Synthesis of Chiral 2,2'-Bipyrrolidine Derivatives

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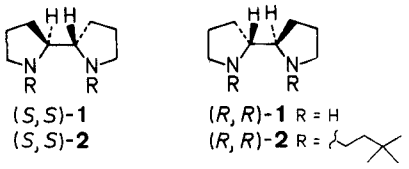
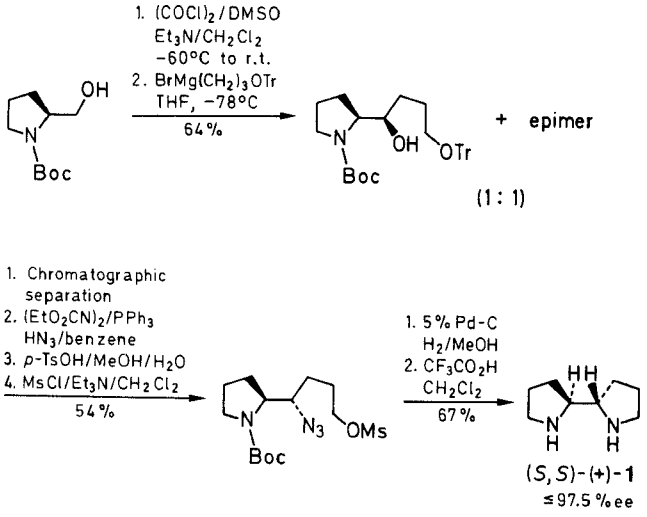
Optically pure 2,2'-bipyrrolidine (**1**) and its 1,1'-disubstituted derivatives have been synthesized from pyrrole and 2-pyrrolidone.

Chiral 2-substituted pyrrolidines serve as a useful auxiliary or metal ligand for asymmetric synthesis.[1] We have reported recently that osmium tetroxide undergoes with chiral 1,1'-bis(3,3-dimethylbutyl)-2,2'-bipyrrolidine (**2**) highly enantioselective dihydroxylation of *trans*-disubstituted and terminal olefins,[2] and also have found that the C_2-chiral bipyrrolidine system has high potential for use in other asymmetric transformations.[3,4]



Easy access to such chiral controllers is essential. Originally, (*S,S*)-(+)-2,2'-bipyrrolidine (**1**) was prepared from (*S*)-(+)-2-pyrrolidinemethanol in a straightforward manner as shown in Scheme **1**. However, it was tedious and very susceptible to racemization; moreover, (*R*)-(−)-2-pyrrolidinemethanol for (*R,R*)-(−)-**1** is expensive. We report herein an alternative synthetic route to **1** which is shorter and provides both enantiomers in optically pure form (Scheme **2**).



