Supporting information

Total Synthesis of the Antiproliferative Macrolide (+)-Neopeltolide

*Xavier Guinchard, Emmanuel Roulland**
Centre de Recherche CNRS de Gif-sur-Yvette,
Institut de Chimie des Substances Naturelles,
Avenue de la Terrasse, 91198 Gif-sur-Yvette, France.
Fax: (+33) 1-6907-7247
E-mail: emmanuel.roulland@icsn.cnrs-gif.fr
Homepage : http://www.icsn.cnrs-gif.fr

General Experimental Procedures

^{1}H NMR-Spectra (300 or 500 MHz), **^{13}C NMR-spectra** (75 MHz) spectra were recorded on Brüker spectrometers. Chemical shifts are given in ppm (δ) and were referenced to the internal solvent signal or to TMS used as an internal standard (^{1}H and ^{13}C NMR). Multiplicities are declared as follow: *s* (singlet), *br s* (broad singlet), *d* (doublet), *t* (triplet), *q* (quadruplet), *quint* (quintuplet), *sept* (septet), *dd* (doublet of doublet), *ddd* (doublet of doublet of doublet), *dt* (doublet of triplet), *m* (multiplet). Coupling constants *J* are given in Hz.

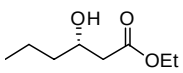
Infrared spectra (IR) were recorded on a Perkin-Elmer FT-IR system using diamond window Dura SamplIR II and the data are reported in reciprocal centimetres (ν, cm^{-1}).

Mass spectra were recorded on a Micromass LCT (ESI).

Reactions were performed using oven dried glasswares under an atmosphere of dry argon. Silica gel 60 (35-70 μm) was used for flash chromatography. Silica gel (5 μm) was used for HPLC. TLC plates (Merck 60 F_{254} aluminum sheets) were rendered visible by ultraviolet and/or spraying with phosphomolybdic acid (5%) in MeOH or vanillin (1%) + sulfuric acid (5%) in EtOH followed by heating.

Solvents: Tetrahydrofuran was distilled under Argon on sodium-benzophenone. Dichloromethane was distilled under Argon on CaH_2. Unless otherwise noted, all reagent-grade chemicals and solvents were obtained from commercial suppliers (Sigma-Aldrich, Acros Organics and Avocado) and were used as received.

Optical rotations were measured on a JASCO P-1010 polarimeter. $[\alpha]_D^{20}$ is expressed in $deg.cm^3.g^{-1}.dm^{-1}$ and *c* is expressed in g/100 cm^3.

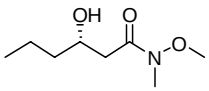


- (*S*)-ethyl 3-hydroxyhexanoate (**6**)[1]

To a stirred solution of [Ru(cod)(MeCHMeCH$_2$)$_2$] (45 mg, 0.14 mmol), (*S*)-Synphos (100 mg, 0.15 mmol) in acetone (15 mL) was added dropwise an HBr solution in MeOH (1.72 mL, 0.18 M, prepared by reaction at 0 °C of AcBr (135 µL, 1.8 mmol) with 10 mL of MeOH). The resulting mixture was stirred at room temperature for 30 min and then acetone was removed under vacuum. The activated catalyst was used directly and added to a solution of ketoester **5** (8.88 g, 56.2 mmol) in EtOH (60 mL). Argon was purged and replaced by hydrogen and the mixture was then heated at 50 °C under 4 bars of H_2 pressure during 10 h. After cooling, the solvent was removed under vacuum and the residue was purified by MPLC (EtOAc/heptane 1/3) yielding ethyl ester **6** (7.78

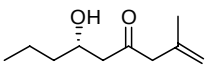
(1) Prepared according to the procedure discribed in: Duprat de Paule, S.; Jeulin, S.; Ratovelomanana-Vidal, V.; Genêt, J.-P.; Champion, N.; Dellis, P. *Eur. J. Org. Chem*. **2003**, 1931.

g, 48.65 mmol, 87%) as a colorless oil. The spectroscopical data of which correspond to those reported in the literature. $[\alpha]_D^{25}$= +8.2 (neat, $CHCl_3$), *lit.*[2] $[\alpha]_D^{20}$= +8.6 (neat, $CHCl_3$).



- (*S*)-3-hydroxy-*N*-methoxy-*N*-methylhexanamide (**7**)

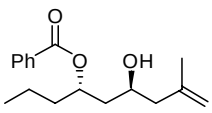
MeONHMe.HCl (7.05 g, 72 mmol) was dissolved in THF (30 mL) at -10 °C and a solution of $AlMe_3$ (2M solution, 36 mL, 72 mmol) was added via syringe over a 30 min period. The reaction mixture was stirred at room temperature for 45 min and then a THF solution (30 mL) of ester **6** (5.23 g, 32.72 mmol) was added and the resulting mixture was stirred at room temperature for 2 h. The reaction was then quenched by a careful addition of a saturated NH_4Cl aqueous solution followed by an addition of EtOAc and by an aqueous saturated solution of Rochelle salt. The resulting mixture was stirred overnight, then the phases were separated and the aqueous phase was extracted by EtOAc twice. Combined organic phases were dried over anhydrous Na_2SO_4, filtered, and evaporated. The amide **7** was obtained as a colorless oil (5.70 g, 32.60 mmol, 100%), the spectroscopical data of which corresponding to those reported in the literature.[3] $[\alpha]_D^{20}$= +55.3 (*c* 1.72, $CHCl_3$) and was used in the next step with no further purification



- (*S*)-6-hydroxy-2-methylnon-1-en-4-one (**8**)

To a solution of amide **7** (9.5 g, 54.28 mmol) in THF (400 mL) under argon at -78 °C was added a solution of methallylmagnesium bromide in Et_2O (prepared by reaction of Mg (19.50 g, 814 mmol) with 2-chloro-2-methylpropene (24.43 g, 271.4 mmol) in Et_2O (400 mL)), via cannula over a 30 min period. The resulting mixture was allowed to reach -10 °C overnight and then was quenched by addition of a saturated aqueous solution of NH_4Cl. After extraction by EtOAc, the combined organic phases were washed with brine, dried over anhydrous Na_2SO_4, filtered and evaporated. The crude was purified by MPLC (EtOAc 1/heptane 7) yielding ketone **8** (7.47 g, 43.92 mmol, 81%) of as a colorless oil. This compound being not stable it has to be used rapidly.

R*f*= 0.28 (EtOAc 1/ heptane 4). IR (neat) ν: 896, 1066, 1246, 1377, 1709, 1770, 2873, 2931, 2958, 3432 cm^{-1}.^{1}H NMR (500 MHz, $CDCl_3$): δ= 0.94 (t, *J*= 7.0 Hz, 3H), 1.34-1.55 (m, 4H), 1.77 (s, 3H), 2.55 (dd, *J*= 8.9 and 17.7 Hz, 1H), 2.64 (dd, *J*= 2.7 and 17.7 Hz, 1H), 3.13 (s, 2H), 4.00-4.10 (m, 1H), 4.84 (s, 1H), 4.97 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ= 14.0, 18.7, 22.7, 38.6, 48.2, 53.0, 67.4, 115.4, 138.8, 210.1. LRMS (ESI): m/z= 193 ($M+Na^+$). HRMS (ESI) calcd for $C_{10}H_{18}O_2Na$: 193.1204. Found: 193.1204.



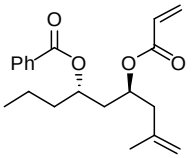
- (4*S*,6*S*)-6-hydroxy-8-methylnon-8-en-4-yl benzoate (**9**)

To a solution of alcohol **8** (1.43 g, 8.41 mmol) and benzaldehyde (3.56 g, 33.6 mmol) in THF (25 mL) at -10 °C was slowly added an SmI_2 solution (0.1 M/THF, 25 mL, 2.52 mmol). The mixture was allowed to reach room temperature over a period of 20 h and was then quenched by adding an $NaHCO_3$ aqueous

(2) Shao, L.; Kawano, H.; Saburi, M.; Uchida, Y. *Tetrahedron* **1993**, *49*, 1997.
(3) Custer, D. W.; Zabawa, T. P.; Scheidt, K. A. *J. Am. Chem. Soc.* **2008**, *130*, 804.

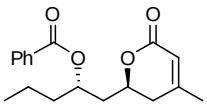
saturated solution. After extraction by EtOAc, the combined organic phases were washed by brine, dried over anhydrous $MgSO_4$, filtered and evaporated. The crude was purified by MPLC (EtOAc 1/heptane 19) yielding **9** as a colorless oil (1.95 g, 7.06 mmol, 84%.).

R*f*= 0.17 (EtOAc 1/heptane 8). IR (neat) ν: 1114, 1276, 1315, 1716, 2934, 2960, 3494 cm^{-1}.^{1}H NMR (300 MHz, $CDCl_3$): δ= 0.94 (t, *J*= 7.3 Hz, 3H), 1.32-1.54 (m, 2H), 1.58-1.90 (m, 4H), 1.70 (s, 3H), 2.13 (dd, *J*= 5.2 and 13.8 Hz, 1H), 2.64 (dd, *J*= 8.0 and 13.8 Hz, 1H), 2.96 (d, *J*= 3.2 Hz, 1H), 3.75 (ddddd, *J*= 2.5, 3.1, 5.2, 8.0 and 10.0 Hz, 1H), 4.72-4.79 (m, 1H), 4.79-4.84 (m, 1H), 5.39 (dddd, *J*= 2.9, 4.7, 7.9 and 10.2 Hz, 1H), 7.40-7.50 (m, 2H), 7.57 (tt, *J*= 1.4 and 7.3 Hz, 1H), 8.02-8.10 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ= 14.0, 18.9, 22.7, 37.4, 42.7, 45.9, 65.3, 72.4, 113.2, 128.5, 129.8, 130.3, 133.2, 142.8, 167.5. LRMS (ESI): m/z= 299 ($M+Na^+$). HRMS (ESI) calcd for $C_{17}H_{24}O_3Na$: 299.1623. Found: 299.1624. $[\alpha]_D^{20}$= +9.3 (*c* 0.92, $CHCl_3$).



- (4*S*,6*S*)-6-(acryloyloxy)-8-methylnon-8-en-4-yl benzoate (**10**)

Acryloyl chloride (4.17 g, 46.4 mmol) was added dropwise to a solution of alcohol **9** (3.20 g, 11.6 mmol) and *i*Pr_2NEt (6.45 g, 50.0 mmol) in CH_2Cl_2 (100 mL) at -10 °C under argon. The mixture was stirred for 40 min and then quenched by adding an aqueous $NaHCO_3$ saturated solution. After extraction by CH_2Cl_2 the combined organic phases were washed with brine, dried over anhydrous $MgSO_4$, filtered and evaporated. The crude was purified by MPLC (Eluent: EtOAc 1/heptane 15) to yield diene **10** as a colorless oil (3.70 g, 11.2 mmol, 97%). R*f*= 0.39 (EtOAc 1/heptane 8). IR (neat) ν: 1110, 1191, 1272, 1720, 2961 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ= 0.92 (t, *J*= 7.3 Hz, 3H), 1.30-1.48 (m, 2H), 1.52-1.80 (m, 3H), 1.74 (s, 3H), 1.86-2.08 (m, 2H), 2.26 (dd, *J*= 6.7 and 13.8 Hz, 1H), 2.41 (dd, *J*= 6.6 and 13.8 Hz, 1H), 4.72-4.79 (m, 1H), 4.79-4.84 (m, 1H), 5.16-5.30 (m, 1H), 5.71 (dd, *J*= 1.6 and 10.5 Hz, 1H), 5.99 (dd, *J*= 10.5 and 17.3 Hz, 1H), 6.30 (dd, *J*= 1.6 and 17.3 Hz, 1H), 7.41 (t, *J*= 7.2 Hz, 2H), 7.53 (tt, *J*= 1.4 and 7.3 Hz, 1H), 7.95-8.05 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ= 14.1, 18.6, 22.6, 36.9, 38.0, 43.2, 69.2, 71.3, 113.9, 128.4, 128.7, 128.7, 130.5, 130.7, 132.9, 141.4, 165.6, 166.2. LRMS (ESI): m/z= 299 ($M+Na^+$). HRMS (ESI) calcd for $C_{20}H_{26}O_4Na$: 353.1729. Found: 353.1734. $[\alpha]_D^{20}$= +38.3 (*c* 1.0, $CHCl_3$).

