Supplementary Information

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Suoplementary Methods

L- and D-proline (99% purity) were purchased from Alfa Aesar. All reactions described were performed at ambient temperature and atmosphere unless otherwise specified. Column chromatography was carried out with 230-400 mesh silica gel (E. Merck, Silica Gel 60). Concentration and removal of trace solvents was done via a Buchi rotary evaporator using acetone-dry-ice condenser and a Welch vacuum pump.

Nuclear magnetic resonance (NMR) spectra were recorded using deuterochloroform ($CDCl_3$), deuteromethanol (CD_3OD) or deuterodimethyl sulfoxide (DMSO-d_6) as the solvent. Signal

positions (δ) are given in parts per million from tetramethylsilane (δ 0) and were measured relative to the signal of the solvent (**^{1}H NMR:** $CDCl_3$: δ 7.26; CD_3OD: δ 3.31; DMSO-d_6: δ 2.50; **^{13}C NMR:** $CDCl_3$: δ 77.16; CD_3OD: δ 49.0; DMSO-d_6: 39.5). Coupling constants (*J* values) are given in Hertz (Hz) and are reported to the nearest 0.1 Hz. ^{1}H NMR spectral data are tabulated in the order: multiplicity (*s*, singlet; *d*, doublet; *t*, triplet; *q*, quartet; *sept*, septet; *m*, multiplet; *br* broad), coupling constants, number of protons. NMR spectra were recorded on a Bruker Avance 600 equipped with a QNP or TCI cryoprobe (600 MHz), Bruker 400 (400 MHz) or Bruker 500 (500 MHz). Diastereomeric ratios (dr) are based on analysis of crude ^{1}H-NMR. Assignments of ^{1}H are based on analysis of ^{1}H-^{1}H-COSY and nOe spectra. Assignments of ^{13}C are based on analysis of HSQC spectra.

High performance liquid chromatography (HPLC) analysis was performed on an Agilent 1100 HPLC, equipped with a variable wavelength UV-Vis detector and a chiral column.

High-resolution mass spectra were performed on an Agilent 6210 TOF LC/MS, Bruker MaXis Impact TOF LC/MS, or Bruker micrOTOF-II LC mass spectrometer. For each compound,

Infrared (IR) spectra were recorded neat on a Perkin Elmer Spectrum Two FTIR spectrometer. Only selected, characteristic absorption data are provided for each compound.

Optical rotation was measured on a Perkin-Elmer Polarimeter 341 at 589 nm.

General Procedure A (α-chlorination/aldol reaction)

A sample of aldehyde (1.0 equiv.) was added to a stirred suspension of *N*-chlorosuccinimide (1.05 equiv.) and L-proline (0.80 equiv.) in CH_2Cl_2 (0.56 M) at 0°C. After 60 minutes, ketone (3.0 equiv.) in DMSO (15.0 M) and H_2O (1% v/v) were added and the resulting reaction mixture was warmed gradually to room temperature. After a total of 24 hrs, or when complete consumption of the aldehyde was observed by ^{1}H NMR spectroscopic analysis of small reaction aliquots, the reaction mixture concentrated under reduced pressure, and the crude product was purified by flash chromatography as indicated.

General Procedure B (α-fluorination/aldol reaction with dioxanone)

A sample of aldehyde (1.5 equiv.) was added to a stirred suspension of *N*-fluorobenzenesulfonimide (1.5 equiv.), L-proline (1.5 equiv.), and $NaHCO_3$ (1.5 equiv.) in DMF (0.75 M) at -10 °C. When complete conversion to the α-fluoroaldehyde was observed by ^{1}H

NMR spectroscopic analysis, 2,2-Dimethyl-1,3-dioxan-5-one (**13**) (1.0 equiv.) in CH_2Cl_2 (0.055 – 0.10 M) was then added and the resulting reaction mixture was allowed to warm gradually to room temperature. After a total of 72 hrs, or when complete consumption of the **13** was observed by ^{1}H NMR spectroscopic analysis of small reaction aliquots, the reaction mixture was diluted with Et_2O and the organic layer was washed twice with water and once with brine. The organic layer was then dried over $MgSO_4$, concentrated under reduced pressure and the crude product was purified by flash chromatography as indicated.

General Procedure C (α-fluorination/aldol reaction with cyclohexanone/thiopyranone 35)

A sample of aldehyde (1.0 equiv.) was added to a stirred suspension of NFSI (1.0 equiv.), L-proline (1.0 equiv.), and $NaHCO_3$ (1.0 equiv.) in DMF (0.75 M) at -10 °C. When complete conversion to the α-fluoroaldehyde was observed by ^{1}H NMR spectroscopic analysis, cyclohexanone or thiopyranone **35** (5.0 – 10.0 equiv.) was then added and the resulting mixture was warmed gradually to room temperature. After a total of 18 hrs, the reaction mixture was diluted with Et_2O and the organic layer was washed twice with water and once with brine. The organic layer was then dried over $MgSO_4$, concentrated under reduced pressure and the crude product was purified by flash chromatography as indicated.

General Procedure D (α-trifluoromethylthiolation/aldol reaction)

A sample of aldehyde (2.0 equiv.) was added to a stirred suspension of *N*-trifluoromethylthiophthalimide (2.0 equiv.), L-proline (2.0 equiv.), and $NaHCO_3$ (2.0 equiv.) in DMSO (0.75 M) at room temperature. When complete consumption of aldehyde was observed by ^{1}H NMR spectroscopic analysis, 2,2-Dimethyl-1,3-dioxan-5-one (**13**) (1.0 equiv.) in CH_2Cl_2 (5 x vol. of DMSO) was then added and the resulting reaction mixture was stirred for a further 48 – 72 hrs. When complete consumption of the **13** was observed by ^{1}H NMR spectroscopic analysis of small reaction aliquots, the reaction mixture was diluted with Et_2O and the organic layer was washed twice with water and once with brine. The organic layer was then dried over $MgSO_4$, concentrated under reduced pressure and the crude product was purified by flash chromatography as indicated.

General Procedure E (olefination/ring-closing metathesis)

To a stirred solution of 5-(methanesulfonyl)-1-phenyl-1H-tetrazole (2 – 2.2 equiv.) in dry THF (0.80 M) at -78^{o}C was added dropwise a 1 M LiHMDS (2 – 2.2 equiv.) and the resulting reaction

mixture was stirred for 30 minutes. A solution of fluorohydrin (or trifluoromethylthiohydrin) (1.0 equiv.) in dry THF (0.30 – 0.50 M) was then added dropwise and the reaction mixture was stirred for 5 hrs at -78°C. Following complete consumption of fluorohydrin (or trifluoromethylthiohydrin), as monitored by TLC analysis, the reaction mixture was quenched with saturated ammonium chloride solution and diluted with CH_2Cl_2. The organic layer was washed twice with water, separated, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude alkene was purified by flash chromatography as indicated. A mixture Grubbs II catalyst (0.05 equiv.) and alkene (1.0 equiv.) in dry toluene (0.025 M) was purged with N_2 for 45 minutes in a sealed reaction vessel and subsequently heated to 80 - 90°C for 6 -12 hrs. The reaction mixture was then diluted with CH_2Cl_2 and washed twice with water. The organic layer was dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The crude carbacycle was purified by flash chromatography as indicated.

General Procedure F (reductive amination)

To a stirred solution of chlorohydrin (1.0 equiv.) in dry THF (0.10 M) was added AcOH (1.0 equiv.) and benzylamine (2 equiv.) and the resulting reaction mixture was allowed to stir for 1 hr. $NaBH_3CN$ (2 equiv.) was added and the reaction mixture stirred for another 1 hr. The reaction mixture was quenched with water and extracted with CH_2Cl_2.The organic layer was separated, dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography as indicated.

General Procedure G (reduction and cyclization)

To a stirred solution of *syn*-chlorohydrin (1.0 equiv) in MeOH (0.50 M) was added sodium borohydride (2.0 equiv), and the resulting mixture was stirred at 0°C for 1 hour or until no starting material remained (as determined by TLC analysis). The reaction mixture was quenched with saturated NH_4Cl, diluted with CH_2Cl_2, and washed with H_2O. The organic layer was removed, dried over $MgSO_4$, concentrated under reduced pressure, and the crude product was purified by flash chromatography. The resulting diols were dissolved in MeOH (0.50 M) and transferred to a microwave vial. The vial was sealed in a CEM Discover LabMate microwave reactor and subjected to microwave irradiation. The reaction mixture was heated for 5 minutes at 90°C, then 110°C (5 minutes), before heating at 120°C for 108 minutes. The reaction mixture was then cooled and concentrated under reduced pressure. The crude material was purified by flash chromatography as indicated.

General Procedure H (reduction and benzoylation)

To a stirred solution of racemic or optically enriched halohydrin (1.0 equiv) in MeOH (0.15 M) was added sodium borohydride (1.5 equiv), and the resulting mixture was stirred at room temperature for 1 hr or until no starting material remained (as determined by TLC analysis). The reaction mixture was then diluted with CH_2Cl_2 and washed with H_2O. The organic layer was removed, dried over $MgSO_4$, concentrated under reduced pressure, and the crude product was purified by flash chromatography. To a solution of purified diol in CH_2Cl_2 (0.10 M) was added triethylamine (6.0 equiv.), either *p*-nitro benzoyl chloride (2.0 - 4.0 equiv.) or *p*-bromo benzoyl chloride (3.0 equiv.), and 4-dimethylaminopyridine (cat.), and left to stir for 1 hr or until no starting material remained (as determined by TLC analysis). The reaction mixture was diluted with CH_2Cl_2 and washed with $NaHCO_3$. The organic layer was removed, dried over $MgSO_4$, concentrated under reduced pressure, and the crude product was purified by flash chromatography.

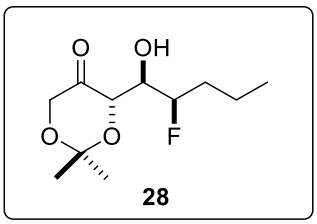
General Procedure I (hydrogenation)

Through a solution of fluorohydrin (1.0 equiv) and Pd/C (50 % by weight) in MeOH (0.10 M) was bubbled H_2 gas for 1 hr. The reaction vial was then sealed and left over night. The reaction mixture was then filtered, concentrated under reduced pressure, and the crude product was purified by flash chromatography.

Preparation and characterization of all compounds

Preparation of aldol adduct 28

Following General Procedure B, a solution of pentanal (0.050 mL, 0.470 mmol), NFSI (0.149 g, 0.470 mmol), L-proline (0.054 g, 0.470 mmol), and $NaHCO_3$ (0.039 g, 0.470 mmol) was stirred for 45 minutes at -10 °C in 0.65 mL of DMF. Dioxanone **13** (0.0380 mL, 0.314 mmol) in CH_2Cl_2 (5.6 mL) was added and the reaction mixture was left to stir at room temperature for 72 hrs. The ratio of diastereomers was determined to be 15:1 by ^{1}H NMR spectroscopic analysis of the crude product. Purification by flash chromatography (pentane:EtOAc – 9:1) afforded *syn*-fluorohydrin **28** (0.045 g, 61 % yield) as a colourless oil.



28

Data for *syn*-fluorohydrin **28**: $[\alpha]_D^{20}$ = -6.2 (*c* 2.27 in $CHCl_3$); **IR** (neat): υ = 3429, 2990, 1742, 1376, 1225, 1091, 864 cm^{-1}; ^{1}**H NMR** (600

MHz, $CDCl_3$): δ 4.69 (dddd, *J* = 47.3, 9.0, 4.0, 1.6 Hz, 1H), 4.39 (dd, *J* = 8.5, 1.1 Hz, 1H), 4.30 (dd, *J* = 17.7, 1.5 Hz, 1H), 4.08 (d, *J* = 17.5 Hz, 1H), 3.80 (ddd, *J* = 27.2, 8.5, 1.5 Hz), 3.29 (s, 1H), 1.94 (m, 1H), 1.61 (m, 1H), 1.52 (m, 1H), 1.50 (s, 3H), 1.43 (s, 3H), 1.42 (m, 1H), 0.97 (t, *J* = 7.0 Hz, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 212.6, 101.8, 91.4 (d, *J* = 175.3), 71.9 (d, *J* = 5.1 Hz), 71.4 (d, *J* = 18.0 Hz), 66.9, 32.6 (d, *J* = 20.8 Hz), 23.8, 23.8, 18.5 (d, *J* = 5.4 Hz), 14.3; **^{19}F NMR** (470 MHz, $CDCl_3$): δ –202.4

HRMS (EI^+) calcd for $[C_{11}H_{20}FO_4]^+$ 235.1340; found 235.1354

Determination of the absolute stereochemistry for fluorohydrin **28**

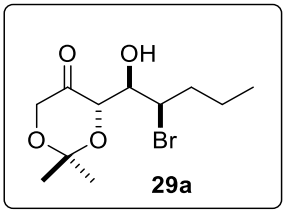
Following General Procedure H, the fluorohydrin **28** (0.105 g, 0.449 mmol) was converted into the corresponding bis-*p*-bromobenzoate **28-XRD.** Recyrstallization in dichloromethane and ethanol (1:1) allowed for the absolute stereochemistry to be assigned using single X-ray crystallography (see X-ray structures).

Determination of enantiomeric excess of fluorohydrin **28**

Following General Procedure B, using a 1:1 mixture of L-:D- proline, a racemic sample of the fluorohydrin **28** was prepared. Following General Procedure H, optically enriched and racemic samples of **28** (0.015 g, 0.064 mmol) were converted into the bis-*p*-nitrobenzoate derivative. The enantiomeric p-nitrobenzoyl diesters were separated by chiral HPLC using a DIACEL CHIRALCEL-OD column; flow rate 1.0 mL/min; eluent: hexanes-*i*PrOH 80:20; detection at 260 nm; retention time = 17.27 min and 22.06 min (see chromatograms).The enantiomeric excess of the optically enriched bis-*p*-nitrobenzoate derivative was determined using the same method (96% ee).

Preparation of *syn*-bromohydrin 29a and *anti*-bromohydrin 29b

A solution of pentanal (0.050 mL, 0.47 mmol), NBS (0.092 g, 0.52 mmol), L-proline (0.044 g, 0.38 mmol) and dioxanone **13** (0.059 mL, 0.494 mmol) in CH_2Cl_2/DMF (2.82 mL: 0.31 mL) was stirred for 96 hours. The reaction mixture was diluted with Et_2O and the organic layer was washed twice with water and once with brine. The organic layer was then dried over $MgSO_4$, concentrated under reduced pressure Purification of the crude bromohydrins **29** (dr 1.7:1) by flash chromatography (pentane-EtOAc 9:1) afforded *syn*-bromohydrin **29a** (14.4 mg, 11 % yield) as a light brown oil and *anti*-bromohydrin **29b** (8.5 mg, 6 % yield) as a light brown oil.



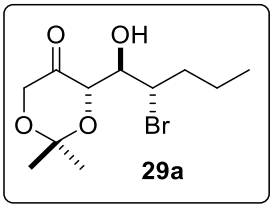
29a

Data for *syn*-bromohydrin **29a**: **^{1}H NMR** (600 MHz, $CDCl_3$): δ 4.40 (dd, *J* = 8.7 , 1.2 Hz, 1H), 4.31 (ddd, *J* = 9.4, 5.3, 1.2 Hz, 1H), 4.28 (dd, *J* = 17.6, 1.1 Hz, 1H), 4.07 (d, *J* = 17.6 Hz, 1H), 3.73 (d, *J* = 8.8 Hz, 1H), 3.41 (br s, 1H), 2.10 (m, 1H), 1.85 (m, 1H), 1.61 (m, 1H), 1.54 (s, 3H), 1.46 (m, 1H), 1.42 (s, 3H), 0.96 (t, *J* = 7.4 Hz, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 212.2, 101.8, 74.3, 71.7, 66.6, 57.0, 37.5, 24.2, 23.6, 21.2, 13.6

HRMS (EI$^+$) calcd for $[C_{11}H_{20}{}^{79}BrO_4]^+$ 295.0539; found 295.0556

Determination of relative stereochemistry for bromohydrin **29a**

The *syn*-bromohydrin **29a** (10 mg, 0.34 mmol) was converted into a *cis* epoxide to confirm the *syn* stereochemistry of the bromohydrin **29a**. Analysis of the ^{1}H NMR spectrum indicated a *cis* epoxide as the two epoxide protons resonated at 3.09 and 2.68 ppm.[1]



29a

Data for *anti*-bromohydrin **29b**: **^{1}H NMR** (600 MHz, $CDCl_3$): δ 4.48 (d, *J* = 7.2, 0.9 Hz, 1H), 4.34 (ddd, *J* = 10.6, 3.5, 3.5 Hz, 1H), 4.29 (dd, *J* = 17.5, 0.9 Hz, 1H), 4.11 (dd, *J* =7.3, 4.2 Hz, 1H), 4.06 (d, *J* = 17.5 Hz, 1H), 3.22 (br s, 1H), 1.93 (m, 1H), 1.80 (m, 1H), 1.67 (m, 1H), 1.50 (s, 3H), 1.44 (s, 3H), 1.43 (m, 1H), 0.94 (t, *J* = 7.4 Hz, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 210.4, 101.5, 74.3, 74.0, 66.8, 57.0, 35.2, 24.0, 23.8, 21.0

HRMS (EI$^+$) calcd for $[C_{11}H_{20}{}^{79}BrO_4]^+$ 295.0539; found 295.0538

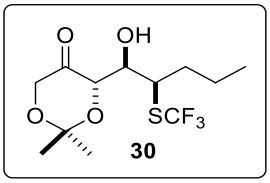
Determination of relative stereochemistry for bromohydrin **29b**

Following General Procedure B, the *anti*-bromohydrin **29b** (10 mg, 0.34 mmol) was converted into the known epoxide **29b** to confirm *anti* stereochemistry of the bromohydrin.[1]

Preparation of aldol adduct 30

Following General Procedure D, a solution of pentanal (0.100 mL, 0.941 mmol), $N(SCF_3)$Phth (0.232 g, 0.941 mmol), L-proline (0.108 g, 0.941 mmol), and $NaHCO_3$ (0.078 g, 0.941 mmol) was stirred for 50 minutes at RT in DMSO (1.30 mL). Dioxanone **13** (0.044 mL, 0.270 mmol) in CH_2Cl_2 (5.6 mL) was stirred for 60 hrs. The ratio of diastereomers was determined to be 6:1 by ^{1}H NMR spectroscopic analysis of the crude product. Purification by flash chromatography

(pentane:Et_2O – 9:1) afforded *syn*-trifluoromethylthiohydrin **30** (0.082 g, 55 % yield) as a light yellow oil**.**



30

Data for *syn*-trifluoromethylthiohydrin **30**: $[\alpha]_D^{20}$ = -111.1 (*c* 3.0 in CH_2Cl_2); **IR** (neat): υ = 3508, 2961, 1735, 1741, 1377, 1110, 861, 735 cm^{-1}; **^{1}H NMR** (600 MHz, $CDCl_3$): δ 4.42 (dd, *J* = 9.1, 1.5 Hz, 1H), 4.30 (dd, *J* = 17.6, 1.5 Hz, 1H), 4.08 (d, *J* = 17.6 Hz, 1H), 4.08 (m, 1H), 3.70 (dd, *J* = 2.2, 1.7 Hz, 1H), 3.46 (m, 1H), 2.00 (m, 1H), 1.87 (m, 1H), 1.48 (s, 3H), 1.42 (s, 3H), 0.95 (dd, *J* = 7.4, 7.4 Hz, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 213.5, 131.6 (q, *J* = 306.6 Hz), 101.7, 72.4, 71.4, 66.5, 47.0, 36.7, 23.8, 23.7, 20.3, 13.8; **^{19}F NMR** (470 MHz, $CDCl_3$): δ –39.4

HRMS (EI^+) calcd for $[C_{12}H_{19}F_3O_4S + NH_4]^+$ 334.1294; found 334.1303

*Determination of relative stereochemistry for trifluoromethylthiohydrin **30***

Following General Procedure I, trifluoromethylthiohydrin **71** was converted to trifluoromethylthiohydrin **30**. ^{1}H NMR analysis revealed identical signals with **30** synthesized using General Procedure D.

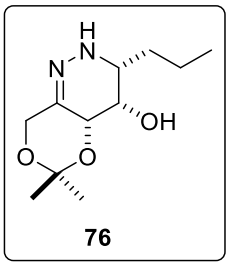
*Determination of enantiomeric excess of trifluoromethylthiohydrin **30***

Following General Procedure H, optically enriched and racemic samples of trifluoromethylthiohydrin **30** were converted into their corresponding *p*-nitrobenzoyl diesters. The enantiomeric *p*-nitrobenzoyl diesters were separated by chiral HPLC using a Lux® 3µm Amylose-1 column; flow rate 0.50 mL/min; eluent: hexanes-*i*PrOH 92.5:7.5; detection at 254 nm; retention time = 6.20 min and 9.35 min (see chromatograms). The enantiomeric excess of the optically enriched Bis-PNB ester was determined using the same method (90% ee).

Preparation of aminohydrin 31 and hydrazone 76

A solution of pentanal (0.054 mL, 0.55 mmol, 1.1 equiv.), dibenzyl azodicarboxylate (0.149 g, 0.50 mmol, 1.0 equiv.), and L-proline (0.046 g, 0.40 mmol, 0.80 equiv.) in nitromethane (1.2 mL) was stirred until complete consumption of dibenzyl azodicarboxylate was observed by TLC analysis. **13** (0.130 g, 1.0 mmol, 2 equiv.) was then added and the reaction mixture was stirred for 48 hours. The reaction mixture was then diluted with CH_2Cl_2, washed with water and brine, dried over MgSO4, filtered, and concentrated under reduced pressure. The crude aldol adduct **31**, without further purification, was dissolved in MeOH (4 mL) containing 1% v/v AcOH. To this

solution, was added Pd/C (100 mg, 25% by weight). H2 gas was bubbled into the reaction mixture until complete consumption of **31** was observed by TLC analysis. The reaction mixture was then filtered through celite and concentrated under reduced pressure. The ratio of diastereomers was determined to be 3:1 by ^{1}H NMR spectroscopic analysis of the crude product. Purification by flash chromatography (pentane:EtOAc:NEt_3 – 60:39:1) afforded hydrazone **76** (0.103 g, 45 % yield over 2 steps) as a white solid.



76

Data for hydrazone **76**: **$[\alpha]_D^{20}$** = -24.5 (*c* 1.75 in $CHCl_3$); **IR** (neat): υ = 3348, 2989, 2871, 1648, 1455, 1373, 1167, 1074, 862 cm^{-1}; ^{1}**H NMR** (400 MHz, $CDCl_3$): δ 5.13 (br s, 1H), 4.43 (m, 1H), 4.40 (d, *J* = 14.6 Hz, 1H), 4.22 (d, *J* = 14.6 Hz, 1H), 3.87 (m, 1H), 3.14 (dd, *J* = 7.1, 6.8 Hz, 1H), 2.46 (br s, 1H), 1.69 (m, 1H), 1.53 (s, 3H), 1.44 (s, 3H), 1.69 – 1.39 (m, 3H), 0.96 (t, *J* = 7.6 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 139.6, 99.9, 66.1, 63.1, 62.9, 55.9, 31.7, 27.2, 21.6, 18.8, 14.1

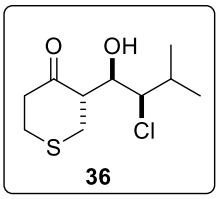
HRMS (EI^+) calcd for $[C_{11}H_{21}N_2O_3]^+$ 229.1547; found 229.1529

Determination of enantiomeric excess of hydrazone **76**

Using a 1:1 mixture of L-:D- proline, a racemic sample of the hydrazone **76** was prepared. The enantiomeric hydrazones were separated by chiral HPLC using a Phenomex Lux Cellulose-3 column; flow rate 0.4 mL/min; eluent: hexanes-*i*PrOH 80:20; detection at 254 nm; retention time = 11.57 min for (+)-**76**; 16.72 min for (-)-**76** (see chromatograms).The enantiomeric excess of the optically enriched **76** was determined using the same method (98% ee).

Preparation of aldol adduct 36

Following General Procedure A, isovaleraldehyde (0.054 mL, 0.50 mmol) was added to a mixture of NCS (71 mg, 0.53 mmol) and L-proline (46 mg, 0.40 mmol) in CH_2Cl_2 (0.9 mL) at 0°C and the resulting reaction mixture was stirred for 1 hr. Thiopyranone **35** (174 mg, 1.5 mmol) in DMSO (0.1 mL) and H_2O (10 µL) were then added and the resulting reaction mixture was stirred for 48 hrs at room temperature. The ratio of diastereomers was determined to be 10:1 by ^{1}H NMR spectroscopic analysis of the crude product. Purification by flash chromatography (pentane:EtOAc – 8:2) afforded *syn*-chlorohydrin **36** (0.053 g, 45 % yield) as a white solid.



36

Data for *syn*-chlorohydrin **36**: **$[\alpha]_D^{20}$** = - 37.4 (*c* = 3.25 in $CHCl_3$); IR (neat): υ = 3539, 2970, 2926, 2872, 1684, 1323, 1307, 1248, 1057, 638, 560, 526 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.31 (dd, *J* = 7.4, 3.7 Hz, 1H), 3.68 (dd, *J* = 8.0, 2.5 Hz, 1H), 3.07 (m, 1H) 3.00 - 2.90 (m, 4H), 2.84 - 2.70 (m, 3H), 2.19 (m, *J* = 6.6, 2.0 Hz, 1H), 1.10 (d, *J* = 6.7 Hz, 3H), 1.05 (d, *J* = 6.7 Hz, 3H) **^{13}C NMR** (100 MHz, $CDCl_3$) δ 210.8, 70.7, 70.5, 56.5, 44.1, 32.2, 31.9, 30.5, 20.3, 20.1

HRMS (ESI) m/z calcd for $C_{10}H_{21}{}^{35}ClO_2NS$ $[M+NH_4]^+$ 254.0976, found 254.0957

m.p.: 91-93°C

Determination of relative stereochemistry for chlorohydrin **36**

Following General Procedure G, the chlorohydrin was converted to **79**. NOE analysis of **94** confirmed relative stereochemistry of chlorohydrin **36**.

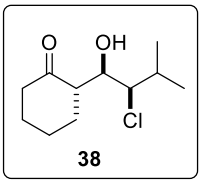
*Determination of enantiomeric excess of chlorohydrin **36***

Following General Procedure H, *bis*-PNB esters were prepared of both the racemic and enantioenriched samples. The enantiomeric *bis*-PNB esters were separated by chiral HPLC using a Phenomex Lux Amylose-3 column; flow rate 0.4 mL/min; eluent: hexanes-*i*PrOH 90:10; detection at 254 nm; retention time = 10.77 min and 16.02 min (see chromatograms).The enantiomeric excess of the optically enriched **36** was determined using the same method (94% ee).

Preparation of aldol adduct 38

Following General Procedure A, isovaleraldehyde (0.108 mL, 1.0 mmol) was added to a mixture of NCS (142 mg, 1.05 mmol) and L-proline (92 mg, 0.80 mmol) in CH_2Cl_2 (1.8 mL) at 0°C and the resulting reaction mixture was stirred for 1 hr. Cyclohexanone (0.200 mL, 2.0 mmol) in DMSO (0.2 mL) and H_2O (20 µL) were then added and the resulting reaction mixture was stirred for 48 hrs at room temperature. The reaction mixture was concentrated under reduced pressure. 2 mL of saturated NH_4Cl was added to the resulting crude reaction mixture which was then extracted with diethyl ether. The organic layer was subsequently washed with saturated $NaHCO_3$ and brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The ratio of diastereomers was determined to be 10:1 by ^{1}H NMR spectroscopic analysis of the

crude product. Purification by flash chromatography (pentane:EtOAc – 9:1) afforded *syn*-chlorohydrin **38** (0.104 g, 48 % yield) as a pale yellow oil.



38

Data for *syn*-chlorohydrin **38**: **$[\alpha]_D^{20}$** = -13.2 (c = 7.9 in $CHCl_3$) IR (neat): υ = 3530, 2939, 2870, 1695, 1241, 1131, 1603, 732, 531 cm-1 **^{1}H NMR** (500 MHz, $CDCl_3$) δ 4.09 (dd, *J* = 8.4, 2.0 Hz, 1H), 3.58 (dd, *J* = 8.7, 1.8 Hz, 1H), 3.51 (br s, 1H), 2.76 (m, 1H), 2.47 - 2.27 (m, 2H), 2.22 (m, 1H), 2.12 (m, 2H), 1.91 (m, 1H), 1.68 (m, 2H), 1.32 (m, 1H), 1.11 (dd, *J* = 6.8, 1.7 Hz, 3H), 1.02 (dd, *J* = 6.5, 2.0 Hz, 3H) **^{13}C NMR** (100 MHz, $CDCl_3$) δ 215.2, 70.9, 70.6, 54.4, 42.6, 32.2, 29.5, 27.5, 24.5, 20.8, 20.1

HRMS: (ESI) m/z calcd for $C_{11}H_{20}{}^{35}ClO_2$ $[M+H]^+$ 219.1146, found 219.1135

Determination of relative stereochemistry for chlorohydrin **38**

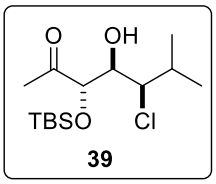
Following General Procedure G, the chlorohydrin was converted to **78**. NOE analysis of **78** confirmed relative stereochemistry of chlorohydrin **38**.

*Determination of enantiomeric excess of chlorohydrin **38***

Following General Procedure H, *bis*-PNB esters were prepared of both the racemic and enantioenriched samples. The enantiomeric *bis*-PNB esters were separated by chiral HPLC using a Phenomex Lux Amylose-5 column; flow rate 0.25 mL/min; eluent: hexanes-*i*PrOH 97:3; detection at 254 nm; retention time = 6.46 min and 7.08 min (see chromatograms).The enantiomeric excess of the optically enriched **38** was determined using the same method (98% ee).

Preparation of aldol adduct 39

Following General Procedure A, isovaleraldehyde (0.054 mL, 0.50 mmol) was added to a mixture of NCS (71 mg, 0.53 mmol) and L-proline (46 mg, 0.40 mmol) in CH_2Cl_2 (0.9 mL) at 0°C and the resulting reaction mixture was stirred for 1 hr. O-TBS-hydroxyacetone (282 mg, 1.5 mmol) in DMSO (0.1 mL) and H_2O (10 µL) were then added and the resulting reaction mixture was stirred for 24 hrs at room temperature. The ratio of diastereomers was determined to be 14:1 by ^{1}H NMR spectroscopic analysis of the crude product. Purification by flash chromatography (pentane:EtOAc:NEt_3 – 95:4:1) afforded *syn*-chlorohydrin **39** (0.108 g, 58 % yield) as a pale yellow oil.



39

Data for *syn*-chlorohydrin **39**: **$[\alpha]_D^{20}$** = -18.9 (c = 6.4 in $CHCl_3$); IR (neat): υ = 3453, 2956, 2930, 1718, 1254, 1102, 835, 777 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 3.96 (dd, *J* = 7.3, 2.0 Hz, 1H), 3.94 (d, *J* = 8.2 Hz, 1H), 3.82 (d, *J* = 8.2 Hz ,1H), 2.26 (br s, 1H), 2.20 (s, 3H), 2.12 (m, *J* = 6.8 Hz, 1H), 1.07 (d, *J* = 6.6 Hz, 3H), 1.03 (d, *J* = 6.7 Hz, 3H), 0.89 (s, 9H), 0.08 (s, 3H), 0.02 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 209.7, 79.0, 73.0, 70.8, 32.5, 25.6, 25.5, 20.3, 20.0, 18.0, -4.9, -5.2 ppm

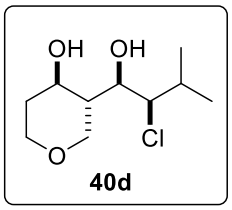
HRMS (ESI) m/z calcd for $C_{14}H_{30}{}^{35}ClO_3Si$ $[M+H]^+$ 309.1647, found 309.1666

*Determination of enantiomeric excess of chlorohydrin **39***

Following General Procedure H, PNB esters were prepared of both the racemic and enantioenriched samples. The enantiomeric PNB esters were separated by chiral HPLC using a Phenomex Lux i-Cellulose-5 column; flow rate 0.15 mL/min; eluent: hexanes-*i*PrOH 95:5; detection at 254 nm; retention time = 2.89 min and 3.61 min (see chromatograms).The enantiomeric excess of the optically enriched **39** was determined using the same method (97% ee).

Preparation of chlorohydrin 40

Following General Procedure A, isovaleraldehyde (0.108 mL, 1.0 mmol) was added to a mixture of NCS (142 mg, 1.05 mmol) and L-proline (90 mg, 0.80 mmol) in CH_2Cl_2 (1.8 mL) at 0°C and the resulting reaction mixture was stirred for 1 hr. Cyclohexanone (0.330 mL, 3.0 mmol) in DMSO (0.2 mL) and H_2O (20 µL) were then added and the resulting reaction mixture was stirred for 48 hrs at room temperature. The reaction mixture was concentrated under reduced pressure. 2 mL of saturated NH_4Cl was added to the resulting crude reaction mixture which was then extracted with diethyl ether. The organic layer was subsequently washed with saturated $NaHCO_3$ and brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product **40** was then dissolved in MeOH (2 mL) and cooled to 0°C. $NaBH_4$ (74 mg, 2.0 mmol) was added to the reaction mixture and stirred for 1 hr. The reaction mixture was quenched with saturated ammonium chloride and extracted with CH_2Cl_2 (10 mL x 3). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The ratio of diastereomers was determined to be 7:1 by ^{1}H NMR spectroscopic analysis of the crude product. Purification by flash chromatography (pentane:EtOAc – 6:4) afforded *syn*-chlorohydrin **40d** (0.980 g, 44 % yield) as a white solid.



40d

Data for *syn*-diol, *syn*-chlorohydrin **40d**: **$[\alpha]_D^{20}$** = - 9.3 (*c* = 6.63 in $CHCl_3$); IR (neat): υ = 3380, 2965, 2872, 1217, 1088, 996, 749, 665, 617 cm^{-1}; **1H NMR** (400 MHz, $CDCl_3$) δ 3.99 - 3.86 (m, 3H), 3.78 (ddd, *J* = 7.6, 6.4, 3.2 Hz, 1H), 3.65 (m, *J* = 7.5, 3.2 Hz, 1H), 3.41-3.33 (m, 2H), 3.18 (d, *J* = 6.4 Hz, 1H), 3.08 (dd, *J* = 11.0 Hz, 1H), 2.17 (m, *J* = 6.7 Hz, 1H), 2.01 - 1.89 (m, 2H), 1.65 (m, 1H), 1.06 (d, *J* = 6.7 Hz, 3H), 1.02 (d, *J* = 6.7 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 74.2, 72.7, 71.5, 67.6, 66.5, 46.5, 34.8, 31.8, 20.4, 19.8.

HRMS (ESI) m/z calcd for $C_{10}H_{20}{}^{35}ClO_3$ $[M+H]^+$ 223.1095, found 223.1082

m.p.: 68 - 72°C

Determination of relative stereochemistry for chlorohydrin **40**

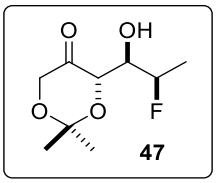
Following General Procedure G, the chlorohydrin was converted to **80**. NOE analysis of **80** confirmed relative stereochemistry of chlorohydrin **40**.

*Determination of enantiomeric excess of chlorohydrin **40***

Following General Procedure H, PNB esters were prepared of both the racemic and enantioenriched samples of **80**. The enantiomeric PNB esters were separated by chiral HPLC using a Phenomex Lux Cellulose-3 column; flow rate 0.40 mL/min; eluent: hexanes-*i*PrOH 90:10; detection at 254 nm; retention time = 1.57 min and 2.50 min (see chromatograms).The enantiomeric excess of the optically enriched **80** was determined using the same method (93% ee).

Preparation of aldol adduct 47

Following General Procedure B, a solution of propanal (0.050 mL, 0.687 mmol), NFSI (0.217 g, 0.687 mmol), L-proline (0.079 g, 0.687 mmol) and $NaHCO_3$ (0.058 g, 0.687 mmol) was stirred for 45 minutes at -10 °C in DMF (0.92 mL). Dioxanone **13** (0.055 mL, 0.458 mmol) in CH_2Cl_2 (8.3 mL) was then added and the reaction mixture was stirred for 48 hrs. The ratio of diastereomers was determined to be 8:1 by ^{1}H NMR spectroscopic analysis of the crude product. Purification by flash chromatography (pentane-EtOAc - 4:1) afforded *syn*-fluorohydrin **47** (0.053 g, 56 % yield) as a yellow oil.



47

Data for *syn*-fluorohydrin **47**: **$[\alpha]_D^{20}$** = -13.5 (*c* 3.42 in $CHCl_3$); **IR** (neat): υ = 3428, 2990, 1742, 1378, 1225, 1091, 864 cm^{-1};**^{1}H NMR** (600 MHz, $CDCl_3$): δ 4.90 (dq, *J* = 47.0 Hz, 6.5 Hz, 1H), 4.38 (dd, *J* = 8.5, 1.4 Hz, 1H), 4.30 (dd, *J* = 17.6, 1.5 Hz, 1H), 4.08 (d, *J* = 17.6, 1H), 3.75 (ddd, *J* = 26.1, 2.5, 2.5, 1H), 3.29 (d, *J* = 2.7), 1.50 (s, 3H), 1.43 (s, 3H), 1.43 (dd, *J* = 24.0, 6.6 Hz, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 212.1, 101.6, 88.0 (d, *J* = 171.0 Hz) , 72.3 (d, *J* = 17.7 Hz), 72.0 (d, *J* = 5.1 Hz), 66.8, 23.7, 23.7, 16.4 (d, *J* = 22.9 Hz); **^{19}F NMR** (470 MHz, $CDCl_3$): δ -195.5

HRMS (EI^+) calcd for $[C_9H_{16}FO_4]^+$ 207.1027; found 207.1054

Determination of relative stereochemistry for fluorohydrin **47**

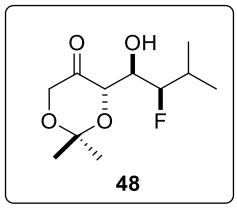
Following General Procedure H, the fluorohydrin **47** (0.105 g, 0.449 mmol) was converted into the corresponding *bis*-PNB ester (**47**-**XRD**). Recyrstallization in ethanol allowed for the relative stereochemistry to be assigned using single X-ray crystallography (see X-ray structures).

Determination of enantiomeric excess of fluorohydrin **47**

Following General Procedure B, using a 1:1 mixture of L-:D- proline, a racemic sample of the fluorohydrin **47** was prepared. Following General Procedure H, optically enriched and racemic samples of **47** (0.040 g, 0.19 mmol) were converted into the corresponding bis-*p*-nitrobenzoate derivative. The enantiomeric *p*-nitrobenzoyl diesters were separated by chiral HPLC using a DIACEL CHIRALCEL-OD column; flow rate 1.0 mL/min; eluent: hexanes-*i*PrOH 80:20; detection at 260 nm; retention time = 28.1 min and 37.4 min (see chromatograms). The enantiomeric excess of the optically enriched *bis*-PNB derivative was determined using the same method (95% ee).

Preparation of aldol adduct 48

Following General Procedure B, a solution of 3-methylbutanal (0.050 mL, 0.465 mmol), NFSI (0.147 g, 0.465 mmol), L-proline (0.053 g, 0.465 mmol), and $NaHCO_3$ (0.039 g, 0.465 mmol) was stirred for 45 minutes at -10 °C in 0.60 mL of DMF. Dioxanone **13** (0.037 mL, 0.31 mmol) in CH_2Cl_2 (5.4 mL) was stirred for 72 hrs. The ratio of diastereomers was determined to be >20:1 by ^{1}H NMR spectroscopic analysis of the crude product. Purification by flash chromatography (pentane-EtOAc - 4:1) afforded *syn*-fluorohydrin **48** (0.049 g, 67 % yield) as a colorless oil**.**



48

Data for *syn*-fluorohydrin **48**: **$[\alpha]_D^{20}$** = -117 (*c* 2.6 in $CHCl_3$); **IR** (neat): υ = 3526, 2968, 1740, 1377, 864;^{1}**H NMR** (600 MHz, $CDCl_3$): δ 4.39 (d, *J* = 8.7 Hz, 1H), 4.30 (d, *J* = 17.8 Hz, 1H), 4.21 (dd, *J* = 46.5, 9.6 Hz, 1H), 4.08 (d, *J* = 17.6 Hz, 1H), 3.95 (dd, *J* = 28.6, 8.8 Hz, 1H), 3.26 (d, *J* = 2.5 Hz, 1H), 2.26 (m, 1H), 1.50 (s, 3H), 1.43 (s, 3H), 1.07 (d, *J* = 6.6 Hz, 3H), 0.92 (d, *J* =6.6 Hz, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 212.8, 101.6, 96.1 (d, *J* = 178.1 Hz), 71.5 (d, *J* = 6.2 Hz), 69.2 (d, *J* = 18.4 Hz), 66.7, 28.1 (d, *J* = 20.0 Hz), 23.6, 23.6, 19.1 (d, *J* = 4.8 Hz), 18.1 (d, *J* = 9.3 Hz); **^{19}F NMR** (470 MHz, $CDCl_3$): δ –203.3

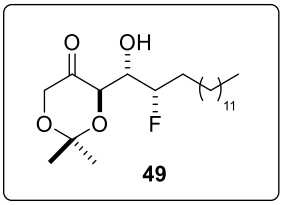
HRMS (EI^+) calcd for $[C_{11}H_{20}FO_4]^+$ 235.1340; found 235.1334

Determination of enantiomeric excess of fluorohydrin **48**

Following General Procedure B, using a 1:1 mixture of L-: D-proline, a racemic sample of the fluorohydrin **48** was prepared. Following General Procedure H, optically enriched and racemic samples of **48** (0.035 g, 0.15 mmol) were converted into the corresponding bis-*p*-nitrobenzoate derivative. The enantiomeric fluorohydrin were separated by chiral HPLC using a DIACEL CHIRALCEL-OD column; flow rate 1.0 mL/min; eluent: hexanes-*i*PrOH 93.5:6.5; detection at 260 nm; retention time = 24.94 min and 27.31 (see chromatograms). The enantiomeric excess of the optically pure *bis*-PNB derivative was determined using the same method (95 % ee).

Preparation of aldol adduct 49

Following General Procedure B, a solution of pentadecanal (0.453 g, 2.0 mmol), NFSI (0.731 g, 2.0 mmol), D-proline (0.23 g, 2.0 mmol) and $NaHCO_3$ (0.168 g, 2.0 mmol) was stirred for 3 hrs at -10 °C in DMF (2.7 mL). Dioxanone **13** (0.287 mL, 1.33 mmol) in CH_2Cl_2 (24 mL) was stirred for 48 hours. The ratio of diastereomers was determined to be 15:1 by ^{1}H NMR spectroscopic analysis of the crude product. Purification by flash chromatography (pentane-EtOAc - 30:1) afforded *syn*-fluorohydrin **49** (0.239 g, 48% yield) as a clear oil**.**



49

Data for *syn*-fluorohydrin **49**: **$[\alpha]_D^{20}$** = -83.0 (*c* 1.2 in $CHCl_3$); **IR** (neat): υ = 3530, 2924, 2854, 1740, 1337, 1224, 1090, 865 cm^{-1}; **^{1}H NMR** (600 MHz, $CDCl_3$): δ 4.66 (ddd, J = 47.3, 8.9, 4.9 Hz, 1H), 4.38 (dd, J = 8.7, 1.4 Hz, 1H), 4.30 (dd, J = 17.5, 1.4 Hz, 1H), 4.07 (d, J = 17.5 Hz, 1H), 3.79 (dddd, J = 27.1, 8.5, 3.1, 1.7 Hz, 2H), 3.31 (d, J = 3.1 Hz, 1H), 1.92 (m, 1H), 1.25-1.63 (26 H), 0.88 (dd, J =6.6, 6.6 Hz, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 212.3, 101.6, 91.5 (d, J = 174.9 Hz) , 71.7 (d, J = 5.3 Hz), 71.2 (d, J = 18.5 Hz), 66.7, 32.1, 30.4 (d, J = 21.3 Hz), 29.8, 29.8, 29.8, 29.8, 29.6, 29.6, 29.5, 25.4, 25.3, 23.6, 23.6, 22.8, 14.2; **^{19}F NMR** (470 MHz, $CDCl_3$): δ –201.9

HRMS (EI^+) calcd for $[C_{21}H_{39}FNaO_4]^+$ 397.2725; found 397.2755

Determination of relative stereochemistry for fluorohydrin **49**

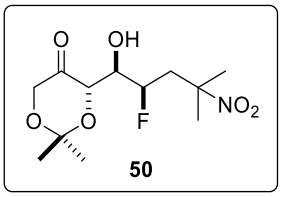
Analysis of ^{1}H-NMR of fluorohydrins **28** and **49** revealed identical signals between 1.60 and 4.70 ppm indicating the two compounds share the same relative stereochemistry.

Determination of enantiomeric excess of fluorohydrin **49**

Following General Procedure B, using a 1:1 mixture of L-:D- proline, a racemic sample of the fluorohydrin **49** was prepared. Following General Procedure H, optically enriched and racemic samples of **49** (0.050 g, 0.13 mmol) were converted into the corresponding bis-*p*-nitrobenzoate derivative. The enantiomeric p-nitrobenzoyl esters were separated by chiral HPLC using a DIACEL CHIRALCEL-OD column; flow rate 1.0 mL/min; eluent: hexanes-*i*PrOH 80:20; detection at 260 nm; retention time = 8.76 min and 12.06 min (see chromatograms). The enantiomeric excess of the optically enriched bis-*p*-nitrobenzoate derivative was determined using the same method (91% ee).

Preparation of aldol adduct 50

Following General Procedure B, a solution of 4-methyl-4-nitropentanal (0.050 mL, 0.379 mmol), NFSI (0.119 g, 0.379 mmol), L-proline (0.044 g, 0.379 mmol), and $NaHCO_3$ (0.032 g, 0.379 mmol) was stirred for 120 minutes at -10 °C in 0.50 mL of DMF. Dioxanone **13** (0.030 mL, 0.253 mmol) in CH_2Cl_2 (5.5 mL) was stirred for 72 hrs. The ratio of diastereomers was determined to be >20:1 by ^{1}H NMR spectroscopic analysis of the crude product. Purification by flash chromatography (pentane-EtOAc - 3:1) afforded *syn*-fluorohydrin **50** (0.034 g, 46 % yield) as a colorless oil**.**



Data for *syn*-fluorohydrin **50**: **$[\alpha]_D^{20}$** = -71.6 (*c* 1.9 in $CHCl_3$); **IR** (neat): υ = 3515, 2989, 1741, 1540, 1376, 861, cm^{-1};**^{1}H NMR** (500 MHz, $CDCl_3$): δ 4.77 (ddd, *J* = 48.7, 10.0, 1.0 Hz, 1H), 4.35 (dd, *J* = 9.0, 1.3 Hz, 1H), 4.30 (dd, *J* = 17.7, 1.4 Hz, 1H), 4.08 (d, *J* = 17.7 Hz, 1H), 3.76 (dddd, *J* = 27.4, 8.9, 2.3, 2.3 Hz, 1H), 3.43 (d, *J* = 2.3 Hz, 1H), 2.57 (m, 1H), 2.30 (m, 1H), 1.69 (s, 3H), 1.67 (s, 3H), 1.48 (s, 3H), 1.40 (s, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 212.5, 101.8, 87.9 (d, *J* = 176.9 Hz), 87.1, 72.2 (d, *J* = 18.6 Hz), 71.2 (d, *J* = 5.5 Hz) 66.5, 41.3 (d, *J* = 20.5 Hz), 28.0, 25.4, 23.6, 23.5; **^{19}F NMR** (470 MHz, $CDCl_3$): δ –201.4

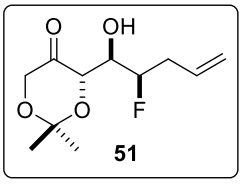
HRMS (EI^+) calcd for $[C_{12}H_{21}FNO_6]^+$ 294.1347; found 294.1359

Determination of enantiomeric excess of fluorohydrin **50**

Following General Procedure B, using a 1:1 mixture of L-:D- proline, a racemic sample of the fluorohydrin **50** was prepared. Following General Procedure H, optically enriched and racemic samples of **50** (0.050 g, 0.171 mmol) were converted into the corresponding bis-*p*-nitrobenzoate derivative. The enantiomeric fluorohydrin were separated by chiral HPLC using a DIACEL CHIRALCEL-OD column; flow rate 1.5 mL/min; eluent: hexanes-*i*PrOH 80:20; detection at 260 nm; retention time = 34.51 min and 37.98 (see chromatograms). The enantiomeric excess of the optically pure bis-*p*-nitrobenzoate derivative was determined using the same method (95% ee).

Preparation of aldol adduct 51

Following General Procedure B, a solution of pentenal (0.050 g, 0.60 mmol), NFSI (0.189 g, 0.60 mmol), L-proline (0.069 g, 0.60 mmol) and $NaHCO_3$ (0.055 g, 0.60 mmol) was stirred at -10 °C in DMF (0.80 mL) for 1 hr. Dioxanone **13** (0.048 mL, 0.40 mmol) in CH_2Cl_2 (7.2 mL) was stirred for 72 hours. The ratio of diastereomers was determined to be 5:1 by ^{1}H NMR spectroscopic analysis of the crude product. Purification by flash chromatography (pentane-EtOAc - 85:15) afforded *syn*-fluorohydrin **51** (0.059 g, 64 % yield) as a light yellow oil**.**



Data for *syn*-fluorohydrin **51**: **$[\alpha]_D^{20}$** = -115.8 (*c* 2.46 in $CHCl_3$); **IR** (neat): υ = 3509, 2989, 1740, 1643, 1422, 1377, 1089, 863 cm^{-1}; **^{1}H NMR** (600 MHz, $CDCl_3$): δ 5.83 (m, 1H), 5.20 (d, *J* = 17.4 Hz, 1H), 5.14 (d, *J* = 9.9, 1.0 Hz, 1H), 4.73 (dddd, *J* = 47.0, 7.0, 7.0, 1.3 Hz, 1H), 4.39 (dd, *J* = 8.9, 1.0 Hz, 1H), 4.30 (dd, *J* = 17.7, 1.0 Hz), 4.08 (d, *J* = 17.6), 2.69 (m, 1H), 2.48 (m, 1H) 1.49 (s, 3H), 1.43 (s, 3H);**^{13}C NMR** (150 MHz, $CDCl_3$): δ 212.4, 133.0 (d, *J* = 7.6 Hz), 118.5, 101.6, 90.5 (d, *J*

= 178.0 Hz), 71.5 (d, *J* = 5.3 Hz), 70.5 (d, *J* = 18.2 Hz), 66.6, 34.9 (d, *J* = 22.2 Hz), 23.6, 23.6; **^{19}F NMR** (470 MHz, $CDCl_3$): δ –201.6

HRMS (EI^+) calcd for $[C_{11}H_{18}FO_4]^+$ 233.1184; found 233.1202

Determination of relative stereochemistry for fluorohydrin **51**

Following General Procedure I, the fluorohydrin **51** (0.105 g, 0.45 mmol) was converted to the fluorohydrin **28**. Comparison of ^{1}H and ^{19}F NMR with fluorohydrin **28** confirmed relative stereochemistry.

Determination of the absolute stereochemistry for fluorohydrin **51**

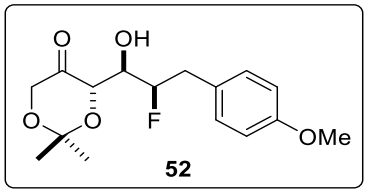
Following General Procedure I, the fluorohydrin **51** (0.105 g, 0.45 mmol) was converted to the fluorohydrin **28**. Comparison of $[\alpha]_D$ values with fluorohydrin **28** confirmed absolute stereochemistry

Determination of enantiomeric excess of fluorohydrin **51**

Following General Procedure I, the optically enriched sample of **51** (0.105 g, 0.45 mmol) was converted into fluorohydrin **28**. Following General Procedure H, the optically enriched and racemic samples of fluorohydrin **28** were converted into their corresponding bis-*p*-nitrobenzoate derivative. The enantiomeric *p*-nitrobenzoyl diesters were separated by chiral HPLC using a DIACEL CHIRALCEL-OD column; flow rate 1.0 mL/min; eluent: hexanes-*i*PrOH 80:20; detection at 260 nm; retention time = 17.27 min and 22.06 min (see chromatograms). The enantiomeric excess of the optically enriched bis-*p*-nitrobenzoate derivative was determined using the same method (93 % ee).

Preparation of aldol adduct 52

Following General Procedure B, a solution of 3-(4-methoxyphenyl)propanal (0.050 mL, 0.317 mmol), NFSI (0.100 g, 0.317mmol), L-proline (0.037 g, 0.317 mmol), and $NaHCO_3$ (0.027 g, 0.317 mmol) was stirred for 90 minutes at -10 °C in 0.43 mL of DMF. Dioxanone **13** (0.025 mL, 0.211 mmol) in CH_2Cl_2 (3.8 mL) was stirred for 72 hrs. The ratio of diastereomers was determined to be >20:1 by ^{1}H NMR spectroscopic analysis of the crude product. Purification by flash chromatography (pentane-EtOAc - 4:1) afforded *syn*-fluorohydrin **52** (0.034 g, 51 % yield) as a white solid**.**



52

Data for *syn*-fluorohydrin **52**: $[\alpha]_D^{20}$ = -233.4 (*c* 3.0 in $CHCl_3$); ^{1}**H NMR** (600 MHz, $CDCl_3$): δ 7.20 (d, *J* = 8.8 Hz, 2H), 6.86 (d, *J* = 8.8Hz, 2H) 4.81 (dddd, *J* = 46.8, 7.3, 7.3 Hz, 0.8 Hz, 1H), 4.40 (d, *J* = 8.8 Hz, 1H), 4.26 (d, *J* = 17.8 Hz, 1H), 4.07 (d, *J* = 17.8 Hz, 1H), 3.79 (s, 3H), 3.77 (d, *J* = 24.1, 8.8 Hz, 1H), 3.39 (br s, 1H), 3.15 (m, 1H), 2.99 (m, 1H), 1.46 (s, 3H), 1.39 (s, 3H); ^{13}**C NMR** (150 MHz, $CDCl_3$): δ 212.7, 158.6, 130.6, 128.9 (d, *J* = 8.0 Hz), 114.1, 101.7, 91.9 (d, *J* = 179.2 Hz), 71.4 (d, *J* = 5.1 Hz), 70.1 (d, *J* =18.1 Hz), 66.6, 55.4, 35.8 (d, *J* = 22.4 Hz), 23.6, 23.5; ^{19}**F NMR** (470 MHz, $CDCl_3$): δ –200.1

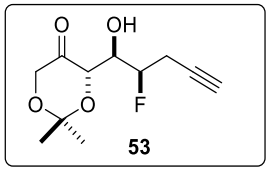
HRMS (EI$^+$) calcd for $[C_{16}H_{22}FO_5]^+$ 313.1446; found 313.1450

Determination of enantiomeric excess of fluorohydrin **52**

Following General Procedure B, using a 1:1 mixture of L-:D- proline, a racemic sample of the fluorohydrin **52** was prepared. Following General Procedure H, optically enriched and racemic samples of **52** (0.040 g, 0.128 mmol) were converted into the corresponding bis-*p*-nitrobenzoate derivative. The enantiomeric fluorohydrin were separated by chiral HPLC using a DIACEL CHIRALCEL-OD column; flow rate 1.5 mL/min; eluent: hexanes-*i*PrOH 93.5:6.5; detection at 260 nm; retention time = 74.8 min and 110.4 min (see chromatograms). The enantiomeric excess of the optically pure bis-*p*-nitrobenzoate derivative was determined using the same method (95% ee).

Preparation of aldol adduct 53

Following General Procedure B, a solution of pentynal (0.050 g, 0.61 mmol), NFSI (0.192 g, 0.61 mmol), L-proline (0.070 g, 0.61 mmol) and $NaHCO_3$ (0.051 g, 0.61 mmol) was stirred for 1.5 hrs at -10°C in DMF (0.81 mL). Dioxanone **13** (0.049 mL, 0.41 mmol) in CH_2Cl_2 (7.3 mL) was stirred for 48 hours. The ratio of diastereomers was determined to be 4.5:1 by ^{1}H NMR spectroscopic analysis of the crude product. Purification by flash chromatography (pentane-EtOAc - 9:1) afforded *syn*-fluorohydrin **53** (0.052 g, 55 % yield) as a light yellow oil**.**



53

Data for *syn*-fluorohydrin **53**: $[\alpha]_D^{20}$ = -62.9 (*c* 3.42 in $CHCl_3$); **IR** (neat): υ = 3512, 3293, 2993, 1743, 1378, 1224, 1033 cm^{-1}; ^{1}**H NMR** (500 MHz, $CDCl_3$): δ 4.86 (dddd, *J* = 46.4, 7.3, 7.3, 1.5 Hz, 1H), 4.38 (dd, *J* = 8.9, 1.5 Hz, 1H), 4.31 (dd, *J* = 17.6, 1.6 Hz, 1H), 4.10 (d, *J* = 17.7 Hz, 1H), 4.00 (ddd, *J* = 27.9, 9.1, 1.5 Hz, 1H), 2.76 (m, 2H), 2.04 (t, *J* = 2.8 Hz, 1H), 1.49 (s, 3H), 1.43

(s, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 212.2, 101.7, 89.0 (d, *J* = 180.0 Hz), 79.0 (d, *J* = 15.4 Hz), 71.3 (d, *J* = 5.1 Hz), 70.8, 69.7 (d, *J* = 17.4 Hz), 66.6, 23.7, 23.6, 20.4 (d, *J* = 28.9 Hz); **^{19}F NMR** (470 MHz, $CDCl_3$): δ –200.1

HRMS (EI^+) calcd for $[C_{11}H_{16}FO_4]^+$ 231.1027; found 231.1042

Determination of relative stereochemistry for fluorohydrin **53**

Following General Procedure **I**, the fluorohydrin **53** (0.10 g, 0.43 mmol) was converted to the fluorohydrin **28**. Comparison of ^{1}H and ^{19}F NMR with fluorohydrin **28** confirmed relative stereochemistry.

Determination of the absolute stereochemistry for fluorohydrin **53**

Following General Procedure **F**, the fluorohydrin **53** (0.10 g, 0.43 mmol) was converted to the fluorohydrin **28**. Comparison of $[\alpha]_D$ values with fluorohydrin **28** confirmed absolute stereochemistry.

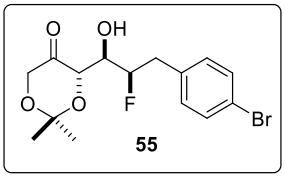
*Determination of enantiomeric excess of fluorohydrin **53***

Following General Procedure **I**, the optically enriched sample of **53** (0.10 g, 0.43 mmol) was converted into fluorohydrin **28**. Following General Procedure **H**, the optically enriched and racemic samples of fluorohydrin **28** were converted into their corresponding bis-p-nitrobenzoate derivative. The enantiomeric p-nitrobenzoyl diesters were separated by chiral HPLC using a DIACEL CHIRALCEL-OD column; flow rate 1.0 mL/min; eluent: hexanes-iPrOH 80:20; detection at 260 nm; retention time = 17.27 min and 22.06 min (see chromatograms). The enantiomeric excess of the optically enriched bis-p-nitrobenzoate derivative was determined using the same method (92% ee).

Preparation of aldol adduct 54

Following General Procedure B, a solution of 3-(4-bromophenyl)propanal (0.050 g, 0.236 mmol), NFSI (0.074 g, 0.236 mmol), L-proline (0.028 g, 0.236 mmol), and $NaHCO_3$ (0.020 g, 0.236 mmol) was stirred for 120 minutes at -10 °C in 0.30 mL of DMF. Dioxanone **13** (0.022 mL, 0.157 mmol) in CH_2Cl_2 (2.8 mL) was stirred for 72 hrs. The ratio of diastereomers was determined to be >20:1 by ^{1}H NMR spectroscopic analysis of the crude product. Purification by

flash chromatography (pentane-EtOAc - 4:1) afforded *syn*-fluorohydrin **55** (0.034 g, 61 % yield) as a white solid**.**



Data for *syn*-fluorohydrin **55** $[\alpha]_D^{20}$ = -76.4 (*c* 0.8 in $CHCl_3$); **IR** (neat): υ = 3513, 2989, 1740, 1490, 1377, 864cm^{-1};**^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.44 (d, *J* = 8.2 Hz), 7.16 (d, *J* = 8.2 Hz), 4.80 (ddd, *J* = 46.8, 7.2, 7.2, 0.9 Hz, 1H), 4.40 (d, *J* = 18.9 Hz, 1H), 4.27 (d, *J* = 17.7 Hz, 1H), 4.08 (d, *J* = 17.7 Hz, 1H), 3.75 (dd, *J* = 27.6, 9.0 Hz, 1H), 3.42 (br s, 1H), 3.18 (m, 1H), 2.97 (m, 1H), 1.46 (s, 3H), 1.39 (s, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 212.6, 136.0 (d, *J* = 7.2 Hz), 131.8, 131.4, 120.8, 101.7, 91.4 (d, *J* = 179.9 Hz) , 71.3 (d, *J* = 5.0 Hz), 70.2 (d, *J* = 17.1 Hz), 66.6, 36.2 (d, *J* = 22.4 Hz), 23.6, 23.5; **^{19}F NMR** (470 MHz, $CDCl_3$): δ –200.6

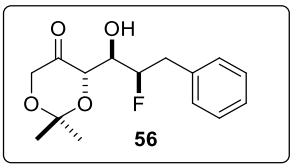
HRMS (EI^+) calcd for $[C_{15}H_{19}{}^{79}BrFO_4]^+$ 361.0445; found 361.0434

Determination of enantiomeric excess of fluorohydrin **55**

Following General Procedure B, using a 1:1 mixture of L-:D- proline, a racemic sample of the fluorohydrin **55** was prepared. Following General Procedure H, optically enriched and racemic samples of **55** (0.037 g, 0.103 mmol) were converted into the corresponding bis-*p*-nitrobenzoate derivative. The enantiomeric fluorohydrin were separated by chiral HPLC using a DIACEL CHIRALCEL-OD column; flow rate 1.0 mL/min; eluent: hexanes-*i*PrOH 80:20; detection at 260 nm; retention time = 52.3 min and 63.5 min (see chromatograms). The enantiomeric excess of the optically pure bis-*p*-nitrobenzoate derivative was determined using the same method (95% ee).

Preparation of aldol adduct 56

Following General Procedure B, a solution of hydrocinnamaldehyde (0.050 mL, 0.38 mmol), NFSI (0.120 g, 0.38 mmol), L-proline (0.044 g, 0.38 mmol), and $NaHCO_3$ (0.032 g, 0.38 mmol) was stirred for 75 minutes at -10 °C in 0.50 mL of DMF. Dioxanone **13** (0.036 mL, 0.30 mmol) in CH_2Cl_2 (4.5 mL) was stirred for 72 hrs. The ratio of diastereomers was determined to be >15:1 by ^{1}H NMR spectroscopic analysis of the crude product. Purification by flash chromatography (pentane-EtOAc - 4:1) afforded *syn*-fluorohydrin **56** (0.053 g, 62 % yield, d.r. > 15:1) as a colorless oil**.**



56

Data for *syn*-fluorohydrin **56**: $[\alpha]_D^{20}$ = -3.1 (*c* 2.1 in $CHCl_3$); **IR** (neat): υ = 3511, 2923, 1739, 1705, 1650, 1585, 1453, 863, 698 cm^{-1};[1]**H NMR** (600 MHz, $CDCl_3$): δ 7.30 (m, 5H), 4.87 (ddd, *J* = 46.5, 7.0, 7.0 Hz, 1H), 4.42 (dd, *J* = 9.0, 0.9 Hz, 1H), 4.27 (dd, *J* = 17.7, 1.0 Hz, 1H), 4.08 (d, *J* = 17.6 Hz, 1H), 3.79 (dd, *J* = 27.6, 9.0 Hz, 1H), 3.42 (br s, 1H), 3.24 (m, 1H), 3.05 (m, 1H), 1.48 (s, 3H), 1.40 (s, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 212.6, 136.9 (d, *J* = 8.1 Hz), 129.6, 128.7, 126.8, 101.7, 91.7 (d, *J* = 177.8 Hz) , 71.4 (d, *J* = 5.2 Hz), 70.2 (d, *J* = 18.1 Hz), 66.6, 36.7 (d, *J* = 22.4 Hz), 23.6, 23.5; **^{19}F NMR** (470 MHz, $CDCl_3$): δ –200.1

HRMS (EI^+) calcd for $[C_{15}H_{20}FO_4]^+$ 283.1340; found 283.1365

Determination of relative stereochemistry for fluorohydrin **56**

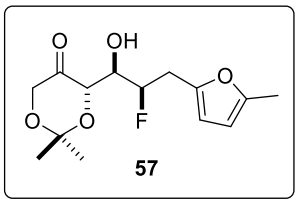
Reduction with sodium borohydride of the fluorohydrin **56** (0.105 g, 0.37 mmol) in methanol allowed for conversion to the corresponding *syn*-diol **56-XRD**. Recyrstallization in ethanol (1:1) allowed for the relative stereochemistry to be assigned using single X-ray crystallography (see X-ray structures)

Determination of enantiomeric excess of fluorohydrin **56**

Following General Procedure B, using a 1:1 mixture of L-:D- proline, a racemic sample of the fluorohydrin **56** was prepared. The enantiomeric fluorohydrin were separated by chiral HPLC using a DIACEL CHIRALCEL-OD column; flow rate 1.5 mL/min; eluent: hexanes-*i*PrOH 97:3; detection at 260 nm; retention time = 12.80 min and 13.64 min (see chromatograms). The enantiomeric excess of the optically pure **56** was determined using the same method (98% ee).

