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A Practical Synthesis of (2*R*,5*R*)-2,5-Hexanediol

P. Saravanan, Sushil Raina, T. Sambamurthy, and
Vinod K. Singh*

*Department of Chemistry, Indian Institute of Technology,
Kanpur, India - 208 016*

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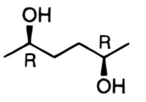
C_2 Symmetric chiral nonracemic ligands have found an important place in asymmetric synthesis as the presence of its axis reduces the number of possible competing diastereomeric transition states.[1,2] Some of the notable examples of such chiral ligands are *trans*-2,5-disubstituted pyrrolidines,[3] tetrahydrofuran,[4] phospholanes,[5] and borolanes.[6] Acquisition of these ligands depends upon availability of 2,5-hexanediol (**1**) in optically active form. As a part of our program in enantioselective deprotonation reactions,[7] we needed to synthesize (2*S*,5*S*)-2,5-dimethylpyrrolidine (**2**). The most obvious precursor for **2** is the diol **1** which has mainly been synthesized using enzymatic methods.[3b,8] The only nonenzymatic method for the diol **1**, to the best of our knowledge, is *via* asymmetric reduction of methyl acetoacetate using Noyori's BINAP chemistry followed by electrochemical Kolbe coupling of the corresponding acid.[5c] Although the method is good, the needed equipment for Kolbe coupling reaction may not be available in every laboratory. In view of this difficulty, we herein describe a simple, convenient, and practical synthesis of **1** from readily available D-mannitol.



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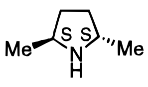

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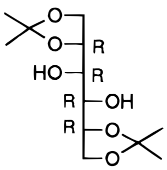
The strategy, involved in the synthesis, was based on protection and deprotection of hydroxyl groups of D-mannitol which is a cheap chiral source for synthesis of precursors for natural products.[9] The hydroxyl groups of mannitol diacetonide **3**[10] were derivatized as tosylates using *p*-tosyl chloride in pyridine to provide ditosylate **4**[11] in quantitative yield. The acetonide groups of crude tosylate **4** were hydrolyzed to give tetraol **5** in 65% overall yield after recrystallization from ethanol. The reaction of tetraol **5** with *p*-tosyl chloride in pyridine at 0 °C gave tetratosylate **6** and tritosylate **7** in 50 and 49% yield, respectively.[12] The yield of the desired tetratosylate **6** was improved to 77% when **7** was further subjected to tosylation using 1 equiv of *p*-tosyl chloride in pyridine. Finally, the reduction of tetratosylate **6** with LAH gave the target diol **1** in 60% yield.[13] In conclusion, a simple three-step sequence, suitable for multigram preparation, provided **1** in 30% overall yield.



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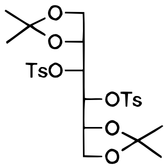

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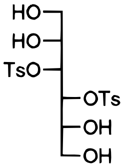

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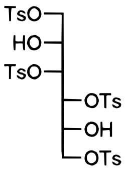

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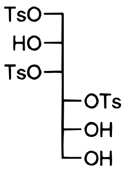

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Experimental Section

General Methods. ^{1}H NMR spectra were recorded on 60 and 80 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 recrysallized before use. Petroleum ether used was of boiling range 60−80 °C. Reactions which 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 sulfate. 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. The rt refers to 20−25 °C.

3,4-Di-*O*-*p*-toluenesulfonyl-D-mannitol (5). Solid *p*-tosyl chloride (45 g, 237 mmol) was added to a solution of 1,2:5,6-Di-*O*-isopropylidene-D-mannitol **3**[10] (25 g, 95.4 mmol) in pyridine (70 mL) at rt. Triethylamine (53 mL, 380 mmol) was added, and the solution was stirred at the same temperature for 48 h. The reaction mixture was diluted with CH_2Cl_2 (300 mL) and washed with water and brine. The organic layer was dried (Na_2SO_4) and concentrated on rotary evaporator to give 54 g of crude ditosylate. This was subjected to the next step without any purification. A small amount of this material (500 mg) from a different batch was purified by crystallization using hexane−CH_2Cl_2 (3:1) to give the pure 1,2:5,6-Di-*O*-isopropylidene-3,4-di-*O*-*p*-toluenesulfonyl-D-mannitol (**4**)[11] as a white crystalline solid for characterization: R_f 0.50 (1:3, EtOAc in petroleum

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ether); mp 113−115 °C; $[\alpha]^{25}_{D}$ +9.0° (*c* 1.0, $CHCl_3$) [lit.[11] maximum $[\alpha]^{25}_{D}$ +9.3° (*c* 1.0, $CHCl_3$); ^1H NMR (CCl_4, 60 MHz) δ 1.26 (s, 6H), 1.40 (s, 6H), 2.47 (s, 6H), 3.9 (bs, 6H), 4.86 (bm, 2H), 7.31 (d, *J* = 8 Hz, 4H), 7.80 (d, *J* = 8 Hz, 4H); MS (FAB, *m*/*z*): 571 (M^+ + 1), 155 (base peak).

