Catalytic Asymmetric Synthesis of Piperidines from Pyrrolidine: Concise Synthesis of (+)-L-733,060

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Supporting Information Available: Full experimental procedures, characterisation data and copies of $^{1}H/^{13}C$ NMR spectra of novel compounds.

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General

All non-aqueous reactions were carried out under oxygen-free N_2 or Ar using oven-dried glassware. Where necessary, solvents were dried on an Mbraun SPS solvent purification system. Et_2O and THF were distilled from sodium and benzophenone. *s*-BuLi was titrated against *N*-benzylbenzamide before use.[1] All diamines used in lithiation reactions were distilled over CaH_2 before use. Petrol refers to the fraction of petroleum ether boiling in the range 40-60 °C and was purchased in Winchester quantities. Brine refers to a saturated aqueous solution. Water is distilled water.

Flash chromatography was carried out using Fluka Chemie GmbH silica (220-440 mesh). Thin layer chromatography was carried out using commercially available Merck F_{254} aluminium-backed silica plates. Proton (400 MHz) and carbon (100.6 MHz) NMR spectra were recorded on a Jeol ECX-400 instrument using an internal deuterium lock. Chemical shifts are quoted in parts per million relative to $CHCl_3$ (δ_H 7.27) and $CDCl_3$ (δ_C 77.0, central line of triplet). Carbon NMR spectra were recorded with broad band proton decoupling and were assigned using DEPT experiments. Coupling constants (*J*) are quoted in Hertz. Melting points were carried out on a Gallenkamp melting point apparatus. Infrared spectra were recorded on an ATI Mattson Genesis FT-IR spectrometer. Chemical ionization high and low resolution mass spectra were recorded on a Fisons Analytical (VG) Autospec spectrometer. Electrospray high and low resolution mass spectra were recorded on a Bruker Daltronics microTOF spectrometer. Optical rotations were recorded at rt on a Jasco DIP-370 polarimeter (using the sodium D line; 259 nm) and $[\alpha]_D$ given in units of 10^{-1}deg cm^3 g^{-1}. Chiral stationary phase HPLC was performed on an Agilent 1200 series chromatograph. GC was performed on an Agilent 6890 gas chromatograph fitted with an Agilent H-5 capillary column (30 m x 0.25 mm x 0.25 μm) using He as the carrier gas.

The following compounds were prepared according to the procedures reported in the literature:

N-Boc pyrrolidine **1**,[2] *N,N´*-dimethyl-2-methoxyethylamine,[3] (–)-sparteine surrogate **6**[4] and (+)-sparteine surrogate **7**.[5]

Experimental procedures and characterisation data

General procedure A: catalytic asymmetric deprotonation-silylation of *N*-Boc pyrrolidine 1

A solution of (–)-sparteine, the (–)-sparteine surrogate **6** or the (+)-sparteine surrogate **7** (0.05-0.3 equiv.) in Et_2O (1 mL) was added dropwise to a stirred solution of *s*-BuLi (1.0-1.3 M solution in cyclohexane, 2.3-2.9 equiv.) in Et_2O (7 mL) at –78 °C under Ar. Then, a solution of dimethylaminoethanol (DMAE) (1.0-1.3 equiv.) in Et_2O (1 mL) was added dropwise. After stirring for 10 min, a solution of *N*-Boc pyrrolidine **1** (347 mg, 2.0 mmol, 1.0 equiv.) in Et_2O (1 mL) was added dropwise *via* a cannula over 10 min. The resulting solution was stirred at –78 °C for 4 h. Then, Me_3SiCl (0.73 mL, 5.8 mmol, 2.9 equiv.) was added dropwise and the reaction mixture was allowed to warm to rt over 4 h and stirred at rt for 12 h. 5% $H_3PO_{4(aq)}$ (10 mL) was added and the reaction mixture was extracted with Et_2O (3 × 10 mL). The combined Et_2O extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 19:1 petrol-Et_2O as eluent gave silylated pyrrolidine (*S*)- or (*R*)-**5** as a colourless oil; chiral GC: 30 m x 0.25 mm i.d.(β-cyclodextrin) T 91 °C isothermal, He carrier gas at 12 psi constant pressure, (*S*)-**5** 102 min, (*R*)-**5** 104 min.

General procedure B: Boc deprotection of *N*-Boc pyrrolidines

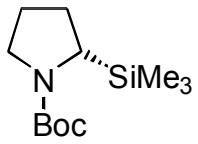
TFA (2.5 mL, 18.0 mmol, 4 equiv.) was added to a stirred solution of *N*-Boc pyrrolidine (4.5 mmol) in CH_2Cl_2 (25 mL) at 0 °C under N_2. The resulting pale yellow solution was allowed to warm to rt and then stirred at rt for 20 h. 33% $NH_4OH_{(aq)}$ (10 mL) was added and the two layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL) and the combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product.

General procedure C: *N*-alkylation of pyrrolidines

Benzyl bromide or allyl bromide (1.2 equiv.) was added to a stirred suspension of pyrrolidinol (0.43 mmol) and K_2CO_3 (1.5 equiv.) in CH_2Cl_2 (3 mL) at 0 °C under N_2. The resulting suspension was allowed to warm to rt and then stirred at rt for 6 h. Water (5 mL) and CH_2Cl_2 (5 mL) were added and the two layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL) and the combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product.

General procedure D: ring expansion of pyrrolidines to piperidines

Trifluoroacetic anhydride (1.5 equiv.) was added to a stirred solution of *N*-alkyl pyrrolidine (0.61 mmol) in THF (4 mL) at –78 °C under Ar. The resulting colourless solution was stirred at –78 °C for 1 h and then Et_3N (3.0 equiv.) was added. After stirring at –78 °C for 1 h, the solution was stirred and heated at reflux for 48-72 h. The resulting brown solution was cooled to 0 °C and 2.0 M $NaOH_{(aq)}$ (2 mL) was added. After warming to rt and stirring for 2 h, CH_2Cl_2 (5 mL) was added and the two layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL) and the combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product.

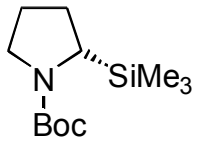


(*S*)-**5**

(*S*)-2-Trimethylsilyl-*N*-*tert*-butoxycarbonylpyrrolidine (*S*)-5

(Scheme 2 and Table 1, entry 3)

Using general procedure A, (–)-sparteine (141 mg, 0.6 mmol, 0.3 equiv.), *s*-BuLi (4.8 mL of a 1.2 M solution in cyclohexane, 5.8 mmol, 2.9 equiv.), dimethylaminoethanol (DMAE) (232 mg, 2.6 mmol, 1.3 equiv.), *N*-Boc pyrrolidine **1** (347 mg, 2.0 mmol, 1.0 equiv.) and Me_3SiCl (0.73 mL, 5.8 mmol, 2.9 equiv.) in Et_2O (10 mL) gave the crude product. Purification by flash column chromatography on silica with 19:1 petrol-Et_2O as eluent gave silylated pyrrolidine (*S*)-**5** (320 mg, 66%, 88:12 er by chiral GC) as a colourless oil, $[\alpha]_D$ +54.8 (*c* 0.9 in $CHCl_3$)(lit.,[6] $[\alpha]_D$ +71.8 (*c* 2.6 in $CHCl_3$) for (*S*)-**2** of 98:2 er); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.36-3.39 (br m, 1H, NCH), 3.38-3.06 (br m, 2H, NCH_2), 2.12-1.92 (br m, 1H, CH_AH_B), 1.89-1.65 (br m, 3H, CH_AH_B and CH_2), 1.47 (s, 9H, CMe_3), 0.06 (s, 9H, $SiMe_3$). The spectroscopic data were consistent with those reported in the literature.[6]

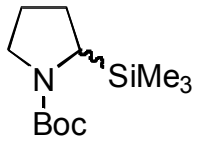


(*S*)-**5**

(*S*)-2-Trimethylsilyl-*N*-*tert*-butoxycarbonylpyrrolidine (*S*)-5

(Scheme 2)

A solution of (–)-sparteine (141 mg, 0.6 mmol, 0.3 equiv.) in Et_2O (1 mL) was added dropwise to a stirred solution of *s*-BuLi (4.6 mL of a 1.3 M solution in cyclohexane, 5.8 mmol, 2.9 equiv.) in Et_2O (7 mL) at –78 °C under Ar. Then, a solution of EtOH (120 mg, 2.6 mmol, 1.3 equiv.) in Et_2O (1 mL) was added dropwise. After stirring for 10 min, a solution of *N*-Boc pyrrolidine **1** (347 mg, 2.0 mmol, 1.0 equiv.) in Et_2O (1 mL) was added dropwise *via* a cannula over 10 min. The resulting solution was stirred at –78 °C for 4 h. Then, Me_3SiCl (0.73 mL, 5.8 mmol, 2.9 equiv.) was added dropwise and the reaction mixture was allowed to warm to rt over 4 h and stirred at rt for 12 h. 5% $H_3PO_{4(aq)}$ (10 mL) was added and the reaction mixture was extracted with Et_2O (3 □ 10 mL). The combined Et_2O extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 19:1 petrol-Et_2O as eluent gave silylated pyrrolidine (*S*)-**5** (160 mg, 33%, 90:10 er by chiral GC) as a colourless oil, $[\square]_D$ +63.4 (*c* 1.1 in $CHCl_3$)(lit.,[6] $[\square]_D$ +71.8 (*c* 2.6 in $CHCl_3$) for (*S*)-**2** of 98:2 er). The spectroscopic data were consistent with those reported in the literature.[6]



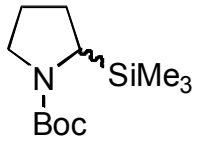
rac-**5**

***rac*-2-Trimethylsilyl-*N*-*tert*-butoxycarbonylpyrrolidine *rac*-5**

(Scheme 2)

A solution of (–)-sparteine (141 mg, 0.6 mmol, 0.3 equiv.) in Et_2O (1 mL) was added dropwise to a stirred solution of *s*-BuLi (2.7 mL of a 1.2 M solution in cyclohexane, 3.2 mmol, 1.6 equiv.) in Et_2O (7 mL) at –78 °C under Ar. Then, a solution of *N,N´*-dimethyl-2-methoxyethylamine ($MeO(CH_2)_2NMe_2$) (268 mg, 2.6 mmol, 1.3 equiv.) in Et_2O (1 mL) was added dropwise. After stirring for 10 min, a solution of *N*-Boc pyrrolidine **1** (347 mg, 2.0 mmol, 1.0 equiv.) in Et_2O (1 mL) was added dropwise *via* a cannula

over 10 min. The resulting solution was stirred at –78 °C for 4 h. Then, Me_3SiCl (0.4 mL, 3.2 mmol, 1.6 equiv.) was added dropwise and the reaction mixture was allowed to warm to rt over 4 h and stirred at rt for 12 h. 5% $H_3PO_{4(aq)}$ (10 mL) was added and the reaction mixture was extracted with Et_2O (3 × 10 mL). The combined Et_2O extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 19:1 petrol-Et_2O as eluent gave silylated pyrrolidine *rac*-**5** (360 mg, 74%, 50:50 er by chiral GC) as a colourless oil, $[\alpha]_D$ 0 (*c* 1.0 in $CHCl_3$)(lit.,[6] $[\alpha]_D$ +71.8 (*c* 2.6 in $CHCl_3$) for (*S*)-**2** of 98:2 er). The spectroscopic data were consistent with those reported in the literature.[6]

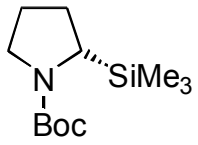


rac-**5**

***rac*-2-Trimethylsilyl-*N*-*tert*-butoxycarbonylpyrrolidine *rac*-5**

(Table 1, entry 1)

s-BuLi (4.3 mL of a 1.2 M solution in cyclohexane, 5.2 mmol, 2.6 equiv.) was added dropwise to a stirred solution of dimethylaminoethanol (DMAE) (232 mg, 2.6 mmol, 1.3 equiv.) in Et_2O (9 mL) at –78 °C under Ar. After stirring for 10 min, a solution of *N*-Boc pyrrolidine **1** (347 mg, 2.0 mmol, 1.0 equiv.) in Et_2O (1 mL) was added dropwise *via* a cannula over 10 min. The resulting solution was stirred at –78 °C for 4 h. Then, Me_3SiCl (0.66 mL, 5.2 mmol, 2.6 equiv.) was added dropwise and the reaction mixture was allowed to warm to rt over 4 h and stirred at rt for 12 h. 5% $H_3PO_{4(aq)}$ (10 mL) was added and the reaction mixture was extracted with Et_2O (3 × 10 mL). The combined Et_2O extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 19:1 petrol-Et_2O as eluent gave silylated pyrrolidine *rac*-**5** (20 mg, 4%) as a colourless oil. The spectroscopic data were consistent with those reported in the literature.[6]

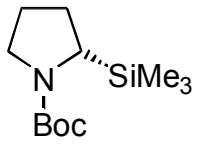


(*S*)-**5**

(*S*)-2-Trimethylsilyl-*N*-*tert*-butoxycarbonylpyrrolidine (*S*)-5

(Table 2, entry 2)

