Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron: Asymmetry
Tetrahedron: *Asymmetry* 18 (2007) 2947–2958

Enantiodivergent synthesis of 3-amino-4,4-dimethyl-1-phenylpyrrolidin-2-one and derivatives: amino analogues of pantolactone

Pelayo Camps,[a,*] Diego Muñoz-Torrero,[a,*] Jordi Rull,[a] Mercè Font-Bardia[b] and Xavier Solans[b]

[a]*Laboratori de Química Farmacèutica (Unitat Associada al CSIC), Facultat de Farmàcia and Institut de Biomedicina de la Universitat de Barcelona (IBUB), Universitat de Barcelona, Av. Diagonal, 643, E-08028 Barcelona, Spain*
[b]*Serveis Científico-Tècnics, Universitat de Barcelona, Av. Martí Franquès, s/n, E-08028 Barcelona, Spain*

Received 5 November 2007; accepted 13 November 2007
Available online 3 December 2007

In memoriam of Professor Dr. Xavier Solans

Abstract—An enantiodivergent preparation of (+)-(*R*)- and (−)-(*S*)-3-amino-4,4-dimethyl-1-phenylpyrrolidin-2-one, (*R*)- and (*S*)-**9**, and several derivatives, from 4,4-dimethyl-1-phenylpyrrolidin-2,3-dione, **4**, and (*R*)- or (*S*)-1-phenylethylamine, (*R*)- or (*S*)-**5**, as the chirality transfer agents, is described. Amine (*S*)-**9** has also been used as a chiral auxiliary in a diastereoselective Michael reaction.

1. Introduction

(*R*)-Pantolactone, (*R*)-**1** (Fig. 1), is a chiral auxiliary, which has been widely used in the past in different diastereoselective transformations.[1] As chiral auxiliaries, (*R*)- and (*S*)-pantolactone have several drawbacks: (i) they are highly hygroscopic compounds, which makes their recovery difficult; (ii) they lack a good chromophore for easy UV detection; and (iii) the (*S*)-pantolactone is about 9-times more expensive than its (*R*)-enantiomer. Several years ago, we developed (*R*)- and (*S*)-3-hydroxy-4,4-dimethyl-1-phenylpyrrolidin-2-one, (*R*)- and (*S*)-*N*-phenylpantolactam, (*R*)- and (*S*)-**2** (Fig. 1),[2,3] as chiral auxiliaries closely related to pantolactone with improved properties: (i) non-hygroscopic crystalline compounds; (ii) easily UV-detectable; and (iii) both enantiomers equally available. These novel chiral auxiliaries have been successfully used in different diastereoselective reactions including the deracemization of α-arylpropionic acids, asymmetric Diels–Alder reactions, dynamic kinetic resolutions of α-halo esters and as resolution agents.[1,4–6] As a continuation of our work on chiral auxiliaries related to pantolactone, we herein report the preparation of (*R*)- and (*S*)-3-amino-4,4-dimethyl-1-phenylpyrrolidin-2-ones of general structure **3** (Fig. 1) and other derivatives, such as (*S*,*S*)-**15** (Scheme 3) and (*S*,*S*)-**18** (Scheme 4), as potential new chiral auxiliaries or chiral ligands.

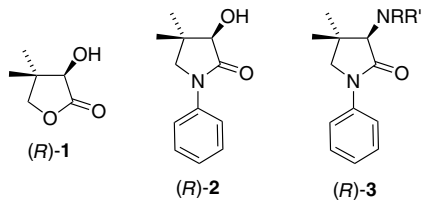


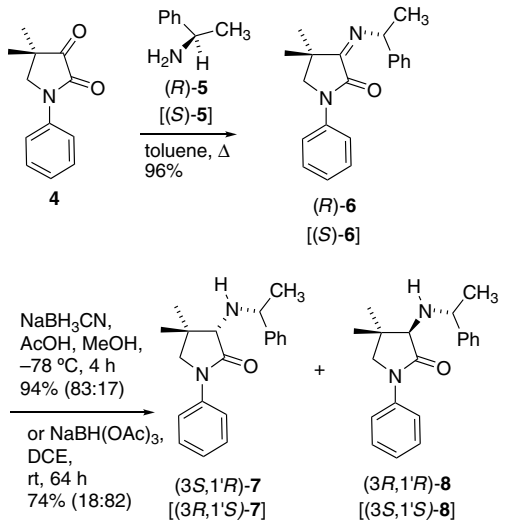
Figure 1. Structures of (*R*)-pantolactone, (*R*)-**1**, (*R*)-*N*-phenylpantolactam, (*R*)-**2**, and substituted (*R*)-3-amino-*N*-phenylpantolactams, (*R*)-**3**.

2. Results and discussion

To prepare these amines in enantiopure form, we chose (*R*)- and (*S*)-1-phenylethylamine, (*R*)- and (*S*)-**5**, as the chirality transfer agents, since both enantiomers are inexpensive and easily available (Scheme 1). The reaction of the known,[3] 4,4-dimethyl-1-phenylpyrrolidine-2,3-dione **4** with

* Corresponding authors. Tel.: +34 93 4024536/4024533; fax: +34 93 4035941; e-mail addresses: camps@ub.edu; dmunoztorrero@ub.edu

0957-4166/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetasy.2007.11.013



Scheme 1. Diastereoselective preparation of amines (3*S*,1′*R*)-**7** and (3*R*,1′*R*)-**8** and their enantiomers (conditions and yields are only given for the firstly indicated enantiomeric series).

(*R*)-**5** in toluene at reflux with azeotropic distillation of the water formed in a Dean–Stark equipment[7] gave almost quantitatively the corresponding imine (*R*)-**6**. It is noteworthy that no racemization of (*R*)-**6** was observed, a process that could have taken place by tautomerization under acidic or basic catalysis. Reduction of imine (*R*)-**6** was studied under different conditions (Table 1). Hydrogenation using different catalysts and conditions gave poor diastereoselectivities (entries 1–4), while sodium cyanoborohydride reduction[8] of (*R*)-**6** in MeOH at −78 °C gave a mixture of (3*S*,1′*R*)-**7** and (3*R*,1′*R*)-**8** in the ratio of 83:17 (entry 5). The use of this reducing agent at higher temperatures gave lower diastereoselectivities (entries 6 and 7).

Table 1. Conditions, yields and diastereoselectivities in the reductions of (*R*)-**6**[a]

Entry	Reducing agent	Solvent	*t* (h)	*P* (atm)	*T* (°C)	dr[a]	Yield (%)
1	H_2/PtO_2	EtOH[b]	10	1	25	60:40	61
2	H_2/10% Pt/C	EtOH[b]	22	1	25	60:40	70
3	H_2/10% Pt/C	EtOH[b]	20	30	25	60:40	62
4	H_2/Raney Ni	EtOH[b]	18	1	25	70:30	56
5	$NaBH_3CN$	MeOH[c]	4	1	−78	83:17	94
6	$NaBH_3CN$	MeOH[c]	20	1	25	70:30	56
7	$NaBH_3CN$	MeOH[c]	1.5	1	−20	73:27	77
8	$NaBH(OAc)_3$	DCE[c]	64	1	25	18:82	74

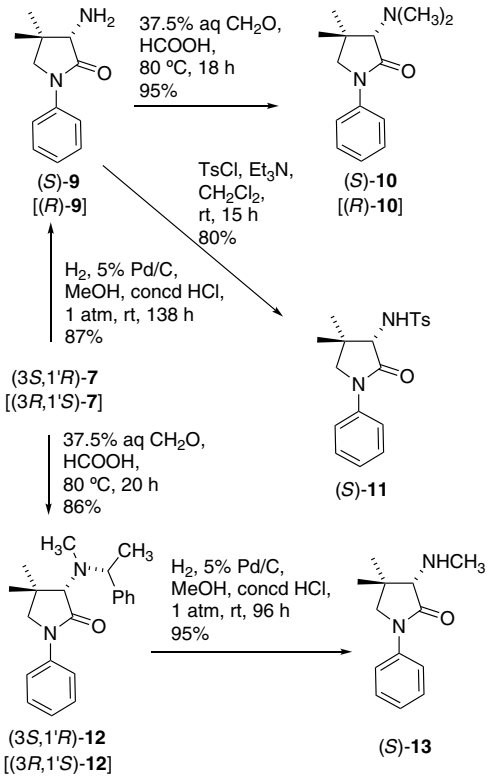
[a] The dr was established by integration of the signal of 3-H in the ^1H NMR spectra of the mixtures.
[b] Absolute EtOH was used.
[c] Anhyd MeOH and DCE were used.

Interestingly, the reduction of (*R*)-**6** with sodium triacetoxyborohydride[9] in DCE at room temperature gave a mixture of (3*S*,1′*R*)-**7** and (3*R*,1′*R*)-**8** in the ratio of 18:82. Isolation of the main diastereoisomer (3*S*,1′*R*)-**7** from the $NaBH_3CN$ reduction of (*R*)-**6** was carried out very conveniently on a gram scale in 66% yield by crystallization of the corresponding mixture of monomaleates from an *i*-PrOH/Et_2O mixture in the ratio of 1:3 (approximately 20 mL/g). From this salt, the free amine was obtained in a conventional way.

Curiously, attempts to apply the same procedure for isolation of the main diastereoisomer (3*R*,1′*R*)-**8** from the $NaBH(OAc)_3$ reduction of (*R*)-**6** failed to give any solid salt. In this case, the isolation of the more polar (3*R*,1′*R*)-**8** was carried out by silica gel column chromatography (heptane/AcOEt mixtures).

The same set of transformations was carried out by using (*S*)-**5** as the chirality transfer agent.

Since we were unable to obtain a single crystal of the (3*S*,1′*R*)-**7** monomaleate salt for X-ray diffraction analysis, to establish its absolute configuration it was transformed into amine (*S*)-**9** by hydrogenation using 5% Pd/C as the catalyst[10] (Scheme 2). For characterization purposes, amine (*S*)-**9** was transformed into its *p*-nitrobenzoate salt. Moreover, in this case, we could obtain a single crystal of a 1:1 salt of (*S*)-**9** and (−)-*O*,*O*-di-*p*-toluoyl-L-tartaric acid and perform an X-ray diffraction analysis (Fig. 2).[11] By knowing the absolute configuration of (*S*)-**9** we could deduce those of amines **7** and **8**.



Scheme 2. Preparation of (*S*)- and (*R*)-**9**, and derivatives from (3*S*,1′*R*)- and (3*R*,1′*S*)-**7** (conditions and yields are only given for the first indicated enantiomeric series).

Similarly, amine (*R*)-**9** was obtained by hydrogenation of (3*R*,1′*S*)-**7**. Also, we obtained (*R*)-**9** by hydrogenation of (3*R*,1′*R*)-**8**. The preparation of (*S*)- and (*R*)-**9** via (3*S*,1′*R*)-**7** and (3*R*,1′*R*)-**8**, respectively, both obtained as

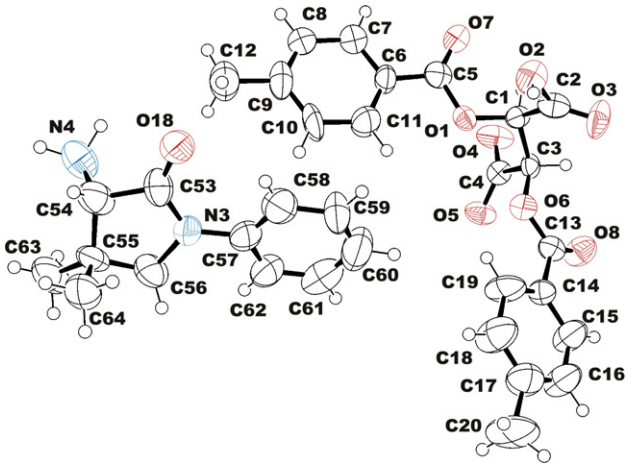
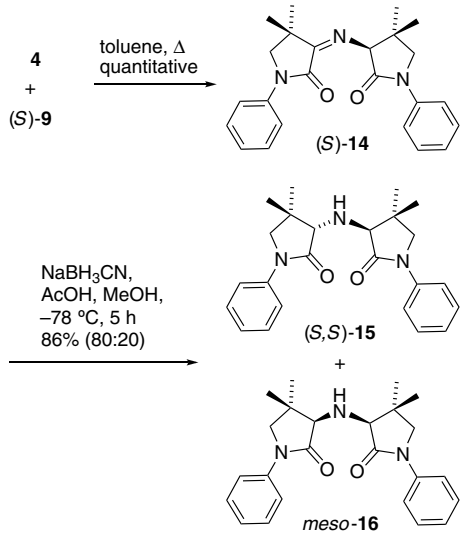


Figure 2. ORTEP representation of (*S*)-**9** mono-*O*,*O*-di-*p*-toluoyl-L-tartrate.

