Supporting information

for

The Development of a Complementary Pathway for the Synthesis of Aliskiren

Le-Le Li,[a,b] Jin-Ying Ding,[a] Lian-Xun Gao,[a] and Fu-She Han*[a,c]

[a] Changchun Institute of Applied Chemistry Chinese Academy of Sciences, 5625 Renmin Street, Changchun, Jilin 130022, China

[b] The University of Chinese Academy of Sciences, Beijing, 100864, China

[c] F.-S. Han, Key Lab of Synthetic Chemistry of Natural Substances, Shanghai Institute of Organic Chemistry, CAS, China

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General methods: Unless otherwise noted, all solvents were purified according to the standard procedures. Allyl bromide, $(COCl)_2$, and $(EtO)_2POH$ were distilled prior to use. Other reagents were reagent grade and were used without purification. The ^{1}H-NMR spectra were recorded at 600, 400, or 300 MHz (Bruker AV) in $CDCl_3$ or DMSO-d_6. The ^{13}C-NMR spectra were recorded at 150 or 100 MHz in $CDCl_3$ or DMSO-d_6. The ^{31}P-NMR spectra were recorded at 162 MHz in $CDCl_3$. Chemical shifts were given in ppm relative to TMS or the appropriate solvent peak. Coupling constants (*J* values) were reported in Hertz (Hz). High resolution mass spectra (HRMS) were measured using an IonSpec Ultima 7.0 TFT-ICR-MS instrument (IonSpec, USA) with a Waters Z-spray source. HPLC analysis was performed on Shimadzu (LC 20AD, UV detection monitored at 254 nm) or Shimadzu (LC 6AD, UV detection monitored at 254 nm). C18 column for *E*/*Z* selectivity measurements (Hypersil ODS 5 μm, 4.6 mm × 250 mm) was purchased from Dalian Elite Analytical Instruments Co., Ltd. Chiralpak AD-H column for enantiomeric excess measurements was purchased from Daicel Chemical Industries, LTD. Optical rotation value was measured by a Perkin Elmer 341LC polarimeter operating on the sodium D-line (589 nm), using a 100 mm path-length cell and are reported as: $[\alpha]_D^T$ (concentration in g/100 mL, solvent). Column chromatography was performed on silica gel 100-200 mesh or 200-300 mesh.

Synthesis of 10a:[3g] To a round-bottom flask was added **9** (2.61 g, 10 mmol, 1.0 equiv) and dried THF (30 mL) under N_2 atmosphere. After being cooled to -78 ^{o}C, LiHMDS solution (1 M in THF, 12 mL, 1.2 equiv) was added dropwise. The cooling bath was then replaced with an ice-water bath and the reaction mixture was allowed to stir at 0 ^{o}C for 3 h. The solution was re-cooled to -78 ^{o}C and allyl bromide (1.3 mL, 15 mmol, 1.5 equiv) was added dropwise. The reaction mixture was stirred overnight at room temperature. The reaction mixture was then quenched with saturated aq. NH_4Cl (30 mL). The resulting solution was evaporated under reduced pressure to remove the volatile materials. The concentrated solution was extracted with CH_2Cl_2 (4 × 40 mL) and the combined organic layer was washed with brine (30 mL), dried over $MgSO_4$, filtered and evaporated under reduced pressure. Purification of the residue by column chromatography (1:10 ethyl acetate-hexane) gave **10a** (2.89 g, 9.6 mmol, 96%) as a light yellow oil. ^{1}H-NMR (600 MHz, $CDCl_3$) δ 7.33 (t, *J* = 7.4 Hz, 2H), 7.27 (d, *J* = 7.3 Hz, 1H), 7.23 (d, *J* = 7.2 Hz, 2H), 5.86–5.79 (m, 1H), 5.09 (d, *J* = 17.1, Hz, 1H), 5.02 (d, *J* = 10.2 Hz, 1H), 4.71–4.67 (m, 1H), 4.15–4.11 (m, 2H), 3.88–3.85 (m, 1H), 3.31 (dd, *J* = 13.4, 3.2 Hz, 1H), 2.64 (dd, *J* = 13.4, 10.1 Hz, 1H), 2.51–2.45 (m, 1H), 2.41–2.37 (m, 1H), 2.02–1.97 (m, 1H), 0.98 (d, *J* = 6.84 Hz, 6H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 175.73, 153.28, 135.66, 135.60, 129.47, 128.94, 127.29, 116.92, 65.77, 55.65, 48.19, 38.06, 33.68, 30.29, 20.91, 19.24.

Synthesis of 10b: To a round-bottom flask was added **9** (13.09 g, 50 mmol, 1.0 equiv) and dried THF (150 mL) under N_2 atmosphere. After being cooled to -78 ^{o}C, LiHMDS solution (1 M in THF, 63 mL) was added dropwise. The solution was stirred for 1 h at -78 ^{o}C and 3 h at 0 ^{o}C. The resulting mixture was then re-cooled to -78 ^{o}C and (*E*)-1,4-dibromobut-2-ene (32.10 g, 150 mmol, 3 equiv) was added. The reaction

mixture was allowed to warm to room temperature and stirred overnight. The reaction mixture was then quenched with saturated aq. NH_4Cl (100 mL). The solution was evaporated under reduced pressure to remove the volatile materials. The concentrated solution was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layer was washed with brine (50 mL), dried over $MgSO_4$, filtered and evaporated under reduced pressure. Purification of the residue by column chromatography (1:10 ethyl acetate-hexane) gave **10b'** (17.82 g, 45.2 mmol, 90%) as a slightly yellow oil. ^{1}H-NMR (600 MHz, $CDCl_3$) δ 7.33 (t, *J* = 7.4 Hz, 2H), 7.28–7.26 (m, 1H), 7.22 (d, *J* = 7.3 Hz, 2H), 5.78 (t, *J* = 5.8 Hz, 2H), 4.70–4.66 (m, 1H), 4.16–4.13 (m, 2H), 3.91 (d, *J* = 4.2 Hz, 2H), 3.87–3.83 (m, 1H), 3.35 (dd, *J* = 13.4, 3.1 Hz, 1H), 2.68 (dd, *J* = 13.3, 10.2 Hz, 1H), 2.53–2.48 (m, 1H), 2.40–2.36 (m, 1H), 2.02–1.96 (m, 1H), 0.97 (d, *J* = 6.6 Hz, 6H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 175.35, 153.29, 135.59, 133.07, 129.44, 128.98, 128.64, 127.33, 65.92, 55.68, 48.21, 38.23, 32.83, 31.68, 30.31, 20.88, 19.15. HRMS (ESI-MS) Found 416.0827 $[M+Na]^+$, $C_{19}H_{24}BrNNaO_3$ requires 416.0837; found 432.0562 $[M+K]^+$, $C_{19}H_{24}BrNKO_3$ requires 432.0562.

To a solution of **10b'** (12.82 g, 32.5 mmol, 1 equiv) in THF (170 mL) was added $NaBH_3CN$ (5.96 g, 95 mmol, 3 equiv). The reaction mixture was heated at 60 ^{o}C for 24 h. The mixture was evaporated under reduced pressure and purified by column chromatography (ethyl acetate:dichloromethane:hexane = 1:1:5) to give **10b** (9.67 g, 30.7 mmol, 94%) as a colorless oil. ^{1}H-NMR (600 MHz, $CDCl_3$) δ 7.33 (t, *J* = 7.4 Hz, 2H), 7.28 (d, *J* = 7.2 Hz, 1H), 7.23 (d, *J* = 7.3 Hz, 2H), 5.53–5.47 (m, 1H), 5.46–5.41 (m, 1H), 4.72–4.68 (m, 1H), 4.15–4.11 (m, 2H), 3.84–3.80 (m, 1H), 3.28 (dd, *J* = 13.4, 3.0 Hz, 1H), 2.63 (dd, *J* = 13.3, 10.0 Hz, 1H), 2.42–2.37 (m, 1H), 2.34–2.29 (m, 1H), 2.01–1.93 (m, 1H), 1.63 (d, *J* = 6.0 Hz, 3H), 0.96 (dd, *J* = 6.6, 3.7 Hz, 6H). ^{13}C-NMR (150 MHz, $CDCl_3$) δ 176.07, 153.31, 135.67, 129.49, 129.01, 128.11, 127.53, 127.36, 65.72, 55.55, 48.79, 38.07, 32.81, 30.36, 20.98, 19.37, 18.04. HRMS (ESI-MS) Found 316.1904 $[M+H]^+$, $C_{19}H_{26}NO_3$ requires 316.1913; found 338.1729 $[M+Na]^+$, $C_{19}H_{25}NNaO_3$ requires 338.1732.

Compound **10c** was synthesized according to the same procedure for the synthesis of **10a** in 96% yield from **9** and 3,3-dimethylallyl bromide. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.36–7.21 (m, 5H), 5.19–5.13 (m, 1H), 4.73–4.65 (m, 1H), 4.17–4.09 (m, 2H), 3.85–3.78 (m, 1H), 3.22 (dd, *J* = 13.3, 3.2 Hz, 1H), 2.63 (dd, *J* = 13.3, 9.7 Hz, 1H), 2.53–2.42 (m, 1H), 2.33–2.20 (m, 1H), 2.04–1.93 (m, 1H), 1.65 (d, *J* = 11.5 Hz, 6H), 0.97 (dd, *J* = 6.7, 3.4 Hz, 6H). ^{13}C-NMR (150 MHz, $CDCl_3$) δ 176.43, 153.32, 135.65, 133.60, 129.51, 129.02, 127.36, 121.43, 65.68, 55.45, 48.88, 37.90, 30.60, 28.42, 25.95, 20.99, 19.45, 17.88. HRMS (ESI-MS) Found 352.1877 $[M+Na]^+$, $C_{20}H_{27}NNaO_3$ requires 352.1889; found 368.1621 $[M+K]^+$, $C_{20}H_{27}NKO_3$ requires 368.1628.

Synthesis of 11a:[3g] To a THF/H_2O (275 mL/70 mL) solution of **10a** (20.72 g, 68.75 mmol, 1 equiv) was added dropwise 30% H_2O_2 (30 mL, 275 mmol, 4 equiv) and $LiOH•H_2O$ (5.77 g, 137.5 mmol, 2 equiv) at room temperature. After being stirred for 5 h, Na_2SO_3 (43.22 g, 343 mmol, 5 equiv) was added slowly and the reaction mixture was stirred for a few hours. The resulting solution was evaporated under reduced

pressure to remove the volatile materials. The concentrated solution was adjusted to *ca.* pH 14 with 1.5 M aq. NaOH and extracted with CH_2Cl_2 (6 × 100 mL). The aqueous layer was acidified to pH 1 with 6 M aq. HCl and extracted with EtOAc (6 × 100 mL). The combined organic layer was washed with brine (100 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give **11a** (8.94 g, 62.9 mmol, 91%) as a slightly yellow oil, which was used in the next transformation without further purification. ^{1}H-NMR (600 MHz, $CDCl_3$) δ 11.19 (s, 1H), 5.81–5.75 (m, 1H), 5.09 (d, *J* = 17.1 Hz, 1H), 5.02 (d, *J* = 10.1 Hz, 1H), 2.37–2.27 (m, 2H), 2.26–2.22 (m, 1H), 1.96–1.89 (m, 1H), 0.98 (dd, *J* = 6.7, 4.2 Hz, 6H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 181.88, 135.72, 116.78, 52.43, 33.69, 30.16, 20.34, 20.17.

Synthesis of **11b** was carried out according to the same procedure as the synthesis of **11a**. **10b** (12.55 g, 40 mmol, 1 equiv) afford **11b** (5.48 g, 35.0 mmol, 88%) as a slightly yellow oil. ^{1}H-NMR (600 MHz, $CDCl_3$) δ 9.60 (s, 1H), 5.53–5.47 (m, 1H), 5.41–5.36 (m, 1H), 2.29–2.16 (m, 3H), 1.92–1.87 (m, 1H), 1.64 (d, *J* = 6.3 Hz, 3H), 0.97 (dd, *J* = 6.7, 4.4 Hz, 6H). ^{13}C-NMR (150 MHz, $CDCl_3$) δ 181.98, 128.09, 127.39, 52.96, 32.61, 30.10, 20.35, 20.24, 18.03. HRMS (ESI-MS) Found 155.1073 $[M-H]^-$, $C_9H_{15}O_2$ requires 155.1072.

Synthesis of **11c** was carried out according to the same procedure as the synthesis of **11a**. The two-step yield was 85% from starting material **9**. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 5.09 (t, *J* = 7.1 Hz, 1H), 2.35–2.12 (m, 3H), 1.97–1.85 (m, 1H), 1.68 (s, 3H), 1.61 (s, 3H), 0.98 (dd, *J* = 6.7, 3.8 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 182.24, 133.69, 121.39, 53.00, 30.20, 28.20, 25.89, 20.40, 20.30, 17.81. HRMS (ESI-MS) Found 169.1230 $[M-H]^-$, $C_{10}H_{17}O_2$ requires 169.1229.

Synthesis of 12a: To a dried CH_2Cl_2 solution (80 mL) of **11a** (2.27 g, 16 mmol, 1 equiv) was added $(COCl)_2$ (4.1 mL, 48 mmol, 3 equiv) dropwise and a few drops of DMF at room temperature. After being stirred at the same temperature for 12 h, the resulting solution was evaporated to remove the volatile materials. The residue was dissolved in CH_2Cl_2 (80 mL) and then dimethylamine hydrochloride (2.65 g, 32 mmol, 2 equiv) and DMAP (97.6 mg, 0.8 mmol, 0.05 equiv) were added and stirred for 5 min. Then Et_3N (8.9 mL, 64 mmol, 4 equiv) was added slowly and the resulting reaction mixture was stirred at room temperature overnight. The reaction mixture was washed with brine (3×100 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification of the residue by column chromatography (CH_2Cl_2) gave **12a** (2.34 g, 13.8 mmol, 86%) as a colorless oil. ^{1}H-NMR (600 MHz, $CDCl_3$) δ 5.76–5.69 (m, 1H), 5.06–5.03 (m, 1H), 4.96–4.93 (m, 1H), 3.00 (s, 6H), 2.50–2.47 (m, 1H), 2.41–2.36 (m, 1H), 2.28–2.24 (m, 1H), 1.95–1.87 (m, 1H), 0.96 (d, *J* = 6.7 Hz, 3H), 0.90 (d, *J* = 6.7 Hz, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 175.29, 136.47, 116.08, 48.12, 37.65, 35.48, 34.56, 30.84, 21.10, 19.87. HRMS (ESI-MS) Found 170.1544 $[M+H]^+$, $C_{10}H_{20}NO$ requires 170.1545; found 192.1362 $[M+Na]^+$, $C_{10}H_{19}NNaO$ requires 192.1364.

Synthesis of **12b** was carried out according to the same procedure as the synthesis of **12a**. **11b** (3.96 g, 25.35 mmol, 1 equiv) afforded **12b** (2.54 g, 17.3 mmol, 69%) as a

colorless oil. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 5.52–5.41 (m, 1H), 5.37–5.27 (m, 1H), 3.02 (s, 3H), 2.97 (s, 3H), 2.47–2.39 (m, 1H), 2.33–2.15 (m, 2H), 1.94–1.83 (m, 1H), 1.61 (d, *J* = 6.1 Hz, 3H), 0.95 (d, *J* = 6.7 Hz, 3H), 0.88 (d, *J* = 6.7 Hz, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 175.62, 128.82, 126.57, 48.64, 37.63, 35.52, 33.44, 30.78, 21.18, 19.95, 17.92. HRMS (ESI-MS) Found 184.1697 $[M+H]^+$, $C_{11}H_{22}NO$ requires 184.1701.

Synthesis of **12c** was carried out according to the same procedure as the synthesis of **12a**. **11c** (3.39 g, 19.9 mmol, 1 equiv) afforded **12c** (2.84 g, 14.4 mmol, 72%) as a colourless oil. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 5.07–5.01 (m, 1H), 3.01 (s, 3H), 2.96 (s, 3H), 2.40 (dd, *J* = 15.1, 7.2 Hz, 1H), 2.25 (t, *J* = 7.2 Hz, 2H), 1.96–1.84 (m, 1H), 1.65 (s, 3H), 1.61 (s, 3H), 0.96 (d, *J* = 6.7 Hz, 3H), 0.88 (d, *J* = 6.7 Hz, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 175.97, 132.85, 122.09, 48.44, 37.71, 35.65, 30.95, 29.04, 25.84, 21.26, 20.12, 17.77. HRMS (ESI-MS) Found 198.1853 $[M+H]^+$, $C_{12}H_{24}NO$ requires 198.1858.

Synthesis of **14**:[3g] To a round-bottom flask equipped with a condenser and a nitrogen balloon was charged 5-bromo-2-methoxyphenol (20.30 g, 0.1 mol, 1.0 equiv) and a magnetic stirrer. The reaction vessel was then flushed with nitrogen and dried acetonitrile (160 mL) was introduced *via* a glass syringe. Then potassium carbonate (41.47 g, 0.3 mol, 3 equiv), KI (33.2 g, 0.2 mol, 2 equiv) and 1-bromo-3-methoxypropane (17 mL, 0.15 mol, 1.5 equiv) were added. The resulting solution was stirred under reflux for 24 h. The reaction mixture was then diluted with water (200 mL) and the bulk of acetonitrile was removed under reduced pressure. The resulting solution was extracted with Et_2O (4 × 200 mL) and the combined organic layer was washed with brine (200 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification of the residue by column chromatography (CH_2Cl_2) gave **14** (27.12 g, 99 mol, 99%) as a lightly yellow solid. ^{1}H-NMR (600 MHz, $CDCl_3$) δ 7.02–7.00 (m, 2H), 6.72 (d, *J* = 8.3 Hz, 1H), 4.08 (t, *J* = 6.5 Hz, 2H), 3.82 (s, 3H), 3.55 (t, *J* = 6.1 Hz, 2H), 3.34 (d, *J* = 2.9 Hz, 3H), 2.11–2.07 (m, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 149.37, 148.78, 123.53, 116.52, 113.07, 112.77, 69.14, 66.33, 58.72, 56.18, 29.53.

Synthesis of **16a**: To a dried CH_2Cl_2 solution (100 mL) of **11a** (2.85 g, 20 mmol, 1 equiv) was added dropwise $(COCl)_2$ (5.1 mL, 60 mmol, 3 equiv) and a few drops of DMF at room temperature. After being stirred for 10 h, the resulting solution was evaporated under reduced pressure to remove the volatile materials. The residue was dissolved in CH_2Cl_2 (100 mL) and *N*,*O*-dimethylhydroxylamine hydrochloride (3.9 g, 40 mmol, 2 equiv) and DMAP (122 mg, 1 mmol, 0.05 equiv) were added. Then, Et_3N (11.2 mL, 80 mmol, 4 equiv) was added slowly and the resulting reaction mixture was stirred overnight. The reaction mixture was washed with brine (3 × 100 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification of the residue by column chromatography (CH_2Cl_2) gave **13a** as a colorless oil. ^{1}H-NMR (600 MHz, $CDCl_3$) δ 5.78–5.71 (m, 1H), 5.07–5.04 (m, 1H), 4.98–4.96 (m, 1H), 3.66 (s, 3H), 3.18 (s, 3H), 2.70 (s, 1H), 2.40–2.34 (m, 1H), 2.30–2.26 (m, 1H), 1.94–1.86 (m, 1H), 0.97 (d, *J* = 6.8Hz, 3H), 0.92 (d, *J* = 6.7Hz, 3H). ^{13}C-NMR (100 MHz,

$CDCl_3$) δ 176.81, 136.57, 116.22, 61.36, 47.43, 34.31, 32.01, 30.61, 21.09, 20.00. HRMS (ESI-MS) Found 186.1487 $[M+H]^+$, $C_{10}H_{20}NO_2$ requires 186.1494; found 208.1308 $[M+Na]^+$, $C_{10}H_{19}NNaO_2$ requires 208.1314.

To a round-bottom flask equipped with a condenser and a magnetic stirrer was charged **14** (11.01 g, 40 mmol, 2.0 equiv). Then dried THF (120 mL) was introduced *via* a glass syringe. The solution was cooled to -78 °C. *n*-butyl lithium solution (1.6 M in hexane, 25 mL, 40 mmol, 2 equiv) was added. The solution was stirred for 3 h at -78 °C. Then Weinreb amide **13a** (1 equiv) was dissolved in a minimal amount of THF and was added dropwise. The resulting solution was further stirred at -78 °C and then room temperature for 1 h, respectively. The reaction mixture was quenched with saturated aq. NH4Cl. The THF solvent was evaporated under reduced pressure. The solution was extracted with CH_2Cl_2 (4 × 100 mL) and the combined organic layer was washed with brine (100 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification of the residue by column chromatography (1:20 ethyl acetate-hexanes) gave **15a** as a slight yellow oil. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.57–7.55 (m, 2H), 6.88 (d, *J* = 8.9 Hz, 1H), 5.76–5.62 (m, 1H), 5.00 (dd, *J* = 17.0 Hz, 1H), 4.90 (d, *J* = 10.0 Hz, 1H), 4.18 (t, *J* = 6.5 Hz, 2H), 3.93 (s, 3H), 3.57 (t, *J* = 6.1 Hz, 2H), 3.36 (s, 3H), 3.32–3.25 (m, 1H), 2.60–2.49 (m, 1H), 2.35–2.27 (m, 1H), 2.17–1.99 (m, 3H), 0.93 (dd, *J* = 6.6, 4.6 Hz, 6H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 202.27, 153.58, 148.54, 136.47, 131.52, 122.80, 116.17, 112.19, 110.32, 69.25, 66.13, 58.71, 56.06, 51.75, 33.48, 30.77, 29.51, 21.29, 19.67. HRMS (ESI-MS) Found 321.2047 $[M+H]^+$, $C_{19}H_{29}O_4$ requires 321.2066; found 343.1861 $[M+Na]^+$, $C_{19}H_{28}NaO_4$ requires 343.1885. The enantiomeric excess of 97% ee was determined by HPLC (Daicel Chiralpak AD-H, hexane/isopropanol = 98/2, flow rate 1.0 mL/min, T = 30 ^{o}C, 254 nm, tR (minor) 16.481 min, tR(major) 13.257 min).

To a dried Et_2O (60 mL) suspension of $AlCl_3$ (5.40 g, 40 mmol, 2 equiv) was added slowly $LiAlH_4$ (759 mg, 20 mmol, 1 equiv) and a Et_2O solution of **15a** at room temperature. The reaction mixture was stirred for 1 h. Then EtOAc (20 mL), H_2O (40 mL), saturated aq. potassium tartrate (40 mL) and 1 M aq. NaOH (40 mL) were added sequentially. The mixture was extracted with Et_2O (3 × 50 mL) and the combined organic layers were washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification of the residue by column chromatography (1:20 ethyl acetate-hexanes) gave **16a** (4.30 g, 14 mmol, 70% for three steps from **11a**) as a colorless oil. ^{1}H-NMR (600 MHz, $CDCl_3$) δ 6.78 (d, *J* = 8.1 Hz, 1H), 6.70–6.67 (m, 2H), 5.78–5.70 (m, 1H), 5.00–4.97 (m, 2H), 4.10 (t, *J* = 6.5 Hz, 2H), 3.83 (s, 3H), 3.58 (t, *J* = 6.2 Hz, 2H), 3.36 (s, 3H), 2.52 (dd, *J* = 13.8, 6.6 Hz, 1H), 2.38 (dd, *J* = 13.8, 8.0 Hz, 1H), 2.10 (m, *J* = 6.3 Hz, 2H), 2.06–2.02 (m, 1H), 1.96–1.91 (m, 1H), 1.76–1.70 (m, 1H), 1.58–1.53 (m, 1H), 0.91 (d, *J* = 6.9 Hz, 3H), 0.88 (d, *J* = 6.9 Hz, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 148.33, 147.63, 138.27, 134.71, 121.44, 115.76, 114.61, 111.84, 69.53, 66.19, 58.78, 56.18, 45.99, 37.57, 36.24, 34.51, 29.79, 28.41, 19.21, 18.96. HRMS (ESI-MS) Found 307.2261 $[M+H]^+$, $C_{19}H_{31}O_3$ requires 307.2273; found 329.2077 $[M+Na]^+$, $C_{19}H_{30}NaO_3$ requires 329.2093.

Synthesis of **16b** was carried out accroding to the same procedure for the synthesis of **16a**. **16b** was afforded in 38% overall yield *via* a three-step transformation from **11b** as a colorless oil.

13b: ^{1}H-NMR (300 MHz, $CDCl_3$) δ 5.53–5.30 (m, 2H), 3.65 (s, 3H), 3.18 (s, 3H), 2.65 (s, 1H), 2.33–2.17 (m, 2H), 1.93–1.81 (m, 1H), 1.62 (d, *J* = 6.0 Hz, 3H), 0.93 (dd, *J* = 16.3, 6.7 Hz, 6H). ^{13}C-NMR (150 MHz, $CDCl_3$) δ 177.13, 129.01, 126.68, 61.32, 47.88, 33.13, 32.03, 30.59, 21.09, 20.09, 17.90. HRMS (ESI-MS) Found 222.1477 $[M+Na]^+$, $C_{11}H_{21}NNaO_2$ requires 222.1470.

15b: ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.55 (dd, *J* = 4.3, 2.5 Hz, 2H), 6.90–6.87 (m, 1H), 5.48–5.24 (m, 2H), 4.18 (t, *J* = 6.5 Hz, 2H), 3.93 (s, 3H), 3.58 (t, *J* = 6.1 Hz, 2H), 3.36 (s, 3H), 3.26–3.19 (m, 1H), 2.50–2.40 (m, 1H), 2.28–2.19 (m, 1H), 2.17–2.08 (m, 2H), 2.06–1.97 (m, 1H), 1.53 (dd, *J* = 6.1 Hz, 3H), 0.92 (dd, *J* = 6.7, 4.4 Hz, 6H). ^{13}C-NMR (150 MHz, $CDCl_3$) δ 202.69, 153.52, 148.54, 131.74, 128.89, 126.71, 122.82, 112.32, 110.36, 69.33, 66.21, 58.78, 56.12, 52.37, 32.33, 30.70, 29.58, 21.33, 19.77, 17.96. HRMS (ESI-MS) Found 335.2218 $[M+H]^+$, $C_{20}H_{31}O_4$ requires 335.2222; found 357.2035 $[M+Na]^+$, $C_{20}H_{30}NaO_4$ requires 357.2042; found 373.1770 $[M+K]^+$, $C_{20}H_{30}KO_4$ requires 373.1781.

16b: ^{1}H-NMR (300 MHz, $CDCl_3$) δ 6.79–6.66 (m, 3H), 5.45–5.29 (m, 2H), 4.10 (t, *J* = 6.5 Hz, 2H), 3.84 (s, 3H), 3.58 (t, *J* = 6.1 Hz, 2H), 3.36 (s, 3H), 2.50 (dd, *J* = 13.8, 6.6 Hz, 1H), 2.36 (dd, *J* = 13.8, 7.9 Hz, 1H), 2.10 (m, *J* = 6.3 Hz, 2H), 2.00–1.81 (m, 2H), 1.77–1.69 (m, 1H), 1.64 (d, *J* = 4.7 Hz, 3H), 1.55–1.44 (m, 1H), 0.88 (dd, *J* = 10.8, 6.9 Hz, 6H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 148.31, 147.58, 134.96, 130.53, 126.11, 121.45, 114.65, 111.85, 69.54, 66.20, 58.76, 56.19, 46.32, 36.26, 33.12, 29.79, 28.39, 19.21, 19.02, 18.11. HRMS (ESI-MS) Found 320.2340 $[M]^+$, $C_{20}H_{32}O_3$ requires 320.2351; found 343.2235 $[M+Na]^+$, $C_{20}H_{32}NaO_3$ requires 343.2249.

Synthesis of **16c** was carried out according to the same procedure for the synthesis of **16a**. 16c was afforded in 26% overall yield *via* a three-step transformation from **11c** as a colorless oil.

13c: ^{1}H-NMR (300 MHz, $CDCl_3$) δ 5.11–5.05 (m, 1H), 3.64 (s, 3H), 3.18 (s, 3H), 2.63 (s, 1H), 2.35–2.19 (m, 2H), 1.94–1.82 (m, 1H), 1.66 (s, 3H), 1.61 (s, 3H), 0.97 (d, *J* = 6.7 Hz, 3H), 0.91 (d, *J* = 6.7 Hz, 3H). ^{13}C-NMR (100 MHz, $CDCl^3$) δ 177.30, 132.76, 122.23, 61.18, 47.62, 32.06, 30.72, 28.57, 25.76, 21.03, 20.18, 17.72. HRMS (ESI-MS) Found 214.1802 $[M+H]^+$, $C_{12}H_{24}NO_2$ requires 214.1807.

15c: ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.56–7.52 (m, 2H), 6.91–6.86 (m, 1H), 5.02–4.97 (m, 1H), 4.18 (t, *J* = 6.5 Hz, 2H), 3.93 (s, 3H), 3.58 (t, *J* = 6.1 Hz, 2H), 3.36 (s, 3H), 3.21 (ddd, *J* = 9.7, 6.9, 4.2 Hz, 1H), 2.49–2.39 (m, 1H), 2.31–2.22 (m, 1H), 2.17–1.98 (m, 3H), 1.58 (d, *J* = 5.0 Hz, 6H), 0.93 (dd, *J* = 7.6, 7.0 Hz,, 6H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 203.00, 153.46, 148.48, 132.77, 131.83, 122.80, 122.21, 112.31, 110.32, 69.31, 66.19, 58.74, 56.08, 52.39, 30.79, 29.57, 27.98, 25.75, 21.34, 19.86, 17.77. HRMS (ESI-MS) Found 349.2372 $[M+H]^+$, $C_{21}H_{33}O_4$ requires 349.2379.

