Pergamon

Tetrahedron: *Asymmetry* 11 (2000) 2565–2577

TETRAHEDRON: *ASYMMETRY*

Synthesis of optically active β′-hydroxy-β-enaminoketones via enzymatic resolution of carbinols derived from 3,5-disubstituted isoxazoles

José Antonio Fuentes, Alicia Maestro, Ana M[a] Testera and José Manuel Báñez*

Departamento de Química Orgánica, E.T.S. Ingenieros Industriales, Universidad de Valladolid, 47071 Valladolid, Spain

Received 2 May 2000; accepted 5 June 2000

Abstract

The preparation of several enantiomerically pure β′-hydroxy-β-enaminoketones from the corresponding isoxazolic carbinols, which have been obtained by enzymatic kinetic resolution of the racemic β-hydroxy-isoxazoles catalyzed by lipases, is described. The enzymatic transesterification of racemic (±)-5-(2-hydroxy-propyl)-3-methylisoxazole **3a**, and racemic (±)-5-(2-hydroxy-2-*p*-tolylethyl)-3-methylisoxazole **3d**, has been studied with respect to the influence of experimental variables such as the used enzyme, the acylating agent or the solvent on the enantioselectivity of the reaction. After the reductive cleavage of the isoxazolic ring of the enantiopure carbinols, (*R*)- and (*S*)-2-amino-4-oxo-2-hepten-6-ol, (*R*)- and (*S*)-**5**, and (*R*)-*2*-amino-6-*p*-tolyl-4-oxo-2-hexen-6-ol, (*R*)-**7** with an enantiomeric excess >98% were obtained.

1. Introduction

The enantioselective preparation of highly functionalized compounds is of central importance in synthetic chemistry. Often, in order to mask a labile functionality, heterocycles are used in these synthetic routes. The isoxazoles are an important class of heterocycles both as key intermediates in the construction of the framework of many natural products[1] and as a masked aldolic moiety.[2] Recently, we reported[3] the extension of the chain of the chiral 2,3-*O*-isopropylidene-D-glyceraldehyde using several alkenylisoxazoles as key intermediates synthesized from isoxazolylphosphonium salts.[4]

The β-enaminoketone unit has received considerable attention in organic synthesis. Unsymmetrical enamino ketones can be used as bidentate ligands in transition metal complexes,[5] as precursor of interesting functionalities, such as γ-aminoalcohols or tetrahydro-1,3-oxazines,[6] or

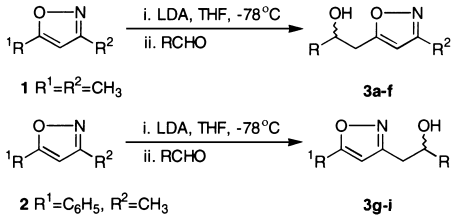
* Corresponding author. E-mail: jmbsanz@dali.eis.uva.es

0957-4166/00/$ - see front matter
PII: S0957-4166(00)00225-1

heterocycles such as pyrazoles,[2a,c] 2-(1*H*)-pyridones[2d] and 2-aminopyrimidines.[7] Recently, the preparation of fluorinated β-enaminoketones,[8] which are useful building blocks for the construction of new compounds of pharmacological interest,[9] has been described. Herein we describe the preparation of various optically active β′-hydroxy-β-enaminoketones from chiral isoxazolic secondary alcohols. The enantioselective synthesis of these polyfunctionalized compounds remains scarcely reported. To our knowledge only one report describes the preparation of an enantiomerically pure enaminoketone.[10] The method consists of the microbial reduction of an 5-isoxazolyl propanone and subsequent reductive cleavage of the isoxazolic ring. We now report the preparation of several racemic isoxazolyl carbinols and their enzymatic kinetic resolution. Nowadays the use of enzymes is a common tool in organic chemistry; however, there are only a few examples of enzymatic resolution of heteroaryl carbinols[11] and, in particular, isoxazolic carbinols.[12] Therefore, a systematic study of the transesterification of isoxazolic carbinols catalyzed by different commercial lipases has also been carried out. The influence of the nature of the substrate, the solvent (polarity and hydrophobicity) and the acylating agent on the enantioselectivity has been examined.

2. Results and discussion

The starting isoxazolic carbinols were synthesized by nucleophilic addition to aldehydes of the isoxazolic carbanion (Scheme 1).



Scheme 1.

The lateral lithiation of 3,5-dimethylisoxazole, **1**, was carried out using LDA in THF solution at –78°C. Subsequent addition of the aldehyde in THF gave the racemic β-hydroxyisoxazoles **3a**–**i** in the yields indicated in the Experimental section. In this way, we achieved better results than those obtained by the traditional lithiation with *n*BuLi.[13]

The racemic carbinols (±)-5-(2-hydroxypropyl)-3-methylisoxazole **3a**, and (±)-5-(2-hydroxy-2-*p*-tolylethyl)-3-methylisoxazole **3d**, were obtained in good chemical yields and moreover they have a very different substituent at the C5 position of the isoxazole ring, so were chosen out of synthesized racemic β-hydroxyisoxazoles to be enzymatically resolved.

The study of the enzymatic transesterification of the racemic alcohols (±)-**3a** and (±)-**3d** was made using six commercial lipases as biocatalysts: *Pseudomonas cepacia* lipase (PSL), porcine pancreatic lipase (PPL), *Candida cylindracea* lipase (CCL), *Candida antarctica* lipase (CAL), lipomod AC and *Aspergillus niger* lipase (ANL). In every biocatalytic process the solvent is a variable that must be optimized. Therefore, hydrophobic and apolar solvents such as hexane or very hydrophilic such as 1,4-dioxane were employed. Finally, the influence of the acylating agent

was also evaluated. All the assays carried out are shown in Tables 1 and 2. The experiments in which the acylated product was produced are indicated with a +' sign and when the untransformed alcohol was recovered, with a '–' sign. In general, it can be pointed out that the isoxazole **3a** is a better recognized substrate by the enzyme than the compound **3d**, probably due to steric reasons. All reactions were carried out at 27°C and shaken at 250 rpm.

Table 1[a]
Assays carried out with the racemic carbinol (±)-**3a**

	1,4-Dioxane	Et_2O	Hexane	THF	CH_2Cl_2	TBME	
PSL	+	+	+	+	+	+	+[b]
PPL	-	+	+	-	-	-	
CAL	+	+	+	+	+	+	+[b]
CCL	+	-	-	+	+	-	
Lipomod AC	-	+	+	+	+	+[b]	
ANL	-	+	+	+	-	-	

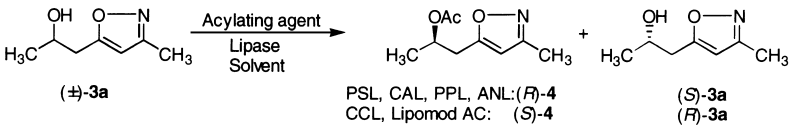
[a] Vinyl acetate. [b] Isopropenyl acetate.

