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Synthesis of enantiopure 5.7-spirodiamines: (*S*)-1,7-diaza[4.6]undecane and related compounds

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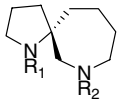
Abstract—The efficient synthesis of enantiomerically pure (*S*)-1,7-diaza[4.6]undecane and (*S*)-7-methyl-1,7-diaza[4.6]undecane and related compounds is reported. These novel diamines are obtained from (*S*)-proline, which is reacted with chloral to give an enantiomerically pure oxazolidinone, which is alkylated at the α-position using *cis*-1,4-dibromobutene. The resulting allylbromide is then reacted with ammonia or methylamine to yield, as intermediates, allylamines, which ring close to give the corresponding spirolactams. The parent and the 7-methyl (*S*)-5.7-spirodiamines are obtained via reduction in two steps of the spirolactams. The expected absolute configuration was confirmed by X-ray structural analysis. Enantiomeric excess (>99.8% ee) was determined using the Mosher amides of the spirodiamines and gas chromatography.

1. Introduction

The stereoselective lithium amide mediated rearrangement of epoxides to yield enantiomerically enriched allylic alcohols is a reaction of great interest.[1] Consequently, chiral amines are being developed as precursors of lithium amide bases to be used in stereoselective deprotonations. In our search using multinuclear NMR, kinetic and computational investigations[2–4] for more efficient enantiomers of lithium amides, we have found spirodiamines to be interesting precursor candidates. Herein, we report the synthesis of (*S*)-5.7-spirodiamines **1** (Fig. 1) starting from (*S*)-proline **2**.



1a: $R_1 = H$, $R_2 = H$
b: $R_1 = H$, $R_2 = Me$
c: $R_1 = Me$, $R_2 = Me$

Figure 1.

Spirodiamines are rare compounds while enantiomerically pure spirodiamines are even more so. To the best of our knowledge, 5.7-spirodiamines have not previously been reported and there exist only a few examples of 5.6-spirodiamines. However, these have one of their nitrogens at the 2-position. Recent interest in aza-spirolactams as β-turn mimetics has resulted in syntheses of some 5.4-,[5] 5.5-[6] and 5.6-aza-spirolactames.[7] However enantiopure aza-spirolactams are still rare.[7]

2. Results and discussion

In the synthesis of **1** (Scheme 1), (*S*)-proline **2** was reacted with chloral to obtain the known oxazolidinone **3**.[8–10] A chloroform solution of (*S*)-proline and chloral was refluxed and the water formed removed azeotropically (Scheme 1). Crystallisation of the product from ethyl acetate gave enantiomer **3**, which is stable in air. Diastereoselective alkylation of the enolates of oxazolidinones has already been reported by Seebach[11] and Germanas.[9] Attempts to alkylate the enolate of **3** with the dielectrophiles **4a** and **4b** or **5a** and **b** were unsuccessful (Fig. 2).

Apparently these electrophiles are not reactive enough to alkylate the enolate, meaning a more reactive electrophile is needed. We therefore turned our attention to the allylic dielectrophile *cis*-1,4-dibromobutene **6** (Fig. 2) and this compound showed the wanted reactivity as an alkylating agent. α-Deprotonation of **3** by LDA and

