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2,3-Anhydrosugars in Glycoside Bond Synthesis. Application to 2,6-Dideoxypyranosides

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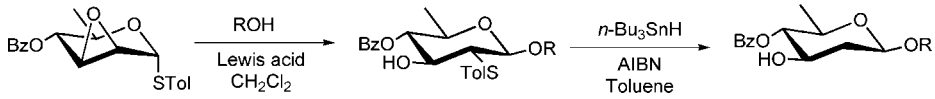

We describe here the first use of 2,3-anhydrosugars as glycosylating agents for the preparation of 2-deoxypyranosides. In particular, the methodology was used to assemble 2,6-dideoxysugar glycosides. Glycosylation of a panel of alcohols with one of two 6-deoxy-2,3-anhydrosugar thioglycosides (**8** and **9**) in the presence of a Lewis acid afforded 2,6-dideoxy-2-thiotolyl glycoside products in generally excellent yields with an exclusively syn relationship between the aglycon and the C-3 hydroxyl group. Removal of the 2-thiotolyl group can be achieved upon reaction with tri-*n*-butyltin hydride and AIBN to give the corresponding 2,6-dideoxy pyranosides. Once developed, the method was applied to the synthesis of oligosaccharide moieties in the natural products apoptolidin and olivomycin A.

Introduction

In previous papers, we have described the use of 2,3-anhydrosugar thioglycosides (e.g., **1**−**3**, Chart 1) for the preparation of glycosidic bonds.[1−8] Depending upon the activation conditions, these species can be used to produce two different classes of products. For example, glycosylation of alcohols with **1** upon treatment with *N*-iodosuccinimide and silver triflate leads to the highly stereoselective formation of 2,3-anhydrosugar glycosides (**4**) in which the newly formed glycosidic bond is cis to the epoxide moiety.[1−7] Alternatively, glycosylation of alcohols with **1** in the presence of a Lewis acid leads to the formation of 2-deoxy-2-thiotolylglycosides **5**, which are precursors to 2-deoxy glycosides **6**.[8] The latter glycosylation also proceeds with a high degree of stereocontrol, which by analogy to other similar migration−glycosylation processes,[9−18] we attributed to the formation of episulfonium ion intermediate (e.g., **7**).

In all of our previous studies,[1−8] the donors employed were in the furanose ring form, and we were curious as the potential of their pyranoside counterparts (e.g., **8** and **9**) in these reactions, particularly in the preparation of 2,6-dideoxysugar glycosides. 2,6-Dideoxypyranosides are an important class of carbohydrates, which are present as essential components of steroidal glycosides, antibiotics, and antitumor compounds.[19−21] Specific examples include the apoptotic agent apoptolidin,[22] the anticancer drug daunomycin,[23,24] and olivomycin A,[25] a member of the aureolic acid family of antitumor antibiotics. As such, 2,6-dideoxypyranosides and other 2-deoxysugar glycosides

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continue to receive attention as synthetic targets.[22,26−35] However, syntheses of these glycosides are typically challenging, as the absence of a stereocontrolling group at C-2 often leads to α/β mixtures of products.[36] Although a number of recent advances in this area have appeared,[37−41] there is still a need for new methods to prepare 2-deoxy- (and 2,6-dideoxy-) glycosides. We report here the use of 6-deoxy-2,3-anhydropyranosyl thioglycosides **8** and **9** for the synthesis of 2,6-dideoxysugar glycosides.

Results and Discussion

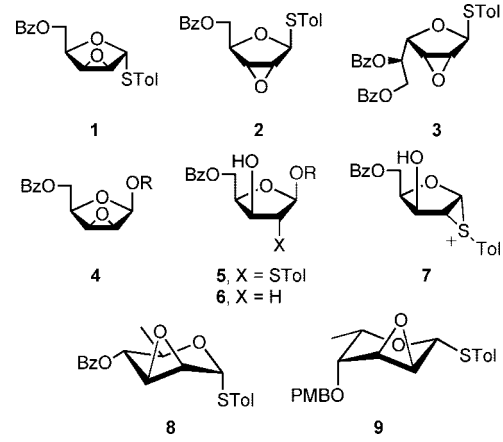
Developing the method required first the preparation of glycosyl donors **8** and **9**. Although in the synthesis of **1** and **3** the epoxide rings were installed via a Mitsunobu reaction of a vicinal diol,[4,6] this approach is generally less successful on more rigid pyranose rings.[42] We therefore chose to introduce the epoxide moieties by way of intramolecular S_N2 reactions, as described previously for the preparation of **2**.[4,43]

Synthesis of Donor 8. The preparation of **8** started with the known benzylidene acetal protected 6-deoxy-D-mannopyranoside **10**[44] (Scheme 1). Application of the Hanessian−Huller reaction[45−47] to **10** led to the formation of **11** in 75% yield. The location of the benzoate ester on C-2 was readily apparent from the chemical shift of H-2 ($\delta_H = 5.50$ ppm) and C-2 ($\delta_C =$ 73.0 ppm). Further support for the structure came from the chemical shift of C-3, which appeared at $\delta_C = 52.3$ ppm, as would be expected for a carbon atom attached to a bromine. The axial orientation of the C−Br bond was ascertained from the $^3J_{H2,H3}$ (3.7 Hz) and $^3J_{H3,H4}$ (3.7 Hz) values of the resonance assigned to H-3 at $\delta_H = 4.51$ ppm. This result provides further evidence that the stereochemistry of the dioxolane benzylidene acetal does not affect the regioselectivity of the Hanessian−Huller reaction, which has been noted previously.[48]

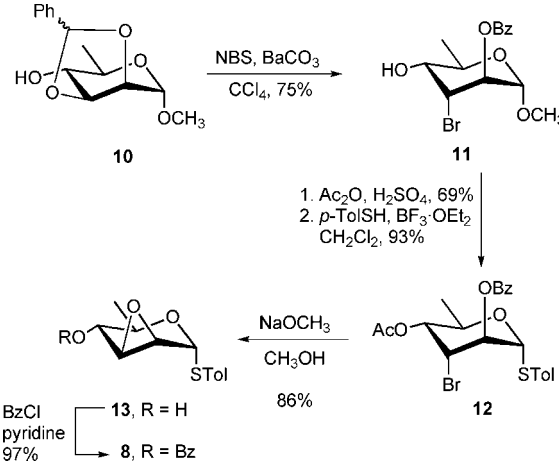
Methyl glycoside **11** was then cleaved upon reaction with a catalytic amount of sulfuric acid in acetic anhydride to afford the corresponding glycosyl acetate in 69% yield. The α-thioglycoside **12** was readily and stereoselectively accessed from this acetate derivative in 93% yield upon treatment with boron trifluoride etherate and *p*-thiocresol in dichloromethane at 0 °C. Subsequently, **12** was reacted with sodium methoxide in methanol and dichloromethane to provide exclusively the 2,3-anhydrosugar **13** in 86% yield. The location of the oxirane was clearly established by the chemical shift of C-2 ($\delta_C = 56.0$ ppm) and C-3 ($\delta_C = 51.5$ ppm) as well as the ^3J of 3.6 Hz in the doublets assigned to H-3 ($\delta_H = 3.41$ ppm) and H-2 ($\delta_H = 3.34$ ppm). It should be noted that **13** has a hydroxyl group trans to the epoxide, which under the basic reaction conditions could, in principle, lead to the formation of an isomeric epoxide spanning C-3 and C-4. However, none of this epoxide rearrangement product was observed, although in another system (see below) such a byproduct was formed. The final step in the synthesis of **8** was the addition of a benzoyl group, which was achieved under standard conditions, giving a nearly quantitative yield of the product.

Synthesis of Donor 9. The preparation of **9** proved more challenging than **8**. The first approach started from fucopyranose tetraacetate **14**[49] (Scheme 2), which was converted in two steps and 73% overall yield into thioglycoside **15**. Reaction of **15** with di-*n*-butyltin oxide in toluene yielded the stannylidene acetal intermediate, which was then treated with methanesulfo-

CHART 1



SCHEME 1



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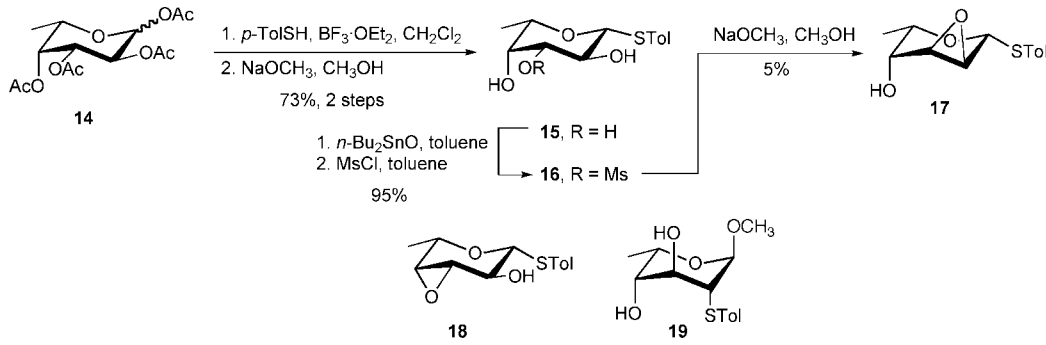
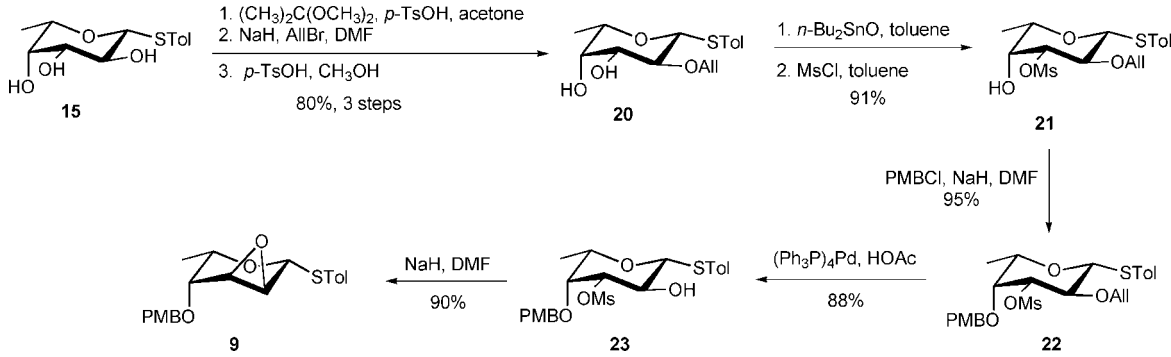
SCHEME 2



SCHEME 3



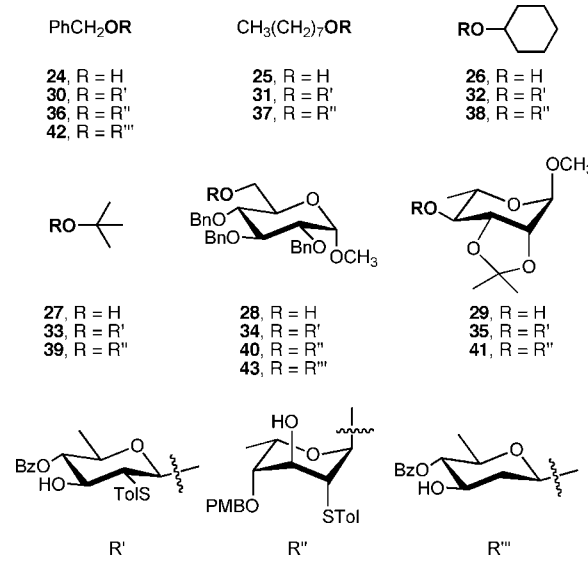
nyl chloride, resulting in the formation of **16** in 95% yield. The location of the methanesulfonyl group was identified by the downfield chemical shift of both H-3 ($\delta_H = 4.56$ ppm) and C-3 ($\delta_C = 84.4$ ppm) in the ^{1}H and ^{13}C NMR spectra, respectively.

Having developed a route for the preparation of **16**, we next hoped to convert it into epoxide **17**. However, when the reaction was attempted by stirring **16** with sodium methoxide in dichloromethane and methanol, the conversion rate was very slow, and after 16 h, less than 5% of the product was generated. Attempts to improve the product yield by allowing the reaction to proceed for a longer period of time (48 h) did not result in a larger amount of the desired epoxide but instead led to the formation of byproducts **18** and **19**, presumably from **17**. Deprotonation of the hydroxyl group in **17** and epoxide rearrangement would generate **18**. Compound **19** can be formed by migration of the thioaryl group in **17** to C-2 with concomitant glycosylation with methoxide or methanol.

Putting a suitable protecting group on the C-4 hydroxyl group before introducing the oxirane functionality as illustrated in Scheme 3 solved this problem. First, **15** was treated with 2,2-dimethoxypropane and catalytic *p*-TsOH in acetone to form a 3,4-*O*-isopropylidene acetal intermediate, which upon allylation (allyl bromide, sodium hydride in DMF) and then acid hydrolysis (*p*-TsOH, methanol) gave the desired diol **20** in 80% overall yield. Subsequent heating of **20** with di-*n*-butyltin oxide in toluene and treatment with methanesulfonyl chloride led to selective sulfonylation of the C-3 hydroxyl group, yielding **21** in 91% yield.

