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NITRILE OXIDES IN MEDICINAL CHEMISTRY. 6. ENZYMATIC RESOLUTION OF A SET OF BICYCLIC Δ^2-ISOXAZOLINES.

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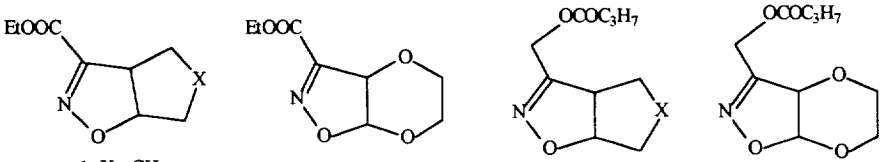
Abstract: Chymotrypsin selectively catalyzed the hydrolysis of a series of 3-ethoxycarbonyl-Δ^2-isoxazolines **1-4**, whereas lipase from *Pseudomonas cepacia* (lipase PS) was remarkably selective in hydrolysing the corresponding 3-hydroxymethyl-Δ^2-isoxazoline butyrates (**5-8**). The enantio-preference of chymotrypsin for the first set of compounds is the same as that observed for the lipase PS-catalyzed hydrolysis of the other series of substrates. The hydrolytic activity of lipase PS for compounds **5-8** was considerably higher than that shown by chymotrypsin for substrates **1-4**. Copyright © 1996 Elsevier Science Ltd

INTRODUCTION

Stereochemistry is an aspect of molecular structure which deeply influences the biological response in terms of activity and selectivity.[1] For this reason nowadays it has attracted the attention both of pharmaceutical companies and regulatory authorities.[2-3] In this context hydrolytic enzymes are increasingly used to perform kinetic resolutions of racemic alcohols, acids and esters of interest to medicinal chemists.[4] In the past we applied the chemoenzymatic approach to the synthesis of the enantiomers of broxaterol,[5] a β_2-adrenergic stimulant presently under clinical investigation for the treatment of bronchial asthma,[6] as well the chiral forms of acetyl-cycloserine, the immediate precursor of cycloserine, whose (R)-enantiomer is a natural broad-spectrum antibiotic.[7] Hydrolytic enzymes were also applied to the synthesis of the enantiomers of muscarone analogs.[8,9]

As an extension of our ongoing interest towards the synthesis of homochiral biologically active compounds, we now report the kinetic resolution of bicyclic 3-ethoxycarbonyl-Δ^2-isoxazolines **1-4** and 3-hydroxymethyl-Δ^2-isoxazoline butyrates **5-8** (Figure 1) which are potential precursors of aminosugars, antibiotics, β-hydroxyacids and α-methylene lactones.[10-13]

Figure 1



1: X= CH_2
2: X= $(CH_2)_2$
3: X= O

4

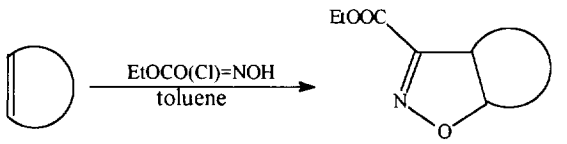
5: X= CH_2
6: X= $(CH_2)_2$
7: X= O

8

RESULTS AND DISCUSSION

Δ^2-Isoxazolines **1-4** have been prepared by refluxing a toluene solution of the appropriate alkene and ethyl chlorooximinoacetate in a 8:1 ratio. Derivatives **5-8** were prepared by treating ethyl Δ^2-isoxazoline-3-carboxylate esters **1-4** with sodium borohydride[14] followed by an esterification with butyryl chloride and pyridine (Scheme I).