16c: ^{1}H-NMR (400 MHz, $CDCl_3$) δ 6.77 (d, *J* = 8.0 Hz, 1H), 6.70–6.67 (m, 2H), 5.09

(t, *J* = 6.9 Hz, 1H), 4.10 (t, *J* = 6.5 Hz, 2H), 3.83 (s, 3H), 3.58 (t, *J* = 6.1 Hz, 2H), 3.36 (s, 3H), 2.50 (dd, *J* = 13.7, 6.7 Hz, 1H), 2.36 (dd, *J* = 13.7, 7.9 Hz, 1H), 2.10 (m, *J* = 6.3 Hz, 2H), 1.98–1.81 (m, 2H), 1.75–1.71 (m, 1H), 1.68 (s, 3H), 1.55 (s, 3H), 1.53–1.48 (m, 1H), 0.89 (dd, *J* = 12.2, 6.9 Hz, 6H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 148.30, 147.57, 135.07, 131.95, 123.98, 121.45, 114.65, 111.86, 69.56, 66.21, 58.77, 56.22, 46.90, 36.48, 29.79, 28.51, 28.42, 25.98, 19.34, 19.01, 17.91. HRMS (ESI-MS) Found 357.2393 $[M+Na]^+$, $C_{21}H_{34}NaO_3$ requires 357.2406; found 373.2133 $[M+K]^+$, $C_{21}H_{34}KO_3$ requires 373.2145.

General synthesis of 2a via the olefin cross-metathesis:

A round-bottom flask equipped with a condenser and a magnetic stirrer bar was charged 16 (1.0 equiv), **12** (3.0 or 4.0 equiv), additives (added or not) and 5 mol% of catalyst under nitrogen atmosphere. The reaction vessel was flushed with nitrogen. Then solvent was added **via** a glass syringe. The resulting reaction mixture was refluxed for 24 h under nitrogen atmosphere. The solvent was then removed under reduced pressure. The product was isolated by column chromatography on silica gel with ethyl acetate and hexane (v/v = 1:5) as eluent to gave **2a** as a slightly yellow oil.

Synthesis of 18: To a THF/H_2O (115/60 mL) solution of **12a** (3.27 g, 19.3 mmol, 1 equiv) was added OsO_4 (0.08 M in *t*BuOH, 2.5 mL, 0.2 mmol, 0.01 equiv) and $NaIO_4$ (16.57 g, 77.5 mmol, 4 equiv) at 0 ^oC. The solution was stirred at 0 ^oC for 4 h and then evaporated under reduced pressure. The resulting mixture was diluted with water (200 mL) and extracted with CH_2Cl_2 (3 × 150 mL). The combined organic layer was washed with brine (200 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification of the residue by column chromatography (1:3 ethyl acetate-hexane) gave **18** (2.28 g, 13.3 mmol, 69%) as a colorless oil. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.78 (s, 1H), 3.16 (s, 3H), 3.13–2.98 (m, 2H), 2.96 (s, 3H), 2.54 (dd, *J* = 18.0, 2.6 Hz, 1H), 1.95–1.84 (m, 1H), 0.93 (dd, *J* = 6.7, 3.7 Hz, 6H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 201.63, 174.54, 44.01, 41.20, 37.70, 35.74, 30.16, 20.74, 19.35. HRMS (ESI-MS) Found 172.1333 $[M+H]^+$, $C_9H_{18}NO_2$ requires 172.1338; found 212.1259 $[M+H_2O+Na]^+$, $C_9H_{19}NNaO_3$ requires 212.1263. The enantiomeric excess of 97% ee was determined by HPLC (Daicel Chiralpak OD-H, hexane/isopropanol = 85/15, flow rate 1.0 mL/min, T = 30 ^oC, 215 nm, tR (minor) 7.857 min, tR(major) 5.839 min).

Synthesis of 19: To a THF/H_2O (60/30 mL) solution of **16a** (3.08 g, 10 mmol, 1 equiv) was added OsO_4 (0.08 M in *t*BuOH, 1.2 mL, 0.1 mmol, 0.01 equiv), NaIO4 (8.61 g, 40.0 mmol, 4 equiv) and DABCO (4.50 g, 40 mmol, 4 equiv) at 0 ^oC. The solution was stirred at 0 ^oC for 4 h and then evaporated under reduced pressure. The resulting mixture was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layer was washed with brine (100 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification of the residue by column chromatography (1:10 ethyl acetate-hexane) gave **19** (2.76 g, 8.94 mmol, 89%) as a colorless oil. ^{1}H-NMR (400MHz, $CDCl_3$) δ 9.56 (s, 1H), 6.79–6.67 (m, 3H), 4.10 (t, *J* = 6.4 Hz, 2H), 3.83 (s, 3H), 3.56 (t, *J* = 6.1 Hz, 2H), 3.36 (s, 3H), 2.70–2.65 (m, 1H), 2.37–2.09 (m, 6H),

1.78–1.72 (m, 1H), 0.92 (dd, J = 10.1, 6.9 Hz, 6H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 203.01, 148.56, 148.07, 133.08, 121.56, 114.52, 111.94, 69.50, 66.26, 58.79, 56.16, 45.00, 41.32, 37.39, 30.02, 29.75, 19.69, 18.74. HRMS (ESI-MS) found 331.1862 $[M+Na]^+$, $C_{18}H_{28}NaO_4$ requires 331.1885.

Synthesis of **22**: A PhMe solution (10 mL) of **19** (308.4 mg, 1 mmol, 1 equiv) and $TsNHNH_2$ (186.0 mg, 1 mmol, 1 equiv) was stirred for 45 min at room temperature and then evaporated under reduced pressure. The *N*-tosylhydrazone **21** thus obtained was re-dissolved in PhMe (10 mL). Then CuI (19.0 mg, 0.1 mmol, 0.1 equiv), K_3PO_4 (1.28 g, 6 mmol, 6 equiv) and $HOP(OEt)_2$ (0.65 mL, 5 mmol, 5 equiv) were added to the reaction vessel. The reaction system was flushed with nitrogen for 3 times and heated under refluxing for 12 h. The reaction mixture was filtered and the filtrate was evaporated under reduced pressure. Purification of the residue by column chromatography (2:1 ethyl acetate-hexane) gave 22 (342.4 mg, 0.80 mmol, 80%) as a colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 6.79–6.67 (m, 3H), 4.11–4.00 (m, 6H), 3.83 (s, 3H), 3.58 (t, J = 6.0 Hz, 2H), 3.36 (s, 3H), 2.57 (dd, J = 13.7, 5.3 Hz, 1H), 2.33 (dd, J = 13.7, 7.5 Hz, 1H), 2.13–2.07 (m, 2H), 1.73–1.41 (m, 6H), 1.28 (td, J = 7.0, 2.6 Hz, 6H), 0.90 (dd, J = 14.0, 6.8 Hz, 6H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 148.37, 147.68, 134.11, 121.28, 114.33, 111.87, 69.40, 66.13, 61.37, 58.68, 56.12, 46.67 (d, J = 16.0 Hz), 36.29, 29.68, 28.66, 23.80 (d, J = 140.0 Hz), 22.54 (d, J = 3.9 Hz), 19.08, 18.87, 16.48, 16.43. ^{31}P-NMR (162 MHz, $CDCl_3$) δ 32.40. HRMS (ESI-MS) Found 431.2556 $[M+H]^+$, $C_{22}H_{40}O_6P$ requires 431.2563; found 453.2378 $[M+Na]^+$, $C_{22}H_{39}NaO_6P$ requires 453.2382.

Synthesis of 24: To a THF solution (1 mL) of **22** (91.9 mg, 0.21 mmol, 1 equiv) was added dropwise *n*-BuLi (1.6 M in hexane, 0.2 mL, 0.32 mmol, 1.5 equiv) at -78 ^{o}C. The reaction mixture was stirred at the same temperature for 40 min. Then allyl bromide **23** (0.1 mL, 1.16 mmol, 5.4 equiv) was added slowly. The mixture was allowed to reach to room temperature gradually and then evaporated under reduced pressure to remove the volatile materials. Purification of the residue by column chromatography (1:6 acetone-CH_2Cl_2) gave **24** (69.3 mg, 0.15 mmol, 69%) as a colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 6.79–6.67 (m, 3H), 5.88–5.61 (m, 1H), 5.09–5.03 (m, 1H), 4.99–4.89 (m, 1H), 4.12–3.98 (m, 6H), 3.83 (d, J = 2.1 Hz, 3H), 3.58 (t, J = 6.1 Hz, 2H), 3.35 (s, 3H), 2.56–2.07 (m, 2H), 1.95–1.45 (m, 2H), 1.32–1.25 (m, 6H), 0.94–0.82 (m, 6H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 148.26, 147.61, 136.02, 134.26, 121.36, 116.75, 114.50, 111.82, 69.39, 66.09, 61.57, 61.35, 58.65, 56.11, 43.02, 36.37, 33.66, 33.36, 29.66, 28.60, 28.37, 18.96, 18.05, 16.49. HRMS (ESI-MS) Found 471.2862 $[M+H]^+$, $C_{25}H_{44}O_6P$ requires 471.2876; found 493.2692 $[M+Na]^+$, $C_{25}H_{43}NaO_6P$ requires 493.2695; found 509.2442 $[M+K]^+$, $C_{25}H_{43}KO_6P$ requires 509.2434.

Synthesis of 26: To a THF solution (2 mL) of methyl 2-(diethoxyphosphoryl)acetate **25** (183 μL, 0.75 mmol, 1.5 equiv) was added *n*-BuLi (1.6 M in hexane, 0.5 mL, 0.75 mmol, 1.5 equiv) at -78 ^{o}C. The reaction mixture was stirred at the same temperature for 40 min. Then **18** (85.6 mg, 0.5 mmol, 1 equiv) in THF was added slowly. The mixture was allowed to reach to room temperature gradually and then evaporated

under reduced pressure to remove the volatile materials. Purification of the residue by column chromatography (2:1 ethyl acetate-hexane) gave **26** (84.1 mg, 0.37 mmol, 74%) in a cis/trans mixture as a colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$) for ***E*-26**: δ 6.90–6.82 (m, 1H), 5.84 (d, *J* = 15.5 Hz, 1H), 3.71 (s, 3H), 3.03 (s, 3H), 2.96 (s, 3H), 2.60–2.53 (m, 2H), 2.42–2.32 (m, 1H), 2.00–1.89 (m, 1H), 0.98 (dd, *J* = 10.9, 6.8 Hz, 6H). for ***Z*-26**: δ 6.30–6.23 (m, 1H), 5.78 (d, *J* = 11.5 Hz, 1H), 3.72 (s, 3H), 3.18–3.11 (m, 1H), 3.02 (s, 3H), 2.97 (s, 3H), 2.69–2.60 (m, 2H), 2.00–1.89 (m, 1H), 0.93 (dd, *J* = 6.7, 2.9 Hz, 6H). ^{13}C-NMR (100 MHz, $CDCl_3$) for ***E*-26**: δ 174.22, 166.83, 147.17, 122.25, 51.34, 47.12, 37.61, 35.58, 32.45, 30.81, 20.95, 19.55. For ***Z*-26**: δ 174.89, 166.59, 148.22, 120.25, 51.01, 47.43, 37.61, 35.54, 30.81, 28.93, 21.05, 19.55. HRMS (ESI-MS) Found 250.1423 $[M+Na]^+$, $C_{12}H_{21}NNaO_3$ requires 250.1419.

Synthesis of 27: To a THF solution (43 mL) of **19** (2.70 g, 8.75 mmol, 1 equiv) was added $LiBH_4$ (235.4 mg, 10.8 mmol, 1.2 equiv) at room temperature. The solution was stirred at room temperature for 1 h and quenched with of saturated aq. NH_4Cl (1 mL). The mixture was extracted with CH_2Cl_2 for three times. The combined organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification of the residue by column chromatography (1:1 ethyl acetate-hexane) gave **27** (2.71 g, 8.74 mmol, 100%) as a colorless oil. ^{1}H-NMR (400MHz, $CDCl_3$) δ 6.79–6.68 (m, 3H), 4.11 (t, *J* = 6.5 Hz, 2H), 3.84 (s, 3H), 3.59–3.55 (m, 4H), 3.36 (s, 3H), 2.61–2.56 (m, 1H), 2.38–2.33 (m, 1H), 2.13–2.07 (m, 2H), 1.75–1.71 (m, 1H), 1.63–1.57 (m, 2H), 1.44–1.39 (m, 1H), 1.31 (s, 1H), 0.93–0.87 (m, 6H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 148.24, 147.60, 134.43, 121.28, 114.39, 111.78, 69.44, 66.09, 61.66, 58.70, 56.08, 42.43, 37.02, 33.30, 29.62, 29.17, 19.16, 18.60. HRMS (ESI-MS) Found 311.2206 $[M+H]^+$, $C_{18}H_{31}O_4$ requires 311.2222.

Synthesis of 28: To a THF solution (60 mL) of **27** (3.67 g, 11.8 mmol, 1 equiv), TsCl (2.55 g, 13.4 mmol, 1.1 equiv) and DMAP (69.5 mg, 0.6 mmol, 0.05 equiv) was added dropwise Et_3N (5 mL, 35.8 mmol, 3 equiv) at room temperature. The solution was stirred at room temperature for 14 h and then evaporated under reduced pressure. The resulting mixture was diluted with of Et_2O (150 mL), filtered and concentrated under reduced pressure. Purification of the residue by column chromatography (1:2 ethyl acetate-hexane) gave **28** (5.25 g, 11.3 mmol, 96%) as a colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.72 (d, *J* = 8.2 Hz, 2H), 7.32 (d, *J* = 8.1 Hz, 2H), 6.75 (d, *J* = 8.1 Hz, 1H), 6.65 (s, 1H), 6.60 (d, *J* = 8.1 Hz, 1H), 4.08 (t, *J* = 6.5 Hz, 2H), 3.92 (t, *J* = 6.9 Hz, 2H), 3.84 (s, 3H), 3.58 (t, *J* = 6.1 Hz, 2H), 3.36 (s, 3H), 2.53 (dd, *J* = 13.7, 6.2 Hz, 1H), 2.44 (s, 3H), 2.27 (dd, *J* = 13.8, 8.0 Hz, 1H), 2.10 (m, *J* = 6.3 Hz, 2H), 1.68–1.46 (m, 4H), 0.84 (dd, *J* = 16.3, 6.8 Hz, 6H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 148.46, 147.83, 144.68, 133.61, 133.32, 129.86, 127.90, 121.24, 114.34, 111.94, 69.72, 69.49, 66.20, 58.76, 56.17, 42.22, 36.71, 29.75, 29.47, 29.02, 21.70, 19.07, 18.51. HRMS (ESI-MS) Found 464.2238 $[M]^+$, $C_{25}H_{36}O_6S$ requires 464.2233; found 487.2111 $[M+Na]^+$, $C_{25}H_{36}NaO_6S$ requires 487.2130.

Synthesis of 30a (**Method A**): A mixture of **28** (4.45 g, 9.6 mmol, 1 equiv), **29a** (3.42 g, 19.2 mmol, 2 equiv) and K_2CO_3 (6.63 g, 48.0 mmol, 5 equiv) in MeCN (60 mL) was heated at 50 ^{o}C for 24 h. The reaction mixture was diluted with CH_2Cl_2 (120 mL),

filtered and concentrated under reduced pressure. Purification of the residue by column chromatography (1:10 ethyl acetate-hexane) gave **30a** (4.27g, 9.1 mmol, 95%) as a colorless oil.

Method B: To a THF solution (80 mL) of **27** (2.48 g, 7.99 mmol, 1 equiv), PPh_3 (3.17 g, 12 mmol, 1.5 equiv) and **29a** (2.85 g, 16 mmol, 2 equiv) was added a THF solution of DEAD (2.6 mL, 16 mmol, 2 equiv) at -40 ^oC. The reaction mixture was stirred at -40 ^oC for 10 min and room temperature for 20 min, and then evaporated under reduced pressure. The resulting mixture was diluted with CH_2Cl_2 (150 mL) and washed with brine (6 × 100 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification of the residue by column chromatography (1:10 ethyl acetate-hexane) gave **30a** (3.01 g, 6.39 mmol, 80%) as a colorless oil. ^{1}H-NMR (400MHz, $CDCl_3$) δ 7.55 (s, 5H), 6.76 (d, *J* = 8.0 Hz, 1H), 6.70–6.67 (m, 2H), 4.08 (t, *J* = 6.4 Hz, 2H), 3.82 (s, 3H), 3.57 (t, *J* = 6.1 Hz, 2H), 3.35–3.23 (m, 5H), 2.65–2.60 (m, 1H), 2.41–2.36 (m, 1H), 2.12–2.06 (m, 2H), 1.84–1.78 (m, 2H), 1.71–1.58 (m, 2H), 0.94–0.88 (m, 6H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 154.36, 148.32, 147.69, 133.81, 133.73, 130.05, 129.76, 123.81, 121.26, 114.28, 111.82, 69.39, 66.11, 58.67, 56.05, 45.51, 36.59, 36.04, 35.23, 32.07, 29.76, 29.64, 29.08, 19.03, 18.80. HRMS (ESI-MS) Found 471.2424 $[M+H]^+$, $C_{25}H_{35}N_4O_3S$ requires 471.2430; found 493.2245 $[M+Na]^+$, $C_{25}H_{34}N_4NaO_3S$ requires 493.2249.

Synthesis of **30b** was carried out according to the method A for the synthesis **30a**. **30b** was obtained in 60% yield from **28** as a colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 6.78 (d, *J* = 8.0 Hz, 1H), 6.71–6.68 (m, 2H), 4.10 (t, *J* = 6.5 Hz, 2H), 3.84 (s, 3H), 3.58 (t, *J* = 6.1 Hz, 2H), 3.36 (s, 3H), 3.32–3.26 (m, 2H), 2.62 (dd, *J* = 13.8, 5.6 Hz, 1H), 2.41 (dd, *J* = 13.8, 7.6 Hz, 1H), 2.10 (m, J = 6.3 Hz, 2H), 1.85–1.73 (m, 2H), 1.70 (s, 9H), 1.67–1.59 (m, 2H), 0.91 (dd, *J* = 16.3, 6.8 Hz, 6H). ^{13}C-NMR (150 MHz, $CDCl_3$) δ 152.80, 148.45, 147.81, 134.03, 121.37, 114.45, 111.94, 69.52, 66.26, 60.95, 58.79, 56.19, 45.68, 36.71, 32.74, 29.78, 29.74, 29.06, 28.78, 19.20, 18.81. HRMS (ESI-MS) Found 473.2551 $[M+Na]^+$, $C_{23}H_{38}N_4NaO_3S$ requires 473.2562; found 489.2293 $[M+K]^+$, $C_{23}H_{38}N_4KO_3S$ requires 489.2302.

Synthesis of **30c** was carried out according to the method A for the synthesis **30a**. **30c** was obtained in 85% yield from **28** as a colorless oil. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 6.77–6.65 (m, 3H), 4.10 (t, *J* = 6.5 Hz, 2H), 3.85 (d, *J* = 1.5 Hz, 6H), 3.58 (t, *J* = 6.1 Hz, 2H), 3.36 (s, 3H), 3.34–3.13 (m, 2H), 2.63 (dd, *J* = 13.7, 5.3 Hz, 1H), 2.35 (dd, *J* = 13.7, 8.0 Hz, 1H), 2.15–2.05 (m, 2H), 1.84–1.70 (m, 2H), 1.70–1.58 (m, 2H), 0.92 (dd, *J* = 14.8, 6.8 Hz, 6H). ^{13}C-NMR (150 MHz, $CDCl_3$) δ 154.34, 148.41, 147.79, 133.90, 121.40, 114.41, 111.84, 69.49, 66.25, 58.78, 56.16, 45.52, 36.69, 33.32, 32.22, 30.00, 29.76, 29.28, 19.08, 18.95. HRMS (ESI-MS) Found 409.2266 $[M+H]^+$, $C_{20}H_{33}N_4O_3S$ requires 409.2273; found 431.2089 $[M+Na]^+$, $C_{20}H_{32}N_4NaO_3S$ requires 431.2093.

Synthesis of 31a: To a EtOH solution (33 mL) of **30a** (1.54 g, 3.3 mmol, 1 equiv) was added a H_2O_2 solution (7 mL) of $(NH_4)_6Mo_7O_{24}{\cdot}4H_2O$ (859.7 mg, 0.7 mmol, 0.2 equiv) at room temperature. The solution was stirred at room temperature for 24 h and

evaporated under reduced pressure. Purification of the residue by column chromatography (1:6 ethyl acetate-hexane) gave **31a** (1.55 g, 3.09 mmol, 94%) as a colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.65–7.58 (m, 5H) , 6.79–6.67 (m, 3H), 4.10 (t, *J* = 6.5 Hz, 2H), 3.84 (s, 3H), 3.65–3.47 (m, 4H), 3.35 (s, 3H), 2.70 (dd, *J* = 14.0, 5.3 Hz, 1H), 2.34 (dd, *J* = 13.7, 9.0 Hz, 1H), 2.13–2.07 (m, 2H), 1.98–1.89 (m, 1H), 1.86–1.72 (m, 2H), 1.70–1.65 (m, 1H), 0.94 (dd, *J* = 12.3, 6.8 Hz, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 153.45, 148.58, 148.00, 133.09, 133.02, 131.49, 129.73, 125.16, 121.20, 114.14, 112.04, 69.44, 66.20, 58.73, 56.13, 54.95, 45.24, 36.62, 29.65, 22.82, 19.01, 18.90. HRMS (ESI-MS) Found 503.2309 $[M+H]^+$, $C_{25}H_{35}N_4O_5S$ requires 503.2328; found 525.2116 $[M+Na]^+$, $C_{25}H_{34}N_4NaO_5S$ requires 525.2148.

Synthesis of **31b** was carried out according to the same procedure for the synthesis **31a**. **31b** was obtained in 90% yield from **30b** as a colorless oil. ^{1}H-NMR (600 MHz, $CDCl_3$) δ 6.79 (d, *J* = 8.0 Hz, 1H), 6.73–6.69 (m, 2H), 4.11 (t, *J* = 6.5 Hz, 2H), 3.84 (s, 3H), 3.74–3.69 (m, 1H), 3.66–3.61 (m, 1H), 3.58 (t, *J* = 6.2 Hz, 2H), 3.36 (s, 3H), 2.69 (dd, *J* = 13.9, 5.9 Hz, 1H), 2.38 (dd, *J* = 13.9, 8.7 Hz, 1H), 2.10 (m, *J* = 6.3 Hz, 2H), 1.99–1.94 (m, 1H), 1.87–1.84 (m, 1H), 1.83 (s, 9H), 1.80–1.75 (m, 1H), 1.73–1.66 (m, 1H), 0.95 (dd, *J* = 15.2, 6.8 Hz, 6H). ^{13}C-NMR (150 MHz, $CDCl_3$) δ 154.11, 148.62, 148.04, 133.22, 121.29, 114.28, 112.10, 69.54, 66.27, 65.47, 58.80, 56.21, 55.68, 45.39, 36.72, 29.78, 29.58, 22.96, 19.18, 18.88. HRMS (ESI-MS) Found 505.2445 $[M+Na]^+$, $C_{23}H_{38}N_4NaO_5S$ requires 505.2461; found 521.2181 $[M+K]^+$, $C_{23}H_{38}N_4KO_5S$ requires 521.2200.

Synthesis of **31c** was carried out according to the same procedure for the synthesis **31a**. **31c** was obtained in 98% yield from **30c** as a colorless oil. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 6.79–6.64 (m, 3H), 4.29 (s, 3H), 4.10 (t, J = 6.5 Hz, 2H), 3.85 (s, 3H), 3.58 (t, *J* = 6.2 Hz, 2H), 3.53–3.34 (m, 5H), 2.70 (dd, *J* = 13.8, 5.4 Hz, 1H), 2.39– 2.27 (m, 1H), 2.15–2.07 (m, 2H), 1.94–1.64 (m, 4H), 0.94 (dd, *J* = 11.1, 6.8 Hz, 6H). ^{13}C-NMR (150 MHz, $CDCl_3$) δ 153.22, 148.65, 148.09, 132.99, 121.21, 114.18, 112.09, 69.48, 66.28, 58.79, 56.20, 54.78, 45.21, 36.70, 36.09, 29.83, 29.72, 22.86, 19.01. HRMS (ESI-MS) Found 441.2157 $[M+H]^+$, $C_{20}H_{33}N_4O_5S$ requires 441.2172; found 463.1971 $[M+Na]^+$, $C_{20}H_{32}N_4NaO_5S$ requires 463.1991; found 479.1711 $[M+K]^+$, $C_{20}H_{33}N_4KO_5S$ requires 479.1730.

General Synthesis of 2a *via* the Julia-Kocienski olefination: A dried tube equipped with a magnetic stirrer was charged **31** (0.2 mmol, 1.0 equiv) and flushed with nitrogen. Then dried solvent (2.5 mL) was added *via* a glass syringe. Unless otherwise noted, the solution was cooled to -70 ^{o}C and a solution of MHMDS base (0.4 mmol in solvent (1mL), where M= Li, Na, or K) was added dropwise. After being stirred at -70 ^{o}C for 1 h, aldehyde **18** (0.8 mmol in solvent (1 mL)) was added dropwise. The resulting reaction mixture was stirred at -70 ^{o}C for 1 h and then allowed to warm gradually to room temperature and stirred for a few hours until **31** has disappeared as monitored by TLC. The reaction mixture was quenched with brine and diluted with CH_2Cl_2. The organic layer was separated, dried over Na_2SO_4, filtered, concentrated and purified by flash column chromatography on silica gel with a mixed ethyl acetate

and hexane (v/v = 1:2) as eluent to gave **2a** as a light yellow oil. ^{1}H-NMR (600 MHz, $CDCl_3$) δ 6.77 (d, *J* = 8.1 Hz, 1H), 6.68–6.65 (m, 2H), 5.41–5.37 (m, 1H), 5.32–5.27 (m, 1H), 4.09 (t, *J* = 6.5 Hz, 2H), 3.83 (s, 3H), 3.58 (t, *J* = 6.2 Hz, 2H), 3.36 (s, 3H), 2.99 (s, 3H), 2.91 (s, 3H), 2.48–2.41 (m, 2H), 2.35–2.28 (m, 2H), 2.22–2.18 (m, 1H), 2.10 (p, *J* = 6.3 Hz, 2H), 1.96–1.90 (m, 1H), 1.89–1.80 (m, 2H), 1.71–1.64 (m, 1H), 1.51–1.45 (m, 1H), 0.95 (d, *J* = 6.7 Hz, 3H), 0.88 (d, *J* = 6.9 Hz, 6H), 0.84 (d, *J* = 6.8 Hz, 3H). ^{1}H-NMR (600 MHz, DMSO) δ 6.83 (d, *J* = 8.1 Hz, 1H), 6.70 (s, 1H), 6.64 (d, *J* = 8.1 Hz, 1H), 5.34–5.29 (m, 1H), 5.27–5.22 (m, 1H), 3.97 (t, *J* = 6.4 Hz, 2H), 3.71 (s, 3H), 3.47 (t, *J* = 6.3 Hz, 2H), 3.24 (s, 3H), 2.95 (s, 3H), 2.76 (s, 3H), 2.54–2.51 (m, 1H), 2.42 (dd, *J* = 13.7, 6.7 Hz, 1H), 2.28 (dd, *J* = 13.7, 8.0 Hz, 1H), 2.12 (t, *J* = 6.8 Hz, 2H), 1.94–1.86 (m, 3H), 1.77–1.68 (m, 2H), 1.63–1.56 (m, 1H), 1.48–1.42 (m, 1H), 0.86 (dd, *J* = 21.1, 6.8 Hz, 6H), 0.81 (dd, *J* = 9.5, 7.0 Hz, 6H). ^{13}C-NMR (100 MHz, DMSO) δ 174.05, 147.78, 147.11, 134.00, 130.31, 129.02, 120.99, 114.20, 112.09, 68.58, 65.37, 57.91, 55.55, 46.93, 45.46, 37.06, 35.37, 34.89, 32.93, 32.38, 30.28, 29.11, 27.72, 20.70, 19.57, 19.06, 18.68. HRMS (ESI-MS) Found 448.3408 $[M+H]^+$, $C_{27}H_{46}NO_4$ requires 448.3427; found 470.3216 $[M+Na]^+$, $C_{27}H_{45}NNaO_4$ requires 470.3246.

Synthesis of Aliskiren HCl salt: The synthesis of **33** from **2a** was carried out according to the reported procedures in ref. 3p and 3s.

Compound 32: ^{1}H-NMR (600 MHz, $CDCl_3$) δ 6.79 (d, *J* = 8.1 Hz, 1H), 6.72 (s, 1H), 6.69 (d, *J* = 8.2 Hz, 1H), 4.34 (q, *J* = 6.7 Hz, 1H), 4.11 (t, *J* = 6.2 Hz, 2H), 4.03–4.00 (m, 1H), 3.85 (s, 3H), 3.58 (t, *J* = 6.1 Hz, 2H), 3.36 (s, 3H), 2.74 (dd, *J* = 13.8, 4.4 Hz, 1H), 2.63–2.59 (m, 1H), 2.24–2.08 (m, 6H), 1.95–1.90 (m, 1H), 1.88–1.78 (m, 2H), 1.62–1.57 (m, 1H), 1.01 (t, *J* = 7.8 Hz, 6H), 0.93 (d, J = 6.8 Hz, 3H), 0.86 (d, *J* = 6.9 Hz, 3H). $[\alpha]_D^{20}$ = 39.2 (*c* 1, $CHCl_3$).

