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Studies on the Synthesis of *C*-Glycoside Sulfones as Potential Glycosyl Transferase Inhibitors[1]

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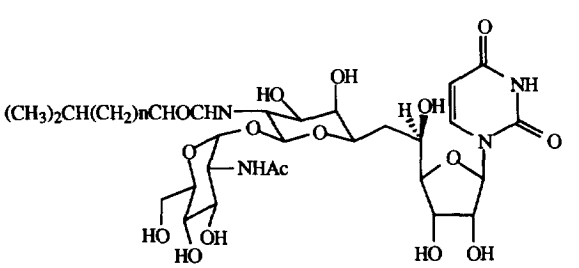
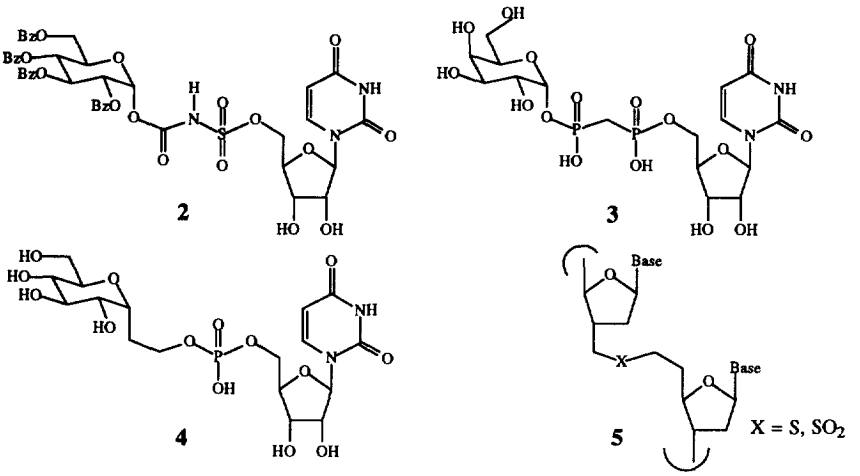
Abstract: β-*C*-Glycoside sulfoxides and sulfones were prepared by radical addition of thiol acetic acid to exocyclic glycals followed by deacetylation, S-alkylation, and selective oxidation. These compounds are representative examples of a new class of molecules designed to be glycosyl transferase inhibitors. © 1997 Elsevier Science Ltd.

Tunicamycin **1** is a naturally occurring antibiotic which is an isosteric analog of nucleoside diphosphates.[2] It interferes with glycoprotein synthesis presumably through inhibition of glycosyl transfer to the protein.[3] Because tunicamycin is highly toxic, syntheses of alternative isosteres have been sought. One design strategy is to produce analogs with more stable functionality than the diphosphate linkage, while still retaining the critical 5-bond distance between the sugar and the 5' nucleoside residue. To date both *O*-, and *C*-glycosidic analogs have been developed. The carbonyl sulfonamide **2** exhibits antiviral activity through inhibition of glycoprotein synthesis.[4] The methylene diphosphate analog **3** inhibits galactosyltransferase activity,[5] and analog **4** is reported to inhibit glycolipid biosynthesis.[6]



tunicamycin **1**



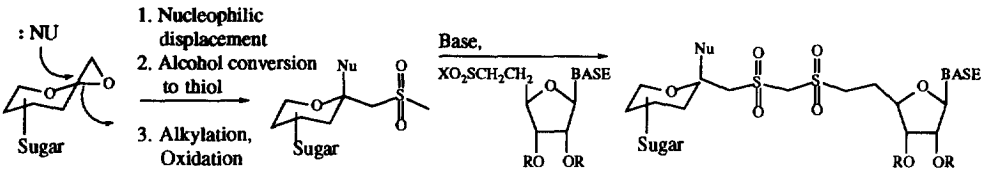
A related area of interest is the development of oligonucleotide "anti-sense" analogs. Here the phosphodiester has been substituted with various functionalities including sulfonate, sulfonamide, sulfone, and dimethylene sulfide linkages **5**.[6] The corresponding sulfone and dimethylene sulfide isosteres of sugar nucleotides have not been reported.

Our interest in this area is fueled by the expectation that sulfone analogs of sugar nucleotides will be exceptionally stable toward glycosidase activity thereby effecting superior glycosyl transferase inhibition. Initially we are targeting inhibitors of the Leloir enzymes which require activated sugars with the general structure sugar-O-PO_2-O-PO_2-O-nucleoside. These include UDP-glucose, UDP-galactose, GDP-mannose, and GDP-fucose. Our target compounds are the isosteric disulfone analogs of these sugar nucleotides containing a sugar-CH_2-SO_2-CH_2-SO_2-CH_2-nucleoside array. Substitution of an *O*-glycosidic linkage with a *C*-glycosidic linkage should render the target molecule resistant to glycosidases. Sulfones are nonionic, achiral isosteres of phosphodiesters that are stable to both chemical and biochemical hydrolysis.[7] Sulfones also increase membrane permeability thereby assisting penetration into cells.[8] Furthermore, since sulfone centers are not stereogenic, problems with diastereomeric mixtures are not an issue.

