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Synthesis of both enantiomers of baclofen using (*R*)- and (*S*)-*N*-phenylpantolactam as chiral auxiliaries

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In memoriam of Dr. Juan Carlos del Amo

Abstract—Esterification of racemic 4-nitro-3-(4-chlorophenyl)butanoic acid with (*R*)- or (*S*)-*N*-phenylpantolactam as the chiral auxiliary allowed us to obtain the (3*R*,3′*R*)- or (3*S*,3′*S*)-nitro esters with >98:2 dr after column chromatography. Hydrolysis of the resulting diastereopure nitro esters gave the corresponding enantiopure nitro acids, which were readily converted in high yields into either (*R*)- or (*S*)-baclofen hydrochloride.

1. Introduction

Baclofen [γ-amino-β-(4-chlorophenyl)butyric acid] **9**, a derivative of γ-aminobutyric acid (GABA), modulates the action of this central inhibitory neurotransmitter and is used as an antispastic agent.[1] Although baclofen has been commercialized in its racemic form, its biological activity resides exclusively in the (−)-(*R*)-enantiomer.[2] Many syntheses of (±)-baclofen as well as its enantiomers have already been described.[3] Many of these syntheses employ hydrolysis of β-(4-chlorophenyl)-γ-butyrolactam as the last step. It is worthy of note that a straightforward synthesis of (±)-baclofen by reduction of the known (±)-4-nitro-3-(4-chlorophenyl)butanoic acid,[4] (±)-**4**, has not yet been described. Such a method could also be applied for the synthesis of (+)- and (−)-baclofen if a procedure to prepare both enantiomers of the nitro acid **4** were developed. Herein we report the first preparation of enantiopure nitro acids (+)- and (−)-**4** by resolution of (±)-**4** using (*R*)- and/or (*S*)-*N*-phenylpantolactam **5**, as chiral auxiliaries,[5] and their conversion into (−)- and (+)-baclofen hydrochloride, respectively.

2. Results and discussion

Nitro acid (±)-**4** was prepared as shown in Scheme 1, by a modification of the only described procedure.[4] Methyl 4-chlorocinnamate, **2**, prepared in 91% yield by reaction of 4-chlorocinnamic acid, **1**, with methanol and thionyl chloride, was reacted with a 10-fold excess of nitromethane, using K_2CO_3/toluene and benzyltriethylammonium chloride for 24 h, instead of 1,1,3,3-tetramethylguanidine/THF for 4 days, to give nitro ester (±)-**3** in comparable yield (72% of distilled product). Saponification of (±)-**3** with 50% KOH/methanol gave an impure product that required purification by silica gel column chromatography, as reported.[4] However, acidic hydrolysis of (±)-**3** (2 M HCl, AcOH, 1 h) gave pure nitro acid (±)-**4** in 85% yield, after selective solid–liquid extraction using CH_2Cl_2 as the solvent, without the need of column chromatography purification. Under these conditions, a small amount of 2-(4-chlorophenyl)succinic acid, formed through a Victor Meyer reaction,[6] was isolated. The amount of this by-product increased when the reaction time or the HCl concentration was increased.

Nitro acid (±)-**4** was esterified with pantolactam (*R*)-**5** to give in good yield a 1:1 diastereomeric mixture of the corresponding pantolactam esters (3*R*,3′*R*)- and (3*S*,3′*R*)-**7**. Carefully conducted column chromatography allowed the isolation of (3*R*,3′*R*)-**7** [>98:2 dr, by ^{1}H

