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Synthesis of Chiral Epoxy Alcohols by Use of Baker's Yeast

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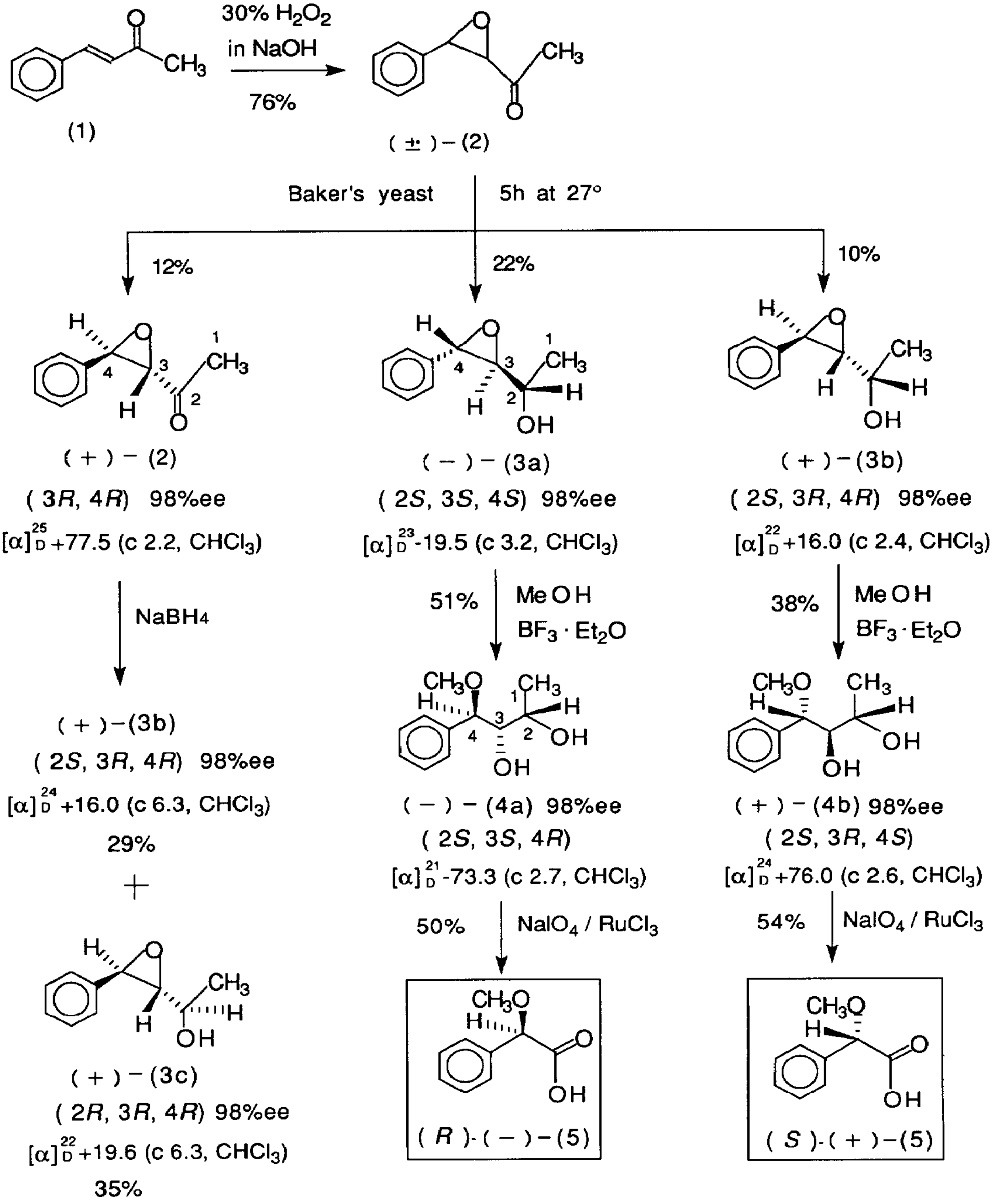
Abstract: Synthesis of optically active 3,4-epoxy-4-phenyl-2-butanols, which are expected to be useful intermediates for the synthesis of biologically active compounds such as β-blocker, was achieved by asymmetric reduction of 3,4-epoxy-4-phenyl-2-butanone with baker's yeast.

