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Stereoelectronic Factors in the Stereoselective Epoxidation of Glycals and 4-Deoxypentenosides

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Abstract

Glycals and 4-deoxypentenosides (4-DPs), unsaturated pyranosides with similar structures and reactivity profiles, can exhibit a high degree of stereoselectivity upon epoxidation with dimethyldioxirane (DMDO). In most cases, the glycals and their corresponding 4-DP isosteres share the same facioselectivity, implying that the pyran substituents are largely responsible for the stereodirecting effect. Fully substituted dihydropyrans are subject to a “majority rule,” in which the epoxidation is directed toward the face opposite to two of the three groups. Removing one of the substituents has a variable effect on the epoxidation outcome, depending on its position and also on the relative stereochemistry of the remaining two groups. Overall, we observe that the greatest loss in facioselectivity for glycals and 4-DPs is caused by removal of the C3 oxygen, followed by the C5/anomeric substituent, and least of all by the C4/C2 oxygen. DFT calculations based on polarized- π frontier molecular orbital (PPFMO) theory support a stereoelectronic role for the oxygen substituents in 4-DP facioselectivity, but less clearly so in the case of glycals. We conclude that the anomeric oxygen in 4-DPs contributes toward a stereoelectronic bias in facioselectivity whereas the C5 alkoxymethyl in glycals imparts a steric bias, which at times can compete with the stereodirecting effects from the other oxygen substituents.

Introduction

The class of 1,2-unsaturated sugar derivatives known as glycals is a widely valued source of starting materials in the synthesis of carbohydrates and their derivatives.^{1, 2, 3} Glycals can be converted by chemical degradation or stereoselective rearrangement into a variety of chiral synthons, but are especially useful as precursors of 1,2-anhydropyranosides, often referred to as glycal epoxides. The efficiency of this synthetic conversion has not always been so efficient: Aside from a few classic examples such as Brigl’s anhydride (3,4,6-tri-*O*-acetyl-1,2-anhydroglucose),⁴ a general method for generating glycal epoxides was not available until little more than 20 years ago, when Halcomb and Danishefsky demonstrated the use of dimethyldioxirane (DMDO) as a mild and stereoselective oxygen transfer agent.⁵ The synthetic potential of glycal epoxides has grown considerably since then, and is now considered as a major route toward the synthesis of *O*- and *C*-glycosides^{2, 6} and glycoconjugates,⁷ as well as highly substituted tetrahydropyrans in natural product syntheses.⁸

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Supporting Information Available. Selected coupling constants for pyranosides **30–45** and related diastereomers (Tables S1 and S2), and ¹H and ¹³C NMR spectra of new compounds **24**, **26**, **27**, **30–40**, **42–45**. This material is available free of charge via the Internet at <http://pubs.acs.org>. Output files for DFT and PPFMO calculations are available from the authors upon request.

4-Deoxypentenosides (4-DPs) are unsaturated pyranoside derivatives bearing a strong resemblance to glycals, but the sp^3 carbon next to the ring oxygen (i.e., C1 or C5) supports heteroatomic substituents rather than carbon (Figure 1).⁹ Like glycals, 4-DPs can be oxidized by DMDO into either 4 α - or 4 β -epoxypyranosides (4-EPs) in a highly facioselective manner.^{10,11} The 4-EPs are stable in solution, but can react with carbon nucleophiles to generate rare or unnatural sugars: For example, 4 β -EPs derived from α -glucosides react with organocuprates for *anti*-selective (S_N2) ring openings to generate novel pyranosides with an *L-altro* configuration,⁹ whereas 4 α -EPs derived from β -glucosides react with organozinc reagents for *syn*-selective ring openings to produce pyranosides with *L-ido* configuration.¹² These studies show that the reactivity profiles of 4-EPs are similar to that of glycal epoxides when treated with carbon nucleophiles, *en route* to the stereoselective formation of C-glycosides.⁶

Our earlier studies have shown that the facioselectivity of 4-DP epoxidation can be predicted on the basis of a “majority rule,” in which the oxygen is delivered *anti* to two of the three substituents on the dihydropyran ring, regardless of their relative position.¹⁰ This selectivity is not readily explained by previously described steric or stereoelectronic effects,¹³ and transition-state geometries derived from density functional theory (DFT) calculations do not suggest any torsional effects or hydrogen bonding interactions that might explain the high levels of stereoselectivity. We have attributed the observed facioselectivities to the asymmetric polarization of the π -bond itself, a notion that is supported by polarized- π molecular orbital (PPFMO) analysis using DFT for energy minimization.^{10,14} This has led us to consider whether the facioselectivity of DMDO-mediated oxidation of glycals is also attributable to a polarized- π effect: while the allylic C3 oxygen has been argued to have a major stereodirecting influence,⁵ the remaining substituents can also contribute toward a stereoelectronic asymmetry in π -bond reactivity.

PPFMO analysis has been previously used to rationalize stereoselective additions to glycals, although with mixed results.^{15,16} This may be due in part to a less than perfect match between theory and experiment, which involved charged species and the generation of cationic intermediates upon reaction with acid or electrophiles (e.g., halonium or sulfenium ions). Perturbation theories such as PPFMO are typically based on energy-minimized structures in the absence of other reactants,¹⁷ and may be more appropriate for investigating reactions with early transition states that do not require a large disturbance in the electronic or conformational ground state. In this regard, the DMDO oxidation of alkenes may be an ideal case because the nucleophilic π -bond experiences minimum distortion in electronic structure, as demonstrated in several transition-state analyses.^{10, 18} Nevertheless, the facioselectivity of glycal oxidation by DMDO has not yet been examined in the context of PPFMO analysis.

In this paper we describe the facioselective epoxidation of a series of glycals and their isosteric 4-DPs, using DMDO at low temperatures. This includes a set of glycals and 4-DP derivatives having only two substituents, whose stereochemical outcomes can no longer be predicted by a “majority rule.” The systematic removal of substituents at various positions enables us to address the relative impact of each on facioselectivity, and provides a useful testing ground for comparing experimental and computational results using PPFMO analysis. In particular, we wished to determine whether PPFMO theory could provide a reliable method for predicting the facioselectivity of these chiral dihydropyrans, based on the ground-state electronic structures of their π -bonds.

Results and Discussion

Synthesis of unsaturated pyranosides

Allal derivatives **1** and **3** and D-gulal derivatives **4** and **6** were prepared respectively from tri-*O*-acetyl-D-glucal and tri-*O*-acetyl-D-galactal, based on a synthetic sequence developed by Danishefsky and coworkers (Schemes 1 and 2).¹⁹ In brief, compound **1** was prepared in 36% overall yield from triacetyl glucal by a Ferrier rearrangement, followed by saponification, acetalization of the 4,6-diol, and benzylation of the remaining C3 alcohol. Perbenzylated allal **2** and 4-deoxyallal **3** were both prepared from 3,6-di-*O*-acetyl allal, which was generated from the Ferrier rearrangement intermediate in 59% yield by DMDO oxidation and Et₂NH-mediated [2,3]-sigmatropic rearrangement with simultaneous acyl migration from O-4 to O-3. Deacetylation followed by perbenzylation afforded **2** in 92% yield over two steps, whereas Barton–McCombie deoxygenation in DMF followed by an exchange of protecting groups yielded **3** in 22% yield over 4 steps. We note that the low isolated yield of the latter sequence was due in part to the volatile nature of 3,6-di-*O*-acetyl-4-deoxyallal, the product immediately following Barton McCombie deoxygenation, and can likely be improved by a judicious choice of organic solvent during extractive workup.

Gulal derivatives **4** and **6** were prepared from tri-*O*-acetyl galactal, as attempts to epimerize the C4 stereocenter of 3,6 di-*O*-acetyl allal proved unsuccessful. Treatment with benzenethiol in the presence of SnCl₄ at –78 °C resulted in a Ferrier rearrangement product in 98% yield (8:1 α:β mixture, Scheme 2), followed by DMDO oxidation, Et₂NH-mediated [2,3]-sigmatropic rearrangement, and chromatographic separation to afford the desired 4,6 di-*O*-acetyl gulal (83% isolated yield); an exchange of protecting groups led to tri-*O*-benzyl gulal **4** in 76% yield over four steps. 4,6-Benzylidene derivative **5** was obtained from the same Ferrier rearrangement product in 70% yield (8:1 α:β mixture), followed by the tandem oxidation–sigmatropic rearrangement and benzylation of the C3 alcohol to afford **6** in high stereochemical purity (45% isolated yield over three steps).

Deoxyglucal derivatives **8**, **9**, and **11** were synthesized from the common D-glucal precursor **7** (Scheme 3). Deoxygenation performed under standard Barton–McCombie conditions²⁰ produced 3-deoxyglucal **8** in 54% isolated yield, as well as a C3 allylstannane byproduct (36% yield). This unexpected byproduct is not without precedent: glycal derivatives have been converted into allylstannanes upon treatment with Bu₃SnH and photochemical activation.²¹ Regioselective cleavage of the 4,6-anisylidene acetal in **8** using dilute Bu₂BOTf²² and subsequent benzylation produced 3-deoxyglucal derivative **9** in 73% isolated yield. 4-Deoxyglucal **11** was prepared straightforwardly from **7** in 50% overall yield by using standard protecting group manipulations to obtain intermediate **10**, followed by Barton–McCombie deoxygenation.

3-Deoxygalactal derivatives **14** and **15** were most efficiently synthesized from 3-deoxygalactoside **13**, as the corresponding galactal was not amenable to various deoxygenation conditions (Scheme 4). C3 deoxygenation of thiophenyl galactoside **12** was achieved again using Barton–McCombie conditions, with careful attention paid to the reaction time and the stoichiometry of Bu₃SnH to avoid reductive desulfurization. Compound **13** was then cleanly converted into 3-deoxygalactal **14** in 78% yield by reductive elimination using lithium naphthalenide. The same chemistry was also applied toward the synthesis of di-*O*-benzyl derivative **15**; in this case, reductive ring cleavage and benzylation were performed prior to reductive elimination, to yield the desired 3-deoxygalactal in 40% overall yield from **13**. It is worth noting that the reductive lithiation approach toward 3-deoxygalactals is much more efficient than methods based on the vinylogous reduction of hex-2-enopyranosides using LiAlH₄²³ or the allylic reduction of galactals using

heterogeneous catalysts,²⁴ but the stoichiometry of Li-naphthalenide (2.5 equiv) and reaction temperature (−40 °C) need to be carefully controlled to avoid debenzylation.

The synthesis of fully substituted 4-DP derivatives (β -*Glc*, β -*Gal*, α -*Man*, α -*Glc*; see Figure 1) has been reported previously,^{9,10} and provide the basis for the synthesis of the 2,4- and 3,4-dideoxypentenosides (DDPs) described below (Scheme 5). 2,4-DDPs were prepared from D-glucosides **16** and **17** by C2 deoxygenation using Barton–McCombie conditions,²⁰ followed by acetal hydrolysis to yield 4,6-diols **18** and **19** respectively in high yields. Each of these was oxidized to a glucuronic acid using catalytic tetramethyl-1-piperidine oxide (TEMPO)²⁵ with bis(acetoxy)iodobenzene (BAIB) as the stoichiometric oxidant,²⁶ then heated under sealed-tube conditions with *N,N*-dimethylformamide dineopentyl acetal (DMFDNA), a reagent developed by Eschenmoser for the decarboxylative elimination of β -hydroxyacids.²⁷ This two-step sequence cleanly produced 2,4-DDPs **20** and **21** in 58% and 60% yields, respectively. 3,4-DDPs were prepared from D-glucosides **22** and **23** in a nearly identical fashion: C3 deoxygenation and acetal hydrolysis yielded 4,6-diols **24** and **25**, which were subjected to TEMPO/BAIB oxidation–decarboxylative elimination to generate 3,4-DDPs **26** and **27** in 60% and 28% overall yields from **22** and **23**. Again, the yields were adversely affected in some cases by the volatility of the desired products.

Lastly, pentopyranose derivatives 3,4-di-*O*-benzyl-D-xylal and -L-arabinal (**28** and **29**) were prepared using the reductive lithiation method described above. These compounds have been previously prepared via reductive elimination of their peracetylated glycosyl halides, typically by treatment with zinc dust/CuSO₄ followed by benzylation.²⁸ However, we found this condition to be too harsh for the synthesis of 3,4-di-*O*-acetyl-D-arabinal, which was obtained in low yields and susceptible to degradation upon storage at −20 °C. In contrast, reductive subjecting the thiophenyl glycosides of tribenzyl-D-xylose and tribenzyl-L-arabinose to Li-naphthalenide at −40 °C produced xylal **28** and arabinal **29** in quantitative yields (Scheme 6), without undue concern over their thermal stability.

Facioselectivity of epoxidation

Oxidations using DMDO are prized for their mildness and chemoselectivity,²⁹ as products can often be obtained in quantitative yields simply by concentrating the reaction mixture, then used without further workup or purification. Indeed, many of the epoxides generated by the DMDO oxidation of glycals and 4-DPs (epoxyglycals and 4-EPs) are stable at ambient temperatures, and react smoothly with good nucleophiles under S_N2 conditions. However, several of the disubstituted cases are susceptible to solvolysis and degrade at an appreciable rate upon warming. Product degradation can be minimized by preparing DMDO under “acetone-free” conditions in CH₂Cl₂, followed by further drying and concentration (see Experimental Section).³⁰ Maximum stereoselectivity can be achieved by conducting DMDO oxidations in CH₂Cl₂ at −55 °C, followed by concentration under reduced pressure at low temperatures to avoid thermal decomposition. Epoxidation at −55 °C often requires reaction times of 2–4 days to reach completion, but ensures the highest possible facioselectivities for systematic comparisons. It is also worth noting that benzylidene acetals can be oxidized by DMDO above 0 °C, generating orthoesters and benzoate esters as byproducts.^{31,32}

The facioselectivity of DMDO oxidation for the various glycals and their isosteric 4-DPs were typically determined by peak integration using the epoxyacetal peaks in the ¹H NMR spectra (Tables 1–4). Facioselectivity was confirmed in each case by epoxide ring opening using strong nucleophiles such as LiAlD₄ and LiSEt (Tables 5 and 6, see next section), and ¹H NMR coupling constant analysis to establish the relative stereochemistry of the S_N2 products. The high isolated yields of the ring-opening products permitted us to validate the stereochemical outcome of preceding DMDO addition. The tabulation of the stereochemical outcomes enables us to establish the following trends:

- i. All fully substituted glycals follow the empirical “majority rule”, independent of the relationship among contiguous stereocenters (Table 1). The facioselectivities of most substrates are 10:1 or higher, the primary exceptions being gual derivatives **4** and **6**, but even these exhibit modest selectivity and produce epoxyglycals favoring the α -epoxide (3:2 and 3:1 ratio respectively).³³ It is worth mentioning that DMDO oxidation of the guals is sluggish compared with other diastereomers and requires a reaction time of 4 days to reach completion at $-55\text{ }^{\circ}\text{C}$, implying a less electron-rich π -orbital.
- ii. The facioselectivities of the glycals essentially mirror those previously observed for the 4-DPs (Table 2).^{9,10} We note that the facioselectivity of α -*glc*-4-DP, the isosteric equivalent of gual, is temperature-dependent and is high only at $-55\text{ }^{\circ}\text{C}$, whereas that of β -*glc*-4-DP, the isosteric equivalent of glugal, remains high even at $0\text{ }^{\circ}\text{C}$.
- iii. For deoxygenated (disubstituted) glycals with unconstrained *cis* substituents (**11** and **15**) the DMDO oxidation remains highly *anti*-selective (Table 3). This selectivity is also maintained for the isosteric 4-DPs (**20** and **27**) and arabinal **29** (Table 4).
- iv. For *trans*-disubstituted dihydropyrans with an allylic C3 substituent (4-deoxyallal **3**, 2,4-dideoxypentenoxide **21**, and xylal **28**), the DMDO oxidation is directed *anti* to the C3 oxygen. In contrast, removal of the C3 group causes a loss in stereodirecting effect; facioselectivity is modest at best, slightly favoring *anti* to the C2/C4 oxygen.
- v. Modifying the conformational behavior of the ring has a variable effect on facioselectivity. Overall, glycal derivatives that are constrained by a 4,6-benzylidene acetal (**1**, **6**, **8**, and **14**) exhibit similar preferences toward DMDO oxidation as their perbenzylated congeners (**2**, **4**, **9**, and **15**). However, gual **6** and 3-deoxyglugal **8** have modestly higher facioselectivities than **4** and **9** respectively, whereas 3-deoxygalactal **14** has a lower facioselectivity than **15**.

