Synthesis of Beta-Proline Like Derivatives and Their Evaluation as Sodium Channel Blockers

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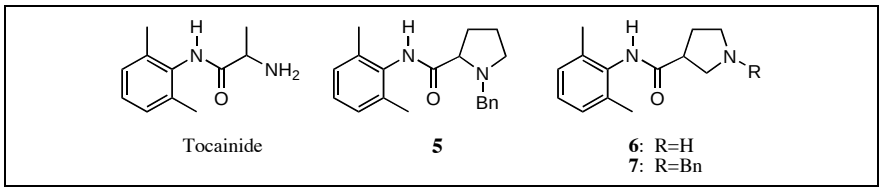

A simple and convenient procedure for the preparation of beta-proline like derivatives in their racemic and optically active forms has been reported. The compounds have been screened for their potential activity as sodium channel blockers.

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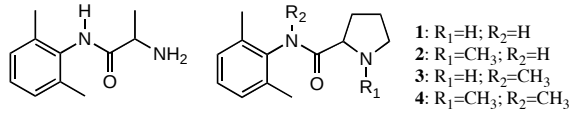
INTRODUCTION

As part of an ongoing program on the research of potent and selective sodium channel blockers, in this article we report the synthesis and biological evaluation of 1-benzyl-*N*-(2,6-dimethylphenyl)-3-pyrrolidinecarboxamide (**7**) both in racemic and optically active forms.

Previously we synthesized some alpha-proline like derivatives (Figure 1) that have partial structural analogy with the cardiovascular drug Tocainide [1-5], a molecule capable of blocking the voltage-gated sodium channel.

Figure 1



Tocainide

The serious disadvantages correlated to its clinical use, lead us to plan and prepare the alpha-proline derivatives.

Our rationale for the preparation of these compounds was that, although the structural requirements for the voltage-gated sodium channel blockers have not yet been fully identified, different theories indicate lipophilicity and basicity as pivotal molecular properties for this activity.

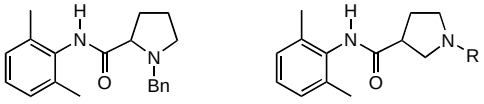
The first important result of this investigation was an improvement of the biological profile obtained by constraining both the stereogenic centre and the terminal aminic group of Tocainide into a rigid pyrrolidine ring (Table 1).

The preliminary structure-activity relationships obtained with this series of compounds suggest that a greater lipophilicity (due to the pyrrolidine ring) and a greater basicity (associated with the secondary aminic group) with respect to Tocainide, are crucial for high sodium channel blocking activity. On the other hand, this activity is strongly reduced by the introduction of methyl groups on one or both the nitrogen atoms, likely following modification of the pK_a and/or constraints of molecular conformation. Among all α-proline-like derivatives (**1**-**4**, Figure 1) the (*R*)-**1** was found to be the most interesting congener [6-7].

On the basis of these results, we decided to synthesize derivatives **5**-**7** (Figure 2), with the aim to investigate further the role of basicity and lipophilicity in drug-receptor interaction.

This was carried out: a) by spacing out the aminic group from the stereogenic centre and freezing it in position 3 of a pyrrolidine ring in order to improve pK_a values (beta-proline like derivatives **6**, **7**); b) by introducing a benzyl group on the nitrogen atom of the pyrrolidine ring, increasing lipophilicity, to produce compounds **5** and **7**.

Figure 2



The most interesting result was observed for 1-benzyl-*N*-(2,6-dimethylphenyl)-3-pyrrolidinecarboxamide **7**, as reported in the "Results and Discussion" section. Such a result prompted us to develop a synthesis for both enantiomers of **7** [(+)-(*R*)-**7** and (−)-(*S*)-**7**], with the aim of evaluating the influence of stereochemistry on sodium channel blocking activity.

In this paper we will report the synthetic procedures and the pharmacological results of this new series of Tocainide analogous.

