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Substituent effect on the enantioselectivity in lipase-catalyzed transesterification of *trans*-2,5-disubstituted pyrrolidines

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Abstract—Kinetic resolutions of *N*-substituted benzyl-*trans*-2-acetoxymethyl-5-(hydroxymethyl)pyrrolidines using lipase-catalyzed transesterification have been systematically studied. The enantioselectivity depends significantly on the position of substituent at the aromatic ring and *N*-3,5-dimethylbenzyl group was found to transform *trans*-2,5-disubstituted pyrrolidine derivative into an efficiently-resolved substrate. Furthermore, the enantioselectivity could be improved up to $E=108$ using the immobilized lipase in alkyl silica gel. © 2001 Elsevier Science Ltd. All rights reserved.

1. Introduction

Recently, lipases have been widely used in organic syntheses, in particular, kinetic resolutions of racemic alcohols because of broad substrate specificities and high enantioselectivities.[1] Although lipases show high enantioselectivity toward secondary alcohols, the enantioselectivity of primary alcohols is generally lower than that of secondary alcohols and is the reversal of enantiopreference when the stereocenter lacks an oxygen atom as shown in Fig. 1. Because it is basically due to the flexibility of the stereogenic center that is remote from the catalytic site.[2]

In accompanying the preparation of optically pure chiral C_2-symmetric *trans*-2,5-disubstituted pyrrolidines,[3] we encountered the challenging question how the enantioselectivity in kinetic resolution of primary alcohols can be increased. Chiral *trans*-2,5-disubstituted pyrrolidines have been demonstrated as efficient chiral auxiliaries for a variety of asymmetric syntheses[4] beside chiral building blocks for the synthesis of pyrrolidine alkaloids possessing biological activity.[5] The several stereoselective syntheses via chiral starting materials[6] and double asymmetric dihydroxylation of symmetric terminal dienes[7] have been reported so far. We previously reported that the lipase-catalyzed transesterifications of *N*-substituted benzyl-*trans*-2-acetoxymethyl-5-(hydroxymethyl)-pyrrolidines possessing an electron-withdrawing or electron-donating substituent and *tert*-butyl group in the *para*-position of the aromatic ring showed moderate enantioselectivities and 3,5-dimethyl benzyl derivative **1f** afforded highest enantioselecitivity for lipase PS ($E=52$).[8] These results suggested that the substituent effect on the enantioselectivity is crucial in orientation rather than polarity and bulkiness. In order to confirm these findings, we have further investigated the

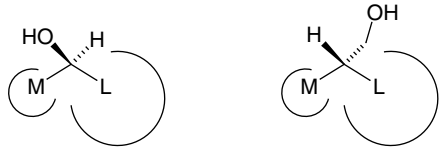
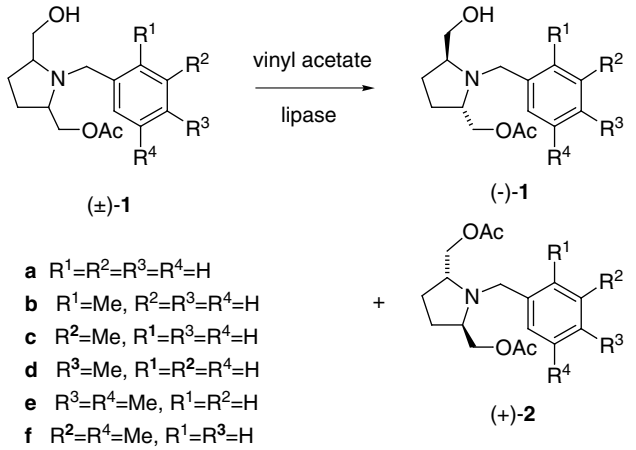


Figure 1. Empirical rules for the lipase-catalyzed kinetic resolution of secondary and primary alcohols.



Scheme 1.

