Electronic Supplementary Information

Oxa/thiazole-tetrahydropyran triazole-linked hybrids with selective antiproliferative activity against human tumour cells

Guillermo Valdomir,[a] María de los Ángeles Fernández,[a] Irene Lagunes,[b] Juan I. Padrón,[b,c] Víctor S. Martín,[b] José M. Padrón,*[b] and Danilo Davyt*[a]

a) Departamento de Química Orgánica, Facultad de Química, UdelaR, Av General Flores 2124, 11800 Montevideo, Uruguay. E-mail: ddavyt@fq.edu.uy
b) Instituto Universitario de Bio-Orgánica "Antonio González" (IUBO-AG), Centro de Investigaciones Biomédicas de Canarias (CIBICAN), Universidad de La Laguna, C/ Astrofísico Francisco Sánchez 2, 38206 La Laguna, Spain. E-mail: jmpadron@ull.es
c) Instituto de Productos Naturales y Agrobiología, CSIC, C/ Astrofísico Francisco Sánchez 3, 38206 La Laguna, Spain.

Contents

1. General Methods (Chemistry)

***Experimental Methods**:* Air and water sensitive reactions were performed under a nitrogen atmosphere in flame-dried glassware. All other reactions were carried out in pre-dried round bottom flasks. All solvents were distilled prior to use. All anhydrous solvents were dried and purified by standard methods.[1] All commercially available reagents were used without further purification. All reactions were magnetically stirred and monitored by thin layer chromatography (TLC). Cooling was performed by using the JULABO FT902 immersion coolers.

***Chromatography**:* Thin-layer chromatography was performed on silica gel plates (TLC Silica gel 60 F_{254}) from Macherey-Nagel or Merck. Column chromatography was performed with silica gel (Geduran® Si60, 230-400 mesh) from Merck.

***NMR spectroscopy**:* NMR spectra were recorded on Bruker Avance 400. Chemical shifts are given in ppm relative to tetramethylsilane (TMS) or residual solvent signal and coupling constants *J* in Hertz. Multiplicities of first order signals are assigned as: s (singlet), br s (broad singlet), d (doublet), t (triplet), q (quartet), dd (doublet of doublets) etc. Signals of higher order are declared as m (multiplet) or m_C (centered multiplet).

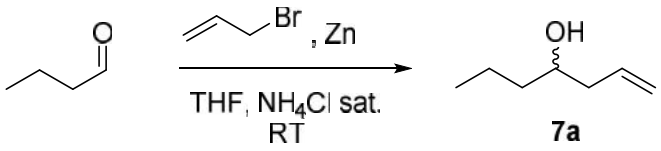
***IR spectroscopy**:* IR spectra were recorded with a FT-IR 8101A spectrophotometer from Shimadzu using NaCl optics.

***Mass spectrometry**:* Electrospray ESI high-resolution mass spectra (HRMS) spectra were recorded on a MicroTOF-Q spectrometer from Bruker Daltronics.

***Abbreviations**:* aq. (aqueous), sat. (saturated solution), eq. (equivalents), THF (tetrahydrofuran), PE (petroleum ether), DABCO (1,4-diazabicyclooctane), TFA (trifluoroacetic acid), TBS (*tert*-butyldimethylsilyl), TBSOTf (*tert*-butyldimethylsilyl trifluoromethanesulfonate), DMSO (dimethyl sulfoxide), Py (pyridine), DAIB ((diacetoxyiodo)benzene), TEMPO (2,2,6,6-tetramethylpiperidinyl 1-oxyl), quant. (quantitative), 4-DMAP (4-(dimethylamino)pyridine).

2. Synthetic Procedures

2.1 Hept-1-en-4-ol (7a).



Zn (3.14 g, 48.0 mmol, 1.20 eq.) was added to NH_4Cl sat. (40 mL) and a solution of butyraldehyde (2.82 g, 3.53 mL, 40.0 mmol, 1.00 eq.) in THF (4 mL) was added. Allyl bromide (5.81 g, 4.15 mL, 48.0 mmol, 1.20 eq.) was added dropwise and the reaction was stirred overnight at room temperature. After completion by TLC, Et_2O (40 mL) was added and the solids were filtered. The phases were separated and the aqueous phase was further extracted with Et_2O (2 $\times$ 40 mL). The combined organic phases were dried over anhydrous Na_2SO_4, and concentrated under reduced pressure at low temperature. The crude reaction mixture was purified by column chromatography (SiO_2, EtOAc:PE 20:80) to obtain compounds **7a** (3.04 g, 26.62 mmol, 67 %) as a solution 76 % in EtOAc.

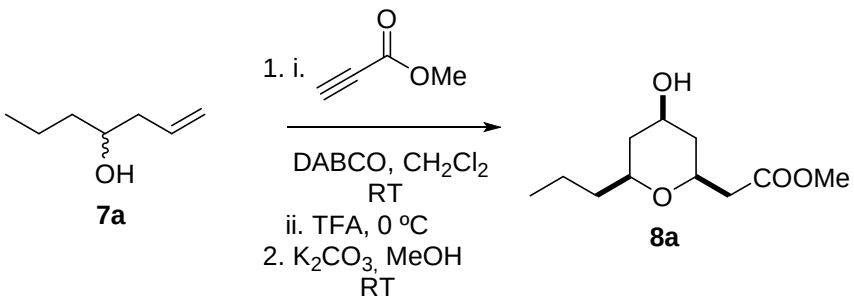
TLC: R_f = 0.45 (EtOAc:PE = 20:80).

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.84 (m_c, 1 H), 5.17-5.12 (m, 2 H), 3.67 (m_c, 1 H), 2.31 (m_c, 1 H), 2.14 (m_c, 1 H), 1.60-1.59 (m, 1 H), 1.51-1.38 (m, 3 H), 0.94 (t, 3 H, *J* = 7.0 Hz) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 135.0, 118.2, 70.5, 42.1, 39.1, 19.0, 14.2 ppm.

Data was comparable to that available in the literature.[2]

2.2 *rel*-Methyl 2-([2*S*,4*R*,6*S*]-4-hydroxy-6-propyltetrahydro-2*H*-pyran-2-yl)acetate (8a).



Alcohols **7a** (1.00 g, 8.76 mmol, 1.00 eq.) was dissolved in CH_2Cl_2 (12 mL) under N_2 atmosphere, and DABCO (49.1 mg, 0.44 mmol, 0.05 eq.) was added. Methyl propiolate

(0.82 g, 0.86 mL, 9.61 mmol, 1.10 eq.) was added dropwise as a solution in CH_2Cl_2 (12 mL) and the solution was stirred at RT for 1 hour. After completion by TLC, the solution was cooled down to 0 °C, and TFA (9.69 g, 6.50 mL, 87.57 mmol, 10.00 eq.) was added dropwise. After completion by TLC, $NaHCO_3$ sat. (50 mL) was added. The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic phases were dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. Under N_2 atmosphere, the crude reaction was dissolved in dry MeOH (12 mL) and dry K_2CO_3 (2.42 g, 17.52 mmol, 2.00 eq.) was added at RT. After completion by TLC, H_2O (40 mL) was added and the aqueous phase was extracted with CH_2Cl_2 (3 × 40 mL). The combined organic phases were dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude reaction mixture was purified by column chromatography (SiO_2, EtOAc:PE 60:40) to obtain compounds **8a** (racemate) (1.11 g, 5.11 mmol, 58 %, three steps) as a colorless oil.

TLC: R_f = 0.36 (EtOAc:PE = 50:50).

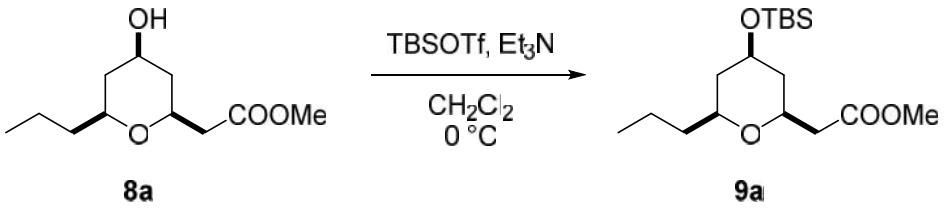
^{1}H NMR (400 MHz, $CDCl_3$) δ 3.82 (dddd, 1 H, *J* = 11.1, 11.1, 4.7, 4.7 Hz), 3.75 (dddd, 1 H, *J* = 11.3, 7.9, 5.5, 1.9 Hz), 3.69 (s, 3 H), 3.32 (dddd, 1 H, *J* = 12.0, 7.7, 4.2, 1.9 Hz), 2.60 (dd, 1 H, *J* = 15.1, 7.9 Hz), 2.47 (dd, 1 H, *J* = 15.1, 5.5 Hz), 2.00 (dddd, 1 H, *J* = 12.2, 4.7, 1.9, 1.9 Hz), 1.93 (dddd, 1 H, *J* = 12.2, 4.7, 1.9, 1.9 Hz), 1.56-1.30 (m, 4 H), 1.23-1.10 (m, 2 H), 0.89 (t, 3 H, *J* = 7.0 Hz) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 171.8, 75.6, 72.2, 68.1, 51.8, 41.1, 41.0, 40.9, 38.1, 18.9, 14.1 ppm.

IR (NaCl, film): $\tilde{\nu}$ (cm^{-1}) = 3425, 2951, 2939, 2870, 1743, 1724, 1438, 1373, 1327, 1269, 1249, 1195, 1141, 1080, 1041, 999, 972, 817, 748.

HRMS (ESI+) **$C_{11}H_{20}O_4$** (216.28): *m/z* $[M+Na]^+$ calcd. for $C_{11}H_{20}O_4Na$: 239.12538; found: 239.12834.

2.3 *rel*-Methyl 2-([2*S*,4*R*,6*S*]-4-[{tert-butyldimethylsilyl}oxy]-6-propyltetrahydro-2*H*-pyran-2-yl)acetate (9a).



8a **9a**

Alcohols **8a** (500.0 mg, 2.31 mmol, 1.00 eq.) was dissolved in CH_2Cl_2 (10 mL) under N_2 atmosphere and Et_3N (467.5 mg, 0.64 mL, 4.62 mmol, 2.00 eq.) was added. The solution was cooled down to 0 °C and TBSOTf (914.6 mg, 0.80 mL, 3.46 mmol, 1.50 eq.) was added dropwise. After 10 minutes at this temperature, the solution was stirred at RT for 1 hour. After completion by TLC, brine (20 mL) was added and the aqueous phase was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic phases were dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude reaction mixture was purified by column chromatography (SiO_2, EtOAc:PE 10:90) to obtain compounds **9a** (racemate) (695.7 mg, 2.10 mmol, 91 %) as a colorless oil.

TLC: R_f = 0.84 (EtOAc:PE = 30:70).

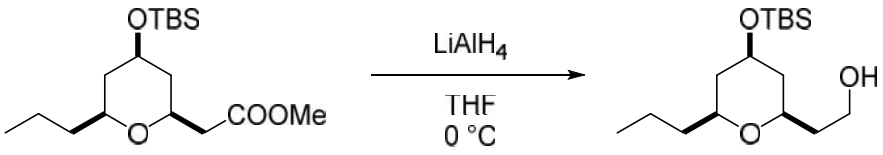
^{1}H NMR (400 MHz, $CDCl_3$) δ 3.82-3.70 (m, 2 H), 3.69 (s, 3 H), 3.28 (dddd, 1 H, *J* = 11.8, 7.7, 4.1, 1.9 Hz), 2.58 (dd, 1 H, *J* = 15.1, 8.2 Hz), 2.41 (dd, 1 H, *J* = 15.1, 5.1 Hz), 1.85 (dddd, 1 H, *J* = 11.6, 4.3, 1.8, 1.8 Hz), 1.78 (dddd, 1 H, *J* = 12.6, 4.4, 1.9, 1.8 Hz), 1.56-1.29 (m, 4 H), 1.27-1.14 (m, 2 H), 0.89 (t, 3 H, *J* = 7.3 Hz), 0.88 (s, 9 H), 0.06 (s, 6 H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 172.0, 75.7, 72.3, 68.8, 51.8, 41.6, 41.4, 41.2, 38.1, 26.0, 25.8, 18.9, 14.1, -4.4 ppm.

IR (NaCl, film): $\tilde{\nu}$ (cm^{-1}) = 2954, 2931, 2858, 1743, 1462, 1438, 1377, 1330, 1253, 1195, 1149, 1122, 1072, 1029, 1006, 937, 837, 775, 671.

HRMS (ESI+) **$C_{17}H_{34}O_4Si$** (330.54): *m/z* $[M+Na]^+$ calcd. for $C_{17}H_{34}O_4SiNa$: 353.21186; found: 353.21151.

2.4 *rel*-2-([2*R*,4*R*,6*S*]-4-[{tert-Butyldimethylsilyl}oxy]-6-propyltetrahydro-2*H*-pyran-2-yl)ethan-1-ol (10a).



9a **10a**

Esters **9a** (475.5 mg, 1.45 mmol, 1.00 eq.) was dissolved in THF (25 mL) under N_2 atmosphere. The solution was cooled down to 0 °C and $LiAlH_4$ (1.0 M in THF, 2.87 mL, 2.87 mmol, 2.00 eq.) was added dropwise. After 10 minutes the solution was stirred at RT for 1 hour. After completion by TLC, EtOH was dropped until no more H_2 is produced, sodium potassium tartrate sat. (50 mL) was added and stirred for 10

minutes. The aqueous phase was extracted with EtOAc (3 × 50 mL). The combined organic phases were dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to obtain compounds **10a** (racemate) (428.6 mg, 1.42 mmol, 98 %) as a colorless oil.

TLC: R_f = 0.19 (EtOAc:PE = 15:85).

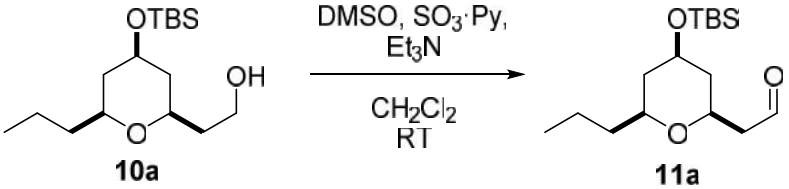
^{1}H NMR (400 MHz, $CDCl_3$) δ 3.79-3.72 (m, 3 H), 3.54 (dddd, 1 H, *J* = 11.4, 5.1, 2.8, 1.8 Hz), 3.32 (dddd, 1 H, *J* = 11.6, 7.5, 4.0, 1.7 Hz), 2.98 (br s, 1 H), 1.83-1.66 (m, 4 H), 1.58-1.17 (m, 6 H), 0.89 (t, 3 H, *J* = 7.3 Hz), 0.88 (s, 9 H), 0.06 (s, 6 H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 76.5, 75.9, 68.7, 61.8, 41.8, 41.6, 38.2, 37.7, 26.0, 19.0, 18.2, 14.2, -4.4 ppm.

IR (NaCl, film): $\tilde{\nu}$ (cm^{-1}) = 3425, 2954, 2935, 2858, 1465, 1377, 1327, 1253, 1153, 1122, 1080, 1006, 956, 910, 856, 837, 775, 671.

HRMS (ESI+) **$C_{16}H_{34}O_3Si$** (302.53): *m/z* $[M+Na]^+$ calcd. for $C_{16}H_{34}O_3SiNa$: 325.21694; found: 325.21895.

2.5 *rel*-2-([2*S*,4*R*,6*S*]-4-[{tert-Butyldimethylsilyl}oxy]-6-propyltetrahydro-2*H*-pyran-2-yl)acetaldehyde (11a).



Alcohols **10a** (200.0 mg, 0.66 mmol, 1.00 eq.) was dissolved in CH_2Cl_2 (20 mL) under N_2 atmosphere and DMSO (671.1 mg, 0.61 mL, 8.59 mmol, 13.00 eq.) and Et_3N (468.5 mg, 0.65 mL, 4.63 mmol, 7.00 eq.) were added. After 15 minutes SO_3·Py (733.2 mg, 4.63 mmol, 7 eq.) was added and the solution stirred overnight. After completion by TLC, brine (20 mL) and H_2O (5 mL) were added and the aqueous phase was extracted with CH_2Cl_2 (2 × 20 mL). The combined organic phases were dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude reaction mixture was purified by column chromatography (SiO_2, EtOAc:PE 10:90) to obtain compounds **11a** (racemate) (120.9 mg, 0.40 mmol, 61 %) as a colorless oil.

TLC: R_f = 0.53 (EtOAc:PE = 20:80).

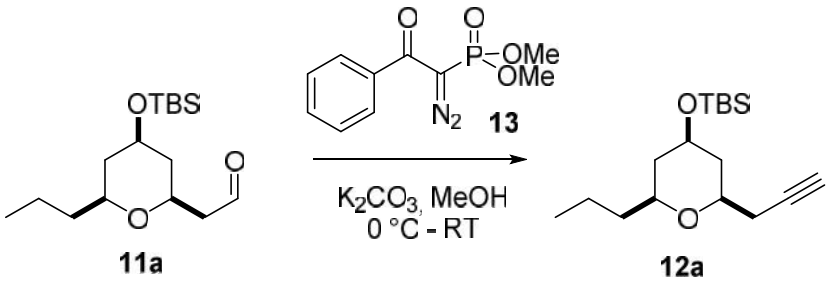
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.79 (dd, 1 H, *J* = 2.2, 2.2 Hz), 3.86-3.75 (m, 2 H), 3.31 (dddd, 1 H, *J* = 11.5, 7.5, 4.2, 1.8 Hz), 2.64 (ddd, 1 H, *J* = 16.4, 8.3, 2.2 Hz), 2.46 (ddd, 1 H, *J* = 16.4, 4.4, 2.2 Hz), 1.87-1.78 (m, 2 H), 1.54-1.16 (m, 6 H), 0.89 (t, 3 H, *J* = 7.3 Hz), 0.88 (s, 9 H), 0.06 (s, 6 H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 201.5, 75.8, 70.9, 68.6, 49.6, 41.6, 38.2, 25.9, 18.9, 18.2, 14.1, -4.4 ppm.

IR (NaCl, film): $\tilde{\nu}$ (cm^{-1}) = 3444, 2954, 2931, 2858, 2715, 1728, 1465, 1377, 1330, 1253, 1153, 1122, 1076, 1033, 956, 906, 856, 837, 775, 671.

HRMS (ESI+) **$C_{16}H_{32}O_3Si$** (300.51): *m/z* $[M+Na]^+$ calcd. for $C_{16}H_{32}O_3SiNa$: 323.20129; found: 323.20045.

2.6 *rel-tert*-Butyldimethyl([{2*R*,4*R*,6*S*}-2-{prop-2-yn-1-yl}-6-propyltetrahydro-2*H*-pyran-4-yl]oxy)silane (12a).



Aldehydes **11a** (119.0 mg, 0.40 mmol, 1.00 eq.) was dissolved in MeOH (3 mL) under N_2 atmosphere and K_2CO_3 (218.9 mg, 1.58 mmol, 4.00 eq.) was added. The reaction was cooled down to 0 °C and the diazo compound **13** (140.9 mg, 0.55 mmol, 1.40 eq.) was added as a solution in MeOH (4 mL). After 10 minutes the solution was allowed to reach room temperature and stirred overnight. After completion by TLC, $NaHCO_3$ sat. (10 mL) and Et_2O (20 mL) were added and the aqueous phase was extracted with Et_2O (2 × 20 mL). The combined organic phases were dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude reaction mixture was purified by column chromatography (SiO_2, EtOAc:PE 5:95) to obtain compounds **12a** (racemate) (79.9 mg, 0.27 mmol, 68 %) as a colorless oil.

TLC: R_f = 0.75 (EtOAc:PE = 10:90).

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.76 (dddd, 1 H, *J* = 10.8, 10.8, 4.6, 4.5 Hz), 3.42 (dddd, 1 H, *J* = 11.4, 7.5, 5.7, 1.9 Hz), 3.28 (dddd, 1 H, *J* = 11.6, 7.0, 4.6, 1.9 Hz), 2.50 (ddd, 1 H, *J*

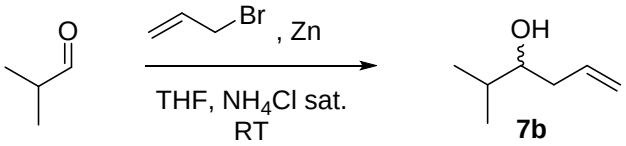
= 16.6, 5.7, 2.7 Hz), 2.32 (ddd, 1 H, *J* = 16.6, 7.5, 2.7 Hz), 2.03 (dddd, 1 H, *J* = 12.5, 4.5, 1.9, 1.9 Hz), 2.01 (dd, 1 H, *J* = 2.7, 2.7 Hz), 1.79 (dddd, 1 H, *J* = 12.5, 4.6, 1.9, 1.9 Hz), 1.57-1.32 (m, 4 H), 1.27-1.15 (m, 2 H), 0.91 (t, 3 H, *J* = 7.1 Hz), 0.89 (s, 9 H), 0.07 (s, 6 H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 81.0, 75.8, 73.9, 70.0, 68.9, 41.6, 40.9, 38.3, 26.0, 25.9, 18.9, 18.2, 14.2, -4.4 ppm.

IR (NaCl, film): $\tilde{\nu}$ (cm^{-1}) = 3313, 2954, 2931, 2858, 1465, 1442, 1381, 1253, 1153, 1122, 1076, 1006, 975, 933, 910, 867, 837, 775, 667, 636.

HRMS (ESI+) **$C_{17}H_{32}O_2Si$** (296.53): *m/z* $[M+Na]^+$ calcd. for $C_{17}H_{32}O_2SiNa$: 319.20638; found: 319.20700.

2.7 2-Methylhex-5-en-3-ol (7b).



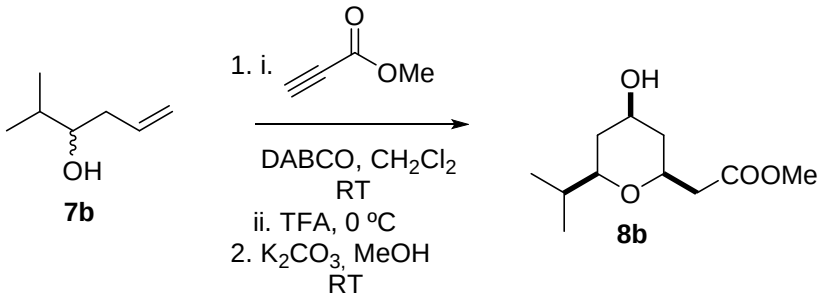
Zn (859.4 mg, 13.1 mmol, 1.20 eq.) was added to NH_4Cl sat. (10 mL) and a solution of isobutyraldehyde (790.0 mg, 1.00 mL, 11.0 mmol, 1.00 eq.) in THF (1 mL) was added. Allyl bromide (1.59 g, 1.14 mL, 13.1 mmol, 1.20 eq.) was added dropwise and the reaction was stirred overnight at room temperature. After completion, Et_2O (20 mL) was added and the solids were filtered. The phases were separated and the aqueous phase was further extracted with Et_2O (2 × 20 mL). The combined organic phases were dried over anhydrous Na_2SO_4, and concentrated under reduced pressure at low temperature. The crude reaction mixture was purified by column chromatography (SiO_2, EtOAc:PE 15:85) to obtain compounds **7b** (766.4 mg, 6.71 mmol, 61 %) as a solution 78 % in EtOAc.

TLC: R_f = 0.36 (EtOAc:PE = 15:85).

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.85 (m_c, 1 H), 5.18-5.13 (m, 2 H), 3.41 (m_c, 1 H), 2.32 (m_c, 1 H), 2.12 (m_c, 1 H), 1.70 (m_c, 1 H), 0.95 (d, 3 H, *J* = 6.8 Hz), 0.94 (d, 3 H, *J* = 6.8 Hz) ppm.

Data was comparable to that available in the literature.[3]

2.8 *rel*-Methyl 2-([2*S*,4*S*,6*R*]-4-hydroxy-6-isopropyltetrahydro-2*H*-pyran-2-yl)acetate (8b).



Alcohols **7b** (766.4 mg, 6.71 mmol, 1.00 eq.) was dissolved in CH_2Cl_2 (10 mL) under N_2 atmosphere and DABCO (37.6 mg, 0.34 mmol, 0.05 eq.) was added. Methyl propiolate (0.62 g, 0.66 mL, 7.38 mmol, 1.10 eq.) was added dropwise as a solution in CH_2Cl_2 (5 mL) and the solution was stirred at RT for 1 hour. After completion by TLC, the solution was cooled down to 0 °C, and TFA (7.65 g, 5.46 mL, 67.10 mmol, 10.00 eq.) was added dropwise. After completion by TLC, $NaHCO_3$ sat. (20 mL) was added. The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 25 mL). The combined organic phases were dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. Under N_2 atmosphere, the crude reaction was dissolved in dry MeOH (6 mL) and dry K_2CO_3 (1.85 g, 13.42 mmol, 2.00 eq.) was added at RT. After completion by TLC, HCl 1 M (20 mL) was added and the aqueous phase was extracted with CH_2Cl_2 (3 × 25 mL). The combined organic phases were dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude reaction mixture was purified by column chromatography (SiO_2, EtOAc:PE 60:40) to obtain compounds **8b** (racemate) (777.9 mg, 3.60 mmol, 54 %, three steps) as a colorless oil.

TLC: R_f = 0.24 (EtOAc:PE = 50:50).

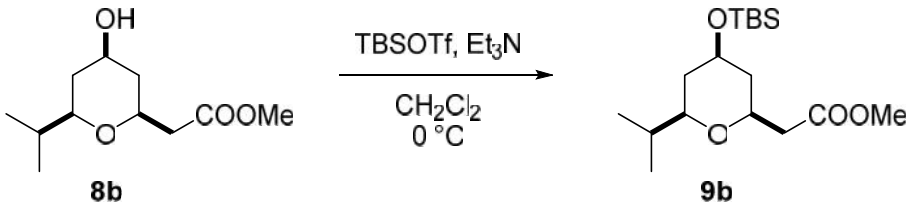
^{1}H NMR (400 MHz, $CDCl_3$) δ 3.82 (dddd, 1 H, *J* = 13.9, 13.9, 4.4, 4.4 Hz), 3.73 (m_c, 1 H), 3.69 (s, 3 H), 2.99 (ddd, 1 H, *J* = 11.3, 6.8, 1.8 Hz), 2.59 (dd, 1 H, *J* = 15.0, 8.2 Hz), 2.44 (dd, 1 H, *J* = 15.0, 5.3 Hz), 2.02-1.95 (m, 2 H), 1.67 (m_c, 1 H), 1.22-1.08 (m, 2 H), 0.91 (d, 3 H, *J* = 6.7 Hz), 0.88 (d, 3 H, *J* = 6.7 Hz) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 171.2, 80.7, 72.0, 68.3, 51.6, 41.0, 40.7, 37.7, 32.8, 18.6, 18.4 ppm.

IR (NaCl, film): $\tilde{\nu}$ (cm^{-1}) = 3385, 2955, 2874, 1734, 1437, 1375, 1332, 1271, 1198, 1152, 1084, 1043, 879.

HRMS (ESI+) **$C_{11}H_{20}O_4$** (216.28): *m/z* $[M+Na]^+$ calcd. for $C_{11}H_{20}O_4Na$: 239.1254; found: 239.1274.

2.9 *rel*-Methyl 2-([2*S*,4*S*,6*R*]-4-[{tert-butyldimethylsilyl}oxy]-6-isopropyltetrahydro-2*H*-pyran-2-yl)acetate (9b).



Alcohols **8b** (778.0 mg, 3.60 mmol, 1.00 eq.) was dissolved in CH_2Cl_2 (14 mL) under N_2 atmosphere and Et_3N (728.0 mg, 1.00 mL, 7.19 mmol, 2.00 eq.) was added. The solution was cooled down to 0 °C and TBSOTf (1.43 g, 1.24 mL, 5.40 mmol, 1.50 eq.) was added dropwise. After 10 minutes at this temperature, the solution was stirred at RT for 7 hour. After completion by TLC, HCl 1M (20 mL) was added and the aqueous phase was extracted with CH_2Cl_2 (3 × 25 mL). The combined organic phases were dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude reaction mixture was purified by column chromatography (SiO_2, EtOAc:PE 10:90) to obtain compounds **9b** (racemate) (752.5 mg, 2.28 mmol, 63 %) as a colorless oil.

TLC: R_f = 0.80 (EtOAc:PE = 20:80).

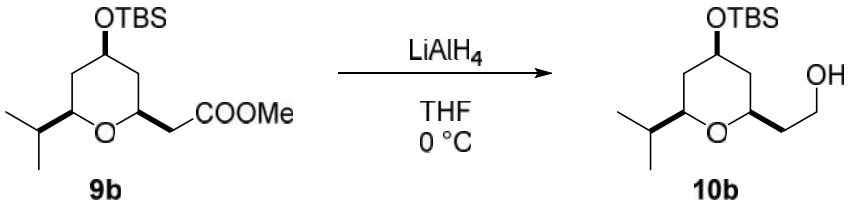
^{1}H NMR (400 MHz, $CDCl_3$) δ 3.79-3.67 (m, 2 H), 3.67 (s, 3 H), 2.95 (ddd, 1 H, *J* = 11.5, 6.6, 1.7 Hz), 2.54 (dd, 1 H, *J* = 15.0, 8.3 Hz), 2.39 (dd, 1 H, *J* = 15.0, 5.0 Hz), 1.85-1.77 (m, 2 H), 1.63 (m_c, 1 H), 1.26-1.11 (m, 2 H), 0.89-0.84 (m, 15 H), 0.05 (s, 3 H), 0.04 (s, 3 H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 171.8, 80.7, 7 2.1, 69.0, 51.5, 41.3, 41.1, 38.2, 32.8, 25.8, 25.7, 18.5, 18.1, -3.0, -4.6 ppm.

IR (NaCl, film): $\tilde{\nu}$ (cm^{-1}) = 2955, 2930, 2886, 2859, 1744, 1464, 1437, 1373, 1254, 1198, 1153, 1119, 1070, 1005, 887, 837, 775, 669.

HRMS (ESI+) **$C_{17}H_{34}O_4Si$** (330.54): *m/z* $[M+Na]^+$ calcd. for $C_{17}H_{34}O_4SiNa$: 353.2119; found: 353.2131.

2.10 *rel*-2-([2*R*,4*S*,6*R*]-4-[{tert-Butyldimethylsilyl}oxy]-6-isopropyltetrahydro-2*H*-pyran-2-yl)ethan-1-ol (10b).



9b **10b**

Esters **9b** (752.5 mg, 2.28 mmol, 1.00 eq.) was dissolved in THF (25 mL) under N_2 atmosphere. The solution was cooled down to 0 °C and $LiAlH_4$ (1.0 M in THF, 4.55 mL, 4.55 mmol, 2.00 eq.) was added dropwise. After 10 minutes the solution was stirred at RT for 1 hour. After completion by TLC, EtOH was dropped until no more H_2 is produced, sodium potassium tartrate sat. (25 mL) was added and stirred for 10 minutes. The aqueous phase was extracted with EtOAc (3 × 25 mL). The combined organic phases were dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to obtain compounds **10b** (racemate) (683.9 mg, 2.26 mmol, 99 %) as a colorless oil.

TLC: R_f = 0.43 (EtOAc:PE = 20:80).

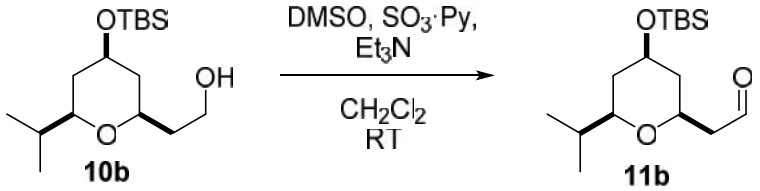
^{1}H NMR (400 MHz, $CDCl_3$) δ 3.79-3.73 (m, 3 H), 3.54 (m_c, 1 H), 3.07 (ddd, 1 H, *J* = 11.8, 5.8, 1.3 Hz), 2.94 (br s, 1 H), 1.87-1.62 (m, 5 H), 1.37-1.18 (m, 2 H), 0.93-0.86 (m, 15 H), 0.07 (s, 6 H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 81.0, 76.5, 68.9, 61.8, 41.7, 38.1, 37.5, 32.7, 25.8, 25.7, 18.6, 18.4, -4.5 ppm.

IR (NaCl, film): $\tilde{\nu}$ (cm^{-1}) = 2955, 2932, 2886, 2859, 2367, 2342, 1471, 1462, 1437, 1426, 1375, 1254, 1157, 1123, 1075, 901, 837, 776.

HRMS (ESI+) **$C_{16}H_{34}O_3Si$** (302.53): *m/z* $[M+Na]^+$ calcd. for $C_{16}H_{34}O_3SiNa$: 325.2169; found: 325.2162.

2.11 *rel*-2-([2*S*,4*S*,6*R*]-4-[{tert-Butyldimethylsilyl}oxy]-6-isopropyltetrahydro-2*H*-pyran-2-yl)acetaldehyde (11b).



Alcohols **10b** (670.0 mg, 2.21 mmol, 1.00 eq.) was dissolved in CH_2Cl_2 (30 mL) under N_2 atmosphere and DMSO (1.73 g, 1.57 mL, 22.15 mmol, 10.00 eq.) and Et_3N (1.34 g, 1.85 mL, 13.29 mmol, 6.00 eq.) were added. After 15 minutes $SO_3{\cdot}Py$ (1.75 g, 11.07 mmol, 5 eq.) was added and the solution stirred overnight. After completion by TLC, brine (30 mL) was added and the aqueous phase was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic phases were dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude reaction mixture was purified by column chromatography (SiO_2, EtOAc:PE 15:85) to obtain compounds **11b** (racemate) (568.4 mg, 1.89 mmol, 85 %) as a colorless oil.

TLC: R_f = 0.63 (EtOAc:PE = 20:80).

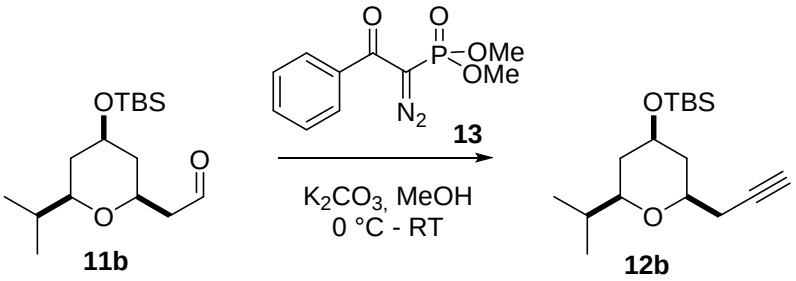
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.79 (dd, 1 H, *J* = 2.6, 2.0 Hz), 3.83-3.74 (m, 2 H), 3.02 (ddd, 1 H, *J* = 11.4, 6.2, 1.7 Hz), 2.61 (ddd, 1 H, *J* = 16.2, 8.3, 2.6 Hz), 2.45 (ddd, 1 H, *J* = 16.2, 4.3, 2.0 Hz), 1.86-1.78 (m, 2 H), 1.66 (m_c, 1 H), 1.30-1.15 (m, 2 H), 0.94-0.85 (m, 6 H), 0.89 (s, 9 H), 0.07 (s, 3 H), 0.06 (s, 3 H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 201.6, 80.8, 70.8, 68.9, 49.4, 41.5, 38.1, 32.8, 25.8, 18.5, 18.4, 18.1, -4.5, -4.6 ppm.

IR (NaCl, film): $\tilde{\nu}$ (cm^{-1}) = 2955, 2930, 2857, 2723, 1728, 1474, 1375, 1254, 1155, 1119, 1070, 891, 837, 775, 669.

HRMS (ESI+) **$C_{16}H_{32}O_3Si$** (300.51): *m/z* $[M+Na]^+$ calcd. for $C_{16}H_{32}O_3SiNa$: 323.2013; found: 323.2012.

2.12 *rel*-*tert*-Butyl([{2*R*,4*S*,6*R*}-2-isopropyl-6-{prop-2-yn-1-yl}tetrahydro-2*H*-pyran-4-yl]oxy)dimethylsilane (12b).



Aldehydes **11b** (250.0 mg, 0.83 mmol, 1.00 eq.) was dissolved in MeOH (6 mL) under N_2 atmosphere and K_2CO_3 (459.9 mg, 3.33 mmol, 4.00 eq.) was added. The reaction was cooled down to 0 °C and the diazo compound **13** (296.0 mg, 1.16 mmol, 1.40 eq.) was added as a solution in MeOH (6 mL). After 10 minutes the solution was allowed to reach room temperature and stirred overnight. After completion by TLC, brine (20 mL) and CH_2Cl_2 (20 mL) were added and the aqueous phase was extracted with CH_2Cl_2 (2 × 20 mL). The combined organic phases were dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude reaction mixture was purified by column chromatography (SiO_2, EtOAc:PE 5:95) to obtain compounds **12b** (racemate) (179.2 mg, 0.60 mmol, 73 %) as a colorless oil.

TLC: R_f = 0.76 (EtOAc:PE = 10:90).

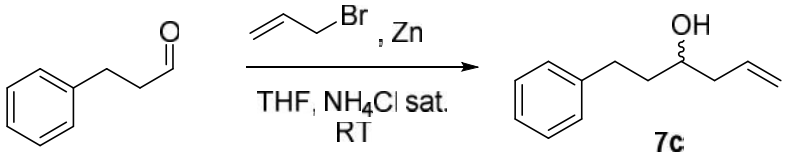
^{1}H NMR (400 MHz, $CDCl_3$) δ 3.74 (dddd, 1 H, *J* = 10.5, 10.5, 4.8, 4.8 Hz), 3.39 (dddd, 1 H, *J* = 11.3, 7.4, 5.9, 1.9 Hz), 2.98 (ddd, 1 H, *J* = 11.4, 6.1, 1.6 Hz), 2.47 (ddd, 1 H, *J* = 16.6, 5.6, 2.7 Hz), 2.30 (ddd, 1 H, *J* = 16.6, 7.3, 2.7 Hz), 2.03-1.97 (m, 1 H), 1.98 (dd, 1 H, *J* = 2.7, 2.7 Hz), 1.78 (m, 1 H), 1.68 (m, 1 H), 1.24-1.23 (m, 2 H), 0.92 (d, 3 H, *J* = 6.7 Hz), 0.88 (d, 3 H, *J* = 6.5 Hz), 0.88 (s, 9 H), 0.06 (s, 6 H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 81.0, 80.7, 73.7, 69.8, 69.1, 40.8, 37.9, 32.8, 29.7, 25.8, 25.7, 18.6, 18.3, -4.5 ppm.

IR (NaCl, film): $\tilde{\nu}$ (cm^{-1}) = 3316, 2955, 2929, 2857, 1464, 1379, 1254, 1155, 1121, 1092, 1072, 1007, 893, 876, 837, 775, 669, 638, 559.

HRMS (ESI+) **$C_{17}H_{32}O_2Si$** (296.53): *m/z* $[M+Na]^+$ calcd. for $C_{17}H_{32}O_2SiNa$: 319.2064; found: 319.2063.

2.13 1-Phenylhex-5-en-3-ol (7c).



Zn (595.5 mg, 9.11 mmol, 1.20 eq.) was added to NH_4Cl sat. (10 mL) and a solution of hydrocinnamaldehyde (1.02 g, 1.00 mL, 7.59 mmol, 1.00 eq.) in THF (1 mL) was added. Allyl bromide (1.10 g, 0.79 mL, 9.11 mmol, 1.20 eq.) was added dropwise and the reaction was stirred overnight at room temperature. After completion, Et_2O (20 mL) was added, the solids were filtered and washed with Et_2O. The phases were separated and the aqueous phase was further extracted with Et_2O (3 × 25 mL). The combined organic phases were dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude reaction mixture was purified by column chromatography (SiO_2, EtOAc:PE 15:85) to obtain compounds **7c** (1.12 g, 6.34 mmol, 83 %) as a colorless oil.

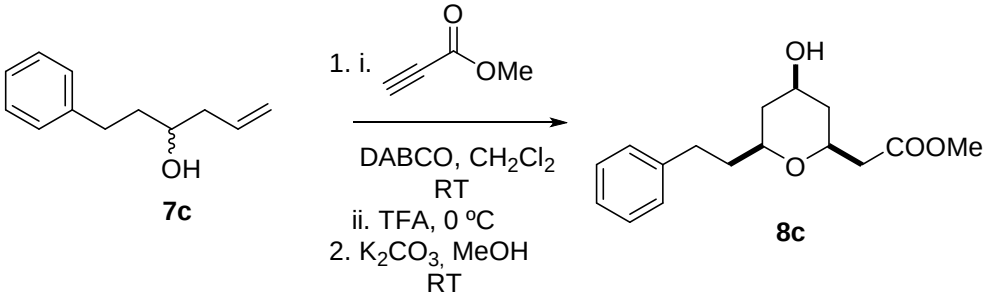
TLC: R_f = 0.36 (EtOAc:PE = 20:80).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30-7.25 (m, 2 H), 7.21-7.16 (m, 3 H), 5.81 (dddd, 1 H, *J* = 19.4, 9.6, 7.9, 6.6 Hz), 5.16 (m_c, 1 H), 5.12 (m_c, 1 H), 3.67 (m_c, 1 H), 2.81 (m_c, 1 H), 2.68 (m_c, 1 H), 2.32 (m_c, 1 H), 2.18 (m_c, 1 H) 1.81-1.76 (m, 2 H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 142.2, 134.8, 128.6, 128.5, 125.9, 118.5, 70.0, 42.2, 38.6, 32.2 ppm.

Data was comparable to that available in the literature.[4]

2.14 *rel*-Methyl 2-([2*S*,4*R*,6*S*]-4-hydroxy-6-phenethyltetrahydro-2*H*-pyran-2-yl)acetate (8c).



Alcohols **7c** (940.4 mg, 5.34 mmol, 1.00 eq.) was dissolved in CH_2Cl_2 (10 mL) under N_2 atmosphere and DABCO (29.9 mg, 0.27 mmol, 0.05 eq.) was added. Methyl propiolate

(493.4 mg, 0.52 mL, 5.87 mmol, 1.10 eq.) was added dropwise as a solution in CH_2Cl_2 (5 mL) and the solution was stirred at RT for 1 hour. After completion by TLC, the solution was cooled down to 0 °C, and TFA (6.09 g, 3.96 mL, 53.36 mmol, 10.00 eq.) was added dropwise. After completion by TLC, $NaHCO_3$ sat. (20 mL) was added. The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic phases were dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. Under N_2 atmosphere, the crude reaction was dissolved in dry MeOH (7 mL) and dry K_2CO_3 (1.47 g, 10.67 mmol, 2.00 eq.) was added at RT. After completion by TLC, reaction was diluted with CH_2Cl_2 (20 mL), filtered through a pad of Celite, washed with CH_2Cl_2 and concentrated under reduce pressure. The residue was taken in CH_2Cl_2 (25 mL) and HCl 1 M (25 mL) and the aqueous phase was extracted with CH_2Cl_2 (2 × 25 mL). The combined organic phases were dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude reaction mixture was purified by column chromatography (SiO_2, EtOAc:PE 70:30) to obtain compounds **8c** (racemate) (703.6 mg, 2.53 mmol, 47 %, three steps) as a colorless oil.

