Oligofuranosides Containing Conformationally Restricted Residues: Synthesis and Conformational Analysis

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The synthesis of a panel of arabinofuranosyl oligosaccharide analogues (**5**−**13**) in which one ring is locked into either the E_3 or ^{O}E conformation is described. The E_3-locked scaffolds **15** and **16** required for the synthesis of **5**−**10** were prepared in one step from known 1,5-anhydroalditols. A number of routes were explored for the preparation of the ^{O}E-locked monosaccharide derivative **17** needed for the preparation of **11**−**13**. The successful synthesis of **17** was achieved in 17 steps from D-arabinose. Subsequent analysis of **5**−**13** by ^{1}H NMR spectroscopy demonstrated that the locked residue does not exert any detectable influence upon the conformers populated by adjacent conformationally unrestricted furanose rings.

Introduction

Furanose rings are found throughout nature as components of nucleic acids,[1] polysaccharides,[2] and other natural products.[3] An important structural characteristic of these and all five-membered rings is their inherent flexibility. Conformationally unrestricted furanose rings can adopt a number of envelope (E) and twist (T) conformers, which can be conveniently depicted on the pseudorotational wheel (Figure 1),[4] where *P* is the pseudorotational phase angle.

The standard model used to assess the conformation of a furanose ring in solution assumes an equilibrium mixture of two conformers, termed north (N) and south (S) on the basis of the hemisphere of the wheel in which they are located.[4] For a given ring, determining these conformers and their populations can be done through the measurement of all intracyclic ring $^3J_{H,H}$ values and subsequent analysis of these data with the program PSEUROT.[5] The identities of the conformers populated at equilibrium are influenced by both the number and orientation of the ring substituents, as well as stereoelectronic effects (e.g., the anomeric effect and gauche effects) involving the ring oxygen.[6] It is well-known that the conformational preferences of the furanose ring significantly influence the biological activity of molecules containing them. For example, in nucleic acids, the A-form and B-form double helix families are differentiated by the conformation of the furanose rings in these entities. These structural differences in turn modulate many critical biological recognition events involving DNA and RNA.[1]

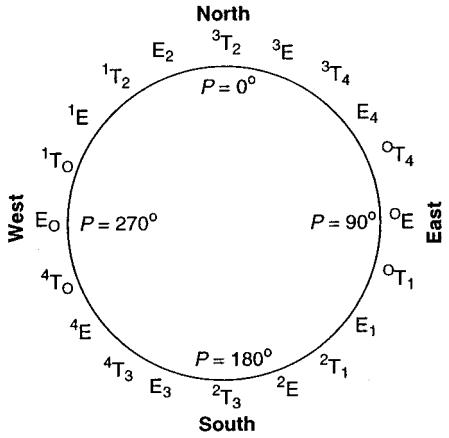

Figure 1. Pseudorotational wheel for a D-aldofuranose ring.

Over the past decade, there has been increasing interest in the synthesis of nucleic acid analogues in which the sugar residues are locked into a single conformer.[7] Research in this area has been motivated largely by the desire to identify antisense oligonucleotides that bind tightly to RNA, thus blocking protein translation.[8]

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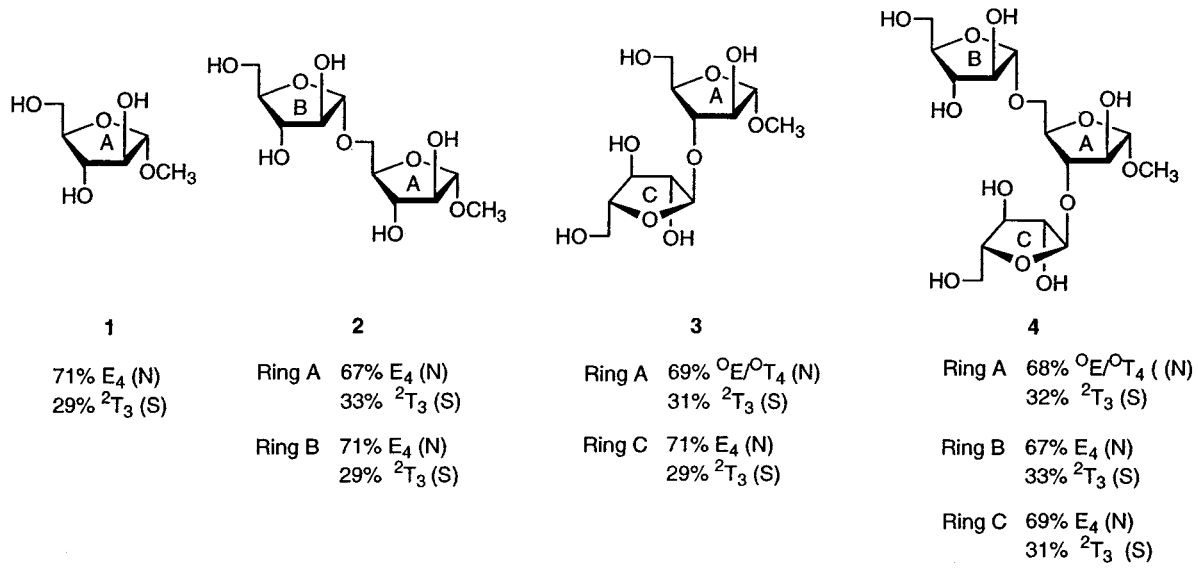

Figure 2. Conformers populated by oligosaccharide fragments of mycobacterial arabinogalactan and lipoarabinomannan.

The rationale for the preparation of oligonucleotides with conformationally restricted furanose residues is that these compounds will be preorganized to bind to complementary sequences of RNA and hence the entropic penalty associated with duplex formation will be diminished. Many classes of such analogues have now been synthesized, and some have significantly greater affinity for RNA than the native oligonucleotide parent structure.[7] A more recent motivation for work in this area has been the realization that conformationally locking or biasing a nucleotide often substantially influences its recognition by various processing enzymes.[9]

Restricting the conformation of a furanose ring is generally achieved by one of two methods. The first is through the attachment of covalent tethers that lock the ring into a single conformation.[7c,9c] The second is by replacement of the hydroxyl groups at C-2 or C-3 with other functionalities. When the substitution involves the replacement of the OH with a strongly electronegative group (e.g., fluorine), conformers in which these substituents are oriented pseudoaxially are favored due to an attractive gauche interaction with the ring oxygen.[6]

Recently, we have probed the conformation of the furanose rings in oligosaccharides containing arabinofuranose residues.[10] These investigations were carried out by applying methods developed for the conformational analysis of nucleosides to the oligosaccharides of interest. In this earlier study, we described the ring conformers populated by methyl α-D-arabinofuranoside (**1**) and oligosaccharides **2**−**4** (Figure 2). These glycans are fragments of two polysaccharides, arabinogalactan and lipoarabinomannan, which are present in the cell wall of *Mycobacterium tuberculosis* and other mycobacteria.[11] In other investigations, we[12] and others[13] have shown that small oligosaccharides, including **2**−**4**, are substrates for the arabinosyltransferases that are involved in the biosynthesis of mycobacterial arabinogalactan and lipoarabinomannan. Our conformational investigations are directed at understanding the structural motifs present in these oligosaccharides, as we anticipate that an appreciation of the conformation of these glycans will facilitate the development of potential inhibitors of mycobacterial arabinosyltransferases. Such compounds are of current interest as anti-mycobacterial agents.[14]

To probe the conformational equilibrium of each ring in **1**−**4**, we measured the $^3J_{H,H}$ values between the ring protons and carried out PSEUROT analyses. A summary of these results is discussed below and presented in Figure 2.[15] In aqueous solution, monosaccharide **1** exists as an equilibrium of an approximately 2:1 ratio of E_4 (N) and $^2T_3$ (S) conformers. For disaccharide **2**, the identities of the conformers and their populations for each ring are essentially the same as those of the monosaccharide. For disaccharide **3** and trisaccharide **4**, the nonreducing end monosaccharide residues (B and/or C) also adopt conformations similar to those of the monosaccharide. However, the conformational equilibrium of the reducing end ring (residue A) in **3** and **4** is altered relative to that of **1**; the identify of the northern conformer changes to one intermediate between $^OT_4$ and ^OE, while the southern conformer remains at $^2T_3$.

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(15) These values differ from those originally published by us in ref 10. The values provided in Figure 2 reflect the populations as calculated by PSEUROT using the most updated generalized Karplus equation (GKE) available. Our earlier studies employed an older GKE.

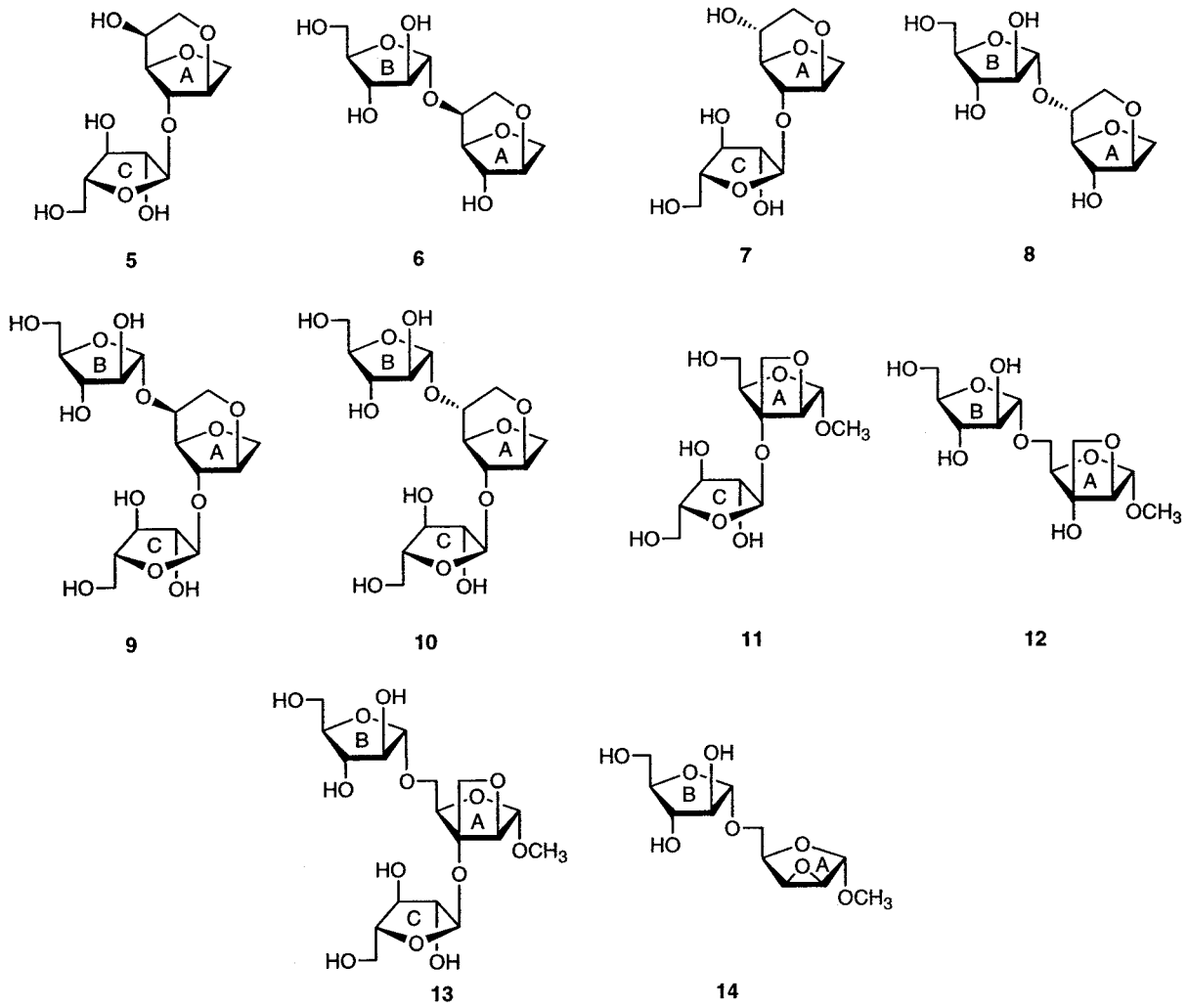

Figure 3. Synthetic targets **5**−**14**. The rings have been lettered to facilitate comparison with **2**−**4**.

With an understanding of the low-energy conformers available to each ring in **2**−**4**, we next became interested in synthesizing analogues of these glycans in which one ring was locked into a single conformer that approximated the N and S minimum-energy structures. On the basis of the previous successes with nucleic acids and nucleosides described above, it was our hope that this modification would provide substrates with improved affinity for the arabinosyltransferases by minimizing the entropic penalty necessary for binding.[16] We also were interested in understanding what effect, if any, biasing one of the rings had on the conformation of adjacent residues. Previous studies on oligonucleotides containing nucleoside residues with conformationally locked or biased furanose rings have shown that these modified residues do influence the conformation of unrestricted sugar residues of adjacent nucleosides in both single- and double-stranded systems.[17]

In this paper, we describe the synthesis of analogues of **2**−**4** in which the reducing end residue (residue A) has been replaced with a monosaccharide locked into a conformation that approximates either the N or S conformer present in the parent oligosaccharides. We have also carried out PSEUROT analyses to determine whether this modification of residue A influences the conformations of rings B and C relative to those of **2**−**4**. The targets we chose to synthesize are shown in Figure 3. In **5**−**10** we predicted that residue A would be locked in the $^{2}T_{3}$ (S) conformation, while in oligosaccharides **11**−**14** this ring is predicted to adopt an ^{O}E (N) geometry.

Results and Discussion

Computational Investigations of Locked Scaffolds. Before proceeding with the synthesis of the targets, we carried out a series of molecular mechanics and ab initio calculations to determine whether the conforma-

(16) The conformation of the ring bound by these arabinosyltransferases is unknown. Clearly, locking the ring into a conformation other than the one bound by the enzyme will likely prevent recognition of the substrate. Another important, but fundamentally different, issue is conformational flexibility about the glycosidic linkages. Previous efforts to enhance protein−carbohydrate interaction through the conformational restriction of glycosidic linkages in oligosaccharides have not resulted in significant increases in affinity: (a) Bundle, D. R.; Alibés, R.; Nilar, S.; Otter, A.; Warwas, M.; Zhang, P. *J. Am. Chem. Soc.* **1998**, *120*, 5317. (b) Navarre, N.; Amiot, N.; van Oijen, A.; Imberty, A.; Poveda, A.; Jimenez-Barbero J.; Cooper, A.; Nutley, M. A.; Boons, G. J. *Chem.—Eur. J.* **1999**, *5*, 2281.