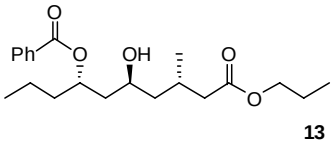


- (*S*)-1-((*S*)-4-methyl-6-oxo-3,6-dihydro-2H-pyran-2-yl)pentan-2-yl benzoate (**11**)

To a solution of olefin **10** (1.0 g, 3.03 mmol) in freshly distilled CH_2Cl_2 (25 mL) under argon was added 2nd generation Grubbs's catalyst (103 mg, 0.0121 mmol, 4 mol%) dissolved in CH_2Cl_2 (3 mL). The resulting mixture was refluxed for 48 h and then cooled. Silica gel was added and CH_2Cl_2 was evaporated under vacuum and the crude was purified by column chromatography (EtOAc 1/ heptane 3), yielding lactone **11** (789 mg, 2.61 mmol, 86%) as a colorless oil. R*f*= 0.20 (EtOAc 1/ heptane 2).

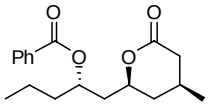
^{1}H NMR (300 MHz, $CDCl_3$): δ= 0.95 (t, *J*= 7.3 Hz, 3H), 1.32-1.52 (m, 2H), 1.60-1.84 (m, 2H), 1.94 (s, 3H), 2.02 (ddd, *J*= 4.0, 8.4 and 14.7 Hz, 1H), 2.11 (ddd, *J*= 3.9, 8.4 and 14.7 Hz, 1H), 2.20 (dd, *J*= 4.1 and 17.8 Hz, 1H), 2.37 (dd, *J*= 11.9 and 17.8 Hz, 1H), 4.51 (tdd, *J*= 4.1, 8.4 and 11.6 Hz, 1H), 5.39 (dddd, *J*= 4.0, 5.3, 7.2 and 8.5, 1H), 5.78 (t, *J*= 1.5 Hz, 1H), 7.40-7.49 (m, 2H), 7.56 (tt, *J*= 1.4 and 7.3 Hz, 1H), 8.00-8.07 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ= 14.0, 18.5, 23.0, 35.1, 37.1, 40.1, 71.5, 74.3, 116.7, 128.5, 139.6, 130.4, 133.0,

156.8, 164.7, 166.1. LRMS (ESI): m/z= 325 ($M+Na^+$). HRMS (ESI) calcd for $C_{18}H_{22}O_4Na$: 325.1416. Found: 325.1420. $[\alpha]_D^{20}= -10.1$ (*c* 0.42, $CHCl_3$).



13

- (4*S*,6*S*,8*S*)-6-hydroxy-8-methyl-10-oxo-10-propoxydecan-4-yl benzoate (**13**) and (S)-1-((2S,4S)-4-methyl-6-oxotetrahydro-2H-pyran-2- yl)pentan-2-yl benzoate (**12**)

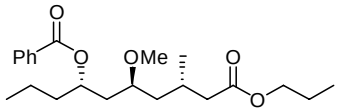


12

To a solution of lactone **11** (4.70 g, 15.56 mmol) in *n*PrOH (100 mL) was added Pd/C (940 mg) and H_2 was bubbled through the solution during 5 min. The mixture was stirred at room temperature for 4 h and was filtered on celite. To the resulting solution was added PPTS (10 mg). After 16 h stirring at room temperature a $NaHCO_3$ saturated aqueous solution and Et_2O were added. The phases were separated and the aqueous phase was extracted twice by Et_2O, the combined organic phases were dried over anhydrous $MgSO_4$, filtered and evaporated. The crude mixture was purified by MPLC (EtOAc 1/ heptane 2) to yield ester **13** (3.364 g, 9.24 mmol, 59%) and the saturated lactone **12** (1.542 g, 5.07 mmol, 33%). Lactone **12** (1.542 g, 5.07 mmol) can be recycled into the desired ester **13** by stirring in *n*-PrOH (30 mL) with PPTS (10 mg) at room temperature for 16 h, yielding alcohol **13** (1.11 g, 3.05 mmol, 60%) and starting saturated lactone **12** (400 mg, 1.31 mmol, 26%).

*Data for alcohol **13*:** R*f*= 0.31 (EtOAc 1/ heptane 2). IR (neat) *ν*: 1113, 1275, 1456, 1716, 2959, 3498 cm^{-1}. ^1H NMR (300 MHz, CD_3COCD_3): *δ*= 0.90 (t, *J*= 7.4 Hz, 3H), 0.90 (d, *J*= 6.4 Hz, 3H), 0.93 (t, *J*= 7.4 Hz, 3H), 1.27 (ddd, *J*= 3.4, 8.6, 13.8 Hz, 1 H), 1.34-1.55 (m, 3H), 1.60 (q, *J*= 7.3 Hz, 2H), 1.64-1.88 (m, 4H), 2.10 (dd, *J*= 7.7 and 13.8 Hz, 1H), 2.32 (dd, *J*= 5.3 and 13.8 Hz, 1H), 3.68 (d, *J*= 5.7 Hz, 1H), 3.68-3.83 (m, 1H), 3.97 (t, *J*= 6.7 Hz, 2H), 5.38 (dddd, *J*= 3.0, 5.3, 6.9 and 9.7, 1H), 5.78 (t, *J*= 1.5 Hz, 1H), 7.50 (t, *J*= 7.3 Hz, 2H), 7.63 (tt, *J*= 1.4 and 7.4 Hz, 1H), 8.00-8.08 (m, 2H). ^{13}C NMR (75 MHz, CD_3COCD_3): *δ*= 10.8, 14.3, 19.3, 19.8, 22.8, 27.9, 38.0, 42.8, 44.1, 45.6, 65.8, 66.0, 73.0, 129.4, 130.2, 131.7, 133.8, 167.0, 173.1. LRMS (ESI): m/z= 387 ($M+Na^+$). HRMS (ESI) calcd for $C_{21}H_{32}O_5Na$: 387.2147. Found: 387.2135. $[\alpha]_D^{20}= -0.351$ (*c* 1.29, $CHCl_3$).

*Data for lactone **12***: R*f*= 0.21 (EtOAc 1/ heptane 2). IR (neat) *ν*: 2957, 2872, 1712, 1450, 1270, 1228, 710 cm^{-1}. ^1H NMR (300 MHz, $CHCl_3$): *δ*= 0.94 (t, *J*= 7.4 Hz, 3H), 1.00 (d, *J*= 6.1 Hz, 3H), 1.15-1.36 (m, 1H), 1.33-1.49 (m, 2H), 1.58-1.83 (m, 2H), 1.85-2.10 (m, 5H), 2.65 (dq, *J*= 1.9 and 11.9 Hz, 1H), 4.00 (dddd, *J*= 2.9, 5.1, 7.2 and 12.0 Hz, 1H), 5.41 (tt, *J*= 5.3 and 7.1 Hz, 1H), , 7.44 (t, *J*= 7.2 Hz, 2H), 7.58 (tt, *J*= 1.4 and 7.4 Hz, 1H), 8.00-8.08 (m, 2H). ^{13}C NMR (75 MHz, CD_3COCD_3): *δ*= 14.0, 18.4, 21.7, 26.6, 37.0, 37.4, 37.9, 41.2, 71.4, 77.3, 128.4, 129.6, 130.4, 132.9, 166.0, 170.9. LRMS (ESI): m/z= 327 ($M+Na^+$). HRMS (ESI) calcd for $C_{18}H_{24}O_4Na$: 329.1572. Found: 327.1576. $[\alpha]_D^{20}= -0.351$ (*c* 1.29, $CHCl_3$).



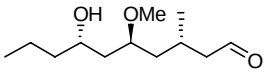
- (4*S*,6*S*,8*S*)-6-methoxy-8-methyl-10-oxo-10-propoxydecan-4-yl benzoate (**14**)

To a solution of alcohol **13** (4.07 g, 11.2 mmol) and proton sponge (24.0 g, 112 mmol) in CH_2Cl_2 (150 mL) at room temperature, was added $Me_3O.BF_4$ (8.28 g, 56 mmol). The resulting mixture was stirred for 3 h then transferred to a separating funnel and twice washed by an aqueous saturated solution of $CuSO_4$ and then washed

three times by a saturated aqueous solution of citric acid. The organic phases were dried over anhydrous $MgSO_4$, filtered, evaporated and purified by MPLC (EtOAc 1/ heptane 7) to yield product **14** (3.942 g, 10.46 mmol, 93%) as a colorless oil.

R*f*= 0.19 (EtOAc 1/ heptane 5). IR (neat): 1070, 1096, 1110, 1173, 1270, 1714, 2875, 2932, 2960 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ= 0.92 (t, *J*= 7.3 Hz, 3H), 0.95 (t, *J*= 7.3 Hz, 3H), 0.96 (d, *J*= 5.7 Hz, 3H), 1.23-1.49 (m, 3H), 1.54-1.76 (m, 5H), 1.76-1.85 (m, 2H), 2.02-2.18 (m, 2H), 2.21-2.35 (m, 1H), 3.26-3.38 (m, 1H), 3.30 (s, 3H), 4.00 (t, *J*= 6.7 Hz, 2H), 5.35 (tt, *J*= 5.0 and 7.5, 1H), 7.44 (t, *J*= 7.4 Hz, 2H), 7.55 (tt, *J*= 1.3 and 7.4 Hz, 1H), 8.00-8.08 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ= 10.5, 14.1, 18.6, 20.2, 22.1, 27.4, 37.4, 39.9, 41.6, 42.1, 57.0, 65.9, 72.3, 76.1, 128.5, 129.7, 130.8, 132.9, 166.3, 173.0. LRMS (ESI): m/z= 401 ($M+Na^+$). HRMS (ESI) calcd for $C_{22}H_{34}O_5Na$: 401.2304. Found: 401.2315. $[\alpha]_D^{20}$= +9.04 (*c* 0.89, $CHCl_3$).

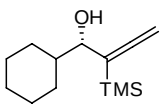
- (3*S*,5*S*,7*S*)-7-hydroxy-5-methoxy-3-methyldecanal (**15**)



To a solution of ester **14** (800 mg, 2.12 mmol) in toluene (10 mL) at -78 °C under argon was slowly added (1.5 mL/h) a DIBALH solution (1.5 M/toluene, 4.24 mL, 6.36 mmol). The resulting solution was stirred for further 2 h and then quenched by addition of MeOH (1 mL) and warmed to room temperature. EtOAc and a saturated aqueous solution of potassium and sodium tartrate (Rochelle salt) were added and the mixture was stirred for 30 min. The phases were separated and the aqueous phase was extracted twice by EtOAc. Combined organic phases were dried over anhydrous $MgSO_4$, filtered and evaporated. The crude mixture was purified by MPLC (EtOAc 1/ heptane 2) yielding aldehyde **15** (440 mg, 2.0 mmol, 94%) as a colorless oil.

R*f*= 0.16 (EtOAc 1/heptane 2). IR (neat): 1087, 1125, 1379, 1461, 1721, 2873, 2931, 2955, 3436 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ= 0.93 (t, *J*= 7.0 Hz, 3H), 1.00 (d, *J*= 6.4 Hz, 3H), 1.23-1.41 (m, 3H), 1.41-1.57 (m, 3H), 1.67-1.79 (m, 2H), 2.20-2.37 (m, 2H), 2.40-2.51 (m, 1H), 3.38 (s, 3H), 3.57 (dddd, *J*= 3.8, 4.4, 5.9 and 8.5 Hz, 1H), 5.35 (dddd, *J*= 2.3, 4.5, 7.1 and 9.6 Hz, 1H), 9.76 (t, *J*= 2.1 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ= 14.2, 18.9, 20.4, 25.3, 39.7, 40.2, 41.1, 51.4, 56.8, 68.5, 77.6, 202.6. LRMS (ESI): m/z= 239 ($M+Na^+$). HRMS (ESI) calcd for $C_{12}H_{24}O_3Na$: 239.1623. Found: 239.1621. $[\alpha]_D^{20}$= +1.66 (*c* 1.11, $CHCl_3$).