The synthetic investigations reported herein primarily utilize D-glucosyl derivatives because they are readily available. However, L-fucosyl derivatives were also studied, since L-fucose is a critical component of cell surface recognition elements involved in tumor metastasis.[9] Successful fucosyl transferase inhibitors would block the incorporation of fucose onto cell surface glycoconjugates, effectively diminishing cellular interactions required for metastasis. The transferase enzymes typically proceed with overall inversion of the starting sugar nucleotide stereochemistry. β-Linked GDP-fucose is the substrate for fucosyl transferases giving rise α-linked fucosides. Therefore β *C*-glycoside sulfone derivatives of fucose are a primary target.

The first generation synthetic sequence is shown in Scheme 1. Stereoselective nucleophilic addition to a 1,2-anhydro sugar, followed by hydroxyl to thiol conversion was the first route we explored. This strategy would easily accommodate nucleophile, sugar, and nucleoside substitutions allowing access to numerous analogs.

Scheme 1



In order to investigate the feasibility of the proposed nucleophilic reactions, we prepared the exocyclic glycal **6** and reacted it with dimethyldioxirane (DMDO) to quantitatively provide the 1,2-anhydrosugars **7** and **8** in a 3:2 ratio (Figure 2).[10]

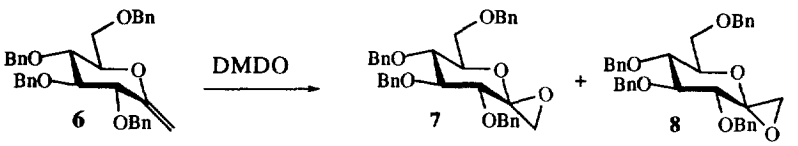


Figure 2

We had already demonstrated that hydride addition to endocyclic glycals occurs with high stereoselectivity,[11] but the exocyclic glycals posed a question of regioselectivity as well. Since $LiAlH_4$ addition proved to be most effective in the endocyclic cases, it was the first reagent we explored. Hydride addition resulted in the formation of four products including the α and β anomers of the primary alcohol (**9a/b**), and the α and β anomers of the tertiary alcohol (**10a/b**) (Figure 3). Despite considerable effort, attempts to isolate all four products, in order to determine ratios, were unsuccessful. Brown has shown that diborane is a useful reagent for hydride delivery at the more sterically hindered center of trisubstituted epoxides.[12] Disappointingly, our studies showed that hydride delivery again occurred at both sites of the epoxide. Triethylsilane and DIBAL[13] also provided mixtures of products.

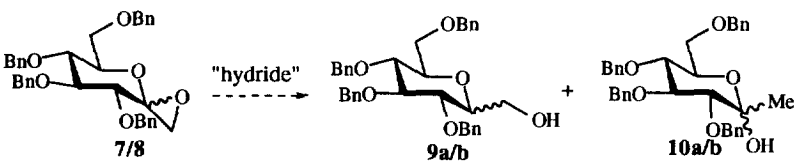


Figure 3

Since the sythetic routes to *C*-glycoside sulfones via nucleophilic addition to oxiranes failed, we decided to explore radical addition to the exocyclic double bond. In 1970, Igarashi reported that free radical addition of thiolacetic acid to tri-*O*-acetyl-D-glucal, using cumene hydroperoxide (CHP) as the free radical initiator, proceeded with C-2 addition of thioacetyl radical give a 7:3 ratio of manno:gluco diastereomers (Figure 4).[14]

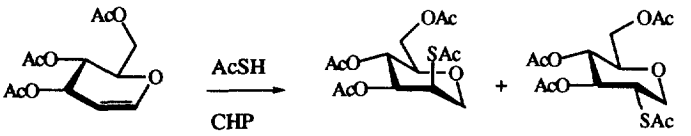
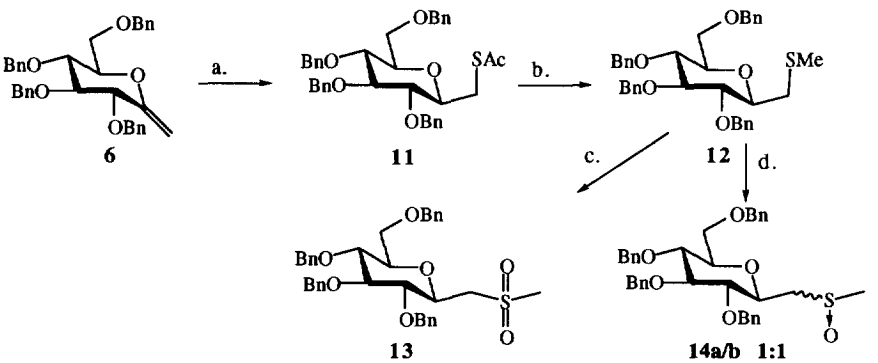