Keywords: lipase; transesterification; enantioselectivity; pyrrolidine.
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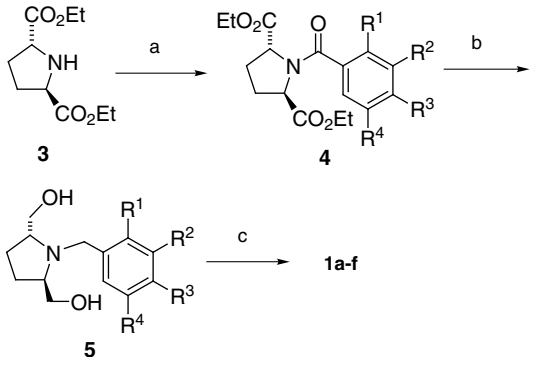
kinetic resolutions of a series of *N*-substituted benzylpyrrolidines bearing the same size of methyl group but in different positions. In this paper, we describe the study on the substituent effect on the enantioselectivity of lipase-catalyzed transesterifications of various *N*-substituted benzyl-*trans*-2-acetoxymethyl-5-(hydroxymethyl)pyrrolidines (Scheme 1).

2. Results and discussion

The substrates were prepared as shown in Scheme 2: *trans*-2,5-diethoxycarbonyl pyrrolidine[3] was acylated with various substituted benzoyl chloride, followed by reduction with $LiAlH_4$ to give the corresponding diols. The subsequent acetylation with acetic anhydride in ether at 0°C afforded the corresponding monoacetate in 50–75% yield.

The enantioselective acylations of a series of the monoacetates **1a**–**f** with lipase PS (Amano) from *Pseudomonas cepacia* (PCL) and lipase AK (Amano) from *P. fluorescens* (PFL) and vinyl acetate as an acylating agent were carried out in hexane at 30°C. In order to compare the reaction rate conveniently, the reactions were carried out for the same reaction time (3 h for PS and 1 h for AK). The enantiomeric excess (ee) values of the monoacetates **1a**–**f** and the diacetates **2a**–**f** were determined by HPLC using a chiral column. The absolute configurations of all the diacetates were determined to be (2*R*,5*R*) by comparison with the authentic diacetates by the similar procedure as described in Ref. 3. These results are summarized in Table 1.

The lipase PS-catalyzed acylations of the substrates (**1b**–**d**) possessing a methyl substituent at the *ortho*-, *meta*-, and *para*-position of the aromatic ring showed similar moderate enantioselectivities as that of **1a** (entries 2, 3, and 4 vs 1), although the reaction rates were increased. On the other hand, the lipase AK-catalyzed acylations of the substrates (**1b** and **c**) bearing a methyl group at its *ortho*- or *meta*-position proceeded with a slightly higher enantioselectivity than that of **1a** (entries 8 and 9 vs 7). Furthermore, significantly higher enantioselectivities were observed in the acylations of the substrate **1e** bearing 3,4-dimethyl groups and, particularly, the substrate **1f** with 3,5-dimethyl group (entries 5, 6, 11 and 12). It is noted that symmetric 3,5-dimethylbenzyl group as the *N*-protecting one effectively



Scheme 2. (a) R^{n}ArCOCl, DMAP, Et_3N, CH_2Cl_2, rt (83–90%); (b) $LiAlH_4$, THF, reflux; (c) Ac_2O, ether, 0°C (59–76%).

Table 1. Substituent effect on the enantioselectivity in lipase-catalyzed transesterifications of *trans*-2,5-disubstituted pyrrolidines

Entry	Substrate, R	Lipase	Time (h)	%ee[a]		c[b]	E[c]
				(*S*,*S*)-**1**	(*R*,*R*)-**2**		
1	**1a** H	PS	3	45	84	0.35	18
2	**1b** 2-Me	PS	3	58	78	0.42	14
3	**1c** 3-Me	PS	3	81	76	0.52	18
4	**1d** 4-Me	PS	3	87	70	0.55	16
5	**1e** 3,4-diMe	PS	3	99	67	0.60	25
6	**1f** 3,5-diMe	PS	3	56	94	0.38	52
7	**1a** H	AK	1	50	61	0.45	7
8	**1b** 2-Me	AK	1	36	82	0.30	15
9	**1c** 3-Me	AK	1	45	80	0.36	14
10	**1d** 4-Me	AK	1	82	48	0.63	7
11	**1e** 3,4-diMe	AK	1	96	71	0.57	22
12	**1f** 3,5-diMe	AK	1	71	85	0.45	26

Reaction conditions: a mixture of substrate (0.2 mmol), vinyl acetate (0.8 mmol), and lipase (60 mg) in hexane (2 ml) was stirred at 30°C.
[a] Determined by HPLC using a Dicel CHIRALCEL OJ.
[b] Conversion calculated from c=ee(*S*,*S*)/[ee(*S*,*S*)+ee(*R*,*R*)].[9]
[c] Calculated from E=ln[(1−c)(1−ee(*S*,*S*))]/ln[(1−c)(1+ee(*S*,*S*))].[9]

modified *trans*-2,5-disubstituted pyrrolidine derivative into an efficiently-resolved substrate.

