Chapter 2

Furanosyl Oxocarbenium Ion Stability and Stereoselectivity

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2.1 Introduction

Furanoses, five-membered ring carbohydrates, are ubiquitous in nature. They form characteristic motifs in many bacterial and plant oligo- and polysaccharides, while they are absent in mammalian oligosaccharides.[1] Furanose-containing bacterial oligosaccharides are therefore attractive targets to use in vaccine applications and the enzymes involved in

their assembly and degradation are appealing therapeutic targets.[2] Furanosyl oxocarbenium ions play crucial roles in both the chemistry and biology of glycosyl furanoses. Insight into the structure of such ions is instructive to both the design of mimics to inhibit furanose-processing enzymes,[3] and to effect stereoselective transformations at the anomeric center of furanosides. Over the years several examples have been reported on furanosylations of conformationally unbiased furanosyl donors, which bear no apparent stereochemistry-directing functionalities, and proceed with striking stereoselectivity to provide 1,2-*cis* glycosides.[4-10]

To account for the stereochemical outcome of reactions involving substituted tetrahydrofuran oxocarbenium ions as intermediates, Woerpel and co-workers have proposed a two-conformer model, in which the equilibrium between the ^3E and E_3 oxocarbenium ions is decisive (Figure 2.1).[11-15] Both envelopes are preferentially attacked on the inside, because this mode of attack leads to a transition state devoid of eclipsing interactions with substituents at C2, and provides a product featuring a favorable staggered C1-C2 conformation.[11,14] Therefore reaction on the ^3E conformer occurs on the top face, where the E_3 envelope is approached at the bottom face.[11,14,16] The nature and orientation of the substituents on the tetrahydrofuran ring play an all-important role in determining the stability of the oxocarbenium ion. Alkoxy substituents at the C2-position preferentially adopt a pseudoequatorial position to allow hyperconjugative stabilization of the oxocarbenium ion by the pseudoaxial C2-H2 bond, while a C3-alkoxy substituent can stabilize the electron-depleted anomeric center in a pseudoaxial position. The orientation of an alkyl group at C4 has been reported to be of little influence on the stability of the oxocarbenium ion.[14] This model explains well the stereochemical outcome of the addition of *C*-nucleophiles, such as allyltrimethylsilane, to monosubstituted tetrahydrofuran cores. For multiple substituted systems, such as genuine furanosyl oxocarbenium ions, the interplay between the ring substituents becomes important and prediction of the energetically most favored oxocarbenium ion envelope is very difficult.

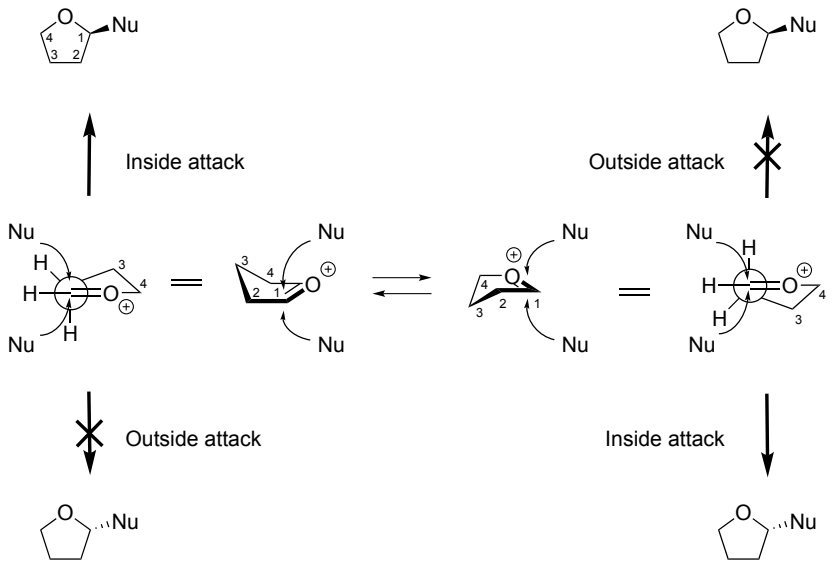


Figure 2.1 The two-conformer model. The two furanosyl ^{3}E and E_3 envelope oxocarbenium ions are preferentially attacked by the incoming nucleophile along an inside trajectory to provide different epimeric products.

This chapter describes a complete survey of the energy landscape of the entire conformational space of the furanosyl oxocarbenium ions for the four possible pentoses, ribose, arabinose, xylose, and lyxose. A clear picture emerges how multiple ring substituents on a furanosyl oxocarbenium ion influence its stability, and therefore its reactivity and stereoselectivity in addition reactions. This study is complemented by a set of substitution reactions to experimentally match the theoretical results.

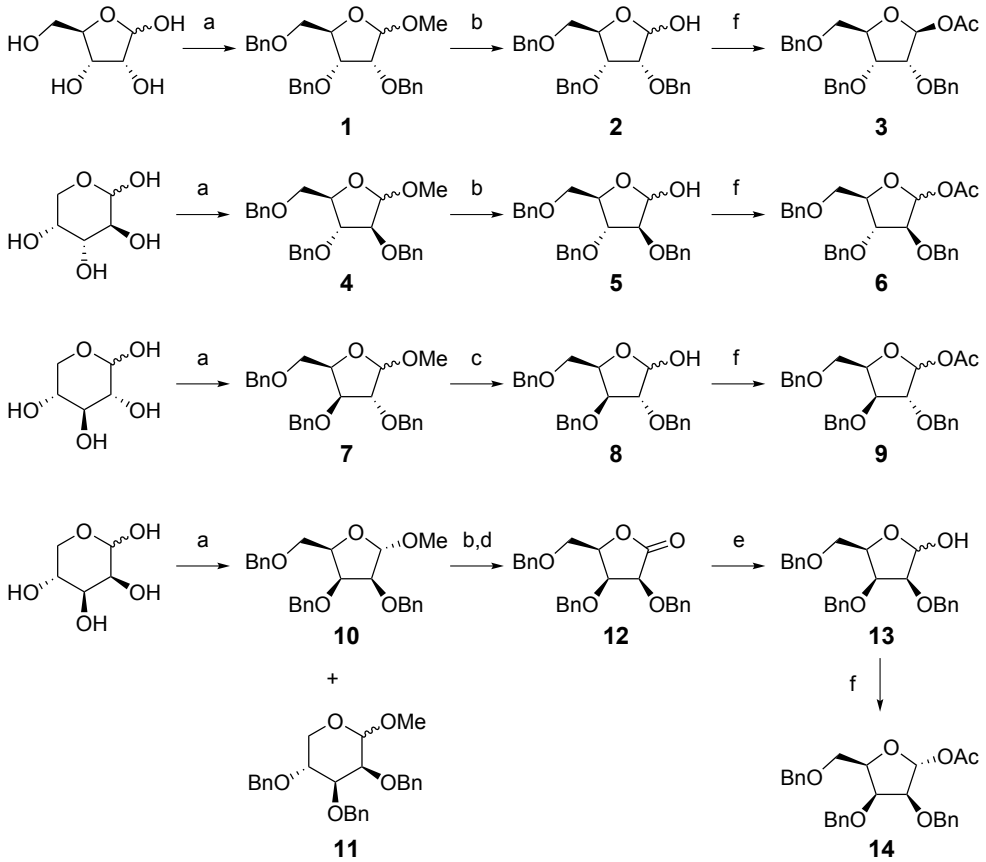
2.2 Results and discussion

Initially the Lewis acid mediated addition of [D]triethylsilane ([D]TES), as model nucleophile, to the four furanosyl acetates 2,3,5-tri-*O*-benzyl-D-ribofuranosyl acetate **3**, 2,3,5-tri-*O*-benzyl-D-arabinofuranosyl acetate **6**, 2,3,5-tri-*O*-benzyl-D-xylofuranosyl acetate **9**, and 2,3,5-tri-*O*-benzyl-D-lyxofuranosyl acetate **14** was investigated (Scheme 2.1). [D]TES was used as a nucleophile because the α- and β-deuterium epimeric products are nearly identical in physical properties, but can be distinguished by ^{1}H NMR spectroscopy, and therefore any isolated sample of the reaction products can be used to reliably determine the α/β product ratio.

The synthesis of the four perbenzylated furanosyl acetates started from the pentoses as depicted in Scheme 2.1. Fischer methylation under kinetic conditions of the pentoses at

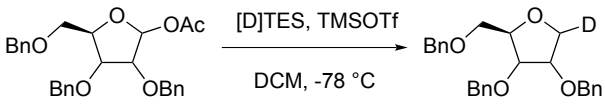
room temperature yielded the methyl furanosides that were subsequently benzylated to give the four benzyl protected methyl furanosides **1**, **4**, **7** and **10**. Only in the case of lyxose, pyranose side products (**11**) formed that could not be completely removed. Each of the four benzyl protected methyl furanosides was subjected to an acid catalyzed hydrolysis to yield the corresponding hemi-acetals. To separate the lyxo pyranose side product from **13** the lactols were oxidized. Pure lactone **12** could now be obtained and transformed into **13** by oxidation using a mixture of acetic anhydride and DMSO followed by reduction using DIBAl-H. All four hemi-acetals were acetylated with acetic anhydride in pyridine, yielding perbenzylated β-acetyl ribofuranose (**3**), perbenzylated α/β-acetyl arabinofuranose (**6**), perbenzylated α/β-acetyl xylofuranose (**9**), and perbenzylated α-acetyl lyxofuranose (**14**).

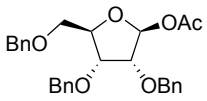
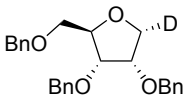
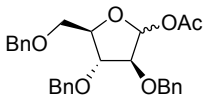
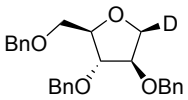
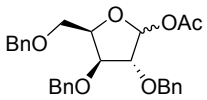
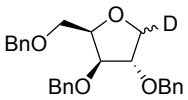
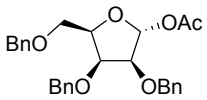
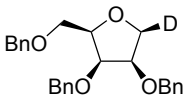
Scheme 2.1 Synthesis of the four furanosyl acetate donors **3**,**6**,**9** and **14**.



Reagents and conditions: (a) i) AcCl, MeOH; ii) BnBr, NaH, TBAI, DMF, **1**: 66% over 2 steps, **4**: 68% over 2 steps, **7**: quant. over 2 steps, **10**, **11**: 84% over 2 steps; (b) AcOH, H_2O, 110 °C, **2**: 86%, **5**: 72%; (c) HCl, H_2O, 1,4-dioxane, 90 °C, 77%; (d) Ac_2O, DMSO, 76% over 2 steps; (e) DiBAL-H, DCM, -78 °C, 94%; (f) Ac_2O, pyridine, **3**: 91%, **6**: 94%, **9**: 86%, **14**: quant.

Table 2.1 Results of the substitution reaction of [D]TES with the various furanosides.



Entry	Furanosyl acetate	Product	1,2-*cis*: 1,2-*trans*[a]	Yield[b]
1			>98:2	50%
	Ribose **3**	**15**		
2			>98:2	62%
	Arabinose **6**	**16**		
3			85:15	40%
	Xylose **9**	**17**		
4			>98:2	100%
	Lyxose **14**	**18**		

[a]Ratio determined by ^{1}H NMR spectroscopy, stereochemistry was identified using ^{2}J coupling-constants measured from HSQC-HECADE NMR spectra. [b]Yield of isolated deuterium-furanosides after column chromatography. The remainders of the mass balance in each entry consist of recovered and hydrolyzed starting materials.

With the four furanosyl acetates in hand, the [D]TES substitution reactions were undertaken. As can be seen in Table 2.1, all furanosyl acetates (**3**, **6**, **9**, **14**) are substituted in a stereoselective manner to provide the 1,2-*cis* products and only xylose **9** delivers a minor amount of the 1,2-*trans* product. Perhaps most striking is the result obtained with lyxose **14**, which features all ring substituents on one side of the ring. Here, the nucleophile attacks the β-face of the molecule with complete stereoselectivity to lead to the counterintuitive all-*cis* product.

The stereoselectivities in the reactions indicate that direct S_N2-type substitution on the (mixtures of) anomeric acetates can be excluded as a major reaction pathway.[17] Also selective substitution reactions on anomeric triflates[18-19] as a major contributing pathway can be excluded because the relative stability of the anomeric triflates cannot be readily reconciled with the experimental results.[20] To probe whether the intermediate

oxocarbenium ions can be at the basis of the observed selectivities, the relative energies of the oxocarbenium ions of the different furanosyl epimers were investigated. To this end the energy associated with the complete conformational space of the permethylated furanosyl oxocarbenium ions **19**-**22** (Figure 2.2a) was calculated using the potential energy surface (PES) scanning method recently introduced by Rhoad, Cagg, and Carver[21], adapted to correct for solvent and zero-point energy. The conformation of a furanose ring can be defined by a phase angle (P) and puckering amplitude (τ_m) and the complete conformational space of such a ring can be displayed using the pseudorotation circle, which was introduced by Altona and Sundaralingam[2,22] (Figure 2.2b). The phase angle defines the conformation of the ring, and the puckering amplitude indicates how far out of the median plane the outlying atoms (denoted with super- or subscripts) are positioned. The energies associated with 81 fixed-ring conformers were calculated with Gaussian 03,[23] by employing the B3LYP density functional and the 6-311G** basis set, and corrected for the solvent (CH_2Cl_2) using the polarizable continuum model (PCM) function. The calculated energies were then mapped in the pseudorotational circle to give free-energy surface (FES) maps.[24] Because orientation of the C4-C5 bond significantly influences the stability[25] of furanosyl rings, the FES of the oxocarbenium ions was scanned for the three individual *gg*, *gt*, and *tg* C4-C5 rotamers (Figure 2.2c). Thus for each furanosyl oxocarbenium ion 243 (3×81) conformers were optimized and the associated energies determined.

