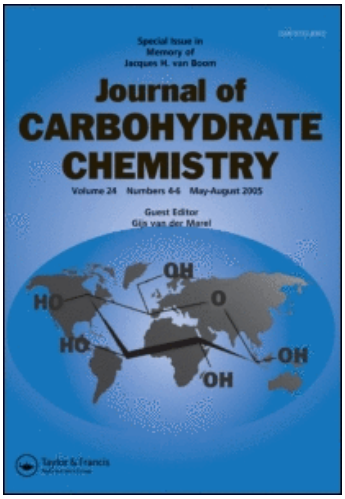

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STEREOSELECTIVITY IN THE HYDROBORATION OF C4-C-METHYLENE GROUPS

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ABSTRACT

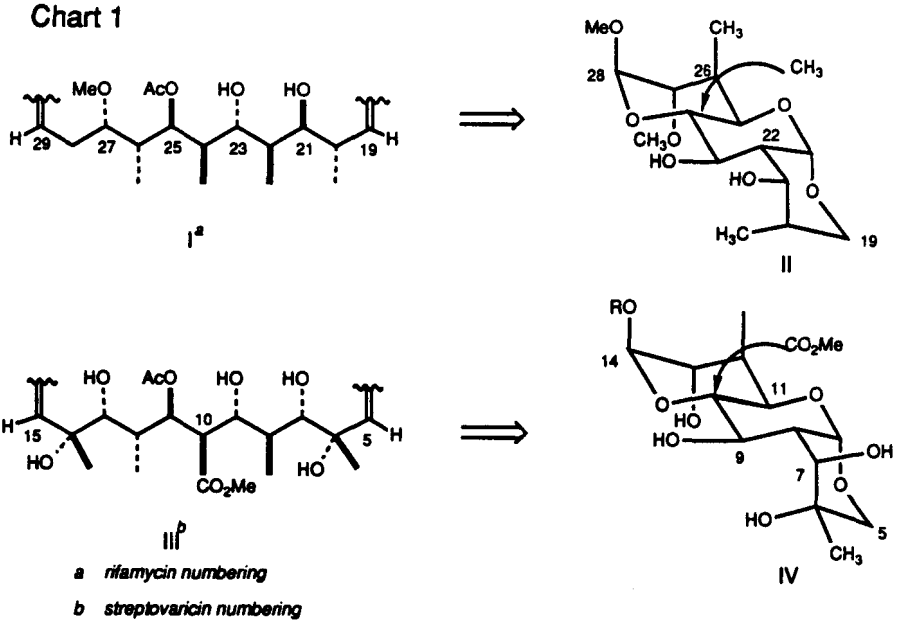
Conditions for the hydroxylation of an exocyclic methylene group at C4 of a pyranoside ring *via* hydroboration have been examined with a view to determining the optimum procedure for obtaining the axially-oriented C4-CH_2OH group. The regio- and stereochemical outcome of the reactions rely not only on the hydroborating reagent used, but, to a surprising degree, on the nature of the protecting group at the "remote" C6-OH. Silyl ethers are preferred because the only by-product formed is the tertiary alcohol, which can be recycled through dehydration to the starting alkene by treatment with thionyl chloride.

INTRODUCTION

We recently described a new strategy for the preparation of extended chiral arrays,[1] such as the ansa chain of rifamycin S, **I**. This target may

be regarded as a *pseudo* higher carbon sugar and many of the problems associated with its synthesis are also faced with authentic higher carbon sugars, such as hikizimycin.[2,3] The retrosynthetic analysis leading from **I** to the tripyranose derivative **II** has been outlined in detail,[1c] and similar treatment of the *ansa* chain of streptovaricin A, **III**, leads to the corresponding tripyranose, **IV**. As indicated in Chart I, both retrosynthetic plans call for the introduction of one-carbon units, with inversion of configuration at oxygen. Thus, the C24-CH_3 of **I** and the C10-$COOCH_3$ of **III** are to be installed at relatively late stages in the synthetic process by "displacement" of the corresponding equatorial oxygens in **II** and **IV**.

