labeled isomers, and high sensitivity and accuracy. For two of the three isomerizations (the two for which substantial quantities of substrates had been synthesized), excellent agreement in measured rate constants based on TDL and FTIR methods was demonstrated.

The mechanistic significance of the rate constants measured by TDL depends on related kinetic work measuring rates of racemization of chiral samples of cyclopropane-*1,2-d*$_2$ and cyclopropane-*1*-^{13}*C-1,2,3-d*$_3$ and on the ways in which kinetic isotope effects are estimated and interpreted. The interpretational issues are by no means simple, and they remain controversial.[24] The TDL spectroscopic methods and kinetic studies reported here should clarify this component of the experimental work on cyclopropane stereomutations. Further experimental and theoretical effort will be needed before the interpretational debate may be concluded.

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Enzymatic Asymmetrization in Organic Media: Synthesis of Unnatural Glucose from Cycloheptatriene

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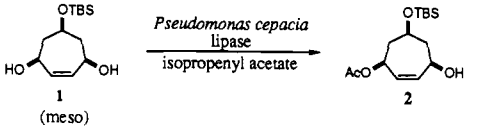
Abstract: *Pseudomonas cepacia* lipase mediated asymmetrization of a *meso*-3-*O*-protected 6-cyclohepten-1,3,5-triol using isopropenyl acetate as solvent produced optically pure monoacetate **2**. Elaboration of **2** by stereoselective oxygenation of the ring system using the Rubottom reaction, diastereoselective reduction, and osmium tetroxide catalyzed cis hydroxylation lead to cycloheptanehexaol derivative **20**. This cyclic polyol was transformed into an allylic alcohol which was subjected to ozonolysis followed by $NaIO_4$ diol cleavage to give L-glucose.

The application of enzymes in syntheses is a topic of much current interest.[1] The use of enzymes, particularly lipases, in organic media has opened the door to a wide variety of substrates unsuitable for aqueous media due to insolubility. Lipases are proving to be very useful due to their stability in organic media and their widespread commercial availability. Enzymatic reactions using prochiral and meso substrates rather than racemic mixtures can be particularly effective, as, in theory, all of the substrate may be processed to a single enantiomer.[2]

In a preliminary report, we recently described the enzymatic asymmetrization of **1** and its C-6 epimer.[3] It was shown that

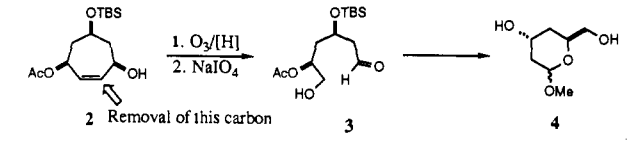


1 (meso) 2

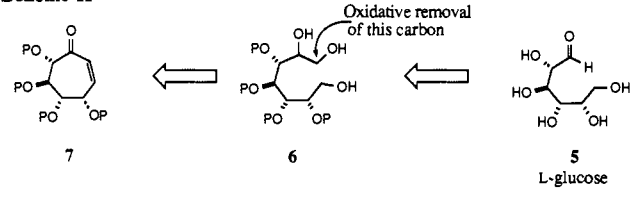
the products of these reactions can be transformed into all possible stereoisomers of 2,4-dideoxyhexose.[4] The efficiency of the synthesis of optically pure monoacetate **2** makes this compound an interesting starting material for the synthesis of a variety of chiral polyoxygenated targets including hexoses and heptoses. There has been much recent interest in the synthesis of unnatural sugars from noncarbohydrate sources.[5] Unnatural sugars, in general, are important as precursors for the synthesis of natural products. The synthesis of the unnatural sugar L-glucose, which has potential use as a noncaloric sweetener,[5c] is the subject of this paper.

Our previous synthesis of 2,4-dideoxyhexose **4** involved ozonolysis of **2**; subsequent reductive workup with sodium borohydride followed by sodium periodate cleavage of the resulting vicinal diol

Scheme I



Scheme II



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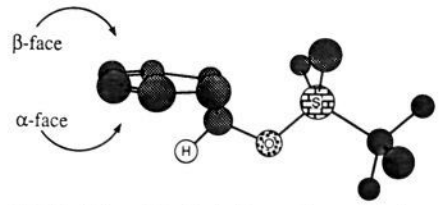
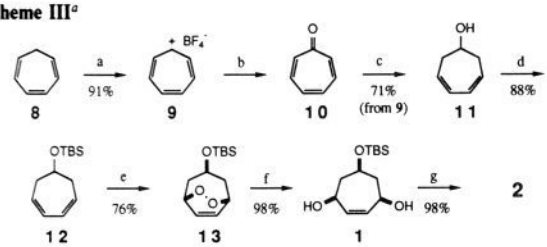


Figure 1. Model of diene **12** with the larger siloxy group in a pseudoaxial conformation.

Scheme III[a]



[a] (a) HBF_4, Ph_3COH. (b) Na_2CO_3, CH_3CN. (c) $NaBH_4$, MeOH. (d) TBS-Cl, imidazole, DMF. (e) $^1O_2$, CH_2Cl_2/MeOH. (f) Zn/HOAc, CH_2Cl_2. (g) Amano PS-30 lipase, isopropenyl acetate. TBS = *tert*-butyldimethylsilyl.

resulted in aldehyde **3**. Deprotection and cyclization then led to our target compound (Scheme I).

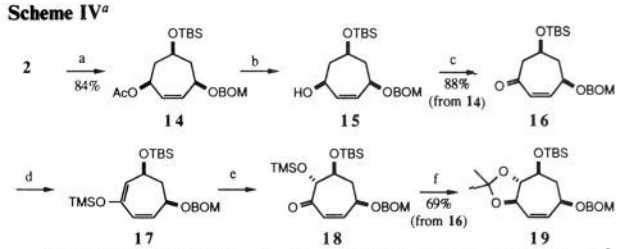
The synthesis of **4** required three carbons to be at the oxidation level of an alcohol, two of which had to posses specific chirality, and one carbon to be at the oxidation level of an aldehyde. For the synthesis of L-glucose (**5**), five carbons require the oxidation level of alcohols, four of which need to be introduced stereoselectivity, and one carbon needs to be at the aldehyde oxidation level. Retrosynthetic analysis (Scheme II) shows hypothesized intermediate **6**, which, upon removal of the indicated CH_2OH and protecting groups, would lead to L-glucose. Previous work in our laboratories, including that summarized in Scheme I, had established a reliable sequence for the removal of the center carbon of a triol derived from an enone such as **7**.

