N-Isopropylsulfinylimines *vs* *N-tert*-butylsulfinylimines in the stereoselective synthesis of sterically hindered amines: An improved synthesis of enantiopure (*R*)- and (*S*)-rimantadine and the trifluoromethylated analogues.

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Supporting Information

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All reactions were run under an atmosphere of dry argon using oven dried glassware and dried solvents. Methanol, toluene, THF, EtOAc, CH_2Cl_2, diethyl ether were dried using molecular sieves, and highest quality solvents were used. Chemicals were obtained from commercial sources, and were used without further purification. TLC was carried out on silica gel GF254 (Merck), and compounds were detected by charring with phosphomolybdic acid/EtOH. For flash chromatography, Merck 230–400 mesh silica gel was used. Chromatographic columns were eluted with a positive pressure of air, and eluents are given as volume to volume ratios (v/v). NMR spectra were recorded with Bruker Avance 500 MHz spectrometers. Chemical shifts are reported in ppm, and coupling constants are reported in Hz. Routine ^1H and ^{13}C spectra were referenced to the residual proton or carbon signals of the solvent, respectively. High-resolution mass spectra (HRMS) were recorded with a Kratos MS-80RFA 241-MC apparatus. Optical rotations were determined with a Perkin–Elmer 341 polarimeter. Melting points were measured with a Stuart SMP3 apparatus in open-ended capillary tubes.

Experimental data for the synthesis of *N-tert*-butylsulfinamides via *N-tert*-butylsulfinylaldimines.

*1-Adamantane carboxaldehyde, **4***

To a suspension of pyridinium chlorochromate (PCC) (7.8 g, 36.08 mmol, 150 mol%) in dry CH_2Cl_2 (200 mL) under argon atmosphere, a solution of adamantyl methanol (4 g, 24.06 mmol, 100 mol%) in dry CH_2Cl_2 (60 mL) was added. After 4 h, the reaction was stopped with dry diethyl ether (400 mL) and the salts were filtred with Florisil 60-100 mesh column. After removing the solvent under vacuum, it was obtained **4** (3.8 g, 22.89 mmol, 95% yield) as a white solid with no further purification; ^1H-NMR (500 MHz, $CDCl_3$): δ 9.32 (s, 1H), 2.07 (s, 3H), 1.80-1.69 (m, 12H) ppm; ^{13}C-NMR (125 MHz, $CDCl_3$): δ 206.2, 45.1, 36.9, 36.2, 27.7 ppm.

*(R)-N-(Adamantylmethylidene) tert-butylsulfinylimine, **5**(R)*

To a solution of (*R*)-*tert*-butanesulfinamide (1.5 g, 12.05 mmol, 110 mol%) and 1-adamantane carboxaldehyde (1.8 g, 10.96 mmol, 100 mol%) in dry THF (20 mL) at room temperature under argon atmosphere, titanium (IV) ethoxide (2.5 mL, 12.05 mmol, 110 mol%) was added. After 24 h, the reaction mixture was quenched with a saturated NaCl aqueous solution (20 mL). The resulting suspension was filtered through a pad of Celite. The aqueous phase was extracted with CH_2Cl_2 (3 x 40 mL) and the combined organic phases were dried with anhydrous Na_2SO_4. The solvent was removed under reduced pressure, and the residue was purified by flash chromatography (EtOAc:hexane, 1:9), to obtain **5**(*R*) (2.5 g, 9.21 mmol, 84% yield) as a yellow solid; mp 128-130°C; $[\alpha]_D^{20}$: -159.6 [*c* 1, $CHCl_3$]; ^1H-NMR (500 MHz, $CDCl_3$): δ 7.78 (s, 1H), 2.06 (s, 3H), 1.79-1.69 (m, 12H), 1.18 (s, 9H) ppm; ^{13}C-NMR (125 MHz, $CDCl_3$): δ 175.3, 56.5, 40.2, 39.3, 36.7, 28.0, 22.5 ppm; HRMS (ESI) m/z: calcd for $C_{15}H_{25}ONSNa$ $[M+Na]^+$ = 290.1549, found: 290.1541.

*(R_S,S_C)/(R_S,R_C)-N-[1-(1'-adamantyl)ethyl] tert-butylsulfinamide, **6**(R_S,S_C)/(R_S,R_C)*

To a solution of (*R*)-sulfinylimine **5**(*R*) (200 mg, 0.75 mmol, 100 mol%) in dry toluene (2.5 mL) at -78 °C under argon atmosphere, a solution of 1.4M MeMgBr (1 mL, 3 mmol, 400 mol%) was added dropwise. The reaction mixture was slowly warmed to room temperature.

After 48 h, the reaction mixture was hydrolyzed with a saturated NH_4Cl aqueous solution. The aqueous phase was extracted with EtOAc (3 × 40 mL) and the combined organic phases was washed with saturated NaCl aqueous solution and dried with anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure to obtained a mixture of **6**(R_S,S_C)/(R_S,R_C) (126 mg, 0.45 mmol, 60%) in a 60% d.e. Purification by column chromatography (EtOAc:hexane, 1:5) gave diastereomerically pure sulfinamides **6**(R_S,S_C) and **6**(R_S,S_C).

*(R_S,S_C) -N-[1-(1'-adamantyl)ethyl] tert-butylsulfinamide, **6**(R_S,S_C)*

It was obtained **6**(R_S,S_C) (100 mg, 0.35 mmol, 47% yield) as a colorless oil; $[\alpha]_D^{20}$: -5.8 [*c* 1, $CHCl_3$]; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 2.87 (dq, J_1 = 9.4 Hz, J_2 = 6.8 Hz, 1H), 2.72 (d, *J* = 9.3 Hz, 1H), 1.98 (s, 3H), 1.72-1.70 (m, 3H), 1.62-1.58 (m, 6H), 1.44-1.40 (m, 3H), 1.23 (s, 9H), 1.22 (d, *J* = 6.9 Hz, 3H) ppm; ^{13}C-NMR (125 MHz, $CDCl_3$): δ 62.5, 56.5, 38.7, 37.3, 37.0, 28.6, 23.1, 17.3 ppm; HRMS (ESI) m/z: calcd for $C_{16}H_{29}ONNaS$ $[M+Na]^+$ = 306.1862, found: 306.1853.

*(R_S,R_C)-N-[1-(1'-adamantyl)ethyl] tert-butylsulfinamide, **6**(R_S,R_C)*

It was obtained **6**(R_S,R_C) (26 mg, 0.09 mmol, 12% yield) as a colorless solid; mp 108-110°C; $[\alpha]_D^{20}$: -68.3 [*c* 1, $CHCl_3$]; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 3.27 (d, *J* = 4.3 Hz, 1H), 2.95 (dq, J_1 = 6.6 Hz, J_2 = 4.8 Hz, 1H), 2.00 (s, 3H), 1.73-1.70 (m, 3H), 1.64-1.58 (m, 6H), 1.52-1.48 (m, 3H), 1.21 (s, 9H), 1.10 (d, *J* = 6.7 Hz, 3H) ppm; ^{13}C-NMR (125 MHz, $CDCl_3$): δ 59.8, 55.7, 38.7, 37.3, 36.2, 28.6, 22.9, 15.1 ppm; HRMS (ESI) m/z: calcd for $C_{16}H_{29}ONSNa$ $[M+Na]^+$ = 306.1862, found: 306.1853.

(R_S,S_C)-N-[1-(1'-adamantyl)-1-trifluoromethyl]methyl tert-butylsulfinamide, **7**(*R_S,S_C)*

To a suspension of (*R*)-*tert*-butylsulfinylimine **5**(*R*) (150 mg, 0.56 mmol, 100 mol%) and tetrabutylammonium difluorotriphenylsilicate (TBAT) (0.5 g, 0.90 mmol, 160 mol%) in dry toluene (8 mL) at -78 °C under argon atmosphere, trifluoromethyltrimethylsilane (0.6 mL, 3.78 mmol, 675 mol%) was added. The reaction mixture was slowly warmed to -40 °C and stirred during 24 h. Then, the reaction was quenched with saturated NH_4Cl aqueous solution and the aqueous layer was extracted with EtOAc (3 × 40 mL). The combined organic phases were washed with saturated aqueous NaCl solution and dried with anhydrous Na_2SO_4. The solvent was removed under reduced pressure to obtain a mixture of **7***(R_S,S_C)/(R_S,R_C)* in a 64% d.e. Purification by column chromatography (EtOAc:hexane, 1:5) gave diastereomerically pure sulfinamide **7**(R_S,S_C) (96 mg, 0.28 mmol, 51% yield) as a yellow solid; mp 130-132°C; $[\alpha]_D^{20}$: -61.8 [*c* 1, $CHCl_3$]; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 3.50 (d, *J* = 7.8 Hz, 1H), 3.27 (quin, $J_{C\text{-}F}$ = 8.4 Hz, 1H), 2.05 (s, 3H), 1.82-1.64 (m, 12H), 1.25 (s, 9H) ppm; ^{13}C-NMR (125 MHz, $CDCl_3$): δ 126.1 (q, $J_{C\text{-}F}$ = 284.2 Hz) 67.3 (q, $J_{C\text{-}F}$ = 26.9 Hz), 57.3, 39.1, 36.6, 35.7, 28.3, 22.7 ppm; ^{19}F-NMR (470 MHz, $CDCl_3$): δ -66.87 (d, $J_{C\text{-}F}$ = 8.8 Hz) ppm; HRMS (ESI) m/z: calcd for $C_{16}H_{26}ONF_3SNa$ $[M+Na]^+$ = 360.1579, found: 360.1577.

Experimental data for the synthesis of *N*-isopropylsulfinamides via *N*-isopropylsulfinylaldimines.

*Isopropylsulfinyl chloride, **8**[1]*

To a solution of diisopropyl disulfide (6.3 g, 42.18 mmol, 100 mol%) in glacial acetic acid (4.8 mL, 83.93 mmol, 200 mol%) at -40 °C, sulfuryl chloride (10.9 mL, 135 mmol, 320 mol%) were

added dropwise. The mixture was stirring at -20 °C for 2 h, at room temperature for 2 h, and finally, at 35 °C for 1 h. The acids were removing under reduced pressure to give **8** (8.8 g, 82.66 mmol, 98% yield) as a yellow liquid; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 3.29 (sep, *J* = 6.9 Hz, 1H), 1.44 (d, *J* = 6.9 Hz, 3H), 1.42 (d, *J* = 6.9 Hz, 3H) ppm; ^{13}C-NMR (125 MHz, $CDCl_3$): δ 62.2, 14.5, 14.4 ppm.

(S)-(1,2:5,6-Di-O-cyclohexylidene-α-D-glucofuranosyl) isopropylsulfinate, ***9****(S)*[2]

To a solution of 1,2:5,6-di-O-cyclohexylidene-α-D-glucofuranose (DCG) (5 g, 14.69 mmol, 100 mol%) in a mixture of dry toluene (210 mL) and dry methylene chloride (20 mL) under argon atmosphere, diisopropylethyl amine (4.5 mL, 26.0 mmol, 180 mol%) was added. The solution was stirred for 20 min at -78 °C, before adding isopropylsulfinyl chloride **8** (2.6 mL, 26.0 mmol, 180 mol%). After 2 hour at -78 °C, the reaction mixture was hydrolysed with 10% HCl aqueous solution (250 mL), and the aqueous phase was extracted with CH_2Cl_2 (3 x 150 mL). The organic layer was washed with saturated $NaHCO_3$ aqueous solution and saturated NaCl aqueous solution and dried over Na_2SO_4. After removing the solvent under vacuum, it was obtained sulfinate ester **9**(*S*) (6.3 g, 14.69 mmol, quant. yield) as an oil in a 96% d.e.; $[\alpha]_D^{20}$: -52 [*c* 0.6, acetone]; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 5.90 (d, *J* = 3.5 Hz, 1H), 4.70 (d, *J* = 2.5 Hz, 1H), 4.56 (d, *J* = 3.5 Hz, 1H), 4.29-4.22 (m, 2H), 4.16-3.92 (m, 2H), 2.77 (sep, *J* = 7.0 Hz, 1H), 1.72-1.25 (m, 20H), 1.22 (d, *J* = 7.0 Hz, 6H) ppm; ^{13}C-NMR (125 MHz, $CDCl_3$): δ 113.1, 109.7, 104.6, 84.2, 80.7, 79.9, 72.0, 66.5, 60.4, 55.6, 36.4, 35.7, 34.6, 25.2, 24.8, 24.0, 23.8, 23.7, 23.5, 13.9 ppm; HRMS (ESI) m/z: calcd for $C_{21}H_{34}O_7S$ $[M]^+$ = 430.2025, found: 430.2016.

(R)-(1,2:5,6-Di-O-cyclohexylidene-α-D-glucofuranosyl) isopropylsulfinate, ***9****(R)*[2]

To a solution of 1,2:5,6-di-O-cyclohexylidene-α-D-glucofuranose (DCG) (4 g, 11.75 mmol, 100 mol%) in dry THF (200 mL) under argon atmosphere, pyridine was added (1.7 mL, 21.15 mmol, 180 mol%). The solution was stirred at -78 °C for 20 min before adding isopropylsulfinyl chloride **8** (2.1 mL, 21.15 mmol, 180 mol%). After 2 h at -78 °C, the reaction mixture was hydrolysed with 10% HCl aqueous solution (100 mL) and the aqueous phase was extracted with CH_2Cl_2 (3 x 60 mL). The organic layer was washed with saturated $NaHCO_3$ aqueous solution and saturated NaCl aqueous solution and dried over Na_2SO_4. After removing the solvent under vacuum, the sulfinate ester **9**(*R*) was obtained in 80% d.e. The resulting mixture of diastereomers can be separated by silica gel column chromatography (EtOAc:hexane, 1:7) to obtain the compound **9**(*R*) (4.9, 11.40 mmol, 97% yield) as an oil; $[\alpha]_D^{20}$: +15 [*c* 0.8, acetone]; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 5.91 (d, *J* = 3.4 Hz, 1H), 4.77 (d, *J* = 3.5 Hz, 1H), 4.73 (d, *J* = 1.8 Hz, 1H), 4.17-4.10 (m, 3H), 3.97-3.95 (m, 1H), 2.83 (sep, *J* = 7.3 Hz, 1H), 1.69-1.39 (m, 20H), 1.28 (d, *J* = 2.0 Hz, 3H), 1.26 (d, *J* = 2.0 Hz, 3H) ppm; ^{13}C-NMR (125 MHz, $CDCl_3$): δ 113.2, 110.1, 105.2, 83.5, 83.3, 81.4, 67.7, 56.2, 36.7, 36.6, 35.8, 35.0, 25.3, 25.0, 24.2, 24.0, 23.9, 23.7, 13.9, 13.8 ppm; HRMS (ESI) m/z: calcd for $C_{21}H_{34}O_7S$ $[M]^+$ = 430.2025, found: 430.2016.

Synthesis of *N*-isopropylsulfinylaldimines: general procedure

To a solution of the corresponding sulfinate ester (100 mol%) in dry THF (50 mL) at -78 °C under argon atmosphere, 1M LHMDS solution in THF (110 mol%) was added. The reaction mixture was stirred at -78 °C for 10 min and then transferred via cannula to a second flask containing a suspension of 1-adamantane carboxyaldehyde **4** (200 mol%) and cesium fluoride (100 mol%) in dry THF (50 mL) under argon atmosphere. After being stirred for 24h

at room temperature, the reaction mixture was quenched with saturated NH_4Cl aqueous solution (100 mL), and the aqueous layer was extracted with CH_2Cl_2 (3 x 60 mL). The organic layer was washed with saturated $NaHCO_3$ aqueous solution and saturated NaCl aqueous solution and dried with anhydrous Na_2SO_4. The solvent was removed under reduced pressure, and the residue was purified by column chromatography to obtain the desired compound.

*(S)-N-(Adamantylmethylidene) isopropylsulfinylimine, **10**(S)*

It was prepared following the general procedure from sulfinate ester **9**(*S*) (3.5 g, 8.13 mmol, 100 mol%), 1M LHMDS solution in THF (8.9 mL, 8.94 mmol, 110 mol%), 1-adamantane carboxyaldehyde **4** (2.7 g, 16.26 mmol, 200 mol%) and cesium fluoride (1.2 g, 8.13 mmol, 100 mol%). The resulting residue was purified by flash chromatography (EtOAc:hexane, 1:10) to give **10**(*S*) (1.7 g, 6.74 mmol, 83% yield) as a yellow solid; mp 144-146°C; $[\alpha]_D^{20}$: +124.9 [*c* 1, $CHCl_3$]; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.78 (s, 1H), 2.81 (sep, *J* = 6.7 Hz, 1H), 2.06 (s, 3H), 1.79-1.69 (m, 12H), 1.22 (d, *J* = 7.1 Hz, 3H), 1.13 (d, *J* = 7.1 Hz, 3H) ppm; ^{13}C-NMR (125 MHz, $CDCl_3$): δ 175.1, 53.2, 40.1, 39.3, 36.7, 28.0, 14.6, 13.2 ppm; HRMS (ESI) m/z: calcd for $C_{14}H_{24}ONS$ $[M+H]^+$ = 254.1573, found: 254.1575.

*(R)-N-(Adamantylmethylidene) isopropylsulfinylimine, **10**(R)*

It was prepared following the general procedure from sulfinate ester **9**(*R*) (2.0 g, 4.60 mmol, 100 mol%), 1M LHMDS solution in THF (5.1 mL, 5.06 mmol, 110 mol%), 1-adamantane carboxyaldehyde **4** (1.5 g, 9.2 mmol, 200 mol%) and cesium fluoride (0.7 g, 4.6 mmol, 100 mol%). The resulting residue was purified by flash chromatography (EtOAc:hexane, 1:4) to obtain **10**(*R*) (0.8 g, 3.2 mmol, 70% yield) as a yellow solid with similar physicochemical and spectroscopic characteristics than **10**(*S*); $[\alpha]_D^{20}$: -125.5 [*c* 1, $CHCl_3$].

Synthesis of trifluoromethylated *N*-isopropylsulfinamides: general procedure

To a suspension of the corresponding *N*-isopropylsulfinylimine (100 mol%) and tetrabutylammonium difluorotriphenylsilicate (TBAT) (400 mol%) in dry toluene (10 mL) at -78 °C and under argon atmosphere, trifluoromethyltrimethylsilane (1720 mol%) was added. The reaction mixture was slowly warmed to -50 °C and stirred for 24 h. Then, the reaction was quenched with saturated NH_4Cl aqueous solution and the aqueous layer was extracted with EtOAc (3 × 40 mL). The combined organic phases were washed with saturated aqueous NaCl solution and dried with anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the residue was purified by flash chromatography to obtain the desired compound.

(R_S,S_C)-N-[1-(1'-adamantyl)-1-trifluoromethyl]methyl isopropylsulfinamide, **11**(*R_S,S_C*)

It was prepared following the general procedure from (*R*)-*N*-isopropylsulfinylimine **10**(*R*) (150 mg, 0.59 mmol, 100 mol%), TBAT (1.3 g, 2.37 mmol, 400 mol%) and trifluoromethyltrimethylsilane (1.5 mL, 10.18 mmol, 1720 mol%). The resulting residue was purified by flash chromatography (EtOAc:hexane, 1:4) to obtain **11**(R_S,S_C) (76 mg, 0.23 mmol, 40%, 80% corrected yield, 75 mg of **10**(*R*)) in a 100% d.e. as a yellow solid; mp 124-126°C; $[\alpha]_D^{20}$: -57.1 [*c* 1, $CHCl_3$]; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 3.69 (d, *J* = 8.2 Hz, 1H), 3.25 (quin, *J* = 8.6 Hz, 1H), 2.81 (sep, *J* = 7.1 Hz, 1H), 2.05 (s, 3H), 1.85-1.65 (m, 12H), 1.30 (d, *J* = 3.5 Hz, 3H), 1.28 (d, *J* = 3.5 Hz, 3H) ppm; ^{13}C-NMR (125 MHz, $CDCl_3$): δ 126.0 (q, $J_{C\text{-}F}$ = 283.3

Hz), 67.4 (q, $J_{C\text{-}F}$ = 26.3 Hz), 55.9, 39.0, 38.9, 37.9, 36.6, 35.6, 28.3, 15.7, 15.3 ppm; ^{19}F-NMR (470 MHz, $CDCl_3$): δ -67.19 (d, $J_{C\text{-}F}$ = 8.1 Hz) ppm; HRMS (ESI) m/z: calcd for $C_{15}H_{24}ONF_3SNa$ $[M+Na]^+$ = 346.1423, found: 346.1419.

*(S_S,R_C)-N-[1-(1'-adamantyl)-1-trifluoromethyl]methyl isopropylsulfinamide, **11**(S_S,R_C)*

It was prepared following the general procedure from (*S*)-*N*-isopropylsulfinylimine **10**(*S*) (150 mg, 0.59 mmol, 100 mol%), TBAT (1.3 g, 2.37 mmol, 400 mol%) and trifluoromethyltrimethylsilane (1.5 mL, 10.18 mmol, 1720 mol%). The resulting residue was purified by flash chromatography (EtOAc:hexane, 1:4) to obtain **11**(S_S,R_C) (80 mg, 0.25 mmol, 42%, 81% corrected yield, 73 mg of **10**(*S*)) in a 100% d.e. as a yellow solid with similar physicochemical and spectroscopic characteristics than **11**(R_S,S_C); $[\alpha]_D^{20}$: +49.4 [*c* 1, $CHCl_3$].

Experimental data for the synthesis of *N-tert*-butylsulfinamides via *N-tert*-butylsulfinylketimines.

*(R)-N-[1-(1'-Adamantyl)ethylidene] tert-butylsulfinylimine, **12**(R)*

To a solution of (*R*)-*N-tert*-butanesulfinamide (0.5 g, 4.13 mmol, 110 mol%) and adamantyl methyl ketone (0.7 g, 3.75 mmol, 100 mol%) in dry THF (7 mL) at 70 °C and under argon atmosphere, titanium (IV) ethoxide (1.9 mL, 9 mmol, 240 mol%) was added. After 24 h, the reaction mixture was quenched with a saturated NaCl aqueous solution (20 mL). The resulting suspension was filtered through a pad of Celite. The aqueous phase was extracted with CH_2Cl_2 (3 x 40 mL) and the combined organic phases were dried with anhydrous Na_2SO_4. The solvent was removed under reduced pressure, and the residue was purified by flash chromatography (EtOAc:hexane, 1:7) to obtain **12**(*R*) (0.6 g, 2.24 mmol, 60% yield) as a yellow solid; mp 68-70°C; $[\alpha]_D^{20}$: -82.2 [*c* 1, $CHCl_3$]; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 2.26 (s, 3H), 2.04 (s, 3H), 1.78-1.65 (m, 12H), 1.22 (s, 9H) ppm; ^{13}C-NMR (125 MHz, $CDCl_3$): δ 190.8, 56.7, 45.1, 39.5, 36.8, 29.9, 28.4, 22.5, 17.7 ppm; HRMS (ESI) m/z: calcd for $C_{16}H_{27}ONSNa$ $[M+Na]^+$ = 304.1706, found: 304.1696.

Stereoselective reduction of *N*-sulfinylketimines: general procedure.

To a stirred solution of the corresponding *N*-sulfinylketimine (100 mol%) in dry THF (10 mL) at -78 °C and under argon atmosphere, 1M L-Selectride solution in THF (440 mol%) or 0.5M DIBAL solution in THF (220 mol%) was added. After 24 h, the reaction mixture was quenched with saturated aqueous NH_4Cl solution (20 mL) or with MeOH (2.5 mL) and 2M NaOH aqueous solution (20 mL) respectively. The aqueous layer was extracted with EtOAc (3 × 40 mL) and the combined organic phases were washed with saturated aqueous NaCl solution and dried with anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure and the reaction crude was purified by flash chromatography to obtain the desired compound.

*(R_S,S_C)-N-[1-(1'-adamantyl)ethyl] tert-butylsulfinamide, **6**(R_S,S_C)*

It was prepared following the general procedure from *N-tert*-butylsulfinylimine **12**(*R*) (150 mg, 0.54 mmol, 100 mol%) and 1.0M L-Selectride solution in THF (2.4 mL, 2.35 mmol, 440 mol%). The reaction mixture was slowly warmed to -40 °C and stirred for 24 h. It was obtained a mixture of **6**(R_S,S_C)/(R_S,R_C) in a 80% d.e. separable by flash chromatography (EtOAc:hexane, 1:3) to obtain **6**(R_S,S_C) (142 mg, 0.50 mmol, 93% yield) as a colorless oil with

similar physicochemical and spectroscopic characteristics than *N-tert*-butylsulfinamide **6**(R_S,S_C) synthesized via *N*-sulfinylaldimines from (*R*)-sulfinylimine **5**(*R*).

*(R_S,R_C)-N-[1-(1'-adamantyl)ethyl] tert-butylsulfinamide, **6**(R_S,R_C)*

It was prepared following the general procedure from *N-tert*-butylsulfinylimine **12**(*R*) (150 mg, 0.54 mmol, 100 mol%) and 0.5M DIBAL solution in THF (2.4 mL, 1.2 mmol, 220 mol%). It was obtained a mixture of **6**(R_S,S_C)/(R_S,R_C) in a 75% d.e. separable by flash chromatography (EtOAc:hexane, 1:3) to obtain **6**(R_S,R_C) (139 mg, 0.49 mmol, 91% yield) as a colorless solid with similar physicochemical and spectroscopic characteristics than *N-tert*-butylsulfinamide **6**(R_S,R_C) synthesized via *N*-sulfinylaldimines from (*R*)-sulfinylimine **5**(*R*).

Experimental data for the synthesis of *N*-isopropylsulfinamides via *N*-isopropylsulfinylketimines.