Recently, in order to increase the activity and stability of lipase, immobilizations of lipases have been studied and, among them, the lipases immobilized in alkyl silica gel have been shown to exhibit not only increased activity and stability but also increased enantioselectivity.[10] Next, the supported lipases by lyophilizing a mixture of lipase and celite in pH 7 phosphate buffer[11] and the immobilized lipases (PCL and PFL, Fluka) in alkyl silica gel were examined in this kinetic resolution of **1f**. These results were summarized in Table 2.

The supported lipase PS and AK provided slight increases of reaction rates but similar enantioselectivities. Using the immobilized lipases in alkyl silica gel resulted in increase of the enantioselectivities. In particular, the immobilized PFL afforded excellent high E-value (E=108). Again the substituent effect on the enantioselectivity was examined in the transesterifications of **1a**–**f** employing the immobilized PFL. As predicted, the similar tendency as

Table 2. Lipase-catalyzed transesterifications of **1f**

Lipase	Time (h)	%ee[a]		c[b]	E[c]
		(*S*,*S*)-**1**	(*R*,*R*)-**2**		
PS	3	56	94	0.38	52
AK	1	71	85	0.45	26
PS[d]	3	64	91	0.41	42
AK[d]	1	81	83	0.49	27
PCL[e]	3	34	96	0.26	63
PFL[e]	2	60	97	0.38	108

Reaction conditions: a mixture of substrate (0.2 mmol), vinyl acetate (0.8 mmol), and lipase (60 mg) in hexane (2 ml) was stirred at 30°C.
[a] Determined by HPLC using a Dicel CHIRALCEL OJ.
[b] Conversion calculated from c=ee(*S*,*S*)/[ee(*S*,*S*)+ee(*R*,*R*)].[9]
[c] Calculated from E=ln[(1−c)(1−ee(*S*,*S*))]/ln[(1−c)(1+ee(*S*,*S*))].[9]
[d] Lyophilized in celite and pH 7 phosphate buffer.
[e] Immobilized in sol–gel-AK (Fluka).

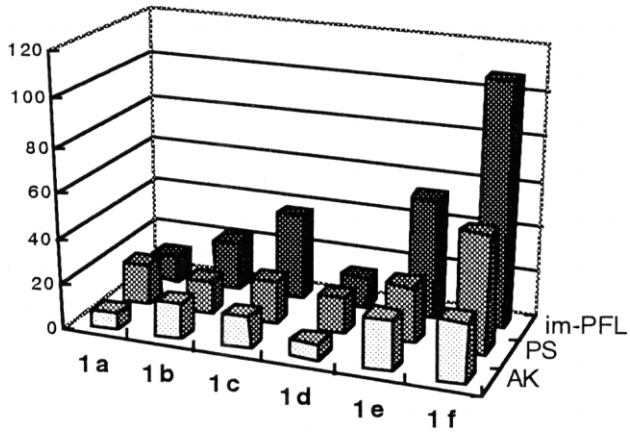


Figure 2. Effect of substituent on the enantioselectivity.

