

Preparation of (+)- and (-)- β -phenyl- and β -(4-chlorophenyl)- γ -butyrolactones: Key Intermediates in the Synthesis of β -phenyl-GABA and Baclofen

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Abstract. The preparation of β -phenyl- and β -(4-chlorophenyl)- γ -butyrolactones (\pm)-**3** and (\pm)-**4** and their resolution to the corresponding (+)-(*S*)-**3**, (-)-(*R*)-**3** and (+)-(*S*)-**4**, (-)-(*R*)-**4** through formation, flash column chromatography separation and subsequent hydrolysis of diastereoisomeric 4-hydroxybutyramides (2'*R*,3*S*)-**5**, (2'*R*,3*R*)-**5**, (2'*R*,3*S*)-**6** and (2'*R*,3*R*)-**6** is described. The absolute configuration assignment of enantiopure **3** and **4** was supported by X-ray crystallographic structures of (2'*R*,3*R*)-**5**, (2'*R*,3*S*)-**6** and (2'*R*,3*R*)-**6**.

Key words: Phenyl- γ -butyrolactones, Resolution, Diastereoisomeric 4-hydroxybutyramides.

Resumen. Se describe la preparación de las β -fenil- y β -(4-clorofenil)- γ -butirolactonas (\pm)-**3** y (\pm)-**4** y su resolución en (+)-(*S*)-**3**, (-)-(*R*)-**3** y (+)-(*S*)-**4**, (-)-(*R*)-**4** mediante la formación, separación por cromatografía en columna rápida y posterior hidrólisis de las 4-hidroxi-butiramidas diastereoisoméricas (2'*R*,3*S*)-**5**, (2'*R*,3*R*)-**5**, (2'*R*,3*S*)-**6** y (2'*R*,3*R*)-**6**. La asignación de la configuración absoluta de las lactonas enantiopuras **3** y **4** se confirmó mediante cristalografía de rayos-X de (2'*R*,3*R*)-**5**, (2'*R*,3*S*)-**6** y (2'*R*,3*R*)-**6**.

Palabras clave: Fenil- γ -butirolactonas, resolución, 4-hidroxi-butiramidas diastereoisoméricas.

Introduction

Enantiopure compounds are important in the chemical and pharmaceutical sciences due to their particular properties, and especially because one enantiomer usually behaves differently than its counterpart when interacting with a biological system [1, 2]. Thus, the absolute configuration of such compounds must be known. In particular, separation of optical isomers by formation of diastereomeric derivatives could offer advantages on their absolute configuration assignment, especially if they can be crystallized and monitored by physical techniques such as NMR spectroscopy or X-ray crystallographic analysis.

The 4-amino-3-phenylbutanoic [3] (β -phenyl-GABA, **1**) and 4-amino-3-(4-chlorophenyl)butanoic acids [4] (baclofen, **2**) (Fig. 1), which are lipophilic analogues of γ -aminobutyric acid (GABA), show different pharmacological activities. Compound **1** is a mood elevator and tranquillizer [5], while **2** is widely used as a muscle relaxant [6]. The biological activity of these compounds resides on the (-)-(*R*)-enantiomer [3,4], however baclofen is commercialized in its racemic form (Lioresal® and Baclon®). Due to the increasing demand of enantiomerically pure drugs for the pharmaceutical industry, the development of new approaches to obtain compounds such as **1** and **2** in enantiomerically pure form is an important target.

Examples of synthesis of (\pm)-**2** [7], enantiomeric and chemoenzymatic synthesis of (*R*)-**1**, (*S*)-**1**, (*R*)-**2** and (*S*)-**2**, and the resolution of racemates of **1** and **2** have been previously reported [3a,6,8]. Besides, it is worth noting that some approaches for the enantiomeric synthesis of (-)-**2** are based on the use of the enantiopure (-)-(*R*)- β -(4-chlorophenyl)- γ -butyrolactone (-)-(*R*)-**4** as the key building block involving a few steps [9].

Due to the important pharmacological activities of γ -amino acids such as **1** and **2** and knowing that lactone **4** is an intermediate in the synthesis of **2**, herein we report the preparation of the enantiopure lactones (+)-(*S*)- and (-)-(*R*)-**3** and (+)-(*S*)- and (-)-(*R*)-**4** through the reaction of racemic **3** and **4** with the chiral auxiliary (+)-(*R*)- α -methylbenzylamine [10] [(+)-(*R*)- α -MBA] to obtain the diastereomerically pure 4-hydroxybutyramides **5** and **6**. Of relevance is the efficient chromatography separation of amides **5** and **6** and their mild acidic transformation to the enantiomerically pure lactones **3** and **4** with recovery of the

