Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron Letters 46 (2005) 7217–7219
Tetrahedron Letters

A convenient approach to (*S*)-2-ethylhexan-1-ol mediated by baker's yeast

Yikang Huang, Fanglin Zhang and Yuefa Gong*

Department of Chemistry, Huazhong University of Science and Technology, Wuhan 430074, Hubei, PR China

Received 16 June 2005; revised 15 August 2005; accepted 16 August 2005
Available online 2 September 2005

Abstract—The baker's yeast (*Saccharomyces cerevisiae*) mediated asymmetric bioreduction of 2-ethylhex-2-enal (**1**) went smoothly under a mild condition and afforded a high yield of (*S*)-2-ethylhexan-1-ol (**2a**) with excellent enantioselectivity in biphasic system.

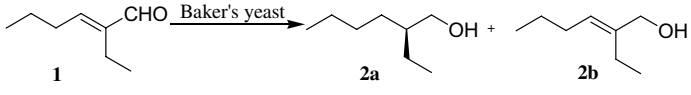
2-Ethylhexan-1-ol as an important building block draws a lot of attention in pharmaceutics, cosmetics, food, and chemical industries.[1] However, (*R*)-2-ethylhexanoic acid, the metabolite of (*R*)-ethylhexan-1-ol, has been proved to be a potent teratogen, while the (*S*)-enantiomer shows no teratogenic effects.[2] Therefore, (*S*)-2-ethylhexan-1-ol (**2a**) is a safer enantiomer and more suitable for pharmaceutics and food uses. Thus, the development of a new way to produce optically pure **2a** has received much attention.

To date, main approaches to optically pure (*R*)- or (*S*)-2-ethylhexan-1-ol reported are the lipase mediated kinetic resolution of racemic 2-ethylhexan-1-ol.[1a,3] We noticed that some primary alcohols with α-chiral center could also be prepared by biocatalytic reduction of α,β-unsaturated aldehydes.[4] It is well-known that baker's yeast (*Saccharomyces cerevisiae*) acts as an efficient biocatalyst not only in the reduction of ketones, but also in the reduction of C=C bonds activated by strongly polarizing groups, such as nitro group,[5a] carbonyl group,[5b] or hydroxyl group.[5c]

In this context, we describe a convenient way to synthesize (*S*)-2-ethylhexan-1-ol (**2a**) via the bioreduction of 2-ethylhex-2-enal (**1**) mediated by commercially available baker's yeast (Angel instant dry yeast). Some interesting phenomena have been observed in our experiments.

The bioreduction was carried out by mixing 60 mg (0.46 mmol) of the substrate **1** and 2.0 g of dry baker's yeast in 25 mL of potassium phosphate buffer (0.1 M, pH 8.0) at 30 °C. The substrate **1** was prepared by aldol condensation of *n*-butyraldehyde according to the typical procedures. Product analysis clearly showed that the reduction products were **2a**[6] and **2b**[6] as characterized by ^{1}H NMR and GC (Scheme 1). Absolute configuration of **2a** was assigned to be (*S*)-isomer by comparing its optical rotation with that of the known (*S*)-(+)-**2a** ($[\alpha]_D^{25}$ +2.57 (*c* 1, benzene)). The yields and ee value of **2a** were determined by gas chromatography with chirasil-dex CB 25 m × 0.25 mm column (DIKMA) under the GC conditions: the carrier gas N_2, the column temperature 110 °C. The retention times for **2a** (*S*-isomer), its enantiomer (*R*-isomer) and **2b** were 5.2, 5.1, and 5.7 min, respectively. All the results are listed in Table 1.

As shown in Table 1, the reduction of unsaturated aldehyde **1** proceeded quickly, and **1** disappeared completely



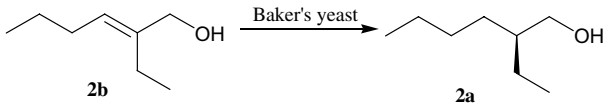
Scheme 1.