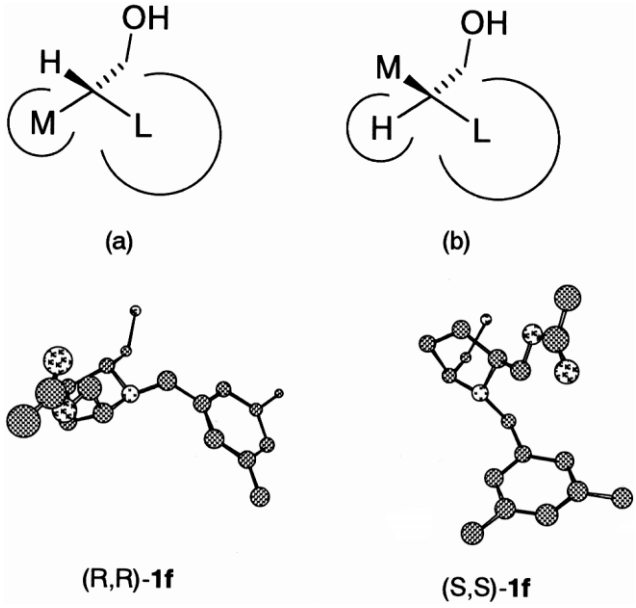


Figure 3. Models of the (a) fast-reacting enantiomer; (b) slow-reacting enantiomer, and energy minimized conformations of (*R*,*R*)- and (*S*,*S*)-enantiomers.

lipase AK (PFL) was observed as shown in Fig. 2 and the substrate **1f** was found to be an excellent substrate.

Although the active site model of PCL by substrate mapping[12] and molecular modeling of transition state analog bound to PCL[13] or RDL (lipase from *Rhizomucor miehei*)[14] based on X-ray structure have been reported, the simple box model proposed by Naemura et al.[15] and other[16] seems to be sufficient to explain our results. Generally, it is considered that two enantiomers have each conformation to occupy the large moiety in large hydrophobic pocket as shown in Fig. 3. This model and the minimized conformations by MM2 suggest that there might be severe interaction between the 3,5-dimethyl group at the aromatic ring of the slow-reacting (*S*,*S*)-enantiomer and 'wall' of active site and, therefore, the reaction rate of (*S*,*S*)-enantiomer should be decreased. Furthermore, it is considered that the immobilization of PFL on the alkyl silica gel might cause larger repulsion with dimethyl substituent of (*S*,*S*)-enantiomer and lead to high enantioselectivity.

3. Conclusions

In summary, we have demonstrated that the efficient modification of substrate structure with 3,5-dimethylbenzyl group as the *N*-protecting one and using the immobilized lipase PFL in alkylated silica gel enhanced the enantioselectivity of the lipase-catalyzed kinetic resolution of *trans*-2,5-disubstituted pyrrolidines. These findings should provide an attractive strategy for lipase-catalyzed kinetic resolution of primary alcohols.

4. Experimental

4.1. General

IR spectra were determined on a Shimadzu IR-435 spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded at 90 and 23 MHz with a JOEL JNM-EX90 spectrometer. All NMR spectra were taken in $CDCl_3$ solution with TMS as the internal standard. Mass spectra were recorded on a JEOL JMS-SX102A mass spectrometer. Optical rotations were determined on a Yanagimoto OR-50 polarimeter. The HPLC analysis was carried out using a Daicel CHIRALCEL OJ column (0.46×25 cm) with a Shimadzu LC-6A. Tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl. TLC was carried out on Merck glass plates precoated with silica gel 60F-254 (0.25 mm) and column chromatography was performed by using Merck 23–400 mesh silica gel.

Lipase PS and AK were presented by courtesy of Amano Pharmaceutical Co. PCL and PFL immobilized in sol–gel-AK were obtained from Fluka Chemie AG.

4.1.1. *N*-4-Methylbenzoyl-*trans*-2,5-bis(ethoxycarbonyl)-pyrrolidine (4d). 4-Methylbenzoyl chloride (0.33 ml, 2.52 mmol) was added to a solution of *trans*-2,5-bis(ethoxycarbonyl)pyrrolidine (**3**) (360 mg, 1.68 mmol) and triethylamine (0.35 ml, 2.52 mmol) in CH_2Cl_2 (2 ml) at 0°C, and the mixture was stirred for 12 h at room temperature. The reaction mixture was diluted with dichloromethane, washed with saturated aqueous $NaHCO_3$ and brine successively, and dried over $MgSO_4$. The residue was purified by flash column chromatography (hexane/ethyl acetate 3:2) to give a white solid **3** (498 mg, 89%); mp 88–89°C; UV (EtOH) 220 nm (ϵ 74500); IR (KBr) 2990, 1740, 1640, 1395, 1185, 1025, 830, 785, 755 cm^{-1}; ^{1}H NMR δ 1.08 (3H, t, J=7.3 Hz), 1.28 (3H, t, J=7.3 Hz), 1.70–2.50 (4H, m), 2.33 (3H, s), 3.97 (2H, q, J=7.5 Hz), 4.29 (2H, q, J=7.3 Hz), 4.49 (1H, d, J=6.8 Hz), 4.80 (1H, d, J=6.2 Hz), 7.00–7.40 (4H, m); ^{13}C NMR δ 13.7, 13.9, 21.1, 27.3, 29.8, 59.5, 60.9, 61.2, 61.4, 126.4, 128.7, 133.2, 139.7, 170.4, 171.6, 171.8. Anal. calcd for $C_{18}H_{23}NO_5$: C, 64.85; H, 6.95; N, 4.20%. Found: C, 64.70; H, 7.20; N, 4.04%.