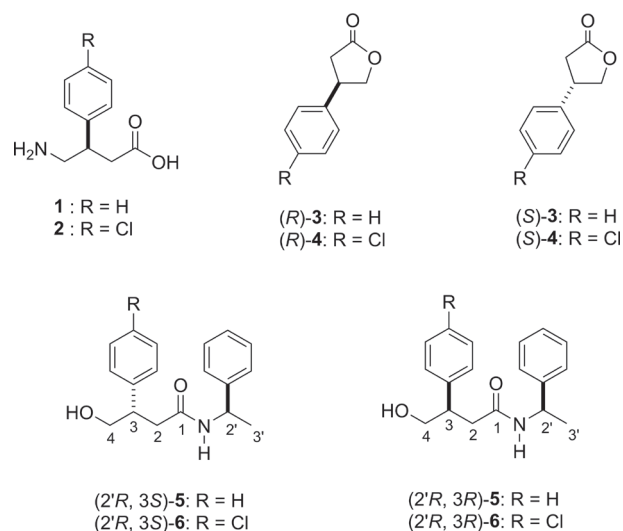


Fig. 1. Structures of β -phenyl-GABA (**1**), baclofen (**2**), γ -butyrolactones **3** and **4**, and 4-hydroxybutyramides **5** and **6**.

chiral auxiliary. An advantage of the present methodology is that the absolute configuration of both enantiomers of **3** and **4** is established by the X-ray structures of the diastereomers (2'*R*,3*R*)-**5**, (2'*R*,3*S*)-**6** and (2'*R*,3*R*)-**6**.

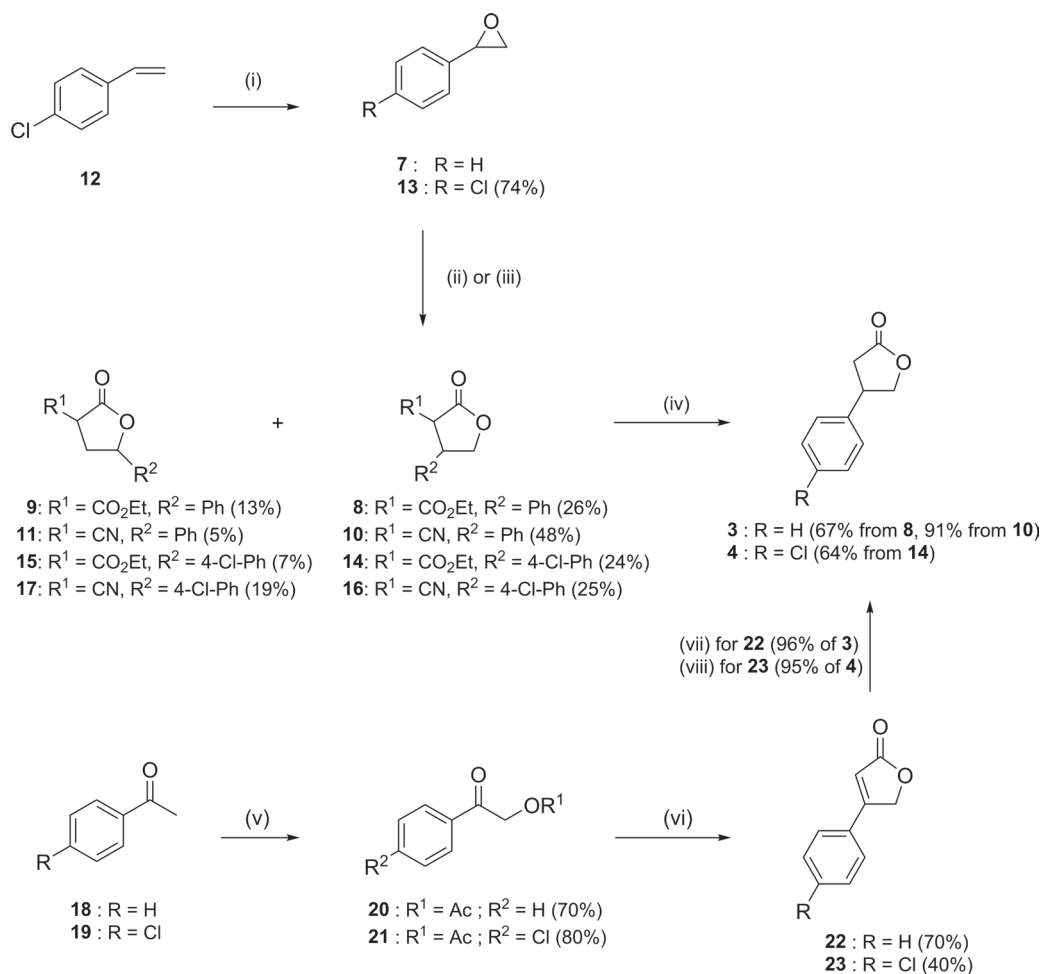
Results and Discussion

The preparation of β -phenyl- γ -butyrolactone (**3**) is shown in Scheme 1. Accordingly, reaction of styrene oxide (**7**) with the sodium salt of diethyl malonate in ethanol [11a,b] afforded the α -carboethoxy- γ -lactones **8** (26%) and **9** (13%) and the remnant was unidentified materials. The subsequent hydrolysis and decarboxylation of **8** was achieved with alumina/H₂O [12] affording **3** in 67% yield. In order to increase the yield of the desired lactone **3**, styrene oxide **7** was treated with ethyl cyanoacetate instead of diethyl malonate [11c,d] to obtain the corresponding α -cyano- γ -butyrolactones **10** (48%) and **11** (5%). The subsequent decyanation of **10** with alumina/H₂O afforded **3** in 91% yield. Decarboalkoxylation of β -keto esters and decyanation of α -cyano- γ -lactones have been carried out

with alumina/H₂O under reflux in different solvents [12]. However, it is remarkable that in this work the decarboethoxylation of **8** and decyanation of **10** proceeded in solid phase at 100 °C in good yields.

