Enzymes in organic synthesis. 40.[1] Evaluation of the enantioselectivity of the pig liver esterase catalyzed hydrolyses of racemic piperidine carboxylic acid esters

ERIC J. TOONE AND J. BRYAN JONES
Department of Chemistry, University of Toronto, Toronto, Ont., Canada M5S 1A1

Received April 29, 1987

ERIC J. TOONE and J. BRYAN JONES. Can. J. Chem. **65**, 2722 (1987).

Pig liver esterase (PLE) catalyzed hydrolysis of racemic piperidine esters proceeds enantioselectively to give product acids and recovered esters in 0–47% enantiomeric excess.

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L'hydrolyse, catalysée par l'EFC (estérase du foie de cochon), d'esters racémiques de la pipéridine se produit d'une façon énantiosélective pour conduire à des produits acides et à des esters récupérés dont l'excès énantiomérique varie de 0 à 47%.

[Traduit par la revue]

Introduction

Enzymes are now established as important tools in the field of asymmetric synthesis (2), with the resolution of racemates being one area in particular where the utility of enzymes has been traditionally recognized (3). While the resolution approach to the preparation of pure stereoisomers suffers from the disadvantage that only half of the starting material is transformed into the desired product, it is often possible to recycle the unwanted enantiomer by epimerization to the racemic form. Furthermore, in many cases a racemic starting material can be very cheap. Resolution can then offer the most cost efficient route to enantiomerically pure chiral synthons (4).

Esterases are a very attractive class of enzymes for use in resolution and other aspects of organic synthesis since they do not require expensive cofactors. One of the most promising of the esterases is pig liver esterase (PLE, E.C. 3.1.1.1). PLE is a commercially available enzyme that catalyses the hydrolysis of a broad range of ester substrates. While several reports of the use of PLE in the asymmetric hydrolysis of symmetrical diesters have appeared (5), there have been relatively few examples of resolution of racemates using PLE (6).

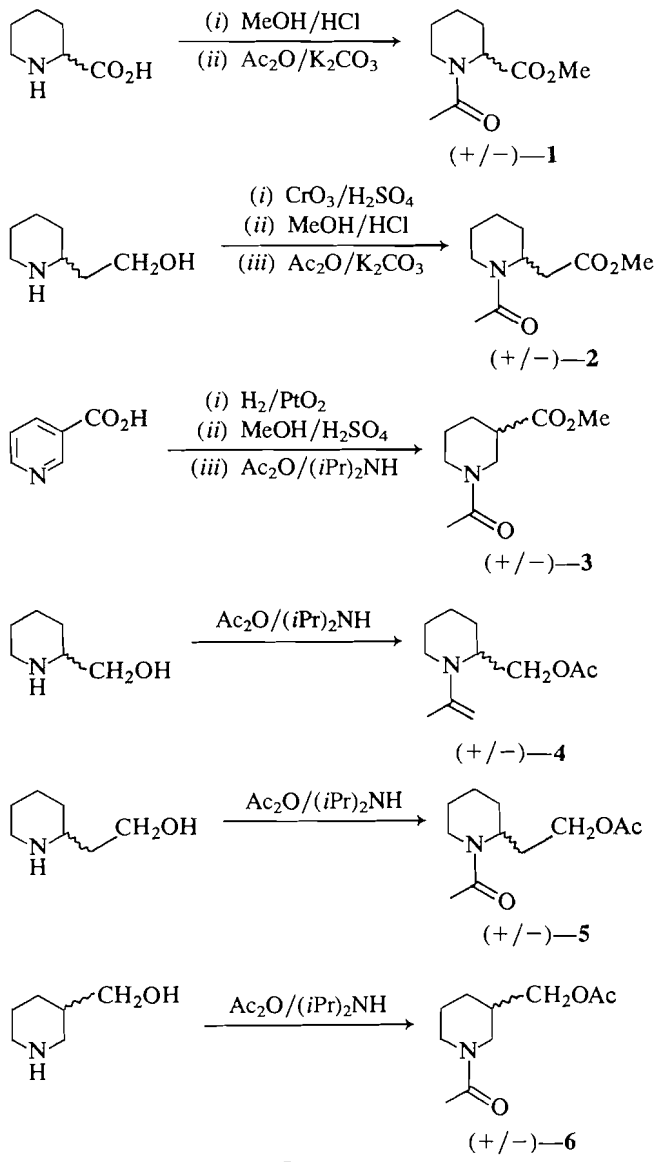
The enzymatic production of enantiomerically pure amino acids for use as chirons in organic synthesis is of considerable interest (7). Enzyme-catalyzed methods for the production of pure enantiomers of natural amino acids are well documented (8), but so far the use of enzymes for the resolution of racemates of unnatural amino acids of chiron value has not been widely explored. We have now begun to investigate the utility of enzymes in the resolution of unnatural amino acids. In this paper, we report on the potential of PLE for the resolution of some unnatural amino acid derivatives of the N-protected monosubstituted piperidine types represented by structures (+/−) **1**–**6**.

