Pergamon

Tetrahedron: *Asymmetry* 11 (2000) 4397–4405

TETRAHEDRON: *ASYMMETRY*

Pig liver esterase (PLE)-mediated resolution of *N*-substituted 4-benzoyloxy-3-carbomethoxypiperidines: a convenient preparation of 4-hydroxy- and 4-benzoyloxy-3-carbomethoxypiperidines in enantiomerically pure form

Marinella Roberti,[a] Riccardo Rondanin,[b] Roberto Ferroni,[b] Riccardo Baruchello,[b] Francesco Paolo Invidiata,[c] Vincenza Andrisano,[a] Carlo Bertucci,[a] Valerio Bertolasi,[d] Stefania Grimaudo,[e] Manlio Tolomeo[e] and Daniele Simoni[b,*]

[a]*Dipartimento di Scienze Farmaceutiche, Università di Bologna, via Belmeloro 6, 40126 Bologna, Italy*
[b]*Dipartimento di Scienze Farmaceutiche, Università di Ferrara, Via Fossato di Mortara 17-19, 44100 Ferrara, Italy*
[c]*Dipartimento Farmacochimico e Biologico, Università di Palermo, via Archirafi 32, 90123 Palermo, Italy*
[d]*Dipartimento di Chimica, Centro di Strutturistica Diffrattometrica, Università di Ferrara, via L. Borsari 46, 44100 Ferrara, Italy*
[e]*Divisione di Ematologia e Servizio AIDS, Policlinico di Palermo, Università di Palermo, Via del Vespro 129, 90127 Palermo, Italy*

Received 2 October 2000; accepted 6 October 2000

Abstract

Pig liver esterase (PLE) afforded smooth chemical resolution of racemic *N*-substituted 4-(benzoyloxy)-3-carbomethoxypiperidines. The enzyme showed good chemo- and enantioselective properties, thus allowing discrimination between the carbomethoxy and benzoate ester groups, the latter being more easily hydrolyzed. The proposed methodology also represents a practical means for the procurement of *N*-substituted 4-hydroxy-3-carbomethoxypiperidines in enantiomerically pure form.

1. Introduction

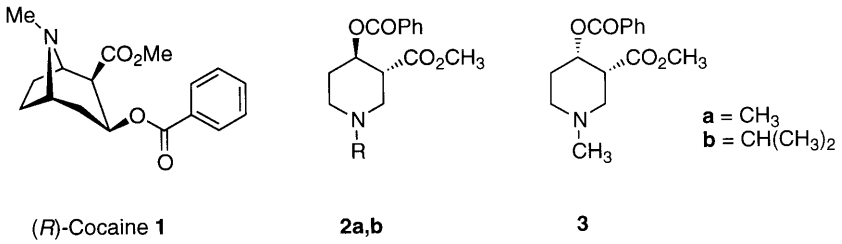
With the aim of obtaining cocaine antagonists for possible use in abuse treatment, particular attention has been recently devoted to the discovery of cocaine analogues that show high-affinity binding to the dopamine transporter, but low potency in the inhibition of dopamine uptake. The

* Corresponding author. Tel: +39-0532-291-291; fax: +39-0532-291-296; e-mail: smd@dns.unife.it

0957-4166/00/$ - see front matter
PII: S0957-4166(00)00404-3

study of cocaine analogues, sterically or electronically differing from the parent structure, appears a logical starting point in this quest for a cocaine antagonist. In this context, we have recently investigated modifications to various regions of the cocaine molecule.[1,2] We reported that two-carbon bridge methoxylated cocaines were found to possess interesting pharmacological properties; in particular, some of these derivatives were found to antagonize, albeit weakly, cocaine's ability to inhibit dopamine reuptake. Thus, in order to explore new areas of structural alteration of cocaine, we believed that it would be informative to examine the effect of removing its two-carbon bridge, thus obtaining the piperidines **2** and **3**, which may be considered as less conformationally restricted analogues. In fact, some piperidines have been recently reported endowed with interesting biological properties and their 3-phenyl bearing analogues were described as possible cocaine antagonists.[3]