*(R)-Isopropanesulfinamide, **13**(R)*

To a solution of sulfinate ester **7**(*R*) (4 g, 9.29 mmol, 100 mol%) in dry THF (20 mL) at 0 °C and under argon atmosphere, 1M LHMDS solution in THF (13.9 mL, 13.94 mmol, 150 mol%) was added. The reaction was stirred for 5 min, then MeOH (20 mL) was added followed by silica gel and the mixture was stirred for 15 min. After evaporation of the solvent, the residue was purified by column chromatography (EtOAc: MeOH, 9:1) affording **13**(*R*) (0.9 g, 8.39 mmol, 90% yield) as a highly hygroscopic white solid; mp 42°C; $[\alpha]_D^{20}$: +16 [*c* 1, $CHCl_3$]; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 3.89 (s, 2H), 2.71 (sep, *J* = 7.0 Hz, 1H), 1.27 (d, *J* = 5.2 Hz, 3H), 1.26 (d, *J* = 5.2 Hz, 3H) ppm; ^{13}C-NMR (125 MHz, $CDCl_3$): δ 54.8, 14.9, 14.8 ppm; HRMS (ESI) m/z: calcd for $C_3H_{10}ONS$ $[M+H]^+$ = 108.0483, found: 108.0484.

*(R)-N-[1-(1'-Adamantyl)ethylidene] isopropylsulfinylimine, **14**(R)*

To a solution of (*R*)-isopropanesulfinamide **13**(*R*) (0.9 g, 8.12 mmol, 110 mol%) and adamantyl methyl ketone (1.3 g, 7.38 mmol, 100 mol%) in dry THF (12 mL) at 70°C and under argon atmosphere, titanium (IV) ethoxide (1.7 mL, 8.12 mmol, 110 mol%) was added. After 24 h, the reaction mixture was quenched with a saturated NaCl aqueous solution (20 mL). The resulting suspension was filtered through a pad of Celite. The aqueous phase was extracted with CH_2Cl_2 (3 x 40 mL) and the combined organic phases were dried with anhydrous Na_2SO_4. The solvent was removed under reduced pressure, and the residue was purified by flash chromatography (EtOAc:hexane, 1:7) to obtain **14**(*R*) (1.6 g, 5.9 mmol, 80% yield) as a yellow solid; mp 170-172°C; $[\alpha]_D^{20}$: -92.1 [*c* 1, $CHCl_3$]; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 2.84 (sep, *J* = 7.2 Hz, 1H), 2.25 (s, 3H), 2.05 (s, 3H), 1.78-1.65 (m, 12H), 1.27 (d, *J* = 4.2 Hz, 3H), 1.25 (d, *J* = 4.2 Hz, 3H) ppm; ^{13}C-NMR (125 MHz, $CDCl_3$): δ 190.3, 54.4, 44.8, 39.4, 36.7, 28.3, 17.6, 14.5, 14.4 ppm; HRMS (ESI) m/z: calcd for $C_{15}H_{25}ONSNa$ $[M+Na]^+$ = 290.1549, found: 290.1542.

*(R_S,S_C)-N-[1-(1'-adamantyl)ethyl] isopropylsulfinamide, **15**(R_S,S_C)*

It was prepared following the general procedure for the stereoselective reduction of *N*-sulfinylketimines describe above from (*R*)-*N*-isopropylsulfinylimine **14**(*R*) (200 mg, 0.75 mmol, 100 mol%) and 1.0M L-Selectride solution in THF (2.5 mL, 2.47 mmol, 330 mol%). The reaction mixture was slowly warmed to -50 °C and stirred for 24 h. It was obtained **15**(R_S,S_C)

(141 mg, 0.52 mmol, 70% yield) in a 100% d.e. as a colorless oil; $[\alpha]_D^{20}$: -5.5 [*c* 1, $CHCl_3$]; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 2.87 (d, *J* = 9.1 Hz, 1H), 2.81 (dq, J_1 = 9.2 Hz, J_2 = 6.7 Hz, 1H), 2.64 (sep, *J* = 6.8 Hz, 1H), 1.92 (s, 3H), 1.65-1.34 (m, 12H), 1.21 (d, *J* = 6.7 Hz, 3H), 1.20 (d, *J* = 6.7 Hz, 3H), 1.14 (d, *J* = 6.6 Hz, 3H) ppm; ^{13}C-NMR (125 MHz, $CDCl_3$): δ 62.2, 55.2, 38.6, 37.3, 36.8, 28.5, 17.3, 15.9, 15.7 ppm; HRMS (ESI) m/z: calcd for $C_{15}H_{28}ONS$ $[M+H]^+$ = 270.1887, found: 270.1892.

*(R_S,R_C)-N-[1-(1'-adamantyl)ethyl] isopropylsulfinamide, **15**(R_S,R_C)*

It was prepared following the general procedure for the stereoselective reduction of *N*-sulfinylketimines describe above from (*R*)-*N*-isopropylsulfinylimine **14**(*R*) (200 mg, 0.75 mmol, 100 mol%) and 1M DIBAL solution in THF (1.7 mL, 1.65 mmol, 220 mol%). It was obtained **15**(R_S,R_C) (183 mg, 0.68 mmol, 90% yield) in a 100% d.e. as a colorless solid; mp 111-113°C; $[\alpha]_D^{20}$: -62.0 [*c* 1, $CHCl_3$]; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 3.46 (d, *J* = 4.8 Hz, 1H), 2.96 (quin, *J* = 5.8 Hz, 1H), 2.71 (sep, *J* = 6.9 Hz, 1H), 2.00 (s, 3H), 1.73-1.46 (m, 12H), 1.26 (d, *J* = 6.9 Hz, 3H), 1.24 (d, *J* = 6.9 Hz, 3H), 1.13 (d, *J* = 6.6 Hz, 3H) ppm; ^{13}C-NMR (125 MHz, $CDCl_3$): δ 59.2, 54.3, 38.6, 37.2, 36.0, 28.5, 16.0, 15.6, 15.5 ppm; HRMS (ESI) m/z: calcd for $C_{15}H_{28}ONS$ $[M+H]^+$ = 270.1886, found: 270.1891.

Experimental data of rimantadine 1(*R*) and 1(*S*) and their trifluoromethylated analogues 2(*R*) and 2(*S*).

Desulfinilation of *N*-sulfinamides: general procedure.

To a stirred solution of the corresponding *N*-sulfinamide (100 mol%) in dry EtOAc (10 mL) at 0 °C and under argon atmosphere, 4.0N HCl (150 mol%) solution in dioxane was added dropwise. The reaction mixture was slowly warmed to room temperature and stirred overnight. Then, the reaction was quenched with dried diethyl ether (5 mL) and the corresponding chlorohydrate salt was precipitated. The compound was filtered and washed with diethyl ether and hexane.

*(S)-N-[1-(1'-adamantyl)-1-trifluoromethyl]methylamine chlorohydrate, **2**(S)*

It was prepared following the general procedure from *N*-isopropylsulfinamide **11**(R_S,S_C) (150 mg, 0.46 mmol, 100 mol%) and 4.0N HCl (0.2 mL, 0.70 mmol, 150 mol%). It was obtained **2**(*S*) (125 mg, 0.46 mmol, quant. yield) as a white solid ; mp 260-262°C; $[\alpha]_D^{20}$: +1.9 [*c* 1, ethanol]; ^{1}H-NMR (500 MHz, CD_3OD): δ 3.75 (q, *J* = 8.6 Hz, 1H), 2.08 (s, 3H), 1.83-1.74 (m, 12H) ppm; ^{13}C-NMR (125 MHz, CD_3OD): δ 125.8 (q, $J_{C\text{-}F}$ = 282.0 Hz), 61.7 (q, $J_{C\text{-}F}$ = 27.7 Hz), 38.7, 37.1, 35.7, 29.4 ppm; ^{19}F-NMR (470 MHz, CD_3OD): δ -67.27 (d, $J_{C\text{-}F}$ = 8.6 Hz) ppm; HRMS (ESI) m/z: calcd for $C_{12}H_{19}F_3N$ $[M]^+$ = 234.1463, found: 234.1464.

*(R)-N-[1-(1'-adamantyl)-1-trifluoromethyl]methylamine chlorohydrate, **2**(R)*

It was prepared following the general procedure from *N*-isopropylsulfinamide **11**(S_S,R_C) (200 mg, 0.62 mmol, 100 mol%) and 4.0N HCl (0.2 mL, 0.93 mmol, 150 mol%). It was obtained **2**(*R*) (156 mg, 0.57 mmol, 93% yield) as a white solid with similar physicochemical and spectroscopic characteristics than **2**(*S*); $[\alpha]_D^{20}$: -1.8 [*c* 1, ethanol].

*(S)-N-[1-(1'-adamantyl)ethyl]amine chlorohydrate, **1**(S)*

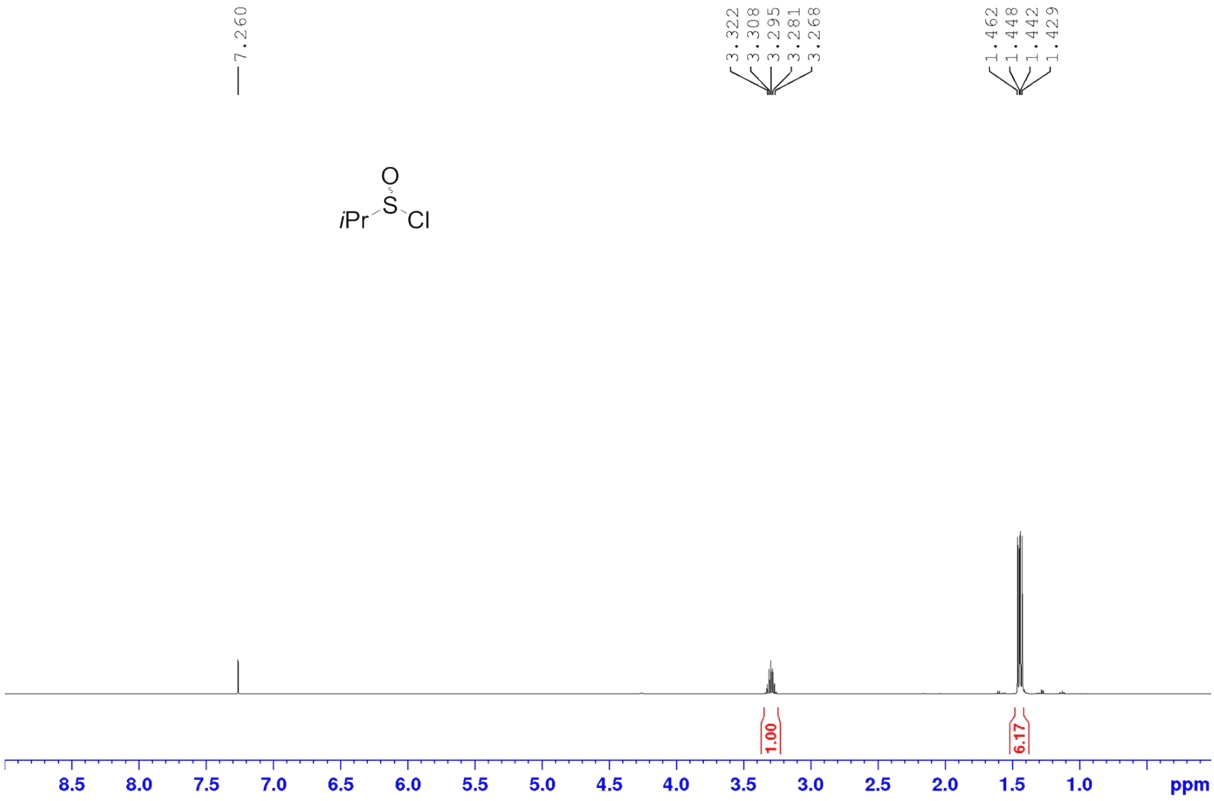
It was prepared following the general procedure from *N*-isopropylsulfinamide **15**(R_S,S_C) (110 mg, 0.39 mmol, 100 mol%) and 4.0N HCl (0.2 mL, 0.59 mmol, 150 mol%). It was obtained **1**(*S*) (80 mg, 0.37 mmol, 95% yield) as a white solid; mp 248-250°C; ^{1}H-NMR (500 MHz, CD_3OD): δ 2.88 (q, *J* = 6.9 Hz, 1H), 2.05 (s, 3H), 1.82-1.57 (m, 12H), 1.22 (d, *J* = 6.9 Hz, 3H) ppm; ^{13}C-NMR (125 MHz, CD_3OD): δ 57.9, 38.7, 37.6, 35.6, 29.5, 13.2 ppm; HRMS (ESI) m/z: calcd for $C_{12}H_{22}NClNa$ $[M+Na]^+$ = 238.1333, found: 238.1334. The residue was passed through a cation-exchange column (Isolute SPE SCX-2) to give the corresponding amine; mp 168-170°C; $[\alpha]_D^{20}$: -7.4 [*c* 1, $CHCl_3$]; ^{1}H-NMR (500 MHz, CD_3OD): δ 2.70 (q, *J* = 6.7 Hz, 1H), 2.02 (s, 3H), 1.80-1.76 (m, 3H), 1.72-1.67 (m, 3H), 1.64-1.54 (m, 6H), 1.2 (d, *J* = 6.8 Hz, 3H) ppm; ^{13}C-NMR (125 MHz, CD_3OD): δ 57.6, 38.8, 37.8, 36.0, 29.6, 14.0 ppm; HRMS (ESI) m/z: calcd for $C_{12}H_{22}N$ $[M+H]^+$ = 180.1747, found: 180.1744.

(R)-N-[1-(1'-adamantyl)ethyl]amine chlorohydrate, ***1****(R)*

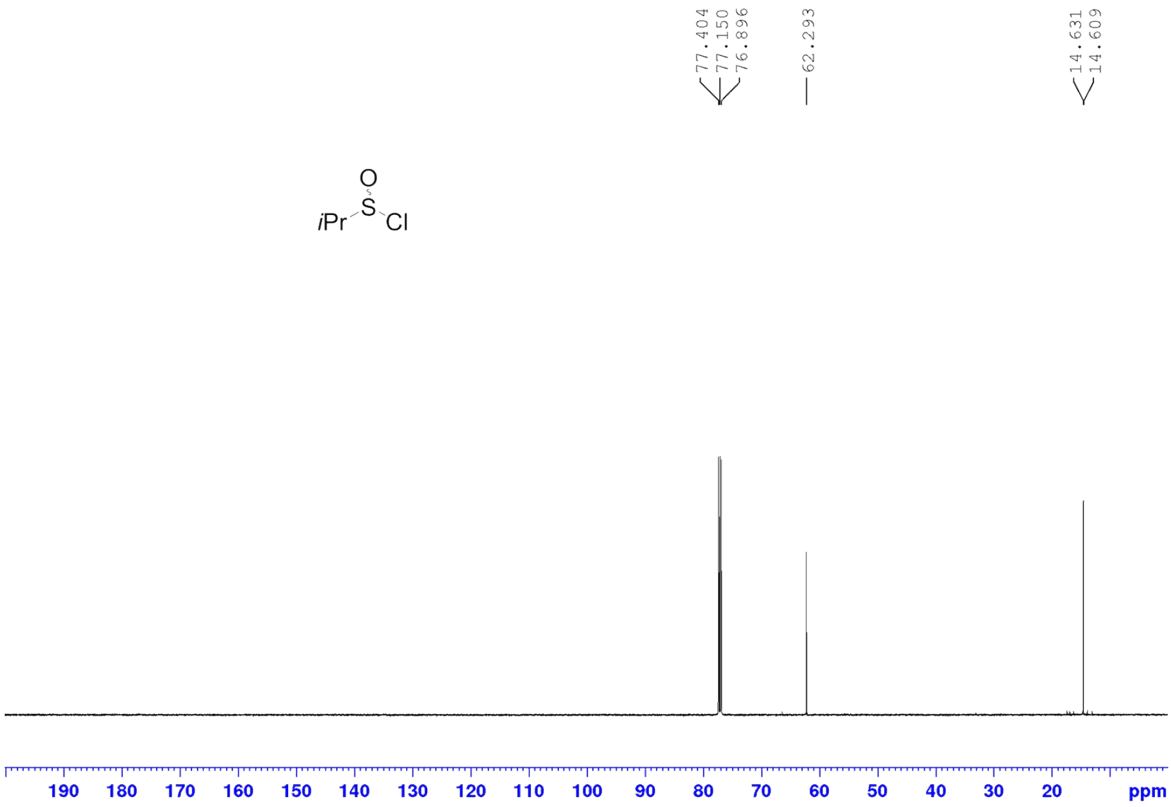
It was prepared following the general procedure from *N*-isopropylsulfinamide **15**(R_S,R_C) (160 mg, 0.58 mmol, 100 mol%) and 4.0N HCl (0.2 mL, 0.86 mmol 150 mol%). It was obtained **1**(*R*) (125 mg, 0.58 mmol, quant. yield) as a white solid. The residue was passed through a cation-exchange column (Isolute SPE SCX-2) to give the corresponding amine, both with similar physicochemical and spectroscopic characteristics than **1**(*S*); $[\alpha]_D^{20}$: +7.8 [*c* 1, $CHCl_3$].

Isopropylsulfinyl chloride, **8**

^{1}H-RMN (500 MHz, $CDCl_3$)

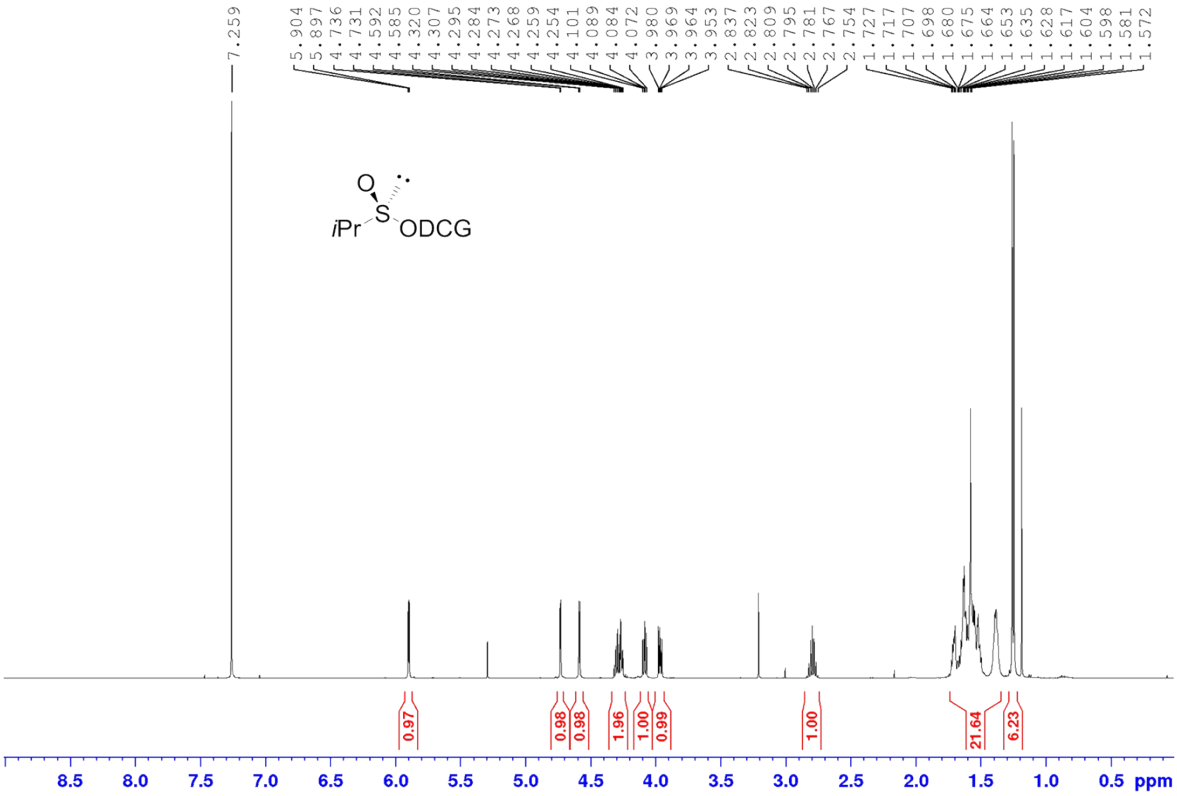


^{13}C-RMN (125 MHz, $CDCl_3$)

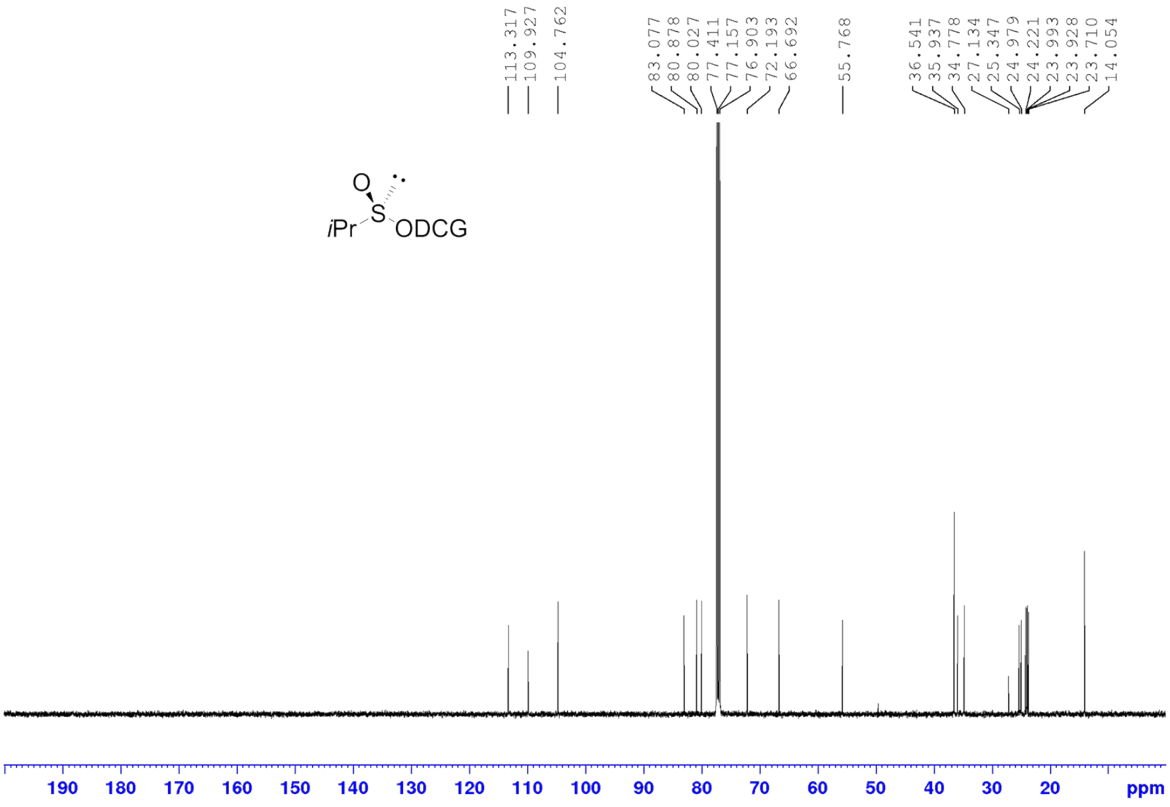


(S)-(1,2:5,6-Di-O-cyclohexylidene-α-D-glucofuranosyl) isopropylsulfinate, **9**(*S*)

^{1}H-RMN (500 MHz, $CDCl_3$)

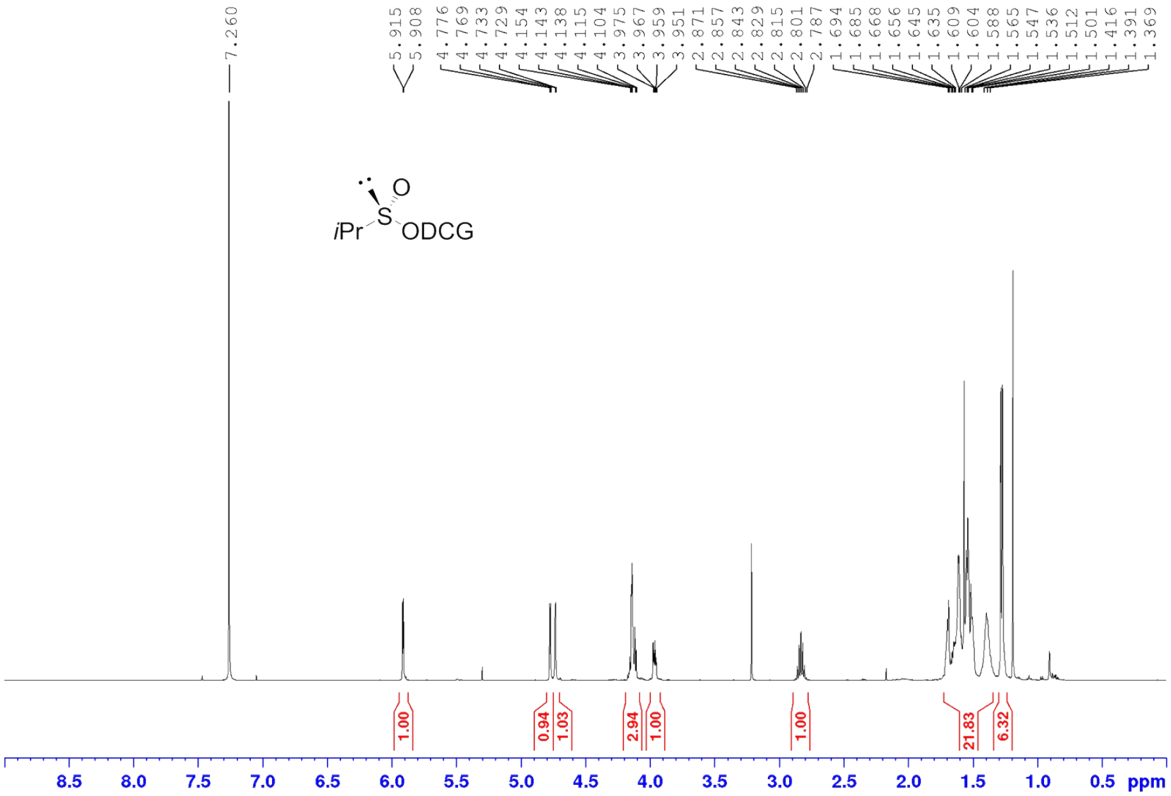


^{13}C-RMN (125 MHz, $CDCl_3$)