Figure 4

Analogously, the radical reaction was attempted with our perbenzylated exocyclic glycal (**6**) using 2,2'-azobis(2-methylpropionitrile) (AIBN) as the initiator. The reaction proceeded smoothly to provide the *S*-acetylated derivative **11** in 83% yield (Scheme 2). The β glycoside was expected based upon the preferred configuration of the anomeric radical.[15] Both TLC and ^{1}H NMR indicated the formation of a single product which was determined to be the β-anomer using COSY and HETCOR.

The *C*-glycoside thiolacetate **11** was only moderately soluble in methanol, therefore a 1:1 methanol-THF solution was used to completely solubilize the thiolacetate. Deprotection of the *S*-acetyl group proceeded rapidly upon addition of a catalytic amount of sodium methoxide. When TLC indicated complete reaction, methyl iodide was added to the solution to yield the *C*-glycoside thiomethyl compound **12**. Precautions were taken to ensure that the deacylation took place under anaerobic conditions in order to prevent disulfide formation. The yields for the one pot procedure of deacylation and alkylation varied from 43-71%. The *C*-glycoside sulfide was then oxidized using an excess of dimethyldioxirane to give a quantitative yield of the sulfone **13**. Alternatively, the sulfide could be oxidized with *m*-CPBA providing the sulfoxides in a 1:1 diastereomeric mixture of **14a/b** as determined by ^{1}H NMR integration of the methyl singlets.

Scheme 2

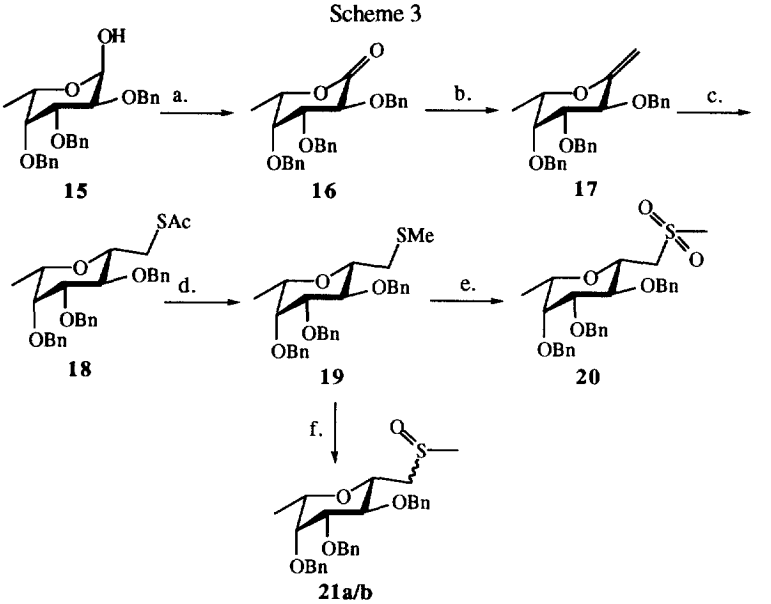


a. AcSH, AIBN, benzene, reflux, 83%. b. MeOH, THF, NaOMe, then MeI, 43-71%. c. Dimethyldioxirane, dichloromethane, 0°C, 100%. d. *m*-CPBA, dichloromethane, 0°C, 34%.

Since the model study employing glucose proved successful, we applied the synthetic sequence to L-fucose as shown in Scheme 3. 2,3,4-Tri-*O*-benzyl-α-L-fucopyranose[16] (**15**) was oxidized to the lactone (**16**) under Swern conditions in 86% yield.[17] Methylenation of the lactone using the Tebbe reagent[18] provided the exocyclic fucosyl glycal (**17**) in 60% yield. Radical addition of thiolacetic acid to **17** afforded

the β-*C*-glycoside **18** in 78% yield which was subsequently deprotected and alkylated to provide the thiomethyl *C*-glycoside **19**. Oxidation of the sulfide to the sulfone (**20**) again proceeded quantitatively upon treatment with an excess of dimethyldioxirane. In addition to the *C*-fucosyl sulfone, the *C*-fucosyl sulfoxide was prepared. Oxidation of the sulfide with *m*-CPBA provided the sulfoxides **21a/b** in 71% yield. A 1:1 mixture of diastereomers was obtained based upon integration of the sulfoxide methyl singlets.