Results

The N-acylated piperidine substrates **1**–**6** were prepared as outlined in Scheme 1.

Each of compounds **1**–**6** was a substrate for PLE. Despite the fact that (+/−)-**1** and (+/−)-**2** were hydrolyzed much more slowly than the reference substrate ethyl butyrate (Table 1), all were sufficiently active to be considered good candidates for preparative scale resolution.

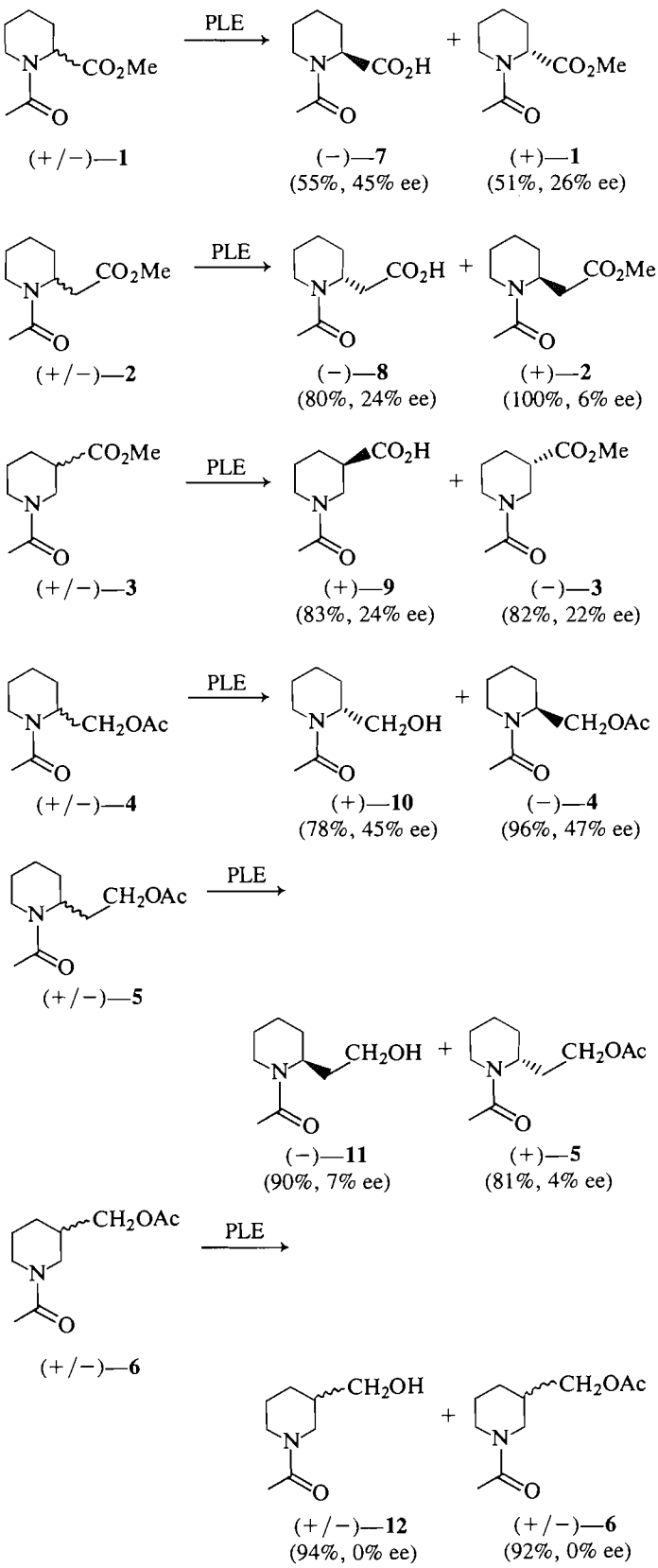
The resolutions were evaluated for each of compounds **1**–**6** on a 1–1.5 g scale at pH 7. The results are summarized in Scheme 2.



SCHEME 1

For the product acids (−)-**7**, (−)-**8**, and (+/−)-**9**, the enantiomeric excess (ee) values were determined by 200-MHz ^{1}H nmr examination of the diastereomeric salts formed between product acids and (−)-*S*-phenethylamine (9). For substrates (+/−) **4**–**6** the product alcohols **10**–**12** were converted by Jones oxidation to the corresponding carboxylic acids, **7**–**9**,

[1]For Part 39 see ref. 1.



SCHEME 2

and their (−)-*S*-phenethyl amine salts again examined. The enantiomeric excesses of the unhydrolyzed acetates (−)-**4** and (+)-**5** were determined similarly, following their conversion to their alcohols (−)-**10** and (+)-**11** by base hydrolysis, and then oxidation to the corresponding acids **7** and **8**. The enantiomeric excesses of unhydrolyzed esters **1**–**3** were determined by esterification of the optically active acids **7**–**9** of known absolute configuration with diazomethane, and comparison of optical rotations.

