Mechanistic Interrogation of the Asymmetric Lithiation-trapping of *N*-Thiopivaloyl Azetidine and Pyrrolidine

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Data is available at: doi 10.15124/f6c60051-fd06-4d8e-94b6-7bf91ac2a69f

1. Experimental details

1.1 General

Water is distilled water. Brine refers to a saturated aqueous solution of NaCl. THF was freshly distilled from sodium and benzophenone ketyl or dried using a Grubbs solvent purification system. Petrol refers to the fraction of petroleum ether boiling in the range 40-60 °C. All reactions were carried out under O_2-free Ar or N_2 using oven-dried and/or flame-dried glassware.

Flash column chromatography was carried out using Fluka Chemie GmbH silica (220-440 mesh). Thin layer chromatography was carried out using Merck F_{254} aluminium-backed silica plates. ^1H (400 MHz) and ^{13}C (100.6 MHz) NMR spectra were recorded on a Jeol ECX-400 instrument with an internal deuterium lock. Chemical shifts are quoted as parts per million and referenced to $CHCl_3$ (δ_H 7.27) and or $CDCl_3$ (δ_C 77.0, central line of triplet). ^{13}C NMR spectra were recorded with broadband proton decoupling. ^{13}C NMR spectra were assigned using DEPT experiments. Coupling constants (*J*) are quoted in Hertz. IR spectra were recorded on an ATI Matteson Genesis FT-IR spectrometer. Melting points were measured on a Gallenkamp melting point apparatus. Electrospray high and low resolution mass spectra were recorded on a Bruker Daltronics microOTOF spectrometer. Chiral stationary phase HPLC was performed on an Agilent 1200 series instrument and a multiple wavelength, UV/Vis diode array detector; integration was normally performed at 230 nm.

The following compounds were made according to the reported procedures: diamines (*R*,*R*)-**4** and (*S*,*S*)-**4**[1] and (+)-sparteine surrogate **21**.[2]

1.2 General Procedures

General Procedure A: *s*-BuLi/diamine-mediated lithiation-electrophilic trapping of *N*-thiopivaloyl azetidine 1

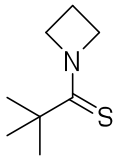
s-BuLi (0.46 mL of a 1.3 M solution in hexanes, 0.60 mmol, 1.2 eq.) was added dropwise to a stirred solution of *N*-thiopivaloyl azetidine **1** (79 mg, 0.50 mmol, 1.0 eq.) and diamine (0.60 mmol, 1.2 eq.) in Et_2O (5 mL) at −78 °C under Ar. The resulting solution was stirred at −78 °C for 30 min. Then, the electrophile (0.75 mmol, 1.5 eq.) was added dropwise and the solution was stirred at −78 °C for 1 h. 1 M $HCl_{(aq)}$ (10 mL) was added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product.

General Procedure B: *s*-BuLi/diamine-mediated lithiation-electrophilic trapping of *N*-thiopivaloyl pyrrolidine 9

s-BuLi (0.50 mL of a 1.3 M solution in hexanes, 0.65 mmol, 1.3 eq.) was added dropwise to a stirred solution of *N*-thiopivaloyl pyrrolidine **9** (86 mg, 0.50 mmol, 1.0 eq.) and diamine (0.65mmol, 1.3 eq.) in Et_2O (5 mL) at −78 °C under Ar. The resulting solution was stirred at −78 °C for 1 h. Then, the electrophile (0.75 mmol, 1.5 eq.) was added dropwise and the solution was stirred at −78 °C for 1 h. 1 M $HCl_{(aq)}$ (10 mL) was added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product.

1.3 Experimental Procedures and Characterisation Data

2,2-Dimethyl-1-azetidinyl-1-ylpropan-1-thione 1[3]

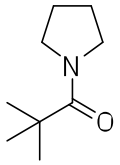


1

Trimethylacetyl chloride (7.21 mL, 58.6 mmol, 1.1 eq.) was added to a stirred solution of azetidine hydrochloride (5.00 g, 53.3 mmol, 1.0 eq.) and Et_3N (37.1 mL, 266 mmol, 5.0 eq.) in CH_2Cl_2 (75 mL) at 0 °C. The resulting solution was allowed to warm to rt and stirred at rt for 16 h. Then, 1 M $HCl_{(aq)}$ (15 mL) was added and the two layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 30 mL). The combined organic layers were dried ($MgSO_4$) and evaporated under reduce pressure to give the crude *N*-pivaloyl azetidine. The residue was dissolved in pyridine (150 mL) and phosphorous(V) sulfide (14.80 g, 66.6 mmol, 1.25 eq.) was added. The resulting solution was heated to 75 °C for 6 h. The solution was allowed to cool to rt and then poured into 1 M $HCl_{(aq)}$ (150 mL). 1 M $HCl_{(aq)}$ was added until pH 3 was obtained. The resulting solution was stirred at rt for 2 h and then extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were washed with 1 M $HCl_{(aq)}$ (50 mL), water (50 mL) and brine (50 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 8:2-7:3 petrol-Et_2O as eluent gave thioamide **1** (6.40 g, 78%) as a yellow oil, R_F (8:2 petrol-Et_2O) 0.2; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.51 (br t, J = 7.5 Hz, 2H, NCH_2), 4.29 (br t, J = 7.5 Hz, 2H, NCH_2), 2.33-2.25 (m, 2H, CH_2), 1.36 (s, 9H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 209.1 (C=S), 56.6 (NCH_2), 56.0 (NCH_2) 43.1 (CMe_3), 29.8 (CMe_3), 14.6 (CH_2). Spectroscopic data consistent with those reported in the literature.[3]

Lab Book Reference: PJR 2/110A

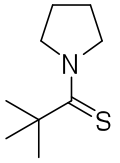
2,2-Dimethyl-1-pyrrolidin-1-yl-propanone S1



S1

Trimethylacetyl chloride (3.87 g, 32.0 mmol, 1.0 eq.) was added to a stirred solution of pyridine (4.30 mL, 54.0 mmol, 1.7 eq.) and pyrrolidine (2.89 mL, 32.0 mmol, 1.0 eq.) in $CHCl_3$ (28 mL) at 0 °C. The resulting solution was heated at 65 °C and stirred for 16 h. The solution was allowed to cool to rt and then water (50 mL) was added. The two layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product as a yellow solid. Recrystallisation from $CHCl_3$ gave amide **S1** (5.09 g, 100%) as colourless needles, mp 53-56 °C (lit.,[4] 56-59 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.54 (br s, 4H, NCH_2), 1.86 (br s, 4H, CH_2), 1.25 (s, 9H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 176.4 (C=O), 47.8 (NCH_2), 38.9 (CMe_3), 27.5 (CMe_3), 23.0 (CH_2). Spectroscopic data consistent with those reported in the literature.[5]
Lab Book Reference: PJR 1/55

2,2-Dimethyl-1-pyrrolidin-1-ylpropan-1-thione 9[3]



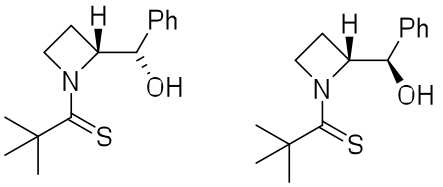
9

Phosphorous(V) sulfide (17.78 g, 80.0 mmol, 1.25 eq.) was added to a stirred solution amide **S1** (10.0 g, 64 mmol, 1.0 eq.) in pyridine (100 mL) at rt under Ar. The resulting solution was heated at 75 °C for 6 h. The solution was allowed to cool to rt and then poured into 1 M $HCl_{(aq)}$ (150 mL). 1 M $HCl_{(aq)}$ was added until pH 3 was obtained. The resulting solution was stirred at rt for 2 h and then extracted with CH_2Cl_2 (3 × 100 mL). The combined organic extracts were washed with 1 M $HCl_{(aq)}$ (100 mL), water (100 mL) and brine (100 mL), dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography

on silica with 7:3 petrol-EtOAc as eluent gave thioamide **9** (5.09 g, 100%) as pale yellow needles, mp 32-35 °C (lit.,[6] 33-35 °C); R_F (7:3 petrol-EtOAc) 0.5; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.83 (t, J = 7.0 Hz, 2H, NCH_2), 3.74 (t, J = 7.0 Hz, 2H, NCH_2), 1.95 (quintet, J = 7.0 Hz, 2H, CH_2), 1.81 (quintet, J = 7.0 Hz, 2H, CH_2), 1.29 (s, 9H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) rotamers δ 208.4 (C=S), 57.5 (NCH_2), 52.7 (NCH_2) 43.4 (CMe_3), 30.1 (CMe_3), 27.2 (CH_2), 22.8 (CH_2). Spectroscopic data consistent with those reported in the literature.[6]

Lab Book Reference: PJR 2/110A

1-[(2*R*)-2-[(*S*)-Hydroxy(phenyl)methyl]azetidin-1-yl]-2,2-dimethylpropane-1-thione (*S*,*R*)-13 and 1-[(2*R*)-2-[(*R*)-hydroxy(phenyl)methyl]azetidin-1-yl]-2,2-dimethylpropane-1-thione (*R*,*R*)-12



(*S*,*R*)-**13** (*R*,*R*)-**12**

(Scheme 3 and Scheme 4)

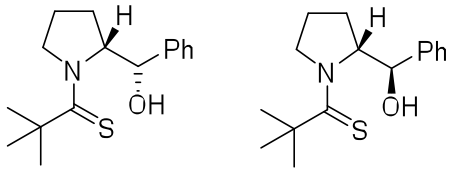
Using general procedure A, *s*-BuLi (0.46 mL of a 1.3 M solution in hexanes, 0.6 mmol, 1.2 eq.), *N*-thiopivaloyl azetidine **1** (79 mg, 0.5 mmol, 1.0 eq.) and (−)-sparteine **3** (0.14 mL, 0.6 mmol, 1.2 eq.) in Et_2O (5 mL) and benzaldehyde (76 μL, 0.75 mmol, 1.5 eq.) gave the crude product which contained an 86:14 mixture of alcohols (*R,R*)-**12** and (*S,R*)-**13** by ^{1}H NMR spectroscopy. Purification by flash column chromatography on silica with 9:1-8:2 petrol-EtOAc as eluent gave alcohol (*S,R*)-**13** (12 mg, 9%, 58:42 er by CSP-HPLC) as a white solid, mp 151-153 °C; R_F (4:1 petrol-EtOAc) 0.3; IR ($CHCl_3$) 3203 (OH), 2921, 1441, 1414, 1341, 1242, 1126, 996, 980, 731 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46-7.43 (m, 2H, *o*-Ph), 7.39-7.35 (m, 2H, *m*-Ph), 7.32 (tt, J = 7.5, 1.5 Hz, 1H, *p*-Ph), 5.47 (br s, 1H, CHO), 5.28 (dddd, J = 9.5, 5.0, 2.0, 2.0 Hz, 1H, NCH), 4.54 (br s, 1H, OH), 4.23 (ddd, J = 9.5, 5.0, 2.0 Hz, 1H, NCH_AH_B), 3.92-3.85 (m, 1H NCH_AH_B), 2.32 (dddd, 11.5, 9.5, 9.5, 7.5 Hz, 1H, CH_AH_B), 2.19-2.06 (m, 1H, CH_AH_B), 1.30 (s, 9H, CMe_3);^{13}C NMR (100.6 MHz, $CDCl_3$) δ 211.1 (C=S), 139.6 (*ipso*-Ph), 128.2 (Ph), 127.7 (Ph), 126.7 (Ph), 73.7 (OCH or NCH), 73.5 (OCH or NCH), 56.1 (NCH_2), 43.4 (CMe_3) 29.5 (CMe_3), 17.2 (CH_2); MS (ESI) *m/z* 286 [$(M + Na)^+$, 100], 264 [$(M + H)^+$, 30], 208 (100); HRMS *m/z* calcd for $C_{15}H_{21}NO_3$ $(M + Na)^+$ 286.1414, found 286.1414 (0.0 ppm error); $[\alpha]_D$ +40.9 (*c* 0.65 in

$CHCl_3$); CSP-HPLC: Chiracel AD-H (95:5 Hexane-*i*PrOH, 1.0 mL min^{-1}) (*S*,*R*)-**13** 7.4 min, (*R*,*S*)-**13** 10.0 min and alcohol (*R,R*)-**12** (99 mg, 75%, 75:25 er by CSP-HPLC) as a white solid, mp 109-111 °C (lit.,[3] 116-117 °C); R_F (4:1 petrol-EtOAc) 0.2; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45-7.43 (m, 2H, Ph), 7.39-7.29 (m, 3H, Ph), 5.32 (d, J = 7.5 Hz, 1H, CHOH), 5.22 (dddd, J = 9.0, 7.5, 5.0, 1.5 Hz, 1H, NCH), 5.17 (br s, 1H, OH), 4.31 (td, J = 10.0, 5.0 Hz, 1H, NCH_AH$_B$), 4.20-4.13 (m, 1H, NCH$_A$$H_B$), 2.20 (dddd, J = 12.0, 10.0, 9.0, 7.5 Hz, 1H, CH_AH$_B$), 1.86 (ddt, J = 12.0, 9.5, 5.0 Hz, 1H, CH$_A$$H_B$), 1.35 (s, 9H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 212.3 (C=S), 139.9 (*ipso*-Ph), 128.3 (Ph), 128.1 (Ph), 127.3 (Ph), 76.3 (OCH or NCH), 73.8 (OCH or NCH), 56.0 (NCH_2), 43.6 (CMe_3), 29.6 (CMe_3), 18.3 (CH_2); $[\alpha]_D$ +74.8 (*c* 0.75 in $CHCl_3$); CSP-HPLC: Chiracel AD-H (95:5 Hexane-*i*PrOH, 1.0 mL min^{-1}) (*R*,*R*)-**12** 17.8 min, (*S*,*S*)-**12** 20.4 min. Spectroscopic data for *rac*-**12** is consistent with those reported in the literature.[3]

Lab Book Reference PJR 8/624

Note: In Hodgson's paper,[3] *rac*-**12** was reported as the only diastereomer generated. In our hands, we always observed two diastereomers, **12** (major) and **13** (minor). Both have been fully characterised, including X-ray crystallography (see Section 2).

1-((*R*)-2-((*S*)-Hydroxy(phenyl)methyl)pyrrolidin-1-yl)-2,2-dimethylpropane-1-thione (*S*,*R*)-15 and 1-((*R*)-2-((*R*)-hydroxy(phenyl)methyl)pyrrolidin-1-yl)-2,2-dimethylpropane-1-thione (*R*,*R*)-14



(*S*,*R*)-**15** (*R*,*R*)-**14**

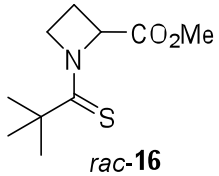
(Scheme 3)

Using general procedure B, *s*-BuLi (0.50 mL of a 1.3 M solution in hexanes, 0.65 mmol, 1.3 eq.), (−)-sparteine **3** (145 μL, 0.65 mmol, 1.3 eq.) and *N*-thiopivaloyl pyrrolidine **9** (86 mg, 0.50 mmol, 1.0 eq.) in Et_2O (5 mL) and benzaldehyde (76 μL, 0.75 mmol, 1.5 eq.) gave the crude product which contained a 58:42 mixture of diastereomeric alcohols (*S*,*R*)-**15** and (*R*,*R*)-**14** by ^{1}H NMR spectroscopy. Purification by flash column chromatography on silica with 8:2-7:3 petrol-Et_2O as eluent gave alcohol (*S*,*R*)-**15** (55 mg, 40%, 86:14 er by CSP-HPLC) as a white solid, mp 169-174

°C; R_F (7:3 petrol-Et_2O) 0.2; IR ($CHCl_3$) 3386 (OH), 2972, 2876, 1604, 1478, 1411, 1383, 1365, 1160, 732 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.53 (d, J = 7.0 Hz, 2H, *o*-Ph), 7.34 (t, J = 7.0 Hz, 2H, *m*-Ph), 7.26 (t, J = 7.0 Hz, 1H, *p*-Ph), 5.90 (br s, 1H, OCH), 5.36-5.32 (m, 1H, NCH), 4.27-4.22 (m, 1H, NCH_AH_B), 3.52 (ddd, , J = 11.0, 11.0, 6.0 Hz, 1H, NCH_AH_B), 2.28 (br s, 1H, OH), 2.12-1.97 (m, 2H, CH), 1.75-1.64 (m, 2H, CH), 1.44 (s, 9H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 210.1 (C=S), 141.9 (*ipso*-Ph), 128.1 (Ph), 127.2 (Ph), 125.5 (Ph), 71.4 (OCH or NCH), 70.4 (OCH or NCH), 54.7 (NCH_2), 44.2 (CMe_3), 30.7 (CMe_3), 25.0 (CH_2), 22.4 (CH_2); MS (ESI) *m/z* 300 [$(M + Na)^+$, 20], 278 [$(M + H)^+$, 100], 260 (30), 125 (40); HRMS *m/z* calcd for $C_{16}H_{23}NOS$ $(M + H)^+$ 278.1573, found 278.1579 (−2.0 ppm error); $[\alpha]_D$ −7.0 (*c* 1.0 in $CHCl_3$); CSP-HPLC: Chiracel AD (95:5 Hexane-*i*PrOH, 1.0 mL min^{-1}) (*S*,*R*)-**15** 11.3 min, (*R*,*S*)-**15** 14.7 min and alcohol (*R*,*R*)-**14** (50 mg, 37%, 82:18 er by CSP-HPLC) as a colourless oil, R_F (7:3 petrol-Et_2O) 0.1; IR (film) 3387 (OH), 2973, 2876, 1605, 1452, 1411, 1383, 1365, 1162, 732 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.41-7.29 (m, 5H, Ph), 5.68 (ddd, J = 8.0, 8.0, 3.5 Hz, 1H, NCH), 5.29-5.26 (m, 1H, OCH), 4.11 (ddd, J = 11.5, , 5.55.5 Hz, 1H, NCH_AH_B), 3.97 (br d, J = 5.0 Hz, 1H, OH), 3.25-3.18 (m, 1H, NCH_AH_B), 1.90-1.73 (m, 4H, CH), 1.45 (s, 9H, CMe_3); ^{13}C NMR rotamers (100.6 MHz, $CDCl_3$) δ 212.6 (C=S), 141.8 (*ipso*-Ph), 128.3 (Ph), 128.5 (Ph), 128.3 (Ph), 127.8 (Ph), 127.6 (Ph), 127.1 (Ph), 127.0 (Ph), 74.4 (br, OCH), 69.8 (NCH), 65.3 (NCH_2), 52.7 (NCH_2), 44.3 (CMe_3), 30.7 (CMe_3), 24.3 (CH_2), 24.1 (CH_2); MS (ESI) *m/z* 300 [$(M + Na)^+$, 20], 278 [$(M + H)^+$, 100], 260 (20), 125 (20); HRMS *m/z* calcd for $C_{16}H_{23}NOS$ $(M + H)^+$ 278.1573, found 278.1570 (1.1 ppm error); $[\alpha]_D$ +94.2 (*c* 0.8 in $CHCl_3$); CSP-HPLC: Chiracel AD (90:10 Hexane-*i*PrOH, 1.0 mL min^{-1}) (*R*,*R*)-**14** 10.6 min, (*S*,*S*)-**14** 22.4 min.

Lab Book Reference PJR 8/636 and 6/501

rac-Methyl 1-(2,2-dimethylpropanethioyl)azetidine-2-carboxylate _rac_-16



rac-**16**

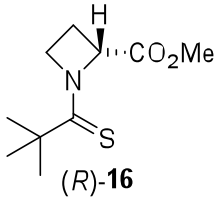
(Racemic standard for Scheme 3)

s-BuLi (0.50 mL of a 1.3 M solution in hexanes, 0.65 mmol, 1.3 eq.) was added to a stirred solution of *N*-thiopivaloyl azetidine **1** (79 mg, 0.08 mL, 0.50 mmol, 1.0 eq.) and TMEDA (0.18

mL, 131 mg, 1.2 mmol, 2.4 eq.) in Et_2O (7 mL) at −100 °C under N_2. The resulting solution was stirred at −100 °C for 2 min. Then, methyl chloroformate (0.077 mL, 95 mg, 1.0 mmol, 2.0 eq.) was added and the solution was stirred at −100 °C for 10 min and allowed to warm to rt over the course of 1 h. 2 M $HCl_{(aq)}$ (3 mL) was added and the two layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 10 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 95:5 hexane-EtOAc as eluent gave methyl ester *rac*-**16** (13.6 mg, 0.063 mmol, 13%) as a pale yellow oil, ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.02-4.96 (m, 1H, CHN), 4.68–4.59 (m, 1H, CH_AH$_B$N), 4.52–4.43 (m, 1H, CH$_A$$H_B$N), 3.75–3.73 (m, 3H, CO_2Me), 2.59–2.48 (m, 1H, CH_AH$_B$), 2.24–2.14 (m, 1H, CH$_A$$H_B$), 1.35–1.33 (m, 9H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 211.6 (C=S), 170.0 (*C*O_2Me), 65.9 (CHN), 56.1 (CH_2N), 52.4 (CO_2*Me*), 43.1 (*C*Me_3), 29.6 (C*Me*$_3$), 19.1 (CH_2). Spectroscopic data consistent with those reported in the literature.[3]

Lab Book Reference: JCS-1-102

(*R*)-Methyl 1-(2,2-dimethylpropanethioyl)azetidine-2-carboxylate (*R*)-16



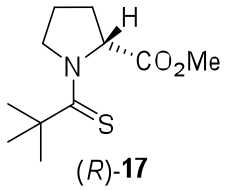
(*R*)-**16**

(Scheme 3)

Using general procedure A, *s*-BuLi (0.46 mL of a 1.3 M solution in hexanes, 0.60 mmol, 1.2 eq), *N*-thiopivaloyl azetidine **1** (0.08 mL, 79 mg, 0.5 mmol, 1.0 eq), (–)-sparteine **3** (0.14 mL, 141 mg, 0.6 mmol, 1.2 eq) in Et_2O (5 mL) and methyl chloroformate (0.06 mL, 71 mg, 0.75 mmol, 1.5 eq) gave the crude product. Purification by flash column chromatography on silica with 8:2-7:3 hexane-EtOAc as eluent gave (*R*)-**16** (48 mg, 0.225 mmol, 45%, 67:33 er by CSP-HPLC) as a pale yellow oil, $[\alpha]_D$ +45.5 (*c* 0.52 in EtOAc); CSP-HPLC: Chiralcel OD-H (98:2 Hexane-*i*PrOH, 1.0 mL min^{-1}) (*S*)-**16** 12.7 min, (*R*)-**16** 13.8 min.

Lab Book Reference: JCS-5-58

(*R*)-Methyl 1-(2,2-dimethylpropanethioyl)pyrrolidine-2-carboxylate (*R*)-17



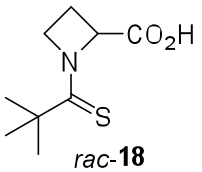
(*R*)-**17**

(Scheme 3)

Using general procedure B, *s*-BuLi (0.46 mL of a 1.3 M solution in hexanes, 0.60 mmol, 1.2 eq), *N*-thiopivaloyl pyrrolidine **9** (0.084 mL, 86 mg, 0.5 mmol, 1.0 eq), (–)-sparteine **3** (0.14 mL, 141 mg, 0.6 mmol, 1.2 eq) in Et_2O (5 mL) and methyl chloroformate (0.06 mL, 71 mg, 0.75 mmol, 1.5 eq) gave the crude product. Purification by flash column chromatography on silica with 8:2 hexane-EtOAc as eluent gave (*R*)-**17** (67 mg, 0.29 mmol, 58%, 76:24 er by CSP-HPLC) as a pale yellow oil, ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.11 (dd, J = 8.5, 5.0 Hz, CHN), 4.04–3.90 (m, 2H, CH_2N), 3.71 (s, 3H, CO_2Me), 2.30–2.10 (m, 2H, CH_2), 2.07–1.90 (m, 2H, CH_2), 1.42 (s, 9H, CMe_3); ^{13}C NMR δ 211.6 (C=S), 171.5 (*C*O_2Me), 68.6 (CHN), 53.4 (CH_2N), 52.3 (CO_2*Me*), 43.8 (*C*Me_3), 30.4 (C*Me*$_3$), 28.0 (CH_2), 26.1 (CH_2); $[\alpha]_D$ +25.3 (*c* 1.08 in EtOAc); CSP-HPLC: Chiralcel OD-H (98:2 Hexane-*i*PrOH, 1.0 mL min^{-1}) (*S*)-**17** 10.6 min, (*R*)-**17** 11.8 min.

Lab Book Reference: JCS-5-59

***rac*-1-(2,2-Dimethylpropanethioyl)azetidine-2-carboxylic acid *rac*-18**



rac-**18**

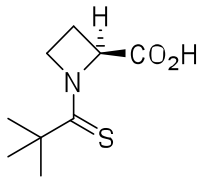
(Racemic standard for Scheme 3)

s-BuLi (0.50 mL of a 1.3 M solution in hexanes, 0.65 mmol, 1.3 eq) was added to a stirred solution of *N*-thiopivaloyl azetidine **1** (0.077 mL, 79 mg, 0.5 mmol, 1.0 eq) and TMEDA (145 mg, 0.2 mL, 1.3 mmol, 2.6 eq) in Et_2O (7 mL) at –100 °C under N_2. The resulting solution was stirred at –100 °C for 2 min. Then, dry CO_2 (generated from solid CO_2 flushed through $CaCl_2$ and added into the reaction *via* cannula) was bubbled through the reaction mixture for 10 min at –100 °C and then allowed to warm to rt over 1 h. The reaction mixture was diluted with Et_2O (10 mL) and extracted with water (6 x 5 mL). The aqueous layer was acidified to pH < 2 with 2 M $HCl_{(aq)}$ and extracted with CH_2Cl_2 (6 x 5 mL). The combined organic extracts were dried ($MgSO_4$) and

evaporated under reduced pressure to give acid *rac*-**18** (47 mg, 0.23 mmol, 46%) as an off-white solid, IR (ATR) 2968, 2924, 2867, 2638 (CO_2H), 2554 (CO_2H), 1705 (C=O), 1455, 1421, 1397, 1365, 1339, 1294, 1254, 1223, 1198, 1164, 1045, 1031, 1005, 931, 825, 780, 721, 680, 655, 563, 537, 528 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.07 (dd, J = 9.0, 5.0 Hz, 1H, CHN), 4.62 (ddd, J = 9.5, 9.5, 9.5 Hz, 1H, CH_AH_BN), 4.49 (ddd, J = 9.5, 9.5, 5.5 Hz, 1H, CH_AH_BN), 2.64-2.53 (m, 1H, CH_AH_B), 2.46-2.35 (m, 1H, CH_AH_B), 1.34 (s, 9H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 212.0 (C=S), 173.8 (CO_2H), 66.5 (CHN), 56.5 (CH_2N), 43.3 (CMe_3), 29.6 (CMe_3), 19.0 (CH_2); MS (ESI) material degraded during analysis.

Lab Book Reference JCS-2-5

(*S*)-1-(2,2-Dimethylpropanethioyl)azetidine-2-carboxylic acid (*S*)–18

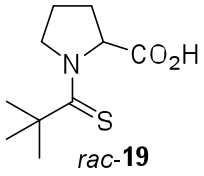


(*S*)-**18**

(Scheme 3)

s-BuLi (0.46 mL of a 1.3 M solution in hexanes, 0.6 mmol, 1.2 eq) was added to a stirred solution of *N*-thiopivaloyl azetidine **1** (0.077 mL, 79 mg, 0.5 mmol, 1.0 eq) and (–)-sparteine **3** (0.14 mL, 141 mg, 0.6 mmol, 1.2 eq) in Et_2O (5 mL) at –78 °C under N_2. The resulting solution was stirred at –78 °C for 30 min. Then, dry CO_2 (generated from solid CO_2 flushed through $CaCl_2$ and added into the reaction *via* cannula) was bubbled through the reaction mixture for 10 min at –78 °C and then allowed to warm to rt over 1 h. The reaction mixture was diluted with Et_2O (10 mL) and extracted with water (6 x 5 mL). The aqueous layer was acidified to pH < 2 with 2 M $HCl_{(aq)}$ and extracted with CH_2Cl_2 (6 x 5 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give acid (*S*)-**18** (97 mg, 0.48 mmol, 96%, 75:25 er by CSP-HPLC of the methyl ester) as an off white solid, mp 126–139 °C; $[\alpha]_D$ –62.2 (*c* 0.93 in EtOAc). Acid (*S*)-**18** was converted into methyl ester (*S*)-**16** by reaction with Me_3SiCHN_2 in MeOH/toluene (4:6 v/v, 2 mL), quenching with glacial AcOH and evaporation under reduced pressure. CSP-HPLC of methyl ester (*S*)-**16**: Chiralcel OD-H (98:2 Hexane-*i*PrOH, 1.0 mL min^{-1}) (*S*)-**16** 14.3 min, (*R*)-**16** 18.2 min.

Rac-1-(2,2-dimethylpropanethioyl)pyrrolidine-2-carboxylic acid _rac_-19

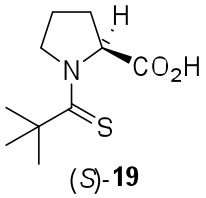


rac-**19**

(Racemic standard for Scheme 3)

_s_-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol, 1.3 eq) was added to a stirred solution of _N_-thiopivaloyl azetidine **9** (0.16 mL, 171 mg, 1.0 mmol, 1.0 eq) and TMEDA (0.20 mL, 155 mg, 1.3 mmol, 1.3 eq) in Et_2O (10 mL) at –78 °C under N_2. The resulting solution was stirred at –78 °C for 30 min. Then, dry CO_2 (generated from solid CO_2 flushed through $CaCl_2$ and added into the reaction *via* cannula) was bubbled through the reaction mixture for 10 min at –78 °C and then allowed to warm to rt over 1 h. The reaction mixture was diluted with Et_2O (10 mL) and extracted with water (6 x 5 mL). The aqueous layer was acidified to pH < 2 with 2 M $HCl_{(aq)}$ and extracted with CH_2Cl_2 (6 x 5 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give acid _rac_-**19** (184 mg, 0.86 mmol, 86%) as an off-white solid, IR (ATR) 2978, 2869 (CO_2H), 2646 (CO_2H), 2553 (CO_2H), 1703 (C=O), 1474, 1416, 1368, 1336, 1297, 1272, 1225, 1173, 1152, 1090, 1058, 1021, 929, 915, 871, 804, 692, 61, 597, 502 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.25-5.13 (m, 1H, CHN), 4.06-3.98 (m, 1H, CH_AH_BN), 3.96-3.88 (m, 1H, CH_AH_BN), 2.31-1.99 (m, 4H, CH_2CH_2), 1.43 (s, 9H, CMe_3); ^{13}C NMR (100 MHz, $CDCl_3$) 211.8 (C=S), 175.2 (CO_2H), 66.6 (CHN), 53.3 (CH_2N), 43.9 (CMe_3), 30.5 (CMe_3), 27.9 (CH_2), 26.1 (CH_2); MS (ESI) _m/z_ 216 [$(M + H)^+$, 55], 238 [$(M + Na)^+$, 100]; HRMS _m/z_ calcd for $C_{10}H_{17}NO_2S$ $(M + Na)^+$ 238.0872, found 238.0878 (–2.2 ppm error).

(_S_)-1-(2,2-Dimethylpropanethioyl)pyrrolidine-2-carboxylic acid (_S_)-19



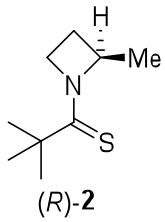
(_S_)-**19**

(Scheme 3)

_s_-BuLi (0.46 mL of a 1.3 M solution in hexanes, 0.6 mmol, 1.2 eq) was added to a stirred solution of _N_-thiopivaloyl azetidine **9** (0.08 mL, 86 mg, 0.5 mmol, 1.0 eq) and (–)-sparteine **3** (0.14 mL, 141 mg, 0.6 mmol, 1.2 eq) in Et_2O (5 mL) at –78 °C under N_2. The resulting solution

was stirred at –78 °C for 1 h. Then, dry CO_2 (generated from solid CO_2 flushed through $CaCl_2$ and added into the reaction *via* cannula) was bubbled through the reaction mixture for 10 min at –78 °C and then allowed to warm to rt over 1 h. The reaction mixture was diluted with Et_2O (10 mL) and extracted with water (6 x 5 mL). The aqueous layer was acidified to pH < 2 with 2 M $HCl_{(aq)}$ and extracted with CH_2Cl_2 (6 x 5 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give acid (*S*)-**19** (79 mg, 0.37 mmol, 74%, 80:20 er by CSP-HPLC of the methyl ester) as an off white solid. Acid (*S*)-**19** was converted into methyl ester (*S*)-**17** by reaction with Me_3SiCHN_2 in MeOH/toluene (4:6 v/v, 2 mL), quenching with glacial AcOH and evaporation under reduced pressure. CSP-HPLC of the methyl ester: Chiralcel OD-H (98:2 Hexane-*i*PrOH, 1.0 mL min^{-1}) (*S*)-**17** 11.6 min, (*R*)-**17** 12.9 min.

(*R*)-2,2-Dimethyl-1-(2-methylazetidin-1-yl)propane-1-thione (*R*)-2



(*R*)-**2**

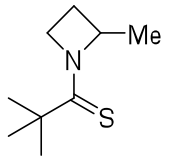
(Scheme 3)

Using general procedure A, *s*-BuLi (0.46 mL of a 1.3 M solution in hexanes, 0.60 mmol, 1.2 eq.), *N*-thiopivaloyl azetidine **1** (79 mg, 0.50 mmol, 1.0 eq.) and (−)-sparteine **3** (0.14 mL, 0.60 mmol, 1.2 eq.) in Et_2O (5 mL) and methyl iodide (47 μL, 0.75 mmol, 1.5 eq.) gave the crude product. Purification by flash column chromatography on silica with 9:1-8:2 petrol-Et_2O as eluent gave methylated azetidine (*R*)-**3** (79 mg, 91%, 59:41 er by CSP-HPLC) as a colourless oil, R_F (8:2 petrol-Et_2O) 0.3; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.91-4.82 (m, 1H, NCH), 4.57 (dddd, J = 10.5, 9.0, 7.0, 1.5 Hz, 1H, NCH_AH$_B$), 4.43 (dddd, J = 10.5, 10.0, 5.0, Hz, 1H, NCH$_A$$H_B$), 2.54 (dddd, J = 11.0, 10.0, 9.0, 7.0 Hz, 1H, CH_AH$_B$), 1.85 (dddd, J = 11.0, 9.5, 5.0, 5.0 Hz, 1H, NCH$_A$$H_B$), 1.62 (d, J = 6.0 Hz, 3H, Me), 1.34 (s, 9H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) rotamers δ 209.6 (C=S), 65.7 (NCH), 64.8 (NCH), 55.6 (NCH_2), 53.7 (NCH_2), 43.3 (*C*Me$_3$), 30.9 (C*Me*$_3$), 29.6 (C*Me*$_3$), 23.1 (CH_2), 18.5 (Me); $[\alpha]_D$ +0.2 (*c* 1.0 in $CHCl_3$) (lit.,[3] $[\alpha]_D$ −21.3 (*c* 1.15 in $CHCl_3$ for (*R*)-**2** of 99:1 er)); CSP-HPLC: Chiracel OD-H (99.9:0.1 Hexane-*i*PrOH, 1.0 mL min^{-1}) (*S*)-**2** 11.1 min, (*R*)-**2** 11.9 min. Spectroscopic data consistent with those reported in the literature.[3]

Note: Optical rotation data is not consistent with that reported in the literature[3] and the configuration was assigned by CSP-HPLC (see Section 2).

Lab Book Reference PJR 8/649

***rac*-2,2-Dimethyl-1-(2-methylazetidin-1-yl)propane-1-thione *rac*-2**



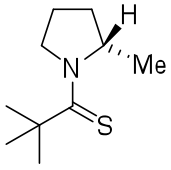
rac-**2**

(Racemic standard for Scheme 3)

Using general procedure A, *s*-BuLi (0.46 mL of a 1.3M solution in hexanes, 0.60 mmol, 1.2 eq.), *N*-thiopivaloyl azetidine **1** (79 mg, 0.50 mmol, 1.0 eq.) and TMEDA (90 μL, 0.60 mmol, 1.2 eq.) in Et_2O (5 mL) and methyl iodide (47 μL, 0.75 mmol, 1.5 eq.) gave the crude product. Purification by flash column chromatography on silica with 9:1-8:2 petrol-Et_2O gave methylated azetidine *rac*-**2** (58 mg, 67%) as a colourless oil.

Lab Book Reference PJR 8/642

(*S*)-2,2-Dimethyl-1-(2-methylpyrrolidin-1-yl)propane-1-thione (*S*)-20



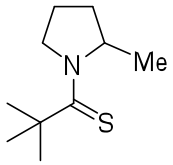
(*S*)-**20**

(Scheme 3)

Using general procedure B, *s*-BuLi (0.50 mL of a 1.3 M solution in hexanes, 0.65 mmol, 1.3 eq.), *N*-thiopivaloyl pyrrolidine **9** (86 mg, 0.50 mmol, 1.0 eq.) and (−)-sparteine **3** (0.15 mL, 0.65 mmol, 1.3 eq.) in Et_2O (5 mL) and methyl iodide (47 μL, 0.75 mmol, 1.5 eq.) gave the crude product. Purification by flash column chromatography on silica with 9:1-8:2 petrol-Et_2O as eluent gave methylated pyrrolidine (*S*)-**20** (78 mg, 84%, 58:42 er by CSP-HPLC) as a colourless oil, R_F (8:2 petrol-Et_2O) 0.3; IR (film) 2975, 2876, 1530, 1458, 1410, 1325, 1116, 730 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 85:15 mixture of rotamers δ 5.15-5.07 (m, 0.85H, NCH), 4.84-4.78 (m, 0.15H, NCH), 4.21 (ddd, J = 14.5, 8.5, 8.5 Hz, 0.15H, NCH_AH_B), 4.00 (ddd, J = 13.5, 12.0, 7.0

Hz, 0.85H, NCH_AH_B), 3.83-3.76 (m, 0.15H, NCH$_A$$H_B$), 3.67 (ddd, J = 13.5, , 6.5, 6.5 Hz, 0.85H, NCH$_A$$H_B$), 2.13-1.86 (m, 3H, CH), 1.66-1.59 (m, 1H, CH), 1.43 (s, 1.35H, CMe_3), 1.39 (s, 7.65H, CMe_3), 1.33 (d, J = 6.5 Hz, 2.55H, Me), 1.24 (d, J = 6.0 Hz, 0.45H, Me); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 208.8 (C=S), 61.8 (NCH), 52.0 (NCH_2), 44.0 (CMe_3), 30.6 (CMe_3), 30.4 (CH_2), 24.9 (CH_2), 17.7 (Me); MS (ESI) *m/z* 208 [$(M + Na)^+$, 100], 186 [$(M + H)^+$, 20]; HRMS *m/z* calcd for $C_{10}H_{19}NS$ $(M + Na)^+$ 208.1136, found 208.1131 (−0.5 ppm error); $[\alpha]_D$ −10.1 (*c* 0.95 in $CHCl_3$); CSP-HPLC: Chiracel OD-H (99.5:0.5 Hexane-*i*PrOH, 1.0 mL min^{-1}) (*S*)-**20** 8.0 min, (*R*)-**20** 9.0 min. Lab Book Reference PJR 8/650

***rac*-2,2-Dimethyl-1-(2-methylpyrrolidin-1-yl)propane-1-thione *rac*-20**



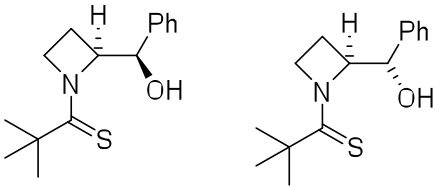
rac-**20**

(Racemic standard for Scheme 3)

Using general procedure B, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol, 1.3 eq.), *N*-thiopivaloyl pyrrolidine **9** (171 mg, 1.0 mmol, 1.0 eq.) and TMEDA (0.195 mL, 1.3 mmol, 1.3 eq.) in Et_2O (5 mL) and methyl iodide (374 μL, 6.0 mmol, 4.6 eq.) gave the crude product. Purification by flash column chromatography on silica with 95:5 petrol-EtOAc as eluent gave methylated pyrrolidine *rac*-**20** (425 mg, 77%) as a yellow oil.

Lab Book Reference JCS 2-33

1-[(2*S*)-2-[(*R*)-Hydroxy(phenyl)methyl]azetidin-1-yl]-2,2-dimethylpropane-1-thione (*R*,*S*)-13 and 1-[(2*S*)-2-[(*S*)-hydroxy(phenyl)methyl]azetidin-1-yl]-2,2-dimethylpropane-1-thione (*S*,*S*)-12



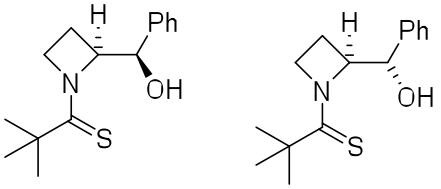
(*R*,*S*)-**13** (*S*,*S*)-**12**

(Scheme 4)

Using general procedure A, *s*-BuLi (0.46 mL of a 1.3 M solution in hexanes, 0.6 mmol, 1.2 eq.), *N*-thiopivaloyl azetidine **1** (79 mg, 0.5 mmol, 1.0 eq.), (+)-sparteine surrogate **21** (116 mg, 0.6 mmol, 1.2 eq.) in Et_2O (5 mL) and benzaldehyde (76 μL, 0.75 mmol, 1.5 eq.) gave the crude product which contained an 86:14 mixture of alcohols (*S,S*)-**12** and (*R,S*)-**13** by ^1H NMR spectroscopy. Purification by flash column chromatography on silica with 9:1-8:2 petrol-EtOAc as eluent gave alcohol (*R,S*)-**13** (9 mg, 7%, 54:46 er by CSP-HPLC) as a white solid, CSP-HPLC: Chiracel AD-H (95:5 Hexane-*i*PrOH, 1.0 mL min^{-1}) (*S*,*R*)-**13** 7.5 min, (*R*,*S*)-**13** 10.2 min and alcohol (*R,R*)-**12** (91 mg, 70%, 54:46 er by CSP-HPLC) as a white solid, CSP-HPLC: Chiracel AD-H (95:5 Hexane-*i*PrOH, 1.0 mL min^{-1}) (*R*,*R*)-**12** 18.2 min, (*S*,*S*)-**12** 20.4 min.

Lab Book Reference PJR 8/660

1-[(2*S*)-2-[(*R*)-Hydroxy(phenyl)methyl]azetidin-1-yl]-2,2-dimethylpropane-1-thione (*R*,*S*)-13 and 1-[(2*S*)-2-[(*S*)-hydroxy(phenyl)methyl]azetidin-1-yl]-2,2-dimethylpropane-1-thione (*S*,*S*)-12



(*R*,*S*)-**13** (*S*,*S*)-**12**

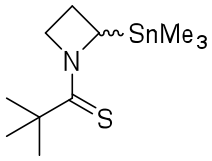
(Scheme 4)

Using general procedure A, *s*-BuLi (0.46 mL of a 1.3 M solution in hexanes, 0.6 mmol, 1.2 eq.), *N*-thiopivaloyl azetidine **1** (79 mg, 0.5 mmol, 1.0 eq.), diamine (*S*,*S*)-**4** (186 mg, 0.6 mmol, 1.2 eq.) in Et_2O (5 mL) and benzaldehyde (76 μL, 0.75 mmol, 1.5 eq.) gave the crude product which

contained a 77:23 mixture of alcohols (*S,S*)-**12** and (*R,S*)-**13** by ^{1}H NMR spectroscopy. Purification by flash column chromatography on silica with 9:1-8:2 petrol-EtOAc as eluent gave alcohol (*R,S*)-**13** (26 mg, 20%, 65:35 er by CSP-HPLC) as a white solid, CSP-HPLC: Chiracel AD-H (95:5 Hexane-*i*PrOH, 1.0 mL min^{-1}) (*S,R*)-**13** 7.5 min, (*R,S*)-**13** 10.2 min and alcohol (*R,R*)-**12** (96 mg, 73%, 53:47 er by CSP-HPLC) as a white solid, CSP-HPLC: Chiracel AD-H (95:5 Hexane-*i*PrOH, 1.0 mL min^{-1}) (*R,R*)-**12** 18.7 min, (*S,S*)-**12** 20.9 min.

Lab Book Reference PJR 8/681

2,2-Dimethyl-1-(2-(trimethylstannyl)azetidin1-yl)propane-1-thione 22

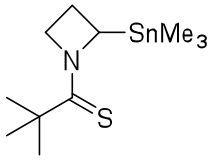


22

Using general procedure A, *s*-BuLi (1.38 mL of a 1.3 M solution in hexanes, 1.8 mmol, 1.2 eq.), *N*-thiopivaloyl azetidine **1** (236 mg, 1.5 mmol, 1.0 eq.) and (−)-sparteine **3** (0.41 mL, 1.8 mmol, 1.2 eq.) in Et_2O (8 mL) and Me_3SnCl (2.25 mL of a 1.0 M solution in hexane, 2.25 mmol, 1.5 eq.) gave the crude product. Purification by flash column chromatography on silica with 95:5-9:1 petrol-Et_2O as eluent gave stannane (*S*)-**22** (263 mg, 55%, 68:32 er by CSP-HPLC) as a colourless oil, R_F (9:1 petrol-Et_2O) 0.3; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.65-4.47 (m, 3H, NCH), 2.57-2.48 (m, 1H, CH), 2.26-2.18 (m, 1H, CH), 1.33 (s, 9H, CMe_3), 0.15 (s, 9H, $SnMe_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 202.4 (C=S), 61.6 (NCH), 56.8 (NCH_2), 42.4 (*C*Me_3), 29.9 (C*Me*$_3$), 18.3 (CH_2), −7.7 (Sn*Me*$_3$); CSP-HPLC: Chiracel OD-H (99.5:0.5 Hexane-*i*PrOH, 1.0 mL min^{-1}) 5.4 min (major), 8.1 min (minor). Spectroscopic data consistent with those reported in the literature.[3]

Lab Book Reference PJR 8/620, 8/637, 8/629

2,2-Dimethyl-1-(2-(trimethylstannyl)azetidin1-yl)propane-1-thione *rac*-22

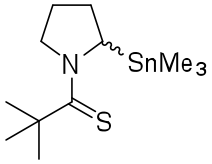


rac-**22**

Using general procedure A, *s*-BuLi (1.38 mL of a 1.3 M solution in hexanes, 1.8 mmol, 1.2 eq.), *N*-thiopivaloyl azetidine **1** (236 mg, 1.5 mmol, 1.0 eq.) and TMEDA (0.27 mL, 1.8 mmol, 1.2 eq.) in Et_2O (8 mL) and Me_3SnCl (2.25 mL of a 1.0 M solution in hexane, 2.25 mmol, 1.5 eq.) gave the crude product. Purification by flash column chromatography on silica with 95:5-9:1 petrol-Et_2O as eluent gave stannane *rac*-**22** (284 mg, 60%) as a colourless oil.