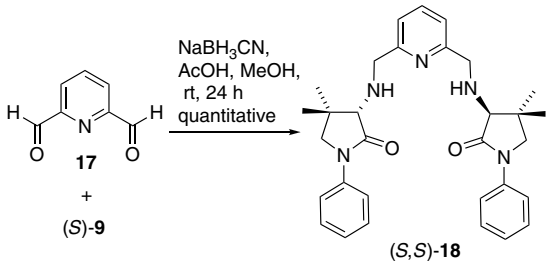
main products from **4** and the same chiral auxiliary, (*R*)-**5**, constitutes an example of enantiodivergent synthesis. Altogether, we have developed an easy access to both enantiomers of amines **7**, **8** and **9** on a gram scale.

These amines were transformed into several simple derivatives. Thus, (*S*)-**9** was dimethylated by reaction with 37.5% aqueous formaldehyde and formic acid[12] to give amine (*S*)-**10** in high yield. The corresponding monomethylated amine, (*S*)-**13**, was obtained by methylation of (3*S*,1′*R*)-**7** as before to give (3*S*,1′*R*)-**12**, followed by Pd/C hydrogenation. Also, tosylamide (*S*)-**11** was obtained in good yield by reaction of (*S*)-**9** with tosyl chloride.[13] Similarly from (3*R*,1′*S*)-**7** or (*R*)-**9**, amines (*R*)-**10** and (3*R*,1′*S*)-**12** were obtained in good yields.

In connection with the preparation of chiral ligands able to polycoordinate with cations to give potential catalysts for enantioselective transformations, we planned the preparation of derivatives of (*S*)-**9** such as (*S*,*S*)-**15** (Scheme 3) or (*S*,*S*)-**18** (Scheme 4).



Scheme 3. Preparation of (*S*,*S*)-**15**.



Scheme 4. Preparation of amine (*S*,*S*)-**18**.

Reaction of ketopantolactam **4** and amine (*S*)-**9** in toluene at reflux with azeotropic distillation of the water formed and in the absence of any catalyst quantitatively gave imine (*S*)-**14** with a high value of its specific rotation, which suggested that no racemization had taken place. Reduction of this imine with $NaBH_3CN$, as previously described for (*R*)-**6**, gave a mixture of (*S*,*S*)-**15** and *meso*-**16**, in a ratio of 80:20 (^1H NMR) in good yield. Column chromatography (aluminum oxide) of this mixture gave pure (*S*,*S*)-**15**, which was fully characterized as such including an X-ray diffraction analysis (Fig. 3).[11] Not enough of *meso*-**16** could be isolated for complete characterization.

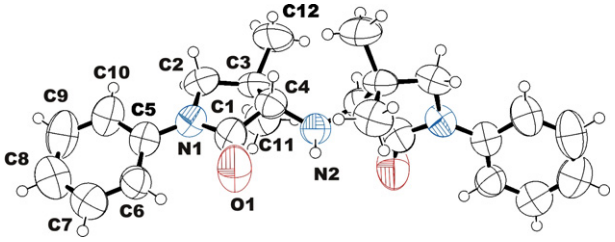
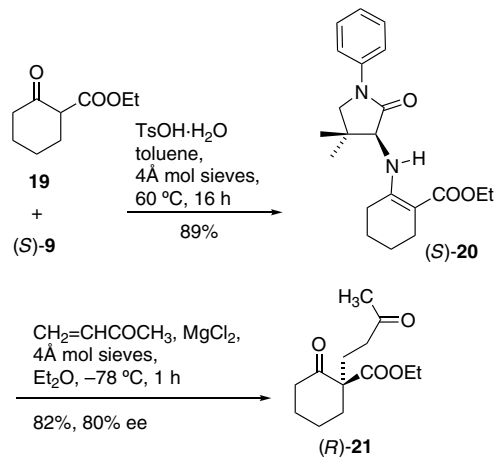


Figure 3. ORTEP representation of (*S*,*S*)-**15**.

Finally, reductive amination of pyridine-2,6-dicarboxaldehyde, **17**, with (*S*)-**9** using $NaBH_3CN$ as the reducing agent, gave triamine (*S*,*S*)-**18** in high yield, which was characterized as its dihydrochloride.

The new amine (*S*)-**9** has successfully been used as a chiral auxiliary in a Michael reaction. Thus, the reaction of ethyl 2-oxocyclohexanecarboxylate, **19**, with (*S*)-**9** under acidic catalysis gave the corresponding enamine (*S*)-**20**, which was reacted with methyl vinyl ketone to give the Michael adduct (*R*)-**21** in 82% yield and 80% ee, established by chiral GC/MS (Scheme 5). This result is comparable to those described by Guingant and d'Angelo using the enamine derived from **19** and (*R*)-1-phenylethylamine.[14–16]

Conversely, all attempts to use the in situ generated complexes of amines (*S*)-**10**, (*S*,*S*)-**15**, and (*S*,*S*)-**18** with $Cu(OTf)_2$, $Sc(OTf)_3$, and $Yb(OTf)_3$, as enantioselective catalysts in the Diels–Alder reaction of *N*-acryloyloxazolidin-2-one and cyclopentadiene in the absence of additives or in the presence of 2,6-lutidine at temperatures from −78 to 0 °C, following the procedure described by Evans et al.,[17] gave good yields of essentially racemic adducts in all cases.



Scheme 5. Diastereoselective Michael addition using (*S*)-**9** as a chiral auxiliary.

Attempts to use tosylate (*S*)-**11** in conjunction with $[RuCl_2(\eta^6(mesitylene)_2]_2$ as a transfer hydrogenation catalyst in the enantioselective reduction of *p*-chloroacetophenone with isopropanol, following a similar procedure to that described by Noyori and co-workers,[18] required the use of a 1–5% molar ratio of catalyst and room temperature for acceptable conversions, always yielding essentially racemic 1-(4-chlorophenyl) ethanol.

3. Conclusion

In conclusion, we have developed an enantiodivergent preparation of amines (*R*)- and (*S*)-**9** from ketopantolactam **4** using (*R*)-1-phenylethylamine as the chirality transfer agent. Several derivatives of (*R*)- or (*S*)-**9** have also been prepared, two of which contain two units of (*S*)-**9**. Amine (*S*)-**9** has shown to be an efficient chiral auxiliary in a Michael reaction. However, Cu(II), Sc(III), or Yb(III) complexes of amines (*S*)-**10**, (*S*,*S*)-**15**, and (*S*,*S*)-**18** failed to induce noticeable enantioselectivity in a Diels–Alder reaction, as it was also the case in a transfer hydrogenation reaction catalyzed by a Ru(II) complex of amine (*S*)-**11**. Hopefully, these new amines could be useful as chiral auxiliaries or chiral ligands in other asymmetric transformations.

4. Experimental

4.1. General experimental detail

Melting points were determined in open capillary tubes. Unless otherwise stated, NMR spectra were recorded in $CDCl_3$: ^1H NMR (300 MHz), ^{13}C NMR (75.4 MHz). Chemical shifts (δ) are reported in ppm related to internal tetramethylsilane (TMS). Assignments given for the NMR spectra are based on DEPT sequence and comparison with 3-hydroxy-4,4-dimethyl-1-phenylpyrrolidin-2-one, **2**. Unless otherwise stated, IR spectra were performed in KBr pellets and the absorption values are given as wavenumbers (cm^{-1}). For chiral HPLC analyses, a Chiralcel OD-H column (25×0.46 cm) containing the chiral stationary phase cellulose tris(3,5-dimethylphenylcarbamate) was used. Conditions A (mixture of hexane/EtOH/Et_2NH 98:2:0.1 as eluent, flow 0.3 mL/min, $\lambda = 254$ nm). For chiral GC/MS analyses, a 30-m (0.25 mm internal diameter) chiral column [containing permethylated β-cyclodextrine (0.25 μm) as the chiral stationary phase; Conditions A: 10 psi, initial temperature: 80 °C (1 min), then heating at a range of 10 °C min^{-1} till 125 °C, after 2 min at this temperature, heating at a range of 0.5 °C min^{-1} till 240 °C, then isothermic] was used. Optical rotations were determined on a polarimeter using 1-dm cells. Column chromatography was performed on silica gel 60 A C.C (35–70 mesh) or basic aluminum oxide. For the thin layer chromatography (TLC), aluminum-backed sheets with silica gel 60 F_{254} or aluminum oxide ALOX N/UV_{254} were used and spots were visualized with UV light and/or 1% aqueous $KMnO_4$.

4.2. (*R*)-4,4-Dimethyl-1-phenyl-3-[(1-phenylethyl)imino]-pyrrolidin-2-one (*R*)-6

A solution of 4,4-dimethyl-1-phenylpyrrolidine-2,3-dione, **4** (4.00 g, 19.7 mmol), and (*R*)-1-phenylethylamine, (*R*)-**5** (2.55 mL, 2.40 g, 19.7 mmol) in toluene (120 mL) was heated at reflux for 24 h in a Dean–Stark equipment. Evaporation of the solvent under reduced pressure gave imine (*R*)-**6** (5.81 g, 96% yield), as a brownish oil. R_f 0.61 (aluminum oxide, 7.8 cm, hexane/AcOEt 9:1); $[\alpha]_D^{20} = +159$ (*c* 0.57, CH_2Cl_2); IR (NaCl) 3082, 3062, 3029, 2970, 2927, 2889, 2867, 1693 (C=O st), 1674 (C=N st), 1597, 1495, 1483, 1458, 1452, 1400, 1377, 1364, 1342, 1319, 1283, 1245, 1187, 1128, 1070, 1048, 760, 700, 690 cm^{-1}; ^1H NMR 1.31 (s, 3H) and 1.36 (s, 3H) [C4–$(CH_3)_2$], 1.48 (d, $J = 6.3$ Hz, 3H, C*H*$_3$–CHPh), 3.70 (s, 2H, 5-H_2), 6.53 (q, $J = 6.3$ Hz, 1H, CH_3–C*H*Ph), 7.18–7.27 (complex signal, 2H, H_{para} N–Ph and H_{para} C–Ph), 7.32 (ddm, $J = J' = 7.5$ Hz, 2H) and 7.41 (ddm, $J = J' = 8.1$ Hz, 2H) (H_{meta} N–Ph and H_{meta} C–Ph), 7.50 (dm, $J = 8.1$ Hz, 2H) and 7.70 (dm, $J = 7.5$ Hz, 2H) (H_{ortho} C–Ph and H_{ortho} N–Ph); ^{13}C NMR 25.3 (CH_3), 25.8 (CH_3) and 26.7 (CH_3) [C4–(*C*H_3)$_2$ and *C*H_3CHPh], 37.8 (C, C4), 56.4 (CH, CH_3*C*HPh), 58.2 (CH_2, C5), 119.7 (CH, C_{ortho} N–Ph), 125.6 (CH) and 126.4 (CH) (C_{para} N–Ph and C_{para} C–Ph), 126.6 (CH, C_{ortho} C–Ph), 128.2 (CH) and 128.9 (CH) (C_{meta} N–Ph and C_{meta} C–Ph), 139.1 (C, C_{ipso} N–Ph), 146.4 (C, C_{ipso} C–Ph), 159.3 (C, C3), 164.2 (C, C2). Anal. Calcd for $C_{20}H_{22}N_2O{\cdot}0.5H_2O$: C, 76.16; H, 7.35; N, 8.88. Found: C, 76.35; H, 7.02; N, 8.86.

