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Synthesis of Mono- and Dihydroxylated Furanoses, Pyranoses, and an Oxepanose for the Preparation of Natural Product Analogue Libraries

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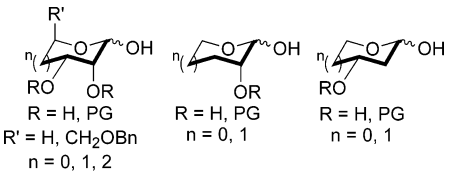

Numerous biologically active natural products contain furanoses and pyranoses with mono- and dihydroxylated substituents. However, much of the structure−activity studies on such molecules is gathered on the aglycons without attention to the corresponding carbohydrate components. Consequently, there are few synthetic procedures that enable the rapid preparation of mono- and dihydroxyfuranoses and mono- and dihydroxypyranoses and no report for a 3,4-dihydroxyoxepanose. In this article we report the practical synthesis of orthogonally protected five-, six-, and seven-membered carbohydrate derivatives. The succinct manner in which these molecules were synthesized allows the rapid preparation of analogues aimed at discovering the role of ring size and individual hydroxyl moieties on the pyranose skeleton.

Introduction

Thousands of natural products bearing carbohydrates have been isolated from nature, and many of these molecules have impressive biological activities that are severely compromised by removal of the sugar moieties.[1−6] Etoposide,[7] bleomycin,[8,9] and novobiocin[10] are three such molecules that contain substituted pyranoses and are clinically used for the treatment of cancer (Figure 1).

The carbohydrate groups in many of these natural products provide increased solubility as compared to their aglycons,[11,12] specific interactions with their biological target,[13] and even substrates for subsequent biological activation/modification.[14] Despite their essential roles, very little attention has been paid toward enhancing their drug discovery potential in comparison to their aglycon counterparts. It is likely that alterations to the pyranose ring will have significant effects on the biological activities manifested by these natural products. These effects may include altered absorption, solubility, lability, and interactions with a specific biological target. In the latter case, it is reasonable to suggest that ring-expanded or -contracted analogues will realign the accompanying hydroxyl moieties into regions of the binding pocket that may result in either increased or decreased affinity. On the other hand, removal of one hydroxyl group may abolish or attenuate interactions with the cognate receptor. Considering the potential effects that can arise from pyranose modifications, it was surprising to realize that practical methods for the preparation of ring-expanded,

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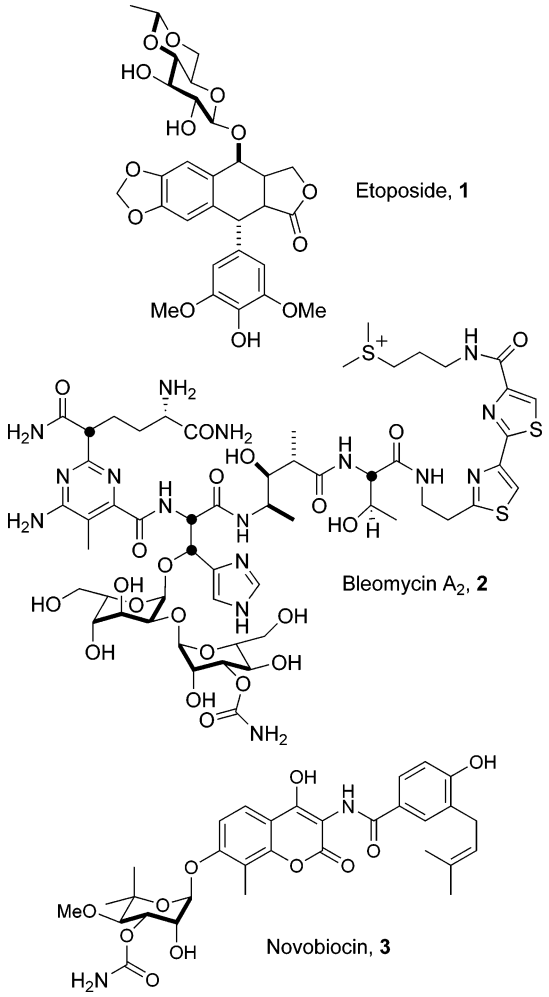


FIGURE 1. Clinically used pyranose-containing drugs.

ring-contracted, and des(hydroxyl) variants of the pyranose skeleton remain largely unreported.[15,16] In this article we describe the synthesis of protected hydroxyl-substituted furanoses, pyranoses, and an oxepanose as precursors for the assembly of carbohydrate-containing natural products as a potential application toward elucidation of structure−activity relationships for 3,4-dihydroxypyranoses.

Results and Discussion

Pyranose Derivatives. In total, eight derivatives of pyranose were envisioned to represent both ring-expanded and ring-contracted analogues as shown in Figure 2, of which four were six-membered cyclic acetals containing hydroxyl replacements at either the 3-, 4-, and/or 6-positions (**4**−**7**). A ring-expanded analogue was prepared in the form of the oxepanose derivative, **8**. Likewise, ring-contracted furanose analogues **9**−**11** were also synthesized. The protected variants of these compounds were prepared so that they can be used directly for subsequent coupling with requisite alcohols/phenols to afford natural product analogues.

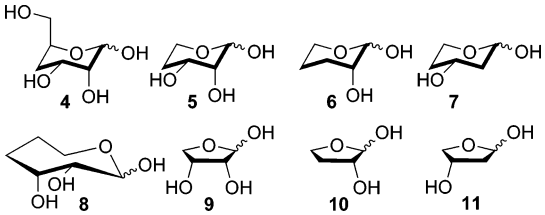
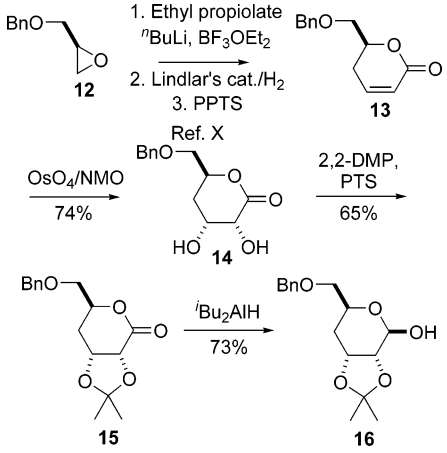


FIGURE 2. Pyranose analogues.

