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A synthesis of levetiracetam based on (*S*)-*N*-phenylpantolactam as a chiral auxiliary

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Abstract—The synthesis of levetiracetam and its enantiomer by deracemization of (±)-2-bromobutyric acid using either (*S*)- or (*R*)-*N*-phenylpantolactam as chiral auxiliaries, followed by S_N2 substitution of the bromine atom by a 2-oxopyrrolidin-1-yl group and amidation of the carboxylic acid, is described.

1. Introduction

Levetiracetam, (*S*)-**1**, or its racemic form (etiracetam) have been used for the treatment of various disorders since 1980. Etiracetam was first used as a piracetam-like cognition-enhancing agent in memory disorders. However, epilepsy studies on etiracetam, initiated in 1992, showed the outstanding pharmacokinetic and pharmacological profile for this new application of the (*S*)-enantiomer, levetiracetam, which led to the fastest approval of an antiepileptic drug (AED) by the FDA, at the end of 1999, as an add-on therapy for partial onset seizures in adults with epilepsy. Epilepsy is a common medical disorder with a prevalence of around 1% of the general population, requiring prolonged and sometimes lifelong drug therapy.[1] In this context, the effectiveness, generally good tolerability, the lack of interactions with other AEDs and especially the cost-effectiveness of the add-on therapy with levetiracetam could afford substantial benefits for patients with epilepsy as well as for healthcare budgets. Indeed, since its launch in the USA in April 2000, levetiracetam has become one of the leading adjunctive antiepileptic drugs prescribed in neurology clinics around the world, in such a way that the worldwide sales of UCB's Keppra® have beaten expectations and the growing demand for Keppra® has made necessary new production installations and adaptation of existing production plants.

Different methods of preparation of levetiracetam have been described. Several of these procedures start from readily available enantiopure α-amino acids and derivatives thereof: (1) from (*S*)-α-aminobutyramide by reaction with ethyl γ-bromobutyrate or γ-chlorobutyryl chloride, followed by cyclization of the resulting intermediates;[2,3] (2) from (*S*)-α-aminobutyric acid by esterification, elaboration of the 2-pyrrolidinone ring and conversion of the ester to the amide functionality;[4] (3) from (*S*)-α-amino-γ-methylthiobutyramide by reaction with ethyl γ-bromobutyrate or γ-chlorobutyryl chloride, and Ra–Ni desulfurization.[5] In other procedures, the resolution of etiracetam, or an advanced racemic intermediate thereof, is performed: (4) resolution of 2-(2-oxopyrrolidin-1-yl)butyric acid with (*R*)-α-methylbenzylamine, followed by consecutive reaction of the (*S*)-acid with ethyl chloroformate and ammonium hydroxide;[2] (5) resolution of etiracetam by preparative chiral HPLC;[6,7] (6) *N*-diethylaminomethylation of the primary amide functionality of etiracetam followed by resolution with L-(+)-tartaric acid, and hydrolysis of the required enantiomer.[8] Finally an enantioselective catalytic synthesis of levetiracetam has also been described: (7) the hydrogenation of (*E*)- or (*Z*)-2-(2-oxopyrrolidin-1-yl)-2-butenamide with Rh(I) or Ru(II) complexes of enantiopure diphosphines.[9,10]

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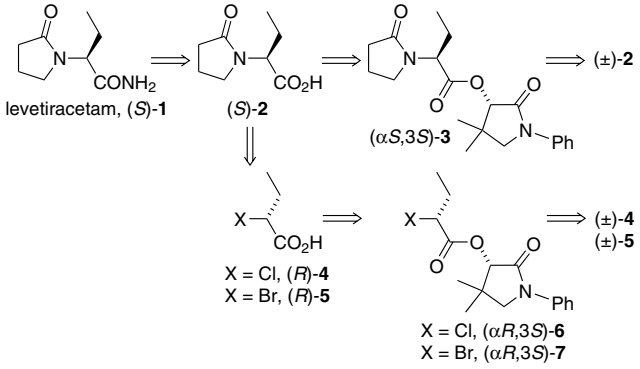
We have described the preparation of (*R*)- and (*S*)-3-hydroxy-4,4-dimethyl-1-phenylpyrrolidin-2-one[11,12] [(*R*)- and (*S*)-*N*-phenylpantolactam, (*R*)- and (*S*)-**8**] and their efficient use as chiral auxiliaries in the deracemization of different α-substituted carboxylic acids.[13–18] Herein we report the use of these chiral auxiliaries in a synthesis of levetiracetam and its enantiomer.

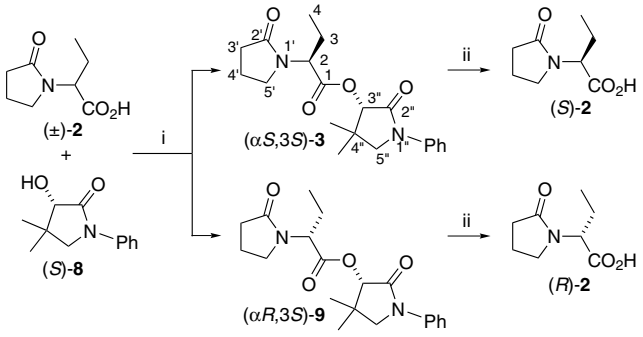
2. Results and discussion

Several possible routes for preparing levetiracetam based on the use of (*R*)- and (*S*)-**8** as chiral auxiliaries are depicted in Scheme 1. The simplest possibility involves the deracemization of the easily available 2-(2-oxopyrrolidin-1-yl)butyric acid, (±)-**2**. Alternatively, deracemization of 2-chloro- or 2-bromo-butyric acids, (±)-**4** or (±)-**5**, provides (*R*)-**4** or (*R*)-**5**, which on nucleophilic substitution with 2-pyrrolidinone via an S_N2 mechanism could provide acid (*S*)-**2**, whose conversion into (*S*)-**1** has previously been described.[2] Deracemizations of α-substituted carboxylic acids with chiral non-racemic alcohols has been proposed to take place via ketene intermediates or by dynamic kinetic resolution processes.[18] While the sense of asymmetric induction in the deracemizations of α-halocarboxylic acids is quite established [acids with an (*R*)-configuration at the stereogenic centre being obtained using (*S*)-pantolactone or (*S*)-*N*-phenylpantolactam as chiral auxiliaries and Et_3N as base],[18] there is no rationale to explain the outcome of these reactions.



