave the *cis* endo tricyclic product **247** (Scheme 59). Elaboration in a fashion

Scheme 59[a]



[a] Reagents: (i) Et_2AlCl, DCM, −20 °C; (ii) $TiCl_3$, EtOH; (iii) OsO_4, Et_3NO, Me_2CO, DMP, TsOH; (iv) LAH, Et_2O; (v) Ni(R) (W-2), EtOH; (vi) Jones' reagent, Me_2CO; CH_2N_2, MeOH, Et_2O; (vii) LHMDS, THF, −78 °C; (viii) TBS-OTf, Et_3N, DCM; (ix) LAH, THF, −18 °C; (x) BH_3−THF; H_2O_2, NaOH; (xi) Ac_2O, py; (xii) TBAF, THF; (xiii) AcOH(aq), 55 °C.

Scheme 58[a]

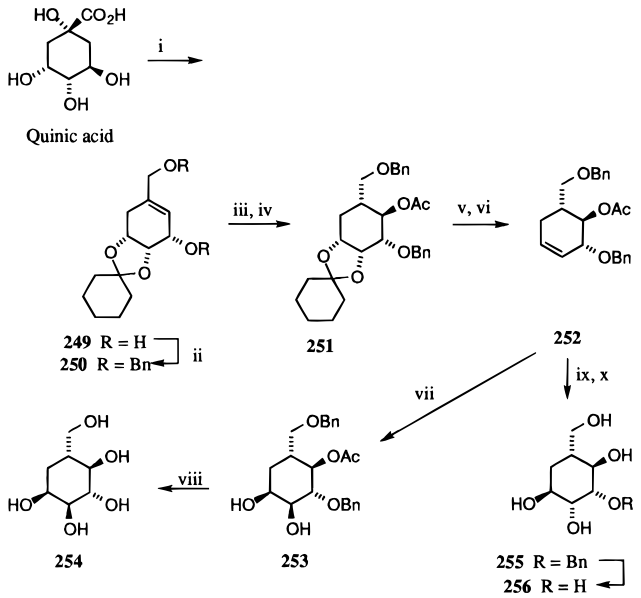


[a] Reagents: (i) Et_2AlCl, DCM, −20 °C; (ii) PBr_3, DMF, 0 °C; (iii) LAH, Et_2O; (iv) Ni(R) (W-2), EtOH; (v) Jones' reagent, Me_2CO; (vi) CH_2N_2, MeOH, Et_2O; (vii) LHMDS, THF, −78 °C; (viii) TBDPS-Cl, imid, DMF; (ix) LAH, THF, −18 °C; (x) BH_3−THF; H_2O_2, NaOH; (xi) Ac_2O, py; (xii) TBAF, THF; (xiii) H_2, Pd/C, EtOH.

similar to that of bicyclic ether **243**, *vide supra*, yielded pseudo-β-D-mannopyranose pentaacetate **248**.

In general, other stereospecific methods of pseudosugar synthesis have relied heavily on long and laborious routes starting from inositols, L-arabinose, D-glucose, and D-ribose.[117] Other chiral pool building blocks have also been used as starting materials. Quinic acid has the requisite number of carbon atoms topologically connected in the same way as those of pseudohexopyranoses. Hence, no new carbon−carbon bonds must be formed, leaving only the adjustment of oxidation state around the ring and peripheral carbons. This is exemplified in the divergent syntheses of pseudo-α-D-glucopyranose and pseudo-α-D-mannopyranose (Scheme 60).[72,73]

Scheme 60[a]