Not only does sugar **4** represent a pyranose derivative, but it can also be envisioned as a ring-expanded analogue of ribose. The 7-benzyloxy-3,4-isopropylidene protected derivative of sugar **4** was prepared from lactone **13**, which in turn was prepared by known methods from benzyl (*R*)-glycidyl ether **12**, Scheme 1.[17,18] Dihydroxylation of the α,β-unsaturated lactone provided the corresponding diol **14** in good yield and with complete diastereoselectivity. The resulting diol was protected as the acetonide, **15**, before reduction of the lactone with diisobutylaluminum hydride to give **16** as a sole anomer. It is well-known that hemiacetals of this type can be activated in the presence of such protecting groups and coupled with requisite alcohols or phenols to produce the corresponding sugar-derived products.[19−22] Afterward, these protecting groups can be removed without affecting the glycosidic linkage and thus providing orthogonally protected precursors to the desired compounds.

SCHEME 1



The protected variant of sugar **5** was synthesized from 2-benzyloxy-5,6-dihydro-2*H*-pyran (**18**), which originated from 3,4-dihydro-2*H*-pyran (**17**), by treatment with phenylselenium chloride and benzyl alcohol, followed by oxidation and elimination (Scheme 2).[23,24] The resulting olefin was oxidized with osmium tetroxide to furnish diol

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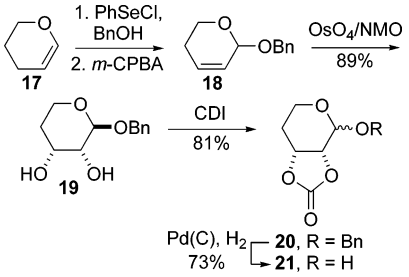
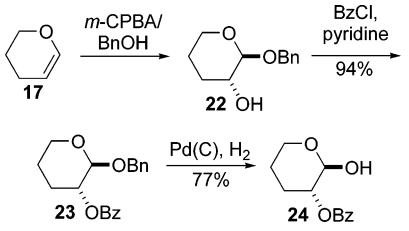
19.[25] In the case of bleomycin and novobiocin, the pyranose moiety contains a carbamate in lieu of the free alcohols. Unfortunately, there is no method for the selective carbamoylation of compounds containing multiple hydroxyl groups. However, it is well precedented that treatment of cyclic carbonates with methanolic ammonia can produce carbamate products in good yields and with reasonable regioselectivity.[26] Alternatively, cyclic carbonates can be removed by treatment with triethylamine and methanol to afford the free alcohols.[27] These conditions are suitable for deprotection/modification of the cyclic carbonate after subsequent coupling of the hemiacetal to the requisite hydroxyl group. Because of these properties, the cyclic carbonate was chosen as a versatile protecting group for various sugar derivatives prepared in this article. As such, the diol was treated with 1,1′-carbonyldiimidazole to afford the cyclic carbonate product, **20**.[28] Hydrogenolysis of the benzyloxy acetal provided the protected analogue of sugar **5**, **21**.

SCHEME 2



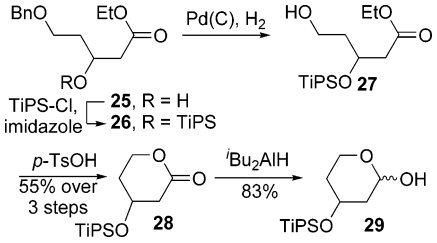
Dihydropyran **17** was also a suitable reagent for the preparation of protected sugar derivative **24** (Scheme 3). As such, the cyclic enol ether was treated with *m*-chloroperoxybenzoic acid in a solution of benzyl alcohol to afford the corresponding benzyloxy acetal **22**.[29] Benzoylation of the secondary alcohol, followed by hydrogenolysis of the benzyl ether, afforded the protected racemic sugar analogue **24**.

SCHEME 3



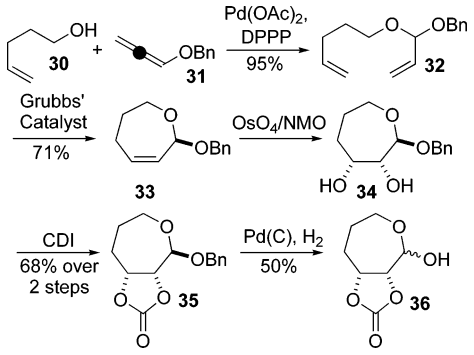
The triisopropylsilyl ether protected version of sugar **7** was prepared from ethyl 5-benzyloxy-3-hydroxypentanoate (**25**, Scheme 4).[30] Conversion of the free alcohol into the silyl ether **26** was accomplished in high yield. Removal of the benzyl-protecting group, followed by treatment with *p*-toluenesulfonic acid, provided **28**, which was reduced with diisobutylaluminum hydride to furnish the racemic hemiacetal, **29**.

SCHEME 4



Oxepanose Analogue. The cyclic seven-membered ring diol **8** was prepared by a more conventional method utilizing ring-closing metathesis to provide the cyclic olefinic product. 4-Penten-1-ol (**30**) was treated with benzyloxy allene **31**, which in the presence of palladium provided the linear benzyl-protected hemiacetal **32** (Scheme 5).[31] Ring-closing metathesis using Grubb's second-generation catalyst[32] provided the unsaturated seven-membered ring **33**. Oxidation of the alkene with osmium tetroxide resulted in anti-dihydroxylation to give **34**, which was converted to the cyclic carbonate before removal of the benzyl group to furnish a racemic mixture of **36**.