The preparation of **4** is also shown in Scheme 1. Thus, the *p*-chlorostyrene (**12**) was oxidized with dimethyldioxirane (DMD) generated in situ from oxone[®] and acetone in a buffer of bicarbonates (pH 7) [13], to afford the *p*-chlorostyrene oxide (**13**) in 74% yield, which was reacted with the sodium salt of diethyl malonate in ethanol to give the α -carboethoxy- γ -lactones **14** and **15** in 24 and 7% yield, respectively. The solid phase decarboethoxylation of **14** with alumina/H₂O afforded **4** in 64% yield. When compound **13** was treated with the sodium salt of ethyl cyanoacetate an inseparable mixture of the α -cyanolactones **16** and **17** was obtained in a 1.3:1 ratio (44% yield) as judged by ¹H NMR.

As the yield of the desired lactones **3** and **4** was poor using the above methodologies specially for compound **4**, we used as an alternative the Reformatsky reaction on acetoxyacetophenones **20** and **21** [11b,14]. Thus, the α -acetoxylation of the readily available **18** and **19** with 30% aq H₂O₂, Ac₂O,

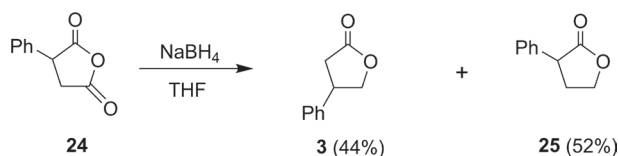


Scheme 1. Reagents and conditions: (i) oxone, acetone, buffer of NaHCO₃ (pH 7); (ii) Na, CH₂(CO₂Et)₂, EtOH; (iii) Na, NCCH₂CO₂Et, EtOH; (iv) Alumina-H₂O, 100°C; (v) 30% aq H₂O₂, Ac₂O, BF₃·OEt₂, PhI; (vi) a) BrCH₂CO₂C₂H₅, Zn, THF, b) HCl; (vii) H₂/Pd-C, EtOAc; (viii) NaBH₄, MeOH.

$\text{BF}_3 \cdot \text{OEt}_2$, PhI [15] afforded **20** (70%) and **21** (80%), respectively. Treatment of **20** with Zn and ethyl bromoacetate followed by hydrolysis and cyclization with AcOH and 38% aq HCl gave the α,β -unsaturated γ -butyrolactone **22** in 70% yield [11b,14]. Catalytic hydrogenation of **22** with H_2 -Pd/C in EtOAc afforded **3** in 96% yield [14]. Similarly, treatment of **21** gave **23** in 40% yield, whose reduction with NaBH_4 in MeOH afforded **4** in 95% yield [11b,14].

In addition, lactone **3** was also prepared through reduction of phenylsuccinic anhydride (**24**) with NaBH_4 in THF [16] affording **3** in 44% yield together with α -phenyl- γ -butyrolactone (**25**) in 52% yield (Scheme 2).

As lactone **4** has been used as a key intermediate for the total synthesis of **2**, but in the process to obtain **4** a partial racemization at the benzylic carbon occurs [9], we used as an alternative methodology the resolution of **4** [9b,17c] with the readily available (+)-(*R*)- α -MBA. This methodology was also applied to the lactone **3** [17a-c] with good results. Thus, reaction of (\pm)-**3** and (\pm)-**4** with (+)-(*R*)- α -MBA gave a mixture of diastereoisomeric ($2'R,3S$)- and ($2'R,3R$)-**5** and ($2'R,3S$)- and ($2'R,3R$)-**6**, respectively [18] (Scheme 3). These compounds were easily separated by flash column chromatography [19] eluting with $\text{CH}_2\text{Cl}_2/\text{EtOAc}/\text{acetone}$ (210:90:1) to give separately ($2'R,3S$)-**5** (41%), ($2'R,3R$)-**5** (41%), ($2'R,3S$)-**6** (40%) and ($2'R,3R$)-**6** (40%). The high yield separation (>99%) of each pair ($2'R,3S$)-**5**, ($2'R,3R$)-**5** and ($2'R,3S$)-**6**, ($2'R,3R$)-**6**



