Rearrangement of Spiroacetals of the 1,6-Dioxaspiro[4.5]decan-10-yl Methanesulfonate Type. Synthesis of Cis-Fused 1,6-Dioxadecalins

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Received July 31, 2000

Compounds isolated from marine sources such as maitotoxin[1] (MXT) and halichondrins[2] consist mainly of fused polycyclic ethers, a remarkable structural feature being the presence of two sets of cis-fused ether rings: rings A/B and F/G in the halichondrins and rings L/M and N/O in maitotoxin.

The important biological activity of such compounds and their complex structures make them interesting targets in natural products chemistry.

We have recently described a new method for the synthesis of steroidal cis- and trans-fused ditetrahydropyrans by reduction with DIBALH of steroidal methanosulfonates.[3] We thought that an extension of this methodology starting from more versatile and less conformationally restricted substrates than steroids could give rise to the cis-fused 1,6-dioxadecalin of the type present in the aforementioned products. The stereochemical properties of carbohydrates,[4] their ready availability, and our successful previous results in the construction of the spiroacetal intermediates[5] make them suitable starting materials.

We wish to report here on the results obtained by reduction with DIBALH of the α-methanosulfonate spiroacetal derivatives that were prepared starting from methyl 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranoside.

Our synthetic approach to the dioxaspiro intermediate is outlined in Scheme 1. Our first target was the enlargement of the side chain at C-1 of the carbohydrate, and for this purpose we prepared the C-glucoside by the Lewis acid-catalyzed allylation of methyl 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranoside with allyltrimethylsilane,[6] which afforded 2,6-anhydro-1,3,4,5-tetra-*O*-benzyl-7,8,9-trideoxy-D-*glycero*-L-*gulo*-non-8-enitol in excellent yield and stereoselection. To obtain α-C-glucosides with the hydroxyl group at C-2 selectively deprotected, we followed the methodology reported by Nicotra.[7] This consists of the treatment with iodine to form a cyclic iodoether that on reductive elimination (Zn/AcOH) results in the debenzylation at C-2 to give **1** (Scheme 1). To transform the double bond in the terminal alcohol, the following group manipulations were realized: (i) protection of the hydroxyl group at C-2 as its *tert*-butyldimethylsilyl ether **2** and (ii) hydroboration−oxidation of the olefin to produce the alcohol **3**. This key molecule presents the number of carbons and the convenient functionality for the elaboration of the dispiro compounds. Thus, the intramolecular hydrogen abstraction reaction was achieved by reaction of compound **3** with (diacetoxyiodo)benzene (DIB) and iodine in cyclohexane at 20 °C yielding the spiroacetal **4** besides its epimer at C-1 **5** in 1:2 ratio and 62% yield. The structures of **4** and **5** and the configuration of the spirocenters were unambiguously established by COSY, HMQC, and HMBC experiments, the major isomer **5** being the less stable thermodynamically. This was also confirmed by the acid-catalyzed isomerization of **5** to **4**.[5e]

Deprotection and subsequent mesylation of compounds **4** and **5** afforded **7** and **9**, respectively, which present the requisites to undergo the reductive rearrangement. When compound **7** was treated with DIBALH under several conditions the a-methanesulfonate spiroacetal derivative was recovered unaltered. However, compound **9** was reduced by DIBAH in CH_2Cl_2 at 42 °C for 76 h to give two products **10** and **11** in a ratio of 3:1 (Scheme 2). This sharp contrast in reactivity may originate from a more easy binding of DIBAH with the spiro oxygens in the case of compound **9**. The ^{1}H NMR spectrum of compound **11** clearly indicates the presence of an equatorial propyl chain in the anomeric position and hence the reduction of the O−C(2) bond with inversion of configuration.

More interesting was the formation of the *cis*-1,6-dioxadecalin **10**. The structure and stereochemistry of this compound have been established by extensive spectroscopic analysis and confirmed by X-ray crystallography of its *p*-nitrobenzoyl derivative.[8] As observed, the rings have a *cis*-fusion and both adopt a double chair conformation. The selective debenzylation at C-4 is noteworthy.

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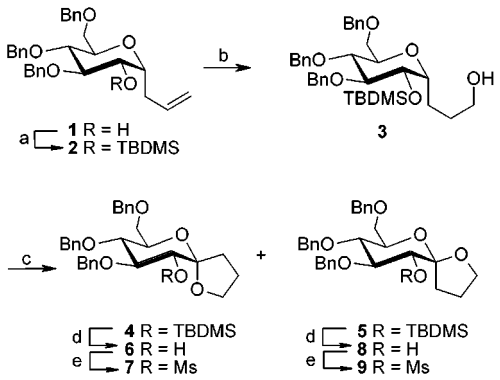
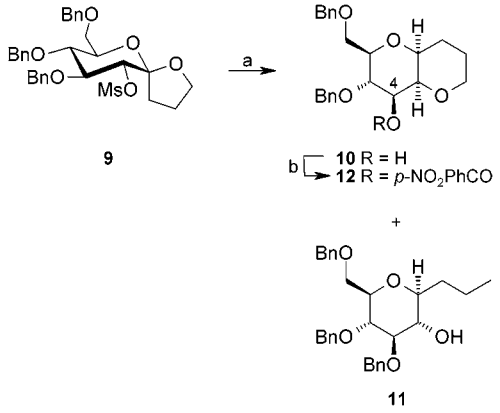
10.1021/jo005593a CCC: $19.00
Published on Web 11/17/2000