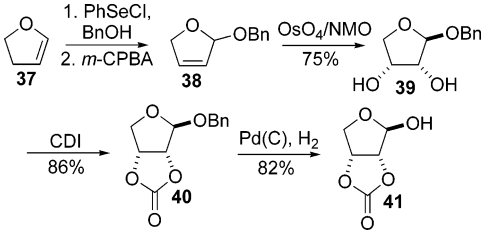
SCHEME 5



Furanose Derivatives. Novobiocin competitively binds to a nucleotide-binding site in the C-terminus of Hsp90 versus ATP.[33] Therefore, one can propose that the noviose component of novobiocin may be interacting with Hsp90 as a surrogate for the ribose ring. Consequently, it may prove valuable to prepare furanose derivatives that project hydroxyl groups into the recognition motif that normally binds the ATP ribose ring.

To prepare the protected sugar analogue of **9**, dihydrofuran was oxidized to the olefinic benzyloxy-acetal **38**,[34] which was further oxidized with catalytic osmium tetroxide and stoichiometric 4-methylmorpholine *N*-oxide

SCHEME 6



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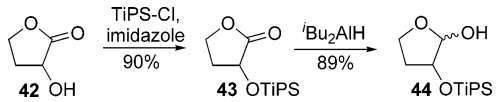
to afford the corresponding diol, **39** (Scheme 6). Once again, the diol was protected as the carbonate before removal of the benzyl group by hydrogenolysis to give racemic **41**.

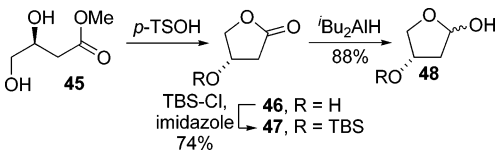
Triisopropylsilyl ether protected 2-hydroxyfuranose **44** was prepared from commercially available 2-hydroxybutyrolactone (**42**) by protection of the free hydroxyl group, followed by reduction of the lactone as shown in Scheme 7.

SCHEME 7



TBS-protected 3-hydroxyfuranose **48** was prepared from methyl 3,4-dihydroxybutanoate, **45** (Scheme 8).[35] Treatment of the diol with *p*-toluenesulfonic acid resulted in formation of the corresponding 2-hydroxylactone **46**. Protection of the hydroxyl substituent, followed by reduction of the lactone, provided the corresponding hemiacetal **48**.

SCHEME 8



Conclusion

Numerous natural products contain modified pyranose rings, and it is important that synthetic procedures are available for the preparation of analogues that can unveil structure−activity relationships with regards to the carbohydrate functionality. In this article we provide practical methods for the construction of eight orthogonally protected pyranose analogues that are suitable for coupling in an effort to elucidate structure−activity relationships for the pyranose moiety. Although many of these compounds were prepared in racemic fashion, it is likely that the utilization of Sharpless' asymmetric dihydroxylation procedure will afford enantioenriched products.

Experimental Section

(3*R*,4*R*,6*S*)-6-(Benzyloxymethyl)-3,4-dihydroxytetrahydropyran-2-one (14). Osmium tetroxide (24.17 mg, 0.128 mmol) was added to a solution of **13** (1.0 g, 4.6 mmol) in H_2O (8 mL) and acetone (8 mL). The mixture was stirred at 25 °C for 15 min before the addition of 4-methylmorpholine *N*-oxide (1.23 g, 10.5 mmol). The homogeneous solution was stirred at 25 °C until **13** was consumed (∼4 h) as evidenced by TLC. H_2O (80 mL) was added, and the aqueous layer was extracted with EtOAc (3 × 80 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated. The residue was purified by chromatography (SiO_2, 50% EtOAc in hexanes) to afford **14** (850 mg, 74% yield) as a colorless oil: $[\alpha]^{25}_D$ +15.7 (*c* 0.92, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.26−7.10 (m, 5H), 4.75 (ddd, J = 11.1, 8.2, 3.7 Hz, 1H), 4.62 (br s, 1H), 4.44 (d, J = 11.8 Hz, 1H), 4.38 (d, J = 11.8 Hz, 1H), 4.21 (m, 1H), 4.16 (br s, 1H), 4.03 (d, J = 4.9 Hz, 1H), 3.99 (d, J = 4.9 Hz, 1H), 3.53 (dd, J = 3.4 Hz, 11.0 Hz, 1H), 3.39 (dd, J = 3.7, 11.0 Hz, 1H), 2.20−1.90 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 174.4, 138.0, 128.9 (2C), 128.3, 128.1 (2C), 77.5, 74.0, 71.4, 70.8, 66.4, 30.3; IR (film) ν_{max} 3433, 3421, 2924, 2864, 1734, 1454, 1367, 1231, 1192, 1101, 1047, 739, 698, 667 cm^{-1}; HRMS (ESI$^+$) *m/z* 275.0896 (M + Na, $C_{13}H_{16}O_5Na_1$ requires 275.0895).

(3a*R*,6*S*,7a*R*)-6-(Benzyloxymethyl)-2,2-dimethyl-dihydro-3a*H*-[1,3]dioxolo[4,5-*c*]pyran-4(6*H*)-one (15). 2,2-Dimethoxypropane (2.25 mL 29.8 mmol) was added to a solution of **14** (900 mg, 3.57 mmol) in acetone (14 mL). *p*-Toluenesulfonic acid (15.6 mg, 0.08 mmol) was added to the solution, which was stirred at 25 °C for 2 h. The solvent was removed in vacuo, and saturated aqueous $NaHCO_3$ (50 mL) was added. The aqueous layer was extracted with EtOAc (3 × 50 mL), and the combined organic layers were dried (Na_2SO_4), filtered, and concentrated to afford **15** (650 mg, 65% yield) as a colorless oil: $[\alpha]^{25}_D$ +36.0 (*c* 0.1, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.29−7.12 (m, 5H), 4.67 (m, 1H), 4.57 (m, 1H), 4.48 (m, 3H), 3.59 (dd, J = 10.9, 3.7 Hz, 1H), 3.53 (dd, J = 10.9, 4.4 Hz, 1H), 2.02−1.85 (m, 2H), 1.40 (s, 3H), 1.27 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 168.5, 138.0, 128.9 (2C), 128.3, 128.2 (2C), 111.0, 74.7, 74.0, 73.2, 72.0, 71.6, 30.9, 26.5, 24.5; IR (film) ν_{max} 2935, 1749, 1456, 1375, 1261, 1209, 1070, 1040, 737, 698, 677 cm^{-1}; HRMS (ESI$^+$) *m/z* 315.1205 (M + Na, $C_{16}H_{20}O_5Na_1$ requires 315.1208).

