Synthesis of Optically Active 1-Phenyl-1,2-propanediol by Use of Baker's Yeast

Mitsuhiro TAKESHITA* and Takumi SATO

Tohoku College of Pharmacy, 4–4–1 Komatsushima, Sendai 981, Japan. *Received September 28, 1988*

Reduction of 1-phenyl-1,2-propanedione with baker's yeast afforded (1*R*,2*S*)-1-phenyl-1,2-propanediol in high chemical and optical yield. (1*R*,2*S*)-, (1*R*,2*R*)- and (1*S*,2*S*)-1,2-propanediols were also prepared *via* (1*R*)- or (2*S*)-α-ketols, which were obtained as intermediates of the above reaction.

Keywords α-diketone; chiral 1,2-propanediol; (1*R*)-1-hydroxy-1-phenyl-2-propanone; (2*S*)-2-hydroxy-1-phenyl-1-propanone; baker's yeast; asymmetric reduction

Baker's yeast (*Saccharomyces cerevisiae*) is useful for the synthesis of chiral compounds in organic chemistry. Syntheses of chiral α-diols, which are important chiral building blocks in asymmetric synthesis, from α-diketones by asymmetric reduction with baker's yeast have been reported, but the selectivity was sometimes low or α-ketols were obtained instead of α-diols.[1)]

We have investigated a facile synthesis of optically active 1-phenyl-1,2-propanediol, which is expected to be a useful chiral synthon in asymmetric synthesis, by direct reduction of the corresponding α-diketone (**1**) with baker's yeast. Though a chiral synthesis of (1*R*,2*S*)-1-phenyl-1,2-propanediol (**2a**) was reported,[2)] the present method is fundamentally different and more efficient. Thus, when 1-phenyl-1,2-propanedione (**1**) was fermented with baker's yeast for 2 h at 27 °C, (1*R*,2*S*)-1-phenyl-1,2-propanediol (**2a**) was obtained in high optical yield (94% ee) and in excellent chemical yield (89%), $[\alpha]_D$ −38.6° (*c*=3.2, $CHCl_3$). Monitoring of this reaction by ^{1}H-nuclear magnetic resonance (^{1}H-NMR) spectroscopy indicated that the α-diketone (**1**) was reduced to give the (1*R*,2*S*)-diol (**2a**) *via* both the (1*R*)- and (2*S*)-ketols (**3** and **4**) as reaction intermediates. Recently, it was reported that the α-diketone (**1**) was reduced by baker's yeast to give only the (2*S*)-ketol (**4**) (at pH 5),[1b)] but both **3** and **4** were isolated in moderate chemical yields when the α-diketone (**1**) was treated with baker's yeast at low temperature (9 h at 5 °C) (**3**[3)]: 36%, 89% ee; **4**[4)]: 46%, 94% ee), and the α-diol (**2a**) was also obtained as a minor product (7%). The reduction of the α-ketol (**3**) with sodium borohydride[5)] in the presence of ammonium chloride afforded the *threo*-isomer (**2a**) preferentially (*erythro* **2a**/*threo* **2b** ratio, 26/74) (total yield 94%), while reduction of the α-ketol (**4**) under the same conditions gave the *erythro*-isomer (**2a**) in excess (*erythro* **2a**/*threo* **2c** ratio, 60/40) (total yield 84%) as an inseparable diastereomeric mixture. After acetylation of those two diastereomers (**2a**, **2b** and **2a**, **2c**) with Ac_2O–pyridine (py), and subsequent purification by silica gel column chromatography, the chiral diacetates (**2d**, **2e** and **2d**, **2f**)[6)] were isolated. Hydrolysis of **2d**, **2e** and **2f** with 20% NaOH at room temperature afforded the corresponding diols, **2a**[2)] (93—96% ee), **2b**[2d,7,8)] (93% ee) and **2c**[2c,d,7)] (90% ee), respectively.

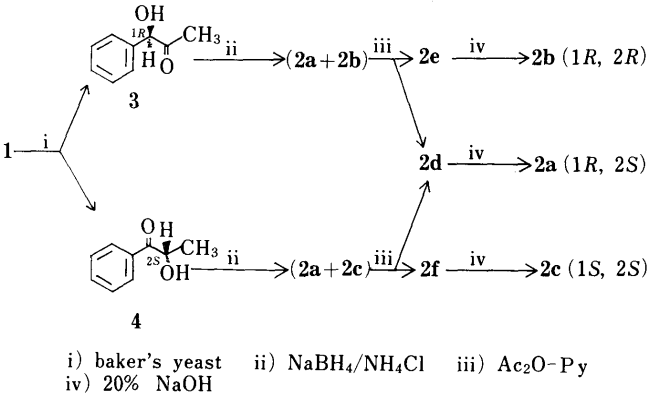
1

2

2a: R_1=H, R_2=H (1*R*,2*S*)
2b: R_1=H, R_2=H (1*R*,2*R*)
2c: R_1=H, R_2=H (1*S*,2*S*)
2d: R_1=Ac, R_2=Ac (1*R*,2*S*)
2e: R_1=Ac, R_2=Ac (1*R*,2*R*)
2f: R_1=Ac, R_2=Ac (1*S*,2*S*)