Scheme 1[a]



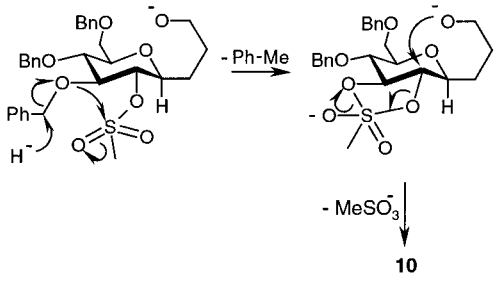
[a] Key: (a) TBDMSOTf, NEt_3, CH_2Cl_2, 0 °C, 30 min, 97%; (b) BH_3·THF, THF, 0 °C, 2h then NaOH (3 N), H_2O_2, rt, 30 min, 83%; (c) DIB/I_2, cyclohexane, 20 °C, 5 h, 62%; (d) TBAF, THF, rt, overnight, 85−95%; (e) MsCl, pyridine, rt, 5−12h, 76−80%.

Scheme 2[a]



[a] Key: (a) DIBALH, CH_2Cl_2, 42 °C, 76 h, 72%; (b) *p*-nitrobenzoyl chloride, pyridine, rt, 4 h, 90%.

Scheme 3



A plausible mechanism for the formation of these products is proposed. In the first step, the aluminum reagent coordinates at the tetrahydrofuran oxygen, which is the more nucleophilic, and reduces the oxonium ion with inversion of configuration. Then, the alkoxy intermediate could undergo a transesterification of the methanesulfonate group to give a more stable primary methanesulfonyl derivative which is subsequently reduced with an excess of DIBALH to give compound **11**. The mechanism proposed for the formation of compound **10** is outlined in Scheme 3. The reductive debenzylation at C-4 is promoted by the hydride ion assisted by the neighboring methanesulfonyl group. The alkoxy anion could now attack the cyclic sulfate via an intramolecular S_N2 displacement with inversion of configuration to afford **10**. Although we are unaware of previous precedents for this reductive debenzylation, similar ionic debenzylations using the iodide anion as nucleophile have been described.[7,9]

Experimental Section

General Methods. Melting points were determined with a hot-stage apparatus and are uncorrected. Optical rotations were measured at the sodium line at ambient temperature in $CHCl_3$ solutions. IR spectra were recorded in $CHCl_3$ solutions. NMR spectra were determined at 500 MHz for ^1H and 125.7 MHz for ^{13}C in $CDCl_3$ unless otherwise stated, in the presence of TMS as internal standard. Mass spectra were determined at 70 eV. Merck silica gel 60 PF (0.063−0.2 mm) was used for column chromatography. Circular layers of 1 mm of Merck silica gel 60 PF_{254} were used on a Chromatotron for centrifugally assisted chromatography. Commercially available reagents and solvents were analytical grade or were purified by standard procedures prior to use.[10] All reactions involving air- or moisture-sensitive materials were carried out under a nitrogen atmosphere. The spray reagents for TLC analysis were conducted with 0.5% vanillin in H_2SO_4−EtOH (4:1) and further heating until development of color.