The crude ditosylate (54 g) was dissolved in methanol (800 mL), treated with acetyl chloride (1.7 mL, 24 mmol) at rt, and stirred for 12 h. The solvent was removed, and the crude material was recrystallized from ethanol to give the pure alcohol **5** (30 g, 65% overall yield) as a white solid: R_f 0.70 (EtOAc); mp 119−122 °C; $[\alpha]^{25}_{D}$ +43.0° (*c* 1.0, $CHCl_3$); IR (film) 3350, 1582, 1350, 1170 cm^{-1}; ^1H NMR ($CDCl_3$, 80 MHz) δ 2.44 (s, 6H), 3.42 (bs, 4H, -OH), 3.71 (bs, 6H), 5.30 (d, *J* = 7.6 Hz, 2H), 7.30 (d, *J* = 8 Hz, 4H), 7.80 (d, *J* = 8 Hz, 4H); ^{13}C NMR (acetone-d_6, 20 MHz) δ 21.3, 62.9, 70.4, 78.9, 128.5, 130.4, 134.7, 145.9; MS (FAB, *m*/*z*): 513 (M^+ + Na, base peak). Anal. Calcd for $C_{20}H_{26}O_{10}S_2$: C, 48.98; H, 5.30, O, 32.65. Found: C, 48.70; H, 5.38; O, 32.74.

1,3,4,6-Tetra-*O*-*p*-toluenesulfonyl-D-mannitol (6). To a solution of the alcohol **5** (25 g, 51 mmol) in pyridine (400 mL) was added a solution of *p*-tosyl chloride (20.3 g, 107 mmol) in pyridine (50 mL) in a dropwise manner at 0 °C. The reaction mixture was stirred at the same temperature for 8 h and then poured into ice-cold water. The ether extracts were sequentially washed with water (five times), 2 N HCl, saturated aqueous $NaHCO_3$, and brine and dried (Na_2SO_4). The solvent was removed *in vacuo*, and the mixture was chromatographed over silica gel to afford **6** (20.5 g, 50% yield) and **7** (16.0 g, 49% yield). The tetratosylate **6** was characterized as a low melting solid: R_f 0.60 (1:1, EtOAc in petroleum ether); $[\alpha]^{25}_{D}$ +40.0° (*c* 1.0, $CHCl_3$); IR (film) 3330, 3060, 3030 cm^{-1}; ^1H NMR (CCl_4, 60 MHz) δ 2.47 (s, 12H), 3.66−4.4 (bm, 6H + 2 OH), 5.0 (m, 2H), 7.33 (d, *J* = 8 Hz, 8H), 7.80 (d, *J* = 8 Hz, 8H); ^{13}C NMR ($CDCl_3$, 20 MHz) δ 21.8, 67.3, 70.5, 76.3, 128.2, 130.0, 130.3, 133.5, 134.0, 145.3, 146.3; MS (FAB, *m*/*z*): 799 (M^+ + 1). Anal. Calcd for $C_{34}H_{38}O_{14}S_4$: C, 51.12; H, 4.76, O, 21.05. Found: C, 51.02; H, 4.80; O, 21.16.

The tritosylate **7** was characterized as a low melting solid: R_f 0.30 (1:1, EtOAc in petroleum ether); IR (film) 3500 cm^{-1}; ^1H NMR ($CDCl_3$, 80 MHz) δ 2.44 (s, 9H), 3.3 (bs, 3H, 3 OH), 3.5−4.4 (m, 6H), 5.1 (m, 2H), 7.34 (d, *J* = 8 Hz, 6H), 7.81 (d, *J* = 8 Hz, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.7, 62.1, 67.2, 68.5, 70.5, 76.3, 76.7, 127.9, 128.0, 129.8, 130.0, 132.5, 132.6, 145, 145.9; MS (FAB, *m*/*z*): 645 (M^+ + 1). The tritosylate **7** was converted to the tetratosylate **6** in 50% yield following the above procedure except that the reaction was done at 10 °C.

(2*R*,5*R*)-2,5-Hexanediol (1). A solution of **6** (16.5 g, 20.7 mmol) in THF:ether (25 mL, 1:4) was treated with a suspension of LAH (6.3 g, 165.4 mmol) in ether (200 mL) at rt for 24 h. Excess LAH was destroyed by addition of 1 mL of EtOAc. Water (5 mL) was added followed by the same amount of 4 N NaOH. After 5 min, 15 mL of water was added and the mixture stirred for 15 min. A white precipitate was filtered off, the filtrate was dried, and solvent evaporated. The crude mixture was purified by silica gel column chromatography followed by recrystallization from ether to give the diol **1** (1.45 g, 60% yield) as a solid: mp 52−53 °C; R_f 0.30 (1:1, EtOAc in petroleum ether); $[\alpha]^{25}_{D}$ −36.2° (*c* 1.0, $CHCl_3$) [lit.[4] maximum $[\alpha]^{25}_{D}$ −35.7° (*c* 1.0, $CHCl_3$); lit.[5c] maximum $[\alpha]^{25}_{D}$ −39.6° (*c* 1.0, $CHCl_3$)]; IR (film) 3350 cm^{-1}; ^1H NMR ($CDCl_3$, 80 MHz) δ 1.20 (d, *J* = 7 Hz, 6H), 1.58 (m, 4H), 2.28 (bs, 2H, OH), 3.84 (m, 2H); ^{13}C NMR ($CDCl_3$, 20 MHz) δ 23.8, 36.1, 68.4.

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