RESULTS AND DISCUSSION

In this paper, we pursued the rationalization of the design and synthesis of compounds potentially useful as sodium channel blockers, with the aim of investigating the molecular determinants responsible for blocking the activity of the channel.

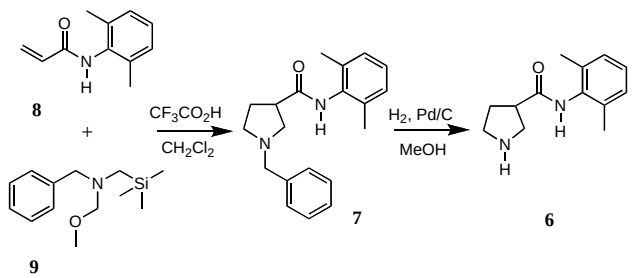
In particular, we planned and synthesized a new series of molecules carrying a beta-proline ring instead of an alpha-proline ring (Scheme 1).

Moreover, we synthesized compound **5** by introducing a benzyl group on the heterocyclic nitrogen atom of **1**, resulted in the production of the most active among the alpha-proline series.

Scheme 1 outlines the synthetic approach used to prepare (*R*,*S*)-1-benzyl-*N*-(2,6-dimethylphenyl)-3-pyrrolidinecarboxamide **7**, which involves a dipolar cycloaddition reaction [8].

N-(2,6-Dimethylphenyl)-2-propenamide **(8)**, obtained by a condensation reaction of 2-propenoyl chloride and 2,6-dimethylaniline in the presence of EEDQ [9] reacting with *N*-benzyl-*N*-(methoxymethyl)trimethylsilylmethylamine (**9**) [10] gave the expected 1,3-cycloaddition reaction, in the presence of a catalytic amount of trifluoroacetic acid, so as to afford the corresponding pyrrolidine-3-carboxamide **7** [11]. Compound **6** was obtained by treating **7** with H_2 in the presence of Pd/C, resulting in a 74% yield.

Scheme 1



The enantiomers (*R*)- and (*S*)-1-benzyl-*N*-(2,6-dimethylphenyl)-3-pyrrolidinecarboxamide [(+)-(*R*)-**7** and (−)-(*S*)-**7**, Scheme 2] were prepared starting from the corresponding, commercially available, optically pure 1-benzylpyrrolidin-3-ol (*S*)-**10** and (*R*)-**10**. (*S*)-**10** and (*R*)-**10** were in turn converted (97% yield) into (*S*)-**11** and (*R*)-**11**, using methanesulfonyl chloride and Et_3N [12]. Nitrile (*R*)-**12** and (*S*)-**12** were obtained by a S_N2 displacement reaction of the mesylates (*S*)-**11** and (*R*)-**11** (99% yield), respectively in the presence of tetrabutylammonium-cyanide and sodium cyanide in DMSO [12].

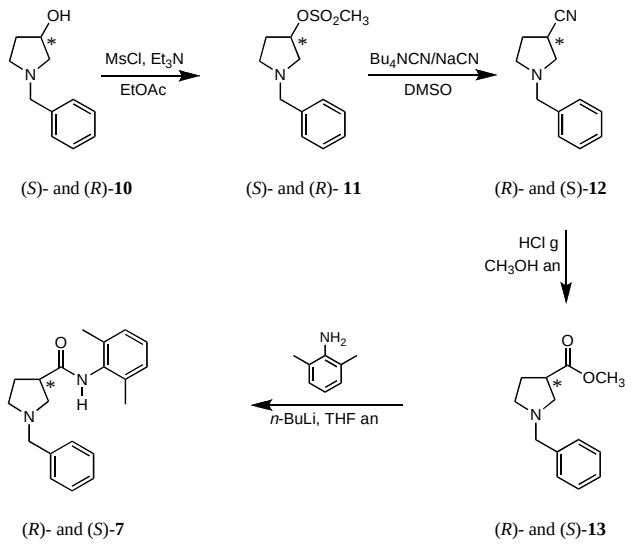
The β-proline esters (*R*)-**13** and (*S*)-**13** were prepared from (*R*)-**12** and (*S*)-**12** by being dissolved in anhydrous CH_3OH, reacted with gaseous HCl followed by a basic workup (98% yield) [12]. In the final step, (*R*)-**13** and (*S*)-**13** were in turn slowly added to a solution of 2,6-dimethylaniline and *n*-BuLi (2.09 *M* in hexane) in anhydrous THF to give the desired (*R*)-**7** and (*S*)-**7** (63%) yield.