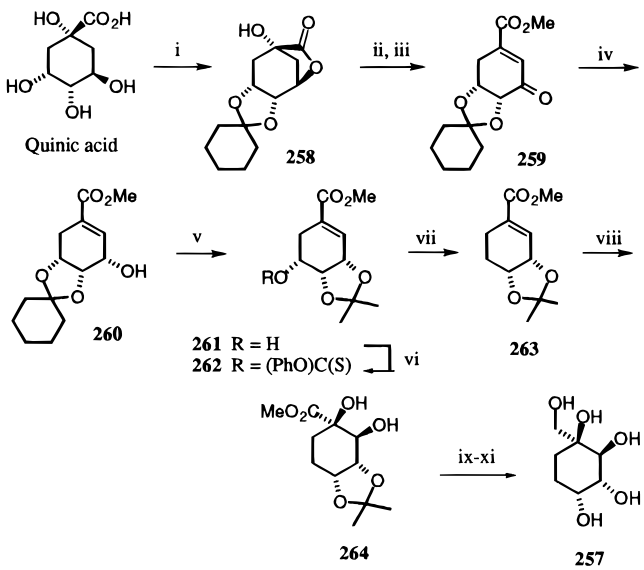


[a] Reagents: (i) see ref 74; (ii) NaH, BnBr, nBu_4NI, THF; (iii) 9-BBN, THF, room temperature then 3 M NaOH, H_2O_2; (iv) Ac_2O, Py, DMAP, DCM; (v) TFA, DCM; (vi) CDI, PhMe, reflux, then $P(OMe)_3$, reflux; (vii) OsO_4, Et_3NO, py, H_2O, ^tBuOH; (viii) MeONa, MeOH, then Rh/C, H_2; (ix) HCO_2H, H_2O_2, reflux, then 5 M NaOH, THF; (x) $Pd(OH)_2$, H_2, EtOH.

Quinic acid was elaborated to the known diol **249**,[74] which was then benzylated to give the dibenzyl ether **250** (Scheme 60). The alkene **250** was then hydroborated in a highly regioselective manner and oxidized with hydrogen peroxide and the resultant alcohol acetylated to give the acetate **251**. After cleavage of the cyclohexylidene the resultant diol was deoxygenated under the Corey−Winter conditions to give the alkene **252**. Selective osmylation on the upper face of the double bond gave the *cis*-diol **253** in high yield. Cleavage of the acetate and hydrogenation of the benzyl ethers revealed pseudo-α-D-glucopyranose **254** in 81% yield. Alternatively epoxidation with performic acid followed by hydrolysis with sodium hydroxide selectively gave the triol **255** which on hydrogenation gave pseudo-α-D-mannopyranose **256** in 45% yield.

More recently quinic acid has been used in the synthesis of pseudo-β-D-fructopyranose, **257**.[76] Pseudo-β-D-fructopyranose and other derivatives are of particular interest as pseudo-β-D-fructopyranose; its enantiomer and racemate have been found to be nearly as sweet as D-fructose (the sweetest naturally occurring sugar) and thus maybe useful as nonnutritive sweeteners. Pseudo-β-D-fructopyranose has been synthesized in the past by two methods, the first using the furan acrylic acid Diels−Alder adduct **234**[75b] and the second using quinic acid. The latter synthesis cuts two steps from the former synthesis and is outlined in Scheme 61.[76]

Scheme 61[a]



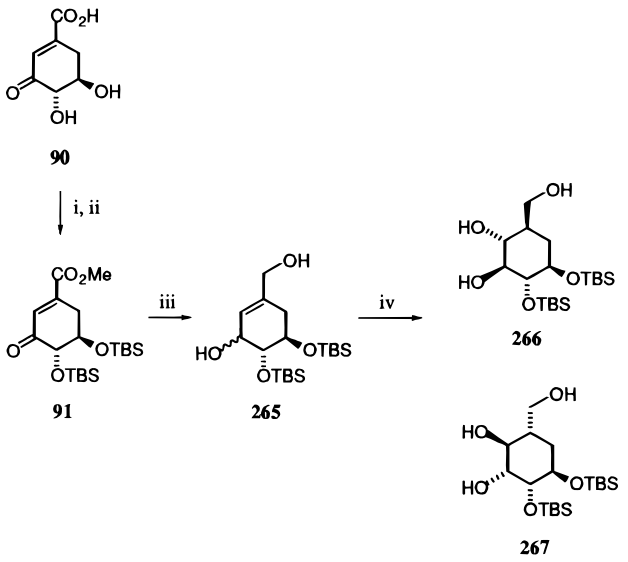
[a] Reagents: (i) cylcohexanone, TsOH·H_2O; (ii) MeONa, MeOH; (iii) PCC, py, 4 Å sieves; (iv) $NaBH_4$; (v) Me_2CO, TsOH·H_2O; (vi) (PhO)CSOCl, py, DCM; (vii) Bu_3SnH, $(tBuO)_2$, PhMe, reflux; (viii) OsO_4, Et_3NO, Py, H_2O, ^tBuOH; (ix) $CH_2C(OMe)Me$, CSA; (x) Dibal-H, THF, −20 °C; (xi) TFA, H_2O.