(3a*R*,6*S*,7a*R*)-6-(Benzyloxymethyl)-2,2-dimethyl-tetrahydro-3a*H*-[1,3]dioxolo[4,5-*c*]pyran-4-ol (16). Compound **15** (480 mg, 1.83 mmol) was dissolved in CH_2Cl_2 (15 mL) before diisobutylaluminum hydride (1.63 mL, 1 M in hexanes, 1.63 mmol) was added dropwise at −78 °C. The resulting solution was stirred at −78 °C for 2 h before EtOAc (20 mL) was added. After the solution was warmed to 25 °C, saturated aqueous sodium potassium tartrate (15 mL) was added, and the heterogeneous solution was stirred for 30 min. The mixture was extracted with EtOAc (3 × 30 mL), and the combined organic layers were washed with saturated aqueous NaCl (50 mL), dried (Na_2SO_4), filtered, and concentrated. The residue was purified by chromatography (SiO_2, 40% EtOAc in hexanes) to afford **16** (350 mg, 73% yield) as colorless oil: $[\alpha]^{25}_D$ −40.0 (*c* 0.42, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.32−7.18 (m, 5H), 4.80 (dd, J = 5.5 Hz, 3.5 Hz, 1H), 4.53 (d, J = 12.1 Hz, 1H), 4.49 (d, J = 12.1 Hz, 1H), 4.40 (m, 1H), 3.97 (m, 1H), 3.81 (t, J = 5.6 Hz, 1H), 3.55 (d, J = 3.5 Hz, 1H), 3.47−3.38 (m, 2H), 1.92−1.84 (m, 2H), 1.44 (s, 3H), 1.30 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 138.2, 128.9 (2C), 128.2, 128.1 (2C), 109.6, 95.9, 76.0, 73.9, 72.7, 72.1, 69.5, 28.6, 28.0, 26.0; IR (film) ν_{max} 3420, 2986, 2934, 2894, 2872, 1454, 1369, 1251, 1236, 1217, 1161, 1095, 1047, 738, 698 cm^{-1}; HRMS (ESI$^+$) *m/z* 317.1368 (M + Na, $C_{16}H_{22}O_5Na_1$ requires 317.1365).

2-(Benzyloxy)-tetrahydro-2*H*-pyran-3,4-diol (19). Osmium tetroxide (0.1 mL, 20 mg/mL in toluene, 0.007 mmol) was added to a solution of **18** (1.6 g, 9.2 mmol) and 4-methylmorpholine *N*-oxide (2.3 g, 20 mmol) in acetone (10 mL) and H_2O (10 mL). The mixture was stirred at 25 °C for 14 h, diluted with H_2O (200 mL) and extracted with EtOAc (3 × 100 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated. The residue was purified by chromatography (SiO_2, 50% EtOAc in hexanes) to afford **4** (1.70 g, 89%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.37 (m, 5H), 4.82 (m, 2H), 4.53 (d, J = 11.6 Hz, 1H), 4.11 (m, 1H), 3.82 (m, 2H), 3.67 (m, 1H), 2.37 (br. s, 2H), 1.84 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 137.7, 128.9 (2C), 128.4(2C), 128.3, 99.9, 70.9, 70.2, 66.6, 59.8, 30.3; IR (film) ν_{max} 3480, 2975, 2867, 1250, 1180, 1068 cm^{-1}; HRMS (FAB$^+$) *m/z* 225.1129 (M + H$^+$, $C_{12}H_{16}O_4$ requires 225.1127).

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4-(Benzyloxy)-tetrahydro-3a*H*-[1,3]dioxolo[4,5-*c*]pyran-2-one (20). A solution of **19** (1.53 g, 7.3 mmol) and 1,1-carbonyl diimidazole (1.95 g, 12 mmol) in 1,2-dichloroethane (20 mL) was heated at reflux for 8 h. The mixture was cooled to 25 °C, diluted with EtOAc (50 mL), and washed with water (3×100 mL). The organic layer was dried (Na_2SO_4), filtered, and concentrated. Purification by chromatography (SiO_2, 25% EtOAc in hexanes) afforded **20** (1.38 g, 81%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.37 (m, 5H), 4.97 (m, 2H), 4.82 (d, J = 11.8 Hz, 1H), 4.60 (d, J = 11.8 Hz, 1H), 4.54 (dd, J = 2.0, 7.6 Hz, 1H), 3.87 (m, 2H), 2.29 (m, 1H), 2.04 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 154.5, 136.9, 129.0 (2C), 128.7, 128.5(2C), 96.0, 74.1, 72.7, 70.5, 57.0, 25.2; IR (film) ν_{max} 2976, 2887, 1803, 1300, 1250, 1163 cm^{-1}; HRMS (FAB$^+$) *m/z* 251.0917 (M + H$^+$, $C_{13}H_{14}O_5$ requires 251.0919).

4-Hydroxy-tetrahydro-3a*H*-[1,3]dioxolo[4,5-*c*]pyran-2-one (21). Palladium on charcoal (10%, 150 mg) was added to a solution of **20** (1.23 g, 4.9 mmol) in methanol (10 mL). The mixture was stirred under H_2 (1 atm) for 48 h and filtered over Celite. The eluent was concentrated, and the residue was purified by chromatography (SiO_2, 50% EtOAc in hexanes) to afford **21** (575 mg, 73%) as a mixture of anomers (4:1): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.26 (s, 1H minor), 5.16 (d, J = 2.8 Hz, 1H major), 5.02 (m, 1H major), 4.95 (m, 1H minor), 4.62 (dd, J = 4.0, 6.8 Hz, 1H minor), 4.51 (dd, J = 2.8, 7.2 Hz, 1H major), 4.20 (m, 1H minor), 3.99 (m, 2H major and 2H minor), 2.29 (m, 1H major), 2.07 (m, 1H major and 2H minor); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 155.0 (major and minor), 92.3 (major), 89.8 (minor), 75.0 (major), 74.3 (minor), 73.5 (major), 72.6 (minor), 57.6 (major), 55.4 (minor), 25.5 (minor), 25.1 (major); IR (film) ν_{max} 3400, 2967, 2870, 1807, 1190, 1074 cm^{-1}; HRMS (FAB$^+$) *m/z* 161.0455 (M + H$^+$, $C_6H_8O_5$ requires 161.0450).