TLC: R_f = 0.18 (EtOAc:PE = 40:60).

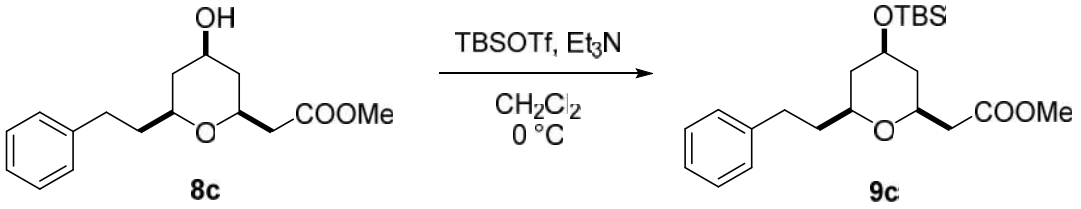
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30-7.26 (m, 2 H), 7.20-7.16 (m, 3 H), 3.84-3.73 (m, 2 H), 3.72 (s, 3 H), 3.28 (dddd, 1 H, *J* = 11.0, 8.9, 3.8, 1.9 Hz), 2.77-2.61 (m, 3 H), 2.47 (dd, 1 H, *J* = 15.1, 5.1 Hz), 2.00 (dddd, 1 H, *J* = 12.1, 6.4, 4.7, 1.8 Hz), 1.92-1.83 (m, 2 H), 1.56-1.30 (m, 4 H), 1.69 (m_c, 1 H), 1.25-1.15 (m, 2 H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 171.8, 142.1, 128.7, 128.5, 125.9, 74.4, 72.2, 67.9, 51.9, 41.2, 41.0, 40.8, 37.6, 31.7 ppm.

IR (NaCl, film): $\tilde{\nu}$ (cm^{-1}) = 2947, 2920, 1736, 1719, 1437, 1375, 1331, 1271, 1198, 1145, 1082, 1059, 1030, 750, 702.

HRMS (ESI+) **$C_{16}H_{22}O_4$** (278.35): *m/z* $[M+Na]^+$ calcd. for $C_{16}H_{22}O_4Na$: 301.1410; found: 301.1415.

2.15 *rel*-Methyl 2-([2*S*,4*R*,6*S*]-4-[{tert-butyldimethylsilyl}oxy]-6-phenethyltetrahydro-2*H*-pyran-2-yl)acetate (9c).



Alcohols **8c** (656.1 mg, 2.36 mmol, 1.00 eq.) was dissolved in CH_2Cl_2 (10 mL) under N_2 atmosphere and Et_3N (715.5 mg, 0.99 mL, 7.07 mmol, 3.00 eq.) was added. The solution was cooled down to 0 °C and TBSOTf (934.6 mg, 0.81 mL, 3.54 mmol, 1.50 eq.) was added dropwise. After 10 minutes at this temperature, the solution was stirred at RT for 1 hour. After completion by TLC, HCl 1 M (20 mL) was added and the aqueous phase was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic phases were washed with $NaHCO_3$ sat. (10 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude reaction mixture was purified by column chromatography (SiO_2, EtOAc:PE 10:90) to obtain compounds **9c** (racemate) (588.5 mg, 1.50 mmol, 64 %) as a colorless oil.

TLC: R_f = 0.79 (EtOAc:PE = 40:60).

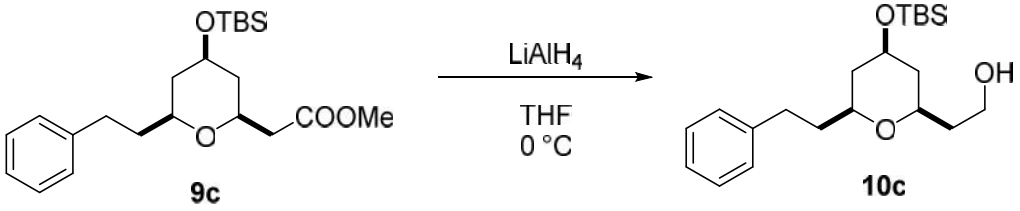
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29-7.26 (m, 2 H), 7.20-7.16 (m, 3 H), 3.77-3.72 (m, 2 H), 3.72 (s, 3 H), 3.24 (m_c, 1 H), 2.73-2.58 (m, 3 H), 2.44 (dd, 1 H, *J* = 15.1, 4.8 Hz), 1.85 (m_c, 1 H), 1.74 (m_c, 1 H), 1.65 (m_c, 1 H), 1.29-1.18 (m, 2 H), 0.87 (s, 9 H), 0.04 (s, 6 H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 172.0, 142.3, 128.8, 128.5, 125.8, 74.3, 72.3, 68.6, 51.8, 41.6, 41.4, 41.3, 37.7, 31.7, 26.0, 18.2, -4.3, -4.4 ppm.

IR (NaCl, film): $\tilde{\nu}$ (cm^{-1}) = 3026, 2951, 2930, 2886, 1744, 1437, 1375, 1328, 1252, 1196, 1150, 1074, 1005, 870, 837, 775, 748, 700, 669.

HRMS (ESI+) **$C_{22}H_{36}O_4Si$** (392.61): *m/z* $[M+Na]^+$ calcd. for $C_{22}H_{36}O_4SiNa$: 415.2275; found: 415.2278.

2.16 *rel*-2-([2*R*,4*R*,6*S*]-4-[{tert-butyldimethylsilyl}oxy]-6-phenethyltetrahydro-2*H*-pyran-2-yl)ethan-1-ol (10c).



Esters **9c** (568.2 mg, 1.45 mmol, 1.00 eq.) was dissolved in THF (20 mL) under N_2 atmosphere. The solution was cooled down to 0 °C and $LiAlH_4$ (1.0 M in THF, 2.17 mL, 2.17 mmol, 1.50 eq.) was added dropwise. After 10 minutes the solution was stirred at RT for 1 hour. After completion by TLC, EtOH was dropped until no more H_2 is produced, sodium potassium tartrate sat. (20 mL) was added and stirred for 10 minutes. The aqueous phase was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic phases were dried over anhydrous Na_2SO_4, and concentrated under reduced

pressure to obtain compounds **10c** (racemate) (508.4 mg, 1.39 mmol, 96 %) as a colorless oil.

TLC: R_f = 0.62 (EtOAc:PE = 40:60).

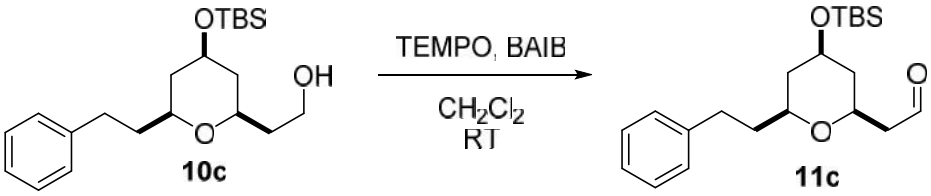
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30-7.26 (m, 2H), 7.20-7.17 (m, 3 H), 3.85-3.81 (m, 2 H), 3.73 (dddd, 1 H, *J* = 10.6, 10.6, 4.7, 4.7 Hz), 3.54 (dddd, 1 H, *J* = 11.2, 4.9, 2.9, 1.9 Hz), 3.28 (m_c, 1 H), 2.78-2.62 (m, 3 H), 1.92-1.68 (m, 5 H), 1.38-1.21 (m, 2 H), 0.88 (s, 9 H), 0.05 (s, 6 H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 141.9, 128.6, 128.5, 125.9, 76.2, 74.9, 68.6, 61.7, 41.8, 41.6, 37.9, 37.7, 31.9, 26.0, 18.2, -4.4 ppm.

IR (NaCl, film): $\tilde{\nu}$ (cm^{-1}) = 2950, 2932, 2857, 1466, 1459, 1372, 1324, 1254, 1156, 1133, 1077, 1005, 838, 776, 749, 701, 670, 517.

HRMS (ESI+) **$C_{21}H_{36}O_3Si$** (364.60): *m/z* $[M+Na]^+$ calcd. for $C_{21}H_{36}O_3SiNa$: 387.2326; found: 387.2323.

2.17 *rel*-2-([2*S*,4*R*,6*S*]-4-[{*tert*-Butyldimethylsilyl}oxy]-6-phenethyltetrahydro-2*H*-pyran-2-yl)acetaldehyde (11c).



Alcohols **10c** (200.0 mg, 0.54 mmol, 1.00 eq.) was dissolved in CH_2Cl_2 (2 mL) and TEMPO (8.6 mg, 0.05 mmol, 0.10 eq.) was added followed by BAIB (194.4 mg, 0.60 mmol, 1.10 eq.) and the solution stirred for 3 h at RT. After completion by TLC, the reaction was diluted with CH_2Cl_2 (5 mL) and washed with sodium thiosulfate sat. (1 mL). The aqueous layer was washed with CH_2Cl_2 (3 x 1 mL) and the combined organic phases were washed with $NaHCO_3$ sat. (1 mL) and brine (1 mL). Both aqueous layers were washed with CH_2Cl_2 (5 mL) and the combined organic phases were dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude reaction mixture was purified by column chromatography (SiO_2, EtOAc:PE 20:80) to obtain compounds **11c** (racemate) (198.6 mg, 0.54 mmol, quant.) as a yellowish oil.

TLC: R_f = 0.64 (EtOAc:PE = 30:70).

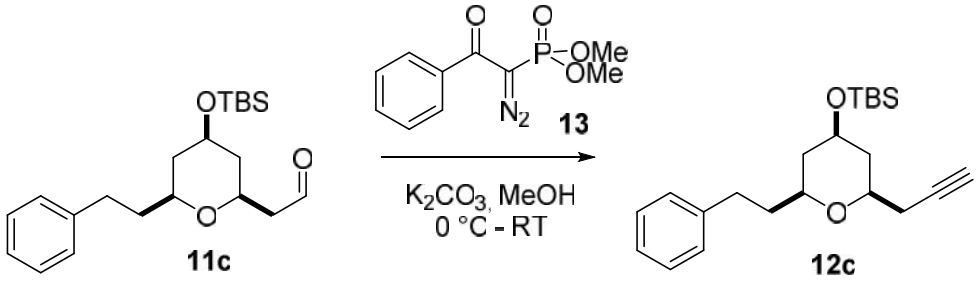
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.83 (dd, 1 H, *J* = 2.0, 2.0 Hz), 7.29-7.24 (m, 2 H), 7.18-7.16 (m, 3 H), 3.85-3.72 (m, 2 H), 3.28 (m_c, 1 H), 2.78-2.61 (m, 3 H), 2.64 (ddd, 1 H, *J* = 16.4, 4.2, 2.0 Hz), 1.89-1.65 (m, 4 H), 1.33-1.20 (m, 2 H), 0.87 (s, 9 H), 0.05 (s, 6 H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 201.1, 141.9, 128.4, 128.2, 125.7, 74.4, 70.6, 68.2, 49.4, 41.3, 37.4, 31.5, 25.7, 18.0, -4.6, -4.7 ppm.

IR (NaCl, film): $\tilde{\nu}$ (cm^{-1}) = 3026, 2951, 2930, 2857, 1734, 1716, 1449, 1375, 1252, 1155, 1128, 1101, 1072, 1030, 1007, 876, 837, 774, 748, 700, 669.

HRMS (ESI+) **$C_{21}H_{34}O_3Si$** (362.56): *m/z* $[M+Na]^+$ calcd. for $C_{21}H_{34}O_3SiNa$: 385.2169; found: 385.2165.

2.18 *rel-tert*-Butyldimethyl([{2*S*,4*R*,6*R*}-2-phenethyl-6-{prop-2-yn-1-yl}tetrahydro-2*H*-pyran-4-yl]oxy)silane (12c).



Aldehydes **11c** (180.0 mg, 0.50 mmol, 1.00 eq.) was dissolved in MeOH (5 mL) under N_2 atmosphere and K_2CO_3 (274.5 mg, 1.99 mmol, 4.00 eq.) was added. The reaction was cooled down to 0 °C and the diazo compound **13** (176.7 mg, 0.70 mmol, 1.40 eq.) was added as a solution in MeOH (4 mL). After 10 minutes the solution was allowed to reach room temperature and stirred for 2 h. After completion by TLC, brine (25 mL) and EtOAc (25 mL) were added and the aqueous phase was extracted with EtOAc (2 × 25 mL). The combined organic phases were dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude reaction mixture was purified by column chromatography (SiO_2, EtOAc:PE 5:95) to obtain compounds **12c** (racemate) (141.5 mg, 0.39 mmol, 79 %) as a colorless oil.

TLC: R_f = 0.77 (EtOAc:PE = 20:80).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29-7.25 (m, 2 H), 7.21-7.18 (m, 3 H), 3.73 (dddd, 1 H, *J* = 10.7, 10.7, 4.7, 4.7 Hz), 3.41 (dddd, 1 H, *J* = 11.4, 8.1, 6.9, 1.8 Hz), 3.23 (dddd, 1 H, *J* = 11.0, 8.6, 4.1, 1.8 Hz), 2.81-2.68 (m, 2 H), 2.53 (ddd, 1 H, *J* = 16.7, 6.1, 2.7 Hz), 2.35

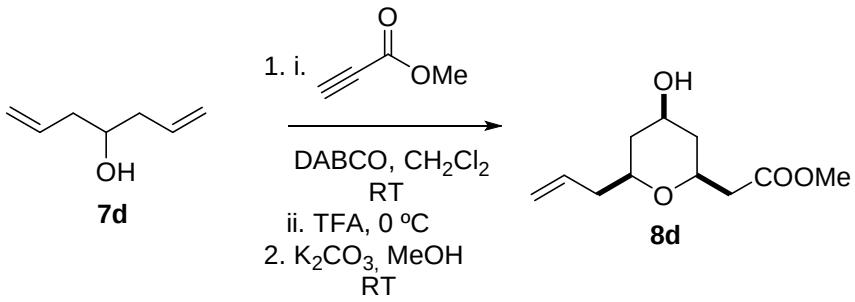
(ddd, 1 H, *J* = 16.7, 6.9, 2.7 Hz), 2.03 (dd, 1 H, *J* = 2.7, 2.7 Hz), 2.00 (dddd, 1 H, *J* = 12.5, 4.1, 1.7, 1.7 Hz), 1.89 (dtd, 1 H, *J* = 13.9, 8.4, 5.6 Hz), 1.76 (dddd, 1 H, *J* = 12.5, 4.2, 1.8, 1.8 Hz), 1.69 (m_c, 1 H), 1.28-1.20 (m, 2 H), 0.88 (s, 9 H), 0.05 (s, 3 H), 0.04 (s, 3 H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 142.2, 128.8, 128.4, 125.8, 81.1, 74.5, 73.9, 70.1, 68.7, 41.6, 41.0, 37.6, 31.7, 26.0, 18.2, -4.4 ppm.

IR (NaCl, film): $\tilde{\nu}$ (cm^{-1}) = 3312, 3026, 2951, 2930, 2856, 1477, 1460, 1377, 1254, 1155, 1130, 1088, 1069, 868, 837, 775, 746, 700, 669, 625.

HRMS (ESI+) **$C_{22}H_{34}O_2Si$** (358.60): *m/z* $[M+Na]^+$ calcd. for $C_{22}H_{34}O_2SiNa$: 381.2220; found: 381.2220.

2.19 *rel*-Methyl 2-([2*S*,4*R*,6*S*]-6-allyl-4-hydroxytetrahydro-2*H*-pyran-2-yl)acetate (8d).



Alcohol **7d**[5] (870.0 mg, 7.76 mmol, 1.00 eq.) was dissolved in CH_2Cl_2 (15 mL) under N_2 atmosphere and DABCO (43.5 mg, 0.39 mmol, 0.05 eq.) was added. Methyl propiolate (717.3 g, 0.76 mL, 8.53 mmol, 1.10 eq.) was added dropwise as a solution in CH_2Cl_2 (10 mL) and the solution was stirred at RT for 1 hour. After completion by TLC, the solution was cooled down to 0 °C, and TFA (8.85 g, 5.78 mL, 77.56 mmol, 10.00 eq.) was added dropwise. After completion by TLC, $NaHCO_3$ sat. (35 mL) was added. The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 25 mL). The combined organic phases were dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. Under N_2 atmosphere, the crude reaction was dissolved in dry MeOH (6 mL) and dry K_2CO_3 (2.15 g, 15.52 mmol, 2.00 eq.) was added at RT. After completion by TLC, H_2O (25 mL) was added and the aqueous phase was extracted with CH_2Cl_2 (3 × 25 mL). The combined organic phases were dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude reaction mixture was purified by column chromatography (SiO_2, EtOAc:PE 60:40) to obtain compounds **8d** (racemate) (758.2 mg, 3.54 mmol, 46 %, three steps) as a colorless oil.

TLC: R_f = 0.51 (EtOAc:PE = 70:30).

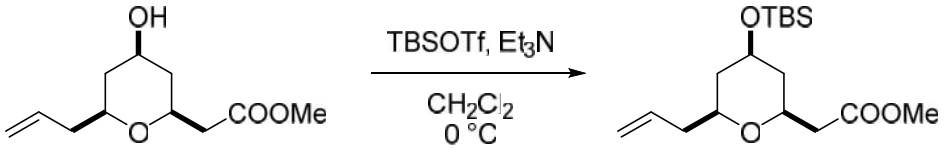
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.79 (dddd, 1 H, *J* = 17.3, 10.2, 7.4, 6.4 Hz), 5.10-5.02 (m, 2 H), 3.86-3.74 (m, 2 H), 3.69 (s, 3 H), 3.38 (dddd, 1 H, *J* = 11.2, 6.5, 6.5, 1.9 Hz), 2.61 (dd, 1 H, *J* = 15.2, 7.8 Hz), 2.43 (dd, 1 H, *J* = 15.2, 5.5 Hz), 2.34 (m_c, 1 H), 2.19 (m_c, 1 H), 2.03-1.94 (m, 2 H), 1.24-1.11 (m, 2 H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 171.7, 134.5, 117.0, 75.3, 72.2, 67.9, 51.8, 41.0, 40.7, 40.4, 40.3 ppm.

IR (NaCl, film): $\tilde{\nu}$ (cm^{-1}) = 3404, 2947, 2920, 2853, 1734, 1641, 1437, 1375, 1333, 1314, 1271, 1196, 1144, 1084, 1032, 1001, 916, 577.

HRMS (ESI+) **$C_{11}H_{18}O_4$** (214.26): *m/z* $[M+Na]^+$ calcd. for $C_{11}H_{18}O_4Na$: 237.1097; found: 237.1080.

2.20 *rel*-Methyl 2-([2*S*,4*R*,6*S*]-6-allyl-4-[{*tert*-butyldimethylsilyl}oxy]tetrahydro-2*H*-pyran-2-yl)acetate (9d).



8d **9d**

Alcohols **8d** (760.0 mg, 3.55 mmol, 1.00 eq.) was dissolved in CH_2Cl_2 (15 mL) under N_2 atmosphere and Et_3N (717.9 mg, 0.99 mL, 7.09 mmol, 2.00 eq.) was added. The solution was cooled down to 0 °C and TBSOTf (1.41 g, 1.22 mL, 5.32 mmol, 1.50 eq.) was added dropwise. After 10 minutes at this temperature, the solution was stirred at RT for 1 hour. After completion by TLC, brine (25 mL) was added and the aqueous phase was extracted with CH_2Cl_2 (3 × 25 mL). The combined organic phases were dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude reaction mixture was purified by column chromatography (SiO_2, EtOAc:PE 10:90) to obtain compounds **9d** (racemate) (951.9 mg, 2.90 mmol, 82 %) as a colorless oil.

TLC: R_f = 0.77 (EtOAc:PE = 40:60).

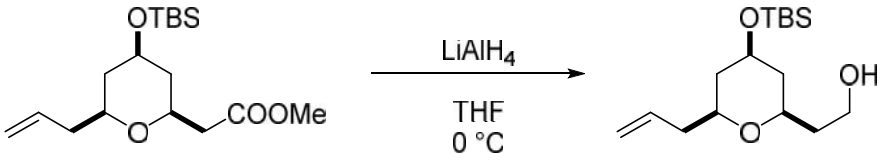
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.79 (dddd, 1 H, *J* = 17.2, 10.2, 7.2, 6.6 Hz), 5.09-5.00 (m, 2 H), 3.82-3.72 (m, 2 H), 3.68 (s, 3 H), 3.35 (dddd, 1 H, *J* = 11.4, 8.6, 6.0, 1.8 Hz), 2.59 (dd, 1 H, *J* = 15.2, 8.0 Hz), 2.41 (dd, 1 H, *J* = 15.2, 5.3 Hz), 2.32 (m_c, 1 H), 2.16 (m_c, 1 H), 1.89-1.78 (m, 2 H), 1.27-1.15 (m, 2 H), 0.88 (m, 9 H), 0.06 (s, 6 H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 171.9, 134.8, 116.8, 75.4, 72.3, 68.6, 51.8, 41.3, 41.1, 41.0, 40.4, 26.0, 18.2, -4.4, -4.4 ppm.

IR (NaCl, film): $\tilde{\nu}$ (cm^{-1}) = 2953, 2930, 2857, 2886, 1744, 1437, 1375, 1254, 1196, 1150, 1130, 1072, 1005, 854, 837, 775.

HRMS (ESI+) **$C_{17}H_{32}O_4Si$** (328.52): *m/z* $[M+Na]^+$ calcd. for $C_{17}H_{32}O_4SiNa$: 351.1962; found: 351.1970.

2.21 *rel*-2-([2*R*,4*R*,6*S*]-6-Allyl-4-[{*tert*-butyldimethylsilyl}oxy]tetrahydro-2*H*-pyran-2-yl)ethan-1-ol and enantiomer (10d).



9d **10d**

Under N_2 atmosphere, esters **9d** (987.2 mg, 3.00 mmol, 1.00 eq.) was dissolved in THF (40 mL). The solution was cooled down to 0 °C and $LiAlH_4$ (1.0 M in THF, 6.00 mL, 6.00 mmol, 2.00 eq.) was added dropwise. After 10 minutes the solution was stirred at RT for 1 hour. After completion by TLC, EtOH was dropped until no more H_2 is produced, sodium potassium tartrate sat. (40 mL) was added and stirred for 10 minutes. The aqueous phase was extracted with CH_2Cl_2 (3 × 40 mL). The combined organic phases were dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to obtain compounds **10d** (racemate) (812.4 mg, 2.70 mmol, 90 %) as a colorless oil.

TLC: R_f = 0.61 (EtOAc:PE = 40:60).

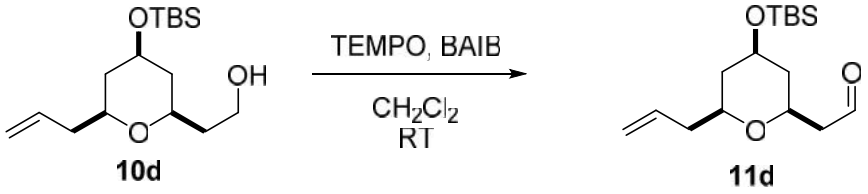
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.76 (dddd, 1 H, *J* = 17.2, 10.2, 7.0, 7.0 Hz),5.07-5.02 (m, 2 H),3.76-3.69 (m, 3 H), 3.51 (m_c, 1 H), 3.35 (m_c, 1 H), 2.97 (br s, 1 H), 2.27-2.15 (m, 2 H), 1.80-1.60 (m, 4 H), 1.33-1.15 (m, 2 H), 0.84 (s, 9 H), 0.02 (s, 6 H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 134.7, 117.4, 76.8, 75.3, 68.5, 61.9, 41.7, 41.2, 40.6, 37.7, 25.9, 18.2, -4.4, -4.5 ppm.

IR (NaCl, film): $\tilde{\nu}$ (cm^{-1}) = 3421, 3078, 2949, 2929, 2886, 2857, 1641, 1464, 1375, 1361, 1352, 1329, 1254, 1152, 1124, 1076, 1005, 964, 914, 837, 775, 669.

HRMS (ESI+) **$C_{16}H_{32}O_3Si$** (300.51): *m/z* $[M+Na]^+$ calcd. for $C_{16}H_{32}O_3SiNa$: 323.2013; found: 323.2020.

2.22 *rel*-2-([2*S*,4*R*,6*S*]-6-Allyl-4-[{*tert*-butyldimethylsilyl}oxy]tetrahydro-2*H*-pyran-2-yl)acetaldehyde (11d).



Alcohols **10d** (100.0 mg, 0.33 mmol, 1.00 eq.) was dissolved in CH_2Cl_2 (1 mL) and TEMPO (5.2 mg, 0.03 mmol, 0.10 eq.) was added followed by BAIB (117.9 mg, 0.37 mmol, 1.10 eq.) and the solution stirred for 3 h at RT. After completion by TLC, the reaction was diluted with CH_2Cl_2 (5 mL) and washed with sodium thiosulfate sat. (1 mL). The aqueous layer was washed with CH_2Cl_2 (3 x 1 mL) and the combined organic phases were washed with $NaHCO_3$ sat. (1 mL) and brine (3 mL). Both aqueous layers were washed with CH_2Cl_2 (5 mL) and the combined organic phases were dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude reaction mixture was purified by column chromatography (SiO_2, EtOAc:PE 15:85) to obtain compounds **11d** (racemate) (62.0 mg, 0.21 mmol, 62 %) as a colorless oil.

TLC: R_f = 0.71 (EtOAc:PE = 20:80).

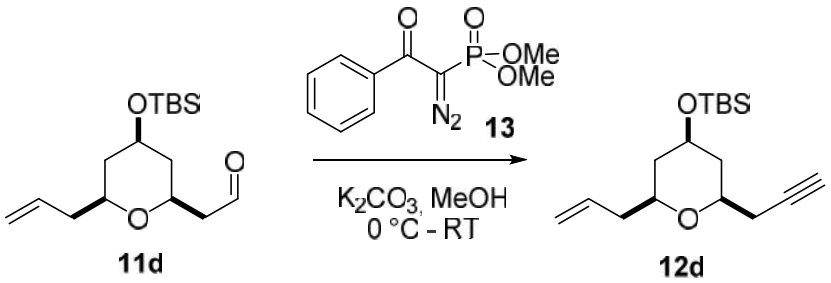
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.77 (dd, 1 H, *J* = 2.5, 1.9 Hz), 5.78 (dddd, 1 H, *J* = 17.1, 10.2, 7.0, 7.0 Hz), 5.08-5.00 (m, 2 H), 3.86-3.73 (m, 2 H), 3.36 (m_c, 1 H), 2.62 (ddd, 1 H, *J* = 16.4, 8.0, 2.5 Hz), 2.45 (ddd, 1 H, *J* = 16.4, 4.5, 1.9 Hz), 2.29 (m_c, 1 H), 2.16 (m_c, 1 H), 1.85-1.79 (m, 2 H), 1.30-1.15 (m, 2 H), 0.87 (s, 9 H), 0.05 (s, 6 H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 201.3, 134.6, 117.0, 75.5, 70.9, 68.5, 49.6, 41.4, 41.0, 40.4, 25.9, 18.2, -4.4, -4.5 ppm.

IR (NaCl, film): $\tilde{\nu}$ (cm^{-1}) = 2953, 2930, 2886, 2857, 1728, 1389, 1375, 1254, 1125, 1074, 916, 866, 837, 775.

HRMS (ESI+) **$C_{16}H_{30}O_3Si$** (298.50): *m/z* $[M+Na]^+$ calcd. for $C_{16}H_{30}O_3SiNa$: 321.1856; found: 321.1872.

2.23 *rel*-([{2*S*,4*R*,6*R*}-2-Allyl-6-{prop-2-yn-1-yl}tetrahydro-2*H*-pyran-4-yl]oxy)(*tert*-butyl)dimethylsilane and enantiomer (12d).



Aldehydes **11d** (62.0 mg, 0.21 mmol, 1.00 eq.) was dissolved in MeOH (2 mL) under N_2 atmosphere and K_2CO_3 (114.8 mg, 0.83 mmol, 4.00 eq) was added. The reaction was cooled down to 0 °C and the diazo compound **13** (73.9 mg, 0.29 mmol, 1.40 eq.) was added as a solution in MeOH (2 mL). After 10 minutes the solution was allowed to reach room temperature and stirred overnight. After completion by TLC, brine (25 mL) was added and the aqueous phase was extracted with EtOAc (3 × 25 mL). The combined organic phases were dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude reaction mixture was purified by column chromatography (SiO_2, EtOAc:PE 5:95) to obtain compounds **12d** (racemate) (51.6 mg, 0.18 mmol, 84 %) as a colorless oil.

TLC: R_f = 0.73 (EtOAc:PE = 10:90).

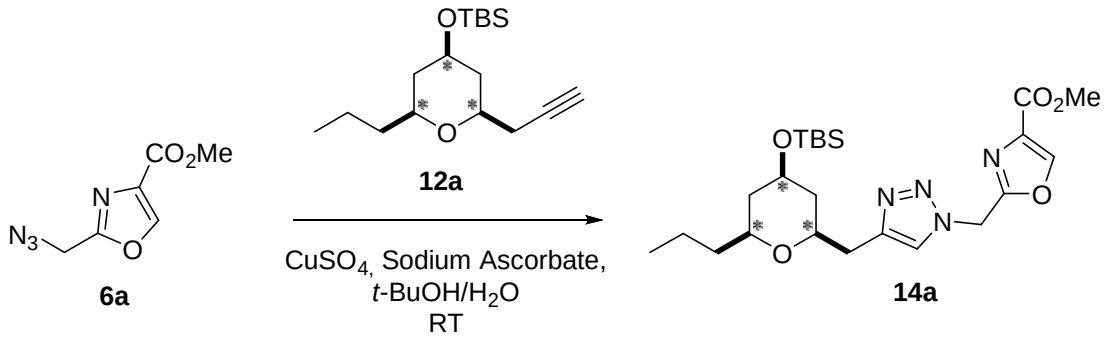
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.83 (dddd, 1 H, *J* = 17.1, 10.1, 6.9, 6.9 Hz), 5.10-5.03 (m, 2 H), 3.76 (dddd, 1 H, *J* = 10.8, 10.8, 4.4, 4.4 Hz), 3.44 (dddd, 1 H, *J* = 11.2, 7.3, 5.7, 1.8 Hz), 3.35 (dddd, 1 H, *J* = 11.6, 6.4, 6.4, 2.0 Hz), 2.50 (ddd, 1 H, *J* = 16.6, 5.5, 2.7 Hz), 2.39-2.27 (m, 2 H), 2.19 (m, 1 H), 2.05-1.98 (m, 2 H), 1.81 (m, 1 H), 1.28-1.16 (m, 2 H), 0.88 (s, 9 H), 0.06 (s, 6 H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 134.8, 117.0, 80.9, 75.5, 74.0, 70.1, 68.7, 41.0, 40.8, 40.5, 26.0, 25.9, 18.2, -4.4 ppm.

IR (NaCl, film): $\tilde{\nu}$ (cm^{-1}) = 3314, 2953, 2930. 2886, 2857, 1464, 1383, 1256, 1153, 1126, 1088, 1069, 1005, 916, 870, 837, 775, 638.

HRMS (ESI+) **$C_{17}H_{30}O_2Si$** (294.51): *m/z* $[M+Na]^+$ calcd. for $C_{17}H_{30}O_2SiNa$: 317.1913; found: 317.1934.

2.24 *rel*-Methyl 2-([4-{([2*R*,4*R*,6*S*]-4-[{*tert*-butyldimethylsilyl}oxy]-6-propyltetrahydro-2*H*-pyran-2-yl)methyl}-1*H*-1,2,3-triazol-1-yl]methyl)oxazole-4-carboxylate (14a).



Azide **6a** (8.0 mg, 43.9 µmol, 1.00 eq.) and ethynyl **12a** (13.0 mg, 43.8 µmol, 1.00 eq.) were dispersed in *t*-BuOH (0.5 mL) and H_2O (0.5 mL). $CuSO_4$•$5H_2O$ (0.2 mg, 0.8 µmol, 0.02 eq.) and sodium ascorbate (1.7 mg, 8.6 µmol, 0.20 eq.) were added and the mixture was stirred overnight at RT. After completion by TLC, brine (10 mL) was added and the aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phases were dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude reaction mixture was purified by column chromatography (SiO_2, EtOAc:PE 60:40) to obtain compounds **14a** (racemate) (10.9 mg, 22.7 µmol, 52 %) as a colorless oil.

TLC: R_f = 0.29 (EtOAc:PE = 40:60).

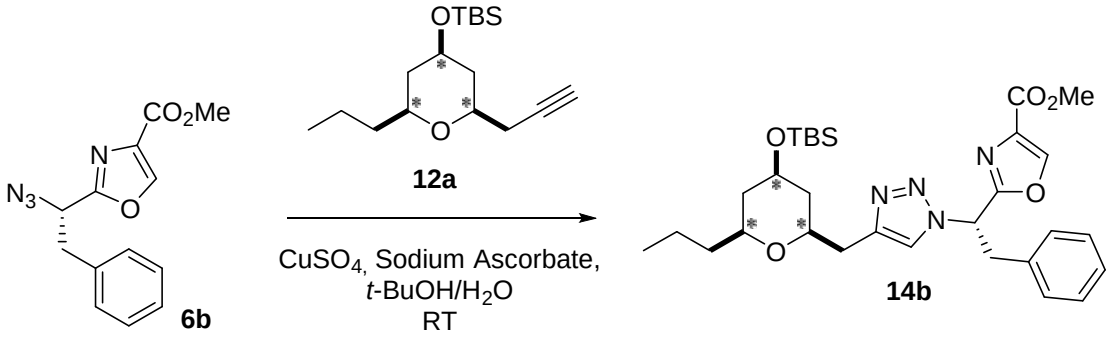
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 (s, 1 H), 7.55 (s, 1 H), 5.69 (s, 2 H), 3.93 (s, 3 H), 3.65 (m, 1 H), 3.52 (dddd, 1 H, *J* = 12.1, 9.1, 5.1, 2.0 Hz), 3.22 (dddd, 1 H, *J* = 11.6, 7.8, 4.0, 1.8 Hz), 2.95-2.83 (m, 2 H), 1.84 (dddd, 1 H, *J* = 12.4, 6.1, 1.5, 1.5 Hz), 1.77 (dddd, 1 H, *J* = 12.4, 6.1, 1.5, 1.5 Hz), 1.54-1.13 (m, 6 H), 0.87 (s, 9 H), 0.85 (t, 3 H, *J* = 7.1 Hz), 0.04 (s, 3 H), 0.03 (s, 3 H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 160.0, 158.1, 146.2, 145.3, 134.0, 122.7, 75.5, 74.5, 68.8, 52.6, 46.3, 41.7, 41.4, 38.3, 32.7, 26.0, 19.0, 18.2, 14.1, -4.4 ppm.

IR (NaCl, film): $\tilde{\nu}$ (cm^{-1}) = 3147, 2954, 2931, 2858, 1743, 1585, 1462, 1438, 1377, 1346, 1323, 1249, 1230, 1195, 1145, 1114, 1076, 1002, 972, 933, 910, 837, 806, 775, 667.

HRMS (ESI+) **$C_{23}H_{38}N_4O_5Si$** (478.67): *m/z* $[M+H]^+$ calcd. for $C_{23}H_{39}N_4O_5Si$: 479.26842; found: 479.26616.

2.25 Methyl 2-([*S*]-1-[4-{([2*R*,4*R*,6*S*]-4-[{*tert*-butyldimethylsilyl}oxy]-6-propyltetrahydro-2H-pyran-2-yl)methyl}-1*H*-1,2,3-triazol-1-yl]-2-phenylethyl)oxazole-4-carboxylate and methyl 2-([*S*]-1-[4-{([2*S*,4*S*,6*R*]-4-[{*tert*-butyldimethylsilyl}oxy]-6-propyltetrahydro-2H-pyran-2-yl)methyl}-1*H*-1,2,3-triazol-1-yl]-2-phenylethyl)oxazole-4-carboxylate (14b).



Azide **6b** (15.0 mg, 55.1 µmol, 1.00 eq.) and ethynyl **12a** (16.2 mg, 55.1 µmol, 1.00 eq.) were dispersed in *t*-BuOH (0.5 mL) and H_2O (0.5 mL). $CuSO_4 \bullet 5H_2O$ (0.3 mg, 1.2 µmol, 0.02 eq.) and sodium ascorbate (2.2 mg, 11.0 µmol, 0.20 eq.) were added and the mixture was stirred overnight at RT. After completion by TLC, brine (10 mL) was added and the aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phases were dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude reaction mixture was purified by column chromatography (SiO_2, EtOAc:PE 30:70) to obtain compounds **14b** (diasteromeric mixture) (24.5 mg, 43.1 µmol, 78 %) as a colorless oil.

TLC: R_f = 0.40 (EtOAc:PE = 40:60).

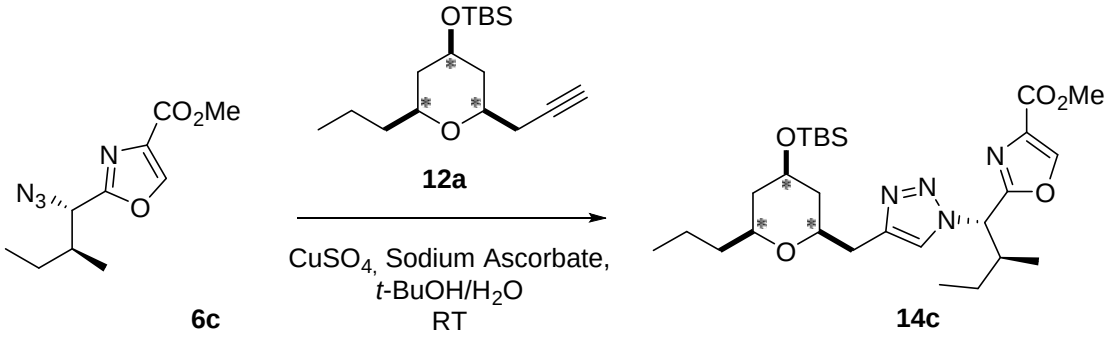
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (s, 2 H), 7.52 (s, 1 H), 7.50 (s, 1 H), 7.26-7.19 (m, 6 H), 7.06-7.04 (m, 4 H), 6.09-6.01 (m, 2 H), 3.93 (s, 6 H), 3.80-3.67 (m, 6 H), 3.53-3.44 (m, 2 H), 3.25-3.18 (m, 2 H), 2.90-2.81 (m, 4 H), 1.83-1.75 (m, 6 H), 1.52-1.10 (m, 12 H), 0.88-0.83 (m, 24 H), 0.04 (s, 12 H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 161.1, 160.7, 160.6, 145.5, 145.0, 134.8, 134.7, 133.8, 133.7, 129.0, 128.9, 127.7, 127.6, 122.0, 121.7, 75.4, 74.6, 74.5, 68.8, 59.5, 59.4, 52.5, 41.8, 41.7, 41.3, 41.2, 39.7, 38.3, 32.7, 32.6, 25.9, 19.0, 18.9, 18.2, 14.2, 14.1, -4.4, -4.5 ppm.

IR (NaCl, film): $\tilde{\nu}$ (cm^{-1}) = 3147, 2954, 2931, 2858, 1743, 1581, 1496, 1458, 1438, 1377, 1342, 1323, 1253, 1199, 1145, 1114, 1076, 1002, 933, 856, 837, 806, 775, 748, 702, 671.

HRMS (ESI+) **$C_{30}H_{44}N_4O_5Si$** (568.79): *m/z* $[M+H]^+$ calcd. for $C_{30}H_{45}N_4O_5Si$: 569.3154; found: 569.3134.

2.26 Methyl 2-([1*S*,2*S*]-1-[4-{([2*R*,4*R*,6*S*]-4-[{*tert*-butyldimethylsilyl}oxy]-6-propyltetrahydro-2*H*-pyran-2-yl)methyl}-1*H*-1,2,3-triazol-1-yl]-2-methylbutyl)oxazole-4-carboxylate and methyl 2-([1*S*,2*S*]-1-[4-{([2*S*,4*S*,6*R*]-4-[{*tert*-butyldimethylsilyl}oxy]-6-propyltetrahydro-2*H*-pyran-2-yl)methyl}-1*H*-1,2,3-triazol-1-yl]-2-methylbutyl)oxazole-4-carboxylate (14c).



Azide **6c** (10.0 mg, 42.0 µmol, 1.00 eq.) and ethynyl **12a** (12.4 mg, 42.0 µmol, 1.00 eq.) were dispersed in *t*-BuOH (0.5 mL) and H_2O (0.5 mL). $CuSO_4$•$5H_2O$ (0.2 mg, 0.8 µmol, 0.02 eq.) and sodium ascorbate (1.7 mg, 8.6 µmol, 0.20 eq.) were added and the mixture was stirred overnight at RT. After completion by TLC, brine (10 mL) was added and the aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phases were dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude reaction mixture was purified by column chromatography (SiO_2, EtOAc:PE 30:70) to obtain compounds **14c** (diasteromeric mixture) (18.2 mg, 34.0 µmol, 81 %) as a colorless oil.

TLC: R_f = 0.51 (EtOAc:PE = 40:60).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (s, 2 H), 7.68 (s, 1 H), 7.67 (s, 1 H), 5.66 (d, 2 H, *J* = 10.6 Hz), 3.93 (s, 6 H), 3.78-3.69 (m, 2 H), 3.58-3.49 (m, 2 H), 3.26-3.19 (m, 2 H), 2.94-2.86 (m, 4 H), 2.65-2.54 (m, 2 H), 1.86-1.74 (m, 4 H), 1.54-1.46 (m, 2 H), 1.46-1.13 (m,

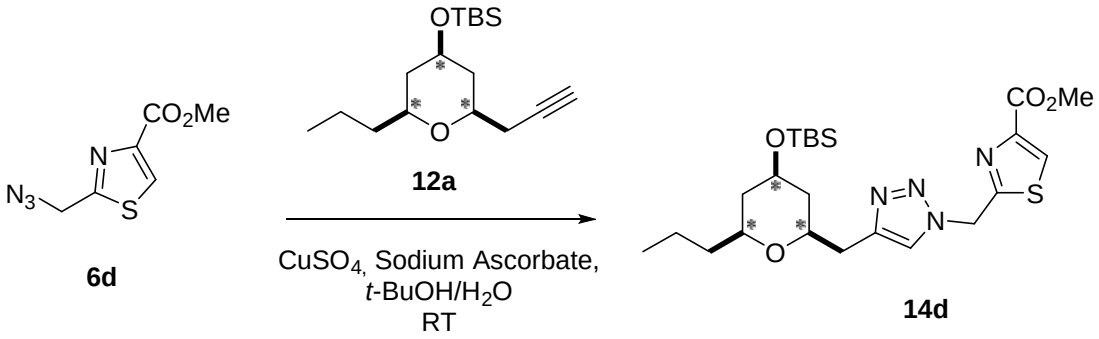
12 H), 1.10-1.00 (m, 2 H), 0.93 (d, 6 H, *J* = 6.7 Hz), 0.88-0.82 (m, 30 H), 0.03 (s, 12 H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 161.2, 161.1, 145.8, 145.7, 144.6, 133.8, 121.5, 75.5, 75.4, 74.7, 74.6, 68.9, 68.8, 62.9, 52.5, 41.9, 41.6, 41.5, 39.0, 38.9, 38.4, 38.3, 32.8, 32.7, 26.0, 25.0, 19.1, 19.0, 18.2, 15.8, 15.7, 14.2, 14.1, 10.5, 10.4, -4.4, -4.5 ppm.

