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Lipase-Catalyzed Kinetic Resolution of *trans*-2,5-Disubstituted Pyrrolidine Derivatives

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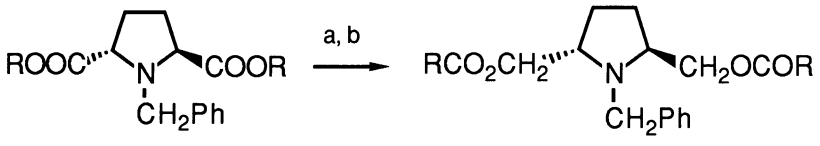
Enantioselective preparation of (-)-(2S,5S)-N-benzyl-*trans*-2,5-bis(acetoxymethyl) pyrrolidine was carried out by the lipase-catalyzed hydrolysis of racemic diacetate in phosphate buffer contained 20% DMSO.

Chiral *trans*-2,5-disubstituted pyrrolidine derivatives with C_2-axis of symmetry have been shown as chiral auxiliaries for various asymmetric syntheses[1] as well as chiral building blocks for the synthesis of pyrrolidine alkaloids[2]. Some stereoselective syntheses of optically active pyrrolidine derivatives using chiral starting materials have been reported.[3] Norin *et al.*[4] reported that pig liver esterase (PLE)-catalyzed hydrolysis of racemic *trans*-2,5-bis(methoxycarbonyl)pyrrolidine (**1a**) proceeded with only moderate enantioselectivity, although high enantioselectivity was observed for the corresponding meso *cis*-derivative. Our initial attempts to resolve the diesters **1a** and **1b** by lipase, which is inexpensive and has been used for enantioselective enzyme-catalyzed reactions, were also unsuccessful. We therefore expected the diacylates **2** to be appropriate substrates for lipase-catalyzed hydrolysis, taking account of the active-site model proposed by Jones[5] for PPL-catalyzed hydrolysis of primary acetates as shown in Fig. 1. Herein we report that the lipase-catalyzed hydrolysis of racemic N-benzyl-*trans*-2,5-bis(acyloxymethyl) pyrrolidine (**2**) proceeded with high enantioselectivity.

The diacylates **2a**, **2b**, and **2c** were prepared from **1b** by reduction and acylation in 80-95% yields. The hydrolyses of the diacylate **2** (1 mmol) with lipase (50 mg) in 0.05 M phosphate buffer solution (pH 7.5, 10 ml) were carried out at 30 °C and the results are summarized in Table 1. Among the lipases screened, lipase PS (from *Pseudomonas* sp., Amano) was selected for this kinetic resolution of (±)-**2** (entries 1-3). Addition of water miscible organic co-solvent influenced the enantioselectivity and 20% dimethyl sulfoxide (DMSO) in the phosphate buffer was found to be the optimal solvent system. The effect of substituent (R) of the diacylates was



1a : R=CH_3
1b : R=CH_2CH_3

2a : R=CH_3
2b : R=CH_2CH_3
2c : R=$(CH_2)_2CH_3$

a) $LiAlH_4$, THF. b) $(RCO)_2O$, Et_3N, cat. DMAP, CH_2Cl_2.

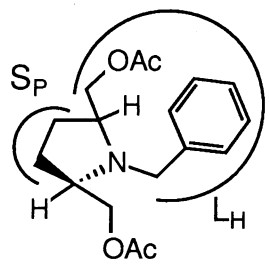
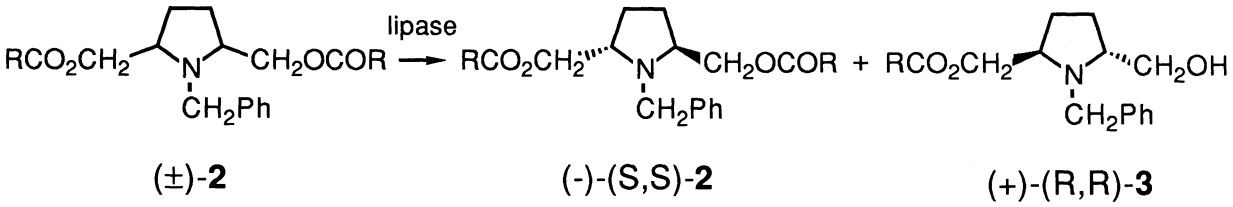


Fig. 1.



(±)-**2** (-)-(S,S)-**2** (+)-(R,R)-**3**

Table 1. Lipase-catalyzed hydrolysis of N-benzyl-*trans*-2,5-disubstituted pyrrolidine (**2**)[a]

Entry	Lipase[b]	Substrate R	Time h	(-)-(S,S)-**2** Yield/%	(-)-(S,S)-**2** ee/% [c]	(+)-(R,R)-**3** Yield/%	(+)-(R,R)-**3** ee/% [c]
1	PPL	**2a** CH_3	4	58	45	34	55
2	PFL	**2a** CH_3	4	45	52	24	81
3	PS	**2a** CH_3	4	54	65	30	75
4	PS	**2a** CH_3	8	38	95	23	62
5	PS	**2b** CH_2CH_3	3.5	39	88	19	44
6	PS	**2c** $(CH_2)_2CH_3$	3	27	61	17	45

a) Conditions; 0.05 M phosphate buffer, pH 7.5, 20% DMSO at 30 °C. b) PPL (Sigma), PFL (Aldrich), PS (Amano). c) Determined by HPLC analysis with Chiralcel OJ (Daicel), hexane / *i*-PrOH= 9/1. The absolute configurations were determined by transformation to the diol [3b].

also examined and the acetate **2a** was found to be the best substrate. The hydrolysis of the dipropionate **2b** and the dibutyrate **2c** proceeded rapidly but with moderate enantioselectivity (entries 4-6). Thus, the lipase-catalyzed kinetic resolution of racemic diacetate **2a** using lipase PS afforded (-)-(2S,5S)-**2a** with 95% ee in 38% yield.

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