Tetrahedron Letters,Vol.30,No.51,pp 7165-7168,1989 0040-4039/89 $3.00 + .00
Printed in Great Britain Pergamon Press plc

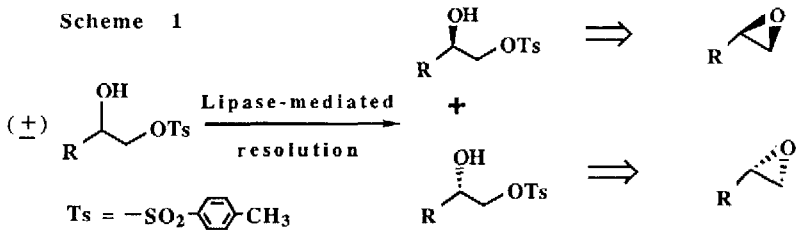
# A CHEMOENZYMATIC ACCESS TO OPTICALLY ACTIVE 1,2-EPOXIDES

Ching-Shih Chen* and Yeuk-Chuen Liu
Department of Pharmacognosy and Environmental Health Sciences
College of Pharmacy, University of Rhode Island
Kingston, RI 02881, USA

**Summary:** Lipase-catalyzed transacylation in organic media was employed to produce optically active α-hydroxy tosylate which could be readily converted to the corresponding 1,2-epoxides with high optical purity.

Conventionally, access to chiral epoxides has relied mainly upon naturally existing chirons such as D-mannitol[1], S-amino acids[2], optically pure α-hydroxy acids[3], etc. Until recently, a number of asymmetric epoxide syntheses have been explored, of which the Sharpless epoxidation merits particular attention because of its predictable high stereochemical selectivity[4]. However, this transition-metal catalysis generally requires allylic alcohol activation to attain high optical yields. In addition to these chemical means, microbial epoxidation of alkenes has also been exploited for the preparation of optically active (R)-epoxyalkanes ($C_6$ - $C_{20}$)[5]. In general, this biological transformation generates products with enantiomeric purities ranging from 70% to 100% in poor chemical yields, largely depending on the substrate, the species of microorganism and the growth conditions employed in the fermentative process. Herein, we describe a facile chemoenzymatic route that allows the preparative synthesis of various optically active 1,2-epoxides, especially those bearing no other functional groups.

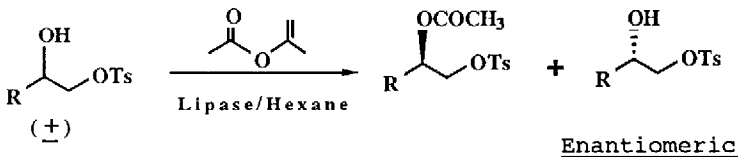
Scheme 1




As shown in Scheme 1, the use of the α-hydroxy tosylate[6] in conjunction with the lipase-mediated resolution permits a direct entry to both antipodes of the title compounds. In light of the potential advantages of enzyme catalysis in nonaqueous media[7], the kinetic resolution was conducted by means of enantioselective acyl-transfer in apolar solvents. Table 1 thus

summarizes the results of the bioconversion in which the acylation of different α-hydroxy tosylates, (±)-1a-e, by isoprenyl acetate[8] was effected by various microbial lipases. In a typical experiment, 4 mmol of substrate, dissolved in 6 ml of isoprenyl acetate, was exposed to crude lipase powder (400 mg) suspended in 18 ml of hexane. After incubating the suspension on a rotary shaker (250 rpm) at 30°C for the indicated time, the reaction was terminated by removing the lipase through centrifugation. After evaporating the solvent *in vacuo*, the resulting residue was subjected to silica gel chromatographic separation. The enantiomeric excess of the product (ee(P)) and remaining substrate (ee(S)) was determined by HPLC analysis[9] after converting them to the corresponding diastereomeric (S)-MTPA esters; the extent of conversion (c) and the E value were then calculated according to the equations developed by Sih *et al.*[10] Among a variety of microbial enzymes screened, lipases from *Pseudomonas fluorescens* and *Humicola lanuginosa* proved to be highly enantiospecific in catalyzing the esterification of the alcohols carrying aliphatic and aromatic side chains, respectively.

