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

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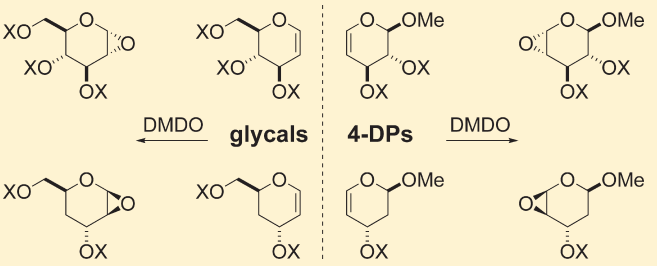
Supporting Information

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.[1−3] 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]

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 4α- or 4β-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, 4β-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 4α-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.

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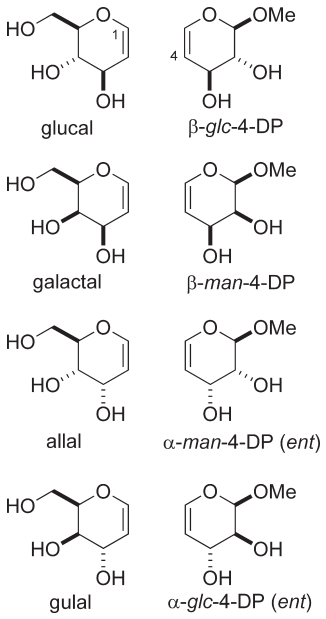


Figure 1. Four diastereomeric glycals, and their 4-deoxypentenoside isosteres.

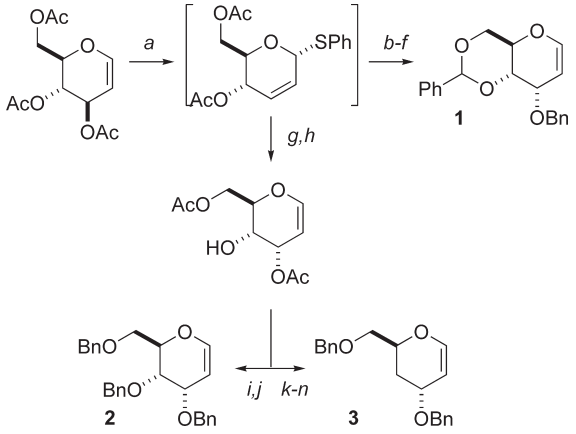
PPFMO analysis has been previously used to rationalize stereoselective additions to glycals, although with mixed results.[15,16] This may be due in part to a less than perfect match between theory and experiment, which involved charged species and the generation of cationic intermediates upon reaction 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

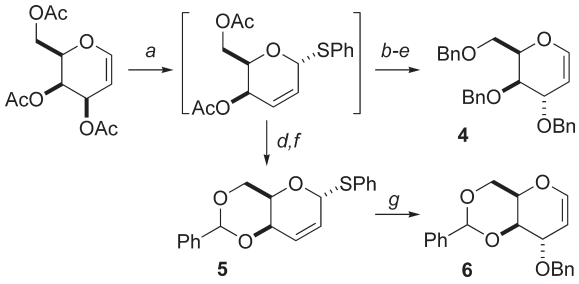
Synthesis of Unsaturated Pyranosides. Allal derivatives **1** and **3** and D-gulal derivatives **4** and **6** were prepared respectively from tri-*O*-acetyl-D-glucal and tri-*O*-acetyl-D-galactal, based on a synthetic sequence developed by Danishefsky and co-workers (Schemes 1 and 2).[19] In brief, compound **1** was prepared in 36% overall yield from triacetyl glucal by a Ferrier rearrangement,

Scheme 1. Synthesis of D-Allal Derivatives[a]



[a] Reagents and conditions: (a) PhSH, $BF_3 \cdot Et_2O$, CH_2Cl_2, −78 °C (69%); (b) NaOMe, MeOH, rt; (c) $PhCH(OMe)_2$, *p*-TsOH, rt; (d) DMDO, CH_2Cl_2, −78 °C; (e) Et_2NH, THF, rt; (f) BnBr, Bu_4NI, 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, CS_2, MeI, THF, rt; (l) Bu_3SnH, AIBN, DMF, 120 °C; (m) NaOMe, MeOH, rt; (n) BnBr, Bu_4NI, NaH, THF, rt (22% over 4 steps).

Scheme 2. Synthesis of D-Gulal Derivatives[a]

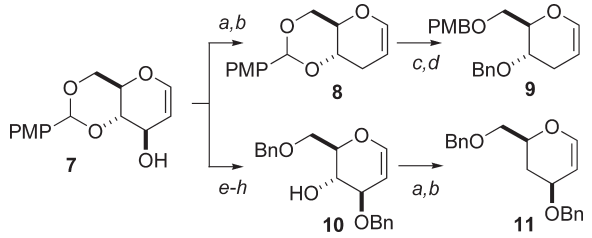


[a] Reagents and conditions: (a) PhSH, $SnCl_4$, CH_2Cl_2, −20 °C (98%); (b) DMDO, CH_2Cl_2, −78 °C; (c) Et_2NH, THF, rt; (d) NaOMe, MeOH, rt; (e) BnBr, Bu_4NI, NaH, THF, rt (76% yield over 4 steps); (f) $PhCH(OMe)_2$, *p*-TsOH, rt (70% over 2 steps); (g) same as steps (b), (c), and (e) (45% over 3 steps).

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 Et_2NH-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.

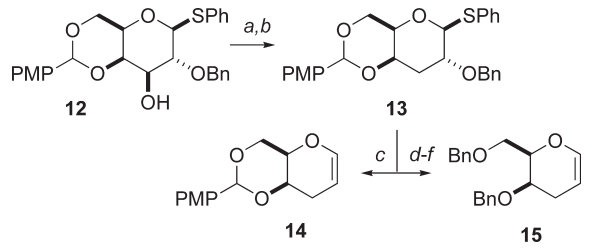
Gulal derivatives **4** and **6** were prepared from tri-*O*-acetyl galactal, as attempts to epimerize the C4 stereocenter of 3,6 di-*O*-acetyl allal proved unsuccessful. Treatment with benzenethiol in the presence of $SnCl_4$ at −78 °C resulted in a Ferrier rearrangement product in

Scheme 3. Synthesis of 3- and 4-Deoxyglucal Derivatives[a]



[a] Reagents and conditions: (a) NaH, CS_2, MeI, THF, rt; (b) Bu_3SnH, AIBN, $PhCH_3$, reflux (54% isolated yield for **8**, 82% for **11**); (c) $BH_3 \cdot THF$, Bu_2BOTf, THF, −78 °C; (d) BnBr, Bu_4NI, NaH, THF, rt (73% over 2 steps); (e) BnBr, Bu_4NI, NaH, DMF, rt; (f) iBu_2AlH, CH_2Cl_2, 0 °C; (g) same as step (e); (h) DDQ, *t*BuOH, pH 7 phosphate buffer, CH_2Cl_2, rt (61% over 4 steps). PMB = *p*-methoxybenzyl; PMP = *p*-methoxyphenyl.

