Tetrahedron: Asymmetry Vol. 4, No. 11, pp. 2323-2326, 1993
Printed in Great Britain

0957-4166/93 $6.00+.00
Pergamon Press Ltd

Synthesis of Enantiomerically Pure (R)-2-Cycloalken-1-ols using Highly Enantioselective Enzymatic Transesterification

Tetsuya Fukazawa and Toshihiko Hashimoto*

Medicinal Chemistry Research Laboratories, Sankyo Co., Ltd., Shinagawa-ku, Tokyo 140, Japan

(*Received in Japan* 6 *September* 1993)

Abstract: Optically pure (R)-2-cycloalken-1-ols were synthesized *via* highly enantioselective lipase-catalyzed transesterification of 2-substituted cycloalkanols.

Optically active 2-cycloalken-1-ols are versatile starting materials for the synthesis of a variety of biologically active compounds and natural products.[1] Several methods have been developed for the synthesis of (R) and (S)-2-cycloalken-1-ols,[2-7] however, a practical and economical method which provides highly optical purity has not been reported to date.

Over the years, enzyme catalyzed enantioselective transformations in organic media have gained considerable importance for providing enantiomerically pure compounds.[8] In the course of our study on the synthesis of optically active fused indole compounds to develop a new drug[9], a practical and economical method for the synthesis of optically pure (R)-2-cyclohexen-1-ol as a key intermediate was required. Here we wish to report the synthesis of optically pure (R)-2-cycloalken-1-ols **5a-c** *via* highly enantioselective lipase-catalyzed transesterification of 2-substituted cycloalkanols **1a-f**.

The enantioselective enzymatic transesterification reactions were carried out at room temperature in organic solvent using lipase with isopropenyl acetate as the acyl donor[10]. *trans*-2-Substituted cycloalkanols were chosen as substrates instead of 2-cycloalkenol since bulky substituents such as a phenylthio or a iodo group were expected to improve the enantioselection. Lipase P from *Pseudomonas fluorescence* (Amano Pharmaceutical) was selected after screening several commercially available lipases. Among a variety of solvents, such as diisopropyl ether, n-hexane, acetonitrile and tetrahydrofran, diisopropyl ether was best because of the solubility of the substrate and high reaction rate. The results of the reactions are shown in the Table 1.[11]

Scheme I

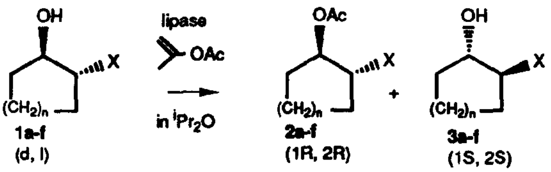

Table 1 Lipase Catalyzed Enantioselective Transesterification

substrate	X	n	reaction time	conversion (%)	2a-f yield[b] (%)	2a-f e.e.[a] (%)	3a-f yield[b] (%)	3a-f e.e.[a] (%)
1a	SPh	2	24	50	47	>99	45	>99
1b	SPh	1	24	50	50	>99	50	>99
1c	SPh	3	24	50	47	>99	50	>99
1d	I	2	6.5	47	47	97	46	96
1e	Br	2	6.5	-[c]	39	93	32	89
1f	Cl	2	6.5	-[c]	46	84	41	79

a) HPLC analysis (Chiralcel OD) was used for **2a,2c** and **3a-c**. **2b** was analyzed by HPLC after hydrolysis to **3b**. **2d-f** were converted to 2-cyclohexenol which was derivatized to the carbamate with chiral isocyanate, and analyzed by HPLC. Optical purity of **3d-f** was determined by the comparison of specific optical rotation between the (R)-acetate **2d-e** and the (S)-acetate prepared from (S)-alcohol **3d-f**. Absolute configurations of **2** and **3** were determined by the derivatization to 2-cycloalken-1-ol and the comparison with the literature[4,7a]. b) Isolated yield. c) Not determined.