Scheme I



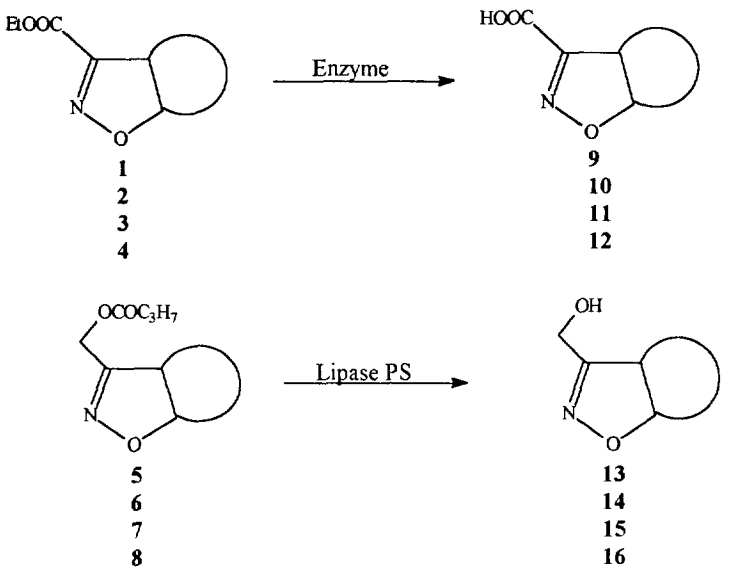
1-4

1-4 $\xrightarrow[2)\ C_3H_7COCl/Py]{1)\ NaBH_4/EtOH}$ **5-8**

In a preliminary investigation esters **1** and **2** were submitted to hydrolysis in a phosphate buffer solution (pH 7) under the catalysis of commercially available enzymes (Scheme II). The results of such a screening are collected in Table I. The degree of conversion and the enantiomeric excess (e.e.) were evaluated by chiral HPLC which gave excellent separation for both the enantiomers of the products and the residual esters (see Experimental Section). Inspection of the data obtained with compounds **1** and **2** (Table I) reveals that all the tested enzymes possess the same enantio-preference but that only chymotrypsin displays a remarkable enantioselectivity. Based on these results, substrates **3** and **4** were submitted to hydrolysis in the presence of this enzyme. As expected, chymotrypsin was able to discriminate the two enantiomers of compounds **3** and **4** with a good degree of selectivity and with the same enantio-preference previously observed with substrates **1** and **2** even though, due to priority rules, the notations are different. Unfortunately, compound **12**, the acid produced by the hydrolysis of ethyl ester **4**, was unstable and decomposed in the reaction medium. Therefore, on a preparative scale, the reaction gave rise to the levorotatory enantiomer only [(4S,5R); (-) **4**].

Furthermore, in spite of the satisfactory selectivity, the rate of hydrolysis was rather slow and chymotrypsin had to be used in a high enzyme-substrate ratio (approx. 1:3). Low reaction rates were also observed with the other enzymes listed in Table I.

Scheme II



A further reduction in reactivity was observed when the resolution of substrates **1-4** was attempted through a transesterification reaction with 1-butanol in benzene under the catalysis of chymotrypsin. This approach, if successful, would have made it possible to overcome the problem associated with the instability of the acid **12** produced by the hydrolysis of (±)-**4**.

The above reported results led us to investigate the enzyme-catalyzed hydrolysis of butyrates **5-8** (Scheme II).

It is worth pointing out that, at the catalytic site, the isoxazoline alcohol behaves as the leaving group whereas the isoxazoline acid acts as the acylating agent of the enzyme. The different role played by the two series of substrates could affect the enantio-preference and/or the extent of the enantioselectivity. The conversion of an acid to the corresponding carbinol[16] or its activation with an acyloxymethyl group[17] had already been reported to improve the resolution of substrates carrying a carboxylic group recalcitrant or non-selective towards lipase hydrolysis.

