TOTAL SYNTHESIS OF THE L-HEXOSES[†]

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Abstract - Enantiomerically pure polyhydroxylated natural products are synthesized by using a reiterative two-carbon extension cycle consisting of four key transformations. The generality and efficiency of this methodology are demonstrated in the total synthesis of all eight L-hexoses.

GENERAL APPROACH AND KEY REACTIONS

Organic chemistry of this decade has witnessed the advent of a conceptually new synthetic strategy. Thanks to the discovery of powerful asymmetric reagents and catalysts which enhance or override the inherent diastereofacial preferences of substrate molecules, it is now possible to construct at will *any* stereochemical combinations, including those that otherwise appear impossible to make. This approach has been called "reagent-control" strategy,[2] contrasted to the traditional "substrate-control" strategy where stereochemistries of newly formed chiral centers are dependent upon the inherent diastereofacial preference of the substrate molecule. Such powerful reagents and catalysts have been prepared for major organic reaction classes such as the aldol reaction,[3,4] epoxidation of allylic alcohols,[5] the hydroboration reaction,[6] and ketone reduction.[7]

Monosaccharides such as the hexoses are excellent targets to demonstrate the power of the "reagent-control" strategy, since all the possible stereoisomers are known. Construction of the hexose stereoisomers by the "substrate-control" strategy would require a totally different synthetic sequence for *each* isomer, and the stereoselectivities are normally expected to be low.[8]

At the initial stages of planning for the synthesis of monosaccharides and related polyhydroxylated compounds, a reiterative application of a two-carbon extension cycle appears to offer a *general* solution to the synthesis of these compounds (Scheme I).

One cycle consists of four key reactions: conversion of an aldehyde to a two-carbon extended allylic alcohol (I); asymmetric epoxidation of the allylic alcohol (II); regioselective (and stereospecific) opening of the epoxy alcohol (III); and oxidation to generate a bis-homologated aldehyde (IV), which sets the stage for another cycle. The stereochemistries of the two newly-created asymmetric centers (thus four stereoisomers) are controlled by selecting the *E*- or *Z*-allylic alcohol in step I *and* L-(+)- or D-(−)-tartrate in step II. The stereochemistry of the epoxy alcohol is then transferred to the final product with retention or inversion at the C-2, C-3 centers, depending on the nature of the epoxide opening reaction (step III).

The Wittig reaction is an obvious choice for the two-carbon extension since methods for both *E* and *Z* olefinations are available.[9] While stabilized Wittig reagents such as $Ph_3P=CHCHO$ or $(MeO)_2POCH_2CO_2Me$ in a non-polar solvent are successfully used for the synthesis of *E*-olefins,[10] $Ph_3P=CHCO_2Me$ in a hydroxylic solvent or Bestmann's reagent, $Ph_3P=CH-CH(OEt)_2$,[11a] are common reagents for the construction of *Z*-olefins.[11b]

The asymmetric epoxidation process plays a key role in the whole cycle. The enantioselectivity of the (+)- or (−)-tartrate-Ti(O*i*Pr)$_4$ reagent is so high that "reagent-controlled" epoxidation can be achieved.

[†] This paper is dedicated to the memory of Larry Reed: he died of leukemia on August 10, 1985 at the age of 30.

Scheme I
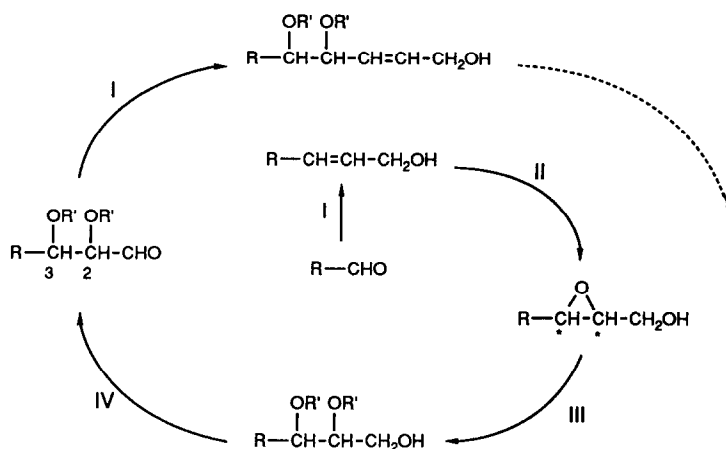
In spite of a large body of literature concerning epoxide syntheses and reactions,[12] only during the past five years has much attention been focused on the regioselective opening of 2,3-epoxy alcohols, and there is already a large and rapidly growing literature on this subject.[13-16] One of the methods, less obvious at the time of this investigation, is the selective epoxy alcohol opening exemplified in equation 1.[13a,17] This process proceeds *via* reversible base-catalyzed epoxide migration (Payne rearrangement[18]) and culminates in irreversible nucleophilic epoxide opening. The selectivity arises through conjunction of the stereospecific nature of the epoxide migration and opening process with the greatly enhanced S_N2 reactivity of a primary (C-1 in 2) over a secondary center.

$$Eq. 1$$
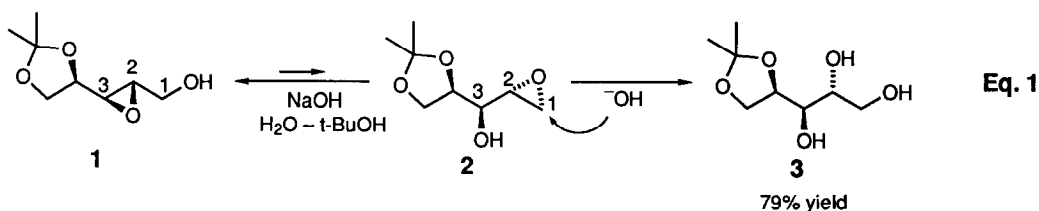
While this facile unraveling of epoxy alcohol 1 to triol 3 (Eq. 1) appears well suited to our goal of carbohydrate synthesis, closer consideration reveals that awkward protection-deprotection steps are needed if triols such as 3 are to be involved in the reiterative cycle (Scheme I). Another problem with the triol route (Eq. 1) is that the selectivity for C-1 opening by hydroxide is not always complete, and C-3 opening of 1 and C-2 opening of 2 produce two different diastereomers of 3. Not all errant hydroxide openings are a problem, however; for example the C-2 opening of 1 also gives 3.

The modification of this process shown in equation 2 better suits the needs of a repeating cycle and is both selective and highly reliable. The process is simply run in the presence of benzenethiolate, which selectively opens the rearranged epoxy alcohol at C-1 to give the 1-thioether-2,3-diols. As reported by Behrens *et*

al., the regioselectivities are generally high with "oxygenated (at C-4)" substrates[13b] and undesired regioisomers are easily separated by chromatography. This route also provides easy access to the aldehyde *via* oxidation


Eq. 2

61% yield
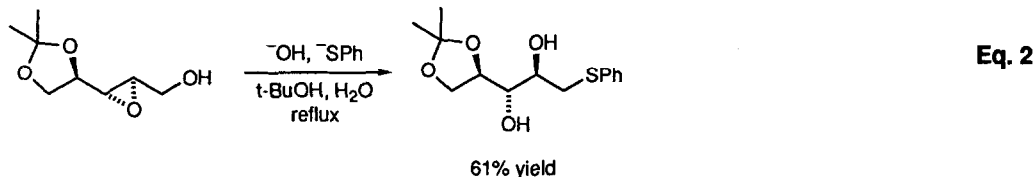
of the phenyl sulfide to the sulfoxide, followed by Pummerer rearrangement,[19] thus avoiding any potential problems during protection-deprotection and oxidation of hydroxyl groups. One notes that the triol route (Eq. 1) and the preferred thioether diol route (Eq. 2) both require about five steps from the epoxy alcohol to the protected aldehyde (III and IV in the cycle, Scheme I). However, the Pummerer route to the aldehyde oxidation level at C-1 gives higher yields, is more reliable and is less likely to lead to epimerization than methods for oxidizing the primary alcohol to the aldehyde. Since working with "sugar" aldehydes is difficult, the Pummerer route has a decisive advantage.

Combined with the benzenethiolate opening reaction, *trans*-2,3-epoxy alcohols give *erythro*-2,3-diols and *cis*-2,3-epoxy alcohols give *threo*-2,3-diols. The asymmetric epoxidation on Z-allylic alcohols, however, is sometimes very slow and/or the enantioselectivities are lower than those of their E-counterparts. These difficulties often prove especially severe for Z-allylic alcohols bearing a chiral moiety close to the reaction site.[20]

The solution to these problems arose from the realization that the *erythro*-2,3-diols, after protection with an isopropylidene group, could be converted to the more stable *threo*-isomers by epimerization at C-2, which in the course of the planned extension sequence lies α to an aldehyde group (Eq. 3).[21] The initial fear of β-elimination, destroying the molecule or epimerizing the C-3 as well as the C-2 center, was unfounded since the

Eq. 3
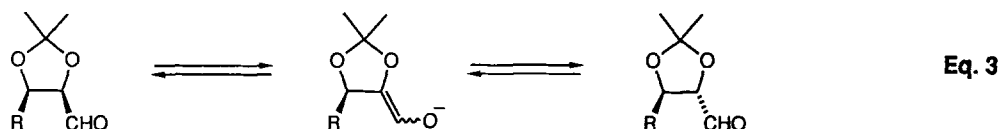
acetonide group helps maintain orthogonality between the enolate π system and the β-alkoxy substituent and suppresses the β-elimination (Eq. 4).[22] This epimerization occurs concurrently with the hydrolysis of the *gem*-acetoxysulfide, the Pummerer product. Thus, when the *erythro*-Pummerer product is treated with K_2CO_3 in

Eq. 4

etc.

Scheme II
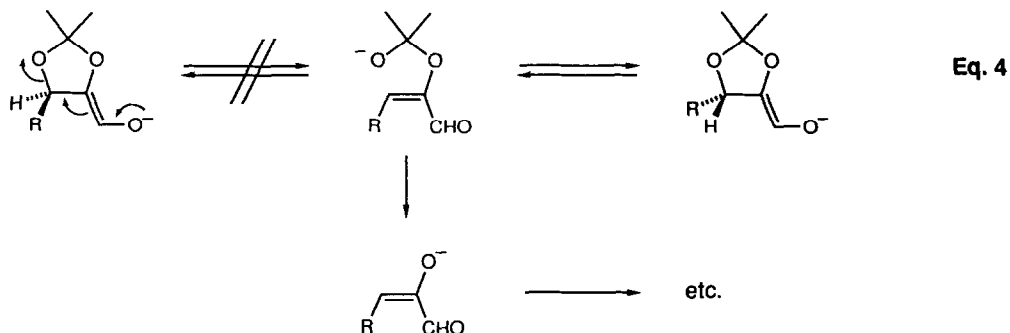
methanol, *threo*-aldehyde **4** is obtained in a 98:2 ratio. Alternatively, when *erythro* stereochemistry is required, the Pummerer product is treated with DIBAL to yield *erythro*-aldehyde **5** (Eq. 5). With these procedures in hand, all possible stereoisomers of saccharides can be made from E-allylic alcohols and full control of stereoselection is now possible by choosing the appropriate conditions from L-(+)- or D-(-)- tartrate and DIBAL or K_2CO_3/MeOH, rather than E- or Z-allylic alcohols and L-(+)- or D-(-)-tartrate (Scheme II).