2,6-Anhydro-1,3,4-tri-*O*-benzyl-5-*O*-[*tert*-butyl(dimethyl)silyl]-7,8,9-trideoxy-D-*glycerol*-L-*gulo*-non-8-enitol (2). To a solution of **1** (106 mg, 0.22 mmol) in dry dichloromethane (7.3 mL) were added triethylamine (244 μL, 1.75 mmol) and *tert*-butyldimethylsilyltrifluoromethane sulfonate (213 μL, 0.93 mmol), and the solution was stirred under nitrogen at 0 °C for 30 min. The reaction mixture was then poured into an aqueous saturated solution of $NaHCO_3$ and extracted with CH_2Cl_2. The combined extracts were dried over Na_2SO_4 and concentrated under reduced pressure. Chromatotron chromatography of the residue (hexanes−EtOAc, 97:3) gave the title compound **2** (128 mg, 0.22 mmol, 97%): $[\alpha]_D = +55$ ($c = 1.2$); IR 3066, 3032, 2955, 2929, 2857, 1945, 1869, 1805, 1726, 1642, 1497, 1454, 1360, 1257 cm^{-1}; ^1H NMR δ 7.40−7.28 (13H, m), 7.11−7.10 (2H, m), 5.90 (1H, dddd, $J = 17.1, 10.1, 6.8, 6.8$ Hz), 5.16 (1H, dd, $J = 17.1, 1.5$ Hz), 5.13 (1H, dd, $J = 10.2, 1.4$ Hz), 4.96 (1H, d, $J = 11.4$ Hz), 4.86 (1H, d, $J = 11.4$ Hz), 4.81 (1H, d, $J = 10.6$ Hz), 4.69 (1H, d, $J = 12.1$ Hz), 4.53 (2H, d, $J = 12.1$ Hz), 4.50 (1H, d, $J = 10.6$ Hz), 4.06 (1H, dd, $J = 13.5, 7.4$ Hz), 3.97 (1H, dd, $J = 6.0, 6.0$ Hz), 3.77 (1H, br d, $J = 10.4$ Hz), 3.68 (3H, m), 2.54 (1H, dd, $J = 7.2, 7.2$ Hz), 0.96 (9H, s), 0.13 (3H, s), 0.12 (3H, s); ^{13}C NMR δ 138.9 (C), 138.2 (C), 138.0 (C), 135.0 (CH), 128.3−127.3 (15 × CH), 116.7 (CH_2), 83.2 (CH), 78.3 (CH), 76.4 (CH), 75.4 (CH_2), 75.0 (CH_2), 73.5 (CH_2), 73.1 (CH), 71.1 (CH), 68.9 (CH_2), 29.0 (CH_2), 25.9 (3 × CH_3), 17.9 (C), −4.5 (CH_3), −4.7 (CH_3); MS *m*/*z* (rel intensity) 589 ($M^+ + 1$, <1), 497 (16), 439 (35), 391 (43), 349 (60), 333 (46), 271 (100); HRMS calcd for $C_{36}H_{49}O_5Si$ 589.3349, found 589.3382. Anal. Calcd for $C_{36}H_{48}O_5Si$: C, 73.43; H, 8.22. Found: C, 73.13; H, 8.56.

2,6-Anhydro-1,3,4-tri-*O*-benzyl-5-*O*-[*tert*-butyl(dimethyl)silyl]-7,8-dideoxy-D-*glycerol*-L-*gulo*-nonitol (3). To a solution of olefin **2** (730 mg, 1.24 mmol) in dry THF (3.5 mL) at 0 °C and under nitrogen was added dropwise a solution of BH_3·THF complex (3.5 mL, 3.5 mmol, 1 M in THF). After 2 h of stirring, the excess borane was quenched carefully by adding a drop of water. Dropwise addition of a mixture of 3 N NaOH (15 mL) and 30% hydrogen peroxide (15 mL), removal of the cooling bath, and continued stirring for 30 min resulted in a white heterogeneous mixture. The reaction mixture was then poured into ice−water and extracted with CH_2Cl_2, washed with brine, dried over Na_2SO_4, and concentrated in a vacuum. Chromatotron chromatography of the residue (hexanes−EtOAc, 90:10, 80:20, 70:30) yielded alcohol **3** (624 mg, 1.03 mmol, 83%): $[\alpha]_D = +28.9$ ($c = 0.79$); IR 3638, 3502, 3066, 3032, 2955, 2929, 2857, 1945, 1869, 1805, 1454, 1359, 1254 cm^{-1}; ^1H NMR δ 7.37−7.25 (13H, m), 7.09−7.07 (2H, m), 4.92 (1H, d, $J = 11.4$ Hz), 4.80 (1H, d, $J =$

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11.4 Hz), 4.78 (1H, d, J = 10.7 Hz), 4.64 (1H, d, J = 12.1 Hz), 4.53 (1H, d, J = 12.1 Hz), 4.44 (1H, d, J = 10.7 Hz), 3.97−3.89 (2H, m), 3.74−3.63 (5H, m), 3.56 (1H, dd, J = 9.2, 9.0 Hz), 2.00 (1H, br s), 1.87−1.81 (2H, m), 1.71−1.67 (2H, m), 0.92 (9H, s), 0.95 (3H, s), 0.88 (3H, s); ^{13}C NMR δ 138.8 (C), 138.1 (C), 137.8 (C), 128.3−127.3 (15 × CH), 83.1 (CH), 78.4 (CH), 77.1 (CH), 75.3 (CH_2), 75.0 (CH_2), 73.5 (CH_2), 73.2 (CH), 71.1 (CH), 69.2 (CH_2), 62.3 (CH_2), 29.4 (CH_2), 25.8 (3 × CH_3), 20.1 (CH_2), 17.9 (C), −4.6 (CH_3), −4.7 (CH_3); MS m/z (rel intensity) 606 (M^+, <1), 549 (9), 515 (9), 441 (82), 409 (58), 351 (67), 259 (65), 243 (100); HRMS calcd for $C_{36}H_{50}O_6Si$ 606.3377, found 606.3375. Anal. Calcd for $C_{36}H_{50}O_6Si$: C, 71.25; H, 8.30. Found: C, 71.26; H, 8.57.