Scheme 3



Reagents: a) $(COCl)_2$, DMSO, DCM, -45°C, then TEA, 86%. b) Tebbe reagent, THF, toluene, pyridine, -45°C, 60%. c) AcSH, AIBN, benzene, reflux, 78%. d) NaOMe, MeOH, MeI, THF. e) DMDO, DCM, 0°C, 100%. f) *m*-CPBA, DCM, 0°C, 71%.

In summary, the synthesis of *C*-glycoside sulfones was targeted as part of a program directed toward the design and synthesis of glycosyl transferase inhibitors. β-*C*-glycoside sulfones and sulfoxides derived from D-glucose and L-fucose were prepared by radical addition of thiolacetic acid to the corresponding exocyclic glycal. Deprotection of the thiolacetate and subsequent alkylation with methyl iodide provided thiomethyl intermediates. Selective oxidation could be achieved affording both *C*-glycoside sulfoxides and *C*-glycoside sulfones. Further studies, targeting incorporation of the nucleotide sugars, are currently underway in our laboratories.

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Experimental Section:

Starting materials and reagents purchased from commercial suppliers were used without further purification. Solvents were dried by distillation prior to use. Diethyl ether and tetrahydrofuran were distilled from sodium and benzophenone under an argon atmosphere. Dichloromethane, acetonitrile, dimethyl sulfoxide and pyridine were distilled from calcium hydride under argon. Methanol was distilled from Mg/I_2 under argon. All reactions were performed under an argon atmosphere.

Thin layer chromatography was performed using silica gel 60 F_{254} plates. Flash column chromatography was performed using silica gel 60 (230-400 mesh ASTM). Proton and carbon nuclear magnetic resonance spectra were recorded on either a Bruker AM-250, Bruker AM-500, or a Varian Unity 300 spectrometer. Chemical shifts are reported in parts per million relative to the residual solvent peak. ^1H NMR data are reported in the order of chemical shift, multiplicity (s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, br=broad), the coupling constant in Hertz (Hz) and the number of protons. Infrared spectra were recorded using a Nicolet 510P FT-IR spectrometer. Melting points were obtained using a Fisher-Johns melting point apparatus and are uncorrected. Specific rotations were determined using an Autopol III polarimeter. Mass spectrometry was performed by the Nebraska Center for Mass Spectrometry, Lincoln NE.

1-*S*-Acetyl-2,6-anhydro-1-deoxy-3,4,5,7-tetra-*O*-benzyl-D-glycero-D-gulo-heptitol (11): 2,6-Anhydro-3,4,5,7-tetra-*O*-benzyl-1-deoxy-D-*gluco*-hept-1-enitol[18] (98 mg, 0.183 mmol) was dissolved in benzene (3 mL). Freshly distilled thiolacetic acid (65 μL, 0.914 mmol) was added followed by AIBN (3 mg, 0.018 mmol). The solution was refluxed for 4h. The solvent was removed *in vacuo* and the crude product chromatographed (5:1 hexanes:ethyl acetate) to give the product as a white solid (93 mg, 83%). R_f = 0.50 (25% ethyl acetate/hexanes). mp 116-118°C. $[\alpha]^{22}_D$ = -6.4°(*c* 4.7 in $CHCl_3$). ^1H NMR (250 MHz, $CDCl_3$) δ 2.33 (s, 3 H, $SCOCH_3$), 3.06 (dd, *J* = 13.0, 5.8 Hz, 1 H), 3.39 - 3.73 (m, 8 H), 4.52 - 4.90 (m, 8 H, OCH_2Ar), 7.15 - 7.34 (m, 20 H, ArH). ^{13}C NMR (63 MHz, $CDCl_3$) δ 30.0, 69.1, 73.6, 78.5, 78.7, 79.8, 81.2, 87.3, 127.6, 127.7, 127.8, 127.9, 128.0, 128.2, 128.4, 128.6, 138.8, 139.2, 139.5. IR ($CDCl_3$) 629, 669, 698, 737, 955, 1028, 1097, 1221, 1362, 1455, 1497, 1694, 2865, 2920, 3031 cm^{-1}. FABMS *m/z* calcd for $C_{37}H_{41}O_6S$: 613.2624 ($M+H^+$); found 613.2632.