Chart 1



a *rifamycin numbering*

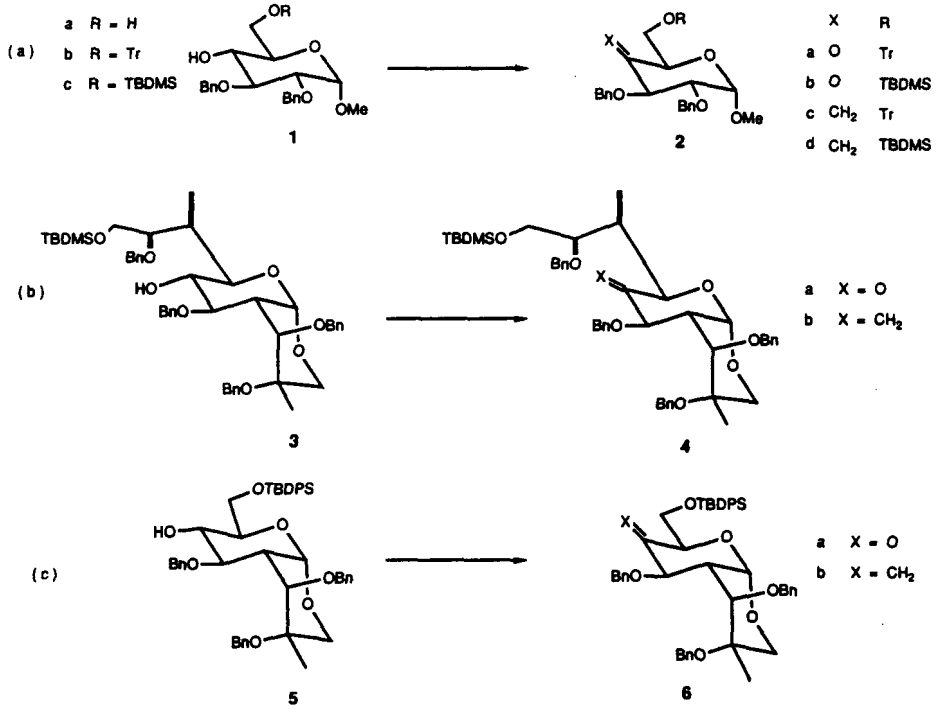
b *streptovaricin numbering*

RESULTS AND DISCUSSION

In view of the common thread running through both retrosyntheses, it would clearly be advantageous to adopt an approach that would be appropriate either for the C24-CH_3 of **I** or the C10-COOMe of **III**. These trans-

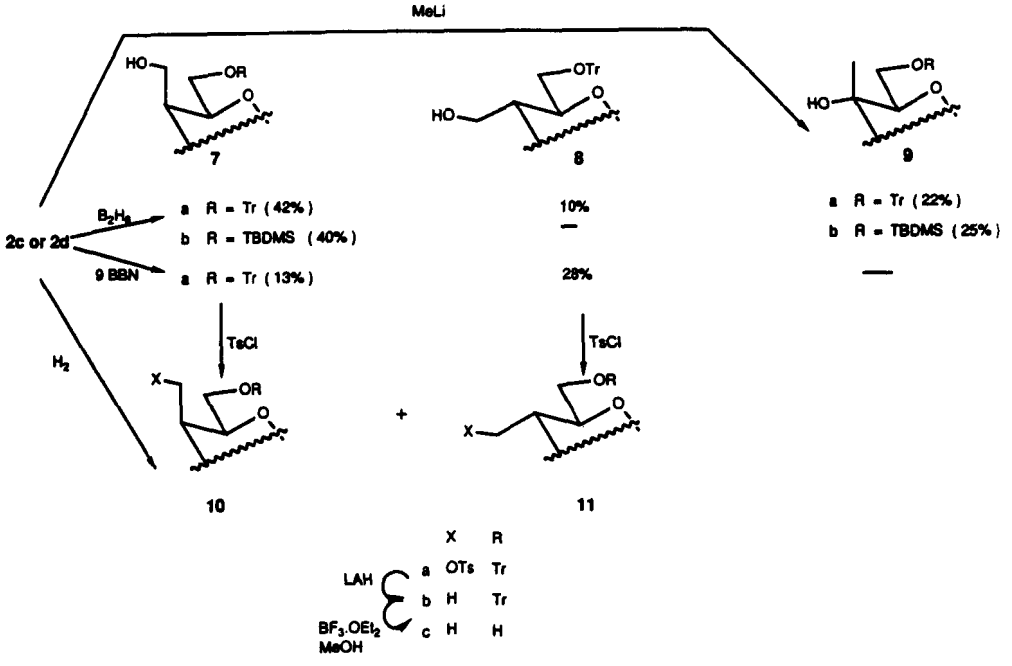
formations are to occur at (what was the original) C4 site of the starting pyranoside, and hence the differentially protected glucopyranosides **1b** and **1c** were appropriate models. Initial attempts directed at displacing a sulfonate from C4 by means of a variety of one-carbon nucleophiles were found to be completely unrewarding. These results were not unexpected in view of the fact that nucleophilic displacements at C4 frequently involve participation of the ring oxygen (O5), leading to ring contraction.[4]

Scheme 1



The alternative route involving hydroboration of the exocyclic olefin was therefore investigated. Preparation of the starting material involved Swern's oxidation[5] of the secondary alcohol, **1b**, followed by reaction of the resulting ketone, **2a** with methylene triphenylphosphorane in tetrahydrofuran at -78 °C. Hydroboration of the resulting olefin, **2c**, with borane-tetrahydrofuran at 0 °C gave two products, the major being assigned as the axial hydroxymethyl derivative **7a** (48%) in view of the coupling constant $J_{3,4}$ = 5.1 Hz. The minor product, **8**, was formed in 10% yield.

Scheme 2

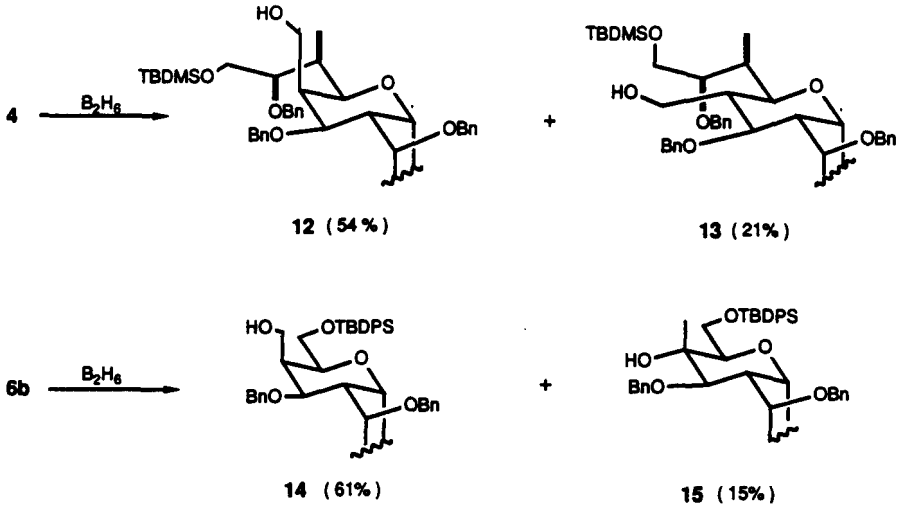


The other product was the tertiary alcohol **9a**, whose configuration was determined by independent synthesis based on a procedure developed by Miljkovic and co-workers.[6] These workers had observed that methyllithium added to ketones, such as **2c** from the β-face only. Indeed, addition of methyllithium to ketone **2c** afforded a single product identical with the material, **9a**, obtained from the hydroboration route.