4.1.2. *N*-2-Methylbenzoyl-*trans*-2,5-bis(ethoxycarbonyl)-pyrrolidine (4b). Yield 90%; UV (EtOH) 232 nm (ϵ 27800); IR (neat) 2970, 1735, 1645, 1385, 1185, 1020,

770, 745 cm^{-1}; ^1H NMR δ 1.09 (3H, t, J=7.1 Hz), 1.33 (3H, t, J=7.3 Hz), 1.71–2.66 (4H, m), 2.39 (3H, s), 3.98 (2H, q, J=7.2 Hz), 4.26 (2H, q, J=7.1 Hz), 4.85 (1H, d, J=6.8 Hz), 6.92–7.48 (4H, m); ^{13}C NMR δ 14.0, 14.2, 18.8, 27.8, 29.8, 59.1, 61.1, 61.3, 125.5, 126.1, 129.2, 130.5, 134.9, 135.9, 170.3, 171.9. Anal. calcd for $C_{18}H_{23}NO_5$: C, 64.85; H, 6.95; N, 4.20%. Found: C, 65.09; H, 6.90; N, 4.18%.

4.1.3. *N*-3-Methylbenzoyl-*trans*-2,5-bis(ethoxycarbonyl)-pyrrolidine (4c). Yield 88%; UV (EtOH) 227 nm (ϵ 41000); IR (neat) 2970, 1735, 1640, 1380, 1180, 1020, 780, 745 cm^{-1}; ^1H NMR δ 1.12 (3H, t, J=7.3 Hz), 1.33 (3H, t, J=7.3 Hz), 1.78–2.63 (4H, m), 2.35 (3H, s), 4.00 (2H, q, J=7.2 Hz), 4.26 (2H, q, J=7.0 Hz), 4.50 (1H, d, J=7.2 Hz), 4.85 (1H, d, J=5.4 Hz), 6.91–7.45 (4H, m); ^{13}C NMR δ 14.0, 14.1, 21.2, 27.6, 30.0, 59.6, 61.2, 61.3, 61.6, 123.5, 127.1, 128.2, 130.5, 136.3, 138.1, 170.6, 171.8, 172.0. Anal. calcd for $C_{18}H_{23}NO_5$: C, 64.85; H, 6.95; N, 4.20%. Found: C, 64.77; H, 7.37; N, 4.24%.

4.1.4. *N*-3,4-Dimethylbenzoyl-*trans*-2,5-bis(ethoxycarbonyl)pyrrolidine (4e). Yield 83%; mp 51–52°C; UV (EtOH) 210 nm (ϵ 41900); IR (KBr) 2970, 1740, 1650, 1410, 1170, 1030, 920, 730 cm^{-1}; ^1H NMR δ 1.05 (3H, t, J=7.0 Hz), 1.25 (3H, t, J=7.0 Hz), 1.77–2.45 (4H, m), 2.14 (6H, s), 3.98 (2H, q, J=6.8 Hz), 4.18 (2H, q, J=7.1 Hz), 4.45 (1H, d, J=6.8 Hz), 4.76 (1H, d, J=6.2 Hz), 6.83–7.34 (4H, m); ^{13}C NMR δ 13.9, 14.1, 19.5, 19.6, 27.5, 30.0, 59.6, 61.1, 61.2, 61.7, 123.9, 127.7, 129.4, 133.7, 136.6, 138.5, 170.6, 172.1. Anal. calcd for $C_{19}H_{25}NO_5$: C, 65.69; H, 7.25; N, 4.03%. Found: C, 65.71; H, 7.37; N, 3.89%.

