Stereochemically Controlled Bakers'-Yeast-Mediated Reductions: Synthesis of (*S*)-(+)-1,2-Propanediol and (*S*)-(−)-1,3-Butanediol, 1-Benzyl Ethers

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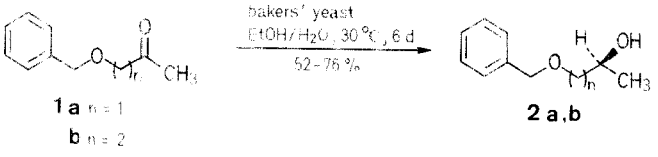
Benzyloxyketones **1a** and **b** can be reduced by fermenting bakers' yeast to the corresponding protected (*S*)-diols **2a** and **b** in 76 and 52% yields, respectively (90 and >95% e.e., respectively, as (*R*)-(+)-MTPA esters).

Variously substituted carbonyl compounds can be efficiently reduced by fermenting bakers' yeast in a highly enantioselective manner, and at present, this bioreduction can be considered a well established, synthetically significant procedure for the preparation of several chiral building blocks.[1] The general feature for the bioreduction of substituted carbonyl compounds is currently well explained by the Prelog's rule.[2]

The above bioreduction should constitute an accessible route for the preparation of optically active 1,2-diols, and in fact, in a classical work hydroxyacetone was cleanly reduced to (*R*)-(−)-1,2-propanediol.[3] Other α-hydroxyketones have also been reduced by bakers' yeast to afford, as a common feature, (*R*)-1,2-diols,[4,5,6] this stereochemical outcome being apparently in conflict with Prelog's rule. Since several asymmetric syntheses of various chiral compounds have been carried out using chiral 1,2-propanediol and its derivatives as starting material,[7,8,9] it seemed worthwhile to explore the feasibility of bakers'-yeast bioreductions of suitably protected hydroxyketones. 1-Benzyloxy-2-propanone (**1a**) was chosen as substrate, since its bioreduction should afford the optically active 1,2-propanediol protected as the 1-benzyl ether (**2a**), a useful chiral synthon which has been employed for asymmetric syntheses by other authors.[10,11,12]

It was conceivable that, relying on Prelog's rule, the hydrogen transfer should proceed on the *Re*-face of the prochiral ketone, and thus the (*S*)-alcohol **2a** should be produced by the bioreduction route. However, in view of the demonstration that at least three carbonyl-reducing enzymes of different stereochemical control are present in yeast,[13] caution must be exercised in drawing any conclusion, and absolute configuration needs to be confirmed.

Benzyloxyketone (**1a**) could be prepared from ethyl 4-benzyloxyacetoacetate[14] by a simple hydrolysis-decarboxylation procedure in 75% yield. More conveniently, ketone (**1a**) could be prepared by hydration[15] of benzylated propargyl alcohol, in turn prepared by a modified experimental protocol of a described procedure[16] in 82% yield. Incubation with fermenting yeast (6 d) proceeded satisfactorily and benzyloxyalcohol (**2a**) was obtained in 76% yield, $[\alpha]_D^{25}$ +11° (*c* = 2, $CHCl_3$). Reaction of alcohol **2a** with (*R*)-(+)-2-methoxy-2-trifluoromethylphenylacetyl (MTPA) chloride[17] afforded the corresponding MTPA ester, which by ^{1}H-NMR analysis was shown to be at least 90% optically pure. Since the optical rotation of the same compound prepared from ethyl (*S*)-lactate was not given in the literature,[10] it was necessary to convert the protected diol **2a** into 1,2-propanediol. This diol showed an $[\alpha]_D$ of +27° (*c* = 5, $CHCl_3$), thus assessing for compound **2a** the (*S*)-configuration. Therefore, the bioreduction of the ketone **1a** had proceeded according with Prelog's rule.



