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Straightforward preparation of enantiopure 3-amino-4,4-dimethylpyrrolidin-2-one and its derivatives

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ABSTRACT

An easy access to both enantiomers of 3-amino- and 3-(dimethylamino)-4,4-dimethylpyrrolidin-2-one from *rac*-pantolactam using (*R*)-α-methylbenzylamine as a chiral auxiliary is described.

Dedicated to Professor Carmen Nájera on the occasion of her 60th anniversary

1. Introduction

(*R*)-Pantolactone, (*R*)-**1** (Fig. 1), is a widely used chiral auxiliary.[1] Several years ago, we prepared an improved, easily available, closely related chiral auxiliary, 3-hydroxy-4,4-dimethyl-1-phenylpyrrolidin-2-one (*N*-phenylpantolactam), **2** (Fig. 1), in both enantiomeric forms.[2] The main advantages of the enantiomers of **2** as chiral auxiliaries over those of **1** are: (i) non-hygroscopic crystalline compounds, which facilitate their recovery; (ii) easily UV-detectable; and (iii) both enantiomers are equally available. Compounds (*R*)- and (*S*)-**2** were used as chiral auxiliaries in different diastereoselective reactions, such as the deracemization of α-arylpropionic acids, Diels–Alder cycloadditions, and dynamic kinetic resolutions of α-haloesters, and as resolution agents.[1,3] Later on, we synthesized derivatives **3**–**5** as potential chiral auxiliaries or ligands for chiral catalysts, with limited success.[4] Although (*S*)-**4** (R = R′ = H) as a chiral auxiliary gave diastereoselectivities around 80% in a Michael reaction, none of the amines **3**–**5** showed any enantioselectivity as chiral ligands of $Cu(OTf)_2$, $Sc(OTf)_3$, and $Yb(OTf)_3$ in catalyzed Diels–Alder reactions or of $RuCl_2[\eta^6$-(mesitylene$)_2]_2$ in catalyzed transfer hydrogenation reactions.[4]

With the aim of increasing the stability of the complexes derived from these ligands and different transition metal cations, as a first stage for the preparation of more efficient chiral catalysts, we planned the preparation of both enantiomers of 3-aminopantolactam **6** and other amino-substituted derivatives, which might give stronger metal complexes than lactams **4**, if the lactam N–H group was deprotonated.

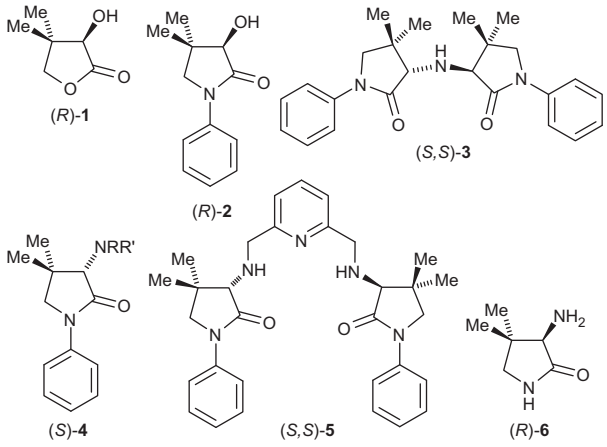

Figure 1. Structures of pantolactone and several pantolactam derivatives.

Since we had previously developed a one-step preparation of different *N*-substituted pantolactams[5] from pantolactone and the known preparation of the 1-unsusbtituted pantolactam requires a three-step sequence,[6] we planned the preparation of (*R*)- and (*S*)-**6** from the new *rac*-*N*-(*p*-methoxybenzyl)pantolactam, *rac*-**8** (Scheme 1). The protecting *p*-methoxybenzyl group might be removed in the last step of the sequence using ammonium cerium(IV) nitrate [$Ce(NH_4)_2(NO_3)_6$, CAN].[7]

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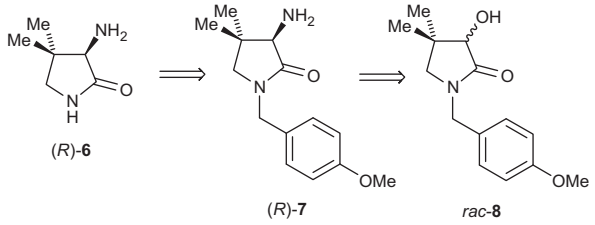
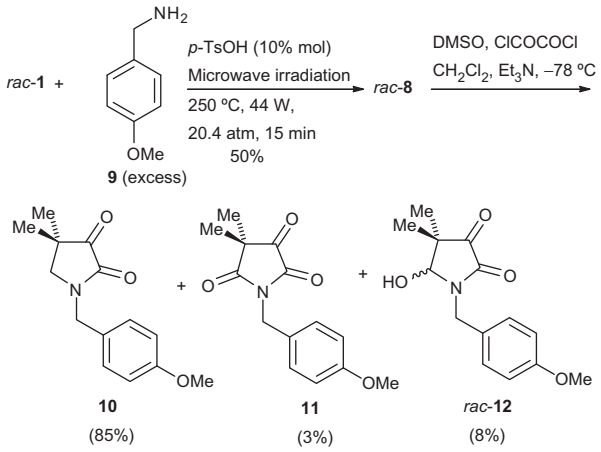


Scheme 1. Planned preparation of (*R*)-**6**.

2. Results and discussion

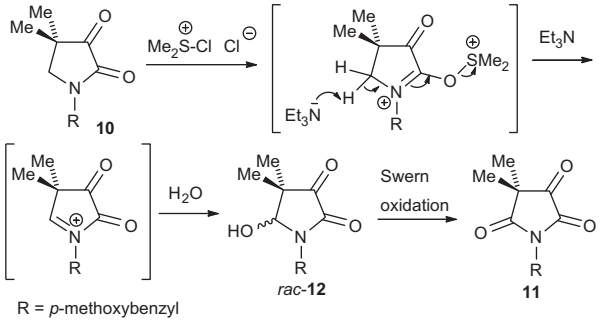
The reaction of *rac*-**1** with excess *p*-methoxybenzylamine, **9**, under *p*-TsOH catalysis and microwave irradiation gave solid *rac*-*N*-(*p*-methoxybenzyl)pantolactam, *rac*-**8**, in 50% yield of chromatographed product. Swern oxidation of *rac*-**8** gave ketolactam **10** in 85% yield after column chromatography (Scheme 2).[8]



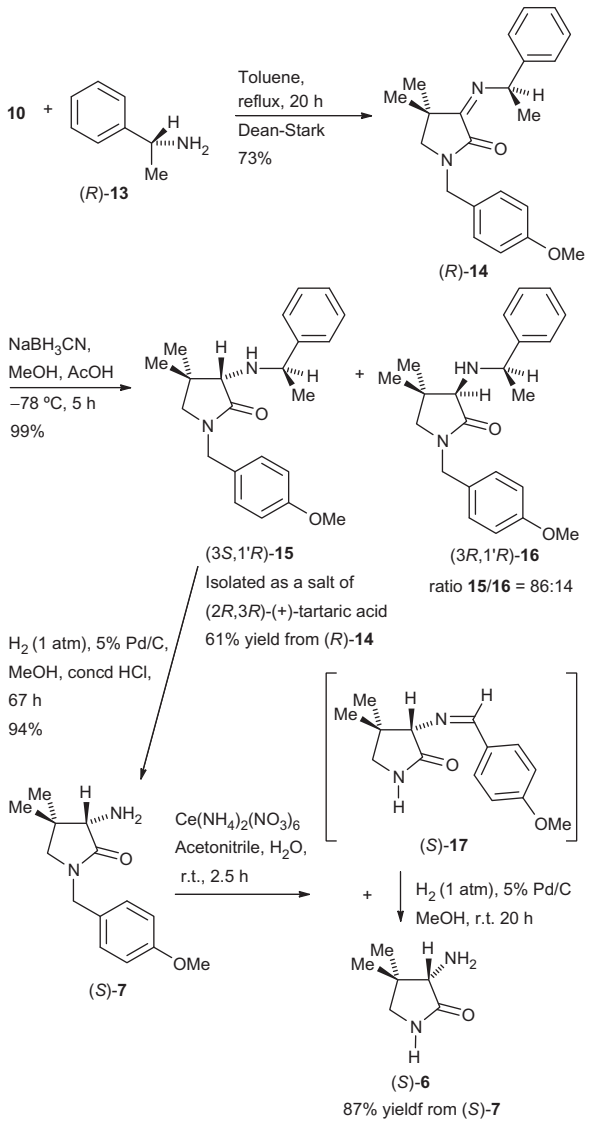
Scheme 2. Preparation of ketolactam **10**.

From this reaction, over-oxidation products **11** (3% yield) and *rac*-**12** (8% yield) were also isolated and fully characterized. The formation of **11** and *rac*-**12** can be envisaged as shown in Scheme 3 by reaction of ketolactam **10** with excess Swern reagent (dimethylchlorosulfonium chloride) to give a new sulfonium cation, which on reaction with triethylamine would give an imonium ion. Reaction of this imonium ion with adventitious water would give *rac*-**12**, which on Swern oxidation would lead to **11**. Alternatively, oxidation of *rac*-**8** using RuO_4 generated from a catalytic amount of $RuCl_3{\cdot}3H_2O$ and trichloroisocyanuric acid as the stoichiometric oxidant under phase-transfer conditions in a biphasic system acetonitrile/water[9] gave ketolactam **10** in only 40% yield. Similarly, chromic acid oxidation[10] of *rac*-**8** gave **10** in 34% yield, some *p*-anisaldehyde (15%) and starting alcohol (8%) also being isolated, thus showing partial oxidation of the protecting group.

The diastereoselective amination of ketolactam **10** was carried out using (*R*)-α-methylbenzylamine, (*R*)-**13**, as a chiral auxiliary (Scheme 4).[4] The reaction of **10** with (*R*)-**13** in refluxing toluene in the absence of any catalyst with continuous removal of water with a Dean–Stark equipment gave imine (*R*)-**14** in 73% yield of chromatographed product. The sodium cyanoborohydride reduction of this imine in methanol at −78 °C gave a mixture of amines (3*S*,1′*R*)-**15**/(3*R*,1′*R*)-**16** in a 86:14 diastereomeric ratio, established by ^{1}H NMR on the basis of the integral of the singlet signal of the 3-H proton [δ = 2.97 ppm for (3*S*,1′*R*)-**15** and 2.83 ppm for (3*R*,1′*R*)-**16**]. The main diastereomer of the mixture was isolated as a white solid by crystallization of its salt with (2*R*,3*R*)-(+)-tartaric acid in 61% overall yield from imine (*R*)-**14**. The corresponding amine



Scheme 3. Proposed mechanism for the formation of **11** and *rac*-**12** during the Swern oxidation of *rac*-**8** to **10**.



Scheme 4. Diastereoselective reductive amination of ketolactam **10** and preparation of amine (*S*)-**6**.

was liberated from the above-mentioned salt and both the products were fully characterized. The absolute configuration of C3 was established as follows; hydrogenation of (3*S*,1′*R*)-**15** at atmospheric pressure using 5% Pd on charcoal as a catalyst in the presence of trace amounts of concentrated HCl gave the debenzylated

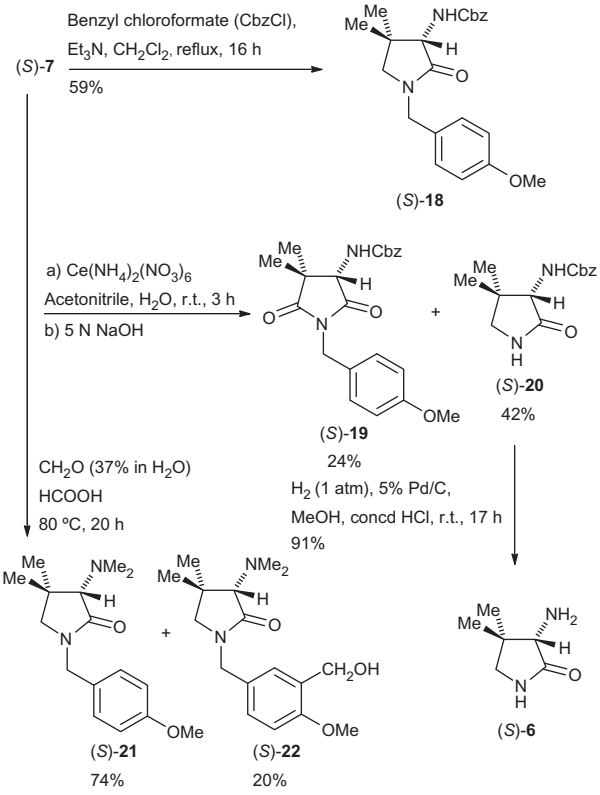
amine (*S*)-**7** which was transformed into the salt derived from (2*R*,3*R*)-di-*O*,*O*′-(*p*-toluoyl)tartaric acid. Single crystal X-ray diffraction analysis of this salt (Fig. 2)[11] allowed us to establish the absolute configuration of (*S*)-**7** and, consequently, of its precursors, amine (3*S*,1′*R*)-**15** and diastereomer (3*R*,1′*R*)-**16**.

Hydrogenation (24 atm, 24 h) of (*S*)-**7** using palladium hydroxide[12] as the catalyst left the starting compound unchanged. The treatment of (*S*)-**7** with an excess of trifluoroacetic acid[13] in $CHCl_3$ solution led to a quantitative recovery of the starting compound. Oxidation of (*S*)-**7** with CAN[7] in acetonitrile/water gave a neutral fraction containing a mixture of imine (*S*)-**17** and *p*-anisaldehyde, and a basic fraction containing (*S*)-**6**. Catalytic hydrogenation of the mixture of imine (*S*)-**17** and *p*-anisaldehyde using 5% Pd/C as the catalyst gave (*S*)-**6**. Altogether, (*S*)-**6** was obtained in 87% total yield.

Alternatively, CAN removal of the *p*-methoxybenzyl group was performed on (*S*)-**18**, the *N*-Cbz-protected derivative of (*S*)-**7** (Scheme 5). The reaction of (*S*)-**7** with benzyl chloroformate gave the Cbz-protected derivative (*S*)-**18**, which on reaction with CAN, followed by treatment with aqueous 5 N NaOH gave a mixture of the oxidation product (*S*)-**19** and the expected product (*S*)-**20**, which were isolated by silica gel column chromatography in 24% and 42% yield, respectively. Hydrogenation of (*S*)-**20** gave (*S*)-**6** in 91% yield.