The *cis*-diol of quinic acid was selectively protected as its cyclohexylidene ketal with concomitant lactonization yielding the bicyclic lactone **258**. Cleavage of the lactone with sodium methoxide, subsequent oxidation of the unveiled secondary alcohol, and elimination of the tertiary alcohol with PCC gave the enone **259**. Reduction with sodium borohydride selectively gave the α-alcohol **260**, which was then transketalized to the hydroxy acetonide **261**. Conversion of **261** to thiocarbonate **262** and exposure to tributyl trihydride and dibutyl peroxide in toluene at reflux gave the deoxygenated product **263**. The alkene **263** was selectively osmylated to give diol **264**. Acetonide protection, ester reduction, and final deprotection gave pseudo-β-D-fructopyranose **257**.

Closely related to quinic acid, dehydroshikimic acid **90** has also been shown to be a useful starting material for pseudosugar synthesis.[46] Reduction of the known keto ester **91**[71] gave a mixture of alcohols **265** (Scheme 62). This mixture was stereoselectively hydroborated *anti* to the *pro* C-3 hydroxyl groups and acetylated to give the, readily separable, 1,2-bis-*O*-(*tert*-butyldimethylsilyl)-3-*O*-,4-*O*-,5-*O*-triacetyl derivatives of pseudo-β-D-glucopyranose **266** and pseudo-α-L-mannopyranose **267** in 28% and 44%, respectively.

The use of *P. putida* 39D-produced dienediols has also been prevalent in pseudosugar synthesis. With these previously described synthons the crucial step is the introduction of the exocyclic carbon atom. There have been four such ways described in the literature.

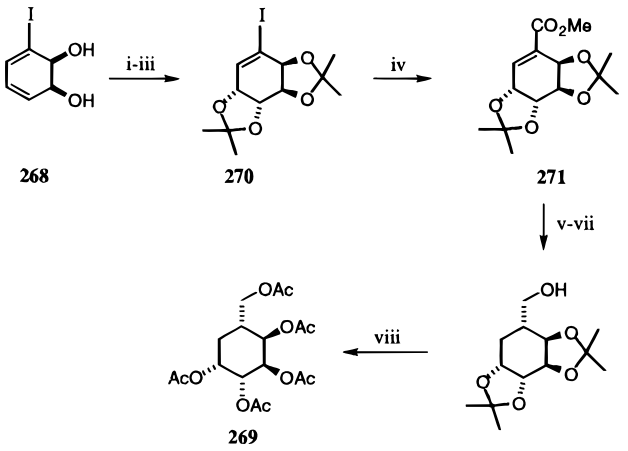
Scheme 62[a]



[a] Reagents: (i) CH_2N_2, −40 °C, Et_2O; (ii) TBSCl, imidazole, DMF; (iii) Dibal-H, PhMe, −78 °C; (iv) (a) BH_3·THF, THF, 0 °C; (b) H_2O_2, NaOH, THF.

1-Iodocyclohexa-1,3-diene-5,6-diol **268** has been used to selectively synthesize pseudo-β-D-altropyranose pentaacetate **269** (Scheme 63).[46] The vinyl

Scheme 63[a]

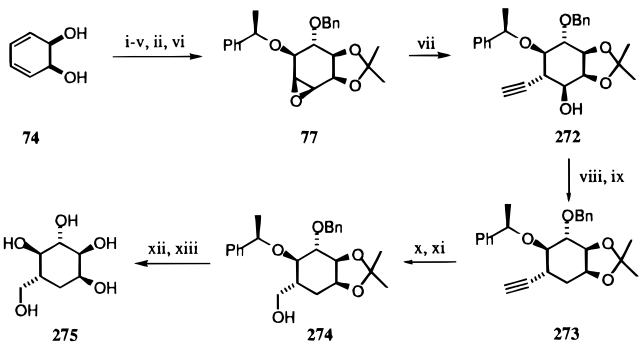


[a] Reagents: (i) DMP, TsOH; (ii) OsO_4, NMO, ^{t}BuOH, H_2O; (iii) DMP, TsOH; (iv) (a) ^{t}BuLi, Et_2O, −78 °C, CO_2; (b) MeI, K_2CO_3, Me_2CO; (v) Pd/C, H_2 50 psi, EtOAc, EtOH; (v) Dibal-H, PhMe, −78 °C; (vii) Amberlyst 15 resin, wet MeOH; (viii) Ac_2O, py, DMAP.