IR (NaCl, film): $\tilde{\nu}$ (cm^{-1}) = 3151, 2954, 2931, 2858, 1747, 1728, 1581, 1465, 1442, 1381, 1323, 1253, 1230, 1195, 1149, 1114, 1076, 1045, 1002, 972, 933, 837, 775, 667.

HRMS (ESI+) **$C_{27}H_{46}N_4O_5Si$** (534.77): *m/z* $[M+H]^+$ calcd. for $C_{27}H_{47}N_4O_5Si$: 535.33102; found: 535.32836.

2.27 *rel*-Methyl 2-([4-{([2*R*,4*R*,6*S*]-4-[{*tert*-butyldimethylsilyl}oxy]-6-propyltetrahydro-2H-pyran-2-yl)methyl}-1*H*-1,2,3-triazol-1-yl]methyl)thiazole-4-carboxylate (14d).



Azide **6d** (8.2 mg, 41.3 µmol, 1.00 eq.) and ethynyl **12a** (12.2 mg, 41.3 µmol, 1.00 eq.) were dispersed in *t*-BuOH (0.5 mL) and H_2O (0.5 mL). $CuSO_4$•$5H_2O$ (0.2 mg, 0.8 µmol, 0.02 eq.) and sodium ascorbate (1.7 mg, 8.6 µmol, 0.20 eq.) were added and the mixture was stirred overnight at RT. After completion by TLC, brine (10 mL) was added and the aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phases were dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude reaction mixture was purified by column chromatography (SiO_2, EtOAc:PE 50:50) to obtain compounds **14d** (racemate) (11.2 mg, 22.6 µmol, 55 %) as a colorless oil.

TLC: R_f = 0.32 (EtOAc:PE = 50:50).

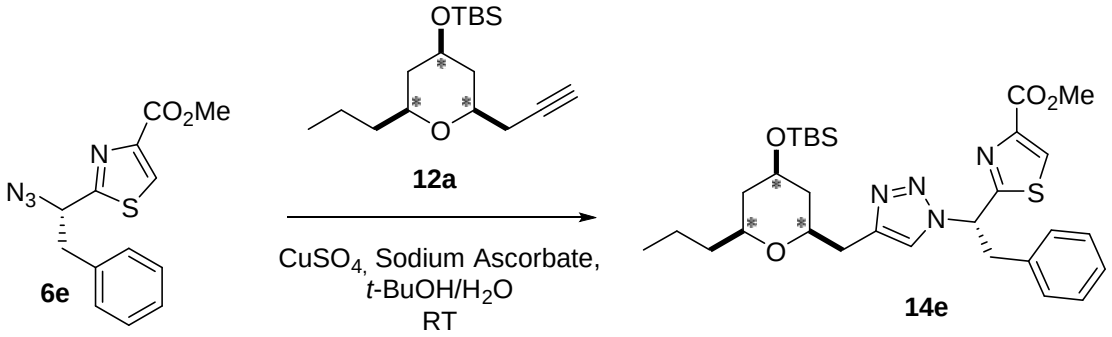
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (s, 1 H), 7.55 (s, 1 H), 5.88 (s, 2 H), 3.98 (s, 3 H), 3.74 (dddd, 1 H, *J* = 10.7, 10.7, 4.7, 4.7 Hz), 3.53 (dddd, 1 H, *J* = 12.1, 6.8, 5.4, 1.8 Hz), 3.22 (dddd, 1 H, *J* = 11.9, 7.8, 4.0, 1.8 Hz), 2.95-2.88 (m, 2 H), 1.83 (dddd, 1 H, *J* = 12.4, 6.3, 1.8, 1.8 Hz), 1.78 (dddd, 1 H, *J* = 12.6, 6.6, 1.8, 1.8 Hz), 1.53-1.12 (m, 6 H), 0.87 (s, 9 H), 0.84 (t, 3 H, *J* = 6.8 Hz), 0.04 (s, 3 H), 0.03 (s, 3 H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 164.7, 161.5, 147.0, 146.2, 129.6, 122.8, 75.5, 74.5, 68.8, 52.8, 51.0, 41.7, 41.4, 38.3, 32.7, 26.0, 19.0, 18.2, 14.1, -4.4 ppm.

IR (NaCl, film): $\tilde{\nu}$ (cm^{-1}) = 3124, 2954, 2931, 2858, 1732, 1631, 1550, 1465, 1438, 1377, 1342, 1323, 1249, 1219, 1153, 1122, 1080, 999, 933, 914, 860, 837, 775, 671.

HRMS (ESI+) **$C_{23}H_{38}N_4O_4SSi$** (494.73): *m/z* $[M+Na]^+$ calcd. for $C_{23}H_{38}N_4O_4SSiNa$: 517.22752; found: 517.22451.

2.28 Methyl 2-([*S*]-1-[4-{([2*R*,4*R*,6*S*]-4-[{*tert*-butyldimethylsilyl}oxy]-6-propyltetrahydro-2*H*-pyran-2-yl)methyl}-1*H*-1,2,3-triazol-1-yl]-2-phenylethyl)thiazole-4-carboxylate and methyl 2-([*S*]-1-[4-{([2*S*,4*S*,6*R*]-4-[{*tert*-butyldimethylsilyl}oxy]-6-propyltetrahydro-2*H*-pyran-2-yl)methyl}-1*H*-1,2,3-triazol-1-yl]-2-phenylethyl)thiazole-4-carboxylate (14e).



Azide **6e** (10.0 mg, 34.7 µmol, 1.00 eq.) and ethynyl **12a** (10.4 mg, 34.6 µmol, 1.00 eq.) were dispersed in *t*-BuOH (0.5 mL) and H_2O (0.5 mL). $CuSO_4$•$5H_2O$ (0.2 mg, 0.8 µmol, 0.02 eq.) and sodium ascorbate (1.7 mg, 8.0 µmol, 0.20 eq.) were added and the mixture was stirred overnight at RT. After completion by TLC, brine (10 mL) was added and the aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phases were dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude reaction mixture was purified by column chromatography (SiO_2, EtOAc:PE

40:60) to obtain compounds **14e** (diasteromeric mixture) (16.6 mg, 28.4 µmol, 82 %) as a colorless oil.

TLC: R_f = 0.59 (EtOAc:PE = 40:60).

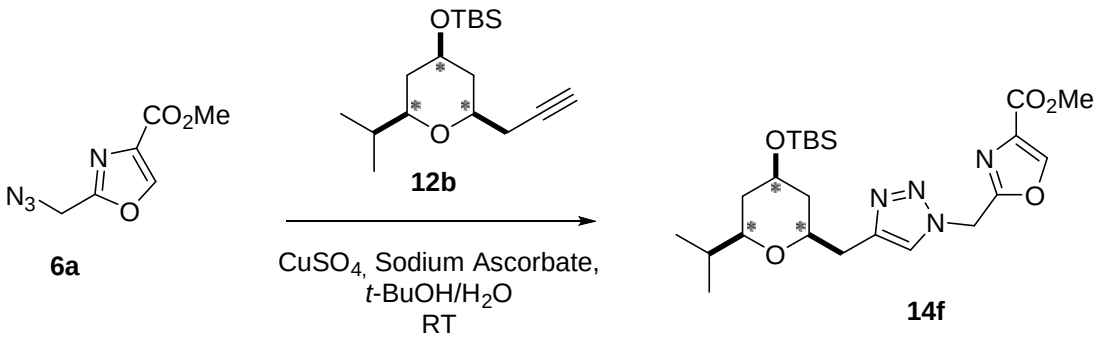
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (s, 2 H), 7.38 (s, 1 H), 7.34 (s, 1 H), 7.24-7.16 (m, 6 H), 7.06-7.03 (m, 4 H), 6.17-6.10 (m, 2 H), 3.97 (s, 6 H), 3.83-3.67 (m, 6 H), 3.48 (dddd, 1 H, *J* = 11.1, 6.6, 5.1, 1.6 Hz), 3.41 (dddd, 1 H, *J* = 11.4, 6.8, 5.3, 1.6 Hz), 3.23-3.12 (m, 2 H), 2.89-2.79 (m, 4 H), 1.81-1.70 (m, 4 H), 1.48-1.06 (m, 12 H), 0.88 (s, 9 H), 0.87 (s, 9 H), 0.83 (t, 6 H, *J* = 7.3 Hz), 0.04 (s, 12 H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 168.5, 168.4, 161.6, 146.6, 146.5, 145.3, 145.1, 135.5, 135.4, 129.5, 129.4, 129.1, 129.0, 128.9, 128.8, 127.5, 127.4, 123.1, 122.9, 75.5, 75.4, 74.6, 74.4, 68.9, 52.8, 42.5, 42.3, 41.7, 41.6, 41.3, 41.1, 38.3, 32.6, 32.5, 26.0, 19.0, 18.9, 18.2, 14.2, -4.4 ppm.

IR (NaCl, film): $\tilde{\nu}$ (cm^{-1}) = 3120, 3089, 3062, 3032, 2954, 2931, 2858, 1735, 1604, 1550, 1462, 1377, 1346, 1327, 1249, 1215, 1153, 1122, 1076, 1002, 933, 914, 860, 837, 775, 756, 702, 671, 624.

HRMS (ESI+) **$C_{30}H_{44}N_4O_4SSi$** (584.85): *m/z* $[M+Na]^+$ calcd. for $C_{30}H_{44}N_4O_4SSi$: 607.27447; found: 607.27225.

2.29 *rel*-Methyl 2-([4-{([2*R*,4*S*,6*R*]-4-[{*tert*-butyldimethylsilyl}oxy]-6-isopropyltetrahydro-2*H*-pyran-2-yl)methyl}-1*H*-1,2,3-triazol-1-yl]methyl)oxazole-4-carboxylate (14f).



Azide **6a** (15.0 mg, 82.3 µmol, 1.00 eq.) and ethynyl **12b** (24.3 mg, 82.1 µmol, 1.00 eq.) were dispersed in *t*-BuOH (0.5 mL) and H_2O (0.5 mL). $CuSO_4 \bullet 5H_2O$ (0.4 mg, 1.6 µmol, 0.02 eq.) and sodium ascorbate (3.4 mg, 17.0 µmol, 0.20 eq.) were added and the mixture was stirred overnight at RT. After completion by TLC, brine (15 mL) was added and the aqueous phase was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic phases were dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude reaction mixture was purified by column chromatography (SiO_2, EtOAc:PE 50:50) to obtain compounds **14f** (racemate) (12.5 mg, 26.1 µmol, 32 %) as a colorless oil.

TLC: R_f = 0.32 (EtOAc:PE = 60:40).

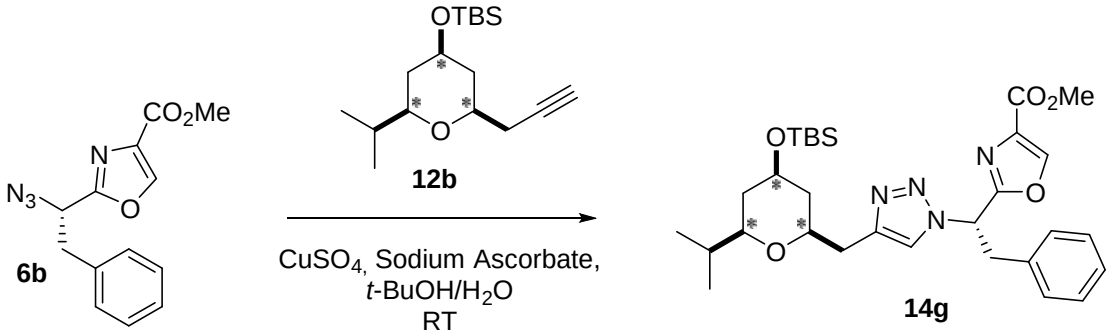
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (s, 1 H), 7.55 (s, 1 H), 5.59 (d, 1 H, *J* = 2.3 Hz), 3.93 (s, 3 H), 3.73 (dddd, 1 H, *J* = 10.4, 10.4, 4.8, 4.8 Hz), 3.48 (m_c, 1 H), 2.94-2.84 (m, 3 H), 1.85-1.75 (m, 2 H), 1.65-1.61 (m, 2 H), 1.26-1.11 (m, 2 H), 0.87 (s, 9 H), 0.84 (d, 3 H, *J* = 2.7 Hz), 0.83 (d, 3 H, *J* = 2.7 Hz), 0.05 (s, 3 H), 0.04 (s, 3 H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 161.0, 158.1, 146.3, 145.3, 134.0, 122.8, 80.6, 74.4, 69.2, 52.6, 46.3, 41.4, 38.4, 33.0, 32.7, 26.0, 18.8, 18.6, 18.2, -4.3, -4.4 ppm.

IR (NaCl, film): $\tilde{\nu}$ (cm^{-1}) = 2995, 2930, 2857, 1744, 1586, 1564, 1466, 1443, 1324, 1266, 1231, 1146, 1113, 1069, 1005, 837, 809, 772, 739.

HRMS (ESI+) **$C_{23}H_{38}N_4O_5Si$** (478.67): *m/z* $[M+H]^+$ calcd. for $C_{23}H_{39}N_4O_5Si$: 479.2684; found: 479.2699.

2.30 Methyl 2-([*S*]-1-[4-{([2*R*,4*S*,6*R*]-4-[{*tert*-butyldimethylsilyl}oxy]-6-isopropyltetrahydro-2*H*-pyran-2-yl)methyl}-1*H*-1,2,3-triazol-1-yl]-2-phenylethyl)oxazole-4-carboxylate and methyl 2-([*S*]-1-[4-{([2*S*,4*R*,6*S*]-4-[{*tert*-butyldimethylsilyl}oxy]-6-isopropyltetrahydro-2*H*-pyran-2-yl)methyl}-1*H*-1,2,3-triazol-1-yl]-2-phenylethyl)oxazole-4-carboxylate (14g).



Azide **6b** (25.0 mg, 91.9 µmol, 1.00 eq.) and ethynyl **12b** (27.2 mg, 91.7 µmol, 1.00 eq.) were dispersed in *t*-BuOH (0.5 mL) and H_2O (0.5 mL). $CuSO_4 \bullet 5H_2O$ (0.4 mg, 1.6 µmol, 0.02 eq.) and sodium ascorbate (3.4 mg, 17.0 µmol, 0.20 eq.) were added and the mixture was stirred overnight at RT. After completion by TLC, brine (10 mL) was added and the aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phases were dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude reaction mixture was purified by column chromatography (SiO_2, EtOAc:PE 40:60) to obtain compounds **14g** (diasteromeric mixture) (34.2 mg, 60.1 µmol, 66 %) as a colorless oil.

TLC: R_f = 0.54 (EtOAc:PE = 40:60).

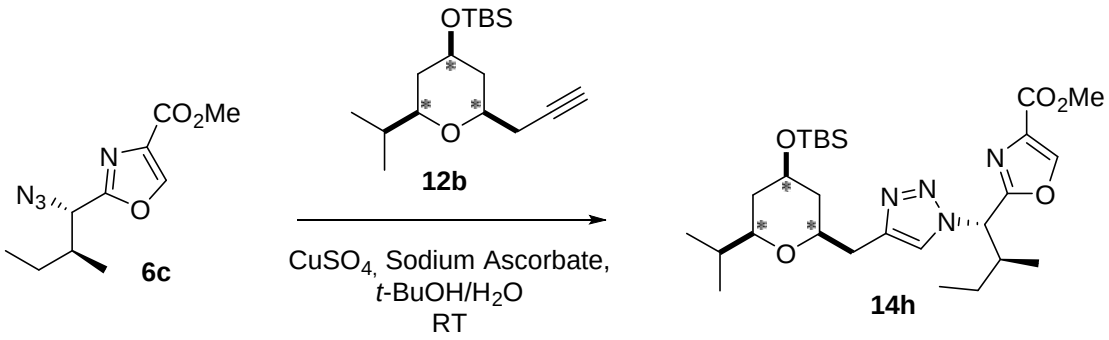
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (s, 2 H), 7.54 (s, 1 H), 7.49 (s, 1 H), 7.25-7.20 (m, 6 H), 7.07- 7.05 (m, 4 H), 6.11-6.01 (m, 2 H), 3.93 (s, 3 H), 3.92 (s, 3 H), 3.81-3.66 (m, 6 H), 3.48-3.43 (m, 2 H), 2.95-2.82 (m, 6 H), 1.82-1.75 (m, 4 H), 1.65-1.59 (m, 2 H), 1.22-1.07 (m, 4 H), 0.88 (s, 18 H), 0.84-0.81 (m, 12 H), 0.05 (s, 6 H), 0.04 (s, 6 H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 161.1, 160.7, 145.6, 145.5, 144.9, 134.8, 134.7, 133.8, 129.0, 128.9, 127.7, 122.1, 121.7, 80.6, 74.4, 69.2, 59.5, 59.4, 52.5, 41.2, 39.8, 39.7, 38.4, 38.3, 33.0, 32.6, 26.0, 18.9, 18.8, 18.6, 18.2, -4.4, -4.5 ppm.

IR (NaCl, film): $\tilde{\nu}$ (cm^{-1}) = 2955, 2932, 2857, 1746, 1727, 1582, 1466, 1441, 1322, 1254, 1113, 1071, 1003, 837, 773, 747, 700.

HRMS (ESI+) **$C_{30}H_{44}N_4O_5Si$** (568.79): *m/z* $[M+H]^+$ calcd. for $C_{30}H_{45}N_4O_5Si$: 569.3164; found: 569.3167.

2.31 Methyl 2-([1*S*,2*S*]-1-[4-{([2*R*,4*S*,6*R*]-4-[{*tert*-butyldimethylsilyl}oxy]-6-isopropyltetrahydro-2*H*-pyran-2-yl)methyl}-1*H*-1,2,3-triazol-1-yl]-2-methylbutyl)oxazole-4-carboxylate and methyl 2-([1*S*,2*S*]-1-[4-{([2*S*,4*R*,6*S*]-4-[{*tert*-butyldimethylsilyl}oxy]-6-isopropyltetrahydro-2*H*-pyran-2-yl)methyl}-1*H*-1,2,3-triazol-1-yl]-2-methylbutyl)oxazole-4-carboxylate (14h).



Azide **6c** (20.1 mg, 84.3 µmol, 1.00 eq.) and ethynyl **12b** (25.0 mg, 84.3 µmol, 1.00 eq.) were dispersed in *t*-BuOH (0.5 mL) and H_2O (0.5 mL). $CuSO_4 \bullet 5H_2O$ (0.4 mg, 1.6 µmol, 0.02 eq.) and sodium ascorbate (3.4 mg, 17.0 µmol, 0.20 eq.) were added and the mixture was stirred overnight at RT. After completion by TLC, brine (10 mL) was added and the aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phases were dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude reaction mixture was purified by column chromatography (SiO_2, EtOAc:PE 30:70) to obtain compounds **14h** (diasteromeric mixture) (43.7 mg, 81.7 µmol, 97 %) as a colorless oil.

TLC: R_f = 0.24 (EtOAc:PE = 30:70).

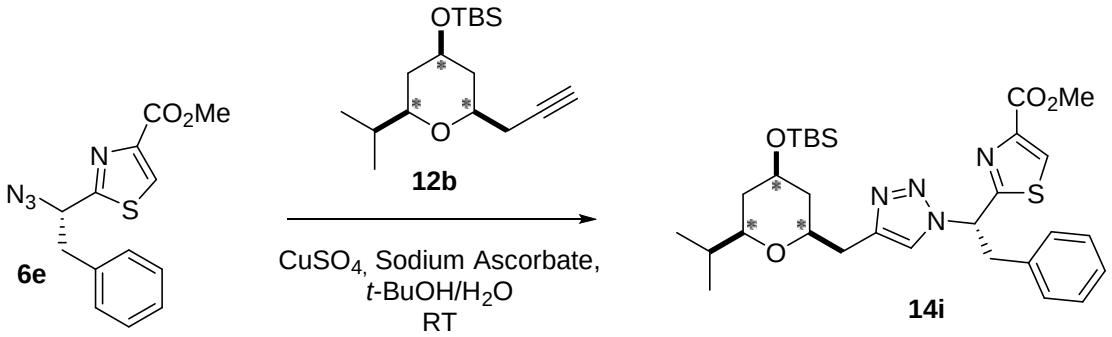
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (s, 1 H), 8.22 (s, 1 H), 7.69 (s, 2 H), 5.57 (d, 1 H, *J* = 10.7 Hz), 5.66 (d, 1 H, *J* = 10.8 Hz), 3.93 (s, 3 H), 3.93 (s, 3 H), 3.78-3.68 (m, 2 H), 3.56-3.44 (m, 2 H), 2.95-2.82 (m, 6 H), 2.65-2.54 (m, 2 H), 1.85-1.77 (m, 4 H), 1.67-1.58 (m, 2 H), 1.23-0.99 (m, 8 H), 0.93 (d, 6 H, *J* = 6.6 Hz), 0.87 (s, 18 H), 0.87-0.83 (m, 18 H), 0.04 (s, 12 H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 161.3, 161.2, 145.9, 145.8, 144.6, 133.8, 121.5, 121.5, 80.7, 80.6, 74.6, 74.5, 69.3, 69.2, 63.0, 62.9, 52.5, 52.4, 41.6, 41.5, 39.0, 39.0, 38.7, 38.6, 33.1, 32.8, 26.0, 25.1, 19.0, 18.9, 18.7, 18.2, 15.8, 15.7, 10.4, 10.4, -4.4, -4.4 ppm.

IR (NaCl, film): $\tilde{\nu}$ (cm^{-1}) = 2954, 2932, 2857, 1751, 1719, 1578, 1381, 1341, 1321, 1252, 1198, 1152, 1113, 1070, 1005, 853, 837, 775.

HRMS (ESI+) **$C_{27}H_{46}N_4O_5Si$** (534.77): *m/z* $[M+H]^+$ calcd. for $C_{27}H_{47}N_4O_5Si$: 535.3310; found: 535.3323; $[M+Na]^+$ calcd. for $C_{27}H_{46}N_4O_5SiNa$: 557.3130; found: 557. 3142.

2.32 Methyl 2-([*S*]-1-[4-{([2*R*,4*S*,6*R*]-4-[{*tert*-butyldimethylsilyl}oxy]-6-isopropyltetrahydro-2*H*-pyran-2-yl)methyl}-1*H*-1,2,3-triazol-1-yl]-2-phenylethyl)thiazole-4-carboxylate and methyl 2-([*S*]-1-[4-{([2*S*,4*R*,6*S*]-4-[{*tert*-butyldimethylsilyl}oxy]-6-isopropyltetrahydro-2*H*-pyran-2-yl)methyl}-1*H*-1,2,3-triazol-1-yl]-2-phenylethyl)thiazole-4-carboxylate (14i).



Azide **6e** (25.0 mg, 86.7 µmol, 1.00 eq.) and ethynyl **12b** (25.7 mg, 86.6 µmol, 1.00 eq.) were dispersed in *t*-BuOH (0.5 mL) and H_2O (0.5 mL). $CuSO_4$•$5H_2O$ (0.4 mg, 1.6 µmol, 0.02 eq.) and sodium ascorbate (3.4 mg, 17.0 µmol, 0.20 eq.) were added and the mixture was stirred overnight at RT. After completion by TLC, brine (10 mL) was added and the aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phases were dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude reaction mixture was purified by column chromatography (SiO_2, EtOAc:PE 40:60) to obtain compounds **14i** (diasteromeric mixture) (43.7 mg, 76.8 µmol, 86 %) as a yellowish oil.

TLC: R_f = 0.27 (EtOAc:PE = 30:70).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (s, 1 H), 8.18 (s, 1 H), 7.41 (s, 1 H), 7.34 (s, 1 H), 7.23-7.16 (m, 6 H), 7.06-7.03 (m, 4 H), 6.17-6.10 (m, 2 H), 3.97 (s, 6 H), 3.79-3.68 (m, 6 H),

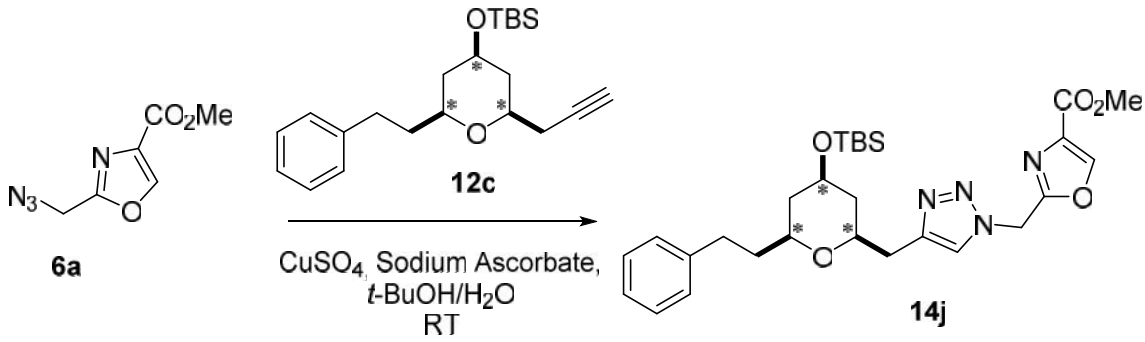
3.49-3.37 (m, 2 H), 2.93-2.79 (m, 6 H), 1.80-1.71 (m, 4 H), 1.63-1.55 (m, 2 H), 1.21-1.03 (m, 4 H), 0.88 (s, 9 H), 0.87 (s, 9 H), 0.81-0.77 (m, 12 H), 0.05 (s, 6 H), 0.04 (s, 6 H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 168.4, 168.3, 161.6, 146.6, 146.5, 145.3, 145.1, 135.5, 129.4, 129.3, 129.0, 129.0, 128.9, 128.8, 127.5, 127.4, 123.1, 122.8, 80.6, 80.5, 74.5, 74.3, 69.2, 52.7, 42.4, 42.2, 41.2, 41.0, 38.3, 38.2, 32.9, 32.5, 32.4, 25.9, 18.8, 18.7, 18.6, 18.5, 18.2, -4.4 ppm.

IR (NaCl, film): $\tilde{\nu}$ (cm^{-1}) = 2955, 2932, 2857, 1729, 1458, 1441, 1374, 1347, 1326, 1250, 1218, 1156, 1119, 1071, 878, 838, 778, 701.

HRMS (ESI+) **$C_{30}H_{44}N_4O_5Si$** (584.85): *m/z* $[M+H]^+$ calcd. for $C_{30}H_{45}N_4O_5Si$: 585.2925; found: 585.2916; $[M+Na]^+$ calcd. for $C_{30}H_{44}N_4O_5SiNa$: 607.2745; found: 607.2731.

2.33 *rel*-Methyl 2-([4-{([2*R*,4*R*,6*S*]-4-[{*tert*-butyldimethylsilyl}oxy]-6-phenethyltetrahydro-2*H*-pyran-2-yl)methyl}-1*H*-1,2,3-triazol-1-yl]methyl)oxazole-4-carboxylate (14j).



Azide **6a** (7.9 mg, 43.4 µmol, 1.00 eq.) and ethynyl **12c** (15.6 mg, 43.4 µmol, 1.00 eq.) were dispersed in *t*-BuOH (0.5 mL) and H_2O (0.5 mL). $CuSO_4$•$5H_2O$ (0.2 mg, 0.8 µmol, 0.02 eq.) and sodium ascorbate (1.7 mg, 8.5 µmol, 0.20 eq.) were added and the mixture was stirred overnight at RT. After completion by TLC, brine (15 mL) was added and the aqueous phase was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic phases were dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude reaction mixture was purified by column chromatography (SiO_2, EtOAc:PE 60:40) to obtain compounds **14j** (racemate) (11.6 mg, 21.4 µmol, 49 %) as a colorless oil.

TLC: R_f = 0.48 (EtOAc:PE = 70:30).

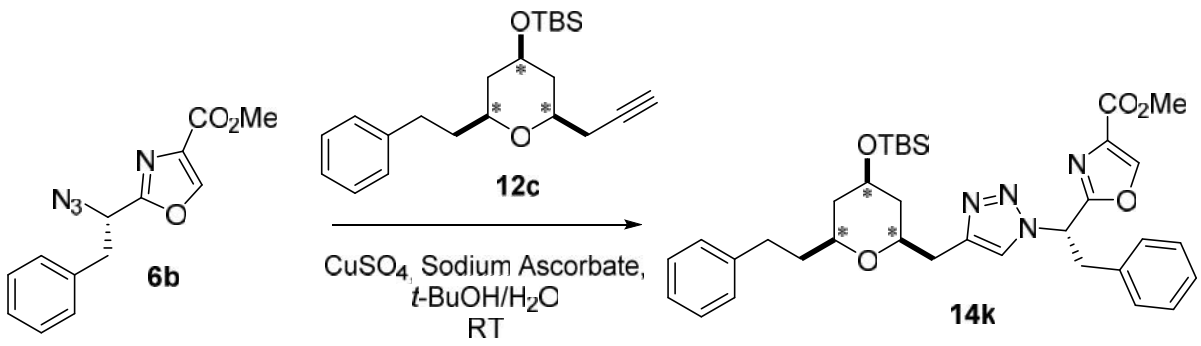
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (s, 1 H), 7.58 (s, 1 H), 7.19 (t, 2 H, *J* = 7.2 Hz), 7.13 (t, 1 H, *J* = 7.2 Hz), 6.89 (d, 2 H, *J* = 7.2 Hz), 5.70 (d, 1 H, *J* = 15.6 Hz), 5.62 (d, 1 H, *J* = 15.6 Hz), 3.85 (s, 3 H), 3.68 (dddd, 1 H, *J* = 10.4, 10.4, 4.4, 4.4 Hz), 3.50 (m_c, 1 H), 3.11 (m_c, 1 H), 2.95-2.84 (m, 2 H), 2.57 (ddd, 1 H, *J* = 13.5, 8.4, 5.0 Hz), 2.47 (ddd, 1 H, *J* = 13.5, 8.3, 8.3 Hz), 1.87-1.74 (m, 2 H), 1.71-1.54 (m, 2 H), 1.28-1.14 (m, 2 H), 0.83 (s, 9 H), 0.02 (s, 6 H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 160.9, 157.9, 146.2, 145.2, 142.0, 133.8, 128.6, 128.5, 125.9, 122.9, 74.6, 74.0, 68.7, 52.4, 46.3, 41.7, 41.5, 37.7, 32.7, 31.7, 26.0, 18.2, -4.4 ppm.

IR (NaCl, film): $\tilde{\nu}$ (cm^{-1}) = 3146, 3026, 2951, 2928, 2857, 1744, 1584, 1560, 1458, 1437, 1375, 1346, 1321, 1252, 1231, 1194, 1144, 1113, 1074, 1005, 868, 837, 806, 775, 702, 669.

HRMS (ESI+) **$C_{28}H_{40}N_4O_5Si$** (540.74): *m/z* $[M+Na]^+$ calcd. for $C_{28}H_{40}N_4O_5SiNa$: 563.2660; found: 563.2682.

2.34 Methyl 2-([*S*]-1-[4-{([2*R*,4*R*,6*S*]-4-[{*tert*-butyldimethylsilyl}oxy]-6-phenethyltetrahydro-2*H*-pyran-2-yl)methyl}-1*H*-1,2,3-triazol-1-yl]-2-phenylethyl)oxazole-4-carboxylate and methyl 2-([*S*]-1-[4-{([2*S*,4*S*,6*R*]-4-[{*tert*-butyldimethylsilyl}oxy]-6-phenethyltetrahydro-2*H*-pyran-2-yl)methyl}-1*H*-1,2,3-triazol-1-yl]-2-phenylethyl)oxazole-4-carboxylate (14k).



Azide **6b** (19.0 mg, 72.0 µmol, 1.00 eq.) and ethynyl **12c** (25.8 mg, 72.0 µmol, 1.00 eq.) were dispersed in *t*-BuOH (0.5 mL) and H_2O (0.5 mL). $CuSO_4$•$5H_2O$ (0.3 mg, 1.0 µmol,

0.02 eq.) and sodium ascorbate (2.8 mg, 14.1 µmol, 0.20 eq.) were added and the mixture was stirred overnight at RT. After completion by TLC, brine (15 mL) was added and the aqueous phase was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic phases were dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude reaction mixture was purified by column chromatography (SiO_2, EtOAc:PE 30:70) to obtain compounds **14k** (diasteromeric mixture) (33.0 mg, 52.3 µmol, 73 %) as a colorless oil.

TLC: R_f = 0.42 (EtOAc:PE = 30:70).

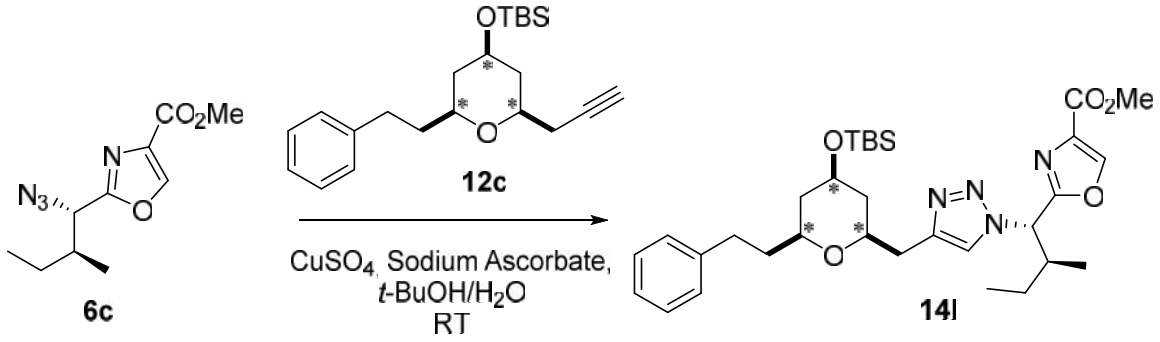
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (s, 1 H), 7.88 (s, 1 H), 7.62 (s, 1 H), 7.51 (s, 1 H), 7.24-7.14 (m, 12 H), 7.06-7.02 (m, 4 H), 6.97-6.96 (m, 2 H), 6.90-6.88 (m, 2 H), 6.11 (dd, 1 H, *J* = 8.3, 7.6 Hz), 6.00 (dd, 1 H, *J* = 7.9, 7.9 Hz), 3.87 (s, 3 H), 3.86 (s, 3 H), 3.79-3.63 (m, 6 H), 3.55-3.45 (m, 2 H), 3.17-3.08 (m, 2 H), 2.95-2.83 (m, 4 H), 2.66-2.44 (m, 4 H), 1.85-1.57 (m, 8 H), 1.27-1.14 (m, 4 H), 0.87 (s, 9 H), 0.86 (s, 9 H), 0.03 (s, 6 H), 0.02 (s, 6 H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 161.1, 161.0, 160.6, 160.5, 145.6, 145.4, 144.9, 144.8, 142.0, 141.9, 134.8, 134.6, 133.7, 133.6, 129.0, 128.9, 128.6, 128.5, 128.4, 128.4, 127.6, 125.8, 122.3, 121.6, 74.6, 74.5, 74.1, 73.9, 68.7, 68.6, 59.5, 59.3, 52.4, 52.3, 41.7, 41.4, 41.3, 39.8, 39.5, 37.7, 32.7, 32.6, 31.8, 31.7, 25.9, 18.2, -4.5 ppm.

IR (NaCl, film): $\tilde{\nu}$ (cm^{-1}) = 2951, 2930, 2857, 1738, 1722, 1582, 1497, 1456, 1439, 1377, 1344, 1323, 1254, 1198, 1113, 1076, 1003, 868, 837, 806, 775, 748, 700, 669.

HRMS (ESI+) **$C_{35}H_{46}N_4O_5Si$** (630.86): *m/z* $[M+Na]^+$ calcd. for $C_{35}H_{46}N_4O_5SiNa$: 653.3130; found: 653.3105.

2.35 Methyl 2-([1*S*,2*S*]-1-[4-{([2*R*,4*R*,6*S*]-4-[{*tert*-butyldimethylsilyl}oxy]-6-phenethyltetrahydro-2*H*-pyran-2-yl)methyl}-1*H*-1,2,3-triazol-1-yl]-2-methylbutyl)oxazole-4-carboxylate and methyl 2-([1*S*,2*S*]-1-[4-{([2*S*,4*S*,6*R*]-4-[{*tert*-butyldimethylsilyl}oxy]-6-phenethyltetrahydro-2*H*-pyran-2-yl)methyl}-1*H*-1,2,3-triazol-1-yl]-2-methylbutyl)oxazole-4-carboxylate (14l).



Azide **6c** (16.6 mg, 69.7 µmol, 1.00 eq.) and ethynyl **12c** (25.0 mg, 69.7 µmol, 1.00 eq.) were dispersed in *t*-BuOH (0.5 mL) and H_2O (0.5 mL). $CuSO_4 \bullet 5H_2O$ (0.3 mg, 1.0 µmol, 0.02 eq.) and sodium ascorbate (2.8 mg, 14.1 µmol, 0.20 eq.) were added and the mixture was stirred overnight at RT. After completion by TLC, brine (15 mL) was added and the aqueous phase was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic phases were dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude reaction mixture was purified by column chromatography (SiO_2, EtOAc:PE 30:70) to obtain compounds **14l** (diasteromeric mixture) (35.3 mg, 59.1 µmol, 85 %) as a colorless oil.

TLC: R_f = 0.32 (EtOAc:PE = 30:70).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (s, 1 H), 7.86 (s, 1 H), 7.77 (s, 1 H), 7.73 (s, 1 H), 7.25-7.11 (m, 6 H), 7.00-6.98 (m, 2 H), 6.83-6.81 (m, 2 H), 5.67 (d, 1 H, *J* = 10.8 Hz), 5.65 (d, 1 H, *J* = 10.6 Hz), 3.88 (s, 3 H), 3.85 (s, 3 H), 3.76-3.65 (m, 2 H), 3.60 (m_c, 1 H), 3.50 (m_c, 1 H), 3.18 (m_c, 1 H), 3.09 (m_c, 1 H), 2.96-2.87 (m, 4 H), 2.68-2.43 (m, 6 H), 1.87-1.52 (m, 8 H), 1.30-1.14 (m, 6 H), 1.09-1.01 (m, 2 H), 0.91 (d, 3 H, *J* = 6.7 Hz), 0.90 (d, 3 H, *J* = 6.7 Hz), 0.86 (s, 9 H), 0.85 (s, 9 H), 0.82 (t, 3 H, *J* = 7.5 Hz), 0.79 (t, 3 H, *J* = 7.3 Hz), 0.02 (s, 6 H), 0.01 (s, 6 H) ppm.

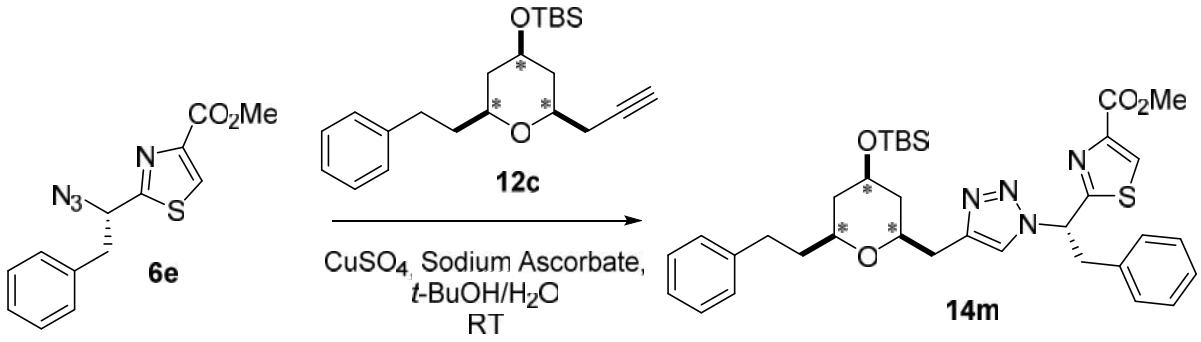
^{13}C NMR (100 MHz, $CDCl_3$) δ 161.1, 161.1, 161.0, 160.9, 145.9, 145.7, 144.6, 144.5, 142.0, 141.8, 133.6, 133.5, 128.6, 128.5, 128.4, 128.4, 125.8, 125.8, 121.8, 121.5, 74.8,

74.6, 74.2, 73.6, 68.7, 68.6, 62.9, 62.8, 52.4, 52.3, 41.8, 41.7, 41.6, 39.0, 38.8, 37.9, 37.7, 32.8, 32.7, 31.9, 31.6, 25.9, 25.1, 25.0, 18.2, 15.7, 15.6, 10.4, 10.3, -4.4, -4.5 ppm.

IR (NaCl, film): $\tilde{\nu}$ (cm^{-1}) = 2951, 2934, 2857, 1751, 1578, 1458, 1437, 1375, 1340, 1321, 1252, 1229, 1198, 1148, 1111, 1074, 1042, 1005, 932, 868, 837, 775, 702, 669.

HRMS (ESI+) **$C_{32}H_{48}N_4O_5Si$** (596.84): *m/z* $[M+Na]^+$ calcd. for $C_{32}H_{48}N_4O_5SiNa$: 619.3286; found: 619.3275.

2.36 Methyl 2-([*S*]-1-[4-{([2*R*,4*R*,6*S*]-4-[{*tert*-butyldimethylsilyl}oxy]-6-phenethyltetrahydro-2*H*-pyran-2-yl)methyl}-1*H*-1,2,3-triazol-1-yl]-2-phenylethyl)thiazole-4-carboxylate and methyl 2-([*S*]-1-[4-{([2*S*,4*S*,6*R*]-4-[{*tert*-butyldimethylsilyl}oxy]-6-phenethyltetrahydro-2*H*-pyran-2-yl)methyl}-1*H*-1,2,3-triazol-1-yl]-2-phenylethyl)thiazole-4-carboxylate (14m).



Azide **6e** (20.1 mg, 69.7 µmol, 1.00 eq.) and ethynyl **12c** (25.0 mg, 69.7 µmol, 1.00 eq.) were dispersed in *t*-BuOH (0.5 mL) and H_2O (0.5 mL). $CuSO_4$•$5H_2O$ (0.3 mg, 1.0 µmol, 0.02 eq.) and sodium ascorbate (2.8 mg, 14.1 µmol, 0.20 eq.) were added and the mixture was stirred overnight at RT. After completion by TLC, brine (15 mL) was added and the aqueous phase was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic phases were dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude reaction mixture was purified by column chromatography (SiO_2, EtOAc:PE 30:70) to obtain compounds **14m** (diasteromeric mixture) (37.1 mg, 57.3 µmol, 82 %) as a colorless oil.