Table 2[a]
Assays carried out with the racemic carbinol (±)-**3d**

	1,4-Dioxane	Et_2O	Hexane	THF	CH_2Cl_2	TBME	
PSL	-	-	+	-	-	-[b]	
PPL	-	-	-	-	-	-	
CAL	-	-	-	-	-	-[b]	
CCL	-	+	+	-	-	+	+[b]
Lipomod AC	-	-	+	-	-	-	+[b]
ANL	-	-	-	-	-	-	

[a] Vinyl acetate. [b] Isopropenyl acetate. In all cases very low conversions were obtained.

The enzymatic transesterification of the β-hydroxyisoxazole (±)-**3** produced the acylation product in a wide range of solvents and enzymes (Scheme 2). The specific rotations of the *O*-acetyl derivative (*R*)-**4**, and the remaining unreacted alcohol (*S*)-**3a**, were measured (Table 3) and based on these rotation values, we decided to determine the enantioselectivity, *E*, for the more promising experiments (Table 4).



Scheme 2.

The best enantiomeric ratio ($E = 35$) for the process was achieved using PSL and vinyl acetate as acylating agent in diethyl ether (Table 4, entry 1). Under these reaction conditions the enantiopure alcohol (*S*)-**3a** could be obtained if the reaction was extended beyond 50% conversion. When CAL catalyzed the reaction in *tert*-butyl methyl ether (TBME) (Table 4, entries 4 and 5)

Table 3
Specific rotation values of the compounds (*R*)-**4** and (*S*)-**3a**

entry	lipase	solvent	time (d)	*O*-acetyl product		remaining substrate	
				$[\alpha]_D^{25}$	c[c]	$[\alpha]_D^{25}$	c[c]
1[a]	PSL	CH_2Cl_2	4	15.0	1.40	16.0	1.45
2[a]	PSL	1,4-Dioxane	5	18.1	1.55	18.1	1.85
3[a]	PSL	Et_2O	1	17.8	1.23	21.6	0.95
4[a]	PSL	TBME	22 h.	16.8	1.65	24.4	1.29
5[b]	PSL	TBME	1	17.8	1.45	16.4	1.70
6[a]	PSL	THF	6	16.8	1.65	22.6	1.27
7[a]	CAL	1,4-Dioxane	1	12.2	1.75	25.8	1.15
8[a]	CAL	Hexane	5 h.	16.9	1.71	22.6	1.35
9[a]	CAL	TBME	3 h	18.5	1.65	20.6	1.65
10[b]	CAL	TBME	3 h.	18.7	1.25	10.6	2.28
11[b]	CAL	TBME	6 h.	18.3	1.69	20.8	1.66
12[a]	PPL	Et_2O	4	8.5	0.59	3.3	1.00
13[a]	PPL	Hexane	4	1.2	0.6	0.6	1.00
14[a]	ANL	THF	9	9.3	0.75	3.3	2.1
15[a]	CCL	CH_2Cl_2	1	-11.8	0.26	-12.9	2.07
16[a]	CCL	1,4-Dioxane	13	-7.5	1.19	-7.6	1.60
17[a]	CCL	THF	9	-7.3	0.76	-1.3	2.45
18[a]	Lipomod	CH_2Cl_2	4	-10.3	0.37	-5.3	2.65
19[a]	Lipomod	Et_2O	4 h.	-8.6	1.18	-5.30	1.95
20[a]	Lipomod	Hexane	1.5 h.	-8.2	1.68	-8.2	1.88
21[b]	Lipomod	TBME	6 h.	-11.7	1.18	-7.5	2.00
22[a]	Lipomod	THF	6	-5.3	0.85	-2.4	2.10

[a] Vinyl acetate. [b] Isopropenyl acetate. [c] g/100cm^3, $CHCl_3$.

Table 4
Enzymatic transesterification of the β-hydroxyisoxazole (±)-**3a**

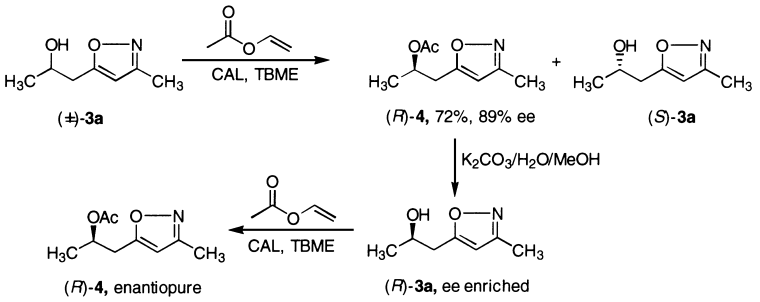
entry	lipase	acyl donor	solvent	t(h)	*c*[c](%)	*O*-acetyl product		remaining substrate		*E*[c]
						yield[d](%)	ee[e](%)	yield[d](%)	ee[e](%)	
1	PSL	VA[a]	Et_2O	24	49	54	86	27	84	35
2	PSL	VA[a]	TBME	22	54	72	77[f]	37	90[f]	23
3	CAL	VA[a]	Dioxane	24	59	76	66	33	>98	21
4	CAL	VA[a]	TBME	3	41	72	89	47	62	32
5	CAL	IPA[b]	TBME	6	43	74	88[f]	47	65[f]	31
6	CCL	VA[a]	CH_2Cl_2	24	45	75	80	59	65	17
7	Lipomod	VA[a]	CH_2Cl_2	96	25	44	70	75	23	7

[a] Vinyl acetate. [b] Isopropenyl acetate. [c] See ref.[14] [d] After flash chromatography. 100% yield at 50% conversion. [e] % ee were determined by ^{1}H-NMR spectroscopy in the presence of Eu(thf)$_3$ (see Experimental Section). [f] Determined by HPLC analysis of the *O*-Cbz derivatives on Chiralcel-OB/H using hexane:propan-2-ol 83:17 as eluent and 0.8 mL/min.

the reaction times substantially decreased. The use of isopropenyl acetate did not result in a significant improvement on the enantiomeric excesses.

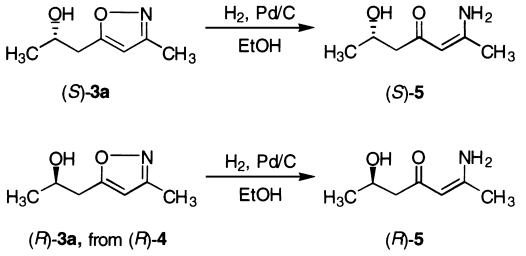
In order to obtain the alcohol (*S*)-**3a** in an enantiomerically pure form, we carried out the acetylation of racemic (±)-**3a** in the presence of CAL, in 1,4-dioxane and using vinyl acetate as acyl donor (Table 4, entry 3). When the reaction was stopped at a conversion of 59% (24 hours) the desired compound was achieved enantiomerically pure, ee >98% (only one diastereomer could be observed in the ^{1}H and ^{13}C NMR spectra) ($[\alpha]_D^{25}=+25.8$, c = 1.15, $CHCl_3$) while the acylated product (*R*)-**4** was recovered with 66% ee ($[\alpha]_D^{25}=+12.2$, c = 1.75, $CHCl_3$).

