Pergamon

Tetrahedron: Asymmetry, Vol. 7, No. 4, pp. 1153-1158, 1996

0957-4166/96 $15.00 + 0.00

S0957-4166(96)00121-8

Highly Selective Resolution of Secondary Alcohols and Acetoacetates with Lipases and Diketene in Organic Media

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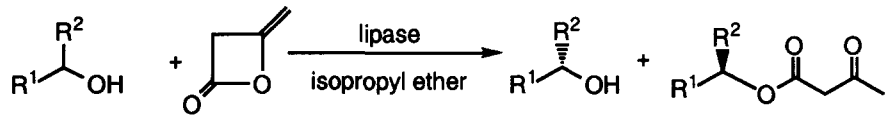
Abstract: By the catalysis of lipases, racemic 1-phenylethanol **1a** is reacted with diketene in isopropyl ether at room temperature to give (*S*)-**1a** (R^1=Me, R^2=Ph, 36%, 99%ee) and (*R*)-1-phenylethyl acetoacetate **2a** (51%, 77%ee). The strategy was also successfully applied to racemic 1-(1-naphthyl)ethanol **1b**, 1-(2-naphthyl)ethanol **1c**, 1-phenyl-2-propanol **1d**, 1,2,3,4-tetrahydro-1-naphthol **1e**, and 2-octanol **1f** with high E-values up to >100.

Asymmetric acylation of racemic alcohols with lipases in organic media has been recognized as an efficient method affording optically active alcohols.[1,2] In order to make the acylation irreversible, several active esters have been employed, including enol esters,[3] 2,2,2-trifluoro- or 2,2,2-trichloroethyl acetate,[4] an acetyl oxime,[5] thioesters,[6] and acid anhydrides.[7] In the course of preparing optically active 2-oxetanones, we found that several racemic 4-alkyl-2-oxetanones were reacted stereoselectively with alcohols by the action of lipases in organic media to give optically active 4-alkyl-2-oxetanones and alkyl 3-hydroxyalkanoates.[8] In this context, we considered that diketene, having 4-membered ring and enol structure, should be a powerful acylating agent for the resolution with lipases in which no by-product such as acetaldehyde and carboxylic acids were produced. Racemic menthol has been acylated with diketene without stereoselectivity by a lipase (CCL) and even heat-treated bovine serum albumin.[2] Recently, a German group independently reported the asymmetric acylation of racemic 2-alkanols ($C_5 \sim C_8$) and 1-phenylethanol with moderate selectivity (E=<12).[9] Here, we describe the lipase promoted asymmetric acylation of a variety of secondary alcohols to give optically active alcohols and alkyl acetoacetates of high ee's.

1-Phenylethanol **1a** was chosen for initial optimization study and reacted with diketene to give 1-phenylethyl acetoacetate **2a** in the presence of PPL (porcine pancreas lipase, Sigma, type II), Amano PS (*Pseudomonas cepacia* lipase, Amano Pharmaceutical Co.) Amano AK (*Pseudomonas fluorescence* lipase, Amano Pharmaceutical Co.), CAL (*Candida antarctica* lipase, Novo Nordisk Co.), and CCL (*Candida cylindracea* lipase, Sigma, type VII) in various organic solvents. Among the above combinations, the reaction proceeded with very high stereoselectivity using Amano PS/AK and CAL in isopropyl ether at room

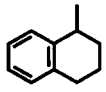


(±)-**1a** : R^1=Ph, R^2=Me

(±)-**1b** : R^1=1-Naph, R^2=Me

(±)-**1c** : R^1=2-Naph, R^2=Me

(±)-**1d** : R^1=Bn, R^2=Me

(±)-**1e** : R^1, R^2= 

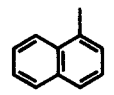
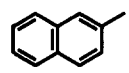
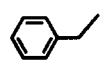
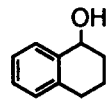
(±)-**1f** : R^1=*n*-C_6H_{13}, R^2=Me

$$E = \frac{\ln[(1-c)(1-ee_s)]}{\ln[(1-c)(1+ee_s)]} \quad \text{eq 1}$$

$$E = \frac{\ln[(ee_p(1-ee_s)/(ee_s+ee_p)]}{\ln[(ee_p(1+ee_s)/(ee_s+ee_p)]}$$

$$c = \frac{ee_s}{(ee_s+ee_p)} \quad \text{eq 2}$$

Table 1. Preliminary resolution of alcohols.