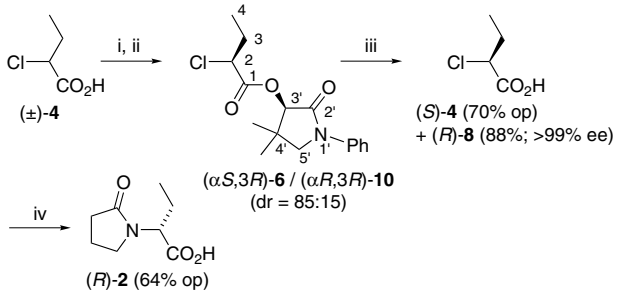
Scheme 1. Retrosynthetic analysis of levetiracetam based on (*R*)- or (*S*)-*N*-phenylpantolactam.

In practice and contrary to our expectations,[17] attempted deracemization of acid (±)-**2** by reaction of the corresponding acid chloride with (*S*)-**8** under different reaction conditions gave, in poor yield, a diastereomeric mixture of the corresponding esters (α*S*,3*S*)-**3** and (α*R*,3*S*)-**9** in ratios close to 1:1 (^{1}H NMR). Not unexpectedly, the reaction of acid (±)-**2** with *N*,*N*′-dicyclohexylcarbodiimide (DCC) and then with (*S*)-**8** in the presence of a catalytic amount of 4-dimethylaminopyridine (DMAP) at −78 °C overnight, gave in quantitative yield a diastereomeric mixture of (α*R*,3*S*)-**9** and (α*S*,3*S*)-**3** in the approximate ratio of 2:3, due to partial deracemization during esterification. From this mixture, samples of (α*R*,3*S*)-**9** [>98:2 diastereomeric ratio (dr)] and (α*S*,3*S*)-**3** (>98:2 dr) could be isolated by silica gel column chromatography and fully characterized. Hydrolysis of each ester (α*S*,3*S*)-**3** and (α*R*,3*S*)-**9** with $LiOH/H_2O_2$ gave the corresponding acids (*S*)- and (*R*)-**2** in 63% and 66% yield, respectively (Scheme 2). The enantiomeric purity of these acids could not be established by chiral HPLC. The specific rotation for (*S*)-**2** {$[\alpha]_D^{20} = -28.0$ (*c* 1.03, acetone)} was similar to that described {$[\alpha]_D^{20} = -26.4$ (*c* 1.00, acetone)}.[2]



Scheme 2. Resolution of acid (±)-**2** using (*S*)-*N*-phenylpantolactam, (*S*)-**8**, as chiral auxiliary. Reagents and conditions: (i) DCC/DMAP/CH_2Cl_2, −78 °C, overnight, quantitative yield of crude (α*R*,3*S*)-**9**/(α*S*,3*S*)-**3** in the ratio of 2:3; after silica gel column chromatography: 25% yield of (α*R*,3*S*)-**9**; 24% yield of (α*S*,3*S*)-**3**; (ii) $LiOH/H_2O_2$/THF, 0 °C, 7 h; (*S*)-**2**: 63% yield; (*R*)-**2**: 66% yield.

As an alternative procedure, we studied the deracemization of (±)-α-chlorobutyric acid, (±)-**4**. As expected,[15,16] by reaction of the corresponding acid chloride with (*R*)-*N*-phenylpantolactam, (*R*)-**8**, a diastereomeric mixture of the esters (α*S*,3*R*)-**6** and (α*R*,3*R*)-**10** in an approximate ratio of 85:15 (^{1}H NMR and HPLC) was obtained (Scheme 3). Unfortunately, chromatographic purification of the main diastereomer by silica gel column chromatography was not possible. Hydrolysis of the above mixture using $LiOH/H_2O_2$ in THF at 0 °C gave (*S*)-**4** [95% yield, 70% optical purity (op)]. Assuming the op to be similar to the ee, this result shows that hydrolysis takes place without racemization. Reaction of (*S*)-**4** (70% op) with the sodium salt of 2-pyrrolidinone in THF overnight at room temperature gave the expected

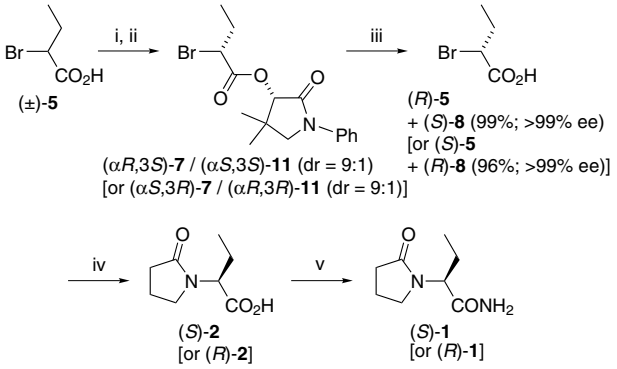


Scheme 3. Attempted synthesis of the enantiomer of levetiracetam via deracemization of 2-chlorobutyric acid with (*R*)-**8**. Reagents and conditions: (i) Cl_2SO; (ii) (*R*)-**8**, CH_2Cl_2, Et_3N, −20 °C, 4 h: (α*S*,3*R*)-**6**/(α*R*,3*R*)-**10** (quantitative yield, 85:15 dr); (iii) $LiOH/H_2O_2$/THF, 0 °C, 7 h: (*S*)-**4** (95%, 70% op); (iv) NaH/2-pyrrolidinone/THF, rt, overnight: (*R*)-**2** (42%, 64% op).

substitution product (*R*)-**2**, but in low yield (42%) and lower op (64%) than that of the starting compound. When the last reaction was carried out under reflux, the yield increased to 52%, but the op decreased to 45%. These results show that some racemization takes place in these transformations, which can be explained by assuming a certain degree of participation of the carboxylate group in the substitution reaction, which would take place with retention of the configuration, thus lowering the op of the main product arising from an S_N2 reaction. Altogether, it seemed clear that a synthesis of levetiracetam from (±)-2-chlorobutyric acid was not adequate. In view of these results we discontinued this approach to levetiracetam.