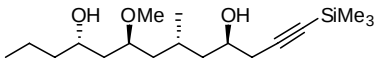
- (*S*)-1-cyclohexyl-2-(trimethylsilyl)buta-2,3-dien-1-ol[4] (**16**)



To a solution of 1-trimethylsilylpropyne (3.0 g, 26.78 mmol) in THF (35 mL) at 0 °C was added dropwise a solution of *t*-BuLi (1.5 N/hexane, 17.85 mL, 26.78 mmol), and the mixture was stirred for 1 h. Then, (+)-*B*-methoxy-diisopinocampheylborane (8.074 g, 25.55 mmol) in Et_2O (30 mL) was added and the reaction mixture was stirred for 10 min before adding $BF_3.OEt_2$ (4.087 g, 26.78 mmol). The resulting reaction mixture was cooled to -100 °C and a solution of cyclohexanecarboxaldehyde (2.86 g, 25.55 mmol) in Et_2O (30 mL) was added dropwise over 90 min. The mixture was stirred for further 3 h and then slowly allowed to warm to room

(4) Prepared according to the method of Brown: Brown, H. C.; Khire, U. R.; Narla G. *J. Org. Chem.* **1995**, *60*, 8130.

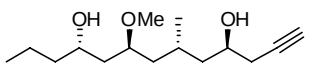
temperature (over 1 h). The reaction was quenched by an addition of NaOH (3 N / H_2O, 14.8 mL, 44.4 mmol) and H_2O_2 (30% / H_2O, 9.9 mL, 87.3 mmol), the mixture was refluxed for 1 h and was then cooled to room temperature. After extraction, the organic phase was washed by H_2O, brine, dried over anhydrous $MgSO_4$, filtered and concentrated under vacuum. The resulting crude was purified by MPLC (EtOAc 1/ heptane 15) affording allene **16** as a colorless oil (3.14 g, 14.0 mmol, 55%) which spectroscopical data are identical to those reported in the literature. $[\alpha]_D^{20}$= +23.4 (*c* 0.96, $CHCl_3$) *lit.*[4] $[\alpha]_D^{20}$= –20.4 (*c* 1.76, $CHCl_3$) for the enantiomer with *ee*= 96%).



- (4*R*,6*R*,8*S*,10*S*)-8-methoxy-6-methyl-1-(trimethylsilyl)tridec-1-yne-4,10-diol (**2**)

To a solution of aldehyde **15** (300 mg, 1.39 mmol) and allene **16** (933 mg, 4.16 mmol) in CH_2Cl_2 (40 mL) was added $InBr_3$ (5 mg, 13.9 µmol) at 20 °C. The resulting mixture was stirred at room temperature for 20 h and then the solvent was evaporated before purification by MPLC (EtOAc 2/ heptane 3) yielding alkyne **2** as a colorless oil (352 mg, 1.07 mmol, 77%).

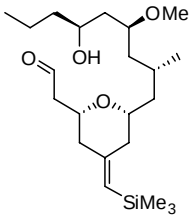
R*f*= 0.18 (EtOAc 1/ heptane 2). IR (neat) ν: 843, 1089, 1249, 2361, 2931, 3376 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ= 0.16 (s, 9H), 0.92 (t, *J*= 7.0 Hz, 3H), 0.96 (d, *J*= 6.7 Hz, 3H), 1.21-1.31 (m, 3H), 1.31-1.59 (m, 7H), 1.65-1.77 (m, 2H), 1.77-1.89 (m, 1H), 2.35 (dd, *J*= 6.7 and 16.8 Hz, 1H), 2.43 (dd, *J*= 5.2 and 16.8 Hz, 1H), 3.37 (s, 3H), 3.57 (dddd, *J*= 3.3, 5.4, 6.1 and 7.4 Hz, 1H), 3.79-3.86 (m, 1H), 3.86-3.93 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ= 0.2, 14.3, 19.0, 20.1, 26.5, 29.8, 39.7, 40.2, 41.6, 43.8, 56.9, 67.9, 68.7, 77.8, 87.8, 103.4. LRMS (ESI): m/z= 351 ($M+Na^+$). HRMS (ESI) calcd for $C_{18}H_{36}O_3NaSi$: 351.2331. Found: 351.2340. $[\alpha]_D^{20}$= +17.46 (*c* 0.29, $CHCl_3$).



- (4*R*,6*R*,8*S*,10*S*)-8-methoxy-6-methyltridec-1-yne-4,10-diol (**18**)

To a solution of alkyne **2** (344 mg, 1.05 mmol) in MeOH (5 mL) was added K_2CO_3 (723 mg, 5.24 mmol) and the resulting mixture was stirred at room temperature for 2 h. After addition of water and extraction by EtOAc, the combined organic phases were dried over anhydrous $MgSO_4$, filtered and evaporated. The crude was purified by MPLC (EtOAc 1/ heptane 1) yielding alkyne **18** as a colorless oil (252 mg, 0.98 mmol, 94%).

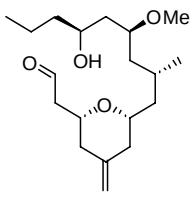
R*f*= 0.22 (EtOAc 1/ heptane 1). IR (neat) ν: 1026, 1086, 1135, 1378, 1461, 2872, 2928, 2954, 3310 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ= 0.93 (t, *J*= 7.7 Hz, 3H), 0.96 (d, *J*= 6.6 Hz, 3H), 1.15-1.90 (m, 12H), 2.06 (t, *J*= 2.6 Hz, 1H), 2.32 (ddd, *J*= 2.6, 6.3 and 16.6 Hz, 1H), 2.41 (dd, *J*= 2.6, 5.3 and 16.6 Hz, 1H), 2.59 (s, 1H), 3.37 (s, 3H), 3.52-3.63 (m, 1H), 3.79-3.96 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ= 14.3, 18.9, 20.1, 26.4, 28.3, 39.7, 40.2, 41.6, 43.7, 56.9, 67.8, 68.7, 70.9, 77.7, 81.1. LRMS (ESI): m/z= 279 ($M+Na^+$). HRMS (ESI) calcd for $C_{15}H_{28}O_3Na$: 279.1936. Found: 279.1942. $[\alpha]_D^{20}$= +28.54 (*c* 0.55, $CHCl_3$).



- 2-((2*R*,6*R*,*E*)-6-((2*S*,4*S*,6*S*)-6-hydroxy-4-methoxy-2-methylnonyl)-4-((trimethylsilyl)methylene)tetrahydro-2H-pyran-2-yl)acetaldehyde (**17**)

To a solution of 3-butenol (500 mg, 6.94 mmol) in CH_2Cl_2 (3.5 mL) and pentane (30 mL) was added $PhI(OAc)_2$ (2.46 g, 7.63 mmol) and TEMPO (108 mg, 0.694 mmol). The resulting mixture was stirred at room temperature for 16 h. After cooling down to 0 °C, a saturated $NaHCO_3$ aqueous solution was added until gas evolution has ceased. Organic phase was separated and dried over anhydrous $MgSO_4$ and then 3-butenal was distilled out using a Vigreux column leading to a 3-butenal CH_2Cl_2/pentane solution (conc. estimated by ^{1}H NMR).

To an acetone solution (1 mL) of alkyne **2** (20 mg, 61.0 µmol) and 3-butenal (500 µL of the above CH_2Cl_2/pentane solution, large excess) was added $CpRu[(MeCN)_3].PF_6$ (5.3 mg, 12.2 µmol, 20 mol%) and AcOH (0.37 mg, 6.1 µmol, 100 µL of 3.7 mg/mL solution in acetone). The resulting mixture was stirred at room temperature for 60 h and then concentrated under vacuum. The crude wad filtered through a pad of silica and purified on preparative HPLC (EtOAc 2/ heptane 3) yielding aldehyde **17** (14 mg, 35 µmol, 58%) as colorless oil. R*f*= 0.34 (EtOAc 1/ heptane 1). IR (neat) ν: 1085, 1247, 1325, 1368, 1622, 1726, 2953, 3447 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ= 0.10 (s, 9H), 0.89-0.97 (m, 6H), 1.13-1.31 (m, 2H), 1.32-1.43 (m, 2H), 1.43-1.55 (m, 2H), 1.55-1.81 (m, 4H), 1.88 (t, *J*= 12.2 Hz, 1H), 2.05-2.24 (m, 2H), 2.38 (dt, *J*= 1.7 and 11.6 Hz, 1H), 2.47 (ddd, *J* = 1.8, 4.3 and 16.1 Hz, 1H), 2.61 (ddd, *J* = 2.7, 8.3 and 16.1 Hz, 1H), 3.00 (br s, 1H), 3.28-3.41 (m, 1H), 3.36 (s, 3H), 3.56 (dtd, *J* = 3.6, 5.8 and 7.3 Hz, 1H), 3.79-3.94 (m, 2H), 5.26 (s, 1H), 9.79 (dd, *J* = 2.0 and 2.6 Hz, 1H).^{13}C NMR (125 MHz, $CDCl_3$): δ= 0.4, 14.3, 19.0, 20.2, 26.3, 39.5, 40.2, 40.7, 41.4, 43.8, 45.3, 49.8, 56.9, 68.7, 73.9, 76.4, 77.9, 124.0, 152.7, 201.3. LRMS (ESI): m/z= 397 (M-H$^+$). HRMS (ESI) calcd for $C_{22}H_{41}O_4Si$: 397.2774. Found: 397.2783. $[\alpha]_D^{20}$= +13.3 (*c* 0.5, $CHCl_3$).

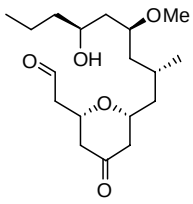


- 2-((2*R*,6*R*)-6-((2*S*,4*S*,6*S*)-6-hydroxy-4-methoxy-2-methylnonyl)-4-methylenetetrahydro-2H-pyran-2-yl)acetaldehyde (**19**)

To a solution of alkyne **18** (25 mg, 97 µmol) and olefin (19.2 mg, 0.146 mmol) in acetone (200 µL, freshly distilled from BaO) was added $Cp^*Ru[(MeCN)_3].PF_6$ (4.9 mg, 9.7 µmol, 10 mol%) and AcOH (0.47 mg, 100 µL of 4.7 mg/mL solution in acetone). The resulting mixture was stirred at room temperature for 6 h before adding a MeCN solution of $LiBF_4$ (1M, 1 mL) and H_2O (20 μL). After 90 min, silica was added and the solvents were evaporated before purification by MPLC (EtOAc 1/ heptane 3) yielding aldehyde **19** (17 mg, 52 µmol, 54%) as a colorless oil.

R*f*= 0.38 (EtOAc 1/ heptane 1). IR (neat) ν: 1085, 1247, 1325, 1376, 1461, 1725, 2930, 3429 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ= 0.91 (d, *J*= 6.7 Hz, 3H), 0.93 (t, *J*= 7.0 Hz, 3H), 1.12-1.28 (m, 3H), 1.30-1.40 (m, 2H), 1.42-1.55 (m, 3H), 1.59 (ddd, *J* = 4.3, 9.0 and 15.9 Hz, 1H), 1.62-1.74 (m, 2H), 1.74-1.84 (m, 1H), 1.93 (t, *J*= 12.2 Hz, 1H), 2.01 (t, *J*= 12.2 Hz, 1H), 2.17 (d, *J*= 13.4 Hz, 1H), 2.25 (d, *J*= 13.1Hz, 1H), 2.45-2.53 (m, 1H), 2.63 (ddd, *J* = 2.6, 8.4 and 16.1 Hz,1H), 3.36 (s, 3H), 3.36-3.42 (m, 1H), 3.51-3.59 (m, 1H), 3.76-3.84 (m, 1H),

3.84-3.92 (m, 1H), 4.76 (s, 2H), 9.79 (t, J = 2.4 Hz, 1H).^{13}C NMR (125 MHz, $CDCl_3$): δ= 14.3, 19.0, 20.2, 26.2, 39.6, 40.2, 40.6, 41.2, 41.4, 43.6, 49.8, 58.8, 68.7, 73.7, 76.6, 77.9, 109.4, 143.9, 201.2. LRMS (ESI): m/z= 349 ($M+Na^+$). HRMS (ESI) calcd for $C_{19}H_{34}O_4Na$: 349.2355. Found: 349.2342. $[\alpha]_D^{20}$= +35.37 (*c* 0.15, $CHCl_3$).