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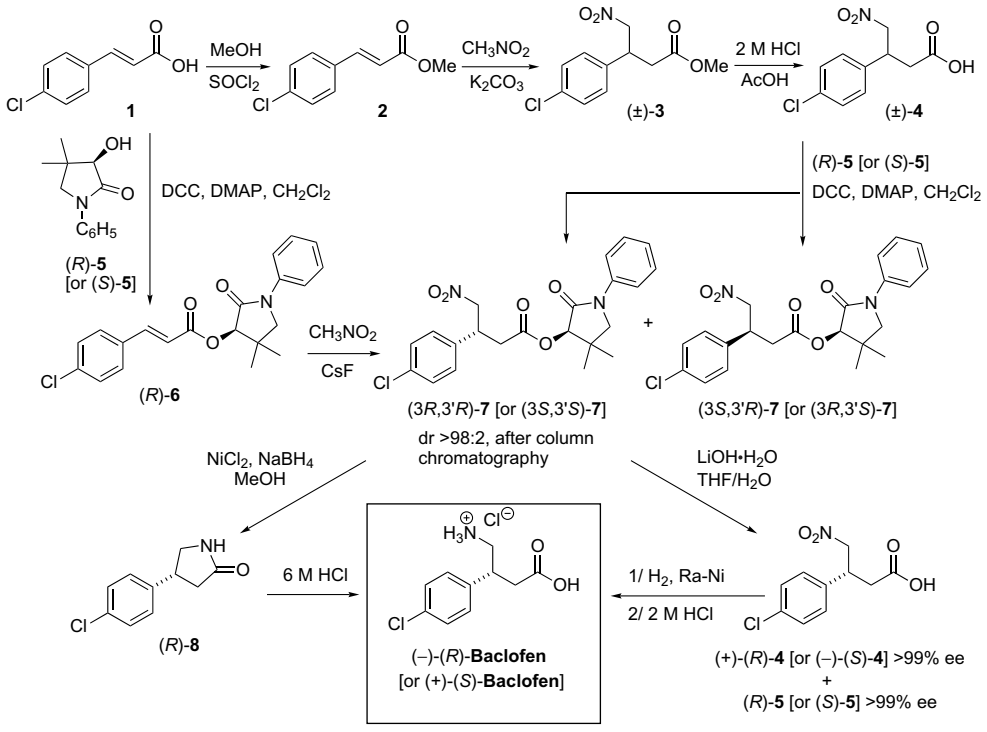

Scheme 1.

NMR, 22.5% yield from (±)-**4**, 45% of the theoretical yield] and diastereoenriched (3*S*,3′*R*)-**7** [92:8 dr, by ^{1}H NMR, 27.5% yield from (±)-**4**]. Hydrolysis of (3*R*,3′*R*)-**7** (>98:2 dr) with LiOH·H_2O in THF/H_2O took place efficiently to give (+)-(*R*)-**4** (84% yield, >99% ee by chiral HPLC). It is noteworthy that in the above reaction, pantolactam (*R*)-**5** was recovered in enantiopure form (91% yield), by simple liquid–liquid extraction taking advantage of its neutral character. In a similar way, hydrolysis of enantioenriched (3*S*,3′*R*)-**7** (92:8 dr) gave (−)-(*S*)-**4** (80% yield, 84% ee, by chiral HPLC). Unfortunately, although the ee of this nitro acid could be increased to 98% ee by repeated crystallization of its cyclohexylamine salt from isopropanol, the yield of this process was low.

Consequently, to obtain enantiopure (*S*)-**4**, we repeated the above resolution using (*S*)-**5** as the chiral auxiliary. In this way, (3*S*,3′*S*)-**7** [>98:2 dr, by ^{1}H NMR, 21% yield from (±)-**4**, 42% of the theoretical yield] and enantioenriched (3*R*,3′*S*)-**7** [84:16 dr, by ^{1}H NMR, 16.5% yield from (±)-**4**] were obtained. Hydrolysis of (3*S*,3′*S*)-**7** (>98:2 dr) with LiOH·H_2O as before gave (*S*)-**4** (91% yield, >99% ee by chiral HPLC), with enantiopure (*S*)-**5** being recovered in 91% yield.

A diastereomeric mixture of (3*R*,3′*R*)- and (3*S*,3′*R*)-**7** in the ratio of 1:1.4 was alternatively prepared by Michael addition of nitromethane to ester (*R*)-**6**, derived from 4-chlorocinnamic acid and (*R*)-*N*-phenylpantolactam, (*R*)-**5**, using CsF as the base. As expected, a lower yield of the first eluted (3*R*,3′*R*)-**7** (17% yield from nitro ester (*R*)-**6**, 96:4 dr) was obtained by column chromatography of the above mixture. Similar Michael reactions carried out with the ester of pantolactam (±)-**5** and cinnamic acid, under different reaction conditions [(a) CsF, toluene, or CH_2Cl_2, benzyltriethylammonium chloride (BTEACl), from −40 °C till room temperature (rt);[7] (b) K_2CO_3, nitromethane as solvent and reagent, BTEACl, rt;[8] (c) KOH, EtOH, ultrasound irradiation, rt],[9] gave mixtures of the corresponding (3*R**,3′*R**)- and (3*S**,3′*R**)-diastereomers in ratios from 1:1 to 1:1.7 (by ^{1}H NMR).