TLC: R_f = 0.23 (EtOAc:PE = 30:70).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (s, 1 H), 8.02 (s, 1 H), 7.46 (s, 1 H), 7.37 (s, 1 H), 7.24-7.14 (m, 12 H), 7.05-7.03 (m, 4 H), 6.96-6.94 (m, 4 H), 6.19-6.10 (m, 2 H), 3.94 (s, 3 H),

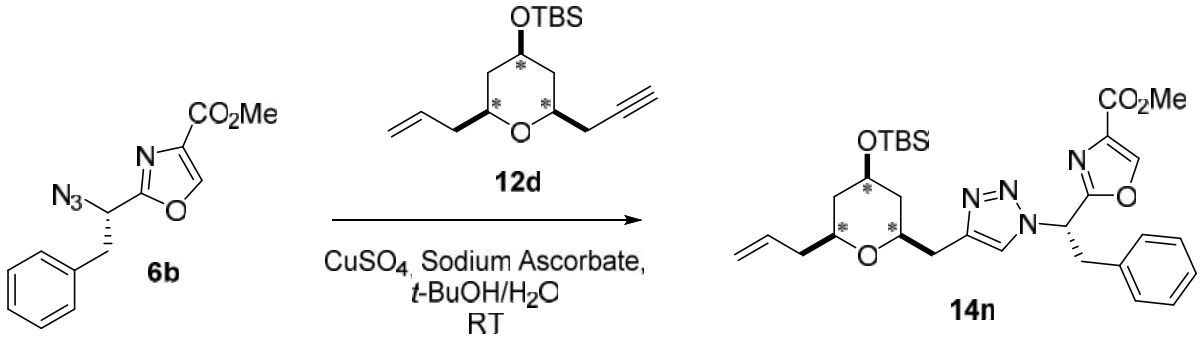
3.92 (s, 3 H), 3.84-3.65 (m, 6 H), 3.53-3.44 (m, 2 H), 3.17-3.09 (m, 2 H), 2.91-2.81 (m, 4 H), 2.60-2.40 (m, 4 H), 1.83-1.67 (m, 6 H), 1.64-1.55 (m, 2 H), 1.23-1.10 (m, 4 H), 0.87 (s, 9 H), 0.86 (s, 9 H), 0.02 (s, 6 H), 0.02 (s, 6 H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 168.2, 168.0, 161.5, 146.6, 146.5, 145.3, 145.0, 142.1, 142.0, 135.5, 135.4, 129.4, 129.3, 129.1, 129.0, 128.9, 128.8, 128.6, 128.4, 128.3, 127.5, 127.4, 125.8, 125.7, 123.2, 122.6, 74.6, 74.4, 74.3, 74.2, 68.7, 64.4, 64.1, 52.7, 52.6, 42.3, 42.1, 41.6, 41.5, 41.3, 41.2, 37.7, 32.6, 32.5, 31.8, 25.9, 18.2, -4.4 ppm.

IR (NaCl, film): $\tilde{\nu}$ (cm^{-1}) = 2951, 2930, 2857, 1738, 1722, 1495, 1477, 1460, 1375, 1344, 1325, 1250, 1217, 1126, 1074, 868, 837, 777, 752, 700, 669.

HRMS (ESI+) **$C_{35}H_{46}N_4O_4SSi$** (646.92): *m/z* $[M+Na]^+$ calcd. for $C_{35}H_{46}N_4O_4SSiNa$: 669.2901; found: 669.2902; $[M+H]^+$ calcd. for $C_{35}H_{47}N_4O_4SSi$: 647.3082; found: 647.3085.

2.37 Methyl 2-([*S*]-1-[4-{([2*R*,4*R*,6*S*]-6-allyl-4-[{*tert*-butyldimethylsilyl}oxy]tetrahydro-2*H*-pyran-2-yl)methyl}-1*H*-1,2,3-triazol-1-yl]-2-phenylethyl)oxazole-4-carboxylate and methyl 2-([*S*]-1-[4-{([2*S*,4*S*,6*R*]-6-allyl-4-[{*tert*-butyldimethylsilyl}oxy]tetrahydro-2*H*-pyran-2-yl)methyl}-1*H*-1,2,3-triazol-1-yl]-2-phenylethyl)oxazole-4-carboxylate (14n).



Azide **6b** (19.5 mg, 71.7 µmol, 1.00 eq.) and ethynyl **12d** (21.1 mg, 71.6 µmol, 1.00 eq.) were dispersed in *t*-BuOH (0.5 mL) and H_2O (0.5 mL). $CuSO_4$•$5H_2O$ (0.3 mg, 1.0 µmol, 0.02 eq.) and sodium ascorbate (2.8 mg, 14.1 µmol, 0.20 eq.) were added and the mixture was stirred overnight at RT. After completion by TLC, brine (10 mL) was added and the aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic

phases were dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude reaction mixture was purified by column chromatography (SiO_2, EtOAc:PE 40:60) to obtain compounds **14n** (diasteromeric mixture) (23.5 mg, 41.5 µmol, 58 %) as a colorless oil.

TLC: R_f = 0.41 (EtOAc:PE = 40:60).

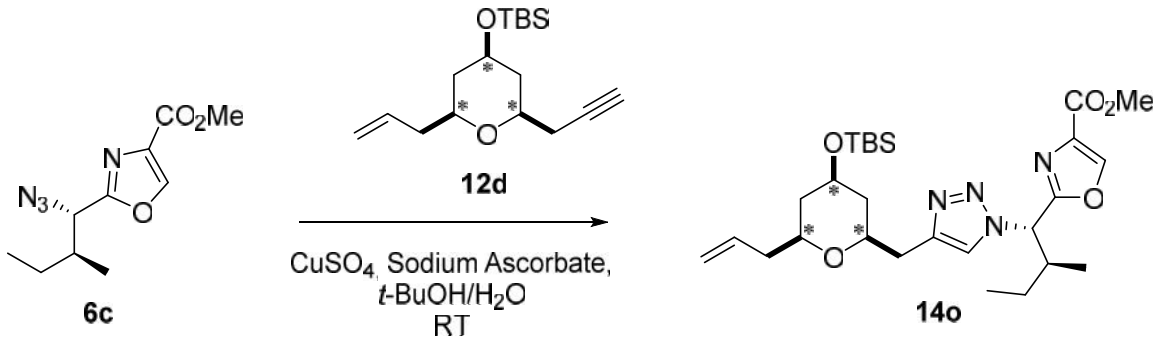
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (s, 1 H), 8.21 (s, 1 H), 7.59 (s, 1 H), 7.55 (s, 1 H), 7.26-7.21 (m, 6 H), 7.07-7.05 (m, 4 H), 6.08-6.01 (m, 2 H), 5.82-5.68 (m, 2 H), 5.09-5.00 (m, 2 H), 3.94 (s, 6 H), 3.81-3.68 (m, 6 H), 3.53-3.44 (m, 2 H), 3.35-3.26 (m, 2 H), 2.94-2.82 (m, 4 H), 2.32-2.14 (m, 4 H), 1.85-1.78 (m, 4 H), 1.27-1.14 (m, 4 H), 0.89 (s, 18 H), 0.06 (s, 12 H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 161.2, 160.8, 160.7, 145.4, 145.0, 144.9, 135.3, 135.2, 134.8, 134.7, 133.8, 133.8, 129.0, 128.9, 127.7, 127.6, 122.4, 122.2, 116.9, 116.8, 75.2, 75.1, 74.6, 74.5, 68.7, 59.5, 59.4, 52.5, 41.2, 41.1, 40.6, 40.5, 39.8, 32.6, 32.5, 25.9, 18.2, -4.4, -4.4 ppm.

IR (NaCl, film): $\tilde{\nu}$ (cm^{-1}) = 2591, 2932, 2857, 1746, 1582, 1457,1441, 1379, 1347, 1323, 1254, 1142, 1115, 1075, 1001, 934, 857, 839, 808, 774, 747, 700.

HRMS (ESI+) **$C_{30}H_{42}N_4O_5Si$** (566.77): *m/z* $[M+Na]^+$ calcd. for $C_{30}H_{42}N_4O_5SiNa$: 589.2817; found: 589.2808.

2.38 Methyl 2-([1*S*,2*S*]-1-[4-{([2*R*,4*R*,6*S*]-6-allyl-4-[{*tert*-butyldimethylsilyl}oxy]tetrahydro-2*H*-pyran-2-yl)methyl}-1*H*-1,2,3-triazol-1-yl]-2-methylbutyl)oxazole-4-carboxylate and methyl 2-([1*S*,2*S*]-1-[4-{([2*S*,4*S*,6*R*]-6-allyl-4-[{*tert*-butyldimethylsilyl}oxy]tetrahydro-2*H*-pyran-2-yl)methyl}-1*H*-1,2,3-triazol-1-yl]-2-methylbutyl)oxazole-4-carboxylate (14o).



Azide **6c** (20.1 mg, 84.4 µmol, 1.00 eq.) and ethynyl **12d** (25.0 mg, 84.3 µmol, 1.00 eq.) were dispersed in *t*-BuOH (0.5 mL) and H_2O (0.5 mL). $CuSO_4$•$5H_2O$ (0.4 mg, 1.2 µmol, 0.02 eq.) and sodium ascorbate (3.3 mg, 16.7 µmol, 0.20 eq.) were added and the mixture was stirred overnight at RT. After completion by TLC, brine (15 mL) was added and the aqueous phase was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic phases were dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude reaction mixture was purified by column chromatography (SiO_2, EtOAc:PE 40:60) to obtain compounds **14o** (diasteromeric mixture) (19.1 mg, 35.9 µmol, 43 %) as a colorless oil.

TLC: R_f = 0.46 (EtOAc:PE = 40:60).

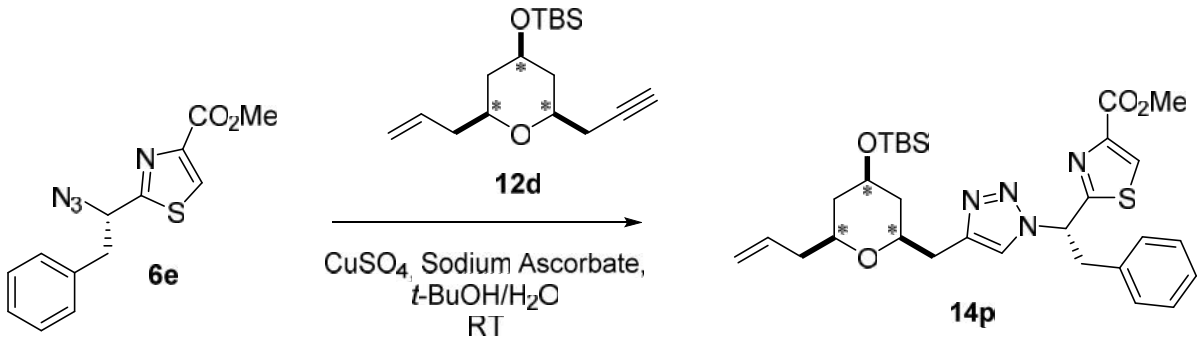
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 (s, 1 H), 8.23 (s, 1 H), 7.73 (s, 1 H), 7.72 (s, 1 H), 5.83-5.72 (m, 2 H), 5.66 (d, 1 H, *J* = 10.6 Hz), 5.65 (d, 1 H, *J* = 10.6 Hz), 5.10-5.00 (m, 4 H), 3.92 (s, 6 H), 3.78-3.70 (m, 2 H), 3.57-3.50 (m, 2 H), 3.35-3.27 (m, 2 H), 2.93-2.83 (m, 4 H), 2.65-2.56 (m, 2 H), 2.33-2.25 (m, 2 H), 2.22-2.16 (m, 2 H), 1.85-1.78 (m, 4 H), 1.28-1.15 (m, 6 H), 1.10-1.02 (m, 2 H), 0.94 (d, 6 H, *J* = 6.7 Hz), 0.89-0.85 (m, 6 H), 0.87 (s, 18 H), 0.01 (s, 12 H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 161.3, 161.2, 145.7, 145.6, 144.7, 144.6, 135.2, 135.2, 133.8, 133.7, 121.9, 121.8, 116.9, 116.8, 75.3, 75.3, 74.7, 74.6, 68.7, 62.9, 52.5, 41.4, 41.3, 40.6, 39.1, 39.0, 32.7, 32.6, 26.0, 25.1, 18.2, 10.5, 10.6, -4.4, -4.5 ppm.

IR (NaCl, film): $\tilde{\nu}$ (cm^{-1}) = 2953, 2932, 2857, 1749, 1722, 1582, 1560, 1545, 1462, 1439, 1379, 1343, 1323, 1252, 1229, 1198, 1146, 1111, 1074, 1043, 1003, 852, 837, 775.

HRMS (ESI+) **$C_{27}H_{44}N_4O_5Si$** (532.76): *m/z* $[M+Na]^+$ calcd. for $C_{27}H_{44}N_4O_5SiNa$: 555.2973; found: 555.2973.

2.39 Methyl 2-([*S*]-1-[4-{([2*R*,4*R*,6*S*]-6-allyl-4-[{*tert*-butyldimethylsilyl}oxy]tetrahydro-2*H*-pyran-2-yl)methyl}-1*H*-1,2,3-triazol-1-yl]-2-phenylethyl)thiazole-4-carboxylate and methyl 2-([*S*]-1-[4-{([2*S*,4*S*,6*R*]-6-allyl-4-[{*tert*-butyldimethylsilyl}oxy]tetrahydro-2*H*-pyran-2-yl)methyl}-1*H*-1,2,3-triazol-1-yl]-2-phenylethyl)thiazole-4-carboxylate (14p).



Azide **6e** (24.3 mg, 84.3 µmol, 1.00 eq.) and ethynyl **12d** (25.0 mg, 84.3 µmol, 1.00 eq.) were dispersed in *t*-BuOH (0.5 mL) and H_2O (0.5 mL). $CuSO_4 \bullet 5H_2O$ (0.4 mg, 1.2 µmol, 0.02 eq.) and sodium ascorbate (3.3 mg, 16.7 µmol, 0.20 eq.) were added and the mixture was stirred overnight at RT. After completion by TLC, brine (15 mL) was added and the aqueous phase was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic phases were dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude reaction mixture was purified by column chromatography (SiO_2, EtOAc:PE 40:60) to obtain compounds **14p** (diasteromeric mixture) (45.6 mg, 78.2 µmol, 93 %) as a yellowish oil.

TLC: R_f = 0.44 (EtOAc:PE = 40:60).

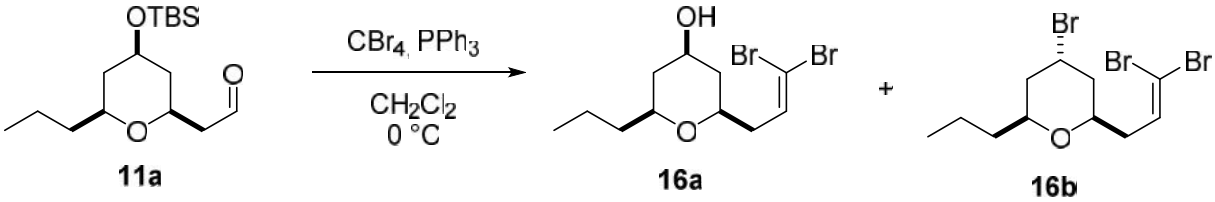
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (s, 1 H), 8.19 (s, 1 H), 7.43 (s, 1 H), 7.39 (s, 1 H), 7.22-7.16 (m, 6 H), 7.04-7.02 (m, 4 H), 6.13-6.09 (m, 2 H), 5.74-5.58 (m, 2 H), 5.03-4.95 (m, 4 H), 3.97 (s, 6 H), 3.78-3.70 (m, 6 H), 3.47 (m_c, 1 H), 3.39 (m_c, 1 H), 3.31-3.19 (m, 2 H), 2.90-2.78 (m, 4 H), 2.26-2.13 (m, 4 H), 1.89-1.72 (m, 4 H), 1.32-1.08 (m, 4 H), 0.88 (s, 9 H), 0.87 (s, 9 H), 0.04 (s, 12 H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 168.5, 168.4, 161.6, 146.6, 146.5, 145.1, 145.0, 135.5, 135.4, 135.3, 135.1, 129.1, 129.0, 128.9, 128.8, 128.4, 127.5, 127.4, 123.4, 116.9, 116.8, 75.1, 74.7, 74.5, 72.2, 68.7, 64.5, 64.4, 52.7, 41.6, 41.4, 41.2, 41.1, 40.5, 32.5, 32.4, 25.9, 18.2, -4.4 ppm.

IR (NaCl, film): $\tilde{\nu}$ (cm^{-1}) = 2951, 2932, 2857, 1738, 1723, 1476, 1460, 1439, 1378, 1250, 1215, 1125, 1077, 997, 837, 776, 701.

HRMS (ESI+) **$C_{30}H_{42}N_4O_4SSi$** (582.84): *m/z* $[M+Na]^+$ calcd. for $C_{30}H_{42}N_4O_4SSiNa$: 605.2588; found: 605.2587.

2.40 *rel*-(2*R*,4*R*,6*S*)-2-(3,3-Dibromoallyl)-6-propyltetrahydro-2*H*-pyran-4-ol (16a); *rel*-(2*R*,4*S*,6*S*)-4-Bromo-2-(3,3-dibromoallyl)-6-propyltetrahydro-2*H*-pyran (16b).



Aldehyde **11a** (241.2 mg, 0.80 mmol, 1.00 eq.) was dissolved in CH_2Cl_2 (6 mL) under N_2 atmosphere. PPh_3 (842.1 mg, 3.21 mmol, 4.00 eq.) was added and after 10 minutes the solution was cooled down to 0 °C. CBr4 (532.4 mg, 1.61 mmol, 2.00 eq.) was added portion wise. After completion by TLC, the reaction was concentrated under reduce pressure. The crude reaction mixture was purified by column chromatography (SiO_2, EtOAc:PE 40:60) to obtain compounds **16a** (racemate) (270.6 mg, 0.59 mmol, 74 %) as a yellowish oil and compounds **16b** (racemate) (83.5 mg, 0.21 mmol, 26 %) as a yellowish oil.

Compounds 16a:

TLC: R_f = 0.12 (EtOAc:PE = 15:85).

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.52 (dd, 1 H, *J* = 7.1, 7.1 Hz), 3.79 (dddd, 1 H, *J* = 10.9, 10.9, 4.7, 4.7 Hz), 3.38 (dddd, 1 H, *J* = 11.4, 7.3, 5.6, 2.0 Hz), 3.28 (dddd, 1 H, *J* = 11.8, 7.1, 4.6, 1.8 Hz), 2.33-2.29 (m, 2 H), 1.97-1.91 (m, 2 H), 1.58-1.33 (m, 4 H), 1.23-1.10 (m, 2 H), 0.92 (t, 3 H, *J* = 7.1 Hz) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 135.2, 90.1, 75.6, 73.6, 68.2, 41.1, 40.8, 39.5, 38.2, 18.9, 14.2 ppm.

IR (NaCl, film): $\tilde{\nu}$ (cm^{-1}) = 3363, 2951, 2935, 2866, 1624, 1458, 1373, 1327, 1253, 1222, 1141, 1114, 1076, 1037, 968, 894, 848, 810, 779.

HRMS (ESI+) **$C_{11}H_{18}Br_2O_2$** (342.07): *m/z* $[M+Na]^+$ calcd. for $C_{11}H_{18}Br_2O_2Na$: 364.95457; found: 364.95279.

Compounds 16b:

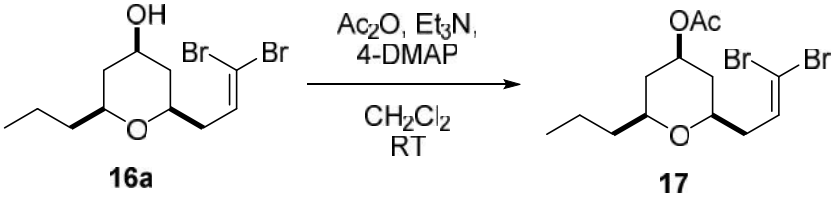
TLC: R_f = 0.66 (EtOAc:PE = 15:85)

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.53 (dd, 1 H, *J* = 7.0, 7.0 Hz), 4.72 (dddd, 1 H, *J* = 3.2, 3.2, 3.1, 3.1 Hz), 3.95 (dddd, 1 H, *J* = 11.0, 7.2, 5.6, 1.7 Hz), 3.85 (dddd, 1 H, *J* = 9.8, 7.4, 4.4, 1.8 Hz), 2.34-2.23 (m, 2 H), 2.00-1.94 (m, 2 H), 1.78-1.65 (m, 2 H), 1.55-1.32 (m, 4 H), 0.93 (t, 3 H, *J* = 7.1 Hz) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 135.1, 90.2, 72.2, 70.5, 50.6, 39.5, 39.3, 39.2, 37.8, 18.8, 14.2 ppm.

IR (NaCl, film): $\tilde{\nu}$ (cm^{-1}) = 2958, 2931, 2900, 2866, 1462, 1427, 1377, 1323, 1230, 1184, 1076, 999, 898, 848, 813, 775, 702.

2.41 *rel*-(2*R*,4*R*,6*S*)-2-(3,3-Dibromoallyl)-6-propyltetrahydro-2*H*-pyran-4-yl acetate (17).



16a **17**

Alcohol **16a** (50.0 mg, 0.15 mmol, 1.00 eq.) was dissolved in CH_2Cl_2 (2 mL) under N_2 atmosphere. EtN_3 (0.12 mL, 0.88 mmol, 6.00 eq.) and 4-DMAP (1.8 mg, 0.02 mmol, 0.1 eq.) were added followed by Ac_2O (0.04 mL, 0.44 mmol, 3.00 eq.) at RT. After completion by TLC, $NaHCO_3$ sat. (10 mL) was added and the aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phases were dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude reaction mixture was purified by column chromatography (SiO_2, EtOAc:PE 15:85) to obtain compounds **17** (racemate) (43.2 mg, 0.11 mmol, 77 %) as a pale yellow oil.

TLC: R_f = 0.53 (EtOAc:PE = 15:85).

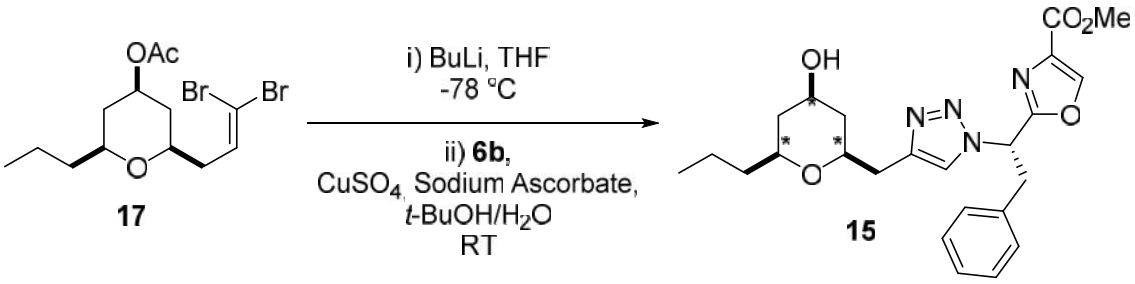
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.51 (dd, 1 H, *J* = 7.1, 7.1 Hz), 4.88 (dddd, 1 H, *J* = 11.3, 11.3, 4.8, 4.8 Hz), 3.44 (dddd, 1 H, *J* = 8.4, 7.4, 5.7, 1.9 Hz), 3.35 (dddd, 1 H, *J* = 9.2, 7.1, 4.6, 1.8 Hz), 2.33-2.29 (m, 2 H), 2.05 (s, 3 H), 1.99-1.93 (m, 2 H), 1.57-1.33 (m, 4 H), 1.32-1.19 (m, 2 H), 0.92 (t, 3 H, *J* = 7.0 Hz) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 170.7, 134.9, 90.3, 75.5, 73.4, 70.4, 39.5, 38.2, 37.2, 36.9, 21.5, 18.8, 14.2 ppm.

IR (NaCl, film): $\tilde{\nu}$ (cm^{-1}) = 3506, 2958, 2931, 2866, 1743, 1720, 1624, 1454, 1435, 1369, 1327, 1242, 1165, 1083, 1033, 975, 906, 852, 810, 779.

HRMS (ESI+) **$C_{13}H_{20}Br_2O_3$** (384.11): *m/z* $[M+Na]^+$ calcd. for $C_{13}H_{20}Br_2O_3Na$: 406.96515; found: 406.96275.

2.42 Methyl 2-([*S*]-1-[4-{([2*R*,4*R*,6*S*]-4-hydroxy-6-propyltetrahydro-2*H*-pyran-2-yl)methyl}-1*H*-1,2,3-triazol-1-yl]-2-phenylethyl)oxazole-4-carboxylate and methyl 2-([*S*]-1-[4-{([2*S*,4*S*,6*R*]-4-hydroxy-6-propyltetrahydro-2*H*-pyran-2-yl)methyl}-1*H*-1,2,3-triazol-1-yl]-2-phenylethyl)oxazole-4-carboxylate (15).



Under N_2 atmosphere, compounds **17** (85.0 mg, 0.22 mmol, 1.00 eq.) was dissolved in THF (2 mL) and the solution was cooled down to -78 °C. BuLi (1.6 M in hexane, 0.31 mL, 0.49 mmol, 2.20 eq.) was added dropwise. After completion by TLC, NH_4CO_3 sat. (10 mL) was added and the aqueous phase was extracted with Et_2O (3 × 10 mL). The combined organic phases were dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude reaction mixture was purified by column chromatography (SiO_2, EtOAc:PE 15:85 to 50:50) to obtain an inseparable mixture of the ethynil (12.3 mg, 0.07 mmol, 31 %, measured by NMR) and the deacetylated SM (25.5 mg, 0.07 mmol, 34 %, measured by NMR) which was used without further purification. The mixture and azide **6b** (18.2 mg, 0.07 mmol, 1.00 eq.) were dispersed in *t*-BuOH (0.5 mL) and H_2O (0.5 mL). $CuSO_4$•$5H_2O$ (0.3 mg, 0.8 µmol, 0.02 eq.) and sodium ascorbate (2.7 mg, 13.6 µmol, 0.20 eq.) were added and the mixture was stirred overnight at RT. After completion by TLC, brine (10 mL) was added and the aqueous phase was extracted

with CH_2Cl_2 (3 × 10 mL). The combined organic phases were dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude reaction mixture was purified by column chromatography (SiO_2, EtOAc) to obtain compounds **15** (diasteromeric mixture) (25.9 mg, 57.0 µmol, 84 %) as a white solid.

TLC: R_f = 0.59 (EtOAc).

MP: 122.5-124.0 °C

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (s, 2 H), 7.52 (s, 1 H), 7.51 (s, 1 H), 7.24-7.22 (m, 6 H), 7.07-7.05 (m, 4 H), 6.09-6.03 (m, 2 H), 3.93 (s, 6 H), 3.80-3.68 (m, 6 H), 3.54-3.46 (m, 2 H), 3.29-3.20 (m, 2 H), 2.89-2.75 (m, 4 H), 1.94-1.90 (m, 8 H), 1.54-1.48 (m, 2 H), 1.39-1.28 (m, 6 H), 1.19-1.07 (m, 4 H), 0.89 (t, 3 H, *J* = 7.1 Hz), 0.86 (t, 3 H, *J* = 7.1 Hz) ppm.

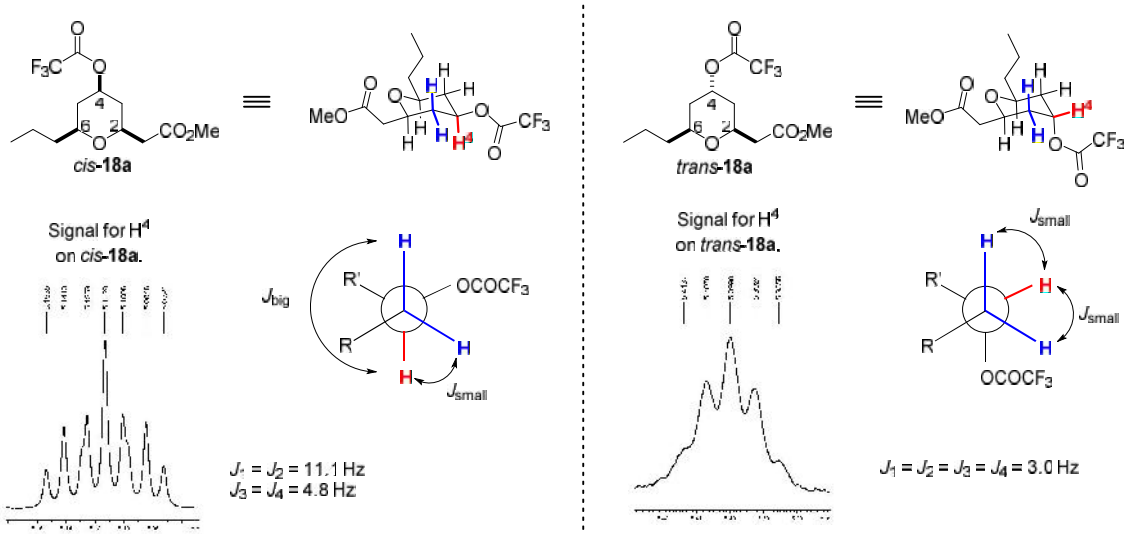
^{13}C NMR (100 MHz, $CDCl_3$) δ 161.1, 160.6, 145.3, 145.2, 145.0, 134.7, 134.6, 133.8, 133.7, 129.0, 128.9, 127.7, 127.6, 122.0, 121.8, 75.5, 75.4, 74.5, 74.4, 68.1, 59.4, 59.3, 52.5, 41.1, 41.0, 40.8, 40.7, 39.8, 39.7, 38.3, 38.2, 32.5, 19.0, 18.9, 14.2, 14.1 ppm.

IR (NaCl, film): $\tilde{\nu}$ (cm^{-1}) = 3425, 3147, 2935, 2866, 1743, 1581, 1546, 1496, 1438, 1373, 1323, 1269, 1230, 1199, 1141, 1111, 1041, 1002, 968, 937, 864, 806, 744, 702.

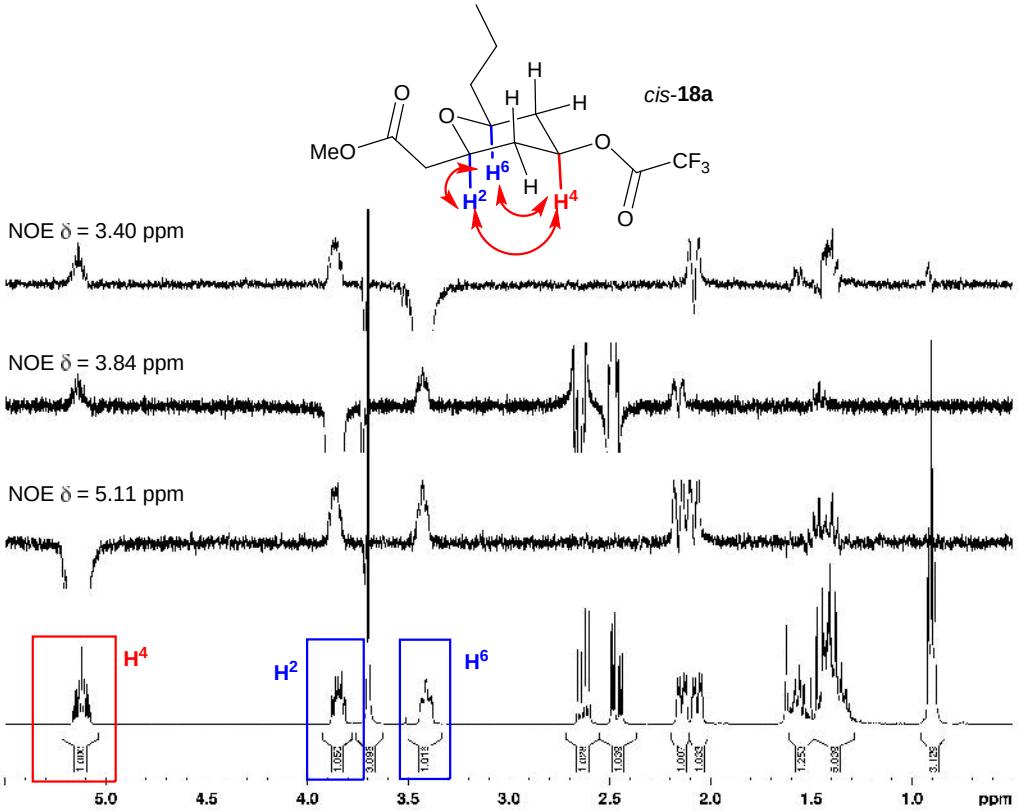
HRMS (ESI+) **$C_{24}H_{30}N_4O_5$** (454.53): *m/z* $[M+H]^+$ calcd. for $C_{24}H_{31}N_4O_5$: 455.2289; found: 455.2312.

3. NMR analysis for *cis*-18a and *trans*-18a (trifluoroacetic ester of 8a)

***Analysis of coupling constants for** cis **and** trans **compounds**:*



***NOE analysis for** cis-**18a**:*



4. General Methods (Biological assays)

***Cell lines and cell cultures**:* The human cancer cell lines HBL-100 (breast), HeLa (cervix), T-47D (breast), WiDr (colon), the non-small human lung cancer cell lines A549, SW1573 and its P-gp overexpressing variant (SW1573/Pgp) were kindly provided by Dr. Godefridus J. Peters (Cancer Center Amsterdam, Vrije Universiteit, Amsterdam, The Netherlands). The human fibroblast cell line BJ-hTert was a kindly provided by Dr. Raimundo Freire (HUC, Universidad de La Laguna, Spain). All cells were grown in RPMI 1640 supplemented with 2 mM glutamine, 5% fetal bovine serum and antibiotics. Cells were grown at 37°C in a humidified atmosphere of 5% CO_2 and maintained at low passage.

***Antiproliferative acivity**:* The antiproliferative activity was tested in vitro against the human cell lines using the protocol of the National Cancer Institute (NCI) of the USA with minor modifications.[6]

***ROS production**:* The level of ROS was measured using the ROS-Glo^{TM} H_2O_2 Assay (Promega Corporation, USA). Cells were exposed to compounds at the indicated dose for 48 h, after which time the nonlytic assay was performed following manufacturer's indications. Luminescence was measured on a Synergy HTX multimode microplate reader (BioTek, USA).

5. Antiproliferative activities

Compounds	CLogP	A549	HBL-100	HeLa	SW1573	T-47D	WiDr
16b	5.28	81	-	> 100	> 100	97	58
17	2.68	> 100	-	> 100	> 100	> 100	> 100

6. References

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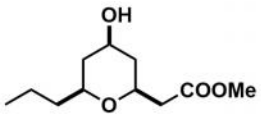
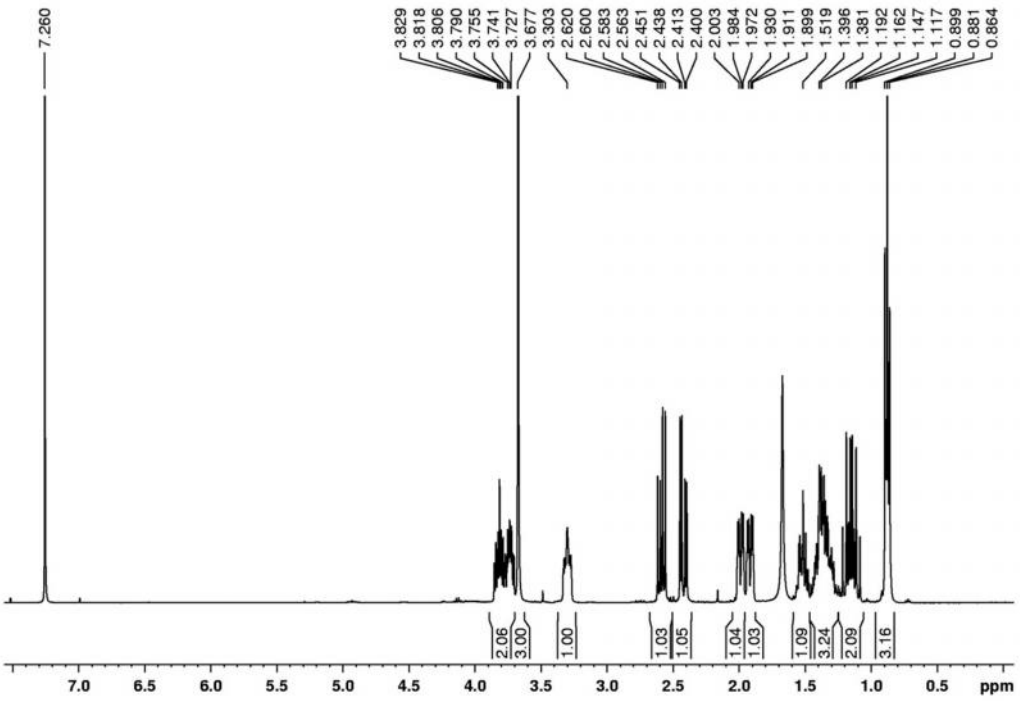
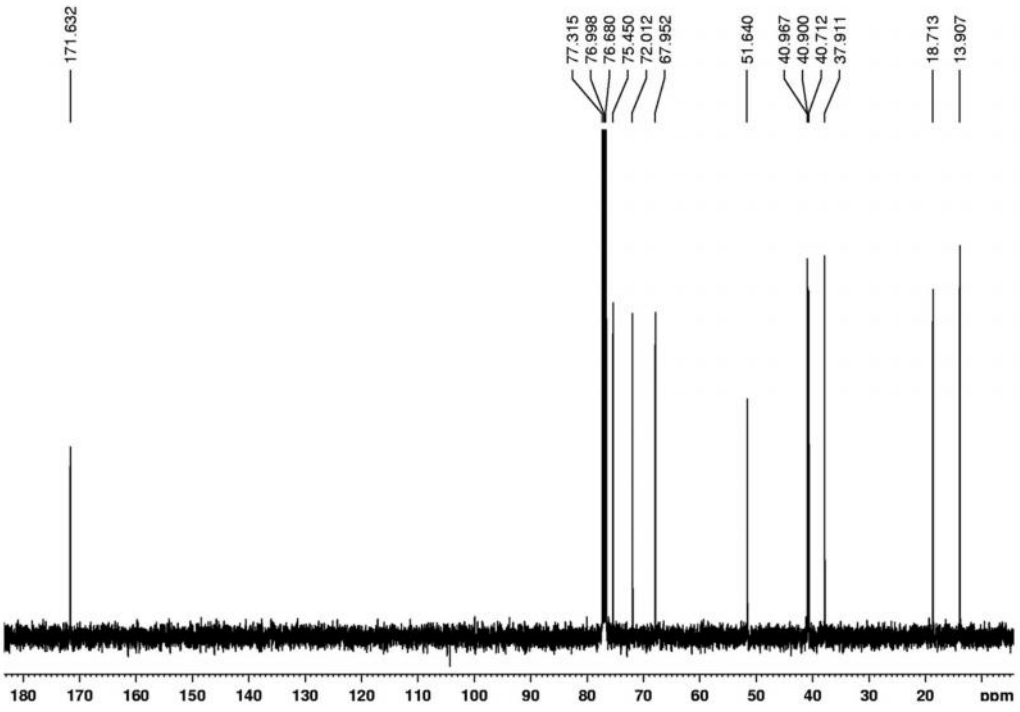
7. NMR spectra