Since it is not possible to obtain the *O*-acetyl derivative (*R*)-**4** in enantiopure form we decided to slightly change the strategy. Following the previously described method, the alcohol (*S*)-**3a** was obtained optically pure, therefore we again carried out the enzymatic transesterification of the enantiomerically enriched (*R*)-**4** (89% ee) (Table 4, entry 4) after hydrolysis on a solution of potassium carbonate in aqueous methanol (Scheme 3). So the reaction of (*R*)-**3a** with vinyl acetate in the presence of CAL, in *tert*-butyl methyl ether, yielded the enantiopure (*R*)-**4** (ee >98%, $[\alpha]_D^{25}=+19.6$, c = 1.64, $CHCl_3$) after 3 hours of reaction. After the hydrolysis of (*R*)-**4**, we could characterize the enantiomerically pure (*R*)-**3a** ($[\alpha]_D^{25}=-26.3$, c = 0.95, $CHCl_3$).



Scheme 3.

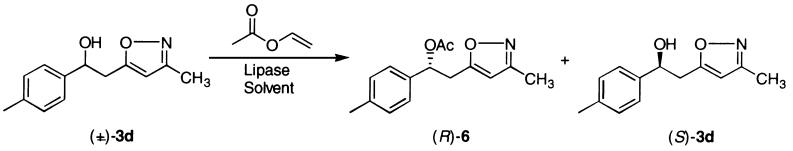
Our group had already worked on the reductive cleavage of the isoxazolic ring using Raney nickel as catalyst to produce several β-diketones.[3] Therefore, we decided to use another catalyst in order to obtain the desired enaminoketones. Effectively, the optically pure isoxazolic carbinol (*S*)-**3a** yielded the β′-hydroxy-β-enaminoketone (*S*)-**5** ($[\alpha]_D^{25}=+48.0$, c = 0.8, $CHCl_3$, lit.[10]) without racemization of the stereogenic center when the hydrogenation was carried out using Pd/C (Scheme 4). When the same reaction scheme was applied to (*R*)-**3a**, after hydrolysis of enantiopure (*R*)-**4**, the enaminoketone (*R*)-**5** ($[\alpha]_D^{25}=-50.6$, c = 0.57, $CHCl_3$) was also obtained.



Scheme 4.

The absolute configuration of (*S*)-**5** was assigned by comparison of it specific rotation with the described value in the literature,[10] which must also be the configuration of the initial alcohol (*S*)-**3a**. Based on these experimental results, we can say that the (*R*)-enantiomer reacts faster than its counterpart when the enzymatic acylation was carried out in the presence of lipases PSL, CAL, PPL and ANL. This fact is in accordance with Kazlauskas' rule[15] for the resolution of secondary alcohols. On the contrary, and despite the specific rotation values indicating a low enantioselectivity for the reaction, it is noteworthy that the lipases CCL and Lipomod AC showed an opposite enantiopreference towards the substrate (±)-**3a** (Table 3, entries 15–22).

The enzymatic transesterification of racemic β-hydroxyisoxazole (±)-**3d** was positive on five out of 34 experiments (Scheme 5). The obtained results are collected in Table 5.



Scheme 5.

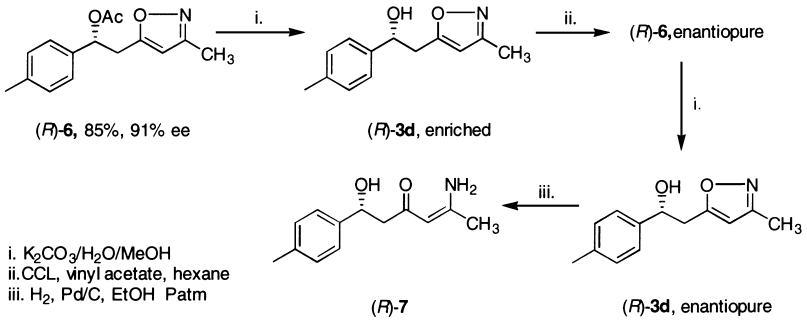
Table 5
Enzymatic transesterification of the β-hydroxyisoxazole (±)-**3d**

					O-acetyl product (*R*)-**6**				remaining substrate (*S*)-**3d**				
entry	lipase	solvent	t(d)	*c*[a]	yield[b]	ee[c]	$[\alpha]_D$	c[d]	yield[b]	ee[c]	$[\alpha]_D$	c[d]	*E*[a]
1	PSL	Hexane	7	22	33	45	29.5	1.05	77	13	-1.5	1.00	3
2	CCL	Hexane	7	39	71	91	42.1	1.02	63	58	-9.2	1.04	38
3	CCL	Hexane	13	42	85	91	42.0	2.37	57	67	-10.4	3.76	43
4	CCL	Et_2O	6	16	35	95	43.1	1.15	59	19	-4.9	3.19	50
5	CCL	TBME	12	31	40	94	42.6	1.29	69	43	-5.8	3.77	49
6	Lipomod	Hexane	6	10	16	>98	44.9	0.52	80	11	-2.2	4.36	110

[a] See ref.[14] [b] After flash chromatography. 100% yield at 50% conversion. [c] % ee were determined by ^{1}H-NMR spectroscopy in the presence of Eu(thf)$_3$ (see Experimental Section). [d] g/100 cm^3, $CHCl_3$.

From the data shown in Table 5 it can be seen that CCL and Lipomod AC seem to be the most suitable lipases for the enzymatic resolution of (±)-**3d**. When the reaction was carried out in the presence of Lipomod AC (Table 5, entry 6) enantiopure (*R*)-**6** was obtained, ee >98% (only one diastereomer could be observed in the ^{1}H and ^{13}C NMR spectra) ($[\alpha]_D^{25}$ = +44.9, c = 0.52, $CHCl_3$). Although the enantioselectivity for the reaction, *E* = 110, indicates that it is possible to produce enantiomerically pure remaining substrate (*S*)-**3d**, this reaction is not interesting for practical purposes due to its low conversion, only 10% after 6 days.

Following a similar procedure to that employed with the substrate (±)-**3a**, CCL catalyzed the acetylation of enantiomerically enriched (*R*)-**6**, 91% ee (Table 5, entry 3) in hexane, using vinyl acetate as acyl donor (Scheme 6). This led to the *O*-acetyl derivative (*R*)-**6** with an enantiomeric excess >98% (only one diastereomer could be observed in the ^{1}H and ^{13}C NMR spectra) ($[\alpha]_D^{25}$ = +49.5, c = 2.0, $CHCl_3$).



Scheme 6.

As shown in Scheme 6, the reductive cleavage of the isoxazolic ring of carbinol (*R*)-**3d** ($[\alpha]_D^{25} = +21.1$, c = 1.4, $CHCl_3$) gave the enantiopure enaminoketone (*R*)-**7** ($[\alpha]_D^{25} = 44.4$, c = 0.5, $CHCl_3$). The absolute configuration of the stereogenic carbon atom of the (*R*)-**7** was assigned by X-ray analysis (Fig. 1; absolute structure parameter 0.0(15)).

