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An Efficient Synthetic Route to Chiral β-Hydroxy-δ-Lactone Moiety of Compactin

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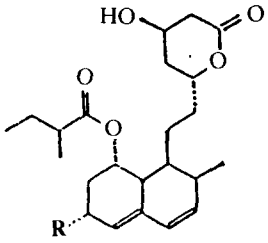
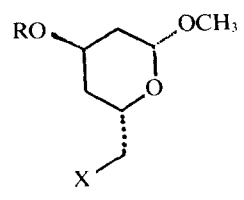
Abstract □ A new synthetic sequence for the chiral lactone moiety of compactin was developed from α-D-glucose in 9 steps *via* simultaneous reductive detosylation and epoxide-ring opening of 2,3-epoxy-4-tosylate using $NaBH_4$ to afford 2,4-dideoxy sugar as a key intermediate.

Keywords □ compactin, HMG-CoA reductase, methyl α-D-glucopyranoside, methyl 2,4-dideoxy-6-*O*-trityl-α-D-*erythro*-hexopyranoside, methyl 3-*O*-benzyl-6-iodo-2,4,6-trideoxy-α-D-*erythro*-hexopyranoside.

After discoveries of compactin (**1a**)[1] and mevinolin (**1b**)[2], potent inhibitors of cholesterol biosynthesis at the level of the major rate-limiting enzyme 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, structure-activity relationship (SAR) studies on this system revealed that the chiral β-hydroxy-δ-lactone moiety **2** is essential for strong biological activity.[3] In the present paper, we describe an efficient and short-cut route to **2** from methyl α-D-glucopyranoside.



1a Compactin (R=H)
1b Mevinolin (R=CH_3)



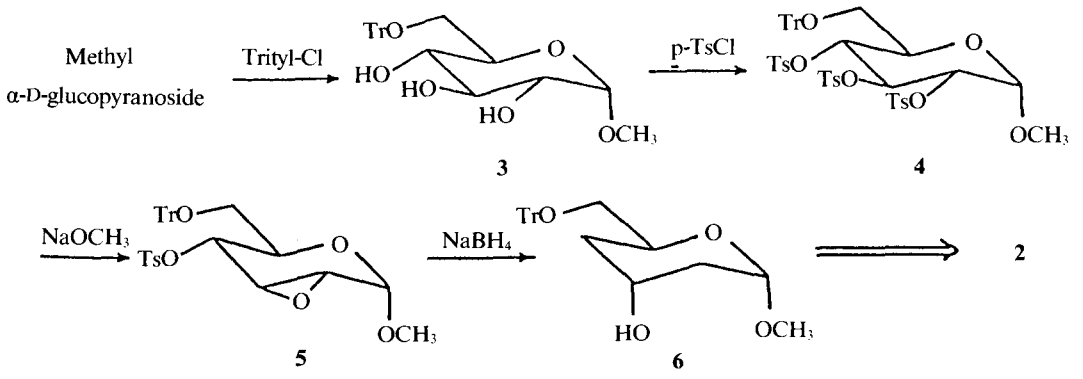
2 R=protecting group (a R=benzyl)
X=leaving group (a X=I)

EXPERIMENTAL

Melting points were determined on Yanaco micro melting point apparatus and are uncorrected. Infrared (IR) spectra were obtained on a Perkin Elmer 1310 spectrophotometer in KBr, except where noted. Nuclear magnetic resonance (NMR) spectra were obtained on a Bruker AM-300 (300 MHz for ^{1}H-NMR and 75.5 MHz for ^{13}C-NMR) spectrometer and chemical shift are reported in parts per million (ppm) downfield from tetramethylsilane (TMS) as an internal standard. Mass spectra were obtained by direct sample introduction into a Hewlett-Packard 5933 A GC-mass spectrometer and are reported herein as *m/e* (relative intensity). Dry pyridine was obtained by distilling over CaH_2 and all other solvents were reagent grade and used directly without further purification.

Methyl 2, 3, 4-O-tritosyl-6-O-trityl-α-D-ribo-hexopyranoside (4)

To a 250 m*l* dry pyridine containing 39.3 g (0.09 mol) of methyl 6-*O*-trityl-α-D-*ribo*-hexopyranoside[4] was added 102.9 g (0.54 mol) of p-TsCl and resulting solution was allowed to be stirred for 24 h. The reaction mixture was diluted with 300 m*l* of water and extracted with ether (100 m*l*×4). The combined organic layers were washed with sat. $NaHCO_3$ solution and dried over $MgSO_4$. Removal of the solvent gave cyrstalline solid, which was recrystallized from *n*-hexane : $CHCl_3$ (3:1) to give the product: mp. 229-230℃; IR (KBr) ν 3180, 2920, 1588, 1440, 1340, 1170, 1035, 960, 905, 810, 690 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 2.39 (s, 3H), 2.41 (s, 3H), 2.44 (s, 3H), 3.26 (dd, J=10.5, 2.0 Hz, 1H), 3.48 (dd, J=10.5, 2.0 Hz,



1H), 3.94 (t, J=8.5 Hz, 1H), 4.27 (dd, J=9.8, 3.6 Hz, 1H), 4.37 (dd, J=10.0, 9.0 Hz, 1H), 4.86 (d, J=3.6 Hz, 1H), 5.05 (dd, J=10.4, 9.2 Hz, 1H), 7.14-7.80 (m, 27 H).