Scheme 4. Synthesis of 3-Deoxygalactal Derivatives[a]



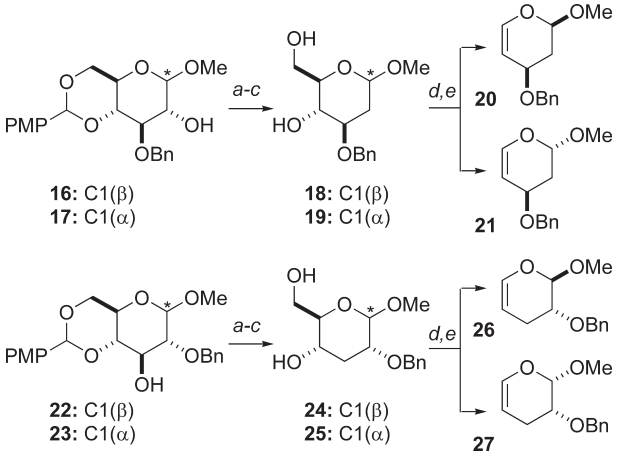
[a] Reagents and conditions: (a) NaH, CS_2, MeI, THF, rt; (b) Bu_3SnH, AIBN, $PhCH_3$, reflux (75% over 2 steps); (c) Li-naphthalenide (2.5 equiv), THF, −40 °C (78%); (d) AcOH/THF/H_2O, 45 °C; (e) BnBr, Bu_4NI, NaH, DMF, rt (66% over 2 steps); (f) same as step (c) (60%).

98% yield (8:1 α:*β* mixture, Scheme 2), followed by DMDO oxidation, Et_2NH-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 conditions[20] 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 Bu_3SnH and photochemical activation.[21] Regioselective cleavage of the 4,6-anisylidene acetal in **8** with dilute Bu_2BOTf[22] 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 by using Barton−McCombie conditions, with careful attention paid to the reaction time and the stoichiometry of Bu_3SnH to avoid reductive desulfurization. Compound **13** was then cleanly converted into 3-deoxygalactal **14** in 78% yield by reductive elimination with use of lithium naphthalenide. The same chemistry was also applied toward the synthesis of di-*O*-benzyl derivative **15**; in this case, acetal hydrolysis 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 with $LiAlH_4$[23] or the allylic reduction of galactals with 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.

Scheme 5. Synthesis of 2,4- and 3,4-Dideoxypentenosides[a]



[a] Reagents and conditions: (a) NaH, CS_2, MeI, THF, rt; (b) Bu_3SnH, AIBN, $PhCH_3$, reflux; (c) AcOH/THF/H_2O, 45 °C (81% over 3 steps for **18**, 56% for **19**, 50% for **24**, 87% for **25**); (d) TEMPO, BAIB, H_2O/CH_2Cl_2, rt; (e) DMFDNPA, DMF, 200 °C (58% isolated yield over 2 steps for **20**, 60% for **21** and **26**, 28% for **27**).

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 provides the basis for the synthesis of the 2,4- and 3,4-dideoxypentenosides (DDPs) described above (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-vessel 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 the latter case by product volatility.

Lastly, pentopyranose derivatives 3,4-di-*O*-benzyl-D-xylal and -L-arabinal (**28** and **29**) were prepared by using the reductive lithiation method described above. These compounds have been

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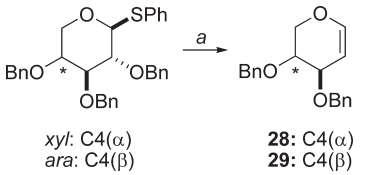
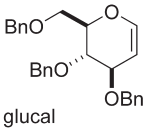
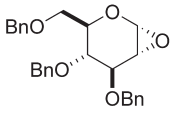
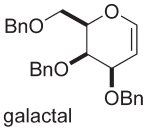
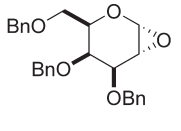
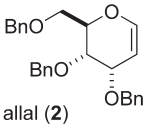
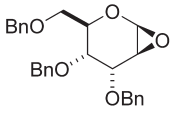
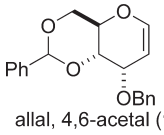
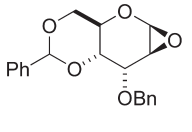
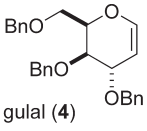
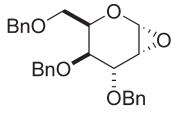
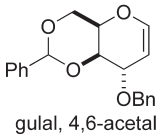
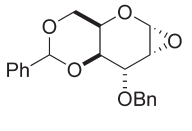
Scheme 6. Synthesis of D-Xylal and L-Arabinal[a]



[a] Reagents and conditions: (a) Li-naphthalenide, THF, −40 °C (quantitative).

Table 1. Facioselective Glycal Epoxidation by DMDO

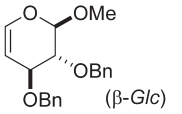
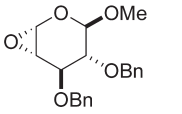
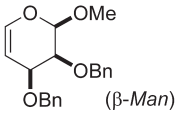
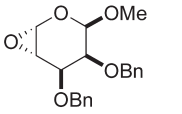
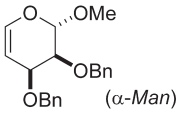
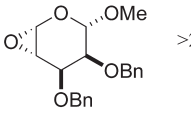
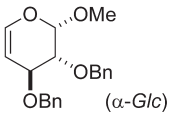
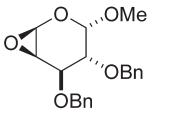
glycal	react cond[a]	epoxide	α:β
 glucal	A B		10:1 10:1[b]
 galactal	A B		>20:1 20:1[b]
 allal (**2**)	A		<1:20
 allal, 4,6-acetal (**1**)	A B		<1:20 1:10[b,c]
 gulal (**4**)	A		3:2
 gulal, 4,6-acetal (**6**)	A B		3:1 1:1[b,c]