Baker's yeast (*Saccharomyces cerevisiae*) have been widely used for the syntheses of versatile chiral synthons for the synthesis of optically active materials. Asymmetric reduction of carbonyl compounds with baker's yeast is well-documented,[1] however, reduction of epoxides (including epoxy ketone) has seldom been reported. In the present paper, we report the facile asymmetric synthesis of homochiral epoxy alcohols such as glycidols, which are valuable chiral building blocks for the synthesis of various biologically active compounds such as β-blockers,[2] by chemoselective reduction or kinetic resolution of epoxy ketones with baker's yeast.

As shown in Scheme 1, when racemic *trans*-3,4-epoxy-4-phenyl-2-butanone (±)-**2**, prepared by epoxydation of *trans*-4-phenyl-3-buten-2-one (**1**) with 30% H_2O_2 / NaOH in 76% yield, was treated with baker's yeast for 5h at 27°C, two 3,4-epoxy-4-pheny-2-butanols **(2*S*,3*S*,4*S*)-(-)-(3a)**(98%ee) and **(2*S*,3*R*,4*R*)-(+)-(3b)** (98%ee) were afforded in 12 and 22 % yields. Kinetically resolved chiral epoxy ketone **(3*R*,4*R*)-(+)-(2)** (98%ee)[3] was also recovered in 10% yield after separation by silica gel column chromatography. The stereochemistry of the products **(-)-3a** and **(+)-3b** could be determined by Mosher's[4] or modified Mosher's methods[5] or by transforming each into the known α-methoxy phenylacetic acids.[6] Thus, methanolysis of the epoxy alcohols **(-)-3a** and **(+)-3b,** in the


30% H2O2
in NaOH
76%
(1)
(±)-(2)
Baker's yeast
5h at 27°
12%
22%
10%
(+)-(2)
(3R, 4R) 98%ee
[α]D25 +77.5 (c 2.2, CHCl3)
(−)-(3a)
(2S, 3S, 4S) 98%ee
[α]D23 -19.5 (c 3.2, CHCl3)
(+)-(3b)
(2S, 3R, 4R) 98%ee
[α]D22 +16.0 (c 2.4, CHCl3)
NaBH4
51%
MeOH
BF3·Et2O
38%
MeOH
BF3·Et2O
(+)-(3b)
(2S, 3R, 4R) 98%ee
[α]D24 +16.0 (c 6.3, CHCl3)
29%
+
(+)-(3c)
(2R, 3R, 4R) 98%ee
[α]D22 +19.6 (c 6.3, CHCl3)
35%
(−)-(4a) 98%ee
(2S, 3S, 4R)
[α]D21 -73.3 (c 2.7, CHCl3)
(+)-(4b) 98%ee
(2S, 3R, 4S)
[α]D24 +76.0 (c 2.6, CHCl3)
50%
NaIO4 / RuCl3
54%
NaIO4 / RuCl3
(R)-(−)-(5)
(S)-(+)-(5)

Scheme 1

presence of ether-boron trifluoride complex, proceeded stereo- and regioselectively to give **(2S, 3S, 4*R*)-** and **(2*S*, 3*R*, 4*S*)**-4-methoxy-4-phenyl-2,3-butanediol **(-)-(4a)** and **(+)-(4b)** in 51 and 38% yields, respectively. The enantiomeric purities of both of the products **(-)-(4a)** and **(+)-(4b)** were determined to be 98%ee by ^{1}H-NMR spectral analysis (400MHz) of (***R***)- and (***S***)-methoxy(trifluoromethyl)phenylacetic acids derivatives. Oxidative cleavage of the diols **(-)-(4a)** and **(+)-(4b)** with sodium periodate[7] (using ruthenium(lll) chloride as catalyst) gave α-methoxy(phenyl)acetic acids **(-)-(5)** and **(+)-(5)** in 50 and 51% yields.[8] The stereochemistries of C3 and C4 in **(-)-3a** and **(+)-3b** were finally deduced from the configuration of **(-)-(5)** and **(+)-(5)**.[6]

Reduction of chiral epoxy ketone **(+)-2** using sodium borohydride furnished the readily separable epoxy alcohols **(+)-3b** and **(+)-3c** in the ratio 1: 1.1 in 64% total yield. The compound **(+)-3c** was proved to be **(2*R*,3*R*,4*R*)**-isomer by optical rotation and ^{1}H-NMR spectral data of **(-)-3a** and its (***R***)- and (***S***)-MTPA esters.