Lab Book Reference PJR 8/680

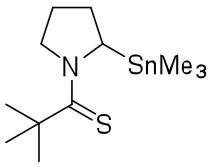
(*S*)-2,2-Dimethyl-1-(2-(trimethylstannyl)pyrrolidin-1-yl)propane-1-thione 23



23

Using general procedure B, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.30 mmol, 1.3 eq.), *N*-thiopivaloyl pyrrolidine **9** (171 mg, 1.00 mmol, 1.0 eq.) and (−)-sparteine **3** (296 μL, 1.30 mmol, 1.3 eq.) in Et_2O (7 mL) and trimethyltin chloride (1.50 mL of a 1.0 M solution in hexanes, 1.5 mmol, 1.5 eq.) gave the crude product. Purification by flash column chromatography on silica with 95:5 petrol-EtOAc as eluent gave stannane **23** (228 mg, 68%, 78:22 er by CSP-HPLC) as a colourless oil, R_F (95:5 petrol-EtOAc) 0.3; IR (film) 2978, 1500, 1482, 1448, 1390, 1370, 1246, 1074, 1036, 912, 809, 730 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.37-4.28 (m, 1H, NCH), 3.91-3.78 (m, 2H, NCH_2), 2.20-2.09 (m, 2H, CH_2), 2.07-2.01 (m, 1H, CH), 1.98-1.88 (m, 1H, CH), 1.40 (s, 9H, CMe_3), 0.07 (s, 9H, $SnMe_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 201.0 (C=S), 63.7 (NCH), 53.1 (NCH_2), 43.1 (CMe_3), 30.7 (CMe_3), 28.2 (CH_2), 27.6 (CH_2), −6.7 ($SnMe_3$); MS (ESI) *m/z* 336 [(M(^{120}Sn) + H)$^+$, 100], 334 [(M(^{118}Sn) + H)$^+$, 70], 332 [(M(^{116}Sn) + H)$^+$, 30]; HRMS *m/z* calcd for $C_{12}H_{25}NS^{120}Sn$ $(M + Na)^+$ 336.0803 (−1.0 ppm error), found 336.0806; $[\alpha]_D$ +290.89 (*c* 0.70 in $CHCl_3$); CSP-HPLC: Chiracel OD-H (99.5:0.5 Hexane-*i*PrOH, 1.0 mL min^{-1}) (*S*)-**18** 4.9 min, (*R*)-**18** 6.4 min. Lab Book Reference: PJR 8/630A

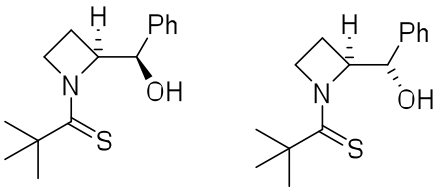
rac-2,2-Dimethyl-1-(2-(trimethylstannyl)pyrrolidin-1-yl)propane-1-thione _rac_-23



rac-**23**

Using general procedure B, *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.30 mmol, 1.3 eq.), *N*-thiopivaloyl pyrrolidine **9** (171 mg, 1.00 mmol, 1.0 eq.) and TMEDA (194 μL, 1.30 mmol, 1.3 eq.) in Et_2O (7 mL) and trimethyltin chloride (1.50 mL of a 1.0 M solution in hexanes, 1.5 mmol, 1.5 eq.) gave the crude product. Purification by flash column chromatography on silica with 95:5 petrol-EtOAc as eluent gave stannane _rac_-**23** (254 mg, 76%) as a colourless oil.
Lab Book Reference PJR 8/699

1-[2-[Hydroxy(phenyl)methyl]azetidin-1-yl]-2,2-dimethylpropane-1-thione _rac_-13 and 1-[(2-[hydroxy(phenyl)methyl]azetidin-1-yl]-2,2-dimethylpropane-1-thione _rac_-12



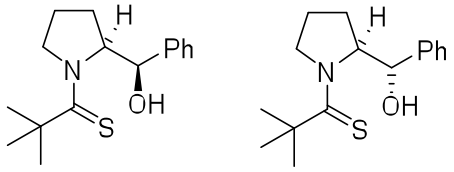
rac-**13** _rac_-**12**

(Scheme 5)
n-BuLi (0.06 mL of a 2.5 M solution in hexanes, 0.14 mmol, 1.1 eq.) was added dropwise to a stirred solution of enantioenriched stannane **22** (43 mg, 0.13 mmol, 1.0 eq., 68:32 er) in THF (5 mL) at −78 °C under Ar. The resulting solution was stirred at −78 °C for 5 min. Then, benzaldehyde (16 μL, 0.16 mmol, 1.2 eq.) was added dropwise. The resulting solution was stirred at −78 °C for 10 min and 1 M $HCl_{(aq)}$ (10 mL) was added. The two layers were separated and the aqueous layer was extracted with Et_2O (3 x 10 mL) and the combined layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product which contained a 75:25 mixture of alcohols _rac_-**12** and _rac_-**13** by ^1H NMR spectroscopy. Purification by flash column chromatography on silica with 9:1-8:2 petrol-EtOAc as eluent gave alcohol _rac_-**13** (9 mg, 26%, 50:50 er by CSP-HPLC) as a white solid, CSP-HPLC: Chiracel AD-H (95:5 Hexane-*i*PrOH, 1.0 mL min^{-1}) (*S*,*R*)-**13** 7.3 min, (*R*,*S*)-**13** 9.8 min and alcohol _rac_-**12** (20 mg, 58%, 50:50

er by CSP-HPLC) as a white solid, CSP-HPLC: Chiracel AD-H (95:5 Hexane-*i*PrOH, 1.0 mL min^{-1}) (*R*,*R*)-**12** 18.0 min, (*S*,*S*)-**12** 20.3 min.
Lab Book Reference PJR 8/628

(Scheme 5)
n-BuLi (0.06 mL of a 2.5 M solution in hexanes, 0.14 mmol, 1.1 eq.) was added dropwise to a stirred solution of enantioenriched stannane **22** (43 mg, 0.13 mmol, 1.0 eq., 68:32 er) and TMEDA (21 μL, 0.14 mmol, 1.1 eq.) in Et_2O (5 mL) at −78 °C under Ar. The resulting solution was stirred at −78 °C for 5 min. Then, benzaldehyde (16 μL, 0.16 mmol, 1.2 eq.) was added dropwise. The resulting solution was stirred at −78 °C for 10 min and 1 M $HCl_{(aq)}$ (10 mL) was added. The two layers were separated and the aqueous layer was extracted with Et_2O (3 x 10 mL). The combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product which contained a 76:24 mixture of alcohols *rac*-**12** and *rac*-**13** by ^1H NMR spectroscopy. Purification by flash column chromatography on silica with 9:1-8:2 petrol-EtOAc as eluent gave alcohol *rac*-**13** (8 mg, 24%, 50:50 er by CSP-HPLC) as a white solid CSP-HPLC: Chiracel AD-H (95:5 Hexane-*i*PrOH, 1.0 mL min^{-1}) (*S*,*R*)-**13** 7.4 min, (*R*,*S*)-**13** 10.1 min and alcohol *rac*-**12** (21 mg, 61%, 50:50 er by CSP-HPLC) as a white solid, CSP-HPLC: Chiracel AD-H (95:5 Hexane-*i*PrOH, 1.0 mL min^{-1}) (*R*,*R*)-**12** 18.5 min, (*S*,*S*)-**12** 20.4 min.
Lab Book Reference PJR 8/629

1-(2-(Hydroxy(phenyl)methyl)pyrrolidin-1-yl)-2,2-dimethylpropane-1-thione *rac*-15 and 1-(2-(hydroxy(phenyl)methyl)pyrrolidin-1-yl)-2,2-dimethylpropane-1-thione *rac*-14



rac-**15** *rac*-**14**

(Scheme 5)
n-BuLi (26 μL of a 2.5 M solution in hexanes, 0.066 mmol, 1.1 eq.) was added to a stirred solution of enantioenriched stannane **23** (20 mg, 0.06 mmol, 1.0 eq., 78:22 er) in THF (5 mL) at −78 °C under Ar. The resulting solution was stirred at −78 °C for 5 min. Then, benzaldehyde (7 μL, 0.07 mmol, 1.2 eq.) was added dropwise. The resulting solution was stirred at −78 °C for 10

min and 1 M $HCl_{(aq)}$ (10 mL) was added. The two layers were separated and the aqueous layer was extracted with Et_2O (3 x 10 mL). The combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product which contained a 60:40 mixture of alcohols *rac*-**14** and *rac*-**15** by ^1H NMR spectroscopy. Purification by flash column chromatography on silica with 9:1-8:2 petrol-EtOAc as eluent gave alcohol *rac*-**15** (7 mg, 42%, 51:49 er by CSP-HPLC) as a white solid, CSP-HPLC: Chiracel AD (95:5 Hexane-*i*PrOH, 1.0 mL min^{-1}) (*S*,*R*)-**15** 11.2 min, (*R*,*S*)-**15** 14.6 min and alcohol *rac*-**14** (9 mg, 52%, 51:49 er by CSP-HPLC) as a white solid, CSP-HPLC: Chiracel AD (90:10 Hexane-*i*PrOH, 1.0 mL min^{-1}) (*R*,*R*)-**14** 10.6 min, (*S*,*S*)-**14** 23.1 min.

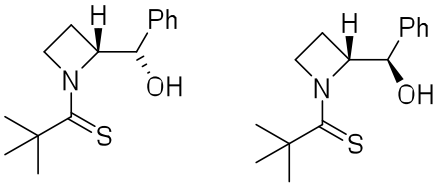
Lab Book Reference PJR 8/634

(Scheme 5)

n-BuLi (26 μL of a 2.5M solution in hexanes, 0.066 mmol, 1.1 eq.) was added to a stirred solution of enantioenriched stannane **23** (20 mg, 0.06 mmol, 1.0 eq., 78:22 er) and TMEDA (10 μL, 0.066 mmol, 1.1 eq.) in Et_2O (5 mL) at −78 °C under Ar. The resulting solution was stirred at −78 °C for 5 min. Then, benzaldehyde (7 μL, 0.07 mmol, 1.2 eq.) was added dropwise. The resulting solution was stirred at −78 °C for 10 min and 1 M $HCl_{(aq)}$ (10 mL) was added. The two layers were separated and the aqueous layer was extracted with Et_2O (3 x 10 mL). The combined layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product which contained a 76:24 mixture of alcohols *rac*-**14** and *rac*-**15** by ^1H NMR spectroscopy. Purification by flash column chromatography on silica with 9:1-8:2 petrol-EtOAc as eluent gave alcohol *rac*-**15** (8 mg, 24%, 50:50 er by CSP-HPLC) as a white solid, CSP-HPLC: Chiracel AD (95:5 Hexane-*i*PrOH, 1.0 mL min^{-1}) (*S*,*R*)-**15** 11.3 min, (*R*,*S*)-**15** 14.7 min and alcohol *rac*-**14** (21 mg, 61%, 50:50 er by CSP-HPLC) as a white solid, CSP-HPLC: Chiracel AD (90:10 Hexane-*i*PrOH, 1.0 mL min^{-1}) (*R*,*R*)-**14** 10.6 min, (*S*,*S*)-**14** 23.0 min.

Lab Book Reference PJR 8/635

1-[(2*R*)-2-[(*S*)-Hydroxy(phenyl)methyl]azetidin-1-yl]-2,2-dimethylpropane-1-thione (*S*,*R*)-13 and 1-[(2*R*)-2-[(*R*)-hydroxy(phenyl)methyl]azetidin-1-yl]-2,2-dimethylpropane-1-thione (*R*,*R*)-12



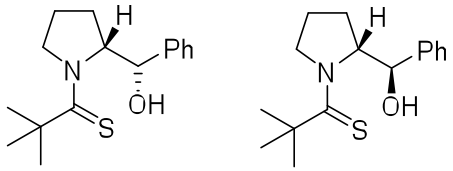
(*S*,*R*)-**13** (*R*,*R*)-**12**

(Scheme 6)

A solution of stannane *rac*-**22** (50 mg, 0.16 mmol, 1.0 eq.) in Et_2O (3 mL) was added dropwise to a stirred solution of *n*-BuLi (0.07 mL of a 2.5 M solution in hexanes, 0.18 mmol, 1.1 eq.) and (−)-sparteine **3** (42 μL, 0.18 mmol, 1.1 eq.) in Et_2O (2 mL) at −78 °C under Ar. The resulting solution was stirred at −78 °C for 5 min. Then, benzaldehyde (19 μL, 0.19 mmol, 1.2 eq.) was added dropwise. The resulting solution was stirred at −78 °C for 10 min and 1 M $HCl_{(aq)}$ (10 mL) was added. The two layers were separated and the aqueous layer was extracted with Et_2O (3 x 10 mL). The combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product which contained an 87:13 mixture of alcohols (*R,R*)-**12** and (*S,R*)-**13** by ^{1}H NMR spectroscopy. Purification by flash column chromatography on silica with 9:1-8:2 petrol-EtOAc as eluent gave alcohol (*S,R*)-**13** (4 mg, 10%, 62:38 er by CSP-HPLC) as a white solid, CSP-HPLC: Chiracel AD-H (95:5 Hexane-*i*PrOH, 1.0 mL min^{-1}) (*S*,*R*)-**13** 7.6 min, (*R*,*S*)-**13** 10.3 min and alcohol (*R,R*)-**12** (37 mg, 88%, 73:27 er by CSP-HPLC) as a white solid, CSP-HPLC: Chiracel AD-H (95:5 Hexane-*i*PrOH, 1.0 mL min^{-1}) (*R*,*R*)-**12** 18.7 min, (*S*,*S*)-**12** 20.8 min.

Lab Book Reference PJR 8/685

1-((*R*)-2-((*S*)-Hydroxy(phenyl)methyl)pyrrolidin-1-yl)-2,2-dimethylpropane-1-thione (*S*,*R*)-15 and 1-((*R*)-2-((*R*)-hydroxy(phenyl)methyl)pyrrolidin-1-yl)-2,2-dimethylpropane-1-thione (*R*,*R*)-14



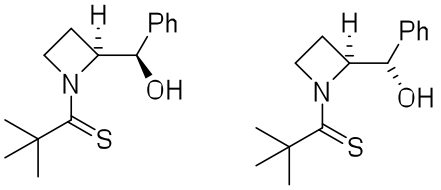
(*S*,*R*)-**15** (*R*,*R*)-**14**

(Scheme 6)

A solution of stannane *rac*-**23** (100 mg, 0.30 mmol, 1.0 eq.) in Et_2O (3 mL) was added to a stirred solution of *n*-BuLi (0.13 mL of a 2.5 M solution in hexane, 0.33 mmol, 1.1 eq.) and (−)-sparteine **3** (77 μL, 0.33 mmol, 1.1 eq.) in Et_2O (2 mL) at −78 °C under Ar. The resulting solution was stirred at −78 °C for 5 min. Then, benzaldehyde (46 μL, 0.45 mmol, 1.5 eq.) was added dropwise. The resulting solution was stirred at −78 °C for 1 h and 1 M $HCl_{(aq)}$ (10 mL) was added. The two layers were separated and the aqueous layer was extracted with Et_2O (3 x 10 mL). The combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product which contained a 55:45 mixture of diastereomeric alcohols (*S*,*R*)-**15** and (*R*,*R*)-**14** by ^1H NMR spectroscopy. Purification by flash column chromatography on silica with 8:2-7:3 petrol-Et_2O as eluent gave alcohol (*S*,*R*)-**15** (32 mg, 39%, 88:12 er by CSP-HPLC) as a white solid, CSP-HPLC: Chiracel AD (95:5 Hexane-*i*PrOH, 1.0 mL min^{-1}) (*S*,*R*)-**15** 11.7 min, (*R*,*S*)-**15** 15.2 min and alcohol (*R*,*R*)-**14** (29 mg, 35%, 82:18 er by CSP-HPLC) as a colourless oil, CSP-HPLC: Chiracel AD (90:10 Hexane-*i*PrOH, 1.0 mL min^{-1}) (*R*,*R*)-**14** 9.8 min, (*S*,*S*)-**14** 18.8 min.

Lab Book Reference PJR 8/700

1-[2-[Hydroxy(phenyl)methyl]azetidin-1-yl]-2,2-dimethylpropane-1-thione *rac*-13 and 1-[(2-[hydroxy(phenyl)methyl]azetidin-1-yl]-2,2-dimethylpropane-1-thione *rac*-12



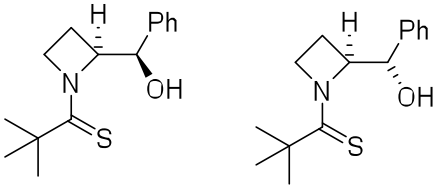
rac-**13** *rac*-**12**

(Control experiment for Scheme 7 – see footnote 20 in main paper)

s-BuLi (0.23 mL of a 1.3 M solution in hexanes, 0.3 mmol, 1.2 eq.) was added dropwise to a stirred solution of *N*-thiopivaloyl azetidine **1** (40 mg, 0.25 mmol, 1.0 eq.) in Et_2O (5 mL) at −40 °C under Ar. The resulting solution was stirred at −40 °C for 30 min. Then, benzaldehyde (38 μL, 0.38 mmol, 1.5 eq.) was added dropwise. The resulting solution was stirred at −40 °C for 10 min and 1 M $HCl_{(aq)}$ (10 mL) was added. The two layers were separated and the aqueous layer was extracted with Et_2O (3 x 10 mL). The combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product which contained a 62:38 mixture of alcohols *rac*-**12** and *rac*-**13** by ^1H NMR spectroscopy. Purification by flash column chromatography on silica with 9:1-8:2 petrol-EtOAc gave alcohol *rac*-**13** (14 mg, 21%) as a white solid and alcohol *rac*-**12** (27 mg, 42%) as a white solid.

Lab Book Reference PJR 8/640

1-[2-[Hydroxy(phenyl)methyl]azetidin-1-yl]-2,2-dimethylpropane-1-thione *rac*-13 and 1-[(2-[hydroxy(phenyl)methyl]azetidin-1-yl]-2,2-dimethylpropane-1-thione *rac*-12



rac-**13** *rac*-**12**

(Scheme 7)

s-BuLi (0.23 mL of a 1.3M solution in hexanes, 0.3 mmol, 1.2 eq.) was added to a stirred solution of *N*-thiopivaloyl azetidine **1** (40 mg, 0.25 mmol, 1.0 eq.) in Et_2O (5 mL) at −40 °C under Ar. The resulting solution was stirred at −40 °C for 30 min and then cooled to −78 °C and stirred at −78 °C for 10 min. Then, (−)-sparteine **3** (68 μL, 0.30 mmol, 1.2 eq.) was added at the

resulting solution was stirred for 30 min. Benzaldehyde (38 μL, 0.38 mmol, 1.5 eq.) was added dropwise. The resulting solution was stirred for 10 min at −78 °C and 1 M $HCl_{(aq)}$ was added. The two layers were separated and the aqueous layer was extracted with Et_2O (3 x 10 mL). 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 alcohols *rac*-**12** and *rac*-**13** by ^{1}H NMR spectroscopy. Purification by flash column chromatography on silica with 9:1-8:2 petrol-EtOAc as eluent gave alcohol *rac*-**13** (12 mg, 19%) as a white solid and alcohol *rac*-**12** (28 mg, 43%) as a white solid.

Lab Book Reference PJR 8/643

(Scheme 7)

s-BuLi (0.46 mL of a 1.3 M solution in hexanes, 0.6 mmol, 1.2 eq.) was added to a stirred solution of *N*-thiopivaloyl azetidine **1** (79 mg, 0.50 mmol, 1.0 eq.) in Et_2O (5 mL) at −40 °C under Ar. The resulting solution was stirred at −40 °C for 30 min. Then, (−)-sparteine **3** (0.14 mL, 0.60 mmol, 1.2 eq.) was added and the resulting solution was stirred for 15 min. The solution was then cooled to −78 °C and stirred at −78 °C for 30 min. Benzaldehyde (38 μL, 0.38 mmol, 1.5 eq.) was added dropwise. The resulting solution was stirred at −78 °C for 10 min and 1 M $HCl_{(aq)}$ was added. The two layers were separated and the aqueous layer was extracted with Et_2O (3 x 10 mL). The combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product which contained an 81:19 mixture of alcohols (*R,R*)-**12** and (*S,R*)-**13** by ^{1}H NMR spectroscopy. Purification by flash column chromatography on silica with 9:1-8:2 petrol-EtOAc as eluent gave alcohol (*S,R*)-**13** (9 mg, 7%, 59:41 er by CSP-HPLC) as a white solid, CSP-HPLC: Chiracel AD-H (95:5 Hexane-*i*PrOH, 1.0 mL min^{-1}) (*S*,*R*)-**13** 7.5 min, (*R*,*S*)-**13** 10.1 min and alcohol (*R,R*)-**12** (76 mg, 57%, 71:29 er by CSP-HPLC) as a white solid, CSP-HPLC: Chiracel AD-H (95:5 Hexane-*i*PrOH, 1.0 mL min^{-1}) (*R*,*R*)-**12** 18.2 min, (*S*,*S*)-**12** 20.2 min.

Lab Book Reference PJR 8/665

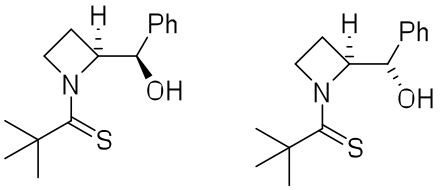
2. Assignment of Stereochemistry

2.1 Assignment of the Configuration of (*R*,*R*)-12 and (*S*,*R*)-13

Relative stereochemistry:

The relative stereochemistry of racemic (*R**,*R**)-**12** and (*S**,*R**)-**13** (generated from a *s*-BuLi/TMEDA reaction, described below) were assigned by X-ray crystallography.

1-[(2*S)-2-[(*R**)-Hydroxy(phenyl)methyl]azetidin-1-yl]-2,2-dimethylpropane-1-thione (*R**,*S**)-13 and 1-[(2*S**)-2-[(*S**)-hydroxy(phenyl)methyl]azetidin-1-yl]-2,2-dimethylpropane-1-thione (*S**,*S**)-12**



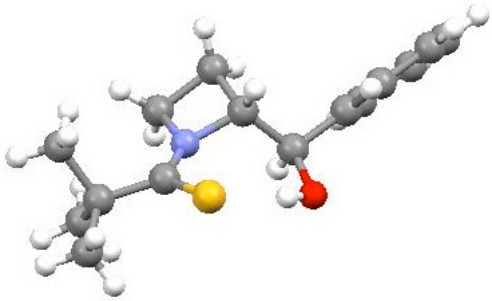
(*R*,*S*)-**13** (*S*,*S*)-**12**

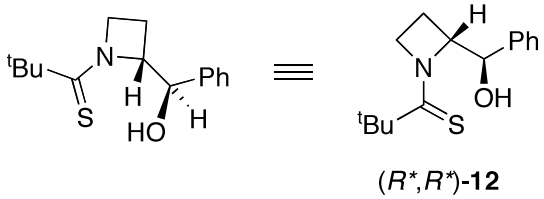
Using general procedure A, *s*-BuLi (0.5 mL of a 1.3 M solution in hexanes, 0.65 mmol, 1.3 eq.), *N*-thiopivaloyl azetidine **1** (79 mg, 0.5 mmol, 1.0 eq.), TMEDA (0.2 mL, 151 mg, 1.3 mmol, 2.5 eq.) in Et_2O (5 mL) and benzaldehyde (100 μL, 1.0 mmol, 2.0 eq.) gave the crude product which contained a 65:35 mixture of alcohols (*S**,*S**)-**12** and (*R**,*S**)-**13** by ^1H NMR spectroscopy. Purification by flash column chromatography on silica with 95:5-8:2 petrol-EtOAc as eluent gave alcohol (*R**,*S**)-**13** (25 mg, 19%) as a white solid and alcohol (*R**,*R**)-**12** (49 mg, 37%) as a white solid.

Lab Book Reference JCS2-26

X-ray crystallography:

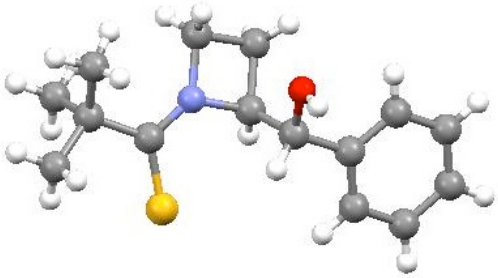
(*R**,*R**)-**12**: CCDC number 1417067

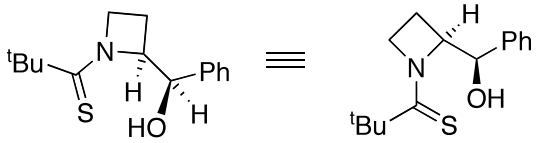




(*R**,*R**)-**12**

(*S**,*R**)-**13**: CCDC number 1417066

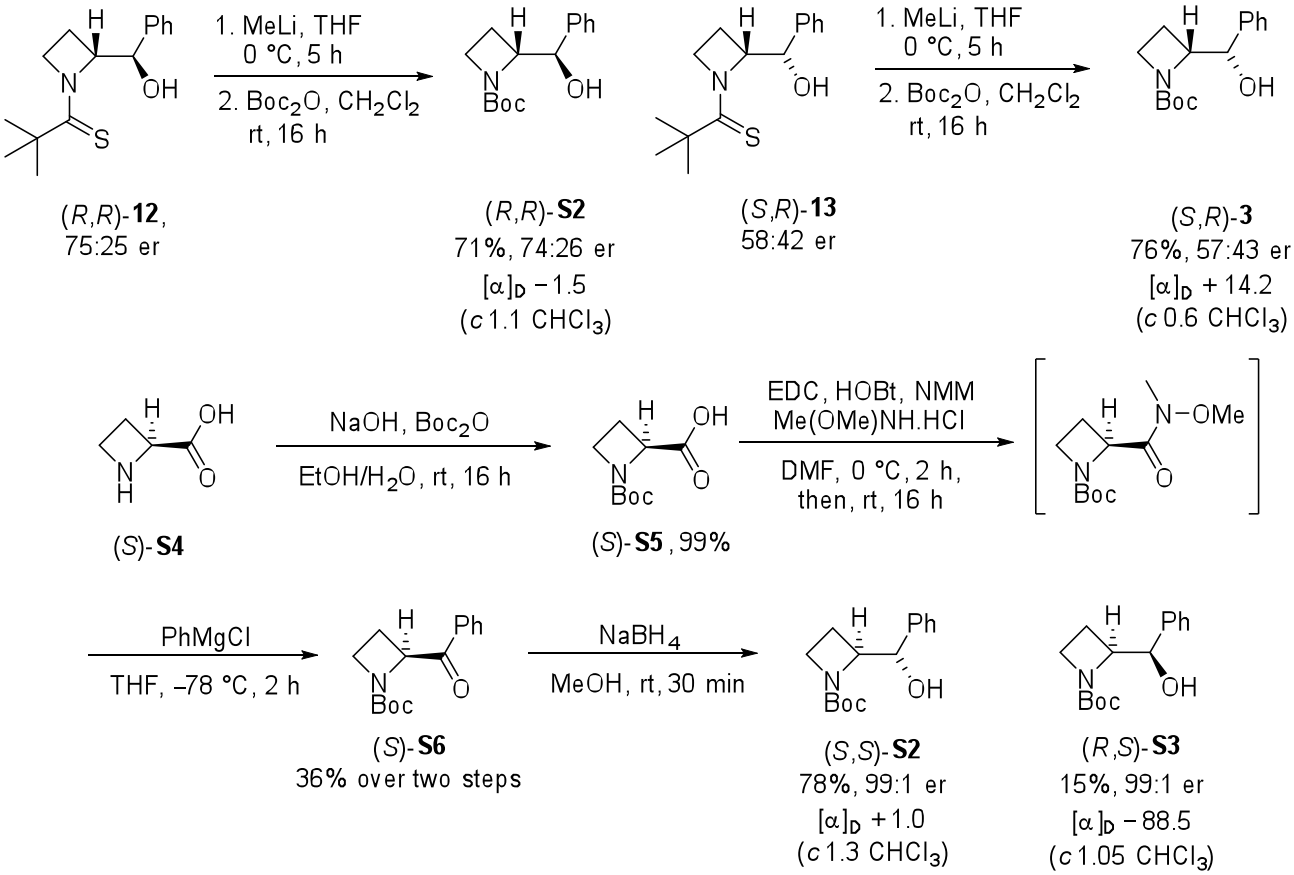




(*S**,*R**)-**13**

Absolute stereochemistry:

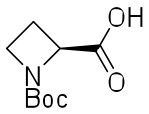
The absolute stereochemistry of (*R*,*R*)-**12** and (*S*,*R*)-**13** was assigned by conversion into *N*-Boc azetidine alcohols (*R*,*R*)-**S2** and (*S*,*R*)-**S3** respectively (Scheme S1). The thiopivaloyl group in each of (*R*,*R*)-**12** and (*S*,*R*)-**13** was removed using MeLi and Boc protection then gave (*R*,*R*)-**S2** and (*S*,*R*)-**S3** respectively. The enantiomeric *N*-Boc azetidine alcohols (*S*,*S*)-**S2** and (*R*,*S*)-**S3** were independently synthesised from commercially available amino acid (*S*)-**S4** (Scheme S1). Comparision of the optical rotation and CSP-HPLC data of the products generated from each of these routes allowed the assignment of configuration.



Scheme S1

Experimental for Scheme S1:

(*S*)-1-(*tert*-Butoxycarbonyl)azetidine-2-carboxylic acid (*S*)-S5[7]

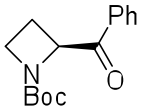


(*S*)-**S5**

NaOH (420 mg, 10.5 mmol, 1.05 eq.) was added to a stirred solution of (*S*)-2-azetidine carboxylic acid (*S*)-**S4** (1.00 g, 10.0 mmol, 1.0 eq.) and di-*tert*-butyl dicarbonate (2.83 g, 12.5 mmol, 1.25 eq.) in 2:1 EtOH-water (30 mL) at rt. The resulting solution was stirred at rt for 16 h. Then, the volatiles were evaporated under reduced pressure and the remaining suspension was acidified with 1 M $HCl_{(aq)}$ (20 mL). The aqueous layer was extracted with EtOAc (3 x 50 mL). The combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give acid (*S*)-**S5** (1.96 g, 99%) as a white solid, mp 97-99 °C (lit.,[8] 97-98 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.03 (br s, 1H, OH), 4.77 (br s, 1H, NCH), 3.96-3.85 (m, 2H, NCH_2), 2.46 (br s, 2H, CH_2), 1.46 (s, 9H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 181.5 (C=O, COOH), 156.6 (C=O, Boc), 82.7 (*C*Me_3), 60.7 (br, NCH), 47.1 (NCH_2), 28.2 (C*Me*$_3$), 19.7 (CH_2); $[\alpha]_D$ −168.1 (*c* 0.7 in $CHCl_3$) (lit.,[3] $[\alpha]_D$ −116.1 (*c* 0.75 in $CHCl_3$)). Spectroscopic data consistent with those reported in the literature.[7]

Lab Book Reference PJR 7/512

***tert*-Butyl 2*S*-benzoylazetidine-1-carboxylate (*S*)-S6**[9]



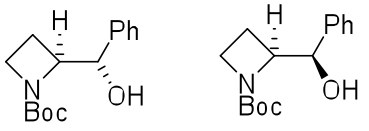
(*S*)-**S6**

N-Me morpholine (0.62 mL, 5.6 mmol, 1.2 eq.), HOBt (870 mg, 5.6 mmol, 1.2 eq.) and EDC (0.98 mL, 5.6 mmol, 1.2 eq.) were added sequentially to a stirred solution of acid (*S*)-**S5** (1.00 g, 4.6 mmol, 1.0 eq.) and *N*,*O*-dimethylhydroxylamine.HCl (550 mg, 5.6 mmol, 1.2 eq.) in DMF (10 mL) at 0 °C under Ar. The resulting solution was stirred at 0 °C for 2 h and then allowed to warm to rt and stirred at rt for 16 h. Then, EtOAc (30 mL) was added and the solution was washed with 1 M $HCl_{(aq)}$ (10 mL), 2 M $NaOH_{(aq)}$ (2 x 10 mL) and brine (3 x 10 mL), dried

($MgSO_4$) and evaporated under reduced pressure to give the crude Weinreb amide (565 mg, 50%) as a pale yellow solid, ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.04 (dd, J = 8.5, 5.5 Hz, 1H, NCH), 4.04 (ddd, J = 9.0, 8.0, 6.0 Hz, 1H, NCH_AH$_B$), 3.87 (ddd, J = 9.0, 8.0, 6.0 Hz, 1H, NCH_AH$_B$), 3.71 (s, 3H, OMe), 3.22 (s, 3H, NMe), 2.51-2.42 (m, 1H, CH_AH$_B$), 2.12 (dddd, J = 11.0, 9.0, 5.5, 5.5 Hz, 1H, CH$_A$$H_B$), 1.43 (s, 9H, CMe_3). PhMgCl (1.72 mL of a 2.0 M solution in THF, 3.44 mmol, 1.5 eq.) was added dropwise to a stirred solution of the crude Weinreb amide (565 mg, 2.3 mmol, 1.0 eq.) in THF (10 mL) at −78 °C under Ar. The resulting solution was stirred at −78 °C for 2 h. Then, saturated $NH_4Cl_{(aq)}$ (15 mL) was added. The two layers were separated and the aqueous layer was extracted with EtOAc (3 x 15 mL). The combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 4:1-3:1 petrol-EtOAc as eluent gave ketone (*S*)-**S6** (430 mg, 36% over two steps) as a white solid, mp 77-79 °C; R_F (3:1 petrol-EtOAc) 0.3; IR ($CHCl_3$) 2981, 1720 (C=O, PhCO), 1675 (C=O, Boc), 1426, 1375, 1210, 1010, 920, 815, 730 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85-7.83 (m, 2H, *o*-Ph), 7.52 (d, J = 7.5 Hz, 1H, *p*-Ph), 7.41 (t, J = 7.5 Hz, 2H, *m*-Ph), 5.50 (dd, J = 9.5, 5.5 Hz, 1H, NCH), 3.99-3.87 (m, 2H, NCH_2), 2.61 (dddd, J = 11.0, 9.5, 9.0, 6.0 Hz, 1H, CH_AH$_B$), 2.06 (dddd, J = 11.0, 9.0, 5.5, 5.5 Hz, 1H, CH$_A$$H_B$), 1.34 (s, 9H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 195.7 (C=O, PhCO), 155.8 (C=O, Boc), 134.4 (*ipso*-Ph), 133.6 (Ph), 128.9 (Ph), 128.2 (Ph), 79.8 (*C*Me_3), 63.6 (br, NCH), 46.9 (br, NCH_2), 28.32 (C*Me*$_3$), 21.3 (CH_2); MS (ESI) *m/z* 284 [(M + Na)$^+$, 100]; HRMS *m/z* calcd for $C_{15}H_{19}NO_3$ (M + Na)$^+$ 284.1257, found 284.1249 (+3.0 ppm error); $[\alpha]_D$ −140.9 (*c* 0.65 in $CHCl_3$).

Lab Book Reference PJR 7/524

tert-Butyl (2*S*)-2-[(*S*)-hydroxy(phenyl)methyl]azetidine-1-carboxylate (*S*,*S*)-S2 and _tert_-butyl (2S)-2-[(*R*)-hydroxy(phenyl)methyl]azetidine-1-carboxylate (*R*,*S*)-S3



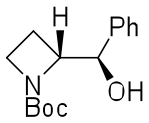
(*S*,*S*)-**S2** (*R*,*S*)-**S3**

$NaBH_4$ (73 mg, 1.93 mmol, 1.2 eq.) was added to a stirred solution of ketone (*S*)-**S6** (420 mg, 1.61 mmol, 1.0 eq.) in MeOH (5 mL) at 0 °C. The resulting solution was stirred at rt for 30 min. Then, the solution was cooled to 0 °C and saturated $NH_4Cl_{(aq)}$ (5 mL) was added dropwise. The

resulting solution was extracted with EtOAc (3 x 10 mL). The combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product which contained an 85:15 mixture of alcohols (*S,S*)-**S2** and (*R,S*)-**S3** by ^{1}H NMR spectroscopy. Purification by flash column chromatography on silica with 9:1-8:2 petrol-EtOAc as eluent gave alcohol (*S,S*)-**S2** (330 mg, 78%, 99:1 er by CSP-HPLC) as a colourless oil, R_F (4:1 petrol-EtOAc) 0.3; IR ($CHCl_3$) 3348 (OH), 2976, 2952, 1687 (C=O), 1445, 1424, 1375, 1246, 1045, 1025, 915, 800, 730 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29-7.36 (m, 2H, *o*-Ph), 7.34-7.25 (m, 3H, Ph), 5.75 (br s, 1H, OH), 4.75 (d, J = 8.0 Hz, 1H, OCH), 4.34 (ddd, J = 8.0, 8.0, 8.0 Hz, 1H, NCH), 3.83-3.72 (m, 2H, NCH_2), 1.93-1.80 (m, 2H, CH_2), 1.48 (s, 9H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 158.1 (C=O), 139.2 (*ipso*-Ph), 128.3 (Ph), 127.9 (Ph), 127.0 (Ph), 80.1 (OCH), 79.1 (CMe_3), 67.8 (NCH), 46.1 (NCH_2), 28.3 (CMe_3), 18.7 (CH_2); MS (ESI) *m/z* 286 [$(M + Na)^+$, 100], 264 [$(M + H)^+$, 50], 208 (100), 190 (90); HRMS *m/z* calcd for $C_{15}H_{21}NO_3$ $(M + Na)^+$ 286.1414, found 286.1408 (+2.1 ppm error); $[\alpha]_D$ +1.0 (*c* 1.3 in $CHCl_3$); CSP-HPLC: Chiracel AD-H (95:5 Hexane-*i*PrOH, 1.0 mL min^{-1}) (*R,R*)-**S2** 11.1 min, (*S,S*)-**S2** 24.0 min and alcohol (*R,S*)-**S3** (65 mg, 15%, 99:1 er by CSP-HPLC) as a colourless oil, R_F (4:1 petrol-EtOAc) 0.2; IR (film) 3421 (OH), 2970, 1692 (C=O), 1446, 1420, 1378, 1186, 1050, 1040, 910, 730 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, OH not visible) δ 7.29-7.36 (m, 2H, *o*-Ph), 7.34-7.25 (m, 3H, Ph), 4.94 (d, J = 2.5 Hz, 1H, OCH), 4.57 (ddd, J = 7.5, 7.5, 2.5 Hz, 1H, NCH), 3.73 (ddd, J = 8.5, 1.5, 1.5 Hz, 1H, NCH_AH_B), 3.48-3.43 (m, 1H, NCH_AH_B), 2.16-2.04 (m, 1H, CH_AH_B), 1.93 (dddd, J = 11.5, 8.5, 7.5 5.0 Hz, 1H, CH_AH_B), 1.48 (s, 9H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 157.4 (C=O), 139.6 (*ipso*-Ph), 128.3 (Ph), 127.6 (Ph), 126.7 (Ph), 80.4 (CMe_3), 75.3 (OCH), 66.8 (NCH), 46.7 (NCH_2), 28.5 (CMe_3), 16.2 (CH_2); MS (ESI) *m/z* 286 [$(M + Na)^+$, 100]; HRMS *m/z* calcd for $C_{15}H_{21}NO_3$ $(M + Na)^+$ 286.1414, found 286.1398 (+5.3 ppm error); $[\alpha]_D$ −88.5 (*c* 1.05 in $CHCl_3$); CSP-HPLC: Chiracel AD-H (95:5 Hexane-*i*PrOH, 1.0 mL min^{-1}) (*R,R*)-**S3** 14.3 min, (*S,S*)-**S3** 15.8 min.

Lab Book Reference PJR 7/527

***tert*-Butyl (2*R*)-2-[(*R*)-hydroxy(phenyl)methyl]azetidine-1-carboxylate (*R*,*R*)-S2**

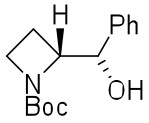


(*R*,*R*)-**S2**

MeLi (0.94 mL of a 1.6 M solution in Et_2O, 1.50 mmol, 6.0 eq.) was added dropwise to a stirred solution of alcohol (*R*,*R*)-**12** (65 mg, 0.25 mmol, 1.0 eq., 75:25 er.) in THF (5 mL) at 0 °C under Ar. The resulting solution was stirred at 0 °C for 5 h. Then, 1 M $HCl_{(aq)}$ (5 mL) was added dropwise. The resulting solution was extracted with Et_2O (10 mL). The aqueous layer was adjusted to pH 12 by dropwise addition of 1 M $NaOH_{(aq)}$ and extracted with Et_2O (3 x 10 mL). The combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude amino alcohol. The residue was dissolved in CH_2Cl_2 (5 mL) and di-*tert*-butyl dicarbonate (60 mg, 0.28 mmol, 1.1 eq.) was added at rt under Ar. The resulting solution was stirred at rt for 16 h. Then, 1 M $HCl_{(aq)}$ (10 mL) was added and the two layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 10 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 9:1-8:2 petrol-EtOAc as eluent gave alcohol (*R,R*)-**S2** (47 mg, 71%, 74:26 er by CSP HPLC) as a colourless oil, $[\alpha]_D$ −1.56 (*c* 1.1 in $CHCl_3$); CSP-HPLC: Chiracel AD-H (95:5 Hexane-*i*PrOH, 1.0 mL min^{-1}) (*R*,*R*)-**S2** 11.1 min, (*S*,*S*)-**S2** 25.5 min.

Lab Book Reference PJR 7/526

***tert*-Butyl (2*R*)-2-[(*S*)-hydroxy(phenyl)methyl]azetidine-1-carboxylate (*S*,*R*)-S3**



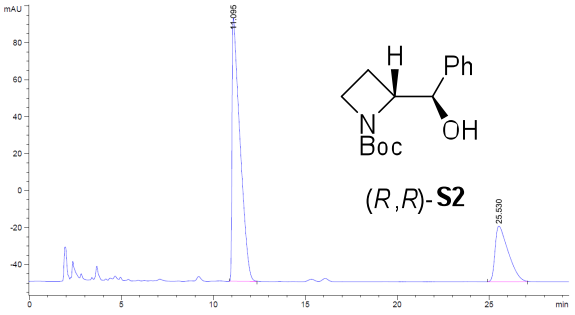
(*S*,*R*)-**S3**

MeLi (0.38 mL of a 1.6 M solution in Et_2O, 0.60 mmol, 6.0 eq.) was added dropwise to a stirred solution of alcohol (*S*,*R*)-**13** (26 mg, 0.25 mmol, 1.0 eq., 58:42 er) in THF (5 mL) at 0 °C under Ar. The resulting solution was stirred at 0 °C for 5 h. Then, 1 M $HCl_{(aq)}$ (5 mL) was added dropwise. The resulting solution was extracted with Et_2O (10 mL). The aqueous layer was adjusted to pH 12 by dropwise addition of 1 M $NaOH_{(aq)}$ and extracted with Et_2O (3 x 10 mL).

The combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude amino alcohol. The residue was dissolved in CH_2Cl_2 (5 mL) and di-*tert*-butyl dicarbonate (60 mg, 0.28 mmol, 1.1 eq.) was added at rt under Ar. The resulting solution was stirred at rt for 16 h. Then, 1 M $HCl_{(aq)}$ (10 mL) was added and the two layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 10 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 9:1-8:2 petrol-EtOAc as eluent gave alcohol (*S,R*)-**S3** (20 mg, 76%, 57:43 er by CSP HPLC) as a colourless oil, $[\alpha]_D$ +14.2 (*c* 0.60 in $CHCl_3$); CSP-HPLC: Chiracel AD-H (95:5 Hexane-*i*PrOH, 0.5 mL min^{-1}) (*S,R*)-**S3** 14.9 min, (*R,S*)-**S3** 15.8 min.