[a] Reaction conditions: (A) DMDO (3 equiv), −55 °C, 2 days; (B) DMDO (2 equiv), 0 °C, 1 h. [b] See ref 5. [c] Ratio obtained with C3 silyl ether.

previously prepared via reductive elimination of their peracetylated glycosyl halides, typically by treatment with zinc dust/$CuSO_4$ 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, 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 with 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 CH_2Cl_2, followed by further drying and concentration (see Experimental Section).[30] Maximum stereoselectivity can be achieved by conducting DMDO oxidations in CH_2Cl_2 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]

Table 2. Facioselectivities of 4-DP Epoxidation by DMDO

4-DP	react cond[a]	epoxide	α:β
 (β-*Glc*)	A B		10:1[b] 8:1
 (β-*Man*)	B		15:1[b]
 (α-*Man*)	B		>20:1[c]
 (α-*Glc*)	A B		1:10[b] 1:4[c]

[a] Reaction conditions: (A) DMDO (3 equiv), −55 °C, 2 days; (B) DMDO (2 equiv), 0 °C, 1 h. [b] See ref 10. [c] See ref 9.

The facioselectivity of DMDO oxidation for the various glycals and their isosteric 4-DPs were typically determined by peak integration by 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 $LiAlD_4$ and LiSEt (Tables 5 and 6, see the 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 gulal derivatives **4**

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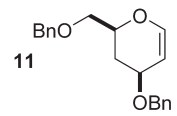
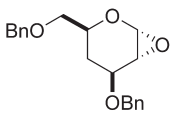
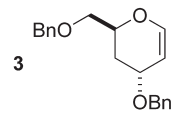
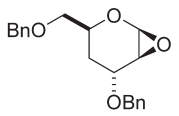
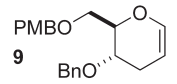
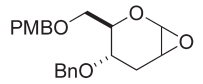
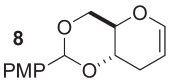
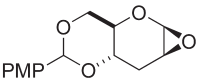
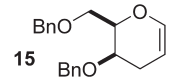
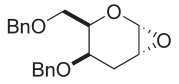
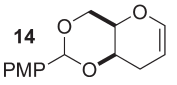
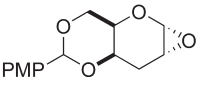
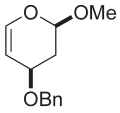
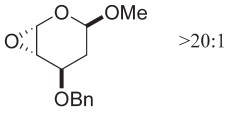
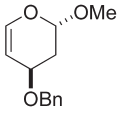
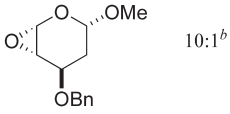
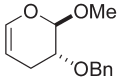
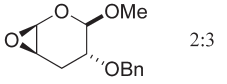
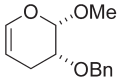
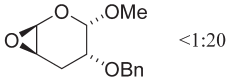
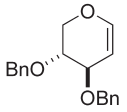
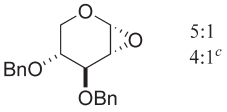
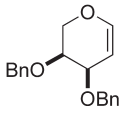
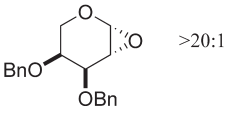
Table 3. Facioselectivities of Deoxyglycal Epoxidation by DMDO

deoxyglycal	react cond[a]	epoxide	α:β
 **11**	A		>20:1
 **3**	A		<1:20
 **9**	A		1:1
 **8**	A		1:2[b]
 **15**	B		>20:1
 **14**	A		4:1

[a] Reaction conditions: (A) DMDO (3 equiv), −55 °C, 2 days; (B) DMDO (3 equiv), −55 °C, 1 day. [b] Determined by ^{1}H NMR peak integration.

Table 4. Facioselectivities of Dideoxypentenoside Epoxidation by DMDO

dideoxypentenoside	react cond[a]	epoxide	α:β
 **20**	A		>20:1
 **21**	A		10:1[b]
 **26**	A		2:3
 **27**	A		<1:20
 xylal (**28**)	A B		5:1 4:1[c]
 arabinal (**29**)	A		>20:1

[a] Reaction conditions: (A) DMDO (3 equiv), −55 °C, 2 days; (B) DMDO (2 equiv) 0 °C, 1 h. [b] Reference 10. [c] Reference 7.

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 gulals is sluggish compared with that of other diastereomers and requires a reaction time of 4 days to reach completion at −55 °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 gulal, is temperature dependent and is high only at −55 °C, whereas that of *β*-*glc*-4-DP, the isosteric equivalent of glucal, remains high even at 0 °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-dideoxypentenoside **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, gulal **6** and 3-deoxyglucal **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 dideoxypentenosides **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 and 6), followed by acetylation in some cases to assist ^{1}H NMR coupling constant analysis. We found deuteride addition to be ideal for this purpose as it does not introduce new peaks to the ^{1}H NMR spectrum, and its low electronegativity (essentially that of H) supports large coupling constants for diaxial vicinal protons