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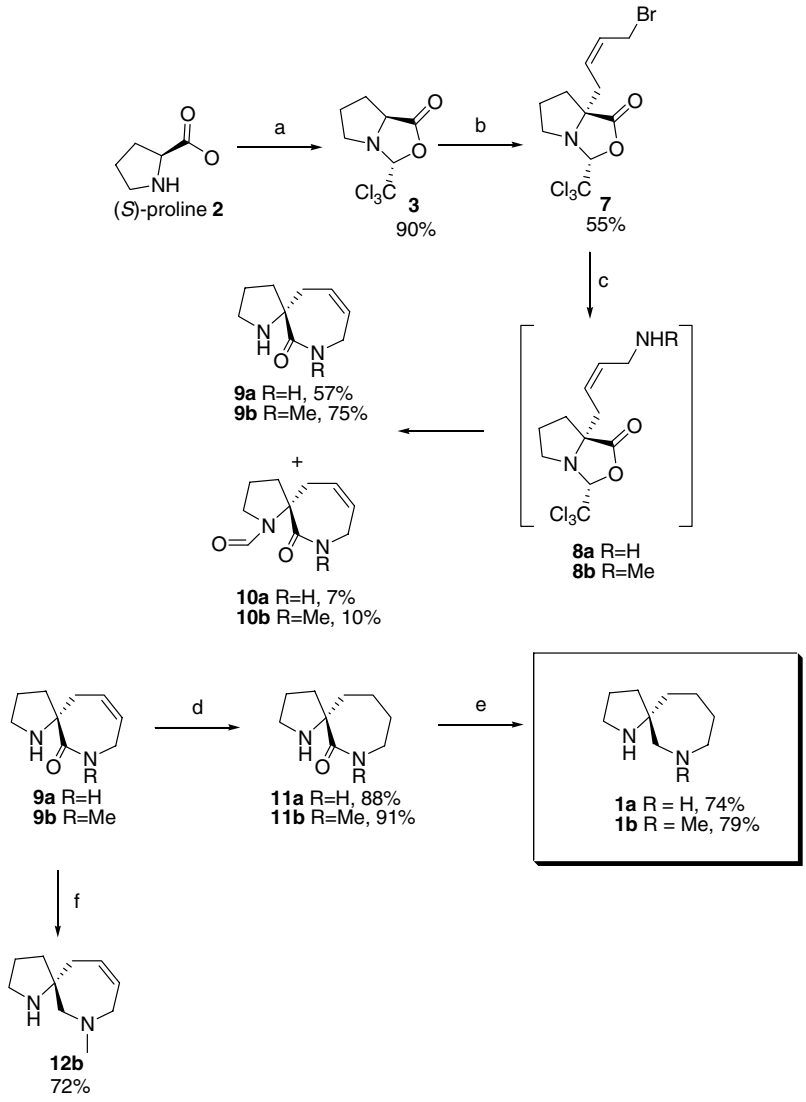


Scheme 1. Reagents and conditions: (a) Chloral, chloroform, reflux, 4.5 h; (b) (i) LDA, THF, −78 °C, (ii) *cis*-2,4-dibromobutene **6**, 4.5 h; (c) Compounds **9a** and **10a**: excess methylamine (33% in EtOH), DCM, 6 h. Compounds **9b** and **10b**: excess ammonia (EtOH), DCM 16 h; (d) 10% Pd/C, H_2 (4 atm), ethyl acetate, 4 h; (e) $LiAlH_4$, THF, 16 h; (f) $LiAlH_4$, THF, 18 h.

then reaction with *cis*-1,4-dibromobutene **6** provided the desired bromide **7** as product. After chromatography, bromide **7** was isolated in 55% yield.

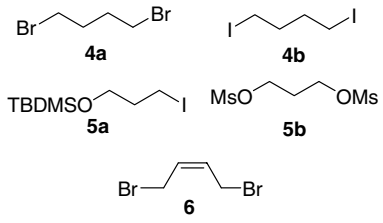
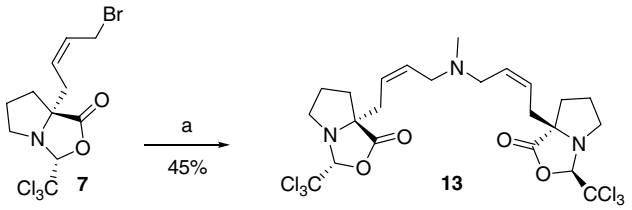


Figure 2.

In the next step, bromide **7** was reacted with the appropriate amines, forming allylic amines suitable for intramolecular reaction with their oxazolidinone moieties. Allylic bromide **7** was reacted with excess methylamine and spiroamide **9b** was obtained in 75% yield. Presumably allyl amine **8b** is an intermediate in this reaction. When ammonia was used instead of methylamine, parent spirolactam **9a** was obtained in 57% yield. Along with these spirolactams minor amounts of the formylated products **10a** and **10b** were also obtained.

Under the conditions described above, the intermediary amine **8** apparently reacts intramolecularly yielding spirolactam **9** rather than intermolecularly with **7**. However, reaction of bromide **7** with 1 equiv of methylamine in dichloromethane (Scheme 2) gave after a few minutes a precipitate of methylammonium bromide. The major product was identified as **13** resulting from the substitution of bromide **7** with methylamine, followed by alkylation of the amine with a second molecule of **7**. Thus, substitution of the bromide in **7** by methyl amine is faster than ring opening by methylamine. It is interesting to note that other studies in our group have shown that intermolecular opening of the oxazolidinone ring by amines is not feasible with



Scheme 2. Reagents and conditions: (a) 1 equiv methylamine (33% in EtOH), DCM, 2 h.