Hydrogenation of enantiopure nitro acid (+)-(*R*)-**4** with Ra-Ni in MeOH at 5 atm and room temperature gave, after a basic work-up followed by treatment with aqueous HCl, enantiopure (−)-(*R*)-baclofen hydrochloride, (−)-(*R*)-**9**·HCl, in 91% yield (Scheme 1), whose NMR data and specific rotation were coincident with the described values.[10] Similarly, hydrogenation of nitro acid (−)-(*S*)-**4** gave (*S*)-baclofen hydrochloride, (+)-(*S*)-**9**·HCl.[11]

Alternatively, (3*R*,3′*R*)-**7** was reduced with nickel boride[7] to give a mixture of lactam (−)-(*R*)-**8**, a known precursor of (*R*)-baclofen,[7] and the chiral auxiliary (*R*)-**5**. Separation of this mixture could be performed by silica gel column chromatography. Consequently, conversion of (3*R*,3′*R*)-**7** into (*R*)-baclofen is more conveniently effected by hydrolysis followed by reduction of the nitro group, which allows a more efficient and practical recovery of the chiral auxiliary.

3. Conclusion

(*R*)- and (*S*)-baclofen hydrochloride have been prepared in enantiopure forms (>99% ee) from the readily avail-

able racemic nitro acid (±)-**4**, through a three-step synthetic sequence, involving the resolution of the above acid via diastereomeric esters derived from the chiral auxiliaries (*R*)- and (*S*)-*N*-phenylpantolactam, (*R*)- and (*S*)-**5**, followed by hydrolysis of the ester function and hydrogenation (Ra-Ni) of the nitro group. The chiral auxiliaries were efficiently recovered in enantiopure forms after the hydrolysis step.

4. Experimental

4.1. General

Melting points were determined in open capillary tubes with an MFB 595010M Gallenkamp melting point apparatus. ^{1}H NMR (300 MHz) and 75.4 MHz ^{13}C NMR spectra were recorded on a Varian Gemini 300 spectrometer and 200 MHz ^{1}H NMR spectra on a Varian Gemini 200 equipment. Chemical shifts are given in ppm (δ scale) relative to internal TMS, while coupling constants are reported in hertz (Hz). For the pantolactam esters **6** and **7**, the terms α or β are assigned to hydrogen atoms or groups of the pantolactam moiety, which are *cis* or *trans* relative to the carboxy substituent, respectively. IR spectra were run on a FTIR Perkin–Elmer model 1600 spectrophotometer. Absorption values are expressed as wave-numbers (cm^{-1}); only significant absorption bands are given. HRMS were performed on a Micromass Autospec spectrometer. Column chromatography was performed on silica gel 60 AC.C. (70–200 mesh, SDS, ref 2100027). Thin-layer chromatography (TLC) was performed with aluminum-backed sheets with silica gel 60 F_{254} (Merck, ref 1.05554), and the spots visualized with UV light and 1% aqueous solution of $KMnO_4$. Optical rotations were measured on a Perkin–Elmer model 241 polarimeter. Chiral HPLC analyses were performed on a Waters model 600 liquid chromatograph provided with a Waters model 486 variable λ detector using a Chiralcel OD-H column (25×0.46 cm) containing the chiral stationary phase cellulose tris(3,5-dimethylphenylcarbamate), with a flow of 0.8 mL/min and UV detection at $\lambda = 254$ nm. Conditions: mixture of hexane/isopropanol/AcOH in the ratio of 95:5:0.1 as eluent. Analytical grade solvents were used for crystallization and chiral HPLC analyses, while pure synthesis for solvents were used in the reactions, extractions, and column chromatography. NMR spectra were performed at the Serveis Científico-Tècnics of the University of Barcelona, while elemental analyses and high resolution mass spectra were carried out at the Mycroanalysis Service of the IIQAB (CSIC, Barcelona, Spain), and at the Mass Spectrometry Laboratory of the University of Santiago de Compostela (Spain), respectively.

4.2. (±)-Methyl 4-nitro-3-(4-chlorophenyl)butanoate (±)-3[4]

To a −40 °C mixture of **2** (7.50 g, 38.1 mmol), K_2CO_3 (10.5 g, 76.2 mmol), and benzyltriethylammonium chloride (0.87 g, 3.82 mmol) in anhydrous toluene (100 mL) was added CH_3NO_2 (20.4 mL, 377 mmol) and the reaction mixture stirred at room temperature for 24 h. Water (300 mL) and Et_2O (300 mL) were added, the organic phase separated, dried over anhydrous Na_2SO_4 and evaporated at reduced pressure. The crude product (9.37 g) was distilled at 150–160 °C/2.0 Torr to give pure (±)-**3** (7.10 g, 72%) as a yellow oil.