Reaction of the compound **1a** was monitored by HPLC (Chiralcel OD, Daicel). The conversion of the reaction reached 50% in 9 hours and remained unchanged even after 24 hours. Enantiomeric purity of the acylated product **2a** was almost 100 % and did not decrease after a prolonged reaction period. The unreacted alcohol **3a** also showed almost 100 % e.e.. The same result was obtained from the cyclopentanol **1b** and the cycloheptanol **1c**. It is presumed from our result and Schneider's report[12] that the presence of a phenyl group in substrates strongly influences the enantioselectivity of lipase. The reaction of compound **1d** which does not contain a phenyl group gave the product **2d** in 97 % e.e. after 6.5 hr, but the enantiomeric purity of **2d** decreased gradually (85 % e.e., 24 hr) when the reaction was continued further. In the reaction of the halogenated substrates, the enantioselectivity decreased as the halogen size became smaller (**1d**, **1e**, **1f**). As these enzymatic reactions were conducted in relatively high concentrations[13] in organic media and furthermore a 100g scale reaction was successfully performed, thus indicating that industrial scale up should be a formidable undertaking.

Cycloalkenols were prepared through two routes shown in scheme II. In the first route[7] (R)-2-cyclohexen-1-ol was prepared from **2a** by oxidation and pyrolysis. Enantiomerically pure acetate **2a** was oxidized by sodium periodate and heated in the presence of $CaCO_3$ followed by hydrolysis, to give an enantiomerically pure (R)-2-cyclohexenol **5a** in 47 % yield from **2a**. The optical purity was determined to be more than 99 % e.e. by derivatization to the carbamate with (S)-(+)-1-(1-naphthyl)ethyl isocyanate, and HPLC analysis. Its specific rotation was higher than the highest one of the antipode reported ($[\alpha]_D$ -112, (c 0.60, $CHCl_3$))[1a]. (R)-2-Cyclopenten-1-ol **5b** and (R)-2-cyclohepten-1-ol **5c** were also prepared from **2b** and **2c** respectively by the same method. The enantiomeric purity of these compounds was also very high as shown in table 2.

In the second route (R)-2-cyclohexenol was prepared by an elimination reaction. Heating of the 2-iodohexyl acetate

Scheme II

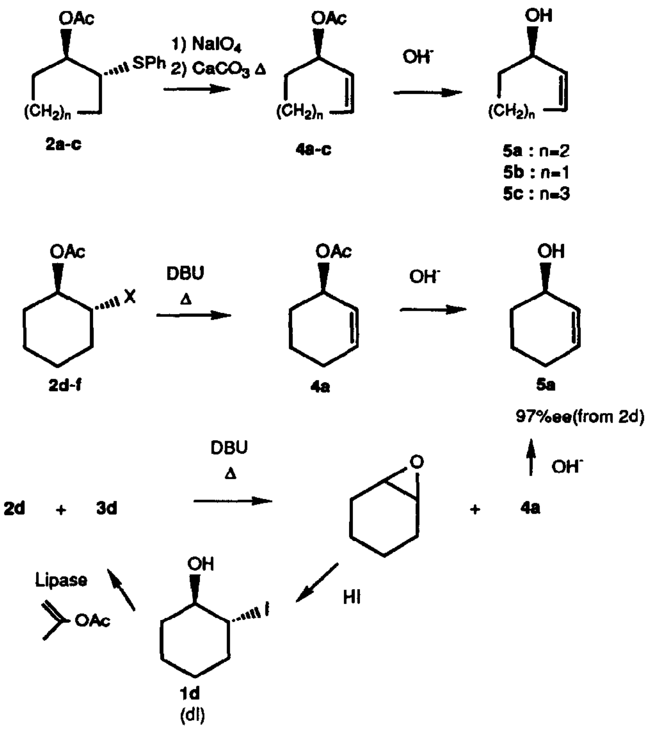

Table 2 Optically Pure 2-Cycloalken-1-ol

Compounds	E.e.	$[\alpha]_D$ ($CHCl_3$)
2-Cyclohexen-1-ol (**5a**)	>99%	+130.6 (c 1.21)
2-Cyclopenten-1-ol (**5b**)	>99%	+116.6 (c 0.64)
2-Cyclohepten-1-ol (**5c**)	>99%	+26.1 (c 1.27)