We also carried out the reductive methylation of (*S*)-**7** with formaldehyde and formic acid. From this reaction, the desired dimethylamino derivative (*S*)-**21** and the hydroxymethylated derivative (*S*)-**22** were isolated in 74% and 20% yield, respectively, by column chromatography of the crude product (Scheme 5).

Although we had succeeded in obtaining (*S*)-**6** from pactolactam *rac*-**8**, in view of the problems associated with the use of the *p*-methoxybenzyl-protecting group in these synthetic sequences: (i) multi-step low yielding synthetic sequences, (ii) formation of imine (*S*)-**17** during CAN deprotection of amine (*S*)-**7**, (iii) oxidation of the lactam ring during CAN deprotection of (*S*)-**18**, and (iv) hydroxymethylation of the protecting group during reductive methylation of amine (*S*)-**7**, we studied the possible preparation of amine **6** from the known *N*-unsubstituted pantolactam *rac*-**23**.[6]



Scheme 5. Preparation of (*S*)-**6** and reductive methylation of (*S*)-**7**.

First, we synthesized *rac*-**6** as shown in Scheme 6. Chromic acid oxidation of *rac*-**23** gave the new ketolactam **24** in 75% isolated yield. The reaction of **24** with benzylamine in toluene at reflux, and removing the water formed with a Dean–Stark equipment gave the corresponding imine **25** in quantitative yield, which was hydrogenated using 5% Pd/C as a catalyst to give *rac*-**6** in high yield.

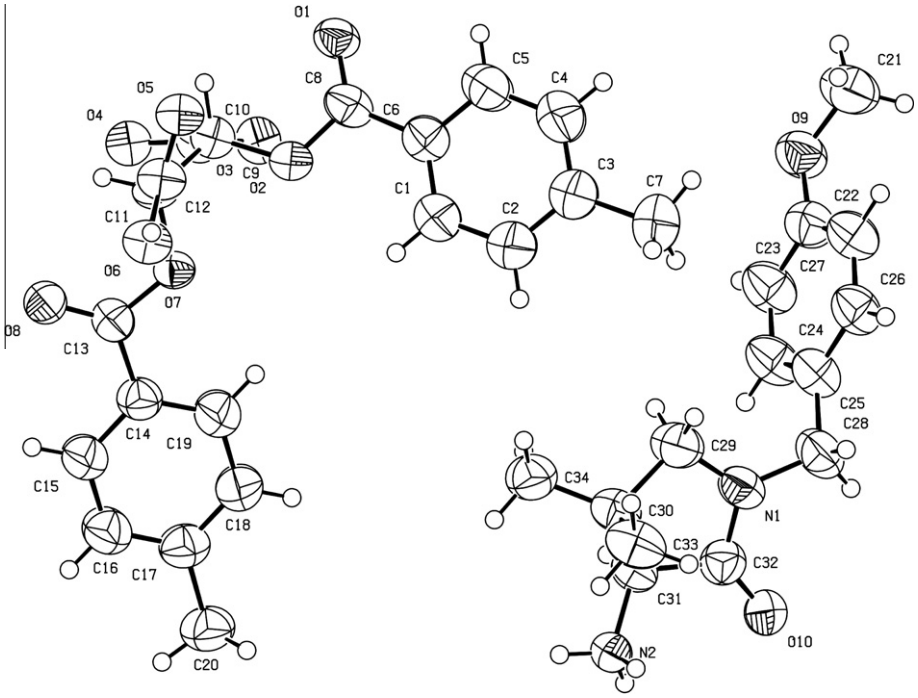
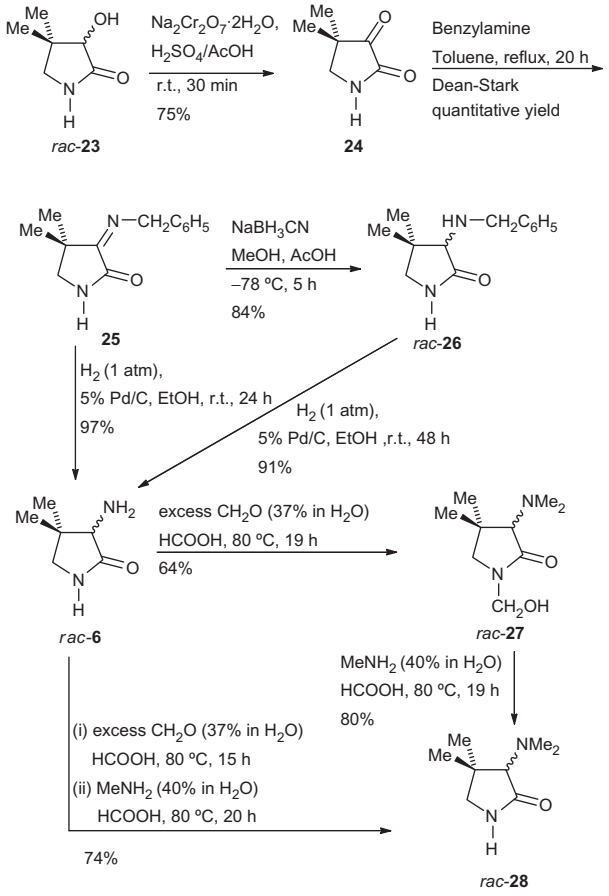
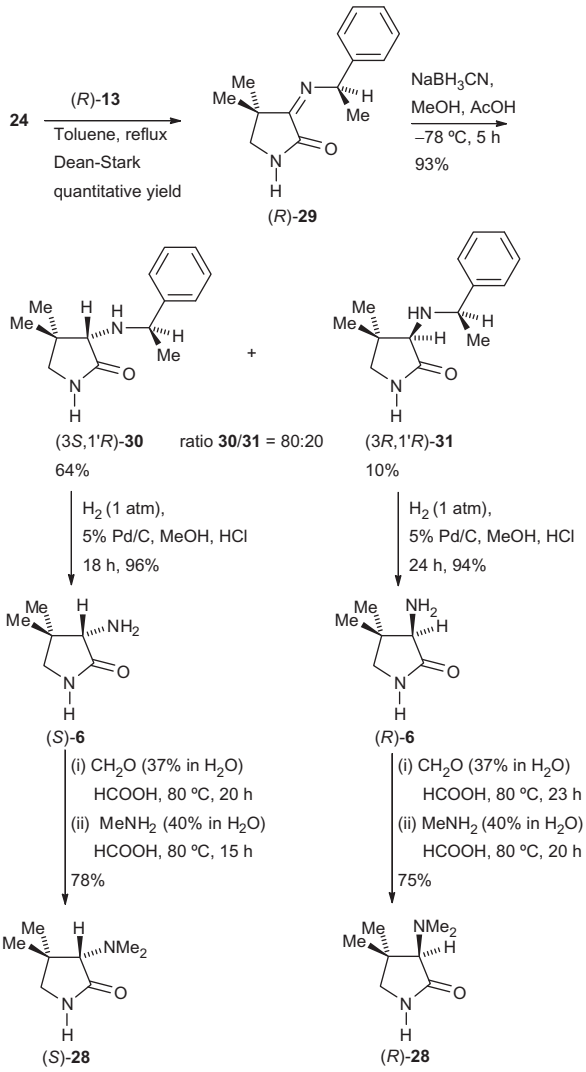


Figure 2. ORTEP representation of (*S*)-**7**·(2*R*,3*R*)-di-*O*,*O*′-(*p*-toluoyl)tartrate.



Scheme 6. Preparation of aminolactams *rac*-**6** and *rac*-**28** from pantolactam *rac*-**23**.



Scheme 7. Preparation of aminolactams (*R*)-**6**, (*S*)-**6**, (*R*)-**28** and (*S*)-**28** from ketolactam **24**.

Alternatively, sodium cyanoborohydride reduction of the imine **25** gave the benzylamino derivative *rac*-**26**, which was hydrogenated as before to *rac*-**6**.

Methylation of *rac*-**6** with an excess of formaldehyde and formic acid gave amine *rac*-**27** in good yield, derived from the complete methylation of the primary amine and the hydroxymethylation of the lactam N–H functionality. Heating *rac*-**27** in water under formic acid catalysis gave a mixture of the starting compound and *rac*-**28**, thus showing that the hydroxymethylation of *rac*-**28** might be reverted. Reaction of *rac*-**27** with 40% aqueous methylamine and formic acid gave the desired amine *rac*-**28** in good yield, the methylamine acting as a formaldehyde trap through its reductive methylation.

Then, we prepared the enantiopure amines (*S*)- and (*R*)-**6** and the corresponding dimethylated derivatives (*S*)- and (*R*)-**28** as shown in Scheme 7. The reaction of **24** with (*R*)-**13** in toluene at reflux with azeotropic removal of water gave imine (*R*)-**29**, which on reduction with sodium cyanoborohydride gave a diastereomeric mixture of amines (3*S*,1′*R*)-**30**/(3*R*,1′*R*)-**31** in 93% yield and an approximate 80:20 diastereomeric ratio, established by ^{1}H NMR on the basis of the integral of the quartet signal of the CH_3CH protons [δ = 3.93 ppm for (3*S*,1′*R*)-**30** and 4.30 ppm for (3*R*,1′*R*)-**31**].

Crystallization of the diastereomeric mixture of (3*S*,1′*R*)-**30** and (3*R*,1′*R*)-**31** from a mixture of Et_2O/hexane gave the less abundant higher melting point amine (3*R*,1′*R*)-**31** (10% yield) and a mixture of both amines (7% yield). Crystallization of the residue from an Et_2O/pentane mixture gave the more abundant lower melting point diastereomeric amine (3*S*,1′*R*)-**30** in 64% yield. Alternatively, the diastereomeric mixture of (3*S*,1′*R*)-**30** and (3*R*,1′*R*)-**31** was separated by silica gel column chromatography. The absolute configuration of (3*R*,1′*R*)-**31** was established by X-ray diffraction analysis (Fig. 3).[11] Consequently, the configuration of the main diastereomeric amine must be (3*S*,1′*R*)-**30**.

The observed diastereoselectivity was similar to that previously observed in the reduction of the *N*-(*p*-methoxybenzyl) imine (*R*)-**14** or the corresponding *N*-phenyl derivatives.[4] Hydrogenation of amines (3*S*,1′*R*)-**30** and (3*R*,1′*R*)-**31** using 5% Pd on charcoal as a catalyst in the presence of trace amounts of concentrated HCl gave the corresponding primary amines (*S*)- and (*R*)-**6** in high yields.

Reductive methylation of these amines with formaldehyde and formic acid followed by treatment with methylamine and formic acid to dehydroxymethylate the lactam N–H group, as described before for the preparation of *rac*-**28**, gave (*S*)- and (*R*)-**28** in good yields.

3. Conclusion

A straightforward preparation of 3-amino-4,4-dimethylpyrrolidin-2-ones unsubstituted at the lactam nitrogen and derivatives thereof, which does not require the protection of the lactam function, has been developed. Work is currently in progress to apply the new aminolactams **6** and **28** as chiral ligands or catalysts for enantioselective transformations.

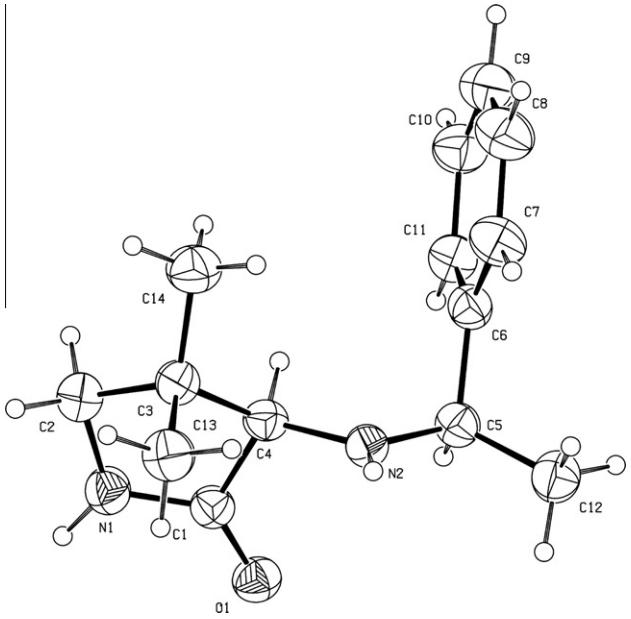


Figure 3. ORTEP representation of (3*R*,1′*R*)-**31**.

4. Experimental

4.1. General experimental details

Melting points were determined in open capillary tubes. Unless otherwise stated, NMR spectra were recorded at 25 °C in $CDCl_3$: ^1H NMR (400 MHz), ^{13}C NMR (100.6 MHz). All chemical shifts (δ_H and δ_C) are reported in parts per million (ppm) related to internal standard ($CHCl_3$ at δ_H = 7.26 ppm, δ_C = 77.0 ppm). Assignments given for the NMR spectra are based on DEPT sequence, $^1H/^1H$ COSY, $^1H/^{13}C$ HETCOR (HSQC sequence), and $^1H/^1H$ NOESY experiments for selected compounds. Coupling constants *J* are given in hertz (Hz). Mass spectra were recorded on a LC/MSD-TOF (2006, Agilent technologies), using electrospray (ESI-MS, positive mode, capillary: 3.5 kV, fragmentor: 215 V). The samples were introduced into the source with an HPLC system (Agilent 1100), using a mixture of H_2O/acetonitrile 1:1 as an eluent (200 μL/min) and depending on the nature of the samples 1% formic acid was added to the eluent. Unless otherwise stated, IR spectra were performed with the attenuated total reflection (ATR) technique and the absorption values are given as wavenumbers (cm^{-1}). Elemental analyses were done at the Microanalysis Service of the IIQAB (CSIC, Barcelona, Spain). Optical rotations were determined on a polarimeter using a 1-dm cell. 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 the spots were visualized with UV light and/or 1% aqueous $KMnO_4$.