entry	lipase	alcohol	R^1	R^2	reaction period (day)	conv. (%)	ee_s (%)	E^d
1	Amano PS				3	53	99[a]	80
2	Amano AK	**1a**		CH_3	3	53	99[a]	80
3	CAL				1	55	97[a]	35
4	Amano PS				14	41	19[a]	2
5	Amano AK	**1b**		CH_3	14	28	13[a]	2
6	CAL				1	52	94[a]	57
7	Amano PS				3	49	88[a]	66
8	Amano AK	**1c**		CH_3	14	49	88[a]	53
9	CAL				0.5	54	97[a]	50
10	Amano PS				1	55	82[b]	13
11	Amano AK	**1d**		CH_3	1	50	93[b]	94
12	CAL				1	61	19[b]	2
13	Amano PS				1	56	98[a]	35
14	Amano AK	**1e**			1	59	96[a]	20
15	CAL				0.5	53	91[a]	29
16	Amano PS				1	45	38[c]	4
17	Amano AK	**1f**	*n*-C_6H_{13}	CH_3	1	55	44[c]	3
18	CAL				0.5	61	99[c]	22

[a] Determined on esters derived from alcohols and (-)-camphanyl chloride by GLC. [b] Determined on ester derived from **1d** and (*R*)-(-)-MTPA-Cl by ^{19}F-NMR. [c] Determined by ^{1}H-NMR using Eu(hfc)$_3$. [d] Calculated from c and ee_s.

temperature (Table 1, entries 1-3). On the other hand, CCL did not catalyze the reaction and PPL acylated (±)-**1a** without enantioselectivity.

The reactions of (±)-1-(2-naphthyl)ethanol **1c** and (±)-1,2,3,4-tetrahydro-1-naphthol **1e** were effectively catalyzed with Amano PS/AK and CAL (Table 1, entries 7-9, 13-15). (±)-1-Phenyl-2-propanol **1d** was resolved by Amano AK with very high enantioselectivity (Table 1. entry 11). Among the three lipases, only CAL exhibited good selectivity toward (±)-1-(1-naphthyl)ethanol **1b** and (±)-2-octanol **1f** (Table 1. entries 6, 18).

Table 2. Optical resolution of alcohols with diketene and lipases.

entry	alcohol	lipase	reacion period (day)	conv.[a] (%)	E[a]	*S*-alcohol			*R*-acetoacetate		
						yield (%)	$[\alpha]_D^{25}$	ee[b] (%)	yield (%)	$[\alpha]_D^{25}$ in $CHCl_3$	ee[c] (%)
1	**1a**	Amano AK	5	56	39	35	-44.3 (*c* 2.9, MeOH)[d]	99	46	+74.3 (*c* 1.0)	77
2	**1b**	CAL	2	55	46	36	-72.4 (*c* 1.0 , EtOH)[e]	99	41	+37.9 (*c* 1.0)	80
3	**1c**	Amano PS	3	53	37	43	-31.1 (*c* 3.6, EtOH)[f]	95	48	+88.9 (*c* 5.1)	82
4	**1d**	Amano AK	3	50	>100	42	+18.3 (*c* 5.2, Et_2O)[g]	99	41	-14.6 (*c* 2.6)	99
5	**1e**	Amano PS	1	55	40	33	+28.2 (*c* 1.0 , $CHCl_3$)[h]	98	39	+64.4 (*c* 1.0)	80
6	**1f**	CAL	0.5	66	14	30	+9.1 (*c* 1.0 , $CHCl_3$)[i]	99	44	-2.3 (*c* 1.0)	50