Finally, the synthesis of (±)-(*R*,*S*)-1-benzyl-*N*-(2,6-dimethylphenyl)-2-pyrrolidinecarboxamide **5**, starting from compound **1**, was performed in the presence of benzyl bromide, K_2CO_3 dissolved in a mixture of dioxane/H_2O (50% yield).

All the new products were characterized by ^1H and ^{13}C-NMR, mass spectra, optical rotation, IR and elemental analysis data. Furthermore free amines of **7** underwent ee evaluation by HPLC as reported in the "Experimental" section.

All proline-like derivatives were tested on sodium currents of adult skeletal muscle fibers by the voltage-clamp method [13].

Scheme 2



It is important to note that the simple exchange of the alpha- with a beta-proline like-ring (**1** *vs* **6**) did not substantially change the drug potency and produces a decrease in the use-dependent behavior, as reported in Table 1. The insertion of a benzyl

Table 1

Ratio of potency values[a] for both tonic and phasic block of **1**-**7**.

Compound	Absolute conf.	Ratio of potency[a]		cLogP[b]	pKa[b]
		Tonic block[c]	Phasic block[d]		
Tocainide	*(R)*	1	1	0.76 ± 0.48	8.10
1	*(R, S)*	3.5	11.6	1.72 ± 0.29	9.37
	(R)	5.3	20.8		
	(S)	2.5	6.1		
2	*(R)*	1.9	2.7	1.48 ± 0.27	8.67
	(S)	5.5	9.6		
3	*(R)*	1.7	1.2	1.71 ± 0.39	9.19
	(S)	5.6	4		
4	*(R)*	< 1	0.6	2.10 ± 0.40	8.49
	(S)	2	1.4		
5	*(R, S)*	19.5	17.1	3.00 ± 0.34	7.83
6	*(R, S)*	6.2	7.1	1.82 ± 0.27	10.01
7	*(R, S)*	20.2	122.7	3.26 ± 0.34	8.47
	(R)	28.6	158.9		
	(S)	22.4	117.4		

[a] The ratio of potency values have been obtained normalizing the IC_{50} values of each compound tested with respect to those of (*R*)-Tocainide, for both tonic (580 ± 11 μM) and phasic block (use-dependent block) at 10 Hz (270 ± 5 μM). [b] Calculated using Advanced Chemistry Development (ACD) Software Solaris V4.76. [c] Tonic block: block of sodium channel at resting conditions evaluated during infrequent depolarizing pulses. [d] Phasic block: cumulative sodium current reduction by the drug at 10 Hz stimulation frequency, obtained by concentration-response curves.

group on the nitrogen atom of the pyrrolidine ring (**5**, **7**) causes an increase of both tonic and phasic block (see Table 1). In particular, the *N*-benzylated compound **7**, having a combined increase of lipophilicity (due to the insertion of a benzyl group) and basicity (the amino group is spaced out from the chiral carbon atom) has shown the highest increment of potency among all synthesized compounds. In fact it was 20.2 fold more potent than Tocainide for tonic block of sodium currents and up to 100 fold (122.7) more potent than the parent compound at high frequency of stimulation [14].

No significative difference was detected between the optically active compounds (+)-(*R*)-**7** and (–)-(*S*)-**7**.