4

98:2, 99%

5

99:1, 86%
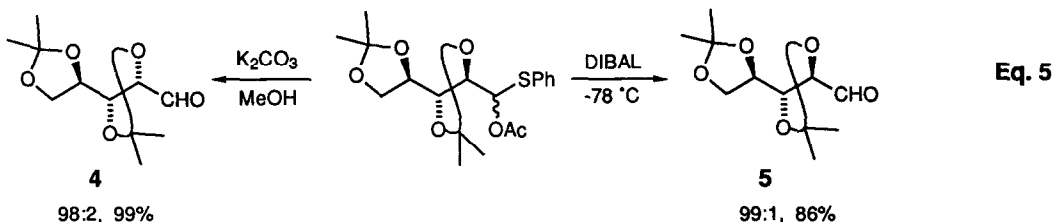
Eq. 5

The symmetry in Scheme II is both interesting and important. All the structures and reaction steps (including reagents) above and below the dotted line have a true mirror image relationship if the R group is achiral, *i.e.*, in the first turn of the two-carbon extension cycle where R = CH_2OR'. In subsequent turns, however, where R groups are chiral, each pair of corresponding structures above and below the dotted line are diastereomeric, so the success of a reaction above the dotted line does not necessarily guarantee the success of the corresponding reaction below the line or *vice versa*. Therefore, although all the major reactions had been developed when the hexose synthesis was undertaken, the concept behind the whole project, "reagent-control strategy", remained unestablished.

RESULTS AND DISCUSSIONS

Total syntheses of the six-carbon aldoses start with a four-carbon unit, 4-benzhydryloxy-E-but-2-en-1-ol (**6**), the common starting material for all sixteen hexoses or any even-numbered polyhydroxylated compound. The choice of the benzhydryl moiety as a protecting group proved essential during the second turn of the cycle (see below, footnote 30).

The mono-protected *E*-allylic diol **6** was prepared readily from commercially available Z-2-buten-1,4-diol *via* successive mono-protection, PCC oxidation/isomerization and reduction. Starting from **6**, the entire reaction sequence leading to all eight L-hexoses is presented in Scheme III. Step I of the first cycle is unnecessary, so the asymmetric epoxidation (step II) becomes the initial step of the reaction sequences. Since the four-carbon unit of **6** corresponds to C-3 through C-6 of the hexoses and, after the asymmetric epoxidation, the stereochemistry at C-3 (which is to be C-5 of the hexoses) does not change in the subsequent epoxide opening reaction or the *erythro/threo* isomerization step, the sense of chirality of the tartrate in this asymmetric epoxidation reaction determines the handedness of the final sugar products. L-(+)-Tartrate is the required enantiomer for this synthesis of L-sugars. D-Hexoses are made *via* the same synthetic scheme simply by changing the sense of chirality of the tartrate in this and subsequent epoxidation steps. It is impossible to synthesize the racemic hexoses using the reagent-control approach, and appreciation of this fact gives many chemists their first real feeling for the significance of this new strategy for diastereocontrol.[23]

Scheme III
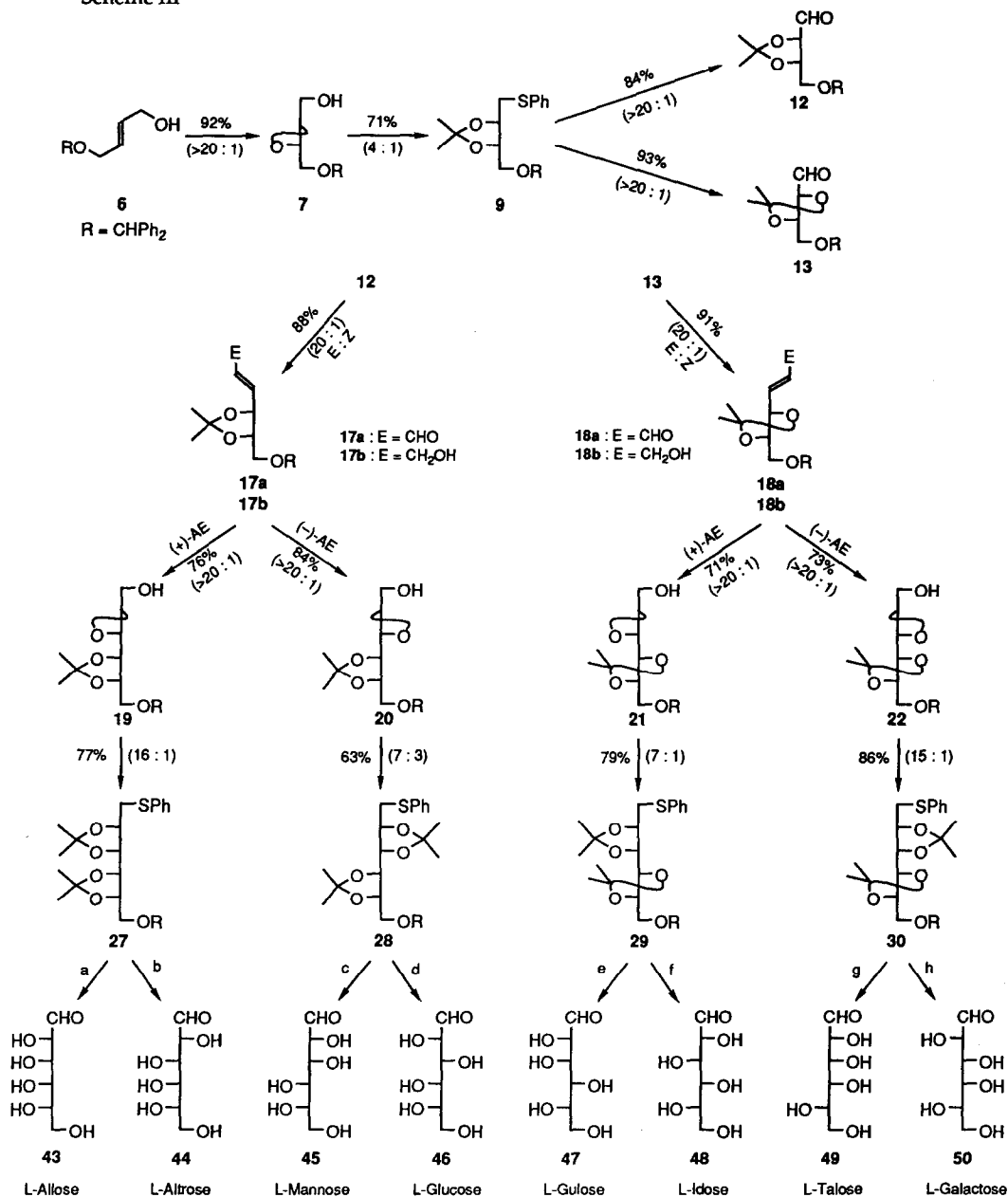
For a, c, e, and g, 1=Pummerer reaction, 2=DIBAL, 3=deprotection. a: 1 (90%), 2 (81%), 3 (90%). c: 1 (90%), 2 (95%), 3 (90%). e: 1 (87%), 2 (81%), 3 (84%). g: 1 (71%), 2 (77%), 3 (61%). For b, d, f, and h, 1=Pummerer reaction, 2=K$_2$CO$_3$/MeOH, 3=deprotection. b: 1 (90%), 2 (48%), 3 (*vide infra*). d: 1 (90%), 2 (65%), 3 (38%). f: 1 (87%), 2 (66%), 3 (85%). h: 1 (71%), 2 (41%), 3 (27%).

Epoxidation of **6** by the standard procedure using (+)-DIPT provides the epoxy alcohol **7** with >95% ee in 92% yield. Treating epoxy alcohol **7** with benzenethiol in a basic medium gives a mixture of regioisomers (step III). The ^{1}H NMR spectrum of the crude product indicates that the ratio of the desired C-1 opening product to the other regioisomers is 4:1. Recrystallization yields the pure C-1 opening product, thioether diol **8** in 71% yield. Although sterically bulkier thiols (e.g., *t*-butylthiol or 2,6-dichlorobenzenethiol) lead to better regioselectivities during rearrangement openings, benzenethiol provides better results in the subsequent steps of this particular study. The thioether diol **8** gives the acetonide **9** in quantitative yield, using 2,2-dimethoxypropane and phosphorus oxychloride catalyst.

A three-step sequence forms the aldehyde group (step IV, Scheme I): oxidation of the thioether to the sulfoxide, Pummerer reaction, then hydrolysis (Eq. 6). Treating **9** with *m*-chloroperbenzoic acid at -78°C provides the sulfoxide **10** as a mixture of diastereomers in quantitative yield. When heated in acetic anhydride in the presence of sodium acetate, **10** affords the *gem*-acetoxy sulfide **11** in 93% yield as a mixture of diastereomers.[19]


Eq. 6
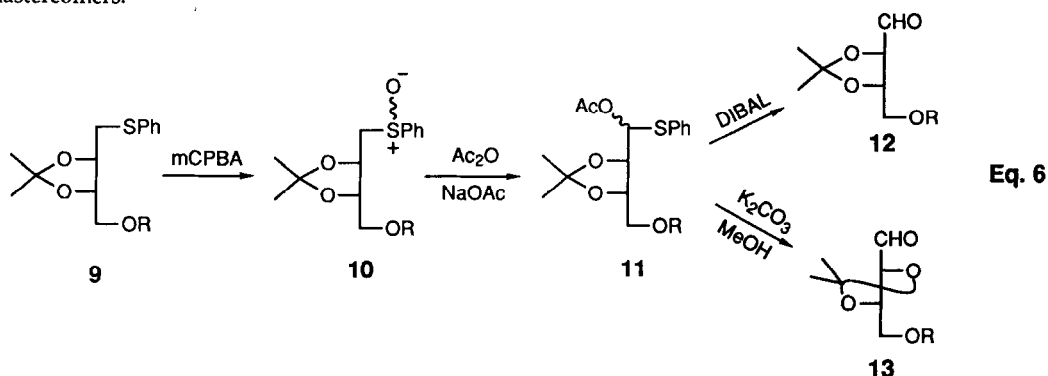
For allose, altrose, mannose and glucose, all with *erythro* stereochemistry at C-4 and C-5 (like that of C-2 and C-3 in the *gem*-acetoxy sulfide **11**), the Pummerer product is treated with DIBAL, giving the *erythro*-aldehyde **12**.[24] For gulose, idose, talose and galactose, all with *threo* stereochemistry at C-4 and C-5, K$_2$CO$_3$/methanol hydrolyzes the *gem*-acetoxy sulfide group in **11** and simultaneously epimerizes the C-2 center. The *threo/erythro* ratio for this epimerization is greater than expected, but examining the mechanism of the epimerization reaction[21b] reveals why.

