



Synthesis of α -phenyl-1-(*R*)-(-)-piperidineacetic esters

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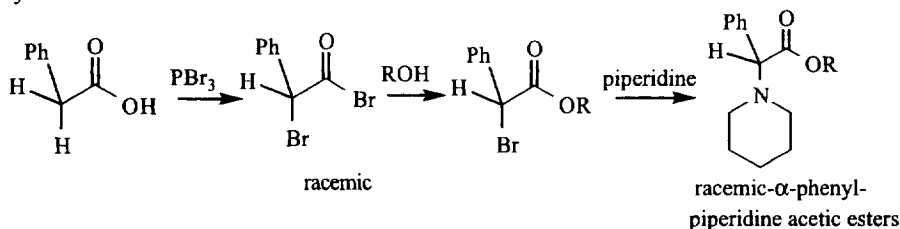
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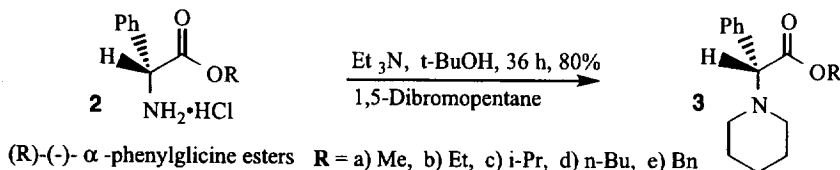
Abstract: Several α -phenyl-1-(*R*)-(-)-piperidineacetic esters **3(a–e)**, were obtained in pure enantiomeric form by condensing (*R*)-(-)- α -phenylglycine esters **2(a–e)** with 1,5-dibromopentane. Similarly, (*R*)-(-)- α -phenylglycine esters, **2(a–e)**, were prepared from (*R*)-(-)- α -phenylglycine **1** with high yields. © 1997 Published by Elsevier Science Ltd. All rights reserved.

Esters of general formula $C_6H_5CHXCOOR$ where **X** represents the piperidine moiety and **R** is the α -phenylacetic methyl, ethyl, isopropyl, benzyl or *n*-butyl esters, are typically available through the racemic synthesis shown below^{1,2}.



The alternative synthetic pathway followed in the present work is shown in Scheme 1; it provides a method for the preparation of the enantiopure products such as **3(a–e)**.

It is known that the reaction between alkyl halides and ammonia is an inadequate method for the preparation of primary or secondary amines since, as substitution on the nitrogen atom occurs, this turns into a stronger base than ammonia itself making the degree of substitution difficult to control. However, when a primary or secondary amine is used as a starting reagent, such reaction is useful for the synthesis of tertiary amines since it allows the inclusion of different alkyl groups on the nitrogen atom. Furthermore, when an intramolecular substitution is involved, cyclic amines can be synthesized.^{3,4} The latter reaction was used successfully in the present work for the preparation of



Scheme 1.

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Table 1.

Compd ¹ 2	R	$[\alpha]_D^{25}$ ² HCl	m.p. ^o HCl	IR, KBr (ν , cm^{-1})	¹ H NMR: D ₂ O (δ , ppm)
a	Me	-140	185	1740.	3.79 (s, 3H), 5.18 (s, 1H), 7.30-7.44 (m, 5H)
b	Et	-90.1	160	1738.	1.1 (t, $J=6.5$ Hz, 3H), 4.1 (m, 2H), 5.1 (s, 1H), 7.4 (m, 5H)
c	i-Pr	-73.1	174	1738.	1.08, 1.11 (d each, $J=6.5$ Hz, 6H) ³ ; 4.99 (hpt, $J=6.5$ Hz, 1H); 5.08 (s, 1H), 7.3 (m, 5H)
d	n-Bu	-76.4	146	1740.	0.6 (t, $J=6.5$ Hz, 3H); 1.0 (sxt, 2H), 1.4 (q, 2H), 4.1, ABX ₂ , ² $J=10.7$ Hz, ³ $J=6.4$ Hz, 2H); 5.14 (s, 1H); 7.36 (s, 5H)
e	Bn	-23.2	170	1743.	5.1 (AB, $J=18$ Hz, 2H), 5.2 (s, 1H); 7.2 (m, 10H)

1. Average yields ca. 96%; 2. $c = 1.0$; H₂O; 3. (CH₃)₂ methyls observed as diastereotopic groups.

Table 2.

