Facile Routes for the Preparation of 3,4-Disubstituted 1,3-Oxazolidines and 1,2,5-Trisubstituted Imidazolidin-4-ones

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Facile, alternative synthetic routes to (RS)-, (R)-, and (S)-3-benzyl-N-(2,6-dimethylphenyl)-1,3-oxazolidine-4-carboxamides (**6**), a chiral oxazolidine derivative of tocainide, are reported. The synthetic routes described herein also afforded (RS)-, (R)-, and (S)-**11**, which present the imidazolidin-4-one core and belong to a class of compounds interesting for their biological activities. All the final compounds and intermediates were fully characterized. Enantiomeric excesses of homochiral **6** and **11** were determined by capillary electrophoresis analysis using 2-hydroxypropyl- β -cyclodextrin or highly sulfated γ -cyclodextrin as chiral selectors.

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INTRODUCTION

Tocainide, 2-amino-N-(2,6-dimethylphenyl)-propanamide (1a, Fig. 1), is a well-known sodium channel blocker belonging to class Ib antiarrhythmic drugs. It was once used in the treatment of symptomatic lifethreatening ventricular arrhythmias [1,2]. It has also a marked analgesic effect in trigeminal neuralgia in humans [3,4] and antinociceptive effect in rats as well [5]. Finally, by virtue of its ability to block sodium channels in a use-dependent manner, that is, with an increased potency in conditions of high-frequency discharges of action potentials, tocainide has been proposed as a clinically useful antimyotonic drug [6]. In fact, myotonic syndromes are hereditary disorders of skeletal muscle due to genetic defects in sodium or chloride channels whose main result is an abnormal membrane hyperexcitability that triggers muscle stiffness. Due to the wide spectrum of pharmacological activity, the use of tocainide as antimyotonic is hindered by unwanted side effects [7]. A few years ago, a comprehensive model of the sodium channel was reported, showing that the increase in lipophilicity and molecular size of antiarrhythmic drugs can reinforce hydrophobic interactions with the binding site during use-dependent block [8,9]. Therefore, we started a program aimed at the development of new antimyotonic drugs, using tocainide as a lead compound. We found that potency and use-dependent behavior were found to be strongly increased by constraining the amino terminal group of **1a** in both a rigid α - and β -proline cycle (**2a** and **3a**). A further improvement was still achieved by introducing a benzyl moiety on the amino group of tocainide (**1b**) and proline-derived compounds (**2b** and **3b**) [10–12].

Thus, the preparation of the corresponding imidazolidine derivative 4, which combines α -and β -proline features, may be envisaged. Nevertheless, it is commonly known that the imidazolidine ring is quite unstable; thus, we designed, synthesized, and tested on voltage-gated skeletal muscle sodium channels the corresponding piperazine analogue 5 [13]. This compound behaved as sodium channel blocker and was much more potent than tocainide both in tonic and phasic block experiments [13]. Herein, on the basis of isosteric relationships, we report the synthesis of the oxazolidine analogue 6. It is noteworthy that, in the final step of the synthesis of 6, we observed the formation of a new compound, deriving from a different intramolecular condensation reaction (see results and discussion), bearing an imidazolidin-4one core (11). It is already known that imidazolidin-4-



Figure 1. Structures of tocainide and its analogues.

ones represent an interesting class of compounds with respect to biological activity [14–16]. Through manipulation of the substituents around the imidazolidin-4-one core, molecules with a variety of biological properties have been discovered. Several examples include com-

pounds that exhibit antibacterial activity [17,18]. Recently, imidazolidin-4-one was suggested as an attractive scaffold in the β -secretase (BACE-1) active site, a promising drug target for Alzheimer disease-modifying therapy [19,20]. The structural diversity of substituted imidazolidin-4-ones makes this compound class versatile for drug discovery research and necessitates the development of efficient and versatile syntheses of such molecules [21,22].