[a] Calculated from ee_s and ee_p. [b] Determined according to the methods described in the note of Table 1. [c] Determined on the alcohols derived from the acetoacetates. [d] Reported *S*-isomer, $[\alpha]_D^{25}$ -45.5 (*c* 4.9, MeOH); Huisgen, R.; Rüchardt, C. *Liebigs Ann. Chem.*, **1956**, *21*, 31. [e] Reported *S*-isomer, $[\alpha]_D^{25}$ -76.0 (*c* 2.4, EtOH); Prelog, V.; Philblin, E.; Watanabe, E.; Wilhelm, M. *Helv. Chim. Acta* **1956**, *129*, 1086. [f] Reported *S*-isomer, $[\alpha]_D^{25}$ -41.9 (*c* 5.0, EtOH); Landor, S. R.; Miller, B. J.; Tatchell, A. R. *J. Chem. Soc. (C)*, **1966**, 1822. [g] Reported *R*-isomer, $[\alpha]_D^{25}$ -20.2 (*c* 5.0, Et_2O); Kenyon, J.; Phillips, H.; Pittman, V. P. *J. Chem. Soc.*, **1935**, 1072. [h] Reported *S*-isomer, $[\alpha]_D^{25}$ +30.0 (*c* 4.5, $CHCl_3$); Davis, A. G.; Foster, R. V.; White, A. M. *J. Chem. Soc.* **1953**, 1541. [i] Reported *S*-isomer, $[\alpha]_D^{25}$ +8.7 (*c* 1.0, $CHCl_3$); Wang, Y. -F.; Lalonde, J. J.; Momongan, M.; Bergbreiter, D. E.; Wong, C. -H. *J. Am. Chem. Soc.*, **1988**, *110*, 7200.

Based on the above preliminary experiments, the alcohols were resolved with lipases and diketene in preparative scales. The remaining (*S*)-**1a** and the product (*R*)-**2a** were separated in good yields by flash chromatography or fractional distillation (Table 2, entry 1). The difference in boiling points of alcohols and acetoacetates facilitated the separation in contrast to the corresponding acetates which should be separated from the remaining alcohols by a more highly efficient fractional distillation. The discrepancy between the E-values in Table 1 and Table 2 is ascribed to the calculation methods. The E-values in Table 1 were obtained with eq 1 in which the two variables, c (conversion) and ee_s (ee of substrate), were easily determined. But,

because of its inherent nature, the equation gives relatively poor estimates of E, particularly for small values of c. On the other hand, the final estimates of E in Table 2 were accurately calculated from ee_s and ee_p (ee of product) using eq 2.[10]

Separations of alcohols and acetoacetates were unsuccessful in the cases of **1b** and **1e**; they were isolated after converting the alcohols to corresponding acetates. The acetoacetates and the acetates were successfully converted to the corresponding alcohols by alkaline hydrolysis. The absolute configurations and ee-values of these acetoacetates were determined on the alcohols. The stereochemistry of all the products was consistent with the model established for the resolution by Amano PS and other lipases with other acylating agents.[11] The *R*-alcohols were more rapidly transformed to the acetoacetate than the *S*-enantiomers.