iodide **268** was converted into the diacetonide derivative **270** as seen previously. Iodide **270** was lithiated with ^{t}BuLi. Quenching of the subsequent vinyllithium reagent with carbon dioxide and esterification of the resulting acid furnished ester **271** in 90% yield. Hydrogenation of the alkene, LAH reduction of the ester, removal of the acetonides, and peracetylation gave pseudo-β-D-altropyranose pentaacetate **269** in good overall yield.

A simpler microbial metabolite, cyclohexa-1,3-diene-5,6-diol **74** has been used in three longer and conceptually different pseudosugar syntheses. The *meso* diol **74** was converted the epoxide **77** as previously described[66] (Scheme 21) and then opened with lithium acetylide ethylene diamine complex to give the alkyne **272** (Scheme 64).[47] After ring deoxygenation, the alkyne **273** was reduced over Lindlar's

Scheme 64[a]



[a] Reagents: (i) $(MeO)_2CO$, MeONa; (ii) *m*CPBA, DCM; (iii) (*R*)-(+)-*sec*-phenethyl alcohol, HBF_4·OEt_2, cat., 67%; (iv) BnBr, Ag_2O, DMF, 72 h, 100%; (v) Et_3N, MeOH, H_2O, 72 h; (vi) DMP, CSA, DCM; (vii) HCCLi·EDA, DMPU; (viii) Tf_2O, py; (ix) Super Hydride; (x) H_2, cat., Lindlar; (xi) O_3, MeOH, $NaBH_4$; (xii) Amberlite IR-120+, MeOH; (xiii) H_2, Pd/C, MeOH.

catalyst, and the resultant alkene was ozonized and reduced to give the alcohol **274**. Deprotection gave the free pseudo-α-D-glucopyranose **275**.

The second method involved the chemoenzymatic conversion of the dienediol **74** to the hydroxy ester **276**, which was transformed to the key (bromomethyl)silyl ether **277** (Scheme 65).[48] Exposure of **277** to standard tributyltin hydride, AIBN conditions resulted in a clean radical cyclization to give the cyclic silyl ether **278**, which was subsequently oxidized to the diol **279**. Deprotection and acetylation furnished pseudo-β-L-gulopyranose pentaacetate, **280**. Interception at the stage of the diol **279** and further elaboration gave pseudo-α-L-gulopyranose pentaacetate, **281**.

The same author has used the stannane **282** also derived from alcohol **276** to affect a 2,3-Wittig rearrangement to produce alkene **283** (Scheme 66).[48] This, after hydroboration, hydroxyl deprotection, and peracetylation, yielded pseudo-α-D-mannopyranose pentaacetate, **284**. Interception at the stage of alkene **283**, after several manipulations, yielded pseudo-β-D-mannopyranose pentaacetate, **285**.

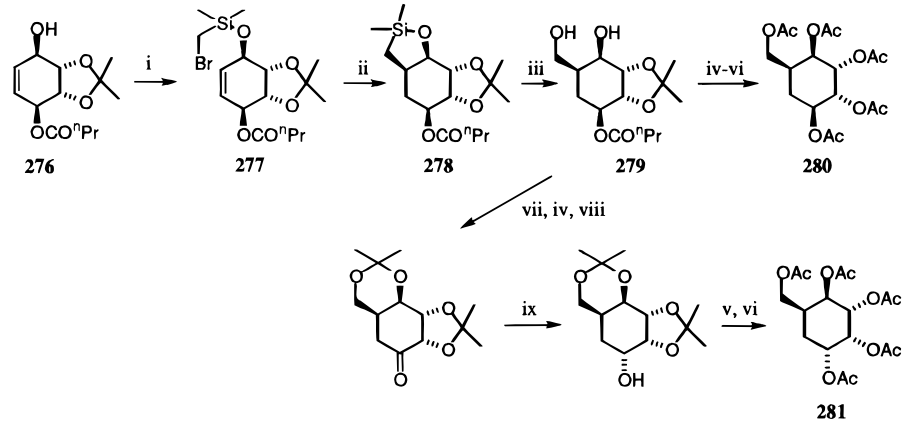
Pseudosugars will continue to attract more attention in the future because of the interest in unnatural surrogates of carbohydrates. Chemical methods of synthesis in this area cannot be supplanted by enzymatic techniques because carba analogs are not recognized by the enzymes.