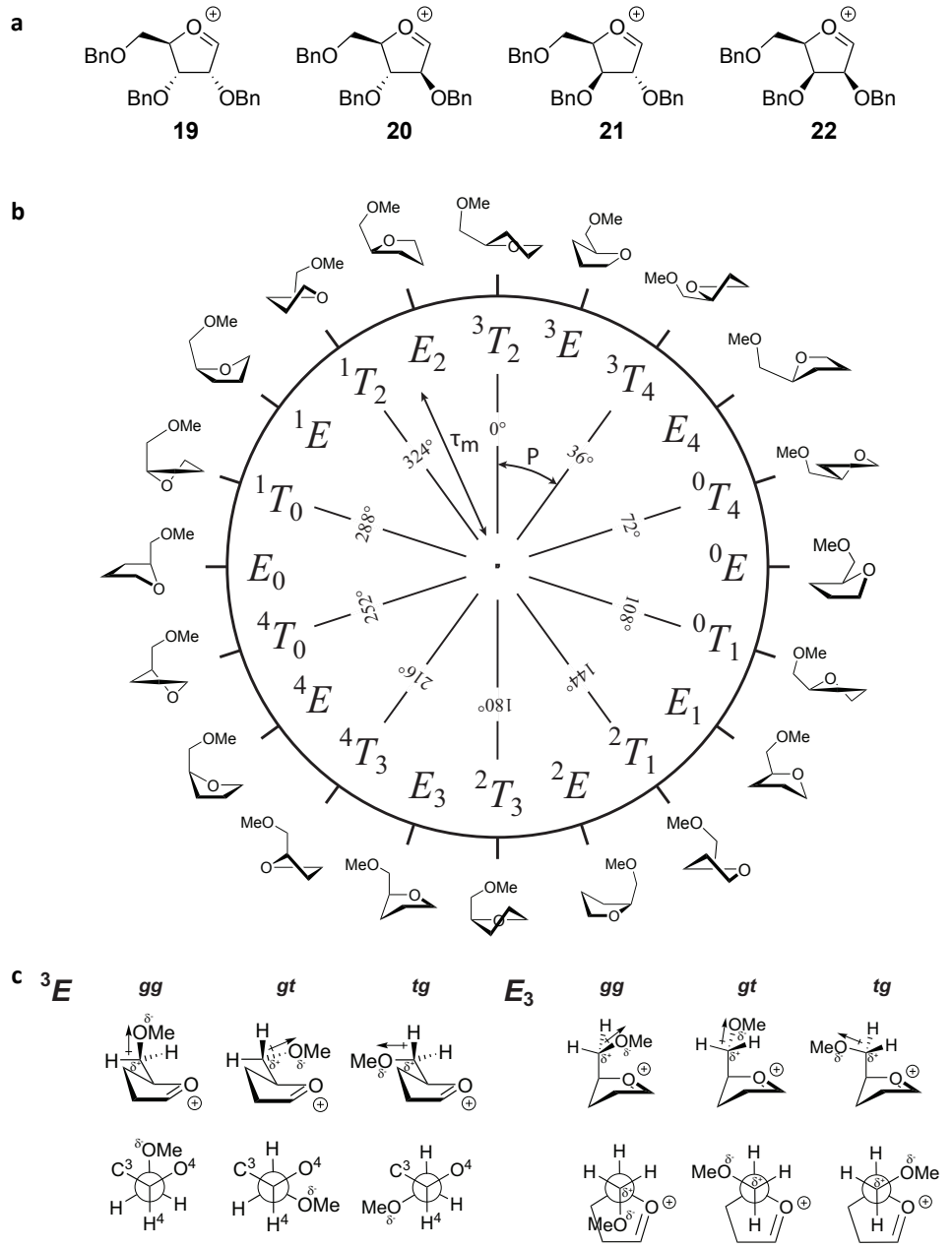


Figure 2.2 a) The investigated furanosyl oxocarbenium ions. b) The pseudorotational circle describing the conformational space a five-membered ring can occupy. The pseudorotational phase angle (P) in combination with the puckering amplitude (τ_m) defines the ring conformation. c) Possible rotamers around the C4-C5 bond in the ^3E (left) and E_3 (right) envelope conformers, in which the dipoles of the C5-OMe moieties are indicated.

The ribofuranose FES map

In Figure 2.3a, the FES maps for the three C4-C5 rotamers of the ribofuranosyl oxocarbenium ion **19** are displayed. The combination of the absolute lowest energies of these three conformers in a single picture leads to the global FES map depicted in Figure 2.3d. From the four graphs it becomes apparent that **19** preferentially adopts an E_3-like structure and that the orientation of the C5-OMe group has a great impact on the stability of the oxocarbenium ion. The *gg* rotamer is significantly more stable than the *gt* structure, which in turn is more favorable than the *tg* conformer. The E_3 *gg* rotamer positions the C5-OMe group above the furanosyl ring to allow through-space stabilization of the oxocarbenium ion. The enhanced stability of the *gt* conformer over its *tg* counterpart can be rationalized by the interaction of the C5-O5 dipole with the positive charge in the oxocarbenium ion ring. As pointed out by Bols and co-workers the interaction of the C5-OMe dipole with the positive charge of the oxocarbenium ion is least favorable in the *tg* conformer (Figure 2.3c).[26-27] In the most stable E_3 conformation, the C3 and C2 methyloxy groups take up a pseudoaxial and pseudoequatorial orientation, respectively, thus lending support to the model devised by Woerpel and co-workers. Notably the E_3 envelope places two out of the three substituents in a pseudoaxial position, which is sterically rather unfavorable.[14] To investigate the steric preference of the system the FES of a ribose-configured 2,3-dimethoxy-4-methylenemethoxy cyclopentene, representing a structural mimic of **19** lacking the positive charge was also calculated. This FES is depicted in Figure 2.4d, and it shows a preference of the noncharged ribo-cyclopentene for the ^3E envelope. Thus in the case of the ribofuranosyl oxocarbenium ion the electronic stabilization in the E_3 conformation outweighs the steric preference of the system.

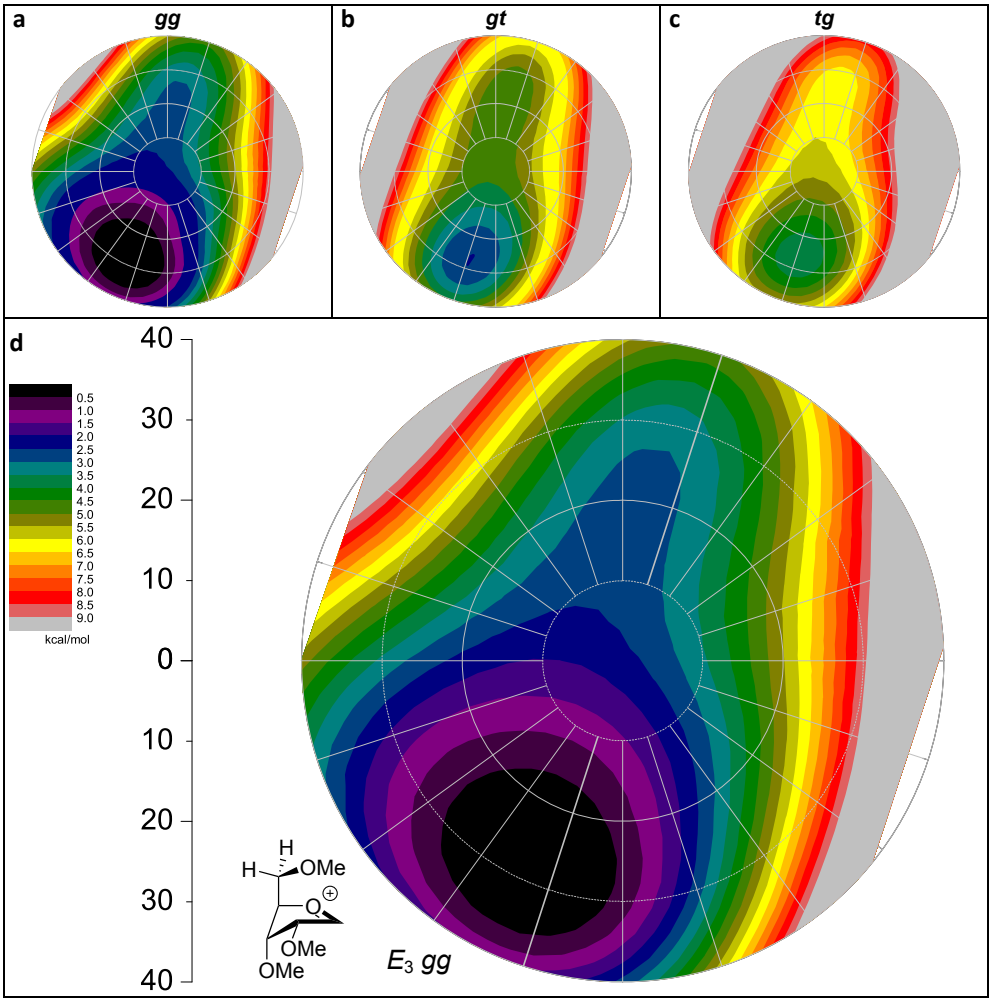


Figure 2.3 The FES maps of ribofuranosyl oxocarbenium ion **19**. a) FES of the *gg* conformer. b) FES of the *gt* conformer. c) FES of the *tg* conformer. d) Global minimal FES of **19** showing the lowest-energy E_3 (*gg*) conformer.

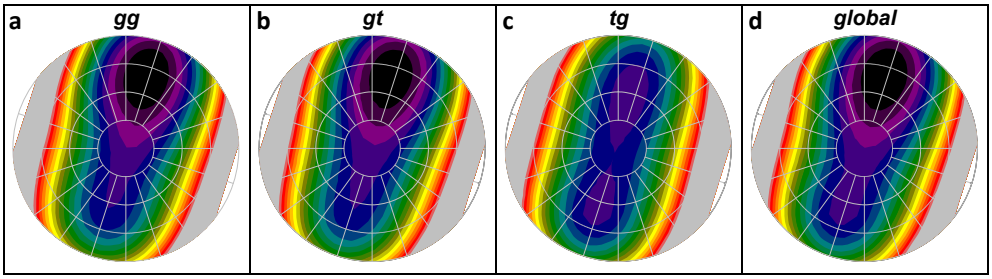


Figure 2.4 The FES maps of ribose configured 2,3-dimethoxy-4-methylenemethoxy cyclopentene. a) FES of the *gg* conformer. b) FES of the *gt* conformer. c) FES of the *tg* conformer. d) Global minimal FES showing the lowest-energy ^3E (*gg*) conformer.

With the FES map of **19**, the stereoselectivity in the substitution reaction of [D]TES with **3** can be readily explained. Attack of the nucleophile on the most favorable oxocarbenium ion, that is, the E_3 conformer, on the inside of the envelope explains the selective formation of the 1,2-*cis* product.

The arabinose FES map

The free energy surfaces of arabinofuranosyl oxocarbenium ion **20** are depicted in Figure 2.5, and from these it becomes apparent that this ion is most stable when taking up the ^3E conformation. Also in this case the relative stability of the three C5-O5 rotamers decreases going from the *gg* to the *gt* to the *tg* rotamer. Because the C5-OMe group cannot be positioned above the ring in the arabinosyl ^3E envelope, this stability trend arises from the different interactions between the C5-OMe dipole with the positive charge of the oxocarbenium ion. This interaction is most favorable for the *gg* C5-OMe, and least favorable for the *tg* conformer, as discussed above (Figure 2.2).[26] In addition to the unfavorable dipole-charge interaction of the C5-OMe *tg* conformer, this conformer also suffers from unfavorable steric and electronic interactions of the C5-OMe with the C3 substituent in the ^3E envelope. Comparison of the FES maps of the ribofuranosyl and arabinofuranosyl oxocarbenium ions shows not only that the two oxocarbenium ions prefer opposite envelope conformers, but also that the FES of the arabinosyl oxocarbenium ion is more shallow. This outcome indicates that the preference for the arabino ^3E envelope is not as strong as the preference for the ribo E_3 envelope, and can be explained by the fact that ribo ^3E envelope positions all substituents in an ideal orientation to maximize the stability of the oxocarbenium ion, which is not the case for the arabino ^3E envelope. Nonetheless, the preference for the arabino ^3E conformer is strong enough to allow a selective substitution reaction as shown by the [D]TES reaction (Table 2.1, entry 2). Only the β-deuterium epimer was isolated in this experiment, the formation of which can be accounted for by inside attack of [D]TES on the ^3E oxocarbenium ion.

The map for arabinose configured 2,3-dimethoxy-4-methylenemethoxy cyclopentene in Figure 2.6 shows that this molecule has a stronger preference for the ^3E conformer oxocarbenium ion. The all equatorial conformer benefits from placing all substituents in a sterically most favorable position. In the E_3 conformation, the oxocarbenium ion benefits from stereoelectronic stabilization by the pseudoaxial C4, but this effect is absent in the cyclopentene.

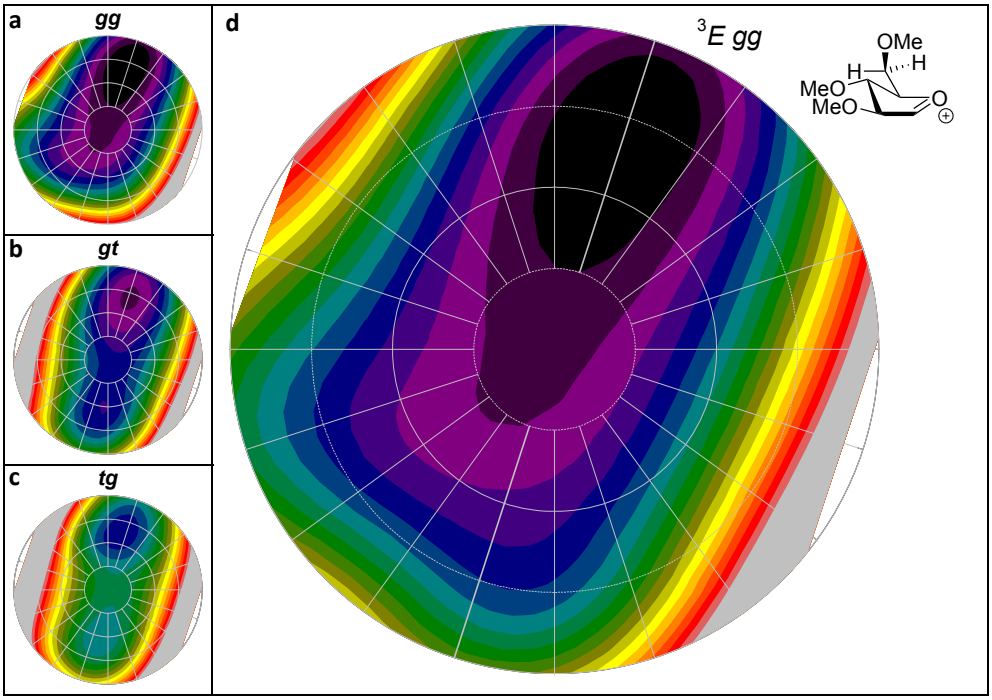


Figure 2.5 The FES maps of arabinofuranosyl oxocarbenium ion **20**. a) FES of the *gg* conformer. b) FES of the *gt* conformer. c) FES of the *tg* conformer. d) Global minimal FES of **20** showing the lowest-energy ^3E (*gg*) conformer.