A preliminary screening carried out on butyrate **8** demonstrated that a number of enzymes were capable to hydrolyse the substrate rapidly and, in some cases, selectively. The best results both in terms of activity and selectivity were obtained with lipase PS which was therefore employed, with comparable results, also for the resolution of substrates **5, 6,** and **7** (Table II). Lipase PS displayed the same enantiopreference for substrates **5-8** and, at least for **5** and **6**, identical to that observed for compounds **1** and **2**. On the contrary, the hydrolysis

of butyrates **5-8** catalyzed by chymotrypsin was sluggish (a substrate/catalyst ratio of 1:1 was employed) and poorly enantioselective (E≤ 4). The enantiopreference was the same observed for esters **1-4**.

Table I. Enzyme-catalyzed hydrolysis of esters **1-4**

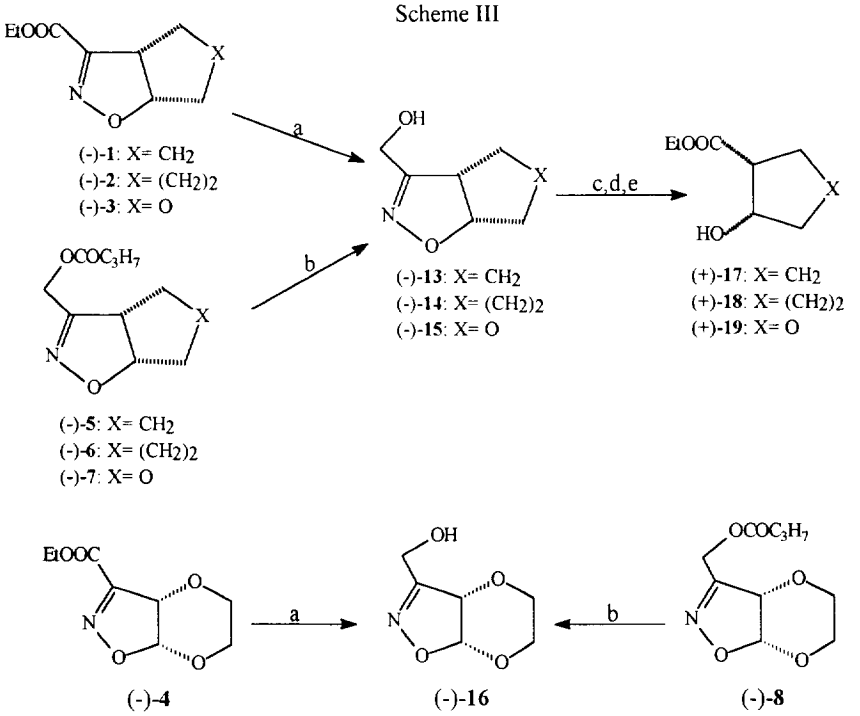
enzyme	substrate	conv. (%)	E^{15}	e.e.(%) of residual ester	e.e.(%) of acid	conf. of residual ester
C.E. NP[a]	**1**	89	1.1	11		4S,5S
C.E. NP	**2**	64	1.0	0		4S,5S
C.C.L.[b]	**1**	32	1.6	9		4S,5S
C.C.L.	**2**	48	1.0	0		4S,5S
lipase PS[c]	**1**	54	3.5	46		4S,5S
lipase PS	**2**	68	3.2	62		4S,5S
P.P.L.[d]	**1**	74	1.1	7		4S,5S
P.P..L.	**2**	77	1.9	45		4S,5S
M.M.L.[e]	**2**	68	2.2	43		4S,5S
C.V.L.[f]	**2**	49	3.5	40		4S,5S
G.L.[g]	**2**	65	4.1	68		4S,5S
C.E.L.[h]	**2**	80	3.5	85		4S,5S
chymotrypsin[i]	**1**	42 55	102	≥98	96	4S,5S
chymotrypsin	**2**	51	27	85	83	4S,5S
chymotrypsin	**3**	45 54	34	≥98	88	4R,5R
chymotrypsin	**4**	52	65	96		4S,5R

[a]Carboxyl esterase NP (International Bio-Synthetics); [b]*Candida cylindracea* lipase (Sigma); [c]*Pseudomonas cepacia* lipase (Amano); [d]Porcine pancreatic lipase (Sigma); [e]*Mucor miehei* lipase (Biocatalyst); [f]*Chromobacterium viscosum* lipase (Finnsugar); [g]*Penicillum cyclopium* (Amano); [h]*Humicola lanuginosa* lipase (Amano); [i](Sigma).