Table 1. Lipase-mediated enantiospecific esterification of (±)-1a-e.

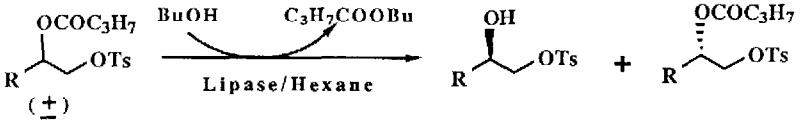



| R | Lipase Origin | R/S[c] | Incubation Time (h) | C (%) | Enantiomeric Excess ee(P) ($[\alpha]_D^{25}$)[d] | ee(S) ($[\alpha]_D^{25}$)[d] | E |
|---|---|---|---|---|---|---|---|
| $ClCH_2$- 1a | *Pseudomonas fluorescens*[a] | S | 68 | 47 | 0.83 (+6.2°) | 0.75 (+3.0°) | 24 |
| n-$C_4H_9$- 1b | *Pseudomonas fluorescens* | R | 92 | 43 | 0.86 (+13.4°) | 0.66 (+4.2°) | 26 |
| n-$C_{10}H_{21}$- 1c | *Pseudomonas fluorescens* | R | 116 | 30 | 0.87 (-3.6°) | 0.37 ( - ) | 21 |
| Ph- 1d | *Humicola lanuginosa*[b] | S | 144 | <5 | 0.95 | - | - |
| $PhOCH_2$- 1e | *Humicola lanuginosa* | R | 144 | <5 | 0.85 | - | - |

[a] Amano lipase P-30; [b] Amano lipase R-10; [c] stereochemical preference[11]; [d] in $CHCl_3$.

However, as shown in Table 1, Humicola lipase-mediated acylation of 1d and 1e proceeded at extremely slow rates, which would prohibit the preparation of both compounds in quantities. Nevertheless, **in principle, the efficiency and the degree of stereoselectivity of an enzymatic transacylation may vary with different forms of the substrate**[7b]. To test this hypothesis, the butyl esters of 1a-e, (±)-2a-e, were exposed to the lipases separately in hexane containing n-butyl alcohol as the acyl acceptor[12] (Table 2). In comparison to the aforementioned results, Humicola lipase catalyzed acyl-transfer from 2d and 2e to butanol at much faster rates without losing its selectivity. Although such an enhancement in reaction rates was not noted for Pseudomonas lipase, the enzyme exhibited higher enantiospecificity in catalyzing the deacylation of 2a and 2c than its acylation counterparts.

Table 2. Lipase-Catalyzed Enantiospecific deacylation of (±)-2a-e.




| R | Lipase Origin | R/S[c] | Incubation Time (h) | C (%) | Enantiomeric Excess ee(P) ($[\alpha]_D^{25}$)[d] | ee(S) ($[\alpha]_D^{25}$)[d] | E |
|---|---|---|---|---|---|---|---|
| $ClCH_2$- 2a | Pseudomonas fluorescens | S | 96 | ~50 | ~0.96 (-3.9°) | ~0.96 (-5.8°) | >100 |
| n-$C_4H_9$- 2b | Pseudomonas fluorescens | R | 120 | 25 | 0.90 (-5.7°) | 0.31 ( - ) | 25 |
| n-$C_{10}H_{21}$- 2c | Pseudomonas fluorescens | R | 120 | 26 | >0.98 (-8.8°) | 0.34 ( - ) | 92 |
| Ph- 2d | Humicola lanuginosa | S | 120 | 36 | 0.96 (+42°) | 0.54 ( - ) | 84 |
| | Candida cylindracea[a] | S | 120 | 42 | 0.95 ( - ) | 0.70 ( - ) | 82 |
| | Alcalligenes sp.[b] | S | 120 | 42 | >0.98 ( - ) | 0.72 ( - ) | >100 |
| $PhOCH_2$- 2e | Humicola lanuginosa | R | 120 | 33 | 0.84 (+5.6°) | 0.42 ( - ) | 17 |

[a] Sigma crude powder; [b] Meito-Sangyo lipase PL; [c] stereochemical preference[11]; [d] in $CHCl_3$.