4.3. (*S*)-4,4-Dimethyl-1-phenyl-3-[(1-phenylethyl)imino]-pyrrolidin-2-one (*S*)-6

This compound was prepared as described before for (*R*)-**6**. From 4,4-dimethyl-1-phenylpyrrolidine-2,3-dione, **4** (5.00 g, 24.6 mmol), and (*S*)-1-phenylethylamine, (*S*)-**5** (3.20 mL, 2.99 g, 24.6 mmol), (*S*)-**6** (7.51 g, quantitative yield) was obtained as a brownish oil. The R_f, IR, ^1H, and ^{13}C NMR data are coincidental with those of (*R*)-**6**. $[\alpha]_D^{20} = -161$ (*c* 0.57, CH_2Cl_2). Anal. Calcd for $C_{20}H_{22}N_2O{\cdot}0.5H_2O$: C, 76.16; H, 7.35; N, 8.88. Found: C, 76.38; H, 7.12; N, 8.85.

4.4. (3*S*,1′R)-4,4-Dimethyl-1-phenyl-3-[(1-phenylethyl)amino]pyrrolidin-2-one monomaleate (3*S*,1′*R*)-7 monomaleate

To a cold (−78 °C) solution of (*R*)-**6** (1.07 g, 3.50 mmol) in anhydrous MeOH (100 mL), a solution of $NaBH_3CN$ (470 mg, 7.48 mmol) and AcOH (0.25 mL, 4.4 mmol) in MeOH (30 mL) was added dropwise and the reaction mixture was stirred at this temperature for 4 h. Water (100 mL) was then added. The organic solvent was evaporated under reduced pressure and the remaining aqueous phase was treated with aqueous 2 M NaOH till pH 12–13 and extracted with CH_2Cl_2 (3 × 100 mL). The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give a diastereomeric mixture of (3*S*,1′*R*)-**7** and (3*R*,1′*R*)-**8** in a ratio of 83:17 (^{1}H NMR) (1.01 g, 94% yield). HPLC (conditions A), (3*S*,1′*R*)-**7**, t_R 18.5 min; (3*R*,1′*R*)-**8**, t_R 22.1 min.

An aliquot of the above mixture (588 mg, 1.91 mmol) was taken in *i*-PrOH (0.75 mL), treated with a solution of maleic acid (243 mg, 2.09 mmol) in *i*-PrOH (1.5 mL) and the mixture was concentrated to dryness in vacuo. The solid obtained was taken in *i*-PrOH (3 mL), Et_2O (9 mL) was added, and the mixture was cooled to 3 °C for 24 h. The precipitated solid was collected by filtration and washed with a mixture *i*-PrOH/Et_2O 1:3 (3 × 5 mL) to give, after drying, (3*S*,1′*R*)-**7** monomaleate (536 mg, 66% yield), mp 126–127 °C (*i*-PrOH/Et_2O 1:3); $[\alpha]_D^{20} = -21$ (*c* 0.61, EtOH); IR 3500–2400 (max at 3406, 2981, 2836, 2663, 2555, 2476, O–H st, $^+$N–H st and C–H st), 1710 (C=O st), 1622, 1592, 1522, 1484, 1457, 1411, 1391, 1354, 1324, 1308, 1279, 1205, 1050, 869, 760, 700, 692, 644 cm^{-1}; ^{1}H NMR 1.27 (s, 3H) and 1.30 (s, 3H), [C4–(CH_3)$_2$], 1.72 (d, $J = 6.9$ Hz, 3H, CH_3CHPh), 3.48 (d, $J = 9.6$ Hz, 1H) and 3.56 (d, $J = 9.6$ Hz, 1H) (5-H_2), 3.60 (s, 1H, 3-H), 4.68 (q, $J = 6.9$ Hz, 1H, CH_3C*H*Ph), 6.25 [s, 2H, 2(3)-H maleate], 7.18 (t, $J = 7.5$ Hz, 1H, H_{para} N–Ph), 7.32–7.40 (complex signal, 5H, H_{meta} N–Ph, H_{meta} C–Ph, H_{para} C–Ph), 7.50 (dm, $J = 8.1$ Hz, 2H) and 7.54 (br d, $J = 7.8$ Hz, 2H) (H_{ortho} N–Ph, H_{ortho} C–Ph), 11.3 (br signal, $^+NH_2$ and COOH); ^{13}C NMR 19.5 (CH_3), 21.0 (CH_3) and 25.0 (CH_3) [C4–(*C*H_3)$_2$ and *C*H_3CHPh], 38.0 (C, C4), 58.6 (CH, CH_3*C*HPh), 58.9 (CH_2, C5), 65.3 (CH, C3), 119.9 (CH, C_{ortho} N–Ph), 125.5 (CH), 127.7 (CH), 129.0 (CH) and 129.1 (CH) (C_{meta} and C_{para} N–Ph, C_{ortho}, C_{meta} and C_{para} C–Ph), 135.2 [CH, C2(3) maleate], 137.9 (C) and 138.3 (C) (C_{ipso} N–Ph and C_{ipso} C–Ph), 168.7 (C) and 169.0 (C) (C2 and COO). Anal. Calcd for $C_{20}H_{24}N_2O\cdot C_4H_4O_4\cdot 0.1H_2O$: C, 67.62; H, 6.67; N, 6.57. Found: C, 67.44; H, 6.76; N, 6.47.

A sample of (3*S*,1′*R*)-**7** as the free base was obtained as follows: (3*S*,1′*R*)-**7** monomaleate (536 mg, 1.26 mmol) was taken in CH_2Cl_2 (10 mL), the solution was washed with aqueous 2 M NaOH (3 × 10 mL), dried over anhydrous Na_2SO_4 and concentrated in vacuo to give (3*S*,1′*R*)-**7** [339 mg, 87% yield, 98.4% area ratio (ar) by HPLC] as a colorless oil. R_f 0.75 (aluminum oxide, 6.5 cm, hexane/AcOEt 9:1); $[\alpha]_D^{25} = -57.2$ (*c* 1.2, CH_2Cl_2); ^{1}H NMR (400 MHz) 1.11 (s, 3H) and 1.24 (s, 3H), [C4–(CH_3)$_2$], 1.42 (d, $J = 6.6$ Hz, 3H, CH_3CHPh), 2.2–2.6 (br signal, 1H, N–H), 3.14 (s, 1H, 3-H), 3.30 (d, $J = 9.4$ Hz, 1H) and 3.39 (d, $J = 9.4$ Hz, 1H) (5-H_2), 3.99 (q, $J = 6.6$ Hz, 1H, CH_3C*H*Ph), 7.11 (tm, $J = 7.4$ Hz, 1H, H_{para} N–Ph), 7.23 (tm, $J = 7.4$ Hz, 1H, H_{para} C–Ph), 7.31–7.37 (complex signal, 6H, H_{meta} N–Ph, H_{ortho} and H_{meta} C–Ph), 7.56 (dm, $J = 8.4$ Hz, 2H, H_{ortho} N–Ph); ^{13}C NMR (100.6 MHz) 21.3 (CH_3), 24.6 (CH_3) and 25.7 (CH_3) [C4–(*C*H_3)$_2$ and *C*H_3CHPh], 38.6 (C, C4), 57.2 (CH, CH_3*C*HPh), 58.1 (CH_2, C5), 66.1 (CH, C3), 119.3 (CH, C_{ortho} N–Ph), 124.4 (CH), 126.7 (CH), 127.0 (CH), 128.6 (CH) and 128.8 (CH) (C_{meta} and C_{para} N–Ph, C_{ortho}, C_{meta} and C_{para} C–Ph), 139.5 (C) and 144.7 (C) (C_{ipso} N–Ph and C_{ipso} C–Ph), 173.7 (C, C2).

4.5. (3*R*,1′*S*)-4,4-Dimethyl-1-phenyl-3-[(1-phenylethyl)amino]pyrrolidin-2-one monomaleate (3*R*,1′*S*)-7 monomaleate

This compound was prepared as described before for (3*S*,1′*R*)-**7** monomaleate. From imine (*S*)-**6** (7.50 g, 24.5 mmol), $NaBH_3CN$ (3.32 g, 52.8 mmol) and AcOH (1.70 mL, 29.7 mmol), a diastereomeric mixture (3*R*,1′*S*)-**7** and (3*S*,1′*S*)-**8** in a ratio of 82:18 (^{1}H NMR) (7.03 g, 93% yield) was obtained. HPLC (conditions A), (3*R*,1′*S*)-**7**, t_R 18.6 min; (3*S*,1′*S*)-**8**, t_R 22.2 min. The monomaleate of this mixture was formed as before by the addition of a solution of maleic acid (2.91 g, 25.1 mmol) in *i*-PrOH to a solution of the above mixture of (3*R*,1′*S*)-**7** and (3*S*,1′*S*)-**8** in the same solvent. After concentration to dryness in vacuo, the mixture of maleates was crystallized from *i*-PrOH/Et_2O in the ratio of 1:3 to give (3*R*,1′*S*)-**7** monomaleate (6.47 g, 67% yield). The mp, IR, ^{1}H, and ^{13}C NMR data of this compound are coincidental with those of (3*S*,1′*R*)-**7** monomaleate. $[\alpha]_D^{20} = +19$ (*c* 0.54, EtOH). Anal. Calcd for $C_{20}H_{24}N_2O\cdot C_4H_4O_4\cdot 0.05H_2O$: C, 67.76; H, 6.66; N, 6.59. Found: C, 67.47; H, 6.64; N, 6.44. A sample of (3*R*,1′*S*)-**7** as the free base was obtained from (3*R*,1′*S*)-**7** monomaleate as described before (98.5% ar). The R_f, ^{1}H and ^{13}C NMR data of this base are coincidental with those of its enantiomer, $[\alpha]_D^{25} = +57.7$ (*c* 1.0, CH_2Cl_2).

4.6. (3*R*,1′*R*)-4,4-Dimethyl-1-phenyl-3-[(1-phenylethyl)amino]pyrrolidin-2-one hydrochloride (3*R*,1′*R*)-8·HCl

AcOH (100 μL, 1.75 mmol) was added dropwise to a suspension of $NaBH_4$ (22 mg, 0.58 mmol) in anhydrous DCE (2 mL) and the mixture was heated at reflux for 30 min. The solution of $NaBH(OAc)_3$ thus obtained was allowed to cool to room temperature, a solution of (*R*)-**6** (100 mg, 0.33 mmol) in anhydrous DCE (1.5 mL) was added and the reaction mixture was stirred at room temperature for 64 h. The resulting mixture was cooled in an ice-water bath and aqueous 5 M HCl (2 mL) was slowly added. When gas evolution ceased, the mixture was basified with aqueous 2 M NaOH (10 mL), the organic phase was separated and washed with aqueous 2 M NaOH (3 × 15 mL), dried over anhydrous Na_2SO_4 and concentrated in vacuo to give a diastereomeric mixture of amines (3*S*,1′*R*)-**7** and (3*R*,1′*R*)-**8** in a ratio of 18:82 (75 mg, 74% yield).

A diastereomeric mixture of amines (3*S*,1′*R*)-**7** and (3*R*,1′*R*)-**8** in a ratio of 23:77 (2.45 g), from several reductions of (*R*)-**6** with $NaBH(OAc)_3$ under different reaction conditions, was subjected to column chromatography (silica gel, 125 g, heptane/AcOEt mixtures). On elution with heptane/AcOEt in the ratio of 10:1, in the order of elution were obtained (3*S*,1′*R*)-**7** (290 mg), a diastereomeric mixture of (3*S*,1′*R*)-**7** and (3*R*,1′*R*)-**8** (ratio 1:1, 440 mg), and pure (3*R*,1′*R*)-**8** (1.38 g, 73% recovery). A solution of HCl in MeOH (1.81 N, 4 mL) was added to a solution of (3*R*,1′*R*)-**8** (1.00 g, 3.25 mmol) in MeOH (5 mL) and the solution was concentrated in vacuo to give a yellow solid (1.12 g), which was crystallized from a mixture MeOH/Et_2O 1:2 (5 mL) to give (3*R*,1′*R*)-**8**·HCl as a yellow solid.