Table II. Lipase PS-catalyzed hydrolysis of esters **5-8**

substrate	conv. (%)	E[13]	e.e.(%) of residual ester	e.e.(%) of alcohol	conf. of residual ester
5	46	32		87	
	61		≥98		4S,5S
6	47	33		87	
	60		≥98		4S,5S
7	50	58	90	90	4R,5R
8	46	67		93	
	55		≥98		4S,5R

Scheme III



a: $NaBH_4$/EtOH; b: K_2CO_3/H_2O; c: H_2/Ra-Ni, H_3BO_3; c: $NaIO_4$; d: EtOH/H^+

Residual esters (-)-**1** and (-)-**2**, obtained by the chymotrypsin-catalyzed hydrolysis of (±)-**1** and (±)-**2** respectively, were correlated to (-)-**5** and (-)-**6**, the residual esters of the lipase PS-catalyzed hydrolysis of the

corresponding racemates, through their transformation into common intermediates (-)-**13** and (-)-**14.** The absolute configurations of (-)-**13** and (-)-**14** were assigned by chemical correlation with known[18] hydroxyesters (+)-**17** and (+)-**18** following the reaction sequence reported in Scheme III. The stereochemical outcome of the enzymatic resolution of substrates (±)-**3**-(±)-**7**, and (±)-**4**-(±)-**8** was inferred by analogy with the above reported results.

In summary, the results of this study further evidence the versatility of the chemoenzymatic approach to the synthesis of different classes of homochiral building blocks. The different role played by the two series of substrates i.e. compounds **1-4** versus **5-8**, at the enzyme active site did not affect the enantio-preference but greatly influenced both the reactivity and the degree of enantioselectivity. As a matter of fact, chymotrypsin emerged as an excellent catalyst, at least in terms of selectivity, for substrates **1-4** but hardly discriminated between the enantiomers of compounds **5-8**. On the contrary, lipase PS catalyzed efficiently the hydrolysis of substrates **5-8** only. These findings, together with literature results, will be taken into account to delineate a model of the enzyme active site for lipase PS.

EXPERIMENTAL SECTION

Materials and Methods. Enzymes listed in Tables 1 and 2 were all commercially available. Organic solvents were reagent or HPLC grade. ^{1}H NMR spectra were recorded at 200 MHz in $CDCl_3$ solution; chemical shifts (δ) are expressed in ppm and coupling constants (J) in hertz. GLC analyses were carried out on a 5 m HP1 capillary silica gel column coated with methylsilicone gum. Chiral HPLC analyses were performed on Chiralcel OB or OD columns (4.6x250 mm). Rotary power determinations were carried out with a Perkin Elmer 241 Polarimeter coupled with a Haake N3-B thermostat. Chiral GLC analyses were conducted on a gaschromatograph equipped with a CP-Cyclodextrin-2,3,6-M-19 fused silica gel column coated with β-cyclodextrin (50 m, 0.25 μm) under the following conditions: 170°C (10 min) to 193°C, heating rate 0.7 °C/min. H_2 was used as the carrier gas at a flow rate of 1.2 mL/min. Liquids were characterized by the oven temperature for bulb to bulb distillations. TLC analyses were carried out on commercial silica gel GF_{254} plates; spots were further evidenced by spraying with a dilute alkaline potassium permanganate solution. Microanalyses of new compounds agree with theoretical value ±0.4%.