Products **7a** and **9a** therefore, result from the approach of the hydroborating reagent from the α-face of the molecule. In the hope of achieving greater regioselectivity, hindered hydroborating reagents were examined. However, olefin **2c** was unreactive to disiamylborane at 0 °C or 9BBN at room temperature. On the other hand, when the hydroboration was carried out with 9BBN in refluxing tetrahydrofuran,[7] two products were obtained. The major one in this case was the equatorial hydroxylmethyl analogue **8**, the axial product **7a** being obtained in only 13% yield. It was, therefore, possible to avoid formation of one of the isomers (**9a**) by this route, but the unfavorable yield of **7a** was unacceptable.

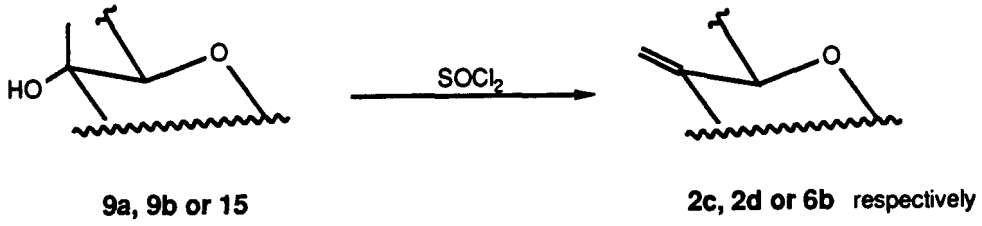
In a surprising development, it was discovered that hydroboration of the silylated analogue **2d** also avoided formation of one of the isomers. Thus, **7b** and **9b** were isolated in 40 and 25% yields, respectively.

Scheme 3



An additional example of the effect of the silyl group on determining the course of hydroboration is seen by comparing the results in Scheme 3 for alkenes **4** and **6b**.[8] Thus, in the case of **6b** (as with **2d**), formation of an equatorial hydroxy-methyl product (e.g., **13**) can be avoided by use of a siloxy derivative at C8. Rationalization of this possible effect of the silicon is premature, but the value of these phenomenological observations stems from the fact that the tertiary alcohols (e.g., **9a**, **9b**, and **15**) can be dehydrated quantitatively to the corresponding alkenes **2c**, **2d**, and **6b**, respectively for recycling.

Scheme 4



9a, 9b or 15 **2c, 2d or 6b** respectively

Hydrogenation of the *exo* cyclic methylene as an alternative route to the C-CH_3 was also investigated and correlations with the foregoing

TABLE 1. Results for the Hydrogenation of Exocyclic Olefin 2d.

Entry	Conditions[a]	Yield, %[b]	Ratio 10/11[c]
i	Raney Ni (W-2), Abs. ethanol	87	1:4
ii	Raney Ni (W-8), Abs. ethanol	88	1:10
iii	$Pd/CaCO_3$, 95% ethanol	71	1:4
iv	5% Pd/C, 95% ethanol	91	1:2
v	$(Ph_3P)_3RhCl$, dry benzene, 60 psi	60	6:5
vi	PtO_2, pentane	96	3:1

a. Reaction time was 4-6 h for all runs.

b. Refers to crude yield of the products after hydrogenation.

c. Ratios indicated were obtained for the desilylated sugar by high field ^1H NMR (200 MHz, $CDCl_3$).

hydroxymethyl derivatives from hydroboration were carried out (Scheme 2). The results of hydrogenation of the silylated olefin **2d** are listed in Table 1. The most advantageous results are in entries ii and vi. Thus, with W-8 Raney nickel the equatorial isomer **11c** predominates, whereas the conditions in entry vi allowed for the best formation of the axial analogue **10c**.

Stereochemical assignments of **10c** and **11c** could not be made directly by ^1H NMR (250 MHz) analyses, and hence, correlations were made with the alcohols **7** and **8** by conversion to the sulfonates and reduction with lithium aluminum hydride.

EXPERIMENTAL

General Procedures. Melting points were determined in capillary tubes using a Buchi Model 510 melting point apparatus and are uncorrected. Elemental analyses were performed by Dr. F. Kasler, University of

Maryland or by M-H-W Laboratories, PO Box 15149, Phoenix, AZ. IR spectra were recorded on a Perkin-Elmer 298 using sodium chloride plates for thin films of liquids, syrups, or solids in nujol mulls. Optical rotations were determined at the sodium D line using Perkin-Elmer 241 polarimeter. ^1H NMR spectra were determined on the following spectrometers: IBM NR-80, Varian XL-100, Varian XL-200, Varian XL-300, or Brucker WM-250. Unless otherwise stated, the solvent used was $CDCl_3$ with internal tetramethylsilane or $CHCl_3$ as the standard. The coupling constants were verified by homonuclear decoupling experiments. For the purpose of ^1H NMR interpretation, compound structures have been numbered in the Schemes. The progress of all reactions was monitored by thin layer chromatography (TLC), which was performed on aluminum plates precoated with silica gel HF-254 (0.2 mm layers) containing a fluorescent indicator (Merck, 5539). The following solvent systems were used: EtOAc-petroleum ether mixtures: A = 1:9; B = 1:4; C, 3:7; D = 1:1, E = 7:3. Detection was first by UV (254 nm), then charring with sulfuric acid spray, or charring with a solution of ammonium molybdate(VI) tetrahydrate (12.5 g), and cerium(IV) sulfate tetrahydrate (5.0 g) in 10% aqueous sulfuric acid (500 mL). Flash chromatography was performed using Kiesselgel 60 (230-400 mesh, Merck).