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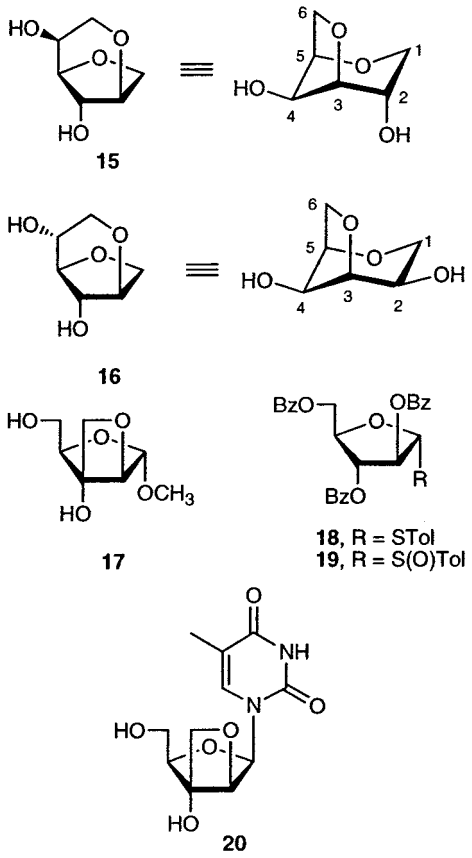
Chart 1



tionally locked monosaccharides do adopt the structures predicted above. To this end, a Monte Carlo search of the locked "scaffolds" **15**−**17** (Chart 1) was carried out, and the low-energy structures were then subjected to higher level calculations. As expected, the Monte Carlo searches identified only a few conformers for each molecule. All of the conformers within 4 kcal/mol of the global minima were then optimized at the HF/6-31G* level of theory, and then B3LYP/6-31+G** single-point energies were determined for each resulting conformer. The furan ring in **15** and **16** is locked in the E_3 ring conformation, which is very similar to the $^2T_3$ we predicted. The pyran ring in **15** and **16** is locked in the $^1C_4$ conformation (see Chart 1 for atom numbers). The furanose ring in the N-locked scaffold **17** was found to exist solely in the predicted ^OE ring conformation. The B3LYP/6-31+G**//HF/6-31G* global minima of **15**−**17** are shown in Figure 4. The other low-energy conformers of **15**−**17** found by the protocol described above differed from the global minima only in the orientation about O−H or exocyclic C−C bonds. The conformations of the rings were unchanged in comparison to those of the lowest energy structures.

In a previous study,[18] we explored the conformation of the 2,3-anhydrofuranoside moiety of disaccharide **14** by ab initio and density functional theory methods. As expected[19] the furanose ring in this anhydrosugar adopts the ^OE conformation.

Synthesis of Conformationally Restricted Scaffolds. We envisioned that oligosaccharides **5**−**13** could

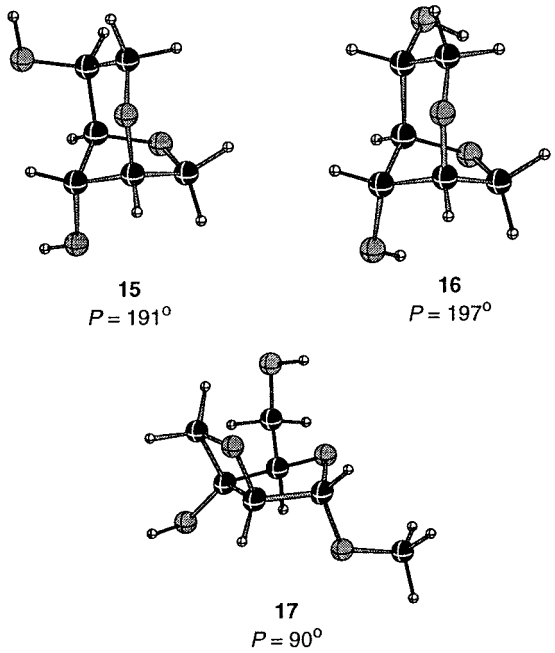
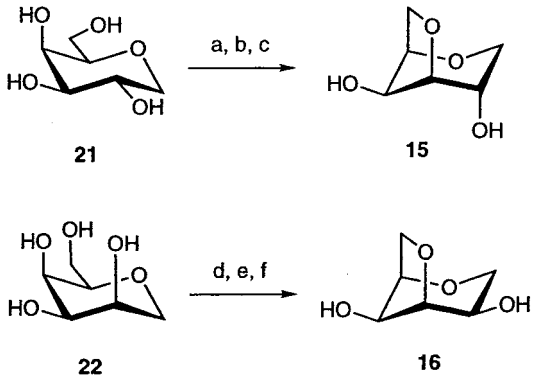


Figure 4. B3LYP/6-31+G**//HF/6-31G* global minima of **15**−**17**.

Scheme 1[a]



[a] Reagents and conditions: (a) PPh_3, I_2, pyridine, rt; (b) Ac_2O, pyridine, rt; (c) $NaOCH_3$, CH_3OH, rt, 63% (three steps); (d) PPh_3, I_2, pyridine, rt; (e) Ac_2O, pyridine, rt; (f) $NaOCH_3$, CH_3OH, rt, 83% (three steps).

be readily synthesized from building blocks **15**−**19** (Chart 1). Disaccharide **14** has previously been reported.[18]

Synthesis of S-Locked Monosaccharide Scaffolds 15 and 16. As shown in Chart 1, the two S-locked scaffolds **15** and **16** are 1,5:3,6-dianhydroalditol derivatives. The formation of 3,6-anhydrosugars from monosaccharides via a two-step process involving installation of a leaving group at C-6 followed by treatment with base is well-known.[20] We therefore postulated that it would be possible to synthesize **15** and **16** in one step from the corresponding 1,5-anhydroalditols, through the in situ generation of an oxyphosphonium leaving group at C-6. Indeed, the reaction of **21**[21] with triphenylphosphine and iodine in pyridine at room temperature proceeded as predicted (Scheme 1), yielding 1,5:3,6-dianhydro-D-galactitol (**15**). Due to the high polarity of **15**, the most efficient method of purification was to acetylate the

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(19) Marquez, V. E.; Siddiqui, M. A.; Ezzitouni, A.; Russ, P.; Wang, J.; Wagner, R. W.; Matteucci, M. D. *J. Med. Chem.* **1996**, *39*, 3739
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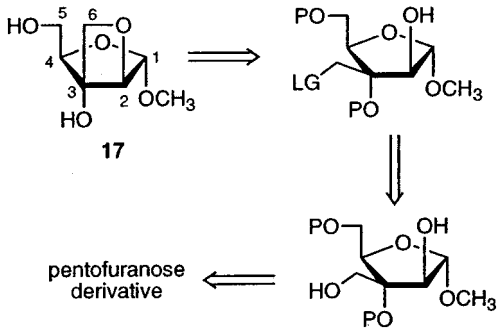


Figure 5. Retrosynthetic analysis of **17**.

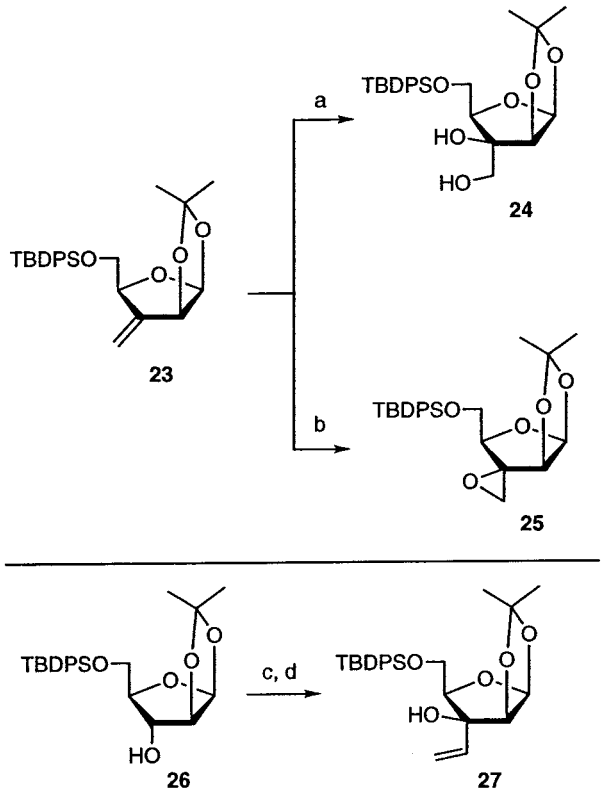
hydroxyl groups, purify the resulting diacetate by chromatography, and then remove the acetate esters with sodium methoxide. This three-step process afforded **15** in 63% yield from **21**.

We initially had hoped that it would be possible to access **16** from **15** by inversion of the axially oriented alcohol at C-2 (see Chart 1 for atom numbers). Unfortunately, our attempts to invert this stereocenter by several variations of the Mitsunobu reaction failed. In all cases, the rate of reaction was very slow and the regioselectivity poor. Presumably, this lack of reactivity is due to the very rigid nature of the molecule, which hinders the formation of the transition state in the substitution reaction. We therefore synthesized **16** by treatment of 1,5-anhydro-D-talitol (**22**)[22] with triphenylphosphine and iodine as was done for the preparation of **15**. Dianhydroalditol **16** was obtained in 83% yield from **22**. For both **15** and **16**, ^{1}H NMR spectral data were consistent with these structures adopting the conformations predicted by our computational investigations.

Synthesis of an N-Locked Monosaccharide Residue. Our synthesis of **17** was considerably more involved than the preparation of **15** and **16**. The initial route we designed was modeled after a previous synthesis of nucleoside **20** (Chart 1).[23] However, our desire to have an α-methyl glycoside instead of a β-nucleoside necessitated modification of the published route. The key aspects of the synthesis are the addition of a hydroxymethyl group to the top face of the ring at C-3, conversion of the hydroxyl group of this moiety into a leaving group, and then displacement by O-2 (Figure 5). An alternate strategy, involving displacement at C-2, was not pursued because we anticipated elimination would be a major side reaction in the displacement.

The primary challenge was the installation of the hydroxymethyl group at C-3 with the correct stereochemistry. Our first attempt (Scheme 2) toward **17** started with alkene **23**.[24] We anticipated that dihydroxylation of this olefin would proceed from the bottom face of the ring due to the steric demands of the isopropylidene protecting group. However, although the reaction of **23** with OsO_4 and *N*-methylmorpholine oxide (NMO) did afford a single diol product in 85% yield, the structure was shown to be **24**, indicating that the dihydroxylation had occurred cis

Scheme 2[a]



[a] Reagents and conditions: (a) OsO_4, NMO, acetone/water (3:1), 0 °C → rt, 85%; (b) *m*-CPBA, $NaHCO_3$, CH_2Cl_2, rt, 33%; (c) PCC, NaOAc, CH_2Cl_2, rt; (d) CH_2=CHMgBr, THF, 0 °C, 45% (from **26**).

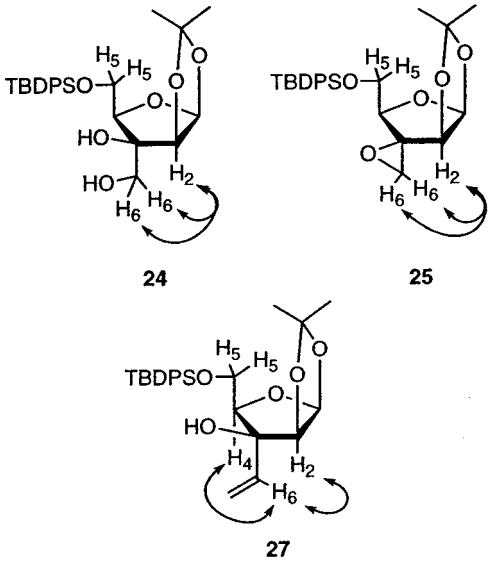


Figure 6. NOEs observed in **24**, **25**, and **27**.

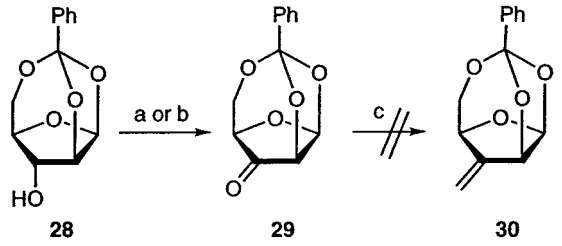
to the isopropylidene moiety. Determination of the structure of **24** was done through the measurement of the NOEs involving the newly formed hydroxymethyl group hydrogens. The presence (Figure 6) of an NOE between the H_6 atoms and H_2, in addition to the absence of an NOE between either H_6 and the H_5 atoms confirmed the stereochemistry at C-3 in **24**. Dihydroxylations with AD mix α and AD mix β were attempted, but these reactions also gave **24** as the only product. We also explored the epoxidation of **23** with *m*-chloroperoxybenzoic acid as a

(22) Estevez, J. C.; Fairbanks, A. J.; Fleet, G. W. J. *Tetrahedron* **1998**, *54*, 13591.

(23) Christensen, N. K.; Petersen, M.; Nielsen, P.; Jacobsen, J. P.; Olsen, C. E.; Wengel, J. *J. Am. Chem. Soc.* **1998**, *120*, 5458.

(24) Prepared from **26** by oxidation and subsequent Wittig reaction with CH_2=PPh_3. The NMR spectrum of the product was identical to that previously described for the L-enantiomer: Doboszewski, B.; Herdewijn, P. *Tetrahedron* **1996**, *52*, 1651.

Scheme 3[a]



[a] Reagents and conditions: (a) PCC, CH_2Cl_2, NaOAc, rt, or TPAP, NMO, rt; (b) CH_3PPh_3Br, *n*-BuLi, THF, −78 °C → rt.

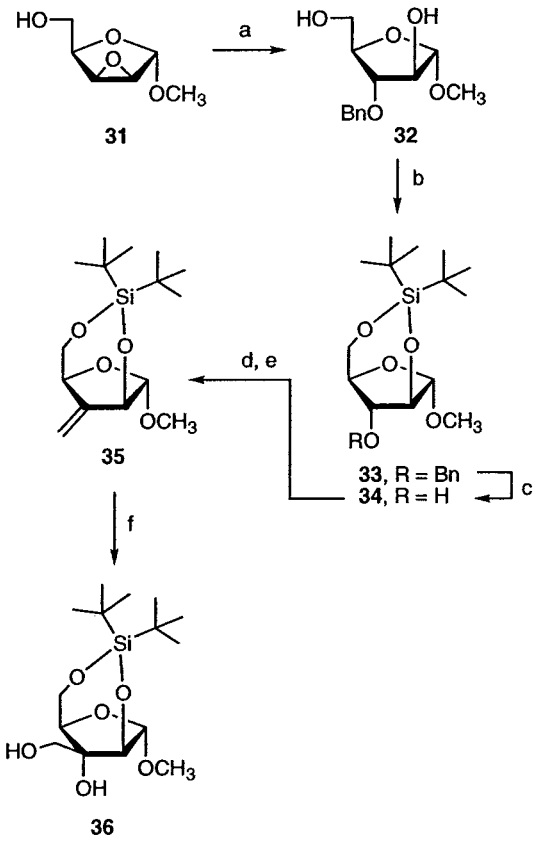
way to install the C-3 stereocenter. However, this reaction proceeded in low yield and afforded only epoxide **25**, with the incorrect C-3 stereochemistry (see Figure 6 for the NOEs).

On the basis of these results, we predicted that oxidation of alcohol **26**[25] to the corresponding ketone followed by addition of a vinyl group would provide a product with the desired stereochemistry at C-3. Unfortunately, reaction of vinylmagnesium bromide with the ketone obtained upon oxidation of **26** produced only **27** in modest yield (see Figure 6 for the observed NOEs). Our inability to set the C-3 stereocenter with the correct stereochemistry starting from **23** forced us to explore other routes.