Commercially available 4-benzyloxy-2-butanone (**1b**) was also a good substrate for yeast mediated-reduction, and by this method, the benzyloxy alcohol **2b** was prepared in 52% yield. The optical purity was >95%, as established by the ^{1}H-NMR spectrum of its (*R*)-(+)-MTPA ester. (*S*)-(−)-1,3-Butanediol 1-benzyl ether (**2b**) had been prepared from ethyl 3-hydroxybutanoate by Mori[18] $[\alpha]_D$ −2.12° (*c* = 1.13, $CHCl_3$), and the stereochemical outcome of the bioreduction of ketone **1b** could therefore be easily assessed. Thus, the protected diol **2b** ($[\alpha]_D^{25}$ −2.45°, *c* = 4, $CHCl_3$) obtained by us, in agreement with the stereochemical outcome predicted by Prelog's rule, has the (*S*)-configuration.

In conclusion, use of fermenting bakers' yeast allows the preparation of protected diols such as **2a** and **2b** in good chemical yields and high optical purity under stereochemically controlled conditions. It should be noted that the bioreductive route can be favorably compared to the chemical syntheses of the same chiral synthons. In fact, starting from chiral hydroxy-

esters such as ethyl (*S*)-lactate[10] and (*S*)-3-hydroxybutanoate,[18] the same benzylated diols **2a** and **2b** can be prepared in four steps in 69 and 56%, respectively.

Bakers' yeast was from ERIDANIA (Italy) and chemicals from Fluka (Switzerland). All m.p. were uncorrected. IR spectra were recorded on a 1420 Perkin Elmer spectrometer as neat liquid films. The 60 MHz ^{1}H-NMR spectra were recorded on a Varian 360 L spectrometer in $CDCl_3$, unless otherwise indicated, using TMS as internal or external standard. The 200 MHz ^{1}H-NMR spectra were recorded on a Varian XL 200 spectrometer. Optical rotations were measured on a Perkin-Elmer Model 141 polarimeter. Distillation for analytical purposes was performed with a Büchi GKR-50 glass tube (Kugelrohr) oven. TLC analyses were carried out on Merck 60 F_{254} silica gel plates. Flash column chromatographies[19] were performed on silica gel (Merck 60, 230–400 mesh).

1-Benzyloxy-2-propyne:
Propargyl alcohol (3.55 mL, 0.06 mol) is slowly added (room temperature) to a well stirred mixture of ground KOH (3.36 g, 0.06 mol) and hexadecyltributylphosphonium bromide (0.46 g, 0.009 mol) in benzene (18 mL). Stirring is continued for 15 min at room temperature, then the mixture is brought to 70 °C and a solution of benzyl chloride (6.9 mL, 0.06 mol) in benzene (6 mL) is slowly added (1 h). The mixture is stirred at 70 °C for an additional 3 h, then cooled to room temperature, and anhydrous Na_2SO_4 (1.1 g) is added with vigorous stirring. The solid is filtered on a sintered glass funnel and washed with benzene (3 × 2 mL). The benzene solution is directly distilled at reduced pressure (24 mbar). The desired product is collected at 100–102 °C (Lit.[20] b.p. 100–101 °C/24 mbar; yield: 7.3 g (83%).

$C_{10}H_{10}O$	calc.	C 82.16	H 6.89
(146.2)	found	82.01	6.79

IR: ν = 3290, 3085, 3060, 3030, 2120 cm^{-1}.

^{1}H-NMR: δ = 2.40 (t, 1 H, J = 2.5 Hz); 4.15 (d, 2 H, J = 2.5 Hz); 4.60 (s, 2 H); 7.40 (s, 5 H).

1-Benzyloxy-2-propanone (1a):
A solution of 1-benzyloxy-2-propyne (3.8 g, 0.026 mol) in MeOH (13 mL) is slowly added (1 h) to a stirred solution of a mixture of mercuric sulphate (0.256 g, 0.86 mmol) and conc. H_2SO_4 (1.02 g) in a mixture of H_2O (13 mL) and MeOH (38 mL). The reaction mixture is stirred at 70 °C for 2 h, then cooled to room temperature and diluted with ice-cooled water containing a few drops of saturated $NaHCO_3$ solution. The solution is saturated with NaCl, filtered on a celite pad, and extracted with Et_2O (5 × 30 mL). The organic extracts are dried (Na_2SO_4) and evaporated to give nearly pure product **1a**; yield: 3.93 g (92%). A sample distilled at 158–160 °C/24 mbar (Lit.[21] b.p. 130 °C/24 mbar).