Selective Silylation of Primary Alcohols. t-Butyldimethylsilyl or t-butyldiphenylsilyl chloride (1.5 mmol/mmol of alcohol) was added to a solution of triethylamine (1.7 mmol/mmol of alcohol), 4-dimethylaminopyridine (0.05 mmol/mmol of alcohol), and the alcohol in dry methylene chloride (10 mL/mmol of alcohol). The reaction was usually completed within 16 h at room temperature, at which time the solution was diluted with methylene chloride and washed successively with saturated solutions of sodium bicarbonate and sodium chloride. The organic phase was dried over anhydrous sodium sulfate, filtered, and evaporated *in vacuo*. The crude residue was purified by flash chromatography.

Swern Oxidation. A solution of dimethylsulfoxide (2.0 equiv.) in dry methylene chloride (4 mL/mmol) was added dropwise to a cooled (-78 °C) solution of oxalyl chloride in dry methylene chloride (4 mL/mmol) under an argon atmosphere. The solution was stirred for 15 min at -78 °C and then a solution of the alcohol in methylene chloride (5 mL/mmol) was added dropwise. The reaction was stirred for 20-30 min and dry triethylamine (5 equiv.) was added dropwise. The work-up for this reaction was identical to the previous procedure.

Methyl 2,3-di-O-Benzyl-6-O-triphenylmethyl-α-D-*xylo*-hexopyranoside-4-ulose (2a). A solution of 2,3-di-O-benzyl-α-D-gluco-pyranoside,[9] **1a**, (3.00 g, 8.01 mmol) in dry dimethylformamide (25 mL) and triethylamine (1.68 mL) was treated with triphenylmethyl chloride (2.46 g, 8.81 mmol) and 4-dimethylaminopyridine (0.039 g). The reaction mixture was stirred at room temperature for 48 h. After this time, the reaction was quenched with water and extracted with ether. The combined ether extracts were washed with water and saturated sodium chloride solution, then dried (Na_2SO_4). The solvents were evaporated *in vacuo* and the residue purified by flash chromatography (C). The title compound, **1b** (4.00 g, 81%) was obtained as a pale yellow syrup, which was dissolved in dry methylene chloride and subjected to Swern oxidation conditions (See General Procedures). Purification of the crude residue by flash chromatography (C) gave the ketone **2a** (3.88 g, 97%) as a pale yellow syrup. TLC: R_f = 0.44 (C); $[\alpha]_D^{18}$ +77.60° (c 1.01, $CHCl_3$); IR (neat) 1730 cm^{-1}; ^1H NMR (80 MHz, $CDCl_3$) δ 3.24-3.65 (m, 2), 3.53 (s, 3, OCH_3), 3.80 (dd, 1, J = 3.5, 10.0 Hz), 4.10-4.47 (overlapping d, 1, J = 10.0 Hz and dd, 1, J = 3.4 Hz), 4.48-5.10 (m, 5), 7.10-7.65 (m, 25).

Anal. Calcd for $C_{40}H_{38}O_6$: C, 78.15; H, 6.23. Found: C, 78.28; H, 6.16.

Methyl 2,3-di-O-Benzyl-4-deoxy-4-C-methylene-6-O-triphenylmethyl-α-D-*xylo*-hexopyranoside (2c). Butyllithium (9.02 mL of a 2.1 M solution in hexane) was added dropwise to a solution of methyltriphenylphosphonium bromide (6.77 g, 19.0 mmol) in dry tetrahydrofuran (50 mL). The reaction mixure was stirred at room temperature for 0.5 h and then cooled to -78 °C. A tetrahydrofuran solution of the ketone **2a** (3.88 g, 6.32 mmol) was added dropwise to the cooled methylenetriphenylphosphorane solution. After 0.5 h, the reaction mixture was slowly warmed to room temperature and stirred for 1 h. The reaction was quenched with saturated ammonium chloride solution (50 mL) and extracted with ether (3 x 75 mL), saturated sodium chloride solution, and dried (Na_2SO_4). The solvents were removed *in vacuo* and the residue was purified by flash chromatography (C) to give the exocyclic olefin **2c** (3.73 g, 96%) as a colorless syrup. TLC R_f = 0.48 (C); $[\alpha]_D^{19}$ +36.0° (c 2.09, $CHCl_3$); IR (neat) 3030, 2930, 1595, 1490, 1450, 1350, 1205, 1125, 1090, 930, 700 cm^{-1}; ^1H NMR (80 MHz, $CDCl_3$) δ 3.30-3.60 (m, 2), 3.49 (s, 3, OCH_3), 4.17-4.46 (m, 3), 4.50-4.95 (m, 5), 5.26 (br s, 2), 7.1-7.6 (m, 25).

Anal. Calcd for $C_{41}H_{40}O_5$: C, 80.36; H, 6.58. Found: C, 80.39; H. 6.69.