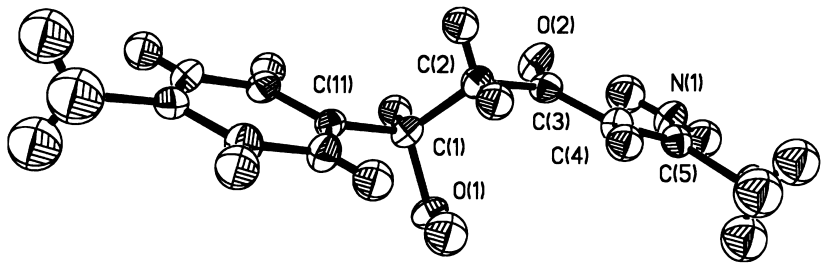


Figure 1. X-Ray structure of enaminoketone (*R*)-**7**

In summary, we have reported a systematic study of the transesterification of isoxazolic carbinols catalyzed by different commercial lipases. The enzymatic resolution of the isoxazolic alcohols constitutes an easy and efficient method to prepare β′-hydroxy-β-enaminoketones in enantiopure form. These are highly interesting compounds in organic synthesis and their synthesis is difficult by other methods.

3. Experimental

3.1. General

All reagents were of commercial quality. Solvents were distilled over an adequate dessicant and stored under argon. Precoated TLC plates of silica gel 60 F254 from Merck were used while for column chromatography, Merck silica gel 60/230–400 mesh was applied. Mps were determined with a Gallenkamp MFB-595 apparatus and are uncorrected. Optical rotations were measured at room temperature with a 141 Perkin–Elmer polarimeter. ^1H and ^{13}C NMR spectra for solutions in $CDCl_3$ were measured using a Bruker AC-300 (^1H 300 MHz and ^{13}C 75 MHz). Chemical-shift values are expressed in ppm (δ), relative to TMS as internal reference: *J* values are given in hertz. IR spectra were measured using a Nicolet FTIR-20-SX spectrometer. Mass spectra were recorded

on a Hewlett–Packard 5988/A spectrometer. Elemental analyses were determined with a Perkin–Elmer Elemental Analyzer 2400 CHN and HPLC analyses were carried out on a Shimadzu LC liquid chromatograph. 3,5-Dimethylisoxazole **1** and 3-methyl-5-phenylisoxazole **2** were prepared following methods described in the literature.[16,17]

3.2. Preparation of racemic β-hydroxyisoxazoles *3a–i*. General procedure

In a three-neck flask THF (30 mL) was placed at –40° C under an argon atmosphere. Then were added, in turn, BuLi (1.6 M, 40 mmol) and diisopropylamine (DIA) (4.45 g, 6.28 mL, 44 mmol). The mixture was slowly allowed to reach rt and stirred for 15 min. To the solution of LDA in THF, the isoxazole (40 mmol) in THF was added dropwise at –78°C. The reaction mixture was stirred for 1 h and the aldehyde (40 mmol) was then slowly added. The mixture was stirred at the same temperature and after that it was hydrolyzed with water and extracted with dichloromethane. The combined organic layers were dried and evaporated to dryness. The residue was chromatographed to give the desired compounds.

3.2.1. (±)-5-(2-Hydroxypropyl)-3-methylisoxazole *3a*

The reaction of 3,5-dimethylisoxazole **1** (0.97 g, 10.0 mmol) with acetaldehyde (0.57 mL, 10.0 mmol) following the previously described method gave the racemic β-hydroxyisoxazole **3a** in a yield of 78%. The product was purified by flash chromatography using ethyl acetate:hexane (1:1) as eluent. It was a yellow syrup.[10] ^{1}H NMR (300 MHz, $CDCl_3$): 1.26 (d, 3H, $J=6.2$ Hz, CH_3), 2.26 (s, 3H, CH_3-isx), 2.86 (d, 2H, $J=6.2$ Hz, CH_2), 4.14–4.20 (m, 1H, C*H*-OH), 5.95 (s, 1H, *H*-isx). ^{13}C NMR (75 MHz, $CDCl_3$): 11.2 (*C*H$_3$), 22.9 (*C*H$_3$), 36.2 (*C*H$_2$), 65.7 (*C*H), 103.0 (*C*-arm), 159.7 (*C*-arm), 170.1 (*C*-arm). MS (EI) *m*/*z*: 141 (0.49%, M$^+$), 126 (1.22, M$^+$–15), 97 (100, $C_5H_7NO^+$), 82 (12.83, $C_4H_4NO^+$), 54 (20.19, $C_3H_4N^+$), 45 (22.08, C_2H_5O). IR (thin layer): 3400, 2990, 1610, 1420 cm^{-1}.

3.2.2. (±)-5-(2-Hydroxy-3-methylbutyl)-3-methylisoxazole *3b*

The reaction of 3,5-dimethylisoxazole **1** (0.97 g, 10.0 mmol) with isobutyraldehyde (0.91 mL, 10.0 mmol)) following the previously described method gave the racemic β-hydroxyisoxazole **3b** in a yield of 24%. The product was purified by flash chromatography using diethyl ether:hexane (3:1) as eluent. It was a yellow syrup. ^{1}H NMR (300 MHz, $CDCl_3$): 0.98 (d, 6H, $J=6.8$ Hz, 2CH_3), 1.69–1.76 (m, 1H, C*H*-OH), 2.09 (d, 1H, $J=4.5$ Hz, O*H*), 2.26 (s, 3H, CH_3-isx), 2.81 (dd, 1H, $J=15.0$ Hz, $J=8.5$ Hz, *H*-CH$_2$), 2.90 (dd, 1H, $J=15.0$ Hz, $J=3.9$ Hz, *H*-CH$_2$), 3.71–3.77 (m, 1H, C*H*-OH), 5.96 (s, 1H, *H*-isx). ^{13}C NMR (75 MHz, $CDCl_3$): 11.2 (*C*H$_3$), 17.1 and 18.5 (*C*H$_3$), 31.7 (*C*H$_2$), 33.2 (*C*H), 74.2 (*C*H), 102.9 (*C*-arm), 159.7 (*C*-arm), 170.8 (*C*-arm). MS (EI) *m*/*z*: 170 (2.31%, M$^+$+1), 97 (100, $C_5H_7NO^+$), 82 (36.05, $C_4H_4NO^+$), 73 (20.98, $C_4H_9O^+$), 54 (32.68, $C_3H_4N^+$). IR (thin layer): 3425, 2950, 1610, 1420 cm^{-1}.