4.1.5. *N*-3,5-Dimethylbenzoyl-*trans*-2,5-bis(ethoxycarbonyl)pyrrolidine (4f). Yield 77%; mp 53–54°C; UV (EtOH) 228 nm (ϵ 72600); IR (KBr) 2970, 1730, 1650, 1390, 1180, 1020, 860, 760 cm^{-1}; ^1H NMR δ 1.13 (3H, t, J=7.3 Hz), 1.32 (3H, t, J=7.3 Hz), 1.70–2.50 (4H, m), 2.29 (6H, s), 4.02 (2H, q, J=7.6 Hz), 4.25 (2H, q, J=7.0 Hz), 4.47 (1H, d, J=7.0 Hz), 4.81 (1H, d, J=6.2 Hz), 6.94–7.28 (4H, m); ^{13}C NMR δ 14.0, 14.1, 21.1, 27.6, 30.0, 59.5, 61.2, 61.3, 61.6, 124.1, 131.4, 136.2, 138.0, 170.8, 171.9, 172.1. Anal. calcd for $C_{19}H_{25}NO_5$: C, 65.69; H, 7.25; N, 4.03%. Found: C, 65.50; H, 7.37; N, 3.89%.

4.1.6. *N*-4-Methylbenzyl-*trans*-2-acetoxymethyl-5-(hydroxymethyl)pyrrolidine (1d). The ester **4d** (498 mg, 1.48 mmol) in THF (3 ml) was added to $LiAlH_4$ (197 mg, 4.92 mmol) in THF (13 ml) at 0°C and the mixture was stirred for 1 h at room temperature. Water (0.5 ml) and aqueous 10% NaOH (0.4 ml) were added to the reaction mixture and stirring was continued over night. The mixture was filtered through celite and washed with dichloromethane. The filtrate was evaporated under reduced pressure to give the colorless viscous oil **5d**. Acetic anhydride (0.20 ml, 2.2 mmol) was added to the diol **5d** in Et_2O (8 ml) at 0°C and the mixture was stirred for 5 h. The reaction mixture was diluted with dichloromethane, washed with saturated aqueous $NaHCO_3$ and brine successively, and dried over $MgSO_4$. The residue was purified by flash column chromatography (hexane/ethyl acetate 1:2) to give a colorless oil **1d** (292 mg, 71%); IR (neat) 3420, 2910, 1720, 1610, 1445, 1360, 1230, 1030, 805 cm^{-1}; ^1H NMR δ 1.58–2.53 (4H, m), 2.04 (3H, s), 2.32 (3H, s), 3.10 (1H, m), 3.22–3.70 (3H, m), 3.79 (2H, d, J=1.8 Hz), 4.10 (2H, d, J=5.1 Hz), 7.05–7.40 (4H, m); ^{13}C NMR δ 21.1, 27.0, 27.5, 51.3, 58.8, 62.1, 62.4, 63.7, 128.1, 129.2, 136.3, 136.7, 171.0; EI HRMS $C_{15}H_{20}NO_2$ (M^+-CH_2OH) 246.1495. Found 246.1498.

4.1.7. *N*-2-Methylbenzyl-*trans*-2-acetoxymethyl-5-(hydroxymethyl)pyrrolidine (1b). Yield 72%; IR (neat) 3430, 2940, 1735, 1605, 1455, 1375, 1365, 1230, 1030, 745, 630, 600 cm^{-1}; ^1H NMR δ 1.55–2.55 (4H, m), 2.00 (3H, s), 2.34 (3H, s), 3.10 (1H, m), 3.25–3.74 (3H, m), 3.87 (2H, d, J=2.7 Hz), 4.09 (2H, d, J=5.1 Hz), 6.98–7.57 (4H, m); ^{13}C NMR δ 19.2, 20.9, 26.9, 27.5, 50.0, 59.5, 62.5, 62.9, 63.9, 125.9, 127.0, 128.4, 130.4, 136.3, 137.1, 170.9, EI HRMS $C_{15}H_{20}NO_2$ (M^+-CH_2OH) 246.1495. Found 246.1497.