Hydration of Alkenes with B_2H_6/THF/Na_2O_2. (a) The olefin **2c** (560 mg, 0.91 mmol), dissolved in dry tetrahydrofuran (25 mL), was added

dropwise to a solution of borane (3.6 mL of a 1 M tetrahydrofuran solution) in tetrahydrofuran (25 mL) at 0 °C under an argon atomosphere. The reaction mixture was stirred for 3-4 h at this temperature, followed by dropwise addition of aqueous sodium hydroxide (5.2 mL of a 3 M solution) and 30% hydrogen peroxide (5.2 mL of an aqueous solution). This mixture was slowly warmed to room temperature over 0.5 h, diluted with water, and extracted with ether. The combined ether extracts were washed with 10% aqueous sodium bisulfite solution, saturated sodium chloride solution, and dried (Na_2SO_4). The solvents were removed *in vacuo* and the residue was purified by flash chromatography (B) to give 2,3-di-O-benzyl-4-deoxy-4-C-hydroxymethyl-6-O-triphenylmethyl-α-D-galactopyranoside **7a** (252 mg, 45%) as a colorless syrup: TLC R_f = 0.32 (E); $[\alpha]_D^{19}$ +26.6° (c 1.14, $CHCl_3$); IR (neat) 3490, 3025, 2930, 1490, 1085, 1030 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 2.26 (m, 1, H4), 3.06-3.14 (m, 2, H6', OH, D_2O ex), 3.30 (dd, 1, $J_{6,6'}$ = 10.5 Hz, $J_{5,6}$ = 6.5 Hz, H6), 3.44 (s, 3, OCH_3), 3.54-3.66 (m, 1, H7), 3.73 (dd, 1, $J_{1,2}$ = 3.8 Hz, $J_{2,3}$ = 10.0 Hz, H2), 3.81-3.98 (m, 2, H5, H7'), 4.03 (dd, 1, $J_{3,4}$ = 5.1 Hz, H3), 4.62-4.86 (m, $PhCH_2$, H1), 7.17-7.50 (m, 25, Ph_3C, $PhCH_2$).

Anal. Calcd for $C_{41}H_{42}O_6$: C, 78.07; H, 6.71. Found: C, 77.81; H, 6.82.

A second product (123 mg, 22%) of lower polarity (R_f = 0.46) was isolated from the chromatographic column whose physical properties proved to be the same as the tertiary alcohol, methyl 2,3-di-O-benzyl-4-C-methyl-6-O-triphenyl methyl α-D-glucopyranoside (**9a**), prepared as described in the following paragraph.

Methyllithium (1.25 mL of a 1.2 M ether solution-low halide content) was added dropwise to a solution of the ketone **2a** (122 mg, 0.199 mmol) in dry ether (10 mL) at -78 °C under an argon atmosphere. The reaction mixture was stirred for 1.5 h at this temperature. Saturated ammonium choride solution (10 mL) was then added, the ether layer separated, and the water layer extracted with ether (3 x 30 mL). The combined ether extracts were washed with saturated sodium chloride solution (1 x 50 mL), dried (Na_2SO_4), and concentrated *in vacuo*. The residue was purified by flash chromatography (E) to give the tertiary alcohol **9a** (110 mg, 88%) as a colorless syrup. TLC R_f = 0.38 (C); $[\alpha]_D^{19}$ +10.2° (c 1.67, $CHCl_3$); ^1H NMR (80 MHz, $CDCl_3$) δ 0.99 (s, 3, CH_3), 2.35 (br s, 1, OH, D_2O ex), 3.20-3.50 (m, 3), 3.47 (s, 3, OCH_3), 3.64-4.00 (m, 5), 7.10-7.60 (m, 25).

The minor product from the chromatogram proved to be 2,3-di-O-benzyl-4-deoxy-4-C-hydroxymethyl-6-O-triphenylmethyl-α-D-glucopyrano-

side **8** (310 mg, 10%), obtained as a colorless syrup. TLC R_f = 0.26 (B); $[\alpha]_D^{19}$ +9.7° (c 0.94, $CHCl_3$); IR (neat) 3480, 3920, 1490, 1450, 1090, 1055 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.84 (m, 1, H4), 1.65 (t, 1, OH, D_2O ex), 3.16 (dd, 1, $J_{5,6}$ = 4.0 Hz, $J_{6,6'}$ = 11.0 Hz, H6), 3.32-3.47 (m, 2, H6', H7), 3.40 (s, 3, OCH_3), 3.53-3.60 (m, 1, H7'), 3.63 (dd, 1, $J_{1,2}$ = 3.2 Hz, $J_{2,3}$ = 9.2 Hz, H2), 3.78 (dt, 1, $J_{4,5}$ = 10.5 Hz, $J_{5,6}$ = $J_{5,6'}$ = 4.0 Hz, H5), 3.90 (t, 1, $J_{3,4}$ = 10.0 Hz, H3), 3.67-3.85 (m, 3, Ph$\underline{CH_2}$, H1), 3.83 (ABq, 2, J = 11.0 Hz, Δδ = 0.32 ppm, Ph$\underline{CH_2}$), 7.18-7.54 (m, 25, $\underline{Ph_3}C$, $\underline{Ph}CH_2$).

Elemental analysis was obtained on the benzoate of **8**. Anal. Calcd for $C_{48}H_{56}O_7$: C, 77.39; H, 7.58. Found: C, 77.46; H, 7.72.