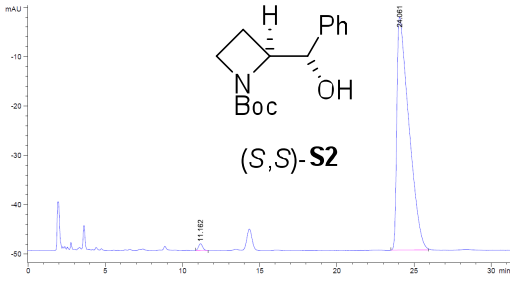
Lab Book Reference PJR 8/684

CSP-HPLC of (*R,R*)-S2 of 74:26 er



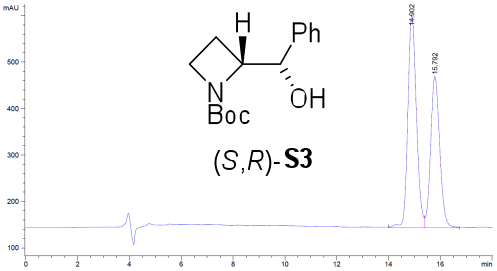
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.095	BB	0.4127	4284.12207	142.50230	74.0968
2	25.530	BB	0.7324	1497.66797	30.10507	25.9032

CSP-HPLC of (*S,S*)-S2 of 99:1 er



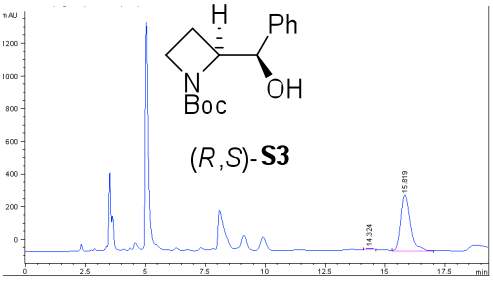
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.162	BB	0.2869	24.89183	1.36396	0.9598
2	24.061	BB	0.7699	2568.67676	47.27539	99.0402

CSP-HPLC of (*S,R*)-S3 of 57:43 er



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.902	MM	0.3858	1.05954e4	457.66769	57.0778
2	15.792	MM	0.4072	7967.68994	326.12051	42.9222

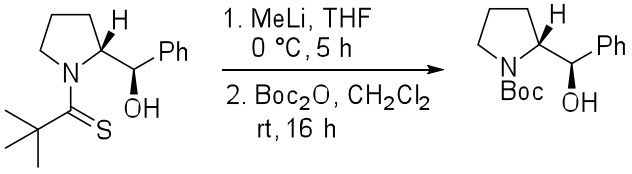
CSP-HPLC of (*R,S*)-S3 of 99:1 er



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.324	MM	0.3111	149.31052	8.00008	1.5374
2	15.819	VB	0.4288	9562.29102	341.41754	98.4626

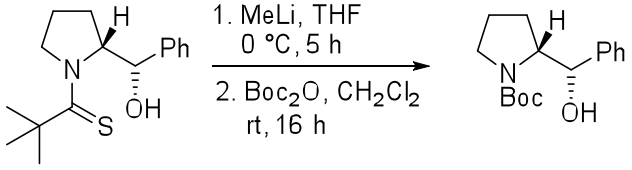
2.2 Assignment of the Configuration of (*R*,*R*)-14 and (*S*,*R*)-15

The absolute stereochemistries of (*R*,*R*)-**14** and (*S*,*R*)-**15** were assigned by conversion into known[10] alcohols (*R*,*R*)-**S7** and (*S*,*R*)-**S8** respectively (Scheme S2). The thiopivaloyl group in each of (*R*,*R*)-**14** and (*S*,*R*)-**15** was removed using MeLi and Boc protection then gave (*R*,*R*)-**S7** and (*S*,*R*)-**S8** respectively.



(*R*,*R*)-**14**
82:18 er

(*R*,*R*)-**S7**, 70%, 82:18 er
$[\alpha]_D$ −0.6
(*c* 0.75 $CHCl_3$)
(lit.[10] $[\alpha]_D$ −1.6 (*c*. 1.0 $CHCl_3$) of 97:3 er)



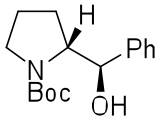
(*S*,*R*)-**15**
86:14 er

(*S*,*R*)-**S8**, 76%, 86:14 er
$[\alpha]_D$ +79.4 (*c* 1.0 $CHCl_3$)
(lit.[10] $[\alpha]_D$ +112.7 (*c*. 1.5 $CHCl_3$) of 96:4 er)

Scheme S2

Experimental for Scheme S2:

***tert*-Butyl (2*R*)-2-[(*R*)-hydroxy(phenyl)methyl]pyrrolidine-1-carboxylate (*R*,*R*)-S7**



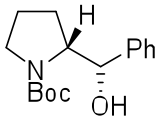
(*R*,*R*)-**S7**

MeLi (0.58 mL of a 1.6 M solution in Et_2O, 0.93 mmol, 6.0 eq.) was added dropwise to a stirred solution of alcohol (*R*,*R*)-**14** (43 mg, 0.16 mmol, 1.0 eq., 82:18 er) in THF (5 mL) at 0 °C under

Ar. The resulting solution was stirred at 0°C for 5 h. Then, 1 M HCl(aq) (5 mL) was added dropwise. The resulting solution was extracted with Et_2O (10 mL). The aqueous layer was adjusted to pH 12 by dropwise addition of 1 M $NaOH_{(aq)}$ and extracted with Et_2O (3 x 10 mL). The combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude amino alcohol. The residue was dissolved in CH_2Cl_2 (5 mL) and di-*tert*-butyl dicarbonate (37 mg, 0.17 mmol, 1.1 eq.) was added at rt under Ar. The resulting solution was stirred at rt for 16 h. Then, 1 M $HCl_{(aq)}$ (10 mL) was added and the two layers separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 10 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 98:2 CH_2Cl_2-acetone as eluent gave alcohol (*R,R*)-**S7** (30 mg, 70%, 82:18 er by CSP HPLC) as a colourless oil, $[\alpha]_D$ −0.6 (*c* 0.75 in $CHCl_3$) (lit.,[10] $[\alpha]_D$ −1.6 (*c* 1.0 in $CHCl_3$ for (*R*,*R*)-**S7** of 97:3 er)); CSP-HPLC: Chiracel OD (98:2 Hexane-*i*PrOH, 0.5 mL min^{-1}) (*R*,*R*)-**S7** 28.6 min, (*S*,*S*)-**S7** 35.7 min. Spectroscopic data consistent with those reported in the literature.[10]

Lab Book Reference PJR 8/648

***tert*-Butyl (2*R*)-2-[(*S*)-hydroxy(phenyl)methyl]pyrrolidine-1-carboxylate (*S*,*R*)-S8**



(*S*,*R*)-**S8**

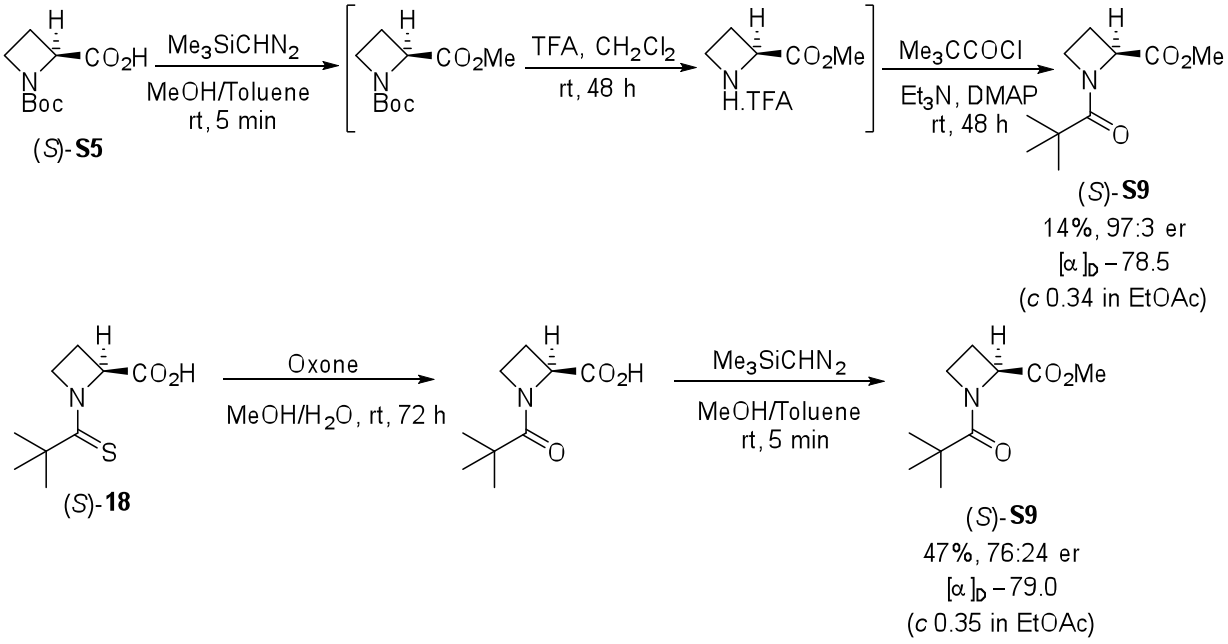
MeLi (0.45 mL of a 1.6 M solution in Et_2O, 0.72 mmol, 6.0 eq.) was added dropwise to a stirred solution of alcohol (*S*,*R*)-**15** (33 mg of 86:14 er, 0.12 mmol, 1.0 eq.) in THF (5 mL) at 0 °C under Ar. The resulting solution was stirred at 0°C for 5 h. Then, 1 M HCl(aq) (5 mL) was added dropwise. The resulting solution was extracted with Et_2O (10 mL). The aqueous layer was adjusted to pH 12 by dropwise addition of 1 M $NaOH_{(aq)}$ and extracted with Et_2O (3 x 10 mL). The combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude amino alcohol. The residue was dissolved in CH_2Cl_2 (5 mL) and di-*tert*-butyl dicarbonate (28 mg, 0.13 mmol, 1.1 eq.) was added at rt under Ar. The resulting solution was stirred at rt for 16 h. Then, 1 M $HCl_{(aq)}$ (10 mL) was added and the two layers separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 10 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 98:2 CH_2Cl_2-acetone as eluent gave alcohol (*S,R*)-**S8** (17 mg, 50%, 86:14 er by CSP HPLC) as a colourless oil, $[\alpha]_D$ +79.4 (*c* 1.0 in $CHCl_3$) (lit.,[10] $[\alpha]_D$ +112.7 (*c* 1.5 in $CHCl_3$ for (*S,R*)-**S8** of 96:4 er)); CSP-HPLC: Chiracel OD (99:1 Hexane-*i*PrOH, 0.5 mL min^{-1}) (*S,R*)-**S8** 25.7 min, (*R,S*)-**S8** 28.3 min. Spectroscopic data consistent with those reported in the literature.[10]

Lab Book Reference PJR 8/647

2.3 Assignment of the Configuration of (*R*)-16 and (*S*)-18

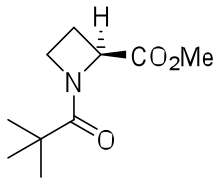
The configuration of (*S*)-**18** was assigned by conversion of (*S*)-**18** into amido ester (*S*)-**S9** which was independently synthesised from *N*-Boc acid (*S*)-**S5** (Scheme S3).



Scheme S3

Experimental for Scheme S3:

(*S*)-Methyl 1-pivaloylazetidine-2-carboxylate (*S*)-S9



(*S*)-**S9**

Me_3SiCHN_2 (0.15 mL of a 2.0 M solution in Et_2O, 0.30 mmol, 1.2 eq) was added dropwise to a stirred solution of acid (*S*)-**S5** (50 mg, 0.248 mmol, 1.0 eq) in MeOH/toluene (4:6 v/v, 3 mL) at rt. After 5 min, glacial AcOH (4 mL) was added and the solvent was evaporated under reduced pressure to give the crude ester (57 mg) as a colourless oil, ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.60 (dd, J = 9.0, 5.5 Hz, 1H, CHN), 4.01 (ddd, J = 8.5, 8.5, 6.0 Hz, 1H, CH_AH$_B$N), 3.87 (ddd, J = 8.5, 8.5, 5.5 Hz, 1H, CH$_A$$H_B$N), 3.76 (s, 3H, CO_2Me), 2.54-2.43 (m, 1H, CH_AH$_B$), 2.16 (dddd, J = 11.0, 8.5, 5.5, 5.5 Hz, 1H, CH$_A$$H_B$), 1.40 (s, 9H, CMe_3). Freshly distilled TFA (0.57 mL, 0.855 g, 7.50 mmol, 30 eq) was added to a stirred solution of the crude methyl ester (57 mg) in CH_2Cl_2 (5 mL) at rt. The resulting solution was stirred at rt for 48 hours. Then, the solvent was evaporated under reduced pressure to give the crude TFA salt (88 mg) as a yellow oil, ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.11 (dd, J = 9.0, 9.0 Hz, 1H, CHN), 4.24 (ddd, J = 10.0, 10.0, 10.0 Hz, 1H, CH_AH$_B$N), 4.10 (ddd, J = 10.0, 10.0, 6.5 Hz, 1H, CH$_A$$H_B$N), 3.84 (s, 3H, CO_2Me), 2.97-2.86 (m, 1H, CH_AH$_B$), 2.75-2.63 (m, 1H, CH$_A$$H_B$). Pivaloyl chloride (0.15 mL, 150 mg, 1.24 mmol, 5 eq) was added to a stirred solution of the crude TFA salt (88 mg), Et_3N (0.35 mL, 251 mg, 2.48 mmol, 10 eq) and DMAP (6.1 mg, 0.05 mmol, 0.2 eq) in CH_2Cl_2 (5 mL) at rt under N_2. The resulting solution was stirred at rt for 48 hours. Then, 2 M $HCl_{(aq)}$ (10 mL) was added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL) and the combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure. The residue was absorbed onto a plug of silica and eluted with 80 mL of EtOAc-pentane (1:1) to give the crude product. Purification by dry column flash chromatography through 13 cm of silica in a 2 cm diameter flash column, eluting with 50 mL aliquots of 5% increasing polarity of EtOAc-pentane (95:5 to 70:30) as eluent gave amido-ester (*S*)-**S9** (6.8 mg, 0.034 mmol, 14% over 3 steps from (*S*)-**S5**, 97:3 er by CSP-HPLC) in the sixth fraction as a pale yellow oil, IR (ATR) 2959, 1744 (C=O), 1631 (C=O), 1573, 1435, 1407, 1381, 1362, 1281, 1242, 1199, 1179, 1159, 1135, 1065, 1025,

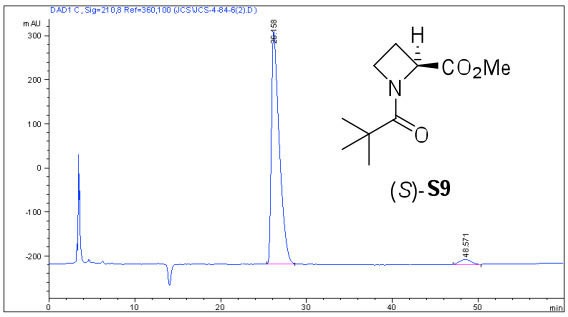
980, 933, 881, 756, 632 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.70 (br s, 1H, CHN), 4.48 (br s, 1H, CH_AH$_B$N), 4.30 (br s, 1H, CH$_A$$H_B$N), 3.76 (s, 3H, CO_2Me), 2.61-2.48 (m, 1H, CH_AH$_B$), 2.22-2.13 (m, 1H, CH$_A$$H_B$), 1.20 (s, 9H, CMe_3); ^{13}C NMR (400 MHz, $CDCl_3$) δ 172.0 (C=O, CO_2Me), 123.6 (NC=O), 60.1 (CHN), 52.4 (CO_2*Me*), 29.8 (CH_2N), 27.1 (C*Me*$_3$), 20.4 (CH_2), 14.3 (*C*Me_3); MS (ESI) *m/z* 200 [$(M + H)^+$, 100], 222 [$(M + Na)^+$, 65]; HRMS *m/z* calcd for $C_{10}H_{18}NO_3$ $(M + Na)^+$ 222.1101, found 222.1097 (+1.7 ppm error); $[\alpha]_D$ −78.5 (c 0.34 in EtOAc); CSP-HPLC: Chiralcel OD-H (98:2 Hexane-*i*PrOH, 1.0 mL min^{-1}) (*S*)-**S9** 26.2 min, (*R*)-**S9** 48.5 min. A second portion of (*S*)-**S9** (13.3 mg, 0.0668 mmol, 26.9% over 3 steps of lesser purity) was isolated from the fifth fraction.

Lab Book Reference: JCS-4-80, JCS-4-81, JCS-4-84

Oxone (142 mg, 0.46 mmol, 5.1 eq) was added to a stirred solution of acid (*S*)-**18** (18.6 mg, 0.092 mmol, 1.0 eq, 75:25 er) in MeOH/water (1:1, 5 mL) at rt. The resulting solution was stirred at rt for 72 hours. Then, the reaction mixture was diluted with EtOAc (50 mL) and washed with water (2 x 5 mL), dried ($MgSO_4$) and the solvent evaporated under reduced pressure to give the crude product (15.9 mg), ^1H NMR (400 MHz, $CDCl_3$) δ 5.04 (dd, J = 8.5, 7.0 Hz, 1H, CHN), 4.45–4.29 (m, 2H, CH_2N), 2.55–2.45 (m, 1H, CH_AH$_B$), 2.22–2.13 (m, 1H, CH$_A$$H_B$), 1.23 (s, 9H, CMe_3). The residues were dissolved in MeOH/toluene (4:6 v/v, 3 mL) and to this stirred solution was added Me_3SiCHN_2 (2.0 M in Et_2O) dropwise at rt until the yellow colour persisted (~0.05 mL). The resulting solution was stirred at rt for 5 min. Then, glacial AcOH (5 mL) was added to destroy excess Me_3SiCHN_2 and the solvent was evaporated under reduced pressure to give (*S*)-**S9** (6.9 mg, 0.044 mmol, 47% over 2 steps, 76:24 er) as a pale yellow oil that did not require further purification, $[\alpha]_D$ −79.0 (*c* 0.35 in EtOAc); CSP-HPLC: Chiralcel OD-H (98:2 Hexane-*i*PrOH, 1.0 mL min^{-1}) (*S*)-**S9** 25.6 min, (*R*)-**S9** 47.4 min.

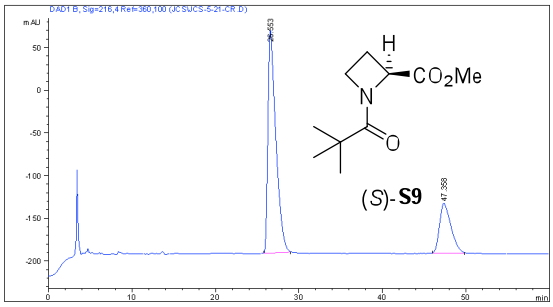
Lab Book Reference: JCS-5-20, JCS-5-21

CSP-HPLC of (*S*)-S9 of 97:3 er



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	26.158	BB	0.8512	3.37006e4	527.63196	96.9264
2	48.571	BV	1.1214	1068.66125	11.25896	3.0736
Totals :				3.47693e4	538.89092	

CSP-HPLC of (*S*)-S9 of 76:24 er



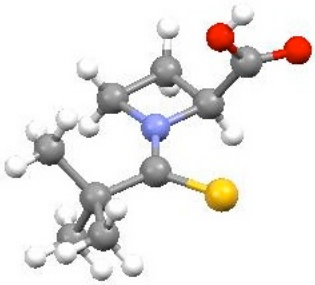
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	26.553	BB	0.8978	1.72184e4	260.95663	75.8516
2	47.358	BB	1.1755	5481.72510	58.05973	24.1484
Totals :				2.27001e4	319.01637	

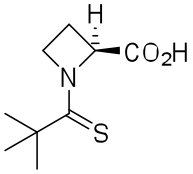
The configuration of acid (*S*)-**18** was also assigned by X-ray crystallography of a sample grown from an enantioenriched sample (of 97:3 er).

Enantioenrichment of (*S*)-18

A stirred solution of acid (*S*)-**18** (60 mg, 75:25 er) in hexane (~ 2 mL) was gently heated to reflux. Then, boiling EtOAc was added until all solid material just dissolved and the solution was allowed to slowly cool to rt. Then, the solution was cooled to 0 °C for 30 min. The formed crystals were collected by filtration to give *rac*-**18** (29 mg). The filtrate was evaporated under reduced pressure to give acid (*S*)-**21** (30 mg, 97:3 er by CSP-HPLC of the methyl ester) as a white solid. Acid (*S*)-**18** was converted into methyl ester (*S*)-**16** by reaction with Me_3SiCHN_2 in MeOH/toluene (4:6 v/v, 2 mL), quenching with glacial AcOH and evaporation under reduced pressure. CSP-HPLC of methyl ester (*S*)-**16**: Chiralcel OD-H (98:2 Hexane-*i*PrOH, 1.0 mL min^{-1}) (*S*)-**16** 13.5 min, (*R*)-**16** 17.0 min.

Crystals suitable of (*S*)-**18** for X-ray crystallography were prepared by dissolving (*S*)-**18** (30 mg, 97:3 er) in the minimum amount of EtOAc. The solution was placed into a small glass vial and placed upright in a sealed vessel containing pentane (~ 20 mL). After several days, suitable crystals had precipitated in the glass vial. These were collected and subjected to X-ray analysis.

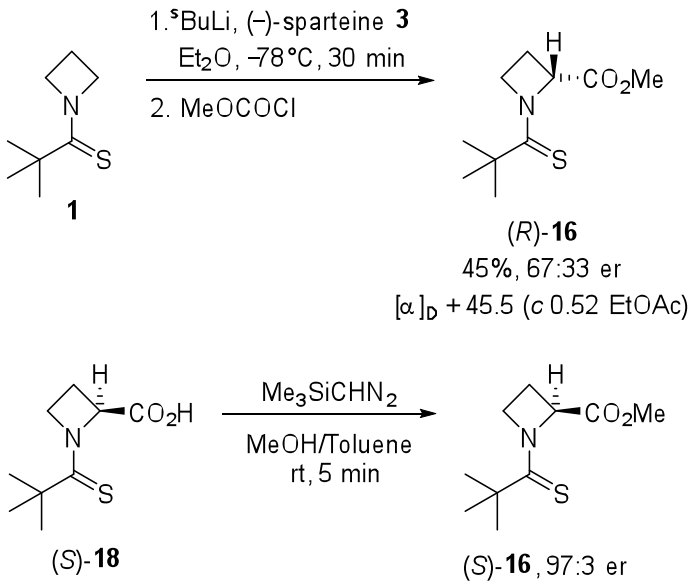




(*S*)-**18**

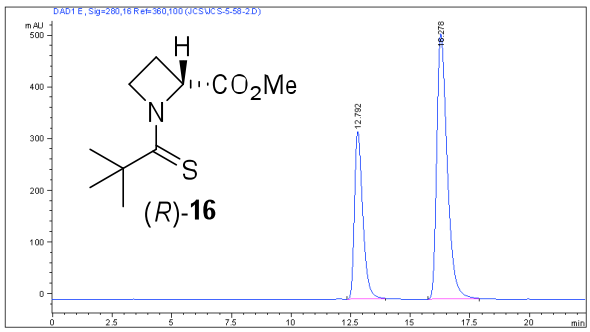
(*S*)-**18**: CCDC number 1417069

The configuration of (*R*)-**16** was assigned by converision of acid (*S*)-**18** of known configuration into (*S*)-**16** and comparision of CSP-HPLC data (Scheme S4).



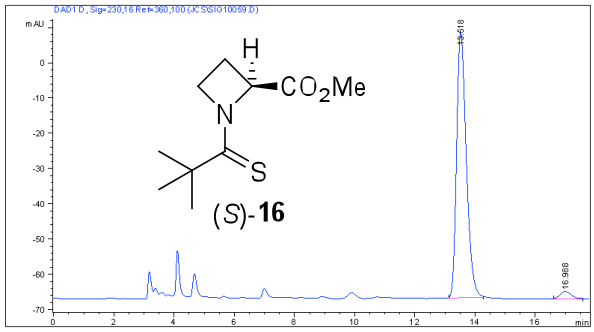
Scheme S4

CSP-HPLC of (*R*)-19 of 67:33 er



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.792	BB	0.3663	7852.21631	324.50208	33.4335
2	16.278	BB	0.4657	1.56338e4	512.79816	66.5665
Totals :				2.34861e4	837.30023	

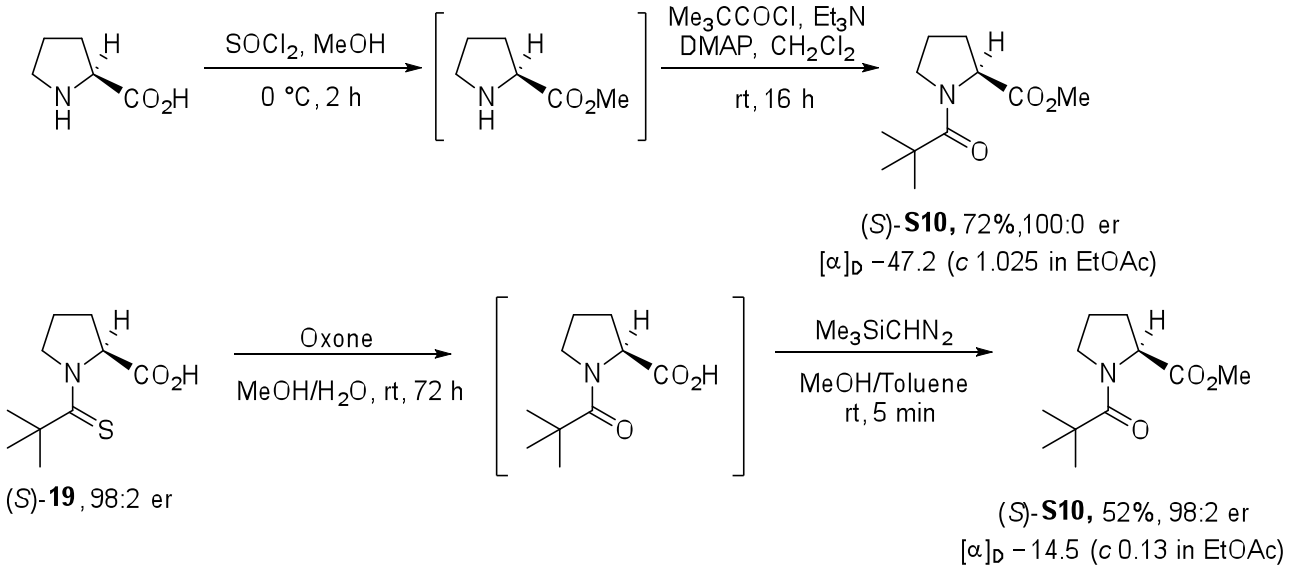
CSP-HPLC of (*S*)-19 of 97:3 er



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	13.518	BB	0.3408	1684.25671	75.34917	97.0404
2	16.988	BB	0.3798	51.36812	2.03996	2.9596
Totals :				1735.62484	77.38912	

2.4 Assignment of the Configuration of (*R*)-17 and (*S*)-19

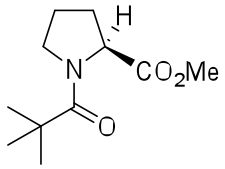
The configuration of acid (*S*)-**19** was assigned by conversion of (*S*)-**19** into amido ester (*S*)-**S10** which was independently synthesised from *N*-Boc acid (*S*)-**S5** (Scheme S5).



Scheme S5

Experimental for Scheme S5

(*S*)-Methyl 1-pivaloylpyrrolidine-2-carboxylate (*S*)-S10



(*S*)-**S10**

Oxone (18 mg, 0.059 mmol, 5 eq) was added to a stirred solution of acid (*S*)-**19** (5 mg, 0.023 mmol, 1.0 eq, 98:2 er) in MeOH/water (1:1 v/v, 1 mL) at rt. The resulting solution was stirred at rt for 72 h. Then, the reaction was diluted with EtOAc (50 mL) and washed with water (2 x 5 mL), dried ($MgSO_4$) and the solvent evaporated under reduced pressure to give the crude product (7.2 mg), ^{1}H NMR (400 MHz, $CDCl_3$) 4.68–4.61 (br m, 1H, CHN), 3.74–3.69 (m, 2H, CH_2N), 2.15–1.87 (m, 4H, CH_2CH_2), 1.29 (s, 9H, CMe_3). The residues were redissolved in MeOH/toluene (4:6 v/v, 2 mL) and Me_3SiCHN_2 (2.0 M soln in Et_2O) was added dropwise at rt until the yellow colour persisted (~0.03 mL). The resulting solution was stirred at rt for 5 min. Then, glacial AcOH (5 mL) was added to destroy excess Me_3SiCHN_2 and the solvent was evaporated under reduced pressure to give the crude product. Purification by flash coloumn chromatography on silica with 80 mL of 1:1 EtOAc-pentane gave (*S*)-**S10** (2.6 mg, 0.012 mmol, 52% over 2 steps, 98:2 er), ^{1}H NMR (400 MHz, $CDCl_3$) 4.52–4.45 (br m, 1H, CHN), 3.82–3.66 (m, 2H, CH_2N), 3.72 (s, 3H, CO_2Me), 2.17–2.01 (m, 2H, CH_2), 2.00–1.81 (m, 2H, CH_2), 1.23 (s, 9H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 176.9 (C=O), 173.5 (C=O), 60.9 (CHN), 52.1 (CH_2N), 48.2 (CO_2Me), 38.8 (CMe_3), 27.9 (CH_2), 27.3 (CMe_3), 26.1 (CH_2); [α] −14.5 (*c* 0.13 in EtOAc); CSP-HPLC: Chiralcel OD-H (96:4 Hexane-*i*PrOH, 1.0 mL min^{-1}) (*S*)-**S10** 13.1 min, (*R*)-**S10** 17.8 min. Spectroscopic data consistent with those reported in the literature.[11]

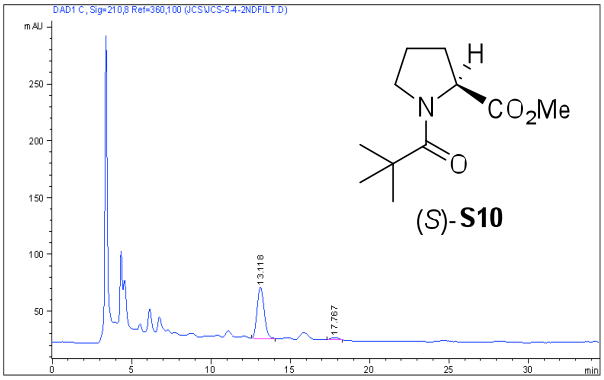
Lab Book Reference: JCS-5-4, JCS-4-90

Thionyl chloride (2.53 mL, 4.13 g, 34.8 mmol, 2.0 eq.) was added dropwise to a stirred solution of *L*-proline (2.0 g, 17.4 mmol, 1.0 eq) in MeOH (18 mL) at 0 °C. The resulting solution was stirred at 0 °C for 2 h. Then, the solvent was evaporated under reduced pressure to give the crude product (2.97 g). A portion of the crude product (0.59 g) was suspended in CH_2Cl_2 (10 mL) and DMAP (74 mg, 0.60 mmol), Et_3N (2.10 mL, 1.53 g, 15.1 mmol) and pivaloyl chloride (0.58 mL, 546 mg, 4.53 mmol) were added sequentially at 0 °C under N_2. The resulting solution was

allowed to warm to rt over 4 h. Then, the reaction was diluted with EtOAc (50 mL) and washed with 2 M HCl (2 x 20 mL), K_2CO_3 (10% w/w, 30 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification through a plug of silica with 8:2 hexane-EtOAc (200 mL) as eluent gave (*S*)-**S10** (509 mg, 2.39 mmol, 69% over 2 steps) as a pale red oil, [α] –47.2 (c 1.025 in EtOAc); CSP-HPLC: Chiralcel OD-H (96:4 Hexane-*i*PrOH, 1.0 mL min^{-1}) (*S*)-**S10** 13.3 min.

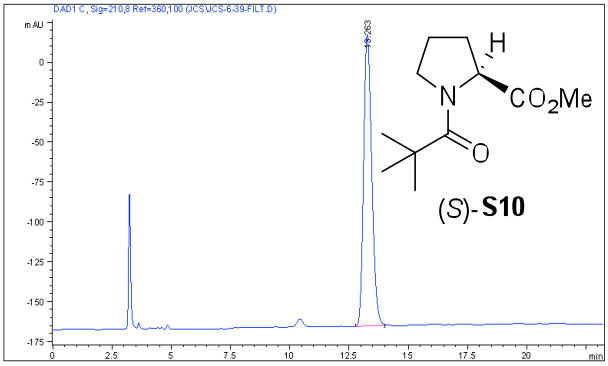
Lab Book Reference: JCS-6-38, JCS-6-39

CSP-HPLC of (*S*)-S10 of 98:2 er



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	13.118	BB	0.4821	1404.90295	44.77237	97.9871
2	17.767	MM	0.4221	28.86036	1.13942	2.0129
Totals :				1433.76332	45.91179	

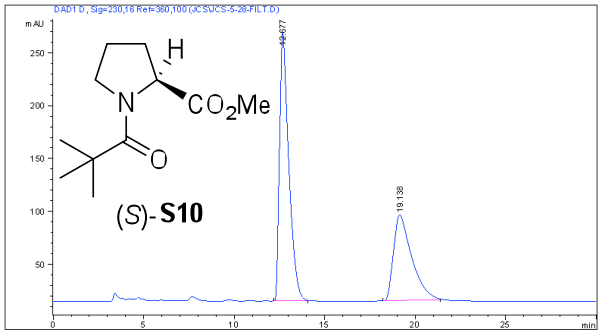
CSP-HPLC of (*S*)-S10 of 100:0 er



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	13.263	BB	0.3697	4351.46973	182.84155	100.0000
Totals :				4351.46973	182.84155	

In a separate experiment, a sample of (*S*)-**S10** of 61:39 er was also prepared.

CSP-HPLC of (*S*)-S10 of 61:39 er



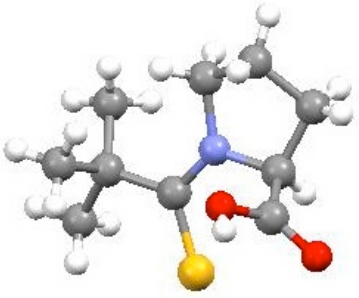
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.677	BB	0.4978	9011.98730	254.08043	61.4294
2	19.138	BB	0.9681	5658.48389	81.28988	38.5706
Totals :				1.46705e4	335.37031	

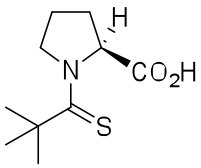
The configuration of acid (*S*)-**19** was also assigned by X-ray crystallography of a sample grown from an enantioenriched sample (of 98:2 er).

Enantioenrichment of (*S*)-19

A stirred solution of acid (*S*)-**19** (80 mg, 80:20 er) in hexane (~ 2 mL) was gently heated to reflux. Then, boiling EtOAc was added until all solid material just dissolved and the solution was allowed to slowly cool to rt. Then, the solution was cooled to 0 °C for 30 min. The formed crystals were collected by filtration to give *rac*-**19** (21 mg). The filtrate was evaporated under reduced pressure to give acid (*S*)-**19** (59 mg, 90:10 er by CSP-HPLC of the methyl ester) as a white solid. This procedure was repeated again to give *rac*-**19** (9.9 mg) and (*S*)-**19** (49.5 mg, 96:4 er by CSP-HPLC of the methyl ester). This procedure was repeated once more to give *rac*-**19** (4.4 mg) and (*S*)-**19** (44.1 mg, 98:2 er by CSP-HPLC of the methyl ester) as a white solid. $[\alpha]_D$ –23.9 (c 0.095 in EtOAc of 98:2 material). Acid (*S*)-**19** was converted into methyl ester (*S*)-**17** by reaction with Me_3SiCHN_2 in MeOH/toluene (4:6 v/v, 2 mL), quenching with glacial AcOH and evaporation under reduced pressure. CSP-HPLC of the methyl ester: Chiralcel OD-H (98:2 Hexane-*i*PrOH, 1.0 mL min^{-1}) (*S*)-**17** 11.6 min, (*R*)-**17** 12.9 min.

Crystals suitable of (S)-**19** for X-ray crystallography were prepared by dissolving (*S*)-**19** (44.1 mg, 98:2 er) in the minimum amount of EtOAc. The solution was placed into a small glass vial and placed upright in a sealed vessel containing pentane (~ 20 mL). After several days, suitable crystals had precipitated in the glass vial. These were collected and subjected to X-ray analysis.
Lab Book Reference: JCS-2-28, JCS-3-72, JCS-2-29

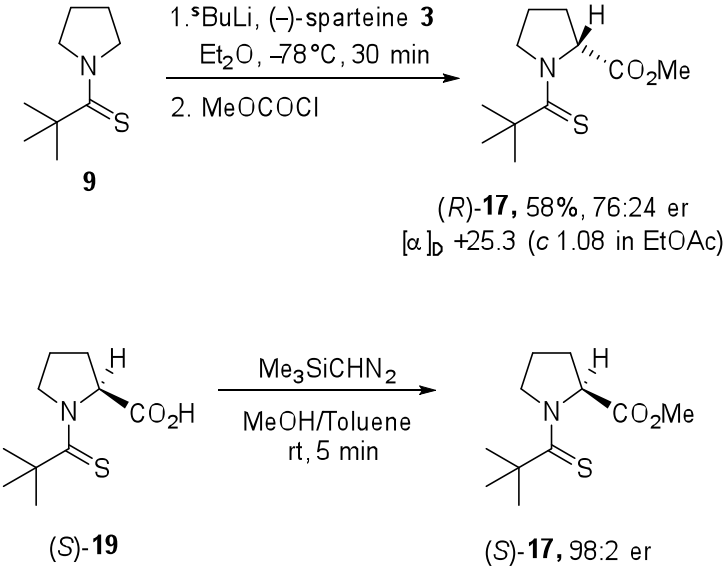




(*S*)-**19**

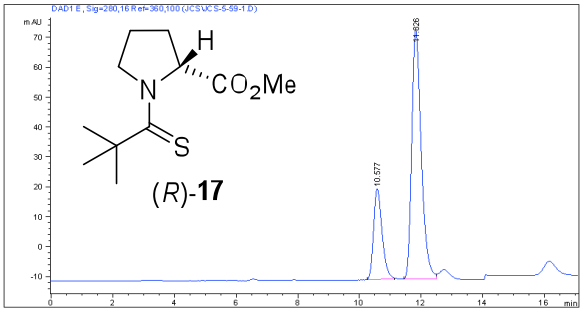
(*S*)-**22**: CCDC number 1417068

The configuration of (*R*)-**17** was assigned by converision of acid (*S*)-**19** of known configuration into (*S*)-**17** and comparision of CSP-HPLC data (Scheme S6).



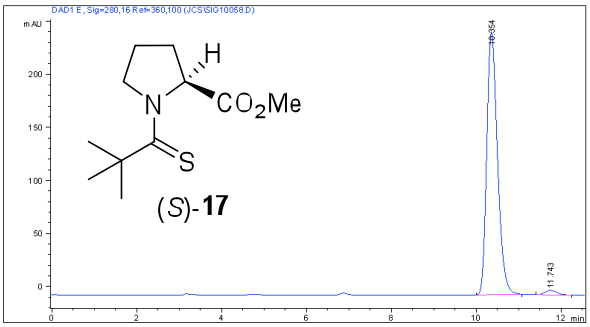
Scheme S6

CSP-HPLC of (*R*)-20 of 76:24 er



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.577	BB	0.2891	580.77203	30.37472	24.4911
2	11.826	BB	0.3268	1790.58789	83.29710	75.5089
Totals :				2371.35992	113.67181	

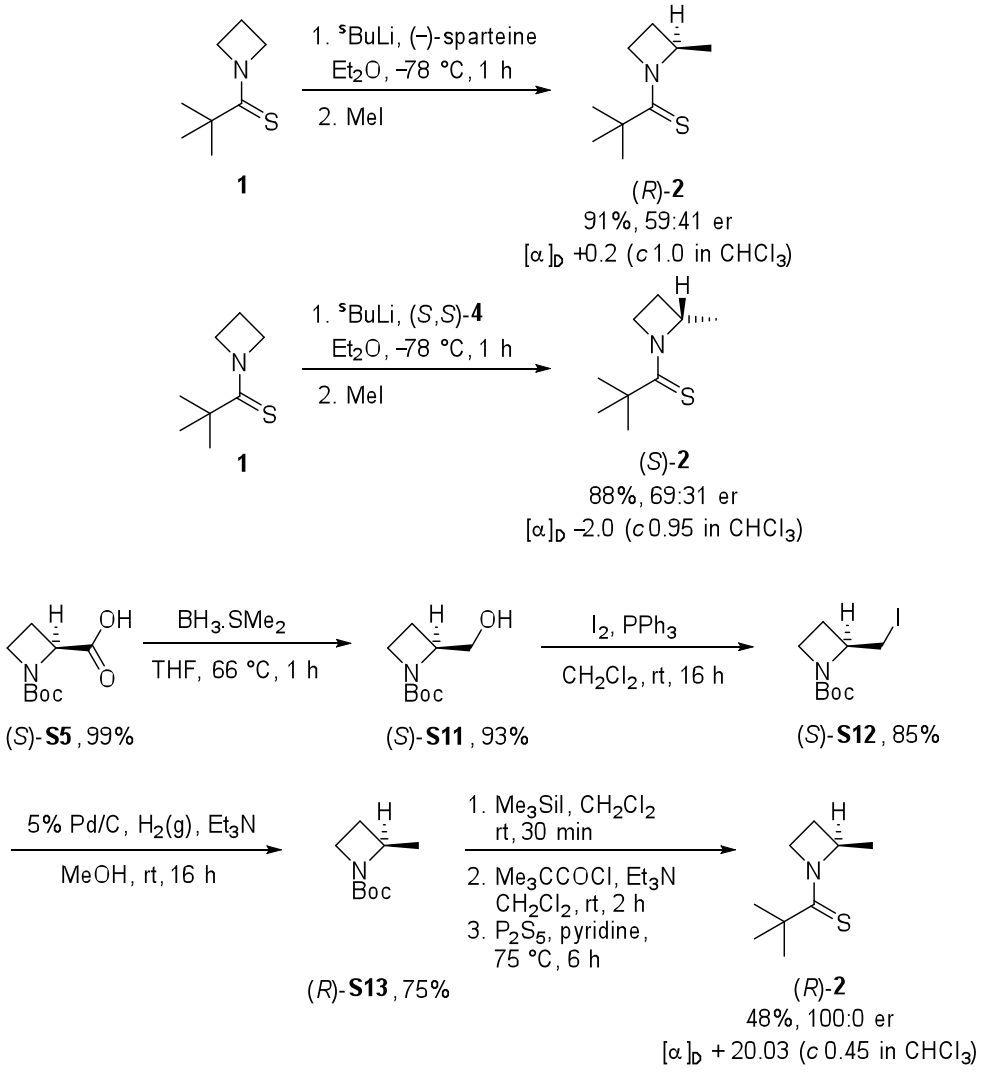
CSP-HPLC of (*S*)-20 of 98:2 er



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.354	BB	0.2708	4340.60693	247.26425	98.1432
2	11.743	BB	0.2908	82.12236	4.33949	1.8568
Totals :				4422.72929	251.60374	

2.5 Assignment of the Configuration of (*R*)-2

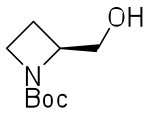
The configuration of (*R*)-**2** was assigned by comparison to (*R*)-**2** which was independently synthesised from *N*-Boc acid (*S*)-**S5** (Scheme S7).