4.2. *rac*-3-Hydroxy-1-(*p*-methoxybenzyl)-4,4-dimethylpyrrolidin-2-one *rac*-8

A solution of *rac*-pantolactone, (±)-**1** (260 mg, 2.00 mmol), *p*-TsOH·H_2O (34 mg, 0.20 mmol), and *p*-methoxybenzylamine (520 μL, 550 mg, 4.01 mmol) was placed in a sealed cylindrical pyrex vessel. The mixture was introduced into a monomode reactor, Synthwave 402 Prolabo focused MW 2.45 GHz, at a power of 44 W, and heated at 250 °C and 20.4 atm for 15 min. The mixture was allowed to cool to room temperature, after which EtOAc (20 mL) was added. The solution was washed with aqueous 2 M HCl (2 × 30 mL) and the aqueous phase was extracted with EtOAc (3 × 30 mL). The combined organic extracts were washed with water (10 mL), dried (anhydrous $MgSO_4$), and concentrated under reduced pressure and the residue (600 mg) was subjected to column chromatography (silica gel, 60 g, hexane/EtOAc 5:1) isolating the lactam *rac*-**8** (250 mg, 50% yield) as a yellow solid. The analytical sample of *rac*-**8** was obtained as a white solid by crystallization from hexane/EtOAc 1:3 (3 mL), mp 120–121 °C (hexane/EtOAc 1:3); R_f 0.46 (silica gel, 7.2 cm, hexane/EtOAc 1:3); IR 3310 (OH), 2955, 2930, 1671 (CO), 1512, 1460, 1301, 1240, 1172, 1128, 1026, 809 cm^{-1}; ^1H NMR 0.93 (s, 3H) and 1.16 (s, 3H) [4-$(CH_3)_2$], 2.82 (d, *J* = 9.6 Hz, 1H) and 2.93 (d, *J* = 9.6 Hz, 1H) (5-H_2), 3.69 (br s, 1H, OH), 3.79 (s, 3H, OCH_3), 4.00 (d, *J* = 3.6 Hz, 1H, 3-H), 4.29 (d, *J* = 14.4 Hz, 1H) and 4.46 (d, *J* = 14.4 Hz, 1H) (N–CH_2), 6.85 [dm, *J* = 8.8 Hz, 2H, Ar-3(5)-H], 7.15 [dm, *J* = 8.8 Hz, 2H, Ar-2(6)-H]; ^{13}C NMR 20.0 (CH_3) and 24.8 (CH_3) [4-$(CH_3)_2$], 38.6 (C, C4), 46.2 (CH_2, N–CH_2), 55.2 (CH_3, OCH_3), 56.1 (CH_2, C5), 77.9 (CH, C3), 114.1 [CH, Ar-C3(5)], 127.8 (C, Ar-C1), 129.6 [CH, Ar-C2(6)], 159.2 (C, Ar-C4), 174.3 (C, C2). Anal. Calcd for $C_{14}H_{19}NO_3$: C, 67.45; H, 7.68; N, 5.62. Found: C, 67.33; H, 7.76; N, 5.59. HRMS (ESI) calcd for ($[M+H]^+$): 250.1438; found 250.1438.

4.3. Swern oxidation of *rac*-8: obtention of 1-(*p*-methoxybenzyl)-4,4-dimethylpyrrolidine-2,3-dione 10 and isolation of 1-(*p*-methoxybenzyl)-4,4-dimethylpyrrolidine-2,3,5-trione 11 and *rac*-5-hydroxy-1-(*p*-methoxybenzyl)-4,4-dimethylpyrrolidine-2,3-dione *rac*-12

To a cooled (−78 °C) solution of oxalyl chloride (1.65 mL, 2.48 g, 19.5 mmol) in anhydrous CH_2C1_2 (20 mL) was added anhydrous DMSO (2.75 mL, 3.02 g, 38.7 mmol). After 1 h at −78 °C, a solution of *rac*-**8** (2.41 g, 9.67 mmol) in anhydrous CH_2Cl_2 (15 mL) was added dropwise, keeping the temperature under −50 °C. After 10 min at −78 °C, freshly distilled Et_3N (8.0 mL, 5.81 g, 57.4 mmol) was added dropwise, keeping the temperature at −78 °C. After 30 min at this temperature, the mixture was allowed to warm to room temperature for 1 h. Then, water (22 mL) was added and the mixture was extracted with Et_2O (3 × 50 mL) and the combined organic phases were washed with saturated aqueous solutions of NH_4Cl (15 mL) and $NaHCO_3$ (20 mL) and with brine (15 mL). The solution was dried (anhydrous $MgSO_4$) and concentrated under reduced pressure to give a residue (2.39 g) that was subjected to column chromatography (silica gel, 123 g, CH_2Cl_2/MeOH mixtures). In the order of elution, product **11** (70 mg, 3% yield), ketolactam **10** (2.02 g, 85% yield) (CH_2Cl_2/MeOH 100:1), and *rac*-**12** (200 mg, 8% yield) (CH_2Cl_2/MeOH 50:1) were isolated.

Compound **10**: The analytical sample was obtained as a white solid by crystallization from EtOAc/Et_2O 3:5 (10 mL), mp 105−106 °C (EtOAc/Et_2O 3:5); R_f 0.36 (silica gel, 5.5 cm, CH_2Cl_2/MeOH 100:1); IR 2968, 2925, 1765 and 1712 (CO), 1610, 1513, 1469, 1443, 1304, 1235, 1180, 1066, 1033, 839, 817 cm^{-1}; ^1H NMR 1.18 [s, 6H, 4-$(CH_3)_2$], 3.24 (s, 2H, 5-H_2), 3.81 (s, 3H, OCH_3), 4.63 (s, 2H, N–CH_2), 6.89 [dm, *J* = 8.8 Hz, 2H, Ar-3(5)-H], 7.21 [dm, *J* = 8.8 Hz, 2H, Ar-2(6)-H]; ^{13}C NMR 23.6 [CH_3, 4-$(CH_3)_2$], 39.9 (C, C4), 47.8 (CH_2, N–CH_2), 55.1 (CH_2, C5), 55.3 (CH_3, OCH_3), 114.4 [CH, Ar-C3(5)], 126.5 (C, Ar-C1), 129.9 [CH, Ar-C2(6)], 159.0 (C) and 159.6 (C) (C2 and Ar-C4), 203.9 (C, C3). Anal. Calcd for $C_{14}H_{17}NO_3$: C, 68.00; H, 6.93; N, 5.66. Found: C, 67.94; H, 7.00; N, 5.60. HRMS (ESI): calcd for ($[M+H]^+$): 248.1281; found 248.1286.

Compound **11**: The analytical sample was obtained as a white solid by crystallization from Et_2O (5 mL), mp 79–80 °C (Et_2O); R_f 0.74 (silica gel, 5.4 cm, CH_2Cl_2/MeOH 100:1); IR 2946, 1800 (CO), 1778 and 1702 (CO), 1610, 1512, 1463, 1429, 1392, 1333, 1293, 1244, 1133, 1062, 1035, 812 cm^{-1}; ^1H NMR 1.33 [s, 6H, 4-$(CH_3)_2$], 3.78 (s, 3H, OCH_3), 4.80 (s, 2H, N–CH_2), 6.85 [d, *J* = 9.0 Hz, 2H, Ar-3(5)-H], 7.35 [d, *J* = 9.0 Hz, 2H, Ar-2(6)-H]; ^{13}C

NMR 19.9 [CH_3, 4-$(CH_3)_2$], 42.2 (CH_2, N–CH_2), 45.9 (C, C4), 55.2 (CH_3, OCH_3), 114.2 [CH, Ar-C3(5)], 126.8 (C, Ar-C1), 130.4 [CH, Ar-C2(6)], 159.6 (C) and 159.8 (C) (C2 and Ar-C4), 176.4 (C, C5), 197.1 (C, C3). Anal. Calcd for $C_{14}H_{15}NO_4$: C, 64.36; H, 5.79; N, 5.36. Found: C, 64.34; H, 5.70; N, 5.31. HRMS (ESI) calcd for ($[M+NH_4]^+$): 279.1339; found 279.1348.

Compound rac-**12**: The analytical sample was obtained as a white solid by crystallization from CH_2Cl_2 (5 mL), mp 179–180 °C (CH_2Cl_2); R_f 0.23 (silica gel, 7.8 cm, CH_2Cl_2/MeOH 40:1); IR 3298 (OH), 2976, 2941, 1769 and 1703 (CO), 1612, 1512, 1469, 1455, 1304, 1235, 1088, 1053, 1034, 866, 839, 815, 678, 662 cm^{-1}; ^1H NMR (DMSO-d_6) 0.98 (s, 3H) and 1.01 (s, 3H) [4-$(CH_3)_2$], 3.73 (s, 3H, OCH_3), 4.25 (d, J = 14.6 Hz, 1H) and 4.77 (d, J = 14.6 Hz, 1H) (N–CH_2), 4.73 (dm, J = 6.6 Hz, 1H, 5-H), 6.55 (d, J = 6.6 Hz, 1H, OH), 6.91 [dm, J = 8.4 Hz, 2H, Ar-3(5)-H], 7.26 [d, J = 8.4 Hz, 2H, Ar-2(6)-H]; ^{13}C NMR (DMSO-d_6) 17.9 (CH_3) and 22.5 (CH_3) [4-$(CH_3)_2$], 43.4 (CH_2, N–CH_2), 45.6 (C, C4), 55.2 (CH_3, OCH_3), 84.2 (CH, C5), 114.1 [CH, Ar-C3(5)], 127.8 (C, Ar-C1), 129.8 [CH, Ar-C2(6)], 158.7 (C) and 158.9 (C) (Ar-C4 and C2), 203.9 (C, C3). Anal. Calcd for $C_{14}H_{17}NO_4{\cdot}0.15CH_2Cl_2$: C, 61.57; H, 6.32; N, 5.07. Found: C, 61.26; H, 6.21; N, 5.10. HRMS (ESI) calcd for ($[M+H]^+$): 264.1230; found 264.1219.

4.4. (*R*)-1-(*p*-Methoxybenzyl)-4,4-dimethyl-3-[(1-phenylethyl)-imino]pyrrolidin-2-one (*R*)-14

A solution of **10** (410 mg, 1.66 mmol) and (*R*)-1-phenylethylamine, (*R*)-**13** (215 μL, 202 mg, 1.67 mmol), in toluene (50 mL) was heated at reflux for 20 h in Dean–Stark equipment. Evaporation of the solvent under reduced pressure gave an oily residue (608 mg) that was subjected to column chromatography (aluminum oxide, 60 g, hexane/EtOAc 10:1) isolating (*R*)-**14** (425 mg, 73% yield) as a colorless oil. $[\alpha]_D^{23} = +39$ (*c* 0.76, CH_2Cl_2); R_f 0.38 (aluminum oxide, 7.1 cm, hexane/EtOAc 9:1); IR 2964, 2925, 1681 (CO), 1611, 1512, 1439, 1302, 1246, 1175, 1032, 761, 699 cm^{-1}; ^1H NMR (300 MHz) 1.15 (s, 3H) and 1.19 (s, 3H) [4-$(CH_3)_2$], 1.46 (d, J = 6.6 Hz, 3H, CH_3-CH), 3.08 (s, 2H, 5-H_2), 3.80 (s, 3H, OCH_3), 4.43 (d, J = 14.4 Hz, 1H) and 4.50 (d, J = 14.4 Hz, 1H) (N–CH_2), 6.57 (q, J = 6.6 Hz, 1H, CH_3-CH), 6.87 [dm, J = 8.5 Hz, 2H, Ar-3(5)-H *p*-methoxybenzyl], 7.18 [dm, J = 8.5 Hz, 2H, Ar-2(6)-H *p*-methoxybenzyl], 7.21 (overlapped tm, J = 7.5 Hz, 1H, Ar-H_{para} phenyl), 7.32 (tm, J = 7.5 Hz, 2H, Ar-H_{meta} phenyl), 7.49 (dm, J = 7.5 Hz, 2H, Ar-H_{ortho} phenyl); ^{13}C NMR (75.4 MHz) 25.4 (CH_3), 25.9 (CH_3) and 26.7 (CH_3) [4-$(CH_3)_2$ and CH_3-CH], 37.8 (C, C4), 46.7 (CH_2, CH_2-N), 55.3 (CH_3, OCH_3), 56.1 (CH, CH_3-CH), 56.5 (CH_2, C5), 114.2 [CH, Ar-C3(5) *p*-methoxybenzyl], 126.3 (CH, Ar-C_{para} phenyl), 126.6 (CH, Ar-C_{ortho} phenyl), 127.5 (C, Ar-C1 *p*-methoxybenzyl), 128.2 (CH, Ar-C_{meta} phenyl), 129.7 [CH, Ar-C2(6) *p*-methoxybenzyl], 146.5 (C, Ar-C_{ipso} phenyl), 159.3 (C) and 160.3 (C) (Ar-C4 *p*-methoxybenzyl and C2), 164.6 (C, C3). Anal. Calcd for $C_{22}H_{26}N_2O_2{\cdot}0.1H_2O$: C, 75.01; H, 7.50; N, 7.95. Found: C, 74.92; H, 7.48; N, 7.78. HRMS (ESI): calcd. for ($[M+H]^+$): 351.2067; found 351.2067.