(b) Alkene **2d** (obtained from **1c**, as described for **2c**) (200 mg, 0.41 mmol) was hydroborated, as described in part (a). Flash chromatography (B) afforded **7b** (80 mg, 40%) and **9b** (25%). For **7b**: TLC R_f = 0.6 (C); $[\alpha]_D^{25}$ +34.1° (c 1.2, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 0.06 (s, 6, $SiMe_2$), 0.88 (s, 9, t-butyl), 2.34 (m, 1, H4), 3.36 (s, 3, OMe), 3.43 (m, 1, OH, D_2O ex), 3.66 (dd, 1, $J_{2,3}$ = 10 Hz, $J_{2,1}$ = 3.3 Hz, H2), 3.70-3.83 (m, 3, H5, H6, H6'), 3.84-4.01 (m, 2, H7, H7'), 4.05 (dd, 1, $J_{3,2}$ = 10Hz, $J_{3,4}$ = 5Hz, H3), 4.64 (d, 1, $J_{1,2}$ = 3.3 Hz, H1), 4.66, 4.81 (AB, 2d, 2, J = 11.5 Hz, $\underline{CH_2}$Ph), 4.72, 4.78 (AB, 2d, 2, J = 11.5 Hz, $\underline{CH_2}$Ph), 7.25-7.43 (m, 10, $CH_2\underline{Ph}$).

Anal. Calcd for $C_{28}H_{41}SiO_6$: C, 67.08; H, 8.17. Found: C, 67.00; H, 8.01.

For **9b**: TLC R_f = 0.76 (C); $[\alpha]_D^{25}$ +22.0° (c 0.9, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 0.07 (s, 6, $SiMe_2$), 0.87 (s, 9, t-butyl), 1.21 (s, 3, CH_3), 2.89 (s, 1, OH, D_2O ex), 3.27 (s, 3, OCH_3), 3.64-3.86 (m, 5, H2, H3, H5, H6, H6'), 4.55 (d, 1, $J_{1,2}$ = 3Hz, H1), 4.61, 4.77 (AB, 2d, 2, J = 12 Hz, $\underline{CH_2}$Ph), 4.84, 4.92 (AB, 2d, 2, J = 12 Hz, $\underline{CH_2}$Ph, 7.21-7.44 (m, 10, $CH_2\underline{Ph}$).

(c) Alkene **4b** (obtained from alcohol **3**,[8] as described for **2c**) (202 mg, 0.26 mmol) was hydroborated, as described in part (a). Flash chromatography afforded a mixture of two products: **12** (111 mg, 54%) and **13** (43 mg, 21%. For **12**: TLC R_f = 0.36 (B); $[\alpha]_D^{25}$ +53° (c 0.60, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 0.01 (s, 6H, $SiMe_2$), 0.78 (d, 3H, J = 6.3 Hz, CH_3-8), 0.83 (br s, 9H, t-butyl), 1.10 (s, 3H, CH_3-2), 1.76 (m, 1H, H-8), 2.13 (m, 1H, H-6), 2.30 (m, 1H, H-4), 3.20 (br d, 1H, J = 9.3 Hz, OH), 3.51 (dd, 1H, $J_{9,10a}$ = 6.3, J_{gem} = 10.5 Hz, H-10a), 3.68 (m, 4H, H-1ax, H-3, H-7'a, H-10b), 4.00 (m, 4H, H-1eq, H-7, H-7'b, H-9), 4.09 (ABq, 2H, J = 10.2 Hz, Δδ = 0.27 ppm, Ph $\underline{CH_2}$), 4.39 (ABq, 2H, J = 10.5 Hz, Δδ = 0.06 ppm, Ph $\underline{CH_2}$), 4.47 (dd, 1H, $J_{4,5}$ = 12.6, $J_{5,6}$ = 5.1 Hz, H-5), 4.50 (ABq, 2H, J =

12.0 Hz, $\Delta\delta$ = 0.15 ppm, Ph $\underline{CH_2}$), 4.72 (br s, 2H, Ph $\underline{CH_2}$), 5.10 (d, 1H, J = 3.0 Hz, H-1'), 7.22 (m, 20H, $\underline{Ph}$ CH_2 x 4).

Anal. Calcd for $C_{48}H_{64}O_8Si$: C, 72.33; H, 8.09. Found: C, 72.27; H, 8.29.

For **13**: TLC R_f = 0.27 (B); $[\alpha]_D^{25}$ +68.5° (c 1.10, $CHCl_3$); IR (neat) 3480 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.02 (s, 6H, $SiMe_2$), 0.88 (s, 9H, t-butyl), 1.15 (d, 3H, J = 6.5 Hz, CH_3-8), 1.19 (s, 3H, CH_3-2), 1.66 (m, 1H, OH), 1.73 (m, 1H, H-6), 2.05 (m, 1H, H-4), 2.26 (m, 1H, H-8), 3.67 (m, 7H, H-1ax, H-3, CH_2-7', H-9, CH_2-10), 3.97 (dd, 1H, $J_{6,7}$ = 10.2, $J_{7,8}$ = 2.4 Hz, H-7), 4.17 (dd, 1H, $J_{1eq,3}$ = 1.5, J_{gem} = 15.6 Hz, H-1eq), 4.28 (ABq, 2H, J = 11.4 Hz, $\Delta\delta$ = 0.36 ppm, Ph $\underline{CH_2}$), 4.34 (t, 1H, J = 11.4 Hz, H-5), 4.41 (m, 2H, Ph $\underline{CH}$ x 2), 4.53 (m, 4H, PH $\underline{CH}$ x 4), 5.14 (d, 1H, J = 3.9 Hz, H-1'), 7.30 (m, 20H, $\underline{Ph}$ CH_2 x 4).

Anal. Calcd for $C_{48}H_{64}O_8Si$: C, 72.33; H, 8.09. Found: C, 72.20; H, 8.36.