RESULTS AND DISCUSSION

The synthesis of (R)- and (S)-3-benzyl-N-(2,6-dimethylphenyl)-1,3-oxazolidine-4-carboxamides (**6**) was obtained by following two alternative routes (Scheme 1). The former starts from homochiral commercially available 3-(benzyloxycarbonyl)-4-oxazolidinecarboxylic acids (**7**), which were reacted with 2,6-dimethylaniline, in the presence of IIDQ (2-isobutoxy-1-isobutoxycarbonyl-1,2-diihydroquinoline) to give homochiral benzyl

Scheme 1. Synthesis of 3-benzyl-*N*-(2,6-dimethylphenyl)-1,3-oxazolidine-4-carboxamides (6) and 1-benzyl-3-(2,6-dimethylphenyl)-5-(hydroxymethyl)imidazolidin-4-ones (11). Reagents and conditions: (i) 2,6-dimethylaniline, IIDQ, Et₃N, CHCl₃, reflux, (ii) Et₃SiH, PdCl₂, Et₃N, CH₂Cl₂, reflux; (iii) benzyl bromide, K₂CO₃, dioxane/water, reflux; (iv) HCHO, 2*N* NaOH, dioxane, 0°C; (v) HCHO, 2*N* NaOH, 0°C; (vi) NH₂OH, HCl, aq. NaOH/acetone, Boc₂O, room temperature; (vii) conc HCl, EtOAc, room temperature.



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4-[(2,6-dimethylphenyl)carbamoyl]-1,3-oxazolidine-3carboxylates (8) according to our previously reported procedure [13]. Deprotection of 8 with triethylsilane and palladium chloride [23] brought to the opening of the oxazolidine ring giving homochiral 2-amino-N-(2,6dimethylphenyl)-3-hydroxypropanamides (9), which were converted into their N-benzyl derivatives 10 by reaction with benzyl bromide. 1,3-Oxazolidine enantiomers 6 were then obtained by treatment of homochiral 10 with formaldehyde by modifying a literature procedure [24]. It is noteworthy that, in this reaction, a different intramolecular reaction also occurred resulting in the formation of the imidazolidin-4-one derivatives [1benzyl-3-(2,6-dimethylphenyl)-5-(hydroxymethyl)imidazolidin-4-one] 11 along with compounds 6. Compounds 6 and 11 possess the same molecular weight and retention times as assessed from GC-MS and LC-MS but differ in their physical properties (6 and 11 being solid and oil, respectively) and have different R_f values by TLC, thus they were isolated by flash chromatography on silica gel. Ee values of 6 and 11 enantiomers were evaluated by capillary electrophoresis using 2-hydroxypropyl- β -cyclodextrin or highly sulfated γ -cyclodextrin as chiral selectors. Ee values were 98% and >99% for (R)- and (S)-6, respectively. It is noteworthy that, the intramolecular reaction that led to 11 occurred with a partial racemization, being ee values 80% and 86% for (R)- and (S)-11, respectively. The alternative route for the synthesis of homochiral 6 and 11 starts from homochiral D- and L-serine (12), which were easily converted into homochiral 3-(tert-butoxycarbonyl)-1,3-oxazolidine-4-carboxylic acids (13) following a procedure reported in the literature [25]. Compounds 13 underwent the same condensation reaction described above affording homochiral 14. Deprotection of (R)- and (S)-14 gave (R)- and (S)-9. The synthesis of racemic 6 and 11 was performed as above described for the enantiomers, starting from DL-serine, since racemic 7 is not commercial.

CONCLUSIONS

Alternative entries to (RS)-, (R)-, and (S)-6, a 2,6-oxazolidinylxylidide analogue of tocainide, have been proposed. The synthetic routes described herein brought also to the formation of a new imidazolidin-4-one derivative, 1-benzyl-3-(2,6-dimethylphenyl)-5-(hydroxymethyl)imidazolidin-4-one, in its racemic and homochiral forms [(RS)-, (R)-, and (S)-11]. The routes described herein also provided new hydroxyl derivatives (9,10) of tocainide (1a) and benzyltocainide (1b). The higher polarity of these compounds with respect to that of the parent compounds may be also useful to meet the need of thorough metabolic studies, considering that both tocainide (1a) and benzyltocainide (1b) act as potent voltage-gated sodium channel blockers [10–12]. All the final compounds and intermediates were fully characterized by routine spectroscopic analyses and enantiomeric excesses of **6** and **11** enantiomers were determined by capillary electrophoresis analysis using 2-hydroxypropyl- β -cyclodextrin or highly sulfated γ -cyclodextrin as chiral selectors. Pharmacological investigations on the newly synthesized compounds will be useful to better study the interaction of LA-like drugs with the binding site in voltage-gated sodium channels (for compounds **6**) and to analyze various potential biological properties (for the imidazolidin-4-one derivatives **11**), as above described and to explore their therapeutic potential usefulness.