VII. Summary

The pursuit of approaches to the synthesis of carbohydrates is now over one hundred years old. The field is a dynamic one, dependent on new technology, new ideas, and the development of structured, general approaches to entire classes of sugars.

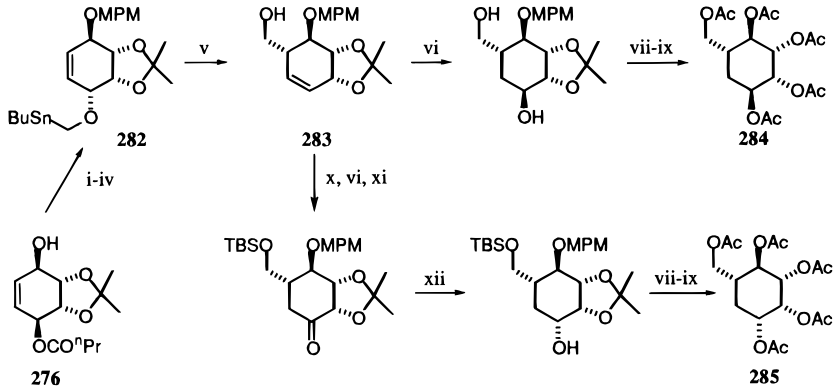
As the field matures further one can expect the consolidation of strategies into unified approaches that are efficient, practical, and fully general. That this process has already begun is exemplified by the emergence of general methods of synthesis. The approaches of Wong, Vogel, Johnson, and Hudlicky begin to address the need for a systematic design of carbohydrates either from a single precursor or by application of a few general methods. The future will witness syntheses of complex oligosaccharides, both

Scheme 65[a]



[a] Reagents: (i) (Bromomethyl)chlorodimethylsilane, Et_3N, DMAP, DCM; (ii) $^nBu_3SnH$, AIBN, PhH, reflux; (iii) KF, $KHCO_3$, H_2O_2, THF, MeOH, then Na_2SO_3; (iv) $KHCO_3$, MeOH; (v) *p*-TSA, MeOH; (vi) Ac2O, py; (vii) DMP, PPTS, DMF; (viii) $(COCl)_2$, DMSO, Et_3N, DCM, −78 °C; (ix) $NaBH_4$, THF, MeOH.

Scheme 66[a]

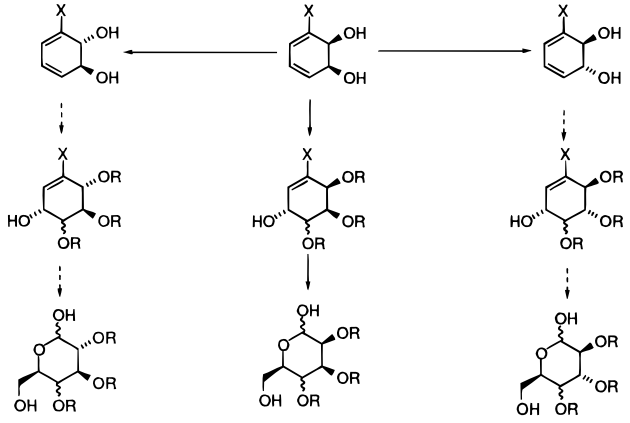


[a] Reagents: (i) MPMO(C=NH)CCl_3, CSA, DCM; (ii) K_2CO_3, MeOH; (iii) Ph_3P, *p*-$NO_2C_6H_4CO_2H$, DEAD, THF, then K_2CO_3, MeOH; (iv) KH, ICH_2SnBu_3, THF; (v) ^nBuLi, THF, −78 °C; (vi) BH_3−THF, −78 °C, then H_2O_2, NaOH; (vii) H_2, Pd/C, MeOH; (viii) *p*-TSA, MeOH; (ix) Ac_2O, py; (x) TBS-Cl, imidazole, DMF; (xi) $(COCl)_2$, DMSO, Et_3N, DCM, −78 °C; (xii) $NaBH_4$, MeOH; (xiii) NaH, THF, BnBr, Bu_4NI; (xiv) DDQ, DCM, H_2O.

