SHORT PAPER

J. Chem. Research (S),
2003, 480–482

Chemoenzymatic synthesis of primary alcohols with a 2-isoxazoline moiety†

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Racemic 2-isoxazoline-5-carboxylate esters were reduced under mild conditions to form the corresponding primary alcohols. These alcohols were enzymically resolved by acylation with succinic anhydride in the presence of Amano AK lipase.

Keywords: 2-isoxazolines, borohydride reduction, kinetic resolution, lipase

Recent years have seen an increasing interest in compounds containing a 2-isoxazoline system. The possibility of utilising such compounds as potential starting materials for the synthesis and modification of antibiotics is one reason for this.

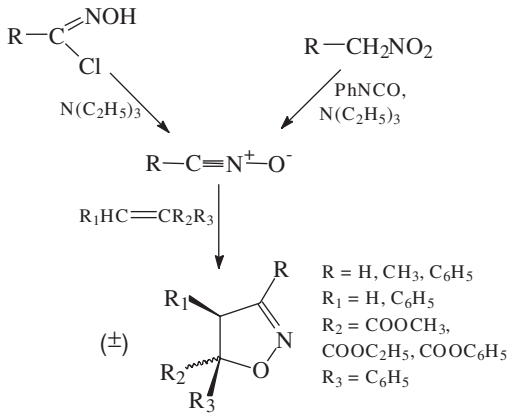
Many compounds including in their structure a 2-isoxazoline ring or its hydrogenated derivative exhibit biological activity. The antibiotics (+)-paliclavin, (-)-vermiculin[1] and nikomycin B[2] are examples. The present work extends earlier efforts in seeking new 2-isoxazoline derivatives of potential biological activity[3-8] and covers the synthesis and chemoenzymatic reactions directed towards the synthesis of optically active primary alcohols.

In the 1,3-dipolar cycloaddition of aliphatic or aromatic nitrile oxides to various atropic[3] and *trans* α-phenylcinnamic acid esters,[6] 2-isoxazolines have been obtained as precursors to optically active primary alcohols with a 2-isoxazoline group. This cycloaddition, as a *syn* reaction, in the case of unsymmetrical olefins leads to the formation of two racemic regioisomers, in which the relative orientation of substituents is determined by the (*E*/*Z*) configuration of the starting alkene.

The 1,3-dipolar cycloaddition reactions of aliphatic nitriles to alkenes, α,β-unsaturated ketones and carboxylic acid esters are widely described in the literature. Many procedures of these reactions are known. However, due to the considerable instability of nitrile oxides, especially of aliphatic ones, methods consisting in generating them *in situ* in the reaction medium are preferred. Two standard methods of the 1,3-dipolar cycloaddition reaction of aliphatic and aromatic nitrile oxides to α,β-unsaturated esters have been utilised – the Mukayama and Hoshino[9] method and the Larsen and Torssell[10] method (Scheme 1). 2-Isoxazolines with an ester substituent at C-5 have thereby been obtained.

Mixtures of primary alcohols with a 2-isoxazoline function have resulted from the reduction of corresponding esters by sodium borohydride ($NaBH_4$).[11] It has been commonly assumed that sodium borohydride is an effective reagent for reducing aldehydes and ketones, but not for carboxylic acid esters. However, in the literature reports can be found of the reduction of esters,[12] stable 2-isoxazoline esters among others,[13] to the corresponding primary alcohols by means of $NaBH_4$.

Many of the compounds undergoing this reaction carry various functional groups in the neighborhood of the ester group, *e.g.* amide, cyano, the presence of which in many cases can affect the course of the reduction.[14-16] The methyl, ethyl and phenyl esters of phenylisoxazoline-5-carboxylic acid were used for the synthesis.



Scheme 1

A series of corresponding primary alcohols in very good yields (of the order of 90%) resulted from the reduction by means of sodium borohydride. The reduction was completed within a relatively short period (1–7 h). This time was longer in the case of sterically hindered molecules.