2-(Benzyloxy)-tetrahydro-2*H*-pyran-3-yl Benzoate (23), Benzoic chloride (420 mg, 3 mmol) was added dropwise to a solution of **22** (416 mg, 2 mmol) in pyridine (6 mL) at 0 °C. The mixture was warmed to 25 °C and stirred for 8 h. H_2O (50 mL) was added and extracted with EtOAc (50 mL). The organic layer was washed with 5% HCl (30 mL), dried (Na_2SO_4), filtered, and concentrated. The residue was purified by chromatography (SiO_2, 25% EtOAc in hexanes) to afford **23** (610 mg, 94%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.10 (m, 2H), 7.59 (m, 1H), 7.47 (m, 2H), 7.37 (m, 5H), 5.07 (m, 1H), 4.84 (m, 2H), 4.61 (d, J = 12.0 Hz, 1H), 3.99 (td, J = 2.8, 10.8 Hz, 1H), 3.68 (m, 1H), 2.23 (m, 1H), 2.07 (m, 1H), 1.89 (m, 1H), 1.55 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 166.1, 138.0, 133.4, 130.6, 130.1 (2C), 128.8 (2C), 128.7 (2C), 128.2 (2C), 128.1, 97.3, 69.6, 69.4, 61.3, 24.5, 21.5; IR (film) ν_{max} 2988, 2875, 1680, 1350, 1240, 1177, 1069 cm^{-1}; HRMS (FAB$^+$) *m/z* 313.1441 (M + H$^+$, $C_{19}H_{20}O_4$ requires 313.1440).

2-Hydroxy-tetrahydro-2*H*-pyran-3-yl Benzoate (24). Palladium on charcoal (10%, 60 mg) was added to a solution of **23** (320 mg, 1 mmol) in THF (4 mL). The mixture was stirred under H_2 (1 atm) for 70 h and filtered over Celite. The eluent was concentrated, and the residue was purified by chromatography (SiO_2, 35% hexanes in EtOAc) to afford **24** (180 mg, 77%) as a mixture of anomers (2:1): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.10 (m, 2H major and 2H minor), 7.59 (m, 1H major and 1H minor), 5.15 (m, 1H major), 4.94 (m, 1H major and 2H minor), 4.07 (m, 1H major and 1H minor), 3.63 (m, 1H major and 1H minor), 3.44 (d, J = 5.6 Hz, 1H major), 3.23 (J = 5.6 Hz, 1H minor), 2.24 (m, 1H major and 1H minor), 1.90 (m, 2H major and 2H minor), 1.70 (m, 1H major and 1H minor); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 166.8 (major), 166.5 (minor), 133.6 (major and minor), 130.3 (2C major and 2C minor), 128.8 (2C major and 2C minor), 95.0 (major), 92.3 (minor), 71.7 (major), 71.1 (minor), 63.3 (major), 62.0 (minor), 26.0 (major), 24.8 (minor), 23.2 (minor), 23.0 (major); IR (film) ν_{max} 3370, 2967, 2875, 1675, 1345, 1261, 1178 cm^{-1}; HRMS (FAB$^+$) *m/z* 223.0975 (M + H$^+$, $C_{12}H_{14}O_4$ requires 223.0970).

4-(*tert*-Butyldiphenylsilyloxy)-tetrahydropyran-2-one (28). Imidazole (136 mg, 2 mmol) was added to a solution of *tert*-butyldiphenylsilyl chloride (412 mg, 1.5 mmol) and methyl 5-(benzyloxy)-3-hydroxypentanoate (270 mg, 1.13 mmol) in DMF (2 mL) at 25 °C. The resulting mixture was stirred for 8 h, poured into H_2O (20 mL), and extracted with EtOAc (30 mL). The organic layer was washed with H_2O (30 mL), dried (Na_2SO_4), filtered, and concentrated. The residue was dissolved in MeOH (6 mL), and palladium on charcoal (10%, 65 mg) was added. The resulting mixture was stirred under H_2 (1 atm) for 48 h and filtered over Celite. The eluent was concentrated and then redissolved in chloroform (30 mL). After *p*-toluenesulfonic acid (20 mg, 0.12 mmol) was added, the mixture was stirred at 25 °C for 24 h and concentrated. The residue was purified by chromatography (SiO_2, 20% EtOAc in hexanes) to afford **28** (220 mg, 55%) as a white solid: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.65 (m, 4H), 7.49−7.40 (m, 6H), 4.61 (m, 1H), 4.23 (m, 2H), 2.76 (m, 1H), 2.59 (m, 2H), 1.85 (m, 2H), 1.09 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.4, 136.0 (4C), 133.5 (2C), 130.4 (2C), 128.3 (2C), 128.2 (2C), 65.7, 65.2, 40.1, 31.4, 27.1 (3C), 19.5; IR (film) ν_{max} 2945, 2873, 1750, 1180, 1130, 859 cm^{-1}; HRMS (FAB$^+$) *m/z* 355.1727 (M + H$^+$, $C_{21}H_{26}O_3Si$ requires 355.1729).