We next investigated the use of ortho ester **28** (Scheme 3), which can be conveniently prepared in four steps from D-arabinose.[26] We postulated that conversion of **28** into alkene **30** would provide a substrate that would necessarily undergo dihydroxylation from the bottom face of the ring. Although oxidation of **28** with either pyridinium chlorochromate or TPAP/NMO was successful, the product was isolated as the hydrate, and all attempts to dehydrate this molecule to ketone **29** failed. We postulate that the reluctance of this hydrate to lose water to provide the corresponding ketone is due to the rigidity of the molecule, which inhibits the necessary flattening of the furanose ring in the ketone. As would be expected, the subsequent conversion of this hydrate to **30**, upon reaction with methylenetriphenylphosphorane, produced only trace amounts of the desired product. This route was therefore abandoned.

Our third approach to **17** involved the use of the silyl acetal **35** (Scheme 4) as a key intermediate. The preparation of **35** proceeded smoothly from epoxide **31**.[27] Opening of the oxirane ring was achieved in 83% yield by heating **31** with sodium in benzyl alcohol at 120 °C. The diol in **32** was then protected as a di-*tert*-butylsilyl acetal, providing **33** in 74% yield. Subsequent hydrogenolysis of the benzyl ether (H_2, $Pd(OH)_2$) proceeded in 94% yield, affording **34**. Oxidation of alcohol **34** using buffered pyridinium chlorochromate provided the corresponding ketone, which was converted immediately to **35** upon treatment with the Petasis reagent[28] at 70 °C. The product was produced in 74% overall yield from **34**. Our initial attempts to olefinate this ketone under Wittig

Scheme 4[a]



[a] Reagents and conditions: (a) NaOBn, BnOH, 120 °C, 83%; (b) $(t\text{-Bu})_2SiCl_2$, pyridine, CH_2Cl_2, −78 °C → 0 °C, 74%; (c) H_2, $Pd(OH)_2$, CH_3OH, rt, 94%; (d) PCC, NaOAc, CH_2Cl_2, rt; (e) $Cp_2Ti(CH_3)_2$), THF, 70 °C, 71% (from **34**); OsO_4, NMO, acetone/water (3:1), 0 °C → rt.

conditions were unsuccessful due to the instability of the di-*tert*-butylsilyl group to the basic conditions of the reaction.

With an efficient route to **35** in place, the key dihydroxylation reaction could be attempted. Upon reaction of olefin **35** with osmium tetroxide and NMO, only trace amounts of the desired diol **36** were produced. Although the product with the correct stereochemistry was formed, the rates of conversion were exceedingly slow (3−10 days), and only low yields (5−15%) of the diol could be isolated. The same results were obtained when the reaction was carried out using potassium permangenate or a stoichiometric amount of osmium tetroxide. Fortunately, the ruthenium trichloride and sodium periodate oxidation system reported by Hegedus and co-workers[29] could be used to efficiently convert olefin **35** into **36** in reasonable yield. Purification of the diol was complicated by its tendency to sublime, and therefore, following workup of the dihyroxylation reaction, the crude product was immediately treated with toluenesulfonyl chloride and pyridine, yielding **37** in 65% overall yield from **35** (Scheme 5).

Having successfully synthesized a molecule with the correct stereochemistry at C-3 and a leaving group at C-6, all that remained was the formation of the oxetane ring. This task required the preparation of a substrate in which both OH-3 and OH-5 were protected, and we

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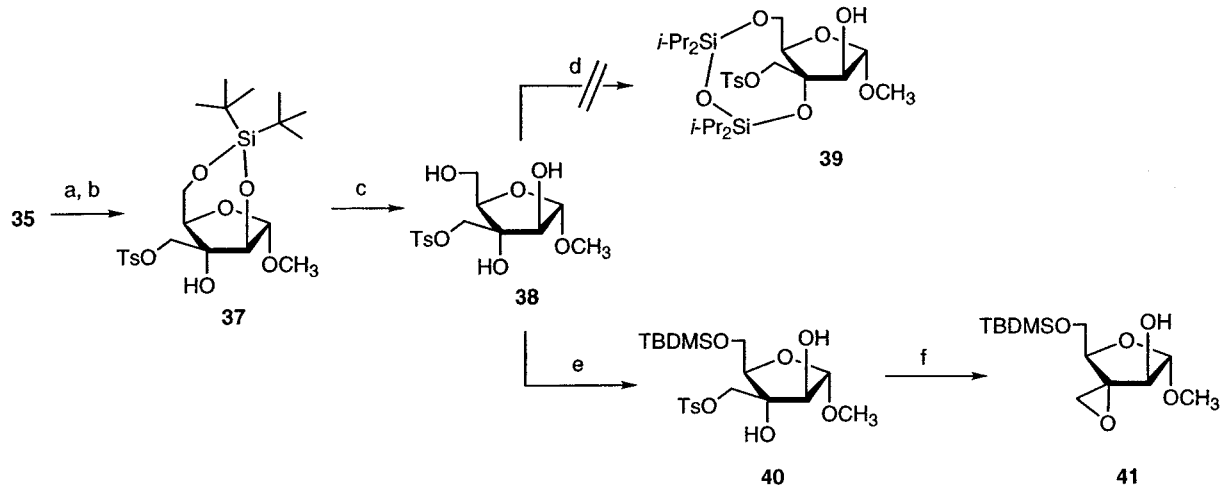
(28) Petasis, N. A.; Bzowej, E. I. *J. Am. Chem. Soc.* **1990**, *112*, 6392.

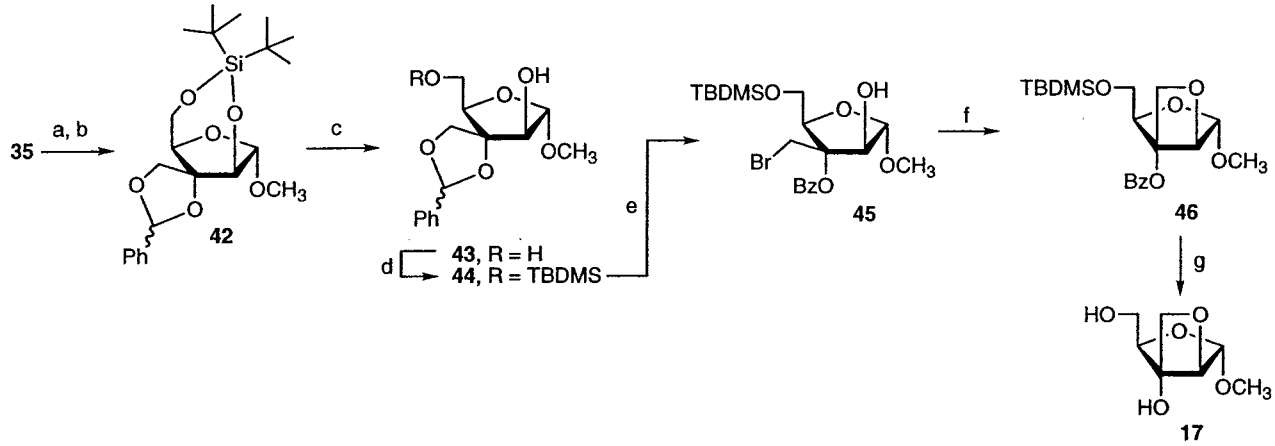
(29) Hegedus, L. S.; Geisler, L. *J. Org. Chem.* **2000**, *65*, 4200.

Scheme 5[a]



[a] Reagents and conditions: (a) $RuCl_3 \cdot H_2O$, $NaIO_4$, EtOAc, CH_3CN, H_2O, 0 °C; (b) TsCl, DABCO, CH_2Cl_2, 0 °C, 65% (from **35**); (c) HF, pyridine, THF, rt, 85%; (d) $(Br(i\text{-}Pr)_2Si)_2O$, pyridine, 0 °C → rt; (e) TBDMSCl, DMF, imidazole, 0 °C, 86%; (f) DBU, THF, 0 °C, 60%.

Scheme 6[a]



[a] Reagents and conditions: (a) $RuCl_3 \cdot H_2O$, $NaIO_4$, EtOAc, CH_3CN, H_2O, 0 °C; (b) $PhCH(OCH_3)_2$, *p*-TsOH, CH_2Cl_2, rt → 40 °C, 60% (from **35**); (c) HF, pyridine, THF, rt, 86%; (d) TBDMSCl, DMF, imidazole, 0 °C, 87%; (e) NBS, $BaCO_3$, CCl_4, reflux; (f) K_2CO_3, DMF, rt, 47% (from **44**); (g) *n*-Bu_4NF, THF, 0 °C, then $NaOCH_3$, CH_3OH, rt, 91%.

initially explored protecting the tertiary hydroxyl group in **37**. However, attempts to protect OH-3 with either an acetate or a benzoate group failed, undoubtedly due to the hindered nature of this alcohol. We next explored the possibility of protecting both OH-3 and OH-5 as a siloxane. To this end, the di-*tert*-butylsilyl acetal was cleaved in 85% yield with HF in pyridine, and the resulting unstable triol **38** was reacted with 1,3-dibromo-1,1,3,3-tetraisopropyldisiloxane[30] in pyridine. Unfortunately, none of the desired product **39** could be isolated. Faced with this failure, and given the difficulty in protecting the 3-hydroxyl group in **37**, we explored an alternate approach. We postulated that if OH-5 in **38** were protected, a large nonnucleophilic base might differentiate between the OH-2 and OH-3 in favor of the former, thus allowing the preparation of the desired oxetane. To investigate this possibility, the primary hydroxyl group in **38** was selectively protected, providing **40** in 86% yield. Several reaction conditions were screened to effect oxetane formation (DBU in THF or DMF, sodium *tert*-butoxide in THF, NaH in DMF), but all provided exclusively epoxide **41**. These results forced us to again reevaluate the route to **17**.

The final, and successful, route to **17** is shown in Scheme 6. Alkene **35** was treated with ruthenium trichloride and sodium periodate, and the resulting diol was then protected as a benzylidene acetal. Acetal **42** was produced in 60% overall yield from **35** as a 1:1 mixture of diastereomers. Also recovered, in 12% yield, was olefin **34** due to incomplete reaction during the dihydroxylation step. The silyl acetal in **42** was then cleaved by HF in pyridine, affording diol **43** in 86% yield. Selective protection of the primary hydroxyl group in **43** was achieved upon reaction with *tert*-butylchlorodimethylsilane and imidazole, providing **44** (87% yield). The benzylidene acetal was then opened via reaction with *N*-bromosuccinimide and barium carbonate in refluxing carbon tetrachloride,[31] which produced bromide **45**. In this manner, a protecting group on O-3 and a leaving group at C-6 were installed in a single step. This task had eluded us in our previous approaches. Upon its formation,

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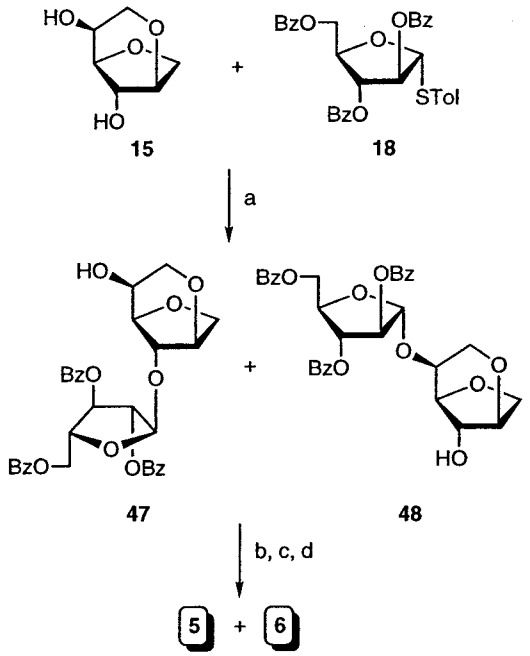
(31) Hanessian, S. *Carbohydr. Res.* **1966**, *1*, 86.

Scheme 7[a]



[a] Reagents and conditions: (a) *N*-iodosuccinimide, silver triflate, CH_2Cl_2, 0 °C; (b) $NaOCH_3$, CH_3OH, rt; (c) Ac_2O, pyridine, rt; (d) $NaOCH_3$, CH_3OH, rt, 20% **5** and 20% **6** (four steps).

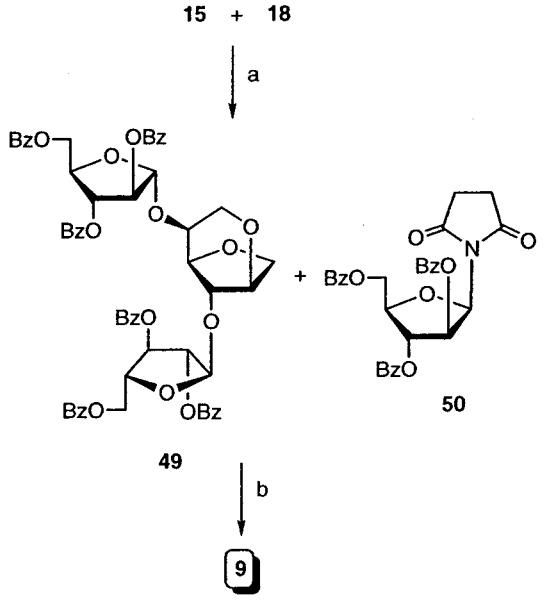
compound **45** was eluted through a short plug of silica gel and immediately treated with base. The use of NaH and DBU proved unsuccessful as rapid debenzoylation occurred, leading to epoxide formation. However, potassium carbonate in DMF was found to efficiently promote formation of the desired 2,3-oxetane. Under these conditions, no epoxide byproducts were observed during the closing of the four-membered ring, and compound **46** could be isolated in 47% overall yield from **44**. Removal of the protecting groups by treatment of **46** with *n*-Bu_4NF and then sodium methoxide provided **17** in 91% yield.

Synthesis of Oligosaccharides. Once **15**−**17** had been synthesized, the assembly of the oligosaccharides was carried out with minimal difficulty. The preparation of **5** and **6** is illustrated in Scheme 7. Glycosylation of **15** with 1 equiv of **18**[18] using *N*-iodosuccinimide and silver triflate promotion yielded a mixture of **47** and **48**, which were not separable by chromatography. The mixture of disaccharides was then debenzoylated and then acetylated to provide two separable products. After purification, each was deprotected, affording **5** and **6** in 20% yield each from **15**. Although the yields are rather modest, we viewed this approach as better than a strategy involving monoprotection of diol **15** followed by glycosylation of the resulting alcohols.

The structures of the glycosylation products were differentiated through the use one- and two-dimensional $^1H/^1H$ and $^1H/^{13}C$ correlation NMR spectroscopy. In the ^{13}C NMR spectrum of **5**, the signal arising from C-4 was shifted downfield relative to that of **15** (76.4 ppm in **5** vs 70.7 ppm in **15**) as would be expected[32] (see Chart 1 for atom numbers). A similar trend was observed for the C-2 resonance in the ^{13}C NMR spectrum of **6** (76.6 ppm in **6** vs 69.5 ppm in **15**). Further support for the structures of these disaccharides could be obtained from the ^1H NMR

(32) Duus, J. Ø.; Gottfredsen, C. H.; Bock, K. *Chem. Rev.* **2000**, *100*, 4589.