1-*S*-Methyl-2,6-anhydro-1-deoxy-3,4,5,7-tetra-*O*-benzyl-D-glycero-D-gulo-heptitol (12): 1-*S*-Acetyl-2,6-anhydro-1-deoxy-3,4,5,7-tetra-*O*-benzyl-D-glycero-D-gulo-heptitol (**11**, 28 mg, 0.0456 mmol) was dissolved in THF (2 mL) and methanol (2 mL). Sodium methoxide (2 mg, 0.037 mmol) was added. After 30 min, methyl iodide (2.7 μL, 0.044 mmol) was added to the solution. After 1h the solvent was removed *in vacuo*, and the residue was chromatographed (5:1 hexanes:ethyl acetate). The product was obtained as a colorless oil (18 mg, 71%). R_f = 0.60 (25% ethyl acetate/hexanes). $[\alpha]^{22}_D$ = -42.1°(*c* 0.95 in $CHCl_3$). ^1H NMR (250 MHz, $CDCl_3$) δ 2.20 (s, 3 H, SMe), 2.68 (dd, *J* = 14.1, 6.2 Hz, 1H, H-1), 2.89 (dd, *J* = 14.4, 1.8 Hz, 1 H, H-1'), 3.44 - 3.76 (m, 7 H), 4.53 - 4.94 (m, 8 H, OCH_2Ar), 7.17 - 7.36

(m, 20 H, ArH). ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.2, 35.7, 69.0, 73.4, 75.0, 78.4, 78.9, 80.2, 80.5, 87.1, 127.6, 127.7, 127.8, 127.9, 128.3, 128.4, 128.5, 138.0, 138.1, 138.2, 138.5. IR ($CDCl_3$) 697, 735, 1028, 1099, 1209, 1309, 1362, 1454, 1497 cm^{-1}. FABMS *m/z* calcd for $C_{36}H_{41}O_5S$: 585.2675 ($M+H^+$); found 585.2696.

1-Methylsulfonyl-2,6-anhydro-1-deoxy-3,4,5,7-tetra-*O*-benzyl-D-glycero-D-gulo-heptitol (13): 1-*S*-Methyl-2,6-anhydro-1-deoxy-3,4,5,7-tetra-*O*-benzyl-D-glycero-D-gulo-heptitol (**12**, 10 mg, 0.017 mmol) was dissolved in dichloromethane and cooled to 0°C. Dimethyldioxirane (685 μL, 0.034 mmol) was added and the reaction stirred for 30 min. The solvent was removed *in vacuo* to provide the sulfone as a white solid (11 mg, 100%). R_f = 0.11 (25% ethyl acetate/hexanes). mp 125-128°C. $[\alpha]^{22}_D$ = -71.4° (*c* 0.28 in $CHCl_3$). ^1H NMR (250 MHz, $CDCl_3$) δ 2.92 (s, 3 H, SO_2Me), 2.93 (t, *J* = 10.0 Hz, 1 H), 3.21 (d, *J* = 14.6 Hz, 1 H), 3.35 (t, *J* = 9.0 Hz, 1 H), 3.54 - 3.86 (m, 6 H), 4.48 - 4.96 (m, 8 H, OCH_2Ar), 7.16 - 7.39 (m, 20 H, ArH). ^{13}C NMR (63 MHz, $CDCl_3$) δ 43.4, 56.3, 58.6, 68.7, 73.3, 74.5, 75.0, 75.7, 78.1, 78.4, 79.3, 86.9, 127.7, 127.8, 128.0, 128.2, 128.4, 128.5, 128.6, 137.3, 137.6, 137.8, 138.1. IR ($CDCl_3$) 503, 639, 736, 937, 1028, 1098, 1130, 1210, 1304, 1362, 1395, 1455, 1497, 2870 cm^{-1}. FABMS *m/z* calcd for $C_{36}H_{40}O_7SNa$: 639.2392 (M+Na); found 639.2384.

1-Methylsulfoxyl-2,6-anhydro-1-deoxy-3,4,5,7-tetra-*O*-benzyl-D-glycero-D-gulo-heptitol (14a/b): 1-Methylsulfonyl-2,6-anhydro-1-deoxy-3,4,5,7-tetra-*O*-benzyl-D-glycero-D-gulo-heptitol (**12**, 139 mg, 0.238 mmol) was dissolved in dichloromethane (5 mL) and cooled to 0°C. 50-60% *m*-CPBA (82.0 mg, 0.238 mmol) was added. After 30 min, the solvent was removed *in vacuo* and the crude product chromatographed (7:3 benzene/acetone). The sulfoxide was obtained as a colorless oil (48 mg, 34%) and as 1:1 mixture of diastereomers based upon integration of the methyl sulfoxide singlets. R_f = 0.20 (30% acetone:benzene). ^1H NMR (250 MHz, $CDCl_3$) δ 2.55 (s, 3 H, $SOCH_3$), 2.64 (s, 3 H, $SOCH_3$), 2.92 - 3.14 (m 2 H), 3.35 (t, *J* = 8.9 Hz, 1 H), 3.47 - 3.80 (m, 6 H), 4.49 - 4.98 (m, 8 H, OCH_2Ar), 7.18 - 7.40 (m, 20 H, ArH). ^{13}C NMR (63 MHz, $CDCl_3$) δ 39.2, 39.9, 54.9, 57.5, 68.4, 68.7, 72.9, 73.1, 73.3, 74.9, 75.5, 75.6, 77.9, 78.0, 78.6, 78.9, 80.0, 80.6, 127.7, 127.8, 127.9, 128.0, 128.2, 128.3, 128.4, 137.6, 137.9, 138.2. IR ($CDCl_3$) 706, 751, 1029, 1072, 1080, 1217, 1361, 1463, 1514, 2868, 2919, 3047 cm^{-1}. FABMS *m/z* calcd for $C_{36}H_{40}O_6SNa$: 623.2443 (M+Na); found 623.2442.