4.3. (±)-4-Nitro-3-(4-chlorophenyl)butanoic acid (±)-4

To a solution of nitro ester (±)-**3** (0.25 g, 0.97 mmol) in AcOH (2 mL) was added 2 M HCl (2 mL) and the reaction mixture heated under reflux for 1 h. The solution was concentrated in vacuo, the residue taken up in CH_2Cl_2 (10 mL) and filtered. The filtrate was evaporated at reduced pressure to yield nitro acid (±)-**4** (0.20 g, 85%) as a white solid. Mp: 110–111 °C (CH_2Cl_2) [described 116–120 °C (AcOEt/CH_2Cl_2 4:1)].[4] Chiral HPLC: (*R*)-**4**, $t_R = 28.7$ min, $k'_1 = 5.15$; (*S*)-**4**, $t_R = 32.8$ min, $k'_2 = 6.02$; $\alpha = 1.17$; Res. = 2.90.

4.4. (3*R*,3′*R*)- and (3*S*,3′*R*)-4,4-Dimethyl-2-oxo-1-phenylpyrrolidin-3-yl 4-nitro-3-(4-chlorophenyl)butanoate (3*R*,3′*R*)-7 and (3*S*,3′*R*)-7

A mixture of nitro acid (±)-**4** (2.40 g, 9.87 mmol), dicyclohexylcarbodiimide (DCC) (2.06 g, 9.98 mmol), 4-(dimethylamino)pyridine (DMAP) (62.5 mg, 0.51 mmol), and (*R*)-**5** (1.42 g, 6.92 mmol) in anhydrous CH_2Cl_2 (56 mL) was stirred at room temperature for 1 h. The precipitated DCU was filtered off and the filtrate washed with 2 M HCl (3×100 mL) and saturated aqueous $NaHCO_3$ (3×100 mL), dried with anhydrous Na_2SO_4 and evaporated at reduced pressure to give a white oily residue (3.11 g), which was submitted to column chromatography [silica gel (300 g), hexane/Et_2O mixtures]. On elution with hexane/Et_2O 45:55, (3*R*,3′*R*)-**7** [702 mg, 22.5% yield from (±)-**4**, 45% of the theoretical yield, >98:2 dr], and mixtures of (3*R*,3′*R*)-**7**/(3*S*,3′*R*)-**7** [412 mg, 80:20 dr; 473 mg, 30:70 dr; 860 mg, 27.5% yield from (±)-**4**, 8:92 dr] were successively isolated as colorless oils.

(3*R*,3′*R*)-**7** (>98:2 dr): $[\alpha]_D^{20} = +40.1$ (*c* 1.00, CH_2Cl_2). R_f 0.60 (SiO_2, hexane/AcOEt 2:3). IR (NaCl) *v*: 1745 (C=O st ester), 1710 (C=O st lactam), 1553 (N=O st) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.06 (s, 3H, 4′α-CH_3), 1.22 (s, 3H, 4′β-CH_3), 2.91 (dd, $J \approx 16.2$ Hz, $J' \approx 7.5$ Hz, 1H) and 2.99 (dd, $J = 16.2$ Hz, $J' = 6.9$ Hz, 1H) (2-H_2), 3.47 (d, $J = 9.6$ Hz, 1H, 5′α -H), 3.59 (d, $J = 9.6$ Hz, 1H, 5′β-H), 4.02 (m, 1H, 3-H), 4.69 (dd, $J = 12.9$ Hz, $J' = 8.1$ Hz, 1H) and 4.87 (dd, $J \approx 12.9$ Hz, $J' \approx 6.5$ Hz, 1H) (4-H_2), 5.36 (s, 1H, 3′-H), 7.14–7.40 (complex signal, 7H, Ar-H *C*-phenyl and Ar-H*para* and Ar-H*meta* *N*-phenyl), 7.56–7.60 (m, 2H, H*ortho* *N*-phenyl). ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 21.0 (CH_3, 4′α-CH_3), 24.6 (CH_3, 4′β-CH_3), 37.3 (CH_2+C, C2+C4′), 39.4 (CH, C3), 57.6 (CH_2,C5′), 78.8 (CH, C3′), 78.9 (CH_2, C4), 119.4 (CH, Ar-C*ortho* *N*-phenyl), 125.0 (CH, Ar-C*para* *N*-phenyl), 128.7 (CH), 128.9 (CH) and 129.2 (CH)