A solution of (–)-sparteine (609 mg, 1.3 mmol, 1.3 equiv.) in Et_2O (1 mL) was added dropwise to a stirred solution of *s*-BuLi (6.5 mL of a 1.2 M solution in cyclohexane, 7.8 mmol, 3.9 equiv.) in Et_2O (7 mL) at –78 °C under Ar. Then, a solution of dimethylaminoethanol (DMAE) (232 mg, 2.6 mmol, 1.3 equiv.) in Et_2O (1 mL) was added dropwise. After stirring for 10 min, a solution of *N*-Boc pyrrolidine **1** (347 mg, 2.0 mmol, 1.0 equiv.) in Et_2O (1 mL) was added dropwise *via* a cannula over 10 min. The resulting solution was stirred at –78 °C for 4 h. Then, Me_3SiCl (0.98 mL, 7.8 mmol, 3.9 equiv.) was added dropwise and the reaction mixture was allowed to warm to rt over 4 h and stirred at rt for 12 h. 5% $H_3PO_{4(aq)}$ (10 mL) was added and the reaction mixture was extracted with Et_2O (3 × 10 mL). The combined Et_2O extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 19:1 petrol-Et_2O as eluent gave silylated pyrrolidine (*S*)-**5** (300 mg, 62%, 98:2 er by chiral GC) as a colourless oil, $[\alpha]_D$ +77.5 (*c* 1.1 in $CHCl_3$)(lit.,[6] $[\alpha]_D$ +71.8 (*c* 2.6 in $CHCl_3$) for (*S*)-**2** of 98:2 er). The spectroscopic data were consistent with those reported in the literature.[6]



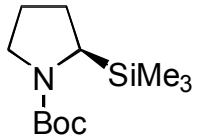
(*S*)-**5**

(*S*)-2-Trimethylsilyl-*N*-*tert*-butoxycarbonylpyrrolidine (*S*)-5

(Table 1, entry 4)

Using general procedure A, (–)-sparteine surrogate **6** (182 mg, 0.6 mmol, 0.3 equiv.), *s*-BuLi (4.6 mL of a 1.3 M solution in cyclohexane, 5.8 mmol, 2.9 equiv.), dimethylaminoethanol (DMAE) (232 mg, 2.6 mmol, 1.3 equiv.), *N*-Boc pyrrolidine **1** (347 mg, 2.0 mmol, 1.0 equiv.) and Me_3SiCl (0.73 mL, 5.8 mmol, 2.9 equiv.) in Et_2O (10 mL) gave the crude product. Purification by flash column chromatography on

silica with 19:1 petrol-Et_2O as eluent gave silylated pyrrolidine (*S*)-**5** (290 mg, 60%, 93:7 er by chiral GC) as a colourless oil, $[\alpha]_D$ +65.4 (*c* 1.0 in $CHCl_3$)(lit.,[6] $[\alpha]_D$ +71.8 (*c* 2.6 in $CHCl_3$) for (*S*)-**2** of 98:2 er). The spectroscopic data were consistent with those reported in the literature.[6]

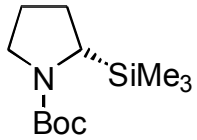


(*R*)-**5**

(*R*)-2-Trimethylsilyl-*N*-*tert*-butoxycarbonylpyrrolidine (*R*)-5

(Table 1, entry 5)

Using general procedure A, (+)-sparteine surrogate **7** (117 mg, 0.6 mmol, 0.3 equiv.), *s*-BuLi (4.5 mL of a 1.3 M solution in cyclohexane, 5.8 mmol, 2.9 equiv.), dimethylaminoethanol (DMAE) (232 mg, 2.6 mmol, 1.3 equiv.), *N*-Boc pyrrolidine **1** (347 mg, 2.0 mmol, 1.0 equiv.) and Me_3SiCl (0.73 mL, 5.8 mmol, 2.9 equiv.) in Et_2O (10 mL) gave the crude product. Purification by flash column chromatography on silica with 19:1 petrol-Et_2O as eluent gave silylated pyrrolidine (*R*)-**5** (340 mg, 70%, 89:11 er by chiral GC) as a colourless oil, $[\alpha]_D$ –55.2 (*c* 1.05 in $CHCl_3$)(lit.,[6] $[\alpha]_D$ +71.8 (*c* 2.6 in $CHCl_3$) for (*S*)-**2** of 98:2 er). The spectroscopic data were consistent with those reported in the literature.[6]



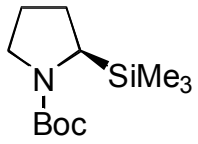
(*S*)-**5**

(*S*)-2-Trimethylsilyl-*N*-*tert*-butoxycarbonylpyrrolidine (*S*)-5

(Table 1, entry 6)

Using general procedure A, (–)-sparteine (94 mg, 0.4 mmol, 0.2 equiv.), *s*-BuLi (4.7 mL of a 1.1 M solution in cyclohexane, 5.2 mmol, 2.6 equiv.), dimethylaminoethanol (DMAE) (214 mg, 2.4 mmol, 1.2 equiv.), *N*-Boc pyrrolidine **1** (347 mg, 2.0 mmol, 1.0 equiv.) and Me_3SiCl (0.65 mL, 5.2 mmol, 2.9 equiv.) in Et_2O (10 mL) gave the crude product. Purification by flash column chromatography on silica with 19:1 petrol-Et_2O as eluent gave silylated pyrrolidine (*S*)-**5** (260 mg, 53%, 88:12 er by chiral GC) as a colourless

oil, $[\alpha]_D$ +61.1 (*c* 1.0 in $CHCl_3$)(lit.,[6] $[\alpha]_D$ +71.8 (*c* 2.6 in $CHCl_3$) for (*S*)-**2** of 98:2 er). The spectroscopic data were consistent with those reported in the literature.[6]

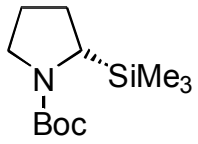


(*R*)-**5**

(*R*)-2-Trimethylsilyl-*N*-*tert*-butoxycarbonylpyrrolidine (*R*)-5

(Table 1, entry 7)

Using general procedure A, (+)-sparteine surrogate **7** (78 mg, 0.4 mmol, 0.2 equiv.), *s*-BuLi (4.3 mL of a 1.2 M solution in cyclohexane, 5.2 mmol, 2.6 equiv.), dimethylaminoethanol (DMAE) (214 mg, 2.4 mmol, 1.2 equiv.), *N*-Boc pyrrolidine **1** (347 mg, 2.0 mmol, 1.0 equiv.) and Me_3SiCl (0.65 mL, 5.2 mmol, 2.6 equiv.) in Et_2O (10 mL) gave the crude product. Purification by flash column chromatography on silica with 19:1 petrol-Et_2O as eluent gave silylated pyrrolidine (*R*)-**5** (360 mg, 74%, 87:13 er by chiral GC) as a colourless oil, $[\alpha]_D$ –54.3 (*c* 1.1 in $CHCl_3$)(lit.,[6] $[\alpha]_D$ +71.8 (*c* 2.6 in $CHCl_3$) for (*S*)-**2** of 98:2 er). The spectroscopic data were consistent with those reported in the literature.[6]

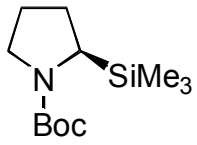


(*S*)-**5**

(*S*)-2-Trimethylsilyl-*N*-*tert*-butoxycarbonylpyrrolidine (*S*)-5

(Table 1, entry 8)

Using general procedure A, (–)-sparteine (47 mg, 0.2 mmol, 0.1 equiv.), *s*-BuLi (4.5 mL of a 1.1 M solution in cyclohexane, 5.0 mmol, 2.5 equiv.), dimethylaminoethanol (DMAE) (214 mg, 2.4 mmol, 1.2 equiv.), *N*-Boc pyrrolidine **1** (347 mg, 2.0 mmol, 1.0 equiv.) and Me_3SiCl (0.63 mL, 5.0 mmol, 2.5 equiv.) in Et_2O (10 mL) gave the crude product. Purification by flash column chromatography on silica with 19:1 petrol-Et_2O as eluent gave silylated pyrrolidine (*S*)-**5** (280 mg, 58%, 88:12 er by chiral GC) as a colourless oil, $[\alpha]_D$ +53.9 (*c* 1.0 in $CHCl_3$)(lit.,[6] $[\alpha]_D$ +71.8 (*c* 2.6 in $CHCl_3$) for (*S*)-**2** of 98:2 er). The spectroscopic data were consistent with those reported in the literature.[6]

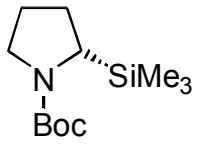


(*R*)-**5**

(*R*)-2-Trimethylsilyl-*N*-*tert*-butoxycarbonylpyrrolidine (*R*)-5

(Table 1, entry 9)

Using general procedure A, (+)-sparteine surrogate **7** (39 mg, 0.2 mmol, 0.1 equiv.), *s*-BuLi (3.9 mL of a 1.3 M solution in cyclohexane, 5.0 mmol, 2.5 equiv.), dimethylaminoethanol (DMAE) (214 mg, 2.4 mmol, 1.2 equiv.), *N*-Boc pyrrolidine **1** (347 mg, 2.0 mmol, 1.0 equiv.) and Me_3SiCl (0.63 mL, 5.0 mmol, 2.5 equiv.) in Et_2O (10 mL) gave the crude product. Purification by flash column chromatography on silica with 19:1 petrol-Et_2O as eluent gave silylated pyrrolidine (*R*)-**5** (210 mg, 43%, 92:8 er by chiral GC) as a colourless oil, $[\alpha]_D$ –64.3 (*c* 0.9 in $CHCl_3$)(lit.,[6] $[\alpha]_D$ +71.8 (*c* 2.6 in $CHCl_3$) for (*S*)-**2** of 98:2 er). The spectroscopic data were consistent with those reported in the literature.[6]

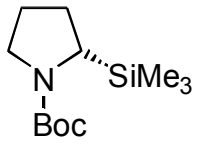


(*S*)-**5**

(*S*)-2-Trimethylsilyl-*N*-*tert*-butoxycarbonylpyrrolidine (*S*)-5

(Table 1, entry 10)

Using general procedure A, (–)-sparteine (47 mg, 0.2 mmol, 0.05 equiv.), *s*-BuLi (7.8 mL of a 1.3 M solution in cyclohexane, 9.8 mmol, 2.5 equiv.), dimethylaminoethanol (DMAE) (428 mg, 4.8 mmol, 1.2 equiv.), *N*-Boc pyrrolidine **1** (694 mg, 4.0 mmol, 1.0 equiv.) and Me_3SiCl (1.24 mL, 9.8 mmol, 2.5 equiv.) in Et_2O (10 mL) gave the crude product. Purification by flash column chromatography on silica with 19:1 petrol-Et_2O as eluent gave silylated pyrrolidine (*S*)-**5** (350 mg, 36%, 77:23 er by chiral GC) as a colourless oil, $[\alpha]_D$ +44.0 (*c* 1.05 in $CHCl_3$)(lit.,[6] $[\alpha]_D$ +71.8 (*c* 2.6 in $CHCl_3$) for (*S*)-**2** of 98:2 er). The spectroscopic data were consistent with those reported in the literature.[6]

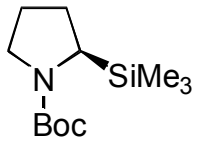


(*S*)-**5**

(*S*)-2-Trimethylsilyl-*N*-*tert*-butoxycarbonylpyrrolidine (*S*)-5

(Table 1, entry 11)

Using general procedure A, (–)-sparteine (141 mg, 0.6 mmol, 0.3 equiv.), *s*-BuLi (4.6 mL of a 1.0 M solution in cyclohexane, 4.6 mmol, 2.3 equiv.), dimethylaminoethanol (DMAE) (178 mg, 2.0 mmol, 1.0 equiv.), *N*-Boc pyrrolidine **1** (347 mg, 2.0 mmol, 1.0 equiv.) and Me_3SiCl (0.58 mL, 4.6 mmol, 2.3 equiv.) in Et_2O (10 mL) gave the crude product. Purification by flash column chromatography on silica with 19:1 petrol-Et_2O as eluent gave silylated pyrrolidine (*S*)-**5** (280 mg, 58%, 97:3 er by chiral GC) as a colourless oil, $[\alpha]_D$ +71.1 (*c* 1.0 in $CHCl_3$)(lit.,[6] $[\alpha]_D$ +71.8 (*c* 2.6 in $CHCl_3$) for (*S*)-**2** of 98:2 er). The spectroscopic data were consistent with those reported in the literature.[6]

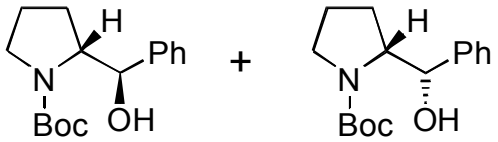


(*R*)-**5**

(*R*)-2-Trimethylsilyl-*N*-*tert*-butoxycarbonylpyrrolidine (*R*)-5

(Table 1, entry 12)

Using general procedure A, (+)-sparteine surrogate **7** (117 mg, 0.6 mmol, 0.3 equiv.), *s*-BuLi (4.6 mL of a 1.0 M solution in cyclohexane, 4.6 mmol, 2.3 equiv.), dimethylaminoethanol (DMAE) 178 mg, 2.0 mmol, 1.0 equiv.), *N*-Boc pyrrolidine **1** (347 mg, 2.0 mmol, 1.0 equiv.) and Me_3SiCl (0.58 mL, 4.6 mmol, 2.3 equiv.) in Et_2O (10 mL) gave the crude product. Purification by flash column chromatography on silica with 19:1 petrol-Et_2O as eluent gave silylated pyrrolidine (*R*)-**5** (360 mg, 74%, 92:8 er by chiral GC) as a colourless oil, $[\alpha]_D$ –62.1 (*c* 1.1 in $CHCl_3$)(lit.,[6] $[\alpha]_D$ +71.8 (*c* 2.6 in $CHCl_3$) for (*S*)-**2** of 98:2 er). The spectroscopic data were consistent with those reported in the literature.[6]



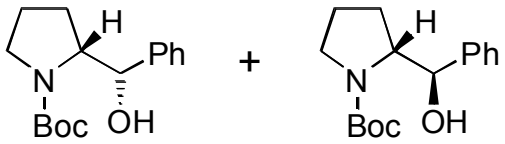
syn-**8** *anti*-**8**

(1*R*,2*R*)- and (1*S*,2*R*)-2-(Hydroxyphenylmethyl)pyrrolidine-1-carboxylic acid *tert*-butyl ester *syn*-8 and *anti*-8