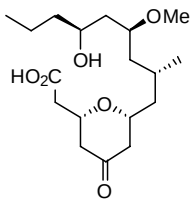


- 2-((2*S*,6*R*)-6-((2*S*,4*S*,6*S*)-6-hydroxy-4-methoxy-2-methylnonyl)-4-oxotetrahydro-2H-pyran-2-yl)acetaldehyde (**20**)

*From olefin **17***: To a solution of olefin **17** (11 mg, 0.0277 mmol) and pyridine (6.5 mg, 81.8 µmol), in *t*-BuOH (300 µL) was added aqueous solutions of $NaIO_4$ (0.5 M/H_2O, 163 µL, 81.8 µmol) and OsO_4 (0.02 M /H_2O, 82 µL, 1.635 µmol). The resulting mixture was stirred at room temperature for 16 h. More $NaIO_4$ was added (0.5 M solution in water, 163 µL, 81.8 µmol) and the mixture was stirred for further 4 h. After addition of brine and extraction by EtOAc, the combined organic phases were dried over anhydrous $MgSO_4$, filtered and evaporated. The crude was purified by MPLC (EtOAc 100%) yielding ketone **20** as colorless oil (9.0 mg, 0.0274 mmol, 100%).

*From olefin **19***: To a solution of olefin **19** (9 mg, 0.0276 mmol) and pyridine (6.5 mg, 81.8 µmol) in *t*-BuOH (300 µL), was added an aqueous solutions of $NaIO_4$ (0.5 M / H_2O, 163 µL, 81.8 µmol) and OsO_4 (0.02 M / H_2O, 82 µL, 1.635 µmol). The reaction mixture was stirred at room temperature for 16 h. Additional $NaIO_4$ was added (0.5 M /H_2O, 163 µL, 81.8 µmol) and the mixture was stirred for further 4 h. Brine was then added and the mixture was extracted twice by EtOAc. Combined organic phases were dried over anhydrous $MgSO_4$, filtered and evaporated. The crude was purified by MPLC (EtOAc 100%) yielding ketone **20** as colorless oil (8.5 mg, 0.026 mmol, 96%).

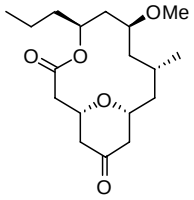
R*f*= 0.35 (EtOAc). IR (neat) ν: 1024, 1086, 1249, 1328, 1375, 1457, 1719, 2871, 2928, 2954, 3448 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ= 0.90-0.98 (m, 6H), 1.20-1.30 (m, 3H), 1.30-1.40 (m, 2H), 1.42-1.55 (m, 3H), 1.62-1.76 (m, 2H), 1.78-1.90 (m, 1H), 2.25 (dd, *J*= 11.7 and 24.6 Hz, 1H), 2.28 (dd, *J*= 11.7 and 24.6 Hz, 1H), 2.37 (d, *J*= 14.5 Hz, 1H), 2.44 (d, *J*= 14.5 Hz, 1H), 2.58 (dd, *J*= 3.8 and 16.4 Hz, 1H), 2.78 (ddd, *J*= 2.2, 8.2 and 26.4 Hz, 1H), 2.88 (br s, 1H), 3.37 (s, 3H), 3.52-3.63 (m, 1H), 3.68-3.78 (m, 1H), 3.85-3.92 (m, 1H), 4.11-4.19 (m, 1H), 9.80 (s, 1H).^{13}C NMR (125 MHz, $CDCl_3$): δ= 14.3, 19.0, 20.0, 26.3, 39.6, 40.2, 41.4, 43.9, 47.3, 48.3, 49.6, 57.0, 68.7, 72.0, 75.2, 77.8, 199.5, 205.9. LRMS (ESI): m/z= 351 ($M+Na^+$). HRMS (ESI) calcd for $C_{18}H_{32}O_5Na$: 351.2147. Found: 351.2155. $[\alpha]_D^{20}$= +17.9 (*c* 0.65, $CHCl_3$).



- 2-((2*R*,6*R*)-6-((2*S*,4*S*,6*S*)-6-hydroxy-4-methoxy-2-methylnonyl)-4-oxotetrahydro-2H-pyran-2-yl)acetic acid (**21**)

To a solution of aldehyde **20** (12 mg, 0.0366 mmol) in *t*-BuOH (1 mL) was added 2-methyl-2-butene (2 M solution in THF, 1.03 mL, 2.06 mmol), $NaClO_2$ (19.8 mg, 0.220 mmol), KH_2PO_4 (14.9 mg, 0.110 mmol) and H_2O (0.5 mL). The resulting mixture was stirred at room temperature for 15 min. EtOAc was then added and the mixture was transferred to a separating funnel. The organic phase was washed by H_2O, dried over anhydrous $MgSO_4$, filtered and evaporated. The crude was purified by MPLC (EtOAc 100%) yielding acid **21** as colorless oil (11 mg, 0.032 mmol, 87%).

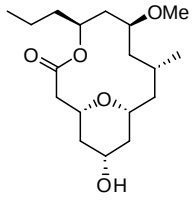
R*f*= 0.14 (EtOAc). IR (neat) ν: 1079, 1124, 1253, 1714, 2872, 2955, 3404 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ= 0.90-0.98 (m, 6H), 1.11-1.19 (m, 1H), 1.22-1.55 (m, 7H), 1.64 (ddd, *J*= 6.6, 8.7 and 14.4 Hz, 1H), 1.74-1.87 (m, 2H), 1.95 (ddd, *J*= 4.8, 8.5 and 14.3 Hz, 1H), 2.20-2.30 (m, 2H), 2.34 (d, *J*= 14.2 Hz, 1H), 2.45 (d, *J*= 14.2 Hz, 1H), 2.50-2.64 (m, 2H), 3.37 (s, 3H), 3.52-3.60 (m, 1H), 3.70 (t, *J*= 11.0 Hz, 1H), 3.97-4.04 (m, 1H), 4.04-4.11 (m, 1H), 5.66 (br s, 1H).^{13}C NMR (125 MHz, $CDCl_3$): δ= 14.3, 18.8, 20.7, 28.0, 38.8, 40.1, 40.7, 41.4, 44.2, 47.1, 48.5, 56.9, 69.0, 73.7, 76.8, 78.2, 173.1, 206.3. LRMS (ESI): m/z= 367 ($M+Na^+$). HRMS (ESI) calcd for $C_{18}H_{32}O_6Na$: 367.2097. Found: 367.2098. $[\alpha]_D^{20}$= +10.9 (*c* 1.3, $CHCl_3$, *lit*. $[\alpha]_D^{25}$= +6.09 (*c* 0.61)).



- (1*R*,5*S*,7*S*,9*S*,11*R*)-7-methoxy-9-methyl-5-propyl-4,15-dioxabicyclo[9.3.1]pentadecane-3,13-dione (**22**)

To a solution of acid **21** (26 mg, 0.0756 mmol) and Et_3N (105 µL, 755 µmol) in THF (3 mL) was added 2,4,6-trichlorobenzoyl chloride (24 mg, 98.3 µmol). The resulting mixture was stirred at room temperature for 1h and was then diluted in toluene (9 mL). The resulting solution was added dropwise (2 mL/h) to a diluted (0.017 M) solution of DMAP (190 mg, 1.56 mmol) in toluene (90 mL) at 80 °C. Once the addition was complete, the mixture was stirred for further 16 h at 80 °C before being filtrated on a pad of silica and concentrated under vacuum. The resulting crude was purified by MPLC (EtOAc 1/ heptane 3) yielding lactone **22** as a colorless oil (21 mg, 0.0644 mmol, 85%) the data of which correspond to those reported in the literature.[3]

R*f*= 0.24 (EtOAc 1/ heptane 3). IR (neat) *ν*: 1090, 1246, 1273, 1724, 2871, 2925, 2956 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ= 0.92 (t, *J*= 7.3 Hz, 3H), 1.00 (t, *J*= 7.0 Hz, 3H), 1.20 (ddd, *J*= 2.4, 10.3 and 13.3 Hz, 1H), 1.32-1.41 (m, 3H), 1.42 (dd, *J*= 9.2 and 15.0 Hz, 1H), 1.45-1.56 (m, 2H), 1.56-1.74 (m, 4H), 2.24 (dd, *J*= 11.6 and 14.6 Hz, 1H), 2.28-2.36 (m, 2H), 2.43 (d, *J*= 14.6 Hz, 1H), 2.51 (dd, *J*= 10.7 and 14.6 Hz, 1H), 2.71 (dd, *J*= 4.0 and 14.6 Hz, 1H), 3.33 (s, 3H), 3.50 (dt, *J*= 3.1 and 9.8 Hz, 1H), 3.58 (t, *J*= 9.8 Hz, 1H), 4.04 (tt, *J*= 3.1 and 10.4 Hz, 1H), 5.17-5.26 (m, 1H).^{13}C NMR (125 MHz, $CDCl_3$): δ= 14.1, 19.1, 25.6, 31.2, 37.2, 40.2, 42.1, 42.7, 44.5, 47.2, 49.0, 56.5, 73.5, 73.6, 75.9, 79.9, 170.1, 206.0. LRMS (ESI): m/z= 349 ($M+Na^+$). HRMS (ESI) calcd for $C_{18}H_{30}O_5Na$: 349.1991. Found: 349.1994. $[\alpha]_D^{20}$= +18.0 (*c* 0.4, $CHCl_3$), *lit*.[3] $[\alpha]_D^{25}$= +16.0 (*c* 0.16, $CHCl_3$).



- (1*R*,5*S*,7*S*,9*S*,11*R*,13*S*)-13-hydroxy-7-methoxy-9-methyl-5-propyl-4,15-dioxabicyclo[9.3.1]pentadecan-3-one (**23**)

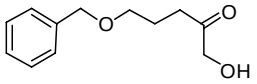
To a solution of ketone **22** (10 mg, 30.67 µmol) in EtOH (0.5 mL) at -10 °C was added $NaBH_4$ (2.3 mg, 61.35 µmol). The resulting mixture was stirred for 20 min. AcOH was then added (15 µL, 0.25 mmol) and the mixture was concentrated under vacuum. The resulting crude was by MPLC (EtOAc 1/ heptane 1) yielding alcool **23** as colorless oil (9.2 mg, 28.05 µmol, 91%) the data of which corresponding to those reported in the literature,[3,5] and **5-*epi*-23** (0.8 mg, 2.44 µmol, 8%).

*Data for **23***: R*f*= 0.20 (EtOAc 1/ heptane 1). IR (neat) *ν*: 991, 1089, 1137, 1273, 1371, 1456, 1729, 2870, 2920, 2421 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ= 0.91 (t, *J*= 7.3 Hz, 3H), 0.99 (t, *J*= 6.9 Hz, 3H), 1.10-1.23 (m, 3H),

(5) Woo, S. K.; Kwon, M. S.; Lee, E. *Angew. Chem.* **2008**, *120*, 3286; *Angew. Chem. Int. Ed.* **2008**, *47*, 3242.

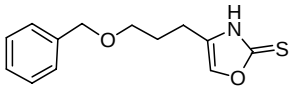
1.23-1.31 (m, 1H), 1.30-1.40 (m, 3H), 1.40-1.52 (m, 3H), 1.55-1.65 (m, 2H), 1.65-1.75 (m, 1H), 1.80-1.90 (m, 2H), 1.94-2.10 (m, 1H), 2.42 (dd, *J*= 10.7 and 14.5 Hz, 1H), 2.62 (dd, *J*= 4.1 and 14.5 Hz, 1H), 3.17 (t, *J*= 10.4 Hz, 1H), 3.31 (s, 3H), 3.58 (t, *J*= 9.8 Hz, 1H), 3.69-3.78 (m, 1H), 3.76-3.85 (m, 1H), 5.15 (ddd, *J*= 4.7, 8.8 and 10.3 Hz, 1H).[13]C NMR (125 MHz, $CDCl_3$): δ= 14.0, 19.1, 25.7, 31.4, 37.1, 40.2, 40.9, 42.1, 42.4, 44.2, 56.4, 68.2, 72.5, 73.4, 75.7, 78.8, 171.0. LRMS (ESI): m/z= 351 ($M+Na^+$). HRMS (ESI) calcd for $C_{18}H_{32}O_5Na$: 351.2147. Found: 351.2144. $[\alpha]_D^{25}$= +22.4 (*c* 0.1, $CHCl_3$) *lit*.[5] $[\alpha]_D^{29}$= +22.2 (*c* 1, $CHCl_3$).