α,α-substituted oxazolidinones. This steric nature of α,α-disubstituted proline derivatives have also been noted by others.[12]

Crystals of hydrochloride of **9b** were obtained during isolation of **9b** after treatment with hydrochloric acid with the crystal structure[13] shown in Figure 3. This structure confirms the predicted absolute configuration of the enantiomer.[13,14]

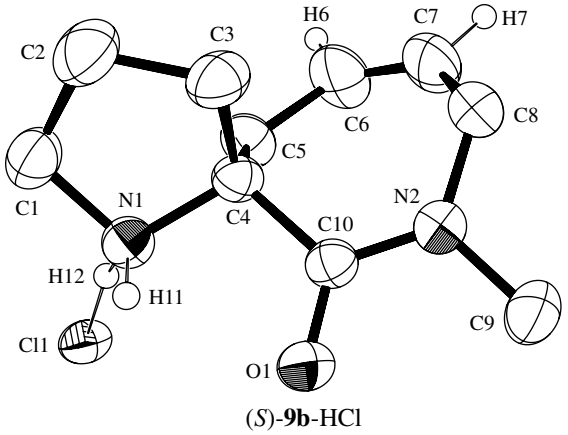


Figure 3. Crystal structure of **9b**-HCl showing the spiro structure with the (*S*)-configuration.

Hydrogenation of the double bonds in **9a** and **9b** gave **11a** and **11b**, respectively, which could be reduced to diamines **1a** and **1b** with lithium aluminium hydride in total yields from (*S*)-proline of 18% and 27%, respectively.

The enantiomeric purity of the spirodiamines and spirolactams was determined by using the corresponding Mosher amides.[15] Coupling of spiroamine **1b** or spirolactam **9a** with Mosher's acid under different reaction conditions (DCC, 1-HOBt, EDC, PYBOP) were unsuccessful, which is probably due to the steric nature of the amines. Therefore the more reactive Mosher's acid chloride was used. Spirodiamine **1b** and spirolactam **9a** were reacted with both enantiomers of the Mosher's acid chloride in the presence of DIPEA in dichloromethane to give (*S*,*S*)-**14** and (*R*,*S*)-**14** and (*S*,*S*)-**15** and (*R*,*S*)-**15**, respectively (Fig. 4). The ^{1}H NMR spectra of these compounds were complex with overlapping signals. The ^{19}F NMR analysis at 25 °C showed broad and overlapping singlets for each diastereomer. Raising the temperature to 65 °C gave sharper peaks, but the

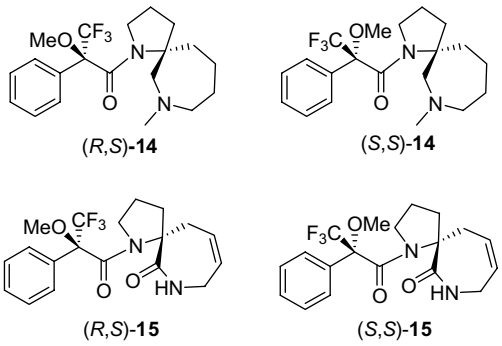
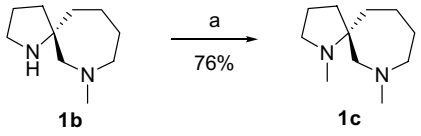


Figure 4.

determination of enantiomeric purities was not possible. However, separations of both diastereomers (*S*,*S*)-**14** and (*R*,*S*)-**14** and (*S*,*S*)-**15** and (*R*,*S*)-**15** by gas chromatography were successful. Base line separated peaks were obtained on both chiral and achiral columns (cf. Section 4). The enantiomeric excess of both **1b** and **9a** was found to be over 99.8%. In view of these results it can be concluded that the oxazolidinone used as reactant was the enantiomer **3** since only the enantiomerically pure spirodiamine products **1b** and **9a** were obtained.

Apart from the precursor diamines **1a** and **1b**, derivative **1c** was obtained from spirodiamine **1b** (Scheme 3). Amine **1c** containing two tertiary nitrogens was obtained by an Eschweiler–Clarke methylation and will be investigated as a chiral ligand in enantioselective deprotonations.[16]



Scheme 3. Reagents and conditions: (a) HCOOH, H_2CO, 70 °C, 21 h.

3. Conclusion

In summary, a facile synthetic route to enantiopure (*S*)-5.7-spirolactams and (*S*)-5.7-spirodiamines and related compounds has been reported. The spirodiamines are interesting precursors to the enantiomers of lithium amides to be used in enantioselective deprotonations and spirodiamines may also show interesting biological properties.