TABLE 1. Relative rates of PLE hydrolysis[a]

Substrate	Relative rate
Ethyl butyrate	100
(+/−)-**1**	<0.01
(+/−)-**2**	<0.01
(+/−)-**3**	14
(+/−)-**4**	1
(+/−)-**5**	3
(+/−)-**6**	1

[a]Determined at pH 7.0, 25°C, in distilled water.

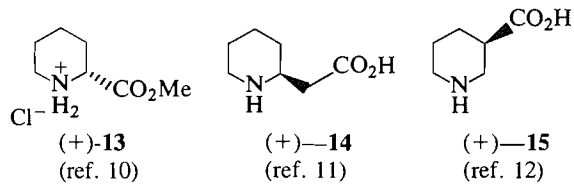


FIG. 1

The absolute configurations were all assigned by optical rotation correlations with known compounds as follows: (−)-**7**, (+)-**1**, (+)-**10**, and (−)-**4** with (+)-**13** (10); (−)-**8**, (+)-**2**, (−)-**11**, and (+)-**5** with (+)-**14** (11); and (+)-**9** and (−)-**3** with (+)-**15** (12).

Discussion

The preparations of substrates were routine, as were their preparative-scale PLE-catalyzed hydrolyses. Hydrolyses were stopped after 50% conversion. The hydrolyses were carried out at pH 7.0 to avoid the possibility of competing chemical hydrolysis or epimerization under the higher pH conditions that have been used in other applications (13). This would have been a significant problem for substrates (+/−)-**1** and (+/−)-**2**, due to the long reaction time. In fact, even at pH 7.0, it appears that some epimerization of optically active ester took place during the relatively long reaction times, as indicated by the fact that for (+/−)-**1** and (+/−)-**2** the enantiomeric excesses of the recovered esters are substantially lower than those of the product acids. In these cases, epimerization of the product acids would be virtually nonexistent since they are present in solution as their carboxylate salts.

The piperidine esters **1**–**6** represent a new class of PLE substrates whose structures are of clear synthetic value, for example as chirons for alkaloids such as coniine and sedrine. While the enantiomeric excess levels observed in the initial study are below the levels required for asymmetric synthesis, they demonstrate that PLE does possess significant enantiomeric stereoselectivity towards each of **1**–**6**. It is possible to increase the enantiomeric excess values of PLE-catalyzed reactions to acceptable asymmetric synthetic levels by manipulation of reaction conditions, particularly by varying organic solvent composition and temperature (14), and we are now exploring this aspect. In addition, in resolutions of this nature, it is always possible to reesterify the product acids and subject optically enriched material to a second enzymic hydrolysis (15). This approach will also be followed if the reaction conditions' improvement of ee is not satisfactory.

Experimental

All melting points were taken on a Electrothermal capillary melting point apparatus, and are uncorrected. The ir spectra were recorded as films for liquids and KBr discs for solids on a Nicolet 5DX FTIR spectrophotometer. All routine ^{1}H nmr spectra were recorded in $CDCl_3$ on a Varian T60 instrument. High field ^{1}H nmr spectra were recorded on a Varian XL200 instrument. Optical rotations were measured in a Perkin–Elmer 141 polarimeter in a thermostated cell. Elemental analyses were carried out by Galbraith Laboratories. Analytical glc work was carried out on a Varian Series 2700 gas chromatograph. The pH stat used was a Radiometer REA 270 pH stat, equipped with a TTT80 titrator and an ABU 80 autoburette. Pig liver esterase (EC 3.1.1.1) was obtained from Sigma Chemical Company.

Synthesis of substrates

N-*Acetyl-2-carbomethoxypiperidine (**1**)*

2-Piperidinecarboxylic acid (Aldrich, 1.5 g, 11.5 mmol) in HCl-saturated methanol (100 mL) was stirred at 21°C for 24 h. The methanol was removed by rotary evaporation and the yellow solid recrystallized once from methanol – ethyl acetate (1:1) to yield (+/−)-2-carbomethoxypiperidine hydrochloride (1.62 g, 78% yield), mp 212°C (lit. (16) mp 213–214°C); ir ν: 1748 cm^{-1}; ^{1}H nmr δ: 1.9–2.1 (m, 6H), 3.1–3.3 (m, 3H), 3.95 (s, 3H), 5.1 (br s, 1H) ppm. To this ester (0.75 g, 4.2 mmol) in ethyl acetate (15 mL) was added K_2CO_3 (2.1 g, 21 mmol) in water (5 mL), and acetic anhydride (1.1 g, 10 mmol), and the mixture was stirred for 24 h at 21°C. The layers were separated and the aqueous phase extracted with ethyl acetate (2 × 25 mL). The combined organic phases were washed with 1 M hydrochloric acid (15 mL), 5% aqueous Na_2CO_3 (15 mL), and saturated aqueous NaCl (15 mL), dried ($MgSO_4$), and concentrated *in vacuo* on a rotary evaporator. The residual oil was Kugelrohr distilled (bp 80°C/0.1 Torr; 1 Torr = 133.3 Pa) to yield *N*-acetyl-2-carbomethoxypiperidine **1** (0.44 g, 56% yield); ir ν: 1748, 1649 cm^{-1}; ^{1}H nmr δ: 1.5–1.9 (m, 6H), 2.2 (s, 3H), 3.2–3.5 (m, 2H), 3.8 (s, 3H), 5.4 (br, 1H) ppm. *Anal.* calcd. for $C_9H_{15}NO_3$: C 58.37, H 8.11, N 7.46; found: C 58.16, H 8.18, N 7.46%.