Results and Discussion

Following a sequence developed by Reingold, cycloheptatriene (**8**) was converted to tropone (**10**).[6] The procedure involved a hydride abstraction from cycloheptatriene by trityl cation to give tropylium tetrafluoborate (**9**), which reacted at 50 °C with sodium carbonate to produce tropone and cycloheptatriene in a disproportionation sequence. Reduction of the crude tropone in methanol with $NaBH_4$[7] provided alcohol **11**, which was protected as the *tert*-butyldimethylsilyl ether **12**. Among the many possible ways of forming **11**,[8] the procedure outlined proved to be the most efficient in terms of time and cost.

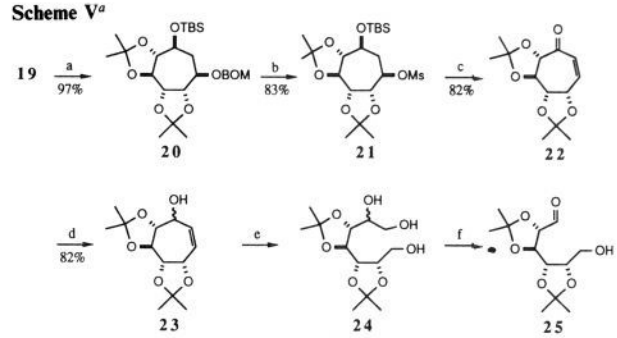
Diene **12** was subjected to singlet oxygen to produce a 6:1 mixture of exo/endo peroxides.[9] The exo selectivity for this reaction can be explained using Figure 1. As can be seen, the hydrogen geminal to the siloxy group blocks the α face from the incoming dienophile. The major exo isomer **13**, after separation using silica gel chromatography, was reduced to meso diol **1** using zinc and acetic acid.[10] The meso diol was then dissolved in isopropenyl acetate,[11] and an equivalent weight of crude *Pseudomonas cepacia* lipase was added. After the reaction mixture was stirred at 50 °C for 36 h and purified by silica gel chromatography, monoacetate **2** was obtained in enantiomerically pure form (determined by its Mosher derivative[12]) in ca. 40% overall yield from cycloheptatriene (Scheme III).

Scheme IV[a]



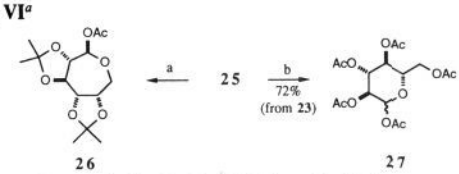
[a] (a) BOM-Cl, *i*-Pr_2EtN, CH_2Cl_2. (b) KOH, MeOH. (c) PDC, 4-Å sieves, CH_2Cl_2. (d) TMS-OTf, Et_3N, Et_2O. (e) *m*-CPBA, pentane. (f) (1) DIBAL-H, Et_2O, −78 °C; (2) DMP, *p*-TsOH. BOM = (benzyloxy)methyl.

Scheme V[a]



[a] (a) (1) OsO_4, *N*-methylmorpholine *N*-oxide, THF/H_2O; (2) dimethoxypropane, *p*-TsOH. (b) (1) H_2, Pd-C, MeOH; (2) MsCl, Et_3N, CH_2Cl_2. (c) (1) Bu_4NF, THF; (2) DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2, −65 °C. (d) DIBAL, Et_2O, −78 °C. (e) O_3, MeOH, then DMS and $NaBH_4$. (f) $NaIO_4/SiO_2$, CH_2Cl_2.

Scheme VI[a]



[a] (a) Acetic anhydride, Et_3N, CH_2Cl_2. (b) HCl, THF, H_2O; then acetic anhydride, DMAP, pyridine.

Allylic alcohol **2** was protected as its (benzyloxy)methyl ether **14**. Removal of the acetyl group using KOH in methanol and subsequent oxidation of the resulting alcohol **15** with PDC led to enone **16**. Enone **16** was transformed into silyloxy diene **17**, which, upon "Rubottom oxidation"[13] with *m*-CPBA, led to the α-oxygenated enone **18**. DIBAL-H reduction of enone **18** produced an unstable allylic diol which was protected as acetonide **19**. Both oxidation of the diene **17** and reduction of enone **18** were highly diastereoselective; no other isomers were observed (Scheme IV).[14]

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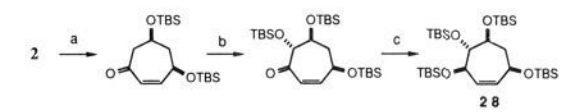
(14) As proof of the relative stereochemistry of the Rubottom oxidation and enone reduction, monoacetate **2** was converted to **28** by the process shown



below.
The relative stereochemistry was determined by X-ray crystallography. (a) (1) TBS-Cl, imidazole, DMF; (2) KOH, MeOH; (3) PDC, 4-Å sieves, CH_2Cl_2. (b) (1) TBS-OTf, Et_3N, Et_2O; (2) *m*-CPBA, pentane. (c) (1) DIBAL, Et_2O, −78 °C; (2) TBS-OTf, 2,6-lutidene, CH_2Cl_2.

cis-Hydroxylation of the olefin[15] **19** proceeded in greater than 20:1 selectivity with the product resulting from the anti-periplanar reaction predominating.[16] Protection of the resulting diol with dimethoxypropane gave compound **20**. Selective removal of the (benzyloxy)methyl group by hydrogenolysis using Degussa type palladium on carbon followed by mesylation led to **21**. Removal of the silyl group followed by Swern oxidation with concomitant elimination of the mesylate produced enone **22**, which corresponded to key advanced intermediate **7** in our retrosynthetic analysis. Reduction of **22** with DIBAL-H yielded allylic alcohol **23** as a mixture of diastereoisomers. Ozonolysis of the mixture followed by reductive workup using sodium borohydride afforded triol **24**. Cleavage of the vicinal diol using $NaIO_4$ supported on silica gel[17] led to (2*S*,3*R*,4*S*,5*S*)-6-hydroxy-2,3:4,5-bis(isopropylidenedioxy)hexanal (**25**), which existed in the hemiacetal form (2,3:4,5-di-*O*-isopropylidene-L-glucoseptanose) (Scheme V).