(Scheme 3)

s-BuLi (4.69 mL of a 1.28 M solution in cyclohexane, 6.0 mmol, 1.3 equiv.) was added dropwise to a stirred solution of *N*-Boc pyrrolidine **1** (790 mg, 0.81 mL, 4.62 mmol) and (–)-sparteine (1.38 mL, 6.0 mmol, 1.3 equiv.) in Et_2O (15 mL) at –78 °C under Ar. After stirring at –78 °C for 3 h, benzaldehyde (0.94 mL, 9.24 mmol, 2.0 equiv.) was added dropwise and the reaction mixture was allowed to warm to rt over 4 h and stirred at rt for 16 h. Saturated $NH_4Cl_{(aq)}$(20 mL) was added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 20 mL) and the combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product which contained a 75:25 mixture of *syn*- and *anti*-**8** (by ^{1}H NMR spectroscopy). Purification by flash column chromatography on silica with 98:2 CH_2Cl_2-acetone as eluent gave pyrrolidine *syn*-**8** (950 mg, 74%, 95:5 er by chiral HPLC) as a pale yellow oil, $[\alpha]_D$ –1.9 (*c* 1.0 in $CHCl_3$); R_F(98:2 CH_2Cl_2-acetone) 0.3; IR ($CHCl_3$) 3334 (OH), 3016, 2981, 1649 (C=O), 1408, 1212, 1164 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31-7.23 (m, 5H, Ph), 5.86 (br s, 1H, OH), 4.50 (br d, J = 8.0 Hz, 1H, CHO), 4.05 (td, J = 8.0, 4.0 Hz, 1H, CHN), 3.46-3.38 (br m, 1H, CH_AH$_B$N), 3.32 (br s, 1H, CH$_A$$H_B$N), 1.66 (br s, 2H, CH_2), 1.54-1.43 (br m, 2H, CH_2), 1.48 (s, 9H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 158.1 (C=O), 142.5 (*ipso*-Ph), 128.1 (CH, Ph), 127.6 (CH, Ph), 127.1 (CH, Ph), 80.6 (*C*Me$_3$), 79.0 (CHO), 64.0 (CHN), 47.6 (CH_2N), 28.4 (CH_2), 28.3 (CMe_3), 23.6 (CH_2); MS (ESI) *m/z* 278 [(M + H),$^+$ 100]; HRMS (ESI) *m/z* calcd for $C_{16}H_{23}NO_3$ (M + H)$^+$ 278.1678, found 278.1751; chiral HPLC: Chiralpak OD (98:2 hexane:*iso*-PrOH, 0.5 mLmin^{-1}) (1*R*,2*R*)-**8** 22.6 min, (1*S*,2*S*)-**8** 26.6 min and pyrrolidine *anti*-**8** (303 mg, 24%, 97:3 er by chiral HPLC) as a white solid, mp 52-53 °C; $[\alpha]_D$ +95.3 (*c* 1.0 in $CHCl_3$); R_F(98:2 CH_2Cl_2-acetone) 0.2; IR ($CHCl_3$) 3317 (OH), 3015, 2980, 1666 (C=O), 1405, 1220, 1165 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) (75:25 mixture of rotamers) δ 7.32-7.25 (m, 5H, Ph), 5.49 (br s, 0.75H, OH), 5.17 (br s, 0.25H, OH), 4.88 (br s, 0.75H, CHO), 4.33 (br s, 0.75H, CHN), 4.02 (br s, 0.25H, CHO), 3.58 (br s, 0.25H, CHN), 3.31 (br s, 1H, CH_AH$_B$N), 2.82 (br s,

0.75H, CH_AH_BN), 2.28 (br s, 0.25H, CH_AH_BN), 1.93 (br s, 1H, CH), 1.78 (br s, 1H, CH), 1.59 (s, 2.25H, CMe_3), 1.55-1.50 (br m, 1H, CH), 1.53 (s, 6.75H, CMe_3), 1.20 (br s, 1H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) □157.1 (C=O), 141.2 (*ipso*-Ph), 128.2 (CH, Ph), 127.6 (CH, Ph), 126.9 (CH, Ph), 81.5 (CMe_3), 80.2 (CHO), 63.1 (CHN), 47.7 (CH_2), 28.4 (CMe_3), 27.2 (CH_2), 23.4 (CH_2); MS (ESI) *m/z* 278 [(M + H),$^+$ 100]; HRMS (ESI) *m/z* calcd for $C_{16}H_{23}NO_3$ $(M + H)^+$ 278.1678, found 278.1751; chiral HPLC: Chiralpak OD (99:1 hexane-*iso*-PrOH, 0.5 mLmin^{-1}) (1*S*,2*R*)-**8** 33.2 min, (1*R*,2*S*)-**8** 35.4 min.



anti-**8** *syn*-**8**

2-(Hydroxyphenylmethyl)pyrrolidine-1-carboxylic acid *tert*-butyl ester (1*S*,2*R*)-8 and (1*R*,2*R*)-8 (*via* transmetallation to magnesium)

(Scheme 3)

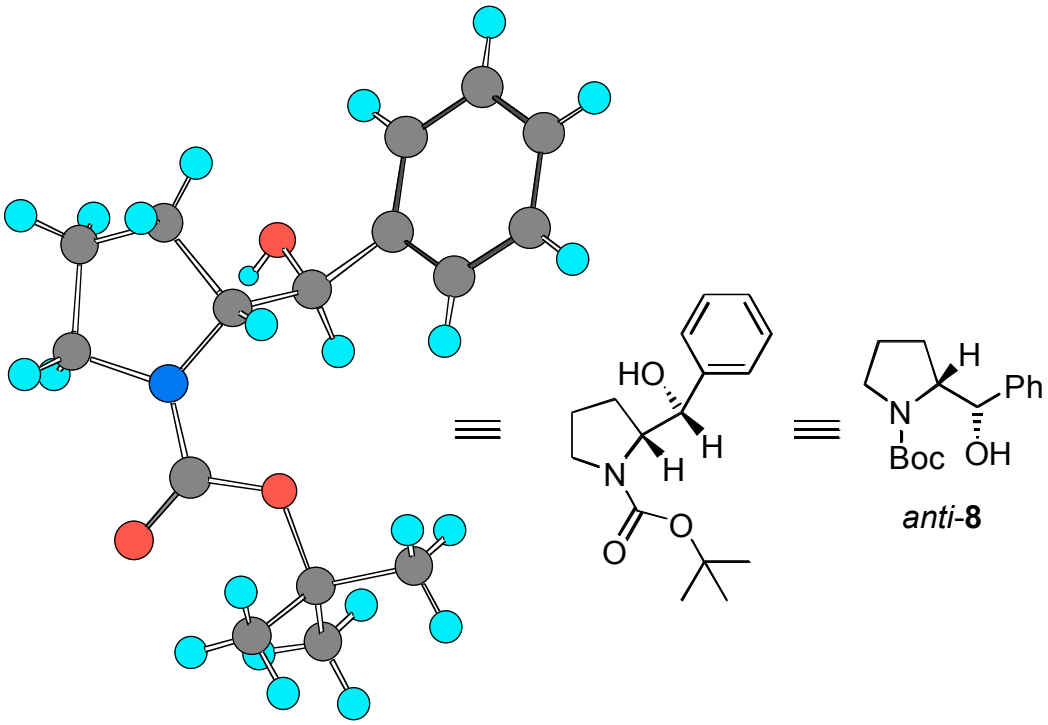
Preparation of anhydrous $MgBr_2$: 1,2-Dibromoethane (0.20 mL, 2.28 mmol) was added dropwise to a stirred suspension of flame-dried Mg turnings (85 mg, 3.50 mmol, 1.5 equiv.) in Et_2O (2 mL) at 0 °C under Ar. The resulting mixture was stirred at 0 °C for 30 min. After warming to rt,the mixture was stirred at rt for 2 h to give a brown solution of $MgBr_2$ in Et_2O.

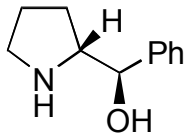
s-BuLi (1.74 mL of a 1.31 M solution in cyclohexane, 2.28 mmol 1.3 equiv.) was added dropwise to a stirred solution of *N*-Boc pyrrolidine **1** (303 mg, 0.31 mL, 1.75 mmol) and (–)-sparteine (0.52 mL, 2.28 mmol, 1.3 equiv.) in Et_2O (5 mL) at –78 °C under Ar. After stirring at –78 °C for 3 h, a freshly prepared solution of $MgBr_2$ in Et_2O (2 mL) [prepared from 1,2-dibromoethane (0.20 mL, 2.28 mmol) and Mg turnings (85 mg, 3.50 mmol) according to the above procedure] was added *via* syringe. The resulting pale brown mixture was allowed to warm to 0 °C and stirred for 30 min before cooling to –78 °C. Then, benzaldehyde (0.36 mL, 3.50 mmol, 2.0 equiv.) was added dropwise and the reaction mixture was allowed to warm to rt over 4 h and stirred at rt for 16 h. Saturated $NH_4Cl_{(aq)}$(20 mL) was added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 □ 20 mL) and the combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product which contained a 70:30 mixture of *anti*- and *syn*-**8** (by ^{1}H NMR spectroscopy). Purification by flash column

chromatography on silica with 98:2 CH_2Cl_2-acetone as eluent gave pyrrolidine *syn*-**8** (84 mg, 17%, 97:3 er by chiral HPLC) as a pale yellow oil, $[\alpha]_D$ −1.6 (*c* 1.0 in $CHCl_3$); chiral HPLC: Chiralpak OD (98:2 hexane:*iso*-PrOH, 0.5 mLmin^{-1}) (1*R*,2*R*)-**8** 22.9 min, (1*S*,2*S*)-**8** 27.0 min, pyrrolidine *anti*-**8** (272 mg, 56%, 96:4 er by chiral HPLC) as a white solid, $[\alpha]_D$ +112.7 (*c* 1.5 in $CHCl_3$); chiral HPLC: Chiralpak OD (99:1 hexane-*iso*-PrOH, 0.5 mLmin^{-1}) (1*S*,2*R*)-**8** 33.05 min, (1*R*,2*S*)-**8** 36.1 min and recovered *N*-Boc pyrrolidine **1** (65 mg, 22%) as a colourless oil.

Crystal structure determination of carboxylic acid *tert*-butyl ester (1*S*,2*R*)-**8**

Crystal data. $C_{16}H_{23}NO_3$, M = 277.35, monoclinic, a = 18.3098(10), b = 6.6867(4), c = 13.8607(8) Å, β = 112.2900°, U = 1570.19(16) Å^3, T = 110(2) K, space group C2, Z = 4, μ(Mo-Kα) = 0.080 mm^{-1}, 10767 reflections measured, 3880 unique (R_{int} = 0.0192) which were used in all calculations. The final R1 was 0.0325 (I>2σ(I)) and wR2 was 0.0844 (all data). The CCDC reference number is 696161.



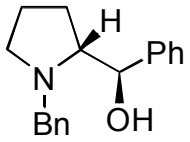


syn

(1*R*,2*R*)-*syn*-1-Phenyl-2-pyrrolidinemethanol

(Scheme 4)

Using general procedure B, TFA (0.5 mL, 3.60 mmol) and pyrrolidine *syn*-**8** (277 mg, 0.82 mmol) in CH_2Cl_2 (5 mL) gave crude (1*R*,2*R*)-*syn*-1-phenyl-2-pyrrolidinemethanol (112 mg, 77%) as a brown oil, $[\alpha]_D$ –43.2 (*c* 1.0 in $CHCl_3$); R_F(95:4.5:0.5 CH_2Cl_2-MeOH-NH_4OH) 0.1; IR ($CHCl_3$) 3500 (NH), 3359 (OH), 2970, 1402, 1236, 1081 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.39-7.26 (m, 5H, Ph), 4.33 (d, *J* = 7.0 Hz, 1H, CHO), 3.93 (br s, 2H, NH and OH), 3.32 (q, *J* = 7.0 Hz, 1H, CHN), 2.95 (br t, *J* = 6.5 Hz, 2H, CH_2N), 1.87-1.77 (m, 1H, CH), 1.74-1.48 (m, 3H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 143.0 (*ipso*-Ph), 128.2 (CH, Ph), 127.3 (CH, Ph), 126.5 (CH, Ph), 75.7 (CHO), 64.8 (CHN), 46.1 (CH_2N), 28.2 (CH_2), 25.7 (CH_2); MS (ESI) *m/z* 178 [$(M + H)^+$ 40], 160 (100); HRMS (ESI) *m/z* calcd for $C_{11}H_{16}NO$ $(M + H)^+$ 178.1232, found 178.1226.