Chart 1

Thus, three optically active 1-phenyl-1,2-propanediols can be prepared from 1-phenyl-1,2-propanedione by the use of baker's yeast. Those alcohols should be useful as intermediates for the synthesis of natural products.



i) baker's yeast ii) $NaBH_4/NH_4Cl$ iii) Ac_2O–Py
iv) 20% NaOH

Chart 2

Experimental

Infrared (IR) spectra were measured with a Hitachi 260-10 spectrometer. ^{1}H-NMR spectra were recorded on JEOL PMX-60 si (60 MHz) or JNM-GMX-400 (400 MHz) spectrometers with tetramethylsilane as an internal standard. Optical rotation was measured with a JASCO DIP-360 automatic polarimeter. Mass spectra (MS) were recorded on a JEOL JMN-DX 303 at 70 eV. For column chromatography silica gel (Wakogel C-200, from Wako Pure Chemical Industries, Ltd.) was used.

(1*R*,2*S*)-1-Phenyl-1,2-propanediol (2a) from 1 A mixture of 1-phenyl-1,2-propanedione (**1**) (3.2 g, 22 mmol) and baker's yeast (250 g) in distilled water (125 ml) was incubated for 2 h at 34 °C. The mixture was extracted continuously with $CHCl_3$ using a Soxlet apparatus, and the $CHCl_3$ extract was dried over Na_2SO_4. Removal of the solvent under reduced pressure gave an oily residue, which was chromatographed on a silica gel column (100 g) using CH_2Cl_2 as an eluent to give **2a** as a colorless oil (3.2 g, 89%): $[\alpha]_D^{21}$ −38.6° (*c*=3.2, $CHCl_3$). IR ($CHCl_3$): 3600 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.10 (3H, d, *J*=6.4 Hz, CH_3), 1.82, 2.29 (1H each, br, OH), 4.20 (1H, dq, *J*=6.4, 3.9 Hz, C<u>H</u>–CH_3), 4.69 (1H, d, *J*=3.9 Hz, Ph–C<u>H</u>–), 7.28—7.38 (5H, m, aromatic H). Dibenzoate: $[\alpha]_D^{22}$ +59.4° (*c*=2.3, $CHCl_3$), mp 90—91 °C [lit.[2a)] $[\alpha]_D^{20}$ +59.9° (*c*=1.0, $CHCl_3$), mp 95—96 °C] or [lit.[2b)] $[\alpha]_D^{20}$ +62.2° (*c*=1.2, $CHCl_3$), mp 93.5 °C]. MS *m/z*: 152 (M^+), 135, 108. The optical purity of **2a** was determined by 400 MHz ^{1}H-NMR ($CDCl_3$) analysis of the corresponding (−)-α-methoxy-α-trifluoromethylphenylacetic acid diester (MTPA ester).[9)] In the NMR spectrum of the (−)-MTPA diester, the methyl protons appeared as two doublet signals due to the two diastereomers at 1.145 (d, *J*=6.4 Hz) and 1.304 (d, *J*=6.4 Hz) (intensity ratio=24:0.8). The optical purity was calculated, based on

© 1989 Pharmaceutical Society of Japan

NII-Electronic Library Service

the relative intensity of those two peaks, as 94% ee.