Preparation of aldol adduct 57

Following General Procedure B, a solution of 3-(5-methylfuran-2-yl)propanal (0.050 mL, 0.376 mmol), NFSI (0.119 g, 0.376 mmol), L-proline (0.029 g, 0.376 mmol), and $NaHCO_3$ (0.032 g, 0.376 mmol) was stirred for 90 minutes at -10 °C in 0.50 mL of DMF. Dioxanone **13** (0.030 mL, 0.251 mmol) in CH_2Cl_2 (4.5 mL) was stirred for 72 hrs. The ratio of diastereomers was determined to be >20:1 by ^{1}H NMR spectroscopic analysis of the crude product. Purification by flash chromatography (pentane-EtOAc - 5:1) afforded *syn*-fluorohydrin **57** (0.038 g, 53 % yield) as a colorless oil**.**



57

Data for *syn*-fluorohydrin **57**: **$[\alpha]_D^{20}$** = 16.4 (*c* 2.5 in $CHCl_3$); ^{1}**H NMR** (600 MHz, $CDCl_3$): δ 6.02 (d, *J* = 3.1 Hz, 1H), 5.88 (d, *J* = 3.1 Hz, 1H), 4.95 (ddd, *J* = 46.8, 6.9, 6.9 Hz, 1H), 4.41 (d, *J* = 9.0 Hz, 1H), 4.29 (d, *J* = 17.6 Hz, 1H), 4.08 (d, *J* = 17.6 Hz, 1H), 3.82 (dd, *J* = 27.4, 8.8 Hz, 1H), 3.34 (d, *J* = 1.5 Hz, 1H), 3.18 (m, 1H), 3.06 (m, 1H), 2.26 (s, 3H), 1.49 (s, 3H), 1.42 (s, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 212.4, 151.4, 149.0 (d, *J* = 9.5 Hz), 108.3, 106.4, 101.7, 89.4 (d, *J* = 179.3 Hz) , 71.4 (d, *J* = 5.1 Hz), 70.4 (d, *J* = 17.7 Hz), 66.6, 29.5 (d, *J* = 25.2 Hz), 23.6, 23.6, 13.7; **^{19}F NMR** (470 MHz, $CDCl_3$): δ –201.2

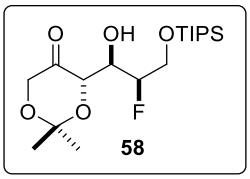
HRMS (EI^+) calcd for $[C_{14}H_{20}FO_5]^+$ 287.1289; found 287.1289

Determination of enantiomeric excess of fluorohydrin **57**

Following General Procedure B, using a 1:1 mixture of L-:D- proline, a racemic sample of the fluorohydrin **57** was prepared. Following General Procedure H, optically enriched and racemic samples of **57** (0.043 g, 0.15 mmol) were converted into the corresponding bis-*p*-nitrobenzoate derivative. The enantiomeric fluorohydrin were separated by chiral HPLC using a DIACEL CHIRALCEL-OD column; flow rate 1.5 mL/min; eluent: hexanes-*i*PrOH 93.5:6.5; detection at 260 nm; retention time = 30.00 min and 40.48 min (see chromatograms). The enantiomeric excess of the optically pure bis-*p*-nitrobenzoate derivative was determined using the same method (95% ee).

Preparation of aldol adduct 58

A solution of 3-OTIPS-propanal (1.152 g, 5.0 mmol, 1.5 equiv.), Selectfluor (1.77 g, 5.0 mmol, 1.5 equiv.), and L-proline (0.576 g, 5.0 mmol, 1.5 equiv.) were dissolved in 50 mL DMF (0.1 M) and stirred at 4 °C for 3 hrs or until the reaction was complete as determined by TLC analysis. The reaction mixture was diluted with 500 mL of diethyl ether and washed 3 x H_2O (100 mL). The organic layer was removed, dried over $MgSO_4$, and concentrated under reduced pressure. Dioxanone **13** (0.434 g, 3.33 mmol, 1.0 equiv.) and L-proline (0.306 g, 2.7 mmol, 0.8 equiv.) were added to the crude α-fluoroaldehyde in 25 mL of CH_2Cl_2 (0.2 M). After 48 hours, the reaction mixture was diluted with CH_2Cl_2 and washed with H_2O. The ratio of diastereomers was determined to be >20:1 by ^{1}H NMR spectroscopic analysis of the crude product. Purification by flash chromatography (pentane-EtOAc - 20:1) afforded *syn*-fluorohydrin **58** (0.692 g, 55 % yield) as a colorless oil**.**



58

Data for *syn*-fluorohydrin **58**: $[\alpha]_D^{20}$ = -25.6 (*c* 5.0 in $CHCl_3$); **IR** (neat): υ = 3503, 2994, 2867, 1741, 1224, 1094, 883 cm^{-1}; **^{1}H NMR** (600 MHz, $CDCl_3$): δ 4.75 (dddd, *J* = 47.1, 5.7, 5.7, 1.9 Hz, 1H), 4.41 (dd, *J* = 8.5, 1.4 Hz, 1H), 4.31 (dd, *J* = 17.5, 1.4 Hz, 1H), 4.08 (d, *J* = 17.6 Hz, 1H), 4.05 (ddd, *J* = 27.4, 9.4, 1.7 Hz, 2H), 4.02 (dd, *J* = 18.5, 5.5 Hz, 1H), 3.33 (br s, 1H), 1.50 (s, 3H), 1.44 (s, 3H), 1.07 (m, 21H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 211.7, 101.6, 91.0 (d, *J* = 178.1 Hz) , 71.7 (d, *J* = 5.2 Hz), 69.6 (d, *J* = 18.2 Hz), 66.8, 62.4 (d, *J* = 27.4 Hz), 23.7, 23.7, 18.1, 12.1; **^{19}F NMR** (470 MHz, $CDCl_3$): δ –209.0

HRMS (EI^+) calcd for $[C_{18}H_{36}FO_5Si]^+$ 379.2311; found 379.2343

Determination of the absolute stereochemistry for fluorohydrin **58**

Following General Procedure H, the fluorohydrin **58** (0.050 g, 0.13 mmol) was converted into the corresponding bis-*p*-bromobenzoate derivative **58-XRD**. Recyrstallization in dichloromethane and ethanol (1:1) allowed for the absolute stereochemistry to be assigned using single X-ray crystallography (see X-ray structures).

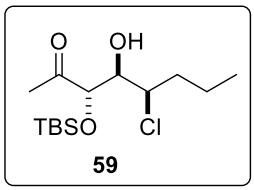
Determination of enantiomeric excess of fluorohydrin **58**

Following General Procedure B, using a 1:1 mixture of L-:D- proline, a racemic sample of the fluorohydrin **58** was prepared. Following General Procedure H, optically enriched and racemic samples of **58** (0.050 g, 0.13 mmol) were converted into the corresponding bis-*p*-nitrobenzoate derivative. The enantiomeric p-nitrobenzoyl diesters were separated by chiral HPLC using a DIACEL CHIRALCEL-OD column; flow rate 1.0 mL/min; eluent: hexanes-*i*PrOH 80:20; detection at 260 nm; retention time = 6.26 min and 8.33 min (see chromatograms). The enantiomeric excess of the optically enriched bis-*p*-nitrobenzoate derivative was determined using the same method (99 % ee).

Preparation of chlorohydrin 59

Following General Procedure A, valeraldehyde (0.054 mL, 0.50 mmol) was added to a mixture of NCS (71 mg, 0.53 mmol) and L-proline (46 mg, 0.40 mmol) in CH_2Cl_2 (0.9 mL) at 0°C and the resulting reaction mixture was stirred for 1 hr. O-TBS-hydroxyacetone (282 mg, 1.5 mmol) in DMSO (0.1 mL) and H_2O (10 µL) were then added and the resulting reaction mixture was stirred for 24 hrs at room temperature. The ratio of diastereomers was determined to be >20:1 by ^{1}H

NMR spectroscopic analysis of the crude product. Purification by flash chromatography (5-10-15% EtOAc in hexanes) afforded *syn*-chlorohydrin **59** (0.044 g, 27 % yield) as a pale yellow oil**.**



59

Data for *syn*-chlorohydrin **59**: **$[\alpha]_D^{20}$** = - 0.8 (*c* = 1.3 in $CHCl_3$)**; IR** (neat): υ = 3446, 2958, 2931, 1716, 1254, 1099, 837, 778, 672 cm^{-1}; **^{1}H NMR** (400 MHz, CDCl3) δ 4.28 (ddd, *J* = 9.2, 5.2, 1.8 Hz, 1H), 3.97 (d, *J* = 8.5 Hz, 1H), 3.67 (ddd, *J* = 10.3, 8.5, 1.7 Hz, 1H), 2.23 (s, 3H), 2.08 (d, *J* = 10.5 Hz, 1H), 1.92 (m, J = 4.6, 9.3, 14.3 Hz, 1H), 1.78 (dddd, *J* = 14.0, 8.9, 6.7, 5.3 Hz, 1H), 1.54 (m, 2H), 0.96 (dd, *J* = 7.4, 7.4 Hz, 3H), 0.91 (s, 9H), 0.12 (s, 3H), 0.05 (s, 3H) **^{13}C NMR** (100 MHz, CDCl3) δ 209.5, 79.1, 74.4, 63.8, 37.0, 25.6, 25.4, 19.9, 18.0, 13.2, -4.8, -5.1

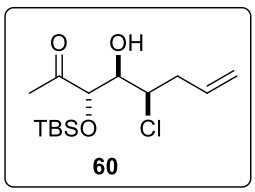
HRMS: (ESI) m/z calcd for $C_{14}H_{33}{}^{35}ClO_3NSi$ $[M+NH_4]^+$ 326.1913, found 326.1889

*Determination of enantiomeric excess of chlorohydrin **59***

Following General Procedure H, PNB esters were prepared of both the racemic and enantioenriched samples. The enantiomeric PNB esters were separated by chiral HPLC using a Phenomex Lux i-Cellulose-5 column; flow rate 0.20 mL/min; eluent: hexanes-*i*PrOH 97:3; detection at 254 nm; retention time = 2.61 min and 3.30 min (see chromatograms).The enantiomeric excess of the optically enriched **59** was determined using the same method (97% ee).

Preparation of chlorohydrin 60

Following General Procedure A, 4-pentenal (0.042 mg, 0.50 mmol) was added to a mixture of NCS (71 mg, 0.53 mmol) and L-proline (46 mg, 0.40 mmol) in CH_2Cl_2 (0.9 mL) at 0°C and the resulting reaction mixture was stirred for 1 hr. O-TBS-hydroxyacetone (282 mg, 1.5 mmol) in DMSO (0.1 mL) and H_2O (10 µL) were then added and the resulting reaction mixture was stirred for 24 hrs at room temperature. The ratio of diastereomers was determined to be 3:1 by ^{1}H NMR spectroscopic analysis of the crude product. Purification by flash chromatography (pentane-EtOAc - 8:2) afforded *syn*-chlorohydrin **60** (0.051 g, 33 % yield) as a clear oil.



60

Data for *syn*-chlorohydrin **60**: **$[\alpha]_D^{20}$** = - 27.7 (*c* = 1.84 in $CHCl_3$); **IR** (neat): υ = 3443, 2955, 2929, 2858, 1716, 1641, 1255, 1097, 837, 778 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 5.83 (dd, *J* = 10.2, 6.9, Hz, 1H), 5.20 (m, 2H), 4.26 (dd, *J* = 7.2, 1.9 Hz, 1H), 3.97 (d, *J* = 8.5 Hz, 1H), 3.73 (m, *J* = 10.3,

8.5 1.9 Hz, 1H), 2.65 (m, 2H), 2.23 (s, 3H), 2.09 (d, *J* = 10.3 Hz, 1H), 0.92 (s, 9H), 0.12 (s, 3H), 0.05 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 209.4, 133.6, 118.5, 78.9, 73.8, 62.8, 39.3, 25.6, 25.4, 18.0, -4.9, -5.1

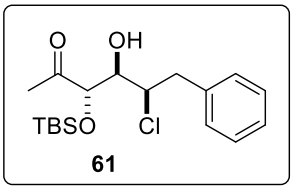
HRMS (ESI) m/z calcd for $C_{14}H_{28}{}^{35}ClO_3Si$ $[M+H]^+$ 307.1491, found 307.1504

*Determination of enantiomeric excess of chlorohydrin **60***

Following General Procedure H, PNB esters were prepared of both the racemic and enantioenriched samples. The enantiomeric PNB esters were separated by chiral HPLC using a Phenomex Lux i-Cellulose-5 column; flow rate 0.40 mL/min; eluent: hexanes-*i*PrOH 95:5; detection at 254 nm; retention time = 1.18 min and 1.50 min (see chromatograms).The enantiomeric excess of the optically enriched **60** was determined using the same method (95% ee).

Preparation of aldol adduct 61

Following General Procedure A, 4-phenylbutanal (0.074 mg, 0.50 mmol) was added to a mixture of NCS (71 mg, 0.53 mmol) and L-proline (46 mg, 0.40 mmol) in CH_2Cl_2 (0.9 mL) at 0°C and the resulting reaction mixture was stirred for 1 hr. O-TBS-hydroxyacetone (282 mg, 1.5 mmol) in DMSO (0.1 mL) and H_2O (10 µL) were then added and the resulting reaction mixture was stirred for 24 hrs at room temperature. The ratio of diastereomers was determined to be 4:1 by ^{1}H NMR spectroscopic analysis of the crude product. Purification by flash chromatography (pentane-EtOAc - 9:1) afforded *syn*-chlorohydrin **61** (0.108 g, 56 % yield) as a white solid.



61

Data for *syn*-chlorohydrin **61**: **$[\alpha]_D^{20}$** = - 9.7 (*c* = 2.0 in $CHCl_3$); **IR** (neat): υ = : 3362, 2958, 2927, 2856, 1708, 1104, 1074, 834, 698 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.28 (m, 2H), 7.21 (m, 3H), 4.15 (ddd, *J* = 10.2, 4.0, 1.6, Hz, 1H), 3.94 (d, *J* = 8.6 Hz , 1H), 3.63 (ddd, J =10.4, 8.5, 1.6 Hz, 1H), 2.91 (ddd, *J* = 12.9, 7.5, 5.0, Hz, 1H), 2.78 (ddd, *J* = 13.9, 8.6, 7.3, Hz, 1H), 2.29 (dddd, J = 14.3, 10.3, 7.4, 5.0 Hz, 1H), 2.20 (s, 3H), 2.13 (d, *J* = 11.0 Hz, 1H), 2.07 (m, 1H), 0.80 (s, 9H), 0.00 (s, 6H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 209.4, 140.3, 128.6, 128.6, 126.3, 79.0, 75.0, 63.1, 36.5, 32.5, 25.6, 25.3, 17.9, -4.9, -5.3

HRMS (ESI) m/z calcd for $C_{19}H_{25}{}^{35}ClO_3NSi$ $[M+NH_4]^+$ 388.2069, found 388.2041

m.p.: 70-73°C

Determination of relative stereochemistry for chlorohydrin **61**

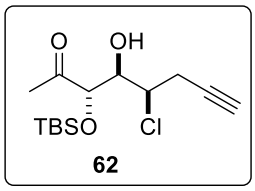
Following General Procedure G, the chlorohydrin **61** was converted to THF **81**. NOE analysis of THF **81** confirmed relative stereochemistry of chlorohydrin **61**.

*Determination of enantiomeric excess of chlorohydrin **61***

Following General Procedure H, PNB esters were prepared of both the racemic and enantioenriched samples. The enantiomeric PNB esters were separated by chiral HPLC using a Phenomex Lux Amylose-5 column; flow rate 0.40 mL/min; eluent: hexanes-*i*PrOH 95:5; detection at 254 nm; retention time = 3.24 min and 3.71 min (see chromatograms).The enantiomeric excess of the optically enriched **61** was determined using the same method (97% ee).

Preparation of chlorohydrin 62

Following General Procedure A, 4-pentynal (41 mg, 0.5 mmol) was added to a mixture of NCS (71 mg, 0.53 mmol) and L-proline (46 mg, 0.40 mmol) in CH_2Cl_2 (0.9 mL) at 0°C and the resulting reaction mixture was stirred for 1 hr. O-TBS-hydroxyacetone (282 mg, 1.5 mmol) in DMSO (0.1 mL) and H_2O (10 µL) were then added and the resulting reaction mixture was stirred for 24 hrs at room temperature. The ratio of diastereomers was determined to be 4:1 by ^{1}H NMR spectroscopic analysis of the crude product. Purification by flash chromatography (pentane-EtOAc; 7:3) afforded *syn*-chlorohydrin **62** (0.075 g, 49 % yield) as a clear oil.



62

Data of *syn*-chlorohydrin **62**: **$[\alpha]_D^{20}$ =** - 34.3 (*c* = 0.80 in $CHCl_3$);); **IR** (neat): υ = 3450, 3311, 2954, 2929, 1716, 1255, 1101, 837, 778, 635, 505 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 4.30 (m, 1H), 3.97 (br s, 2H), 2.83 (m, 2H), 2.25 (s, 3H), 2.18 (s, 1H), 2.14 (d, *J* = 2.7 Hz, 1H), 0.93 (s, 9H), 0.13 (s, 3H), 0.06 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 209.7, 79.4, 78.7, 73.1, 71.5, 60.4, 25.6, 25.5, 25.1, 18.0, -4.8, -5.1

HRMS: (ESI) m/z calcd for $C_{14}H_{29}{}^{35}ClO_3NSi$ $[M+NH_4]^+$ 322.1600, found 322.1604

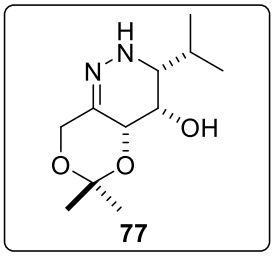
*Determination of enantiomeric excess of chlorohydrin **62***

Following General Procedure H, PNB esters were prepared of both the racemic and enantioenriched samples. The enantiomeric PNB esters were separated by chiral HPLC using a

Phenomex Lux i-Cellulose-5 column; flow rate 0.40 mL/min; eluent: hexanes-*i*PrOH 99:1; detection at 254 nm; retention time = 3.06 min and 3.79 min (see chromatograms).The enantiomeric excess of the optically enriched **62** was determined using the same method (97% ee).

Preparation of aldol adduct 63 and hydrazone 77

A solution of isovaleraldehyde (54 µL, 0.55 mmol, 1.1 equiv.), dibenzyl azodicarboxylate (0.149 g, 0.50 mmol, 1.0 equiv.), and L-proline (0.046 g, 0.40 mmol, 0.80 equiv.) in nitromethane (1.2 mL) was stirred until complete consumption of dibenzyl azodicarboxylate was observed by TLC analysis. **13** (0.130 g, 1.0 mmol, 2 equiv.) was then added and the reaction mixture was stirred for 48 hours. The reaction mixture was then diluted with CH_2Cl_2, washed with water and brine, dried over MgSO4, filtered, and concentrated under reduced pressure. The crude aldol adduct **63**, without further purification, was dissolved in MeOH (4 mL) containing 1% v/v AcOH. To this solution, was added Pd/C (100 mg, 25% by weight). H2 gas was bubbled into the reaction mixture until complete consumption of **63** was observed by TLC analysis. The reaction mixture was then filtered through celite and concentrated under reduced pressure. The ratio of diastereomers was determined to be 3:1 by ^{1}H NMR spectroscopic analysis of the crude product. Purification by flash chromatography (pentane:EtOAc:NEt_3 – 60:39:1) afforded hydrazone **77** (0.146 g, 64 % yield over 2 steps) as a white solid.



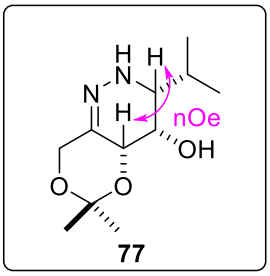
77

Data for hydrazone **77**: **$[\alpha]_D^{20}$ =** -22.9 (*c* = 3.19 in $CHCl_3$);); **IR** (neat): υ = 3359, 2961, 2872, 1643, 1380, 1372, 1165, 1074, 862 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.33 (br s, 1H), 4.41 (m, 1H), 4.39 (d, *J* = 15.6 Hz, 1H), 4.22 (d, *J* = 15.6 Hz, 1H), 4.03 (m, 1H), 2.71 (d, *J* = 9.4 Hz, 1H), 2.47 (br s, 1H), 1.99 (m, 1H), 1.52 (s, 3H), 1.43 (s, 3H), 1.00 (d, *J* = 6.8 Hz, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 139.4, 99.78, 66.4, 62.77, 62.14, 61.8, 27.4, 27.2, 21.6, 19.5, 19.0

HRMS (ESI) m/z calcd for $C_{11}H_{21}N_2O_3$ $[M+H]^+$ 229.1547, found 229.1534

*Determination of relative stereochemistry for **63/77***

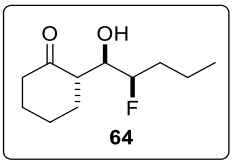
NOE analysis of hydrazone **77** confirmed relative stereochemistry of **63**.



77

Preparation of aldol adduct 64

Following General Procedure C, a solution of pentanal (0.050 mL, 0.47 mmol), NFSI (0.148 g, 0.47 mmol), L-proline (0.054 g, 0.47 mmol) and $NaHCO_3$ (0.039 g, 0.47 mmol) was stirred at -10 °C in DMF (0.63 mL) for 75 minutes. Cyclohexanone (0.488 mL, 4.70 mmol) was added and the reaction mixture was stirred for 18 hours. The ratio of diastereomers was determined to be 10:1 by ^{1}H NMR spectroscopic analysis of the crude product. Purification by flash chromatography (pentane:EtOAc – 95:5 → 90:10) afforded *syn*-fluorohydrin **64** (0.051 g, 54% yield) as an off-white solid**.**



64

Data for *syn*-fluorohydrin **64**: $[\alpha]_D^{20}$ = -16.4 (*c* 1.65 in CH_2Cl_2); **IR** (neat): υ = 3498, 2957, 2938, 2863, 1698, 1450, cm^{-1}; **^{1}H NMR** (600 MHz, $CDCl_3$): δ 4.55 (ddd, *J* = 47.8, 8.3, 4.2 Hz, 1H), 3.77 (dddd, *J* = 29.0, 8.3, 4.2, 2.1 Hz, 1H), 3.55 (d, *J* = 4.2 Hz, 1H), 2.45 (m, 1H), 2.36 (dddd, *J* = 13.4, 13.4, 6.2, 1.1 Hz, 1H), 2.23 (m, 1H), 2.12 (m, 1H), 1.85 – 1.97 (2H), 1.55 – 1.78 (3H), 1.36 – 1.55 (3H), 0.96 (dd, *J* = 7.4, 7.4 Hz, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 215.7, 92.7 (d, *J* = 174.1 Hz), 72.2 (d, *J* = 19.3 Hz), 52.8 (d, *J* = 3.5 Hz), 42.9, 32.8 (d, *J* = 21.2), 30.1, 27.8, 24.8; **^{19}F NMR** (470 MHz, $CDCl_3$): δ –199.3

HRMS (EI^+) calcd for $[C_{11}H_{20}FO_2]^+$ 203.1442; found 203.1421

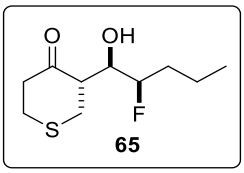
Determination of enantiomeric excess of fluorohydrin **64**

Following General Procedure H, the optically enriched and racemic samples of fluorohydrin **64** were converted into their corresponding p-nitrobenzoyl diesters. The enantiomeric *p*-nitrobenzoyl diesters were separated by chiral HPLC using a Lux® 3µm Amylose-1 column; flow rate 0.40 mL/min; eluent: hexanes-*i*PrOH 90:10; detection at 254 nm; retention times = 8.96 min and 10.37 min (see chromatograms). The enantiomeric excess of the optically enriched p-nitrobenzoyl diesters was determined using the same method (94 % ee).

Preparation of aldol adduct 65

Following General Procedure C, a solution of pentanal (0.0.50 mL, 0.47 mmol), NFSI (0.148 g, 0.47 mmol), L-proline (0.054 g, 0.47 mmol) and $NaHCO_3$ (0.039 g, 0.47 mmol) was stirred for 75 minutes at -10 °C in DMF (0.63 mL). Thiopyranone **35** (0.546 g, 4.70 mmol) was added and the

reaction mixture was stirred for 24 hours at 4°C. The ratio of diastereomers was determined to be 10:1 by ^{1}H NMR spectroscopic analysis of the crude product. Purification by flash chromatography (pentane-Et_2O - 4:1) afforded *syn*-fluorohydrin **65** (0.049 g, 47% yield) as a white solid**.**



65

Data for *syn*-fluorohydrin **65**: $[\alpha]_D^{20}$ = -16.4° (*c* 1.65 in CH_2Cl_2); **IR** (neat): υ = 3353, 2952, 1706, 1428, 510 cm^{-1}; **^{1}H NMR** (600 MHz, $CDCl_3$): δ 4.58 (ddd, *J* = 48.0, 8.8, 2.3 Hz, 1H), 3.95 (ddd, *J* = 26.7, 6.6, 2.3 Hz, 1H), 3.07 (m, 1H), 3.06 (m, 1H), 2.94 – 3.02 (3H), 2.72 – 2.86 (3H), 1.88 (m, 1H), 1.64 (m, 1H), 1.60 (m, 1H), 1.51 (m, 1H), 1.42 (m 1H), 0.97 (dd, *J* = 7.4, 7.4 Hz, 3H);**^{13}C NMR** (150 MHz, $CDCl_3$): δ 211.7, 92.8 (d, *J* = 173.6 Hz), 71.8 (d, *J* = 20.8 Hz), 55.2 (d, *J* = 3.1 Hz), 44.7, 32.9 (d, *J* = 20.9 Hz), 32.5 (d, *J* = 1.2 Hz), 30.9, 18.7 (d, *J* = 4.9 Hz), 14.0; **^{19}F NMR** (470 MHz, $CDCl_3$): δ –197.6

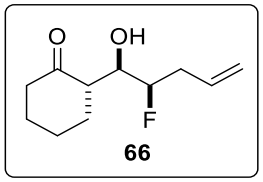
HRMS (EI^+) calcd for $[C_{10}H_{18}FO_2S]^+$ 221.1006; found 221.0999

*Determination of enantiomeric excess of fluorohydrin **65***

Using a 1:1 mixture of L-: D-proline, a racemic sample of fluorohydrin **65** was prepared. The enantiomeric fluorohydrins were separated by chiral HPLC using a Lux® 3µm Amylose-1 column; flow rate 0.40 mL/min; eluent: hexanes-*i*PrOH 90:10; detection at 254 nm; retention time = 7.14 min and 8.89 min (see chromatograms). The enantiomeric excess of the optically enriched fluorohydrin **65** was determined using the same method (84% ee).

Preparation of aldol adduct 66

Following General Procedure **C**, a solution of pentenal (0.050 g, 0.595 mmol), NFSI (0.188 g, 0.595 mmol), L-proline (0.069 g, 0.595 mmol) and $NaHCO_3$ (0.050 g, 0.595 mmol) was stirred for 1.5 hrs at -10°C in DMF (0.79 mL). Cyclohexanone (0.62 mL, 5.95 mmol) was added and the reaction mixture stirred for 16 hours. The ratio of diastereomers was determined to be 7:1 by ^{1}H NMR spectroscopic analysis of the crude product. Purification by flash chromatography (pentane:EtOAc – 95:5 → 90:10) afforded *syn*-fluorohydrin **66** (0.059 g, 50% yield) as a white solid**.**



66

Data for *syn*-fluorohydrin **66**: $[\alpha]_D^{20}$ = +22.2 (*c* 0.60 in CH_2Cl_2); **IR** (neat): υ = 3513, 2937, 2863, 1698, 1449, 1132 cm^{-1}; ^{1}**H NMR** (600 MHz, $CDCl_3$): δ 5.83 (dddd, *J* = 17.2, 10.3, 7.2, 7.0 Hz, 1H), 5.19 (dd, *J* = 17.2, 1.5 Hz, 1H), 5.13 (d, *J* = 10.3 Hz, 1H), 4.57 (ddd, *J* = 47.7, 8.3, 4.7 Hz, 1H), 3.80 (dddd, *J* = 29.7, 8.3, 4.1, 2.0 Hz, 1H), 3.58 (d, *J* = 4.1 Hz, 1H), 2.74 (m, 1H), 2.67 (m, 1H), 2.42 – 2.55 (2H), 2.36 (dddd, *J* = 13.4, 13.4, 6.1, 1.1 Hz, 1H), 2.22 (m, 1H), 2.12 (m, 1H), 1.93 (m, 1H), 1.73 (ddddd, *J* = 13.0, 13.0, 13.0, 3.6, 3.6 Hz, 1H), 1.67 (ddddd, *J* = 13.0, 13.0, 13.0, 3.6, 3.6 Hz, 1H), 1.42 (dddd, *J* = 12.7, 12.7, 12.7, 3.6, 3.6 Hz, 1H); ^{13}**C NMR** (150 MHz, $CDCl_3$): δ 215.6, 133.3 (d, *J* = 7.5 Hz), 118.4, 92.0 (d, *J* = 177.6 Hz), 71.6 (d, *J* = 18.8 Hz), 52.7 (d, *J* = 3.6 Hz), 42.8, 35.4 (d, *J* = 23.4 Hz), 30.0, 27.8 24.8; ^{19}**F NMR** (470 MHz, $CDCl_3$): δ – 198.7

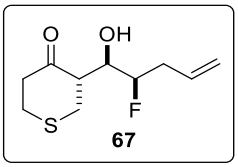
HRMS (EI^+) calcd for $[C_{11}H_{18}FO_2]^+$ 201.1285; found 201.1260

Determination of relative stereochemistry for fluorohydrin **66**

Following General Procedure E, the fluorohydrin **66** was converted to carbacycle **91**. NOE analysis of carbacycle **91** confirmed relative stereochemistry of fluorohydrin **66**.

Preparation of aldol adduct 67

Following General Procedure C, a solution of pentenal (0.100 mL, 1.02 mmol), NFSI (0.319 g, 1.02 mmol), L-proline (0.118 g, 1.02 mmol) and $NaHCO_3$ (0.086 g, 1.02 mmol) was stirred for 60 minutes at -10 °C in DMF (1.35 mL). Thiopyranone **35** (1.19 g, 10.2 mmol) was then added and the reaction mixture was stirred for 24 hrs at 4°C. The ratio of diastereomers was determined to be 8:1 by ^{1}H NMR spectroscopic analysis of the crude product. Purification by flash chromatography (pentane:Et_2O – 4:1) afforded *syn*-fluorohydrin **67** (0.069 g, 31 % yield) as a waxy white solid.



67

Data for *syn*-fluorohydrin **67**: $[\alpha]_D^{20}$ = -11.0 (*c* 0.30 in CH_2Cl_2); **IR** (neat): υ = 3455, 2929, 1703, 1428, 1117, 923 cm^{-1};^{1}**H NMR** (600 MHz, $CDCl_3$): δ 5.82 (dddd, *J* = 17.1, 10.3, 7.0, 6.9 Hz, 1H), 5.21 (dd, *J* = 17.1, 1.4 Hz, 1H), 5.15 (d, *J* = 10.3, 1H), 4.61 (ddd, *J* = 47.7, 5.9, 2.0 Hz, 1H), 3.97 (ddd, *J* = 27.5, 6.4, 2.0 Hz, 1H), 3.09 (m, 1H), 3.05 (m, 1H), 3.04 (m, 1H), 2.99 (m, 1H), 2.97 (m, 1H), 2.81 (m, 2H), 2.76 (m, 1H), 2.64 (m, 1H), 2.51 (m, 1H) ; ^{13}**C NMR** (150 MHz, $CDCl_3$): δ 211.7,

132.8 (d, *J* = 7.3 Hz), 118.7, 92.1 (d, *J* = 176.3 Hz), 71.2 (d, *J* = 19.3 Hz), 55.1 (d, *J* = 3.0 Hz), 44.7, 35.4 (d, *J* = 22.2 Hz), 32.4, 30.8; **^{19}F NMR** (470 MHz, $CDCl_3$): δ -197.0

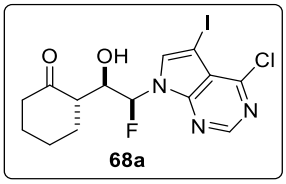
HRMS (EI^+) calcd for $[C_{10}H_{16}FO_2S]^+$ 219.0850; 219.0833

Determination of relative stereochemistry for fluorohydrin **67**

Following General Procedure E, the fluorohydrin **67** was converted to carbacycle **92**. NOE analysis of carbacycle **92** confirmed relative stereochemistry of fluorohydrin **67**.

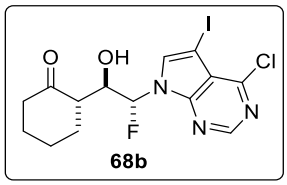
Preparation of syn-fluorohydrin 68a and anti-fluorohydrin 68b

Following General Procedure C, a solution of aldehyde (2.00 g, 5.86 mmol, 1.0 equiv.), NFSI (1.85 g, 5.86 mmol, 1.0 equiv.), L-proline (0.674 g, 5.86 mmol, 1.0 equiv.) and $NaHCO_3$ (0.984 g, 11.71 mmol, 2 equiv.) was stirred at rt in DMF (10 mL) for 2 hrs. Cyclohexanone (1.15 g, 11.71 mmol) was added and the reaction mixture was stirred for 18 hours. The reaction mixture was then diluted with ethyl acetate (100 mL) and water (30 mL). The organic layer was washed with brine (2 x 30 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification of crude fluorohydrins **68** by flash chromatography (25-75% ethyl acetate in hexanes) afforded *syn*-fluorohydrin **68a** (0.92 g, 36 % yield) and *anti*-fluorohydrin **68b** (1.21 g, 47% yield) as white solids**.**



68a

Data for *syn*-fluorohydrin **68a**: **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.73 (s, 1H), 8.27 (s, 1H), 7.02 (dd, *J* = 50.0, 5.6 Hz, 1H), 5.82 (d, *J* = 6.9 Hz, 1H), 4.47 (m, 1H), 2.43 (m, 1H), 2.24 (m, 1H), 2.16 (m, 1H), 2.05 (m, 1H), 1.80 – 1.86 (m, 2H), 1.73 (m, 1H), 1.55 – 1.60 (m, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 209.9, 151.5, 151.3, 151.0, 134.0, 116.6, 92.5 (d, *J* = 205.2 Hz), 69.7 (d, *J* = 24.4 Hz), 55.3, 51.5, 51.5, 41.5, 29.2, 26.3, 23.5; **^{19}F NMR** (470 MHz, $CDCl_3$): δ –147.6



68b

Data for *anti*-fluorohydrin **68b**: **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.75 (s, 1H), 8.34 (s, 1H), 7.05 (dd, J = 47.6, 7.3 Hz, 1H), 5.59 (d, J = 6.7 Hz, 1H), 4.55 (m ,1H), 2.70 (m, 1H), 2.39 (m, 1H), 2.27 (m, 1H), 1.87 – 1.99 (m, 2H), 1.84 (m, 1H), 1.56 – 1.76 (m, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$): 210.1, 151.6, 151.4, 151.3, 133.8, 116.6, 91.5 (d, J = 204.6 Hz), 68.9 (d, J = 30.5 Hz), 55.2, 51.1, 41.7, 29.1, 26.4, 23.5

Determination of relative stereochemistry for syn-fluorohydrin **68a**

Fluorohydrin **68a** was converted into nucleoside **86**. NOE analysis of nucleoside **86** confirmed relative stereochemistry of fluorohydrin **68a**.

*Determination of enantiomeric excess of fluorohydrin **68a***

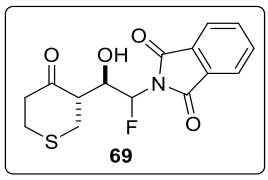
Using a 1:1 mixture of L-: D-proline, a racemic sample of fluorohydrin **68a** was prepared. The enantiomeric fluorohydrins were separated by chiral SFC using Daicel OJ-3; 2900 PSI CO_2, 40 °C, 3 ml/min, gradient of 20-30% 25mM isobutylamine in isopropanol:CO2 over seven minutes; retention times = 2.57 min and 2.77 min (see chromatograms). The enantiomeric excess of the optically enriched fluorohydrin **68a** was determined using the same method (94% ee).

*Determination of enantiomeric excess of fluorohydrin **68b***

Using a 1:1 mixture of L-: D-proline, a racemic sample of fluorohydrin **68b** was prepared. The enantiomeric fluorohydrins were separated by chiral SFC using Daicel OJ-3; 2900 PSI CO_2, 40 °C, 3 ml/min, gradient of 1-20% 25mM diethylamine in methanol:CO_2 over five minutes; retention times = 3.10 min and 3.32 min (see chromatograms). The enantiomeric excess of the optically enriched fluorohydrin **68b** was determined using the same method (93% ee).

Preparation of aldol adduct 69

Following General Procedure C, a solution of phthalimidoacetaldehyde (0.050 g, 0.265 mmol), NFSI (0.84 g, 0.265 mmol), L-proline (0.031 g, 0.265 mmol) and 2,6-lutidine (0.031 mL, 0.265 mmol) was stirred at 4°C in DMF (0.35 mL) for 15 hrs. Thiopyranone **35** (0.307 g, 2.65 mmol) was added and the reaction mixture was stirred for 18 hours. The ratio of diastereomers was determined to be 5:1 by ^{1}H NMR spectroscopic analysis of the crude product. Purification by flash chromatography (pentane:EtOAc – 60:40) afforded an inseparable mixture of *syn*- and *anti*-fluorohydrins **69** (0.075 g, 87% yield, d.r. = 5:1) as a white solid**.**



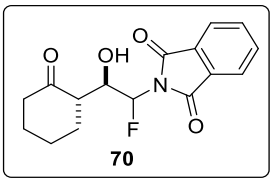
69

Data for fluorohydrin **69**: **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.93, 7.92, 7.79, 7.79, 6.26, 6.11, 5.37, 4.78, 3.44, 3.25, 3.24, 3.16, 3.11, 3.09, 3.03, 2.99, 2.98, 2.85, 2.80, 2.79; **^{13}C NMR** (150 MHz, $CDCl_3$): δ 212.8, 210.2, 167.1, 167.1, 135.1, 134.9, 131.6, 131.5, 124.3, 124.2, 89.6, 88.3, 70.1, 66.1, 54.6, 53.6, 45.7, 44.9, 34.6, 31.3, 30.7, 30.1; **^{19}F NMR** (470 MHz, $CDCl_3$): δ –155.5, –158.5

HRMS (EI$^+$) calcd for $[C_{15}H_{14}FNO_4S + NH_4]^+$ 341.0966; observed 341.0938

Preparation of aldol adduct 70

Following General Procedure C, a solution of phthalimidoacetaldehyde (0.050 g, 0.265 mmol), NFSI (0.84 g, 0.265 mmol), L-proline (0.031 g, 0.265 mmol) and 2,6-lutidine (0.031 mL, 0.265 mmol) was stirred at 4°C in DMF (0.35 mL) for 16 hrs. cyclohexanone (0.275 mL, 2.65 mmol) was added and the reaction mixture was stirred for 18 hours. The ratio of diastereomers was determined to be 5:1 by ^{1}H NMR spectroscopic analysis of the crude product. Purification by flash chromatography (pentane:EtOAc – 60:40) afforded an inseparable mixture of *syn*-and *anti* - fluorohydrin **70** (0.068 g, 84% yield, d.r. = 5:1) as a white solid**.**



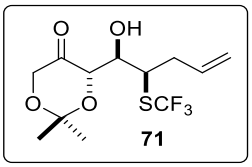
70

Data for fluorohydrin **70**: **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.92, 7.91, 7.78, 7.78, 6.29, 6.07, 5.37, 4.63, 3.51, 2.93, 2.92, 2.89, 2.80, 2.44, 2.41, 2.30, 2.25, 2.16, 2.01. 1.99, 1.87, 1.78, 1.71; **^{13}C NMR** (150 MHz, $CDCl_3$): δ 215.9, 213.5, 167.1, 167.1, 134.9, 134.8, 131.7, 131.6, 124.1, 124.1, 89.9, 88.3, 69.9, 65.5, 51.8, 51.0, 43.3, 42.7, 32.4, 28.3, 27.8, 26.1, 25.4, 24.8; **^{19}F NMR** (470 MHz, $CDCl_3$): δ –156.0, –160.7

HRMS (EI$^+$) calcd for $[C_{16}H_{17}FNO_4]^+$ 306.1136; observed 306.1135

Preparation of aldol adduct 71

Following General Procedure D, a solution of pentenal (0.100 mL, 1.01 mmol), N(SCF_3)Phth (0.250 g, 1.01 mmol), L-proline (0.116 g, 1.01 mmol), and $NaHCO_3$ (0.085 g, 1.01 mmol) was stirred for 50 minutes at RT in DMSO (1.35 mL). Dioxanone **13** (0.061 mL, 0.506 mmol) in CH_2Cl_2 (6.7 mL) was added and the reaction mixture was stirred for 60 hrs. The ratio of diastereomers was determined to be 6:1 by ^{1}H NMR spectroscopic analysis of the crude product. Purification by flash chromatography (pentane-Et_2O 4:1) afforded *syn*-trifluoromethylthiohydrin **71** (0.103 g, 65 % yield) as a light yellow oil**.**



71

Data for *syn*-trifluoromethylthiohydrin **71**: **$[\alpha]_D^{20}$** = -100.5° (*c* 1.28 in CH_2Cl_2); **IR** (neat): υ = 3650, 3150, 1737, 1377, 1224, 1109 cm^{-1};**^{1}H NMR** (600 MHz, $CDCl_3$): δ 5.79 (m, 1H), 5.18 (d, *J* = 17.0 Hz, 1H), 5.14 (d, *J* = 10.3 Hz, 1H), 4.42 (d, *J* = 9.0 Hz, 1H), 4.29 (d, *J* = 17.8 Hz, 1H), 4.12 (d, *J* = 9.0 Hz, 1H), 4.07 (d, *J* = 17.8 Hz, 1H), 3.63 (s, 1H), 3.51 (dd, *J* = 10.1, 4.8 Hz, 1H), 2.78 (ddd, *J* = 14.3, 9.9, 7.9 Hz, 1H), 2.68 (ddd, *J* = 14.3, 6.6, 5.1 Hz, 1H), 1.48 (s, 3H), 1.42 (s, 3H); **^{13}C**

NMR (150 MHz, $CDCl_3$): δ 213.3, 134.4, 131.6 (q, *J* = 303.5 Hz), 118.7, 101.8, 72.3, 70.4, 66.4, 46.3, 38.9, 23.8, 23.6; **^{19}F NMR** (470 MHz, $CDCl_3$): δ –39.7

HRMS (EI$^+$) calcd for $[C_{12}H_{17}F_3O_4S + NH_4]^+$ 332.1138; found 332.1110

*Determination of relative stereochemistry for trifluoromethylthiohydrin **71***

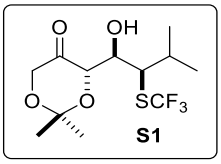
Following General Procedure E, the trifluoromethylthiohydrin **71** was converted to carbacycle **90**. NOE analysis of carbacycle **93** confirmed relative stereochemistry of trifluoromethylthiohydrin **71**.

*Determination of enantiomeric excess of trifluoromethylthiohydrin **71***

Following General Procedure I, trifluoromethylthiohydrin **71** was converted to trifluoromethylthiohydrin **30**. Following General Procedure H, optically enriched and racemic samples of trifluoromethylthiohydrin **30** were converted into their corresponding p-nitrobenzoyl diesters. The enantiomeric p-nitrobenzoyl diesters were separated by chiral HPLC using a Lux® 3µm Amylose-1 column; flow rate 0.50 mL/min; eluent: hexanes-*i*PrOH 92.5:7.5; detection at 254 nm; retention time = 6.92 min and 10.52 min (see chromatograms). The enantiomeric excess of the optically enriched p-nitrobenzoyl diester was determined using the same method (91% ee).

Preparation of aldol adduct S1

Following General Procedure D, a solution of isovaleraldehyde (0.050 mL, 0.456 mmol), $N(SCF_3)Phth$ (0.113 g, 0.456 mmol), L-proline (0.053 g, 0.456 mmol), and $NaHCO_3$ (0.038 g, 0.456 mmol) was stirred for 50 minutes at RT in DMSO (0.61 mL). Dioxanone **13** (0.027 mL, 0.228 mmol) in CH_2Cl_2 (3.04 mL) was added and the reaction mixture was stirred for 60 hrs. The ratio of diastereomers was determined to be 10:1 by ^{1}H NMR spectroscopic analysis of the crude product. Purification by flash chromatography (pentane:Et_2O – 88:12) afforded *syn*-trifluoromethylthiohydrin **S1** (0.060 g, 42 % yield) as a colorless oil**.**



S1

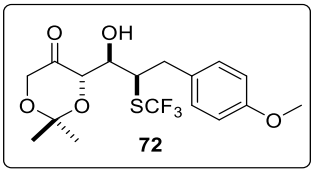
Data for *syn*-trifluoromethylthiohydrin **S1**: **$[\alpha]_D^{20}$** = -106.0° (*c* 2.15 in CH_2Cl_2); **IR** (neat): υ = 3508, 2967, 173, 1101, 865 cm^{-1};**^{1}H NMR** (600 MHz, $CDCl_3$): δ 4.41 (dd, *J* = 9.0, 1.3 Hz, 1H), 4.30 (dd, *J* = 17.6, 1.5 Hz, 1H), 4.19 (d, *J* = 9.0 Hz, 1H), 4.08 (d, *J* = 17.6 Hz, 1H), 3.73 (dd, *J* = 2.3, 1.3 Hz, 1H), 3.35 (d, *J* = 5.5 Hz, 1H), 2.18 (m, 1H), 1.47 (s, 3H), 1.43 (s, 3H), 1.10 (dd, *J* = 5.8, 5.7 Hz, 3H); **^{13}C NMR**

(150 MHz, $CDCl_3$): δ 213.6, 131.6 (q, *J* = 305.0 Hz), 101.7, 72.2, 70.4, 66.5, 53.5, 33.1, 23.8, 23.7, 20.8, 19; **^{19}F NMR** (470 MHz, $CDCl_3$): δ –38.6

HRMS (EI^+) calcd for $[C_{12}H_{19}F_3O_4S + NH_4]^+$ 334.1294; found 334.1266

Preparation of aldol adduct 72

Following General Procedure D, a solution of 3-(4-methoxyphenyl)propanal (0.050 mL, 0.317 mmol), PhthN(SCF_3) (0.078 g, 0.317 mmol), L-proline (0.037 g, 0.317 mmol), and $NaHCO_3$ (0.027 g, 0.317 mmol) was stirred for 50 minutes at RT in DMSO (0.42 mL). Dioxanone **13** (0.019 mL, 0.228 mmol) in CH_2Cl_2 (2.11 mL) was added and the reaction mixture stirred for 60 hrs. The ratio of diastereomers was determined to be 10:1 by ^{1}H NMR spectroscopic analysis of the crude product. Purification by flash chromatography (pentane:Et_2O – 80:20) afforded *syn*-trifluoromethylthiohydrin **72** (0.032 g, 56 % yield) as a yellow oil**.**



72

Data for *syn*-trifluoromethylthiohydrin **72**: **$[\alpha]_D^{20}$** = -61.4° (*c* 1.6 in CH_2Cl_2); **IR** (neat): υ = 3518, 1736, 1512, 1108, 863 cm^{-1};**^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.15 (d, *J* = 8.5 Hz, 2H), 6.85 (d, *J* = 8.5 Hz, 2H), 4.40 (dd, *J* = 9.1, 1.3 Hz, 1H), 4.20 (dd, *J* = 17.6, 1.5 Hz, 1H), 4.01 (d, *J* = 17.6 Hz, 1H), 3.89 (d, *J* = 9.1 Hz, 1H), 3.80 (s, 3H), 3.58-3.62 (2H), 3.26 (dd, *J* = 13.7, 11.0 Hz, 1H), 3.21 (dd, *J* = 13.7, 5.5 Hz, 1H), 1.46 (s, 3H), 1.34 (s, 3H;**^{13}C NMR** (150 MHz, $CDCl_3$): δ 213.6, 158.6, 131.6 (q, *J* = 306.0 Hz), 130.5, 130.0, 114.1, 101.7, 72.4, 69.2, 66.4, 55.4, 48.2, 39.2, 23.8, 23.6; **^{19}F NMR** (470 MHz, $CDCl_3$): δ –39.7

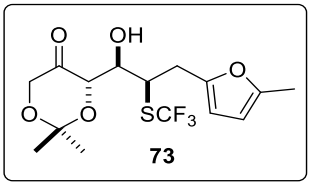
HRMS (EI^+) calcd for $[C_{17}H_{21}F_3O_5S + NH_4]^+$ 412.1400.1340; found 412.1369

Determination of enantiomeric excess of trifluoromethylthiohydrin **72**

Using sodium borohydride in methanol, optically enriched and racemic samples of trifluoromethylthiohydrin **72** were converted into their corresponding diols. The enantiomeric diols were separated by chiral HPLC using a Lux® 3µm Amylose-1 column; flow rate 0.50 mL/min; eluent: hexanes-*i*PrOH 95:5; detection at 254 nm; retention time = 6.01 min and 8.49 min (see chromatograms). The enantiomeric excess of the optically enriched diol was determined using the same method (93% ee).

Preparation of aldol adduct 73

Following General Procedure D, a solution of 3-(5-methylfuran-2-yl)propanal (0.050 mL, 0.376 mmol), N(SCF_3)Phth (0.093 g, 0.376 mmol), L-proline (0.043 g, 0.376 mmol), and $NaHCO_3$ (0.032 g, 0.376 mmol) was stirred for 50 minutes at RT in DMSO (0.50 mL). Dioxanone **13** (0.023 mL, 0.188 mmol) in CH_2Cl_2 (2.50 mL) was added and the reaction mixture stirred for 60 hrs. The ratio of diastereomers was determined to be >10:1 by ^{1}H NMR spectroscopic analysis of the crude product. Purification by flash chromatography (pentane:Et_2O – 85:15) afforded *syn*-trifluoromethylthiohydrin **73** (0.032 g, 46 % yield) as a colorless oil**.**



73

Data for *syn*-trifluoromethylthiohydrin **73**: $[\alpha]_D^{20}$ = -101.7° (*c* 1.0 in CH_2Cl_2); **IR** (neat): υ = 3517, 2995, 1736, 1386, 1113, 737 cm^{-1};**^{1}H NMR** (600 MHz, $CDCl_3$): δ 6.00 (d, *J* = 2.8 Hz, 1H), 5.86 (d, *J* = 2.8 Hz, 1H), 4.42 (dd, *J* = 9.0, 1.3 Hz, 1H), 4.26 (dd, *J* = 17.6, 1.3 Hz, 1H), 4.05 (d, *J* = 17.6 Hz, 1H), 4.03 (d, *J* = 9.0 Hz, 1H), 3.76 (dd, *J* = 10.6, 5.1 Hz, 1H), 3.62 (dd, *J* = 2.3, 1.3 Hz, 1H), 3.31 (dd, *J* = 15.1, 10.6 Hz, 1H), 3.18 (dd, *J* = 15.1, 5.1 Hz, 1H), 2.26 (s, 3H), 1.48 (s, 3H), 1.40 (s, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 213.6, 151.6, 149.9, 131.4 (q, *J* = 306.0 Hz), 108.6, 106.2, 101.7, 72.4, 70.3, 66.4, 45.8, 33.2, 23.8, 23.6, 13; **^{19}F NMR** (470 MHz, $CDCl_3$): δ –39.8

HRMS (EI$^+$) calcd for $[C_{15}H_{19}F_3O_5S + NH_4]^+$ 386.1244; found 386.1227

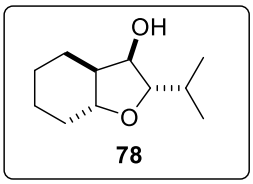
*Determination of enantiomeric excess of trifluoromethylthiohydrin **73***

Following General Procedure H, optically enriched and racemic samples of trifluoromethylthiohydrin **73** were converted into their corresponding *p*-nitrobenzoyl diesters. The enantiomeric p-nitrobenzoyl diesters were separated by chiral HPLC using a Lux® 3µm Amylose-1 column; flow rate 0.50 mL/min; eluent: hexanes-*i*PrOH 95:5; detection at 254 nm; retention time = 20.83 min and 22.46 min (see chromatograms). The enantiomeric excess of the optically enriched p-nitrobenzoyl diester was determined using the same method (93% ee).

Preparation of THF 78

Following General Procedure G, to a stirred solution of chlorohydrin **38** (100 mg, 0.45 mmol) in MeOH (2 mL) was added $NaBH_4$ (74 mg, 2.0 mmol) in MeOH (2 mL). Once TLC analysis indicated complete consumption of **36**, the reaction mixture was quenched with aqueous NH_4Cl (5 mL), extracted 3x with 10 mL of CH_2Cl_2, and concentrated under reduced pressure to afford diol **S38**. Without further purification, the crude reduction product dissolved in MeOH (2 mL) and

subjected to microwave irradiation. Purification of crude **78** by flash column chromatography (hexanes:EtOAc – 80:20) afforded **78** (60 mg, 74% yield) as a white solid.



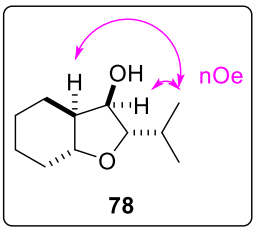
78

Data for THF **78**: $[\alpha]_D^{20}$ = +4.7 (*c* = 4.2 in $CHCl_3$); **IR** (neat): υ = 3368, 2931, 2865, 1446, 1081, 1070, 978, 641 cm^{-1}; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 3.97 (m, 1H), 3.47 (m, *J* = 6.5 Hz, 1H), 3.39 (m, *J* = 11.0, 4.9 Hz, 1H), 2.15 (m, 1H), 1.84-1.70 (m, 5H), 1.37-1.17 (m, 4H), 1.13 (m, 1H), 0.95 (d, *J* = 6.7 Hz, 3H), 0.92 (d, *J* = 6.7 Hz, 3H); **^{13}C NMR** (150 MHz, CDCl3) δ 93.1, 79.4, 76.6, 50.2, 31.5, 31.1, 25.5, 23.9, 23.3, 18.49, 18.47

HRMS: (ESI) m/z calcd for $C_{11}H_{21}O_2$ $[M+H]^+$ 185.1536, found 185.1541

Determination of relative stereochemistry for THF 78

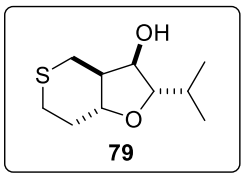
Analysis of 2D NOESY of THF **78** supported the indicated stereochemistry.



78

Preparation of THF 79

Following General Procedure G, to a stirred solution of chlorohydrin **36** (250 mg, 1.0 mmol) in MeOH (2 mL) was added $NaBH_4$ (74 mg, 2.0 mmol) in MeOH (2 mL). Once TLC analysis indicated complete consumption of **36**, the reaction mixture was quenched with aqueous NH_4Cl (5 mL), extracted 3x with 10 mL of CH_2Cl_2, and concentrated under reduced pressure to afford diol **S36**. Without further purification, the crude reduction product dissolved in MeOH (2 mL) and subjected to microwave irradiation. Purification of crude **79** by flash column chromatography (pentane:EtOAc – 80:20) afforded **79** (30 mg, 15% yield) as a white solid.



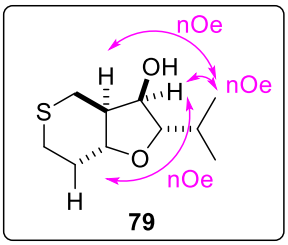
79

Data for THF **79**: $[\alpha]_D^{20}$ = + 4.7 (*c* = 2.7 in $CHCl_3$); **IR** (neat): υ = 3398, 2924, 1437, 1382, 1072, 1015, 945, 880, 634 cm^{-1}; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 4.06 (m, 1H), 3.43 (d, *J* = 6.5 Hz, 1H), 3.38 (ddd, *J* = 10.9, 10.9, 3.7 Hz, 1H), 2.84 (dd, *J* = 13.0, 11.6 Hz, 1H), 2.73-2.61 (m, 3H), 2.46 (dd, *J* = 11.1, 3.5 Hz, 1H), 1.74 (m, 1H), 1.66 (m, 1H), 1.60 (m, 1H), 0.95 (d, *J* = 6.8 Hz, 3H), 0.92 (d, *J* = 6.7 Hz, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 91.9, 78.7, 74.7, 49.9, 33.6, 31.0, 27.3, 18.4, 18.3.

HRMS: (ESI) m/z calcd for $C_{10}H_{19}O_2S$ $[M+H]^+$ 203.1100, found 203.1098

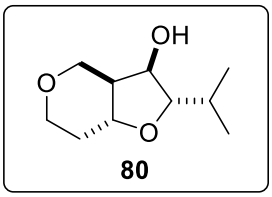
Determination of relative stereochemistry for THF 79

Analysis of 2D NOESY of THF **79** supported the indicated stereochemistry.



Preparation of THF 80

Following General Procedure G, **40d** (20 mg, 0.09 mmol) was dissolved in MeOH (0.18 mL) and subjected to microwave irradiation. The cyclized product **80** was purified by flash chromatography (CH_2Cl_2:MeOH – 97:3) to yield **80** (11.1 mg, 60% yield) as a clear oil.

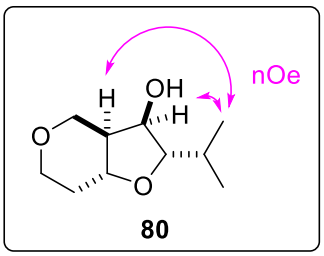


Data for THF **80**: $[\alpha]_D^{20}$ = +8.9 (*c* = 1.1 in $CHCl_3$); **IR** (neat): υ = 3349, 2969, 2924, 1084, 1046, 880, 635 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 4.17 (m, 2H), 4.03 (dd, *J* = 11.7, 4.5 Hz, 1H), 3.70 (dd, *J* = 11.0, 4.2 Hz, 1H), 3.52 (m, 1H), 3.30 (m, *J* = 12.0, 2.2 Hz, 1H), 2.11 (m, 1H), 1.76 (m, 1H), 1.69 (m, 1H), 1.39 (bs, 1H), 0.97 (d, *J* = 6.0 Hz, 3H), 0.94 (d, *J* = 6.0 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 93.0, 77.2, 73.6, 67.2, 65.5, 48.9, 33.1, 31.0, 18.6, 18.4

HRMS: (ESI) m/z calcd for $C_{10}H_{22}O_3N$ $[M+NH_4]$ + 204.1594, found 204.1600

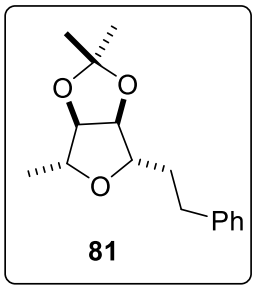
Determination of relative stereochemistry for THF 80

Analysis of 2D NOESY of THF **80** supported the indicated stereochemistry.



Preparation of THF 81

Following General Procedure G, to a stirred solution of chlorohydrin **61** (194 mg, 0.50 mmol) in MeOH (1 mL) was added $NaBH_4$ (37 mg, 1.0 mmol) in MeOH (2 mL). Once TLC analysis indicated complete consumption of **61**, the reaction mixture was quenched with aqueous NH_4Cl (5 mL), extracted 3x with 10 mL of CH_2Cl_2, and concentrated under reduced pressure to afford diol **S61**. Without further purification, the crude reduction product dissolved in MeOH (1 mL) and subjected to microwave irradiation. Purification of crude **S81** by flash column chromatography (pentane:EtOAc – 60:40) afforded a white solid (20 mg, 18% yield). **S81** was stirred in acetone (0.90 mL) with TsOH (0.1 eq, 30 mg) and two heaping spatula tips of $MgSO_4$ to form the acetonide protected THF. The crude product **81** was purified by flash column chromatography (hexanes:EtOAc – 60:40) to afford **81** (18 mg) as a clear oil.



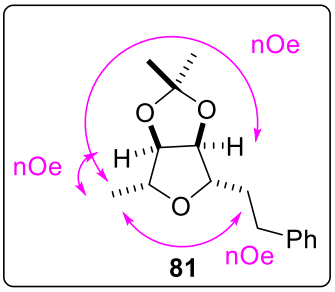
81

Data for THF **81**: $[\alpha]_D^{20}$ = -14.7 (*c* = 2.2 in $CHCl_3$); **IR** (neat): υ = 3027, 2957, 2929, 2871, 1708, 1381, 1210, 1074, 865, 699, 512 cm^{-1}; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.29 (m, 2H), 7.21 (m, 3H), 4.37 (dd, *J* = 7.2, 4.9 Hz, 1H), 4.27 (dd, *J* = 7.2, 5.0 Hz, 1H), 3.92 (m, 1H), 3.83 (td, *J* = 6.7, 4.9 Hz, 1H), 2.78 (m, 1H), 2.72 (m, 1H), 1.93 (m, 2H), 2.53 (s, 3H), 1.34 (s, 3H), 1.33 (d, *J* = 7.7 Hz, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 141.6, 128.4, 128.3, 125.8, 114.9, 86.2, 85.3, 83.3, 79.9, 35.4, 31.8, 29.7, 27.3, 25.4, 19.0

HRMS: (ESI) m/z calcd for $C_{16}H_{23}O_3[M+H]^+$ 263.1642, found 263.1635

Determination of relative stereochemistry for THF 81

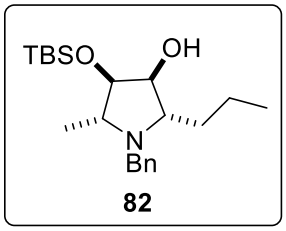
Analysis of 2D NOESY of THF **81** supported the indicated stereochemistry.



81

Preparation of iminosugar 82

Following General Procedure F, chlorohydrin **59** (95 mg, 0.29 mmol) was dissolved in dry THF (3 mL) with AcOH (17 µL, 0.29 mmol) and benzylamine (84 µL, 0.80 mmol). The resulting reaction was stirred for 1 hr. $NaBH_3CN$ (49 mg, 0.8 mmol) was added and the reaction mixture stirred for another 1hr. The crude product was purified by flash chromatography (hexanes:Et_2O – 90:10) to afford **82** (24 mg, 21% yield) as a clear oil. Stereochemistry was assigned by analogy to the other iminosugars made by this process.



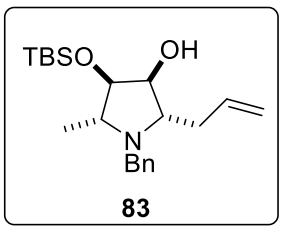
82

Data for iminosugar **82**: **$[\alpha]_D^{20}$** = +12.3 (*c* = 2.3 in $CHCl_3$); **IR** (neat): υ = 3549, 2956, 2929, 1253, 1123, 835, 776, 732, 698 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.29 (m, 4H), 7.22 (m, 1H), 3.76 (d, J = 14.2 Hz, 1H), 3.72 (d, J = 14.2 Hz, 1H), 3.64 (m, J = 3.3, 5.7 Hz, 1H), 3.60 (m, J = 5.5, 6.7 Hz, 1H), 2.67 (m, 2H), 2.61 (d, J = 3.3 Hz, 1H), 1.41 (bs, 1H), 1.49-1.36 (m, 2H), 1.31-1.16 (m, 2H), 1.02 (d, J = 6.2 Hz, 3H), 0.91 (s, 9H), 0.85 (t, J = 7.1 Hz, 3H), 0.10 (s, 3H), 0.09 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 139.5, 129.0, 127.0, 126.7, 77.8, 74.6, 70.1, 62.9, 56.8, 35.8, 25.7, 18.9, 18.1, 18.0, 14.3, -4.6, -4.8

HRMS: (ESI) m/z calcd for $C_{21}H_{38}NO_2Si$ $[M+H]^+$ 364.2666, found 364.2668

Preparation of iminosugar 83

Following General Procedure F, chlorohydrin 60 (54 mg, 0.18 mmol) was dissolved in dry THF (2 mL) with AcOH (10 µL, 0.18 mmol) and benzylamine (49 µL, 81 0.46 mmol). The resulting reaction mixture was stirred for 1 hr. $NaBH_3CN$ (28 mg, 0.46 mmol) was added and stirred for another 1 hr. The crude product **83** was purified by flash chromatography (hexanes:EtOAc – 90:10) to afford **83** (16 mg, 25% yield) a clear oil. Stereochemistry was assigned by analogy to the other iminosugars made by this process.



83

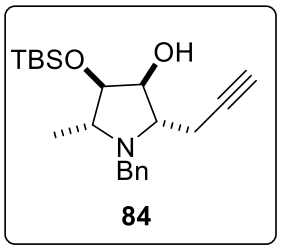
Data for iminosugar **83**: **$[\alpha]_D^{20}$** = +21.4 (*c* = 1.4 in $CHCl_3$); **IR** (neat): υ = 3550, 3028, 2065, 2955, 2928, 1253, 1124, 1092, 835, 776, 698 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.29 (m, 4H), 7.23 (m, 1H), 5.85 (m, 1H), 5.02 (m, J = 1.7, 13.8 Hz, 2H), 3.80 (d, *J* = 14.1 Hz, 1H), 3.71 (d, *J* = 14.1 Hz, 1H), 3.68 (m, 1H), 3.60 (dd, *J* = 6.8, 5.3 Hz, 1H), 2.80 (dd, J = 7.4, 3.5 Hz, 1H), 2.72 (m, *J* = 6.3 Hz, 1H), 2.57 (d, *J* = 3.6 Hz, 1H), 2.13 (dddd, *J* = 13.8, 7.3, 3.5, 1.1 Hz, 1H), 2.00 (m, *J* = 14.3, 7.8, 1.3 Hz, 1H), 1.01 (d, *J* = 6.2 Hz, 3H), 0.91 (s, 9H), 0.11

(s, 3H), 0.09 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 139.8, 135.6, 128.9, 128.0, 126.8, 116.4, 77.8, 74.1, 69.7, 63.3, 57.4, 37.7, 25.8, 18.3, 18.0, -4.6, -4.8

HRMS: (ESI) m/z calcd for $C_{21}H_{36}NO_2Si$ $[M+H]^+$ 362.2510, found 362.2501

Preparation of iminosugar 84

Following General Procedure F, chlorohydrin **62** (24 mg, 0.07 mmol) was dissolved in dry THF (1 mL) with AcOH (4.5 µL, 0.07 mmol) and benzylamine (22 µL, 0.21 mmol). The resulting reaction mixture was stirred for 1 hr. $NaBH_3CN$ (12.5 mg, 0.21 mmol) was added and stirred for another 1 hr. The crude product **84** was purified by flash chromatography (hexanes:Et_2O – 80:20) to afford **84** (9 mg, 32% yield) a clear oil.