(d) The silylated bipyranoside **5**[8] (2.84 g, 3.75 mmol) was oxidized to ketone **6a** (2.77 g, 98%) TLC R_f = 0.25 (A); IR (neat) 1730 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.05 (s, 9H, t-butyl), 1.20 (s, 3H, CH_3-2), 2.55 (dt, 1H, $J_{1',4}$ = $J_{3,4}$ = 2.0, $J_{4,5}$ = 11.7 Hz, H-4), 3.82 (m, 4H), 4.08 (dd, 1H, J = 3.3, 10.2 Hz), 4.26 (dd, 1H, J = 1.5, 12.0 Hz, H-1eq), 4.39, 4.45 (both d of ABq, 1H *ea*, J = 11.7, 11.4 Hz, respectively, Ph $\underline{CH}$ x 2), 4.57 (m, 4H), 4.96 (d, 1H, J = 12.3 Hz), 5.26 (d, 1H, J = 3.6 Hz, H-1'), 7.27, 7.70 (both m, 25H, $\underline{Ph}$ CH_2 x 3, $\underline{Ph_2}$ Si).

Anal. Calcd for $C_{47}H_{52}O_7Si$: C, 74.57; H, 6.92. Found: C, 74.41; H, 6.88, from which the olefin **6b** (2.63 g, 95%) was obtained as a colorless oil TLC R_f = 0.30 (A); $[\alpha]_D^{25}$ +31.7° (c 1.00, $CHCl_3$); IR (neat) 1605 w, 920 w cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.06 (s, 9H, t-butyl), 1.40 (s, 3H, CH_3-2), 2.18 (m, 1H, H-4), 3.65, 3.70 (both d, 1H *ea*, J = 11.1, 9.6, respectively, H-1ax, H-8a), 3.99 (m, 3H, H-1eq, H-3, H-8b), 4.16 (d of ABq, 1H, J = 11.7 Hz, Ph $\underline{CH}$), 4.31 (d, 1H, J = 3.3 Hz, H-7), 4.48 (m, 5H, H-5, Ph $\underline{CH}$ x 4), 4.81 (d of ABq, 1H, J = 11.7 Hz, Ph $\underline{CH}$), 4.92, 5.19 (both br s, 1H *ea*, $=CH_2$), 5.26 (d, 1H, J = 3.0 Hz, H-1'), 7.25, 7.51 (both m, 25H, $\underline{Ph}$ CH_2 x 3), $\underline{Ph_2}$ Si.

Anal. Calcd for $C_{48}H_{54}O_6Si$: C, 76.36; H, 7.21. Found: C, 76.18; H, 7.30.

The olefin **6b** (2.63 g, 3.45 mmol) was hydroborated, as described in part (a), and flash chromatography of the crude product gave tertiary

alcohol **15** (410 mg, 15%) and primary alcohol **14** (1.63 g, 61%). For **15**: TLC R_f = 0.33 (A); ^{1}H NMR (300 MHz $CDCl_3$); δ 1.05, 1.06 (both s, 9H, t-butyl), 1.12, 1.28 (both s, 3H *ea*, CH_3-2, CH_3-6), 1.93 (br d, 1H, $J_{4,5}$ = 10.0 Hz, H-4), 3.45 (s, 1H, OH), 3.65 (d, 1H, J = 10.0 Hz, H-1ax), 3.80 (m, 3H, H-3, CH_2-8), 4.10 (m, 2H, H-1eq, H-7), 4.35 (m, 4H, H-5, Ph CH x 3), 4.58, 4.64, 4.76 (all d of ABq, 1H *ea*, J = 10.0, 9.0, 10.0 Hz, respectively, Ph CH x 3), 4.99 (d, 1H, J = 3.0 Hz, H-1'), 7.30, 7.48 (both m, 25H, Ph CH_2 x 3, Ph_2 Si). For **14**: TLC R_f = 0.15 (A); $[\alpha]_D^{25}$ +57.6° (c 2.48, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.06 (br s, 9H t-butyl), 1.17 (s, 3H, CH_3-2), 2.18 (m, 1H, H-4), 2.27 (m, 1H, H-6), 3.40 (m, 1H, OH), 3.68 (d, 1H, J = 13.2 Hz, H-1ax), 3.80 (m, 4H, H-3, CH_2-7', H-8a), 4.10 (m, 3H, H-1eq, H-7, H-8b), 4.17 (ABq, 1H, J = 11.4 Hz, Δδ = 0.31 ppm, Ph CH_2), 4.44 (m, 3H, H-5, Ph CH x 2), 4.55, 4.63 (both d of ABq, 1H *ea*, J = 10.2, 11.7, respectively Ph CH x 2), 5.10 (d, 1H, J = 2.4 Hz, H-1'), 7.25, 7.65 (both m, 25H, Ph CH_2 x 3, Ph_2 Si).

Anal. Calcd for $C_{48}H_{26}O_7Si$: C, 74.58; H, 7.30. Found: C, 74.65; H, 7.13.

Hydration of Alkene 2c with 9BBN/THF/Na_2O_2. A solution of the olefin **2c** (1.082 g, 1.77 mmol) in dry tetrahydrofuran was added to a solution of 9-borabicyclo [3.3.1] nonane (17.7 mL of a 0.5 M THF solution) in dry THF (50 mL). The reaction mixture was refluxed for 3 h under an argon atmosphere and then cooled to 0 °C, followed by dropwise addition of aqueous sodium hydroxide (17.7 mL of a 3 M solution) and 30% hydrogen peroxide (17.7 mL of an aqueous solution). Processing, as described in the preceeding section, afforded a residue which was purified by flash chromatography (B). The products were **8** (310 mg, 28%) and **7a** (145 mg, 13%), as described above.