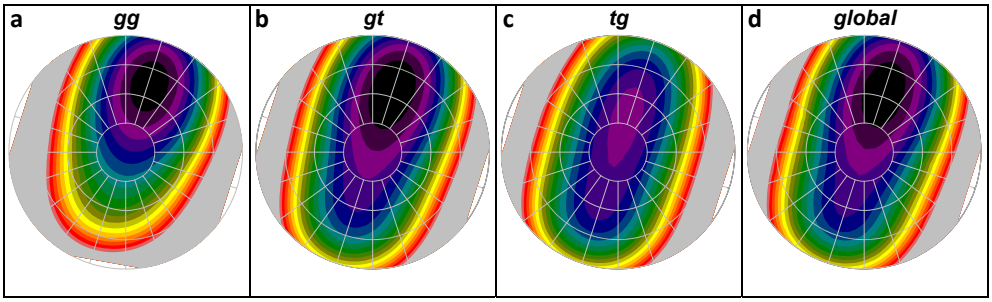


Figure 2.6 The FES maps of arabinose configured 2,3-dimethoxy-4-methylenemethoxy cyclopentene. a) FES of the *gg* conformer. b) FES of the *gt* conformer. c) FES of the *tg* conformer. d) Global minimal FES showing the lowest-energy ^3E (*gt*) conformer.

The xylose FES map

The FES maps for the xylofuranosyl oxocarbenium ion **21**, depicted in Figure 2.7, give a different picture than the above described maps of the ribo- and arabino oxocarbenium ions **19** and **20**. Now there are two energy minima, one on the side of the ^3E envelope and one on the opposite side, around P=216°, thus indicating that a $^4T_3$ conformer is

energetically most favorable on the southern hemisphere. The two minima have different C4-C5 rotamers which contribute most favorably to the overall oxocarbenium ion energy.

The stability of the $^{4}T_{3}$ *gg* rotamer originates from the stabilizing interaction of the C5-OMe with the underlying oxocarbenium ion. Distortion from the E_{3} envelope to the flanking $^{4}T_{3}$ twist structure can be explained by the fact that in these structures there is no stabilizing contribution from the C3-OMe group and in order to maximize stabilization by the C5-OMe group, the furanose ring twists from the E_{3} envelope to position this group closer to the oxocarbenium ion. In the ^{3}E envelope, in contrast, the *gg* rotamer suffers from destabilizing steric and dipole interactions with the pseudoaxial C3-OMe. The most stable orientation for the C5-OMe group in the ^{3}E envelope is achieved in the *gt* rotamer, because the *tg* conformer puts the C5-OMe group in an unfavorable antiparallel orientation with respect to the C4-O4 bond (Figure 2.2). The two energy minima found for the xylose furanosyl oxocarbenium ion explain the mixture of products obtained in the [D]TES substitution reaction (Table 2.1, Entry 3), and the 85:15 α/β-ratio fits well with the difference in energy between the two envelope oxocarbenium ions, a difference which the calculations show to be about 1 kcal mol^{-1}.

In Figure 2.8, the FES map for the xylose configured cyclopentene is depicted. The E_{3} conformer is the most favored conformer and the *gt* rotamer is favored for both the ^{3}E and E_{3} envelopes. This indicates that the electronic stabilization of the oxocarbenium ion in the $^{4}T_{3}$ *gg* rotamer outweighs the steric preference of the C4-substituent.

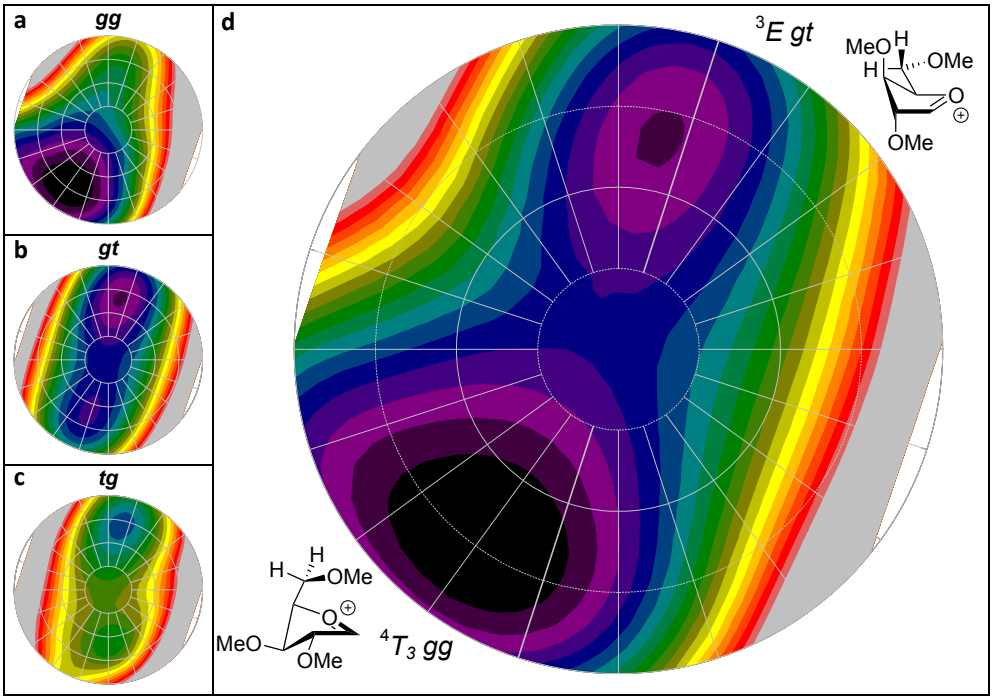


Figure 2.7 The FES maps of xylofuranosyl oxocarbenium ion **21**. a) FES of the *gg* conformer. b) FES of the *gt* conformer. c) FES of the *tg* conformer. d) Global minimal FES of **21** showing the lowest-energy E_3 (*gg*) conformer.

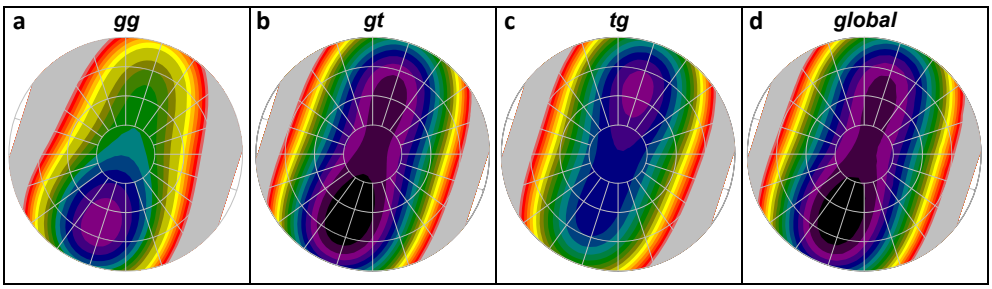


Figure 2.8 The FES maps of xylose configured 2,3-dimethoxy-4-methylenemethoxy cyclopentene. a) FES of the *gg* conformer. b) FES of the *gt* conformer. c) FES of the *tg* conformer. d) Global minimal FES showing the lowest-energy E_3 (*gt*) conformer.

The lyxose FES map

When the lyxofuranosyl acetate **14**, featuring an all-*cis* substituent decoration, is reacted with [D]TES/TMSOTf, the β-deuterium lyxofuranoside **18** is isolated as the sole product (Table 2.1, entry 4). Also in this case the stereoselectivity can be adequately explained by considering the FES of the intermediate oxocarbenium ion **22**, which shows a single, rather deep energy minimum for the ^3E conformation (Figure 2.9d). Besides showing the steepest

energy well, the FES of ion **22** also indicates that the ring of the lyxofuranose oxocarbenium ion is the most puckered of the four oxocarbenium ions studied. In the ^{3}E structure, both the C2 and the C3 substituent adopt positions allowing maximum stabilization of the oxocarbenium ion. The C4 group has a pseudoequatorial orientation thereby avoiding steric interactions. In the ^{3}E envelope the C5-OMe group preferentially adopts a *gt* position, because the *gg* rotamer is rather unfavorable due to the destabilizing interaction with the C3-OMe. Inside attack on the ^{3}E envelope oxocarbenium ion leads to the all-*cis* product. When the charge is removed from the lyxose oxocarbenium ion as in the lyxo configured cyclopentene (Figure 2.10), the strong conformer preference disappears.

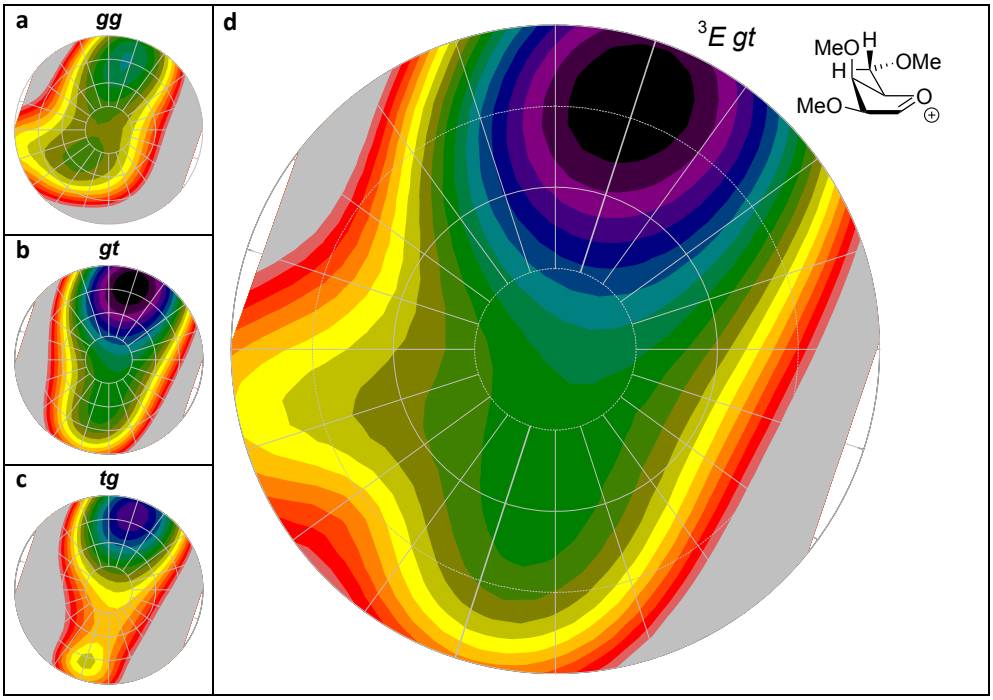


Figure 2.9 The FES maps of lyxofuranosyl oxocarbenium ion **22**. a) FES of the *gg* conformer. b) FES of the *gt* conformer. c) FES of the *tg* conformer. d) Global minimal FES of **22** showing the lowest-energy ^3E (*gt*) conformer.

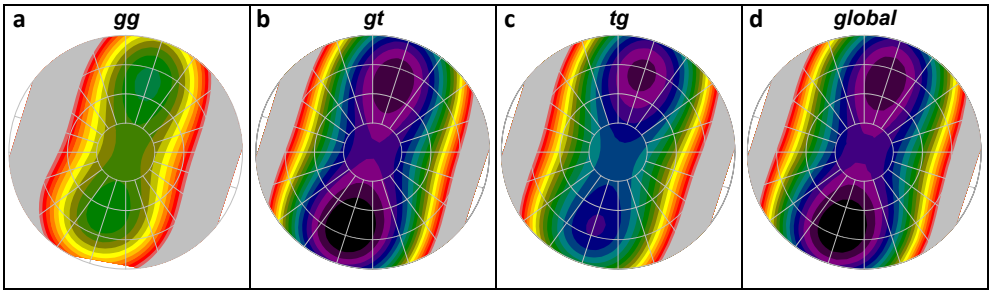


Figure 2.10 The FES maps of lyxose configured 2,3-dimethoxy-4-methylenemethoxy cyclopentene. a) FES of the *gg* conformer. b) FES of the *gt* conformer. c) FES of the *tg* conformer. d) Global minimal FES showing the lowest-energy E_3 (*gt*) conformer.

The obtained results can be summarized to indicate the following ring substituent effects: the stability of the furanosyl oxocarbenium ions benefits from equatorially oriented alkoxy groups at C2, as previously shown by Woerpel and co-workers; a pseudoaxial alkoxy function at C3 leads to a more stable oxocarbenium ion than a C3-alkoxy group in a pseudoequatorial position, corroborating the studies of the Woerpel group and the vast amount of literature data, reporting higher reactivity for glycosides having more axially

oriented substituents[14,15]; the methylenealkoxy group at C4 significantly adds to the stability of the oxocarbenium ion if steric interactions allow proper positioning. The calculations indicate that the nature of the C4-C5 rotamer is an important factor in determining the stability and that the difference in the ground state energy of the C4-C5 rotamers can be as much as ~4 kcal mol^{-1}.