Compound **25** was treated with acetic anhydride in pyridine to produce known acetate **26** in a mixture with the α isomer. Separation using column chromatography afforded the pure β anomer **26**, $[\alpha]^{22}_D$ +76.0° (*c* 1.09, $CHCl_3$). The enantiomer, prepared from D-glucose, was reported to have $[\alpha]^{22}_D$ −77.7° (*c* 1.53, $CHCl_3$).[18] Deprotection of **25** using HCl in aqueous THF produced L-glucose (**5**) as a mixture of anomers. This mixture was then treated with acetic anhydride in pyridine to produce L-glucose pentaacetate **27** in 72% yield from **23**. The overall yield from **2** to **27** is approximately 20%. Purification using HPLC afforded pure β-L-glucose pentaacetate, $[\alpha]^{20}_D$ −4.6° (*c* 1.0, $CHCl_3$) (Scheme VI).

The production of L-glucose from achiral cycloheptatriene is the result of a stereochemical cascade that originates from the first tetrahedral functionality, namely the hydroxylated carbon of **11**, introduced into the system. The stereochemical flow which includes the diastereofacial selective singlet oxygen cycloaddition, the enantioselective enzymatic asymmetrization, the trans-selective Rubottom oxidation and subsequent reduction, and the anti-periplanar osmylation allows all necessary glucose stereogenic centers to be set in the seven-membered framework. The synthesis emphasizes the utility of lipases in organic media and the virtues of using a ring as a surrogate for an acyclic stereochemical array.

Experimental Section

^1H NMR spectra were recorded on a GE QE300 spectrometer with $CDCl_3$ as the solvent and internal standard unless otherwise stated. Optical rotations were measured with a Perkin-Elmer Model 241 polarimeter. Column chromatography was carried out with Merck Kieselgel 60 (230–400 mesh). All chromatographic separations were monitored by TLC analyses, performed on Merck DC Alufolien Kieselgel 60F-254. Yields are reported for chromatographically pure compounds. Amano PS-30 lipase was obtained from the Amano International Enzyme Co., Troy, VA.

3,5-Cycloheptadienol (11).[10] Tropylium tetrafluoroborate[19] (112.4 g, 0.632 mol) was dissolved in 1.5 L of acetonitrile. To this mixture was added 100.2 g (0.945 mol) of sodium carbonate. The reaction flask was placed on a rotary evaporator and rotated without vacuum at 50 °C for 3 h, at which time a vacuum was applyed and the acetonitrile was removed. Dichloromethane (500 mL) was then added; the reaction mixture was filtered and concentrated in vacuo to yield 35.7 g of crude tropone. To the crude tropone in methanol (750 mL) was added sodium borohydride (18 g, 0.476 mmol) in four portions. The mixture was stirred overnight. The solvent was then removed in vacuo, and 1 L of diethyl ether was added. The ether solution was washed with water (100 mL) and with brine (2 × 100 mL). The solvent was removed, and the resultant oil was distilled (62 °C, 2 Torr) to give 3,5-cycloheptadienol (24.3 g, 0.221 mol, 70%) as a clear oil. ^1H NMR δ 5.87–5.80 (m, 2 H), 5.67–5.58 (m, 2 H), 4.14 (t, *J* = 5.3 Hz, 1 H), 2.50 (t, *J* = 4.9 Hz, 4 H); ^{13}C NMR δ 128.0, 126.2, 68.4, 39.3; IR (neat) 3340, 3022, 2900, 1440, 1426, 1054, 1019, 675 cm^{-1}.

6-((*tert*-Butyldimethylsilyl)oxy)-1,3-cycloheptadiene (12).[20] A mixture of dimethylformamide (117 mL), 3,5-cycloheptadienol (24.0 g, 0.218 mol), *tert*-butyldimethylsilyl chloride (36.2 g, 0.240 mol), and imidazole (37.8 g, 0.555 mol) was stirred at room temperature overnight. The reaction mixture was then poured into pentane (1.2 L), and the DMF layer was removed. The pentane layer was washed with water (50 mL) and with brine (2 × 50 mL). The combined aqueous layers were washed with pentane (200 mL). The pentane layer was washed with 50 mL of water. The combined pentane layers were concentrated, and the resultant oil was chromatographed (silica gel, hexanes), to yield diene **12** (43.0 g, 0.192 mol, 88%) as a clear oil. ^1H NMR δ 5.84–5.76 (m, 2 H), 5.72–5.60 (m, 2 H), 4.12–4.01 (m, 1 H), 2.52–2.42 (m, 4 H), 0.90 (s, 9 H), 0.07 (s, 6 H); ^{13}C NMR δ 128.0, 126.0, 71.3, 40.9, 25.8, 18.2, −4.8.

***exo*-3-((*tert*-Butyldimethylsilyl)oxy)-8,9-dioxabicyclo[3.2.2]non-6-ene (13).** Silyl diene **12** (20.0 g, 0.089 mol) was dissolved in dichloromethane (500 mL) and methanol (200 mL), and *meso*-tetraphenylporphine (20 mg) was added. The reaction mixture, after cooling to 0 °C, was irradiated with a 400-W sodium lamp (General Electric, model LU 400) while O_2 was bubbled through the reaction mixture. When the reaction was judged to be complete (TLC, 5% ethyl acetate in hexanes), the solvent was removed and the oil was chromatographed (silica gel, 3% ethyl acetate in petroleum ether, switching to 5% after the peroxides began eluting). This procedure yielded the pure exo peroxide **13** (17.3 g, 0.0675 mol, 76%), a mixture of exo/endo peroxides (2.2 g, 8.58 mmol, 10%), and pure endo peroxide (epimeric at C-3) (2.0 g, 7.80 mmol, 8.8%). Exo isomer **13**: ^1H NMR δ 6.39 (dd, J_1 = 4.8 Hz, J_2 = 3.3 Hz, 2 H), 4.73–4.62 (m, 2 H), 3.72 (tt, J_1 = 10.5 Hz, J_2 = 6.3 Hz, 1 H), 2.26–1.99 (m, 4 H), 0.86 (s, 9 H), 0.02 (s, 6 H); ^{13}C NMR δ 128.67, 73.39, 66.21, 40.97, 25.74, 18.00, −4.74. Endo isomer: ^1H NMR δ 6.48 (dd, $J_1 = J_2$ = 3.9 Hz, 2 H), 4.69 (m, 2 H), 4.57 (tt, $J_1 = J_2$ = 6.6 Hz, 1 H), 2.44–2.29 (m, 2 H), 1.81 (dd, J_1 = 13.7 Hz, J_2 = 7.7 Hz, 2 H), 0.86 (s, 9 H), 0.05 (s, 6 H); ^{13}C NMR δ 131.1, 74.0, 67.8, 41.6, 25.7, 17.9, −4.9.