It is worth pointing out that while the allylic C3 oxygen has the strongest stereodirecting effect, it is certainly not the sole determinant in facioselectivity for either the glycals or 4-DPs, as the remaining substituents can compensate for its absence in the case of *cis*-disubstituted dihydropyrans. It is also interesting to compare the facioselectivity of the glycals and 4-DPs with xylal derivative **28** (Table 4). This pentose-derived dihydropyran exhibits a lower stereochemical bias in its reaction with DMDO, indicating significant competition between the C2 and C3 substituents. Furthermore, comparison of xylal **28** with dideoxypentenoxides **21** and **26** (Table 4) and α -*glc*-4-DP (Table 2) shows that the C1 oxygen by itself has a weaker influence than either the C3 or C2 oxygen, yet can provide synergistic support to the C2 oxygen to completely override the allylic stereodirecting effect.

Stereochemical assignments based on epoxide ring opening

The facioselectivities of DMDO oxidations listed in Tables 1–4 were established by subjecting the epoxyglycals or 4-EPs to ring-opening reactions under S_N2 conditions (Tables 5–6), followed by acetylation in some cases to assist ^1H NMR coupling constant analysis. We found deuteride addition to be ideal for this purpose as it does not introduce new peaks to the ^1H NMR spectrum, and its low electronegativity (essentially that of H) supports large coupling constants for diaxial vicinal protons based on the parameterized Karplus equation.³⁴ However, some disubstituted species were less compatible with strong reducing agents such as LiAlD_4 , so were subjected instead to LiSEt in THF or to methanolysis at low temperature, all of which proceeded with inversion of configuration according to the large $J_{1,2}$ or $J_{4,5}$ values ($>8\text{ Hz}$; see Tables S1 and S2, Supporting

Information).³⁵ We note that the remaining coupling constants of the pyranosides listed in Tables 5 and 6 did not clearly indicate a preference for the ⁴C₁ chair conformation, as most of these values were small (see Experimental section). On the other hand, the *J* values of pyranosides **30** and **32** (derived from allal **2** and gulal **4**, respectively) are very similar to those of **31** and **33**, which are conformationally constrained by 4,6-benzylidene acetals and so likely to favor low-energy chair conformations.

Comparison between facioselective DMDO addition and PPFMO analysis

The PPFMO approach is based on a perturbation method that desymmetrizes the 2p orbitals of alkenes, following an energy minimization step.^{14,17} A qualitative analysis of stereoelectronic bias is made possible by introducing additional 1s-functions near the lobes of each 2p orbital; linear combination of these wavefunctions produces facially dependent coefficients (*c_α* and *c_β*) that describes the relative polarization in electron density. The polarization of each 2p orbital is calculated as $p = |c_{\alpha}^2 - c_{\beta}^2|$, and is assigned *α* or *β* according to the larger of the two coefficients. It should be noted that *c_α* is negative and *c_β* is positive by convention (see below), but *p* is presented as a positive value regardless of the polarization direction.

Although both 2p orbitals contribute toward the overall polarization of the *π*-bond their relative influences are unlikely to be equal, as the coefficients of the C2 orbital in glycals (or C4 orbital in 4-DPs) are larger in value than those at the other end of the double bond. Nevertheless, it is unnecessary to introduce a weighting factor for each 2p orbital because the *p* values scale with their coefficients. For example, if the relative difference between *c_α* and *c_β* is 5%, then the corresponding *p* value for that 2p orbital is approximately 0.1 *c_β*. Therefore, we consider the direct comparison of *p* values at C1 and C2 to be the simplest method of evaluating the polarized-*π* effect in glycals, analogous to the comparison of *p* values at C4 and C5 in 4-DPs.¹⁰ By the same token, one should be mindful that such comparisons are intended to be qualitative and are applicable for correlation with facioselectivity, but less appropriate for quantitative outcomes.

Here we use PPFMO analysis to address the facioselectivities of DMDO addition to disubstituted glycals and dideoxypentenoses (DDPs), several of which cannot be predicted straightforwardly by the empirical “majority rule.” The application of PPFMO analysis toward 4-DP facioselectivity has been previously described,¹⁰ and is concisely illustrated below using dimethyl 4-deoxyallal, the electronic analog of **3** (Figure 2). In brief, the structure is first subjected to energy minimization using DFT calculations (B3LYP/6–31+G(d,p)), starting from the idealized half-chair (⁴H₅) conformation. A pair of 1s orbitals is then introduced at set distances above and below the symmetric lobes of each 2p orbital as previously described,¹⁴ followed by PPFMO analysis to generate hybrid wavefunctions *χ* with asymmetric lobes, labeled here as *χ*(1*α*), *χ*(1*β*), *χ*(2*α*), and *χ*(2*β*). Each wavefunction contains the facially sensitive coefficients *c_α* and *c_β*, which are used to calculate the final *p* values for the desymmetrized 2p orbitals. In this case, the hybrid orbitals at C1 and C2 are polarized in different directions (*α* and *β* respectively), however the value of *p*(2) is greater than that of *p*(1) so the overall polarization of the *π*-bond is in the *β* direction, which is in accord with the experimental result.

We note that substituting each phenyl (C₆H₅) unit with H greatly reduces computational time and can be expected to have a minimum impact on PPFMO analysis, as determined by preliminary studies on various O3-substituted glycals (not shown). On the other hand, we observe that relatively small changes in the conformation of exocyclic substituents can have a strong influence on the polarization outcome of the 2p orbitals. The hybrid *χ* orbital at C2 (C4 in the case of 4-DPs) is especially sensitive to the dihedral angle of the C3–O3 bond because it can overlap with a nonbonding electron lone pair on O3, causing the value of *c_α*

to be artificially high. As a case in point, PPFMO analysis of 4-deoxyglucal **11** indicates a significant polarization in the α direction, as predicted, when the O3 methyl group adopts a *trans-gauche* (*tg*) orientation (C2-C3-O3-CH₃ dihedral angle = +180°), but an unusually large polarization in the β direction is observed when the O3 methyl group adopts a *gauche-trans* (*gt*) orientation (dihedral angle = +60°). Inspection of electron density maps confirms that the latter case is grossly distorted by the incidental overlap between χ (C2) and O3, which does not exist in the *tg* conformer (Figure 3). The gas-phase conformational energy of *gt* is also higher than that of *tg* (by *ca.* 3 kcal/mol), so should be less favored during DMDO oxidation because of potential steric interactions between the C3 substituent and the incoming oxidant. This leads us to conclude that hyperconjugative interactions between χ (C2) and O3 are not stabilizing and have no meaningful impact on the PPFMO analysis.

PPFMO analysis was performed on all disubstituted glycals and DDPs in their permethylated forms, starting from their lowest energy half-chair conformations (⁴H₅ and ²H₁, respectively). The use of low-energy conformations in PPFMO analysis is appropriate and does not violate the Curtin Hammett principle, as their geometries are very close to those observed in previous transition-state analyses of DMDO addition.^{10,18} Overall, these yielded polarization values that correlated well with the experimental outcomes from DMDO oxidation (Table 7). As expected, the polarized- π effect for structures corresponding to *cis*-disubstituted glycals (**11**, **14**, and **15**), 4-DPs (**20** and **27**) and arabinol **29** are clearly in line with the high *anti* selectivities observed after epoxidation. In the case of *trans*-disubstituted derivatives, those having a C3 oxygen such as 4-deoxyallal **3**, 2-deoxy- α -*glc*-4-DP **21**, and xylal **28** also exhibit polarizations that are well matched with the observed facioselectivities. On the other hand, the *p* values nearly cancel each other for analogs corresponding to 3-deoxyglucal **8** (4,6-acetal derivative) and 3-deoxy- β -*glc*-4-DP **26**, giving rise to ambiguous interpretations with respect to facioselectivity. This is also reflected by the experimental results, which indicate facioselectivities of 2:1 or less.

In the case of 3-deoxyglucal **9** the experimental results do not suggest any stereochemical preferences, but the ⁴H₅ conformation of the 3,6-di-*O*-methyl analog produces *p* values predicting α facioselectivity. However, energy minimization and PPFMO analysis of the alternate ⁵H₄ half-chair conformation indicates both C1 and C2 orbitals to be polarized in the β direction, opposite that of the ⁴H₅ conformer (Figure 4, *left*). The energy difference between conformations ($\Delta\Delta G_{\text{conf}}$) can be expected to be less than 1 kcal/mol,^{18d} meaning that neither ⁵H₄ nor ⁴H₅ is dominant under the DMDO oxidation conditions. A parallel study was conducted on the analog of the isosteric DDP, 3-deoxy- β -*glc* **26**: again, PPFMO analysis of the ¹H₂ conformation revealed the polarizations of the C4 and C5 orbitals to be essentially mirror images of those found in the ²H₁ conformer (Figure 4, *right*).

PPFMO analysis also yielded a strong correlation between π -bond polarization and facioselective DMDO oxidation for fully substituted 4-DPs,¹⁰ but was less successful in the case of fully substituted glycals. In particular, we were unable to correlate the facioselective epoxidation of D-glucal or D-allal derivatives (α or β respectively, see Table 1) with the polarization values derived from their tri-*O*-methyl analogs in their ⁴H₅ conformations, even after taking into account the variable effects of exocyclic conformations. However, PPFMO analysis of unprotected glucal and allal (i.e. 3,4,6-triols) produced net polarizations in agreement with the experimental results, as well as with earlier calculations derived from AM1 calculations.¹⁵ This may indicate that relatively remote effects like *O*-alkylation can exert a significant electronic influence on the outcome of perturbation-based models such as PPFMO, which limits its ability to predict stereochemical outcomes for complex organic compounds. Nevertheless, we find PPFMO analysis to be a useful probe of stereoelectronic bias for relatively simple molecules with multiple stereocenters, such as the substituted dihydropyrans investigated here.

Glycals and 4-DPs may also be different in their conformational behavior despite their apparent structural similarities, which may have some subtle ramifications for the basis of their facioselectivities. The C5 hydroxymethyl units in glycals are sterically more demanding than the C1 alkoxy substituents in 4-DPs; the latter may even be predisposed toward a pseudoaxial position due to the anomeric effect.¹³ The steric difference implies that 4-DPs are more flexible than glycals and experience less torsional strain when adopting transition-state geometries, possibly reducing their facioselectivities. Recent transition-state analyses of the DMDO oxidation of simple glycal and 4-DP derivatives support this notion: the α/β selectivity for glycals is defined by a difference in activation energy ($\Delta\Delta G^\ddagger$) on the order of 3 kcal/mol,^{18d} whereas that for 4-DPs is closer to 2 kcal/mol.¹⁰ Nevertheless, glycals and 4-DPs are clearly comparable in their facioselectivities (Tables 1 and 2), leading us to posit that the conformational flexibility of 4-DPs may be compensated for by the contribution of the C1 oxygen toward a stereoelectronic bias in reactivity, namely the polarized- π effect.

In summary, we find that 4-DPs and their isosteric glycals have similar facioselectivities, as demonstrated by DMDO oxidation at low temperatures. Epoxidation is highly stereoselective for the fully substituted 4-DPs and nearly all of the glycals, as well as for many disubstituted derivatives. In most cases, the high facioselectivities correlate well with a polarization of the alkene 2p orbitals by nearby oxygen substituents, as elucidated by PPFMO analysis. We find that while the allylic C3 oxygen provides the strongest polarization effect, the remaining exocyclic oxygens are also significant and can even override the allylic substituent. The C5 hydroxymethyl unit in glycals is less likely to contribute toward π -bond polarization and may even oppose it in some cases, but may influence facioselectivity instead through differential torsional strain. Conversely, the C1 alkoxy unit in 4-DPs is sterically less demanding but contributes significantly toward the polarized- π effect.

Experimental Section

General experimental methods

See Supporting Information.

Synthesis of glycals by reductive elimination

In a typical experiment, a 1.0 M lithium naphthalenide solution (100 mL) was prepared by dissolving naphthalene (12.8 g, 0.1 mol) in anhydrous, deoxygenated THF (100 mL), followed by the portionwise addition of finely divided Li metal (690 mg, 98.6 mmol). The reaction mixture was stirred at rt under an argon atmosphere for 16 h, until the lithium was completely dissolved. We note that this dark green solution can be maintained for at least two weeks at -20°C , under an inert atmosphere. A portion of Li-naphthalenide (2.4 mL, 1.0 M in THF) was added dropwise *via* addition funnel to a solution of thiophenyl glycoside (0.25 g, 0.54 mmol) in anhydrous THF (11 mL) at -40°C . Consumption of the Li-naphthalenide was determined by the loss of color from the reaction mixture, which was also monitored by TLC. The starting material was completely consumed after several hours at -40°C , and the reaction mixture was neutralized by the dropwise addition of 4:1 THF:AcOH (5 mL), then diluted with CH_2Cl_2 (10 mL) and washed with 0.5 M NaOH (10 mL). The combined organic extracts were washed with brine (20 mL) and dried over anhydrous Na_2SO_4 to afford the desired glycal.