Overall, the calculated FES maps provide a detailed picture of the substituent effects on the stability of furanosyl oxocarbenium ions. Individual stabilizing or destabilizing influences and the interplay between the substituents have become apparent. There is a very good agreement between the calculated lowest-energy furanosyl oxocarbenium ion conformers and the experimental results obtained in the substitution reactions. In a Curtin-Hammett scenario[28] the product stereoselectivity solely depends on the relative ground-state energies of the oxocarbenium ions depicted in Figure 2.1, if both conformers react at the same rate. If the more stable conformer reacts more quickly, the product distribution will be even more outspoken, whereas the stereoselectivity erodes (or even inverts) in the case where the more stable conformer reacts slower. During the attack of the nucleophile on the furanosyl ring, interactions will develop between the incoming nucleophile and the furanosyl ring substituents. Rehybridization of the furanosyl ring will alter the mutual interactions of the ring substituents. In the ribose case, a prominent 1,3-diaxial-like interaction will emerge upon inside attack (Figure 2.1) of the nucleophile on the ribosyl E_3 oxocarbenium ion between the nucleophile and the substituent at C3. Where this will be unfavorable from a steric point of view, the lone pairs of *O*-atom at C3 can help stabilize the development of positive charge on the incoming nucleophile. A similar situation unfolds in the ^3E xylo and lyxo case, while inside attack of the nucleophile on the ^3E arabino and $^4T_3$ xylo oxocarbenium ions can occur relatively unhindered. In all, it appears that none of these interactions prevail here as judged from the agreement between the calculated FES maps and the experimental results.[29]

2.3 Conclusion

The set of substitution experiments, supported by the in-depth quantum mechanical calculations, show that all furanosyl oxocarbenium ions intrinsically react in a 1,2-*cis*-selective manner. These results in turn imply that stereoselective *cis*-glycosylation reactions can be effected if they are persuaded to proceed via the furanosyl oxocarbenium ion as the product-forming intermediate. In combination with glycosylation methodology relying on anchimeric assistance by a suitable neighboring group at the C2 hydroxy, which allows for the reliable installation of 1,2-*trans*-furanosidic linkages, the stereoselective construction of all furanosidic linkages is in theory feasible. It should be noted that given the differences between the nucleophile used in this study and *O*

nucleophiles, such as typical glycosyl acceptors, transposition of the reaction pathway described here to an *O*-glycosylation event will not be trivial.[27] The detailed furanosyl oxocarbenium ion energy maps presented here will also be useful for gaining insight into the reaction mechanisms by which furanose-processing enzymes, such as glycosyl hydrolases and transferases, operate and the FES maps will be valuable in the analysis of conformational itineraries used by furanosyl-processing enzymes.[30] This analysis in turn can guide inhibitor design and understanding of inhibitor structure-activity relationships.[31]

Supplementary data

FES maps of mono and di-substituted tetrahydrofuran oxocarbenium ions and the anomeric triflates can be found in the Appendix. The maps of the mono- and di-substituted tetrahydrofuran oxocarbenium ions provide information on the stereoelectronic and steric effects of the individual substituents.

Experimental section

Calculations. In all calculations, methyl ethers were used because of their reduced calculation time over benzyl ethers. All calculations were performed with DFT *ab initio* calculations with the B3LYP model. The starting conformer for the Free Energy Surface (FES) was optimized by starting from a conformer distribution search option included in the Spartan 04[32] program in gas phase at 6-31G* as basis set. All generated geometries were optimized with Gaussian 03[23] at 6-311G**, their zero-point energy (ZPE) corrections calculated, and further optimized with incorporated polarizable continuum model (PCM) to correct for solvation in dichloromethane. The geometry with the lowest, ZPE corrected, solvated free energy was selected as the starting point for the FES. Two dihedral angles of the five-membered ring were constrained, namely C4-O4-C1-C2 (τ_0, θ_3) and C1-C2-C3-C4 (τ_2, θ_0), with angles from -40° up to 40° over 9 steps (10° per step) giving a total of 81 conformers and dictating the entire pseudo rotational space within a maximum amplitude (τ_m) of 40°. All other internal coordinates were unconstrained. The geometries were optimized, their ZPE calculated and corrected for solvation with Gaussian 03 at 6-311G**. The FES was visualized as polar contour plot through the Origin 8.5 graphing software by putting the phase angle (P) as θ, the amplitude (τ_m) at *r* and the energy, corrected for ZPE and optimized in solvent, at the Z-axis. The starting conformer was modified by rotating the O4-C4-C5-O5 dihedral to each of the three staggered conformations (gauche-gauche = -65°, gauche-trans = 65°, trans-gauche = 175°) and then generating the FES through the above mentioned method generating a total of 243 optimized geometries. These three FES maps were graphed individually and in a combined plot by comparing the corrected free energies, and for each point selecting the geometry of lowest energy from the three entities. The geometries of the anomeric triflates were calculated using the same method as applied for finding the starting point of the FES, but using 6-31G* instead of 6-311G** in Gaussian 03 for geometry optimization followed by a single point energy calculation at 6-311G**.

Synthesis

General. All reagents were of commercial grade and used as received. All moisture sensitive reactions were performed under an argon atmosphere. DCM used in the [D]TES reaction was distilled over P_2O_5 and stored on activated 4Å molecular sieves before use. Reactions were performed at room temperature unless stated otherwise and were monitored by TLC analysis with detection by UV (254 nm) and where applicable by spraying

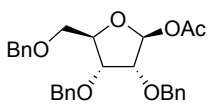
with 20% sulfuric acid in EtOH or with a solution of $(NH_4)_6Mo_7O_{24}{\cdot}4H_2O$ (25 g/l) and $(NH_4)_4Ce(SO_4)_4{\cdot}2H_2O$ (10 g/l) in 10% sulfuric acid (aq.) followed by charring at ~150 °C. Flash column chromatography was performed on silica gel (40-63µm). ^{1}H and ^{13}C spectra were recorded on a Bruker AV 400 in $CDCl_3$ or CD_3OD. Chemical shifts (δ) are given in ppm relative to tetramethylsilane as internal standard (^{1}H NMR in $CDCl_3$) or the residual signal of the deuterated solvent. Coupling constants (*J*) are given in Hz. All ^{13}C spectra are proton decoupled. NMR peak assignments were made using COSY and HSQC experiments. Where applicable NOESY, HMBC and HSQC-HECADE[33] experiments were used to further elucidate the structure. The anomeric product ratios were analysed through integration of proton NMR signals.

2,3,5-Tri-*O*-benzyl-1-*O*-methyl-D-ribofuranose (1). D-Ribose (25 g, 167 mmol) was dissolved in a mixture of acetyl chloride (3.6 ml, 50 mmol) and MeOH (600 ml) and stirred overnight. The reaction mixture was quenched by adjusting the pH to neutral by addition of $NaHCO_3$ (s, 70 g), the solid was filtered off and the filtrate concentrated under reduced pressure. The crude product was coevaporated twice with toluene before being dissolved in DMF (850 ml). Benzyl bromide (83 ml, 700 mmol) and tetrabutyl ammonium iodide (0.6 g, 1.7 mmol) were added and the mixture was cooled to 0 °C. Sodium hydride (28 g, 700 mmol, 60% in mineral oil) was added and the mixture slowly allowed to warm to room temperature where it was stirred overnight. The reaction mixture was concentrated under reduced pressure before being dissolved in Et_2O and subsequently washed with 1M HCl (aq.). The combined aqueous layers were extracted with Et_2O and the organic layers combined before being washed with $NaHCO_3$ (sat. aq.) and brine. The organic layer was dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The product was purified by flash chromatography (7-19% Et_2O/pentane) yielding an anomeric mixture (α:β; 1:10) of the title compound (48 g, 111 mmol, 66 % yield). R_f = 0.30 (10/90 EtOAc/pentane). β-Anomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.23 (m, 15H, CH_{Ar} Bn), 4.92 (s, 1H, C-1), 4.66 (d, *J* = 12.1 Hz, 1H, C*H*H Bn), 4.61 (d, *J* = 11.8 Hz, 1H, C*H*H Bn), 4.57 – 4.51 (m, 3H, 3xC*H*H Bn), 4.44 (d, *J* = 11.9 Hz, 1H, C*H*H Bn), 4.38 – 4.31 (m, 1H, C-4), 4.02 (dd, *J* = 7.0, 4.7 Hz, 1H, C-3), 3.84 (d, *J* = 4.7 Hz, 1H, C-2), 3.61 (dd, *J* = 10.6, 3.7 Hz, 1H, C-5a), 3.51 (dd, *J* = 10.5, 5.7 Hz, 1H, C-5b), 3.31 (s, 3H, OCH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.4, 137.9, 137.9 (C_q Bn), 128.5, 128.4, 128.4, 128.0, 128.0, 127.9, 127.9, 127.7, 127.6 (CH_{Ar} Bn), 106.4 (*C*-1), 80.5 (*C*-4), 79.8 (*C*-2), 78.5 (*C*-3), 73.2, 72.5, 72.4 (3xCH_2 Bn), 71.4 (*C*-5), 55.2 (OCH_3). IR (neat): 602, 694, 733, 779, 820, 853, 970, 945, 1026, 1065, 1103, 1206, 1258, 1312, 1360, 1452, 1497, 2862, 2911. HR-MS: [M+H$^+$] Calculated for $C_{27}H_{30}O_5$: 435.21660; found: 435.21686. Analysis data matches literature data.[34]

2,3,5-Tri-*O*-benzyl-D-ribofuranose (2). 2,3,5-Tri-*O*-benzyl-1-*O*-methyl-D-ribofuranose (**1**, 42 g, 97 mmol) was dissolved in a mixture of acetic acid (500 ml) and water (125 ml) and refluxed (110 °C) overnight. The reaction was allowed to cool down to room temperature before being neutralized with 6M NaOH (aq.) and extracted with EtOAc (3x). The organic layers were combined and washed with $NaHCO_3$ (sat. aq.) and brine, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (27.5%-70% Et_2O/pentane) yielding an anomeric mixture (α:β; 3:2) of the title compound (35 g, 84 mmol, 86 % yield). R_f = 0.55 (25/75 EtOAc/toluene). α-Anomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.18 (m, 15H, CH_{Ar} Bn), 5.34 – 5.29 (m, 1H, C-1), 4.72 – 4.38 (m, 6H, 6xC*H*H Bn), 4.38 – 4.34 (m, 1H, C-4), 4.00 – 3.93 (m, 2H, C-2, C-3), 3.51 – 3.43 (m, 2H, C-5). ^{13}C NMR (101 MHz, $CDCl_3$) δ 137.9, 137.5, 137.5 (C_q Bn), 128.6, 128.6, 128.5, 128.5, 128.1, 128.0, 128.0, 128.0, 128.0, 128.0, 127.9, 127.9, 127.9, 127.8, 127.6 (CH_{Ar} Bn), 96.3 (*C*-1), 81.1 (*C*-4), 77.8, 77.7 (*C*-2, *C*-3), 73.6, 72.9, 72.5 (3xCH_2 Bn), 70.1 (*C*-5). β-Anomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.20 (m, 15H, CH_{Ar} Bn), 5.31 (s, 1H, C-1), 4.72 – 4.38 (m, 6H, 6xC*H*H Bn), 4.33 – 4.28 (m, 1H, C-4), 4.20 (dd, *J* = 6.8, 4.7 Hz, 1H, C-3), 3.84 (d, *J* = 4.6 Hz, 1H, C-2), 3.65 (dd, *J* = 10.4, 2.9 Hz, 1H, C-5a), 3.46 – 3.40 (m, 1H, C-5b). ^{13}C NMR (101 MHz, $CDCl_3$) δ 137.9, 137.8, 137.4 (C_q Bn), 128.6, 128.6, 128.5, 128.5, 128.1, 128.0, 128.0, 128.0, 128.0, 128.0, 127.9, 127.9, 127.9, 127.8, 127.6 (CH_{Ar} Bn), 100.4 (*C*-1), 80.8, 80.8 (*C*-2, *C*-4), 77.3 (*C*-3), 73.5, 72.5, 72.3 (3xCH_2 Bn), 69.7 (*C*-5). IR (neat): 604, 654, 694, 733, 820, 851, 910, 943, 1024, 1074, 1207, 1256, 1314, 1329, 1362, 1398, 1454, 1497,

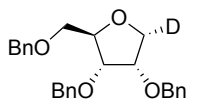
2864, 2922, 3418. HR-MS: [M+Na$^+$] Calculated for $C_{26}H_{28}O_5$: 443.18290; found: 443.18225. Analysis data matches literature data.[34]

2,3,5-Tri-*O*-benzyl-1-β-*O*-acetyl-D-ribofuranose (3). 2,3,5-Tri-*O*-benzyl-D-ribofuranose (**2**, 3.5 g, 8.3 mmol) was



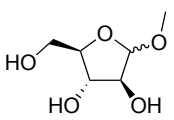
dissolved in pyridine (13 ml) and added to cooled (0 °C) acetic anhydride (8.6 ml, 92 mmol). The reaction was allowed to continue to stir at room temperature for 4 hours and quenched by pouring it into 1M HCl (aq.) before being diluted with EtOAc. The layers were separated and the organic layer washed with 1M HCl (aq.), $NaHCO_3$ (sat. aq.) and brine, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (10-15% EtOAc/pentane) yielding the title compound (3.5 g, 7.6 mmol, 91 % yield). R_f = 0.75 (20/80 EtOAc/pentane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.25 (m, 15H, CH_{Ar} Bn), 6.20 (s, 1H, C-1), 4.76 (d, *J* = 12.1 Hz, 1H, C*H*H Bn-2), 4.62 (d, *J* = 12.1 Hz, 1H, C*H*H Bn-2), 4.58 (d, *J* = 12.0 Hz, 1H, C*H*H Bn-5), 4.54 (d, *J* = 12.0 Hz, 1H, C*H*H Bn-3), 4.50 (d, *J* = 12.1 Hz, 1H, C*H*H Bn-5), 4.42 (d, *J* = 11.8 Hz, 1H, C*H*H Bn-3), 4.37 (ddd, *J* = 7.6, 4.4, 3.1 Hz, 1H, C-4), 4.14 (dd, *J* = 7.8, 4.6 Hz, 1H, C-3), 3.92 (d, *J* = 4.5 Hz, 1H, C-2), 3.70 (dd, *J* = 11.0, 3.1 Hz, 1H, C-5a), 3.58 (dd, *J* = 11.1, 4.4 Hz, 1H, C-5b), 1.93 (s, 3H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.9 (*C*=O), 138.4, 137.7, 137.5 (C_q Bn), 128.5, 128.5, 128.4, 128.2, 128.1, 128.0, 127.9, 127.6, 127.5 (CH_{Ar} Bn), 99.1 (*C*-1), 81.6 (*C*-4), 78.8 (*C*-2), 76.9 (*C*-3), 73.3 (CH_2 Bn-5), 72.5 (CH_2 Bn-3), 72.2 (CH_2 Bn-2), 69.7 (*C*-5), 21.3 (CH_3). $[\alpha]^{20}_D$ = 54° (c = 1, $CHCl_3$). IR (neat): 602, 650, 694, 733, 781, 820, 854, 945, 1011, 1043, 1092, 1125, 1217, 1310, 1369, 1454, 1497, 1744, 2864, 2926. HR-MS: [M+Na$^+$] Calculated for $C_{28}H_{30}O_6$: 485.19346; found: 485.19283. Analysis data is in line with literature data.[35]