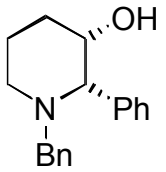
syn-**9**

(1*R*,2*R*)-(1-Benzylpyrrolidin-2-yl)phenylmethanol *syn*-9

(Scheme 4)

Using general procedure C, (1*R*,2*R*)-*syn*-1-phenyl-2-pyrrolidinemethanol (76 mg, 0.43 mmol), benzyl bromide (0.06 mL, 0.52 mmol) and K_2CO_3 (89 mg, 0.64 mmol) in CH_2Cl_2 (3 mL) gave the crude product. Immediate purification by flash column chromatography on silica with 95:5 CH_2Cl_2-MeOH as eluent gave pyrrolidine *syn*-**9** (99 mg, 86%) as a pale yellow amorphous solid, $[\alpha]_D$ –65.1 (*c* 1.0 in $CHCl_3$) [lit.,[7] $[\alpha]_D$ +98.0 (*c* 1.03 in $CHCl_3$) for (1*S*,2*S*)-**9**]; R_F(95:5 CH_2Cl_2-MeOH) 0.2; ^1H NMR (400 MHz, $CDCl_3$) δ 7.41-7.22 (m, 10H, Ph), 4.76 (br s, 1H, OH), 4.44 (d, *J* = 5.0 Hz, 1H, CHO), 3.74 (d, *J* = 13.0 Hz, 1H, $PhCH_AH_BN$), 3.40 (d, *J* = 13.0 Hz, 1H, $PhCH_AH_BN$), 3.12 (ddd, *J* = 8.5, 5.0, 3.5 Hz, 1H, CHN), 3.02-2.97 (m, 1H, CH_AH_BN), 2.44 (dt, *J* = 10.0, 7.5 Hz, 1H, CH_AH_BN), 1.99-1.90 (m, 1H, CH), 1.82-1.74 (m, 3H,

CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 143.5 (*ipso*-Ph), 138.9 (*ipso*-Ph), 128.8 (CH, Ph), 128.3 (CH, Ph), 128.2 (CH, Ph), 127.2 (CH, Ph), 127.1 (CH, Ph), 126.2 (CH, Ph), 75.1 (CHO), 70.3 (CHN), 61.1 ($PhCH_2N$), 54.1 (CH_2N), 29.2 (CH_2), 24.2 (CH_2); MS (ESI) *m/z* 268 [(M + H),$^+$ 100], 250 (35); HRMS (ESI) *m/z* calcd for $C_{18}H_{21}NO$ $(M + H)^+$ 268.1701, found 268.1696. The spectroscopic data were consistent with those reported in the literature.[7]

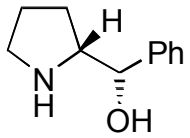


syn-**10**

(2*S*,3*S*)-1-Benzyl-2-phenylpiperidin-3-ol *syn*-10

(Scheme 4)

Using general procedure D, pyrrolidine *syn*-**9** (128 mg, 0.48 mmol), trifluoroacetic anhydride (0.10 mL, 0.72 mmol) and Et_3N (0.20 mL, 1.44 mmol) in THF (3 mL) for 48 h gave the crude product. Purification by flash column chromatography on silica with 3:1 petrol-EtOAc as eluent gave piperidine *syn*-**10** (108 mg, 84%) as a yellow oil, $[\alpha]_D$ +17.9 (*c* 1.5 in MeOH) (lit.,[8] $[\alpha]_D$ +29.9 (*c* 0.39 in MeOH)); R_F (3:1 petrol-EtOAc) 0.2; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (d, *J* = 7.5 Hz, 2H, *o*-Ph), 7.39 (t, *J* = 7.5 Hz, 1H, *p*-Ph), 7.34-7.23 (m, 8H, Ph), 3.90 (d, *J* = 14.0 Hz, 1H, $PhCH_AH_BN$), 3.77 (br s, 1H, CHO), 3.37 (d, *J* = 1.0 Hz, 1H, CHN), 3.02 (br d, *J* = 9.0 Hz, 1H, CH_AH_BN), 2.91 (d, *J* = 14.0 Hz, 1H, $PhCH_AH_BN$), 2.39 (d, *J* = 7.0 Hz, 1H, OH), 2.06-2.01 (m, 2H, CH), 1.94 (tt, *J* = 13.0, 3.5 Hz, 1H, CH), 1.64 (tdd, *J* = 13.0, 4.5, 3.0 Hz, 1H, CH), 1.53-1.48 (m, 1H, CH). The spectroscopic data were consistent with those reported in the literature.[8]

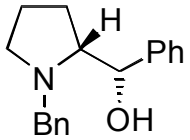


anti

(1*S*,2*R*)-*anti*-1-Phenyl-2-pyrrolidinemethanol

(Scheme 4)

Using general procedure B, TFA (1.0 mL, 7.19 mmol) and pyrrolidine *anti*-**8** (431 mg, 1.55 mmol) in CH_2Cl_2 (10 mL) gave crude (1*S*,2*R*)-*anti*-1-phenyl-2-pyrrolidinemethanol (236 mg, 86%) as an opaque gum, $[\alpha]_D$ +71.3 (*c* 1.0 in $CHCl_3$); R_F(85:14:1 CH_2Cl_2-MeOH, NH_4OH) 0.1; IR (film) 3289 (OH and NH), 2967, 1413, 1215 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.38-7.31 (m, 4H, Ph), 7.28-7.23 (m, 1H, Ph), 4.73 (d, *J* = 4.5 Hz, 1H, CHO), 3.37 (td, *J* = 7.5, 4.5 Hz, CHN), 3.03-2.98 (m, 3H, C$H_A$$H_B$N, OH and NH), 2.92-2.86 (m, 1H, CH), 1.77-1.59 (m, 3H, CH), 1.49-1.42 (m, 1H, CH); MS (ESI) *m/z* 178 [(M + H),$^+$ 100], 160 (12); HRMS (ESI) *m/z* calcd for $C_{11}H_{15}NO$ (M + H)$^+$ 278.1232, found 178.1226. The spectroscopic data were consistent with those reported in the literature.[9]



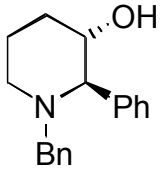
anti-**9**

(1*S*,2*R*)-(1-Benzylpyrrolidin-2-yl)phenylmethanol *anti*-9

(Scheme 4)

Using general procedure C, (1*S*,2*R*)-*anti*-1-phenyl-2-pyrrolidinemethanol (63 mg, 0.36 mmol,), benzyl bromide (0.05 mL, 0.43 mmol) and K_2CO_3 (74 mg, 0.53 mmol) in CH_2Cl_2 (3 mL) gave the crude product. Immediate purification by flash column chromatography on silica with 95:5 CH_2CH_2-MeOH as eluent gave pyrrolidine *anti*-**9** (65 mg, 68%) as a pale yellow oil, $[\alpha]_D$ +71.9 (*c* 1.0 in $CHCl_3$); R_F(95:5 CH_2Cl_2-MeOH) 0.1; IR ($CHCl_3$) 3423 (OH), 2971, 2808, 1452, 1200, 1116 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.44-7.27 (m, 10H, Ph), 4.95 (d, *J* = 3.0 Hz, 1H, CHO), 4.24 (d, *J* = 13.0 Hz, 1H, PhC$H_A$$H_B$N), 3.75 (br s, 1H, OH), 3.51 (d, *J* = 13.0 Hz, 1H, PhC$H_A$$H_B$N), 3.08 (ddd, *J* = 9.0, 6.5, 3.0 Hz, 1H, C$H_A$$H_B$N), 2.94 (ddd, *J* = 9.0, 6.5, 3.0 Hz, 1H, CHN), 2.38 (q, *J* = 9.0 Hz, 1H, C$H_A$$H_B$N), 1.83-1.75 (m, 1H, CH), 1.70-1.62 (m, 2H, CH), 1.37 (dq, *J* = 12.5, 8.5 Hz, 1H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 141.4 (*ipso*-Ph), 139.0

(*ipso*-Ph), 128.7 (CH, Ph), 128.3 (CH, Ph), 128.0 (CH, Ph), 127.1 (CH, Ph), 126.7 (CH, Ph), 125.4 (CH, Ph), 70.3 (CHO), 69.1 (CHN), 58.2 ($PhCH_2N$), 54.6 (CH_2N), 23.9 (CH_2), 23.1 (CH_2); MS (ESI) *m/z* 268 [(M + H),$^+$ 100]; HRMS (ESI) *m/z* calcd for $C_{18}H_{21}NO$ $(M + H)^+$ 268.1701, found 268.1696.

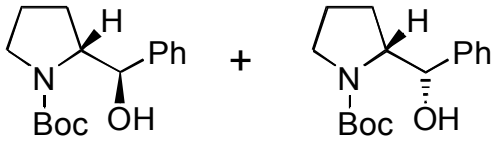


anti-**10**

(2*R*,3*S*)-1-Benzyl-2-phenylpiperidin-3-ol *anti*-10

(Scheme 4)

Using general procedure D, pyrrolidine *syn*-**9** (162 mg, 0.61 mmol), trifluoroacetic anhydride (0.13 mL, 0.91 mmol) and Et_3N (0.26 mL, 1.83 mmol) in THF (4 mL) for 48 h gave the crude product. Purification by flash column chromatography on silica with 3:1 petrol-EtOAc as eluent gave piperidine *syn*-**10** (156 mg, 96%) as a white solid, mp 135-137 °C; $[\alpha]_D$ –22.8 (*c* 1.0 in $CHCl_3$) [lit.,[10] $[\alpha]_D$ –27.0 (*c* 1.3 in $CHCl_3$)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (d, *J* = 7.0 Hz, 2H, *o*-Ph), 7.42 (t, *J* = 8.0 Hz, 1H, *p*-Ph), 7.34-7.24 (m, 8H, Ph), 3.72 (d, *J* = 14.0 Hz, 1H, $PhCH_AH_BN$), 3.64 (ddd, *J* = 11.5, 9.0, 4.5 Hz, 1H, CHO), 2.98-2.92 (m, 1H, CH_AH_BN), 2.97 (d, *J* = 9.0 Hz, 1H, CHN), 2.90 (d, *J* = 14.0 Hz, 1H, $PhCH_AH_BN$), 2.16-2.13 (m, 1H, CH), 1.99 (td, *J* = 11.5, 3.5 Hz, 1H, CH), 1.73-1.64 (m, 2H, CH), 1.60 (br s, 1H, OH), 1.44 (qd, *J* = 12.0, 5.5 Hz, 1H, CH). The spectroscopic data were consistent with those reported in the literature.[10]



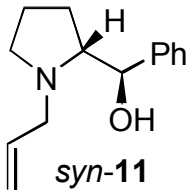
syn-**8** *anti*-**8**

(1*R*,2*R*)- and (1*S*,2*R*)-2-(Hydroxyphenylmethyl)pyrrolidine-1-carboxylic acid *tert*-butyl ester *syn*-8 and *anti*-8

(Scheme 5)

A solution of (–)-sparteine (423 mg, 1.8 mmol, .0.3 equiv.) in Et_2O (1 mL) was added dropwise to a stirred solution of *s*-BuLi (11.25 mL of a 1.2 M solution in cyclohexane, 13.5 mmol, 2.3 equiv.) in Et_2O

(17 mL) at –78 °C under Ar. Then, a solution of dimethylaminoethanol (DMAE) (535 mg, 6.0 mmol, 1.0 equiv.) in Et_2O (1 mL) was added dropwise. After stirring for 10 min, a solution of *N*-Boc pyrrolidine **1** (1.04 g, 6.0 mmol, 1.0 equiv.) in Et_2O (1 mL) was added dropwise *via* a cannula over 10 min. The resulting solution was stirred at –78 °C for 3 h. Then, a solution of benzaldehyde (849 mg, 8.0 mmol, 1.3 equiv.) was added dropwise and the reaction mixture was allowed to warm to rt over 4 h and stirred at rt for 16 h. Saturated $NH_4Cl_{(aq)}$(10 mL) was added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 10 mL) and the combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product which contained a 75:25 mixture of *syn*- and *anti*-**8** (by ^{1}H NMR spectroscopy). Purification by flash column chromatography on silica with 97:3 CH_2Cl_2-acetone as eluent gave pyrrolidine *syn*-**8** (1.06 g, 64%, 90:10 er by chiral HPLC) as a colourless oil, $[\alpha]_D$ –1.5 (*c* 0.95 in $CDCl_3$); chiral HPLC: Chiralpak OD (99:1 hexane:*iso*-PrOH, 0.5 mLmin^{-1}) (1*R*,2*R*)-**8** 38.85 min, (1*S*,2*S*)-**8** 48.60 min and pyrrolidine *anti*-**8** (410 mg, 25%, 89:11 er by chiral HPLC) as colourless crystals, $[\alpha]_D$ +96.0 (*c* 0.8 in $CDCl_3$); chiral HPLC: Chiralpak OD (99:1 hexane-*iso*-PrOH, 0.5 mLmin^{-1}) (1*S*,2*R*)-**8** 35.08 min, (1*R*,2*S*)-**8** 36.65 min.



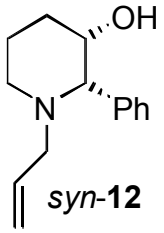
syn-**11**

(1*R*,2*R*)-(1-Allylpyrrolidin-2-yl)phenylmethanol *syn*-11

(Scheme 5)

Using general prodecure B, pyrrolidine *syn*-**8** (950 mg, 3.34 mmol) and TFA (2 mL, 14.4 mmol) in CH_2Cl_2 (20 mL) gave crude pyrrolidine (1*R*,2*R*)-*syn*-1-phenyl-2-pyrrolidinemethanol. Then, using general procedure C, the crude pyrrolidine (1*R*,2*R*)-*syn*-1-phenyl-2-pyrrolidinemethanol, allyl bromide (0.36 mL, 4.12 mmol) and K_2CO_3 (711 mg, 5.15 mmol) in CH_2Cl_2 (10 mL) gave the crude product. Immediate purification by flash column chromatography on silica with 9:1 CH_2Cl_2-MeOH as eluent gave pyrrolidine *syn*-**11** (436 mg, 58% over 2 steps) as a brown oil, $[\alpha]_D$ –53.3 (*c* 1.0 in $CHCl_3$); R_F(9:1 CH_2Cl_2-MeOH) 0.2; IR ($CHCl_3$) 3342 (OH), 2972, 2620, 1454, 1235 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-7.25 (m, 5H, Ph), 7.12 (br s, 1H, OH), 6.08 (dddd, *J* = 17.0, 10.0, 8.5, 6.0 Hz, 1H, C*H*=CH_2), 5.39 (d, *J* = 17.0 Hz,

1H, *trans*-CH=CH_AH$_B$), 5.37 (d, J = 10.0 Hz, 1H, *cis*-CH=CH$_A$$H_B$), 4.94 (d, J = 8.5 Hz, 1H, CHO), 3.95 (dd, J = 13.5, 6.0 Hz, 1H, CH_AH$_B$CH=CH$_2$), 3.59-3.51 (m, 2H, CH$_A$$H_B$CH=CH$_2$ and CH_AH$_B$N), 3.46 (td, J = 8.5, 6.0 Hz, 1H, CHN), 2.90 (dt, J = 11.0, 7.0 Hz, 1H, CH$_A$$H_B$N), 2.06-1.95 (m, 1H, CH), 1.93-1.84 (m, 1H, CH), 1.83-1.74 (m, 1H, CH), 1.74-1.66 (m, 1H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 140.5 (*ipso*-Ph), 129.3 (=CH), 128.5 (CH, Ph), 128.1 (CH, Ph), 126.6 (CH, Ph), 122.9 (=CH$_2$), 73.7 (CHO), 72.1 (CHN), 59.4 (CH$_2$N), 53.4 (CH$_2$N), 28.2 (CH$_2$), 23.5 (CH$_2$); MS (ESI) m/z 218 [(M + H),$^+$ 100]; HRMS (ESI) m/z calcd for $C_{14}H_{19}NO$ (M + H)$^+$ 218.1545, found 218.1539.