Scheme 1

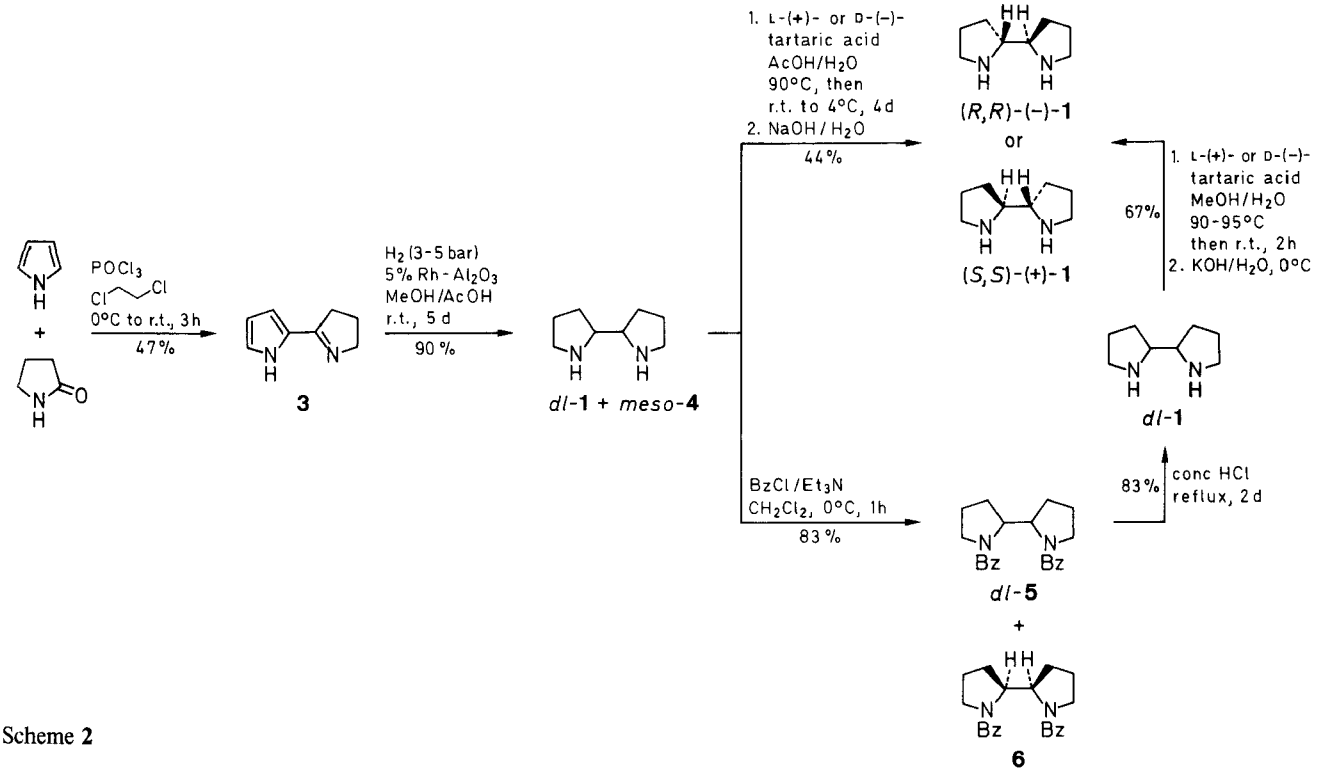
2-(3,4-Dihydro-2*H*-pyrrol-5-yl)pyrrole (**3**) was prepared in 97% yield via the coupling of pyrrole and 2-pyrrolidone according to Rapoport's procedure.[5] Catalytic hydrogenation of **3** on rhodium on alumina afforded a 1.2:1 mixture of *dl*-**1** and *meso*-bipyrrolidine **4** (90%). When *dl*-**1** and **4** are benzoylated, *dl*-amide **5** (45%) was readily separated from *meso*-amide **6** (38%) by chromatography. Subsequent acid hydrolysis of **5** afforded racemic *dl*-**1** (83% yield), which was then resolved by using L-(+)- or D-(−)-tartaric acid: addition of L-(+)-tartaric acid to the *dl* mixture in 75% aqueous methanol solution preferentially produced the crystalline salt of (*R,R*)-(−)-**1**, which was recrystallized twice to give after liberation enantiomerically pure (*R,R*)-(−)-**1** in 33% yield (67% yield based on isomer content). The residual salt in the mother liquor was liberated and retreated with D-(−)-tartaric acid in 75% aqueous methanol similarly to afford (*S,S*)-(+)-**1** (33% yield; 67% based on isomer content). Their enantiomeric purities were determined by HPLC analysis (DAICEL CHIRALCEL OD; hexane/2-propanol, 10:1) after conversion to the corresponding dibenzoyl amides **5** and the absolute configuration *S,S* was unambiguously assigned to (+)-**1** derived from (*S*)-(+)-2-pyrrolidinemethanol (Scheme **1**).