[[(5*R*,7*S*,8*S*,9*S*,10*R*)-8,9-Bis(benzyloxy)-7-[(benzyloxy)-methyl]-1,6-dioxaspiro[4.5]dec-10-yl]oxy](*tert*-butyl)dimethylsilane (4) and [[(5*S*,7*S*,8*S*,9*S*,10*R*)-8,9-Bis(benzyl-oxy)-7-[(benzyloxy)methyl]-1,6-dioxaspiro[4.5]dec-10-yl]oxy](*tert*-butyl)-dimethylsilane (5). A solution of **3** (542 mg, 0.89 mmol) in dry cyclohexane (114 mL) containing (diacetoxyiodo)benzene (DIB) (699 mg, 2.17 mmol) and iodine (272 mg, 1.07 mmol) was stirred under nitrogen at 20 °C for 5 h. The reaction mixture was then poured into a 10% aqueous sodium thiosulfate solution, extracted with CH_2Cl_2, dried (Na_2SO_4), and concentrated in a vacuum. Chromatotron chromatography of the residue (hexanes−EtOAc, 95:5) yielded **4** (112 mg, 0.185 mmol, 21%) and **5** (221 mg, 0.366 mmol, 41%). Compound **4**: $[\alpha]_D$ = +22 (c = 0.33); IR 3032, 2955, 2929, 2857, 1945, 1869, 1805, 1726, 1549, 1496, 1454, 1361, 1252 cm^{-1}; ^{1}H NMR δ 7.39−7.22 (13H, m), 7.05−7.04 (2H, m), 4.99 (1H, d, J = 12.0 Hz), 4.87 (1H, d, J = 12.0 Hz), 4.73 (1H, d, J = 10.8 Hz), 4.66 (1H, d, J = 12.2 Hz), 4.54 (2H, d, J = 12.2 Hz), 4.52 (2H, d, J = 10.8 Hz), 4.01−3.94 (2H, m), 3.88−3.84 (2H, m), 3.77−3.64 (4H, m), 2.19 (1H, ddd, J = 12.1, 9.3, 9.3 Hz), 2.11−2.03 (1H, m), 1.93−1.86 (2H, m), 0.93 (9H, s), 0.12 (3H, s), 0.03 (3H, s); ^{13}C NMR δ 139.2 (C), 138.2 (C), 138.1 (C), 128.3−126.6 (15 × CH), 107.9 (C), 83.5 (CH), 79.1 (CH), 74.8 (CH_2), 74.5 (CH_2), 73.5 (CH), 73.4 (CH_2), 71.0 (CH), 68.8 (CH_2), 68.3 (CH_2), 33.4 (CH_2), 26.0 (3 × CH_3), 23.8 (CH_2), 18.1 (C), −3.5 (CH_3), −4.5 (CH_3); MS m/z (rel intensity) 604 (M^+, 8), 547 (18), 513 (22), 440 (36), 439 (100), 397 (48), 331 (20), 277 (73); HRMS calcd for $C_{36}H_{48}O_6Si$ 604.3220, found 604.3234. Anal. Calcd for $C_{36}H_{48}O_6Si$: C, 71.49; H, 8.00. Found: C, 71.18; H, 8.24. Compound **5**: $[\alpha]_D$ = 0 (c = 0.32); IR 3032, 2955, 2929, 2857, 1945, 1869, 1805, 1726, 1454, 1361, 1252 cm^{-1}; ^{1}H NMR δ 7.36−7.22 (13H, m), 7.06−7.04 (2H, m), 4.90 (1H, d, J = 11.5 Hz), 4.85 (2H, d, J = 11.5 Hz), 4.73 (1H, d, J = 10.6 Hz), 4.61 (1H, d, J = 12.1 Hz), 4.54 (1H, d, J = 12.1 Hz), 4.48 (1H, d, J = 10.6 Hz), 4.04 (1H, ddd, J = 13.8, 7.7, <1 Hz), 3.89 (1H, ddd, J = 13.6, 7.1, <1 Hz), 3.74 (1H, d, J = 9.7 Hz), 3.72−3.66 (2H, m), 3.57 (1H, dd, J = 9.4, 9.4 Hz), 3.47 (1H, ddd, J = 9.9, 4.6, 2.2 Hz), 3.41 (1H, dd, J = 9.4, 9.4 Hz), 2.15−2.10 (1H, m), 2.04−2.00 (1H, m), 1.97−1.91 (1H, m), 0.89 (9H, s), 0.11 (3H, s), 0.05 (3H, s); ^{13}C NMR δ 138.8 (C), 138.2 (C), 137.9 (C), 128.2−126.9 (15 × CH), 109.7 (C), 85.1 (CH), 78.6 (CH), 75.2 (CH_2), 74.9 (CH_2), 74.2 (CH), 73.7 (CH), 73.4 (CH_2), 69.5 (CH_2), 67.8 (CH_2), 26.5 (CH_2), 25.9 (3 × CH_3), 24.4 (CH_2), 18.0 (C), −4.5 (2 × CH_3); MS m/z (rel intensity) 604 (M^+, 2), 547 (6), 513 (6), 455 (6), 440 (32), 439 (100), 331 (24), 277 (66); HRMS calcd for $C_{36}H_{48}O_6Si$ 604.3220, found 604.3224. Anal. Calcd for $C_{36}H_{48}O_6Si$: C, 71.49; H, 8.00. Found: C, 71.37; H, 8.10.