4.5. (3*S*,1′*R*)-1-(*p*-Methoxybenzyl)-4,4-dimethyl-3[(1-phenylethyl)amino]pyrrolidin-2-one·(2*R*,3*R*)-tartrate, (3*S*,1′*R*)-15·(2*R*,3*R*)-tartrate

To a cold (−78 °C) solution of (*R*)-**14** (360 mg, 1.03 mmol) in anhydrous MeOH (20 mL), a solution of $NaBH_3CN$ (95% purity, 137 mg, 2.18 mmol) and AcOH (100 μL, 100 mg, 1.67 mmol) in anhydrous MeOH (5 mL) was added dropwise and the reaction mixture was stirred at this temperature for 4 h. Then more $NaBH_3CN$ (80 mg, 1.27 mmol) was added and the mixture was stirred for 1 h. Water (50 mL) was then added and the organic solvent was evaporated under reduced pressure. The remaining aqueous phase was treated with aqueous 2 M NaOH until pH 12–13 and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were dried (anhydrous $MgSO_4$) and concentrated under reduced pressure to give a diastereomeric mixture of (3*S*,1′*R*)-**15** and (3*R*,1′*R*)-**16** (359 mg, 99% yield) in a ratio of 86:14 (^1H NMR). This mixture (359 mg, 1.02 mmol) was taken in MeOH (2 mL) and treated with a solution of (2*R*,3*R*)-(+)-tartaric acid (160 mg, 1.06 mmol) in MeOH (3 mL), and the mixture was concentrated to dryness in vacuo. The obtained solid was taken in a mixture of Et_2O/EtOAc/acetonitrile 3:2:1 (13 mL) and the mixture was cooled to −20 °C for 24 h. The precipitated solid was collected by filtration and washed with a mixture of Et_2O/EtOAc 5:1 (2 mL) to give, after drying, (3*S*,1′*R*)-**15**·(2*R*,3*R*)-tartrate (315 mg, 61% yield) as a white solid, mp 112–113 °C (Et_2O/EtOAc/acetonitrile 3:2:1). $[\alpha]_D^{23} = +9$ (*c* 1.10, MeOH); IR 3600–2400 (max at 3420, 2967, 2940, 2842, 2713, OH, $^+$NH and CH), 1700 (CO), 1610, 1586, 1513, 1441, 1242, 1207, 1176, 1125, 1071, 1029, 896, 834, 814, 763, 699, 670 cm^{-1}; ^1H NMR (CD_3OD) 0.95 (s, 3H) and 1.16 (s, 3H) [4-$(CH_3)_2$], 1.48 (d, J = 6.8 Hz, 3H, CH_3-CH), 2.83 (d, J = 9.6 Hz, 1H) and 2.97 (d, J = 9.6 Hz, 1H) (5-H_2), 3.40 (s, 1H, 3-H), 3.77 (s, 3H, OCH_3), 4.20 (d, J = 14.4 Hz, 1H) and 4.49 (d, J =14.4 Hz, 1H) (N–CH_2), 4.29 (q, J = 6.8 Hz, 1H, CH_3-C*H*), 4.48 (s, 2H, CH tartrate), 4.88 (br s, 5H, COOH, 2OH and $^+NH_2$), 6.87 [dm, J = 8.8 Hz, 2H, Ar-3(5)-H *p*-methoxybenzyl], 7.16 [dm, J = 8.8 Hz, 2H, Ar-2(6)-H *p*-methoxybenzyl], 7.31 (tt, J = 7.4, 1.7 Hz, 1H, Ar-H_{para} phenyl), 7.39 (tm, J = 7.4 Hz, 2H, Ar-H_{meta} phenyl), 7.45 (dm, J = 7.4 Hz, 2H, Ar-H_{ortho} phenyl); ^{13}C NMR (CD_3OD) 21.4 (CH_3), 22.4 (CH_3) and 25.6 (CH_3) [4-$(CH_3)_2$ and CH_3-CH], 39.5 (C, C4), 47.0 (CH_2, N–CH_2), 55.7 (CH_3, OCH_3), 57.9 (CH_2, C5), 58.7 (CH, CH_3-C*H*), 66.2 (CH, C3), 73.7 [CH, C2(3) tartrate], 115.1 [CH, Ar-C3(5) *p*-methoxybenzyl], 128.3 (CH, Ar-C_{ortho} phenyl), 129.0 (CH, Ar-C_{para} phenyl), 129.1 (C, Ar-C1 *p*-methoxybenzyl), 129.9 (CH, Ar-C_{meta} phenyl), 130.7 [CH, Ar-C2(6) *p*-methoxybenzyl], 143.3 (C, Ar-C_{ipso} phenyl), 160.9 (C, Ar-C4 *p*-methoxybenzyl), 173.8 (C, C2), 175.5 [C, C1(4) tartrate]. Anal. Calcd for $C_{22}H_{28}N_2O_2{\cdot}C_4H_6O_6{\cdot}0.75H_2O$: C, 60.51; H, 6.93; N, 5.43. Found: C, 60.17; H, 6.61; N, 5.32.

A sample of (3*S*,1′*R*)-**15** as the free base was obtained as follows: (3*S*,1′*R*)-**15**·(2*R*,3*R*)-tartrate (136 mg, 0.27 mmol) was taken in EtOAc (30 mL); the solution was washed with aqueous 2 M NaOH (3 × 5 mL), dried (anhydrous $MgSO_4$), and concentrated in vacuo to give (3*S*,1′*R*)-**15** (85 mg, 90% yield) as a colorless oil. $[\alpha]_D^{23} = +14$ (*c* 0.54, CH_2Cl_2); R_f 0.43 (aluminum oxide, 7.7 cm, CH_2Cl_2); IR 2959, 2925 (NH and CH), 1686 (CO), 1612, 1512, 1438, 1244, 1174, 1151, 1032, 816, 762, 700 cm^{-1}; ^1H NMR 0.93 (s, 3H) and 1.09 (s, 3H) [C4−$(CH_3)_2$], 1.37 (d, J = 6.6 Hz, 3H, CH_3CH), 1.7–2.1 (br s, 1H, N-H), 2.68 (d, J = 9.6 Hz, 1H) and 2.78 (d, J = 9.6 Hz, 1H) (5-H_2), 2.97 (s, 1H, 3-H), 3.78 (s, 3H, OCH_3), 3.92 (q, J = 6.6 Hz, 1H, CH_3C*H*), 4.18 (d, J = 14.4 Hz, 1H) and 4.46 (d, J = 14.4 Hz, 1H) (N–CH_2), 6.82 [dm, J = 8.4 Hz, 2H, Ar-3(5)-H *p*-methoxybenzyl], 7.11 [dm, J = 8.4 Hz, 2H, Ar-2(6)-H *p*-methoxybenzyl], 7.22–7.25 (m, 2H) and 7.32–7.34 (complex signal, 3H) (Ar-H phenyl); ^{13}C NMR 21.4 (CH_3), 24.9 (CH_3) and 26.1 (CH_3) [4-$(CH_3)_2$ and CH_3-CH], 38.9 (C, C4), 46.2 (CH_2, N–CH_2), 55.2 (CH_3, OCH_3), 56.6 (CH_2, C5), 56.9 (CH, CH_3-C*H*), 65.1 (CH, C3), 114.0 [CH, Ar-C3(5) *p*-methoxybenzyl], 126.7 (CH, Ar-C_{ortho} phenyl), 126.9 (CH, Ar-C_{para} phenyl), 128.3 (C, Ar-C1 *p*-methoxybenzyl), 128.5 (CH, Ar-C_{meta} phenyl), 129.6 [CH, Ar-C2(6) *p*-methoxybenzyl], 145.1 (C, Ar-C_{ipso} phenyl), 159.0 (C, Ar-C4 *p*-methoxybenzyl), 174.2 (C, C2). Anal. Calcd for $C_{22}H_{28}N_2O_2{\cdot}0.25H_2O$: C, 74.02; H, 8.05; N, 7.85. Found: C, 74.09; H, 8.02; N, 7.82. HRMS (ESI) calcd for ($[M+H]^+$): 353.2224; found 353.2209.

4.6. (*S*)-3-Amino-1-(*p*-methoxybenzyl)-4,4-dimethylpyrrolidin-2-one (*S*)-7

A mixture of (3*S*,1′*R*)-**15** (620 mg, 1.76 mmol), concentrated HCl (56 μL), and 5% Pd/C (1.61 g) in MeOH (50 mL) was hydrogenated

at 1 atm and room temperature for 67 h. The mixture was filtered through a pad of Celite® washing the filter with MeOH (10 mL). The filtrate was basified with aqueous 2 M NaOH (15 mL) and extracted with EtOAc (3 × 40 mL). The combined organic extracts were dried (anhydrous $MgSO_4$) and concentrated under reduced pressure to give (*S*)-**7** (410 mg, 94% yield) as a colorless oil. $[\alpha]_D^{23} = -43$ (*c* 0.90, CH_2Cl_2); IR 2955, 2930, 1689 (CO), 1611, 1512, 1442, 1243, 1175, 1109, 1031, 811, 621 cm^{-1}; ^1H NMR 0.87 (s, 3H) and 1.13 (s, 3H) [C4-$(CH_3)_2$], 1.60 (br s, 3H, NH_2 and water), 2.80 (d, *J* = 9.6 Hz, 1H) and 2.94 (d, *J* = 9.6 Hz, 1H) (5-H_2), 3.17 (s, 1H, 3-H), 3.80 (s, 3H, OCH_3), 4.31 (d, *J* = 14.4 Hz, 1H) and 4.45 (d, *J* = 14.4 Hz, 1H) (N–CH_2), 6.85 [dm, *J* = 8.6 Hz, 2H, Ar-3(5)-H], 7.15 [dm, *J* = 8.6 Hz, 2H, Ar-2(6)-H]; ^{13}C NMR 20.2 (CH_3) and 25.0 (CH_3) [4-$(CH_3)_2$], 38.0 (C, C4), 46.3 (CH_2, N–CH_2), 55.3 (CH_3, OCH_3), 56.7 (CH_2, C5), 62.5 (CH, C3), 114.0 [CH, Ar-C3(5)], 128.3 (C, Ar-C1), 129.6 [CH, Ar-C2(6)], 159.1 (C, Ar-C4), 175.2 (C, C2). Anal. Calcd for $C_{14}H_{20}N_2O_2{\cdot}0.5H_2O$: C, 65.34; H, 8.23; N, 10.89. Found: C, 65.35; H, 8.11; N, 10.61. HRMS (ESI): calcd for ($[M+H]^+$): 249.1598; found 249.1594.

4.7. (*S*)-7·Mono-(2*R*,3*R*)-*O*,*O*′-di-(*p*-toluoyl)tartrate

Amine (*S*)-**7** (183 mg, 0.74 mmol) was taken in MeOH (3 mL) and a solution of (2*R*,3*R*)-(−)-*O*,*O*-di-(*p*-toluoyl)tartaric acid (97% purity, 327 mg, 0.81 mmol) in MeOH (5 mL) was added. The resulting solution was concentrated to dryness in vacuo to give a white solid, which was crystallized from a mixture of MeOH/Et_2O/hexane 1:1:1 (25 mL) to give (*S*)-**7**·mono-(2*R*,3*R*)-*O*,*O*′-di-(*p*-toluoyl)tartrate (389 mg, 81% yield), mp 186–187 °C (MeOH/Et_2O/hexane 1:1:1). $[\alpha]_D^{23} = -117$ (*c* 0.95, MeOH); IR 3200–2500 (max at 3204, 2956, 2922, COOH, OH, $^+$NH and CH), 1708 (CO), 1670, 1610, 1513, 1272, 1242, 1176, 1134, 1123, 1111, 1028, 834, 747, 690, 679 cm^{-1}; ^1H NMR (CD_3OD) 0.95 (s, 3H) and 1.20 (s, 3H) [C4–$(CH_3)_2$], 2.41 (s, 6H, CH_3 *p*-toluoyl), 2.95 (d, *J* = 10.0 Hz, 1H) and 3.15 (d, *J* = 10.0 Hz, 1H) (5-H_2), 3.78 (s, 3H, OCH_3), 3.83 (s, 1H, 3-H), 4.25 (d, *J* = 14.4 Hz, 1H) and 4.53 (d, *J* = 14.4 Hz, 1H) (N–CH_2), 4.89 (s, mobile H), 5.88 [s, 2H, 2(3)-H tartrate], 6.89 [dm, *J* = 8.4 Hz, 2H, Ar-3(5)-H], 7.20 [dm, *J* = 8.4 Hz, 2H, Ar-2(6)-H], 7.29 [d, *J* = 8.0 Hz 4H, 3(5)-H *p*-toluoyl], 8.01 [d, *J* = 8.0 Hz, 4H, 2(6)-H *p*-toluoyl]; ^{13}C NMR (CD_3OD) 21.0 (CH_3) and 24.6 (CH_3) [4-$(CH_3)_2$], 21.7 (CH_3, toluoyl CH_3), 38.1 (C, C4), 47.0 (CH_2, N–CH_2), 55.7 (CH_3, OCH_3), 58.0 (CH_2, C5), 61.2 (CH, C3), 74.8 [CH, C2(3) tartrate], 115.2 [CH, Ar-C3(5)], 128.4 (C, C1 *p*-toluoyl), 128.7 (C, Ar-C1), 130.1 [CH, C3(5) *p*-toluoyl], 130.8 [CH, Ar-C2(6)], 131.1 [CH, C2(6) *p*-toluoyl], 145.4 (C, C4 *p*-toluoyl), 161.0 (C, Ar-C4), 167.4 (C, CO *p*-toluoyl), 170.0 (C, C2), 171.5 [C, C1(4) tartrate]. Anal. Calcd for $C_{14}H_{20}N_2O_2{\cdot}C_{20}H_{18}O_8$: C, 64.34; H, 6.03; N, 4.41. Found: C, 64.44; H, 6.14; N, 4.28.

4.8. (*S*)-3-Amino-4,4-dimethylpyrrolidin-2-one, (*S*)-6, from (*S*)-7

To a solution of (*S*)-**7** (150 mg, 0.60 mmol) in acetonitrile (2 mL), a solution of $Ce(NH_4)_2(NO_3)_6$ (CAN, 1.35 g, 2.46 mmol) in water (2 mL) was added dropwise and the mixture was stirred for 2.5 h at room temperature until no more starting compound (TLC) was observed. The mixture was basified with aqueous 2 M NaOH until pH 7–8 and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were washed with water, dried (anhydrous $MgSO_4$), and concentrated under reduced pressure to give a residue, mixture of *p*-anisaldehyde and imine (*S*)-**17** (75 mg). The aqueous phase was alkalinized with 5 M NaOH (5 mL) and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were washed with water, dried (anhydrous $MgSO_4$), and concentrated under reduced pressure to give (*S*)-**6** (37 mg) as a white solid. A solution of the above-mentioned mixture of (*S*)-**17** and *p*-anisaldehyde (75 mg) in MeOH (5 mL) was hydrogenated at 1 atm and room temperature for 20 h, using 5% Pd/C (500 mg) as the catalyst. The mixture was filtered through a pad of Celite® washing the residue with MeOH (10 mL). The combined filtrate and washing were concentrated under reduced pressure to give (*S*)-**6** (30 mg, total yield of (*S*)-**6** as a white solid from (*S*)-**7**, 67 mg, 87%). The analytical sample was obtained by crystallization from EtOAc/MeOH 11:1, mp 95–96 °C (EtOAc/MeOH 11:1); $[\alpha]_D^{23} = -17$ (*c* 0.53, CH_2Cl_2). The IR, ^1H and ^{13}C NMR are coincidental with those of (*R*)-**6**, which are described later on. Anal. Calcd for $C_6H_{12}N_2O{\cdot}0.15H_2O$: C, 55.06; H, 9.47; N, 21.40. Found: C, 54.95; H, 9.63; N, 21.37. HRMS (ESI) calcd for ($[M+H]^+$): 129.1022; found 129.1021.