2,3,4-Tri-*O*-benzyl-6-deoxy-L-galactopyrano-1,5-lactone (16): Oxalyl chloride (435 μL, 5.07 mmol) was dissolved in dichloromethane (25 mL), and the solution was cooled to -50°C. A solution of dimethyl sulfoxide (785 μL, 11.1 mmol) in dichloromethane (5 mL) was added dropwise to the oxalyl chloride solution. After 5 min, a solution of 2,3,4-tri-*O*-benzyl-L-fucose[16] (1.00 g, 2.30 mmol) in dichloromethane (5 mL) was added to oxalyl chloride-DMSO solution. After 1h, triethylamine (1.60 mL, 11.5 mmol) was added, and the solution was allowed to warm to room temperature. The organic phase was extracted with water (3x100 mL) and saturated NaCl solution (100 mL). The organic phase was collected, dried (Na_2SO_4), concentrated *in vacuo* and chromatographed (3:1 hexanes/ethyl acetate) to afford the

product as a colorless oil (867 mg, 86%). R_f = 0.26 (25% ethyl acetate/hexanes). $[\alpha]^{22}_D$ = -80.7° (*c* 15.0 in $CHCl_3$). ^1H NMR (250 MHz, $CDCl_3$) δ 1.26 (d, *J* = 6.5 Hz, 3 H, CH_3), 3.74 (m, 1 H, H-4), 3.82 (dd, *J* = 9.7, 2.16 Hz, 1 H, H-3), 4.23 (qd, *J* = 6.4, 1.1 Hz, 1H, H-5), 4.41 (d, *J* = 9.7 Hz, 1 H, H-2), 4.60 - 4.75 (m, 4 H, OCH_2Ar), 4.91 (d, *J* = 11.4 Hz, 1 H, OCH_2Ar), 5.14 (d, *J* = 11.0 Hz, 1 H, OCH_2Ar), 7.23 - 7.39 (m, 15 H, ArH). ^{13}C NMR (63 MHz, $CDCl_3$) δ 17.1, 72.9, 74.6, 75.1, 75.4, 75.7, 76.8, 80.3, 127.4, 127.7, 127.8, 128.1, 128.3, 128.4, 137.6, 137.8, 170.5. IR ($CDCl_3$) 586, 700, 744, 864, 912, 1028, 1103, 1363, 1456, 1497, 1736, 2878, 2990, 3032, 3065 cm^{-1}. FABMS *m/z* calcd for $C_{27}H_{28}O_5Na$: 455.1834 (M+Na); found 455.1815.

2,6-Anhydro-3,4,5-tri-*O*-benzyl-1,7-dideoxy-L-galacto-hept-1-enitol (17): 2,3,4-Tri-*O*-benzyl-6-deoxy-L-galactopyrano-1,5-lactone (**16**, 1.10 g, 2.53 mmol) was dissolved in a solution of toluene (6 mL), THF (2 mL), and pyridine (50 μL). The solution was cooled to -45°C, and Tebbe reagent (6.60 mL, 3.29 mmol) was added slowly. After 1h at -45°C, the solution was kept at 0°C for 30 min. After 30 min, the solution was cooled to -15°C and 10% NaOH (1 mL) was added to the solution dropwise. The solution was warmed to room temperature and diethyl ether was added (50 mL). The solution was passed over a short pad of celite and concentrated *in vacuo*. The crude product was chromatographed (6:1 hexanes/diethyl ether) to afford the exocyclic methylene as a colorless oil (648 mg, 60%). R_f = 0.62 (25% ethyl acetate:hexanes). $[\alpha]^{22}_D$ = -76.9° (*c* 5.2 in $CHCl_3$). ^1H NMR (250 MHz, $CDCl_3$) δ 1.23 (d, *J* = 6.4 Hz, 3 H, CH_3), 3.62 - 3.71 (m, 3 H, H-4, H-5, H-6), 4.39 (d, *J* = 9.4 Hz, 1 H, H-3), 4.65 - 4.83 (m, 7 H, H-1, H-1', OCH_2Ar), 4.97 (d, *J* = 11.6 Hz, 1 H, OCH_2Ar), 7.26 - 7.37 (m, 15 H, ArH). ^{13}C NMR (63 MHz, $CDCl_3$) δ 17.3, 74.2, 74.9, 76.2, 77.1, 77.6, 83.1, 94.2, 127.8, 127.9, 128.2, 128.5, 128.6, 128.7, 138.6, 138.8, 138.9, 158.7. IR ($CDCl_3$) 698, 733, 817, 844, 924, 999, 1028, 1064, 1089, 1126, 1201, 1307, 1361, 1454, 1496, 2880, 2934, 2988, 3030 cm^{-1}. FABMS *m/z* calcd for $C_{28}H_{30}O_4Na$: 453.2042 (M+Na); found 453.2024

