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AN EFFICIENT SYNTHESIS OF (*3R,4R*)-*O*-ISOPROPYLIDENE-1,6-HEXANEDIOL

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ABSTRACT

(*3R,4R*)-*O*-isopropylidene-1,6-Hexanediol **1** has been synthesized from a readily available D-mannitol derivative in few steps.

The growing importance of asymmetric synthesis involving C_2 symmetric molecules as chiral directors provides an impetus for the preparation of such compounds.[1–3] Optically active diols with a C_2 axis of symmetry play a significant role as chiral auxiliaries in the synthesis of biologically active compounds.[4–9] (*3R,4R*)-*O*-Isopropylidene-1,6-Hexanediol **1** is one such important diol, which is useful for the preparation of synthetic receptor molecules for peptides[10] and cyclo-BINOL ligand **2**[11,12] for asymmetric synthesis. While working on a part of our program on design, synthesis, and application of chiral non-racemic diols[13–15] and diamines,[16,17] we realized that, by changing the strategy of protection and deprotection, it is possible to synthesize the diol **1** in an efficient manner from D-mannitol. In this paper, we delineate our efforts in this direction.[18]

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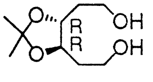

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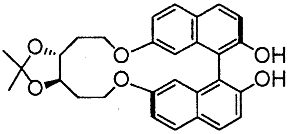

2

The mannitol-3,4-monoacetonide tetraol **3**[19] was selectively protected as benzoate at the primary hydroxyl position using benzoyl chloride in pyridine in 29% yield. The resulting dibenzoate diol **4** was subjected to tosylation using *p*-TsCl in pyridine-Et$_3$N to give the desired ditosyl dibenzoate **5** in quantitative yield.[19] Deoxygenation of tosylates and removal of the benzoate groups were performed in one step using LiAlH$_4$ as reducing agent in THF-ether to give the tethered C_2 symmetric diol **1** in 60% yield.

Although the final diol **1** was synthesized in just three steps, lower yield (29%) in the first step of benzoylation reaction forced us to explore an alternative method for the protection of primary hydroxyl groups. Thus, the primary hydroxyl groups of the tetraol **3** were selectively protected as TBDMS ethers in 94% yield. The secondary hydroxyl groups of TBDMS ether **6** were converted into ditosylates **7**, followed by removal of TBDMS ethers using CAN/MeOH[20] to give **8**. It is worth mentioning here that other reagents such as FeCl$_3$/MeOH or aq HCl/THF failed to give the clean deprotection of

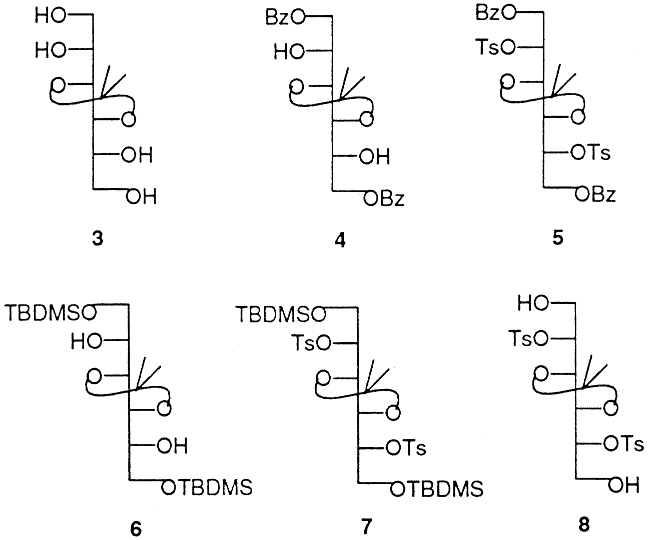

Figure.

TBDMS ethers, and there was always some concomitant cleavage of acetonide group. The LAH reduction of the tosylate **8** gave the final diol **1** in an overall yield of 50%. In conclusion, a simple and short synthetic route for a chiral diol **1** was developed from cheap and commercially available D-mannitol.

GENERAL METHODS

^{1}H NMR spectra were recorded on 60 and 400 MHz spectrometers. Chemical shifts are expressed in ppm downfield from TMS as internal standard, and coupling constants are reported in hertz. Routine monitoring of reactions was performed by TLC using silica gel-G obtained from Acme. All the column chromatographic separations were done by using silica gel (Acme's, 60–120 mesh). *p*-Tosyl chloride was recrystallized before use. Petroleum ether used was of boiling range 60°–80°C. Reactions that needed anhydrous conditions were run under an atmosphere of dry nitrogen or argon using flame-dried glassware. The organic extracts were dried over *anhydrous* sodium sulphate. Evaporation of solvents was performed at reduced pressure. Tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl under nitrogen. Dichloromethane and pyridine were distilled from CaH_2 Room temperature (rt) refers to 25°–30°C.