Synthesis of 3-Ethoxycarbonyl-Δ^2-isoxazolines (±)-**1**-(±)-**4.** A toluene solution (20 mL) of ethyl chlorooximinoacetate (15 mmol) was added dropwise to a refluxing solution of the dipolarophile (0.12 mol) in toluene (50 mL). After 36 h at reflux under an inert atmosphere, the reaction mixture was washed with a 20% aqueous solution of sodium bicarbonate (2x20 mL), then dried over anhydrous sodium sulfate. Volatiles were stripped at reduced pressure and the resulting residue was column chromatographed.

(±)-**1**[19]: Yield (%) 76, bp 125-130°C/0.5 mmHg; R_F (cyclohexane-ethyl acetate 7:3) 0.40; ^{1}H NMR 5.35 (m, 1, H-5), 4.37 (q, 2, OCH_2; J=6.9), 3.94 (m, 1, H-4), 2.40-1.35 (m, 6, $3CH_2$), 1.32 (t, 3, CH_3; J=6.9).

(±)-**2**[15]: Yield (%) 89, bp 140-145°C/0.5 mmHg; R_F (cyclohexane-ethyl acetate 7:3) 0.42; ^{1}H NMR 4.72 (m, 1, H-5), 4.38 (m, 2, OCH_2), 3.21 (m, 1, H-4), 2.50-1.02 (m, 8, $4CH_2$), 1.36 (t, 3, CH_3).

(±)-**3**[14]: Yield (%) 43, bp 145-150°C/0.5 mmHg; R_F (cyclohexane-ethyl acetate 7:3) 0.16; ^{1}H NMR 5.41 (m, 1, H-5), 4.40-4.18 (m, 4, $2OCH_2$), 4.07 (m, 1, H-4), 3.72 (m, 2, OCH_2), 1.35 (t, 3, CH_3; J=7.2).

(±)-**4**: Yield (%) 71.5, bp 145-150°C/0.5 mmHg; R_F (cyclohexane-ethyl acetate 7:3) 0.22; ^{1}H NMR 5.65 (d, 1, H-5; J=5.6), 4.73 (d, 1, H-4; J=5.6), 4.33 (q, 2, OCH_2CH_3; J=7.1), 3.88 and 3.83 (m, 2, OCH_2); 3.72 (m, 2, OCH_2); 1.33 (t, 3, CH_3; J=7.1). *Anal.* Calcd for $C_8H_{11}NO_5$: C, 47.76; H, 5.51; N, 6.96. Found: C, 47.55; H, 5.72, N, 7.07.

Synthesis of butyrates (±)-5-(±)-8. A. A ten fold excess of sodium borohydride was added portionwise to a solution of the ester (8 mmol) in ethanol (35 mL). The reaction mixture was stirred at room temperature until disappearance of the starting material (3-4 h). The suspension was then poured into water (25 mL) then concentrated and extracted with dichloromethane (4x20 mL). The combined extracts were dried (anhyd. Na_2SO_4) and concentrated at reduced pressure. The crude alcohols were not purified but directly submitted to esterification.

B. To a mixture of the above prepared alcohols (5 mmol) and pyridine (0.8 mL, 10 mmol) in anhydrous dichloromethane (20 mL) was added dropwise at 0°C butyryl chloride (1.05 mL, 10 mmol) in dichloromethane (5 mL). The disappearance of the starting material was monitored by TLC (eluent: ethyl acetate). The mixture was washed with 3% HCl (2x5 mL) and the organic layer was dried and concentrated. The residue was purified by silica gel column chromatography.

(±)-**5**: Yield (%) 49, bp 125-130°C/0.5 mmHg; R_F (cyclohexane-ethyl acetate 1:1) 0.53; ^{1}H NMR 5.11 (m, 1, H-5), 4.86 and 4.79 (d, 2, OCH_2; J= 13.2), 3.62 (m, 1, H-4), 2.35 (t, 2, $COCH_2$; J=7.3), 2.18-1.34 (m, 8, $4CH_2$); 0.96 (t, 3, CH_3; J=7.4). *Anal.* Calcd for $C_{11}H_{17}NO_3$: C, 62.54; H, 8.11; N, 6.63. Found: C, 62.73; H, 7.92, N, 6.61.