Compound 33: ^{1}H-NMR (600 MHz, $CDCl_3$) δ 6.79 (d, *J* = 8.1 Hz, 1H), 6.73 (s, 1H), 6.70 (d, *J* = 8.1 Hz, 1H), 6.38 (t, *J* = 6 Hz, 1H), 5.98 (s, 1H), 5.37 (s, 1H), 4.10 (t, *J* = 6.4 Hz, 2H), 3.84 (s, 3H), 3.58 (t, J = 6.2 Hz, 2H), 3.47–3.42 (m, 2H), 3.36 (s, 3H), 3.35–3.26 (m, 1H), 3.02 (d, *J* = 4.8 Hz, 1H), 2.90–2.87 (m, 1H), 2.55–2.51 (m, 1H), 2.49–2.46 (m, 1H), 2.12–2.06 (m, 3H), 1.90–1.84 (m, 1H), 1.78–1.70 (m, 2H), 1.68–1.55 (m, 3H), 1.38–1.32 (m, 1H), 1.23 (s, 6H), 0.93–0.87 (m, 12H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 180.32, 176.02, 148.44, 147.79, 133.94, 121.32, 114.35, 111.97, 72.21, 69.44, 66.55, 66.17, 58.66, 56.13, 50.80, 47.31, 43.10, 42.59, 37.48, 34.37, 31.78, 30.29, 29.91, 29.61, 24.20, 24.06, 21.22, 20.37, 19.99, 17.50.

Conversion of **33** into the aliskiren HCl salt was performed as following: To a MeOH solution (4 mL) of **33** (21.6 mg, 0.037 mmol, 1 equiv) and 2-aminoethanol (6.7 mg, 0.11 mmol, 3 equiv) was added 10% Pd/C (24.0 mg) and stirred at room temperature under H_2 atmosphere for 3 h. The mixture was filtered and evaporated under reduced pressure. The residue was dissolved in CH_2Cl_2 (3 mL) and washed with de-ionized H_2O (6 × 1 mL), then acidified with 17% HCl in MeOH (0.14 mL). The solution was evaporated under reduced pressure and the residue was dried under vacuum at room temperature to give Aliskiren HCl salt (18.1 mg, 0.031 mmol, 82%) as a white solid.

^{1}H-NMR (DMSO, 400 MHz) δ 7.70 (s, 3H), 7.59 (t, *J* = 6.0 Hz, 1H), 7.15 (s, 1H), 6.83 (d, *J* = 7.7 Hz, 3H), 6.71 (d, *J* = 7.2 Hz, 1H), 3.99 (t, *J* = 6.1 Hz, 2H), 3.72 (s, 3H), 3.47 (t, *J* = 6.2 Hz, 2H), 3.32 (dd, *J* = 13.2, 7.3 Hz, 1H), 3.25 (s, 4H), 3.10–3.05 (m, 1H), 2.70 (s, 1H), 2.46–2.35 (m, 2H), 2.30–2.26 (m, 1H), 1.97–1.90 (m, 2H), 1.81 (s, 1H), 1.73–1.53 (m, 3H), 1.48–1.28 (m, 3H), 1.06 (s, 6H), 0.87–0.79 (m, 12H). ^{13}C-NMR (DMSO,100 MHz) δ 178.46, 174.61, 147.89, 147.20, 133.15, 121.17, 114.27, 111.97, 68.66, 68.00, 65.41, 57.95, 55.57, 54.29, 48.76, 46.34, 42.51, 36.42, 33.89, 30.64, 30.32, 29.18, 28.12, 23.63, 23.52, 20.76, 20.01, 19.09, 17.38. HRMS (ESI-MS) Found 552.3992 $[M\text{-}Cl]^+$, $C_{30}H_{54}N_3O_6$ requires 552.4013; found 574.3815 $[M\text{-}HCl+Na]^+$, $C_{30}H_{53}N_3NaO_6$ requires 574.3832. $[\alpha]_D^{20}$ = –5.5 (*c* 1, DMSO).

Conversion of **33** into the Aliskiren Hemifumarate salt was performed as following: To a MeOH solution (3 mL) of **33** (17.3 mg, 0.03 mmol, 1 equiv) and 2-aminoethanol (5.5 mg, 0.09 mmol, 3 equiv) was added 10% Pd/C (8.0 mg) and stirred at room temperature under H_2 atmosphere for 3 h. The mixture was filtered and evaporated under reduced pressure. The residue was dissolved in CH_2Cl_2 (3 mL) and washed with de-ionized H_2O (6 × 1 mL), then acidified with 13.5 mM fumaric acid in MeOH (1 mL, 0.45 equiv). The solution was evaporated under reduced pressure and the residue was dried under vacuum at room temperature to give aliskiren hemifumarate salt (16.7 mg, 0.027 mmol, 91%) as a white solid. ^{1}H-NMR (600 MHz, DMSO) δ 7.57 (t, J = 5.8 Hz, 1H), 7.16 (s, 1H), 6.82 (d, *J* = 7.4 Hz, 2H), 6.80 (s, 1H), 6.70 (d, *J* = 7.8 Hz, 1H), 6.39 (s, 1H), 3.97 (t, *J* = 6.1 Hz, 2H), 3.71 (s, 3H), 3.47 (t, *J* = 6.0 Hz, 3H), 3.30–3.26 (m, 1H), 3.24 (s, 3H), 3.16–3.07 (m, 2H), 2.57 (s, 1H), 2.49–2.43 (m, 1H), 2.40–2.33 (m, 1H), 2.31–2.24 (m, 1H), 1.97–1.89 (m, 2H), 1.78 (s, 1H), 1.71–1.51 (m, 3H), 1.37–1.24 (m, 3H), 1.04 (s, 6H), 0.89–0.75 (m, 12H). $[\alpha]_D^{20}$ = –20.8 (*c* 1, DMSO).

Copies of NMR spectra and HPLC charts

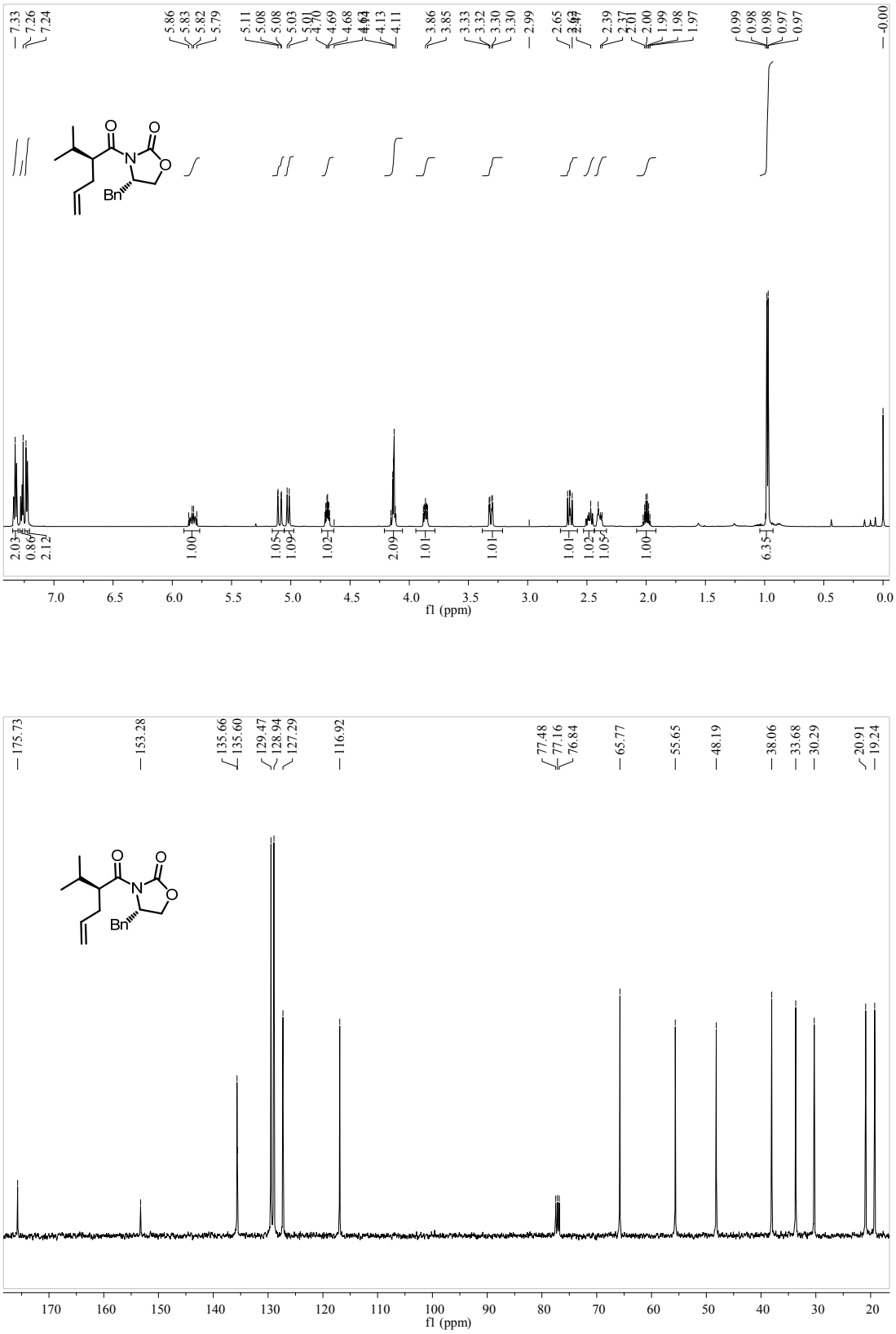


Figure S1. ^{1}H- (upper) and ^{13}C-NMR (lower) spectra of compound **10a**

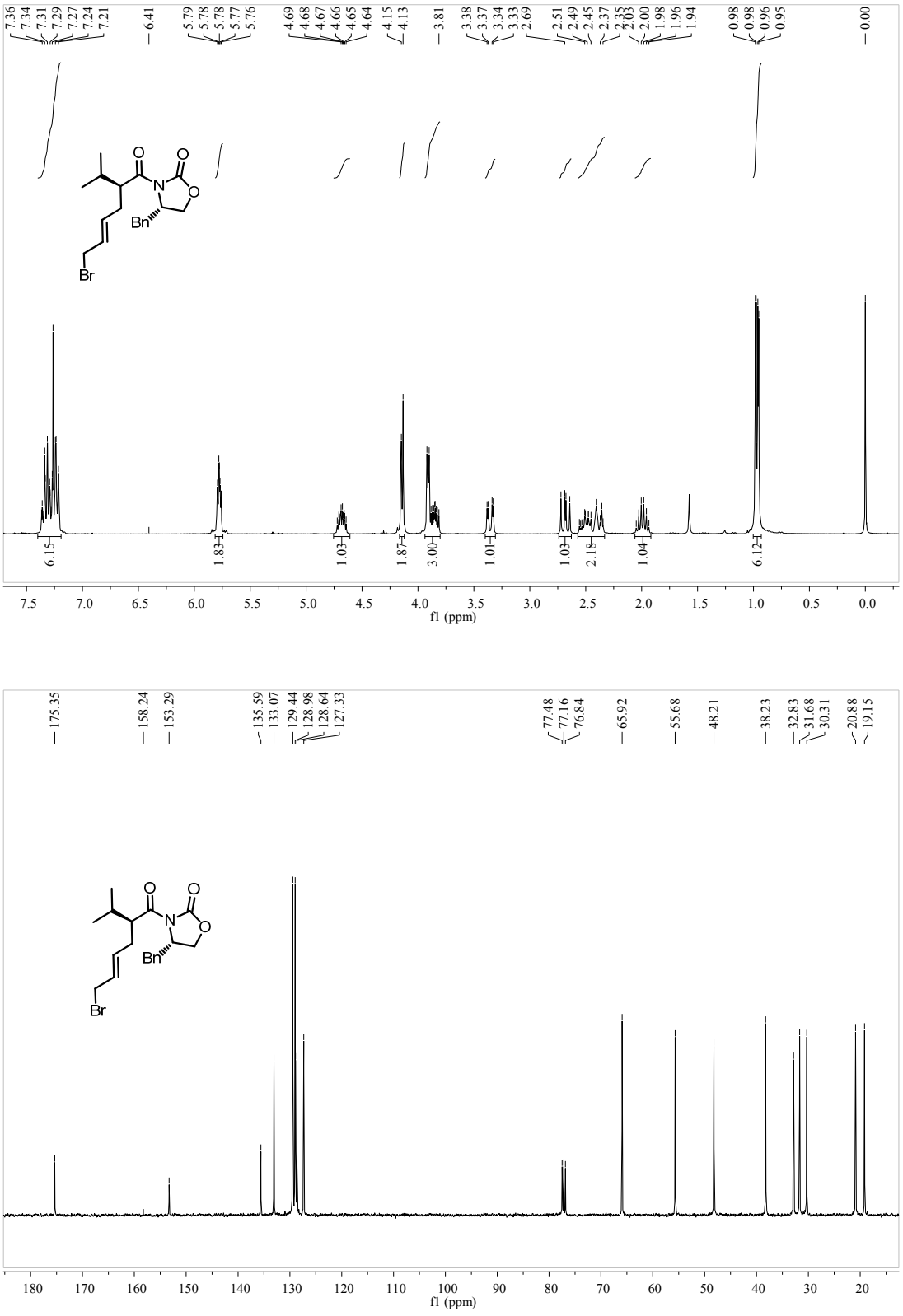


Figure S2. ^{1}H- (upper) and ^{13}C-NMR (lower) spectra of compound **10b'**

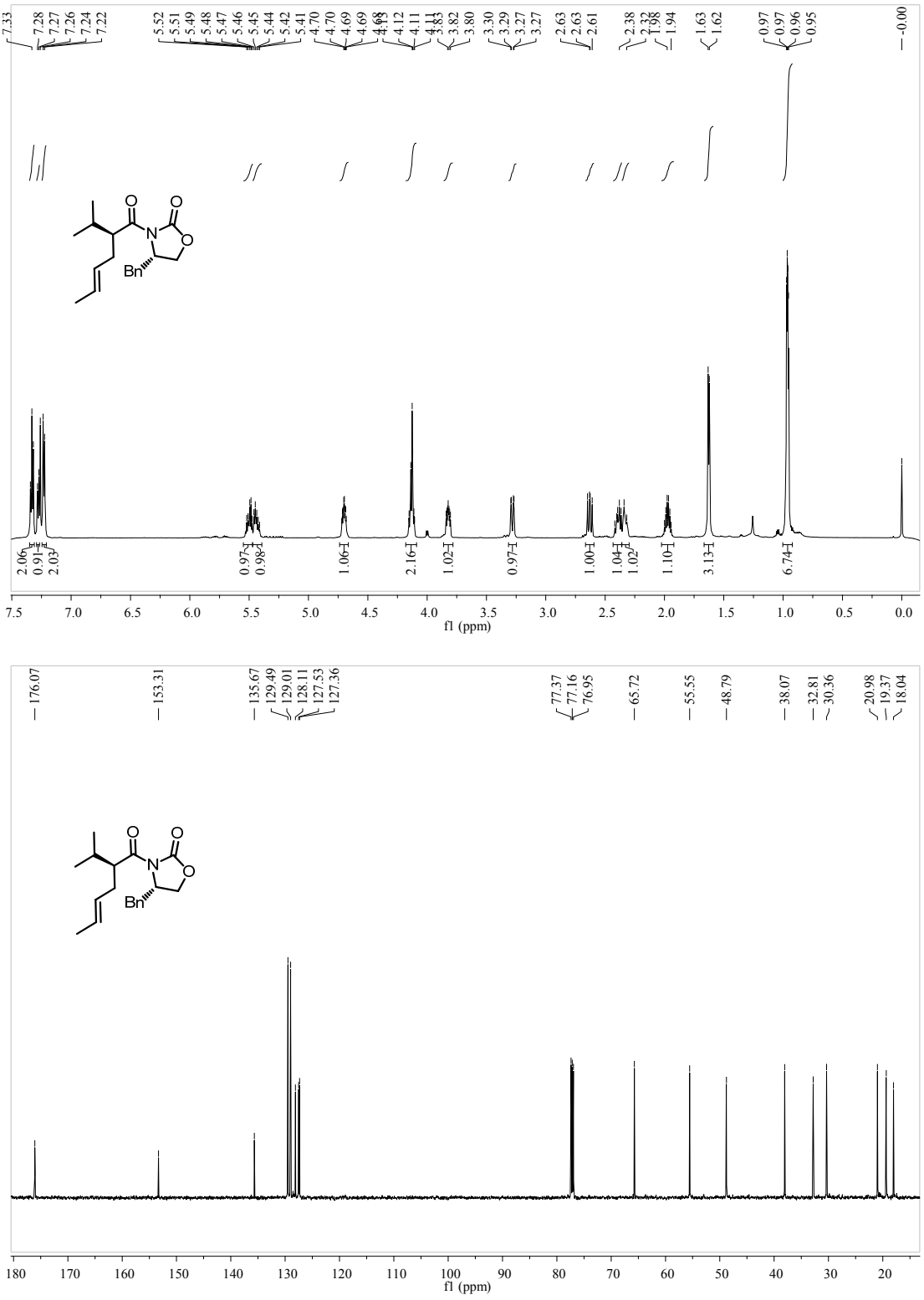


Figure S3. ^{1}H- (upper) and ^{13}C-NMR (lower) spectra of compound **10b**

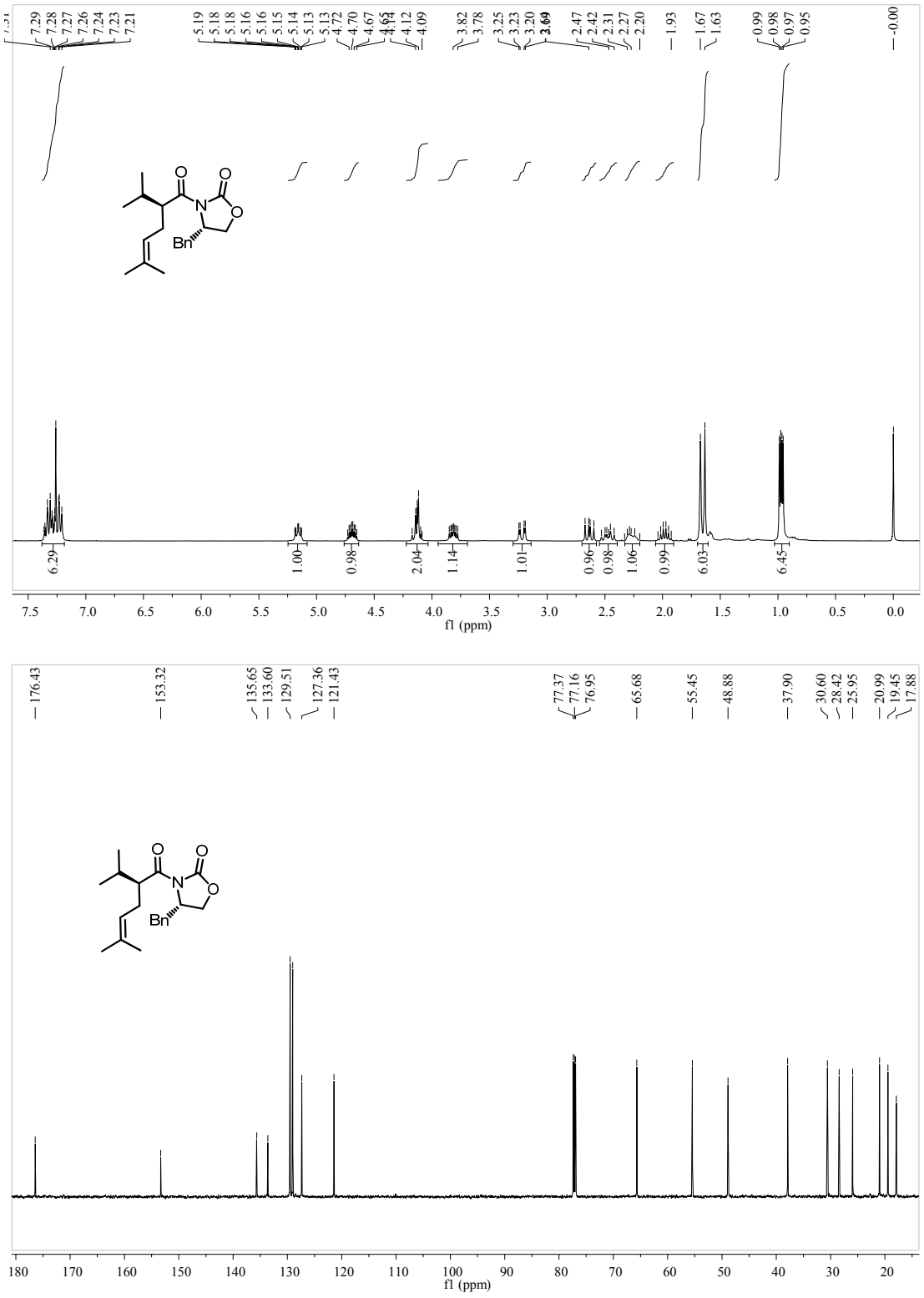
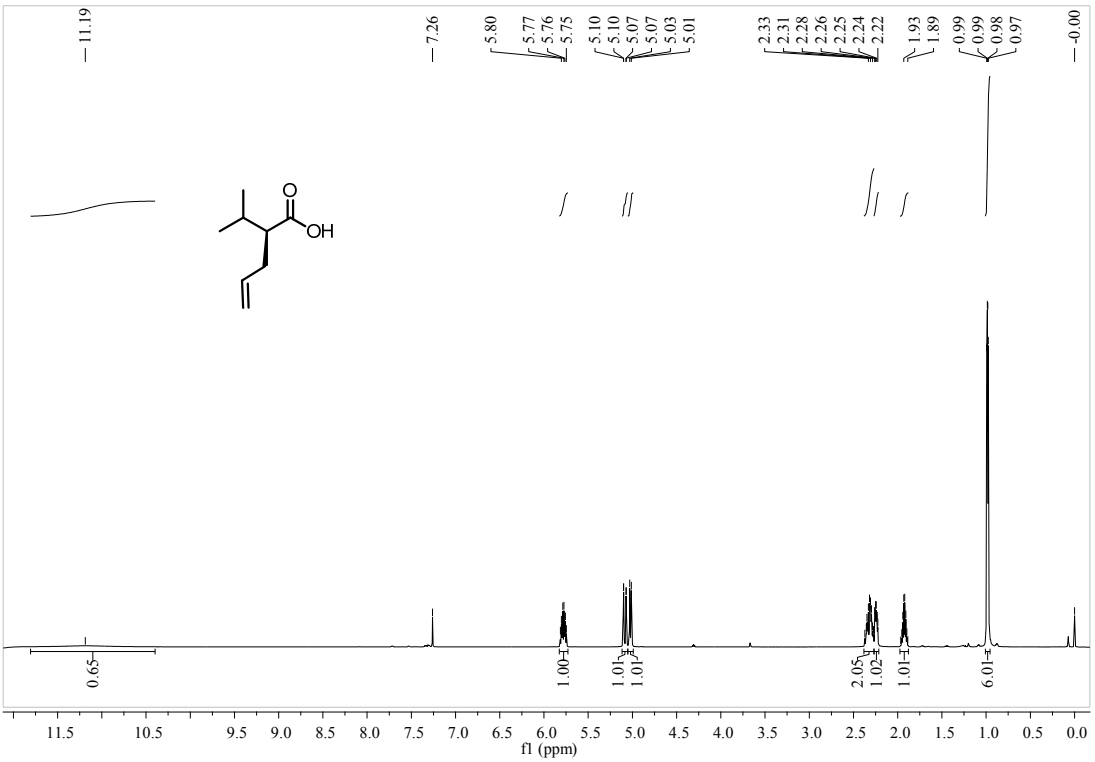