2,3,5-Tri-*O*-benzyl-1-deoxy-1-α-deutero-D-ribofuranose (15). 2,3,5-Tri-*O*-benzyl-1-β-*O*-acetyl-D-ribofuranose (**3**,



93 mg, 0.20 mmol) was coevaporated with toluene (3x), dissolved in DCM (2.7 ml) and cooled to -78 °C. [D]Triethylsilane (64 µl, 0.4 mmol) was added before slowly adding a solution of trimethylsilyl trifluoromethanesulfonate (47 µl, 0.26 mmol) in DCM (300 µl) and the reaction stirred at -78 °C for 3 days. The reaction was quenched by addition of NaH_2PO_4 (sat. aq., 5 ml) and then allowed to warm to room temperature. The suspension was extracted with EtOAc and the combined organic layers washed with $NaHCO_3$ (sat. aq.) and brine, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The residue was dissolved in a mixture of sodium methoxide (0.04 mmol) in MeOH (4 ml) and stirred for 5 hours. The reaction was quenched with acetic acid (4 µl in 400 µl MeOH) and concentrated. The residue was taken up in EtOAc, washed with $NaHCO_3$ (sat. aq.) and brine, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (3-5% EtOAc/toluene) yielding the title compound (40 mg, 0.10 mmol, 50% yield) as a single diastereomeric product. R_f = 0.40 (8/92 EtOAc/toluene). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.25 (m, 15H, CH_{Ar} Bn), 4.63 (d, *J* = 11.9 Hz, 1H, C*H*H Bn-3), 4.61 (d, *J* = 12.1 Hz, 1H, C*H*H Bn-2), 4.58 (d, *J* = 12.1 Hz, 1H, C*H*H Bn-2), 4.56 (d, *J* = 12.2 Hz, 1H, C*H*H Bn-5), 4.50 (d, *J* = 12.0 Hz, 1H, C*H*H Bn-3), 4.49 (d, *J* = 12.1 Hz, 1H, C*H*H Bn-5), 4.16 (ddd, *J* = 6.5, 4.3, 3.3 Hz, 1H, C-4), 4.02 (t, *J* = 4.9 Hz, 1H, C-2), 3.97 (d, *J* = 4.8 Hz, 1H, C-1), 3.93 (dd, *J* = 6.4, 5.0 Hz, 1H, C-3), 3.62 (dd, *J* = 10.7, 3.3 Hz, 1H, C-5a), 3.51 (dd, *J* = 10.7, 4.3 Hz, 1H, C-5b). ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.3, 138.1, 138.0 (C_q Bn), 128.5, 128.5, 128.5, 128.1, 128.0, 127.9, 127.9, 127.8, 127.7 (CH_{Ar} Bn), 80.5 (*C*-4), 78.4 (*C*-3), 76.5 (*C*-2), 73.5 (CH_2 Bn-5), 72.3 (CH_2 Bn-3), 71.9 (CH_2 Bn-2), 70.4 (t, *J* = 23 Hz ,*C*-1), 70.1 (*C*-5). $[\alpha]^{20}_D$ = 52° (c = 0.7, $CHCl_3$). IR (neat): 602, 696, 737, 1003, 1026, 1053, 1088, 1130, 1206, 1273, 1312, 1339, 1362, 1454, 1497, 1717, 2860, 2920. HR-MS: [M+H$^+$] Calculated for $C_{26}H_{27}DO_4$: 406.21231; found: 406.21235.

Methyl-D-arabinofuranose (23). D-Arabinose (30 g, 200 mmol) was dissolved in MeOH (700 ml), acetyl chloride



(4.3 ml, 60 mmol) was added and the reaction stirred overnight. The reaction mixture was quenched by adjusting the pH to neutral by addition of $NaHCO_3$ (s), the solid was filtered off and the filtrate concentrated under reduced pressure. The residue was coevaporated with toluene before being purified by flash chromatography (75% EtOAc/Pentane - 20%

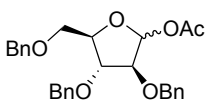
MeOH/EtOAc) yielding an anomeric mixture (α:β; 2:1) of the title compound (35 g, 195 mmol, 98% yield). R_f = 0.65 (2/8 MeOH/DCM). α-Anomer: ^{1}H NMR (400 MHz, MeOD) δ 4.73 (d, *J* = 1.6 Hz, 1H, C-1), 3.96 – 3.85 (m, 2H, C-2, C-4), 3.84 – 3.78 (m, 1H, C-3), 3.75 – 3.69 (m, 1H, C-5a), 3.62 (dd, *J* = 11.9, 5.4 Hz, 1H, C-5b), 3.34 (s, 3H, O*C*H$_3$). ^{13}C NMR (101 MHz, MeOD) δ 110.5 (*C*-1), 85.5 (*C*-4), 83.4 (*C*-2), 78.7 (*C*-3), 63.0 (*C*-5), 55.2 (O*C*H$_3$). β-Anomer: ^{1}H NMR (400 MHz, MeOD) δ 4.74 (d, *J* = 4.4 Hz, 1H, C-1), 3.98 – 3.87 (m, 2H, C-2, C-3), 3.80 – 3.74 (m, 1H, C-4), 3.68 (dd, *J* = 11.6, 3.7 Hz, 1H, C-5a), 3.55 (dd, *J* = 11.7, 7.1 Hz, 1H, C-5b), 3.41 (s, 3H, O*C*H$_3$). ^{13}C NMR (101 MHz, MeOD) δ 104.0 (*C*-1), 84.4 (*C*-4), 79.0 (*C*-2), 76.8 (*C*-3) , 65.5 (*C*-5), 55.5 (O*C*H$_3$). IR (neat): 882, 942, 990, 1002, 1021, 1093, 1191, 1314, 1366, 1415, 1451, 2836, 2923, 3351. HR-MS: [M+H$^+$] Calculated for $C_6H_{12}O_5$: 165.07575; found: 165.07553. Spectroscopic data was identical to literature data.[36]

2,3,5-Tri-*O*-benzyl-1-*O*-methyl-D-arabinofuranose (4). Methyl-D-arabinofuranose (**23**, 33 g, 200 mmol) was coevaporated twice with toluene before being dissolved in DMF (1 l) and cooled to 0 °C. Benzyl bromide (86 ml, 720 mmol), a catalytic amount of tetrabutyl ammonium iodide (0.7 g, 2 mmol) and sodium hydride (28.8 g, 720 mmol, 60% in mineral oil) were added. The reaction mixture was then allowed to gradually warm to room temperature while stirring and the reaction continued overnight. The reaction mixture was concentrated under reduced pressure before being taken up in EtOAc/1M HCl (aq.). The layers were separated and the organic layer washed with 1M HCl (aq.). The aqueous layers were combined and extracted with EtOAc. The organic layers were combined and washed with $NaHCO_3$ (sat. aq.) and brine. The solution was dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (1-12% Et_2O/pentane) yielding an anomeric mixture (α:β; 3:1) of the title compound (59 g, 135 mmol, 68 % yield). R_f = 0.30 and 0.45 (10/90 EtOAc/pentane). α-Anomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.21 (m, 15H, C*H*$_{Ar}$ Bn), 4.96 (s, 1H, C-1), 4.59 – 4.50 (m, 4H, 4xC*H*H Bn), 4.48 (d, *J* = 12.5 Hz, 1H, C*H*H Bn), 4.45 (d, *J* = 12.0 Hz, 1H, C*H*H Bn), 4.25 – 4.18 (m, 1H, C-4), 3.99 (dd, *J* = 3.0, 1.1 Hz, 1H, C-2), 3.90 (dd, *J* = 6.4, 2.8 Hz, 1H, C-3), 3.62 (dd, *J* = 10.1, 3.5 Hz, 1H, C-5a), 3.58 (dd, *J* = 10.0, 4.6 Hz, 1H, C-5b), 3.39 (s, 3H, O*C*H$_3$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.1, 137.8, 137.5 (3x*C*$_q$ Bn), 128.5, 128.5, 128.4, 128.4, 128.2, 127.9, 127.9, 127.8, 127.8, 127.7, 127.7 (*C*H$_{Ar}$ Bn), 107.3 (*C*-1), 88.1 (*C*-2), 83.4 (*C*-3), 81.0 (*C*-4), 73.4, 72.2, 71.9 (3x*C*H$_2$ Bn), 69.8 (*C*-5), 55.0 (O*C*H$_3$). β-Anomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.21 (m, 15H, C*H*$_{Ar}$ Bn), 4.72 (d, *J* = 4.0 Hz, 1H, C-1), 4.66 – 4.60 (m, 4H, 4xC*H*H Bn), 4.59 – 4.50 (m, 2H, 2xC*H*H Bn), 4.16 – 4.03 (m, 3H, *C*-2, *C*-3, *C*-4), 3.57 – 3.52 (m, 1H, *C*-5a), 3.53 – 3.48 (m, 1H, *C*-5b), 3.31 (s, 3H, O*C*H$_3$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.1, 137.8, 137.6 (3x*C*$_q$ Bn), 128.5, 128.5, 128.4, 128.4, 128.2, 128.0, 127.9, 127.9, 127.8, 127.8, 127.7, 127.7 (*C*H$_{Ar}$ Bn), 101.7 (*C*-1), 84.2 (*C*-2), 83.3 (*C*-3), 80.4 (*C*-4), 73.4, 72.6, 72.6 (3x*C*H$_2$ Bn), 72.3 (*C*-5), 55.0 (O*C*H$_3$). IR (neat): 611, 667, 695, 733, 908, 943, 1027, 1047, 1098, 1192, 1207, 1313, 1363, 1453, 1496, 2862, 2906. HR-MS: [M+H$^+$] Calculated for $C_{27}H_{30}O_5$: 435.21660; found: 435.21656. Analytical data matches literature data.[37]

2,3,5-Tri-*O*-benzyl-D-arabinofuranose (5). 2,3,5-Tri-*O*-benzyl-1-*O*-methyl-D-arabinofuranose (**4**, 31 g, 70 mmol) was dissolved in a mixture of acetic acid (360 ml) and water (90 ml). The mixture was refluxed (110 °C) for 3 days. The reaction was quenched by neutralizing the acid with 6M NaOH (aq.) and the aqueous layer extracted thrice with EtOAc. The organic layers were combined and washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (10-30% EtOAc/pentane) yielding an anomeric mixture (α:β; 5:4) of the title compound (21 g, 51 mmol, 72 % yield). R_f = 0.60 (25/75 EtOAc/pentane). α-Anomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.24 (m, 15H, C*H*$_{Ar}$ Bn), 5.39 (d, *J* = 5.3 Hz, 1H, C-1), 4.67 – 4.42 (m, 7H, 6xC*H*H Bn, C-4), 3.99 – 3.90 (m, 2H, C-2, C-3), 3.59 (dd, *J* = 10.0, 5.9 Hz, 1H, C-5a), 3.56 – 3.51 (m, 1H, C-5b), 3.41 (d, *J* = 7.0 Hz, 1H, OH). ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.1, 137.4, 137.4 (*C*$_q$ Bn), 128.6, 128.6, 128.5, 128.5, 128.1, 128.0, 128.0, 128.0, 127.9, 127.9, 127.9, 127.8, 127.8 (*C*H$_{Ar}$ Bn), 101.2 (*C*-1), 86.6 (*C*-2), 82.8 (*C*-3), 82.0 (*C*-4), 73.4, 72.1, 71.8 (3x*C*H$_2$ Bn), 70.2 (*C*-5). β-Anomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.24 (m, 15H, C*H*$_{Ar}$ Bn), 5.32 (dd, *J* = 9.7, 4.3 Hz, 1H, C-1), 4.65 (d, *J* = 11.6 Hz, 1H, C*H*H Bn), 4.62 – 4.42

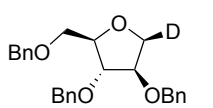
(m, 5H, 5xC*H*H Bn), 4.16 (t, *J* = 4.7 Hz, 1H, C-3), 4.11 – 4.07 (m, 1H, C-4), 4.01 (t, *J* = 4.6 Hz, 1H, C-2), 3.98 – 3.94 (m, 1H, OH), 3.58 – 3.53 (m, 1H, C-5a), 3.50 (dd, *J* = 10.1, 3.9 Hz, 1H, C-5b).^{13}C NMR (101 MHz, $CDCl_3$) δ 137.9, 137.5, 137.4 (C_q Bn), 128.6, 128.6, 128.5, 128.5, 128.1, 128.0, 128.0, 128.0, 127.9, 127.9, 127.9, 127.8, 127.8 (CH_{Ar} Bn), 96.3 (*C*-1), 84.1 (*C*-2), 81.9 (*C*-3), 80.6 (*C-4)*, 73.6, 72.3, 72.1 (3xCH_2 Bn), 70.6 (*C*-5). IR (neat): 608, 618, 638, 694, 730, 741, 753, 778, 823, 834, 852, 914, 976, 998, 1021, 1030, 1053, 1081, 1095, 1115, 1140, 1157, 1205, 1216, 1309, 1351, 1366, 1374, 1452, 1452, 1497, 2873, 3030, 3392. HR-MS: [M+Na^+] Calculated for $C_{26}H_{28}O_5$: 443.18290; found: 443.18209.