When a solution of **12** in CDCl$_3$ is treated with methanol-d_4, one observes a rapid diminution in the aldehyde resonance in the ^{1}H NMR spectrum (Scheme IV) as well as the concurrent emergence of signals attributed to the hemi-acetal **15**. Within two hours, only the signals of the hemi-acetal **15** are observed. Upon adding K$_2$CO$_3$ to the NMR sample, a new set of acetonide signals appears. The new signals emerge at the expense of the old and completely replace the latter overnight. The new compound has the structure **16-***d* since concentration of the sample yields the *threo*-aldehyde **13-***d*. Deuterium is incorporated at the C-2 position of **13** and of **16**.

After similarly treating *threo*-aldehyde **13** with methanol-d_4, aldehyde signals almost disappear in 5 min. The new signals are similar to those of **16-***d* described above except for an additional doublet of doublets at 3.83 ppm (integrating for one proton). Adding K$_2$CO$_3$, the signals at 3.83 ppm decrease gradually.

These results support the involvement of the hemi-acetals **15** and **16** in the equilibria. The participation of the sterically bulkier hemi-acetal group, compared to the formyl group, shifts the equilibrium more toward the *threo* isomer.[25]

Scheme IV
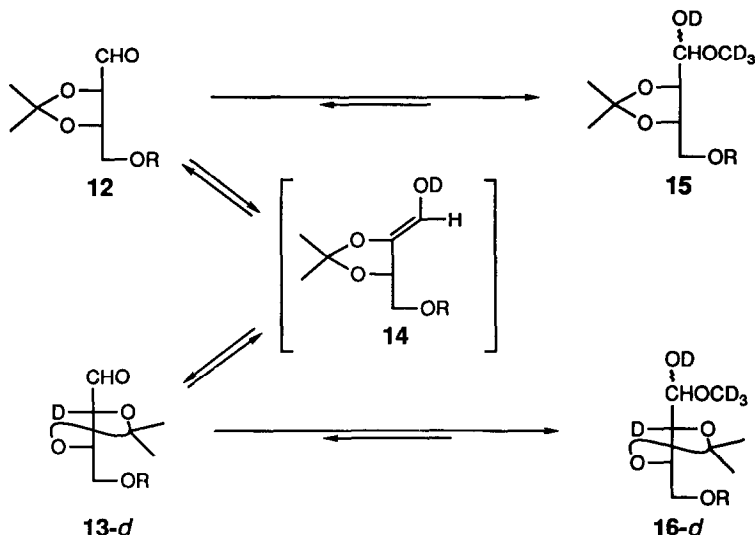
One turn of the cycle is thus traversed and, with the *erythro*- and *threo*-aldehydes **12** and **13** in hand, the stage is set for the second turn. The Wittig reaction using formylmethylenetriphenylphosphorane[26] achieves the two-carbon extension in high yield. The stereoselectivity (*E:Z* ratio) is greater than 20:1, with no epimerization in the product aldehydes. Treating the α,β-unsaturated aldehydes **17a** and **18a** with sodium borohydride affords the allylic alcohols **17b** and **18b**, respectively.

The hope was that asymmetric epoxidation would deliver an oxygen atom with the desired diastereocontrol to the two olefinic carbons of the allylic alcohols (**17b** and **18b**). From the outset, these second asymmetric epoxidation steps were expected to be the most critical for the success of the entire synthesis. Although the asymmetric epoxidation of simple achiral reactants such as **6** proceeds with good enantioselectivity, the enantioselectivity of the reagent must be high enough to enhance or override any preexisting diastereofacial bias in the chiral substrates (i.e., **17b** and **18b**) for the reagent control strategy to succeed. The following model study (Table I) investigates this critical issue.[27]

Homochiral allylic alcohol **A** is epoxidized by various methods and the two diastereomeric products are analyzed by gas chromatography. All the achiral reagents studied (entries 1-3) exhibit a slight preference for the erythro isomer **C**. Although the reaction with Ti(O*i*Pr)$_4$ - TBHP (entry 3) does not go to completion and the epoxy alcohol product seems to decompose under the reaction conditions, the *erythro/threo* ratio remains constant at various stages of the reaction, indicating that neither **B** nor **C** selectively decomposes. The *erythro*-preference is a bias *inherent* to this particular substrate. Getting the *threo* isomer **B** as a major product from **A** using only achiral reagents is therefore unlikely unless one devises alternative synthetic sequences, a weakness

of the substrate-control strategy. Note also that none of the reactions in entries 1-3 is really satisfactory even for the *erythro*-epoxy alcohol because the diastereoselectivities are not high enough.

Table I
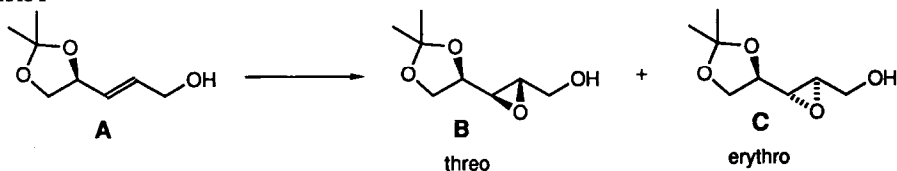
Entry	Reagent	Ratio (threo : erythro)
1	*m*CPBA	1 : 1.4
2	VO(acac)$_2$-TBHP	1 : 1.8
3	Ti(O*i*Pr)$_4$-TBHP[a]	1 : 2.3
4	Ti(O*i*Pr)$_4$-(–)-tartrate-TBHP	1 : 90
5	Ti(O*i*Pr)$_4$-(+)-tartrate-TBHP	22 : 1

a: See reference 28.

When epoxidizing the allylic alcohol A using Ti(O*i*Pr)$_4$-(–)-DIPT (or DET) and TBHP (entry 4), a very high stereoselectivity (90:1) results, reflecting the consonance (a matched pair) of the reagent preference for

α-attack and the substrate bias for *erythro* product. Entry 5 demonstrates the uniqueness of reagent-control. Using (+)-tartrate, the reagent's preference is now switched to the β-face, which is opposite to the substrate's bias (a mismatched pair). The high *threo* selectivity (22:1) observed in this reaction shows the overriding power of the reagent. Recall that this diastereomer could not be obtained as a major product using any of the achiral reagents.[29]

The asymmetric epoxidation steps in the second turn of the cycle for the hexose syntheses provide an even more stringent test for reagent-control. In the event, all four of the crucial second stage asymmetric epoxidations in Scheme III proceed flawlessly with diastereoselectivities of >20:1.[30]

One of these successful epoxidations is followed, unexpectedly, by the least selective step in the entire synthesis. In the mannose-glucose branch, the rearrangement-opening reaction of epoxy alcohol 20 with thiophenoxide occurs with a regioselectivity of only 7:3 (Scheme III). The regioselectivities of the other three rearrangement-opening reactions in the second turn are higher (7:1 to 16:1) than the 4:1 ratio realized with the four-carbon epoxy alcohol 7 in the first turn, predictable results given the greater steric crowding in the six-carbon epoxy alcohols at the C-4 center. The probable preferred ground state conformations of 19 and 20 could account for the anomalous reactivity of 20: the important features of this speculation become apparent upon comparison of molecular models and need not be discussed here.[31]

Treatment of the thioether diol 24 (derived from 20) with 2-methoxypropene and acid catalyst affords 28 in quantitative yield, without scrambling of the isopropylidene group already present in the molecule.[32] Oxidation and Pummerer reaction of 28 proceeds as described in the first turn of the cycle to provide the *gem*-

acetoxy sulfide **32** (see Scheme V). (The structures of synthetic intermediates **23, 25, 26,** and **35-42** which are not discussed in the text are shown in the Experimental Section.)

Glucose synthesis requires epimerization of the C-2 center; hydrolysis of the Pummerer product **32** by K_2CO_3/MeOH successfully accomplishes this task. Removing the isopropylidene groups (trifluoroacetic acid) and the benzhydryl group (H_2, Pd/C) gives rise to free L-glucose!

Altrose, idose and galactose are prepared using the same reaction sequences from the corresponding Pummerer products, **31, 33,** and **34,** respectively. Allose, mannose, gulose and talose are prepared via DIBAL reduction of **31, 32, 33,** and **34,** respectively, followed by deprotections. All the synthetic L-hexoses, excepting altrose, are identical to their D-counterparts with respect to TLC mobility and ¹H NMR spectra. Attempts to deprotect the L-altrose precursor under acidic conditions invariably produce a mixture of the free sugar and 1,6-anhydro-β-L-altropyranose (Eq. 7).[33] From the rotation value of the synthetic L-altrose sample and the literature rotation values of L-altrose and L-altrosan, a 4:1 ratio of the free sugar to the anhydro-sugar is supposed.