Methyl 2, 3-anhydro-4-O-tosyl-6-trityl-α-D-allopyranoside (5)

To a 150 m*l* of freshly distilled $CHCl_3$ was dissolved 17.96 g (0.02 mol) of methyl 2,3,4-*O*-tritosyl-6-*O*-trityl-α-D-*ribo*-hexopyranoside (**4**) and the resulting solution was cooled to 0℃. Sodium methoxide (newly prepared from 2.53 g of Na and 40 m*l* of dry methanol) was added by dropwise and the reaction mixture was allowed to be stirred for 24 h, followed by 48 h's standing in the refrigerator. The reaction mixture was poured into 100 m*l* of water and extracted with $CHCl_3$ (200 m*l*×3). The combined organic layers were dried over $MgSO_4$ and removal of solvent afforded crystalline solid, which was recrystallized from *n*-hexane : $CHCl_3$ (3:1) to give 7.62 g (67%) of white crystals: mp. 185-187℃; IR (KBr) ν 3200, 3010, 2995, 1585, 1435, 1363, 1170, 1072, 980, 810, 760, 695 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 2.39 (s, 3H, CH_3), 2.93 (dd, J_{gem}=10.4 Hz, $J_{6A,5a}$=6.6 Hz, 1H, H_{6A}), 3.20 (dd, J_{gem}=10.4 Hz, $J_{6B,5a}$=1.6 Hz, H_{6B}), 3.50 (s, 3H, OCH_3), 3.53 (d, $J_{2a,1e}$=2.8 Hz, H_{2a}), 3.55 (dd, $J_{4a,5a}$=9.7 Hz, $J_{4a,3e}$=1.5 Hz, H_{4a}), 4.01 (m, 1H, H_{5a}), 4.73 (dd, $J_{3e,2}$=4.1 Hz. $J_{4a,3e}$=1.5 Hz, H_{3e}), 4.90 (d, J=2.8 Hz, H_{1e}), 7.14 (d, J=8.3 Hz, 2H), 7.54 (d, J=8.3 Hz, 2H), 7.20-7.37 (m, 15H, trityl H).

Methyl 2, 4-dideoxy-6-O-trityl-α-D-erythro-hexopyranoside (6)

Under N_2 atmosphere, 3.43 g (0.006 mol) of methyl 2,3-anhydro-4-*O*-tosyl-6-*O*-trityl-α-D-allopyranoside was dissolved in 30 m*l* of freshly distilled DMSO. To the resulting solution was added 1.37 g (0.036 mol) of $NaBH_4$ and the reaction mixture was heated at 80℃ for 5 days. After cooling to room temperature, the mixture was diluted with 160 m*l* of ether and 150 m*l* of water and extracted with ether (100 m*l*×2). The combined organic layers were dried over $MgSO_4$ and work-up as usual afforded oily material, which was chromatographed on silica gel eluting with CH_2Cl_2. From the early eluent 1.0 g (41%) of oil as a product. IR (thin film) ν 3180, 2920, 1480, 1435, 1258, 1170, 1132, 985, 895, 735 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 1.53 (dt, $J_{2a,2e}$=13.5 Hz, $J_{2a,1}$=$J_{2a,3e}$=2.7 Hz, H_{2a}), 1.75 (d, $J_{2a,2e}$=13.5 Hz, H_{2e}), 1.81 (dt, $J_{4a,4e}$=14.4 Hz, $J_{4a,5a}$=$J_{4a,3e}$=3.4 Hz, H_{4a}), 1.93 (d, $J_{4a,4e}$=14.4 Hz, H_{4e}), 3.05 (AB quartet, J=9.6, 4.1 Hz, H_{6A}), 3.24 (AB quartet, J=9.6 Hz, J=6.5 Hz, H_{6B}), 3.45 (s, 3H, OCH_3), 3.62 (d, J=9.7 Hz, OH), 4.05 (m, 1H, H_{3e}), 4.20 (m, 1H, H_{5a}), 4.30 (d, J=2.8 Hz, H_1), 7.19-7.49 (m, 15H, trityl H); ^{13}C-NMR ($CDCl_3$, 75.5 MHz) δ 144.1, 128.7, 127.7, 126.9, 99.1, 86.4, 67.0, 63.0, 35.0, 34.9; mass spectrum, *m/e* (rel. intensity) 405 (2.6, M+1), 404 (1.2, M), 373 (22.4), 326 (24.5), 259 (37.3), 258 (64.6), 245 (25.5), 244 (78.7), 243 (100), 242 (45.4), 241 (46.6), 240 (16.9), 239 (27.3), 215 (18.3), 167 (40.0), 166 (50.0), 165 (90.0), 161 (68.0), 154 (28.3), 131 (42.0), 128 (58.0), 113 (82.0), 84 (70.5), 59 (70.5), 43 (85.5).