Scheme S7

Experimental for Scheme S7

(*S*)-*tert*-Butyl 2-(hydroxymethyl)azetidine-1-carboxylate (*S*)-S11

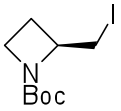


(*S*)-**S11**

Borane dimethyl sulfide complex (0.51 mL, 5.42 mmol, 1.3 eq.) was added dropwise to a stirred solution of *N*-Boc acid (*S*)-**S5** (840 mg, 4.17 mmol, 1.0 eq.) in THF (10 mL) at 0 °C under Ar. After gas evolution ceased, the resulting solution was stirred and heated at 66 °C for 1 h. Then, the solution was cooled to rt and MeOH (5 mL) was added dropwise. The solvent was evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 6:4-1:1 petrol-EtOAc as eluent gave alcohol (*S*)-**S11** (725 mg, 93%) as a colourless oil, R_F (1:1 petrol-EtOAc) 0.2; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.42 (br s, 1H, NCH), 4.25 (br s, 1H, OH), 3.88-3.82 (m, 1H, NCH_AH$_B$), 3.79-3.68 (m, 3H, NCH$_A$$H_B$ + OCH$_2$), 2.16 (dddd, J = 11.5, 11.5, 9.0, 5.0 Hz, 1H, CH_AH$_B$), 1.91 (br s, 1H, CH$_A$$H_B$), 1.43 (s, 9H, CMe$_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 157.5 (C=O), 80.3 (*C*Me$_3$), 67.0 (OCH$_2$), 63.6 (NCH), 46.7 (NCH$_2$), 28.3 (C*Me*$_3$), 17.9 (CH$_2$); $[\alpha]_D$ −19.8 (*c* 0.45 in $CHCl_3$) (lit.,[3] $[\alpha]_D$ −21.5 (*c* 0.83 in $CHCl_3$)). Spectroscopic data consistent with those reported in the literature.[3]

Lab Book Reference PJR 8/686

(*S*)-*tert*-Butyl 2-(iodomethyl)azetidine-1-carboxylate (*S*)-S12[12]

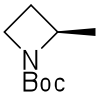


(*S*)-**S12**

Iodine (1.28 g, 5.06 mmol, 1.5 eq.) was added in three portions to a stirred solution of imidazole (459 mg, 6.74 mmol, 2.0 eq.) and triphenylphosphine (1.33 g, 5.06 mmol, 1.5 eq.) in CH_2Cl_2 (15 mL) at 0 °C over 30 min. The resulting solution was allowed to warm to rt and then stirred at rt for 10 min. Then, a solution of alcohol (*S*)-**S11** (630 mg, 4.17 mmol, 1.0 eq.) in CH_2Cl_2 (5 mL) was added dropwise and the resulting solution was stirred at rt for 16 h. The solids were removed by filtration and the filtrate was evaporated under reduced pressure. The residue was

dissolved in Et_2O (25 mL) and the solids were removed by filtration. The organic layer was washed with sat. $Na_2S_2O_{3(aq)}$ (15 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 9:1 petrol-EtOAc as eluent gave iodide (*S*)-**S12** (851 mg, 85%) as a colourless oil, R_F (9:1 petrol-EtOAc) 0.4; IR ($CHCl_3$) 2975, 2968, 1695 (C=O), 1510, 1446, 1420, 1278, 1190, 1035, 915, 815, 731 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.21-4.15 (m, 1H, NCH), 3.81-3.69 (m, 2H, NCH), 3.51 (br d, J = 9.0 Hz, 1H, CH_AH$_B$I), 3.37 (dd, J = 9.0, 9.0 Hz, CH$_A$$H_B$I), 2.29 (dddd, J = 11.5, 9.0, 8.0, 5.5 Hz, 1H, CH_AH$_B$), 1.89 (dddd, J = 11.5, 9.0, 6.5, 6.0 Hz, 1H, CH$_A$$H_B$), 1.43 (s, 9H, CMe$_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 155.6 (C=O), 79.7 (*C*Me$_3$), 61.1 (NCH), 44.9 (NCH$_2$), 28.3 (C*Me*$_3$), 23.4 (CH$_2$), 11.6 (CH$_2$I); MS (ESI) *m/z* 320 [(M + Na)$^+$, 60], 241 (100); HRMS *m/z* calcd for $C_9H_{16}INO_2$ (M + Na)$^+$ 320.0118, found 320.0108 (+3.0 ppm error); $[\alpha]_D$ −88.7 (*c* 0.95 in $CHCl_3$). Lab Book Reference PJR 8/687

(*R*)-*tert*-Butyl-2-methylazetidine-1-carboxylate (*R*)-S13[13]



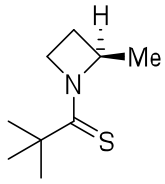
(*R*)-**S13**

5% Pd/C (65 mg, 10 wt% of (*S*)-**S12**) was added to a stirred solution of iodide (*S*)-**S12** (650 mg, 2.18 mmol, 1.0 eq.) and Et_3N (0.30 mL, 2.18 mmol, 1.0 eq.) in MeOH (10 mL) at rt. Then, the reaction flask evacuated under reduced pressure and back-filled with Ar three times. After a final evacuation, a balloon of H_2 was attached and the reaction mixture was stirred vigorously at rt under H_2 for 16 h. The solids were removed by filtration through Celite® and washed with CH_2Cl_2 (15 mL). Then, the filtrate was evaporated under reduced pressure and the residue was dissolved in CH_2Cl_2 (15 mL) and washed with 1 M $HCl_{(aq)}$ (10 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 4:1 petrol-Et_2O as eluent gave methyl azetidine (*R*)-**S13** (280 mg, 75%) as a colourless oil, R_F (4:1 petrol-Et_2O) 0.3; ^1H NMR (400 MHz, $CDCl_3$) δ 4.26 (dq, J = 6.5, 6.5 Hz 1H, NCH), 3.81-3.77 (m, 2H, NCH$_2$), 2.30-2.21 (m, 1H, CH_AH$_B$), 1.74 (dddd, J = 11.0, 8.0, 8.0, 6.0 Hz, 1H, CH$_A$$H_B$), 1.42 (s, 9H, CMe$_3$), 1.35 (d, J = 6.5 Hz, Me); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 156.4 (C=O), 78.9 (*C*Me$_3$), 57.9 (br, NCH), 45.7 (br, NCH$_2$), 28.4

(C*Me*$_3$), 23.6 (CH_2), 21.5 (Me); $[\alpha]_D$ −38.1 (*c* 1.0 in $CHCl_3$) (lit.,[3] $[\alpha]_D$ −40.5 (*c* 0.80 in $CHCl_3$)). Spectroscopic data consistent with those reported in the literature.[3]

Lab Book Reference: PJR 8/688A

(*R*)-2,2-Dimethyl-1-(2-methylazetidin-1-yl)propane-1-thione (*R*)-2

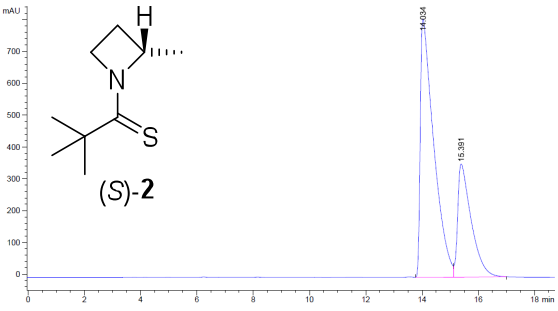


(*R*)-**2**

Trimethylsilyliodide (16 μL, 0.11 mmol, 1.2 eq.) was added dropwise to a stirred solution of *N*-Boc methyl azetidine (*R*)-**S13** (16 mg, 0.09 mmol, 1.0 eq.) in CH_2Cl_2 (5 mL) under N_2 at rt. The resulting solution was stirred at rt for 30 min. Then, Et_3N (18 μL, 0.14 mmol, 1.5 eq.) and trimethylacetylchloride (17 μL, 0.14 mmol, 1.5 eq.) were added sequentially and the resulting solution was stirred at rt for 2 h. 1 M $HCl_{(aq)}$ (10 mL) was added and the two layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 x 10 mL). The combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure. The residue was dissolved in pyridine (20 mL) and phosphorus(V) sulfide (32 mg, 0.14 mmol, 1.5 eq.) was added. The resulting solution was stirred heated at 75 °C for 6 h. The solution was allowed to cool to rt and then poured into 1 M $HCl_{(aq)}$ (15 mL). Conc. HCl was added until pH 3 was obtained. The resulting solution was stirred at rt for 2 h and then extracted with CH_2Cl_2 (3 × 15 mL). The combined organic extracts were washed with 1 M $HCl_{(aq)}$ (100 mL), water (100 mL) and brine (100 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 9:1-8:2 hexane-Et_2O as eluent gave methylazetidine (*R*)-**2** (7.6 mg, 48%, 100:0 er by CSP-HPLC) as a pale yellow oil, R_F (8:2 petrol-Et_2O) 0.3; $[\alpha]_D$ +20.03 (*c* 0.45 in $CHCl_3$) (lit.,[3] $[\alpha]_D$ −21.3 (*c* 1.15 in $CHCl_3$ for (*R*)-**2** of >99:1 er)); CSP-HPLC: Chiracel OD-H (99.9:0.1 Hexane-*i*PrOH, 1.0 mL min^{-1}) (*R*)-**2** 19.2 min.

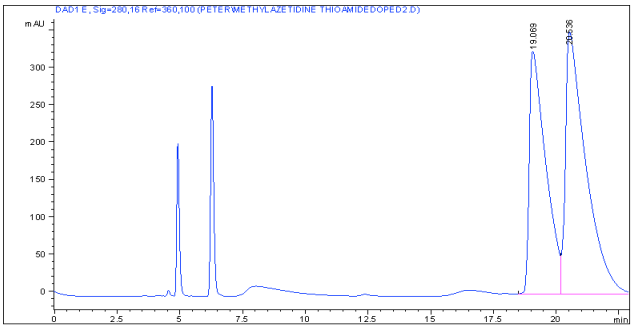
Note: Optical rotation data is not consistent with that reported in the literature and the absolute stereochemical configuration was assigned by CSP-HPLC.

CSP-HPLC of (*S*)-2 of 69:31 er



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.034	VV	0.4737	2.69269e4	810.32404	69.4040
2	15.391	VB	0.4837	1.18704e4	355.40292	30.5960
Totals :				3.87974e4	1165.72696	

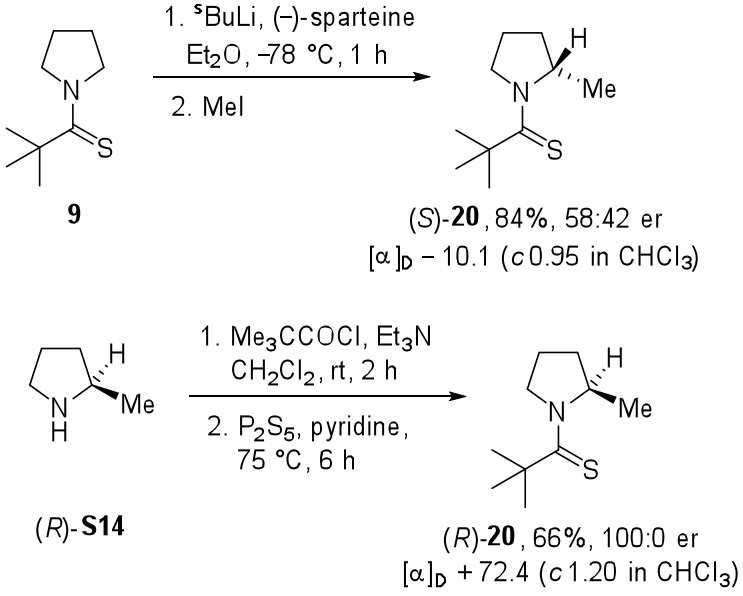
CSP-HPLC of (*S*)-2 (69:31 er) doped with (*R*)-2 (>99:1 er)



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	19.069	BV	0.6505	1.48530e4	325.39377	42.8168
2	20.536	VBA	0.7834	1.98367e4	350.97443	57.1832
Totals :				3.46898e4	676.36819	

2.6 Assignment of the Configuration of (*S*)-20

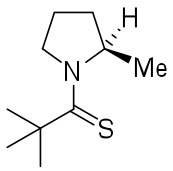
The configuration of (*S*)-**20** was assigned by comparison to (*R*)-**20** which was independently synthesised from commercially available (*R*)-(−)-methylpyrrolidine (*R*)-**S14** (Scheme S8).



Scheme S8

Experimental for Scheme S8

(*R*)-2,2-Dimethyl-1-(2-methylpyrrolidin-1-yl)propane-1-thione (*R*)-20



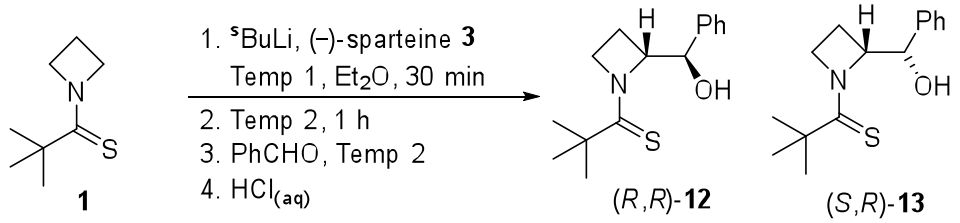
(*R*)-**20**

Trimethylacetyl chloride (320 μL, 2.6 mmol, 1.3 eq.) was added to a stirred solution of (*R*)-(−)-methylpyrrolidine (202 μL, 2.0 mmol, 1.0 eq.) and Et_3N (338 μL, 2.6 mmol, 1.3 eq.) in CH_2Cl_2 (10 mL) at 0 °C. The resulting solution was allowed to warm to rt and stirred at rt for 2 h. Then, 1 M $HCl_{(aq)}$ (10 mL) was added and the two layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were dried ($MgSO_4$) and evaporated under reduce pressure to give the crude *N*-pivaloyl pyrrolidine. The residue was dissolved in pyridine (35 mL) and phosphorous(V) sulfide (556 mg, 2.50 mmol, 1.25 eq.) was added. The resulting solution was heated to 75 °C for 6 h. The solution was allowed to cool to rt and then poured into 1 M $HCl_{(aq)}$ (30 mL). 1 M $HCl_{(aq)}$ was added until pH 3 was obtained. The resulting solution was stirred at rt for 2 h and then extracted with CH_2Cl_2 (3 × 15 mL). The combined organic extracts were washed with 1 M $HCl_{(aq)}$ (50 mL), water (50 mL) and brine (50 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 9:1-8:2 petrol-Et_2O as eluent gave methylated pyrrolidine (*R*)-**20** (243 mg, 66%, 100:0 er by CSP-HPLC) as a colourless oil, R_F (8:2 petrol-Et_2O) 0.2; $[\alpha]_D$ +72.4 (*c* 1.20 in $CHCl_3$); CSP-HPLC: Chiracel OD-H (99.5:0.5 Hexane-*i*PrOH, 1.0 mL min^{-1}) (*R*)-**20** 13.9 min.

3. Additional Experiments

Having established that a dynamic resolution of diastereomeric lithiated intermediates was responsible for the enantioselectivity in the lithiation-trapping of **1**, we briefly explored different temperatures and additional electrophiles with azetidine **1** (Table S1).

Table S1. Asymmetric lithiation-PhCHO trapping of *N*-thiopivaloyl azetidine **1** at different temperatures.

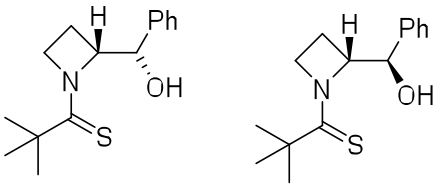


Entry	Temp 1 / °C[a]	Temp 2 / °C[b]	Product	Yield/%[c]	Er[d]
1	–100	–100	(*R*,*R*)-**12**	66	77:23
			(*S*,*R*)-**13**	7	57:43
2	–78	–78	(*R*,*R*)-**12**	75	75:25
			(*S*,*R*)-**13**	9	58:42
3	–78	–50	(*R*,*R*)-**12**	82	68:32
			(*S*,*R*)-**13**	13	58:42
4	–78	–40	(*R*,*R*)-**12**	14	56:44
			(*S*,*R*)-**13**	84	62:38
5	–78	–30	(*R*,*R*)-**12**	76	59:41
			(*S*,*R*)-**13**	11	55:45
6	–78	–30[e]	(*R*,*R*)-**12**	72	75:25
			(*S*,*R*)-**13**	7	59:41

[a] Temp 1 = lithiation temperature. [b] Temp 2 = incubation temperature. [c] % Yield after purification by chromatography. [d] Er determined by CSP-HPLC after purification by chromatography (see Supporting Information). [e] Reaction cooled to –78 °C for 30 min before addition of PhCHO.

Experimental for Table S1

1-[(2*R*)-2-[(*S*)-Hydroxy(phenyl)methyl]azetidin-1-yl]-2,2-dimethylpropane-1-thione (*S*,*R*)-13 and 1-[(2*R*)-2-[(*R*)-hydroxy(phenyl)methyl]azetidin-1-yl]-2,2-dimethylpropane-1-thione (*R*,*R*)-12



(*S*,*R*)-**13** (*R*,*R*)-**12**

(Table S1, entry 1)

s-BuLi (0.46 mL of a 1.3 M solution in hexanes, 0.6 mmol, 1.2 eq.) was added to a stirred solution of *N*-thiopivaloyl azetidine **1** (79 mg, 0.5 mmol, 1.0 eq.) and (−)-sparteine **3** (0.14 mL, 0.6 mmol, 1.2 eq.) in Et_2O (5 mL) at −100 °C under Ar. The resulting solution was stirred at −100 °C for 30 min. Then, benzaldehyde (76 μL, 0.75 mmol, 1.5 eq.) was added dropwise and the resulting solution was stirred at −100 °C for 1 h. Then, 1 M $HCl_{(aq)}$ (10 mL) was added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 x 10 mL). The combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product which contained an 87:13 mixture of alcohols (*R,R*)-**12** and (*S,R*)-**13** by ^1H NMR spectroscopy. Purification by flash column chromatography on silica with 9:1-8:2 petrol-EtOAc as eluent gave alcohol (*S,R*)-**13** (9 mg, 7%, 57:43 er by CSP-HPLC) as a white solid, CSP-HPLC: Chiracel AD-H (95:5 Hexane-*i*PrOH, 1.0 mL min^{-1}) (*S*,*R*)-**13** 7.4 min, (*R*,*S*)-**13** 10.0 min and alcohol (*R,R*)-**12** (87 mg, 66%, 77:23 er by CSP-HPLC) as a white solid, CSP-HPLC: Chiracel AD-H (95:5 Hexane-*i*PrOH, 1.0 mL min^{-1}) (*R*,*R*)-**12** 18.4 min, (*S*,*S*)-**12** 20.8 min.

Lab Book Reference PJR 8/625

(Table S1, entry 3)

s-BuLi (0.46 mL of a 1.3 M solution in hexanes, 0.6 mmol, 1.2 eq.) was added to a stirred solution of *N*-thiopivaloyl azetidine **1** (79 mg, 0.5 mmol, 1.0 eq.) and (−)-sparteine **3** (0.14 mL, 0.6 mmol, 1.2 eq.) in Et_2O (5 mL) at −78 °C under Ar. The resulting solution was stirred at −78 °C for 30 min. Then, the solution was warmed to −50 °C and stirred for 1 h. Benzaldehyde (76 μL, 0.75 mmol, 1.5 eq.) was added dropwise and the resulting solution was stirred at −50 °C for

10 min. Then, 1 M $HCl_{(aq)}$ was added. The two layers were separated and the aqueous layer was extracted with Et_2O (3 x 10 mL). The combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product which contained an 80:20 mixture of alcohols (*R,R*)-**12** and (*S,R*)-**13** by ^1H NMR spectroscopy. Purification by flash column chromatography on silica with 9:1-8:2 petrol-EtOAc as eluent gave alcohol (*S,R*)-**13** (17 mg, 13%, 58:42 er by CSP-HPLC) as a white solid, CSP-HPLC: Chiracel AD-H (95:5 Hexane-*i*PrOH, 1.0 mL min^{-1}) (*S*,*R*)-**13** 7.5 min, (*R*,*S*)-**13** 10.2 min and alcohol (*R,R*)-**12** (108 mg, 82%, 68:32 er by CSP-HPLC) as a white solid, CSP-HPLC: Chiracel AD-H (95:5 Hexane-*i*PrOH, 1.0 mL min^{-1}) (*R*,*R*)-**12** 18.4 min, (*S*,*S*)-**12** 20.9 min.

Lab Book Reference PJR 8/657

(Table S1, entry 4)

s-BuLi (0.46 mL of a 1.3 M solution in hexanes, 0.6 mmol, 1.2 eq.) was added to a stirred solution of *N*-thiopivaloyl azetidine **1** (79 mg, 0.5 mmol, 1.0 eq.) and (−)-sparteine **3** (0.14 mL, 0.6 mmol, 1.2 eq.) in Et_2O (5 mL) at −78 °C under Ar. The resulting solution was stirred at −78 °C for 30 min. Then, the solution was warmed to −40 °C and stirred for 1 h. Benzaldehyde (76 μL, 0.75 mmol, 1.5 eq.) was added dropwise and the resulting solution was stirred at −40 °C for 10 min. Then, 1 M $HCl_{(aq)}$ was added. The two layers were separated and the aqueous layer was extracted with Et_2O (3 x 10 mL). The combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product which contained an 80:20 mixture of alcohols (*R,R*)-**12** and (*S,R*)-**13** by ^1H NMR spectroscopy. Purification by flash column chromatography on silica with 9:1-8:2 petrol-EtOAc as eluent gave alcohol (*S,R*)-**13** (19 mg, 14%, 56:44 er by CSP-HPLC) as a white solid, CSP-HPLC: Chiracel AD-H (95:5 Hexane-*i*PrOH, 1.0 mL min^{-1}) (*S*,*R*)-**13** 7.5 min, (*R*,*S*)-**13** 10.1 min and alcohol (*R,R*)-**12** (111 mg, 84%, 62:38 er by CSP-HPLC) as a white solid, CSP-HPLC: Chiracel AD-H (95:5 Hexane-*i*PrOH, 1.0 mL min^{-1}) (*R*,*R*)-**12** 18.2 min, (*S*,*S*)-**12** 20.8 min.

Lab Book Reference PJR 8/656

(Table S1, entry 5)

s-BuLi (0.46 mL of a 1.3 M solution in hexanes, 0.6 mmol, 1.2 eq.) was added to a stirred solution of *N*-thiopivaloyl azetidine **1** (79 mg, 0.5 mmol, 1.0 eq.) and (−)-sparteine **3** (0.14 mL, 0.6 mmol, 1.2 eq.) in Et_2O (5 mL) at −78 °C under Ar. The resulting solution was stirred at −78 °C for 30 min. Then, the solution was warmed to −30 °C and stirred for 1 h. Benzaldehyde (76 μL, 0.75 mmol, 1.5 eq.) was added dropwise and the resulting solution was stirred at −30 °C for 10 min. Then, 1 M $HCl_{(aq)}$ was added. The two layers were separated and the aqueous layer was extracted with Et_2O (3 x 10 mL). 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 alcohols (*R,R*)-**12** and (*S,R*)-**13** by ^{1}H NMR spectroscopy. Purification by flash column chromatography on silica with 9:1-8:2 petrol-EtOAc as eluent gave alcohol (*S,R*)-**13** (15 mg, 11%, 55:45 er by CSP-HPLC) as a white solid, CSP-HPLC: Chiracel AD-H (95:5 Hexane-*i*PrOH, 1.0 mL min^{-1}) (*S*,*R*)-**13** 7.5 min, (*R*,*S*)-**13** 10.2 min and alcohol (*R,R*)-**12** (100 mg, 76%, 59:41 er by CSP-HPLC) as a white solid, CSP-HPLC: Chiracel AD-H (95:5 Hexane-*i*PrOH, 1.0 mL min^{-1}) (*R*,*R*)-**12** 18.5 min, (*S*,*S*)-**12** 20.5 min.

Lab Book Reference PJR 8/658

(Table S1, entry 6)

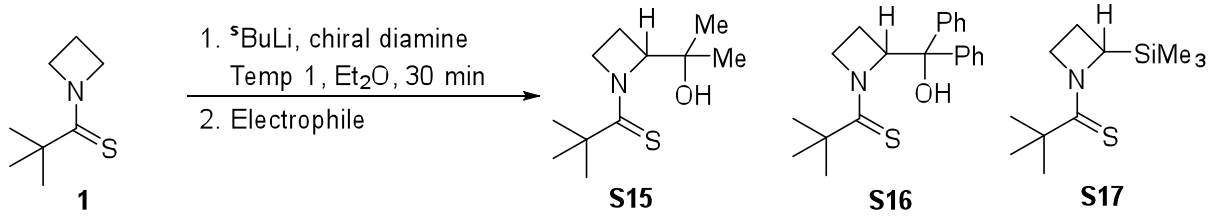
s-BuLi (0.46 mL of a 1.3 M solution in hexanes, 0.6 mmol, 1.2 eq.) was added to a stirred solution of *N*-thiopivaloyl azetidine **1** (79 mg, 0.5 mmol, 1.0 eq.) and (−)-sparteine **3** (0.14 mL, 0.6 mmol, 1.2 eq.) in Et_2O (5 mL) at −78 °C under Ar. The resulting solution was stirred at −78 °C for 30 min. Then, the solution was warmed to −30 °C and stirred for 1 h. The solution was then cooled to −78 °C and stirred at −78 °C for 30 min. Benzaldehyde (76 μL, 0.75 mmol, 1.5 eq.) was added dropwise and the resulting solution was stirred at −30 °C for 10 min. Then, 1 M $HCl_{(aq)}$ was added. The two layers were separated and the aqueous layer was extracted with Et_2O (3 x 10 mL). The combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product which contained a 86:14 mixture of alcohols (*R,R*)-**12** and (*S,R*)-**13** by ^{1}H NMR spectroscopy. Purification by flash column chromatography on silica with 9:1-8:2 petrol-EtOAc as eluent gave alcohol (*S,R*)-**13** (9 mg, 7%, 59:41 er by CSP-HPLC) as a white solid, CSP-HPLC: Chiracel AD-H (95:5 Hexane-*i*PrOH, 1.0 mL min^{-1}) (*S*,*R*)-**13** 7.4 min, (*R*,*S*)-**13** 10.1 min and alcohol (*R,R*)-**12** (95 mg, 72%, 75:25 er by CSP-HPLC) as a white solid,

CSP-HPLC: Chiracel AD-H (95:5 Hexane-*i*PrOH, 1.0 mL min^{-1}) (*R*,*R*)-**12** 18.3 min, (*S*,*S*)-**12** 20.5 min.

Lab Book Reference PJR 8/664

In an attempt to explore the dynamic resolution mechanism further, we briefly explored two other carbonyl electrophiles and Me_3SiCl. In these cases, we have been unable to determine the absolute configuration of the major enantiomers of the products, **S15**-**S17**.

Table S2. Asymmetric lithiation-trapping of *N*-thiopivaloyl azetidine 1 with different electrophiles.

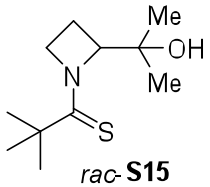


Entry	Diamine	Electrophile	Product	Yield /%[a]	Er[b]
1	**3**	$Me_2C=O$	**S15**	34	60:40
2	**3**	$Ph_2C=O$	**S16**	36	56:44
3	**3**	Me_3SiCl	**S17**	56	56:44
4	(*S*,*S*)-**4**	Me_3SiCl	**S17**	45	47:53

[a] % Yield after purification by chromatography. [b] Er determined by CSP-HPLC after purification by chromatography (see Supporting Information).

Experimental for Table S2

***rac*-1-(2-(2-hydroxypropan-2-yl)azetidin-1-yl)-2,2-dimethylpropane-1-thione S15**



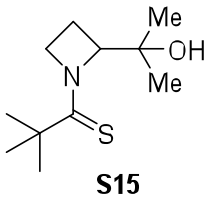
(Racemic standard for Table S2, entry 1)

s-BuLi (0.50 mL of a 1.3 M solution in hexanes, 0.65 mmol, 1.3 eq.) was added to a stirred solution of *N*-thiopivaloyl azetidine **1** (79 mg, 0.08 mL, 0.50 mmol, 1.0 eq.) and TMEDA (0.18

mL, 131 mg, 1.2 mmol, 2.4 eq.) in Et_2O (7 mL) at −100 °C under N_2. The resulting solution was stirred at −100 °C for 2 min. Then, distilled, dry acetone (0.073 mL, 58 mg, 1.0 mmol, 2.0 eq.) was added and the solution was stirred at −100 °C for 10 min and allowed to warm to rt over the course of 1 h. 2 M $HCl_{(aq)}$ (3 mL) was added and the two layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 10 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 8:2-7:3 hexane-EtOAc as eluent gave alcohol *rac*-**S15** (40 mg, 0.187 mmol, 37%) as a brown solid, mp 74–77 °C; IR (ATR) 3264 (OH), 2967, 2924, 1464, 1433, 1402, 1362, 1300, 1255, 1173, 1136, 986, 948, 541, 474 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.00 (br s, 1H, OH), 4.96 (dd, J = 10.0, 6.0 Hz, 1H, CHN), 4.46-4.40 (m, 2H, CH_2N), 2.52–2.41 (m, 1H, CH_AH_B), 1.97-1.87 (m, 1H, CH_AH_B), 1.36 (s, 9H, CMe_3), 1.30 (s, 3H, Me), 1.15 (s, 3H, Me); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 212.5 (C=S), 79.1 (CHN), 73.3 ($C(Me)_2OH$), 56.3 (CH_2N), 43.8 (CMe_3), 29.8 (CMe_3), 25.7 (Me), 23.2 (Me), 19.5 (CH_2); MS (ESI) *m/z* 238 [$(M+Na)^+$, 85] 216 [$(M+H)^+$, 100]; HRMS *m/z* calcd for $C_{11}H_{22}NOS$ $(M+Na)^+$ 238.1236, found 238.1229 (+3.0 ppm error). Spectroscopic data consistent with those reported in the literature.[3]

Lab Book Reference: JCS-2-6

1-(2-(2-Hydroxypropan-2-yl)azetidin-1-yl)-2,2-dimethylpropane-1-thione S15



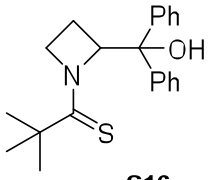
S15

(Table S2, entry 1)

Using general procedure A, *s*-BuLi (0.46 mL of a 1.3 M solution in hexanes, 0.60 mmol, 1.2 eq), *N*-thiopivaloyl azetidine **1** (0.08 mL, 79 mg, 0.5 mmol, 1.0 eq), (–)-sparteine **3** (0.14 mL, 141 mg, 0.6 mmol, 1.2 eq) in Et_2O (5 mL) and freshly distilled, dry acetone (0.06 mL, 48 mg, 0.75 mmol, 1.5 eq) gave the crude product. Purification by flash column chromatography on silica with 8:2-7:3 hexane-EtOAc as eluent gave **S15** (23 mg, 0.107 mmol, 22%, 60:40 er by CSP-HPLC) as a brown solid, mp 70–75 °C; $[\alpha]_D$ –7.5 (*c* 0.95 in EtOAc); CSP-HPLC: Chiralcel OD-H (98:2 Hexane-*i*PrOH, 1.0 mL min^{-1}) 13.0 min (major), 14.1 min (minor).

Lab Book Reference: JCS-2-14

***Rac*-1-(2-(Hydroxydiphenylmethyl)azetidin-1-yl)-2,2-dimethylpropane-1-thione S16**



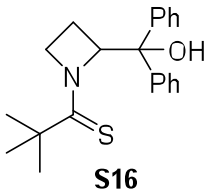
rac-**S16**

(Racemic standard for Table S2, entry 2)

s-BuLi (0.50 mL of a 1.3 M solution in hexanes, 0.65 mmol, 1.3 eq.) was added to a stirred solution of *N*-thiopivaloyl azetidine **1** (79 mg, 0.08 mL, 0.50 mmol, 1.0 eq.) and TMEDA (0.18 mL, 131 mg, 1.2 mmol, 2.4 eq.) in Et_2O (7 mL) at −100 °C under N_2. The resulting solution was stirred at −100 °C for 2 min. Then, a solution of benzophenone (182 mg, 1.0 mmol, 2.0 eq.) in Et_2O (0.5 mL) was added and the solution was stirred at −100 °C for 10 min and allowed to warm to rt over the course of 1 h. 2 M $HCl_{(aq)}$ (3 mL) was added and the two layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 10 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 95:5-8:2 hexane-EtOAc as eluent gave alcohol *rac*-**S16** (55 mg, 0.16 mmol, 32%) as a white solid, mp 191–193 °C; R_F (8:2 petroleum ether-EtOAc) 0.4; IR (ATR) 3163 (O–H), 2961, 2929, 1467, 1395, 1366, 1316, 1287, 1247, 1214, 1060, 1013, 767, 704, 587 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.49–7.45 (m, 2H, Ph), 7.38–7.30 (m, 6H, Ph), 7.27–7.24 (m, 2H, Ph), 5.93 (ddd, J = 9.5, 5.0, 1.5 Hz, 1H, CHN), 4.16 (ddd, J = 10.0, 10.0, 4.5 Hz, 1H, CH_AH$_B$N), 3.41–3.32 (m, 1H, CH$_A$$H_B$N), 2.72–2.61 (m, 1H, C$H_AH_B$), 2.11–2.02 (m, 1H, CH$_A$$H_B$), 1.18 (s, 9H, CMe$_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 212.6 (C=S), 144.6 (*ipso*-Ph), 142.6 (*ipso*-Ph), 128.5 (*m*-Ph), 128.1 (*m*-Ph), 127.8 (*p*-Ph), 127.7 (*p*-Ph), 127.5 (*o*-Ph), 127.3 (*o*-Ph), 82.8 (*C*(Ph)$_2$OH), 77.3 (CHN), 56.7 (CH$_2$N), 43.7 (*C*Me$_3$), 29.7 (C*Me$_3$*), 21.0 (CH$_2$); MS (ESI) *m/z* 340 [(M + H)$^+$, 100]; HRMS *m/z* calcd for $C_{21}H_{26}NOS$ (M+H)$^+$ 340.1730, found 340.1723 (+2.0 ppm error).

Lab Book Reference: JCS-2-2

1-(2-(Hydroxydiphenylmethyl)azetidin-1-yl)-2,2-dimethylpropane-1-thione S16



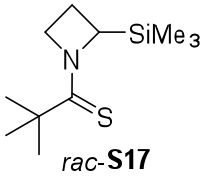
S16

(Table S2, entry 2)

Using general procedure A, *s*-BuLi (0.5 mL of a 1.3 M solution in hexanes, 0.65 mmol, 1.3 eq), *N*-thiopivaloyl azetidine **1** (0.08 mL, 79 mg, 0.5 mmol, 1.0 eq), (–)-sparteine **3** (0.14 mL, 141 mg, 0.6 mmol, 1.2 eq) in Et_2O (7 mL) and a solution of benzophenone (182 mg, 1.0 mmol, 2.0 eq) in Et_2O (0.5 mL) gave the crude product. Purification by flash column chromatography on silica eluting with 95:5-8:2 hexane-EtOAc as eluent gave alcohol **S16** (61 mg, 0.18 mmol, 36%, 56:44 er by CSP-HPLC) as a white solid, mp 179–183 °C; $[\alpha]_D$ +23.6 (*c* 0.85 in $CHCl_3$). CSP-HPLC: Chiralcel OD-H (98:2 Hexane-*i*PrOH, 1.0 mL min^{-1}) 8.0 min (minor), 12.9 min (major).

Lab Book Reference: JCS-2-10

***rac*-2,2-Dimethyl-1-(2-(trimethylsilyl)azetidin-1-yl)propane-1-thione *rac*-S17**



rac-**S17**

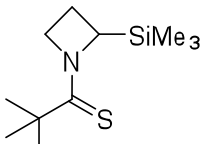
(Racemic standard for Table S2, entries 3 and 4)

s-BuLi (0.50 mL of a 1.3 M solution in hexanes, 0.65 mmol, 1.3 eq.) was added to a stirred solution of *N*-thiopivaloyl azetidine **1** (79 mg, 0.08 mL, 0.50 mmol, 1.0 eq.) and TMEDA (0.18 mL, 131 mg, 1.2 mmol, 2.4 eq.) in Et_2O (5 mL) at −100 °C under N_2. The resulting solution was stirred at −100 °C for 2 min. Then, trimethylsilyl chloride (0.133 mL, 109 mg, 1.0 mmol, 2.0 eq.) was added and the solution was stirred at −100 °C for 10 min and allowed to warm to rt over the course of 1 h. 2 M $HCl_{(aq)}$ (3 mL) was added and the two layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 10 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 98:2 petrol-EtOAc as eluent gave silane *rac*-**S17** (73 mg, 0.32 mmol, 64%) as a white solid, R_F (8:2 petrol ether–EtOAc) 0.46; IR (ATR) 2950, 1474, 1441,

1361, 1244, 1134, 1016, 1110, 1003, 945, 833, 752, 687, 645, 496 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.61 (ddd, J = 11.0, 6.5, 2.0 Hz, 1H, CHN), 4.52–4.39 (m, 2H, CH_2N), 2.47–2.35 (m, 1H, CH_AH_B), 2.10–2.00 (m, 1H, CH_AH_B), 1.33 (s, 9H, CMe_3), 0.18 (s, 9H, $SiMe_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 206.1 (C=S), 62.2 (CHN), 57.1 (CH_2N), 42.9 (CMe_3), 30.0 (CMe_3), 17.1 (CH_2), –1.30 ($SiMe_3$); MS (ESI) m/z 230 [$(M + H)^+$, 100]; HRMS m/z calcd for $C_{11}H_{24}NSSi$ $(M + H)^+$ 230.1393, found 230.1388 (+2.3 ppm error). Spectroscopic data consistent with those reported in the literature.[3]

Lab Book Reference: JCS-1-103

2,2-Dimethyl-1-(2-(trimethylsilyl)azetidin-1-yl)propane-1-thione S17



S17

(Table S2, entry 3)

Using general procedure A, *s*-BuLi (0.46 mL of a 1.3 M solution in hexanes, 0.60 mmol, 1.2 eq), *N*-thiopivaloyl azetidine **1** (0.08 mL, 79 mg, 0.5 mmol, 1.0 eq), (–)-sparteine **3** (0.14 mL, 141 mg, 0.6 mmol, 1.2 eq) in Et_2O (5 mL) and trimethylsilyl chloride (95 μL, 81 mg, 0.75 mmol, 1.5 eq) gave the crude product. Purification by flash column chromatography on silica with 9:1 hexane-EtOAc as eluent gave silane **S17** (64 mg, 0.28 mmol, 56%, 56:46 er by CSP-HPLC) as a white solid, mp 49–52 °C; $[\alpha]_D$ +15.6 (*c* 0.52 in EtOAc); CSP-HPLC: Chiralcel OD-H (98:2 Hexane-*i*PrOH, 1.0 mL min^{-1}) 4.7 min (major), 5.9 min (minor).

Lab Book Reference: JCS-2-11

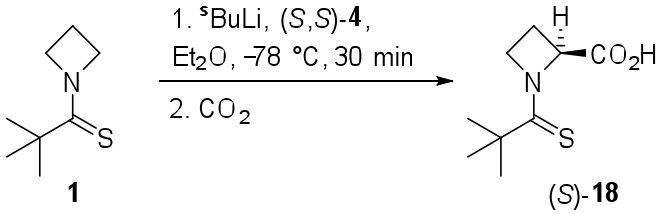
(Table S2, entry 4)

Using general procedure A, *s*-BuLi (0.46 mL of a 1.3 M solution in hexanes, 0.60 mmol, 1.2 eq), *N*-thiopivaloyl azetidine **1** (0.08 mL, 79 mg, 0.5 mmol, 1.0 eq), diamine (*S*,*S*)-**4** (186 mg, 0.6 mmol, 1.2 eq) in Et_2O (5 mL) and trimethylsilyl chloride (95 μL, 81 mg, 0.75 mmol, 1.5 eq) gave the crude product. Purification by flash column chromatography on silica with 9:1 hexane-EtOAc as eluent gave silane **S17** (51 mg, 0.22 mmol, 45%, 47:53 er by CSP-HPLC) as a white

solid, mp 46–49 °C; $[\alpha]_D$ +19.2 (*c* 1.145 in EtOAc); CSP-HPLC: Chiralcel OD-H (98:2 Hexane-*i*PrOH, 1.0 mL min^{-1}) 4.7 min (minor), 5.5 min (major).
Lab Book Reference: JCS-2-12

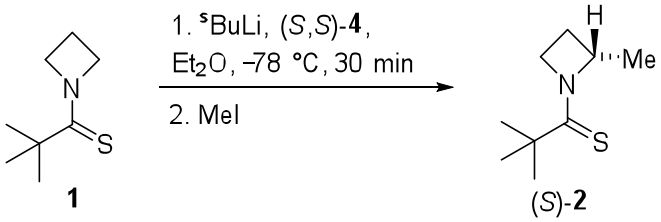
Experiments were also conducted using alternative ligand/electrophile combinations and the experimental detail is reported below.

(*S*)-1-(2,2-Dimethylpropanethioyl)azetidine-2-carboxylic acid (*S*)–18



s-BuLi (0.46 mL of a 1.3 M solution in hexanes, 0.6 mmol, 1.2 eq) was added to a solution of *N*-thiopivaloyl azetidine **1** (0.077 mL, 79 mg, 0.5 mmol, 1.0 eq) and (*S*,*S*)-diamine **4** (178 mg, 0.6 mmol, 1.2 eq) in Et_2O (5 mL) at –78 °C under N_2. The resulting solution was stirred at –78 °C for 30 min. Then, dry CO_2 (generated from solid CO_2 flushed through $CaCl_2$ and added into the reaction *via* cannula) was bubbled through the reaction mixture for 10 min at –78 °C and then allowed to warm to rt over 1 h. The reaction mixture was diluted with Et_2O (10 mL) and extracted with water (6 x 5 mL). The aqueous layer was acidified to pH < 2 with 2 M $HCl_{(aq)}$ and extracted with CH_2Cl_2 (6 x 5 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give acid (*S*)-**18** (71 mg, 0.36 mmol, 71%, 57:43 er by CSP-HPLC of the methyl ester) as an off-white solid. Acid (*S*)-**18** was converted into methyl ester (*S*)-**16** by reaction with Me_3SiCHN_2 in MeOH/toluene (4:6 v/v, 2 mL), quenching with glacial AcOH and evaporation under reduced pressure. CSP-HPLC of methyl ester (*S*)-**16**: Chiralcel OD-H (98:2 Hexane-*i*PrOH, 1.0 mL min^{-1}) (*S*)-**16** 14.5 min, (*R*)-**16** 18.3 min.
Lab Book Reference: JCS-2-15, JCS-3-69

(*S*)-2,2-Dimethyl-1-(2-methylazetidin-1-yl)propane-1-thione (*S*)-2

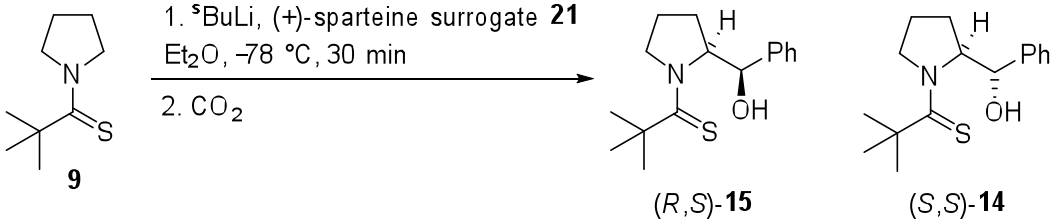


Using general procedure A, *s*-BuLi (0.46 mL of a 1.3M solution in hexanes, 0.60 mmol, 1.2 eq.), *N*-thiopivaloyl azetidine **1** (79 mg, 0.50 mmol, 1.0 eq.) and diamine (*S*,*S*)-**4** (186 mg, 0.60 mmol, 1.2 eq.) in Et_2O (5 mL) and methyl iodide (47 μL, 0.75 mmol, 1.5 eq.) gave the crude product. Purification by flash column chromatography on silica with 9:1-8:2 petrol-Et_2O gave methylated azetidine (*S*)-**2** (76 mg, 88%, 69:31 er by CSP-HPLC) as a colourless oil, $[\alpha]_D$ −2.0 (*c* 0.95 in $CHCl_3$) (lit.,[3] $[\alpha]_D$ −21.3 (*c* 1.15 in $CHCl_3$ for (*R*)-**2** of 99:1 er)); CSP-HPLC: Chiracel OD-H (99.9:0.1 Hexane-*i*PrOH, 1.0 mL min^{-1}) (*S*)-**2** 14.0 min, (*R*)-**2** 15.4 min.

Note: Optical rotation data is not consistent with that reported in the literature[3] and the configuration was assigned by CSP-HPLC (see Section 2).