(Ar-C*meta* *C*-phenyl, Ar-C*meta* *N*-phenyl and Ar-C*ortho* *C*-phenyl), 133.9 (C, Ar-C*para* *C*-phenyl), 136.6 (C, Ar-C*ipso* *C*-phenyl), 138.7 (C, Ar-C*ipso* *N*-phenyl), 168.3 (C, C2′), 169.5 (C, C1). Anal. Calcd for $C_{22}H_{23}ClN_2O_5$: C, 61.33; H, 5.38; N, 6.50; Cl, 8.23. Found: C, 61.39; H, 5.66; N, 6.42; Cl, 8.09.

(3*S*,3′*R*)-**7** (92:8 dr): $[\alpha]_D^{20} = +24.3$ (*c* 1.04, CH_2Cl_2). R_f 0.60 (SiO_2, hexane/AcOEt 2:3). IR (NaCl) *v*: 1744 (C=O st ester), 1711 (C=O st lactam), 1553 (N=O st) cm^{-1}. ^1H NMR (main diastereomer, 300 MHz, $CDCl_3$) δ 0.97 (s, 3H, 4′α-CH_3), 1.15 (s, 3H, 4′β-CH_3), 2.85 (dd, $J = 15.9$ Hz, $J' = 8.1$ Hz, 1H) and 2.96 (dd, $J = 15.9$ Hz, $J' = 7.5$ Hz, 1H) (2-H_2), 3.46 (d, $J = 9.6$ Hz, 1H, 5′α-H), 3.58 (d, $J = 9.6$ Hz, 1H, 5′β-H), 4.04 (m, 1H, 3-H), 4.64 (dd, $J = 12.6$ Hz, $J' = 8.7$ Hz, 1H) and 4.84 (dd, $J = 12.6$ Hz, $J' = 6.3$ Hz, 1H) (4-H_2), 5.34 (s, 1H, 3′-H), 7.15–7.40 (complex signal, 7H, Ar-H *C*-phenyl and Ar-H*para* and Ar-H*meta* *N*-phenyl), 7.56–7.60 (m, 2H, H*ortho* *N*-phenyl). ^{13}C NMR (main diastereomer, 75.4 MHz, $CDCl_3$) δ 21.0 (CH_3, 4′α-CH_3), 24.6 (CH_3, 4′β-CH_3), 37.3 (C, C4′), 37.7 (CH_2, C2), 40.0 (CH, C3), 57.7 (CH_2, C5′), 78.8 (CH, C3′), 79.0 (CH_2, C4), 119.5 (CH, Ar-C*ortho* *N*-phenyl), 125.1 (CH, Ar-C*para* *N*-phenyl), 128.8 (CH), 129.0 (CH), and 129.2 (CH) (Ar-C*meta* *C*-phenyl, Ar-C*meta* *N*-phenyl and Ar-C*ortho* *C*-phenyl), 134.0 (C, Ar-C*para* *C*-phenyl), 136.5 (C, Ar-C*ipso* *C*-phenyl), 138.8 (C, Ar-C*ipso* *N*-phenyl), 168.3 (C, C2′), 169.8 (C, C1). Anal. Calcd for $C_{22}H_{23}ClN_2O_5$: C, 61.33; H, 5.38; N, 6.50; Cl, 8.23. Found: C, 61.55; H, 5.61; N, 6.51; Cl, 8.27.

4.5. (3*S*,3′*S*)- and (3*R*,3′*S*)-4,4-Dimethyl-2-oxo-1-phenylpyrrolidin-3-yl 4-nitro-3-(4-chlorophenyl)butanoate (3*S*,3′*S*)-7 and (3*R*,3′*S*)-7