Figure S4. ^{1}H- (upper) and ^{13}C-NMR (lower) spectra of compound **10c**



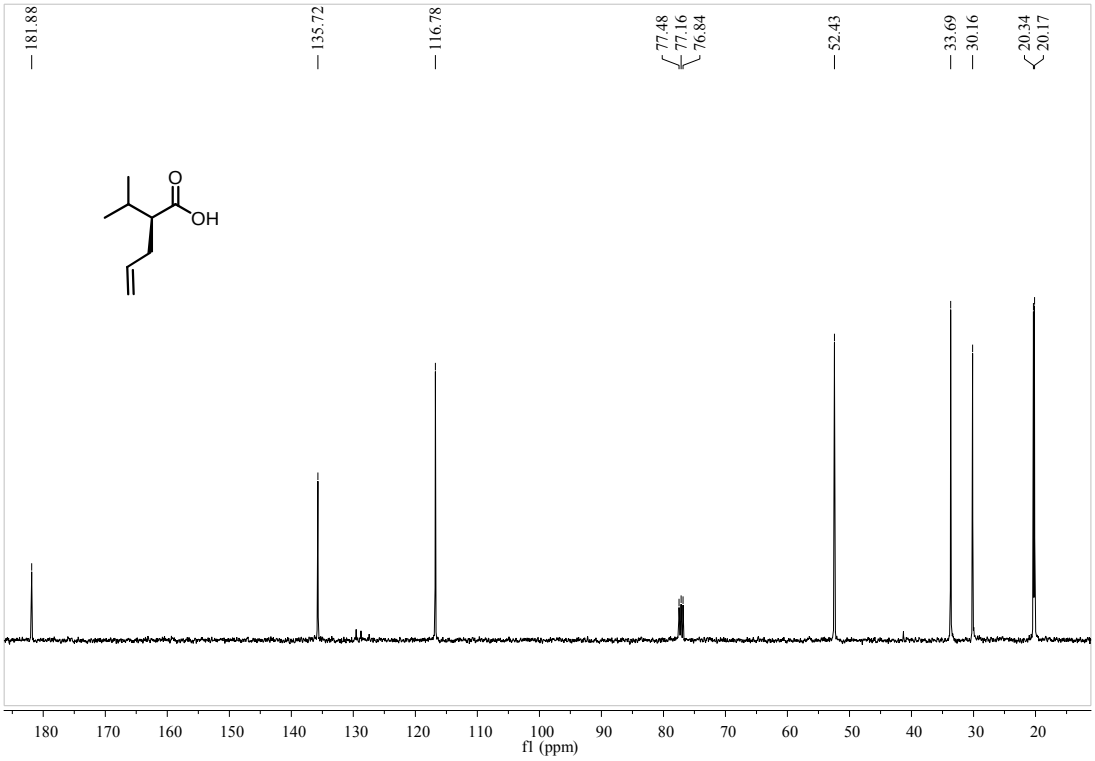


Figure S5. ^{1}H- (upper) and ^{13}C-NMR (lower) spectra of compound **11a**

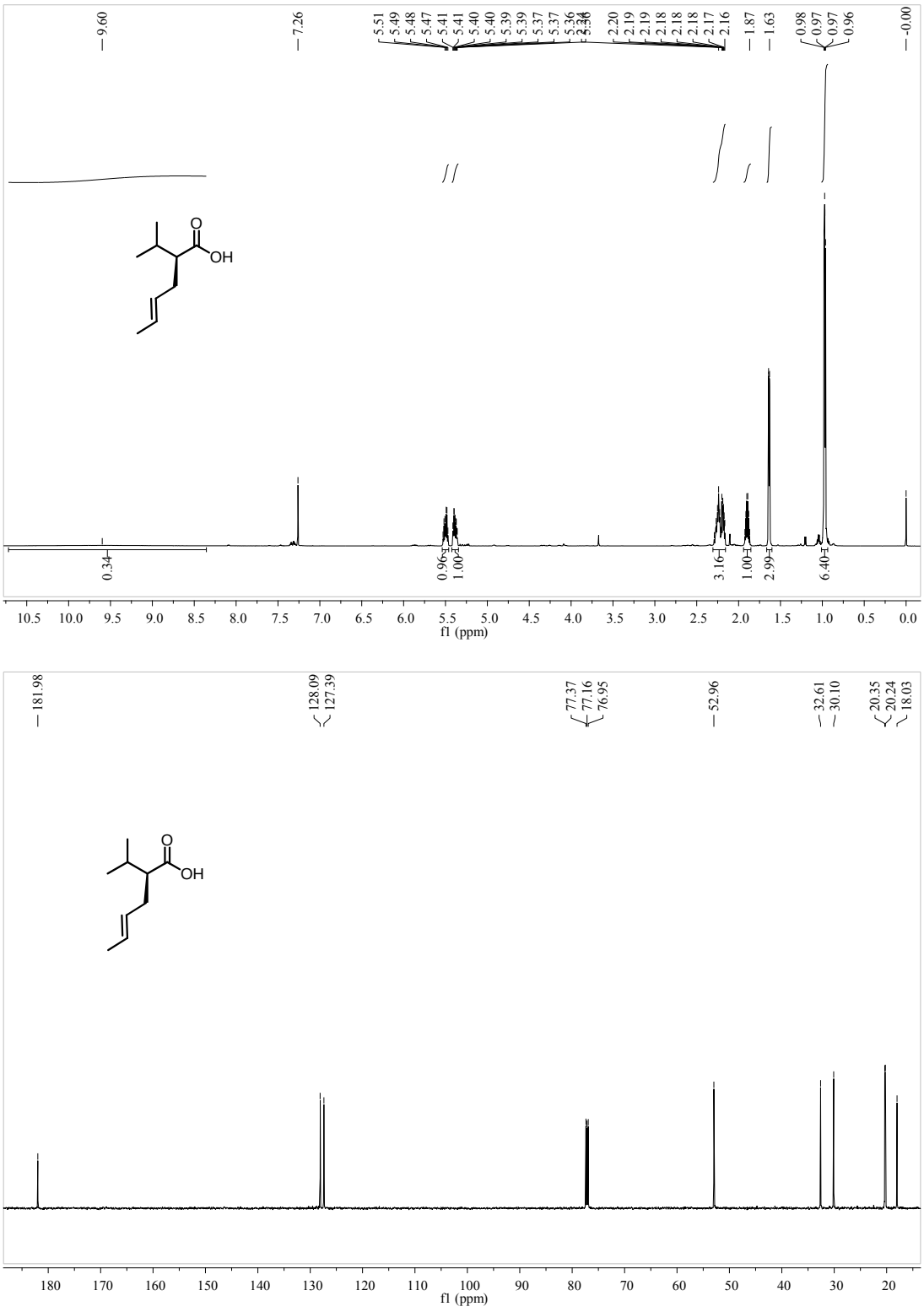


Figure S6. ^{1}H- (upper) and ^{13}C-NMR (lower) spectra of compound **11b**

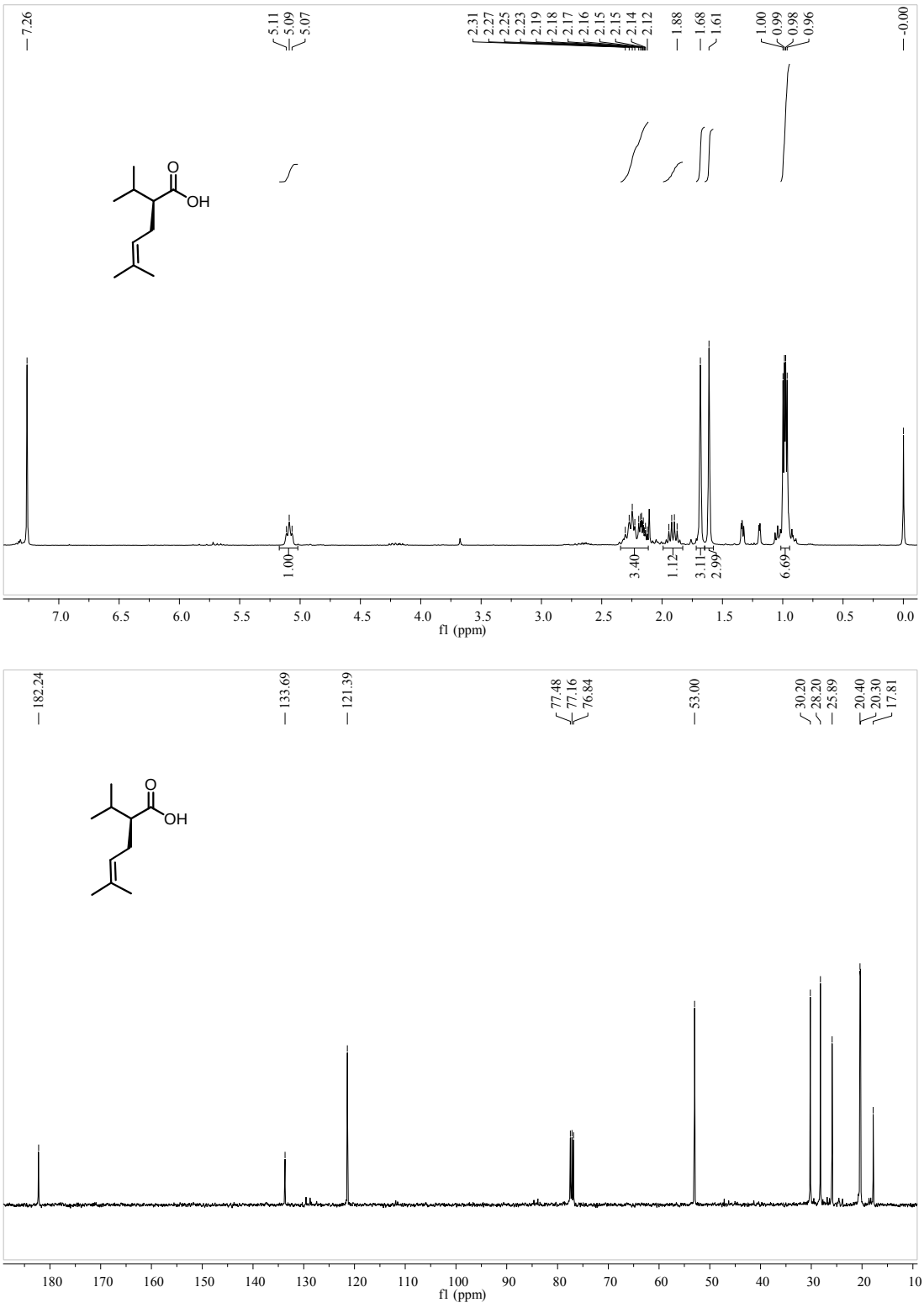
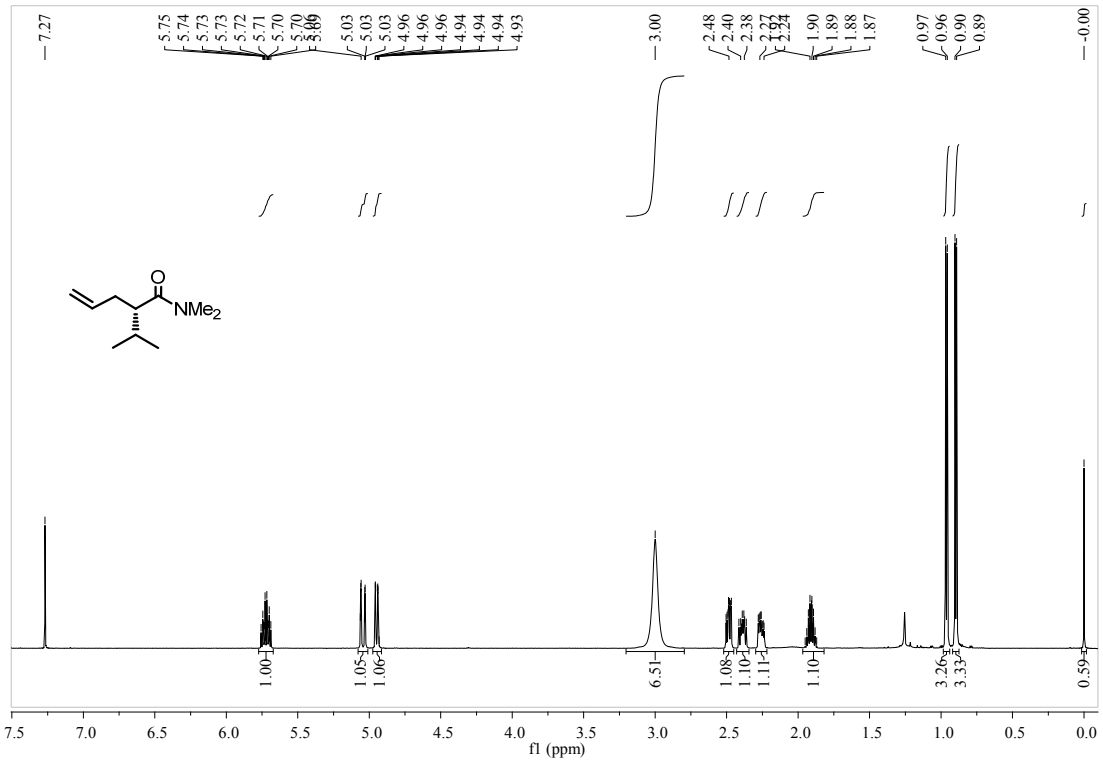


Figure S7. ^{1}H- (upper) and ^{13}C-NMR (lower) spectra of compound **11c**



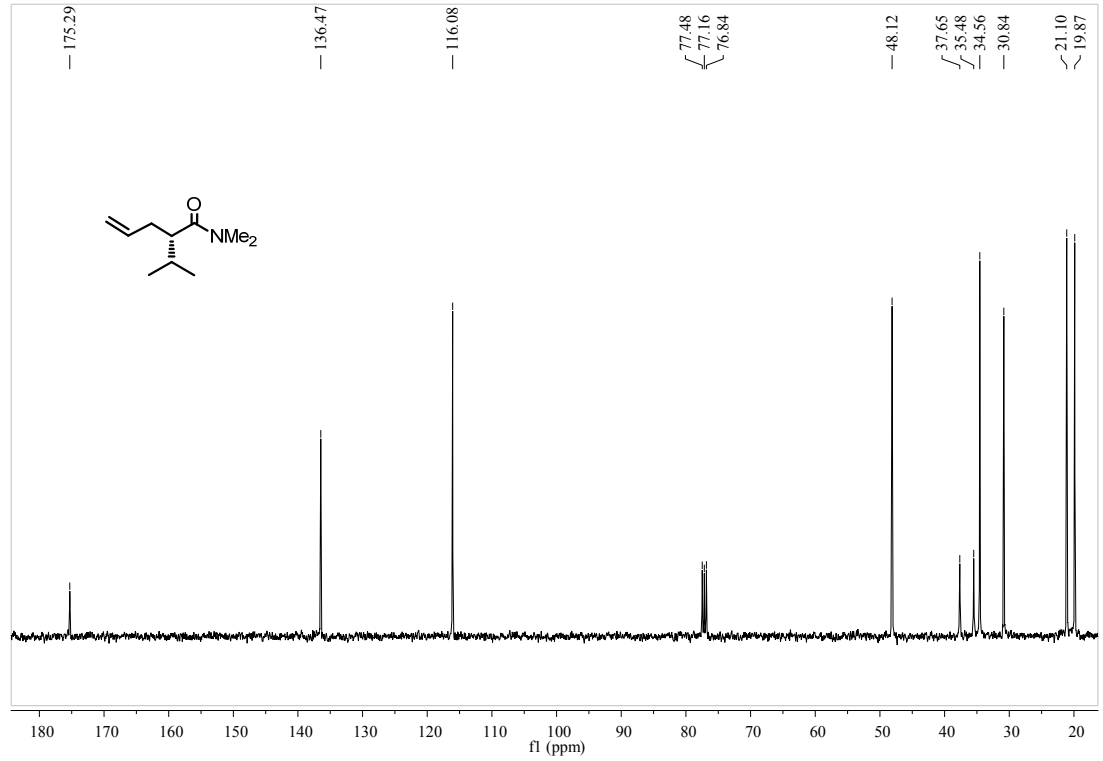
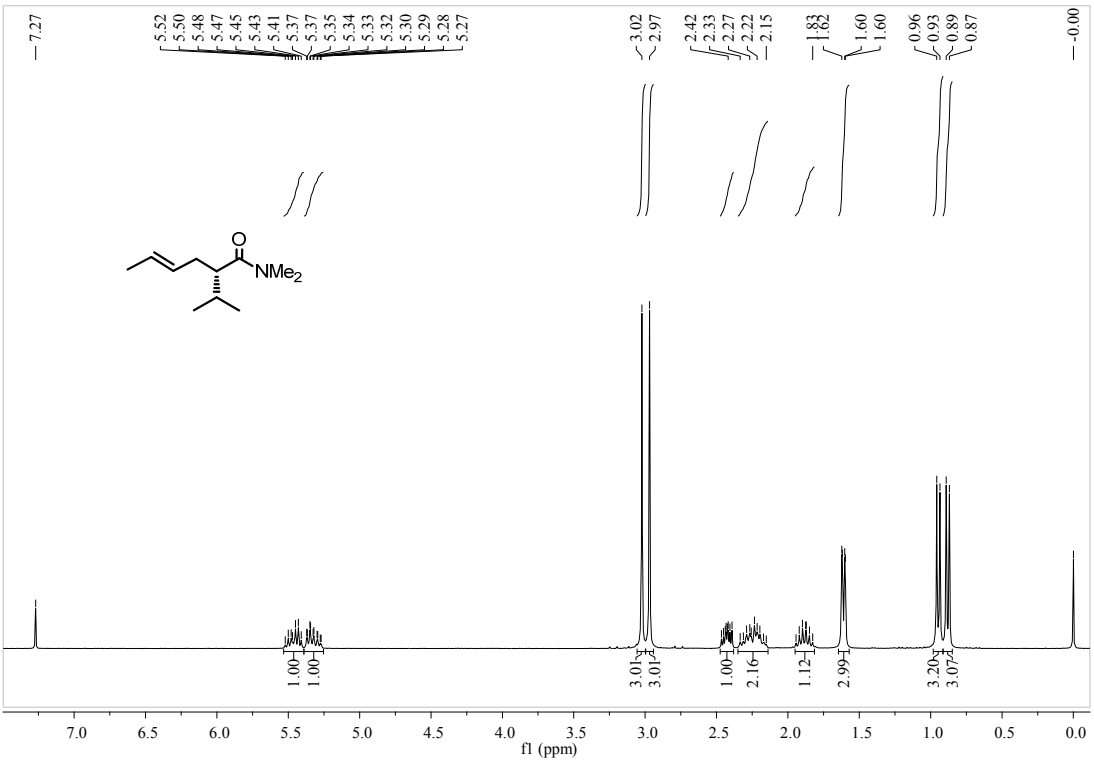


Figure S8. ^{1}H- (upper) and ^{13}C-NMR (lower) spectra of compound **12a**



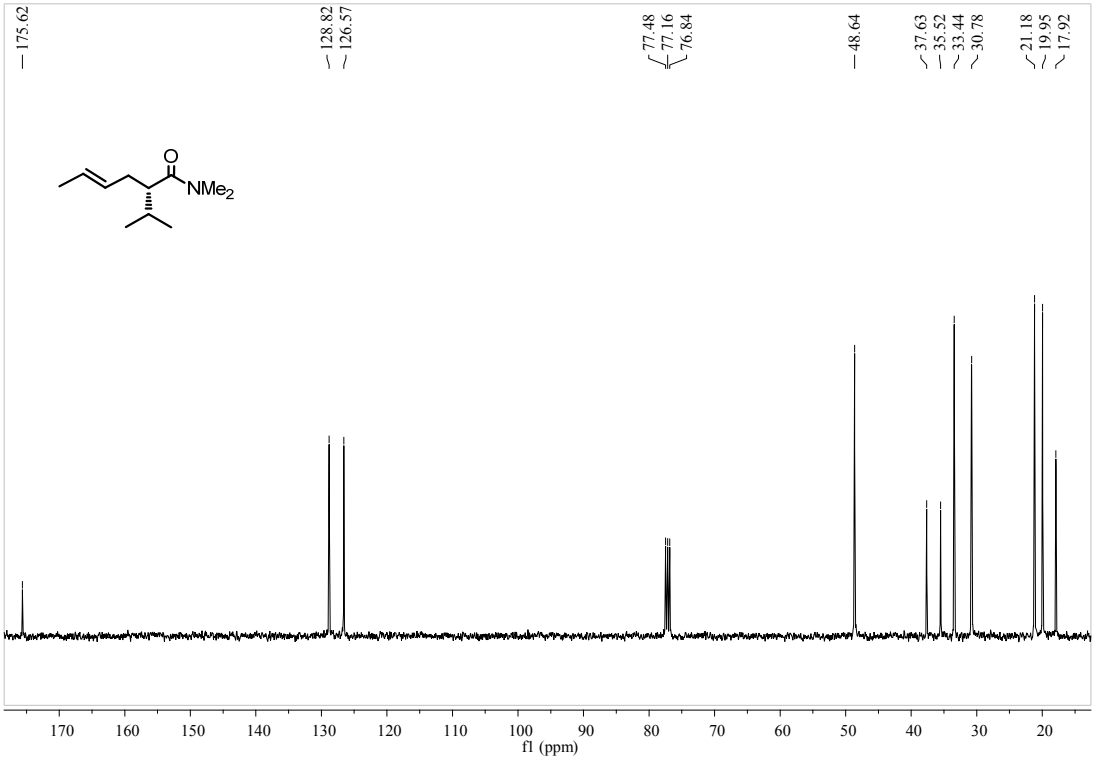


Figure S9. ^{1}H- (upper) and ^{13}C-NMR (lower) spectra of compound **12b**

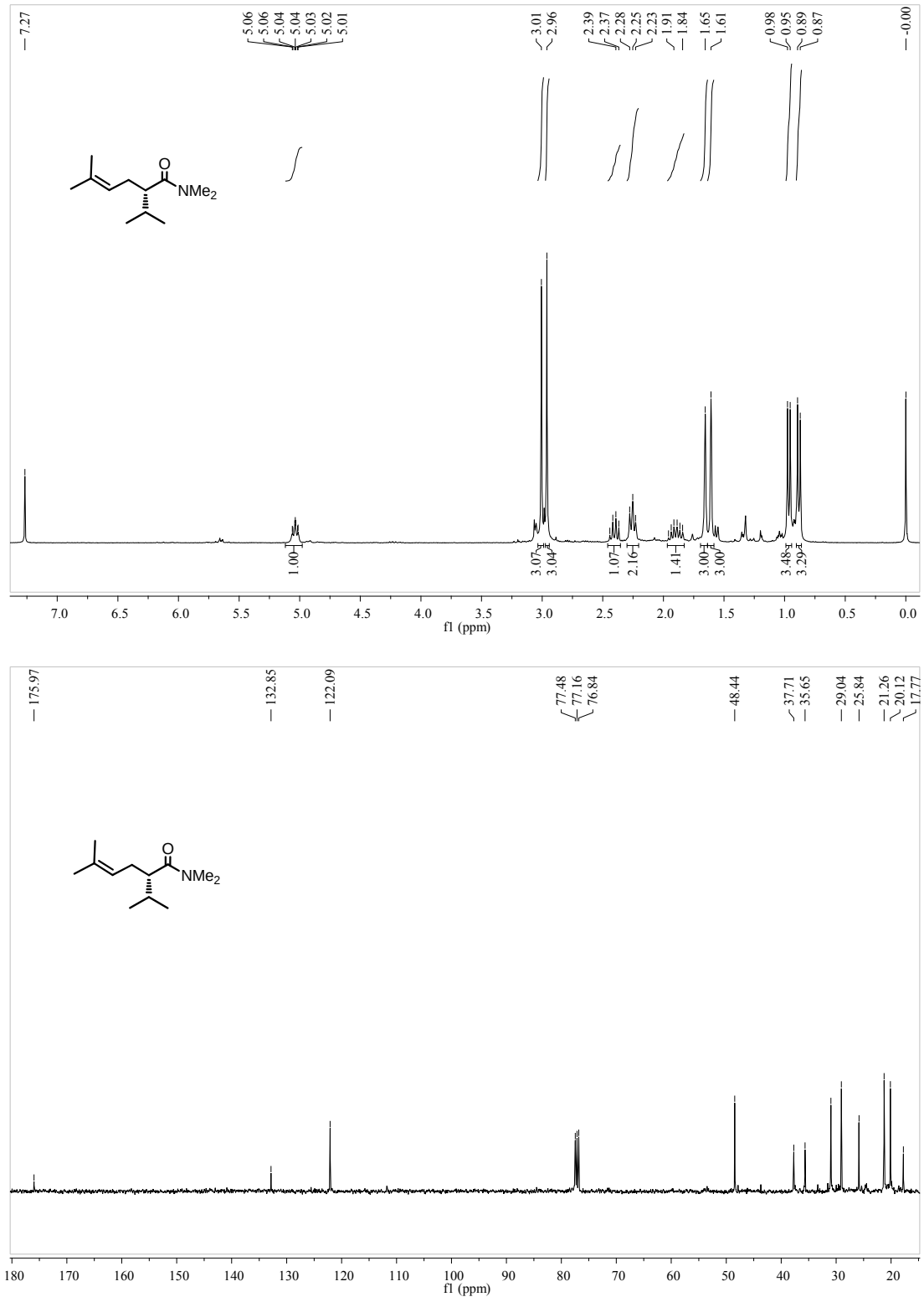
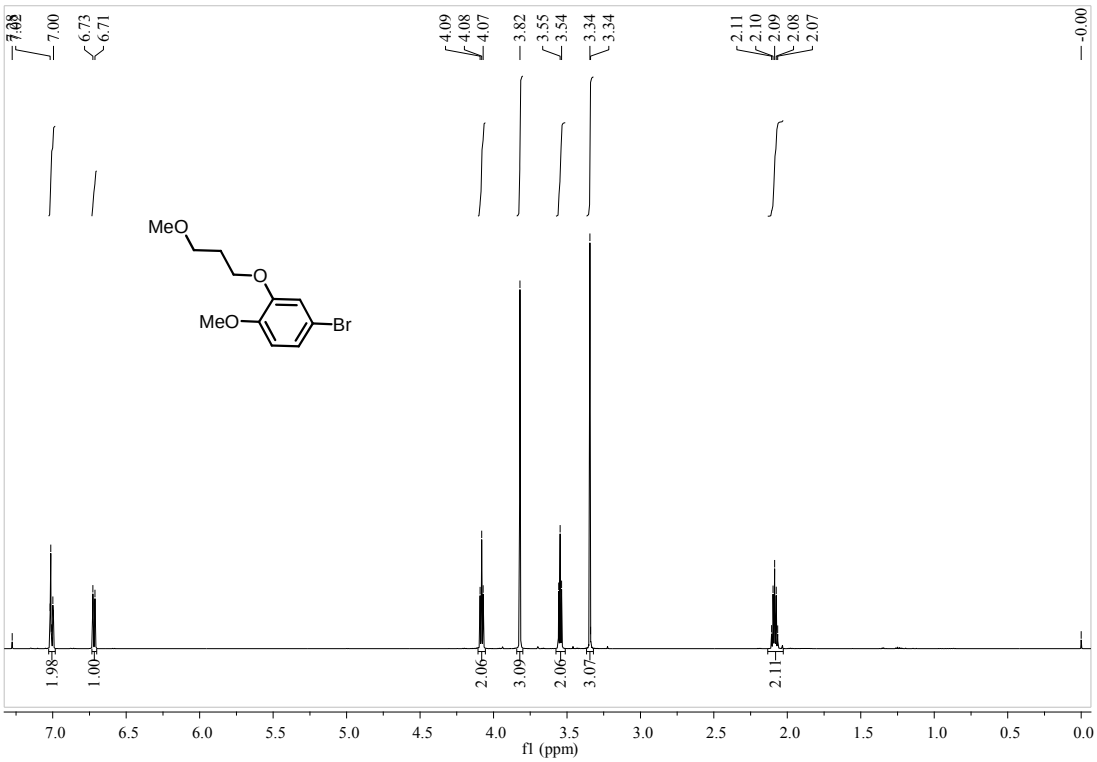