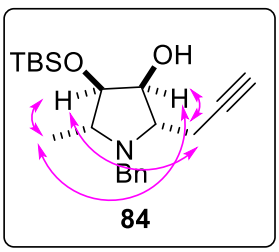
84

Data for iminosugar **84**: **$[\alpha]_D^{20}$** = +12.6 (*c* = 11 mg/mL in $CHCl_3$); **IR** (neat): υ = 3547, 3310, 2955, 2928, 2119, 1253, 1130, 835, 777, 699, 632 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.36 - 7.27 (m, 4H), 7.23 (m, 1H), 3.89-3.81 (m, 2H), 3.75 (dd, *J* = 6.2, 4.8 Hz, 1H), 3.71 (d, *J* = 13.8 Hz, 1H), 2.91 (ddd, *J* = 6.9, 4.2, 2.8 Hz, 1H), 2.80 (m, 1H), 2.62 (d, *J* = 3.3 Hz, 1H), 2.19 (ddd, *J* = 16.9, 4.1, 2.7 Hz, 1H), 2.05 (ddd, *J* = 16.9, 6.8, 2.6 Hz, 1H), 1.94 (t, *J* = 2.6 Hz, 1H), 1.04 (d, *J* = 6.2 Hz, 3H), 0.92 (s, 9H), 0.12 - 0.11 (s, 6H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 139.7, 128.9, 128.1, 126.9, 82.2, 77.8, 74.6, 69.2, 68.7, 63.3, 57.5, 25.8, 23.5, 18.2, 18.0, -4.6, -4.7

HRMS: (ESI) m/z calcd for $C_{21}H_{34}NO_2Si$ $[M+H]^+$ 360.2353, found 360.2348

Determination of relative stereochemistry for iminosugar 84

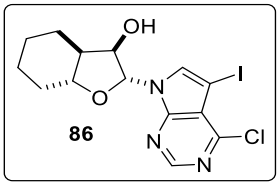
Analysis of 2D NOESY of iminosugar **84** supported the indicated stereochemistry.



84

Preparation of nucleoside analogue 86

To a suspension of **68a** (100 mg, 0.228 mmol) in MeCN (2.0 mL) at 0 °C was added acetic acid (131 µl, 2.285 mmol), followed by sodium triacetoxyborohydride (242 mg, 1.142 mmol). The mixture was stirred at room temperature for 16h, at which time LCMS indicated complete conversion to the reduced product in approximately 2.5:1 selectivity. The reaction mixture was then diluted with water and ethyl acetate. The organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude reduced product was then diluted with MeCN (2.0 mL) and indium chloride (50.5 mg, 0.228 mmol) was added. The resulting reaction mixture was stirred overnight at 50 °C. The reaction mixture was then concentrated under reduced pressure and purified by flash column chromatography (25-100% ethyl acetate in hexanes) to afford nucleoside **86** (43 mg, 45%) as a white solid.

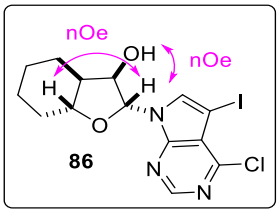


Data for nucleoside analogue **86**: $[\alpha]_D^{20}$ = -15.0 (*c* 0.17 in MeOH); **IR** (neat): υ = 3298, 2938, 2852, 1537, 1442, 1204, 1108 cm^{-1}; **^{1}H NMR** (600 MHz, $CDCl_3$): δ 8.68 (s, 1H), 7.98 (s, 1H), 6.11 (s, 1H), 5.59 (d, J = 4.7 Hz, 1H), 4.23 (dd, J = 4.7, 4.4 Hz, 1H), 3.64 (ddd, J = 11.1, 11.1, 4.0 Hz, 1H), 2.08 (m, 1H), 1.72 – 1.82 (4H), 1.49 (m, 1H), 1.19 – 1.40 (m, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 151.1, 150.7, 150.1, 133.3, 116.5, 91.0, 80.9, 76.1, 53.4, 47.7, 40.8, 24.8, 23.6, 23.3

HRMS (EI^+) calcd for $C_{14}H_{16}ClIN_3O_2^+$ 419.9970; Found 419.9952.

Determination of relative stereochemistry for nucleoside 86

Analysis of 2D NOESY of nucleoside **86** supported the indicated stereochemistry

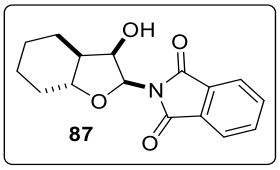


Preparation of nucleoside analogue 87

To a stirred solution of fluorohydrins **70** (0.105 g, 0.344 mmol, 1.0 equiv) in MeCN (3.00 mL) at -15˚C was added tetramethylammoniumtriacetoxyborohydride (0.453 g, 1.72 mmol, 5.0 equiv) and acetic acid (0.190 mL, 3.44 mmol, 10 equiv). The resulting mixture was stirred 16 hours. The reaction mixture was then diluted with a saturated solution of Rochelle salt and washed three times with CH_2Cl_2. The organic layer was separated, dried over $MgSO_4$, filtered, and

concentrated under reduced pressure. The crude product **S70** was purified by flash chromatography (EtOAc:pentane – 70:30) to afford **S70** as a white solid (0.076 g, 72%)

To a stirred solution of *syn*-diol-fluorohydrins **S70** (0.076, 0.248 mmol, 1.0 equiv.) in MeCN (2.50 mL) was added $InCl_3$ (0.014 g, 0.062 mmol, 0.25 equiv.) and the reaction mixture was stirred for 24 hours. The reaction mixture was diluted with CH_2Cl_2 and was washed with saturated sodium bicarbonate solution. The organic layer was separated, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The ratio of anomers (α:β) was determined to be 2.5:1 by ^1H NMR spectroscopic analysis of the crude product. The crude product **87** was purified by flash chromatography (EtOAc:pentane – 25:75) to afford nucleoside **87** (α-anomer) as a colorless oil (42.7 mg, 60%)

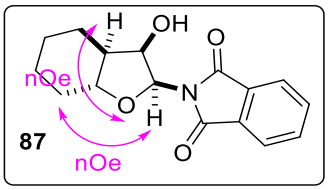


Data for nucleoside analogue **87** (α-anomer): $[\alpha]_D^{20}$ = +46.6 (*c* 0.38 in CH_2Cl_2); **IR** (neat): υ = 3475, 2935, 1708, 1370, 720 cm^{-1}; **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.88 (m, 2H), 7.77 (m, 2H), 6.13 (d, *J* = 5.0 Hz, 1H), 4.40 (ddd, *J* = 11.8, 5.0, 4.8 Hz, 1H), 4.03 (ddd, *J* = 10.6, 10.6, 4.1 Hz, 1H), 3.13 (d, *J* =11.9 Hz, 1H), 2.22 (m, 1H), 1.94 (m, 1H), 1.85 (m, 2H), 1.62 (dddd, *J* = 11.9, 11.9, 4.6, 3.2 Hz, 1H), 1.51 (m, 1H), 1.23 – 1.40(3H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 169.1, 134.6, 132.1, 123.8, 84.4, 81.1, 75.3, 51.4, 31.7, 25.4, 24.0, 24.0

HRMS (EI^+) calcd for $C_{16}H_{18}NO_4$ [M + H^+] 288.1230; found 288.1246

Determination of relative stereochemistry for nucleoside 87

Analysis of 2D NOESY of nucleoside **87** (α-anomer) supported the indicated stereochemistry

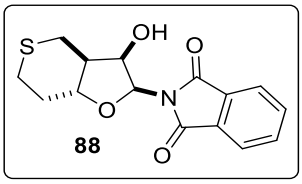


Preparation of nucleoside analogue 88

To a stirred solution of fluorohydrins **69** (0.097 g, 0.30 mmol, 1.0 equiv) in MeCN (3.00 mL) at -15˚C was added tetramethylammoniumtriacetoxyborohydride (0.395 g, 1.50 mmol, 5.0 equiv) and acetic acid (0.172 mL, 1.50 mmol, 10 equiv). The resulting mixture was stirred 16 hours. The reaction mixture was then diluted with a saturated solution of Rochelle salt and washed

three times with CH_2Cl_2. The organic layer was separated, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product **S69** was purified by flash chromatography (EtOAc:pentane – 70:30) to afford **S69** as a white solid (0.068 g, 70%)

To a stirred solution of *syn*-diol-fluorohydrins **S69** (0.047, 0.143 mmol, 1.0 equiv.) in MeCN (1.43 mL) was added $InCl_3$ (7.9 mg, 0.036 mmol, 0.25 equiv.) and the reaction mixture was stirred for 24 hours. The reaction mixture was diluted with CH_2Cl_2 and was washed with saturated sodium bicarbonate solution. The organic layer was separated, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The ratio of anomers (α:β) was determined to be 3:1 by ^1H NMR spectroscopic analysis of the crude product. The crude product **88** was purified by flash chromatography (EtOAc:pentane – 40:60) to afford **88** (α-anomer) as a colorless oil (23.7 mg, 73%).



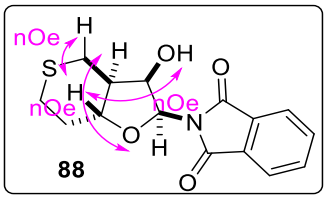
88

Data for nucleoside analogue **88** (α-anomer): $[\alpha]_D^{20}$ = +18.6 (*c* 2.37 in CH_2Cl_2); **IR** (neat): υ = 3475, 2923, 1774, 1709, 1373, 719 cm^{-1}; **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.88 (m, 2H), 7.77 (m, 2H), 6.13 (d, *J* = 4.9 Hz, 1H), 4.40 (ddd, *J* = 11.5, 4.7, 4.7 Hz, 1H), 4.03 (ddd, *J* = 11.2, 11.2, 3.6 Hz, 1H), 3.35 (d, *J* = 11.9 Hz, 1H), 2.98 (dd, *J* = 13.1 11.9 Hz, 1H), 2.82 (m ,2H), 2.69 (m, 1H), 2.50 (m, 1H), 2.10 (m ,1H), 1.74 (m , 1H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 169.2, 134.8, 131.9, 124.0, 83.0, 80.2, 75.2, 51.3, 33.5, 27.6, 27.4

HRMS (EI$^+$) calcd for $C_{15}H_{19}N_2O_4S$ [M + NH_4^+] 323.1060; found 323.1037

Determination of relative stereochemistry for nucleoside 88

Analysis of 2D NOESY of nucleoside **88** (α-anomer) supported the indicated stereochemistry

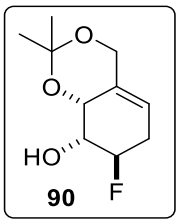


88

Preparation of carbocycle 90

Following General Procedure E, to a stirred solution of 5-(methanesulfonyl)-1-phenyl-1H-tetrazole (0.126 g, 0.560 mmol) in dry THF (0.70 mL) at -78^{o}C was added dropwise a 1 M LiHMDS (0.560 mL, 0.560 mmol) and the resulting reaction mixture was stirred for 30 minutes.

A solution of fluorohydrin **51** (0.052 g, 0.224 mmol) in dry THF (0.45 mL) was then added dropwise and the reaction mixture was allowed to stir for 5 hrs at -78°C. Purification of crude alkene **S51** by flash chromatography (pentane:EtOAc – 80:20) afforded alkene **S51** (0.034 g, 65 % yield) as a colorless oil**.** A mixture Grubbs II catalyst (2.9 mg) and alkene **S51** (0.034 g, 0.148 mmol) in dry toluene (5.91 mL) was purged with N_2 for 45 minutes in a sealed reaction vessel and subsequently heated to 80°C for 6 hrs. Purification of crude carbacycle **90** by flash chromatography (pentane:EtOAc – 75:25) afforded carbacycle **90** (0.019 g, 63 % yield) as a white solid.



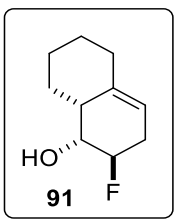
90

Data for carbacycle **90**: $[\alpha]_D^{20}$ = -32.8 (*c* 0.50 in CH_2Cl_2); ^{1}**H NMR** (600 MHz, $CDCl_3$): δ 5.45 (s, 1H), 4.96 (m, 1H), 4.61 (s, 1H), 4.51 (d, *J* = 13.5 Hz, 1H), 4.13 (m, 1H), 4.10 (d, *J* = 13.5 Hz, 1H), 2.71 (dd, J = 3.8, 1.5 Hz, 1H), 2.62 (dddd, *J* = 43.7, 19.2, 5.6, 2.6 Hz, 1H), 2.31 (dd, *J* = 21.2, 19.2 Hz, 1H), 1.57 (s, 3H), 1.44 (s, 3H); ^{13}**C NMR** (150 MHz, $CDCl_3$): δ 128.2, 117.8, 99.4, 88.5 (d, *J* = 166.5 Hz), 66.1 (d, *J* = 2.7 Hz), 65.9 (d, *J* = 27.7 Hz), 63.7, 29.0, 27.4 (d, *J* = 22.1), 20.0.

HRMS (EI$^+$) calcd for $[C_{10}H_{16}FO_3]^+$ 203.1078; found 203.1058

Preparation of carbacycle 91

Following General Procedure E, to a stirred solution of 5-(methanesulfonyl)-1-phenyl-1H-tetrazole (0.134 g, 0.60 mmol) in dry THF (0.75 mL) at -78ºC was added dropwise a 1 M LiHMDS (0.60 mL, 0.60 mmol) and the resulting reaction mixture was stirred for 30 minutes. A solution of fluorohydrin **66** (0.060 g, 0.30 mmol) in dry THF (1.20 mL) was then added dropwise and the reaction mixture was allowed to stir for 5 hrs at -78°C. Purification of the crude alkene **S66** by flash chromatography (pentane:EtOAc – 90:10) afforded alkene **S66** (0.031 g, 52 % yield) as a white solid**.** A mixture Grubbs II catalyst (5.5 mg, 0.05 equiv.) and alkene **S66** (0.026 g, 0.13 mmol) in dry toluene (5.30 mL) was purged with N_2 for 30 minutes in a sealed reaction vessel and subsequently heated to 80°C for 8 hrs. Purification of the crude carbacycle **91** by flash chromatography (pentane:Et_2O – 85:15) afforded carbacycle **91** (15.9 mg, 72 % yield) as a colorless oil.



91

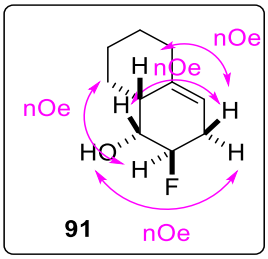
Data for carbacycle **91**: $[\alpha]_D^{20}$ = -111.3 (*c* 0.3 in CH_2Cl_2); **IR** (neat): υ = 3418, 2925, 2853, 1447, 1003 cm^{-1};^{1}**H NMR** (600 MHz, $CDCl_3$): δ 5.17 (m, 1H), 4.68 (dddd, J = 52.2, 13.8, 8.2, 5.6 Hz, 1H), 3.99 (m, 1H), 2.50 (m, 1H), 2.44 (m,

1H), 2.26 (m, 1H), 2.23 (m, 1H), 2.09 (d, J = 3.7 Hz), 2.06 (m, 1H), 1.95 (m, 1H), 1.87 (m ,1H), 1.81 (m ,1H), 1.39 (ddd, J = 13.2, 3.8, 3.8 Hz, 1H), 1.24 (ddd, J = 13.0, 3.8, 3.8 Hz, 1H), 1.13 (dd, J = 12.8, 3.7 Hz, 1H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 136.9 (d, J = 1.8 Hz), 113.0 (d, J = 8.8 Hz), 90.6 (d, J = 171.2 Hz) , 71.2 (d, J = 19.2 Hz), 42.4 (d, J = 4.8 Hz), 35.4, 29.8 (d, J = 19.8 Hz), 28.7, 28.3; **^{19}F NMR** (470 MHz, $CDCl_3$): δ –191.8

HRMS (EI^+) calcd for $C_{10}H_{16}FO_4$ 171.1180; found 171.1154

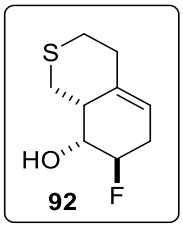
Determination of relative stereochemistry for carbacycle 91

Analysis of 2D NOESY of carbacycle **91** supported the indicated stereochemistry



Preparation of carbocycle 92

Following General Procedure E, to a stirred solution of 5-(methanesulfonyl)-1-phenyl-1H-tetrazole (0.099 g, 0.44 mmol) in dry THF (0.55 mL) at -78°C was added dropwise a 1 M LiHMDS (0.440 mL, 0.440 mmol) and the resulting reaction mixture was stirred for 30 minutes. A solution of fluorohydrin **67** (0.048 g, 0.220 mmol) in dry THF (2.20 mL) was then added dropwise and the reaction mixture was allowed to stir for 3 hrs at -78°C. Purification of the crude alkene **S67** by flash chromatography (pentane:EtOAc – 85:15) afforded alkene **S67** (0.029 g, 61 % yield) as a off-white solid**.** A mixture Grela catalyst (5.9 mg, 0.10 equiv.) and alkene **S67** (0.019 g, 0.088 mmol) in dry toluene (3.52 mL) was purged with N_2 for 30 minutes in a sealed reaction vessel and subsequently heated to 80°C for 8 hrs. Purification of the crude carbacycle **92** by flash chromatography (pentane:EtOAc – 90:10) afforded carbacycle **92** (0.013 g, 71 % yield) as a white solid.



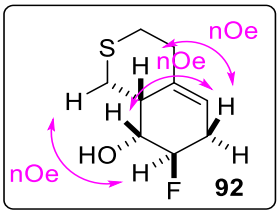
Data for carbacycle **92**: **$[\alpha]_D^{20}$** = -77.2 (*c* 0.53 in CH_2Cl_2); **IR** (neat): υ = 3424, 2924, 1426, 1290, 1088, 1057, 1021 cm^{-1};**^{1}H NMR** (600 MHz, $CDCl_3$): δ 5.27 (m, 1H), 4.64 (dddd, J = 52.7, 15.5, 9.3, 6.3 Hz, 1H), 4.00 (ddd, J = 16.3, 9.3, 7.1 Hz, 1H), 3.01 (dd, J = 12.9, 2.9 Hz, 1H), 2.85 (m, 1H), 2.63 (m, 2H), 2.55 (m, 1H), 2.53 (m, 1H), 2.43 (dd, J = 12.8, 12.4 Hz, 1H), 2.35 (m, 1H), 2.32 (m, 1H), 2.27 (m, 1H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 138.9, 116.2 (d, J = 10.4 Hz), 90.3 (d, J =

172.2 Hz), 71.5 (d, J = 17.8 Hz), 45.3 (d, J = 5.6 Hz), 31.8, 30.8, 30.3 (d, J = 20.0 Hz); **^{19}F NMR** (470 MHz, $CDCl_3$): δ –191.4

HRMS (EI^+) calcd for $[C_9H_{14}FOS]^+$ 189.0744; found 189.0757

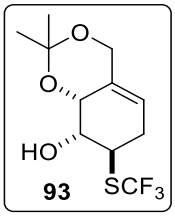
Determination of relative stereochemistry for carbacycle 92

Analysis of 2D NOESY of carbacycle **92** supported the indicated stereochemistry



Preparation of carbocycle 93

Following General Procedure E, to a stirred solution of 5-(methanesulfonyl)-1-phenyl-1H-tetrazole (0.066 g, 0.295 mmol) in dry THF (0.37 mL) at -78ºC was added dropwise a 1 M LiHMDS (0.295 mL, 0.295 mmol) and the resulting reaction mixture was stirred for 30 minutes. A solution of fluorohydrin **71** (0.042 g, 0.134 mmol) in dry THF (0.54 mL) was then added dropwise and the reaction mixture was allowed to stir for 3 hrs at -78°C. Purification of the crude alkene **S71** by flash chromatography (pentane:Et_2O – 80:20) afforded alkene **S71** (0.023 g, 56 % yield) as a colorless oil**.** A mixture Grubbs II catalyst (2.9 mg) and alkene **S71** (0.021 g, 0.067 mmol) in dry toluene (2.70 mL) was purged with N_2 for 30 minutes in a sealed reaction vessel and subsequently heated to 90°C for 6 hrs. Purification of the crude carbacycle **93** by flash chromatography (pentane:EtOAc – 80:20) afforded carbacycle **93** (0.013 g, 74 % yield) as a white solid.

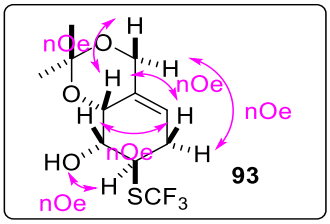


Data for carbacycle **93**: **$[\alpha]_D^{20}$** = -54.3 (*c* 0.83 in CH_2Cl_2); **IR** (neat): υ = 3470, 1430, 1111, 879, cm^{-1};**^{1}H NMR** (600 MHz, $CDCl_3$): δ 5.52 (m, 1H), 4.62 (m, 1H), 4.48 (dd, *J* = 13.4, 2.6 Hz, 1H), 4.11 (m, 1H), 4.06 (d, *J* = 13.4 Hz, 1H), 3.75 (m, 1H), 3.00 (d, *J* = 18.8 Hz, 1H), 2.94 (d, *J* = 1.4 Hz, 1H), 2.21 (ddd, *J* = 18.8, 4.4, 2.1 Hz, 1H), 1.58 (s, 3H), 1.43 (s, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 130.9 (q, *J* = 307.7 Hz), 128.8, 119.6, 99.6, 67.6, 65.7, 63.8, 41.5 (q, *J* = 1.6 Hz), 29.0, 27.4, 20.1; **^{19}F NMR** (470 MHz, $CDCl_3$): δ –39.9

HRMS (EI^+) calcd for $[C_{11}H_{16}F_3O_3S]^+$ 285.0767; found 285.0780

Determination of relative stereochemistry for carbacycle 93

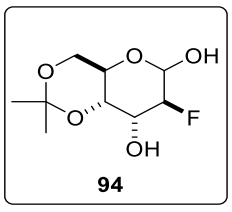
Analysis of 2D NOESY for carbacycle **93** supported the indicated stereochemistry



Synthesis of 2-fluoro-2-deoxy- D-altrose acetonide (94)

The fluorohydrin **58** (0.150 g, 0.397 mmol, 1 equiv.) in MeCN (0.45 mL, 0.9 M) was added to a stirred solution of $Me_4NBH(OAc)_3$ (0.520 g, 1.98 mmol, 5 equiv.) and AcOH (0.23 mL, 3.97 mmol, 10 equiv.) in MeCN (2.0 mL, 0.2 M) at -25°C and the resulting mixture was stirred for 24 hrs. The reaction mixture was then quenched by addition of a saturated aqueous solution of sodium tartrate. The aqueous layer was removed and extracted four times with CH_2Cl_2, and the combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. Purification of the crude product by flash chromatography (hexanes:EtOAc – 75:25) afforded the 1,3 *syn*-fluorodiol (0.114 g, 76 %).

To a cold solution (0 °C) of the 1,3-*syn*-fluorodiol (0.060 g, 0.16 mmol) in THF (1.6 mL) was added a solution of tetrabutylammonium fluoride in THF (1 M, 0.18 mL, 0.18 mmol), and the reaction mixture was stirred for 30 minutes. The reaction mixture was then diluted with Et_2O (2 mL) and was washed with a solution of saturated aqueous ammonium chloride. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. Purification of the crude product by flash chromatography (CH_2Cl_2-MeOH 95:5) afforded the deprotected 1,3-*syn*-fluorotriol (32 mg, 91% yield). To a cold (0°C) solution of bis-(acetoxy)iodobenzene (35 mg, 0.108 mmol) and the 1,3-*syn*-fluorotriol (23 mg, 0.103 mmol), in CH_2Cl_2 (1.1 mL), was added 2,2,6,6-tetramethylpiperidinyloxy (1 mg, cat.) and the reaction mixture was allowed to gradually warm to room temperature and stirred for 5 hrs and the reaction mixture was concentrated under reduced pressure. Purification of the crude fluorohydrin **94** (dr = 1:1) by flash chromatography (pentane-EtOAc 5:5) afforded **94** (15 mg, 65% yield) as a clear oil.



Data for 2-fluoro-2-deoxy- L-altrose acetonide (**94**) $[\alpha]_D^{20}$ = + 2.5 (*c* 0.83 in $CHCl_3$); **IR** (neat)**:** υ = 3413, 2918, 1078, 1043 cm^{-1}; **^{1}H NMR** (600 MHz, $CDCl_3$): δ 5.12 (2H), 4.68 (2H), 4.38 (1H), 4.27 (2H), 4.16 (1H), 3.91 (7H), 3.27 (1H), 2.68 (1H), 2.30 (1H), 1.49 (12H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ

100.4, 100.3, 92.9, 91.8, 89.2, 86.5, 69.0, 68.7, 67.7, 67.6, 64.4, 62.6, 62.3, 59.4, 29.2, 29.1, 19.5, 19.4 **^{19}F NMR** (470 MHz, $CDCl_3$): δ -194.9, -216.5

HRMS (ESI) *m/z* calcd for $C_9H_{16}FO_5$ $[M + H]^+$ 223.0976, found 223.0965

Synthesis of 2-fluoro-2-deoxy-L-galactose (95)

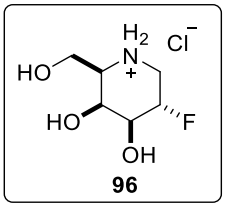
To a cold (0 °C), stirred solution of fluorohydrin **58** (0.189 g, 0.500 mmol, 1.0 equiv.) in dry THF (0.1 M) was added a solution of catechol borane in THF (1.1 mL, 1.0 M, 2.2 equiv.). The resulting mixture was allowed to warm gradually to room temperature and was then stirred for an additional 45 minutes or until complete consumption of starting chlorohydrin was observed by TLC analysis. The mixture was then diluted with MeOH (to 0.05 M) and a solution of saturated aqueous sodium tartrate was added. The biphasic mixture was stirred vigorously for 2 hours, after which time the aqueous layer was removed and extracted three times with Et_2O. The combined organic layers were dried over $MgSO_4$, concentrated under reduced pressure, and the crude product was purified by flash chromatography (pentane- EtOAc; 2:1) to yield the 1,3-*anti*-fluorodiol (0.056 g, 82 %)

To a cold solution (0 °C) of the 1,3-*anti*-fluorodiol (0.076 g, 0.20 mmol, 1 equiv.) in THF (2.0 mL) was added a solution of tetrabutylammonium fluoride in THF (1 M, 0.22 mL, 0.22 mmol, 1.1 equiv.), and the reaction mixture was stirred for 4 hrs. The reaction mixture was then diluted with Et_2O (2 mL) and was washed with a solution of saturated aqueous ammonium chloride. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. Purification of the crude product by flash chromatography (CH_2Cl_2-MeOH 95:5) afforded the deprotected 1,3-*anti*-fluorotriol (41 mg, 91% yield) (See **Pre95**-**XRD** for X-ray). To a cold (0°C) solution of bis-(acetoxy)iodobenzene (12.9 mg, 0.040 mmol) and the 1,3-*anti*-fluorotriol (9 mg, 0.04 mmol), in CH_2Cl_2 (0.40 mL), was added 2,2,6,6-tetramethylpiperidinyloxy (1 mg, cat.) and the reaction mixture was allowed to gradually warm to room temperature and stirred for 8 hrs and the reaction mixture was concentrated under reduced pressure. Purification of the crude fluorohydrin (dr 1:0.1.0) by flash chromatography (pentane-EtOAc 5:5) afforded (4.6 mg, 51 % yield) as a clear oil. The purified product (4.6 mg, 0.020 mmol) was then dissolved in CH_2Cl_2 (0.20 mL) and and 0.05 mL of TFA was added. The reaction mixture was left to stir for 24 hrs and the solvent was removed under reduced pressure to give pure **95** (4.3 mg, 100%) as a colorless oil. The data for **95** matched those of previously reported for 2-fluoro-2-deoxy-D-galactose.[2]

Synthesis of fluorohydrin 54 and 2-fluoro-2-deoxy migalastat (96)

Following General Procedure B, a solution of 3-*N*-*Cbz*-aminopropanal (0.10 g, 0.483 mmol), NFSI (0.152 g, 0.483 mmol), D-proline (0.056 g, 0.483 mmol) and $NaHCO_3$ (0.041 g, 0.483 mmol) was stirred for 3 hours at -10 °C in DMF (0.65 mL). Dioxanone **13** (0.039 mL, 0.322 mmol) in CH_2Cl_2 (5.8 mL) was stirred for 24 hours. Purification of the crude fluorohydrin **54** by flash chromatography (pentane-EtOAc 3:1) afforded fluorohydrin **54** (0.056 g, 49 % yield) as a yellow oil. ^{1}H-NMR spectroscopic analysis of this material indicated that it exists as a complicated 1:1 mixture of fluorohydrin **54**:hemiminals (1:1 mixture of diastereomers).

Following General Procedure I, the fluorohydrin **54** (0.051 g, 0.144 mmol) and Pd/C powder were stirred in MeOH (1.4 mL) with bubbling in H_2 gas for 18 hrs. The Pd/C was filtered off, the solvent was removed under reduced pressure, and the crude product (dr 7:1) was purified with flash chromatography (EtOAc: pentanes; 40:60) to give a white powder (0.024 g, 83 %). The purified product (0.028 g, 0.139 mmol) was then dissolved in MeOH (1.4 mL) and 0.5 mL of 1 M HCl was added. The reaction mixture was left to stir for 24 hrs and the solvent was removed under reduced pressure to give pure **96** (0.022 g, 97%).



96

Data for 2-fluoro-2-deoxy migalastat (**96**): **$[\alpha]_D^{20}$** = + 10.7 (*c* 1.88 in MeOH); **IR** (neat)**:** υ = 3307, 2952, 2464, 1406, 1111, 1055 cm^{-1}; **^{1}H NMR** (500 MHz, MeOD): δ 5.25 (dddd, *J* = 49.2, 10.8, 9.3, 5.6 Hz, 1H), 4.06 (m, 1H), 3.80 (m, 3H), 3.57 (ddd, *J* = 12.4, 5.6, 2.3 Hz, 1H), 3.40 (dd, *J* = 8.1, 5.3 Hz, 1H), 3.08 (m, 1H); **^{13}C NMR** (150 MHz, MeOD): δ 88.5 (*J* = 175.5 Hz), 73.1 (d, *J* = 17.7 Hz), 68.9 (d, *J* = 10.1 Hz), 62.0, 60.4, 45.0 (d, *J* = 32.6); **^{19}F NMR** (470 MHz, MeOD):δ -204.5

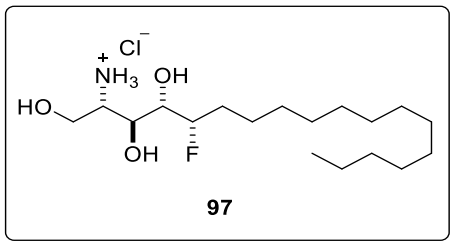
HRMS (ESI) *m/z* calcd for $C_6H_{13}FNO_3^+$ $[M + H]^+$ 166.0874, found 166.0893

*Determination of enantiomeric excess of fluorohydrin **54***

Following General Procedure B, using a 1:1 mixture of L: D - proline, a racemic sample of the fluorohydrin **54** was prepared. Following General Procedure **I**, the optically enriched and racemic samples of fluorohydrin **54** (0.055 g, 0.155 mmol) were converted into their corresponding cyclized products. These were then diacylated with (*R*)-(+)-MTPA-OH (3 equiv.), DIC (6 equiv.), pyridine (3 equiv.), and 4-dimethylaminopyridine (cat.) in CH_2Cl_2 (0.10 M). By analysis of ^{19}F NMR it was determined that the enantiomeric excess was 92 %.

Synthesis of (*5R*)-5-D-ribo-fluorophytosphingosine (97)

To a stirred solution of the fluorohydrin **54** (0.187 g, 0.50 mmol, 1.0 equiv.) in 5.0 mL of THF (0.1 M) was added to benzylamine (0.137 mL, 1.25 mmol, 2.5 equiv.) and glacial acetic acid (0.030 g, 0.50 mmol, 1.0 equiv.), and the resulting mixture was stirred at 20°C for 2 hrs or until complete conversion into the corresponding imine was accomplished (as determined by 1H NMR spectroscopic analysis of small samples removed from the reaction mixture). $NaCNBH_3$ (0.080 g, 1.25 mmol, 2.5 equiv.) was then added and the mixture was stirred for a further 1 hr. The reaction mixture was then diluted with CH_2Cl_2 to a concentration of 0.05 M and treated with water. The layers were separated and the organic layer was washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure. The crude product was purified by flash chromatography (CH_2Cl_2-MeOH; 15:1) to afford the reductive amination product (0.206 g, 88 % yield). Pd/C (2 mg) was added to a stirred solution of purified product (9.3 mg, 0.02 mmol, 1.0 equiv.) in 0.20 mL of MeOH (0.1 M) under a H_2 atmosphere. After 24 hrs the reaction was filtered, concentrated under reduced pressure, and purified by flash column chromatography (CH_2Cl_2-MeOH; 20:1) to give the debenzylated product (7 mg, 93 %). A solution of the debenzylated product (9 mg, 0.024 mmol) in 0.25 mL MeOH (0.1 M) was added 0.05 mL of 1 M HCl and left for 24 hrs. The reaction mixture was then concentrated under reduced pressure to afford pure **97** (8.7 mg, 98 %).

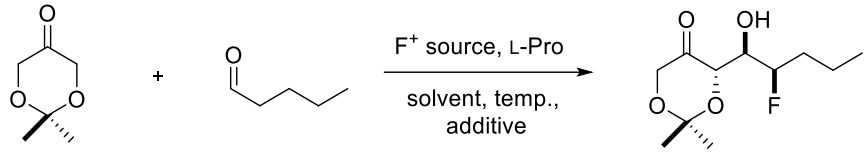


97

Data for (5*R*)-5-D-ribo-fluorophytosphingosine (**97**): $[\alpha]_D^{20}$ = -4.5 (*c* 0.75 in DMSO-d_6); **IR** (neat)**:** υ = 3425, 2924, 1025, 1005, 822, 760, 614 cm^{-1}; **^{1}H NMR** (600 MHz, DMSO-d_6): δ = 7.84 (br s), 4.69 (ddd, *J* = 47.5, 8.6, 4.7 Hz, 1H), 3.80 (dd, *J* = 9.8, 2.7 Hz, 1H), 3.75 (dd, *J* = 11.2, 3.8 Hz, 1H), 3.58 (dd, *J* = 11.0, 9.4 Hz, 1H), 3.28 (dd, *J* = 29.6, 9.8 Hz, 1H), 1.77 (m, 1H), 1.56 (m, 1H), 1.26 (m, 26 H), 0.87 (dd, J = 6.8, 6.8 Hz, 3H); **^{13}C NMR** (150 MHz, DMSO-d_6): δ = 91.8 (*J* = 173.1 Hz), 71.1 (d, *J* = 18.1 Hz), 67.8 (d, *J* = 5.0 Hz), 56.9, 54.5, 31.3, 30.4 (d, *J* = 21.4 Hz), 29.0, 29.0, 29.0, 29.0, 28.9, 28.9, 28.7, 24.8, 24.8, 22.1, 13.9; **^{19}F NMR** (470 MHz, DMSO-d_6):δ -201.0

HRMS (ESI) *m/z* calcd for $C_{18}H_{39}FNO_3^+$ $[M + H]^+$ 336.2908, found 336.2920

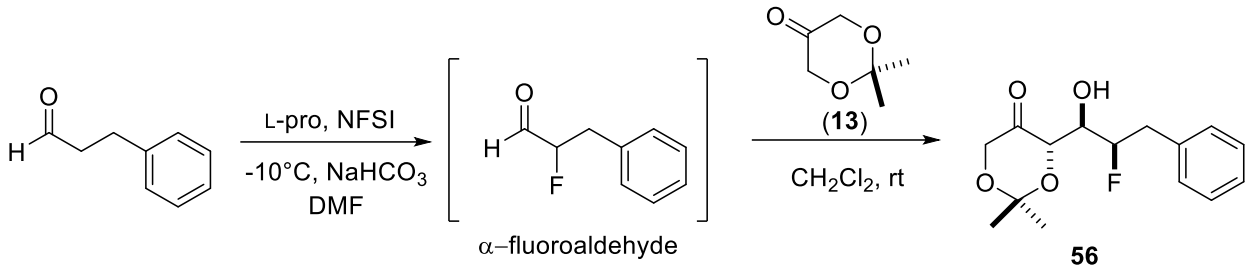
Supplementary Tables and Figures



Entry	(*S*)-Pro equiv.	Temp. (˚C)	Solvent (M)	Additive	F^+ source	Yield
1	0.8	RT	CH_3CN	None	Selectfluor	19 %
2	0.8	0	CH_2Cl_2	None	NFSI	< 5%
3	0.8	0	CH_2Cl_2	TFA	NFSI	< 5 %
4	0.3	RT	CH_3CN /CH_2Cl_2	None	Selectfluor	32 %
5	0.8	RT	THF/IPA	None	Selectfluor	< 5%
6	1.5	4	DMF/CH_2Cl_2	TFA	NFSI	21%
7	1.0	4	DMF/CH_2Cl_2	$NaHCO_3$	NFSI	54%
8	1.0	-10	DMF/CH_2Cl_2	None	NFSI	18%

Supplementary Table 1. Optimization of αFAR reaction.

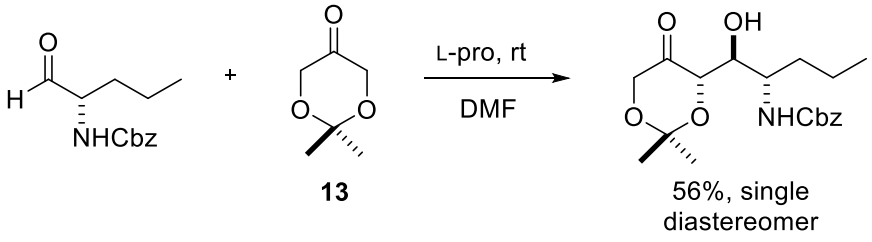
Determination of DKR in αFAR



Entry	Time (hrs)	% ee	Conversion to 56[c]
1	0[a]	23	-
2	1[b]	23	Not detected
3	2[b]	23	46%
4	4[b]	23	53%
5	8[b]	23	83%

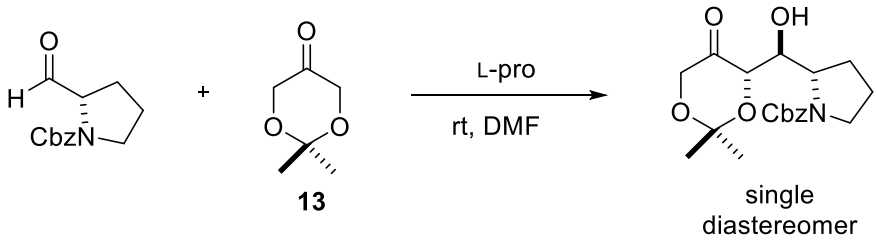
Supplementary Table 2. Monitoring %ee of α-fluoroaldehyde.[a]Before addition of ketone.[b]After addition of ketone.[c]Based on remaining ketone.

Following General Procedure B, the aFAR was stopped at different time intervals to monitor the enantiopurity of the α-fluoroaldehyde over the course of the reaction. The enantiomeric α-fluoroaldehydes were reduced in situ with $NaBH_4$ and separated by chiral HPLC using a CHIRALPAK IG column; flow rate 0.6 mL/min; eluent: hexanes-*i*PrOH 98:2; detection at 260 nm; retention time = 33.57 min and 35.10 min.The enantiomeric excess of the intermediate α-fluoroaldehydes were determined using the same method for each time interval shown above (Table S1).

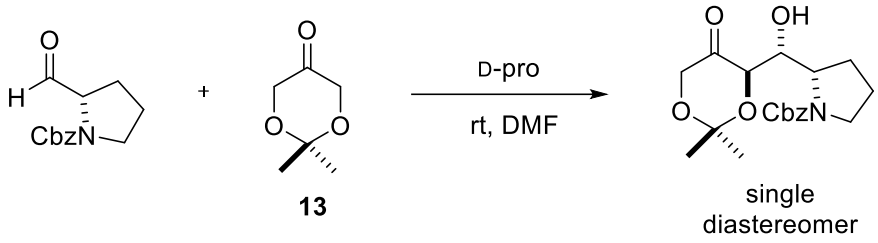


Supplementary Scheme 1. L-proline catalyzed aldol reaction between (*S*)-2-Cbz-aminopentanal and dioxanone (**13**).

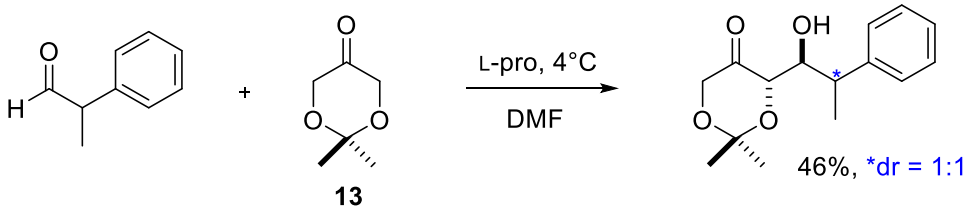
L-proline catalyzed aldol reaction



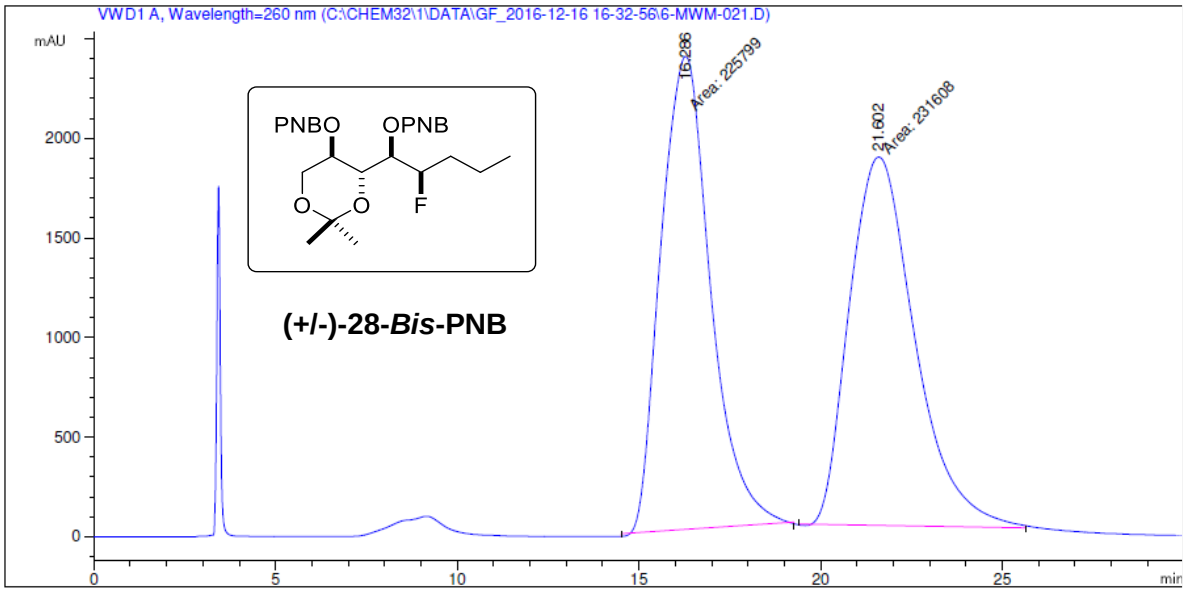
D-proline catalyzed aldol reaction



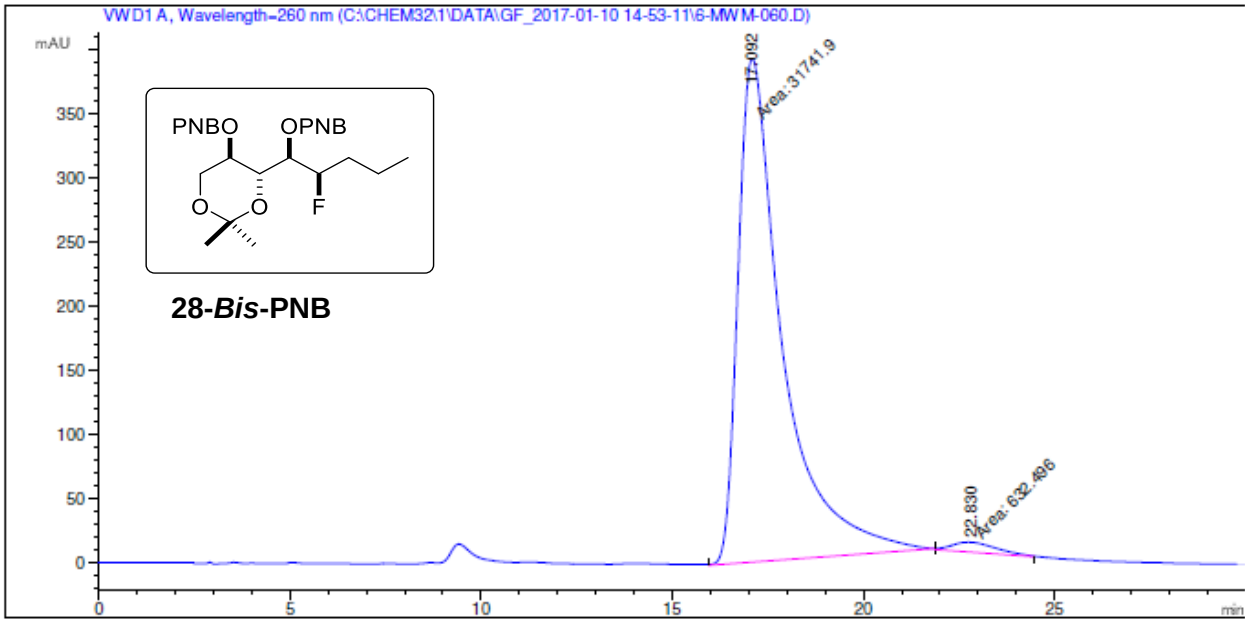
Supplementary Scheme 2 L- and D-proline catalyzed aldol reactions between (*S*)-N-Cbz-prolinal and dioxanone (**13**).



Supplementary Scheme 3. L-proline catalyzed aldol reaction between 2-phenylpropanal and dioxanone (**13**).

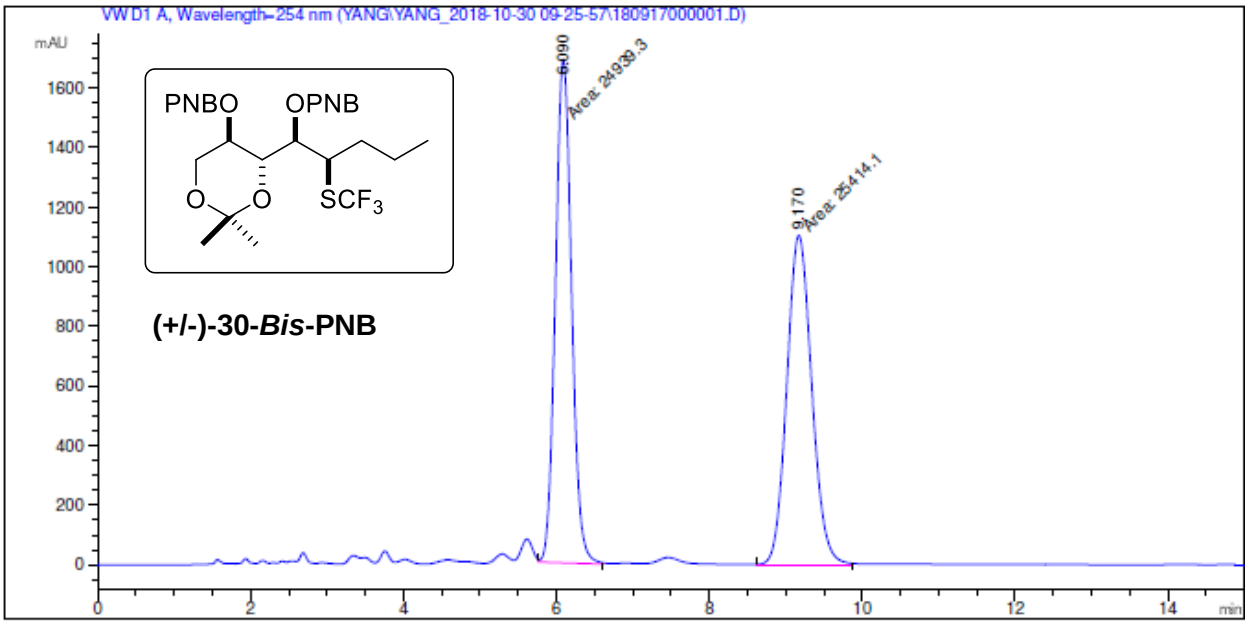


Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	16.286	MM	1.5841	2.25799e5	2375.75269	49.3650
2	21.602	MM	2.0865	2.31608e5	1850.00977	50.6350

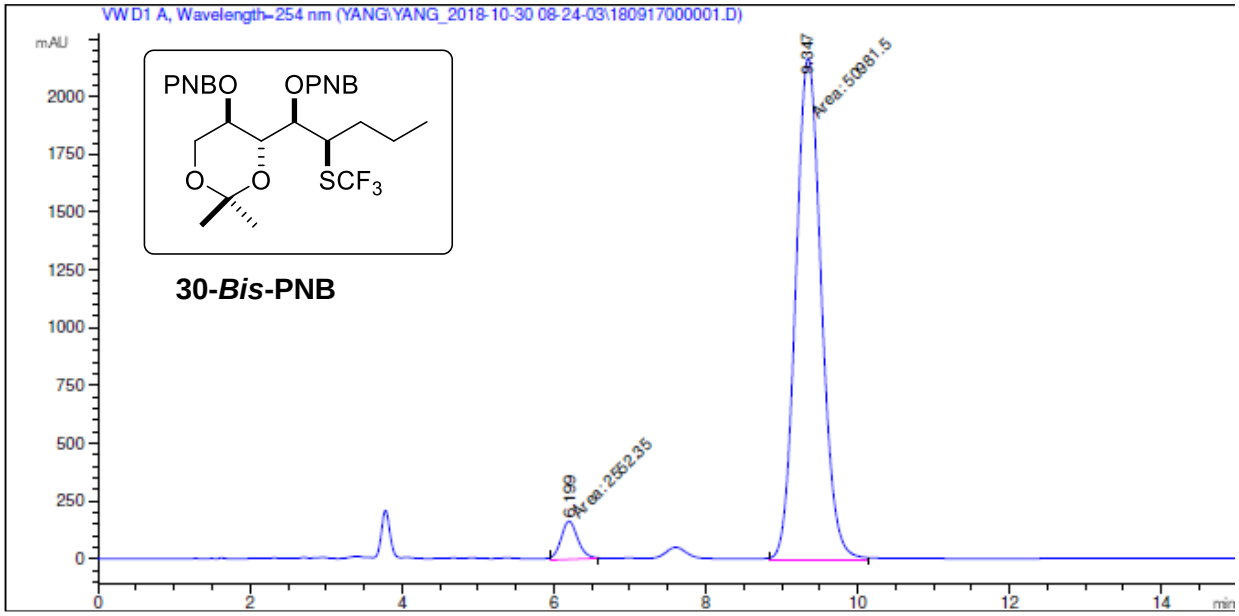


Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	17.092	MM	1.3494	3.17419e4	392.04599	98.0463
2	22.830	MM	1.3567	632.49640	7.76991	1.9537

Supplementary Figure 1. Determination of enantiomeric excess of **28**.

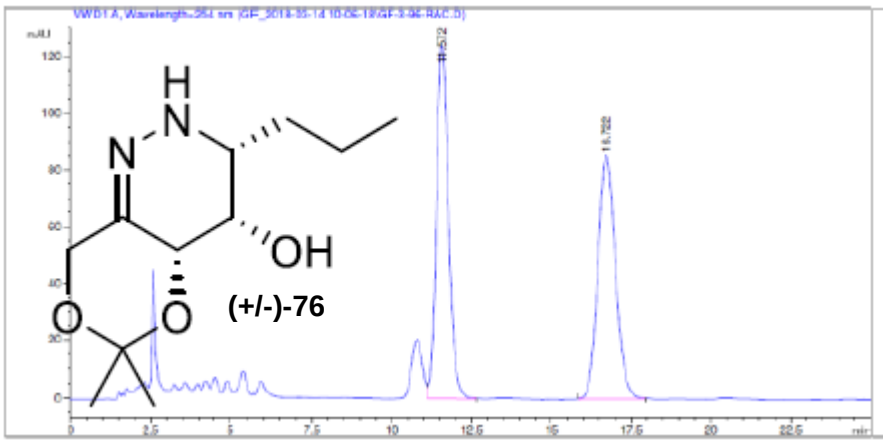


Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	6.090	MM	0.2459	2.49393e4	1690.62378	49.5286
2	9.170	MM	0.3815	2.54141e4	1110.22144	50.4714

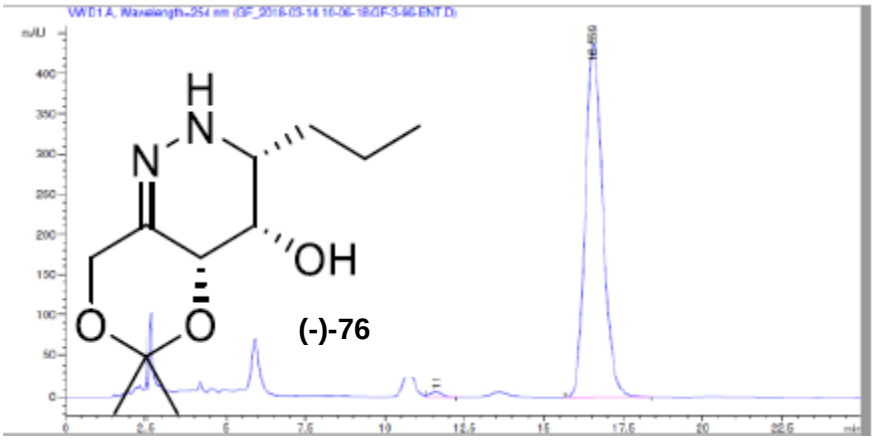


Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	6.199	MM	0.2574	2552.35303	165.24725	4.7677
2	9.347	MM	0.3910	5.09815e4	2172.87427	95.2323

Supplementary Figure 2. Determination of enantiomeric excess of **30**.

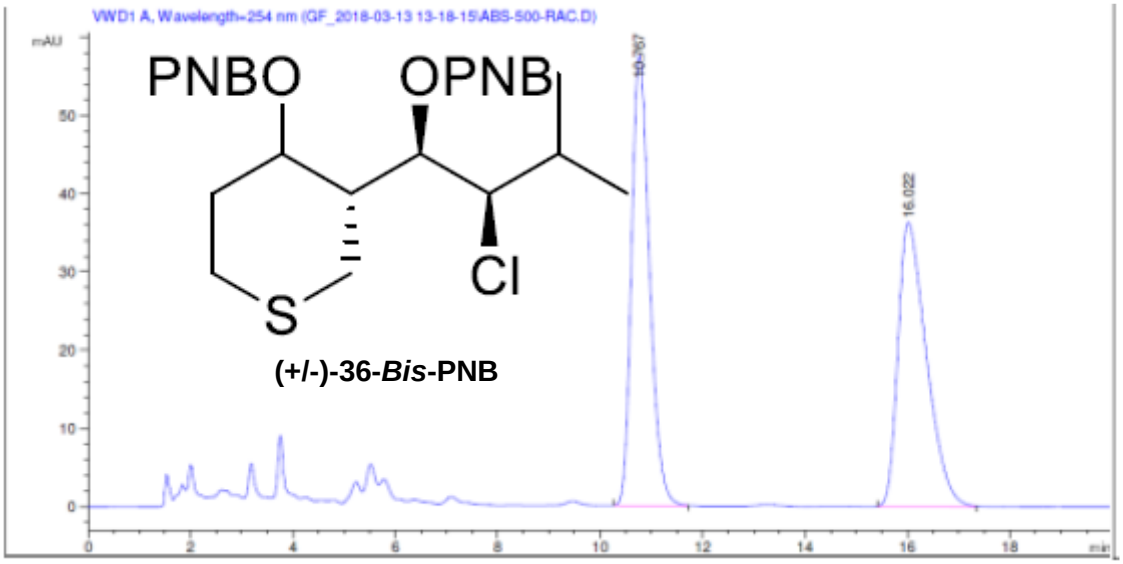


Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	11.572	VB	0.3993	3222.68481	123.99079	49.7858
2	16.722	BB	0.6037	3250.41846	85.20957	50.2142

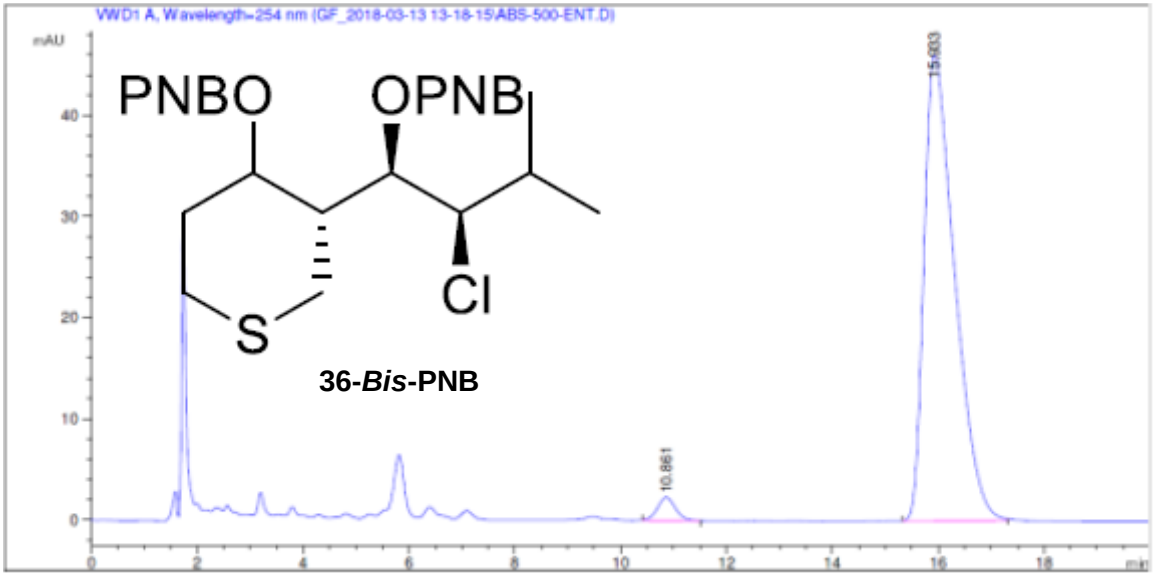


Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	11.596	VB	0.4016	154.58374	5.84761	0.9159
2	16.559	BB	0.5943	1.67232e4	436.26291	99.0841

Supplementary Figure 3. Determination of enantiomeric excess of **76**.

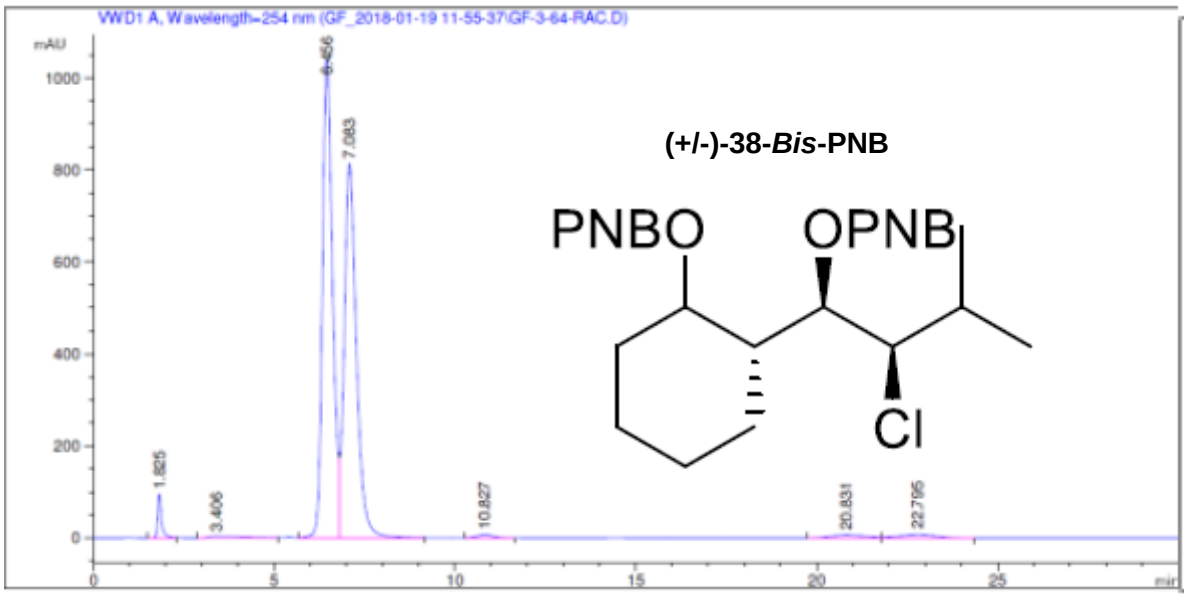


Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	10.767	BB	0.3784	1406.09375	57.52106	50.0987
2	16.022	BB	0.5694	1400.55212	36.31229	49.9013

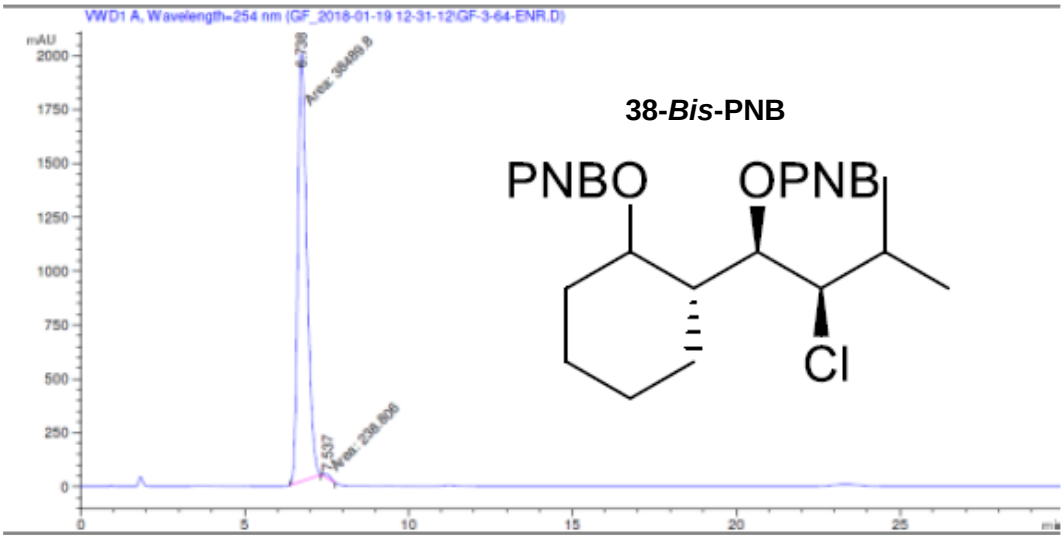


Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	10.861	BB	0.3750	54.24590	2.26922	2.8605
2	15.933	BB	0.6066	1842.12866	46.03395	97.1395

Supplementary Figure 4. Determination of enantiomeric excess of **36**.