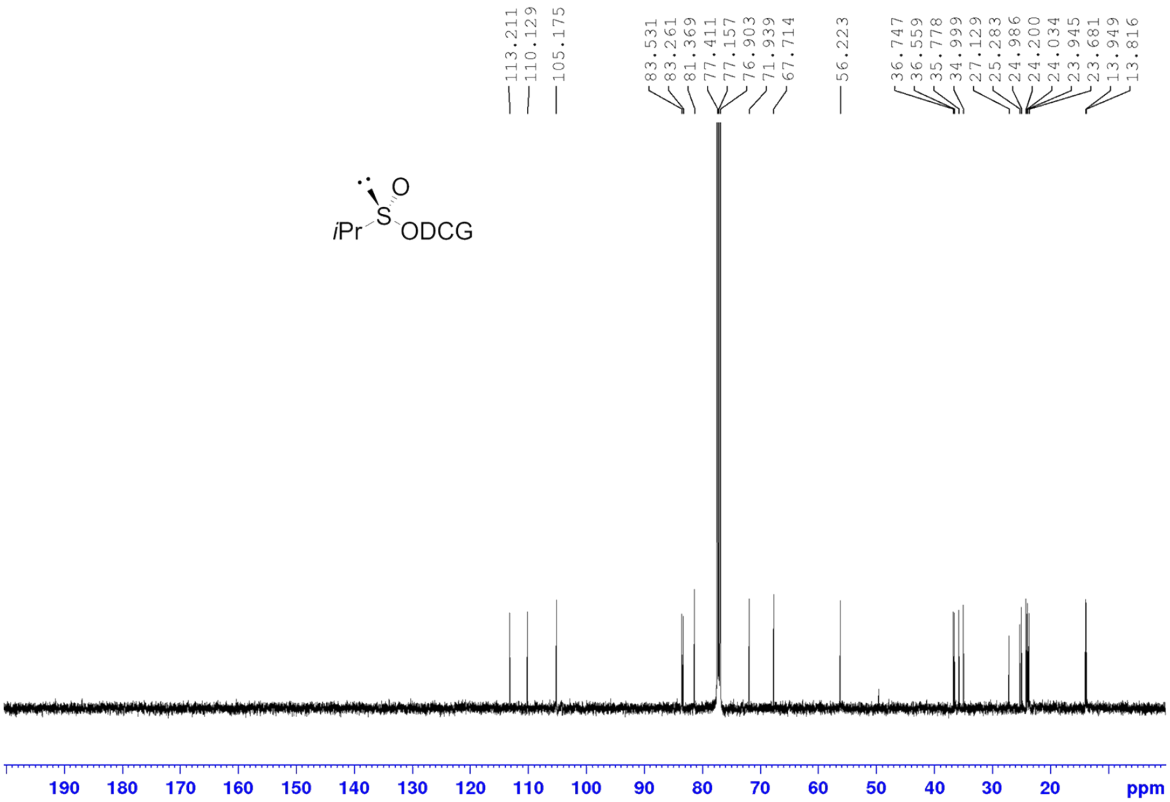


(R)-(1,2:5,6-Di-O-cyclohexylidene-α-D-glucofuranosyl) isopropylsulfinate, **9**(*R*)

^{1}H-RMN (500 MHz, $CDCl_3$)

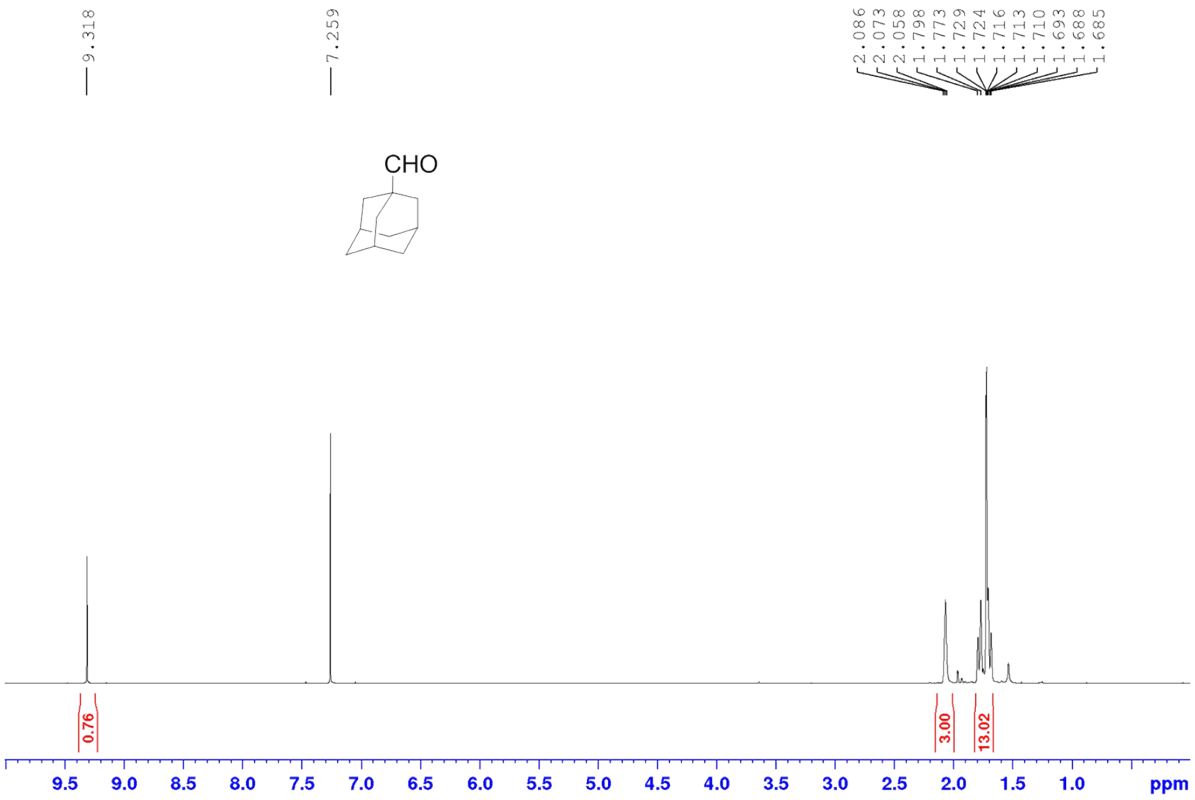


^{13}C-RMN (125 MHz, $CDCl_3$)

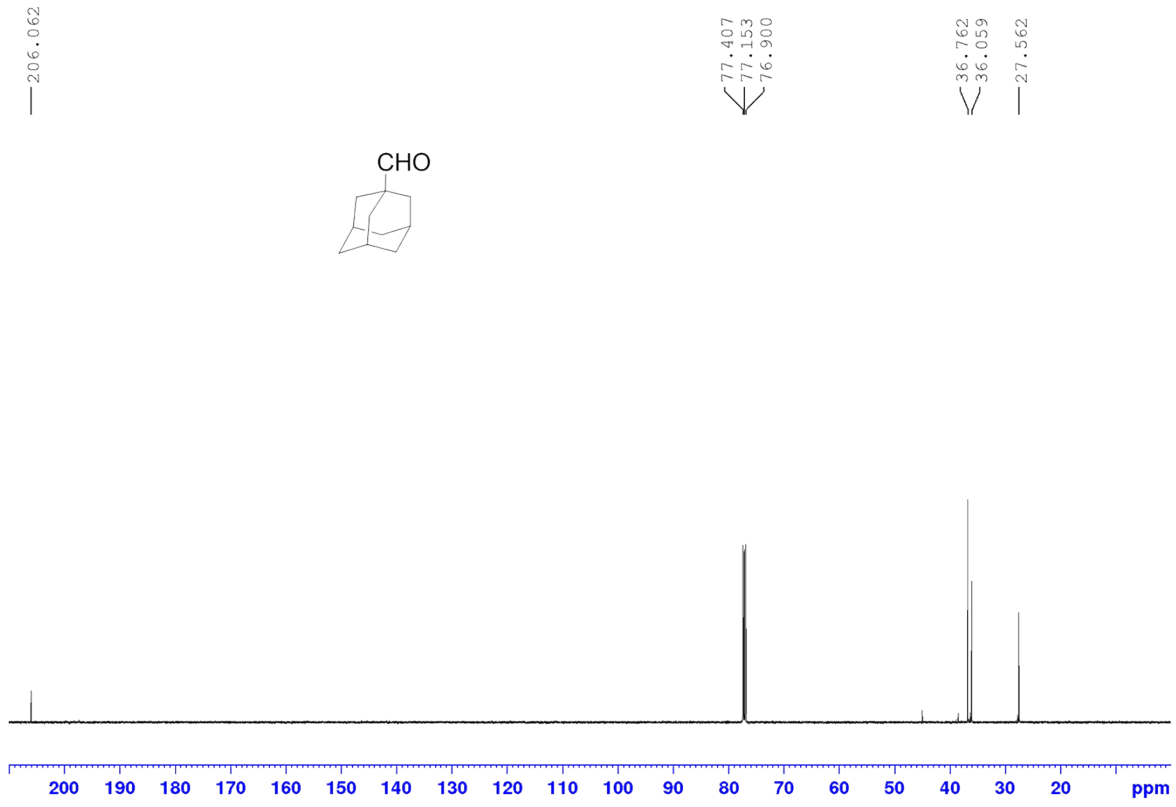


1-Adamantane carboxaldehyde, **4**

^{1}H-RMN (500 MHz, $CDCl_3$)

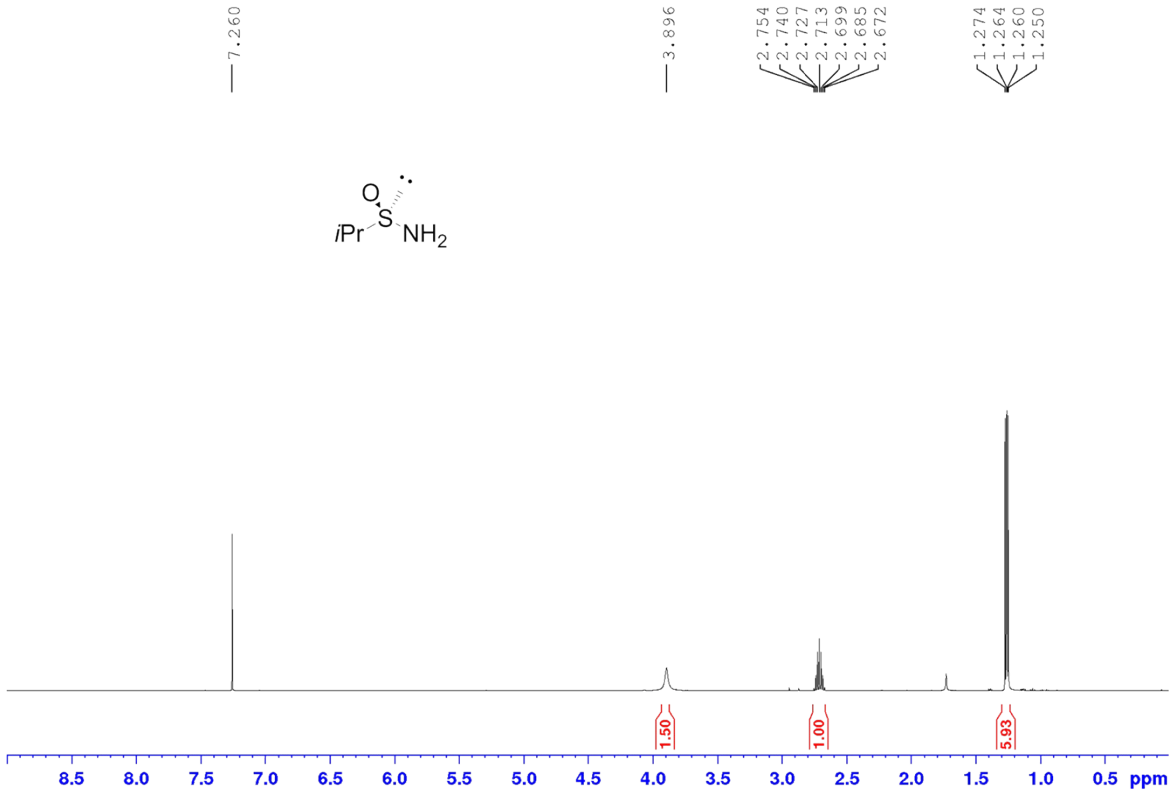


^{13}C-RMN (125 MHz, $CDCl_3$)

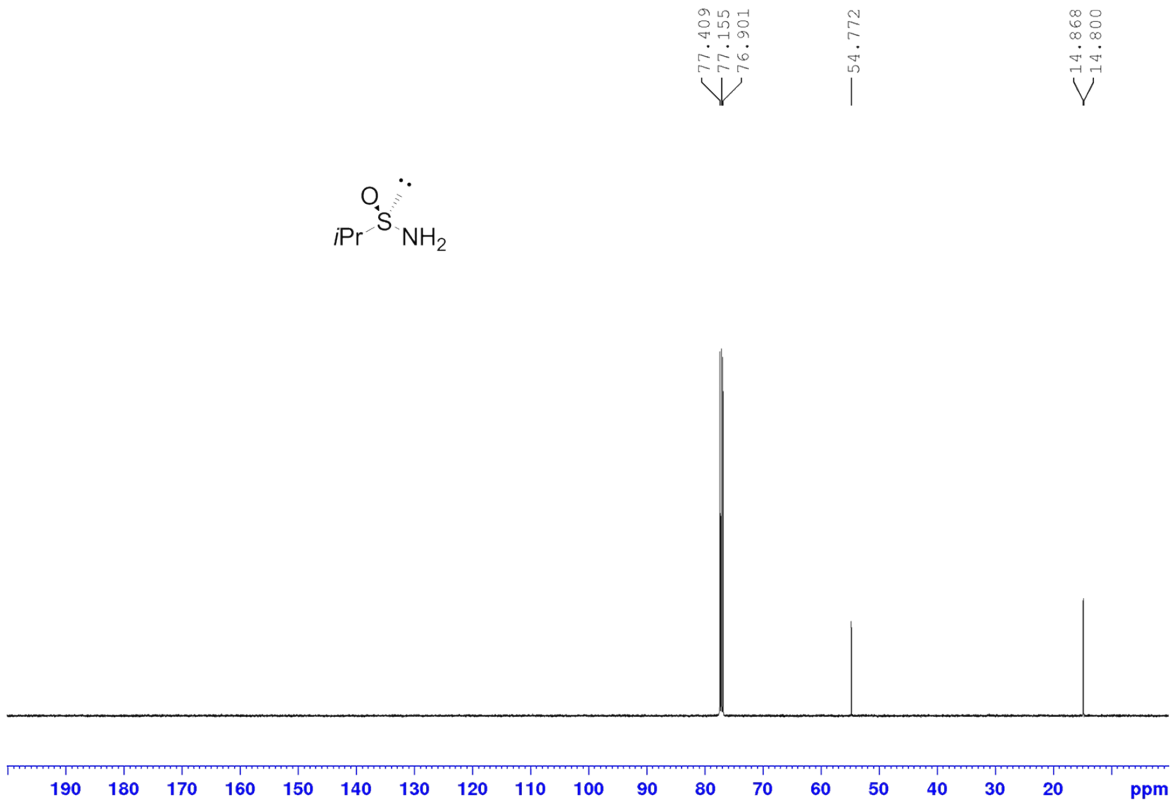


(R)-Isopropanesulfinamide, **13**(*R*)

^{1}H-RMN (500 MHz, $CDCl_3$)

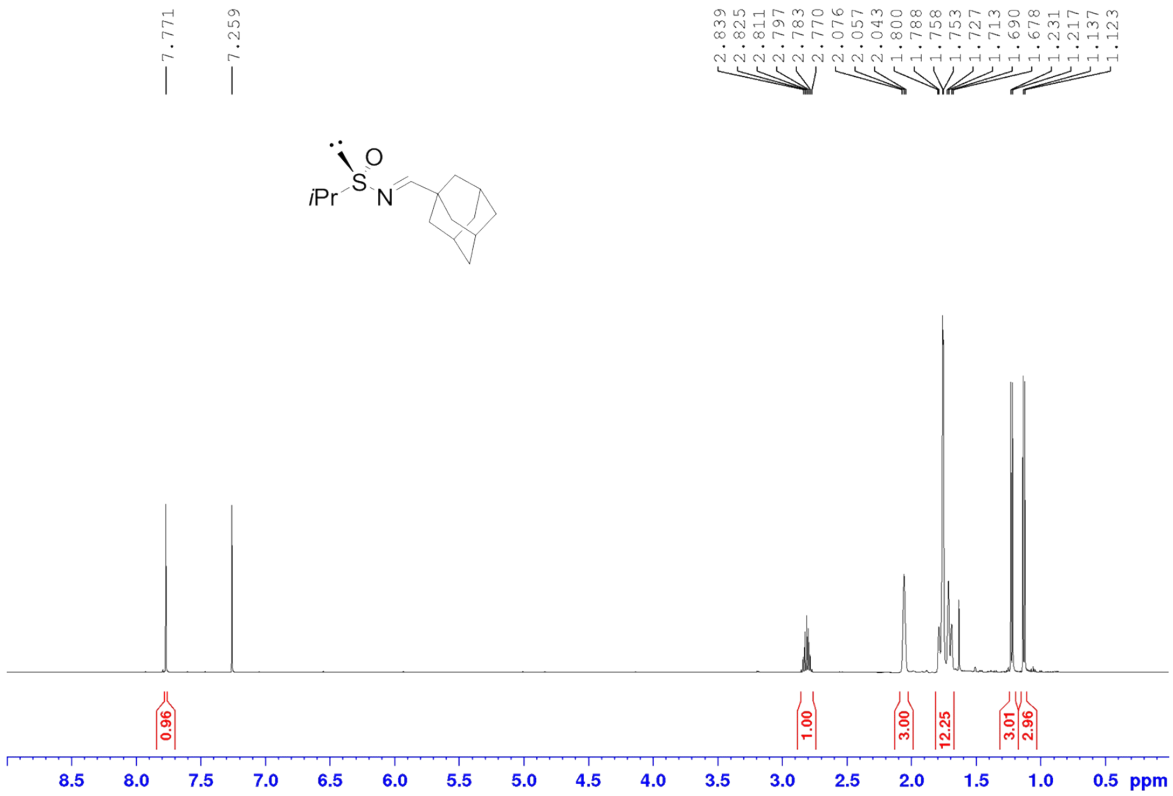


^{13}C-RMN (125 MHz, $CDCl_3$)

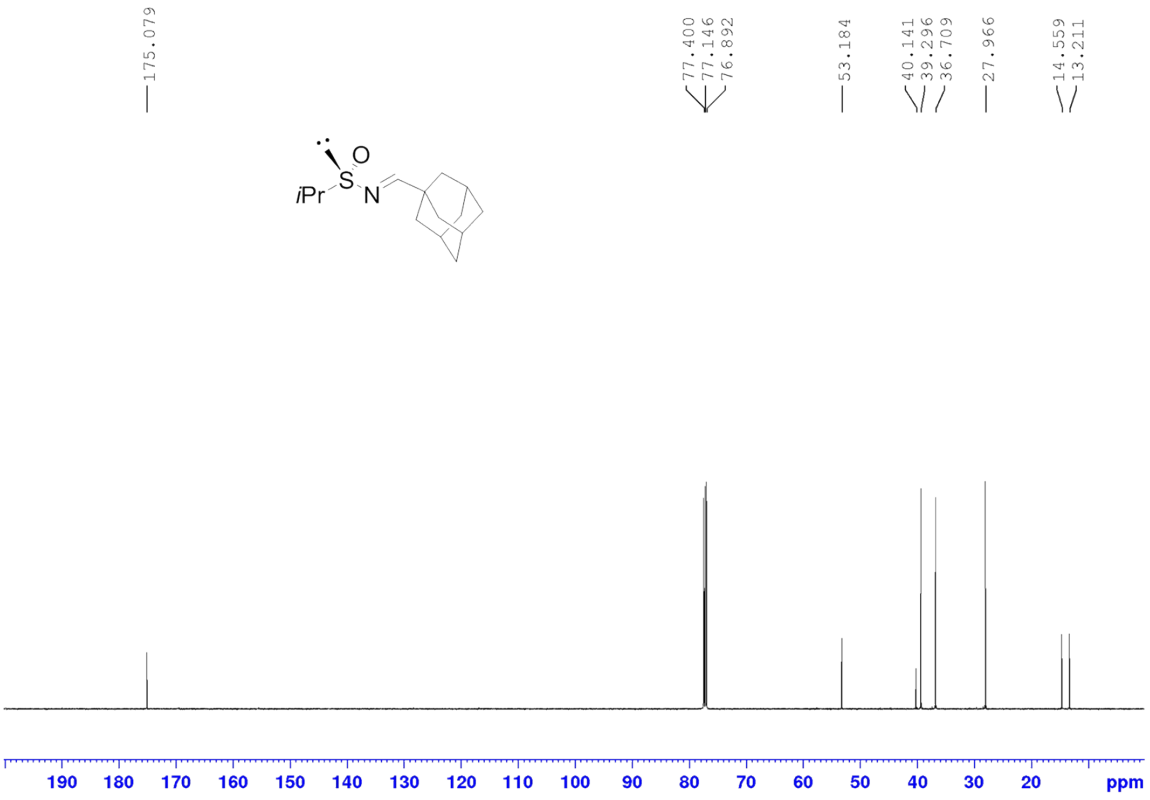


(S)-N-(Adamantylmethylidene) isopropylsulfinylimine, **10**(*S*)

^{1}H-RMN (500 MHz, $CDCl_3$)

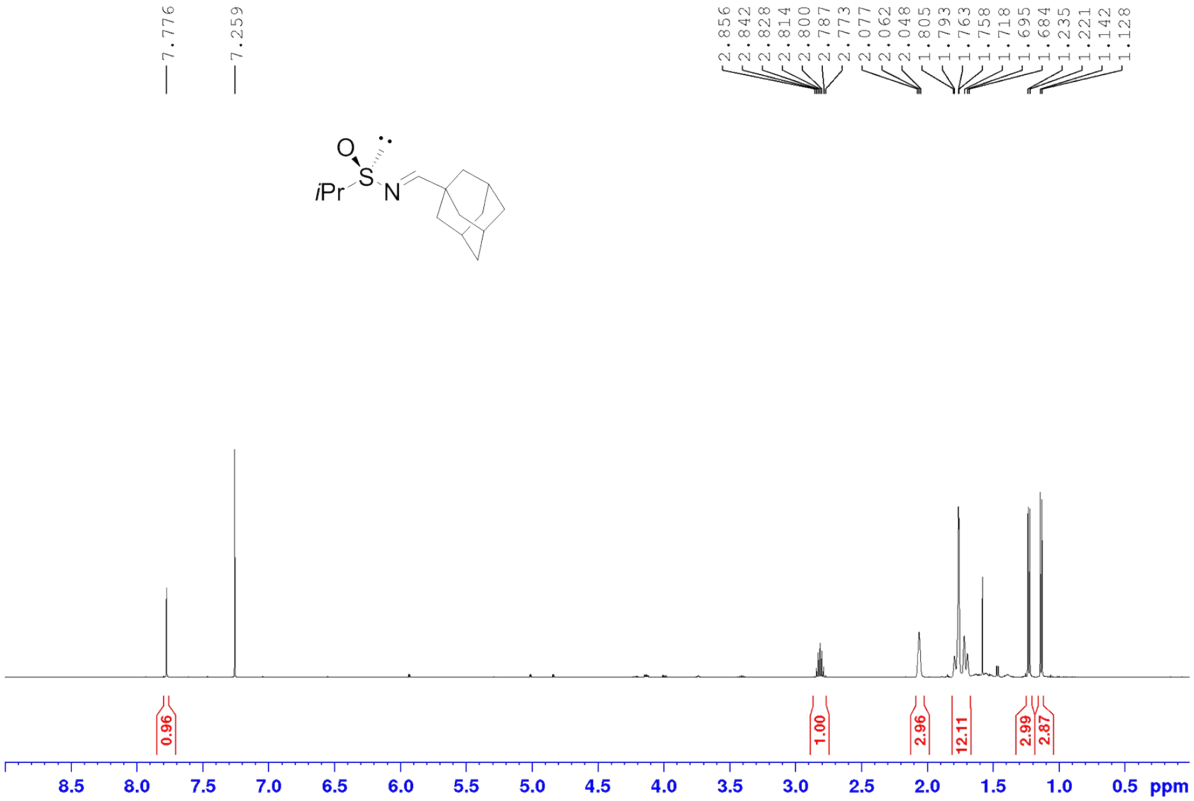


^{13}C-RMN (125 MHz, $CDCl_3$)