N-*Acetyl-2-carbomethoxymethylpiperidine (**2**)*

2-Carboxymethylpiperidine was prepared by the method of Marshall *et al.* (17), and esterified as above to give 2-carbomethoxymethylpiperidine hydrochloride, in 83% yield, mp 218–221°C (lit. (17) mp 218–220°C); ir ν: 1741 cm^{-1}; ^{1}H nmr δ: 1.7–2.1 (m, 6H), 2.9–3.1 (m, 5H), 3.7 (s, 3H) ppm. This ester (0.42 g, 2.2 mmol) was acetylated with acetic anhydride (0.45 g, 4.4 mmol) and K_2CO_3 (1.2 g, 8.8 mmol) as above to yield *N*-acetyl-2-carbomethoxymethylpiperidine **2** (0.3 g, 72% yield), bp 85°C/0.1 Torr; ir ν: 1737, 1644 cm^{-1}; ^{1}H nmr δ: 1.6–2.0 (m, 6H), 2.1 (s, 3H), 2.7–2.9 (m, 3H), 4.8–5.1 (m, 2H) ppm. *Anal.* calcd. for $C_{10}H_{17}NO_3$: C 60.28, H 8.60, N 7.03; found: C 60.31, H 8.66, N 6.99%.

N-*Acetyl-3-carboxymethylpiperidine (**3**)*

To nicotinic acid (10 g, 80 mmol) in water (100 mL) was added 6 M hydrochloric acid (13.5 mL, 6 M, 1 equiv.). PtO_2 (200 mg) was added and the mixture was stirred under hydrogen (50 psi; 1 psi = 6.9 kPa). After 24 h (3 equiv. H_2 uptake), the water was removed by rotary evaporation, and the residual solid recrystallized from absolute EtOH to give 3-carboxypiperidine hydrochloride (12.7 g, 95% yield), mp 239–240°C (dec.) (lit. (18) mp 240–242°C); ir ν: 1625 cm^{-1}; ^{1}H nmr δ: 1.8–2.1 (m, 6H), 3.2–3.4 (m, 5H), 9.2 (s, 1H) ppm. This ester (1.0 g, 6 mmol) was dissolved in dry MeOH (50 mL) containing 2 drops concentrated sulfuric acid and the mixture was stirred for 24 h at 20°C. The methanol was removed by rotary evaporation and the residual oil taken up in THF (50 mL) and cooled to 0°C. Acetic anhydride (6.2 g, 60 mmol), diisopropyl amine (4.0 g, 40 mmol), and catalytic dimethylaminopyridine (DMAP) were then added and the solution warmed to 20°C. After stirring for 24 h the solvent was removed and the desired product was obtained in pure form by Kugelrohr distillation (bp 85°C/0.25 Torr) (0.67 g, 58% yield); ir ν: 1733, 1648 cm^{-1}; ^{1}H nmr δ: 1.8–2.1 (m, 4H), 2.2 (s, 3H), 2.8–3.6 (m, 4H), 3.8 (s, 3H) ppm. *Anal.* calcd. for $C_9H_{15}NO_3$: C 58.37, H 8.11, N 7.46; found: C 58.37, H 8.08, N 7.50%.

N-*Acetyl-2-acetoxymethylpiperidine (**4**)*

2-Hydroxymethylpiperidine (1.5 g, 13 mmol) was dissolved in dry diethyl ether (50 mL). To this was added dropwise at 0°C acetic anhydride (16.2 g, 130 mmol), diisopropyl amine (3.95 g, 39 mmol), and catalytic DMAP, and the resulting solution was stirred at 20°C for 2 days. The solvent was removed by rotary evaporation, and the excess acetic anhydride and diisopropyl amine by Kugelrohr distillation (40°C/0.25 Torr). The residual oil was taken up in ethyl acetate (50 mL) and washed with 1 M hydrochloric acid (2 × 20 mL), followed by saturated aqueous $NaHCO_3$ (2 × 20 mL) and saturated aqueous NaCl (2 × 20 mL). The organic phase was dried ($MgSO_4$) and concentrated *in vacuo* on a rotary evaporator. The residual oil was purified by flash chromatography on silica (ether–methanol (5:1) elution) to give *N*-acetyl-2-acetoxymethylpiperidine (**4**, 1.05 g, 38% yield); ir ν: 1742, 1644 cm^{-1}; ^{1}H nmr δ: 1.7 (m, 6H), 2.15 (s, 3H), 2.2 (s, 3H), 2.45 (m, 2H), 4.1–4.4 (m, 3H) ppm. *Anal.* calcd. for $C_{10}H_{17}NO_3$: C 60.35, H 8.54, N 7.01; found: C 60.29, H 8.60, N 7.11%.