From literature reports it is known that the kinetic separation of enantiomers of primary and secondary alcohols can be carried out by the transesterification reaction, transforming one of the alcohol enantiomers into the ester, leaving the second enantiomer unreacted. Acyclic[17] and cyclic carboxylic anhydrides[18] can be used as acylating agents. In the reaction with acyclic anhydrides (acetic, propionic, butyric), an ester of the more active enantiomer, the unreacted alcohol enantiomer, and an acid molecule are formed. With a cyclic anhydride a monoester of the more active enantiomer (it is usually the R enantiomer) and a molecule of the unreacted alcohol are formed. In the case of the acyclic anhydride there arises the difficulty in separation of the ester formed from the unreacted alcohol. It often happens that both compounds have similar boiling points, which precludes their separation by distillation. The use of a cyclic anhydride solves this problem. The monoester formed can be separated from the unreacted alcohol by extraction of the organic phase with an aqueous solution of sodium bicarbonate ($NaHCO_3$), and the monoester sodium salt formed is then treated with aqueous hydrochloric acid, resulting in ester hydrolysis and formation of an optically active alcohol.[17]

The reduction of previously obtained esters with a 2-isoxazoline group to corresponding alcohols was carried out following Yang *et al.*[13] (Scheme 2). The reaction yields and times are presented in Table 1. When the 2-isoxazolines differ in only the ester group (COOEt and COOPh) the same primary alcohol was obtained. ^{1}H NMR, ^{13}C NMR and IR analysis permitted a complete interpretation of the compounds obtained.

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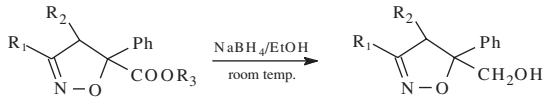
† This is a Short Paper, there is therefore no corresponding material in *J Chem. Research (M).*

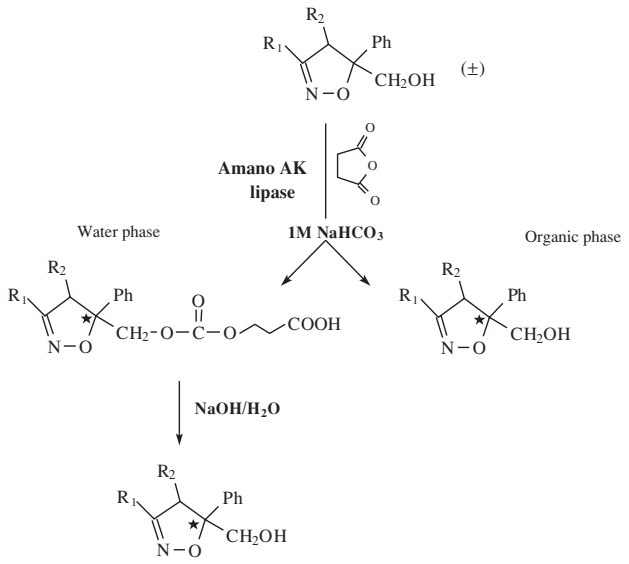


Scheme 2

Table 1 Reduction of esters with 2-isoxazoline groups

	R_1	R_2	R_3	Time /h	Product	Yield /%
1	H	H	C_2H_5	2.5	**7**	96
2	CH_3	H	C_2H_5	1	**8**	94
3	C_6H_5	H	C_2H_5	7	**9**	88
4	C_6H_5	C_6H_5	CH_3	17	**10**	92
5	CH_3	C_6H_5	CH_3	5	**11**	98
6	CH_3	H	C_6H_5	20	**8**	86

A modified method of acylation with succinic anhydride of a racemic mixture of alcohols in the presence of Amano AK lipase (*Pseudomonas fluorescens*), was applied on the basis of the data of Gutman *et al.*[18] for the resolution of primary alcohol enantiomers (Scheme 3). These authors used *tert*-butyl-methyl ether as solvent for the separation of enantiomers of primary and secondary alcohols. In the case of alcohols with a 2-isoxazoline group this solvent did not give the desired results. Benzene was used in its place; for compound **7** diethyl ether was used as solvent (in benzene separation did not occur). From the literature data[17-19] it appears that in the case of a racemic mixture of alcohols (a variety of structures were investigated) subjected to enzymatic resolution with Amano AK lipase in reaction with succinic anhydride, a monoester of the more active enantiomer (it is usually the *R* enantiomer) is formed, leaving the *S*-alcohol unreacted. Therefore, we assume that in the case of alcohols with a 4-unsubstituted 2-isoxazoline moiety (compounds **7**–**9**) a *R*-monoester of succinic acid and unreacted *S*-enantiomer of the alcohol were obtained. The succinic acid *R*-monoester subjected to hydrolysis yields an optically active alcohol of *R* configuration, and the unreacted *S*-enantiomer subjected to further enzymatic acylation yields pure enantiomer *S*.