Data for **5-*epi* 23:** R*f*= 0.24 (EtOAc 1/ heptane 1). IR (neat) ν: 985, 1030, 1079, 1276, 1730, 2918, 3450 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ= 0.84 (t, *J*= 7.3 Hz, 3H), 0.91 (t, *J*= 6.4 Hz, 3H), 1.02-1.17 (m, 2H), 1.23-1.36 (m, 5H), 1.36-1.50 (m, 5H), 1.50-1.60 (m, 3H), 1.79 (dd, *J*= 10.8 and 14.9 Hz, 1H), 2.28 (dd, *J*= 10.9 and 14.6 Hz, 1H), 2.52 (dd, *J*= 4.4 and 14.6 Hz, 1H), 3.24 (s, 3H), 3.53 (ddd, *J* = 2.2, 8.7 and 11.3 Hz, 1H), 3.61 (dd, *J*= 4.1 and 9.5 Hz, 1H), 4.12 (ddt, *J*= 2.3, 4.1 and 11.3 Hz, 1H), 4.18 (t, *J*= 2.7 Hz, 1H), 5.07-5.18 (m, 1H).[13]C NMR (125 MHz, $CDCl_3$): δ= 14.1, 19.1, 25.8, 29.9, 31.6, 37.2, 38.5, 39.6,40.3, 42.5, 42.6, 44.4, 56.4, 65.2, 69.3, 73.0, 75.0, 75.8, 171.2. LRMS (ESI): m/z= 351 ($M+Na^+$). HRMS (ESI) calcd for $C_{18}H_{32}O_5Na$: 351.2147. Found: 351.2147. $[\alpha]_D^{25}$= +24.5 (*c* 0.1, $CHCl_3$).



- 5-(benzyloxy)-1-hydroxypentan-2-one (**24**)

To a solution of 1-benzyloxy-4-pentene[6] (1 g, 4.81 mmol) in acetone (38 mL), H_2O (8.7 mL) and AcOH (1.8 mL) was added dropwise a solution of $KMnO_4$ (1.24 g, 7.25 mmol) in acetone (15 mL) and H_2O (4.8 mL). The resulting mixture was stirred at room temperature until total disappearance of the starting material by TLC (*ca* 2 h 30 min). EtOH was added (2 mL) and the mixture was filtered on celite and concentrated under vacuum. The aqueous phase was extracted by EtOAc three times. Combined organic phases were dried over Na_2SO_4, filtered and evaporated under vacuum. The resulting crude was purified by MPLC (Et_2O 100%) yielding hydroxyketone **24** as a colorless oil (527 mg, 2.205 mmol, 46%) the data of which corresponding to those reported in the literature.[7]



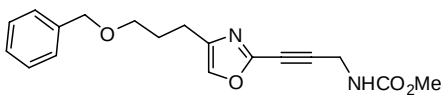
- 4-(3-(benzyloxy)propyl)oxazole-2(3H)-thione (**3**)

To a solution of ketone **24** (208 mg, 1 mmol) in EtOH (2 mL) was added KSCN (146 mg, 1.5 mmol) and a concentrated aqueous HCl solution (11.2 M, 123 µL, 1.4 mmol). The resulting mixture was refluxed for 16 h and then cooled. EtOAc and H_2O were added and the phases were separated. The organic phase was washed by brine, dried over anhydrous $MgSO_4$, filtered and evaporated. The crude was purified by MPLC (EtOAc 1/ heptane 1) yielding thione **3** as a viscous oil (230 mg, 0.92 mmol, 92%).

R*f*= 0.53 (Et_2O). IR (neat) ν: 738, 931, 1073, 1099, 1251, 1453, 1469, 1649, 2920, 3063, 3155 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ= 1.88 (tt, *J*= 5.7 and 7.1 Hz, 2H), 2.56 (dt, *J*= 1.1 and 7.0 Hz, 2H), 3.52 (t, *J*= 5.7 Hz, 2H), 4.54 (s, 2H), 6.97 (t, *J*= 1.1 Hz, 1H), 7.28-7.42 (m, 5H), 11.32 (br s, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ= 20.5,

(6) Lowik, D. W. P. M.; Liskamp, R. M. J. *Eur. J. Org. Chem.* **2000**, 1219.
(7) Langille, N. F.; Dakin, L. A.; Panek, J. S. *Org.Lett.* **2002**, *4*, 2485.

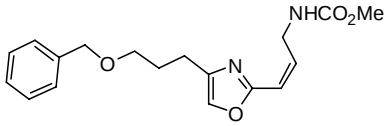
27.6, 68.8, 73.4, 128.0, 128.1, 128.8, 130.6, 132.8, 137.7. LRMS (ESI): m/z= 272 ($M+Na^+$). HRMS (ESI) calcd for $C_{13}H_{15}NO_2NaS$: 272.0721. Found: 272.0723.



- methyl 3-(4-(3-(benzyloxy)propyl)oxazol-2-yl)prop-2-ynylcarbamate (**25**)

To a solution of oxazolethione **3** (48 mg, 0.192 mmol) in DMF (0.96 mL) was added copper thiophenecarboxylate (CuTc) (33.5 mg, 0.115 mmol), alkyne **4** (65 mg, 0.576 mmol),[8] Et_3N (2.5 mL), CuI (28 mg, 0.096 mmol) and $Pd(PPh_3)_4$ (11.1 mg, 9.6 µmol). The vial was sealed and heated at 100 °C under pressure in a micro-wave oven during 15 min. The mixture was then filtered on a short pad of silica (elution by Et_2O) and concentrated under vacuum. The crude was purified on preparative HPLC (EtOAc 1/ heptane 1) yielding alkyne **25** as a pale yellow oil (33 mg, 0.100 mmol, 52%).

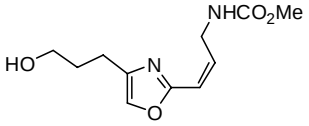
R*f*= 0.38 (Et_2O). IR (neat) *ν*: 738, 1073, 1099, 1252, 1530, 1712, 3307 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): *δ*= 1.89-1.98 (m, 2H), 2.62 (t, *J*= 7.3, 2H), 3.49 (t, *J*= 6.1 Hz, 2H), 3.70 (s, 3H), 4.16-4.26 (m, 2H), 4.49 (s, 2H), 5.24 (br s, 1H), 7.25-7.30 (m, 3H), 7.30-7.37 (m, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$): *δ*= 22.9, 28.3, 31.4, 52.7, 69.2, 71.6, 73.0, 88.0, 127.7, 127.8, 128.5, 135.4, 138.6, 141.7, 145.7, 156.6. LRMS (ESI): m/z= 351 ($M+Na^+$). HRMS (ESI) calcd for $C_{18}H_{20}N_2O_4Na$: 351.1321. Found: 351.1326.



- (*Z*)-methyl 3-(4-(3-(benzyloxy)propyl)oxazol-2-yl)allylcarbamate (**26**)

A solution of alkyne **25** (30 mg, 0.0915 mmol), quinoline (11.8 mg, 0.0915 mmol) and Lindlar catalyst (20 mg), in EtOAc (2 mL) was purged by H_2. After 2 h of stirring at room temperature, the reaction mixture was filtered on a celite pad and concentrated under vacuum. The crude mixture was purified on preparative HPLC (EtOAc 1/ heptane 1) yielding alkene **26** as a pale yellow oil (28 mg, 0.0849 mmol, 93%).

R*f*= 0.35 (EtOAc 1/ heptane 1). IR (neat) *ν*: 738, 1073, 1100, 1254, 1522, 1540, 1705, 1717, 2852, 2946, 3317 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): *δ*= 1.90-2.02 (m, 2H), 2.64 (t, *J*= 7.6, 2H), 3.53 (t, *J*= 6.2 Hz, 2H), 3.68 (s, 3H), 4.30 (t, *J*= 6.2 Hz, 2H), 4.51 (s, 2H), 5.59 (br s, 1H), 6.00-6.15 (m, 1H), 6.28 (d, *J*= 11.2 Hz, 1H), 7.24-7.32 (m, 2H), 7.32-7.36 (m, 4H). ^{13}C NMR (75.5 MHz, $CDCl_3$): *δ*= 23.1, 28.6, 39.5, 52.3, 69.4, 73.1, 116.9, 127.7, 127.8, 128.5, 133.9, 136.1, 138.6, 141.9, 152.3, 160.0. LRMS (ESI): m/z= 353 ($M+Na^+$). HRMS (ESI) calcd for $C_{18}H_{22}N_2O_4Na$: 353.1477. Found: 353.1481.



- (*Z*)-methyl 3-(4-(3-hydroxypropyl)oxazol-2-yl)allylcarbamate (**27**)

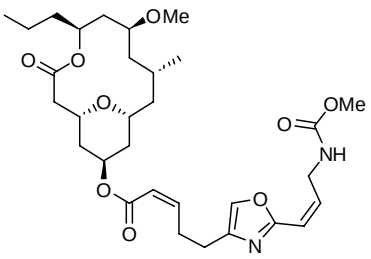
To a solution of benzyl derivative **26** (45 mg, 0.136 mmol) in CH_2Cl_2 (2 mL) at -78 °C was added BCl_3 (1M / hexane, 818 μL, 0.818 mmol). The reaction was allowed to slowly reach -10 °C

(8) Prepared according to the procedure described in: Hornberger, K. R.; Hamblett, C. L.; Leighton, J. L. *J. Am. Chem. Soc.* **2000**, *122*, 12894.

over 4 h and was then quenched by addition of an aqueous saturated solution of $NaHCO_3$ (2 mL). The resulting mixture was warmed to room temperature and then extracted three times by EtOAc. Combined organic phases were dried over anhydrous Na_2SO_4, filtered and evaporated under vacuum. The crude mixture was purified on preparative HPLC (EtOAc 100%) yielding alcohol **27** as a colorless oil (32 mg, 0.133 mmol, 98%), the data of which corresponding to those reported in the literature.[9]

R*f*= 0.16 (EtOAc). IR (neat) ν: 1052, 1266, 1520, 1697, 2946, 3318 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ= 1.90 (q, *J*= 6.6 Hz, 2H), 2.19 (br s, 1H), 2.66 (t, *J*= 7.0, 2H), 3.68 (br s, 3H), 3.72 (t, *J*= 6.1 Hz, 2H), 4.32 (br s, 2H), 5.52 (br s, 1H), 6.09 (dt, *J*= 5.2, and 11.6 Hz, 1H), 6.29 (d, *J*= 11.6 Hz, 1H), 7.37 (s, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ= 22.8, 31.3, 39.6, 52.3, 62.0, 116.4, 134.0, 136.7, 141.6, 157.3, 160.1. LRMS (ESI): m/z= 263 ($M+Na^+$). HRMS (ESI) calcd for $C_{11}H_{16}N_2O_4Na$: 263.1008. Found: 263.1003.