NMR data of (*S*)-**17** from the spectrum of the mixture with *p*-anisaldehyde: ^1H NMR δ 1.14 (s, 3H) and 1.15 (s, 3H) [4-$(CH_3)_2$], 3.12 (d, *J* = 9.6 Hz, 1H) and 3.28 (dd, *J* = 9.6, 1.2 Hz, 1H) (5-H_2), 3.50 (s, 1H, 3-H), 3.83 (s, 3H, OCH_3), 6.84–6.90 (broad s, 1H, 1-H), 6.90 [dm, *J* = 9.0 Hz, 2H, Ar-3(5)-H], 7.73 [dm, *J* = 9.0 Hz, 2H, Ar-2(6)-H], 8.26 (s, 1H, CH=N); ^{13}C NMR 22.0 (CH_3) and 26.0 (CH_3) [4-$(CH_3)_2$], 41.3 (C, C4), 53.5 (CH_2, C5), 55.3 (CH, C3), 79.1 (CH_3, OCH_3), 113.8 [CH, Ar-C3(5)], 129.0 (C, Ar-C1), 130.1 [CH, Ar-C2(6)], 161.8 (C) and 163.1 (C) (C=N and Ar-C4), 176.3 (C2).

4.9. Benzyl (*S*)-*N*-[1-(*p*-methoxybenzyl)-4,4-dimethyl-2-oxopyrrolidin-3-yl]carbamate (*S*)-18

A solution of (*S*)-**7** (580 mg, 2.34 mmol) in dry CH_2Cl_2 (10 mL) and freshly distilled Et_3N (500 μL, 363 mg, 3.56 mmol) were chilled in an ice-bath. While the solution was stirred, a solution of benzyl chloroformate (500 μL, 598 mg, 3.56 mmol) in dry CH_2Cl_2 (5 mL) was added dropwise. After 15 min, the reaction mixture was allowed to warm to room temperature and the solution was heated at reflux for 16 h. The reaction mixture was cooled to room temperature and poured into aqueous 2 M HCl (30 mL). The organic phase was separated and the aqueous one was extracted with CH_2Cl_2 (3 × 40 mL). The combined organic phase and extracts were dried (anhydrous $MgSO_4$) and concentrated in vacuo to give a viscous residue which was purified by column chromatography (silica gel, 90 g, hexane/EtOAc 1:1) obtaining (*S*)-**18** (528 mg, 59% yield) as a colorless oil. $[\alpha]_D^{23} = +25$ (*c* 0.62, CH_2Cl_2); R_f 0.58 (silica gel, 7.4 cm, EtOAc/hexane 1:1); IR (NaCl) 3290 (NH), 2960, 2931, 1713 and 1694 (CO), 1613, 1514, 1454, 1315, 1247, 1176, 1052, 817, 739, 698 cm^{-1}; ^1H NMR 0.83 (s, 3H) and 1.21 (s, 3H) [4-$(CH_3)_2$], 2.80 (d, *J* = 9.6 Hz, 1H) and 3.03 (d, *J* = 9.6 Hz, 1H) (5-H_2), 3.79 (s, 3H, OCH_3), 4.25 (d, *J* = 6.6 Hz, 1H, 3-H), 4.33 (d, *J* = 14.4 Hz, 1H) and 4.43 (d, *J* = 14.4 Hz, 1H) (N–CH_2), 5.13 (s, 2H, CH_2-Ph), 5.19 (br d, *J* = 6.6 Hz, 1H, NH), 6.85 [dm, *J* = 8.8 Hz, 2H, Ar-3(5)-H *p*-methoxybenzyl], 7.14 [dm, *J* = 8.8 Hz, 2H, Ar-2(6)-H *p*-methoxybenzyl], 7.29–7.37 (m, 5H, Ar-H phenyl); ^{13}C NMR 21.0 (CH_3) and 25.2 (CH_3) [4-$(CH_3)_2$], 38.9 (C, C4), 46.5 (CH_2, N–CH_2), 55.2 (CH_3, OCH_3), 56.4 (CH_2, C5), 62.0 (CH, C3), 67.1 (CH_2, CH_2-Ph), 114.1 [CH, Ar-C3(5) *p*-methoxybenzyl], 127.8 (C, Ar-C1 *p*-methoxybenzyl), 128.09 (CH), 128.13 (CH) and 128.5 (CH) (Ar-C_{ortho}, Ar-C_{meta} and Ar-C_{para} phenyl), 129.6 [CH, Ar-C2(6) *p*-methoxybenzyl], 136.2 (C, Ar-C1 phenyl), 157.0 (C, OCON), 159.2 (C, Ar-C4 *p*-methoxybenzyl), 171.4 (C, C2); Anal. Cald for $C_{22}H_{26}N_2O_4{\cdot}0.2H_2O$: C, 68.45; H, 6.89; N, 7.26. Found: C, 68.44; H, 6.89; N, 7.18. HRMS (ESI): calcd for ($[M+H]^+$) 383.1965; found 383.1958.

4.10. Oxidation of (*S*)-18 with ammonium cerium(IV) nitrate. Isolation of benzyl (*S*)-*N*-[1-(*p*-methoxybenzyl)-4,4-dimethyl-2,5-dioxopyrrolidin-3-yl]carbamate (*S*)-19 and benzyl (*S*)-*N*-[4,4-dimethyl-2-oxopyrrolidin-3-yl]carbamate (*S*)-20

To a solution of (*S*)-**18** (517 mg, 1.35 mmol) in acetonitrile (7 mL), a solution of ammonium cerium(IV) nitrate (CAN, 2.00 g,

3.65 mmol) in water (7 mL) was added dropwise and the mixture was stirred for 3 h at room temperature until no more starting compound (TLC) was observed. The mixture was basified with aqueous 5 M NaOH (5 mL) and extracted with EtOAc (3 × 50 mL). The combined organic extracts were dried (anhydrous $MgSO_4$) and concentrated under reduced pressure. The residue (450 mg) was subjected to column chromatography (silica gel, 54 g, CH_2Cl_2 and CH_2Cl_2/MeOH mixtures). On elution with CH_2Cl_2, *p*-anisaldehyde (90 mg) was isolated and on elution with CH_2Cl_2/MeOH 20:1, a mixture of (*S*)-**19** and (*S*)-**20** (331 mg) was obtained. This mixture was subjected to a new column chromatography (silica gel, 30 g, hexane/EtOAc mixtures). On elution with hexane/EtOAc 1:1, (*S*)-**19** (127 mg, 24% yield) was isolated as a colorless oil, and on elution with hexane/EtOAc 1:10, (*S*)-**20** (331 mg, 42% yield) was isolated as a white solid. The analytical sample of (*S*)-**20** was obtained as a white solid by crystallization from EtOAc (5 mL).

Compound (*S*)-**19**: $[\alpha]_D^{23} = -28$ (*c* 0.46, CH_2Cl_2); R_f 0.89 (silica gel, 5.5 cm, EtOAc); IR 3318 (NH), 2960, 1714 and 1667 (CO), 1604, 1537, 1511, 1303, 1251, 1174, 1052, 1027, 842, 762, 697 cm^{-1}; ^1H NMR (main rotamer) 1.03 (s, 3H) and 1.32 (s, 3H) [4-$(CH_3)_2$], 3.54 (d, *J* = 11.2 Hz, 1H) and 3.87 (d, *J* = 11.2 Hz, 1H) (N–CH_2), 3.85 (s, 3H, OCH_3), 4.49 (d, *J* = 7.6 Hz, 1H, 3-H), 5.05 (br d, *J* = 7.6 Hz, 1H, NH), 5.13 (s, 2H, CH_2-Ph), 6.90 [dm, *J* = 8.8 Hz, 2H, Ar-3(5)-H *p*-methoxybenzyl], 7.32–7.39 [m, 5H, Ar-H phenyl], 7.61 [dm, *J* = 8.8 Hz, 2H, Ar-2(6)-H *p*-methoxybenzyl]; ^{13}C NMR 20.5 (CH_3) and 24.6 (CH_3) [4-$(CH_3)_2$], 37.7 (C, C4), 55.0 (CH_2, N–CH_2), 55.4 (CH_3, OCH_3), 63.3 (CH, C3), 67.4 (CH_2, CH_2-Ph), 113.2 [CH, Ar-C3(5) *p*-methoxybenzyl], 125.7 (C, Ar-C1 *p*-methoxybenzyl), 128.1 (CH), 128.3 (CH) and 128.6 (CH) (Ar-C_{ortho}, Ar-C_{meta} and Ar-C_{para} phenyl), 131.7 [CH, Ar-C2(6) *p*-methoxybenzyl], 135.9 (C, Ar-C1 phenyl), 156.8 (C, NHCOO), 159.6 (C, Ar-C4 *p*-methoxybenzyl), 169.2 (C), 172.0 (C) (C2 and C5). Anal. Calcd for $C_{22}H_{24}N_2O_5$: C, 66.65; H, 6.10; N, 7.07. Found: C, 66.60; H, 6.15; N, 7.04. HRMS (ESI) calcd for ($[M+H]^+$) 397.1758; found 397.1755.

Compound (*S*)-**20**: Mp 173–174 °C (EtOAc); $[\alpha]_D^{23} = -12$ (*c* 0.30, CH_2Cl_2); R_f 0.35 (silica gel, 5.8 cm, EtOAc); IR (KBr) 3298 (NH), 3225, 3106, 3065, 3033, 2960, 2926, 2858, 1736 and 1691 (CO), 1543, 1449, 1390, 1378, 1367, 1327, 1244, 1050, 1024, 753, 694 cm^{-1}; ^1H NMR (main rotamer) 0.97 (s, 3H) and 1.26 (s, 3H) [4-$(CH_3)_2$], 3.01 (d, *J* = 9.2 Hz, 1H) and 3.17 (d, *J* = 9.2 Hz, 1H) (5-H_2), 4.24 (d, *J* = 8.0 Hz, 1H, 3-H), 5.12 (s, 2H, CH_2-Ph), 5.24 (br s, 1H, NHCOO), 6.29 (br s, 1H, 1-H), 7.31–7.37 [m, 5H, Ar-H]; ^{13}C NMR 20.9 (CH_3) and 25.3 (CH_3) [4-$(CH_3)_2$], 41.1 (C, C4), 52.3 (CH_2, C5), 61.1 (CH, C3), 67.2 (CH_2, CH_2-Ph), 128.1 (CH), 128.2 (CH) and 128.5 (CH) (Ar-C_{ortho}, Ar-C_{meta} and Ar-C_{para}), 136.2 (C, Ar-C1), 157.0 (C, NHCOO), 174.9 (C, C2). Anal. Calcd for $C_{14}H_{18}N_2O_3$: C, 64.11; H, 6.92; N, 10.68. Found: C, 64.13; H, 6.93; N, 10.42. HRMS (ESI) calcd for ($[M+H]^+$): 263.1390; found 263.1391.

4.11. Compound (*S*)-6 from (*S*)-20

A mixture of (*S*)-**20** (92 mg, 0.35 mmol), concentrated HCl (150 μL), and 5% Pd/C (400 mg) in MeOH (30 mL) was hydrogenated at 1 atm and room temperature for 17 h. The mixture was filtered through a pad of Celite® washing the filter with MeOH (10 mL). The solvent from the combined filtrate and washing was eliminated under reduced pressure and the residue was basified with aqueous 2 M NaOH (5 mL) and extracted with CH_2Cl_2 (3 × 30 mL). The combined organic extracts were dried (anhydrous $MgSO_4$) and concentrated in vacuo to give (*S*)-**6** (41 mg, 91% yield) as a white solid, whose analytical and spectroscopic data are coincidental with those of the sample previously prepared.

4.12. Methylation of (*S*)-7. Obtention of (*S*)-3-(dimethylamino)-1-(*p*-methoxybenzyl)-4,4-dimethylpyrrolidin-2-one (*S*)-21 and (*S*)-3-(dimethylamino)-1-[3-(hydroxymethyl)-4-methoxybenzyl]-4,4-dimethylpyrrolidin-2-one (*S*)-22

Formic acid (1.55 mL, 1.90 g, 41.2 mmol) was added to a cold mixture (ice-water bath) of aqueous formaldehyde (37%, 1.55 mL, 20.8 mmol) and (*S*)-**7** (218 mg, 0.88 mmol) and 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 (30 mL), and extracted with Et_2O (3 × 30 mL). The combined organic extracts were dried (anhydrous $MgSO_4$) and concentrated under reduced pressure to give a crude product (227 mg) that was subjected to column chromatography (aluminum oxide, 20 g, hexane/EtOAc 1:2 and MeOH). In the order of elution, (*S*)-**21** (180 mg, 74% yield) as a colorless oil and (*S*)-**22** (54 mg, 20% yield) as a yellowish oil were obtained.

(*S*)-**21**: $[\alpha]_D^{23} = -76$ (*c* 0.58, CH_2Cl_2); R_f 0.68 (aluminum oxide, 6.8 cm, hexane/EtOAc 1:2); IR 2956, 2928, 2865, 1677 (CO), 1611, 1512, 1440, 1367, 1304, 1244, 1173, 1031, 844, 819 cm^{-1}; ^1H NMR 1.04 (s, 3H) and 1.05 (s, 3H) [C4–$(CH_3)_2$], 2.46 [s, 6H, N$(CH_3)_2$], 2.77 (d, *J* = 9.6 Hz, 1H) and 2.92 (d, *J* = 9.6 Hz, 1H) (5-H_2), 2.85 (s, 1H, 3-H), 3.80 (s, 3H, OCH_3), 4.34 (d, *J* = 14.4 Hz, 1H) and 4.43 (d, *J* = 14.4 Hz, 1H) (N–CH_2), 6.84 [dm, *J* = 8.6 Hz, 2H, Ar-3(5)-H], 7.20 [dm, *J* = 8.6 Hz, 2H, Ar-2(6)-H]; ^{13}C NMR 21.5 (CH_3) and 29.4 (CH_3) [4-$(CH_3)_2$], 36.2 (C, C4), 43.7 [CH_3, N$(CH_3)_2$], 45.8 (CH_2, N–CH_2), 55.2 (CH_3, OCH_3), 58.5 (CH_2, C5), 74.4 (CH, C3), 114.0 [CH, Ar-C3(5)], 128.5 (C, Ar-C1), 129.8 [CH, Ar-C2(6)], 159.1 (C, Ar-C4), 172.3 (C, C2). Anal. Calcd for $C_{16}H_{24}N_2O_2$: C, 69.53; H, 8.75; N, 10.14. Found: C, 69.20; H, 8.88; N, 9.80. HRMS (ESI) calcd for ($[M+H]^+$): 277.1911; found 277.1918.