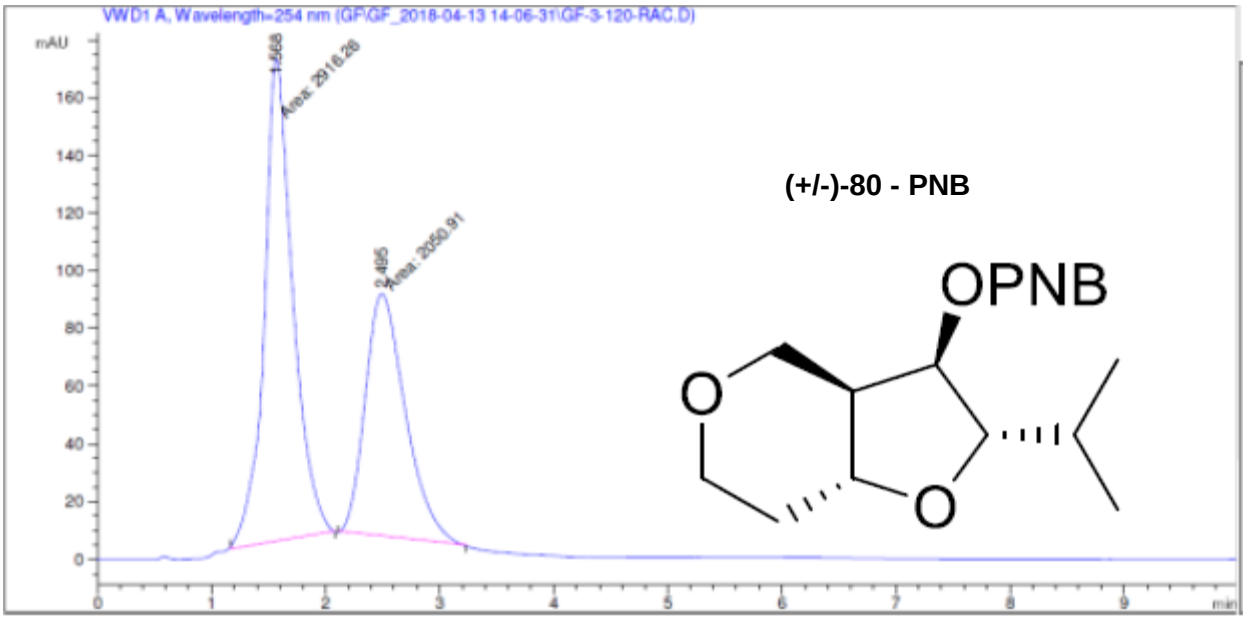


Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	1.825	BV	0.1105	715.49103	95.71639	1.7298
2	3.406	BB	0.8502	254.80144	3.87467	0.6160
3	6.456	VV	0.2971	2.02611e4	1040.47473	48.9826
4	7.083	VB	0.3514	1.90217e4	813.52588	45.9864

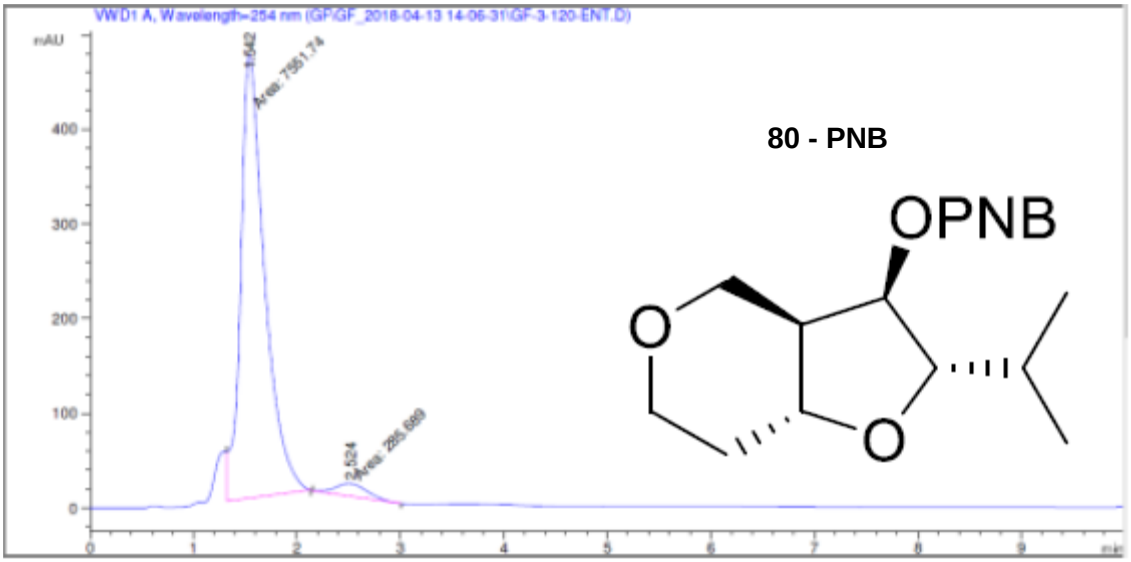


Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	6.738	MM	0.3231	3.84898e4	1985.21973	99.3834
2	7.537	MM	0.2245	238.80635	17.72810	0.6166

Supplementary Figure 5. Determination of enantiomeric excess of **38**.

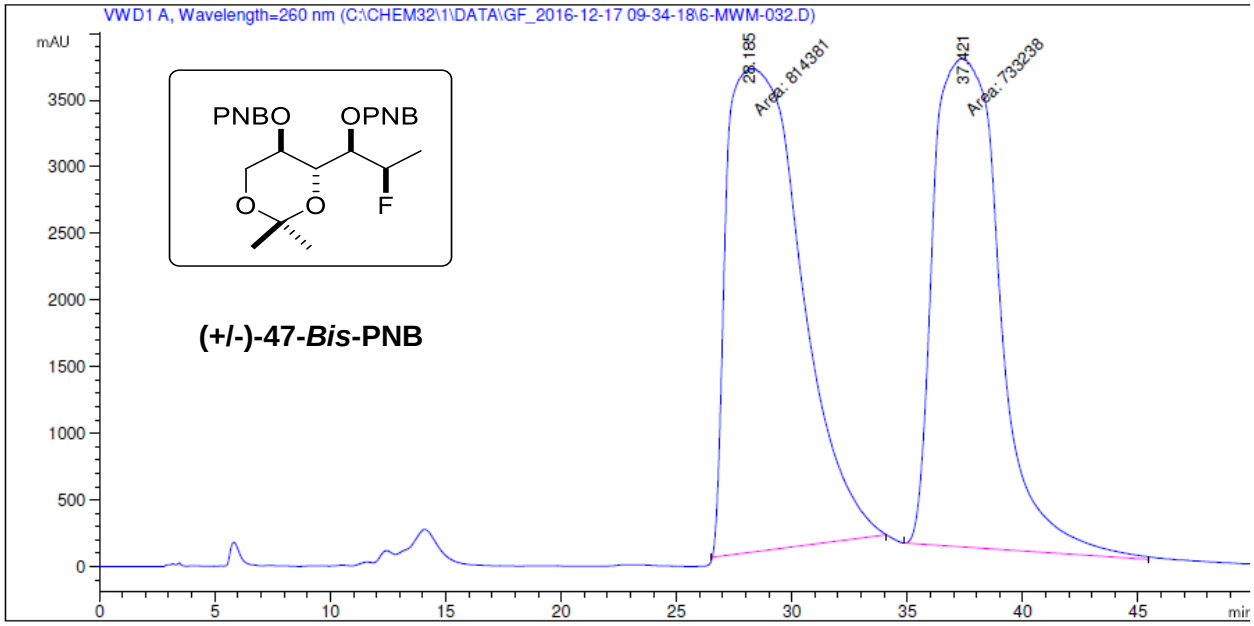


Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	1.568	MM	0.2907	2916.25854	167.17921	58.7107
2	2.495	MM	0.4077	2050.90723	83.83390	41.2893

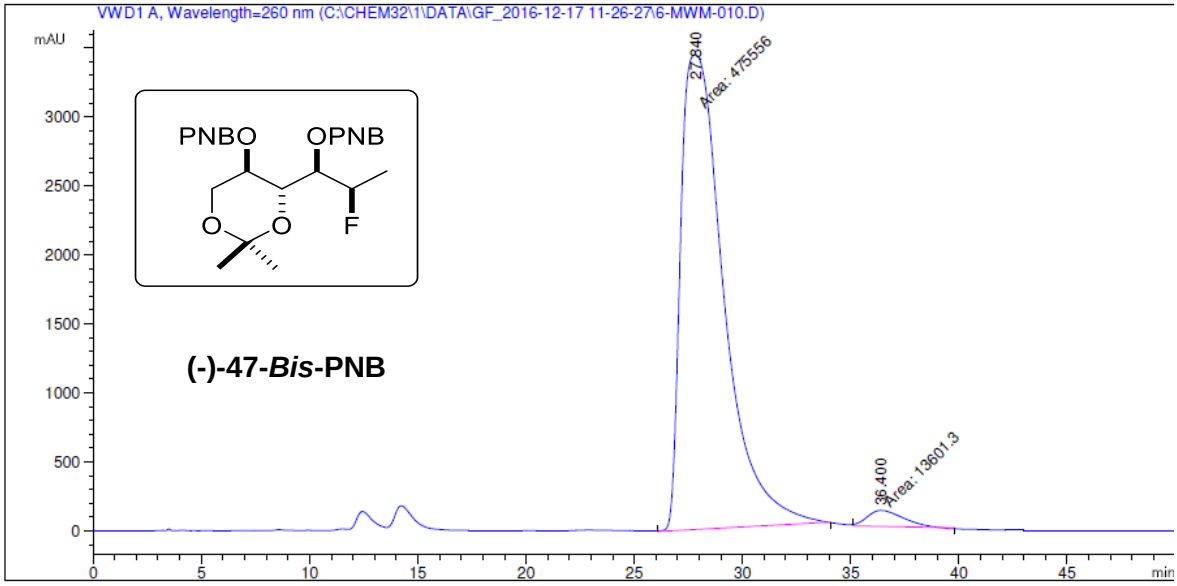


Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	1.542	MM	0.2686	7551.74268	468.56067	96.3548
2	2.524	MM	0.3519	285.68860	13.53053	3.6452

Supplementary Figure 6. Determination of enantiomeric excess of **80**.

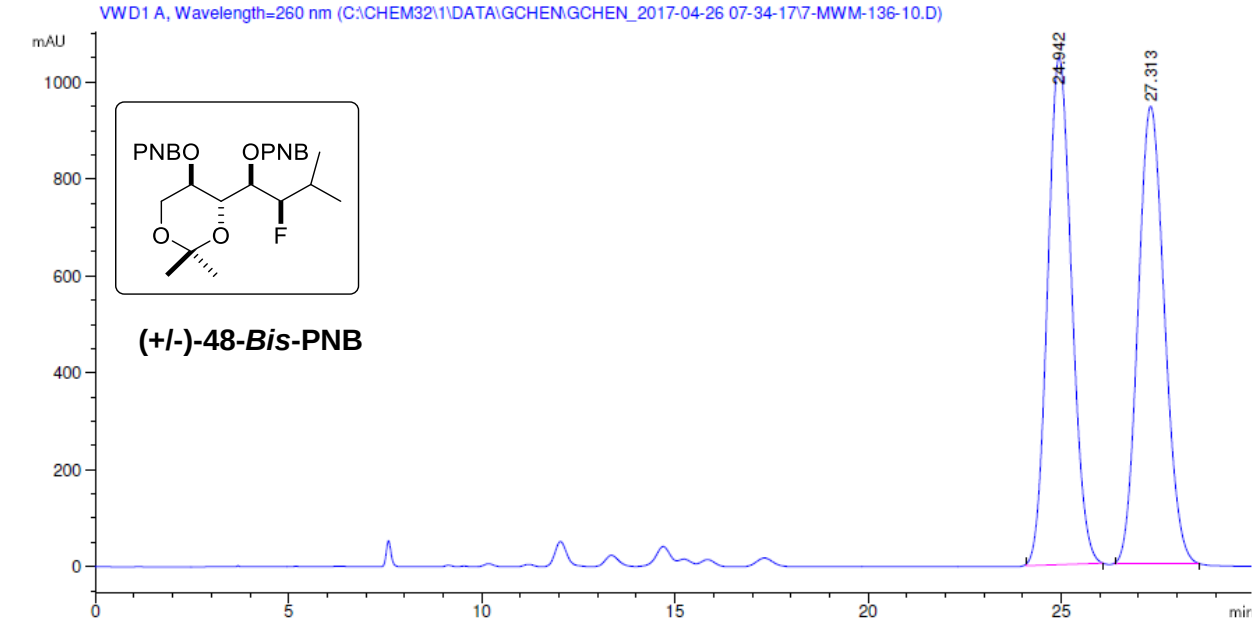


Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	28.185	MM	3.7371	8.14381e5	3631.99609	52.6215
2	37.421	MM	3.3336	7.33238e5	3665.93579	47.3785



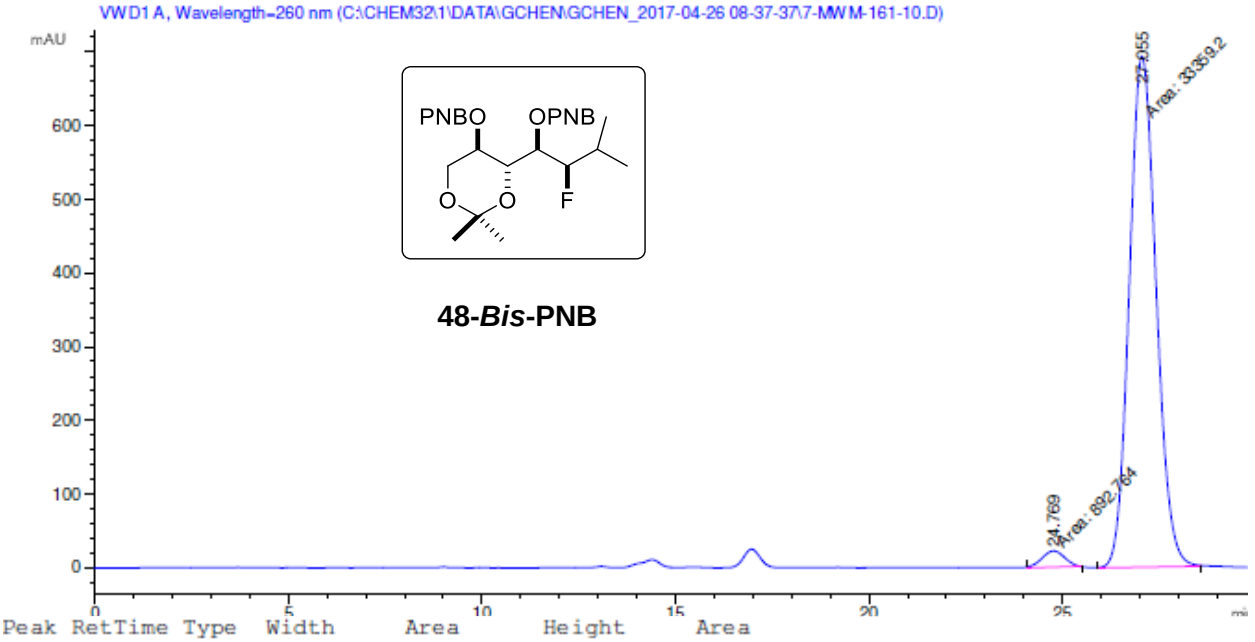
Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	27.840	MM	2.3335	4.82563e5	3446.58838	97.2990
2	36.405	MM	1.9430	1.33957e4	114.90332	2.7010

Supplementary Figure 7. Determination of enantiomeric excess of **47**.



(+/-)-48-*Bis*-PNB

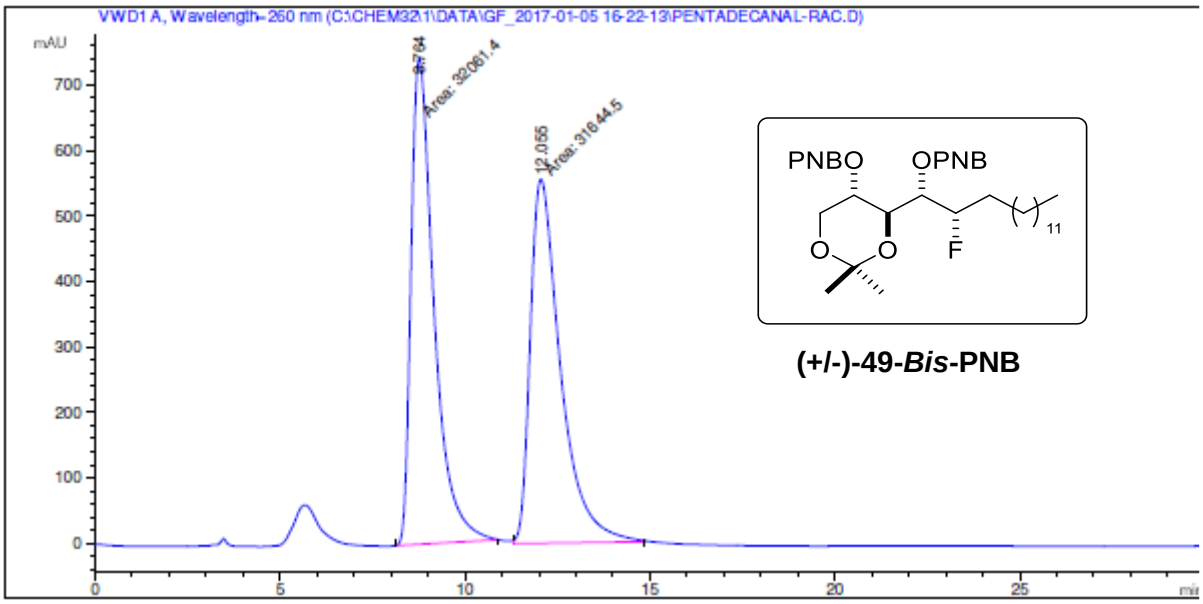
Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	24.942	BB	0.6736	4.51681e4	1047.10242	50.1981
2	27.313	BB	0.7400	4.48115e4	944.25000	49.8019



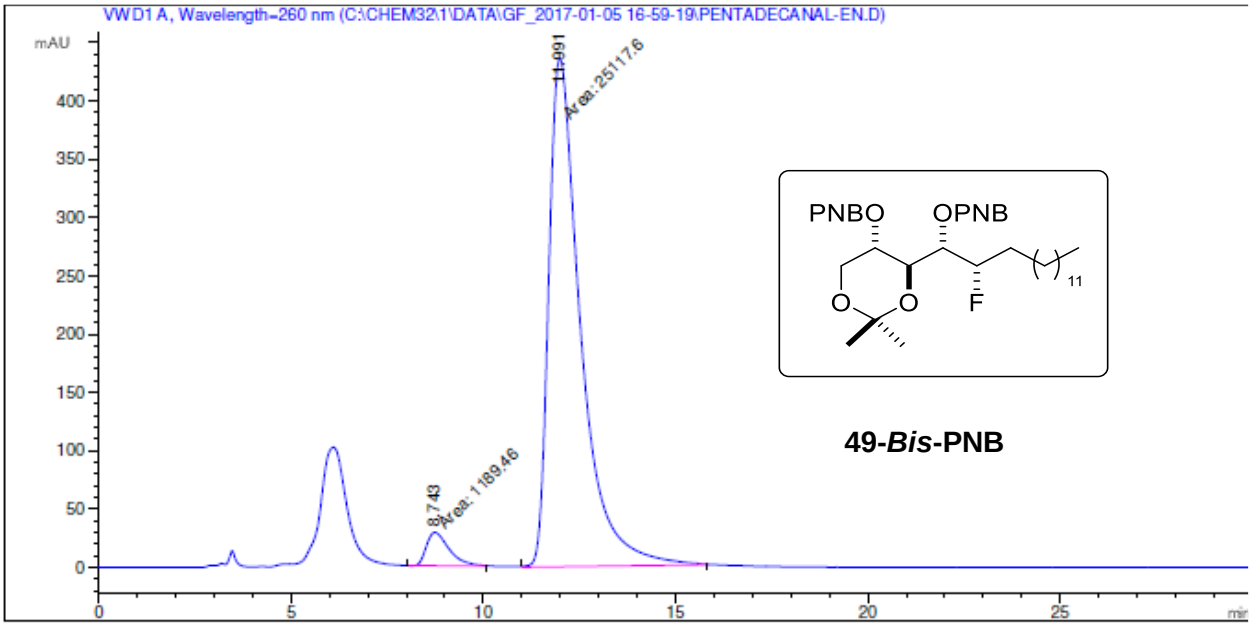
48-*Bis*-PNB

Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	24.769	MM	0.6788	892.76361	21.91918	2.6065
2	27.055	MM	0.8022	3.33592e4	693.12097	97.3935

Supplementary Figure 8. Determination of enantiomeric excess of **48**.

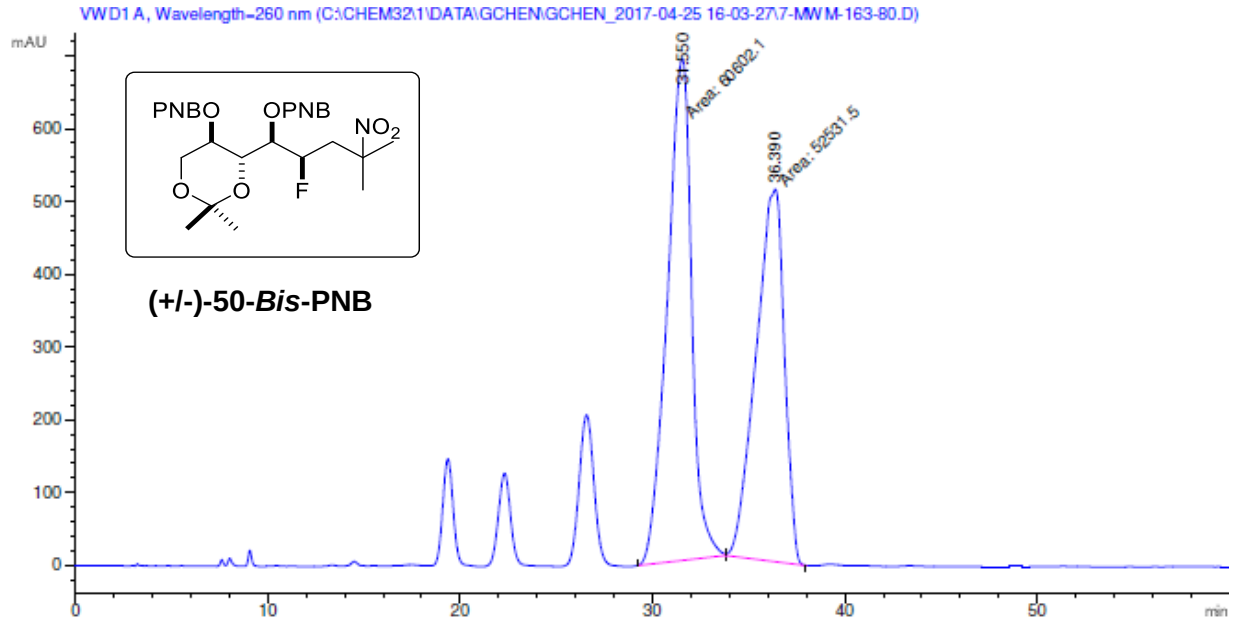


Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	8.764	MM	0.7202	3.20614e4	741.96558	50.3272
2	12.055	MM	0.9481	3.16445e4	556.26318	49.6728

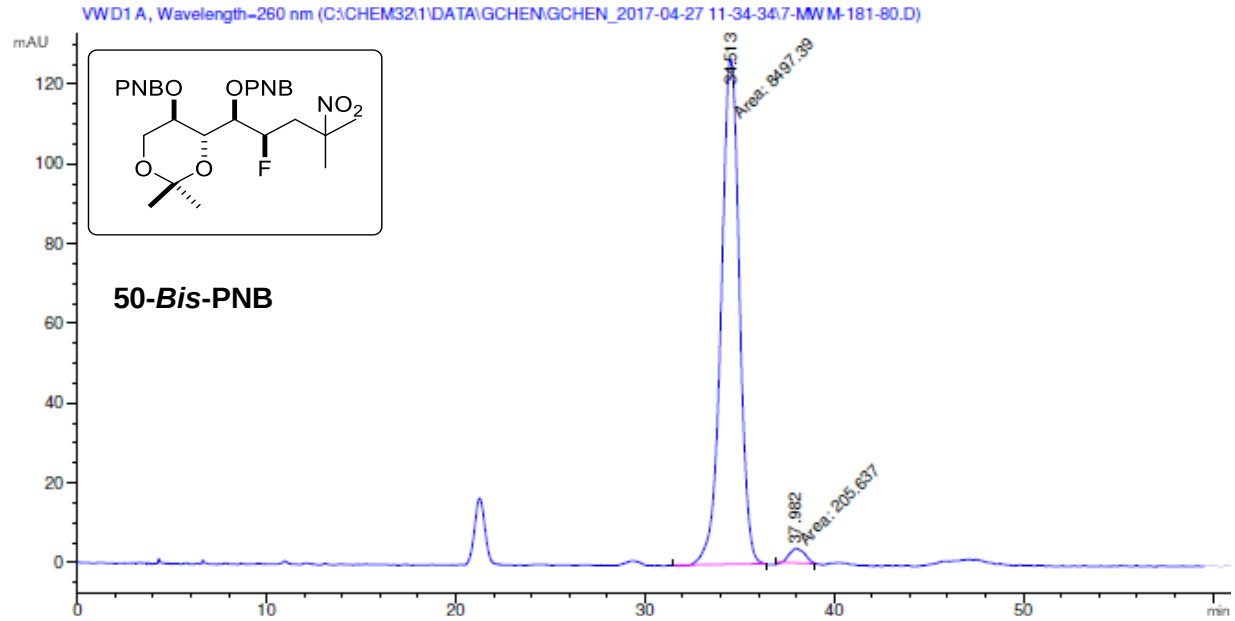


Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	8.743	MM	0.6916	1189.46448	28.66516	4.5215
2	11.991	MM	0.9600	2.51176e4	436.05441	95.4785

Supplementary Figure 9. Determination of enantiomeric excess of **49**.

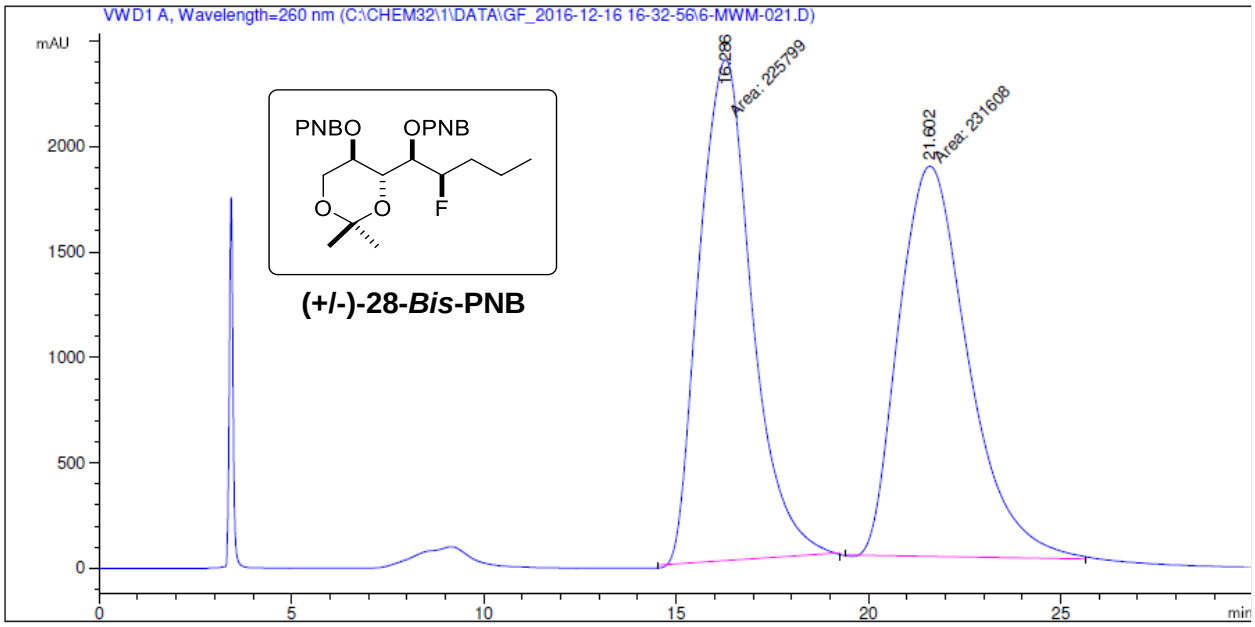


Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	31.550	MM	1.4641	6.06021e4	689.87817	53.5668
2	36.390	MM	1.7093	5.25315e4	512.21033	46.4332

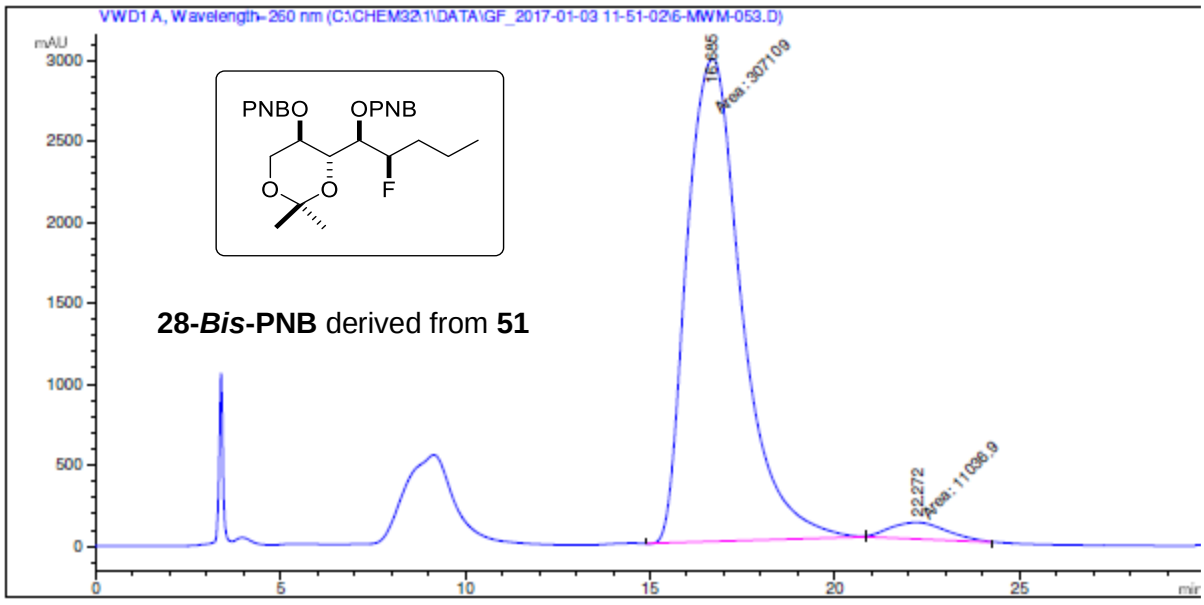


Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	34.513	MM	1.1163	8497.39453	126.87410	97.6372
2	37.982	MM	0.9360	205.63655	3.66148	2.3628

Supplementary Figure 10. Determination of enantiomeric excess of **50**.

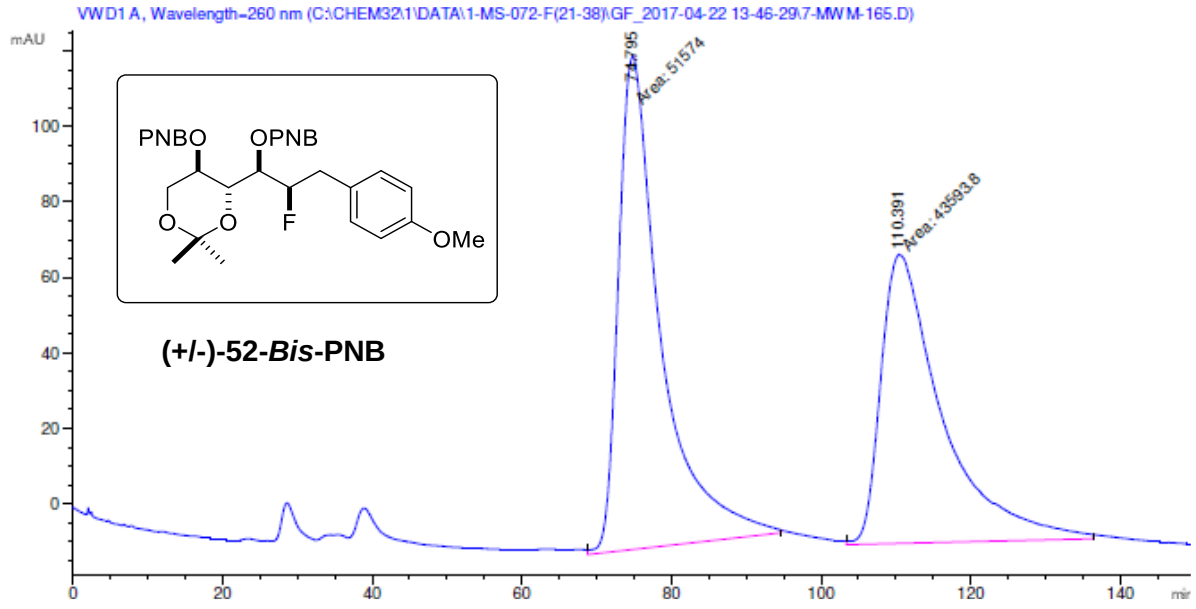


Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	16.286	MM	1.5841	2.25799e5	2375.75269	49.3650
2	21.602	MM	2.0865	2.31608e5	1850.00977	50.6350

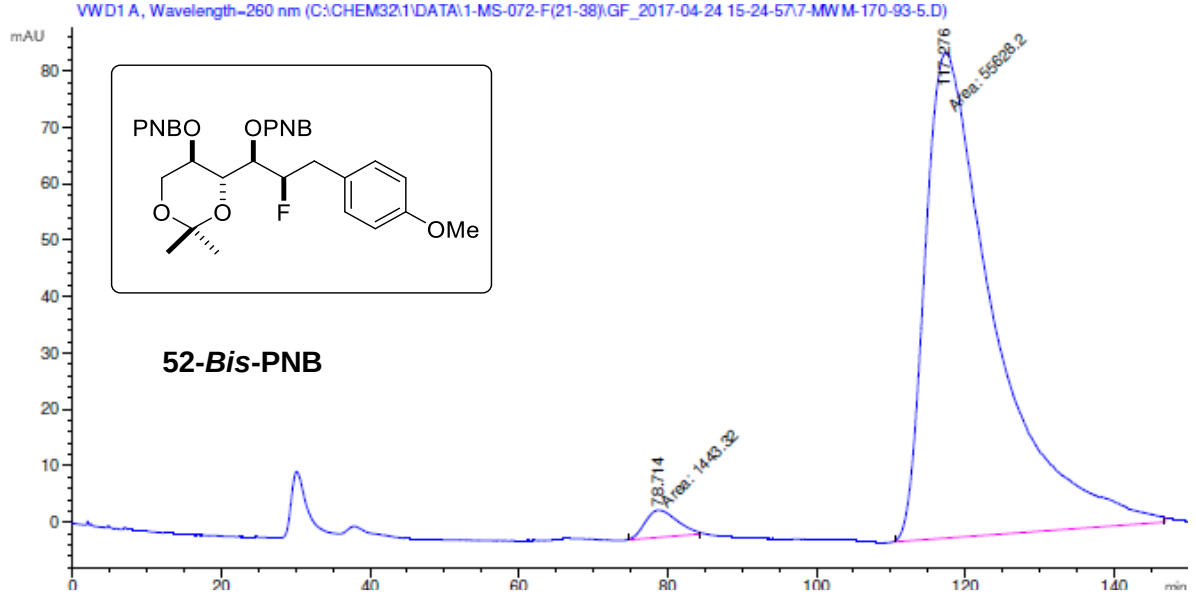


Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	16.685	MM	1.7169	3.07109e5	2981.22705	96.5309
2	22.272	MM	1.7879	1.10369e4	102.88731	3.4691

Supplementary Figure 11. Determination of enantiomeric excess of **51**.

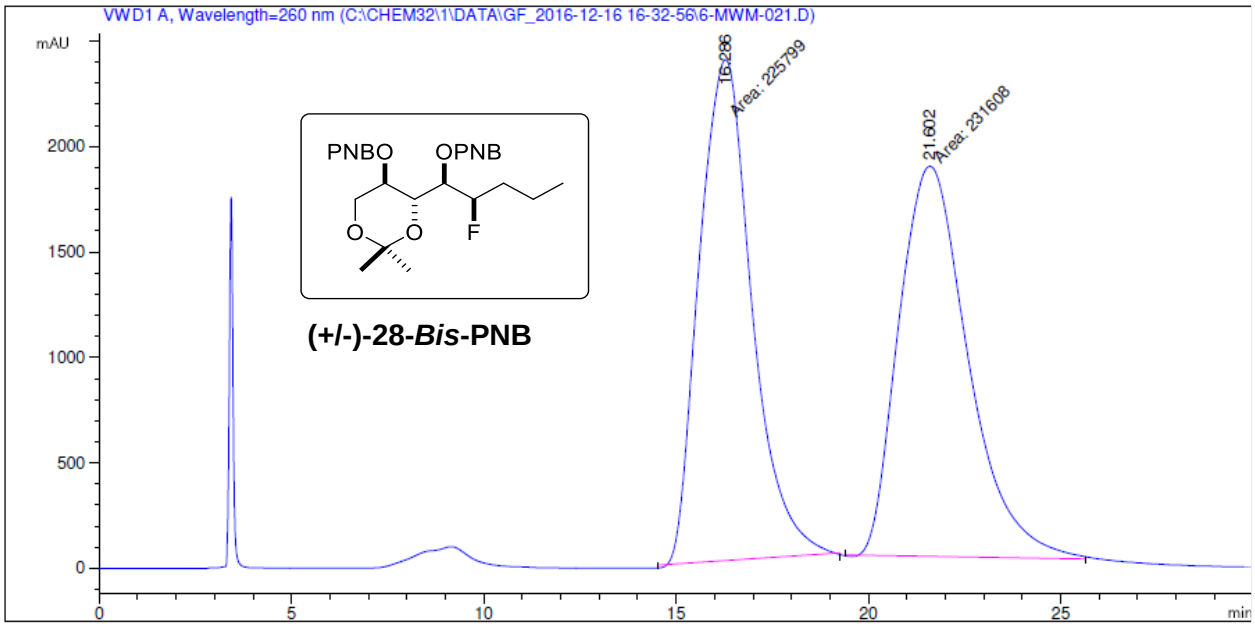


Peak #	RetTime [min]	Type	Width [min]	Area mAU	Area *s	Height [mAU]	Area %
1	74.795	MM	6.5718	5.15740e4	130.79599	54.1927	
2	110.391	MM	9.4860	4.35938e4	76.59305	45.8073	

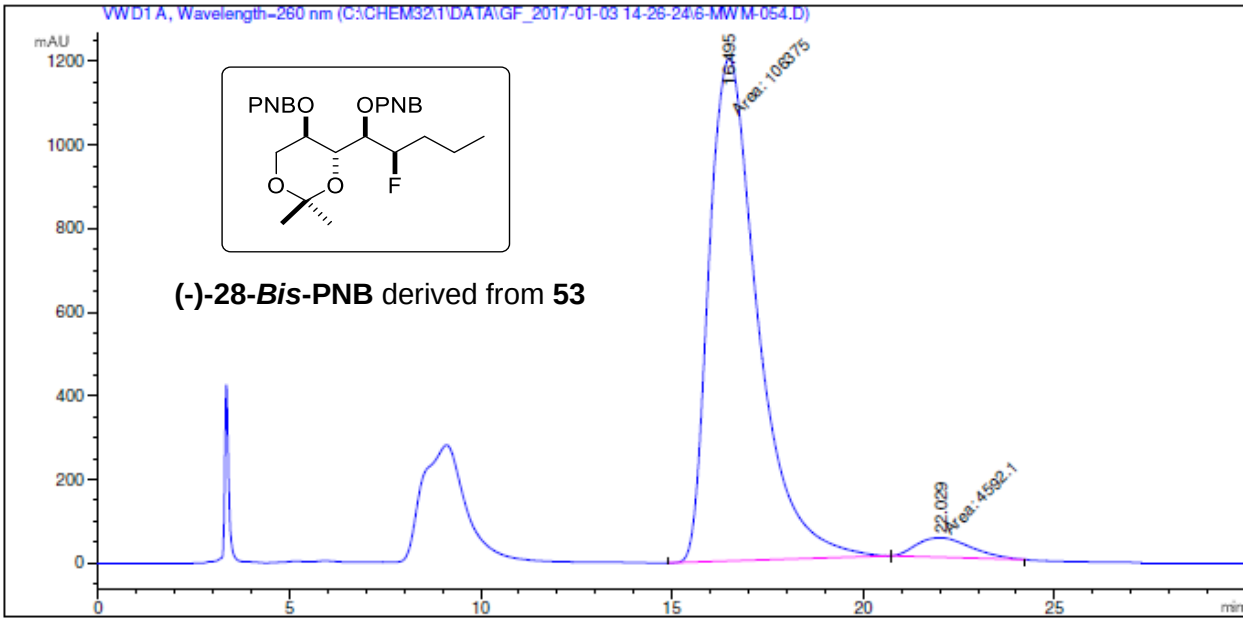


Peak #	RetTime [min]	Type	Width [min]	Area mAU	Area *s	Height [mAU]	Area %
1	78.714	MM	4.9697	1443.32019	4.84036	2.5290	
2	117.276	MM	10.7686	5.56282e4	86.09621	97.4710	

Supplementary Figure 12. Determination of enantiomeric excess of **52**.

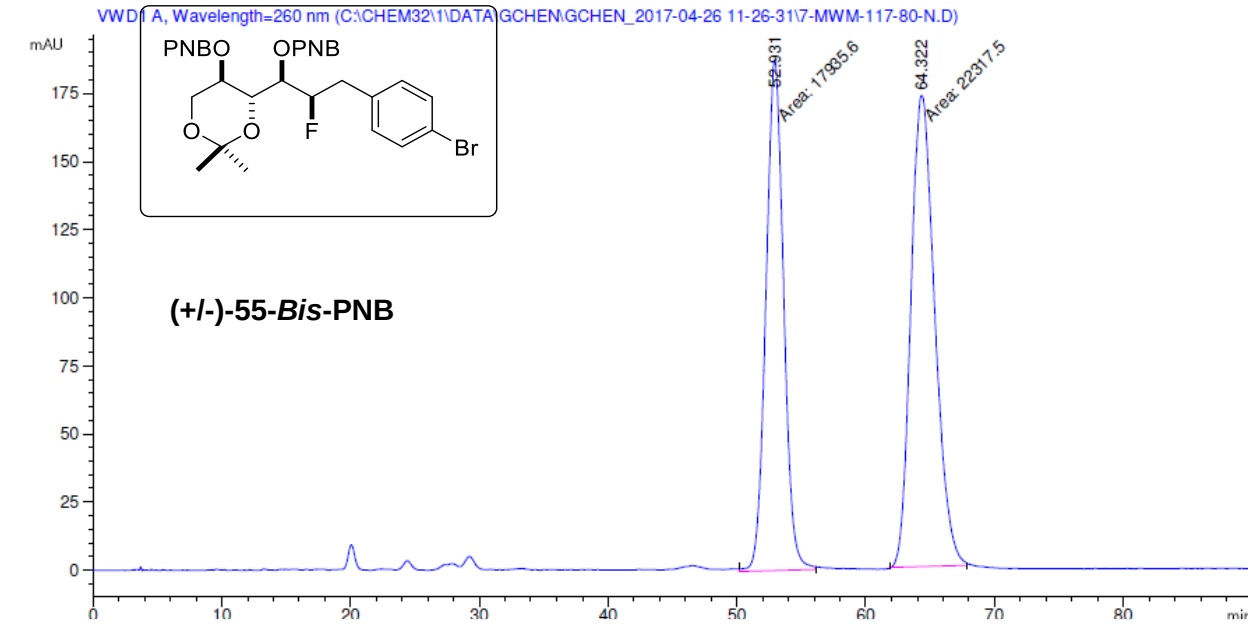


Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	16.286	MM	1.5841	2.25799e5	2375.75269	49.3650
2	21.602	MM	2.0865	2.31608e5	1850.00977	50.6350

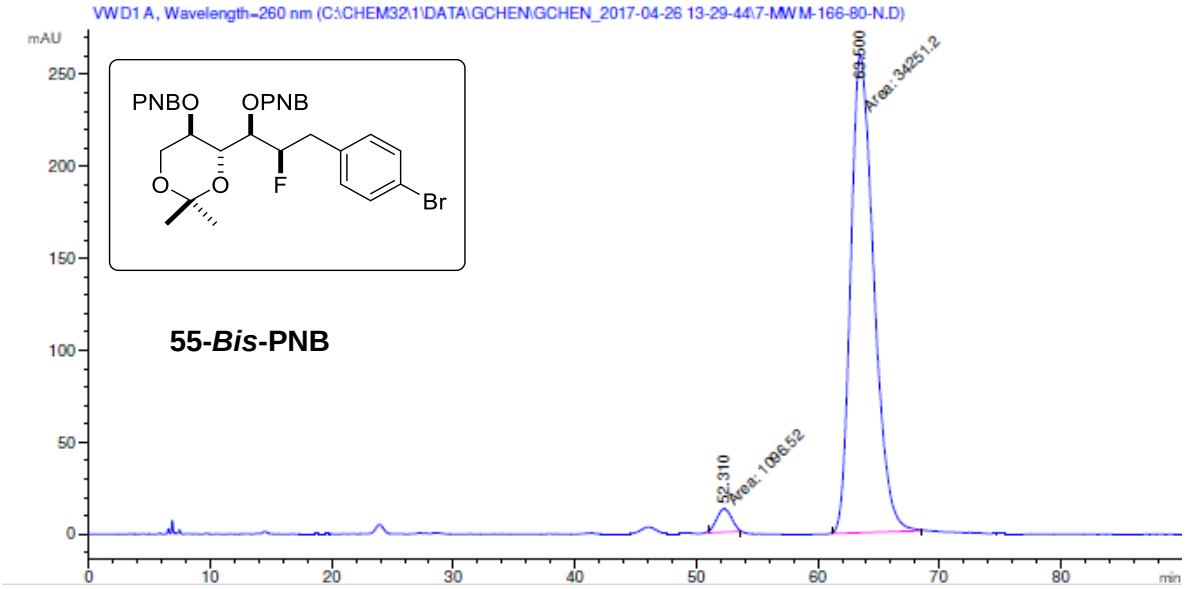


Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	16.495	MM	1.4751	1.06375e5	1201.89160	95.8617
2	22.029	MM	1.6457	4592.09717	46.50721	4.1383

Supplementary Figure 13. Determination of enantiomeric excess of **53**.

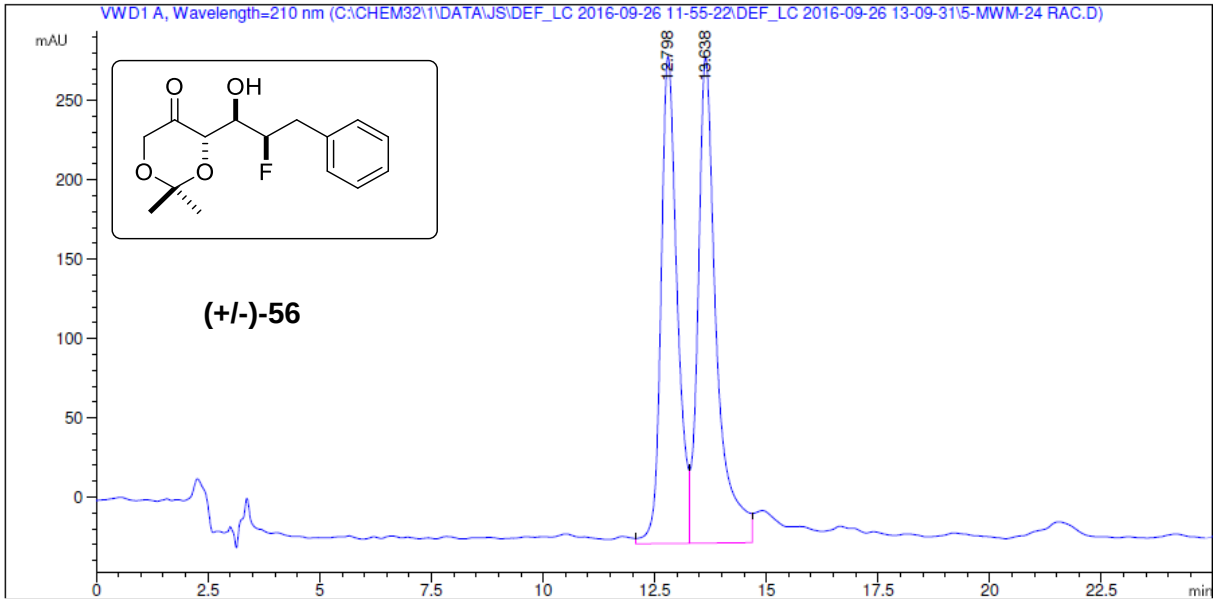


Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	52.931	MM	1.5954	1.79356e4	187.36581	44.5571
2	64.322	MM	2.1503	2.23175e4	172.98358	55.4429

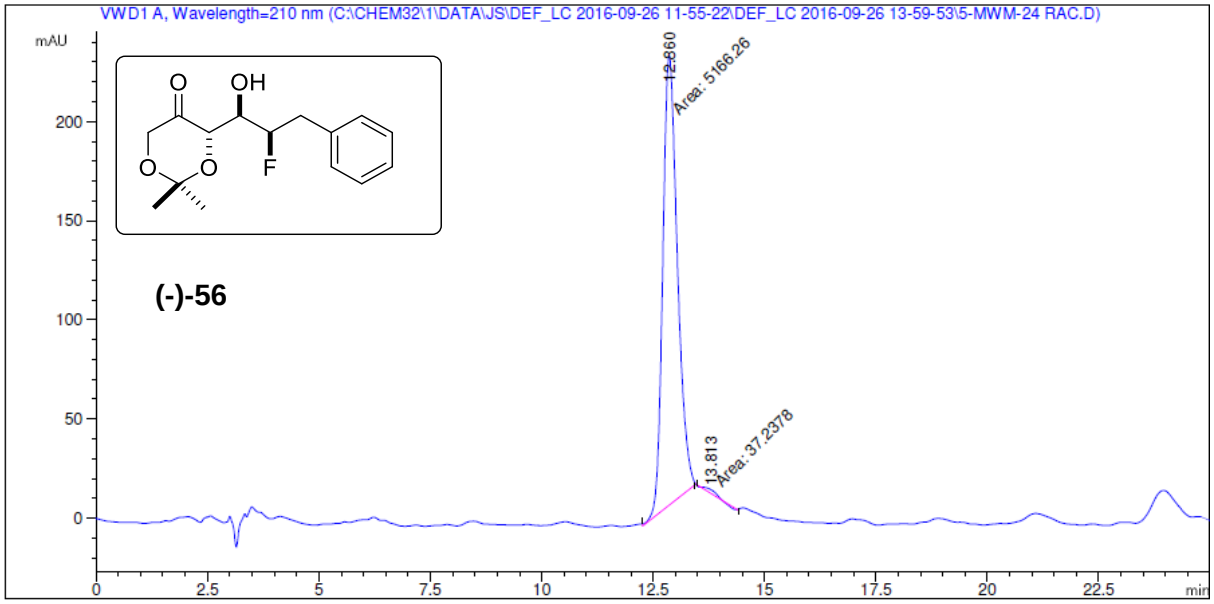


Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	52.310	MM	1.4265	1096.51550	12.81092	3.1021
2	63.500	MM	2.1938	3.42512e4	260.21017	96.8979

Supplementary Figure 14. Determination of enantiomeric excess of **55**.

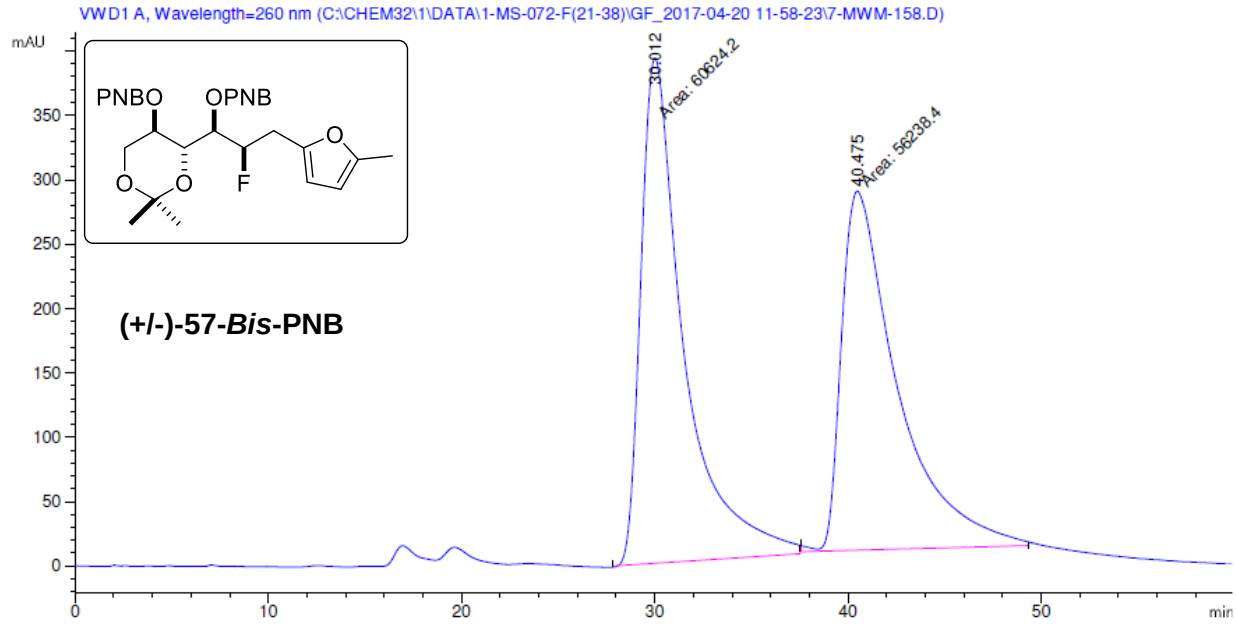


Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	12.798	VV	0.3747	7717.89990	307.11288	46.8503
2	13.638	VV	0.4151	8755.62305	306.19824	53.1497

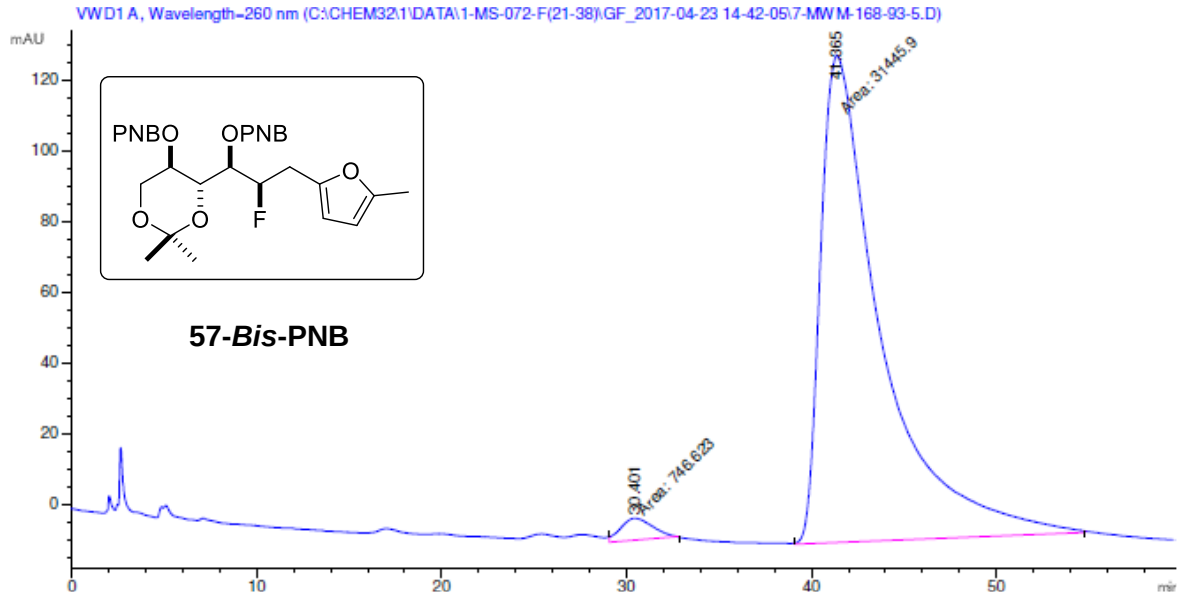


Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	12.860	MM	0.3800	5166.26025	226.59462	99.2844
2	13.813	MM	0.3651	37.23775	1.97158	0.7156

Supplementary Figure 15. Determination of enantiomeric excess of **56**.

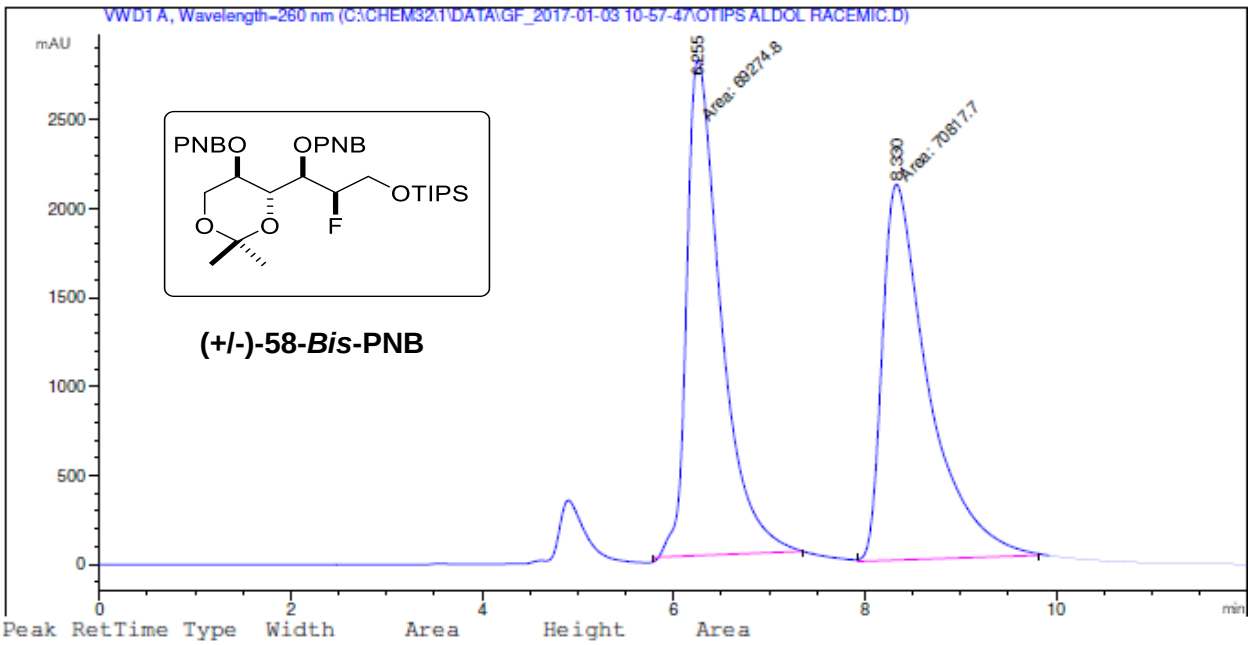


Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	30.012	MM	2.5741	6.06242e4	392.52161	51.8765
2	40.475	MM	3.3601	5.62384e4	278.94772	48.1235

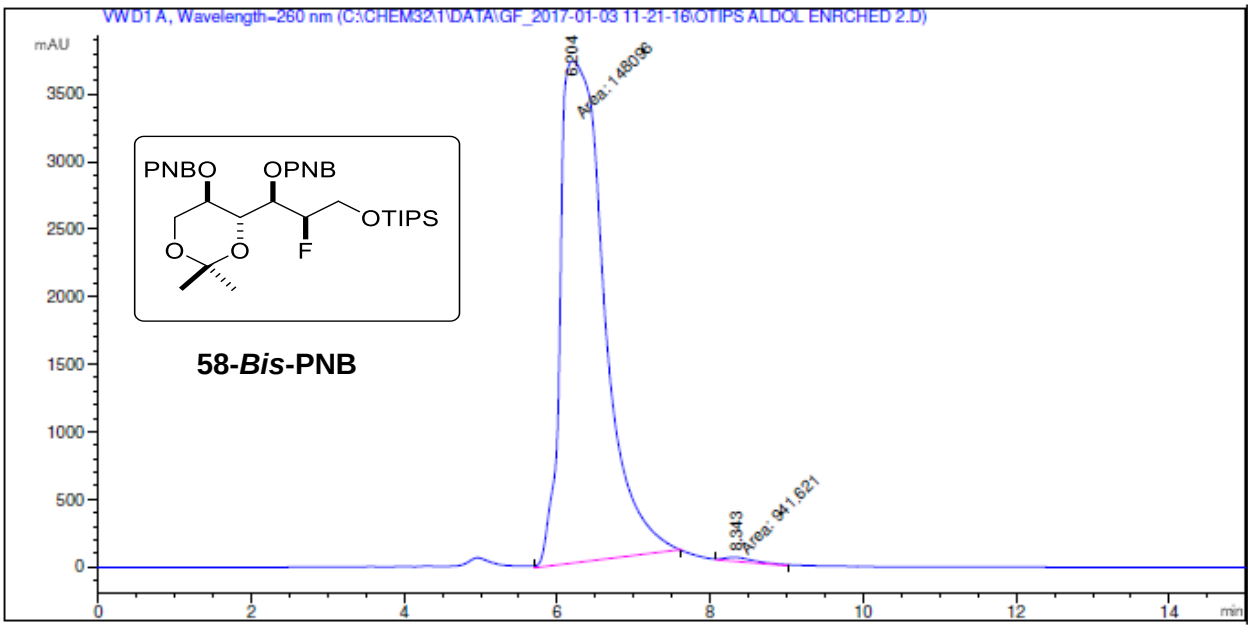


Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	30.401	MM	1.9979	746.62323	6.22836	2.3192
2	41.365	MM	3.8032	3.14459e4	137.80399	97.6808

Supplementary Figure 16. Determination of enantiomeric excess of **57**.

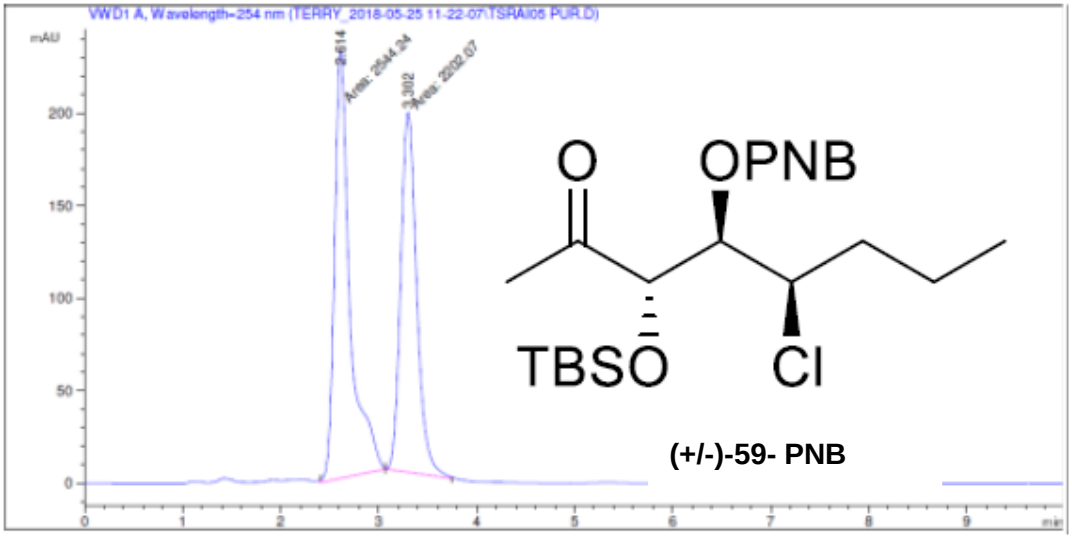


Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	6.255	MM	0.4144	6.92748e4	2785.93945	49.4493
2	8.330	MM	0.5587	7.08177e4	2112.64746	50.5507

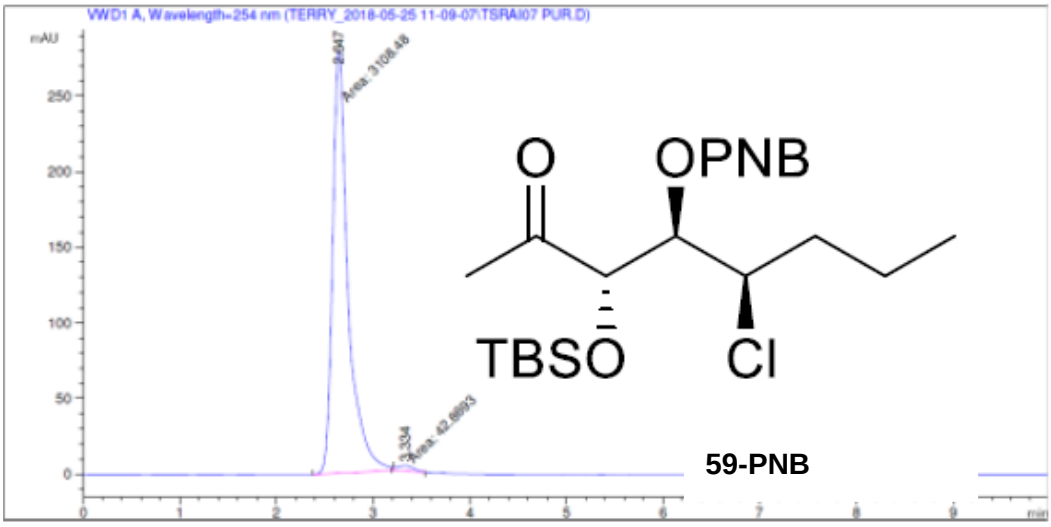


Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	6.204	MM	0.6642	1.48096e5	3716.41406	99.3682
2	8.343	MM	0.4924	941.62128	31.87027	0.6318

Supplementary Figure 17. Determination of enantiomeric excess of **58**.

