Lipase-Catalyzed Transesterification of *trans*-2,5-Disubstituted Pyrrolidines: Effect of Substituent on Enantioselectivity

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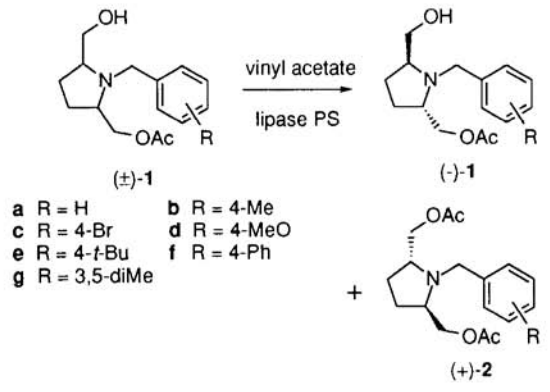
Kinetic resolution of racemic N-arylmethylated *trans*-2-acetoxy-methyl-5-hydroxymethylpyrrolidines by using lipase-catalyzed transesterification has been studied. The enantioselectivity depends significantly on the structure of the aryl ring and N-3,5-dimethylbenzylpyrrolidine was found to be the best substrate for the present reaction.

Chiral C_2-symmetric *trans*-2,5-disubstituted pyrrolidines have been demonstrated to be efficient chiral auxiliaries for a variety of asymmetric syntheses.[1] Furthermore, they serve as chiral building blocks for the synthesis of pyrrolidine alkaloids possessing biological activity.[2] Many enatiospecific syntheses of optically active *trans*-2,5-disubstituted pyrrolidines using chiral starting materials,[3] or double asymmetric dihydroxylation of symmetric terminal dienes[4] has been reported so far.

Recently, lipases have been widely used in organic synthesis, in particular, kinetic resolution of racemic alcohols.[5] We previously reported the synthesis of optically active N-benzyl-*trans*-2,5-bis(acetoxymethyl)pyrrolidine by using lipase-catalyzed hydrolysis as a key step.[6] On the other hand, Sibi *et al.* reported their synthesis by using lipase-catalyzed sequential acylation of racemic *trans*-2,5-bis(hydroxymethyl)pyrrolidine.[7] However, the methodology provided equal amount of the starting diol, monoacetate, and diacetate and the enantiomeric excess (ee) of the monoacetate showed quite low.

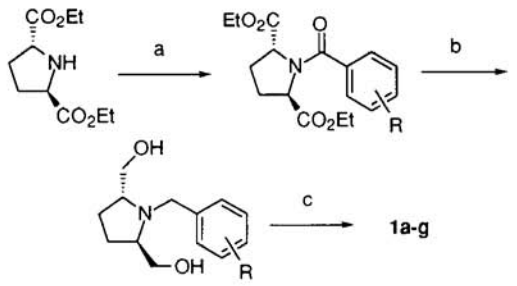
In this paper, we describe highly efficient lipase-catalyzed transesterification of racemic *trans*-2,5-disubstituted pyrrolidines taking advantage of the active site model of lipase from *Pseudomonas cepacia* (PCL), which has been recently proposed to explain and predict the stereochemical outcome for the kinetic resolution of secondary alcohols and primary alcohols by substrate-mapping.[8-10]



Scheme 1.

The lipase-catalyzed transesterification of *trans*-2,5-bis (hydroxymethyl)pyrrolidine afforded the complex reaction mixture as mentioned above and so it is not simple to evaluate the effectiveness of kinetic resolution, E value.[11] Therefore, we examined the lipase-catalyzed acylation of the corresponding monoacetate, since the second acylation step is expected to be highly enantioselective judging from the lipase-catalyzed hydrolysis of the similar substrate.[6]

The substrates were prepared from readily available *trans*-2,5-diethoxycarbonyl pyrrolidine,[6] which was acylated with various substituted benzoyl cholide, followed by reduction with $LiAlH_4$ to give the corresponding diols (Scheme 2). The subsequent acetylation of the resulting diols with acetic anhydride in ether at 0 °C afforded the monoacetates in 57-79% yield.



a) RC_6H_4COCl, DMAP, Et_3N, CH_2Cl_2, rt (70-93%). b) $LiAlH_4$, THF, reflux (94-99%). c) Ac_2O, ether, 0 °C (57-79%).