4. Experimental

4.1. General

Unless otherwise noted, all starting materials and solvents were obtained from commercial suppliers and used without purification. THF was distilled from sodium and benzophenone, dichloromethane was distilled from calcium chloride and NEt_3 was distilled from CaH_2 prior to use. Reactions were performed under a nitrogen

atmosphere. Visualisation of TLC-spots was effected by exposure to 1% ninhydrin solution in EtOH or 5% sulfuric acid in EtOH. ^{1}H and ^{13}C NMR spectra were recorded at 400 and 100 MHz, respectively, using TMS as the internal standard. Chiral GC analyses were performed on a CP-Chiralsil-DEX CB. GC/MS analyses were performed on a CP-Sil 8 CB (Low Bleed/MS-column) with helium as carrier gas using chemical ionisation (CH_4) for detection. LC/MS analyses were run using a Synergi MAX-RP C12 3 × 50 mm, 4 μm particles at pH 7 (10 mM ammonium acetate). Mobile phase A: 95% acetonitrile/5% de-ionized water/buffer. Mobile phase B: 5% acetonitrile/95% de-ionized water/buffer. A gradient from 100% B to 100% A was used. Elemental analyses were performed by H. Kolbe Micro Analytisches Laboratorium. Published procedures for the preparation of (2*R*,5*S*)-2-trichloromethyl-1-aza-3-oxabicyclo[3.3.0]-octan-4-one **3**,[17] 1-(*t*-butyldimethylsiloxy)-3-iodopropane **5a**,[18] 1,3-propanediol, dimethanesulfonate **5b**[19] and *cis*-1,4-dibromobutene **6**[20] have been utilized.

4.2. (2*R*,5*R*)-5-(4-Bromo-2-butenyl)-2-trichloromethyl-1-aza-3-oxabicyclo[3.3.0]octan-4-one 7

An LDA solution [prepared by adding *n*-BuLi (123 mmol, 2.5 M, 50.0 mL) to a stirred solution of diisopropylamine (17.3 mL, 123 mmol) in dry THF (170 mL) at −78 °C under nitrogen atmosphere] was added via a flex needle for 15 min to a stirred solution of oxazolidinone **3** (20.0 g, 82 mmol) in dry THF (250 mL) at −78 °C under a nitrogen atmosphere. After another 20 min at −78 °C, *cis*-1,2-dibromobutene **6** (164 mmol, 35.0 g) was added and the solution kept at −78 °C for 4.5 h. After raising the temperature to −40 °C, the reaction was quenched by the addition of water (200 mL). The mixture was extracted with chloroform (1 × 250 mL, 1 × 100 mL) and the combined extracts dried over $MgSO_4$ and evaporated to give a dark oil. Diethyl ether (50 mL) was added to the residue and the precipitate filtrated and washed with diethyl ether (2 × 50 mL). The filtrate was evaporated to give a dark clear oil (44.6 g). Column chromatography of 10.15 g (7.5 × 13.5 cm, SiO_2 60–230 mesh) using dichloromethane/hexane (1:10 750 mL, 1:1 2000 mL) gave **7** as a clear oil (4.26 g, total 55%). $[\alpha]_D^{25} = -7.5$ (*c* 4.552, $CHCl_3$), LC/MS 378 $(M+H)^+$. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.67 (m, 1H), 1.95 (m, 1H), 2.02 (m, 1H), 2.19 (m, 1H), 2.71 (m, 2H), 3.23 (m, 2H), 3.97 (m, 1H), 4.06 (m, 1H), 5.00 (s, 1H), 5.75 (m, 1H), 5.95 (m, 1H). ^{13}C NMR δ 25.50 (CH_2), 26.81 (CH_2), 34.80 (CH_2), 35.79 (CH_2), 58.74 (CH_2), 71.80 (C), 100.4 (C), 102.7 (CH), 128.4 (CH), 129.9 (CH), 176.06 (C). Anal. Calcd for $C_{11}H_{13}BrCl_3NO_2$ (377.49): C, 35.00; H, 3.47. Found: C, 35.06; H, 3.51.