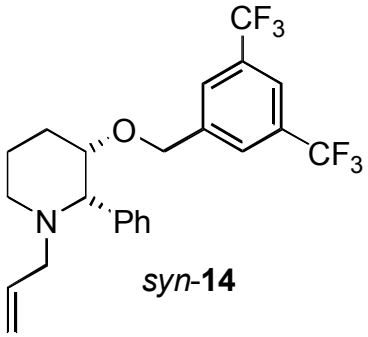


syn-**12**

(2*S*,3*S*)-1-Allyl-2-phenylpiperidin-3-ol *syn*-12

(Scheme 5)

Using general procedure D, pyrrolidine *syn*-**11** (215 mg, 1.0 mmol), trifluoroacetic anhydride (0.21 mL, 1.5 mmol) and Et_3N (0.41 mL, 3.0 mmol) in THF (5 mL) for 72 h gave the crude product. Purification by flash column chromatography on silica with 95:5 CH_2Cl_2-MeOH as eluent gave piperidine *syn*-**12** (180 mg, 83%) as a brown oil, $[\alpha]_D$ +92.9 (*c* 0.7 in $CHCl_3$); R_F(95:5 CH_2Cl_2-MeOH) 0.2; IR ($CHCl_3$) 3580 (OH), 3066, 2945, 2799, 1450, 1391, 1216, 1112 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.29-7.24 (m, 3H, Ph), 7.21-7.17 (m, 2H, Ph), 5.72 (dddd, J = 17.0, 10.5, 8.5, 5.0 Hz, 1H, CH=CH$_2$), 4.99 (br d, J= 10.5 Hz, 1H, *cis*-CH=CH$_A$$H_B$), 4.97 (br d, J = 17.0 Hz, 1H, *trans*-CH=CH_AH$_B$), 3.62 (br s, 1H, CHO), 3.19 (d, J = 1.5 Hz, 1H, CHN), 3.17 (ddt, J = 14.5, 4.5, 2.0 Hz, 1H, CH_AH$_B$CH=CH$_2$), 3.07 (br d, J = 12.0 Hz, 1H, CH_AH$_B$N), 2.44 (dd, J = 14.5, 8.0 Hz, 1H, CH$_A$$H_B$CH=CH$_2$), 2.24 (br s, 1H, OH), 2.00 (dq, J = 12.0, 2.0 Hz, 1H, CH$_A$$H_B$N), 1.95-1.86 (m, 2H, CH), 1.56-1.43 (m, 2H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 140.7 (*ipso*-Ph), 135.1 (=CH), 128.4 (CH, Ph), 128.3 (CH, Ph), 127.3 (CH, Ph), 117.2 (=CH$_2$), 71.9 (CHN), 69.9 (CHO), 58.2 (CH$_2$N), 53.2 (CH$_2$N), 31.5 (CH$_2$), 19.8 (CH$_2$); MS (ESI) m/z [218 (M + H),$^+$ 100], 191 (10), 150 (16); HRMS (ESI) m/z calcd for $C_{14}H_{19}NO$ (M + H)$^+$ 218.1545, found 218.1539.

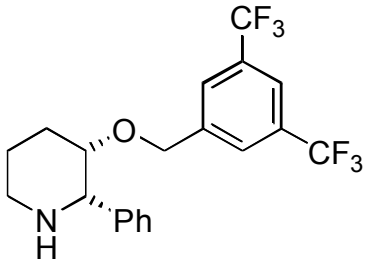


syn-**14**

(2*S*,3*S*)-1-Allyl-3-[3,5-bis-(trifluoromethyl)benzyl]oxy-2-piperidine *syn*-14

(Scheme 5) 72.4 (0.84)

A solution of piperidine *syn*-**12** (165 mg, 0.76 mmol) in THF (2 mL) was added dropwise to a stirred suspension of NaH [61 mg of a 60% dispersion in mineral oil, 1.5 mmol, washed with Et_2O (2 x 2 mL)] in THF (2 mL) at 0 °C under Ar. The resulting creamy white suspension was stirred at 0 °C for 30 min and then 3,5-*bis*-(trifluoromethyl)benzyl bromide **13** (0.30 mL, 1.5 mmol) was added. The resulting creamy white suspension was allowed to warm to rt and stirred for 16 h. The resulting creamy yellow suspension was cooled to 0 °C and water (5 mL) and then Et_2O (5 mL) were added. The layers were separated and the aqueous layer was extracted with Et_2O (3 x 5 mL). The combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 7:1 petrol-EtOAc as eluent gave piperidine *syn*-**14** (330 mg, 98%) as a pale yellow oil, $[\alpha]_D$ +72.4 (*c* 0.8 in $CHCl_3$); R_F(8:1 petrol-EtOAc) 0.2; IR ($CHCl_3$) 2939, 1280, 1177, 1139 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.63 (s, 1H, *p*-$C_6H_3CH_2$), 7.43 (s, 2H, *o*-$C_6H_3CH_2$), 7.37 (d, *J* = 7.0 Hz, 2H, *o*-Ph), 7.27-7.19 (m, 3H, Ph), 5.79 (dddd, *J* = 17.0, 10.0, 8.5, 5.0 Hz, 1H, C*H*=CH_2), 4.99 (d, *J* = 10.0 Hz, 1H, *cis*-CH=CH_AH_B), 4.94 (d, *J* = 17.0 Hz, 1H, *trans*-CH=CH_AH_B), 4.40 (d, *J* = 12.5 Hz, 1H, CH_AH_BO), 3.97 (d, *J* = 12.5 Hz, 1H, CH_AH_BO), 3.48 (d, *J* = 2.0 Hz, 1H, CHO), 3.25-3.18 (m, 1H, CH_AH_BCH=CH_2), 3.22 (d, *J* = 2.0 Hz, 1H, CHN), 3.14 (br d, *J* = 11.0 Hz, 1H, CH_AH_BN), 2.49 (dd, *J* = 14.0, 8.5 Hz, 1H, CH_AH_BCH=CH_2), 2.10-1.90 (m, 3H, CH_AH_BN, CH), 1.55-1.43 (m, 2H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 141.0 (*ipso*-Ar), 140.5 (*ipso*-Ar), 134.8 (=CH), 131.2 (q, *J* = 34.0 Hz, *ipso*-$C_6H_3CF_3$), 129.0 (CH, Ar), 127.9 (CH, Ar), 127.8 (CH, Ar). 127.3 (CH, Ar), 123.3 (q, *J* = 272.5 Hz, CF_3), 121.2 (CH, Ar), 117.6 (=CH_2), 78.4 (CHO), 71.2 (CHN), 70.4 (CH_2O), 58.8 (CH_2N), 53.0 (CH_2N), 28.0 (CH_2), 20.2 (CH_2); MS (ESI) *m/z* 444 [(M + H),$^+$ 100]; HRMS (ESI) *m/z* calcd for $C_{23}H_{23}F_6NO$ (M + H)$^+$ 444.1762, found 444.1757.



(+)-L-733,060

(2*S*,3*S*)-2-Phenyl-3-[3,5-bis-(trifluoromethyl)benzyl]oxy-piperidine, (+)-L-733,060

(Scheme 5)

$Pd(PPh_3)_4$ (41 mg, 0.03 mmol) was added to a stirred solution of piperidine *syn*-**14** (315 mg, 0.7 mmol) and *N*,*N*′-dimethylbarbituric acid (353 mg, 2.1 mmol) in CH_2Cl_2 (4 mL) under N_2 in the dark. The resulting brown solution was stirred in the dark at rt for 16 h. CH_2Cl_2 (4 mL) and 2.0 M $NaOH_{(aq)}$(10 mL) were added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were washed with $NaHCO_{3(aq)}$ (5 mL) and brine (5 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 95:4.5:0.5 CH_2Cl_2-MeOH-NH_4OH as eluent gave (+)-L733,061 (280 mg, 99%, 90:10 er by chiral shift NMR) as a pale brown oil, $[\alpha]_D$ +55.0 (*c* 1.0 in $CHCl_3$) [lit.,[11] $[\alpha]_D$ +73.9 (*c* 0.64 in $CHCl_3$)]; R_F(95:4.5:0.5 CH_2Cl_2-MeOH-NH_4OH) 0.5; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (s, 1H, *p*-$C_6H_3CH_2$), 7.45 (s, 2H, *o*-$C_6H_3CH_2$), 7.39-7.25 (m, 5H, Ar), 4.54 (d, *J* = 12.5 Hz, 1H, CH_AH_BO), 4.14 (d, *J* = 12.5 Hz, 1H, CH_AH_BO), 3.85 (s, 1H, CHN), 3.69 (br s, 1H, CHO), 3.30 (dt, *J* = 12.0, 2.0 Hz, 1H, CH_AH_BN), 2.86 (td, *J* = 12.0, 3.0 Hz, 1H, CH_AH_BN), 2.23 (br d, *J* = 14.0 Hz, 1H, CH), 1.95-1.83 (m, 2H, CH), 1.72 (tdd, *J* = 13.5, 4.5, 2.5 Hz, 1H, CH), 1.54 (br d, *J* = 13.5 Hz, 1H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 141.9 (*ipso*-Ar), 141.2 (*ipso*-Ar), 131.2 (q, *J* = 34.0 Hz, *ipso*-$C_6H_3CF_3$), 130.7 (CH, Ar), 128.1 (CH, Ar), 127.4 (CH, Ar). 126.7 (CH, Ar), 123.2 (q, *J* = 272.5 Hz, CF_3), 121.1 (CH, Ar), 77.3 (CHO), 70.0 (CH_2O), 64.3 (CHN), 47.1 (CH_2N), 28.4 (CH_2), 20.5 (CH_2). The spectroscopic data were consistent with those reported in the literature.[11,12]

Enantiomer ratio of L-733,060 was determined by high resolution ^{1}H NMR spectroscopy (400 MHz, $CDCl_3$) in the presence of 4.0 equivalents of (*R*)- or (*S*)-2,2,2-trifluoro-1-(9-anthryl)-ethanol: A solution of (+)-L-733,060 (11 mg, 0.03 mmol) and (*R*)-2,2,2-trifluoro-1-(9-anthryl)-ethanol (28 mg, 0.11 mmol) in

$CDCl_3$ (~2 mL) gave the following key signals: ^{1}H NMR (400 MHz, $CDCl_3$) □ 3.68 (s, 1H, CHN), 3.53 (s, 1H, CHO); a solution of (+)-L-733,060 (11 mg, 0.03 mmol) and (*S*)-2,2,2-trifluoro-1-(9-anthryl)-ethanol (28 mg, 0.11 mmol) in $CDCl_3$ (~2 mL) gave the following key signals: ^{1}H NMR (400 MHz, $CDCl_3$) □ 3.40 (s, 1H, CHN), 3.23 (s, 1H, CHO). Integration of the major and minor CHN and CHO signals in each of the ^{1}H NMR spectra indicated that (+)-L-733,060 is present in 90:10 er.