Since stereochemistry is an aspect of molecular structure which deeply influences the biological response in terms of activity and selectivity and, from a medicinal chemistry point of view, the availability of both enantiomers is essential for determination of structure–activity relationships of chiral compounds, we have investigated the preparation of the above cited piperidine derivatives in enantiomerically pure form. As we recently reported that pig liver esterase (PLE)-catalyzed hydrolysis of racemic pseudococaine and its 6- and 7-methoxylated derivatives represents a practical means to achieve their resolution, we now detail our experiments regarding the chemo- and diastereoselective hydrolysis of the racemic piperidines **2a**,**b** and **3** by means of PLE. The proposed methodology proved important for the procurement of both enantiomerically pure 4-benzoyloxy-3-carbomethoxypiperidines and the 4-hydroxy-3-carbomethoxypiperidine derivatives (Fig. 1).



(*R*)-Cocaine **1** **2a,b** **3**

Figure 1.

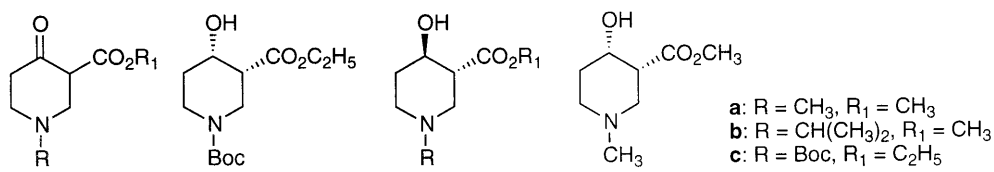
2. Results and discussion

Encouraged by the observation that (+)-**5** may be achieved with high diastereo- and enantioselectivity by baker's yeast reduction of the readily available BOC-protected piperidine derivative **4c**,[4] we initially attempted to obtain our desired compounds by means of this approach. Indeed, retrosynthetic analysis suggested that homochiral (+)-**5** would constitute, at least in part, the appropriate precursor of our desired piperidine derivatives. However, when we attempted the reduction of **4c** by means of baker's yeast, we were unable to reproduce the literature results but, at the same time, we noted with surprise that large discrepancies emerged recently about the enantioselective transformation of **4c** to enantiomerically pure (+)-**5**.[5,6] In brief, data claimed by Knight et al. were not confirmed by other authors[4] and it is likely that the baker's yeast reduction of the ketone **4c** may produce at most a racemic mixture. In this regard, our own

data[7] are completely in agreement with those recently reported in the literature.[5,6] Even more disappointingly and somewhat surprisingly, repeated attempts involving the enantioselective baker's yeast reduction of the β-ketoester **4a** resulted only in its transformation to the *N*-methyl-4-piperidone. Although a large body of literature exists concerning the use of β-keto ester moieties in microbial transformations aimed at the production of chiral building blocks, the present finding was surprising and, to our knowledge, unprecedented. Thus, an enantioselective PLE-mediated enzymatic hydrolysis of the racemic **2a**,**b** and **3** was envisaged as a potentially convenient entry to both enantiomers of the desired benzoate ester derivatives.

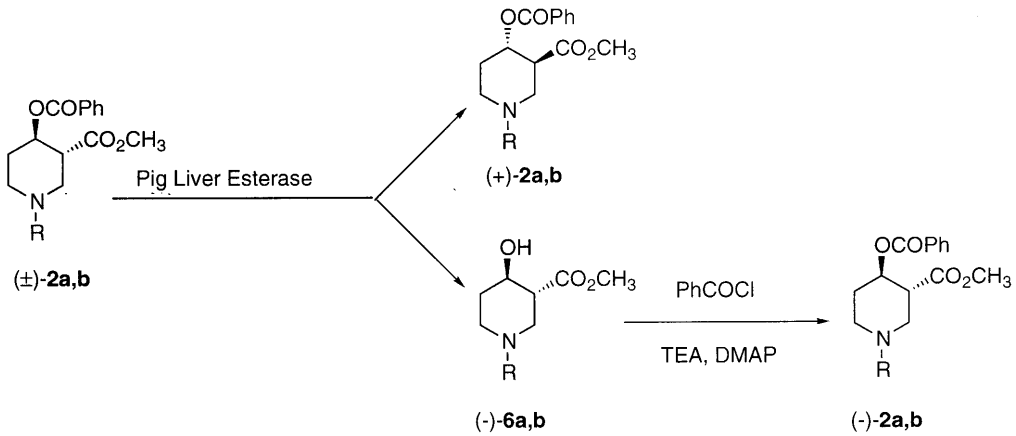
Our choice to make use of an esterase (PLE) for the resolution of the above cited piperidine derivatives was driven by our own observations that PLE can bring about the enantioselective hydrolysis of racemic cocaine and its derivatives and, in particular, by the observation that this enzyme has a particular affinity for the benzoate esters.[8] In this context, it is well documented that PLE has found widespread application as a selective reagent for the resolution of racemic alcohols, carboxylic acids and esters.[9] Therefore, on the basis of these observations, it appeared of interest to examine the use of this enzyme for the resolution of our piperidine derivatives.