4.3. (5*R*)-1,7-Diaza-spiro[4.6]undec-9-en-6-one 9a

Compound **7** (9.0 g, 23.9 mmol) in dichloromethane (40 mL) was added dropwise for 30 min to an ethanolic solution of NH_3 [120 mL, prepared by bubbling NH_3(g) to ice-cold EtOH for 20 min]. The solution was stirred at room temperature for 16 h and then evaporated to give a residue, which was dissolved in 2 M HCl (20 mL). The acidic layer was washed with ethyl acetate (2 × 15 mL) and then made basic (pH 12) by the addition of solid NaOH. Extraction with dichloromethane (5 × 20 mL) and drying over $MgSO_4$ followed by evaporation gave 3.75 g of a yellow oil. NMR- and GC/MS-analyses showed that the product contained 7% of formylated product **10a**. Column chromatography (6.5 × 13.5 cm, SiO_2 60–230 mesh) using DCM/MeOH(NH_3) 9:1–8:2 gave **9a** as a clear yellow oil (2.25 g, 57%) which crystallized. $[\alpha]_D^{25} = -133.9$ (*c* 0.85, $CHCl_3$), mp = 220–221 °C, GC/MS 167 $(M+H)^+$. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.73–189 (m, 2H), 2.01–2.15 (m, 2H), 2.35–2.48 (m, 2H), 2.80 (br s, 1H), 2.79–2.99 (m, 2H), 3.66 (m, 1H), 4.01 (m, 1H), 5.70 (m, 2H), 6.32 (br s, 1H). ^{13}C NMR δ 26.41 (CH_2), 33.07 (CH_2), 39.43 (CH_2), 41.43 (CH_2), 46.75 (CH_2), 66.99 (C), 124.0 (CH), 128.6 (CH), 179.1 (C). Anal. Calcd for $C_9H_{14}NO_2$ (165.212): C, 65.03; H, 8.49. Found: C, 64.88, H, 7.57.

4.4. (5*R*)-7-Methyl-1,7-diaza-spiro[4.6]undec-9-en-6-one 9b

Compound **7** (10.5 g, 27.8 mmol) in dichloromethane (120 mL) was added dropwise for 30 min to $MeNH_2$ (33% in EtOH, 36.3 mL, ca. 290 mmol). The solution was stirred at room temperature for 6 h and then evaporated to give a semi solid (10.1 g). Water (10 mL) was added and the pH adjusted to 10 by the addition of NaOH(s). The aqueous layer was extracted with dichloromethane (5 × 20 mL). The organic phase was dried over $MgSO_4$ and then evaporated to give a clear yellow oil (4.05 g). NMR- and GC/MS-analyses showed that the product contained 10% of formyl product **10b**. The oil was dissolved in HCl (2 M, 30 mL) and washed with ethyl acetate (2 × 20 mL). The aqueous layer was basified with NaOH (4 M) to pH 12 and then extracted by dichloromethane (4 × 25 mL). The organic layer was dried ($MgSO_4$) and evaporated to yield the product **9b** (3.78 g, 75%) as a clear yellow oil. $[\alpha]_D^{25} = -113.5$ (*c* 1.36, $CHCl_3$), LC/MS 181 $(M+H)^+$. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.77 (m, 2H), 1.83 (m, 2H), 2.03 (m, 2H), 2.35 (t, 2H), 2.89 (m, 1H), 2.96 (m, 1H), 3.06 (s, 3H), 3.01–3.10 (br s, 1H), 3.69 (m, 1H), 4.23 (m, 1H), 5.68 (m, 2H). ^{13}C NMR δ 26.61 (CH_2), 33.87 (CH_2), 38.80 (CH_3), 40.26 (CH_2), 46.93 (CH_2), 49.46 (CH_2), 67.61 (C), 123.4 (CH), 129.9 (CH), 176.47 (C). Anal. Calcd for $C_{10}H_{16}NO_2$ (180.247): C, 66.63; H, 8.95. Found: C, 66.46; H, 9.04.

4.5. (5*R*)-7-Methyl-1,7-diaza-spiro[4.6]undec-9-ene 12b

A suspension of lithium aluminium hydride (0.56 g) in dry THF (15 mL) was put under a nitrogen atmosphere and cooled in an ice bath. To the suspension was added **9b** (0.9 g, 5.0 mmol) in dry THF (35 mL) by dropwise addition over 10 min. The ice bath was removed and the mixture stirred overnight (16 h). The mixture was again cooled with an ice bath and then quenched by the careful addition of water (0.5 mL), NaOH (2 M, 0.5 mL) and water (1.5 mL). The mixture was stirred for 30 min and the resulting white precipitate filtered off and washed with THF (20 mL). To the filtrate was added toluene (100 mL). After evaporation, a clear yel-