Finally, we studied the deracemization of (±)-2-bromobutyric acid, (±)-**5**. Reaction of (±)-**5** with Cl_2SO, followed by reaction of the resulting racemic 2-bromobutyryl chloride with (*S*)-**8**, gave in a quantitative yield a diastereomeric mixture of esters (α*R*,3*S*)-**7** and (α*S*,3*S*)-**11** in the approximate ratio of 9:1 (^{1}H NMR). In this case, the main diastereomer (α*R*,3*S*)-**7** was isolated in 67% yield and >98:2 dr, after silica gel column chromatography of the diastereomeric mixture. Hydrolysis of (α*R*,3*S*)-**7** using $LiOH/H_2O_2$ in THF at 0 °C afforded (*R*)-2-bromobutyric acid, (*R*)-**5**, in 91% yield, with an $[\alpha]_D^{28} = +33.6$ (*c* 2.74, MeOH) {described for (*S*)-**5** $[\alpha]_D^{20} = -31.0$ (*c* 2.50, MeOH)}.[19] This result is in contrast with previous results obtained in the hydrolysis of related α-bromo esters of *N*-phenylpantolactam, such as α-bromopropionate and α-bromo-β-methylbutyrate, carried out with 2 M HCl/AcOH under reflux for 2 h or with $LiOH{\cdot}H_2O$ in THF from −20 °C to room temperature, which took place with noticeable racemization of the α-bromo acid.[15] However, we have previously observed a similar situation in the hydrolysis of the α-chloropropionate of (*R*)-*N*-phenylpantolactam.[16] The reaction of (*R*)-**5** with the sodium salt of 2-pyrrolidinone in THF at room temperature overnight gave the substitution product (*S*)-**2** in 55% yield, showing an $[\alpha]_D^{20} = -27.3$ (*c* 1.01, acetone), similar to the described value, $[\alpha]_D^{20} = -26.4$ (*c* 1.00, acetone).[2] This presumably shows that the substitution reaction takes place by an S_N2 mechanism. This compound was transformed into the corresponding amide (*S*)-**1**, by consecutive reaction with ethyl chloroformate and ammonium hydroxide, following a known procedure.[2] The enantiomeric excess (ee) of the crude product thus obtained (80% yield, 92% ee) was established by chiral HPLC analysis. After recrystallization from acetone, (*S*)-**1** (>99% ee) was obtained in 65% overall yield. This result shows that amidation of (*S*)-**2** to levetiracetam (*S*)-**1** takes place with partial racemization, which may be due to the increased acidity of the α-carboxylic proton in the intermediate mixed anhydride formed during the amidation reaction and the basic reaction conditions during the reaction with ammonium hydroxide. Similarly, partial racemization during the amidation of the ethyl ester of (*S*)-**2** had been previously observed (Scheme 4).[4]

In a similar way, by starting from (±)-**5**, via (α*S*,3*R*)-**7** (71% yield, >98:2 dr), (*S*)-**5** (96% yield) and (*R*)-**2**



Scheme 4. Synthesis of levetiracetam and its enantiomer via deracemization of 2-bromobutyric acid with (*S*)-**8** or (*R*)-**8**. Reagents and conditions: (i) Cl_2SO; (ii) (*S*)-**8** [or (*R*)-**8**], CH_2Cl_2, Et_3N, −20 °C, 4 h: (α*R*,3*S*)-**7** (67%, >98:2 dr) [or (α*S*,3*R*)-**7** (71%, >98:2 dr)] from (±)-**5**, after column chromatography; (iii) $LiOH/H_2O_2$/THF, 0 °C, 7 h: (*R*)-**5** (91%) [or (*S*)-**5** (96%)]; (iv) NaH/2-pyrrolidinone/THF, rt, overnight: (*S*)-**2** (55%) [or (*R*)-**2** (62%)]; (v) (a) $ClCO_2Et/CH_2Cl_2$, Et_3N, 0 °C, 30 min, (b) NH_4OH, rt, 16 h: (*S*)-**1** (80% crude yield, 92% ee; 65% yield, >99% ee, after recrystallization from acetone) [or (*R*)-**1** (90% crude yield, 91% ee; 63% yield, >99% ee, after recrystallization from acetone)].

(62% yield), (*R*)-**1** (90% crude yield, 91% ee; 63% yield after recrystallization from acetone, >99% ee) was obtained.

3. Conclusion

In conclusion, we have developed a synthesis of levetiracetam by deracemization of (±)-2-bromobutyric acid, (±)-**5** to the (*R*)-enantiomer with (*S*)-*N*-phenylpantolactam, (*S*)-**8**, followed by nucleophilic substitution with the sodium salt of 2-pyrrolidinone to give (*S*)-2-(2-oxopyrrolidin-1-yl)butyric acid, (*S*)-**2**, a known precursor of levetiracetam. The key points of the synthesis are: (1) the good diastereomeric ratio (9:1) in the esterification of (±)-**5** with the chiral auxiliary and the easy purification of the main diastereomer by column chromatography, (2) the $LiOH/H_2O_2$ hydrolysis of the diastereopure ester (α*R*,3*S*)-**7** to give acid (*R*)-**5** without racemization and (3) the S_N2 transformation of (*R*)-**5** to the immediate acid precursor of levetiracetam, (*S*)-**2**. This sequence has also been applied to the preparation of the enantiomer of levetiracetam.