While the above procedure (Scheme **2**) provides all the three stereoisomers of **1** in pure form, a direct one-step isolation of (*R,R*)-(−)- or (*S,S*)-(+)-**1** from the *dl*, *meso*-mixture can be achieved via the tartrate salts. Thus, addition of L-(+)-tartaric acid (0.5 molar equiv) and glacial acetic acid (1 molar equiv) to an aqueous solution of the 1:1 mixture of *dl*-**1** and **4** resulted in preferential crystallization of only the tartrate salt of (*R,R*)-(−)-**1**. Recrystallization (two times) of this salt yielded after liberation enantiomerically pure (*R,R*)-(−)-**1** (44% yield based on isomer content).

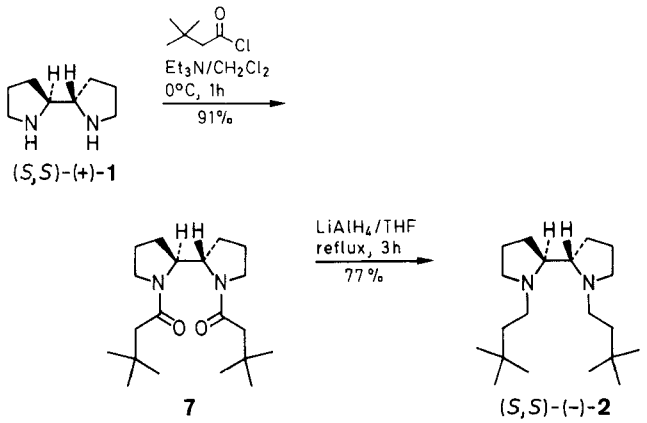
The derivatives **2** of **1** were prepared according to standard procedures as shown in Scheme **3**.

THF was distilled from benzophenone ketyl. CH_2Cl_2 was dried over anhydrous $CaCl_2$. Et_3N was distilled over CaH_2. Benzoyl chloride was distilled prior to use. Merck silica gel 60 (70–230 mesh) was used for column chromatography. Melting points are uncorrected. ^{1}H-NMR spectra were taken on either a JEOL FX90Q, Varian XL-200, or JEOL GX-400 spectrometer. IR spectra were recorded on a JASCO IRA-2-spectrometer. Low resolution mass spectra were taken on a HITACHI M-52 spectrometer, and JEOLJMS-HX110 spectrometer was used for high resolution measurement. Optical rotations were recorded on a JASCO DIP-370 polarimeter. HPLC analysis was performed on JASCO 880-PU and 875-UV system using YMC SIL-5 column (4.6 × 250 mm) or DAICEL CHIRALCEL OD column (4.6 × 250 mm). HPLC separation was performed on a Waters PrepLC/System 500A using YMC SIL-5 column (50 × 300 mm) by RI detection.

2-(3,4-Dihydro-2*H*-pyrrol-5-yl)pyrrole (3):
To a stirred solution of pyrrole (25 mL, 0.36 mol) and 2-pyrrolidone (13.7 mL, 0.18 mol) in $ClCH_2CH_2Cl$ (100 mL) at 0°C is added $POCl_3$ (25.2 mL, 0.27 mol) dropwise over a period of 1 h. After stirring is continued at r. t. for 2 h, the mixture is diluted with $CHCl_3$ (60 mL) and poured into an ice-cold solution of NaOAc (100 g, 0.75 mol) in H_2O (250 mL), and then 10 M aq KOH solution is added slowly at 0°C under vigorous stirring until the



Scheme 2



Scheme 3

aqueous layer becomes pH 11. The organic layer is separated, and the aqueous layer is extracted with $CHCl_3$ (2 × 60 mL). The combined organic extracts are washed with H_2O (2 × 25 mL), dried (K_2CO_3) and the solvent is removed under reduced pressure to give a slurry, which is crystallized from $CHCl_3$ to afford **3** as colorless needles; yield: 11.26 g (47%); mp 163.5–164°C (Lit.[5] mp 162–163°C).

$C_8H_{10}N_2$ (134.18) calc. C 71.61 H 7.51 N 20.88
found 71.46 7.62 20.73

MS (EI: 25 eV, 80°C): *m/z* (%) = 134 (M^+, 100), 133 (43), 132 (3), 107 (6), 106 (44), 105 (8), 92 (17), 80 (6), 79 (8).