For the procurement of the racemic **2a**,**b** and **3**, we took advantage, to some extent, of known procedures:[10] the NaH-promoted Dieckmann cyclization of the opportune *N*-substituted 3,3′-amino-dipropionic acid dimethyl ester produced in high yields the β-ketoesters **4a**,**b**, which were in turn reduced with $NaBH_4$ providing in good yields the racemic stereoisomers (±)-**6a**,**b** and (±)-**7**; the latter were benzoylated by means of benzoyl chloride in the presence of triethylamine (TEA) and a catalytic amount of dimethylaminopyridine (DMAP) to afford the desired racemic **2a**,**b** and **3** in good yields. The PLE-catalyzed hydrolysis of **2a**,**b** and **3** was readily performed in aqueous solution at 37°C, maintaining the pH at 7. The hydrolysis was continued until one-half equivalent of sodium hydroxide had been consumed. The reaction time was about 1 h for **2a**,**b** and 6 h for **3**. As expected, PLE was able to discriminate the two enantiomers of the racemic mixtures with good enantiopreference (96–100% ee).[11] The alcohol derivatives (−)-**6a**,**b** and (−)-**7** were simply reacted with benzoyl chloride to provide the final benzoic acid esters in good chemical yields and enantiomeric excesses (Fig. 2). Inspection of the data reveals that PLE possesses the same enantiopreference towards the different stereoisomers and the reaction occurs preferably with the (−)-isomers (Scheme 1). The smooth hydrolysis of the benzoate ester functionalities was notable, whereas the carbomethoxy ester was not affected. The conversion of the *trans*-derivatives (±)-**2a**,**b** was faster than that of the *cis*-stereoisomer (±)-**3**, but in both cases, unlike cocaine and its 6- and 7-methoxylated derivatives, the ee's were very high.[7] With regard to the chemoselective hydrolysis of the benzoate ester group with respect to that of the carbomethoxy group, we may hypothesize that, together with a higher susceptibility of the



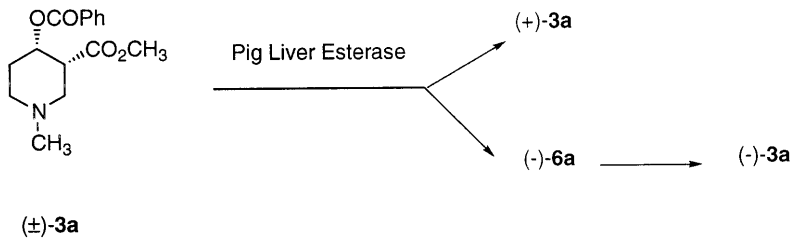
4a-c (+)-**5** (±)-**6a**,**b** (±)-**7**

Figure 2.



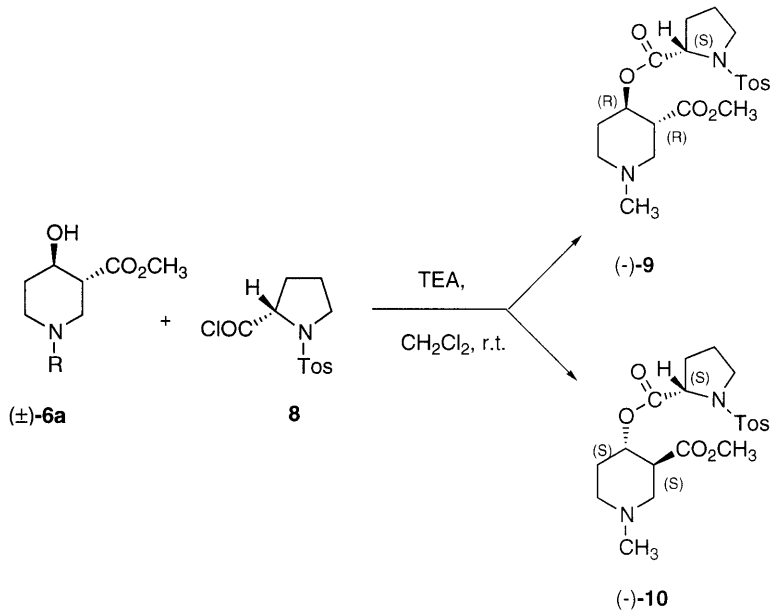
Scheme 1.