4. Experimental

4.1. General

Melting points were determined in open capillary tubes with an MFB 595010 M Gallenkamp melting point apparatus. Unless otherwise stated, ^{1}H NMR (300 MHz) and ^{13}C NMR (75.4 MHz) spectra were recorded in $CDCl_3$ in a Varian Gemini 300 spectrometer. Chemical shifts (δ) are reported in ppm related to internal tetramethylsilane (TMS). For the numbering of representative pantolactam esters, see Schemes 2 and 3. For the pantolactam esters **3**, **6**, **7** and **9**, the terms α or β are assigned to

hydrogen atoms or groups of the pantolactam moiety, which are *cis* or *trans* relative to the 3-carboxy substituent, respectively. Assignments given for the NMR spectra are based on DEPT and comparison with related compounds previously described by the research group.[13–15] MS spectra were taken on a Hewlett–Packard 5988A spectrometer using the chemical ionization (CH_4) technique; only significant ions are given. IR spectra were recorded on a Perkin–Elmer Spectrum RX I equipment. Absorption values are expressed as wave-numbers (cm^{-1}); only significant bands are given. 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, and using a CHIRALCEL OD-H column (25×0.46 cm) containing the chiral stationary phase cellulose tris(3,5-dimethylphenylcarbamate). Conditions A (mixture of hexane/ethanol 95:5 as eluent, flow 0.8 mL/min, $\lambda = 240$ nm) were used for the resolution of the enantiomers of etiracetam, **1**. Conditions B (mixture of hexane/isopropanol 93:7 as eluent, flow 0.8 mL/min, $\lambda = 254$ nm) were used for the analysis of *N*-phenylpantolactam, **8**, and the esters **6** and **10**. Column chromatography was performed on silica gel 60 AC.C. (35–70 mesh, SDS, ref. 2000027). Thin-layer chromatography (TLC) was performed with aluminium-backed sheets with silica gel 60 F_{254} (Merck, ref. 1.05554), and spots were visualized with UV light and 1% aqueous solution of $KMnO_4$. NMR spectra were performed at the 'Serveis Científico-Tècnics' of the University of Barcelona, while elemental analyses were carried out at the Microanalysis Service of the IIQAB (CSIC, Barcelona, Spain).

4.2. (α*R*,3*S*)- and (α*S*,3*S*)-4,4-Dimethyl-2-oxo-1-phenylpyrrolidin-3-yl 2-(2-oxopyrrolidin-1-yl)butyrate, (α*R*,3*S*)-9 and (α*S*,3*S*)-3

To a cold (0 °C) solution of acid (±)-**2** (1.40 g, 8.19 mmol, 1.1 equiv) in CH_2Cl_2 (20 mL), DCC (1.69 g, 8.19 mmol, 1.1 equiv) was added in several portions and the mixture stirred at this temperature for 20 min. The solution was cooled to −78 °C, a solution of (*S*)-**8** (1.53 g, 7.46 mmol) in CH_2Cl_2 (18 mL) and DMAP (46 mg, 0.38 mmol, 0.05 equiv) were successively added and the reaction mixture was stirred at −78 °C for 16 h. The resulting solution was allowed to warm to room temperature, the precipitated *N*,*N*′-dicyclohexylurea (DCU) filtered off through a pad of Celite® and the filtrate concentrated under reduced pressure. Water (30 mL) and brine (5 mL) were added to the residue and the mixture extracted with AcOEt (3×60 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo to give a mixture of (α*R*,3*S*)-**9** and (α*S*,3*S*)-**3** [2.67 g, quantitative yield, approximate diastereomeric ratio (dr) = 2:3, by ^{1}H NMR] as a yellow oil. This mixture was submitted to column chromatography [silica gel (54 g/g mixture), hexane/Et_2O mixtures]. On elution with hexane/Et_2O 30:70, (α*R*,3*S*)-**9** (669 mg, 25% yield, >98:2 dr by ^{1}H NMR), mixtures of (α*R*,3*S*)-**9** and (α*S*,3*S*)-**3** (1.02 g, 35:65 dr) and (α*S*,3*S*)-**3** (630 mg, 24% yield, >98:2 dr) were successively isolated as yellow oils.

(α*S*,3*S*)-**3**: $[\alpha]_D^{20} = -42.3$ (*c* 0.96, $CHCl_3$); R_f 0.30 (silica gel, 8 cm, hexane/AcOEt 2:1); IR (NaCl) *v*: 1751 (C=O st ester), 1714 and 1692 (C=O st lactams); ^{1}H NMR *δ*: 0.99 (dd, $J_{3\text{-Ha}/4\text{-H}} = J_{3\text{-Hb}/4\text{-H}} = 7.2$ Hz, 3H, 4-H_3), 1.16 (s, 3H, 4″α-CH_3), 1.30 (s, 3H, 4″β-CH_3), 1.86 (ddq, $J_{3\text{-Ha}/3\text{-Hb}} = 14.4$ Hz, $J_{2\text{-H}/3\text{-Ha}} = 10.8$ Hz, $J_{3\text{-Ha}/4\text{-H}} = 7.2$ Hz, 1H, 3-H_a), 1.97–2.22 (complex signal, 3H, 4′-H_2 and 3-H_b), 2.45 (m, 2H, 3′-H_2), 3.40 (m, 1H) and 3.70 (m, 1H) (5′-H_2), 3.54 (d, $J_{5''\alpha\text{-H}/5''\beta\text{-H}} = 9.6$ Hz, 1H, 5″α-H), 3.62 (d, $J_{5''\alpha\text{-H}/5''\beta\text{-H}} = 9.6$ Hz, 1H, 5″β-H), 4.81 (dd, $J_{2\text{-H}/3\text{-Ha}} = 10.8$ Hz, $J_{2\text{-H}/3\text{-Hb}} = 4.8$ Hz, 1H, 2-H), 5.39 (s, 1H, 3″-H), 7.17 (tt, $J_{Hp/Hm} = 7.5$ Hz, $J_{Hp/Ho} = 1.2$ Hz, 1H, Ar–H*para N*-phenyl), 7.38 (m, 2H, Ar–H*meta N*-phenyl), 7.61 (m, 2H, Ar–H*ortho N*-phenyl); ^{13}C NMR *δ*: 10.9 (CH_3, C4), 18.4 (CH_2, C3), 21.1 (CH_3, 4″α-CH_3), 22.5 (CH_2, C4′), 24.7 (CH_3, 4″β-CH_3), 30.9 (CH_2, C3′), 37.2 (C, C4″), 43.7 (CH_2, C5′), 55.3 (CH, C2), 57.7 (CH_2, C5″), 78.7 (CH, C3″), 119.4 (CH, Ar–C*ortho N*-phenyl), 124.9 (CH, Ar–C*para N*-phenyl), 128.9 (CH, Ar–C*meta N*-phenyl), 138.9 (C, Ar–C*ipso N*-phenyl), 168.4 (C, C2″), 170.5 (C, C2′), 175.9 (C, C1). MS (CI, CH_4), *m*/*z* (%): 387 [$(M+C_2H_5)^+$, 18], 360 (23), 359 [$(M+H)^+$, 100], 154 (20), 126 (10). Elemental analysis: calcd for $C_{20}H_{26}N_2O_4 \cdot 2/5H_2O$: C 65.70, H 7.39, N 7.66. Found: C 65.94, H 7.76, N 7.24.