4-(*tert*-Butyldiphenylsilyloxy)-tetrahydro-2*H*-pyran-2-ol (29). Diisobutylaluminum hydride (1 M in hexanes, 0.65 mL, 0.65 mmol) was added to a solution of **28** (220 mg, 0.62 mmol) in CH_2Cl_2 (15 mL) at −78 °C. The resulting mixture was stirred at −78 °C for 30 min and warmed to 25 °C. Saturated aqueous sodium potassium tartrate (20 mL) was added, and the heterogeneous solution was stirred for 1 h. The organic layer was separated, washed with H_2O (30 mL), dried (Na_2SO_4), filtered, and concentrated. The residue was purified by chromatography (SiO_2, 25% EtOAc in hexanes) to afford **29** (182 mg, 83%) as a mixture of anomers (2:1): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.69−7.66 (m, 4H major and 4H minor), 7.44−7.39 (m, 6H major and 6H minor), 5.28 (m, 1H minor), 5.04 (m, 1H major), 4.25 (m, 1H major and 1H minor), 4.18 (m, 1H minor), 3.85 (m, 2H major), 3.60 (m, 1H minor), 2.68 (br. s, 1H), 1.85 (m, 2H major), 1.68 (m, 2H major and 1H minor), 1.45 (m, 3H minor), 1.12 (Minor, 9H), 1.09 (s, 9H major); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 136.1 (4C major and 4C minor), 134.5 (major), 134.4 (minor), 133.4 (major), 133.2 (minor),130.5 (2C minor), 130.4 (2C major), 128.3 (2C minor), 128.1 (2C major), 128.0 (2C major and 2Cminor), 93.4 (minor), 93.3 (major), 67.8 (minor), 66.2 (major), 60.5 (major), 56.2 (minor), 40.6 (major), 38.3 (minor), 34.4 (major), 32.9 (minor), 27.1 (3C major and 3C minor), 19.6 (major), 19.4 (minor); IR (film) ν_{max} 3400, 2960, 2868, 1175, 1049, 897 cm^{-1}; HRMS (FAB$^+$) *m/z* 357.1891 (M + H$^+$, $C_{21}H_{28}O_3Si$ requires 357.1886).

1-((1-(Pent-4-enyloxy)allyloxy)methyl)benzene (32). A solution of 4-pantene-1-ol (430 mg, 5 mmol), 1-benzyloxylallene (1.33 g, 9.1 mmol), and Et_3N (760 mg, 7.5 mmol) in acetonitrile (10 mL) was added to a dry flask containing $Pd(OAc)_2$ (56 mg, 0.25 mmol) and DPPP (103 mg, 0.25 mmol) under argon. The resulting mixture was heated at reflux for 2 h and concentrated. The residue was dissolved in hexanes (50 mL), washed with H_2O (50 mL), dried (Na_2SO_4), filtered, and concentrated. The residue was purified by chromatography (SiO_2, 2% EtOAc in hexanes) to afford **32** (1.1 g, 95%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.36 (m, 5H), 5.90 (m, 2H), 5.47 (d, J = 16.0 Hz, 1H), 5.35 (d, J = 9.2 Hz, 1H), 5.03 (m, 3H), 4.67 (d, J = 12.0 Hz, 1H), 4.57 (d, J = 12.0 Hz, 1H), 3.65 (m, 1H), 3.50 (m, 1H), 2.17 (m, 2H), 1.73 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 138.6, 138.5, 135.5, 128.8 (2C), 128.1 (2C), 127.9, 119.0, 115.2, 101.3, 67.4, 65.4, 30.8, 29.3; IR (film) ν_{max} 2927, 2873, 1272, 1176, 1112 cm^{-1}; HRMS (FAB$^+$) *m/z* 233.1542 (M + H$^+$, $C_{15}H_{20}O_2$ requires 233.1542).

(*Z*)-2-(Benzyloxy)-2,5,6,7-tetrahydrooxepine (33). Grubbs second generation catalyst (100 mg, 0.11 mmol) was added to a solution of **32** (1.32 g, 5.6 mmol) in CH_2Cl_2 (100 mL). The resulting mixture was heated at reflux for 4 h and cooled to 25 °C. The solvent was evaporated, and the residue purified by chromatography (SiO_2, 2% ethyl acetate in hexanes) to afford **33** (820 mg, 71%) as a colorless oil: ^{1}H NMR ($CDCl_3$,

400 MHz) δ 7.36 (m, 5H), 5.88 (m, 1H), 5.66 (m, 1H), 5.24 (d, J = 1.2 Hz, 1H), 4.80 (d, J = 12.0 Hz, 1H), 4.57 (d, J = 12.0 Hz, 1H), 4.12 (m, 1H), 3.73 (m, 1H), 2.35 (m, 1H), 2.27 (m, 1H), 1.87 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 138.3, 132.7, 131.2, 128.8 (2C), 128.4 (2C), 128.0, 100.3, 69.5, 65.0, 29.5, 26.6; IR (film) ν_{max} 2978, 2875, 1640, 1277, 1190, 1087 cm^{-1}; HRMS (FAB$^+$) *m/z* 205.1235 (M + H$^+$, $C_{13}H_{16}O_2$ requires 205.1229).

4-(Benzyloxy)-hexahydro-[1,3]dioxolo[4,5-*c*]oxepin-2-one (35). Osmium tetroxide (0.1 mL, 4% in H_2O, 0.007 mmol) was added to a solution of **33** (820 mg, 4 mmol) and 4-methylmorpholine *N*-oxide (702 mg, 6.0 mmol) in acetone (4 mL) and H_2O (4 mL). The mixture was stirred at 25 °C for 12 h, diluted with H_2O (40 mL), and extracted with EtOAc (3 × 50 mL). The organic layers were combined, dried (Na_2SO_4), filtered, and concentrated. The residue was dissolved in 1,2-dichloroethane (5 mL), and 1,1-carbonyl diimidazole (486 mg, 3 mmol) was added. The resulting mixture was heated at reflux for 14 h, diluted with EtOAc (30 mL), washed with H_2O (3 × 30 mL), dried (Na_2SO_4), filtered, and concentrated. The residue was purified by chromatography (SiO_2, 30% EtOAc in hexanes) to afford **35** (720 mg, 68%) as a colorless oil: ^{1}H NMR (CD_3CN, 400 MHz) δ 7.36 (m, 5H), 4.95 (m, 2H), 4.81 (d, J = 1.2 Hz, 1H), 4.68 (t, J = 8.0 Hz, 1H), 4.58 (d, J = 12.0 Hz, 1H), 4.06 (m, 1H), 3.59 (m, 1H), 2.01 (m, 1H), 1.96 (m, 1H), 1.78 (m, 1H), 1.67 (m, 1H); ^{13}C NMR (CD_3CN, 125 MHz) δ 154.5, 137.9, 128.8 (2C), 128.4 (2C), 128.2, 102.1, 79.7, 78.2, 70.4, 69.8, 29.2, 27.0; IR (film) ν_{max} 2975, 2860, 1806, 1178, 1049 cm^{-1}; HRMS (FAB$^+$) *m/z* 265.1078 (M + H$^+$, $C_{14}H_{16}O_5$ requires 265.1076).