In conclusion, this report describes an efficient resolution of secondary alcohols with diketene and lipases. The alcohols of 95-99%ee are prepared in all the entries by using appropriate lipases. A practical resolution of 1-(1-naphthyl)ethanol **1b** was performed at 60℃ over 14 days with a large amount of PPL and 2,2,2-trichloroethyl butyrate.[12] Now, the resolution has become much efficient using CAL and diketene. Moreover, the present method provides optically active acetoacetates which are useful building blocks for pyrrolizidine alkaloids[13] and starting materials for chiral diazo-esters.[14]

Experimental

All mp's (measured on a Yanagimoto micro melting point apparatus) and bp's are uncorrected. ^{1}H-, ^{13}C-, and ^{19}F-NMR spectra were recorded in $CDCl_3$ with a JEOL-EX-270. *J* Values are given in Hz. IR spectra were recorded with a Horiba FT-300 spectrophotometer. Elementary analyses were done on a Yanaco MT-5. Optical rotation was measured with a Perkin-Elmer R-241 polarimeter (with a 1 dm cell). GLC analyses were done on a Shimazu 14A equipped with a capillary column DB-1 (25 m, J & W SCIENTIFIC, INC.). Distillation was done on a Büchi Kugelrohr apparatus.

Typical Procedures for Asymmetric Acylation of Alcohols with Diketene.

(A) for **1a**, **1c**, **1d**, and **1f** ----- A mixture of (±)-**1a** (1.22 g, 10 mmol), diketene (0.84 g, 10 mmol), Amano AK (1.22 g) and isopropyl ether (25 mL) was stirred at room temperature during which the reaction conversion was assessed by ^{1}H-NMR. After 5 days, the lipase was filtered off and washed with ether (20 mL) and the combined filtrate and washing were evaporated. The residue was purified by silica gel flash chromatography (20% EtOAc in hexane).

(B) for **1b** and **1e** ----- A mixture of (±)-**1e** (1.47 g, 10 mmol), diketene (0.84 g, 10 mmol), Amano PS (1.47 g) and isopropyl ether (25 mL) was stirred at room temperature during which the reaction conversion was assessed by ^{1}H-NMR. After 1 day, the lipase was filtered off and washed with ether (20 mL) and the combined filtrate and washing were evaporated. The residue was dissolved in pyridine (3.44 mL) and acetic anhydride (0.86 g, 8.4 mmol) was added to the solution. After stirring at room temperature for 6 h, the mixture was evaporated, the residue was purified by silica gel flash chromatography (5% EtOAc in hexane) to afford (*R*)-**2e** and the corresponding *S*-acetate.

Typical Procedures for Hydrolysis of Acetoacetates (and Acetates). ----- To a solution of acetoacetate (*R*)-**2b** (0.87 g, 3.4 mmol) in methanol (34 mL), 6N NaOH (4.9 mL, 29 mmol) was added. The mixture was stirred at room temperature for 3 h and evaporated. The residue was dissolved in ether (30 mL) and the solution was washed successively with 5% citric acid (10 mL x 2) and saturated NaCl and dried (Na_2SO_4). Distillation gave (*R*)-**1b** [0.57 g, 97%, bp 125℃ (1.4 mm)].

(*R*)-**2a**: colorless oil; bp 98℃ (1.4 mm); $[\alpha]_D^{25}$ +74.3 (*c* 1.0, $CHCl_3$), 77%ee; ^{1}H-NMR δ 1.57 (d, *J*=6.5, 3H), 2.22 (s, 3H), 3.46 (s, 2H), 5.94 (q, *J*=6.5, 1H), 7.27-7.36 (m, 5H); ^{13}C-NMR δ 21.9, 30.1, 50.4, 73.6, 126.1, 128.1, 128.6, 140.9, 166.4, 200.4; IR (neat) 1739, 1722. Anal. Calcd for $C_{12}H_{14}O_3$: C, 69.89; H, 6.84. Found: C, 69.82; H, 6.81.

(*R*)-**2b**: colorless oil; bp 130℃ (0.5 mm); $[\alpha]_D^{25}$ +37.9 (*c* 1.0, $CHCl_3$), 80%ee; ^{1}H-NMR δ 1.75 (d, *J*=6.5, 3H), 2.24 (s, 3H), 3.51 (s, 2H), 6.71 (q, *J*=6.5, 1H), 7.44-7.60, 7.80-7.90, 8.05-8.08 (m, 7H); ^{13}C-NMR δ 21.5, 30.1, 50.3, 70.6, 123.0, 123.3, 125.3, 125.5, 125.7, 126.4, 128.6, 128.9, 133.8, 136.6, 166.4, 200.4; IR (neat) 1739, 1718. Anal. Calcd for $C_{16}H_{16}O_3$: C, 74.98; H, 6.29. Found: C, 74.88; H, 6.31.