Because the epoxide-forming reaction proceeds under strongly basic conditions, a base-stable protecting group was needed for O-4. Thus, reaction of **21** with *p*-methoxybenzyl chloride and sodium hydride gave the corresponding intermediate **22** in 95% yield. The allyl group in **22** was removed in 88% yield with $Pd(Ph_3P)_4$ in acetic acid to provide **23**. Finally, treatment of **23** with sodium hydride led to the formation of **9** in 79% yield

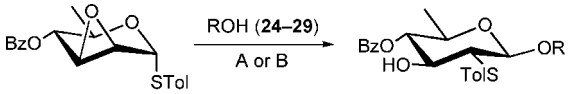
CHART 2



over two steps. The position of the epoxide was apparent from the chemical shift of C-2 ($\delta_C = 55.1$ ppm) and C-3 ($\delta_C = 52.0$ ppm) in the ^{13}C NMR spectrum. Further support came from the ^{1}H NMR spectrum, in which both H-2 ($\delta_H = 3.43$ ppm) and H-3 ($\delta_H = 3.24$ ppm) appeared as doublets with a $^3J = 3.1$ Hz.

Glycosylation Reactions. With the 6-deoxy-2,3-anhydrosugar donors in hand, their use in glycosylation reactions for the formation of 2,6-dideoxy-2-thiotolylpyranosides was investigated. On the basis of previous work in the furanoside series,[8] donor **8** was reacted with benzyl alcohol (**24**, Chart 2), *n*-octanol (**25**), cyclohexanol (**26**), or *tert*-butyl alcohol (**27**) in the presence of 10 equiv of 4 Å molecular sieves in dichloromethane at reflux. As detailed in Table 1, these reactions gave the corresponding

TABLE 1. Glycosylation of 2,3-Anhydro-D-rhamnopyranoside Donor 8

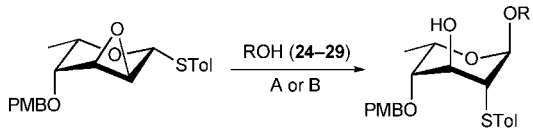


8 30–35

entry	donor	alcohol	activation[a]	product[b]	yield[c] (%)	β/α ratio[d]
1	**8**	**24**	A	**30**	91	β only
2	**8**	**25**	A	**31**	90	β only
3	**8**	**26**	A	**32**	90	β only
4	**8**	**27**	A	**33**	70	β only
5	**8**	**28**	B	**34**	84	β only
6	**8**	**29**	B	**35**	74	β only

[a] Method A: 4 Å MS (10 equiv), CH_2Cl_2, reflux. Method B: $Cu(OTf)_2$ (1 equiv), 4 Å MS (1 equiv, by weight), CH_2Cl_2, rt. [b] See Chart 2 for structures of products. [c] Isolated yield after chromatography. [d] Ratio determined by ^{1}H NMR spectroscopy after chromatography.

TABLE 2. Glycosylation of 2,3-Anhydro-6-deoxy-L-gulopyranoside Donor 9



9 36–41

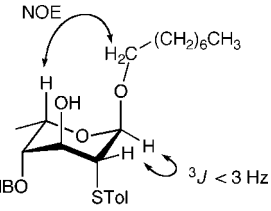
entry	donor	alcohol	activation[a]	product[b]	yield[c] (%)	β/α[d] ratio[d]
1	**9**	**24**	A	**36**	90	α only
2	**9**	**25**	A	**37**	88	α only
3	**9**	**26**	A	**38**	90	α only
4	**9**	**27**	A	**39**	79	α only
5	**9**	**29**	B	**40**	74	α only
6	**9**	**29**	B	**41**	73	α only

[a] Method A: 4 Å MS (10 equiv), CH_2Cl_2, reflux. Method B: $Cu(OTf)_2$ (1 equiv), 4 Å MS (1 equiv, by weight), CH_2Cl_2, rt. [b] See Chart 2 for structures of products. [c] Isolated yield after chromatography. [d] Ratio determined by ^{1}H NMR spectroscopy after chromatography.

β-glycosides (**30**−**33**, Chart 2) in high yield. The stereochemistry of the β-glycosides was determined from the $^3J_{H1,H2}$, which was approximately 10 Hz, as would be expected for a glycoside with the β-glucopyranosyl (1,2-trans) stereochemistry. Also shown in Table 1 is that when the less reactive carbohydrate alcohols (**28** and **29**) were used as the acceptor, 1 equiv of copper(II) triflate was needed to promote the glycosylation. These results are consistent with what was observed with the furanoside donors.[8] Under these conditions, the primary carbohydrate alcohol **28** produced the expected disaccharide **34** in 84% yield. The secondary carbohydrate alcohol acceptor **29** gave similar results, and the 2,6-dideoxy-2-thiotolyldisaccharide **35** was obtained in 74% yield. The β-glycoside was the only glycoside product detected in both cases.

Encouraged by the success in using **8** for the synthesis of 2,6-dideoxy-2-thiotolylglucopyranosides with excellent selectivity, we next explored the potential of the 2,3-anhydro-6-deoxy-L-gulopyranoside donor **9** in these reactions. As outlined in Table 2, applying the conditions used for **8** to **9** led to clean reactions. The products of the glycosylations (**36**−**41**) were obtained in 73−90% yield, and in all cases, the stereochemistry at the anomeric center was α.

The products had the 2,6-dideoxy-2-thioaryl-α-L-idopyranosyl stereochemistry. As was observed with thioglycoside **8**, in the reaction between **9** and the less reactive carbohydrate alcohols **28** and **29**, copper(II) triflate was used as the promotor. The lower yield in contrast to the reactions with the simple alcohols (Table 2, entries 1−4) is ascribed to donor hydrolysis under the reaction conditions. Similar byproducts were observed in the reactions with **8**.



37

FIGURE 1. Key NOE interactions and $^3J_{1,2}$ present in **37**.

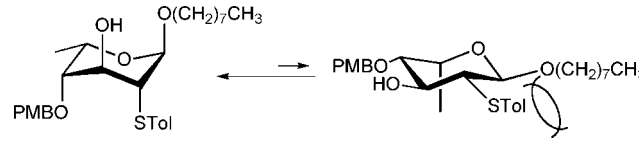


FIGURE 2. $_4C^1$ and $^4C_1$ conformer of **37**.

The products arising from **9** have the α-idopyranose stereochemistry, and these rings often adopt conformations different from the canonical chair forms, given that both chair conformers have an unfavorable orientation of substituents.[50,51] Thus, the analysis of the product structures was less straightforward than in those resulting from **8**, which given the β-glucopyranose stereochemistry, adopts a single ($^4C_1$) chair form. NMR studies on the products resulting from **9** gave clear evidence that the α-L-idopyranoside products adopt the $_4C^1$ conformation (Figure 1). In particular, the observed ^3J between H-1 and H-2 was smaller than 3 Hz in all cases (except **41**, where $J_{H1,H2} = 4.7$ Hz). In addition, the other ^3J on the ring were small (∼4 Hz) as would be expected for this conformer. Moreover, an NOE study on **37** showed a significant correlation between H-5 and the octyl group hydrogens immediately adjacent to the glycosidic oxygen (Figure 1).

All of these data support the proposal that the conformation of **37**, and the other products formed in these reactions, is predominantly the $_4C^1$ conformer, which has four axial substituents. Despite the axial orientation of the groups at C-1, C-2, C-3, and C-4, this conformer is presumably stabilized by the anomeric effect and by the minimization of a steric clash between the bulky aryl group at C-2 and the aglycon in the $^4C_1$ conformer (Figure 2). In the case of **41**, in which $J_{H1,H2} = 4.7$ Hz, it appears that the idopyranose ring adopts a conformation between the two idealized chair conformations or a mixture of a number of rapidly interconverting structures.

Desulfurization Reactions. After the glycosylation reactions, we explored the reductive desulfurization of the 2-thiotolyl glycosides to generate the 2-deoxy glycosides. In our earlier studies,[8] we had used hydrogenation over Raney nickel to achieve this transformation, but the yields were somewhat modest. Therefore, we explored the possibility of a radical reduction, and monosaccharide **31** and disaccharide **34** were chosen as representatives to evaluate this desulfurization method. In both cases, the reactions with tri-*n*-butyltin hydride and AIBN in toluene proceeded smoothly and gave the corresponding products in modest to good yield (Scheme 4). The structure of

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SCHEME 4

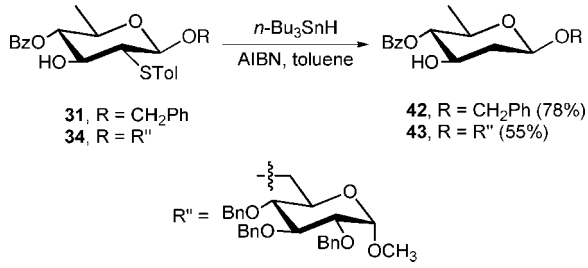
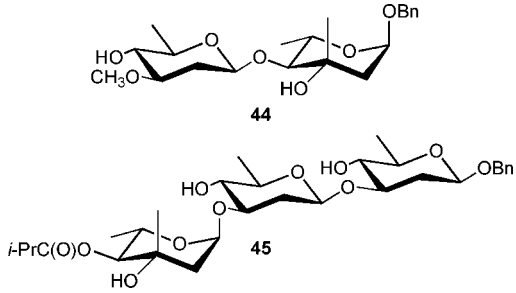


CHART 3



2-deoxy glycosides was clearly confirmed by the chemical shift of C-2 in compounds **42** (δ_C = 39.5 ppm) and **43** (δ_C = 39.3 ppm).

Application of the Methodology to Target Molecules. Once the methodology was developed, we applied it to the preparation of two naturally occurring 2,6-dideoxysugar-containing oligosaccharides. As targets we chose components of two natural products: the disaccharide moiety of apoptolidin[22] (**44**, Chart 3) and the trisaccharide unit in olivomycin A[25] (**45**). The deoxysugar residues in these and other antibiotics have customarily been considered as molecular components that affect only the pharmacokinetic properties of the drug. However, studies on olivomycin A[52] and apoptolidin[53] indicate that the presence of the carbohydrate moieties is key to the bioactivity of these natural products.

The disaccharide unit in apoptolidin (**44**) contains a β-glycoside linkage between two 2,6-dideoxysugar units. Several groups have reported studies toward the synthesis of this disaccharide, either alone or in the context of the synthesis of the natural product,[22,26−29] and our methodology is also well suited for its preparation. We envisioned that it could be produced from the 2,3-anhydro-D-rhamnopyranosyl donor **8** and the L-olivomycose acceptor **46** (Figure 3).

The preparation of **46** began from glycal **47**[54] (Scheme 5). Regioselective protection of the diol was accomplished by reaction with 1.1 equiv of acetic anhydride with DMAP at room temperature in pyridine giving an 84% yield of **48**. Subsequent reaction of the alcohol in **48** with *tert*-butyldimethylsilyl triflate and 2,6-lutidine provided **49** in 75% yield. NIS-promoted glycosylation between **48** and benzyl alcohol provided the α-glycoside **50** as a single anomer in 59% yield. The stereochemistry of anomeric center was established by the measurement of the $^1J_{C1,H1}$ (173.4 Hz), which clearly confirmed the stereochemistry of the glycosidic linkage as α.[55]

The deprotection of **50** proved to be more difficult than anticipated. Treatment with sodium methoxide in dichloromethane and methanol failed to remove the acetyl group; only the starting material was recovered. This problem was overcome by cleavage of the acetate group in **50** with DIBALH at −78 °C to give the corresponding alcohol **46** in 77% yield. Presumably, the bulky silyl group hinders the attack of methoxide on the acetyl carbonyl group, and the use of the smaller hydride ion circumvents this problem. The difficulty in converting **50** into **46** foreshadowed a problem in using this compound as a glycosyl acceptor. Attempts to glycosylate **46** with **8** using copper(II) triflate as the catalyst yielded the expected disaccharide only in trace amount (as confirmed by mass spectrometry). This failure is presumably because the presence of the bulky silyl protecting group next to the C-4 hydroxyl group in **46** decreases the nucleophilicity of the alcohol.

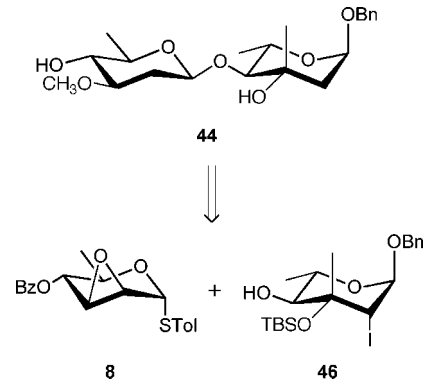


FIGURE 3. Retrosynthetic analysis of **44**.

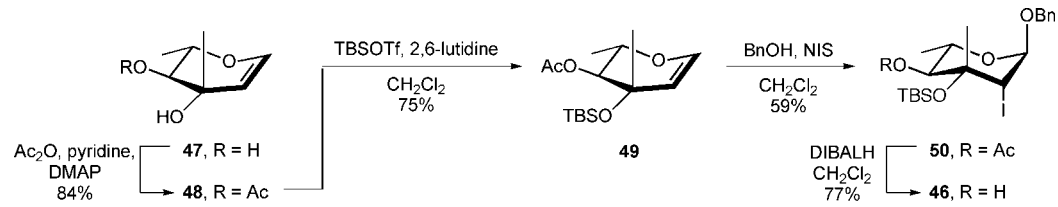
After realizing that the silyl group appeared to be suppressing the glycosylation, diol **51**, which has no TBS group, was prepared from glycal **47** in 86% yield by reaction with NIS and benzyl alcohol (Scheme 6). It was hoped that it would be possible to glycosylate the less hindered secondary alcohol in **51** in preference to the tertiary alcohol. Indeed, the glycosylation of **51** with **8** proceeded efficiently, affording two β-linked disaccharides **52** and **53** in an overall yield of 64%. Although the glycosylation had proceeded without difficulty, the reaction was not as regioselective as we had hoped and, frustratingly, the two regioisomers were inseparable. Nevertheless, using ^{1}H NMR spectroscopy, it was possible to establish that they were both β-glycosides, and that they were formed in a 3:1 ratio with **52** predominating.