L-Altrose   1,6-anhydro-β-L-altropyranose   **Eq. 7**
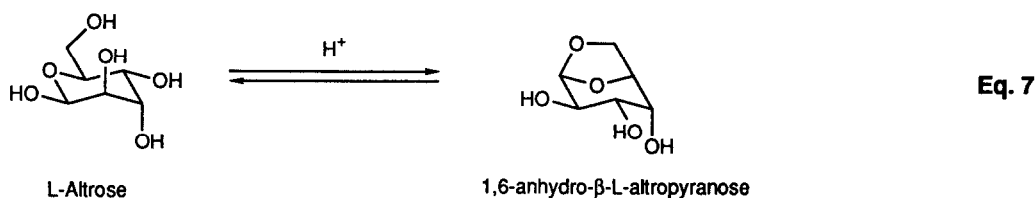
Excepting altrose (accounted for above), the optical rotations of all the synthetic L-sugars show the opposite sign from those of their D-counterparts. However, satisfactory optical rotation values for some of the synthetic sugars remain unattainable, due primarily to the inaccuracies associated with weighing small quantities of *hydrated* samples, rather than to low optical purities of the products.[34] The optical purities of the synthetic sugars are confirmed by transforming them into peracetylated hexitols (Scheme V). The

Scheme V
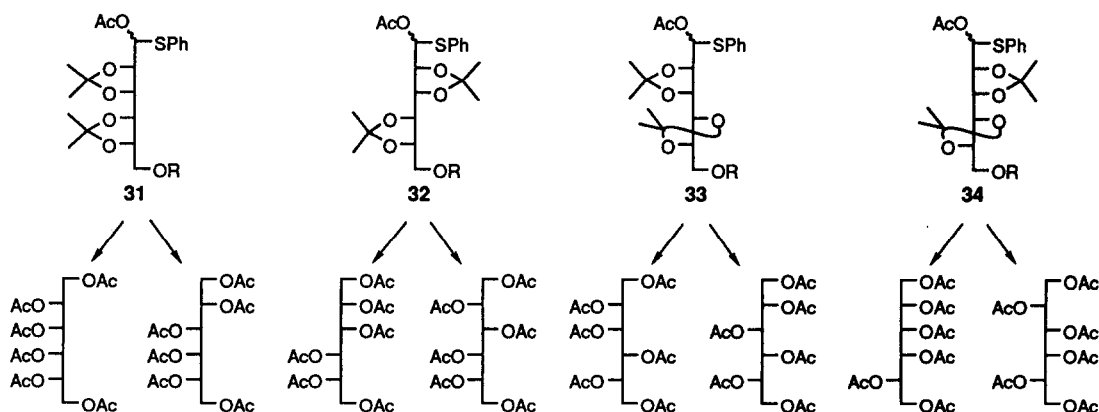
peracetylated hexitols of allose, mannose, gulose and talose, prepared by LAH reduction of the corresponding Pummerer products followed by deprotection and acetylation, and the peracetylated hexitols of the other four sugars, prepared via hydrolysis/epimerization (K_2CO_3/MeOH) of the Pummerer products, NaBH₄ reduction,

deprotection and acetylation, are identical with the corresponding authentic materials on the basis of IR, ^{1}H NMR, mp and magnitude of optical rotation.

CONCLUSION

The hexose syntheses are a paradigm for the stereocontrolled synthesis of molecules having multiple asymmetric centers. The hexoses, whose catenated -CHOH- units make them seem deceptively simple, belie the difficulties faced in selective syntheses of individual stereoisomers. The reiterative cycle for the synthesis of polyhydroxylated compounds described herein enables the selective construction of any one of the sixteen hexose stereoisomers while, at the same time, demonstrating the power of a reagent-control strategy.

EXPERIMENTAL SECTION

<u>General</u>

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Infrared (IR) spectra were measured with a Perkin-Elmer Model 597 grating infrared spectrophotometer. The 1601 cm^{-1} absorption band of polystyrene film was used to calibrate the chart paper. ^{1}H NMR spectra were measured with Brucker 250-MHz or 270-MHz spectrometers. Tetramethylsilane was used as an internal standard. The chemical shifts are given in δ(ppm) downfield from Me$_4$Si and the coupling constants are in Hertz. Optical rotations were measured with a Perkin-Elmer Model 241 polarimeter using a 1 cm^3 capacity (1 dm path length) quartz cell. Elemental analyses were performed by the Robertson Laboratory Inc., Florham Park, NJ.

Analytical thin-layer chromatography (TLC) was performed using aluminum plates coated with 0.20 mm thickness of Merck silica gel 60 F-254. Flash chromatography was performed using Merck silica gel 60 (230-400 mesh) as described by Still.[35] Gas chromatography (GC) was performed on a Perkin-Elmer Model 3920 gas chromatograph. High performance liquid chromatography was performed on a Perkin-Elmer Series 2 liquid chromatograph.

All commercial chemicals and reagents were used as received unless otherwise noted. Solvents were dried according to standard procedures.

Since the reaction sequences leading to each hexose are very similar, only the synthesis of glucose is described in detail in the Experimental Section.[36]

<u>Preparation of 4-Benzhydryloxy-E-2-buten-1-al.</u>

To a suspension of sodium hydride (60%, 4.70 g, 0.117 mol) in DMF (400 mL) under a nitrogen atmosphere, was added dropwise Z-2-butene-1,4-diol (20.0 g, 0.227 mol) with stirring and cooling (0°C). After stirring for 1 h, it was warmed to room temperature and benzhydryl bromide (dried under vacuum, 28.4 g, 0.115 mol) in DMF (200 mL) was added dropwise. After stirring overnight at room temperature, aqueous treatment was followed by extraction with portions of ether. The combined ether extracts were washed with water, dried over Na$_2$SO$_4$ and concentrated to give an oil.

A small amount of this crude product was purified by flash chromatography on silica gel (4:1 pet ether-EtOAc) to afford pure 4-benzhydryloxy-Z-2-buten-1-ol: IR (neat) 3400, 3020, 2860, 1490, 1450 cm^{-1}; ^{1}H NMR(CDCl$_3$)δ 7.34 (m, 4 H), 5.91 (m, 2H), 5.42 (s, 1 H), 4.09-4.13 (m, 4 H), 1.56 (t, J = 5.8 Hz, 1 H).

The remainder of the crude product (benzhydryl bromide being the main impurity) was dissolved in methylene chloride (200 mL) and added to a mixture of pyridinium chlorochromate (38 g, 0.176 mol) and Celite 545 (38 g) in dry methylene chloride (1.2 L). The mixture was stirred at room temperature overnight. The reaction mixture was diluted with ether (2 L) and filtered through a pad of silica gel, washing the pad with additional ether. Evaporation of the solvents gave a light green solid, from which white needles of 4-benzhydryloxy-E-2-buten-1-al (10.605 g, 0.042 mol, 36.5%) were obtained by recrystallization (ethyl acetate-hexane): mp 96.5-97.5°C; IR(KBr) 3020, 2830, 2750, 1670 cm^{-1}; ^{1}H NMR (CDCl$_3$)δ 9.59 (d, J = 7.8 Hz, 1 H), 7.36 (m, 10 H), 6.87 (dt, J = 15.7, 4.0 Hz, 1 H), 6.50 (ddt, J = 15.7, 7.8, 1.9 Hz, 1 H), 5.44 (s, 1 H), 4.29 (dd, J = 3.9, 1.9 Hz, 2 H). Anal. Calcd for C$_{17}$H$_{16}$O$_2$: C, 80.93; H, 6.39. Found: C, 80.90; H, 6.41.

<u>Preparation of 4-Benzhydryloxy-E-2-buten-1-ol (6).</u>

To a methanol solution (250 mL) of sodium borohydride (1.8 g, 47.5 mmol) at -40°C, was added crystals of 4-benzhydryloxy-E-2-buten-1-al (8.623 g, 34.18 mmol). The resulting solution was warmed to -20° to -10 °C for 2-3 h. The reaction was quenched with brine (6 mL) and stirred at room temperature for 30 min. Concentration was followed by dilution with methylene chloride (200 mL), washing with aqueous NH_4Cl solution and brine, and drying over Na_2SO_4. Evaporation of solvent yielded 4-benzhydryloxy-E-2-buten-1-ol as an oil (8.69 g, ca. 100%): IR (neat) 3400, 3020, 1720, 1650 cm^{-1}; ^{1}H NMR (CDCl$_3$)δ 7.34 (m, 10 H), 5.90 (m, 2 H), 5.42 (s, 1 H), 4.17 (m, 2 H), 4.03 (d, J = 4.1 Hz, 2 H), 1.32 (t, J = 6.7 Hz, 1 H).

The Asymmetric Epoxidation of 6 to give 7.

A 1-L, 1-necked round-bottomed flask equipped with a stirring bar was oven dried, fitted with a septum, and flushed with nitrogen. The flask was charged with dry methylene chloride (400 mL) and cooled to -20°C. The following liquids were added sequentially via syringes while stirring in the cooling bath: Titanium tetraisopropoxide (12.6 mL, 12.0 g, 42.3 mmol); L-(+)-diisopropyl tartrate (12.33 g, 52.7 mmol) in dry methylene chloride (20 mL), stirred for 10 min before the next addition; 6 (8.69 g, 34.18 mmol) in methylene chloride (30 mL); and finally $tert$-butylhydroperoxide (3.34 M in methylene chloride solution, 21 mL, 70 mmol). The resulting homogeneous solution was stirred for 10 min. at -20°C and then stored overnight in a freezer maintained at -20°C.

After 18 h, aqueous saturated Na_2SO_4 solution (46 mL) and ether (46 mL) were added to the reaction mixture which was stirred for 1 h at room temperature. After filtration through Celite, the filtrate was concentrated and diluted with ether (350 mL). One normal NaOH solution (160 mL) was added to the ethereal solution and the resulting mixture was stirred at 0°C for 30 min. The ether layer was separated. The aqueous layer was extracted with portions of ether and the combined ether extracts were washed with brine, dried (Na_2SO_4) and concentrated. The crude product was purified by flash chromatography on silica gel (1:1 pet ether-EtOAc) to give pure (2S,3S)-4-benzhydryloxy-2,3-epoxy-1-butanol (7) as an oil (8.501 g, 31.45 mmol, 92%): [α]$^{25}_D$ -17.59° (c 1.08, CHCl$_3$); IR (neat) 3430, 3020, 2860, 1490, 1450 cm^{-1}; NMR (CDCl$_3$) δ 7.35 (m, 10 H), 5.44 (s, 1 H), 3.94 (ddd, J = 12.7, 5.4, 2.7 Hz, 1 H), 3.76 (dd, J = 11.5, 3.1 Hz, 1 H), 3.64 (ddd, J = 12.7, 7.7, 4.1 Hz, 1 H), 3.55 (dd, J = 11.6, 5.3 Hz, 1 H), 3.27 (m, 1 H), 3.10 (m, 1 H), 1.64 (dd, J = 7.6, 5.4 Hz, 1 H).

The Payne Rearrangement-PhSH Opening Reaction of 7 to give 8.

A vigorously stirred mixture of 7 (8.075 g, 29.87 mmol) in $tert$-butanol (150 mL) and 0.5 N NaOH solution (150 mL, 75 mmol) was heated under reflux in a nitrogen atmosphere. To this mixture was added thiophenol (4 mL, 38.8 mmol) in $tert$-butanol (40 mL) via a syringe over a period of 3 h. When all the thiophenol had been added, the reaction mixture was cooled to room temperature and the two layers were separated. The organic layer was concentrated and diluted with methylene chloride (150 mL) while the aqueous layer was extracted with portions of methylene chloride. The combined methylene chloride layers were washed successively with 1N NaOH solution, water and brine, dried over Na_2SO_4 and concentrated to give the crude diol 8 as a solid. It was recrystallized from methylene chloride-hexane to yield pure (2S,3S)-1-benzhydryloxy-4-thiophenyl-2,3-butanediol (8) as white needles (8.070 g, 21.20 mmol, 71%): mp 76-77.5°C; [α]$^{25}_D$ + 43.39° (c 1.15, C$_2$H$_5$OH); IR (KBr) 3400, 2900 cm^{-1}; ^{1}H NMR (CDCl$_3$)δ 7.40-7.20 (m, 15 H), 5.38 (s, 1 H), 3.88-3.77 (m, 2 H), 3.68 (dd, J = 9.6, 3.8 Hz, 1 H), 3.61 (dd, J = 9.6, 5.8 Hz, 1 H), 3.33 (dd, J = 13.9, 3.6 Hz, 1 H), 2.99 (dd, J = 13.9, 8.6 Hz, 1 H), 2.71 (d, J = 4.1 Hz, 1 H), 2.55 (d, J = 5.1 Hz, 1 H). Anal. Calcd for C$_{23}$H$_{24}$O$_3$S: C, 72.60; H, 6.36; S, 8.43. Found: C, 72.75; H, 6.46; S, 8.42.