Thus, treatment of *trans*-3,4-epoxy-4-phenyl-2-butanone **(±)-2** with baker's yeast provides a new method for the preparation of three chiral epoxy alcohols **(-)-3a**, **(+)-3b**, and **(+)-3c** which would be useful chiral building blocks for the synthesis of optically active compounds.

References and Notes

1) For example, a) Csuk, R.; Glanzer, B. I., *Chem. Rev.*, **1991**, 91, 49. b)Jones, J. B., *Tetrahedron*, **1986**, 42, 3351 and references cited therein.

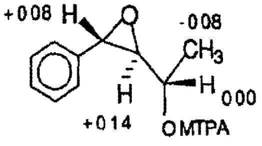
2) a) Terao, Y.; Murata, M.; Achiwa, K., *Tetrahedron Lett.*, **1988**, 29, 5137. b) Duke, M.; Smith, L. H., *J. Med. Chem.*, **1971**, 14, 326. c)Price, B. J.; Roberts, S.M. in: *Medicinal Chemistry, The Role of Organic Chemistry In Drug Research*, Academic Press, New York 1985.

3) Optical purity was evaluated by NMR (400MHz) analysis using optically active shift reagent, [Eu(hfc)3].

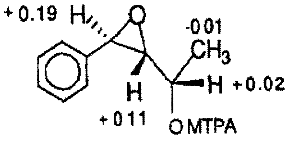
4) a) Dale, J. A.; Dull, D. L.; Mosher, H. S., *J. Org. Chem.*, **1969**, 34, 2543. b) Dale, D.A.; Mosher, H. S., *J. Am. Chem. Soc.*, **1973**, 95, 512. c) Yamaguchi, S., in : *Asymmetric Synthesis*, Morrison, J. D. (ed.), Vol. 1, Academic Press, New York, 1983, p. 125.

5) The configurations of C2 at (-)- **3a** or **(+)-3b** were determined by comparison with the Δδ values (ppm) obtained from (*S*) and (*R*)-MTPAesters of (-)- **3a** or (+)-**3b**.

Δδ (ppm) = δ[(*R*)-MTPA derivative] - δ[(*S*)-MTPA derivative]



MTPA ester of (-)-(3a)



MTPA ester of (+)-(3b)

See: a) Takano, S.; Takahashi, M.; Yanase, M.; Sekiguchi, Y.; Iwabuchi, Y.; Ogasawara, K., *Chemistry Lett.*, **1988**, 1827. b) Takeshita, M.; Yanagihara, H.; Yoshida, S., *Heterocycles*, **1992**, 33, 489.; Kusumi, T.; Fujita, Y.; Ohtani, I.; Kakisawa, H., *Tetrahedron Lett.*, **1991**, 32, 2923. c) Natsume, M. Yasui, K.; Kondo, S., Marumo, S., *Tetrahedron Lett.*, **1991**, 32, 3087.

6) a) Takano, S.; Yanase, M.; Ogasawara, K., *Synthesis*, **1989**, 39.

7) Charlson, P. H. J.; Katsuki, T.; Martin, V.S.; Sharpless, K.B., *J. Org. Chem.*, **1981**, 46, 3936.

8) Spectral data of (*R*)- and (*S*)-α-methoxy(phenyl)acetic acids (-)-(**5**) and (+)-(**5**) were identical with those of authentic samples purchased from Aldlich Chemical Company, Inc. The optical rotation of the acids, **(*R*)-(-)-(5)**: $[\alpha]_D$ -120.8 (c 1.3, EtOH)(ref. $[\alpha]_D$ -150 (c 1.0, EtOH)), **(*S*)-(+)-(5)**: $[\alpha]_D$ +142.8 (c 2.9, EtOH)(ref. $[\alpha]_D$ +150 (c 1.0, EtOH))(ref.: Aldrich's Catalog Handbook of Fine Chemicals, 1988-1989, p.972) were lower than the reference values, but the optical purities of the epoxy alcohols (-)- **3a**, **(+)-3b**, **(+)-3c** and the diols **(-)-(4a)** and **(+)-(4b)** were confirmed by Mosher or modified mosher's methods (ref. 4, 5).