Compound (*S*)-**22**: $[\alpha]_D^{23} = -40$ (*c* 0.59, CH_2Cl_2); R_f 0.19 (aluminum oxide, 6.8 cm, hexane/EtOAc 1:2); IR (NaCl) 3600–2400 (max at 3398, 3049, 2956, 2933, 2869, 2838, 2786, OH and CH), 1674 (CO), 1612, 1499, 1460, 1388, 1369, 1309, 1289, 1249, 1220, 1178, 1152, 1126, 1045, 822, 734 cm^{-1}; ^1H NMR 1.03 (s, 3H) and 1.04 (s, 3H) [C4–$(CH_3)_2$], 2.44 [s, 6H, N$(CH_3)_2$], 2.77 (d, *J* = 9.6 Hz, 1H) and 2.92 (d, *J* = 9.6 Hz, 1H) (5-H_2), 2.84 (s, 1H, 3-H), 3.84 (s, 3H, OCH_3), 4.34 (d, *J* = 14.4 Hz, 1H) and 4.39 (d, *J* = 14.4 Hz, 1H) (N–CH_2), 4.64 (s, 2H, CH_2OH), 6.81 [d, *J* = 8.4 Hz, 1H, Ar-5-H], 7.14 [overlapped d, *J* = 8.4 Hz, 1H, Ar-6-H], 7.16 (s, 1H, Ar-2-H); ^{13}C NMR 21.4 (CH_3) and 29.4 (CH_3) [4-$(CH_3)_2$], 36.2 (C, C4), 43.7 [CH_3, N$(CH_3)_2$], 45.8 (CH_2, N–CH_2), 55.3 (CH_3, OCH_3), 58.5 (CH_2, C5), 61.7 (CH_2, Ar-CH_2OH), 74.4 (CH, C3), 110.3 (CH, Ar-C5), 128.4 (C, Ar-C3), 128.8 (CH) and 128.9 (CH) (Ar-C2 and Ar-C6), 129.3 (C, Ar-C1), 156.8 (C, Ar-C4), 172.3 (C, C2). Anal. Calcd for $C_{17}H_{26}N_2O_3$: C, 66.64; H, 8.55; N, 9.14. Found: C, 66.32; H, 8.46; N, 9.08. HRMS (ESI) calcd for ($[M+H]^+$): 307.2016; found 307.2024.

4.13. (*S*)-21·Mono-(2*R*,3*R*)-*O*,*O*′-di-(*p*-toluoyl)tartrate

An aliquot of (*S*)-**21** (130 mg, 0.52 mmol) was taken in MeOH (5 mL) and a solution of (2*R*,3*R*)-(−)-*O*,*O*′-di-(*p*-toluoyl)tartaric acid (97% purity, 200 mg, 0.52 mmol) in MeOH (5 mL) was added. The resulting solution was concentrated to dryness in vacuo and the white residue was crystallized from a mixture of EtOAc/hexane 5:2 (7 mL) to give (*S*)-**21**·mono-(2*R*,3*R*)-*O*,*O*′-di-(*p*-toluoyl)tartrate as a white solid (248 g, 75% yield), mp 190–191 °C (EtOAc/hexane 5:2); $[\alpha]_D^{23} = -105$ (*c* 0.79, MeOH); IR (KBr) 3600–2500 (max at 3429, 3035, 2953, 2879, 2842, OH, $^+$NH and CH), 1709 and 1697 (CO), 1610, 1513, 1487, 1455, 1338, 1304, 1267, 1248, 1179, 1126, 1111, 1033, 839, 750, 694 cm^{-1}; ^1H NMR (CD_3OD) 1.09 (s, 3H) and 1.18 (s, 3H) [C4-$(CH_3)_2$], 2.41 (s, 6H, CH_3 *p*-toluoyl), 2.91 [s, 6H, N$(CH_3)_2$], 2.98 (d, *J* = 10.0 Hz, 1H) and 3.02 (d, *J* = 10.0 Hz, 1H) (5-H_2), 3.67 (s, 1H, 3-H), 3.77 (s, 3H, OCH_3), 4.33 (d,

J = 14.4 Hz, 1H) and 4.45 (d, J = 14.4 Hz, 1H) (N–CH_2), 4.88 (s, mobile H), 5.90 [s, 2H, 2(3)-H tartrate], 6.90 [dm, J = 8.4 Hz, 2H, Ar-3(5)-H], 7.21 [dm, J = 8.4 Hz, 2H, Ar-2(6)-H], 7.30 [d, J = 8.0 Hz, 4H, 3(5)-H p-toluoyl], 8.01 [d, J = 8.0 Hz, 4H, 2(6)-H p-toluoyl]; ^{13}C NMR (CD_3OD) 21.3 (CH_3) and 27.4 (CH_3) [4-(CH_3)$_2$], 21.7 (CH_3, p-toluoyl CH_3), 38.9 (C, C4), 44.1 [CH_3, N(CH_3)$_2$], 47.0 (CH_2, N–CH_2), 55.7 (CH_3, OCH_3), 58.6 (CH_2, C5), 74.4 (CH, C3), 74.5 [CH, C2(3) tartrate], 115.2 [CH, Ar-C3(5)], 128.2 (C, C1 p-toluoyl), 128.7 (C, Ar-C1), 130.2 [CH, C3(5) p-toluoyl], 131.0 [CH, Ar-C2(6)], 131.1 [CH, C2(6) p-toluoyl], 145.6 (C, C4 p-toluoyl), 161.0 (C, Ar-C4), 167.3 (C, CO p-toluoyl), 169.2 (C, C2), 171.1 [C, C1(4) tartrate]. Anal. Calcd for $C_{16}H_{24}N_2O_2{\cdot}C_{20}H_{18}O_8$: C, 65.24; H, 6.39; N, 4.23. Found: C, 65.26; H, 6.46; N, 4.00.

4.14. 4,4-Dimethylpyrrolidine-2,3-dione 24

To a cooled (0 °C) solution of *rac*-**23** (1.43 g, 11.1 mmol) in AcOH (70 mL), a solution of $Na_2Cr_2O_7{\cdot}2H_2O$ (1.87 g, 6.30 mmol) in H_2SO_4 (20% aqueous solution, 17 mL) was added dropwise. After 30 min at room temperature, water (20 mL) was added, and the mixture was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic phases were concentrated in vacuo. The residue was taken in CH_2Cl_2 (200 mL) and washed with saturated aqueous $NaHCO_3$ (2 × 50 mL) and brine (15 mL). The solution was dried (anhydrous $MgSO_4$) and concentrated under reduced pressure to give a residue (1.53 g) that was subjected to column chromatography (silica gel, 31 g, CH_2Cl_2 and CH_2Cl_2/MeOH 20:1), isolating **24** (1.05 g, 75% yield) as a white solid. The analytical sample was obtained by crystallization from CH_2Cl_2 (17 mL), mp 198–200 °C (CH_2Cl_2); R_f 0.47 (silica gel, 6.6 cm, CH_2Cl_2/MeOH 10:1); IR 3259 (NH), 2962, 2930, 2904, 2863, 1755 (CO), 1742 and 1698 (CO), 1467, 1437, 1317, 1203, 1057, 1042, 1012, 717, 662 cm^{-1}; ^{1}H NMR (DMSO-d_6) 1.11 [s, 6H, 4-(CH_3)$_2$], 3.30 (s, 2H, 5-H_2), 9.57 (s, 1H, NH); ^{13}C NMR (DMSO-d_6) 23.2 [CH_3, 4-(CH_3)$_2$], 40.8 (C, C4), 50.2 (CH_2, C5), 161.0 (C, C2), 206.3 (C, C3). Anal. Calcd for $C_6H_9NO_2{\cdot}0.1H_2O$: C, 55.89; H, 7.19; N, 10.86. Found: C, 55.93; H, 7.07; N, 10.84. HRMS (ESI) calcd for ([M+H]$^+$) 128.0706; found 128.0704.

4.15. *rac*-3-(Benzylamino)-4,4-dimethylpyrrolidin-2-one *rac*-26

A solution of **24** (1.28 g, 10.1 mmol) and freshly distilled benzylamine (1.10 mL, 1.08 g, 10.1 mmol) in toluene (50 mL) was heated at reflux for 24 h in Dean–Stark equipment. Evaporation of the solvent under reduced pressure gave the corresponding imine **25** (2.18 g, quantitative yield) as a yellow solid, which was used as such in the next step. A part of the above mentioned imine **25** (1.00 g, 4.62 mmol) was taken in anhydrous MeOH (40 mL), and a solution of $NaBH_3CN$ (95% purity, 650 mg, 9.84 mmol) in anhydrous MeOH (5 mL) and AcOH (350 μL, 263 mg, 6.12 mmol) were added and the reaction mixture was stirred at room temperature for 4 h. Then, more $NaBH_3CN$ (125 mg, 1.89 mmol) was added and stirring was continued for 45 min. Water (20 mL) was added and the organic solvent was evaporated under reduced pressure. The remaining aqueous phase was treated with aqueous 2 M NaOH until pH 12–13 and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were dried (anhydrous $MgSO_4$) and concentrated under reduced pressure to give *rac*-**26** (850 mg, 84% yield). The analytical sample was obtained as a white solid by crystallization from EtOAc, mp 97–98 °C (EtOAc); IR (KBr) 3315 and 3192 (NH), 2959 and 2868 (CH), 1698 and 1661 (CO), 1492, 1451, 1363, 1311, 1201, 1152, 730, 696 cm^{-1}; ^{1}H NMR 1.06 (s, 3H) and 1.14 (s, 3H) [4-(CH_3)$_2$], 1.88 (br s, 1H, N–H), 2.95 (dd, J = 9.6, 1.6 Hz, 1H) and 3.02 (d, J = 9.6 Hz) (5-H_2), 3.05 (s, 1H, 3-H), 3.95 (d, J = 13.6 Hz, 1H) and 4.01 (d, J = 13.6 Hz, 1H) (CH_2-Ph), 6.00 (s, 1H, 1-H), 7.24 (t, J = 7.2 Hz, 1H, Ar-H_{para}), 7.32 (tm, J = 7.2 Hz, 2H, Ar-H_{meta}), 7.38 (d, J = 7.2 Hz, 2H, Ar-H_{ortho}); ^{13}C NMR 21.0 (CH_3) and 26.0 (CH_3) [4-(CH_3)$_2$], 40.9 (C, C4), 52.4 (CH_2, C5), 53.5 (CH_2, N–CH_2), 66.6 (CH, C3), 127.0 (CH, Ar-C_{para}), 128.2 (CH) and 128.3 (CH) (Ar-C_{ortho} and Ar-C_{meta}), 140.3 (C, Ar-C_{ipso}), 177.9 (C, C2). Anal. Calcd for $C_{13}H_{18}N_2O$: C, 71.53; H, 8.31; N, 12.83. Found: C, 71.53; H, 8.41; N, 12.83. HRMS (ESI) calcd for ([M+H]$^+$): 219.1492; found 219.1494.

4.16. *rac*-3-Amino-4,4-dimethylpyrrolidin-2-one *rac*-6

4.16.1. By hydrogenation of *rac*-26

A mixture of *rac*-**26** (820 mg, 3.76 mmol), concentrated HCl (2.0 mL), and 5% Pd/C (2.50 g) in EtOH (20 mL) was hydrogenated at 1 atm and room temperature for 48 h. The mixture was filtered through a pad of Celite® and the residue was washed with EtOH (10 mL). The combined filtrate and washing were concentrated under reduced pressure, and the residue was basified with aqueous 2 M NaOH (10 mL) and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were dried (anhydrous $MgSO_4$) and concentrated under reduced pressure to give *rac*-**6** (440 mg, 91% yield) as a white solid. The analytical sample was obtained by crystallization from a mixture of EtOAc/MeOH 11:1 giving a white solid, mp 96–97 °C (EtOAc/MeOH 11:1). IR 3204 (NH), 2948, 2894, 2868, 1701 and 1677 (CO), 1591, 1464, 1355, 1309, 1140, 948, 841, 775, 659 cm^{-1}; ^{1}H NMR (300 MHz) 1.02 (s, 3H) and 1.21 (s, 3H) [C4-(CH_3)$_2$], 1.48 (br s, 2H, NH_2), 3.01 (dd, J = 9.6, 1.5 Hz, 1H) and 3.11 (d, J = 9.6 Hz, 1H) (5-H_2), 3.15 (s, 1H, 3-H), 5.70 (br s, 1H, N-H); ^{13}C NMR (75.4 MHz) 20.1 (CH_3) and 25.1 (CH_3) [4-(CH_3)$_2$], 40.3 (C, C4), 52.5 (CH_2, C5), 61.5 (CH, C3), 178.6 (C, C2). Anal. Calcd for $C_6H_{12}N_2O{\cdot}0.5H_2O$: C, 52.53; H, 9.55; N, 20.42. Found: C, 52.76; H, 9.20; N, 20.07. HRMS (ESI) calcd for ([M+H]$^+$): 129.1022; found 129.1019.

4.16.2. By hydrogenation of the benzylimine 25

A mixture of the above-mentioned benzylimine **25** (1.41 g, 6.52 mmol) and 5% Pd/C (3.90 g) in EtOH (30 mL) was hydrogenated at 1 atm and room temperature for 24 h. The mixture was filtered through a pad of Celite® and the residue was washed with EtOH (10 mL). The combined filtrate and washing were concentrated under reduced pressure to give *rac*-**6** (810 mg, 97% yield) as a white solid.