N-*Acetyl-2-acetoxyethylpiperidine (**5**)*

This was prepared, as was **4** above, from 2-hydroxyethylpiperidine (2 g, 17 mmol), acetic anhydride (15.8 g, 155 mmol), and diisopropyl amine (4.56 g, 45 mmol) with ether–methanol (4:1) elution from silica, giving pure *N*-acetyl-2-acetoxyethylpiperidine (**5**, 1.4 g, 40% yield); ir ν: 1736, 1618 cm^{-1}; ^{1}H nmr δ: 1.7 (br s, 6H), 2.15 (s, 3H), 2.20 (s, 3H) 2.3–2.6 (m, 2H), 3.6 (br s, 2H), 3.8–4.2 (m, 3H) ppm. *Anal.* calcd. for $C_{11}H_{19}NO_3$: C 61.95, H 8.98, N 6.57; found: C 62.01, H 8.88, N 6.49%.

N-*Acetyl-3-acetoxymethylpiperidine (**6**)*

This was prepared, as was **4** above, from 3-hydroxymethylpiperidine (2 g, 17 mmol), acetic anhydride (21.6 g, 170 mmol), and diisopropyl amine (5.3 g, 52 mmol), to give *N*-acetyl-3-acetoxymethylpiperidine (**6**, 1.5 g, 38% yield); ir ν: 1742, 1618 cm^{-1}; ^{1}H nmr δ: 1.2–1.8 (m, 5H), 2.05 (s, 6H), 2.2–2.5 (m, 2H), 3.6 (m 1H), 3.9 (m, 2H), 4.2–4.4 (m, 1H) ppm. *Anal.* calcd. for $C_{10}H_{17}NO_3$: C 60.35, H 8.54, N 7.01; found: C 59.96, H 8.44, N 6.92.

*Preparative-scale PLE-catalysed hydrolyses of racemic esters **1**–**6***

(a) Of N-*acetyl-2-carbomethoxypiperidine ((+/−)-**1**)*

The ester (+/−)-**1** (1 g, 5.4 mmol) was dissolved in distilled water (75 mL), pH was adjusted to 7.0 with 0.25 M NaOH, and PLE (3600 units) was added. The pH was held constant at 7.0 by addition of 0.25 M aqueous NaOH from a pH stat. When one-half equivalent of base had been added (10 days) there was no further uptake of base, and the reaction was stopped by saturating the solution with NaCl. The pH was readjusted to 7.0 and the solution extracted with ethyl acetate (3 × 50 mL). The combined organic phase was dried ($MgSO_4$) and concentrated *in vacuo* on a rotary evaporator to give (2*R*)-*N*-acetyl-2-carbomethoxypiperidine ((+)-**1**, 260 mg, 51% yield, 26% ee), $[\alpha]_D^{25}$ +19.4° (*c* 5.44, $CHCl_3$); spectral characteristics were identical to those of racemic **1** above. The aqueous solution was then acidified to pH 2.0 with 6 M hydrochloric acid and reextracted with ethyl acetate (3 × 50 mL). The combined organic phase was dried ($MgSO_4$) and concentrated *in vacuo* on a rotary evaporator to give (2*S*)-*N*-acetyl-2-piperidinecarboxylic acid ((−)-**7**, 259 mg, 55% yield, 45% ee) as a slowly crystallizing oil, mp 140–141°C; $[\alpha]_D^{25}$ −7.4° (*c* 10, $CHCl_3$); ir ν: 1728, 1608 cm^{-1}; ^{1}H nmr δ: 1.6–2.0 (m, 6H), 2.25 (s, 3H), 3.4–3.8 (m, 2H), 5.5 (m, 1H), 8.8 (s, 1H) ppm.

(b) Of N-*acetyl-2-carbomethoxymethylpiperidine ((+/−)-**2**)*

The above procedure was followed using (+/−)-**2** (1 g, 5 mmol) in water (25 mL) and PLE (1774 units) for 2.5 days, yielding (2*S*)-*N*-acetyl-2-carbomethoxymethylpiperidine ((+)-**2**, 502 mg, 100% yield, 6% ee); $[\alpha]_D^{25}$ +1.0 (*c* 11.6, $CHCl_3$) (spectra identical to racemic **2** above) and (2*R*)-*N*-acetyl-2-carboxymethylpiperidine ((−)-**8**, 372 mg, 80% yield, 24% ee), mp 91–93°C; $[\alpha]_D^{25}$ −1.7° (*c* 7.2, $CHCl_3$); ir ν: 1722, 1588 cm^{-1}; ^{1}H nmr δ: 1.5–1.7 (m, 6H), 2.1 (br s, 2H), 2.2 (s, 3H), 2.4–2.8 (m, 2H), 4.6 (br, 1H), 10.5 (s, 1H) ppm.