$C_{10}H_{12}O_2$	calc.	C 73.15	H 7.37
(164.2)	found	73.08	7.28

IR: ν = 3085, 3060, 3030, 1740 cm^{-1}.

^{1}H-NMR: δ = 2.15 (s, 3 H); 4.10 (s, 2 H); 4.60 (s, 2 H); 7.40 (s, 5 H).

(*S*)-(+)-1,2-Propanediol, 1-Benzyl Ether (2a):
A solution of 1-benzyloxy-2-propanone (**1a**; 0.45 g, 2.74 mmol) in EtOH (50 mL) is added slowly (8 h) to fermenting bakers' yeast [yeast (100 g) and sucrose (100 g) in tap water (1000 mL)]. The mixture is shaken at 30 °C for 6 d, then filtered through a celite pad and extracted with EtOAc (5 × 120 mL). The extracts are dried (Na_2SO_4) and evaporated at reduced pressure, leaving a residue (0.8 g), which is purified by column chromatography. Elution with light petroleum ether (b.p. 40–70 °C)/ethyl acetate (8:2) affords alcohol **2a**; yield: 0.346 g (76%); b.p. 92 °C/0.9 mbar (Lit.[10] 85 °C/0.59 mbar; $[\alpha]_D^{25}$ +11.0° (c = 2, $CHCl_3$).

$C_{10}H_{14}O_2$	calc.	C 72.26	H 8.49
(166.2)	found	72.38	8.62

IR: ν = 3380, 3085, 3060, 3030, 2960, 2920, 2860 cm^{-1}.

^{1}H-NMR (CCl_4): δ = 1.05 (d, 3 H, J = 6 Hz); 2.75 (s, 1 H); 3.05–3.40 (m, 2 H); 3.85 (m, 1 H); 4.45 (s, 2 H) 7.25 (s, 5 H).

The enantiomeric excess of **2a** is calculated from the ^{1}H-NMR spectrum of its (*R*)-(+)-2-methoxy-2-trifluorophenylacetic (MTPA) ester. The derivative from the racemic alcohol shows at 60 MHz two broad singlets for the methylene protons of the benzyl ether moiety centered at 4.54 and 4.63 ppm (ratio 30:40). The 3-methyl groups present two overlapped doublets centered at 1.28 and 1.38 ppm (J = 6.5 Hz; ratio 40:30). At 200 MHz the methylene peaks are resolved into doublets (J = 2.5 Hz), and the methyl signals are two well separated doublets. In the derivative from optically active alcohol, the ratios are 95:5 (90% e.e.).

(*S*)-(+)-1,2-Propanediol:
To a solution of alcohol **2a** (0.364 g, 2.2 mmol) prepared as above, in MeOH (6 mL), 10% palladium on activated carbon (50 mg) is added. The suspension is stirred under a hydrogen atmosphere for 30 h. The reaction mixture is filtered and evaporated to dryness. Benzene (2 mL) is added and evaporated in order to remove water from the hygroscopic product; yield: 0.160 g (96%).

IR and NMR spectra were identical to an authentic sample (Aldrich). A distilled sample (b.p. 187–188/1020 mbar) showed $[\alpha]_D^{25}$ +27° (c = 5, $CHCl_3$). A solution of an authentic sample at the same concentration showed $[\alpha]_D^{25}$ +29.5°.

(*S*)-(−)-1,3-Butanediol, 1-Benzyl Ether (2b):
To a slurry of fermenting bakers' yeast [yeast (100 g) and sucrose (100 g) in tap water (1 L)], a solution of commercial 4-benzyloxy-2-butanone (**1b**; 0.45 g, 2.5 mmol) in EtOH (50 mL) is added slowly (18 h) with mechanical stirring. The mixture is stirred at 30 °C for 6 d, then filtered through a celite pad, and extracted with EtOAc (5 × 150 mL). The extracts are dried (Na_2SO_4) and evaporated at reduced pressure leaving a residue (0.75 g), which is purified by flash chromatography (CH_2Cl_2/acetone, 99:1, as eluant) to give **2b**; yield: 0.24 g (52%); b.p. 98–100 °C/2.0 mbar (Lit.[18] 98–102 °C/2.0 mbar); $[\alpha]_D^{25}$ −2.45 (c = 4, $CHCl_3$) (Lit.[18] $[\alpha]_D^{25}$ −2.12° (c = 1.13, $CHCl_3$)