EXPERIMENTAL

General. Yields refer to purified products and were not optimized. The structures of the compounds were confirmed by routine spectrometric analyses. Only spectra for compounds not previously described are given. Compounds 13 were prepared as previously described [25]. Melting points were determined on a Gallenkamp apparatus in open glass capillary tubes and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer (Norwalk, CT) Spectrum One FT spectrophotometer and band positions are given in reciprocal centimeters (cm^{-1}) . ¹H NMR and ¹³C NMR spectra were recorded on a Bruker 300-MHz spectrometer (ASPECT 3000), operating at 300 and 75 MHz for ¹H and ¹³C, respectively, using CDCl₃ as solvent unless otherwise indicated. Chemical shifts are reported in parts per million (ppm) relative to solvent resonance: CDCl₃, δ 7.26 (¹H NMR), and δ 77.3 (¹³C NMR); DMSO-*d*₆, δ 2.50 (¹H NMR) and δ 40.2 (¹³C NMR); CD₃OD, δ 3.30 (¹H NMR) and δ 47.8 (¹³C NMR). J values are given in Hz. GC-MS was performed on a Hewlett-Packard 6890-5973 MSD at low resolution. LC-MS was performed on an Agilent 1100 series LC-MSD Trap System VL spectrometer. Elemental analyses were performed on a Eurovector Euro EA 3000 analyzer. GC was performed on a Varian 3800 gas chromatograph equipped with a flame ionization detector and a Jew Scientific DB-5 capillary column (30 m, 0.25 mm i. d., 0.25 µm film thickness). Electrophoretic runs were performed by CZE on a P/ACETM MDQ Capillary Electrophoresis System (Beckman Coulter). A fused silica capillary of 60 cm (effective length 50 cm) and 0.05 mm i.d. (Quadrex Corp.) thermostated at 20°C was used as a separation tube. The samples (0.1 mg/mL) were pressure injected (0.5 psi/5 s) and detected at 214 nm. Phosphate buffer, in the presence of 2-hydroxypropyl-\beta-cyclodextrin or highly sulfated y-cyclodextrin as chiral selectors, was used as background electrolyte. Optical rotations were measured on a Perkin-Elmer (Norwalk, CT) Mod 341 spectropolarimeter. Chromatographic separations were performed on silica gel columns by flash chromatography (Kieselgel 60, 0.040-0.063 mm, Merck, Darmstadt, Germany) as described by Still et al. [26]. TLC analyses were performed on precoated silica gel on aluminum sheets (Kieselgel 60 F254, Merck, Darmstadt, Germany).

(+)-(R)-Benzyl-4-[(2,6-dimethylphenyl)carbamoyl]-1,3-oxazolidine-3-carboxylate [(R)-8]. IIDQ (0.42 mL, 1.4 mmol), 2,6-dimethylaniline (0.16 mL, 1.3 mmol), and Et₃N (0.25 mL, 1.8 mmol) were added successively to a stirred solution of (R)-7 (0.30 g, 1.2 mmol) in CHCl₃ (37 mL). The mixture was heated under reflux for 6 h. The solvent was removed under reduced pressure and the residue was taken up with EtOAc. The organic layer was washed three times with a solution of 2N HCl and twice with a solution of 2N NaOH, and then dried over anhydrous Na₂SO₄. The evaporation of the solvent under reduced pressure gave 0.25 g (62%) of a white solid, which was recrystallized from CHCl₃/hexane to give 0.17 g (40%) of white crystals: mp 170–172°C; $[\alpha]_{D}^{20} = +111$ (*c* 2, CHCl₃); IR (CHCl₃): 1710 (C=O) cm⁻¹; ¹H NMR δ 2.12 (s, 6H, CH₃), 4.21 (br t, J = 8.0 Hz, 1H, OCHH), 4.41 (br s, 1H, OCHH), 4.56-4.64 (m, 1H, CH), 4.94-5.04 (m, 1H, OCHHN), 5.06-5.14 (m, 1H, OCHHN), 5.21 (s, 2H, CH₂-Ph), 7.00-7.16 (m, 3H, Ar), 7.28–7.42 (m, 5H, Ar), 7.79 ppm (br s, 1H, NH); ¹³C NMR & 18.4 (2C), 59.1 (1C), 68.4 (1C), 70.8 (1C), 80.1 (1C), 127.8 (3C), 128.4 (3C), 128.6 (2C), 128.9 (2C), 133.1 (1C), 135.6 (1C), 154.8 (1C), 168.4 ppm (1C); GC-MS MS (70 eV, electron impact) m/z (%) 354 (M⁺, 18), 91 (100). Anal. Calcd for (C₂₀H₂₂N₂O₄): C, 67.78; H, 6.26; N, 7.90. Found: C, 67.53; H, 6.20; N, 7.88.