(α*R*,3*S*)-**9**: $[\alpha]_D^{20} = +50.3$ (*c* 1.03, $CHCl_3$); R_f 0.38 (silica gel, 8 cm, hexane/AcOEt 2:1); IR (NaCl) *v*: 1748 (C=O st ester), 1712 and 1692 (C=O st lactams); ^{1}H NMR *δ*: 0.96 (dd, $J_{3\text{-Ha}/4\text{-H}} = J_{3\text{-Hb}/4\text{-H}} = 7.2$ Hz, 3H, 4-H_3), 1.10 (s, 3H, 4″α-CH_3), 1.29 (s, 3H, 4″β-CH_3), 1.80 (ddq, $J_{3\text{-Ha}/3\text{-Hb}} = 14.4$ Hz, $J_{2\text{-H}/3\text{-Ha}} = 10.5$ Hz, $J_{3\text{-Ha}/4\text{-H}} = 7.2$ Hz, 1H, 3-H_a), 1.95–2.20 (complex signal, 3H, 4′-H_2 and 3-H_b), 2.33–2.51 (complex signal, 2H, 3′-H_2), 3.36 (m, 1H) and 3.62 (m, 1H) (5′-H_2), 3.52 (d, $J_{5''\alpha\text{-H}/5''\beta\text{-H}} = 9.6$ Hz, 1H, 5″α-H), 3.61 (d, $J_{5''\alpha\text{-H}/5''\beta\text{-H}} = 9.6$ Hz, 1H, 5″β-H), 4.86 (dd, $J_{2\text{-H}/3\text{-Ha}} = 10.5$ Hz, $J_{2\text{-H}/3\text{-Hb}} = 4.8$ Hz, 1H, 2-H), 5.40 (s, 1H, 3″-H), 7.17 (tt, $J_{Hp/Hm} = 7.5$ Hz, $J_{Hp/Ho} = 1.2$ Hz, 1H, Ar–H*para N*-phenyl), 7.38 (m, 2H, Ar–H*meta N*-phenyl), 7.59 (m, 2H, Ar–H*ortho N*-phenyl); ^{13}C NMR *δ*: 10.7 (CH_3, C4), 18.4 (CH_2, C3), 21.1 (CH_3, 4″α-CH_3), 21.9 (CH_2, C4′), 24.6 (CH_3, 4″β-CH_3), 30.9 (CH_2, C3′), 37.3 (C, C4″), 43.6 (CH_2, C5′), 55.2 (CH, C2), 57.7 (CH_2, C5″), 78.7 (CH, C3″), 119.4 (CH, Ar–C*ortho N*-phenyl), 125.0 (CH, Ar–C*para N*-phenyl), 128.9 (CH, Ar–C*meta N*-phenyl), 138.8 (C, Ar–C*ipso N*-phenyl), 168.4 (C, C2″), 170.1 (C, C2′), 176.0 (C, C1). MS (CI, CH_4), *m*/*z* (%): 387 [$(M+C_2H_5)^+$, 19], 360 (22), 359 [$(M+H)^+$, 100], 154 (51), 126 (30). Elemental analysis: calcd for $C_{20}H_{26}N_2O_4$: C 67.02, H 7.31, N 7.82. Found: C 66.66, H 7.45, N 7.45.

4.3. (*S*)-2-(2-Oxopyrrolidin-1-yl)butyric acid, (*S*)-2, by hydrolysis of (α*S*,3*S*)-3

To a cold (0 °C) solution of (α*S*,3*S*)-**3** (466 mg, 1.30 mmol, >98:2 dr) in THF (23 mL), 30% w/v H_2O_2 (0.70 mL, 6.18 mmol, 4.7 equiv) and $LiOH \cdot H_2O$ (165 mg, 3.93 mmol, 3.0 equiv) were added and the mixture stirred at this temperature for 7 h. A solution of Na_2SO_3 (0.75 M, 7.5 mL) was added, the final pH being about 9. This mixture was extracted with CH_2Cl_2

(3 × 15 mL) and the combined organic extracts dried over Na_2SO_4 and concentrated in vacuo to give (*S*)-**8** (250 mg, 94% yield, >99% ee, by chiral HPLC, conditions B). The aqueous phase was made acidic (pH = 2–3) with 1 M HCl and extracted with AcOEt (3 × 15 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo to give (*S*)-**2** (140 mg, 63% yield) as a white solid, $[\alpha]_D^{20} = -28.0$ (*c* 1.03 acetone) {described $[\alpha]_D^{20} = -26.4$ (*c* 1.00, acetone)}.[2] The analytical and spectroscopic data of (*S*)-**2** coincide with those obtained for the product of Section 4.12.

4.4. (*R*)-2-(2-Oxopyrrolidin-1-yl)butyric acid, (*R*)-2, by hydrolysis of (α*R*,3*S*)-9

It was prepared as described for the preparation of (*S*)-**2** from (α*S*,3*S*)-**3**. From (α*R*,3*S*)-**9** (445 mg, 1.24 mmol, >98:2 dr), (*S*)-**8** (244 mg, 96% yield, >99% ee, by chiral HPLC) and (*R*)-**2** (141 mg, 66% yield) were obtained as white solids. The analytical and spectroscopic data of (*R*)-**2** coincide with those obtained for the product from Section 4.13.