Scheme 3

In order to determine the optical purity, the enantiomeric alcohols were subjected to ^{1}H NMR analysis with a chemical shift chiral reagent (Eu(thf)$_3$) (**7**, **8** and **9**) as well as analysis on a chiral chromatographic column (**10** and **11**) (Table 2).

Table 2 Resolution of enantiomers of alcohols*

	% conversion	ee [%] (R)	$[\alpha]_D^{25}$	ee [%] (S)	$[\alpha]_D^{25}$
7	46	91	-24.8°	66	+15.4°
8	42	95	-13.3°	60	+6.2°
9	55	88	-29.8°	63	+19.2°
10	57	84	+33.4°	59	-20.1°
11	44	~100	+45.9°	56	-10.2°

* The differences in the relative values of optical rotation for the alcohols obtained after enzymatic resolution result from the different enantiomeric excess.

Conclusions

Atropic acid and *trans*-α-phenylcinnamic acid esters show high regioselectivity in 1,3-dipolar cycloaddition reactions with formyl-, aceto- and benzonitrile oxides resulting in 2-isoxazolines with ester groups at position 5.

Sodium borohydride appeared to be the reagent of choice for selectively reducing an ester group in the 2-isoxazoline ring.

The reaction of enzymatic acylation with succinic acid in the presence of Amano AK lipase permitted the separation into enantiomers racemic primary alcohols containing a 2-isoxazoline group with good optical purity.

The enantiomeric excesses were determined by two methods, ^{1}H NMR analysis with a chiral chemical shift reagent Eu(thf)$_3$ and by separation on a chiral chromatographic column. They appeared to be 84–98% for enantiomers of alcohols of *R* configuration and 56-63% for enantiomers of *S* configuration. Alcohols of *R* configuration obtained from atropic acid esters show a negative optical rotation, while the methyl esters derived from *trans*-α-phenylcinnamic acid, possessing two centers of asymmetry at carbons C-4 and C-5, proved to be dextrotatory to Na(D) light.

Experimental

IR spectra were measured by means of a Specord 71 IR spectrophotometer; the band positions are expressed in cm^{-1}. ^{1}H NMR spectra were recorded on a Varian Gemini 200 spectrometer in chloroform-d. The chemical shift values are expressed in δ ppm. The optical rotation measurements were carried out in CH_2Cl_2 in a 50 mm cell. The enantiomeric excesses were determined by ^{1}H NMR spectroscopy using Eu(hfc)$_3$ as shift reagent, or by GC (a Daicel Chiralpot AD column). Column chromatography was performed on silica gel (100–200 mesh). The reactions were controlled by TLC. Elemental analysis was performed on a Perkin-Elmer CHNO analyzer.

Phenyl atropate: The ester was prepared from atropic acid (0.054 M; 8 g) and phenol (0.27 M; 25.4 g) in the presence of DCC (0.059 M; 12.15 g) and DMAP (catalytic) in CH_2Cl_2 (150 ml). The reaction mixture was filtered to remove dicyclohexylurea and the ester (oil, 9.8 g, 80%) was purified by flash chromatography on silica gel (hexane : ethyl ether 7 : 2). IR (film) cm^{-1}: 1752 (C=O). ^{1}H NMR δ 6.04: (d, 1H, CH_2, J = 1 Hz); 6.57 (d, 1H, CH_2, J = 1 Hz); 7.38 (m, 10H, Ar).

Synthesis of 2-isoxazolines from aliphatic nitrile oxides: A mixture consisting of dipolarophile (0.01 mol), nitroalkane (0.01 mol), phenyl isocyanate (0.02 mol), 1 cm^3 of triethylamine and 50 cm^3 of benzene was heated for 72 hours at 45–50 °C. Diphenylurea precipitating during the reaction was filtered off after its completion. The reaction course was monitored by means of thin layer chromatography. The chromatography was performed on silica gel 254 plates in a developing system composed of chloroform, ethyl acetate and hexane (1 : 1 : 7). The crude products were purified by distillation *in vacuo* or recrystallisation.