Compd. 3 ¹	R	$[\alpha]_D^{25}$ HCl	m.p. ^o , ³ HCl	IR, KBr (ν , cm^{-1})	yield (%) ⁴
a	Me	-13.8	167	1747.	79
b	Et	-16.3	160	1743.	79
c	i-Pr	-15.3	-	1738.	80
d	n-Bu	-15.7	-	1744.	82
e	Bn	-18.8	-	1746.	82

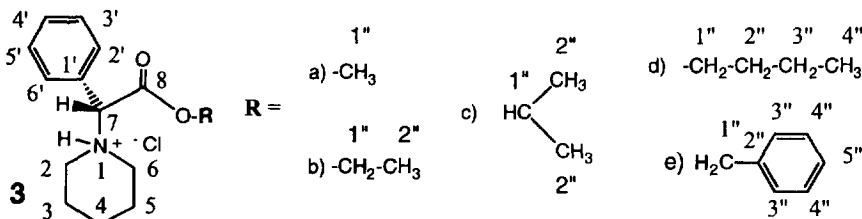
1. Average yield ca. 80%; 2. $c = 1.0$ (EtOH); 3. Some hydrochlorides were not obtained in crystalline form. The free bases are oils; 4. yields after recrystallization.

the six-membered cyclic amines in enantiopure form, i.e. α -phenyl-1-(*R*)-(-)-piperidineacetic esters **3(a-e)**.

The chiral starting materials **2(a-e)** for the preparation of the products **3(a-e)**, were obtained with higher yields than those previously reported.⁵ Thus, (*R*)-(-)- α -phenylglycine **1** was treated with thionyl chloride at room temperature and later with an excess of the esterifying alcohol, and the corresponding esters were obtained with methanol, ethanol, isopropanol, n-butanol and benzyl alcohol.

After the reaction was completed, the solvent was removed *in vacuo* and the residue dissolved in the minimum amount of ethanol, then diethyl ether was added to induce precipitation of the corresponding esters **2(a-e)**. Physical and relevant spectroscopic data are shown in Table 1.

The products of the cyclization **3(a-e)** were prepared following standard procedures. Thus, a solution the esters **2(a-e)** in tert-butanol and triethylamine⁶ was warmed to 45°C,⁷ and 1,5-dibromopentane was added dropwise with stirring. The products were obtained as free bases and then converted to the corresponding hydrochlorides **3(a-e)**. Their physical, IR data and yields, are summarized in Table 2 (see Experimental for ¹H and ¹³C NMR characterization).



The optical purity of esters **3(a-e)** was measured after reduction with LiAlH₄⁸ (yield ca. 90%). The value $[\alpha]_D^{25}$ of product **4** was found essentially to be identical to that of the product obtained by direct cyclization of *R*-(-)-2-phenylglycinol with 1,5-dibromopentane. Product **4** was further characterized by its ¹H NMR spectrum.⁹

Experimental

NMR spectra were obtained on a 500 MHz Varian Unity instrument equipped with an inverse detection probe. Spectra were run in D₂O or CDCl₃ at 25°C using 3-(trimethylsilyl)-1-propanesulfonic acid sodium salt and TMS respectively as internal reference. The IR spectra were recorded on a spectrophotometer Shimadzu FTIR 8101. The optical rotations were measured on a polarimeter Perkin Elmer M 241.