(3*R*,1′*R*)-**8**: R_f 0.67 (aluminum oxide, 6.5 cm, hexane/AcOEt 9:1); HPLC (conditions A), t_R 22.09 min, 98.4% ar; $[\alpha]_D^{25} = +128$ (*c* 1.3, CH_2Cl_2); ^{1}H NMR 0.91 (s, 3H) and 1.01 (s, 3H), [C4–(CH_3)$_2$], 1.43 (d, $J = 6.6$ Hz, 3H, CH_3CHPh), 1.70 (br signal, 1H, N–H), 3.00 (s, 1H, 3-H), 3.29 (d, $J = 9.3$ Hz, 1H) and 3.38 (d, $J = 9.3$ Hz, 1H) (5-H_2), 4.39 (q, $J = 6.6$ Hz, 1 H, CH_3CHPh), 7.12 (tm, $J = 7.5$ Hz, 1H, H_{para} N–Ph), 7.20–7.43 (complex signal, 7H) and 7.59 (dm, $J = 7.8$ Hz, 2H) (H_{ortho} and H_{meta} N–Ph, H_{ortho}, H_{meta} and H_{para} C–Ph); ^{13}C NMR (100.6 MHz) 20.8 (CH_3), 24.3 (CH_3) and 25.1 (CH_3) [C4–(CH_3)$_2$ and CH_3CHPh], 37.8 (C, C4), 57.6 (CH, CH_3CHPh), 58.1 (CH_2, C5), 67.2 (CH, C3), 119.4 (CH, C_{ortho} N–Ph), 124.3 (CH, C_{para} N–Ph), 127.0 (CH), 127.5 (CH), 128.2 (CH) and 128.8 (CH) (C_{meta} N–Ph, C_{ortho}, C_{meta} and C_{para} C–Ph), 139.7 (C, C_{ipso} N–Ph), 144.8 (C, C_{ipso} C–Ph), 173.9 (C, C2).

(3*R*,1′*R*)-**8**·HCl: mp 153–154 °C (MeOH/Et_2O 1:2); $[\alpha]_D^{20} = +126$ (*c* 0.51, MeOH); IR 3500–2400 (max at 3396, 3033, 2958, 2930, 2873, 2783, 2725, 2680, 2658, 2523, 2437, $^+$N–H st and C–H st), 1708 (C=O st), 1597, 1499, 1458, 1422, 1410, 1391, 1327, 1209, 1121, 1067, 764, 703 cm^{-1}; ^{1}H NMR (D_2O) 1.12 (s, 3H) and 1.28 (s, 3H), [C4–(CH_3)$_2$], 1.81 (d, $J = 6.9$ Hz, 3H, CH_3CHPh), 3.56 (d, $J = 9.9$ Hz, 1H) and 3.67 (d, $J = 9.9$ Hz, 1H) (5-H_2), 3.79 (s, 1H, 3-H), 4.78 (s, mobile H), 5.15 (q, $J = 6.9$ Hz, 1H, CH_3CHPh), 7.36 (m, 1H, H_{para} N–Ph), 7.46–7.58 (complex signal, 9H, H_{meta} and H_{ortho} N–Ph, H_{meta}, H_{ortho} and H_{para} C–Ph); ^{13}C NMR (D_2O) 19.0 (CH_3), 19.7 (CH_3) and 21.9 (CH_3) [C4–(CH_3)$_2$ and CH_3CHPh], 37.2 (C, C4), 58.9 (CH, CH_3CHPh), 58.9 (CH_2, C5), 64.0 (CH, C3), 121.7 (CH, C_{ortho} N–Ph), 126.7 (CH, C_{para} N–Ph), 127.8 (CH), 129.2 (CH) and 129.6 (CH) (C_{meta} N–Ph, C_{ortho} and C_{meta} C–Ph), 129.9 (CH, C_{para} C–Ph), 135.0 (C, C_{ipso} N–Ph), 137.1 (C, C_{ipso} C–Ph), 168.1 (C, C2). Anal. Calcd for $C_{20}H_{24}N_2O$·HCl·H_2O: C, 66.19; H, 7.50; N, 7.72; Cl, 9.77. Found: C, 66.21; H, 7.52; N, 7.75; Cl, 9.53.

4.7. (3*S*,1′*S*)-4,4-Dimethyl-1-phenyl-3-[(1-phenylethyl)-amino]pyrrolidin-2-one hydrochloride (3*S*,1′*S*)-8·HCl

This compound was prepared as described before for (3*R*,1′*R*)-**8**. From imine (*S*)-**6** (1.05 g, 3.43 mmol) and $NaBH(OAc)_3$ [prepared from AcOH (1.10 mL, 19.2 mmol) and $NaBH_4$ (228 mg, 6.03 mmol)] a diastereomeric mixture of (3*R*,1′*S*)-**7** and (3*S*,1′*S*)-**8** in a ratio of 19:81 (^{1}H NMR) (790 mg, 75% yield) was obtained. Column chromatography (silica gel, 80 g, heptane/AcOEt 15:1) of the above mixture (1.56 g, 5.06 mmol, from two reduction runs) gave in the order of elution (3*R*,1′*S*)-**7** (184 mg), a mixture of (3*R*,1′*S*)-**7** and (3*S*,1′*S*)-**8** in a ratio of 1:1 (280 mg) and (3*S*,1′*S*)-**8** [872 mg, 69% recovery, 98.3 ar by HPLC (conditions A)]. The ^{1}H and ^{13}C NMR data of (3*S*,1′*S*)-**8** are coincidental with those of its enantiomer, $[\alpha]_D^{25} = -130$ (*c* 1.3, CH_2Cl_2).

The hydrochloride of (3*S*,1′*S*)-**8** was formed as before by addition of a solution of HCl in MeOH (1.81 M, 2.5 mL) to a solution of (3*S*,1′*S*)-**8** (600 mg, 1.95 mmol) in MeOH (3 mL). After concentration to dryness in vacuo, the product was crystallized from MeOH/Et_2O 1:2 to give (3*S*,1′*S*)-**8**·HCl (610 mg, 91% yield), mp 151–152 °C (MeOH/Et_2O 1:2). The IR, ^{1}H, and ^{13}C NMR data of this compound are coincidental with those of (3*R*,1′*R*)-**8**·HCl. $[\alpha]_D^{20} = -125$ (*c* 0.54, MeOH). Anal. Calcd for $C_{20}H_{24}N_2O$·HCl·0.75H_2O: C, 67.03; H, 7.45; N, 7.82; Cl, 9.89. Found: C, 67.23; H, 7.56; N, 7.59; Cl, 9.68.

4.8. (*S*)-3-Amino-4,4-dimethyl-1-phenylpyrrolidin-2-one *p*-nitrobenzoate (*S*)-9 *p*-nitrobenzoate

A mixture of (3*S*,1′*R*)-**7** (132 mg, 0.43 mmol), concd HCl (150 μL), and 5% Pd/C (370 mg) in MeOH (12 mL) was hydrogenated at 1 atm and room temperature for 138 h. The mixture was filtered through a pad of Celite® washing the filter with MeOH (25 mL). The filtrate was basified with aqueous 2 M NaOH (12 mL) and extracted with CH_2Cl_2 (3 × 25 mL). The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give (*S*)-**9** (76 mg, 87% yield) as a colorless oil. $[\alpha]_D^{24} = -24.5$ (*c* 1.1, CH_2Cl_2); ^{1}H NMR 1.04 (s, 3H) and 1.29 (s, 3H), [C4–(CH_3)$_2$], 1.53 (br s, 2H, NH_2), 3.34 (s, 1H, 3-H), 3.43 (d, $J = 9.6$ Hz, 1H) and 3.56 (d, $J = 9.6$ Hz, 1H) (5-H_2), 7.15 (tm, $J = 6.9$ Hz, 1H, H_{para}), 7.35–7.40 (m, 2H, H_{meta}), 7.62 (dm, $J = 7.8$ Hz, 2H, H_{ortho}); ^{13}C NMR 20.1 (CH_3) and 24.7 (CH_3) [C4–(CH_3)$_2$], 37.6 (C, C4), 58.3 (CH_2, C5), 62.3 (CH, C3), 119.3 (CH, C_{ortho}), 124.3 (CH, C_{para}), 128.8 (CH, C_{meta}), 139.5 (C, C_{ipso}), 174.8 (C, C2).

An analytical sample of (*S*)-**9** *p*-nitrobenzoate was obtained as follows: amine (*S*)-**9** (118 mg, 0.58 mmol) was taken in MeOH (3 mL) and a solution of *p*-nitrobenzoic acid (101 mg, 0.60 mmol) in MeOH (5 mL) was added. The resulting solution was concentrated to dryness in vacuo and the solid residue was recrystallized from MeOH (4 mL) to give (*S*)-**9** *p*-nitrobenzoate as a white solid (167 mg from two crops, 78% yield). Mp 191–192 °C (MeOH); $[\alpha]_D^{25} = -15$ (*c* 0.51, MeOH); IR 3500–2500 (max at 3437, 3110, 2981, 2960, 2938, 2882, 2664, O–H st, $^+$N–H st and C–H st), 1718 (C=O st), 1595, 1564, 1537 (N=O st), 1497, 1482, 1414, 1388, 1344 (N=O st), 1280, 824, 802, 761, 728 cm^{-1}; ^{1}H NMR (CD_3OD) 1.16 (s, 3H) and 1.38 (s, 3H), [C4–(CH_3)$_2$], 3.60 (d, $J = 9.6$ Hz, 1H) and 3.79 (d, $J = 9.6$ Hz, 1H) (5-H_2), 3.93 (s, 1H, 3-H), 4.86 (s, mobile H), 7.21 (tm, $J = 7.5$ Hz, 1H, H_{para}), 7.40 (dd, $J = 8.4$ Hz, $J' = 7.5$ Hz, 2H, H_{meta}),

7.62 (dm, $J = 8.4$ Hz, 2H, H_{ortho}), 8.15 (dm, $J = 9.0$ Hz, 2H) and 8.26 (dm, $J = 9.0$ Hz, 2H) [2(6)-H and 3(5)-H *p*-nitrobenzoate]; ^{13}C NMR (CD_3OD) 21.0 (CH_3) and 24.5 (CH_3) [C4–(CH_3)$_2$], 38.0 (C, C4), 59.9 (CH_2, C5), 62.4 (CH, C3), 121.4 (CH, C_{ortho}), 126.6 (CH, C_{para}), 124.2 [CH, C3(5) *p*-nitrobenzoate], 129.3 (CH, C_{meta}), 131.5 [CH, C2(6) *p*-nitrobenzoate], 140.1 (C, C_{ipso}), 142.8 (C, C1 *p*-nitrobenzoate), 150.9 (C, C4 *p*-nitrobenzoate), 170.7 (C) and 171.0 (C) (C2 and COO). Anal. Calcd for $C_{12}H_{16}N_2O{\cdot}C_7H_5NO_4{\cdot}0.5H_2O$: C, 59.99; H, 5.83; N, 10.55. Found: C, 60.08; H, 5.85; N, 10.61.