Lab Book Reference PJR 8/668

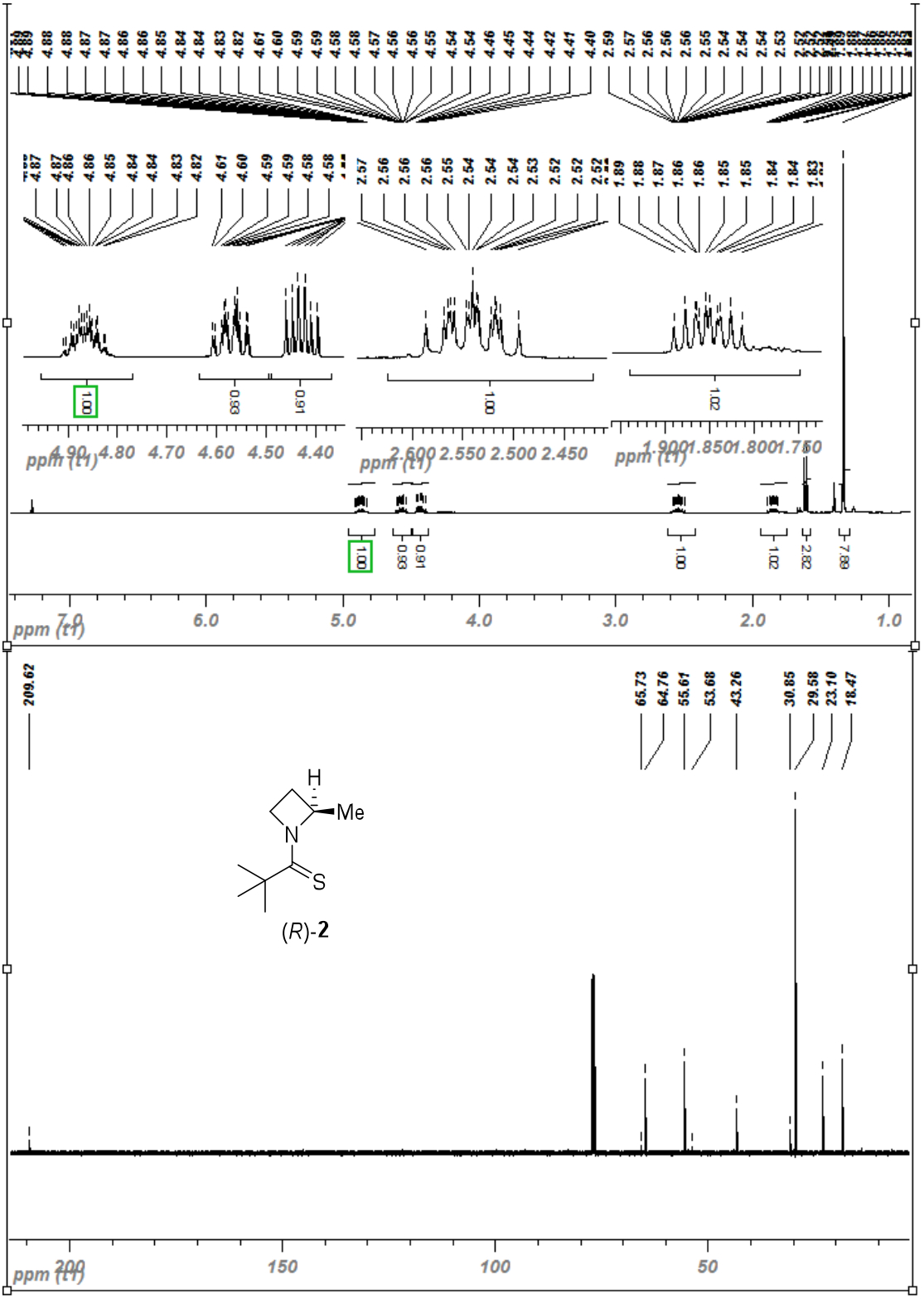
1-((*S*)-2-((*R*)-Hydroxy(phenyl)methyl)pyrrolidin-1-yl)-2,2-dimethylpropane-1-thione (*R*,*S*)-15 and 1-((*S*)-2-((*S*)-hydroxy(phenyl)methyl)pyrrolidin-1-yl)-2,2-dimethylpropane-1-thione (*S*,*S*)-14

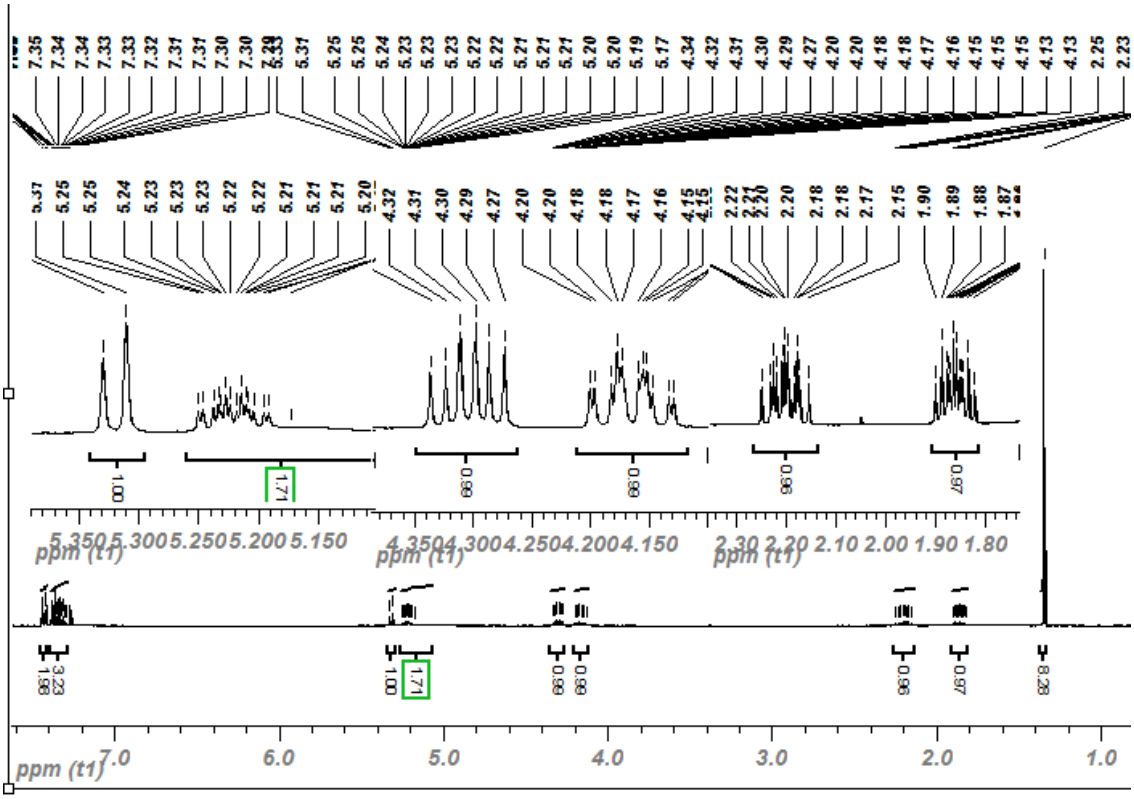


Using general procedure B, *s*-BuLi (0.50 mL of a 1.3 M solution in hexanes, 0.65 mmol, 1.3 eq.), (+)-sparteine surrogate **21** (120 mg, 0.65 mmol, 1.3 eq.) and *N*-thiopivaloyl pyrrolidine **9** (86 mg, 0.50 mmol, 1.0 eq.) in Et_2O (5 mL) and benzaldehyde (76 μL, 0.75 mmol, 1.5 eq.) gave the crude product which contained a 78:22 mixture of diastereomeric alcohols (*R*,*S*)-**15** and (*S*,*S*)-**14** by ^1H NMR spectroscopy. Purification by flash column chromatography on silica with 8:2-7:3 petrol-Et_2O as eluent gave alcohol (*R*,*S*)-**15** (86 mg, 62%, 85:15 er by CSP-HPLC) as a white solid,

CSP-HPLC: Chiracel AD (95:5 Hexane-*i*PrOH, 1.0 mL min^{-1}) (*S*,*R*)-**15** 11.2 min, (*R*,*S*)-**15** 14.6 min and alcohol (*S*,*S*)-**14** (33 mg, 24%, 92:8 er by CSP-HPLC) as a colourless oil, CSP-HPLC: Chiracel AD (90:10 Hexane-*i*PrOH, 1.0 mL min^{-1}) (*R*,*R*)-**14** 10.8 min, (*S*,*S*)-**14** 19.8 min.
Lab Book Reference PJR 8/662

4. $^{1}H/^{13}C$ NMR Spectra

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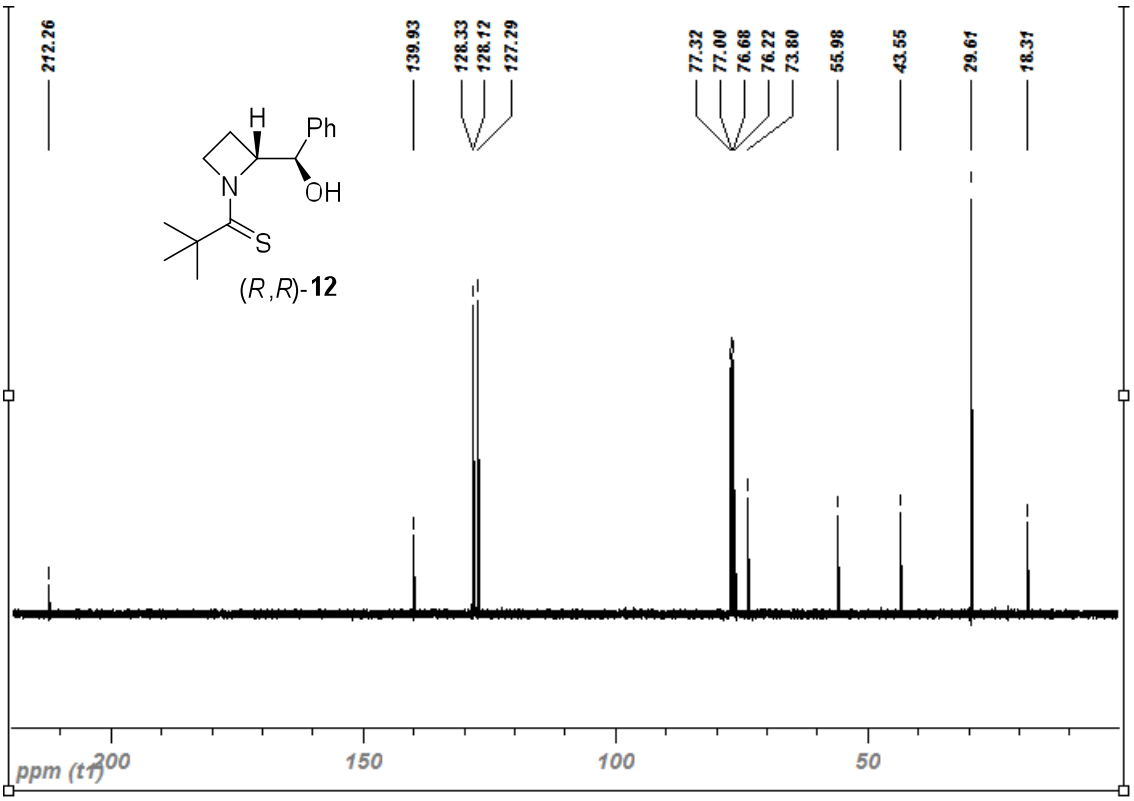
3.0
2.0
1.0


H
Ph
N
OH
S
(R,R)-12
ppm (t1)
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100
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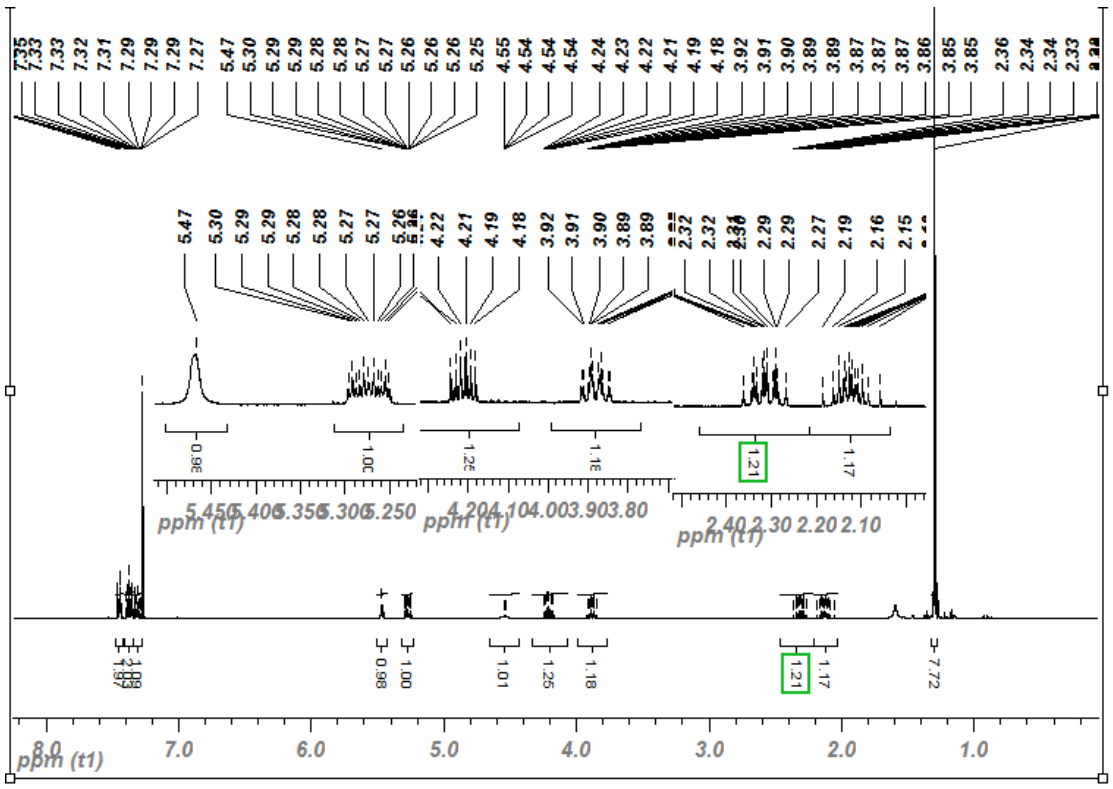
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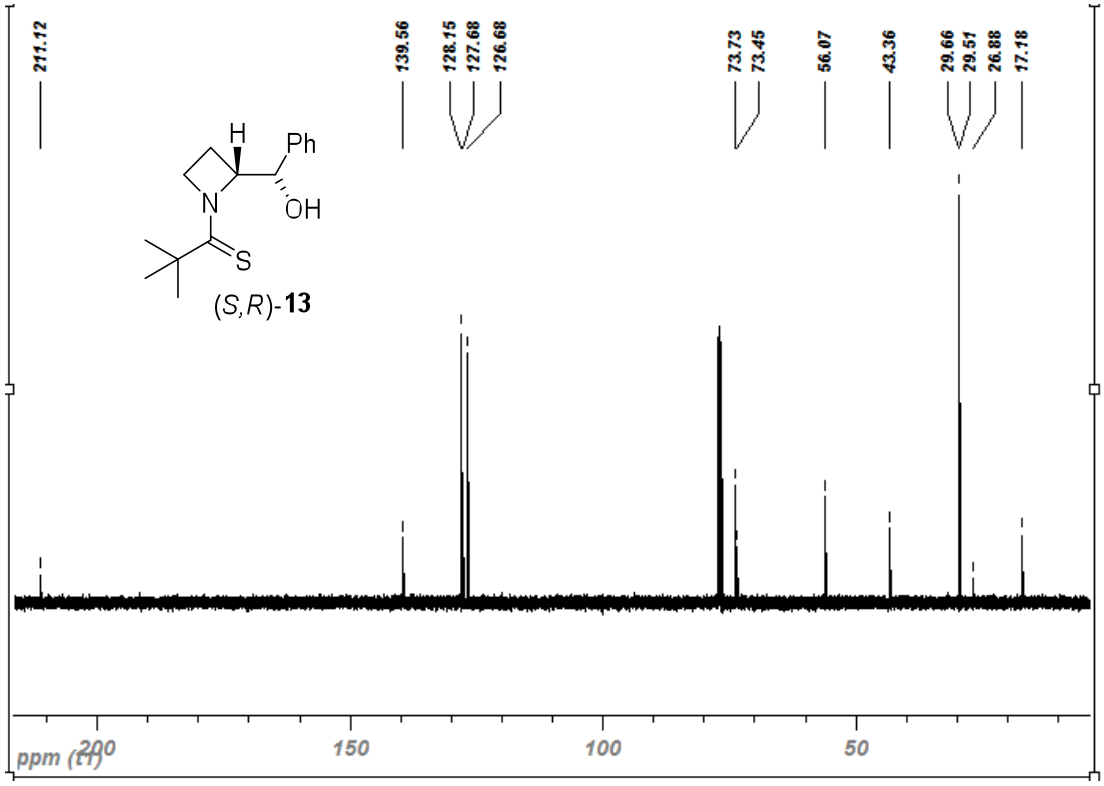
2.0
1.0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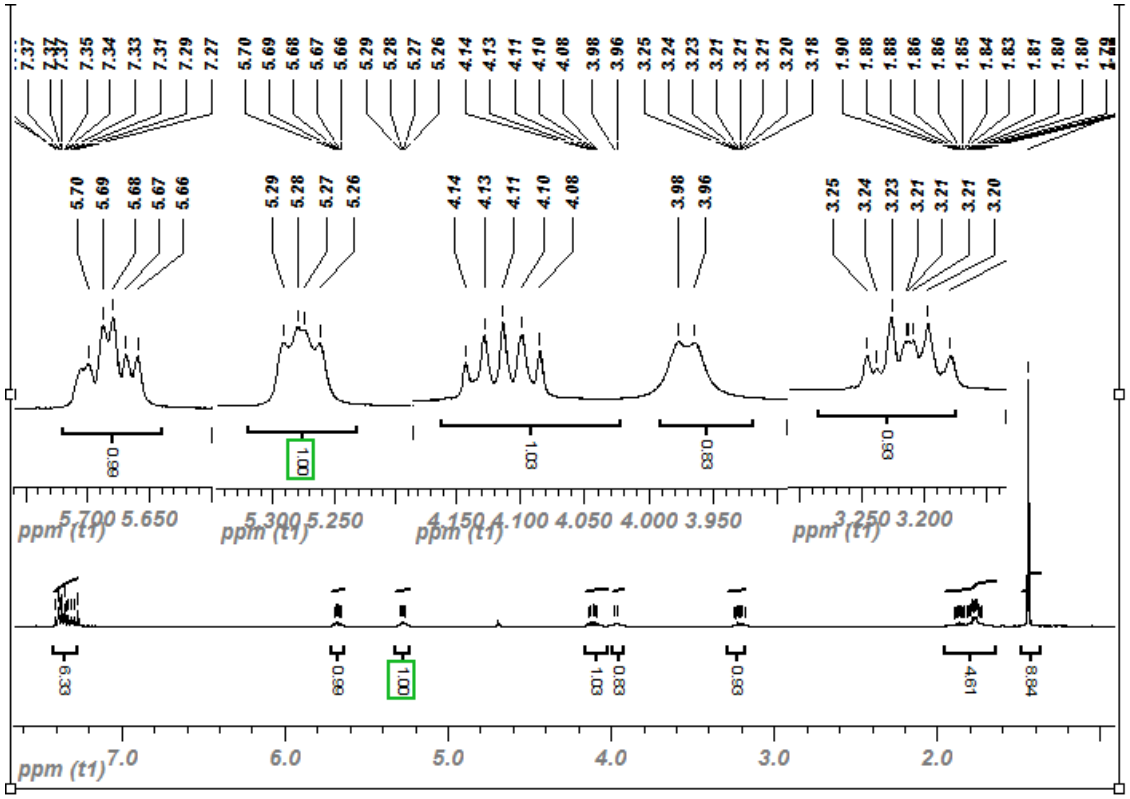
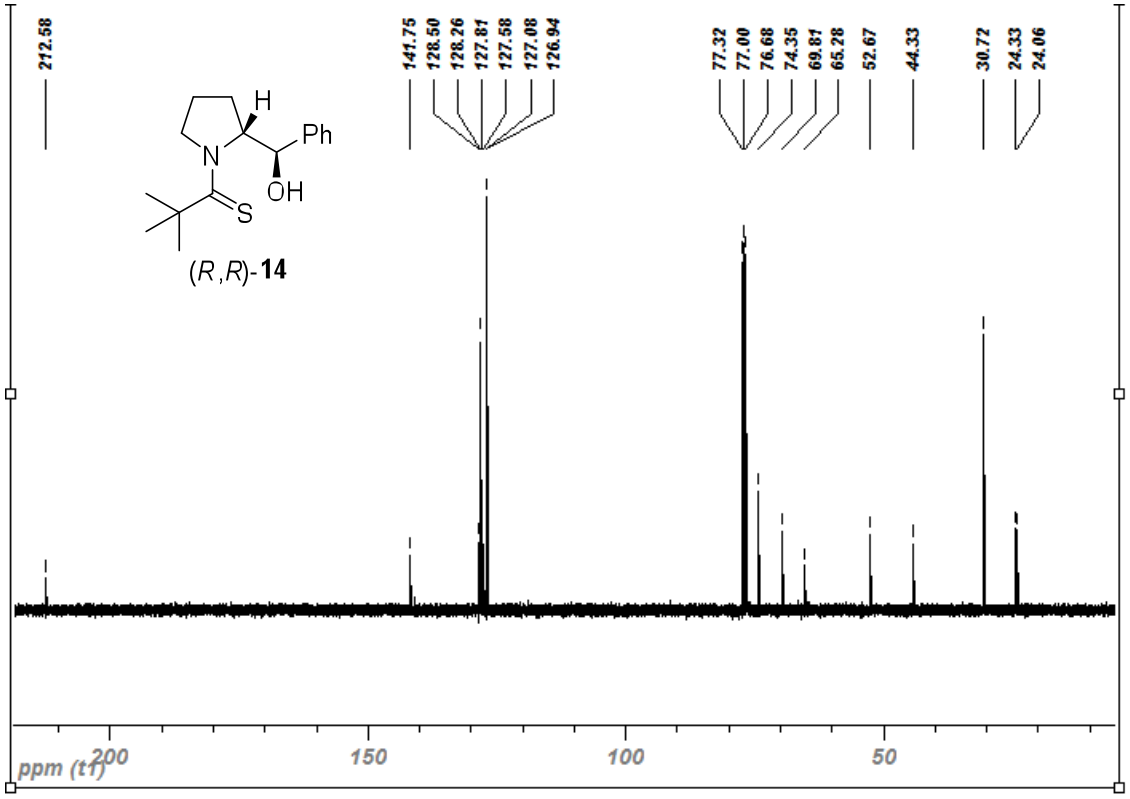
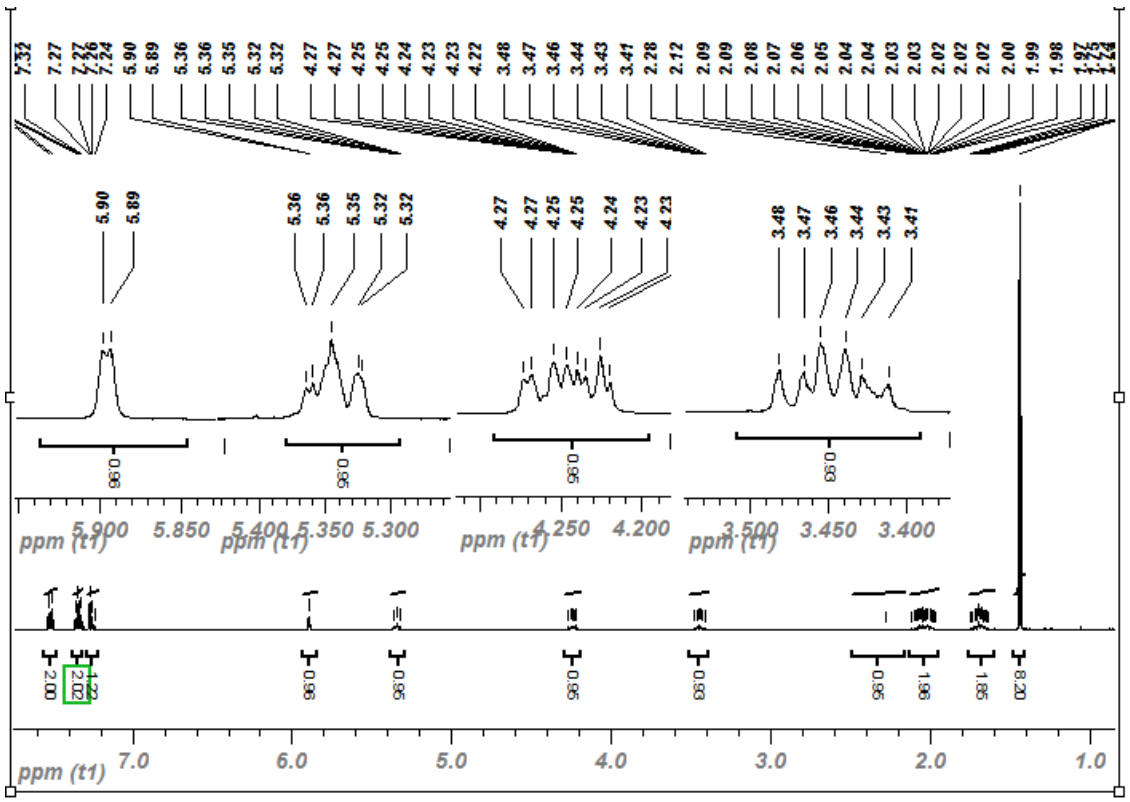
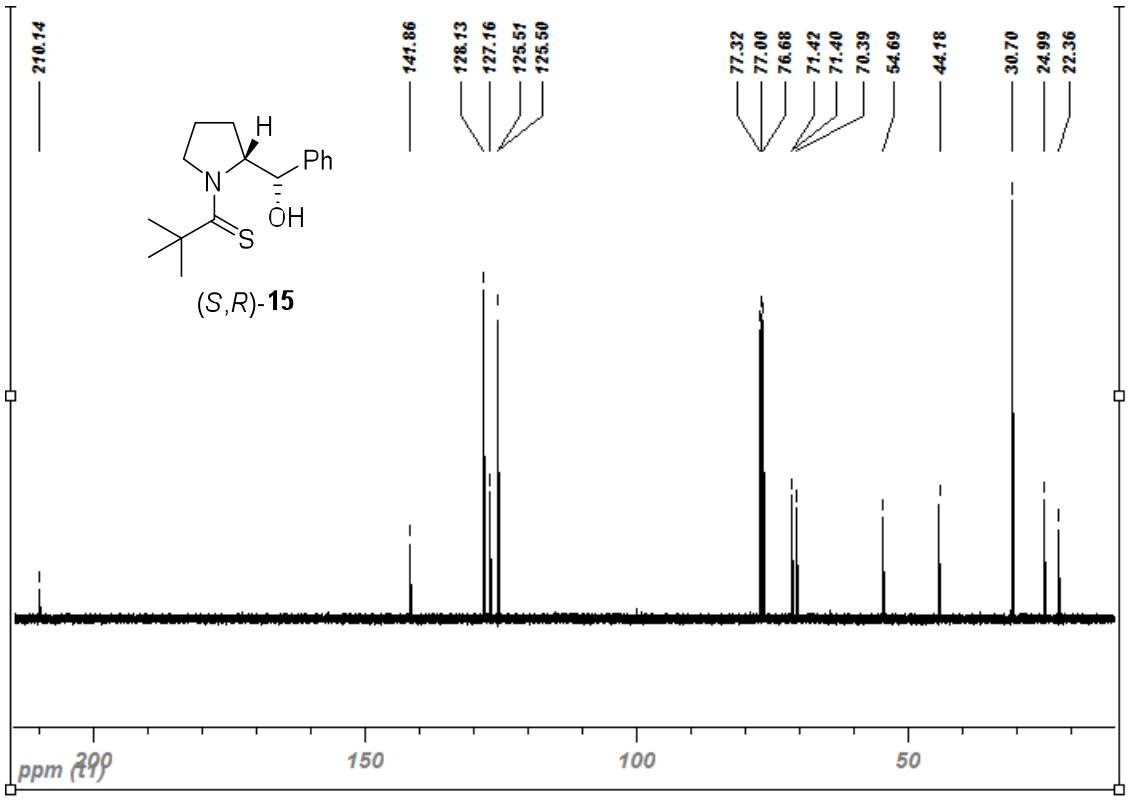
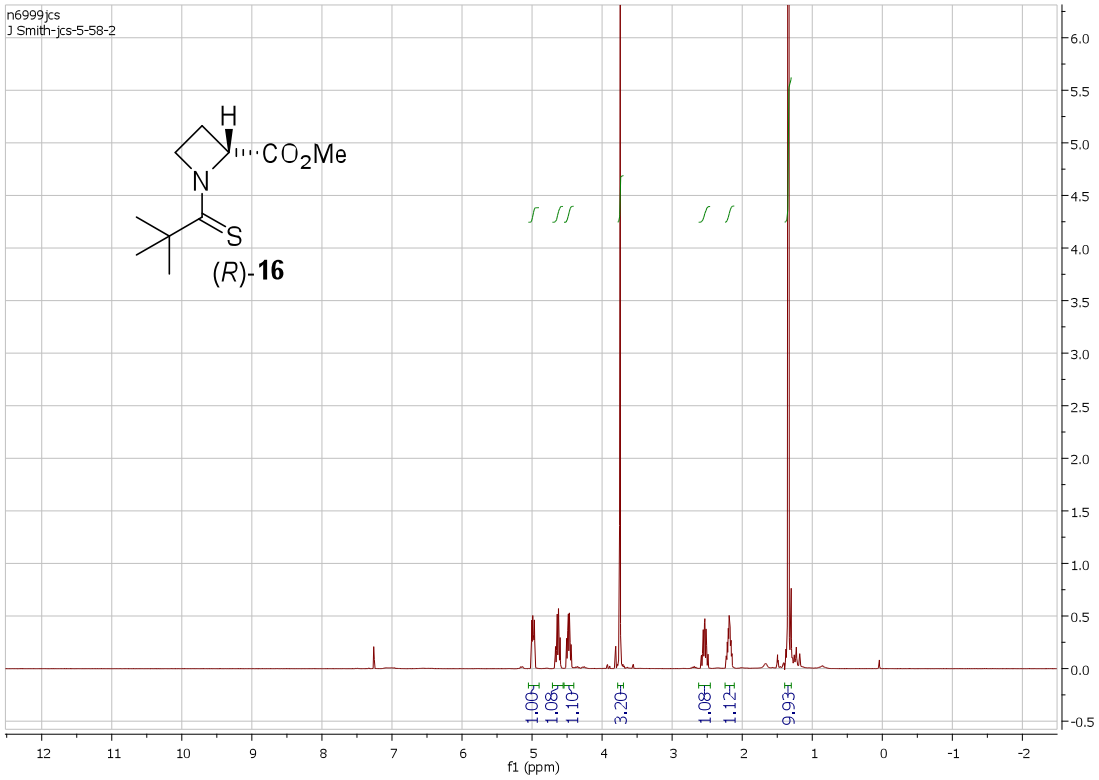
50

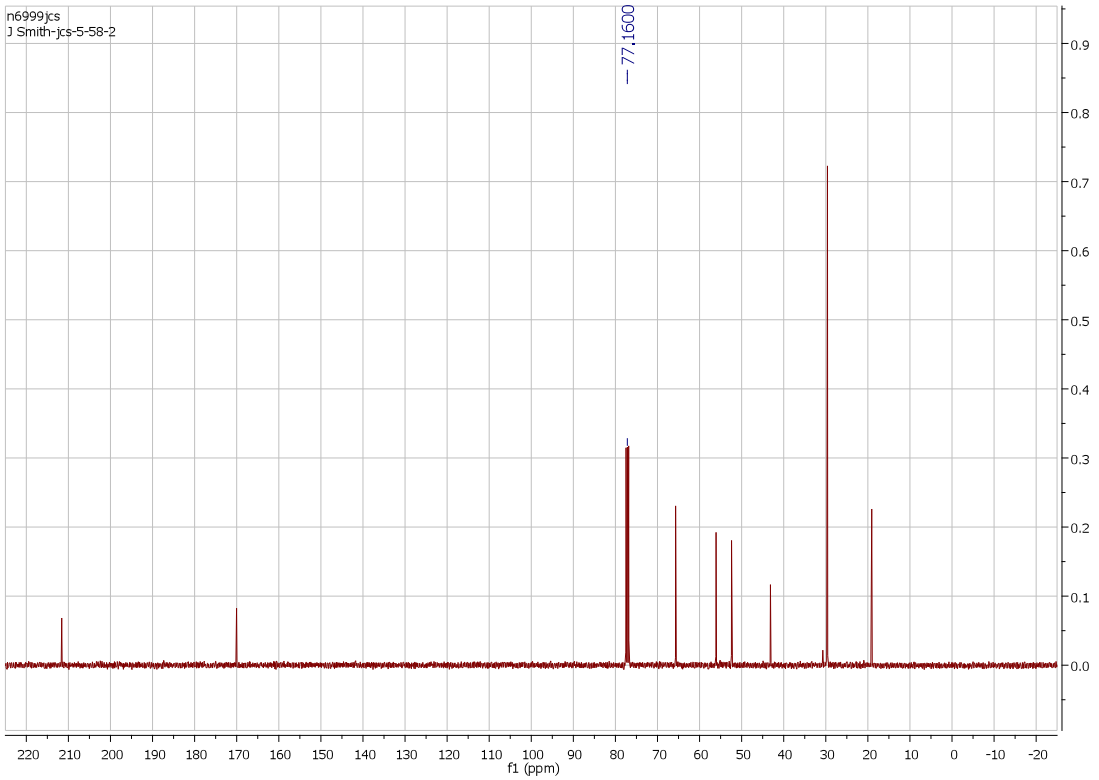


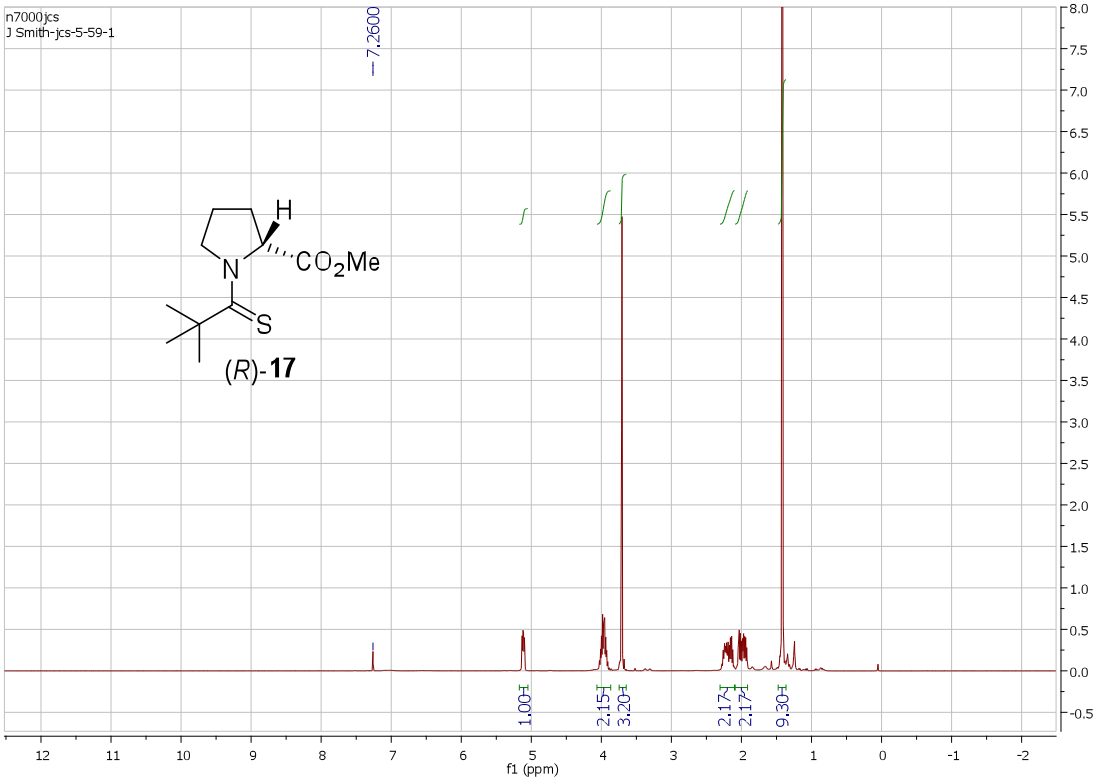

H
Ph
N
OH
S
(R,R)-14


7.32 7.27 7.27 7.26 7.24 5.90 5.89 5.36 5.36 5.35 5.32 5.32 4.27 4.27 4.25 4.25 4.24 4.23 4.23 4.22 3.48 3.47 3.46 3.44 3.43 3.41 2.28 2.12 2.09 2.09 2.08 2.07 2.06 2.05 2.04 2.04 2.03 2.02 2.02 2.02 2.00 1.99 1.98 1.97 1.25 1.24
5.90 5.89 5.36 5.36 5.35 5.32 5.32 4.27 4.27 4.25 4.25 4.24 4.23 4.23 3.48 3.47 3.46 3.44 3.43 3.41
0.96 0.96 0.96 0.93
5.900 5.850 5.400 5.350 5.300 4.250 4.200 3.500 3.450 3.400
ppm (t1)
2.00 2.02 1.22 0.96 0.96 0.96 0.93 0.96 1.96 1.85 8.30
7.0 6.0 5.0 4.0 3.0 2.0 1.0

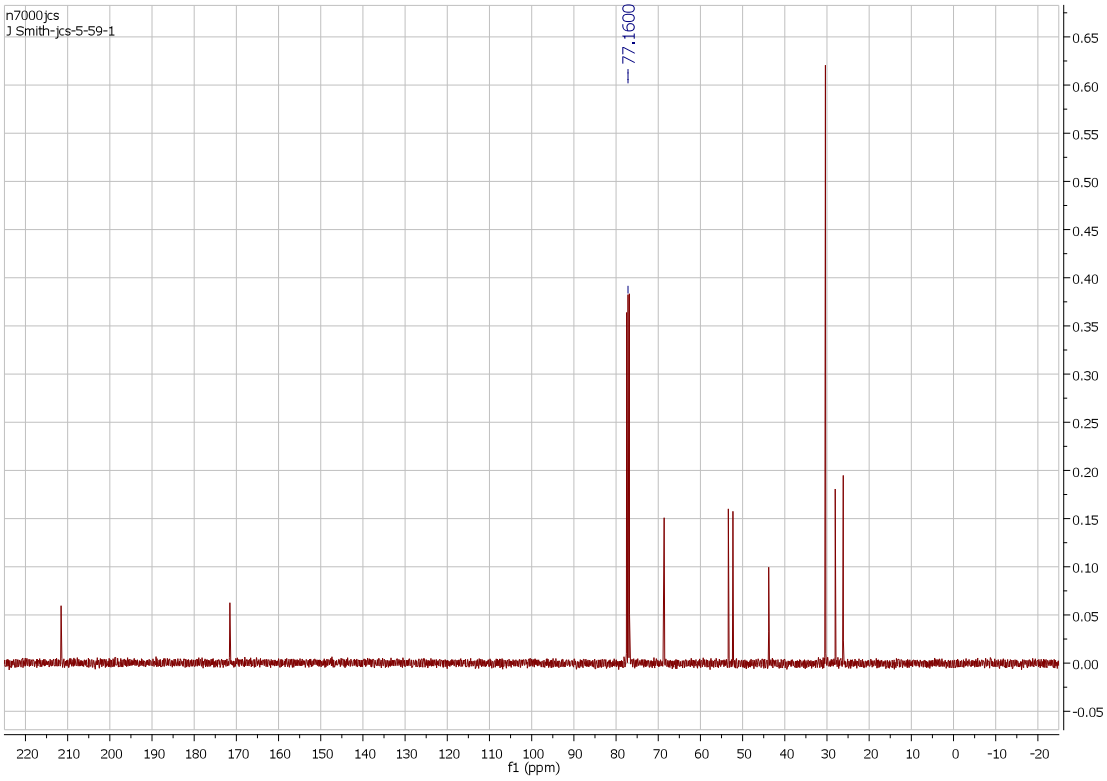

210.14
141.86 128.13 127.16 125.51 125.50
77.32 77.00 76.68 71.42 71.40 70.39 54.69 44.18 30.70 24.99 22.36
H
Ph
N
OH
S
(S,R)-15
200 150 100 50
ppm (t1)

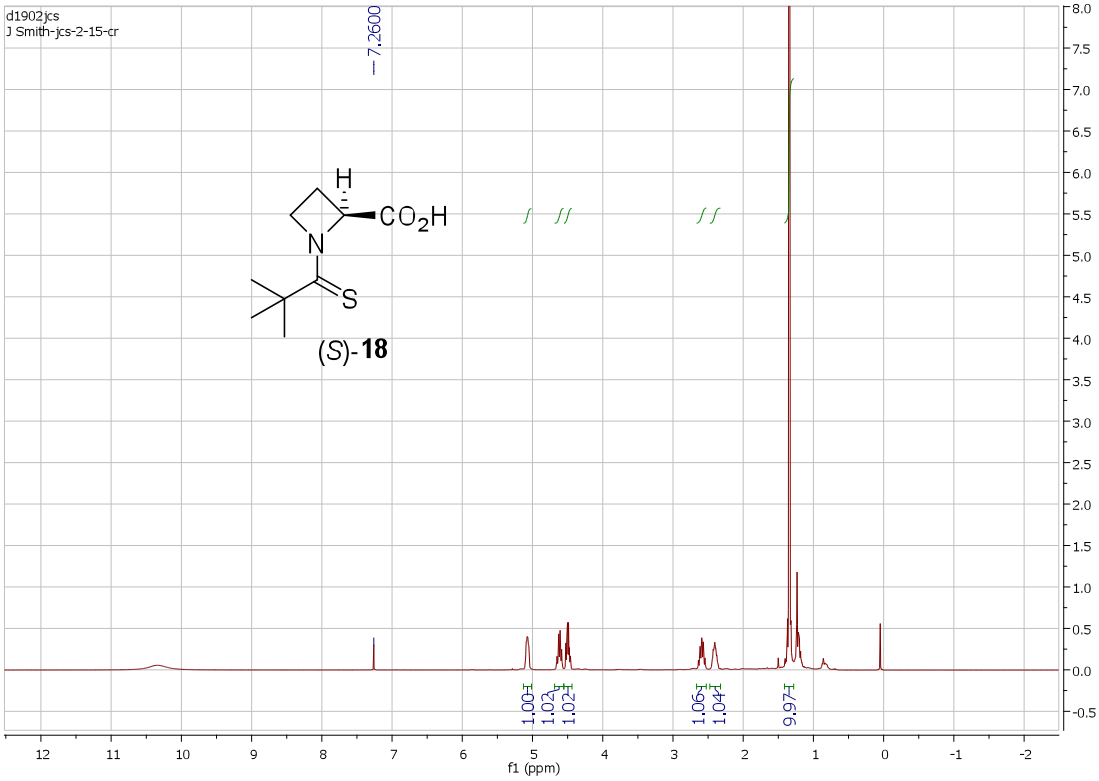

n6999jcs
J Smith-jcs-5-58-2
H
CO2Me
N
S
(R)-16
1.00
1.08
1.10
3.20
1.08
1.12
9.93
f1 (ppm)

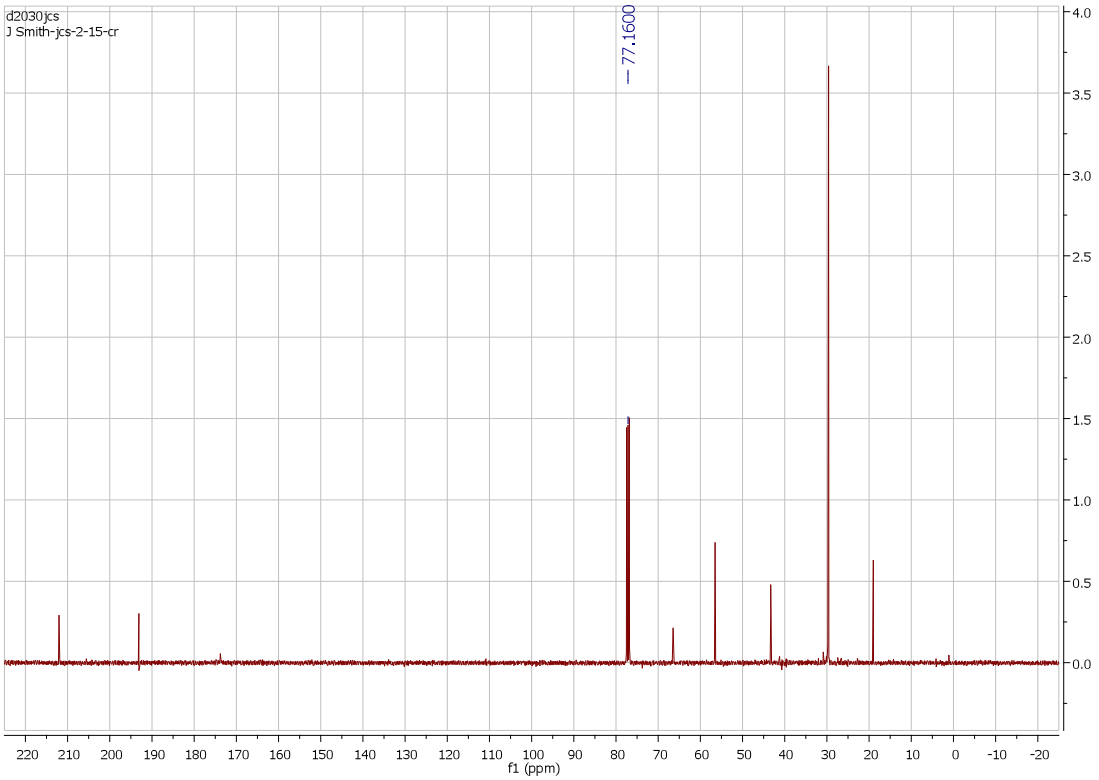

n6999jcs
J Smith-jcs-5-58-2
77.1600
f1 (ppm)

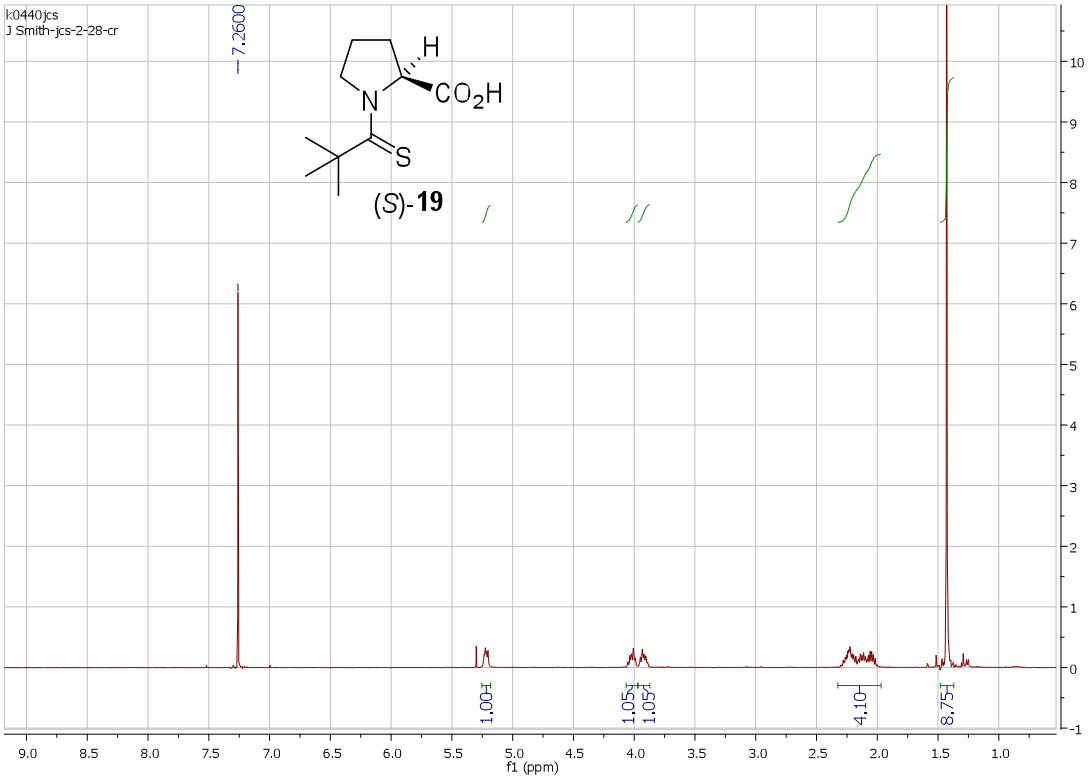

n7000jcs
J Smith-jcs-5-59-1
7.2600
1.00
2.15
3.20
2.17
2.17
9.30
f1 (ppm)