Scheme 8[a]



[a] Reagents and conditions: (a) *N*-iodosuccinimide, silver triflate, CH_2Cl_2, 0 °C; (b) $NaOCH_3$, CH_3OH, rt, 68% (two steps).

spectra of products arising from exhaustive acetylation of **5** and **6**. In the case of **5**, peracetylation clearly resulted in a downfield shift of H-2; a similar shift of H-4 was seen in the peracetate derivative of **6**.

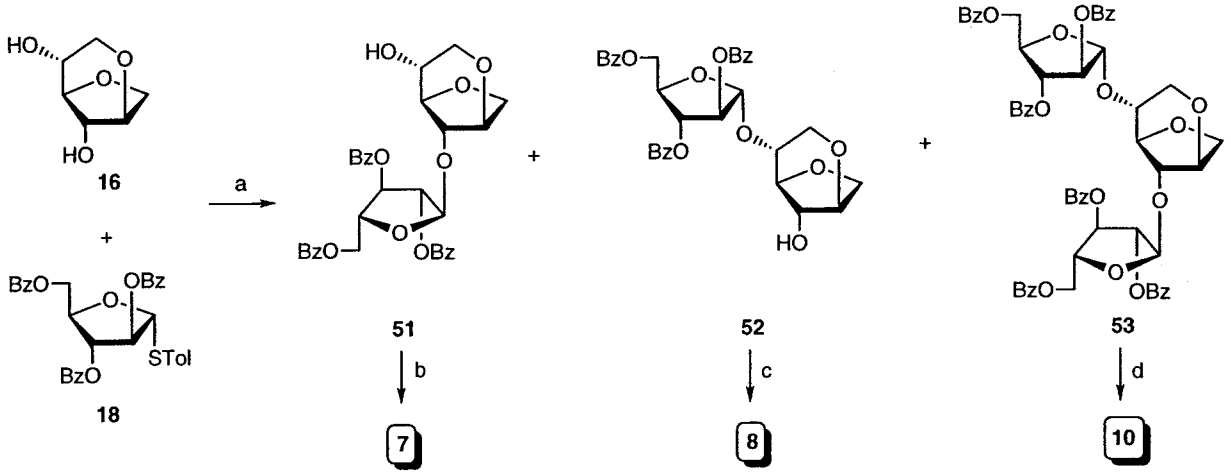
As outlined in Scheme 8, the preparation of trisaccharide **9** was also straightforward. Reaction of **15** with 2 equiv of **18** yielded trisaccharide **49**. Purification of the product was complicated by the presence of the glycosylsuccinimide adduct **50**,[33] which had chromatographic properties essentially identical to those of **49**. Therefore, the crude product was treated with sodium methoxide in methanol to provide **9**, which could easily be separated from the deacylated derivative of **50**. Trisaccharide **9** was isolated in 68% overall yield from **15**.

The conversion of **16** into **7**, **8**, and **10** (Scheme 9) was achieved in a manner similar to that of the synthesis of **5**, **6**, and **9**. Glycosylation of **16** with a limiting amount of **18** provided a mixture of disaccharides **51** and **52** in addition to trisaccharide **53**. These oligosaccharides were separated by chromatography and immediately deprotected. After removal of the benzoyl groups, **7**, **8**, and **10** were obtained in 6%, 34%, and 17% yields, respectively. The structures of **7** and **8** were differentiated as described for **5** and **6** (see Figure S1 in the Supporting Information).

In the synthesis of oligosaccharide analogues from **17**, we anticipated that glycosylation of the tertiary hydroxyl group would pose a particular challenge. We therefore chose to use sulfoxide **19**[34] (Chart 1) as the glycosyl donor. Glycosyl sulfoxides are highly reactive glycosylating agents, which have often been used to provide good yields of glycosides from hindered alcohols.[35] As illustrated in Scheme 10, reaction of **17** with 2.5 equiv of **19** and triflic anhydride in the presence of di-*tert*-butylmethylpyridine provided both disaccharide **54** and trisaccharide **55**. Following their separation by chromatography, each

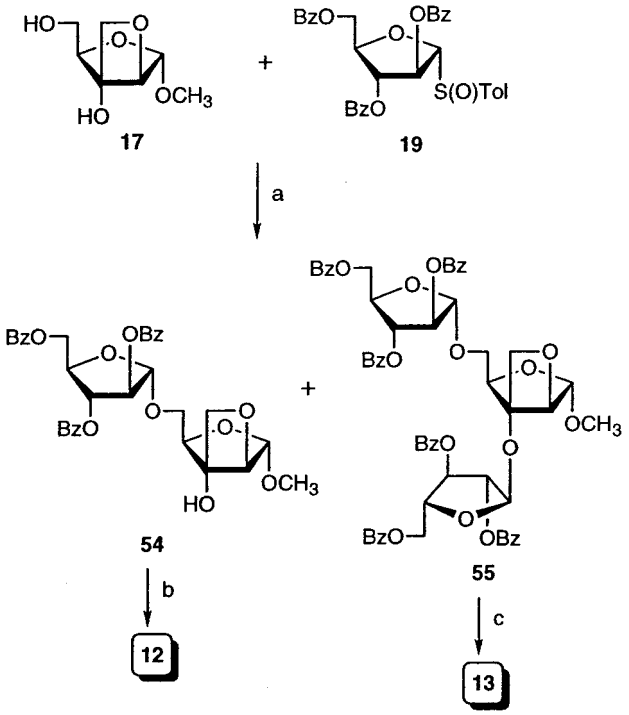
(33) McCarren, P. R.; Lowary, T. L. Unpublished results.
(34) Prepared by reaction of **18** with *m*-CPBA; see the Experimental Section for details.
(35) Kahne, D.; Walker, S.; Cheng, Y.; Van Engen, D. *J. Am. Chem. Soc.* **1989**, *111*, 6881.

Scheme 9[a]



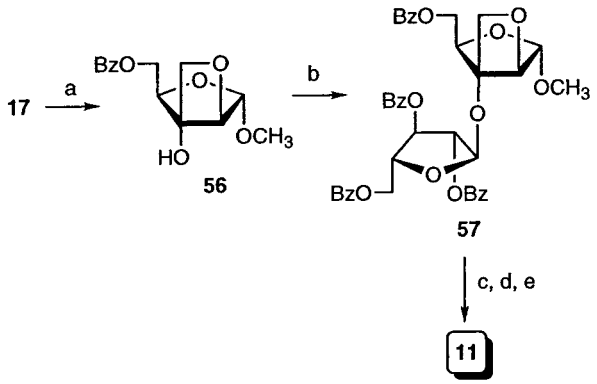
[a] Reagents and conditions: (a) *N*-iodosuccinimide, silver triflate, CH_2Cl_2, 0 °C; (b) $NaOCH_3$, CH_3OH, rt, 6% (from **16**); (c) $NaOCH_3$, CH_3OH, rt, 34% (from **16**); (d) $NaOCH_3$, CH_3OH, rt, 17% (from **16**).

Scheme 10[a]



[a] Reagents and conditions: (a) **19**, Tf_2O, DTBMP, CH_2Cl_2, −78 °C → rt; (b) $NaOCH_3$, CH_3OH, rt, 37% (from **17**); (c) $NaOCH_3$, CH_3OH, rt, 29% (from **17**).

Scheme 11[a]



[a] Reagents and conditions: (a) BzCl, DMAP, pyridine, 0 °C, 87%; (b) **19**, Tf_2O, DTBMP, CH_2Cl_2, −78 °C → rt, (c) $NaOCH_3$, CH_3OH, rt; (d) Ac_2O, pyridine, DMAP, rt; (e) $NaOCH_3$, CH_3OH, rt, 9% (from **56**).

oligosaccharide was debenzoylated to provide **12** (37%) and **13** (29%). The structure of **12** was determined by ^{13}C NMR spectroscopy as described above for **5** and **6**. The hydroxymethyl group carbon in **17** resonates at 59.9 ppm, whereas in the disaccharide this signal appears at 65.6 ppm.

The remaining disaccharide target **11** was prepared as outlined in Scheme 11. Protection of the primary hydroxyl group was achieved by reaction of **17** with benzoyl chloride in pyridine to provide **56** in 87% yield. As expected, glycosylation of this alcohol was difficult; reaction of **56** with an excess of **19** proceeded slowly and produced only small amounts of **57**. Following deprotection, the 3-linked disaccharide **11** was obtained in 9% yield from **17**. Although the yield of the product is very low, we were nevertheless able to synthesize sufficient quantities for the required NMR studies.

NMR Investigations. With oligosaccharides **5**−**14** in hand, we used ^1H NMR spectroscopy in combination with PSEUROT analysis to investigate the conformers populated by the rings in these molecules with no conformational constraints (residues B and C). Measurement of the vicinal $^1H-^1H$ coupling constants required for these calculations was possible in all cases except **11**. In this disaccharide analogue, spectral overlap prohibited the measurement of the appropriate $^3J_{H,H}$. The results of the PSEUROT analyses of rings B and C in **5**−**14** are provided in Table 1. For purposes of comparison, the conformers in **2**−**4** are also included. These analyses required that the α-arabinofuranosyl residues in **9**, **10**, and **13** be differentiated. For **9** and **13**, this could be done through the use of ^{13}C and ^1H NMR chemical shifts (see Figure S1 in the Supporting Information). This was not possible for **10**, and therefore the conformer populations presented in Table 1 for residues B and C in this molecule could be reversed.

From these data, the major conclusion that can be drawn is that locking ring A in **2**−**4** into either the E_3 or ^OE conformation has essentially no effect upon the

Table 1. PSEUROT Analysis of Residues B and C in 2−14[a]

	2	3	4		5	6	7	8	9		10		11	12	13		14
ring[b]	B	C	B	C	C	B	C	B	B	C	B[g]	C[g]	C[h]	B	B	C	B
P_N[c] (deg)	68	66	65	65	62	65	63	66	65	65	66	64	ND[i]	66	61	62	68
N conformer[d]	E_4	E_4	E_4	E_4	E_4	E_4	E_4	E_4	E_4	E_4	E_4	E_4	ND	E_4	E_4	E_4	E_4
$\boldsymbol{X}_N$[e] (%)	71	71	67	69	72	74	72	73	76	67	73	71	ND	70	73	69	69
P_S[c] (deg)	185	185	185	185	184	185	184	185	185	185	185	184	ND	185	184	184	185
S conformer[d]	$^2T_3$	$^2T_3$	$^2T_3$	$^2T_3$	$^2T_3$	$^2T_3$	$^2T_3$	$^2T_3$	$^2T_3$	$^2T_3$	$^2T_3$	$^2T_3$	ND	$^2T_3$	$^2T_3$	$^2T_3$	$^2T_3$
X_S[f] (%)	29	29	33	31	28	26	28	27	24	33	27	29	ND	30	27	31	31
RMS (Hz)	0.21	0.12	0.13	0.10	0.16	0.14	0.07	0.04	0.12	0.34	0.04	0.13	ND	0.14	0.08	0.35	0.11

[a] Calculated using a constant $t_m = 39°$. [b] See Figure 3 for the assignment of ring letters. [c] P = pseudorotational phase angle and is defined in ref 4. [d] See Figure 1 for conformer definitions. [e] Population of the N conformer. [f] Population of the S conformer. [g] Results could be reversed. [h] Analysis could not be due to spectral overlap that prohibited the measurement of coupling constants. [i] Not determined.

conformers populated by rings B and C. Similar to those in the parent structures, these residues in **5**−**14** adopt approximately 1:1 ratios of $^3T_4/E_4$ (N) and E_1 (S) conformers. The results presented in Table 1 are in contrast to the previous investigations on oligonucleotides. In those studies[17] it was demonstrated that a nucleoside containing a conformationally locked or biased furanose ring does influence the conformations of adjacent rings in the oligonucleotide. Our results suggest that the conformational effects seen in those systems depend on the presence of the nucleotide base. However, it is also possible that in larger oligosaccharides, possessing more than one conformationally restricted residue, the transmission of conformational information may be more significant. In particular, one could imagine that such effects might be larger in cyclic arabinofuranosyl oligosaccharides (e.g., cyclodextrin-like species) that contain conformationally locked residues.

Conclusions

In conclusion, described here is the synthesis of a panel of arabinofuranosyl oligosaccharide analogues (**5**−**13**) in which one ring is locked into either the E_3 or ^OE conformation. Subsequent analysis of these glycans, as well as disaccharide **14**, by ^{1}H NMR spectroscopy has demonstrated that in these oligosaccharides the locked residue does not exert any detectable influence upon the conformers populated by adjacent conformationally unrestricted furanose rings. We are currently testing **5**−**14** as substrates for mycobacterial arabinosyltransferases.

Experimental Section

General Methods. Solvents were distilled from the appropriate drying agents before use. Unless stated otherwise, all reactions were carried out under a positive pressure of argon and were monitored by TLC on silica gel 60 F_{254} (0.25 mm). Spots were detected under UV light, by charring with 10% H_2SO_4 in ethanol, or by charring with anisaldehyde in ethanol. Solvents were evaporated under reduced pressure and below 40 °C (bath). Organic solutions of crude products were dried over anhydrous Na_2SO_4. Column chromatography was performed on silica gel 60 (40−60 mM). The ratio between silica gel and crude product ranged from 100:1 to 50:1 (w/w). Optical rotations were measured at 21 ± 2 °C. ^{1}H NMR spectra were recorded at 400, 500, or 800 MHz, and chemical shifts are referenced to either TMS (δ 0.0, $CDCl_3$) or external dioxane (δ 3.75, D_2O). ^{13}C NMR spectra were recorded at 100 or 125 MHz, and ^{13}C chemical shifts are referenced to $CDCl_3$ (δ 77.00, $CDCl_3$) or external dioxane (δ 68.11, D_2O). Elemental analyses were performed by Atlantic Microlab Inc., Norcross, GA. Electrospray mass spectra were recorded on samples suspended in THF or CH_3OH.