2,3,5-Tri-*O*-benzyl-1-*O*-acetyl-D-arabinofuranose (6). 2,3,5-Tri-*O*-benzyl-D-arabinofuranose (**5**, 3.2 g, 7.6 mmol) in



pyridine (11.5 ml) was added to cooled (0 °C) acetic anhydride (8.0 ml, 85 mmol) and stirred at room temperature for 3 hours. The reaction mixture was poured into 1M HCl (aq.) and diluted with EtOAc, the layers separated and the organic layer washed with 1M HCl (aq.), $NaHCO_3$ (sat. aq.) and brine. The solution was dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (10-20% EtOAc/pentane) yielding an anomeric mixture (α:β; 2:1) of the title compound (3.3 g, 7.1 mmol, 94 % yield). R_f = 0.8 (20/80 EtOAc/pentane). α-Anomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.21 (m, 15H, CH_{Ar} Bn), 6.25 (s, 1H, C-1), 4.65 – 4.47 (m, 6H, 6xC*H*H Bn), 4.36 (q, *J* = 5.3 Hz, 1H, C-4), 4.07 (d, *J* = 2.2 Hz, 1H, C-2), 3.98 (dd, *J* = 5.7, 2.2 Hz, 1H, C-3), 3.61 (d, *J* = 5.1 Hz, 2H, C-5), 2.06 (s, 3H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.0 (*C*=O), 138.0, 137.7, 137.3 (3xC_q Bn), 128.6, 128.5, 128.5, 128.4, 128.4, 128.0, 128.0, 127.9, 127.8, 127.8, 127.8, 127.7 (CH_{Ar} Bn), 100.6 (*C*-1), 87.1 (*C*-2), 83.8 (*C*-2), 83.4 (*C*-4), 73.5, 72.2, 72.1 (3xCH_2 Bn), 69.7 (*C*-5), 21.3 (CH_3). β-Anomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.22 (m, 15H, CH_{Ar} Bn), 6.28 (d, *J* = 4.0 Hz, 1H, C-1), 4.68 (d, *J* = 11.8 Hz, 1H, C*H*H Bn), 4.65 – 4.47 (m, 5H, 5xC*H*H Bn), 4.22 – 4.13 (m, 3H, C-2, C-3, C-4), 3.59 – 3.54 (m, 2H, C-5), 1.97 (s, 3H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.0 (*C*=O), 138.1, 137.7, 137.4 (3xC_q Bn), 128.6, 128.5, 128.5, 128.4, 128.4, 128.1, 128.0, 128.0, 127.9, 127.8, 127.8, 127.8, 127.7 (CH_{Ar} Bn), 94.4 (*C*-1), 83.8 (*C*-4), 81.7, 81.3 (*C*-2, *C*-3), 73.3, 73.2, 72.6 (3xCH_2 Bn), 71.2 (*C*-5), 21.3 (CH_3). IR (neat): 603, 695, 734, 886, 910, 940, 1006, 1027, 1047, 1090, 1227, 1364, 1454, 1734, 1748, 2865, 2926, 3031. HR-MS: [M+Na^+] Calculated for $C_{28}H_{30}O_6$: 485.19346; found: 485.19274.

2,3,5-Tri-*O*-benzyl-1-deoxy-1-β-deutero-D-arabinofuranose (16). 2,3,5-Tri-*O*-benzyl-1-*O*-acetyl-D-

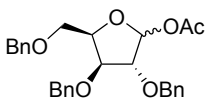


arabinofuranose (**6**, 93 mg, 0.20 mmol) was coevaporated with toluene (3x), dissolved in DCM (2.7 ml) and cooled to -78 °C. [D]Triethylsilane (64 µl, 0.4 mmol) was added before slowly adding a solution of trimethylsilyl trifluoromethanesulfonate (47 µl, 0.26 mmol) in DCM (300 µl) and the reaction stirred at -78 °C for 1 week. The reaction was quenched by addition of $NaHCO_3$ (sat. aq., 5 ml) and then allowed to warm to room temperature. The suspension was extracted with EtOAc and the combined organic layers washed with $NaHCO_3$ (sat. aq.) and brine, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The residue was dissolved in a mixture of sodium methoxide (0.04 mmol) in MeOH (4 ml) and stirred for 5 hours. The reaction was quenched with acetic acid (4 µl in 400 µl MeOH) and concentrated. The residue was taken up in EtOAc, washed with $NaHCO_3$ (sat. aq.) and brine, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (1.5-3% EtOAc/toluene) yielding the title compound (51 mg, 0.13 mmol, 63 % yield) as a single diastereomeric product. R_f = 0.70 (20/80 EtOAc/pentane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.24 (m, 15H, CH_{Ar} Bn), 4.58 (d, *J* = 12.1 Hz, 1H, C*H*H Bn-5), 4.54 (d, *J* = 12.1 Hz, 1H, C*H*H Bn-5), 4.53 (s, 2H, 2xC*H*H Bn-3), 4.48 (d, *J* = 12.0 Hz, 1H, C*H*H Bn-2), 4.44 (d, *J* = 11.9 Hz, 1H, C*H*H Bn-2), 4.09 – 4.04 (m, 2H, C-2, C-4), 3.96 (dd, *J* = 3.9, 1.6 Hz, 1H, C-3), 3.92 (d, *J* = 4.4 Hz, 1H, C-1), 3.62 (dd, *J* = 10.0, 6.1 Hz, 1H, C-5a), 3.57 (dd, *J* = 10.0, 5.7 Hz, 1H, C-5b). ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.3, 137.9 (C_q Bn), 128.6, 128.5, 127.9, 127.9, 127.9, 127.8, 127.7 (CH_{Ar} Bn), 84.6 (*C*-3), 83.3 (*C*-2), 82.8 (*C*-4), 73.5 (CH_2 Bn-5), 71.8 (CH_2 Bn-3), 71.3 (t, *J* = 23 Hz, *C*-1), 71.3 (CH_2 Bn-2), 70.5 (*C*-5). $[\alpha]^{20}_D$ = -1° (c = 1, $CHCl_3$). IR (neat): 667, 694, 733, 908, 969, 1002, 1024, 1071, 1088, 1206, 1363, 1453, 1496, 2862, 2919, 3031. HR-MS: [M+H^+] Calculated for $C_{26}H_{27}DO_4$: 406.21231; found: 406.21218.

2,3,5-Tri-*O*-benzyl-1-*O*-methyl-D-xylofuranose (7). D-Xylose (30 g, 200 mmol) was dissolved MeOH (700 ml), acetyl chloride (4.3 ml, 60 mmol) was added to the reaction and the mixture stirred overnight. The reaction mixture was quenched by adjusting the pH to neutral by addition of $NaHCO_3$ (s, 90g), the solid was filtered off and the filtrate concentrated under reduced pressure. The residue was coevaporated twice with toluene before being dissolved in DMF (1 ml) and cooled to 0 °C. Benzyl bromide (143 ml, 1.2 mol), a catalytic amount of tetrabutylammonium iodide (0.7 g, 2 mmol) and sodium hydride (48 g, 1.2 mol, 60% in mineral oil) were added to the mixture. After 1 hour of stirring at 0 °C, the mixture was allowed to gradually warm up to room temperature and stirred overnight. The reaction mixture was concentrated under reduced pressure before being taken up in Et_2O and washed with 1M HCl (aq.). The combined aqueous layers were extracted with Et_2O and the organic layers then combined before being washed with $NaHCO_3$ (sat. aq.) and brine. The solution was dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (2,5%-30% Et_2O/pentane) yielding an anomeric mixture (α:β; 7:8) of the title compound (87 g, 200 mmol, quant.). R_f = 0.35 and 0.45 (10/90 EtOAc/pentane). α-Anomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.21 (m, 15H, CH_{Ar} Bn), 4.81 (d, *J* = 4.3 Hz, 1H, C-1), 4.69 – 4.47 (m, 6H, 6xC*H*H Bn), 4.42 – 4.36 (m, 1H, C-4), 4.31 (dd, *J* = 7.2, 6.0 Hz, 1H, C-3), 4.02 (dd, *J* = 6.0, 4.3 Hz, 1H, C-2), 3.70 (dd, *J* = 10.5, 3.6 Hz, 1H, C-5a), 3.59 (dd, *J* = 10.6, 6.7 Hz, 1H, C-5b), 3.40 (s, 3H, OCH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.3, 138.2, 137.8 (C_q Bn), 128.6, 128.5, 128.4, 128.4, 128.2, 128.0, 128.0, 127.9, 127.9, 127.8, 127.7, 127.7, 127.7 (CH_{Ar} Bn), 100.6 (*C*-1), 84.0 (*C*-2), 81.6 (*C*-3), 76.0 (*C*-4), 73.6, 72.7, 72.0 (3xCH_2 Bn), 69.5 (*C*-5), 55.4 (OCH_3). β-Anomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.21 (m, 15H, CH_{Ar} Bn), 4.91 (d, *J* = 1.5 Hz, 1H, C-1), 4.69 – 4.47 (m, 6H, 6xC*H*H Bn), 4.49-4.41 (m, 1H, C-4), 4.05 (dd, *J* = 5.9, 2.6 Hz, 1H, C-3), 3.97 (dd, *J* = 2.6, 1.5 Hz, 1H, C-2), 3.78 (dd, *J* = 10.2, 4.9 Hz, 1H, C-5a), 3.72 (dd, *J* = 10.3, 7.0 Hz, 1H, C-5b), 3.40 (s, 3H, OCH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.4, 137.8, 137.6 (C_q Bn), 128.6, 128.5, 128.4, 128.4, 128.2, 128.0, 128.0, 127.9, 127.9, 127.8, 127.7, 127.7, 127.7 (CH_{Ar} Bn), 108.3 (*C*-1), 86.9 (*C*-2), 81.5 (*C*-3), 80.2 (*C*-4), 73.5, 72.7, 72.3 (3xCH_2 Bn), 69.8 (*C*-5), 55.8 (OCH_3). IR (neat): 605, 695, 732, 889, 908, 953, 1001, 1026, 1056, 1081, 1097, 1194, 1206, 1340, 1363, 1453, 2865, 2915, 3030. HR-MS: [M+H^+] Calculated for $C_{27}H_{30}O_5$: 435.21660; found: 435.21677.

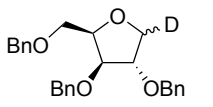
2,3,5-Tri-*O*-benzyl-D-xylofuranose (8). 2,3,5-Tri-*O*-benzyl-1-*O*-methyl-D-xylofuranose (**7**, 35 g, 81 mmol) was dissolved in 1,4-dioxane (280 ml) before addition of aqueous HCl (4M, 280 ml) and the mixture was heated (90 °C) for a total of 2,5 hours. The mixture was cooled down and quenched by pouring the mixture into a $NaHCO_3$ solution (sat. aq.) and extracting the mixture with EtOAc. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (15-40% Et_2O/pentane) yielding an anomeric mixture (α:β; 1:2) of the title compound (26 g, 62 mmol, 77 % yield). R_f = 0.30 (20/80 EtOAc/pentane). α-Anomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.21 (m, 15H, CH_{Ar} Bn), 5.47 (d, *J* = 4.2 Hz, 1H, C-1), 4.64 – 4.43 (m, 6H, 6xC*H*H Bn), 4.43 – 4.34 (m, 1H, C-4), 4.03 (dd, *J* = 4.5, 2.3 Hz, 1H, C-3), 3.93 (dd, *J* = 4.2, 2.3 Hz, 1H, C-2), 3.73 – 3.69 (m, 1H, C-5a), 3.66 (dd, *J* = 9.9, 5.8 Hz, 1H, C-5b). ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.2, 137.8, 136.9 (C_q Bn), 128.7, 128.6, 128.6, 128.6, 128.4, 128.4, 128.1, 128.0, 128.0, 128.0, 127.9, 127.9, 127.9, 127.8, 127.7 (CH_{Ar} Bn), 96.3 (*C*-1), 81.3 (*C*-3), 81.1 (*C*-2), 77.4 (*C*-4), 73.6, 73.1, 72.4 (3xCH_2 Bn), 68.4 (*C*-5). β-Anomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.21 (m, 15H, CH_{Ar}), 5.25 (s, 1H, C-1), 4.65 – 4.43 (m, 6H, 6xC*H*H Bn), 4.42 – 4.35 (m, 1H, C-4), 4.10 (dd, *J* = 5.5, 3.1 Hz, 1H, C-3), 4.00 (d, *J* = 3.0 Hz, 1H, C-2), 3.75 (dd, *J* = 10.0, 5.0 Hz, 1H, C-5a), 3.73 – 3.69 (m, 1H, C-5b). ^{13}C NMR (101 MHz, $CDCl_3$) δ 137.6, 137.5, 137.4 (C_q Bn), 128.7, 128.6, 128.6, 128.6, 128.4, 128.4, 128.1, 128.0, 128.0, 128.0, 127.9, 127.9, 127.9, 127.8, 127.7 (CH_{Ar} Bn), 101.8 (*C*-1), 86.7 (*C*-2), 81.4 (*C*-3), 79.9 (*C*-4), 73.8, 72.7, 71.9 (3xCH_2 Bn), 68.8 (*C*-5). IR (neat): 604, 694, 733, 779, 920, 845, 908, 941, 1026, 1053, 1207, 1350, 1366, 1454, 1497, 2864, 2920, 3421. HR-MS: [M+Na^+] Calculated for $C_{26}H_{28}O_5$: 443.18290; found: 443.18216.