(c) Of N-acetyl-3-carboxymethylpiperidine ((+/−)-**3**)

The above procedure was followed using (+/−)-**3** (1.0 g, 5.3 mmol) in water (25 mL) and PLE (260 units) for 2.6 h, yielding (3*R*)-*N*-acetyl-

3-carbomethyoxypiperidine ((−)-**3**, 411 mg, 82% yield, 22% ee); $[\alpha]_D^{25}$ −14.6° (*c* 8.2, $CHCl_3$) (spectra identical to racemic ester **3** above), and (3*S*)-*N*-acetyl-3-piperidinecarboxylic acid ((+)-**9**, 385 mg, 83% yield, 24% ee), mp 114–116; $[\alpha]_D^{25}$ +11.6° (*c* 4.1, $CHCl_3$); ir *ν*: 1604, 1703 cm^{-1}; ^1H nmr δ: 1.6–1.8 (m, 4H), 2.1 (s, 3H), 2.4–2.8 (m, 2H), 3.6–3.8 (m, 2H), 10.7 (s, 1H) ppm.

(d) Of N-acetyl-2-acetoxymethylpiperidine ((+/−)-*4*)

(+/−)-**4** (1.0 g, 5 mmol) was dissolved in distilled water (20 mL). The pH was adjusted to 7.0 with 0.25 M NaOH, and PLE (523 units) was added. The pH was kept constant at 7.0 with 0.25 M NaOH, using a pH stat. After addition of one-half equivalent of base (10.5 h), the reaction was stopped by freezing, followed by lyophilization. The residual product was taken up in ethyl acetate (2 × 50 mL), filtered through Celite, dried ($MgSO_4$), and concentrated *in vacuo* on a rotary evaporator. The remaining oil was separated using a Chromatatron (silica, ether–acetone (3:2) development). The high R_f fraction was identified as (2*R*)-*N*-acetyl-2-acetoxymethylpiperidine ((−)-**4**, 494 mg, 96% yield, 47% ee); $[\alpha]_D^{25}$ −18.3 (*c* 9.6, $CHCl_3$) (spectra identical to racemic acetate **4** above), The low R_f fraction was identified as (2*S*)-*N*-acetyl-2-hydroxymethylpiperidine ((+)-**10**, 326 mg, 78% yield, 45% ee); $[\alpha]_D^{25}$ +20.5 (*c* 4.0, $CHCl_3$); ir *ν*: 3400 (br), 1618 cm^{-1}; ^1H nmr δ: 1.4–1.8 (m, 6H), 2.2 (s, 3H), 3.6–3.8 (m, 3H), 4.0–4.3 (m, 2H), 4.8 (br, 1H) ppm.

(e) Of N-acetyl-2-acetoxyethylpiperidine ((+/−)-*5*)

The above procedure was followed using (+/−)-**5** (1.0 g, 4.7 mmol) in water (20 mL) with PLE (300 units) for 4 h, followed by chromatography on silica (ether–THF (4:1)), yielding (2*R*)-*N*-acetyl-2-acetoxyethylpiperidine ((+)-**5**, 507 mg, 100% yield, 4% ee); $[\alpha]_D^{25}$ +2.6° (*c* 14, $CHCl_3$) (spectra identical to racemic acetate **5** above), and (2*S*)-*N*-acetyl-2-hydroxyethylpiperidine ((−)-**11**, 383 mg, 90% yield, 7% ee); $[\alpha]_D^{25}$ −1.7° (*c* 16, $CHCl_3$); ir *ν*: 3400 (br), 1625 cm^{-1}; ^1H nmr δ: 1.4–1.6 (m, 6H), 2.1 (s, 3H), 2.8–3.0 (m, 2H), 3.4–3.6 (m, 2H), 3.8–4.2 (m, 2H), 4.5–5.0 (m, 2H) ppm.

(f) Of N-acetyl-3-acetoxymethylpiperidine ((+/−)-*6*)

The above procedure was followed using (+/−)-**6** (1.0 g, 5 mmol) in water (30 mL) with PLE (110 units) for 12 h, followed by chromatography on silica (ethyl acetate – methanol (98:2) elution) yielding racemic *N*-acetyl-3-acetoxymethylpiperidine ((+/−)-**6**, 496 mg, 94% yield); $[\alpha]_D^{25}$ 0.0 (*c* 9.4, $CHCl_3$) (spectra identical to racemic acetate **6** above), and racemic *N*-acetyl-3-hydroxymethylpiperidine ((+/−)-**12**, 384 mg, 92% yield); $[\alpha]_D^{25}$ 0.0° (*c* 12.0, $CHCl_3$); ir *ν*: 3370 (br), 1622 cm^{-1}; ^1H nmr δ: 1.2–1.8 (m, 5H), 2.1 (s, 3H), 2.6–3.0 (m, 1H), 3.3–3.6 (m, 3H), 3.8–4.5 (m, 3H) ppm.