Protection of the Diol 8 to give 9.

The diol 8 (19.74 g, 0.0519 mol) in methylene chloride (300 mL) was treated with 2,2-dimethoxypropane (15 mL, 0.12 mol) and phosphorus oxychloride (10 drops). The solution was stirred overnight at room temperature. Addition of 15% aqueous NaOH solution (7.5 mL) was followed by stirring for 30 min at room temperature and drying (Na_2SO_4). Evaporation of solvent yielded 9 as a white solid (21.73 g, 100%). The crude product was used directly for the next step. Only a small amount of the crude product was purified (silica gel column, 9:1 pet. ether - EtOAc) for analytical purposes; mp 56-57.5°C; [α]$^{25}_D$ -9.34° (c 1.22, C$_2$H$_5$OH); IR (KBr) 2980, 2480, 2450 cm^{-1}; ^{1}H NMR (CDCl$_3$)δ 7.34-7.25 (m, 15 H), 5.39 (s, 1 H), 4.38 (m, 2 H), 3.58 (m, 2 H), 3.24 (dd, J = 13.4, 4.1 Hz, 1 H), 3.07 (dd, J = 13.4, 7.5 Hz, 1 H), 1.44 (s, 3 H), 1.35 (s, 3 H). Anal. Calcd for C$_{26}$H$_{28}$O$_3$S: C,74.25; H, 6.71; S, 7.62. Found: C, 74.48, H, 6.55; S, 7.71.

Oxidation and Pummerer Reaction of 9 to give 11.

To compound **9** (5.879 g, 13.98 mmol) in methylene chloride (300 mL) at -78°C, was added *m*-chloroperoxybenzoic acid (80%, 3.0 g) in methylene chloride (30 mL) dropwise *via* an addition funnel. When just 1 equivalent of *m*-chloroperoxybenzoic acid had been added (checked on TLC), the reaction was quenched by washing with 1*N* NaOH solution (two times), water (two times) and brine. Drying (Na$_2$SO$_4$) and evaporation of solvent gave the crude sulfoxide **10** as an oil: IR (neat) 3000, 1490, 1450, 1250, 1220, 1070, 1045 cm^{-1}; ^{1}H NMR (CDCl$_3$, *mixture* of diastereomers)δ 7.62-7.12 (m, 15 H), 5.34, 5.24 (singlets, 1H), 4.81-4.24 (m, 2 H), 3.51-2.82 (m, 4 H), 1.47, 1.42, 1.40, 1.29 (singlets, 6 H); MS (70 eV) m/e = 436 (12%), 420 (89%), 167 (100%).

To an acetic anhydride solution (140 mL, reagent grade) of the crude sulfoxide **10**, was added sodium acetate (6.8 g, 83 mmol) and the resulting mixture was heated at reflux under a nitrogen atmosphere for 8 h. Concentration of the reaction mixture on a rotary evaporator was followed by dilution with methylene chloride (200 mL), filtration of sodium acetate, washing with aqueous NaHCO$_3$ solution, water and brine, and drying (Na$_2$SO$_4$). Purification by flash chromatography on silica gel (9:1 pet ether-EtOAc) yielded pure **11** as a diastereomeric mixture (6.214 g, 13.00 mmol, 93%): IR (CCl$_4$) 2980, 1750, 1490, 1450, 1370, 1220 cm^{-1}; ^{1}H NMR (CDCl$_3$, *mixture* of diastereomers)δ 7.41-7.23 (m, 15 H), 6.24 (m, 1 H), 5.38, 5.35 (singlets, 1 H), 4.42-4.24 (m, 2 H), 3.69-3.57 (m, 2 H), 2.05, 1.84 (singlets, 3 H), 1.49, 1.46, 1.32 (singlets, 6 H); MS (70 eV) m/e = 478 (6%), 418 (100%), 276 (61%), 167 (47%).

Release of Aldehyde 12 without Epimerization.

To the solution of **11** (5.334 g, 11.15 mmol) in methylene chloride (160 mL) at -78°C, was added diisobutylaluminum hydride (1.0 M in hexane, 24 mL, 24 mmol) and the reaction mixture was stirred for 30 min. Aqueous saturated Na$_2$SO$_4$ solution (9 mL) was added to the reaction mixture at -78°C. The reaction mixture was allowed to warm to room temperature over a period of 1 h. Addition of anhydrous MgSO$_4$ was followed by filtration. The filtrate was concentrated and purified by flash chromatography on silica gel (6:1 pet ether-EtOAc) to give the pure *erythro*-aldehyde **12** as an oil (3.307 g, 10.14 mmol, 91%): [α]^{25}$_D$ -34.47° (maximum) -20.44° (final) (*c* 1.14, CHCl$_3$); IR (neat) 3000, 1720, 1490, 1450 cm^{-1}; ^{1}H NMR (CDCl$_3$)δ 9.65 (d, J = 2.0 Hz, 1 H), 7.26 (m, 10 H), 5.31 (s, 1 H), 4.60 (m, 1 H), 4.47 (dd, J = 7.9, 2.0 Hz, 1 H), 3.61 (dd, J = 10.6, 4.0 Hz, 1 H), 3.46 (dd, J = 10.6, 3.5 Hz, 1 H), 1.61 (s, 3 H), 1.40 (s, 3 H).

Hydrolysis of the Pummerer Product 11 with Epimerization to give 13

A solution of **11** (9.570 g, 0.02 mol) in methanol (150 mL) was treated with potassium carbonate (6.9 g, 0.05 mol). The resulting mixture was stirred overnight at room temperature, which resulted in a clear solution. Concentration was followed by dilution with methylene chloride (200 mL), washing with 0.5 *N* NaOH solution and brine, and drying (Na$_2$SO$_4$). Purification by flash chromatography on silica gel (3:1 pet ether-EtOAc) gave the pure *threo*-aldehyde **13** as an oil (6.53 g, ca. 100%): [α]^{25}$_D$ +14.24° (*c* 1.32, CHCl$_3$); IR (neat) 3400, 3000, 1730, 1490, 1450 cm^{-1}; ^{1}H NMR (CDCl$_3$)δ 9.78 (d, J = 1.6 Hz, 1 H), 7.34 (m, 10 H), 5.44 (s, 1 H), 4.32 (m, 2 H), 3.66 (d, J = 4.4 Hz, 2 H), 1.48 (s, 3 H), 1.43 (s, 3 H).

Wittig Reaction of 12 to give 17a.

To a solution of formylmethylenetriphenylphosphorane (0.53 g, 1.74 mmol) in benzene (30 mL), was added **12** (0.47 g, 1.44 mmol) in benzene (5 mL) and the mixture was stirred overnight at room temperature. Concentration and purification by column chromatography (4:1 pet ether-EtOAc) yielded pure **17a** as an oil (0.488 g, 1.27 mmol, 88%): [α]^{25}$_D$ + 5.51° (*c* 3.25, C$_2$H$_5$OH); IR (neat) 3000, 1700 cm^{-1}; ^{1}H NMR (CDCl$_3$)δ 9.38 (d, J = 7.8 Hz, 1 H), 7.28 (m, 10 H), 6.82 (dd, J = 15.5, 4.8 Hz, 1 H), 6.36 (ddd, J = 15.6, 7.8, 1.6 Hz, 1 H), 5.28 (s, 1 H), 4.95 (m, 1 H), 4.55 (m, 1 H), 3.52 (dd, J = 9.5, 4.6 Hz, 1 H), 3.36 (dd, J = 7.9 Hz, 9.5 Hz, 1 H), 1.47 (s, 3 H), 1.40 (s, 3 H).

Reduction of 17a to give Allylic Alcohol 17b.

The allylic alcohol **17b** was prepared in 91% yield from **17a** by the same procedure used to prepare **6**: [α]^{25}$_D$ -8.86° (*c* 2.80, C$_2$H$_5$OH); IR (neat) 3440, 2980, 1725, 1490, 1450 cm^{-1}; ^{1}H NMR (CDCl$_3$)δ 7.26 (m, 10 H), 5.95 (dt, J = 15.5, 5.1 Hz, 1 H), 5.72 (m, 1 H), 5.34 (s, 1 H), 4.68 (t, J = 6.7 Hz, 1 H), 4.40 (q, J = 6.1 Hz, 1 H), 4.10 (m, 2 H), 3.47 (d, J = 5.8 Hz, 2 H), 1.45 (s, 3 H), 1.38 (s, 3 H), 1.13 (t, J = 6.3 Hz, 1 H).

The Asymmetric Epoxidation of 17b to give 20.

The epoxy alcohol **20** was prepared in 84% yield from **17b** using D-(-)-diisopropyl tartrate by the same procedure used to prepare **7** from **6**: mp 101-102°C (ether/hexane); $[\alpha]^{25}_D$ + 14.7° (*c* 0.6, C_2H_5OH); IR (KBr) 3430, 2860, 2450 cm⁻¹; ¹H NMR $(CDCl_3)\delta$ 7.34-7.25 (m, 10 H), 5.43 (s, 1 H), 4.44 (dd, J = 12, 5.5 Hz, 1 H), 4.01 (t, J = 6.1 Hz, 1 H), 3.67 (m, 3 H), 3.45 (m, 1 H), 3.15 (dd, J = 5.9, 2.2 Hz, 1 H), 3.02 (m, 1 H), 1.51 (dd, J = 8.2, 5 Hz, 1 H), 1.46 (s, 3 H), 1.35 (s, 3 H). Anal. Calcd for $C_{22}H_{26}O_5$: C, 71.35; H, 7.03. Found: C, 71.43; H, 6.81.