4.5. (α*S*,3*R*)-4,4-Dimethyl-2-oxo-1-phenylpyrrolidin-3-yl 2-chlorobutyrate, (α*S*,3*R*)-6

(±)-2-Chlorobutyric acid, (±)-**4** (7.0 mL, 8.33 g, 68.0 mmol) was added dropwise to cold (0 °C) and magnetically stirred $SOCl_2$ (7.25 mL, 11.9 g, 100 mmol, 1.5 equiv). Once the addition was complete, the mixture was heated at reflux for 2 h. The excess of $SOCl_2$ and the acid chloride were fractionally distilled at atmospheric pressure. In this way, (±)-2-chlorobutyryl chloride (6.40 g, 67% yield, bp 100–120 °C) was obtained as a colourless liquid.

To a cold (−20 °C) solution of (*R*)-**8** (3.47 g, 16.9 mmol) in anhydrous CH_2Cl_2 (50 mL), a solution of (±)-2-chlorobutyryl chloride (3.39 g, 24.1 mmol, 1.4 equiv) in anhydrous CH_2Cl_2 (77 mL) and a solution of anhydrous Et_3N (7.8 mL, 5.66 g, 55.9 mmol, 3.3 equiv) in anhydrous CH_2Cl_2 (100 mL) were successively added, and the reaction mixture stirred at −20 °C for 2 h. [All of the dichloromethane solutions were previously dried by stirring with 3 Å molecular sieves (about 0.3 g/mL) at 0 °C for 45 min.] The mixture was successively washed with 1 M HCl (2 × 120 mL) and saturated aqueous solution of $NaHCO_3$ (2 × 120 mL). The organic phase was dried over Na_2SO_4 and concentrated in vacuo to give a mixture of (α*S*,3*R*)-**6** and (α*R*,3*R*)-**10** [5.24 g, quantitative yield, 85:15 dr, by ^{1}H NMR and chiral HPLC, conditions B: (α*S*,3*R*)-**6**, rt 17.34 min; (α*R*,3*R*)-**10**, rt 19.43 min; $k_1 = 3.35$, $k_2 = 3.87$; $\alpha = 1.16$; Res = 1.75]. Column chromatography of this mixture [silica gel (43 g/g mixture), hexane/AcOEt mixtures] did not allow us to separate their components. IR (KBr) *ν*: 1753 (C=O st ester), 1716 (C=O st lactam); NMR data of [(α*S*,3*R*)-**6**]: ^{1}H NMR *δ*: 1.12 (dd, $J_{3\text{-Ha/4-H}} = J_{3\text{-Hb/4-H}} = 7.5$ Hz, 3H, 4-H_3), 1.17 (s, 3H, 4′α-CH_3), 1.31 (s, 3H, 4′β-CH_3), 1.96–2.25 (complex signal, 2H, 3-H_2), 3.53 (d, $J_{5'\alpha\text{-H}/5'\beta\text{-H}} = 9.9$ Hz, 1H, 5′α-H), 3.63 (d, $J_{5'\alpha\text{-H}/5'\beta\text{-H}} = 9.9$ Hz, 1H, 5′β-H), 4.42 (dd, $J_{2\text{-H}/3\text{-Ha}} = 7.5$ Hz, $J_{2\text{-H}/3\text{-Hb}} = 6.0$ Hz, 1H, 2-H), 5.43 (s, 1H, 3′-H), 7.17 (tt, $J_{Hp/Hm} = 7.5$ Hz, $J_{Hp/Ho} = 1.2$ Hz, 1H, Ar–H*para N*-phenyl), 7.37 (m, 2H, Ar–H*meta N*-phenyl), 7.62 (m, 2H, Ar–H*ortho N*-phenyl); ^{13}C NMR *δ*: 10.5 (CH_3, C4), 21.1 (CH_3, 4′α-CH_3), 24.8 (CH_3, 4′β-CH_3), 28.6 (CH_2, C3), 37.5 (C, C4′), 57.6 (CH_2, C5′), 59.0 (CH, C2), 79.1 (CH, C3′), 119.4 (CH, Ar–C*ortho N*-phenyl), 125.0 (CH, Ar–C*para N*-phenyl), 128.9 (CH, Ar–C*meta N*-phenyl), 138.8 (C, Ar–C*ipso N*-phenyl), 168.0 (C, C2′), 168.7 (C, C1). MS (CI, CH_4), *m/z* (%): 338 [$(M+C_2H_5)^+$, 14], 312 (33), 311 (23), 310 [$(M+H)^+$, 100], 309 (15), 274 [$(M-Cl)^+$, 22], 188 (24). Elemental analysis of the (α*S*,3*R*)-**6**/(α*R*,3*R*)-**10** mixture in the ratio of 85:15: calcd for $C_{16}H_{20}ClNO_3$: C 62.03, H 6.51, N 4.52, Cl 11.44. Found: C 61.73, H 6.64, N 4.40, Cl 11.78.

4.6. (*S*)-2-Chlorobutyric acid, (*S*)-4

It was obtained in the same manner described for the preparation of (*S*)-**2** from its pantolactam ester (α*S*,3*S*)-**3**. From the mixture (α*S*,3*R*)-**6**/(α*R*,3*R*)-**10** in the ratio 85:15 (4.26 g, 13.8 mmol), (*S*)-**4** (1.60 g, 95% yield, 70% op) was obtained as a colourless liquid, $[\alpha]_D^{20} = -8.9$ (*c* 2.50, MeOH) {described for (*R*)-**4** $[\alpha]_D^{20} = 12.7$ (*c* 0.4, MeOH)}.[21] Furthermore, (*R*)-**8** (2.50 g, 88% yield, >99% ee by chiral HPLC) was also recovered.

4.7. (*R*)-2 from (*S*)-4

A suspension of 2-pyrrolidinone (1.52 mL, 1.70 g, 20.0 mmol, 3 equiv) and NaH [55% oily dispersion, 872 mg, 20.0 mmol, 3.0 equiv, washed with hexane (3 × 10 mL) prior to use] in anhydrous THF (15 mL) was stirred at room temperature for 45 min. A solution of chloroacid (*S*)-**4** (815 mg, 6.65 mmol, 70% op) in anhydrous THF (4 mL) was added and the reaction mixture stirred at room temperature for 48 h. After acidification with 10% aqueous HCl (6 mL), the organic phase was separated and the aqueous layer extracted with Et_2O (4 × 25 mL). The combined organic phase and extracts were dried (Na_2SO_4) and concentrated in vacuo to give a residue (0.99 g), which on trituration with Et_2O (5 mL) gave (*R*)-**2** (474 mg, 42% yield, 64% op) as a white solid, $[\alpha]_D^{20} = 17.5$ (*c* 1.03, acetone) {described $[\alpha]_D^{20} = 27.3$ (*c* 1.00, acetone)}.[20] Note: When this reaction was carried out at reflux for 16 h, the yield increased to 52% but the op was reduced to 45%.