These were prepared in a similar manner to that described for (3*R*,3′*R*)-**7** and (3*S*,3′*R*)-**7**. From nitro acid (±)-**4** (3.50 g, 14.4 mmol), DCC (3.00 g, 14.5 mmol), DMAP (91 mg, 0.74 mmol), (*S*)-**5** (2.07 g, 10.1 mmol) and anhydrous CH_2Cl_2 (82 mL), a diastereomeric mixture of (*S*)-pantolactam esters (4.33 g) was obtained. An aliquot part of this crude product (3.84 g) was submitted to column chromatography [silica gel (300 g), hexane/Et_2O mixtures]. On elution with hexane/Et_2O 45:55, (3*S*,3′*S*)-**7** [805 mg, 21% from (±)-**4**, 42% of the theoretical yield, >98:2 dr], and mixtures of (3*S*,3′*S*)-**7**/(3*R*,3′*S*)-**7** [740 mg, 80:20 dr; 680 mg, 33:67 dr; 642 mg, 16.5% yield from (±)-**4**, 16:84 dr] were successively isolated as colorless oils.

(3*S*,3′*S*)-**7** (>98:2 dr): $[\alpha]_D^{20} = -41.0$ (*c* 1.80, CH_2Cl_2). The IR, ^1H and ^{13}C NMR spectra are coincidental with those of (3*R*,3′*R*)-**7**. Anal. Calcd for $C_{22}H_{23}ClN_2O_5$: C, 61.33; H, 5.38; N, 6.50; Cl, 8.23. Found: C, 61.22; H, 5.58; N, 6.35; Cl, 8.36.

(3*R*,3′*S*)-**7** (84:16 dr): $[\alpha]_D^{20} = -26.4$ (*c* 0.98, CH_2Cl_2). The IR spectra and the ^1H and ^{13}C NMR signals of the main diastereomer are coincidental with those of the main diastereomer of (3*S*,3′*R*)-**7**/(3*R*,3′*R*)-**7** (92:8 dr). Anal. Calcd for $C_{22}H_{23}ClN_2O_5$: C, 61.33; H, 5.38; N, 6.50; Cl, 8.23. Found: C, 61.53; H, 5.52; N, 6.41; Cl, 8.36.

4.6. (*R*)-4,4-Dimethyl-2-oxo-1-phenylpyrrolidin-3-yl 3-(4-chlorophenyl)-2-propenoate (*R*)-6

A mixture of 4-chlorocinnamic acid **1** (681 mg, 3.73 mmol), DCC (776 mg, 3.73 mmol), DMAP (22.7 mg, 0.19 mmol) and (*R*)-**5** (765 mg, 3.73 mmol) in anhydrous CH_2Cl_2 (20 mL) was stirred at room temperature for 3 days. The precipitated DCU was filtered off and the filtrate washed with 2 M HCl (3×40 mL) and saturated aqueous $NaHCO_3$ (3×40 mL), dried over anhydrous Na_2SO_4 and evaporated at reduced pressure to give a brown oily residue (1.09 g), which was submitted to column chromatography [silica gel (75 g); hexane/Et_2O mixtures]. On elution with hexane/Et_2O 65:35, pure ester (*R*)-**6** was obtained as a white solid (701 mg, 51% yield). Mp: 130–131 °C (hexane/Et_2O 65:35). R_f 0.38 (SiO_2, hexane/Et_2O 1:1). $[\alpha]_D^{20} = -46.1$ (*c* 1.04, $CHCl_3$). IR (KBr) *v*: 1730 (C=O st ester), 1701 (C=O st lactam) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.19 (s, 3H, 4′α-CH_3), 1.35 (s, 3H, 4′β-CH_3), 3.55 (d, $J = 9.5$ Hz, 1H, 5′α-H), 3.66 (d, $J = 9.5$ Hz, 1H, 5′β-H), 5.54 (s, 1H, 3′-H), 6.55 (d, $J = 16.1$ Hz, 1H, 2-H), 7.18 (tt, $J = 7.4$ Hz, $J' = 1.2$ Hz, 1H, Ar-H*para* *N*-phenyl), 7.35–7.51 (complex signal, 6H, Ar-H *C*-phenyl and Ar-H*meta* *N*-phenyl), 7.62–7.66 (m, 2H, H*ortho* *N*-phenyl), 7.75 (d, $J = 16.1$ Hz, 1H, 3-H). ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 21.3 (CH_3, 4′α-CH_3), 25.0 (CH_3, 4′β-CH_3), 37.6 (C, C4′), 57.8 (CH_2, C5′), 78.4 (CH, C3′), 117.6 (CH, C2), 119.4 (CH, Ar-C*ortho* *N*-phenyl), 124.9 (CH, Ar-C*para* *N*-phenyl), 128.9 (CH), 129.1 (CH) and 129.3 (CH) (Ar- C*meta* *C*-phenyl, Ar-C*meta* *N*-phenyl and Ar-C*ortho* *C*-phenyl), 132.7 (C, Ar-C*para* *C*-phenyl), 136.4 (C, Ar-C*ipso* *C*-phenyl), 139.0 (C, Ar-C*ipso* *N*-phenyl), 144.6 (CH, C3), 165.8 (C, C2′), 168.9 (C, C1). Anal. Calcd for $C_{21}H_{20}ClNO_3$: C, 68.20; H, 5.45; N, 3.79; Cl, 9.59. Found: C, 68.41; H, 5.58; N, 3.80; Cl, 9.75.