IR (KBr): ν = 3125, 3080, 2955, 2870, 1614, 1426, 1346, 1308, 1142, 1112, 1060, 1024, 974, 880, 870, 848, 734, 606 cm^{-1}.

^{1}H-NMR ($CDCl_3$/TMS): δ = 1.80–2.20 (m, 2H), 2.70–3.10 (m, 2H), 3.80–4.20 (m, 2H), 6.22 (dd, 1H, J = 3.5, 2.5 Hz), 6.52 (dd, 1H, J = 3.5, 1.1 Hz), 6.93 (dd, 1H, J = 2.5, 1.1 Hz), 8.7 (br, 1H).

2,2'-Bipyrrolidine (*dl*-1 and 4):

5% Rh on alumina (1.70 g) and AcOH (100 mL) are added to a solution of **3** (20.3 g, 0.152 mol) in MeOH (100 mL). The mixture is shaken for 5 d under a H_2 atmosphere (3–5 bar) at r.t. and then filtered through Celite Hyflo Super-Cel.® The filtrate is concentrated to ca. 80 mL under reduced pressure and diluted with Et_2O (200 mL). Under vigorous stirring at 0°C, 10 M aq KOH solution (50 mL) is added and further basified to pH 11 with KOH pellets. The organic layer is separated and the aqueous layer is extracted with Et_2O (4 × 200 mL). The combined extracts are dried (K_2CO_3) and the solvent is concentrated. The residue is distilled under reduced pressure to give a mixture of *dl*-**1** and *meso*-**4** (19.1 g, 90%, bp 114–117°C/12 Torr); to prevent solidifying, the condenser of distillation apparatus is not cooled by cold H_2O but the receiver flasks are cooled by ice-water.

dl-1,1'-Dibenzoyl-2,2'-bipyrrolidine (*dl*-5) and *meso*-1,1'-Dibenzoyl-2,2'-bipyrrolidine (6):

To a solution of the above mixture (12.9 g, ca. 92 mmol) and Et_3N (28.1 mL, 202 mmol) in CH_2Cl_2 (200 mL) is added slowly a solution of benzoyl chloride (23.4 mL, 202 mmol) in CH_2Cl_2 (25 mL) at 0°C over a period of 10 min. After stirring at 0°C for 1 h, sat. aq NH_4Cl (70 mL) is added and extracted with EtOAc (300 mL). The aqueous layer is extracted with EtOAc (2 × 100 mL) and the combined extracts are washed with sat. aq $NaHCO_3$ (100 mL), sat. aq NaCl (100 mL), and dried ($MgSO_4$). The solvent is removed *in vacuo* and the residue is filtered through silica gel column (hexane/EtOAc, 3:1 and then EtOAc) to yield a mixture of *dl*-**5** and **6** (29.7 g, 93%), which is separated by HPLC (Waters PrepLC/System 500A, hexane/*i*-PrOH, 10:1) to give pure *dl*-**5** (t_R 15 min) as colorless prims; yield: 14.5 g (45%); mp 156.0–156.5°C, and **6** (t_R 19 min) as colorless prisms; yield: 12.1 g (38%); mp 146.0–146.5°C.

dl-**5**:

$C_{22}H_{24}N_2O_2$ (348.45) calc. C 75.83 H 6.94 N 8.04
found 75.60 6.89 7.93

MS (EI: 25 eV, 80°C): *m/z* (%) = 349 (M + 1, 2), 348 (M, 6), 244 (5), 105 (100), 243 (30), 176 (3), 175 (16), 174 (42), 106 (8), 105 (100).

IR (KBr): ν = 3070, 2980, 2880, 1616, 1602, 1574, 1454, 1420, 1358, 800, 788, 740, 722, 708, 674 cm^{-1}.