This mixture of glycosides was then carried forward in the hope that it could be separated at a later step. Next, the introduction of a methyl ether on the free hydroxyl group was explored. To do this, methylation was attempted with trimethyloxonium tetrafluoroborate and a proton sponge in dichloromethane. These conditions were used to prevent removal or migration of the benzoyl protecting group, which we anticipated would occur under more usual methylation conditions involving the use of a base. Unfortunately, when the mixture of **52** and **53** was reacted under these conditions, no product was detected after stirring at room temperature overnight.

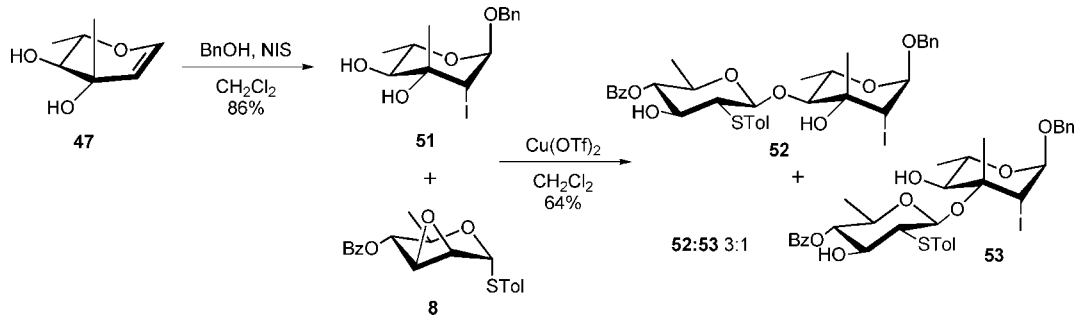
Faced with these failures, we re-evaluated the approach to the target. In the new route, we changed the structure of the glycosyl donor to include a sufficiently stable protecting group for O-4, one that could survive a methylation process under basic conditions. As a consequence, the benzoate ester in **8** was replaced with a benzyl ether. As shown in Scheme 7, this compound, **54**, could be prepared in a straightforward manner from **13** in 96% yield. In this new approach, we also changed the structure of the acceptor from the benzyl glycoside **51** to

(52) Daniel, P. T.; Koert, U.; Schuppan, J. *Angew. Chem., Int. Ed.* **2006**, *45*, 872–893.
(53) Sastry, M.; Patel, D. J. *Biochemistry* **1993**, *32*, 6588–6604.
(54) Jung, G.; Klemer, A. *Chem. Ber.* **1981**, *114*, 740–745.
(55) Bock, K.; Pedersen, C. *J. Chem. Soc., Perkin Trans. 2* **1974**, 293–297.

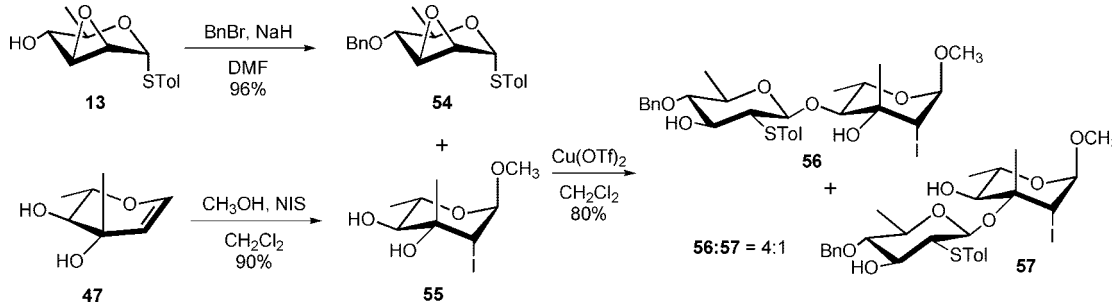
SCHEME 5



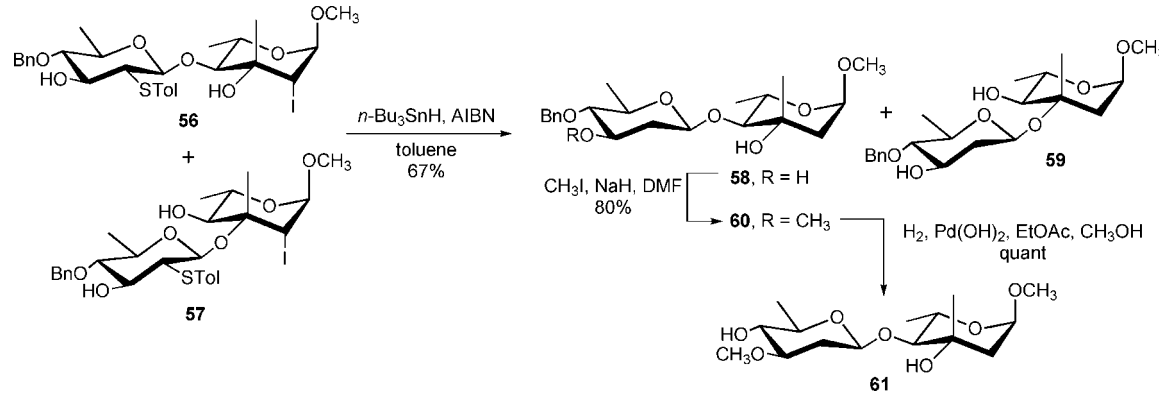
SCHEME 6



SCHEME 7



SCHEME 8



the methyl glycoside **55**, which was derived from **47** in 90% yield (Scheme 7). The reason for this change was due to fact that the benzyl glycoside moiety in **51** would not survive in the last deprotection step en route to the target molecule, hydrogenolysis.

Having synthesized both donor **54** and diol **55**, they were reacted to give two β-linked disaccharides **56** and **57** in a ratio of 4:1 in 80% total yield (Scheme 7). As was observed with the products arising from glycosylation of **51**, disaccharides **56** and **57** could not be separated and were then carried forward to the next step as a mixture. Treatment with tri-*n*-butyltin hydride and AIBN led to the simultaneous reduction of the C−I and C−S bonds in 67% yield (Scheme 8), and at this stage, the two disaccharides, **58** and **59**, could be separated and their structures determined. In the HMBC spectrum of the major isomer, a correlation between H-4 and C-1′ as well as C-4 and H-1′ indicated that the major disaccharide is the desired product **58**. The remaining steps were straightforward. First, a methyl group was introduced in 80% yield to the secondary hydroxyl group in **58** using standard conditions. That the methylation had occurred on O-3′ was apparent from the chemical shift of C-3 (80.8 ppm), which was further downfield from where this resonance occurred in the spectrum of **58**. The final step involved hydrogenolysis of the benzyl ether using palladium hydroxide on carbon as the catalyst to afford **61** in quantitative yield.

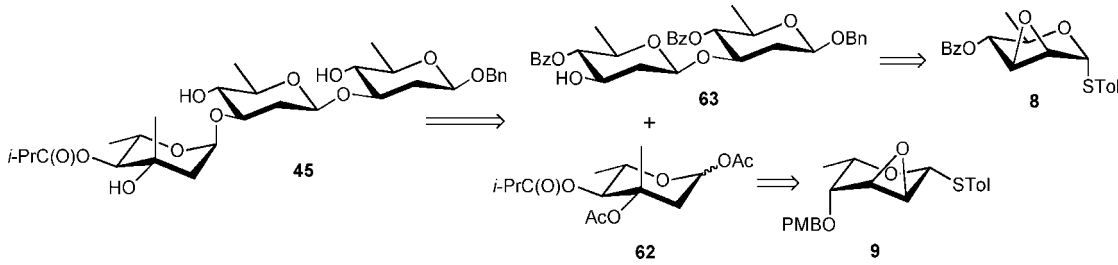
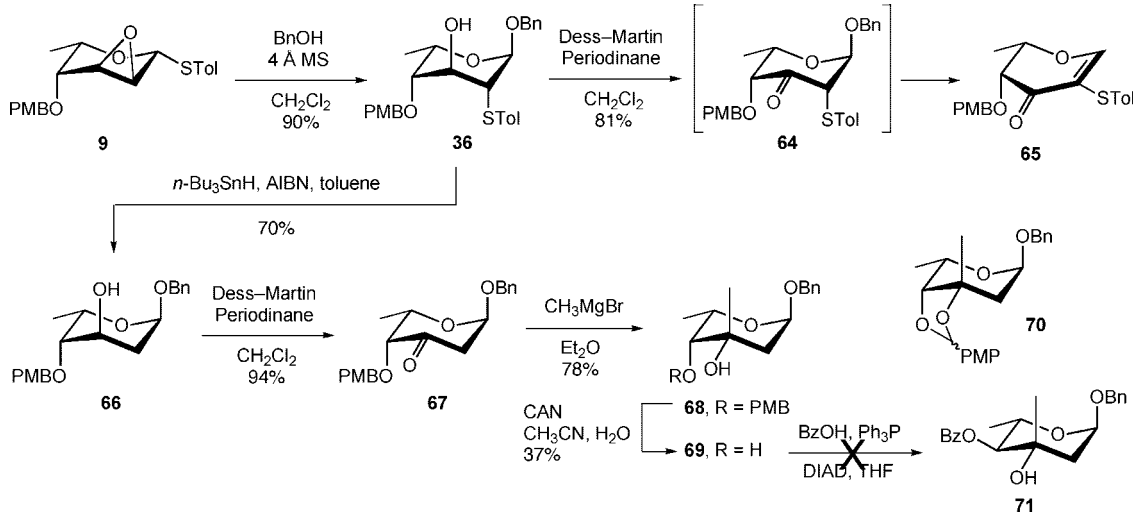


FIGURE 4. Retrosynthetic analysis of **45**.

SCHEME 9

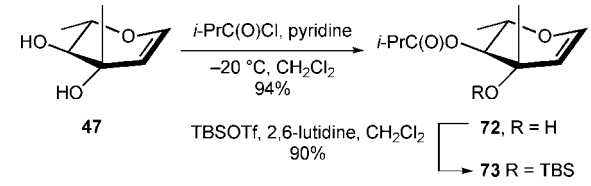


Having completed the synthesis of the disaccharide moiety in apoptolidin we turned our attention to the trisaccharide motif in olivomycin A. Other groups have previously synthesized this oligosaccharide, and we viewed our methodology as very well suited for its preparation.[30−34] The retrosynthetic analysis for the assembly of this trisaccharide, as its benzyl glycoside (**45**), is shown in Figure 4. We envisioned that glycosyl acetate **62** could be the precursor to the terminal α-L-olivomycose residue, whereas the two other β-linked residues could both be introduced using thioglycoside **8** by way of disaccharide **63**. Monosaccharide **62** could, in turn, be produced from epoxide **9**.

The synthesis of **62** began with benzyl 2-thiotolyl-α-L-idopyranoside **36**, which was obtained from **9** in 90% yield upon reaction with 4 Å molecular sieves and benzyl alcohol (Table 2 and Scheme 9). Oxidation of the hydroxyl group in compound **36** was achieved with Dess−Martin periodinane in dichloromethane. The resulting ketone **64** could be detected by TLC and by mass spectrometry of the crude reaction mixture. However, after chromatography, the elimination product **65** was isolated as the major product in 81% yield.

To overcome the elimination side reaction, the thiotolyl group was removed before the oxidation step. Thus, reaction of **36** with tri-*n*-butyltin hydride and AIBN yielded **66** in 70% yield. Oxidation of the hydroxyl group in **66** was accomplished with Dess−Martin periodinane in 94% yield without any elimination product being detected. Addition of a methyl group to ketone **67**, via methyl magnesium bromide, occurred at −78 °C to afford the desired product in 78% yield. The stereoselectivity of the methyl group addition to the top face of the ring was presumably due to steric hindrance from the *p*-methoxybenzyl ether at C-4. The C-3 stereochemistry of **68** was established by a TROESY experiment, by a strong NOE correlation between H-5 and methyl group at C-3. Having installed the branching methyl group, ceric ammonium nitrate was then used to cleave off the *p*-methoxybenzyl ether, which afforded under the reaction conditions diol **69** in 37% yield, together with the 3,4-*O*-*p*-methoxybenzylidene acetal byproduct **70** in 41% yield.

SCHEME 10

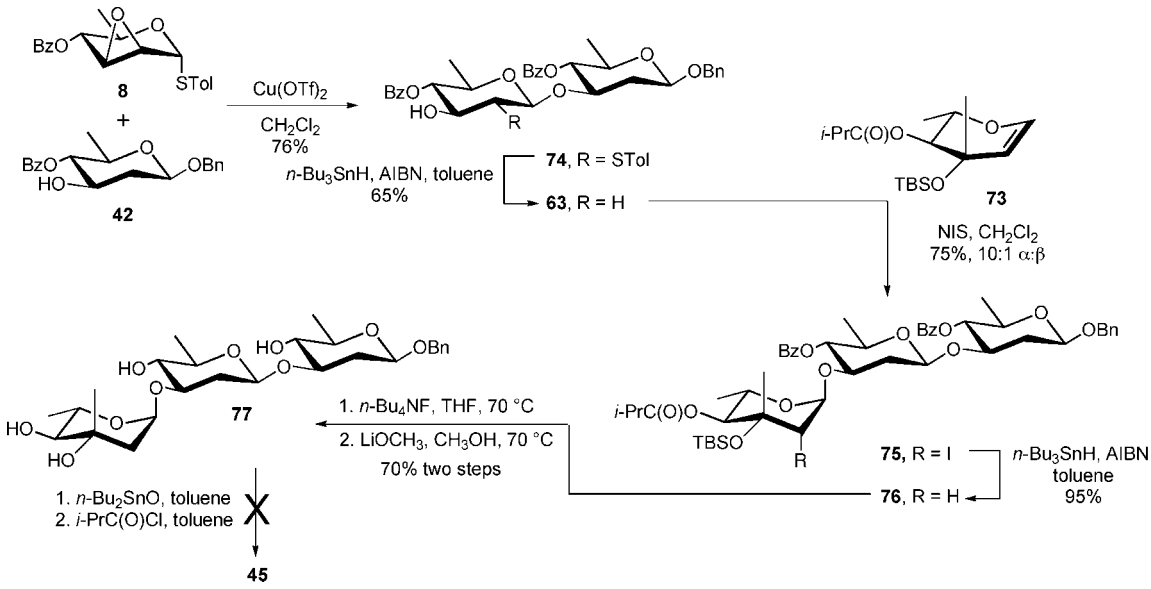


Different approaches were examined to convert the axial hydroxyl group at C-4 in **69** to equatorial stereochemistry. Standard Mitsunobu reaction conditions were applied to compound **69**, but none of the product, **71**, could be detected, even though the reaction mixture was heated to 50 °C for 16 h. Attempted inversion by way of an oxidation−reduction sequence also failed, as oxidation of the secondary alcohol with Dess−Martin periodinane was also unsuccessful and only unreacted starting alcohol was obtained.