Methyl 3-O-benzyl-2,4-dideoxy-α-D-erythro-hexopyranoside (7)

Under N_2 atmosphere, a suspension of 4.04 g (0.01 mol) of methyl 2,4-dideoxy-6-*O*-trityl-α-D-*erythro*-hexopyranoside and 0.96 g (0.04 mol) of NaH in 10 m*l* of DMF was added 0.95 g (0.02 mol) of benzyl chloride and resulting mixture was heated for 4 h at 160℃. The reaction mixture was cooled

to room temperature and poured into 200 ml of ice water to afford white crystal which showed no OH band in the IR. This material was dissolved in 25 ml of CH_2Cl_2 and treated with 1.06 ml of 70% trifluoroacetic acid for 5 min with vigorous stirring. To the reaction mixture was added 2.3 ml of sat. $NaHCO_3$ and stirred for 20 min. The organic layer was dried over $MgSO_4$ and work-up as usual gave a gummy material, which was purified by flash chromatography[5] eluting with acetone : CH_2Cl_2 (3:17) to give 2.08 g (83%) of gum as a product. IR (thin film) ν 3400, 2910, 1630, 1430, 1190, 1120, 1090, 1040, 730, 690 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 1.61 (ddd, $J_{4a,4e}$=15.1 Hz, $J_{4a,5a}$=11.1 Hz, $J_{4a,3e}$=3.3 Hz, H_{4a}), 1.72-1.81 (m, H_{2a} & H_{4e}), 1.87 (br. s, OH), 2.07 (dm, J=14.8 Hz, H_{2e}), 3.40 (s, OCH_3), 3.51 (dd, J=8.4, 6.0 Hz, H_{6A}), 3.64 (dm, J=6.0 Hz, H_{6B}), 3.79 (quintet, J=3.4 Hz, H_{3e}), 4.21 (m, H_5), 4.49 (AB quartet, benzylic H), 4.64 (AB quartet, benzylic H), 4.79 (d, J=4.3 Hz, H_1), 7.32 (m, 5H); ^{13}C-NMR ($CDCl_3$, 75.5 MHz) δ 138.8, 128.2, 127.4, 127.3, 98.2, 69.6, 69.0, 65.9, 64.4, 55.1, 32.3, 30.9; mass spectrum, *m/e* (rel. intensity) 252 (0.1, M+1), 251 (0.4, M), 221 (3.4, M-31), 157 (9.3), 114 (37.2), 91 (100), 87 (40.0).

Methyl 3-O-benzyl-6-O-tosyl-2,4-dideoxy-α-D-erythro-hexopyranoside (8)

The solution of 5.0 g (0.02 mol) of methyl 3-*O*-benzyl-2,4-dideoxy-α-D-*erythro*-hexopyranoside in 50 ml of dry pyridine was cooled to 0℃ and added 7.56 g (0.04 mol) of p-TsCl. The reaction solution was stirred for 8 h and was slowly added 10 ml of water. The resulting mixture was extracted with ether (100 ml×2) and evaporation of solvent gave 6.5 g of sticky material, which was purified by flash chromatography eluting with acetone : CH_2Cl_2 (1:19) to afford 6.20 g (78%) of product as a gum: IR (thin film) ν 3040, 2970, 1590, 1430, 1350, 1095, 1035, 950, 820, 730 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 1.55 (ddd, $J_{4a,4e}$=14.8 Hz, $J_{4a,5a}$=12.0 Hz, $J_{4a,3e}$=3.0 Hz, H_{4a}), 1.66-1.74 (m, H_{2a} & H_{4e}), 2.03 (dt, J=14.8 Hz, J=1.2 Hz, H_{2e}), 2.42 (s, CH_3), 3.31 (s, OCH_3), 3.76 (quintet, J=3.3 Hz, H_{3e}), 4.02 (d, J=6.7 Hz, H_{6A}), 4.30 (m, H_{5a}), 4.44 (AB quartet, benzylic H), 4.60 (AB quartet, benzylic H), 4.70 (d, J=4.2 Hz, H_1), 7.23-7.32 (m, 7H), 7.78 (d, J=8.2 Hz, 2H); ^{13}C-NMR ($CDCl_3$, 75.5 MHz) δ 144.6, 138.6, 133.1, 129.7, 128.2, 127.9, 127.5, 127.4, 98.1, 72.3, 69.9, 68.7, 61.9, 55.2, 32.0, 31.0, 21; mass spectrum, *m/e* (rel. intensity) 407 (0.1, M+1), 406 (0.77, M), 375 (5.8), 155 (20.8), 127 (30.0), 117 (45.0), 107 (40.0), 95 (76.6), 91 (100), 79 (45.2), 69 (70.5).