4.9. (*S*)-3-Amino-4,4-dimethyl-1-phenylpyrrolidin-2-one·-mono-*O*,*O*-di-*p*-toluoyl-L-tartrate ((*S*)-9 mono-*O*,*O*-di-*p*-toluoyl-L-tartrate

To a solution of amine (*S*)-**9** (157 mg, 0.77 mmol) in MeOH (1 mL), a solution of (−)-*O*,*O*-di-*p*-toluoyl-L-tartaric acid (297 mg, 0.77 mmol) in MeOH (2 mL) was added. The resulting mixture was concentrated to dryness in vacuo and the residue was crystallized from MeOH/Et_2O 1:1 (6 mL) to yield (*S*)-**9**·mono-*O*,*O*-di-*p*-toluoyl-L-tartrate (376 mg, from two crops, 83% yield) as a white solid. Mp 195–196 °C (MeOH/Et_2O 1:1); $[\alpha]_D^{24} = -99.8$ (*c* 1.17, MeOH); IR 3500–2500 (max at 3443, 3177, 3061, 3029, 2949, 2884, 2636, O–H st, $^+$N–H st and C–H st), 1721 and 1704 (C=O st), 1611, 1596, 1540, 1498, 1413, 1377, 1332, 1271, 1176, 1121, 1109, 1045, 1021, 900, 840, 750, 693 cm^{-1}; ^{1}H NMR (400 MHz, CD_3OD) 1.15 (d, $J = 2.0$ Hz, 3H) and 1.35 (s, 3H), [C4–(CH_3)$_2$], 2.40 [s, 6H, Ar–CH_3], 3.57 (d, $J = 9.8$ Hz, 1H) and 3.76 (br d, $J = 9.8$ Hz, 1H) (5-H_2), 4.01 (s, 1H, 3-H), 4.91 (s, mobile H), 5.89 (s, 2H, 2(3)-H tartrate), 7.21 (t, $J = 7.4$ Hz, 1H, H_{para} *N*-phenyl), 7.28 (d, $J = 8.0$ Hz, 4H, 3(5)-H *p*-toluoyl], 7.40 (pseudo t, $J = 8.2$ Hz, 2H, H_{meta} *N*-phenyl), 7.61 (dm, $J = 8.4$ Hz, 2H, H_{ortho} *N*-phenyl), 8.01 (d, $J = 8.0$ Hz, 4H, 2(6)-H *p*-toluoyl]; ^{13}C NMR (CD_3OD) 21.1 (CH_3) and 24.4 (CH_3) [C4–(CH_3)$_2$], 21.7 (CH_3, toluoyl CH_3), 37.8 (C, C4), 59.9 (CH_2, C5), 61.9 (CH, C3), 74.9 [CH, C2(3) tartrate], 121.3 (CH, C_{ortho} *N*-phenyl), 126.6 (CH, C_{para} *N*-phenyl), 128.4 (C, C1 toluoyl), 130.1 (CH, C_{meta} *N*-phenyl), 130.2 [CH, C3(5) toluoyl], 131.1 [CH, C2(6) toluoyl], 140.0 (C, C_{ipso} *N*-phenyl), 145.4 (C, C4 toluoyl), 167.5 (C, CO toluoyl), 169.5 (C, C2), 171.6 [C, C1(4) tartrate]. Anal. Calcd for $C_{12}H_{16}N_2O{\cdot}C_{20}H_{18}O_8$: C, 65.07; H, 5.80; N, 4.74. Found: C, 64.96; H, 5.70; N, 4.71.

4.10. (*R*)-3-Amino-4,4-dimethyl-1-phenylpyrrolidin-2-one *p*-nitrobenzoate ((*R*)-9 *p*-nitrobenzoate

This compound was prepared as described before for (*S*)-**9**. From (3*R*,1′*S*)-**7** (2.15 g, 6.98 mmol), concd HCl (2.50 mL), and 5% Pd/C (6.00 g) in MeOH (195 mL), after 92 h hydrogenation at 1 atm and room temperature, (*R*)-**9** (1.22 g, 86% yield) was obtained as a colorless oil, $[\alpha]_D^{24} = +24.0$ (*c* 0.95, CH_2Cl_2). The ^{1}H and ^{13}C NMR spectra of this compound are coincidental with those of its enantiomer. A sample of (*R*)-**9** (121 mg, 0.59 mmol) on reaction with *p*-nitrobenzoic acid (104 mg, 0.62 mmol) was transformed as before into the corresponding (*R*)-**9** *p*-nitrobenzoate (175 mg from two crops, 78% yield), after crystallization from MeOH, mp 190–191 °C (MeOH); $[\alpha]_D^{25} = +14$ (*c* 0.50, MeOH). The IR, ^{1}H, and ^{13}C NMR data of this compound are coincidental with those of (*S*)-**9** *p*-nitrobenzoate. Anal. Calcd for $C_{12}H_{16}N_2O{\cdot}C_7H_5NO_4{\cdot}0.5H_2O$: C, 59.99; H, 5.83; N, 11.05. Found: C, 59.96; H, 5.49; N, 10.84.

4.11. (*R*)-3-Amino-4,4-dimethyl-1-phenylpyrrolidin-2-one ((*R*)-9 from (3*R*,1′*R*)-8

A mixture of (3*R*,1′*R*)-**8** (140 mg, 0.45 mmol), concd HCl (150 μL), and 5% Pd/C (394 mg) in MeOH (12 mL) was hydrogenated at 1 atm and room temperature for 96 h. The mixture was filtered through a pad of Celite® washing the filter with MeOH (25 mL). The filtrate was basified with aqueous 2 M NaOH (12 mL) and was extracted with CH_2Cl_2 (3 × 25 mL). The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give (*R*)-**9** (80 mg, 86% yield), as a colorless oil. $[\alpha]_D^{23} = +25.0$ (*c* 1.0, CH_2Cl_2). The ^{1}H NMR spectrum is coincidental with the previously described for (*S*)-**9**.

4.12. (*S*)-3-(Dimethylamino)-4,4-dimethyl-1-phenylpyrrolidin-2-one ((*S*)-10

Aqueous formaldehyde (37.5%, 8.5 mL, 106 mmol) was added to (*S*)-**9** (998 mg, 4.89 mmol). Formic acid (8.50 mL, 10.4 g, 225 mmol) was added to the cold mixture (ice-water bath) and then the reaction mixture was heated at 80 °C for 18 h. The mixture was allowed to cool to room temperature, basified with aqueous 5 M NaOH (50 mL) and was extracted with Et_2O (3 × 50 mL). The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give (*S*)-**10** (1.08 g, 95% yield) as a yellow solid. An analytical sample of (*S*)-**10** was obtained by crystallization from Et_2O, mp 56–57 °C (Et_2O); $[\alpha]_D^{20} = -35$ (*c* 0.61, CH_2Cl_2); IR 3050, 3024, 2960, 2935, 2871, 2833, 2785, 1763 and 1694 (C=O st), 1598, 1500, 1460, 1400, 1379, 1315, 1291, 1213, 1175, 1121, 1078, 1063, 1041, 759, 691 cm^{-1}; ^{1}H NMR 1.20 (s, 3H) and 1.23 (s, 3H), [C4–(CH_3)$_2$], 2.53 [s, 6H, N(CH_3)$_2$], 3.02 (s, 1H, 3-H), 3.41 (d, $J = 9.6$ Hz, 1H) and 3.56 (d, $J = 9.6$ Hz, 1H) (5-H_2), 7.14 (tm, $J = 7.5$ Hz, 1H, H_{para}), 7.36 (m, 2H, H_{meta}) 7.63 (dm, $J = 8.7$ Hz, 2H, H_{ortho}); ^{13}C NMR 21.6 (CH_3) and 29.1 (CH_3) [C4–(CH_3)$_2$], 36.2 (C, C4), 43.9 [CH_3, N(CH_3)$_2$], 60.1 (CH_2, C5), 75.3 (CH, C3), 119.8 (CH, C_{ortho}), 124.6 (CH, C_{para}), 128.8 (CH, C_{meta}), 139.3 (C, C_{ipso}), 172.2 (C, C2). Anal. Calcd for $C_{14}H_{20}N_2O{\cdot}0.2H_2O$: C, 71.27; H, 8.72; N, 11.87. Found: C, 71.19; H, 8.71; N, 11.63.

4.13. (*R*)-3-(Dimethylamino)-4,4-dimethyl-1-phenylpyrrolidin-2-one ((*R*)-10

This compound was prepared as described before for (*S*)-**10**. From (*R*)-**9** (1.01 g, 4.95 mmol), aqueous formaldehyde (37.5%, 8.60 mL, 107 mmol), and formic acid (8.60 mL, 10.5 g, 228 mmol), (*R*)-**10** (1.07 g, 93% yield) was obtained as a yellow viscous oil. An analytical solid sample was obtained by crystallization from Et_2O, mp 54–55 °C (Et_2O); $[\alpha]_D^{20} = +36$ (*c* 0.75, CH_2Cl_2). The IR, ^{1}H, and ^{13}C NMR data are coincidental with those of (*S*)-**10**. Anal. Calcd

for $C_{14}H_{20}N_2O{\cdot}0.4H_2O$: C, 70.20; H, 8.75; N, 11.70. Found: C, 70.16; H, 8.38; N, 11.64.

4.14. (*S*)-4,4-Dimethyl-1-phenyl-3-(*p*-toluenesulfonylamino)-pyrrolidin-2-one (*S*)-11

Tosyl chloride (470 mg, 2.47 mmol) was added to a cold (0 °C) solution of (*S*)-**9** (505 mg, 2.47 mmol) and anhyd Et_3N (0.68 mL, 4.88 mmol) in anhyd CH_2Cl_2 (10 mL) and the mixture was stirred at room temperature for 15 h. The reaction mixture was cooled (−10 °C, ice-NaCl bath) and a mixture of ice/ 10% aqueous HCl (70 mL) was added. The organic phase was separated and the aqueous one was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ solution (3 × 20 mL) and brine (40 mL) and were dried over anhydrous Na_2SO_4 and concentrated in vacuo to give (*S*)-**11** (710 mg, 80% yield) as a white solid, mp 149–150 °C (CH_2Cl_2); $[\alpha]_D^{20} = -6$ (*c* 0.51, CH_2Cl_2); IR 3323 and 3286 (N–H st), 3125, 3063, 3042, 2968, 2927, 2885, 1720 and 1709 (C=O st), 1595, 1495, 1478, 1460, 1401, 1382, 1350, 1314 (S=O st), 1278, 1235, 1217, 1162 (S=O st), 1132, 1109, 1091, 940, 923, 812, 760, 721, 692, 665 cm^{-1}; ^1H NMR 1.09 (s, 3H) and 1.36 (s, 3H), [C4–(CH_3)$_2$], 2.40 (s, 3H, CH_3 *p*-tosyl), 3.40 (d, $J = 9.9$ Hz, 1H) and 3.56 (d, $J = 9.9$ Hz, 1H) (5-H_2), 3.66 (d, $J = 5.4$ Hz, 1H, 3-H), 5.23 (d, $J = 5.4$ Hz, 1H, NH), 7.14 (tt, $J = 7.2$ Hz, $J' = 1.2$ Hz, 1H, H_{para}), 7.28–7.37 [complex signal, 4H, H_{meta} and 3(5)-H *p*-tosyl], 7.50 [dm, $J = 9.0$ Hz, 2H, 2(6)-H *p*-tosyl], 7.84 (dm, $J = 8.7$ Hz, 2H, H_{ortho}); ^{13}C NMR 21.1 (CH_3), 21.5 (CH_3) and 26.0 (CH_3) [C4–(CH_3)$_2$ and CH_3 *p*-tosyl], 38.6 (C, C4), 58.2 (CH_2, C5), 64.3 (CH, C3), 119.4 (CH, C_{ortho}), 125.1 (CH, C_{para}), 127.5 (CH), 128.9 (CH) and 129.7 (CH) [C_{meta}, C2(6) and C3(5) *p*-tosyl], 136.0 (C, C1 *p*-tosyl), 138.8 (C_{ipso}), 143.7 (C, C4 *p*-tosyl), 169.8 (C, C2). Anal. Calcd for $C_{19}H_{22}N_2O_3S$: C, 63.66; H, 6.19; N, 7.82; S, 8.95. Found: C, 63.68; H, 6.13; N, 7.73; S, 8.81.