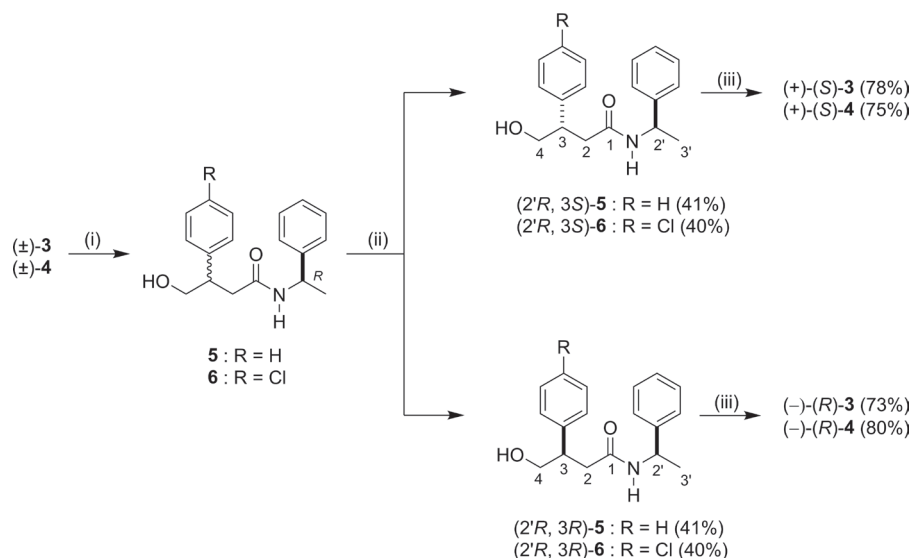
Scheme 2. Obtention of β -phenyl- γ -butyrolactone (**3**) by reduction of anhydride **24**.

was determined on the basis of significant peaks in their respective ^1H NMR spectra.

With the methodology developed in this work, the absolute configuration of both enantiomers of **3** and **4** could be established through the X-ray crystallographic analysis of diastereoisomeric ($2'R,3R$)-**5**, ($2'R,3S$)-**6** and ($2'R,3R$)-**6**. Fig. 2 shows the X-ray diffraction structures revealing the absolute configuration at C-3 in ($2'R,3R$)-**5**, ($2'R,3S$)-**6** and ($2'R,3R$)-**6**. The pure diastereoisomers ($2'R,3S$)-**5**, ($2'R,3R$)-**5**, ($2'R,3S$)-**6** and ($2'R,3R$)-**6** were hydrolyzed and cyclized in acidic medium to give (+)-(*S*)-**3** (78%) [$[\alpha]_D^{20} = +48.3^\circ$ ($c = 1.0$, CHCl_3)] {lit. [17c], [$[\alpha]_D^{20} = +46.5^\circ$ ($c = 0.5$, CHCl_3)}}, (–)-(*R*)-**3** (73%) [$[\alpha]_D^{20} = -48.9^\circ$ ($c = 1.0$, CHCl_3)], (+)-(*S*)-**4** [9b,20] (75%) [$[\alpha]_D^{20} = +47.9^\circ$ ($c = 1.0$, CHCl_3)] {lit. [17c], [$[\alpha]_D^{20} = +52.0^\circ$ ($c = 0.4$, CHCl_3)}}, and (–)-(*R*)-**4** (80%) [$[\alpha]_D^{20} = -48.6^\circ$ ($c = 1.0$, CHCl_3)], respectively. The chemical nature of the stereogenic center at C-3 together with values and signals of optical rotation of each pair of enantiomers confirm that the hydrolysis proceed without significant racemization.

Conclusion

The β -phenyl- and - β -(4-chlorophenyl)- γ -butyrolactones **3** and **4** were resolved with (+)-(*R*)- α -MBA based on the efficient and simple silica gel flash column chromatography separation and subsequent mild acidic hydrolysis of the corresponding diastereoisomeric 4-hydroxybutyramides ($2'R,3S$)-**5**, ($2'R,3R$)-**5** and ($2'R,3S$)-**6**, ($2'R,3R$)-**6**. The absolute configuration of enantiomers of **3** and **4** was indirectly determined using the X-ray crystallographic structures of ($2'R,3R$)-**5**, ($2'R,3S$)-**6** and ($2'R,3R$)-**6**. Due to **3** and **4** are key intermediates for β -phenyl-GABA (**1**) and baclofen (**2**), respectively, this methodology constitutes a convenient approach for the enantiomeric synthesis of these important compounds.



Scheme 3. Reagents and conditions: (i) (+)-(*R*)- α -MBA, 55°C ; (ii) flash column chromatography; (iii) HCl, EtOH- H_2O 1:1, reflux.