4.17. *rac*-3-(Dimethylamino)-1-(hydroxymethyl)-4,4-dimethylpyrrolidin-2-one *rac*-27

To an ice-cold stirred suspension of *rac*-**6** (1.69 g, 13.2 mmol) in water (10 mL), formaldehyde (2.5 mL, 37% aqueous solution, 33.6 mmol) and formic acid (1.2 mL, 31.8 mmol) were added and the reaction mixture was heated at reflux for 4 h. Then, it was allowed to cool to room temperature, after which more formaldehyde (1.2 mL, 37% aqueous solution, 16.1 mmol) and formic acid (0.6 mL, 15.9 mmol) were added and the mixture was heated at reflux for 19 h. The solution was allowed to cool to room temperature, was basified with aqueous 5 M NaOH, and extracted with CH_2Cl_2 (3 × 150 mL). The combined organic extracts were washed with water, dried (anhydrous $MgSO_4$), and concentrated in vacuo to give a residue (2.40 g) that was crystallized from hexane/Et_2O 10:1 (50 mL) to give *rac*-**27** (1.57 g, 64% yield), mp 46–47 °C (hexane/Et_2O 10:1); R_f 0.22 (silica gel, 6.0 cm, EtOAc/MeOH/Et_3N 100:1:0.1); IR 3312 and 3294 (OH), 2966, 2956, 2937, 1660 (C=O), 1462, 1453, 1431, 1313, 1295, 1275, 1206, 1176, 1094, 1076, 1059, 1036, 1018, 972, 854, 709, 639, 628 cm^{-1}; ^{1}H NMR (300 MHz) 1.10 (s, 3H) and 1.13 (s, 3H) [C4-(CH_3)$_2$], 2.43 [s, 6H, N-(CH_3)$_2$], 2.81 (s, 1H, 3-H), 3.14 (d, J = 9.6 Hz, 1H) and 3.11 (d, J = 9.6 Hz, 1H) (5-H_2), 4.70 (d, J = 11.0 Hz, 1H) and 4.82 (d, J = 11.0 Hz, 1H) (N–CH_2OH); ^{13}C NMR (75.4 MHz) 21.4 (CH_3) and 29.0 (CH_3) [4-(CH_3)$_2$], 36.8 (C, C4), 43.7 [CH_3, N(CH_3)$_2$], 57.9 (CH_2,

C5), 66.4 (CH_2, N–CH_2OH), 74.6 (CH, C3), 173.6 (C, C2). Anal. Calcd for $C_9H_{18}N_2O_2$: C, 58.04; H, 9.74; N, 15.04. Found: C, 57.92; H, 10.09; N, 15.10. HRMS (ESI) calcd for ($[M+H]^+$): 187.1441; found 187.1441.

4.18. *rac*-3-(Dimethylamino)-4,4-dimethylpyrrolidin-2-one *rac*-28

4.18.1. From *rac*-27

To an ice-cold stirred suspension of *rac*-**27** (884 mg, 4.75 mmol) in water (20 mL), methylamine (1.0 mL, 40% aqueous solution, 11.6 mmol) and formic acid (600 μL, 15.9 mmol) were added and the mixture was heated at reflux for 19 h. The solution was allowed to cool to room temperature, then basified with aqueous 5 M NaOH, and extracted with CH_2Cl_2 (3 × 150 mL). The combined organic extracts were washed with water, dried (anhydrous $MgSO_4$), and concentrated in vacuo to give a residue (967 mg) that was crystallized from hexane to give *rac*-**28** (600 mg, 80% yield).

4.18.2. From *rac*-6

To an ice-cold stirred suspension of *rac*-**6** (508 mg, 3.96 mmol) in water (5 mL), formaldehyde (620 μL, 37% aqueous solution, 8.32 mmol) and formic acid (5 mL, 132 mmol) were added and the reaction mixture was heated at reflux for 15 h. Then, it was allowed to cool to room temperature, was basified with aqueous 2 M NaOH, and extracted with CH_2Cl_2 (3 × 100 mL). The combined organic extracts were washed with water, dried (anhydrous $MgSO_4$), and concentrated *in vacuo* to give a residue (560 mg), mixture of *rac*-**27** and *rac*-**28** (about 2:1 by ^{1}H NMR). The mixture was taken in water (5 mL), cooled (ice-water bath), and methylamine (1.0 mL, 40% aqueous solution, 11.6 mmol) and formic acid (800 μL, 21.2 mmol) were added and the mixture was heated at reflux for 20 h. The mixture was allowed to cool to room temperature, then basified with aqueous 5 M NaOH, and extracted with CH_2Cl_2 (3 × 100 mL). The combined organic extracts were washed with water, dried (anhydrous $MgSO_4$), and concentrated in vacuo to give a residue (600 mg), that was crystallized from hexane (15 mL) to give *rac*-**28** (455 mg, 74% yield). The analytical sample was obtained as a white solid by crystallization from hexane/EtOAc 3:1 (20 mL), mp 118–120 °C (hexane/EtOAc 3:1). The IR, ^{1}H and ^{13}C NMR are coincidental with those of *rac*-**28**. Anal. Calcd for $C_8H_{16}N_2O{\cdot}0.15H_2O$: C, 60.46; H, 10.34; N, 17.63. Found: C, 60.44; H, 10.30; N, 17.51. HRMS (ESI) calcd for ($[M+H]^+$) 157.1335; found 157.1335.

4.19. (*R*)-4,4-Dimethyl-3-[(1-phenylethyl)imino]pyrrolidin-2-one (*R*)-29

A solution of **24** (530 mg, 4.17 mmol) and (*R*)-1-phenylethylamine, (*R*)-**13** (540 μL, 508 mg, 4.17 mmol) in toluene (30 mL) was heated at reflux for 20 h in a Dean–Stark equipment. Evaporation of the solvent under reduced pressure gave (*R*)-**29** (1.05 g, quantitative yield) as a colorless oil. $[\alpha]_D^{23} = +44$ (*c* 0.80, CH_2Cl_2); IR (NaCl) 3212 (NH), 3062, 2970, 2927, 2890, 2868, 1701 and 1678 (CO), 1601, 1492, 1464, 1450, 1382, 1362, 1313, 1208, 1069, 1044, 763, 700 cm^{-1}; ^{1}H NMR (300 MHz) δ 1.22 (s, 3H) and 1.27 (s, 3H) [4-(CH_3)$_2$], 1.44 (d, *J* = 6.4 Hz, 3H, C*H*$_3$–CH), 3.24 (dd, *J* = 9.9, 6.4 Hz, 1H) and 3.28 (dd, *J* = 9.9, 6.4 Hz, 1H) (5-H_2), 6.47 (q, *J* = 6.4 Hz, 1H, CH_3–C*H*), 7.20 (tm, *J* = 7.5 Hz, 1H, Ar-H_{para}), 7.31 (tm, *J* = 7.5 Hz, 2H, Ar-H_{meta}), 7.47 (dm, *J* = 7.5 Hz, 2H, Ar-H_{ortho}), 7.70 (br s, 1H, *N*-H); ^{13}C NMR (75.4 MHz) 25.1 (CH_3, *C*H_3–CH), 25.9 (CH_3) and 26.7 (CH_3) [4-(CH_3)$_2$], 40.0 (C, C4), 52.5 (CH_2, C5), 56.0 (CH, CH_3-*C*H), 126.3 (CH, Ar-C_{para}), 126.5 (CH, Ar-C_{ortho}), 128.1 (CH, Ar-C_{meta}), 146.2 (C, Ar-C_{ipso}), 163.8 (C), 164.3 (C) (C2 and C3). Anal. Calcd for $C_{14}H_{18}N_2O{\cdot}0.25H_2O$: C, 71.61; H, 7.94; N, 11.93. Found: C, 71.82; H, 8.03; N, 11.72. HRMS (ESI) calcd for ($[M+Na]^+$) 253.1311; found 253.1313.

4.20. (3*S*,1′*R*)-4,4-Dimethyl-3-[(1-phenylethyl)amino]pyrrolidin-2-one (3*S*,1′*R*)-30 and (3*R*,1′*R*)-4,4-dimethyl-3-[(1-phenylethyl)-amino]pyrrolidin-2-one (3*R*,1′*R*)-31

To a cold (−78 °C) solution of (*R*)-**29** (1.05 g, 4.56 mmol) in anhydrous MeOH (30 mL), a solution of $NaBH_3CN$ (95% purity, 650 mg, 9.88 mmol) and AcOH (350 μL, 367 mg, 6.10 mmol) in anhydrous MeOH (5 mL) was added dropwise and the reaction mixture was stirred at this temperature for 4 h. Then more $NaBH_3CN$ (95% purity, 350 mg, 5.29 mmol) was added and stirring was continued for 1 h. Water (20 mL) was then added and the organic solvent was evaporated under reduced pressure. The remaining aqueous phase was treated with aqueous 2 M NaOH until pH 12–13 and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were dried (anhydrous $MgSO_4$) and concentrated under reduced pressure to give a diastereomeric mixture of (3*S*,1′*R*)-**30** and (3*R*,1′*R*)-**31** (987 mg, 93% yield) in a ratio of 80:20 (^{1}H-NMR). The mixture was taken in Et_2O/hexane 5:4 (9 mL) and the solution was cooled to −20 °C for 24 h. The precipitated solid was collected by filtration and washed with Et_2O/hexane 1:1 (2 mL) to give (3*R*,1′*R*)-**31** (110 mg, 10% yield) as a white solid. The mother liquors were kept at −20 °C for 48 h precipitating an equimolar mixture of amines (3*S*,1′*R*)-**30** and (3*R*,1′*R*)-**31** (78 mg, 7% yield). The mother liquors were concentrated to dryness to give a viscous solid [790 mg, (3*S*,1′*R*)-**30** >95% de] that was crystallized from Et_2O/pentane 7:2 (10 mL). Filtration of the precipitate gave (3*S*,1′*R*)-**30** (350 mg) as a white solid. The filtrate was concentrated to dryness and the residue (440 mg) was crystallized from a mixture of Et_2O/pentane 5:2 (4 mL), obtaining a new crop of (3*S*,1′*R*)-**30** (330 mg, 64% total yield).

In another operation, starting from (*R*)-**29** (10.21 g, 44.3 mmol), the obtained mixture of (3*S*,1′*R*)-**30** and (3*R*,1′*R*)-**31** (9.69 g, 94% yield) was separated by column chromatography (silica gel, 158 g, hexane/EtOAc/NH_4OH mixtures). On elution with hexane/EtOAc/concentrated NH_4OH 3:1:0.1, (3*S*,1′*R*)-**30** (3.33 g, 32% yield) as a white solid and a mixture of (3*S*,1′*R*)-**30** and (3*R*,1′*R*)-**31** (3.85 g, 86:14) were obtained. On elution with hexane/EtOAc/concentrated NH_4OH 2:1:0.1, a mixture of (3*S*,1′*R*)-**30** and (3*R*,1′*R*)-**31** (1.92 g, 1:1) and (3*R*,1′*R*)-**31** as a white solid (590 mg, 6% yield) were isolated. Column chromatography (silica gel, 72 g, hexane/EtOAc/concentrated NH_4OH mixtures) of the mixture of (3*S*,1′*R*)-**30** and (3*R*,1′*R*)-**31** (3.85 g, 86:14) gave, on elution with hexane/EtOAc/concentrated NH_4OH 5:1:0.1, a new portion of pure (3*S*,1′*R*)-**30** (1.52 g, 47% total yield).

Compound (3*S*,1′*R*)-**30**: R_f 0.44 (silica gel, 6.1 cm, hexane/EtOAc/concentrated NH_4OH 1:1:0.1); Mp 79–80 °C (Et_2O/pentane 5:4); $[\alpha]_D^{23} = +26$ (*c* 1.30, CH_2Cl_2); IR (KBr) 3600–2800 (max at 3247, 3110, 3061, 3025, 2961, 2928, 2867, 2808), 1703 (CO), 1602, 1485, 1462, 1451, 1384, 1368, 1316, 1262, 1237, 1204, 1154, 1084, 1055, 1017, 909, 807, 762, 701, 666 cm^{-1}; ^{1}H NMR (300 MHz) 1.08 (s, 3H) and 1.16 (s, 3H) [C4-(CH_3)$_2$], 1.37 (d, *J* = 6.9 Hz, 3H, C*H*$_3$CH), 1.4–2.2 (br s, 1H, 3-NH), 2.88 (dd, *J* = 9.6, 1.8 Hz, 1H) and 2.92 (d, *J* = 9.6 Hz, 1H) (5-H_2), 2.94 (s, 1H, 3-H), 3.93 (q, *J* = 6.9 Hz, 1H, CH_3C*H*), 5.79 (s, 1H, 1-H), 7.23 (m, 1H, Ar-H_{para}), 7.30–7.33 (m, 4H, Ar-H_{meta} and Ar-H_{ortho}); ^{13}C NMR (75.4 MHz) 21.2 (CH_3), 24.9 (CH_3) and 26.2 (CH_3) [4-(CH_3)$_2$ and *C*H_3–CH], 41.1 (C, C4), 52.2 (CH_2, C5), 56.9 (CH, CH_3–*C*H), 64.1 (CH, C3), 126.6 (CH, Ar-C_{ortho}), 126.9 (CH, Ar-C_{para}), 128.5 (CH, Ar-C_{meta}), 145.0 (C, Ar-C_{ipso}), 177.7 (C, C2). Anal. Calcd for $C_{14}H_{20}N_2O$: C, 72.38; H, 8.68; N, 12.06. Found: C, 72.25; H, 8.76; N, 11.87. HRMS (ESI) calcd for ($[M+H]^+$) 233.1648; found 233.1649.