3.2.3. (±)-5-(2-Hydroxy-2-phenylethyl)-3-methylisoxazole *3c*

The reaction of 3,5-dimethylisoxazole **1** (0.97 g, 10.0 mmol) with benzaldehyde (1.02 mL, 10.0 mmol) following the previously described method gave the racemic β-hydroxyisoxazole **3c** in a yield of 77%. The product was purified by flash chromatography using ethyl acetate:hexane (1:2) as eluent. It was a white solid, mp 66–67°C (hexane–isopropanol) (lit.[18]). ^{1}H NMR (300 MHz, $CDCl_3$): 2.16 (s, 3H, CH_3-isx), 2.75 (br s, 1H, O*H*), 3.02 (dd, 1H, $J=15.2$ Hz, $J=5.0$ Hz, *H*-CH$_2$), 3.12 (dd, 1H, $J=15.2$ Hz, $J=8.2$ Hz, *H*-CH$_2$), 4.99 (dd, 1H, $J=8.2$ Hz, $J=5.0$ Hz, C*H*-OH), 5.82

(s, 1H, *H*-isx), 7.25–7.33 (m, 5H, *H*-arm). ^{13}C NMR (75 MHz, $CDCl_3$): 11.2 (CH_3), 36.5 (CH_2), 71.8 (*C*H), 103.3 (*C*H), 125.6, 127.8 and 128.4 (*C*H-arm), 143.0 (*C*-arm), 159.7 (*C*-arm), 169.6 (*C*-arm). MS (EI) *m*/*z*: 204 (19.16%, M^++1), 97 (100, $C_5H_7NO^+$), 77 (96.91, $C_6H_5^+$), 107 (28.61, C_7H_7O). IR (KBr): 3390, 2925, 1607, 1497, 1420, 1055 cm^{-1}. $C_{12}H_{13}NO_2$ calcd: C, 70.92%; H, 6.45; N, 6.89; found: C, 71.01%; H, 6.57; N, 6.86.

*3.2.4. (±)-5-(2-Hydroxy-2-*p*-tolylethyl)-3-methylisoxazole* **3d**

The reaction of 3,5-dimethylisoxazole **1** (0.97 g, 10.0 mmol) with *p*-toluylaldehyde (1.18 mL, 10.0 mmol) following the previously described method gave the racemic β-hydroxyisoxazole **3d** in a yield of 88%. The product was purified by flash chromatography using ethyl acetate:hexane (1:2) as eluent. It was a white solid, mp 51–52°C (hexane–isopropanol) (lit.[18]). ^{1}H NMR (300 MHz, $CDCl_3$): 2.20 (s, 3H, C*H*$_3$-isx), 2.33 (s, 3H, C*H*$_3$-Ph), 3.03 (dd, 1H, J = 15.2 Hz, J = 5.0 Hz, *H*-CH_2), 3.13 (dd, 1H, J = 15.2 Hz, J = 8.3 Hz, *H*-CH_2), 4.98 (dd, 1H, J = 8.3 Hz, J = 5.0 Hz, C*H*-OH), 5.85 (s, 1H, *H*-isx), 7.13–7.24 (m, 4H, *H*-arm). ^{13}C NMR (75 MHz, $CDCl_3$): 11.1 (CH_3), 20.9 (CH_3-Ph), 36.3 (CH_2), 71.5 (*C*H), 103.1 (*C*H), 125.5 and 129.0 (*C*H-arm), 137.3 and 140.0 (*C*-arm), 159.6 (*C*-arm), 169.7 (*C*-arm). MS (EI) *m*/*z*: 217 (1.52%, M^+), 121 (65.55, $C_8H_9O^+$), 97 (100, $C_5H_7NO^+$), 91 (33.96, $C_7H_7^+$), 65 (7.42, $C_5H_5^+$), 54 (5.13, $C_3H_4N^+$). IR (KBr): 3375, 2950, 1607, 1515, 1420, 780 cm^{-1}. $C_{13}H_{15}NO_2$ calcd: C, 71.86%; H, 6.96; N, 6.45; found: C, 71.90%; H, 7.11; N, 6.17.

*3.2.5. (±)-5-(2-Hydroxy-2-*p*-methoxyphenylethyl)-3-methylisoxazole* **3e**

The reaction of 3,5-dimethylisoxazole **1** (0.97 g, 10.0 mmol) with *p*-methoxybenzaldehyde (1.21 mL, 10.0 mmol) following the previously described method gave the racemic β-hydroxyisoxazole **3e** in a yield of 79%. The product was purified by flash chromatography using ethyl acetate:hexane (1:2) as eluent. It was a white solid, mp 42–43°C (hexane–isopropanol) (lit.[18]). ^{1}H NMR (300 MHz, $CDCl_3$): 2.16 (s, 3H, C*H*$_3$-isx), 2.75 (br s, 1H, O*H*), 3.00 (dd, 1H, J = 15.2 Hz, J = 5.3 Hz, *H*-CH_2), 3.12 (dd, 1H, J = 15.2 Hz, J = 8.1 Hz, *H*-CH_2), 3.76 (s, 3H, OC*H*$_3$), 4.94 (dd, 1H, J = 8.1 Hz, J = 5.3 Hz, C*H*-OH), 5.81 (s, 1H, *H*-isx), 6.82–7.24 (m, 4H, *H*-arm). ^{13}C NMR (75 MHz, $CDCl_3$): 11.0 (CH_3), 36.2 (CH_2), 54.9 (O*C*H$_3$), 71.2 (*C*H), 103.0 (*C*H), 113.5 and 126.8 (*C*H-arm), 135.1 and 158.8 (*C*-arm), 159.5 (*C*-arm), 169.6 (*C*-arm). MS (EI) *m*/*z*: 233 (0.77%, M^+), 137 (91.80, $C_8H_9O_2^+$), 109 (55.02, $C_7H_9O^+$), 97 (100, $C_5H_7NO^+$), 77 (57.69, $C_6H_5^+$). IR (thin layer): 3400, 2950, 1610, 1515, 1250, 1420, 1035 cm^{-1}. $C_{13}H_{15}NO_3$ calcd: C, 66.94%; H, 6.48; N, 6.00; found: C, 67.10%; H, 6.46; N, 5.69.

*3.2.6. (±)-5-(2-Hydroxy-2-*p*-nitrophenylethyl)-3-methylisoxazole* **3f**

The reaction of 3,5-dimethylisoxazole **1** (0.97 g, 10.0 mmol) with *p*-nitrobenzaldehyde (1.52 g, 10.0 mmol) following the previously described method gave the racemic β-hydroxyisoxazole **3f** in a yield of 5%. The product was purified by flash chromatography using diethyl ether:hexane (3:1) as eluent. It was a yellow solid, mp 75–76°C (hexane–isopropanol). ^{1}H NMR (300 MHz, $CDCl_3$): 2.26 (s, 3H, C*H*$_3$), 2.63 (d, 1H, J = 3.7 Hz, O*H*), 3.08–3.21 (m, 2H, C*H*$_2$), 5.19–5.24 (m, 1H, C*H*-OH), 5.89 (s, 1H, *H*-isx), 7.50–7.57 (m, 2H, *H*-arm), 8.19–8.24 (m, 2H, *H*-arm). ^{13}C NMR (75 MHz, $CDCl_3$): 11.2 (CH_3), 36.5 (CH_2), 70.9 (*C*H), 103.8 (*C*H), 123.7 and 126.5 (*C*H-arm), 147.3 and 150.2 (*C*-arm), 159.9 (*C*-arm), 168.6 (*C*-arm). MS (EI) *m*/*z*: 249 (0.52%, M^++1), 152 (15.74, $C_7H_6NO_3^+$), 97 (100, $C_5H_7NO^+$), 77 (13.72, $C_6H_5^+$), 54 (15.77, $C_3H_4N^+$). IR (KBr): 3375, 2950, 1610, 1525, 1420, 1350 cm^{-1}. $C_{12}H_{12}N_2O_4$ calcd: C, 58.07%; H, 4.87; N, 11.28; found: C, 58.54%; H, 4.98; N, 11.27.

