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Lipase-mediated resolution of racemic benzo-15-crown-5 ether derivatives

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Abstract

Racemic large secondary alcohol, 4′-hydroxyethyl-benzo-15-crown-5-ether, (±)-**1** was kinetically resolved in high optical yield by asymmetric transformation with *Candida antarctica* lipase and *Pseudomonas cepacia* lipase.

Keywords: crown ether; enzyme and enzyme reaction; transesterification; resolution.

Lipases have recently been recognized as effective catalysts in synthetic organic reactions as well as in biological reactions and provide an interesting alternative method for resolution of enantiomers.[1] They catalyze esterification and hydrolysis of various alcohol substrates having fluorinated, organometallic, and other exotic functional groups.[2] Optically active crown compounds are of great interest in view of their pathological and physiological properties.[3] Recently, lipase was observed to resolve crown ether compounds.[4] We now report that *Candida antarctica* (CA) and *Pseudomonas cepacia* (PS) lipases are an effective catalyst for resolution of racemic large secondary alcohol having a crown ether ring as a variation of 1-phenylethanol.

Among several enzymes,[5] CA lipase (CAL) and lipase PS were found to accelerate transesterification of crown (±)-**1**[6,11] in toluene at 30°C in the presence of vinyl acetate to give the corresponding ester **2a** in excellent yield and ee (enantiomeric excess), Scheme 1. Other lipases such as lipase MY, lipase OF, lipase AY, CCL (*Candida cylindracea* lipase) and PPL (Porcine pancreas lipase) were less reactive than CAL and lipase PS under the same reaction conditions. Commercially available acyl donors (vinyl butyrate, vinyl hexanoate and vinyl octanoate) were effective[7] under the present reaction conditions. The reaction can be carried out in THF using CAL as catalyst. The results are summarized in Table 1.

As a typical experiment, CAL (200 mg) and vinyl acetate (3 mmol) were added to a solution of (±)-**1** (0.6 mmol) in toluene (10 ml) and the mixture was vigorously stirred at 30°C. The reaction was quenched by filtering off the enzyme, and the enzyme portion was washed with 30 ml of chloroform. Standard

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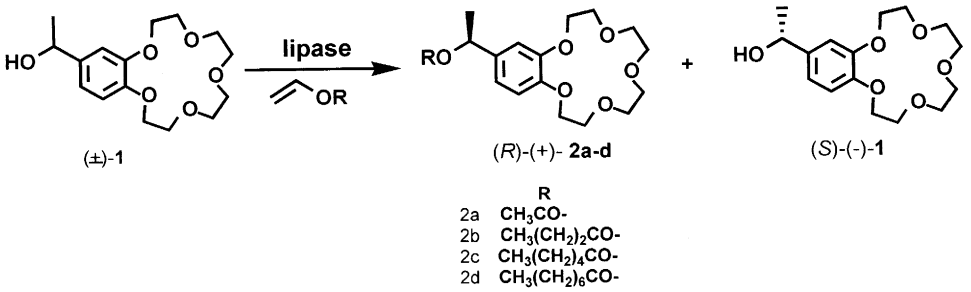

Scheme 1.

Table 1
Lipase-catalyzed enantioselective transesterification of (±)-**1**

				Product (R)-**2a-d**			Recovered Alcohol (S)-**1**			
Lipase	Solvent	Acyl donor[a]	Time/h	yield/%[b]	ee/%[c]	$[\alpha]^{25}_{D}$[d]	yield/%	ee/%	$[\alpha]^{25}_{D}$	E[e]
PS[f]	Toluene	A	20	40	>99	+71.9	42	35	-8.5	280
CAL[g]	Toluene	A	1	48	>99	+71.6	45	96	-17.6	790
CAL	THF	A	3	38	98	+69.9	32	87	-16.9	283
CAL	Toluene	B	1	22	>99	+12.0	30	85	-15.6	544
CAL	Toluene	H	4	29	>99	+44.7	25	79	-13.5	483
CAL	Toluene	O	4	30	>99	+48.8	28	38	-6.5	289

(a) A, Vinyl Acetate; B, Vinyl Butyrate; H, Vinyl Hexanoate; O, Vinyl Octanoate
(b) Isolated yield (c) Determined by HPLC (Daicel chiralcel OD column (n-hexane:2-propanol = 9 : 1)
(d) Optical rotations were measured in chloroform at 25 ℃.
(e) Calculated from E = ln[1-c(1+ee(2))] / ln[1-c(1-ee(2))] according to ref.9
(f) *Pseudomonas cepacia* lipase (g) *Candida antarctica* lipase

work-up and column chromatography of silica gel (chloroform) gave (*R*)-(+)-**2a** in 48% yield[8] (99% ee) together with (*S*)-(−)-**1** in 45% yield (96% ee).