- (+)-Neopeltolide (**1**)

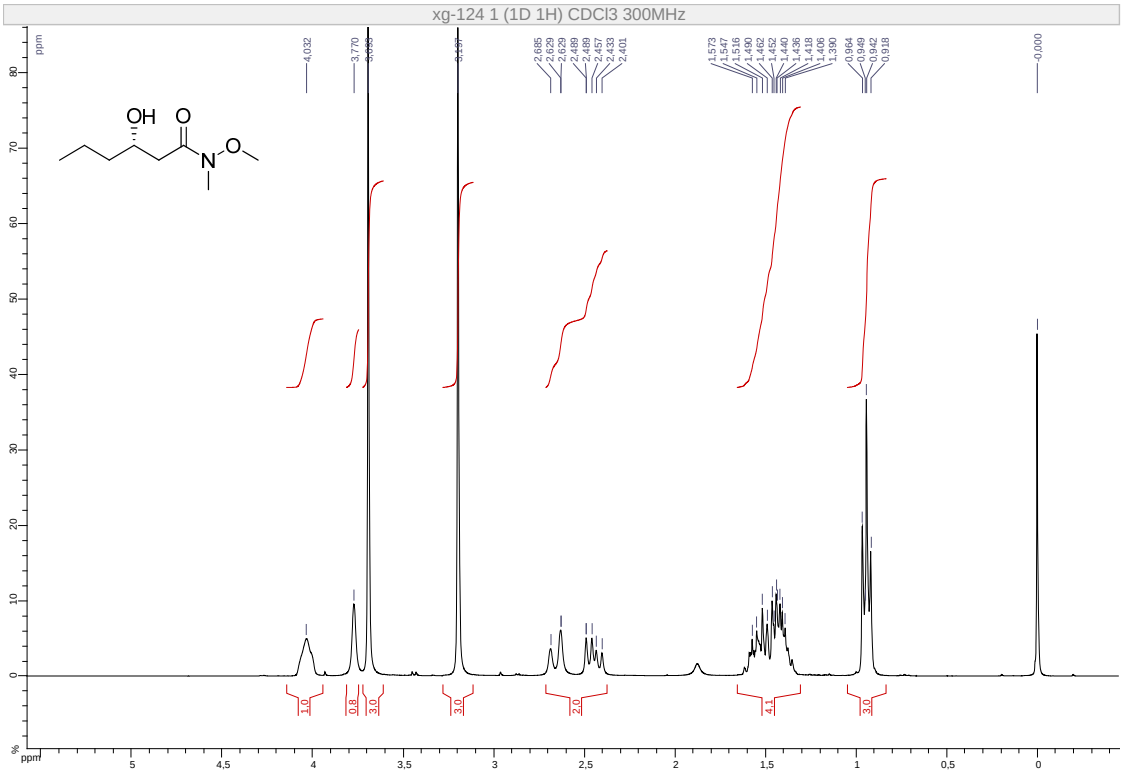


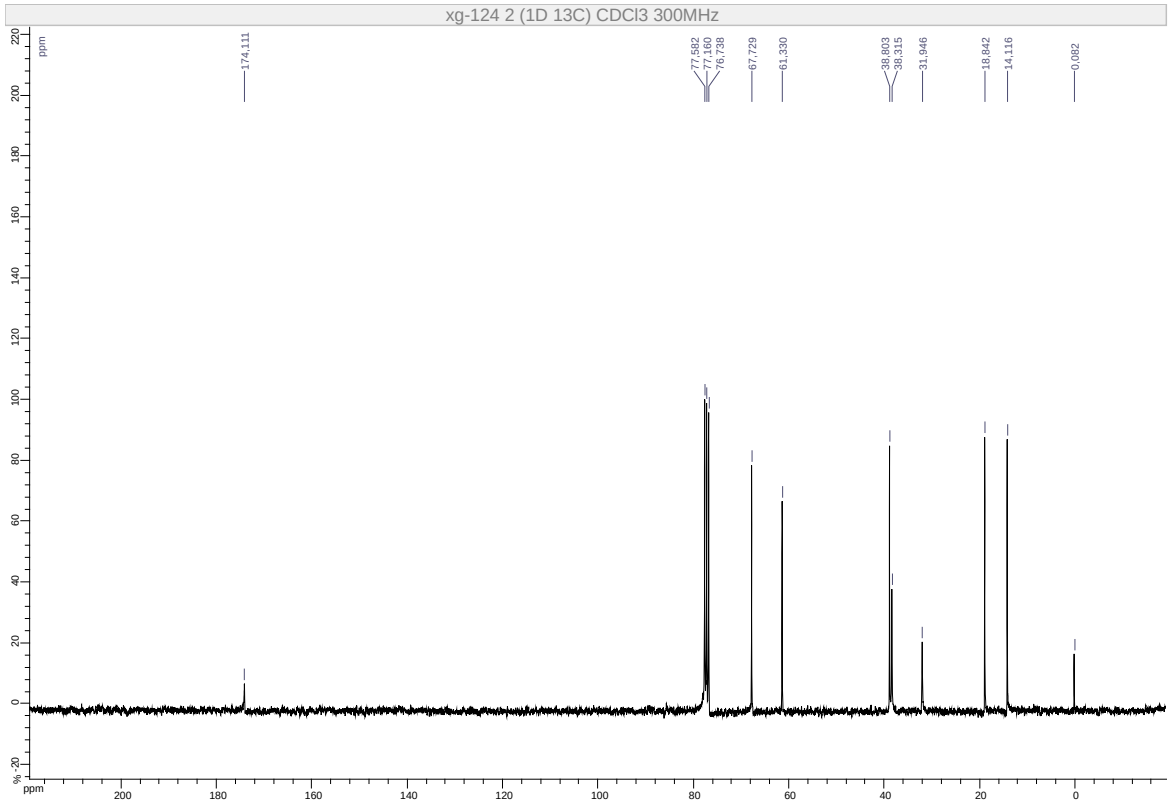
To a solution of alcohol **23** (5.5 mg, 16.36 µmol), acid **28** (6.6 mg, 23.57 µmol) and PPh_3 (7.5 mg, 28.6 µmol) in dry benzene (0.7 mL) was added DIAD (0.5 M solution, 57 µL, 28.6 µmol) and the resulting mixture was stirred at room temperature for 70 min. Then, the reaction mixture was concentrated under vacuum and the residue was purified by preparative HPLC (EtOAc 2/ heptane 3) yielding (+)-Neopeltolide (**1**) (7.5 mg, 12.69 µmol, 75%) as a colorless oil, the data of which matching those reported in the literature.[10]

R*f*= 0.25 (EtOAc 1/ heptane 1). IR (neat) ν: 991, 1031, 1063, 1083, 1179, 1247, 1271, 1518, 1713, 2871, 2917, 2952, 3342. ^1H NMR (500 MHz, CD_3OD): δ= 0.94 (t, *J*= 7.3 Hz, 3H), 0.97 (d, *J*= 6.7 Hz, 3H), 1.12 (ddd, *J* = 2.2, 10.5 and 13.3 Hz, 1H), 1.22–1.46 (m, 6H), 1.47–1.62 (m, 4H), 1.64–1.76 (m, 2H), 1.80-1.85 (m, 1H), 1.86 (dd, *J*= 11.3 and 14.6 Hz, 1H), 2.29 (dd, *J*= 11.0 and 14.6 Hz, 1H), 2.66–2.71 (m, 1H), 2.72 (t, *J*= 7.3 Hz, 2H), 2.97–3.05 (m, 2H), 3.28 (s, 3H), 3.57 (t, *J*= 9.8 Hz, 1H), 3.63–3.71 (m, 1H), 3.65 (s, 3H), 4.02–4.11 (m, 1H), 4.30 (d, *J*= 4.6 Hz, 2H), 5.17 (dt, *J*= 4.6 and 9.5 Hz, 1H), 5.19-5.22 (m, 1H), 5.88 (d, *J*= 11.6 Hz, 1H), 6.04 (td, *J*= 6.1 and 11.9 Hz, 1H), 6.27 (dt, *J*=2.1 and 11.9 Hz, 1H), 6.37 (td, *J*= 7.5 and 11.5 Hz, 1H), 7.66 ppm (s, 1H). ^{13}C NMR (125 MHz, CD_3OD): δ= 14.1, 20.0, 26.0, 26.4, 29.0, 32.6, 36.2, 37.4, 38.0, 41.0, 43.2, 43.5, 45.2, 52.6, 56.4, 69.2, 71.3, 73.9, 77.06, 77.12, 115.9, 121.7, 135.9, 139.2, 142.3, 150.0, 159.6, 161.9, 166.9, 173.0. LRMS (ESI): m/z= 613 ($M+Na^+$). HRMS (ESI) calcd for $C_{31}H_{46}N_2O_9Na$: 613.3101. found: 613.3101. $[\alpha]_D^{27}$= +24.4 (*c* 0.24, MeOH), *lit*.[3,10] $[\alpha]_D^{20}$= +24.0 (*c* 0.24, MeOH).

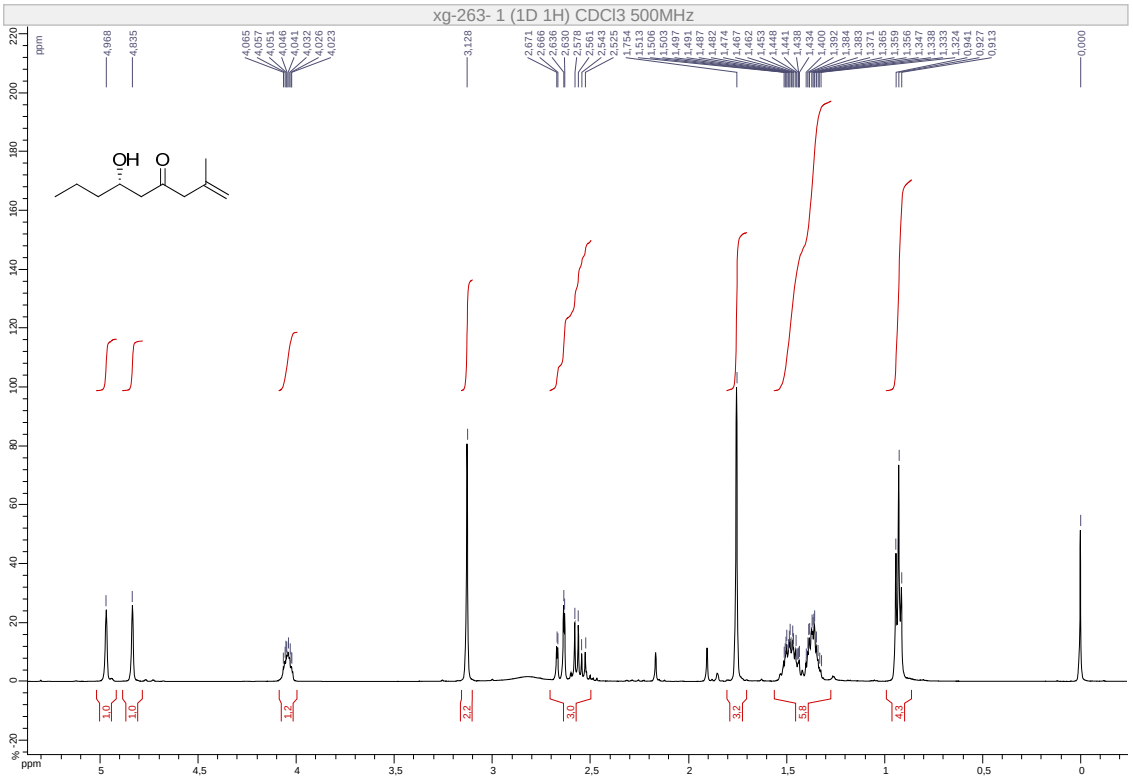
(9) Dakin, L. A.; Langille, N. F.; Panek, J. S. *J. Org. Chem.* **2002**, *67*, 6812.
(10) Wright, A. E.; Cook Botelho, J.; Guzma´n, E.; Harmody, D.; Linley, P.; McCarthy, P. J.; Pitts, T. P.; Pomponi, S. A.; Reed, J. K. *J. Nat. Prod.* **2007,** *70,* 412.