^{1}H-NMR ($CDCl_3$/TMS): δ = 1.70–2.40 (m, 8H), 3.20 (dt, 2H, J = 10.5, 7.3 Hz), 3.80 (ddd, 2H, J = 10.5, 8.0, 5.0 Hz), 4.50–5.70 (m, 2H), 7.20–7.50 (m, 10H).

6:

$C_{22}H_{24}N_2O_2$ (348.45) calc. C 75.83 H 6.94 N 8.04
found 75.85 7.17 8.03

MS (EI: 25 eV, 80°C): *m/z* (%)= 349 (M + 1, 1), 348 (M^+, 2), 244 (4), 243 (18), 186 (6), 176 (3), 175 (16), 174 (42), 106 (8), 105 (100).

IR (KBr): ν = 2995, 2945, 2900, 1616, 1602, 1580, 1500, 1450, 1416, 1404, 1182, 1148, 792, 774, 730, 702, 660 cm^{-1}.

^{1}H-NMR ($CDCl_3$/TMS): δ = 1.60–2.20 (m, 8H), 3.30–3.70 (m, 4H), 4.78 (br, 2H), 7.30–7.70 (m, 10H).

dl-2,2'-Bipyrrolidine (*dl*-1):

Amide *dl*-**5** (46.4 g, 133 mmol) is ground into powder and refluxed in conc. HCl (200 mL) for 2d. The resulting benzoic acid is removed by extraction with Et_2O (300 mL). The aqueous layer is basified to pH 11 with solid KOH pellets at 0°C and extracted with Et_2O (5 × 300 mL). The combined extracts are dried (K_2CO_3) and concentrated. The residue is distilled under reduced pressure to afford *dl*-**1** as hygroscopic colorless needles (15.6 g, 83%); bp 110–115°C/12 Torr; mp 34–37°C; caution should be paid to prevent the distillate from solidifying in the distillation apparatus.

MS (FAB): *m/z* = 141 (M + 1).

MS (EI: 25 eV, 80°C): *m/z* (%) = 70 (100).

IR (neat): ν = 3040, 2950, 2860 cm^{-1}.

^{1}H-NMR ($CDCl_3$/TMS): δ = 1.10–2.20 (m, 8H), 2.44 (br s, 2H), 2.60–3.20 (m, 6H).

Resolution of *dl*-2,2'-Bipyrrolidine (*dl*-1):

To a solution of *dl*-**1** (14.0 g, 100 mmol) in MeOH (30 mL) is added a solution of L-(+)-tartaric acid (14.9 g, 100 mmol) in H_2O (30 mL) and the solvent is removed under reduced pressure. A mixed solvent (MeOH/H_2O, 3:1) is added slowly to the colorless residual solid on water bath (90–95°C) to dissolve it. Addition of 320 mL of MeOH/H_2O (3:1) results in a clear solution which is then cooled to r.t. After 2 h, the resulting colorless needles (19.1 g) are filtrated, recrystallized twice from MeOH/H_2O (3:1, 550 mL and 630 mL), and dried *in vacuo* at 80°C for 12 h to yield 10.8 g (75% yield based on isomer content) of the L-(+)-tartrate salt of (*R,R*)-(−)-**1** as colorless needles; mp 211.0–212.0°C (dec); $[\alpha]_D^{24}$ −18.0° (*c* = 1.03, H_2O).

$C_{12}H_{22}O_6N_2$ (290.3) calc. C 49.65 H 7.64 N 9.65
found 49.29 7.63 9.62

IR (KBr): ν = 3150, 2900, 2700, 1685, 1610, 1580, 1454, 1384, 1320, 1296, 1124, 1076, 710 cm^{-1}.

^{1}H-NMR (D_2O/TMS): δ = 1.60–2.40 (m, 8H), 3.37 (t, 4H, *J* = 7.0 Hz), 3.70–3.90 (m, 2H), 4.29 (s, 2H), 4.69 (s, 6H).