1,5:3,6-Dianhydro-D-galactitol (15). 1,5-Anhydro-D-galactitol (**21**;[21] 444 mg, 2.71 mmol) was dissolved in pyridine (15 mL). Iodine (1.38 g, 5.4 mmol) and triphenylphosphine (1.42 g, 5.4 mmol) were added, and the reaction mixture was stirred for 3 h before CH_3OH was added and the solvents were evaporated. Chromatography (CH_2Cl_2/CH_3OH, 20:1) yielded the diol contaminated with iodine. This oil was dissolved in pyridine (10 mL) and acetic anhydride (10 mL), and the solution was stirred for 12 h. The reaction mixture was then cooled to 0 °C, CH_3OH was added, and then the reaction mixture was diluted with CH_2Cl_2. The resulting solution was washed with 0.1 M HCl and brine and then dried. Evaporation of the solvent and chromatography (hexanes/EtOAc, 3:1) yielded the pure diacetylated product. This solid was dissolved in CH_3OH (5 mL), 1 M sodium methoxide (5 drops) was added, and the reaction mixture was stirred for 12 h. The solution was then neutralized with Amberlite IR 120 (H+) resin and filtered. Evaporation of the solvent gave **15** as a white solid (248 mg, 63%): R_f 0.23 (CH_2Cl_2/CH_3OH, 6:1); $[\alpha]_D$ +43.2 (*c* 1.3, CH_3OH); ^{1}H NMR (800 MHz, D_2O, δ) 4.36 (d, 1 H, J = 1.9 Hz), 4.32 (dd, 1 H, J = 1.9, 1.9 Hz), 4.25 (d, 1 H, J = 5.5 Hz), 4.15 (d, 1 H, J = 10.8 Hz), 3.96 (dd, 1 H, J = 3.2, 10.8 Hz), 3.93 (dd, 1 H, J = 2.8, 5.5 Hz), 3.79 (dd, 1 H, J = 2.9, 13.3 Hz), 3.51 (d, 1 H, J = 13.3 Hz); ^{13}C NMR (100.6 MHz, D_2O, δ) 80.8, 78.6, 70.6, 69.4, 68.1, 65.2; HRMS (EI) *m/z* calcd for $C_6H_{10}O_4Na^+$ 169.0471, found 169.0478.

1,5:3,6-Dianhydro-D-talitol (16). 1,5-Anhydro-D-talitol (**22**;[22] 99 mg, 0.60 mmol) was dissolved in pyridine (2 mL). To this solution were added iodine (316 mg, 1.21 mmol) and triphenylphosphine (304 mg, 1.21 mmol). After 4 h, CH_3OH was added and the solution concentrated. Chromatography (CH_2Cl_2/CH_3OH, 20:1) yielded the desired diol contaminated with iodine. The crude product was therefore dissolved in pyridine (5 mL) and acetic anhydride (5 mL), and the solution was stirred for 12 h, at which point it was cooled to 0 °C and CH_3OH was added. The reaction mixture was diluted with CH_2Cl_2 and washed with 0.1 M HCl and brine and the organic layer dried. Evaporation of the solvent and chromatography of the resulting residue (hexanes/EtOAc, 3:1) yielded the pure, fully acetylated product. This solid was dissolved in CH_3OH (5 mL), 1 M sodium methoxide (5 drops) was added, and the reaction mixture was stirred for 12 h. The solution was neutralized with Amberlite IR 120 (H+) resin and filtered. Evaporation of the solvent gave **16** as a white solid (73 mg, 83%): R_f 0.28 (CH_2Cl_2/CH_3OH, 6:1); $[\alpha]_D$ +51.9 (*c* 0.7, CH_3OH); ^{1}H NMR (800 MHz, D_2O, δ) 4.27 (dd, 1 H, J = 2.4, 2.4 Hz), 4.17 (s, 1 H), 3.99 (d, 1 H, J = 10.8 Hz), 3.95 (dd, 1 H, J = 3.0, 10.8 Hz), 3.87 (d, 1 H, J = 1.8 Hz), 3.80 (dd, 1 H, J = 6.7, 11.1 Hz), 3.76 (dd, 1 H, J = 1.2, 6.7 Hz), 3.23 (dd, 1 H, J = 9.3, 11.0 Hz); ^{13}C NMR (150.9 MHz, D_2O, δ) 83.7, 77.4, 73.0, 68.7, 67.3, 63.3; HRMS (EI) *m/z* calcd for $C_{12}H_{20}O_8Na^+$ (dimer) 315.1050, found 315.1044.

5-*O*-*tert*-Butyldiphenylsilyl-3-*C*-hydroxymethyl-1,2-*O*-isopropylidene-*β*-D-lyxofuranoside (24). Olefin **23** (33.0 mg, 0.078 mmol) and 4-methylmorpholine *N*-oxide (15.7 mg, 0.117 mmol) were dissolved in acetone and water (3:1) and the solution cooled to 0 °C. To this solution was added OsO_4 (0.2 mg, 0.001 mmol), and the reaction mixture was stirred for 12 h at 0 °C. The solution was then stirred for an additional 1 d at room temperature before a saturated aqueous solution of sodium sulfite and CH_2Cl_2 were added. The organic layer

was then separated, washed with water and brine, and dried. Chromatography (hexanes/EtOAc, 2:1) yielded diol **24** (30 mg, 85%): R_f 0.42 (hexanes/EtOAc, 1:1); $[\alpha]_D$ +10.4 (*c* 1.5, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, δ) 7.727.67 (m, 4 H), 7.49−7.31 (m, 6 H), 5.92 (d, 1 H, J = 3.8 Hz), 4.44 (d, 1 H, J = 3.8 Hz), 4.29−4.24 (m, 2 H), 4.06 (dd, 1 H, J = 10.5, 10.5 Hz), 3.91 (dd, 1 H, J = 9.6, 12.2 Hz), 3.74 (dd, 1 H, J = 3.9, 10.5 Hz), 3.22 (s, 1 H), 2.92 (dd, 1 H, J = 4.5, 9.6 Hz), 1.26 (s, 3 H), 1.23 (s, 3 H), 1.13 (s, 9 H); ^{13}C NMR (125.8 MHz, $CDCl_3$, δ) 135.5, 135.4, 131.9, 130.1, 128.0, 112.5, 106.0, 88.8, 85.4, 82.4, 77.3, 77.0, 76.7, 64.1, 62.6, 26.8, 26.3, 25.5, 19.1; HRMS (EI) *m*/*z* calcd for $C_{25}H_{34}O_6SiNa^+$ 481.2017, found 481.2032.

3,6-Anhydro-5-*O*-*tert*-butyldiphenylsilyl-3-*C*-hydroxymethyl-1,2-*O*-isopropylidene-*β*-D-lyxofuranoside (25). Olefin **23** (100 mg, 0.236 mmol) was dissolved in CH_2Cl_2, and a saturated aqueous solution of $NaHCO_3$ (1 mL) was added. *m*-Chloroperoxybenzoic acid (233 mg, 0.944 mmol) was added, and the solution was stirred for 2 d. The reaction mixture was then diluted with CH_2Cl_2 and the organic layer washed with a saturated aqueous solution of sodium sulfite, then water, and brine. The organic layer was dried and concentrated; chromatography (hexanes/EtOAc, 10:1) yielded epoxide **25** (34 mg, 33%): R_f 0.51 (hexanes/EtOAc, 6:1); $[\alpha]_D$ +6.7 (*c* 0.7, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, δ) 7.70−7.68 (m, 4 H), 7.45−7.43 (m, 6 H), 6.00 (d, 1 H, J = 4.1 Hz), 4.39 (d, 1 H, J = 4.1 Hz), 4.07 (dd, 1 H, J = 4.9, 8.6 Hz), 4.00 (dd, 1 H, J = 8.8, 10.1 Hz), 3.82 (dd, 1 H, J = 4.9, 10.1 Hz), 3.45 (d, 1 H, J = 4.8 Hz), 3.21 (d, 1 H, J = 4.8 Hz), 1.41 (s, 3H), 1.33 (s, 3H), 1.09 (s, 9H); ^{13}C NMR (125.8 MHz, $CDCl_3$, δ) 135.6, 135.5, 134.8, 133.1, 132.8, 129.8, 129.7, 129.6, 127.8, 127.8, 127.7, 112.7, 105.1, 84.3, 82.8, 64.7, 64.3, 46.2, 26.8, 26.7, 26.6, 26.0, 19.1; HRMS (EI) *m*/*z* calcd for $C_{25}H_{32}O_5SiNa^+$ 463.1911, found 463.1932.

5-*O*-*tert*-Butyldiphenylsilyl-1,2-*O*-isopropylidene-3-*C*-vinyl-*β*-D-lyxofuranoside (27). Alcohol **26** (100 mg, 0.23 mmol) was added to a mixture of NaOAc (115 mg, 1.40 mmol), PCC (152 mg, 0.70 mmol), and crushed 4 Å molecular sieves in CH_2Cl_2. The solution was stirred for 4 h before diethyl ether and hexanes were added. The reaction mixture was then filtered through silica gel and eluted with diethyl ether. Evaporation of the solvent yielded the crude ketone, which was dissolved in THF, and the solution was cooled to 0 °C. A solution of 1 M vinylmagnesium bromide (0.51 mL, 0.51 mmo1) in THF was then added slowly, and the reaction mixture was stirred for 12 h before CH_3OH was added. The reaction mixture was diluted with CH_2Cl_2 and then washed with water and brine before being dried and evaporated. Chromatography (hexanes/EtOAc, 10:1) yielded the pure olefin **27** (48 mg, 45%): R_f 0.62 (hexanes/EtOAc, 4:1); $[\alpha]_D$ +5.3 (*c* 1.6, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, δ) 7.75−7.73 (m, 4 H), 7.43−7.42 (m, 6 H), 5.91 (dd, 1 H, J = 10.7, 17.2 Hz), 5.80 (d, 1 H, J = 4.1 Hz), 5.51 (dd, 1 H, J = 1.2, 17.2 Hz), 5.24 (dd, 1 H, J = 1.1, 10.7 Hz), 4.41 (d, 1 H, J = 4.1 Hz), 4.14 (dd, 1 H, J = 5.2, 10.5 Hz), 3.98 (dd, 1 H, J = 6.1, 6.1 Hz), 3.93 (dd, 1 H, J = 6.2, 10.5 Hz), 3.41 (s, 1 H), 1.54 (s, 3 H), 1.42 (s, 3 H), 1.10 (s, 9 H); ^{13}C NMR (125.8 MHz, $CDCl_3$, δ) 139.6, 135.7, 135.6, 133.3, 133.1, 129.7, 127.7, 127.7, 114.7, 114.6, 104.6, 85.4, 85.4, 78.0, 63.0, 27.0, 26.9, 26.8, 19.1; HRMS (EI) *m*/*z* calcd for $C_{26}H_{34}O_5SiNa^+$ 477.2068, found 477.2048.

Methyl 3-*O*-Benzyl-α-D-arabinofuranoside (32). Benzyl alcohol (15 mL) was heated at 120 °C while sodium (2.8 g, 123.3 mmol) was added in small portions. The suspension was stirred until the sodium was completely dissolved. Epoxide **31** (6.0 g, 41.1 mmol) was added to the solution in one portion, and the reaction mixture was stirred for 3 h. The solution was then neutralized with acetic acid, and silica gel was added to absorb the entire reaction mixture. The resulting solid was transferred to the top of a column of silica gel, and the column was eluted (hexanes/EtOAc, 20:1 → 10:1 → 1:2) to yield diol **32** as a colorless oil (8.71 g, 83%): R_f 0.51 (hexanes/EtOAc, 1:4); $[\alpha]_D$ +109.3 (*c* 1.9, CH_3OH); ^{1}H NMR (400 MHz, $CDCl_3$, δ) 7.35−7.28 (m, 5 H), 4.87 (s, 1 H), 4.70 (d, 1 H, J = 12.2 Hz), 4.56 (d, 1 H, J = 12.2 Hz), 4.20−4.17 (m, 1 H), 4.16 (s, 1 H), 3.84−3.80 (m, 2 H), 3.56 (dd, 1 H, J = 2.5, 11.9 Hz), 3.39 (s, 3 H); ^{13}C NMR (100.6 MHz, $CDCl_3$, δ) 137.6, 128.5, 127.9, 127.9, 110.0, 84.7, 83.8, 78.7, 72.2, 62.0, 55.1; HRMS (EI) *m*/*z* calcd for $C_{13}H_{18}O_5Na^+$ 277.1046, found 277.1031.

Methyl 3-*O*-Benzyl-2,5-*bis*-*O*-di-*tert*-butylsilyl-α-D-arabinofuranoside (33). Diol **32** (126 mg, 0.049 mmol) was dissolved in CH_2Cl_2 and the solution cooled to −78 °C. Freshly distilled pyridine (120 μL, 1.47 mmol) and then di-*tert*-butylsilyl bis(trifluoromethanesulfonate) (220 μL, 0.59 mmol) were added to this solution via syringe. The reaction mixture was warmed to 0 °C over 4 h before CH_3OH was added. Evaporation of the solvent and chromatography (hexanes/EtOAc, 20:1) yielded **33** (144 mg, 74%): R_f 0.63 (hexanes/EtOAc, 4:1); $[\alpha]_D$ +102.0 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, δ) 7.34−7.26 (m, 5 H), 4.96 (s, 1 H), 4.69 (d, 1 H, J = 12.6 Hz), 4.58 (d, 1 H, J = 12.5 Hz), 4.43 (s, 1 H), 4.42 (s, 1 H), 4.10−4.07 (m, 2 H), 3.80 (dd, 1 H, J = 12.4,2.2 Hz), 3.44 (s, 3 H), 0.98 (s, 9 H), 0.84 (s, 9 H); ^{13}C NMR (100.6 MHz, $CDCl_3$, δ) 137.5, 128.5, 128.0, 127.9, 110.1, 86.2, 81.8, 79.1, 71.9, 66.9, 55.5, 28.0, 27.5, 21.6, 21.2. Anal. Calcd for $C_{21}H_{34}O_5Si$: C, 63.92; H, 8.69. Found: C, 63.58; H, 8.71.

Methyl 2,5-*Bis*-*O*-di-*tert*-butylsilyl-α-D-arabinofuranoside (34). Benzyl ether **33** (853 mg, 2.16 mmol) was dissolved in CH_3OH, and $Pd(OH)_2$ (133 mg, 0.22 mmol) was added. The flask was then flushed with H_2, and the reaction mixture was stirred for 3 d before being filtered through Celite. The filtrate was evaporated, and the resulting residue was chromatographed (hexanes/EtOAc, 10:1), yielding pure **34** as a clear oil (618 mg, 94%): R_f 0.53 (hexanes/EtOAc, 4:1); $[\alpha]_D$ +84.6 (*c* 2.6, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, δ) 4.96 (s, 1 H), 4.34−4.26 (m, 3 H), 4.11 (dd, 1 H, J = 12.6, 1.2 Hz), 4.05 (dd, 1 H, J = 12.6, 2.2 Hz), 3.42 (s, 3 H), 3.39 (d, 1 H, J = 12.2 Hz), 0.99 (s, 18 H); ^{13}C NMR (100.6 MHz, $CDCl_3$, δ) 109.0, 89.1, 80.5, 76.2, 66.2, 55.0, 28.0, 27.6, 21.7, 21.3. Anal. Calcd for $C_{14}H_{28}O_5Si$: C, 55.23; H, 9.27. Found: C, 55.21; H, 9.37.