benzoate ester to hydrolysis, the preferred ES-complex certainly allows the –OCOPh group to be better located into the catalytic serine domain, thus arranging the carbomethoxy function in a different region. Similar results were also obtained during our PLE resolution of cocaine and its derivatives, but with cocaine and its methoxylated derivatives the hydrolysis of the $COOCH_3$ was observed to be more consistent in the case of the cocaine-like configuration and yields were in some cases very low. Moreover, unlike cocaine, in the piperidine series the enantiomeric excesses were very high for all the stereoisomers. It is also worth noting that while the regioselective ability of lipases to discriminate between chemically identical hydroxy or acyl groups by acylation and deacylation, respectively, has been satisfactorily investigated, less is known about their chemoselective capability towards different ester moieties (Scheme 2).[9,12]



Scheme 2.

Finally, the absolute configuration of (−)-**6a** was determined by its conversion into the prolyl derivative **9** by reaction with *N*-tosyl-L-prolyl chloride **8**. In the same manner the racemic (±)-**6a** was also reacted with *N*-tosyl-L-prolyl chloride and converted into the corresponding diastereoisomeric mixture by which pure **10** was obtained by crystallization and its absolute configuration determined by X-ray analyses (Scheme 3).[13,14]



Scheme 3.

3. Conclusion

In summary, PLE-mediated enantioselective hydrolysis of the racemic benzoate esters **2a**,**b** and **3** appears an interesting tool for the resolution of racemic *N*-substituted 4-(benzoyloxy)-3-carbomethoxypiperidines. The methodology also provides important means for the preparation of enantiomerically pure 4-hydroxy-3-carbomethoxypiperidines: a class of compounds which has recently yielded conflicting data in literature. Furthermore, we have also demonstrated the extraordinary ability of PLE to provide chemo- and enantioselective hydrolysis of substrates bearing both the benzoyloxy and carbomethoxy esters functions, and the 4-(benzoyloxy)-3-carbomethoxypiperidines, as well as the 4-hydroxy-3-carbomethoxypiperidines were obtained for the first time in high enantiomeric excess.[15]

4. Experimental

4.1. General

Melting points were obtained in open capillary tubes and are uncorrected. Reaction courses and product mixtures were routinely monitored by thin-layer chromatography (TLC) on silica gel precoated F_{254} Merck plates. Infrared (IR) spectra were measured on a Perkin–Elmer 257 instrument. Nuclear magnetic resonance (^{1}H NMR) spectra were determined, when not specified, in $CDCl_3$ solution with a Bruker AC-200 spectrometer and peak positions are given in parts per million downfield from tetramethylsilane as internal standard. Column chromatography (medium pressure) was carried out using 'flash' techniques.

4.2. (±)-1-Isopropyl-3-carbomethoxypiperidin-4-ol **6b**

The β-ketoester **4b** (3 g, 15.1 mmol) was dissolved in methanol (30 mL) and cooled at 0°C, and sodium borohydride (1.7 g, 45.2 mmol) was added. The resulting reaction mixture was left at room temperature for 30 min. Cold concentrated HCl (10 mL) was added slowly at 0°C and methanol was removed under vacuum. The solid residue was dissolved in water (40 mL), neutralized with concentrated NH_4OH, and repeatedly extracted with $CHCl_3$ (4×50 mL). The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by flash chromatography to give **6b** as an oil. 1.8 g, 60% yield, mp 40–42°C (diethyl ether), IR (KBr) 3400, 1730, 1593 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.01 (d, $J=6.4$ Hz, 6H), 1.45–1.75 (m, 4H), 1.8–2.18 (m, 2H), 2.45–3.15 (m, 3H), 3.71 (s, 3H), 3.72 (m, 1H). Anal. calcd for $C_{10}H_{19}NO_3$: C, 59.68; H, 9.52; N, 6.96. Found: C, 59.77; H, 9.56; N, 7.01.