(5*S*,7*S*,8*S*,9*S*,10*R*)-8,9-Bis(benzyloxy)-7-[(benzyloxy)methyl]-1,6-dioxaspiro[4.5]decan-10-ol (6). To a deoxygenated solution of compound **4** (32 mg, 0.053 mmol) in dry THF (2 mL) was added tetrabutylammonium fluoride (185 μL, 185 mmol, 1 M in THF), and the mixture was stirred at room temperature overnight. The solvent was removed under reduced pressure, and the residue was dissolved in $CHCl_3$, washed with aqueous saturated $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated. Chromatotron chromatography (hexanes−EtOAc, 70:30) gave the alcohol **6** (22.1 mg, 0.045 mmol, 85%): mp 75−76 °C (from n-pentane−ethyl ether); $[\alpha]_D$ = +72 (c = 0.91); IR 3568, 3066, 3032, 2889, 1945, 1869, 1805, 1726, 1496, 1454, 1361 cm^{-1}; ^{1}H NMR δ 7.38−7.27 (13H, m), 7.20−7.18 (2H, m), 4.91 (1H, d, J = 11.2 Hz), 4.87 (1H, d, J = 11.2 Hz), 4.83 (1H, d, J = 11.0 Hz), 4.63 (1H, d, J = 12.2 Hz), 4.55 (1H, d, J = 11.0 Hz), 4.52 (1H, d, J = 12.2 Hz), 4.00−3.94 (2H, m), 3.82 (1H, ddd, J = 9.9, 3.8, 1.8 Hz), 3.76−3.71 (2H, m), 3.68−3.63 (3H, m), 2.23 (1H, ddd, J = 12.3, 9.6, 7.6 Hz), 2.08−2.01 (1H, m), 2.00−1.95 (1H, m), 1.92−1.86 (1H, m); ^{13}C NMR δ 138.8 (C), 138.4 (C), 138.2 (C), 128.5−127.4 (15 × CH), 107.5 (C), 84.8 (CH), 77.9 (CH), 75.3 (CH_2), 74.7 (CH_2), 73.6 (CH), 73.4 (CH_2), 71.5 (CH), 68.8 (CH_2), 68.7 (CH_2), 33.6 (CH_2), 24.0 (CH_2); MS m/z (rel intensity) 490 (M^+, 52), 399 (100), 293 (24), 275 (40), 253 (36), 240 (86), 203 (90), 181 (84); HRMS calcd for $C_{30}H_{34}O_6$ 490.2355, found 490.2367. Anal. Calcd for $C_{30}H_{34}O_6$: C, 73.45; H, 6.99. Found: C, 73.34; H, 7.01.