(-)-(*S*)-Benzyl-4-[(2,6-dimethylphenyl)carbamoyl]-1,3-oxazolidine-3-carboxylate [(*S*)-8]. Prepared as reported above for (*R*)-8. White crystals, 64% yield: mp 172–173°C (CHCl₃/ hexane); $[\alpha]_{\rm D}^{20} = -105$ (*c* 1.9, CHCl₃). All the spectroscopic data were in agreement with those found for the (*R*)enantiomer.

(*RS*)-2-Amino-*N*-(2,6-dimethylphenyl)-3-hydroxypropanamide [(*RS*)-9]. To a stirred solution of (*RS*)-14 (3.50 g, 10.9 mmol) in EtOAc (120 mL), 37% HCl (28 mL) was added. The reaction mixture was kept at room temperature for 1 h, then the solvent was evaporated and the water was azeotropically removed giving the hydrochloride salt as a white solid [(*RS*)-9, HCl], which was recrystallized from MeOH/Et₂O to give 2.15 g (86%) as white crystals. (*RS*)-9, as free amine (white solid), was recovered by extraction of a sample of the corresponding hydrochloride salt.

(*RS*)-9. IR (KBr): 3253 (NH + OH), 1657 (C=O) cm⁻¹; ¹H NMR δ 2.0–2.30 (m overlapping s at 2.22, exch D₂O, 3H, NH₂ + OH), 2.22 (s overlapping m at 2.0–2.30, 6H, *CH*₃), 3.64 (t, *J* = 5.1 Hz, 1H, *CH*), 3.79 (dd, *J* = 10.7, 5.5 Hz, 1H, *CH*H), 4.01 (dd, *J* = 10.7, 5.0 Hz, 1H, *CHH*), 7.0–7.2 (m, 3H, Ar), 8.92 ppm (br s, exch D₂O, 1H, NHCO).

(*RS*)-9·HCl. Melting point 244–245°C (MeOH/Et₂O); ¹H NMR (DMSO- d_6) δ 2.14 (s, 6H, CH₃), 3.91 (br s, 2H, CH₂), 4.09 (br s, 1H, CH), 5.60 (br s, exch D₂O, 1H, OH), 6.95–7.15 (m, 3H, Ar), 8.28 (br s, exch D₂O, 2H, NH₂), 9.94 ppm (br s, exch D₂O, 1H, NH); ¹³C NMR (DMSO- d_6) δ 18.2 (2C), 59.0 (1C), 59.8 (1C), 129.1 (2C), 129.7 (1C), 132.5 (1C), 137.5 (2C), 166.5 ppm (1C). Anal. Calcd for C₁₁H₁₆N₂O₂·HCl (244.72): C, 53.99; H, 7.00; N, 11.45. Found: C, 54.16; H, 6.81; N, 11.52.

(*R*)-2-Amino-*N*-(2,6-dimethylphenyl)-3-hydroxypropanamide [(*R*)-9]

Method A. A suspension of (*R*)-14 (92 mg, 0.26 mmol), triethylsilane (0.17 mL, 1.04 mmol), triethylamine (25 μ L, 0.18 mmol), and PdCl₂ (13.8 mg, 0.078 mmol) in dichloromethane (1 mL) was heated at reflux for 3 h. The reaction mix-

ture was quenched with saturated aqueous ammonium chloride solution and extracted with ether several times. The combined organic phases were washed with water and then brine, dried, and concentrated *in vacuo* to give 22 mg (38%) of a white solid.