Figure S10. ^{1}H- (upper) and ^{13}C-NMR (lower) spectra of compound **12c**



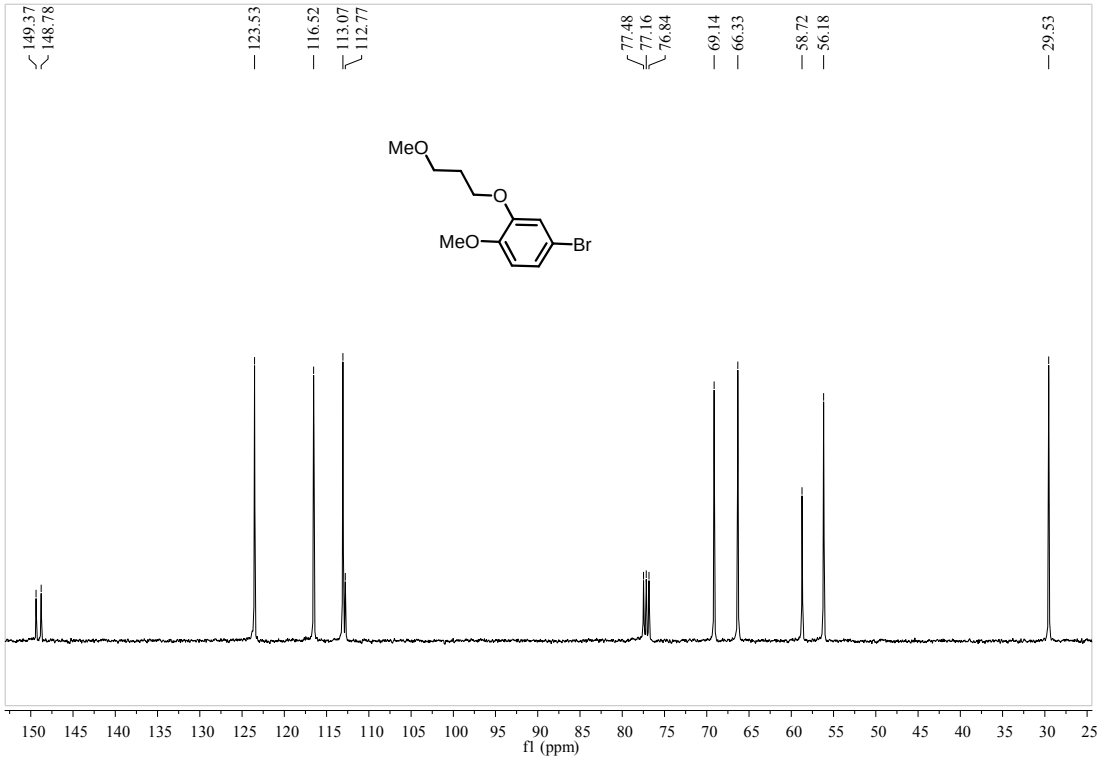


Figure S11. ^{1}H- (upper) and ^{13}C-NMR (lower) spectra of compound **14**

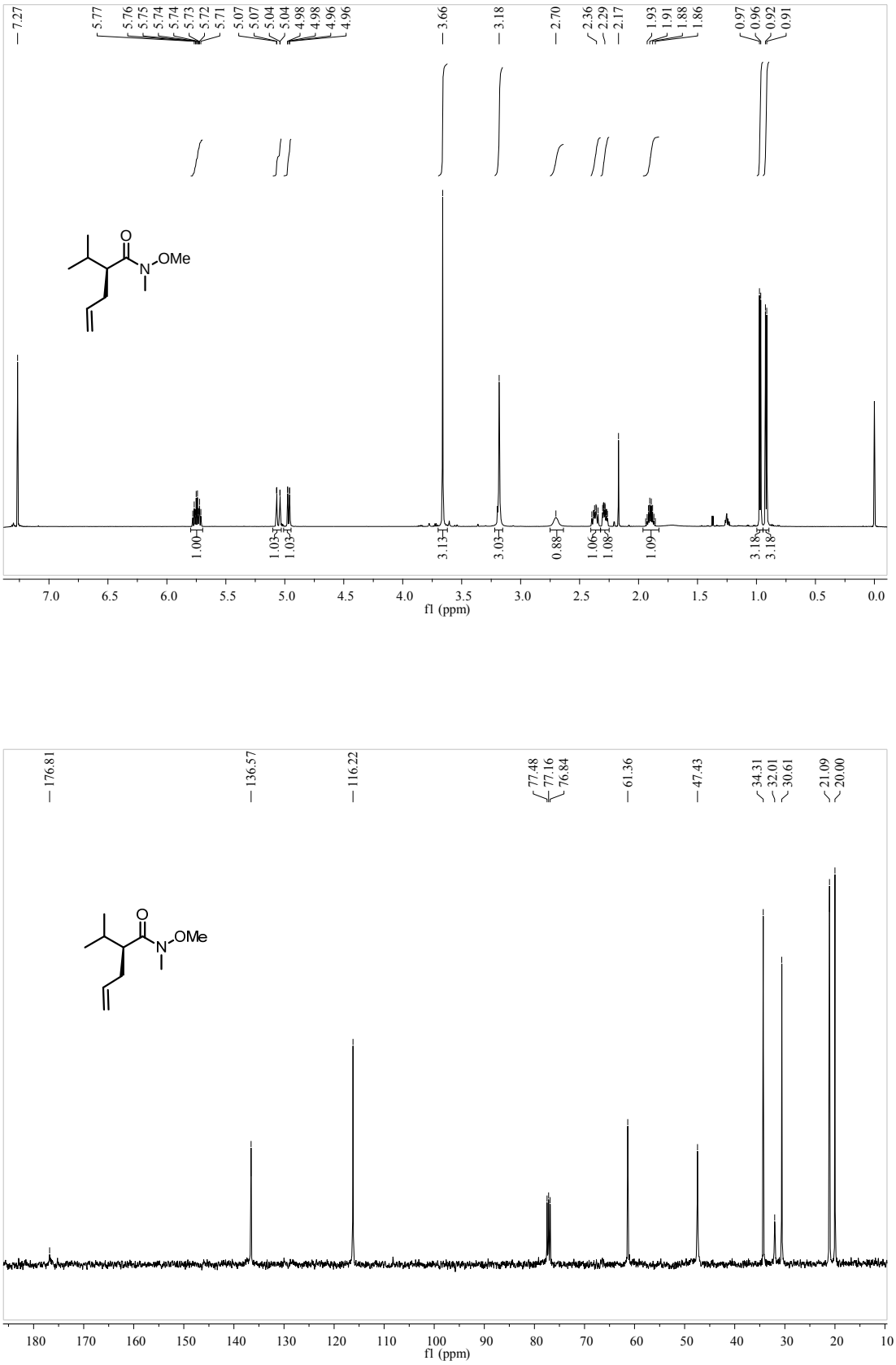


Figure S12. ^{1}H- (upper) and ^{13}C-NMR (lower) spectra of compound **13a**

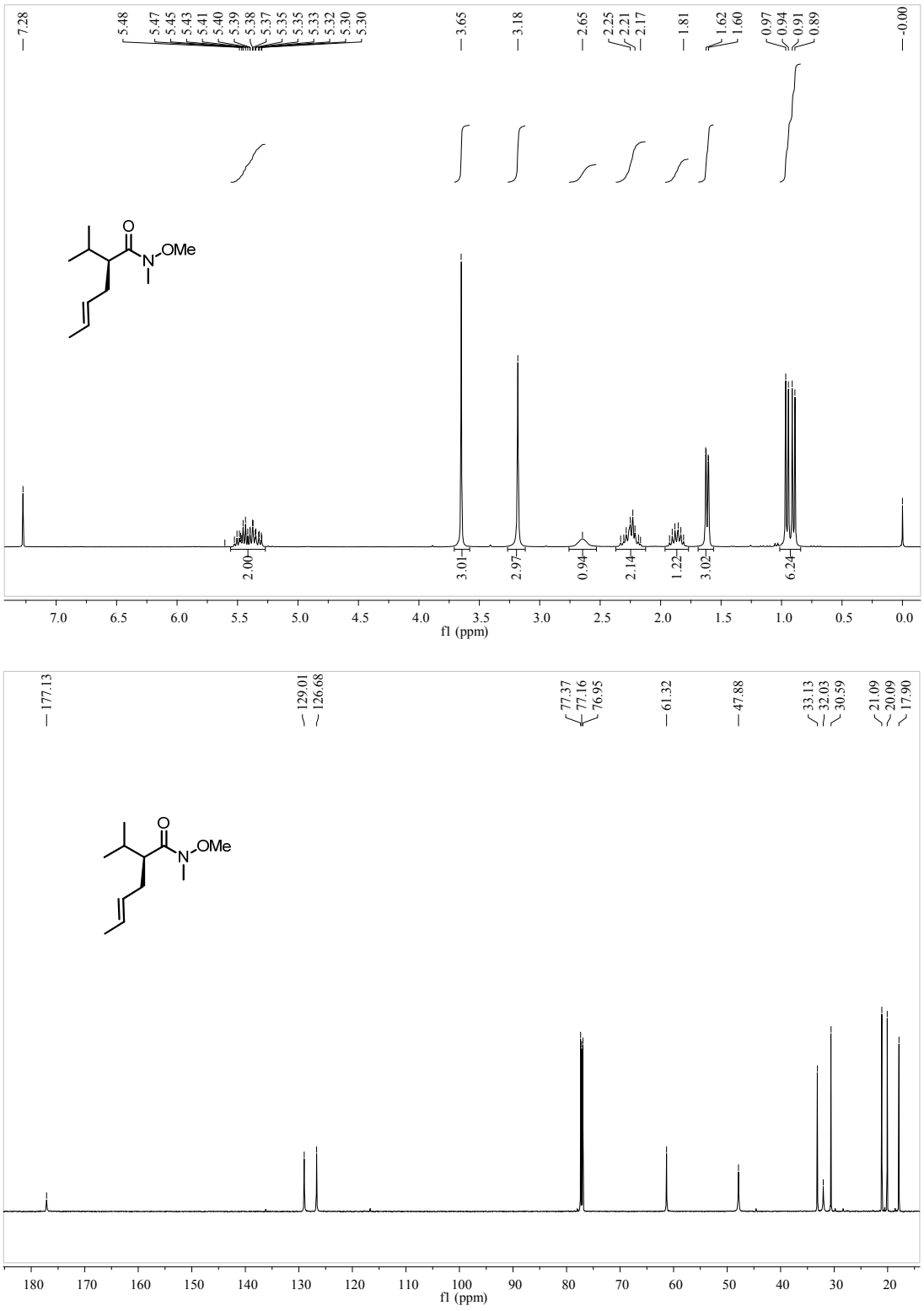


Figure S13. ^{1}H- (upper) and ^{13}C-NMR (lower) spectra of compound **13b**

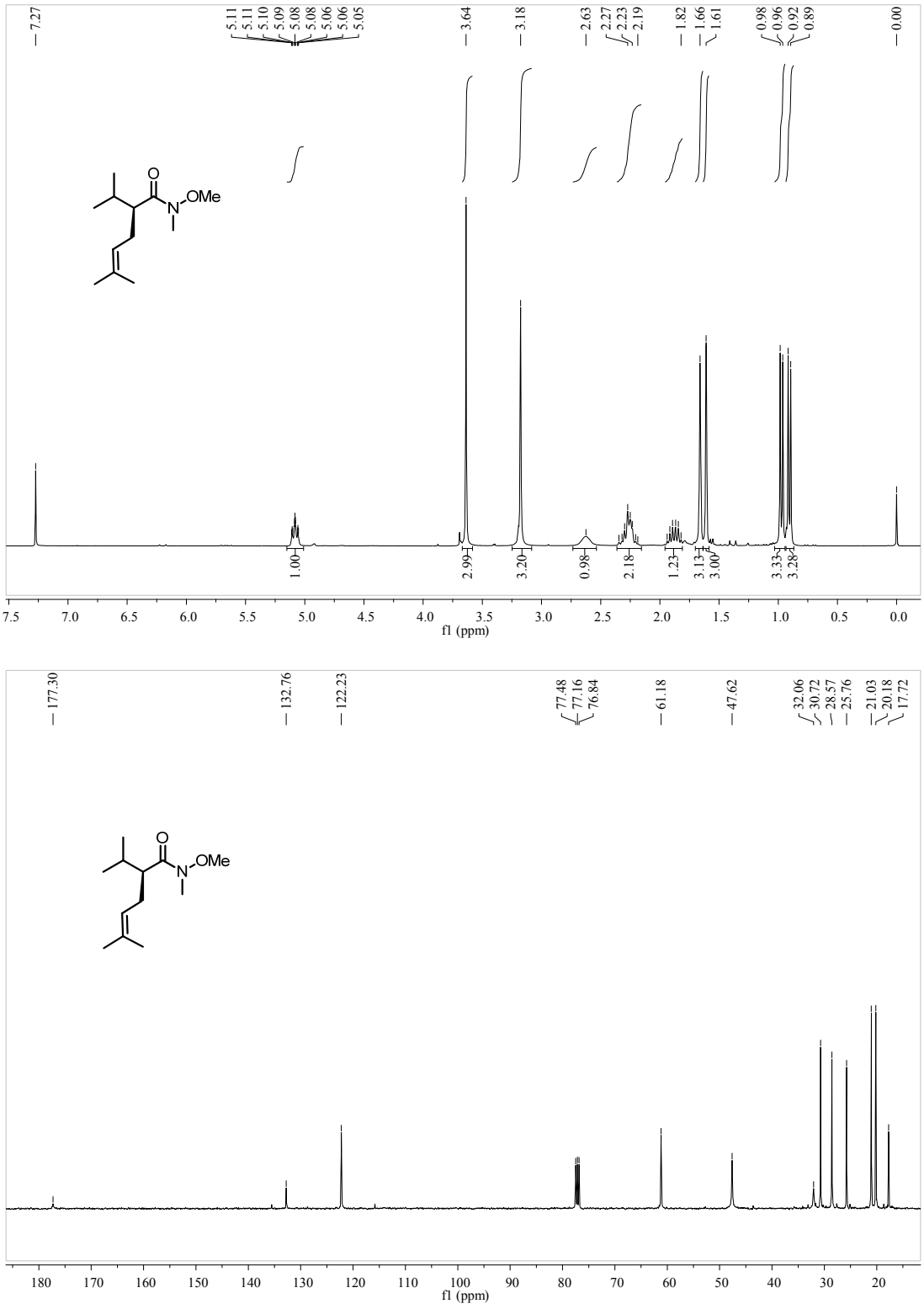


Figure S14. ^{1}H- (upper) and ^{13}C-NMR (lower) spectra of compound **13c**

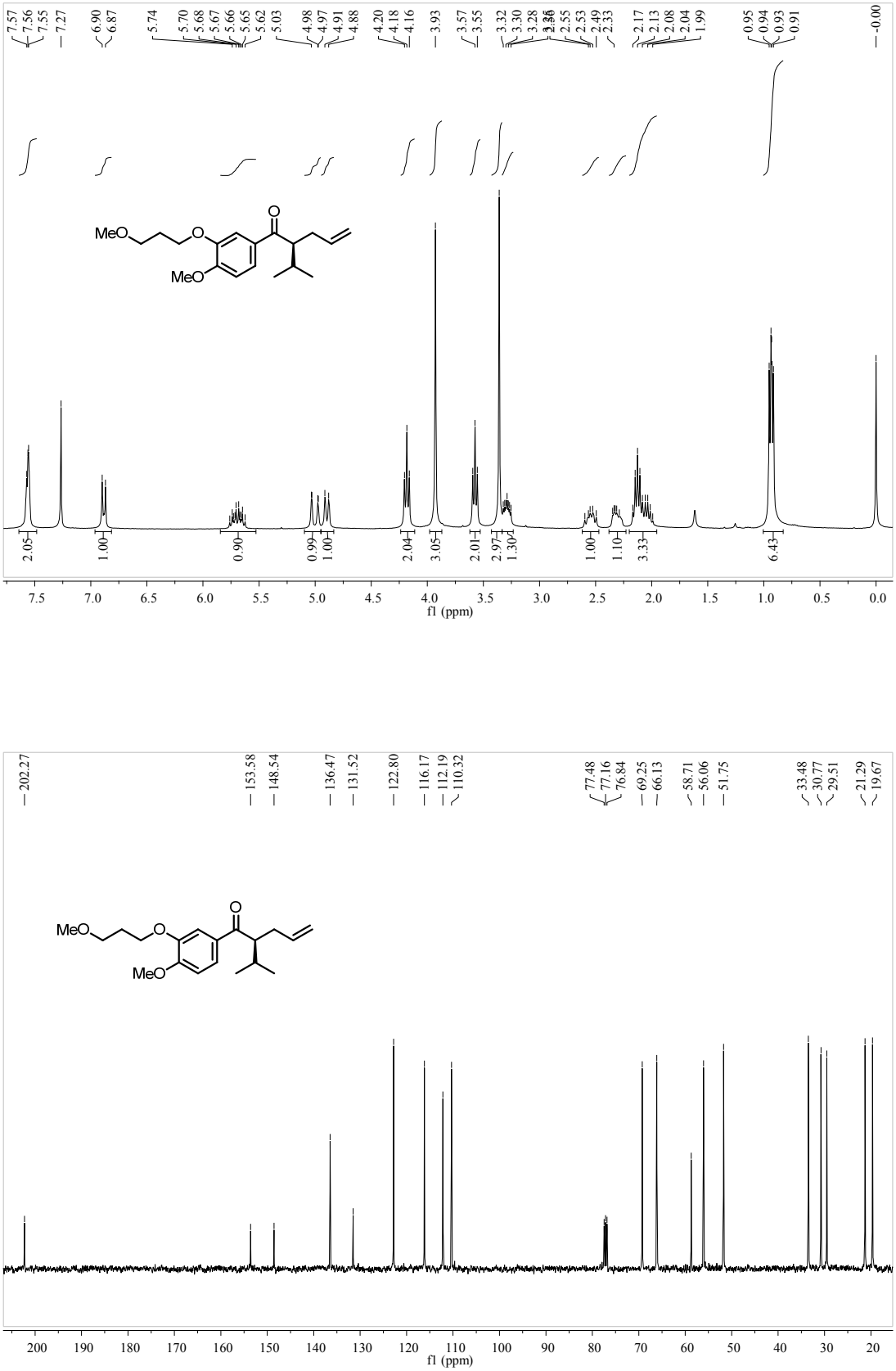


Figure S15. ^{1}H- (upper) and ^{13}C-NMR (lower) spectra of compound **15a**

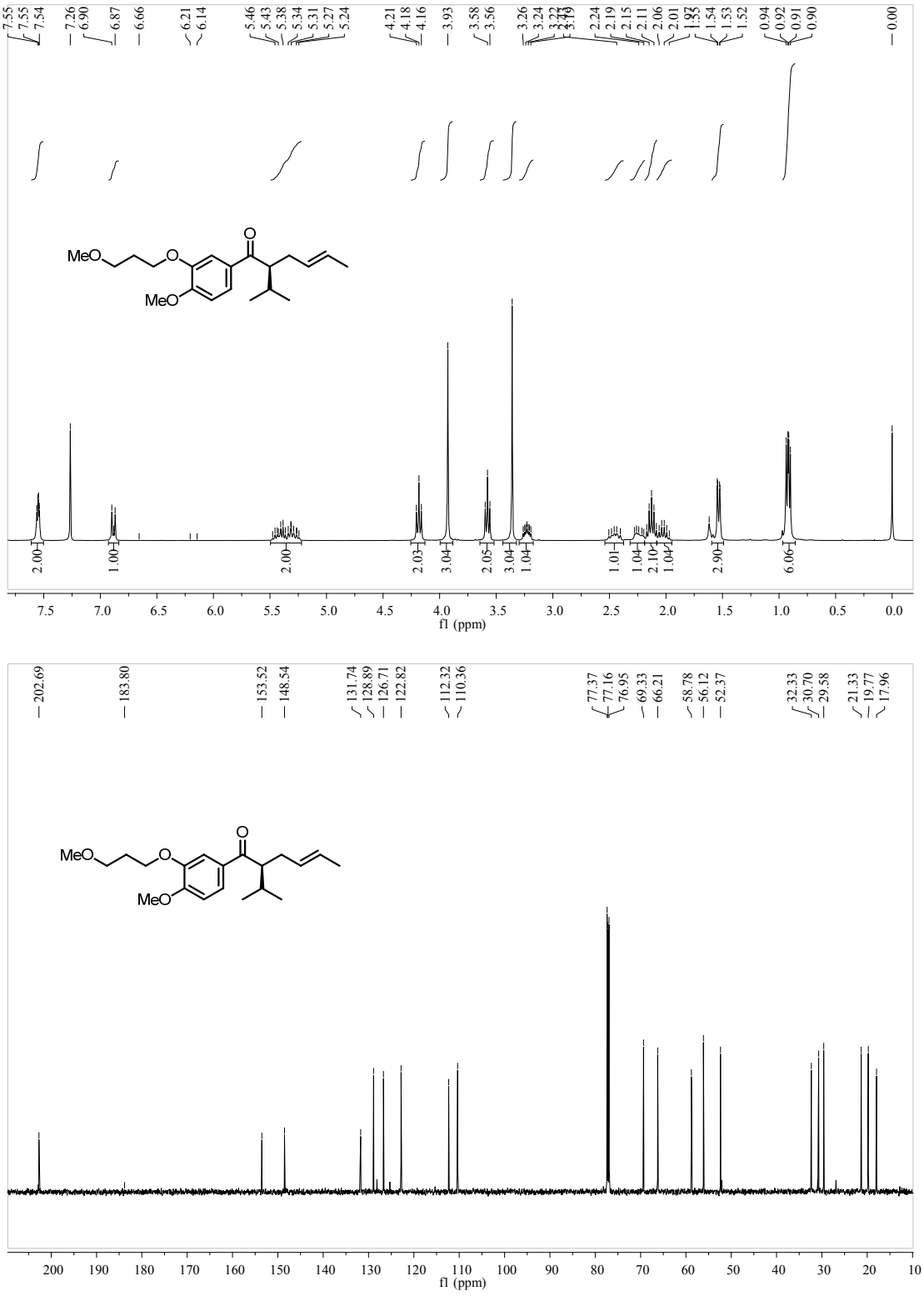


Figure S16. ^{1}H- (upper) and ^{13}C-NMR (lower) spectra of compound **15b**

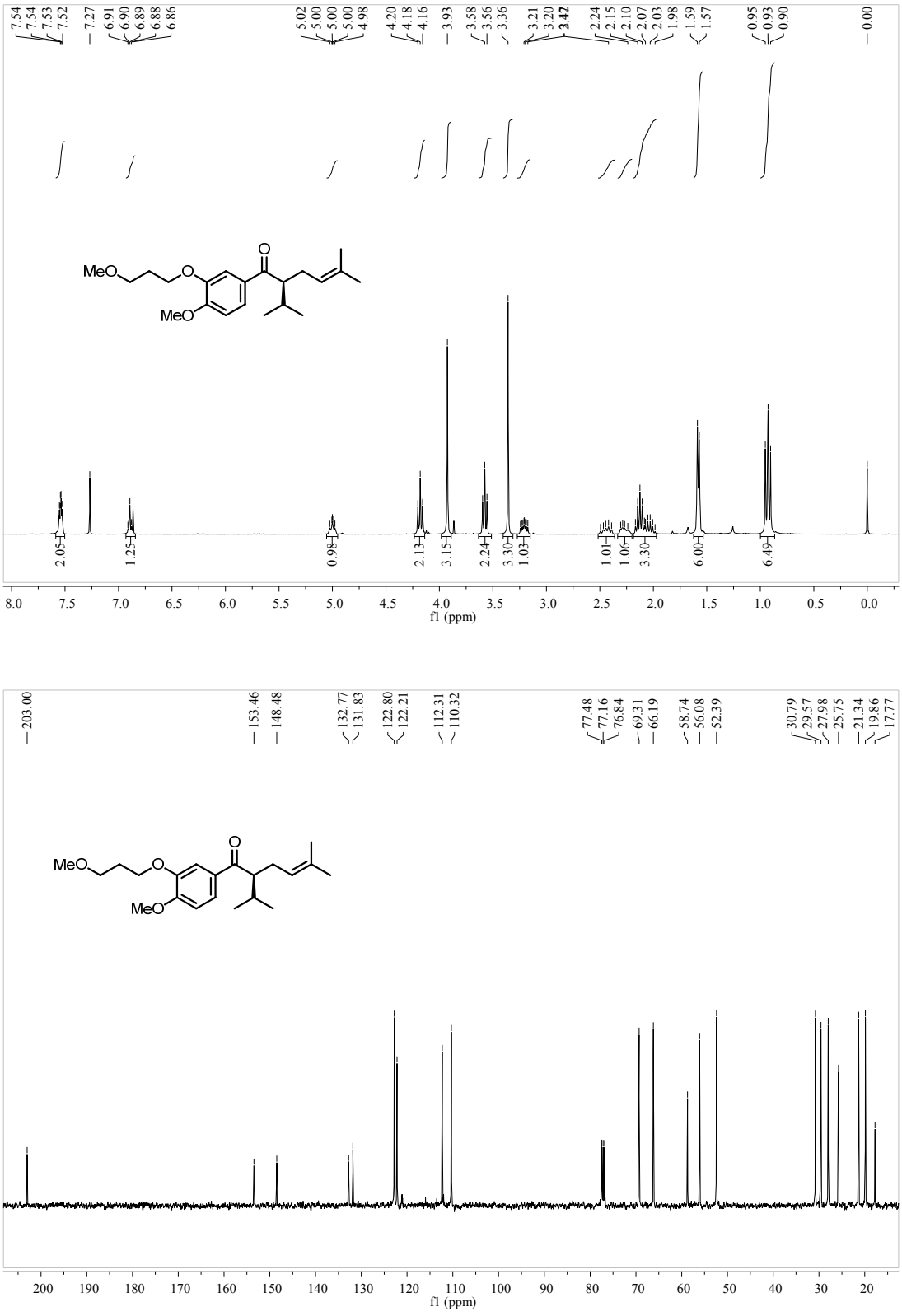


Figure S17. ^{1}H- (upper) and ^{13}C-NMR (lower) spectra of compound **15c**

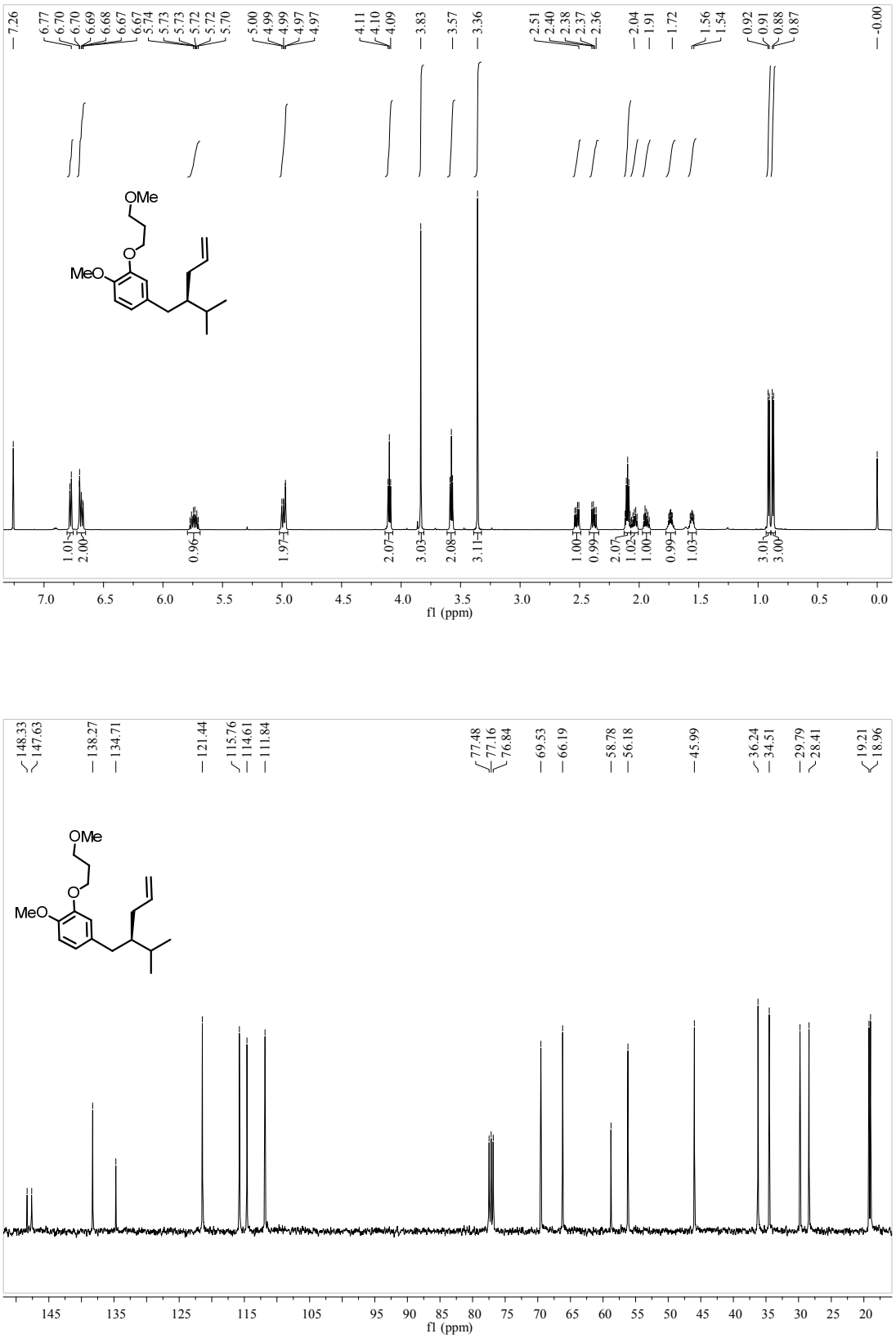
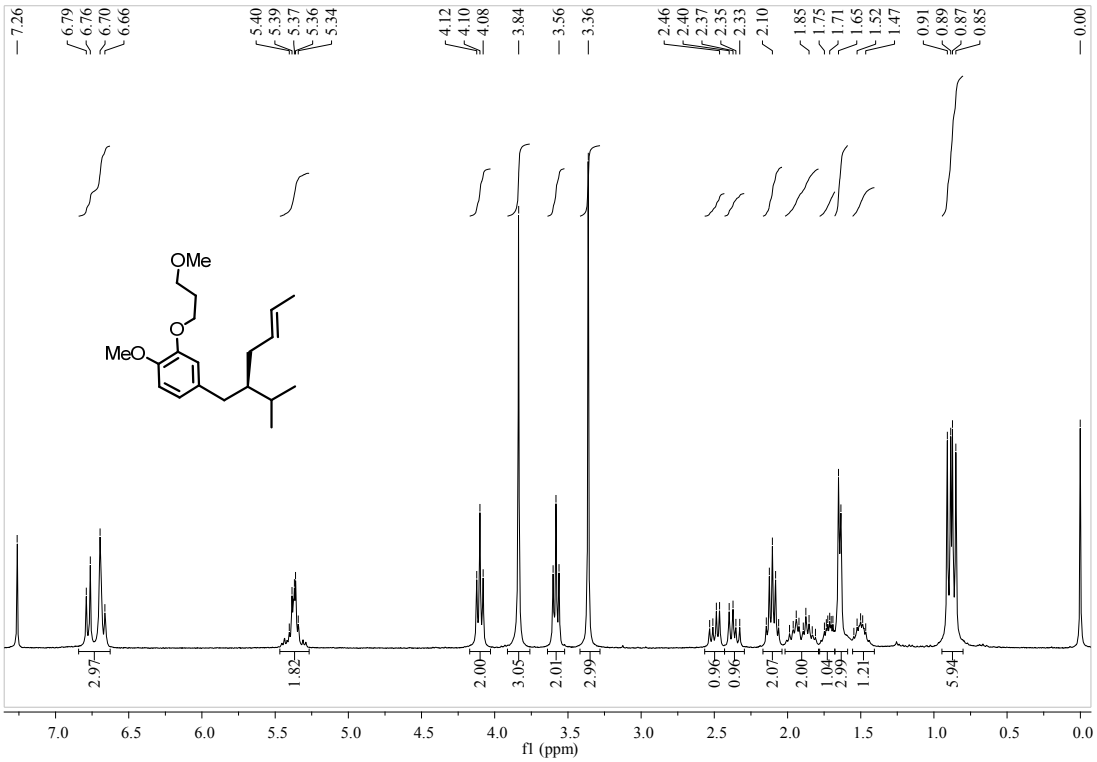