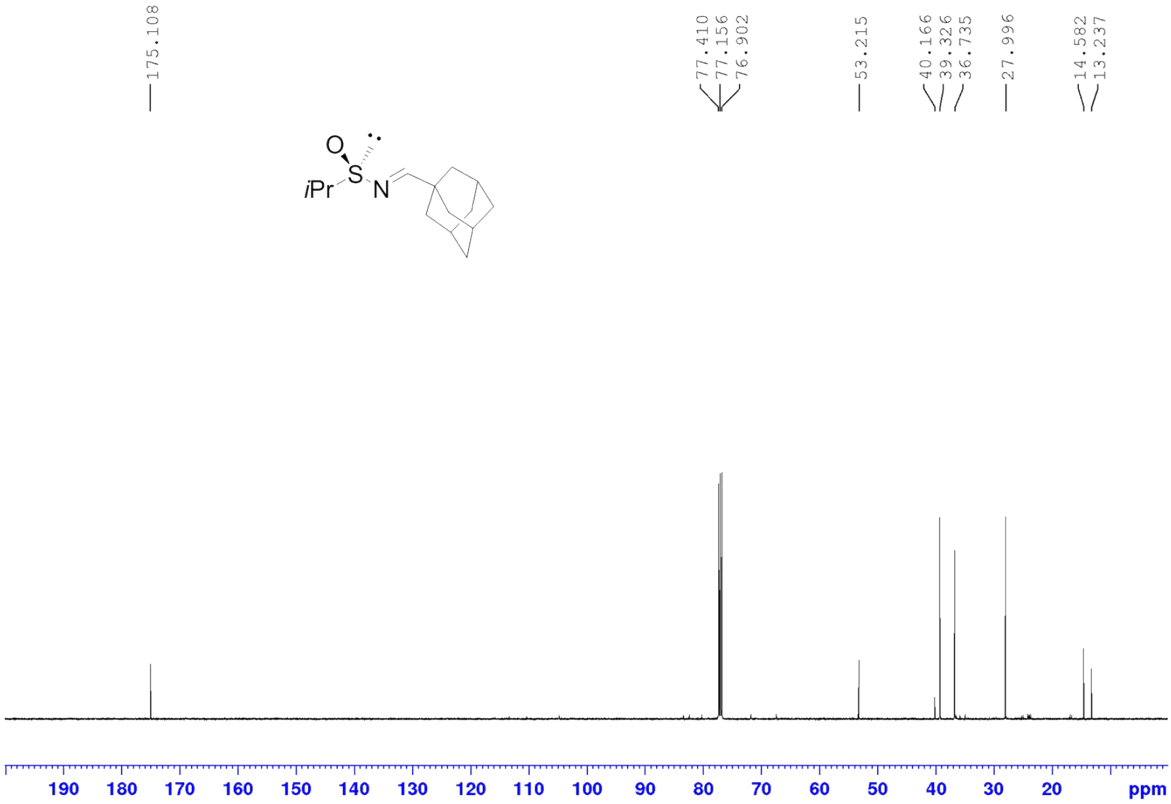


(R)-N-(Adamantylmethylidene) isopropylsulfinylimine, **10**(*R*)

^{1}H-RMN (500 MHz, $CDCl_3$)

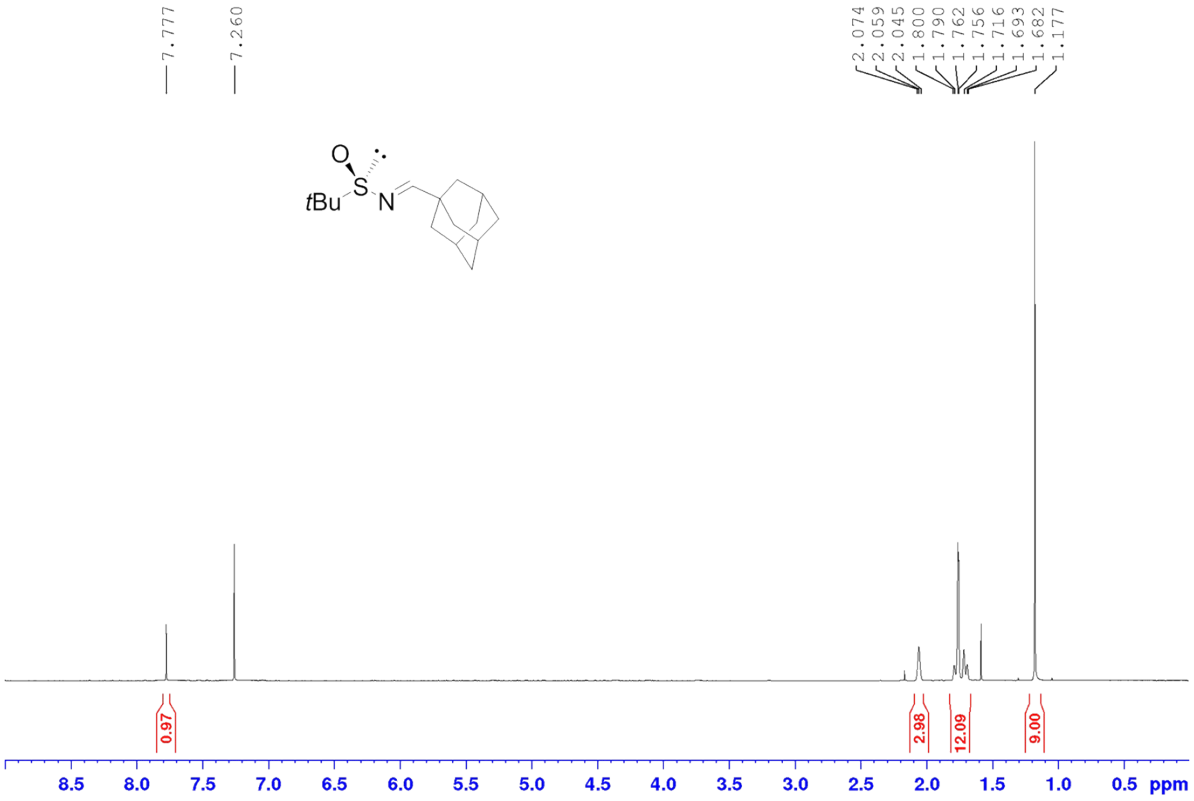


^{13}C-RMN (125 MHz, $CDCl_3$)

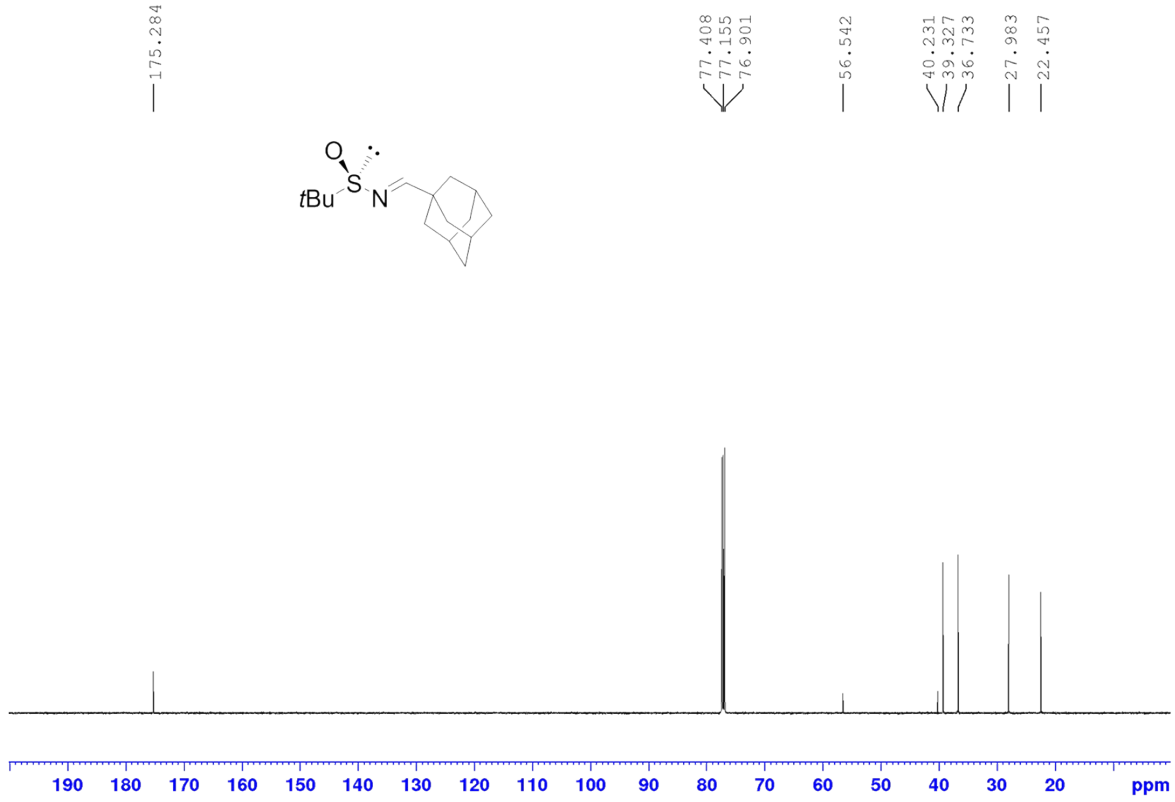


(R)-N-(Adamantylmethylidene) tert-butylsulfinylimine, **5**(*R*)

^{1}H-RMN (500 MHz, $CDCl_3$)

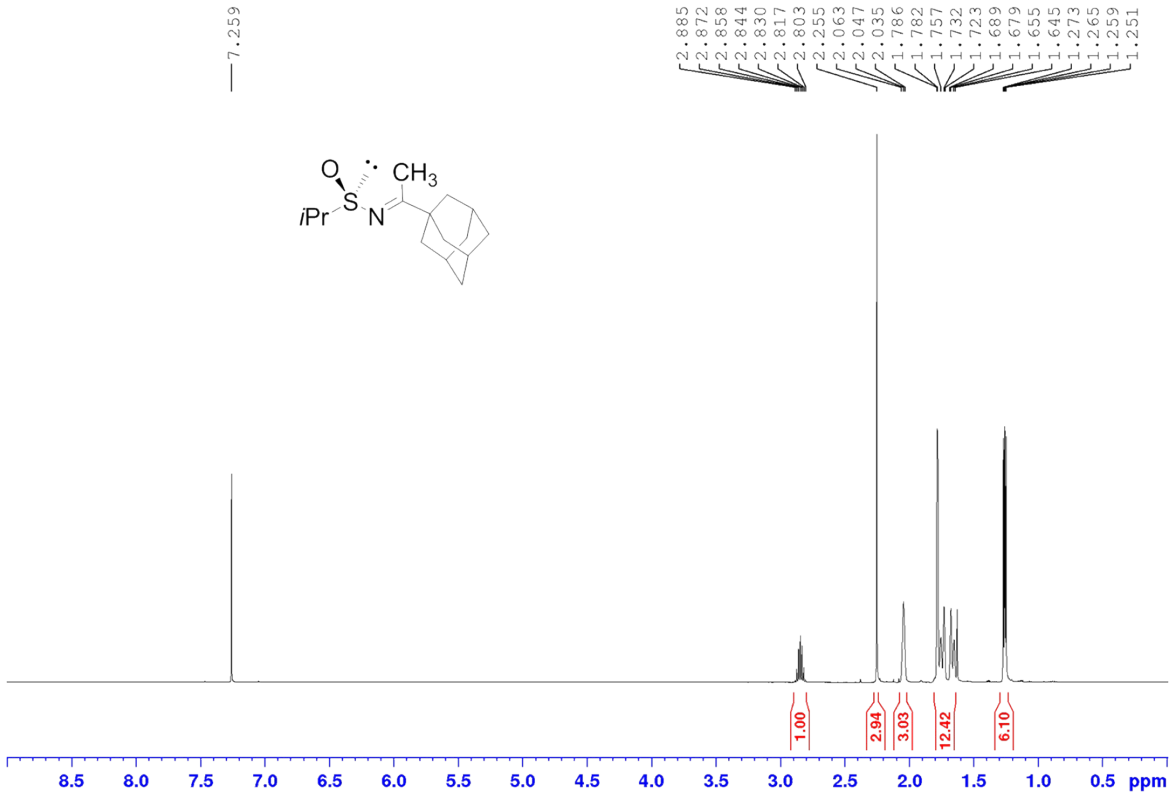


^{13}C-RMN (125 MHz, $CDCl_3$)

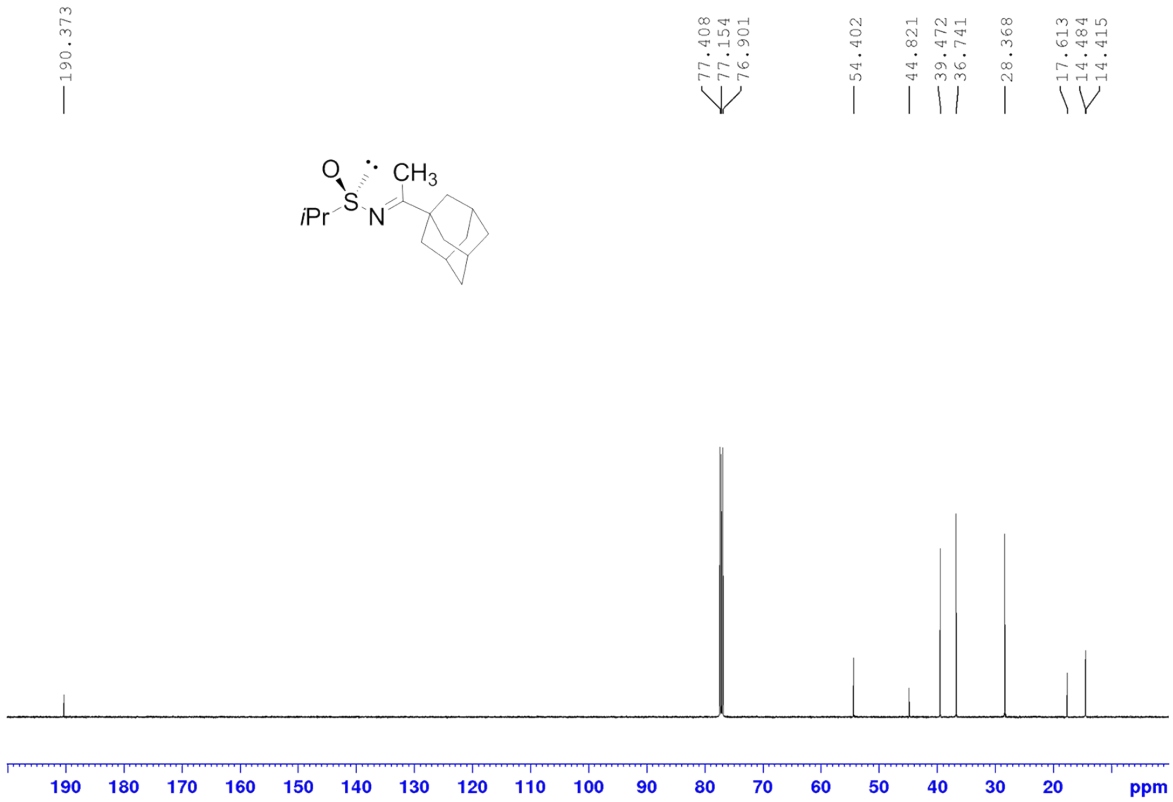


(R)-N-[1-(1'-Adamantyl)ethylidene] isopropylsulfinylimine, **14**(*R*)

^{1}H-RMN (500 MHz, $CDCl_3$)

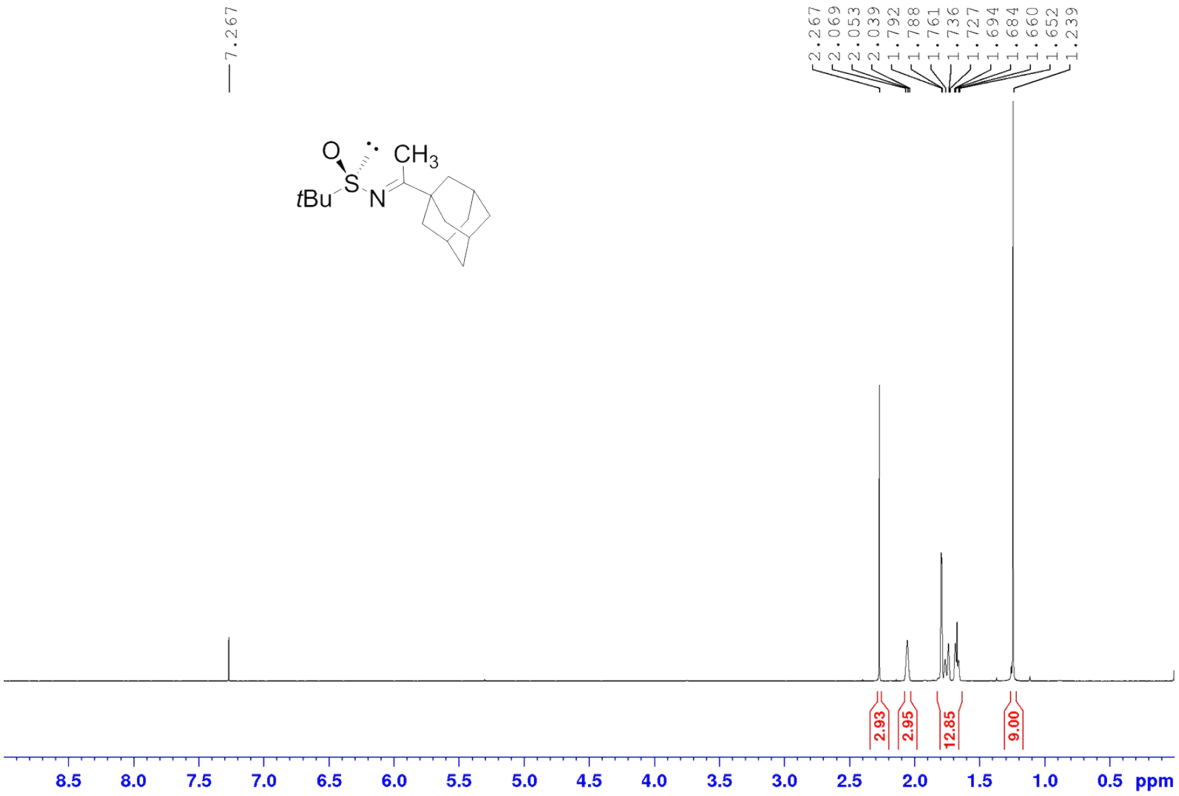


^{13}C-RMN (125 MHz, $CDCl_3$)

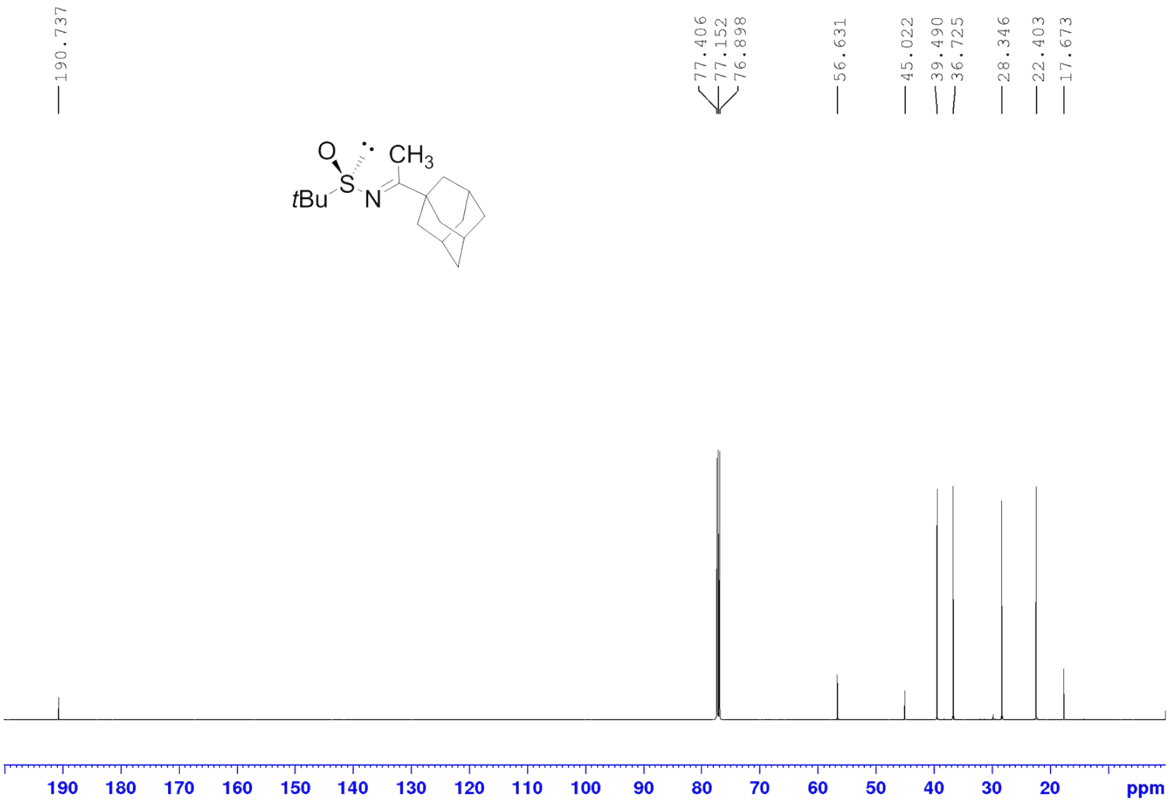


(R)-N-[1-(1'-Adamantyl)ethylidene] tert-butylsulfinylimine, **12**(*R*)

^{1}H-RMN (500 MHz, $CDCl_3$)

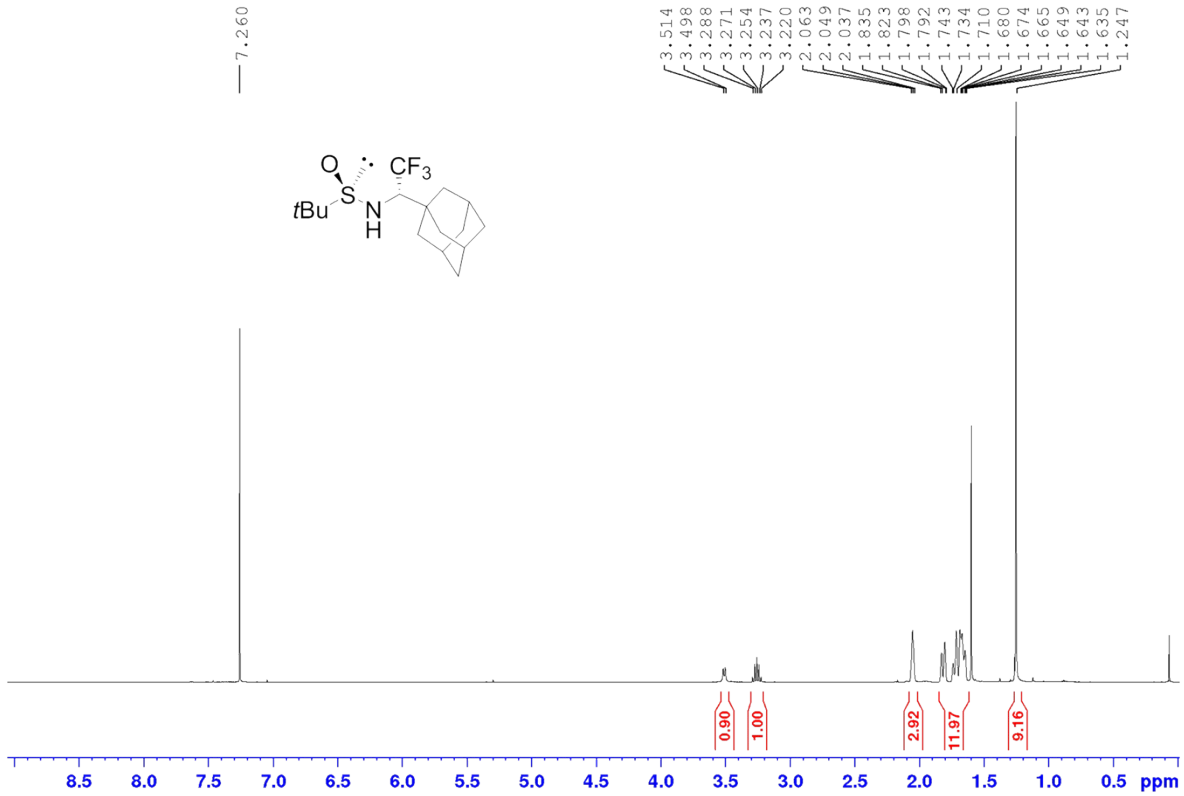


^{13}C-RMN (125 MHz, $CDCl_3$)