Synthesis of 4-deoxypentenoses by decarboxylative elimination

In a typical experiment, a 4,6-diol (0.15 g, 0.56 mmol) was dissolved at rt in CH_2Cl_2 (20 mL) and H_2O (20 mL), then treated with TEMPO (17.3 mg, 0.11 mmol) and BAIB (0.54 g,

1.67 mmol) with vigorous stirring. After 1 h, the reaction mixture was quenched with satd $\text{Na}_2\text{S}_2\text{O}_3$ solution, extracted with EtOAc (3×20 mL), washed once with brine, dried over Na_2SO_4 , concentrated under reduced pressure and used without further purification. A solution of crude carboxylic acid (46.8 mg, 0.17 mmol) in degassed DMF (5 mL) was treated with DMF dineopentyl acetal (0.23 mL, 0.83 mmol) in a high-pressure reaction vessel. This was placed in a preheated oil bath at 200°C for 2 h, then cooled to rt and concentrated under reduced pressure to afford a dark brown oil. The residue was washed with H_2O (3×20 mL) and extracted with Et_2O (3×20 mL). The combined organic extracts were washed once with brine and dried over Na_2SO_4 prior to purification by silica gel chromatography.

Preparation of DMDO.²⁹

A 3-L, two-necked rb flask equipped with a large stirring bar and a condenser for reduced pressure distillation was charged with deionized H_2O (250 mL), NaHCO_3 (58 g), and acetone (200 mL). This mixture was stirred vigorously at 5°C and treated with potassium persulfate (120 g) in five portions at 3 min intervals. After the last addition, a moderate vacuum (20–30 mm Hg) was applied and the DMDO solution was condensed in a recovery flask (250 mL) at -78°C for 2 h. The DMDO was decanted from excess ice into a precooled flask, further dried over K_2CO_3 for a minimum of 10 min, then filtered to obtain a DMDO solution as a pale yellow liquid. The volume and concentration of the DMDO solution was typically 100 mL and 0.08 M respectively, as determined by NMR titration with thioanisole.

DMDO in “acetone-free” CH_2Cl_2 was prepared by diluting freshly distilled DMDO as described above (50 mL) with cold deionized water (50 mL), followed by extraction with CH_2Cl_2 (2×5 mL).³⁰ The organic extracts were washed at 5°C with a 0.01 M phosphate buffer, pH 7 (15 mL), then cooled to -78°C for 1 h to produce a thin layer of ice at the surface, which was removed by hand. The DMDO solution (0.4 M in CH_2Cl_2 as determined by thioanisole oxidation) was carefully transferred via syringe or cannula to a cold, dry flask, and stored at -20°C for up to two weeks.

DMDO epoxidation

In a typical reaction, a solution of 4-deoxypentenoside (55.1 mg, 0.123 mmol) in CH_2Cl_2 (1.5 mL) was treated at -55°C with a precooled solution of DMDO (0.92 mL, 0.4 M in CH_2Cl_2), stirred for 2 days, then concentrated under reduced pressure at -55°C for 15 min. The cooling bath was removed, and further concentrated under reduced pressure at 0°C for 30 min. The epoxide was used immediately without further purification.

Epoxide $\text{S}_{\text{N}}2$ ring opening

Three methods were developed for the nucleophilic ring opening of epoxypyranosides, using LiAlD_4 (Procedures 1 and 2) or MeOH (Procedure 3). Procedure 1 was applied toward derivatives bearing benzylidene acetals, whereas Procedure 2 was applied toward perbenzylated derivatives. Procedure 3 was applied toward epoxypyranosides that were determined to be incompatible with LiAlD_4 treatment. *Procedure 1:* A solution of epoxide (41 mg, 0.11 mmol) in 4:1 Et_2O :THF (1.25 mL) was treated with LiAlD_4 (43.2 mg, 0.99 mmol) at -78°C , then warmed slowly to rt and stirred for 18 h. The reaction was then cooled to -55°C and diluted with cold Et_2O (2 mL), prior to treatment with finely ground Glauber's salt ($\text{Na}_2\text{SO}_4 \cdot 10 \text{H}_2\text{O}$) to precipitate the aluminum salts. After stirring for 15 min at -55°C , the reaction mixture was warmed to rt and stirred until a clear separation between the organic and aqueous layers was observed. The combined organic layers were washed with brine and dried over Na_2SO_4 . *Procedure 2:* A solution of epoxide (42.1 mg, 0.123 mmol) in 4:1 Et_2O :THF (1.25 mL) was cooled to -78°C , followed by the portionwise addition of LiAlD_4 (46.7 mg, 1.11 mmol). The mixture was warmed to -10°C and stirred

for 7 h. The reaction was then cooled to $-55\text{ }^{\circ}\text{C}$ and quenched with K,Na-tartrate solution, followed by dilution with Et_2O (2 mL). The cooling bath was removed and the solution was warmed to rt and stirred for 1 h. The organic layers were extracted with EtOAc ($3 \times 20\text{ mL}$), washed once with brine, and dried over anhydrous Na_2SO_4 . *Procedure 3:* A rb flask containing epoxide (9.5 mg, 0.036 mmol) was charged with anhydrous MeOH (15 mL) precooled to $-78\text{ }^{\circ}\text{C}$, then slowly warmed to rt over a period of 14 hours. MeOH was removed by rotary evaporation followed by azeotropic distillation with toluene, then dried *in vacuo* to afford the desired methyl glycoside.

3,6-Di-*O*-benzyl-4-deoxy-D-allal (3)

A solution of 3,6-di-*O*-acetyl-D-allal³⁶ (184 mg, 0.80 mmol) in 1:1 $\text{THF}:\text{CS}_2$ (18 mL) was treated with a 60% dispersion of NaH in mineral oil (97 mg, 2.40 mmol) at $0\text{ }^{\circ}\text{C}$. After 15 min, the ice bath was removed and stirred for a further 30 min at rt, after which MeI (500 μL , 7.98 mmol) was added. The reaction mixture was stirred for 16 hours or until TLC indicated the disappearance of starting material, then quenched at $0\text{ }^{\circ}\text{C}$ with satd NH_4Cl (20 mL) and extracted with Et_2O ($3 \times 20\text{ mL}$). The combined organic extracts were washed with brine (20 mL), dried over Na_2SO_4 , and concentrated under reduced pressure. The resulting oil was purified by silica gel chromatography using a 0–15% EtOAc –hexanes gradient with 0.1% of Et_3N to afford the xanthate as a white solid (232 mg, 91%). The xanthate was redissolved in degassed DMF at rt (7.2 mL) and then treated with Bu_3SnH (0.97 mL, 4.15 mmol) and AIBN (5.9 mg, 0.36 mmol). The reaction mixture was heated at $120\text{ }^{\circ}\text{C}$ in a sealed tube for 30 min. The solution was allowed to cool to rt, and then diluted with Et_2O ($3 \times 10\text{ mL}$). The mixture was extracted, washed with H_2O ($3 \times 10\text{ mL}$) and brine (10 mL), dried over Na_2SO_4 and concentrated. The resulting residue was redissolved in CH_3CN (10 mL) and extracted with hexane ($3 \times 10\text{ mL}$). The acetonitrile extracts were concentrated under reduced pressure to afford a volatile oil. The crude 3,6-di-*O*-acetyl-4-deoxy-D-allal was redissolved in MeOH (7.2 mL), treated at $0\text{ }^{\circ}\text{C}$ with NaOMe (1.4 mL, 1.0 M in MeOH , 1.44 mmol) and stirred for 15 min. The ice bath was removed and the reaction mixture was stirred at rt for an additional 16 h. The reaction mixture was concentrated under reduced pressure and residual MeOH was removed by azeotropic distillation with toluene ($3 \times 5\text{ mL}$). The crude diol was then redissolved in anhydrous DMF (7.2 mL), cooled to $0\text{ }^{\circ}\text{C}$ under argon, and treated with BnBr (428 μL , 3.60 mmol), TBAI (53 mg, 0.14 mmol) and a 60% dispersion of NaH in mineral oil (144 mg, 3.60 mmol). The reaction was stirred at rt overnight, quenched at $0\text{ }^{\circ}\text{C}$ with satd NH_4Cl (10 mL), then extracted with Et_2O ($3 \times 10\text{ mL}$). The combined organic phase was washed with H_2O ($3 \times 10\text{ mL}$) and brine (10 mL), dried over Na_2SO_4 , and concentrated under reduced pressure. The residue was purified by silica gel chromatography using a 0–5% Et_2O –pentanes gradient to afford dibenzylated 4-deoxyallal **3** as a white solid (49.2 mg, 22% overall yield). ^1H NMR (300 MHz, C_6D_6): δ 7.17–7.05 (m, 10 H), 6.49 (d, 1 H, $J = 6.0\text{ Hz}$), 4.87 (dt, 1 H, $J = 1.8, 6.0\text{ Hz}$), 4.44–4.26 (m, 5 H), 3.66 (m, 1 H), 3.43 (d, 2 H, $J = 3.9\text{ Hz}$), 1.94 (br dd, 1 H, $J = 1.8, 14.4\text{ Hz}$), 1.64 (ddd, 1 H, $J = 3.9, 12.3, 14.7\text{ Hz}$). ^{13}C NMR (75 MHz, C_6D_6): δ 146.9, 139.4, 138.7, 128.2, 100.5, 73.1, 72.2, 71.1, 69.1, 66.0, 31.1. IR (NaCl): 3447, 2971, 1454, 1377, 1103 cm^{-1} . $[\alpha]^{25} = +45.0^{\circ}$ (c 0.2, CHCl_3). HRESI-MS: m/z calcd for $\text{C}_{20}\text{H}_{22}\text{O}_3$ $[\text{M}+\text{Na}]^+$ 333.1467, found 333.1465.

3,4,6-Tri-*O*-benzyl-D-gulal (3,4,6-Tri-*O*-benzyl-D-xylohex-1-enitol) (4)

Phenyl 4,6-di-*O*-acetyl-2,3-dideoxy-1-thio- α -D-threo-hex-2-enopyranoside³⁷ (188 mg, 0.58 mmol) was dissolved in CH_2Cl_2 (6 mL) and treated with a precooled solution of DMDO in acetone (0.08 M, 1 equiv) at $-78\text{ }^{\circ}\text{C}$ for 1 h. The reaction mixture was concentrated under reduced pressure in an ice bath to a colorless solid, redissolved at rt in THF (12 mL), then treated with diethylamine (0.3 mL, 3 mmol) and stirred for 16 h. The reaction mixture was concentrated under reduced pressure and purified by silica gel chromatography using a 0–

40% EtOAc–hexanes gradient with 0.1% Et₃N to afford the desired 4,6-di-*O*-acetyl-D-gulal as a dark brown oil (112 mg, 83%).

A portion of this intermediate (52 mg, 0.22 mmol) was redissolved in MeOH (2.5 mL), treated at 0 °C with NaOMe (1.0 M in MeOH, 0.11 mmol) and stirred for 15 min. The ice bath was removed and the reaction mixture was stirred at rt for an additional 16 h. The reaction mixture was concentrated under reduced pressure and residual MeOH was removed by azeotropic distillation with toluene (3 × 5 mL). The crude triol was dried by azeotropic distillation with toluene, then redissolved in anhydrous DMF (2.5 mL), cooled to 0 °C under argon, and treated with BnBr (0.12 mL, 0.99 mmol), TBAI (16 mg, 0.04 mmol) and a 60% dispersion of NaH in mineral oil (53 mg, 1.32 mmol). The reaction was stirred at rt overnight, quenched at 0 °C with satd NH₄Cl (10 mL), then extracted with Et₂O (3 × 10 mL). The combined organic phase was washed with H₂O (3 × 10 mL) and brine (10 mL), dried over Na₂SO₄, and concentrated under reduced pressure. The residue was purified by silica gel chromatography using a 0–15% EtOAc–hexanes gradient with 0.1% Et₃N to afford tribenzyl-D-gulal **4** as white solid (83.7 mg, 91% over 3 steps). ¹H NMR (300 MHz, C₆D₆): δ 7.24–7.08 (m, 15 H), 6.56 (d, 1 H, *J* = 6.6 Hz), 4.89 (dd, 1 H, *J* = 1.8, 6.3 Hz), 4.51 (dt 1 H, *J* = 1.8, 5.1 Hz), 4.51–4.25 (m, 6 H), 3.89–3.84 (m, 3 H), 3.81 (dd, 1 H, *J* = 1.8, 5.4 Hz). ¹³C NMR (75 MHz, C₆D₆): δ 146.7, 139.0, 128.3, 128.3, 128.1, 98.5, 73.3, 73.1, 72.9, 72.0, 69.4, 68.7, 67.2. IR (NaCl): 2873, 1640, 1452, 1245, 1098, 1062 cm^{−1}. [α]_D²⁵ = −37° (*c* 0.7, CH₂Cl₂). HRESI-MS: *m/z* calcd for C₂₇H₂₈O₄ [M+H]⁺ 439.1885, found 439.1891.

Phenyl 4,6-*O*-Benzylidene-2,3-dideoxy-1-thio- α -D-*erythro*-hex-2-enopyranoside (**5**)

Phenyl 4,6-di-*O*-acetyl-2,3-dideoxy-1-thio- α -D-*threo*-hex-2-enopyranoside³⁷ (514 mg, 1.59 mmol) was redissolved in MeOH (4 mL) and treated with NaOMe in MeOH (1 M, 1.16 mmol) at 0 °C and stirred for 15 min. The ice bath was removed and the reaction mixture was stirred at rt for an additional 16 h. The reaction mixture was concentrated under reduced pressure and the residual MeOH was removed by azeotropic distillation with toluene (3 × 5 mL). The crude 4,6-diol (487 mg, 2.0 mmol) was redissolved in DMF (20 mL) and treated with benzaldehyde dimethyl acetal (0.92 mL, 12 mmol) and *p*-toluenesulfonic acid (78 mg, 0.4 mmol). After stirring at rt for 2 h, the reaction was heated to 30 °C for another 2 h with partial removal of solvent under reduced pressure (10 mm Hg). The reaction mixture was neutralized with satd NaHCO₃ (20 mL) and then extracted with Et₂O (3 × 20 mL). The combined organic phase was washed with H₂O (3 × 20 mL) and brine (20 mL), dried over Na₂SO₄, and concentrated under reduced pressure. The residue was purified by silica gel chromatography using a 10–50% EtOAc–hexanes gradient with 0.1% Et₃N to afford benzylidene acetal **5** as white crystals (468 mg, 70% over 2 steps). ¹H NMR (300 MHz, CDCl₃): δ 7.67–7.32 (m, 10 H), 6.33 (dd, 1 H, *J* = 3.6, 9.9 Hz), 6.20 (ddd, 1 H, *J* = 1.8, 5.7, 9.9 Hz), 6.15 (dd, 1 H, *J* = 2.1, 3.3 Hz), 5.71 (s, 1 H), 4.48 (d, 1 H, *J* = 12.9 Hz), 4.40–4.35 (m, 2 H), 4.30 (br s, 1 H). ¹³C NMR (75 MHz, CDCl₃): δ 137.9, 137.9, 135.5, 131.1, 130.8, 129.1, 128.3, 127.3, 126.3, 125.3, 100.9, 84.2, 70.0, 67.9, 62.7. IR (NaCl): 2865, 1583, 1478, 1383, 1330, 1140, 1058 cm^{−1}. [α]_D²⁵ = −0.02° (0.4, CH₂Cl₂). HRESI-MS: *m/z* calcd for C₁₉H₁₈O₃ S [M+H]⁺ 349.0874, found 349.0870.