The Payne Rearrangement-PhSH Opening Reaction of **20** to give **24**

The diol **24** was prepared in 63% yield from **20** by the same procedure used to prepare **8** from **7**: mp 66-68°C (benzene/hexane); $[\alpha]^{25}_D$ -34.5° (*c* 1.65, C_2H_5OH); IR (CCl_4) 3460, 2980, 2920, 1580, 1450, 1380 cm⁻¹; ¹H NMR $(CDCl_3)\delta$ 7.38-7.16 (m, 15 H), 5.42 (s, 1 H), 4.44 (m, 2 H), 3.77 (m, 1 H), 3.66 (m, 3 H), 3.44 (dd, J = 14.3, 2.5 Hz, 1 H), 2.86 (dd, J = 14, 8 Hz, 1 H), 2.80 (d, J = 6.1 Hz, 1 H), 2.74 (d, J = 5.1 Hz, 1 H), 1.47 (s, 3 H), 1.37 (s, 3 H).

Protection of Diol **24** to give **28**.

To a solution of **24** (0.740 g, 1.54 mmol) in methylene chloride (30 mL), were added 2-methoxypropene (0.18 mL, 0.135 g, 1.9 mmol) and *d*-10-camphorsulphonic acid (8 mg). The solution was stirred for 0.5 h at room temperature. After washing with 10% aqueous NaOH solution, drying (Na_2SO_4) and concentration gave **28** as an oil (0.800 g, 100%): $[\alpha]^{25}_D$ + 4.3° (*c* 2.8, C_2H_5OH); IR (neat) 2980, 2580, 2450, 1380, 1210 cm⁻¹; ¹H NMR $(CDCl_3)\delta$ 7.37-7.19 (m, 15 H), 5.32 (s, 1 H), 4.44 (m, 1 H), 4.28 (m, 3 H), 3.63 (dd, J = 9.5, 8 Hz, 1 H), 3.47 (dd, J = 9.6, 4.5 Hz, 1 H), 3.16 (m, 2 H), 1.48 (s, 3 H), 1.44 (s, 3 H), 1.37 (s, 3 H), 1.28 (s, 3 H); MS (70 eV) m/e = 520 (79%), 505 (100%), 353 (90%), 167 (90%).

Oxidation and Pummerer Reaction of **28** to give **32**.

The sulfoxide was prepared in 97% yield from **28** by the same procedure used to prepare **10** from **9**: IR (CCl_4) 2980, 1450, 1380, 1210 cm⁻¹; ¹H NMR $(CDCl_3,$ *mixture* of diastereomers)δ 7.63 (m, 2 H), 7.50 (m, 3 H), 7.35-7.16 (m, 10 H), 5.36, 5.28 (singlets, 1 H), 4.77, 4.4-4.07 (multiplets, 4 H), 3.67-3.31, 3.07-2.94 (multiplets, 4 H), 1.50, 1.46, 1.43, 1.40, 1.36, 1.30, 1.28, 1.20 (singlets, 12 H).

The Pummerer reaction was performed with the sulfoxide to yield **32** in 90% yield by the same procedure used to prepare **11** from **10**: IR (neat) 2980, 1750, 1490, 1450, 1380, 1370, 1210 cm⁻¹; ¹H NMR $(CDCl_3,$ *mixture* of diastereomers)δ 7.50 (m, 2 H), 7.33-7.23 (m, 13 H), 6.30 (d, J = 5.9 Hz) and 6.11 (d, J = 6.6 Hz, 1 H), 5.35, 5.33 (singlets, 1 H), 4.30 (m, 4 H), 3.53 (m, 2 H), 2.06, 2.01 (singlets, 3 H), 1.49, 1.42, 1.31, 1.28, 1.26 (singlets, 12 H).

Hydrolysis of the Pummerer Product **32** with Epimerization to give **38**.

The epimerized diisopropylidene aldehyde **38** was prepared in 65% yield from **32** by the same procedure used to prepare **13** from **11**: $[\alpha]^{25}_D$ + 37.8° (*c* 1.45, $CHCl_3$); IR (neat) 3440, 3020, 2980, 1730, 1490, 1450, 1370 cm⁻¹; ¹H NMR $(CDCl_3)\delta$ 9.66 (d, J = 1 Hz, 1 H), 7.33-7.22 (m, 10 H), 5.35 (s, 1 H), 4.51 (dd, J = 13, 6.4 Hz, 1 H), 4.32 (dd, J = 9.6, 1.8 Hz, 1 H), 4.27 (dd, J = 6.7, 2 Hz, 1 H), 4.09 (dd, J = 7.5, 2.2 Hz, 1 H), 3.75 (d, J = 6.5 Hz, 2 H), 1.47 (s, 3 H), 1.45 (s, 3 H), 1.37 (s, 3 H), 1.24 (s, 3 H).

Preparation of L-Glucose **46**.

The aldehyde **38** (71 mg, 0.167 mmol) was treated with 90 % trifluoroacetic acid-water for 10 min at room temperature. After complete evaporation of trifluoroacetic acid (rotary evaporator then high vacuum at room temperature), the residue was dissolved in methanol (5 mL) and stirred overnight under a hydrogen atmosphere with 10% Pd/C (50 mg). The filtered reaction mixture was concentrated. The residue was triturated with methylene chloride and chromatographed (7:2:1 EtOAc-MeOH-H_2O) through silica gel. The combined fractions were concentrated and dissolved in water. The aqueous solution was filtered through a sintered glass frit (UF) and the filtrate was lyophilized to yield pure L-glucose **46** (11.5 mg, 0.064 mmol, 38%). $[\alpha]^{25}_D$ -47.2° (*c* 0.83, H_2O).

The following are optical rotations for the synthetic L-hexoses, hexose pentaacetate and hexitol hexaacetates.

L-Allose $[\alpha]^{21}_D$ -10.8° (*c* 1.41, H_2O), Lit. [37] +14.5° (D-form)

pentaacetate $[\alpha]^{21}_D$ +14.0° (*c* 0.82, CHCl$_3$), Lit. -13.7° (D-form)

allitol hexaacetate $[\alpha]^{21}_D$ 0.00° (*c* 1.27, CHCl$_3$)

L-Altrose $[\alpha]^{21}_D$ +17.6° (*c* 1.96, H$_2$O),[38] Lit. -32.3° (L-altrose),
                        +213° (L-altrosan)

L-altritol hexaacetate $[\alpha]^{20}_D$ -38.7° (*c* 0.59, CHCl$_3$)

L-Mannose $[\alpha]^{25}_D$ -13.5° (*c* 1.02, H$_2$O), Lit. +14.6° (D-form)

pentaacetate $[\alpha]^{21}_D$ -23.5° (*c* 3.40, CHCl$_3$), Lit. +25.3° (D-form,
                calculated on the basis of α:β-anomer ratio)

L-mannitol hexaacetate $[\alpha]^{20}_D$ -25.0° (*c* 1.46, CHCl$_3$), Lit. +25.0° (D-form)
                        mp 125-126 °C, Lit. 126 °C.

L-Glucose $[\alpha]^{21}_D$ -47.2° (*c* 0.83, H$_2$O), Lit. -51.4° (L-form)

pentaacetate $[\alpha]^{21}_D$ -38.9° (*c* 3.41, CHCl$_3$), Lit. +49.8° (D-form,
                calculated on the basis of α:β-anomer ratio)

L-glucitol hexaacetate $[\alpha]^{22}_D$ -10.0° (*c* 0.97, CHCl$_3$), Lit. +10.0° (D-form)

L-Gulose $[\alpha]^{25}_D$ +16.0° (*c* 1.28, H$_2$O), Lit. -20° (D-form)

L-gulitol hexaacetate $[\alpha]^{21}_D$ +10.0° (*c* 1.25, CHCl$_3$), Lit. +10° (L-form)
                        mp 98-99 °C, Lit. 99 °C.

L-Idose $[\alpha]^{25}_D$ -10.6° (*c* 0.98, H$_2$O), Lit. +15.8° (D-form)

L-iditol hexaacetate $[\alpha]^{21}_D$ -24.6° (*c* 1.06, CHCl$_3$), Lit. +25° (D-form)
                        mp 116-118 °C, Lit. 121.5 °C.

L-Talose $[\alpha]^{20}_D$ -19.7° (*c* 0.31, H$_2$O), Lit. +21° (D-form)

L-talitol hexaacetate (cf. same as altritol hexaacetate)
                        $[\alpha]^{20}_D$ -38.7° (*c* 1.66, CHCl$_3$)

L-Galactose $[\alpha]^{23}_D$ -72.2° (*c* 0.70, H$_2$O), Lit. -81° (L-form)

galactitol hexaacetate $[\alpha]^{18}_D$ 0.0° (*c* 0.95, CHCl$_3$)
                        mp 167-168°C, Lit. 168-169°C.

Those synthetic intermediates (R = CHPh$_2$) which are not described above exhibit the following spectroscopic data and optical rotations.
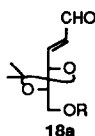
18a $[\alpha]^{25}_D$ -19.43° (*c* 1.05, CHCl$_3$); IR (neat) 3000, 1690, 1490, 1450 cm^{-1}; NMR (CDCl$_3$)δ 9.57 (d, J = 7.8 Hz, 1 H), 7.33-7.28 (m, 10 H), 6.82 (dd, J = 15.7, 4.9 Hz, 1 H), 6.37 (dd, J = 15.7, 7.8 Hz, 1 H), 5.43 (s, 1 H), 4.64 (m, 1 H), 4.01 (m, 1 H), 3.71 (dd, J = 10.1, 4.3 Hz, 1 H), 3.63 (dd, J = 10.1, 5.7 Hz, 1 H), 1.45 (s, 3 H), 1.44 (s, 3 H).
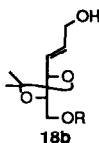
18b $[\alpha]^{25}_D$ -24.30° (*c* 1.42, EtOH); IR (neat) 3400, 2980, 1490, 1450 cm^{-1}; NMR (CDCl$_3$)δ 7.37-7.21 (m, 10 H), 5.94 (dt, J = 15.3, 4.9 Hz, 1 H), 5.74 (dd, J = 16.4, 7.4 Hz, 1 H), 5.42 (s, 1 H), 4.37 (t, J = 7.8 Hz, 1 H), 4.14 (br s, 2 H), 3.93 (m, 1 H), 3.60 (d, J = 4.4 Hz, 2 H), 1.44 (s, 3 H), 1.42 (s, 3 H), 1.37 (br s, 1 H).

L-Allose, L-Altrose Series

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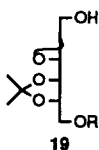
$[\alpha]^{25}_D$ -9.6° (*c* 1.0, EtOH); IR (neat) 3480, 2930, 1490, 1450 cm^{-1}; NMR (CDCl$_3$)δ 7.39-7.25 (m, 10 H), 5.44 (s, 1 H), 4.47 (dd, J = 11.9, 5.8 Hz, 1 H), 4.03 (t, J = 6 Hz, 1 H), 3.89-3.54 (m, 4 H), 3.16 (m, 2 H), 1.52 (dd, J = 7.6, 5.5 Hz, 1 H), 1.46 (s, 3 H), 1.36 (s, 3 H); MS (70 eV) m/e = 370 (7%), 354 (84%), 339 (28%), 166 (100%).