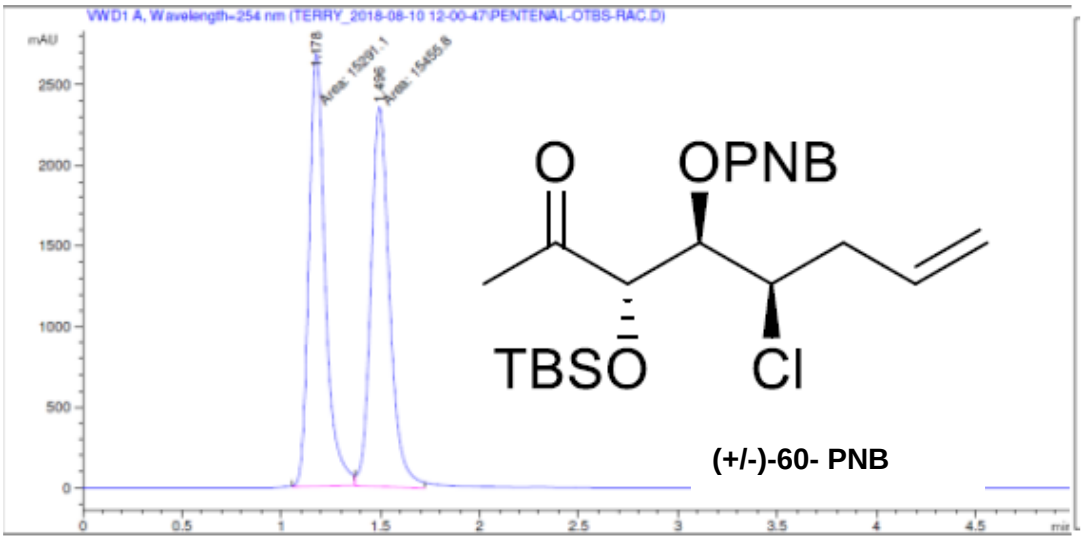


Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	2.614	MM	0.1835	2544.23975	231.07678	53.6046
2	3.302	MM	0.1887	2202.07080	194.44383	46.3954

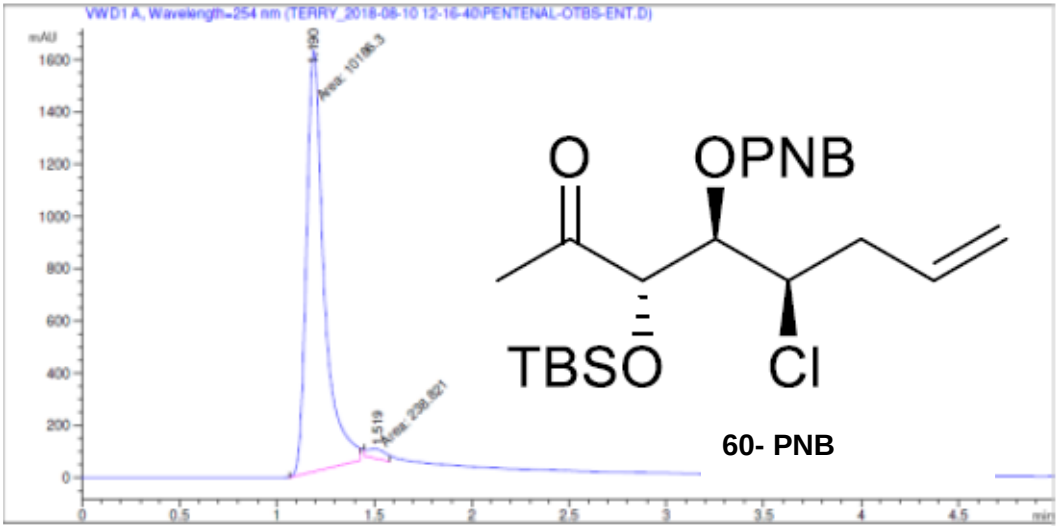


Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	2.647	MM	0.1856	3108.48022	279.20975	98.6397
2	3.334	MM	0.1951	42.86931	3.66210	1.3603

Supplementary Figure 18. Determination of enantiomeric excess of **59**.

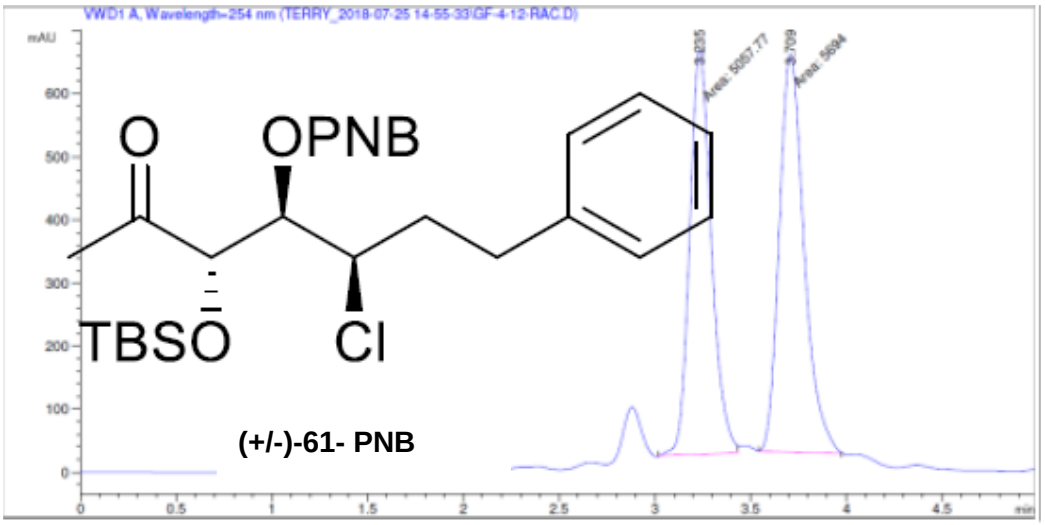


Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	1.178	MM	0.0948	1.52911e4	2687.56836	49.7322
2	1.496	MM	0.1094	1.54558e4	2354.75977	50.2678

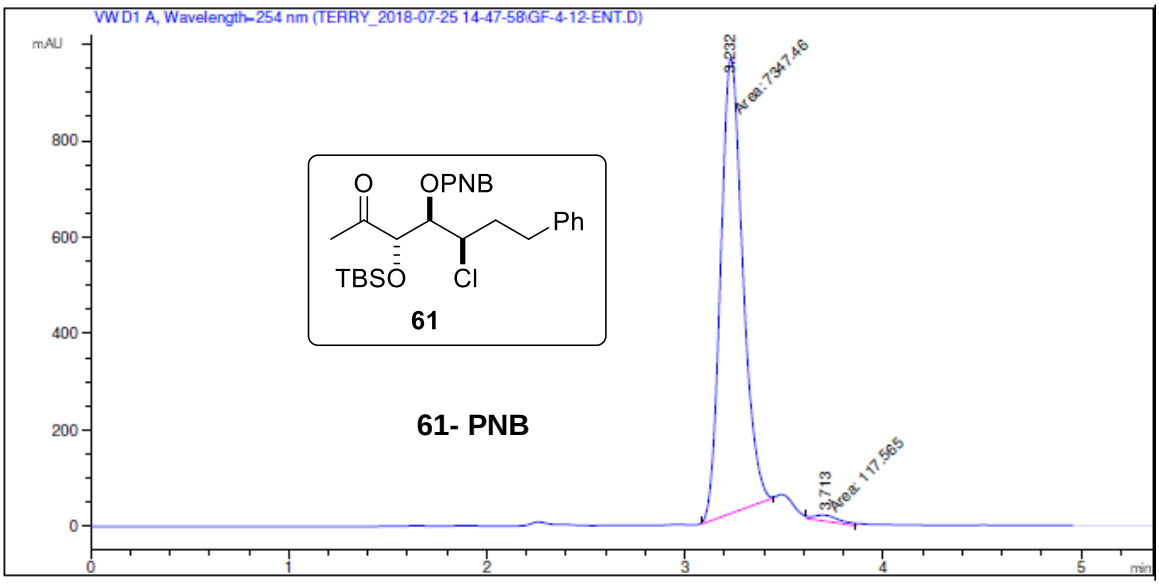


Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	1.190	MM	0.1051	1.01863e4	1615.77222	97.7092
2	1.519	MM	0.1092	238.82076	36.45218	2.2908

Supplementary Figure 19. Determination of enantiomeric excess of **60**.

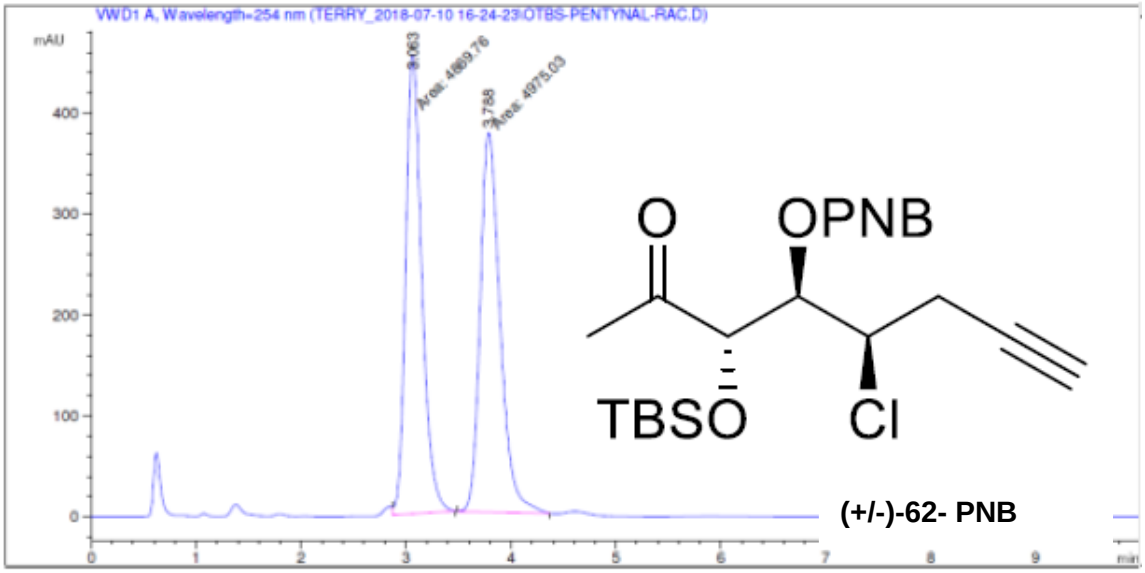


Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	3.235	MM	0.1316	5057.76611	640.45544	47.0413
2	3.709	MM	0.1504	5693.99561	631.12048	52.9587

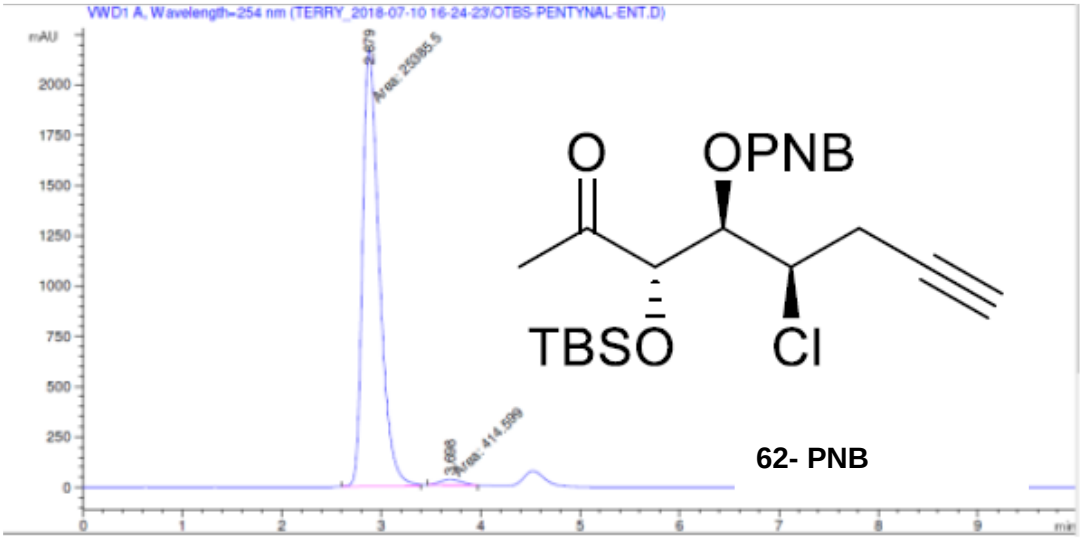


Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	3.232	MM	0.1295	7347.46143	945.41620	98.4251
2	3.713	MM	0.1557	117.56458	12.58270	1.5749

Supplementary Figure 20. Determination of enantiomeric excess of **61**.

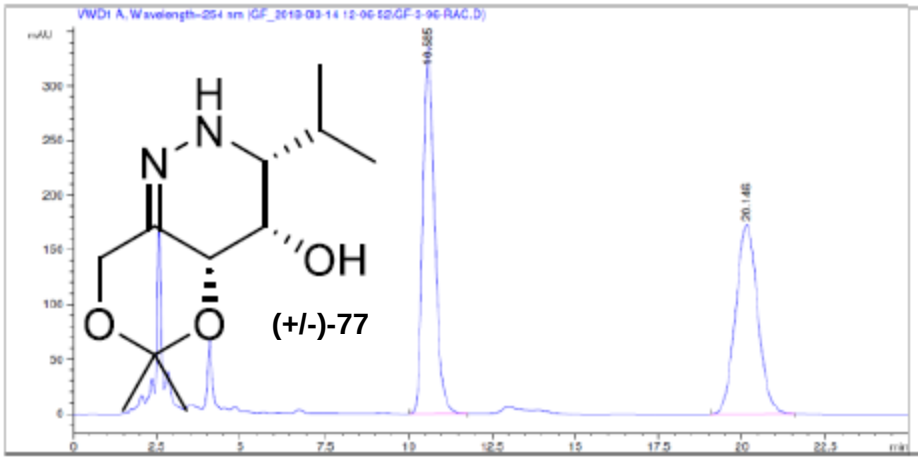


Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	3.063	MM	0.1783	4869.75928	455.25430	49.4653
2	3.788	MM	0.2202	4975.03027	376.62704	50.5347

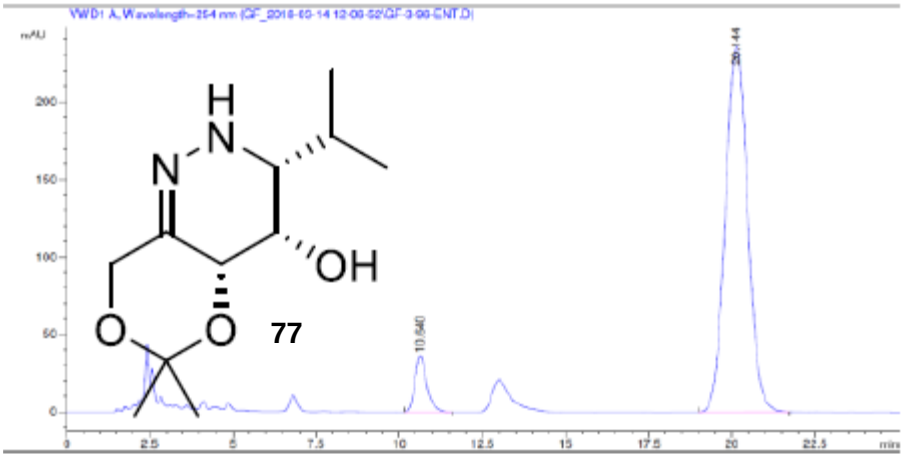


Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	2.879	MM	0.1952	2.53855e4	2167.88501	98.3930
2	3.698	MM	0.2541	414.59915	27.19168	1.6070

Supplementary Figure 21. Determination of enantiomeric excess of **62**.

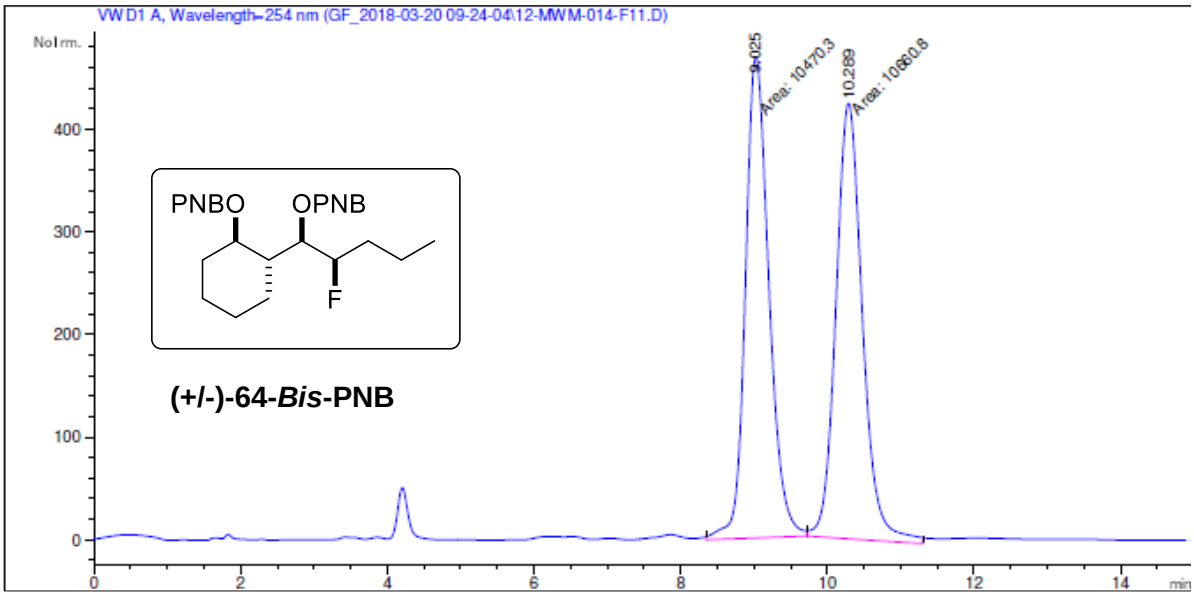


Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	10.585	BB	0.3739	8127.26758	336.03912	50.3763
2	20.146	BB	0.7194	8005.85010	172.87167	49.6237

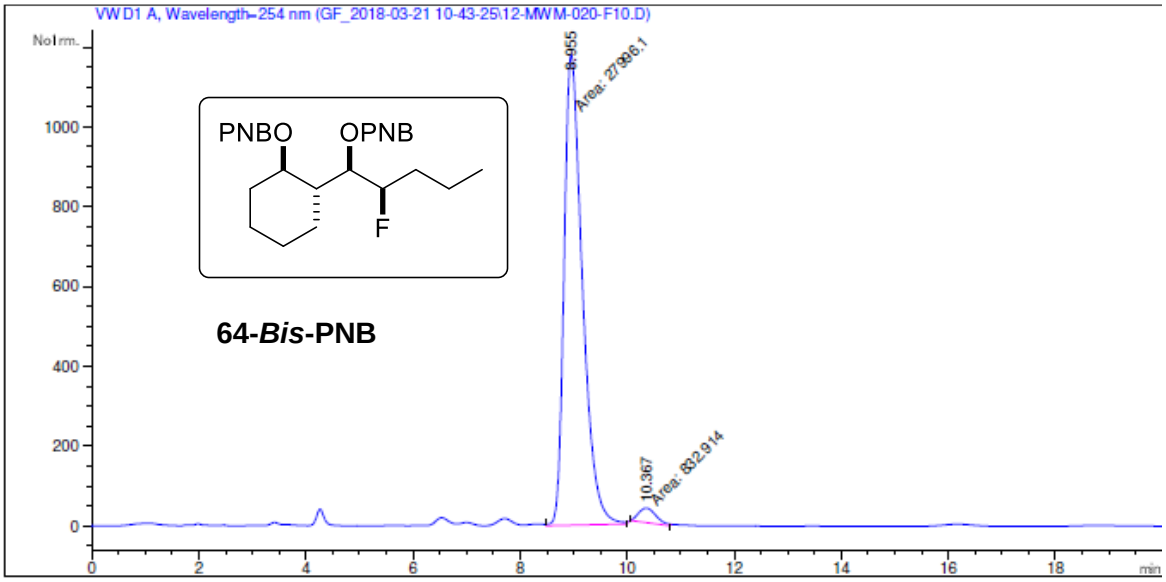


Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	10.640	BB	0.3770	888.06750	35.76637	7.4649
2	20.144	BB	0.7259	1.10085e4	235.51138	92.5351

Supplementary Figure 22. Determination of enantiomeric excess of **77**.

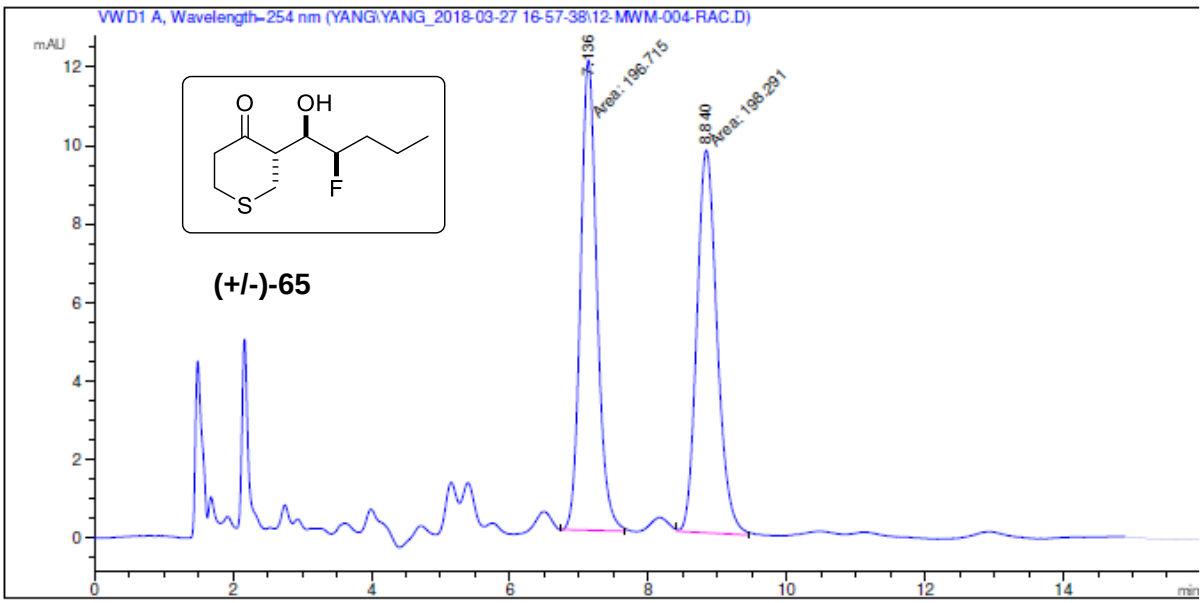


Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	9.025	MM	0.3722	1.04703e4	468.78464	49.5493
2	10.289	MM	0.4186	1.06608e4	424.43393	50.4507

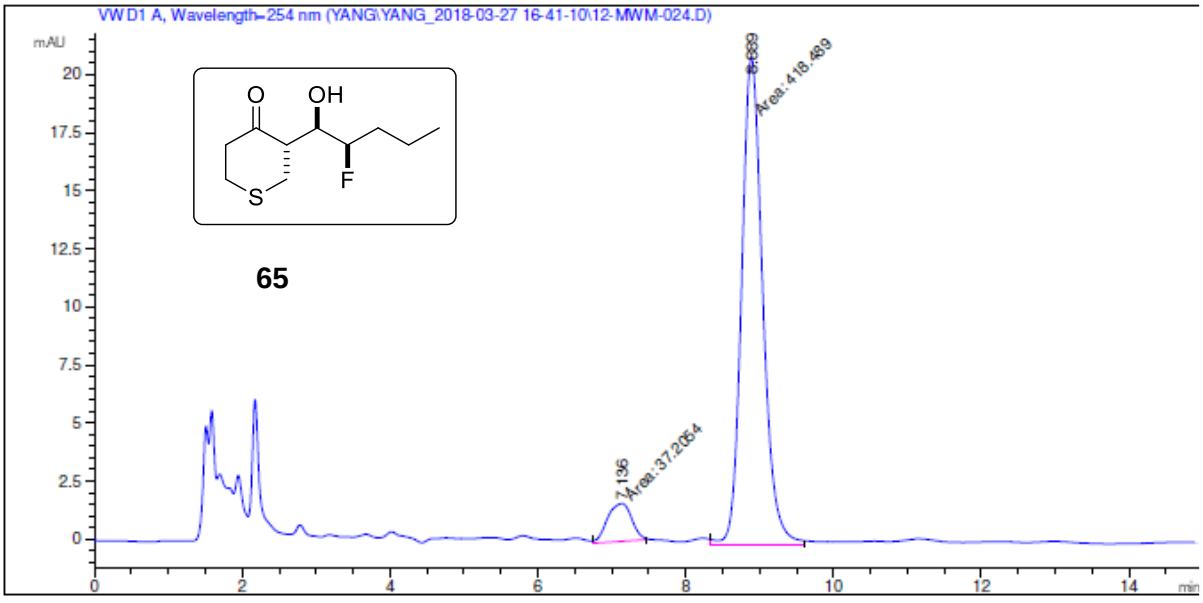


Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	8.955	MM	0.3957	2.79961e4	1179.06384	97.1108
2	10.367	MM	0.3787	832.91437	36.66050	2.8892

Supplementary Figure 23. Determination of enantiomeric excess of **64**.

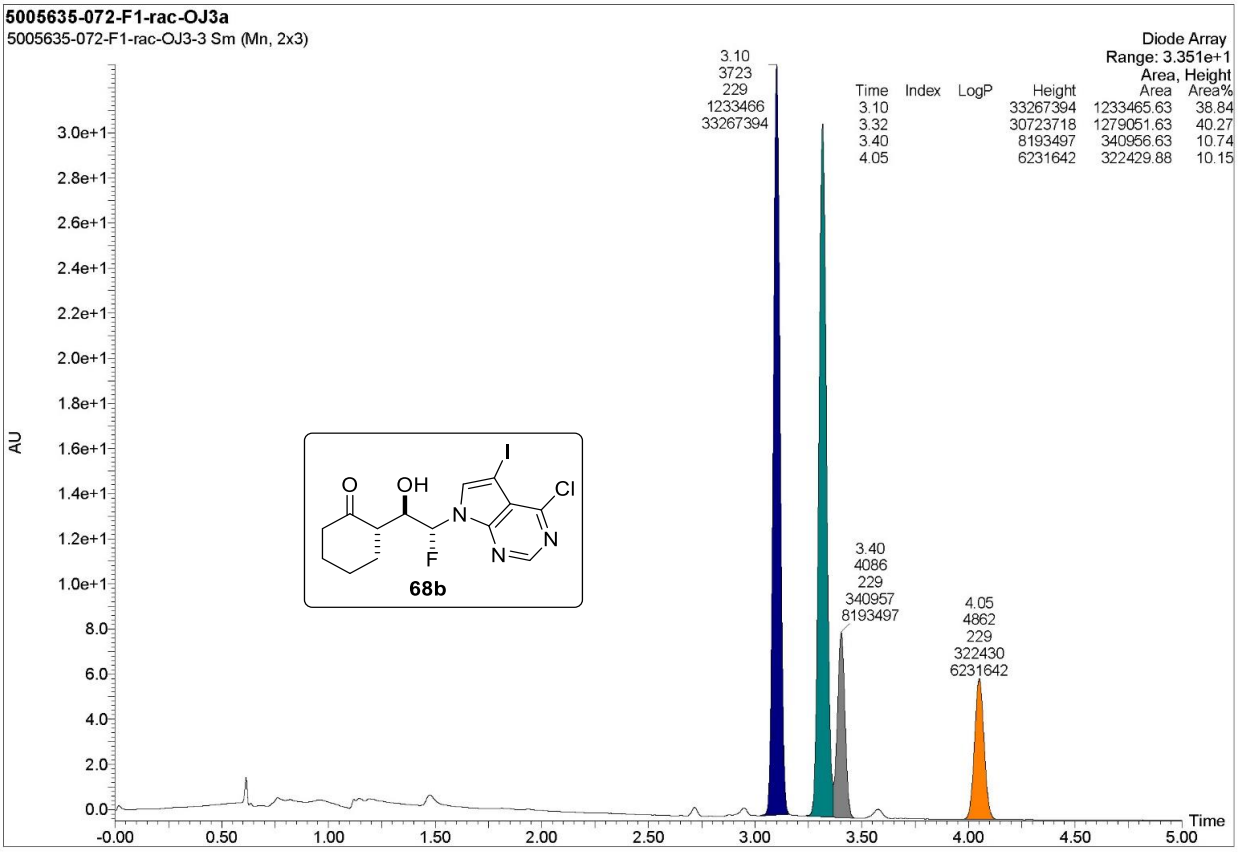


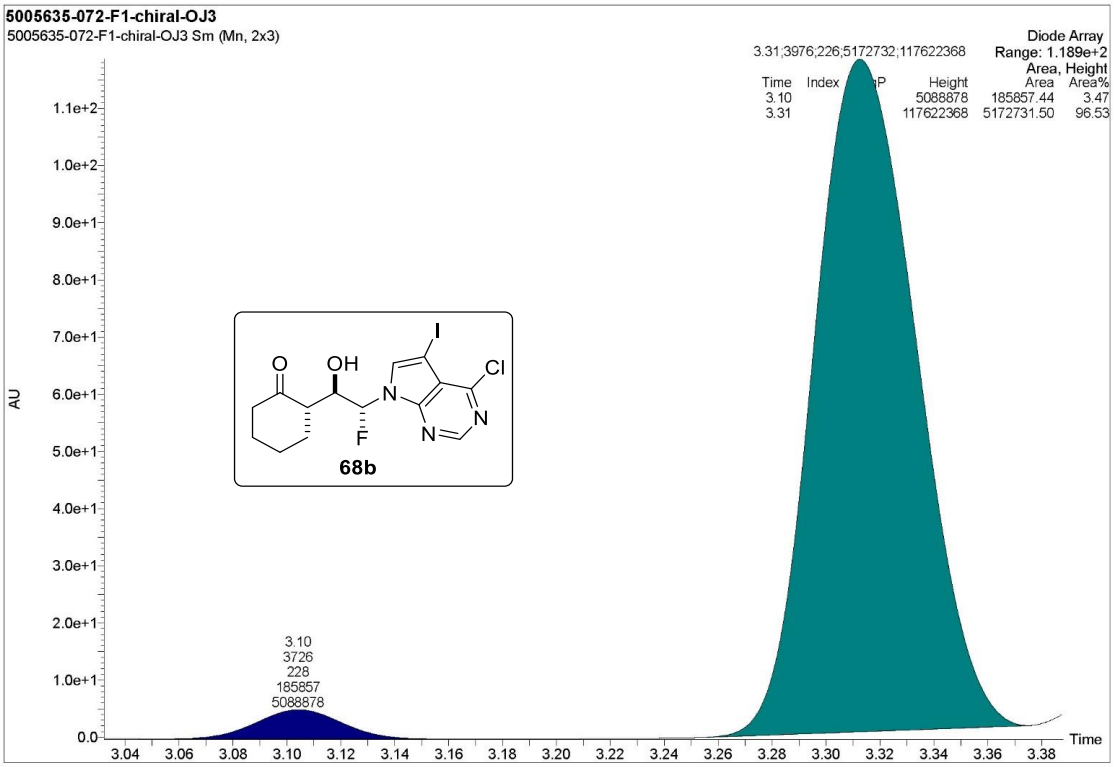
Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	7.136	MM	0.2735	196.71518	11.98946	49.8005
2	8.840	MM	0.3388	198.29149	9.75485	50.1995



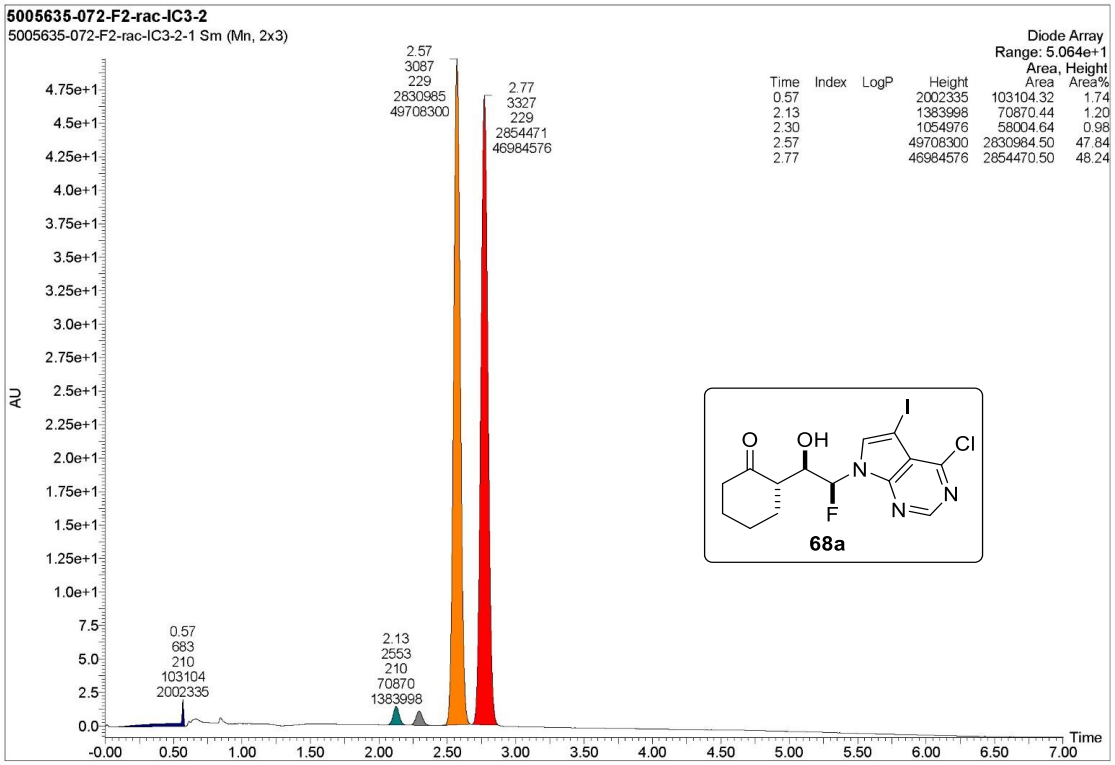
Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	7.136	MM	0.3817	37.20538	1.62468	8.1645
2	8.889	MM	0.3323	418.48904	20.98671	91.8355

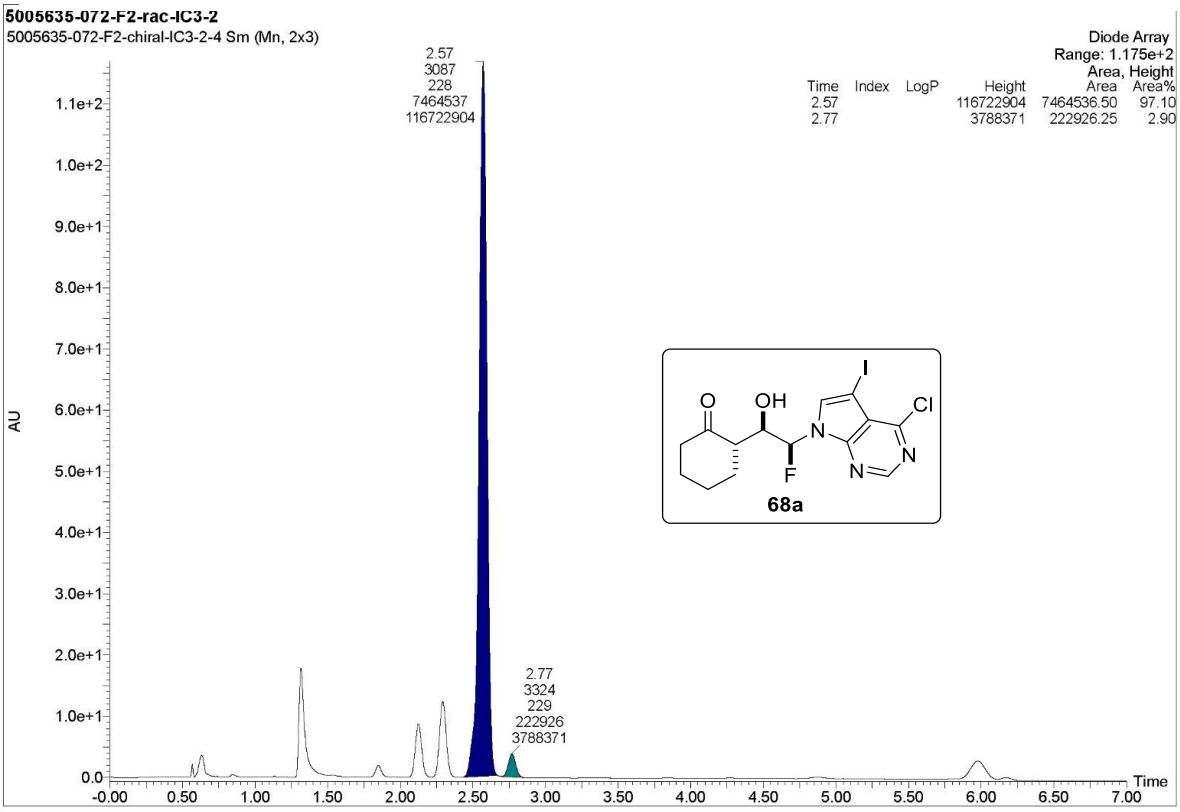
Supplementary Figure 24. Determination of enantiomeric excess of **65**.



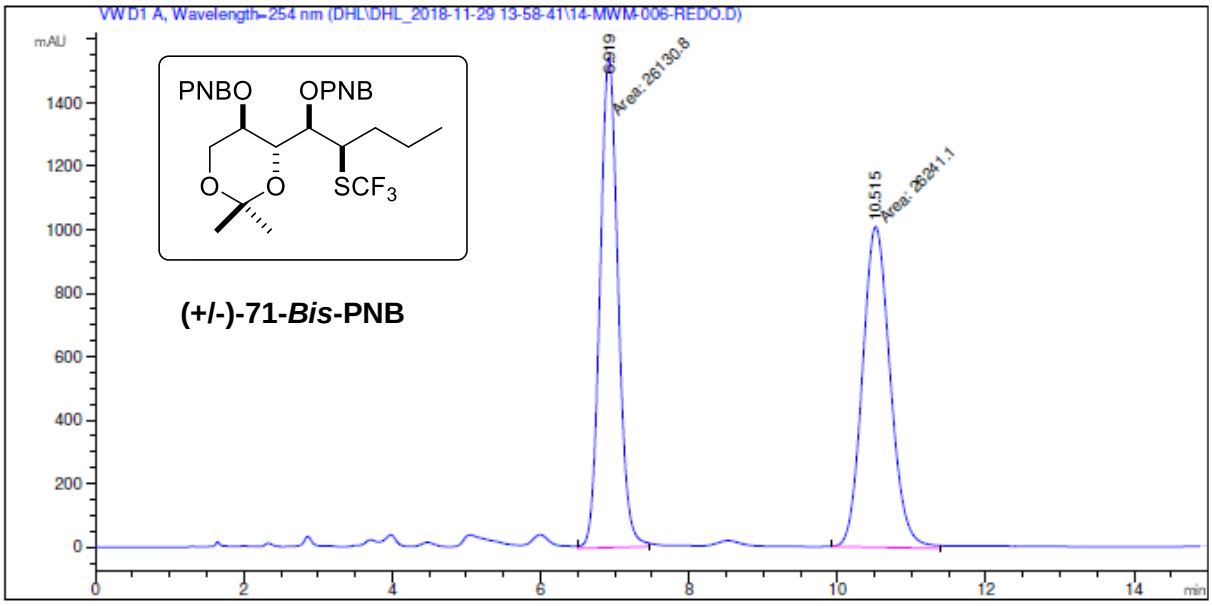


Supplementary Figure 25. Determination of enantiomeric excess of **68b**.

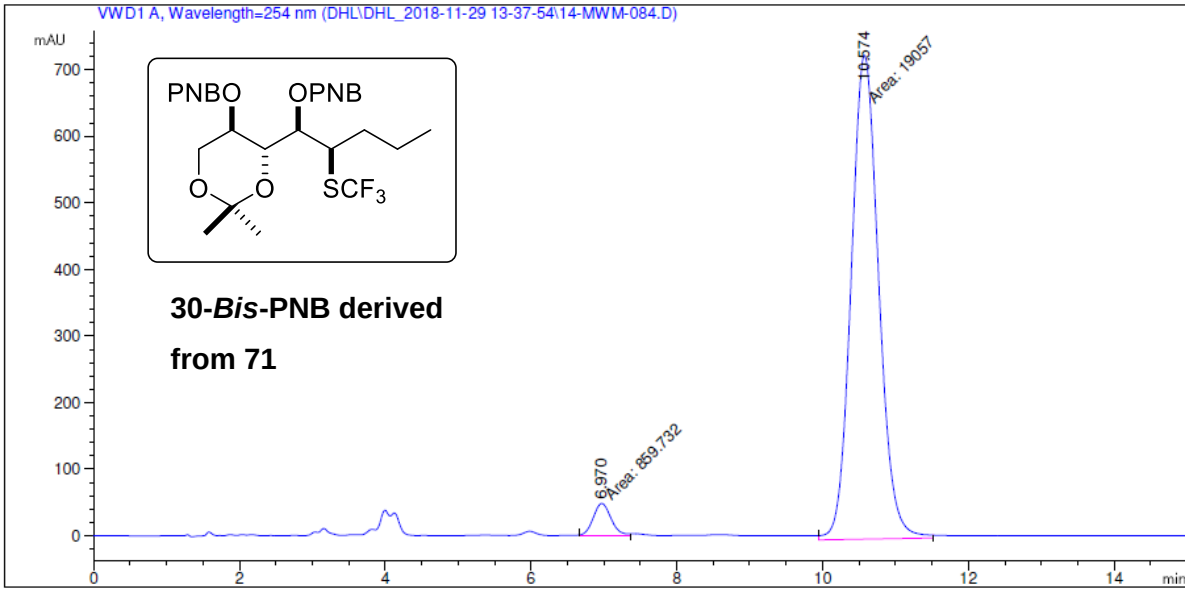




Supplementary Figure 26. Determination of enantiomeric excess of **68a**.

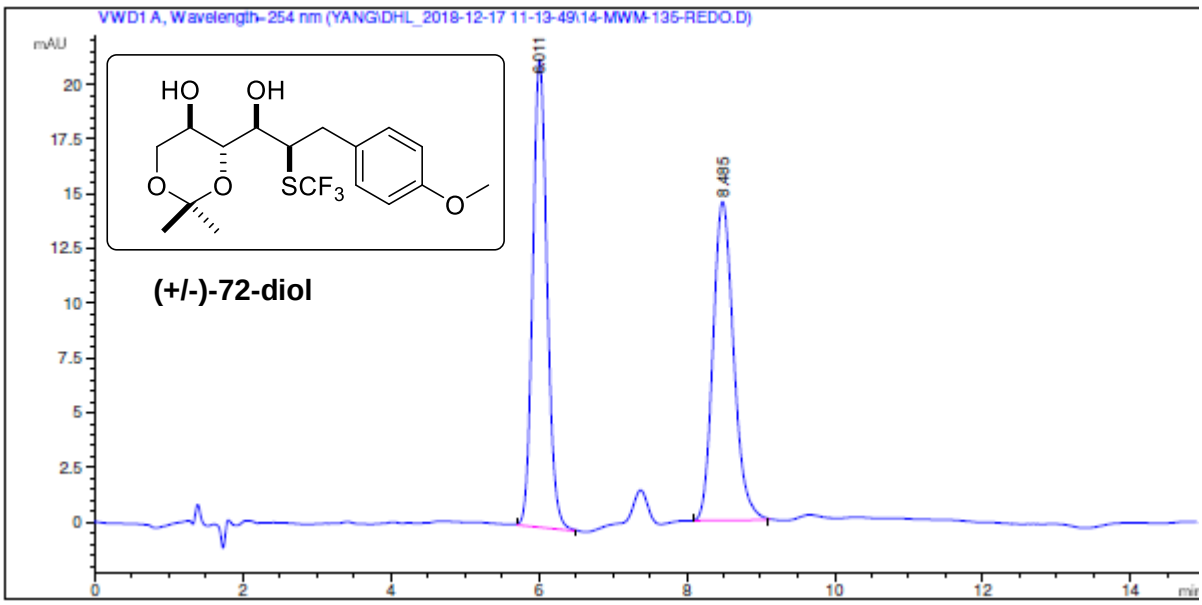


Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	6.919	MM	0.2820	2.61308e4	1544.30896	49.8947
2	10.515	MM	0.4330	2.62411e4	1009.98901	50.1053

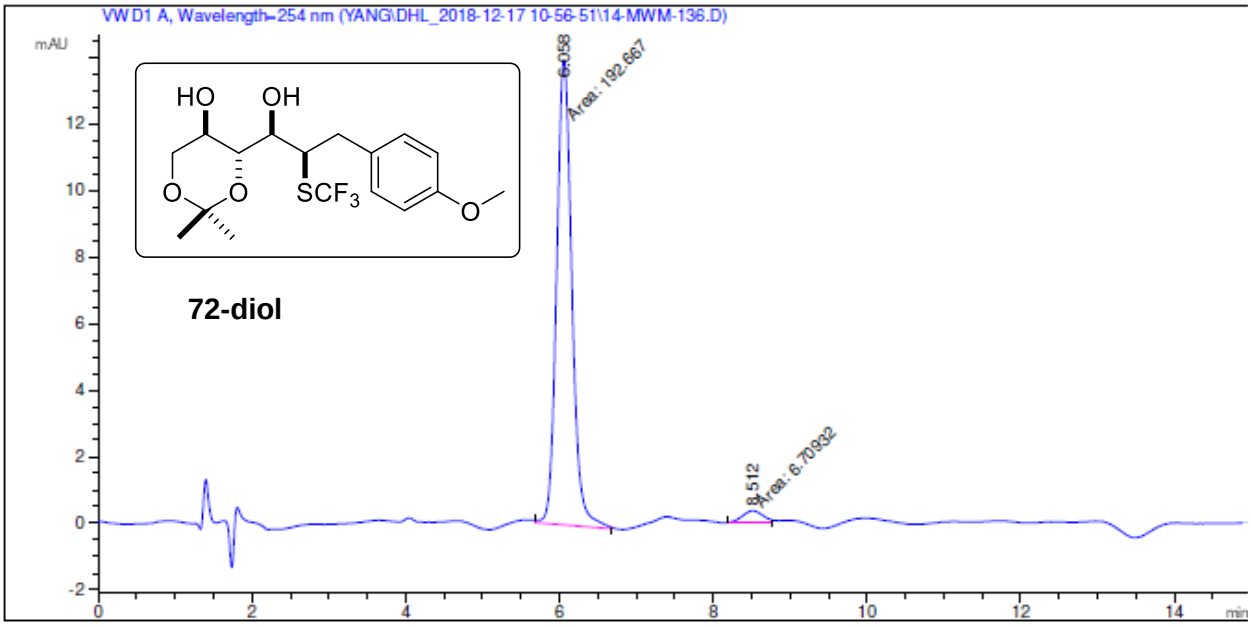


Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	6.970	MM	0.2922	859.73206	49.03386	4.3166
2	10.574	MM	0.4371	1.90570e4	726.57654	95.6834

Supplementary Figure 27. Determination of enantiomeric excess of **71**.

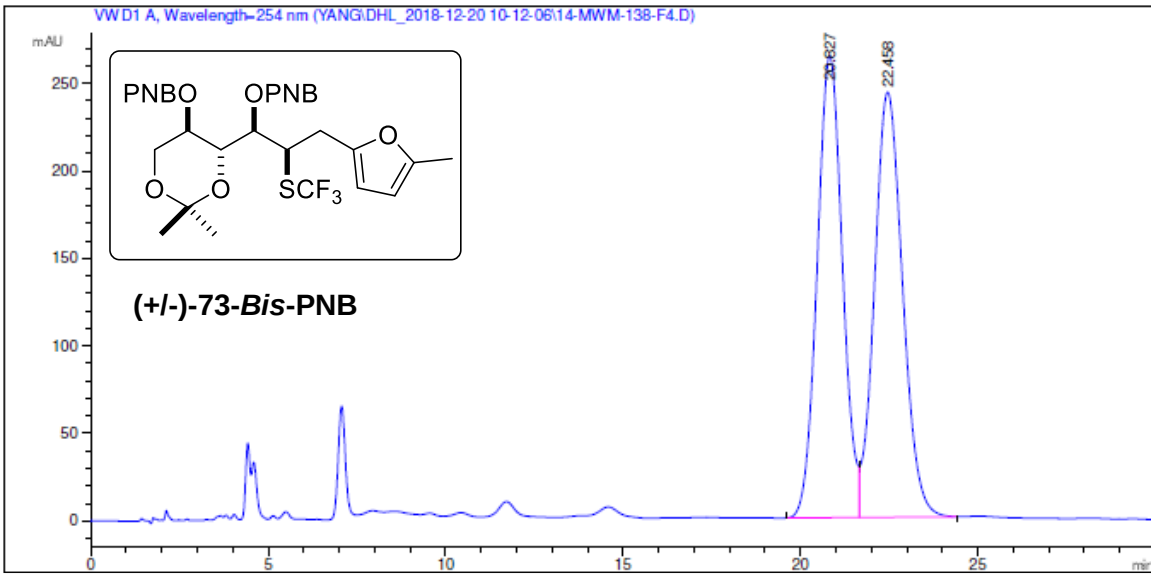


Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	6.011	BB	0.2080	287.88373	21.38168	50.5259
2	8.485	BB	0.3015	281.89120	14.56703	49.4741

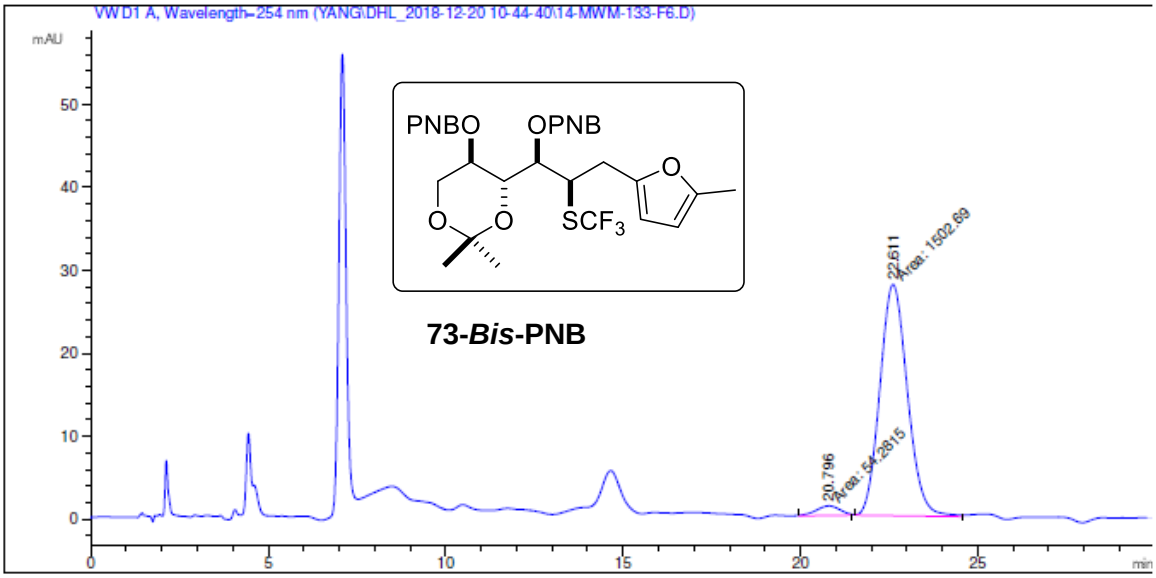


Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	6.058	MM	0.2298	192.66653	13.97408	96.6348
2	8.512	MM	0.3107	6.70932	3.59961e-1	3.3652

Supplementary Figure 28. Determination of enantiomeric excess of **72**.

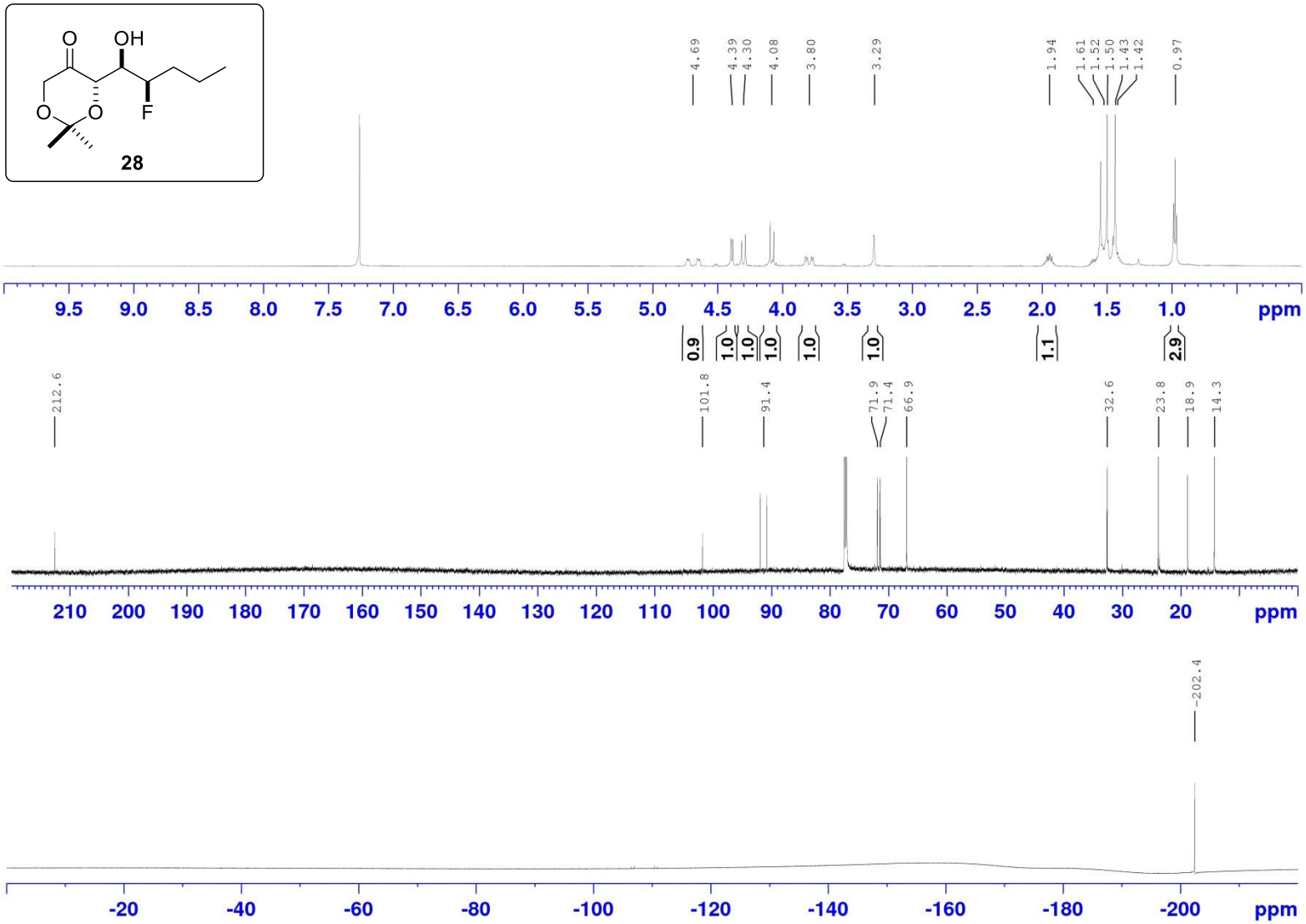


Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	20.827	BV	0.7663	1.30500e4	263.85162	49.2945
2	22.458	VB	0.8541	1.34235e4	243.01193	50.7055

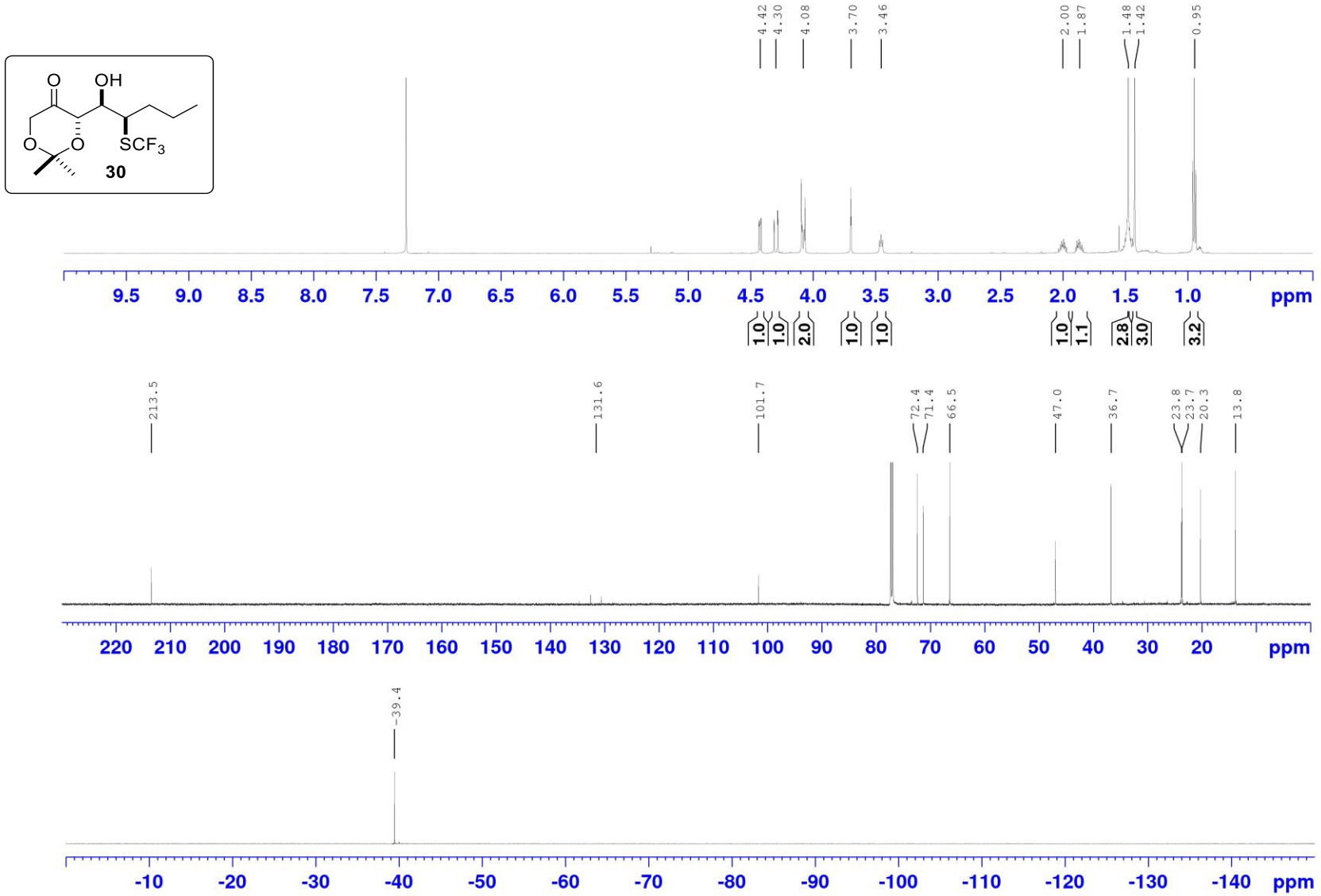


Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	20.796	MM	0.7802	54.28146	1.15951	3.4864
2	22.611	MM	0.8990	1502.68835	27.85789	96.5136

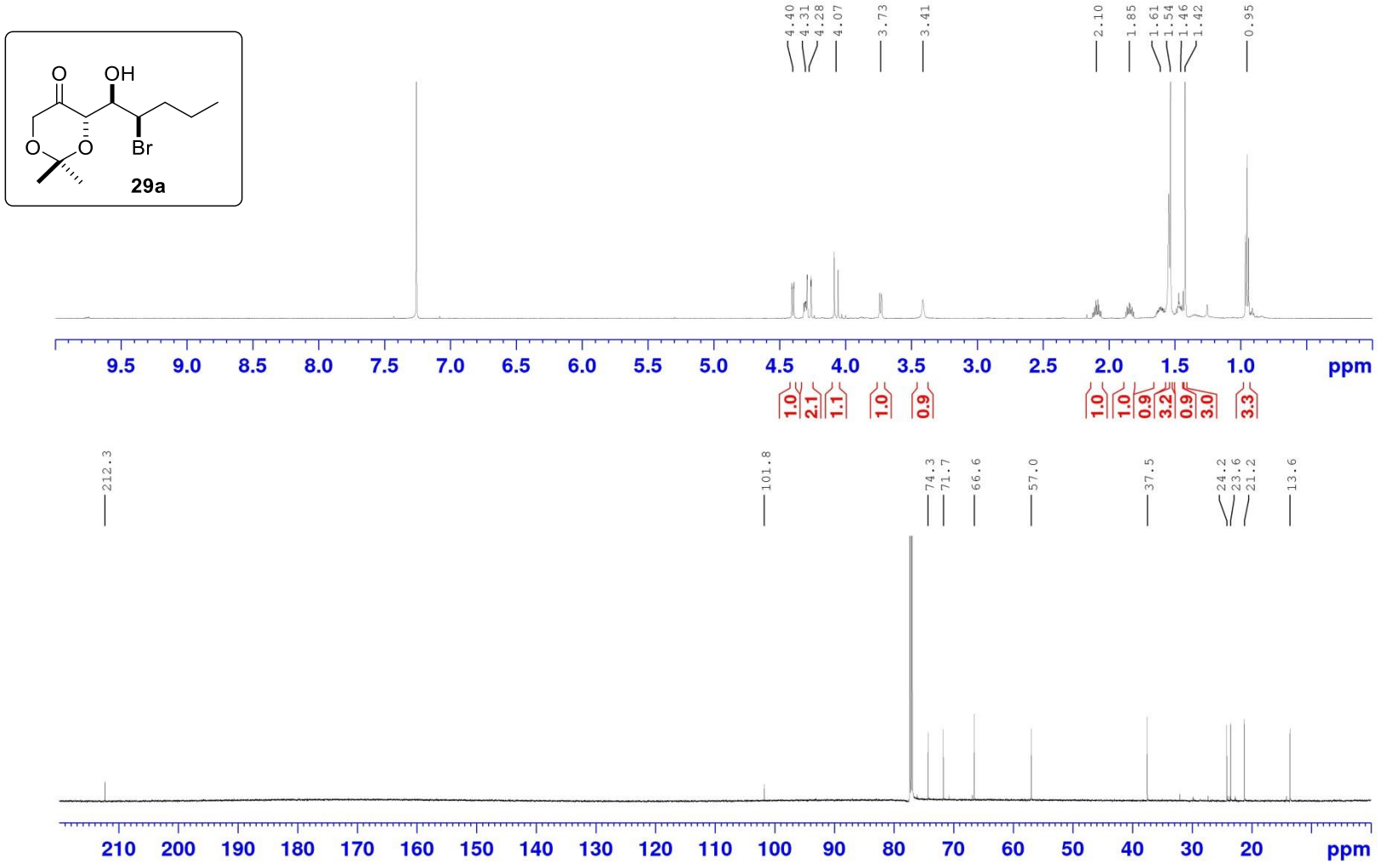
Supplementary Figure 29. Determination of enantiomeric excess of **73**.



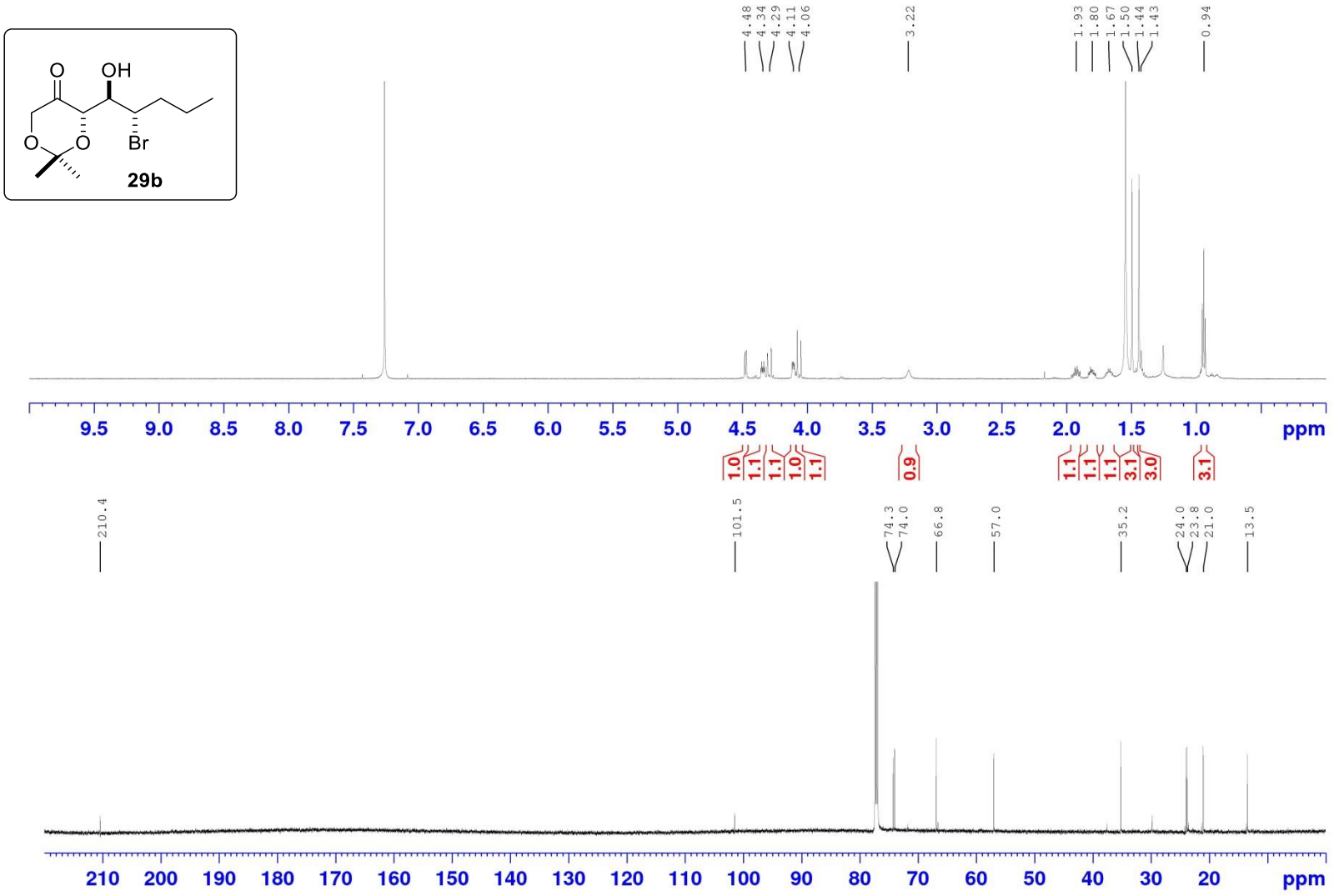
Supplementary Figure 30. NMR spectra of **28**.