Figure S18. ^{1}H- (upper) and ^{13}C-NMR (lower) spectra of compound **16a**



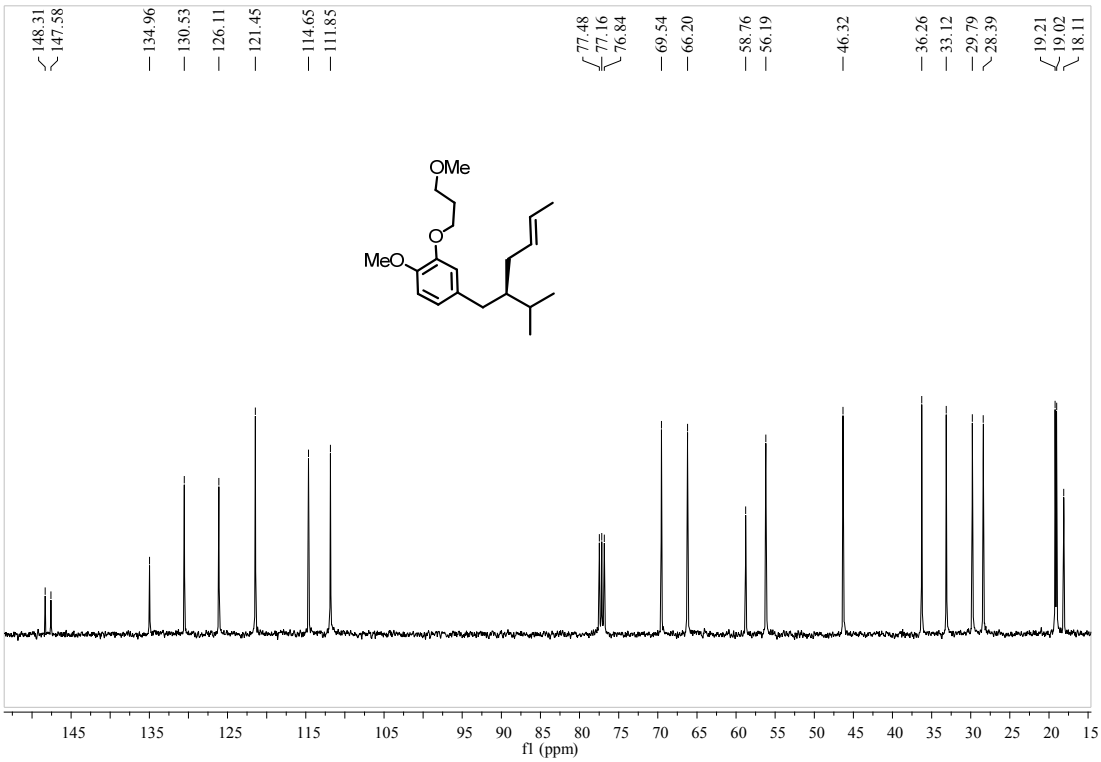


Figure S19. ^{1}H- (upper) and ^{13}C-NMR (lower) spectra of compound **16b**

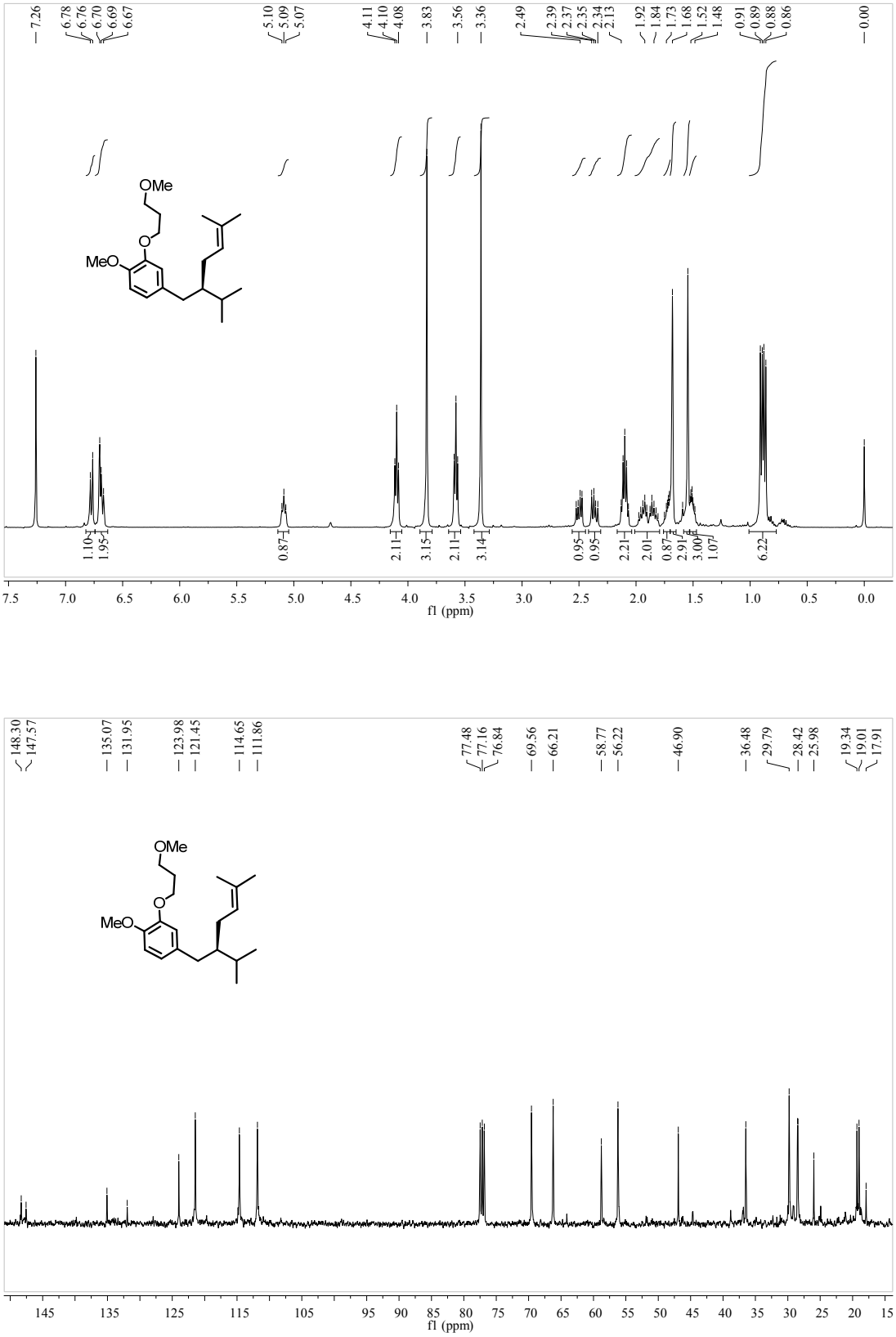


Figure S20. ^{1}H- (upper) and ^{13}C-NMR (lower) spectra of compound **16c**

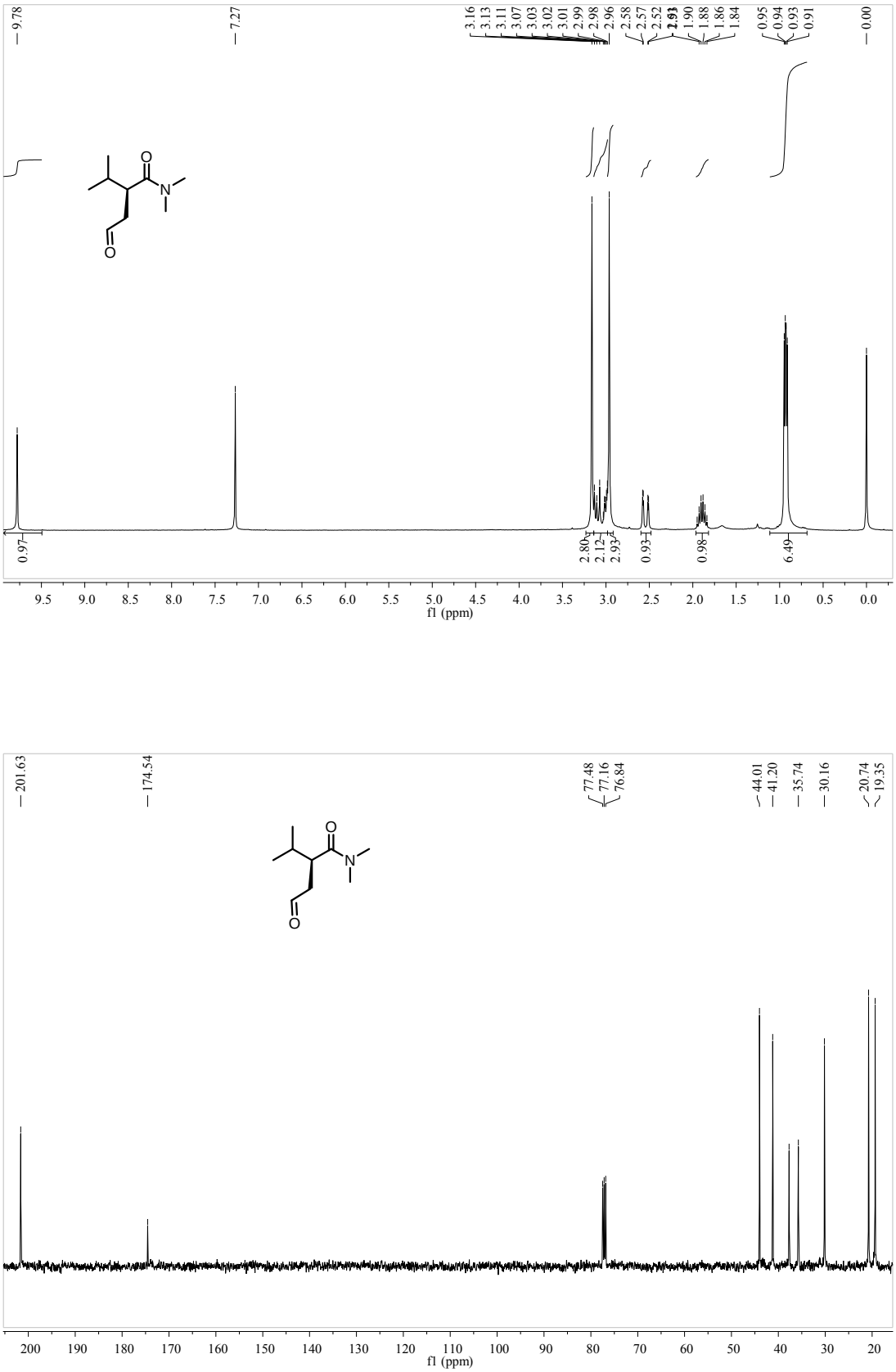
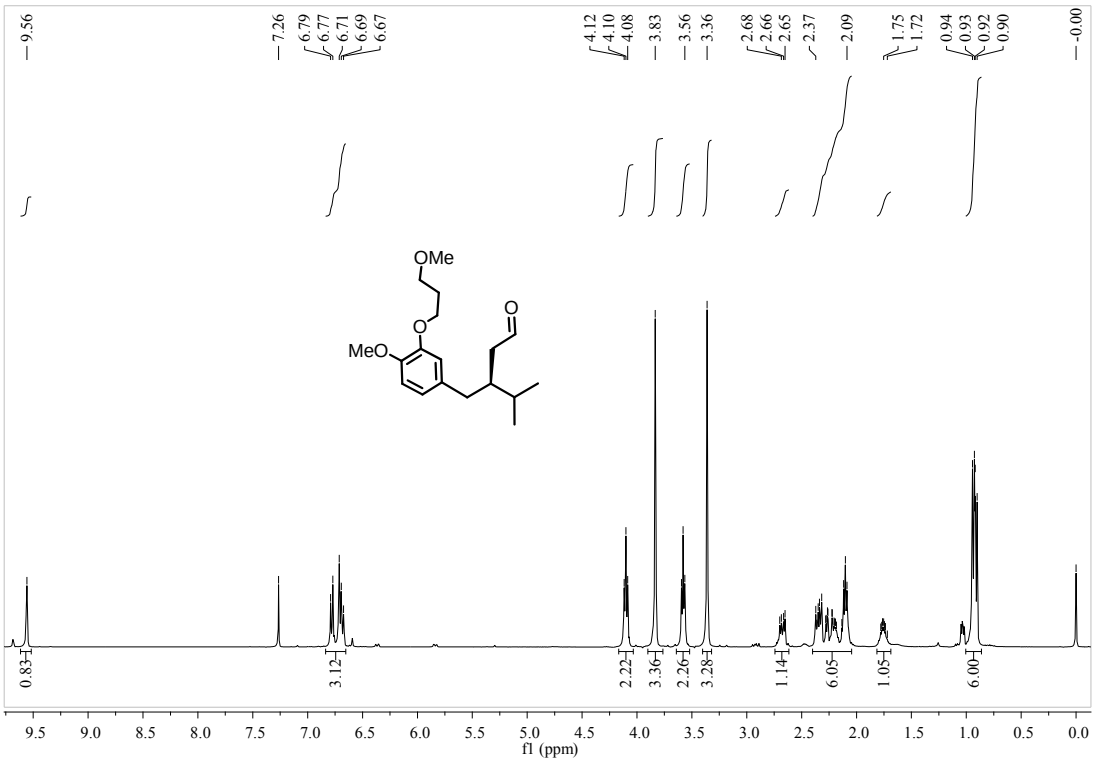


Figure S21. ^{1}H- (upper) and ^{13}C-NMR (lower) spectra of compound **18**



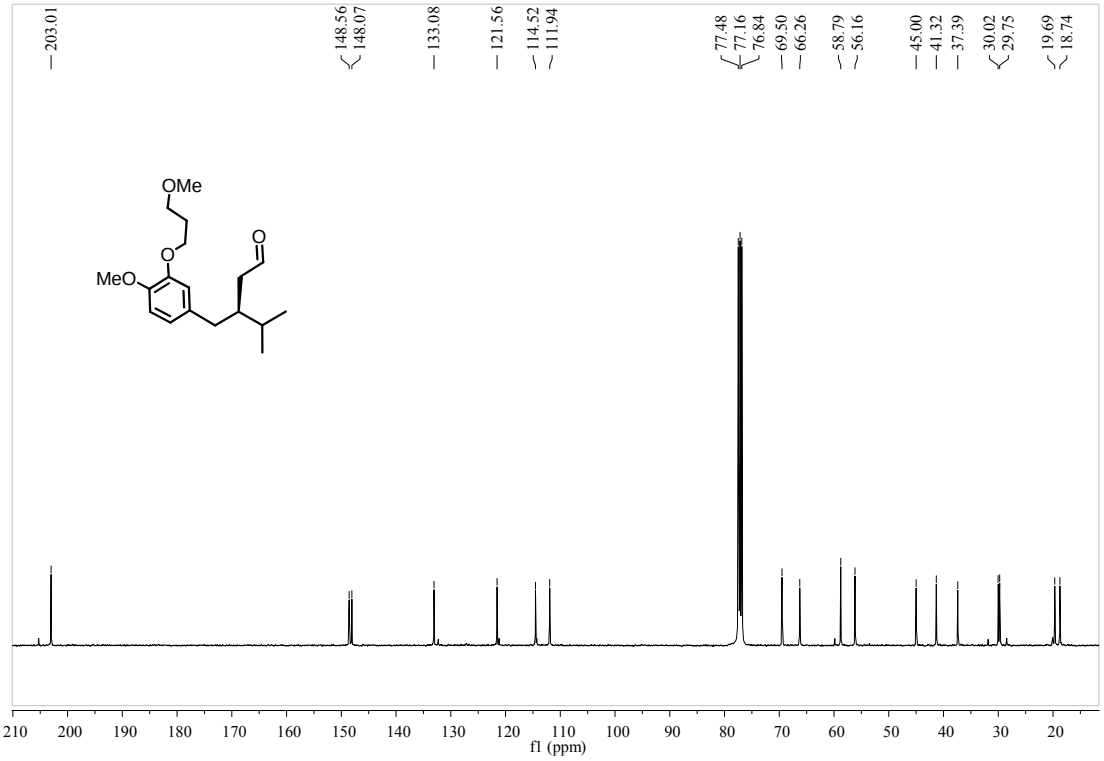
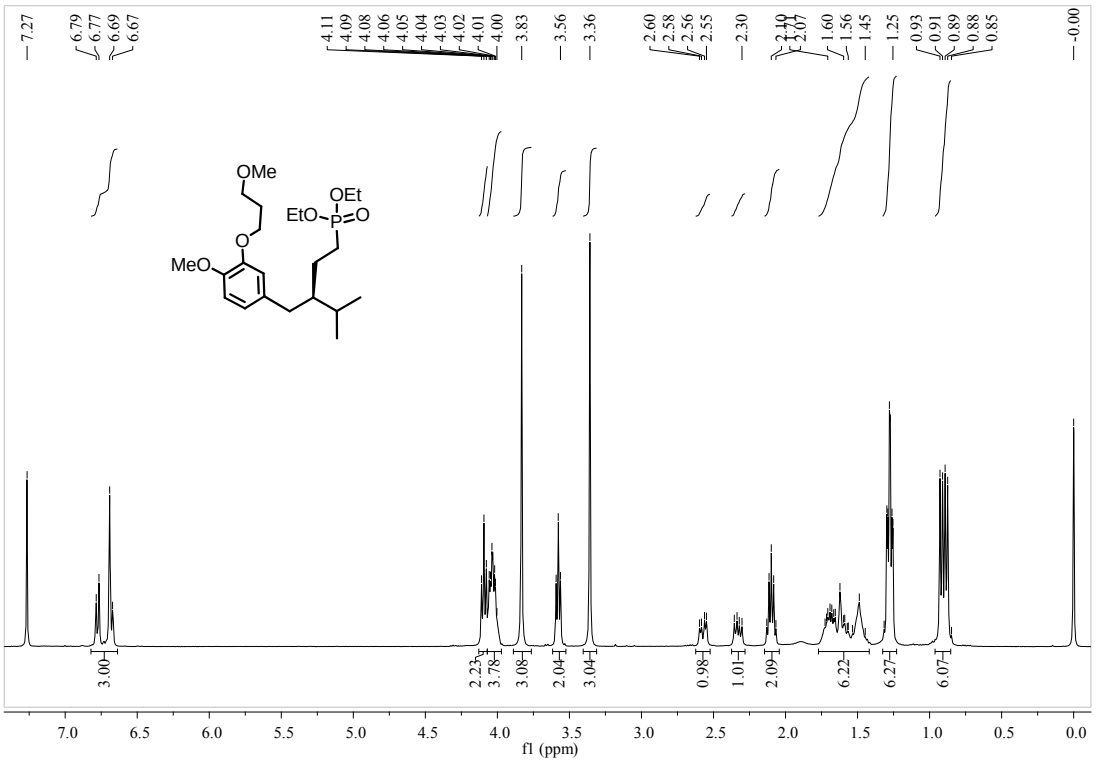
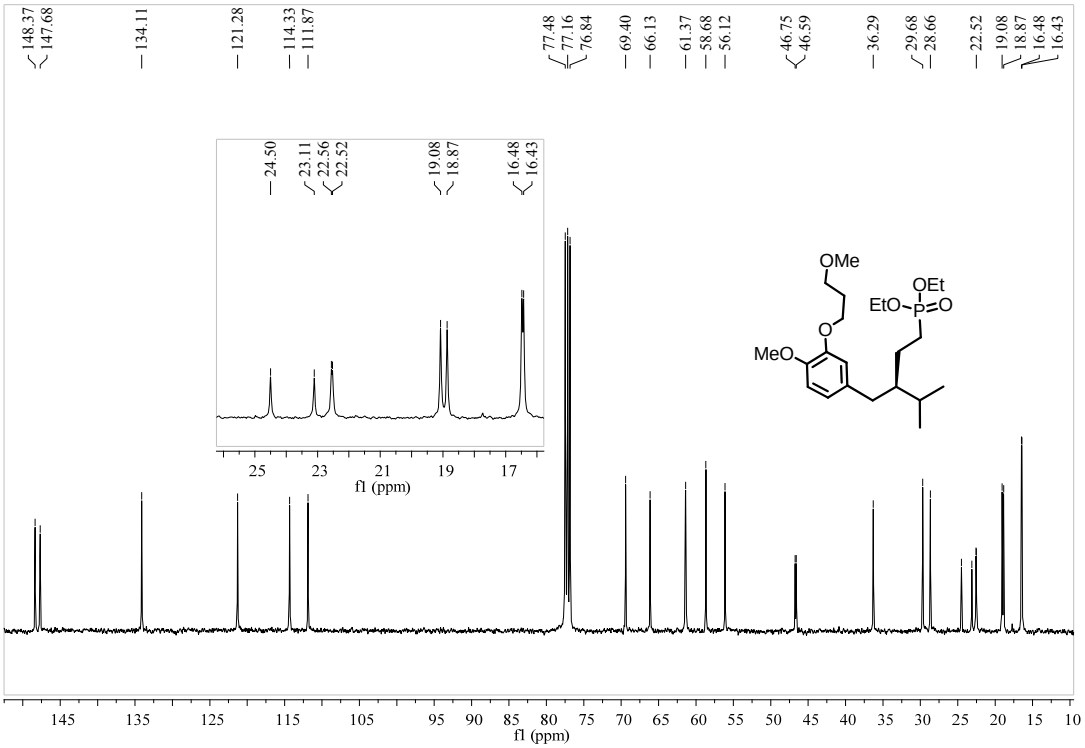


Figure S22. ^{1}H- (upper) and ^{13}C-NMR (lower) spectra of compound **19**


7.27
6.79
6.77
6.69
6.67
4.11
4.09
4.08
4.06
4.05
4.04
4.03
4.02
4.01
4.00
3.83
3.56
3.36
2.60
2.58
2.56
2.55
2.30
2.10
2.07
1.60
1.56
1.45
1.25
0.93
0.91
0.89
0.88
0.85
-0.00
OMe
OEt
EtO
P
O
MeO
3.00
2.23
3.78
3.08
2.04
3.04
0.98
1.01
2.09
6.22
6.27
6.07
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


148.37
147.68
134.11
121.28
114.33
111.87
77.48
77.16
76.84
69.40
66.13
61.37
58.68
56.12
46.75
46.59
36.29
29.68
28.66
22.52
19.08
18.87
16.48
16.43
24.50
23.11
22.56
22.52
19.08
18.87
16.48
16.43
25
23
21
19
17
f1 (ppm)
OMe
OEt
EtO
P
O
MeO
145
135
125
115
105
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
10
f1 (ppm)