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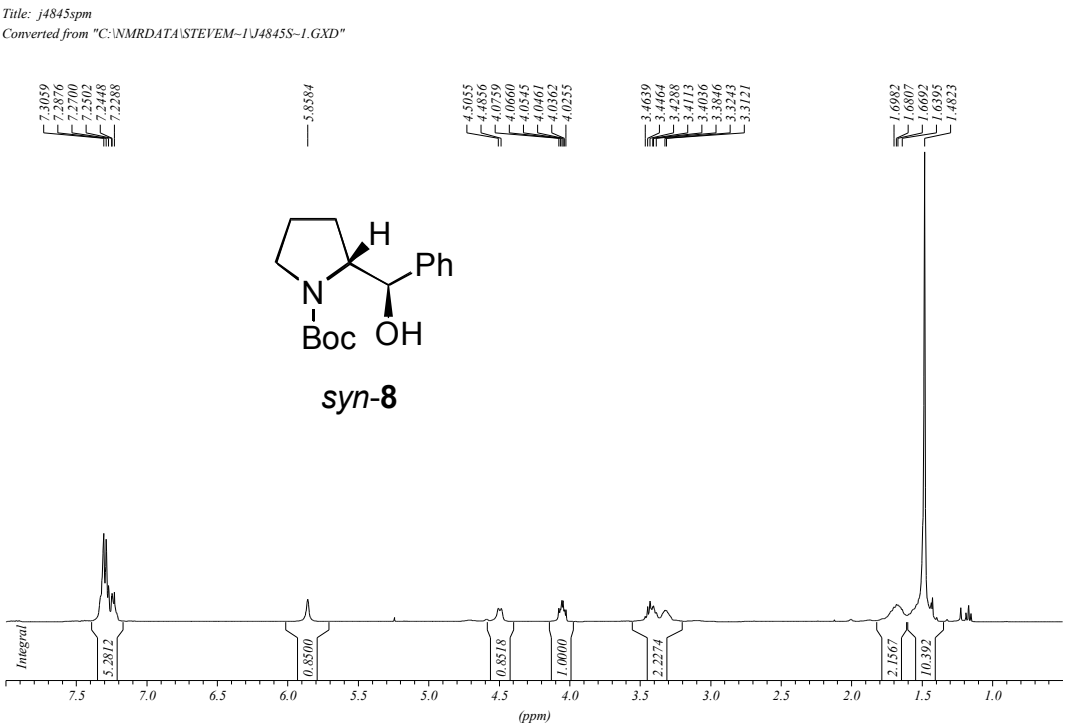
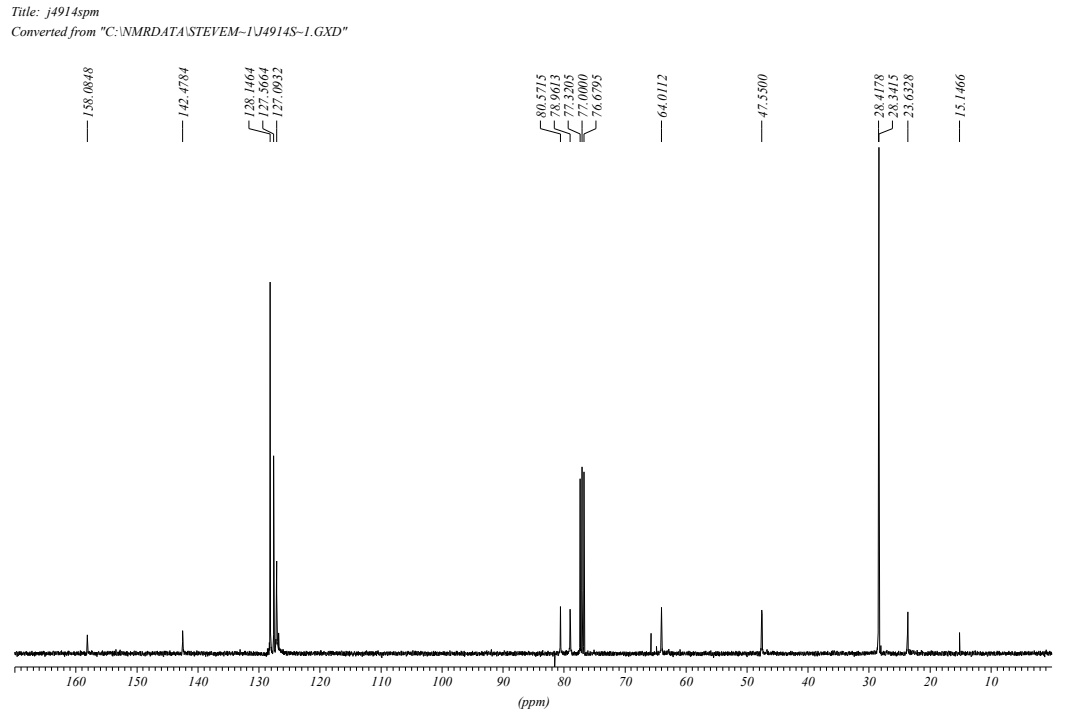
$^{1}H/^{13}C$ NMR spectra:





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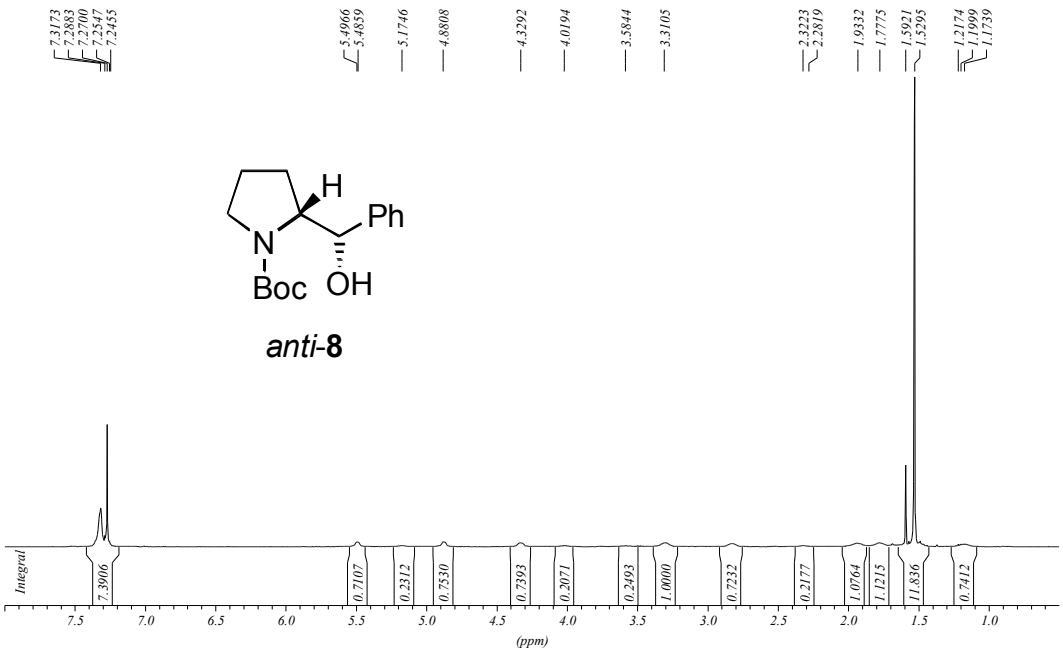

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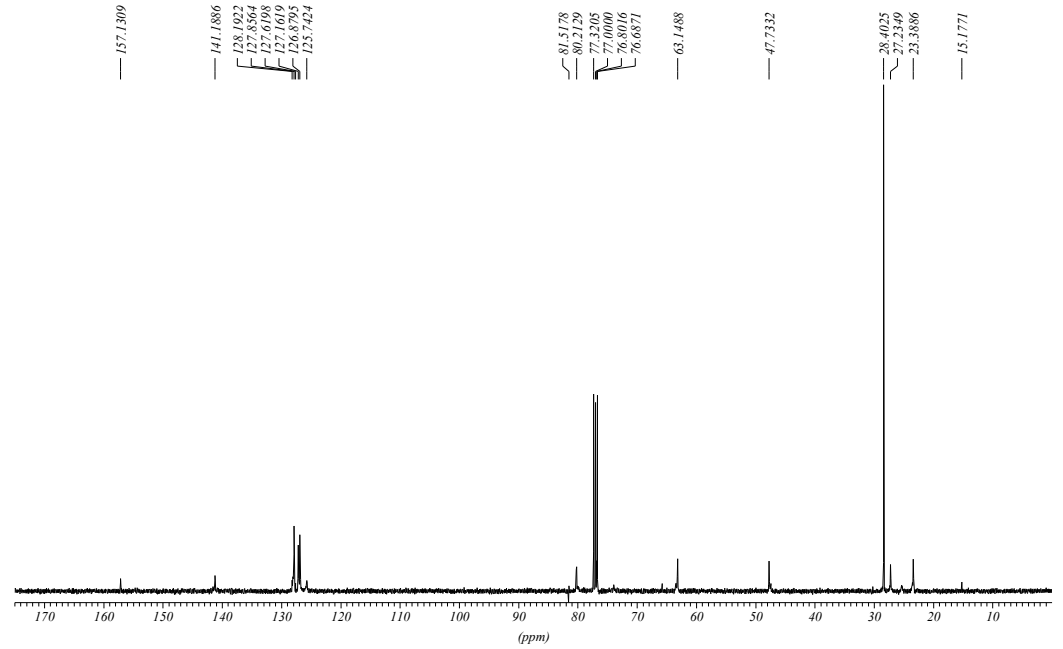

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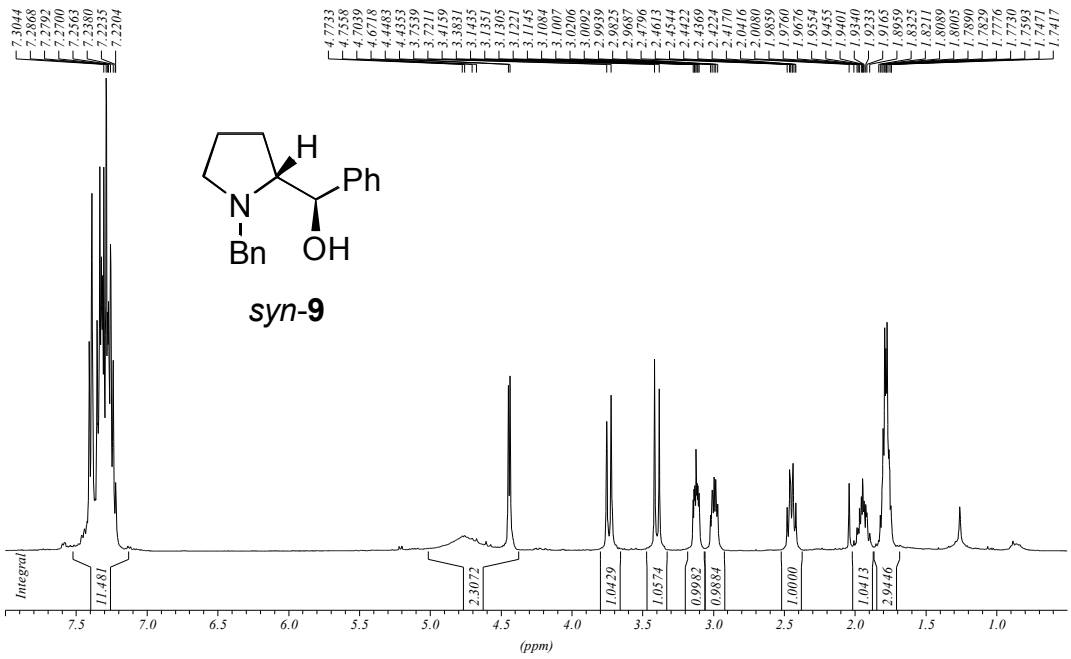

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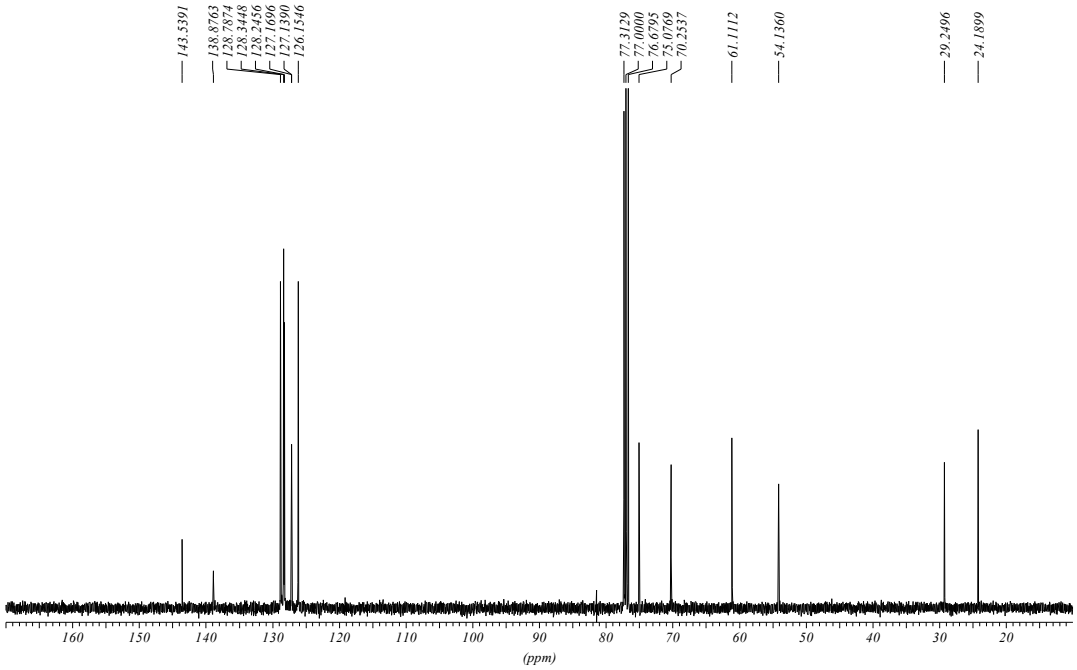

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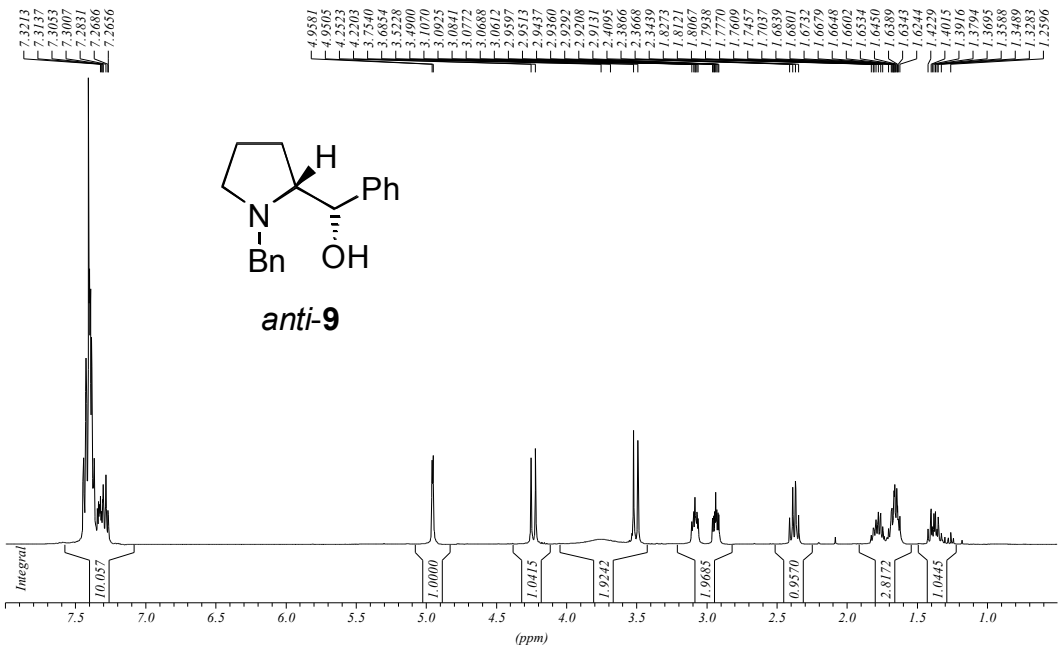