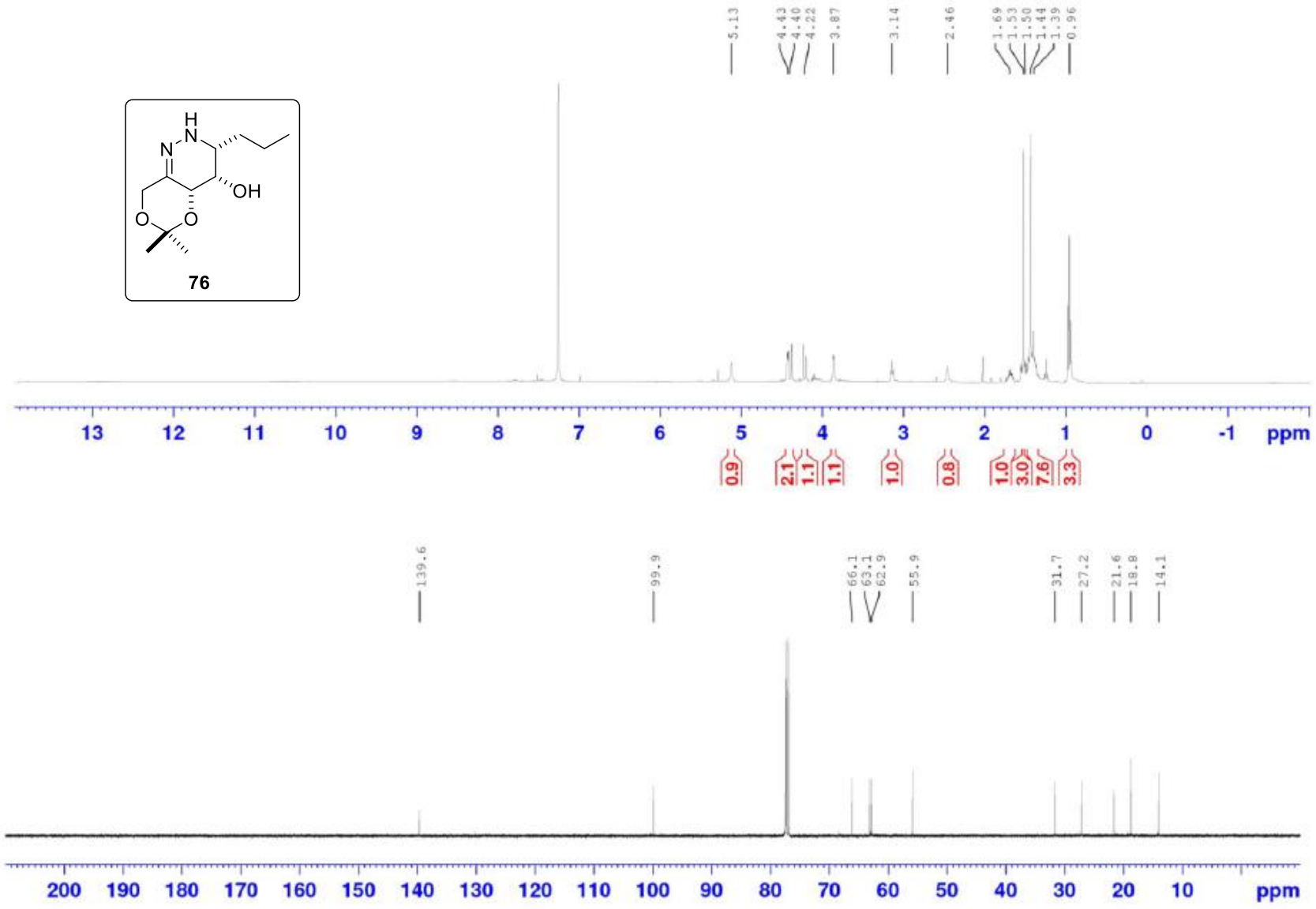
Supplementary Figure 31. NMR spectra of **30**.



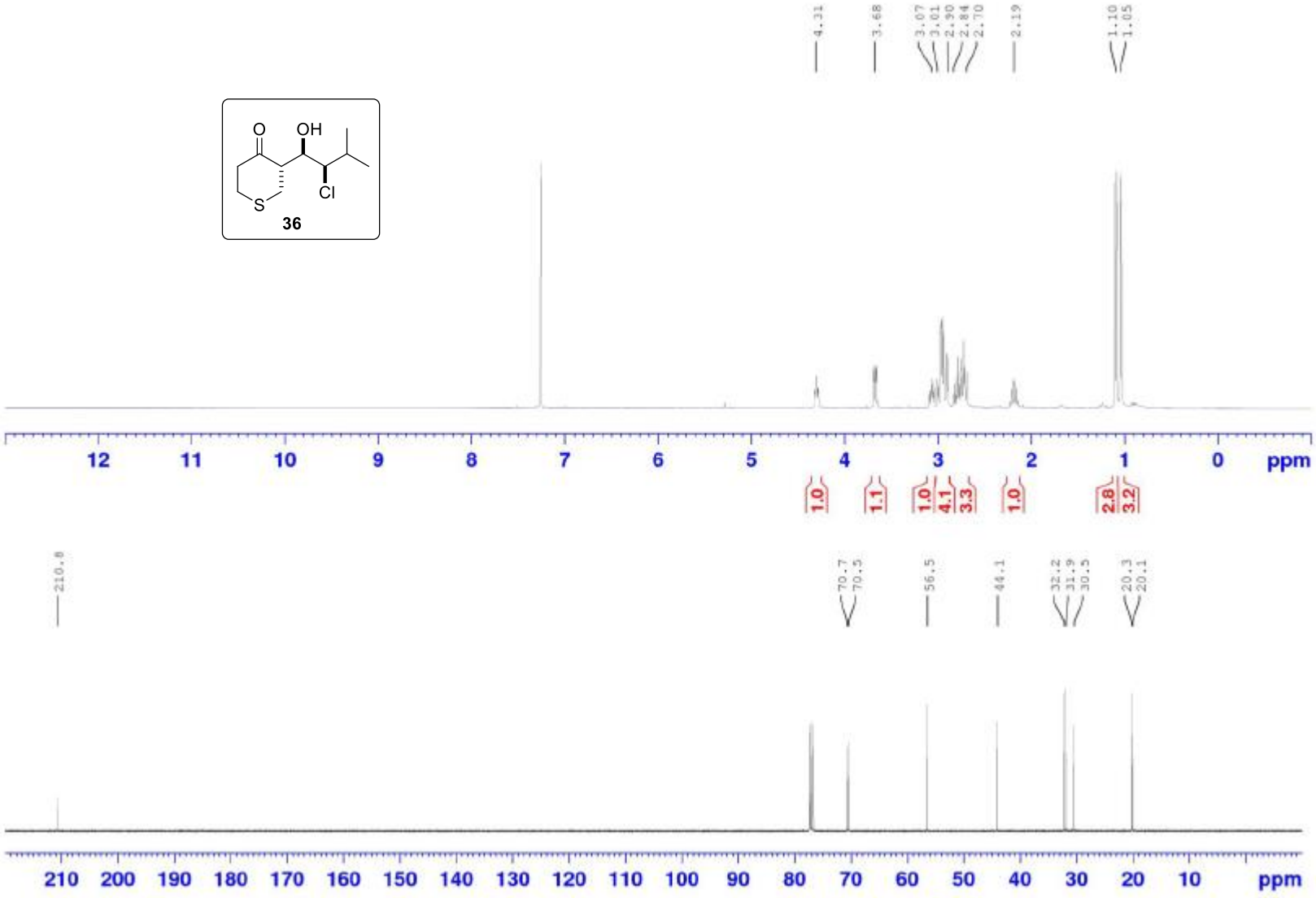
Supplementary Figure 32. NMR spectra of **29a**.



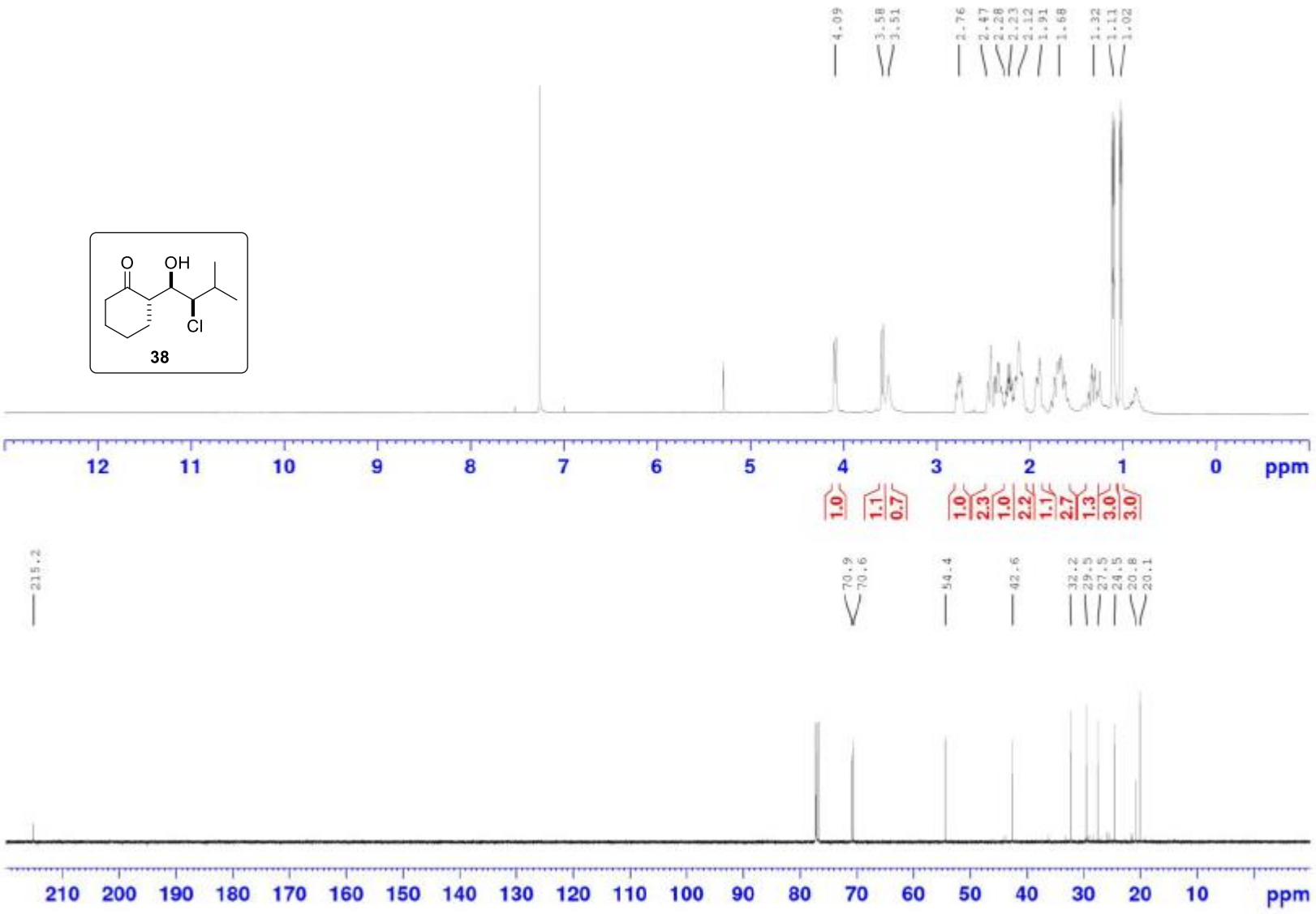
Supplementary Figure 33. NMR spectra of **29b**.



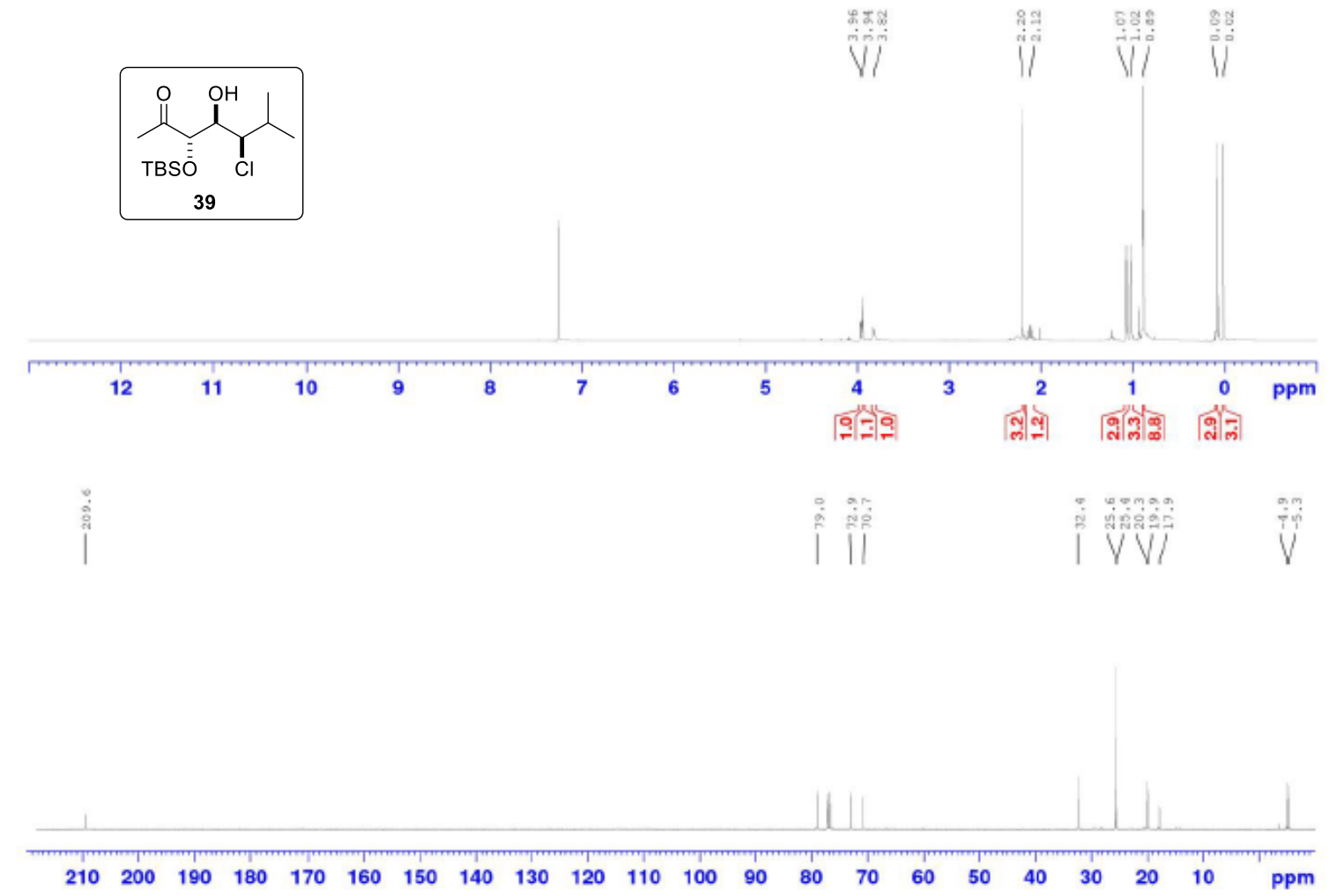
Supplementary Figure 33. NMR spectra of **76**.



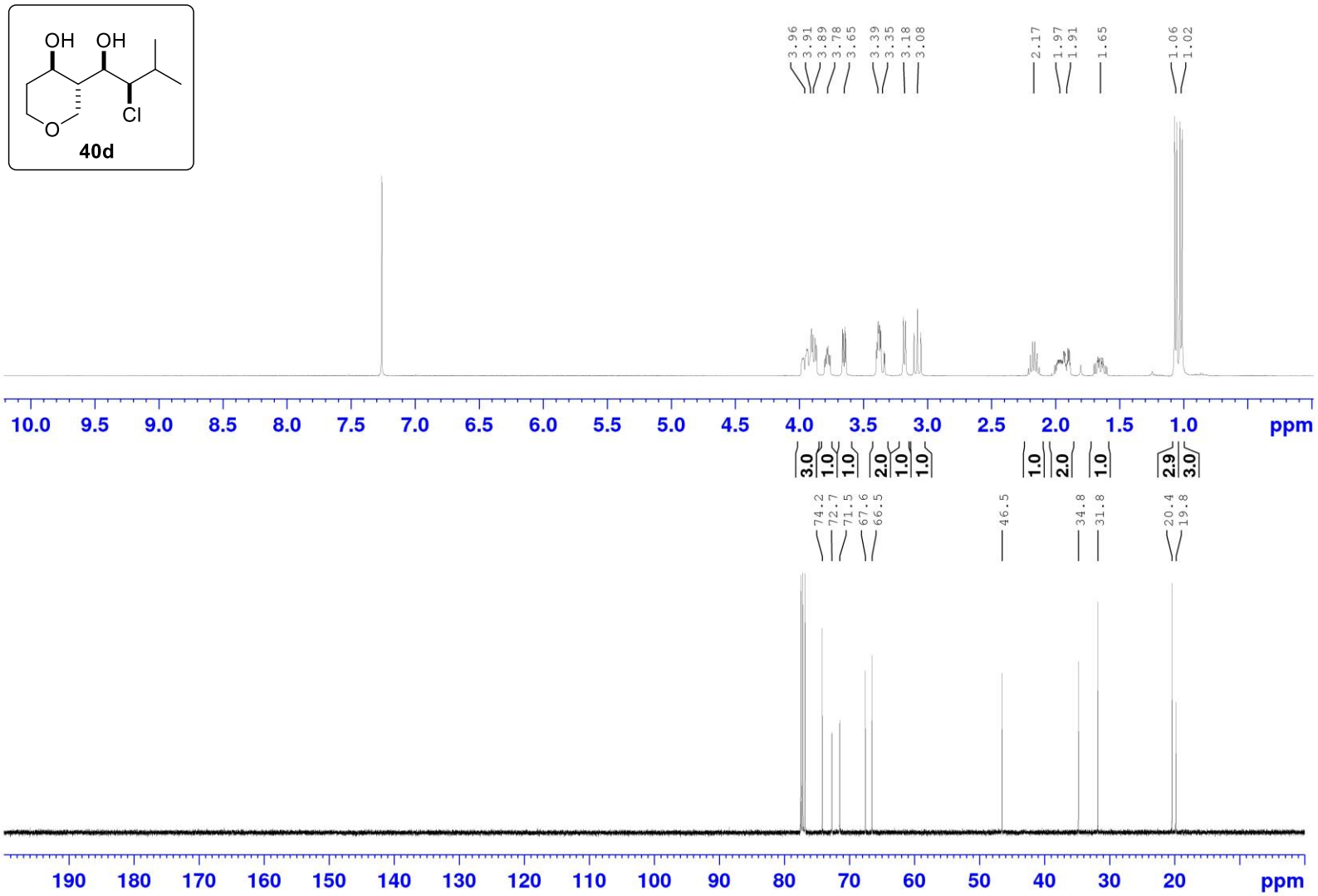
Supplementary Figure 33. NMR spectra of **36**.



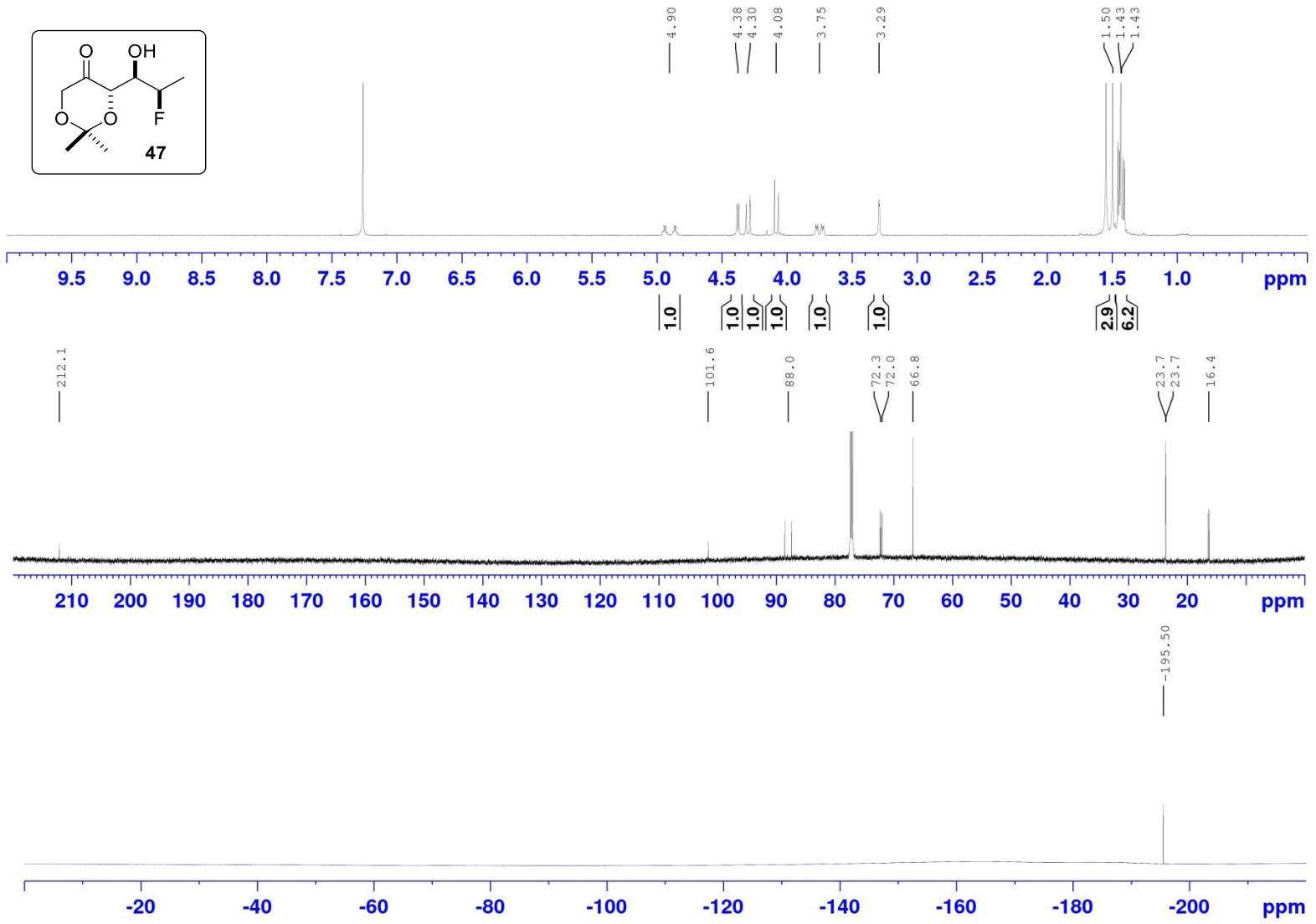
Supplementary Figure 34. NMR spectra of **38**.



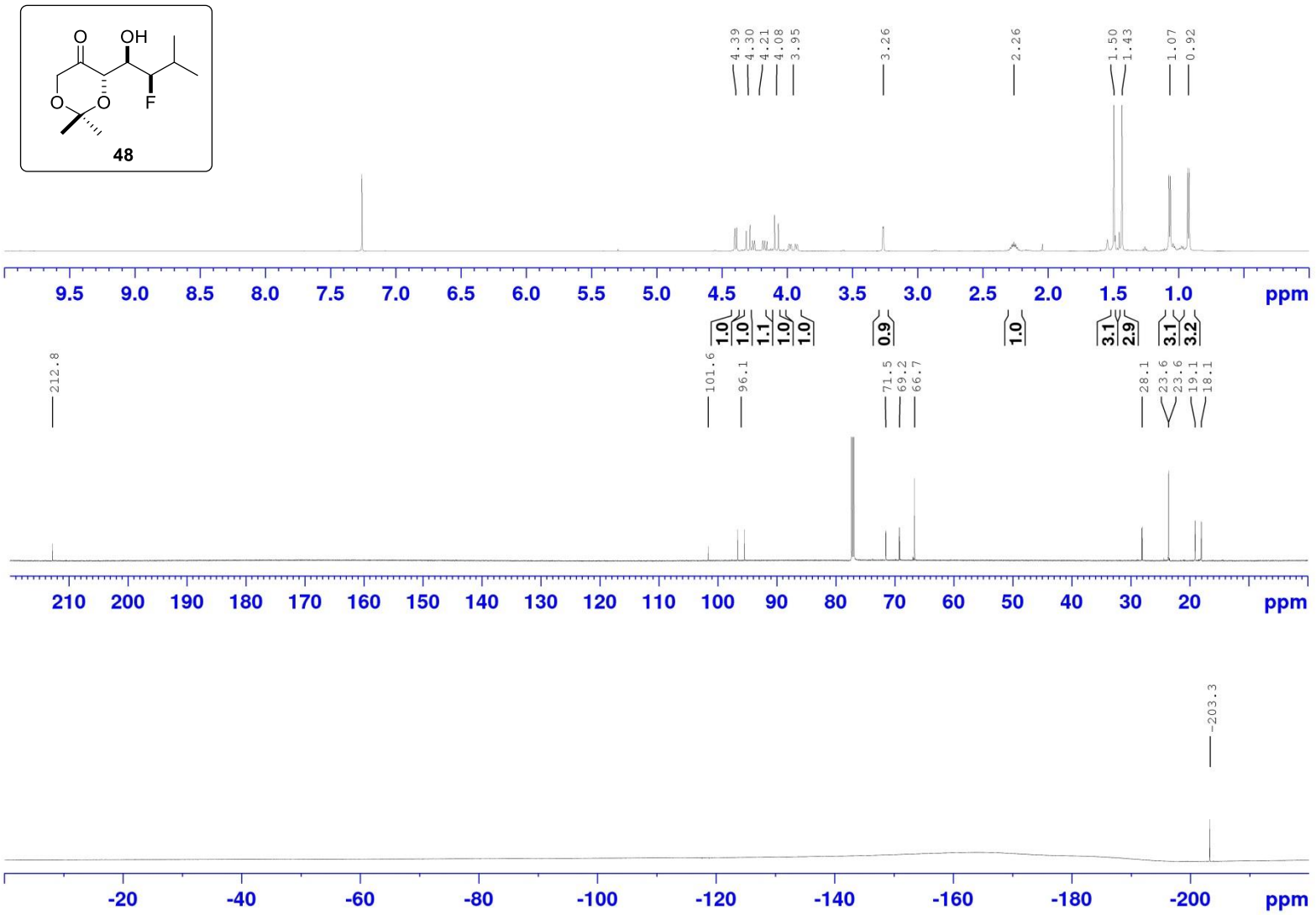
Supplementary Figure 35. NMR spectra of **39**.



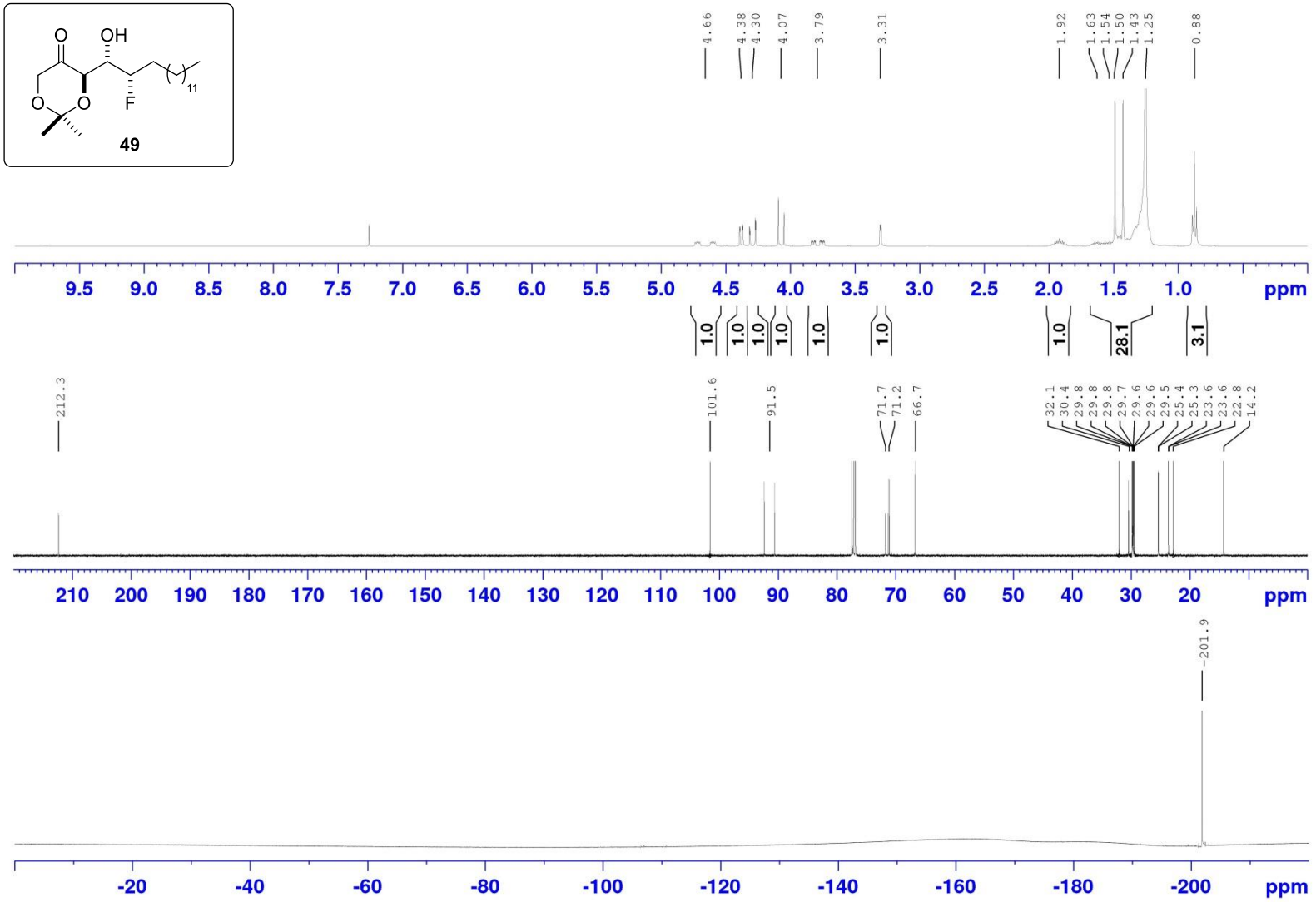
Supplementary Figure 36. NMR spectra of **40d**.



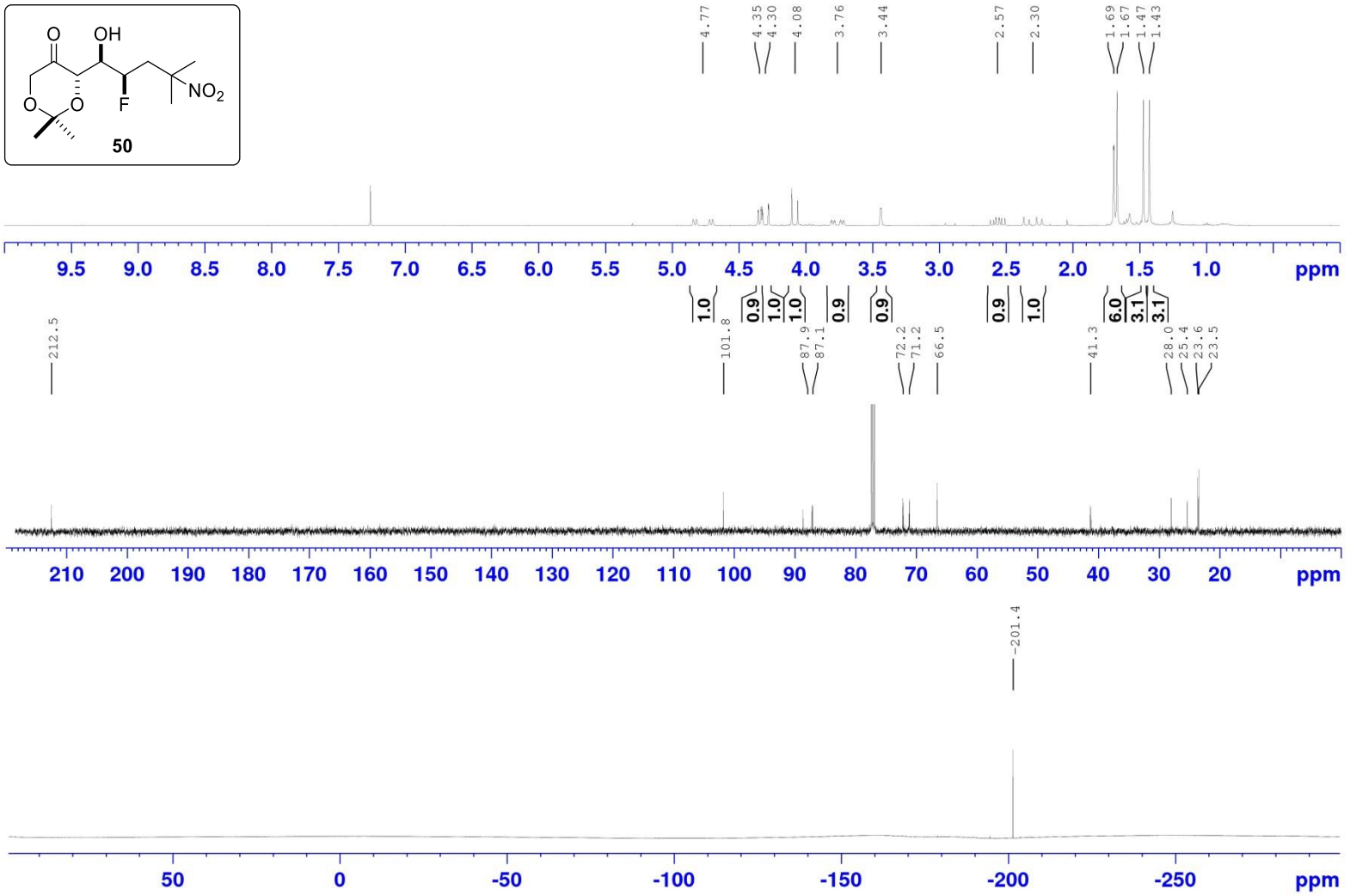
Supplementary Figure 37. NMR spectra of **47**.



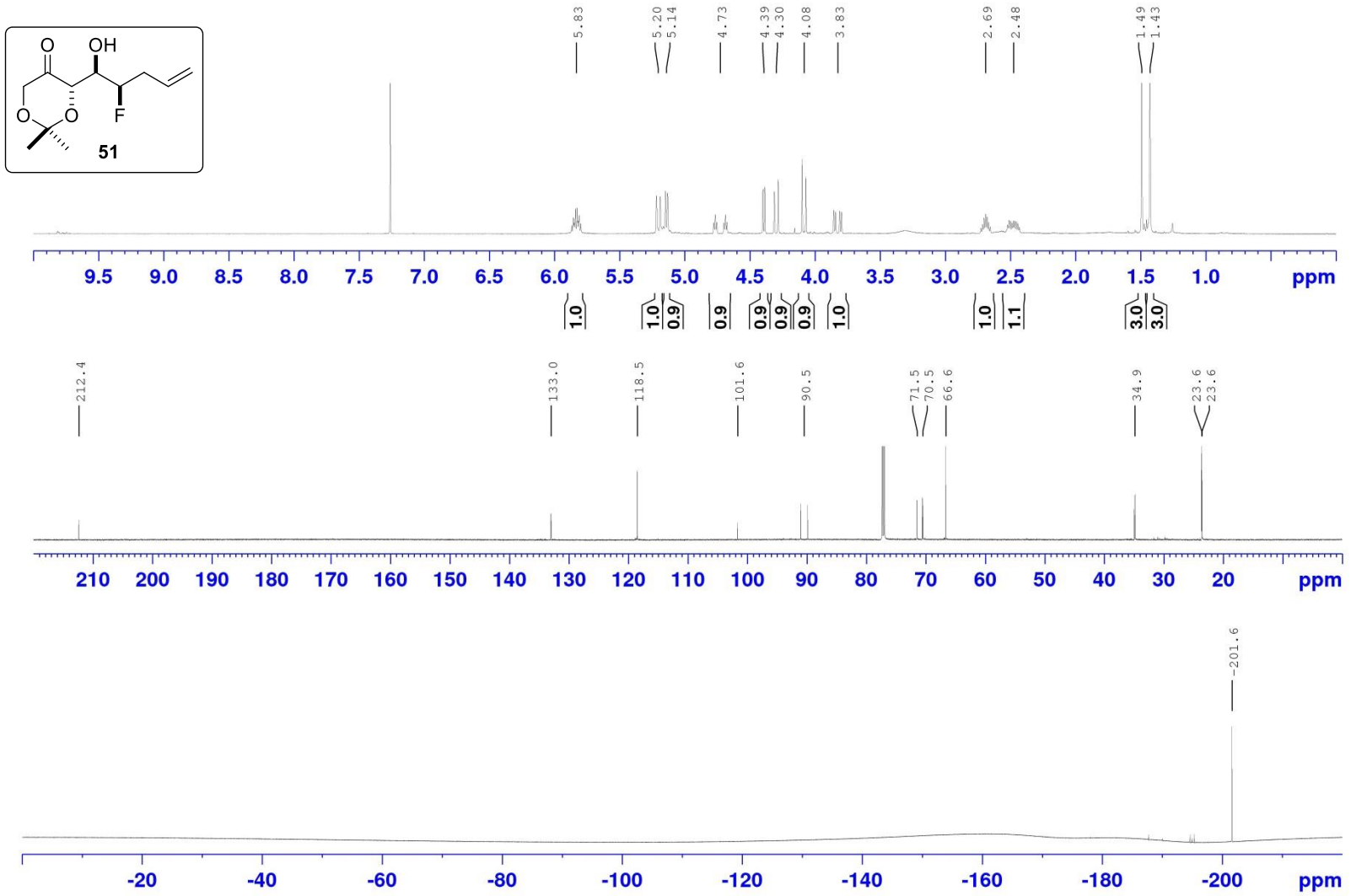
Supplementary Figure 38. NMR spectra of **48**.



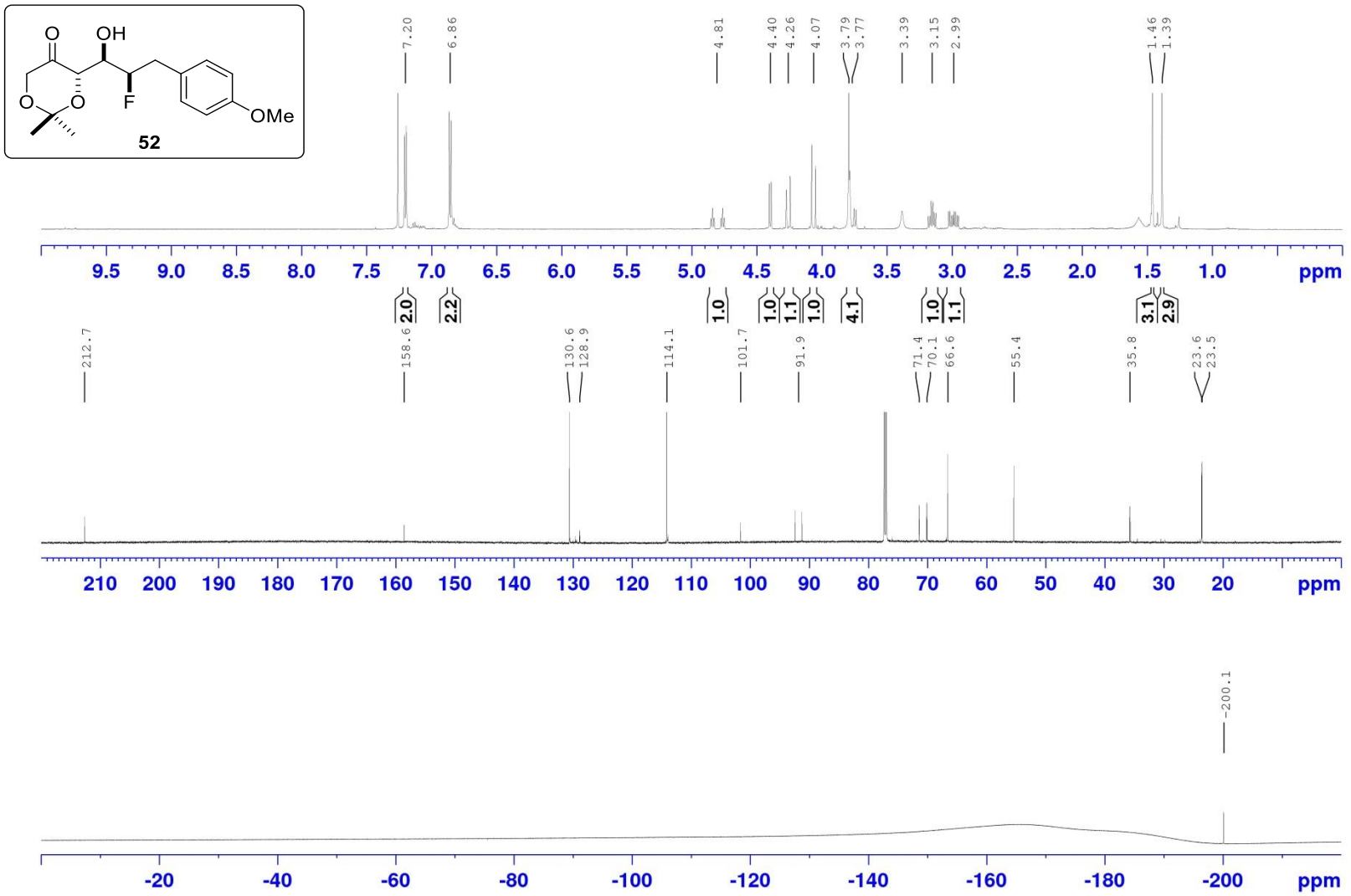
Supplementary Figure 39. NMR spectra of **49**.



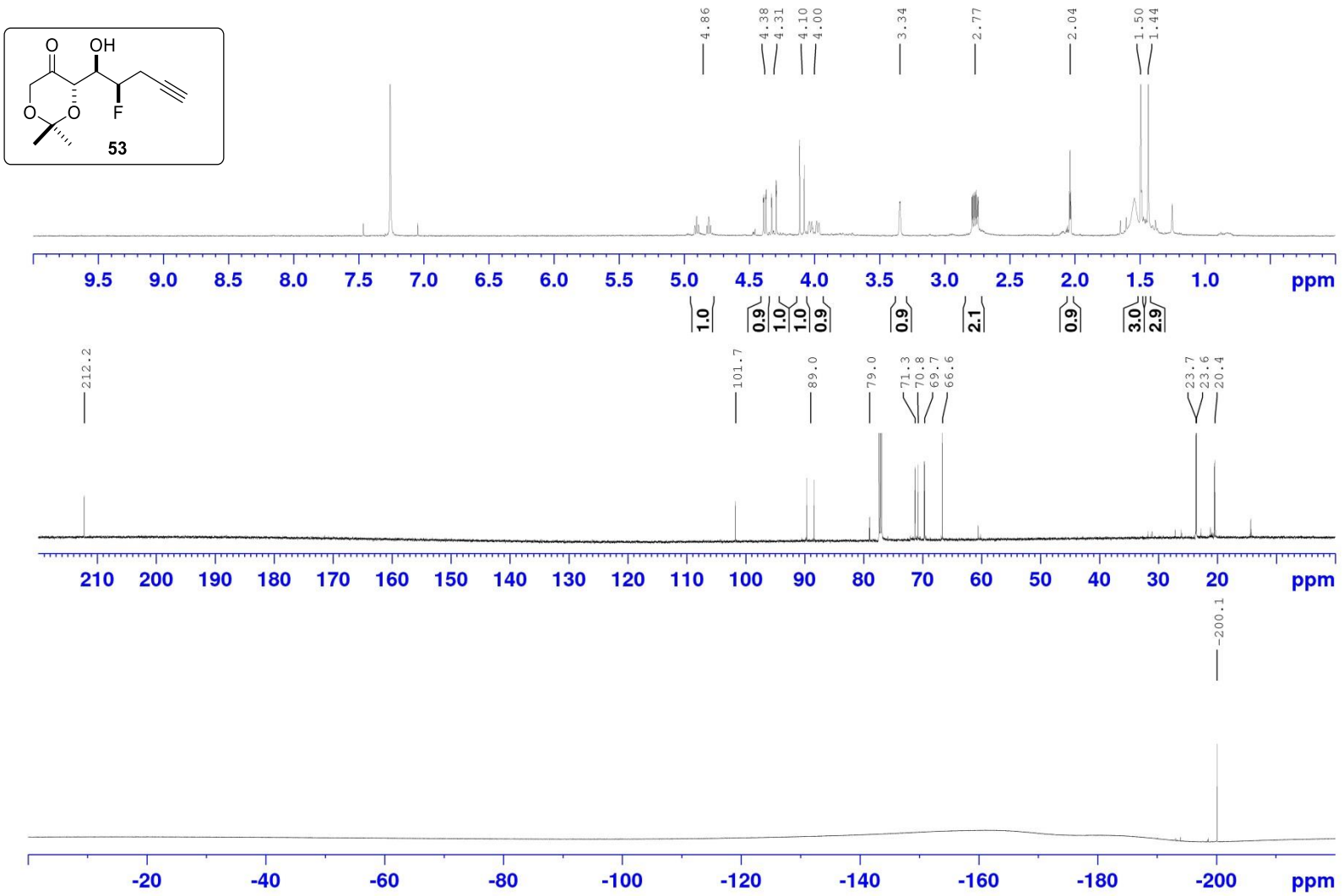
Supplementary Figure 40. NMR spectra of **50**.



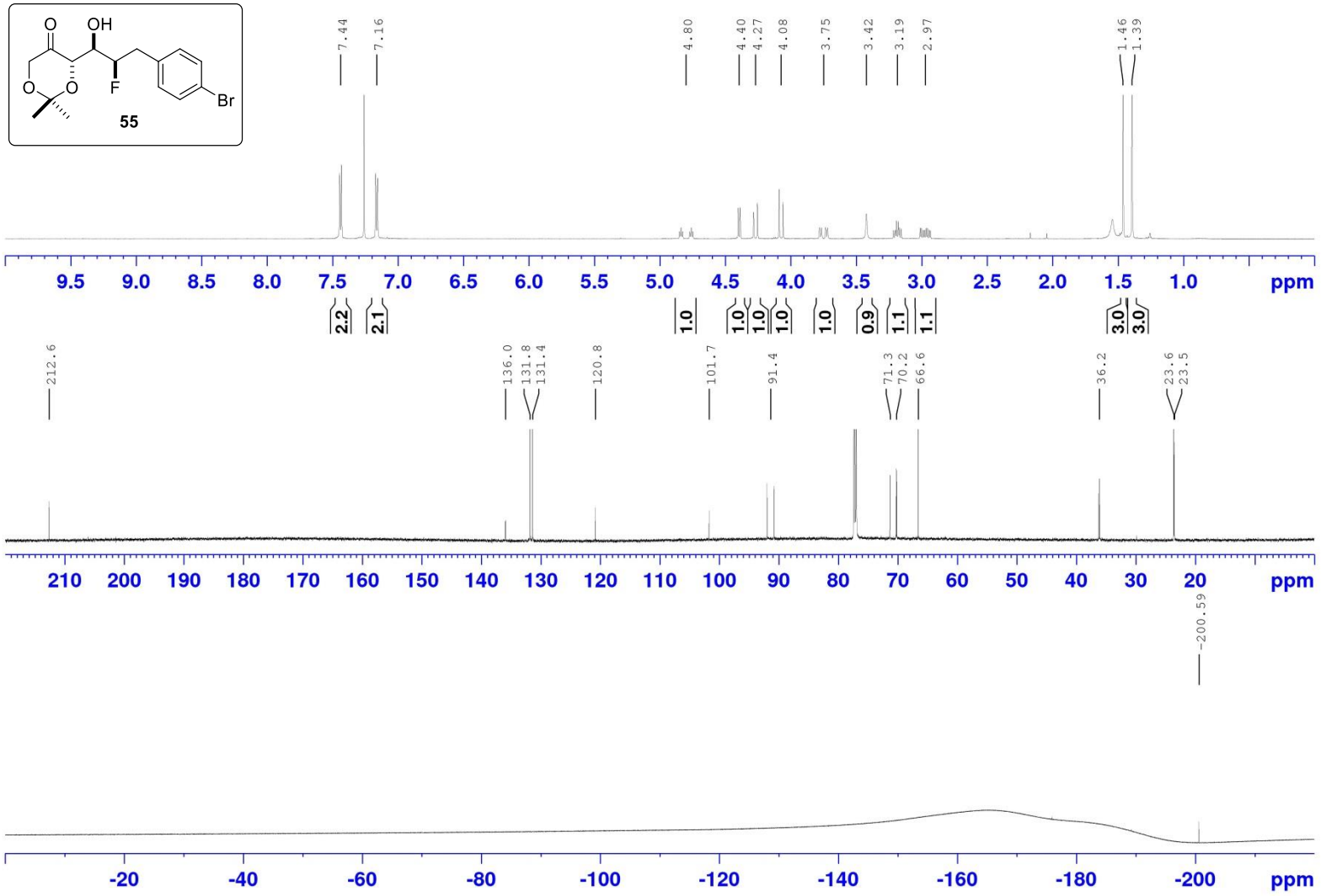
Supplementary Figure 41. NMR spectra of **51**.



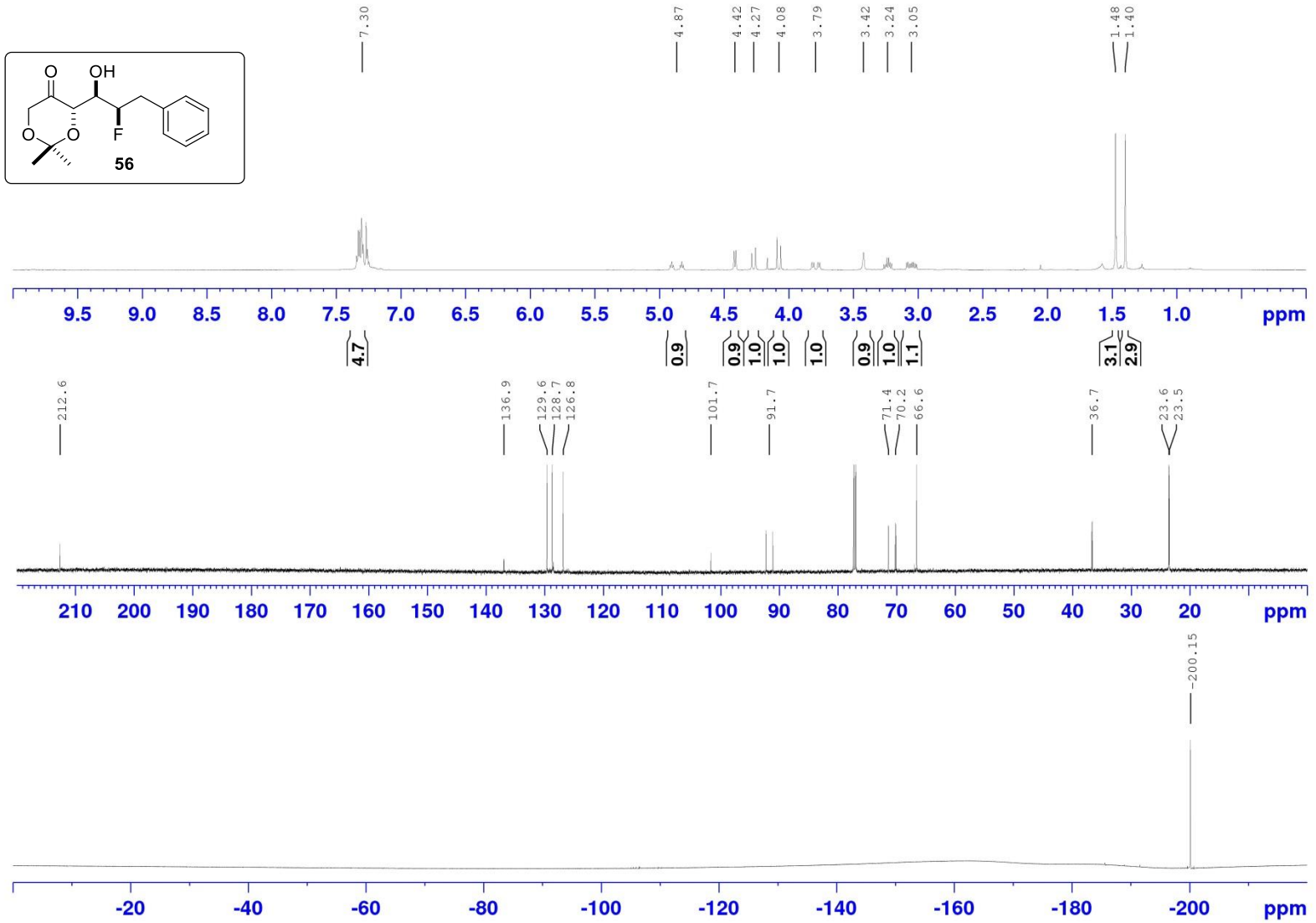
Supplementary Figure 42. NMR spectra of **52**.



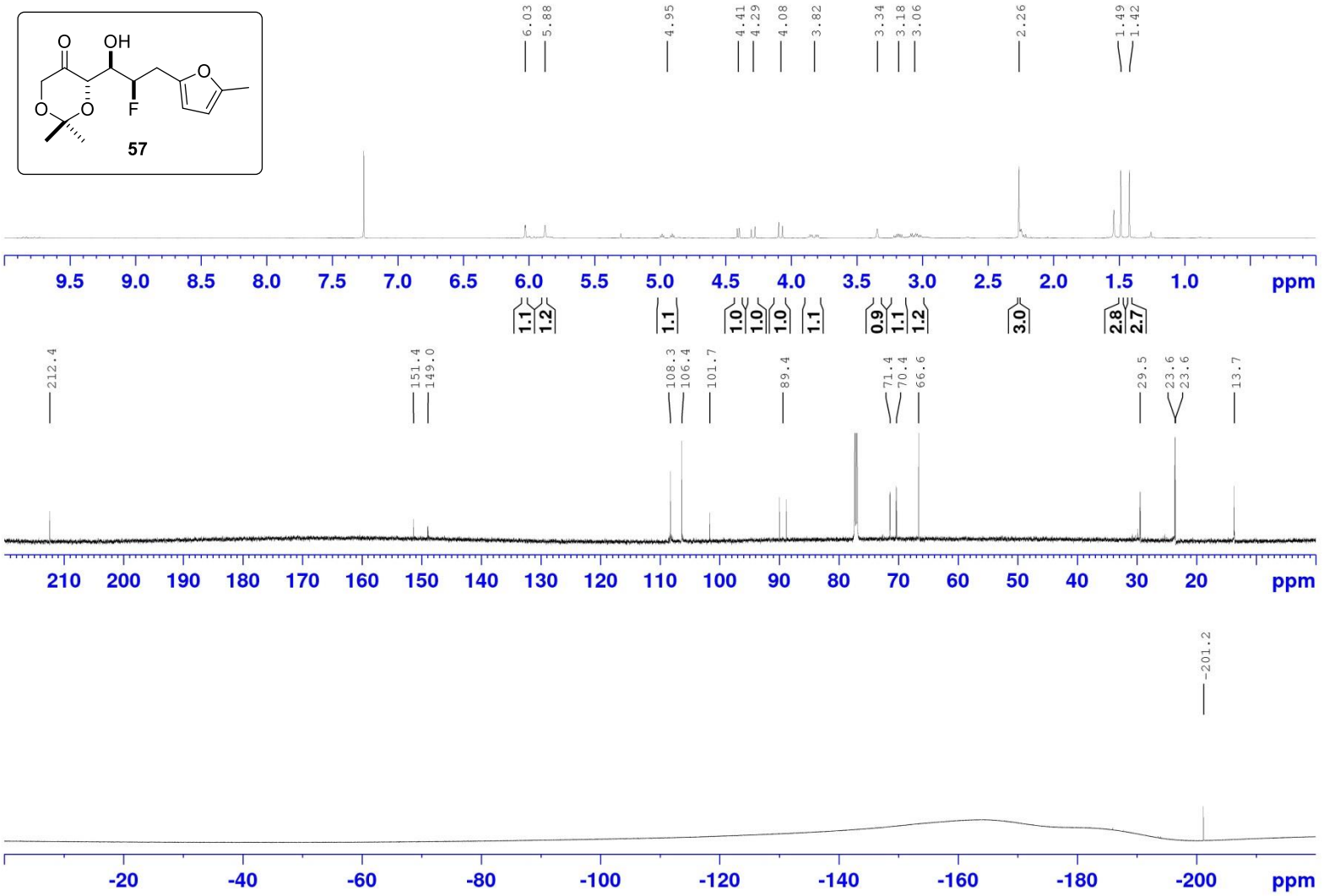
Supplementary Figure 43. NMR spectra of **53**.



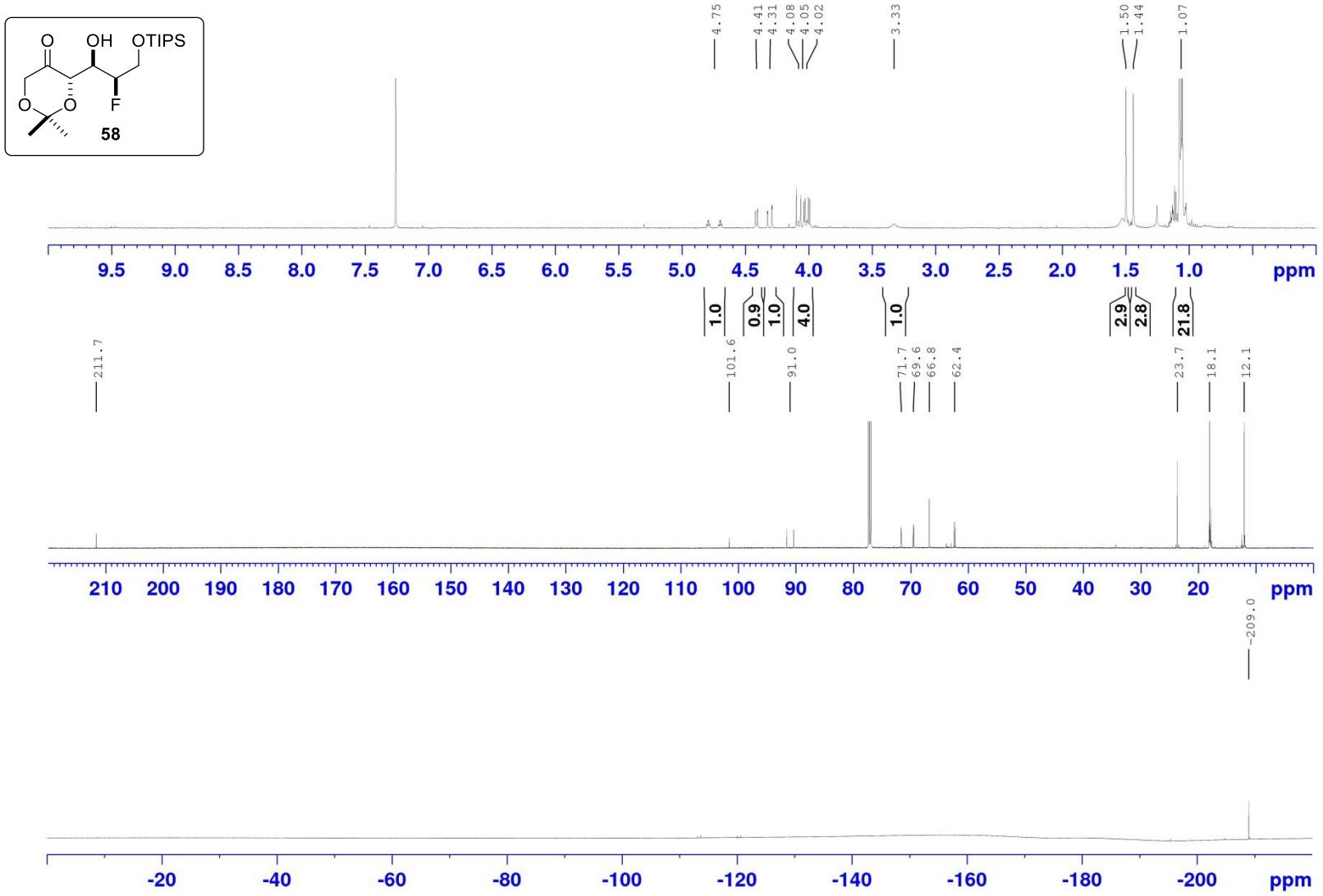
Supplementary Figure 44. NMR spectra of **55**.



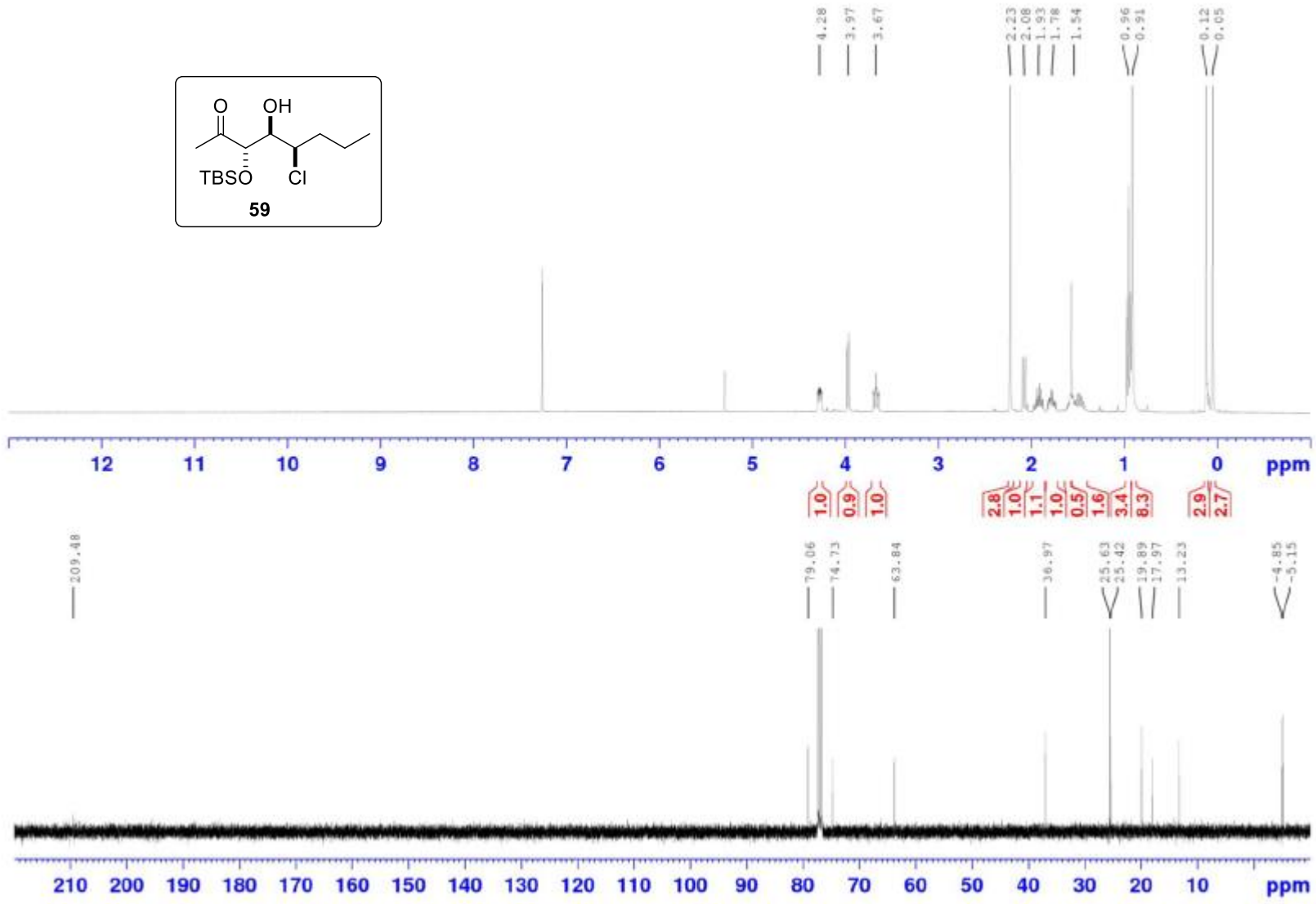
Supplementary Figure 45. NMR spectra of **56**.