4.3. General procedure for the PLE-catalyzed hydrolysis of racemic 4-benzoyloxy-3-carbomethoxypiperidines **2a**,**b**, **3**

The following procedure is representative. To a stirred solution of the appropriate piperidine derivative in phosphate buffer (pH 7, 0.05 M) containing methanol at 37°C, pig liver esterase (PLE) was added in one portion. The pH was maintained at 7 by a dropwise addition of 0.5 M aqueous NaOH. The hydrolysis was allowed to proceed until one-half equivalent of NaOH had been consumed. The mixture was cooled to −78°C, then slowly warmed to room temperature and filtered through a membrane filter (Millipore, 0.45 mm). The aqueous layer was partly concentrated under reduced pressure (to a volume of approximately 5 mL) and extracted with CH_2Cl_2 (3×15 mL). The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by flash chromatography to give the *N*-substituted 4-(hydroxy)-3-carbomethoxypiperidine together with a small amount of the starting material. Specific details are given below.

4.3.1. (3S,4S)-(+)-1-Methyl-3-carbomethoxy-4-benzoyloxypiperidine **2a** and (3R,4R)-(−)-1-methyl-3-carbomethoxypiperidin-4-ol **6a**

Prepared from (±)-**2a** (100 mg, 0.36 mmol) solubilized in methanol (5 mL) and buffer (15 mL) and treated with PLE (141 U). The reaction time was 1 h. Purification by flash chromatography (ethyl acetate/methanol, 9:1).

(+)-**2a**: 34 mg, 69% yield; mp 73–75°C (diethyl ether); 100% ee; $[\alpha]_D^{25}=+59.8$ ($c=1$, MeOH), IR (KBr) 1721, 1712, 1603, 1450 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.82 (m, 1H), 2.20–2.60 (m, 3H), 2.39 (s, 3H), 2.84 (m, 1H), 3.04 (m, 2H), 3.73 (s, 3H), 5.36 (m, 1H), 7.40–7.60 (m, 3H), 8.08 (m, 2H). Anal. calcd for $C_{15}H_{19}NO_4$: C, 64.97; H, 6.91; N, 5.05. Found: C, 64.77; H, 6.98; N, 5.08.

(−)-**6a**: 17 mg, 55% yield; mp 90–92°C (diethyl ether/hexane); 98.9% ee; $[\alpha]_D^{25}=-21.7$ ($c=1$, MeOH), IR (KBr) 3400, 1725, 1590 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.45–1.65 (m, 1H), 1.8–2 (m, 3H), 2.45–2.6 (m, 4H), 2.7–2.8 (m, 1H), 2.95–3.05 (m, 2H), 3.64 (s, 3H), 3.71 (m, 1H). Anal. calcd for $C_8H_{15}NO_3$: C, 55.47; H, 8.73; N, 8.09. Found: C, 55.21; H, 8.74; N, 8.01.

4.3.2. (3S,4S)-(+)-1-Isopropyl-3-carbomethoxy-4-benzoyloxypiperidine **2b** and (3R,4R)-(−)-1-isopropyl-3-carbomethoxypiperidin-4-ol **6b**

Prepared from (±)-**2b** (120 mg, 0.40 mmol) solubilized in methanol (5 mL) and buffer (15 mL) and treated with PLE (153 U). The reaction time was 1 h. Purification by flash chromatography (ethyl acetate/methanol, 9:1).

(+)-**2b**: 24 mg, 40% yield; yellow oil; 95% ee; $[\alpha]_D^{25}=+50$ ($c=0.4$, MeOH). IR (Neat) 1728, 1715, 1600, 1450 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.07 (d, $J=6.6$ Hz, 6H), 1.79 (m, 1H), 2.28 (m, 2H), 2.35–2.65 (m, 1H), 2.80–3.30 (m, 4H), 3.64 (s, 3H), 5.23 (m, 1H), 7.35–7.65 (m, 3H), 8.05 (m, 2H). Anal. calcd for $C_{17}H_{23}NO_4$: C, 66.86; H, 7.59; N, 4.59. Found: C, 66.93; H, 7.54; N, 4.59.