(1*R*)-1-Hydroxy-1-phenyl-2-propanone (3) and (2*S*)-2-Hydroxy-1-phenyl-1-propanone (4) A mixture of 1-phenyl-1,2-propanedione (2.5 g, 16 mmol) (**1**) and baker's yeast (250 g) in distilled water (125 ml) was incubated for 9 h at 5 °C. The mixture was extracted with $CHCl_3$ and the $CHCl_3$ extract was dried over Na_2SO_4. Removal of the solvent under reduced pressure gave an oily residue, which was chromatographed on a silica gel column (100 g) using 10—15% AcOEt in hexane (v/v) as an eluent to give **3** (910 mg, 36%) from the first eluate, **4** (1.2 g, 46%) from the second eluate and **2a** (190 mg, 7%) from the third eluate. **3**: A colorless oil, $[\alpha]_D^{22}$ −408.7° (*c*=1.1, $CHCl_3$), $[\alpha]_D^{22}$ −133.1° (*c*=1.1, EtOH) [lit.[3a] $[\alpha]_D^{20}$ −58.3° (*c*=2.5, EtOH)]. IR ($CHCl_3$): 3480, 1720 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.06 (3H, s, $COCH_3$), 5.08 (1H, s, Ph–C<u>H</u>–), 7.33 (5H, s, aromatic H). MS *m/z*: 150 (M^+), 107. (+)-MTPA ester of **3**: 2.167, 2.120 (each s, $COCH_3$) (intensity ratio = 100 : 6), 89% ee. **4**: A colorless oil, $[\alpha]_D^{24}$ −92.0° (*c*=6,7, $CHCl_3$)]. [lit.[4c] $[\alpha]_D$ −86.7° (*c*=2, $CHCl_3$)]. IR ($CHCl_3$): 3400, 1700 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.40 (3H, d, *J*=7.0 Hz, CH_3), 5.10 (1H, d, *J*=7.0 Hz, C<u>H</u>–CH_3), 7.26—7.67 (5H, m, aromatic H). MS *m/z*: 150 (M^+), 107. (+)-MTPA ester of **4**: 1.635 (d, *J*=7.3 Hz, CH_3), 1.561 (d, *J*=7.3 Hz, CH_3) (intensity ratio = 97 : 3), 94% ee.

Reduction of (1*R*)-1-Hydroxy-1-phenyl-2-propanone (3) $NaBH_4$ (100 mg, 2.6 mmol) was added slowly to a solution of **4** (100 mg, 0.6 mmol), NH_4Cl (100 mg, 1.8 mmol) and MeOH (20 ml) at 0 °C with stirring, and the mixture was stirred for 1 h. The mixture was extracted with $CHCl_3$ (3 × 20 ml) and the $CHCl_3$ extract was dried over Na_2SO_4. Removal of the solvent under reduced pressure gave a mixture of **2a** and **2b** in a ratio of 26 : 74 as an oily residue (total yield 95 mg, 94%), and this mixture was used without further purification.

Reduction of (2*S*)-2-Hydroxy-1-phenyl-1-propanone (4) $NaBH_4$ (100 mg, 2.6 mmol) was added slowly to a solution of **4** (100 mg, 0.6 mmol), NH_4Cl (100 mg, 1.8 mmol) and MeOH (20 ml) at 0 °C with stirring, and stirring was continued for 1 h. The mixture was worked up in the same manner as after the reduction of **3** to give a mixture of **2a** and **2c** in a ratio of 60 : 40 as an oily residue (total yield 85 mg, 84%), and this mixture was used without further purification.

(1*R*,2*S*)- and (1*R*,2*R*)-1,2-Diacetoxy-1-phenylpropane (2d, 2e) Pyridine (6 ml) was slowly added to a solution of the α-diols (**2a**+**2b**) (90 mg, 0.6 mmol) and Ac_2O (6 ml) at 0 °C. The mixture was stirred for 15 h at room temperature. After usual work-up of the reaction mixture, the $CHCl_3$ extract was chromatographed on a silica gel column (4 g) using 10—15% AcOEt in hexane (v/v) as an eluent to give **2d** (40 mg, 29%) from the first eluate and **2e** (94 mg, 69%) from the second eluate. **2d**: A colorless oil, $[\alpha]_D^{22}$ −46.4° (*c*=5.6, $CHCl_3$). IR ($CHCl_3$): 1730 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.18 (3H, d, *J*=6.8 Hz, CH_3), 2.00, 2.14 (3H each, s, $COCH_3$), 5.22 (1H, dq, *J*=6.8, 3.9 Hz, C<u>H</u>CH_3), 5.92 (1H, d, *J*=3.9 Hz, PhC<u>H</u>–), 7.30—7.38 (5H, s, aromatic H). MS *m/z*: 237 (M^++1), 177. **2e**: A colorless oil, $[\alpha]_D^{22}$ −46.6° (*c*=5.2, $CHCl_3$). IR ($CHCl_3$): 1730 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.09 (3H, d, *J*=6.4 Hz, CH_3), 2.06, 2.08 (3H each, s, $COCH_3$), 5.27 (1H, dq, *J*=6.4, 7.3 Hz, C<u>H</u>CH_3), 5.77 (1H, d, *J*=7.3 Hz, PhC<u>H</u>–), 7.30—7.37 (5H, m, aromatic H). MS *m/z*: 237 (M^++1), 177.