1-*S*-Acetyl-2,6-anhydro-1,7-dideoxy-3,4,5-tri-*O*-benzyl-L-glycero-L-galacto-heptitol (18): 2,6-Anhydro-3,4,5-tri-*O*-benzyl-1,7-dideoxy-L-galacto-hept-1-enitol (**17**, 557 mg, 1.30 mmol) was dissolved in benzene (7 mL). Freshly distilled thiolacetic acid (463 μL, 6.50 mmol) was added to the solution along with AIBN (21 mg, 0.130 mmol). The solution was heated at reflux for 1h. The solution was concentrated *in vacuo* and chromatographed (3:1 hexanes/diethyl ether). The product was obtained as a colorless oil (510 mg, 78%). R_f = 0.54 (25% ethyl acetate:hexanes). $[\alpha]^{22}_D$ = -7.9° (*c* 7.6 in $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$) δ 1.18 (d, *J* = 6.6 Hz, 3 H, CH_3), 2.34 (s, 3 H, $SCOCH_3$), 2.99 (dd, *J* = 13.5, 8.4 Hz, 1 H, H-1), 3.38 (td, *J* = 9.3, 2.7 Hz, 1 H, H-2), 3.47 (q, *J* = 6.3 Hz, 1 H, H-6), 3.60 - 3.69 (m, 3 H, H-1', H-4, H-5), 3.79 (t, *J* = 9.3, 1 H, H-3), 4.71 - 4.81 (m, 4 H, OCH_2Ar), 5.00 (t, *J* = 12.3 Hz, 2 H, OCH_2Ar), 7.30 - 7.45 (m, 15 H, ArH). ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.1, 30.4, 31.4, 72.4, 74.3, 74.5, 75.3, 76.3, 77.7, 78.5, 84.8, 127.5, 127.6, 127.7, 128.1, 128.2, 128.3, 128.4, 138.1, 138.2,

138.5, 195.4. IR ($CDCl_3$) 621, 697, 740, 1114, 1370, 1463, 1506, 1693, 2868, 2936 cm^{-1}. FABMS *m/z* calcd for $C_{30}H_{35}O_5S$: 507.2205 ($M+H^+$); found 507.2221.

1-*S*-Methyl-2,6-anhydro-1,7-dideoxy-3,4,5-tri-*O*-benzyl-L-glycero-L-galacto-heptitol (19): 1-*S*-Acetyl-2,6-anhydro-1,7-dideoxy-3,4,5-tri-*O*-benzyl-L-glycero-L-galacto-heptitol (**18**, 79 mg, 0.16 mmol) was dissolved in methanol (3 mL). Sodium methoxide (0.84 mg, 0.016 mmol) was added. After 30 min, the methanol was removed *in vacuo*. The flask was flushed with argon upon removal of the vacuum. THF (3 mL) was added to the crude product followed by methyl iodide (9.2 μL, 0.15 mmol). After 1h, the solvent was removed *in vacuo* and the crude product chromatographed (3:1 hexanes/diethyl ether). The product was obtained as a colorless oil (24 mg, 34%). Rf = 0.58 (25% ethyl acetate:hexanes). $[\alpha]^{22}_D$ = +33.3° (*c* 0.3 in $CHCl_3$). ^1H NMR (250 MHz, $CDCl_3$) δ 1.21 (d, *J* = 6.3, 3 H, CH_3), 2.18 (s, 3 H, SCH_3), 2.65 (dd, *J* = 14.0,8.4 Hz, 1 H, H-1), 2.90 (d, *J* = 14.0 Hz, 1 H, H-1'), 3.41 - 3.53 (m, 2 H, H-2, H-6), 3.60 - 3.66 (m, 2 H, H-4, H-5), 3.82 (t, *J* = 9.2 Hz, 1 H, H-3), 4.66 - 4.81 (m, 4 H, OCH_2Ar), 4.96 - 5.03 (m, 2 H, OCH_2Ar), 7.26 - 7.41 (m, 15 H, ArH). ^{13}C NMR (63 MHz, $CDCl_3$) δ 17.3, 35.8, 72.3, 74.2, 74.5, 75.3, 76.5, 77.5, 80.8, 85.1, 127.5, 127.6, 127.7, 128.1, 128.2, 128.4, 138.3, 138.7. IR ($CDCl_3$) 680, 740, 1098, 1361, 1463, 1489, 1651, 2876, 2953, 3438 cm^{-1}. FABMS *m/z* calcd for $C_{29}H_{34}O_4SNa$: 501.2076 (M+Na); found 501.2058.