Method B. Prepared in 60% yield as reported above for (*RS*)-9.

(+)(*R*)-9. $[\alpha]_D^{20} = +22.3$ (*c* 2, MeOH); IR (KBr): 3253 (NH + OH), 1657 (C=O) cm⁻¹; ¹H NMR δ 2.10–2.30 (m overlapping s at 2.22, exch D₂O, 3H, NH₂ + OH), 2.22 (s overlapping m at 2.10–2.30, 6H, CH₃), 3.65 (t, *J* = 5.1 Hz, 1H, CH), 3.79 (dd, *J* = 10.7, 5.2 Hz, 1H, CHH), 4.02 (dd, *J* = 10.7, 5.0 Hz, 1H, CHH), 7.0–7.15 (m, 3H, Ar), 8.92 ppm (br s, exch D₂O, 1H, NHCO).

(-)(*R*)-9 HCL. $[\alpha]_D^{20} = -34.9$ (*c* 2, MeOH); mp > 250°C (MeOH/Et₂O); ¹H NMR (CD₃OD) δ 2.23 (s, 6H, *CH*₃), 6.45 (dd, *J* = 11.4, 6.5, 1H, *CH*), 4.16 (dd, *J* = 11.4, 4.3 Hz, 1H, *CH*H), 4.26 (dd, *J* = 6.6, 4.1 Hz, 1H, *CHH*), 7.05–7.15 ppm (m, 3H, Ar); ¹³C NMR (CD₃OD) δ 17.3 (2C), 55.2 (1C), 60.8 (1C), 127.6 (3C), 128.0 (2C), 135.7 (1C), 166.0 ppm (1C). Anal. Calcd for C₁₁H₁₆N₂O₂·HCl·1.33H₂O (268.72): C, 49.16; H, 7.38; N, 10.42. Found: C, 49.54; H, 7.66; N, 10.73.

(S)-2-Amino-N-(2,6-dimethylphenyl)-3-hydroxypropanamide [(S)-9]. Prepared in 40% (*Method A*) and 86% (*Method B*) as above reported for (R)-9.

(-)-(S)-9. $[\alpha]_{\rm D}^{20} = -24.3$ (c 2, MeOH). All the spectroscopic data were in agreement with those found for the (R)-enantiomer.

(+)-(S)-9·HCl. $[\alpha]_D^{20} = +33.5$ (c 2, MeOH); mp > 250°C (MeOH/Et₂O). All the spectroscopic data were in agreement with those found for the (*R*)-enantiomer. Anal. Calcd for $C_{11}H_{16}N_2O_2$ ·HCl (244.72): C, 53.99; H, 7.00; N, 11.45. Found: C, 53.65; H, 7.02; N, 11.49.

(*RS*)-2-(Benzylamino)-*N*-(2,6-dimethylphenyl)-3-hydroxypropanamide [(*RS*)-10]. To a stirring solution of (*RS*)-9 (0.90 g, 4.44 mmol) in dioxane (50 mL), a solution of K_2CO_3 (1.75 g, 12.6 mmol) in H₂O (50 mL) was added. The reaction mixture was heated to 70°C, and then a solution of benzyl bromide (0.83 g, 0.58 mL, 4.88 mmol) in dioxane (15 mL) was added dropwise. The heating was continued for 45 min. Then, dioxane was removed under reduced pressure and the aqueous residue was taken up with EtOAc and extracted twice with 2*N* HCl. The aqueous phase was made alkaline with 2*N* NaOH and extracted twice with EtOAc. The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated under vacuum to give 0.50 g (38% yield) of (*RS*)-10 as a white solid.

(*RS*)-10. mp 119–120°C; IR (KBr): 3272 (NH + OH), 1664 (C=O) cm⁻¹; ¹H NMR (DMSO- d_6) δ 2.13 (s, 6H, *CH*₃), 3.26 (t, J = 5.6 Hz, 1H, *CH*), 3.35 (br s, 1H, *NH*), 3.50–3.75 (m overlapping 2d at 7.39, 2H, *CH*₂OH), 3.79 (2d overlapping m at 3.50–3.75, J = 13.2 Hz, 2H, benzylic protons), 4.91 (br s, exch D₂O, 1H, OH), 7.00–7.10 (m, 3H, Ar), 7.18–7.45 (m, 5H, Ar), 9.32 ppm (br s, exch D₂O, 1H, *NHCO*); GC-MS (70 eV, electron impact) m/z (%) 298 (M⁺, <1), 91 (100).