(±)-Ethyl 5-phenyl-2-isoxazoline-5-carboxylate (**1**): m.p. 113–115 °C; yield 41%. IR (KBr) cm^{-1}: 1736 (C=O); 1600 (C=N). ^{1}H NMR: 1.25 (t, 3H, C$\underline{H}_3$CH$_2$, J = 7.2 Hz); 3.59 and 4.29 (2 × d, 2H, 4-CH$_2$, J = 18.4 Hz); 4.25 (q, 2H, CH$_3$C$\underline{H}_2$, J = 7.0 Hz); 7.44 (m, 5H, Ar); ^{13}C NMR: 13.91 ($\underline{C}$H$_3$CH$_2$); 43.8 (C-4); 62.77 (CH$_3\underline{C}$H$_2$); 92.5 (C-5); 119.8, 124.9, 129.2, 138.3 (Ar); 154.3 (C-3); 169.9 (C=O). Anal: $C_{12}H_{13}NO_3$ requires C 65.75, H 5.94, N 6.39; found C 65.73, H 5.96, N 6.35%.

(±)-Ethyl 3-methyl-5-phenyl-2-isoxazoline-5-carboxylate (**2**): m.p. 63–65 °C; yield 43%. IR (KBr) cm^{-1}: 1734 (C=O); 1600 (C=N). ^1H NMR: 1.20 (t, 3H, $C\underline{H}_3CH_2$, J = 7.2 Hz); 1.98 (s, 3H, 3-CH_3); 3.13 and 3.96 (2 × dd, 2H, 4-CH_2, J = 1 and 17.4 Hz); 4.19 (q, 2H, $CH_3C\underline{H}_2$, J = 7.2 Hz); 7.38 (m, 5H, Ar); ^{13}C NMR: 13.0 ($\underline{C}H_3CH_2$); 13.9 (CH_3); 49.2 (C-4); 62.35 ($CH_3\underline{C}H_2$); 89.3 (C-5); 124.9, 128.3, 128.6, 139.6 (Ar); 155.7 (C-3); 171.3 (C=O). Anal: $C_{13}H_{15}NO_3$ requires C 66.95, H 6.44, N 6.01; found: C 66.97, H 6.40, N 5.99%.

(±)-Methyl 4,5-diphenyl-3-methyl-2-isoxazoline-5-carboxylate (**5**): m.p. 111–113 °C; yield 15%. IR (KBr) cm^{-1}: 1724 (C=O); 1602 (C=N). ^1H NMR: 1.91 (s, 3H, 3-CH_3), 3.76 (s, 3H, CH_3O); 5.13 (s, 1H, 4-CH); 6.88 (m, 2H, Ar); 7.06 (m, 6H, Ar); 7.19 (m, 2H, Ar). ^{13}C NMR: 12.5 (C-4); 13.6 (CH_3); 53.5 (CH_3O); 93.0 (C-5); 126.0, 127.7, 127.8, 128.3, 129.3, 133.1, 134.4 (Ar); 159.9(C-3); 173.15 (C=O). Anal: $C_{18}H_{17}NO_3$ requires C 73.22, H 5.76, N 4.75. Found: C 73.20, H 5.77, N 4.79%.

(±)-Phenyl 3-methyl-5-phenyl-2-isoxazoline-5-carboxylate (**6**): yellow oil; yield 4%. IR (KBr) cm^{-1}: 1748 (C=O); 1602 (C=N). ^1H NMR: 1.99 (d, 3H, 3-CH_3, J = 9.2 Hz); 3.18 and 4.01 (2 × dd, 2H, 4-CH_2, J = 1 and 17.4 Hz); 7.39 (m, 10H, Ar). ^{13}C NMR: 13.9 (CH_3); 49.2 (C-4); 89.3 (C-5); 124.9, 127.8, 128.0, 128.3, 128.6, 136.2, 139.6 (Ar); 155.7 (C-3); 171.3 (C=O). Anal: $C_{17}H_{15}NO_3$ requires C 72.60, H 5.34, N 4.98. Found: C 72.63, H 5.39, N 4.94%.

Synthesis of 2-isoxazolines from aromatic nitrile oxides: In a three-necked flask benzaldehyde oxime (10 g) was dissolved in of dry CH_2Cl_2 (150 cm^3). N-Chlorosuccinimide (10 g, 0.082 mol) was added portionwise (2 g at 15 min intervals) to the oxime solution while stirring. The temperature was maintained at 25–26 °C. After the addition was complete, the whole was heated at 30 °C for 2 h. After reaction completion methylene chloride was distilled off under reduced pressure and then 100 cm^3 of dry diethyl ether was added to cause complete crystallisation of the succinimide, which was filtered off. The filtrate was concentrated under reduced pressure to provide the hydroxamic acid chloride. The chloride (13.42 g, 0.086 mol) and the dipolarophile (0.08 mol) were stirred in toluene (100cm^3) and triethylamine (8.1g, 0.08 mol) in toluene (25cm^3) was added dropwise. The stirring was continued for 48 hours at 40 °C, monitoring the reaction course by t.l.c. on silica gel, developing with ethyl acetate, chloroform and hexane (1 : 1 : 7). After the reaction was comple the triethylamine hydrochloride formed was filtered off and the product was distilled under reduced pressure, then recrystallised if solid.