Compound (3*R*,1′*R*)-**31**: R_f 0.30 (silica gel, 6.1 cm, hexane/EtOAc/concentrated NH_4OH 1:1:0.1); Mp 164–165 °C (Et_2O/hexane 7:2); $[\alpha]_D^{23} = +136$ (*c* 0.70, CH_2Cl_2); IR (KBr) 3600–2800 (max at 3297, 3238, 2961, 2865, 2850, 1693 (CO), 1462, 1452, 1351, 1308, 1277, 1214, 1148, 728, 700, 673 cm^{-1}; ^1H NMR (300 MHz) 0.82 (s, 3H) and 0.98 (s, 3H) [C4-$(CH_3)_2$], 1.39 (d, *J* = 6.8 Hz, 3H, CH_3CH), 1.60 (br s, 1H, 3-NH), 2.83 (s, 1H, 3-H), 2.87 (dd, *J* = 9.6, 2.1 Hz, 1H) and 2.93 (d, *J* = 9.6 Hz, 1H) (5-H_2), 4.30 (q, *J* = 6.8 Hz, 1H, CH_3CH), 5.90 (s, 1H, 1-H), 7.22 (tm, *J* = 7.2 Hz, 1H, Ar-H_{para}), 7.30 (tm, *J* = 7.2 Hz, 2H, Ar-H_{meta}) 7.39 (dm, *J* = 7.2 Hz, 2H, Ar-H_{ortho}); ^{13}C NMR (75.4 MHz) 20.7 (CH_3) and 24.7 (CH_3) [4-$(CH_3)_2$], 25.2 (CH_3, CH_3CH), 40.5 (C, C4), 52.3 (CH_2, C5), 57.5 (CH, CH_3CH), 65.4 (CH, C3), 126.9 (CH, Ar-C_{para}), 127.4 (CH, Ar-C_{ortho}), 128.2 (CH, Ar-C_{meta}), 145.9 (C, Ar-C_{ipso}), 179.2 (C, C2). Anal. Calcd for $C_{14}H_{20}N_2O$: C, 72.38; H, 8.68; N, 12.06. Found: C, 72.48; H, 8.75; N, 11.95. HRMS (ESI) calcd for ($[M+Na]^+$) 255.1468; found 255.1467.

4.21. (*R*)-3-Amino-4,4-dimethylpyrrolidin-2-one (*R*)-6

A mixture of (3*R*,1′*R*)-**31** (200 mg, 0.86 mmol), concentrated HCl (100 μL), and 5% Pd/C (600 mg) in MeOH (10 mL) was hydrogenated at 1 atm and room temperature for 24 h. The mixture was filtered through a pad of Celite® and the residue was washed with MeOH (10 mL). The combined filtrate and washings were concentrated to dryness under reduced pressure. The residue was basified with aqueous 2 M NaOH (5 mL) and extracted with CH_2Cl_2 (3 × 40 mL). The combined organic extracts were dried (anhydrous $MgSO_4$) and concentrated under reduced pressure to give (*R*)-**6** (104 mg, 94% yield) as a white solid. The analytical sample was obtained by crystallization from a mixture of EtOAc/MeOH 11:1 (6 mL), mp 96–97 °C (AcOEt/MeOH 11:1). $[\alpha]_D^{23} = +17$ (*c* 0.45, CH_2Cl_2); IR 3204 (NH), 2948, 2894, 2868, 1701 and 1677 (CO), 1617, 1591, 1480, 1464, 1355, 1309, 1140, 1018, 995, 948, 841, 775, 713, 659 cm^{-1}; ^1H NMR (300 MHz) 1.02 (s, 3H) and 1.21 (s, 3H) [C4–$(CH_3)_2$], 1.48 (br s, 2H, NH_2), 3.01 (dd, *J* = 9.6, 1.5 Hz, 1H) and 3.11 (d, *J* = 9.6 Hz, 1H) (5-H_2), 3.15 (s, 1H, 3-H), 5.80 (br s, 1H, 1-H); ^{13}C NMR (75.4 MHz) 20.1 (CH_3) and 25.1 (CH_3) [4-$(CH_3)_2$], 40.3 (C, C4), 52.5 (CH_2, C5), 61.5 (CH, C3), 178.6 (C, C2). Anal. Calcd for $C_6H_{12}N_2O{\cdot}0.5H_2O$: C, 52.53; H, 9.55; N, 20.42. Found: C, 52.76; H, 9.20; N, 20.07. HRMS (ESI) calcd for ($[M+H]^+$) 129.1022; found 129.1027.

4.22. Compound (*S*)-6 from (3*S*,1′*R*)-30

A mixture of (3*S*,1′*R*)-**30** (4.03 g, 17.4 mmol), concentrated HCl (6.5 mL), and 5% Pd/C (10 g) in MeOH (100 mL) was hydrogenated at 1 atm and room temperature for 20 h. The mixture was filtered through a pad of Celite® and the residue was washed with MeOH (50 mL). The combined filtrate and washings were concentrated to dryness under reduced pressure. The residue was basified with aqueous 5 M NaOH (20 mL) and extracted with CH_2Cl_2 (3 × 100 mL). The combined organic extracts were dried (anhydrous $MgSO_4$) and concentrated under reduced pressure to give (*S*)-**6** (2.13 g, 96% yield) as a white solid, whose analytical data are coincidental with those of the sample previously prepared from (*S*)-**7**.

4.23. (*R*)-3-(Dimethylamino)-4,4-dimethylpyrrolidin-2-one (*R*)-28

To an ice-cold stirred suspension of (*R*)-**6** (174 mg, 1.36 mmol) in water (3 mL), formaldehyde (213 μL, 37% aqueous solution, 2.86 mmol) and formic acid (125 μL, 3.31 mmol) were added and the reaction mixture was heated at reflux for 23 h. Then it was allowed to cool to room temperature, basified with aqueous 5 M NaOH and extracted with CH_2Cl_2 (3 × 100 mL). The combined organic extracts were washed with water, dried (anhydrous $MgSO_4$), and concentrated in vacuo to give a residue (210 mg), mixture of (*R*)-**27** and (*R*)-**28** (about 2:1 by ^1H NMR). The mixture was taken in water (2 mL), cooled (ice-water bath); methylamine (500 μL, 40% aqueous solution, 5.80 mmol) and formic acid (400 μL, 10.6 mmol) were added and the mixture was heated at reflux for 20 h. Then it was allowed to cool to room temperature, basified with aqueous 5 M NaOH, and extracted with CH_2Cl_2 (3 × 100 mL). The combined organic extracts were washed with water, dried (anhydrous $MgSO_4$), and concentrated in vacuo to give a residue (350 mg) that was crystallized from hexane (15 mL) to give (*R*)-**28** (158 mg, 75% yield). The analytical sample was obtained as a white solid by crystallization from hexane/EtOAc 3:1 (6 mL), mp 118–119 °C (hexane/EtOAc 3:1). $[\alpha]_D^{23} = +19$ (*c* 0.52, CH_2Cl_2); IR 3354 (NH), 2958, 2937, 2870, 2787, 1672 (CO), 1453, 1434, 1366, 1296, 1266, 1176, 1033, 641 cm^{-1}; ^1H NMR 1.11 (s, 3H) and 1.15 (s, 3H) [C4-$(CH_3)_2$], 2.47 [s, 6H, $N(CH_3)_2$], 2.76 (s, 1H, 3-H), 2.97 (dd, *J* = 10.0, 1.2 Hz, 1H) and 3.06 (d, *J* = 10.0 Hz, 1H) (5-H_2), 6.54 (br s, 1H, 1-H); ^{13}C NMR 21.5 (CH_3) and 29.3 (CH_3) [4-$(CH_3)_2$], 39.2 (C, C4), 43.6 [CH_3, $N(CH_3)_2$], 54.3 (CH_2, C5), 73.4 (CH, C3), 176.1 (C, C2). Anal. Calcd for $C_8H_{16}N_2O{\cdot}0.2H_2O$: C, 60.12; H, 10.34; N, 17.53. Found: C, 59.98; H, 10.18; N, 17.36. HRMS (ESI) calcd for ($[M+H]^+$) 157.1335; found 157.1338.

4.24. (*S*)-3-(Dimethylamino)-4,4-dimethylpyrrolidin-2-one (*S*)-28

To an ice-cold stirred suspension of (*S*)-**6** (1.03 g, 8.04 mmol) in water (15 mL), formaldehyde (1.27 mL, 37% aqueous solution, 16.9 mmol) and formic acid (783 μL, 19.5 mmol) were added and the reaction mixture was heated at reflux for 20 h. Then it was allowed to cool to room temperature, basified with aqueous 5 M NaOH, and extracted with CH_2Cl_2 (3 × 150 mL). The combined organic extracts were washed with water, dried (anhydrous $MgSO_4$), and concentrated in vacuo to give a residue (1.45 g), mixture of (*S*)-**27** and (*S*)-**28** (about 2:1 by ^1H NMR). The mixture was taken in water (10 mL), cooled (ice-water bath); methylamine (3 mL, 40% aqueous solution, 34.2 mmol) and formic acid (2.4 mL, 63.6 mmol) were added and the mixture was heated at reflux for 15 h. Then it was allowed to cool to room temperature, basified with aqueous 5 M NaOH solution, and extracted with CH_2Cl_2 (3 × 150 mL). The combined organic extracts were washed with water, dried (anhydrous $MgSO_4$), and concentrated in vacuo to give a residue (1.73 g) that was crystallized from hexane (30 mL) to give (*S*)-**28** (978 mg, 78% yield). The analytical sample was obtained as a white solid by crystallization from hexane/EtOAc 3:1 (40 mL), mp 119–120 °C (hexane/EtOAc 3:1). $[\alpha]_D^{23} = -20$ (*c* 0.78, CH_2Cl_2); The IR, ^1H, and ^{13}C NMR data are coincidental with those of (*R*)-**28**. Anal. Calcd for $C_8H_{16}N_2O{\cdot}0.3H_2O$: C, 59.45; H, 10.35; N, 17.33. Found: C, 59.42; H, 10.08; N, 17.23. HRMS (ESI) calcd for ($[M+H]^+$) 157.1335; found 157.1333.

4.25. X-ray crystal-structure determination of (*S*)-7·mono-(2*R*,3*R*)-*O*,*O*′-di-(*p*-toluoyl)tartrate (Table 1)

A prismatic crystal (0.09 × 0.08 × 0.07 mm) was selected and mounted on a MAR345 diffractometer with an image plate detector. Unit-cell parameters were determined from 1120 reflections ($3° < \theta < 31°$) and refined by least-squares method. Intensities were collected with graphite monochromatized Mo Kα radiation. 10,249 reflections were measured in the range $2.62 \leqslant \theta \leqslant 32.41$. 5977 of which were non-equivalent by symmetry (R_{int}(on *I*) = 0.028). 4329 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 methods, using SHELXS computer program[14] and refined by full-matrix least-squares method

Table 1
Experimental data of the X-ray crystal-structure determination of compound (*S*)-**7**·mono-(2*R*,3*R*)-*O*,*O*-di-(*p*-toluoyl)tartrate and (3*R*,1′*R*)-**31**

Compound	(*S*)-**7**·mono-*O*,*O*′-di-(*p*-toluoyl)tartrate	(3*R*,1′*R*)-**31**
Molecular formula	$C_{34}H_{38}N_2O_{10}$	$C_{14}H_{20}N_2O$
Molecular mass weight	634.66	232.32
Crystal system	Monoclinic	Orthorhombic
Space group	*C*2	$P2_12_12_1$
Cell parameters		
a (Å)	25.711(13)	6.262(4)
b (Å)	7.936(5)	7.780(6)
c (Å)	19.739(6)	27.410(12)
α (°)	90	90
β (°)	119.59(2)	90
γ (°)	90	90
V (Å^3)	3502(3)	1335.4(15)
Z	4	4
F (000)	1344	504
d_{calc} [Mg m^3]	1.204	1.156
Crystal size (mm)	0.09 × 0.08 × 0.07	0.2 × 0.09 × 0.02
Measured reflect.	10,249	7930
Independent reflect.	5977	2529
Observed reflect.	4329	2311
μ(Mo Kα)[a] (mm^1)	0.089	0.073
R	0.084	0.047
R_w	0.171	0.134
$\Delta\rho_{max}$[b] (e Å^{-3})	0.205	0.260
$\Delta\rho_{min}$[c] (e Å^{-3})	−0.216	−0.358
Refined parameters	416	157
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.

with SHELX97 computer program[15] using 10,249 reflections (very negative intensities were not assumed). The function minimized was $\Sigma w||F_o|^2 - |F_c|^2|^2$, where $w = [\sigma^2(I) + (0.0529P)^2 + 1.6160P]^{-1}$, and $P = (|F_o|^2 + 2|F_c|^2)/3$, *f*, *f*′ and *f*″ were taken from International Tables of X-ray Crystallography.[16] All H atoms were computed and refined, using a riding model, with an isotropic temperature factor equal to 1.2 times the equivalent temperature factor of the atom to which are linked. The final *R*(on *F*) factor was 0.084, *wR*(on $|F|^2$) = 0.171, and goodness of fit = 1.233 for all observed reflections. Number of refined parameters was 416. Max shift/esd = 0.00, mean shift/esd = 0.00. Max and min peaks in final difference synthesis were 0.205 and −0.216 eÅ^3, respectively.

4.26. X-ray crystal-structure determination of (3*R*,1′*R*)-4,4-dimethyl-3-[(1-phenylethyl)amino]pyrrolidin-2-one (3*R*,1′*R*)-31 (Table 1)

A prismatic crystal (0.2 × 0.09 × 0.02 mm) was selected and mounted on a MAR345 diffractometer with an image plate detector. Unit-cell parameters were determined from 2311 reflections (3° < θ < 31°) and refined by least-squares method. Intensities were collected with graphite monochromatized Mo Kα radiation. 7930 reflections were measured in the range 2.72 ⩽ θ ⩽ 32.10. 2529 of which were non-equivalent by symmetry (R_{int}(on *I*) = 0.060). 2311 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 methods, using SHELXS computer program[14] and refined by full-matrix least-squares method with SHELX97 computer program[15] using 7930 reflections, (very negative intensities were not assumed). The function minimized was $\Sigma w||F_o|^2 - |F_c|^2|^2$, where $w = [\sigma^2(I) + (0.0793P)^2 + 0.0660P]^{-1}$, and $P = (|F_o|^2 + 2|F_c|^2)/3$, *f*, *f*′ and *f*″ were taken from International Tables of X-ray Crystallography.[16] All H atoms were computed and refined, using a riding model, with an isotropic temperature factor equal to 1.2 times the equivalent temperature factor of the atom to which are linked. The final *R*(on *F*) factor was 0.047, *wR*(on $|F|^2$) = 0.134, and goodness of fit = 1.121 for all observed reflections. Number of refined parameters was 157. Max shift/esd = 0.00, mean shift/esd = 0.00. Max and min peaks in final difference synthesis were 0.260 and −0.358 eÅ^{-3}, respectively.

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