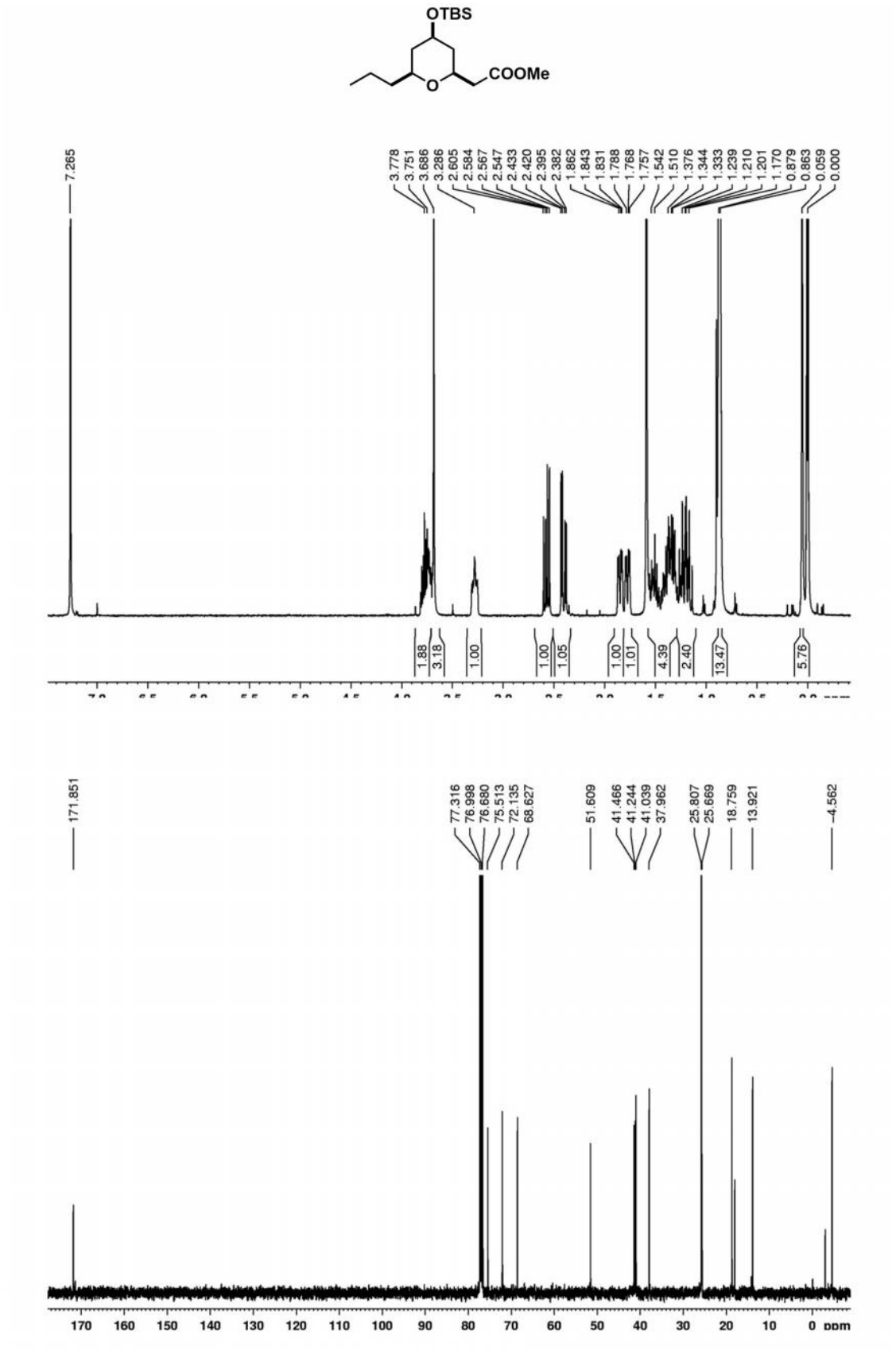
Compounds **8a**



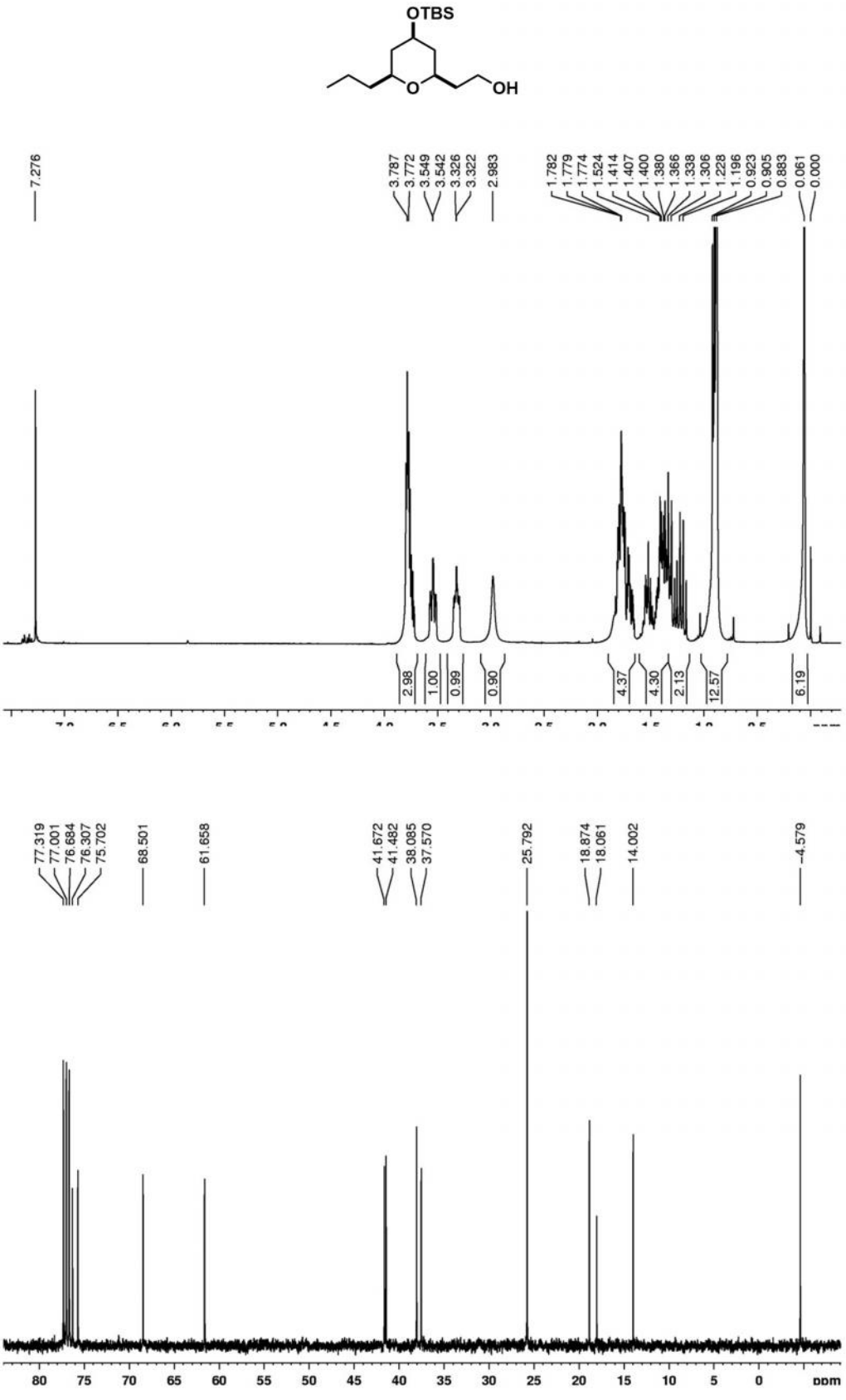




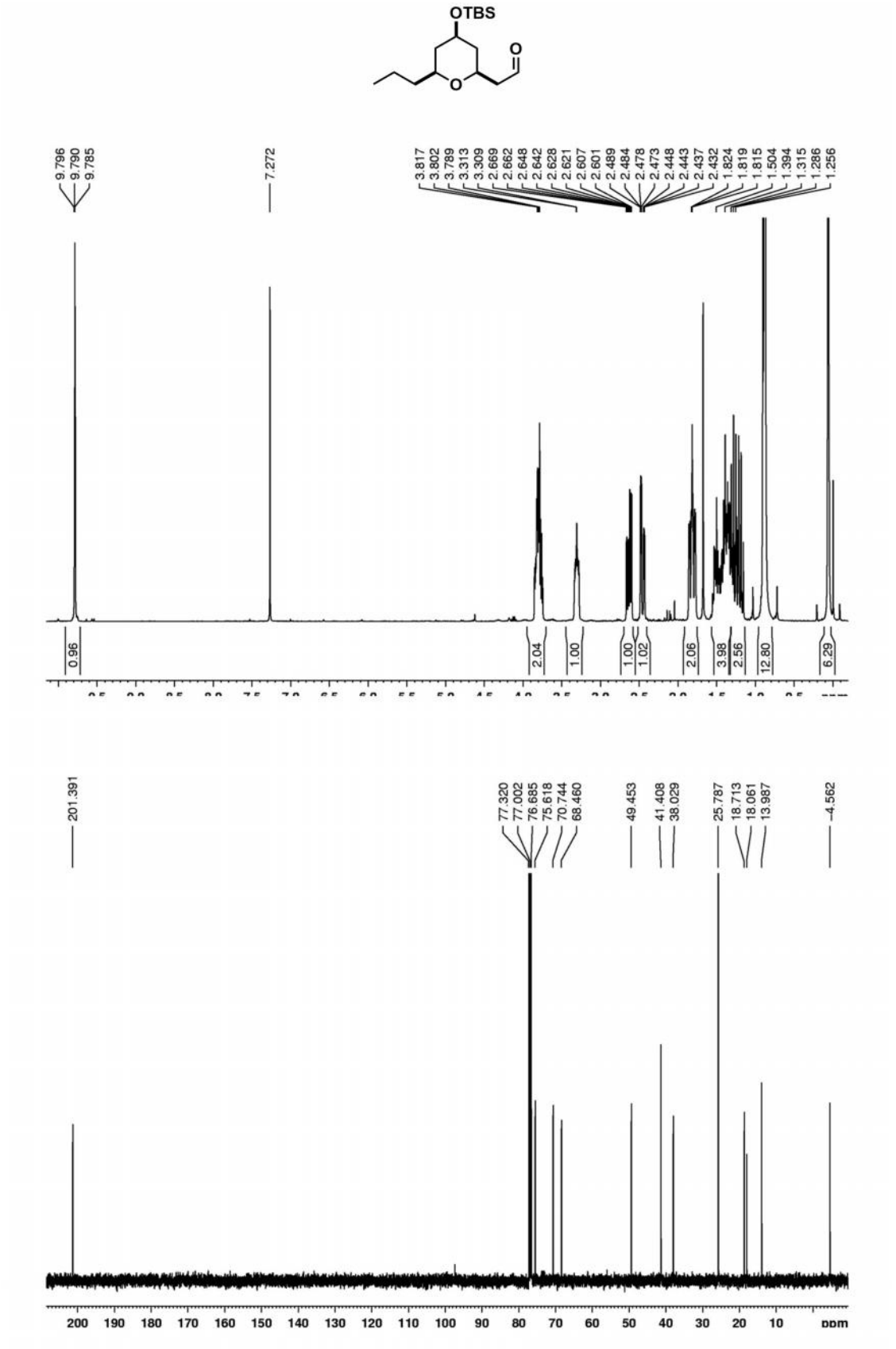
Compounds **9a**



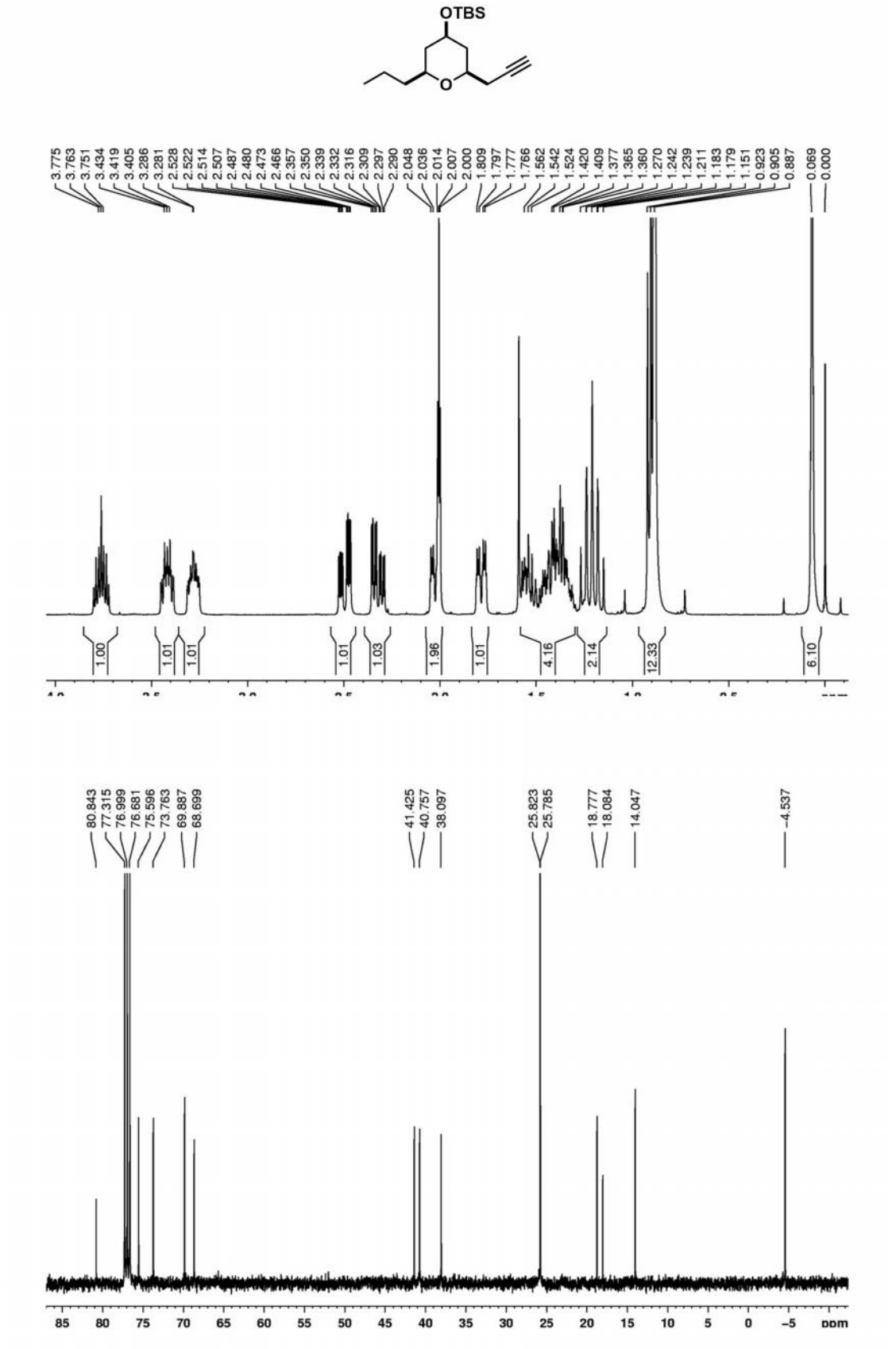
Compounds **10a**



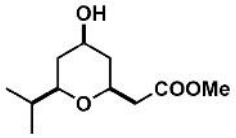
Compounds **11a**

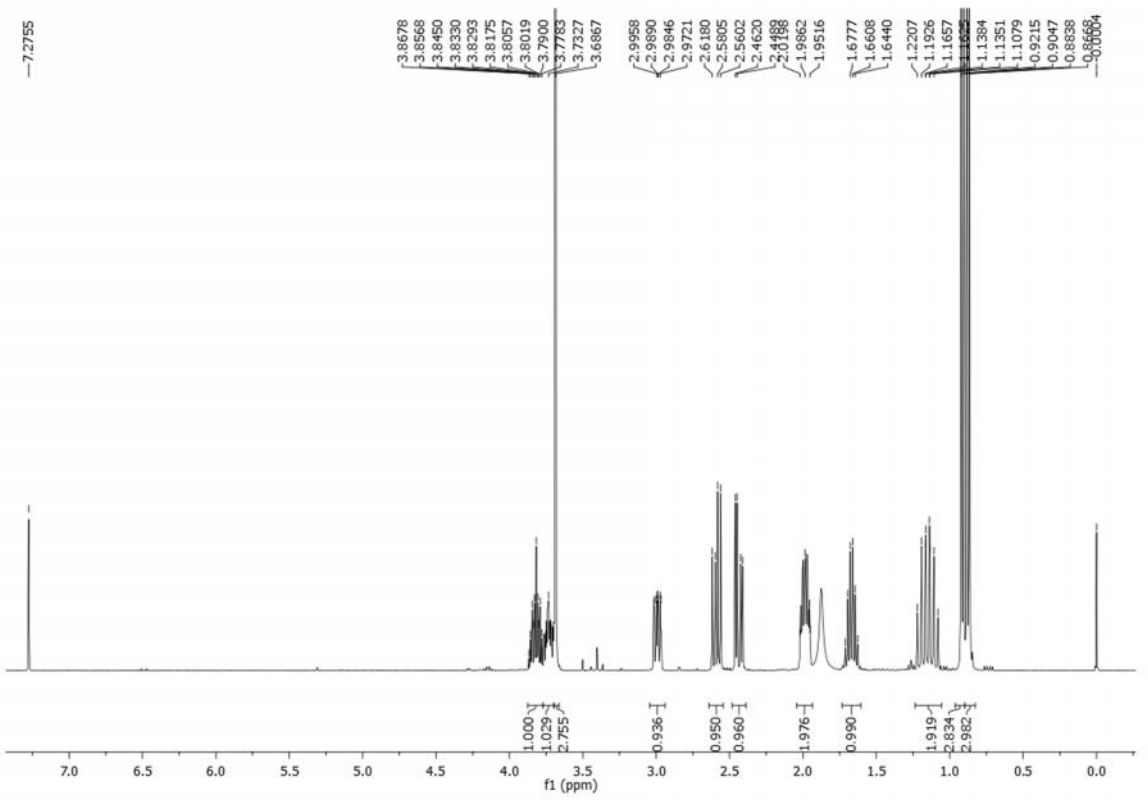


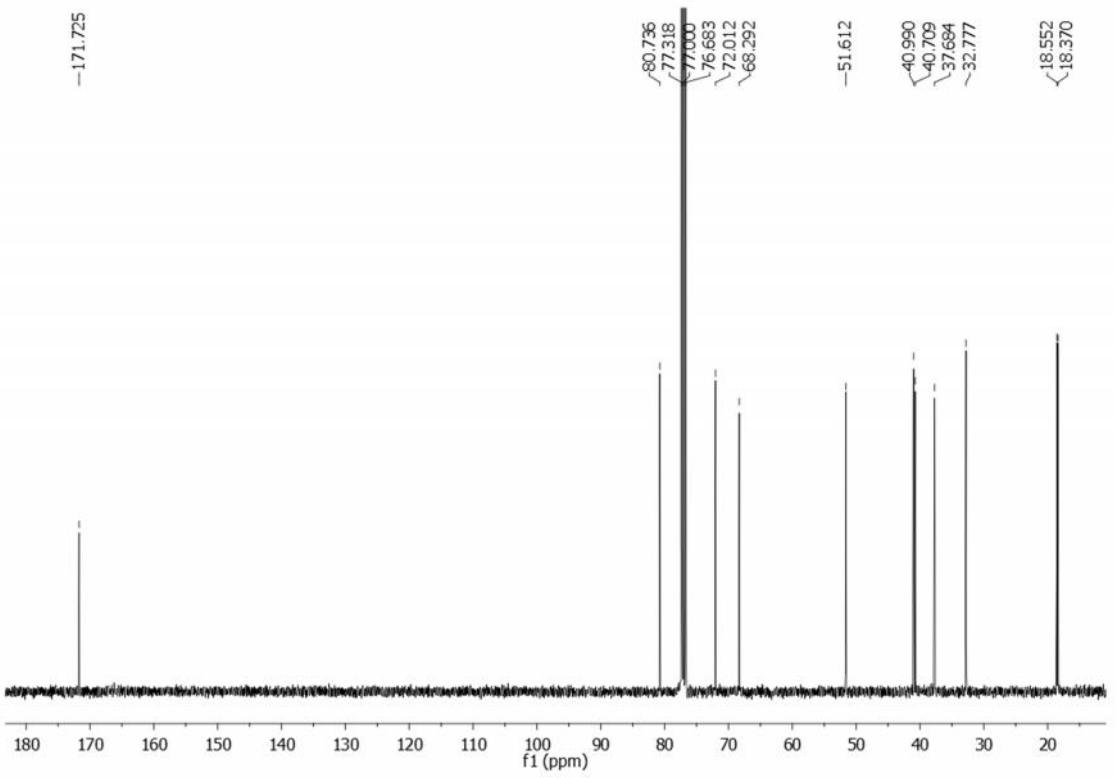
Compounds **12a**



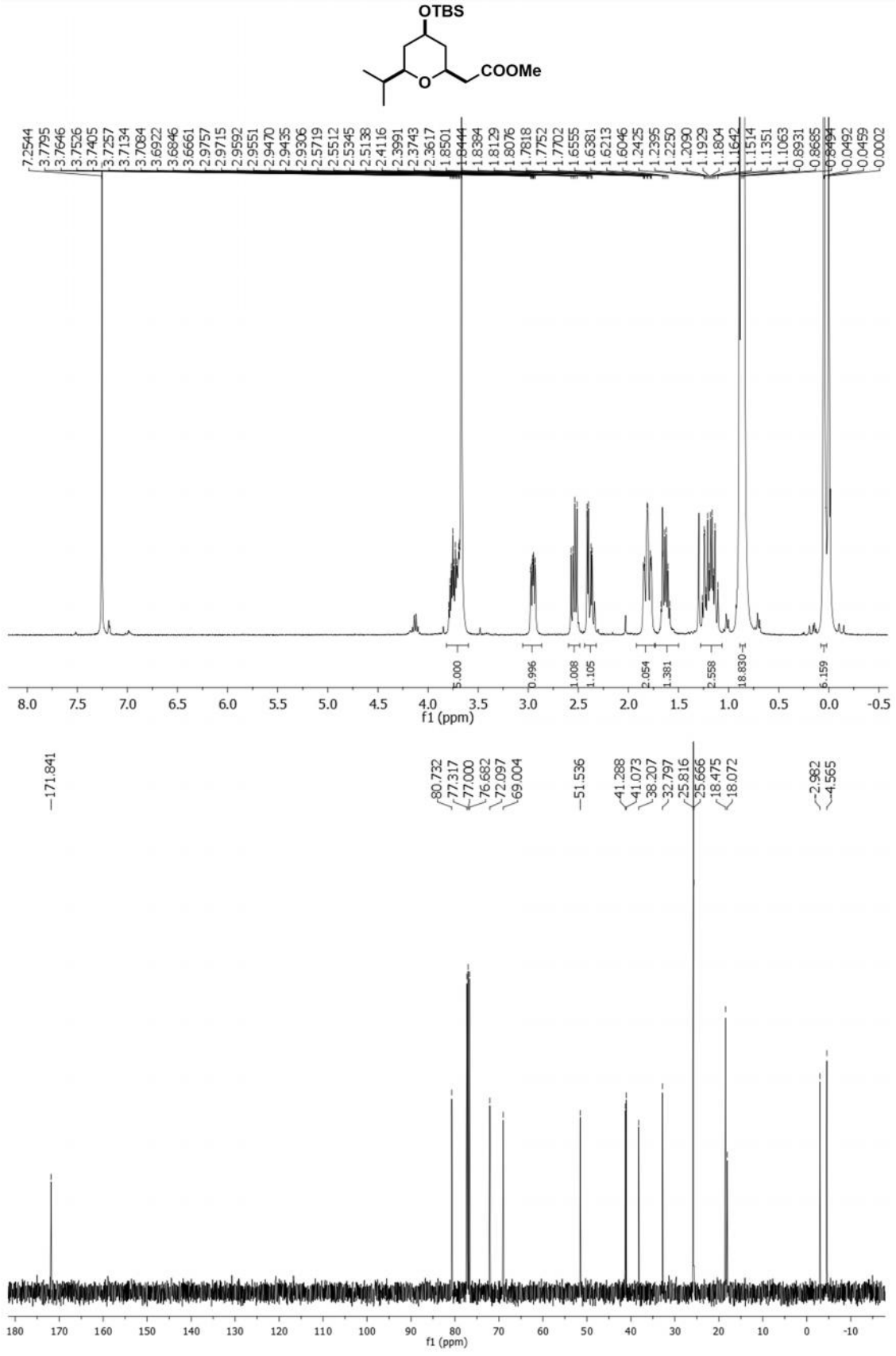
Compounds **8b**



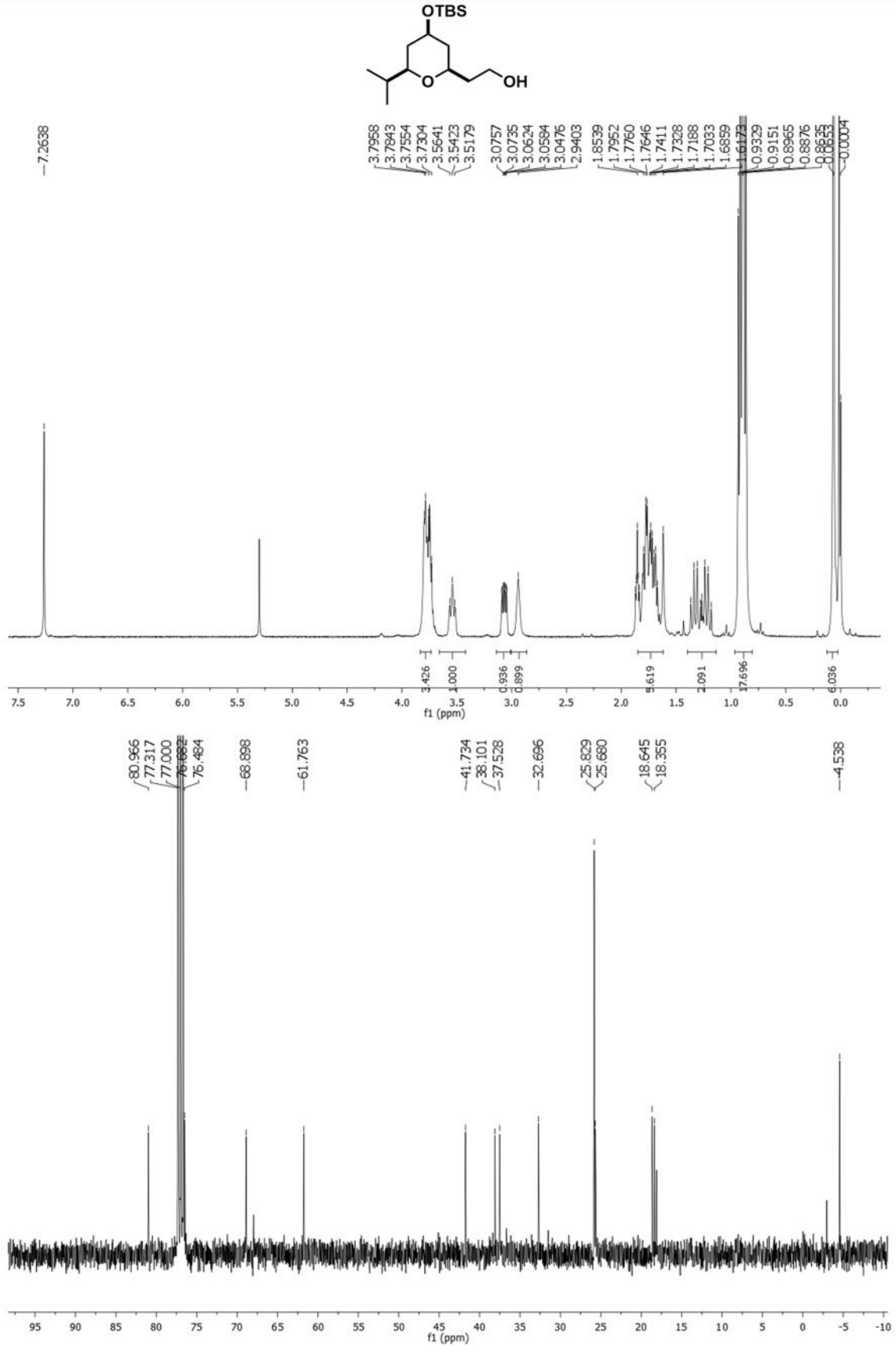




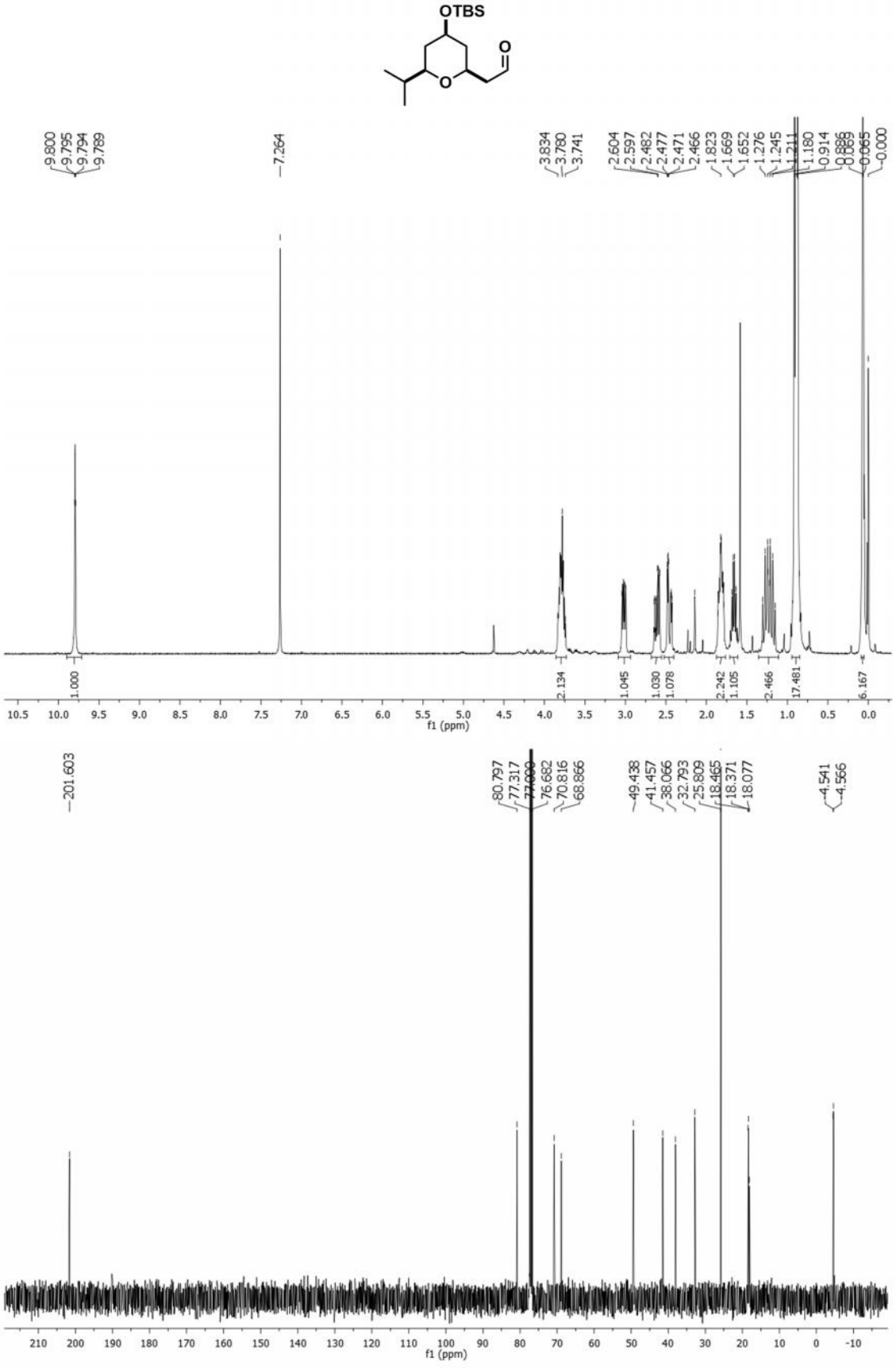
Compounds **9b**



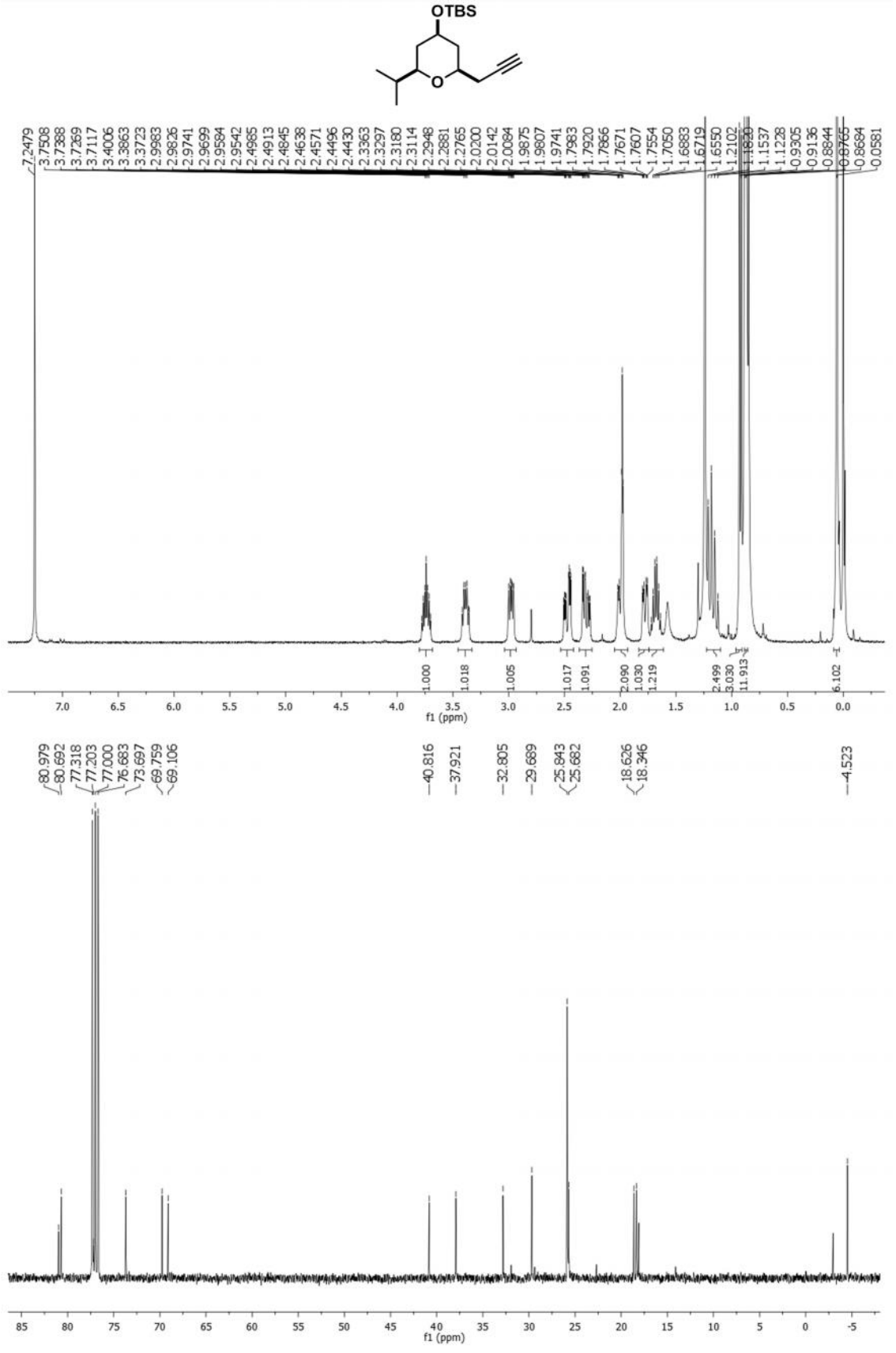
Compounds **10b**



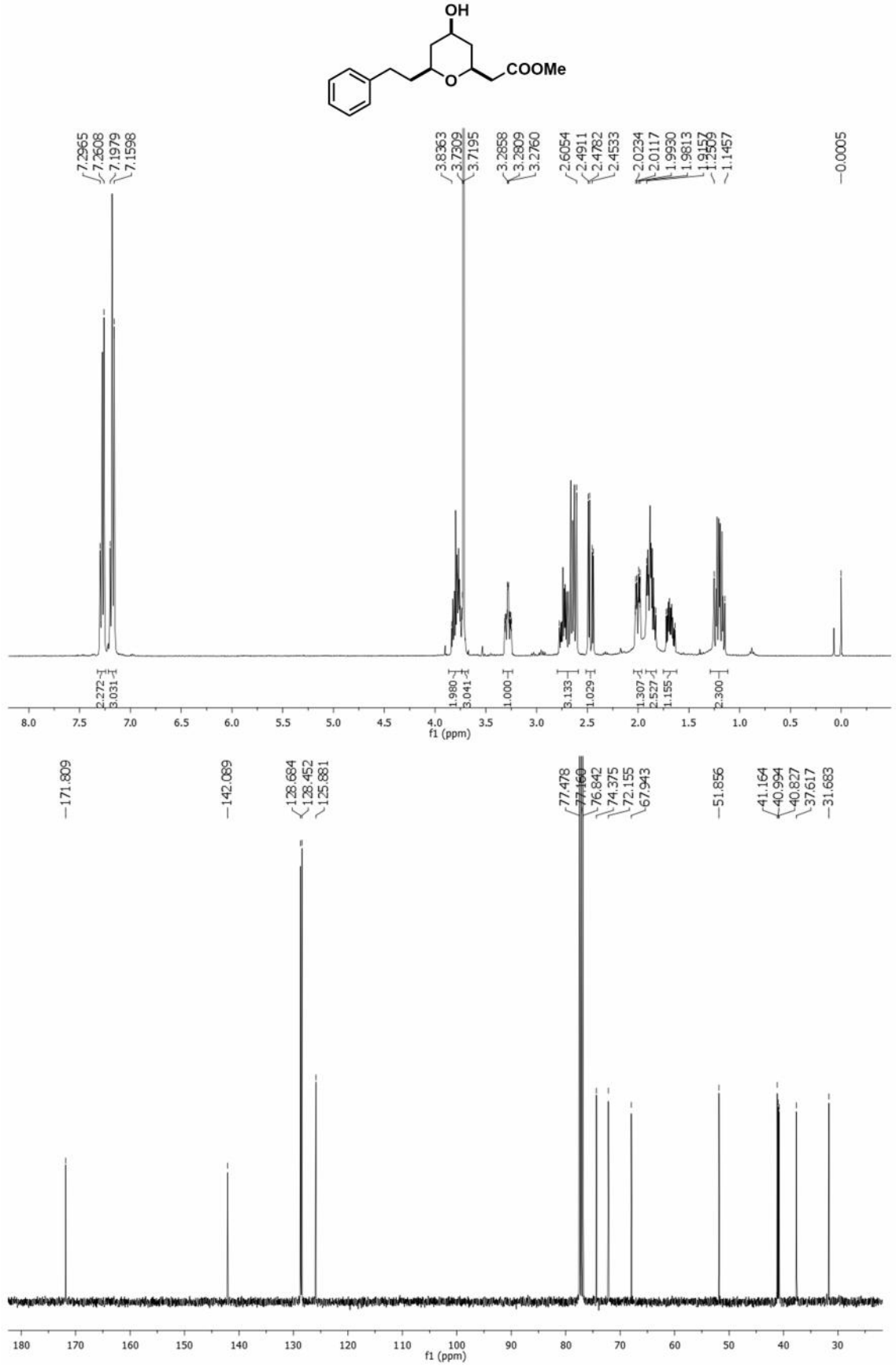
Compounds **11b**



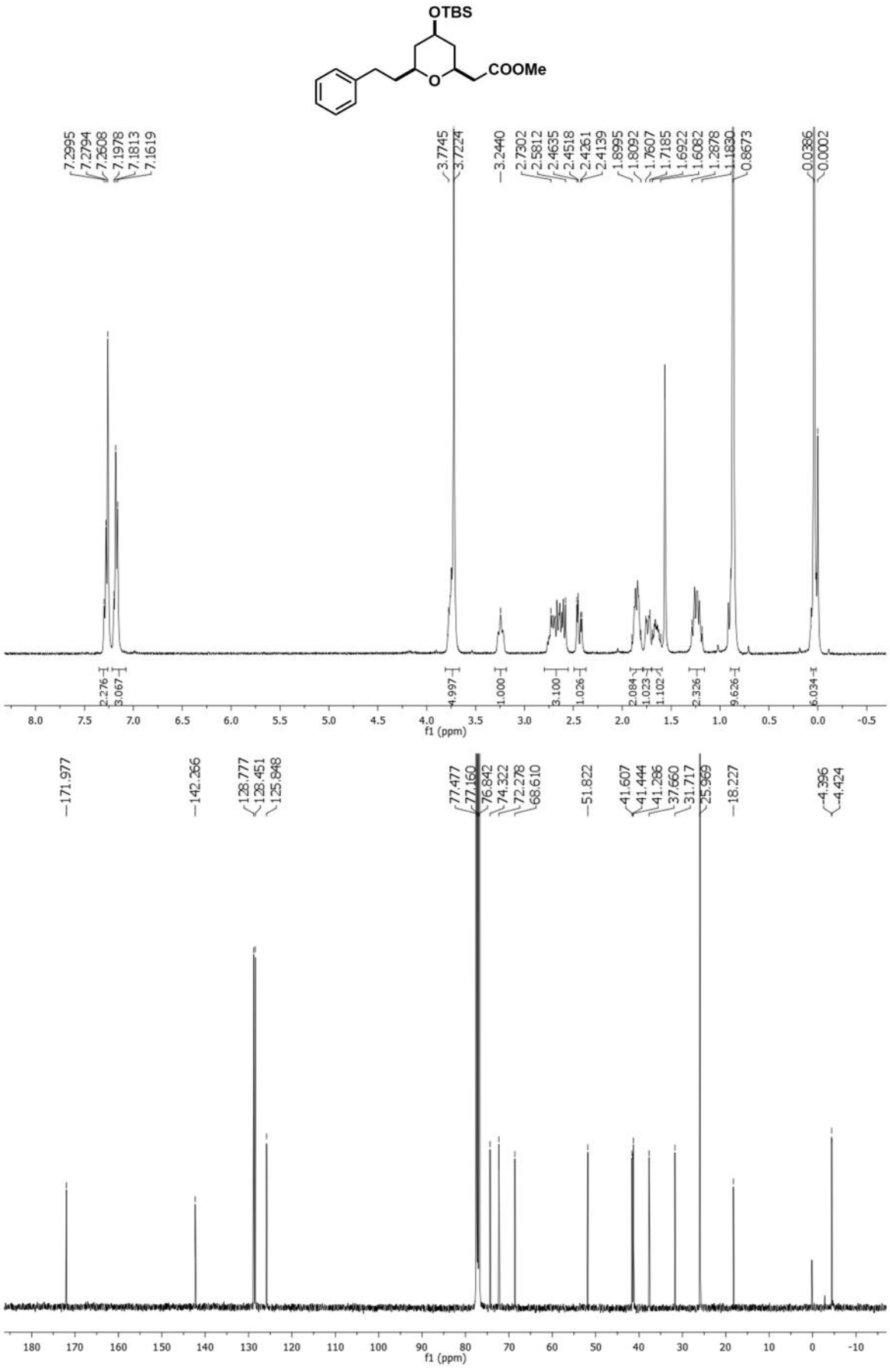
Compounds **12b**