Methyl 3-Deoxy-2,5-*bis*-*O*-di-*tert*-butylsilyl-3-*C*-methylene-α-D-arabinofuranoside (35). PCC (833 mg, 3.84 mmol), sodium acetate (629 mg, 7.68 mmol), and crushed 4 Å molecular sieves were stirred in CH_2Cl_2 for 30 min. To this solution was added dropwise a solution of alcohol **34** (388 mg, 1.28 mmol) dissolved in CH_2Cl_2. After the addition was complete the solution was stirred for 8 h before hexanes and ether were added. After being stirred for an additional 1 h, the reaction mixture was filtered through a column of silica gel and the column washed with ether. The solvents were evaporated to yield the desired ketone as a light brown oil. A stir bar and a 0.5 M solution of Petasis reagent (15.4 mL, 7.68 mmol) in THF were then added, and the reaction mixture was heated at reflux for 13 h. The solution was then cooled to room temperature, and petroleum ether was added. The resultant suspension was filtered, and the filtrate was concentrated. Chromatography (hexanes/EtOAc, 20:1) yielded olefin **35** as a clear oil (273 mg, 71%): R_f 0.54 (hexanes/EtOAc, 6:1); $[\alpha]_D$ +107.8 (*c* 1.7, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, δ) 5.48 (d, 1 H, J = 1.6 Hz), 5.31 (d, 1 H, J = 1.3 Hz), 4.89 (s, 1 H), 4.63 (dd, 1 H, J = 1.6, 1.6 Hz), 4.40 (s, 1 H), 4.22 (dd, 1 H, J = 12.0, 1.5 Hz), 3.90 (dd, 1 H, J = 12.0, 1.9 Hz), 3.37 (s, 3 H), 1.01 (s, 9 H), 0.92 (s, 9 H); ^{13}C NMR (100.6 MHz, $CDCl_3$, δ) 146.0, 113.7, 107.8, 81.3, 78.7, 77.2, 68.6, 54.8, 28.0, 27.9, 21.5, 21.0. Anal. Calcd for $C_{15}H_{28}O_4Si$: C, 59.96; H, 9.39. Found: C, 60.12; H, 9.25.

Methyl 2,5-*Bis*-*O*-di-*tert*-butylsilyl-3-*C*-hydroxymethyl-6-*O*-toluenesulfonyl-α-D-arabinofuranoside (37). Olefin **35** (25 mg, 0.83 mmol) was dissolved in EtOAc (8 mL) and acetonitrile (8 mL) and the solution cooled to 0 °C. To this stirred solution was added a mixture of $RuCl_3 \cdot H_2O$ (17 mg, 0.08 mmol) and sodium periodate (267 mg, 1.25 mmol) in water (4 mL). After 30 min the reaction mixture was poured into a saturated aqueous solution of $Na_2S_2O_3$ and the resulting mixture stirred for 30 min. The layers were separated, and then the aqueous layer was extracted with EtOAc. The combined organic layers were washed with water and brine before being dried with $MgSO_4$. Evaporation yielded the crude diol, which was dissolved in CH_2Cl_2, and the solution was cooled to 0 °C. DABCO (372 mg, 3.32 mmol) and then TsCl (476 mg, 2.5 mmol) were added, and the reaction mixture was stirred for 2 h. The reaction mixture was filtered through

Celite, and the Celite was rinsed with CH_2Cl_2. The filtrate was washed with water and brine, then dried, and evaporated. Chromatography (hexanes/EtOAc, 10:1) yielded alcohol **37** as a white solid (264 mg, 65%): R_f 0.48 (hexanes/EtOAc, 2:1); $[\alpha]_D$ +25.5 (*c* 1.5, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, δ) 7.82−7.80 (m, 2 H), 7.34−7.32 (m, 2 H), 5.01 (s, 1 H), 4.59−4.56 (m, 2 H), 4.43 (dd, 1 H, J = 10.1, 1.2 Hz), 4.29 (dd, 1 H, J = 1.6, 1.6 Hz), 4.22 (s, 1 H), 4.13 (dd, 1 H, J = 13.6, 1.8 Hz), 3.90 (dd, 1 H, J = 13.6, 1.7 Hz), 3.42 (s, 3 H), 2.43 (s, 3 H), 1.03 (s, 9 H), 0.95 (s, 9 H); ^{13}C NMR (125.8 MHz, $CDCl_3$, δ) 144.7, 133.0, 129.7, 128.1, 108.1, 89.3, 89.2, 80.9, 80.4, 69.5, 64.8, 55.3, 29.1, 29.0, 28.0, 27.8, 22.5, 21.6, 21.3; HRMS (EI) *m*/*z* calcd for $C_{22}H_{36}O_5SSiNa^+$ 511.1792, found 511.1812.

Methy1 5-*O*-*tert*-Butyldiphenylsilyl-3-*C*-hydroxymethyl-6-*O*-toluenesulfonyl-α-D-arabinofuranoside (40). Alcohol **37** (225 mg, 0.46 mmol) was dissolved in THF (15 mL) and the solution transferred to a plastic syringe, with the tip sealed. A stir bar and 1.2 M HF−pyridine (1.2 mL, 1.4 mmol) were added, and the reaction mixture was stirred for 4 h. Evaporation of the solvent and chromatography (hexanes/EtOAc, 1:3) yielded **38** (135 mg, 85%).

Triol **38** (112 mg, 0.32 mmol) was immediately dissolved in DMF and the solution cooled to 0 °C. Imidazole (55 mg, 0.81 mmol) and then TBDMSCl (74 mg, 0.49 mmol) were added, and the reaction mixture was stirred for 3 h. The solution was diluted with water and ether, and the layers were separated. The aqueous layer was extracted with ether (3×), and the combined organic extracts were washed with water and brine before being dried and evaporated. Chromatography (hexanes/EtOAc, 3:1) yielded diol **40** (127 mg, 86%): R_f 0.42 (hexanes/EtOAc, 1:1); $[\alpha]_D$ +38.2 (*c* 2.3, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, δ) 7.86−7.85 (m, 2 H), 7.38−7.36 (m, 2 H), 4.91 (s, 1 H), 4.42 (d, 1 H, J = 10.2 Hz), 4.33 (d, 1 H, J = 10.2 Hz), 4.27 (dd, 1 H, J = 2.4 Hz), 3.86 (s, 1 H), 3.82 (d, 2 H, J = 2.4 Hz), 3.44 (s, 3 H), 2.48 (s, 3 H), 0.90 (s, 9 H), 0.13 (s, 6 H); ^{13}C NMR (125.8 MHz, $CDCl_3$, δ) 144.8, 132.6, 129.8, 128.1, 109.2, 88.4, 80.8, 78.3, 69.9, 61.9, 55.2, 25.6 (×2), 21.6, 18.2, −5.8 (×2); HRMS (EI) *m*/*z* calcd for $C_{20}H_{34}O_8SSiNa^+$ 485.1636, found 485.1645.

Methyl 3,6-Anhydro-5-*O*-*tert*-butyldiphenylsilyl-3-*C*-hydroxymethyl-α-D-arabinofuranoside (41). Diol **40** (33 mg, 0.07 mmol) was dissolved in THF and the solution cooled to 0 °C. DBU (12 mL, 0.08 mmol) was added slowly, and the reaction mixture was stirred for 4 h. Evaporation of the solvent and chromatography (hexanes/EtOAc, 6:1) yielded epoxide **41** (12 mg, 60%): R_f 0.34 (hexanes/EtOAc, 3:1); $[\alpha]_D$ +104.2 (*c* 1.1, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, δ) 4.97 (s, 1 H), 4.09 (d, 1 H, J = 11.6 Hz), 4.06 (dd, 1 H, J = 1.6, 1.6 Hz), 3.94 (dd, 1 H, J = 11.3, 1.9 Hz), 3.62 (d, 1 H, J = 11.6 Hz), 3.58 (dd, 1 H, J = 11.3, 1.5 Hz), 3.48 (s, 3 H), 3.20 (d, 1 H, J = 4.4 Hz), 2.91 (d, 1 H, J = 4.4 Hz), 0.96 (s, 9 H), 0.17 (s, 6 H); ^{13}C NMR (125.8 MHz, $CDCl_3$, δ) 108.5, 80.0, 75.5, 65.1, 63.0, 54.8, 46.0, 25.8, 18.3, −5.7; HRMS (EI) *m*/*z* calcd for $C_{13}H_{26}O_5SiNa^+$ 313.1442, found 313.1436.

Methyl 3,6-Di-*O*-(benzylidene acetal)-2,5-*bis*-*O*-di-tert-butylsilyl-3-*C*-hydroxymethyl-α-D-arabinofuranoside (42). Olefin **35** (67 mg, 2.23 mmol) was dissolved in EtOAc (20 mL) and acetonitrile (20 mL) and the solution cooled to 0 °C. To this stirred solution was added a solution of $RuCl_3 \cdot H_2O$ (45 mg, 0.22 mmol) and sodium periodate (716 mg, 3.35 mmol) in water (10 mL). After 20 min the reaction mixture was poured into a saturated aqueous solution of $Na_2S_2O_3$ and the resulting mixture stirred for 30 min. The aqueous layer was separated and then extracted with EtOAc. The combined organic layers were washed with water and brine before being dried with $MgSO_4$. Evaporation yielded the crude diol, which was then dissolved in CH_2Cl_2. Benzylidene dimethyl acetal (0.66 mL, 4.46 mmol) and *p*-TsOH (catalytic) were added, and the solution was stirred for 6 h, before being heated at 40 °C, with stirring for 12 h. The reaction mixture was cooled, and a saturated aqueous solution of $NaHCO_3$ was added followed by CH_2Cl_2. The organic layer was then washed with water and brine, dried, and evaporated. Chromatography (hexanes/EtOAc, 40:1) yielded **42** (569 mg, 60%) as a 1:1 diastereomeric mixture: R_f 0.4 (hexanes/EtOAc, 6:1); $[\alpha]_D$ +49.8 (*c* 4.6, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, δ) 7.53−7.52 (m, 2 H), 7.43−7.41 (m, 3 H), 6.07 (s, 0.5 H), 5.95 (s, 0.5 H), 5.11 (s, 1 H), 4.63−4.60 (m, 1 H), 4.50−4.48 (m, 1 H), 4.41−4.39 (m, 1 H), 4.36 (s, 0.5 H), 4.31 (dd, 0.5 H, J = 14.6, 1.2 Hz), 4.24 (dd, 0.5 H, J = 14.6, 1.2 Hz), 4.17 (d, 0.5 H, J = 9.5 Hz), 4.06−4.00 (m, 1 H), 3.51 (s, 1.5 H), 3.48 (s, 1.5 H), 1.15 (s, 9 H), 1.08 (s, 4.5 H), 1.05 (s, 4.5 H); ^{13}C NMR (125.8 MHz, $CDCl_3$, δ) 137.6, 136.9, 129.3, 129.1, 128.3, 128.2, 126.7, 126.4, 108.8, 108.2, 104.1, 103.9, 88.9, 88.3, 88.0, 87.1, 81.3, 69.0, 66.9, 65.9, 65.8, 56.0, 55.6, 29.2, 28.2, 22.8, 22.7, 21.3, 21.2; HRMS (EI) *m*/*z* calcd for $C_{22}H_{34}O_6SiNa^+$ 445.2017, found 445.2049.

Methyl 3,6-Di-*O*-(benzylidene acetal)-3-*C*-hydroxymethyl-α-D-arabinofuranoside (43). Compound **42** (340 mg, 0.80 mmol) was dissolved in THF (20 mL) and the solution transferred to a plastic syringe, with the tip sealed. To the syringe were added a stir bar and 1.2 N HF−pyridine (2.0 mL, 2.4 mmol). The syringe was sealed, and the solution was stirred for 4 h before the solvent was evaporated. Chromatography (hexanes/EtOAc, 1:2) yielded **43** (195 mg, 86%) as a white foam: R_f 0.49 (hexanes/EtOAc, 1:4); $[\alpha]_D$ +104.3 (*c* 1.4, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, δ) 7.53−7.52 (m, 2 H), 7.43−7.41 (m, 3 H), 6.01 (s, 0.5 H), 5.94 (s, 0.5 H), 4.59 (d, 0.5 H, J = 9.6 Hz), 4.51 (dd, 0.5 H, J = 2.3, 2.3 Hz), 4.47−4.45 (m, 1 H), 4.17 (d, 0.5 H, J = 9.7 Hz), 4.13−4.09 (m, 1 H), 4.05 (d, 0.5 H, J = 9.7 Hz), 4.00−3.94 (m, 1 H), 3.84−3.68 (m, 2 H), 3.48 (s, 3 H), 2.67−2.63 (m, 1 H); ^{13}C NMR (125.8 MHz, $CDCl_3$, δ) 137.4, 137.0, 129.4, 129.3, 128.4, 128.3, 126.7, 126.5, 109.5, 109.2, 104.5, 104.0, 88.9, 88.7, 85.6, 85.0, 79.0, 78.3, 66.7, 66.5, 61.2, 61.0, 55.7, 55.5; HRMS (EI) *m*/*z* calcd for $C_{14}H_{18}O_6Na^+$ 305.0996, found 305.1001.

Methyl 3,6-Di-*O*-(benzylidene acetal)-5-*O*-*tert*-butyldiphenylsilyl-3-*C*-hydroxymethyl-α-D-arabinofuranoside (44). Diol **43** (17 mg, 0.06 mmol) was dissolved in DMF and the solution cooled to 0 °C. Imidazole (10 mg, 0.15 mmol) and then TBDMSCl (14 mg, 0.09 mmol) were added, and the reaction mixture was stirred for 4 h before water and then ether were added. The layers were separated, and the aqueous layer was extracted with ether (3×). The combined organic extracts were then washed with water (3×) and brine before being dried. Chromatography (hexanes/EtOAc, 4:1) yielded **44** (20 mg, 87%) as a clear syrup: R_f 0.6 (hexanes/EtOAc, 2:1); $[\alpha]_D$ +88.7 (*c* 1.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, δ) 7.47−7.45 (m, 2 H), 7.36−7.34 (m, 3 H), 5.96 (s, 0.5 H), 5.89 (s, 0.5 H), 4.94−4.91 (m, 1 H), 4.57−4.42 (m, 2 H), 4.05−3.73 (m, 5 H), 3.43 (s, 3 H), 0.93 (s, 9 H), 0.14 (s, 6 H); ^{13}C NMR (100.6 MHz, $CDCl_3$, δ) 137.5, 137.1, 129.3, 129.2, 128.3, 128.2, 126.7, 126.6, 109.8, 109.5, 104.6, 104.0, 88.9, 88.8, 86.3, 85.8, 78.3, 77.7, 77.3, 66.8, 66.7, 62.7, 62.5, 55.7, 55.5, 25.7, 18.2, −5.7; HRMS (EI) *m*/*z* calcd for $C_{20}H_{32}O_6SiNa^+$ 419.1860, found 419.1843.