3-*O*-Benzyl-4,6-*O*-benzylidene-D-gulal (**6**)

Thiophenyl glycoside **5** (468 mg, 1.43 mmol) dissolved in CH₂Cl₂ (14 mL) was treated with a precooled solution of DMDO in acetone (0.08 M, 1 equiv) at −78 °C for 1 h. The resulting sulfoxide was concentrated under reduced pressure in an ice bath to a colorless solid, redissolved in THF (29 mL), then treated with diethylamine (0.7 mL, 7.15 mmol), and stirred at rt for 16 h. The reaction mixture was concentrated under reduced pressure and purified by silica gel chromatography using a 10–50% EtOAc–hexanes gradient with 0.1%

Et₃N to yield a D-gulal intermediate as white crystals (148 mg, 44%) along with recovered thiophenyl glycoside (47 mg, 14%).

A portion of this intermediate (147 mg, 0.63 mmol) was dried by azeotropic distillation with toluene, then redissolved in anhydrous THF (6 mL), cooled to 0 °C under argon, and then treated with BnBr (0.19 mL, 1.57 mmol) and TBAI (46 mg, 0.12 mmol), and a 60% dispersion of NaH in mineral oil (75 mg, 1.89 mmol). The reaction was stirred at rt overnight, then quenched at 0 °C with satd NH₄Cl (20 mL) and then extracted with Et₂O (3 × 20 mL). The combined organic extracts were washed with H₂O (3 × 20 mL) and brine (20 mL), dried over Na₂SO₄, and concentrated under reduced pressure. The residue was purified by silica gel chromatography using a 0–20% EtOAc–hexanes gradient with 0.1% of Et₃N to afford 3-*O*-benzyl-D-gulal **6** as white solid (158 mg, 77%). ¹H NMR (300 MHz, C₆D₆): δ 7.67–7.15 (m, 10 H), 6.56 (d, 1 H, *J* = 6.6 Hz), 5.37 (s, 1 H), 4.86 (ddd, 1 H, *J* = 1.2, 4.8, 7.5 Hz), 4.51–4.30 (m, 2 H), 4.19 (dd, 1 H, *J* = 1.8, 12.3 Hz), 3.92 (br s, 1 H), 3.81 (dd, 1 H, *J* = 2.1, 4.8 Hz), 3.62 (br s, 1 H), 3.44 (dd, 1 H, *J* = 0.9, 12.3 Hz). ¹³C NMR (75 MHz, C₆D₆): δ 146.5, 138.6, 128.3, 128.1, 128.0, 127.8, 126.5, 100.9, 97.2, 73.8, 69.3, 69.0, 68.7, 65.6. IR (NaCl): 1643, 1451, 1259 cm⁻¹. [α]_D²⁵ = +197° (*c* 0.5, CH₂Cl₂). HRESI-MS: *m/z* calcd for C₂₀H₂₀O₄ [M+H]⁺ 325.1440, found 325.1444.

3-Deoxy-4,6-*p*-methoxybenzylidene-D-glucal (**8**)

A solution of acetal **7** (75 mg, 0.28 mmol) in 1:1 THF/CS₂ (7 mL) was treated with a 60% dispersion of NaH in mineral oil (34 mg, 0.85 mmol) at 0 °C. After 15 min, the ice bath was removed and stirred for a further 30 min at rt, after which MeI (0.18 mL, 2.83 mmol) was added. The reaction mixture was stirred for 16 hours or until TLC indicated the disappearance of starting material, then quenched at 0 °C with satd NH₄Cl (10 mL) and extracted with CH₂Cl₂ (3 × 15 mL). The combined organic extracts were washed with brine (15 mL), dried over Na₂SO₄, and concentrated under reduced pressure. The resulting residue was purified by silica gel chromatography using a 0–15% EtOAc–hexanes gradient with 0.1% of Et₃N to afford the C3 xanthate as a white solid (82 mg, 81%).

The intermediate xanthate (0.95 g, 2.68 mmol) was redissolved in degassed toluene at rt (27 mL) and then treated with Bu₃SnH (3.6 mL, 13.40 mmol) and AIBN (22 mg, 1.34 mmol). The reaction mixture was heated at reflux for 30 min. The solution was allowed to cool to rt, and the volatiles were removed under reduced pressure. The residue was purified by silica gel chromatography using a 0–5% EtOAc–hexanes gradient with 0.1% of Et₃N to afford 4,6-*p*-methoxybenzylidene acetal **8** as a white solid (360 mg, 54% over 2 steps) along with a C3 allylstannane byproduct as a single diastereomer (611 mg). ¹H NMR (400 MHz, C₆D₆): δ 7.55–6.79 (m, 4 H), 6.16 (dt, 1 H, *J* = 1.2, 6.0 Hz), 5.36 (s, 1 H), 4.40 (dt, 1 H, *J* = 2.4, 5.6 Hz), 4.26 (dd, 1 H, *J* = 4.8, 10.4 Hz), 3.70 (dd, 1 H, *J* = 4.8, 9.2 Hz), 3.64 (dd, 1 H, *J* = 2.8, 9.2 Hz), 3.56 (m, 1 H), 3.25 (s, 3 H), 2.14 (m, 2 H). ¹³C NMR (100 MHz, C₆D₆): δ 160.2, 143.1, 130.7, 113.4, 113.4, 101.6, 98.4, 74.8, 70.2, 68.7, 54.5, 26.4. IR (NaCl): 2875, 1641, 1609, 1517, 1248, 1085, 1000 cm⁻¹. [α]_D²⁵ = +40.9° (*c* 0.2, CH₂Cl₂). HR-EI-MS: *m/z* calcd for C₁₄H₁₆O₄ [M]⁺ 248.1049, found 248.1049.

4-*O*-Benzyl-3-deoxy-6-*O*-*p*-methoxybenzylidene-D-glucal (**9**)

Acetal **8** (279 mg, 1.12 mmol) was dissolved in freshly distilled THF (23 mL), cooled to –78 °C under argon and then treated with borane–THF complex (5.6 mL of a 1 M solution in THF). After 15 min, the mixture was treated with Bu₂BOTf (2.8 mL of a 1 M solution in THF) and stirred for another 16 h at –78 °C. The reaction mixture was quenched at this temperature with Et₃N (1.4 mL), followed by dropwise addition of MeOH (5 mL). The cooling bath was removed and the mixture was allowed to warm to rt and stirred for 30 min, then concentrated under reduced pressure to yield a 4:1 mixture of 6- and 4-*O*-PMB ethers,

which were separated by silica gel chromatography using a 5–20% EtOAc–hexanes gradient with 0.1% Et₃N. It is worth noting that the alcohol can be contaminated by residual Bu₂BOH (formed upon aqueous workup), but this impurity can be removed by multiple rounds of azeotropic distillation with MeOH.

The 6-*O*-PMB ether (273 mg, 1.09 mmol) was dried by azeotropic distillation with toluene, then dissolved in anhydrous THF (11 mL), cooled to 0 °C under argon, and then treated with BnBr (0.32 mL, 2.72 mmol) and TBAI (81 mg, 0.22 mmol), and a 60% dispersion of NaH in mineral oil (131 mg, 3.27 mmol). The reaction was stirred at rt overnight, then quenched at 0 °C with satd NH₄Cl (20 mL) and then extracted with Et₂O (3 × 20 mL). The combined organic extracts were washed with H₂O (3 × 20 mL) and brine (20 mL), dried over Na₂SO₄, and concentrated under reduced pressure. The residue was purified by silica gel chromatography using a 0–10% EtOAc–hexanes gradient with 0.1% of Et₃N to afford benzyl ether **9** as white solid (270 mg, 73% over 2 steps). ¹H NMR (300 MHz, (CD₃)₂CO): δ 7.41–7.01 (m, 9 H), 6.39 (d, 1 H, *J* = 5.7 Hz), 4.77–4.56 (m, 5 H), 3.92–3.82 (m, 4 H) 3.86 (s, 3 H), 2.49 (dt, 1 H, *J* = 16.8, 4.8 Hz), 2.11 (d, 1 H, *J* = 7.5 Hz). ¹³C NMR (75 MHz, CDCl₃): δ 159.4, 143.3, 138.9, 130.7, 129.2, 128.3, 128.1, 113.8, 97.3, 77.3, 73.0, 70.8, 70.6, 68.8, 54.5, 26.7. IR (NaCl): 2907, 2865, 1654, 1609, 1512, 1240 cm⁻¹. [α]_D²⁵ = +44.3° (*c* 1.1, CH₂Cl₂). HR-EI-MS: *m/z* calcd for C₂₁H₂₄O₄ [M]⁺ 340.1675, found 340.1679.

3,6-Di-*O*-benzyl-D-glucal (10)

A solution of C3 alcohol **7** (1.79 g, 6.78 mmol) was dried by azeotropic distillation with toluene, then redissolved in anhydrous DMF (66 mL), cooled to 0 °C under argon, and then treated BnBr (1.21 mL, 10.18 mmol), TBAI (0.50 g, 1.36 mmol), and a 60% dispersion of NaH in mineral oil (0.41 g, 10.18 mmol). The reaction was stirred at rt overnight, then quenched at 0 °C with satd NH₄Cl (50 mL) and extracted with Et₂O (3 × 50 mL). The combined organic extracts were washed with H₂O (3 × 50 mL) and brine (50 mL), dried over Na₂SO₄, and concentrated under reduced pressure. The residue was purified by silica chromatography using a 5–30% EtOAc–hexanes gradient with 0.1% of Et₃N to afford the corresponding 3-*O*-benzyl ether as white solid (2.21 g, 92%).

A portion of this protected glucal (770 mg, 2.17 mmol) was redissolved in CH₂Cl₂ (13 mL) and cooled to 0 °C, then treated with *i*Bu₂AlH (10 mL of a 1 M solution in hexanes) and stirred for 2 h, after which the reaction mixture was quenched with satd NH₄Cl (25 mL) and satd K, Na-tartrate (20 mL). The organic layers were extracted with CHCl₃ (3 × 50 mL), then dried over Na₂SO₄ and purified by silica gel chromatography using a 30–50% EtOAc–hexanes gradient with 0.1% Et₃N to afford the desired 4-*O*-PMB ether as a clear syrup (712 mg, 92%).

A portion of the 4-*O*-PMB ether (540 mg, 1.51 mmol) was dried by azeotropic distillation with toluene, then redissolved in anhydrous DMF (10 mL), cooled to 0 °C under argon, and then treated with BnBr (0.63 mL, 5.29 mmol), and a 60% dispersion of NaH in mineral oil (220 mg, 5.29 mmol). The reaction was stirred at rt overnight, then quenched at 0 °C with satd NH₄Cl (20 mL) and extracted with Et₂O (3 × 20 mL). The combined organic extracts were washed with H₂O (3 × 20 mL) and brine (20 mL), dried over Na₂SO₄, then concentrated and purified by silica gel chromatography using a 10–25% EtOAc–hexanes gradient with 0.1% Et₃N to afford the corresponding 6-*O*-benzyl ether as a colorless syrup (633 mg, 93%). This was redissolved in CH₂Cl₂ (40 mL), *i*BuOH (2.5 mL), and pH 7 phosphate buffer (7 mL), then treated at 0 °C with DDQ (965 mg, 4.26 mmol). The reaction mixture was stirred vigorously at rt for another 3 h, quenched with satd NaHCO₃ (20 mL) and extracted with CH₂Cl₂ (3 × 20 mL). The organic layers were washed with brine (25 mL), dried over Na₂SO₄, then concentrated and purified by silica gel chromatography using

a 10–50% EtOAc–hexanes gradient with 0.1% Et₃N to afford 4,6-dibenzyl glucal **10** as a colorless syrup (360 mg, 78%). ¹H NMR (300 MHz, C₆D₆): δ 7.30–7.07 (m, 10 H), 6.20 (dd, 1 H, *J* = 1.4, 7.5 Hz), 4.67 (dd, 1 H, *J* = 2.3, 6.2 Hz), 4.52–4.42 (m, 2 H), 4.34–4.26 (m, 2 H), 4.08 (ddd, 1 H, *J* = 3.8, 6.7, 9.0 Hz), 3.98 (dt, 1 H, *J* = 6.7, 1.8 Hz), 3.90–3.85 (m, 1 H), 3.71 (dd, 1 H, *J* = 4.8, 10.6 Hz), 3.66 (dd, 1 H, *J* = 3.6, 10.6 Hz), 2.26 (d, 1 H, *J* = 3.9 Hz). ¹³C NMR (100 MHz, C₆D₆): δ 144.8, 139.4, 138.8, 128.1, 128.0, 127.9, 127.8, 100.6, 78.0, 76.8, 73.7, 70.8, 69.5, 68.8. IR (NaCl): 2861, 1642, 1453, 1235, 1095, 1069, 1028, 735, 697 cm^{−1}.

3,6-Di-O-benzyl-4-deoxy-D-glucal (**11**)

A solution of glucal **10** (60 mg, 0.18 mmol) in 1:1 THF:CS₂ (5 mL) was treated with a 60% dispersion of NaH in mineral oil (30 mg, 0.54 mmol) at 0 °C. After 15 min, the ice bath was removed and stirred for a further 30 min at rt, then treated with CH₃I (0.4 mL, 6.42 mmol) and stirred for 16 hours or until TLC indicated the disappearance of starting material. This reaction mixture was quenched with saturated NH₄Cl solution (5 mL), extracted with CH₂Cl₂ (3 × 25 mL), washed with brine (5 mL), dried over anhydrous Na₂SO₄, and concentrated under reduced pressure. The crude C4 xanthate was redissolved in degassed toluene (3 mL) and then treated with Bu₃SnH (0.4 mL, 2.39 mmol) and AIBN (2 mg, 0.01 mmol) at rt. After 5 min, the reaction mixture was heated at reflux and stirred for a further 15 min. The solution was allowed to cool to rt, and the volatiles were removed under reduced pressure. The residue was purified by silica gel chromatography using a 10–20% EtOAc–hexanes gradient with 0.1% of Et₃N to afford 4-deoxyglucal **11** as a colorless oil (47 mg, 82% over 2 steps). ¹H NMR (300 MHz, C₆D₆): δ 7.30–7.10 (m, 10 H), 6.32 (d, 1 H, *J* = 6.6 Hz), 4.82 (dt, 1 H, *J* = 6.3, 1.2 Hz), 4.32 (d, 4 H), 4.02 (m, 1 H), 3.93 (ddt, 1 H, *J* = 2.4, 1.2, 6.6 Hz), 3.54 (ddd, 1 H, *J* = 1.2, 6.0, 10.2 Hz), 3.38 (ddd, 1 H, *J* = 0.9, 6.0, 10.2 Hz), 1.96–1.78 (m, 2 H). ¹³C NMR (75 MHz, C₆D₆): δ 144.8, 139.3, 138.7, 128.3, 128.2, 128.1, 127.7, 127.5, 127.4, 127.3, 102.8, 73.7, 73.1, 72.0, 69.5, 68.7, 31.1. [α]_D²⁵ = −16.0° (c 1.0, CHCl₃).