3.2.7. (±)-3-(2-Hydroxy-2-phenylethyl)-5-phenylisoxazole ***3g***

The reaction of 3-methyl-5-phenylisoxazole **2** (1.59 g, 10.0 mmol) with benzaldehyde (1.02 mL, 10.0 mmol) following the previously described method gave the racemic β-hydroxyisoxazole **3g** in a yield of 47%. The product was purified by flash chromatography using ethyl acetate:hexane (1:4) as eluent. It was a white solid, mp 103–104°C (hexane–isopropanol) (lit.[19]). ^{1}H NMR (300 MHz, $CDCl_3$): 3.00 (d, 1H, $J=3.4$ Hz, O*H*), 3.06–3.17 (m, 2H, CH_2), 5.05–5.10 (m, 1H, C*H*-OH), 6.35 (s, 1H, *H*-isx), 7.24–7.46 (m, 8H, *H*-arm), 7.68–7.73 (m, 2H, *H*-arm). ^{13}C NMR (75 MHz, $CDCl_3$): 36.2 (*C*H_2), 75.5 (*C*H), 100.1 (*C*H), 125.7, 127.9, 128.5, 128.9 and 130.1 (*C*H-arm), 127.3 and 143.1 (*C*-arm), 161.8 (*C*-arm), 169.7 (*C*-arm). MS (EI) *m*/*z*: 265 (3.88%, M^+), 188 (1.10, M^+–$C_6H_5^+$), 159 (100, $C_{10}H_9NO^+$), 77 (88.90, $C_6H_5^+$), 51 (21.22, $C_4H_3^+$). IR (KBr): 3425, 2954, 1608, 1510, 1420, 1059 cm^{-1}. $C_{17}H_{15}NO_2$ calcd: C, 76.96%; H, 5.57; N, 5.28; found: C, 76.82%; H, 5.82; N, 5.60.

*3.2.8. (±)-3-(2-Hydroxy-2-*p*-tolylethyl)-5-phenylisoxazole* ***3h***

The reaction of 3-methyl-5-phenylisoxazole **2** (1.59 g, 10.0 mmol) with *p*-toluylaldehyde (1.18 mL, 10.0 mmol) following the previously described method gave the racemic β-hydroxyisoxazole **3h** in a yield of 61%. The product was purified by flash chromatography using ethyl acetate:hexane (1:2) as eluent. It was a white solid, mp 115–116°C (hexane–isopropanol). ^{1}H NMR (300 MHz, $CDCl_3$): 2.24 (s, 3H, CH_3), 2.94 (br s, 1H, O*H*), 2.94–3.13 (m, 2H, CH_2), 4.95 (dd, 1H, $J=7.5$ Hz, $J=5.3$ Hz, C*H*-OH), 6.29 (s, 1H, *H*-isx), 7.05–7.37 (m, 7H, *H*-arm), 7.61–7.64 (m, 2H, *H*-arm). ^{13}C NMR (75 MHz, $CDCl_3$): 21.1 (*C*H_3-Ph), 36.0 (*C*H_2), 72.4 (*C*H), 100.1 (*C*H), 125.7, 128.8, 129.1 and 130.0 (*C*H-arm), 127.3, 137.5 and 140.1 (*C*-arm), 161.9 (*C*-arm), 169.5 (*C*-arm). MS (EI) *m*/*z*: 279 (0.65%, M^+), 159 (72.49, $C_{10}H_9NO^+$), 121 (23.95, $C_8H_9O^+$), 91 (49.21, $C_7H_7^+$), 77 (100, $C_6H_5^+$), 51 (41.21, $C_4H_3^+$). IR (KBr): 3419, 2912, 1572, 1498, 1420, 1060 cm^{-1}. $C_{18}H_{17}NO_2$ calcd: C, 77.40%; H, 6.13; N, 5.01; found: C, 77.19%; H, 6.19; N, 4.63.

*3.2.9. (±)-3-(2-Hydroxy-2-*p*-methoxyphenyl)-5-phenylisoxazole* ***3i***

The reaction of 3-methyl-5-phenylisoxazole **2** (1.59 g, 10.0 mmol) with *p*-methoxybenzaldehyde (1.21 mL, 10.0 mmol) following the previously described method gave the racemic β-hydroxyisoxazole **3i** in a yield of 43%. The product was purified by flash chromatography using ethyl acetate:hexane (1:1) as eluent. It was a white solid, mp 120–122°C (hexane–isopropanol). ^{1}H NMR (300 MHz, $CDCl_3$): 2.63 (d, 1H, $J=3.1$ Hz, O*H*), 3.06-3.24 (m, 2H, CH_2), 3.81 (s, 3H, OCH_3), 5.04–5.10 (m, 1H, C*H*-OH), 6.38 (s, 1H, *H*-isx), 6.88–6.93 (m, 2H, *H*-arm), 7.26–7.49 (m, 5H, *H*-arm), 7.73–7.77 (m, 2H, *H*-arm). ^{13}C NMR (75 MHz, $CDCl_3$): 36.1 (*C*H_2), 55.2 (O*C*H_3), 72.2 (*C*H), 100.1 (*C*H), 113.9, 125.7, 127.0, 128.9 and 130.1 (*C*H-arm), 127.4, 135.3 and 159.2 (*C*-arm), 161.9 (*C*-arm), 169.6 (*C*-arm). MS (EI) *m*/*z*: 295 (2.53%, M^+), 159 (100, $C_{10}H_9NO^+$), 137 (52.73, $C_8H_9O_2^+$), 77 (40.01, $C_6H_5^+$), 51 (10.39, $C_4H_3^+$). IR (KBr): 3433, 2951, 1612, 1512, 1420, 1255, 1009 cm^{-1}. $C_{18}H_{17}NO_3$ calcd: C, 73.21%; H, 5.80; N, 4.74; found: C, 73.09%; H, 5.82; N, 4.61.

*3.3. General procedure for the enzymatic resolution of the racemic isoxazolic carbinols (±)-****3a*** *and (±)-****3d***

Carbinol (±)-**3a** or (±)-**3d** (1 mmol) and vinyl or isopropenyl acetate (10 mmol) were added to a suspension of the enzyme (360 mg when ANL, CCL, LIPOMOD AC, PPL or PSL were used or 60 mg if CAL was used) in a suitable solvent (9 mL) under an argon atmosphere. The mixture

was shaken at 27°C and 250 rpm for the times indicated in Tables 4 and 5. Then the biocatalyst was filtered off and washed with dichloromethane (2×10) and the organic solvents evaporated. The crude was subjected to column chromatography using ethyl acetate:hexane (1:2) as eluent in the case of carbinol (±)-**3a**, or diethyl ether:hexane (1:3) for the carbinol (±)-**3d**.