(−)-**6b**: 15 mg, 38% yield; mp 40–42°C (diethyl ether); 40% ee; $[\alpha]_D^{25}=-10$ ($c=0.2$, MeOH). IR and ^1H NMR are the same as described for (±)-**6b**.

*4.3.3. (3R,4S)-(+)-1-Methyl-3-carbomethoxy-4-benzoyloxypiperidine **3** and (3S,4R)-(−)-1-methyl-3-carbomethoxypiperidin-4-ol **7***

Prepared from (±)-(**3**) (200 mg, 0.72 mmol) solubilized in methanol (8 mL) and buffer (20 mL) and treated with PLE (280 U). The reaction time was 6 h. Purification by flash chromatography (ethyl acetate/methanol, 8:2).

(+)-**3**: 71 mg, 71% yield; yellow oil; 99% ee; $[\alpha]_D^{25}=+51.1$ ($c=0.4$, MeOH). IR (Neat) 1728, 1720, 1600, 1450 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.90 (m, 3H), 2.38 (s, 3H), 2.67 (m, 2H), 3.03 (m, 2H), 3.62 (s, 3H), 5.63 (m, 1H), 7.40–7.65 (m, 3H), 7.99 (m, 2H). Anal. calcd for $C_{15}H_{19}NO_4$: C, 64.97; H, 6.91; N, 5.05. Found: C, 64.88; H, 6.93; N, 5.07.

(−)-**7**: 28 mg, 45%; mp 88–89°C (diethyl ether/hexane); 97% ee; $[\alpha]_D^{25}=-33$ ($c=0.7$, MeOH). IR (Neat) 3400, 1727, 1593 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.70–1.95 (m, 2H), 2.31 (s, 3H), 2.40–2.50 (m, 2H), 2.6–3 (m, 4H), 3.73 (s, 3H), 4.23 (s, 1H). Anal. calcd for $C_8H_{15}NO_3$: C, 55.47; H, 8.73; N, 8.09. Found: C, 55.55; H, 8.74; N, 8.19.

*4.4. General procedure for benzoylation of (−)-**6a,b** and (−)-**7***

The alcohol (0.23 mmol) was dissolved in methylene dichloride and the solution was cooled at 0°C. Triethylamine (80 μL, 0.54 mmol), benzoyl chloride (40 μL, 0.345 mmol) and a catalytic amount of 4-(dimethylamino)pyridine were added. The reaction mixture was stirred for 10 min at 0°C and then for 3 h at room temperature. The solution was washed with brine, dried over Na_2SO_4 and concentrated in vacuo. The residual oil was purified by flash chromatography (CH_2Cl_2/MeOH, 10:0.5).

*4.4.1. (3R,4R)-(−)-1-Methyl-3-carbomethoxy-4-benzoyloxypiperidine **2a***

83% yield; 96% ee; $[\alpha]_D^{25}=-58.9$ ($c=0.35$, MeOH); IR, ^1H NMR and mp are the same as described for (+)-**2a**.

*4.4.2. (3R,4R)-(−)-1-Isopropyl-4-benzoyloxy-3-carbomethoxypiperidine **2b***

Oil, 66% yield, yellow oil; $[\alpha]_D^{25}=-20$ ($c=0.3$, MeOH); 40% ee. IR and ^1H NMR are the same as described for (+)-**2b**.

*4.4.3. (3S,4R)-(−)-1-Methyl-3-carbomethoxy-4-benzoyloxypiperidine **3***

Oil, 75% yield, $[\alpha]_D^{25}=-50$ ($c=0.9$, MeOH); 97% ee. IR and ^1H NMR are the same as described for (+)-**3**.