1-Methylsulfonyl-2,6-anhydro-1,7-dideoxy-3,4,5-tri-*O*-benzyl-L-glycero-L-galacto-heptitol (20): 1-*S*-Methyl-2,6-anhydro-1,7-dideoxy-3,4,5-tri-*O*-benzyl-L-glycero-L-galacto-heptitol (**19**, 18 mg, 0.038 mmol) was dissolved in dichloromethane (1 mL) and cooled to 0°C. Dimethyldioxirane (1.8 mL, 0.083 mmol) was added. After 30 min, the solvent was removed *in vacuo* to provide the sulfone as a colorless oil (19 mg, 99%). Rf = 0.15 (25% ethyl acetate:hexanes). $[\alpha]^{22}_D$ = -90.9° (*c* 0.22 in $CHCl_3$). ^1H NMR (250 MHz, $CDCl_3$) δ 1.13 (d, *J* = 6.3, 3 H, CH_3), 2.94 (s, 3 H, SO_2CH_3), 3.10 (dd, *J* = 14.9, 9.3 Hz, 1 H, H-1), 3.27 (d, *J* = 14.9 Hz, 1 H, H-1'), 3.53 - 3.83 (m, 5 H, H-2, H-3, H-4, H-5, H-6), 4.62 - 4.81 (m, 4 H, OCH_2Ar), 4.95 - 5.01 (m, 2 H, OCH_2Ar), 7.28 - 7.39 (m, 15 H, ArH). ^{13}C NMR (63 MHz, $CDCl_3$) δ 17.0, 43.4, 56.5, 72.6, 74.6, 74.8, 75.0, 75.1, 75.8, 76.1, 84.8, 127.7, 127.9, 128.0, 128.2, 128.3, 128.6, 137.6, 138.1. IR ($CDCl_3$) 706, 740, 1029, 1089, 1131, 1310, 1463, 2876, 2927, 3412 cm^{-1}. FABMS *m/z* calcd for $C_{29}H_{34}O_6SNa$: 533.1973 (M+Na); found 533.1949.

1-Methylsulfoxyl-2,6-anhydro-1,7-dideoxy-3,4,5-tri-*O*-benzyl-L-glycero-L-galacto-heptitol (21a/b): 1-Methylsulfonyl-2,6-anhydro-1,7-dideoxy-3,4,5-tri-*O*-benzyl-L-glycero-L-galacto-heptitol (**19**, 21.3 mg, 0.0446 mmol) was dissolved in dichloromethane (2 mL) and cooled to 0°C. 50-60% *m*-CPBA (15.4 mg, 0.045 mmol) was added. After 30 min, the solvent was concentrated *in vacuo* and the crude product chromatographed (7:3 benzene/acetone). The sulfoxide was obtained as a colorless oil (15.6 mg, 71%) and as a 1:1 mixture of diastereomers based upon integration of the methyl sulfoxide singlets. Rf = 0.40 (30% acetone:benzene). ^1H NMR (250 MHz, $CDCl_3$) δ 1.14 (d, *J* = 6.4 Hz, 3 H, CH_3), 2.52 (s, 3 H, $SOCH_3$), 2.62 (s, 3 H, $SOCH_3$), 2.91 (dd, *J* = 13.5, 7.2 Hz, 1 H, H-1), 3.06 (d, *J* = 13.1 Hz, 1 H,

H-1'), 3.52 (dd, J = 12.2, 5.2 Hz, 1 H), 3.62 - 3.78 (m, 3 H), 3.86 (t, J = 8.9 Hz, 1 H, H-3), 4.62 - 4.80 (m, 4 H, OCH_2Ar), 4.99 (dd, J = 11.4, 3.2 Hz, OCH_2Ar), 7.29 - 7.36 (m, 15 H, ArH). ^{13}C NMR (63 MHz, $CDCl_3$) δ 16.9, 17.2, 38.9, 39.8, 54.4, 57.7, 72.4, 72.5, 72.8, 73.2, 74.5, 74.7, 74.8, 75.0, 75.1, 76.2, 76.3, 77.2, 84.8, 85.0, 127.6, 127.7, 127.8, 128.2, 128.3, 128.4, 128.5, 138.1, 138.4. IR ($CDCl_3$) 706, 740, 1021, 1055, 1098, 1157, 1344, 1463, 1489, 1634, 2885, 3038, 3072, 3455 cm^{-1}. FABMS *m/z* calcd for $C_{29}H_{34}O_5SNa$: 517.2025 (M + Na); found 517.2015.

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