Methyl 2,3-di-O-Benzyl-4-deoxy-4-C-methyl-α-D-galactopyranoside (10c). A solution of the alcohol **7a** (192.9 mg, 0.306 mmol) in dry pyridine (3 mL) was treated with p-toluenesulfonyl chloride (87.6 mg, 0.459 mmol). The reaction mixture was stirred at room temperature for 16 h, quenched with water and processed in the usual way to afford the sulfonate **10a** (204.9 mg, 85%) as a colorless syrup. A portion of the material (170.4 mg, 0.218 mmol) in dry tetrahydrofuran (6 mL) was treated with lithium aluminum hydride (40 mg, 1.06 mmol). The reaction mixture was quenched at 0 °C with a sodium sulfate-water slurry and after customary work-up, the residue was purified by flash chromatography (C) to afford compound **10b** (36.8 mg, 28%) as a colorless syrup. TLC R_f = 0.57 (C). A portion of the

material (25.6 mg, 0.0416 mmol) in dry methylene chloride (2 mL) and absolute methanol (0.1 mL) was treated with boron trifluoride etherate (0.05 mL) for 0.25 h. Customary work-up gave a residue which was purified by flash chromatography (D) to give the title compound **10c** (8.5 mg, 58%) as a colorless syrup. TLC R_f = 0.38 (ethyl acetate); $[\alpha]_D^{19}$ +63° (c 0.77, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 0.93 (d, 3, $J_{4,CH}$ = 7.1 Hz, CH_3), 1.75 (br s, 1, OH, D_2O ex), 2.22 (m, 1, H4), 3.39 (s, 3, OCH_3), 3.45-3.76 (m, 3), 3.90-4.00 (m, 2, H3, H5), 4.61-4.90 (m, 5, Ph$\underline{CH_2}$, H1), 7.25-7.50 (m, 10, $\underline{Ph}CH_2$).

Anal. Calcd for $C_{22}H_{28}O_5$: C, 70.94; H, 7.58. Found: C, 70.73; H, 7.70.

Methyl 2,3-di-O-Benzyl-4-deoxy-4-C-methyl-α-D-glucopyranoside (11c). By a similar sequence of reactions, as described in the preceeding section (**7a** ---> **10c**), the alcohol **8** (188 mg, 0.299 mmol) was treated with p-toluenesulfonyl chloride (86 mg, 0.449 mmol). The reaction mixture was stirred at room temperature for 16 h and then quenched with water (15 mL). Processing, as described in the preceeding section, led to **11a**, **11b**, and thence to the title compound **11c** as a colorless syrup. TLC R_f = 0.38 (ethyl acetate); $[\alpha]_D^{19}$ +20.1° (c 1.09, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 0.96 (d, 3, $J_{4,CH}$ = 7.7 Hz, CH_3), 1.74 (m, 1, H4), 1.90 (br s, 1, OH, D_2O ex), 3.40 (s, 3, OCH_3), 3.42-3.82 (m, 5), 4.55-5.10 (m, 5, Ph$\underline{CH_2}$, H1), 7.23-7.55 (m, 10, $\underline{Ph}CH_2$).

Anal. Calcd for $C_{22}H_{28}O_5$: C, 70.94; H, 7.58. Found: C, 70.88; H, 7.52.

Hydrogenation of Exocyclic Olefin 2d. *Alternative Routes to* **10c** and **11c**. The conditions for hydrogenation of olefin **2d** are listed in Table 1. Prior to hydrogenation, the olefin was stirred in ethyl acetate with Raney nickel (W-2 grade) to absorb impurities that would poison the hydrogenation catalysts. The scale of the reaction was typically between 100-150 mg of the olefin in 10 mL of solvent. Most reactions were conducted in a 100 mL round bottom flask fitted with a teflon magnetic sitrring bar and hydrogen balloon. The hydrogenation, using triphenylphosphine rhodium chloride catalyst, involved using a Parr shaker hydrogenator with a hydrogen atmosphere of 60 psi. Reactions were monitored by ^1H NMR (80 MHz, by disappearance of olefin protons at 5.31). Upon completion, the reaction mixture was filtered through a Celite pad and concentrated *in vacuo*. The crude material was dissolved in tetrahydrofuran and desilylated with *tetra*-n-butylammonium fluoride in the usual way. Upon work-up, the epimeric mixture of **10c** and **11c** was obtained as a colorless syrup. The ratio was determined (at 200 MHz) by integration of the H4 methine multiple (δ 2.22

in **10c** and δ 1.74 in **11c**) and the relative intensities of the methyl doublets (δ 0.93 and δ 0.96, respectively). These assignments were based on correlation with materials made from alcohols **7b** and **8**.

Dehydration of Tertiary Alcohols. Thionyl chloride (0.01 mL, 1.23 mmol) was added to a solution of tertiary alcohol **15** (45 mg, 0.058 mmol) in dry pyridine (2 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 20 min, diluted with methylene chloride (20 mL), and washed successively with dilute hydrochloric acid (10 mL), and solutions of saturated sodium bicarbonate (10 mL) and sodium chloride (10 mL). The organic phase was dried over anhydrous sodium sulfate, filtered, and evaporated *in vacuo*. Flash chromatography of the crude gave a product (38 mg, 85%), which was identical to olefin **6b** (TLC, ^{1}H NMR). The tertiary alcohols **9a** and **9b** were dehydrated similarly to **2c** and **2d**, respectively.

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