The enantiomeric excess (% ee) values of **1** and **2** obtained by the kinetic resolutions were determined by means of HPLC (Daicel, Chiralcel OD column, hexane:2-propanol 9:1). The E values were calculated according to the literature.[9] It was confirmed by a control experiment without lipase that the crown compound **1** itself cannot function as a catalyst for the transesterification. The absolute configurations of the ester **2** and the remaining alcohol **1**, the former of which was converted into the alcohol, were determined by ^{1}H NMR (500 MHz) $CDCl_3$, from the diastereomeric differences in chemical shifts made by the methyl group in (*S*)-*O*-methylmanderate esters.[10]

In conclusion, CAL is an excellent catalyst for the transesterification of crown (±)-**1** in organic media. Considering the broad substrate specificity of lipases, this approach is expected to be synthetically useful for asymmetric preparation of other optically pure alcohols. Further work is under way to resolve crown compounds of different ring size.

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References

1. (a) Wong, C. H.; Whitesides, G. M. *Enzymes in Synthetic Organic Chemistry*; Tetrahedron Organic Chemistry. Pergamon: Oxford, 1994. (b) Theil, F. *Chem. Rev*. **1995**, *95*, 2203–2227. (c) Nakamura, K.; Hirose, Y. *J. Synth. Org. Chem. Jpn.* **1995**, *53*, 668–677.
2. (a) Izumi, T.; Aratani, S. *J. Chem. Technol. Biotechnol.* **1995**, *63*, 25–32. (b) Kijima, T.; Yaginuma, Y.; Izumi, T. *J. Chem. Technol. Biotechnol.* **1999**, *74*, 501–508. (c) Ema, T.; Jittani, M.; Sakai, T.; Utaka, M. *Tetrahedron Lett*. **1998**, *39*, 6311–6314. (d) Kazlauskas, R. J.; Weissfloch, A. N. E.; Rappaport, A. T.; Cuccia, L. A. *J. Org. Chem*. **1991**, *56*, 2656–2665. (e) Nakamura, K.; Kawasaki, M.; Ohno, A. *Bull. Chem. Soc. Jpn.* **1996**, *69*, 1079–1085.
3. (a) Fujii, I.; Togame, H.; Kanematsu, K. *Chem. Pharm. Bull.* **1986**, *34*, 4439–4442. (b) Vogtle, V. F.; Jansen, B. *Tetrahedron Lett.* **1976**, *52*, 4895–4898.
4. (a) Tsukube, H.; Betchaku, A.; Hiyama, Y.; Itoh, T. *J. Chem. Soc., Chem. Commun.* **1992**, 1751–1752. (b) Tsukube, H.; Betchaku, A.; Hiyama, Y.; Itoh, T. *J. Org. Chem*. **1994**, *59*, 7014–7018. (c) Muraoka, M.; Ueda, A.; Zhang, W.; Kida, T.; Nakatsuji, Y.; Ikeda, I.; Kanehisa, N.; Kai, Y. *Tetrahedron Lett*. **1998**, *39*, 9493–9496.
5. Lipase PS and AY (Amano Pharmaceutical Co.); CCL and PPL (Sigma Chemical Co.); Lipase MY and OF (Meito Sangyo Co.); CAL (Novozyme 435®, Novo Nordisk Bio Industry Co.)
6. Compound (±)-**1** was prepared from benzo 15-crown-5 ether, by acetylation (see Ref. 11) with acetic anhydride-polyphosphoric acid and reduction with $NaBH_4$, subsequently. (±)-**1** was obtained in 77% yield of the starting crown compound (benzo-15-crown-5 ether) and confirmed by its spectroscopic properties. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.83–6.94 (m, 3H, Cp), 4.83 (q, 1H, J=3 Hz, CH), 3.74–4.15 (m, 16H, -O-CH_2-CH_2-), 3.44 (s, 1H, OH), 1.47 (d, 3H, J=6.5 Hz, CH_3), IR ν (neat), cm^{-1}: 3400 (OH), 2964 (CH_2), 1138 (C-O-C), 941 and 860 (1,2,4-substituted benzene), MS *m/z*: 312 M^+.
7. Kazlauskas, R. J. *Biotechnology*; Wiley-VCH: Weinheim, 1998; Vol. 8a, pp. 37–192.
8. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.80–6.89 (m, 3H, Cp), 5.80 (q, 1H, J=7 Hz, CH_2), 3.74–4.18 (m, 16H, -O-CH_2-CH_2-), 2.10 (s, 3H, OCH_3), 1.47 (d, 3H, J=6.5 Hz, CH_3).
9. Chen, C. S.; Fujimoto, Y.; Girdaukas, G.; Sih, C. J. *J. Am. Chem. Soc.* **1982**, *104*, 7294–7299.
10. Trost, B. M.; Belletire, J. L.; Goldleski, S.; McDougal, P. G.; Balkovec, J. M.; Baldwin, J. J.; Christy, M. E.; Ponticello, G. S.; Varga, S. L.; Springer, J. P. *J. Am. Chem. Soc.* **1986**, *51*, 2370–2374.
11. Wada, F.; Arata, R.; Goto, T.; Kikukawa, K.; Matsuda, T. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 2061–2063.