Keywords: 2-Ethylhexan-1-ol; Bioreduction; Baker's yeast; Biphasic system.
* Corresponding author. Tel.: +86 27 87543032; fax: +86 27 87543632; e-mail: gongyf@mail.hust.edu.cn

0040-4039/$ - see front matter
doi:10.1016/j.tetlet.2005.08.063

Table 1. Bioreduction of **1** in aqueous media at 30 °C

Entry	Time (h)	Conv. (%)	**2a**:**2b**	ee	Abs. confgn. of **2a**
1	1	>99	46:54	89	*S*
2	2	>99	60:40	91	*S*
3	6	>99	72:28	93	*S*
4	10	>99	88:12	93	*S*
5	24	>99	88:12	93	*S*



Scheme 2.

Table 2. Bioreduction of **2b** in aqueous media at 30 °C

Entry	Time (h)	Yield (%)	ee	Abs. confgn. of **2a**
1	0.5	14	48	*S*
2	1.0	24	73	*S*
3	1.5	35	80	*S*
4	2.0	43	83	*S*
5	6	86	88	*S*
6	10	92	88	*S*
7	24	93	88	*S*

within 1 h. Product **2a** and the allylic alcohol **2b** were formed in a ratio of 46:54 (entry 1). It was found that **2b** could be further reduced to saturated alcohol **2a** during the reaction, but the rate was comparatively slow. After 10 h, the yield of **2a** reached 88% with a high ee value of 93%. A slight increase of ee value was also observed during the bioreduction of **2b** (Scheme 2).

The bioreduction of **2b** was carried out according to the same procedures described above. As shown in Table 2, the reduction of **2b** underwent smoothly, giving **2a** in 24% yield after 1 h. Apparently, the formation rate of **2a** was much slower than that (46%) in the case of **1**. However, the reaction of **2b** was almost completed after 10 h and gave **2a** in 92% yield despite the lower rate. This was an unexpected high yield in comparison with the corresponding bioreductions reported hitherto. To our knowledge, the conversion of the known bioreduction of other aliphatic unsaturated aldehydes or allylic alcohols was rather low, even though the reaction was proceeded for several days.[4]

Meanwhile, we found that the ee value of the product **2a** increased with the progress of the reduction, and the final value (88%) was slightly lower than that observed in the reduction of **1**. As far as we know, the gradual increase of ee value has not been reported during the reduction of unsaturated aldehydes and allylic alcohols, though similar phenomenon was reported in the reduction of ketone.[7] This phenomenon implies that the reductases with opposite enantioselectivity could be selectively inhibited by the product **2a**.

Table 3. Bioreduction of **1** in biphasic system at 30 °C for 24 h

Entry	Water (%)	Conv. (%)	**2a**:**2b**	ee	Abs. confgn. of **2a**
1	10	68	77:23	>99	*S*
2	20	>99	88:12	>99	*S*
3	30	>99	87:13	>99	*S*
4	40	>99	87:13	98	*S*
5	50	>99	85:15	96	*S*
6	100	>99	88:12	92	*S*
7[a]	30	>99	91:9	>99	*S*

[a] 4.0 g of dry baker's yeast used.

The reaction medium was studied next since it has a marked effect on yeast reductions.[8] For this purpose, water–petroleum ether biphasic system was used as the reaction medium. As a consequence, a high yield of **2a** was obtained in perfect enantioselectivity up to 99% (Table 3). We noticed that water content, substrate concentration and the weight of baker's yeast had an effect on the reduction rate and the ee value to some extent. The ideal result was obtained when the ratio of water and petroleum ether was 3:7. In fact, a marked increase of the enantiomeric excess in the bioreduction of γ-nitroketones mediated by *S. cerevisiae* has been reported, when a hexane–water biphasic system was used instead of pure water.[9] Moreover, other factors were also studied, including pH value in aqueous phase, additives as selective reductase inhibitors and hydrogen donors, but no considerable change in yield or ee value was observed.

