

Synthesis of (3*R*,4*R*)-Hexane-3,4-diol from D-Mannitol†

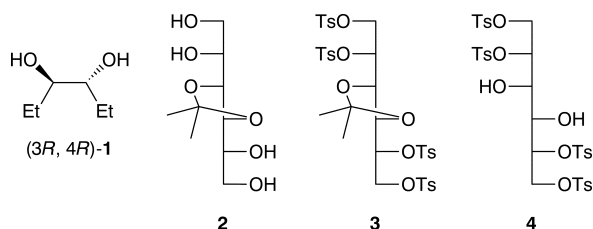
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(3*R*,4*R*)-Hexane-3,4-diol was synthesized from D-mannitol by using a strategy of protection and deprotection of hydroxyl groups.

Enantiomerically pure vicinal diols are very useful chiral synthons in organic synthesis. Recently we reported a short and convenient synthesis of (2*R*,5*R*)-hexane-2,5-diol from D-mannitol.¹ While working in this area, we realized that (3*R*,4*R*)-hexane-3,4-diol² **1** can also be synthesized from D-mannitol only by changing the strategy of protection and deprotection of hydroxyl groups. Thus, a tetraol **2**³ was treated with Et₃N and *p*-tosyl chloride in pyridine at 0 °C and further stirred at room temperature (r.t.) for 48 h to provide a tetraosylate **3** in 79% yield. The acetonide group of the tetraosylate **3** was deprotected using CuCl₂ · 2H₂O⁴ in MeCN at reflux temperature for 24 h to give a diol tosylate **4** in 96% yield. The diol tosylate **4** was treated with LiAlH₄ in THF–diethyl ether at r.t. for 24 h to provide the final diol **1**^{2a} in 49% yield.

In conclusion, (3*R*,4*R*)-hexane-3,4-diol was synthesized in three steps from an easily available precursor in an efficient manner.



Experimental

Acetonide Tetraosylate 3.—Solid *p*-toluenesulfonyl chloride (7 g, 36 mmol) was added in portions to a stirred solution of tetraol **2**³ (1 g, 4.5 mmol) in pyridine (15 mL) and Et₃N (2.5 mL, 18 mmol) at 0 °C. The reaction mixture was stirred for 48 h (0 °C to r.t.). It was diluted with CH₂Cl₂ (50 mL) and the organic layer washed with 1 M HCl, water, brine, and dried over anhydrous Na₂SO₄. The solvent was removed on a rotary evaporator, and the crude compound chromatographed over silica gel to afford tetraosylate **3** (3.8 g, 79% yield) as a white crystalline solid; mp 118–119 °C; *R*_f 0.60 (2:3, EtOAc in light petroleum); [α]_D²⁵ + 12.0° (*c* 1.0, CHCl₃); ¹H NMR (CCl₄, 60 MHz) δ 1.26 (s, 6 H), 2.50 (s, 12 H), 3.9–4.8 (m, 8 H),

7.35 (d, *J* = 8, 8 H), 7.80 (d, *J* = 8 Hz, 8 H). (Found: C, 52.78; H, 5.10, O, 26.82. Calc. for C₃₇H₄₂O₁₄S₄: C, 52.98; H, 5.01, O, 26.73%).

Tetraosylate Diol 4.—A solution of acetonide **3** (3.5 g, 4.2 mmol) in MeCN (50 mL) was treated with CuCl₂ · 2H₂O (2.1 g, 12.6 mmol) at r.t. and the reaction mixture stirred under reflux for 24 h. The flask was cooled and the solvent removed on a rotary evaporator. The crude mixture was chromatographed over silica gel to afford the tetraosylate diol **4** (3.2 g, 96% yield) as a white crystalline solid; mp 107–108 °C; *R*_f 0.80 (2:3, EtOAc in light petroleum); [α]_D²⁵ – 38.9° (*c* 1.0, CHCl₃); IR (KBr) 3500 cm⁻¹; ¹H NMR (CCl₄, 60 MHz) δ 2.5 (s, 12 H), 3.6–4.85 (m, 8 H), 7.35 (d, *J* = 8, 8 H), 7.80 (d, *J* = 8 Hz, 8 H). (Found: C, 51.08; H, 4.78, O, 28.22. Calc. for C₃₄H₃₈O₁₄S₄: C, 51.13; H, 4.76, O, 28.07%).

(3*R*,4*R*)-Hexane-3,4-diol 1.—A solution of tetraosylate **4** (2.5 g, 3.1 mmol) in THF (10 mL) was added slowly to a stirred suspension of LiAlH₄ (1.2 g, 31.5 mmol) in ether (50 mL) at r.t. The reaction mixture was stirred at the same temperature for 24 h. The excess of LiAlH₄ was destroyed by adding a few drops of EtOAc and the mixture treated with water (500 μL), 4 M NaOH (aq) (400 μL), and then water (1 mL) and stirred for 15 min. The white precipitate was filtered off, the filtrate was dried over anhydrous Na₂SO₄ and the solvent removed on a rotary evaporator. The crude mixture was purified over silica gel to afford the diol **1** (180 mg, 49% yield) as an oil; *R*_f 0.50 (1:1, EtOAc in light petroleum); [α]_D²⁵ + 16.6° (*c* 1.2, CHCl₃) {lit.^{2a} (95% e.e. for its enantiomer) [α]_D²⁵ – 12.4° (*c* 2.0, CHCl₃)}.

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