*3.3.1. (*R*)-5-(2-Acetylpropyl)-3-methylisoxazole (*R*)-**4***

The enzymatic resolution of (±)-**3a** in the presence of CAL and using vinyl acetate as acyl donor and TBME as solvent yielded (*R*)-**4** as a colorless oil. Then this compound was hydrolyzed using a mixture of K_2CO_3 in aqueous methanol and the enriched alcohol was acylated in the presence of CAL. In this manner the compound (*R*)-**4** showed ee >98%. The determination of the enantiomeric excess for the *O*-acylated product was made by ^{1}H NMR spectroscopy in the presence of 3.0 mol equiv. of Eu(tfc)$_3$ (on the spectrum only one signal was observed). $[\alpha]_D^{25}$ = +19.6 (c = 1.64, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): 1.25 (d, 3H, J = 6.4 Hz, CH_3), 2.00 (s, 3H, CH_3-COO), 2.24 (s, 3H, CH_3-isx), 2.91 (dd, 1H, J = 15.0 Hz, J = 5.8 Hz, H-CH_2), 2.98 (dd, 1H, J = 15.0 Hz, J = 6.5 Hz, H-CH_2), 5.09–5.20 (m, 1H, CH-OAc), 5.87 (s, 1H, H-isx). ^{13}C NMR (75 MHz, $CDCl_3$): 11.4 (*C*H$_3$), 19.6 (*C*H$_3$), 21.2 (*C*H$_3$-COO), 33.0 (*C*H$_2$), 68.4 (*C*H), 103.1 (*C*H-arm), 159.8 (*C*-arm), 168.9 (O*C*O), 170.4 (*C*-arm). MS (EI) *m*/*z*: 184 (0.16%, M$^+$+1), 97 (17.48, $C_5H_7NO^+$), 82 (5.98, $C_4H_4NO^+$), 54 (6.75, $C_3H_4N^+$), 43 (100, $C_2H_3O^+$). IR (thin layer): 2950, 1740, 1610, 1420, 1245 cm^{-1}.

*3.3.2. (*S*)-5-(2-Hydroxypropyl)-3-methylisoxazole (*S*)-**3a***

The enantiopure carbinol (*S*)-**3a** was obtained as a yellow oil; ee >98%, $[\alpha]_D^{25}$ = +25.8, c = 1.15, $CHCl_3$. The determination of the enantiomeric excess was made by ^{1}H NMR spectroscopy in the presence of 3.0 mol equiv. of Eu(tfc)$_3$, determined from its *O*-acetyl derivative and on the spectrum only one signal was observed.

*3.3.3. (*R*)-5-(2-Acetyl-2-*p*-tolylethyl)-3-methylisoxazole (*R*)-**6***

The double enzymatic resolution of (±)-**3d** in the presence of CCL and using vinyl acetate as acyl donor and hexane as solvent yielded (*R*)-**6** as a colorless oil. This compound showed ee >98%. The determination of the enantiomeric excess was made by ^{1}H NMR spectroscopy in the presence of 4.0 mol equiv. of Eu(tfc)$_3$ and on the spectrum only one signal was observed. $[\alpha]_D^{25}$ = +49.5 (c = 2.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): 2.02 (s, 3H, CH_3-COO), 2.20 (s, 3H, CH_3-isx), 2.30 (s, 3H, CH_3-Ph), 3.15 (dd, 1H, J = 15.4 Hz, J = 5.6 Hz, H-CH_2), 3.30 (dd, 1H, J = 15.4 Hz, J = 8.2 Hz, H-CH_2), 5.78 (s, 1H, H-isx), 6.02 (dd, 1H, J = 8.2 Hz, J = 5.6 Hz, CH-OAc), 7.11–7.22 (m, 4H, H-arm). ^{13}C NMR (75 MHz, $CDCl_3$): 11.1 (*C*H$_3$), 20.8 (*C*H$_3$-COO), 20.9 (*C*H$_3$-Ph), 33.4 (*C*H$_2$), 72.8 (*C*H), 102.8 (*C*H-arm), 126.1 and 129.0 (*C*H-arm), 135.7 and 137.9 (*C*-arm), 159.4 (*C*-arm), 168.2 (O*C*O), 169.6 (*C*-arm). MS (EI) *m*/*z*: 259 (0.20%, M$^+$), 216 (0.12, M$^+$–$C_2H_3O^+$), 121 (22.74, $C_8H_9O^+$), 97 (100, $C_5H_7NO^+$), 65 (7.17, $C_5H_5^+$), 43 (100, $C_2H_3O^+$). IR (thin layer): 2950, 1745, 1610, 1520, 1420 cm^{-1}.

3.4. General procedure for the catalytic hydrogenation of the enantiopure isoxazolic carbinols

A solution of isoxazolic carbinol (1 mmol) in ethanol (10 mL) was reduced in the presence of 10% Pd on carbon under H_2 at atmospheric pressure. The mixture was stirred until the starting product disappeared and then was filtered through Celite and concentrated under reduced pressure.

The flash chromatography of the crude product (diethyl ether) achieved the desired β′-hydroxy-β-enaminoketones.

*3.4.1. 2-Amino-4-oxo-2-hepten-6-ol (*R*)-**5***

The previously described procedure led to the compound (*R*)-**5** in a yield of 88% as a white solid, mp 82–85°C (hexane–isopropanol). $[\alpha]_D^{25} = -50.6$ (c = 0.57, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): 1.19 (d, 3H, $J = 6.4$ Hz, CH_3), 1.94 (s, 3H, CH_3), 2.33 (dd, 1H, $J = 15.7$ Hz, $J = 9.1$ Hz, *H*-CH_2), 2.46 (dd, 1H, $J = 15.7$ Hz, $J = 2.9$ Hz, *H*-CH_2), 4.17 (m, 1H, C*H*-OH), 4.32 (br s, 1H), 4.99 (s, 1H, C*H*), 5.35 (br s, 1H), 9.75 (br s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): 22.2 (CH_3), 22.6 (CH_3), 48.5 (CH_2), 65.4 (*C*H), 95.4 (*C*H), 162.7 (CNH_2), 198.3 (*C*O). MS (EI) *m*/*z*: 143 (12.97%, M^+), 128 (1.32, $C_6H_{10}NO_2^+$), 84 (100, $C_4H_6NO^+$), 42 (17.17, $C_2H_2O^+$). IR (KBr): 3405, 2959, 2919, 1620, 1534, 1414, 1295, 1076, 937, 639 cm^{-1}.