***meso*-(1*R*,4*S*,6*R*)-6-((*tert*-Butyldimethylsilyl)oxy)-2-cycloheptene-1,4-diol (1).**[21] To exo peroxide **13** (25 g, 0.098 mol) in 1.5 L of dichloromethane was added 25 g of freshly activated zinc. Acetic acid (6.4 mL, 0.112 mol) was added in 2-mL aliquots over 3 h. The reaction mixture was then filtered through Celite, the solvent was removed, and the resulting white solid was taken up in ethyl acetate and filtered through silica gel to yield diol **1** (24.7 g, 0.096 mol, 98%) as a white solid: mp 132–133 °C; ^1H NMR δ 5.72 (s, 2 H), 4.27 (m, 2 H), 4.02 (m, 1 H), 2.16 (br d, *J* = 5.0 Hz, 2 H), 2.06 (br d, *J* = 13.0 Hz, 2 H), 1.90–1.76 (m, 2 H), 0.89, (s, 9 H), 0.09 (s, 6 H); ^{13}C NMR δ 134.7, 69.0, 67.2, 45.0, 25.7, 18.0, −4.8.

(1*R*,4*S*,6*S*)-4-Acetoxy-6-((*tert*-butyldimethylsilyl)oxy)-2-cyclohepten-1-ol (2). To diol **1** (24.7 g, 0.096 mol) in isopropenyl acetate (500 mL) was added crude Amano PS-30 lipase (25 g). The reaction mixture was stirred at 50 °C for 36 h. The enzyme was removed by filtration, and the filtrate was concentrated in vacuo. The residue was chromatographed (silica gel, 2:1 petroleum ether/ethyl acetate) to give monoacetate **2** (28.0 g, 0.0932 mol, 98%) as a clear oil: $[\alpha]^{25}_D$ +36.4° (*c* 1.25, $CHCl_3$); IR (neat) 3446.6, 1740, 837, 700 cm^{-1}; ^1H NMR δ 5.73 (br d, *J* = 10.0 Hz, 1 H), 5.49 (br d, *J* = 12.0 Hz, 1 H), 5.13 (br d, 10.0 Hz, 1 H), 4.32–4.22 (m, 1 H), 4.02–3.93 (m, 1 H), 3.19–3.08 (m, 1 H), 2.00 (s, 3 H), 2.00–1.92 (m, 2 H), 1.72–1.57 (m, 2 H), 0.81 (s, 9 H), 0.02, (s, 3 H), 0.01 (s, 3 H); ^{13}C NMR δ 170.2, 135.6, 130.7, 68.9, 68.5, 66.6, 44.8, 42.1, 25.6, 21.1, 17.8, −4.9, −4.9. Anal. Calcd for $C_{15}H_{28}O_4Si$: C, 59.96; H, 9.39. Found: C, 59.79; H, 9.33.

(3*S*,5*S*,7*R*)-3-Acetoxy-7-((benzyloxy)methoxy)-5-((*tert*-butyldimethylsilyl)oxy)cycloheptene (14). Monoacetate **2** (2.9 g, 9.7 mmol), *N*,*N*-diisopropylethylamine (2.97 g, 4.00 mL, 23 mmol), and benzyl chloromethyl ether (technical grade 60%, 3.12 g, 2.78 mL, 12 mmol) were dissolved in dichloromethane (30 mL) at room temperature in a round-bottomed flask equipped with a drying tube. The reaction was followed by TLC (hexane/ethyl acetate, 85:15). After ca. 3 h, the reaction mixture was partitioned between diethyl ether (200 mL) and 0.1 N HCl (100 mL). The organic layer was washed with sodium bicarbonate (150 mL), dried ($MgSO_4$), filtered, and evaporated. The oily residue was purified by chromatography (hexane/ethyl acetate, 95:5 to 9:1) to give **14** (3.53 g, 8.4 mmol, 87%) as a clear oil: $[\alpha]^{25}_D$ +20.5° (*c* 1.30, $CHCl_3$); IR (neat) 2925, 1738, 1242, 1090, 1040, 837 cm^{-1}; ^1H NMR δ 7.40–7.29 (m, 5 H), 5.84–5.76 (m, 1 H), 5.66–5.58 (m, 1 H), 5.26–5.18 (m, 1 H), 4.81 (s, 2 H), 4.63 (d, *J* = 2.1 Hz, 2 H), 4.26 (m, 1 H), 3.91 (tt, J_1 = 10.8 Hz, J_2 = 3.6 Hz, 1 H), 2.08 (s, 3 H), 2.17–2.00 (m, 2 H), 1.73–1.60 (m, 2 H), 0.98 (s, 9 H), 0.09 (s, 3 H), 0.08 (s, 3 H); ^{13}C NMR δ 170.1, 137.5, 134.0, 131.5, 128.4, 127.9, 127.8, 92.7, 70.8,

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69.5, 68.9, 42.9, 42.0, 25.7, 21.2, 18.0, −4.8. Anal. Calcd for $C_{23}H_{36}O_5Si$: C, 65.67; H, 8.63. Found: C, 65.84; H, 8.89.

(4*R*,6*S*)-4-((Benzyloxy)methoxy)-6-((*tert*-butyldimethylsilyl)oxy)-cyclohept-2-en-1-one (16). Acetate **14** (2.52 g, 6.00 mmol) was dissolved in methanol (20 mL), and powdered potassium hydroxide (56 mg, 1.00 mmol) was added. After 45 min, the reaction mixture was poured into water (500 mL) and extracted with diethyl ether (3 × 100 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), and evaporated. The crude oily product **15** was dissolved in dichloromethane (60 mL) followed by the addition of crushed molecular sieves (4 Å, ca. 5 g) and pyridinium dichromate[21] (6.77 g, 18.00 mmol). The reaction was followed by TLC (hexane/ethyl acetate, 9:1) and was complete after ca. 4 h. A hexane/ethyl acetate mixture (9:1, 400 mL) was added, and after 10 min of stirring, the mixture was filtered through a silica gel pad. The filtrate was evaporated (and then coevaporated with 100 mL of toluene), and the oily residue was purified by chromatography (hexane/ethyl acetate, 95:5 to 9:1) to give enone **16** (1.85 g, 4.90 mmol, 82%) as a clear oil: $[\alpha]^{25}_D$ +44.0° (*c* 0.8, $CHCl_3$); IR ($CDCl_3$) 2957, 2860, 1673, 1259 cm^{-1}; ^1H NMR δ 7.34 (s, 5 H), 6.67 (dd, J_1 = 12.0 Hz, J_2 = 1.9 Hz, 1 H), 5.99 (dd, J_1 = 12.0 Hz, J_2 = 2.0 Hz, 1 H), 4.83 (s, 2 H), 4.66 (s, 2 H), 4.49 (dt, J_1 = 11.0 Hz, J_2 = 2.0 Hz, 1 H), 4.23 (dt, J_1 = 8.6 Hz, J_2 = 2.0 Hz, 1 H), 2.79 (dd, J_1 = 15.0 Hz, J_2 = 6.0 Hz, 1 H), 2.67 (dd, J_1 = 15.0 Hz, J_2 = 3.0 Hz, 1 H), 2.55–2.41 (m, 1 H), 2.05–1.90 (m, 1 H), 0.87 (s, 9 H), 0.11 (s, 6 H); ^{13}C NMR δ 198.7, 149.9, 137.4, 131.6, 128.7, 128.0, 93.4, 72.3, 70.0, 64.3, 51.7, 43.5, 25.8, 18.0, −4.8. Anal. Calcd for $C_{21}H_{32}SiO_4$: C, 66.98; H, 8.57. Found: C, 66.85; H, 8.81.