Scheme 2.

The enantioselective acylations of the monoacetate **1a-g** were carried out in hexane at 30 °C with *Pseudomonas cepacia* lipase (lipase Amano PS, one of the most popular lipase used in organic synthesis) and vinyl acetate as an acylating agent. The ee's of the monoacetate and diacetate were determined by HPLC using a column with a chiral stationary phase.[12] The absolute configurations of all the diacetates **2a-g** were determined to be 2R, 5R by comparison of specific rotations with the authentic specimens by the similar procedure as described Ref. 6. The results are summarized in Table 1.

Table 1. Lipase-catalyzed transesterification of monoacetates (**1a-g**)[a]

Substrate	Time h	(S,S)-**1** %ee	(R,R)-**2** %ee	Conv. %	E
1a	2	35	82	30	15
1b	1	57	77	40	13
1c	1.5	97	60	60	16
1d	1.5	99	56	60	20
1e	2	84	82	50	26
1f	4	19	63	23	5.3
1g	2.5	33	95	26	50
1g	4	98	84	54	52

[a]The reaction condition: A mixture of substrate (0.5 mmol), vinyl acetate (1 mmol), lipase PS (150 mg), and hexane (5 ml) was stirred at 30 °C.

The lipase-catalyzed acylation of the substrate possessing an electron-withdrawing (**1c**, R=Br) or electron-donating (**1d**, R=OMe) substituent in the *para*-position of the aromatic ring showed enantioselectivity comparable to that of **1a** (R=H), suggesting that electronic effect does not play a major role in enantioselection, although the reaction rate was increased. The substrate (**1e**) possessing bulky *tert*-butyl substituent showed higher enantioselectivity, while acylation of the substrate (**1f**) with a planar and larger phenyl substituent resulted in a significantly lower enantioselectivity and a decrease of the reaction rate.[13] This result suggests that the larger *para*-phenyl group at the aromatic ring may not allow only slow-reacting (S,S)-enantiomer but also fast-reacting (R,R)-enantiomer to be accommodated to a hydrophobic binding site (Figure 1. **A**, R_1=Ph, R_2=H) and led to the slow reaction and poor enantioselectivity.

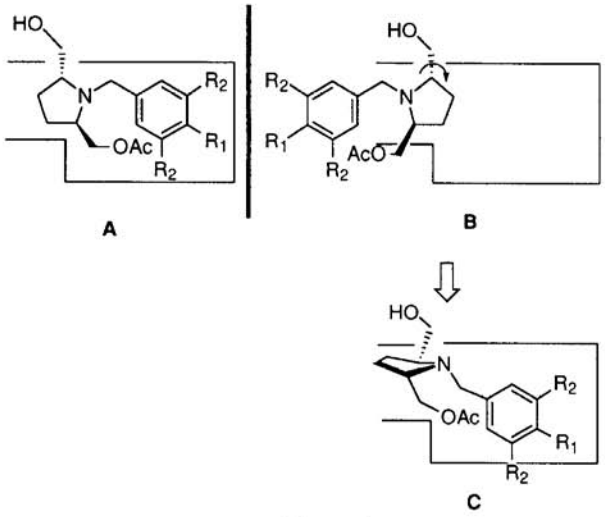


Figure 1.

On the other hand, 3,5-dimethylbenzyl derivative (**1g**) was efficiently resolved substrate for PCL (E=50-52). Generally, it is difficult to discriminate two enantiomers of primary alcohols in lipase-catalyzed kinetic resolution due to the flexibility of rotation of C-CH_2OH such as shown Figure 1. **B**.[8] However, this result suggests that introduction of the *meta*-dimethyl group at the aryl ring should lead (R,R)-enantiomer to be accommodated (Figure 1. **A**, R_1=H, R_2=Me) and (S,S)-enantiomer to be not accommodated in the hydrophobic site of active site model (Figure 1. **C**, R_1=H, R_2=Me) and therefore increase the enantioselectivity. Thus it is noteworthy that the shape of substrate is more crucial than the size for the enantioselectivity of PCL, which is in accordance with Theil's findings.[9]

In summary, we have demonstrated that the lipase-catalyzed kinetic resolution of *trans*-2,5-disubstituted pyrrolidine using PCL was accomplished by efficient modification of the substrate structure and this substrate-tuning strategy should be predictable and effective for enhancing the enantioselectivity of PCL toward primary alcohols which are generally poor resolved-substrates, compared with secondary alcohols. Further studies on the substituent effect on the enantioselectivity by molecular modeling are now under way.