After these failed attempts, a different glycosyl donor was synthesized and evaluated for the preparation of the target (Scheme 10). The secondary hydroxyl group in **47** was reacted with isobutyryl chloride and pyridine in dichloromethane at −20 °C to afford compound **72** selectively in 94% yield. Next, a *tert*-butyldimethylsilyl protecting group was installed at the tertiary hydroxyl group to afford **73** in 90% yield.

With a practical route to glycosyl donor **73** in place, we turned our attention to the synthesis of the olivomycin A trisaccharide (Scheme 11). First, alcohol **42** (see Chart 2) was reacted with

SCHEME 11



8 in the presence of copper (II) triflate. The product, **74**, was obtained in 76% yield. Next, using tri-*n*-butyltin hydride and AIBN, **74** was reduced to disaccharide **63** in 65% yield.[56] The construction of trisaccharide **75** proceeded smoothly through coupling of **63** with **73** in the presence of NIS. A 75% yield of the product was obtained in an α/β ratio of 10:1. The α-glycosidic linkage in **75** was established by the measurement of the coupling constant $^3J_{H1,H2}$ (3.6 Hz) as well as the $^1J_{C1,H1}$ (173.4 Hz), which clearly confirmed the α-stereochemistry.[55]

Once the trisaccharide was assembled, reaction of **75** with tri-*n*-butyltin hydride and AIBN resulted in cleavage of the carbon−iodine bond in 95% yield, giving **76**. However, selective removal of the TBS ether in **76** by TBAF or hydrogen fluoride−pyridine proved unsuccessful. Although we anticipated that it would be possible to remove the silyl ether in the presence of the hindered isobutyl ester, both were cleaved by reaction with TBAF at 70 °C for 16 h. The use of heat was required because at room temperature the reaction did not proceed at an appreciable rate. While cleavage of the isobutyl ester was efficient, removal of the benzoyl groups with sodium methoxide proved sluggish. The successful completion of the reaction required that the solution be heated at reflux in methanol and THF using lithium methoxide and lithium fluoride for 16 h. The fully deprotected product **77** was obtained in 70% yield over the two steps. With regard to the difficulty in removing the benzoate esters, it should mentioned that in the only total synthesis of olivomycin A reported to date,[34] much more labile chloroacetyl protecting groups were used at these positions. This choice was made on the basis of earlier work[57] on model systems demonstrating that acetate groups could not be removed in the presence of the isobutyl ester moiety. Thus, it appears that esters at these positions are resistant to nucleophilic attack.

In an attempt to synthesize the natural trisaccharide motif of olivomycin A, which contains the isobutyl ester at the C-4″ position, we attempted to install this group in **77**. Thus, this trisaccharide was heated with di-*n*-butyltin oxide in toluene for five hours, which we hoped would form a stannylidene acetal. However, upon subsequent addition of isobutyryl chloride no desired product (**45**) was observed, and efforts to install this ester were therefore abandoned.

In conclusion, we have described the first use of 2,3-anhydrosugars as glycosylating agents for the preparation of 2-deoxypyranosides. In the particular application described here, the methodology was used to assemble 2,6-dideoxysugar glycosides. Glycosylation of a panel of alcohols with **8** and **9** afforded 2-deoxy-2-thiotolyl glycoside products in generally excellent yields with exclusive stereoselectivity. The relationship between the anomeric group and that at C-3 is syn. The 2-thiotolyl group can be readily removed upon reaction with tri-*n*-butyltin hydride and AIBN to give the corresponding 2-deoxypyranosides. This method was successfully applied to the synthesis of the disaccharide unit in apoptolidin (**61**). The key step of this synthesis involved a highly stereoselective β-glycosylation of the secondary alcohol in **55** using **54** as the glycosyl donor. We also accomplished a convergent and stereoselective synthesis of the trisaccharide moiety of olivomycin A (**77**). A key feature of this synthesis was the construction of two β-glycosidic linkages using 2,3-anhydro-D-rhamnopyranosyl donor **8**, which afforded the products in high yield and stereoselectivity.

Experimental Section

***p*-Tolyl 2,3-Anhydro-4-*O*-benzoyl-1-thio-α-D-rhamnopyranoside (8).** Alcohol **13** (1.81 g, 7.18 mmol) was dissolved in CH_2Cl_2 (30 mL) and cooled to 0 °C, and then pyridine (2.9 mL, 35.91 mmol) and benzoyl chloride (1.25 mL, 10.77 mmol) were added. The reaction mixture was stirred for 4 h at rt and then concentrated. The resulting crude product was purified by chromatography (6:1 hexane−EtOAc) to give **8** (2.48 g, 97%) as a colorless oil: R_f 0.90 (2:1 hexane−EtOAc); $[\alpha]_D$ +368.8 (*c* 0.5, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$, δ_H) 8.14−8.11 (m, 2H, Ar), 7.66−7.59 (m, 1H, Ar), 7.53−7.40 (m, 4H, Ar), 7.19−7.14 (m, 2H, Ar), 5.65 (s, 1H, H-1), 4.98 (d, 1H, $J_{4,5}$ = 9.6 Hz, H-4), 4.36−4.26 (m, 1H, H-5), 3.43 (d, 1H, $J_{2,3}$ = 3.5 Hz, H-3), 3.41 (d, 1H, $J_{2,3}$ = 3.5 Hz, H-2), 2.36 (s, 3H, tolyl CH_3), 1.27 (d, 3H, $J_{5,6}$ = 6.2 Hz, 3 × H-6); ^{13}C NMR

(56) We also explored the possibility of producing a disaccharide containing two 2-thiotolyl groups by reaction of **30** with **8** (Table 1), thus providing a compound in which both C−S bonds could be reduced in a single step. Although the glycosylation reaction was successful, it was difficult to purify the product, and therefore, we adopted the approach outlined in Scheme 11, in which the thioaryl groups were removed in separate steps.

(57) Roush, W. R.; Briner, K.; Kesler, B. S.; Murphy, M.; Gustin, D. J. *J. Org. Chem.* **1996**, *61*, 6098–6099.

(125 MHz, $CDCl_3$, δ_C) 165.3 (*C*═O), 138.0 (Ar), 133.5 (2 × Ar), 132.4 (2 × Ar), 129.8 (2 × Ar), 129.7 (2 × Ar), 129.3 (Ar), 128.5 (2 × Ar), 83.8 (C-1), 69.2 (C-4), 64.0 (C-5), 53.9 (C-2), 50.8 (C-3), 21.0 (tolyl *C*H_3), 18.3 (C-6); HRMS (ESI) calcd (M + Na)$^+$ $C_{20}H_{20}O_4S$ 379.0975, found 379.0973.

***p*-Tolyl 2,3-Anhydro-6-deoxy-4-*O*-*p*-methoxybenzyl-1-thio-β-L-gulopyranoside (9).** To a solution of **23** (4.44 g, 9.49 mmol) in DMF (100 mL) at 0 °C was added sodium hydride (60% in mineral oil, 0.57 g, 14.25 mmol). The reaction mixture was stirred at rt for 5 h before it was quenched by the addition of water (10 mL). After concentration of the solution, it was diluted with CH_2Cl_2 (100 mL) and washed with water (2 × 100 mL). The organic layer was dried (Na_2SO_4), filtered, and concentrated, and the crude product was purified by chromatography (5:1 hexane−EtOAc) to give **9** (3.19 g, 90%) as a colorless oil: R_f 0.88 (2:1 hexane−EtOAc); $[\alpha]_D$ +14.7 (*c* 0.1, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$, δ_H) 7.54−7.48 (m, 2H, Ar), 7.32−7.27 (m, 2H, Ar), 7.07−7.01 (m, 2H, Ar), 6.94−6.88 (m, 2H, Ar), 5.08 (s, 1H, H-1), 4.60 (s, 2H, ArCH_2), 3.83 (s, 3H, ArOCH_3), 3.65 (dq, 1H, $J_{5,6}$ = 6.6 Hz, $J_{4,5}$ = 2.0 Hz, H-5), 3.54 (dd, 1H, $J_{3,4}$ = 2.2 Hz, $J_{4,5}$ = 2.0 Hz, H-4), 3.43 (d, 1H, $J_{2,3}$ = 3.1 Hz, H-2), 3.24 (dd, 1H, $J_{2,3}$ = 3.1 Hz, $J_{3,4}$ = 2.2 Hz, H-3), 2.31 (s, 3H, tolyl CH_3), 1.25 (d, 3H, $J_{5,6}$ = 6.6 Hz, 3 × H-6); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 159.4 (Ar), 137.6 (Ar), 132.4 (2 × Ar), 130.2 (Ar), 129.6 (2 × Ar), 129.5 (2 × Ar), 129.2 (Ar), 113.8 (2 × Ar), 80.6 (C-1), 72.8 (ArCH_2), 72.1 (C-4), 69.6 (C-5), 55.3 (ArOCH_3), 55.1 (C-2), 52.0 (C-3), 21.1 (tolyl *C*H_3), 16.4 (C-6); HRMS (ESI) calcd (M + Na)$^+$ $C_{21}H_{24}O_4S$ 395.1288, found 395.1289.

Methyl 2-*O*-Benzoyl-3-bromo-3,6-dideoxy-α-D-altropyranoside (11). To a solution of **10**[44] (4.77 g, 17.93 mmol) and $BaCO_3$ (7.08 g, 35.87 mmol) suspended in CCl_4 (200 mL) was added *N*-bromosuccinimide (4.47 g, 25.11 mmol). The mixture was heated at reflux for 2 h and then cooled to rt and filtered; the reaction flask was washed with CH_2Cl_2 (100 mL), and the solution was filtered. The combined filtrate was concentrated, and the resulting residue was purified by chromatography (4:1 hexane−EtOAc) to yield **11** (4.50 g, 73%) as a colorless oil: R_f 0.61 (2:1 hexane−EtOAc); $[\alpha]_D$ −13.9 (*c* 0.7, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$, δ_H) 8.05−8.00 (m, 2H, Ar), 7.60−7.54 (m, 1H, Ar), 7.46−7.40 (m, 2H, Ar), 5.50 (dd, 1H, $J_{2,3}$ = 3.7 Hz, $J_{1,2}$ = 1.4 Hz, H-2), 4.71 (br s, 1H, H-1), 4.51 (dd, 1H, $J_{2,3}$ = 3.7 Hz, $J_{3,4}$ = 3.7 Hz, H-3), 4.09−4.00 (m, 1H, H-5), 3.59 (dd, 1H, $J_{4,5}$ = 8.5 Hz, $J_{3,4}$ = 3.7 Hz, H-4), 3.41 (s, 3H, OCH_3), 2.38 (br s, 1H, 4-OH), 1.37 (d, 3H, $J_{5,6}$ = 6.4 Hz, 3 × H-6); ^{13}C NMR (100 MHz, $CDCl_3$, δ_C) 164.9 (*C*═O), 133.6 (Ar), 129.9 (2 × Ar), 129.0 (Ar), 128.5 (2 × Ar), 99.0 (C-1), 73.0 (C-2), 69.6 (C-4), 65.7 (C-5), 55.4 (OCH_3), 52.3 (C-3), 17.2 (C-6); HRMS (ESI) calcd (M + Na)$^+$ $C_{14}H_{17}O_5Br$ 367.0152, found 367.0154.