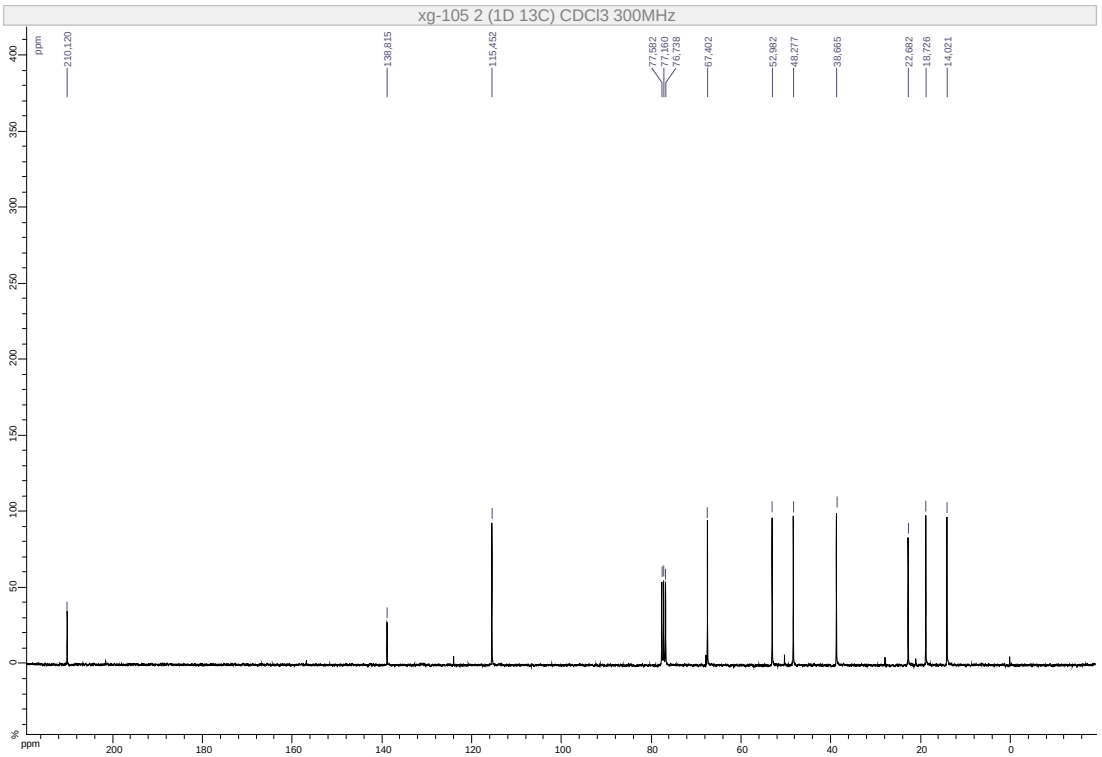
7, ^{1}H NMR (300 MHz, $CDCl_3$) and ^{13}C NMR (75.5 MHz, $CDCl_3$)



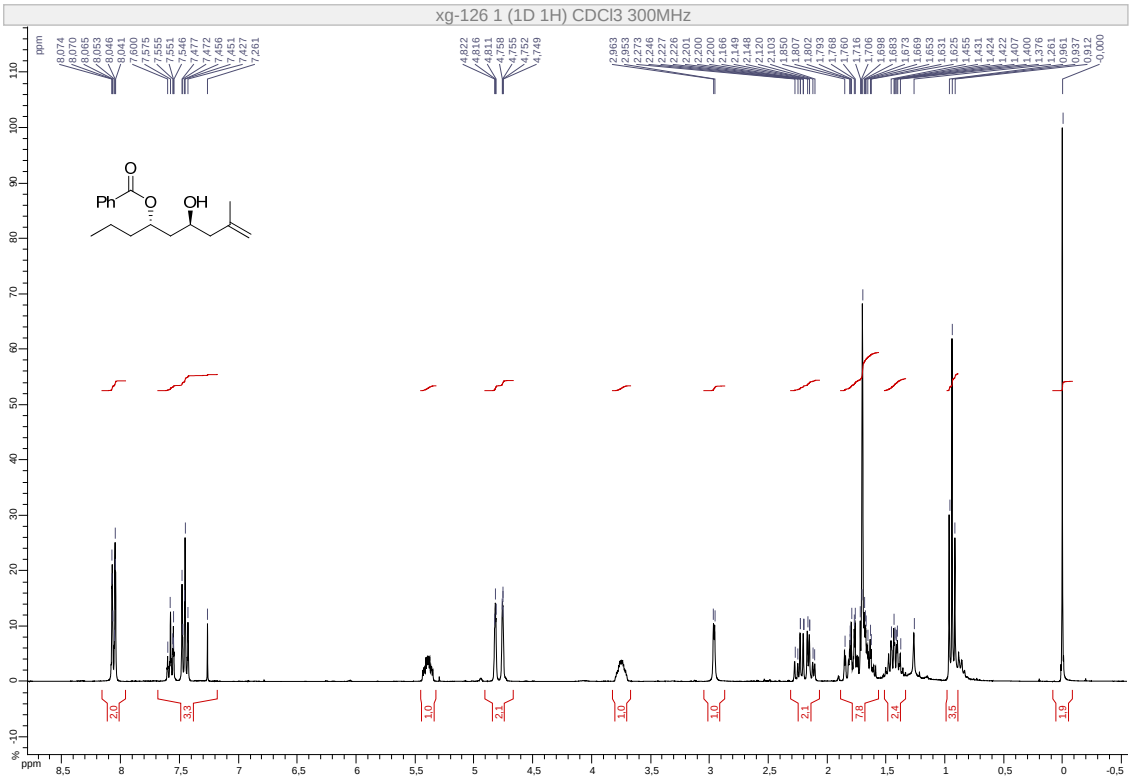


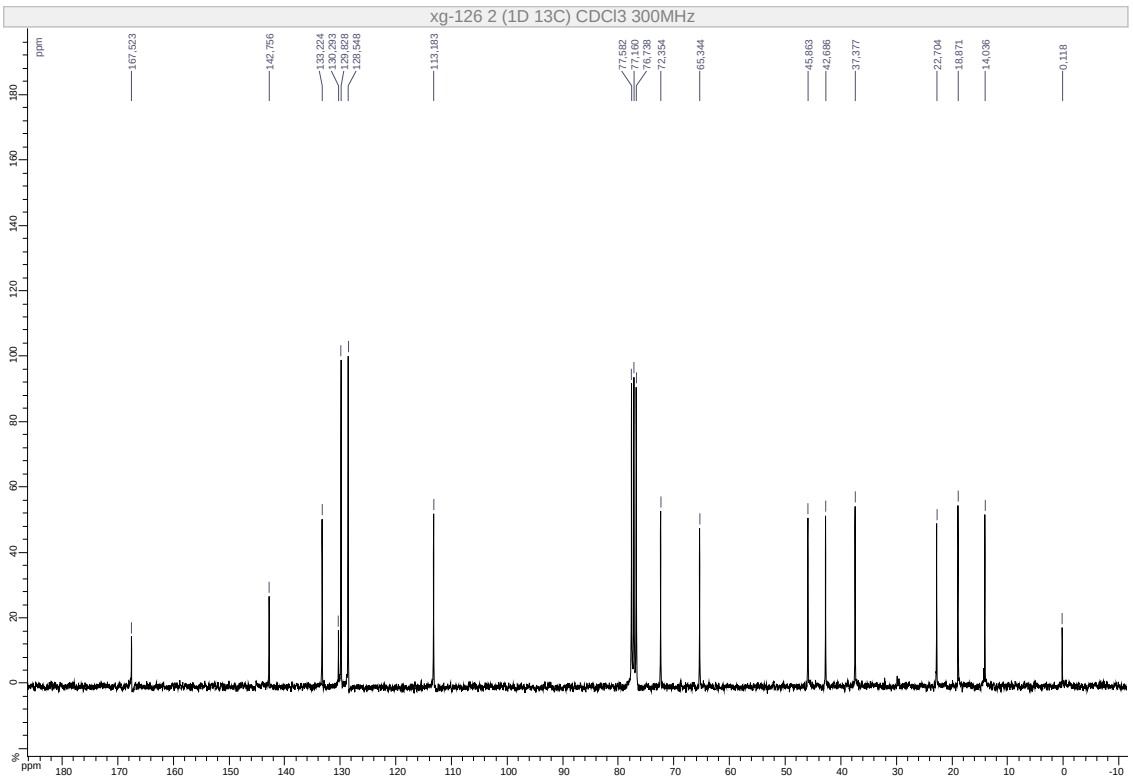
8, ^{1}H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (75.5 MHz, $CDCl_3$)



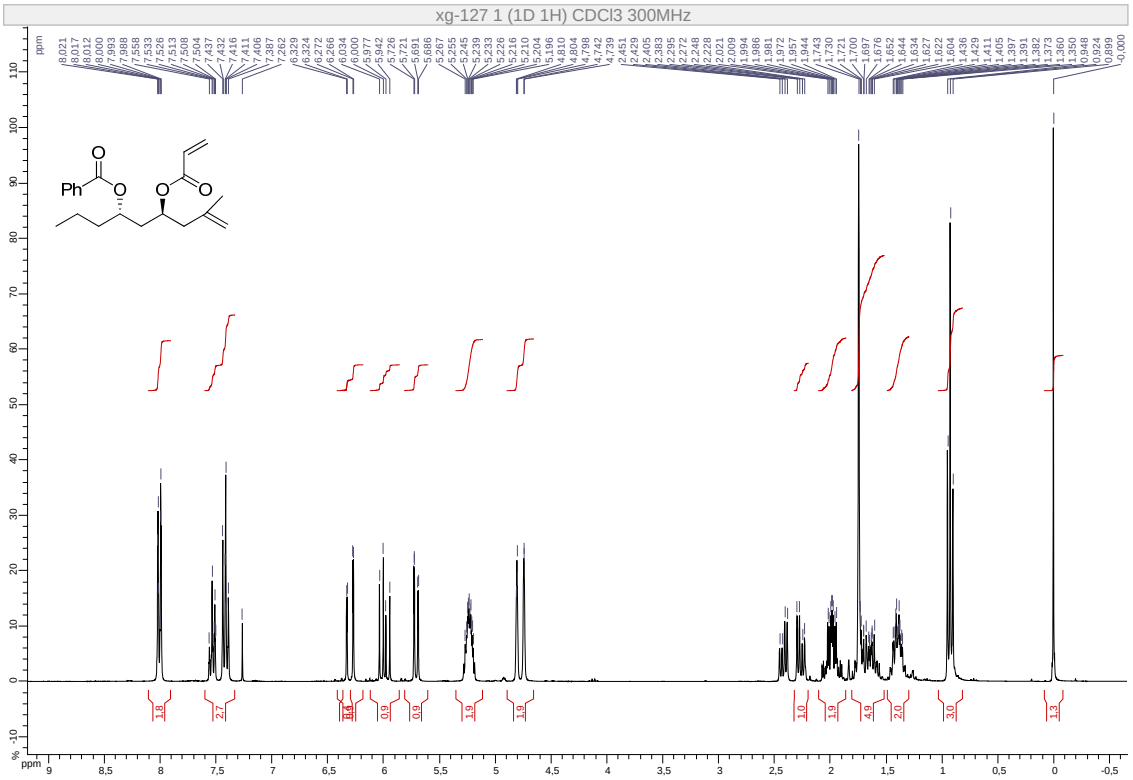


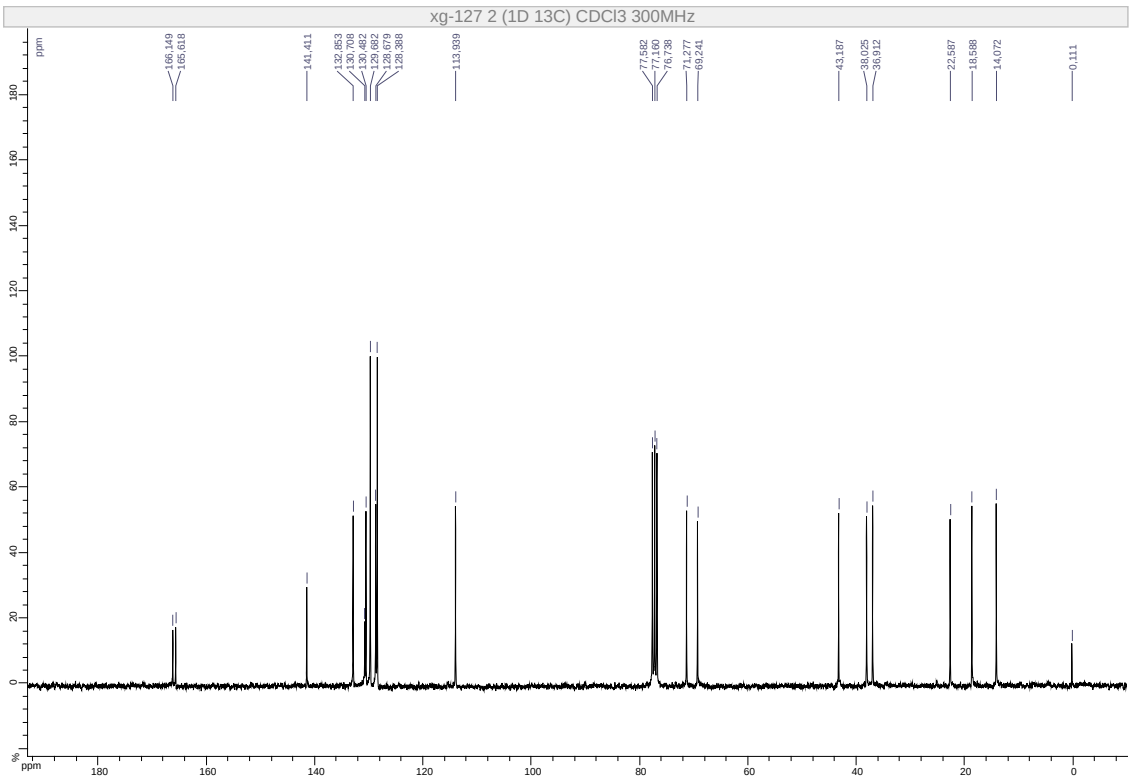
9, ^{1}H NMR (300 MHz, $CDCl_3$) and ^{13}C NMR (75.5 MHz, $CDCl_3$)