natural and unnatural, by the combinations of the best available techniques. With further advancements of molecular modeling, bioactive molecules will be submitted to rational alterations and simpler or more active surrogates will be developed. In this regard there need not be the fear that organic synthesis is not applicable to such problems. Already it has been demonstrated that the best results in the preparation of sugar derivatives are obtained by the judicious combination of traditional and enzymatic methods. Recent demonstration that halocyclohexadiene-*cis*-diols are chemically convertible to both *trans derivatives*[125] allows the simple crossover between mannose and glucose diastereoselection, for example, as shown in Scheme 67. Thus all of the principles applied to the stereoselective manipulation of *cis*-diols **24** demonstrated in the synthesis of most derivatives of mannose-type monosaccharides can now yield hexoses of the remaining biologically important types. It is therefore appropriate to conclude this section with the demonstration that hitherto unknown classes of compounds, the inositol conjugates shown in Scheme 68, can be prepared by simple, iterative techniques from a simple precursor.

Once a combinatorial strategy of sugar synthesis is reduced to practice, the iterative construction of oligomers can be initiated, again driven by the simple

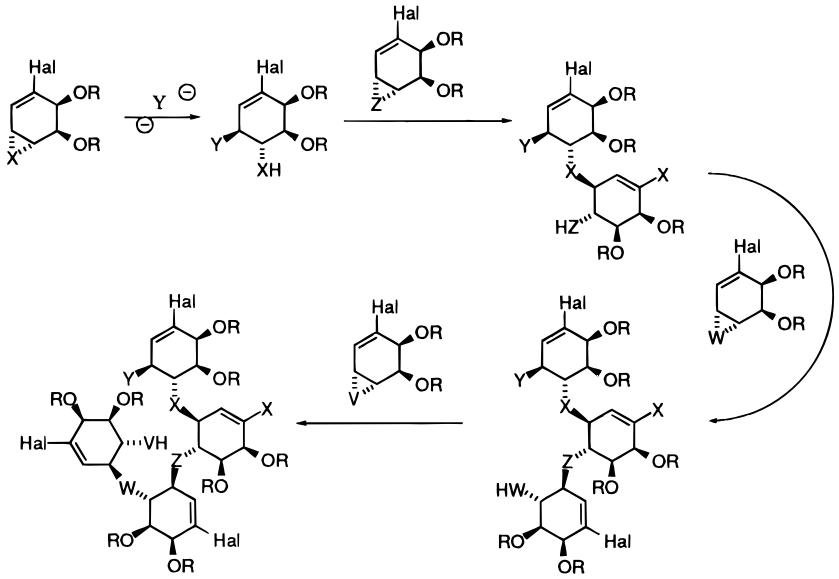
Scheme 67



principles of functional differentiation and management as illustrated in recent publications.[126]

The new class of inositol oligomers shown in Scheme 68 contains compounds that are accessible by simple procedures and with premeditated control of regio-, stereo-, and enantiodisposition of functionality. Such compounds would not be easily made by the application of either enzymatic or traditional methods, and thus their synthesis demonstrates well

Scheme 68



the need for an open-minded union of chemical and biological means of achieving preparative goals.

Where is the field of carbohydrate synthesis heading? The question is impossible to answer, but one may return to the prophetic pronouncement of Brown quoted in the introduction of this review. The synthesis of natural and unnatural oligomers of sugars, a marginally explored area today, holds a great deal of potential in medicine and material science, especially in the field of biodegradable polymers. The combinatorial possibilities in carbohydrates are much greater than in peptides and therefore promise an almost infinite variability of new structures.

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