***p*-Tolyl 4-*O*-Acetyl-2-*O*-benzoyl-3-bromo-3,6-dideoxy-1-thio-α-D-altropyranoside (12).** To a solution of **11** (3.81 g, 11.08 mmol) in acetic anhydride (100 mL) was added concd H_2SO_4 (1 mL) at 0 °C. The reaction mixture was stirred for 2 h at 0 °C and then quenched by the addition of anhydrous $NaHCO_3$. The reaction mixture was filtered and the filtrate concentrated. The resulting oil was dissolved in CH_2Cl_2 (100 mL) and washed successively with water (50 mL) and satd aq $NaHCO_3$ (50 mL). The organic phase was dried (Na_2SO_4), filtered, and concentrated, and the crude product was purified by chromatography (4:1 hexane−EtOAc) to give 1,4-di-*O*-acetyl-2-*O*-benzoyl-3-bromo-3,6-dideoxy-D-altropyranose (3.0 g, 65%) as a colorless oil: R_f 0.65 (2:1 hexane−EtOAc). The material was used immediately in the next step without further characterization. To a solution of *p*-thiocresol (1.36 g, 10.97 mmol) and 1,4-di-*O*-acetyl-2-*O*-benzoyl-3-bromo-3,6-dideoxy-D-altropyranose (3.78 g, 9.13 mmol) in CH_2Cl_2 (100 mL) at 0 °C was added BF_3·OEt_2 (3.47 mL, 27.39 mmol) dropwise over 10 min. The reaction mixture was stirred for 5 h at 0 °C and was then diluted with CH_2Cl_2 (50 mL) and washed with satd aq $NaHCO_3$ solution (100 mL) and brine (100 mL). The organic layer was dried (Na_2SO_4), filtered, and concentrated, and the crude product was purified by chromatography (4:1 hexane−EtOAc) to yield **12** (4.06 g, 93%) as a colorless oil: R_f 0.85 (2:1 hexane−EtOAc); $[\alpha]_D$ +64.5 (*c* 0.3, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$, δ_H) 8.08−8.03 (m, 2H, Ar), 7.62−7.57 (m, 1H, Ar), 7.49−7.38 (m, 4H, Ar), 7.14−7.09 (m, 2H, Ar), 5.71 (dd, 1H, $J_{2,3}$ = 4.7 Hz, $J_{1,2}$ = 2.9 Hz, H-2), 5.35 (d, 1H, $J_{1,2}$ = 2.9 Hz, H-1), 4.98 (dd, 1H, $J_{4,5}$ = 7.7 Hz, $J_{3,4}$ = 3.8 Hz, H-4), 4.70−4.62 (m, 2H, H-3, H-5), 2.33 (s, 3H, tolyl CH_3), 2.16 (s, 3H, CH_3C═O), 1.36 (d, 3H, $J_{6,5}$ = 6.5 Hz, 3 × H-6); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 169.9 (*C*═O), 164.8 (*C*═O), 138.0 (Ar), 133.6 (Ar), 132.3 (2 × Ar), 131.8 (Ar), 129.9 (2 × Ar), 129.8 (2 × Ar), 129.1 (Ar), 128.5 (2 × Ar), 85.9 (C-1), 74.3 (C-2), 71.7 (C-4), 65.9 (C-5), 47.1 (C-3), 21.1 (tolyl *C*H_3), 20.9 (*C*H_3C═O), 16.7 (C-6); HRMS (ESI) calcd (M + Na)$^+$ $C_{22}H_{23}O_5SBr$ 501.0342, found 501.0340.

***p*-Tolyl 2,3-Anhydro-1-thio-α-D-rhamnopyranoside (13).** To a solution of **12** (4.0 g, 8.33 mmol) in 1:1 CH_2Cl_2−CH_3OH (160 mL) was added 1 M $NaOCH_3$ in CH_3OH (16 mL). After being stirred for 2 h at rt, the reaction mixture was neutralized with Amberlite IR-120 H^+ resin, filtered, and concentrated. The resulting oil was purified by chromatography (4:1 hexane−EtOAc) to afford **13** (1.81 g, 86%) as a white solid: R_f 0.29 (4:1 hexane−EtOAc); $[\alpha]_D$ +332.1 (*c* 0.4, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$, δ_H) 7.43−7.37 (m, 2H, Ar), 7.16−7.11 (m, 2H, Ar), 5.57 (s, 1H, H-1), 3.95−3.86 (m, 1H, H-5), 3.62 (d, 1H, $J_{4,5}$ = 8.9 Hz, H-4), 3.41 (d, 1H, $J_{2,3}$ = 3.6 Hz, H-3), 3.34 (d, 1H, $J_{2,3}$ = 3.6 Hz, H-2), 2.34 (s, 3H, tolyl CH_3), 2.27 (br s, 1H, 4-OH), 1.28 (d, 3H, $J_{5,6}$ = 6.2 Hz, 3 × H-6); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 137.9 (Ar), 132.4 (2 × Ar), 130.0 (Ar), 129.9 (2 × Ar), 83.8 (C-1), 68.2 (C-4), 66.8 (C-5), 56.0 (C-2), 51.5 (C-3), 21.1 (tolyl *C*H_3), 18.4 (C-6); HRMS (ESI) calcd (M + Na)$^+$ $C_{13}H_{16}O_3S$ 275.0712, found 275.0715.

***p*-Tolyl 1-Thio-β-L-fucopyranoside (15).** To a solution of **14**[49] (10 g, 30.1 mmol) and *p*-thiocresol (4.48 g, 36.1 mmol) in CH_2Cl_2 (200 mL) at 0 °C was added BF_3·OEt_2 (4.57 mL, 36.1 mmol) dropwise over 10 min. The reaction mixture was stirred for 5 h at 0 °C, diluted with CH_2Cl_2 (100 mL), and washed with satd aq $NaHCO_3$ solution (100 mL) and brine (100 mL). The organic layer was dried with Na_2SO_4, filtered, and concentrated. The resulting residue was dissolved in 1:1 CH_2Cl_2−CH_3OH (200 mL), and 1 M $NaOCH_3$ in CH_3OH (30 mL) was added. After being stirred for 15 h at rt, the reaction mixture was neutralized with Amberlite IR-120 H^+ resin, filtered, and concentrated. The resulting oil was purified by chromatography (10:1 CH_2Cl_2−CH_3OH) to afford compound **15** (5.94 g, 73%) as a white amorphous solid: R_f 0.39 (10:1 CH_2Cl_2−CH_3OH); $[\alpha]_D$ +41.3 (*c*, 0.2 CH_3OH); ^{1}H NMR (500 MHz, CD_3OD, δ_H) 7.43−7.38 (m, 2H, Ar), 7.13−7.08 (m, 2H, Ar), 4.46 (d, 1H, $J_{1,2}$ = 9.4 Hz, H-1), 3.65−3.58 (m, 2H, H-4, H-5), 3.52 (dd, 1H, $J_{1,2}$ = 9.4 Hz, $J_{2,3}$ = 9.3 Hz, H-2), 3.46 (dd, 1H, $J_{2,3}$ = 9.3 Hz, $J_{3,4}$ = 3.3 Hz, H-3), 2.30 (s, 3H, tolyl CH_3), 1.25 (d, 3H, $J_{5,6}$ = 6.5 Hz, 3 × H-6); ^{13}C NMR (125 MHz, CD_3OD, δ_C) 138.5 (Ar), 133.0 (2 × Ar), 132.1 (Ar), 130.5 (2 × Ar), 90.4 (C-1), 76.5 (C-3), 76.0 (C-4), 73.2 (C-5), 70.9 (C-2), 21.1 (tolyl *C*H_3), 17.0 (C-6); HRMS (ESI) calcd (M + Na)$^+$ $C_{13}H_{18}O_4S$ 293.0818, found 293.0818.

***p*-Tolyl 3-*O*-Methanesulfonyl-1-thio-β-L-fucopyranoside (16).** Compound **15** (3.5 g, 13.0 mmol) was dissolved in toluene (100 mL), and *n*-Bu_2SnO (3.55 g, 14.3 mmol) was added. The reaction mixture was heated to 105 °C, stirred for 4 h, and then cooled to room temperature before MsCl (5.03 mL, 65.0 mol) was added. The reaction mixture was stirred at rt for 16 h and concentrated, and the crude product was purified by chromatography (2:1 hexane−EtOAc) to give **16** (4.30 g, 95%) as a white solid: R_f 0.21 (1:1 hexane−EtOAc); $[\alpha]_D$ +18.6 (*c*, 0.2 CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$, δ_H) 7.48−7.44 (m, 2H, Ar), 7.17−7.13 (m, 2H, Ar), 4.56 (dd, 1H, $J_{2,3}$ = 9.5 Hz, $J_{3,4}$ = 3.2 Hz, H-3), 4.44 (d, 1H, $J_{1,2}$ = 9.5 Hz, H-1), 3.97 (br s, 1H, H-4), 3.81 (dd, 1H, $J_{1,2}$ = $J_{2,3}$ = 9.5 Hz, H-2), 3.70 (q, 1H, $J_{5,6}$ = 6.4 Hz, H-5), 3.16 (s, 3H, OSO_2CH_3), 2.65 (br s, 1H, OH), 2.35 (s, 3H, tolyl CH_3), 2.23 (br s, 1H, OH), 1.36 (d, 3H, $J_{5,6}$ = 6.4 Hz, 3 × H-6); ^{13}C NMR (125 MHz, CD_3Cl, δ_C) 138.9 (Ar), 133.5 (2 × Ar), 129.9 (2 × Ar),

127.3 (Ar), 88.8 (C-1), 84.4 (C-3), 74.6 (C-5), 71.4 (C-4), 66.9 (C-2), 38.6 (OSO_2CH_3), 21.2 (tolyl CH_3), 16.5 (C-6); HRMS (ESI) calcd $(M + Na)^+$ $C_{14}H_{20}O_6S_2$ 371.0594, found 371.0596.

***p*-Tolyl 2-*O*-Allyl-1-thio-β-L-fucopyranoside (20).** To a solution of **15** (4.57 g, 16.90 mmol) in acetone (150 mL) were added 2,2-dimethoxypropane (4.16 mL, 33.80 mmol) and *p*-TSA (0.30 g, 1.69 mmol). After being stirred for 16 h at rt, the reaction mixture was neutralized with Et_3N (5 mL) and concentrated. The resulting oil was dissolved in DMF (20 mL), and allyl bromide (2.83 mL, 32.70 mmol) was added. To this solution was added sodium hydride (60% in mineral oil, 1.31 g, 32.70 mmol) at 0 °C. The reaction mixture was stirred at rt for 5 h before it was quenched by the addition of water (10 mL). The mixture was concentrated and then diluted with CH_2Cl_2 (100 mL) before being washed with water (2 × 100 mL). The organic layer was dried (Na_2SO_4), filtered, and concentrated. The resulting oil was dissolved in CH_3OH (150 mL), and *p*-TsOH (0.30 g, 1.69 mmol) was added. After being stirred for 16 h at rt, the reaction mixture was neutralized with Et_3N (5 mL) and concentrated. The crude product was purified by chromatography (2:1 hexane−EtOAc) to give **20** (4.20 g, 80%) as a white solid: R_f 0.19 (2:1 hexane−EtOAc); $[\alpha]_D$ +4.8 (*c* 0.1, CH_2Cl_2); ^1H NMR (500 MHz, $CDCl_3$, δ_H) 7.48−7.43 (m, 2H, Ar), 7.15−7.09 (m, 2H, Ar), 6.04−5.94 (m, 1H, CH_2=C*H*CH_2O), 5.33−5.19 (m, 2H, 2 × CH_2=$CHCH_2O$), 4.48 (d, 1H, $J_{1,2}$ = 9.6 Hz, H-1), 4.47−4.41 (m, 1H, CH_2=CHCH_2O), 4.24−4.18 (m, 1H, CH_2=CHCH_2O), 3.76 (br s, 1H, H-4), 3.65−3.58 (m, 2H, H-3, H-5), 3.40 (dd, 1H, $J_{1,2}$ = 9.6 Hz, $J_{2,3}$ = 9.1 Hz, H-2), 2.61 (br s, 1H, OH), 2.34 (3H, tolyl CH_3), 2.09 (br s, 1H, OH), 1.35 (d, 3H, $J_{5,6}$ = 6.5 Hz, 3 × H-6); ^{13}C NMR (125 MHz, CD_3Cl, δ_C) 137.7 (Ar), 134.7 (CH_2=*C*HCH_2O), 132.5 (2 × Ar), 130.0 (Ar), 129.6 (2 × Ar), 117.8 (*C*H_2=$CHCH_2O$), 87.7 (C-1), 78.0 (C-2), 75.3 (C-5), 74.4 (C-3), 74.2 (CH_2=CH*C*H_2O), 71.8 (C-4), 21.1 (tolyl *C*H_3), 16.6 (C-6); HRMS (ESI) calcd $(M + Na)^+$ $C_{16}H_{22}O_4S$ 333.1131, found 333.1129.

***p*-Tolyl 2-*O*-Allyl-3-*O*-methanesulfonyl-1-thio-β-L-fucopyranoside (21).** Diol **20** (4.11 g, 13.24 mmol) was dissolved in toluene (100 mL), and *n*-Bu_2SnO (3.96 g, 15.91 mmol) was added. The reaction mixture was heated to 105 °C, stirred for 4 h, and then cooled to rt before MsCl (5.13 mL, 66.2 mmol) was added. The reaction mixture was stirred at rt for 16 h and then concentrated. The crude product was purified by chromatography (3:1 hexane−EtOAc) to give **21** (4.68 g, 91%) as a colorless oil: R_f 0.49 (2:1 hexane−EtOAc); $[\alpha]_D$ +0.4 (*c* 0.2, CH_2Cl_2); ^1H NMR (500 MHz, $CDCl_3$, δ_H) 7.48−7.44 (m, 2H, Ar), 7.15−7.11 (m, 2H, Ar), 5.98−5.89 (m, 1H, CH_2=C*H*CH_2O), 5.30−5.16 (m, 2H, CH_2=$CHCH_2O$), 4.53−4.48 (m, 2H, H-1, H-3), 4.47−4.41 (m, 1H, allyl CH_2=CHCH_2O), 4.17−4.11 (m, 1H, CH_2=CHCH_2O), 4.00 (br s, 1H, H-4), 3.67−3.61 (m, 2H, H-2, H-5), 3.09 (s, 3H, OSO_2CH_3), 2.34 (s, 3H, tolyl CH_3), 2.00 (br s, 1H, 4-OH), 1.34 (d, 3H, $J_{5,6}$ = 6.5 Hz, 3 × H-6); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 138.1 (Ar), 134.1 (CH_2=*C*HCH_2O), 132.7 (2 × Ar), 129.8 (2 × Ar), 129.4 (Ar), 117.7 (*C*H_2=$CHCH_2O$), 88.1 (C-1), 84.8 (C-3), 74.4 (C-2), 74.3 (CH_2=CH*C*H_2O), 74.1 (C-5), 71.3 (C-4), 38.5 (OSO_2CH_3), 21.1 (tolyl *C*H_3), 16.5 (C-6); HRMS (ESI) calcd $(M + Na)^+$ $C_{17}H_{24}O_6S_2$ 411.0907, found 411.0907.