Thiophenyl 2-O-Benzyl-3-deoxy-4,6-*p*-methoxybenzylidene-D-galactoside (**13**)

A solution of alcohol **12** (0.40 g, 0.85 mmol) in 1:1 THF:CS₂ (16 mL) was treated with a 60% dispersion of NaH in mineral oil (61 mg, 2.55 mmol) at 0 °C. After 15 min, the ice bath was removed and the reaction mixture was stirred for 30 min at rt, then treated with CH₃I (0.26 mL, 4.26 mmol) and stirred for 16 hours or until TLC indicated the disappearance of starting material. The reaction mixture was quenched with saturated NH₄Cl solution (5 mL), extracted with CH₂Cl₂ (3 × 25 mL), washed with brine (5 mL), dried over anhydrous Na₂SO₄, and concentrated under reduced pressure. The resulting residue was purified by silica gel chromatography using 20% EtOAc in hexanes with 0.1% of Et₃N to afford the C3 xanthate as a white solid (0.44 g, 91%). This was redissolved in degassed toluene (8 mL) and treated with Bu₃SnH (1.04 mL, 3.88 mmol) and AIBN (64 mg, 0.39 mmol), then heated to reflux and stirred for another 30 min. The reaction mixture was allowed to cool to rt, and the volatiles were removed under reduced pressure. The residue was purified by silica gel chromatography using a 0–30% EtOAc–hexanes gradient with 0.1% Et₃N to afford 3-deoxygalactoside **13** as a white solid (0.26 g, 75%). ¹H NMR (400 MHz, C₆D₆): δ 7.88–6.84 (m, 14 H), 5.24 (s, 1 H), 4.61 (d, 1 H, *J* = 9.3 Hz), 4.52–4.17 (m, 2 H), 4.08 (d, 1 H, *J* = 11.7 Hz), 3.89 (dt, 1 H, *J* = 10.8, 5.4 Hz), 3.38–3.35 (m, 2 H), 3.26 (s, 3 H), 2.55 (s, 1 H), 2.31 (ddd, 1 H, *J* = 4.8, 7.8, 10.5 Hz), 1.37 (ddd, 1 H, *J* = 3.6, 10.4, 11.1 Hz). ¹³C NMR (100 MHz, C₆D₆): δ 138.8, 138.7, 135.7, 131.7, 128.7, 128.7, 128.2, 128.2, 128.1, 127.9, 127.7, 127.4, 126.7, 89.5, 79.1, 73.1, 72.9, 72.2, 71.8, 70.9, 69.3, 34.1. IR (NaCl): 2854, 1612, 1517, 1391, 1517, 1248, 1101 cm^{−1}. [α]_D²⁵ = −6.7° (c 0.7, CHCl₃). HRESI-MS: *m/z* calcd for C₂₇H₂₈O₅S [M+H]⁺ 465.1736, found 465.1738.

3-Deoxy-4,6-*p*-methoxybenzylidene-D-galactal (14)

A solution of thiophenyl galactoside **13** (249 mg, 0.54 mmol) in THF (11 mL) was subjected to reductive elimination conditions as previously described, then purified by silica gel chromatography using a 5–30% EtOAc–hexanes gradient with 0.1% Et₃N to afford the desired 3-deoxygalactal **14** as a white solid (104 mg, 78%). ¹H NMR (400 MHz, C₆D₆): δ 7.62 (d, 2 H), 6.78 (d, 2 H), 6.43 (d, 1 H, *J* = 6.3 Hz), 5.37 (s, 1 H), 4.45 (m, 1 H), 4.16 (dd, 1 H, *J* = 1.8, 12.3 Hz), 3.52 (br s, 1 H), 3.43 (dd, 1 H, *J* = 1.8, 12.3 Hz), 3.23 (s, 3 H), 3.09 (br s, 1 H), 2.00 (br s, 2 H). ¹³C NMR (100 MHz, C₆D₆): δ 160.1, 143.0, 131.4, 127.9, 127.8, 127.7, 127.4, 113.3, 101.3, 96.0, 70.7, 69.3, 67.2, 54.4, 25.9. IR (NaCl): 2918, 1733, 1649, 1520, 1396, 1248, 1074 cm⁻¹. [α]_D²⁵ = +2.5° (*c* 0.2, CH₂Cl₂). HR-EI-MS: *m/z* calcd for C₁₄H₁₆O₄ [M]⁺ 248.1049, found 248.1044.

4,6-Di-*O*-benzyl-3-deoxy-D-galactal (15)

A 50 mL round bottom flask containing **13** (82 mg, 0.18 mmol) was dissolved in 8:1:1 AcOH:THF:H₂O (1.8 mL) and heated to 45 °C for 5 h. The reaction mixture was neutralized with NaHCO₃ (20 mL), washed with brine (20 mL), dried over Na₂SO₄, concentrated to dryness and used without further purification. The crude 4,6-diol was dried by azeotropic distillation with toluene, then redissolved in anhydrous DMF (1.8 mL), cooled to 0 °C under argon, and treated with BnBr (63 μL, 0.53 mmol), TBAI (13 mg, 0.04 mmol), and a 60% dispersion of NaH in mineral oil (28 mg, 0.7 mmol). The reaction was stirred at rt overnight, then quenched at 0 °C with satd NH₄Cl (20 mL) and extracted with Et₂O (3 × 20 mL). The combined organic extracts were washed with H₂O (3 × 20 mL) and saturated brine (20 mL), dried over Na₂SO₄, and concentrated under reduced pressure. The residue was purified by silica gel chromatography using a 0–10% EtOAc–hexanes gradient to afford the corresponding 4,6-dibenzyl ether as a white solid (61 mg, 66% over 2 steps). This intermediate (55 mg, 0.10 mmol) was dissolved in anhydrous THF was subjected to the reductive elimination conditions described above, and purified by silica gel chromatography using a 5–20% EtOAc–hexanes gradient with 0.1% Et₃N to afford desired 3-deoxygalactal **15** as a white solid (20 mg, 60%). ¹H NMR (400 MHz, C₆D₆): δ 7.27–7.08 (m, 10 H), 6.39 (dt, 1 H, *J* = 4.7, 1.8 Hz), 4.44 (m, 1 H), 4.38–4.18 (m, 5 H), 3.85–3.76 (m, 2 H), 3.65 (m, 1 H), 1.90–1.88 (m, 2 H). ¹³C NMR (100 MHz, C₆D₆): δ 143.0, 138.8, 128.1, 127.9, 127.7, 127.4, 127.3, 97.1, 75.2, 73.0, 70.7, 70.2, 68.6, 23.9. HRESI-MS: *m/z* calcd for C₂₀H₂₂O₃ [M+ Na]⁺ 333.1467, found 333.1470.

Methyl 3-*O*-Benzyl-2,4-dideoxy-β-pent-4-enopyranoside (20)

Compound **18** (methyl 3-*O*-benzyl-2-deoxy-β-D-glucoside; 47 mg, 0.18 mmol) was subjected to the standard TEMPO oxidation–decarboxylative elimination conditions as previously described. The residue was purified by preparative TLC using 60% EtOAc in hexanes with 0.1% Et₃N to afford 2,4-dideoxy-4-pentenoid **20** as a volatile colorless syrup (22 mg, 58% over 2 steps). ¹H NMR (300 MHz, C₆D₆): δ 7.34–7.11 (m, 5 H), 6.25 (dd, 1 H, *J* = 1.2, 6.3 Hz), 4.89 (ddd, 1 H, *J* = 0.9, 3.0, 6.3 Hz), 4.58 (dd, 1 H, *J* = 2.7, 6.3 Hz), 4.36 (s, 2 H), 4.00 (ddt, 1 H, *J* = 1.2, 2.7, 7.5 Hz), 3.27 (s, 3 H), 2.16 (m, 1 H), 2.02 (dddd, 1 H, *J* = 0.9, 2.4, 6.3, 12.9 Hz). ¹³C NMR (75 MHz, C₆D₆): δ 142.5, 139.2, 128.2, 128.1, 103.1, 99.4, 69.4, 68.0, 55.5, 34.3. IR (NaCl): 2923, 1644, 1454, 1388, 1227, 1190, 1090 cm⁻¹. [α]_D²⁵ = –10.0° (*c* 0.2, CH₂Cl₂). HRESI-MS: *m/z* calcd for C₁₃H₁₆O₃ [M+H–CH₃OH]⁺ 189.0916, found 189.0918.

Methyl 2-*O*-Benzyl-3,4-dideoxy-β-pent-4-enopyranoside (26)

Compound **24** (methyl 2-*O*-benzyl-3-deoxy-β-D-glucoside; ³⁸ 68 mg, 0.25 mmol) was subjected to the standard TEMPO oxidation–decarboxylative elimination conditions as previously described. The volatile residue was carefully purified by silica gel

chromatography using a 0–5% diethyl ether–pentanes gradient to afford the desired 3,4-dideoxy-4-pentenose **26** as a colorless syrup (37 mg, 66% over 2 steps). ^1H NMR (300 MHz, C_6D_6): δ 7.29–7.07 (m, 5 H), 6.25 (dt, 1 H, $J = 2.1, 6.3$ Hz), 4.77 (d, 1 H, $J = 3.9$ Hz), 4.56 (m, 1 H), 4.43–4.34 (m, 2 H), 3.54 (m, 1 H), 3.23 (s, 3 H), 2.24 (ddt, 1 H, $J = 17.4, 5.1, 2.7$ Hz), 1.98 (dt, 1 H, $J = 17.4, 4.5$ Hz). ^{13}C NMR (75 MHz, C_6D_6): δ 140.3, 139.2, 128.5, 128.3, 128.0, 127.7, 127.7, 127.6, 127.6, 99.0, 98.9, 71.9, 71.2, 55.4, 23.0. IR (NaCl): 2913, 1658, 1453, 1231, 1190, 1092 cm^{-1} . $[\alpha]_{\text{D}}^{25} = -93.0^\circ$ (c 1.0, CHCl_3). HRESI-MS: m/z calcd for $\text{C}_{13}\text{H}_{16}\text{O}_3$ $[\text{M}+\text{H}]^+$ 221.1178, found 221.1184.

Methyl 2-O-Benzyl-3,4-dideoxy- α -pent-4-enopyranoside (**27**)

Compound **25** (methyl 2-*O*-benzyl-3-deoxy- α -D-glucoside; ³⁹ 162 mg, 0.60 mmol) was subjected to the standard TEMPO oxidation–decarboxylative elimination conditions as previously described. The volatile residue was carefully purified by silica gel chromatography using a 0–5% diethyl ether–pentanes gradient to afford the desired 3,4-dideoxy-4-pentenose **27** as a colorless syrup (38 mg, 28% over 2 steps). ^1H NMR (300 MHz, C_6D_6): δ 7.30–7.09 (m, 5 H), 6.14 (ddd, 1 H, $J = 1.2, 3.0, 5.7$ Hz), 4.90 (d, 1 H, $J = 2.4$ Hz), 4.60 (dt, 1 H, $J = 2.4, 6.0$ Hz), 4.39–4.29 (m, 2 H), 3.63 (ddd, 1 H, $J = 2.4, 6.0, 10.8$ Hz), 3.29 (s, 3 H), 2.51 (ddd, 1 H, $J = 2.1, 11.4, 16.1$ Hz), 2.05 (dt, 1 H, $J = 15.9, 5.7$ Hz). ^{13}C NMR (100 MHz, C_6D_6): δ 139.3, 128.2, 127.9, 127.7, 127.4, 99.5, 97.4, 73.4, 70.7, 55.3, 22.3. IR (NaCl): 2918, 1649, 1451, 1232, 1177, 1093, 1029 cm^{-1} . $[\alpha]_{\text{D}}^{25} = +96.6^\circ$ (c 0.5, CHCl_3). HRESI-MS: m/z calcd for $\text{C}_{13}\text{H}_{16}\text{O}_3$ $[\text{M}+\text{H}-\text{CH OH}]^+$ 189.0916, found 189.0917.

3,4,6-Tri-O-benzyl-1-deoxy-1*R*-deuterio-D-altrose (**30**)

Tribenzyl-D-allal **2** (40.5 mg, 0.10 mmol) was dissolved in CH_2Cl_2 (1.0 mL) and cooled to -55°C , then treated for 2 d with a precooled solution of DMDO (3.8 mL of a 0.4 M solution in CH_2Cl_2) followed by a low-temperature workup as previously described to yield the corresponding epoxyallal. The crude epoxide was redissolved in Et_2O (2.5 mL) and subjected to $\text{S}_{\text{N}}2$ ring opening with LiAlD_4 as previously described (see Procedure 1). The residue was purified by preparative TLC using 60% EtOAc in hexanes with 0.1% of Et_3N to afford deuteride adduct **30** as a white solid (35.5 mg, 84%). ^1H NMR (300 MHz, C_6D_6): δ 7.31–7.08 (m, 15 H), 4.60 (d, 1 H, $J = 9.0$ Hz), 4.49–4.40 (m, 3 H), 4.42 (dd, 1 H, $J = 4.2, 11.7$ Hz), 4.35 (dd, 1 H, $J = 8.0, 11.7$ Hz), 4.05 (s, 2 H), 3.91 (d, 1 H, $J = 4.8$ Hz), 3.78 (d, 1 H, $J = 7.9$ Hz), 3.72 (d, 1 H, $J = 7.7$ Hz), 3.65 (m, 1 H), 3.57 (s, 1 H), 2.50 (s, 1 H). ^{13}C NMR (75 MHz, C_6D_6): δ 159.4, 139.2, 138.9, 130.8, 129.4, 128.2, 113.8, 75.4, 75.0, 74.0, 73.0, 72.9, 71.3, 69.7, 68.7. IR (NaCl): 3416, 2919, 1612, 1516, 1250, 1103 cm^{-1} . $[\alpha]_{\text{D}}^{25} = +47.3^\circ$ (c 1.0, CH_2Cl_2). HRESI-MS: m/z calcd for $\text{C}_{27}\text{H}_{29}\text{DO}_5$ $[\text{M}+\text{Na}]^+$ 458.2064, found 458.2069.