The ratio of potency values for tonic and phasic block, reported in Table 1, suggests that potency and use-dependent behaviour are strongly increased both by the introduction of a benzyl group on the aminic nitrogen and also by increasing the distance between the two aromatic rings. This probably means that the introduction of a hydrophobic group in the molecule, together with an increment in lipophilicity of the whole molecule, would play an important role in establishing specific hydrophobic interactions with the binding site. Among all Tocainide analogous evaluated *in vitro* and reported in this paper, compound **7** has been identified as the most potent sodium channel blocker.

CONCLUSIONS

In conclusion, we have reported synthetic procedures for the synthesis of beta-proline like derivatives in their racemic and optically active forms.

The methodologies described here may find useful applications in the synthesis of drug intermediates and other bioactive compounds carrying the beta-proline heterocyclic moiety.

Currently compound **7** is a highly promising molecule that could be used both for pharmacological investigations such as channelopathies (*e.g.* myotonia) and as a new "lead" for searching still more potent and selective sodium channel blockers.

EXPERIMENTAL

All chemicals were purchased from Aldrich in the highest quality commercially available. The structures of the compounds were confirmed by routine spectrometric and spectroscopic analyses. Only spectra for compounds not previously described are given.

Melting points are uncorrected and were recorded on Gallenkamp melting point apparatus in open glass capillary tubes. The IR spectra were recorded on a Perkin-Elmer Spectrum One FT spectrophotometer and band positions were given in reciprocal centimeters (cm^{-1}). ^1H NMR spectra (300 MHz) were recorded on a FT Bruker Aspect 3000 spectrometer using $CDCl_3$ as the solvent, unless otherwise indicated. Chemical shifts were reported in part per million (ppm) relative to solvent resonance: $CDCl_3$, δ 7.26 (^1H NMR). Amino proton assignments were confirmed by D_2O exchange. *J* values are given in Hz. EIMS spectra were recorded with a Hewlett-Packard 6890-5973 MSD gas chromatograph/mass spectrometer at low resolution. Elemental analyses were performed on a Eurovector Euro EA 3000 elemental analyzer, were indicated, C, H, and N were within ± 0.4 of the theoretical values. Optical rotations were measured on a Perkin-Elmer Mod 341 spectropolarimeter; concentrations were expressed in g/100 mL and the cell length was 1 dm, thus $[\alpha]^{20}_D$ values were given in units of 10^{-1} deg cm^2 g^{-1}. Silica gel chromatographic separations

were performed by chromatography with silica gel (Kieselgel 60, 40-63 μm, Merk) packed in glass columns, using the technique described by Still *et al.* [15]. The weight of the silica gel was approximately 100 times that of the substance, unless otherwise noted. The eluting solvent indicated in parentheses, for each purification was determined by TLC, that was performed on precoated silica gel on aluminium sheets (Kieselgel 60 F_{254}, Merck). TLC plates were visualised with UV light and/or in an iodine chamber. HPLC analyses were performed on an Agilent chromatograph model 1100 equipped with a diode array detector. The *ee* of **7** and its enantiomers was determined by direct HPLC analysis on a Daicel Chiralpak IA column (flow 0.8 ml/min, λ 230 nm, eluent: hexane/*i*-PrOH/Et_2NH, 85/15/0.15).