*4.5. General procedure for the preparation of the prolyl derivatives (−)-**9** and (+)-**10***

The piperidine derivative (±)-**6a** or (−)-**6a** (400 mg, 2.3 mmol) was dissolved in dry methylene dichloride and the solution was cooled at 0°C. Triethylamine (317 μL, 2.28 mmol), *N*-tosyl-L-

prolyl chloride **8** (1.4 g, 4.56 mmol) and DMAP (25 mg, 0.228 mmol) were added. The reaction mixture was stirred for 10 min under dry N_2 at 0°C and then for 12 h at room temperature. The solution was washed with brine, dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash chromatography ($CHCl_3$/MeOH, 97:3) and the pale yellow oil treated with 1N HCl to give the desired hydrochloride salts.

*4.5.1. (–)-(3*R,*4*R*)-1-Methyl-3-carbometoxy-4-(*N*-tosyl-L-prolyloxy)piperidine **9***

640 mg, 65% yield; yellow oil; 85% ee; $[\alpha]_D^{25} = -84$ ($c = 0.5$, MeOH); ^{1}H NMR ($CDCl_3$) δ 1.6–1.8 (m, 2H), 1.9–2.2 (m, 6H), 2.34 (s, 3H), 2.46 (s, 3H), 2.7–3 (m, 3H), 3.2–3.3 (m, 1H), 3.4–3.5 (m, 1H), 3.73 (s, 3H), 4.2–4.3 (m, 1H), 5–5.1 (m, 1H), 7.3–7.4 (m, 2H), 7.7–7.8 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 21.5, 24.5, 29.3, 30.9, 45.7, 46.8, 48.3, 52.1, 52.8, 55.5, 60.5, 71.5, 127.5, 129.6, 135.4, 143.5, 171.2, 171.8. Anal. calcd for $C_{20}H_{28}N_2O_6S$: C, 56.59; H, 6.65; N, 6.60. Found: C, 55.95; H, 6.65; N, 6.63.

*4.5.2. (3*S,*4*S*)-(–)-1-Methyl-3-carbometoxy-4-(*N*-tosyl-L-prolyloxy)piperidine hydrochloride **10***

A mixture of **9** and **10** (0.900 g) was dissolved in anhydrous THF (10 mL). The solution was allowed to stand at 4°C for 3 days. A sample of pure (–)-**8** was recovered as white needles. Mp 178°C, $[\alpha]_D^{25} = -29$ ($c = 0.6$, MeOH); ^{1}H NMR (D_2O) δ 1.55–1.88 (m, 2H), 1.85–2.05 (m, 4H), 2.1–2.2 (m, 2H), 2.34 (s, 3H), 2.46 (s, 3H), 2.7–3 (m, 3H), 3.2–3.35 (m, 1H), 3.4–3.55 (m, 1H), 3.68 (s, 3H), 4.2–4.3 (m, 1H), 5–5.15 (m, 1H), 7.25–7.34 (m, 2H), 7.7–7.8 (m, 2H). ^{13}C NMR (D_2O) δ 23.6, 27.3, 27.9, 33.4, 45.5, 46.4, 46.8, 51.9, 52.5, 56.3, 63.9, 70.8, 130.3, 133.1, 135.2, 148.7, 173.8, 176.0. Anal. calcd for $C_{20}H_{29}N_2O_6SCl$: C, 52.11; H, 6.34; N, 6.08. Found: C, 52.33; H, 6.38; N, 6.11.

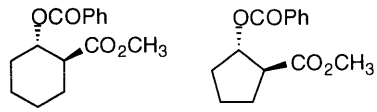
Acknowledgements

This work was in part supported by the Ministero dell'Università e della Ricerca Scientifica e Tecnologica (Rome).