Methyl 2,6-Anhydro-3-*O*-benzoyl-5-*O*-*tert*-butyldiphenylsilyl-3-*C*-hydroxymethyl-α-D-arabinofuranoside (46). Alcohol **44** (31 mg, 0.08 mmol) was dissolved in dry CCl_4 (5 mL), and barium carbonate (102 mg) and *N*-bromosuccinimide (17 mg, 0.10 mmol) were added. The mixture was then heated at reflux for 3 h before being filtered through Celite. The filtrate was concentrated, and the resulting residue was purified by chromatography (10:1, hexanes/EtOAc), yielding bromide **45**, which was immediately dissolved in DMF. Potassium carbonate (83 mg, 0.6 mmol) was then added, and the reaction mixture was stirred for 36 h. Water and ether were then added, the layers were separated, and the ether layer was washed several times with water and then brine. The combined organic extracts were concentrated, and the resulting residue was purified by chromatography (hexanes/EtOAc, 10:1), yielding oxetane **46** (15 mg, 47%): R_f 0.52 (hexanes/EtOAc, 4:1); $[\alpha]_D$ +81.6 (*c* 1.3, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, δ) 8.05−8.04 (m, 2 H), 7.61−7.58 (m, 1 H), 7.47−7.44 (m, 2 H), 5.26 (s, 1 H), 5.02 (d, 1 H, J = 8.0 Hz), 5.01 (s, 1 H), 4.87 (d, 1 H, J = 7.7 Hz), 4.19−4.16 (m, 2 H), 4.11 (dd, 1 H, J = 12.0, 7.6 Hz), 3.44 (s, 3 H), 0.88 (s, 9 H), 0.09 (s, 6 H); ^{13}C NMR (125.8 MHz, $CDCl_3$, δ) 165.0, 133.6, 129.9, 129.1, 128.5, 128.4, 105.4, 91.3, 82.6, 81.3, 74.8, 62.4, 54.6, 25.8, 18.3, −5.3 (×2); HRMS (EI) *m*/*z* calcd for $C_{20}H_{30}O_6SiNa^+$ 417.1704, found 417.1724.

Methyl 2,6-Anhydro-3-*C*-hydroxymethyl-α-D-arabinofuranoside (17). Compound **46** (62 mg, 0.157 mmol) was dissolved in THF (5 mL) and the solution cooled to 0 °C. A solution of 1 M TBAF in THF (0.47 mL, 0.47 mmol) was added, and the reaction mixture was stirred for 2 h. A solution of 1 M sodium methoxide in CH_3OH (1 mL) was then added, and the solution was stirred for another 2 h. The reaction mixture was then neutralized with acetic acid, and the solvent was evaporated. Chromatography (CH_2Cl_2/CH_3OH, 20:1) yielded diol **17** (25 mg, 91%) as a white solid: R_f 0.26 (CH_2Cl_2/CH_3OH, 12:1); $[\alpha]_D$ +108.1 (*c* 0.6, CH_3OH); ^{1}H NMR (500 MHz, D_2O, δ) 5.00 (s, 1 H), 4.92 (s, 1 H), 4.76 (d, 1 H, J = 7.8 Hz), 4.63 (dd, 1 H, J = 7.8, 1.1 Hz), 4.00 (ddd, 1 H, J = 7.6, 3.7, 0.9 Hz), 3.91 (dd, 1 H, J = 12.0, 7.7 Hz), 3.82 (dd, 1 H, J = 12.0, 3.8 Hz), 3.39 (s, 3 H); ^{13}C NMR (125.8 MHz, D_2O, δ) 105.5, 93.9, 81.3, 78.5, 77.8, 59.9, 54.7; HRMS (EI) *m/z* calcd for $C_7H_{12}O_5Na^+$ 199.0577, found 199.0595.

2,3,5-Tri-*O*-benzoyl-α-D-arabinofuranosyl *p*-Tolyl-(R/S) Sulfoxide (19). Thioglycoside **18** (1.00 g, 1.76 mmol) was dissolved in CH_2Cl_2 and cooled to 0 °C. *m*-Chloroperoxybenzoic acid (407 mg, 2.37 mmol) was added, and the reaction mixture was allowed to warm slowly to room temperature. A saturated aqueous solution of $Na_2S_2O_3$ was added, and the reaction mixture was diluted with CH_2Cl_2. After the reaction mixture was stirred for 30 min, the layers were separated, and the organic layer was washed with water and brine. Chromatography (hexanes/EtOAc, 4:1) yielded sulfoxide **19** in a diastereomeric ratio of 7:3 (962 mg, 94%) as a clear oil: R_f 0.4 (hexanes/EtOAc, 2:1); $[\alpha]_D$ −10.4 (*c* 1.4, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, δ) 8.18−7.23 (m, 19 H), 6.42 (dd, 0.7 H, J = 3.4 Hz), 6.09 (dd, 0.3 H, J = 3.0 Hz), 5.85 (dd, 0.3 H, J = 5.8, 3.2 Hz), 5.79 (dd, 0.7 H, J = 5.3, 3.5 Hz), 5.08 (d, 0.7 H, J = 3.3 Hz), 5.04 (dd, 0.3 H, J = 9.5, 5.4 Hz), 4.99 (d, 0.3 H, J = 2.8 Hz), 4.86 (dd, 0.7 H, J = 9.5, 5.2 Hz), 4.77−4.72 (m, 1 H), 4.68−4.64 (m, 1 H), 2.36 (s, 1 H), 2.20 (s, 2 H). ^{13}C NMR (125.8 MHz, $CDCl_3$, δ) 166.0, 165.9, 165.6, 165.4, 164.5, 142.4, 142.1, 136.5, 133.6, 133.4, 133.1, 130.1, 130.0, 130.0, 129.9, 129.9, 129.7, 129.6, 129.5, 128.8, 128.5, 128.5, 128.3, 128.3, 128.3, 125.2, 124.2, 100.3, 100.0, 83.9, 83.5, 78.9, 77.6, 75.0, 63.5, 63.3, 21.4, 21.1; HRMS (EI) *m/z* calcd for $C_{33}H_{28}O_8SNa^+$ 607.1397, found 607.1351.

4-*O*-(α-D-Arabinofuranosyl)-1,5:3,6-dianhydro-D-galactitol (5) and 2-*O*-(α-D-Arabinofuranosyl)-1,5:3,6-dianhydro-D-galactitol (6). Diol **15** (50 mg, 0.342 mmol), thioglycoside **18** (233 mg, 0.41 mmol), and a stir bar were dried overnight with P_2O_5 in vacuo in a round-bottom flask. The flask was cooled to 0 °C, and then 10:3 CH_2Cl_2/acetonitrile (6.5 mL) was added. Crushed 4 Å molecular sieves were added, and the mixture was stirred for 20 min before NIS (115 mg, 0.51 mmol) and AgOTf (17 mg, 0.07 mmol) were added. After the mixture was stirred for 5 min, triethylamine (5 drops) was added, and the reaction mixture was then filtered through Celite and diluted with CH_2Cl_2. The organic layer was washed successively with a saturated aqueous solution of $Na_2S_2O_3$, water, and brine, before being dried and concentrated. Chromatography (hexanes/EtOAc, 1:1) yielded an inseparable mixture of the two disaccharides. This oil was then dissolved in CH_3OH (5 mL), 1 M sodium methoxide (5 drops) was added, and the solution was stirred for 14 h. The solution was then neutralized with Amberlite IR 120 (H+) resin and filtered and the solvent evaporated. The deprotected disaccharides were still inseparable by chromatography, so the mixture was dissolved in pyridine (1 mL) and acetic anhydride (1 mL). The reaction mixture was stirred for 6 h and cooled to 0 °C, and then CH_3OH was added. The solvent was evaporated, and the products were separated by chromatography (hexanes/EtOAc, 3:2). Each pure, fully acetylated disaccharide was dissolved, separately, in CH_3OH (5 mL), and 1 M sodium methoxide (3 drops) was added. After being stirred for 2 h, the solution was neutralized with Amberlite IR 120 (H+) resin, filtered, and concentrated. Each disaccharide was obtained in 20% yield (18 mg) from **15**.

Data for **5**: R_f 0.55 (CH_2Cl_2/CH_3OH, 3:1); $[\alpha]_D$ = +137.5 (*c* 0.6, CH_3OH); ^{1}H NMR (800 MHz, D_2O, δ) 5.10 (d, 1 H, J = 1.9 Hz), 4.48 (dd, 1 H, J = 2.1 Hz), 4.40 (d, 1 H,J = 1.8 Hz), 4.37 (d, 1 H, J = 5.5 Hz), 4.16 (d, 1 H, J = 10.8 Hz), 3.98 (ddd, 1 H, J = 3.2, 6.1, 6.1 Hz), 3.97 (dd, 1 H, J = 1.9, 3.7 Hz), 3.94−3.92 (m, 2 H), 3.84 (dd, 1 H, J = 3.7, 6.4 Hz), 3.78 (dd, 1 H, J = 2.8, 13.3 Hz), 3.74 (dd, 1 H, J = 3.2, 12.3 Hz), 3.62 (dd, 1 H, J = 5.8, 12.3 Hz), 3.51 (d, 1 H, J = 13.4 Hz); ^{13}C NMR (150.9 MHz, D_2O, δ) 106.9, 84.2, 81.8, 80.2, 76.8, 76.4, 69.6, 68.6, 65.5, 61.6; HRMS (EI) *m/z* calcd for $C_{11}H_{18}O_8Na^+$ 301.0894, found 301.902.

Data for **6**: R_f 0.55 (CH_2Cl_2/CH_3OH, 3:1); $[\alpha]_D$ +118.7 (*c* 0.6, CH_3OH); ^{1}H NMR (800 MHz, D_2O, δ) 5.02 (d, 1 H, J = 1.7 Hz), 4.42 (d, 1 H, J = 5.5 Hz), 4.39 (d, 1 H, J = 1.9 Hz), 4.33 (dd, 1 H, J = 2.5 Hz), 4.15 (d, 1 H, J = 10.9 Hz), 4.05 (d, 1 H, J = 1.7 Hz), 4.01 (dd, 1 H, J = 1.7, 3.6 Hz), 3.98 (dd, 1 H, J = 3.1, 10.8 Hz), 3.88 (dd, 1 H, J = 2.7, 5.5 Hz), 3.87 (dd, 1 H, J = 3.5, 6.5 Hz), 3.78 (dd, 1 H, J = 2.8, 13.5 Hz), 3.76 (dd, 1 H, J = 3.3, 12.4 Hz), 3.66 (d, 1 H, J = 13.4 Hz), 3.64 (dd, 1 H, J = 6.0, 12.4 Hz); ^{13}C NMR (150.9 MHz, D_2O, δ) 107.9, 84.3, 81.9, 80.4, 78.7, 77.0, 76.6, 71.2, 68.5, 63.5, 61.7; HRMS (EI) *m/z* calcd for $C_{11}H_{18}O_8Na^+$ 301.0894, found 301.0878.

α-D-Arabinofuranosyl-(1→2)-[α-D-arabinofuranosyl-(1→4)]-1,5:3,6-dianhydro-D-galactitol (9). Diol **15** (50 mg, 0.342 mmol), thioglycoside **18** (486 mg, 0.856 mmol), and a stir bar were dried overnight with P_2O_5 in vacuo in a round-bottom flask. The flask was cooled to 0 °C, and then 5:1 CH_2Cl_2/acetonitrile (6 mL) was added, followed by crushed 4 Å molecular sieves. The mixture was stirred for 20 min before NIS (241 mg, 1.07 mmol) and AgOTf (37 mg, 0.143 mmo1) were added. After the mixture was stirred at 0 °C for 5 min, triethylamine (5 drops) was added, and the reaction mixture was filtered through Celite and then diluted with CH_2Cl_2. The organic layer was then washed in succession with a saturated aqueous solution of $Na_2S_2O_3$, water, and brine, before being dried and concentrated. Chromatography (hexanes/EtOAc, 3:1) yielded the crude product (346 mg, 98%) contaminated with **50**: R_f 0.47 (hexanes/EtOAc, 2:1).

The crude trisaccharide was dissolved in CH_3OH (5 mL), and 1 M sodium methoxide (5 drops) was added. The solution was stirred for 14 h, then neutralized with Amberlite IR 120 (H+) resin, filtered, and concentrated. Chromatography (CH_2Cl_2/CH_3OH, 3:1) yielded the pure trisaccharide **9** (93.7 mg, 68%): R_f 0.38 (CH_2Cl_2/CH_3OH, 3:1); $[\alpha]_D$ +141.1 (*c* 1.3, CH_3OH); ^{1}H NMR (800 MHz, D_zO, δ) 5.09 (d, 1 H, J = 1.9 Hz), 5.00 (d, 1 H, J = 1.7 Hz), 4.55 (d, 1 H, J = 5.6 Hz), 4.49 (dd, 1 H, J = 1.8, 2.2 Hz), 4.43 (d, 1 H, J = 1.8 Hz), 4.16 (d, 1 H, J = 10.8 Hz), 4.04 (dd, 1 H, J = 1.7, 3.5 Hz), 4.03 (ddd, 1 H, J = 3.4, 5.8, 5.8 Hz), 3.99−3.97 (m, 2 H), 3.95 (dd, 1 H, J = 3.2, 10.9 Hz), 3.88−3.85 (m, 3 H), 3.78 (dd, 1 H, J = 2.8, 13.4 Hz), 3.73 (dd, 1 H, J = 2.4, 12.4 Hz), 3.73 (dd, 1 H, J = 2.3, 12.4 Hz), 3.66 (d, 1 H, J = 13.4 Hz), 3.63 (d, 1 H, J = 12.4 Hz), 3.61 (d, 1 H, J = 12.4 Hz); ^{13}C NMR (150.9 MHz, D_2O, δ) 108.1, 106.8, 84.5, 84.2, 81.8, 79.7, 77.0, 76.8, 76.7, 68.8, 63.9, 61.6, 61.5; HRMS (EI) *m/z* calcd for $C_{16}H_{26}O_{12}Na^+$ 433.1322, found 433.1324.

4-*O*-(α-D-Arabinofuranosyl)-1,5:3,6-dianhydro-D-talitol (7), 2-*O*-(α-D-Arabinofuranosyl)-1,5:3,6-dianhydro-D-talitol (8), and α-D-arabinofuranosyl-(1→2)-[α-D-arabinofuranosyl-(1→4)]-1,5:3,6-dianhydro-D-talitol (10). Diol **16** (169 mg, 1.16 mmol), thiog1ycoside **18** (723 mg, 1.27 mmol), and a stir bar were dried overnight with P_2O_5 in vacuo in a round-bottom flask. The flask was cooled to 0 °C, and then 5:2 CH_2Cl_2/acetonitrile (14 mL) was added, followed by crushed 4 Å molecular sieves. The mixture was stirred for 20 min before NIS (115 mg, 0.51 mmol) and AgOTf (17 mg, 0.07 mmol) were added. After the mixture was stirred at 0 °C for 10 min, triethylamine (5 drops) was added, and the reaction mixture was then filtered through Celite and diluted with CH_2Cl_2. The organic layer was washed successively with a saturated aqueous solution of $Na_ZS_2O_3$, water, and brine, before being dried and concentrated. The three possible products were separated by chromatography (hexanes/EtOAc, 2:1), dissolved separately in CH_3OH, and then treated with 1 M sodium methoxide (5 drops). After being stirred for 2 h, each reaction was then neutralized by addition of acetic acid. Chromatography (CH_2Cl_2/CH_3OH, 6:1) yielded the trisaccharide analogue (82 mg, 17%) and the 2-linked disaccharide analogue (109 mg,

34%). The 4-linked disaccharide analogue was also isolated, but only in 6% yield.