23
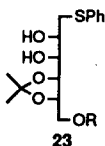
mp 129-130 °C; $[\alpha]^{25}_D$ +15.3° (*c* 1.0, EtOH); IR (KBr) 3400, 2880, 1585, 1450 cm^{-1}; NMR (CDCl$_3$)δ 7.41-7.13 (m, 15 H), 5.44 (s, 1 H), 4.49 (m, 1 H), 4.27 (dd, J = 9.2, 5.5 Hz, 1 H), 3.91 (m, 2 H), 3.69 (ABq, J = 7 Hz, 2 H), 3.50 (dd, J = 9.7, 3.9 Hz, 1 H), 3.37 (dd, J = 13.7, 3.0 Hz, 1 H), 3.09 (dd, J = 13.6, 8.1 Hz, 1 H), 3.05 (d, J = 3.5 Hz, 1 H), 1.33 (s, 3 H), 1.32 (s, 3 H). Anal. Calcd for C$_{28}$H$_{32}$O$_5$S: C, 70.0; H, 6.67. Found: C, 70.31; H, 6.36.

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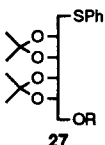
$[\alpha]^{25}_D$ +13.4° (*c* 1.4, EtOH); IR (neat) 2990, 1590, 1450, 1380, 1370 cm^{-1}; NMR (CDCl$_3$)δ 7.39-7.15 (m, 15 H), 5.43 (s, 1 H), 4.44 (m, 1 H), 4.30 (m, 1 H), 4.20 (m, 2 H), 3.76 (dd, J = 10.7, 3.5 Hz, 1 H), 3.60 (dd, J = 10.6, 6.8 Hz, 1 H), 3.40 (dd, J = 13.4, 3.3 Hz, 1 H), 3.02 (dd, J = 13.3, 9.6 Hz, 1 H), 1.42 (s, 3 H), 1.39 (s, 3 H), 1.36 (s, 3 H), 1.22 (s, 3 H).
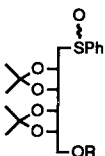
IR (neat) 3000, 1500, 1460, 1450, 1385, 1376, 1250, 1220, 1050 cm^{-1}; NMR (CDCl$_3$, mixture of diastereomers)δ 7.72-7.16 (m, 15 H), 5.39, 5.38 (singlets, 1 H), 4.7-4.0 (m, 4 H), 3.75-2.75 (m, 4 H), 1.41, 1.33, 1.32, 1.27, 1.23, 1.18 (singlets, 12 H).

31
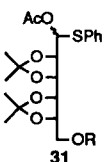
IR (neat) 2980, 1750, 1450, 1370, 1220 cm^{-1}; NMR (CDCl$_3$, mixture of diastereomers)δ 7.56-7.51 (m, 2 H), 7.39-7.22 (m, 13 H), [6.47 (d, J = 3.9 Hz), 6.37 (d, J = 6.3 Hz), 1 H], 5.41 (s, 1 H), 4.40 (m, 2 H), 4.15 (m, 2 H), 3.70 (dd, J = 10.4, 3.6 Hz, 1 H), 3.56 (dd, J = 10.3, 6.3 Hz, 1 H), 2.05, 2.02 (singlets, 3 H), 1.48, 1.46, 1.40, 1.37, 1.30, 1.28, 1.23, 1.19 (singlets, 12 H).

**35**
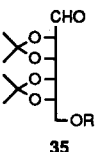
$[\alpha]^{25}_D$ -2.7° (*c* 1.66, CHCl$_3$); IR (neat) 2980, 1734, 1490, 1450, 1380, 1370, 1220 cm^{-1}; NMR (CDCl$_3$)δ 9.68 (d, J = 1.8 Hz, 1 H), 7.40-7.23 (m, 10 H), 5.43 (s, 1 H), 4.45 (m, 3 H), 4.18 (m, 1 H), 3.73 (dd, J = 10.6, 4.4 Hz, 1 H), 3.61 (dd, J = 10.6, 6.0 Hz, 1 H), 1.50 (s, 3 H), 1.43 (s, 3 H), 1.32 (s, 3 H), 1.27 (s, 3 H).

36
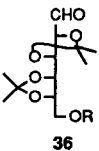
$[\alpha]^{25}_D$ -9.06° (*c* 2.56, CHCl$_3$); IR (neat, hydrate) 3450, 2980, 1740, 1490, 1450, 1380, 1370, 1220, 1070 cm^{-1}; NMR (CDCl$_3$)δ 9.67 (s, 1 H), 7.40-7.23 (m, 10 H), 5.44 (s, 1 H), 4.47 (m, 2 H), 4.17 (m, 2 H), 3.78 (dd, J = 10.7, 4.3 Hz, 1 H), 3.64 (dd, J = 10.6, 6.3 Hz, 1 H), 1.42 (s, 3 H), 1.41 (s, 3 H), 1.36 (s, 3 H), 1.29 (s, 3 H).

L-Mannose Series

37
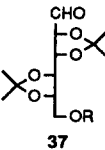
$[\alpha]^{25}_D$ +18.1° (*c* 1.75, CHCl$_3$); IR (neat) 2980, 1740, 1500, 1450, 1380, 1370, 1210, 1070 cm^{-1}; NMR (CDCl$_3$)δ 9.63 (d, J = 3.1 Hz, 1 H), 7.37-7.22 (m, 10 H), 5.38 (s, 1 H), 4.47 (m, 2 H), 4.27 (m, 2 H), 3.63 (m, 2 H), 1.57 (s, 3 H), 1.44 (s, 3 H), 1.32 (s, 3 H), 1.29 (s, 3 H).

L-Gulose, L-Idose Series

21

[α]$^{25}_D$ -24.6° (*c* 1.25, EtOH); IR (neat) 3450, 2980, 1490, 1450 cm^{-1}; NMR (CDCl$_3$)δ 7.33-7.26 (m, 10 H), 5.41 (s, 1 H), 4.17 (m, 1 H), 3.86 (dd, J = 8.0, 5.2 Hz, 1 H), 3.79 (m, 1 H), 3.70 (dd, J = 10.1, 4.4 Hz, 1 H), 3.60-3.52 (m, 2 H), 3.14 (dd, J = 5.3, 2.3 Hz, 1 H), 3.06 (m, 1 H), 1.57 (br dd, 1 H), 1.42 (s, 3 H), 1.39 (s, 3 H).

25
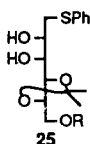
[α]$^{25}_D$ +14.5° (*c* 1.00, EtOH); IR (neat) 3460, 2980, 1480, 1450 cm^{-1}; NMR (CDCl$_3$)δ 7.39-7.20 (m, 15 H), 5.40 (s, 1 H), 4.32-4.23 (m, 2 H), 3.71-3.54 (m, 4 H), 3.42 (dd, J = 14.0, 3.7 Hz, 1 H), 3.02 (dd, J = 13.9, 8.0 Hz, 1 H), 2.74 (d, J = 5.5 Hz, 1 H), 2.46 (d, J = 9 Hz, 1 H), 1.42 (s, 3 H), 1.39 (s, 3 H).

29
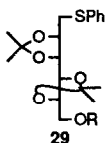
[α]$^{25}_D$ -47.1° (*c* 1.02, EtOH); IR (neat) 2980, 1480, 1450, 1380 cm^{-1}; NMR (CDCl$_3$)δ 7.38-7.20 (m, 15 H), 5.42 (s, 1 H), 4.36 (m, 1 H), 4.23 (m, 2 H), 4.10 (d, J = 8.4 Hz, 1 H), 3.61 (m, 2 H), 3.40 (dd, J = 13.3, 6.3 Hz, 1 H), 3.29 (dd, J = 13.4, 7.6 Hz, 1 H), 1.53 (s, 3 H), 1.44 (s, 3 H), 1.41 (s, 3 H), 1.37 (s, 3 H).
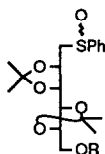
IR (neat) 2980, 1450, 1440, 1380, 1250, 1210, 1050 cm^{-1}; NMR (CDCl$_3$, mixture of diastereomers)δ 7.66 (m, 2 H), 7.51 (m, 3 H), 7.32-7.22 (m, 10 H), 5.42, 5.39 (singlets, 1 H), 4.82, 4.27-3.98 (multiplets, 4 H), 3.74-3.46, 3.22-2.97 (multiplets, 4 H), 1.47, 1.43, 1.40, 1.28 (singlets, 12 H).

33
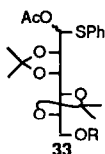
IR (neat, polar diastereomer) 2980, 1750, 1490, 1450, 1370 cm^{-1}; NMR (CDCl$_3$, polar diastereomer)δ 7.40-7.20 (m, 15 H), 6.47 (d, J = 9.4 Hz, 1 H), 5.43 (s, 1 H), 4.46 (d, J = 8.5 Hz, 1 H), 4.38-4.25 (m, 3 H), 3.65 (dd, J = 9.9, 4.4 Hz, 1 H), 3.56 (dd, J = 10.0, 5.6 Hz, 1 H), 2.13 (s, 3 H), 1.48 (s, 3 H), 1.42 (s, 3 H), 1.29 (s, 3 H), 1.26 (s, 3 H).
IR (CCl$_4$, less polar diastereomer) 2980, 1760, 1490, 1470, 1450, 1435, 1380, 1365 cm^{-1}; NMR (CDCl$_3$, less polar diastereomer)δ 7.58 (m, 2 H), 7.36-7.21 (m, 13 H), 6.22 (d, J = 9.2 Hz, 1 H), 5.38 (s, 1 H), 4.20 (m, 1 H), 4.10-4.03 (m, 2 H), 3.89 (d, J = 8.2 Hz, 1 H), 3.56 (d, J = 4.0 Hz, 2 H), 1.85 (s, 3 H), 1.51 (s, 3 H), 1.41 (s, 3 H), 1.35 (s, 3 H), 1.29 (s, 3 H).

39
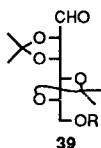
[α]$^{25}_D$ -47.1° (*c* 1.5, CHCl$_3$); IR (CHCl$_3$) 3425, 2950, 1725, 1380, 1210, 1075 cm^{-1}; NMR (CDCl$_3$)δ 9.63 (d, J = 2.2 Hz, 1 H), 7.34-7.22 (m, 10 H), 5.40 (s, 1 H), 4.49-4.29 (m, 3 H), 3.98 (dd, J = 7.8, 2.4 Hz, 1 H), 3.59 (m, 2 H), 1.59 (s, 3 H), 1.40 (s, 3 H), 1.38 (s, 3 H), 1.32 (s, 3 H).