(R)-(-)-2-phenylglycine esters hydrochlorides 2(a-e)

To 1.0 g (R)-(-)-phenylglycine (6.62 mmol), 4.2 mL of recently distilled thionyl chloride (10.1 eq., d=1.63 g/mL) were added. The suspension was vigorously stirred for 2h at room temperature (20°C) to complete dissolution and 25 mL of the corresponding esterifying alcohol were added. The reaction was allowed to stand at room temperature for 3 h and monitored by SiO₂ TLC (CH₂Cl₂-MeOH; 95:5). The solvent was removed *in vacuo* and a white amorphous crude ester was obtained almost quantitatively. Recrystallizations were done in EtOH-Et₂O with yields ca. 96% in all cases.

α -Phenyl-1-(R)-(-)-piperidineacetic esters hydrochlorides 3(a-e)

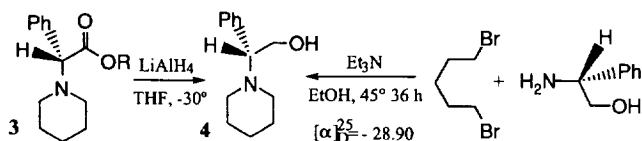
To a solution of (R)-(-)-2-phenylglycine ester hydrochloride 2(a-e) (2.48 mmol) and triethylamine (3 eq.) in 50 mL of tert-butanol was added 1,5-dibromopentane (1.1 eq.). The reaction was heated at 45°C for 36 h with stirring. The mixture obtained after evaporation *in vacuo*, was dissolved in CH₂Cl₂ and the precipitated Et₃NHBr was filtered off. The organic layer was dried over anhydrous Na₂SO₄ and submitted to Al₂O₃ column chromatography, eluting with CH₂Cl₂-pet. ether (6:4). The products were dissolved and stirred at room temperature for 2 h in a 1% HCl EtOH. After the ethanol was evaporated *in vacuo*, the hydrochlorides were redissolved in a minimum of EtOH and precipitated by addition of diethyl ether, collected by filtration, washed with Et₂O and dried. Recrystallization from EtOH-Et₂O gives colorless crystals for 3(a-b) and hygroscopic oils for 3(c-e). Average yield ca. 80%. ¹H and ¹³C NMR in CDCl₃ chemical shifts and average J values were assigned for 3a from 1D, HMQC and HMBC spectra; 3a δ^1 H(ax-eq): H-2(2.86, 3.79); H-3(2.48, 1.81); H-4(1.38, 1.86); H-5(2.32, 1.82); H-6(3.14, 3.47); H-7(12.45); OCH₃(3.82); H-2'(7.70); H-3'(7.48); H-4'(7.49); H-5'(7.48); H-6'(7.70); NH(12.45); average J values: ³J_{C α H-NH} 3.5 Hz; ²J_{Hax-eq} 12 Hz; ³J_{Hax-ax} 12 Hz; ³J_{Hax-eq} 3 Hz; ³J_{NH-C2ax} 12 Hz; ³J_{Heq-eq} 3 Hz; ³J_{NH-C2eq} 3 Hz; δ^{13} C: C-2(51.56); C-3(22.58); C-4(22.11); C-5(22.79); C-6(50.83); C-7(69.64); C-8(166.96); C-1'(127.15); C-2'(130.84); C-3'(129.53); C-4'(130.91); C-5'(129.53); C-6'(130.84); 3b δ^1 H(ax-eq): H-2(2.87, 3.79); H-3(2.50, 1.83); H-4(1.39, 1.86); H-5(2.30, 1.81); H-6(3.15, 3.39); H-2', -3', -4', -5, -6'(7.45-7.75, 5H); H-1'', AB sys.(4.26, 4.33, 2H); H-2''(1.26, 3H); δ^{13} C: C-2(51.5); C-3(22.5); C-4(22.0); C-5(23.0); C-6(50.5); C-1''(63.0); C-2''(14.0); C-7(69.5); C-1'(127.5); 2C-2', C-4'(131.0); 2C-3'(129.5); C-8(166.5); 3c δ^1 H(ax-eq): H-2(2.88, 3.75); H-3(2.48, 1.83); H-4(1.39, 1.83); H-5(2.27, 1.83); H-6(3.16, 3.38); H-7(5.03) H-8(5.16); -(CH₃)₂(1.31, 1.16); H-2', H-6'(7.70); H-3', H-5', 4'(7.48); NH(12.3); δ^{13} C: C-2, C-6(50.0, 51.5); C-3, C-5(21.5, 22.5); C-4(21.0); C-8(166.0); C-7(71.0); C-1''(69.0); 2C-2''(22.0); C-1'(127.5); 2C-2', C-4'(131.0); 2C-3'(129.5); 3d δ^1 H(ax-eq): H-2(2.89, 3.77); H-3(2.49, 1.83); H-4(1.39, 1.83); H-5(2.29, 1.83); H-6(3.17, 3.42); H-7(5.10); n-butyl(4.23, 1.38, 1.24, 0.85); 2', 6'(7.71); 3', 5', 4'(7.48); NH(12.33); δ^{13} C: C-2, C-6(50.5, 52.0); C-3, C-5(21.5, 22.0); C-4(21.0); C-7(70.0); C-8(166.0); C-1'(127.5); 2C-2', C-4'(131.0); C-3', C-5'(129.5); C-1''-C-4''(66.5, 30.0, 19.5, 13.5); 3e δ^1 H(ax-eq): H-2(2.92, 3.85); H-3(3.42, 3.60); H-4, H-5(1.7-2.4); H-7(5.05); CH₂(Bn)(AB, 5.08, 5.18, J=18 Hz); δ^{13} C: C-2, C-6(50.6, 51.1); C-3, C-5(22.1, 22.2); C-4(22.2); C-7(70.0); C-8(166.7); C-1'(127.2); C-2', C-6'(130.6); C-3', C-5'(129.5); C-4'(130.7); C-1''(67.0); C-2''(135.2); 2C-3''(128.3); 2C-4''(128.4); C-5''(128.5).