(±)-**6**: Yield (%) 56, bp 120-130°C/1.0 mmHg; R_F (cyclohexane-ethyl acetate 1:1) 0.54; ^{1}H NMR 4.90 and 4.82 (d, 2, OCH_2; J= 13.3), 4.45 (m, 1, H-5), 2.94 (m, 1, H-4), 2.34 (t, 2, $COCH_2$; J=7.4), 2.11-1.20 (m, 10, $5CH_2$); 0.96 (t, 3, CH_3; J=7.4). *Anal.* Calcd for $C_{12}H_{19}NO_3$: C, 63.98; H, 8.50; N, 6.22. Found: C, 63.95; H, 8.19, N, 6.43.

(±)-**7**: Yield (%) 43, bp 120-130°C/0.5 mmHg; R_F (cyclohexane-ethyl acetate 1:1) 0.31; ^{1}H NMR 5.26 (m, 1, H-5), 4.94 and 4.83 (d, 2, CH_2OCO; J=13.4), 4.22 and 3.66 (m, 4, $2OCH_2$), 3.85 (m, 1, H-4), 2.34 (t, 2, $COCH_2$; J=7.3), 1.67 (m, 2, CH_2CH_3), 0.95 (t, 3, CH_2CH_3; J=7.4). *Anal.* Calcd for $C_{10}H_{15}NO_4$: C, 56.33; H, 7.09; N, 6.57. Found: C, 56.60; H, 6.84, N, 6.63.

(±)-**8**: Yield (%) 55, bp 120-130°C/0.5 mmHg; R_F (cyclohexane-ethyl acetate 1:1) 0.42; ^{1}H NMR 5.57 (d, 1, H-5; J=5.6), 4.92 (s, 2, CH_2OCO), 4.75 (d, 1, H-4, J=5.6), 3.73 (m, 4, $2OCH_2$), 2.35 (t, 2, $COCH_2$; J=7.3); 1.67 (m, 2, CH_2CH_3), 0.96 (t, 3, CH_3; J=7.4). *Anal.* Calcd for $C_{10}H_{15}NO_5$: C, 52.40; H, 6.60; N, 6.11. Found: C, 52.13; H, 6.41, N, 6.28.

Standard procedure for enzyme-catalyzed hydrolyses of (±)-1-(±)-4. The following procedure is representative. A 500 mL Erlenmeyer flask was charged with (±)-**1** (2.00 g, 10.9 mmol), chymotrypsin (0.6 g), 0.1 M potassium phosphate buffer, pH 7 (200 mL) and acetone (20 mL). The mixture was stirred at room temperature for 5h (42% conversion), then it was lyophilized. The residue was extracted with acetone (3x20 mL) and column chromatographed on silica gel (eluent: cyclohexane/ethyl acetate 7:3) to yield 1.056 g of **1**. Acid (+)-**9** (0.640 g) was eluted with cyclohexane/ethyl acetate/acetic acid 6:3:1. Unreacted **1** was resubmitted to enzymatic hydrolysis up to 55% total conversion. The mixture was worked-up as reported above, and the residue was chromatographed to yield 0.740 g of (-)-**1**.

(-)-**1**: $[\alpha]^{25}_{D}$ -158.04 (c1.154, $CHCl_3$); e.e. 96%.

(+)-**9**: $[\alpha]^{25}_{D}$ +141.84 (c1.128, $CHCl_3$); e.e. ≥98%.

The same protocol was applied, on an analytical scale (100 mg substrate), to the hydrolyses of (±)-**1** catalyzed by the enzymes listed in Table I.