***p*-Tolyl 2-*O*-Allyl-3-*O*-methanesulfonyl-4-*O*-*p*-methoxybenzyl-1-thio-β-L-fucopyranoside (22).** Alcohol **21** (9.43 g, 24.30 mmol) was dissolved in DMF (100 mL), and *p*-methoxybenzyl chloride (3.95 mL, 29.16 mmol) was added. This solution was cooled to 0 °C, and sodium hydride (60% in mineral oil, 1.17 g, 29.16 mmol) was added. The reaction mixture was stirred at rt for 5 h before it was quenched by the addition of water (10 mL). The solution was concentrated, diluted with CH_2Cl_2 (100 mL), and washed with water (2 × 100 mL). The organic layer was dried (Na_2SO_4), filtered, and concentrated, and the resulting crude product was purified by chromatography (5:1 hexane−EtOAc) to give **22** (12.35 g, 95%) as a colorless oil: R_f 0.70 (2:1 hexane−EtOAc); $[\alpha]_D$ −4.4 (*c* 0.4, CH_2Cl_2); ^1H NMR (500 MHz, $CDCl_3$, δ_H) 7.47−7.42 (m, 2H, Ar), 7.36−7.31 (m, 2H, Ar), 7.07−7.02 (m, 2H, Ar), 6.93−6.86 (m, 2H, Ar), 5.99−5.86 (m, 1H, CH_2=C*H*CH_2O), 5.28−5.15 (m, 2H, CH_2=$CHCH_2O$), 4.89 (d, 1H, *J* = 11.1 Hz, ArCH_2), 4.63 (d, 1H, *J* = 11.1 Hz, ArCH_2), 4.50 (dd, 1H, $J_{3,4}$ = 9.5 Hz, $J_{2,3}$ = 3.0 Hz, H-3), 4.47 (d, 1H, $J_{1,2}$ = 9.7 Hz, H-1), 4.46−4.39 (m, 1H, CH_2=CHCH_2O), 4.15−4.08 (m, 1H, CH_2=CHCH_2O), 3.83−3.74 (m, 5H, 3 × PhOCH_3, H-2, H-4), 3.54 (dd, 1H, $J_{4,5}$ = 6.4 Hz, $J_{5,6}$ = 6.4 Hz, H-5), 3.07 (s, 3H, OSO_2CH_3), 2.32 (s, 3H, tolyl CH_3), 1.18 (d, 3H, $J_{5,6}$ = 6.4 Hz, 3 × H-6); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 159.3 (Ar), 137.6 (Ar), 134.2 (CH_2=*C*HCH_2O), 132.2 (2 × Ar), 130.1 (2 × Ar), 130.0 (Ar), 129.9 (Ar), 129.6 (2 × Ar), 117.5 (*C*H_2=$CHCH_2O$), 113.6 (2 × Ar), 88.0 (C-1), 85.2 (C-3), 77.5 (C-2), 74.9 (ArCH_2), 74.6 (C-4), 74.3 (C-5), 74.1 (CH_2=CH*C*H_2O), 55.3 (ArO*C*H_3), 38.0 (OSO_2CH_3), 21.1 (tolyl *C*H_3), 16.8 (C-6); HRMS (ESI) calcd $(M + Na)^+$ $C_{25}H_{32}O_7S_2$ 531.1482, found 531.1478.

***p*-Tolyl 3-*O*-Methanesulfonyl-4-*O*-*p*-methoxybenzyl-1-thio-β-L-fucopyranoside (23).** To a solution of **22** (5.49 g, 10.81 mmol) in AcOH (100 mL) at rt was added $Pd(PPh_3)_4$ (1.25 g, 1.08 mmol). The reaction mixture was stirred at rt for 48 h and then diluted with CH_2Cl_2 (100 mL). The resulting solution was then washed with water (2 × 100 mL) and satd aq $NaHCO_3$ (2 × 100 mL). The organic layer was dried (Na_2SO_4), filtered, and concentrated, and the resulting crude product was purified by chromatography (3:1 hexane−EtOAc) to give **23** (4.44 g, 88%) as a colorless oil: R_f 0.40 (2:1 hexane−EtOAc); $[\alpha]_D$ +6.8 (*c* 0.9, CH_2Cl_2); ^1H NMR (500 MHz, $CDCl_3$, δ_H) 7.46−7.42 (m, 2H, Ar), 7.30−7.26 (m, 2H, Ar), 7.09−7.06 (m, 2H, Ar), 6.90−6.84 (m, 2H, Ar), 4.85 (d, 1H, *J* = 11.2 Hz, ArCH_2), 4.60 (d, 1H, *J* = 11.2 Hz, ArCH_2), 4.59 (dd, 1H, $J_{2,3}$ = 9.5 Hz, $J_{3,4}$ = 3.0 Hz, H-3), 4.42 (d, 1H, $J_{1,2}$ = 9.5 Hz, H-1), 3.94 (dd, 1H, $J_{1,2}$ = 9.5 Hz, $J_{2,3}$ = 9.5 Hz, H-2), 3.82 (s, 3H, ArOCH_3), 3.76 (d, 1H, $J_{4,5}$ = 3.0 Hz, H-4), 3.63−3.57 (m, 1H, H-5), 3.13 (s, 3H, OSO_2CH_3), 2.56 (br s, 1H, 2-OH), 2.33 (s, 3H, tolyl CH_3), 1.22 (d, 3H, $J_{5,6}$ = 6.4 Hz, 3 × H-6); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 159.3 (Ar), 138.3 (Ar), 132.9 (2 × Ar), 130.0 (Ar), 129.9 (2 × Ar), 129.8 (2 × Ar), 127.9 (Ar), 113.6 (2 × Ar), 89.1 (C-1), 84.7 (C-3), 77.5 (C-4), 74.9 (ArCH_2), 74.8 (C-5), 67.3 (C-2), 55.3 (ArO*C*H_3), 38.3 (-OSO_2CH_3), 21.2 (tolyl *C*H_3), 16.8 (C-6); HRMS (ESI) calcd $(M + Na)^+$ $C_{22}H_{28}O_7S_2$ 491.1169, found 491.1167.

Methyl 4-*O*-Benzyl-2,6-dideoxy-2-*p*-tolylthio-β-D-glucopyranosyl-(1→4)-2,6-dideoxy-2-iodo-3-*C*-methyl-α-L-mannopyranoside (56) and Methyl 2,6-Dideoxy-4-*O*-benzyl-2-*p*-tolylthio-β-D-glucopyranosyl-(1→3)-2,6-dideoxy-2-iodo-3-*C*-methyl-α-L-mannopyranoside (57). To a solution of **54** (253 mg, 0.74 mmol) and **55** (186 mg, 0.62 mmol) in CH_2Cl_2 (25 mL) was added crushed 4 Å molecular sieves (500 mg). After the mixture was stirred at rt for 30 min, $Cu(OTf)_2$ (223 mg, 0.62 mmol) was added, and the reaction mixture was stirred for an additional 2 h. After neutralization with Et_3N, the reaction mixture was concentrated to give a crude residue that was purified by chromatography (4:1 hexane−EtOAc) to afford an inseparable 4:1 ratio of **56** and **57** (317 mg, 80%) as a colorless oil: R_f 0.70 (2:1 hexane−EtOAc). This material was not further characterized but was carried on to the next step.

Methyl 4-*O*-Benzyl-2,6-dideoxy-β-D-*arabino*-hexopyranosyl-(1→4)-2,6-dideoxy-3-*C*-methyl-α-L-*arabino*-hexopyranoside (58) and Methyl 2,6-Dideoxy-4-*O*-benzyl-β-D-*arabino*-hexopyranosyl-(1→3)-2,6-dideoxy-3-*C*-methyl-α-L-*arabino*-hexopyranoside (59). The mixture of **56** and **57** (340 mg, 0.53 mmol) was dissolved in toluene (30 mL), and *n*-Bu_3SnH (2.84 mL, 10.55 mmol) was added. The solution was heated at 105 °C, and then AIBN (866 mg, 5.27 mmol) dissolved in toluene (10 mL) was added in portions over 1 h. The solution was stirred for an additional 1 h at 105 °C and then cooled to rt. The solvent was removed, and the residue was purified by chromatography (2:1 hexane−EtOAc) to afford **58** (112 mg, 54%) and **59** (28 mg, 13%) both as colorless oils. Data for **58**: R_f 0.25 (1:1 hexane−EtOAc); $[\alpha]_D$ −106.3 (*c* 1.1, CH_2Cl_2); ^1H NMR (500 MHz, $CDCl_3$, δ_H) 7.39−7.29 (m, 5H, Ar), 4.82 (dd, 1H, $J_{1',2ax'}$ = 9.9 Hz, $J_{1',2eq'}$ = 2.0 Hz, H-1′), 4.77 (d, 1H, *J* = 11.4 Hz, ArCH_2), 4.72−4.67 (m, 2H, 1 × ArCH_2, H-1), 3.74−3.66 (m,

1H, H-3′), 3.62 (dq, 1H, $J_{4,5}$ = 9.5 Hz, $J_{5,6}$ = 6.2 Hz, H-5), 3.41−3.33 (m, 2H, H-4, H-5′), 3.30 (s, 3H, OCH_3), 2.98 (dd, 1H, $J_{3′,4′}$ = 9.0 Hz, $J_{4′,5′}$ = 9.0 Hz, H-4′), 2.44 (s, 1H, OH), 2.22−2.16 (m, 2H, OH, H-2eq′), 1.96 (dd, 1H, $J_{2eq,2ax}$ = 13.6 Hz, $J_{1,2eq}$ =1.4 Hz, H-2eq), 1.85 (dd, 1H, $J_{2eq,2ax}$ = 13.6 Hz, $J_{1,2ax}$ = 4.5 Hz, H-2ax), 1.69 (ddd, 1H, $J_{2eq′,2ax′}$ = 12.0 Hz, $J_{2ax′,3′}$ = 12.0 Hz, $J_{1′,2′ax}$ = 9.9 Hz, H-2ax′), 1.38−1.35 (m, 6H, 3 × H-6′, 3 × H-7), 1.28 (d, 3H, $J_{5,6}$ = 6.2 Hz, 3 × H-6); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 138.2 (Ar), 128.7 (2 × Ar), 128.1 (Ar), 127.9 (2 × Ar), 99.7 (C-1′), 98.2 (C-1), 85.8 (C-4′), 84.0 (C-4), 75.1 (ArCH_2), 71.8 (C-3), 71.5 (C-5′), 71.3 (C-3′), 65.9 (C-5), 54.7 (OCH_3), 43.2 (C-2), 38.3 (C-2′), 23.4 (C-7), 18.4 (C-6′), 18.2 (C-6); HRMS (ESI) calcd (M + Na)$^+$ $C_{21}H_{32}O_7$ 419.2040, found 419.2041. Data for **59**: R_f 0.30 (1:1 hexane−EtOAc); $[\alpha]_D$ −81.1 (*c* 3.6, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$, δ_H) 7.40−7.30 (m, 5H, Ar), 4.79−4.67 (m, 4H, 2 × PhCH_2, H-1′, H-1), 3.73−3.67 (m, 2H, H-5, H-3′), 3.39−3.34 (m, 2H, H-4, H-5′), 3.31 (s, 3H, OCH_3), 2.99 (dd, 1H, $J_{3′,4′}$ = 8.9 Hz, $J_{4′,5′}$ = 8.9 Hz, H-4′), 2.96 (d, 1H, $J_{OH,4}$ = 2.9 Hz, 4-OH), 2.17 (d, 1H, $J_{OH,3′}$ = 3.4 Hz, 3′-OH), 2.06−2.01 (m, 1H, H-2eq′), 1.98−1.93 (m, 1H, H-2eq), 1.92−1.89 (m, 1H, H-2ax), 1.72−1.64 (m, 1H, H-2ax′), 1.42 (s, 3H, 3 × H-7), 1.35 (d, 3H, $J_{5′,6′}$ = 6.2 Hz, 3 × H-6′), 1.31 (d, 3H, $J_{5,6}$ = 6.1 Hz, 3 × H-6); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 138.1 (Ar), 128.7 (2 × Ar), 128.1 (Ar), 127.9 (2 × Ar), 98.4 (C-1′), 92.8 (C-1), 85.5 (C-4′), 78.9 (C-3), 76.0 (C-5′), 75.2 (ArCH_2), 71.33 (C-3′), 71.27 (C-4), 66.2 (C-5), 54.8 (OCH_3), 40.0 (C-2), 39.7 (C-2′), 20.5 (C-7), 18.4 (C-6′), 18.3 (C-6); HRMS (ESI) calcd (M + Na)$^+$ $C_{21}H_{32}O_7$ 419.2040, found 419.2042.