Acknowledgements

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References

1. Blicke, F. F.; Faust, J. A.; Raffelson, H. *J. Am. Chem. Soc.* **1954**, 76, 3156; *ibid.* **1954**, 76, 3161.
2. Kevin, K.; Robert, N. B.; Durst, T. *Tetrahedron Lett.* **1994**, 35, 3, 375, and references therein; Chabrier, P.; Najer, H.; Giudicelli, R.; Joannic, M. *Bull. Soc. Chim. France* **1957**, 1365; Najer, H.; Chabrier, P.; Giudicelli, R. *Bull. Soc. Chim. France* **1958**, 355.
3. Sommer, H. Z.; Jackson, I. L. *J. Org. Chem.* **1970**, 35, 1558 and references therein.
4. Juaristi, E.; Madrigal, D. *Tetrahedron* **1989**, 45, 629.
5. Grant, G. S.; Thipamon, S. *J. Org. Chem.* **1983**, 48, 627; Nagai, Y.; Kusumi, T. *Tetrahedron Lett.* **1995**, 36, 1853 and references therein.
6. The reaction was always carried out in tert-butanol because other alcohols induce up to ca. 50% trans-esterification.
7. The use of triethylamine at a maximum temperature of 45°C was found suitable for avoiding racemization of the aminoacid ester.
8. Jens, A.; Peter, S. *Tetrahedron* **1995**, 51, 9747.
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4·HCl: NMR (δ , CDCl₃): 10.7 (br, 1H), 7.44 (s, 5H), 5.26 (br, 1H), 4.46 (m, 2H), 4.10 (d, 1H), 3.73 (d, 1H), 3.59 (d, br, 1H), 2.69 (t, br, 1H), 2.45 (m, 2H), 2.29 (dt, 1H), 1.84 (m, br, 3H), 1.28 (m, 1H).

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