Experimental

General Experimental Procedures

Flash column chromatography [19] was carried out using silica gel Merck grade 60 (230-400 mesh) eluting with the specified solvent mixture. Analytical thin layer chromatography was performed on silica gel 60 F₂₅₄ coated aluminum sheets (0.25 mm thickness) with a fluorescent indicator. Visualization was accomplished with UV light (254 nm). All commercially available reagents were used as received. All of the solvents employed were distilled prior to use or were spectral or HPLC grade. Melting points were determined on a Büchi B-504 apparatus and are uncorrected. IR spectra were recorded on a Perkin Elmer 2000 FT-IR spectrophotometer. Optical rotation measurements were performed on a Perkin-Elmer 341 polarimeter. The ¹H and ¹³C NMR spectra were obtained on a JEOL Eclipse+ 400 spectrometer working at 400 and 100 MHz, respectively, using DMSO-*d*₆ or CDCl₃ as the solvent. Data are reported as follows: chemical shifts in ppm from TMS, multiplicity (s singlet, d doublet, t triplet, q quartet, m multiplet, br broad), coupling constants (Hz), integration and assignment. Low-resolution mass spectra were recorded at an ionizing voltage of 70 eV on a Hewlett Packard 5989-A spectrometer. High-resolution (HR) mass spectra were measured on a JEOL JMS-SX 102A mass spectrometer at Instituto de Química UNAM-México. Microanalytical determinations were performed on a Perkin-Elmer 2400 series PCII apparatus.

Preparation of 2-(4-chlorophenyl)oxirane (**13**)

To a solution of **12** (400 mg, 2.89 mmol) in acetone (15 mL) was added a solution of NaHCO₃ (840 mg, 10 mmol) in H₂O (5 mL). The resulting thick mixture was treated dropwise with a solution of oxone monopersulfate complex (2.22 g, 3.6 mmol) and disodium EDTA (7 mg) in water (7 mL) and the resulting reaction mixture was stirred at room temperature for 2 h. The acetone was evaporated under reduced pressure and the residue was dissolved in EtOAc (30 mL), washed with brine (2 × 20 mL), dried over anhydrous Na₂SO₄ and concentrated. The crude product was purified by flash column chromatography on silica gel (EtOAc-hexane 1:8) to afford **13** (330 mg, 74%).

General procedure for the decarboethoxylation of **8** and **14** and decyanation of **10**

To a solution of appropriate γ -lactone **8** (500 mg, 2.13 mmol), **14** (500 mg, 1.86 mmol) or **10** (100 mg, 0.53 mmol) in THF (25 mL for **8** and **14**, and 9 mL for **10**) and water (1.4 mL for **8** and **14**, and 0.3 mL for **10**) was added activated neutral alumina (3.5 g for **8** and **14**, and 1.0 g for **10**) (Brockmann 1, 150 mesh, 58 Å, $d = 3.970$ from Aldrich Co.). The mixture was stirred for 5 min and the THF was evaporated. The impregnated alumina was heated at 100 °C for 26 h for **8** and **14**, and 5 h for **10**. The reaction mixture was cooled to room temperature, ethyl acetate was added and the alumina was filtered and washed with ethyl