4.15. (3*S*,1′*R*)-4,4-Dimethyl-1-phenyl-3-[(1-phenylethyl)-methylamino]pyrrolidin-2-one monomaleate, (3*S*,1′*R*)-12 monomaleate

Aqueous formaldehyde (37.5%, 1.94 mL, 24.3 mmol) was added to (3*S*,1′*R*)-**7** (700 mg, 2.27 mmol). Formic acid (1.94 mL, 2.37 g, 51.5 mmol) was added to the cold mixture (ice-water bath) and then the reaction mixture was heated at 80 °C for 20 h. The mixture was allowed to cool to room temperature, basified with aqueous 2 M NaOH and was extracted with Et_2O (3 × 35 mL). The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give (3*S*,1′*R*)-**12** (629 mg, 86% yield) as a colorless oil, $[\alpha]_D^{25} = -74.8$ (*c* 1.1, CH_2Cl_2); ^1H NMR (400 MHz) 0.87 (s, 3H) and 1.11 (s, 3H), [C4–(CH_3)$_2$], 1.48 (d, $J = 6.8$ Hz, 3H, CH_3CHPh), 2.42 (s, 3H, NCH_3), 3.39 (s, 1H, 3-H), 3.36 (d, $J = 9.6$ Hz, 1H) and 3.47 (d, $J = 9.6$ Hz, 1H) (5-H_2), 4.06 (q, $J = 6.8$ Hz, 1H, CH_3CHPh), 7.13 (tm, $J = 7.4$ Hz, 1H, H_{para} N–Ph), 7.22 (tm, $J = 7.2$ Hz, 1H, H_{para} C–Ph), 7.29–7.41 (complex signal, 6H, H_{meta} N–Ph, H_{ortho} and H_{meta} C–Ph), 7.61 (dm, $J = 8.4$ Hz, 2H, H_{ortho} N–Ph); ^{13}C NMR (100.6 MHz) 18.3 (CH_3), 22.3 (CH_3) and 27.7 (CH_3) [C4–(CH_3)$_2$ and CH_3CHPh], 36.5 (C, C4), 38.0 (CH_3, N–CH_3), 59.6 (CH_2, C5), 63.1 (CH, CH_3CHPh), 68.3 (CH, C3), 119.7 (CH, C_{ortho} N–Ph), 124.4 (CH, C_{para} N–Ph), 126.8 (CH), 127.9 (CH) and 128.1 (CH) (C_{meta} N–Ph, C_{ortho} and C_{meta} C–Ph), 128.7 (CH, C_{para} C–Ph), 139.5 (C) and 145.4 (C) (C_{ipso} N–Ph and C_{ipso} C–Ph), 173.2 (C, C2).

An aliquot of the above product (384 mg, 1.19 mmol) was taken in *i*-PrOH (3 mL) and a solution of maleic acid (152 mg, 1.31 mmol) in *i*-PrOH (3 mL) was added and the solution was concentrated to dryness in vacuo. The solid residue was recrystallized from *i*-PrOH/Et_2O 1:2 (9 mL) to give (3*S*,1′*R*)-**12** monomaleate (504 mg, 97% yield) as a white solid, mp 92–93 °C (*i*-PrOH/Et_2O 1:2); $[\alpha]_D^{20} = -24$ (*c* 0.55, CH_2Cl_2); IR 3500–2400 (max at 3422, 3074, 3032, 2968, 2861, 2615, O–H st, $^+$N–H st and C–H st), 1706 (C=O st), 1668, 1614, 1583, 1500, 1484, 1459, 1414, 1388, 1349, 1320, 1284, 1210, 1189, 1119, 1073, 1054, 1031, 1013, 864, 762, 728, 702, 692 cm^{-1}; ^1H NMR 1.09 (s, 3H) and 1.37 (s, 3H), [C4–(CH_3)$_2$], 1.84 (d, $J = 7.2$ Hz, 3H, CH_3CHPh), 2.96 (s, 3H, NCH_3), 3.49 (d, $J = 9.6$ Hz, 1H) and 3.54 (d, $J = 9.6$ Hz, 1H) (5-H_2), 3.93 (s, 1H, 3-H), 4.96 (q, $J = 7.2$ Hz, 1H, CH_3CHPh), 6.40 [s, 2H, 2(3)-H maleate], 7.24 (tm, $J = 7.5$ Hz, 1H, H_{para} N–Ph), 7.38–7.45 (complex signal, 5H) and 7.52–7.60 (complex signal, 4H) (H_{ortho} and H_{meta} N–Ph, H_{ortho}, H_{meta} and H_{para} C–Ph), 11.73 (br signal, $^+$NH and COOH); ^{13}C NMR 15.7 (CH_3), 21.9 (CH_3) and 25.1 (CH_3) [C4–(CH_3)$_2$ and CH_3CHPh], 38.1 (C, C4), 38.4 (CH_3, NCH_3), 59.2 (CH_2, C5), 67.0 (CH, CH_3CHPh), 68.7 (CH, C3), 120.1 (CH, C_{ortho} N–Ph), 125.9 (CH, C_{para} N–Ph), 129.1 (2 CH) and 129.3 (CH) (C_{meta} N–Ph, C_{ortho} and C_{meta} C–Ph), 129.9 (CH, C_{para} C–Ph), 135.6 [CH, C2(3) maleate], 136.0 (C) and 138.0 (C) (C_{ipso} N–Ph and C_{ipso} C–Ph), 166.4 (C), 168.9 (C) (C2 and COO). Anal. Calcd for $C_{21}H_{26}N_2O{\cdot}C_4H_4O_4{\cdot}0.75H_2O$: C, 66.43; H, 7.02; N, 6.20. Found: C, 66.31; H, 6.80; N, 6.01.

4.16. (3*R*,1′*S*)-4,4-Dimethyl-1-phenyl-3-[(1-phenylethyl)-methylamino]pyrrolidin-2-one monomaleate (3*R*,1′*S*)-12 monomaleate

This compound was prepared as described before for (3*S*,1′*R*)-**12** monomaleate. From (3*R*,1′*S*)-**7** (2.03 g, 6.59 mmol), aqueous formaldehyde (37.5%, 5.60 mL, 69.9 mmol), and formic acid (5.60 mL, 6.83 g, 148 mmol), (3*R*,1′*S*)-**12** (1.75 g, 82% yield) was obtained as a colorless oil, $[\alpha]_D^{25} = +74.0$ (*c* 1.2, CH_2Cl_2). The ^1H and ^{13}C NMR data of this compound are coincidental with those of its enantiomer.

The above product was transformed into the corresponding monomaleate as before. After recrystallization of the crude salt (2.40 g) from *i*-PrOH/E_2O 1:2 (40 mL) pure (3*R*,1′*S*)-**12** monomaleate (2.20 g, 93% yield) was obtained as a white solid, mp 90–92 °C (*i*-PrOH/E_2O 1:2); $[\alpha]_D^{20} = +25$ (*c* 0.52, CH_2Cl_2). The IR, ^1H, and ^{13}C NMR data are coincidental with those of (3*S*,1′*R*)-**12** monomaleate. Anal. Calcd for $C_{21}H_{26}N_2O{\cdot}C_4H_4O_4{\cdot}1.15H_2O$: C, 65.39; H, 7.09; N, 6.10. Found: C, 65.14; H, 6.86; N, 5.86.

4.17. (*S*)-4,4-Dimethyl-3-methylamino-1-phenylpyrrolidin-2-one (*S*)-13

A mixture of (3*S*,1′*R*)-**12** (100 mg, 0.31 mmol), concd HCl (80 μL) and 5% Pd/C (265 mg) in MeOH (10 mL) was hydrogenated at 1 atm and room temperature for 96 h. The mixture was filtered through a pad of Celite®, washing the filter with MeOH (30 mL). The filtrate was basified with aqueous 2 M NaOH (5 mL). The organic solvent was eliminated under reduced pressure and the aqueous residue was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated in vacuo to give (*S*)-**13** (64 mg, 95% yield) as a light yellow solid, mp 52–53 °C (CH_2Cl_2); $[\alpha]_D^{20} = -35$ (*c* 0.59, CH_2Cl_2); IR 3321 (N–H st), 3082, 2972, 2945, 2876, 2848, 2793, 1700 (C=O st), 1598, 1502, 1486, 1459, 1407, 1381, 1367, 1340, 1323, 1284, 1222, 1211, 1175, 1136, 1122, 1012, 899, 759, 691 cm^{-1}; ^1H NMR 1.06 (s, 3H) and 1.32 (s, 3H), [C4–(CH_3)$_2$], 1.67 (br s, 1H, NH), 2.62 (s, 3H, NCH_3), 3.09 (s, 1H, 3-H), 3.38 (d, $J = 9.6$ Hz, 1H) and 3.52 (d, $J = 9.6$ Hz, 1H) (5-H_2), 7.14 (tm, $J = 7.2$ Hz, 1H, H_{para}), 7.37 (m, 2H, H_{meta}), 7.61 (dm, $J = 8.7$ Hz, 2H, H_{ortho}); ^{13}C NMR 21.0 (CH_3) and 26.0 (CH_3) [C4–(CH_3)$_2$], 37.2 (CH_3, NCH_3), 38.2 (C, C4), 58.4 (CH_2, C5), 71.6 (CH, C3), 119.5 (CH, C_{ortho}), 124.4 (CH, C_{para}), 128.8 (CH, C_{meta}), 139.5 (C_{ipso}), 173.7 (C, C2). Anal. Calcd for $C_{13}H_{18}N_2O$: C, 71.53; H, 8.31; N, 12.83. Found: C, 71.50; H, 8.51; N, 12.75.

4.18. (*S*)-3-[(4,4-dimethyl-2-oxo-1-phenylpyrrolidin-3-yl)-imino]-4,4-dimethyl-1-phenylpyrrolidin-2-one (*S*)-14

A solution of 4,4-dimethyl-1-phenylpyrrolidine-2,3-dione **4** (0.98 g, 4.83 mmol), and amine (*S*)-**9** (0.98 g, 4.80 mmol) in toluene (30 mL) was heated at reflux for 24 h in a Dean–Stark equipment. Evaporation of the solvent under reduced pressure gave imine (*S*)-**14** (1.87 g, quantitative yield) as a yellow solid. Crystallization of (*S*)-**14** (205 mg) from hexane/AcOEt 6:1 (2 mL) provided the analytical sample (176 mg, 86% recovery). Mp 133–134 °C (hexane/AcOEt 6:1); R_f 0.52 (aluminum oxide, 7.3 cm, hexane/AcOEt 4:1); $[\alpha]_D^{25} = -187$ (*c* 0.50, CH_2Cl_2); IR 3062, 3045, 2958, 2927, 2869, 1701 and 1692 (C=O st), 1677 (C=N st), 1597, 1495, 1481, 1458, 1398, 1376, 1319, 1189, 1057, 767, 758, 723, 690, 627 cm^{-1}; ^1H NMR (400 MHz) 1.24 (s, 3H), 1.26 (s, 3H), 1.36 (s, 3H) and 1.40 (s, 3H) [C4–(CH_3)$_2$ and C4′-(CH_3)$_2$], 3.62 (d, $J = 9.4$ Hz, 1H) and 3.65 (d, $J = 9.4$ Hz, 1H) (5-H_2), 3.73 (d, $J = 9.6$ Hz, 1H) and 3.79 (d, $J = 9.6$ Hz, 1H) (5′-H_2), 6.12 (s, 1H, 3′-H), 7.12 (t, $J = 7.4$ Hz, 1H) and 7.21 (t, $J = 7.4$ Hz, 1H) (2 × H_{para}), 7.34 (pseudo t, $J = J' = 8.0$ Hz, 2H) and 7.39 (pseudo t, $J = J' = 8.0$ Hz, 2H) (2 × H_{meta}), 7.64 (d, $J = 7.6$ Hz, 2H) and 7.70 (d, $J = 8.0$ Hz, 2H) (2 × H_{ortho}); ^{13}C NMR (100.6 MHz) 21.5 (CH_3), 25.6 (CH_3), 25.8 (CH_3) and 27.0 (CH_3) [C4–(CH_3)$_2$ and C4′-(CH_3)$_2$], 38.5 (C) and 38.9 (C) (C4 and C4′), 58.1 (CH_2) and 59.0 (CH_2) (C5 and C5′), 68.7 (CH, C3′), 119.5 (CH) and 119.8 (CH) (2 × C_{ortho}), 124.2 (CH) and 125.7 (CH) (2 × C_{para}), 128.7 (CH) and 128.9 (CH) (2 × C_{meta}), 139.1 (C) and 139.9 (C) (2 × C_{ipso}), 159.5 (C, C3), 170.4 (C) and 170.7 (C) (C2 and C2'). Anal. Calcd for $C_{24}H_{27}N_3O_2$: C, 74.01; H, 6.99; N, 10.69. Found: C, 73.88; H, 7.32; N, 10.35.