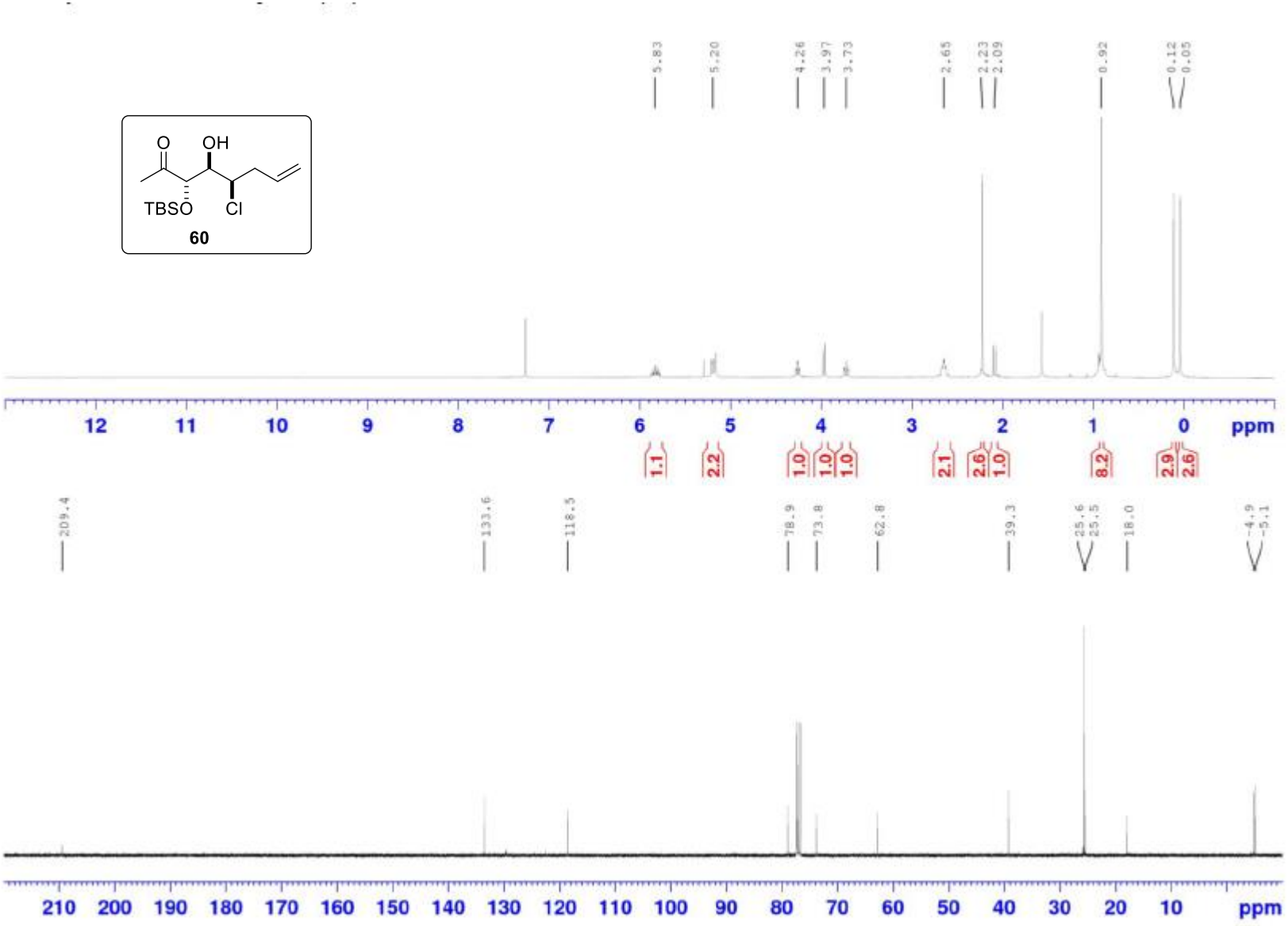
Supplementary Figure 46. NMR spectra of **57**.



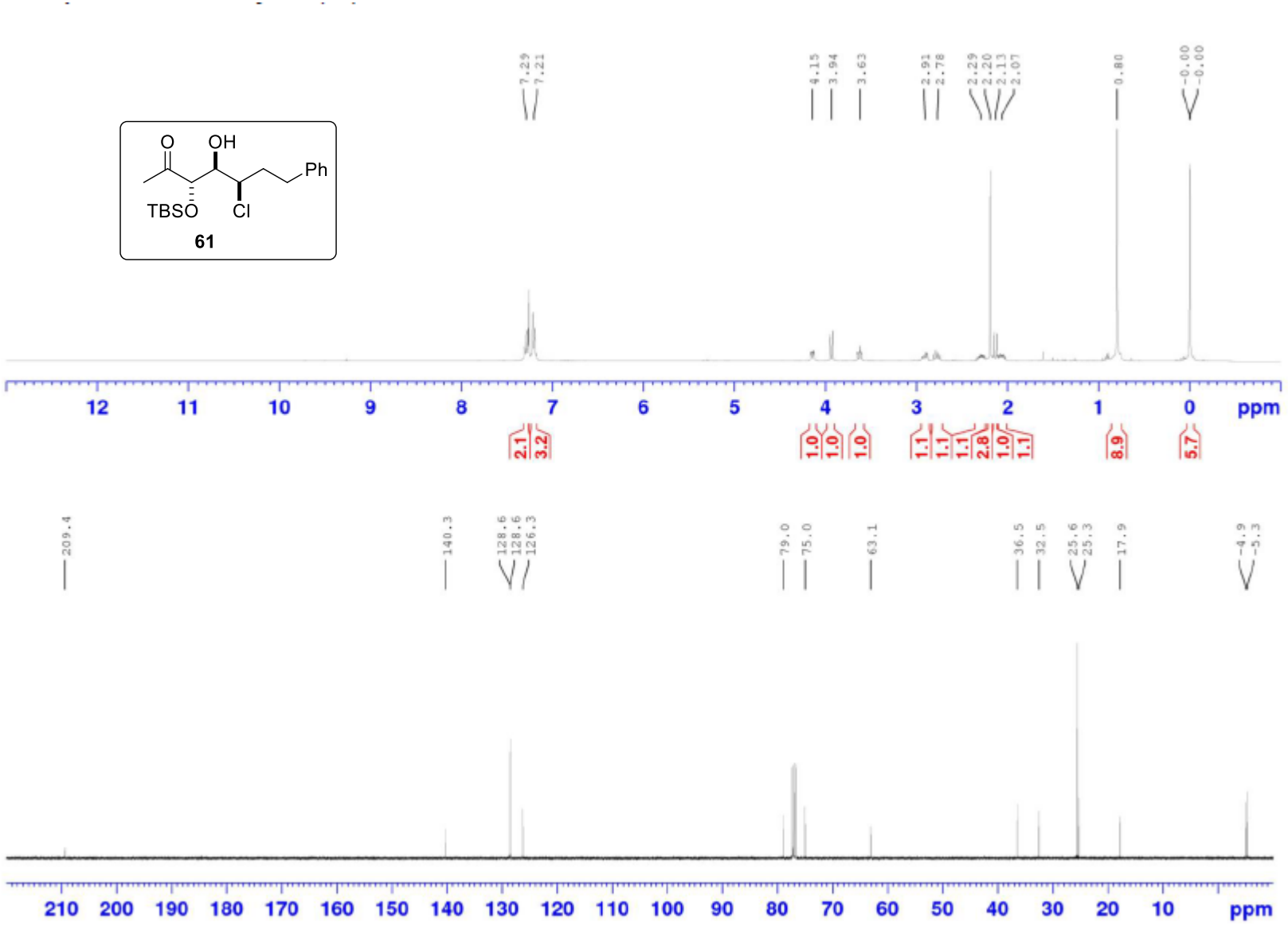
Supplementary Figure 47. NMR spectra of **58**.



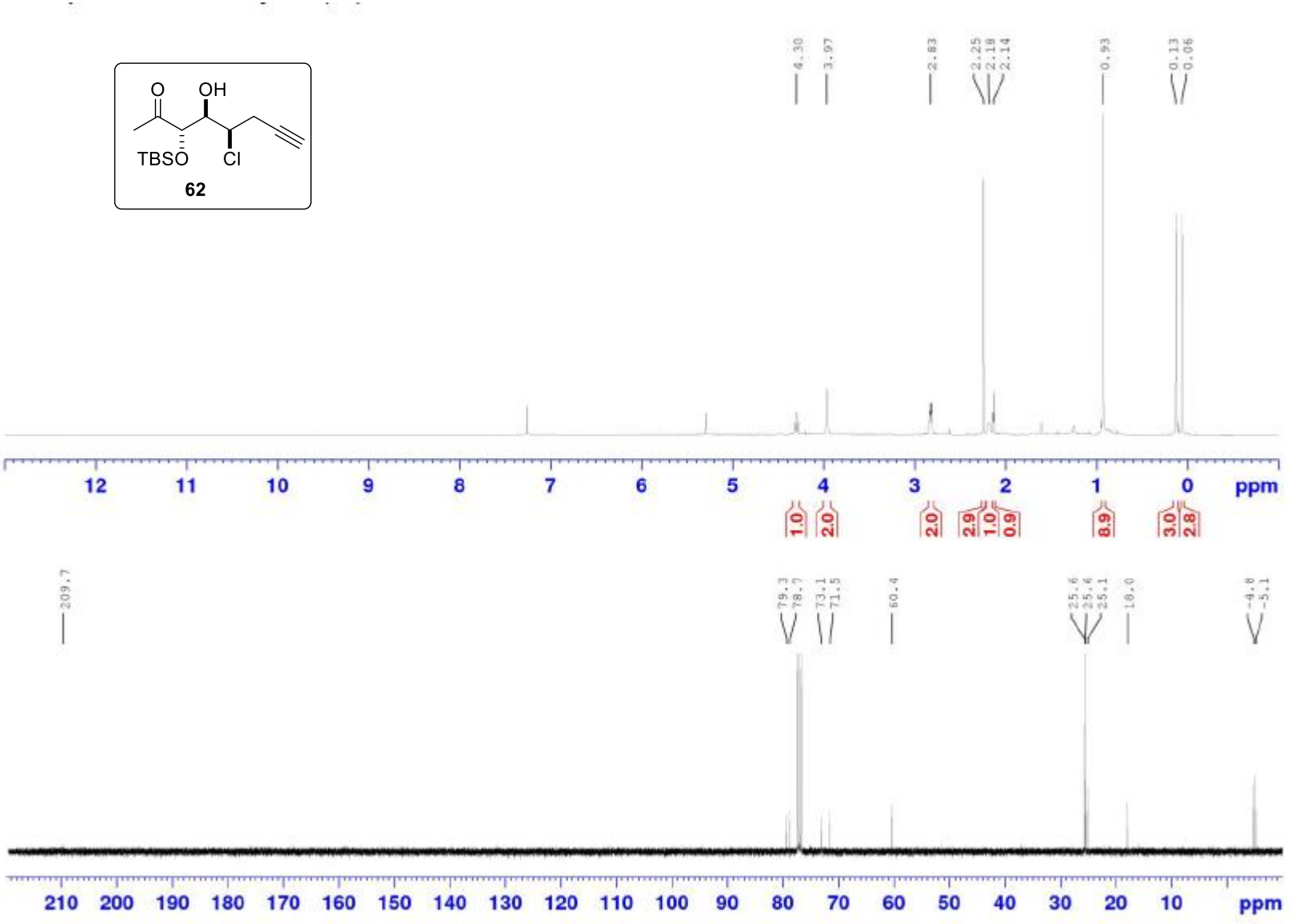
Supplementary Figure 48. NMR spectra of **59**.



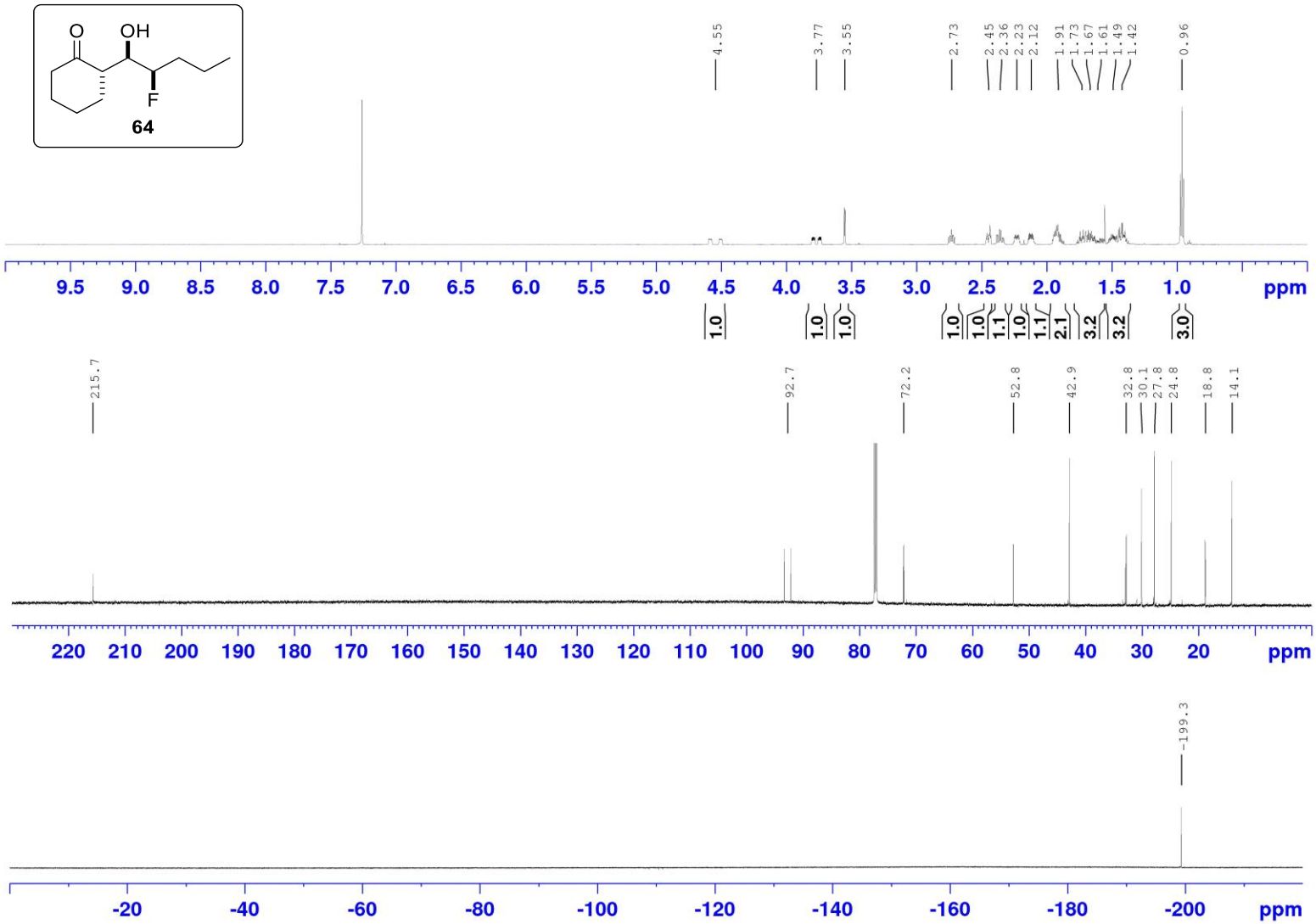
Supplementary Figure 49. NMR spectra of **60**.



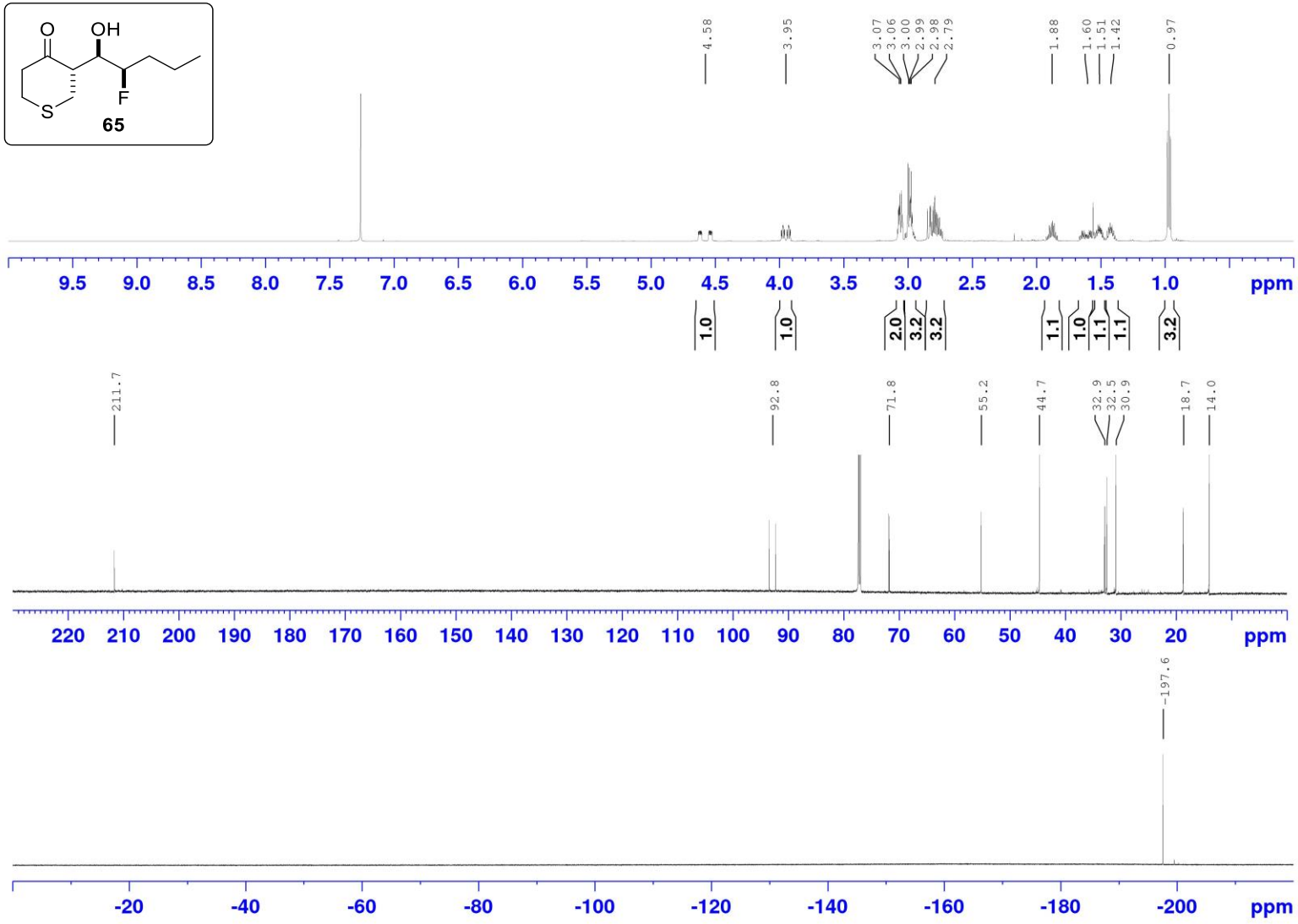
Supplementary Figure 50. NMR spectra of **61**.



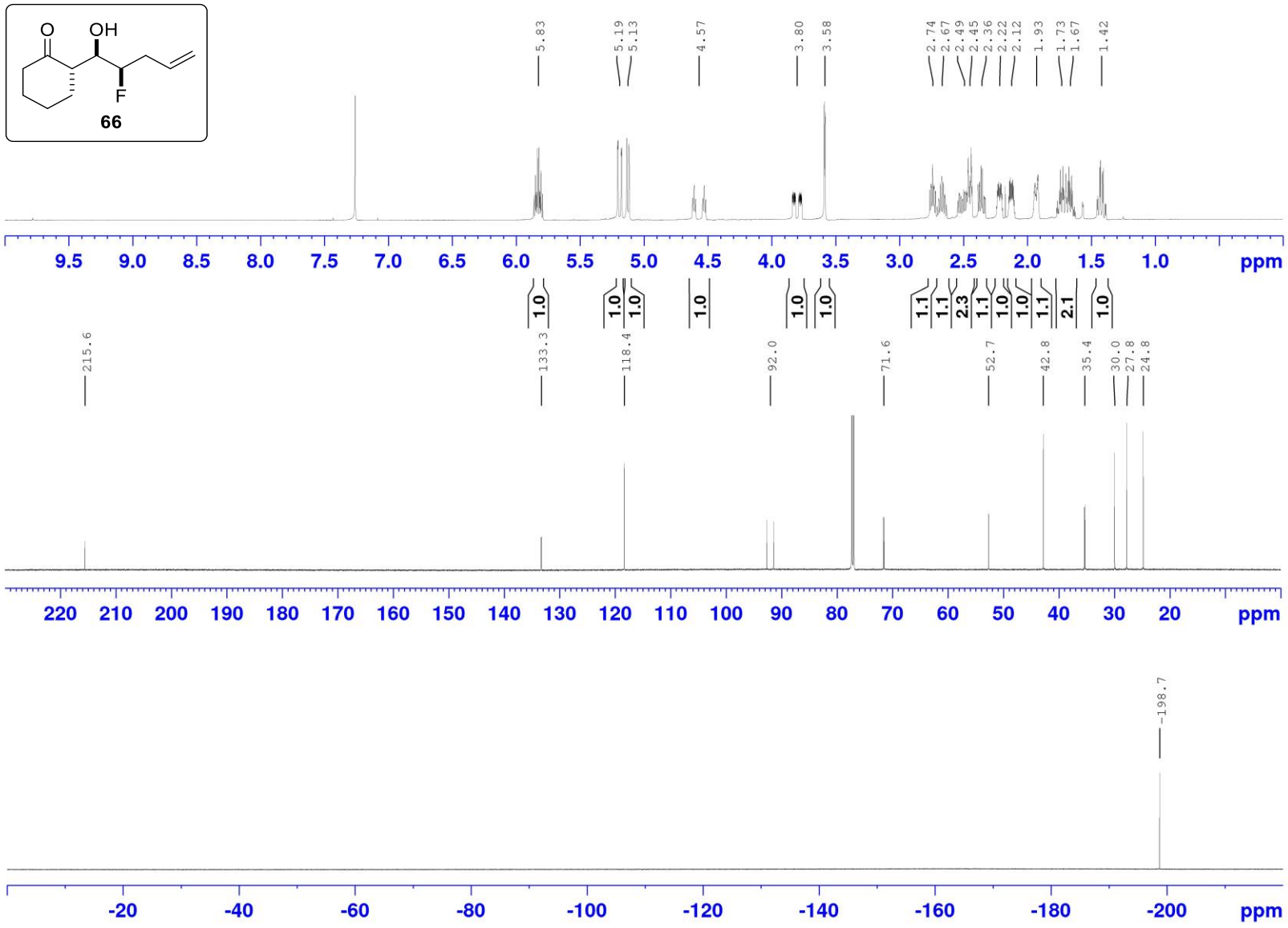
Supplementary Figure 51. NMR spectra of **62**.



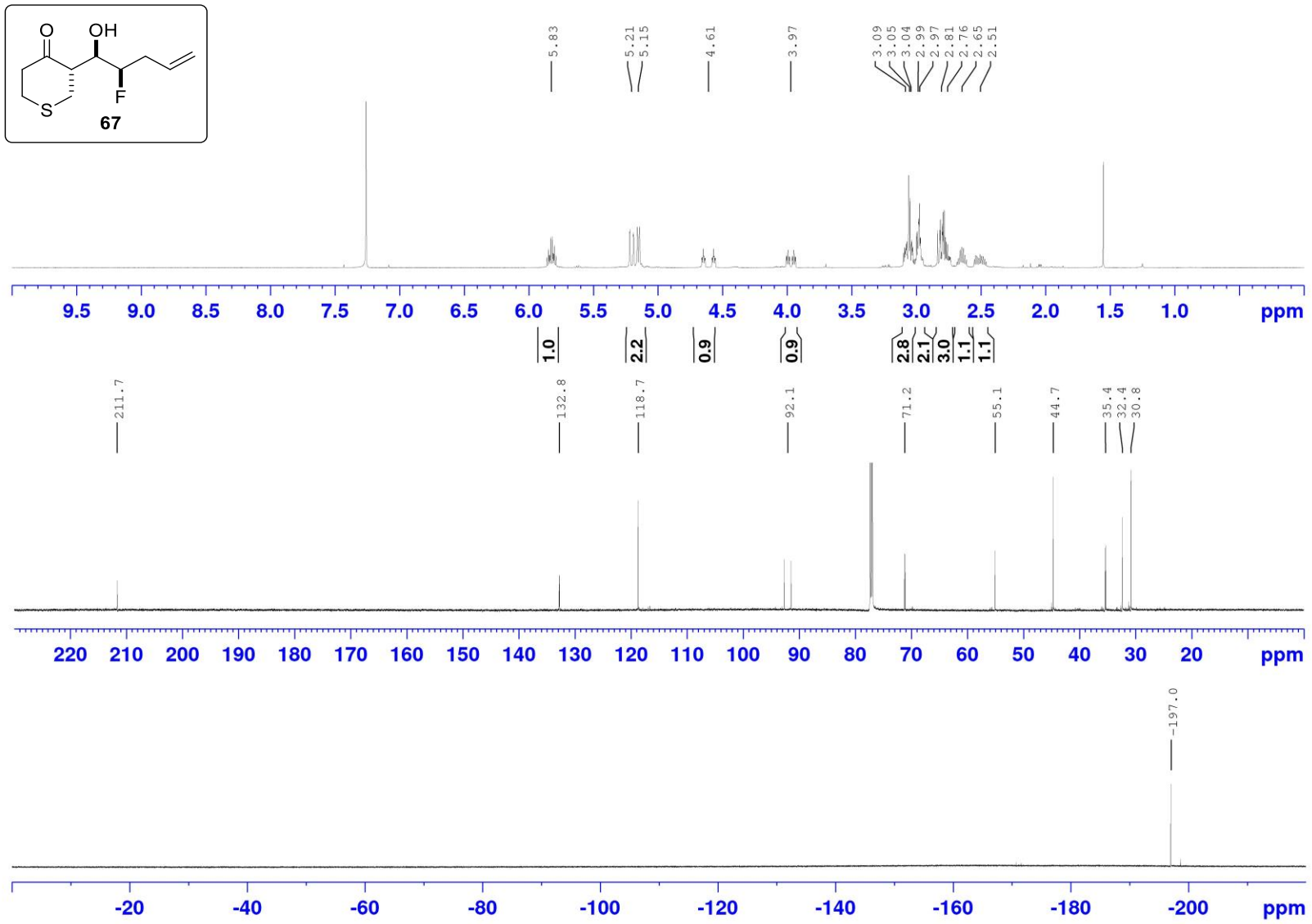
Supplementary Figure 52. NMR spectra of **64**.



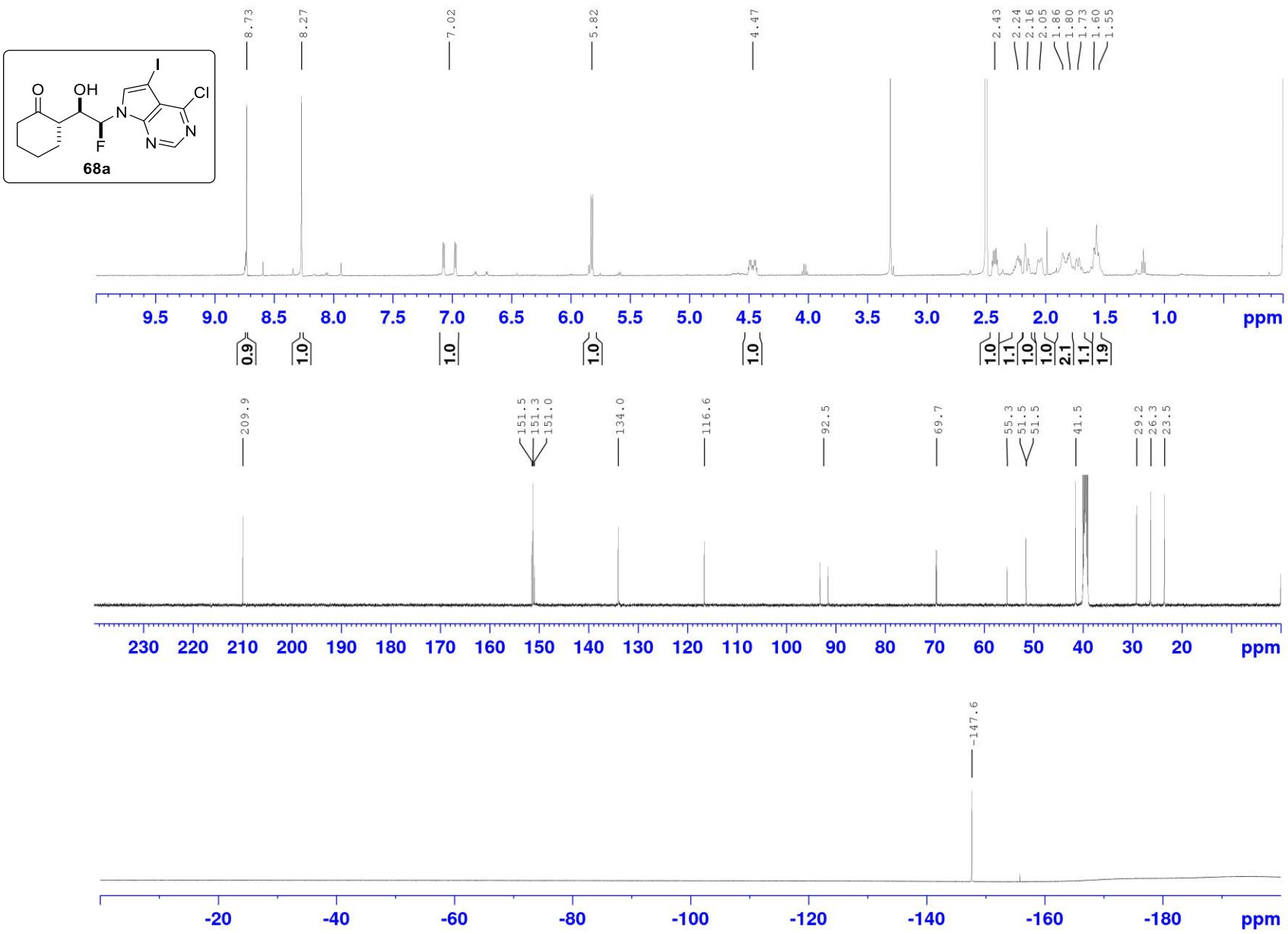
Supplementary Figure 53. NMR spectra of **65**.



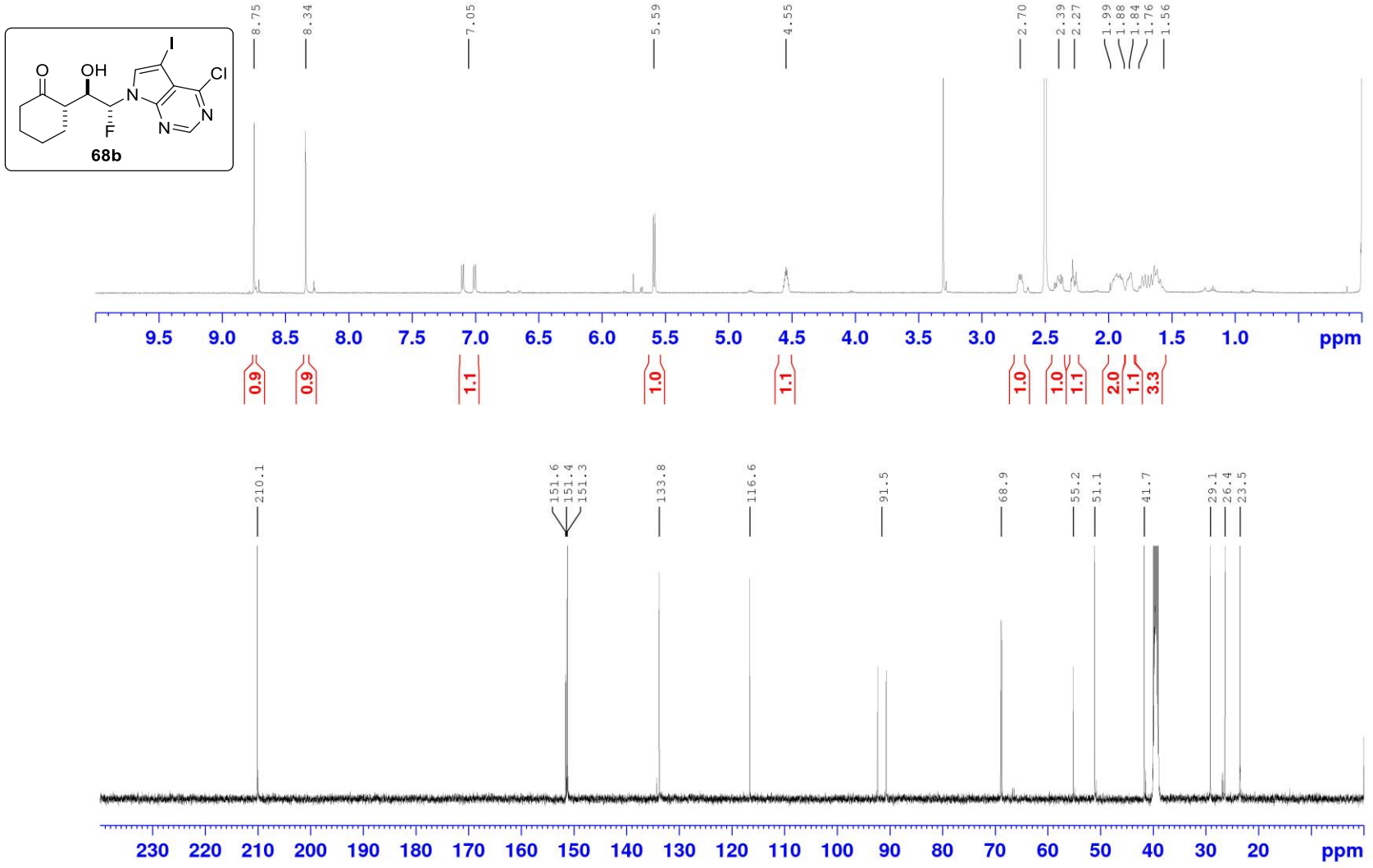
Supplementary Figure 54. NMR spectra of **66**.



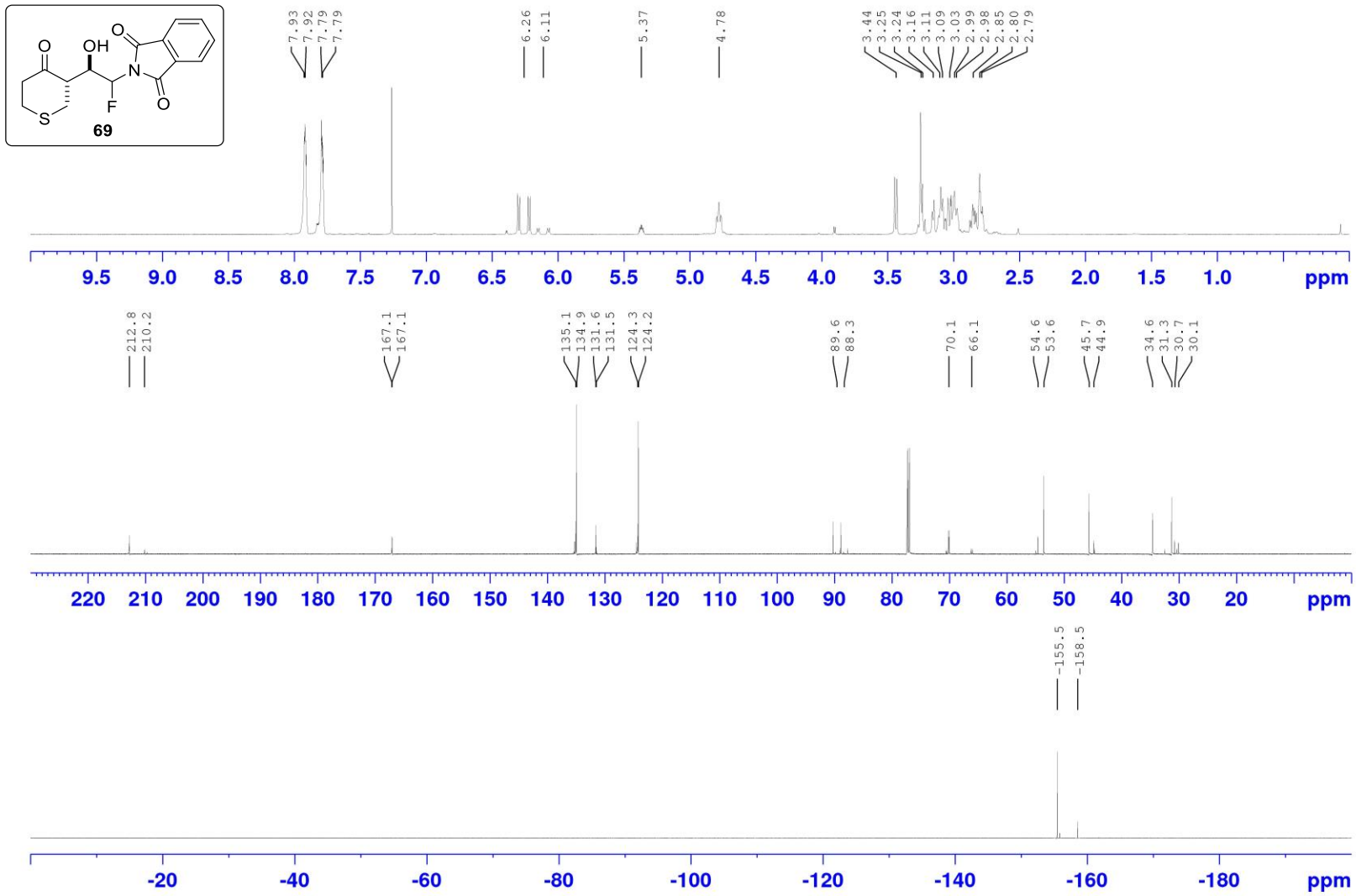
Supplementary Figure 55. NMR spectra of **67**.



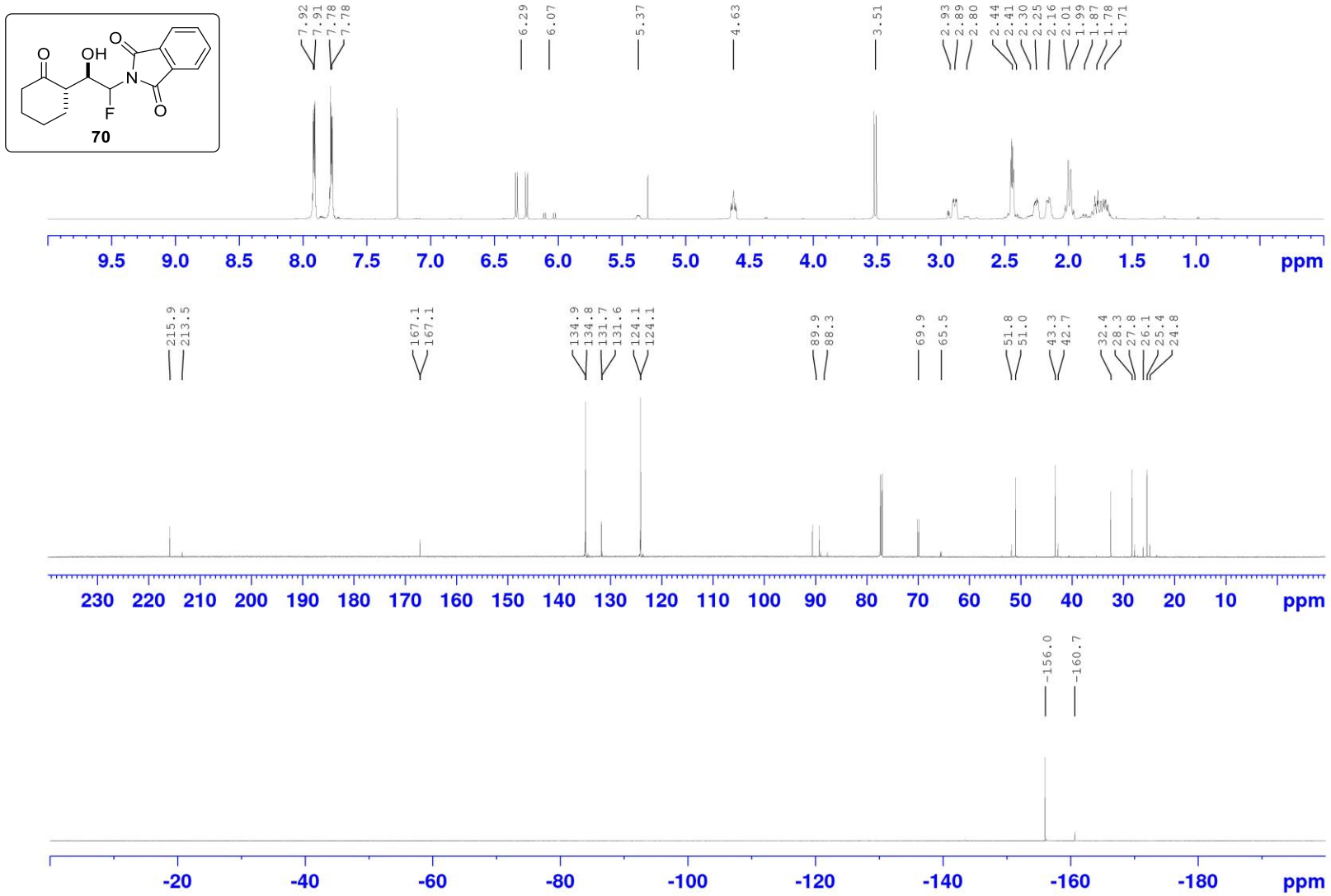
Supplementary Figure 56. NMR spectra of **68a**.



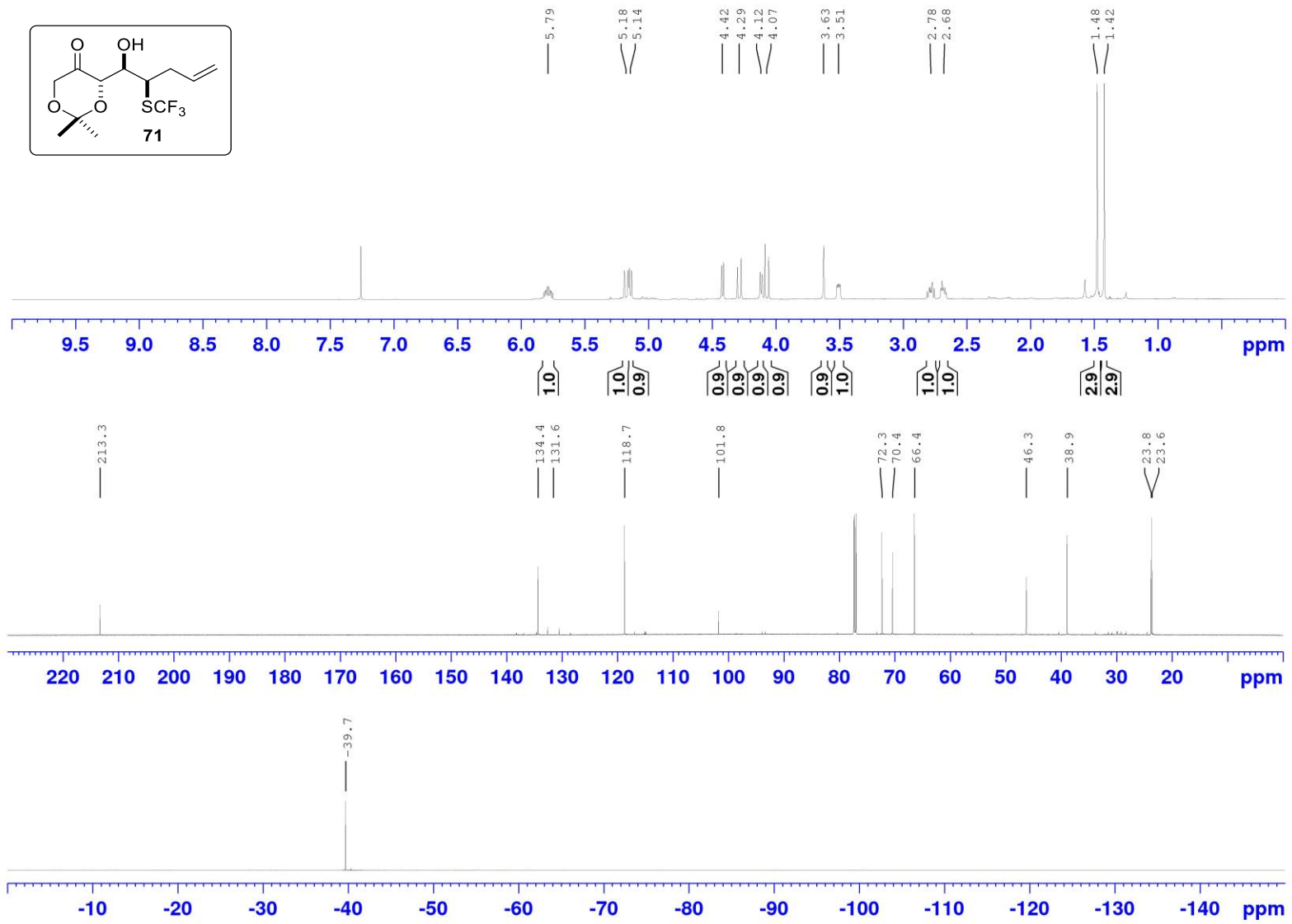
Supplementary Figure 57. NMR spectra of **68b**.



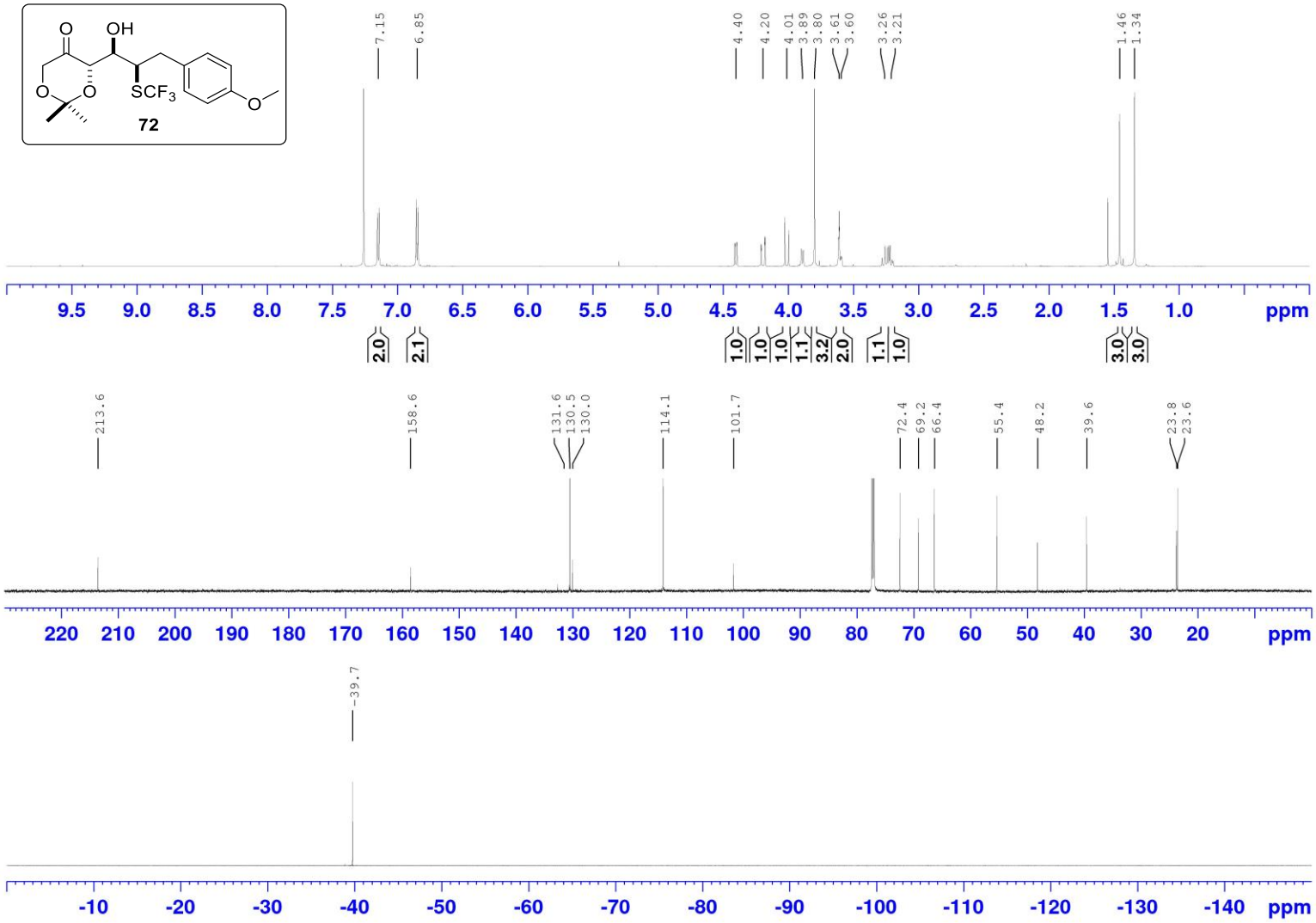
Supplementary Figure 58. NMR spectra of **69**.



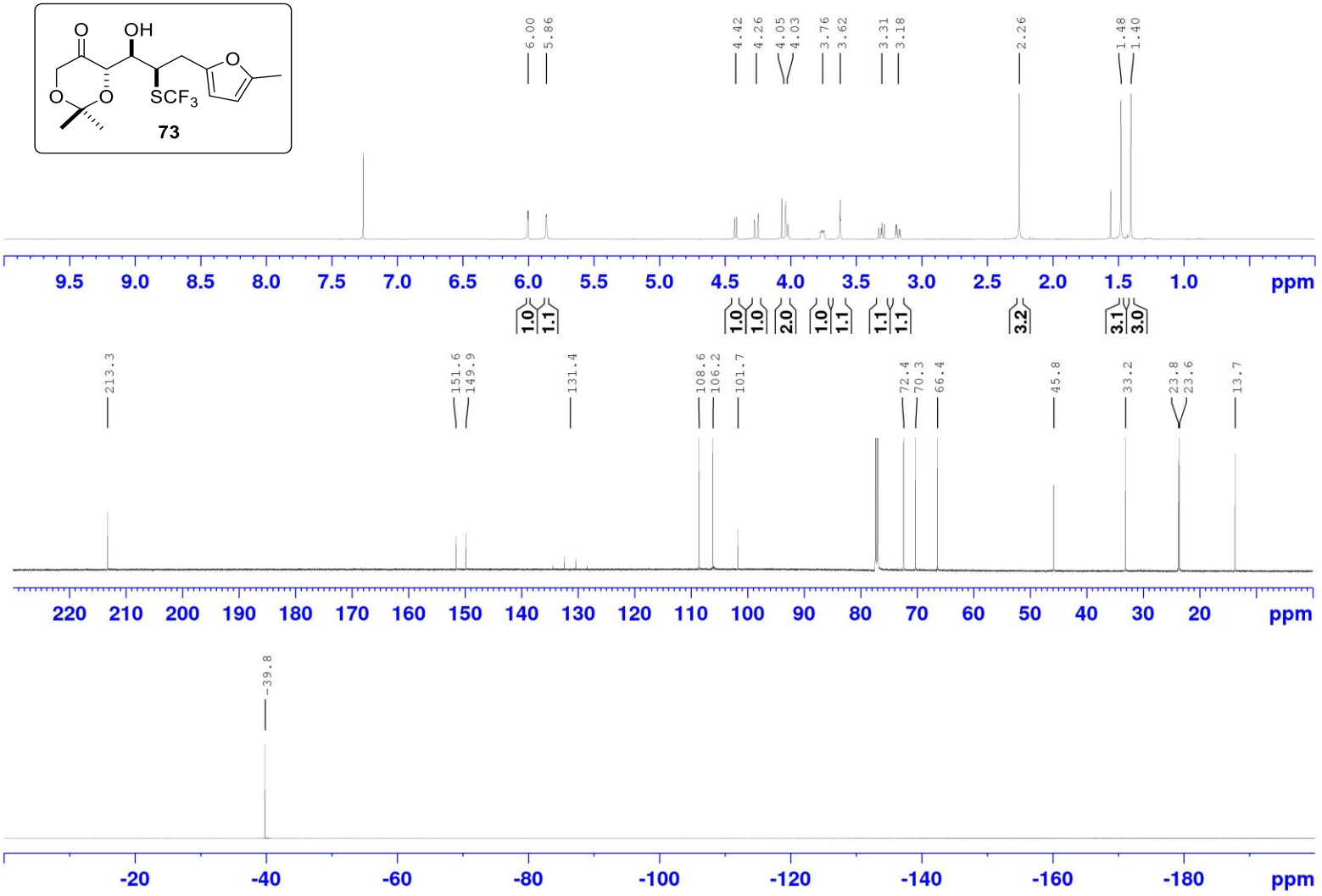
Supplementary Figure 59. NMR spectra of **70**.



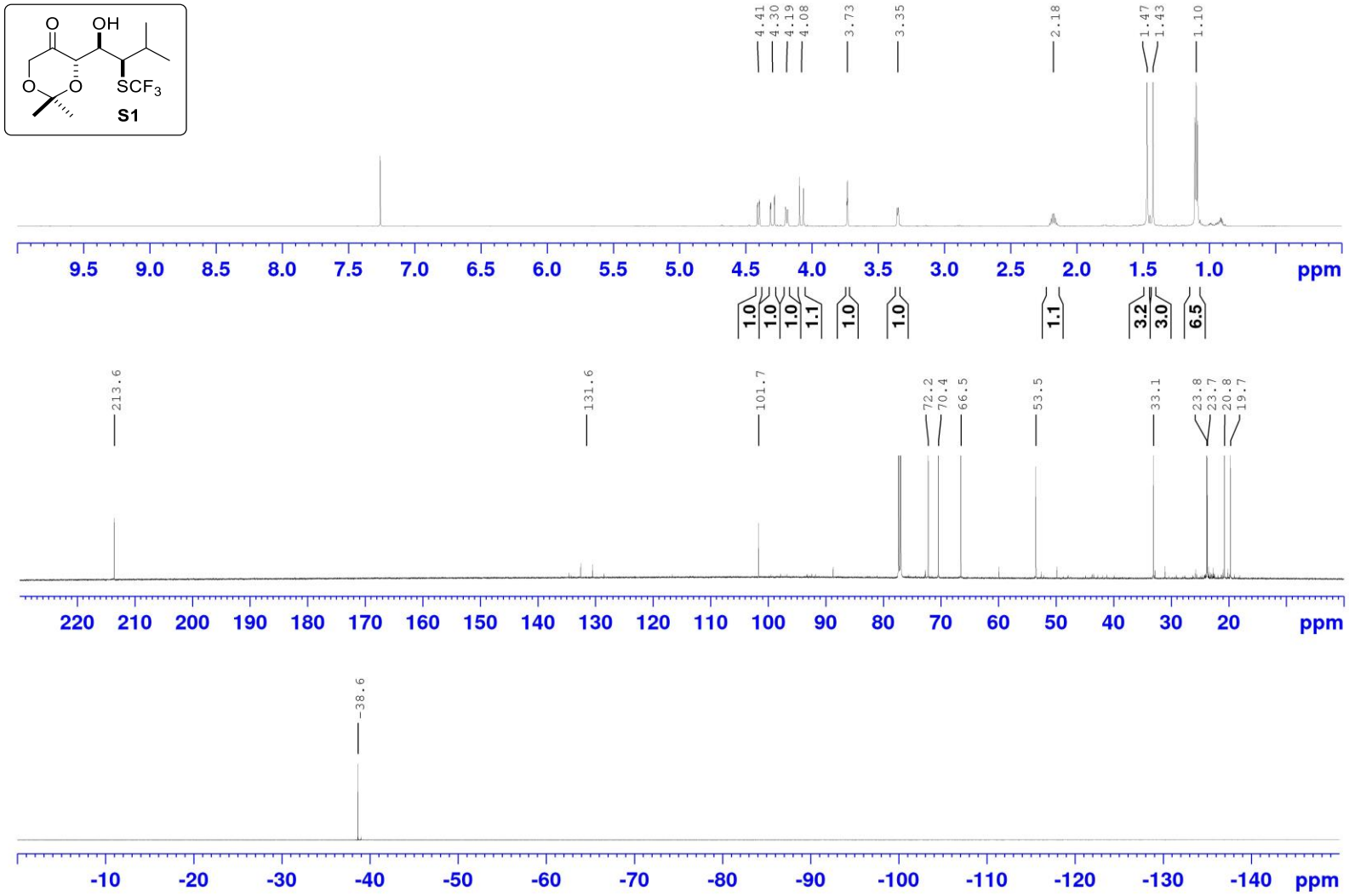
Supplementary Figure 60. NMR spectra of **71**.



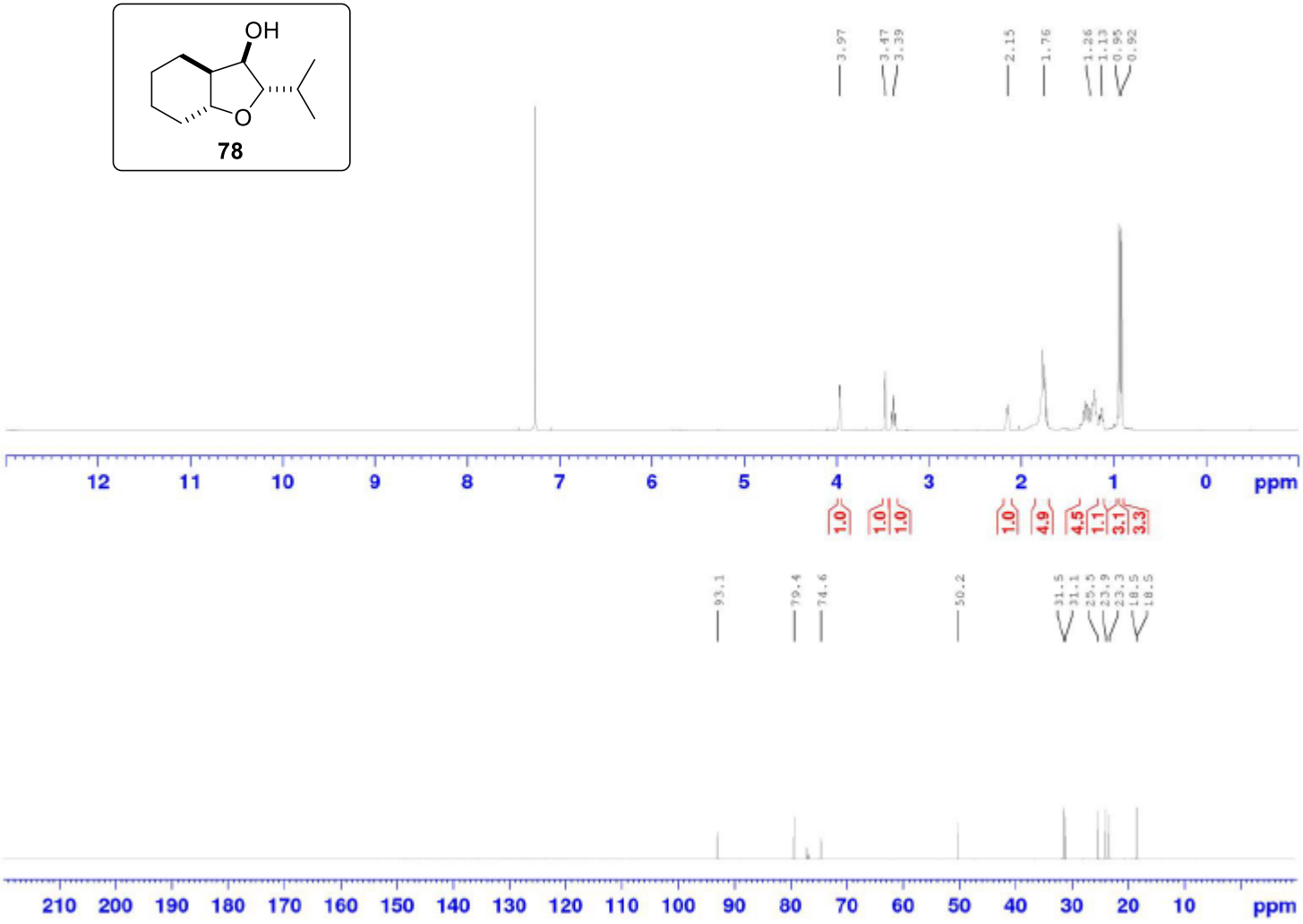
Supplementary Figure 61. NMR spectra of **72**.



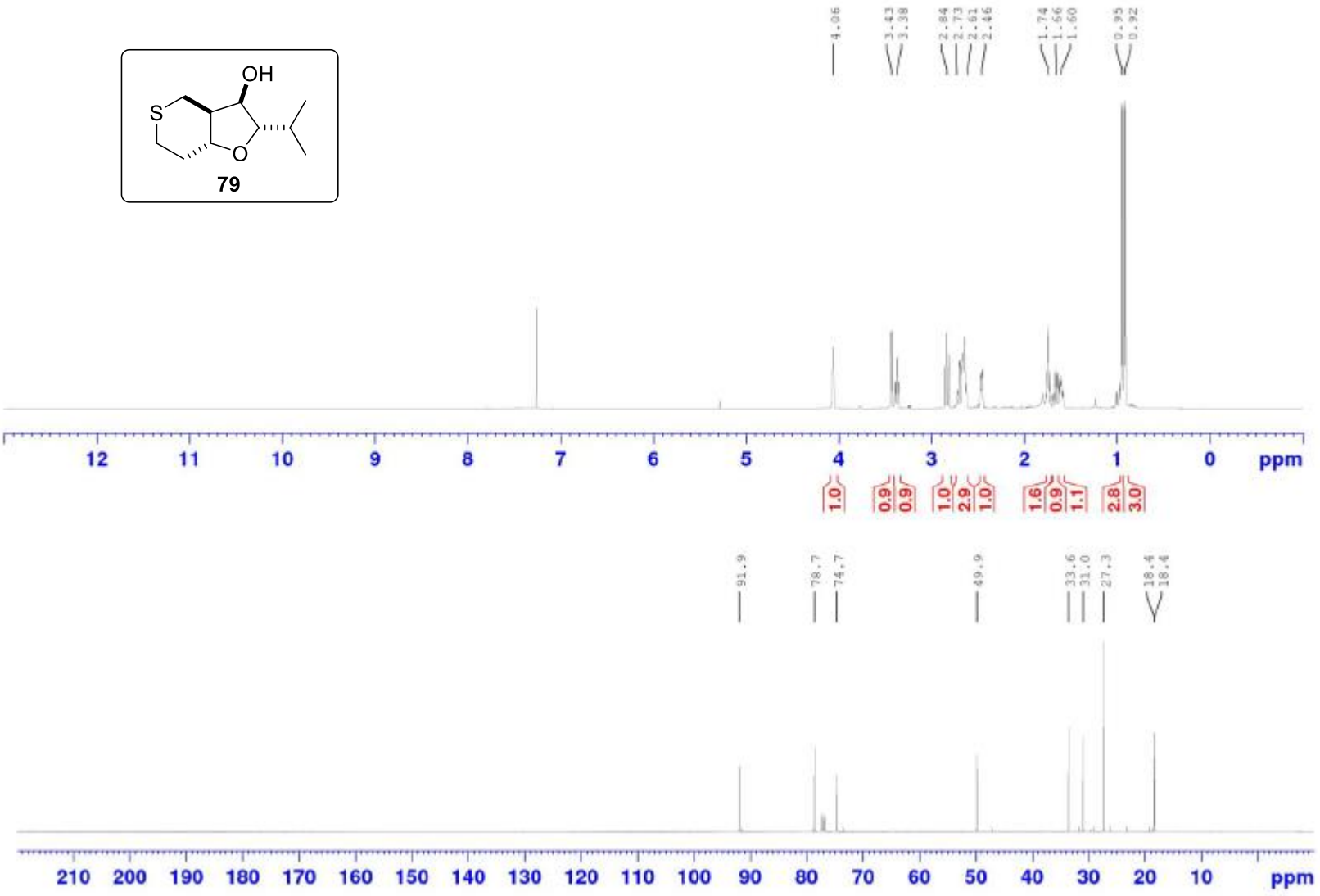
Supplementary Figure 62. NMR spectra of **73**.



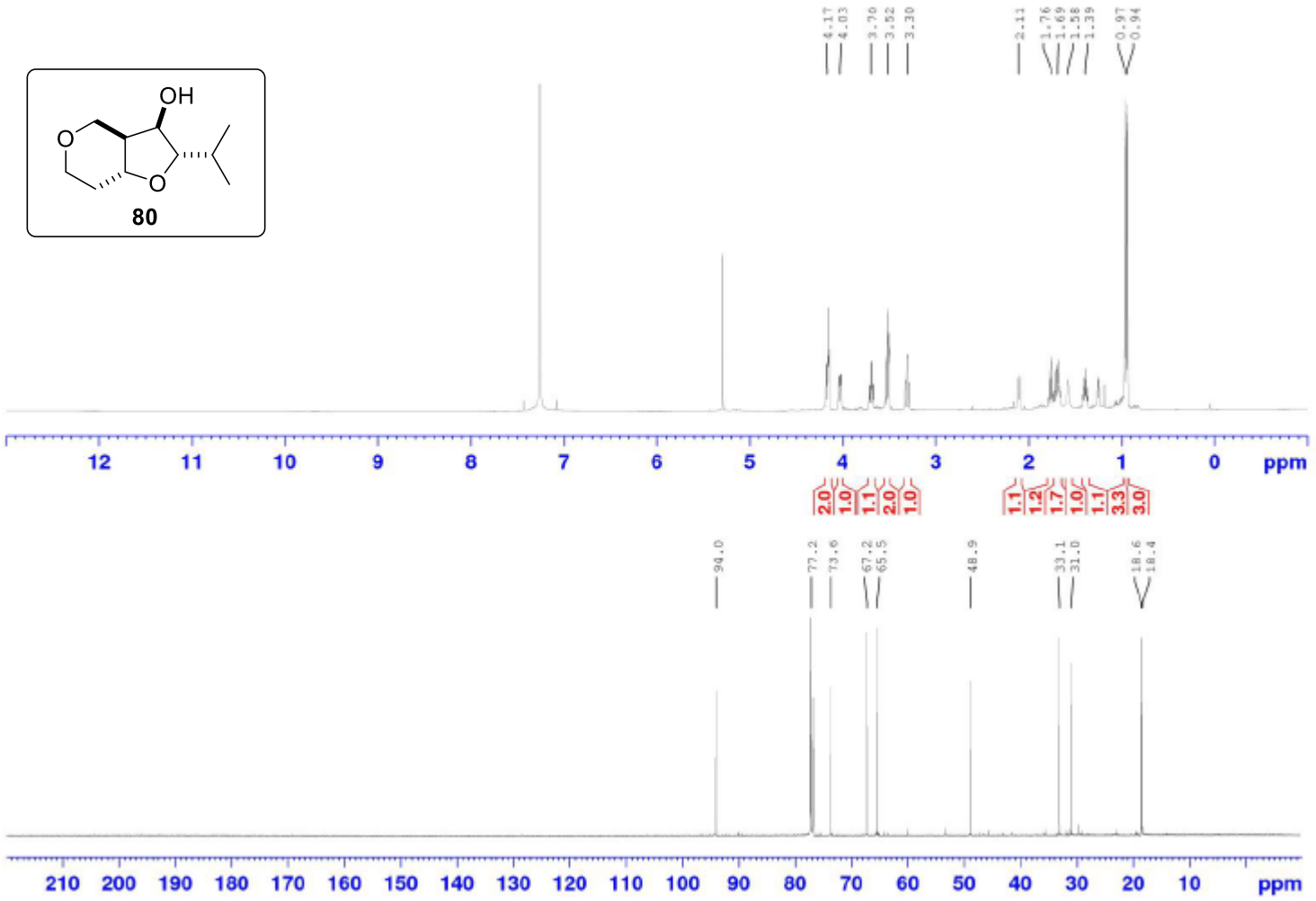
Supplementary Figure 63. NMR spectra of **S1**.