(1*R*,2*S*)- and (1*S*,2*S*)-1,2-Diacetoxy-1-phenylpropane (2d, 2f) Pyridine (6 ml) was slowly added to a solution of the α-diols (**2a**+**2b**) (80 mg, 0.5 mmol) and Ac_2O (6 ml) at 0 °C. The mixture was stirred for 10 h at room temperature. After the same work-up of the reaction mixture as in the case of acetylation of the α-diol (**2a**+**2b**), the $CHCl_3$ extract was chromatographed on a silica gel column (4 g) using 10—15% AcOEt in hexane as an eluent to give **2d** (76 mg, 61%) from the first eluate and **2f** (30 mg, 30%) from the second eluate. **2d**: A colorless oil, $[\alpha]_D^{22}$ −50.8° (*c*=6.5, $CHCl_3$). This **2d** was identical with an authentic sample that we prepared. **2f**: A colorless oil, $[\alpha]_D^{22}$ +57.6° (*c*=1.6, $CHCl_3$). IR ($CHCl_3$): 1730 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.09 (3H, d, *J*=6.4 Hz, CH_3), 1.03, 2.08 (3H each, s, $COCH_3$), 5.27 (1H, dq, *J*=6.4, 7.3 Hz, C<u>H</u>CH_3), 5.75 (1H, d, *J*=7.3 Hz, PhC<u>H</u>–), 7.30—7.35 (5H, m, aromatic H). MS *m/z*: 237 (M^++1), 177.

2a by Hydrolysis of 2d, Prepared from 3 A 20% NaOH solution (10 ml) was added dropwise to a solution of **2d** (510 mg, 2.2 mmol) and MeOH (10 ml) at 0 °C, and the mixture was stirred for 6 h at room temperature. The mixture was extracted with $CHCl_3$ and the $CHCl_3$ extract was dried over Na_2SO_4. Removal of the solvent under reduced pressure gave an oily residue, which was chromatographed on a silica gel column (10 g) using 10—15% AcOEt in hexane (v/v) as an eluent to give **2a** as a colorless oil (325 mg, 98%), $[\alpha]_D^{20}$ −35.0° (*c*=2.3, $CHCl_3$). This **2a** was identical with an authentic sample that we prepared. (−)-MTPA diester: 1.145 (d, *J*=6.4 Hz, CH_3), 1.304 (d, *J*=6.4 Hz, CH_3) (intensity ratio = 51 : 1.8), 93% ee.

2a by Hydrolysis of 2d, Prepared from 4 A 20% NaOH solution (10 ml) was added dropwise to a solution of **2d** (610 mg, 4 mmol) and MeOH (10 ml) at 0 °C, and the mixture was stirred for 6 h at room temperature. The mixture was worked up in the same manner as above (hydrolysis of **2d**) and the $CHCl_3$ extract was chromatographed on a silica gel column (10 g) using 10—15% AcOEt in hexane (v/v) as an eluent to give **2a** as a colorless oil (380 mg, 96%), $[\alpha]_D^{22}$ −34.9° (*c*=3.8, $CHCl_3$). This **2a** was identical with an authentic sample that we prepared. (−)-MTPA diester: 1.145 (d, *J*=6.4 Hz, CH_3), 1.304 (d, *J*=6.4 Hz, CH_3) (intensity ratio = 43.8 : 0.8), 96% ee.

(1*R*,2*R*)-1-Phenyl-1,2-propanediol (2b) A 20% NaOH solution (10 ml) was added dropwise to a solution of **2e** (500 mg) and MeOH (10 ml) at 0 °C, and the mixture was stirred for 6 h at room temperature. The mixture was worked up in the same manner as described for the hydrolysis of **2d**, and the $CHCl_3$ extract was chromatographed on a silica gel column (10 g) using 10—15% AcOEt in hexane (v/v) as an eluent to give **2b** as a colorless oil (310 mg, 93%), $[\alpha]_D^{21}$ −48.2° (*c*=2.5, $CHCl_3$) [lit.[8] $[\alpha]_D^{22}$ −60.6° (*c*=0.94, $CHCl_3$)]. IR ($CHCl_3$): 3580, 1600 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.07 (3H, d, *J*=6.4 Hz, CH_3), 2.48, 2.67 (1H each, m, OH), 3.86 (1H, dq, *J*=6.4, 7.3 Hz, C<u>H</u>CH_3), 4.38 (1H, d, *J*=7.3 Hz, PhC<u>H</u>–), 7.29—7.38 (1H, m, aromatic H). MS *m/z*: 152 (M^+), 135, 108. (−)-MTPA diester: 1.198 (d, *J*=6.4 Hz, CH_3), 1.247 (d, *J*=6.4 Hz, CH_3) (intensity ratio = 7.1 : 94.3), 86% ee.