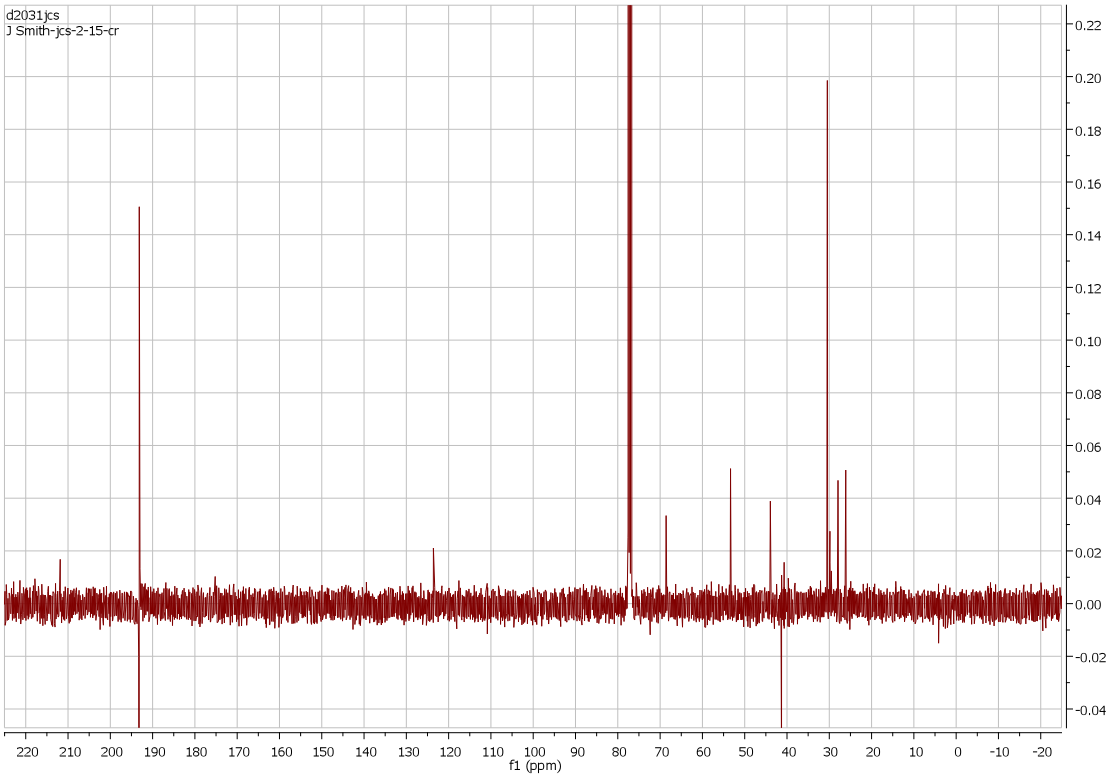
(*R*)-**17**

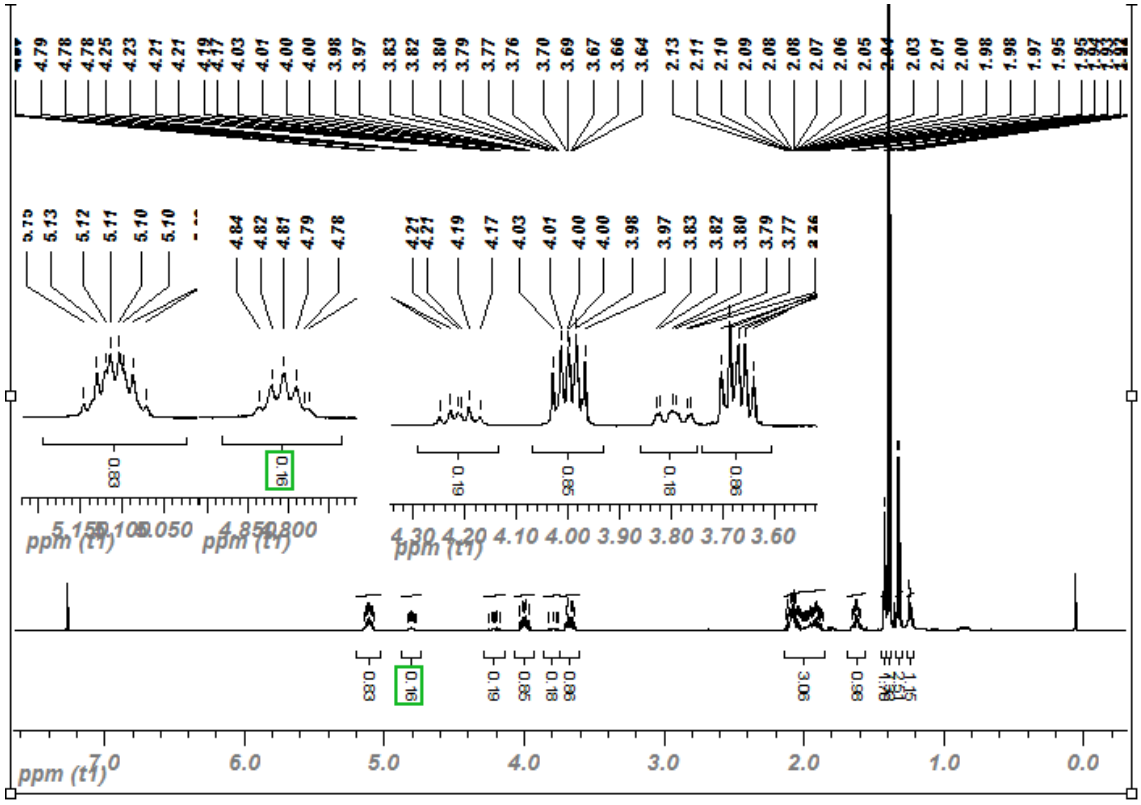

n7000jcs
J Smith-jcs-5-59-1
77.1600
f1 (ppm)

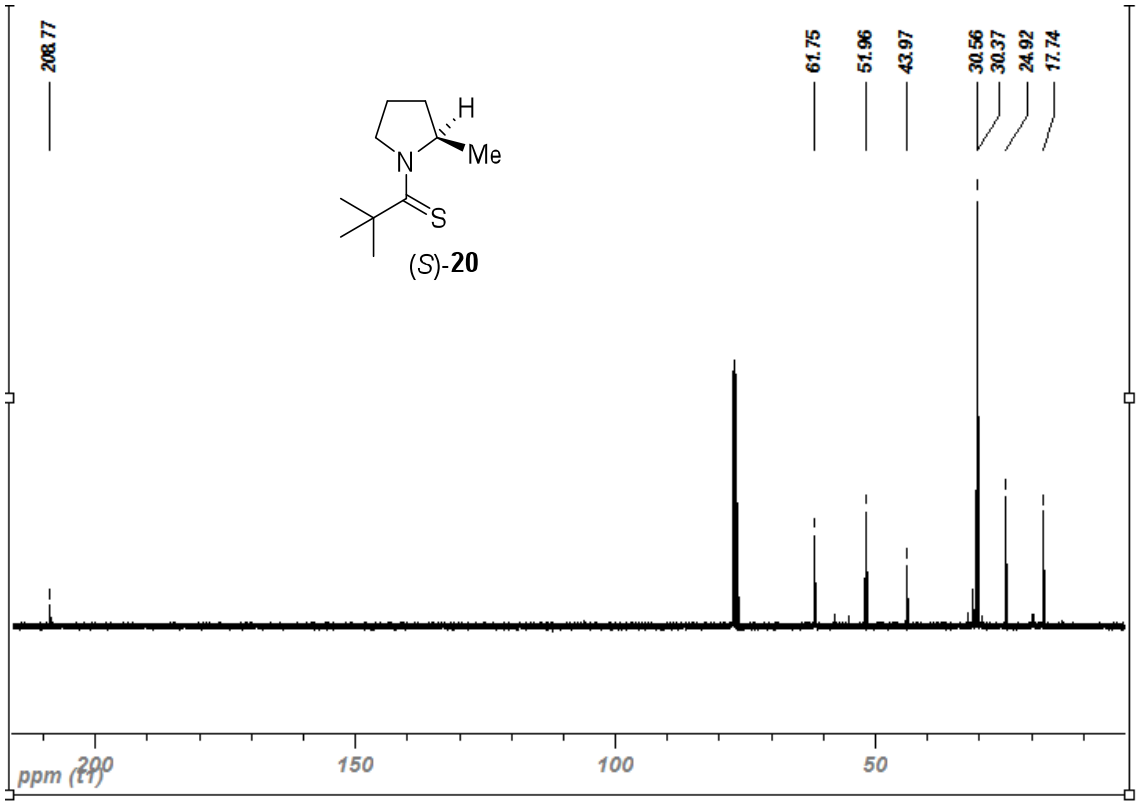

d1902jcs
J Smith-jcs-2-15-cr
7.2600
H
CO2H
N
S
(S)-18
1.00
1.03
1.02
1.06
1.04
9.97
f1 (ppm)

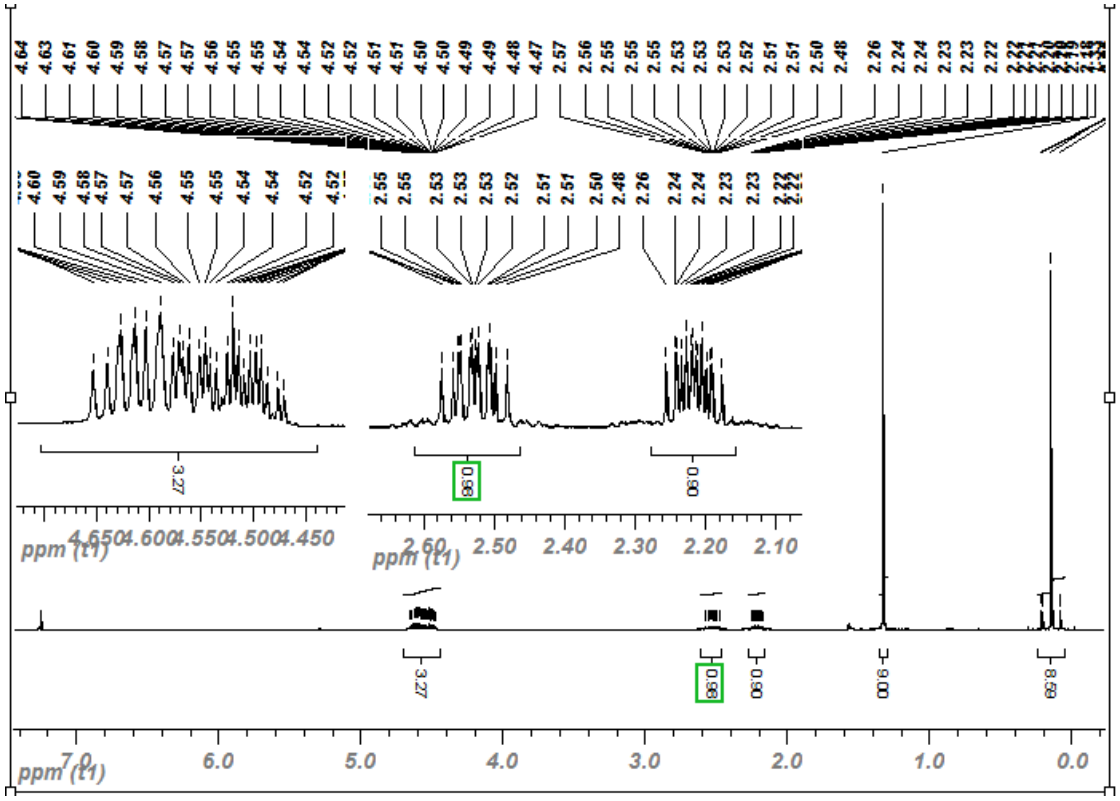

d2030jcs
J Smith-jcs-2-15-cr
77.1600
f1 (ppm)

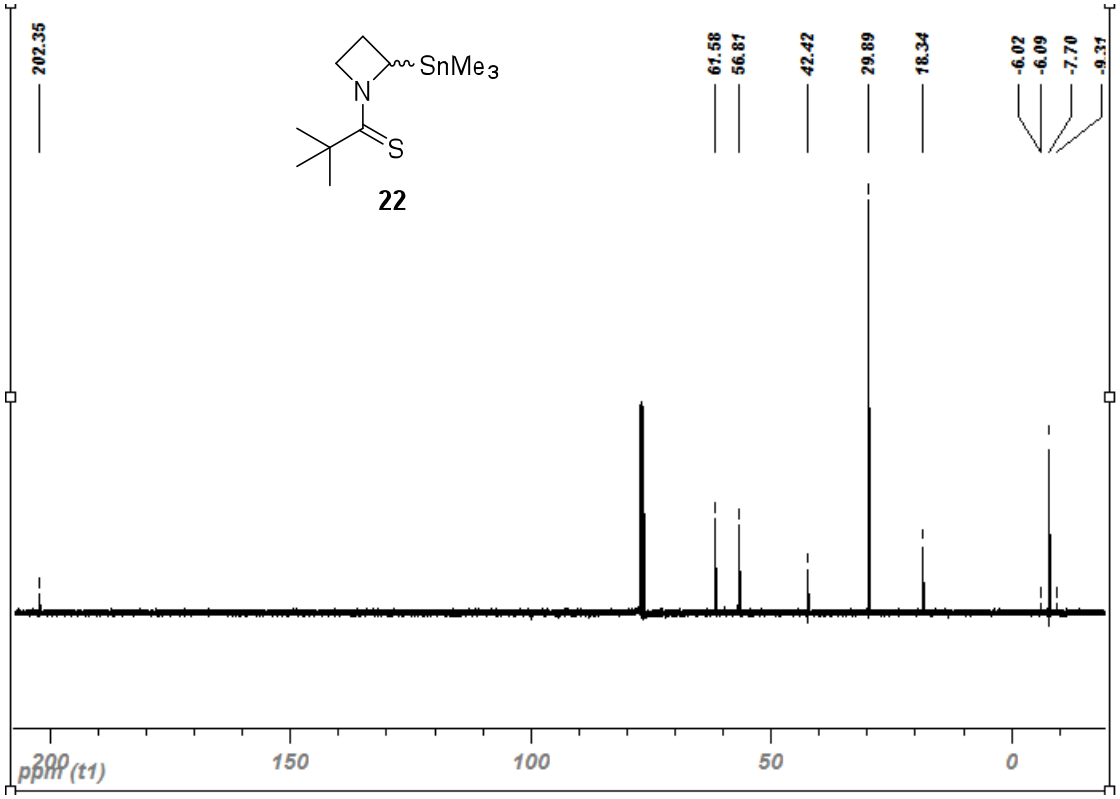

k0440jcs
J Smith-jcs-2-28-cr
7.2600
H
N
CO2H
S
(S)-19
1.00
1.05
1.05
4.10
8.75
f1 (ppm)

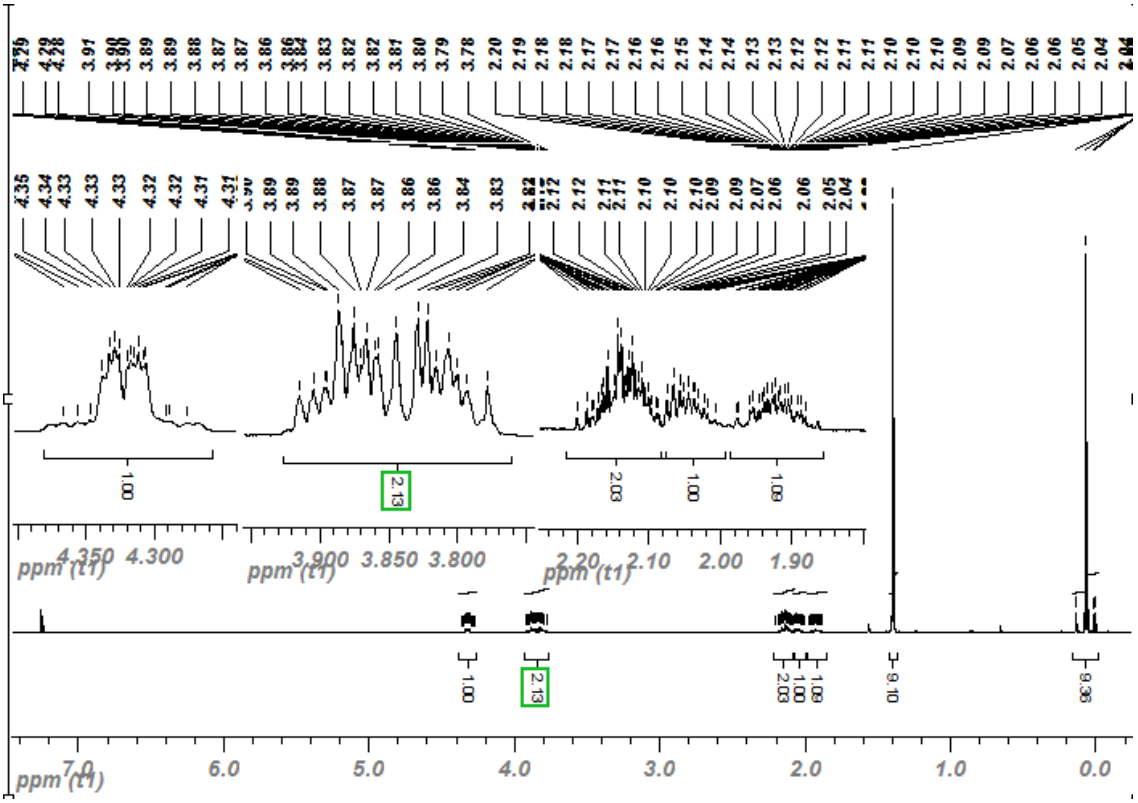

d2031jcs
J Smith-jcs-2-15-cr
f1 (ppm)

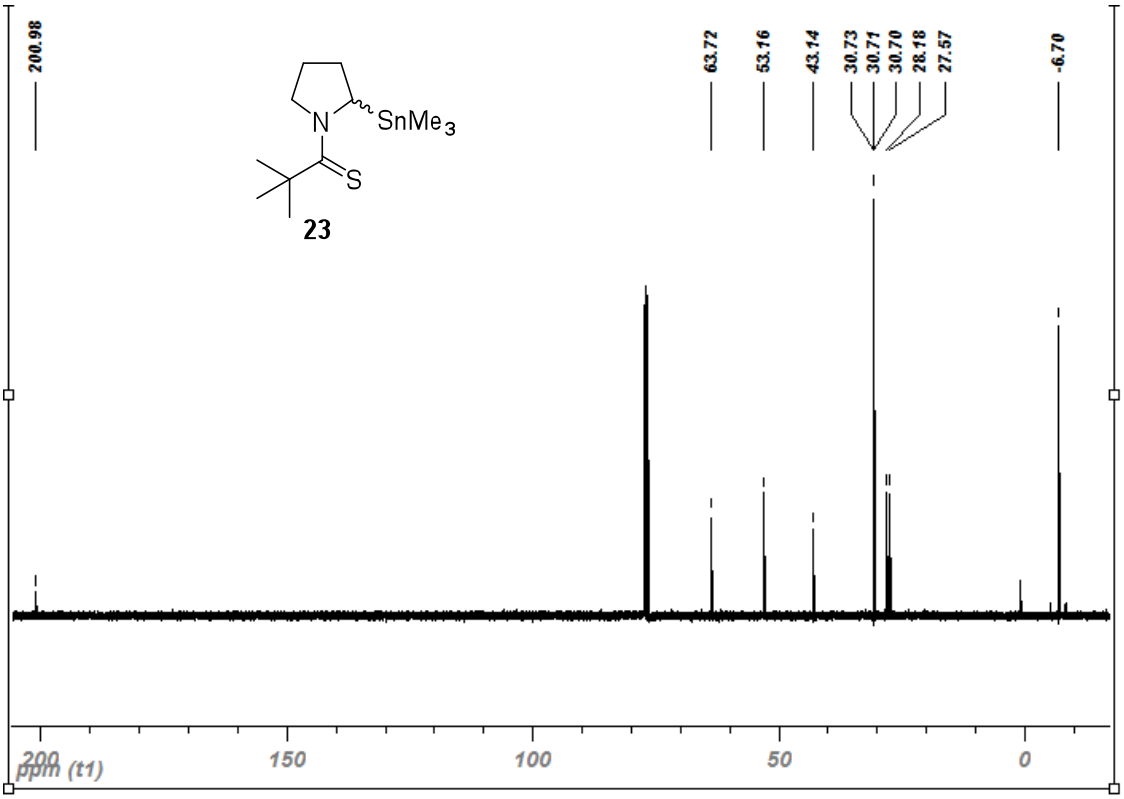

ppm (t1)
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0

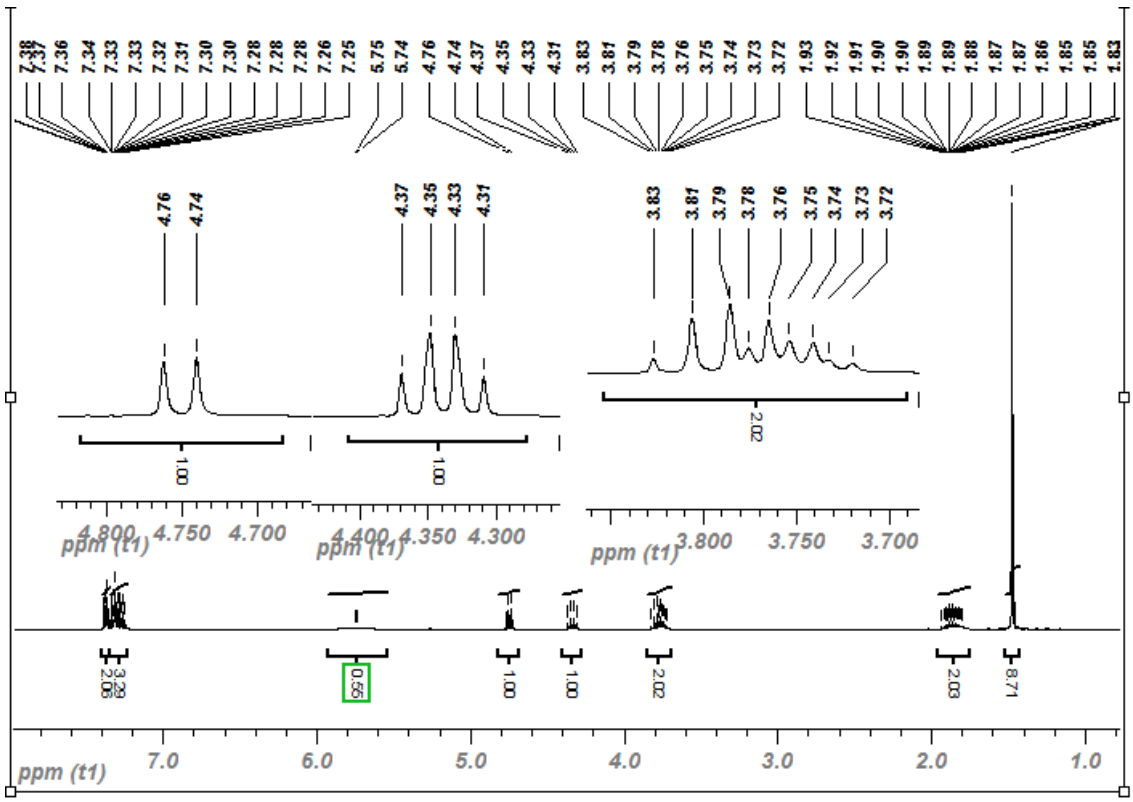

208.77
61.75
51.96
43.97
30.56
30.37
24.92
17.74
H
Me
N
S
(S)-20
ppm (t1)
200
150
100
50

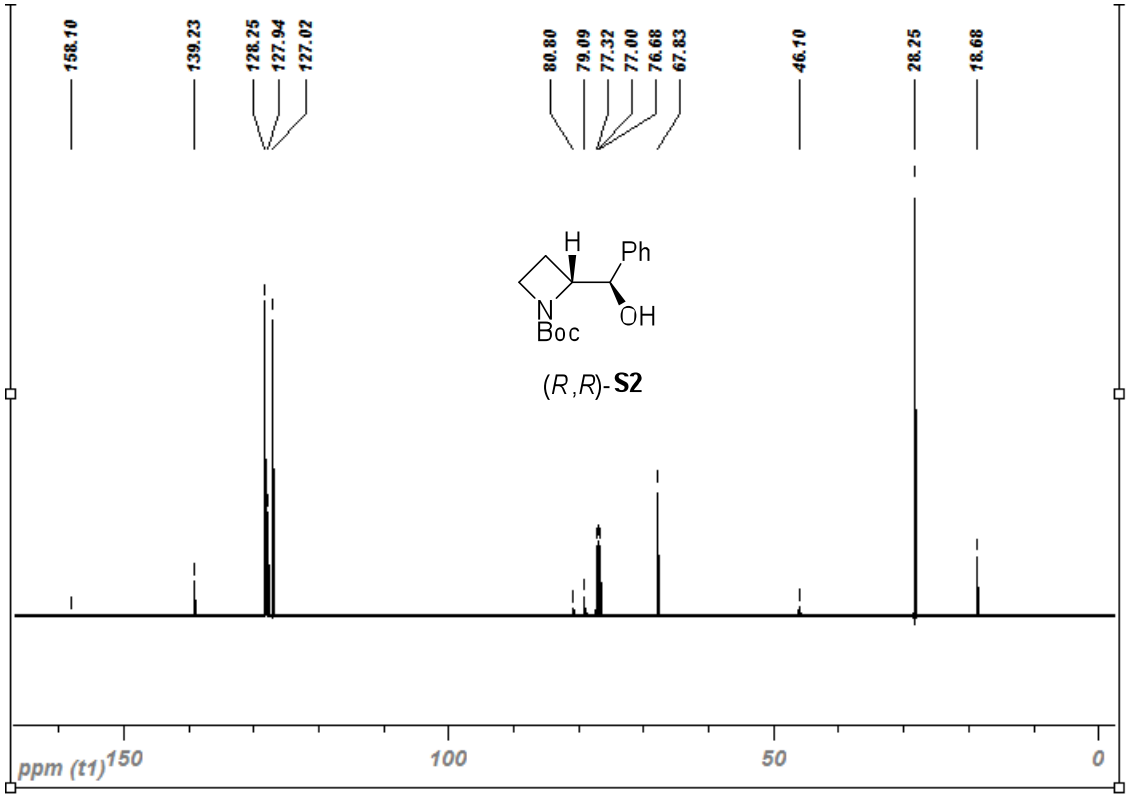

ppm (t1)
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0


SnMe3
N
S
22
ppm (t1)
200
150
100
50
0

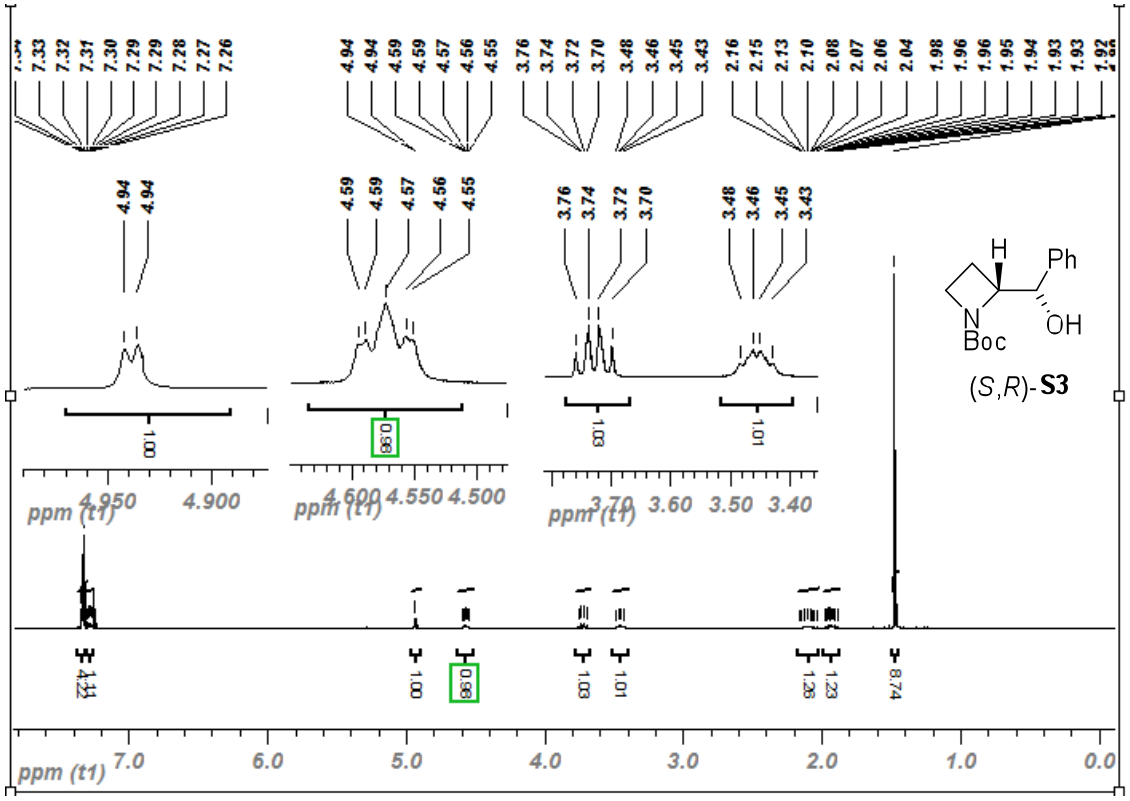

ppm (t1)
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0

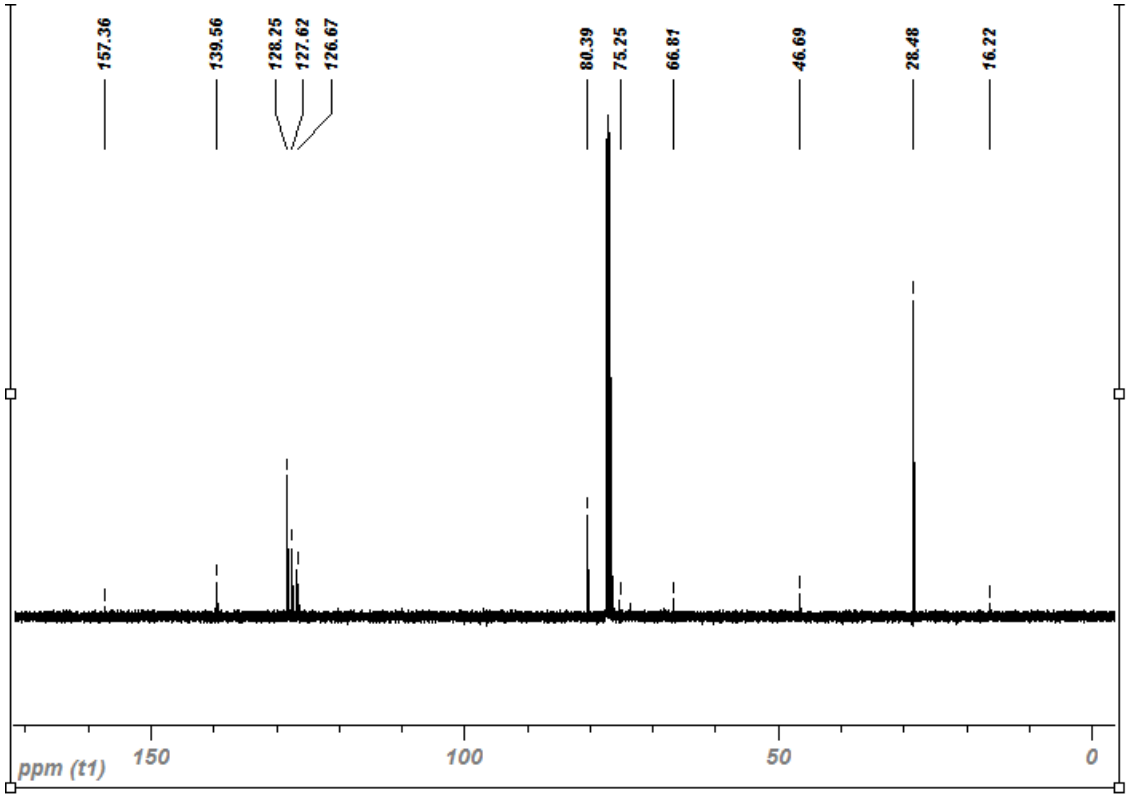

200.98
63.72
53.16
43.14
30.73
30.71
30.70
28.18
27.57
-6.70
N
SnMe3
S
23
ppm (t1)
200
150
100
50
0

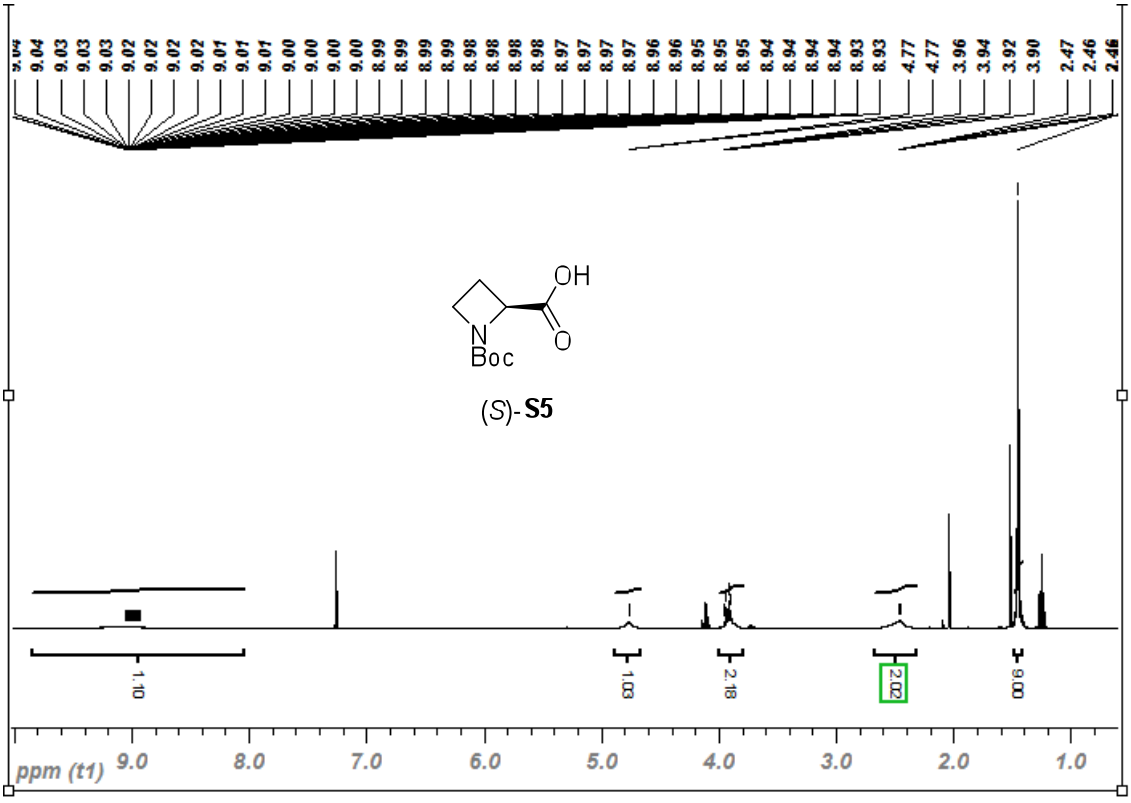

7.38 7.37 7.36 7.34 7.33 7.33 7.32 7.31 7.30 7.30 7.28 7.28 7.28 7.26 7.25 5.75 5.74 4.76 4.74 4.37 4.35 4.33 4.31 3.83 3.81 3.79 3.78 3.76 3.75 3.74 3.73 3.72 1.93 1.92 1.91 1.90 1.90 1.89 1.89 1.88 1.87 1.87 1.86 1.85 1.85 1.83
4.76 4.74
4.37 4.35 4.33 4.31
3.83 3.81 3.79 3.78 3.76 3.75 3.74 3.73 3.72
1.00
1.00
2.02
ppm (t1) 4.800 4.750 4.700
ppm (t1) 4.400 4.350 4.300
ppm (t1) 3.800 3.750 3.700
3.29
2.06
0.99
1.00
1.00
2.02
2.03
8.71
ppm (t1) 7.0 6.0 5.0 4.0 3.0 2.0 1.0


158.10
139.23
128.25
127.94
127.02
80.80
79.09
77.32
77.00
76.68
67.83
46.10
28.25
18.68
H
Ph
N
Boc
OH
ppm (t1) 150 100 50 0

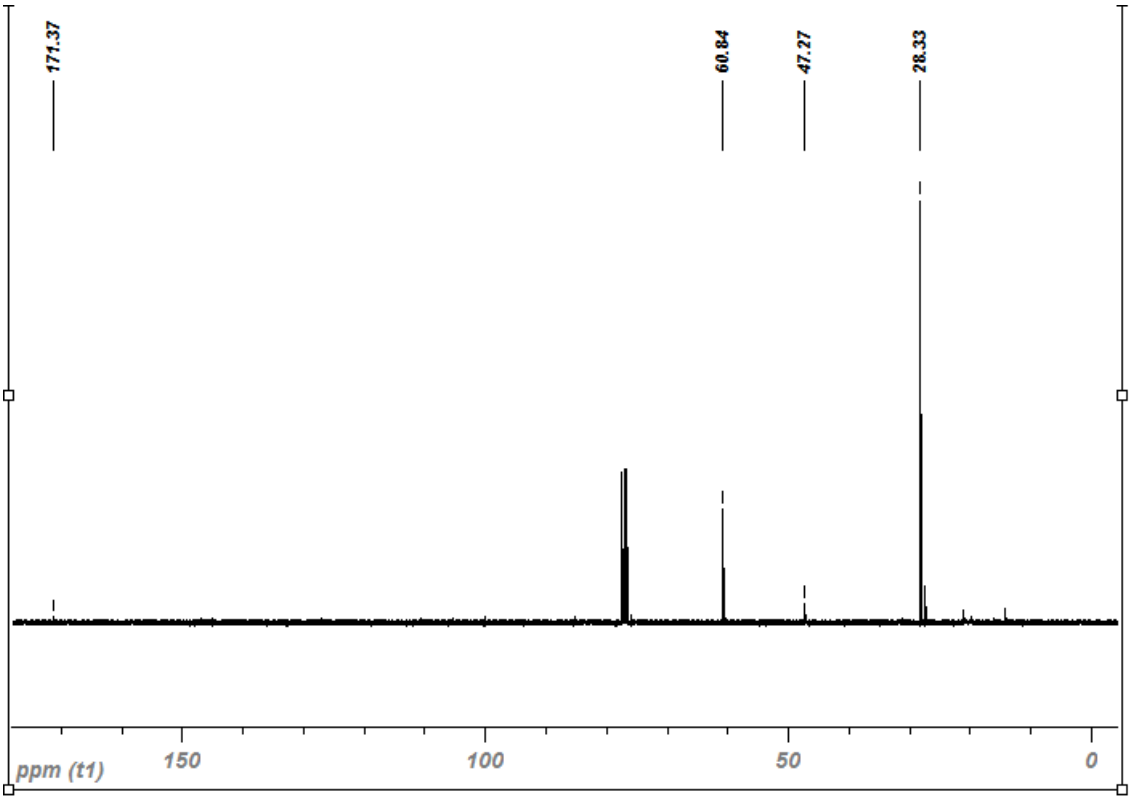
(*R*,*R*)-**S2**

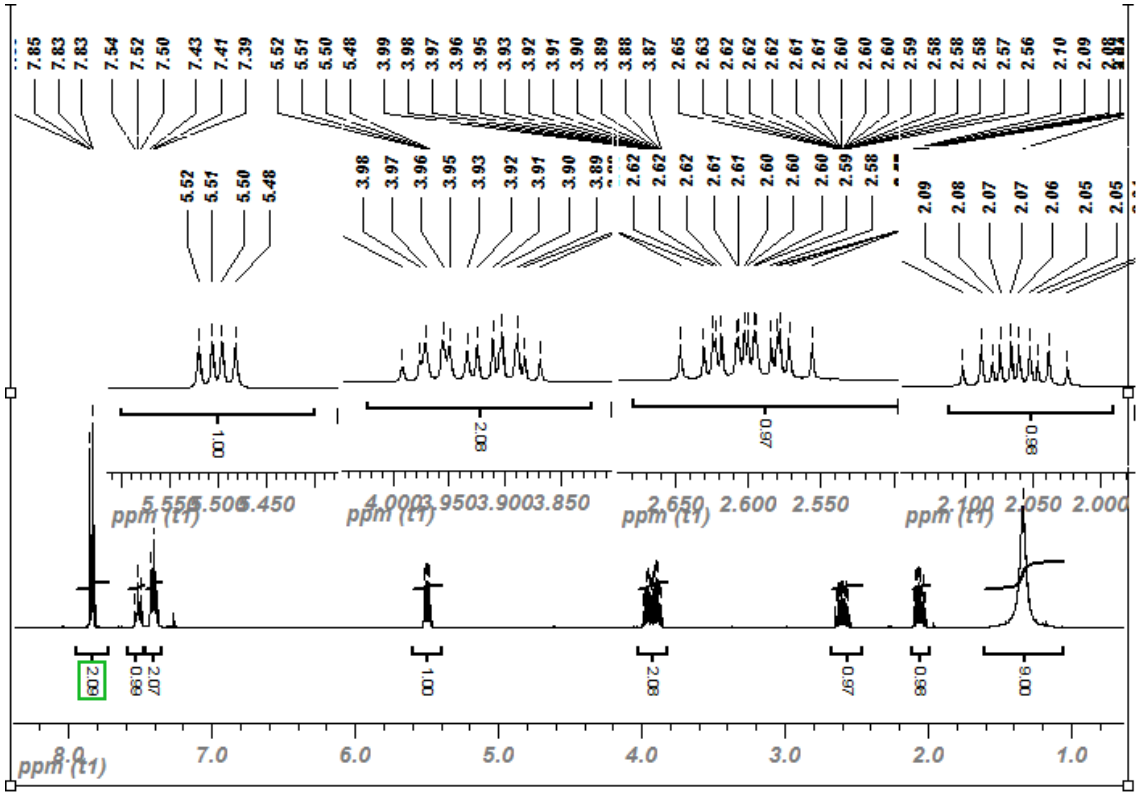

7.33 7.32 7.31 7.30 7.29 7.29 7.28 7.27 7.26
4.94 4.94 4.59 4.59 4.57 4.56 4.55
3.76 3.74 3.72 3.70 3.48 3.46 3.45 3.43
2.16 2.15 2.13 2.10 2.08 2.07 2.06 2.04 1.98 1.96 1.96 1.95 1.94 1.93 1.92
1.00 0.98 1.03 1.01
ppm (t1) 4.950 4.900
ppm (t1) 4.600 4.550 4.500
ppm (t1) 3.70 3.60 3.50 3.40
H Ph N OH Boc
(S,R)-S3
1.41 1.00 0.98 1.03 1.01 1.26 1.23 8.74
ppm (t1) 7.0 6.0 5.0 4.0 3.0 2.0 1.0 0.0

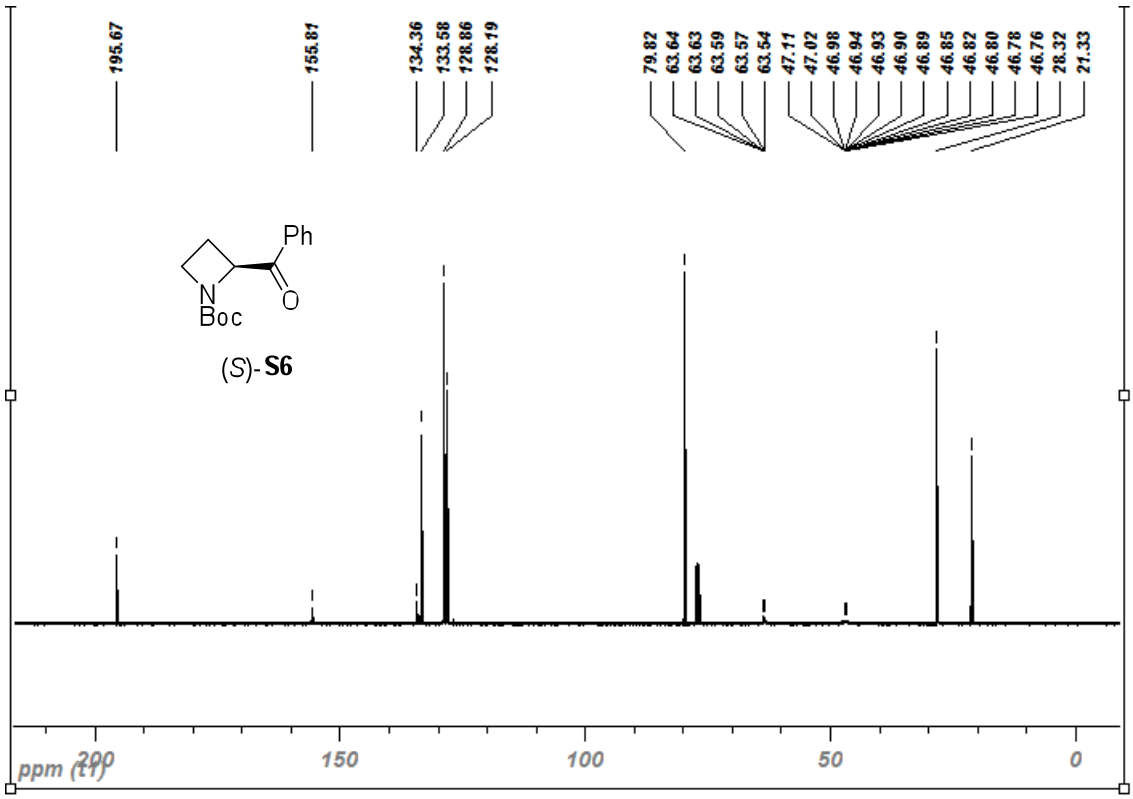

157.36 139.56 128.25 127.62 126.67 80.39 75.25 66.87 46.69 28.48 16.22
ppm (t1) 150 100 50 0