Data for **7**: R_f 0.49 (CH_2Cl_2/CH_3OH, 3:1); $[\alpha]_D$ +102.0 (*c* 0.8, CH_3OH); ^1H NMR (800 MHz, D_2O, δ) 5.10 (d, 1 H, J = 1.7 Hz), 4.48 (dd, 1 H, J = 2.3, 2.3 Hz), 4.33 (s, 1 H), 4.03 (d, 1 H, J = 10.8 Hz), 4.00 (ddd, 1 H, J = 6.1, 6.1, 3.2 Hz), 3.99 (dd, 1 H, J = 3.7, 1.8 Hz), 3.96 (d, 1 H, J = 1.8 Hz), 3.95 (dd, 1 H, J = 10.9, 3.1 Hz), 3.86−3.81 (m,3 H), 3.75 (dd, 1 H, J = 12.4, 3.1 Hz), 3.63 (dd, 1 H, J = 12.4, 5.8 Hz), 3.27 (dd, 1 H, J = 10.0, 8.3 Hz); ^{13}C NMR (125.8 MHz, D_2O, δ) 106.9, 84.3, 83.0, 81.9, 78.4, 77.0, 75.7, 69.1, 67.4, 63.7, 61.7; HRMS (EI) *m*/*z* calcd for $C_{11}H_{18}O_8Na^+$ 301.0894, found 301.0921.

Data for **8**: R_f 0.49 (CH_2Cl_2/CH_3OH, 3:1); $[\alpha]_D$ +161.8 (*c* 0.7, CH_3OH); ^1H NMR (800 MHz, D_2O, δ) 5.03 (d, 1 H, J = 1.5 Hz), 4.37 (s, 1 H), 4.29 (dd, 1 H, J = 2.3, 2.3 Hz), 4.01 (d, 1 H, J = 10.8 Hz), 3.99 (dd, 1 H, J = 3.5, 1.6 Hz), 3.96 (dd, 1 H, J = 10.8, 3.0 Hz), 3.92 (dd, 1 H, J = 11.5, 6.7 Hz), 3.90−3.89 (m, 2 H), 3.81 (dd, 1 H, J = 6.3, 3.5 Hz), 3.79 (ddd, 1 H, J = 9.5, 6.9, 1.1 Hz), 3.71 (dd, 1 H, J = 12.4, 3.2 Hz), 3.58 (dd, 1 H, J = 12.4, 5.9 Hz), 3.33 (dd, 1 H, J = 11.4, 9.6 Hz); ^{13}C NMR (125.8 MHz, D_2O, δ) 106.9, 84.2, 81.6, 81.6, 77.6, 76.9, 73.7, 73.0, 68.8, 62.6, 61.5; HRMS (EI) *m*/*z* calcd for $C_{11}H_{18}O_8Na^+$ 301.0894, found 301.0922.

Data for **10**: R_f 0.83 (CH_2Cl_2/CH_3OH, 3:1); $[\alpha]_D$ +140.0 (*c* 2.0, CH_3OH); ^1H NMR (800 MHz, D_2O, δ) 5.09 (d, 1 H, J = 1.7 Hz), 5.03 (d, 1 H, J = 1.5 Hz), 4.51 (s, 1 H), 4.48 (dd, 1 H, J = 2.3, 2.3 Hz), 4.04 (d, 1 H, J = 10.8 Hz), 4.00−3.97 (m, 4 H), 3.96−3.93 (m, 2 H), 3.89 (ddd, 1 H, J = 6.1, 6.1, 3.2 Hz), 3.85−3.83 (m, 2 H), 3.81 (dd, 1 H, J = 6.3, 3.5 Hz), 3.74 (dd, 1 H, J = 12.4, 3.1 Hz), 3.71 (dd, 1 H, J = 12.3, 3.2 Hz), 3.61 (dd, 1 H, J = 12.3, 5.9 Hz), 3.58 (dd, 1 H, J = 12.3, 5.9 Hz), 3.35 (dd, 1 H, J = 11.4, 9.6 Hz); ^{13}C NMR (125.8 MHz, D_2O, δ) 107.0, 106.8, 84.2, 84.2, 81.7, 81.6, 80.9, 78.2, 76.9, 76.8, 75.6, 73.6, 69.1, 62.9, 61.5, 61.5; HRMS (EI) *m*/*z* calcd for $C_{16}H_{26}O_{12}Na^+$ 433.1316, found 433.1278.

Methyl α-D-Arabinofuranosyl-(l→5)-2,6-anhydro-3-*C*-hydroxymethyl-α-D-arabinofuranoside (12) and Methyl α-D-Arabinofuranosyl-(l→3)-[α-D-arabinofuranosyl-(l→5)]-2,6-anhydro-3-*C*-hydroxymethyl-α-D-arabinofuranoside (13). Sulfoxide **19** (91 mg, 0.16 mmol) and crushed 4 Å molecular sieves were dried overnight in vacuo in a round-bottom flask. Di-*tert*-butylmethylpyridine (64 mg, 0.31 mmol) was then added, and the mixture was dried for another 20 min. This mixture was then dissolved in CH_2Cl_2 (10 mL) and the solution cooled to −78 °C. Triflic anhydride (32 mL, 0.19 mmol) was then added and the solution stirred for 5 min. Diol **17** (11 mg, 0.06 mmol) was then added as a solution in CH_3CN (5 drops) and CH_2Cl_2 (3 mL). The solution was then stirred for 5 h and allowed to warm slowly to room temperature, before a saturated aqueous solution of $NaHCO_3$ was added. The reaction mixture was then diluted with CH_2Cl_2. The layers were separated, and the organic layer was dried and concentrated to provide a residue that was chromatographed (hexanes/EtOAc, 3:1) to afford the separated products. These two products were dissolved, separately, in CH_3OH (5 mL) and treated with 1 M sodium methoxide (5 drops) and the solutions stirred for 4 h. Neutralization of the reaction mixture with acetic acid (2 drops), concentration, and then chromatography (CH_2Cl_2/CH_3OH, 10:1) yielded the desired trisaccharide **13** (8 mg, 29%) as well as the 5-linked disaccharide **12** (7 mg, 37%).

Data for **12**: R_f 0.41 (CH_2Cl_2/ CH_3OH, 6:1); $[\alpha]_D$ +133.3 (*c* 0.3, CH_3OH); ^1H NMR (800 MHz, D_2O, δ) 4.99 (d, 1 H, J = 1.5 Hz), 4.98 (s, 1 H), 4.88 (s, 1 H), 4.79 (d, 1 H, J = 7.9 Hz), 4.61 (dd, 1 H, J = 7.9, 1.0 Hz), 4.08 (ddd, 1 H, J = 7.1, 3.5, 1.0 Hz), 4.05 (dd, 1 H, J = 3.3, 1.7 Hz), 4.05−4.01 (m, 2 H), 3.88 (dd, 1 H, J = 6.1, 3.3 Hz), 3.76−3.74 (m, 2 H), 3.64 (dd, 1 H, J = 12.3, 5.8 Hz), 3.35 (s, 3H); ^{13}C NMR (125.8 MHz, D_2O, δ) 107.9, 105.7, 93.6, 84.4, 81.3, 79.4, 78.6, 78.0, 76.9, 65.6, 61.5, 54.9; HRMS (EI) *m*/*z* calcd for $C_{12}H_{20}O_9Na^+$ 331.1000, found 331.1002.

Data for **13**: R_f 0.36 (CH_2Cl_2/CH_3OH, 3:1); $[\alpha]_D$ +166.6 (*c* 0.5, CH_3OH); ^1H NMR (800 MHz, D_2O, δ) 5.22 (d, 1 H, J = 2.1 Hz), 5.15 (s, 1 H), 5.00 (s, 1 H), 4.99 (d, 1 H, J = 1.6 Hz), 4.80 (dd, 1 H, J = 8.2, 1.2 Hz), 4.76 (d, 1 H, J = 8.0 Hz), 4.21 (ddd, 1 H, J = 7.1, 3.0, 1.0 Hz), 4.07−4.04 (m, 4 H), 4.02 (ddd, 1 H, J = 5.8, 5.8, 3.3 Hz), 3.90−3.86 (m, 3 H), 3.75 (dd, 1 H, J = 12.3, 3.3 Hz), 3.74 (dd, 1 H, J = 12.4, 3.2 Hz), 3.64 (dd, 1 H, J = 12.4, 5. 7 Hz), 3.63 (dd, 1 H, J = 12.5, 5.6 Hz), 3.36 (s, 3 H); ^{13}C NMR (125.8 MHz, D_2O, δ) 107.8, 105.3, 105.1, 90.8, 84.4, 84.3, 82.9, 81.8, 81.4, 79.0, 76.9, 76.2, 76.1, 65.8, 61.5, 61.5, 54.9; HRMS (EI) *m*/*z* calcd for $C_{17}H_{28}O_{13}Na^+$ 463.1422, found 463.1452.

Methyl 2,6-Anhydro-5-*O*-benzoyl-3-*C*-hydroxymethyl-α-D-arabinofuranoside (56). Diol **17** (16 mg, 0.09 mmol) was dissolved in pyridine (1 mL) and the solution cooled to 0 °C. Benzoyl chloride (0.12 mL, 1.02 mmol) was then added, and the reaction mixture was stirred for 12 h. DMAP (catalytic) was then added, and the solution was stirred for a further 4 h before CH_3OH was added. The reaction mixture was diluted with CH_2Cl_2 and then washed successively with a saturated aqueous solution of $NaHCO_3$, water, and brine. Chromatography (hexanes/EtOAc, 2:1) yielded monobenzoate **56** as a white solid (23 mg, 87%): R_f 0.34 (hexanes/EtOAc, 1:1); $[\alpha]_D$ +72.0 (*c* 0.8, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$, δ) 8.10−8.08 (m, 2 H), 7.64−7.61 (m, 1 H), 7.51−7.48 (m, 2 H), 5.00 (s, 1 H), 4.91−4.90 (m, 2 H), 4.71−4.67 (m, 3 H), 4.26 (ddd, 1 H, J = 5.7, 5.7, 0.8 Hz), 3.46 (s, 3 H), 3.31 (s, 1 H); ^{13}C NMR (125.8 MHz, $CDCl_3$, δ) 166.8, 133.4, 129.7, 129.4, 128.5, 106.0, 93.2, 79.8, 78.7, 77.5, 62.7, 54.7; HRMS (EI) *m*/*z* calcd for $C_{14}H_{16}O_6Na^+$ 303.0839, found 303.0853.

Methyl α-D-arabinofuranosyl-(l→3)-2,6-anhydro-3-*C*-hydroxymethyl-α-D-arabinofuranoside (11). The sulfoxide donor **19** (79 mg, 0.14 mmol) and crushed 4 Å molecular sieves were dried overnight in vacuo in a round-bottom flask. Di-*tert*-butylmethylpyridine (56 mg, 0.27 mmol) was then added and the mixture dried for another 20 min. This mixture was then dissolved in CH_2Cl_2 (10 mL) and the solution cooled to −78 °C. Triflic anhydride (28 mL, 0.16 mmol) was then added, and the reaction mixture was stirred for 5 min. Benzoate **56** (19 mg, 0.07 mmol) was then added as a solution in CH_2Cl_2 (3 mL). The reaction mixture was then stirred 5 h and allowed to warm slowly to room temperature. Addition of a saturated aqueous solution of $NaHCO_3$, dilution with CH_2Cl_2, separation of the layers, drying of the organic layer, and chromatography (hexanes/EtOAc, 6:1) yielded a mixture of products. These products were dissolved in CH_3OH (5 mL), 1 M sodium methoxide (5 drops) was added, and the reaction mixture was stirred for 12 h. Neutralization with acetic acid (2 drops) and chromatography (CH_2Cl_2/CH_3OH, 10:1) yielded the crude 3-linked disaccharide. The crude disaccharide was dissolved in pyridine (1 mL) and acetic anhydride (1 mL), and dimethylaminopyridine (catalytic) was added. The reaction mixture was stirred for 6 h before CH_3OH was added, and the solution was concentrated. Chromatography (hexanes/EtOAc, 2:1), followed by Zemplen deacylation, and chromatography (CH_2Cl_2/CH_3OH, 10:1) provided the pure disaccharide **11** in poor yield (2 mg, 9%): R_f 0.18 (CH_2Cl_2/CH_3OH, 6: 1); $[\alpha]_D$ +153.6 (*c* 0.1, CH_3OH); ^1H NMR (800 MHz, D_2O, δ) 5.23 (s, 1 H), 5.16 (s, 1 H), 4.98 (s, 1 H), 4.78 (d, 1 H, J = 7.9 Hz), 4.69 (d, 1 H, J = 7.9 Hz), 4.08 (dd, 1 H, J = 5.5, 5.5 Hz), 4.07−4.04 (m, 2 H), 3.89−3.88 (m, 3 H), 3.74 (dd, 1 H, J = 12.4, 3.0 Hz), 3.62 (dd, 1 H, J = 12.5, 5.8 Hz), 3.35 (s, 3 H); ^{13}C NMR (125.8 MHz, D_2O, δ) 105.1, 105.1, 90.9, 84.4, 82.9, 81.8, 80.6, 76.2, 76.0, 61.5, 60.1, 54.7; HRMS (EI) *m*/*z* calcd for $C_{12}H_{20}O_9Na^+$ 331.1000, found 331.0981.

Computational Investigations. The SPMC search protocol available in MacroModel Version 6.5[36] was used to generate an initial family of 1000 structures of **15**−**17**. Each conformer was then minimized in the gas phase using the AMBER* force field. The conformers within 5 kcal/mol of their respective global minimum (at the AMBER* level of theory) were then optimized at the Hartree−Fock level of theory[37] with the 6-31G* basis set. The Cartesian coordinates for the optimized conformers are given in the Supporting Information. Single-point energy calculations on the HF conformers were carried out at the B3LYP[38] level of theory with the 6-31+G**

(36) (a) MacroModel V6.5: Mohamadi, F.; Richards, N. G. J.; Guida, W. C.; Liskamp, R.; Lipton, M.; Caulfield, C.; Chang, G.; Hendrickson, T.; Still, W. C. *J. Comput. Chem.* **1990**, *11*, 440. (b) Goodman, J.; Still, W. C. *J. Comput. Chem.* **1991**, *12*, 1110.

basis set; these energies can be found in the Supporting Information (Table S1). All HF and DFT calculations were conducted using Gaussian 98.[39]

NMR and PSEUROT Calculations. The $^3J_{H,H}$ values used in all PSEUROT calculations were measured from 1D ^{1}H NMR spectra recorded on samples at 15−20 mM concentration in 0.6 mL of D_2O (pH 6.0) at 300 K. These data are included in Table S2 in the Supporting Information. Where necessary, assignments were confirmed by 2D ^{1}H−^{1}H correlation spectroscopy (COSY, TOCSY) and by simulation of the spectra by NMRSim.[40] All PSEUROT 6.2 calculations were done using the default parameters (e.g., electronegativities, phase angles, A_i, B_i) provided in that program for the α-D-arabinofuranosyl ring (see example 7 in the PSEUROT manual). In the calculations the puckering amplitude, τ_m, was kept constant at 39°; this value corresponds to the puckering observed in the crystal structure of **1**.[41] This approach has previously been used successfully in these calculations in other systems.[42]

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra of all new compounds, Cartesian coordinates for the HF/6-31G*-optimized geometries of **15**−**17** (global minima), a table containing relative energies, a table of $^3J_{H,H}$ values used in PSEUROT calculations, and a figure with ^{13}C and ^{1}H NMR chemical shifts used in determining the structures of **5**−**14**. This material is available free of charge via the Internet at http://pubs.acs.org.

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