In summary, we consider that the bioreduction of 2-ethylhex-2-enal by baker's yeast is an efficient way to prepare (*S*)-2-ethylhexan-1-ol. The bioreduction in biphasic medium resulted in high yield (91%) and excellent optical purity (>99% ee). An unexpectedly high reduction rate of allylic alcohol (**2b**) was observed in this work. This result implied that the β-substituents could have a marked effect on the reduction rate of allylic alcohols, and the details are on further investigation.

References and notes

1. (a) Majerić, M.; Šunjić, V. *Tetrahedron: Asymmetry* **1996**, *7*, 815–824; (b) He, X. L.; Chen, B. Q.; Tan, T. W. *J. Mol. Catal. B: Enzym.* **2002**, *18*, 333–339.
2. Sundberg, C.; Wachtmeister, C.; Lundgren, B.; DePierre, J. W. *Chirality* **1994**, *6*, 17–24.
3. (a) Baczko, K.; Larpent, C. *J. Chem. Soc., Perkin Trans. 2* **2000**, 521–526; (b) Ervinas, G. *Chemija* **2004**, *15*, 37–43; (c) Macherey, A. C.; Gregoire, S.; Tainturier, G.; Lhuguenot, J. C. *Chirality* **1992**, *4*, 478–483.
4. (a) Hans, E. H.; Erik, H.; Jonas, F.; Stefano, S. *J. Org. Chem.* **1992**, *57*, 2052–2059; (b) Gramatica, P.; Speranza, S. *Tetrahedron* **1988**, *44*, 1299–1306; (c) Gramatica, P.; Manitto, P.; Poli, L. *J. Org. Chem.* **1985**, *50*, 4625–4628; (d) Fuganti, C.; Grasselli, P.; Seneci, P. F.; Casati, P. *J. Chem. Soc., Perkin Trans. 1* **1988**, 3061–3065.
5. (a) Kawai, Y.; Inaba, Y.; Hayashi, M.; Tokitoh, N. *Tetrahedron Lett.* **2001**, *42*, 3367–3368; (b) Kawai, Y.; Hayashi, M.; Tokitoh, N. *Tetrahedron: Asymmetry* **2001**, *12*, 3007–3013; (c) Fuganti, C.; Serra, S. *J. Chem. Soc., Perkin Trans. 1* **1999**, 279–282.
6. ^{1}H NMR data (Varian Mercury Plus–400 MHz, TMS, $CDCl_3$) for **2a**: δ 3.55 (d, $J = 7.2$ Hz, 2H), 2.08 (br s, 1H), 1.61 (m, 1H), 1.26–1.40 (m, 6H), 1.10–1.20 (m, 2H), 0.89

(t, $J = 7.0$ Hz, 6H); for **2b**: δ 5.39 (d, $J = 7.2$ Hz, 1H), 4.05 (s, 2H), 2.11 (q, $J = 7.2$ Hz, 2H), 2.02 (q, $J = 7.2$ Hz, 2H), 1.50 (br s, 1H), 1.40 (m, $J = 7.2$ Hz, 2H), 0.95 (t, $J = 7.2$ Hz, 3H), 0.90 (t, $J = 7.2$ Hz, 3H).

7. Griffin, D. R.; Yang, F. X.; Carta, G.; Gainer, J. L. *Biotechnol. Prog.* **1998**, *14*, 588–593.
8. (a) Dumanski, P. G.; Florey, P.; Knettig, M.; Smallridge, A. J.; Trewhella, M. A. *J. Mol. Catal. B: Enzym.* **2001**, *11*, 905–908; (b) Smallridge, A. J.; Ten, A.; Trewhella, M. A. *Tetrahedron Lett.* **1998**, *39*, 5121–5124.
9. Molinari, F.; Occhiato, E. G.; Aragozzini, F.; Guarna, A. *Tetrahedron: Asymmetry* **1998**, *9*, 1389–1394.