2,3,5-Tri-*O*-benzyl-1-*O*-acetyl-D-xylofuranose (9). 2,3,5-Tri-*O*-benzyl-D-xylofuranose (**8**, 4.2 g, 10 mmol) was



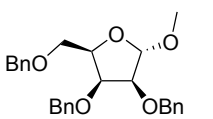
dissolved in pyridine (15 ml) and slowly added to cooled (0 °C) acetic anhydride (10 ml, 106 mmol). The mixture was then stirred at room temperature for 4 hours. The mixture was poured into 1M HCl (aq.) and diluted with EtOAc. The two layers were separated and the organic layer washed with 1M HCl (aq.), $NaHCO_3$ (sat. aq.) and brine. The solution was dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (10-20% EtOAc/pentane) yielding an anomeric mixture (α:β; 1:3) of the title compound (4.2 g, 8.6 mmol, 86 % yield). R_f = 0.60 (20/80 EtOAc/pentane). α-Anomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.22 (m, 15H, CH_{Ar} Bn), 6.35 (d, *J* = 4.2 Hz, 1H, C-1), 4.66 – 4.45 (m, 7H, 6xC*H*H Bn, C-4), 4.29 – 4.24 (t, *J* = 6.2 ,1H, C-3), 4.21 (dd, *J* = 5.7, 4.3 Hz, 1H, C-2), 3.72 (dd, *J* = 10.4, 4.2 Hz, 1H, C-5a), 3.61 (dd, *J* = 10.6, 5.9 Hz, 1H, C-5b), 2.07 (s, 3H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.2 (*C*=O), 138.3, 137.8, 137.5 (C_q Bn), 128.6, 128.5, 128.4, 128.1, 128.1, 128.1, 127.9, 127.9, 127.8, 127.8, 127.7, 127.7, 127.6, 127.6 (*C*H$_{Ar}$ Bn), 94.3 (*C*-1), 83.4 (*C*-2), 80.9 (*C*-3), 78.2 (*C*-4), 73.6, 73.3, 72.8 (3x*C*H$_2$ Bn), 68.9 (*C*-5), 21.3 (*C*H$_3$). β-Anomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.20 (m, 15H, CH_{Ar} Bn), 6.18 (s, 1H, C-1), 4.67 – 4.49 (m, 6H, 5xC*H*H Bn, C-4), 4.46 (d, *J* = 12.1 Hz, 1H, C*H*H Bn), 4.10 – 4.04 (m, 2H, C-2, C-3), 3.82 (dd, *J* = 10.2, 5.4 Hz, 1H, C-5a), 3.74 (dd, *J* = 10.3, 6.6 Hz, 1H, C-5b), 2.02 (s, 3H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.2 (*C*=O), 138.3, 137.8, 137.4 (C_q Bn), 128.6, 128.5, 128.4, 128.1, 128.1, 127.9, 127.9, 127.8, 127.8, 127.7, 127.7, 127.6, 127.6 (*C*H$_{Ar}$ Bn), 100.6 (*C*-1), 85.2 (*C*-3), 82.2 (*C*-4), 81.1 (*C*-2), 73.5, 72.2, 72.1 (3x*C*H$_2$ Bn), 68.9 (*C*-5), 21.4 (*C*H$_3$). IR (neat): 602, 696, 733, 781, 820, 845, 914, 945, 1007, 1090, 1231, 1371, 1454, 1497, 1744, 2864, 2926. HR-MS: [M+Na$^+$] Calculated for $C_{28}H_{30}O_6$: 485.19346; found: 485.19274.

2,3,5-Tri-*O*-benzyl-1-deoxy-1-α/β-deutero-D-xylofuranose (17). 2,3,5-Tri-*O*-benzyl-1-*O*-acetyl-D-xylofuranose (**9**,



93 mg, 0.2 mmol) was coevaporated with toluene (3x), dissolved in DCM (2.7 ml) and cooled to -78 °C. [D]Triethylsilane (64 µl, 0.4 mmol) was added before slowly adding a solution of trimethylsilyl trifluoromethanesulfonate (47 µl, 0.26 mmol) in DCM (300 µl) and the reaction stirred at -78 °C for 1 week. The reaction was quenched by addition of $NaHCO_3$ (sat.aq., 5 ml) and then allowed to warm to room temperature. The suspension was extracted with EtOAc and the combined organic layers washed with $NaHCO_3$ (sat. aq.) and brine, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The residue was dissolved in a mixture of sodium methoxide (0.04 mmol) in MeOH (4 ml) and stirred for 5 hours. The reaction was quenched with acetic acid (4 µl in 400 µl MeOH) and concentrated. The residue was taken up in EtOAc, washed with $NaHCO_3$ (sat. aq.) and brine, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (2-3.5% EtOAc/toluene) yielding an anomeric mixture (α:β; 85:15) of the title compound (32 mg, 0.08 mmol, 40 % yield). R_f = 0.70 (20/80 EtOAc/pentane). ^{1}H NMR (400 MHz, $CDCl_3$) α-Anomer: δ 4.14 (d, *J* = 5.0 Hz, 1H). β-Anomer: δ 3.80 (d, *J* = 2.4 Hz, 1H). Both: δ 7.39 – 7.25 (m, 15H, CH_{Ar} Bn), 4.62 (d, *J* = 12.0 Hz, 1H, C*H*H-Bn-5), 4.57 (d, *J* = 12.1 Hz, 1H, C*H*H Bn-3), 4.52 (d, *J* = 12.0 Hz, 1H, C*H*H Bn-5), 4.53 – 4.46 (m, 1H, C*H*H Bn-3), 4.47 (s, 2H, 2xC*H*H Bn-2), 4.24 (ddd, *J* = 6.5, 5.5, 3.9 Hz, 1H, C-4), 4.08 (dd, *J* = 5.0, 1.2 Hz, 1H, C-2), 4.02 (dd, *J* = 3.9, 1.2 Hz, 1H, C-3), 3.76 (dd, *J* = 10.0, 5.5 Hz, 1H, C-5a), 3.71 (dd, *J* = 10.0, 6.6 Hz, 1H, C-5b). ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.4, 138.0, 137.8 (C_q Bn), 128.6, 128.6, 128.5, 128.0, 127.9, 127.9, 127.7, 127.7, 127.7 (*C*H$_{Ar}$ Bn), 82.2 (*C*-2), 82.1 (*C*-3), 79.7 (*C*-4), 73.6 (*C*H$_2$ Bn-5), 72.1 (*C*H$_2$ Bn-3), 71.5 (*C*H$_2$ Bn-2), 71.4 (t, *J* = 23 Hz, *C*-1), 68.5 (*C*-5). IR (neat): 602, 694, 733, 814, 908, 966, 1026, 1072, 1206, 1348, 1454, 1497, 2857, 2920. HR-MS: [M+H$^+$] Calculated for $C_{26}H_{27}DO_4$: 406.21231; found: 406.21209.

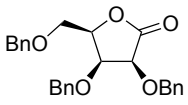
2,3,5-Tri-*O*-benzyl-α-1-*O*-methyl-D-lyxofuranose (10). D-Lyxose (25 g, 167 mmol) was dissolved in MeOH (430



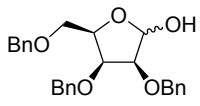
ml), a solution of acetyl chloride (2.5 ml, 35 mmol) in MeOH (130 ml) added and the reaction mixture stirred overnight. The reaction was quenched by adjusting the pH of the reaction mixture to ~7 by addition of 3M NaOH (aq.) before being concentrated and coevaporated with toluene (4x). The crude product was dissolved in DMF (850 ml) and

cooled down (0 °C). Benzyl bromide (83 ml, 700 mmol), a catalytic amount of tetrabutylammonium iodide and sodium hydride (28 g, 700 mmol, 60% in mineral oil) were added and the reaction allowed to slowly warm to room temperature whilst stirring. After the reaction was stirred overnight, the mixture was concentrated under reduced pressure, the mixture taken up in a mixture of EtOAc/1M HCl (aq.) and the layers separated. The organic layer was washed with 1M HCl (aq.), with $NaHCO_3$ (sat. aq.) and brine, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (2-20% Et_2O/pentane) yielding the title compound (61 g, 140 mmol, 84 % yield) with a minor fraction of its pyranose side product. R_f = 0.30 (10/90 EtOAc/pentane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.23 (m, 15H, CH_{Ar} Bn), 5.02 (d, *J* = 2.3 Hz, 1H, C-1), 4.70 – 4.57 (m, 3H, C*H*H Bn), 4.58 (d, *J* = 12.1 Hz, 1H, C*H*H Bn), 4.52 (d, *J* = 12.0 Hz, 1H, C*H*H Bn), 4.50 (d, *J* = 12.0 Hz, 1H, C*H*H Bn), 4.39 – 4.31 (m, 1H, C-4), 4.19 (t, *J* = 5.0 Hz, 1H, C-3), 3.88 (dd, *J* = 4.6, 2.4 Hz, 1H, C-2), 3.80 – 3.72 (m, 2H, C-5), 3.36 (s, 3H, O*CH*$_3$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.3, 138.2, 137.9 (C_q Bn), 128.5, 128.4, 128.0, 127.8, 127.8, 127.8, 127.7 (*C*H$_{Ar}$ Bn), 106.4 (*C*-1), 82.5 (*C*-2), 78.3 (*C*-4), 77.9 (*C*-3), 73.5, 73.3, 72.6 (3x*C*H$_2$ Bn), 69.8 (*C*-5), 55.7 (O*C*H$_3$). $[\alpha]^{20}_D$ = 10° (c = 0.8, $CHCl_3$). IR (neat): 604, 650, 694, 733, 808, 920, 851, 910, 968, 1026, 1047, 1099, 1206, 1271, 1314, 1346, 1362, 1452, 1497, 1722, 2913. HR-MS: [M+H$^+$] Calculated for $C_{27}H_{30}O_5$: 435.21660; found: 435.21665. Spectroscopic data was identical to literature data.[38]

2,3,5-Tri-*O*-benzyl-D-lyxofuranolactone (12). 2,3,5-Tri-*O*-benzyl-α-1-*O*-methyl-D-lyxofuranose (**10**, 25 g, 58 mmol) was dissolved in acetic acid (300 ml) and H_2O (75 ml). The mixture was refluxed (110 °C) overnight and allowed to cool down before being neutralized with 6M NaOH and extracted with EtOAc. The organic layers were combined and washed with $NaHCO_3$ (sat. aq.) and brine. The organic layer was dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (25-75% Et_2O/pentane) yielding 2,3,5-Tri-*O*-benzyl-D-lyxofuranose (18 g, 44 mmol, 76 % yield) with minor fractions of its pyranose isomer (R_f = 0.40, 25/75 EtOAc/pentane) which was used without any further identification in the next step. The hemiacetal was dissolved in dimethyl sulfoxide (350 ml) and acetic anhydride (230 ml) was added. The mixture was stirred overnight and diluted with Et_2O, washed twice with H_2O, twice with $NaHCO_3$ (sat. aq.) and once with brine. The organic layer was dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The residue was crystallized from methanol yielding the pure title compound (14 g, 33 mmol, 76 % yield). R_f = 0.55 (25/75 EtOAc/pentane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 – 7.24 (m, 15H, CH_{Ar} Bn), 4.98 (d, *J* = 12.1 Hz, 1H, C*H*H Bn-2), 4.85 (d, *J* = 11.7 Hz, 1H, C*H*H Bn-3), 4.79 (d, *J* = 12.1 Hz, 1H, C*H*H Bn-2), 4.56 (d, *J* = 11.2 Hz, 1H, C*H*H Bn-3), 4.48 (d, *J* = 11.8 Hz, 1H, C*H*H Bn-5a), 4.48 (d, *J* = 11.8 Hz, 1H, C*H*H Bn-5b), 4.44 (dt, *J* = 6.1, 3.1 Hz, 1H, C-4), 4.22 (dd, *J* = 4.5, 3.2 Hz, 1H, C-3), 4.19 (d, *J* = 4.6 Hz, 1H, C-2), 3.79 (d, *J* = 6.1 Hz, 2H, C-5). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.2 (*C*=O), 137.6, 137.5, 136.9 (C_q Bn), 128.7, 128.6, 128.5, 128.3, 128.1, 128.1, 128.0, 128.0, 127.9 (*C*H$_{Ar}$ Bn), 78.5 (*C*-4), 76.2 (*C*-2), 75.1 (*C*-3), 73.8 (*C*H$_2$ Bn-5), 73.7 (*C*H$_2$ Bn-3), 72.7 (*C*H$_2$ Bn-2), 67.6 (*C*-5). $[\alpha]^{20}_D$ = -26° (c = 1, $CHCl_3$). IR (neat): 611, 644, 662, 692, 725, 779, 827, 880, 891, 910, 953, 993, 1024, 1053, 1078, 1103, 1132, 1159, 1198, 1213, 1267, 1344, 1360, 1410, 1452, 1497, 1802, 2876, 2916, 3028. HR-MS: [M+Na$^+$] Calculated for $C_{26}H_{26}O_5$: 441.16725; found: 441.16651.

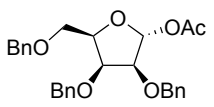


2,3,5-Tri-*O*-benzyl-D-lyxofuranose (13). 2,3,5-Tri-*O*-benzyl-D-lyxofuranolactone (**12**, 2.1 g, 5 mmol) was dissolved in DCM (25 ml) and cooled to -78 °C. Diisobutylaluminum hydride (7 ml, 7 mmol, 1M in hexanes) was added slowly over 10-15 minutes and the reaction mixture kept at -78 °C for 1 hour. Methanol (2 ml) was added dropwise to quench the reaction and the solution allowed to warm to room temperature. The solution was diluted with DCM and washed with potassium sodium tartrate (1M aq.). The solution was dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The product was purified by flash chromatography (30-40% EtOAc/pentane) yielding an anomeric mixture (α:β; 1:4) of the title compound (2.0 g, 4,7 mmol, 94 % yield). R_f = 0.15 (20/80 EtOAc/pentane). α-Anomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.23 (m, 15H, CH_{Ar} Bn), 5.49 (d, *J* = 2.7 Hz, 1H, C-1), 4.68 (d, *J* = 12.0 Hz, 1H, C*H*H Bn), 4.66 (d, *J* = 12.0 Hz, 1H, C*H*H Bn), 4.62 – 4.47 (m, 4H, 4xC*H*H Bn),



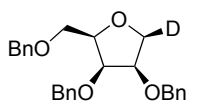
4.47 – 4.42 (m, 1H, C-4), 4.21 (t, *J* = 4.9 Hz, 1H, C-3), 3.92 – 3.85 (m, 1H, C-2), 3.76 – 3.73 (m, 2H, C-5). ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.2, 138.1, 137.9 (C_q Bn), 128.6, 128.5, 128.5, 128.4, 128.4, 128.0, 128.0, 127.9, 127.9, 127.8, 127.8, 127.7, 127.6 (CH_{Ar} Bn), 100.1 (*C*-1), 83.4 (*C*-2), 78.4 (*C*-4), 77.9 (*C*-3), 73.5, 73.3, 72.5 (3xCH_2-Bn), 69.8 (*C*-5). β-Anomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.23 (m, 15H, CH_{Ar} Bn), 5.25 (dd, *J* = 12.1, 4.4 Hz, 1H, C-1), 4.84 (d, *J* = 11.3 Hz, 1H, C*H*H Bn), 4.73 (d, *J* = 11.7 Hz, 1H, C*H*H Bn), 4.64 – 4.46 (m, 4H, 4xC*H*H Bn), 4.28 (d, *J* = 12.2 Hz, 1H, OH), 4.15 – 4.06 (m, 2H, C-3, C-4), 3.91 – 3.87 (m, 1H, C-2), 3.81 (dd, *J* = 9.5, 6.6 Hz, 1H, C-5a), 3.69 (dd, *J* = 9.5, 5.5 Hz, 1H, C-5b). ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.0, 137.7, 137.5 (C_q Bn), 128.6, 128.5, 128.5, 128.4, 128.4, 128.0, 128.0, 127.9, 127.8 (CH_{Ar} Bn), 95.6 (*C*-1), 79.3 (*C*-2), 78.2, 77.4 (C-3, C-4), 74.4, 73.7, 72.0 (3xCH_2 Bn), 69.3 (*C*-5). IR (neat): 602, 648, 694, 733, 820, 849, 885, 910, 947, 1026, 1045, 1078, 1146, 1207, 1308, 1346, 1454, 1497, 2866, 2922, 3418. HR-MS: [M+H$^+$] Calculated for $C_{26}H_{28}O_5$: 421.20095; found: 421.20090.