4.8. (α*R*,3*S*)-4,4-Dimethyl-2-oxo-1-phenylpyrrolidin-3-yl 2-bromobutyrate, (α*R*,3*S*)-7

It was prepared as described for (α*S*,3*R*)-**6**. Starting from (±)-2-bromobutyric acid, (±)-**5** (20.0 mL, 31.3 g, 187 mmol), (±)-2-bromobutyryl chloride (28.1 g, 81% yield, bp 55–65 °C/40 Torr) was obtained as a colourless liquid, which on reaction with (*S*)-**8** (4.84 g, 23.6 mmol) for 4 h afforded a mixture of (α*R*,3*S*)-**7** and (α*S*,3*S*)-**11** (8.35 g, quantitative yield, approximate dr = 9:1, by ^{1}H NMR). Column chromatography of this mixture [silica gel (50 g/g mixture), hexane/Et_2O mixtures] allowed us to isolate (α*R*,3*S*)-**7** (5.23 g) as the first eluted product (hexane/Et_2O 85:15). Column chromatography of the

fractions corresponding to mixtures of both diastereomers under similar conditions gave more (αR,3S)-**7** (0.38 g, total yield 5.61 g, 67% yield, >98:2 dr, by ^{1}H NMR). $[\alpha]_D^{20} = -36.6$ (*c* 1.19, $CHCl_3$); R_f 0.21 (silica gel, 8 cm, hexane/Et_2O 3:1); mp 64–65 °C (hexane/Et_2O 85:15); IR (KBr) *ν*: 1742 (C=O st ester), 1712 (C=O st lactam); ^{1}H NMR *δ*: 1.11 (dd, $J_{3\text{-Ha}/4\text{-H}} = J_{3\text{-Hb}/4\text{-H}} = 7.2$ Hz, 3H, 4-H_3), 1.20 (s, 3H, 4′α-CH_3), 1.32 (s, 3H, 4′β-CH_3), 2.10 (ddq, $J_{3\text{-Ha}/3\text{-Hb}} = 14.4$ Hz, $J_{2\text{-H}/3\text{-Ha}} = J_{3\text{-Ha}/4\text{-H}} = 7.2$ Hz, 1H, 3-H_a), 2.24 (ddq, $J_{3\text{-Ha}/3\text{-Hb}} = 14.4$ Hz, $J_{2\text{-H}/3\text{-Hb}} = J_{3\text{-Hb}/4\text{-H}} = 7.2$ Hz, 1H, 3-H_b), 3.54 (d, $J_{5'\alpha\text{-H}/5'\beta\text{-H}} = 9.6$ Hz, 1H, 5′α-H), 3.63 (d, $J_{5'\alpha\text{-H}/5'\beta\text{-H}} = 9.6$ Hz, 1H, 5′β-H), 4.31 (dd, $J_{2\text{-H}/3\text{-Ha}} = J_{2\text{-H}/3\text{-Hb}} = 7.2$ Hz, 1H, 2-H), 5.42 (s, 1H, 3′-H), 7.17 (tt, $J_{Hp/Hm} = 7.2$ Hz, $J_{Hp/Ho} = 1.2$ Hz, 1H, Ar–H*para N*-phenyl), 7.37 (m, 2H, Ar–H*meta N*-phenyl), 7.62 (m, 2H, Ar–H*ortho N*-phenyl); ^{13}C NMR *δ*: 11.9 (CH_3, C4), 21.1 (CH_3, 4′α-CH_3), 24.8 (CH_3, 4′β-CH_3), 28.6 (CH_2, C3), 37.6 (C, C4′), 47.7 (CH, C2), 57.7 (CH_2, C5′), 79.0 (CH, C3′), 119.4 (CH, Ar–C*ortho N*-phenyl), 124.9 (CH, Ar–C*para N*-phenyl), 128.9 (CH, Ar–C*meta N*-phenyl), 138.8 (C, Ar–C*ipso N*-phenyl), 168.2 (C, C2′), 168.8 (C, C1). MS (CI, CH_4), *m*/*z* (%): 384 (13), 382 [$(M+C_2H_5)^+$, 13], 357 (17), 356 (97), 355 (33), 354 [$(M+H)^+$, 100], 274 [$(M-Br)^+$, 31], 206 (34), 188 (52), 69 (42). Elemental analysis: calcd for $C_{16}H_{20}BrNO_3$: C 54.25, H 5.69, N 3.95, Br 22.56. Found: C 54.46, H 5.71, N 3.91, Br 22.48.

4.9. (αS,3R)-4,4-Dimethyl-2-oxo-1-phenylpyrrolidin-3-yl 2-bromobutyrate, (αS,3R)-7

It was obtained as described for (αR,3S)-**7**. Starting from the same amount of starting components, a mixture of (αS,3R)-**7** and (αR,3R)-**11** (8.36 g, quantitative yield, 9:1 dr, by ^{1}H NMR) was obtained. After a first column chromatography of the crude product, (αS,3R)-**7** (4.85 g) was isolated. After a second column chromatography of the fractions corresponding to mixtures of both diastereomers, a second crop of (αS,3R)-**7** (1.13 g, total yield 5.98 g, 71% yield, >98:2 dr, by ^{1}H NMR) was isolated. $[\alpha]_D^{20} = 38.2$ (*c* 1.15, $CHCl_3$); mp 65–66 °C (hexane/Et_2O 85:15). MS (CI, CH_4), *m*/*z* (%): 384 (13), 382 [$(M+C_2H_5)^+$, 13], 357 (17), 356 (99), 355 (30), 354 [$(M+H)^+$, 100], 353 (14), 274 [$(M-Br)^+$, 24], 206 (18), 188 (31), 69 (14). Elemental analysis: calcd for $C_{16}H_{20}BrNO_3$: C 54.25, H 5.69, N 3.95, Br 22.56. Found: C 53.76, H 5.69, N 3.78, Br 22.44. The R_f, IR, ^{1}H NMR and ^{13}C NMR data of this compound coincide with those of its enantiomer.