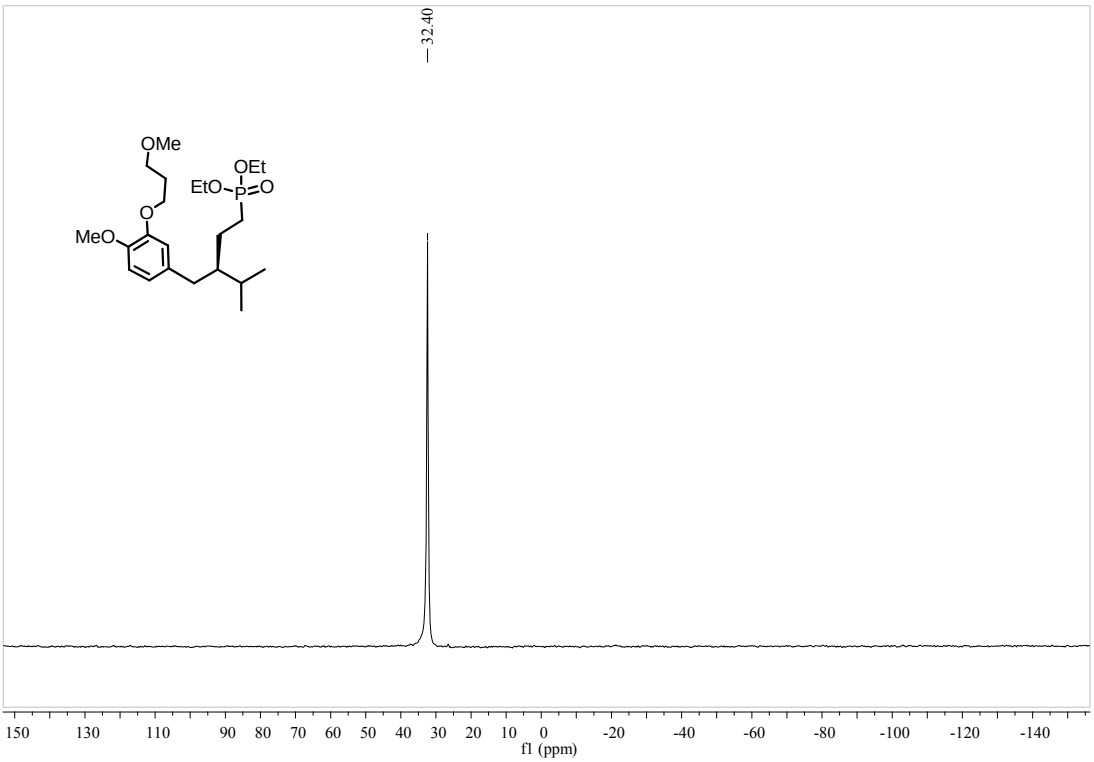


Figure S23. ^{1}H- (upper), ^{13}C- (mid) and ^{31}P-NMR (bottom) of **22**

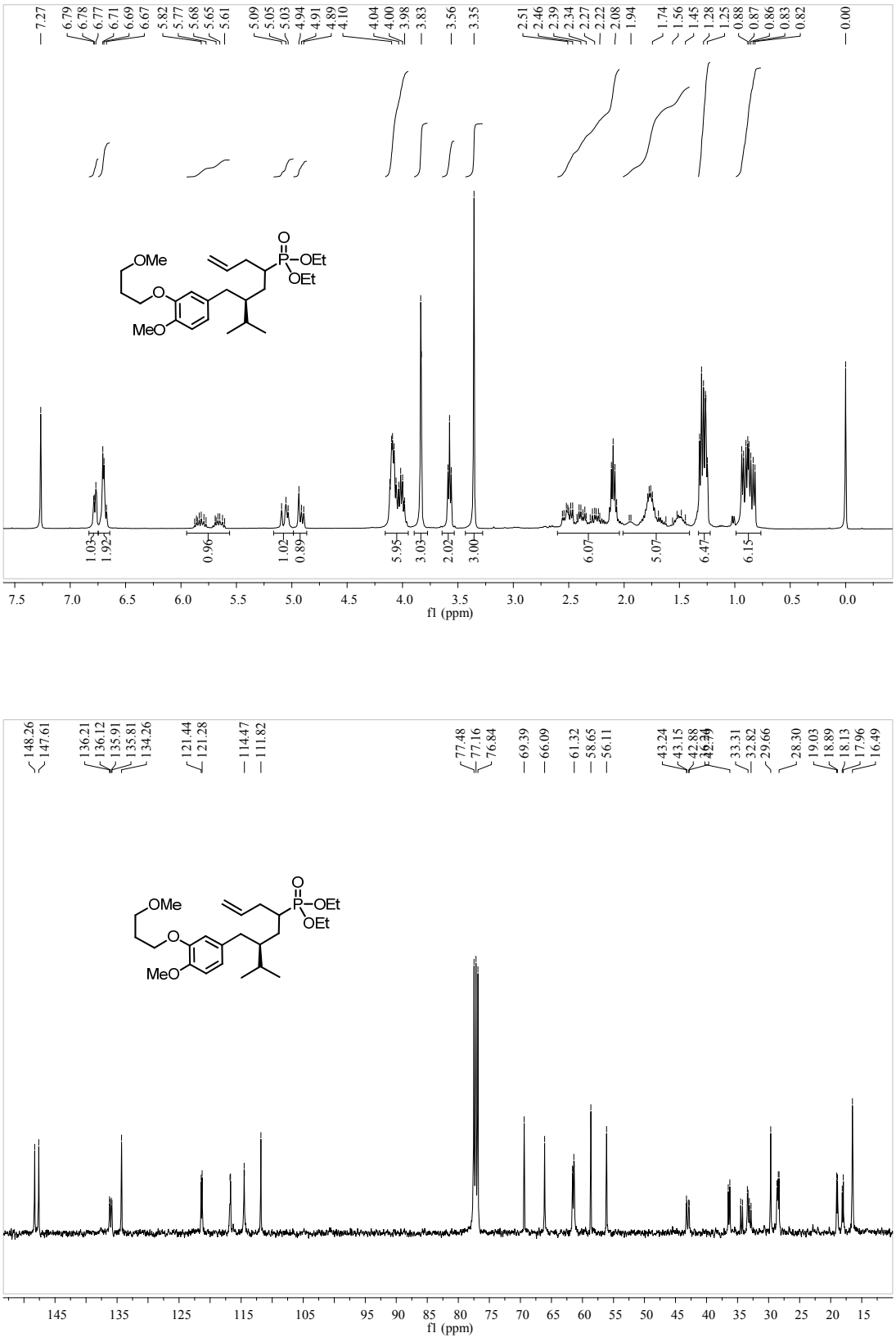


Figure S24. ^{1}H- (upper) and ^{13}C-NMR (lower) spectra of compound **24**

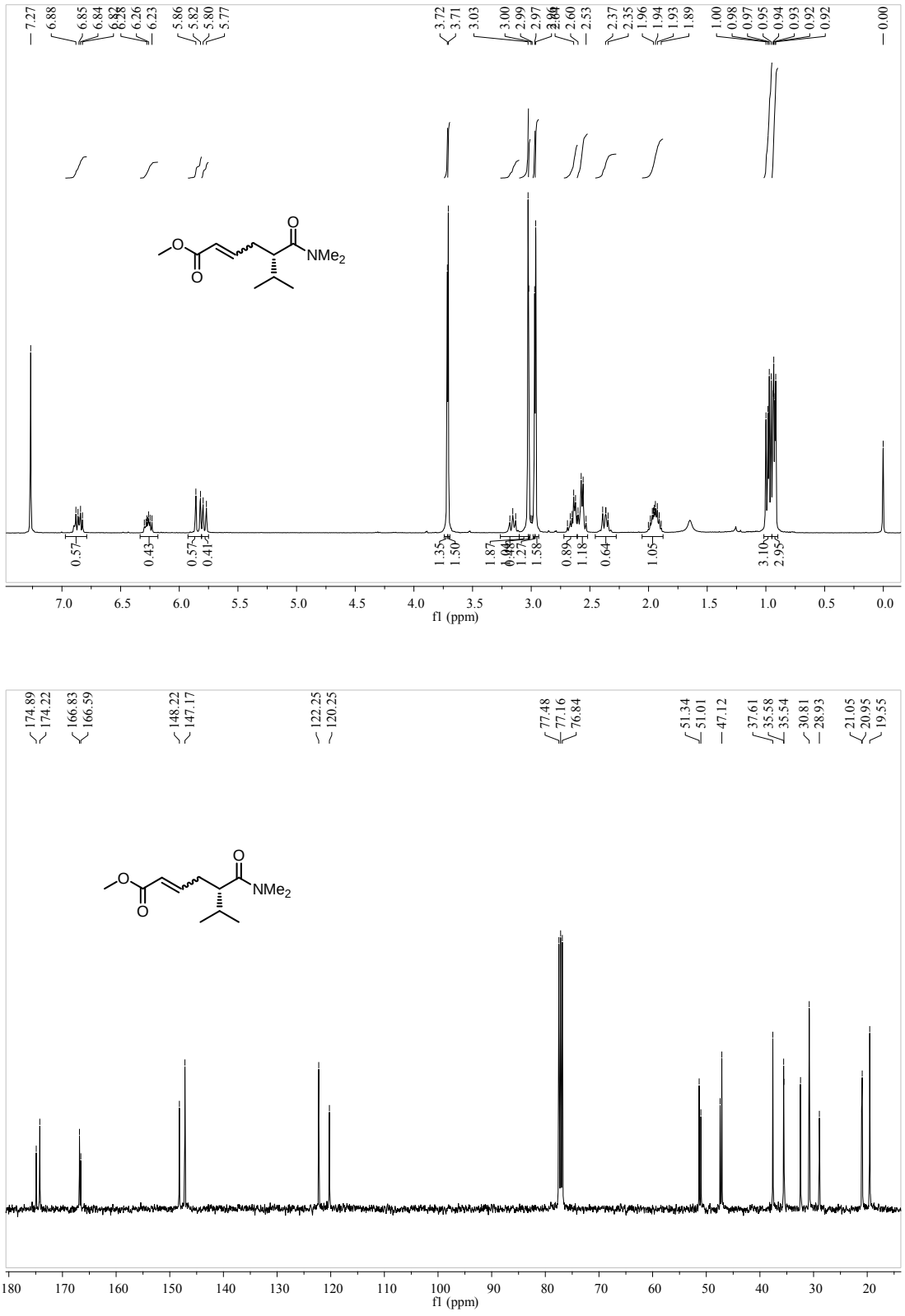


Figure S25. ^{1}H- (upper) and ^{13}C-NMR (lower) spectra of compound **26**

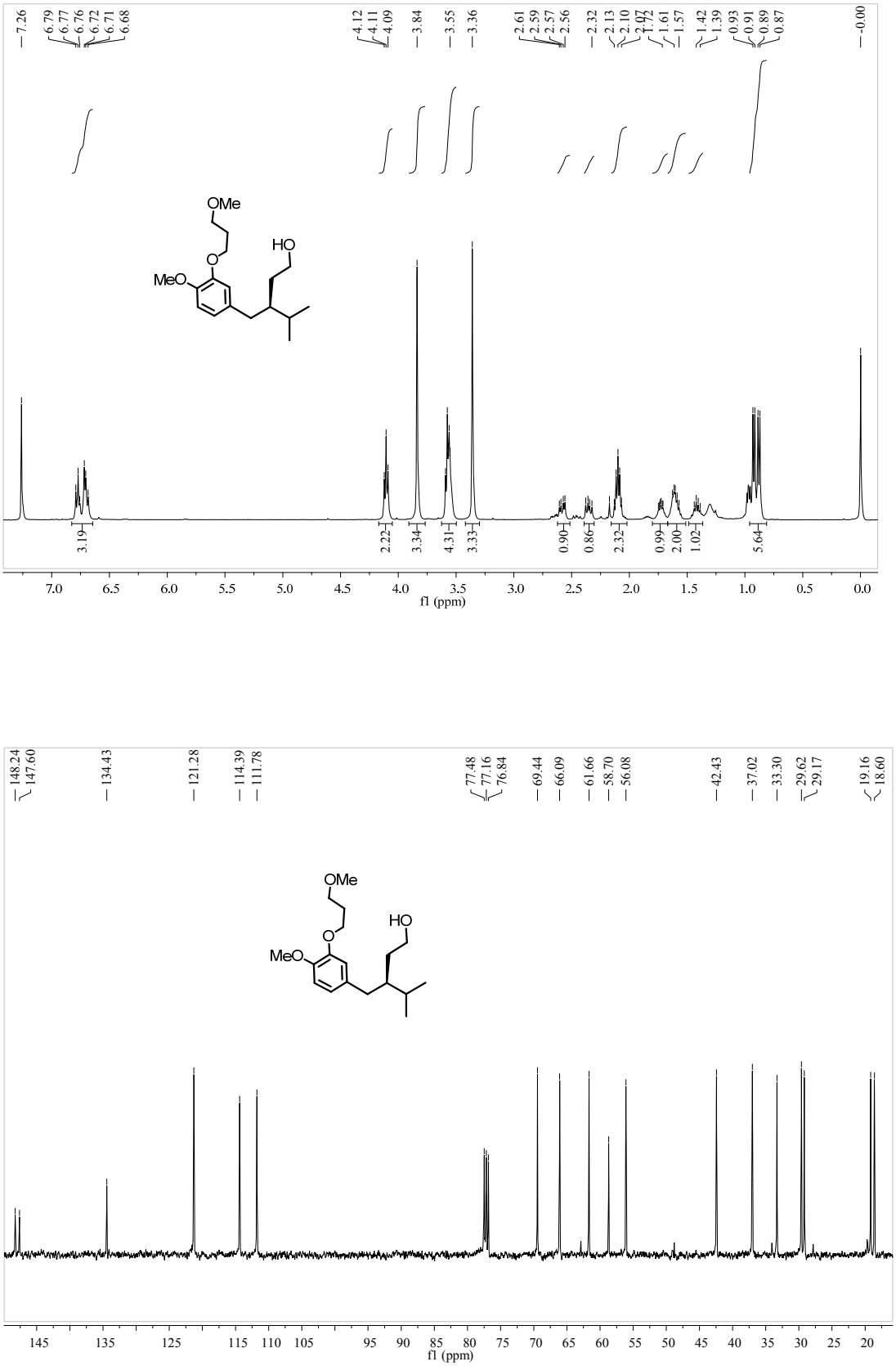
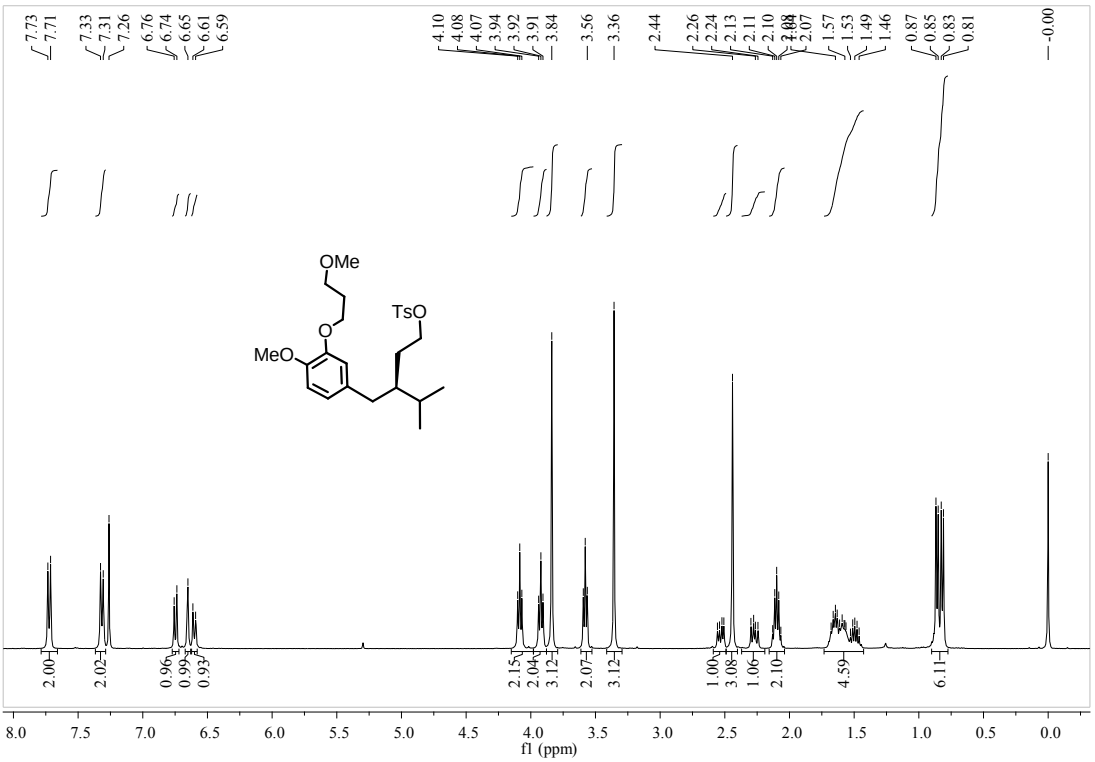


Figure S26. ^{1}H- (upper) and ^{13}C-NMR (lower) spectra of compound **27**



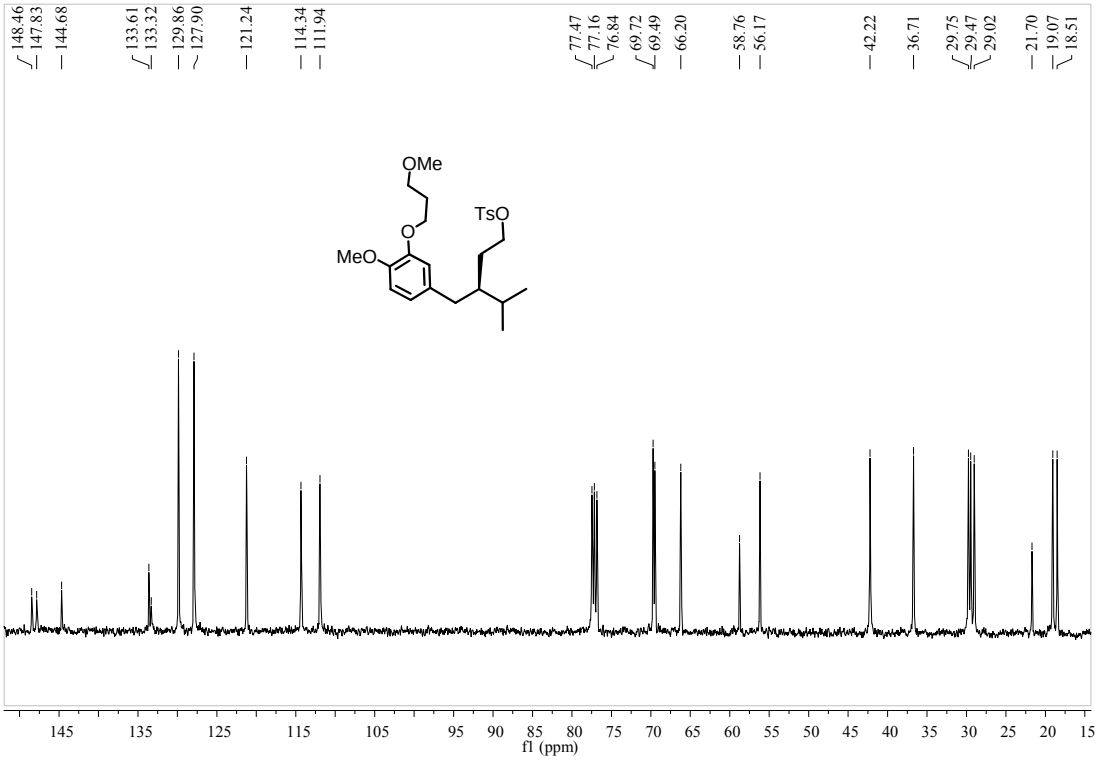


Figure S27. ^{1}H- (upper) and ^{13}C-NMR (lower) spectra of compound **28**

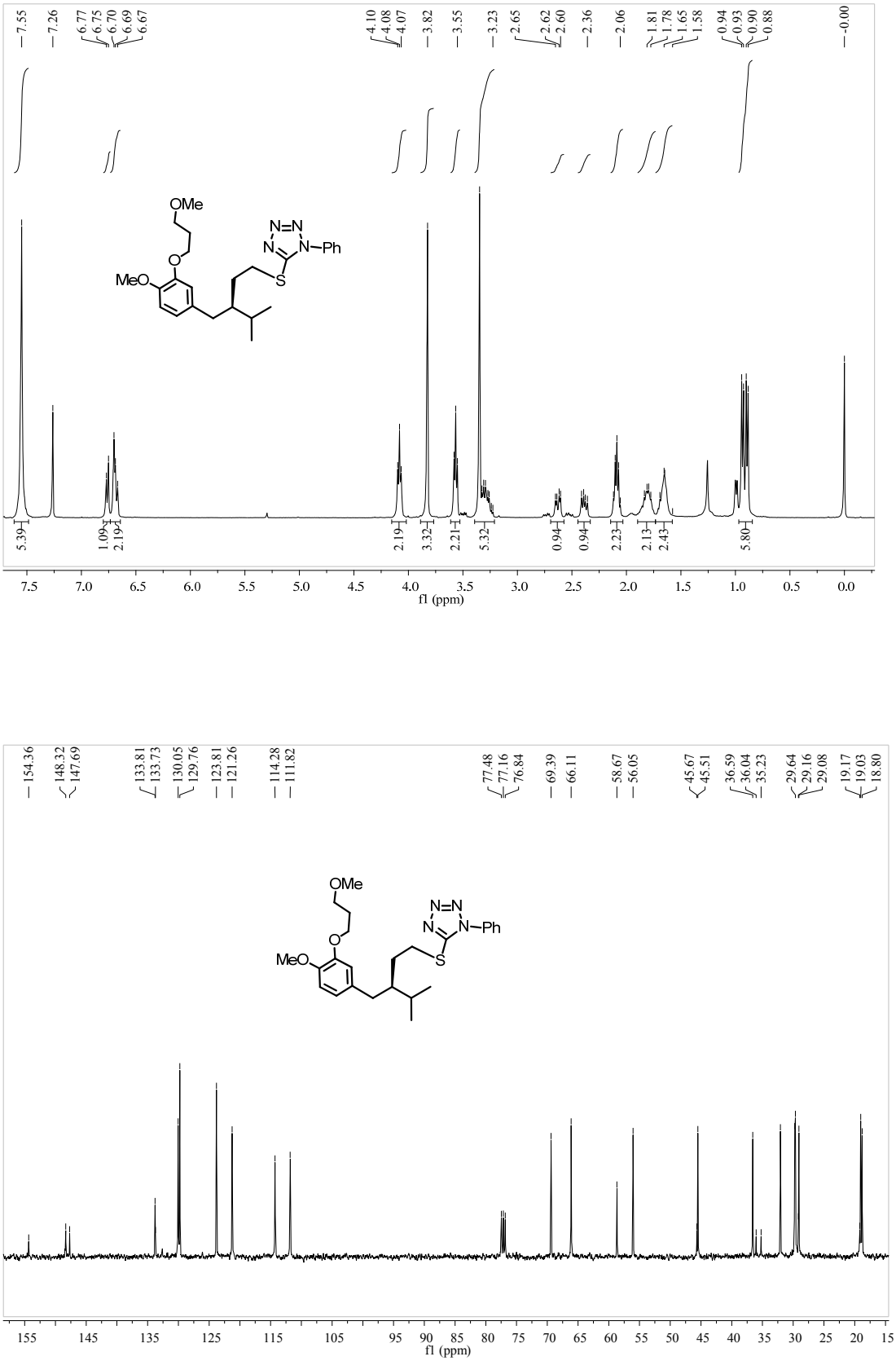


Figure S28. ^{1}H- (upper) and ^{13}C-NMR (lower) spectra of compound **30a**

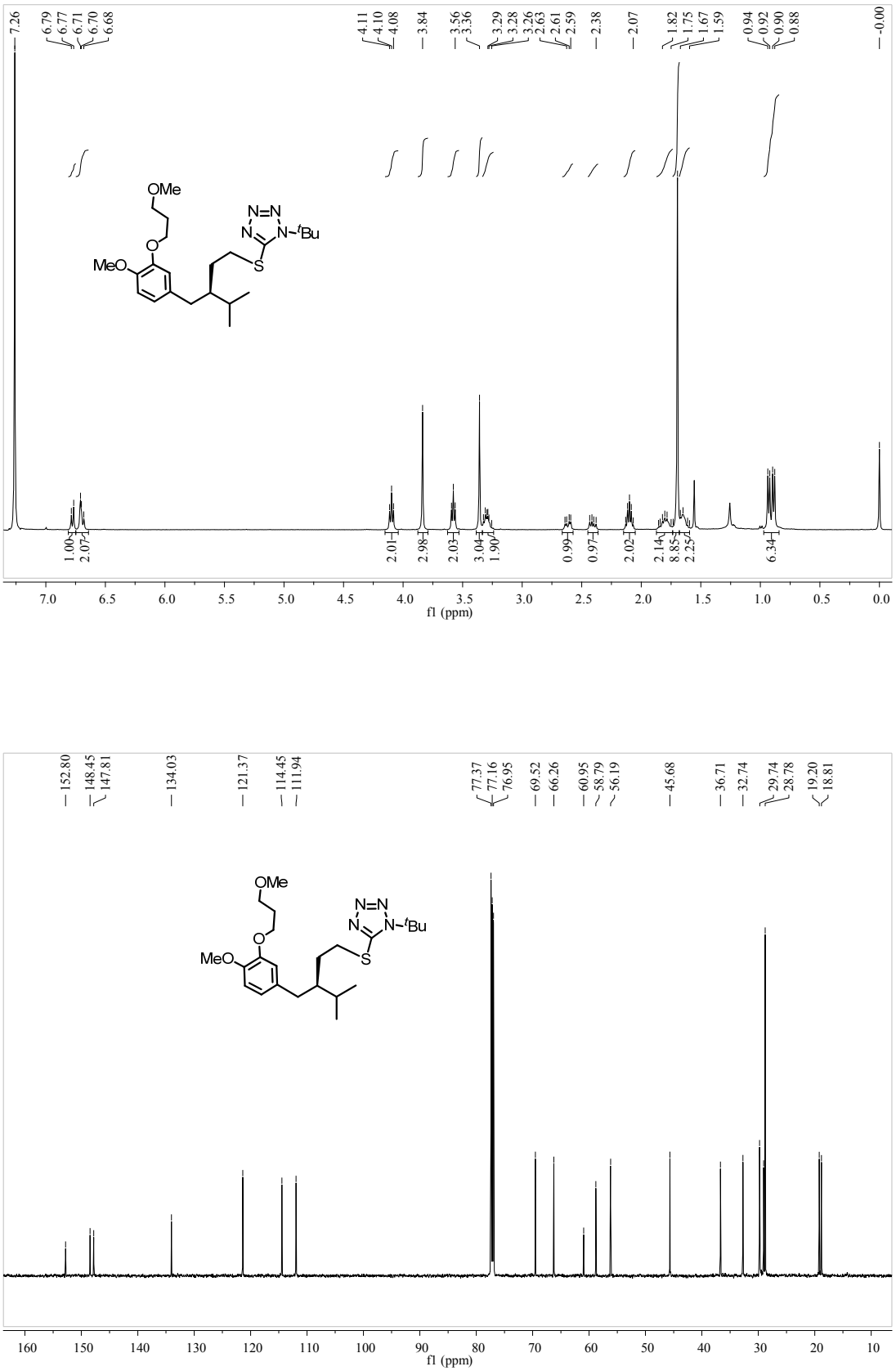
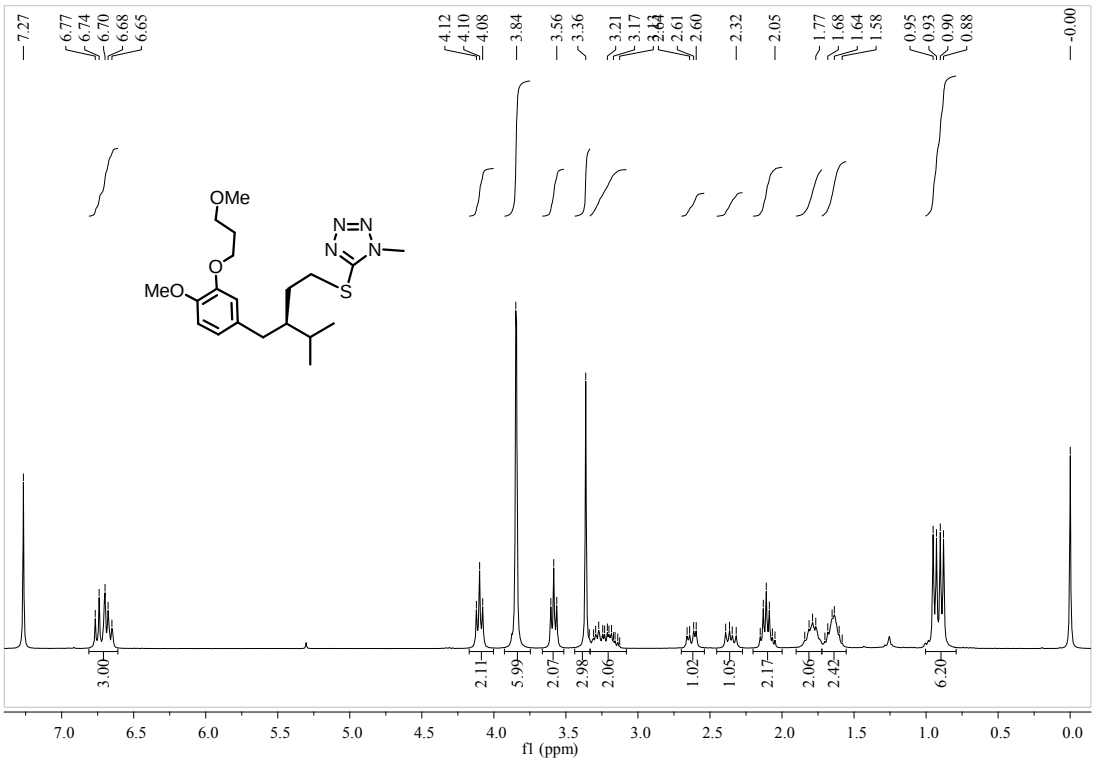