References

1. Simoni, D.; Roberti, R.; Rondanin, R.; Kozikowski, A. P. *Tetrahedron Lett*. **1999**, *40*, 4425–4428 and references cited therein.
2. Simoni, D.; Roberti, M.; Andrisano, V.; Manferdini, M.; Rondanin, R.; Kozikowski, A. P. *J. Org. Chem*. **1998**, *63*, 4834–4837 and references cited therein.
3. Kozikowski, A. P.; Araldi, G. L.; Boja, J.; Meil, W. M.; Johnson, K. M.; Flippen-Anderson, J. L.; George, C.; Saiah, E. *J. Med. Chem*. **1998**, *41*, 1962–1969.
4. Knight, D. W.; Lewis, N.; Share, A. C. *Tetrahedron*: *Asymmetry* **1993**, *4*, 625–628.
5. Willert, M.; Bols, M. *Acta Chem. Scand*. **1998**, *62*, 461–468.
6. Byrgesen, E.; Nielsen, J.; Willert, M.; Bols, M. *Tetrahedron Lett*. **1997**, *38*, 5697–5700.
7. Repeated attempts to reduce **4c** by means of baker's yeast under fermenting conditions produced a specific rotation of only 0–3 as reported by other authors and therefore in sharp contrast with previously published +25.[4]
8. Kozikowski, A. P.; Simoni, D.; Baraldi, P. G.; Lampronti, I.; Manfredini, S. *Bioorg. Med. Chem. Lett*. **1996**, *6*, 441–444.
9. Toone, E. J.; Jones, J. B. *Tetrahedron: Asymmetry* **1991**, *2*, 207–222 and references cited therein.
10. Singh, S.; Basmadjian, G. P.; Avor, K. S.; Pouw, B.; Seale, T. W. *J. Med. Chem*. **1997**, *40*, 2474–2481.

11. For the determination of the enantiomeric excesses of our synthesized chiral compounds the solvent delivery system consisted of a Jasco Bip I HPLC pump equipped with a Rheodyne Model 7125 injector with a 20 μl sample loop. The eluents were monitored by a UV Detector set at 270 nm and the chromatographic column was a Chiral OD (250×4.6 mm I.D.) (Daicel Chemical Industries, Ltd). The mobile phase composition was a 2-propanol/hexane solution.
12. Pedrocchi-Fantoni, G.; Servi, S. *J. Chem. Soc., Perkin Trans. 1* **1992**, 1029–1033 and references cited therein.
13. *Crystal data*: $C_{20}H_{29}N_20_6S^+\cdot Cl^-$, $M=490.96$, monoclinic, space group $P2_1$, $a=10.914(2)$, $b=6.816(3)$, $c=16.121(2)$ Å, $\beta=105.93(1)°$, $V=1153.2.(1)$ Å^3, $Z=2$, $D_c=1.328$ g cm^{-3}, $F(000)=488$, crystal dimensions: 0.60×0.17×0.12 mm. *Data collection and processing*. Enraf–Nonius CAD-4 diffractometer, graphite-monochromated Mo Kα radiation, $T=296$ K, 2988 unique reflections measured, $\theta\leq 20°$, giving 2132 observed reflections with $I\geq 2\sigma(I)$. The data were corrected for Lorentz and polarization effects, no absorption correction was applied. The structure was solved by direct methods using SIR92 system of programs.[16] The non-hydrogen atoms were refined anisotropically while the hydrogen atoms were placed in calculated positions and allowed to ride on their parent atom carbons, except for the hydrogen H100 bonded to N1 which was refined isotropically. Refinement by full-matrix least-squares using SHELXL-97,[17] on F^2, with R (observed reflections) = 0.0627 and wR (all reflections) = 0.1682, 278 parameters, $S=1.28$. Crystallographic data (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Centre.
14. The absolute configuration of (−)-**7** and (+)-**3** were attributed on the basis of their CD spectra (data will be published elsewhere); moreover, as lipases usually show the same enantiopreference throughout a series of analogous substrates,[18] we expected that (−)-**6b** also has the same absolute stereochemistry as (−)-**6a**.
15. Attempts to extend the transformation to the carbocyclic derivatives (±)-**11** and (±)-**12**, thus rendering the procedure of general applicability, have proven somewhat disappointing to date: it appears that for these compounds the reaction is limited by competing side reactions such as hydrolysis of both ester groups. (+)-**11** and (+)-**12** were obtained in 73 and 75% ee (25–30% chemical yield for both compounds).



(+)-**11** (+)-**12**

16. Altomare, A.; Cascarano, G.; Giacovazzo, C.; Guagliardi, A.; Burla, M. C.; Polidori, G.; Camalli, M. *J. Appl. Crystallogr.* **1994**, *27*, 435.
17. Sheldrick, G. M. SHELXL-97, Program for Crystal Structure Refinement, University of Göttingen, Germany, 1997.
18. Kazlauskas, R. J.; Weissfloch, A. N. E.; Rappaport, A. T.; Cuccia, L. A. *J. Org. Chem.* **1991**, *56*, 2656–2665.