Methyl 4-*O*-Benzyl-2,6-dideoxy-3-*O*-methyl-β-D-*arabino*-hexopyranosyl-(1→4)-2,6-dideoxy-3-*C*-methyl-α-L-*arabino*-hexopyranoside (60). Diol **58** (90 mg, 0.23 mmol) was dissolved in DMF (10 mL), CH_3I (15.6 μL, 0.25 mmol) was added, and the mixture was cooled to 0 °C. To this solution was added sodium hydride (60% in mineral oil, 14 mg, 0.34 mmol). The reaction mixture was stirred at rt for 5 h before it was quenched by the addition of CH_3OH (5 mL). After concentration of the reaction mixture, it was diluted with CH_2Cl_2 (20 mL) and washed with water (2 × 20 mL). The organic layer was dried (Na_2SO_4), filtered, and concentrated, and the crude product was purified by chromatography (4:1 hexane−EtOAc) to give **60** (75 mg, 80%) as a colorless oil: R_f 0.29 (2:1 hexane−EtOAc); $[\alpha]_D$ −97.4 (*c* 0.6, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$, δ_H) 7.36−7.27 (m, 5H, Ar), 4.89 (d, 1H, *J* = 11.1 Hz, ArCH_2), 4.77 (dd, 1H, $J_{1′,2ax′}$ = 10.1 Hz, $J_{1′,2eq′}$ = 2.0 Hz, H-1′), 4.71 (dd, 1H, $J_{1,2ax}$ = 4.5 Hz, $J_{1,2eq}$ = 1.1 Hz, H-1), 4.63 (d, 1H, *J* = 11.1 Hz, ArCH_2), 3.62 (dq, 1H, $J_{4,5}$ = 9.5 Hz, $J_{5,6}$ = 6.3 Hz, H-5), 3.44 (s, 3H, OCH_3), 3.41−3.33 (m, 3H, H-4, H-3′, H-5′), 3.30 (s, 3H, OCH_3), 3.02 (dd, 1H, $J_{3′,4′}$ = 9.0 Hz, $J_{4′,5′}$ = 9.0 Hz, H-4′), 2.37 (s, 1H, 3-OH), 2.32 (ddd, 1H, $J_{2eq′,2ax′}$ = 12.1 Hz, $J_{2eq′,3′}$ = 5.1 Hz, $J_{1′,2eq′}$ = 2.0 Hz, H-2eq′), 1.98−1.84 (m, 2H, H-2ax, H-2eq), 1.56 (ddd, 1H, $J_{2ax′,2eq′}$ = 12.1 Hz, $J_{2ax′,3′}$ = 11.9 Hz, $J_{1′,2ax′}$ = 10.1 Hz, H-2ax′), 1.38 (s, 3H, 3 × H-7), 1.30 (d, 3H, $J_{5′,6′}$ = 6.3 Hz, 3 × H-6′), 1.29 (d, 3H, $J_{5,6}$ = 6.3 Hz, 3 × H-6); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 138.6 (Ar), 128.4 (2 × Ar), 128.0 (2 × Ar), 127.7 (Ar), 99.7 (C-1′), 98.2 (C-1), 84.0 (C-4), 83.4 (C-4′), 81.4 (C-3′), 75.0 (ArCH_2), 71.8 (C-3), 71.5 (C-5′), 66.0 (C-5), 57.0 (OCH_3), 54.7 (OCH_3), 43.3 (C-2), 35.8 (C-2′), 23.4 (C-7), 18.5 (C-6), 18.1 (C-6′); HRMS (ESI) calcd (M + Na)$^+$ $C_{22}H_{34}O_7$ 433.2197, found 433.2195.

Methyl 2,6-Dideoxy-3-*O*-methyl-β-D-*arabino*-hexopyranosyl-(1→4)-2,6-dideoxy-3-*C*-methyl-α-L-*arabino*-hexopyranoside (61). To a solution of **60** (50 mg, 0.12 mmol) in 1:1 CH_3OH−EtOAc (10 mL) was added 20% $Pd(OH)_2$ on carbon (10 mg), and the reaction mixture was stirred for 24 h under a hydrogen atmosphere. The reaction mixture was filtered through Celite and then concentrated. The crude product was purified by chromatography (2:1 hexane−EtOAc) to give **61** (39 mg, 100%) as a colorless oil: R_f 0.17 (2:1 hexane−EtOAc); $[\alpha]_D$ −136.1 (*c* 1.4, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$, δ_H) 4.80 (dd, 1H, $J_{1′,2ax′}$ = 10.0 Hz, $J_{1′,2eq′}$ = 2.0 Hz, H-1′), 4.71 (dd, 1H, $J_{1,2ax}$ = 4.5 Hz, $J_{1,2eq}$ = 1.2 Hz, H-1), 3.62 (dq, 1H, $J_{4,5}$ = 9.6 Hz, $J_{5,6}$ = 6.2 Hz, H-5), 3.42−3.39 (m, 4H, H-4, OCH_3), 3.34−3.28 (m, 4H, H-5′, OCH_3), 3.22−3.10 (m, 2H, H-3′, H-4′), 2.51 (d, 1H, $J_{OH,4′}$ = 1.9 Hz, 4′-OH), 2.35−2.31 (m, 2H, H-2eq′, 3-OH), 1.97 (dd, 1H, $J_{2eq,2ax}$ = 13.7 Hz, $J_{1,2eq}$ = 1.2 Hz, H-2eq), 1.86 (dd, 1H, $J_{2eq,2ax}$ = 13.7 Hz, $J_{1,2ax}$ = 4.5 Hz, H-2ax), 1.51 (ddd, 1H, $J_{2ax′,2eq′}$ = 12.1 Hz, $J_{2ax′,3′}$ = 11.3 Hz, $J_{1′,2ax′}$ = 10.0 Hz, H-2ax′), 1.38 (s, 3H, 3 × H-7), 1.33 (d, 3H, $J_{5′,6′}$ = 6.1 Hz, 3 × H-6′), 1.29 (d, 3H, $J_{5,6}$ = 6.2 Hz, 3 × H-6); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 99.9 (C-1′), 98.2 (C-1), 84.0 (C-4), 80.8 (C-3′), 75.5 (C-4′), 71.9 (C-3), 71.8 (C-5′), 66.0 (C-5), 56.4 (OCH_3), 54.7 (OCH_3), 43.4 (C-2), 34.6 (C-2′), 23.4 (C-7), 18.4 (C-6), 17.8 (C-6′); HRMS (ESI) calcd (M + Na)$^+$ $C_{15}H_{28}O_7$ 343.1727, found 343.1726.

Benzyl 4-*O*-Benzoyl-2,6-dideoxy-β-D-*arabino*-hexopyranosyl-(1→3)-4-*O*-benzoyl-2,6-dideoxy-β-D-*arabino*-hexopyranoside (63). Disaccharide **74** (177 mg, 0.25 mmol) was dissolved in toluene (20 mL), and *n*-Bu_3SnH (1.36 mL, 5.06 mmol) was added. The solution was heated to 105 °C, and then AIBN (208 mg, 1.27 mmol) dissolved in toluene (10 mL) was added in portions over 1 h. The mixture was stirred for an additional 1 h at 105 °C. After the mixture was cooled to rt, the solvent was removed and the resulting residue was purified by chromatography (3:1 hexane−EtOAc) to give **63** (95 mg, 65%) as a white foam: R_f 0.43 (2:1 hexane−EtOAc); $[\alpha]_D$ −58.0 (*c* 0.4, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$, δ_H) 8.09−8.04 (m, 2H, Ar), 8.02−7.98 (m, 2H, Ar), 7.60−7.53 (m, 2H, Ar), 7.47−7.30 (m, 9H, Ar), 4.98−4.91 (m, 2H, H-4, 1 × ArCH_2), 4.67−4.58 (m, 3H, 1 × ArCH_2, H-1, H-1′), 4.53 (dd, 1H, $J_{3′,4′}$ = 9.2 Hz, $J_{4′,5′}$ = 9.2 Hz, H-4′), 4.10−4.04 (m, 1H, H-3), 3.84−3.76 (m, 1H, H-3′), 3.59 (dq, 1H, $J_{4,5}$ = 9.6 Hz, $J_{5,6}$ = 6.2 Hz, H-5), 3.44 (dq, 1H, $J_{4′,5′}$ = 9.2 Hz, $J_{5′,6′}$ = 6.2 Hz, H-5′), 2.40−2.31 (m, 2H, 3′-OH, H-2eq), 2.20 (ddd, 1H, $J_{2eq′,2ax′}$ = 12.8 Hz, $J_{1′,2eq′}$ = 5.2 Hz, $J_{2eq′,3′}$ = 2.0 Hz, H-2eq′), 1.86 (ddd, 1H, $J_{2eq,2ax}$ = 12.3 Hz, $J_{2ax,3}$ = 12.3 Hz, $J_{21,2ax}$ = 9.8 Hz, H-2ax), 1.62 (ddd, 1H, $J_{2eq′,2ax′}$ = 12.8 Hz, $J_{2ax′,3′}$ = 11.8 Hz, $J_{21′,2ax′}$ = 9.6 Hz, H-2ax′), 1.33 (d, 3H, $J_{5,6}$ = 6.2 Hz, 3 × H-6), 1.04 (d, 3H, $J_{5′,6′}$ = 6.2 Hz, 3 × H-6′); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 167.0 (*C*═O), 165.9 (*C*═O), 137.4 (Ar), 133.4 (Ar), 132.9 (Ar), 130.4 (Ar), 129.85 (Ar), 129.76 (2 × Ar), 129.5 (2 × Ar), 128.54 (Ar), 128.50 (2 × Ar), 128.46 (2 × Ar), 128.2 (Ar), 128.09 (Ar), 128.06 (Ar), 127.9 (Ar), 98.1 (C-1′), 96.4 (C-1), 79.0 (C-4′), 75.3 (C-4), 74.3 (C-3), 70.44 (ArCH_2), 70.37 (C-5′), 70.1 (C-5), 69.9 (C-3′), 39.7 (C-2′), 36.8 (C-2), 17.9 (C-6), 17.6 (C-6′); HRMS (ESI) calcd (M + Na)$^+$ $C_{33}H_{36}O_9$ 599.2252, found 599.2250.

Benzyl 4-*O*-Benzoyl-2,6-dideoxy-2-*p*-tolylthio-β-D-glucopyranosyl-(1→3)-4-*O*-benzoyl-2,6-dideoxy-β-D-*arabino*-hexopyranoside (74). To a solution of **42** (50 mg, 0.15 mmol) and **8** (62 mg, 0.17 mmol) in CH_2Cl_2 (15 mL) was added crushed 4 Å molecular sieves (100 mg). After the mixture was stirred at rt for 30 min, $Cu(OTf)_2$ (53 mg, 0.15 mmol) was added, and the reaction mixture was stirred for an additional 2 h. After neutralization with Et_3N, the reaction mixture was concentrated to a crude residue that was purified by chromatography (4:1 hexane−EtOAc) to give **74** (78 mg, 76%) as a white foam: R_f 0.59 (2:1 hexane−EtOAc); $[\alpha]_D$ −70.3 (*c* 1.7, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$, δ_H) 8.09−8.04 (m, 2H, Ar), 8.01−7.96 (m, 2H, Ar), 7.58−7.53 (m, 2H, Ar), 7.46−7.30 (m, 11H, Ar), 7.10−7.07 (m, 2H, Ar), 4.97 (dd, 1H, $J_{4,5}$ = $J_{3,4}$ = 9.3 Hz, H-4), 4.94 (d, 1H, *J* = 12.0 Hz, 1 × ArCH_2), 4.89 (dd, 1H, $J_{4′,3′}$ = 9.3 Hz, $J_{4′,5′}$ = 9.3 Hz, H-4′), 4.65 (d, 1H, *J* = 12.0 Hz, 1 × ArCH_2), 4.61 (dd, 1H, $J_{1,2ax}$ = 9.9 Hz, $J_{1,2eq}$ = 1.9 Hz, H-1), 4.44 (d, 1H, $J_{1′,2′}$ = 8.8 Hz, H-1′), 4.11−4.04 (m, 1H, H-3), 3.61−3.52 (m, 2H, H-3′, H-5), 3.38−3.31 (m, 1H, H-5′), 2.92 (dd, 1H, $J_{2′,3′}$ = 11.0 Hz, $J_{1′,2′}$ = 8.8 Hz, H-2′), 2.85 (d, 1H, $J_{OH,3′}$ = 2.6 Hz, 3′-OH), 2.43 (ddd, 1H, $J_{2ax,2eq}$ = 12.6 Hz, $J_{2eq,3}$ = 5.2 Hz, $J_{1,2eq}$ = 1.9 Hz, H-2eq), 2.33 (s, 3H, tolyl CH_3), 1.87 (ddd, 1H, $J_{2ax,2eq}$ = 12.6 Hz, $J_{2ax,3}$ =12.3 Hz, $J_{1,2ax}$ = 9.9 Hz, H-2ax), 1.34 (d, 3H, $J_{5,6}$ = 6.2 Hz, 3 × H-6), 0.90 (d, 3H, $J_{5′,6′}$ = 6.2 Hz, 3 × H-6′); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 165.9 (*C*═O), 165.6 (*C*═O), 137.7 (Ar), 137.4 (Ar), 133.2 (Ar), 133.0 (Ar), 132.5 (2 × Ar), 130.4 (Ar), 129.82 (2 × Ar), 129.80 (2 × Ar), 129.76 (2 × Ar), 129.7 (Ar), 129.6 (Ar), 128.5 (2 × Ar), 128.4 (2 × Ar), 128.3

(2 × Ar), 128.1 (2 × Ar), 127.9 (Ar), 100.9 (C-1′), 98.1 (C-1), 76.4 (C-4′), 76.3 (C-4), 75.8 (C-3), 72.4 (C-3′), 70.5 (C-5′), 70.4 (Ar*C*H$_2$), 69.7 (C-5), 58.1 (C-2′), 36.8 (C-2), 21.1 (tolyl *C*H$_3$), 17.9 (C-6), 17.1 (C-6′); HRMS (ESI) calcd (M + Na)$^+$ $C_{40}H_{42}O_9S$ 721.2442, found 721.2444.