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References and Notes

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1 a) J. K. Whitesell, *Chem. Rev.*, **89**, 1581 (1989). b) Y. Kawanami, I. Fujita, S.Ogawa, and T. Katsuki, *Chem. Lett.*, **1989**, 2063. c) Y. Kawanami and K. Katayama, *Chem. Lett.*, **1990**, 1749. d) K. Fuji, M. Node, Y. Naniwa, and T. Kawabata, *Tetrahedron Lett.*, **31**, 3175 (1990). e) V. Gouverneur and L. Ghosez, *Tetrahedron Lett.*, **32**, 5349 (1991). f) H. Moon, S. W. E. Eisenberg, M. E. Wilson, N. E. Schore, and M. J. Kurth, *J. Org. Chem.* **59**, 6504 (1994).

2 For example, G. Impellizzeri, S. Mangiafico, G. Oriente, M Piateli, and S. Sciuto, *Phytochemistry*, **14**, 1549 (1975).

3 M. Pichon and B. Figadere, *Tetrahedron: Asymmetry*, **7**, 927 (1996) and references cited therein.

4 H. Takahata, S. Takahashi, S. Kouno, and T. Momose, *J. Org. Chem.*, **63**, 2224 (1998).

5 a) R. D. Schmid and R. Verger, *Angew. Chem. Int. Ed. Engl.*, **37**, 1608 (1998). b) K. Faber and S. Riva, *Synthesis*, **1992**, 895. c) C. -H. Wong and G. M. Whitesides, "Enzymes in Synthetic Organic Chemistry," Pergamon, Oxford (1994).

6 Y. Kawanami, H. Moriya, and Y. Goto, *Chem. Lett.*, **1994**, 1161; Y. Kawanami, H. Moriya, Y. Goto, K. Tsukao, and M. Hashimoto, *Tetrahedron*, **52**, 565 (1996).

7 M. P. Sibi and J. Lu, *Tetrahedron Lett.*, **35**, 4915 (1994).

8 A. N. E. Weissfloch and R. J. Kazlauskas, *J. Org. Chem.*, **60**, 6959 (1995).

9 K. Lemke, M. Lemke, and F. Theil, *J. Org. Chem.*, **62**, 6268 (1997).

10 For the related lipase YS; K. Naemura, H. Ida, and R. Fukunaga, *Bull. Chem. Soc. Jpn.*, **66**, 573 (1993); K. Naemura, R. Fukuda, N. Takahashi, M. Konishi, and Y. Tobe, *Tetrahedron Asymmetry*, **4**, 911 (1993); K. Naemura, R. Fukuda, M. Murata, M. Konishi, K. Hirose, and Y. Tobe, *Tetrahedron Asymmetry*, **6**, 2385 (1995).

11 C. -S. Chen, Y. Fujimoto, G. Girdaukas, and C. J. Sih, *J. Am. Chem. Soc.*, , **104**, 7294 (1982); Z.-W. Guo, S. -H. Wu, C. -S. Chen, G. Girdaukas, and C. J. Sih, *J. Am. Chem. Soc.*, **112**, 4942 (1990); G. Caron and R. Kazlauskas, *J. Org. Chem.*, **56**, 7251 (1991).

12 CHIRALCEL OJ (Daicel Chemical Industries, Ltd.), for example, **1g**: 19 and 27 min, **2g**: 17 and 25 min, hexane/2-propanol=20/1. The diacetate **2f** could not be separated and so it was determined after conversion to **2a**.

13 Kazlauskas *et al.* also found that increasing the difference in the size of the substituents of primary alcohols did not always provided an increase in the enantioselectivity of PCL, see Ref. 8.