(±)-(*R*,*S*)-1-Benzyl-*N*-(2,6-dimethylphenyl)-2-pyrrolidine carboxamide [(±)-(*R*,*S*)-5]. **1** (0.196 g; 0.92 mmol) in dioxane (16 mL), was added to a solution of K_2CO_3 (0.362 g, 2.622 mmol) in water (8 mL). The reaction mixture was stirred at 70 °C. Then, a solution of benzylbromide (173 mg, 1.012 mmol) in dioxane (12 mL) was dropwise added over 15 minutes. When the addition was completed the resulting mixture was stirred for 1 h. The dioxane was evaporated under reduced pressure and the residue was diluted with water and extracted with EtOAc. The organic layer was washed with 2 *N* HCl. The aqueous phase was treated with 2 *N* NaOH (up to pH=11) and extracted with EtOAc (3x25 mL). The latter organic layers were dried over Na_2SO_4, filtered, and evaporated to dryness. The crude product was recrystallized from EtOAc/petroleum ether to give **5** as a white solid in 50% yield. Mp 134-138 °C (EtOAc/hexane); ir: ($CHCl_3$) 3800-3700, 3060, 3000, 2977, 2941, 1671, 1590, 1495, 941, 920, 810 cm^{-1}. ^1H nmr (300 MHz, $CDCl_3$), δ 9.10-8.90 (br s, 1H, NHCO: exchange with D_2O), 7.34-7.26 (m, 5H, phenyl protons), 7.10-7.08 (m, 3H, phenyl protons), 4.17-4.08 (m, 2H), 3.78-3.40 (m, 2H), 3.20-3.12 (m, 1H), 2.50-2.26 (m, 2H), 2.19 (s, 6H), 1.96-1.82 (m, 2H); ms (70 eV, electron impact) m/z 308 (M^+, 2), 161 (27), 160 (100), 92 (9), 91 (74), 65 (7). *Anal.* Calcd for $C_{20}H_{24}N_2O$: C, 77.89; H, 7.84; N, 9.08. Found: C, 77.85; H, 7.83; N, 9.09.

(±)-(*R*,*S*)-*N*-(2,6-Dimethylphenyl)-3-pyrrolidinecarboxamide [(±)-(*R*,*S*)-6]. Compound **7** (0.150 g, 0.53 mmol) and 10% Pd/C (0.06 g) were suspended in CH_3OH (20 mL) and treated with H_2 (6 bar) for 5 h at room temperature. Then, the catalyst was filtered off and the organic layer was evaporated under reduced pressure to give 6 as a white solid in 74% yield. Mp 127–128 °C; ir ($CHCl_3$): 3264, 1652 (C=O) cm^{-1}; ^1H nmr (300 MHz, $CDCl_3$), δ 8.10–7.98 (br s, 1H, NHCO that exchange with D_2O), 7.13–7.07 (m, 3H, phenyl protons), 3.39–3.36 (m, 1H), 3.26–3.17 (m, 1H), 3.03–2.87 (m, 3H), 2.27–2.10 (m, 9H: 2H of the pyrrolidine ring, 6H of the two CH_3 and 1H of NH: exchange with D_2O); ms (70 eV, electron impact) m/z 218 (M^+, 25), 203 (26), 176 (90), 121 (100), 91 (16), 70 (47), 41 (24).

(±)-(*R*,*S*)-1-Benzyl-*N*-(2,6-dimethylphenyl)-3-pyrrolidinecarboxamide [(±)-(*R*,*S*)-7]. To a solution of **9** [10] (1.0 g, 4.03 mmol) in CH_2Cl_2 (10 mL) kept at 0 °C were added *N*-(2,6-dimethylphenyl)-2-propenamide (**8**) (0.847 g; 4.84 mmol) and 1 *M* CF_3COOH solution in CH_2Cl_2 (0.4 mL). Then, the stirred reaction mixture was allowed to reach room temperature and stirred for further 3 h. The organic layer was washed with saturated aqueous $NaHCO_3$ (2x25 mL) and with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum. Column chromatography (silica gel, eluent: EtOAc) of the reaction crude provided 1-benzyl-*N*-(2,6-dimethylphenyl)-3-pyrrolidinecarboxamide (**7**) which was recrystallized from EtOAc/hexane to give white crystals in 51% yield. Mp 105.7–107.7 °C; ir ($CHCl_3$): 3662, 3057, 1709, 1368, 1107 cm^{-1}. IR (KBr): 3620, 3050, 1660, 1640, 1550, 1250, 770, 700 cm^{-1}; ^1H nmr (300 MHz, $CDCl_3$), δ: 8.90–8.70 (br s, 1H, NH that exchange with D_2O), 7.40–7.28 (m, 5H, phenyl protons), 7.10–7.03 (s, 3H, phenyl protons), 3.77–3.73 (d, 1H, *J*= 12.57 Hz, C*H*HPh), 3.72–3.68 (d, 1H, *J*= 12.57 Hz, CH*H*Ph), 3.25–2.97 (m, 3H), 2.53–2.30 (m, 3H), 2.26–2.08 (multiplet overlapped to a singlet at 2.13ppm, 7H: 1H of the pyrrolidine ring and 6H of the two CH_3);ms (70 eV, electron impact) m/z 308 (M^+, 11), 293 (14), 217 (14), 188 (11), 176 (13), 160 (25), 132 (27), 120 (25), 91 (100). *Anal.* Calcd for $C_{20}H_{24}N_2O$: C, 77.89; H, 7.84; N, 9.08. Found: C, 77.90; H, 7.87; N, 9.10.