(1*S*,2*S*)-1-Phenyl-1,2-propanediol (2c) A 20% NaOH solution (10 ml) was added dropwise to a solution of **2f** (328 mg, 2.2 mmol) and MeOH (10 ml) at 0 °C, and the mixture was stirred for 6 h at room temperature. The mixture was worked up in the same manner as described for the hydrolysis of **2d**, and the $CHCl_3$ extract was chromatographed on a silica gel column (10 g) using 10—15% AcOEt in hexane (v/v) as an eluent to give **2c** as a colorless oil (187 mg, 89%), $[\alpha]_D^{22}$ +55.9° (*c*=1.9, $CHCl_3$) [*Cf.* lit.[7b] $[\alpha]_D^{20}$ +24.56° (*c*=1.9, EtOH)]. IR ($CHCl_3$): 3580, 1600 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.05 (3H, d, *J*=6.4 Hz, CH_3), 2.62, 2.78 (1H each, m, OH), 3.84 (1H, dq, *J*=6.4, 7.3 Hz, C<u>H</u>CH_3), 4.36 (1H, d, *J*=7.3 Hz, PhC<u>H</u>–), 7.30—7.38 (5H, m, aromatic H). MS *m/z*: 152 (M^+), 135, 108. (−)-MTPA diester: 1.198 (d, *J*=6.4 Hz, CH_3), 1.247 (d, *J*=6.4 Hz, CH_3) (intensity ratio = 96 : 5), 90% ee.

References

1) *a*) C. Neuberg, *Adv. Carbohydr. Chem.*, **4**, 75 (1945) and references cited therein; *b*) R. Chenevert and S. Thiboubot, *Chem. Lett.*, **1988**, 1911.
2) *a*) C. Fuganti and P. Grasselli, *Chem. Ind.* (London), **1977**, 983; *b*) H. Ohta, K. Ozaki, J. Konishi and G. Tsuchihashi, *Agric. Biol. Chem.*, **50**, 1261 (1986); *c*) M. Fujita and T. Hiyama, *J. Am. Chem. Soc.*, **106**, 4629 (1984); *d*) C. Zioudrou and P. Chrysochou, *Tetrahedron*, **33**, 2103 (1977).
3) *a*) Y. Ohgo, Y. Natori, S. Takeuchi and J. Yoshimura, *Chem. Lett.*, **1974**, 709; *b*) R. Roger, *Biochem. Z.*, **230**, 320 (1930); *c*) J. H. Brewster, *J. Am. Chem. Soc.*, **78**, 4061 (1956).
4) *a*) K. Harada and S. Shono, *Bull. Chem. Soc. Jpn.*, **57**, 1040 (1984); *b*) N. Maigrot, J-P. Mazaleyrat and Z. Welvart, *J. Org. Chem.*, **50**, 3916 (1985); *c*) F. A. Davis and M. S. Haque, *ibid.*, **51**, 4083 (1986); *d*) H. Ohta, M. Ikemoto, H. II, Y. Okamoto and G. Tsuchihashi, *Chem. Lett.*, **1986**, 1169; *e*) D. Enders, H. Lotter, N. Maigrot, J-P. Mazaleyrat and Z. Welvart, *Nouv. J. Chim.*, **8**, 747 (1984).
5) *a*) T. Nakata, T. Tanaka and T. Oishi, *Tetrahedron Lett.*, **24**, 2653 (1983); and see reference 2*c*.
6) *a*) W. E. Friestad and J. R. Peterson, *J. Org. Chem.*, **50**, 10 (1985); *b*) R. O. Norman and C. B. Thomas, *J. Chem. Soc. B*, **1968**, 994; *c*) A. Citterio and C. Arnoldi, *J. Chem. Soc., Perkin Trans. 1*, **1983**, 891.
7) *a*) T. Kokubo, T. Sugimoto, T. Uchida, S. Tanimoto and M. Okano, *J. Chem. Soc., Chem. Commun.*, **1983**, 769; *b*) F. Fischer, *Chem. Ber.*, **94**, 893 (1961).
8) B. Witkop and C. M. Foltz, *J. Am. Chem. Soc.*, **79**, 197 (1957).
9) J. A. Dale, D. L. Dull and H. S. Mosher, *J. Org. Chem.*, **34**, 2543 (1969).

NII-Electronic Library Service