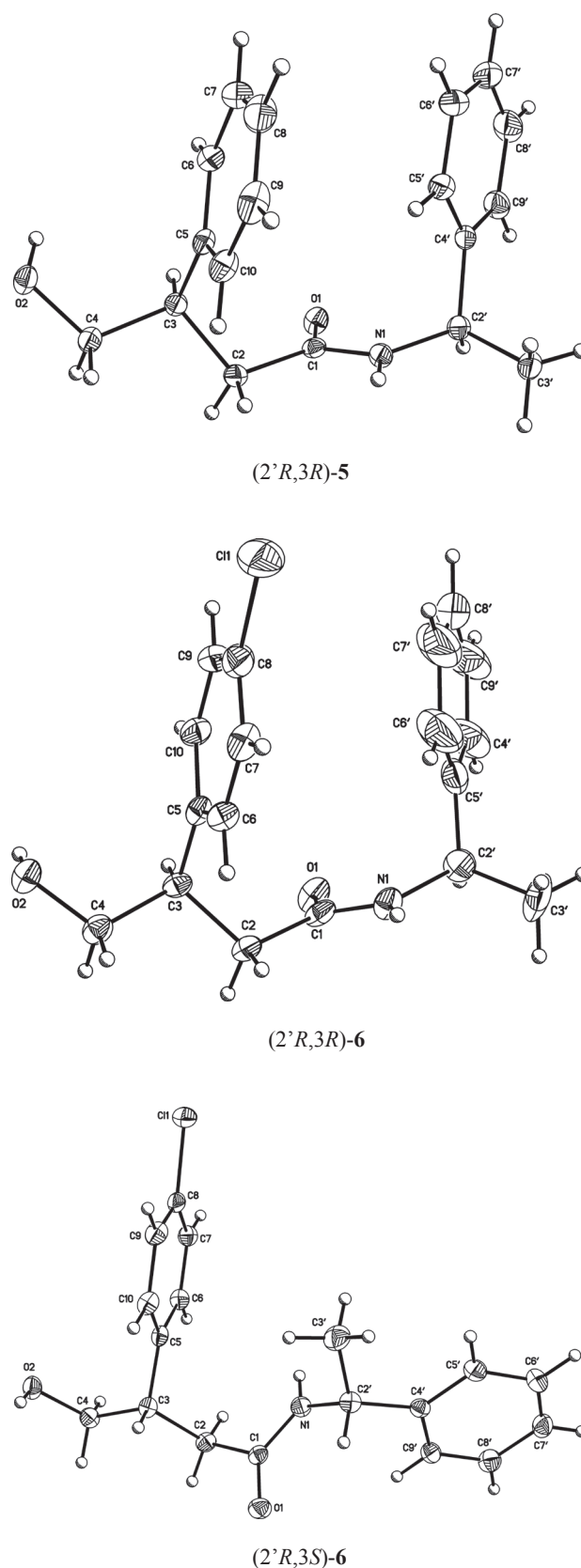


Fig. 2. ORTEP representation of the molecular structure of compounds (2',3R)-5, (2',3S)-6 and (2',3R)-6 (ellipsoids with 30% probability).

acetate (3 × 20 mL). The resulting solution was evaporated affording **3** (232 mg, 67% from **8** and 78 mg, 91% from **10**) and **4** (247 mg, 64% from **14**).

General procedure for the preparation of 4-hydroxylamides **5** and **6**

A solution of **3** (200 mg, 1.23 mmol) or **4** (300 mg, 1.53 mmol) in (*R*)-(+)- α -MBA (1.26 mL for **3** and 1.56 mL for **4**; 8 equiv/mol) was heated at 55 °C for 9 h. The mixture was cooled to room temperature and diluted with ethyl acetate (30 mL), washed with aqueous 10% HCl (3 × 15 mL), brine (3 × 15 mL), dried over anhydrous Na₂SO₄, and concentrated. The (*R*)-(+)- α -MBA was recovered from aqueous phase with saturated NaHCO₃ aqueous solution. The residue was separated by flash column chromatography on silica gel (CH₂Cl₂-EtOAc-acetone 210:90:1) to give, in sequence, pure (2'*R*,3*S*)-**5** and (2'*R*,3*R*)-**5** from **3** and (2'*R*,3*S*)-**6** and (2'*R*,3*R*)-**6** from **4**.

(S)-4-Hydroxy-3-phenyl-N-[(R)-1-phenylethyl]butanamide [(+)-(2'*R*,3*S*)-5**]**. Obtained from **3** as a white solid (143 mg, 41%): mp 73-74°C; [α]_D²⁰ +106.0° (*c* 1.0, EtOH); IR (KBr) ν_{\max} 3328, 3246, 3030, 2973, 1638, 1554, 1450 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) δ 7.29-7.14 (10H, m, H-6 to H-10 and H-5' to H-9'), 6.28 (1H, d, *J* = 6.9 Hz, NH), 4.96 (1H, q, *J* = 6.9 Hz, H-2'), 3.70 (1H, dd, *J* = 11.0, 5.9 Hz, H-4A), 3.64 (1H, dd, *J* = 11.0, 7.4 Hz, H-4B), 3.52 (1H, br s, OH), 3.23 (1H, q, *J* = 6.9 Hz, H-3), 2.66 (1H, dd, *J* = 14.3, 7.4 Hz, H-2A), 2.43 (1H, dd, *J* = 14.3, 7.0 Hz, H-2B), 1.25 (3H, d, *J* = 7.0 Hz, C-3' Me); ¹³C NMR (CDCl₃, 100 MHz) δ 171.3 (C-1), 143.0 (C-4'), 141.6 (C-5), 128.6 and 128.4 (C-7, C-9 and C-6', C-8'), 127.6 (C-6, C-10), 127.0 and 126.8 (C-7' and C-8), 126.0 (C-5', C-9'), 66.8 (C-4), 48.7 (C-2'), 44.9 (C-3), 40.2 (C-2), 21.4 (C-3'); EIMS *m/z* (rel. int.): 283 [M]⁺ (6), 265 (12), 162 (18), 132 (23), 120 (35), 105 (100), 77 (35); HRMS (FAB) *m/z* 284.1645 (calc. for C₁₈H₂₂O₂N ([M+H]⁺), requires 284.1651); *Anal.* C 75.73, H 7.30, N 4.28, calcd for C₁₈H₂₁O₂N, C 76.33, H 7.42, N 4.95.