1-Benzyl-*N*-(2,6-dimethylphenyl)-3-pyrrolidinecarboxamide [(+)-(*R*)-7 and (–)-(*S*)-7]. *n*-BuLi (2.09 *M* in hexane; 0.72 mL, 1.496 mmol) was added to a solution of 2,6-dimethylaniline (0.18 mL, 1.496 mmol) in anhydrous THF (3 mL) kept at -15 °C and under nitrogen atmosphere. The resulting yellow mixture was stirred for 1 h at -15 °C. Then, a solution of methyl 1-benzylpirrolidine-3-carboxylate [(*R*)-13 or (*S*)-13)] (0.150 g, 0.68 mmol) in THF (7 mL) was slowly added. The reaction mixture was first stirred at -15°C for 6 h, and then for 12 h at room temperature. Hence, the solvent was evaporated under vacuum. The residue was washed with water (3x25 mL) and extracted three times with EtOAc. The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Column chromatography (silica gel; mobile phase: EtOAc) of the reaction crude gave 1-benzyl-*N*-(2,6-dimethylphenyl)-3-pyrrolidinecarboxamide [(*R*)-**7** or (*S*)-**7**] as a yellow oil in 63% yield. (+)-(*R*)-**7** had $[\alpha]^{20}_D$ = +1.8 (*c* 1, $CHCl_3$, *ee* 98%, t_R 8.5 min); (–)-(*S*)-**7** had $[\alpha]^{20}_D$ = –1.56 (*c* 0.6, $CHCl_3$, *ee* 97%, t_R 7.7 min). Both (*R*)- and ir, ^1H nmr and ms spectra were identical with those reported for (*R*,*S*)-**7**. *Anal.* Calcd for (*R*)-**7** ($C_{20}H_{24}N_2O$): C, 77.89; H, 7.84; N, 9.08. Found: C, 77.56; H, 7.98; N, 8.71. *Anal.* Calcd for (*S*)-**7** ($C_{20}H_{24}N_2O \cdot$ 0.125 EtOAc): C, 77.08; H, 7.89; N, 8.77. Found: C, 77.48; H, 8.03; N, 8.39.

***N*-(2,6-Dimethylphenyl)-2-propenamide (8).** To 2,6-dimethylaniline (1 g, 8.2 mmol, 1 mL) in 100 mL of anhydrous CH_2Cl_2 under a nitrogen atmosphere and cooled to 0 °C, Et_3N (3.6 g, 35 mmol, 4.87 mL) was added. Then, a solution of 2-propenoyl chloride (1.06 g, 11.7 mmol, 0.95 mL) in anhydrous CH_2Cl_2 (5 mL) was added dropwise over 10 minutes. The resulting mixture was first stirred at 0 °C for 2 h, and then at room temperature for further 12 h. Then, the reaction mixture was treated with 1 *N* HCl (2 x 25 mL). The organic layer, separated from the aqueous phase, was washed with saturated aqueous $NaHCO_3$ and then with brine until the pH became neutral. The organic phase was dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum. The crude product was recrystallized from EtOAc/petroleum ether to give **8** as yellow crystals (98% yield). Mp 146–147 °C [lit. [9] 143–144 °C (EtOAc)]; ir ($CHCl_3$): 3662, 3058, 2990, 2929, 1709 (C=O) cm^{-1}; ^1H nmr (300 MHz, $CDCl_3$), δ 8.45–8.24 (br s, 1H, NHCO: exchange with D_2O), 7.20–7.05 (m, 3H, phenyl protons), 6.52–6.40 (dd, 1H, *J*= 17.30 Hz and 2.33 Hz), 6.39–6.29 (dd, 1H, *J*= 17.30 Hz and 9.34 Hz), 5.81–5.77 (dd, 1H, *J*= 9.34 Hz and 2.33 Hz), 2.24 (s, 6H); ms (70 eV,electron impact) m/z 175 (M^+, 75), 147 (15), 122 (13), 121 (100), 55 (52).