Benzyl 3-*O*-*tert*-Butyldimethylsilyl-4-*O*-isobutyryl-2,6-dideoxy-2-iodo-3-*C*-methyl-α-L-mannopyranosyl-(1→3)-4-*O*-benzoyl-2,6-dideoxy-*β*-D-*arabino*-hexopyranosyl-(1→3)-4-*O*-benzoyl-2,6-dideoxy-*β*-D-*arabino*-hexopyranoside (75). Glycal **73** (46 mg, 0.14 mmol) and disaccharide **63** (41 mg, 0.07 mmol) were dissolved in CH_2Cl_2 (15 mL), and crushed 4 Å molecular sieves (100 mg) were added. After the mixture was stirred at rt for 30 min, NIS (48 mg, 0.21 mmol) was added, and the solution was then stirred at rt for 16 h before concentration. The resulting residue was purified by chromatography (8:1 hexane−EtOAc) to give **75** (55 mg, 75%) as a colorless oil: R_f 0.71 (3:1 hexane−EtOAc); $[\alpha]_D$ −68.5 (*c* 0.6, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$, δ_H) 8.09−8.05 (m, 2H, Ar), 8.00−7.96 (m, 2H, Ar), 7.59−7.56 (m, 2H, Ar), 7.47−7.30 (m, 9H, Ar), 5.19 (d, 1H, $J_{1'',2''}$ = 3.6 Hz, H-1″), 4.97−4.91 (m, 2H, 1 × ArC*H*$_2$, H-4), 4.82−4.78 (m, 2H, H-4″, H-4′), 4.64 (d, 1H, *J* = 12.1 Hz, 1 × ArC*H*$_2$), 4.62−4.56 (m, 2H, H-1, H-1′), 4.10−4.03 (m, 1H, H-3), 4.01 (d, 1H, $J_{1'',2''}$ = 3.6 Hz, H-2″), 3.91−3.84 (m, 1H, H-3′), 3.58 (dq, 1H, $J_{4,5}$ = 9.5 Hz, $J_{5,6}$ = 6.2 Hz, H-5), 3.47 (dq, 1H, $J_{4',5'}$ = 9.5 Hz, $J_{5',6'}$ = 6.2 Hz, H-5′), 3.34 (dq, 1H, $J_{5'',4''}$ = 9.1 Hz, $J_{5'',6''}$ = 6.2 Hz, H-5″), 2.38−2.21 (m, 3H, H-2eq, H-2eq′, $(CH_3)_2CH$), 1.89−1.80 (m, 1H, H-2ax′), 1.64−1.52 (m, 1H, H-2ax), 1.33 (d, 3H, $J_{5,6}$ = 6.2 Hz, 3 × H-6), 1.27 (s, 3H, 3 × H-7″), 1.01 (d, 3H, $J_{5',6'}$ = 6.2 Hz, 3 × H-6′), 0.98 (d, 3H, *J* = 7.0 Hz, $(CH_3)_2CH$), 0.93 (d, 3H, *J* = 7.0 Hz, $(CH_3)_2CH$), 0.84 (s, 9H, $(CH_3)_3CSi(CH_3)_2$), 0.75 (d, 3H, *J* = 6.2 Hz, 3 × H-6″), 0.14 (s, 3H, $(CH_3)_3CSi(CH_3)_2$), 0.03 (s, 3H, $(CH_3)_3CSi(CH_3)_2$); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 175.3 (*C*═O), 165.9 (*C*═O), 165.5 (*C*═O), 137.4 (Ar), 133.1 (Ar), 133.0 (Ar), 130.4 (Ar), 129.8 (2 × Ar), 129.6 (2 × Ar), 128.5 (2 × Ar), 128.3 (2 × Ar), 128.2 (2 × Ar), 128.1 (2 × Ar), 127.9 (2 × Ar), 100.4 (C-1″), 98.1 (C-1′), 96.2 (C-1), 75.8 (C-4″), 75.3 (C-4′), 75.2 (C-4), 74.2 (C-3), 74.0 (C-3″), 73.1 (C-3′), 70.43 (C-5′), 70.36 (Ar*C*H$_2$), 70.1 (C-5), 66.8 (C-5″), 43.2 (C-2″), 36.8 (C-2′), 36.0 (C-2), 34.0 (*C*H(CH$_3$)$_2$), 26.1 ((*C*H$_3$)$_3$CSi(CH$_3$)$_2$), 18.9 (C-6′), 18.5 (C-6), 18.4 ((CH$_3$)$_3$*C*Si(CH$_3$)$_2$), 18.0 (C-7″), 17.9 (C-6″), 17.5 (2 × CH(*C*H$_3$)$_2$), −1.9 ((CH$_3$)$_3$CSi(*C*H$_3$)$_2$), −2.1 ((CH$_3$)$_3$CSi(*C*H$_3$)$_2$); HRMS (ESI) calcd (M + Na)$^+$ $C_{50}H_{67}IO_{13}Si$ 1053.3288, found 1053.3286.

Benzyl 3-*O*-*tert*-Butyldimethylsilyl-4-*O*-isobutyryl-2,6-dideoxy-3-*C*-methyl-α-L-*arabino*-hexopyranosyl-(1→3)-4-*O*-benzoyl-2,6-dideoxy-*β*-D-*arabino*-hexopyranosyl-(1→3)-4-*O*-benzoyl-2,6-dideoxy-*β*-D-*arabino*-hexopyranoside (76). Trisaccharide **75** (37 mg, 0.04 mmol) was dissolved in toluene (10 mL), and *n*-Bu_3SnH (0.11 mL, 0.4 mmol) was added. The solution was heated to 100 °C, and following the addition of AIBN (6 mg, 0.04 mmol), it was stirred for 3 h at this temperature. The reaction mixture was then cooled to rt and concentrated, and the resulting residue was purified by chromatography (5:1 hexane−EtOAc) to give **76** (31 mg, 95%) as a colorless oil: R_f 0.71 (3:1 hexane−EtOAc); $[\alpha]_D$ −58.3 (*c* 0.3, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$, δ_H) 8.08−8.05 (m, 2H, Ar), 8.01−7.97 (m, 2H, Ar), 7.57−7.52 (m, 2H, Ar), 7.46−7.31 (m, 9H, Ar), 4.95−4.91 (m, 2H, 1 × ArC*H*$_2$, H-4′), 4.81 (dd, 1H, $J_{4,5}$ = 9.4 Hz, $J_{4,5}$ = 9.4 Hz, H-4), 4.77 (dd, 1H, $J_{1'',2eq''}$ = 3.7 Hz, $J_{1'',2ax''}$ = 1.7 Hz, H-1″), 4.64 (d, 1H, *J* = 12.0 Hz, 1 × ArC*H*$_2$), 4.63−4.57 (m, 2H, H-1, H-1′), 4.52 (d, 1H, $J_{4'',5''}$ = 10.2 Hz, H-4″), 4.10−4.04 (m, 1H, H-3′), 3.90−3.84 (m, 1H, H-3), 3.58 (dq, 1H, $J_{4',5'}$ = 9.5 Hz, $J_{5',6'}$ = 6.2 Hz, H-5′), 3.42 (dq, 1H, $J_{4,5}$ = 9.5 Hz, $J_{5,6}$ = 6.2 Hz, H-5), 3.33 (dq, 1H, $J_{4'',5''}$ = 10.2 Hz, $J_{5'',6''}$ = 6.2 Hz, H-5″), 2.36−2.31 (m, 1H, H-2eq′), 2.30 (hept, 1H, *J* = 7.1 Hz, $(CH_3)_2CH$), 2.22−2.17 (m, 1H, H-2eq), 1.87−1.80 (m, 3H, H-2ax′, H-2eq″, H-2ax″), 1.68−1.61 (m, 1H, H-2ax), 1.33 (d, 3H, $J_{5',6'}$ = 6.2 Hz, 3 × H-6′), 1.10 (s, 3H, 3 × H-7″), 0.95 (d, 3H, $J_{5,6}$ = 6.2 Hz, 3 × H-6), 0.94 (d, 6H, *J* = 7.1 Hz, 2 × $(CH_3)_2CH$), 0.76 (d, 3H, $J_{5'',6''}$ = 6.2 Hz, 3 × H-6″), 0.73 (s, 9H, $(CH_3)_3CSi(CH_3)_2$), 0.00 (s, 3H, $(CH_3)_3CSi(CH_3)_2$), −0.05 (s, 3H, $(CH_3)_3CSi(CH_3)_2$); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 175.3 (*C*═O), 165.9 (*C*═O), 165.5 (*C*═O), 137.4 (Ar), 133.1 (Ar), 132.9 (Ar), 130.4 (Ar), 129.9 (Ar), 129.8 (2 × Ar), 129.6 (2 × Ar), 128.5 (2 × Ar), 128.3 (2 × Ar), 128.2 (2 × Ar), 128.1 (2 × Ar), 127.9 (Ar), 98.1 (C-1′), 96.3 (C-1), 92.7 (C-1″), 78.6 (C-4″), 75.4 (C-4′), 75.0 (C-4), 73.9 (C-3′), 72.8 (C-3″), 71.1 (C-3), 70.41 (C-5′), 70.38 (Ar*C*H$_2$), 70.3 (C-5), 65.1 (C-5″), 44.5 (C-2″), 36.9 (C-2′), 35.5 (C-2), 34.1 (*C*H(CH$_3$)$_2$), 25.5 ((*C*H$_3$)$_3$CSi(CH$_3$)$_2$), 18.9 (C-6′), 18.7 (C-6), 17.9 (C-6″), 17.5 ((CH$_3$)$_3$*C*Si(CH$_3$)$_2$), 17.3 (2 × CH(*C*H$_3$)$_2$), 13.6 (C-7″), −2.1 ((CH$_3$)$_3$CSi(*C*H$_3$)$_2$), −2.2 ((CH$_3$)$_3$CSi(*C*H$_3$)$_2$); HRMS (ESI) calcd (M + Na)$^+$ $C_{50}H_{68}O_{13}Si$ 927.4321, found 927.4323.

Benzyl 2,6-Dideoxy-3-*C*-methyl-α-L-*arabino*-hexopyranosyl-(1→3)-2,6-dideoxy-*β*-D-*arabino*-hexopyranosyl-(1→3)- 2,6-dideoxy-*β*-D-*arabino*-hexopyranoside (77). To a solution of **76** (33 mg, 0.04 mmol) in THF (10 mL) was added 1 M TBAF in THF (0.1 mL, 0.08 mmol). The reaction mixture was heated to 70 °C and stirred at this temperature for 15 h. After being cooled to rt, the solution was diluted with EtOAc (20 mL) and washed with brine (15 mL). The organic layer was dried (Na_2SO_4), filtered, and concentrated, and the resulting residue was dissolved in 1:1 THF−CH_3OH (20 mL) containing $LiOCH_3$ (10 mg) and LiF (10 mg). The solution was heated to 70 °C and stirred at this temperature for 15 h. The reaction mixture was then neutralized with Amberlite IR-120 H^+ resin, filtered, and concentrated. The resulting residue was purified by chromatography (20:1 CH_2Cl_2−CH_3OH) to yield **77** (13 mg, 70%) as a white foam: R_f 0.34 (10:1 CH_2Cl_2−CH_3OH); $[\alpha]_D$ −53.9 (*c* 0.3, CH_3OH); ^{1}H NMR (500 MHz, $CDCl_3$, δ_H) 7.36−7.27 (m, 5H, Ar), 4.97 (dd, 1H, $J_{1'',2ax''}$ = 4.4 Hz, $J_{1'',2eq''}$ = 1.2 Hz, H-1″), 4.90 (d, 1H, *J* = 12.0 Hz, 1 × ArC*H*$_2$), 4.60 (d, 1H, *J* = 12.0 Hz, 1 × ArC*H*$_2$), 4.51 (dd, 1H, $J_{1',2ax'}$ = 9.9 Hz, $J_{1',2eq'}$ = 2.0 Hz, H-1′), 4.51 (dd, 1H, $J_{1,2ax}$ = 9.9 Hz, $J_{1,2eq}$ = 2.0 Hz, H-1), 4.42 (s, 1H, OH), 4.16 (s, 1H, OH), 3.87 (dq, 1H, $J_{4'',5''}$ = 9.3 Hz, $J_{5'',6''}$ = 6.2 Hz, H-5″), 3.51−3.41 (m, 2H, H-3′, H-3), 3.33−3.21 (m, 3H, H-4″, H-5′, H-5), 3.15−3.06 (m, 2H, H-4′, H-4), 2.25−2.10 (m, 2H, H-2eq, H-2eq′), 2.08−1.90 (m, 3H, H-2eq″, H-2ax″, OH), 1.83−1.62 (m, 2H, H-2ax, H-2ax′), 1.42−1.38 (m, 6H, 3 × H-7″, 3 × H-6′), 1.37 (d, 3H, $J_{5,6}$ = 6.1 Hz, 3 × H-6), 1.33 (d, 3H, $J_{5'',6''}$ = 6.2 Hz, 3 × H-6″); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 137.5 (Ar), 128.4 (2 × Ar), 128.0 (2 × Ar), 127.8 (Ar), 99.6 (C-1′), 98.1 (C-1), 97.6 (C-1″), 82.3 (C-4″), 80.9 (C-4′), 79.1 (C-4), 75.3 (C-3′), 75.2 (C-3), 72.1 (C-5′), 72.0 (C-5), 71.1 (C-3″), 70.3 (Ar*C*H$_2$), 68.1 (C-5″), 43.4 (C-2″), 37.5 (C-2′), 37.1 (C-2), 22.1 (C-6′), 18.0 (C-6), 18.0 (C-7″), 17.8 (C-6″); HRMS (ESI) calcd (M + Na)$^+$ $C_{26}H_{40}O_{10}$ 535.2514, found 535.2505.

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Supporting Information Available: Details on the synthesis of and data for additional new compounds not included in text; ^{1}H and ^{13}C NMR spectra for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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