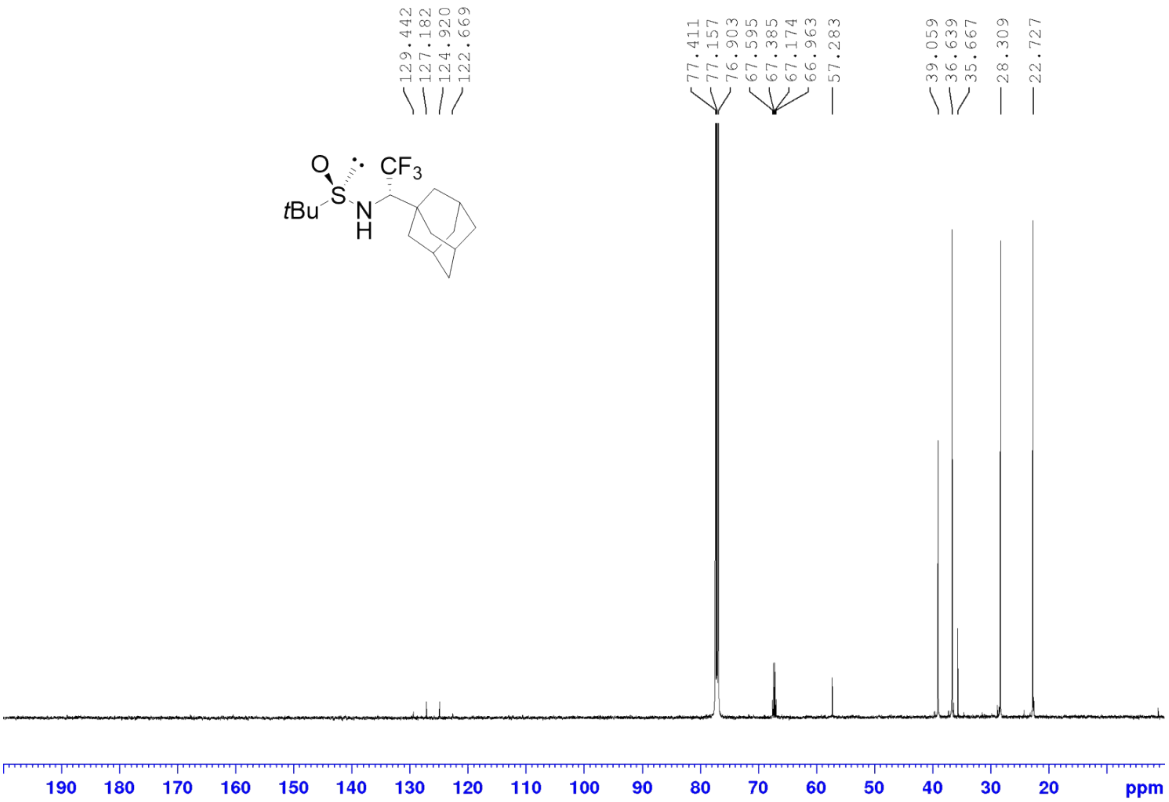


(R_S,S_C)-N-[1-(1'-adamantyl)-1-trifluoromethyl]methyl tert-butylsulfinamide, **7**(R_S,S_C)

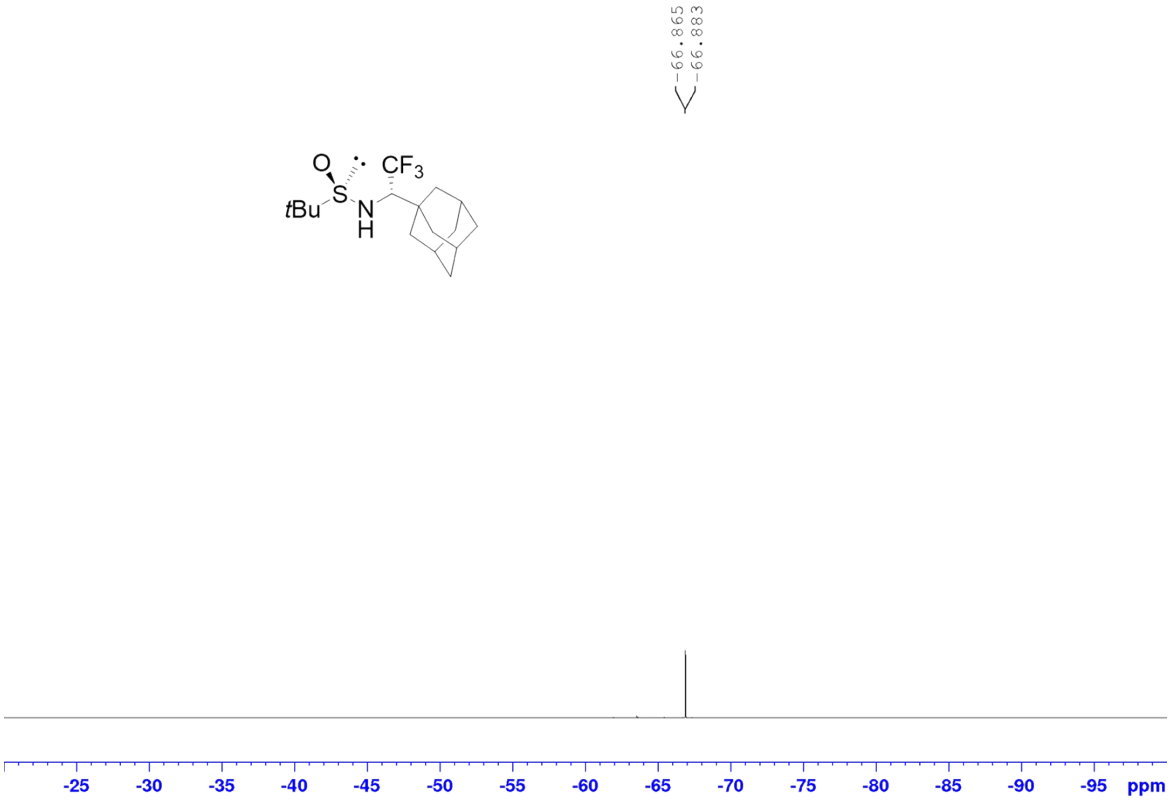
^{1}H-RMN (500 MHz, $CDCl_3$)



^{13}C-RMN (125 MHz, $CDCl_3$)

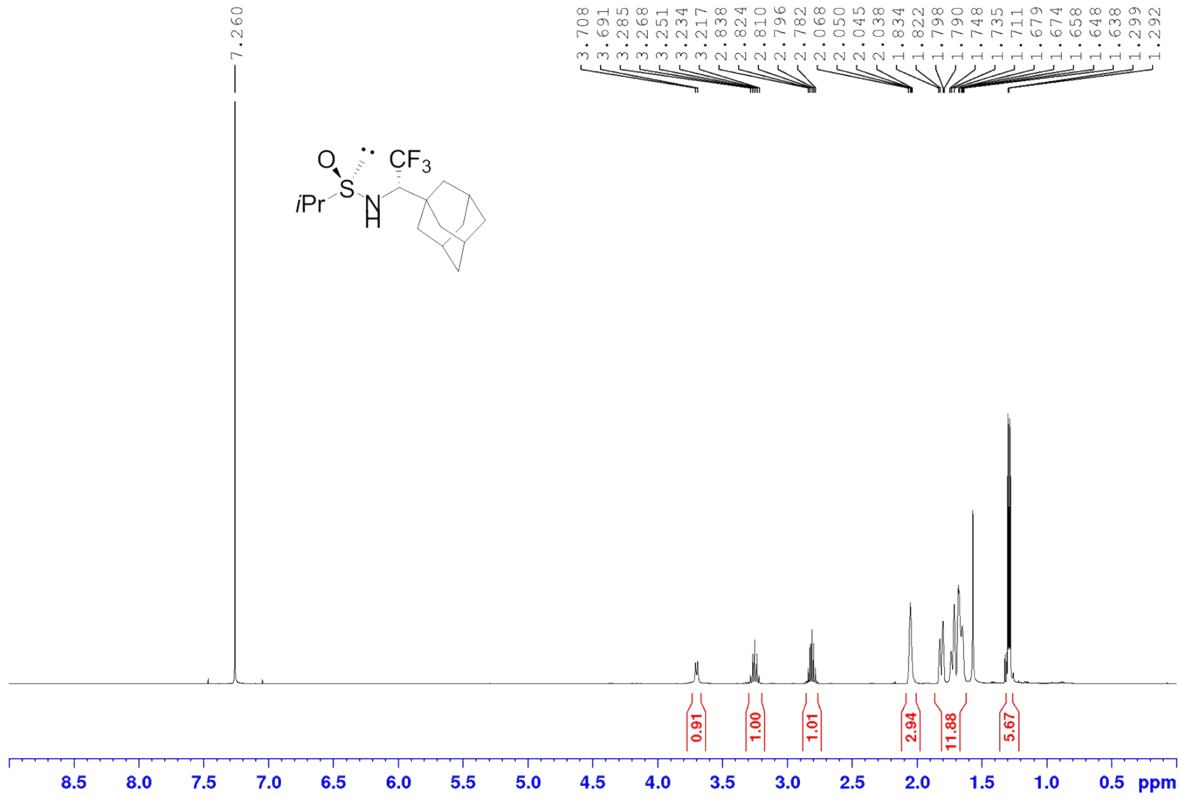


^{19}F-NMR (470 MHz, $CDCl_3$)

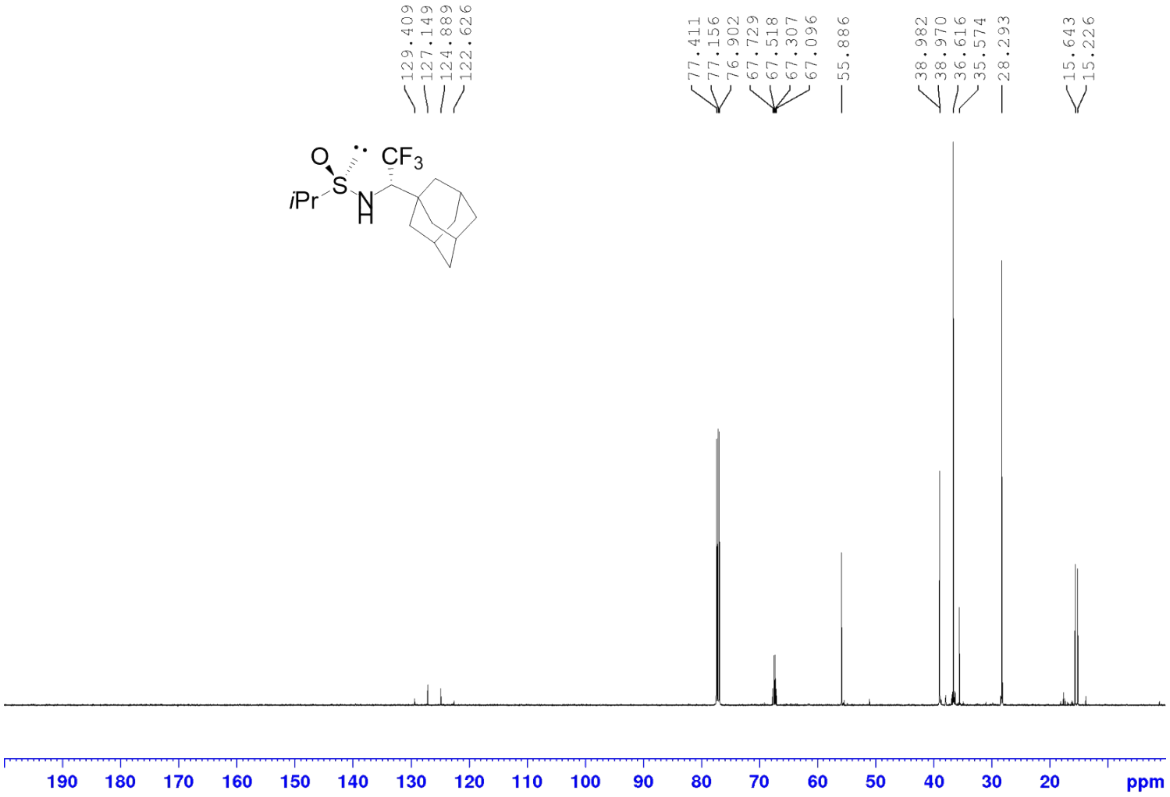


(R_S, S_C)-N-[1-(1'-adamantyl)-1-trifluoromethyl]methyl isopropylsulfinamide, **11**(R_S,S_C)

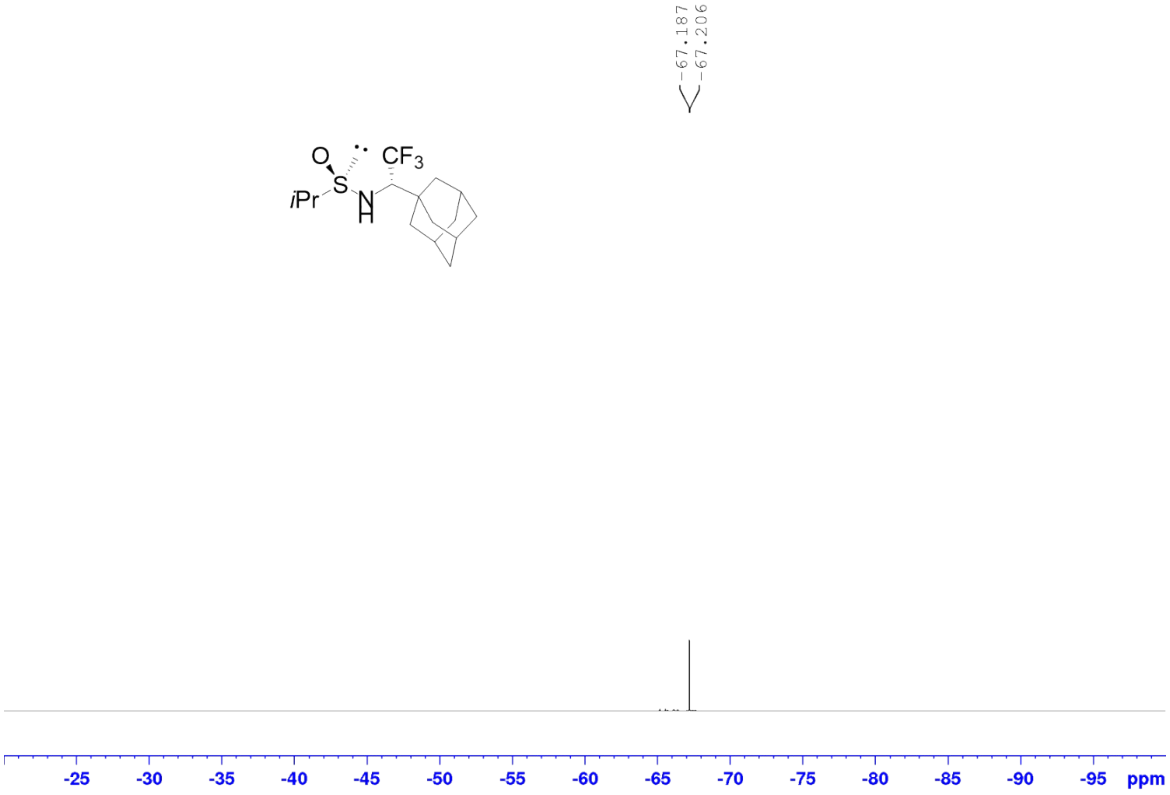
^{1}H-RMN (500 MHz, $CDCl_3$)



^{13}C-RMN (125 MHz, $CDCl_3$)

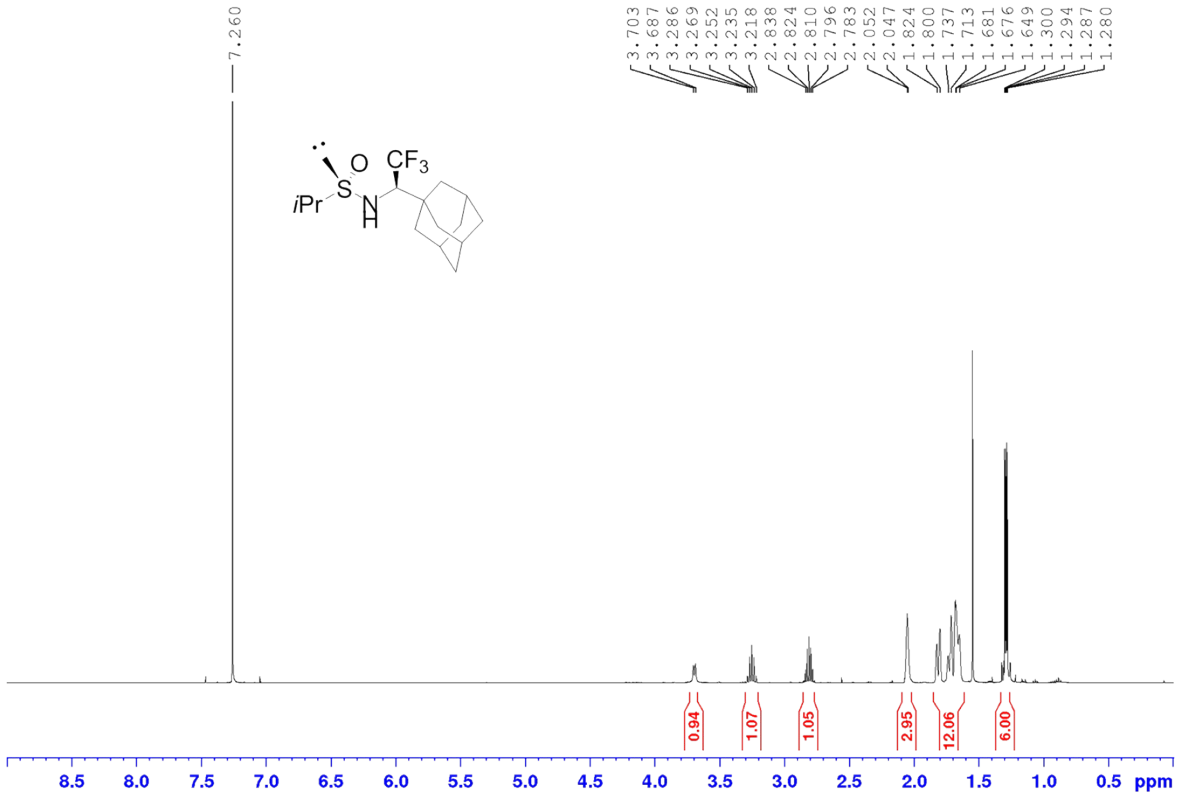


^{19}F-NMR (470 MHz, $CDCl_3$)

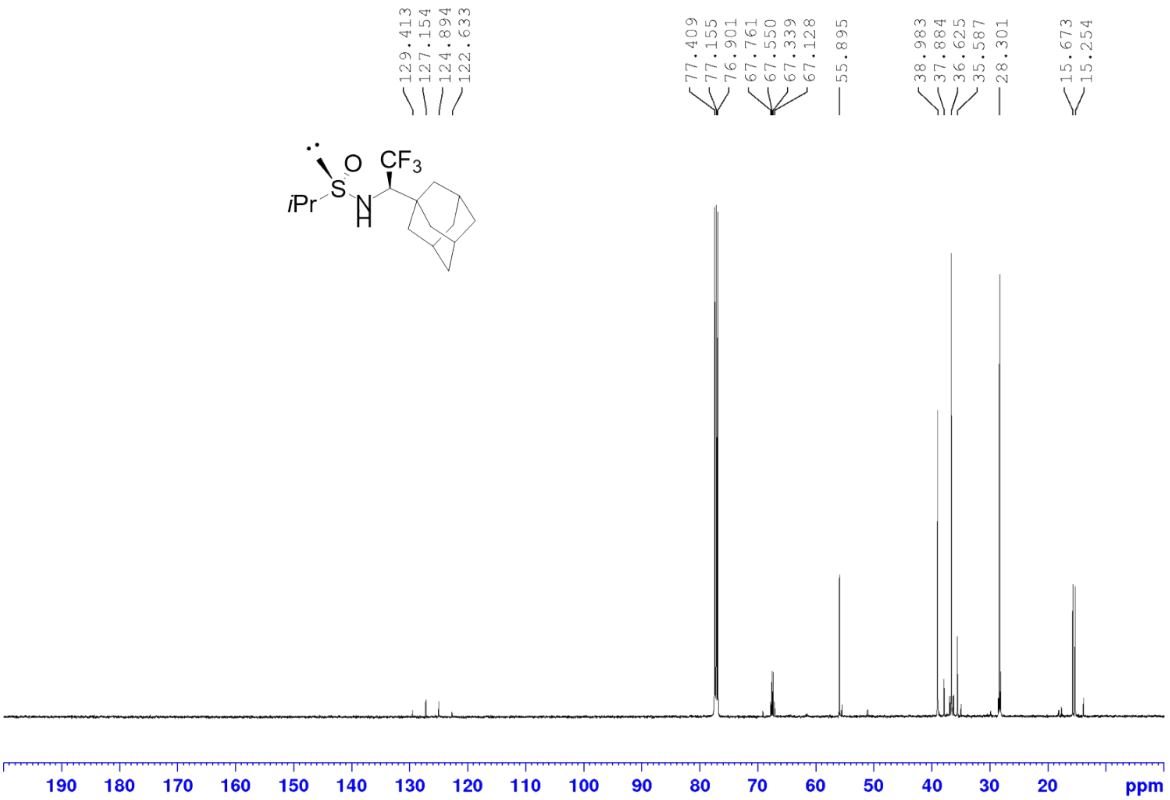


(S_S, R_C)-N-[1-(1'-adamantyl)-1-trifluoromethyl]methyl isopropylsulfinamide, **11**(S_S,R_C)

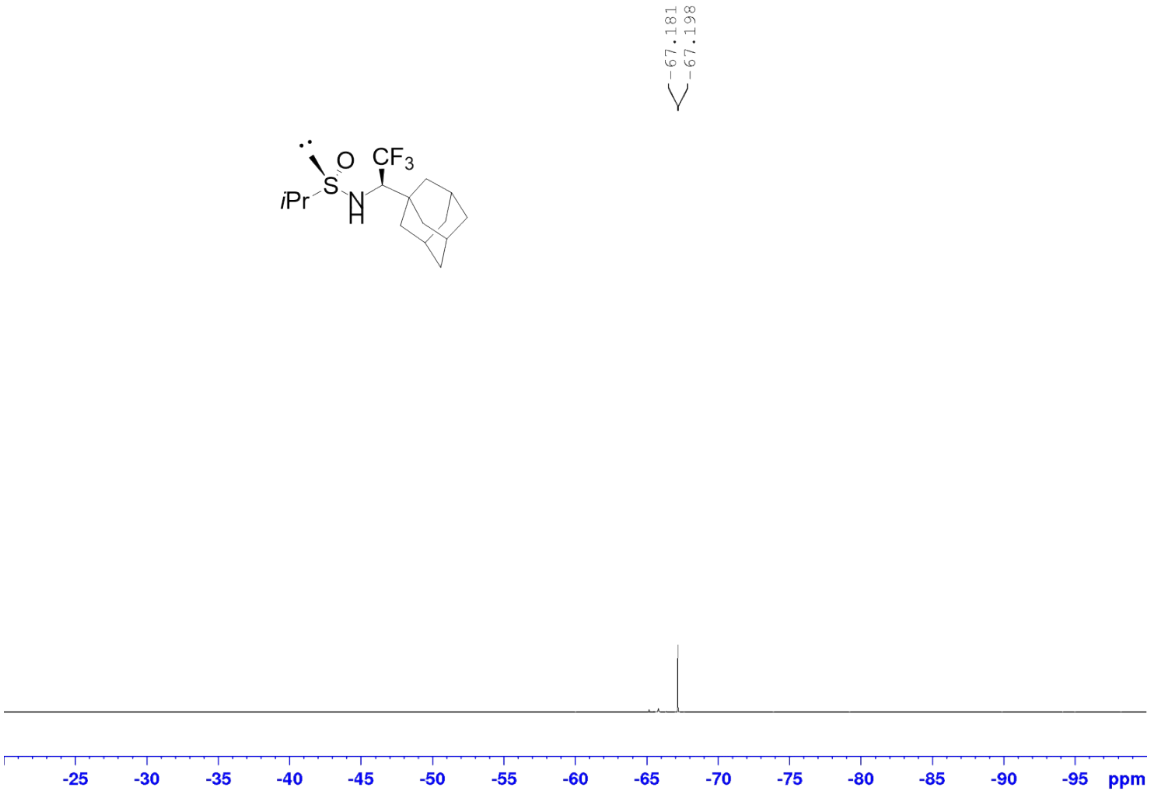
^{1}H-RMN (500 MHz, $CDCl_3$)



^{13}C-RMN (125 MHz, $CDCl_3$)

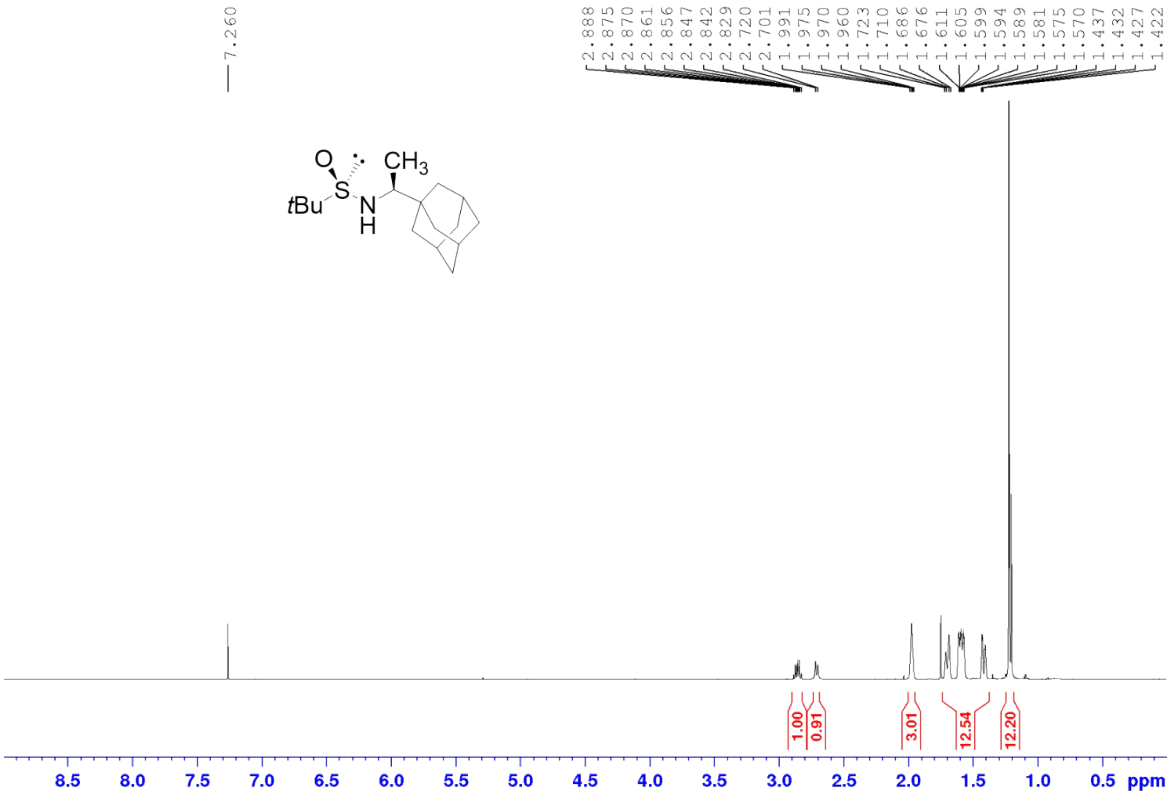


^{19}F-NMR (470 MHz, $CDCl_3$)