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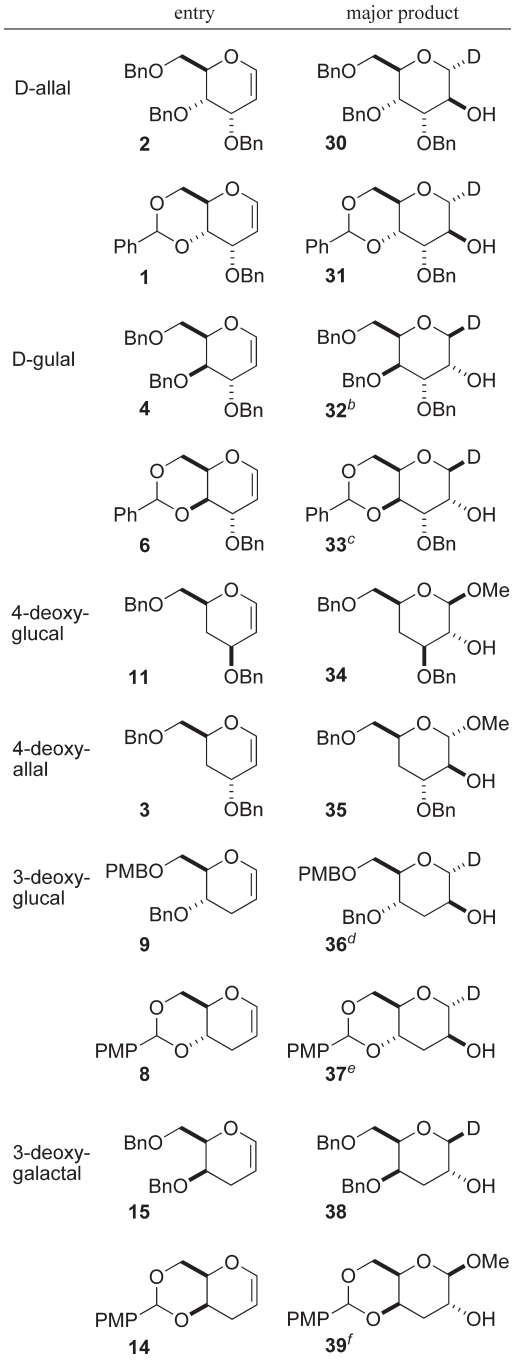
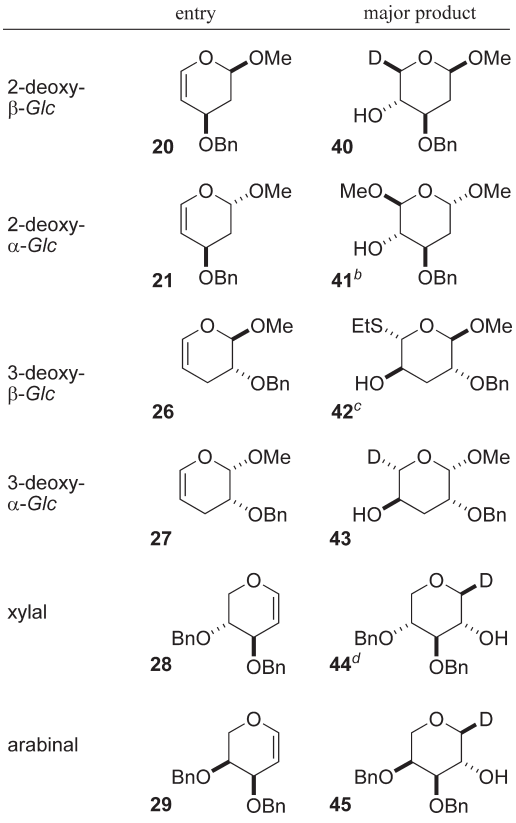
Table 5. S_N2 Ring-Opening Products of Epoxides Derived from Glycals[a]



[a] Relative stereochemistry of major products (facioselectivity ≥10:1, unless otherwise noted) confirmed by ^{1}H NMR coupling constant analysis (see Table S1, Supporting Information). [b] 3:2 ratio. [c] 3:1 ratio. [d] 1:1 ratio. [e] 2:1 ratio. [f] 4:1 ratio.

based on the parametrized 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 Hz; see Tables S1 and S2, Supporting Information).[35]

Table 6. S_N2 Ring-Opening Products of Epoxides Derived from Dideoxypentenosides[a]



[a] Relative stereochemistry of major products (facioselectivity ≥10:1, unless otherwise noted) confirmed by ^{1}H NMR coupling constant analysis (see Table S2, Supporting Information). [b] See ref 10. [c] 3:2 ratio. [d] 5:1 ratio.

We note that the remaining coupling constants of the pyranosides listed in Tables 5 and 6 did not always clearly indicate a preference for the $^4C_1$ chair conformation, as most of these values were small (see the 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 wave functions produces facially dependent coefficients (c_α and c_β) that describe 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

dx.doi.org/10.1021/jo102382r |J. Org. Chem. 2011, 76, 2532–2547

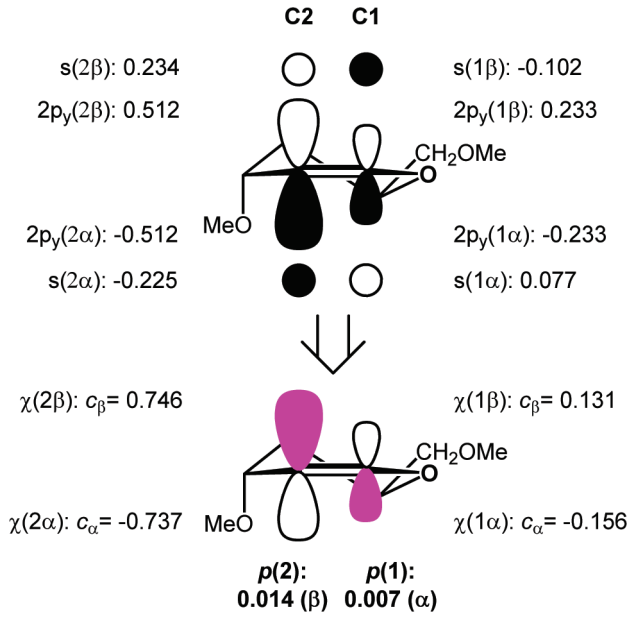


Figure 2. PPFMO analysis of the dimethyl ether of 4-deoxyallal (analogue of **3**). Pairs of 1s functions are superimposed onto the 2p$_y$ orbitals at C1 and C2 to produce asymmetric wave functions (χ), whose coefficients c_α and c_β are used to derive p, the net electronic polarization per orbital (in 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).

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 $0.1c_\beta$. 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 dideoxypentenosides (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 above by using dimethyl 4-deoxyallal, the electronic analogue of **3** (Figure 2). In brief, the structure is first subjected to energy mimimization by using DFT calculations (B3LYP/6-31+G(d,p)), starting from the idealized half-chair ($^4H_5$) 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 wave functions χ with asymmetric lobes, labeled here as $\chi(1\alpha)$, $\chi(1\beta)$, $\chi(2\alpha)$, and $\chi(2\beta)$. Each wave function 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.

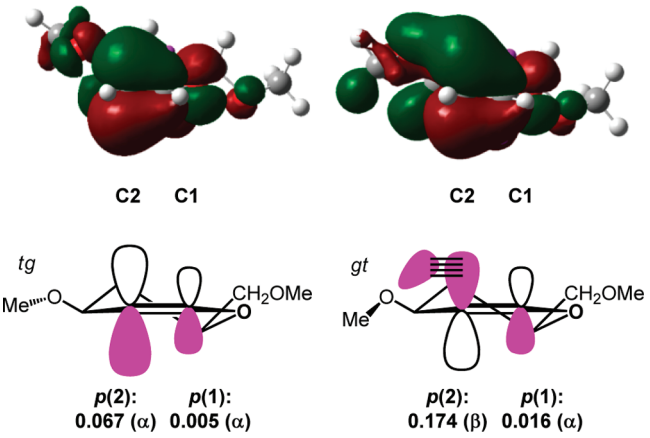


Figure 3. Electron density maps of the 4-deoxyglucal derivative (analogue of **11**) with the C3 methyl ether in the *tg* conformation (left) or the *gt* conformation (right). In the case of *gt*, the electron density map reveals an incidental (but superfluous) hyperconjugation between the hybrid orbital at C2 and a lone pair on O3 (extended green lobe), creating an artificial polarization in the β direction.