(5*S*,7*S*,8*S*,9*S*,10*R*)-8,9-Bis(benzyloxy)-7-[(benzyloxy)methyl]-1,6-dioxaspiro[4.5]dec-10-yl Methanesulfonate (7). A solution of the alcohol **6** (9.7 mg, 0.020 mmol) in dry pyridine (0.5 mL) was treated at room temperature for 5 h with methanesulfonyl chloride (20 μL, 0.24 mmol). Then the mixture was poured over an aqueous solution of HCl (10%) and extracted with CH_2Cl_2. The combined extracts were washed with saturated aqueous $NaHCO_3$ and brine, dried, filtered, and evaporated under pressure. Chromatotron chromatography (hexanes−EtOAc, 85:15) of the residue gave compound **7** (8.6 mg, 0.015 mmol, 76%): mp 95−96 °C (from n-pentane−ethyl ether); $[\alpha]_D$ +8.8 (c = 0.26); IR 3066, 3032, 2926, 2854, 1945, 1870, 1806, 1726, 1456, 1365 cm^{-1}; ^{1}H NMR δ 7.37−7.25 (13H, m), 7.13−7.12 (2H, m), 5.03 (1H, d, J = 11.4 Hz), 4.76 (1H, d, J = 10.8 Hz), 4.74 (1H, d, J = 11.4 Hz), 4.65 (1H, d, J = 12.2 Hz), 4.62 (1H, d, J = 10.0 Hz), 4.59 (1H, d, J = 10.8 Hz), 4.53 (1H, d, J = 12.2 Hz), 4.06 (1H, dd, J = 9.2, 9.2 Hz), 4.01 (1H, ddd, J = 7.2, 7.2, 7.2 Hz), 3.95 (1H, ddd, J = 7.4, 7.4, 7.4 Hz), 3.88 (1H, ddd, J = 9.8, 1.2, <1 Hz), 3.81 (1H, dd, J = 9.2, 9.2 Hz), 3.77 (1H, dd, J = 10.9, 3.1 Hz), 3.66 (1H, dd, J = 10.9, <1 Hz), 2.82 (3H, s), 2.35−2.30 (1H, m), 2.07−2.01 (2H, m), 1.99−1.95 (1H, m); ^{13}C NMR (50.3 MHz) δ 138.0 (C), 137.9 (C), 137.8 (C), 128.5−127.1 (15 × CH), 106.2 (C), 81.0 (CH), 80.4 (CH), 79.1 (CH), 75.2 (CH_2), 74.8 (CH_2), 73.5 (CH_2), 71.4 (CH), 68.9 (CH_2), 68.3 (CH_2), 38.6 (CH_3), 33.9 (CH_2), 24.0 (CH_2); MS m/z (rel intensity) 477 ($M^+ - C_7H_7$, 32), 472 (19), 275 (9), 273 (13), 256 (100), 245 (6), 216 (9), 203 (56); HRMS calcd for $C_{24}H_{29}O_8S$ 477.1583, found 477.1578. Anal. Calcd for $C_{31}H_{36}O_8S$: C, 65.47; H, 6.38; S, 5.64. Found: C, 65.46; H, 6.57; S, 5.32.

(5*R*,7*S*,8*S*,9*S*,10*R*)-8,9-Bis(benzyloxy)-7-[(benzyloxy)methyl]-1,6-dioxaspiro[4.5]decan-10-ol (8). As described for the preparation of **6**. Compound **5** (181 mg, 0.30 mmol) gave after Chromatotron chromatography (hexanes−EtOAc, 75:25) the alcohol **8** (139 mg, 0.28 mmol, 95%): $[\alpha]_D$ = +21 (c = 0.67); IR 3603, 3474, 3089, 3066, 3032, 2894, 1945, 1870, 1806, 1726, 1497, 1454, 1360 cm^{-1}; ^{1}H NMR δ 7.41−7.27 (13H, m), 7.19−7.17 (2H, m), 4.93 (1H, d, J = 11.3 Hz), 4.88 (1H, d, J = 11.3 Hz), 4.84 (1H, d, J = 10.7 Hz), 4.64 (1H, d, J = 12.1 Hz), 4.55 (1H, d, J = 12.1 Hz), 4.54 (1H, d, J = 10.7 Hz), 4.09 (1H, dd, J = 7.3, 7.3 Hz), 3.98 (1H, dd, J = 7.4, 7.4 Hz), 3.79 (1H, d, J = 9.7 Hz), 3.75−3.70 (2H, m), 3.64 (1H, dd, J = 9.3, 9.3 Hz), 3.55 (1H, dd, J = 9.3, 9.3 Hz), 3.53−3.50 (1H, m), 2.47 (1H, br s), 2.18−2.11 (1H, m), 2.09−2.03 (1H, m), 2.00−1.92 (2H, m); ^{13}C NMR (50.3 MHz) δ 138.6 (C), 138.2 (C), 138.0 (C), 128.6−127.6 (15 × CH), 109.3 (C), 83.9 (CH), 78.0 (CH), 75.1 (CH_2), 75.0 (CH_2), 74.1 (2 × CH), 73.4 (CH_2), 69.4 (CH_2), 68.6 (CH_2), 27.0 (CH_2), 25.0 (CH_2); MS m/z (rel intensity) 490 (M^+, 66), 399 (64), 275 (27), 253 (41), 240 (92), 219 (71), 203 (79), 181 (100); HRMS calcd for $C_{30}H_{34}O_6$ 490.2355, found 490.2350. Anal. Calcd for $C_{30}H_{34}O_6$: C, 73.45; H, 6.99. Found: C, 73.39; H, 7.16.