Optically active 1 thus obtained by either route could be readily

converted to the corresponding epoxides by alkaline treatments[13] in high yields. This approach is currently employed to produce useful chiral epoxides for natural product synthesis in this laboratory.

**Acknowledgement.** The authors are indebted to the Petroleum Research Fund administered by American Chemical Society for financial support.

**REFERENCES.**

1. J. J. Baldwin, A. W. Raab, K. Mensler, B. H. Arison, and D. E. McClure (1978) J. Org. Chem., 43, 4876-4878.
2. B. Koppenhoefer, R. Weber, and V. Schurig (1982) Synthesis, p.316-318.
3. For examples, a) Diethyl (2R,3R)-tartrate: E. Hungerbuhler, D. Seebach, and D. Wasmuth (1981) Helv. Chim. Acta, 64, 1467-1487; b) ethyl (S)-malate: D. L. Boger, and J. S. Panek (1981) J. Org. Chem., 46, 1208-1210.
4. B. E. Rossiter (1985) in Asymmetric Synthesis (J. D. Morrison, ed.) Vol. 5, Chapter 7. Academic Press, Orlando.
5. a) H. Ohta, and H. Tetsukawa (1978) J. Chem. Soc. Chem. Commun., p.849-850; b) M.-J. de Smet, B. Witholt, and H. Wynberg (1981) J. Org. Chem., 46, 3128-3131, and references therein.
6. Compounds 1a and 1d were prepared by reacting epichlorohydrin and styrene oxide, respectively, with 1.1 equiv. of p-toluenesulfonic acid in $CH_2Cl_2$ under reflux for 3 h. Compounds 1b, 1c, and 1e were prepared by the regioselective tosylation of the corresponding diols.
7. a) M. W. Empie, and A. Gross (1988) Ann. Rep. Med. Chem., 23, 305-313; b) C. S. Chen, and C. J. Sih (1989) Angew. Chem. Int. Ed. Engl., 28, 695-707.
8. Enol esters such as isoprenyl acetate and vinyl acetate have been favorably used as acyl donors in lipase-catalyzed transesterification due to their ability to shift the equilibrium toward the forward direction. Y.-F. Wang, J. J. Lalonde, M. Momongan, D. E. Bergbreiter, and C.-H. Wong (1988) J. Am. Chem. Soc., 110, 7200-7205.
9. A Whatman Partisil (10μm) column was used. The column was eluted with a solvent mixture of hexane-ether (4:1). Flow rates, 1a-MTPA: 2.0 ml/min; 1b- and 1c-MTPA: 1.2 ml/min; 1d- and 1e-MTPA: 1.5 ml/min. Retention times, 1a-MTPA, R: 7 min 40 sec, S: 8 min 40 sec; 1b-MTPA, S: 7 min, R: 7 min 40 sec; 1c-MTPA, S: 5 min 20 sec, R: 5 min 50 sec; 1d-MTPA, S: 6 min 40 sec, R: 7 min 30 sec; 1e-MTPA, R: 9 min 40 sec, S: 10 min 40 sec.
10. C. S. Chen, Y. Fujimoto, G. Girdaukas, and C. J. Sih (1982) J. Am. Chem. Soc., 104, 7294-7299.
11. The products obtained were transformed to their corresponding epoxides, and the absolute configuration of each compound was thus determined by comparing the optical rotation with that reported in literature or of the authentic compound from Aldrich Chemical Co. (Milwaukee, USA)
12. The reaction conditions were the same as described for the acylation of 1 except that isoprenyl acetate was replaced by the same amount of butyl alcohol.
13. 1a: see ref. 1; 1b-e: 1 equiv. $CH_3ONa/CH_3OH$; 0° - r.t.; 1h.

(Received in USA 23 August 1989)