(R)-4-Hydroxy-3-phenyl-N-[(R)-1-phenylethyl]butanamide [(+)-(2'*R*,3*R*)-5**]**. Obtained from **3** as colorless crystals (142 mg, 41%): mp 117-118°C (EtOAc-CH₂Cl₂); [α]_D²⁰ +33.1° (*c* = 1.0, EtOH); IR (KBr) ν_{\max} 3234, 3031, 2966, 1645, 1565, 1451 cm⁻¹; ¹H NMR (DMSO-*d*₆, 400 MHz) δ 7.29-7.15 (8H, m, H-6 to H-10 and H-6' to H-8'), 7.03 (2H, dd, *J* = 7.7, 1.5 Hz, H-5', H-9'), 6.16 (1H, d, *J* = 8.1 Hz, NH), 4.99 (1H, q, *J* = 7.0 Hz, H-2'), 3.75 (1H, dt, *J* = 11.0, 5.5 Hz, H-4A), 3.69 (1H, dt, *J* = 10.6, 6.6 Hz, H-4B), 3.34 (1H, t, *J* = 5.9 Hz, OH), 3.25 (1H, q, *J* = 6.9 Hz, H-3), 2.71 (1H, dd, *J* = 14.3, 7.0 Hz, H-2A), 2.45 (1H, dd, *J* = 14.3, 7.0 Hz, H-2B), 1.37 (3H, d, *J* = 7.0 Hz, C-3' Me); ¹³C NMR (DMSO-*d*₆, 100 MHz) δ 171.2 (C-1), 142.8 (C-4'), 141.5 (C-5), 128.6 and 128.4 (C-7, C-9 and C-6', C-8'), 127.6 (C-6, C-10), 127.0 and 126.8 (C-7' and C-8), 126.0 (C-5', C-9'), 66.8 (C-4), 48.6 (C-2'), 44.9 (C-3), 40.3 (C-2), 21.5 (C-3'); EIMS *m/z* (rel. int.) 283 [M]⁺ (6), 265 (12), 162 (18), 132 (23), 120 (35), 105 (100), 77 (35); HRMS (FAB) *m/z* 284.1652 (calc. for C₁₈H₂₂O₂N ([M+H]⁺), requires 284.1651);

Anal. C 75.96, H 7.38, N 5.19, calcd for C₁₈H₂₁O₂N, C 76.33, H 7.42, N 4.95.

(S)-3-(4-Chlorophenyl)-4-hydroxy-N-[(R)-1-phenylethyl]butanamide [(+)-(2'*R*,3*S*)-6**]**. Obtained from **4** as colorless crystals (195 mg, 40%): mp 153-154°C (EtOAc-CH₂Cl₂); [α]_D²⁰ +96.4° (*c* = 1.0, EtOH); IR (KBr) ν_{\max} 3397, 3329, 3090, 2982, 1633, 1541, 1446 cm⁻¹; ¹H NMR (DMSO-*d*₆, 400 MHz) δ 8.18 (1H, d, *J* = 7.7 Hz, NH), 7.37-7.15 (9H, H-6, H-7, H-9, H-10 and H-5' to H-9'), 4.81 (1H, m, H-2'), 4.73 (1H, m, OH), 3.50 (2H, m, H-4A and H-4b), 3.17 (1H, m, H-3), 2.57 (1H, dd, *J* = 14.3, 6.2 Hz, H-2A), 2.39 (1H, dd, *J* = 14.6, 9.1 Hz, H-2B), 1.17 (3H, d, *J* = 7.0 Hz, C-3' Me); ¹³C NMR (DMSO-*d*₆, 100 MHz) δ 169.8 (C-1), 144.6 (C-4'), 141.8 (C-5), 130.6 (C-8), 129.8 (C-6', C-8'), 128.1 and 127.8 (C-6, C-10 and C-7, C-9), 126.5 (C-7'), 125.9 (C-5', C-9'), 65.1 (C-4), 47.6 (C-2'), 44.1 (C-3), 38.2 (C-2), 22.3 (C-3'); EIMS *m/z* (rel. int.) 252 [M]⁺-65, 7], 224 (3), 125 (27), 111 (55), 97 (100), 83 (98), 69 (79), 57 (100), 55 (90); HRMS (FAB) *m/z* 318.1258 (calc. for C₁₈H₂₁O₂NCl ([M+H]⁺), requires 318.1261); *Anal.* C 67.93, H 6.38, N 4.53, calcd for C₁₈H₂₀O₂NCl, C 68.04, H 6.30, N 4.41.

(R)-3-(4-Chlorophenyl)-4-hydroxy-N-[(R)-1-phenylethyl]butanamide [(+)-(2'*R*,3*R*)-6**]**. Obtained from **4** as colorless crystals (193 mg, 40%): mp 112-113°C (CHCl₃); [α]_D²⁰ +18.7° (*c* = 1.0, EtOH); IR (KBr) ν_{\max} 3257, 3068, 2965, 1634, 1558, 1442 cm⁻¹; ¹H NMR (DMSO-*d*₆, 400 MHz) δ 8.18 (1H, d, *J* = 8.1 Hz, NH), 7.30 (2H, d, *J* = 6.6 Hz, H-7 and H-9), 7.22 (2H, d, *J* = 6.6 Hz, H-6 and H-10), 7.16-7.12 (m, 3H, H-6' to H-8'), 6.86 (2H, m, H-5', H-9'), 4.80 (1H, q, *J* = 7.3 Hz, H-2'), 4.78 (1H, t, *J* = 5.5 Hz, OH), 3.51 (2H, m, H-4A and H-4b), 3.15 (1H, m, H-3), 2.57 (1H, dd, *J* = 14.2, 5.5 Hz, H-2A), 2.43 (1H, dd, *J* = 13.9, 9.9 Hz, H-2B), 1.27 (3H, d, *J* = 7.0 Hz, C-3' Me); ¹³C NMR (DMSO-*d*₆, 100 MHz) δ 169.9 (C-1), 144.4 (C-4'), 141.4 (C-5), 130.8 (C-8), 130.0 (C-6, C-10), 127.9 (C-7, C-9), 127.8 (C-6', C-8'), 126.2 (C-7'), 125.5 (C-5', C-9'), 65.3 (C-4), 47.3 (C-2'), 44.6 (C-3), 38.4 (C-2), 22.3 (C-3'); EIMS *m/z* (rel. int.) 252 [M]⁺-65, 3], 224 (1), 125 (15), 111 (35), 97 (73), 83 (80), 69 (73), 57 (100), 55 (100); HRMS (FAB) *m/z* 318.1256 (calc. for C₁₈H₂₁O₂NCl ([M+H]⁺), requires 318.1261); *Anal.* C 68.04, H 6.42, N 4.53, calcd for C₁₈H₂₀O₂NCl, C 68.04, H 6.30, N 4.41.