4-Hydroxy-hexahydro-[1,3]dioxolo[4,5-*c*]oxepin-2-one (36). Palladium on charcoal (10%, 75 mg) was added to a solution of **35** (700 mg, 2.65 mmol) in THF (5 mL). The mixture was stirred under H_2 (1 atm) for 60 h and filtered over Celite. The eluent was concentrated, and the residue was purified by chromatography (SiO_2, 65% EtOAc in hexanes) to afford **36** (232 mg, 50%) as a mixture of anomers (3:2): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.09 (d, J = 7.6 Hz, 1H major), 5.04 (t, J = 8.0 Hz, 1H minor), 4.99 (s, 1H minor), 4.87 (m, 1H major and 1H minor), 4.66 (t, J = 8.0 Hz, 1H major), 4.08 (m, 1H major and 1H minor), 3.65 (m, 1H major), 3.55 (t, J = 10.4 Hz, 1H minor), 2.36 (m, 1H minor), 2.15 (m, 1H major), 1.96 (m, 1H major and 2H minor), 1.81 (m, 1H major), 1.66 (m, 1H major and 1H minor); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 154.4 (minor), 154.3 (major), 97.3 (major), 97.2 (minor), 81.0 (minor), 80.8 (major), 78.1 (major), 76.0 (minor), 70.1 (major), 69.7 (minor), 29.7 (major), 28.3 (minor), 27.1 (major), 25.1 (minor); IR (film) ν_{max} 3400, 2973, 2868, 1806, 1179, 1082 cm^{-1}; HRMS (FAB$^+$) *m/z* 175.0610 (M + H$^+$, $C_7H_{10}O_5$ requires 175.0606).

2-(Benzyloxy)-tetrahydrofuran-3,4-diol (39). Osmium tetroxide (0.2 mL, 20 mg/mL in toluene, 0.014 mmol) was added to a solution of **38** (2.0 g, 11.3 mmol) and 4-methylmorpholine *N*-oxide (2.3 g, 20 mmol) in acetone (10 mL) and H_2O (10 mL). The mixture was stirred at 25 °C for 6 h, diluted with H_2O (200 mL), and extracted with EtOAc (3×100 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated. The residue was purified by chromatography (SiO_2, 60% EtOAc in hexanes) to afford **39** (1.78 g, 75%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.44−7.42 (m, 5H), 5.16 (s, 1H), 4.73 (d, J = 11.6 Hz, 1H), 4.55 (m, 2H), 4.13 (m, 2H), 3.87 (m, 1H), 2.92 (s, 1H), 2.71 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 137.7, 128.9 (2C), 128.4(2C), 128.3, 107.4, 76.3, 72.7, 71.3, 69.8; IR (film) ν_{max} 3350, 2955, 2923, 1448, 1380, 1254, 1136, 1067, 993 cm^{-1}; HRMS (FAB$^+$) *m/z* 211.0972 (M + H$^+$, $C_{11}H_{14}O_4$ requires 211.0970).

4-(Benzyloxy)-tetrahydrofuro[3,4-*d*][1,3]dioxol-2-one (40). A solution of **39** (1.7 g, 8.0 mmol) and 1,1-carbonyl diimidazole (1.95 g, 12 mmol) in 1,2-dichloroethane (20 mL) was heated at reflux for 8 h. The mixture was cooled to 25 °C, diluted with EtOAc (50 mL), washed with H_2O (3 × 100 mL), and dried (Na_2SO_4). The dried solution was filtered and concentrated, and the residue was purified by chromatography (SiO_2, 30% EtOAc in hexanes) to afford **40** (1.62 g, 86%) as a white solid: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.35 (m, 5H), 5.32 (s, 1H), 5.24 (dd, J = 3.6, 6.8 Hz, 1H), 5.01 (d, J = 6.8 Hz, 1H), 4.72 (d, J = 11.6 Hz, 1H), 4.52 (d, J = 11.6 Hz, 1H), 4.26 (d, J = 11.2 Hz, 1H), 4.06 (dd, J = 3.6, 11.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 154.3, 1376.6, 129.0 (2C), 128.7(2C), 128.6, 104.4, 83.0, 79.7, 71.0, 69.6; IR (film) ν_{max} 2950, 2875, 1812, 1179, 1140, 1079, 1054 cm^{-1}; HRMS (FAB$^+$) *m/z* 237.0765 (M + H$^+$, $C_{12}H_{12}O_5$ requires 237.0763).

4-Hydroxy-tetrahydrofuro[3,4-*d*][1,3]dioxol-2-one (41). Palladium on charcoal (10%, 150 mg) was added to a solution of **40** (1.5 g, 6.3 mmol) in methanol (10 mL). The mixture was stirred under H_2 (1 atm) for 40 h and filtered over Celite. The eluent was concentrated, and the residue was purified by chromatography (SiO_2, 50% EtOAc in hexanes) to afford **41** (752 mg, 82%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.72 (s, 1H), 5.27 (dd, J = 3.2, 6.4 Hz, 1H), 5.01 (d, J = 6.4 Hz, 1H), 4.23 (m, 2H), 2.74 (s, 1H); ^{13}C NMR (CD_3OD, 125 MHz) δ 155.3, 100.1, 84.0, 80.0, 70.1; IR (film) ν_{max} 3400, 2967, 2870, 1809, 1366, 1176 cm^{-1}; HRMS (FAB$^+$) *m/z* 147.0289 (M + H$^+$, $C_5H_6O_5$ requires 147.0293).