4.7. (3*R*,3′*R*)-7 and (3*S*,3′*R*)-7 from the Michael addition of nitromethane to (*R*)-6

To a −40 °C solution of (*R*)-**6** (500 mg, 1.35 mmol), CsF (2.05 g, 13.5 mmol), benzyltriethylammonium chloride (30.7 mg, 0.13 mmol) in anhydrous toluene (3.25 mL) was added CH_3NO_2 (0.73 mL, 13.5 mmol) and the reaction mixture stirred at room temperature for 4 h. Water (20 mL) and Et_2O (20 mL) were added, the organic phase was separated, dried over anhydrous Na_2SO_4 and evaporated at reduced pressure to give a brown oily residue consisting of a mixture of (3*R*,3′*R*)-**7** and (3*S*,3′*R*)-**7** (516 mg, dr 1:1.4), which was submitted to column chromatography [silica gel (52 g), hexane/Et_2O mixtures]. On elution with hexane/Et_2O 55:45, (3*R*,3′*R*)-**7** (99 mg, 17% yield from the nitro ester (*R*)-**6**, 96:4 dr) and mixtures of (3*R*,3′*R*)-**7**/(3*S*,3′*R*)-**7** [85 mg, 56:44 dr; 94 mg, 10:90 dr; 51 mg, 9:91 dr] were successively eluted as light white oils.

4.8. (*R*)-4-Nitro-3-(4-chlorophenyl)butanoic acid (*R*)-4

To a 0 °C solution of ester (3*R*,3′*R*)-**7** (650 mg, 1.51 mmol, >98:2 dr) in THF/H_2O 2:1 (9 mL) was added LiOH·H_2O (69 mg, 1.66 mmol) and the reaction mixture was stirred at room temperature for 4 h. More LiOH·H_2O (25 mg, 0.60 mmol) was added and stirring at room temperature continued for 16 h. Finally, more LiOH·H_2O (31 mg, 0.75 mmol) was added and the mixture stirred at room temperature for 5 h. The organic solvent was removed at reduced pressure, the aqueous phase extracted with CH_2Cl_2 (3×15 mL), and the combined organic extracts dried with anhydrous Na_2SO_4 and evaporated at reduced pressure, recovering pantolactam (*R*)-**5** (282 mg, 91% yield, >99% ee by chiral HPLC). The aqueous phase was acidified with 2 M HCl (2 mL) and extracted with AcOEt (3×15 mL). The combined organic extracts were dried over anhydrous Na_2SO_4 and evaporated at reduced pressure to yield nitro acid (*R*)-**4** (309 mg, 84% yield, >99% ee by chiral HPLC) as a light yellow solid. $[\alpha]_D^{20} = +10.5$ (*c* 2.04, MeOH). Chiral HPLC: (*R*)-**4**, $t_R = 28.7$ min. Mp: 79–81 °C (AcOEt). R_f 0.17 (SiO_2, hexane/Et_2O 1:1). IR (KBr) *v*: 3500–2500 (O–H st), 1699 (C=O st), 1557 (N=O st) cm^{-1}. The ^1H and ^{13}C NMR spectra are coincidental with those of (±)-**4**. HRMS calcd for $C_{10}H_{10}ClNO_4$: 243.0298. Found: 243.0296.