(3*R*,4*S*,5*S*,7*R*)-7-((Benzyloxy)methoxy)-5-((*tert*-butyldimethylsilyl)oxy)-3,4-(isopropylidenedioxy)cycloheptene (19). To a solution of enone **16** (1.75 g, 4.65 mmol) in dry diethyl ether (25 mL) was added triethylamine (1.51 g, 2.08 mL, 15.0 mmol), followed by trimethylsilyl trifluoromethanesulfonate (1.89 g, 1.60 mL, 8.0 mmol), under an argon atmosphere. After 40 min, the ether solution was decanted from an insoluble oil and the oil was washed with diethyl ether (3 × 35 mL). The combined diethyl ether layers were washed with saturated aqueous sodium bicarbonate (100 mL), dried ($MgSO_4$), and evaporated. The slightly yellow, oily diene **17** was dissolved in pentane (10 mL) and added to a stirred slurry of *m*-chloroperoxybenzoic acid (60% pure, 1.72 g, 6 mmol) and $MgSO_4$ (ca. 2 g) in pentane (50 mL) which had been precooled to −20 °C (CCl_4–dry ice bath, drying tube). After 5 min, the cooling bath was removed and the stirring was continued for an additional 20 min. The reaction mixture was filtered, and the solvent was evaporated in vacuo. The semicrystalline product was purified by flash chromatography (hexane/ethyl acetate, 95:5) to give unstable enone **18** (1.85 g, 80%), which was dissolved in dry diethyl ether (50 mL) and cooled to −78 °C under argon; then diisobutylaluminum hydride (1.5 M solution in toluene, 7 mL, 10.5 mmol) was added slowly over 15 min) so that the temperature did not rise above −65 °C. After 40 min, methanol (2 mL) was added slowly followed by a saturated aqueous solution of potassium sodium tartrate (150 mL); the cooling bath was removed, and reaction mixture was stirred at room temperature until all white solids dissolved (ca. 2 h). The mixture was separated, and the aqueous layer was washed with diethyl ether (3 × 75 mL). The combined organics were dried ($MgSO_4$) and evaporated. The oily residue was dissolved in 2,2-dimethoxypropane (25 mL), and a catalytic amount (10 mg) of *p*-toluenesulfonic acid was added. The reaction progress was followed by TLC (hexane/ethyl acetate 95:5); after ca. 20 min, solid sodium bicarbonate (200 mg) was added. The reaction mixture was evaporated to dryness, and the residue was purified by flash chromatography (hexane/ethyl acetate, 95:5) to give product **19** as an oil (1.39 g, 3.20 mmol, 69%): $[\alpha]^{25}_D$ 25.4° (*c* 1.8, $CHCl_3$); IR (neat) 2984, 2951, 1462, 1456, 1380, 1371, 1237, 875, 838, 697 cm^{-1}; ^1H NMR δ 7.42–7.29 (m, 5 H), 5.90–5.80 (m, 2 H), 4.82 (s, 2 H), 4.64 (s, 2 H), 4.35 (d, *J* = 11.1 Hz, 1 H), 4.18 (d, *J* = 9.0 Hz, 1 H), 3.84 (ddd, J_1 = 13.1 Hz, J_2 = 8.8 Hz, J_3 = 4.5 Hz, 1 H), 3.35 (dd, J_1 = 9.0 Hz, J_2 = 8.8 Hz, 1 H), 2.07 (ddd, J_1 = 12.8 Hz, J_2 = 4.1 Hz, J_3 = 1.7 Hz, 1 H), 1.76 (ddd, J_1 = 13.0 Hz, J_2 = 12.8 Hz, J_3 = 11.2 Hz, 1 H), 1.42 (s, 3 H), 1.41 (s, 3 H), 0.92 (s, 9 H), 0.12 (s, 6 H); ^{13}C NMR 137.6, 134.8, 128.5, 127.9, 127.8, 127.5, 108.8, 92.73, 82.6, 75.1, 72.6, 70.6, 69.7, 40.6, 26.9, 26.8, 25.8, 18.3, −4.4, −5.0. Anal. Calcd for $C_{24}H_{38}O_5Si$: C, 66.32; H, 8.81. Found: C, 66.32; H, 8.61.

(1*R*,2*S*,3*R*,4*S*,5*S*,7*R*)-7-((Benzyloxy)methoxy)-6-((*tert*-butyldimethylsilyl)oxy)-3,4-(isopropylidenedioxy)-1,2-cycloheptanediol. To a solution of compound **19** (971 mg, 2.23 mmol) in THF (40 mL) was added H_2O (1.0 mL), OsO_4 (5.6 mL of a 0.039 M solution in THF), and *N*-methylmorpholine *N*-oxide (2.2 mL of a 60% solution in H_2O).[15] The mixture was stirred until the substrate was no longer detectable by TLC, at which time 3.6 g of $NaHSO_3$ was added and the reaction mixture was stirred for an additional 2 h. Florisil (24 g) was added, and the reaction mixture was stirred for 1 h. The resulting mixture was filtered, concentrated, and chromatographed (1:10 MeOH/$CHCl_3$) to give the title diol (1.028 g, 2.19 mmol, 98%) as a clear oil: ^1H NMR δ 7.38–7.26 (m, 5 H), 4.96 (d, *J* = 7.0 Hz, 1 H), 4.76 (d, *J* = 7.0 Hz, 1 H), 4.67 (d, *J* = 11.7 Hz, 1 H), 4.56 (d, *J* = 11.7 Hz, 1 H), 4.10 (dd, J_1 = J_2 = 7.2 Hz, 1 H), 3.98–3.82 (m, 4 H), 3.71 (dd, J_1 = J_2 = 9.0 Hz, 1 H), 3.09 (d, 0.6 Hz, 1 H), 2.98 (s, 1 H), 2.30 (ddd, J_1 = 15.6 Hz, J_2 = 6.3 Hz, J_3 = 1.2 Hz, 1 H), 1.86 (ddd, J_1 = 15.3 Hz, J_2 = 8.4 Hz, J_3 = 3.9 Hz, 1 H), 1.39 (s, 6 H), 0.87 (s, 9 H), 0.07 (s, 3 H), 0.06 (s, 3 H); ^{13}C NMR δ 137.5, 128.4, 127.8, 109.3, 92.9, 81.1, 76.3, 72.2, 71.7, 71.2, 70.9, 69.8, 33.3, 27.2, 27.1, 25.8, 18.2, −4.5, −5.1. Anal. Calcd for $C_{24}H_{40}O_7Si$: C, 61.64; H, 8.41. Found: C, 61.63; H, 8.64.