2-O-Acetyl-3-O-benzyl-4,6-benzylidene-1-deoxy-1*R*-deuterio-D-altrose (**31**)

4,6-Benzylidene-protected D-allal **1** (37.4 mg, 0.12 mmol) was converted to the corresponding epoxyallal as described above (see compound **30**), then redissolved in 4:1 Et_2O :THF (2.5 mL) and subjected to $\text{S}_{\text{N}}2$ ring opening with LiAlD_4 as previously described (see Procedure 2). Deuteride adduct **31** was characterized as the 2-*O*-acetate by treatment with Ac_2O (1 mL) in pyridine (2 mL) at rt for 12 h, concentrated to dryness with azeotropic distillation with toluene, and purified by preparative TLC using 30% EtOAc in hexanes with 0.1% Et_3N to afford the acetate as a colorless oil (43.6 mg, 98%). **2-O-Acetyl-3-O-benzyl-4,6-benzylidene-1-deoxy-1*R*-deuterio-D-altrose (2-O-acetyl 31)**: ^1H NMR (400 MHz, C_6D_6): δ 7.31–7.18 (m, 10 H), 5.60 (s, 1H), 4.97 (d, 1 H, $J = 2.1$ Hz), 4.92–4.71 (m, 2 H), 4.34 (dd, 1 H, $J = 5.1, 10.3$ Hz), 4.06 (ddd, 1 H, $J = 9.7, 10.0, 10.8$ Hz), 3.95–3.92 (m, 2 H), 3.82 (br s, 1 H), 3.75 (t, 1 H, $J = 10.4$ Hz), 2.06 (s, 3 H). ^{13}C NMR (75 MHz, C_6D_6): δ 169.9, 138.1, 137.5, 129.0, 128.2, 128.2, 128.0, 126.1, 102.2, 78.0, 73.3, 72.6, 70.8, 69.1,

66.4, 21.1. IR (NaCl): 2873, 1736, 1371, 1234, 1141 cm^{-1} . $[\alpha]^{25}_{\text{D}} = +14.8^{\circ}$ (c 0.6, CH_2Cl_2). HRESI-MS: m/z calcd for $\text{C}_{22}\text{H}_{23}\text{DO}_6$ $[\text{M}+\text{Na}]^+$ 408.1433, found 408.1430.

2-O-Acetyl-3,4,6-tri-O-benzyl-1-deoxy-1R-deuterio-D-glucose (32)

Tribenzyl-D-gulal **4** (49.9 mg, 0.12 mmol) was converted to the corresponding epoxygulal as described above (see compound **30**), then redissolved in 4:1 $\text{Et}_2\text{O}:\text{THF}$ (2.5 mL) and subjected to $\text{S}_{\text{N}}2$ ring opening with LiAlD_4 as previously described (see Procedure 2). The deuteride adduct **32** and its diastereomer **32'** were characterized as 2-O-acetates by treatment with Ac_2O (1 mL) in pyridine (2 mL) at rt for 12 h, concentration with azeotropic distillation with toluene, and separation by preparative TLC using 25% EtOAc in hexanes with 0.1% Et_3N (42 mg, 2:3 $\alpha:\beta$ (C1), 81% combined yield). **2-O-Acetyl-3,4,6-tri-O-benzyl-1-deoxy-1R-deuterio-D-glucose (2-O-acetyl 32)**: ^1H NMR (300 MHz, C_6D_6): δ 7.36–7.21 (m, 15 H), 5.28 (dd, 1 H, $J = 3.0, 11.1$ Hz), 4.66–4.46 (m, 6 H), 4.10–4.03 (m, 2 H), 3.84 (d, 1 H, $J = 11.1$ Hz), 3.70 (dd, 1 H, $J = 6.3, 9.9$ Hz), 3.62 (dd, 1 H, $J = 1.8, 4.2$ Hz), 3.54 (dd, 1 H, $J = 6.0, 9.3$ Hz), 2.03 (s, 3 H). ^{13}C NMR (75 MHz, C_6D_6): δ 170.0, 137.9, 137.5, 128.3, 128.3, 128.1, 127.9, 127.8, 127.7, 127.6, 74.4, 73.5, 73.4, 73.0, 72.6, 72.2, 69.1, 68.1, 20.9. IR (NaCl): 2870, 1739, 1454, 1367, 1235, 1093 cm^{-1} . $[\alpha]^{25}_{\text{D}} = -16.9^{\circ}$ (c 1.0, CH_2Cl_2). HRESI-MS: m/z calcd for $\text{C}_{29}\text{H}_{31}\text{DO}_6$ $[\text{M}+\text{Na}]^+$ 500.2159, found 500.2154. **2-O-Acetyl-3,4,6-tri-O-benzyl-1-deoxy-1S-deuterio-D-idose (2-O-acetyl 32')**: ^1H NMR (300 MHz, C_6D_6): δ 7.44–7.24 (m, 15 H), 4.86 (br s, 1 H), 4.78–4.38 (m, 6 H), 4.01 (d, 2 H, $J = 1.8$ Hz), 3.87 (br s, 1 H), 3.80 (dd, 1 H, $J = 6.6, 9.3$ Hz), 3.62 (dd, 1 H, $J = 5.1, 9.3$ Hz), 3.49 (d, 1 H, $J = 1.2$ Hz), 2.12 (s, 3 H). ^{13}C NMR (75 MHz, C_6D_6): δ 170.6, 138.2, 137.9, 137.8, 128.3, 128.2, 128.0, 127.8, 127.7, 127.6, 127.4, 74.3, 73.7, 73.4, 72.3, 70.9, 69.4, 68.1, 21.0. IR (NaCl): 2870, 1728, 1454, 1369, 1240, 1090 cm^{-1} . $[\alpha]^{25}_{\text{D}} = +1.1^{\circ}$ (c 1.1, CH_2Cl_2). HRESI-MS: m/z calcd for $\text{C}_{29}\text{H}_{31}\text{DO}_6$ $[\text{M}+\text{Na}]^+$ 500.2159, found 500.2155.

3-O-Benzyl-4,6-benzylidene-1-deoxy-1S-deuterio-D-glucose (33)

4,6-Benzylidene-protected D-gulal **6** (40.1 mg, 0.12 mmol) was converted to the corresponding epoxygulal as described above (see compound **30**), then redissolved in 4:1 $\text{Et}_2\text{O}:\text{THF}$ (1.3 mL) and subjected to $\text{S}_{\text{N}}2$ ring opening with LiAlD_4 as previously described (see Procedure 2) to afford deuteride adduct **33** and its diastereomer **33'** (30.6 mg, 2:3 $\alpha:\beta$ (C1), 72% combined yield). The diastereomers were separated by preparative TLC, developing twice with 30% EtOAc in hexanes with 0.1% Et_3N . **3-O-Benzyl-4,6-benzylidene-1-deoxy-1S-deuterio-D-glucose (33)**: ^1H NMR (300 MHz, C_6D_6): δ 7.52–7.36 (m, 10 H), 5.53 (s, 1 H), 4.81–4.65 (m, 2 H), 4.30 (d, 1 H, $J = 12.4$ Hz), 4.18 (d, 1 H, $J = 3.0$ Hz), 4.16 (m, 1 H), 4.03 (dd, 1 H, $J = 1.6, 12.6$ Hz), 3.91 (t, 1 H, $J = 3.0$ Hz), 3.57 (d, 1 H, $J = 11.9$ Hz), 3.56 (s, 1 H), 2.05 (br s, 1 H). ^{13}C NMR (75 MHz, C_6D_6): δ 137.5, 129.0, 128.6, 128.2, 127.6, 126.1, 101.3, 76.4, 73.9, 73.2, 69.8, 66.2, 64.1. IR (NaCl): 3439, 2873, 1456, 1396, 1157, 1157, 1094 cm^{-1} . $[\alpha]^{25}_{\text{D}} = +8.41^{\circ}$ (c 1.0, CH_2Cl_2). HRESI-MS: m/z calcd for $\text{C}_{20}\text{H}_{21}\text{DO}_5$ $[\text{M}+\text{Na}]^+$ 366.1428, found 366.1422. **3-O-Benzyl-4,6-benzylidene-1-deoxy-1R-deuterio-D-idose (33')**: ^1H NMR (400 MHz, C_6D_6): δ 7.49–7.32 (m, 10 H), 5.50 (s, 1 H), 4.70–4.66 (m, 2 H), 4.33 (dd, 1 H, $J = 1.2, 12.4$ Hz), 4.09 (br s, 1 H), 4.03 (dd, 1 H, $J = 1.6, 12.4$ Hz), 3.97 (s, 1 H), 3.79 (s, 1 H), 3.66 (s, 1 H), 3.64 (d, 1 H, $J = 1.2$ Hz), 1.50 (br s, 1 H). ^{13}C NMR (75 MHz, C_6D_6): δ 137.5, 129.1, 128.5, 128.3, 128.0, 127.5, 125.9, 101.4, 74.4, 73.9, 72.3, 70.3, 66.9, 65.6. IR (NaCl): 3505, 1648, 1451, 1399, 1127 cm^{-1} . $[\alpha]^{25}_{\text{D}} = +9.64^{\circ}$ (c 0.5, CH_2Cl_2). HRESI-MS: m/z calcd for $\text{C}_{20}\text{H}_{21}\text{DO}_5$ $[\text{M}+\text{Na}]^+$ 366.1428, found 366.1429.

Methyl 3,6-Di-O-benzyl-4-deoxy-1S-D-galactose (34)

4-Deoxy-D-glucal **11** (10.0 mg, 0.03 mmol) was dissolved in CH_2Cl_2 (0.5 mL) then converted to the corresponding epoxygalactal as previously described, but using a 0.08 M solution in acetone (0.09 mmol). The crude epoxide was subjected to methanolysis as

previously described (see Procedure 3). The residue was purified by preparative TLC with 40% EtOAc in hexanes with 0.1% Et₃N to afford the methyl glycoside **34** as a white solid (11.5 mg, quantitative yield). S_N2 ring opening was confirmed by coupling constant analysis. ¹H NMR (300 MHz, C₆D₆): δ 7.30–7.21 (m, 10 H), 4.66 (m, 4 H), 4.09 (d, 1 H, *J* = 7.5 Hz), 3.57–3.30 (m, 8 H), 2.02 (dd, 1 H, *J* = 1.6, 12.6 Hz), 1.52–1.35 (m, 2 H). HRESI-MS: *m/z* calcd for C₂₁H₂₆O₅ [M+H]⁺ 359.1859, found 359.1864.

Methyl 3,6-Di-*O*-benzyl-4-deoxy-*S*-D-altrose (**35**)

4-Deoxy-D-allal **3** (10.3 mg, 0.03 mmol) was converted into the corresponding epoxyallal as described above (see compound **34**), then subjected to methanolysis as previously described (see Procedure 3) and purified by preparative TLC developing twice with 40% EtOAc in hexanes with 0.1% Et₃N to afford the methyl glycoside **35** as a white solid (9.1 mg, 76%). S_N2 ring opening was confirmed by coupling constant analysis. ¹H NMR (300 MHz, C₆D₆): δ 7.34–7.13 (m, 10 H), 4.69 (d, 1 H, *J* = 2.4 Hz), 4.54–4.40 (m, 5 H), 3.82 (br s, 1 H), 3.67 (m, 1 H, *J* = 4.5 Hz), 3.44 (dd, 1 H, *J* = 6.0, 10.2 Hz), 3.36 (dd, 1 H, *J* = 4.2, 10.2 Hz), 3.30 (s, 3 H), 2.12 (br s, 1H), 1.95 (ddd, 1 H, *J* = 4.2, 9.9, 14.1 Hz), 1.64 (dt, 1 H, *J* = 13.5, 4.2 Hz). ¹³C NMR (75 MHz, C₆D₆): δ 139.2, 138.7, 128.2, 128.2, 102.5, 75.1, 73.1, 72.9, 70.8, 68.6, 64.9, 54.9, 28.8. IR (NaCl): 3477, 2914, 1493, 1454, 1098, 1041 cm⁻¹. [α]_D²⁵ = +34.0° (*c* 0.5, CH₂Cl₂). HRESI-MS: *m/z* calcd for C₂₁H₂₆O₅ [M+Na]⁺ 381.1678, found 381.1676.

4-*O*-Benzyl-1,3-dideoxy-1*R*-deuterio-6-*O*-*p*-methoxybenzyl-D-mannose (**36**)

3-Deoxyglucal **9** (39.4 mg, 0.11 mmol) was converted to the corresponding epoxyglucal as described above (see compound **30**), then redissolved in 4:1 Et₂O:THF (1.3 mL) and subjected to S_N2 ring opening with LiAlD₄ as previously described (see Procedure 1) to afford deuteride adduct **36** and minor diastereomer **36'** (30 mg, 2:1 α:β (C1), 72% combined yield). These were also characterized as 2-*O*-acetates by treatment with Ac₂O (1 mL) in pyridine (2 mL) at rt for 12 h, then concentrated with azeotropic distillation with toluene. These were separated by preparative TLC using 60% EtOAc in hexanes with 0.1% Et₃N. **4-*O*-Benzyl-1*R*-deuterio-1,3-dideoxy-6-*O*-*p*-methoxybenzyl-D-mannose (**36**):** ¹H NMR (400 MHz, CDCl₃): δ 7.33–7.25 (m, 7 H), 6.85 (d, 2 H), 4.57–4.36 (m, 4 H), 3.97 (br s, 1 H), 3.89 (s, 1 H), 3.76 (m, 1 H), 3.79 (s, 3 H), 3.74 (dd, 1 H, *J* = 2.0, 10.0 Hz), 3.73 (dd, 1 H, *J* = 5.2, 10.4 Hz), 3.39 (ddd, 1 H, *J* = 2.0, 5.2, 9.6 Hz), 2.46 (m, 1 H), 2.02 (br s, 1 H), 1.55 (m, 1 H). ¹³C NMR (100 MHz, CDCl₃): δ 159.16, 138.07, 129.98, 129.55, 128.29, 127.63, 113.68, 80.44, 73.08, 71.07, 69.77, 69.07, 66.61, 55.16, 36.04. IR (NaCl): 3428, 2917, 2862, 1610, 1511, 1248, 1094 cm⁻¹. [α]_D²⁵ = +36.1° (*c* 0.8, CH₂Cl₂). HRESI-MS: *m/z* calcd for C₂₁H₂₅DO₅ [M+Na]⁺ 382.1741, found 382.1740. **4-*O*-Benzyl-1*S*-deuterio-1,3-dideoxy-6-*O*-*p*-methoxybenzyl-D-glucose (**36'**):** ¹H NMR (400 MHz, CDCl₃): δ 7.32–7.21 (m, 8 H), 6.85 (d, 2 H), 4.58–4.39 (m, 4 H), 3.78 (s, 3 H), 3.76 (dd, 1 H, *J* = 4.0, 10.0 Hz), 3.69 (dd, 1 H, *J* = 2.4, 10.4 Hz), 3.61 (dd, 1 H, *J* = 5.2, 10.8 Hz), 3.48 (ddd, 1 H, *J* = 4.8, 8.8, 12.2 Hz), 3.36 (ddd, 1 H, *J* = 2.4, 4.8, 8.4 Hz), 3.14 (d, 1 H, *J* = 9.6 Hz), 2.52 (dt, 1 H, *J* = 4.4, 1.6 Hz), 1.45 (d, 1 H, *J* = 10.4 Hz). ¹³C NMR (100 MHz, CDCl₃): δ 159.1, 137.9, 130.0, 129.5, 128.3, 127.7, 113.7, 79.0, 73.1, 72.1, 71.0, 68.6, 65.2, 55.2, 38.0. IR (NaCl): 3401, 2923, 2862, 1607, 1511, 1248, 1056 cm⁻¹. [α]_D²⁵ = +54° (*c* 0.7, CH₂Cl₂). HRESI-MS: *m/z* calcd for C₂₁H₂₅DO₅ [M+Na]⁺ 382.1741, found 382.1739.