We note that substituting each phenyl (C_6H_5) 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 when the O3 methyl group adopts a *trans-gauche* (*tg*) orientation (C2−C3−O3−CH_3 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 ($^4H_5$ and $^2H_1$, 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 arabinal **29** is clearly in line with the high *anti* selectivities observed after epoxidation. In the case of *trans*-disubstituted derivatives, those having a C3 oxygen

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Table 7. PPFMO Analysis of Disubstituted Glycals and Dideoxypentenosides (Permethylated)[a]

deoxyglycal	atom	c_α[b]	c_β[b]	p[c]	exptl[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**), $^4H_5$	C1	−0.213	0.180	0.013 (α)	neither (1:1)
	C2	−0.726	0.713	0.019 (α)	
3-deoxyglucal (**9**), $^5H_4$	C1	−0.169	0.214	0.017 (β)	neither (1:1)
	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_α[b]	c_β[b]	p[c]	exptl[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**), $^2H_1$	C5	−0.221	0.172	0.019 (α)	β (3:2)
	C4	−0.679	0.690	0.015 (β)	
3-deoxy-β-*glc* (**26**), $^1H_2$	C5	−0.074	0.162	0.021 (β)	β (3:2)
	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-xylal (**28**)	C1	−0.077	0.129	0.011 (β)	α (5:1)
	C2	−0.311	0.200	0.056 (α)	
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)) prior to insertion of s-functions. Unless otherwise stated, glycals and DDPs were optimized starting from their respective $^4H_5$ and $^2H_1$ conformations. [b] Each coefficient is calculated as the linear combination of s-function and $2p_y$; ± 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.

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 analogues 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 facioselectivites of 2:1 or less.

In the case of 3-deoxyglucal **9** the experimental results do not suggest any stereochemical preferences, but the $^4H_5$ conformation of the 3,6-di-*O*-methyl analogue produces *p* values predicting α facioselectivity. However, energy minimization and PPFMO analysis of the alternate $^5H_4$ half-chair conformation indicates both C1 and C2 orbitals to be polarized in the β direction, opposite that of the $^4H_5$ conformer (Figure 4, left). The energy difference between conformations ($\Delta\Delta G_{conf}$) can be expected to be less than 1 kcal/mol,[18d] meaning that neither $^5H_4$ nor $^4H_5$ is dominant under the DMDO oxidation conditions. A parallel study was conducted on the analogue of the isosteric DDP, 3-deoxy-β-*glc* **26**: again, PPFMO analysis of the $^1H_2$ conformation revealed the polarizations of the C4 and C5 orbitals to be essentially mirror images of those found in the $^2H_1$ conformer (Figure 4, right).

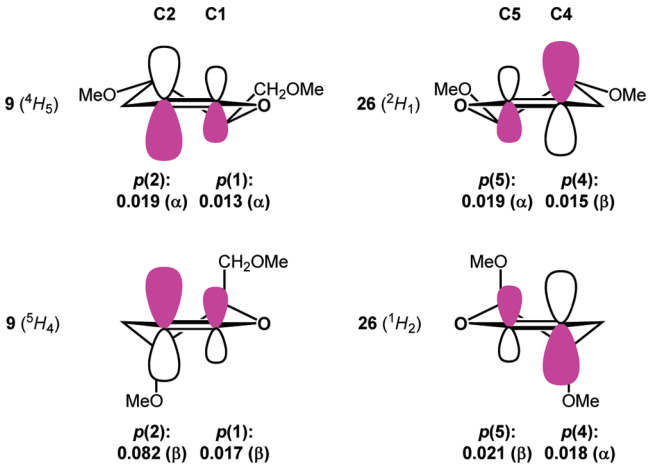

Figure 4. PPFMO analysis of dimethyl ether analogues of 3-deoxyglucal (**9**) and 3-deoxy-β-*glc* (**26**), starting from alternate half-chair conformations. For each 2p orbital, $p(n)$, the net electronic polarization is presented as a filled lobe (purple).

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 analogues in their $^4H_5$ 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

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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 the 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-Deoxypentenosides 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 $Na_2S_2O_3$ 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 mmHg) 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 were 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, then further concentrated under reduced pressure at 0 °C for 30 min. The epoxide was used immediately without further purification.

Epoxide S_N2 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 ($Na_2SO_4 \cdot 10H_2O$) to precipitate the aluminum salts. After being stirred 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 °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 × 20 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 °C, then slowly warmed to rt over a period of 14 h. 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-allal[36] (184 mg, 0.80 mmol) in 1:1 THF:CS_2 (18 mL) was treated with a 60% dispersion of NaH in mineral oil (97 mg, 2.40 mmol) at 0 °C. After 15 min, the ice bath was removed and the solution was 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 h or until TLC indicated the disappearance of starting material, then quenched at 0 °C with satd NH_4Cl (20 mL) and extracted with Et_2O (3 × 20 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 °C in a sealed tube for 30 min. The solution was allowed to cool to rt, and then diluted with Et_2O (3 × 10 mL). The mixture was extracted, washed with H_2O (3 × 10 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 × 10 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 °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 × 5 mL). The crude diol was then redissolved in anhydrous DMF (7.2 mL), cooled to 0 °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 °C with satd NH_4Cl (10 mL), then extracted with Et_2O (3 × 10 mL). The combined organic phase was washed with H_2O (3 × 10 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 Hz), 4.87 (dt, 1 H, *J* = 1.8, 6.0 Hz), 4.44−4.26 (m, 5 H), 3.66 (m, 1 H), 3.43 (d, 2 H, *J* = 3.9 Hz), 1.94 (br dd, 1 H, *J* = 1.8, 14.4 Hz), 1.64 (ddd, 1 H, *J* = 3.9, 12.3, 14.7 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}. $[\alpha]^{25}_D$ +45.0 (*c* 0.2, CH_2Cl_2). HRESI-MS: *m*/*z* calcd for $C_{20}H_{22}O_3$ $[M + Na]^+$ 333.1467, found 333.1465.