Enantiomeric excess determinations

(A) By nuclear magnetic resonance

The method of Schneider *et al.* (9) was employed. The general method was as follows: to approximately 20 mg optically active acid was added 1.5 equivalents of (−)-(*S*)-phenethylamine. The resulting oil was dissolved in $CDCl_3$ and the proton spectrum examined at 200 MHz. In all cases, the separation of the diastereotopic *N*-acetate methyl peaks was sufficient to permit the ee values to be determined. The racemic acids (+/−) **1**–**3**, were used as standards.

This technique was applied to the product acids (−)-**7**, (−)-**8**, and (+)-**9** directly, and to alcohol products (+)-**10** and (−)-**11** following oxidation.

*Oxidation of optically active alcohols **10** and **11***

1. Of N-*acetyl-2-hydroxymethylpiperidine ((+)-**10**)*

N-Acetyl-2-hydroxymethylpiperidine ((+)-**10**, 100 mg, 0.6 mmol) from PLE hydrolysis was dissolved in 1 M aqueous phosphate buffer (20 mL, pH 6.5). To this was added $KMnO_4$ (0.7 g, 3 mmol), and the mixture stirred at 70°C for 8 h. The mixture was cooled to 20°C and $Na_2S_2O_5$ added until the purple colour was destroyed. The resulting mixture was filtered through Celite, and the filtrate saturated with NaCl. The pH was readjusted to 6.5 and the solution extracted with dichloromethane (2 × 25 mL). The aqueous phase was acidified to pH 2.0 with 6 M hydrochloric acid and reextracted with dichloromethane (3 × 25 mL). The pH 2.0 extract was dried ($MgSO_4$) and concentrated *in vacuo* on a rotary evaporator to give (2*S*)-*N*-acetyl-2-piperidinecarboxylic acid ((−)-**7**, 22 mg, 21% yield); $[\alpha]_D^{25}$ −7.5° (*c* 2.0, $CHCl_3$). Spectra were identical to **7** above.

2. Of N-*acetyl-2-hydroxyethylpiperidine ((+)-**11**)*

The above procedure was followed with *N*-acetyl-2-hydroxyethylpiperidine ((+)-**11**, 100 mg, 0.5 mmol) and $KMnO_4$ (0.7 g, 3 mmol) for 7 h to yield (2*S*)-*N*-acetyl-2-carboxymethylpiperidine ((+)-**8**, 15 mg, 16% yield); $[\alpha]_D^{25}$ +0.65° (*c* 1.4, $CHCl_3$). Spectra were identical to **8** above.

(B) By optical rotation

The enantiomeric excesses of the remaining products were determined by comparison of optical rotations with compounds of known enantiomeric excess. Thus, optically active acids **7**–**9** were esterified, giving the enantiomeric excesses of product esters **1**–**3** by rotation. Optically active acetates **4** and **5** were deacylated and enantiomeric excesses obtained by comparison of rotations with product alcohols **10** and **11**.

*1. Esterification of optically active acids **7**–**9***

(a) Of (2S)-N-*acetyl-2-piperidinecarboxylic acid ((−)-**7**).* Optically active *N*-acetyl-2-piperidinecarboxylic acid ((−)-**7**, 290 mg, 1.7 mmol) from PLE catalysed hydrolysis was dissolved in methanol (5 mL). Ethereal diazomethane was added until persistence of colour. Colour was removed by dropwise addition of acetic acid. The resulting solution was dried ($MgSO_4$) and concentrated *in vacuo* on a rotary evaporator to give (2*S*)-*N*-acetyl-2-carbomethoxypiperidine ((−)-**1**, 305 mg, 95% yield); $[\alpha]_D^{25}$ −33.1° (*c* 6.0, $CHCl_3$). Spectra were identical to racemic **1** above.

(b) Of (2R)-N-*acetyl-2-carboxymethylpiperidine ((−)-**8**).* The above procedure was followed with *N*-acetyl-2-carboxymethylpiperidine ((−)-**8**, 210 mg, 1.7 mmol) to give (2*R*)-*N*-acetyl-2-carbomethoxypiperidine ((−)-**2**, 241 mg, 93% yield); $[\alpha]_D^{25}$ −4.3° (*c* 2.1, $CHCl_3$). Spectra were identical to racemic **2** above.

(c) Of (3S)-N-*acetyl-3-piperidinecarboxylic acid ((+)-**9**).* The above procedure was followed with *N*-acetyl-3-piperidinecarboxylic acid ((+)-**9**, 50 mg, 0.2 mmol), to give (3*S*)-*N*-acetyl-3-carbomethoxypiperidine ((+)-**3**, 36 mg, 96% yield); $[\alpha]_D^{25}$ +13.3 (*c* 4.0, $CHCl_3$). Spectra were identical to racemic **3** above.