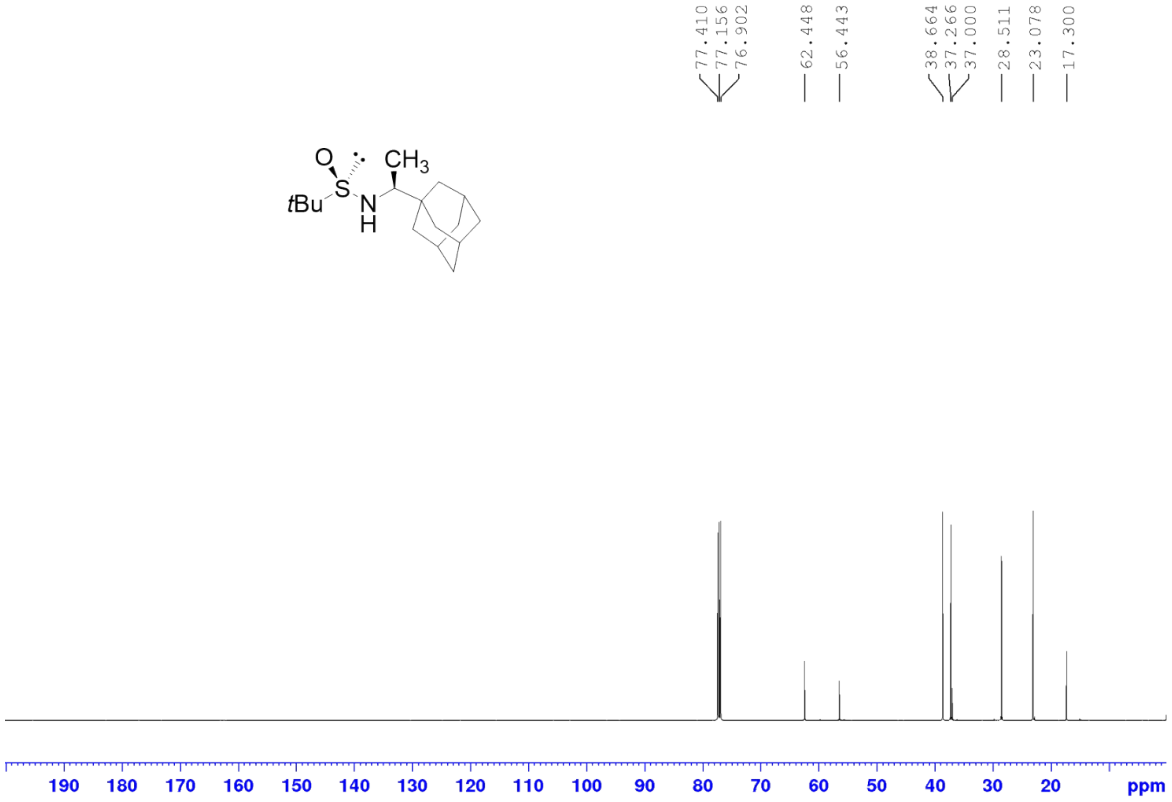


(R_S, S_C) -N-[1-(1'-adamantyl)ethyl] tert-butylsulfinamide, **6**(*Rs*,S_C)

^{1}H-RMN (500 MHz, $CDCl_3$)

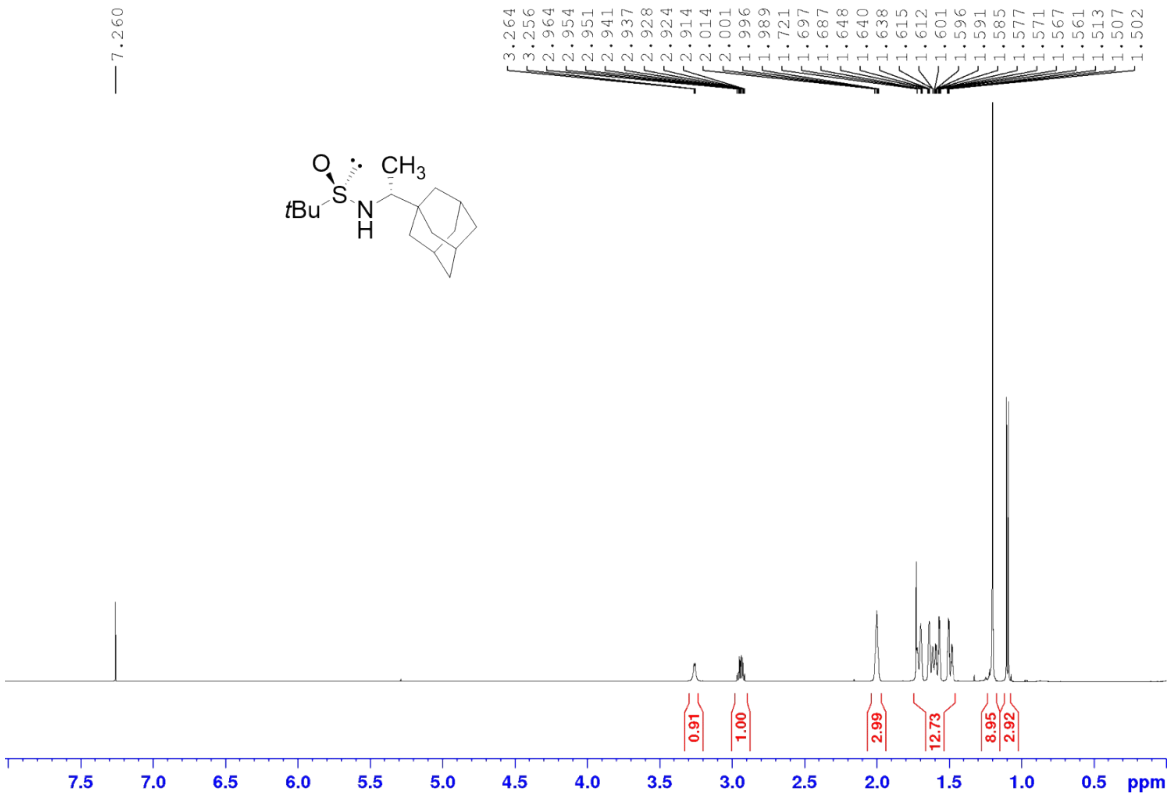


^{13}C-RMN (125 MHz, $CDCl_3$)

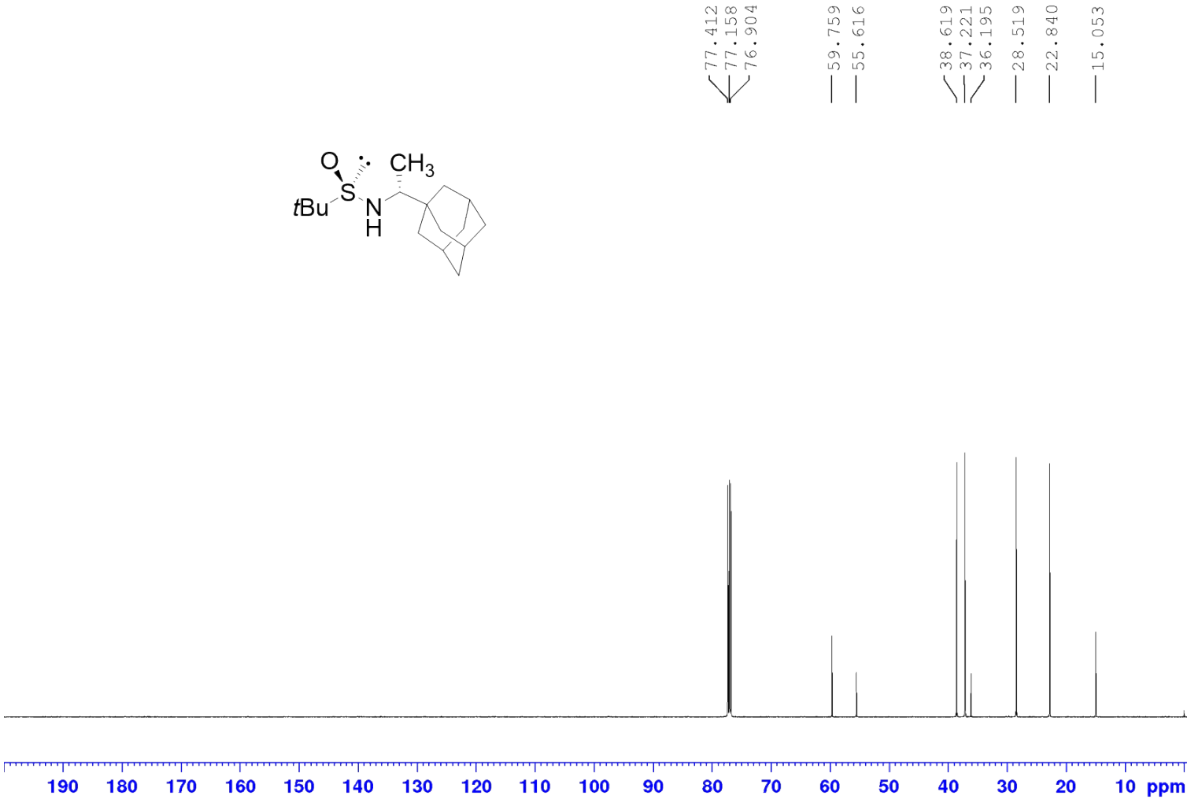


(R_S, R_C)-N-[1-(1'-adamantyl)ethyl] tert-butylsulfinamide, **6**(*Rs*,R_C)

^{1}H-RMN (500 MHz, $CDCl_3$)

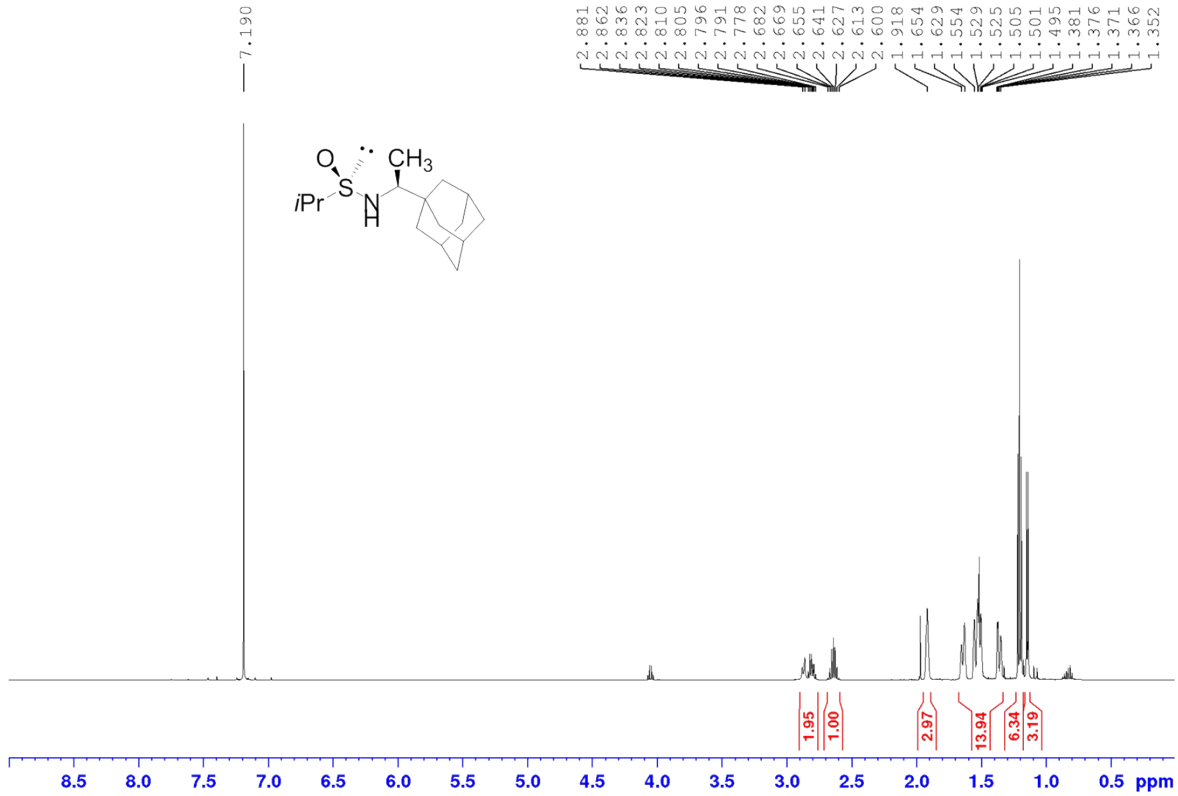


^{13}C-RMN (125 MHz, $CDCl_3$)

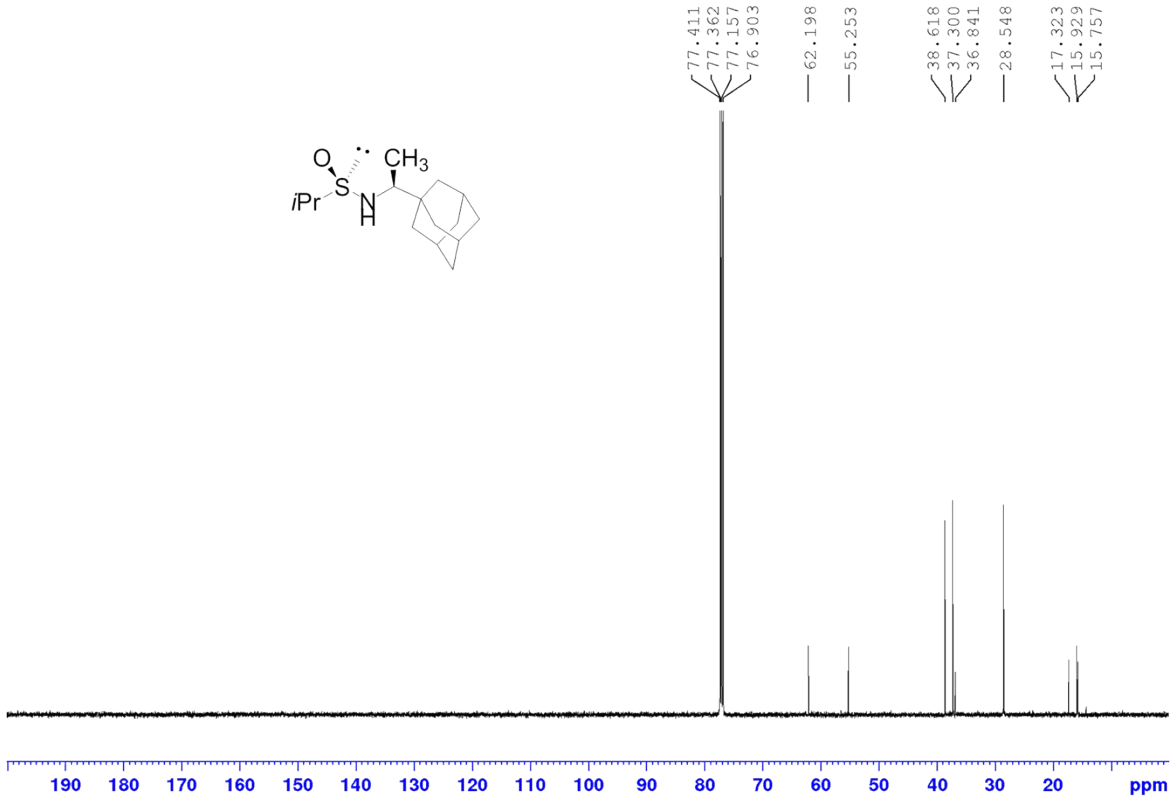


(R_S, S_C)-N-[1-(1'-adamantyl)ethyl] isopropylsulfinamide, **15**(R_S,S_C)

^{1}H-RMN (500 MHz, $CDCl_3$)

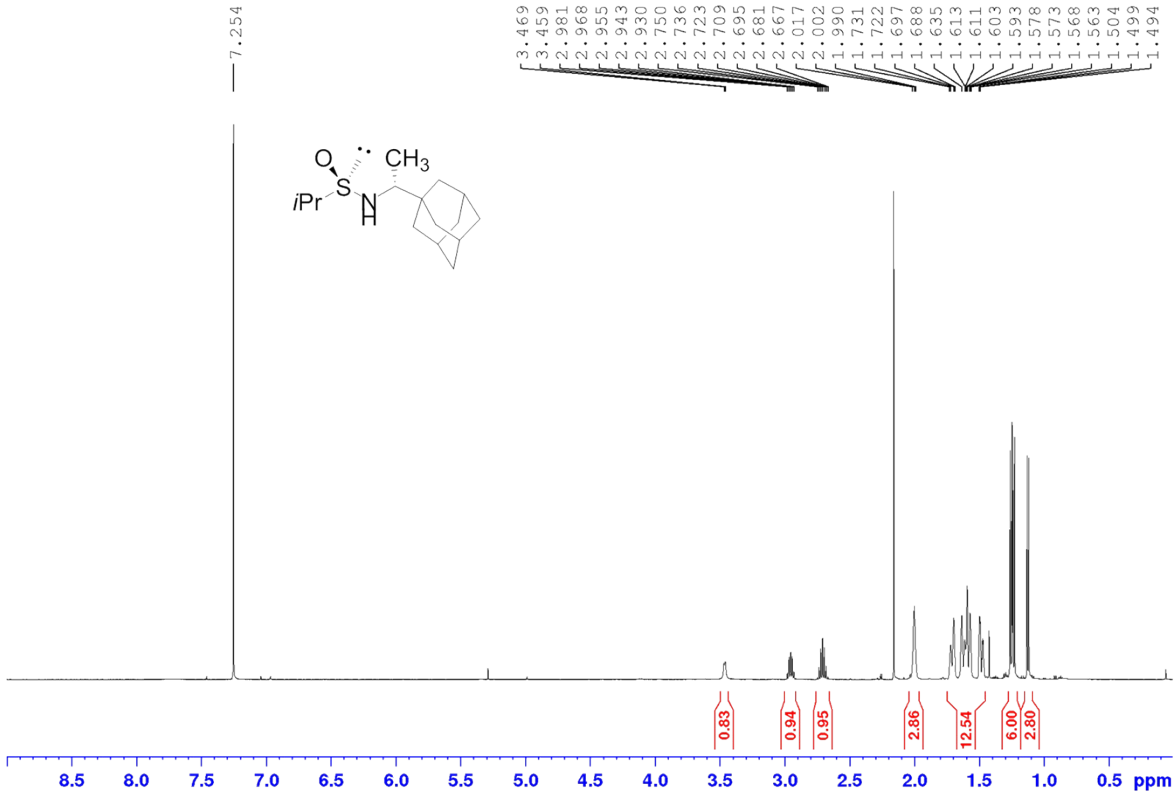


^{13}C-RMN (125 MHz, $CDCl_3$)

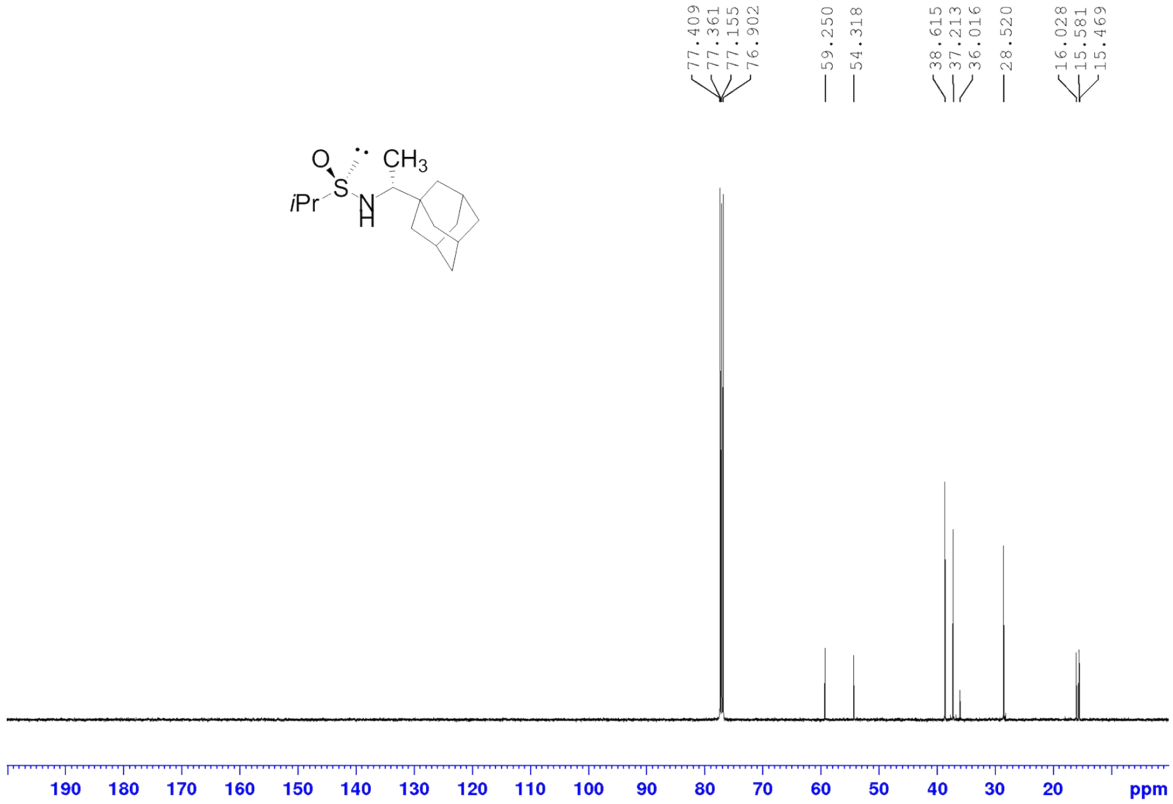


(R_S, R_C)-N-[1-(1'-adamantyl)ethyl] isopropylsulfinamide, **15**(R_S,R_C)

^{1}H-RMN (500 MHz, $CDCl_3$)

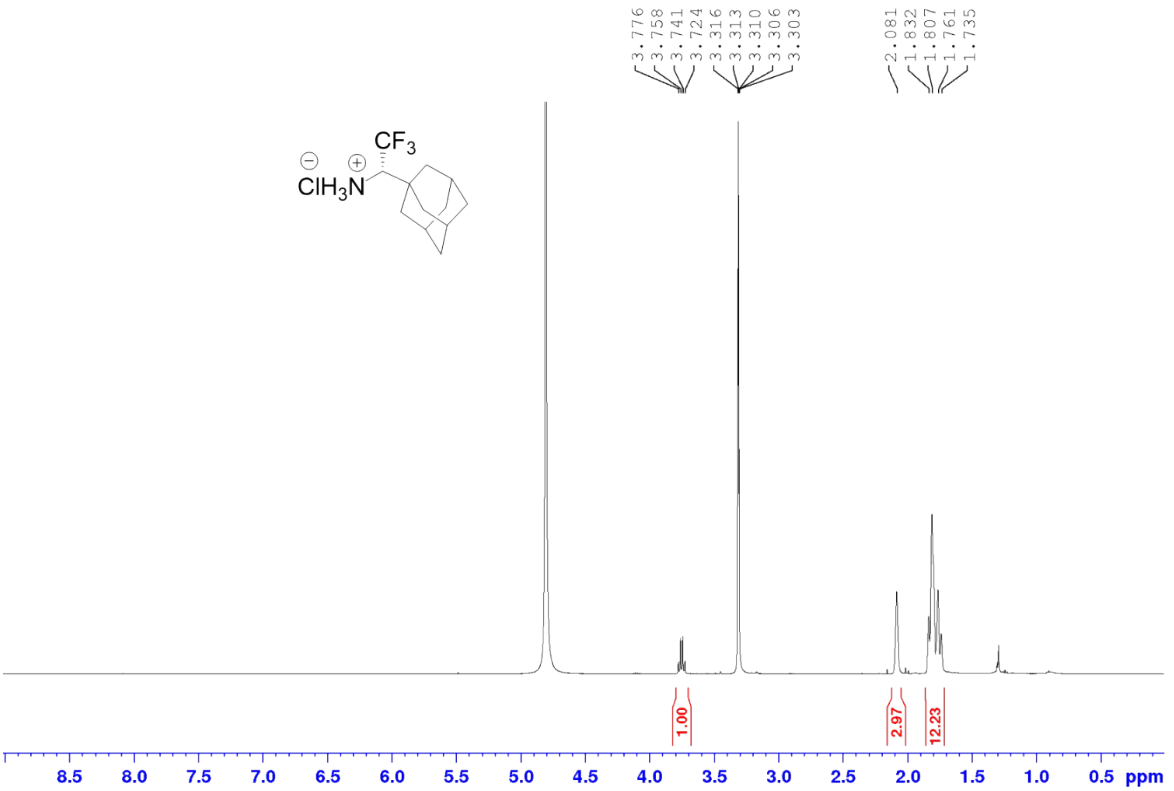


^{13}C-RMN (125 MHz, $CDCl_3$)