4.1.8. *N*-3-Methylbenzyl-*trans*-2-acetoxymethyl-5-(hydroxymethyl)pyrrolidine (1c). Yield 59%; IR (neat) 3430, 2940, 1735, 1605, 1450, 1365, 1380, 1230, 1030, 885, 780, 695, 600 cm^{-1}; ^1H NMR δ 1.45–2.53 (4H, m), 2.00 (3H, s), 2.32 (3H, s), 3.09 (1H, m), 3.24–3.72 (3H, m), 3.81 (2H, d, J=2.6 Hz), 4.11 (2H, d, J=4.8 Hz), 6.82–7.44 (4H, m); ^{13}C NMR δ 21.0, 21.4, 26.9, 27.4, 51.5, 58.8, 62.0, 62.4, 63.7, 125.1, 127.8, 128.3, 128.8, 138.0, 139.2, 170.9; EI HRMS $C_{15}H_{20}NO_2$ (M^+-CH_2OH) 246.1495. Found 246.1499.

4.1.9. *N*-3,4-Dimethylbenzyl-*trans*-2-acetoxymethyl-5-(hydroxymethyl)pyrrolidine (1e). Yield 74%; IR (neat) 3450, 2940, 1730, 1610, 1450, 1380, 1240, 1030, 820 cm^{-1}; ^1H NMR δ 1.74–2.49 (4H, m), 2.04 (3H, s), 2.23 (6H, s), 3.10 (1H, m), 3.21–3.70 (3H, m), 3.75 (2H, brs), 4.11 (2H, d, J=5.1 Hz), 6.92–7.32 (3H, m); ^{13}C NMR δ 19.4, 19.8, 21.1, 27.0, 27.5, 51.3, 58.8, 62.0, 62.4, 63.7, 125.6, 129.5, 129.7, 135.3, 136.6, 171.0; EI HRMS $C_{16}H_{22}NO_2$ (M^+-CH_2OH) 260.1652. Found 246.1661.

4.1.10. *N*-3,5-Dimethylbenzyl-*trans*-2-acetoxymethyl-5-(hydroxymethyl)pyrrolidine (1f). Yield 77%; IR (neat) 3430, 2940, 1730, 1610, 1455, 1360, 1240, 1030, 842 cm^{-1}; ^1H NMR δ 1.56–2.42 (4H, m), 2.04 (3H, s), 2.30 (6H, s), 3.10 (1H, m), 3.23–3.74 (3H, m), 3.77 (2H, d, J=2.9 Hz), 4.11 (2H, d, J=4.8 Hz), 6.84–7.26 (3H, m); ^{13}C NMR δ 21.1, 21.3, 26.9, 27.5, 51.5, 58.8, 62.0, 62.5, 63.8, 125.9, 128.7, 138.0, 139.2, 171.0; EI HRMS $C_{16}H_{22}NO_2$ (M^+-CH_2OH) 260.1652. Found 246.1666.

4.1.11. Typical procedure for lipase-catalyzed acetylation of monoacetate (1f). Vinyl acetate (74 μl, 0.8 mmol) was added to a suspension of the monoacetate **1f** (58.3 mg, 0.2 mmol) and lipase (60 mg) in water-saturated hexane (2 ml) and the mixture was stirred at 30°C. The reaction was monitored by TLC. The reaction mixture was filtered off on celite and washed with dichloromethane. The extract was dried over $MgSO_4$ and evaporated under reduced pressure. Purification of the residue by flash column chromatography (hexane/ethyl acetate 1:1) afforded the diacetate **2f** (HPLC, CHIRALCEL OJ, hexane/*i*-PrOH 10:1, 0.5 ml min^{-1}, typical retention times; 20 and 27 min for the (*S*,*S*)- and (*R*,*R*)-enantiomer, respectively) and the

monoacetate **1f** (HPLC, CHIRALCEL OJ, hexane/*i*-PrOH 10:1, 0.5 ml min^{-1}, typical retention times; 17 and 23 min for the (*S*,*S*)- and (*R*,*R*)-enantiomer, respectively).

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