(1*R*,2*S*,3*S*,4*R*,5*S*,6*S*)-1-((Benzyloxy)methoxy)-6-((*tert*-butyldimethylsilyl)oxy)-2,3:4,5-bis(isopropylidenedioxy)cycloheptane (20). To a solution of the above diol (1.028 g, 2.19 mmol) in dimethoxypropane (75 mL) was added a catalytic amount of *p*-toluenesulphonic acid. The reaction mixture was stirred at room temperature overnight. The solvent was removed in vacuo, and the residue was chromatographed (5:1 petroleum ether/ethyl acetate) to give **20** (1.10 g, 2.16 mmol, 99%) as a clear oil: $[\alpha]^{25}_D$ +4.4° (*c* 0.86, $CHCl_3$); IR (neat) 2858, 1372, 1249, 1100 cm^{-1}; ^1H NMR δ 7.36–7.23 (m, 5 H), 4.90 (d, *J* = 7.2 Hz, 1 H), 4.84 (d, *J* = 7.2 Hz, 1 H), 4.71 (d, *J* = 11.4 Hz, 1 H), 4.60 (d, *J* = 11.4 Hz, 1 H), 4.26 (dd, J_1 = 8.7 Hz, J_2 = 8.1 Hz, 1 H), 4.16 (dd, J_1 = J_2 = 8.1 Hz, 1), 3.80–3.68 (m, 2 H), 3.65 (dd, J_1 = J_2 = 9.3 Hz, 1 H), 3.44 (dd, J_1 = 9.3 Hz, J_2 = 9.0 Hz, 1 H), 2.07 (ddd, J_1 = 14.1 Hz, J_2 = 3.9 Hz, J_3 = 0.9 Hz, 1 H), 1.64 (ddd, J_1 = 14.1 Hz, J_2 = J_3 = 11.4 Hz, 1 H), 1.48 (s, 3 H), 1.39 (s, 6 H), 1.36 (s, 3 H), 0.86 (s, 9 H), 0.07 (s, 3 H), 0.06 (s, 3 H); ^{13}C NMR δ 137.4, 128.2, 127.6, 127.2, 109.4, 109.0, 93.3, 81.4, 80.2, 76.7, 76.6, 76.0, 71.1, 71.0, 69.5, 38.4, 26.9, 26.8, 25.6, 23.6, 18.0, −4.6, −5.2. Anal. Calcd for $C_{27}H_{44}O_7Si$: C, 63.75; H, 8.72. Found: C, 63.65; H, 8.78.

(1*R*,2*S*,3*S*,4*R*,5*S*,6*S*)-6-((*tert*-Butyldimethylsilyl)oxy)-2,3:4,5-bis(isopropylidenedioxy)-1-cycloheptanol. (Benzyloxy)methyl ether **20** (102 mg, 0.201 mmol) was dissolved in MeOH (5 mL). After the system was purged with argon, ca. 150 mg of Pd-C (Degussa type) was added. H_2 was bubbled through the reaction mixture for 1 h. The Pd-C was removed by filtration, and the filtrate was concentrated in vacuo. The residue was purified by column chromatography (2:1 petrol/ethyl acetate) to give the title alcohol (73 mg, 0.188 mmol, 94%) as a clear oil: $[\alpha]^{25}_D$ −0.4° (*c* 1.2, $CHCl_3$); IR (neat) 3503, 2955, 1382, 1373, 838, 779 cm^{-1}; ^1H NMR δ 4.24 (dd, J_1 = J_2 = 8.1 Hz, 1 H), 3.90 (dd, J_1 = 9.3 Hz, J_2 = 8.1 Hz, 1 H), 3.76–3.52 (m, 3 H), 3.45 (dd, J_1 = J_2 = 9.3 Hz, 1 H), 2.75 (s, 1 H), 2.05 (dd, J_1 = 14.1 Hz, J_2 = 4.8 Hz, 1 H), 1.52 (ddd, J_1 = 14.1 Hz, J_2 = J_3 = 11.1 Hz, 1 H), 1.44 (s, 3 H), 1.34 (s, 6 H), 1.32 (s, 3 H), 0.82 (s, 9 H), 0.03 (s, 6 H); ^{13}C NMR δ 109.6 (2 C's), 81.2, 80.9, 77.1, 76.2, 71.2, 66.4, 39.5, 27.1, 26.9, 26.7, 25.6, 24.3, 18.0, −4.6, −5.2.