2-*O*-Acetyl-1,3-dideoxy-1*R*-deuterio-4,6-*p*-methoxybenzylidene-D-mannose (**37**)

Benzylidene-protected 3-deoxyglucal **8** (25.1 mg, 0.1 mmol) was converted to the corresponding epoxyglucal as described above (see compound **30**), then redissolved in 4:1 Et₂O:THF (2.5 mL) and subjected to S_N2 ring opening with LiAlD₄ as previously described (see Procedure 2). The deuteride adduct **37** and its diastereomer **37'** were characterized as 2-*O*-acetates by treatment with Ac₂O (1 mL) in pyridine (2 mL) at rt for 12 h, then

concentrated and azeotropic distillation with toluene and purified by preparative TLC using 30% EtOAc in hexanes with 0.1% Et₃N as an inseparable mixture (26 mg, 2:1 α : β (C1), 83% combined yield). **2-O-Acetyl-1,3-dideoxy-1R-deuterio-4,6-p-methoxybenzylidene-D-mannose (2-O-acetyl 37)**: ¹H NMR (300 MHz, CDCl₃): δ 7.42–7.39 (m, 2 H), 6.91–6.86 (m, 2 H), 5.56 (s, 1 H), 5.10 (m, 1 H), 4.27 (dd, 1 H, J = 4.8, 10.5 Hz), 3.99 (br s, 1 H), 3.92 (ddd, 1 H, J = 4.8, 9.3, 12.3 Hz), 3.75 (m, 1 H), 3.78 (s, 3 H), 3.38 (dt, 1 H, J = 9.9, 4.8 Hz), 2.30 (m, 1 H), 2.13 (s, 3 H), 1.88 (ddd, 1 H, J = 3.6, 12.3, 13.5 Hz). **2-O-Acetyl-1,3-dideoxy-1S-deuterio-4,6-p-methoxybenzylidene-D-glucose (2-O-acetyl 37')**: ¹H NMR (300 MHz, CDCl₃): δ 7.42–7.39 (m, 2 H), 6.91–6.86 (m, 2 H), 5.45 (s, 1 H), 4.77 (dt, 1 H, J = 5.1, 9.9 Hz), 4.36 (dd, 1 H, J = 5.1, 10.5 Hz), 4.06 (m, 1 H), 3.59 (t, 1 H, J = 10.5 Hz), 2.08 (s, 3 H), 1.75 (m, 1 H). ¹³C NMR (diastereomeric mixture, 100 MHz, CDCl₃): δ 190.8, 170.3, 160.0, 131.9, 129.9, 127.3, 114.2, 113.6, 113.6, 101.8, 101.0, 81.1, 78.5, 74.1, 73.7, 69.3, 69.1, 68.9, 68.6, 67.9, 66.7, 64.0, 63.3, 55.5, 55.2, 36.1, 33.0, 28.0, 21.2, 20.9, 20.8. IR (NaCl): 2928, 1733, 1612, 1514, 1367, 1246 cm⁻¹. HRESI-MS: m/z calcd for C₁₆H₁₉DO₆ [M+H]⁺ 310.1401, found 310.1399.

4,6-Di-O-benzyl-1,3-dideoxy-1S-deuterio-D-galactose (38)

3-Deoxygalactal **15** (19.7 mg, 0.06 mmol) was converted to the corresponding epoxygalactal as described above (see compound **30**), then redissolved in 4:1 Et₂O:THF (1.3 mL) and subjected to S_N2 ring opening with LiAlD₄ as previously described (see Procedure 1). The residue was purified by preparative TLC using 70% EtOAc in hexanes with 0.1% Et₃N to afford deuteride adduct **38** as a white solid (19.0 mg, 91%). ¹H NMR (400 MHz, C₆D₆): δ 7.27–7.06 (m, 10 H), 4.40–4.16 (m, 4 H), 3.90 (m, 1 H), 3.80–3.71 (m, 2 H), 3.47 (m, 1 H), 3.45 (dt, 1 H, J = 1.6, 4.2 Hz), 2.98 (d, 1 H, J = 10.0 Hz), 2.19 (dt, 1 H, J = 13.2, 4.0 Hz), 1.08 (ddd, 1 H, J = 2.4, 11.2, 13.4 Hz), 0.72 (d, 1 H, J = 5.2 Hz). ¹³C NMR (100 MHz, C₆D₆): δ 138.9, 138.8, 128.2, 127.9, 127.7, 127.4, 127.3, 77.8, 73.1, 71.0, 69.6, 62.4, 62.4, 35.5. IR (NaCl): 3435, 2923, 2860, 2364, 1449, 1101 cm⁻¹. $[\alpha]^{25}_D$ = +3.5° (c 0.3, CH₂Cl₂). HRESI-MS: m/z calcd for C₂₀H₂₃DO₄ [M+Na]⁺ 352.1635, found 352.1637.

Methyl 2-O-Acetyl-3-deoxy-4,6-p-methoxybenzylidene- β -D-galactose (39)

3-Deoxygalactal **14** (8.7 mg, 0.03 mmol) was converted to the corresponding epoxygalactal as described above (see compound **30**), then subjected to methanolysis as previously described (see Procedure 3). 3-Deoxygalactoside **39** and its diastereomer **39'** were characterized as their 2-O-acetates by treatment with Ac₂O (1 mL) in pyridine (2 mL) at rt for 12 h, then concentrated with azeotropic distillation with toluene. These were separated by preparative TLC developing twice with 30% EtOAc in hexanes with 0.1% Et₃N (9 mg, 1:4 α : β (C1), 76% combined yield). **Methyl 2-O-Acetyl-3-deoxy-4,6-p-methoxybenzylidene- β -D-galactose (2-O-acetyl 39)**: ¹H NMR (400 MHz, C₆D₆): δ 7.58 (d, 2 H), 6.73 (d, 2 H), 5.55 (ddd, 1 H, J = 8.1, 11.7 Hz), 5.26 (s, 1 H), 4.29 (d, 1 H, J = 8.4 Hz), 4.08 (dd, 1 H, J = 1.2, 12.3 Hz), 3.44 (dd, 1 H, J = 1.8, 12.3 Hz), 3.39 (s, 3 H), 3.31 (br s, 1 H), 3.24 (s, 3 H), 2.64 (d, 1 H, J = 1.2 Hz), 2.43 (ddd, 1 H, J = 2.7, 8.1, 13.5 Hz), 1.70 (s, 3 H), 1.37 (ddd, 1 H, J = 4.2, 11.7, 13.5 Hz). ¹³C NMR (100 MHz, C₆D₆): δ 169.5, 161.2, 132.0, 129.7, 128.9, 128.6, 128.4, 114.4, 109.6, 104.0, 102.2, 73.3, 69.7, 68.1, 55.9, 55.3, 34.8, 21.3. IR (NaCl): 2850, 1736, 1517, 1370, 1249, 1172, 1080, 827 cm⁻¹. $[\alpha]^{25}_D$ = -61.8° (c 0.2, CH₂Cl₂). HRESI-MS: m/z calcd for C₁₇H₂₂O₇ [M+Na]⁺ 361.1263, found 361.1268. **Methyl 2-O-Acetyl-3-deoxy-4,6-p-methoxybenzylidene- α -D-idose (2-O-acetyl 39')**: ¹H NMR (400 MHz, C₆D₆): δ 7.64 (d, 2 H), 6.79 (d, 2 H), 5.52 (ddd, 1 H, J = 3.6, 8.8, 11.6 Hz), 5.29 (s, 1 H), 5.11 (d, 1 H, J = 3.2 Hz), 4.09 (dd, 1 H, J = 0.8, 12.0 Hz), 3.50–3.47 (m, 2 H), 3.24 (s, 3 H), 3.11 (s, 3 H), 3.09 (d, 1 H, J = 1.2 Hz), 2.18 (dd, 1 H, J = 3.2, 12.8 Hz), 2.13 (m, 1 H), 1.65 (s, 3 H).

Methyl 3-O-Benzyl-2-deoxy-5R-deuterio-D-xylose (40)

2-Deoxy- β -*glc*-4-DP **20** (37.4 mg, 0.17 mmol) was converted to the corresponding 4,5-epoxypyranoside as described above (see compound **30**), then subjected to S_N2 ring opening with LiAlD₄ as previously described (see Procedure 1), and purified by preparative TLC using 40% EtOAc in hexanes with 0.1% Et₃N to afford deuteride adduct **40** as a colorless oil (26 mg, 66%). ¹H NMR (300 MHz, C₆D₆): δ 7.35–7.15 (m, 5 H), 4.50–4.27 (m, 2 H), 4.03 (dd, 1 H, J = 2.4, 8.7 Hz), 3.62 (t, 1 H, J = 9.0 Hz), 3.31 (s, 3 H), 3.27 (ddd, 1 H, J = 4.8, 7.5, 10.5 Hz), 3.08 (d, 1 H, J = 9.6 Hz), 2.40 (brs, 1 H), 2.13 (ddd, 1 H, J = 2.4, 4.8, 12.9 Hz), 1.69 (dd, 1 H, J = 8.4, 12.9 Hz). ¹³C NMR (75 MHz, C₆D₆): δ 138.8, 128.3, 128.1, 127.7, 127.6, 127.4, 101.0, 78.1, 70.4, 70.0, 64.7, 55.7, 34.8. IR (NaCl): 3435, 2918, 1725, 1451, 1388, 1074 cm⁻¹. $[\alpha]^{25}_D$ = -8.3° (*c* 0.5, CH₂Cl₂). HRESI-MS: *m/z* calcd for C₁₃H₁₇DO₄ [M+Na]⁺ 262.1166, found 262.1169.

Methyl 2-O-Benzyl-3-deoxy-5R-thioethyl-D-xylose (42)

3-Deoxy- β -*glc*-4-DP **26** (5.0 mg, 0.02 mmol) was converted to the corresponding 4,5-epoxypyranoside as described above (see compound **30**), but without concentration. S_N2 epoxide ring opening was achieved in situ using LiSEt, prepared as a stock solution of EtSH (0.5 mL, 6.75 mmol) in anhydrous THF (8 mL) treated at 0 °C with *n*-BuLi (0.25 mL, 2.5 M in hexanes). The reaction mixture containing epoxides was treated by the dropwise addition of LiSEt (3 mL of a 0.75 M solution) via cannula at -55 °C, then warmed slowly to 0 °C over a period of 5 hours. The reaction was quenched with satd NaHCO₃, extracted with EtOAc, dried over Na₂SO₄, and concentrated to yield a mixture of diastereomers (4.4 mg, 2:3 α : β (C5), 66% combined yield). Thioacetal **42** was characterized as the 2-*O*-acetate by treatment with Ac₂O (1 mL) in pyridine (2 mL) at rt for 12 h then concentrated with azeotropic distillation with toluene, followed by preparative TLC using a 0–20% EtOAc–hexanes gradient. **Methyl 4-O-Acetyl-2-O-benzyl-3-deoxy-5R-thioethyl-D-xylose (2-O-acetyl 42)**: ¹H NMR (300 MHz, C₆D₆): δ 7.40–6.99 (m, 5 H), 5.41 (m, 1 H), 5.18 (d, 1 H, J = 6.2 Hz), 4.82 (d, 1 H, J = 4.2 Hz), 4.63–4.47 (m, 2 H), 3.65 (m, 1 H), 3.19 (s, 3 H), 2.71–2.45 (m, 2 H), 2.22 (ddd, 1 H, J = 3.3, 4.8, 13.5 Hz), 2.02 (ddd, 1 H, J = 4.0, 7.6, 13.5 Hz), 1.60 (s, 3 H), 1.11 (t, 3 H, J = 9.0 Hz).

Methyl 2-O-Benzyl-3-deoxy-5S-deuterio-L-arabinose (43)

3-Deoxy- α -*glc*-4-DP **27** (34.7 mg, 0.16 mmol) was converted into the corresponding 4,5-epoxypyranoside as described above (see compound **34**), then subjected to S_N2 ring opening with LiAlD₄ as previously described (see Procedure 1) and purified by preparative TLC using 80% EtOAc in hexanes with 0.1% Et₃N to afford deuteride adduct **43** as a white solid (37 mg, 98%). ¹H NMR (400 MHz, C₆D₆): δ 7.36–7.12 (m, 5 H), 4.73 (d, 1 H, J = 2.9 Hz), 4.43 (s, 2 H), 3.96 (dt, 1 H, J = 11.4, 3.3), 3.59 (br s, 1 H), 3.26 (br s, 1 H), 3.24 (s, 3 H), 2.10 (dt, 1 H, J = 3.2, 11.7 Hz), 1.96 (m, 1 H), 1.71 (d, 1 H, J = 3.0 Hz). ¹³C NMR (100 MHz, C₆D₆): δ 139.1, 128.1, 127.9, 127.9, 127.7, 127.4, 127.3, 98.2, 71.7, 70.6, 66.3, 54.7, 31.7. IR (NaCl): 3445, 2934, 1451, 1098, 1079, 1040, 992 cm⁻¹. $[\alpha]^{25}_D$ = +197° (*c* 1.1, CH₂Cl₂). HRESI-MS: *m/z* calcd for C₁₃H₁₇DO₄ [M+Na]⁺ 262.1163, found 262.1166.