The above first and second mother liquor are combined and most of MeOH is evaporated, and 10M aq KOH (10 mL) and the KOH pellets (38 g) are added at 0°C. The mixture is extracted with Et_2O (3 × 200 mL) and the combined extracts are dried (K_2CO_3) and concentrated. To the residual oil (7.76 g, 55.3 mmol) D-(−)-tartaric acid (8.31 g, 55.3 mmol) is added and the mixture is dissolved in hot MeOH/H_2O (3:1, 460 mL). After the solution is allowed to stand at r.t. for 2 h, 15.49 g of colorless needles are filtrated and recrystallized twice from MeOH/H_2O (3:1, 570 mL and 660 mL), and dried at 80°C under reduced pressure to give colorless needles of the D-(−)-tartrate salt of (*S,S*)-(+)-**1**; yield: 10.7 g (74% based on isomer content); mp 211.0–212.0°C; $[\alpha]_D^{24}$ +17.9° (*c* = 1.02, H_2O).

$C_{12}H_{22}O_6N_2$ (290.3) calc. C 49.65 H 7.64 N 9.65
found 49.24 7.83 9.75

Et_2O (50 mL), 10M aq KOH (15 mL) and KOH pellets (10 g) are added to the above D-(−)-tartrate salt of (*S,S*)(+)-**1** (6.00 g, 20.7 mmol) at 0°C and the mixture is stirred vigorously. The organic layer is separated and the aqueous layer is extracted with Et_2O (3 × 50 mL). The combined extracts are dried (K_2CO_3) and concentrated. Bulb-to-bulb distillation (110°C/12 Torr) gives (*S,S*)-(+)-**1** as colorless oil; yield: 2.61 g (90%); $[\alpha]_D^{24}$ +20.3° (*c* = 0.374, MeOH).

MS (FAB): *m/z* = 141 (M + 1).

MS (EI: 25 eV, 80°C): *m/z* (%) = 70 (100).

IR (neat): ν = 3260, 2955, 2875, 1548, 1450, 1400, 1330, 1280, 1172, 1108, 900 cm^{-1}.

^{1}H-NMR ($CDCl_3$/TMS): δ = 1.20–2.20 (m, 8H), 2.12 (br, 2H), 2.60–3.20 (m, 6H).

^{13}C-NMR ($CDCl_3$/TMS): δ = 25.41, 29.05, 46.39, 63.74.

Direct Separation and Resolution of *dl*-2,2'-Bipyrrolidine (*dl*-1):

To a solution of the 1:1 mixture of *meso*- **4** and *dl*-2,2'-bipyrrolidine (*dl*-**1**) (9 g, 64 mmol) in H_2O (35 mL), L-(+)-tartaric acid (4.84 g, 32 mmol) and glacial AcOH (3.7 mL, 64 mmol) are added. Heating the solution to ca. 90°C and then cooling to r.t, and finally to 4°C provides after 4 d, colorless crystals (4.0 g) of the L-(+)-tartrate salt of (*R,R*)-(−)-**1**. Recrystallization with heating from H_2O (16 mL) yields the tartrate salt (3.4 g). This is recrystallized one more from H_2O (12 mL) to provide the salt (3.1 g), which is then dissolved into H_2O (15 mL) and solid NaOH pellets (12.0 g) are added. Extraction with benzene (4 × 15 mL), drying (Na_2SO_4), and removal of solvent provides after bulb-to-bulb distillation (100°C/15 Torr), (*R,R*)-(−)-**1** as a colorless oil; yield: 1.1 g (44% based on isomer content); $[\alpha]_D^{25}$ −10.9° (*c* = 1.03, benzene).

(*R,R*)-(−)-**1** and (*S,S*)-(+)-**1** are transformed to the corresponding benzoyl amides (*R,R*)-**5** and (*S,S*)-**5**, respectively, with benzoyl chloride and Et_3N in CH_2Cl_2, and their enantiomeric purities are determined to be >99% ee by HPLC analysis [DAICEL CHIRALCEL OD, hexane/*i*-PrOH (10:1) as eluant, t_R 4.27 min for (*R,R*)-**5** and 6.48 min for (*S,S*)-**5**].