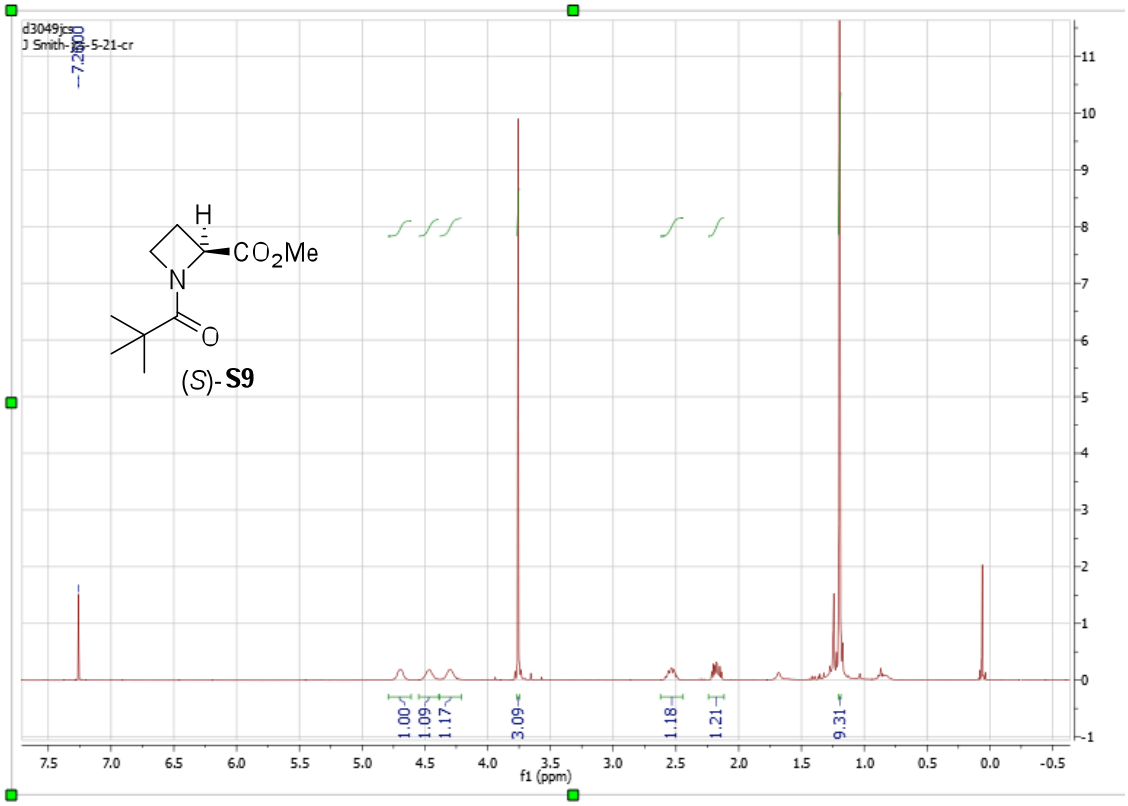

OH
O
N
Boc
1.10
1.03
2.18
2.02
9.00
ppm (t1)
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0

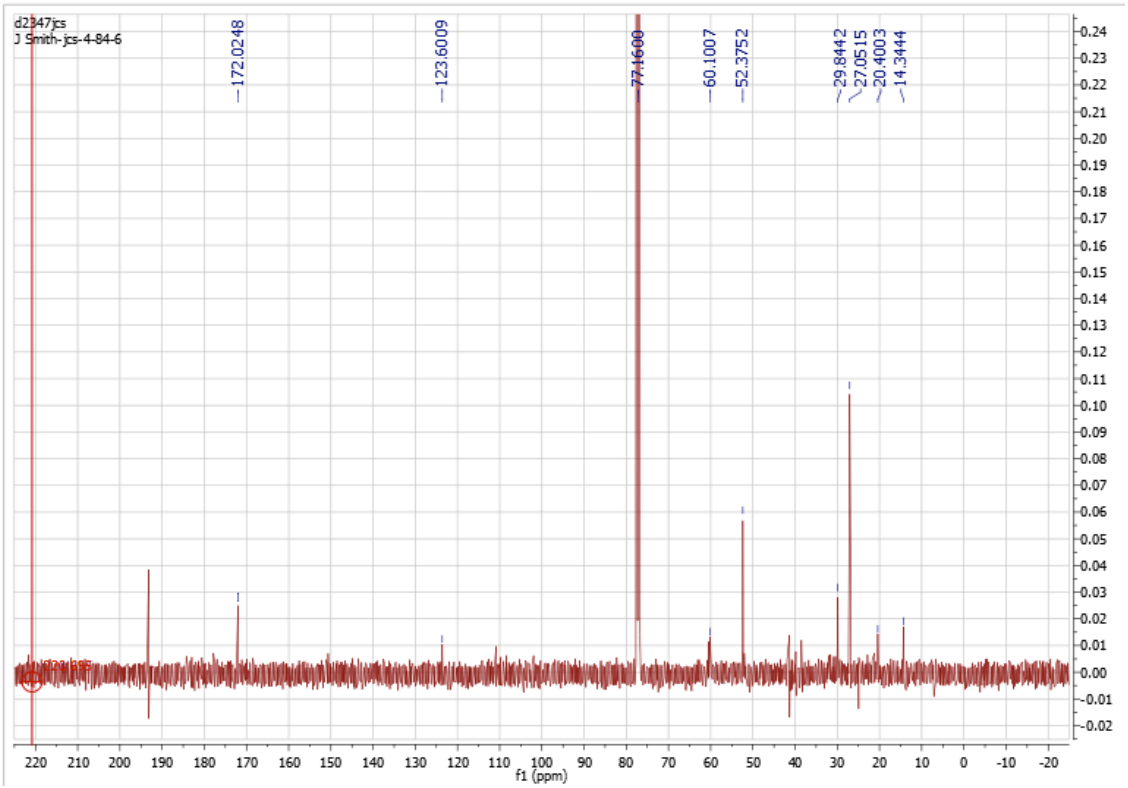
(*S*)-**S5**

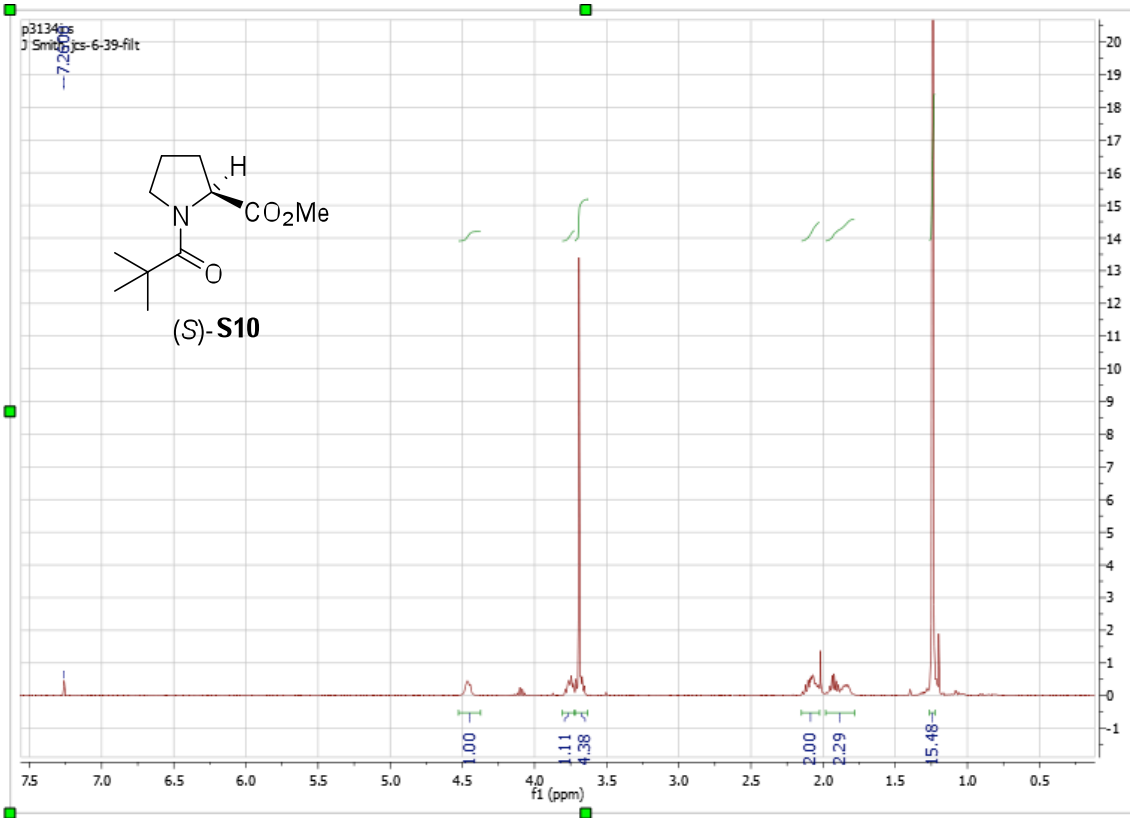

171.37
60.84
47.27
28.33
ppm (t1)
150
100
50
0


7.85 7.83 7.83 7.54 7.52 7.50 7.43 7.41 7.39 5.52 5.51 5.50 5.48 3.99 3.98 3.97 3.96 3.95 3.93 3.92 3.91 3.90 3.89 3.88 3.87 2.65 2.63 2.62 2.62 2.62 2.61 2.61 2.60 2.60 2.60 2.59 2.58 2.58 2.58 2.57 2.56 2.10 2.09
5.52 5.51 5.50 5.48 3.98 3.97 3.96 3.95 3.93 3.92 3.91 3.90 2.62 2.62 2.62 2.61 2.61 2.60 2.60 2.60 2.59 2.58 2.09 2.08 2.07 2.07 2.06 2.05 2.05
1.00 2.08 0.97 0.98
5.555.505.450 4.0003.9503.9003.850 2.650 2.600 2.550 2.100 2.050 2.000
ppm (t1)
2.09 0.99 2.07 1.00 2.08 0.97 0.98 9.00
8.0 7.0 6.0 5.0 4.0 3.0 2.0 1.0
ppm (t1)

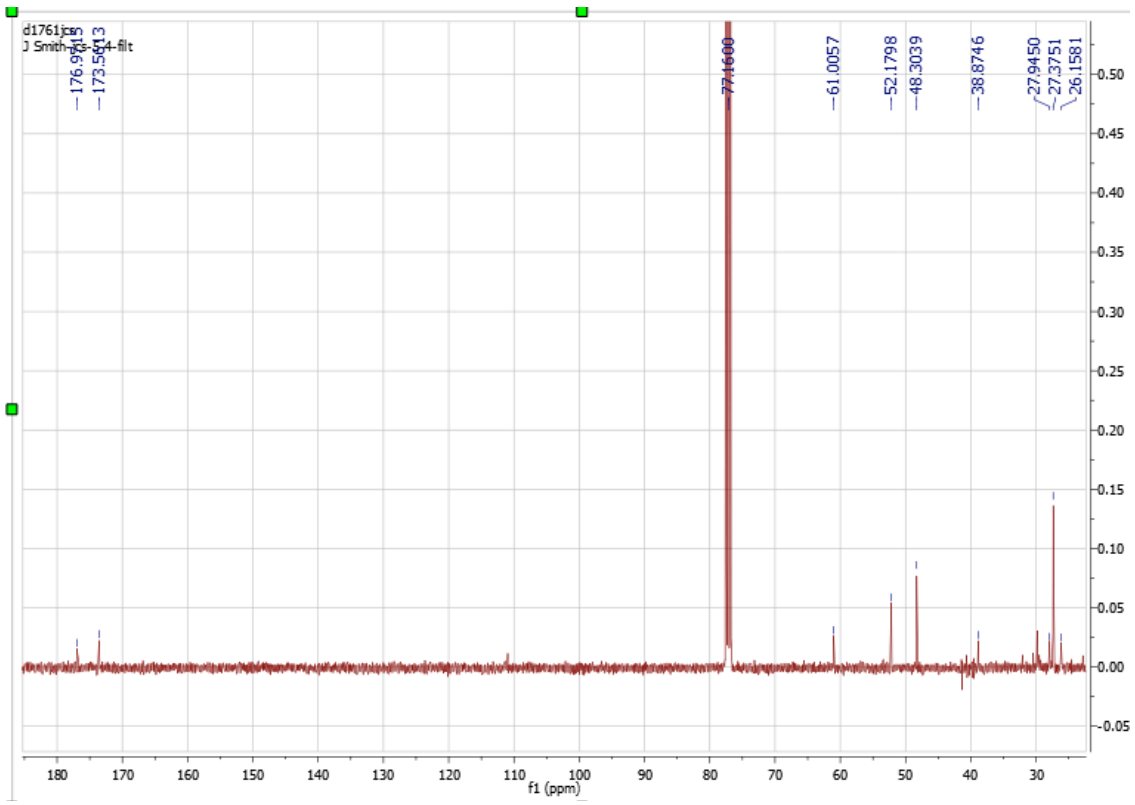

195.67 155.87 134.36 133.58 128.86 128.19 79.82 63.64 63.63 63.59 63.57 63.54 47.11 47.02 46.98 46.94 46.93 46.90 46.89 46.85 46.82 46.80 46.78 46.76 28.32 21.33
Ph
N
Boc
O
(S)-S6
200 150 100 50 0
ppm (t1)

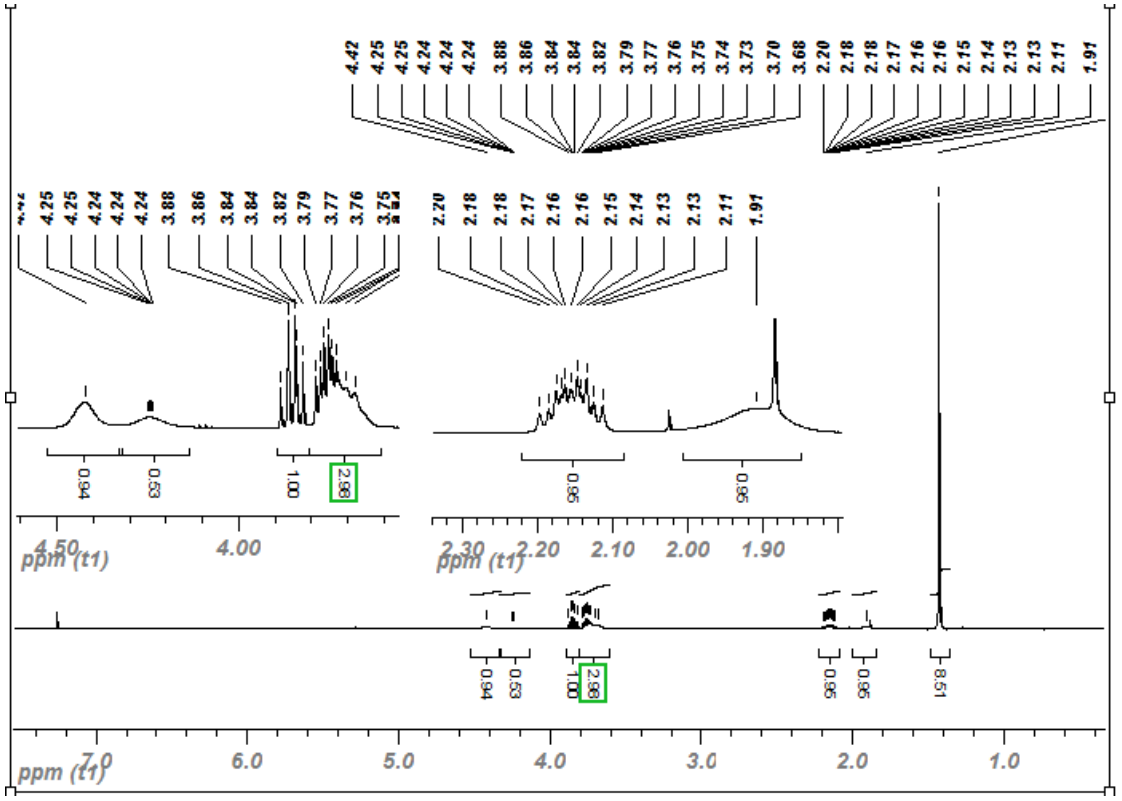

d3049jcs
J Smith-jcs-5-21-cr
7.2600
H
CO2Me
N
O
(S)-S9
1.00
1.09
1.17
3.09
1.18
1.21
9.31
f1 (ppm)

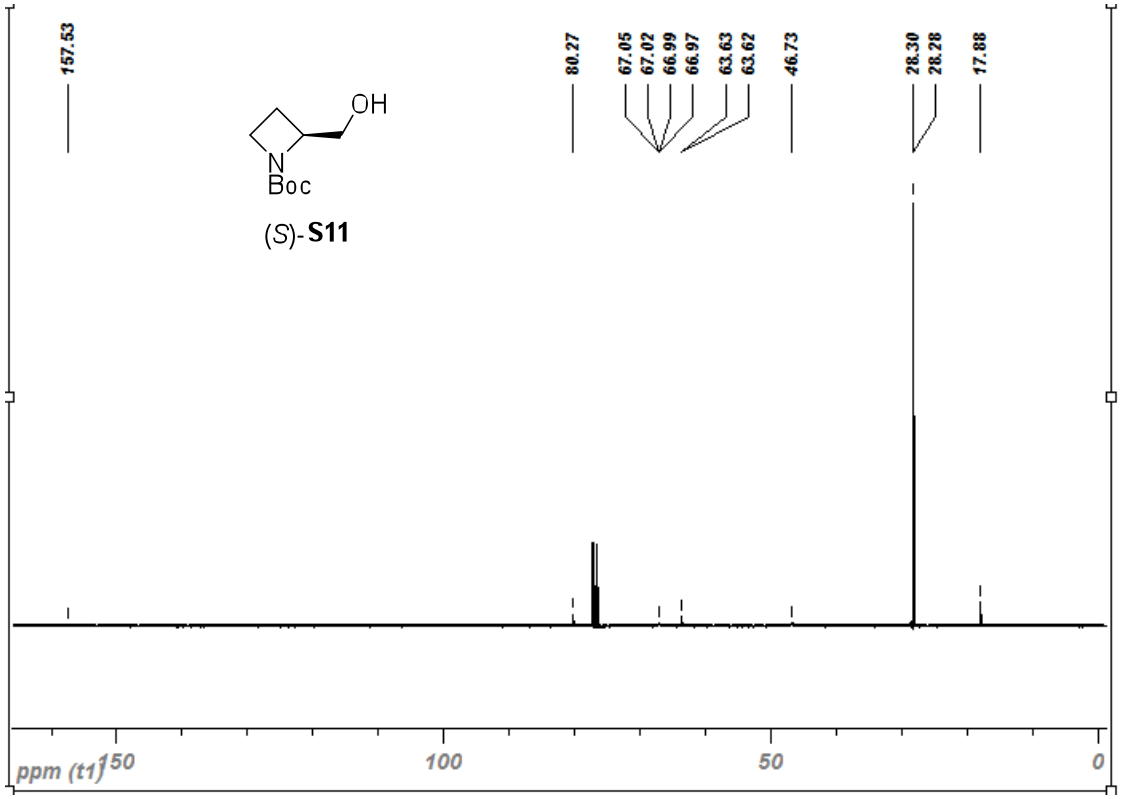

d2247jcs
J Smith-jcs-4-84-6
172.0248
123.6009
77.1600
60.1007
52.3752
29.8442
27.0515
20.4003
14.3444
f1 (ppm)

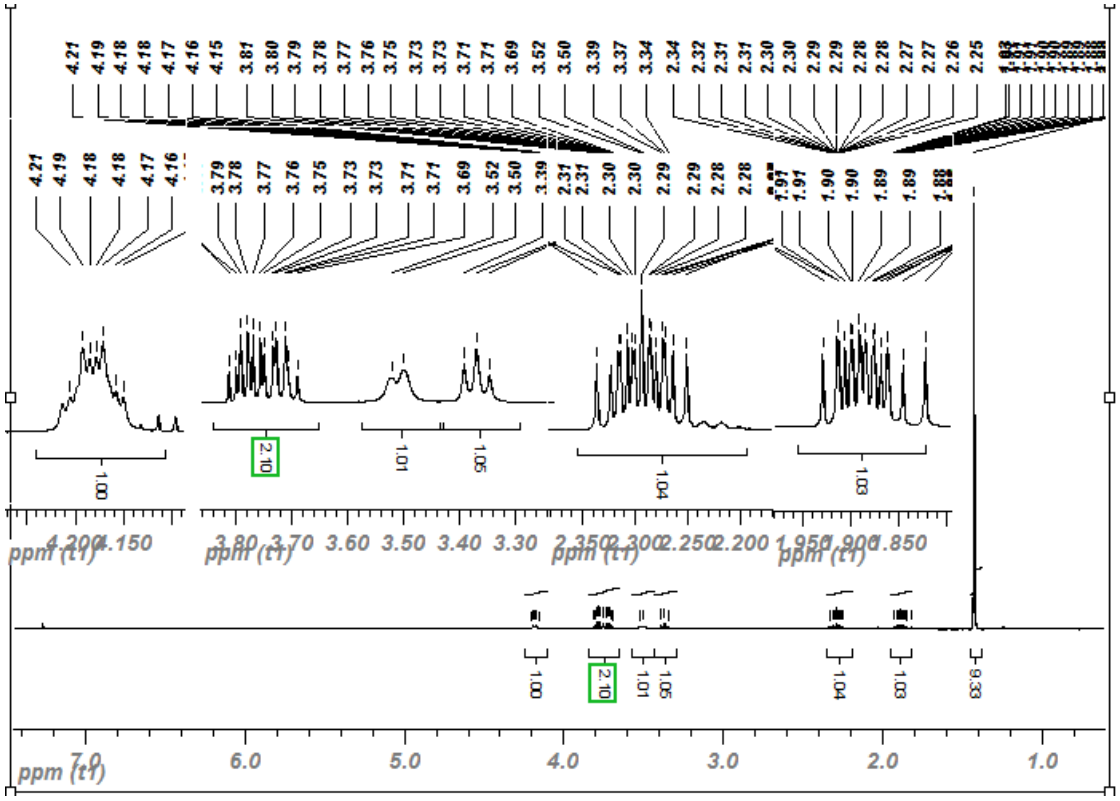

p3134jcs
J Smith-jcs-6-39-filt
7.2606
H
N
CO2Me
O
1.00
1.11
4.38
2.00
2.29
15.48
f1 (ppm)

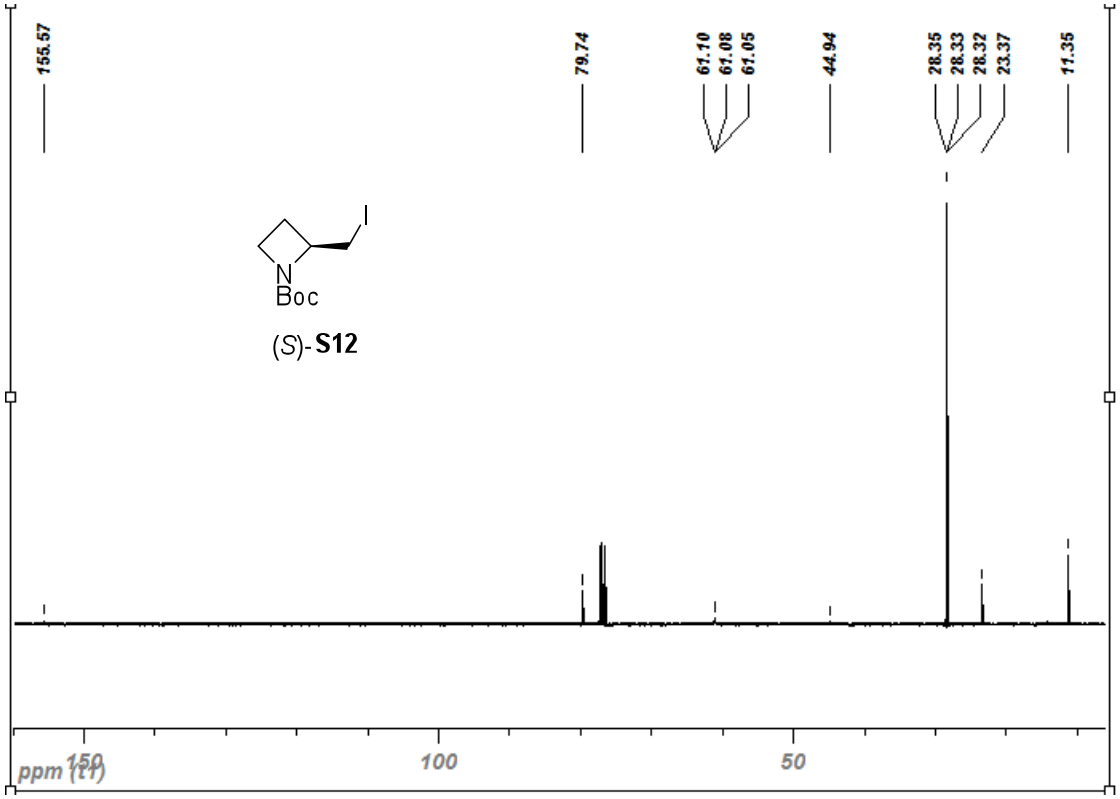
(*S*)-**S10**

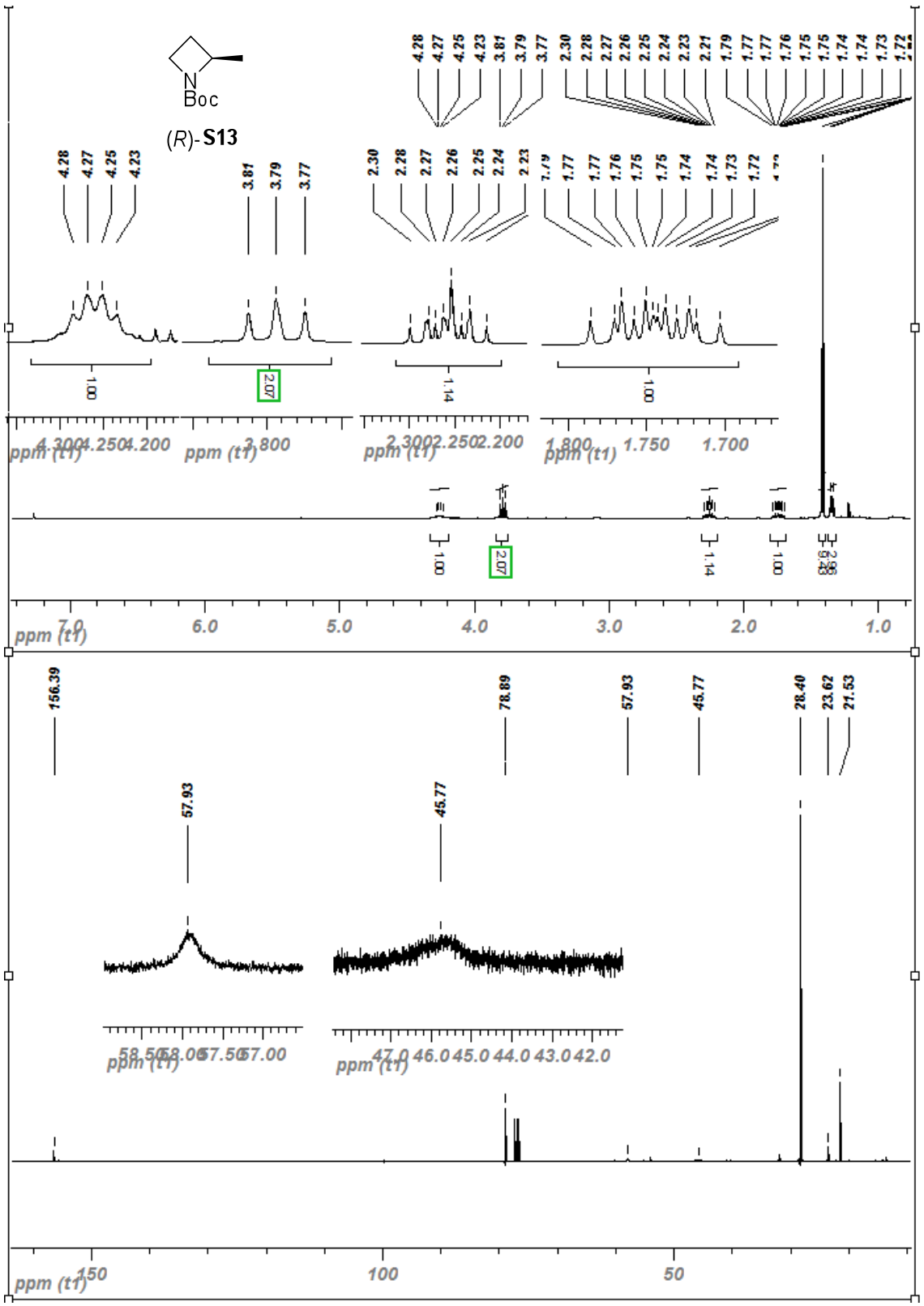

d1761jcs
J Smith-jcs-5-4-filt
176.9615
173.5513
77.1600
61.0057
52.1798
48.3039
38.8746
27.9450
27.3751
26.1581
f1 (ppm)

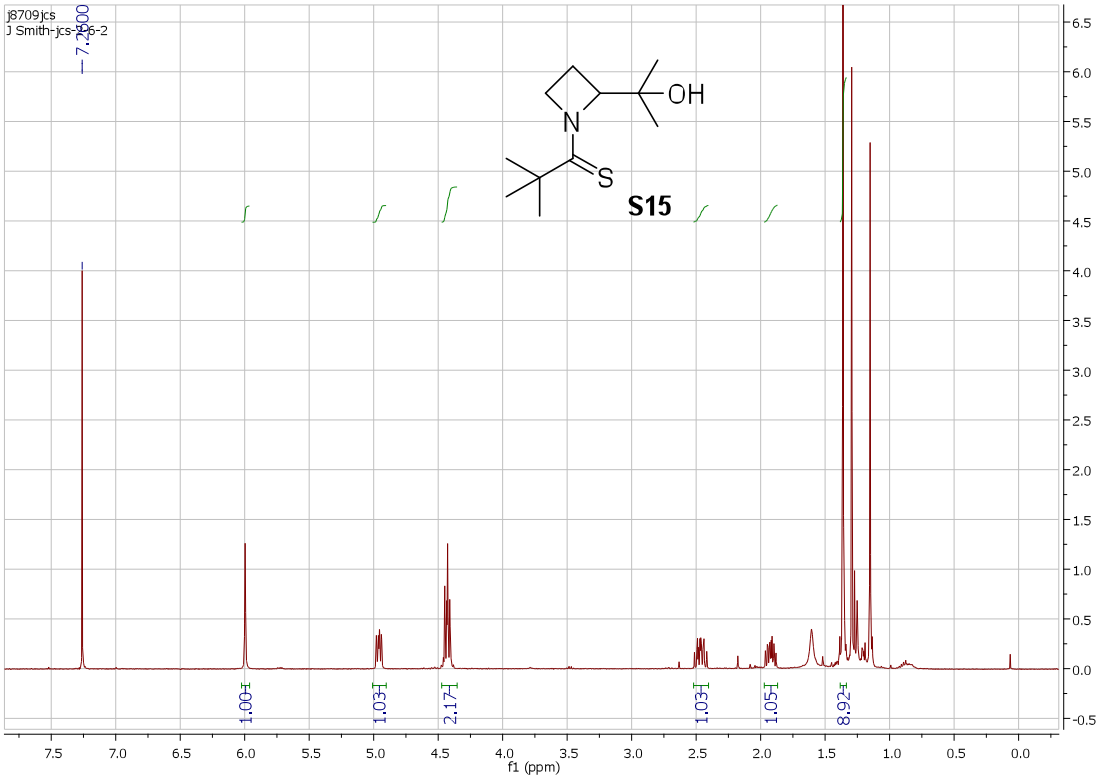

4.42 4.25 4.25 4.24 4.24 4.24 3.88 3.86 3.84 3.84 3.82 3.79 3.77 3.76 3.75 3.74 3.73 3.70 3.68
2.20 2.18 2.18 2.17 2.16 2.16 2.15 2.14 2.13 2.13 2.11 1.91
0.34 0.53 1.00 2.98 0.96 0.96
4.50 4.00 ppm (t1)
2.30 2.20 2.10 2.00 1.90 ppm (t1)
0.34 0.53 1.00 2.98 0.96 0.96 8.51
7.0 6.0 5.0 4.0 3.0 2.0 1.0 ppm (t1)

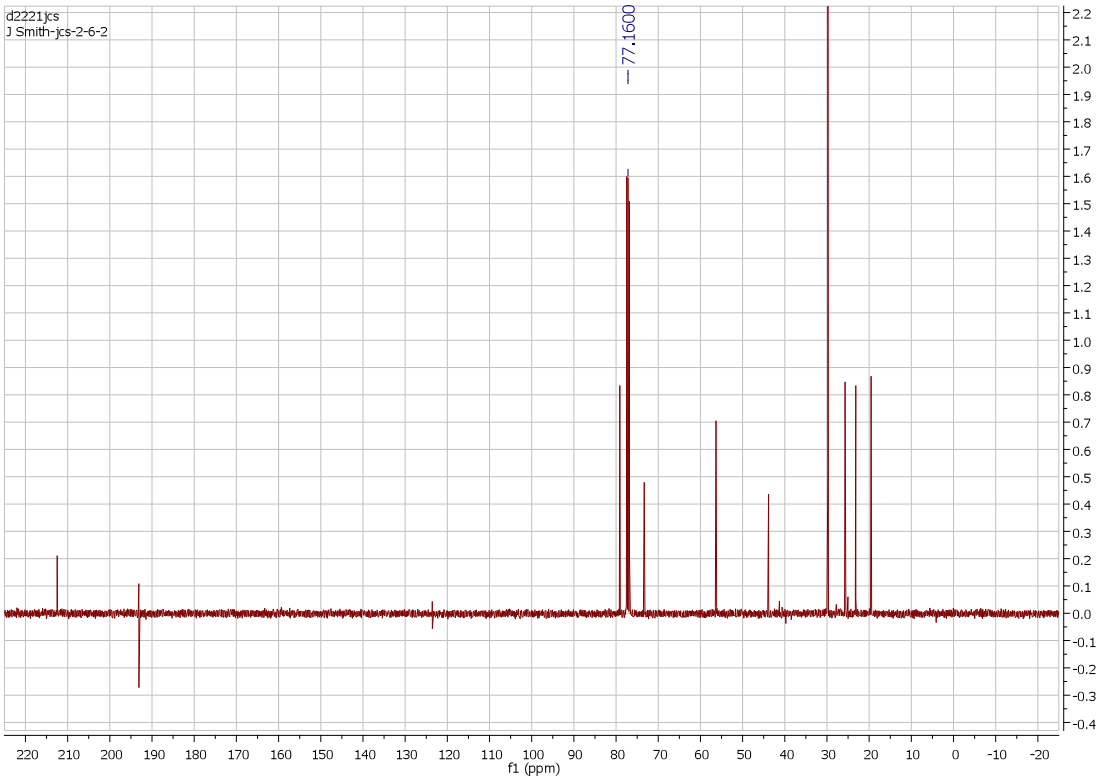

157.53
80.27
67.05 67.02 66.99 66.97
63.63 63.62
46.73
28.30 28.28
17.88
OH
N
Boc
(S)-S11
150 100 50 0 ppm (t1)

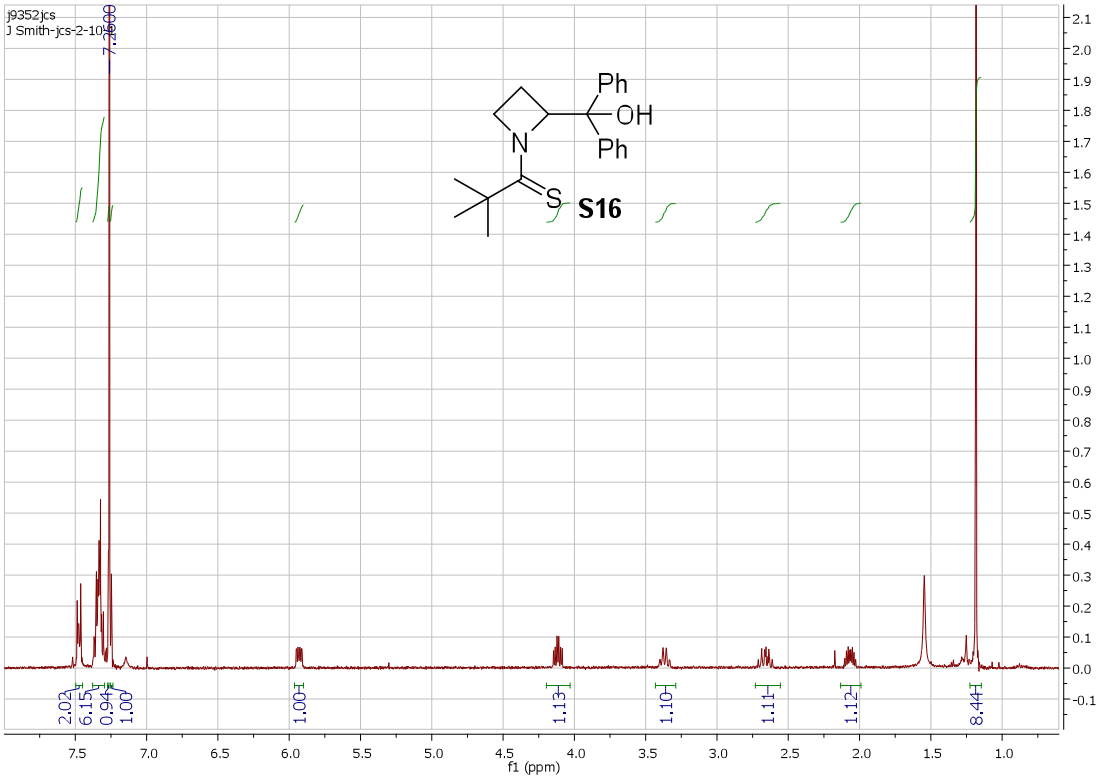


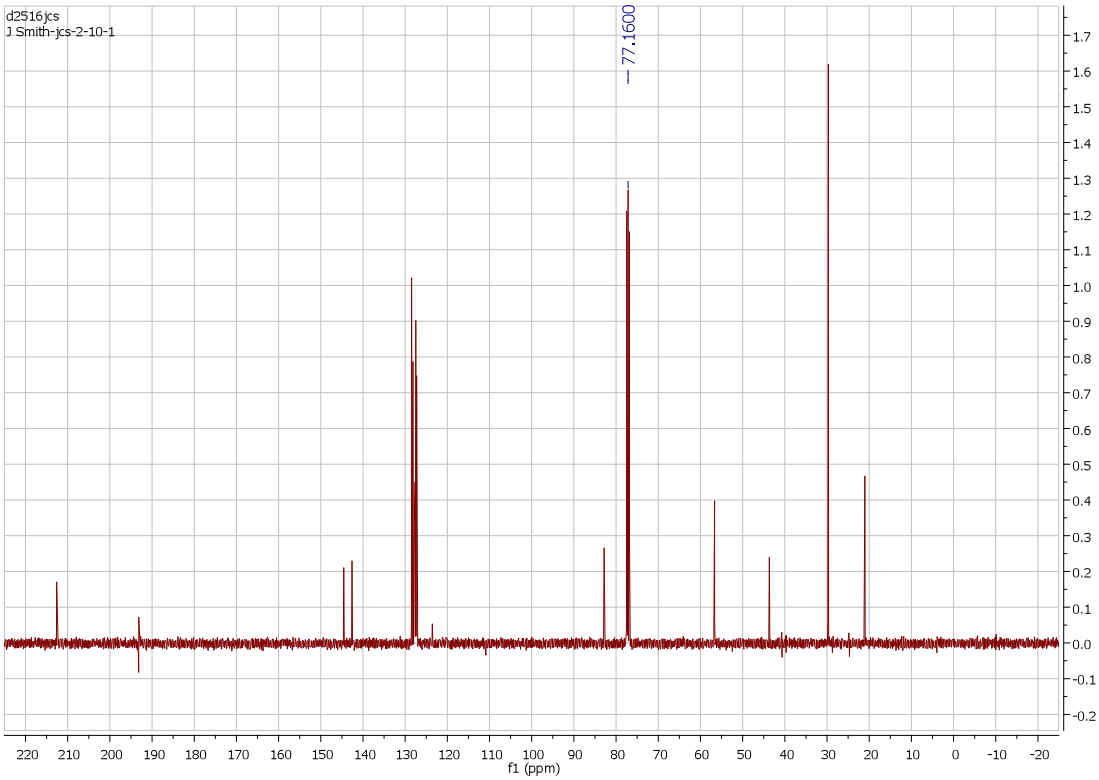

155.57
79.74
61.10
61.08
61.05
44.94
28.35
28.33
28.32
23.37
11.35
N
Boc
I
(S)-S12

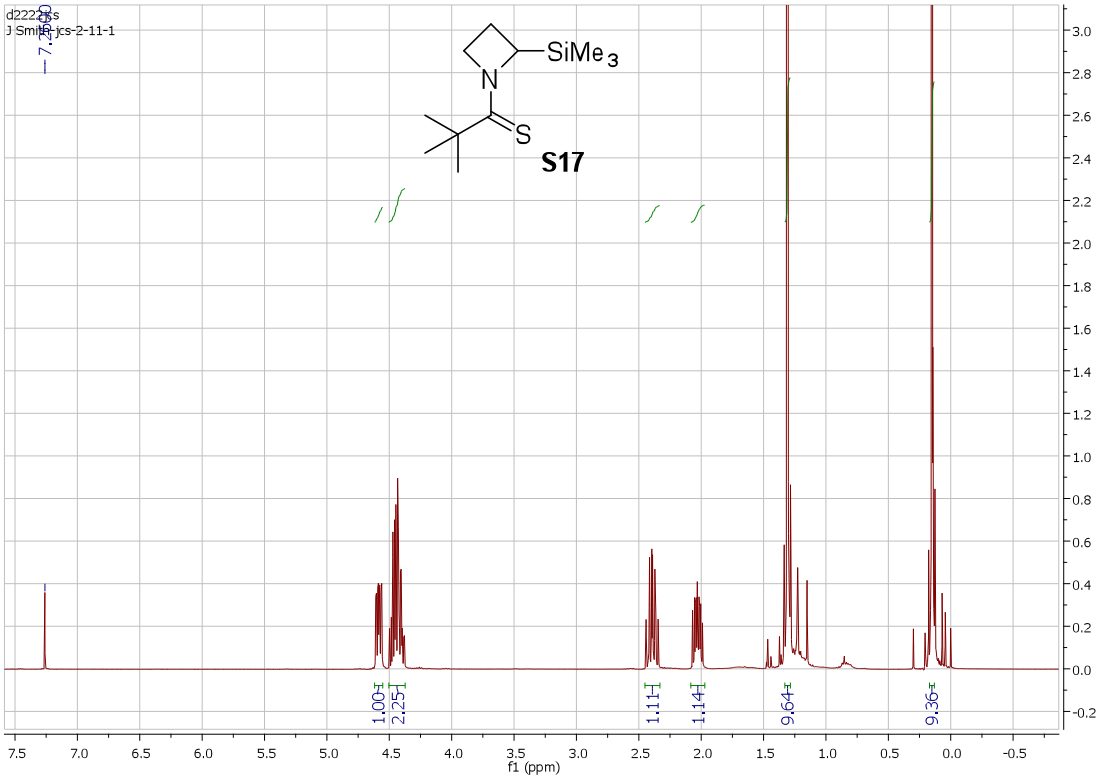

(R)-S13
Boc
N
4.28
4.27
4.25
4.23
3.81
3.79
3.77
2.30
2.28
2.27
2.26
2.25
2.24
2.23
2.21
1.79
1.77
1.77
1.76
1.75
1.75
1.74
1.74
1.73
1.72
1.00
2.07
1.14
1.00
ppm (t1)
7.0
6.0
5.0
4.0
3.0
2.0
1.0
156.39
78.89
57.93
45.77
28.40
23.62
21.53
150
100
50

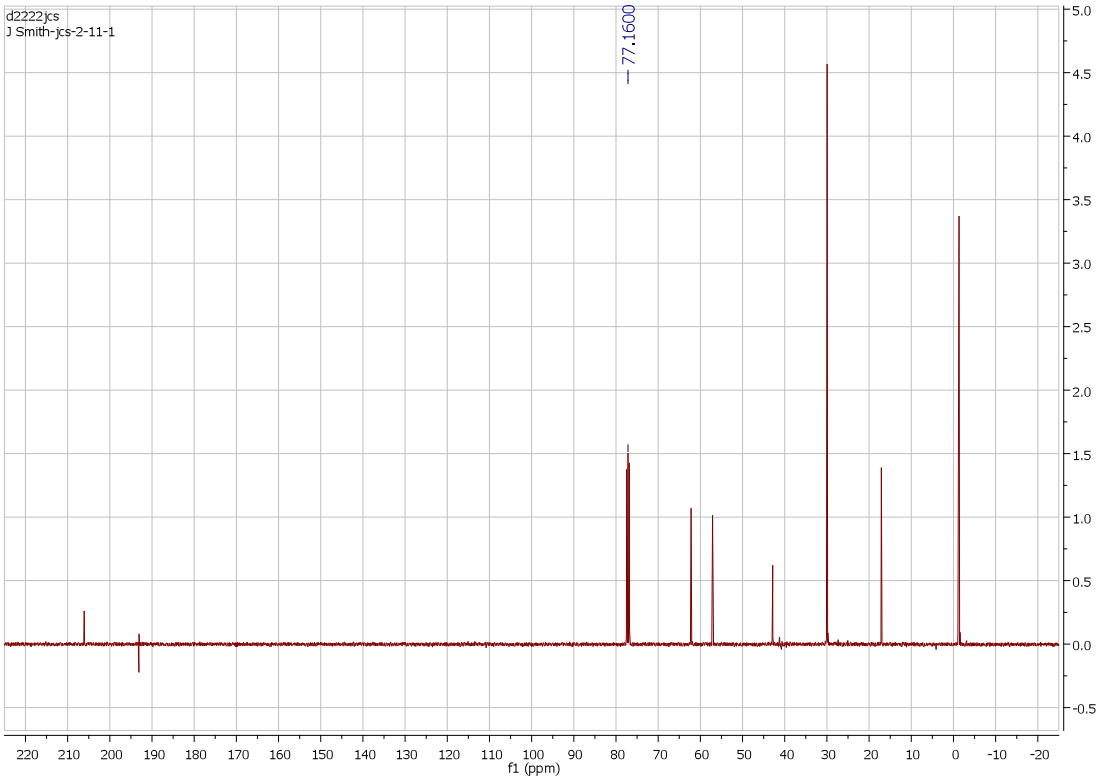

j8709jcs
J Smith-jcs-2-6-2
7.2600
OH
N
S
S15
1.00
1.03
2.17
1.03
1.05
8.92
f1 (ppm)


d2221jcs
J Smith-jcs-2-6-2
77.1600
f1 (ppm)


j9352jcs
J Smith-jcs-2-10-1
7.2600
Ph
OH
Ph
N
S
S16
2.02
6.15
0.94
1.00
1.00
1.13
1.10
1.11
1.12
8.44
f1 (ppm)