(5*R*,7*S*,8*S*,9*S*,10*R*)-8,9-Bis(benzyloxy)-7-[(benzyloxy)methyl]-1,6-dioxaspiro[4.5]dec-10-yl Methanesulfonate (9). As described for the preparation of **7**. Alcohol **8** (52 mg, 0.11 mmol) gave compound **9** (48 mg, 0.084 mmol, 80%): mp 90−91 °C (from n-pentane−ethyl ether); $[\alpha]_D$ = 0 (c = 0.34); IR 3066, 3032, 2893, 1945, 1870, 1806, 1729, 1497, 1454, 1375, 1181 cm^{-1}; ^{1}H NMR δ 7.43−7.27 (13H, m), 7.14−7.13 (2H, m), 4.95 (1H, d, J = 10.5 Hz), 4.80 (1H, d, J = 10.5 Hz), 4.81 (1H, d, J = 10.7 Hz), 4.70 (1H, d, J = 9.8 Hz), 4.61 (1H, d, J = 12.1 Hz), 4.52 (1H, d, J = 12.1 Hz), 4.51 (1H, d, J = 10.7 Hz), 4.14−4.08 (1H, m), 3.98−3.94 (1H, m), 3.73 (1H, dd, J = 9.4, 9.4 Hz), 3.69 (2H, m), 3.67 (1H, dd, J = 9.3, 9.3 Hz), 3.49 (1H, ddd, J = 9.6, 3.2, 3.2 Hz), 3.03 (3H, s), 2.13−2.07 (3H, m), 2.04−1.99 (1H, m); ^{13}C NMR (50.3 MHz) δ 138.0 (C), 137.7 (C), 137.5 (C), 128.4−127.6 (15 × CH), 107.5 (C), 82.1 (CH), 81.4 (CH), 78.2 (CH), 75.7 (CH_2), 75.2 (CH_2), 74.0 (CH), 73.4 (CH_2), 68.8 (CH_2), 68.5 (CH_2), 38.9 (CH_3), 28.1 (CH_2), 24.6 (CH_2); MS m/z (rel intensity) 477 ($M^+ - C_7H_7$, 20), 472 (74), 381 (16), 371 (6), 364 (8), 322 (8), 273 (41), 256 (22), 244 (31), 216 (27), 203 (100); HRMS calcd for $C_{24}H_{29}O_8S$

477.1583, found 477.1489. Anal. Calcd for $C_{31}H_{36}O_8S$: C, 65.47; H, 6.38; S, 5.64. Found: C, 65.55; H, 6.56; S, 5.34.

Reduction of (5*R*,7*S*,8*S*,9*S*,10*R*)-8,9-Bis(benzyloxy)-7-[(benzyloxy)methyl]-1,6-dioxaspiro[4.5]dec-10-yl Methanesulfonate (9). To a stirred solution of the β-mesyl derivative **9** (51.4 mg, 0.09 mmol) in dry CH_2Cl_2 (3 mL) at 42 °C under nitrogen was added DIBALH in toluene (1 mL, 1 mmol). The solution was stirred for 76 h, and the reaction was quenched by careful addition of saturated aqueous NH_4Cl. The mixture was filtered through filter paper, and the residue was washed with CH_2Cl_2. The combined filtrates were washed with brine, dried, and concentrated. The residue was purified by chromatotron chromatography (benzene−EtOAc, 95:5) to give 1-(3′,4′,6′-tri-*O*-benzyl)-α-D-glucopyranosyl)-2-propane (**11**) (7.0 mg, 0.016 mmol, 18%) and (2*R*,3*R*,4*R*,4a*R*,8a*S*)-3-(benzyloxy)-2-(phenoxymethyl)-octahydropyrano[3,2-*b*]pyran-4-ol (**10**) (18.7 mg, 0.049 mmol, 54%). Compound **11**: $[\alpha]_D = +9.2$ ($c = 0.52$); IR 3482, 3066, 3030, 2869, 1945, 1869, 1805, 1723, 1454, 1270, 1094 cm^{-1}; ^1H NMR δ 7.33−7.26 (15H, m), 4.57−4.47 (6H, m), 4.27 (1H, ddd, J = 3.2, 6.0, 6.0 Hz), 4.07 (1H, dd, J = 3.0, 3.0 Hz), 4.03 (1H, dd, J = 2.6, 4.4 Hz), 3.88 (1H, dd, J = 4.86, 4.86 Hz), 3.62 (1H, ddd, J = 5.1, 8.7, 8.7 Hz), 3.60−3.54 (2H, m), 2.38 (1H, d, J = 5.4 Hz), 1.57−1.47 (2H, m), 1.41−1.36 (2H, m), 0.91 (3H, dd, J = 7.1, 7.1 Hz); ^{13}C NMR δ 138.0 (C), 137.6 (C), 137.5 (C), 128.4−127.6 (15 × CH), 85.7 (CH), 84.8 (CH), 84.6 (CH), 82.0 (CH), 73.3 (CH_2), 71.8 (CH_2), 71.7 (CH_2), 70.9 (CH), 69.8 (CH_2), 35.7 (CH_2), 18.8 (CH_2), 14.0 (CH_3); MS *m*/*z* (rel intensity) 385 ($M^+ - C_7H_7$, <1), 384 (14), 383 (62), 296 (35), 277 (35), 261 (12); HRMS calcd for $C_{23}H_{29}O_5$ 385.2015, found 385.2026. Anal. Calcd for $C_{30}H_{36}O_5$: C, 75.60; H, 7.61. Found: C, 75.69; H, 7.68. Compound **10**: $[\alpha]_D = -4.9$ ($c = 0.69$); IR 3566, 2924, 2854, 1945, 1870, 1806, 1729, 1454, 1114 cm^{-1}; ^1H NMR δ 7.36−7.22 (10H, m), 4.86 (1H, d, J = 11.1 Hz), 4.65 (1H, d, J = 12.2 Hz), 4.59 (1H, d, J = 12.2 Hz), 4.57 (1H, d, J = 11.1 Hz), 4.07−4.04 (1H, m), 3.77−3.69 (2H, m), 3.66 (1H, ddd, J = 8.8, 8.8, 3.7 Hz), 3.59−3.58 (1H, m), 3.56 (1H, d, J = 9.2 Hz), 3.46−3.45 (1H, m), 3.43−3.38 (2H, m), 2.55 (1H, d, J = 8.7 Hz), 2.08−1.98 (2H, m), 1.65−1.58 (2H, m), 1.37−1.32 (1H, m); ^{13}C NMR (50.3 MHz) δ 138.5 (C), 128.3−127.5 (10 × CH), 78.8 (CH), 76.7 (CH), 76.6 (CH), 75.3 (CH), 74.9 (CH_2), 73.4 (CH_2), 71.1 (CH), 69.6 (CH_2), 68.3 (CH_2), 28.1 (CH_2), 21.0 (CH_2); MS *m*/*z* (rel intensity) 384 (M^+, <1), 294 (18), 293 (100), 187 (18), 169 (36), 151 (14), 139 (31); HRMS calcd for $C_{23}H_{28}O_5$ 384.1937, found 384.1924. Anal. Calcd for $C_{23}H_{28}O_5$: C, 71.85; H, 7.34. Found: C, 71.70; H, 7.61.