(*S,S*)-(−)-1,1'-Bis(3,3-dimethylbutanoyl)-2,2'-bipyrrolidine (7):

To a stirred solution of (*S,S*)-(+)-**1** (0.350 g, 2.50 mmol) and Et_3N (0.763 mL, 5.49 mmol) in CH_2Cl_2 (10 mL) is added dropwise a solution of 3,3-dimethylbutanoyl chloride (0.765 mL, 5.49 mmol) in CH_2Cl_2 (5 mL) at 0°C. After stirring at 0°C for 1 h sat. NH_4Cl (70 mL) is added and extracted with EtOAc (3 × 70 mL). The combined extracts are washed with sat. $NaHCO_3$, sat. NaCl and dried ($MgSO_4$). Removal of the solvent followed by silica gel column chromatography affords **7** as colorless oil; yield: 0.760 g (91%); $[\alpha]_D^{25}$ −86.4° (*c* = 1.04, $CHCl_3$).

HRMS (EI: 70 eV): *m/z*, $C_{20}H_{36}N_2O_2$ calc.: 336.2777; found: 336.2776.

MS (EI: 25 eV, 80°C): *m/z* (%)= 336 (M, < 1), 237 (13), 169 (4), 168 (11), 113 (6), 112 (5), 99 (3), 98 (6), 87 (3), 71 (10), 70 (100), 69 (5), 59 (4), 58 (5), 57 (11).

IR (neat): ν = 2950, 2870, 1636, 1416, 1382, 1360, 1304, 1276, 1200, 890 cm^{-1}.

^{1}H-NMR ($CDCl_3$/TMS): δ = 1.04 (s, 18H), 1.60–2.00 (m, 8H), 1.98 (d, 2H, *J* = 15 Hz), 2.20 (d, 2H, *J* = 15 Hz), 3.33 (td, 2H, *J* = 9.4, 8.9 Hz), 3.60 (td, 2H, *J* = 9.4, 2.9 Hz), 4.10–4.20 (m, 2H).

(*S,S*)-1,1'-Bis(3,3-dimethylbutyl)-2,2'-bipyrrolidine (2):

To a stirred suspension of $LiAlH_4$ (0.250 g, 6.61 mmol) in dry THF (10 mL) is added dropwise a solution of **7** (0.740 g, 2.20 mmol) in dry THF (5 mL) at 0°C and refluxed for 3 h. 10M KOH (1 mL) is added carefully at 0°C and the resulting white precipitates are removed by suction, washed with Et_2O (100 mL). The filtrate is dried (K_2CO_3) and the solvent is evaporated. The residue is purified by aluminum column chromatography to yield **2** as colorless oil; yield: 0.520 g (77%); $[\alpha]_D^{24}$ −137°(*c* = 1.01, $CHCl_3$).

$C_{20}H_{40}N_2$ (308.55) calc. C 77.85 H 13.07 N 9.08
found 77.69 13.06 9.11

HRMS (EI: 70 eV): *m/z*, $C_{20}H_{40}N_2$ calc.: 308.3191; found: 308.3207.

MS (EI: 25 eV, 80°C): *m/z* (%) = 280 (M, < 1), 223 (3), 141 (19), 140 (100), 139 (12), 82 (33), 70 (28).

IR (neat): ν = 2955, 2925, 2870, 2805, 2790, 1470, 1394, 1366, 1244, 1212, 1138, 1116, 1058, 936 cm^{-1}.

^{1}H-NMR ($CDCl_3$/TMS): δ = 0.91 (s, 18H), 1.38 (ddd, 2H, *J* = 13.0, 11.3, 5.2 Hz), 1.45 (ddd, 2H, *J* = 13.0, 11.3, 5.2 Hz),

1.60–1.75 (m, 8H), 2.00–2.10 (m, 2H), 2.11 (td, 2H, J = 11.3, 5.2 Hz), 2.54 (m, 2H), 2.82 (td, 2H, J = 11.3, 5.2 Hz), 3.11–3.18 (m, 2H).

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