(1*S*,2*S*,3*R*,4*R*,5*R*,6*R*)-1-((*tert*-Butyldimethylsilyl)oxy)-2,3:4,5-bis(isopropylidenedioxy)-6-((methylsulfonyl)oxy)cycloheptane (21). To the above alcohol (440 mg, 1.13 mmol) in dichloromethane (25 mL) was added triethylamine (172 mg, 1.70 mmol) followed by mesyl chloride (0.11 mL, 1.36 mmol). The reaction mixture was stirred at 25 °C for 1 h, poured into saturated aqueous ammonium chloride, and extracted with dichloromethane (3 × 20 mL). The combined extracts where dried over $MgSO_4$, filtered, concentrated, and purified by column chromatography (2:1 petrol/ethyl acetate) to give **21** (463 mg, 0.992 mmol, 88%) as a viscous oil: $[\alpha]^{25}_D$ −13.2° (*c* 1.2, $CHCl_3$); IR (neat) 2957, 1361, 1175, 840 cm^{-1}; ^1H NMR δ 4.48 (dd, J_1 = 10.5 Hz, J_2 = 10.2 Hz, 1 H), 4.26 (dd, J_1 = J_2 = 8.4 Hz, 1 H), 4.15 (dd, J_1 = 9.0 Hz, J_2 = 8.4 Hz, 1 H), 3.80–3.70 (m, 1 H), 3.63–3.56 (m, 1 H), 3.39 (dd, J_1 = 9.3 Hz, J_2 = 9.0 Hz, 1 H), 2.99 (s, 3 H), 2.17 (dd, J_1 = 14.1 Hz, J_2 = 3.9 Hz, 1 H), 1.86–1.72 (m, 1 H), 1.42 (s, 3 H), 1.32 (s, 3 H), 1.32 (s, 3 H), 1.29 (s, 3 H), 0.79 (s, 9 H), 0.00 (s, 6 H); ^{13}C NMR δ 109.7 (two C's overlap), 80.8, 78.3, 78.1, 76.5, 75.7, 70.2, 39.5, 38.2, 26.7, 26.6, 26.4, 25.4, 23.5, 17.9, −4.9, −5.3. Anal. Calcd for $C_{20}H_{38}O_8SSi$: C, 51.48; H, 8.21. Found: C, 51.39; H, 8.24.

(1*S*,2*R*,3*S*,4*R*,5*R*,6*R*)-2,3:4,5-Bis(isopropylidenedioxy)-6-((methylsulfonyl)oxy)-1-cycloheptanol. To silyl ether **21** (398 mg, 0.853 mmol) in THF (40 mL was added a solution of tetrabutylammonium fluoride (1.3 mL of 1 M, 1.3 mmol), and the mixture was stirred at 25 °C overnight. The solvent was removed in vacuo. The remaining oil was dissolved in ethyl acetate and washed three times with brine. The organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was chromatographed (ethyl acetate) to give the title alcohol (274 mg, 0.778 mmol, 91%) as a white solid: mp 178 °C; $[\alpha]^{25}_D$ −24.1° (*c* 0.87, $CHCl_3$); IR (neat) 3475, 2995, 2937, 1389, 1376, 1357, 1344, 1228, 1173, 1069, 1049, 947 cm^{-1}; ^1H NMR ($CDCl_3/D_2O$) δ 4.59 (ddd, J_1 = 12.0 Hz, J_2 = 9.9 Hz, J_3 = 1.8 Hz, 1 H), 4.36 (dd, J_1 = J_2 = 8.6 Hz, 1 H), 4.24 (dd, J_1 = 9.6 Hz, J_2 = 8.1 Hz, 1 H), 3.87 (ddd, J_1 = 11.4 Hz, J_2 = 9.3 Hz, J_3 = 4.8 Hz, 1 H), 3.71 (dd, J_1 = J_2 = 9.2 Hz, 1 H), 3.48 (dd, J_1 = J_2 = 9.3 Hz, 1 H), 3.08 (s, 3 H), 2.42 (ddd, J_1 = 13.8 Hz, J_2

= 4.5 Hz, J_3 = 1.5 Hz, 1 H), 1.84 (ddd, J_1 = 13.8 Hz, $J_2 = J_3$ = 11.7 Hz, 1 H), 1.52, (s, 3 H), 1.44 (s, 6 H), 1.38 (s, 3 H); ^{13}C NMR δ 110.9, 110.2, 80.8, 78.5, 78.4, 76.7, 76.1, 69.6, 38.6, 37.7, 27.0, 26.9, 26.6, 23.8. Anal. Calcd for $C_{14}H_{24}O_8S$: C, 47.72; H, 6.86. Found: C, 47.84; H, 6.93.

(4*S*,5*S*,6*R*,7*S*)-4,5:6,7-Bis(isopropylidenedioxy)-2-cyclohepten-1-one (22). Oxalyl chloride (0.05 mL, 0.54 mmol) was dissolved in dichloromethane (4 mL) and cooled to −60 °C. Dimethyl sulfoxide (0.08 mL, 1.097 mmol) was added as a solution in dichloromethane over a 10-min period. (1*S*,2*R*,3*S*,4*R*,5*R*,6*R*)-2,3:4,5-bis(isopropylidenedioxy)-6-((methylsulfonyl)oxy)-1-cycloheptanol (159 mg, 0.451 mmol) was dissolved in dichloromethane (3 mL) and added dropwise over 2 min. After 20 min, triethylamine (0.3 mL, 2.15 mmol) was added and the reaction mixture was stirred an additional 10 min before being warmed to room temperature. The reaction mixture was then poured into cold water and extracted with dichloromethane (3 × 15 mL). The combined extracts were dried over $MgSO_4$, filtered, and concentrated in vacuo. The resulting oil was adsorbed onto silica gel and purified by column chromatography (1:1 petrol/ethyl acetate) to give enone **22** (103 mg, 0.405 mmol, 90%) as a clear oil: $[\alpha]^{25}_D$ +66.4° (*c* 1.1, $CHCl_3$); IR (neat) 2992, 2939, 2896, 1686, 1458, 1386, 1375, 1169, 1051, 872, 839 cm^{-1}; ^{1}H NMR δ 6.58 (ddd, J_1 = 12.9 Hz, J_2 = 2.1 Hz, J_3 = 0.6 Hz, 1 H), 5.99 (dd, J_1 = 12.9 Hz, J_2 = 2.7 Hz, 1 H), 5.01 (ddd, J_1 = 7.5 Hz, $J_2 = J_3$ = 2.4 Hz, 1 H), 4.55 (dd, $J_1 = J_2$ = 7.5 Hz, 1 H), 4.39 (d, J_1 = 9.9 Hz, 1 H), 4.15 (dd, J_1 = 10.2 Hz, J_2 = 7.5 Hz, 1 H), 1.52, (s, 3 H), 1.49 (s, 3 H), 1.43 (s, 6 H); ^{13}C NMR δ 193.6, 147.4, 126.3, 113.1, 111.0, 81.1, 78.0, 77.1, 75.0, 27.1, 26.7, 25.9, 25.1.