General procedure for the hydrolysis of 4-hydroxylamides **5** and **6**

To a solution of the appropriate 4-hydroxylamides **5** (200 mg, 0.71 mmol) and **6** (200 mg, 0.63 mmol) in EtOH-H₂O 1:1 (0.4 mL) was added a solution of aqueous 36% HCl (0.15 mL). The resulting white suspension was heated to 120°C for 6 h in a sealed tube. The reaction mixture was cooled to room temperature, the solvent was evaporated under reduced pressure and the residue dissolved in CH₂Cl₂ (30 mL). This solution was washed with brine (2 × 20 mL), dried over anhydrous Na₂SO₄ and concentrated. The crude product was purified by flash column chromatography on silica gel (1:8 EtOAc-hexane) to afford

Table 1. Crystallographic data for (2'R,3R)-5, (2'R,3S)-6 and (2'R,3R)-6.

Compound	(2'R,3R)-5	(2'R,3S)-6	(2'R,3R)-6
Empirical formula	C ₁₈ H ₂₁ NO ₂	C ₁₈ H ₂₀ ClNO ₂	C ₁₈ H ₂₀ ClNO ₂
Formula weight	283.36	317.81	317.81
Crystal size (mm)	0.58 × 0.54 × 0.40	0.40 × 0.65 × 0.57	0.33 × 0.19 × 0.35
Crystal system	Orthorhombic	Orthorhombic	Orthorhombic
Space group	P2 ₁ 2 ₁ 2	P2 ₁ 2 ₁ 2 ₁	P2 ₁ 2 ₁ 2
a (Å)	10.4186(7)	11.0539(13)	10.1853(16)
b (Å)	23.5737(18)	20.321(2)	25.797(4)
c (Å)	6.6968(5)	7.2388(8)	6.8075(11)
α (°)	90.00	90.00	90.00
β (°)	90.00	90.00	90.00
γ (°)	90.00	90.00	90.00
Volume (Å ³)	1644.77(2)	1626.0(3)	1788.7(5)
ρ_{calc} (g cm ⁻³)	1.14	1.30	1.18
Z	4	4	4
μ (mm ⁻¹)	0.074	0.24	0.22
T (K)	293	293	293
2 θ_{range} (°)	1.73-26.02	2.00-26.01	1.58-26.00
Total reflections	10889	10651	11992
Unique reflections	3221	3183	3513
R _{int} (%)	0.04	0.11	0.10
Observed reflections	2295	2431	1092
Parameters	198	204	191
R (%), R _w (%)	3.7, 8.5	4.5, 10.4	4.9, 11.1
ρ_{max} (eÅ ⁻³)	0.15	0.19	0.25

(+)-(*S*)-3 (89.6 mg, 78% from (2'R,3S)-5) and (-)-(*R*)-3 (84.0 mg, 73% from (2'R,3R)-5), and (+)-(*S*)-4 (92.4 mg, 75% from (2'R,3S)-6) and (-)-(*R*)-4 (98.6 mg, 80% from (2'R,3R)-6).

Single crystal X-ray analyses

Compounds (2'R,3R)-5 and (2'R,3R)-6 were crystallized from AcOEt/CH₂Cl₂, while (2'R,3S)-6 from CHCl₃. X-ray data were collected on a Bruker Smart 6000 CCD diffractometer. A total of 1321 frames were collected at a scan width of 0.3° and an exposure time of 10s/frame, using Mo K α radiation (λ 0.7073 Å). The frames were processed with the SAINT software package, provided by diffractometer manufacturer, by using a narrow-frame integration algorithm, and the structure was solved and

refined by using the SHELXS-97 program [20] included in the WINGX VI.6 crystallographic software package [21]. The non-hydrogen atoms were treated anisotropically, and the hydrogen atoms, included in the structure factor calculation, were refined isotropically. Crystallographic data for the structures reported in this paper are in deposit at the Cambridge Crystallographic Data Center. Table 1 summarizes the relevant data of the X-ray procedures.

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