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A FACILE SYNTHESIS OF (R)-(-)-HEXAHYDROMANDELIC ACID WITH FERMENTING BAKER'S YEAST

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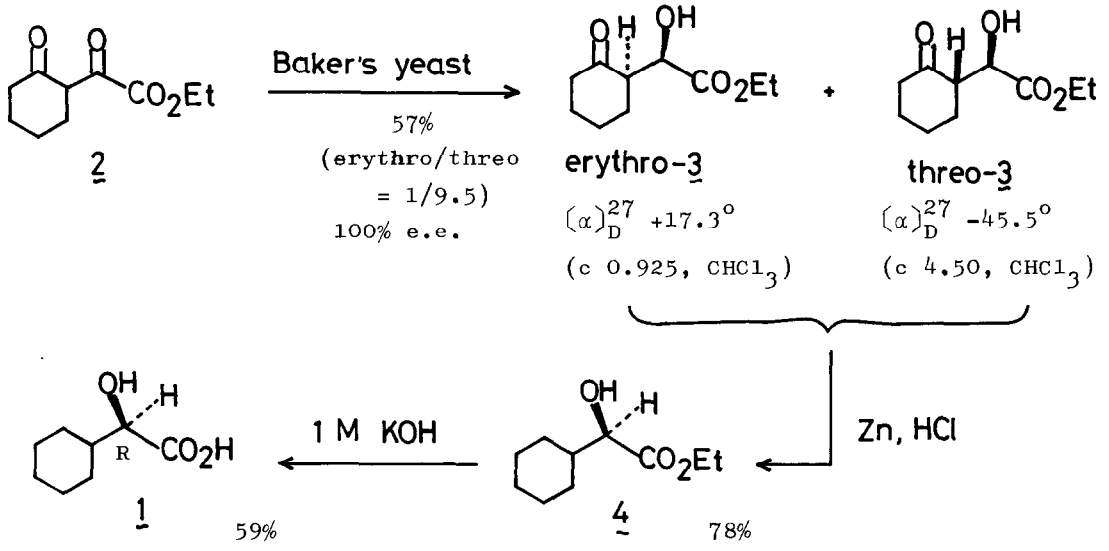
Summary: Optically pure (R)-(-)-hexahydromandelic acid has been prepared stereoselectively in two steps by the asymmetric reduction of ethyl α,2-dioxocyclohexaneacetate with fermenting baker's yeast followed by Clemmensen reduction.

The use of optically active hexahydromandelic acid (1) has become increasingly important in the synthesis of optically active polymers[1] and macrolides.[2] The synthesis of 1 has been so far accomplished by the hydrogenation of optically active mandelic acid in the presence of rhodium catalyst.[3] The present communication describes the facile synthesis of optically pure (R)-(-)-1 via the asymmetric reduction of ethyl α,2-dioxocyclohexaneacetate (2) with fermenting baker's yeast. The reaction sequence is summarized below.



Compound 2, which can be easily obtained by the oxalylation of cyclohexanone,[4] was treated with baker's yeast. A suspension of baker's yeast (6 g, Oriental Yeast Co.), glucose (75 g), KH_2PO_4 (1 g), $MgSO_4$ (0.5 g), $CaCO_3$

(2.5 g), and $NH_4H_2PO_4$ (1 g) in boiled water (500 ml) was stirred for 20 min at 32 °C. To the fermenting mixture was added 2 (4.90 g, 24.7 mmol). The resulting mixture was then kept for 50 h at 32 °C. The mixture was extracted with EtOAc and the extract was then worked up as usual. The crude oil was purified by short column chromatography (silica gel, hexane-EtOAc) to give 2.93 g (59% yield, 96% purity by HPLC) of ethyl α-hydroxy-2-oxocyclohexane-acetate (3): $[\alpha]_D^{28}$ -25.2° (c 28.0, $CHCl_3$). Preparative HPLC [SA-I (6 mm x 250 mm), hexane-EtOAc-EtOH (20:1:1)] gave optically pure erythro (αR,1R)-3[5,6] and threo (αR,1S)-3.[5,7]

Clemmensen reduction of 3 with Zn-HCl (2 h at -5—0 °C) gave optically active ethyl α-hydroxycyclohexaneacetate (4) in 78% yield, which was hydrolyzed with 1 M KOH (25 °C, 8 h) to afford (R)-(-)-hexahydromandelic acid (1) with 99% e.e. in 59% yield: mp 127-129 °C (benzene)(lit.[3a] 129 °C); $[\alpha]_D^{22}$ 25.3° (c 1.00, HOAc)(lit.[3a] $[\alpha]_D^{20}$ -25.5° (c 1.0, HOAc)). The present process offers a practical and economically feasible method for the preparation of (R)-(-)-hexahydromandelic acid. Full description of experimental details and further extension to other α,2-dioxocycloalkaneacetates will be published in due course.

References and Notes

1) T. Hirano, S. Inoue, and T. Tsuruta, Makromol. Chem., 177, 3237 (1976).

2) (a) S. Masamune, W. Choy, F. A. J. Kerdesky, and B. Imperial, J. Am. Chem. Soc., 103, 1566 (1981). (b) S. Masamune, M. Hirama, S. Mori, SK. A. Ali, and P. S. Garvey, ibid., 103, 1568 (1981). (c) D. Boschelli, J. W. Ellingboe, and S. Masamune, Tetrahedron Lett., 25, 3395 (1984).

3) (a) J. H. Stocker, J. Org. Chem., 27, 2288 (1962). (b) D. P. Riley and R. E. Shumate, J. Org. Chem., 45, 5187 (1980).

4) H. R. Snyder, L. A. Brooks, and S. H. Shapiro, "Organic Syntheses", John Wiley & Sons, Inc. (1943), Collect. Vol. II, p. 531.

5) Optical purity was determined by HPLC fitted with Sumipax OA-3000 after the conversion of the alcohol to 3,5-dinitrophenylcarbamate, and also by ^1H NMR analysis using Eu(hfc)$_3$.

6) Erythro-3: $[\alpha]_D^{27}$ +17.3° (c 0.925, $CHCl_3$); IR (neat) 3500, 1735, 1720 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.25 (t, J = 7.5 Hz, 3, $CO_2CH_2C\underline{H}_3$), 1.42-2.24 (m, 9, $4CH_2$, OH), 2.82 (m, 1, COCH<), 4.24 (q, J = 7.5 Hz, 2, $CO_2C\underline{H}_2CH_3$), 4.70 (d, J = 2.6 Hz, 1, >CHOH); ^{13}C NMR ($CDCl_3$) δ 14.2 (q), 24.5 (t), 26.8 (t), 27.0 (t), 41.8 (t), 53.8 (d), 61.7 (t), 69.2 (d), 173.5 (s), 210.3 (s).

7) Threo-3: $[\alpha]_D^{27}$ -45.5° (c, 4.50, $CHCl_3$); IR (neat) 3500, 1735, 1720 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.25 (t, J = 7.5 Hz, 3, $CO_2CH_2C\underline{H}_3$), 1.2-2.4 (m, 8, $4CH_2$), 2.90 (m, 2, OH, COCH<), 4.04 (d, J = 3.2 Hz, 1, >CHOH), 4.25 (q, J = 7.5 Hz, 2, $CO_2C\underline{H}_2CH_3$); ^{13}C NMR ($CDCl_3$) δ 14.2 (q), 24.8 (t), 26.9 (t), 30.1 (t), 41.9 (t), 53.7 (d), 61.5 (t), 71.1 (d), 173.3 (s), 210.7 (s).

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