2,3-Di-O-benzyl-1-deoxy-1S-deuterio-D-xylose (44)

Dibenzyl-D-xylal **28** (34.9 mg, 0.12 mmol) was converted to the corresponding epoxyxylal as described above (see compound **34**), then redissolved in 4:1 Et₂O:THF (1.4 mL) and subjected to S_N2 ring opening with LiAlD₄ as previously described (see Procedure 1) to afford deuteride adduct **44** and its minor diastereomer **44'** as a white solid (20 mg, 1:5 α : β (C1), 76%). These were separated by preparative TLC using 60% EtOAc in hexanes with 0.1% Et₃N. **2,3-Di-O-benzyl-1-deoxy-1S-deuterio-D-xylose (44)**: ¹H NMR (400 MHz, C₆D₆): δ 7.23–7.07 (m, 10 H), 4.56–4.44 (m, 2 H), 4.27–4.26 (m, 2 H), 3.76 (dd, 1 H, J =

3.1, 11.7 Hz), 3.62 (m, 1 H), 3.51–3.45 (m, 2 H), 3.41 (dd, 1 H, $J = 8.0, 11.6$ Hz), 3.33 (m, 1 H), 2.96 (d, 1 H, $J = 6.8$ Hz). ^{13}C NMR (100 MHz, C_6D_6): δ 138.8, 138.1, 128.3, 127.9, 27.7, 127.5, 127.4, 79.5, 76.4, 73.1, 71.5, 69.5, 69.3, 69.1, 68.5, 66.6. IR (NaCl): 3432, 2916, 2360, 1722, 1454, 1075 cm^{-1} . $[\alpha]^{25}_{\text{D}} = -13.7^\circ$ (c 0.4, CH_2Cl_2). HRESI-MS: m/z calcd for $\text{C}_{19}\text{H}_{21}\text{DO}_4$ $[\text{M}+\text{Na}]^+$ 338.1479, found 338.1482. **2,3-Di-O-benzyl-1,5-deoxy-1R-deuterio-D-mannose (44')**: ^1H NMR (400 MHz, C_6D_6): δ 7.31–6.99 (m, 10 H), 4.41–4.34 (m, 4 H), 3.82 (dd, 1 H, $J = 3.2, 9.2$ Hz), 3.78–3.75 (m, 2 H), 3.66 (m, 1H), 3.37 (dd, 1 H, $J = 2.4, 5.6$ Hz), 3.20 (dd, 1 H, $J = 6.0, 9.2$ Hz), 2.09 (d, 1 H, $J = 3.6$ Hz). HRESI-MS: m/z calcd for $\text{C}_{19}\text{H}_{21}\text{DO}_4$ $[\text{M}+\text{Na}]^+$ 338.1479, found 338.1477.

2,3-Di-O-benzyl-1-deoxy-1S-deuterio-L-arabinose (45)

Dibenzyl-D-arabinal **29** (46.7 mg, 0.158 mmol) was converted to the corresponding epoxyarabinal as described above (see compound **30**), then redissolved in 4:1 $\text{Et}_2\text{O}:\text{THF}$ (1.3 mL) and subjected to $\text{S}_{\text{N}}2$ ring opening with LiAlD_4 as previously described (see Procedure 1) and purified by preparative TLC with 50% EtOAc in hexanes with 0.5% Et_3N to afford a colorless oil (36.4 mg, 73%). ^1H NMR (400 MHz, C_6D_6): δ 7.22–7.05 (m, 10 H), 4.36–4.23 (m, 2 H), 4.23–4.10 (m, 2 H), 4.10 (s, 1 H), 4.08 (q, 1 H, $J = 2.8$ Hz), 3.95 (s, 1 H), 3.94 (dd, 1 H, $J = 0.9, 1.9$ Hz), 3.91 (s, 1 H), 3.47 (dd, 1 H, $J = 3.5, 10.9$ Hz), 3.24 (dd, 1 H, $J = 3.1, 10.2$ Hz). ^{13}C NMR (100 MHz, C_6D_6): δ 139.0, 138.3, 129.0, 128.0, 128.6, 128.4, 128.3, 128.2, 87.6, 84.1, 75.3, 75.1, 74.0, 72.0, 71.2. $[\alpha]^{25}_{\text{D}} = 16.2^\circ$ (c 0.5, CH_2Cl_2). HRESI-MS: m/z calcd for $\text{C}_{19}\text{H}_{21}\text{DO}_4$ $[\text{M}+\text{Na}]^+$ 338.1479, found 338.1476.

Supplementary Material

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Acknowledgments

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FIGURE 1.
Four diastereomeric glycals, and their 4-deoxypentenoside isosteres.

FIGURE 2.

PPFMO analysis of the dimethyl ether of 4-deoxyallal (analog of **3**). Pairs of $1s$ functions are superimposed onto the $2p_y$ orbitals at C1 and C2 to produce asymmetric wavefunctions (χ), whose coefficients c_α and c_β are used to derive p , the net electronic polarization per orbital (in purple). $2p$ orbitals and added s -functions are spatially separated for clarity, and $+/-$ values refer to the sign of the coefficients for each lobe (open/filled).

FIGURE 3.

Electron density maps of the 4-deoxyglucal derivative (analog of **11**) with the C3 methyl ether in the *tg* conformation (*left*) or the *gt* conformation (*right*). In the case of *gt*, the electron density map reveals an incidental (but superfluous) hyperconjugation between the hybrid orbital at C2 and a lone pair on O3 (extended green lobe), creating an artificial polarization in the β direction.

FIGURE 4.

PPFMO analysis of dimethyl ether analogs of 3-deoxyglucal (**9**) and 3-deoxy- β -glc (**26**), starting from alternate half-chair conformations. For each 2p orbital, $p(n)$, the net electronic polarization is presented as a filled lobe (purple).

SCHEME 1.

Synthesis of D-allal derivatives.^a

^aReagents and conditions: (a) PhSH, BF₃, Et₂O, CH₂Cl₂, -78 °C (69%); (b) NaOMe, MeOH, rt; (c) PhCH(OMe)₂, *p*-TsOH, rt; (d) DMDO, CH₂Cl₂, -78 °C; (e) Et₂NH, THF, rt; (f) BnBr, Bu₄NI, NaH, DMF, rt (36% over 5 steps); (g,h) same as steps (d,e) (59% over 2 steps); (i,j) same as steps (b,f) (92% over 2 steps); (k) NaH, CS₂, MeI, THF, rt; (l) Bu₃SnH, AIBN, DMF, 120 °C; (m) NaOMe, MeOH, rt; (n) BnBr, Bu₄NI, NaH, THF, rt (22% over 4 steps).

SCHEME 2.

Synthesis of D-gulal derivatives.^a

^aReagents and conditions: (a) PhSH, SnCl₄, CH₂Cl₂, -20 °C (98%); (b) DMDO, CH₂Cl₂, -78 °C; (c) Et₂NH, THF, rt; (d) NaOMe, MeOH, rt; (e) BnBr, Bu₄NI, NaH, THF, rt (76% yield over 4 steps); (f) PhCH(OMe)₂, *p*-TsOH, rt (70% over 2 steps); (g) same as steps (b), (c), and (e) (45% over 3 steps).

SCHEME 3.

Synthesis of 3- and 4-deoxyglucal derivatives.^a

^a Reagents and conditions: (a) NaH, CS, MeI, THF, rt; (b) Bu SnH, AIBN, PhCH, reflux (54% isolated yield for **8**, 82% for **11**); (c) BH₃-THF, Bu₂BOTf, THF, -78 °C; (d) BnBr, Bu₄NI, NaH, THF, rt (73% over 2 steps); (e) BnBr, Bu₄NI, NaH, DMF, rt; (f) *i*Bu₂AlH, CH₂Cl₂, 0 °C; (g) same as step (e); (h) DDQ, *t*BuOH, pH 7 phosphate buffer, CH₂Cl₂, rt (61% over 4 steps). PMB = *p*-methoxybenzyl; PMP = *p*-methoxyphenyl.

SCHEME 4.

Synthesis of 3-deoxygalactal derivatives.^a

^a Reagents and conditions: (a) NaH, CS₂, MeI, THF, rt; (b) Bu₃SnH, AIBN, PhCH₃, reflux (75% over 2 steps); (c) Li-naphthalenide (2.5 equiv), THF, -40 °C (78%); (d) AcOH/THF/H₂O, 45 °C; (e) BnBr, Bu₄NI, NaH, DMF, rt (66% over 2 steps); (f) same as step (c) (60%).

SCHEME 5.

Synthesis of 2,4- and 3,4-dideoxypentenosides.^a

^a Reagents and conditions: (a) NaH, CS₂, MeI, THF, rt; (b) Bu₃SnH, AIBN, PhCH₃, reflux; (c) AcOH/THF/H₂O, 45 °C (81% over 3 steps for **18**, 56% for **19**, 50% for **24**, 87% for **25**); (d) TEMPO, BAIB, H₂O/CH₂Cl₂, rt; (e) DMFDNPA, DMF, 200 °C (58% isolated yield over 2 steps for **20**, 60% for **21** and **26**, 28% for **27**).

SCHEME 6. Synthesis of D-xylal and L-arabinal.^a^a Reagents and conditions: (a) Li/naphthalenide, THF, -40 °C (quantitative).

TABLE 1

Facioselective glycal epoxidation by DMDO

glycal	react cond ^a	epoxide	$\alpha:\beta$
glucal	A B		10:1 10:1
galactal	A B		>20: 20:1
allal (2)	A		<1:2

glycal	react cond ^a	epoxide	$\alpha:\beta$
allal, 4,6-acetal (1)	A B		<1:2 ^b 1:10 ^b
gulal (4)	A		3:2
gulal 4,6-acetal (6)	A B		3:1 1:1 ^b

^aReaction conditions: (A) DMDO (3 equiv), -55 °C, 2 days; (B) DMDO (2 equiv), 0 °C, 1 hour.

^bSee Ref. 5.

^cRatio obtained using C3 silyl ether.

TABLE 2

Facioselectivities of 4-DP epoxidation by DMDO

4-DP	react cond ^a	epoxide	$\alpha:\beta$
(β-Glc)	A B		10:1 ^b 8:1
(β-Man)	B		15:1 ^b
(α-Man)	B		>20:1 ^c

4-DP	react cond ^a	epoxide	$\alpha:\beta$
	A		1:10 ^b
	B		1:4 ^c

(α-Glc)

^a Reaction conditions: (A) DMDO (3 equiv), -55 °C, 2 days; (B) DMDO (2 equiv), 0 °C, 1 hour.

^b See Ref. 10.

^c See Ref. 9.

TABLE 3

Facioselectivities of deoxyglycal epoxidation by DMDO

4-DP	react cond ^a	epoxide	$\alpha:\beta$
11 	A		20:1
3 	A		<1:20
9 	A		1:1
8 	A		1:2 ^b

4-DP	react cond ^a	epoxide	$\alpha:\beta$
15	B		>20:1
14	A		4:1

^aReactio conditions: (A) DMDO (3 equiv), -55°C , 2 days; (B) DMDO (3 equiv), -55°C , 1 day.

^bDetermined by ^1H NMR peak integration.

TABLE 4

Facioselectivities of dideoxypentenoxide epoxidation by DMDO

dideoxypentenoxide	react cond ^a	epoxide	$\alpha:\beta$
 20	A		20:1
 21	A		10:1 ^b
 26	A		2:3
 27	A		<1:2

dideoxypentenoside	react cond ^a	epoxide	$\alpha:\beta$
 xylal (28)	A		5:1
	B		4:1 ^c
 arabinal (29)	A		>20:1
	B		

^aReaction conditions: (A) DMDO (3 equiv), -55°C , 2 days; (B) DMDO (2 equiv) 0°C , 1 hour.

^bRef. 10.

^cRef. 7.

TABLE 5

 S_N2 ring-opening products of epoxides derived from glycals^a

	entry	major product
D-allal	2	30
D-gulal	1 4 6	31 32^b 33^c

	entry	major product
4-deoxy-glucal	11 	34
4-deoxy-allal	3 	35
3-deoxy-glucal	9 	36 ^d
	8 	37 ^e

	entry	major product
3-deoxy-glucal	15	38
	14	39 ^f

^aRelative stereochemistry of major products (facioselectivity $\geq 10:1$, unless otherwise noted) confirmed by ^1H NMR coupling constant analysis (see Table S1, Supporting Information).

^b3:2 ratio.

^c3:1 ratio.

^d1:1 ratio.

^e2:1 ratio.

^f4:1 ratio.

TABLE 6

 S_N2 ring-opening products of epoxides derived from dideoxypentenosides^a

	entry	major product
2-deoxy- β -Glc	20 	40
2-deoxy- α -Glc	21 	41 ^b
3-deoxy- β -Glc	26 	42 ^c

	entry	major product
3-deoxy- α -Glc	27	43
xylal	28	44 ^d
arabinal	29	45

^aRelative stereochemistry of major products (facioselectivity $\geq 10:1$, unless otherwise noted) confirmed by ^1H NMR coupling constant analysis (see Table S2, Supporting Information).

^bSee Ref. 10.

^c3:2 ratio.

^d5:1 ratio.

TABLE 7

PPFMO analysis of disubstituted glycals and dideoxypentenosides (permethylated)^a

deoxyglycal	atom	c_a^b	c_b^b	p^c	expt ^d
4-deoxyglucal (11)	C1	-0.182	0.169	0.005 (α)	α (>20:1)
	C2	-0.739	0.692	0.067 (α)	
4-deoxyallal (3)	C1	-0.156	0.131	0.007 (β)	β (>20:1)
	C2	-0.737	0.746	0.014 (β)	
3-deoxyglucal (9), ⁴ H ₅	C1	-0.213	0.180	0.013 (α)	neither (1:1)
	C2	-0.726	0.713	0.019 (α)	
3-deoxyglucal (9), ⁵ H ₄	C1	-0.169	0.214	0.017 (β)	"
	C2	-0.651	0.711	0.082 (β)	
3-deoxyglucal, 4,6-acetal (8)	C1	-0.188	0.204	0.006 (β)	β (2:1)
	C2	-0.676	0.674	0.003 (α)	
3-deoxygalactal (15)	C1	-0.217	0.183	0.013 (α)	α (>20:1)
	C2	-0.723	0.674	0.069 (α)	
3-deoxygalactal, 4,6-acetal (14)	C1	-0.134	0.095	0.009 (α)	α (4:1)
	C2	-0.454	0.430	0.021 (α)	
dideoxypentenoside	atom	c_a^b	c_b^b	p^c	expt ^e
2-deoxy- β -glc (20)	C5	-0.139	0.226	0.032 (β)	α (>20:1)
	C4	-0.391	0.182	0.120 (α)	
2-deoxy- α -glc (21)	C5	-0.201	0.180	0.008 (α)	α (10:1)
	C4	-0.719	0.719	0.000	
3-deoxy- β -glc (26), ² H ₁	C5	-0.221	0.172	0.019 (α)	β (3:2)
	C4	-0.679	0.690	0.015 (β)	
3-deoxy- β -glc (26), ¹ H ₂	C5	-0.074	0.162	0.021 (β)	"
	C4	-0.477	0.457	0.018 (α)	
3-deoxy- α -glc (27)	C5	-0.230	0.184	0.019 (α)	β (>20:1)
	C4	-0.639	0.691	0.069 (β)	
D-xytal (28)	C1	-0.077	0.129	0.011 (β)	α (5:1)
	C2	-0.311	0.200	0.056 (α)	

deoxyglycal	atom	c_a^b	c_β^b	p^c	expt ^d
L-arabinal (29)	C1	-0.174	0.221	0.019 (α)	α (>20:1)
	C2	-0.709	0.753	0.064 (α)	

^a All structures optimized by DFT-B3LYP calculations (6-31+G(d,p)) using prior to insertion of *s*-functions. Unless otherwise stated, glycols and DDPs were optimized starting from their respective ⁴*H*/5 and ²*H*/1 conformations.

^b Each coefficient is calculated as the linear combination of *s*-function and 2*py*; +/- values refer to the sign of the coefficients for each lobe.

^c Net polarization of each orbital in parentheses.

^d α : β selectivities from Table 3.

^e α : β selectivities from Table 4.