$C_{11}H_{16}O_2$	calc.	C 73.30	H 8.95
(180.25)	found	73.22	9.04

IR: ν = 3400, 3020, 2950, 2920, 2850 cm^{-1}.

^{1}H-NMR (CCl_4): δ = 1.10 (d, 3 H, J = 6 Hz); 1.65 (dt, 2 H, J = 6 Hz, 5.5 Hz); 2.75 (s, 1 H); 3.60 (t, 2 H, J = 6 Hz); 3.95 (1 H, m); 4.50 (2 H, s); 7.30 (1 H, s).

The enantiomeric excess of **2b** is calculated from the 60 MHz ^{1}H-NMR of the MTPA ester. In this case the racemic alcohol shows two singlets centered at 4.38 and 4.46 ppm (97:84) for the methylene protons of benzyl moiety and two overlapped doublets centered at 1.26 and 1.35 ppm (J = 6 Hz) for the methyl group. In the derivative of optically active alcohol, only the singlet at 4.38 and the doublet at 1.35 ppm are detectable.

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(1) Seebach, D., Sutter, M.A., Weber, R.H., Zuger, M.F. *Org. Synth.* **1985**, *63*, 1.
(2) Prelog, V. *Pure Appl. Chem.* **1964**, *9*, 119.
(3) Levene, P.A., Walti, A. *Org. Synth. Coll. Vol. II* **1943**, 545.
(4) Guette, J.P., Spassky, N. *Bull. Soc. Chim. Fr.* **1972**, 4217.
(5) Ridley, D.D., Stralow, M. *J. Chem. Soc. Chem. Commun.* **1975**, 400.
(6) Barry, J., Kagan, H.G. *Synthesis* **1981**, 453.
(7) Golding, B.T., Hall, D.R., Sakrikar, S. *J. Chem. Soc., Perkin Trans. 1* **1973**, 1214.
(8) Gombos, J., Haslinger, E., Schmidt, U. *Chem. Ber.* **1976**, *109*, 2645.
(9) Fryzuk, M.D., Bosnich, B. *J. Am. Chem. Soc.* **1978**, *100*, 5491.
(10) Buchwald, S.L., Pliura, D.H., Knowles, J.R. *J. Am. Chem. Soc.* **1984**, *106*, 4916.
(11) Sugawara, F., Nakayama, H., Ogawa, T. *Carbohydr. Res.* **1983**, *123*, 25.
(12) Malanga, C., Spassky, N., Menicagli, R., Chiellini, E. *Polym. Bull. (Berlin)* **1983**, *9*, 528.
(13) Shieh, W.R., Gopalan, A.S., Sih, C.J. *J. Am. Chem. Soc.* **1985**, *107*, 2993.
(14) Häbich, D., Hartwig, W. *Tetrahedron* **1984**, *40*, 3667.
(15) Sato, K., Inoue, S., Ota, S. *J. Org. Chem.* **1970**, *35*, 565.

(16) Shikhiev, I.A., Karaev, S.F., Alieva, S.Z., Yur'eva, G.A. *Zh. Org. Khim.* **1975**, *11*, 2134; *C.A.* **1976**, *84*, 30573.
(17) Dale, J.A., Mosher, H.S. *J. Am. Chem. Soc.* **1973**, *95*, 512.
(18) Mori, K., Tanida, K. *Tetrahedron* **1981**, *37*, 3221.
(19) Still, W.C., Kahn, M., Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.
(20) Guermont, J.P. *Mem. Serv. Chim. État* **1955**, *40*, 147; *C.A.* **1958**, *52*, 2737.
(21) Quarterman, J., Stevens, T.S. *J. Chem. Soc.* **1955**, 3292.