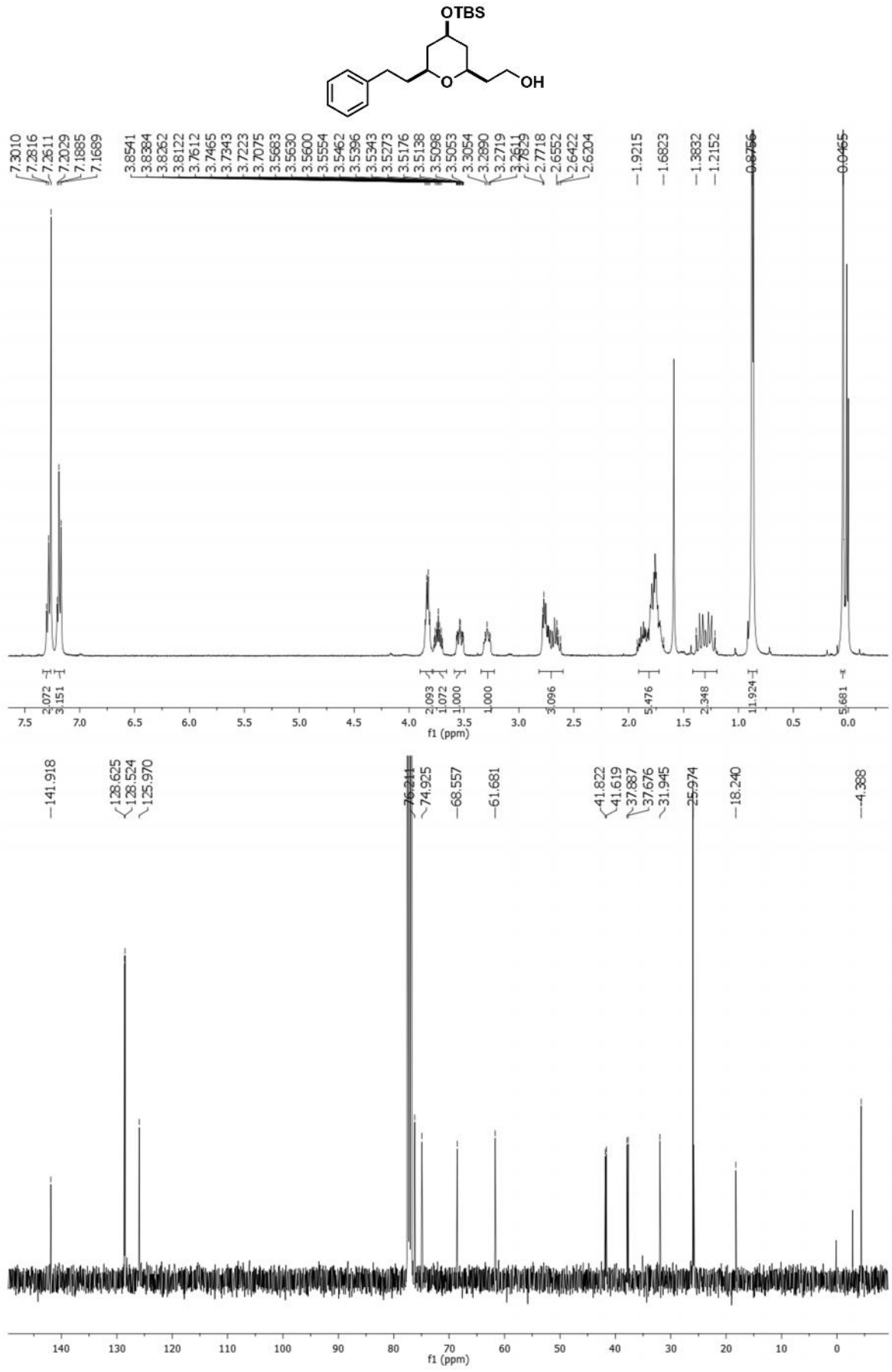
Compounds **8c**



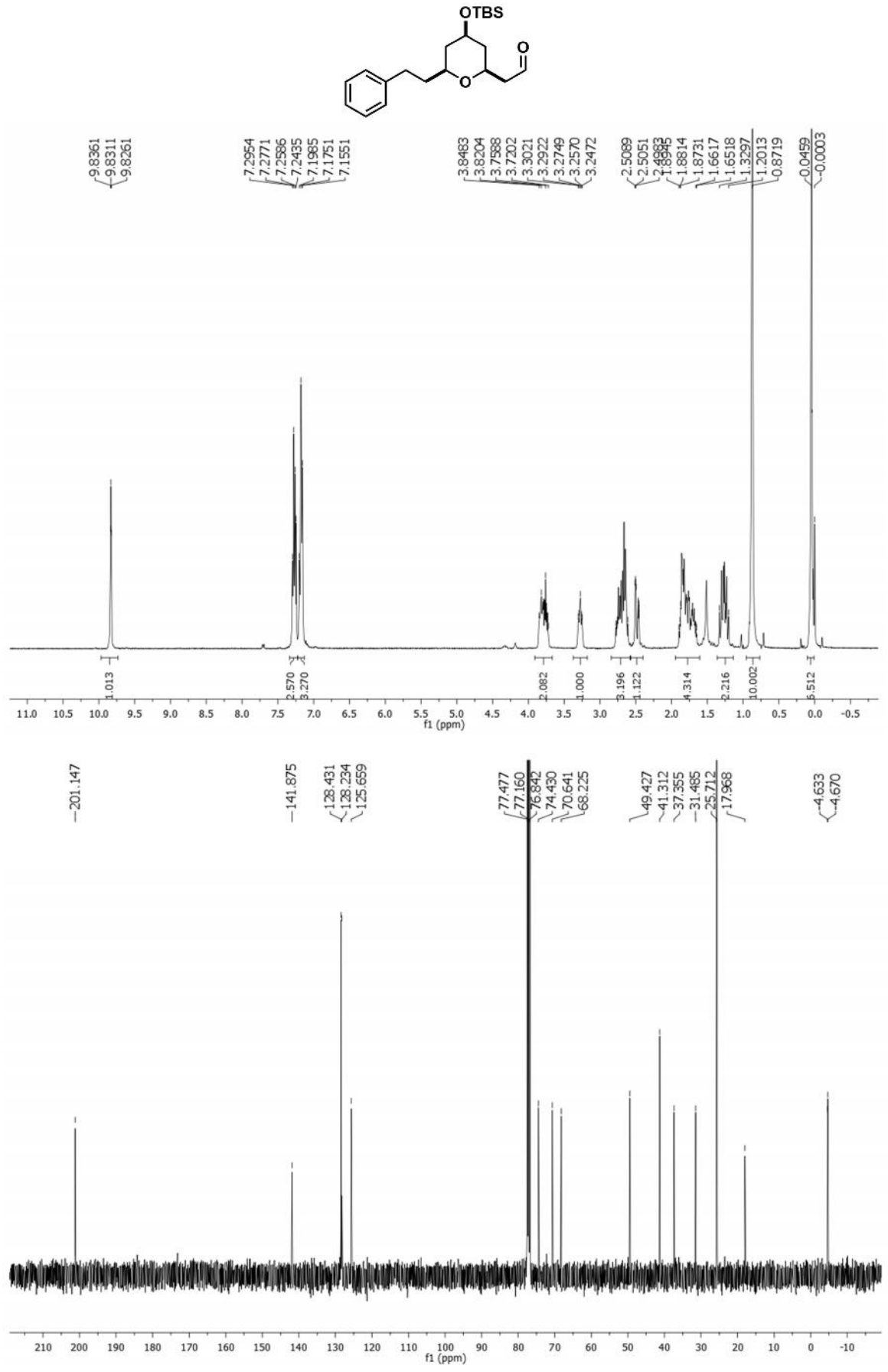
Compounds **9c**



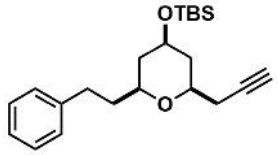
Compounds **10c**

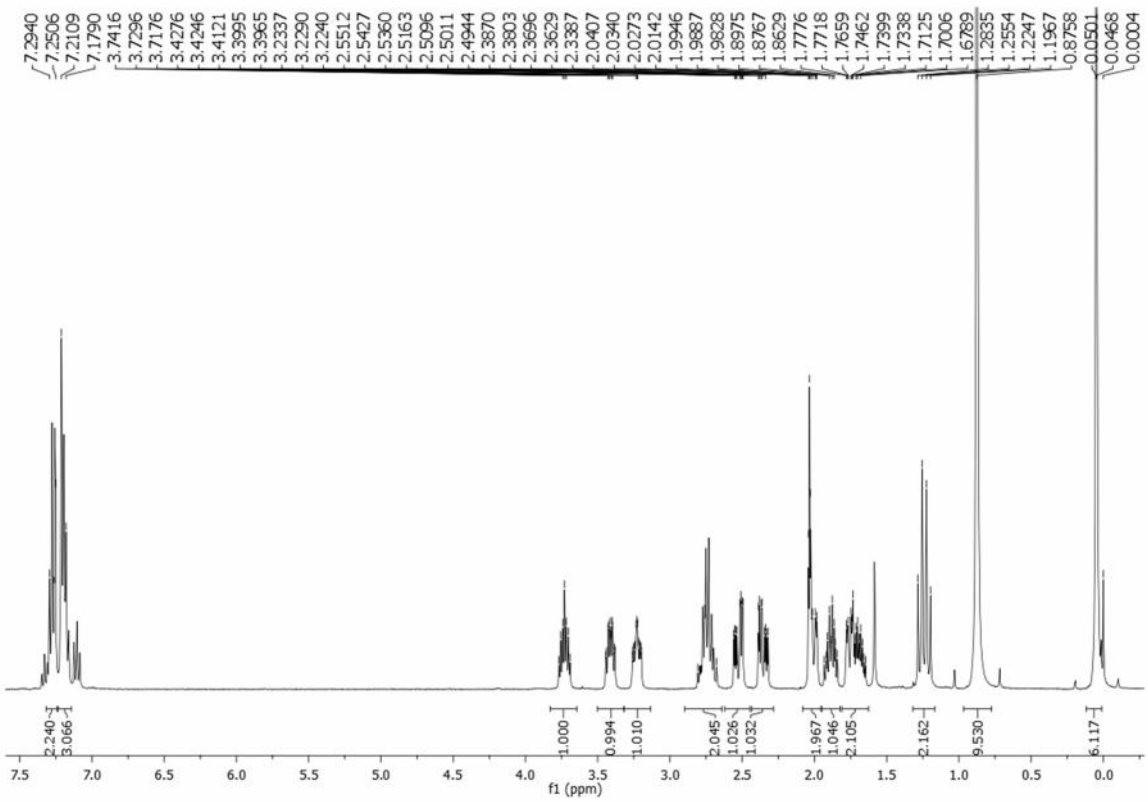


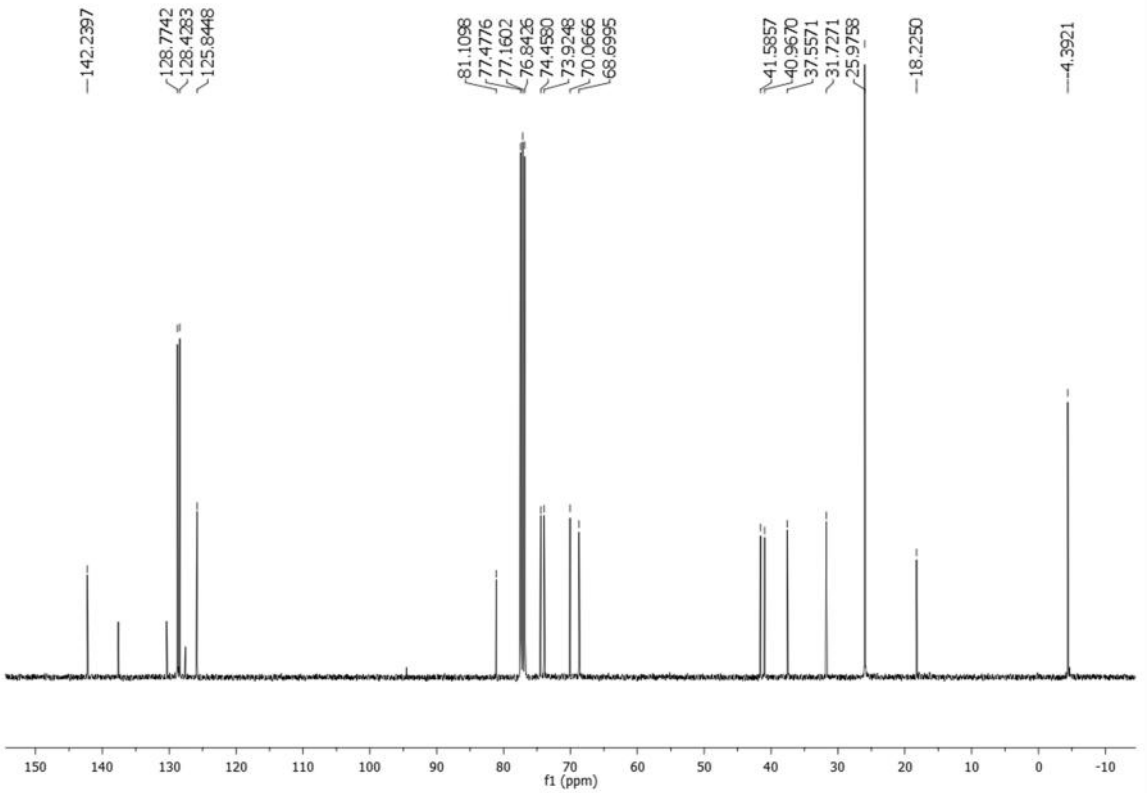
Compounds **11c**



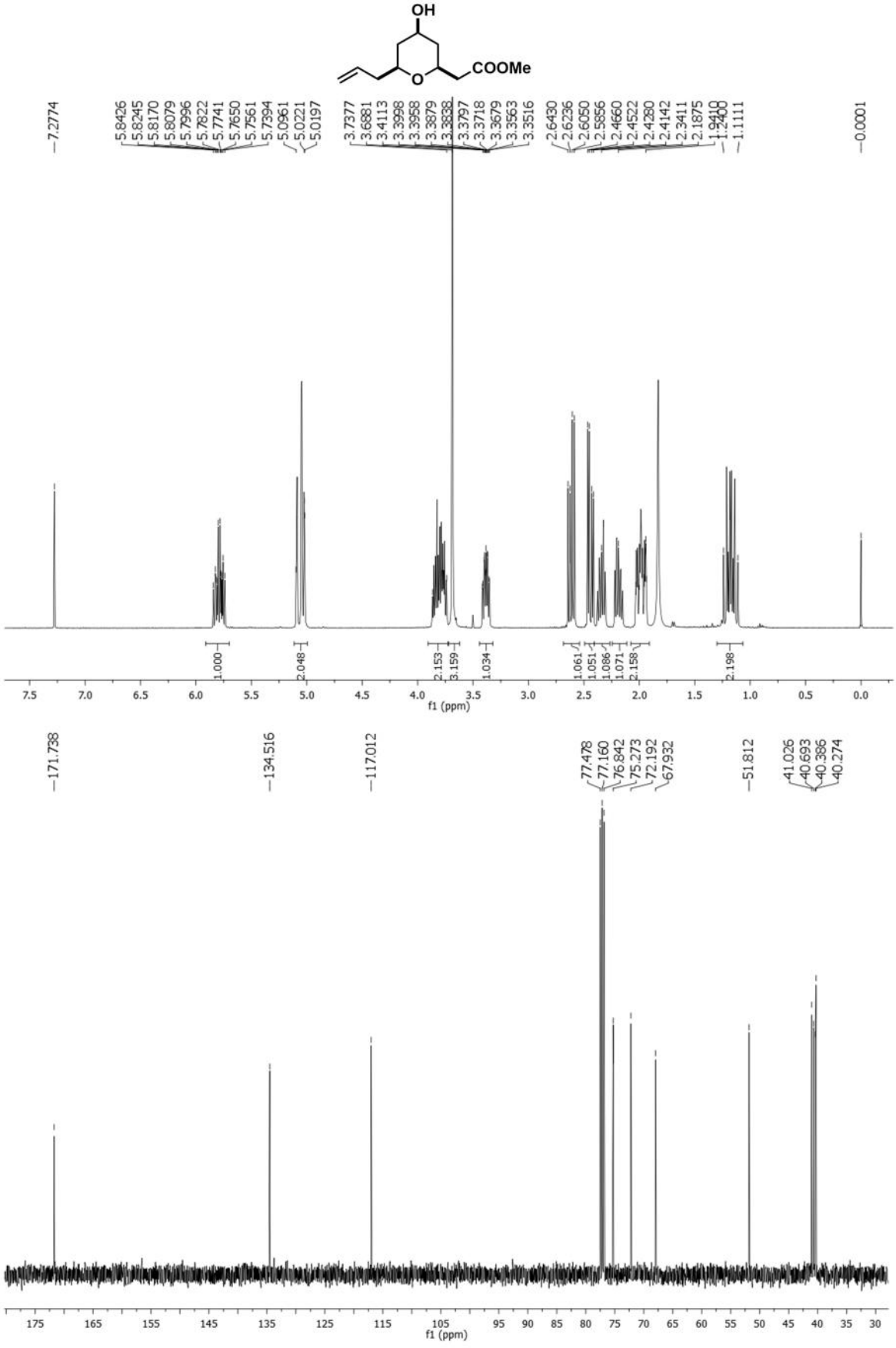
Compounds **12c**



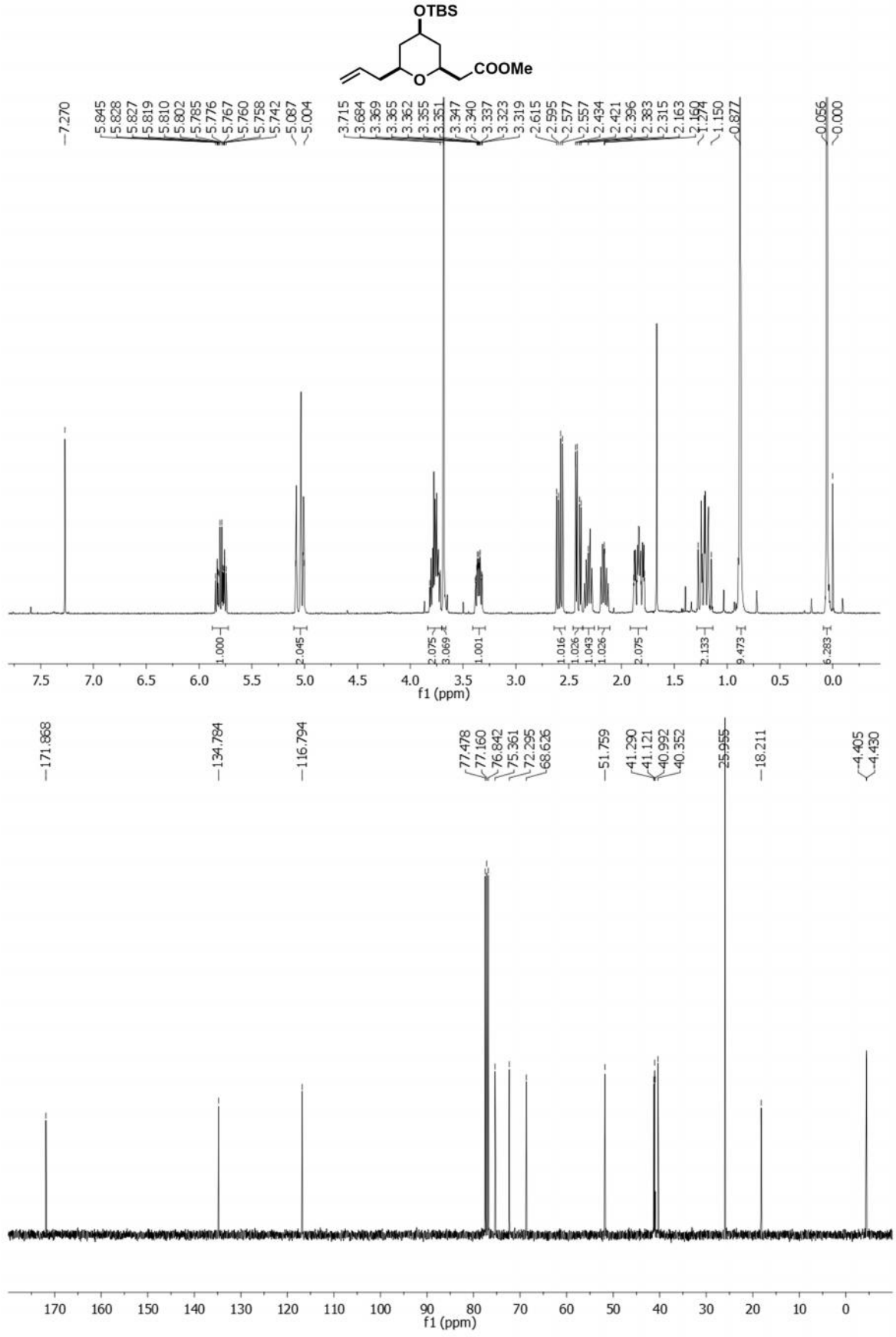




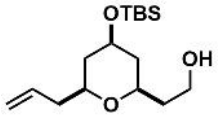
Compounds **8d**

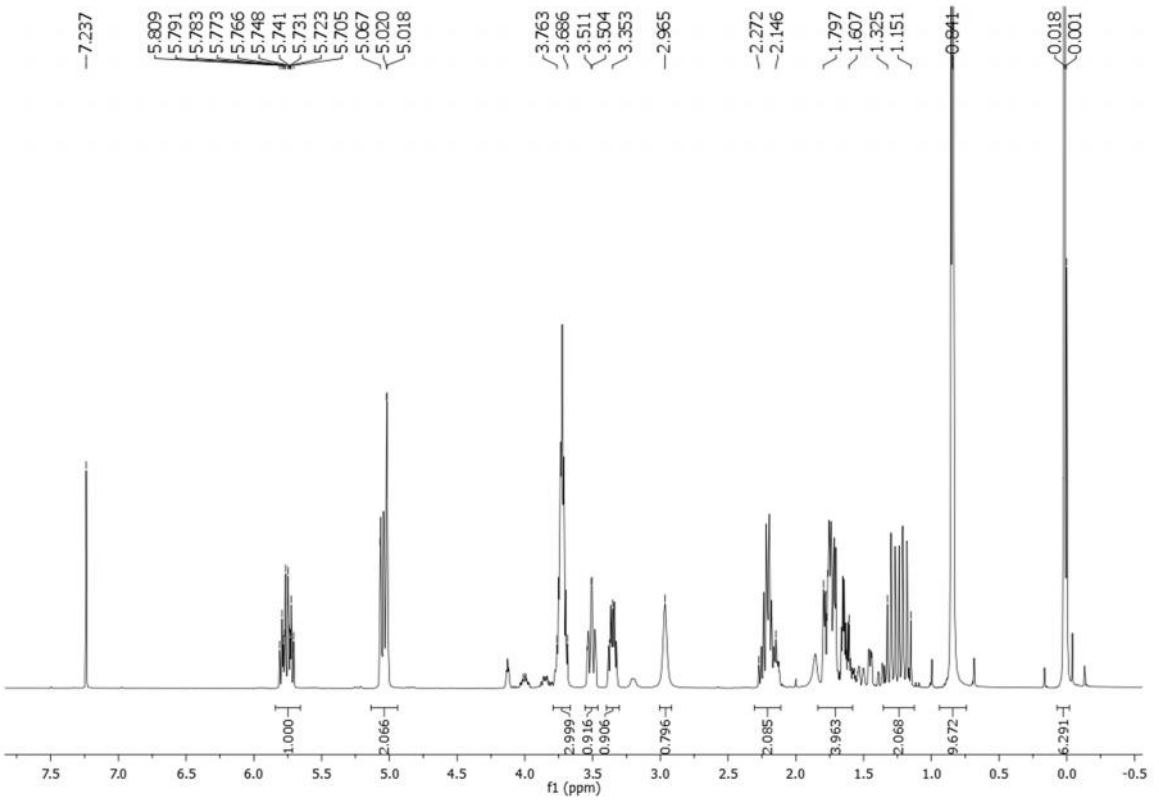


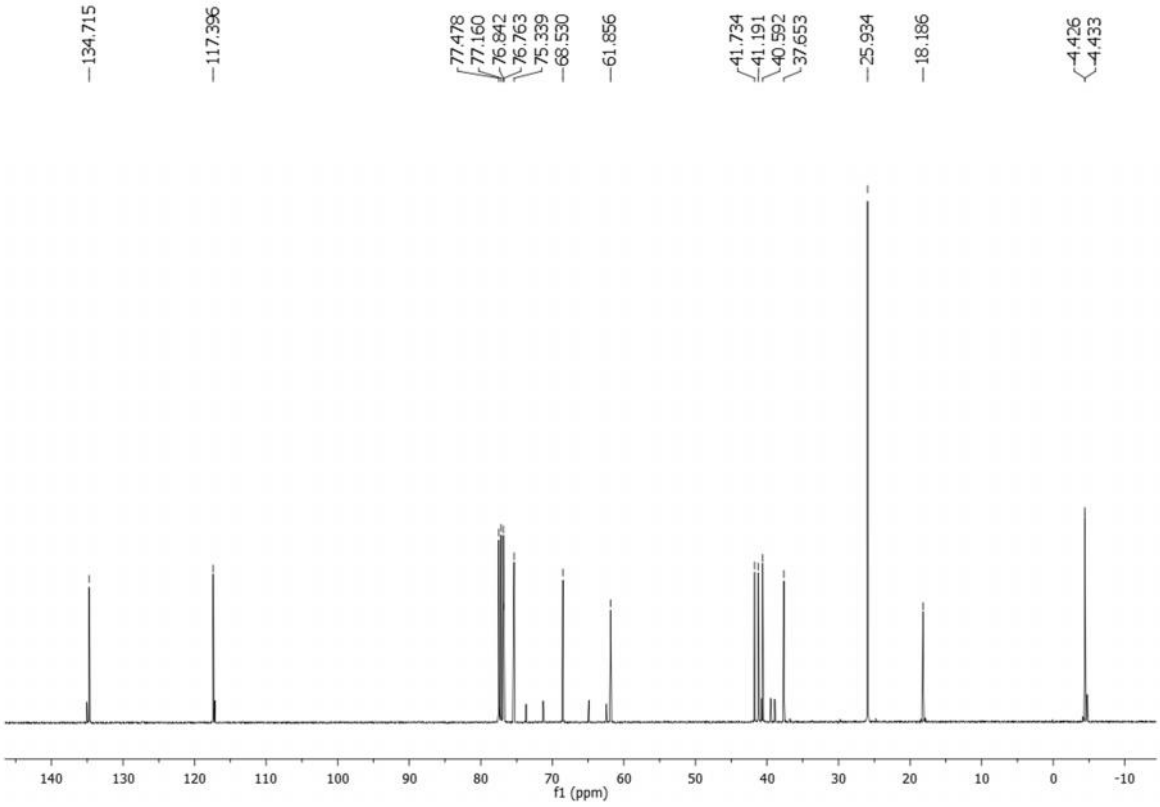
Compounds **9d**



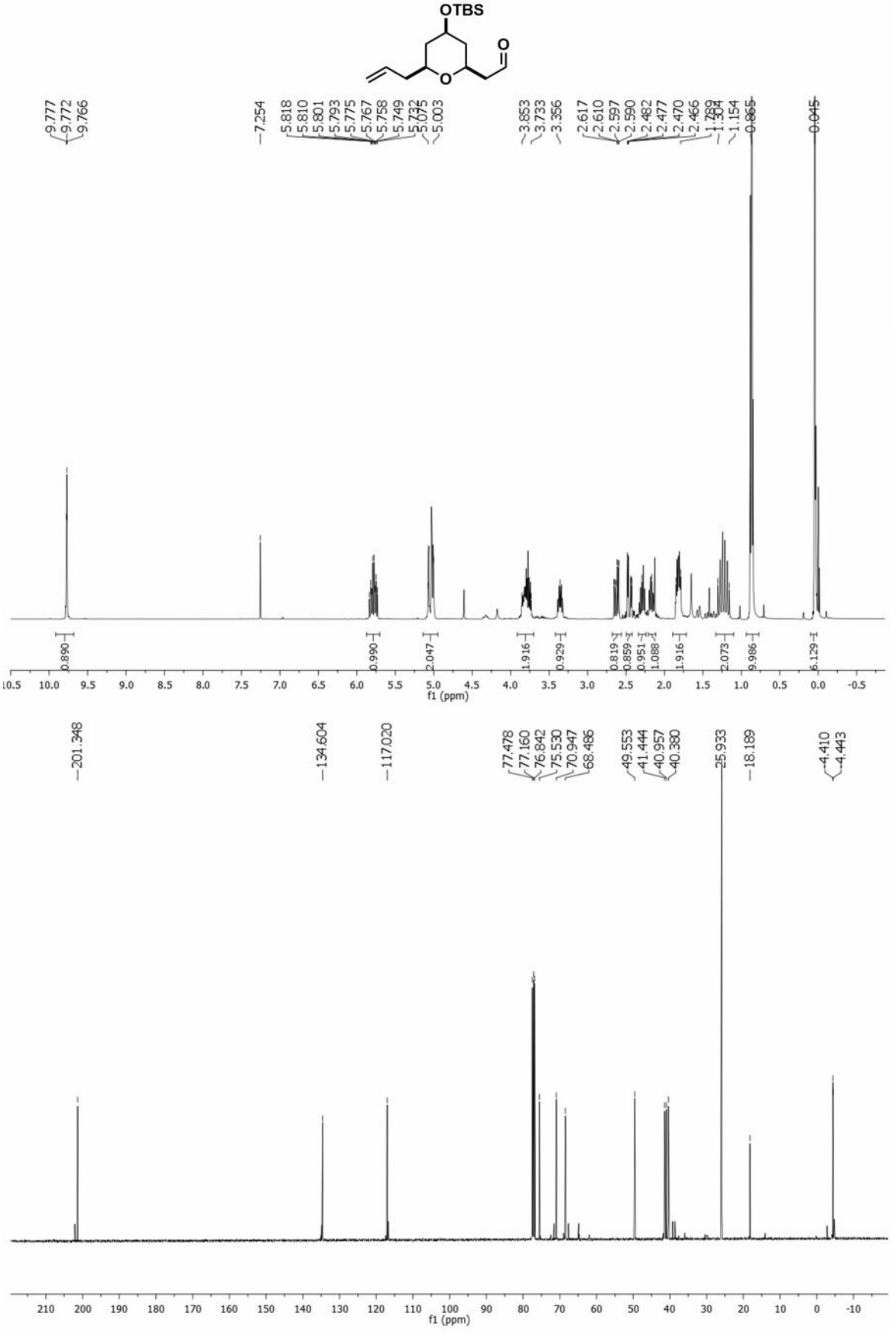
Compounds **10d**



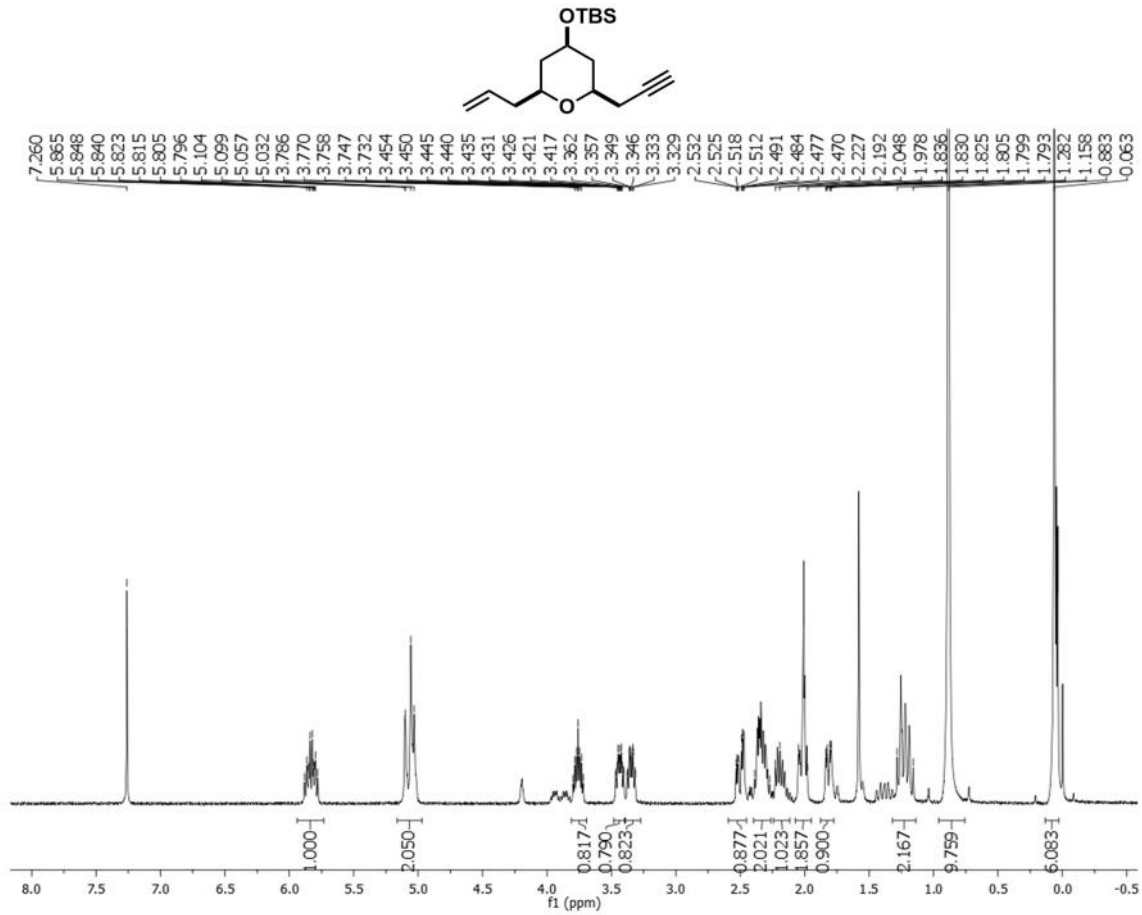


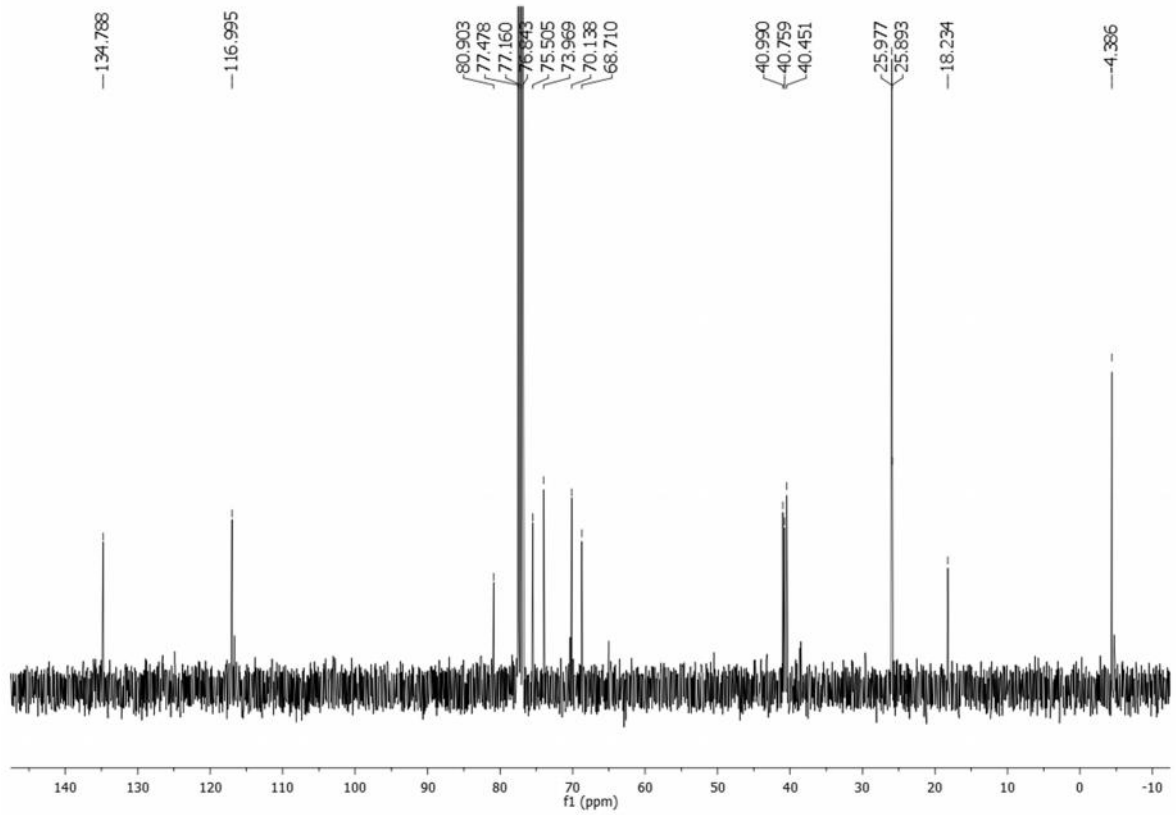


Compounds **11d**

