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Synthesis and structural characterization of enantiopure (2*R*,5*R*)-(+)-2,5-dimethylthiolane

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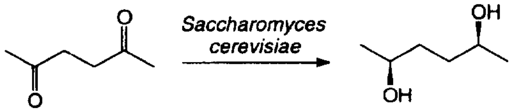
Abstract

Enantiopure (2*R*,5*R*)-(+)-2,5-dimethylthiolane was synthesized by cyclization with sodium sulfide of the dimesylate of (2*S*,5*S*)-(+)-2,5-hexanediol, which was obtained by baker's yeast (*Saccharomyces cerevisiae*) reduction of acetonyl acetone in high enantiomeric purity. The structure of the diol and absolute stereochemistry of the sulfone derived from the title molecule were determined by X-ray crystal structure analysis. © 1998 Elsevier Science Ltd. All rights reserved.

Enantiopure thioethers became interesting auxiliaries in asymmetric syntheses such as the non-racemic preparation of epoxides via sulfur ylides[1] or the electrophilic sulfenylation of unsaturated carbon–carbon bonds[2] in recent years. We succeeded in the synthesis of the enantiopure (2*R*,5*R*)-(+)-2,5-dimethylthiolane **3**. The analogous C_2-symmetric heterocycles (2*R*,5*R*)-2,5-dimethylpyrrolidine,[3] (2*R*,5*R*)-2,5-dimethylphosphalane,[4] (2*R*,5*R*)-2,5-dimethylborolane[5] and (2*R*,5*R*)-2,5-dimethyltetrahydrofuran[6] have been used successfully for several applications.[7]



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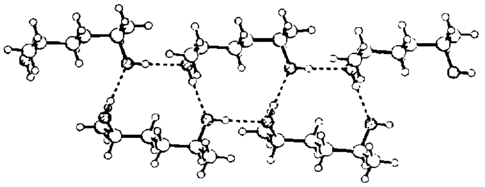

The starting material (2*S*,5*S*)-(+)-2,5-hexanediol **1** was synthesized by reduction of acetonyl acetone with *Saccharomyces cerevisiae* originating from fresh baker's yeast. Performing this reaction with a higher substrate concentration than proposed in the literature[8] improved both the reaction rate and the selectivity. The diol was obtained with >99% d.e. and >99% e.e. in 59% yield. No trace of other stereoisomers could be found by chiral GC.[9] An X-ray structure analysis[10] of the pure diol showed a ladder structure with two different kinds of hydrogen bridges.[11]

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† X-Ray analysis.

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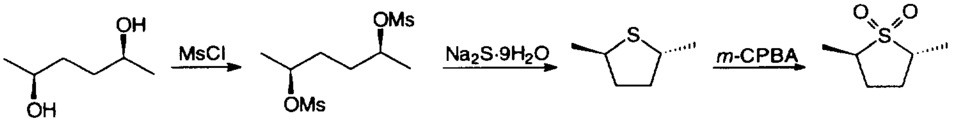
Syntheses of the corresponding tosylate and mesylate were achieved by established methods in almost quantitative yield. We found that only the cyclization of the mesylate **2** in DMSO with $Na_2S \cdot 9H_2O$ lead to highly pure (99% d.e. and >99% e.e.) (2*R*,5*R*)-(+)-2,5-dimethylthiolane **3**,[12] while the reaction of the tosylate in DMSO or an ethanol/water system lead to a lower diastereomeric excess.



1 **2** **3** **4**

To prove the absolute stereochemistry of (2*R*,5*R*)-(+)-2,5-dimethylthiolane **3** the compound was oxidized with *m*-chloroperbenzoic acid in dichloromethane to obtain the corresponding sulfone **4** in quantitative yield[13] which was analyzed by X-ray.[14]