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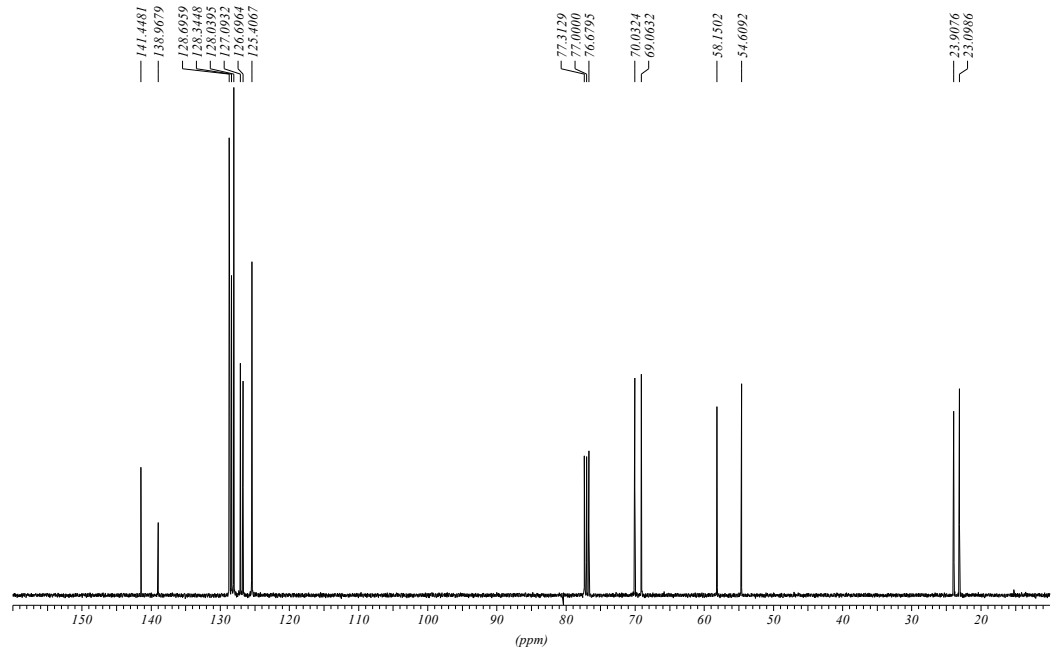

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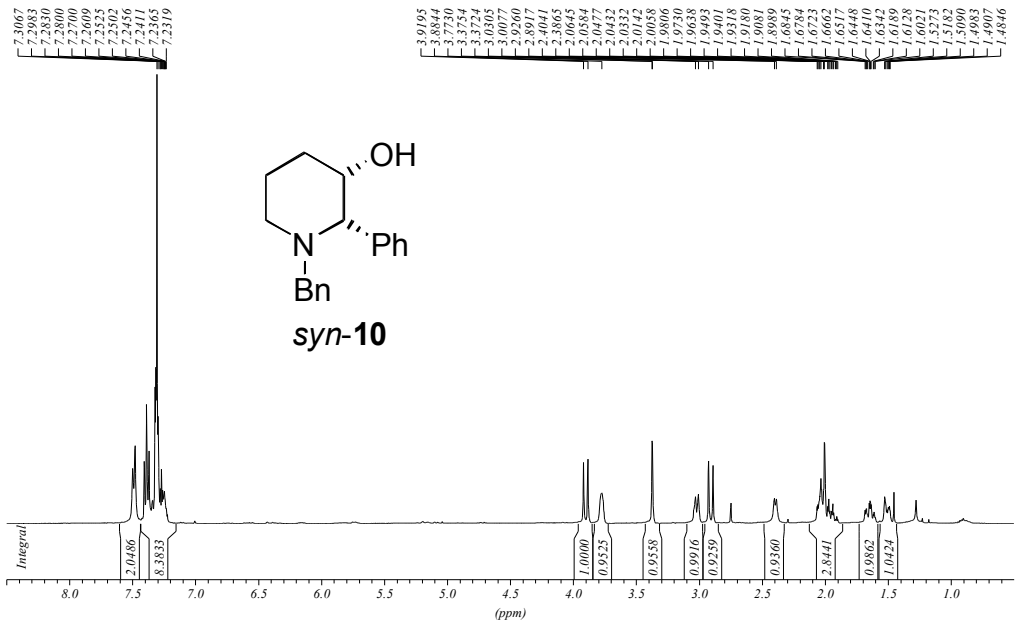

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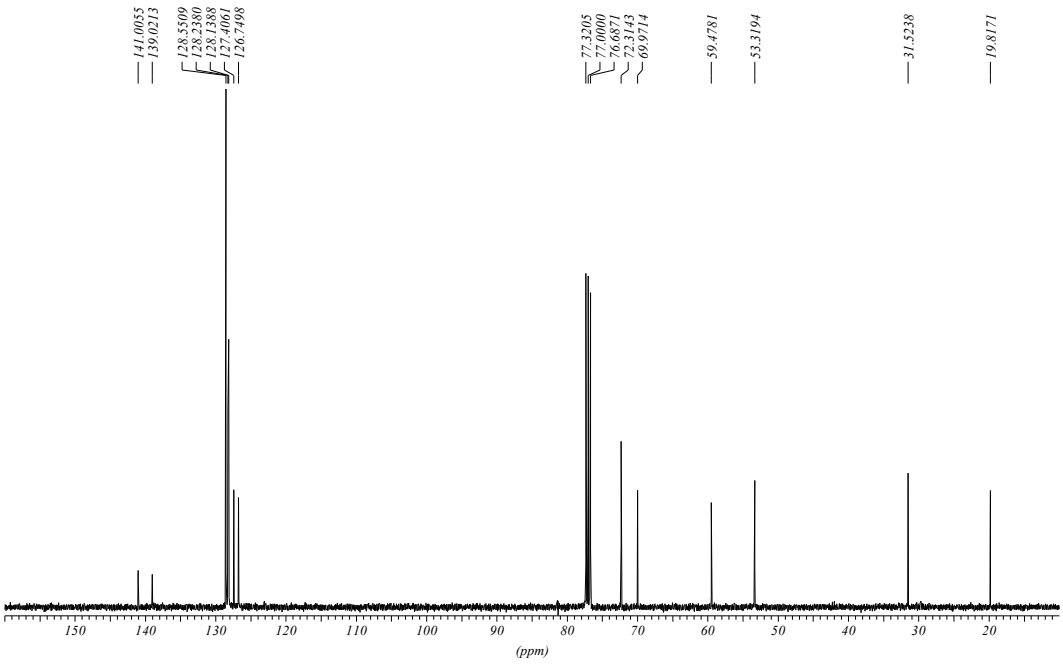

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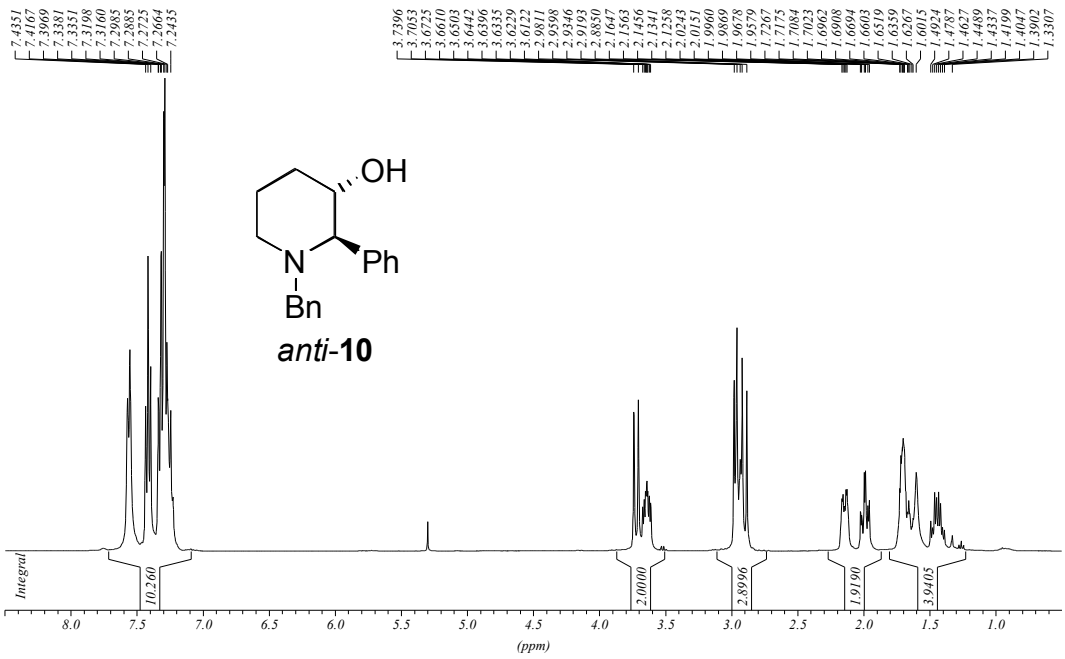

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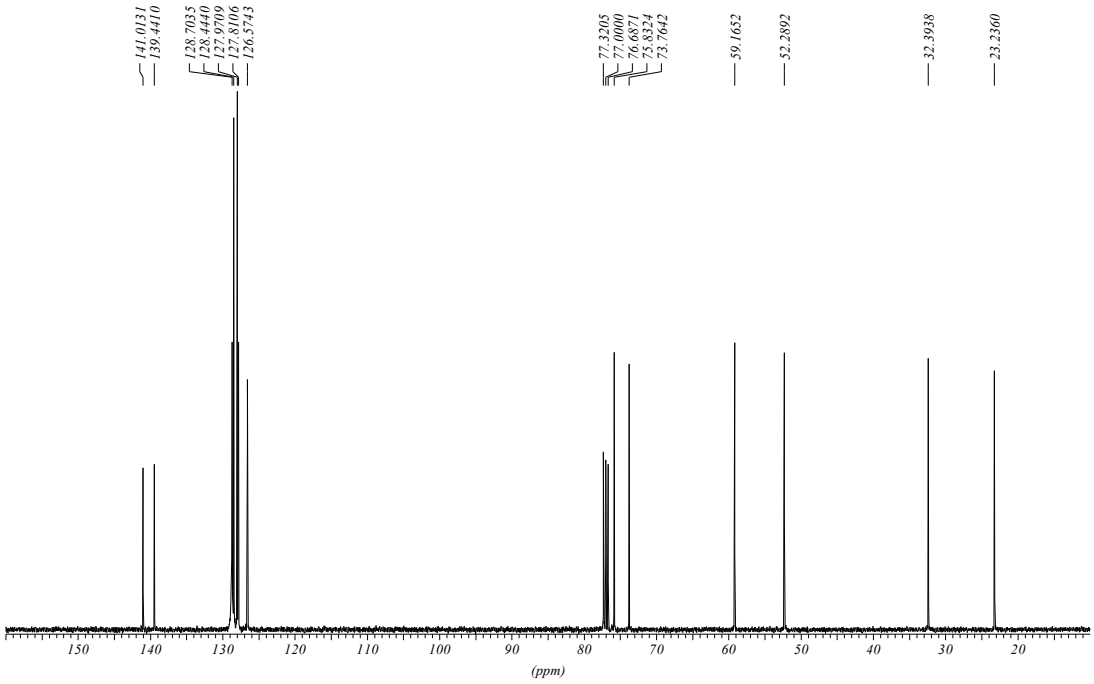

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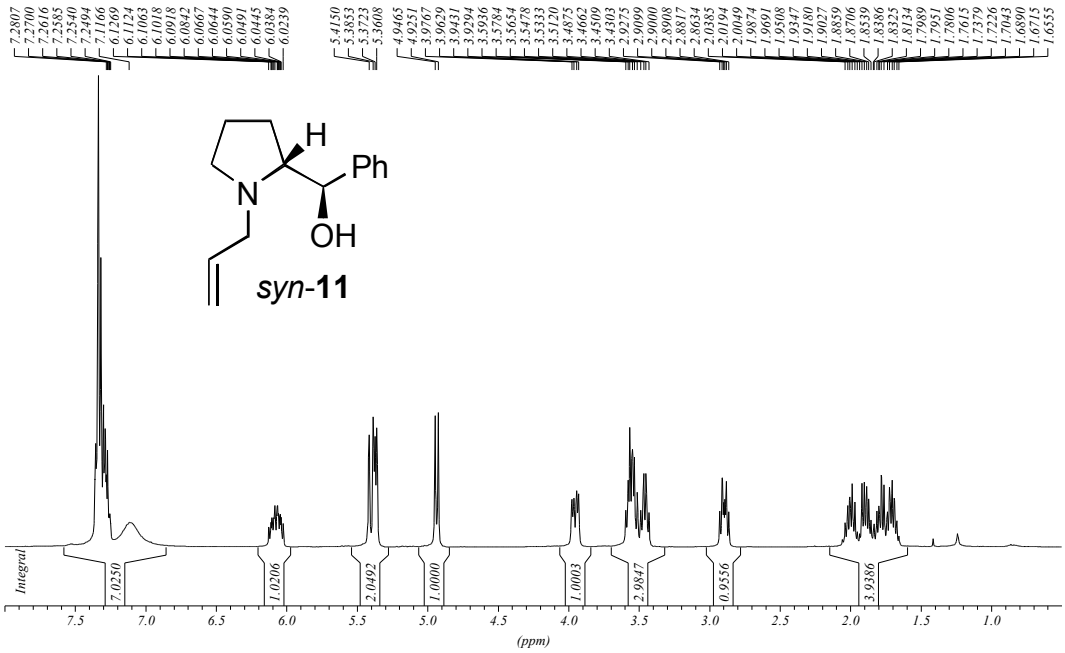