2,3,5-Tri-*O*-benzyl-1-α-*O*-acetyl-D-lyxofuranose (14). 2,3,5-Tri-*O*-benzyl-D-lyxofuranose (**13**, 2.3 g, 5.5 mmol) was



dissolved in pyridine (8 ml) and cooled (0 °C). Acetic anhydride (5.7 ml, 60 mmol) was added and the reaction allowed to stir at room temperature for 5 hours. The mixture was then poured into a solution of 1M HCl (aq.) and extracted with EtOAc. The organic phase was washed twice with 1M HCl (aq.), $NaHCO_3$ (sat. aq.) and brine before being dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (15-22.5% EtOAc/pentane) yielding the title compound (2.6 g, 5.5 mmol, quantitative) as a single diastereomer. R_f = 0.45 (20/80 EtOAc/pentane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.25 (m, 15H, CH_{Ar} Bn), 6.29 (d, *J* = 2.2 Hz, 1H, C-1), 4.68 (d, *J* = 12.1 Hz, 1H, C*H*H Bn), 4.66 (d, *J* = 11.9 Hz, 1H, C*H*H Bn), 4.60 (d, *J* = 12.1 Hz, 1H, C*H*H Bn), 4.59 (d, *J* = 11.9 Hz, 1H, C*H*H Bn), 4.52 (d, *J* = 11.8 Hz, 1H, C*H*H Bn), 4.50 (d, *J* = 11.9 Hz, 1H, C*H*H Bn), 4.48 – 4.42 (m, 1H, C-4), 4.22 (t, *J* = 5.2 Hz, 1H, C-3), 3.99 (dd, *J* = 4.7, 2.2 Hz, 1H, C-2), 3.82 (dd, *J* = 10.3, 4.9 Hz, 1H, C-5a), 3.75 (dd, *J* = 10.3, 7.0 Hz, 1H, C-5b), 2.03 (s, 3H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.9 (*C*=O), 138.2, 137.9, 137.5 (C_q Bn), 128.5, 128.5, 128.4, 128.0, 127.9, 127.9, 127.7, 127.7 (CH_{Ar} Bn), 99.3 (*C*-1), 81.4 (*C*-4), 79.9 (*C*-2), 77.0 (*C*-3), 73.5, 73.2, 72.5 (3xCH_2 Bn), 69.4 (*C*-5), 21.3 (CH_3). $[\alpha]^{20}_D$ = 15° (c = 1, $CHCl_3$). IR (neat): 602, 694, 733, 820, 851, 907, 945, 1009, 1053, 1090, 1552, 1227, 1369, 1454, 1497, 1744, 2866. HR-MS: [M+Na$^+$] Calculated for $C_{28}H_{30}O_6$: 485.19346; found: 485.19270.

2,3,5-Tri-*O*-benzyl-1-deoxy-1-β-deutero-D-lyxofuranose (18). 2,3,5-Tri-*O*-benzyl-1-α-*O*-acetyl-D-lyxofuranose



(**14**, 93 mg, 0.2 mmol) was coevaporated with toluene (3x), dissolved in DCM (2.7 ml) and cooled to -78 °C. [D]Triethylsilane (64 µl, 0.4 mmol) was added before slowly adding a solution of trimethylsilyl trifluoromethanesulfonate (47 µl, 0.26 mmol) in DCM (300 µl) and the reaction stirred at -78 °C for 1 week. The reaction was quenched by addition of $NaHCO_3$ (sat. aq., 5 ml) and allowed to warm to room temperature. The suspension was extracted thrice with EtOAc and the combined organic layers washed with $NaHCO_3$ (sat. aq.) and brine, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (2-4.5% EtOAc/toluene) yielding the title compound (88 mg, 0.2 mmol, quantitative) as a single diastereomer. R_f = 0.45 (10/90 EtOAc/toluene). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.23 (m, 15H, CH_{Ar} Bn), 4.75 (d, *J* = 11.9 Hz, 1H, C*H*H Bn-3), 4.63 – 4.52 (m, 4H, 2xC*H*H Bn-2, C*H*H Bn-3, C*H*H Bn-5), 4.50 (d, *J* = 11.9 Hz, 1H, C*H*H Bn-5), 4.21 – 4.15 (m, 1H, C-4), 4.12 – 4.05 (m, 2H, C-2, C-3), 3.88 (d, *J* = 5.6 Hz, 1H, C-1), 3.77 (dd, *J* = 10.5, 5.4 Hz, 1H, C-5a), 3.73 (dd, *J* = 10.5, 7.4 Hz, 1H, C-5b). ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.4, 138.3, 138.0 (C_q Bn), 128.5, 128.4, 128.4, 127.9, 127.8, 127.8, 127.7, 127.6 (CH_{Ar} Bn), 79.0 (*C*-4), 78.5 (*C*-2), 77.8 (*C*-3), 73.5 (CH_2 Bn-5), 73.3 (CH_2 Bn-3), 72.3 (CH_2 Bn-2), 69.5 (*C*-5), 68.9 (t, *J* = 23 Hz, *C*-1). $[\alpha]^{20}_D$ = -9° (c = 1, $CHCl_3$). IR (neat): 608, 635, 694, 733, 808, 849, 910, 1026, 1059, 1074, 1148, 1207, 1260, 1346, 1452, 1497, 2860, 2920. HR-MS: [M+H$^+$] Calculated for $C_{26}H_{27}DO_4$: 406.21231; found: 406.21219.

References and notes

[1] Richards, M. R.; Lowary, T. L. *Chembiochem* **2009**, *10*, 1920-1938, 10.1002/cbic.200900208.

[2] Taha, H. A.; Richards, M. R.; Lowary, T. L. *Chem. Rev.* **2013**, *113*, 1851-1876, 10.1021/cr300249c.

[3] Schramm, V. L. *ACS Chem. Biol.* **2013**, *8*, 71-81, 10.1021/cb300631k.

[4] Yin, H. F.; D'Souza, F. W.; Lowary, T. L. *J. Org. Chem.* **2002**, *67*, 892-903, 10.1021/jo010910e.

[5] Joe, M.; Sun, D.; Taha, H.; Completo, G. C.; Croudace, J. E.; Lammas, D. A.; Besra, G. S.; Lowary, T. L. *J. Am. Chem. Soc.* **2006**, *128*, 5059-5072, 10.1021/ja057373q.

[6] Lee, Y. J.; Lee, K.; Jung, E. H.; Jeon, H. B.; Kim, K. S. *Org. Lett.* **2005**, *7*, 3263-3266, 10.1021/ol0510668.

[7] Baek, J. Y.; Joo, Y. J.; Kim, K. S. *Tetrahedron Lett.* **2008**, *49*, 4734-4737, 10.1016/j.tetlet.2008.05.118.

[8] Mukaiyama, T.; Suda, S. *Chem. Lett.* **1990**, 1143-1146, 10.1246/cl.1990.1143.

[9] Czernecki, S.; Ville, G. *J. Org. Chem.* **1989**, *54*, 610-612, 10.1021/jo00264a020.

[10] Sollogoub, M.; Fox, K. R.; Powers, V. E. C.; Brown, T. *Tetrahedron Lett.* **2002**, *43*, 3121-3123, 10.1016/s0040-4039(02)00481-1.

[11] Larsen, C. H.; Ridgway, B. H.; Shaw, J. T.; Woerpel, K. A. *J. Am. Chem. Soc.* **1999**, *121*, 12208-12209, 10.1021/ja993349z.

[12] Smith, D. M.; Tran, M. B.; Woerpel, K. A. *J. Am. Chem. Soc.* **2003**, *125*, 14149-14152, 10.1021/ja0375176.

[13] Smith, D. M.; Woerpel, K. A. *Org. Lett.* **2004**, *6*, 2063-2066, 10.1021/ol0492647.

[14] Larsen, C. H.; Ridgway, B. H.; Shaw, J. T.; Smith, D. M.; Woerpel, K. A. *J. Am. Chem. Soc.* **2005**, *127*, 10879-10884, 10.1021/ja0524043.

[15] Smith, D. M.; Woerpel, K. A. *Org. Biomol. Chem.* **2006**, *4*, 1195-1201, 10.1039/b600056h.

[16] Zhu, X. M.; Kawatkar, S.; Rao, Y.; Boons, G. J. *J. Am. Chem. Soc.* **2006**, *128*, 11948-11957, 10.1021/ja0629817.

[17] Krumper, J. R.; Salamant, W. A.; Woerpel, K. A. *Org. Lett.* **2008**, *10*, 4907-4910, 10.1021/ol8019956.

[18] Huang, M.; Garrett, G. E.; Birlirakis, N.; Bohe, L.; Pratt, D. A.; Crich, D. *Nat. Chem.* **2012**, *4*, 663-667, 10.1038/nchem.1404.

[19] Crich, D. *Acc. Chem. Res.* **2010**, *43*, 1144-1153, 10.1021/ar100035r.

[20] The relative stabilitity of the anomeric triflates was calculated using B3LYP/6--311G**//B3LYP/6-31G*. Relative energy of *cis* to *trans*; ribose: +1.0 kcal mol^{-1}; arabinose: +0.1 kcal mol^{-1}; xylose: +0.6 kcal mol^{-1}, lyxose: +1.0 kcal mol^{-1}. See appendix for FES maps of the triflates.

[21] Rhoad, J. S.; Cagg, B. A.; Carver, P. W. *J. Phys. Chem. A* **2010**, *114*, 5180-5186, 10.1021/jp9100448.

[22] Altona, C.; Sundaralingan, M. *J. Am. Chem. Soc.* **1972**, *94*, 8205-8212, 10.1021/ja00778a043.

[23] Gaussian 03 (Revision E.01), Frisch, M. J. *et al.*, Gaussian, Inc. **2004**.

[24] Kim, Y.; Mohrig, J. R.; Truhlar, D. G. *J. Am. Chem. Soc.* **2010**, *132*, 11071-11082, 10.1021/ja101104q.

[25] Houseknecht, J. B.; Lowary, T. L.; Hadad, C. M. *J. Phys. Chem. A* **2003**, *107*, 5763-5777, 10.1021/jp027716w.

[26] Jensen, H. H.; Nordstrom, L. U.; Bols, M. *J. Am. Chem. Soc.* **2004**, *126*, 9205-9213, 10.1021/ja047578j.

[27] Moume-Pymbock, M.; Crich, D. *J. Org. Chem.* **2012**, *77*, 8905-8912, 10.1021/jo3011655.

[28] Seeman, J. I. *Chem. Rev.* **1983**, *83*, 83-134, 10.1021/cr00054a001.

[29] Calculations to determine the transition states of S_N1 reactions on glycosyl oxocarbenium ions are notoriously difficult because these require the use of counterions, both on the side of the electrophile and the nucleophile, to prevent the barrierless formation of noncharged species. See for example: Ref 27; Whitfield, D. M. *Adv. Carbohydr. Chem. Biochem.* **2009**, *62*, 83-159, 10.1016/s0065-2318(09)00004-3.

[30] Davies, G. J.; Planas, A.; Rovira, C. *Acc. Chem. Res.* **2012**, *45*, 308-316, 10.1021/ar2001765.

[31] Zhang, Y.; Luo, M. K.; Schramm, V. L. *J. Am. Chem. Soc.* **2009**, *131*, 4685-4694, 10.1021/ja808346y.

[32] Spartan '04, Kong, J. *et al.*, Wavefunction Inc. **2004**.

[33] Daranas, A. H.; Napolitano, J. G.; Gavin, J. A.; Garcia, C.; Norte, M.; Fernandez, J. J. *Chem. Eur. J.* **2011**, *17*, 6338-6347, 10.1002/chem.201100412.

[34] Xu, G. X.; Moeller, K. D. *Org. Lett.* **2010**, *12*, 2590-2593, 10.1021/ol100800u.

[35] Mukaiyama, T.; Kobayashi, S. *Carbohydr. Res.* **1987**, *171*, 81-87, 10.1016/s0008-6215(00)90880-2.

[36] Barry, C. S.; Backus, K. M.; Barry, C. E.; Davis, B. G. *J. Am. Chem. Soc.* **2011**, *133*, 13232-13235, 10.1021/ja204249p.

[37] van der Klein, P. A. M.; de Nooy, A. E. J.; van der Marel, G. A.; van Boom, J. H. *Synthesis* **1991**, 347-349, 10.1055/s-1991-26461.

[38] Kawana, M.; Kuzuhara, H.; Emoto, S. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 1492-1504, 10.1246/bcsj.54.1492.