4.19. (*S*,*S*)-Bis(4,4-dimethyl-2-oxo-1-phenylpyrrolidin-3-yl)-amine (*S*,*S*)-15

To a cold (−78 °C) solution of (*S*)-**14** (331 mg, 0.85 mmol) in anhyd MeOH (15 mL), a solution of $NaBH_3CN$ (114 mg, 1.82 mmol) and AcOH (60 μL, 1.05 mmol) in MeOH (5 mL) was added and the reaction mixture was stirred at this temperature for 5 h. Water (15 mL) was then added. The organic solvent was evaporated under reduced pressure and the remaining aqueous phase was treated with aqueous 2 M NaOH till pH 12–13 and extracted with CH_2Cl_2 (3 × 15 mL). The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give a diastereomeric mixture of (*S*,*S*)-**15** and *meso*-**16** in a ratio of 80:20 (^1H NMR) (285 mg, 86% yield). The above mixture was subjected to column chromatography (aluminum oxide, 41 g, hexane/AcOEt 9:1). In the order of elution were obtained (*S*,*S*)-**15** (171 mg, 51% isolated yield) as a white solid, a mixture of (*S*,*S*)-**15** and *meso*-**16** (ratio 1:1, 11 mg) and *meso*-**16** (8 mg, 2% isolated yield) as a yellowish oil. Crystallization of (*S*,*S*)-**15** (138 mg) from hexane/AcOEt 6:1 (1.75 mL) gave the analytical sample (120 mg, 87% recovery). (*S*,*S*)-**15**: R_f 0.21 (aluminum oxide, 9.4 cm, hexane/AcOEt 9:1), mp 144–145 °C (hexane/AcOEt 6:1); $[\alpha]_D^{25} = -53$ (*c* 0.51, CH_2Cl_2); IR 3357 (N–H st), 3060, 3044, 2966, 2935, 2876, 2812, 1706 and 1697 (C=O st), 1596, 1498, 1478, 1461, 1402, 1379, 1368, 1335, 1309, 1278, 1203, 1170, 1118, 756, 692 cm^{-1}; ^1H NMR 1.16 (s, 6H) and 1.35 (s, 6H), [2 × C4–(CH_3)$_2$], 3.46 (d, $J = 9.3$ Hz, 2H) and 3.54 (d, $J = 9.3$ Hz, 2H) (2 × 5-H_2), 3.64 (s, 2H, 2 × 3-H), 7.14 (tm, $J = 7.2$ Hz, 2H, 2 × H_{para}), 7.37 (dd, $J = 8.4$ Hz, $J' = 7.5$ Hz, 4H, 2 × H_{meta}), 7.63 (dm, $J = 7.5$ Hz, 4H, 2 × H_{ortho}); ^{13}C NMR 20.7 (CH_3) and 25.0 (CH_3) [2 × C4–(CH_3)$_2$], 38.3 (C, 2 × C4), 58.2 (CH_2, 2 × C5), 68.9 (CH, 2 × C3), 119.4 (CH, 2 × C_{ortho}), 124.3 (CH, 2 × C_{para}), 128.8 (CH, 2 × C_{meta}), 139.6 (C, 2 × C_{ipso}), 174.2 (C, 2 × C2). Anal. Calcd for $C_{24}H_{29}N_3O_2$: C, 73.63; H, 7.47; N, 10.73. Found: C, 73.41; H, 7.56; N, 10.66. *Meso*-**16**: R_f 0.14 (aluminum oxide, 9.4 cm, hexane/AcOEt 9:1); ^1H NMR 1.12 (s, 6H) and 1.33 (s, 6H), [2 × C4–(CH_3)$_2$], 3.41 (d, $J = 9.3$ Hz, 2H) and 3.53 (d, $J = 9.3$ Hz, 2H) (2 × 5-H_2), 3.72 (s, 2H, 2 × 3-H), 7.13 (tm, $J = 7.5$ Hz, 2H, 2 × H_{para}), 7.36 (dd, $J = 8.7$ Hz, $J' = 7.2$ Hz, 4H, 2 × H_{meta}), 7.65 (dm, $J = 7.5$ Hz, 4H, 2 × H_{ortho}).

4.20. (*S*,*S*)-2,6-Bis[(4,4-dimethyl-2-oxo-1-phenylpyrrolidin-3-yl)aminomethyl]pyridine dihydrochloride (*S*,*S*)-18·2HCl

To a solution of (*S*)-**9** (500 mg, 2.45 mmol) in anhydrous MeOH (30 mL), a solution of $NaBH_3CN$ (231 mg, 3.68 mmol) and AcOH (0.92 mL, 16.1 mmol) in MeOH (5 mL) and pyridine-2,6-dicarboxaldehyde, **17** (165 mg, 1.22 mmol) was added and the reaction mixture was stirred at room temperature for 24 h. Water (15 mL) was then added. The organic solvent was evaporated under reduced pressure and the remaining aqueous phase was treated with aqueous 2 M NaOH until pH 12–13 and extracted with

CH_2Cl_2 (3 × 15 mL). The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give crude (*S*,*S*)-**18** (636 mg, quantitative yield) as a yellowish oil. The above product was taken in anhydrous MeOH (5 mL), treated with a solution of HCl in MeOH (0.4 M, 30 mL) and the solution was concentrated under reduced pressure to give a white solid (802 mg), which was crystallized from MeOH/Et_2O 3:4 (10 mL) to give (*S*,*S*)-**18**·2HCl (453 mg, 56% yield). Mp 168–170 °C (MeOH/Et_2O 3:4); $[\alpha]_D^{22} = -87.2$ (*c* 0.51, MeOH); IR 3500–2400 (max at 3420, 2964, 2929, 2781, 2708, 2596, O–H st, $^+$N–H st and C–H st), 1703 (C=O st), 1633, 1596, 1498, 1458, 1425, 1392, 1323, 763, 692 cm^{-1}; ^1H NMR (400 MHz, CD_3OD) 1.40 (s, 6H) and 1.50 (s, 6H), [2 × C4–$(CH_3)_2$], 3.64 (d, $J = 9.8$ Hz, 2H) and 3.78 (d, $J = 9.8$ Hz, 2H) (2 × 5-H_2), 4.27 (s, 2H, 2 × 3-H), 4.85 (s, mobile H), 4.91 (d, $J = 15.0$ Hz, 2H) and 4.94 (d, $J = 15.0$ Hz, 2H) (2 × CH_2N), 7.23 (t, $J = 7.2$ Hz, 2H, 2 × H_{para}), 7.40 (pseudo t, $J = 8.0$ Hz, 4H, 2 × H_{meta}), 7.63 (d, $J = 8.8$ Hz, 4H, 2 × H_{ortho}), 7.65 [overlapped d, 2H, pyridine 3(5)-H], 8.03 (t, $J = 7.8$ Hz, 1H, pyridine 4-H); ^{13}C NMR (100.6 MHz, CD_3OD) 21.4 (CH_3), 24.7 (CH_3) [2 × C4–(CH_3)$_2$], 38.8 (C, 2 × C4), 51.9 (CH_2, 2 × C5), 60.0 (CH_2, 2 × CH_2N), 67.3 (CH, 2 × C3), 121.6 (CH, 2 × C_{ortho}), 125.1 (CH, 2 × C_{para}), 126.8 [CH, pyridine C3(5)], 130.1 (CH, 2 × C_{meta}), 139.8 (C, 2 × C_{ipso}), 140.5 (CH, pyridine C4), 152.3 [C, pyridine C2(6)], 168.8 (C, 2 × C2). Anal. Calcd for $C_{31}H_{37}N_5O_2$·2.15HCl·2H_2O: C, 59.47; H, 6.95; N, 11.19; Cl, 12.17. Found: C, 59.68; H, 6.77; N, 11.25; Cl, 12.22.

A sample of (*S*,*S*)-**18** as the free base was liberated from the above dihydrochloride as follows: (*S*,*S*)-**18**·2HCl (101 mg) was treated with aqueous 2 M NaOH (5 mL) and the mixture was extracted with AcOEt (3 × 10 mL). The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give (*S*,*S*)-**18** (84 mg, quantitative yield) as a colorless oil. (*S*,*S*)-**18**: R_f 0.71 (aluminum oxide, 7.0 cm, CH_2Cl_2); $[\alpha]_D^{22} = -41.2$ (*c* 0.45, CH_2Cl_2); ^1H NMR 1.13 (s, 6H) and 1.27 (s, 6H), [2 × C4–(CH_3)$_2$], 2.3–2.6 (br s, 2H, 2 × NH), 3.31 (s, 2H, 2 × 3-H), 3.39 (d, $J = 9.6$ Hz, 2H) and 3.49 (d, $J = 9.6$ Hz, 2H) (2 × 5-H_2), 4.13 (d, $J = 14.7$ Hz, 2H) and 4.18 (d, $J = 14.7$ Hz, 2H) (2 × CH_2N), 7.13 (tm, $J = 7.2$ Hz, 2H, 2 × H_{para}), 7.32 [d, $J = 7.8$ Hz, 2H, pyridine 3(5)-H], 7.35 (pseudo t, $J = 8.1$ Hz, 4H, 2 × H_{meta}), 7.60 (d, $J = 8.1$ Hz, 4H, 2 × H_{ortho}), 7.61 (overlapped t, 1H, pyridine 4-H); ^{13}C NMR 21.1 (CH_3), 25.8 (CH_3) [2 × C4–(CH_3)$_2$], 38.3 (C, 2 × C4), 54.5 (CH_2, 2 × C5), 58.4 (CH_2, 2 CH_2N), 68.8 (CH, 2 × C3), 119.4 (CH, 2 × C_{ortho}), 120.3 [CH, pyridine C3(5)], 124.3 (CH, 2 × C_{para}), 128.8 (CH, 2 × C_{meta}), 136.9 (CH, pyridine C4), 139.5 (C, 2 × C_{ipso}), 159.1 [C, pyridine C2(6)], 173.6 (C, 2 × C2).

4.21. Ethyl 2-{(*S*)-[(4,4-dimethyl-2-oxo-1-phenylpyrrolidin-3-yl)amino]}cyclohex-1-enecarboxylate (*S*)-20

A mixture of ethyl 2-oxocyclohexanecarboxylate, **19** (757 mg, 4.45 mmol), amine (*S*)-**9** (1.00 g, 4.90 mmol), *p*-TsOH·H_2O (86 g, 0.45 mmol), and dried 4 Å molecular sieves (2.5 g) in toluene (10 mL) was heated at 60 °C for 16 h. The mixture was allowed to cool to room temperature and was filtered through a basic aluminum oxide pad (10 g, 1.5 cm internal diameter) washing the pad with CH_2Cl_2 (100 mL). After concentration of the fractions containing the desired product, (*S*)-**20** (1.41 g, 89% yield) was obtained as a yellow oil. R_f 0.47 (aluminum oxide, 7.1 cm, hexane/AcOEt 5:1); $[\alpha]_D^{25} = +56.9$ (*c* 0.65, CH_2Cl_2); IR (NaCl) 3255 (N–H st), 3169, 3061, 2938, 2900, 2874, 2831, 1701 (C=O st), 1640, 1598, 1499, 1485, 1469, 1402, 1379, 1321, 1233, 1165, 1106, 1080, 1063, 830, 776, 757, 690, 621 cm^{-1}; ^1H NMR 1.22 (s, 3H) and 1.31 (s, 3H) [pyrrolidinone C4–(CH_3)$_2$], 1.27 (t, $J = 7.0$ Hz, 3H, OCH_2CH_3), 1.56–1.72 (m, 4H, cyclohexene 4-H_2 and 5-H_2), 2.17–2.42 (m, 3H) and 2.52–2.62 (m, 1H) (cyclohexene 3-H_2 and 6-H_2), 3.48 (d, $J = 9.6$ Hz, 1H) and 3.64 (d, $J = 9.6$ Hz, 1H) (pyrrolidinone 5-H_2), 4.10 (d, $J = 9.9$ Hz, 1H, pyrrolidinone 3-H), 4.14 (m, 2H, OCH_2CH_3), 7.14 (t, $J = 7.2$ Hz, $J' = 1.5$ Hz, 1H, H_{para}), 7.36 (m, 2H, H_{meta}), 7.61 (m, 2H, H_{ortho}), 9.33 (d, $J = 9.9$ Hz, 1H, NH); ^{13}C NMR 14.6 (CH_3, OCH_2CH_3), 21.4 (CH_3) and 25.0 (CH_3) [pyrrolidinone C4–(CH_3)$_2$], 22.3 (CH_2), 22.6 (CH_2), 23.9 (CH_2) and 26.4 (CH_2) (cyclohexene C3, C4, C5 and C6), 37.6 (C, pyrrolidinone C4), 58.1 (CH_2, pyrrolidinone C5), 58.8 (CH_2, OCH_2CH_3), 63.4 (CH, pyrrolidinone C3), 92.7 (C, cyclohexene C1), 119.3 (CH, C_{ortho}), 124.5 (CH, C_{para}), 128.8 (CH, C_{meta}), 139.4 (C, C_{ipso}), 158.6 (C, cyclohexene C2), 170.9 (C, pyrrolidinone C2), 171.8 (C, COO). Anal. Calcd for $C_{21}H_{28}N_2O_3$: C, 70.76; H, 7.92; N, 7.86. Found: C, 70.78; H, 8.06; N, 7.61.