3,4,6-Tri-*O*-benzyl-D-gulal (3,4,6-Tri-*O*-benzyl-D-*xylo*-hex-1-enitol) (4). Phenyl 4,6-di-*O*-acetyl-2,3-dideoxy-1-thio-α-D-*threo*-hex-2-enopyranoside[37] (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 °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% Et_3N, 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 NH_4Cl (10 mL), then extracted with Et_2O (3 × 10 mL). The combined organic phase was washed with H_2O (3 × 10 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 0−15% EtOAc−hexanes gradient with 0.1% Et_3N, to afford tribenzyl-D-gulal **4** as a white solid (83.7 mg, 91% over 3 steps). ^1H NMR (300 MHz, C_6D_6): 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). ^{13}C NMR (75 MHz, C_6D_6): 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}. $[\alpha]^{25}_D$ −37 (*c* 0.7, CH_2Cl_2). HRESI-MS: *m*/*z* calcd for $C_{27}H_{28}O_4$ $[M + H]^+$ 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-enopyranoside[37] (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 being stirred 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 mmHg). The reaction mixture was neutralized with satd $NaHCO_3$ (20 mL) and then extracted with Et_2O (3 × 20 mL). The combined organic phase was washed with H_2O (3 × 20 mL) and brine (20 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel chromatography, using a 10−50% EtOAc−hexanes gradient with 0.1% Et_3N, to afford benzylidene acetal **5** as white crystals (468 mg, 70% over 2 steps). ^1H NMR (300 MHz, $CDCl_3$): 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). ^{13}C NMR (75 MHz, $CDCl_3$): 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}. $[\alpha]^{25}_D$ −0.02 (0.4, CH_2Cl_2). HRESI-MS: *m*/*z* calcd for $C_{19}H_{18}O_3S$ $[M + H]^+$ 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 CH_2Cl_2 (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% Et_3N, 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 NH_4Cl (20 mL) and extracted with Et_2O (3 × 20 mL). The combined organic extracts were washed with H_2O (3 × 20 mL) and brine (20 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel chromatography, using a 0−20% EtOAc−hexanes gradient with 0.1% of Et_3N, to afford 3-*O*-benzyl-D-gulal **6** as a white solid (158 mg, 77%). ^1H NMR (300 MHz, C_6D_6): 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). ^{13}C NMR (75 MHz, C_6D_6): 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}. $[\alpha]^{25}_D$ +197 (*c* 0.5, CH_2Cl_2). HRESI-MS: *m*/*z* calcd for $C_{20}H_{20}O_4$ $[M + H]^+$ 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:CS_2 (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 the solution was

stirred for a further 30 min at rt, after which CH_3I (0.18 mL, 2.83 mmol) was added. The reaction mixture was stirred for 16 h or until TLC indicated the disappearance of starting material, then quenched at 0 °C with satd NH_4Cl (10 mL) and extracted with CH_2Cl_2 (3 × 15 mL). The combined organic extracts were washed with brine (15 mL), dried over Na_2SO_4, 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 Et_3N, 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 Bu_3SnH (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 Et_3N, 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, C_6D_6): 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). ^{13}C NMR (100 MHz, C_6D_6): 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}. $[\alpha]^{25}_D$ +40.9 (*c* 0.2, CH_2Cl_2). HR-EI-MS: *m*/*z* calcd for $C_{14}H_{16}O_4$ $[M]^+$ 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 Bu_2BOTf (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 Et_3N (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 chromatograph,y using a 5−20% EtOAc−hexanes gradient with 0.1% Et_3N. It is worth noting that the alcohol can be contaminated by residual Bu_2BOH (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 NH_4Cl (20 mL) and extracted with Et_2O (3 × 20 mL). The combined organic extracts were washed with H_2O (3 × 20 mL) and brine (20 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel chromatography, using a 0−10% EtOAc−hexanes gradient with 0.1% of Et_3N, to afford benzyl ether **9** as a white solid (270 mg, 73% over 2 steps). ^1H NMR (300 MHz, $(CD_3)_2CO$): 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). ^{13}C NMR (75 MHz, $CDCl_3$): 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}. $[\alpha]^{25}_D$ +44.3 (*c* 1.1, CH_2Cl_2). HR-EI-MS: *m*/*z* calcd for $C_{21}H_{24}O_4$ $[M]^+$ 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 with 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 NH_4Cl (50 mL) and extracted with Et_2O (3 × 50 mL). The combined organic extracts were washed with H_2O (3 × 50 mL) and brine (50 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica chromatography, using a 5−30% EtOAc−hexanes gradient with 0.1% of Et_3N, 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 CH_2Cl_2 (13 mL) and cooled to 0 °C, then treated with *i*Bu_2AlH (10 mL of a 1 M solution in hexanes) and stirred for 2 h, after which the reaction mixture was quenched with satd NH_4Cl (25 mL) and satd K,Na-tartrate (20 mL). The organic layers were extracted with $CHCl_3$ (3 × 50 mL), then dried over Na_2SO_4 and purified by silica gel chromatography, using a 30−50% EtOAc−hexanes gradient with 0.1% Et_3N, 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 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 NH_4Cl (20 mL) and extracted with Et_2O (3 × 20 mL). The combined organic extracts were washed with H_2O (3 × 20 mL) and brine (20 mL), dried over Na_2SO_4, then concentrated and purified by silica gel chromatography, using a 10−25% EtOAc−hexanes gradient with 0.1% Et_3N, to afford the corresponding 6-*O*-benzyl ether as a colorless syrup (633 mg, 93%). This was redissolved in CH_2Cl_2 (40 mL), *t*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 $NaHCO_3$ (20 mL), and extracted with CH_2Cl_2 (3 × 20 mL). The organic layers were washed with brine (25 mL), dried over Na_2SO_4, then concentrated and purified by silica gel chromatography, using a 10−50% EtOAc−hexanes gradient with 0.1% Et_3N, to afford 4,6-dibenzyl glucal **10** as a colorless syrup (360 mg, 78%). ^1H NMR (300 MHz, C_6D_6): 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). ^{13}C NMR (100 MHz, C_6D_6): 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:CS_2 (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 the solution was stirred for a further 30 min at rt, then treated with CH_3I (0.4 mL, 6.42 mmol) and stirred for 16 h or until TLC indicated the disappearance of starting material. This reaction mixture was quenched with saturated NH_4Cl solution (5 mL), extracted with CH_2Cl_2 (3 × 25 mL), washed with brine (5 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude C4 xanthate was redissolved in degassed toluene (3 mL) and then treated with Bu_3SnH (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 Et_3N, to afford 4-deoxyglucal **11** as a colorless oil (47 mg, 82% over 2 steps). ^1H NMR (300 MHz, C_6D_6): 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). ^{13}C NMR (75 MHz, C_6D_6): 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. $[\alpha]^{25}_{D}$ −16.0 (*c* 1.0, $CHCl_3$).