*3.4.2. 2-Amino-6-*p*-tolyl-4-oxo-2-hexen-6-ol (*R*)-7*

The previously described procedure led to the compound (*R*)-**7** in a yield of 82% as a white solid, mp 138–139°C (hexane–isopropanol) $([\alpha]_D^{25} = +44.4$ (c = 0.5, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): 1.93 (s, 3H, CH_3), 2.33 (s, 3H, CH_3-Ph), 2.63 (d, 2H, $J = 6.3$ Hz, CH_2), 4.65 (br s, 1H), 5.00 (s, 1H, C*H*), 5.07 (dd, 1H, $J = 6.3$ Hz, C*H*-OH), 5.26 (br s, 1H), 7.13–7.29 (m, 4H, *H*-arm), 9.78 (br s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): 21.1 (CH_3-Ph), 22.3 (CH_3), 49.3 (CH_2), 71.3 (*C*H), 95.6 (*C*H), 125.6 and 128.9 (*C*H-arm), 136.8 and 140.7 (*C*-arm), 162.7 (CNH_2), 197.9 (*C*O). MS (EI) *m*/*z*: 219 (18.88%, M^+), 134 (3.26, $C_9H_{10}O^+$), 99 (12.27, $C_5H_9NO^+$), 84 (100, $C_4H_6NO^+$), 42 (28.11, $C_2H_2O^+$). IR (KBr): 3362, 2952, 2919, 1613, 1534, 1388, 1136, 997, 811, 566 cm^{-1}.

*3.5. Crystal structure determination for compound (*R*)-7*

Crystals suitable for X-ray study were grown from hexane–isopropanol solutions. A crystal of dimensions $0.1 \times 0.2 \times 0.4$ mm^3 was attached to a glass fiber and transferred to a Bruker AXS SMART 1000 diffractometer with graphite monochromatized Mo-Kα X-radiation and a CCD area detector. A hemisphere of the reciprocal space was collected up to $2\theta = 46.6°$. Raw frame data were integrated with the SAINT program.[20] The structure was solved by direct methods with SHELXTL.[21] An empirical absorption correction was applied with the SADABS program.[22] All non-hydrogen atoms were refined anisotropically. Hydrogen atoms were set in calculated positions and refined as riding atoms, with a common thermal parameter. All calculations were made with SHELXTL. Final *R* values were $R_1 = 0.0324$ for 1342 reflections with $I > 2\sigma(I)$, and $wR_2 = 0.0806$ (for all 1695 data). Additional material is available from the Cambridge Crystallographic Data Centre, Cambridge, UK, including atomic coordinates, thermal parameters and a full list of bond lengths and angles.

Acknowledgements

We are grateful to Professor Vicente Gotor for the generous gift of lipases used in this investigative work. Alicia Maestro would also like to thank Professor Gotor for accepting her into his investigation group during the postdoctoral period. We also thank Daniel Miguel San José for the crystal X-ray analysis, and financial support from the JCYL, Spain (Project VA08/00B).

References

1. De Simoni, G.; Tacconi, G.; Barco, A.; Pollini, G. P. *Natural Products Synthesis Through Pericyclic Reactions*; ACS: Washington, 1983.
2. (a) Alberola, A.; Andrés, C.; González Ortega, A.; Pedrosa, R.; Vicente, M. *An. Chim.* **1987**, *83*, C, 55; (b) Kashima, C. *Heterocycles* **1979**, *12*, 1343; (c) Alberola, A.; Andrés, C.; González Ortega, A.; Pedrosa, R. *J. Heterocyclic Chem.* **1984**, *21*, 1575; (d) Alberola, A.; Andrés, C.; González Ortega, A.; Pedrosa, R.; Vicente, M. *J. Heterocyclic Chem.* **1987**, *24*, 709.
3. Maestro, A.; Báñez, J. M.; López, J. A.; Romero-Ávila, M. C. *Synthesis* **1998**, 1023.
4. Maestro, A.; Báñez, J. M.; López, J. A.; Romero-Ávila, M. C. *Synthesis* **1998**, 1104.
5. Sharma, R. K.; Singh, R. V.; Tandon, J. P. *J. Inorg. Nuclear Chem.* **1980**, *42*, 1382.
6. Bartoli, G.; Cimarelli, C.; Palmieri, G. *J. Chem. Soc., Perkin Trans. 1* **1994**, 537.
7. Alberola, A.; Andrés, C.; González Ortega, A.; Pedrosa, R.; Vicente, M. *Synth. Commun.* **1987**, *17*, 1309.
8. Fustero, S.; García de la Torre, M.; Pina, B.; Fuentes, A. S. *J. Org. Chem.* **1999**, *64*, 5551.
9. (a) Uneyama, K.; Kobayashi, M. *J. Org. Chem.* **1994**, *59*, 3003; (b) Uneyama, K.; Kobayashi, M. *Tetrahedron Lett.* **1991**, *32*, 5981; (c) Uneyama, K.; Morimoto, O.; Yamashita, F. *Tetrahedron Lett.* **1989**, *30*, 4821; (d) Arnone, A.; Bravo, P.; Capelli, S.; Fronza, G.; Meille, S. V.; Zanda, M.; Cavicchio, G.; Crucianelli, M. *J. Org. Chem.* **1996**, *61*, 3375. Corrigenda: *J. Org. Chem.* **1996**, *61*, 9635.
10. Fogagnolo, M.; Giovannini, P. P.; Guerrini, A.; Medici, A.; Pedrini, P.; Colombi, N. *Tetrahedron: Asymmetry* **1998**, *9*, 2317.
11. (a) Drueckhammer, D. G.; Barbas III, C. F.; Nozaki, K.; Wong, C.-H. *J. Org. Chem.* **1988**, *53*, 1607; (b) Altenbach, H.-J.; Merhof, G. F.; Brauer, D. J. *Tetrahedron: Asymmetry* **1996**, *7*, 2493; (c) Schieweck, F.; Altenbach, H.-J. *Tetrahedron: Asymmetry* **1998**, *9*, 403; (d) Kang, S.-K.; Jeon, J.-H.; Yamaguchi, T.; Kim, J.-S.; Ko, B.-S. *Tetrahedron: Asymmetry* **1995**, *9*, 2139.
12. De Amici, M.; De Micheli, C.; Carrea, G.; Spezia, S. *J. Org. Chem.* **1989**, *54*, 2646.
13. Brunelle, D. J. *Tetrahedron Lett.* **1981**, *22*, 3699.
14. Chen, C.; Fujimoto, Y.; Girdaukas, G.; Sih, C. J. *J. Am. Chem. Soc.* **1982**, *104*, 7294.
15. Kazlauskas, R. J.; Weissfloch, A.; Rappaport, A. T.; Cuccia, L. A. *J. Org. Chem.* **1991**, *56*, 2656.
16. Morgan, G. T.; Burgess, H. *J. Chem. Soc.* **1921**, 697.
17. Lampe, W.; Smolinska, J. *Roczniki Chem.* **1954**, *28*, 163.
18. Kashima, C.; Uemori, M.; Tsuda, Y.; Omote, Y. *Bull. Chem. Soc. Jpn.* **1976**, *49*, 2254.
19. Alberola, A.; Pérez Serrano, A.; Rodríguez, M. T.; Orozco, C. *Heterocycles* **1989**, *29*, 667.
20. SAINT+, SAX area detector integration program, Version 6.02, Bruker AXS, Inc. Madison, WI, 1999.
21. Sheldrick, G. M. SHELXTL, an integrated system for solving, refining, and displaying crystal structures from diffraction data, Version 5.1, Bruker AXS, Inc. Madison, WI, 1998.
22. Sheldrick, G. M. SADABS, Empirical Absorption Correction Program, University of Göttingen: Göttingen, Germany, 1997.