4.10. (R)-2-Bromobutyric acid, (R)-5

It was obtained in the same manner described for the preparation of (*S*)-**2** from its pantolactam ester (αS,3S)-**3**. From (αR,3S)-**7** (2.75 g, 7.77 mmol, >98:2 dr) in THF (132 mL), H_2O_2 (30% w/v, 4.07 mL, 35.9 mmol, 4.6 equiv) and $LiOH{\cdot}H_2O$ (0.99 g, 23.6 mmol, 3.0 equiv), (*S*)-**8** (1.53 g, 96% yield, >99% ee, by chiral HPLC) and (*R*)-**5** (1.18 g, 91% yield), $[\alpha]_D^{20} = 33.6$ (*c* 2.74, MeOH) {described for (*S*)-**5** $[\alpha]_D^{28} = -31.0$ (*c* 2.50, MeOH)},[19] were obtained as a white solid and a colourless oil, respectively.

4.11. (S)-2-Bromobutyric acid, (S)-5

It was obtained in a similar manner to that described for (*R*)-**5**. From the same amount of starting materials, (*R*)-**8** (1.57 g, 99% yield, >99% ee, by chiral HPLC) and acid (*S*)-**5** (1.24 g, 96% yield), $[\alpha]_D^{20} = -32.9$ (*c* 2.50, MeOH) {described $[\alpha]_D^{28} = -31.0$ (*c* 2.50, MeOH)},[19] were obtained as a white solid and a colourless oil, respectively.

4.12. (S)-2 from (R)-5

It was obtained as described for the preparation of (*R*)-**2** from (*S*)-**4**. From (*R*)-**5** (1.18 g, 7.07 mmol), after 16 h at room temperature, crude acid (*S*)-**2** (1.54 g) was obtained, which on trituration with Et_2O (6 mL) gave (*S*)-**2** (660 mg, 55% yield) as a white solid, $[\alpha]_D^{20} = -27.3$ (*c* 1.01, acetone) {described $[\alpha]_D^{20} = -26.4$ (*c* 1.00, acetone)};[2] mp 124–126 °C (Et_2O) [described 125.9 °C (toluene)].[2]

4.13. (R)-2 from (S)-5

It was obtained as described for the preparation of (*R*)-**2** from (*S*)-**4**. From (*S*)-**5** (1.30 g, 7.78 mmol), (*R*)-**2** (830 mg, 62% yield) was obtained as a white solid, $[\alpha]_D^{20} = 26.5$ (*c* 1.02, acetone) {described $[\alpha]_D^{20} = 27.3$ (*c* 1.00, acetone)};[20] mp 124–126 °C (Et_2O) (described 126 °C).[20]

4.14. (±)-2-(2-Oxopyrrolidin-1-yl)butyramide, (±)-1

To a cold (0 °C) solution of acid (±)-**2** [500 mg, 2.92 mmol, prepared from (±)-**5** as described for the preparation of (*S*)-**2** from (*R*)-**5**] and Et_3N (0.43 mL, 0.31 g, 3.07 mmol, 1.05 equiv) in anhydrous THF (2 mL), ethyl chloroformate (0.29 mL, 0.33 g, 3.04 mmol, 1.04 equiv) was added and the mixture stirred at 0 °C for 30 min. Ammonium hydroxide (25% w/v aqueous solution, 1.90 mL, 13.6 mmol, 4.6 equiv) was added and the reaction mixture was stirred at room temperature for 16 h. After the addition of K_2CO_3 (414 mg, 3.00 mmol, 1.03 equiv), the mixture was filtered and the volatile materials (solvent and Et_3N) distilled off in vacuo. The solid residue was extracted with CH_2Cl_2 (3 × 8 mL) and the combined organic extracts dried over Na_2SO_4 and concentrated in vacuo, to give a crude amide (±)-**1** (429 mg, 86% yield) as a yellowish solid. Recrystallization from acetone (10 mL) gave (±)-**1** (328 mg, 66% yield) as a white solid, mp 113–114 °C (acetone) [described 122 °C (AcOEt)].[22] Chiral HPLC, conditions A: (*R*)-**1**, rt 21.13 min; (*S*)-**1**, rt 27.31 min; $k'_1 = 3.70$, $k'_2 = 5.07$; $\alpha = 1.37$; Res = 3.38.

4.15. (S)-2-(2-Oxopyrrolidin-1-yl)butyramide, (S)-1

It was obtained in a similar manner to that described for (±)-**1**. From (*S*)-**2** (454 mg, 2.65 mmol), (*S*)-**1** (361 mg, 80% yield, 92% ee, by chiral HPLC, conditions A) was obtained as a yellowish solid. On recrystallization from acetone (10 mL), (*S*)-**1** (293 mg, 65% yield, >99% ee, by chiral HPLC) was obtained as a white solid, $[\alpha]_D^{20} = -90.5$ (*c* 0.99, acetone) {described $[\alpha]_D^{25} = -90.0$ (*c* 1.00, acetone)};[2] chiral HPLC:

rt 27.31 min; mp 115–117 °C (acetone) [described 117 °C (AcOEt)].[2]

4.16. (*R*)-2-(2-Oxopyrrolidin-1-yl)butyramide, (*R*)-1

It was obtained in a similar manner to that described for (±)-**1**. From (*R*)-**2** (960 mg, 5.61 mmol), (*R*)-**1** (859 mg, 90% yield, 91% ee, by chiral HPLC, conditions A) was obtained as a yellowish solid. On recrystallization from acetone (3 mL), (*R*)-**1** (605 mg, 63% yield, >99% ee, by chiral HPLC) was obtained as a white solid, $[\alpha]_D^{20} = 89.8$ (*c* 1.00, acetone) {described $[\alpha]_D^{25} = 90.7$ (*c* 1.00, acetone)};[20] chiral HPLC: rt 21.13 min; mp 114–116 °C (acetone) [described 115–117 °C (AcOEt)].[20]

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