(±)-Ethyl 3,5-diphenyl-2-isoxazoline-5-carboxylate (**3**): m.p. 160–163 °C; yield 33%. IR (KBr) cm^{-1}: 1744 (C=O), 1602 (C=N). ^1H NMR: 1.25 (t, 3H, $C\underline{H}_3CH_2$, J = 7.2 Hz); 3.56 and 4.40 (2 × d, 2H, 4-CH_2, J = 17.2 Hz); 4.24 (q, 2H, $CH_3C\underline{H}_2$, J = 7.2 Hz); 7.40 (m, 6H, Ar); 7.54 (m, 2H, Ar); 7.71 (m, 2H, Ar). ^{13}C NMR: 13.9 ($\underline{C}H_3CH_2$); 45.7 (C-4); 62.5 ($CH_3\underline{C}H_2$); 90.2(C-5); 125.0, 126.8, 127.95, 128.4, 128.70, 128.73, 130.5, 139.4 (Ar); 156.6 (C-3); 171.1 (C=O); Anal: $C_{18}H_{17}NO_3$ requires C 73.22, H 5.76, N 4.75. Found: C 73.24, H 5.77, N 4.74%.

(±)-Methyl 3,4,5-triphenyl-2-isoxazoline-5-carboxylate (**4**): m.p. 132–136 °C; yield 2%. IR (KBr) cm^{-1}: 1744 (C=O); 1602 (C=N). ^1H NMR: 3.79 (s, 3H, CH_3O); 5.65 (s, 1H, 4-CH); 7.03 (m, 8H, Ar); 7.31 (m, 5H, Ar); 7.65 (m, 2H, Ar). ^{13}C NMR: 12.5 (C-4); 53.5 (CH_3O); 94.0 (C-5); 126.5, 127.1, 127.2, 127.35, 127.7, 128.3, 128.5, 128.8, 129.3, 129.9 (Ar); 157.8 (C-3); 172.3 (C=O). Anal: $C_{23}H_{19}NO_3$ requires C 77.31, H 5.32, N 3.92. Found: C 77.29, H 5.33, N 3.95%.

Rreduction of 2-isoxazoline esters: The ester (5 mmol) was added to $NaBH_4$ (0.02 mol) in ethanol (30ml) at room temperature. After stirring (see Table I) the reaction was quenched by careful addition of dilute hydrochloric acid. The mixture was extracted three times with CH_2Cl_2, the combined extracts were dried ($MgSO_4$), and CH_2Cl_2 was removed *in vacuo*.

(±)-5-Hydroxymethyl-5-phenyl-2-isoxazoline (**7**): m.p. 149–150 °C; yield 96%. IR (KBr) cm^{-1}: 3372 (OH); 1604 (C=N). ^1H NMR: 1.25 (t, 3H, $C\underline{H}_3CH_2$, J = 7.2 Hz); 3.59 and 4.29 (2 × d, 2H, 4-CH_2, J = 18.4 Hz); 4.25 (q, 2H, $CH_3C\underline{H}_2$, J = 7 Hz); 7.15 (t, 1H, 3-H, J = 7.4 Hz); 7.44 (m, 5H, Ar). ^{13}C NMR: 41.0 (C-4); 67.9 (CH_2); 94.4 (C-5); 124.9, 128.8, 129.1, 140.55 (Ar); 157.2 (C-3); Anal: $C_{10}H_{11}NO_2$ requires C 67.80, H 6.21, N 7.91. Found: C 67.82, H 6.18, N 7.90%.

(±)-5-Hydroxymethyl-3-methyl-5-phenyl-2-isoxazoline (**8**): m.p. 52–54 °C; yield 94%. IR (KBr) cm^{-1}: 3372 (OH); 1604 (C=N). ^1H NMR: 1.95 (s, 3H, 3-CH_3); 3.01 and 3.52 (2 × dd, 2H, 4-CH_2, J = 1 and 17 Hz); 3.69 and 3.81 (2 × d, 2H, $C\underline{H}_2OH$, J = 12.2 Hz); 7.38 (m, 5H, Ar). ^{13}C NMR: 13.2 (CH_3); 46.5 (C-4); 67.75 (CH_2); 89.9 (C-5); 125.0, 127.7, 128.5, 142.1 (Ar); 156.1 (C-3). Anal: $C_{11}H_{13}NO_2$ requires C 69.11, H 6.81, N 7.33. Found: C 69.08; H 6.79; N 7.30%.