(2*R*,3*R*,4*R*,4a*R*,8a*S*)-3-(Benzyloxy)-2-(phenoxymethyl)-octahydropyrano[3,2-*b*]pyran-4-yl 4-Nitrobenzoate (12). To a stirred solution of compound **10** (5.2 mg, 0.013 mmol) in CH_2Cl_2 (0.1 mL) and pyridine (4 μL) was added *p*-nitrobenzoyl chloride (6 mg, 0.032 mmol). The solution was stirred at room temperature for 4 h, and then the mixture was poured over an aqueous solution of HCl (10%) and extracted with CH_2Cl_2. The combined extracts were washed with saturated aqueous $NaHCO_3$ and brine, dried, and evaporated under reduced pressure to give compound **12** (6.5 mg, 0.012 mmol, 90%): mp 97−99 °C (from *n*-pentane−ethyl ether); $[\alpha]_D = -27.5$ ($c = 0.24$); IR 2926, 2854, 1945, 1870, 1806, 1728, 1606, 1532, 1455, 1347, 1275, 1114 cm^{-1}; ^1H NMR δ 8.30−8.14 (4H, m), 7.39−7.02 (10H, m), 5.14 (1H, dd, J = 3.5, 9.8 Hz), 4.72 (1H, d, J = 12.2 Hz), 4.60 (1H, d, J = 12.2 Hz), 4.59 (1H, d, J = 11.3 Hz), 4.57 (1H, d, J = 11.3 Hz), 4.12 (1H, dd, J = 9.8, 9.8 Hz), 4.01 (1H, ddd, J = <1, 4.0, 11.2 Hz), 3.89 (1H, d, J = 3.4 Hz), 3.82 (1H, dd, J = 4.7, 11.1 Hz), 3.76 (1H, dd, J = 1.4, 11.2 Hz), 3.59 (1H, br s), 3.56 (1H, ddd, J = 1.4, 4.7, 9.7 Hz), 23.36 (1H, dd, J = 11.6, 11.6 Hz), 2.09−2.05 (2H, m), 1.65−1.60 (1H, m), 1.34−1.32 (1H, m); ^{13}C NMR δ 164.2 (C), 150.5 (C), 138.3 (C), 137.8 (C), 135.3 (C), 130.9−123.4 (CH), 79.4 (CH), 78.2 (CH), 75.0 (CH_2), 74.6 (CH), 73.4 (CH_2), 73.3 (CH), 70.9 (CH), 69.1 (CH_2), 68.1 (CH_2), 28.0 (CH_2), 20.6 (CH_2); MS *m*/*z* (rel intensity) 442 ($M^+ - C_7H_7$, 13), 336 (9), 169 (31), 150 (23), 139 (8), 120 (12), 105 (8), 91 (100); HRMS calcd for $C_{23}H_{24}NO_8$ 442.1101, found 442.1428.

Acknowledgment. This work was supported by the Investigation Program No. PB96-1461 of the Dirección General de Investigación Científica y Técnica, Spain.

Supporting Information Available: X-ray data for compound **12**, including tables of atomic coordinates, bond lengths, and bond angles. This material is available free of charge via the Internet at http://pubs.acs.org.

JO005593A