(1*RS*,4*S*,5*S*,6*S*,7*R*)-4,5:6,7-Bis(isopropylidenedioxy)-2-cyclohepten-1-ol (23). Enone **22** (227 mg, 0.893 mmol) was dissolved in toluene (20 mL) and cooled to −78 °C. A 1.5 M solution of DIBAL-H in toluene (1.2 mL, 1.78 mmol) was added. The reaction mixture was stirred for 45 min and quenched with water at −78 °C. A saturated solution of sodium potassium tartrate (20 mL) and diethyl ether (20 mL) were added, and the reaction mixture was stirred for 3 h. The organic layer was separated, and the aqueous layer was washed with diethyl ether (3 × 20 mL). The organic layers were combined, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by column chromatography (5% MeOH in chloroform) to give a mixture of (1*RS*,4*S*,5*S*,6*S*,7*R*)-4,5:6,7-bis(isopropylidenedioxy)-2-cyclohepten-1-ols (**23**) (187 mg, 0.73 mmol, 82%) as a clear oil.

(2*RS*,3*R*,4*S*,5*S*,6*S*)-3,4:5,6-Bis(isopropylidenedioxy)-1,2,7-heptanetriol (24). The mixture of alcohols (187 mg, 0.73 mmol) was dissolved in methanol/dichloromethane (1:1) (20 mL) and cooled to −78 °C. The system was purged with O_2; then O_3 was bubbled through the reaction mixture until the faint blue color of ozone was detected. The reaction mixture was purged with O_2 until the blue color disappeared, at which time dimethyl sulfide (0.3 mL) followed by sodium borohydride (53 mg, 1.40 mmol) was added and the reaction mixture was allowed to warm to room temperature. The reaction mixture was adsorbed on silica gel, and the product was eluted with MeOH to give (2*RS*,3*R*,4*S*,5*S*,6*S*)-3,4:5,6-bis(isopropylidenedioxy)-1,2,7-heptanetriol (**24**) as a clear oil.

(2*S*,3*R*,4*S*,5*S*)-6-Hydroxy-2,3:4,5-bis(isopropylidenedioxy)hexanal (25). Sodium periodate (300 mg, 1.40 mmol) dissolved in water (2.2 mL) was added to a stirred suspension of silica gel (2.1 g) in dichloromethane (15 mL). Triol **24** (213 mg, 0.73 mmol) dissolved in dichloromethane (3 mL) was added, and the reaction mixture was stirred overnight. The reaction mixture was filtered and concentrated in vacuo to give crude aldehyde **25** (198 mg) as a clear oil. The crude aldehyde, which existed in hemiacetal form, was carried forward to derivatives **26** and **27**.

1-*O*-Acetyl-2,3:4,5-di-*O*-isopropylidene-β-L-glucoseptanose (26). Crude aldehyde **25** (42 mg, 0.161 mmol) was dissolved in dichloromethane (5 mL). Triethylamine (50 mg, 0.494 mmol) followed by acetic anhydride (25 mg, 0.245 mmol) was added. The reaction was stirred at 25 °C for 2 h and then poured into saturated aqueous ammonium chloride solution and extracted with dichloromethane (4 × 10 mL). The combined extracts where combined, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by column chromatography (1:1 hexanes/ethyl acetate) to separate the anomers. 1-*O*-acetyl-2,3:4,5-di-*O*-isopropylidene-α-L-glucoseptanose (11 mg, 0.036 mmol, 23%): ^{1}H NMR (C_6D_6) δ 5.98 (d, *J* = 7.5 Hz, 1 H), 4.12–4.04 (m, 1 H), 3.94–3.86 (m, 1 H), 3.74–3.67 (m, 1 H), 3.64–3.55 (m, 2 H), 3.49–3.39 (m, 1 H), 1.58 (s, 3 H), 1.37 (s, 3 H), 1.28 (s, 3 H), 1.16 (s, 3 H), 1.11 (s, 3 H). 1-*O*-acetyl-2,3:4,5-di-*O*-isopropylidene-β-L-glucoseptanose (a white foam) (33 mg, 0.109 mmol, 68%): $[\alpha]^{22}_D$ +76.0° (*c* 1.09, $CHCl_3$), lit.[18] $[\alpha]^{22}_D$ −77.7° (*c* 1.525, $CHCl_3$); ^{H} NMR δ 5.77 (d, *J* = 7.5 Hz, 1 H), 4.29–3.97 (m, 4 H), 3.81–3.78 (m, 2 H), 2.14 (s, 3 H), 1.52 (s, 3 H), 1.44 (s, 3 H), 1.43 (s, 3 H), 1.36 (s, 3 H); ^{13}C NMR δ 169.3, 111.8, 109.9, 95.1, 78.1, 77.4, 75.8, 74.8, 62.2, 27.5, 27.0, 26.6, 24.8, 21.1.

β-L-Glucose Pentaacetate (27). Aldehyde **25** (198 mg) was dissolved in THF (10 mL). To this was added water (6 drops) and concentrated hydrochloric acid (12 drops). After the reaction mixture was stirred overnight at 25 °C, the volatiles where removed in vacuo. The resulting oil was taken up in pyridine (10 mL), and acetic anhydride (700 mg, 6.5 mmol) along with a catalytic amount of DMAP was added. After being stirred overnight at 25 °C, the reaction mixture was poured into water (100 mL) and extracted with dichloromethane (5 × 25 mL). The combined extracts where dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by column chromatography (1:1 hexanes/ethyl acetate) to give **27** (204 mg, 0.523 mmol, 72% from **23**) as a white solid. HPLC (silica gel column, 1:1 hexanes/ethyl acetate) gave the pure β anomer: $[\alpha]^{20}_D$ −4.6° (*c* 1.0, $CHCl_3$); ^{1}H NMR δ 5.69 (d, *J* = 8.1 Hz, 1 H), 5.26–5.20 (m, 1 H), 5.13–5.07 (m, 2 H), 4.26 (dd, J_1 = 12.6 Hz, J_2 = 4.5 Hz, 1 H), 4.08 (dd, J_1 = 12.3 Hz, J_2 = 2.1 Hz, 1 H), 3.82 (ddd, J_1 = 9.9 Hz, J_2 = 4.5 Hz, J_3 = 2.1 Hz, 1 H), 2.08 (s, 3 H), 2.05 (s 3 H), 2.00 (s, 6 H), 1.98, (s 3 H); ^{13}C NMR δ 170.5, 170.0, 169.3, 169.2, 168.9, 91.6, 72.7, 72.60, 70.17, 67.6, 61.3, 20.7, 20.6, 20.4. A sample of β-D-(+)-glucose pentaacetate was obtained from Aldrich. It was identical with compound **27** by ^{1}H and ^{13}C NMR but opposite in optical rotation, $[\alpha]^{20}_D$ +4.2° (*c* 1.0, $CHCl_3$).

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