(±)-3,5-Diphenyl-5-hydroxymethyl-2-isoxazoline (**9**): m.p. 107–108 °C; yield 88%. IR (KBr) cm^{-1}: 3389 (OH); 1600 (C=N). ^1H NMR: 3.46 and 3.95 (2 × d, 2H, 4-CH_2, J = 16.6 Hz); 3.86 (d, 2H, $C\underline{H}_2OH$, J = 12.2 Hz); 7.38 (m, 6H, Ar); 7.45 (m, 2H, Ar); 7.65 (m, 2H, Ar). ^{13}C NMR: 43.0 (C-4); 67.8 (CH_2); 91.1 (C-5); 125.05, 126.65, 127.95, 128.7, 129.3, 130.2, 141.8 (Ar); 157.2 (C-3). Anal: $C_{16}H_{15}NO_2$ requires C 75.89, H 5.93, N 5.53. Found: C 75.88; H 5.94; N 5.52%.

(±)-5-Hydroxymethyl-3,4,5-triphenyl-2-isoxazoline (**10**)**:** m.p. 184–186 °C; yield 91%. IR (KBr) cm^{-1}: 3512 (OH); 1600 (C=N). ^1H NMR: 4.02 (s, 2H, $C\underline{H}_2OH$); 5.14 (s, 1H, 4-CH); 7.07 (m, 8H, Ar); 7.28 (m, 5H, Ar); 7.65 (m, 2H, Ar); ^{13}C NMR: 59.6 (C-4); 68.7 (CH_2); 95.0 (C-5); 126.5, 127.1, 127.2, 127.35, 127.7, 128.3, 128.5, 128.8, 129.3, 129.9, 135.2 (Ar); 157.0 (C-3). Anal: $C_{22}H_{19}NO_2$ requires C 80.24, H 5.77, N 4.25. Found: C 80.25; H 5.80; N 4.29%.

(±)-5-Hydroxymethyl-3-methyl-4,5-diphenyl-2-isoxazoline (**11**): m.p. 129–130 °C; yield 97%. IR (KBr) cm^{-1}: 3284 (OH); 1600 (C=N); ^1H NMR: 1.84 (s, 3H, CH_3), 3.91 (s, 2H, $C\underline{H}_2OH$); 4.59 (s, 1H, 4-CH); 6.78 (m, 2H, Ar); 7.04 (m, 8H, Ar); ^{13}C NMR: 12.45 (CH_3); 62.65 (C-4); 68.6 (CH_2); 93.5 (C-5); 126.35, 127.0, 127.3, 127.7, 128.2, 129.5, 134.6, 137.5 (Ar); 159.0 (C-3); Anal: $C_{17}H_{17}NO_2$ requires C 76.40; H 6.37; N 5.24; Found: C 76.40; H 6.35; N 5.28%.

Kinetic resolution of the racemic alcohols: The racemic alcohol (1.05mmol), of succinic anhydride (1.25mmol) and Amano AK lipase (Sigma) (10mg) in benzene (2cm^3) (or dimethyl ether for **7**) were placed in a 50ml screw-cap vial for 48 h at room temperature. After stirring the reaction was stopped by filtering off the enzyme, which was extracted twice with benzene (10cm^3) (or dimethyl ether for **7**). The combined organic solution was extracted with saturated aqueous $NaHCO_3$ (3 × 5cm^3), dried ($MgSO_4$) and evaporated to give the (*S*)-enriched unreacted alcohol. The water phase was stirred for 3 h with NaOH (85mg) to hydrolyse the ester, and then extracted with CH_2Cl_2 (3 × 10cm^3). This solution was dried ($MgSO_4$) and evaporated to give the (*R*)-enriched alcohol. The optical purities of *S* or *R*-alcohols were determined by HPLC analysis on a chiral column with a mixture of hexane and 2-propanol as the mobile phase or by ^1H NMR using the chiral chemical shift reagent Eu(thf)$_3$.

Received 28 October 2002; accepted 16 May 2003
Paper 02/1640

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