(*R*)-**2c**: mp 38℃; bp 115℃ (0.3 mm); $[\alpha]_D^{25}$ +88.9 (*c* 5.1, $CHCl_3$), 82%ee; ^{1}H-NMR δ 1.65 (d, *J*=6.8, 3H), 2.22 (s, 3H), 3.48 (s, 2H), 6.10 (q, *J*=6.8, 1H), 7.45-7.51, 7.80-7.86 (m, 7H); ^{13}C-NMR δ 21.9, 30.1, 50.4, 73.6, 123.9, 125.2, 126.2, 126.3, 127.6, 128.0, 128.4, 133.1, 138.2, 166.4, 200.4; IR (neat) 1739, 1720. Anal. Calcd for $C_{16}H_{16}O_3$: C, 74.98; H, 6.29. Found: C, 74.86; H, 6.35.

(*R*)-**2d**: colorless oil; bp 100℃ (0.5 mm); $[\alpha]_D^{25}$ -14.6 (*c* 2.6, $CHCl_3$), 99%ee; ^{1}H-NMR δ 1.26 (d, *J*=6.2, 3H), 2.14 (s, 3H), 2.75-2.98 (m, 2H), 3.37 (s, 2H), 5.19 (q, *J*=6.2, 1H), 7.17-7.32 (m, 5H); ^{13}C-NMR δ 19.4, 29.9, 42.1, 50.4, 72.8, 126.6, 128.4, 129.4, 137.3, 166.6, 200.5; IR (neat) 1739, 1718. Anal. Calcd for $C_{13}H_{16}O_3$: C, 70.89; H, 7.32. Found: C, 70.62; H, 7.41.

(*R*)-**2e**: colorless oil; bp 110℃ (0.9 mm); $[\alpha]_D^{25}$ +64.4 (*c* 1.0, $CHCl_3$), 80%ee; ^{1}H-NMR δ 1.79-2.11 (m, 4H), 2.24 (s, 3H), 2.71-2.92 (m, 2H), 3.47 (s, 2H), 5.98-6.13 (m, 1H), 7.11-7.31 (m, 4H); ^{13}C-NMR δ 18.6, 28.8, 28.9, 30.0, 50.4, 71.1, 126.1, 128.2, 129.0, 129.5, 133.8, 137.9, 166.7, 200.5; IR (neat) 1738, 1718. Anal. Calcd for $C_{14}H_{16}O_3$: C, 72.39; H, 6.94. Found: C, 72.31; H, 7.02.

(*R*)-**2f**: colorless oil; bp 120℃ (25 mm); $[\alpha]_D^{25}$ -2.3 (*c* 1.0, $CHCl_3$), 50%ee; ^{1}H-NMR δ 0.83 (t, *J*=6.5, 3H), 1.11-1.60 (m, 10H), 1.24 (d, *J*=6.5, 3H), 2.21 (s, 3H), 3.36 (s, 2H), 4.78-5.00 (m, 1H);

^{13}C-NMR δ 14.0, 19.8, 22.6, 25.3, 29.0, 30.0, 31.7, 35.8, 50.5, 72.5,166.8, 200.6; IR (neat) 1734, 1722. Anal. Calcd for $C_{12}H_{22}O_3$: C, 67.26; H, 10.35. Found: C, 66.80 ; H, 10.32.

Acknowledgments We thank Amano Pharmaceutical Co. for the gift of Amano PS and Amano AK and Novo Nordisk Co. for the gift of CAL.

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(*Received in Japan* 7 *February* 1996)