1-Benzylpyrrolidin-3-yl-methanesulfonate [(+)-(*R*)-11 and (–)-(*S*)-11]. (*R*)- or (*S*)-1-benzylpyrrolidin-3-ol (**10**) (5 g, 28.2

mmol) was dissolved in EtOAc (11 mL). To the mixture cooled by an ice-salt bath, Et_3N (5.69 g, 56.5 mmol, 7.83 mL) and methanesulfonyl chloride (3.85 g, 33.9 mmol) were added. After 3 h, 2 *N* NaOH (38 mL) was added to the reaction mixture kept at -5 °C. The biphasic mixture was vigorously stirred for 10 minutes at -5 °C. The layers were separated and the organic phase was washed three times with water. The combined extracts were dried over anhydrous Na_2SO_4, filtered, and evaporated under reduced pressure to afford 5.762 g (97% yield) of (*R*)-**11** or (*S*)-**11** as a yellow clear oil. (+)-(*R*)-11: $[\alpha]^{20}_D$ = +13.6 (*c* 1, CH_3OH); (–)-(*S*)-11: $[\alpha]^{20}_D$ = –12.8 (*c* 1, CH_3OH); ir, ^{1}H nmr and ms spectra were in agreement with those reported in the literature [12].

1-Benzylpyrrolidin-3-carbonitrile [(–)-(*R*)-12 and (+)-(*S*)-12]. Compounds (–)-(*R*)-**12** and (+)-(*S*)-**12** were prepared according to the literature procedure starting from compound (-)-(*S*)-11 and(+)-(*R*)-11 respectively. $[\alpha]^{20}_D$ = –25.8 (*c* 1, $CHCl_3$) for (*R*)-enantiomer; $[\alpha]^{20}_D$ = + 26.2 (*c* 1, $CHCl_3$) for (*S*)-enantiomer. Both (*R*)- and (*S*)-12 ir, ^{1}H nmr and ms spectra were in agreement with those reported in the literature [12].

Methyl 1-benzylpyrrolidine-3-carboxylate [(–)-(*R*)-13 and (+)-(*S*)-13]. Anhydrous CH_3OH (41 mL) was saturated with gaseous HCl at 0 °C, under a nitrogen atmosphere. Then, 1-benzylpyrrolidin-3-carbonitrile [(*R*)-**12** or (*S*)-**12**] (0.5 g, 268 mmol) and water (0.5 mL) were added and the mixture allowed to reach room temperature. The pink reaction mixture obtained was vigorously stirred at room temperature for 21 h. Then, the solvent was removed under reduced pressure and the residue treated with 4 *N* NaOH (up to pH=11). The aqueous layer was then extracted with EtOAc (3x25mL). The combined organic phases were washed twice with water, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to afford the product (–)-(*R*)-**13** or (+)-(*S*)-**13** as a brown oil (98% yield). (–)-(*R*)-13 had $[\alpha]^{20}_D$ = –17.5 (*c* 1, $CHCl_3$); (+)-(*S*)-13 had $[\alpha]^{20}_D$ = +17 (*c* 1, $CHCl_3$); ir, ^{1}H nmr and ms spectra were in agreement with those reported in the literature [12].

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