low oil (0.90 g) was obtained. Distillation using a vigreux column gave diamine **12b** as a colourless oil (0.60 g, 72%, 50 °C/0.1 mbar). $[\alpha]_D^{25} = -37.22$ (*c* 0.395, $CHCl_3$). ^1H NMR ($CDCl_3$, 400 MHz): δ 1.55 (m, 2H), 1.78, 1.74–1.88 (m, 2H) 1.95 (br s, 1H), 2.26 (m, 2H), 2.36 (s, 3H), 2.42–2.60 (m, 3H), 2.78 (m, 1H), 2.90–3.12 (m, 4H). ^{13}C NMR: δ 24.64 (CH_2), 37.08 (CH_2), 39.64 (CH_2), 45.28 (CH_2), 48.81 (CH_3), 57.96 (CH_2), 62.83 (C), 70.90 (CH_2), 129.2 (CH), 129.4 (CH).

4.6. Bis-(4-[(2*R*,5*R*)-2-trichloromethyl-1-aza-3-oxabicyclo[3.3.0]octan-4-one-5-yl]-2-butenyl)-methylamine 13

Bromide **7** (0.39 g, 1 mmol) was dissolved in dichloromethane (10 mL). Methylamine (33% in EtOH, 125 μL, 1 mmol) was added in one portion. A precipitate started to form after a few minutes. The mixture was stirred at room temperature for 2 h and then washed with NaOH (1 M, 5 mL) and dried over $MgSO_4$. The volatiles were removed by evaporation to yield a viscous oil (0.25 g). Column chromatography (2.5 × 13.5 cm, SiO_2 60–230 mesh) using ethyl acetate gave **13** as a clear oil (0.14 g, total 45%). $[\alpha]_D^{25} = -5.9$ (*c* 0.17, $CHCl_3$), LC/MS 626 $(M+H)^+$. ^1H NMR ($CDCl_3$, 400 MHz): δ 1.65 (m, 2H), 1.95 (m, 4H), 2.15 (m, 2H), 2.21 (s, 3H), 2.65 (m, 4H), 3.04 (br s, 4H), 3.22 (br s, 4H), 4.98 (s, 2H), 5.65 (m, 4H). ^{13}C NMR: δ 25.28 (CH_2), 30.23 (CH_2), 35.15 (CH_2), 35.41 (CH_2), 42.17 (CH_3), 54.25 (CH_2), 58.41 (CH_2), 71.72 (C), 100.3 (C), 102.3 (CH), 125.7 (CH), 131.4 (CH), 176.1 (C).

4.7. (5*S*)-1,7-Diaza-spiro[4.6]undecane 1a

To spiroamide **9a** (1.1 g, 6.62 mmol) in ethyl acetate (20 mL) and MeOH (10 mL) was added palladium on carbon (0.5 g, 10%). The mixture was hydrogenated for 4 h at 4 atm using a Parr apparatus and then filtered through a 1 cm pad of Celite. The catalyst was washed with MeOH (3 × 10 mL). Evaporation of the volatiles gave a clear yellow oil **11a** (0.98 g, 88%). This product was pure enough for the next step. An analytical sample was crystallized from chloroform. $[\alpha]_D^{25} = -45.9$ (*c* 1.36, $CHCl_3$), mp = 216–218 °C, GC/MS (CI/CH_4) 169 $(M+H)^+$. ^1H NMR ($CDCl_3$, 400 MHz): δ 1.40–1.52 (m, 2H), 1.60–2.15 (m, 9H), 3.02 (m, 1H), 3.12 (m, 1H) 3.23 (m, 2H) 6.47 (br s, 1H). ^{13}C NMR: δ 25.26 (CH_2), 25.47 (CH_2), 28.52 (CH_2), 31.95 (CH_2), 35.30 (CH_2), 41.69 (CH_2), 45. 36 (CH_2), 68.91 (C), 178.1 (C). A suspension of lithium aluminium hydride (1.0 g, 26 mmol) in dry THF (15 mL) in nitrogen atmosphere was cooled in an ice bath. To the suspension was added a suspension of **11a** (0.98 g, 5.80 mmol) in dry THF (20 mL) by dropwise addition under 20 min. The ice bath was removed and the mixture stirred overnight (16 h). The mixture was again cooled with an ice bath and then quenched by careful addition of water (1.0 mL), NaOH (2 M, 1.0 mL) and water (3.0 mL). The mixture was stirred for 30 min and the resulting white precipitate was filtered off and washed with THF (20 mL). To the combined filtrate was added toluene (50 mL) and the volatiles then removed by evaporation to give a clear yellow oil **1a** (0.66 g, 74%). An analytical sample was obtained, by short-path distillation, as a colourless oil. $[\alpha]_D^{25} = -1.6$ (*c* 2.12, $CHCl_3$), GC/MS (CI/CH_4) 155 $(M+H)^+$. ^1H NMR ($CDCl_3$, 400 MHz): δ 1.56–1.78 (m, 10H), 1.80–1.95 (br s, 2H), 2.63 (m, 2H), 2.82–2.92 (m 3H), 2.92–3.00 (m, 1H). ^{13}C NMR: δ 22.41 (CH_2), 25.23 (CH_2), 30.74 (CH_2), 36.99 (CH_2), 41.75 (CH_2), 45.44 (CH_2), 49.46 (CH_2), 57.79 (CH_2), 65.81 (C). 155.1548. HRMS *m*/*z* calcd for $C_9H_{18}N_2$ 155.1548. Found 155.1530.