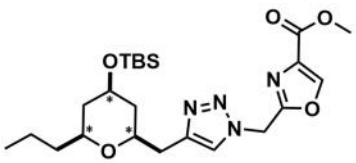


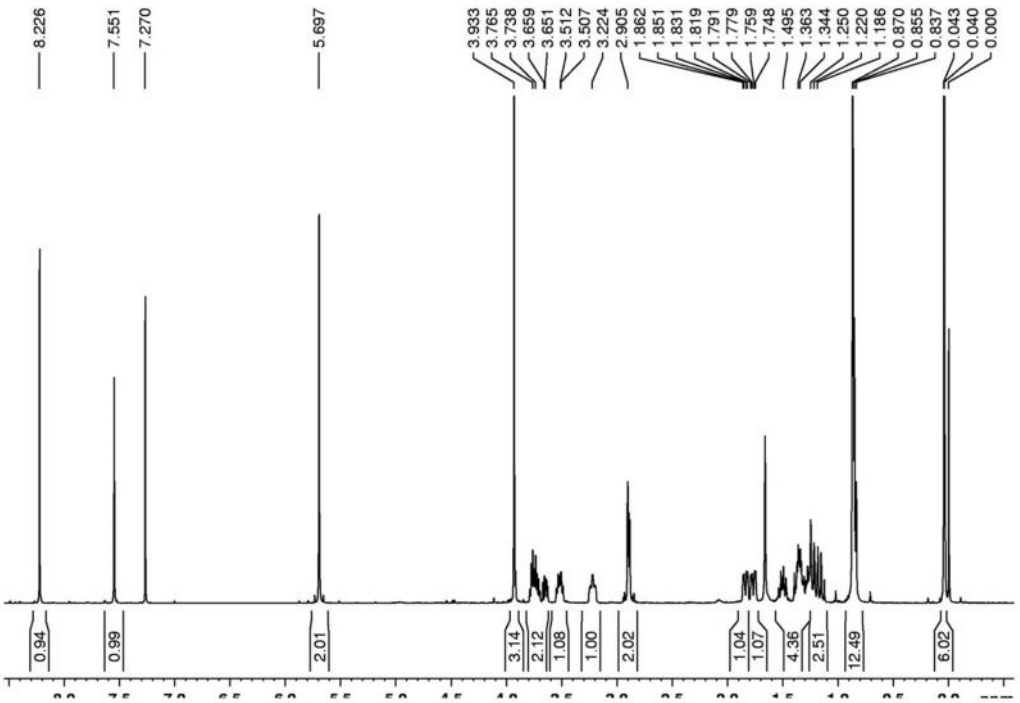
Compounds **12d**

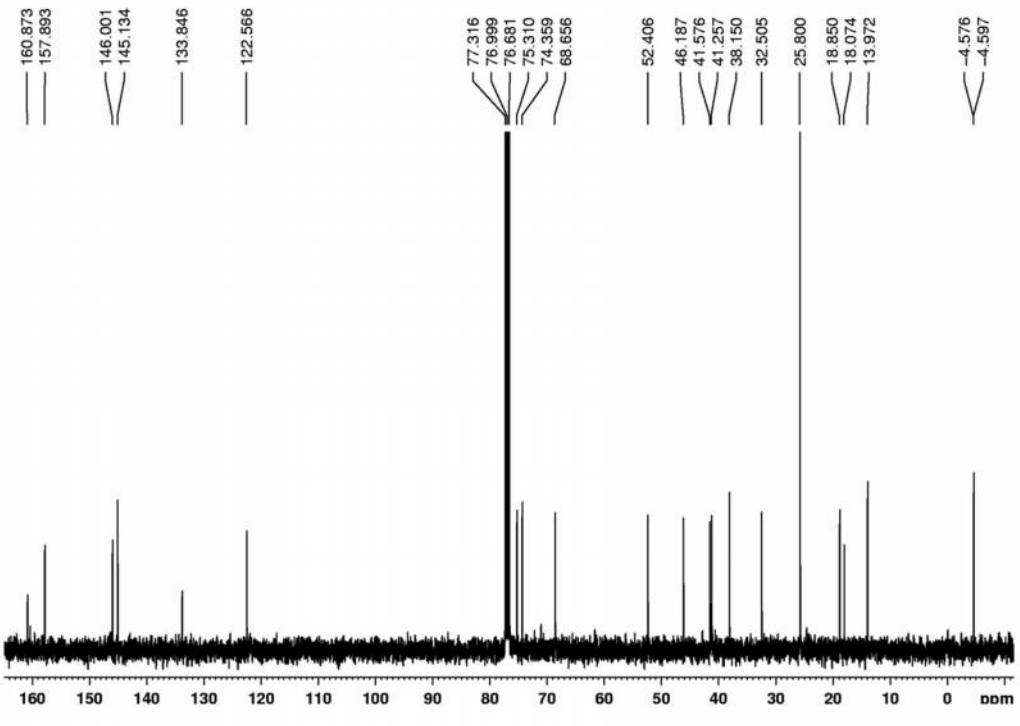




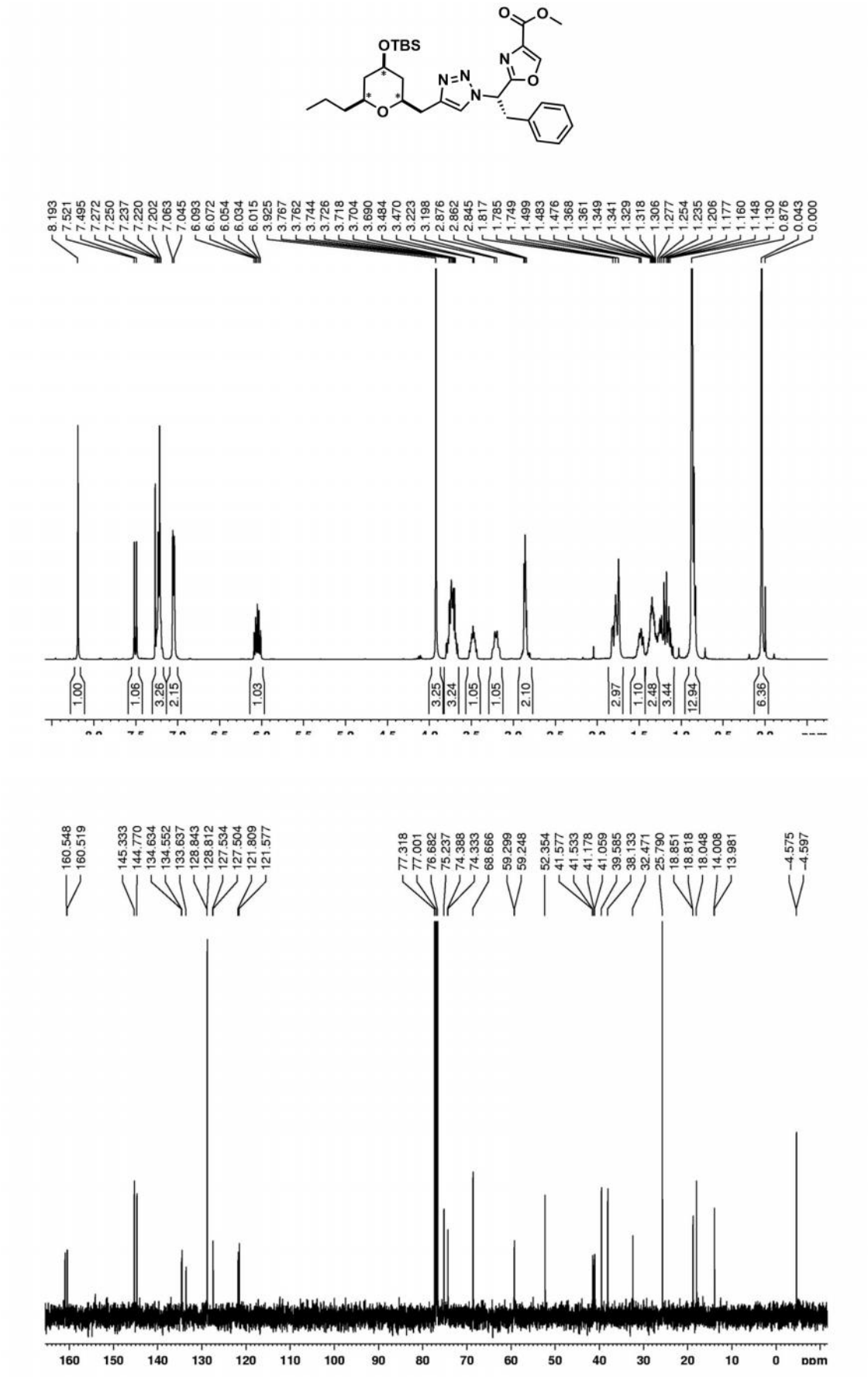
Compounds **14a**



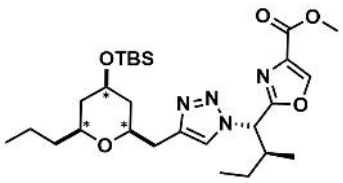


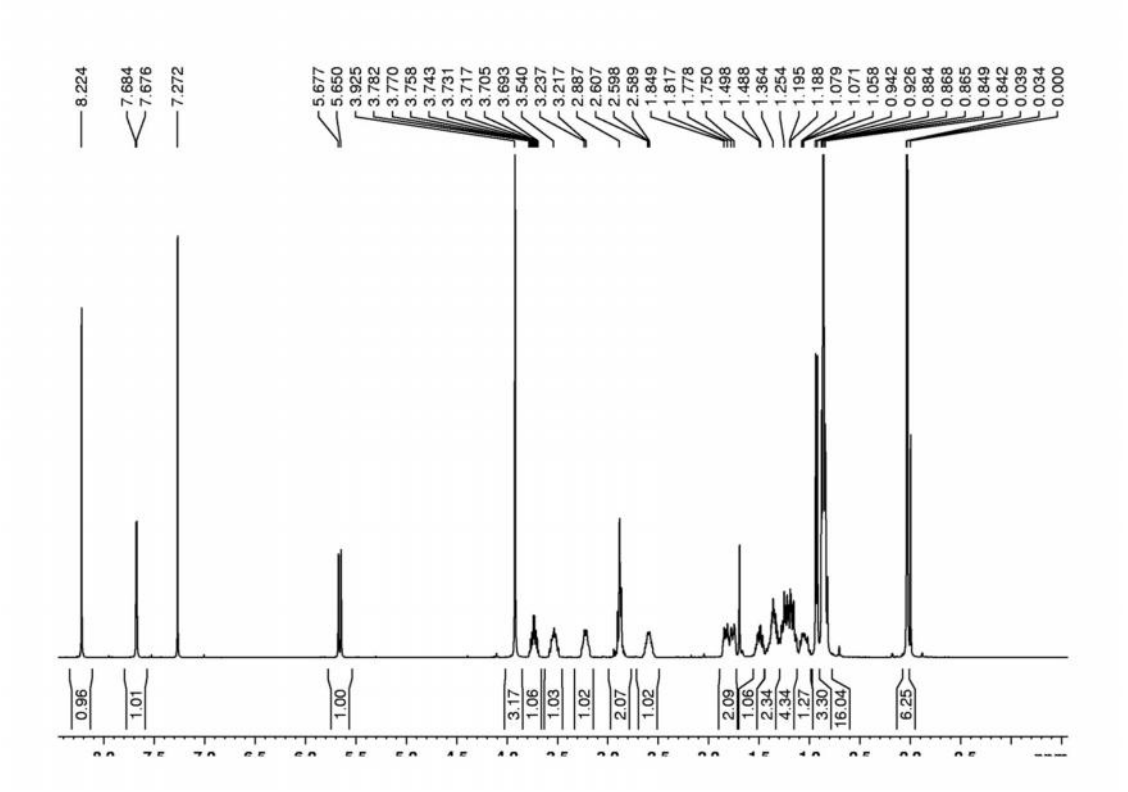


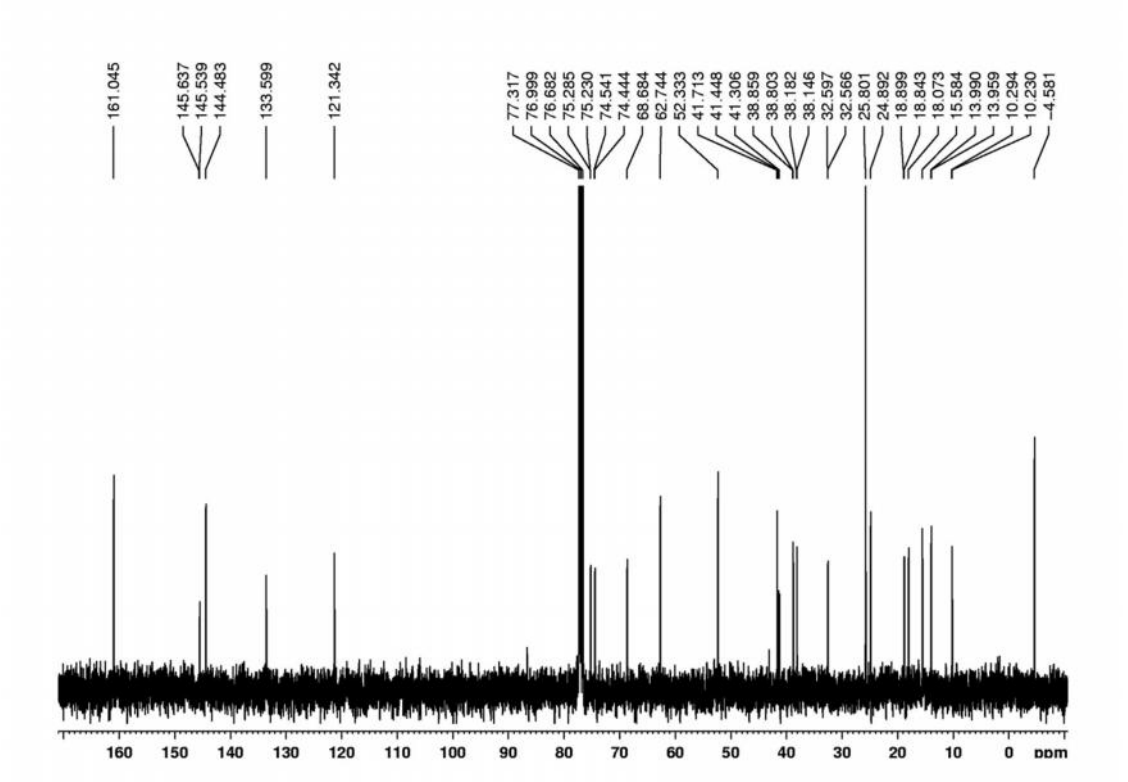
Compounds **14b**



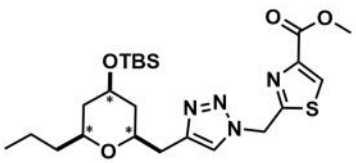
Compounds **14c**

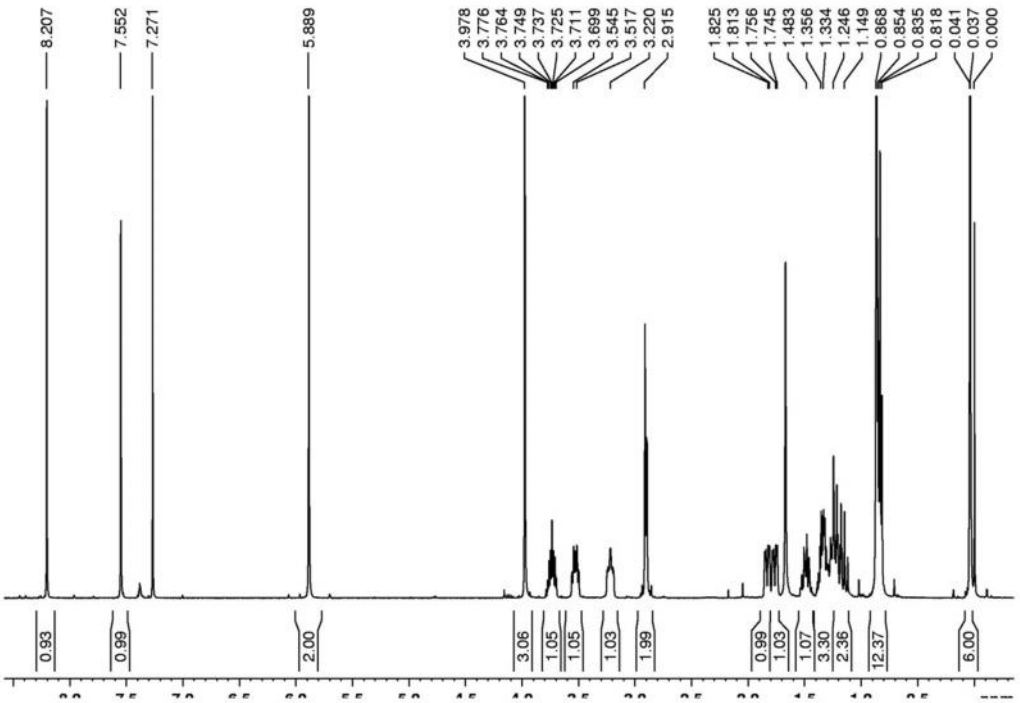


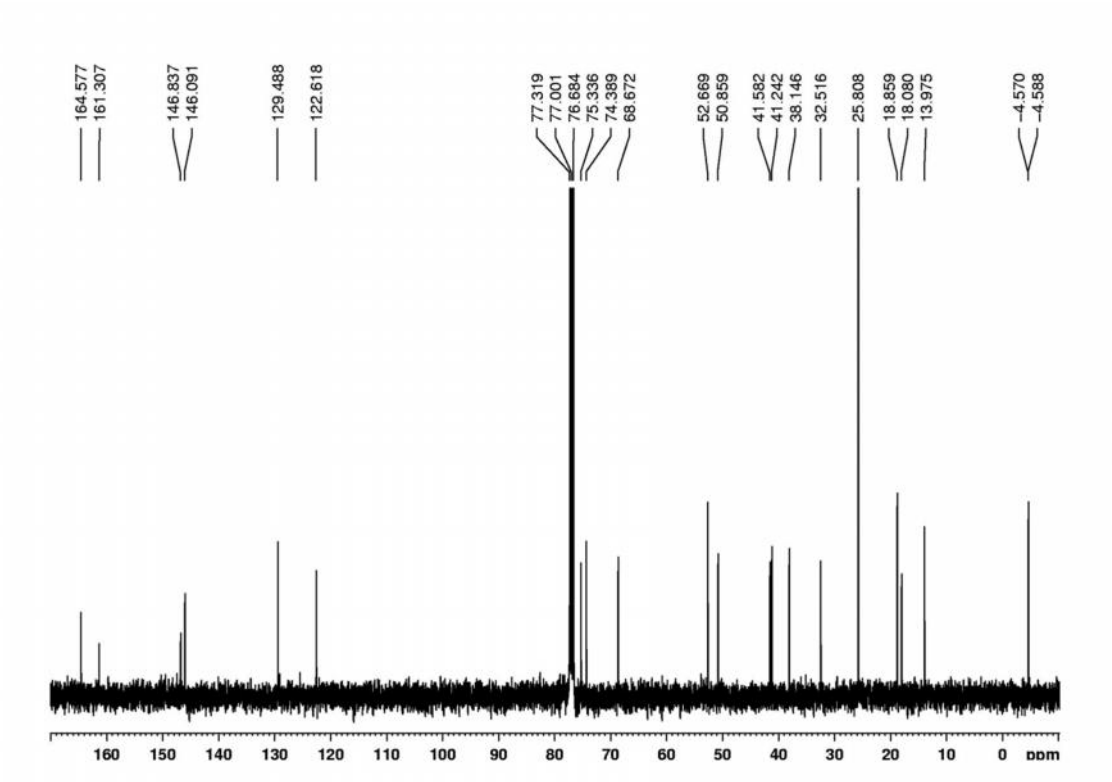




Compounds **14d**







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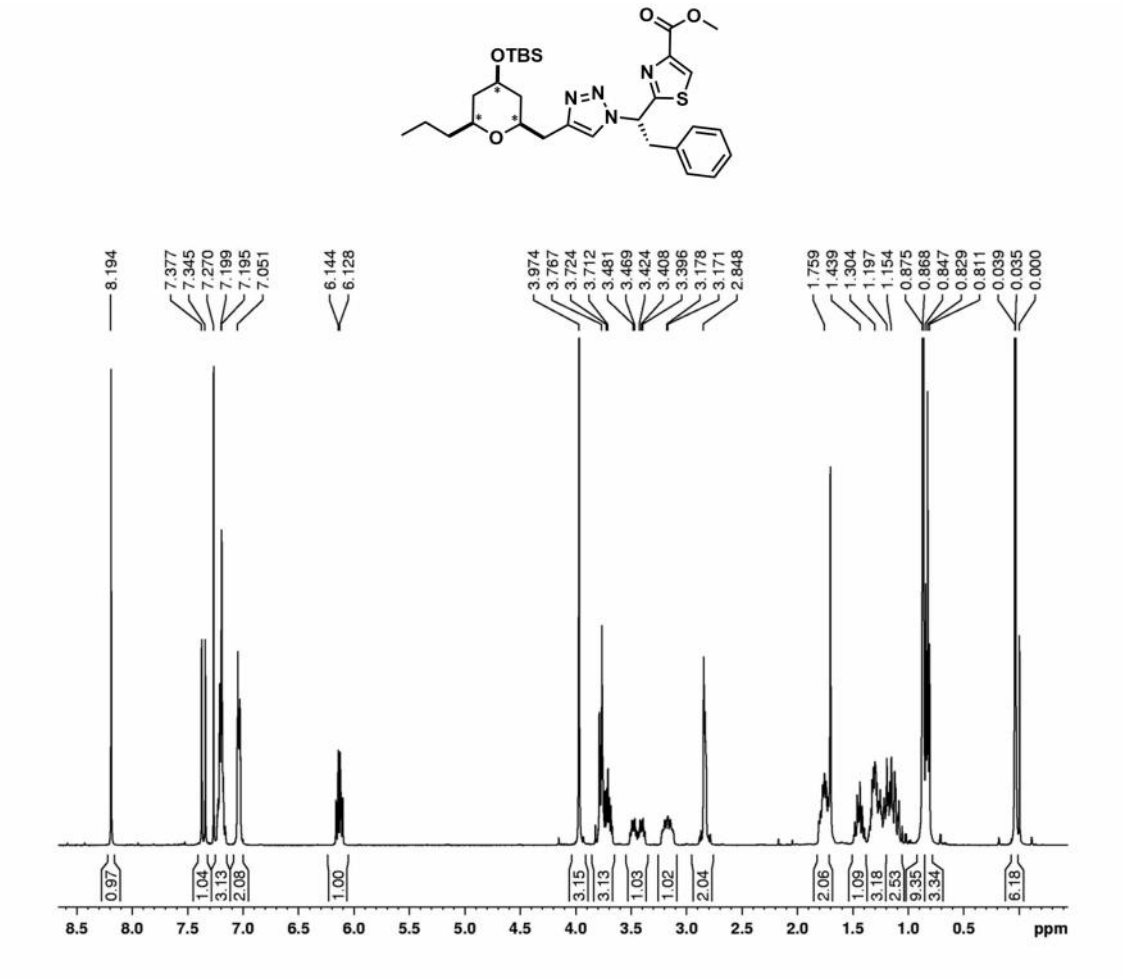
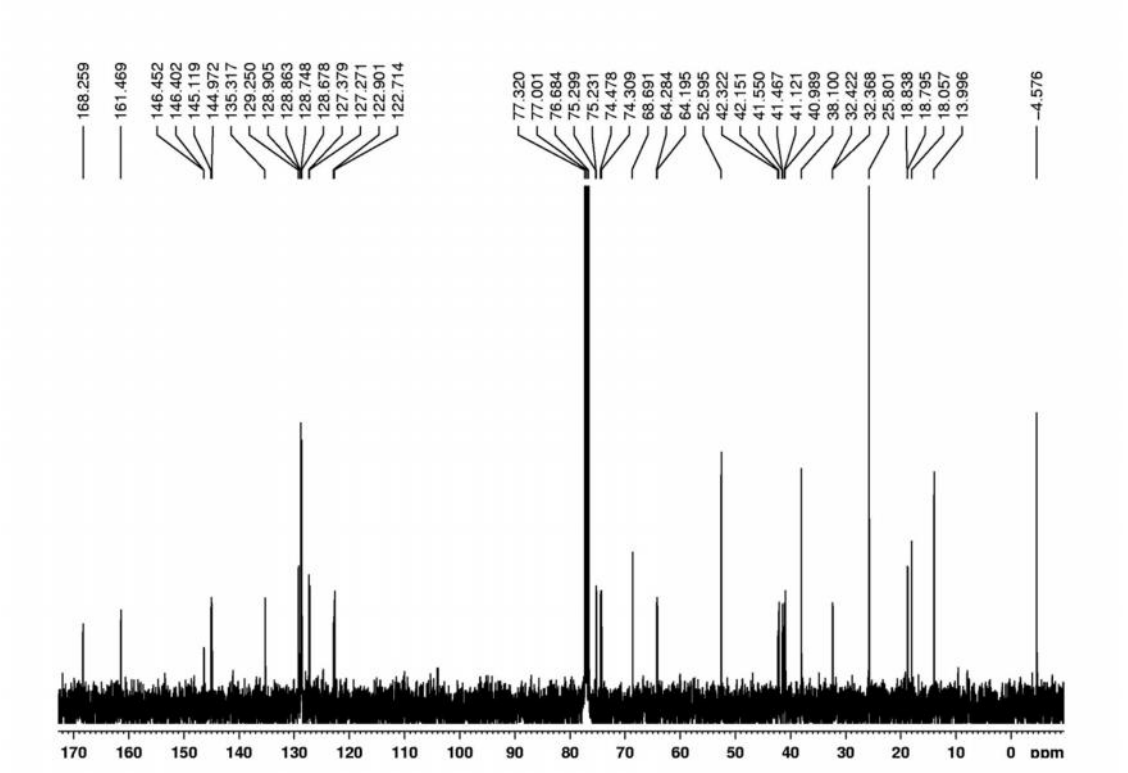
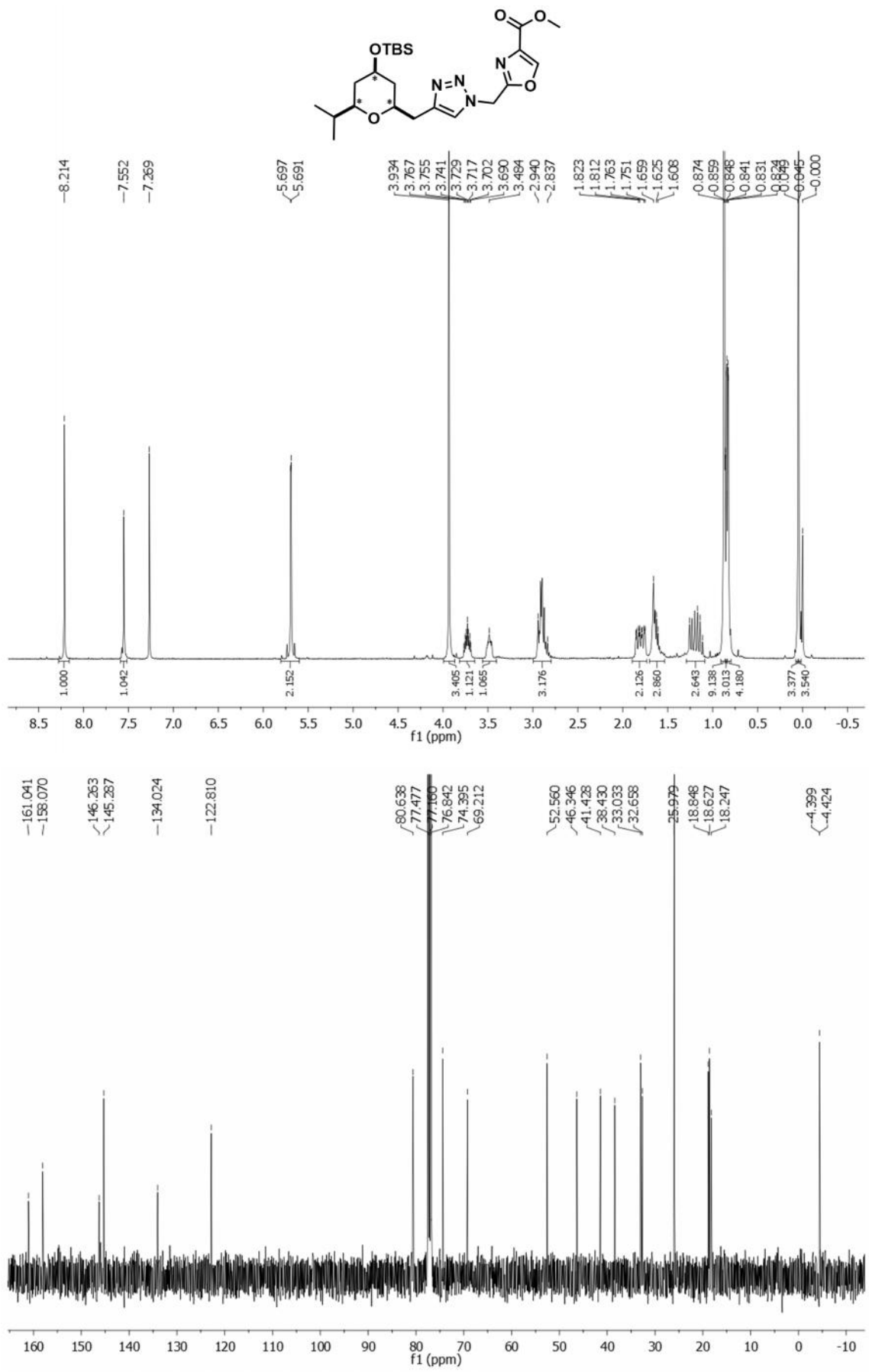
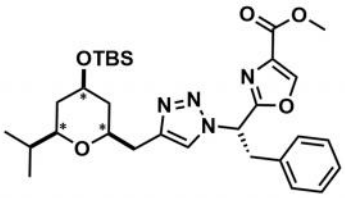