40
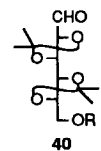
[α]$^{25}_D$ -12.7° (*c* 1.55, CHCl$_3$); IR (CHCl$_3$) 3490, 2950, 1724, 1365, 1240, 1075 cm^{-1}; NMR (CDCl$_3$) δ 9.73 (d, J = 1.7, Hz, 1 H), 7.39-7.23 (m, 10 H), 5.40 (s, 1 H), 4.40 (dd, J = 7.2, 1.7 Hz, 1 H), 4.29 (m, 1 H), 4.17 (dd, J = 7.2, 3.8 Hz, 1 H), 4.07 (dd, J = 7.7, 3.8 Hz, 1 H), 3.62 (m, 2 H), 1.49 (s, 3 H), 1.43 (s, 3 H), 1.41 (s, 3 H), 1.39 (s, 3 H).

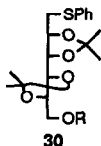L-Talose, L-Galactose Series

22

[α]$^{25}_D$ +2.7° (*c* 1.01, EtOH); IR (CHCl$_3$) 3460, 2950, 1495 cm^{-1}; NMR (CDCl$_3$)δ 7.36-7.21 (m, 10 H), 5.42 (s, 1 H), 4.19-4.12 (m, 1 H), 3.95-3.88 (m, 2 H), 3.69-3.58 (m, 3 H), 3.19-3.13 (m, 2 H), 2.01 (br s, 1 H), 1.42 (s, 3 H), 1.40 (s, 3 H).

26
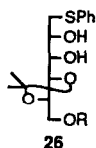
$[\alpha]^{25}_D$ -36.8° (*c* 1.71, EtOH); IR (neat) 2980, 2940, 1500 cm^{-1}; NMR (CDCl$_3$)δ 7.42-7.15 (m, 15 H), 5.44 (s, 1 H), 4.23-4.16 (m, 1 H), 3.99 (t, J = 7.4 Hz, 1 H), 3.89-3.61 (m, 3 H), 3.40 (dd, J = 14, 2.8 Hz, 1 H), 3.09-3.00 (m, 3 H), 1.39 (s, 3 H), 1.38 (s, 3 H).

30

$[\alpha]^{25}_D$ -3.29° (*c* 1.43, CHCl$_3$); IR (neat) 2980, 1450, 1380, 1225 cm^{-1}; NMR (CDCl$_3$)δ 7.39-7.18 (m, 15 H), 5.46 (s, 1 H), 4.39-4.33 (m, 1 H), 4.20-4.16 (m, 1 H), 4.01-3.90 (m, 2 H), 3.78 (dd, J = 10.8, 1.9 Hz, 1 H), 3.56 (dd, J = 5.1, 3.7 Hz, 1 H), 3.39 (dd, J = 13, 3.6 Hz, 1 H), 3.05 (dd, J = 13, 2.2 Hz, 1 H), 1.41 (s, 6 H), 1.29 (s, 6 H).
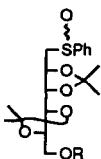
IR (neat) 2980, 1490, 1450, 1440, 1380, 1370, 1250, 1210, 1040 cm^{-1}; NMR (CDCl$_3$, mixture of diastereomers) δ 7.68 (m, 2 H), 7.51 (m, 3 H), 7.35-7.23 (m, 10 H), 5.45, 5.43 (singlets, 1 H), 4.80, 4.33-3.59, 3.35-3.17, 2.86 (multiplets, 8 H), 1.48-1.21 (singlets, 12 H).

34
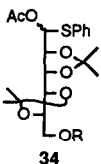
IR (neat) 2950, 1750, 1690, 1370 cm^{-1}; NMR (CDCl$_3$, mixture of diastereomers)δ 7.57-7.18 (m, 15 H), 6.41-6.37 (m, 1 H), 5.44 (s, 1 H), 4.50-3.54 (m, 6 H), 2.03, 1.88 (singlets, 3 H), 1.38-1.24 (singlets, 12 H).

41
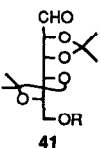
$[\alpha]^{25}_D$ -9.36° (*c* 1.25, CHCl$_3$); IR (neat) 2950, 1730 cm^{-1}; NMR (CDCl$_3$)δ 9.66 (d, J = 2.1 Hz, 1 H), 7.35-7.20 (m, 10 H), 5.42 (s, 1 H), 4.58-4.39 (m, 2 H), 4.15-4.10 (m, 1 H), 4.00 (t, J = 7.6 Hz, 1 H), 3.63 (ddd, J = 17, 10.6, 4.7 Hz, 2 H), 1.45 (s, 3 H), 1.39 (s, 3 H), 1.36 (s, 3 H), 1.35 (s, 3 H).

42
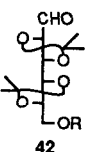
NMR (CDCl$_3$)δ 9.74 (br s, 1 H), 7.23-7.18 (m, 10 H), 5.44 (s, 1 H), 4.23-3.61 (m, 6 H), 1.61-1.19 (singlets, 12 H).

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1. a) A preliminary report of this work has been disclosed as Part 5 of Synthesis of Saccharides and Polyhydroxylated Natural Products. See Ko, S. Y.; Lee, A. W. M.; Masamune, S.; Reed, III, L. A.; Sharpless, K. B.; Walker, F. J. *Science* **1983**, *220*, 949, b) For Part 4, see Reed III, L. A.; Ito, Y.; Masamune, S.; Sharpless, K. B. *J. Am. Chem. Soc.* **1982**, *104*, 6468.
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23. a) This subject is elaborated on in references 2. b) See also reference 29.

24. A few attempts at buffered hydrolysis were unsuccessful. Lee, A. W. M. unpublished results.

25. This explanation was first suggested to us, prior to these experiments, by Professor William R. Roush.

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28. Due to the complex nature of the asymmetric epoxidation catalyst, the validity of this achiral model system is questionable.
29. These results can be extended further to the reactions of the racemic substrate. Imagine that racemic **A** is allowed to react with Ti(O*i*Pr)$_4$-TBHP, (S)-**A** will give a 1:2.3 mixture of **B** and **C** (entry 3, Table I). At the same time, (R)-**A** will also react with the achiral reagent to give a 1:2.3 mixture of **B'** and **C'**. Thus one expects a racemic mixture of the two diastereomers **B** and **C** in a ratio of 1:2.3.
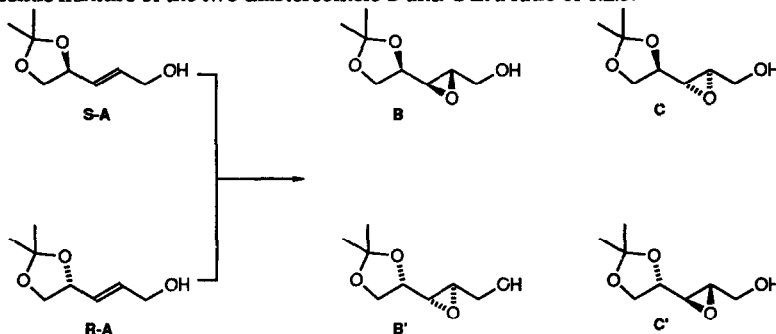
If racemic **A** is allowed to react with Ti(O*i*Pr)$_4$-(-)-tartrate and TBHP, (S)-**A** will give a 1:90 mixture of **B** and **C** (a matched pair, entry 4). On the other hand, (R)-**A** will produce a 22:1 mixture of **B'** and **C'** (cf. a mismatched pair, entry 5). Thus, when the reaction is forced to completion one expects a mixture of four stereoisomers, **B**, **C**, **B'**, and **C'** with 1:90:87:4 ratio, or an approximately 1:1.1 mixture of the two diastereomers **B'** (97.7%ee) and **C** (91.5%ee), and the racemic synthesis terminates. By the same arguments, the reaction using (+)-tartrate will produce a 1:1.1 mixture of **B** (97.7%ee) and **C'** (91.5%ee). It is interesting, albeit purely academic, to note that in this reaction with racemic substrate, the modest (*ca.* 2:1) diastereofacial bias of the substrate (for the *erythro*-epoxy alcohol) results in only a slight excess production of the erythro diastereomer with a lower optical purity, regardless of the sense of chirality of tartrate used.
30. A serious but easily solved problem was encountered in earlier work in which a benzyl unit was used as the protecting group for the C(6)-hydroxyl (i.e., C(4)-hydroxyl group of 6). In the presence of the titanium reagent, in the 4,5-erythro series the oxygen atom of the C(6)-benzyloxy group opened the epoxide to form the corresponding tetrahydrofurans. Changing the protecting group to the sterically bulkier benzhydryl unit prevented the unwanted anchimerically assisted opening by the ether oxygen.
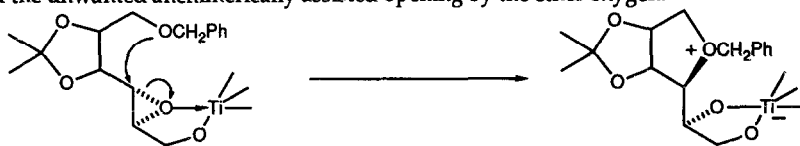
31. See p 31 of reference 27 for details.
32. Fanton, E.; Gelas, J.; Horton, D.; Karl, H.; Kahn, R.; Lee, C.-K.; Patel, G. *J. Org. Chem.* **1981**, *46*, 4057.
33. a) Peat, S. In "Advances in Carbohydrate Chemistry"; Pigman, W. W.; Wolfram, M. L., Eds.; Academic Press: New York, 1946; Vol. 2. b) Richtmyer, N. K.; Hudson, C. S. *J. Am. Chem. Soc.* **1935**, *57*, 1716.
34. Since each asymmetric epoxidation in the first and second turn of the cycle proceeded with >95:5 selectivity, the enantiomeric impurity (D-counterpart) present in each synthetic L-sugar should be less than 0.25%.
35. Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.
36. The yield of every reaction is shown in Scheme III. Optical rotations of all the synthetic hexoses, hexose pentaacetates and hexitol hexaacetates are given in the Experimental Section along with the literature values for comparison (see reference 37).
37. a) "Rodd's Chemistry of Carbon Compounds", 2nd Ed.; Coffey, S. Ed.; Elsevier Publishing Co.: Amsterdam, 1967; Vol. 1, Part F. b) "Handbook of Biochemistry and Molecular Biology, Lipids, Carbohydrates, Steroids", 3rd Ed.; Fasman, G. D. Ed.; CRC Press: Cleveland, 1975.
38. The synthetic L-altrose sample contains ca. 20% of 1,6-anhydro-β-L-altro-pyranose (*vide supra*).