4.8. (5*S*)-7-Methyl-1,7-diaza-spiro[4.6]undecane 1b

To the spirodiamine **96** (3.7 g, 20.5 mmol) in ethyl acetate (50 mL) and was added palladium on carbon (1 g, 10%). The mixture was hydrogenated for 4 h at 4 atm using a Parr apparatus and then filtered through 1 cm pad of Celite. The catalyst was washed with ethyl acetate (3 × 20 mL). Evaporation of the volatiles gave a clear yellow oil **11b**, which was pure enough for the next step (3.40 g, 91%). $[\alpha]_D^{25} = -45.0$ (*c* 2.77, $CHCl_3$), GC/MS (CI/CH_4) 183 $(M+H)^+$. ^1H NMR ($CDCl_3$, 400 MHz): δ 1.60–1.78 (m, 4H), 1.78–1.90 (m, 2H), 1.95 (m, 3H), 2.70 (br s, 1H), 2.67 (m, 2H), 2.93 (m, 1H), 3.03 (s, 3H), 3.29 (m, 1H), 3.54 (m, 1H). Compound **1b** was obtained by reduction of **11b** using the procedure described for **1a** using lithium aluminium hydride (3.2 g, 84 mmol) and **11b** (3.4 g, 18.7 mmol). Distillation using a vigreux column gave diamine **1b** as a colourless oil (2.49 g, 79%, 55 °C/0.1 mbar). $[\alpha]_D^{25} = -9.9$ (*c* 3.25, $CHCl_3$). ^1H NMR ($CDCl_3$, 400 MHz): δ 1.45–1.68 (m, 6H), 1.68–1.83 (m, 4H), 2.11 (br s, 1H), 2.37–2.40 (m, 2H), 2.35 (s, 3H), 2.44 (m, 1H) 2.59 (m, 1H), 2.83–2.97 (m, 2H). ^{13}C NMR: δ 22.74 (CH_2), 25.19 (CH_2), 29.81 (CH_2), 37.20 (CH_2), 42.93 (CH_2), 45.68 (CH_2), 49.18 (CH_3), 59.27 (CH_2), 64.40 (CH_2), 66.41 (C). Anal. Calcd for $C_{10}H_{20}N_2$ (168.279): C, 71.37; H, 11.98. Found: C, 71.26; H, 11.91.

4.9. (5*S*)-1,7-Dimethyl-1,7-diaza-spiro[4.6]undecane 1c

Diamine **1b** (0.29 g, 1.7 mmol) was added to a mixture of formaldehyde (35%, 1.4 mL) and formic acid (0.62 mL). The mixture was held at 70 °C for 24 h. The pH was then adjusted to 12 by the addition of NaOH (4 M) and the solution extracted with dichloromethane (5 × 5 mL). The organic phase was then dried over $MgSO_4$ and evaporated to give **1c** as an oil (0.24 g, 76%). $[\alpha]_D^{25} = -2.9$ (*c* 0.58, $CHCl_3$), GC/MS 183 $(M+H)^+$. ^1H NMR ($CDCl_3$, 400 MHz): δ 1.43 (m, 2H), 1.62 (m, 2H), 1.62–1.85 (m, 6H), 2.23 (m, 2H), 2.34 (s, 3H), 2.39 (s, 3H), 2.58 (m, 2H), 2.68 (m, 2H). ^{13}C NMR: δ 21.27 (CH_2), 22.85 (CH_2), 31.08 (CH_2), 33.74 (CH_2), 34.68 (CH_3), 37.72 (CH_2), 48.89 (CH_3), 54.89 (CH_2), 61.26 (CH_2), 65.06 (C), 65.84 (CH_2).