1,6-Di-*O*-benzoyl-3,4-*O*-isopropylidene-D-mannitol (4)

To a solution of tetraol **3** (2.2 g, 10 mmol) in pyridine (10 mL) was added benzoyl chloride (2.8 g, 20 mmol) at 0°C and stirred for 3 h. The reaction mixture was diluted with CH_2C1_2 (50 mL), washed with water, brine, and dried. Removal of the solvent under reduced pressure gave crude product. Purification over silica gel column afforded the pure product as a crystalline solid (1.2 g, 29%); m.p. 92°–93°C (lit.[19] m.p. 94°C; *Rf* 0.40 (25% EtOAc in petroleum ether); $[\alpha]_D^{25}+13°$ (*c* 3.3, $CHCl_3$) {lit.[19] $[\alpha]_D^{25}+24.1°$ (*c* 1.45, Pyridine)}; IR (KBr) 3450, 1710, 1590, 760 cm^{-1}; ^{1}H NMR (CCl_4, 60 MHz) δ 1.32 (s, 6H), 3.90 (m, 4H), 4.1–4.80 (m 6H), 7.20–7 80 (m, 10H).

1,6-Di-*O*-benzoyl-3,4-*O*-isopropylidene-2,5-Di-*O*-*p*-toluenesulphonyl-D-mannitol (5)

To a solution of Dibenzoate **4** (1 g, 2.4 mmol) in (CH_2Cl_2 (10 mL) was added triethylamine (665 µl, 4.8 mmol) and pyridine (10 mL) at rt. The reaction mixture was cooled to 0°C and solid *p*-tosyl chloride (1.1 g, 6 mmol) was added. The pink solution was stirred for 48 h (0°C to rt). The reaction mixture was diluted with CH_2Cl_2 (50 mL), washed with water, and brine. The organic layer was dried and condensed. The crude product was purified over silica gel column to provide the pure product **5** as a crystalline solid (1.46 g, 91%); m.p. 96°–98°C (lit.[19] m.p. 99°C; R_f 0.80 (25% EtOAc in petroleum ether); $[\alpha]_D^{25}$+25° (*c* 1.0, $CHCl_3$) {lit.[19] $[\alpha]_D^{25}$ +27° (*c* 3.0, $CHCl_3$)}; IR (KBr) 1710, 1580, 840. 760 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.39 (s, 6H), 2.28 (s, 6H), 4.35–4.61 (m, 6H), 5.0 (m, 2H), 7.14 (d, $J = 8.5$ Hz, 4H), 7.40 (t, $J = 6.5$ Hz, 5H), 7.54 (m, 1H), 7.75 (d, $J = 8$ Hz, 4H) 7.95 (d, $J = 8$ Hz, 4H); ^{13}C NMR ($CDCl_3$ 100 MHz) δ 22.2, 28.0, 63.5, 78.0, 79.1, 112, 128.5, 128.9, 130.0, 130.4, 130.5, 133.8, 134.3, 145.6, 166.6; MS (FAB, *m*/*z*): 738 (M^+). Anal. calc. for ($C_{37}H_{38}O_{12}S_2$: C, 60.16; H, 5.14; S, 8.67. Found: C, 59.78; H, 5.28; S, 8.79.

1,6-Di-*O*-*tert*-butyldimethylsilyl-3,4-*O*-isopropylidene-D-mannitol (6)

To a solution of tetraol **3** (2 g, 10 mmol), triethylamine (3.5 mL, 25 mmol), and DMAP (catalytic) in CH_2Cl_2 (50 mL) was added TBDMSCl (3.1 g, 20 mmol) at rt, and the reaction mixture was stirred for 8 h. It was diluted with CH_2Cl_2 (25 mL), washed with water, brine, and dried. Removal of the solvent under reduced pressure gave the crude product, which was purified over silica gel column to provide the pure product **6** as a colorless oil (3.8 g, 94%); R_f 0.50 (10% EtOAc in petroleum ether); $[\alpha]_D^{25}$+21.2° (*c* 1.0, $CHCl_3$); IR (neat) 3450, 1210, 1050 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.03 (s, 12H), 0.82 (s, 18H), 1.29 (s, 6H), 3.35 (bs, 2H, *OH*), 3.56–3.84 (m, 8H); MS (FAB, *m*/*z*): 450 (M^+), 434, 392, 334, 298 (base peak). Anal. calc. for $C_{12}H_{46}O_6Si_2$: C, 56.01; H, 10.22. Found: C, 56.24; H, 9.68.