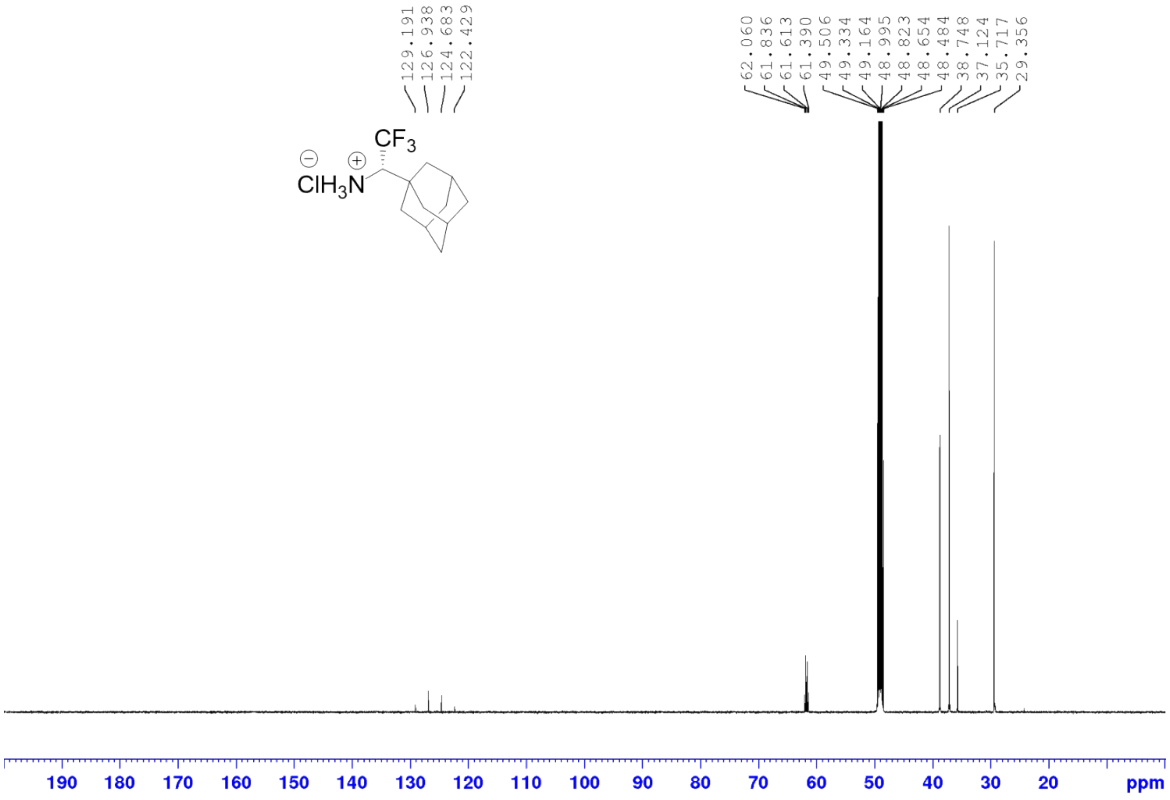


(S)-N-[1-(1'-adamantyl)-1-trifluoromethyl]methylamine chlorohydrate, **2**(*S*)

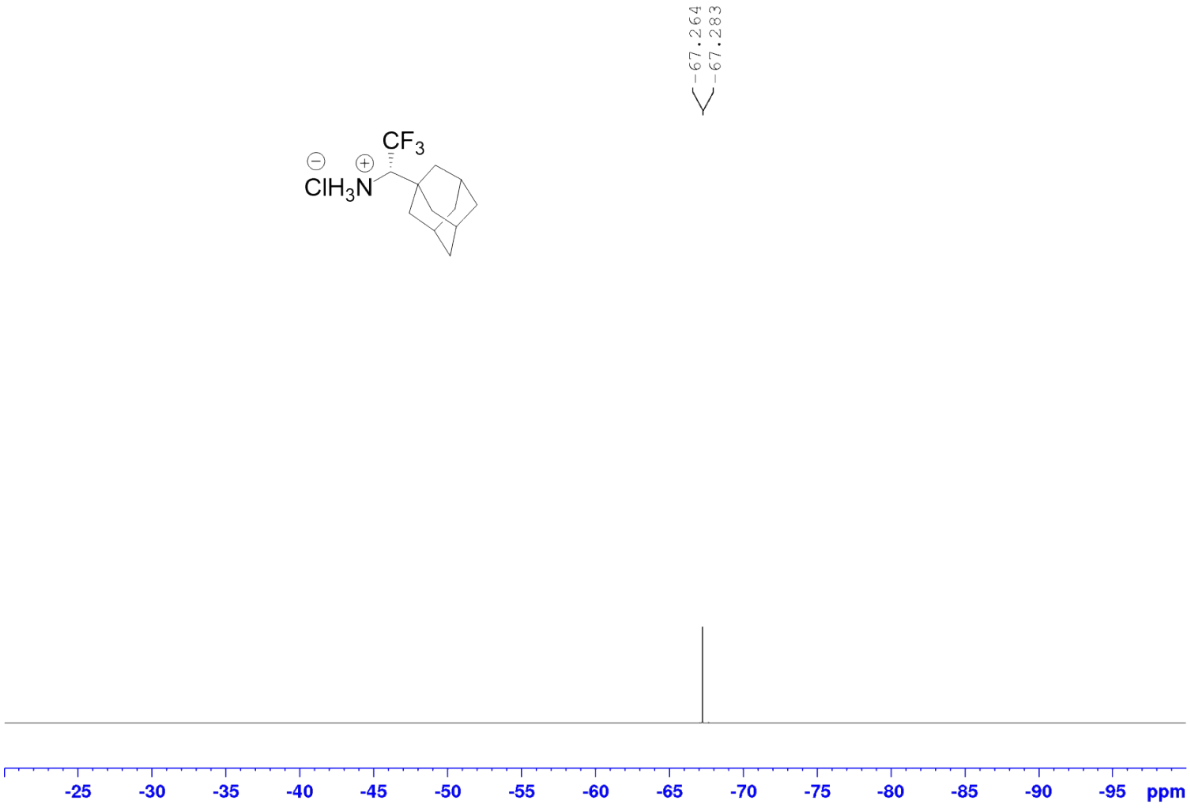
^{1}H-RMN (500 MHz, CD_3OD)



^{13}C-RMN (125 MHz, CD_3OD)

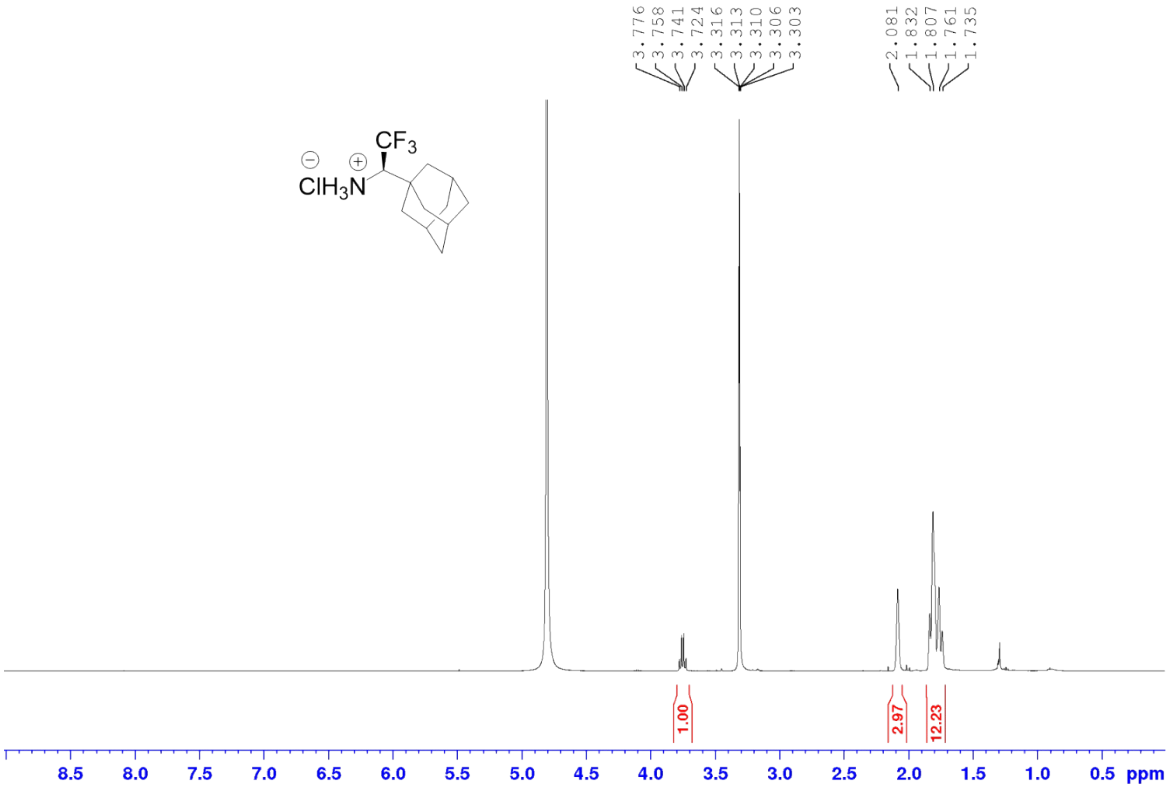


^{19}F-NMR (470 MHz, CD_3OD)

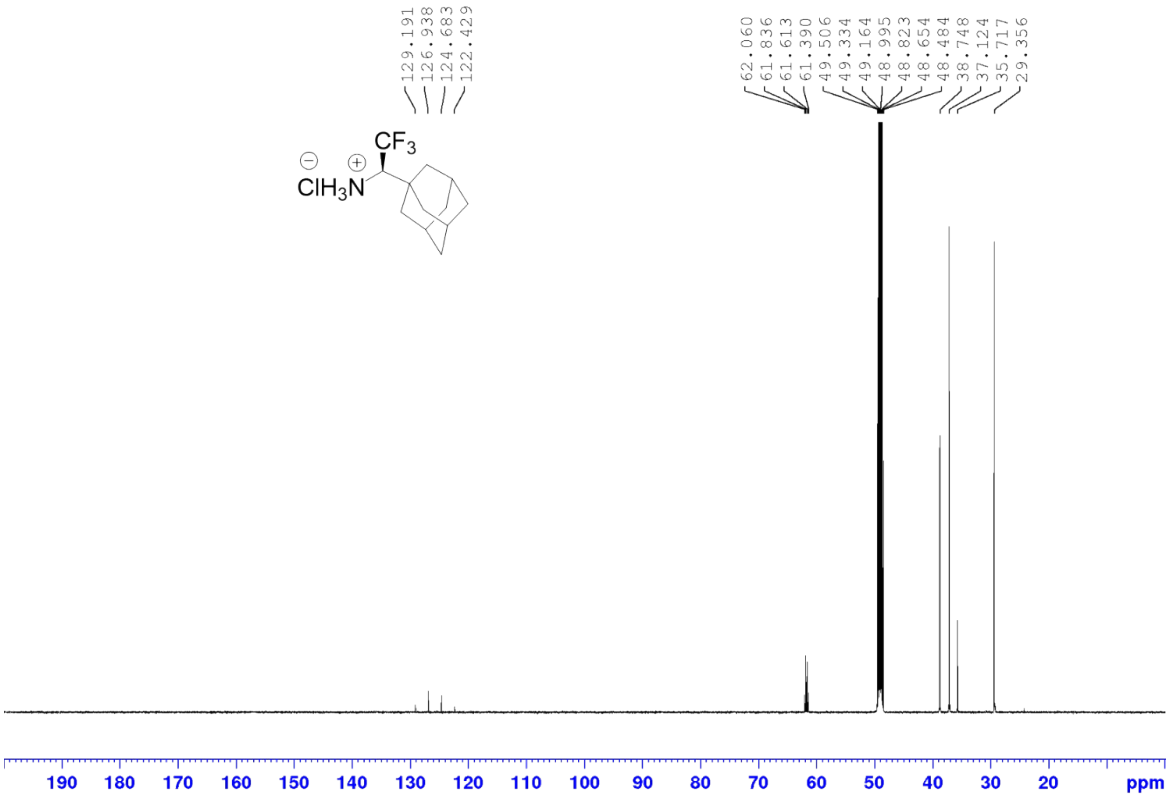


(R)-N-[1-(1'-adamantyl)-1-trifluoromethyl]methylamine chlorohydrate, **2**(*R*)

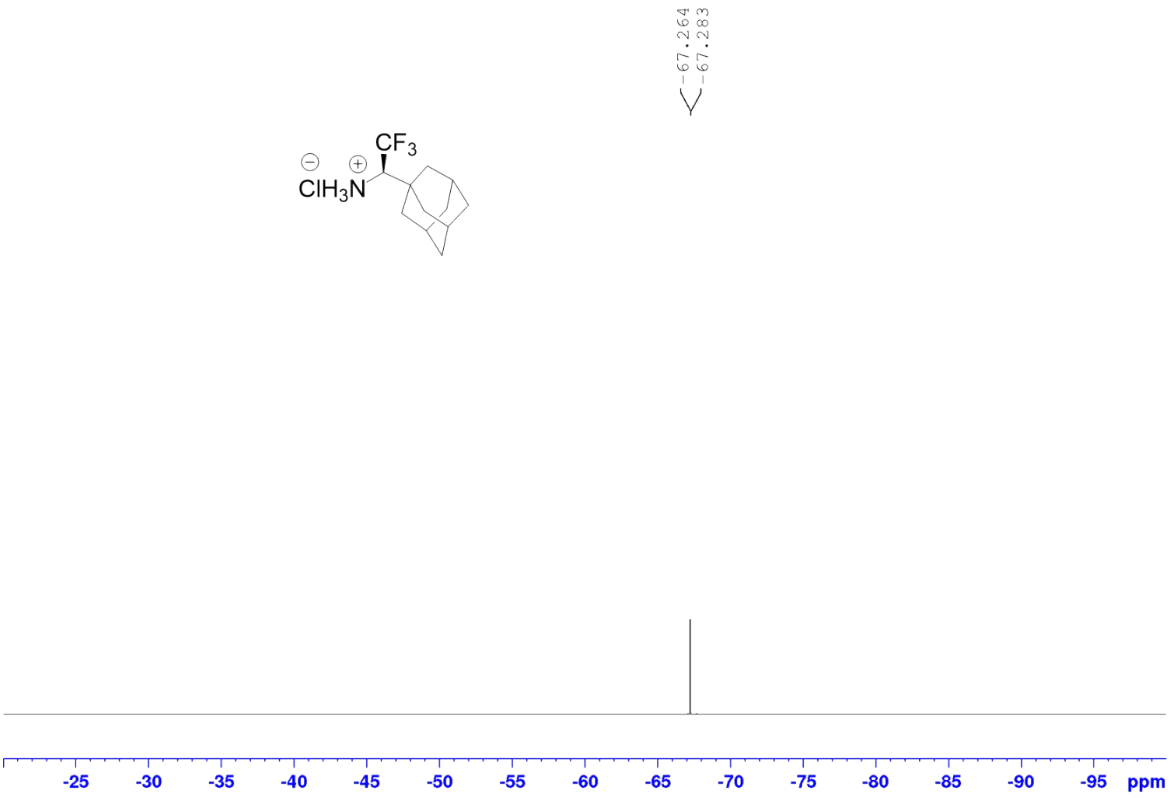
^{1}H-RMN (500 MHz, CD_3OD)



^{13}C-RMN (125 MHz, CD_3OD)

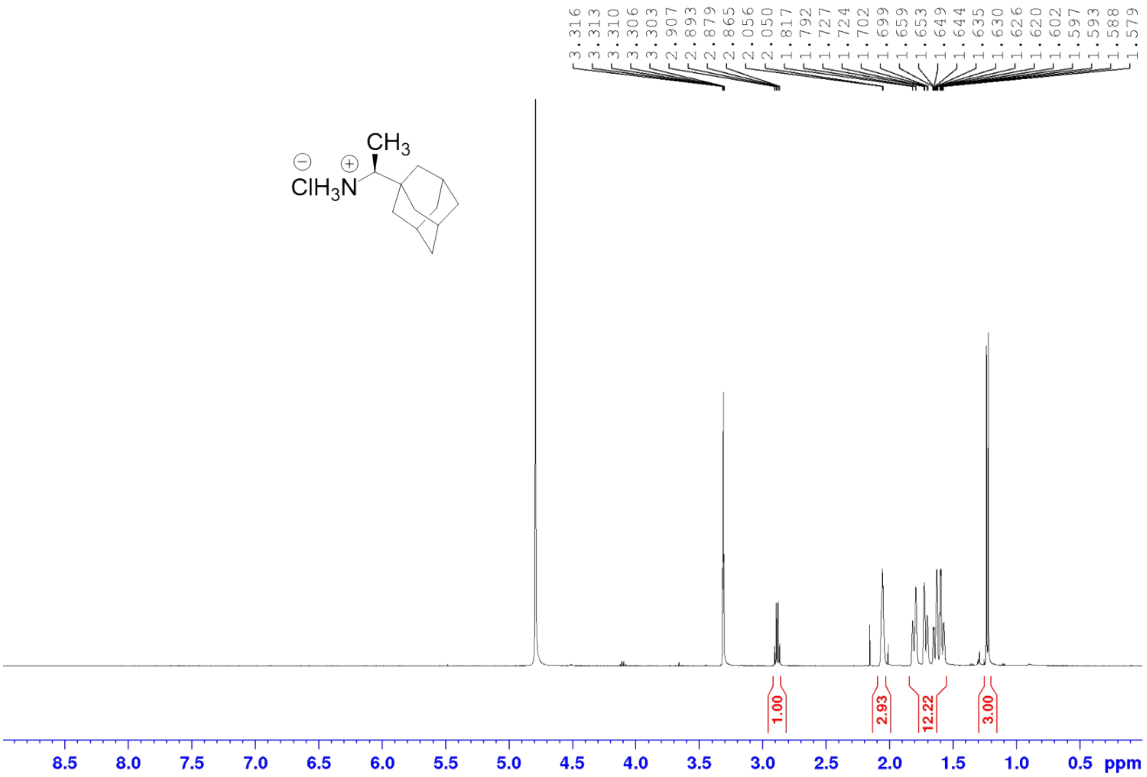


^{19}F-NMR (470 MHz, CD_3OD)

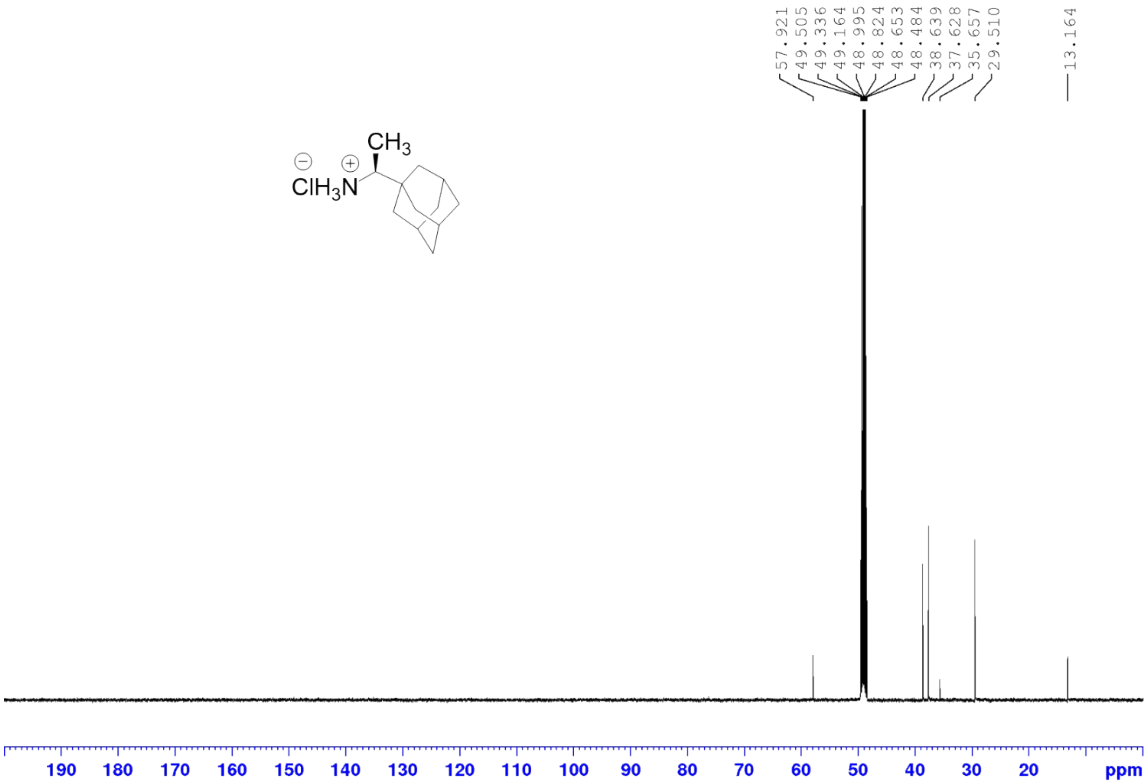


(S)-N-[1-(1'-adamantyl)ethyl]amine chlorohydrate, **1**(*S*)

^{1}H-RMN (500 MHz, CD_3OD)

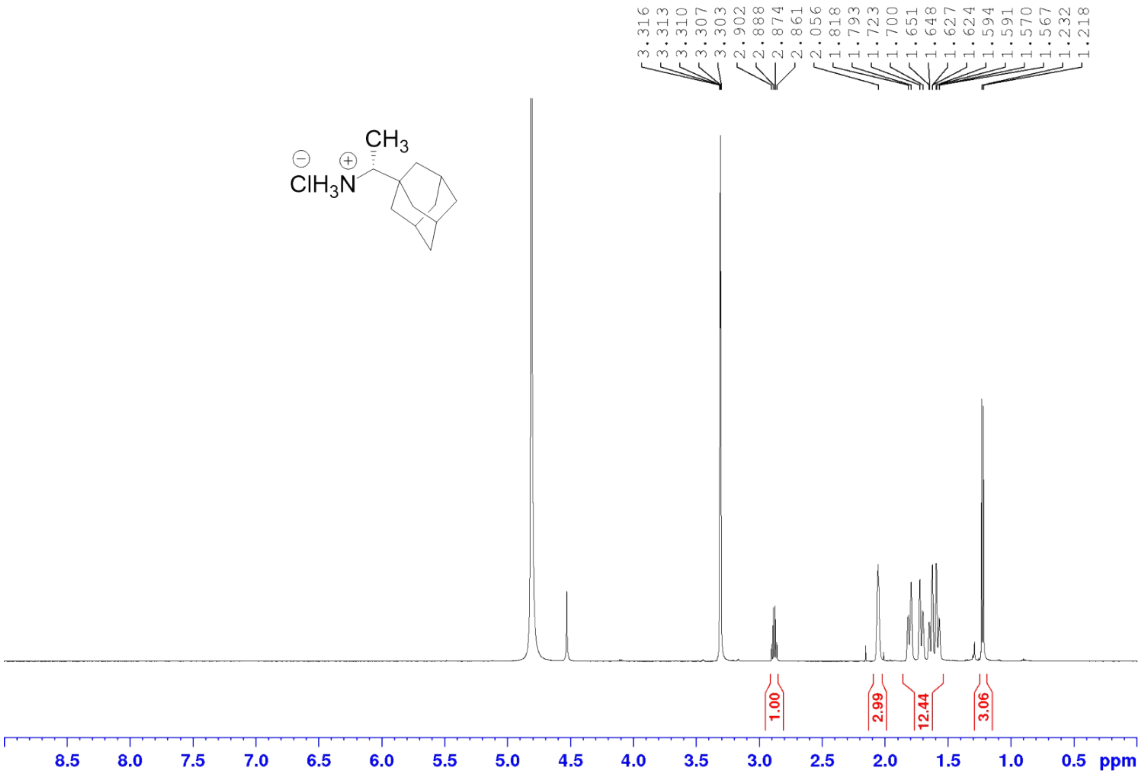


^{13}C-RMN (125 MHz, CD_3OD)

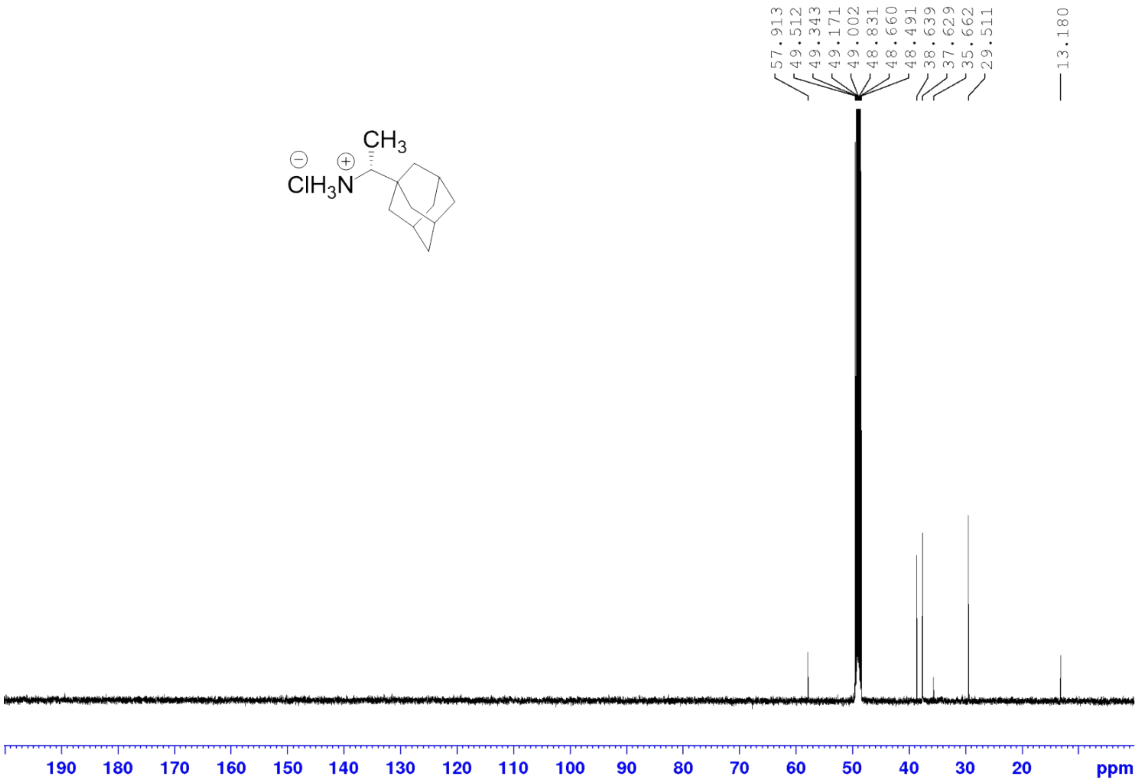


(R)-N-[1-(1'-adamantyl)ethyl]amine chlorohydrate, **1**(*R*)