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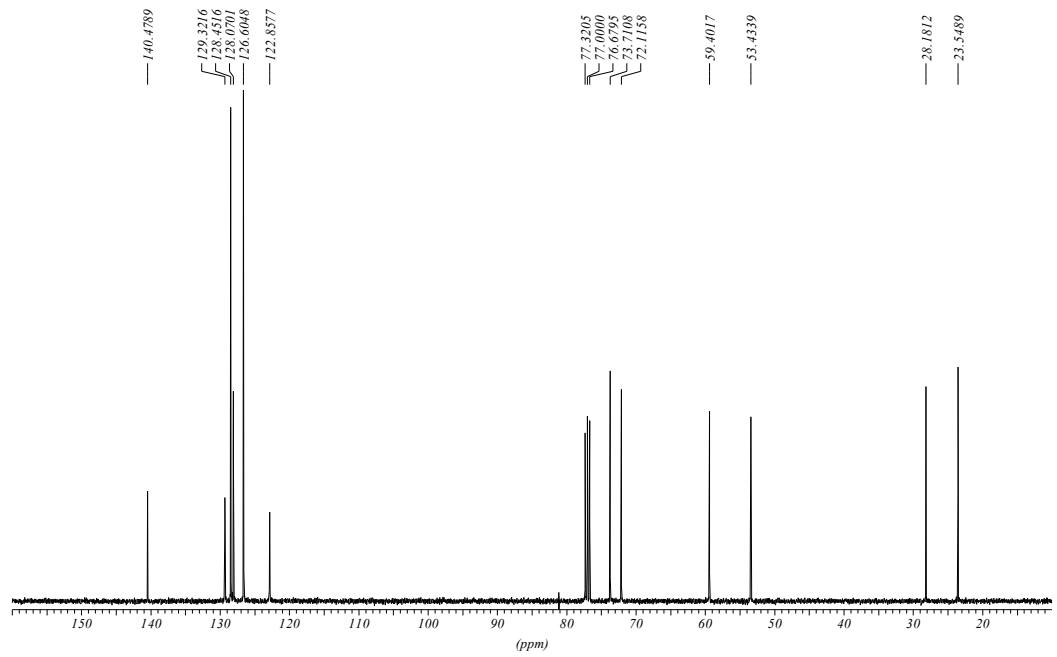

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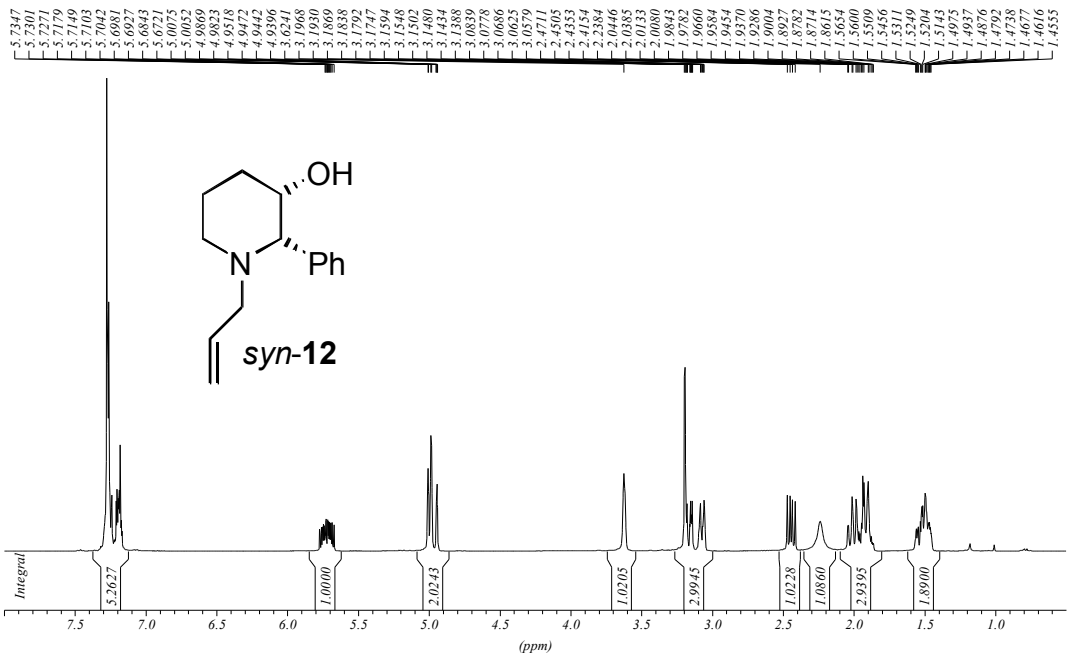

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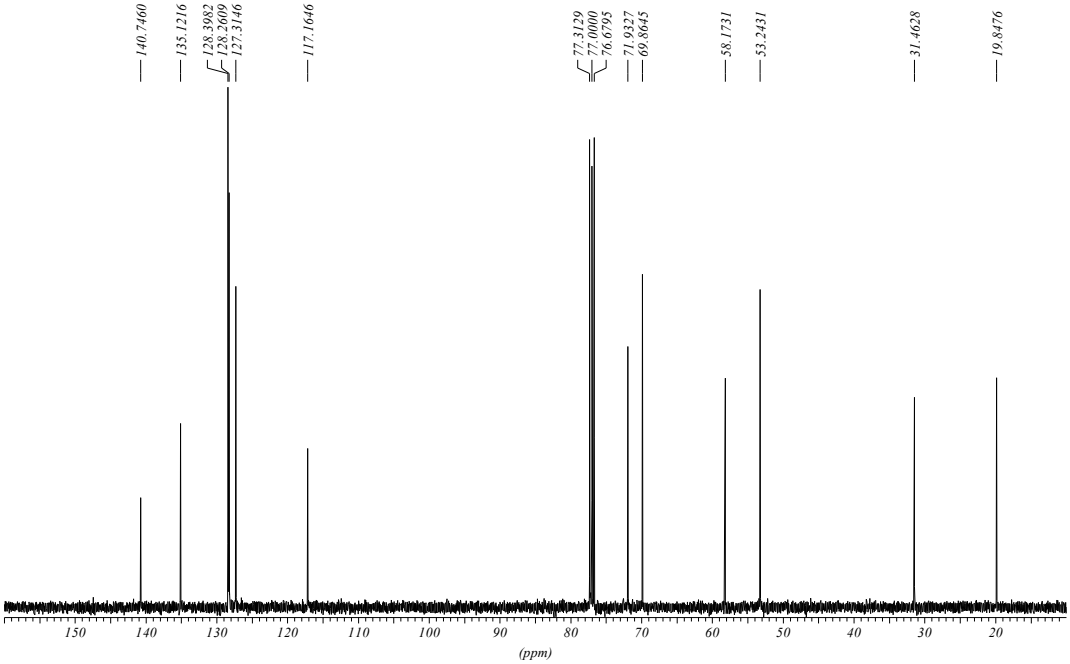

Title: k3810spm
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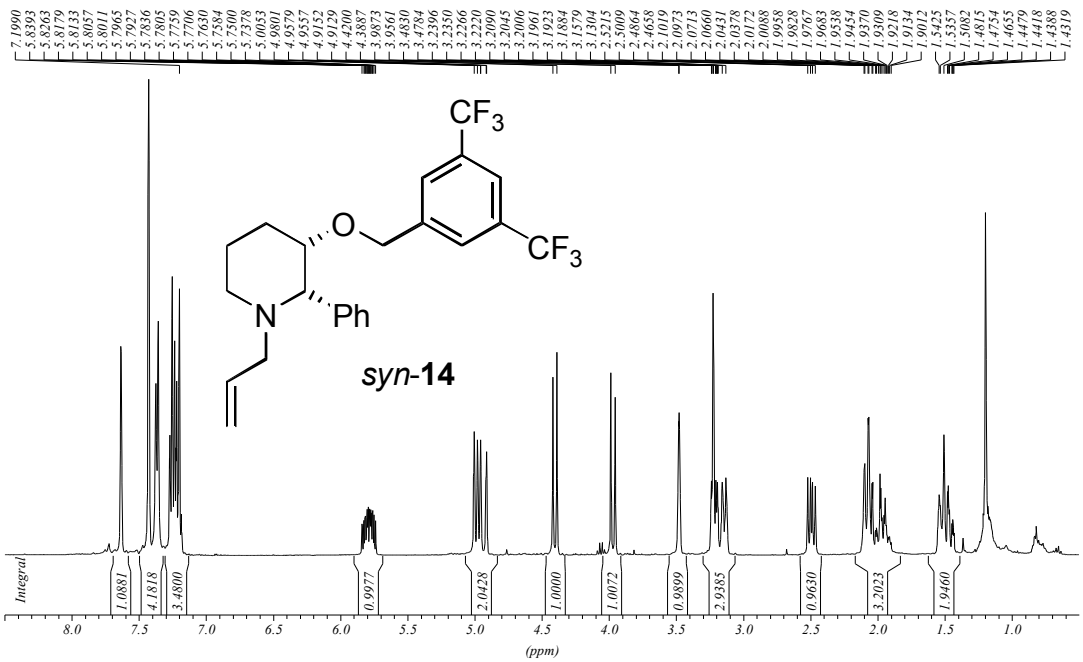

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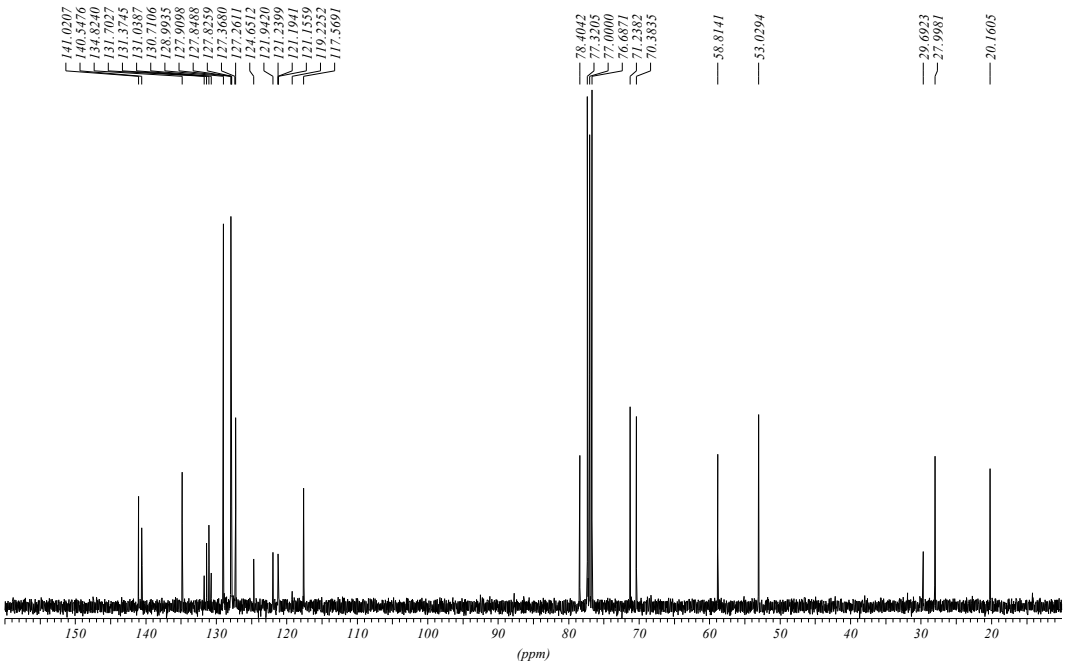

Title: k4035spm
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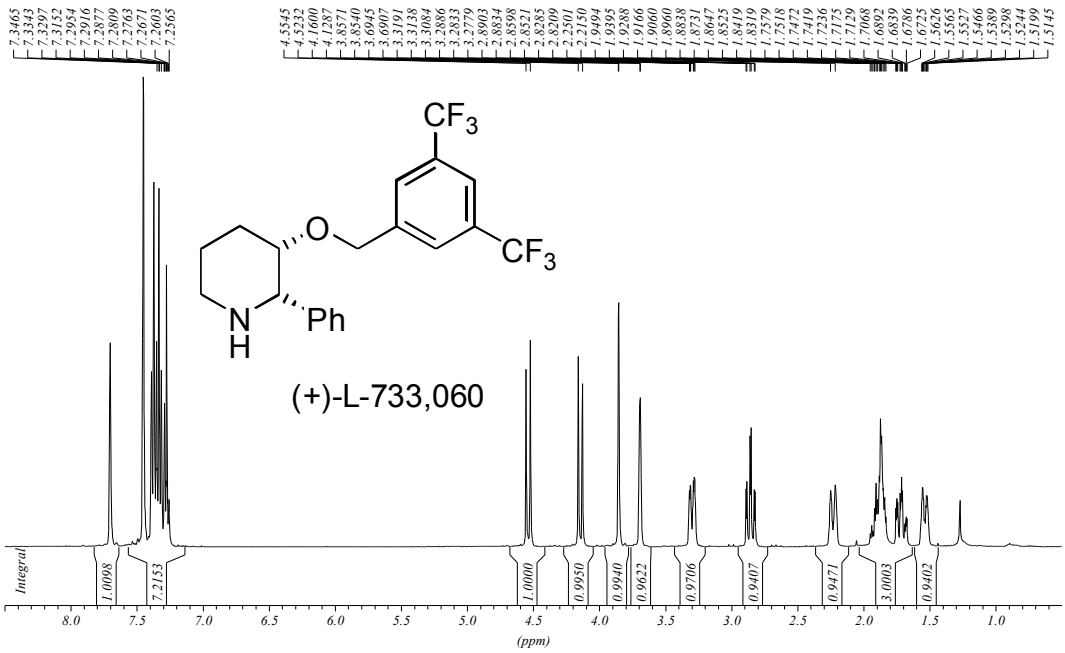

Title: k4118spm
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