4.9. (*S*)-4-Nitro-3-(4-chlorophenyl)butanoic acid (*S*)-4

This was prepared in a similar manner to that described for (*R*)-**4**. From (3*S*,3′*S*)-**7** (588 mg, 1.37 mmol, >98:2 dr), LiOH·H_2O (63 mg, 1.50 mmol+23 mg, 0.54 mmol+28 mg, 0.68 mmol), pantolactam (*S*)-**5** (254 mg, 91% yield, >99% ee by chiral HPLC) and nitro acid (*S*)-**4** (309 mg, 93% yield, >99% ee by chiral HPLC) were separately obtained. $[\alpha]_D^{20} = -10.1$ (*c* 2.00, MeOH). Chiral HPLC: (*S*)-**4**, $t_R = 32.8$ min. Mp: 78–79 °C (AcOEt). R_f 0.17 (SiO_2, hexane/Et_2O 1:1). IR (KBr) *v*: 3500–2500 (O–H st), 1698 (C=O st), 1556 (N=O st) cm^{-1}. The ^1H and ^{13}C NMR spectra are coincidental with those of (±)-**4**. HRMS calcd for $C_{10}H_{10}ClNO_4$: 243.0298. Found: 243.0295.

4.10. (*R*)-4-(4-Chlorophenyl)pyrrolidin-2-one (*R*)-8

To a stirred solution of (3*R*,3′*R*)-**7** (485 mg, 1.13 mmol, >98:2 dr) in MeOH (8 mL) was added $NiCl_2·6H_2O$ (536 mg, 2.25 mmol) at room temperature. After stirring for 5 min, $NaBH_4$ (461 mg, 12.1 mmol) was added in four portions. The reaction mixture was stirred for 30 min at room temperature and filtered in vacuo through Celite®. The solid material was thoroughly washed with MeOH. The combined filtrate and washings were evaporated under reduced pressure to obtain a residue (1.05 g), that was submitted to column chromatography [silica gel (25 g), Et_2O/AcOEt mixtures]. On elution with Et_2O, (*R*)-**5** (200 mg, 98% yield, >99% ee) was recovered; on elution with Et_2O/AcOEt 50:50, (*R*)-**8** (97 mg, 44% yield) was obtained as a white solid. $[\alpha]_D^{20} = -38$ (*c* 1.02, EtOH), lit. $[\alpha]_D^{28} = -39$ (*c* 1.0, EtOH).[12] Mp: 105–107 °C (EtOH) [lit. 112 °C (CH_2Cl_2/MeOH 95:5)].[12]

4.11. (*R*)-4-Amino-3-(4-chlorophenyl)butanoic acid hydrochloride, [(*R*)-baclofen hydrochloride] (*R*)-9·HCl

A mixture of (*R*)-**4** (88 mg, 0.36 mmol), MeOH (15 mL) and Ra-Ni (50% water content, 200 mg) was hydrogenated at 5 atm at room temperature for 24 h. The reaction mixture was made basic with 0.1 M NaOH (3.6 mL, 0.36 mmol) and the catalyst filtered off in vacuo through Celite®. The filtrate was evaporated under reduced pressure, the residue taken up in 2 M HCl (0.5 mL), and the resulting aqueous phase washed with AcOEt (2×10 mL) and evaporated at reduced pressure. The resulting solid was taken up in MeOH (3 mL) and filtered. The filtrate was evaporated at reduced pressure to give (*R*)-**9**·HCl (83 mg, 91% yield) as a white solid. $[\alpha]_D^{20} = -2.0$ (*c* 0.60, H_2O), lit. $[\alpha]_D^{28} = -2$ (*c* 0.6, H_2O).[10] Mp: 194–195 °C (MeOH) [lit. 195 °C (isopropanol)].[10] R_f 0.12 (SiO_2, hexane/Et_2O 1:1). The IR, ^1H NMR and ^{13}C NMR data are coincidental with those described.[10]

4.12. (*S*)-4-Amino-3-(4-chlorophenyl)butanoic acid hydrochloride, [(*S*)-baclofen hydrochloride] (*S*)-9·HCl

It was prepared in a similar manner to that described for (*R*)-**9**·HCl. From the nitro acid (*S*)-**4** (101 mg, 0.41 mmol), MeOH (15 mL) and Ra-Ni (50% water content, 200 mg), amino acid (*S*)-**9**·HCl (94 mg, 91% yield) was obtained as a white solid. $[\alpha]_D^{20} = +2.0$ (*c* 0.60, H_2O) [lit. $[\alpha]_D^{28} = +1.4$ (*c* 1.0, H_2O)].[11] Mp: 194–195 °C (MeOH) [lit. 215 °C (EtOH/Et_2O)].[13] The R_f, IR, ^1H NMR and ^{13}C NMR spectra are coincidental with those of (*R*)-**9**·HCl.

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