Figure S29. ^{1}H- (upper) and ^{13}C-NMR (lower) spectra of compound **30b**



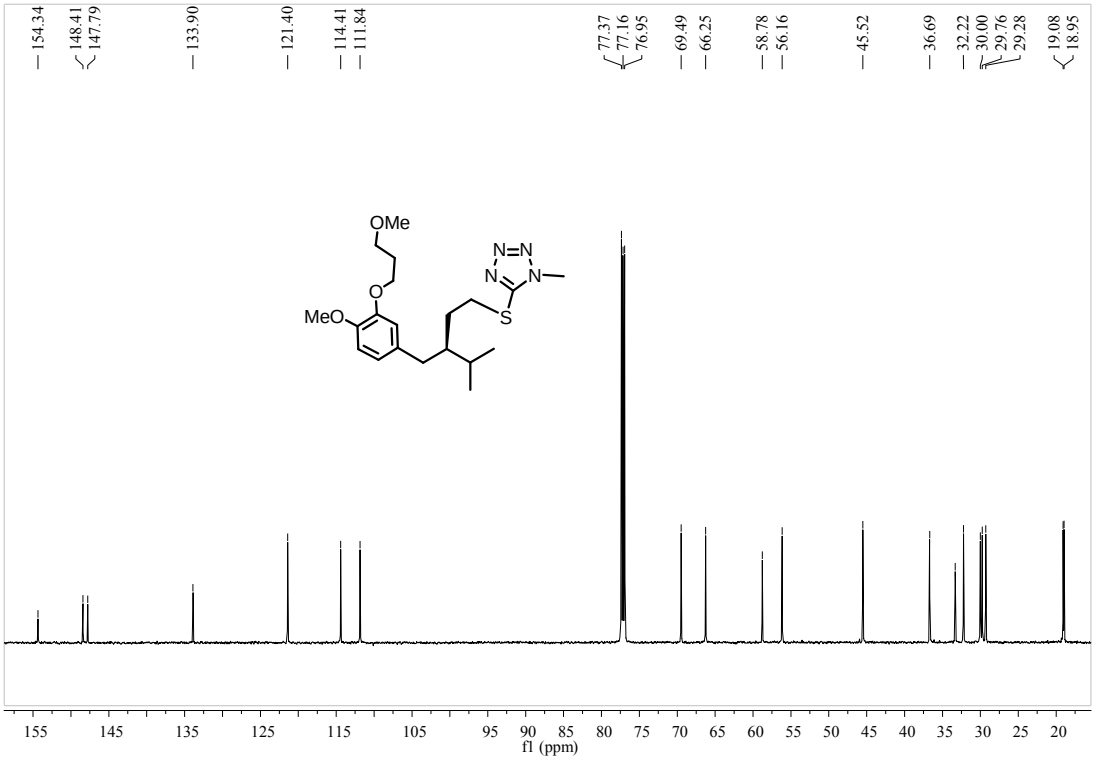


Figure S30. ^{1}H- (upper) and ^{13}C-NMR (lower) spectra of compound **30c**

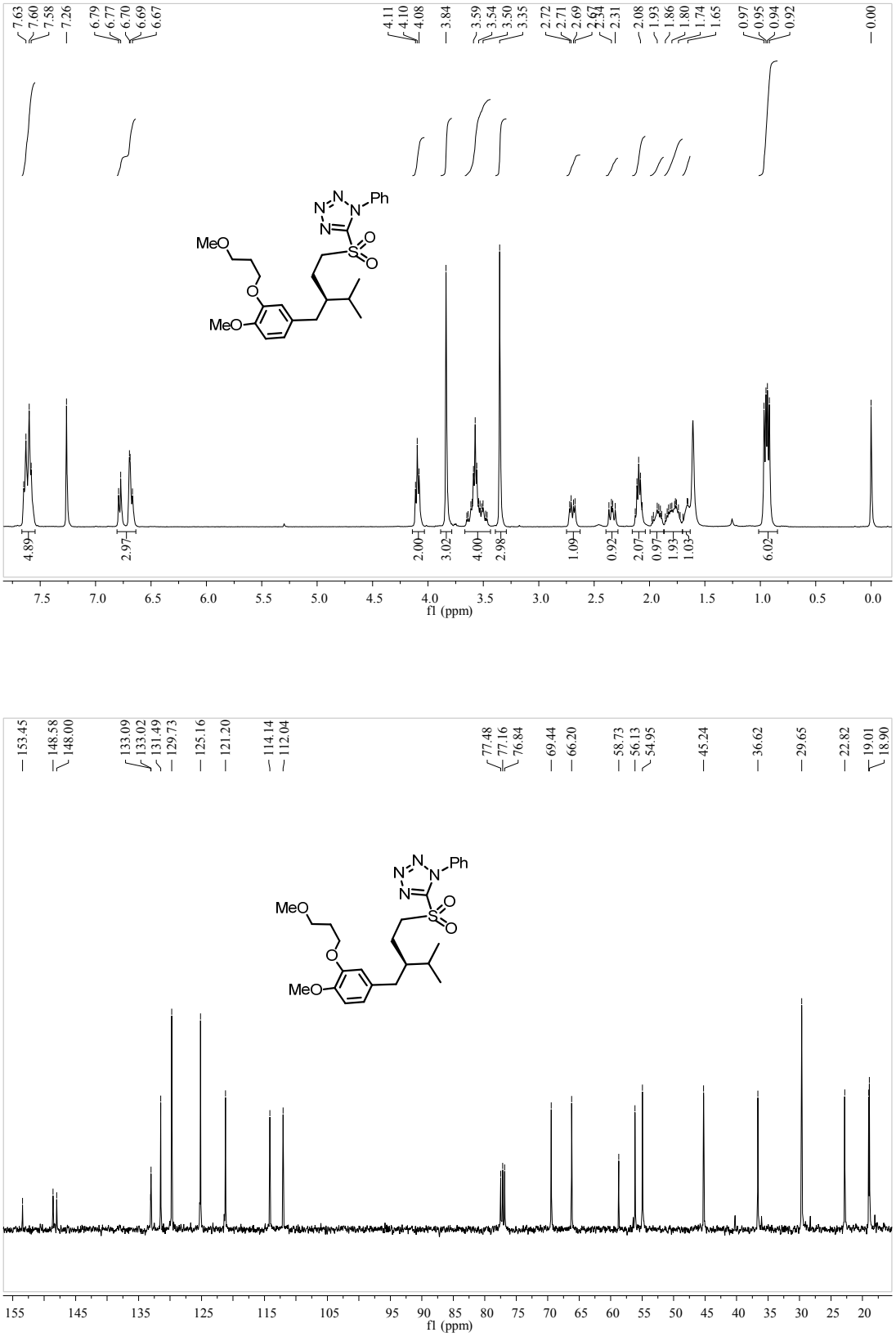


Figure S31. ^{1}H- (upper) and ^{13}C-NMR (lower) spectra of compound **31a**

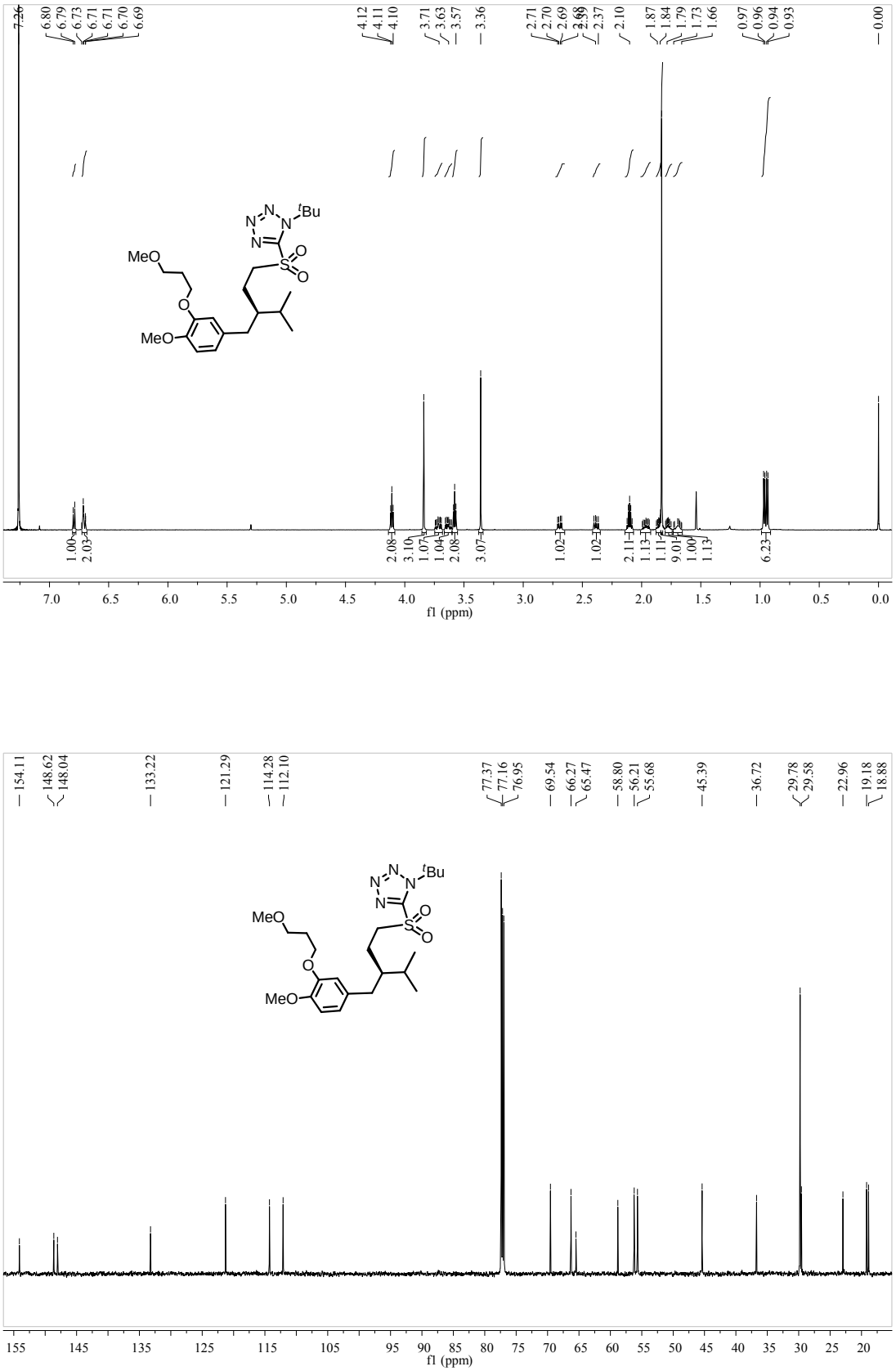


Figure S32. ^{1}H- (upper) and ^{13}C-NMR (lower) spectra of compound **31b**

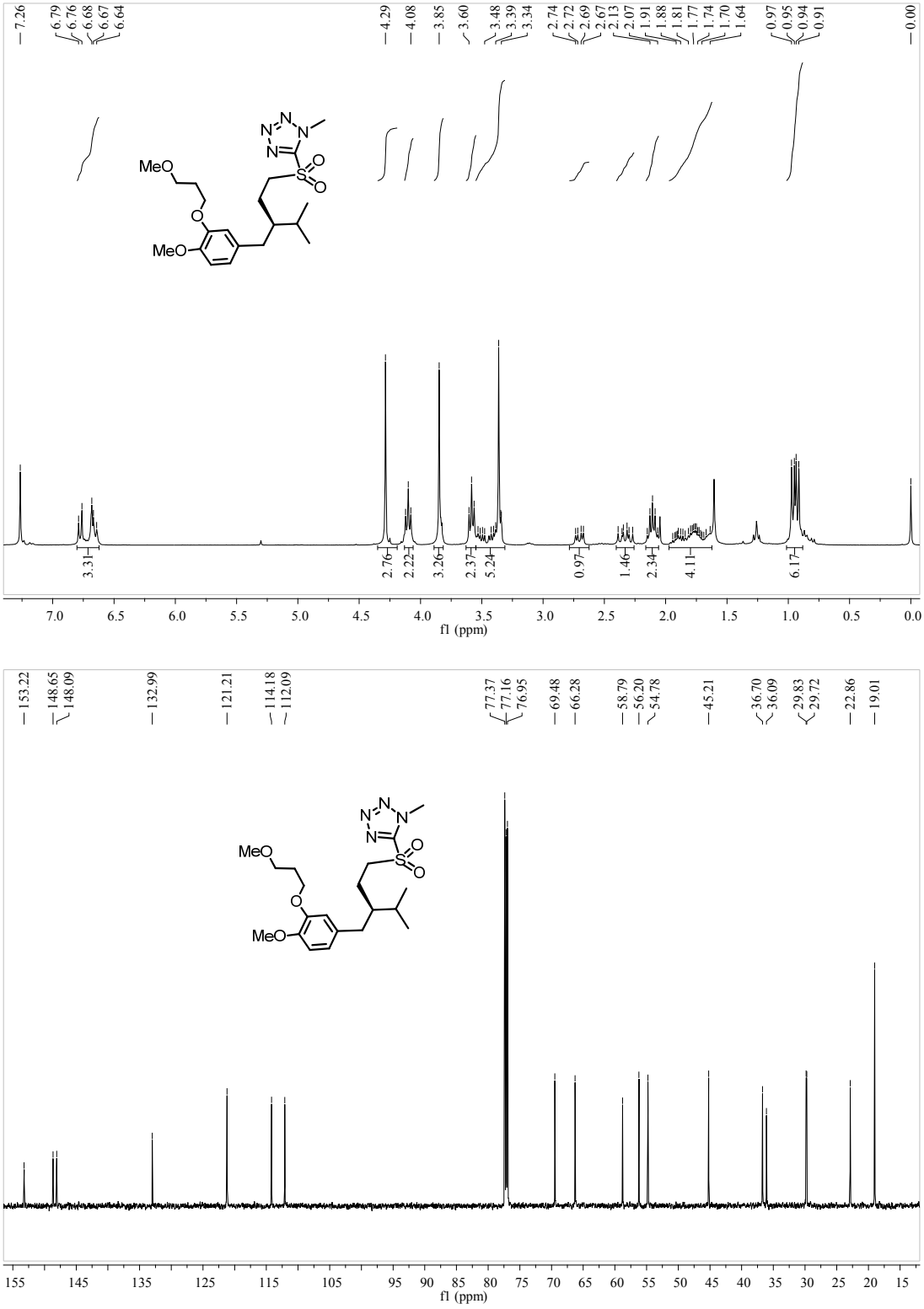


Figure S33. ^{1}H- (upper) and ^{13}C-NMR (lower) spectra of compound **31c**

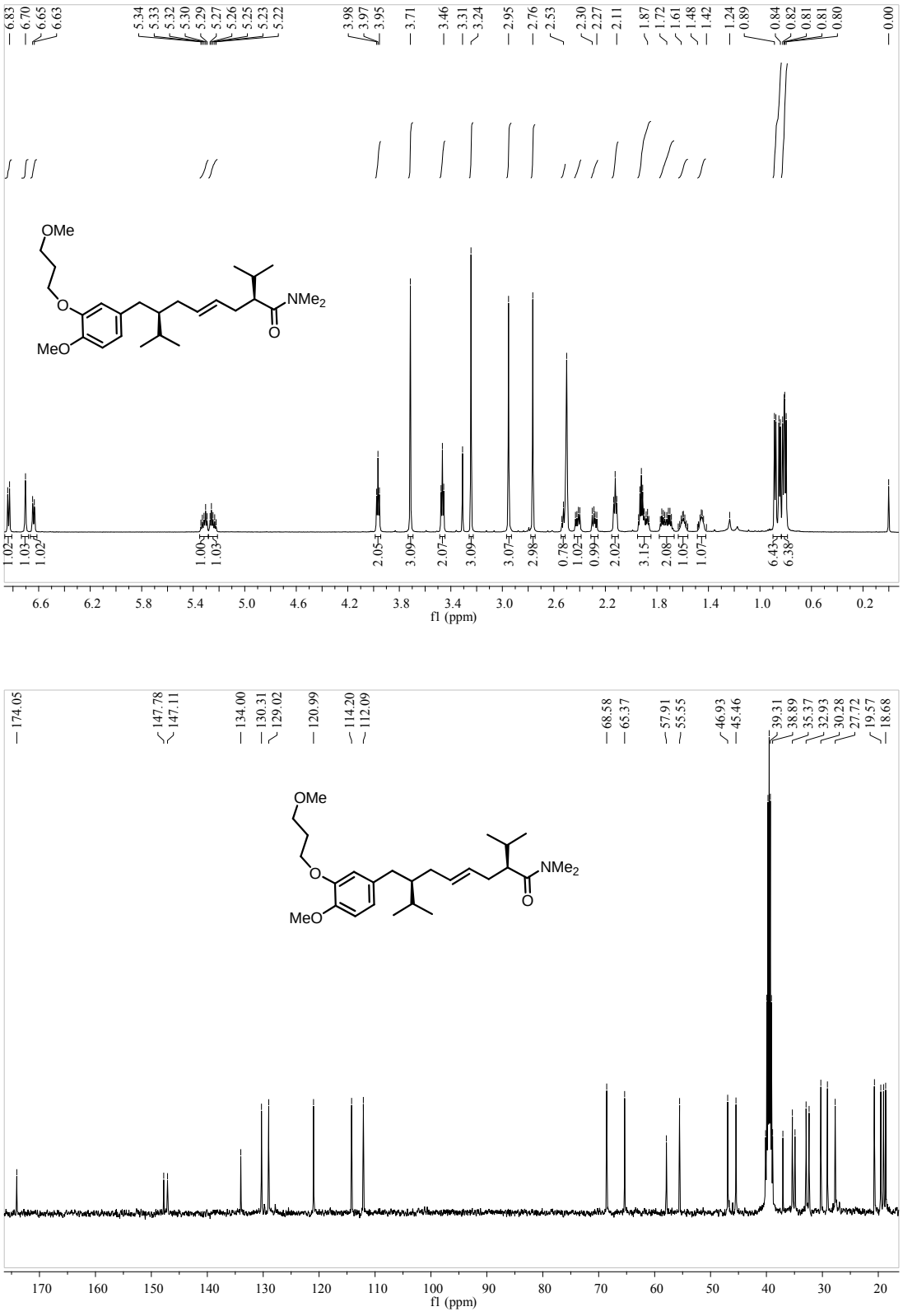


Figure S34. ^{1}H- (upper) and ^{13}C-NMR (lower) spectra of compound **2a**

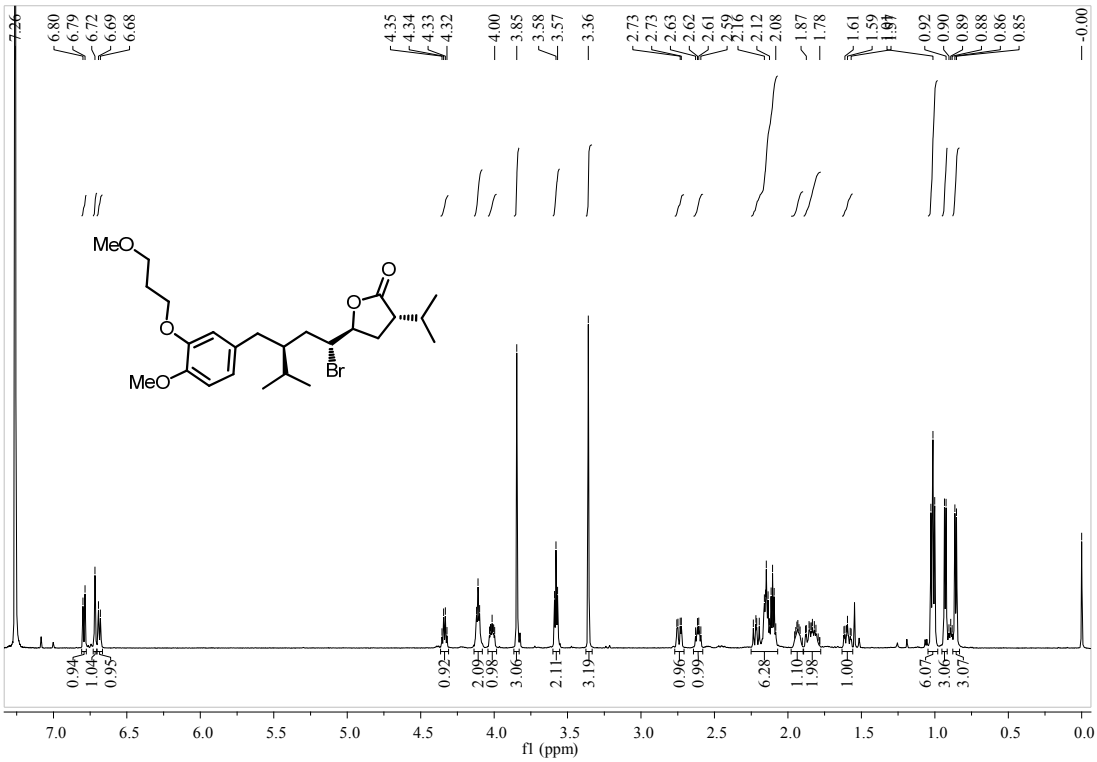


Figure S35. ^{1}H-NMR spectra of compound **32**

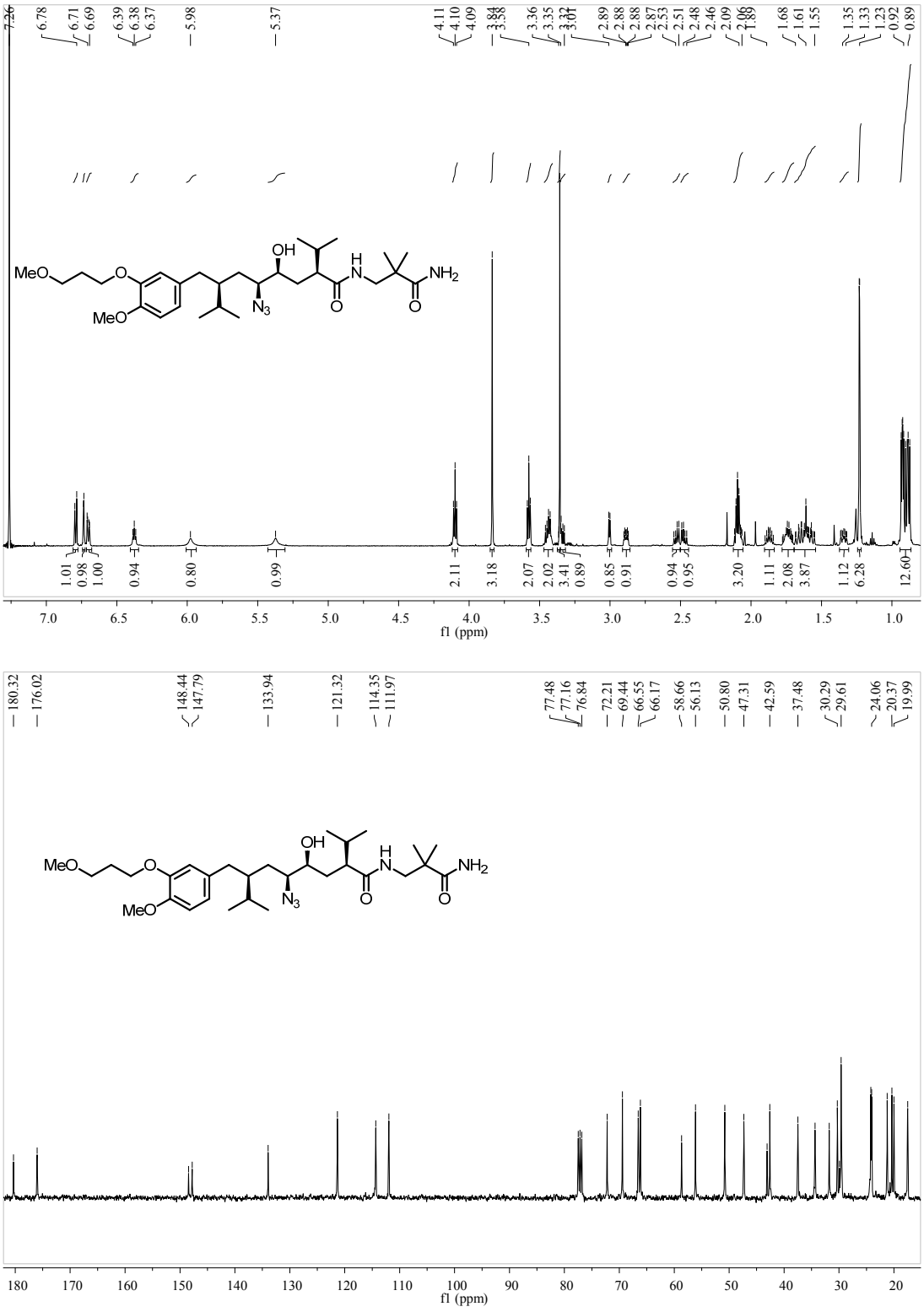


Figure S36. ^{1}H- (upper) and ^{13}C-NMR (lower) spectra of compound **33**

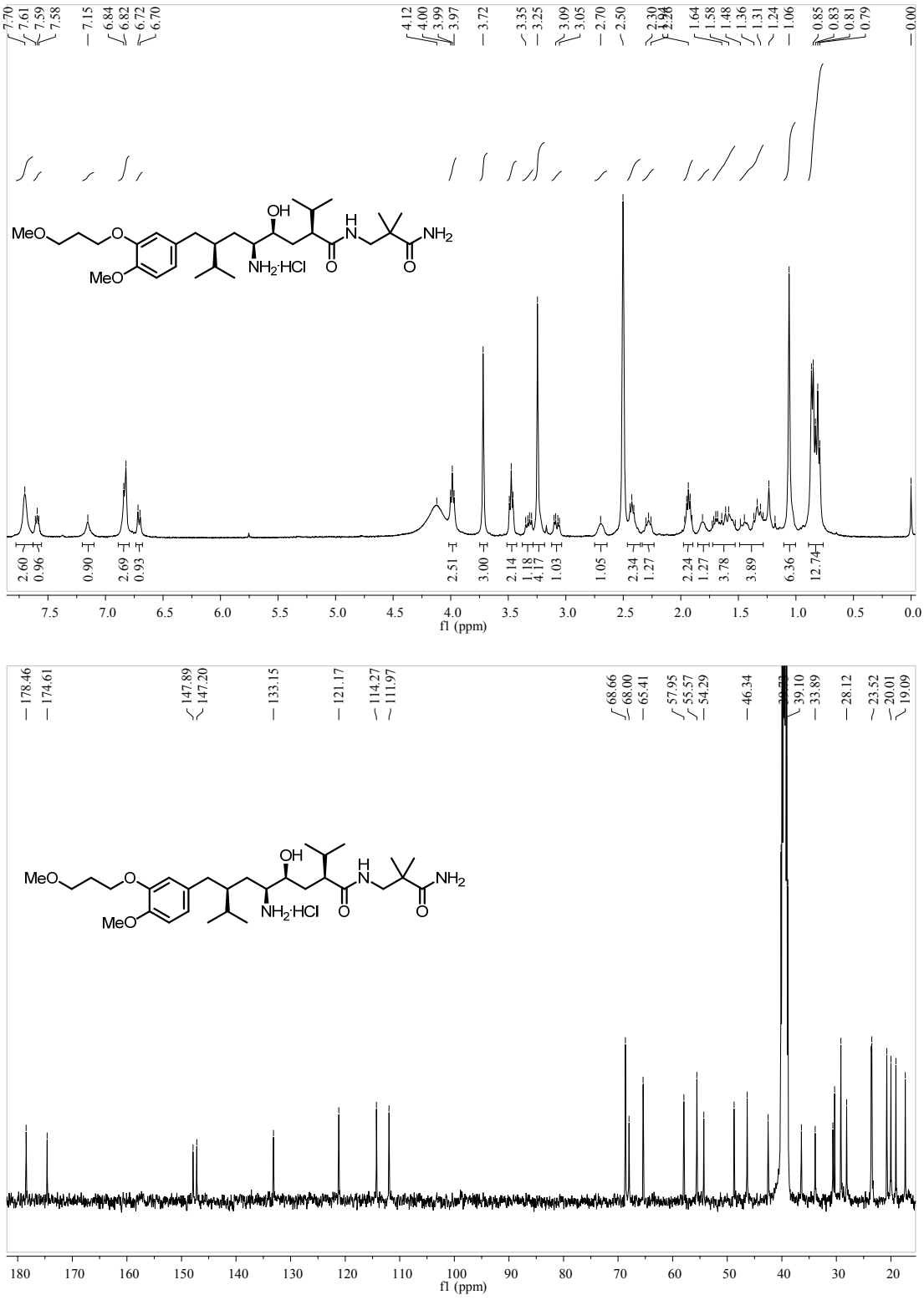


Figure S37. ^{1}H- (upper) and ^{13}C-NMR (lower) spectra of compound **Aliskiren HCl salt**

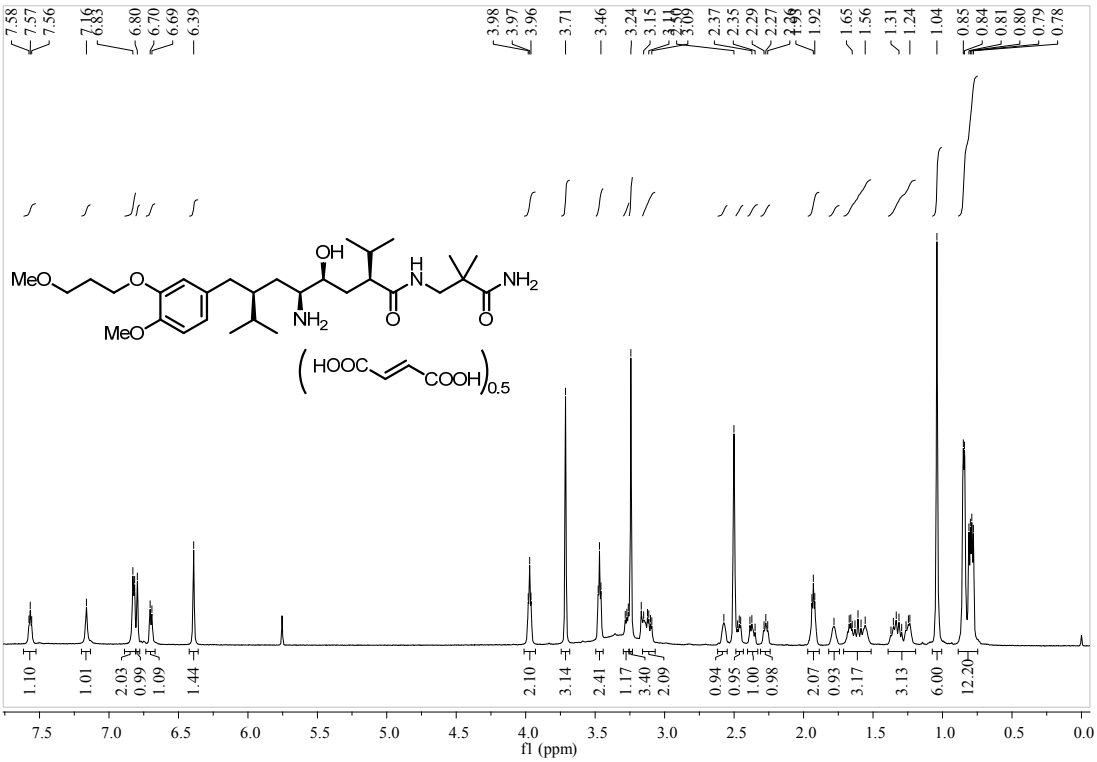
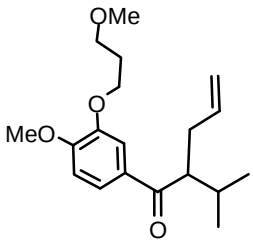
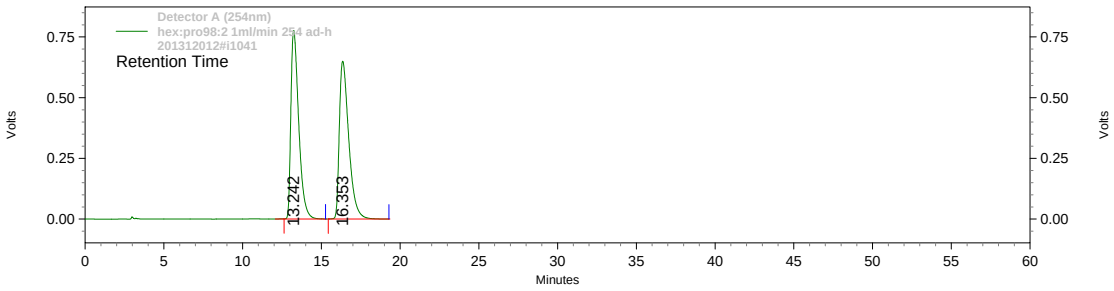


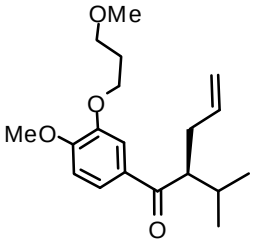
Figure S38. ^{1}H-NMR spectra of compound **Aliskiren hemifumarate salt**



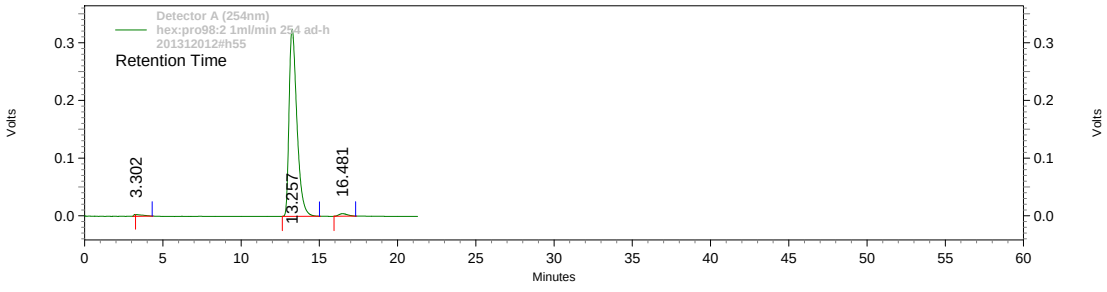
rac-15a



Peak	Retention Time	Area	Area %	Height	Height %
1	13.242	26800538	49.846	776304	54.422
2	16.353	26965871	50.154	650138	45.578

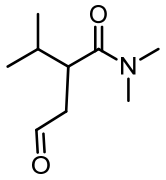


(*S*)-15a

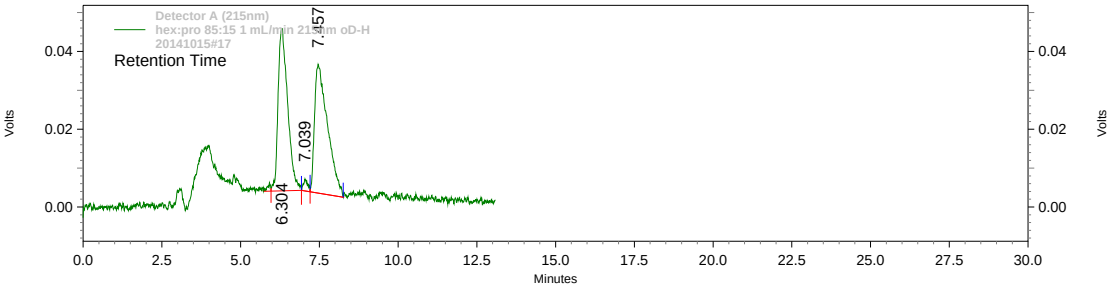


Peak	Retention Time	Area	Area %	Height	Height %
1	13.257	11303394	97.748	324447	97.812
2	16.481	165987	1.435	4359	1.314

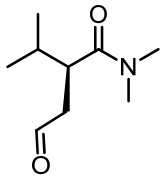
Figure S39. Chiral HPLC chart of compound **15a**



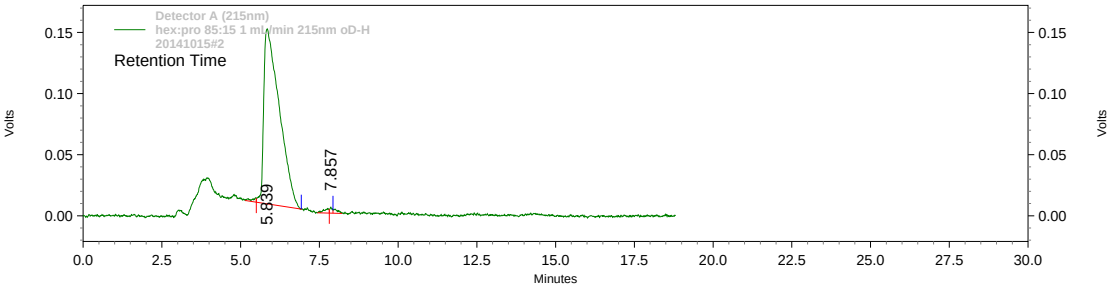
rac-18



Peak	Retention Time	Area	Area %	Height	Height %
1	6.304	882278	47.417	41650	53.500
2	7.039	29724	1.598	3123	4.011
3	7.457	948664	50.985	33078	42.489

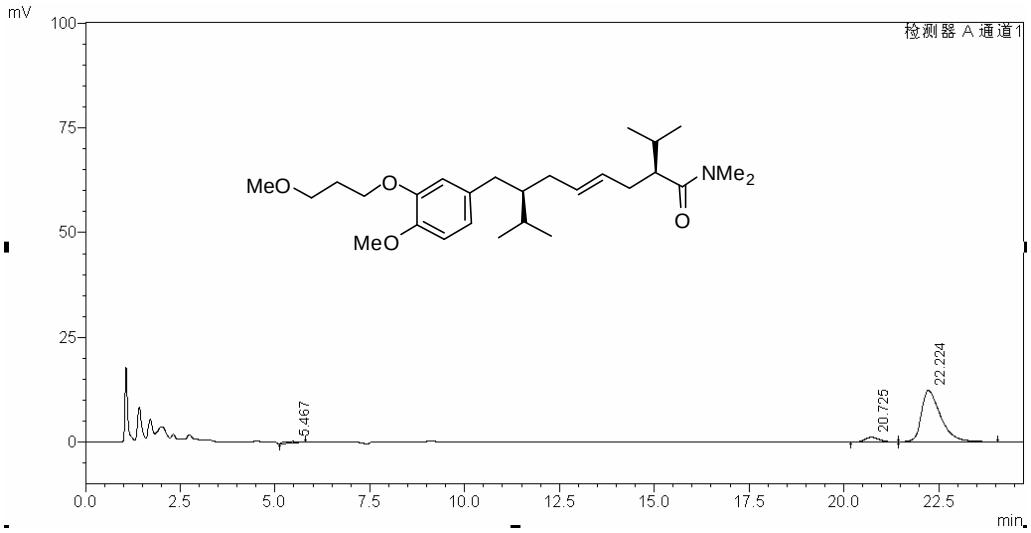


(*S*)-18



Peak	Retention Time	Area	Area %	Height	Height %
1	5.839	4934492	98.524	143112	96.655
2	7.857	73931	1.476	4953	3.345

Figure S40. Chiral HPLC chart of compound **18**



Peak	Retention Time	Area	Area %	Height	Height %
1	20.725	32382	6.721	1169	8.453
2	22.224	439945	91.309	12298	88.936

Figure S41. HPLC chart of compound **2a** synthesized under the conditions of entry 14 in Table 2