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:CS_2 (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 CH_3I (0.26 mL, 4.26 mmol) and stirred for 16 h or until TLC indicated the disappearance of starting material. The reaction mixture was quenched with saturated NH_4Cl solution (5 mL), extracted with CH_2Cl_2 (3 × 25 mL), washed with brine (5 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The resulting residue was purified by silica gel chromatography, using 20% EtOAc in hexanes with 0.1% of Et_3N, to afford the C3 xanthate as a white solid (0.44 g, 91%). This was redissolved in degassed toluene (8 mL) and treated with Bu_3SnH (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% Et_3N to afford 3-deoxygalactoside **13** as a white solid (0.26 g, 75%). ^{1}H NMR (400 MHz, C_6D_6): 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). ^{13}C NMR (100 MHz, C_6D_6): 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}. $[\alpha]^{25}_{D}$ −6.7 (*c* 0.7, CH_2Cl_2). HRESI-MS: *m*/*z* calcd for $C_{27}H_{28}O_5S$ $[M + H]^+$ 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% Et_3N, to afford the desired 3-deoxygalactal **14** as a white solid (104 mg, 78%). ^{1}H NMR (400 MHz, C_6D_6): 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). ^{13}C NMR (100 MHz, C_6D_6): 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}. $[\alpha]^{25}_{D}$ +2.5 (*c* 0.2, CH_2Cl_2). HR-EI-MS: *m*/*z* calcd for $C_{14}H_{16}O_4$ $[M]^+$ 248.1049, found 248.1044.

4,6-Di-*O*-benzyl-3-deoxy-D-galactal (15). A 50 mL rb flask containing **13** (82 mg, 0.18 mmol) was dissolved in 8:1:1 AcOH:THF:H_2O (1.8 mL) and heated to 45 °C for 5 h. The reaction mixture was neutralized with $NaHCO_3$ (20 mL), washed with brine (20 mL), dried over Na_2SO_4, 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 NH_4Cl (20 mL) and extracted with Et_2O (3 × 20 mL). The combined organic extracts were washed with H_2O (3 × 20 mL) and saturated brine (20 mL), dried over Na_2SO_4, 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 then subjected to the reductive elimination conditions described above and purified by silica gel chromatography, using a 5−20% EtOAc−hexanes gradient with 0.1% Et_3N, to afford the desired 3-deoxygalactal **15** as a white solid (20 mg, 60%). ^{1}H NMR (400 MHz, C_6D_6): 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). ^{13}C NMR (100 MHz, C_6D_6): 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 $C_{20}H_{22}O_3$ $[M + Na]^+$ 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% Et_3N, to afford 2,4-dideoxy-4-pentenoside **20** as a volatile colorless syrup (22 mg, 58% over 2 steps). ^{1}H NMR (300 MHz, C_6D_6): 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). ^{13}C NMR (75 MHz, C_6D_6): 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}. $[\alpha]^{25}_{D}$ −10.0 (*c* 0.2, CH_2Cl_2). HRESI-MS: *m*/*z* calcd for $C_{13}H_{16}O_3$ $[M + H - CH_3OH]^+$ 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-pentenoside **26** as a colorless syrup (37 mg, 66% over 2 steps). ^{1}H 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}. $[\alpha]^{25}_{D}$ −93.0 (*c* 1.0, $CHCl_3$). HRESI-MS: *m*/*z* calcd for $C_{13}H_{16}O_3$ $[M + H]^+$ 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-pentenoside **27** as a colorless syrup (38 mg, 28% over 2 steps). ^{1}H 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}. $[\alpha]^{25}_{D}$ +96.6 (*c* 0.5, CH_2Cl_2). HRESI-MS: *m*/*z* calcd for $C_{13}H_{16}O_3$ $[M + H - CH_3OH]^+$ 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 S_N2 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%). ^{1}H 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}. $[\alpha]^{25}_D$ +47.3 (*c* 1.0, CH_2Cl_2). HRESI-MS: *m*/*z* calcd for $C_{27}H_{29}DO_5$ $[M + Na]^+$ 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 S_N2 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}. $[\alpha]^{25}_D$ +14.8 (*c* 0.6, CH_2Cl_2). HRESI-MS: *m*/*z* calcd for $C_{22}H_{23}DO_6$ $[M + Na]^+$ 408.1433, found 408.1430.

2-*O*-Acetyl-3,4,6-tri-*O*-benzyl-1-deoxy-1*R*-deuterio-D-gulose (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 Et_2O:THF (2.5 mL) and subjected to S_N2 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 α:β (C1), 81% combined yield). **2-*O*-Acetyl-3,4,6-tri-*O*-benzyl-1-deoxy-1*R*-deuterio-D-gulose (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}. $[\alpha]^{25}_D$ −16.9 (*c* 1.0, CH_2Cl_2). HRESI-MS: *m*/*z* calcd for $C_{29}H_{31}DO_6$ $[M + Na]^+$ 500.2159, found 500.2154. **2-*O*-Acetyl-3,4,6-tri-*O*-benzyl-1-deoxy-1*S*-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, 127.8, 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}. $[\alpha]^{25}_D$ +1.1 (*c* 1.1, CH_2Cl_2). HRESI-MS: *m*/*z* calcd for $C_{29}H_{31}DO_6$ $[M + Na]^+$ 500.2159, found 500.2155.

3-*O*-Benzyl-4,6-benzylidene-1-deoxy-1*S*-deuterio-D-gulose (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 Et_2O:THF (1.3 mL) and subjected to S_N2 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 α:β (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-1*S*-deuterio-D-gulose (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}. $[\alpha]^{25}_D$ +8.41 (*c* 1.0, CH_2Cl_2). HRESI-MS: *m*/*z* calcd for $C_{20}H_{21}DO_5$ $[M + Na]^+$ 366.1428, found 366.1422. **3-*O*-Benzyl-4,6-benzylidene-1-deoxy-1*R*-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}. $[\alpha]^{25}_D$ +9.64 (*c* 0.5, CH_2Cl_2). HRESI-MS: *m*/*z* calcd for $C_{20}H_{21}DO_5$ $[M + Na]^+$ 366.1428, found 366.1429.