1,6-Di-*O*-*tert*-butyldimethylsilyl-2,5-Di-*O*-*p*-toluenesulphonyl-3, 4-*O*-isopropylidene-D-mannitol (7)

To a stirred solution of the diol **6** (3 g, 6.7 mmol) in CH_2Cl_2 (20 mL) was added pyridine (20 mL) and triethylamine (1.9 mL, 13.5 mmol) at rt and the reaction mixture was cooled to 0°C *p*-Tosyl chloride (2.5 g, 13.5 mmol) was added in portions to give the pink solution, which was allowed to warm to rt, and stirring was continued for 24 h. After completion of the reaction (by TLC), the mixture was diluted with some more CH_2Cl_2 (50 mL), washed several times with water, brine, and dried. Removal of the solvent gave crude product, which was purified over silica gel to afford the pure product

7 as a viscous liquid (4.6 g, 91%); R_f 0.80 (10% EtOAc in petroleum ether); $[\alpha]_D^{25}$+11.9° (*c* 18, $CHCl_3$; IR (neat) 1590, 1360, 1180, 1060 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.02 (s, 12H), 0.82 (s, 18H), 1.30 (s, 6H), 2.39 (s, 6H), 3.7 2–3.87 (m, 4H), 4.40 (m, 2H), 4.70 (m, 2H), 7.30 (d, $J = 8.5$ Hz, 4H), 7.82 (d, $J = 8.5$ Hz, 4H); MS (FAB, *m/z*): 759 (M^++1), 637. Anal. calc. for $C_{35}H_{58}O_{10}S_2Si_2$: C, 55.40; H, 7.65; S, 8.44. Found: C, 55.62; H, 7.54.

2,5-Di-*O*-*p*-toluenesulphonyl-3,4-*O*-isopropylidene-D-mannitol (8)

To a stirred solution of ditosylate **7** (4 g, 5.3 mmol) in MeOH (40 mL), was added ceric ammonium nitrate (6.4 g, 11.6 mmol) at 0°C. The reaction mixture was stirred at that temperature for 12 h. Solvent was removed in vacuo at rt and the resulting oily material was diluted with ether (50 mL), washed with saturated aqueous sodium bicarbonate, water, brine, and dried. Solvent removal gave the crude product, which was purified over silica gel to afford the pure product **8** as a viscous oil (2.32 g, 83%); R_f 0.50 (50% EtOAc in petroleum ether); $[\alpha]_D^{25}$ +15.2° (*c* 1.25, $CHCl_3$; IR (neat) 3380, 1360, 1060 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.29 (s, 6H), 2.46 (s, 6H), 3.72 (d, $J =$ 10 Hz, 2H), 3.83 (d, $J = 10$ Hz, 2H), 4.15 (m, 2H), 4.62 (m, 2H), 7.35 (d, $J = 8$ Hz, 4H), 7.80 (d, $J = 8$ Hz, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.7, 27.1, 61.6, 76.3, 81.6, 111.3, 128.0, 129.8, 133.0, 145.0. Anal. calc. for $C_{23}H_{30}O_{10}S_2$: C, 52.07; H, S.66: S, 12.07. Found: C, 51.89; H, 5.68.

(*3R,4R*)-*O*-isopropylidene-1,6-hexanediol (1)

(*From* **5**): To a suspension of LAH (630 mg, 16.5 mmol) in ether (80 mL), ditosylate **5** (1.5 g, 2.0 mmol) in THF (10 mL) was added at 0°C, and stirred for 24 h (0°C to rt). Excess LAH was destroyed by the addition of EtOAc (0.5 mL). It was worked up by adding water (0.5 mL), followed by the same amount of 4N aq. NaOH. It was stirred for 5 m, water (0.5 mL) was introduced, and the mixture was further stirred for 20 m. Resulting white precipitate was filtered through celite. The filtrate was dried, concentrated in vacuo, and the resulting material was purified by column chromatography using petroleum ether/ethy acetate as an eluent on silica gel to afford the final diol **1** as a low melting solid (225 mg, 60%): R_f 0.20 (50% EtOAC in petroleum ether); $[\alpha]_D^{25}$ +22.0° (c 3.4, $CHCl_3$); IR (film) 3450 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.38 (s, 6H), 1.74–1.86 (m, 4H), 2.55 (bs, 2H, *OH*), 3.78–3.83 (m, 4H), 3.84–3.85 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 27.1, 34.3, 60.4, 79.6, 108.7; Anal. calc. for $C_9H_{18}O_4$: C, 56.84; H, 9.47. found: C, 56.92; H, 9.38.

(*From* **8**): To a suspension of LAH (600 mg, 16.0 mmol) in ether (60 mL) the compound **8** (2.1 g, 4.0 mmol) in THF(10 mL) was added at 0°C, and stirred for 24 h (0°C to rt). It was worked up as above to provide the final diol **1** (520 mg, 71%) as a low melting solid.

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