(+)-(*R*)-2-(Benzylamino)-*N*-(2,6-dimethylphenyl)-3-hydroxypropanamide [(*R*)-10]. Prepared in 30% yield as reported above for (*RS*)-10. White solid, $[\alpha]_D^{20} = +38.8$ (*c* 1.2, MeOH); mp 119–120°C; IR (KBr): 3275 (NH + OH), 1663 (C=O) cm⁻¹; ¹H NMR (DMSO-*d*₆) δ 2.13 (s, 6H, C*H*₃), 2.55 (br s, 1H, exch D₂O, N*H*), 3.26 (t, *J* = 5.6 Hz, 1H, C*H*), 3.62 (q overlapping d, *J* = 5.7 Hz, 2H, C*H*₂OH), 3.78 (2d, *J* = 13.5 Hz, 2H, benzylic protons), 4.90 (br t, exch D_2O , 1H, OH), 6.95–7.10 (m, 3H, Ar), 7.20–7.42 (m, 5H, Ar), 9.31 ppm (br s, exch D_2O , 1H, NHCO).

(-)-(S)-2-(Benzylamino)-*N*-(2,6-dimethylphenyl)-3-hydroxypropanamide [(S)-10]. Prepared in 32% yield as reported above for (*RS*)-10. White solid, $[\alpha]_{D}^{20} = -30.6$ (*c* 1, MeOH); mp 119–120°C. All the spectroscopic data were in agreement with those found for the (*R*)-enantiomer.

(RS)-3-Benzyl-N-(2,6-dimethylphenyl)-1,3-oxazolidine-4-carboxamide [(RS)-6]. To a stirred suspension of (RS)-10 (0.30 g, 1 mmol) in a mixture of dioxane (7 mL) and 2N NaOH (11.5 mL) at $0^\circ C,$ a solution of aqueous formaldehyde 37% (6.9 mL) was added. Then, the dioxane was removed under reduced pressure and the aqueous residue was extracted twice with EtOAc. The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated under vacuum. Purification of the residue by flash chromatography (EtOAc/petroleum ether 7:3) gave (RS)-6 as white needles, which were recrystallized from EtOAc/petroleum ether to give 48 mg (23%) of white crystals: mp 145-147°C; IR (KBr): 3240 (NH), 1665 (C=O) cm⁻¹; ¹H NMR δ 2.10 (s, 6H, CH₃), 3.79 (dd, J = 8.2, 5.0 Hz, 1H, CHHCH), 3.94 (d, J = 7.7 Hz, 2H, benzylic protons), 3.97-4.06 (m, 1H, CHHCH), 4.34 (t, J = 8.5 Hz, 1H, CH), 4.44 (d, J = 6.0 Hz, 1H, NCHHO), 4.57 (d, J = 6.0Hz, 1H, NCHHO), 7.0-7.15 (m, 3H, Ar), 7.25-7.45 (m, 5H, Ar), 8.79 ppm (br s, 1H, NH); GC-MS (70 eV) m/z (%) 310 $(M^+, <1), 91 (100); LC-MS m/z (\%): 311 (M^+ + H).$ Anal. Calcd for C₁₉H₂₂N₂O₂ (310.39): C, 73.52; H, 7.14; N, 9.03. Found: C, 73.51; H, 7.11; N, 8.98.