4.22. Ethyl (*R*)-2-oxo-1-(2-oxobutyl)cyclohexanecarboxylate (*R*)-21

To a cold (−78 °C) mixture of enamine (*S*)-**20** (357 mg, 1.00 mmol), $MgCl_2$ (95 mg, 1.00 mmol) and 4 Å molecular sieves (171 mg) in anhydrous Et_2O (4 mL), freshly distilled methyl vinyl ketone (179 mg, 207 μL, 2.55 mmol) was added and the reaction mixture was stirred for 1 h at −78 °C. The molecular sieves were separated by decantation and the solvent and volatile components were eliminated from the solution under reduced pressure to give a residue (220 mg), which was subjected to column chromatography (silica gel, hexane/AcOEt 2:1) to give (*R*)-**21** (197 mg, 82% yield) as a yellow oil. R_f 0.55 (silica gel, 7.3 cm, hexane/AcOEt 2:1); $[\alpha]_D^{25} = +67.5$ (*c* 2.5, CH_2Cl_2) {lit.[19] $[\alpha]_D^{25} = +84.5$ (neat)}. Chiral GC (conditions A)/MS: (*R*)-**21**, t_R 67.6 min; (S)-**21**, t_R 67.2 min; 80% ee.

4.23. X-ray crystal-structure determination of (*S*)-9 mono-*O*,*O*-di-*p*-toluoyl-L-tartrate (Table 2)[11]

A prismatic crystal (0.1 × 0.1 × 0.2 mm) was selected and mounted on a MAR345 diffractometer with an image plate detector. Unit-cell parameters were determined from 1785 reflections ($3 < \theta < 31°$) and refined by least-squares method. Intensities were collected with graphite monochromatized Mo Kα radiation. 16,883 reflections were measured in the range $2.59 \leqslant \theta \leqslant 32.46$. 9766 of which were non-equivalent by symmetry [R_{int} (on *I*) = 0.021]. 5691 reflections were assumed as observed applying the condition $I > 2\sigma(I)$. Lorentz-polarization but no absorption corrections were made. The structure was solved by Direct meth-

Table 2. Experimental data of the X-ray crystal-structure determination of compounds of (*S*)-**9** mono-*O*,*O*-di-*p*-toluoyl-L-tartrate and of (*S*,*S*)-**15**[11]

Compound	(*S*)-**9** (salt)	(*S*,*S*)-**15**
Molecular formula	$C_{12}H_{16}N_2O{\cdot}C_{20}H_{18}O_8$	$C_{24}H_{29}N_3O_2$
Molecular mass	590.61	391.50
Crystal system	Orthorhombic	Orthorhombic
Space group	*P*212121	*P*22121
Cell parameters		
a (Å)	15.435(7)	6.070(5)
b (Å)	15.738(6)	8.276(2)
c (Å)	26.223(6)	21.562(4)
α (Å)	90	90
β (Å)	90	90
γ (Å)	90	90
V (Å^3)	6370(4)	1083.2(10)
Z	8	2
F(000)	2496	420
d_{calcd} [Mg m^{-3}]	1.232	1.200
Size of crystal (mm)	0.1 × 0.1 × 0.2	0.1 × 0.1 × 0.2
Measured reflect.	16,883	1849
Independent reflect.	9766	1849
Observed reflect.	5691	544
μ(Mo Kα) (mm^{-1})[a]	0.091	0.077
R	0.055	0.066
Rw	0.122	0.125
$\Delta\rho_{max}$[b] (e Å^{-3})	0.220	0.114
$\Delta\rho_{min}$[c] (e Å^{-3})	−0.151	−0.123
Refined parameters	803	137
Max. shift/esd	0.00	0.00

[a] μ(Mo Kα) linear absorption coefficient. Radiation Mo Kα (λ = 0.71073 Å).
[b] Maximum peaks in final difference synthesis.
[c] Minimum peaks in final difference synthesis.

ods, using SHELXS computer program,[20] and refined by full-matrix least-squares method with SHELX97 computer program,[21] using 16,883 reflections (very negative intensities were not assumed). The function minimized was $\Sigma w||F_o|^2 - |F_c|^2|^2$, where $w = [\sigma^2(I) + (0.0510P)^2]^{-1}$, and $P = (|F_o|^2 + 2|F_c|^2)/3$, *f*, *f*′ and *f*″ were taken from International Tables of X-ray Crystallography.[22] 6H atoms were located from a difference synthesis and refined with an overall isotropic temperature factor and 62H atoms were computed and refined, using a riding model, with an isotropic temperature factor equal to 1.2 time the equivalent temperature factor of the atom to which are linked. The final *R* (on *F*) factor was 0.055, *wR* (on $|F|^2$) = 0.122 and goodness of fit = 0.966 for all observed reflections. Number of refined parameters was 803. Max shift/esd = 0.00, Mean shift/esd = 0.00. Max and min peaks in final difference synthesis was 0.220 and −0.151 e Å^{-3}, respectively.

4.24. X-ray crystal-structure determination of (*S*,*S*)-15 (Table 2)[11]

A prismatic crystal (0.1 × 0.1 × 0.2 mm) was selected and mounted on an Enraf-Nonius four-circle diffractometer. Unit-cell parameters were determined from automatic centering of 25 reflections ($12 < \theta < 21°$) and refined by least-squares method. Intensities were collected with graphite monochromatized Mo Kα radiation using $\omega/2\theta$ scan technique. 1849 reflections were measured in the range $2.64 \leqslant \theta \leqslant 29.96$. 544 reflections were assumed as observed applying the condition $I > 2\sigma(I)$. Three reflections were measured every two hours as orientation and intensity control, significant intensity decay was not observed. Lorentz-polarization but no absorption corrections were made. The structure was solved by Direct methods, using SHELXS computer program,[20] and refined by full-matrix least-squares method with SHELX97 computer program,[21] using 1849 reflections (very negative intensities were not assumed). The function minimized was $\Sigma w||F_o|^2 - |F_c|^2|^2$, where $w = [\sigma^2(I) + (0.0678P)^2]^{-1}$, and $P = (|F_o|^2 + 2|F_c|^2)/3$, *f*, *f*′ and *f*″ were taken from International Tables of X-ray Crystallography.[22] All H atoms were computed and refined, using a riding model, with an isotropic temperature factor equal to 1.2 time the equivalent temperature factor of the atom to which are linked. The final *R* (on *F*) factor was 0.066, *wR* (on $|F|^2$) = 0.125 and goodness of fit = 0.950 for all observed reflections. Number of refined parameters was 137. Max shift/esd = 0.00, Mean shift/esd = 0.00. Max and min peaks in final difference synthesis was 0.114 and −0.123 e Å^{-3}, respectively.

Acknowledgments

Financial support from *Ministerio de Educación y Ciencia* (Project CTQ2005-02192) and *Comissionat per a Universitats i Recerca* (Project 2005-SGR-00180) is gratefully acknowledged. We thank the *Serveis Científico-Tècnics* of the University of Barcelona for the NMR and MS facilities, and Ms. P. Domènech from the IIQAB (CSIC, Barcelona, Spain) for carrying out the elemental analyses.

References

1. For a recent review, see: Camps, P.; Muñoz-Torrero, D. *Curr. Org. Chem.* **2004**, *8*, 1339–1380.
2. Camps, P.; Giménez, S.; Font-Bardia, M.; Solans, X. *Tetrahedron: Asymmetry* **1995**, *6*, 985–990.
3. Camps, P.; Pérez, F.; Soldevilla, N. *Tetrahedron Lett.* **1999**, *40*, 6853–6856.
4. Camps, P.; Muñoz-Torrero, D.; Sánchez, L. *Tetrahedron: Asymmetry* **2004**, *15*, 2039–2044.
5. Boschi, F.; Camps, P.; Comes-Franchini, M.; Muñoz-Torrero, D.; Ricci, A.; Sánchez, L. *Tetrahedron: Asymmetry* **2005**, *16*, 3739–3745.
6. Ayats, C.; Camps, P.; Font-Bardia, M.; Solans, X.; Vázquez, S. *Tetrahedron* **2007**, *63*, 8027–8036.
7. Lauktien, G.; Volk, F. J.; Frahm, A. W. *Tetrahedron: Asymmetry* **1997**, *8*, 3457–3466.
8. Hutchins, R. O.; Hutchins, M. K. In *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L. A., Ed.; John Wiley and Sons: West Sussex, England, 1995; Vol. 7, pp 4539–4542.
9. Gribble, G. W. In *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L. A., Ed.; John Wiley and Sons: West Sussex, England, 1995; Vol. 7, pp 4649–4653.
10. Couty, F.; Evano, G.; Vargas-Sánchez, M.; Bouzas, G. *J. Org. Chem.* **2005**, *70*, 9028–9031.
11. Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 665856 [(*S*)-**9** mono-*O*,*O*-di-*p*-toluoyl-L-tartrate] and CCDC 665857 [(*S*,*S*)-**15**]. Copies of

the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(0) 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].
12. Casanova, J.; Devi, P. *Synth. Commun.* **1993**, *23*, 245–251.
13. Camps, P.; Gómez, E.; Muñoz-Torrero, D. *Tetrahedron* **2004**, *60*, 5423–5431.
14. Guingant, A.; Hammami, H. *Tetrahedron: Asymmetry* **1991**, *2*, 411–414.
15. Pfau, M.; Revial, G.; Guingant, A.; d'Angelo, J. *J. Am. Chem. Soc.* **1985**, *107*, 273–274.
16. d'Angelo, J.; Desmaele, D.; Dumas, F.; Guingant, A. *Tetrahedron: Asymmetry* **1992**, *3*, 459–505.
17. Evans, D.; Lectka, T.; Miller, S. *Tetrahedron Lett.* **1993**, *34*, 7027–7030.
18. Hashiguchi, S.; Fujii, A.; Takehara, J.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1995**, *117*, 7562–7563.
19. Szöllösi, G.; Bartók, M. *Chirality* **2001**, *13*, 614–618.
20. Sheldrick, G. M. SHELXS*: A Computer Program for Automatic Solution of Crystal Structure Refinement*; University of Göttingen: Germany, 1997.
21. Sheldrick, G. M. SHELX-*97: A Computer Program for Crystal Structure Refinement*; University of Göttingen: Germany, 1999.
22. *International Tables of X-ray Crystallography*; Kynoch Press: Birmingham, 1974; Vol. IV, pp 99–100 and 149.