4.10. Mosher amides (*S*,*S*)-14 and (*R*,*S*)-14

To a solution of **1b** (0.0144 g, 0.086 mmol) and diisopropylethyl amine (DIPEA) (22.3 μL, 0.13 mmol) in anhydrous dichloromethane (855 μL) was added (*S*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (20.0 μL, 0.11 mmol). The solution was stirred overnight for approx. 16 h. The solution was diluted with ethyl

acetate (3 mL), washed with water (2 mL) and then dried over $MgSO_4$. The solvent was then removed by evaporation to give (*S*,*S*)-**14** as a solid. GC/MS 385 $(M+H)^+$. The same procedure using (*R*)-(−)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride was used to obtain (*R*,*S*)-**14**. GC analysis was performed on a CP-Chirasil-DEX CB (25 m, 0.32 μm, He_2) at 170 °C. Compound (*S*,*S*)-**14**: 31.98 min. ^{19}F NMR ($CDCl_3$, 376.3 MHz, 65 °C, using 1,3,5-tris(trifluoromethyl)benzene at 100.0 ppm as internal reference): δ 93.10. Compound (*R*,*S*)-**14**: 34.01 min. ^{19}F NMR ($CDCl_3$, 376.3 MHz, 65 °C, using 1,3,5-tris(trifluoromethyl)benzene at 100.0 ppm as internal reference): δ 93.20.

4.11. Mosher amides (*S*,*S*)-15 and (*R*,*S*)-15

To a solution of **9a** (0.0142 g, 0.0855 mmol) and diisopropylethyl amine (DIPEA) (22.3 μL, 0.13 mmol) in anhydrous dichloromethane (855 μL) was added (*S*)-(−)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (20.0 μL, 0.11 mmol). The solution was stirred overnight for approx. 16 h. The solution was diluted with ethyl acetate (3 mL) and washed with citric acid (10%, 2 mL) and $NaHCO_3$ (5%, 2 mL) and then dried over $MgSO_4$. The solvent was then removed by evaporation to give (*S*,*S*)-**15** as a solid. GC/MS 383 $(M+H)^+$. The same procedure using (*R*)-(−)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride was used to obtain (*R*,*S*)-**15**. GC analysis was performed on a CP-Chirasil-DEX CB (25 m, 0.32 μm, He_2) at 195 °C. Compound (*S*,*S*)-**15**: 56.78 min. ^{19}F NMR ($CDCl_3$, 376.3 MHz, 65 °C, using 1,3,5-tris(trifluoromethyl)benzene at 100.0 ppm as internal reference): δ 92.74. Compound (*R*,*S*)-**15** 53.79 min, ^{19}F NMR ($CDCl_3$, 376.3 MHz, 65 °C, using 1,3,5-tris(trifluoromethyl)benzene at 100.0 ppm as internal reference): δ 92.91.

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13. The crystal structure determination was performed by Dr. Anna Johansson at our department. Crystallographic data: at 293(2) K, crystals of **9b**–HCl are orthorhombic, space group $P212121$, $a = 8.9139(2)$, $b = 16.8762(6)$ and $c = 7.4771(3)$ Å, $V = 1124.8(7)$ Å3, $Z = 4$, $M = 216.71$, $d_{calcd} = 1.280$ g cm^{-3}, μ(Cu K_a) = 2.774 mm^{-1}. Diffracted intensities were measured using graphite-monochromated Cu K_a radiation from a Rigaku RU200 rotating anode operated at 50 kV and 180 mA and 971 independent reflections were used during refinement. A multi-scan absorption correction was applied using the REQAB program under CrystalClear. The structure was solved using SHELXS-9722 and refined using SHELXL-9722 (full-matrix least-squares calculations on *F*2) operating in the WINGX program package. Anisotropic thermal displacement parameters were refined for all the nonhydrogen atoms. The refinement converged to $R1 = 0.0653$ for 971 reflections with $I > 2s(I)$ and $wR2 = 0.1606$ for all reflections. The assignment as (*S*)-**9b**–HCl was confirmed by the Flack parameter 19 (−0.016(7)). Crystallographic data (excluding structure factors) for (*S*)-**9b**–HCl have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 260423.
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