Methyl 3,6-Di-*O*-benzyl-4-deoxy-1*S*-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% Et_3N 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, C_6D_6): δ7.30−7.21 (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 $C_{21}H_{26}O_5$ $[M + H]^+$ 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% Et_3N 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, C_6D_6): 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). ^{13}C NMR (75 MHz, C_6D_6): 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}. $[\alpha]^{25}_D$ +34.0 (*c* 0.5, CH_2Cl_2). HRESI-MS: *m*/*z* calcd for $C_{21}H_{26}O_5$ $[M + Na]^+$ 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 Et_2O:THF (1.3 mL) and subjected to S_N2 ring opening with $LiAlD_4$ 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 Ac_2O (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% Et_3N. **4-*O*-Benzyl-1*R*-deuterio-1,3-dideoxy-6-*O*-*p*-methoxybenzyl-D-mannose (36):** ^1H NMR (400 MHz, $CDCl_3$): 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). ^{13}C NMR (100 MHz, $CDCl_3$): 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}. $[\alpha]^{25}_D$ +36.1 (*c* 0.8, CH_2Cl_2). HRESI-MS: *m*/*z* calcd for $C_{21}H_{25}DO_5$ $[M + Na]^+$ 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, $CDCl_3$): 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). ^{13}C NMR (100 MHz, $CDCl_3$): 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}. $[\alpha]^{25}_D$ +54 (c 0.7, CH_2Cl_2). HRESI-MS: m/z calcd for $C_{21}H_{25}DO_5$ $[M + Na]^+$ 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 Et_2O:THF (2.5 mL) and subjected to S_N2 ring opening with $LiAlD_4$ as previously described (see procedure 2). The deuteride adduct **37** and its diastereomer **37′** were characterized as 2-*O*-acetates by treatment with Ac_2O (1 mL) in pyridine (2 mL) at rt for 12 h, concentrated with azeotropic distillation with toluene, and purified by preparative TLC using 30% EtOAc in hexanes with 0.1% Et_3N, gave an inseparable mixture (26 mg, 2:1 α:β (C1), 83% combined yield). **2-*O*-Acetyl-1,3-dideoxy-1*R*-deuterio-4,6-*p*-methoxybenzylidene-D-mannose (2-*O*-acetyl 37):** ^{1}H NMR (300 MHz, $CDCl_3$): 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-1*S*-deuterio-4,6-*p*-methoxybenzylidene-D-glucose (2-*O*-acetyl 37′):** ^{1}H NMR (300 MHz, $CDCl_3$): 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). ^{13}C NMR (diastereomeric mixture, 100 MHz, $CDCl_3$): 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 $C_{16}H_{19}DO_6$ $[M + H]^+$ 310.1401, found 310.1399.

4,6-Di-*O*-benzyl-1,3-dideoxy-1*S*-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 Et_2O:THF (1.3 mL) and subjected to S_N2 ring opening with $LiAlD_4$ as previously described (see procedure 1). The residue was purified by preparative TLC using 70% EtOAc in hexanes with 0.1% Et_3N, to afford deuteride adduct **38** as a white solid (19.0 mg, 91%). ^{1}H NMR (400 MHz, C_6D_6): 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). ^{13}C NMR (100 MHz, C_6D_6): 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, CH_2Cl_2). HRESI-MS: m/z calcd for $C_{20}H_{23}DO_4$ $[M + Na]^+$ 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 Ac_2O (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% Et_3N (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):** ^{1}H NMR (400 MHz, C_6D_6): 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). ^{13}C NMR (100 MHz, C_6D_6): 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, CH_2Cl_2). HRESI-MS: m/z calcd for $C_{17}H_{22}O_7$ $[M + Na]^+$ 361.1263, found 361.1268. **Methyl 2-*O*-Acetyl-3-deoxy-4,6-*p*-methoxybenzylidene-α-D-idose (2-*O*-acetyl 39′):** ^{1}H NMR (400 MHz, C_6D_6): 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-5*R*-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 $LiAlD_4$ as previously described (see procedure 1), and purified by preparative TLC using 40% EtOAc in hexanes with 0.1% Et_3N, to afford deuteride adduct **40** as a colorless oil (26 mg, 66%). ^{1}H NMR (300 MHz, C_6D_6): 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 (br s, 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). ^{13}C NMR (75 MHz, C_6D_6): 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, CH_2Cl_2). HRESI-MS: m/z calcd for $C_{13}H_{17}DO_4$ $[M + Na]^+$ 262.1166, found 262.1169.

Methyl 2-*O*-Benzyl-3-deoxy-5*R*-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 by 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 h. The reaction was quenched with satd $NaHCO_3$, extracted with EtOAc, dried over Na_2SO_4, 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 Ac_2O (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-5*R*-thioethyl-D-xylose (2-*O*-acetyl 42):** ^{1}H NMR (300 MHz, C_6D_6): 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-5*S*-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 $LiAlD_4$ as previously described (see procedure 1) and purified by preparative TLC using 80% EtOAc in hexanes with 0.1% Et_3N, to afford deuteride adduct **43** as a white solid (37 mg, 98%). ^{1}H NMR (400 MHz, C_6D_6): 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). ^{13}C NMR (100 MHz, C_6D_6): 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, CH_2Cl_2). HRESI-MS: m/z calcd for $C_{13}H_{17}DO_4$ $[M + Na]^+$ 262.1163, found 262.1166.

2,3-Di-*O*-benzyl-1-deoxy-1*S*-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 Et_2O:THF (1.4 mL) and subjected to S_N2 ring opening with $LiAlD_4$ 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% Et_3N. **2,3-Di-*O*-benzyl-1-deoxy-1*S*-deuterio-D-xylose (44):** ^{1}H NMR (400 MHz, C_6D_6): 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}. $[\alpha]^{25}_D$ −13.7 (*c* 0.4, CH_2Cl_2). HRESI-MS: *m*/*z* calcd for $C_{19}H_{21}DO_4$ $[M + Na]^+$ 338.1479, found 338.1482. **2,3-Di-*O*-benzyl-1,5-deoxy-1*R*-deuterio-D-mannose (44′):** ^{1}H 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 $C_{19}H_{21}DO_4$ $[M + Na]^+$ 338.1479, found 338.1477.

2,3-Di-*O*-benzyl-1-deoxy-1*S*-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 Et_2O:THF (1.3 mL) and subjected to S_N2 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%). ^{1}H 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. $[\alpha]^{25}_D$ 16.2 (*c* 0.5, CH_2Cl_2). HRESI-MS: *m*/*z* calcd for $C_{19}H_{21}DO_4$ $[M + Na]^+$ 338.1479, found 338.1476.

■ ASSOCIATED CONTENT

Supporting Information. Selected coupling constants for pyranosides **30**−**45** and related diastereomers (Tables S1 and S2), and ^{1}H and ^{13}C NMR spectra of new compounds **24**, **26**, **27**, **30**−**40**, and **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.

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