2d in DBU at 120 °C followed by hydrolysis gave the (R)-2-cyclohexenol 5 (97 % e.e.) in 45 % yield. Under the same condition as the reaction of 2d, the other acetates 2e and 2f were also converted to 5a which exhibited 93 % and 84 % e.e. respectively. When the crude enzymatic reaction product (2d + 3d) was heated in DBU, a mixture of the acetate 4a and cyclohexene oxide was obtained and separated readily by fractional distillation. As the regeneration of substrate racemic 2-iodohexanol 1d from cyclohexene oxide could be successfully implemented, this route can provide a practical and economical method for the synthesis of highly optically pure (R)-2-cyclohexen-1-ol 5a.

In summary, enantiomerically pure (R)-2-cycloalken-1-ols **5a-c** were prepared *via* lipase-catalyzed enantioselective transesterification of 2-substituted cycloalkanols.

Acknowledgement: We thank Dr. K. Kojima for his helpful discussion.

References and Notes

1) (a) Yamada, S.; Takamura, N.; Mizoguchi, T. Chem. Pharm. Bull., **1975**, 23, 2539. (b) Sato, T.; Watanabe, M.; Honda, N.; Fujisawa, T. Chem. Lett., **1984**, 1175. (c) Strauss, H. F.; Wiechers, A. Tetrahedron Lett., **1979**, 4495.
2) Asami, M. Chem. Lett., **1984**, 829.
3) Kawasaki, M.; Suzuki, Y.; Terashima, S. Chem. Lett., **1984**, 239.
4) Sato, T.; Gotoh, Y.; Wakabayashi, Y.; Fujisawa, T. Tetrahedron Lett., **1983**, 24, 4123.
5) Kitamura, M.; Kasahara, I.; Manabe, K.; Noyori, R.; Takaya, H. J. Org. Chem. **1988**, 53, 708.
6) Martin, V.; Woodard, S.; Katsuki, T.; Yamada, Y.; Ikeda, M.; Sharpless, K. J. Am. Chem. Soc., **1981**, 103, 6237.
7) (a) Yamashita, H.; Mukaiyama, T. Chem. Lett., **1985**, 1643. (b) Yamashita, H. Chem. Lett., **1987**, 525.
8) (a) Chen, C.; Sih, C. J. Angew. Chem. Int. Ed. Engl., **1989**, 28, 695. (b) Klivanov, A. Acc. Chem. Res., **1990**, 23, 114. (c) Hsu, S. H.; Wu, S. S.; Wang, Y. F.; Wong, C. H. Tetrahedron Lett., **1990**, 31, 6403.
9) Shimoji, Y.; Tomita, K.; Hashimoto, T.; Saito, F.; Morisawa, Y.; Mizuno, H.; Yorikane, R.; Koike, H. J. Med. Chem., **1992**, 35, 816.
10) Hiratake, J.; Inagaki, M.; Nishioka, T.; Oda, J. J. Org. Chem., **1988**, 53, 6130.
11) Preparation of **3a** and **3b** by asymmetric reduction with Baker's yeast has been reported: Fujisawa, T.; Yamanaka, K.; Mobele, B. I.; Shimizu, M. Tetrahedron Lett. **1991**, 32, 399.
12) Laumen, K.; Seemayer, R.; Schneider, M. P. J. Chem. Soc., Chem. Commun., **1990**, 49.
13) A general experiment is as follows: Lipase P (5.15 g) and Isopropenyl acetate (2.3 ml) were added to a solution of **2b** (2.0 g) in diisopropyl ether (52 ml) at 25°C. After stirring for 24 hrs at the same temperature, lipase was filtered off and washed with diisopropyl ether. The filtrate and the washing were combined and concentrated under reduced pressure. The residue was chromatographed on a silica gel eluting with cyclohexane - ethyl acetate (20 : 1) to give **2b** (1.21 g, >99 % e.e.) and **3b** (0.99 g, >99 % e.e.).