The chymotrypsin-catalyzed hydrolyses of esters (±)-**2**, (±)-**3**, and (±)-**4** were carried out according to the procedure reported above for (±)-**1**.

(-)-**2**: $[\alpha]^{25}_{D}$ -174.30 (c1.066, $CHCl_3$); e.e. 85%.

(-)-**3**: $[\alpha]^{25}_{D}$ -222.65 (c1.108, $CHCl_3$); e.e. ≥98%.

(-)-**4**: $[\alpha]^{25}_{D}$ -178.54 (c1.006, $CHCl_3$); e.e. 96%.

Chiral HPLC analyses of (±)-**1**-(±)-**9**, and (±)-**3**-(±)-**11** were performed with a Chiralcel OB column, whereas the analyses of (±)-**2**-(±)-**10**, and (±)-**4** were carried out on a Chiralcel OD colunm.

(±)-**1**: eluent: n.hexane/1-propanol 96:4 with 0.25% formic acid; flow rate: 1.0 mL/min; λ 248 nm; retention times (min): (-)-**1**, 14.3; (+)-**1**, 20.9; (-)-**9**, 26.1; (+)-**9**, 38.3.

(±)-**2**: eluent: n.hexane/2-propanol 84:16 with 0.4% formic acid; flow rate: 0.5 mL/min; λ 254 nm; retention times (min): (-)-**2**, 10.8; (+)-**2**, 12.8; (-)-**10**, 48.0; (+)-**10**, 50.8.

(±)-**3**: eluent: n.hexane/1-propanol 60:40; flow rate: 0.5 mL/min; λ_{max} 242 nm; retention times (min): (-)-**3**, 11.1; (+)-**3**, 16.4.

(±)-**11**: eluent: n.hexane/1-propanol 50:50 with 0.3% formic acid; flow rate: 0.5 mL/min; λ 242 nm; retention times (min): (-)-**11**, 11.6; (+)-**11**, 16.3.

(±)-**4**: eluent: n.hexane/1-propanol 82:18; flow rate: 0.5 mL/min; λ 225 nm; retention times (min): (-)-**4**, 21.3; (+)-**4**, 23.5.

Standard procedure for Lipase PS-catalyzed hydrolyses of butyrates (±)-5-(±)-8. The following procedure is representative. A 500 mL Erlenmeyer flask was charged with (±)-**8** (2.00 g, 8.7 mmol), lipase PS (0.02 g), 0.1 M potassium phosphate buffer, pH 7 (200 mL) and acetone (20 mL). The mixture was stirred at room temperature for 4.5h (46% conversion), then it was lyophilized. The residue was extracted with acetone (3x20 mL) and column chromatographed on silica gel (eluent: ethyl acetate) to yield 0.541 g of (+)-**16**.

Unreacted **8** (0.982 g) was resubmitted to enzymatic hydrolysis up to 55% total conversion. The mixture was worked up as reported above, and the residue was chromatographed to yield 0.815 g of (-)-**8**.

The conversion as well as the enantiomeric excess of the product and residual substrate were evaluated by chiral gaschromatography with the conditions reported under Materials and Methods.

Retention times (min): (+)-**8**, 42.4; (-)-**8**, 43.7; (+)-**16**, 30.7; (-)-**16**, 31.5.

(-)-**8**: $[\alpha]^{25}_D$ -84.23 (c1.148, $CHCl_3$); e.e. ≥98%.

(+)-**16**: $[\alpha]^{25}_D$ +52.05 (c1.138, $CHCl_3$); e.e. 93%.

The lipase PS-catalyzed hydrolysis of esters (±)-**5**, (±)-**6**, and (±)-**7** were carried out according to the procedure reported above for (±)-**8**.

(-)-**5**: $[\alpha]^{25}_D$ -72.86 (c1.010, $CHCl_3$); e.e. ≥98%.