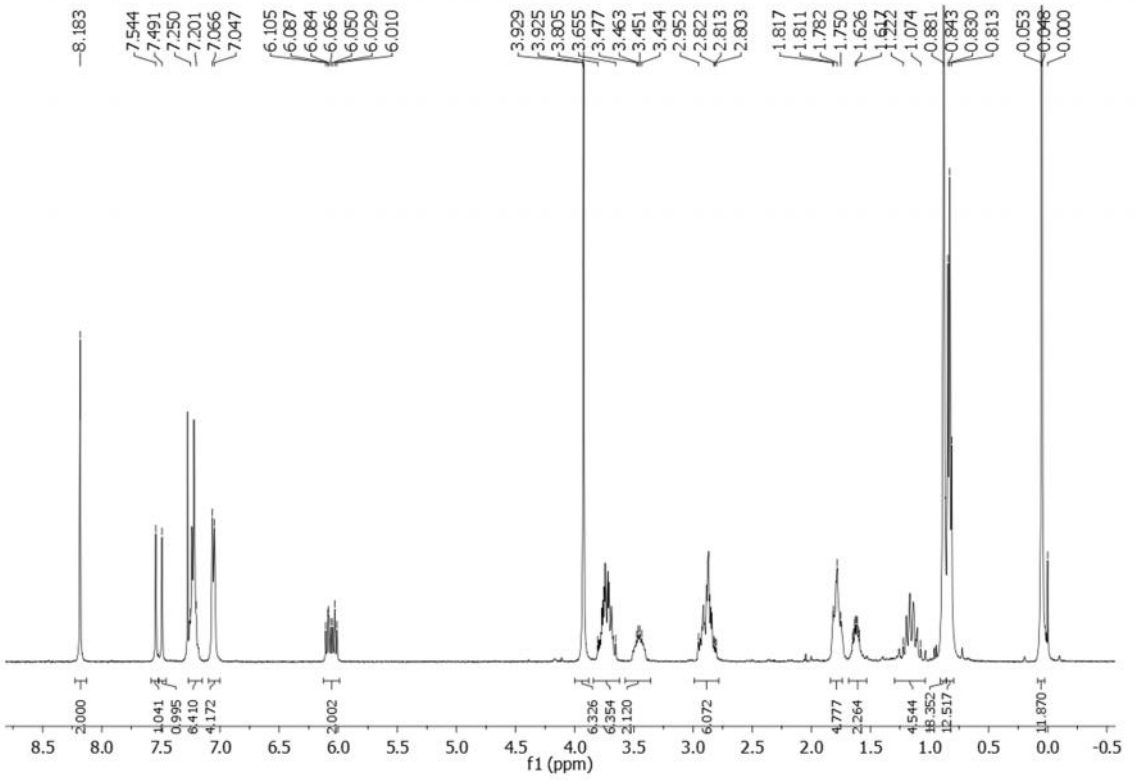


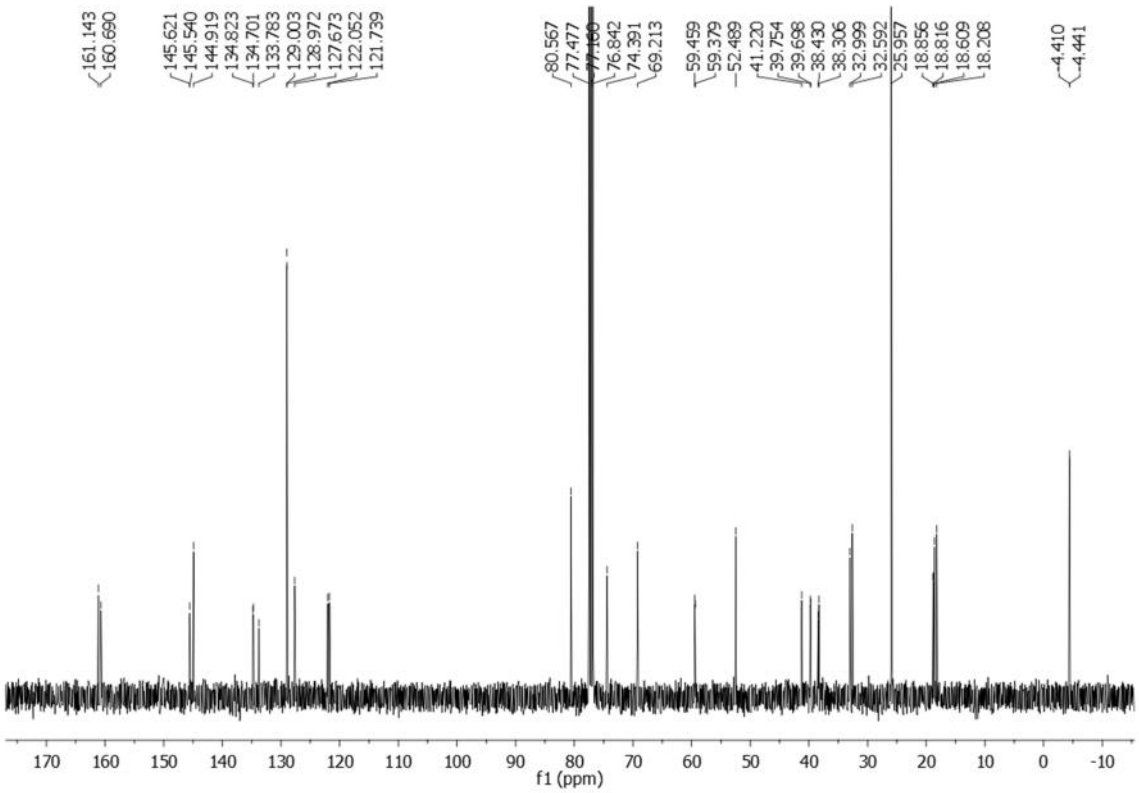
Compounds **14f**



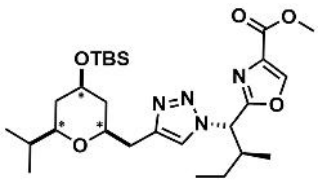
Compounds **14g**

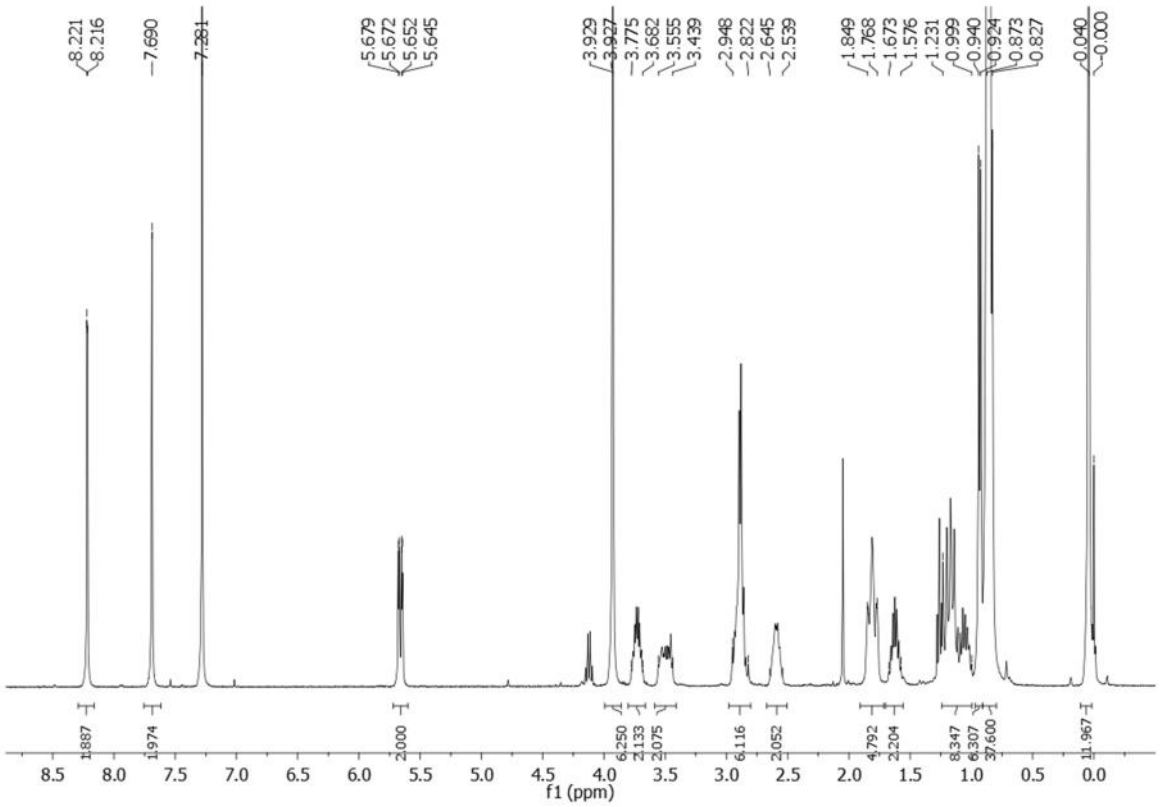


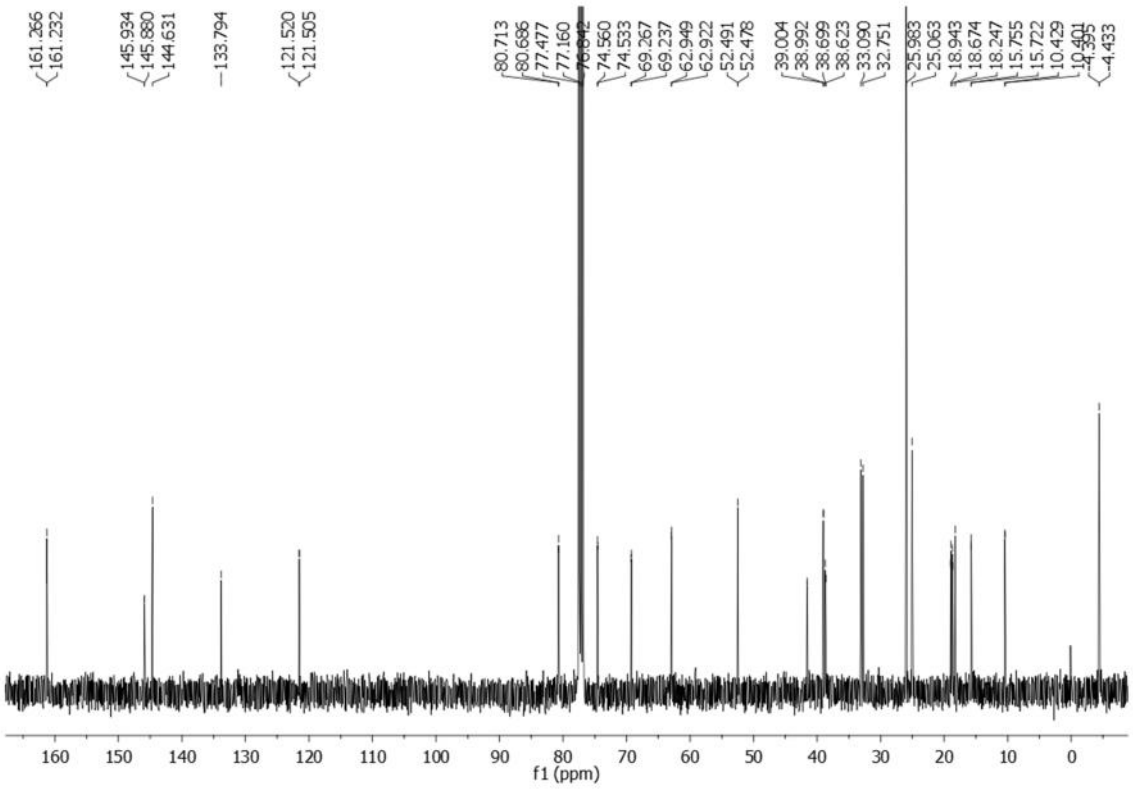




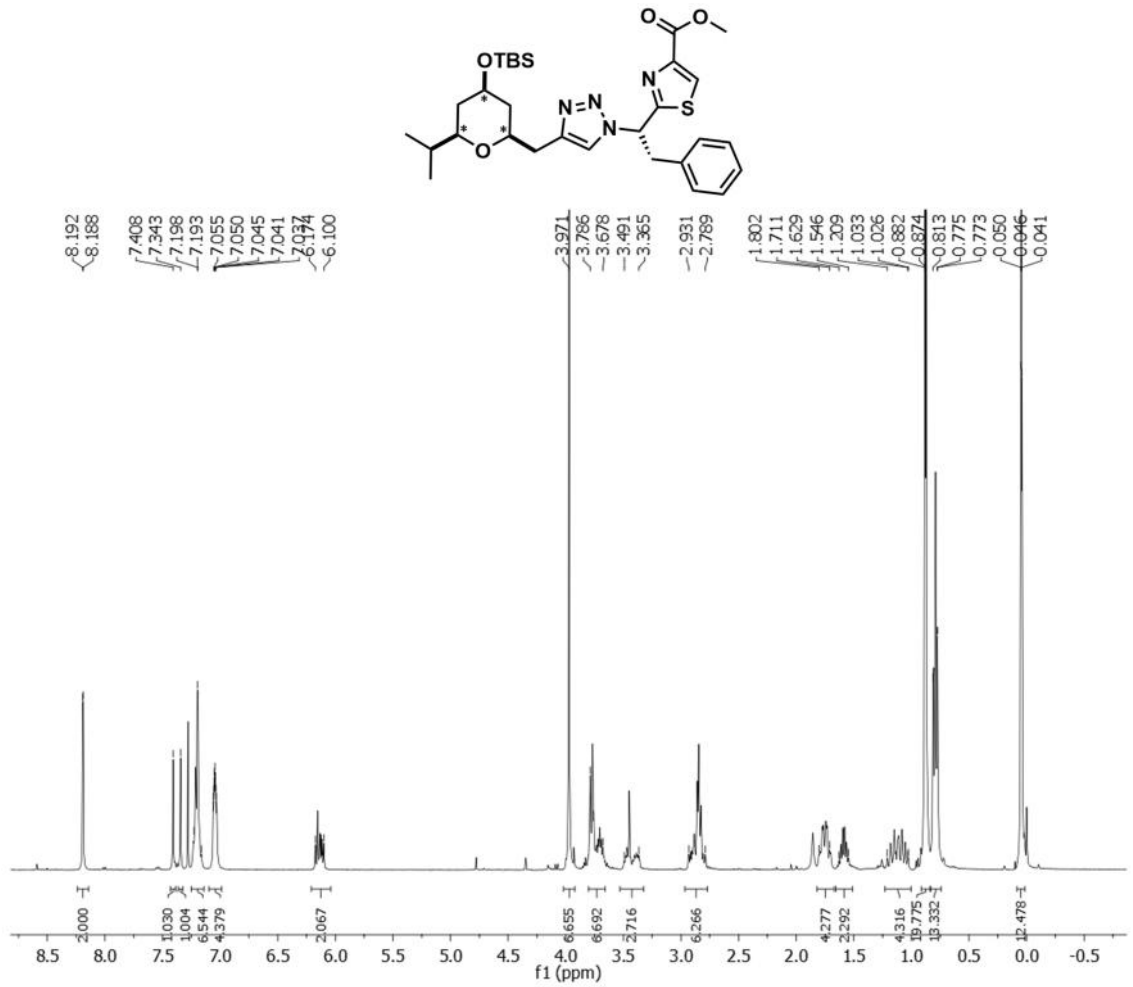
Compounds **14h**

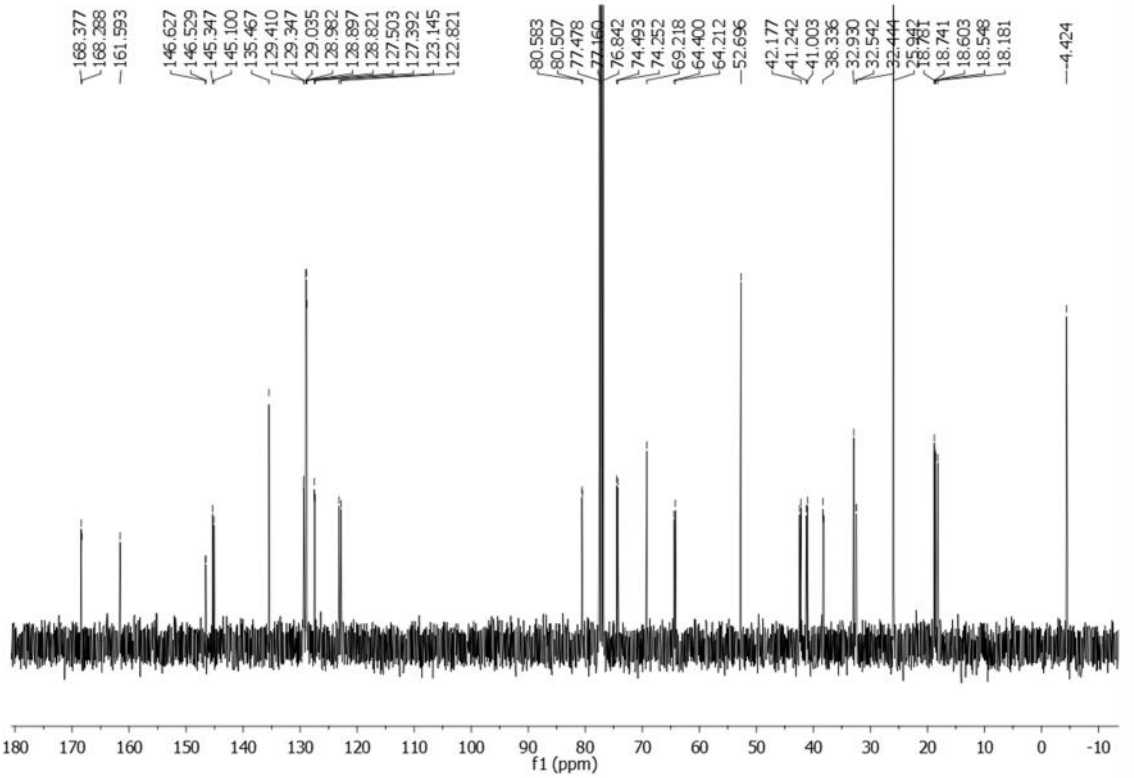




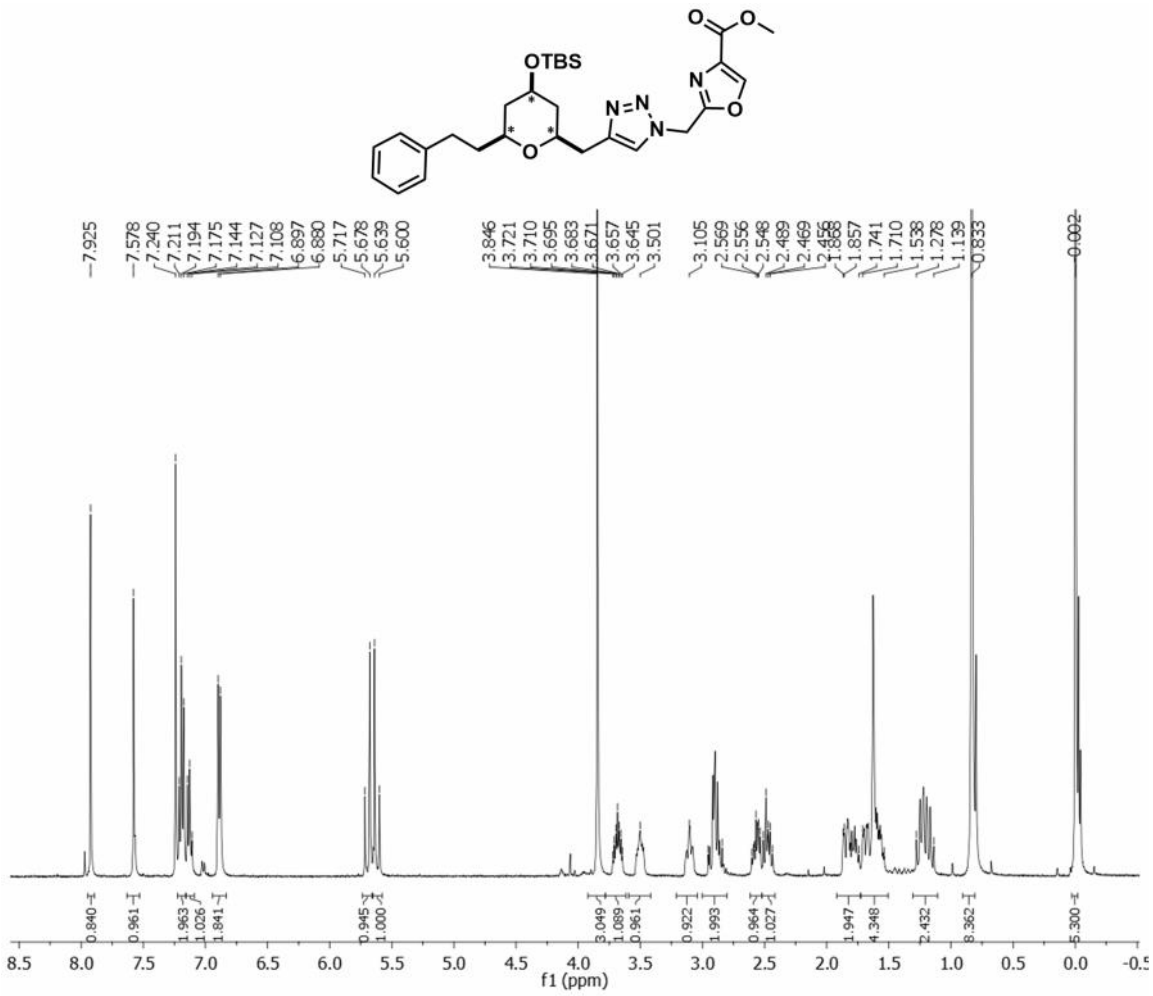


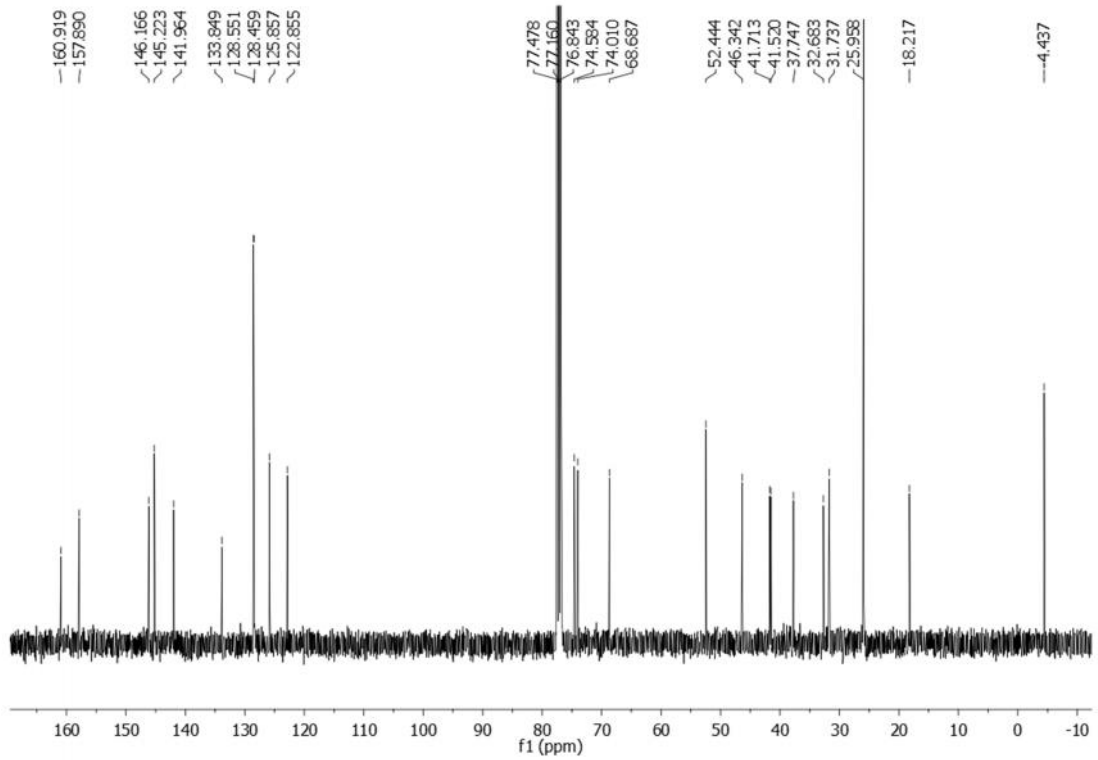
Compounds **14i**



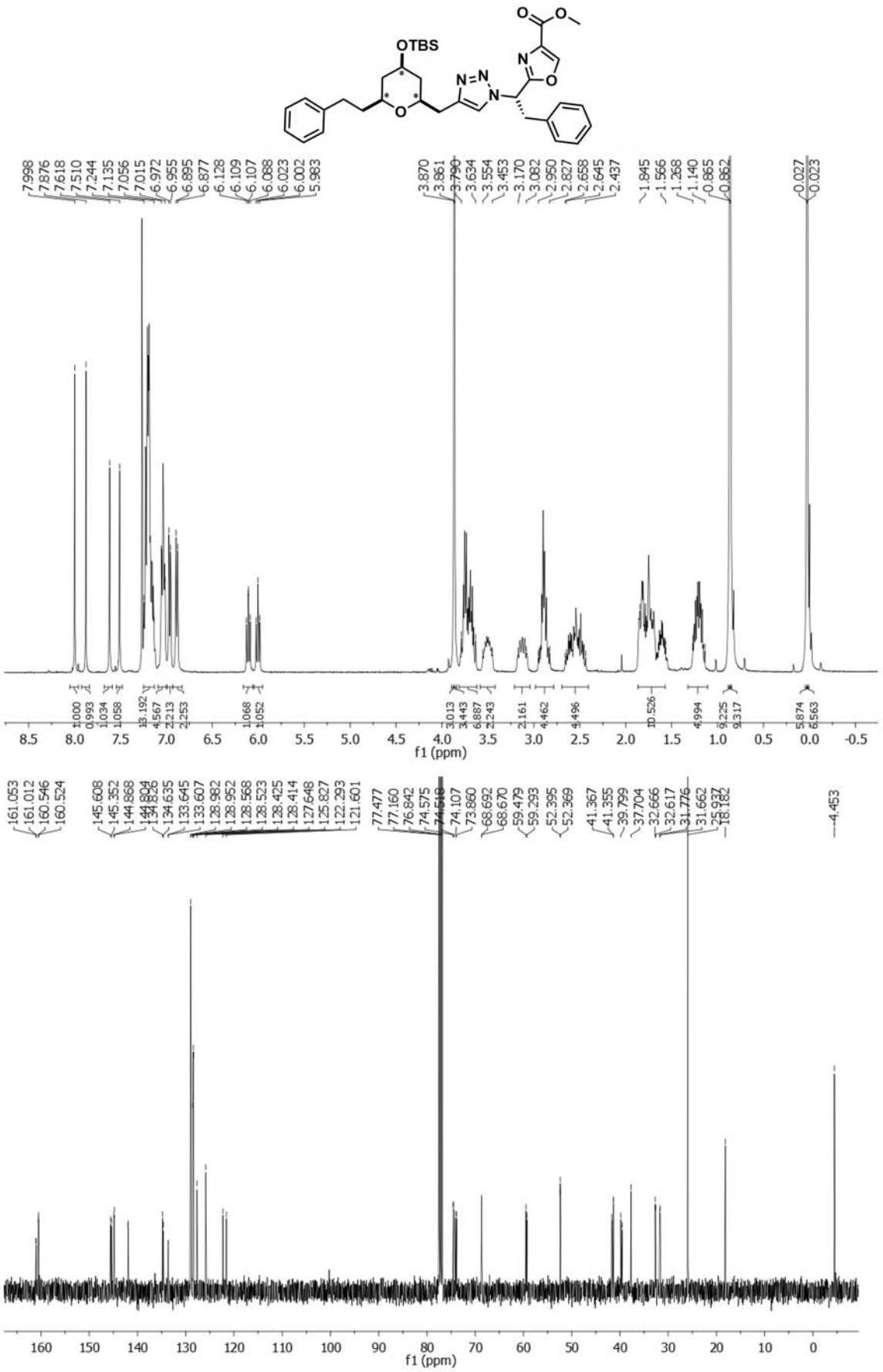


Compounds **14j**

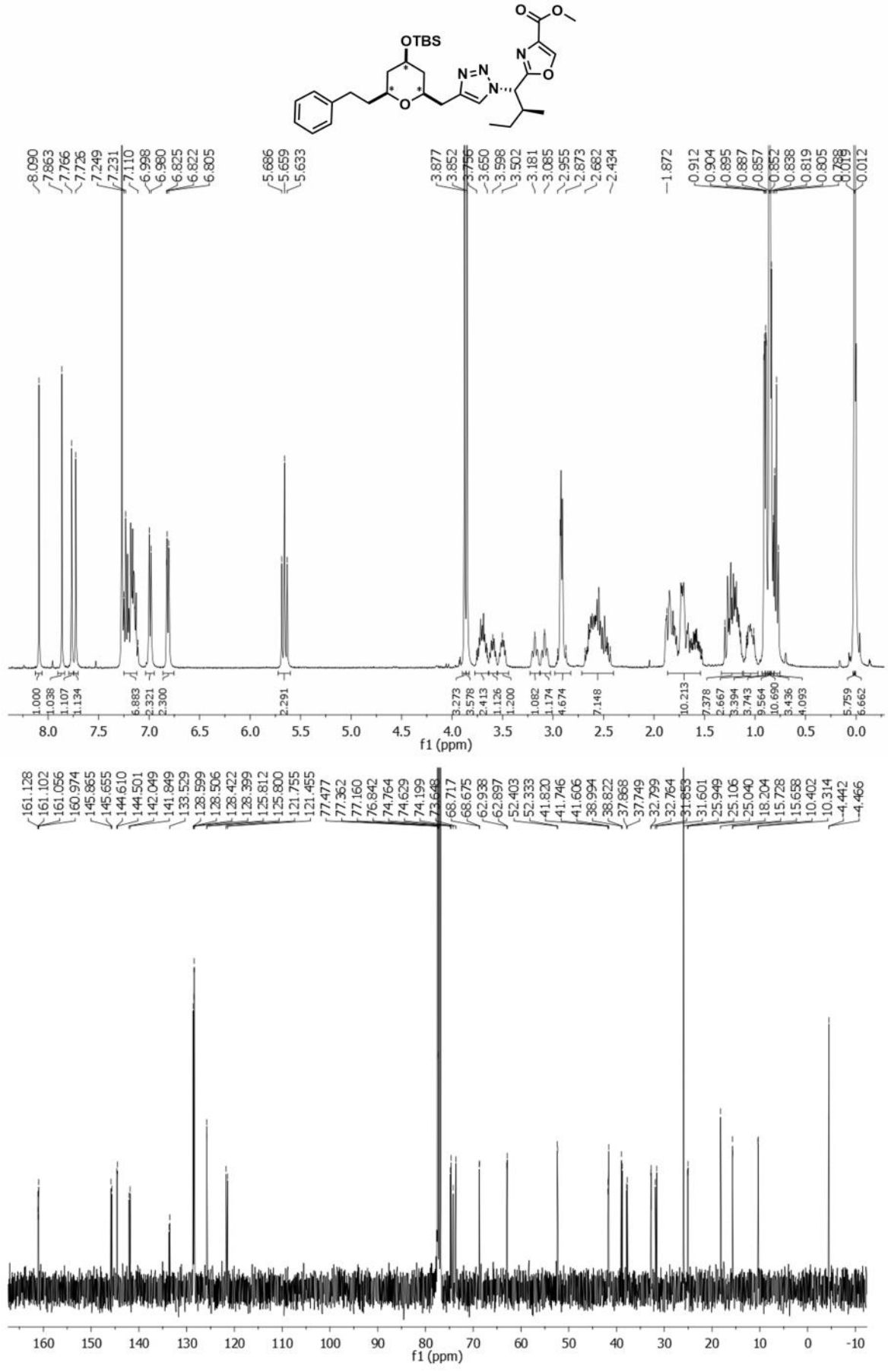




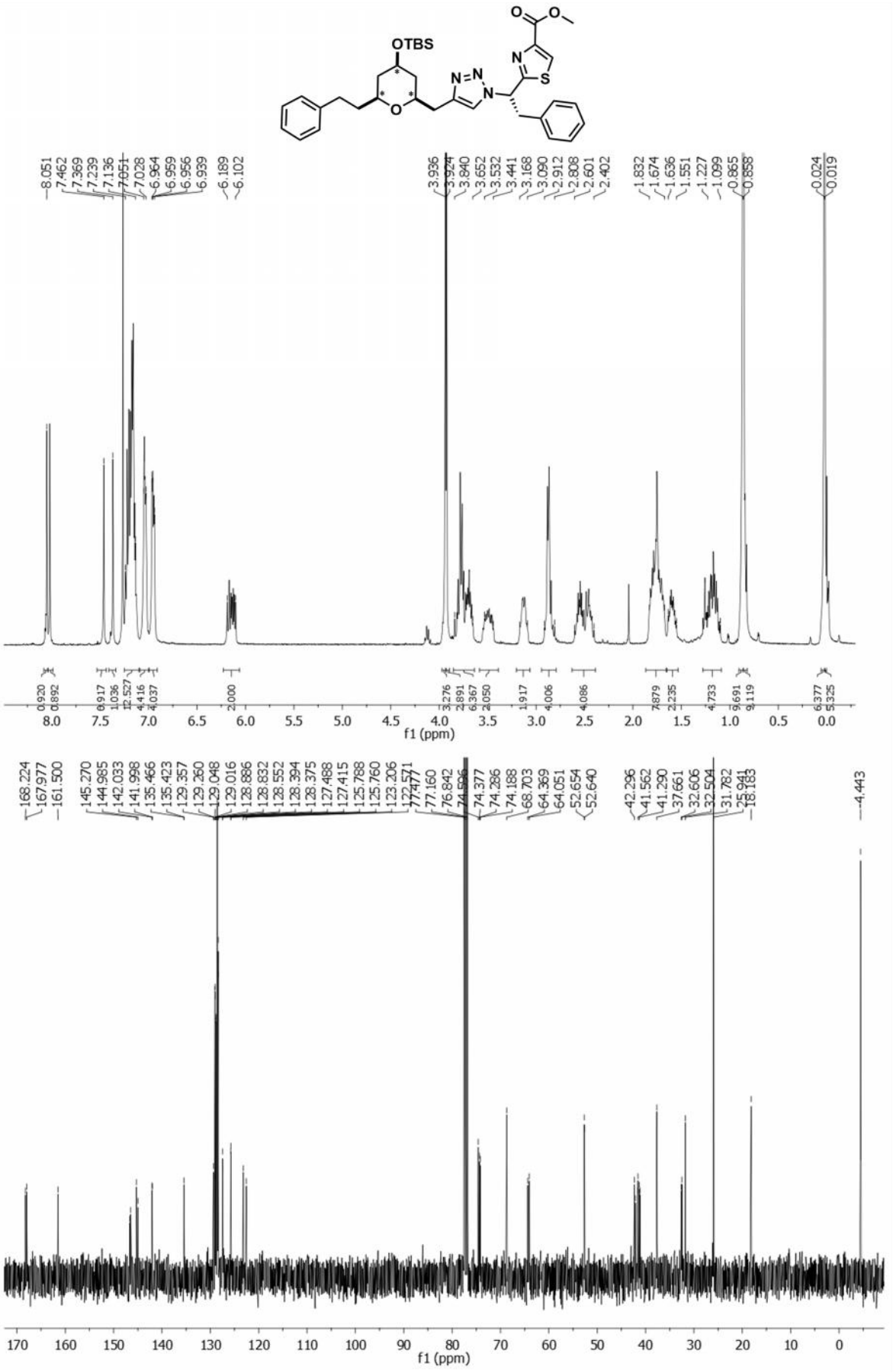
Compounds **14k**



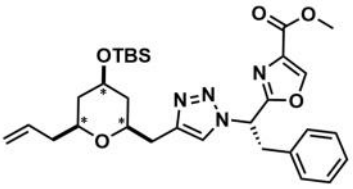
Compounds **14l**

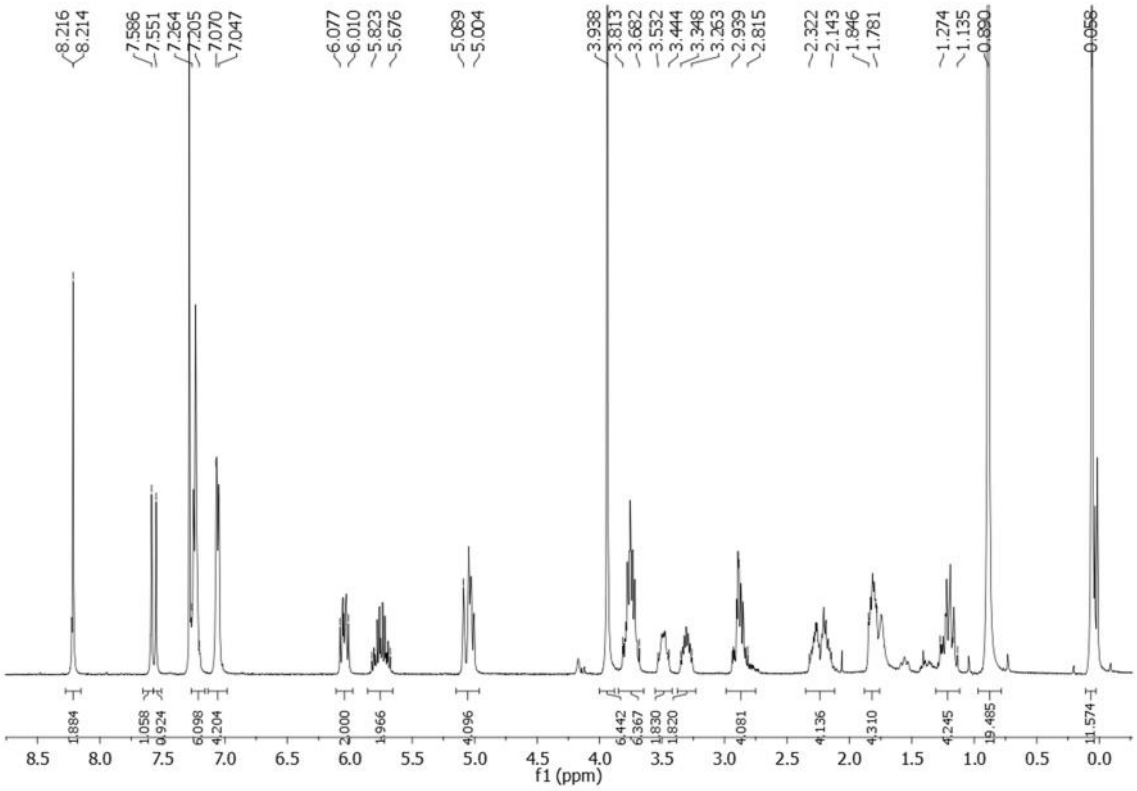


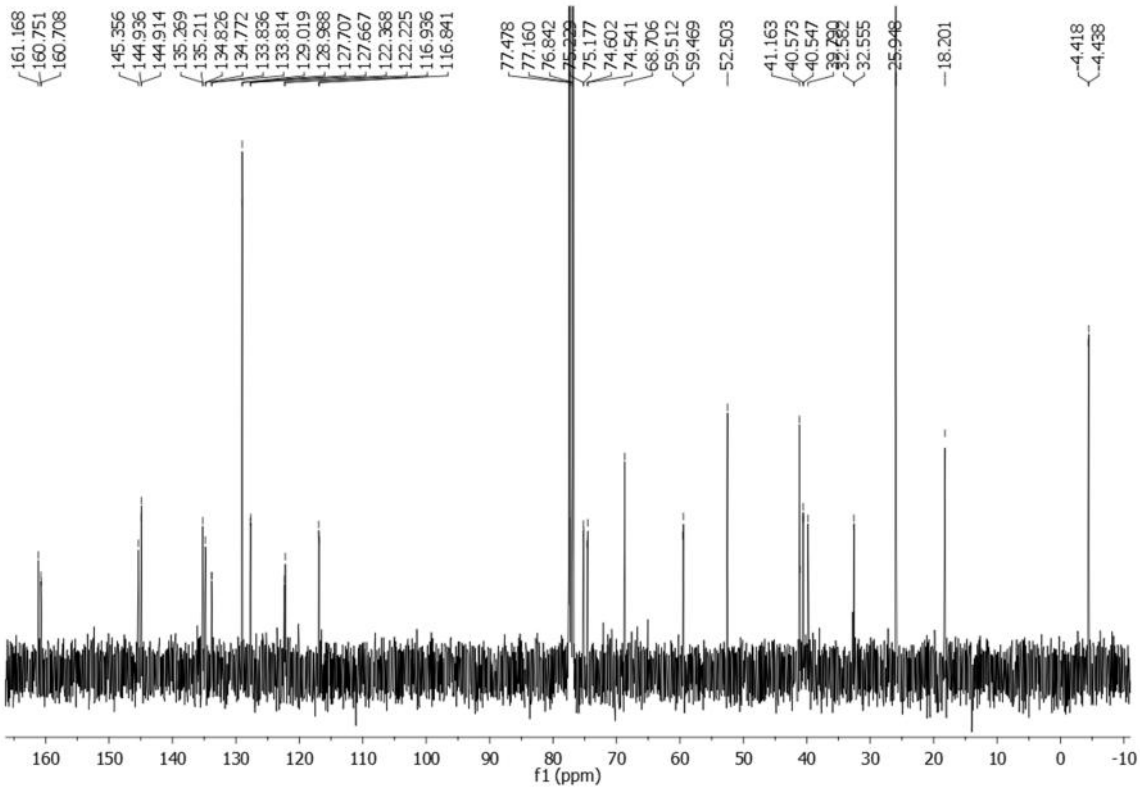
Compounds **14m**



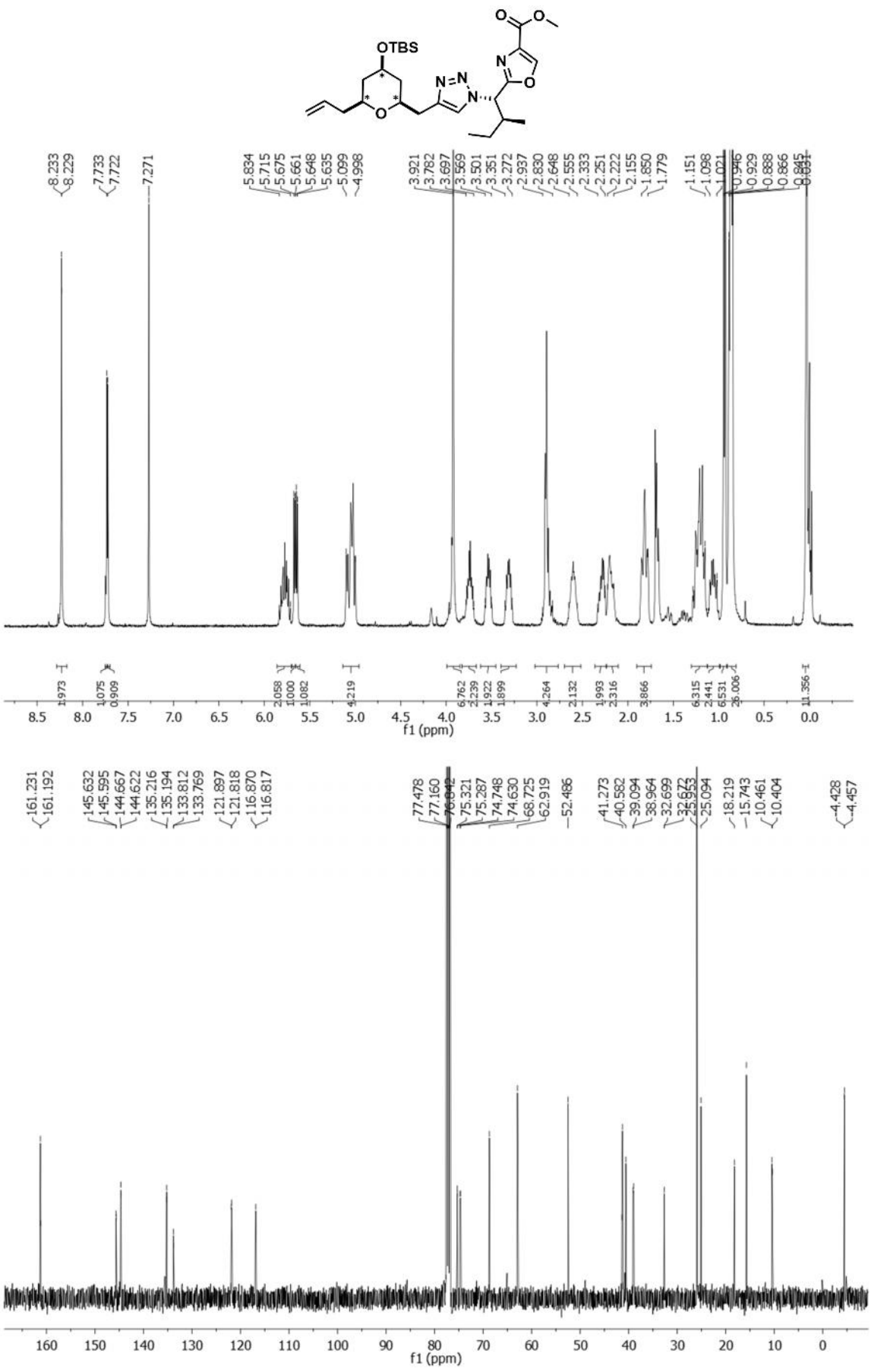
Compounds **14n**



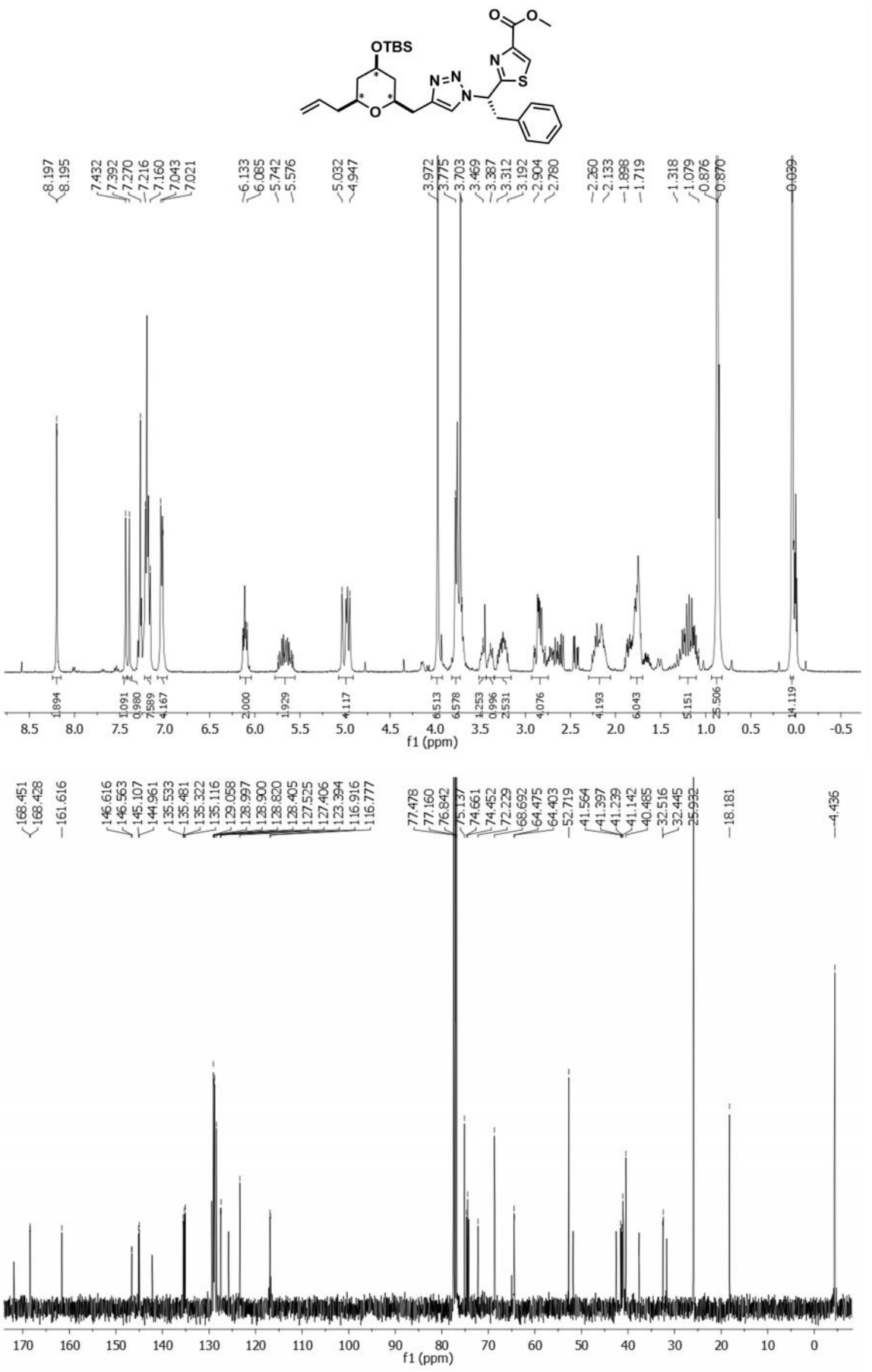




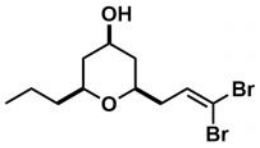
Compounds **14o**

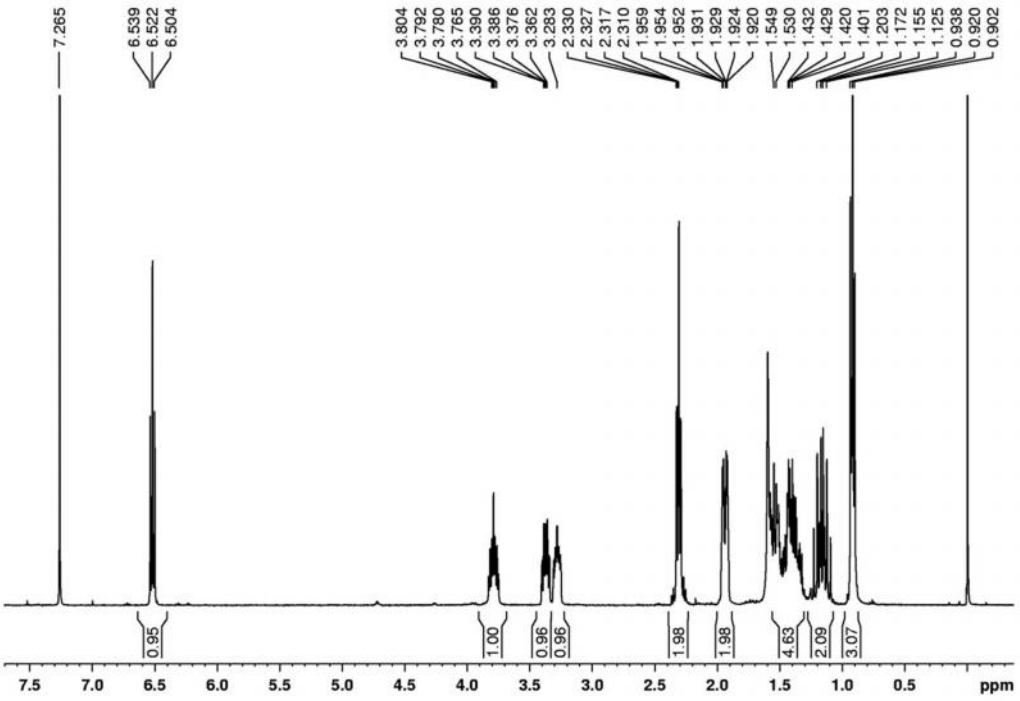


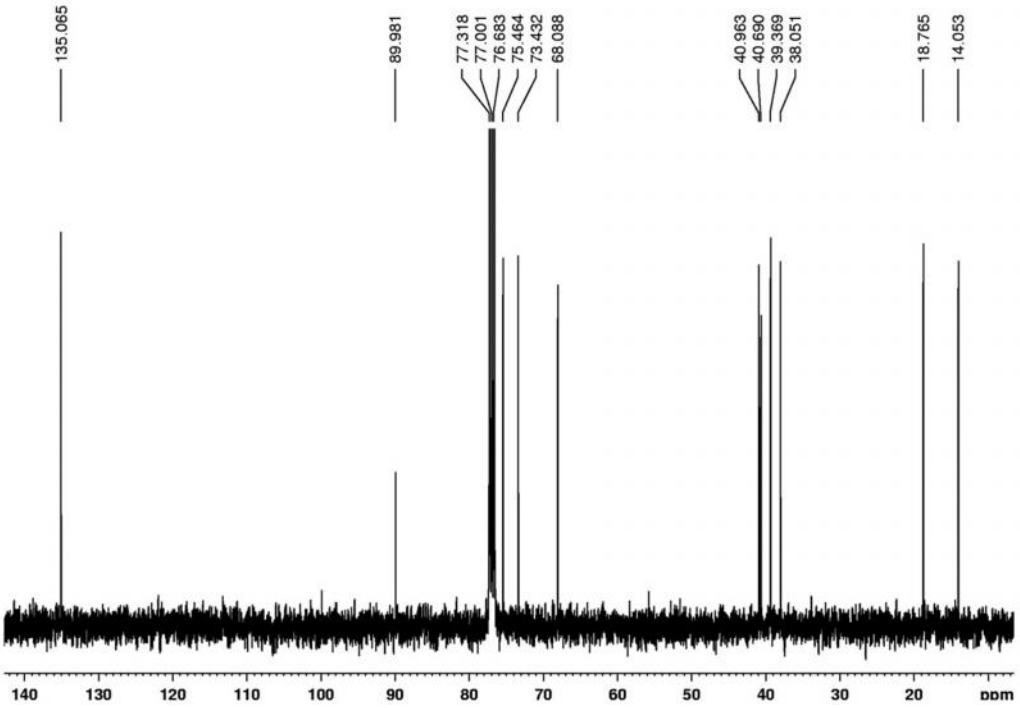
Compounds **14p**



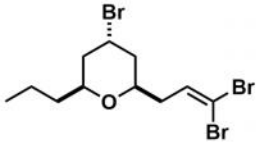
Compounds **16a**

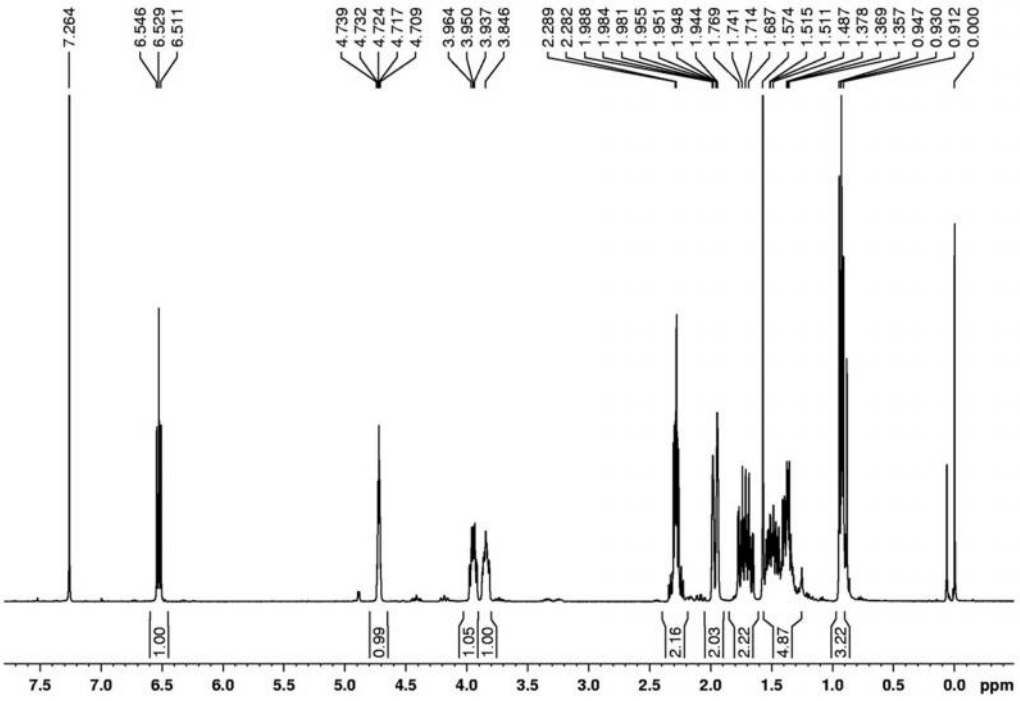


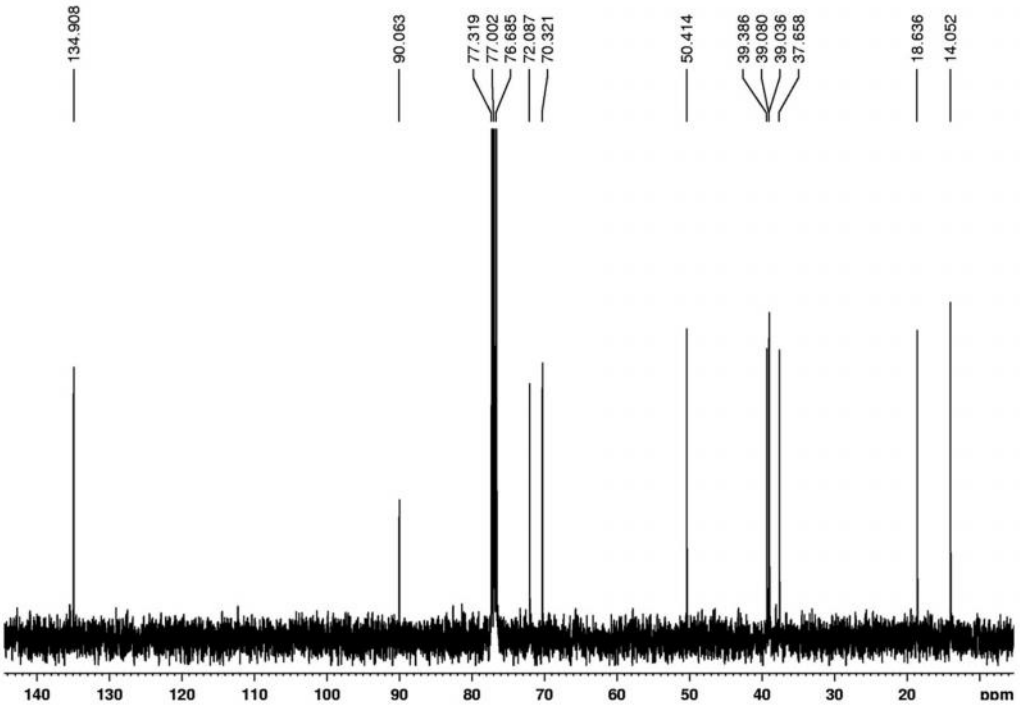




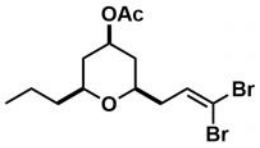
Compounds **16b**

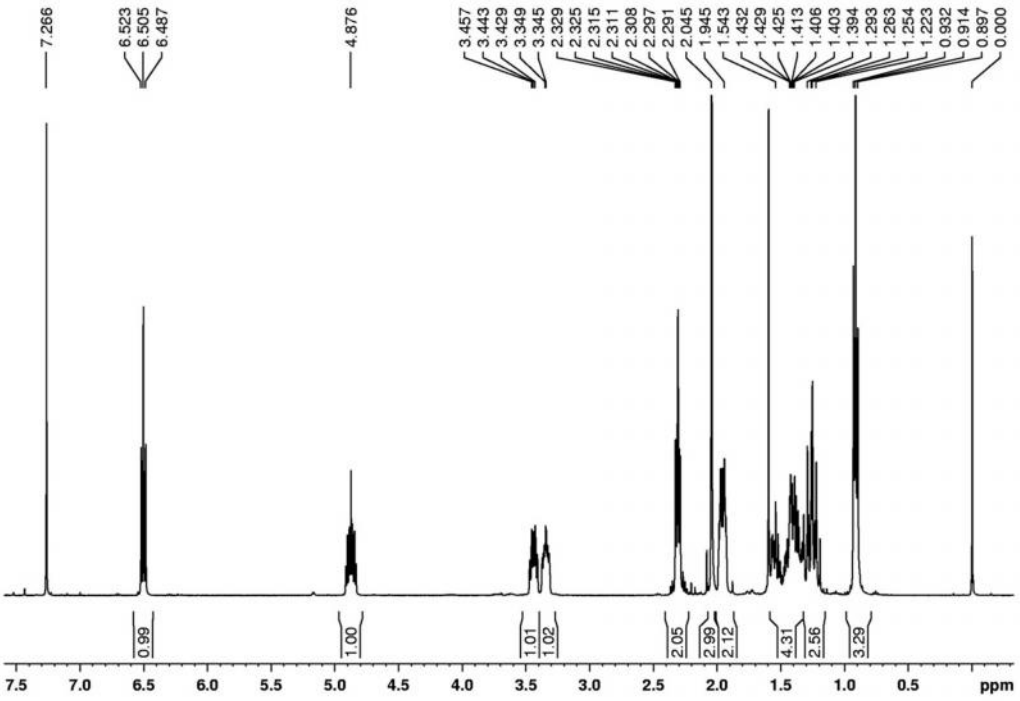


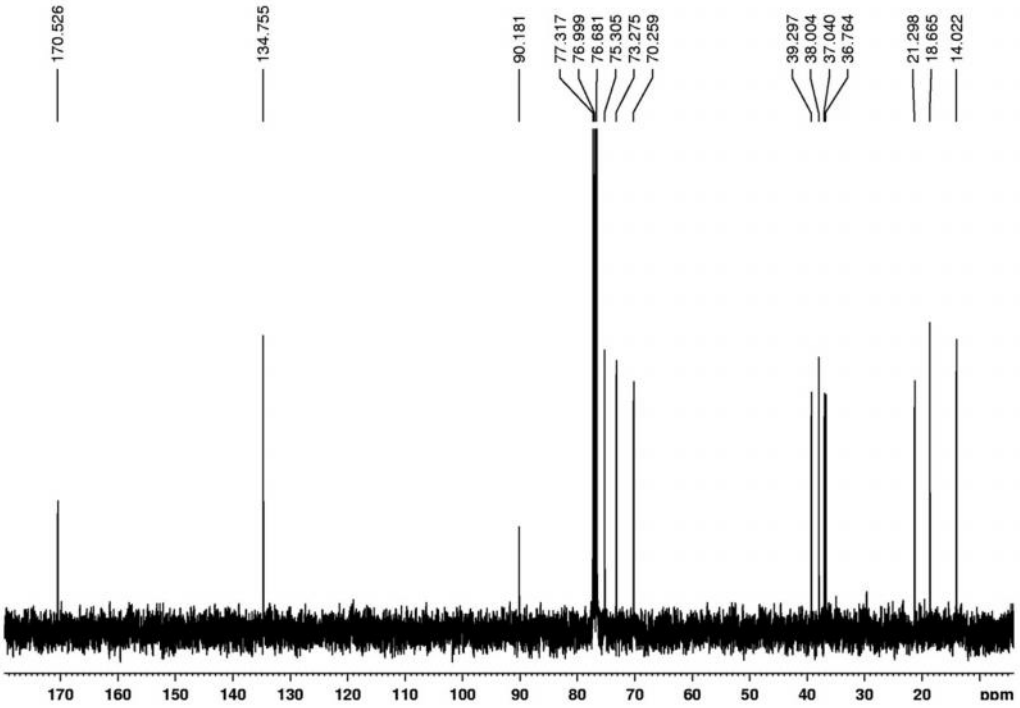




Compounds **17**







Compounds **15**