(+)-(*R*)-3-Benzyl-*N*-(2,6-dimethylphenyl)-1,3-oxazolidine-4carboxamide [(*R*)-6]. Prepared in 22% yield as reported above for (*RS*)-6. White crystals: $[α]_D^{20} = +1.1$ (*c* 1.5, CHCl₃); 98% ee (capillary electrophoresis, BGE: phosphate buffer 0.050*M* at pH 3.5; chiral selector: 2-hydroxypropyl-β-cyclodextrin (40 mg/mL); voltage: 20 kV); mp 182–183°C; ¹H NMR δ 2.11 (s, 6H, *CH*₃), 3.79 (dd, *J* = 8.5, 5.0 Hz, 1H, *CH*HCH), 3.94 (d, *J* = 7.7 Hz, 2H, benzylic protons), 3.98–4.06 (m, 1H, *CHHCH*), 4.34 (t, *J* = 8.5 Hz, 1H, *CH*), 4.45 (d, *J* = 6.0 Hz, 1H, NCHHO), 4.57 (d, *J* = 6.0 Hz, 1H, NCHHO), 7.02–7.15 (m, 3H, Ar), 7.25–7.45 (m, 5H, Ar), 8.79 ppm (br s, 1H, *NH*); GC-MS (70 eV, electron impact) *m*/*z* (%) 310 (M⁺, <1), 91 (100). Anal. Calcd for C₁₉H₂₂N₂O₂ (310.39): C, 73.52; H, 7.14; N, 9.03. Found: C, 73.20; H, 7.27; N, 8.99.

(−)-(*S*)-3-Benzyl-*N*-(2,6-dimethylphenyl)-1,3-oxazolidine-4-carboxamide [(*S*)-6]. Prepared in 22% yield as reported above for (*RS*)-6. White crystals: $[\alpha]_{20}^{20} = -1.5$ (*c* 2, CHCl₃); ≥99% ee (capillary electrophoresis using the conditions described for the *R*-enantiomer); mp 144–147°C. All the spectroscopic data were in agreement with those found for the (*R*)enantiomer. Anal. Calcd for C₁₉H₂₂N₂O₂·0.25 H₂O (314.89): C, 72.47; H, 7.20; N, 8.90. Found: C, 72.80; H, 7.02; N, 8.98.

(*RS*)-1-Benzyl-3-(2,6-dimethylphenyl)-5-(hydroxymethyl) imidazolidin-4-one [(*RS*)-11]. It was obtained in 21% yield in mixture with (*RS*)-6. Slightly yellowish oil; IR (neat): 3429 (OH), 1700 (C=O) cm⁻¹; ¹H NMR δ 2.19 (s, 3H, CH₃), 2.23 (s, 3H, CH₃), 2.92 (br s, exch. D₂O, 1H, OH), 3.50–3.56 (m, 1H, CH), 3.76 (d overlapping d at 3.78, J = 12.9 Hz, 1H, CHHPh), 3.78 (d overlapping d at 3.76, J = 11.0 Hz, 1H, CHHCH), 3.98 (br d, J = 11.0 Hz, 1H, CHHCH), 4.13 (d overlapping d at 4.17, J = 12.9 Hz, 1H, NCHHPh), 4.17 (dd overlapping d at 4.13, J = 5.5, 1.9 Hz, 1H, NCHHN), 4.31 (dd, J = 5.5, 1.4 Hz, 1H, NCH*H*N), 7.02–7.18 (m, 3H, Ar), 7.26–7.38 ppm (m, 5H, Ar); GC-MS (70 eV, electron impact) m/z (%) 310 (M⁺, <1), 91 (100); LC-MS m/z (%): 311 (M⁺ + H).

(-)-(R)-1-Benzyl-3-(2,6-dimethylphenyl)-5-(hydroxymethyl) imidazolidin-4-one [(R)-11]. It was obtained in 43% yield in mixture with (R)-6. Slightly yellowish oil; $\left[\alpha\right]_{D}^{20} = -30.9$ (c 1, CHCl₃); 80% ee (capillary electrophoresis, BGE: phosphate buffer 0.025M at pH 5.9; chiral selector: highly sulfated γ cyclodextrin (24 mg/mL); voltage: 10 kV); IR (neat): 3421 (OH), 1699 (C=O) cm⁻¹; ¹H NMR δ 2.21 (apparent d, 6H, CH_3), 2.92 (br d, J = 9.6 Hz, exch. D_2O , 1H, OH), 3.50–3.56 (m, 1H, CH), 3.76 (d overlapping d at 3.78, J = 12.9 Hz, 1H, CHHPh), 3.78 (d overlapping d at 3.76, J = 11.0 Hz, 1H, CHHCH), 3.92-4.06 (m, 1H, CHHCH), 4.13 (d overlapping dd at 4.17, J = 12.9 Hz, 1H, CHHPh), 4.17 (dd overlapping d at 4.13, J = 5.5, 1.9 Hz, 1H, NCHHN), 4.31 (dd, J = 5.5, 1.4 Hz, 1H, NCHHN), 7.02-7.18 (m, 3H, Ar), 7.24-7.38 ppm (m, 5H, Ar); GC-MS (70 eV, electron impact) m/z (%) 310 (M⁺, <1); LC-MS m/z (%): 311 (M⁺ + H).