Acknowledgements

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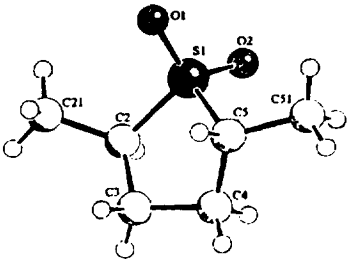
9. Preparation of **1**: 750 g of purchasable sucrose dissolved in 3 L of water was mixed with 500 g of ordinary baker's yeast at room temperature. The solution was stirred at 100 rpm for 1 hour (CO_2 production occurs) and 25 mL (0.208 mol) of acetonyl acetone were added. After 18 hours of stirring, a further 750 g of sucrose and 25 ml of acetonyl acetone dissolved in 2.5 L of water were added. The reaction was monitored by TLC. Every 12 hours, 250 g of sucrose were added. After 12 days, 250 g of Celite were added and the liquid was separated by centrifugation followed by removal of most of the water by evaporation. The remaining liquid (500 mL) was continuously extracted with ether for 24 hours. The solvent was removed and the residue was distilled at reduced pressure to obtain the diol **1** (28.7 g, 59%). Mp 51–53°C; $[\alpha]_D^{20}$ +36.0 (c=7, $CHCl_3$), [lit.[3a] mp 52–53°C, $[\alpha]_D^{24}$ +34.9 (c 9.48, $CHCl_3$), >98% ee]; ^1H NMR (300 MHz, $CDCl_3$): δ 1.11 (d, 6H, $^3J_{HH}$=6.2 Hz, CH_3); 1.42–1.51 (m, 4H, CH_2); 3.68–3.75 (m, 2H, CH); 4.90 (s, br, 2H, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 23.4 (q); 35.8 (t); 68.1 (d); MS (m/z): 118 (1); 100 (70); 85 (45); 83 (100); 45 (78); 41 (65).
10. Intensity data were collected on a CAD-4 diffractometer with $\omega/2\theta$ scan mode, T=223 K, using monochromated CuKα radiation. Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre.
11. Crystal data of (2*S*,5*S*)-(+)-2,5-hexanediol (**1**): formula $C_6H_{14}O_2$, M_r=118.17; monoclinic $P2_1$ (No.4); *a*=5.9436(3), *b*=7.3708(4), *c*=8.8027(5) Å, β=107.143(4), *V*=368.51(3) Å^3, Z=2. Data were measured with a 2θ range of 5.26° to 74.09°. A total of 890 reflections were collected. Among them, 805 were considered to be observed ($I>2\sigma(I)$). Final agreement indices are R(F)=0.035, WR^2=0.101, GoF=1.175, based on anisotropic refinement of all non-hydrogen atoms. H atoms calculated and refined riding.
12. Preparation of **3**: 22.0 g (80.1 mmol) of the mesylate **2** and 21.6 g (90 mmol) of $Na_2S \cdot 9H_2O$ were dissolved in 300 mL of DMSO and refluxed for 15 hours. The cooled reaction mixture was diluted with 300 mL of cold water and extracted six

times with diethyl ether. The combined organic layers were washed with 100 mL of 1 N HCl and six times with 100 mL of water. The solution was dried with $MgSO_4$. The solvent was removed and the residue was distilled to obtain the thiolane **3** (5.0 g, 53%). Bp 143°C; $[\alpha]_D^{20}$ +169.6 (c=1.1, diethyl ether); ^1H NMR (300 MHz, $CDCl_3$): δ 1.06 (d, $^3J_{HH}$=6.7 Hz, 6H, CH_3); 1.27–1.33 (m, 2H, CH_2); 1.93–1.97 (m, 2H, CH_2); 3.29–3.39 (m, 2H, CH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 22.2 (q); 39.1 (t); 43.8 (d); MS (m/z): 116 (20); 101 (78); 86 (25); 67 (35); 59 (60); 39 (100); elemental analysis calcd for $C_6H_{12}S$ (116.22), C 62.01, H 10.41, found C 61.97, H 10.47.

13. Preparation of **4**: 0.50 g (4.3 mmol) of the thiolane **3** were added at 0°C dropwise to a solution of 1.68 g (9.7 mmol) of *m*-chloroperbenzoic acid in 20 mL of dichloromethane. After stirring for 48 hours the solid was filtered off and the organic layer was washed twice with diluted $NaHCO_3$ solution and once with water. The solution was dried with $MgSO_4$, the solvent was distilled and the colorless oil of the sulfone **4** crystallized (0.63 g, 99%). Mp 50°C, $[\alpha]_D^{20}$ +183.4 (c=1.0, diethyl ether); ^1H NMR (300 MHz, $CDCl_3$): δ 1.28 (d, $^3J_{HH}$=6.7 Hz, 6H, CH_3); 1.48–1.63 (m, 2H, CH_2); 2.15–2.30 (m, 2H, CH_2); 2.85–2.98 m, 2H, CH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 12.8 (q); 28.8 (t); 55.7 (d); MS (m/z): 148 (57); 83 (38); 69 (12); 65 (6); 59 (3); 55 (25); 41 (72); 39 (100); elemental analysis calcd for $C_6H_{12}SO_2$ (148.22), C 48.62, H 8.16, found C 48.41, H 8.05.
14. Crystal data of (2*R*,5*R*)-(+)-2,5-dimethylsulfolane **4**: formula $C_6H_{12}O_2S$, M_r=148.22; orthorhombic $P2_12_12_1$ (No. 19); a=6.196(1), b=7.229(1), c=16.906(2) Å, V=757.2(2) Å^3, Z=4. Data were measured with a 2θ range of between 5.23° and 74.01°. A total of 1516 reflections were collected. Among them, 918 were considered to be observed ($I>2.0\ \sigma\ (I)$). Final agreement indices are $R(F)$=0.044, WR^2=0.120, GoF=1.083, based on anisotropic refinement of all non-hydrogen atoms, Flack parameter 0.09(3). H atoms calculated and refined riding.



4