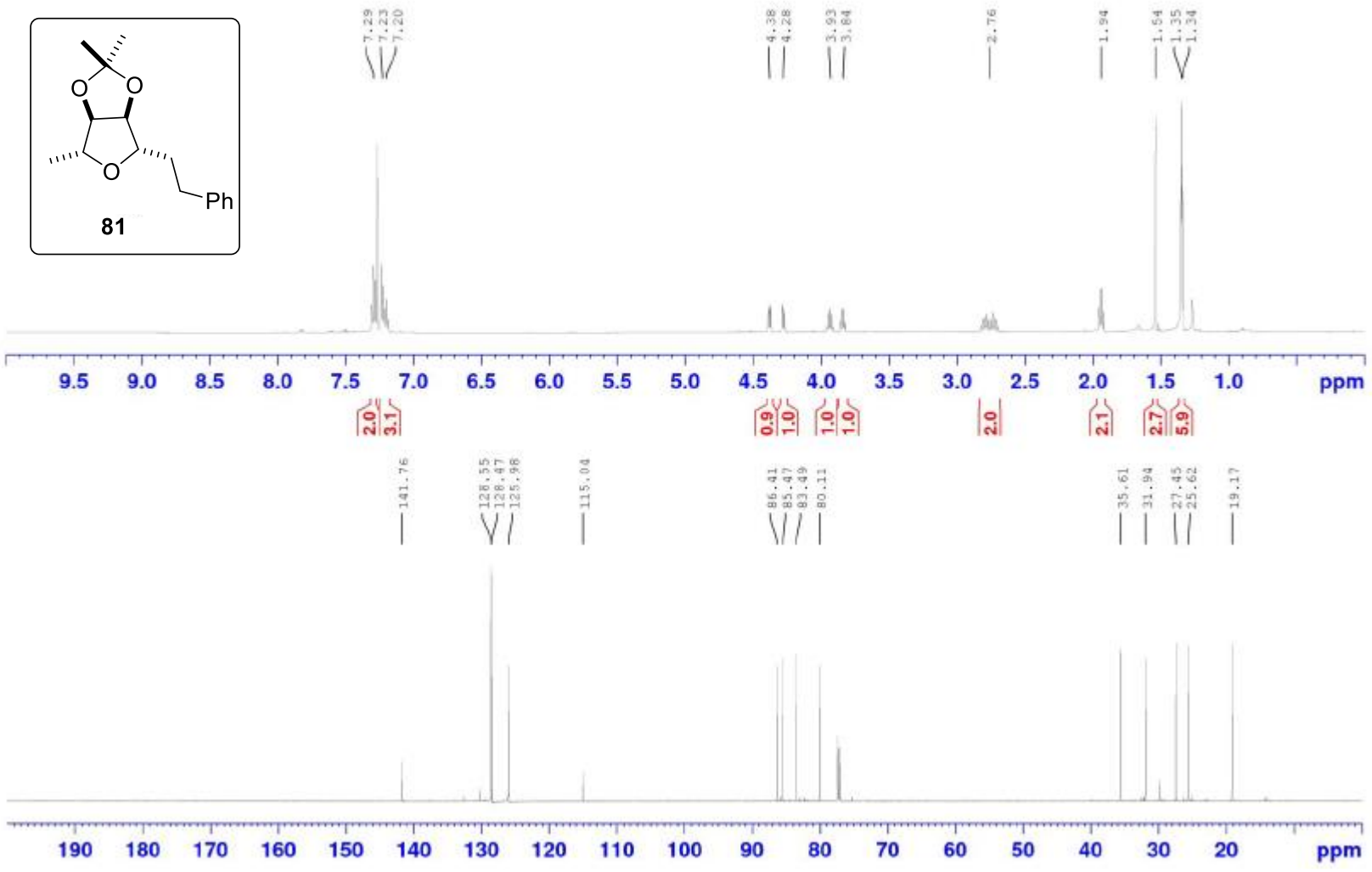
Supplementary Figure 64. NMR spectra of **78**.



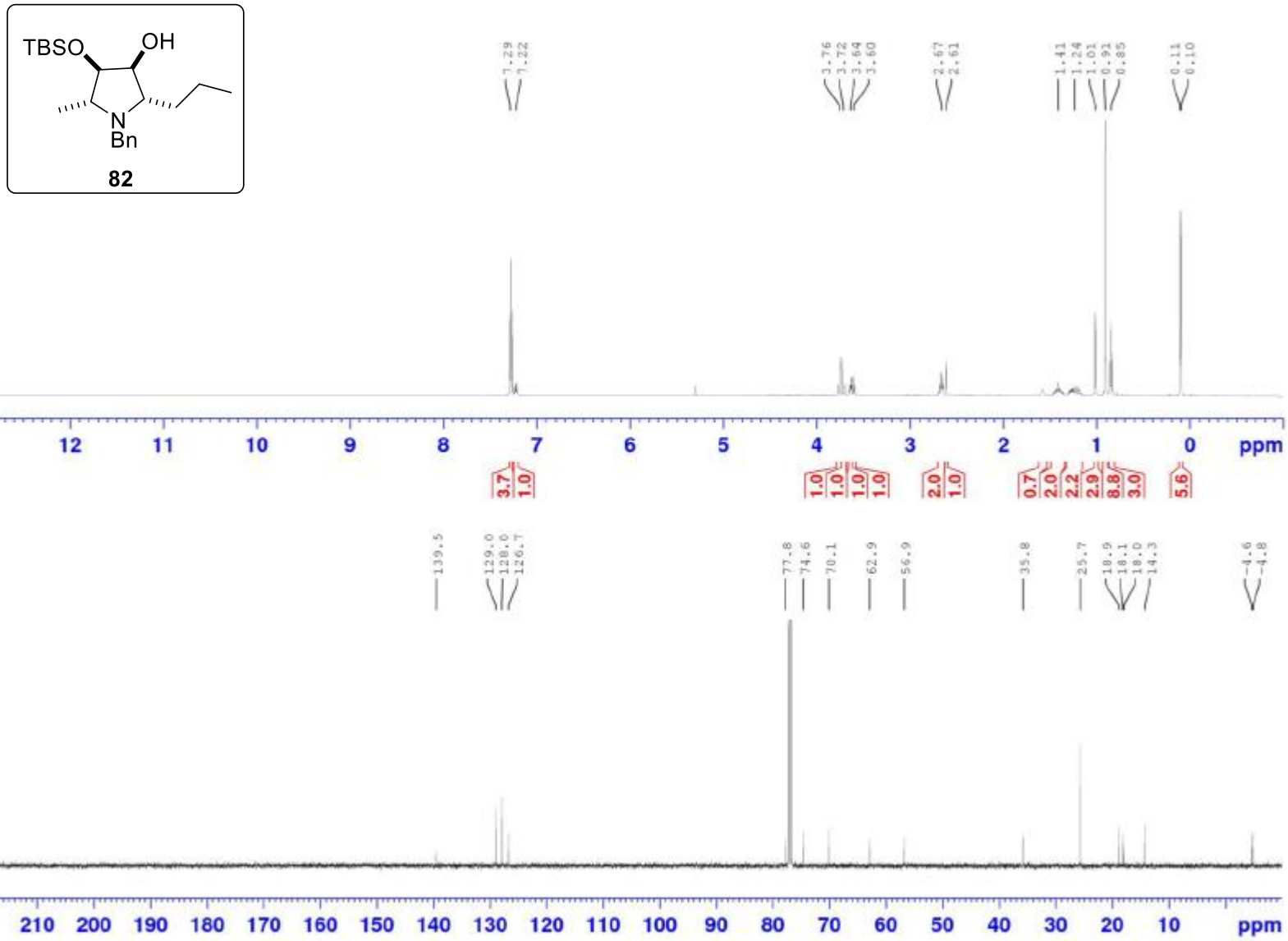
Supplementary Figure 65. NMR spectra of **79**.



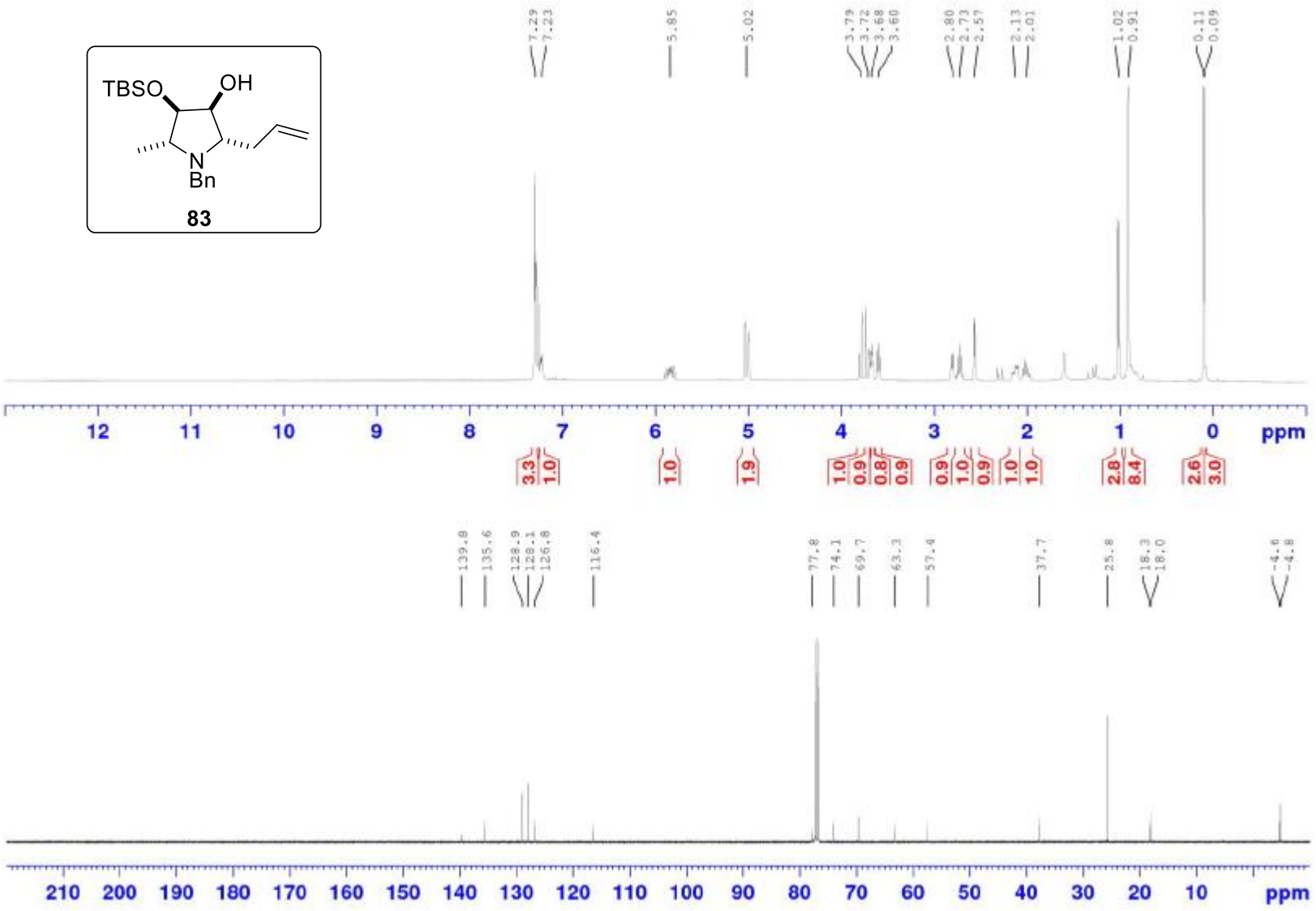
Supplementary Figure 66. NMR spectra of **80**.



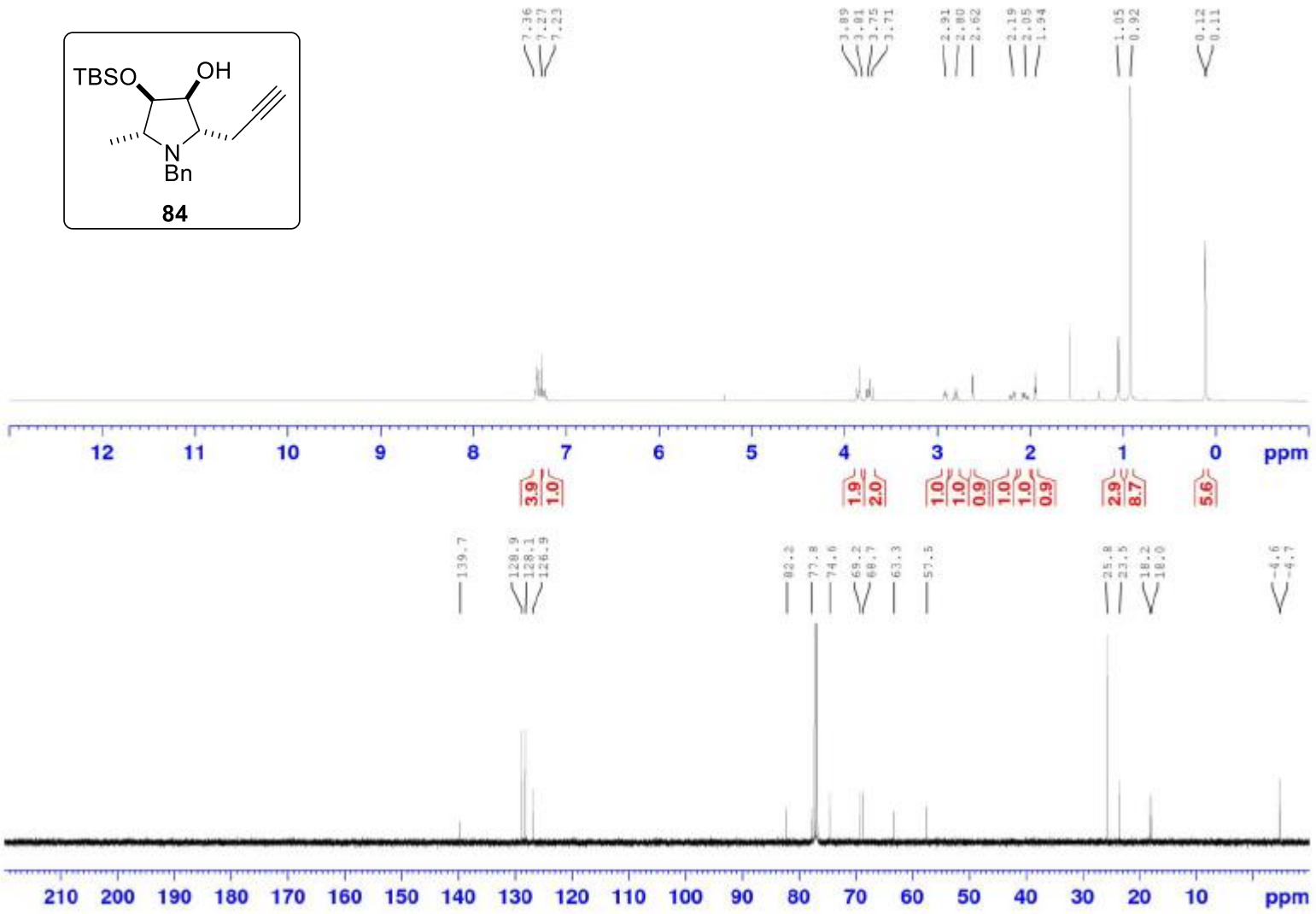
Supplementary Figure 67. NMR spectra of **81**.



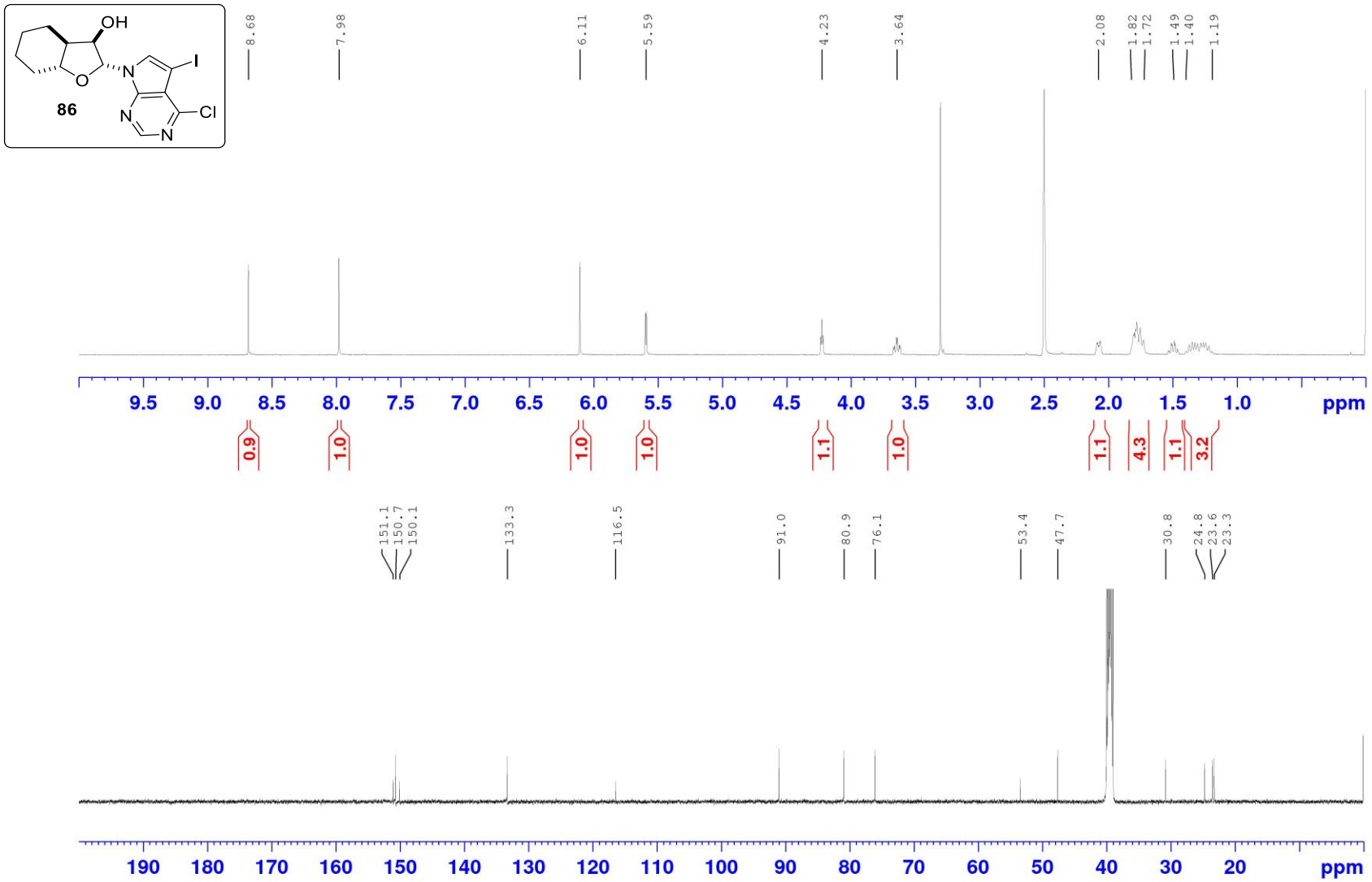
Supplementary Figure 68. NMR spectra of **82**.



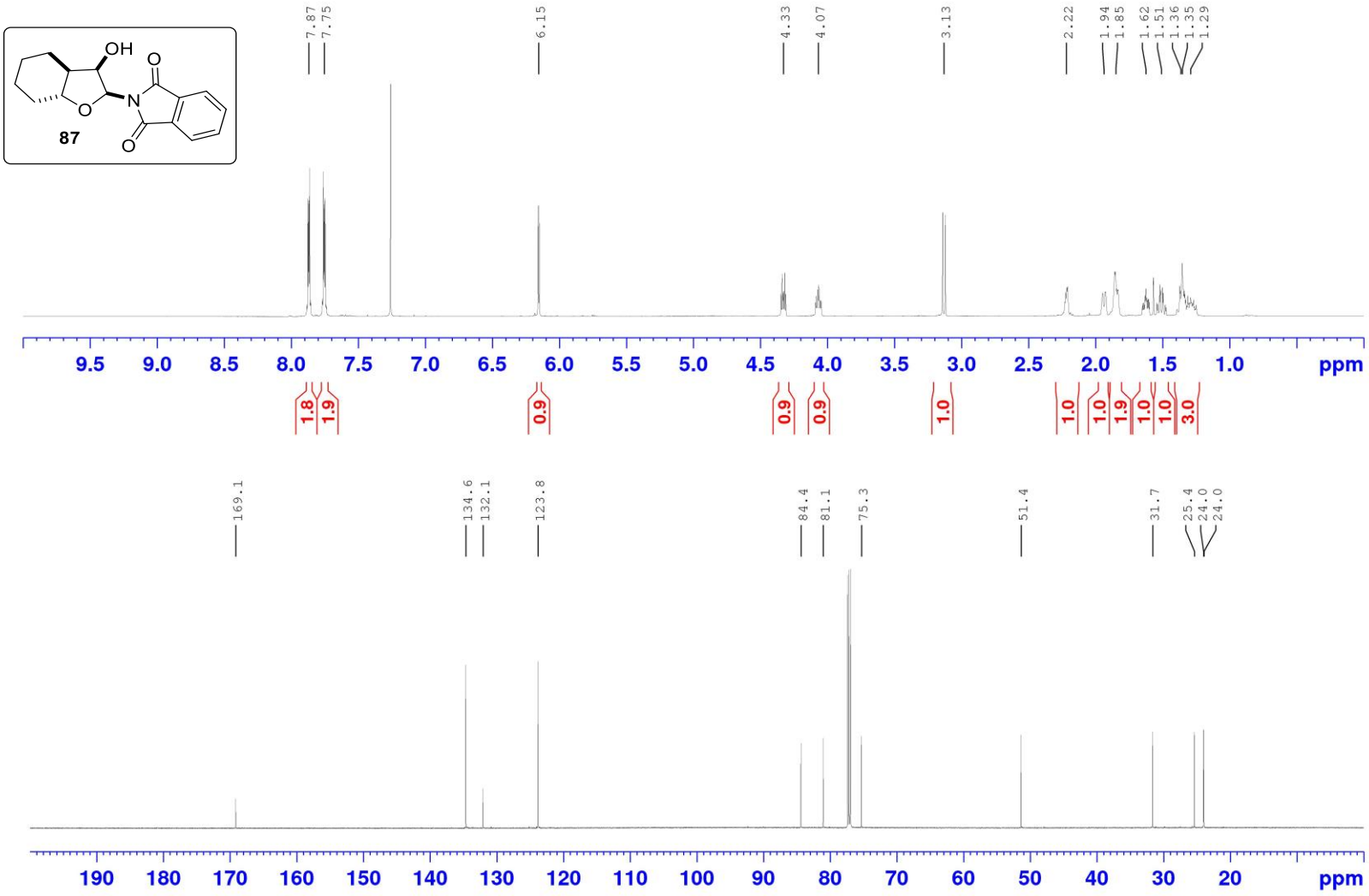
Supplementary Figure 69. NMR spectra of **83**.



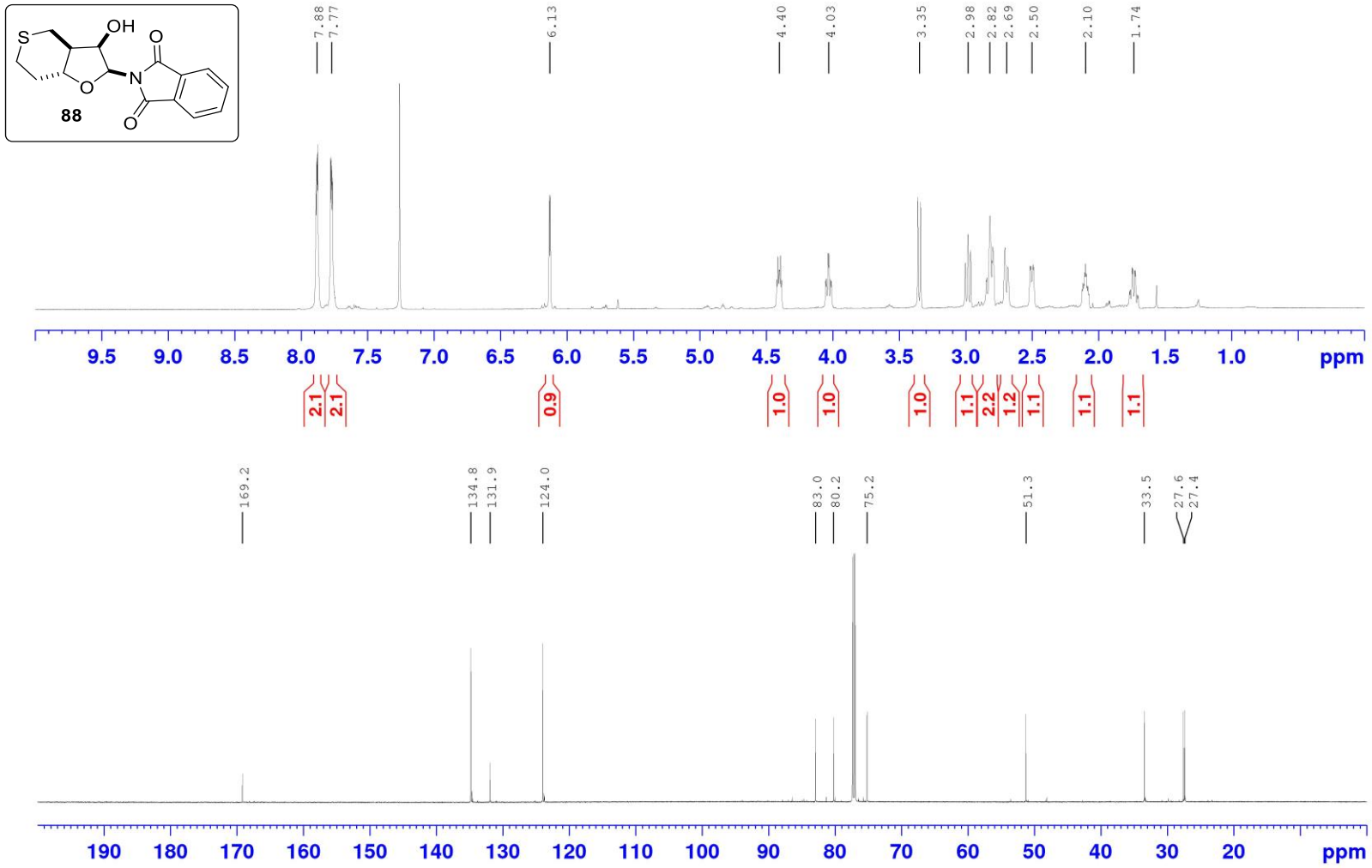
Supplementary Figure 70. NMR spectra of **84**.



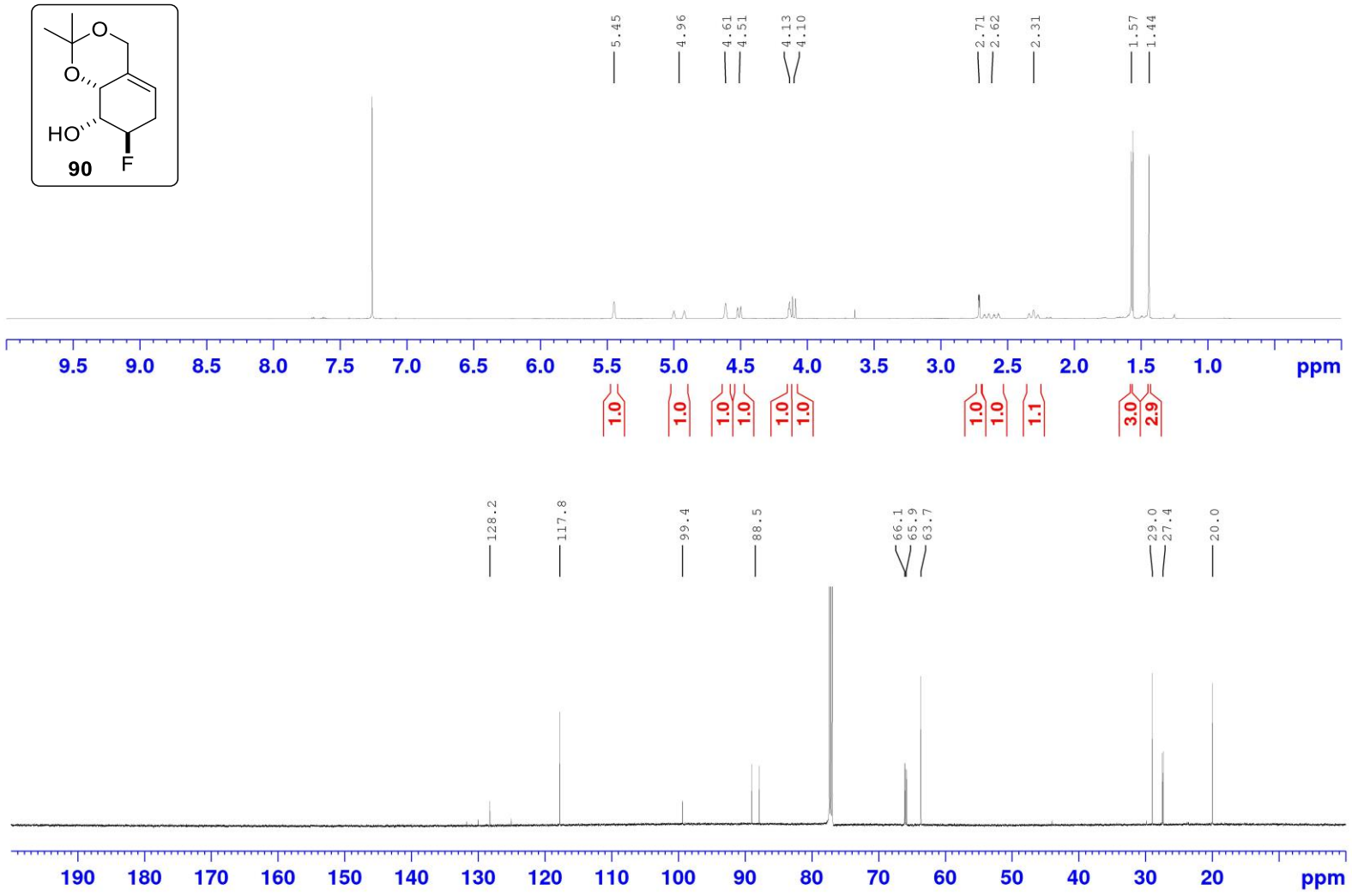
Supplementary Figure 71. NMR spectra of **86**.



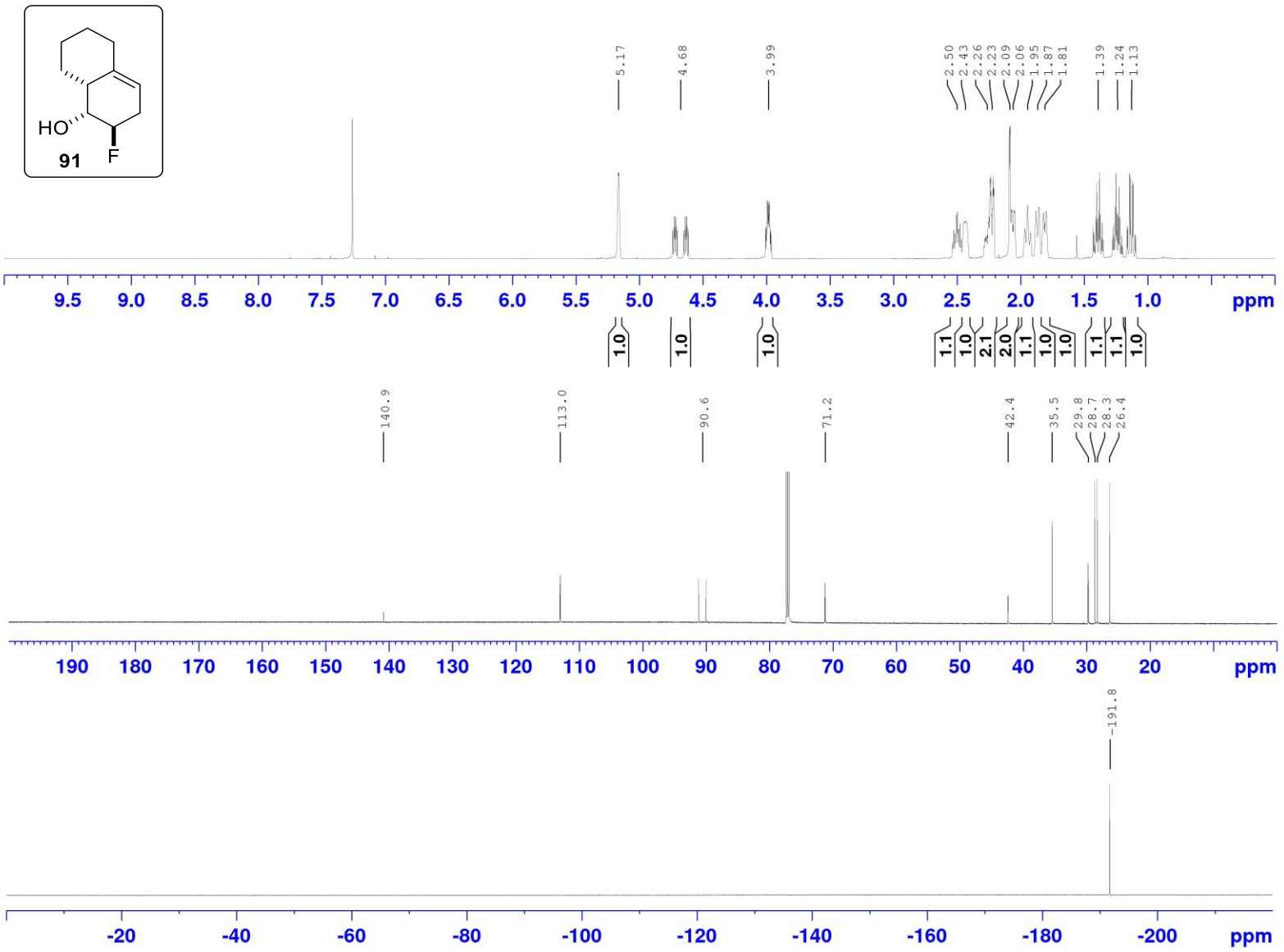
Supplementary Figure 72. NMR spectra of **87**.



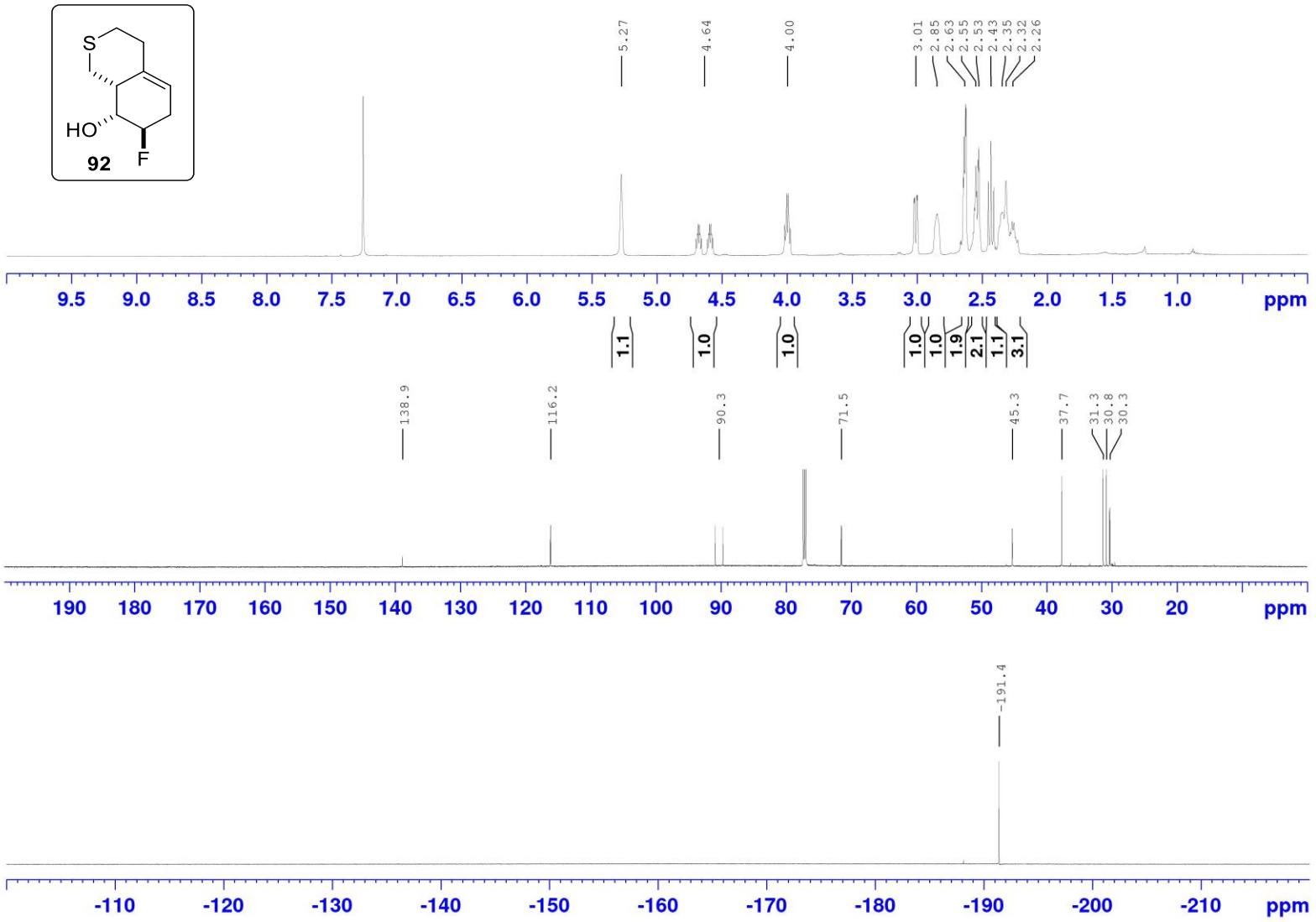
Supplementary Figure 73. NMR spectra of **88**.



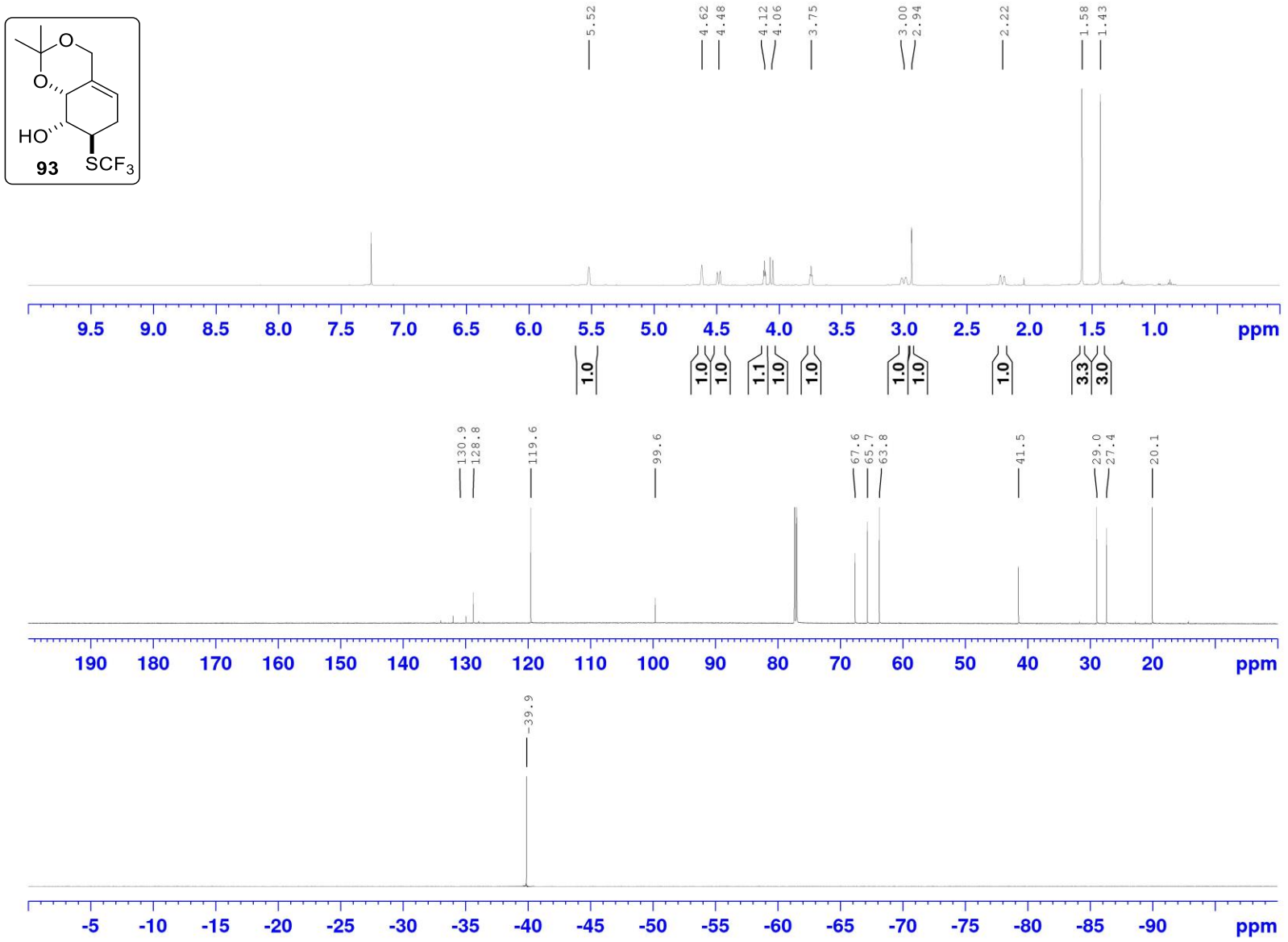
Supplementary Figure 74. NMR spectra of **90**.



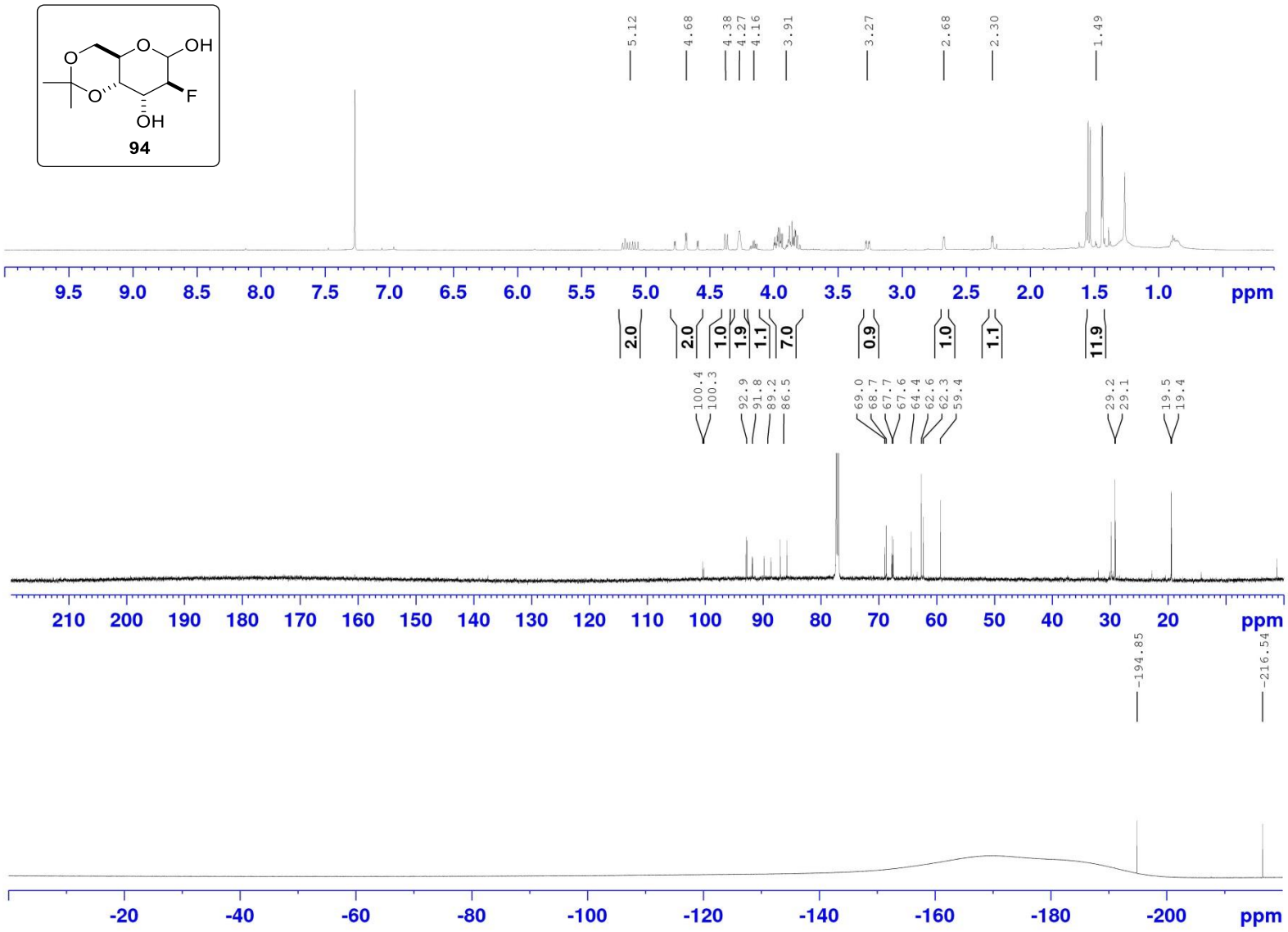
Supplementary Figure 75. NMR spectra of **91**.



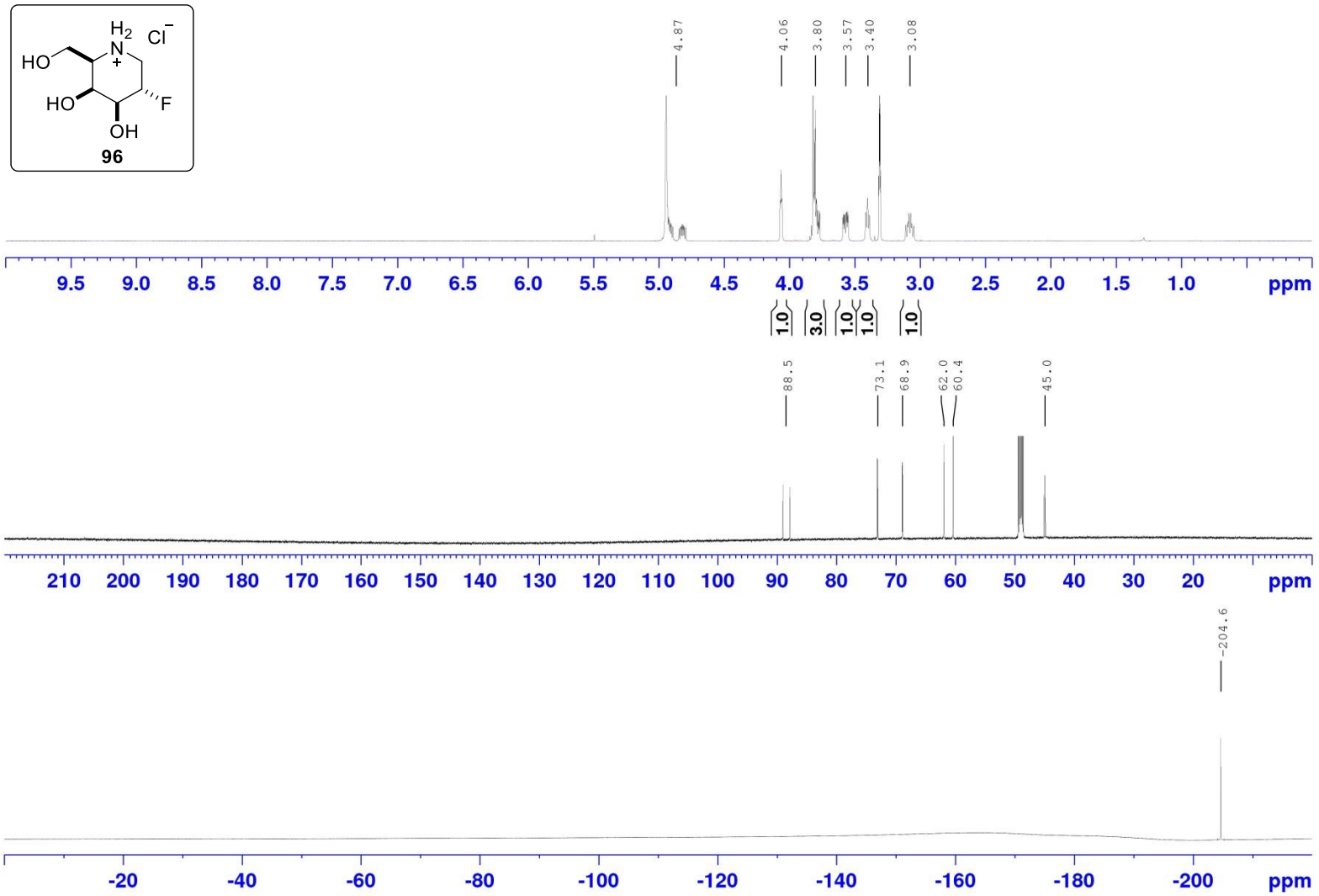
Supplementary Figure 76. NMR spectra of **92**.



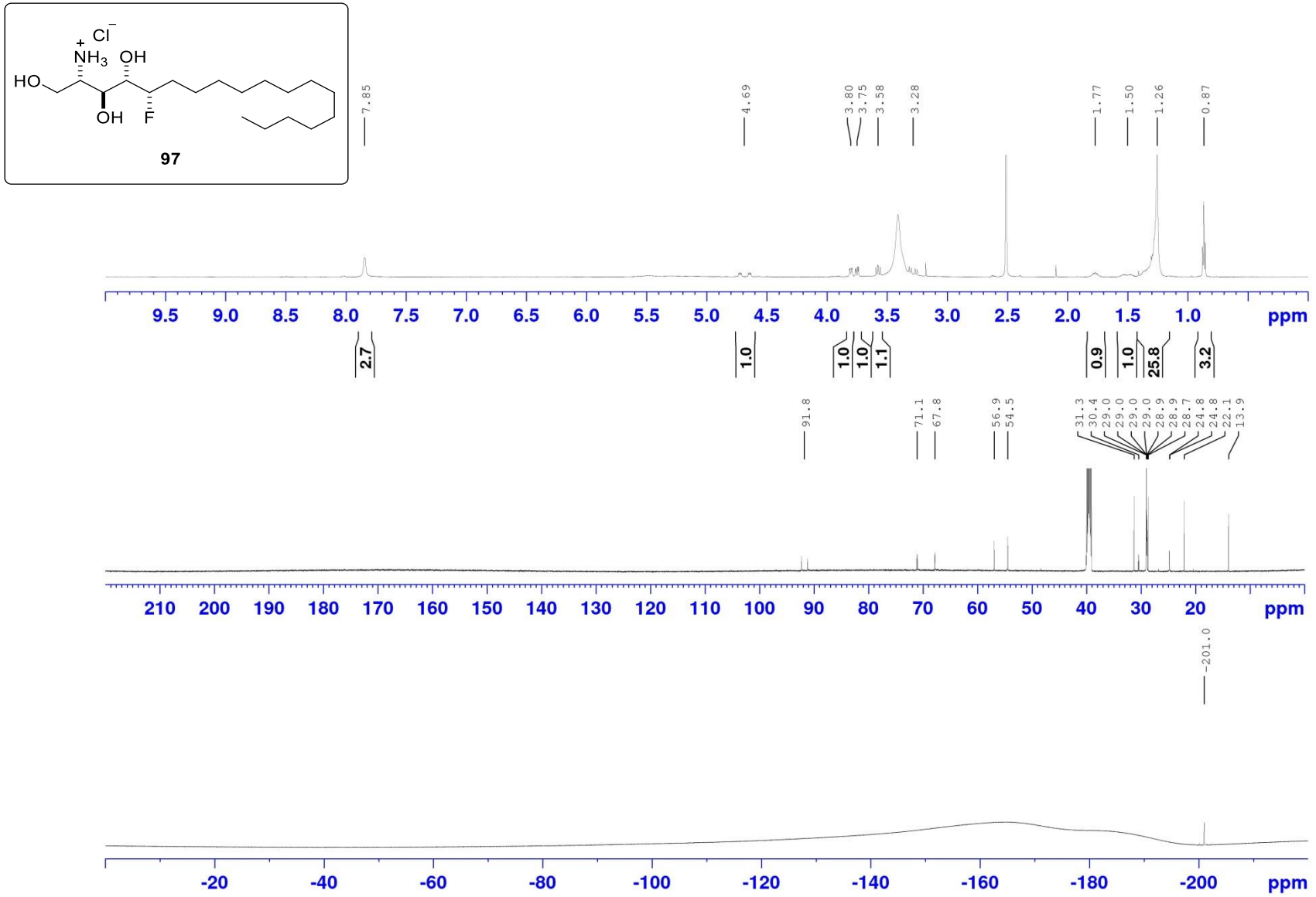
Supplementary Figure 77. NMR spectra of **93**.



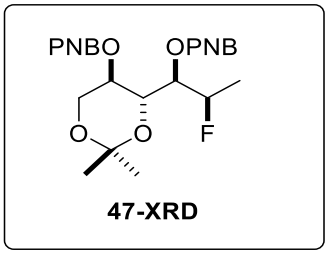
Supplementary Figure 78. NMR spectra of **94**.

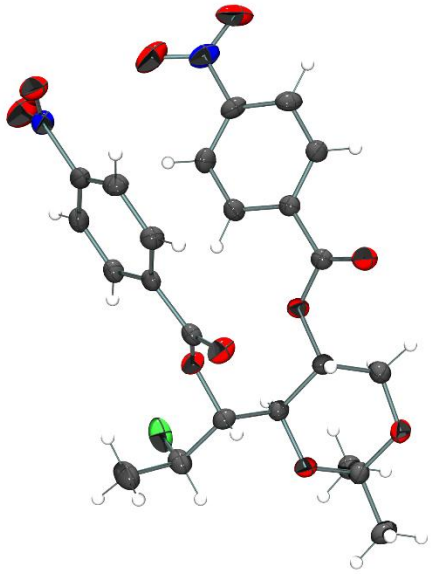


Supplementary Figure 79. NMR spectra of **95**.

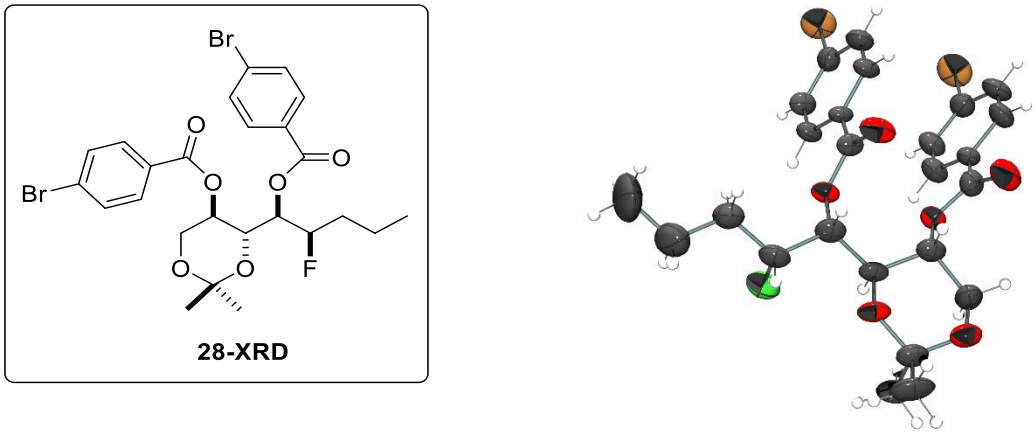


Supplementary Figure 80. NMR spectra of **97**.

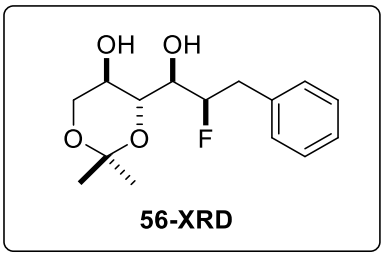


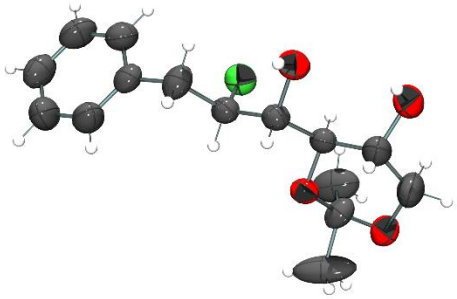


Supplementary Figure 81. XRD structure of compound **47-XRD (CCDC number: 1556393; CIF label: 6-MWM-010)**

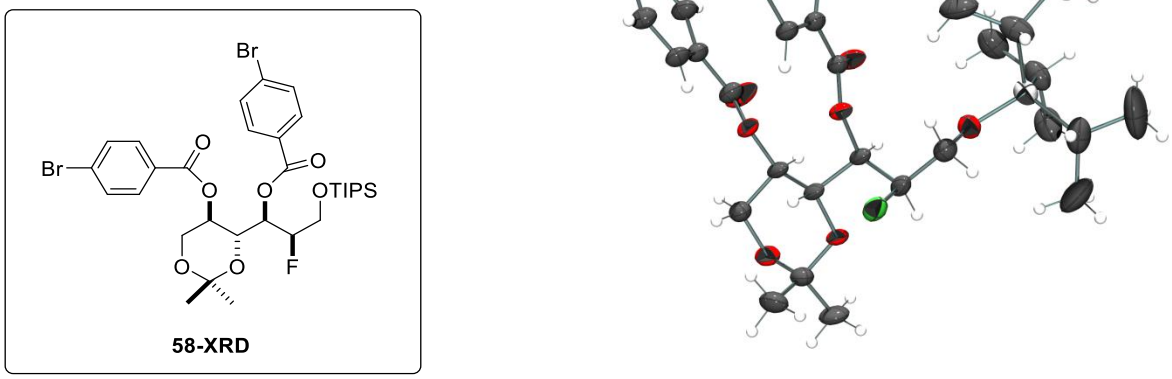


Supplementary Figure 82. XRD structure of compound **28-XRD (CCDC number: 1556394; CIF label: 6-MWM-110)**

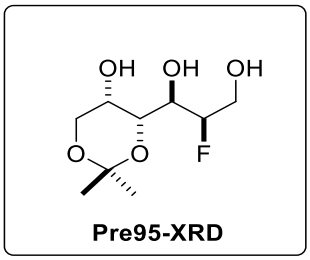


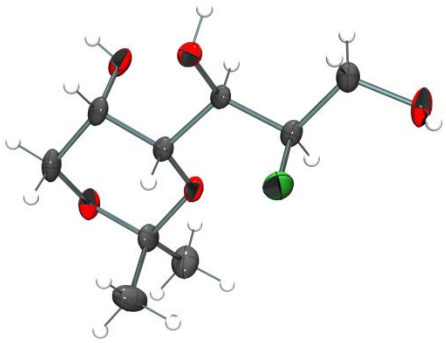


Supplementary Figure 83. XRD structure of compound **56-XRD (CCDC number: 1556395; CIF label: 5-MWM-110)**



Supplementary Figure 84. XRD structure of compound **58-XRD (CCDC number: 1556396; CIF label: 5-MWM-135)**



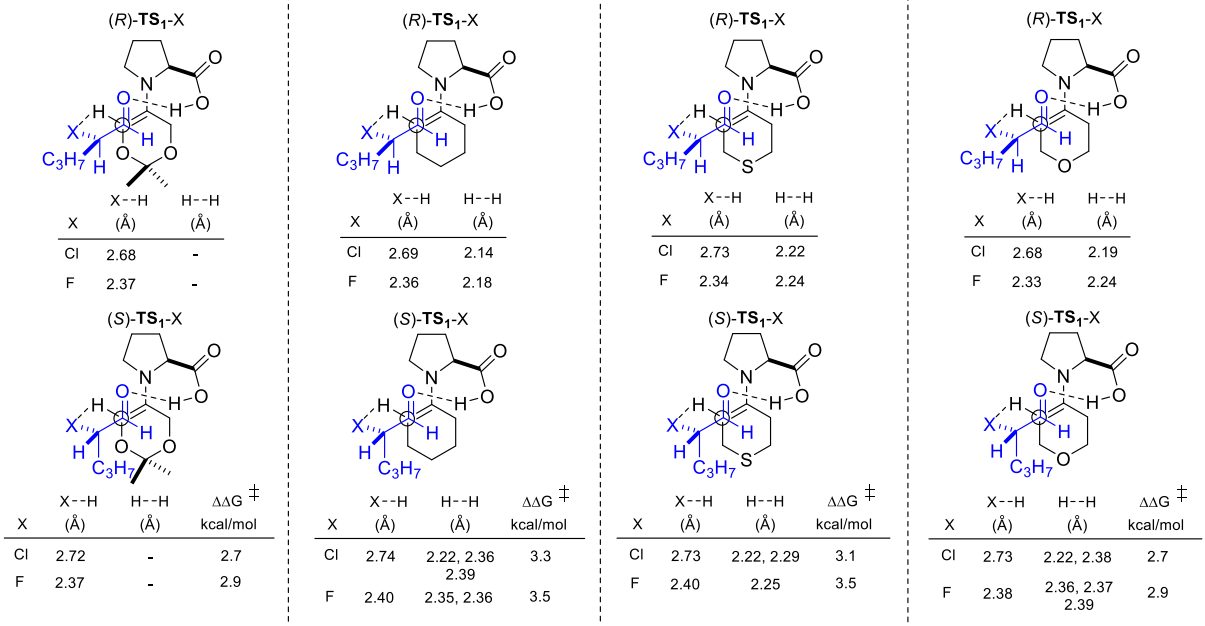


Supplementary Figure 85. XRD structure of compound **Pre95-XRD (CCDC number: 1556397; CIF label: MWM-565)**

Compound Reference	**47-XRD**	**28-XRD**	**56-XRD**	**58-XRD**	**Pre95-XRD**
Chemical Formula	$C_{23}H_{23}N_2O_{10}F$	$C_{25}H_{27}O_6Br_2F$	$C_{15}H_{21}O_4F$	$C_{32}H_{43}Br_2FO_7Si$	$C_9H_{17}FO_5$
FW	506.43	602.28	284.32	746.57	224.22
Crystal System	Orthorhombic	Orthorhombic	Orthorhombic	Monoclinic	Triclinic
Space group	$P2_12_12_1$	$P2_12_12_1$	$P2_12_12_1$	$P2_1$	P1
a/Å	7.8910(2)	5.5445(4)	5.60440(10)	12.6483(4)	9.3287(6)
b/Å	11.8417(3)	18.6627(13)	13.0932(3)	11.3201(4)	9.3568(5)
c/Å	24.9605(6)	24.3453(19)	20.2022(4)	13.4868(4)	25.3029(15)
α/°	90	90	90	90	91.911(2)
β/°	90	90	90	115.6810(10)	97.536(2)
γ/°	90	90	90	90	90.195(3)
Unit cell volume/Å^3	2332.38(10)	2519.1(3)	1482.43(5)	1740.29(10)	2188.2(2)
Z	4	4	4	2	8
Temperature/K	150(2)	150(2)	296(2)	150(2)	150(2)
Radiation type	Cu Kα	Cu Kα	Cu Kα	Cu Kα	Cu Kα
Absorption coefficient, μ/mm^{-1}	1.023	4.476	0.83	3.689	1.038
All Reflections	16537	16215	9652	25308	60788
Unique Reflections	4273	4631	2610	6336	14635
Flack parameter	0.03(4)	0.002(8)	0.07(5)	0.001(5)	0.04(3)
R_{int}	0.0337	0.0389	0.0205	0.0305	0.0532

Final R_1 values ($I>2\sigma(I)$)	0.0281	0.0251	0.0368	0.0351	0.0436
Final $wR(F^2)$ values ($I>2\sigma(I)$)	0.0735	0.0642	0.1023	0.0916	0.1146
Final R_1 values (all data)	0.0286	0.0258	0.0388	0.0361	0.0437
Final $wR(F^2)$ (all data)	0.074	0.0648	0.1048	0.0927	0.1147
Goodness of fit	1.049	1.034	1.085	1.031	1.044

Supplementary Table 3. Summary of parameters from XRD analysis



Supplementary Figure 86. Intermolecular interactions of (*R*) or (*S*)-2-fluoro- and chloropentanal with **13**, cyclohexanone, **35**, and tetrahydropyranone observed in (*R*)- and (*S*)-TS_1 transition state structures. DFT calculations were performed using $IEFPCM_{(DCM)}$M06-2X/6-311++G(2d,2p)//$IEFPCM_{(DCM)}$M06-2X/6-31+G(d,p) level of theory

Supplementary References

1. Bergeron-Brlek, M.; Teoh, T.; Britton, R. *Org. Lett.* **2013**, *15* (14), 3554

2. J.N. Barlow, J.S.Blanchard, *Carbohydrate Research*, **2000**, *328*, 473