Methyl 3-O-benzyl-6-iodo-2,4,6-trideoxy-α-D-erythro-hexopyranoside (2)

To a light protected round bottomed flask, 1.5 g (3.67 mmol) of **8** and 6.5 g (43.4 mmol) of NaI was dissolved in 70 ml of acetone. After refluxing 24 h under N_2 gas, solvent was removed under reduced pressure. The residue was poured into ether : water (1:1) mixture and extracted with ether (50 ml×2). The combined organic layers were washed with dilute $NaHSO_4$ and dried over $MgSO_4$. Removal of solvent gave on oily material, which was chromatographed on silica gel eluting with CH_2Cl_2 to afford 1.12 g (85%) of pale yellow oil. IR (thin film) ν 2980, 1440, 1355, 1255, 1170, 1050 (br), 730 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 1.55 (ddd, $J_{4a,4e}$=15.0 Hz, $J_{4a,5a}$=12.0 Hz, $J_{4a,3e}$=3.0 Hz, H_{4a}), 1.76 (dt, $J_{2a,2e}$=15.0 Hz, $J_{2a,1}$=$J_{2a,3e}$=4.5 Hz, H_{2a}), 1.95 (br. d, J=15.0 Hz, H_{4e}), 2.04 (br. d, J=15.0 Hz, H_{2e}), 3.17 (dd, J=10.5, 7.5 Hz, H_{6A}), 3.27 (dd, J=10.5 Hz, J=3.4 Hz, H_{6B}), 3.46 (s, OCH_3), 3.76 (quintet, J=3.3 Hz, H_{3e}), 4.09 (m, H_{5e}), 4.51 (AB, quartet, benzylic, H), 4.64 (AB quartet, benzylic H), 4.82 (d, J=4.5 Hz, H_{1e}), 7.25-7.40 (m, 5H); ^{13}C-NMR ($CDCl_3$, 75.5 MHz) δ 138.6, 128.2, 127.5, 127.4, 98.5, 69.9, 69.2, 63.4, 55.5, 35.5, 32.0, 10.2.

RESULTS AND DISCUSSION

Our synthetic strategy is based on the fact that $NaBH_4$ is a practical and efficient reagent for reduction of tosyl group to alkane[6] as well as epoxide to alcohol[7].

Commercially available methyl α-D-glucopyranoside[8] was selectively *O*-tritylated of primary alcohol moiety (triphenylmethyl chloride, pyridine, r.t., 6 days) followed by treatment of the product with 6 eq. p-TsCl in pyridine to afford **4** in 76% overall yield. Tritosylate was then treated with sodium methoxide to afford epoxy tosylate **5** in 67% yield.

Simultaneous reductive detosylation and epoxide-ring opening of **5** using 6 equivalents $NaBH_4$ in DMSO at 80℃ for 5 days[9] under N_2 was found to afford 2,4-dideoxy derivatives **6** in 41% yield[10]. This appears to be a new method for the preparations of 2,4-dideoxy sugars. The compound **6** can be converted to known chiral synthon **2a**[7] after protection at C_4 (NaH, benzyl bromide, DMF),

detritylation at C_6 (70% aq. trifluoroacetic acid, CH_2Cl_2, r.t., 5 min), and tosylation followed by treatment of the product with NaI.

The sequences, so far reported for the preparation of above lactone from α-D-glucose were required more than 13 steps[9], thus this sequence appears to be the shortest as well as should have general synthetic applicability for the preparation of various deoxy sugars. Attempts to increase the yield of the key step as well as coupling reactions of **2** are in progress which will be reported in the future.

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10. This reaction was proceeded with 78% of isolated yield, where the other portion of product was turned out to be 3,4-dideoxy sugar. Although $LiAlH_4$ reduction of 2,3-epoxy sugar showed high regioselectivity to afford 2-deoxy-3-*axial*-hydroxy sugar only[11], BH_3-$NaBH_4$ reduction of 2,3-epoxy sugar reported to produce 2-deoxy as well as 3-deoxy sugar in a 3: 1 ratio[4].
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