*2. Deacetylation of optically active acetates **4** and **5***

(a) Of (2S)-N-*acetyl-2-acetoxymethylpiperidine ((−)-**4**).* (2*S*)-*N*-Acetyl-2-acetoxymethylpiperidine ((−)-**4**, 352 mg, 1.8 mmol) from PLE hydrolysis, was dissolved in distilled water (25 mL). To this was added NaOH (72 mg, 1.8 mmol) and the solution stirred for 10 h. The mixture was saturated with NaCl, and extracted with dichloromethane (3 × 50 mL). The combined organic phase was dried ($MgSO_4$), and concentrated *in vacuo* on a rotary evaporator to give (2*S*)-*N*-acetyl-2-hydroxymethylpiperidine ((−)-**10**, 265 mg, 79% yield); $[\alpha]_D^{25}$ −22.9° (*c* 3.95, $CHCl_3$). Spectra were identical to **10** above.

(b) Of (2R)-N-*acetyl-2-acetoxymethylpiperidine ((+)-**5**).* The above procedure with (2*R*)-*N*-acetyl-2-acetoxymethylpiperidine ((+)-**5**, 200 mg, 1 mmol) in water (25 mL) and NaOH (40 mg, 1 mmol) for 10 h gave (2*R*)-*N*-acetyl-2-hydroxymethylpiperidine ((+)-**11**, 143 mg, 79% yield); $[\alpha]_D^{25}$ +0.48° (*c* 12 in $CHCl_3$). Spectra were identical to **11** above.

Absolute configuration determinations

(a) N-*Acetyl-2-carbomethoxypiperidine (**1**)*

2-Piperidinecarboxylic acid was resolved as its (+)-tartrate salt according to the method of Portoghese *et al.* (10), to yield (2*R*)-(+)-2-carbomethoxypiperidine hydrochloride, mp 175–176°C (lit. (10) mp 177–180°C); $[\alpha]_D^{25}$ +9.3° (*c* 9, H_2O) (lit. (9) $[\alpha]_D^{25}$ +9.8 (*c* 1, 6 M HCl)). Optically active ester (200 mg, 1.4 mmol) was dissolved in dry THF (25 mL). To this was added acetic anhydride (1.43 g, 14 mmol) and diisopropyl amine (0.7 g, 7 mmol). This was stirred at 20°C for 48 h. THF was removed by rotary evaporation and excess acetic anhydride and diisopropyl amine removed by Kugelrohr distillation (40°C/0.25 Torr). The residual oil was purified by flash chromatography (silica, diethyl ether elution) to yield (2*R*)-(+)-*N*-acetyl-2-carbomethoxypiperidine (2*R*-(+)-**1**, 140 mg, 53% yield); $[\alpha]_D^{25}$ +65.2° (*c* 9.53, $CHCl_3$). Spectra were identical to racemic **1** above.

(b) N-*Acetyl-2-carboxymethylpiperidine (8)*

(2*R*)-*N*-Acetyl-2-carboxymethylpiperidine (−)-**8**, 180 mg, 1 mmol) from the PLE catalysed hydrolysis was dissolved in water (25 mL). To this was added NaOH (100 mg, 2.5 mmol) and the solution stirred at 70°C for 12 h. The solution was cooled to 20°C and extracted with methylene chloride (4 × 50 mL). The combined organic phase was dried ($MgSO_4$) and concentrated *in vacuo* on a rotary evaporator to yield (2*R*)-(−)-2-carboxymethylpiperidine, the enantiomer of which is of known absolute configuration (11) (128 mg, 78% yield), mp 216–220°C (lit. (11) mp 218–221°C); $[\alpha]_D^{25}$ −8.2° (*c* 9, H_2O) (lit. (11) $[\alpha]_D^{25}$ +22.1° (*c* 0.6, H_2O), 64% ee reported); ir *ν*: 3400, 1591 cm^{-1}; ^1H nmr (D_2O/ppts) δ: 1.5–1.7 (m, 6H), 2.1 (br s, 2H), 2.4–2.8 (m, 2H), 4.6–5.5 (m, 3H), 11.2 (s, 1H) ppm.

(c) N-*Acetyl-3-piperidinecarboxylic acid (9)*

The above procedure was followed using (3*S*)-*N*-acetyl-3-piperidinecarboxylic acid ((+)-**9**, 210 mg, 1.2 mmol) in water (25 mL) with NaOH (121 mg, 3 mmol) for 10 h, yielding (3*S*)-(+)-3-piperidinecarboxylic acid of known absolute configuration (12) (125 mg, 69% yield), mp 255–258°C (dec.) (lit. (12) mp 259–260°C); $[\alpha]_D^{25}$ +0.9° (*c* 11.5, H_2O) (lit. (12) $[\alpha]_D^{25}$ +3.6° (*c* 5, H_2O)). Spectra were identical to racemic acid above.

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