^{1}H-RMN (500 MHz, CD_3OD)

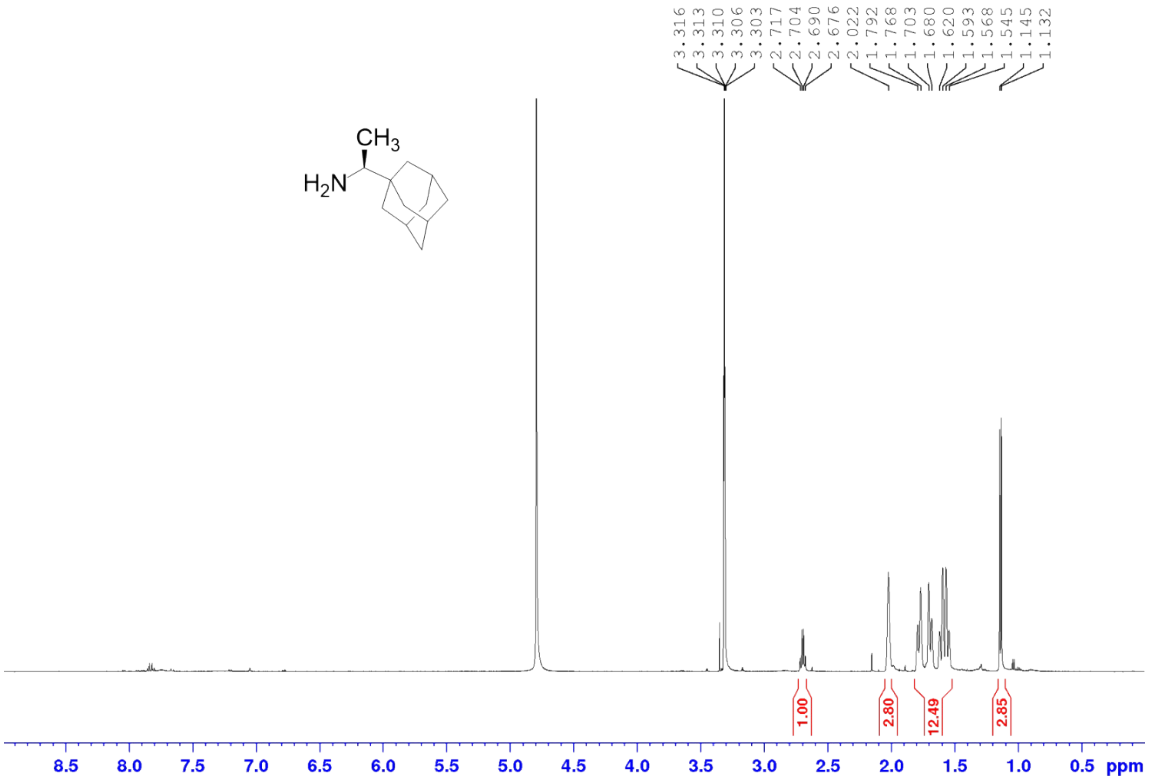


^{13}C-RMN (125 MHz, CD_3OD)

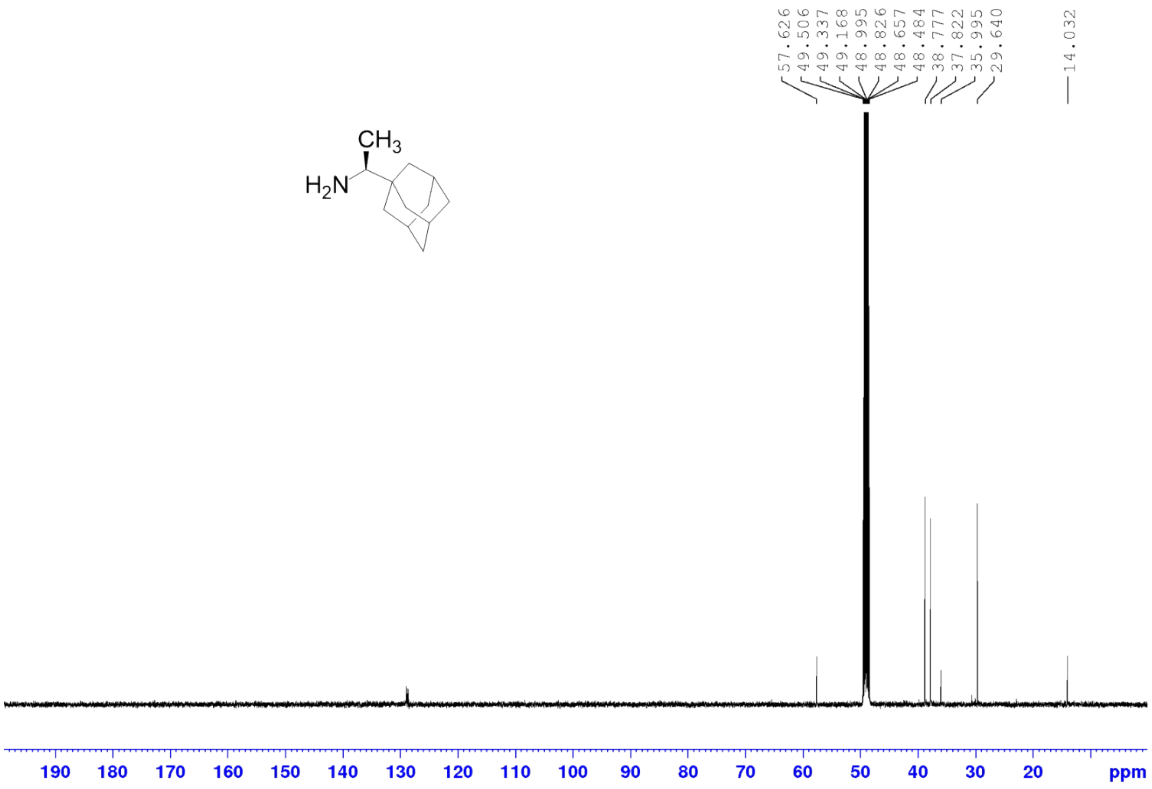


(S)-N-[1-(1'-adamantyl)ethyl]amine

^{1}H-RMN (500 MHz, CD_3OD)

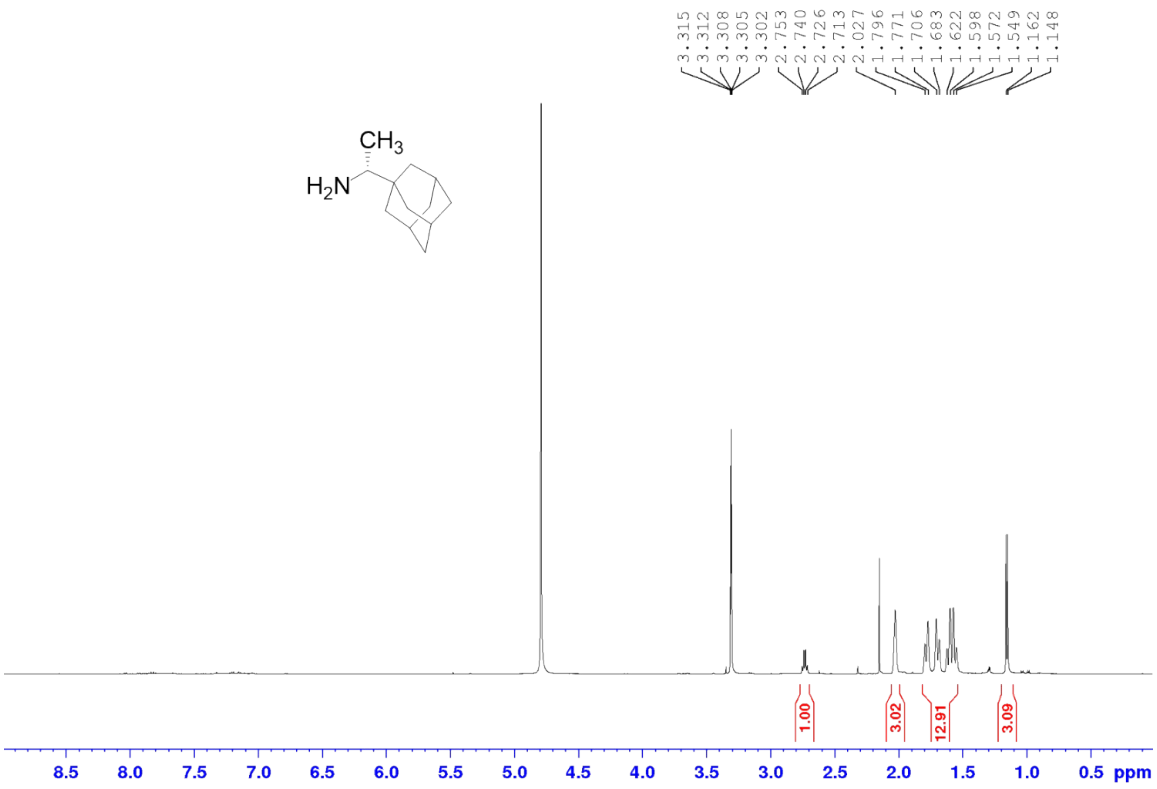


^{13}C-RMN (125 MHz, CD_3OD)

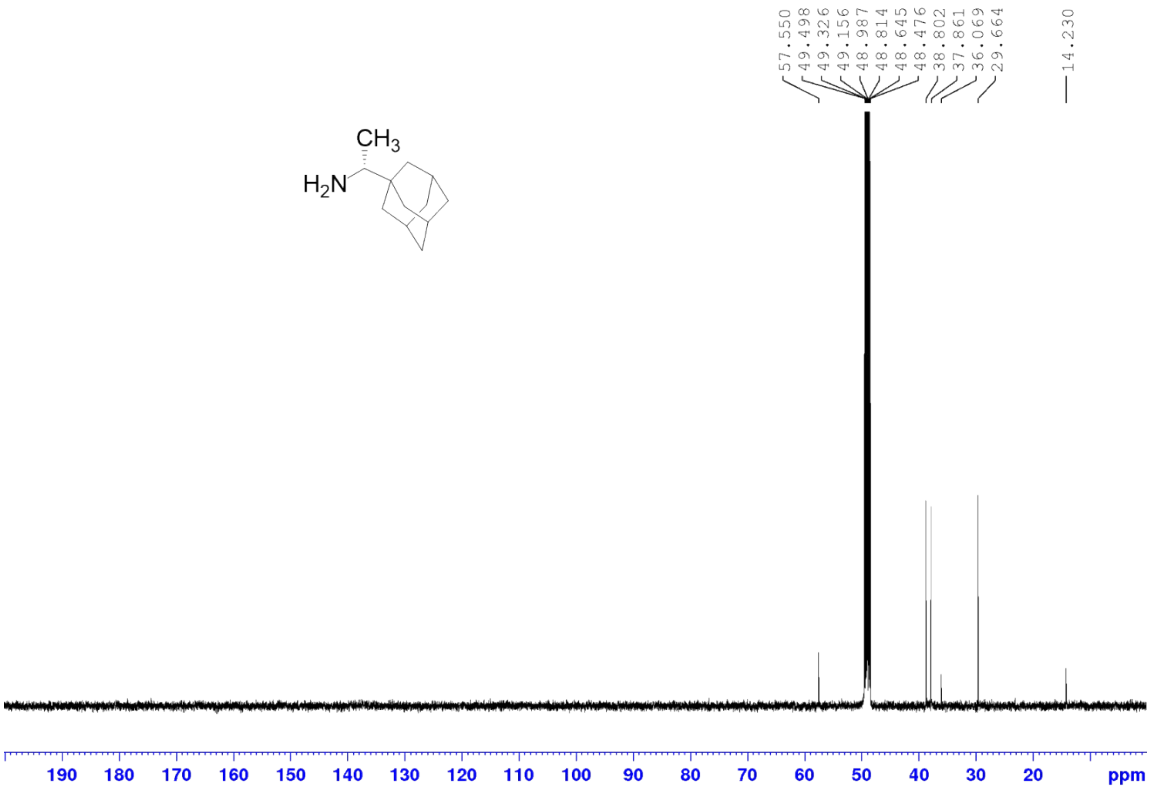


(R)-N-[1-(1'-adamantyl)ethyl]amine

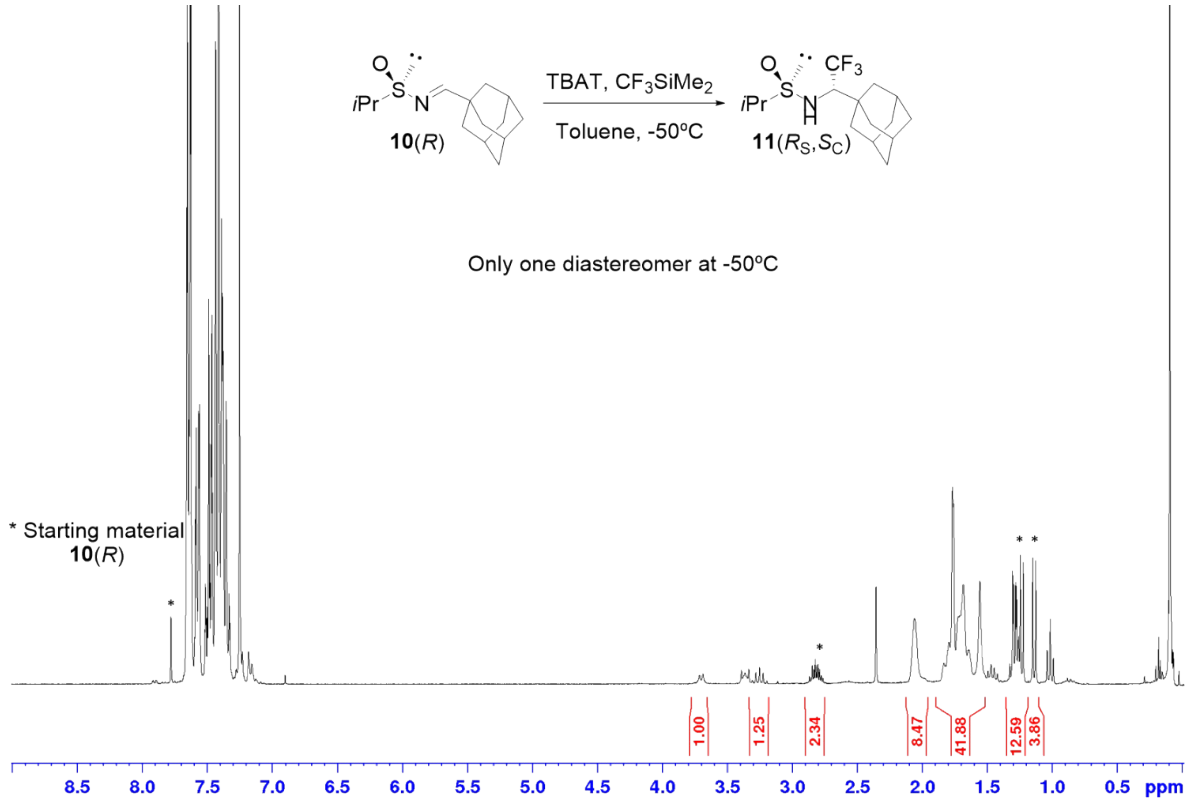
^{1}H-RMN (500 MHz, CD_3OD)

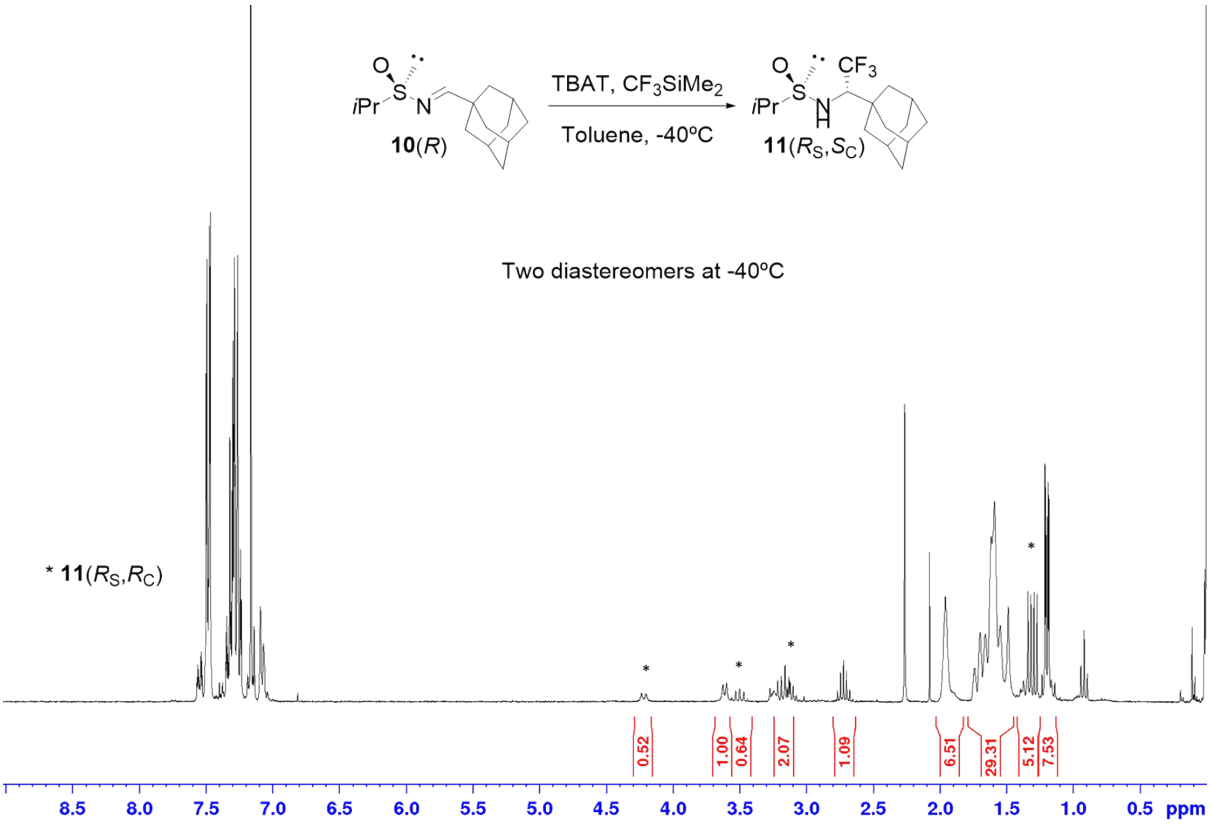


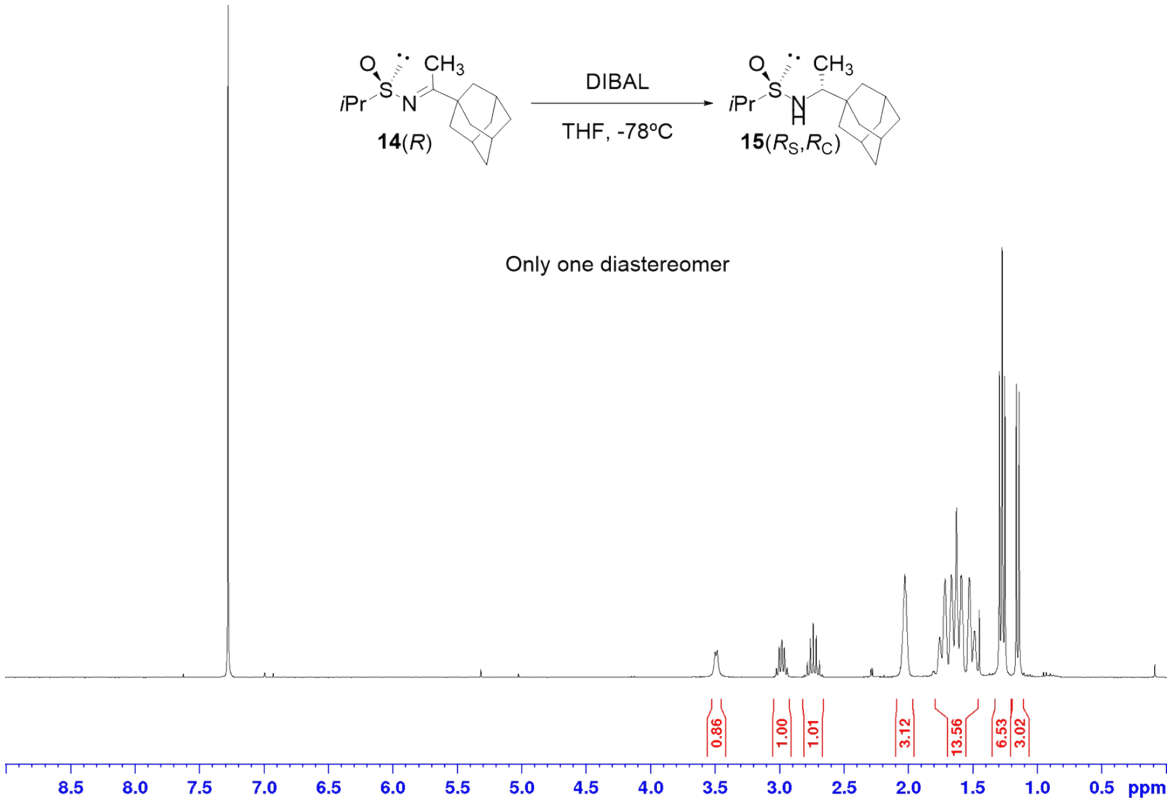
^{13}C-RMN (125 MHz, CD_3OD)

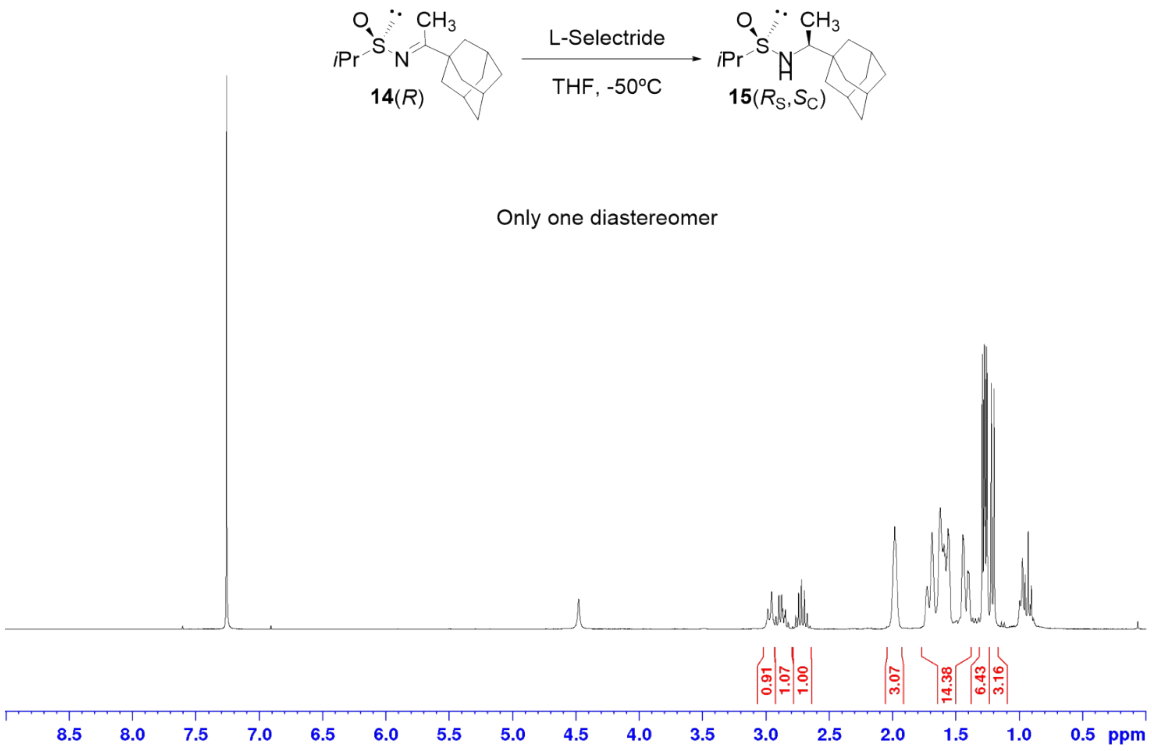


^{1}H-NMR spectra of crude reaction mixtures






DIBAL
THF, -78°C
14(R)
15(RS,RC)
Only one diastereomer
0.86
1.00
1.01
3.12
13.56
6.53
3.02
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm


L-Selectride
THF, -50°C
14(R)
15(RS,SC)
Only one diastereomer
0.91
1.07
1.00
3.07
14.38
6.43
3.16
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm

References

1. J.H. Yoon, R. Hermann, *Tetrahedron Lett.*, 1986, **27**, 1493; J.H. Yoon, R. Hermann, *Synthesis*, 1987, **72**.
2. I. Fernandez, V. Valdivia, N. Khiar, *J. Org. Chem.,* 2008, **73**, 745; I. Fernandez, V. Valdivia, A. Alcudia, A. Chelouan, N. Khiar, *Eur. J. Org. Chem.,* 2010, **8**, 1502.