(+)-**13**: $[\alpha]^{25}_D$ +71.02 (c1.076, $CHCl_3$); e.e. 87%.

(-)-**6**: $[\alpha]^{25}_D$ -29.94 (c1.062, $CHCl_3$); e.e. ≥98%.

(+)-**14**: $[\alpha]^{25}_D$ +32.74 (c1.016, $CHCl_3$); e.e. 87%.

(-)-**7**: $[\alpha]^{25}_D$ -76.39 (c1.148, $CHCl_3$); e.e. 90%.

(+)-**15**: $[\alpha]^{25}_D$ +96.31 (c1.066, $CHCl_3$); e.e. 90%.

Chiral HPLC analyses of the couples (±)-**5**-(±)-**13**, and (±)-**6**-(±)-**14** were carried out on a Chiralcel OB column; eluent: n-hexane/1-propanol 97.5:2.5; flow rate 0.5 ml/min; λ 215 nm; retention times (min): (-)-**5**, 18.5; (+)-**5**, 28.2; (-)-**13**, 35.5; (+)-**13**, 45.4; (-)-**6**, 16.3; (+)-**6**, 25.7; (-)-**14**, 30.2; (+)-**14**, 35.1.

Chiral HPLC analysis of the couple (±)-**7**-(±)-**15** was carried out on a Chiralcel OD column; eluent: n-hexane/2-propanol 98:2; flow rate 0.5 ml/min; λ 215 nm; retention times (min): (+)-**7**, 42.3; (-)-**7**, 48.0; (-)-**15**, 52.6; (+)-**15**, 54.7.

Synthesis of (+)-18. A. A solution of (-)-**1** (1.5 g, 8.2 mmol) in ethanol (50 mL) was treated with sodium borohydride following the protocol previously described for the racemic substrate to produce (-)-**14** in 72% yield.

B. Alcohol (-)-**14** was not further characterized but directly submitted to catalytic hydrogenation. A solution of (-)-**14** and boric acid (2.5 g, 40.4 mmol) in methanol/water (50 mL, 5:1) was hydrogenated over Nickel-Raney W-2 at atmospheric pressure until absorption of one equivalent of hydrogen. Removal of the catalyst by filtration under vacuum through a Celite pad and evaporation of the solvents at reduced pressure gave a residue of the product which was purified by a silica gel column chromatography (eluent: ethyl acetate) and directly submitted to the subsequent reaction.

C. To a solution of the above prepared hydroxyketone in 10 mL of MeOH-H_2O (3:1) was added sodium periodate in water (16.5 mL - 0.23 M). After being stirred at room temperature for 1 h, the mixture was filtered through a Celite pad. The solution was concentrated at reduced pressure and the residue was purified by column chromatography on silica gel (eluent: ethyl acetate/methanol 9:1).

D. The residue of the preceding reaction was treated with 10 mL of a 3 M solution of HCl in abs. EtOH and refluxed for 30 min. The solvent and excess HCl were removed under vacuo and the residue was chromatographed on silica gel (eluent. cyclohexane-ethyl acetate 4:1) to produce (+)-**18** in 32% overall yield.

(+)-**18**: bp 90-95°C/0.2 mmHg; R_F (cyclohexane-ethyl acetate 7:3) 0.32, $[\alpha]^{25}_D$ +22.87 (c1.01, $CHCl_3$) [lit.[18] $[\alpha]^{25}_D$ +28.06 (c3.51, $CHCl_3$].

The same reaction sequence was carried out on (-)-**1** and (-)-**3** to produce (+)-**17** and (+)-**19** respectively in comparable yields.

(+)-**17**: $[\alpha]^{25}_D$ +11.64 (c0.773, $CHCl_3$) [lit.[18] $[\alpha]^{25}_D$ +14.66 (c2.08, $CHCl_3$].

(+)-**19**: $[\alpha]^{25}_D$ +17.95 (c1.17, $CHCl_3$).

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