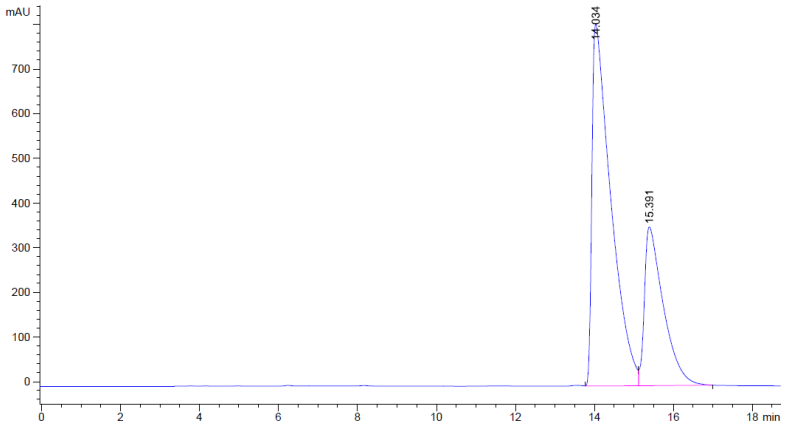

d2516jcs
J Smith-jcs-2-10-1
77.1600
f1 (ppm)

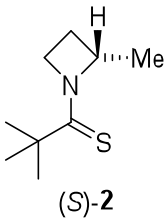

d2222jcs
J Smith-jcs-2-11-1
7.2600
SiMe3
N
S
S17
1.00
2.25
1.11
1.14
9.64
9.36
f1 (ppm)


d2222jcs
J Smith-jcs-2-11-1
77.1600
f1 (ppm)

5. CSP-HPLC Data

CSP-HPLC of (*S*)-2 of 69:31 er

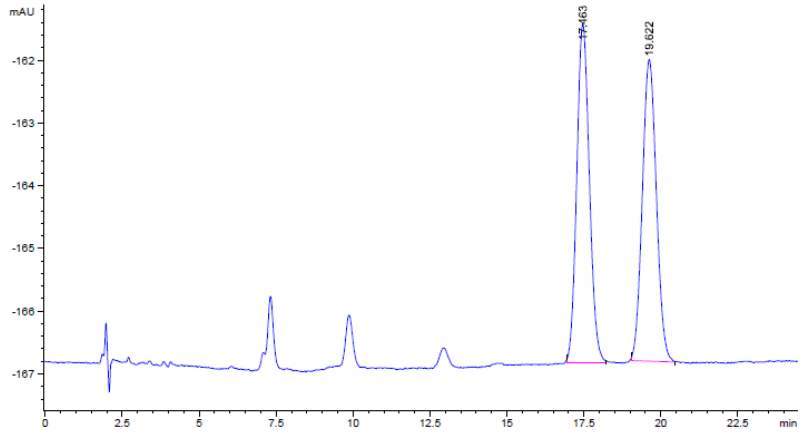


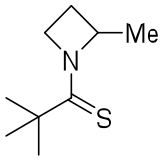


(*S*)-**2**

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.034	VV	0.4737	2.69269e4	810.32404	69.4040
2	15.391	VB	0.4837	1.18704e4	355.40292	30.5960
Totals :				3.87974e4	1165.72696	

CSP-HPLC of *rac*-2 of 50:50 er

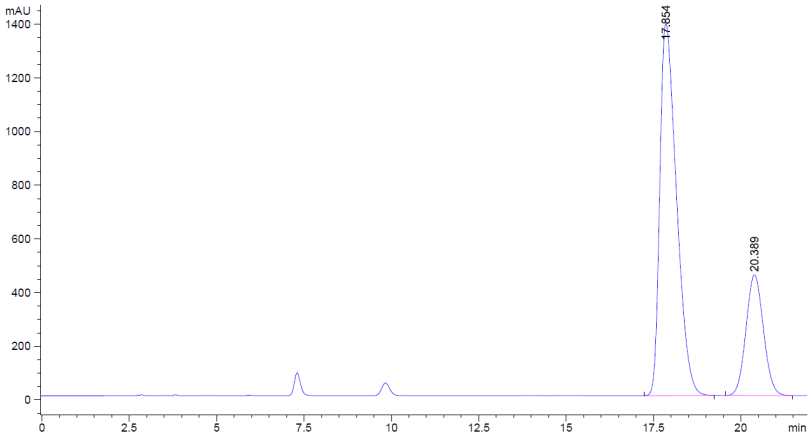


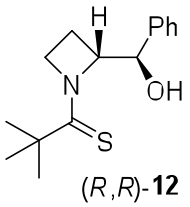


rac-**2**

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	17.463	BB	0.4374	153.38583	5.39962	50.1224
2	19.622	BB	0.4940	152.63655	4.81314	49.8776
Totals :				306.02238	10.21277	

CSP-HPLC of (*R*,*R*)-12 of 75:25 er

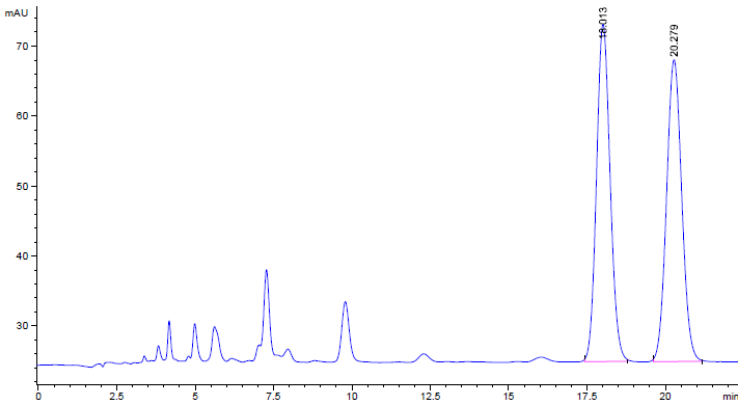


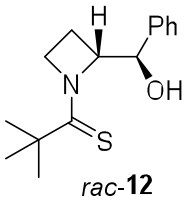


(*R*,*R*)-**12**

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	17.854	BB	0.5086	4.59537e4	1386.68506	74.6128
2	20.389	BB	0.5441	1.56358e4	449.21460	25.3872
Totals :				6.15895e4	1835.89966	

CSP-HPLC of *rac*-12 of 50:50 er

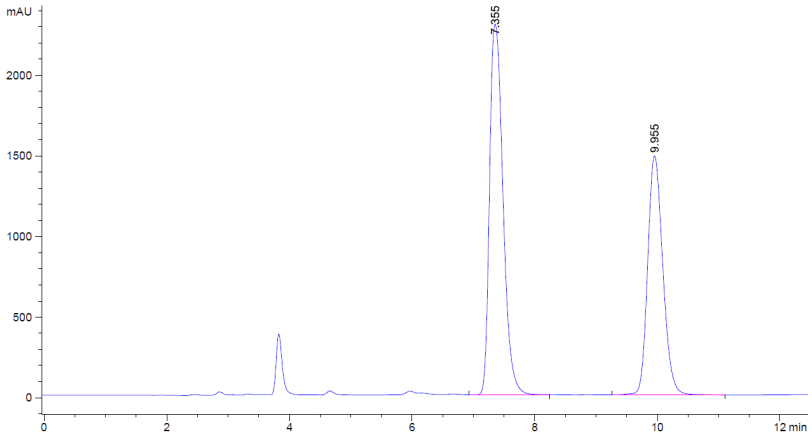


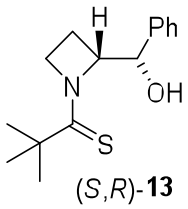


rac-**12**

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	18.013	BB	0.4679	1454.58008	48.22639	50.0486
2	20.279	BB	0.5248	1451.75439	43.11607	49.9514
Totals :				2906.33447	91.34246	

CSP-HPLC of (*S*,*R*)-13 of 58:42 er

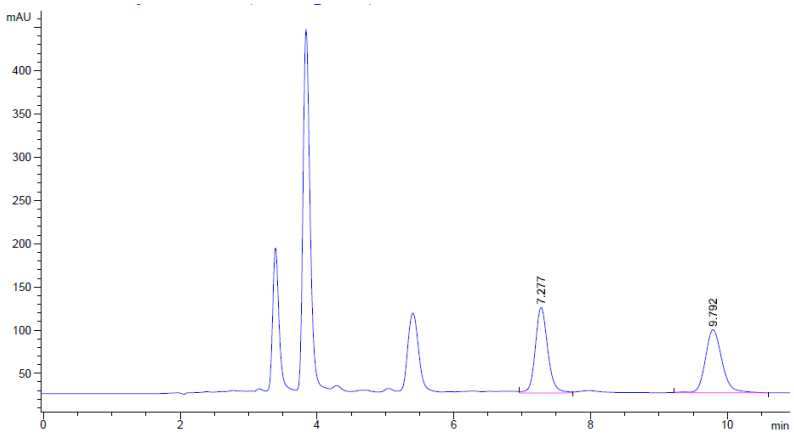


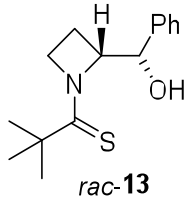


(*S*,*R*)-**13**

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.355	VB	0.2373	3.49309e4	2298.66528	57.8267
2	9.955	VB	0.2665	2.54752e4	1482.22449	42.1733
Totals :				6.04061e4	3780.88977	

CSP-HPLC of *rac*-13 of 50:50 er

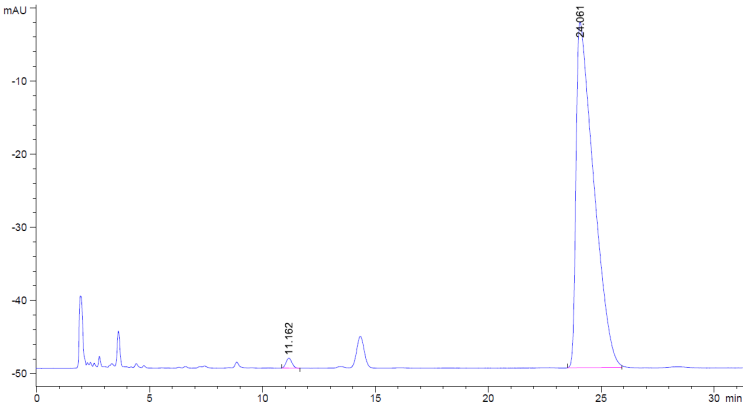


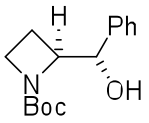


rac-**13**

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.277	VV	0.1932	1245.49988	98.73417	50.4340
2	9.792	BB	0.2602	1224.06494	72.78902	49.5660
Totals :				2469.56482	171.52319	

CSP-HPLC of (*S*,*S*)-S2 of 99:1 er

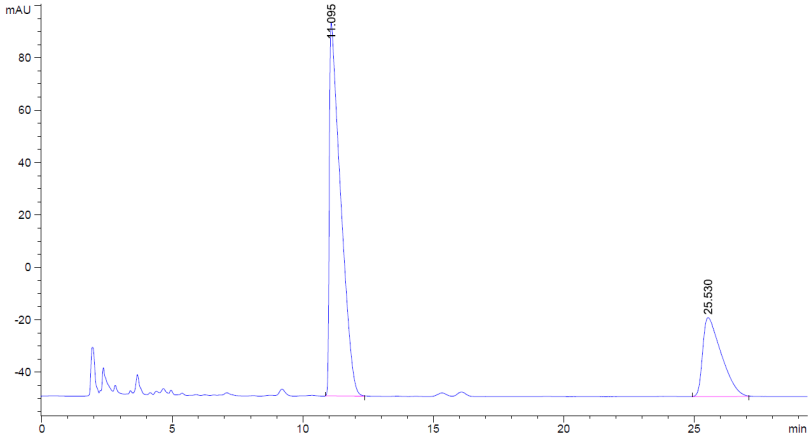


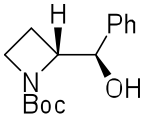


(*S*,*S*)-**S2**

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.162	BB	0.2869	24.89183	1.36396	0.9598
2	24.061	BB	0.7699	2568.67676	47.27539	99.0402

CSP-HPLC of (*R*,*R*)-S2 of 75:25 er

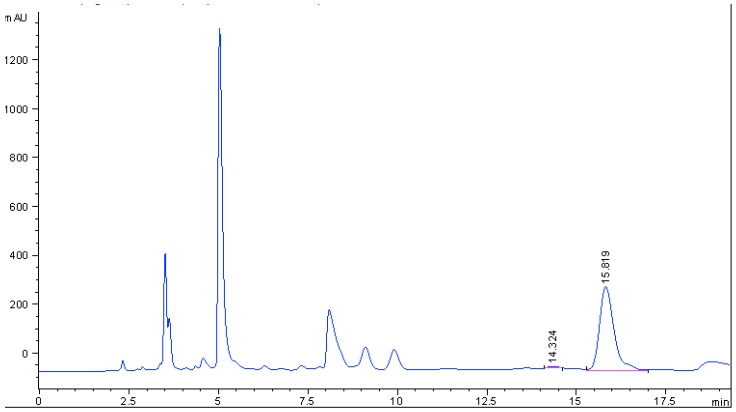


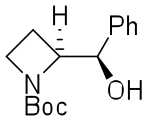


(*R*,*R*)-**S2**

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.095	BB	0.4127	4284.12207	142.50230	74.0968
2	25.530	BB	0.7324	1497.66797	30.10507	25.9032

CSP-HPLC of (*R*,*S*)-S3 of 99:1 er

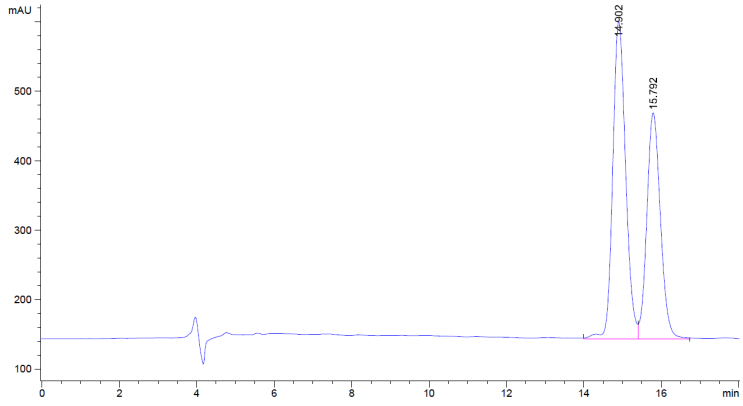


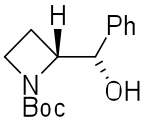


(*R*,*S*)-**S3**

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.324	MM	0.3111	149.31052	8.00008	1.5374
2	15.819	VB	0.4288	9562.29102	341.41754	98.4626
Totals :				9711.60153	349.41762	

CSP-HPLC of (*S*,*R*)-S3 of 57:43 er

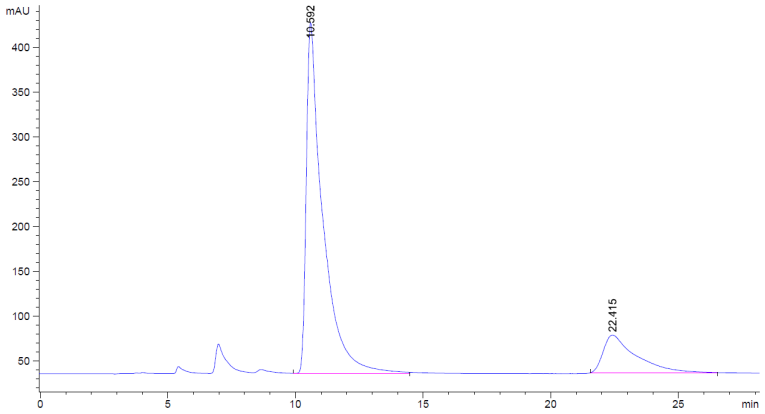


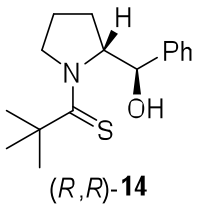


(*S*,*R*)-**S3**

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.902	MM	0.3858	1.05954e4	457.66769	57.0778
2	15.792	MM	0.4072	7967.68994	326.12051	42.9222

CSP-HPLC of (*R*,*R*)-14 of 82:18 er

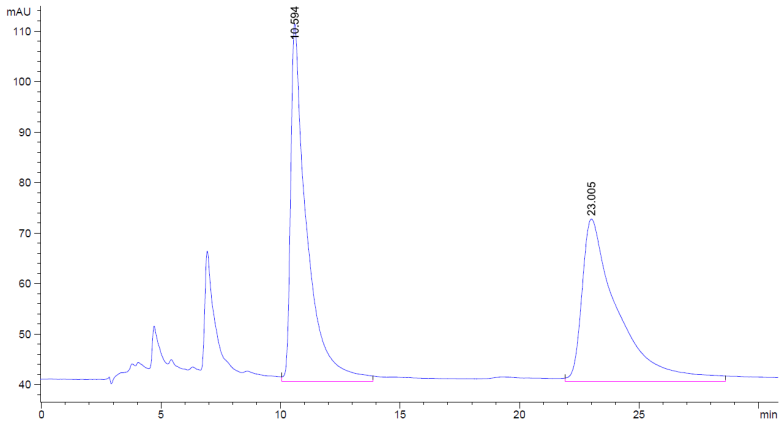


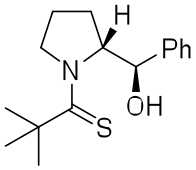


(*R*,*R*)-**14**

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.592	MM	0.7530	1.76860e4	391.46387	82.1876
2	22.415	MM	1.5051	3833.06519	42.44429	17.8124
Totals :				2.15190e4	433.90815	

CSP-HPLC of *rac*-14 of 50:50 er

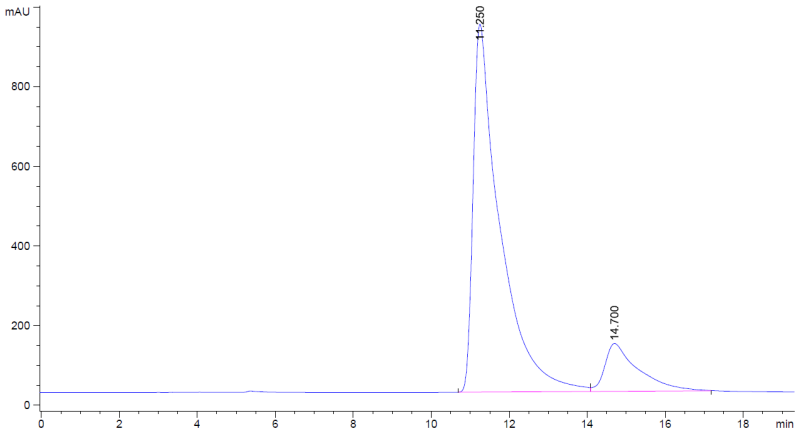


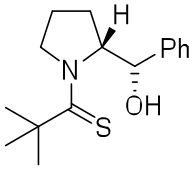


rac-**14**

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.594	MM	0.7766	3294.32764	70.70055	49.5635
2	23.005	MM	1.7412	3352.35986	32.08914	50.4365
Totals :				6646.68750	102.78968	

CSP-HPLC of (*S*,*R*)-15 of 86:14 er

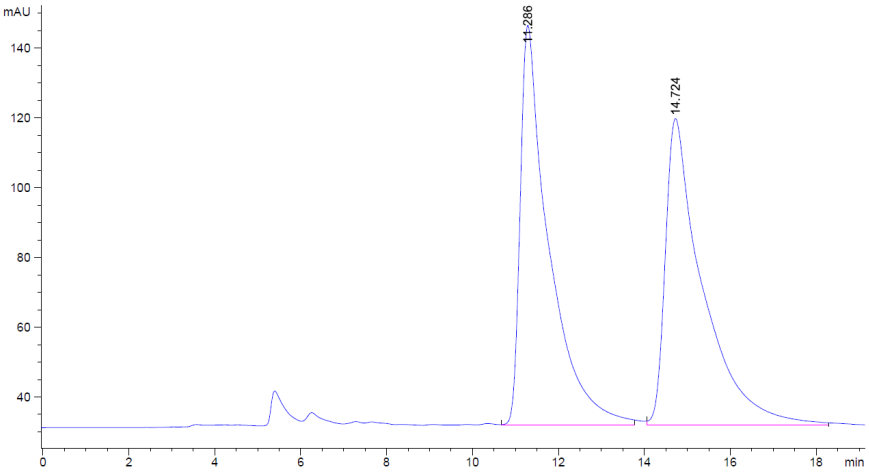


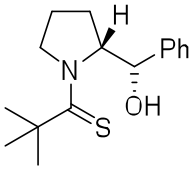


(*S*,*R*)-**15**

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.250	BB	0.6559	4.42020e4	924.32855	86.1597
2	14.700	BB	0.8139	7100.40234	120.06983	13.8403
Totals :				5.13024e4	1044.39838	

CSP-HPLC of *rac*-15 of 50:50 er

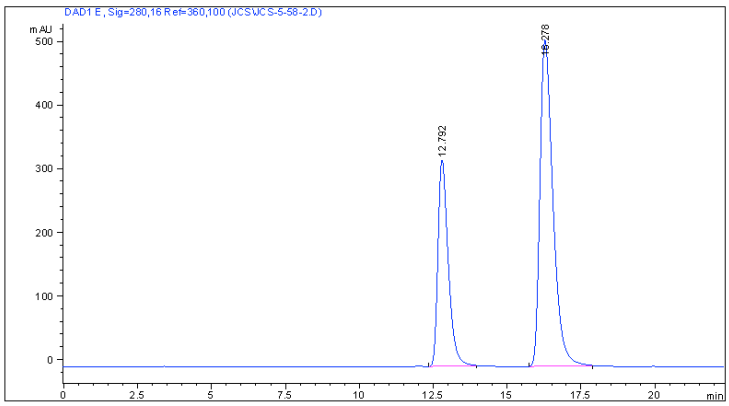


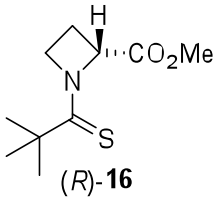


rac-**15**

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.286	MM	0.7699	5288.37939	114.47649	49.9415
2	14.724	MM	1.0068	5300.76758	87.74789	50.0585
Totals :				1.05891e4	202.22438	

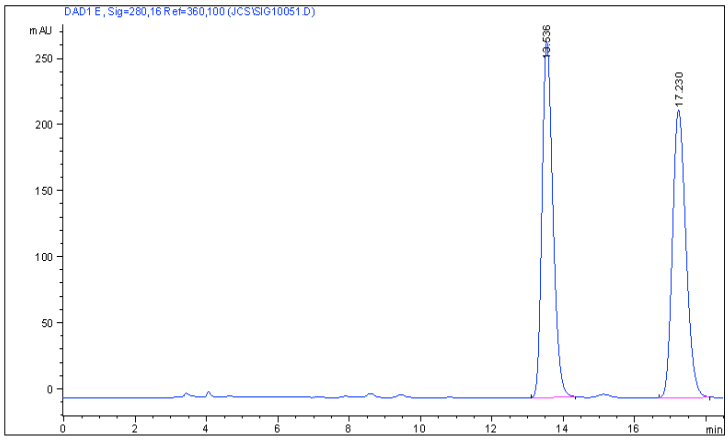
CSP-HPLC of (*R*)-16 of 67:33 er

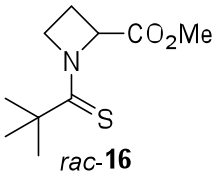




Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.792	BB	0.3663	7852.21631	324.50208	33.4335
2	16.278	BB	0.4657	1.56338e4	512.79816	66.5665
Totals :				2.34861e4	837.30023	

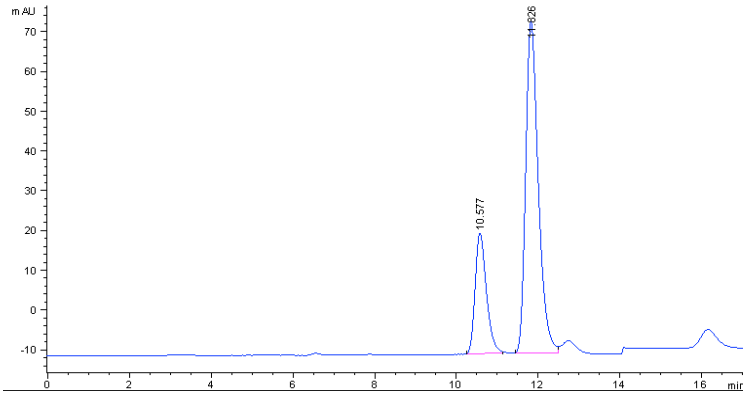
CSP-HPLC of *rac*-16 of 50:50 er

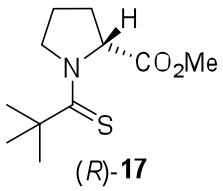




Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	13.536	BB	0.3271	5703.49072	269.24261	50.0292
2	17.230	BB	0.4050	5696.83545	217.90982	49.9708
Totals :				1.14003e4	487.15244	

CSP-HPLC of (*R*)-17 of 76:24 er

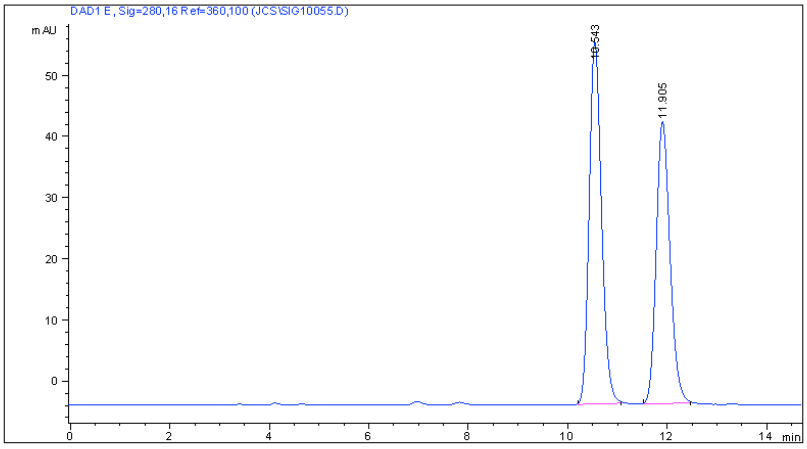


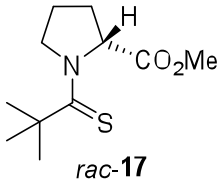


(*R*)-**17**

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.577	BB	0.2891	580.77203	30.37472	24.4911
2	11.826	BB	0.3268	1790.58789	83.29710	75.5089
Totals :				2371.35992	113.67181	

CSP-HPLC of *rac*-17 of 54:46 er

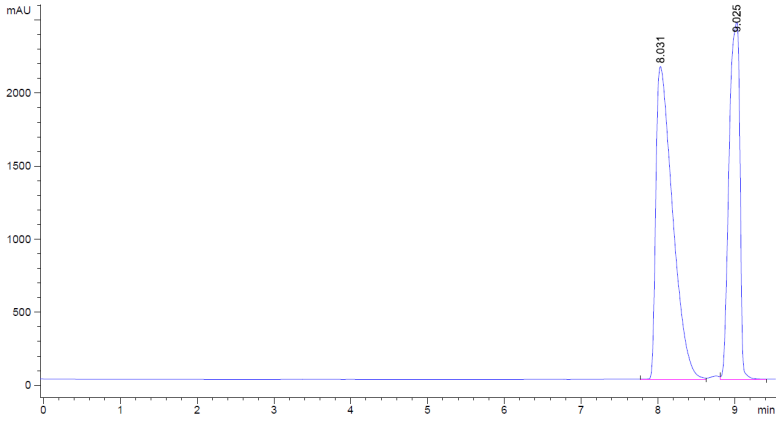


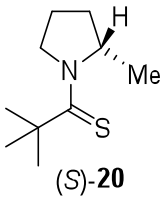


rac-**17**

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.543	BB	0.2674	1022.90955	59.25338	53.5426
2	11.905	BB	0.2963	887.54871	46.16060	46.4574
Totals :				1910.45825	105.41398	

CSP-HPLC of (*S*)-20 of 58:42 er

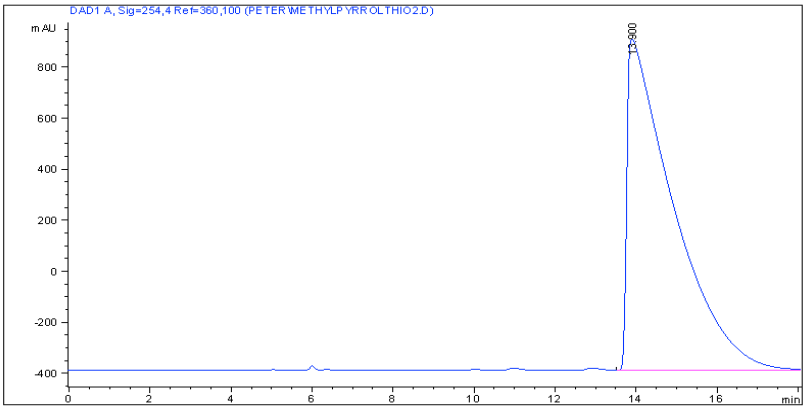


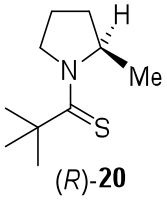


(*S*)-**20**

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.031	BV	0.2329	3.24516e4	2140.43945	57.8625
2	9.025	VB	0.1609	2.36324e4	2442.75171	42.1375
Totals :				5.60840e4	4583.19116	

CSP-HPLC of (*R*)-20 of 100:0 er

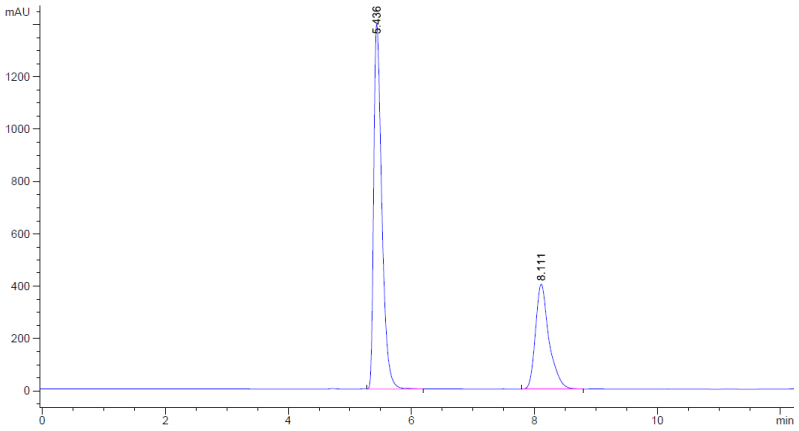


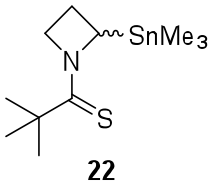


(*R*)-**20**

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	13.900	BBA	1.0214	1.02801e5	1298.89954	100.0000
Totals :				1.02801e5	1298.89954	

CSP-HPLC of 22 of 68:32 er

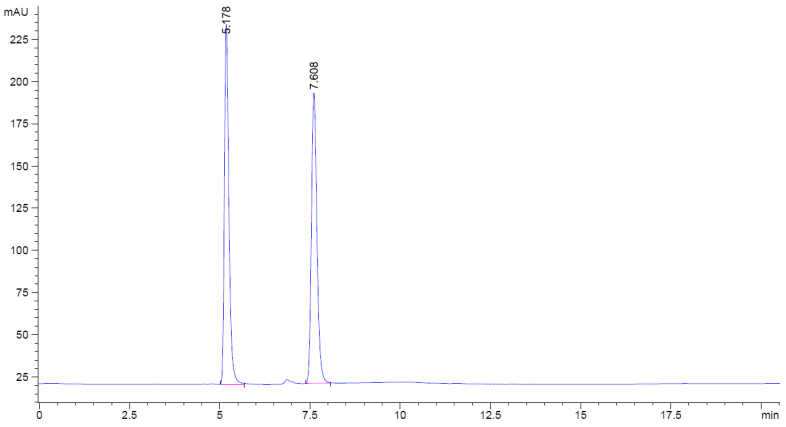


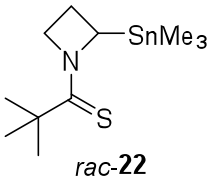


22

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.436	VB	0.1385	1.27282e4	1394.87549	67.5019
2	8.111	BB	0.2283	6127.86621	400.88623	32.4981
Totals :				1.88561e4	1795.76172	

CSP-HPLC of *rac*-22 of 50:50 er

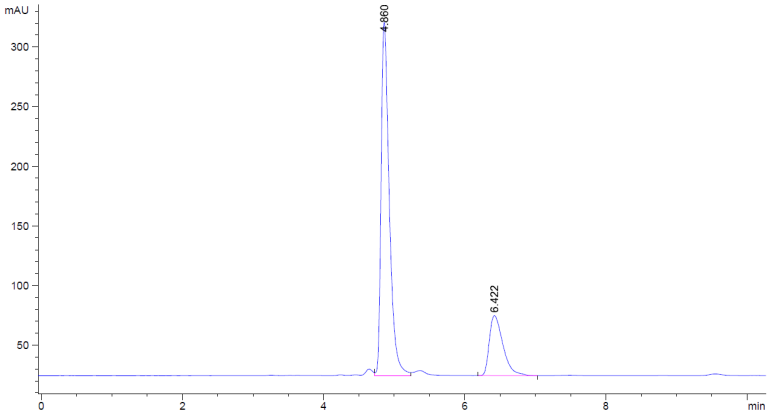


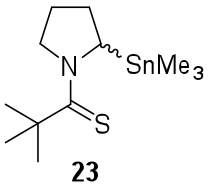


rac-**22**

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.178	BB	0.1305	1838.65198	213.35065	50.0619
2	7.608	BB	0.1641	1834.10852	172.38014	49.9381
Totals :				3672.76050	385.73079	

CSP-HPLC of 23 of 78:22 er

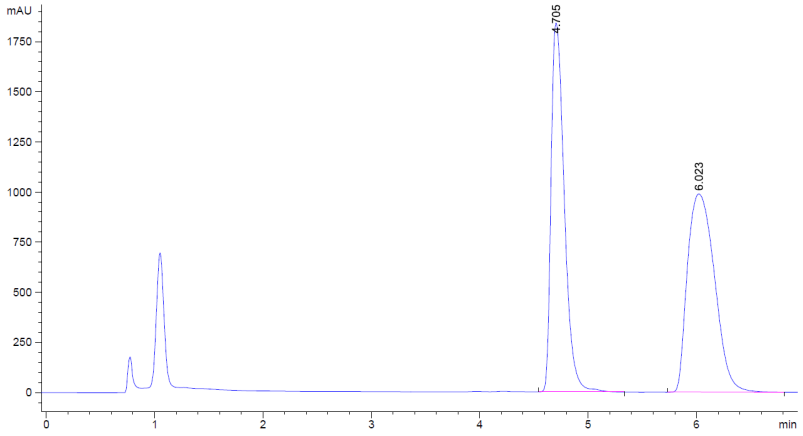


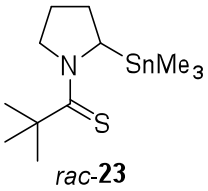


23

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.860	VV	0.1216	2382.31567	296.87918	77.8709
2	6.422	BB	0.2091	676.99817	50.27295	22.1291
Totals :				3059.31384	347.15213	

CSP-HPLC of *rac*-23 of 50:50 er

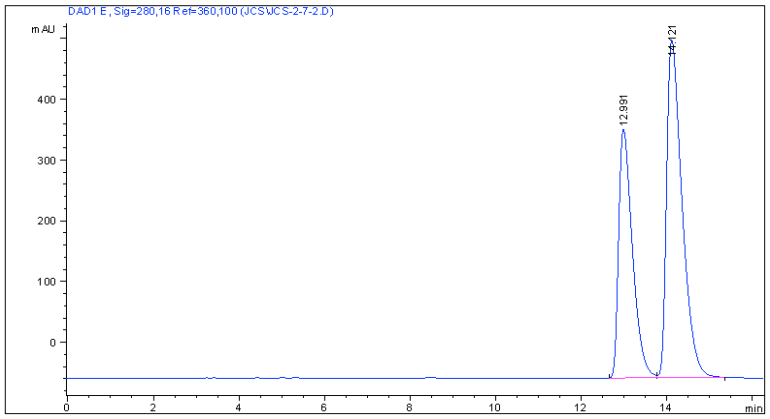


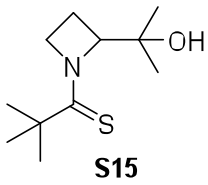


rac-**23**

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.705	BB	0.1331	1.56368e4	1840.94458	47.5946
2	6.023	VB	0.2891	1.72174e4	988.85254	52.4054
Totals :				3.28542e4	2829.79712	

CSP-HPLC of S15 of 60:40 er

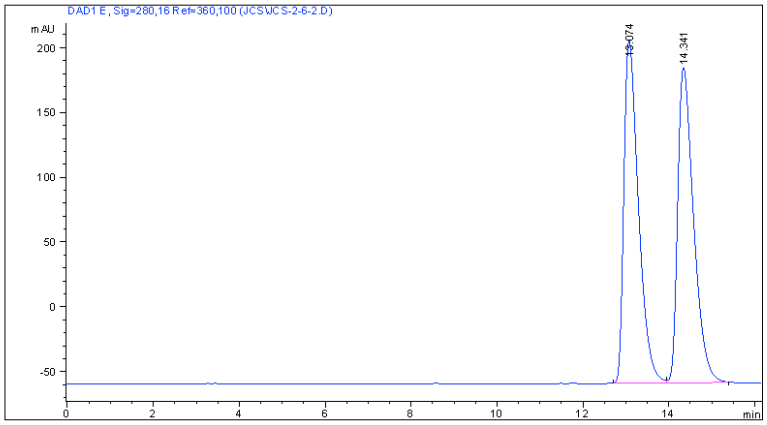


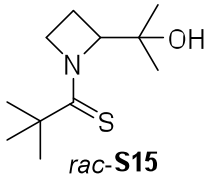


S15

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.991	BV	0.3409	9157.42285	409.49518	39.6060
2	14.121	VB	0.3810	1.39639e4	556.09570	60.3940
Totals :				2.31213e4	965.59088	

CSP-HPLC of *rac*-S15 of 50:50 er

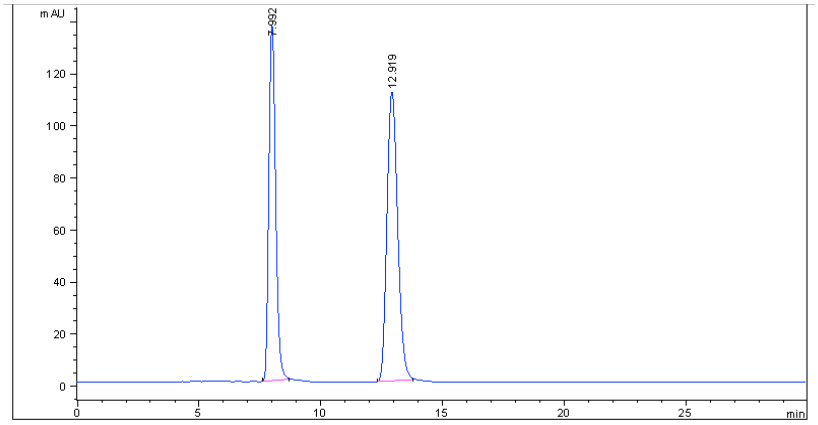


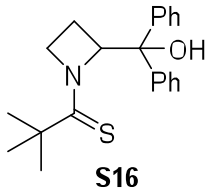


rac-**S15**

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	13.074	BV	0.3565	6233.15088	264.94638	49.9182
2	14.341	VB	0.3896	6253.57422	243.53642	50.0818
Totals :				1.24867e4	508.48280	

CSP-HPLC of 16 of 56:44 er

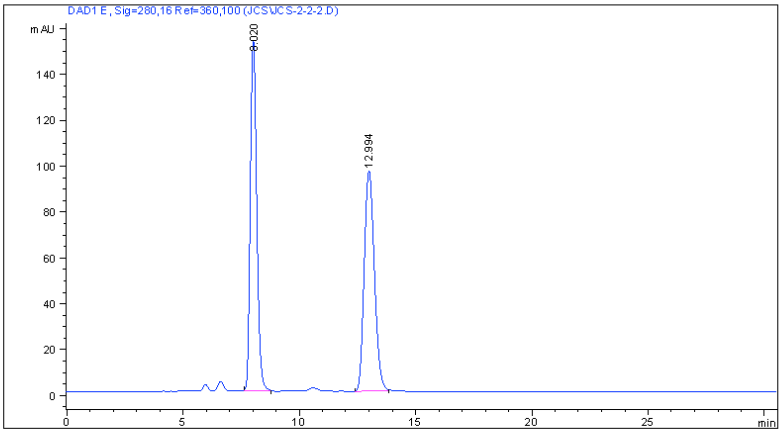


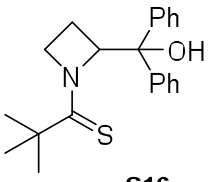


S16

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.992	BB	0.3047	2654.87158	136.62863	43.7902
2	12.919	BB	0.4819	3407.83398	111.08730	56.2098
Totals :				6062.70557	247.71593	

CSP-HPLC of *rac*-S16 of 50:50 er

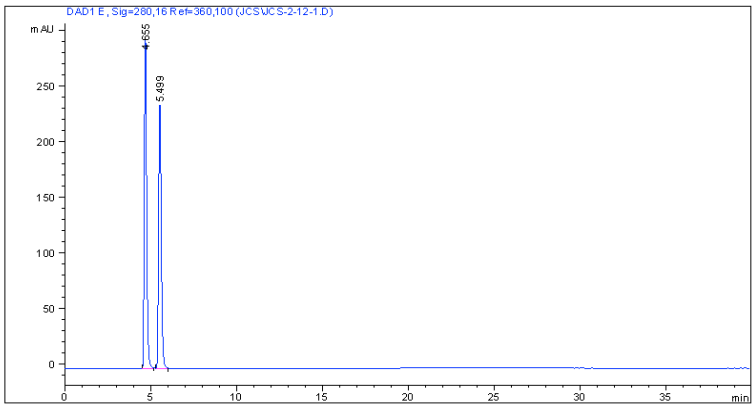


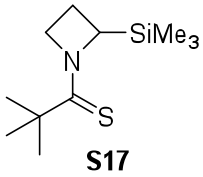


rac-**S16**

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.020	BB	0.3037	2954.64209	152.71715	50.3148
2	12.994	BB	0.4786	2917.67456	95.99203	49.6852
Totals :				5872.31665	248.70918	

CSP-HPLC of S17 of 53:47 er

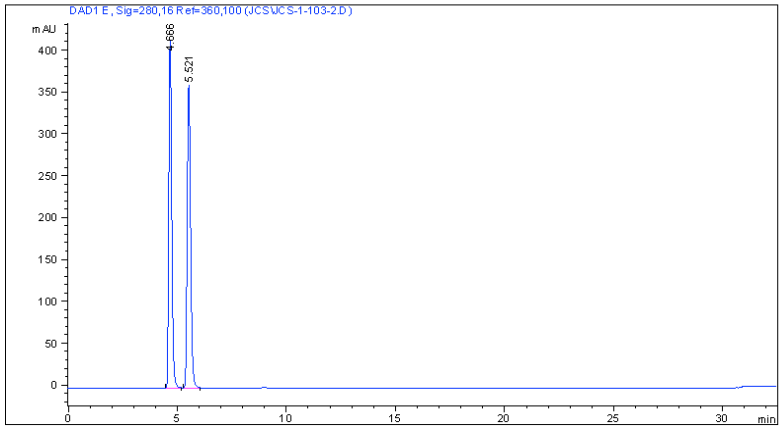


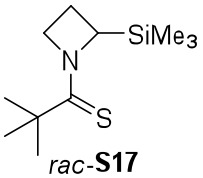


S17

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.655	BB	0.1501	2843.43530	296.02966	52.4863
2	5.499	BB	0.1708	2574.04126	236.88319	47.5137
Totals :				5417.47656	532.91286	

CSP-HPLC of *rac*-S17 of 50:50 er





rac-**S17**

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.666	BB	0.1464	3931.13916	415.39651	50.0459
2	5.521	BB	0.1706	3923.92236	361.69928	49.9541
Totals :				7855.06152	777.09579	

6. References for Supporting Information

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