(+)-(S)-1-Benzyl-3-(2,6-dimethylphenyl)-5-(hydroxymethyl) imidazolidin-4-one [(S)-11]. It was obtained in 41% yield in mixture with (*RS*)-6. Slightly yellowish oil; $[\alpha]_D^{20} = +33.8$ (*c* 1.9, CHCl₃). 86% ee (capillary electrophoresis using the conditions described for the *R*-enantiomer). All the spectroscopic data were in agreement with those found for the (*R*)enantiomer.

(*RS*)-*tert*-Butyl-4-{[(2,6-dimethylphenyl)amino]carbonyl}-1,3-oxazolidine-3-carboxylate [(*RS*)-14]. Prepared in 72% yield as reported above for (*R*)-8. White crystals: mp 158– 159°C (EtOAc/EP); IR (KBr): 3224 (NH), 1654, 1710 (C=O) cm⁻¹; ¹H NMR δ 1.51 (s, 9H, *t*-Bu), 2.22 (s, 6H, CH₃), 4.21 (apparent t, 1H, CHHO), 4.41 (br s, 1H, CH), 4.48–4.60 (m, 1H, CHHO), 4.84–4.94 (br s, 1H, CHHN), 4.98–5.08 (m, 1H, CHHN), 7.02–7.17 (m, 3H, Ar), 7.99 ppm (br s, 1H, NH); ¹³C NMR δ 18.5 (2C), 28.5 (3C), 58.8 (1C), 70.7 (1C), 80.1 (1C), 82.5 (1C), 127.7 (2C), 128.4 (1C), 133.3 (2C), 135.6 (1C), 154.3 (1C), 168.8 ppm (1C); GC-MS (70 eV, electron impact) *m/z* (%) 320 (M⁺, 7), 57 (100).

(+)-(*R*)-*tert*-Butyl-4-{[(2,6-dimethylphenyl)amino]carbonyl} -1,3-oxazolidine-3-carboxylate [(*R*)-14]. Prepared in 66% yield as reported above for (*R*)-8. White crystals: $[\alpha]_D^{20} =$ +111.3 (*c* 2, CHCl₃); mp 170–171°C (EtOAc/EP). IR (KBr): 3204 (NH), 1658, 1712 (C=O) cm⁻¹; ¹H NMR δ 1.52 (s, 9H, *t*-Bu), 2.22 (s, 6H, CH₃), 4.21 (apparent t, 1H, CHHO), 4.41 (br s, 1H, CH), 4.48–4.60 (m, 1H, CHHO), 4.82–4.94 (m, 1H, CHHN), 4.98–5.10 (m, 1H, CHHN), 7.02–7.16 (m, 3H, Ar), 7.92 ppm (br s, 1H, NH); ¹³C NMR δ 18.5 (2C), 28.5 (3C), 58.8 (1C), 70.6 (1C), 80.1 (1C), 82.4 (1C), 127.7 (2C), 128.4 (1C), 133.4 (2C), 135.6 (1C), 154.2 (1C), 168.8 ppm (1C); GC-MS (70 eV, electron impact) *m*/*z* (%) 320 (M⁺, 4), 57 (100).

(-)-(*S*)-*tert*-Butyl-4-{[(2,6-dimethylphenyl)amino]carbonyl}-1,3-oxazolidine-3-carboxylate [(*S*)-14]. Prepared in 46% yield as reported above for (*R*)-8. White crystals: $[\alpha]_{D}^{2D} = -111.2$ (*c* 2, CHCl₃); mp 173–174°C (EtOAc/EP). All the spectroscopic data were in agreement with those found for the (*R*)enantiomer.

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