3-(Triisopropylsilyloxy)-dihydrofuran-2-(3*H*)-one (43). Imidazole (1.02 g, 15 mmol) was added to a solution of triisopropylsilyl chloride (2.90 g, 15 mmol) and 2-hydroxybutrylactone (900 mg, 10 mmol) in DMF (5 mL) at 25 °C. The resulting mixture was stirred for 8 h, poured into H_2O (30 mL), and extracted with EtOAc (30 mL). The organic layer was washed with H_2O (30 mL), dried (Na_2SO_4), filtered, and concentrated. The residue was purified by chromatography (SiO_2, 20% EtOAc in hexanes) to afford **43** (2.17 g, 90%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.52 (t, J = 8.9 Hz, 1H), 4.36 (m, 1H), 4.18 (m, 1H), 2.62 (m, 1H), 2.25 (m, 1H), 1.10 (m, 21H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 176.1, 68.7, 65.0, 33.2, 18.1 (6C), 12.5 (3C); IR (film) ν_{max} 2943, 2866, 1787, 1463, 1218, 1135 cm^{-1}; HRMS (ES$^+$) *m/z* 257.1733 (M + H $C_{13}H_{27}O_3Si$ requires 283.1729).

3-(Triisopropylsilyloxy)-tetrahydrofuran-2-ol (44). Diisobutylaluminum hydride (1 M in hexanes, 2 mL, 2 mmol) was added to a solution of **43** (500 mg, 2 mmol) in CH_2Cl_2 (10 mL) at −78 °C. The mixture was stirred at −78 °C for 15 min and warmed to 25 °C. Saturated aqueous sodium potassium tartrate (15 mL) was added, and the heterogeneous solution was stirred for 1 h. The organic layer was separated, washed with H_2O (30 mL), dried (Na_2SO_4), filtered, and concentrated. The residue was purified by chromatography (SiO_2, 25% EtOAc in hexanes) to afford **44** (445 mg, 89%) as a mixture of anomers (5:4): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.25 (m, 1H major and 1H minor), 4.40 (m, 1H major), 4.31 (m, 1H minor), 4.05 (m, 2H major and 2H minor), 3.79 (m, 1H major), 3.02 (br. s, 1H minor), 2.20 (m, 1H minor), 2.10 (m, 1H major), 1.91 (m, 1H major), 1.83 (m, 1H minor), 1.15−1.03 (m, 21H major and 21H minor); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 103.8 (minor), 97.3 (major), 72.8 (1C major, 1C minor), 67.7 (minor), 65.1 (major), 34.1 (major), 33.5 (minor), 18.2 (6C major and 6C minor), 12.4 (3C major and 3C minor); IR (film) ν_{max} 3420, 2943, 2866, 1463, 1126, 1058 cm^{-1}; HRMS (ES$^+$) *m/z* 283.1699 (M + Na$^+$ $C_{13}H_{28}O_3Si$ requires 283.1705).

4-(*tert*-Butyldimethylsilyloxy)-dihydrofuran-2(3*H*)-one (47). Imidazole (1.36 g, 20 mmol) was added to a solution of *tert*-butyldimethylsilyl chloride (1.57 g, 10.5 mmol) and **46** (700 mg, 7 mmol) in DMF (4 mL) at 25 °C. The resulting mixture was stirred for 8 h, poured into H_2O (20 mL), and extracted with EtOAc (30 mL). The organic layer was washed with H_2O (30 mL), dried (Na_2SO_4), filtered, and concentrated. The residue was purified by chromatography (SiO_2, 20% EtOAc in hexanes) to afford **47** (1.13 g, 74%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.62 (m, 1H), 4.38 (dd, J = 4.8, 10.0 Hz, 1H), 4.18 (dd, J = 2.4, 10.0 Hz, 1H), 2.70 (dd, J = 5.4, 17.6 Hz, 1H), 2.45 (dd, J = 2.8, 17.6 Hz, 1H), 0.89 (s, 9H), 0.09 (s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 176.1, 76.5, 68.5, 38.5, 26.0, 18.3, −4.4, −4.5; IR (film) ν_{max} 2963, 2866, 1780, 1169, 1130 cm^{-1}; HRMS (FAB$^+$) *m/z* 217.1262 (M + H$^+$ $C_{10}H_{20}O_3Si$ requires 217.1260).

4-(*tert*-Butyldimethylsilyloxy)-tetrahydrofuran-2-ol (48). Diisobutylaluminum hydride (1 M in hexanes, 5 mL, 5 mmol) was added to a solution of **47** (1.1 g, 5 mmol) in CH_2Cl_2 (20 mL) at −78 °C. The mixture was stirred at −78 °C for 15 min and warmed to 25 °C. Saturated aqueous sodium potassium tartrate (30 mL) was added, and the heterogeneous solution was stirred for 1 h. The organic layer was separated, washed with H_2O (30 mL), dried (Na_2SO_4), filtered, and concentrated. The residue was purified by chromatography (SiO_2, 25% EtOAc in hexanes) to afford **48** (965 mg, 88%) as a mixture of anomers (5:1): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.67 (m, 1H minor), 5.43 (m, 1H major), 4.60 (m, 1H minor), 4.49 (br. s, 1H), 4.11 (m, 1H minor), 4.07 (d, J = 9.2 Hz, 1H major), 4.01 (d, J = 12.0 Hz, 1H major), 3.91 (m, 1H major), 3.72 (m, 1H minor), 2.07 (m, 1H major and 2H minor), 0.91 (s, 9H major), 0.89 (s, 9H minor), 0.13 (s, 6H major), 0.08 (s, 6H minor); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 99.7 (major), 99.2 (minor), 76.5 (major), 74.8 (minor), 72.7 (major), 72.1 (minor), 44.0 (minor), 42.8 (major), 26.1 (3C major and 3C minor), 18.4 (major), 18.3 (minor), −4.3 (minor), −4.4 (minor), −4.5 (major), −4.6 (major); IR (film) ν_{max} 3435, 2947, 2873, 1469, 1140, 1060 cm^{-1}; HRMS (ES$^+$) *m/z* 241.1239 (M + Na^+ $C_{10}H_{22}O_3Si$ requires 241.1236).

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Supporting Information Available: Spectra for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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