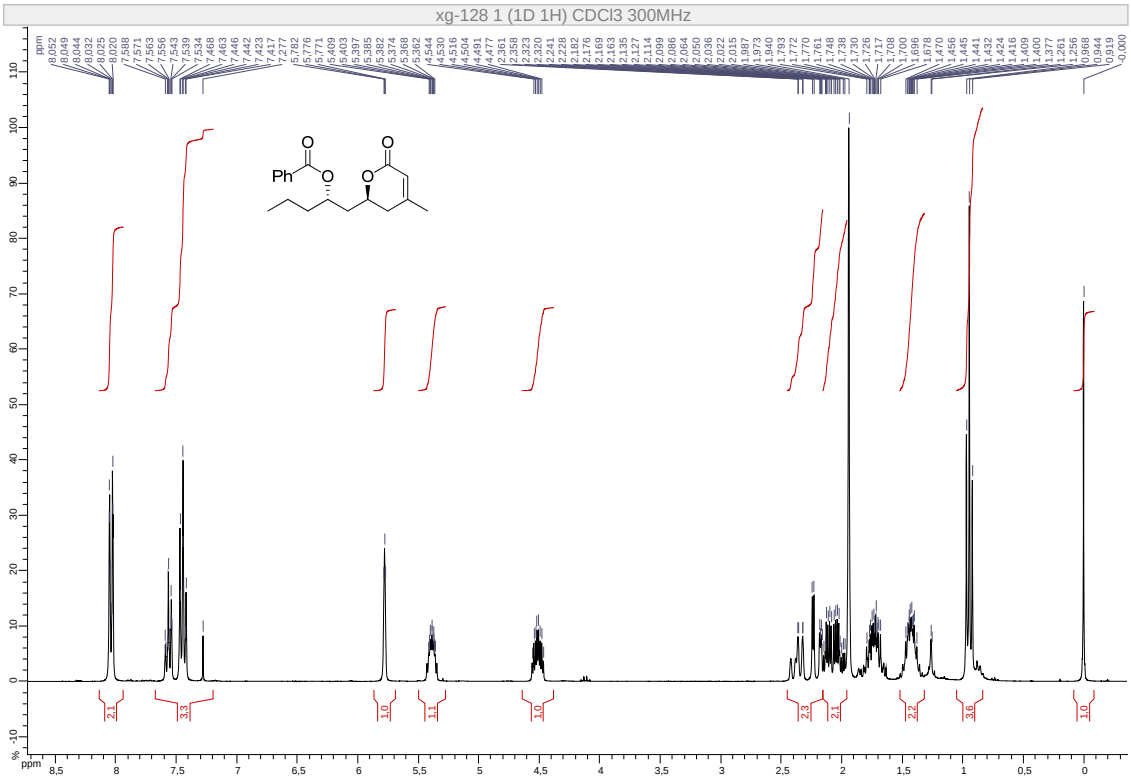


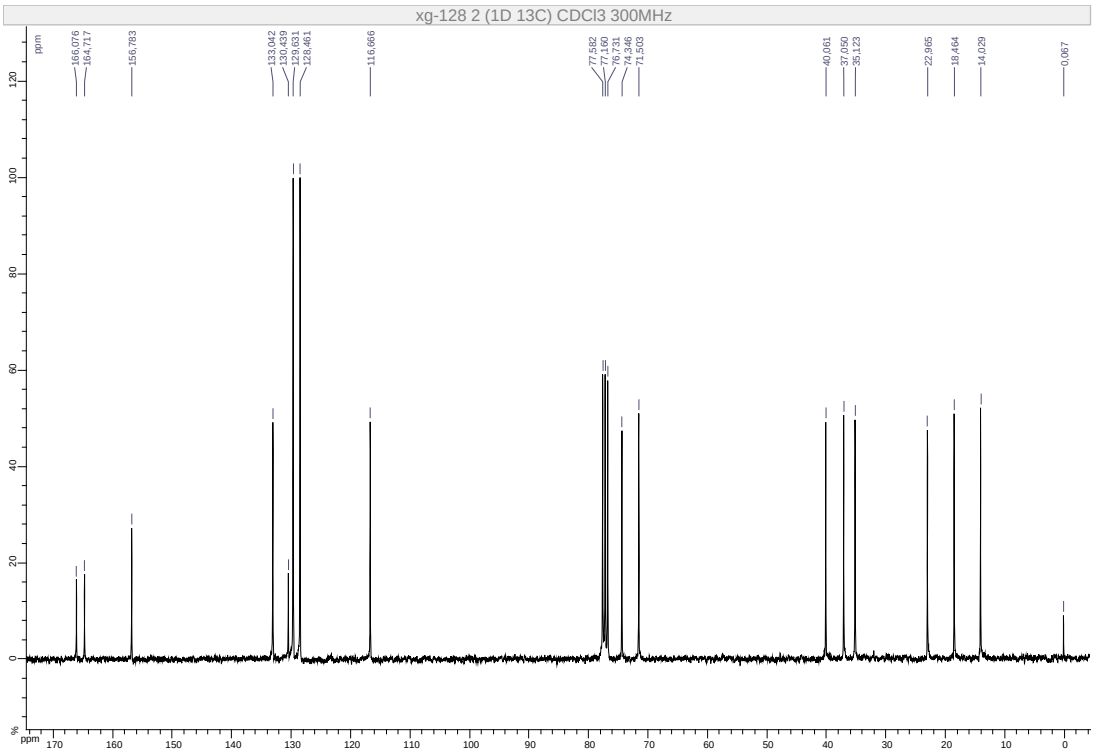
10, ^{1}H NMR (300 MHz, $CDCl_3$) and ^{13}C NMR (75.5 MHz, $CDCl_3$)



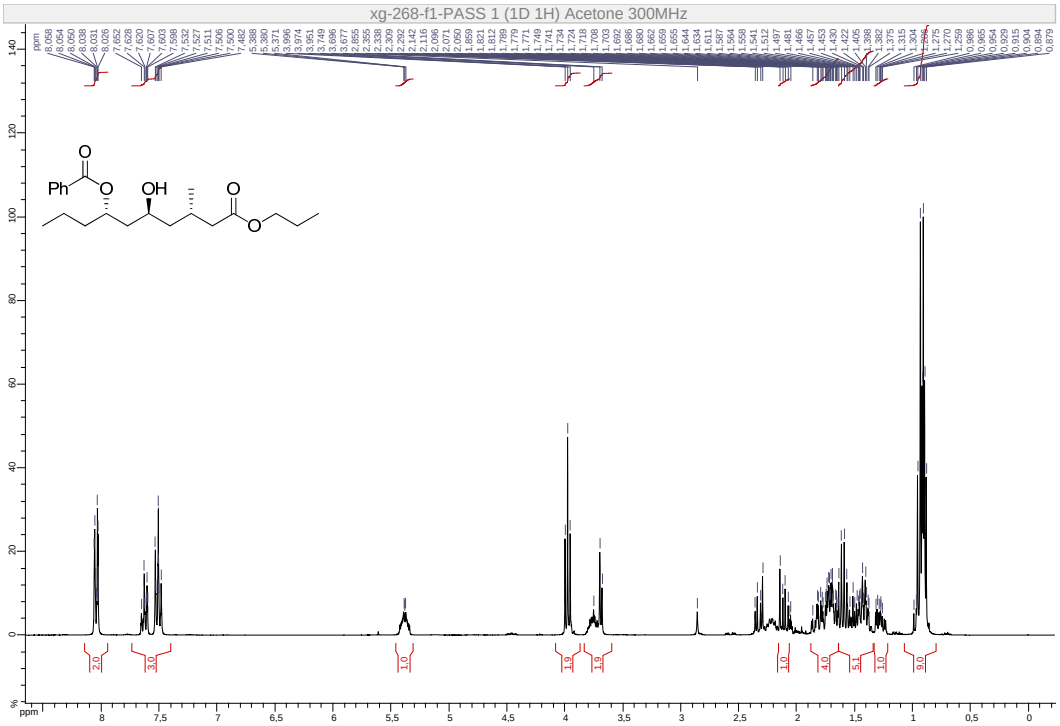


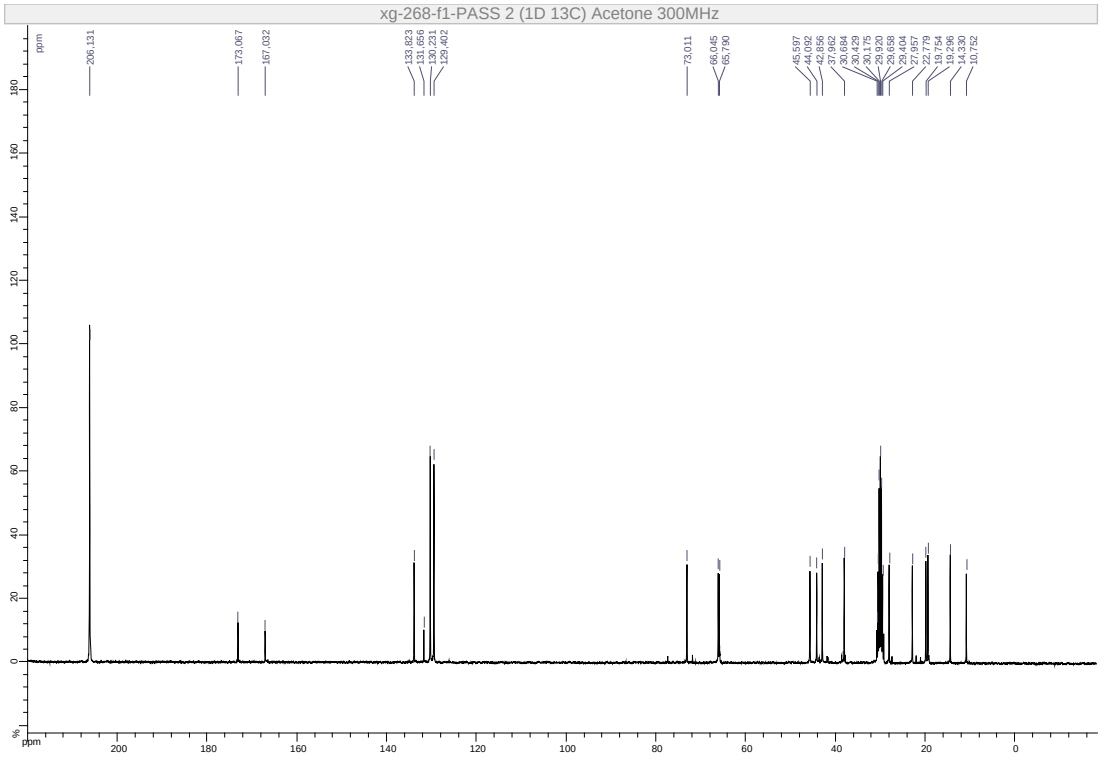
11, ^{1}H NMR (300 MHz, $CDCl_3$) and ^{13}C NMR (75.5 MHz, $CDCl_3$)



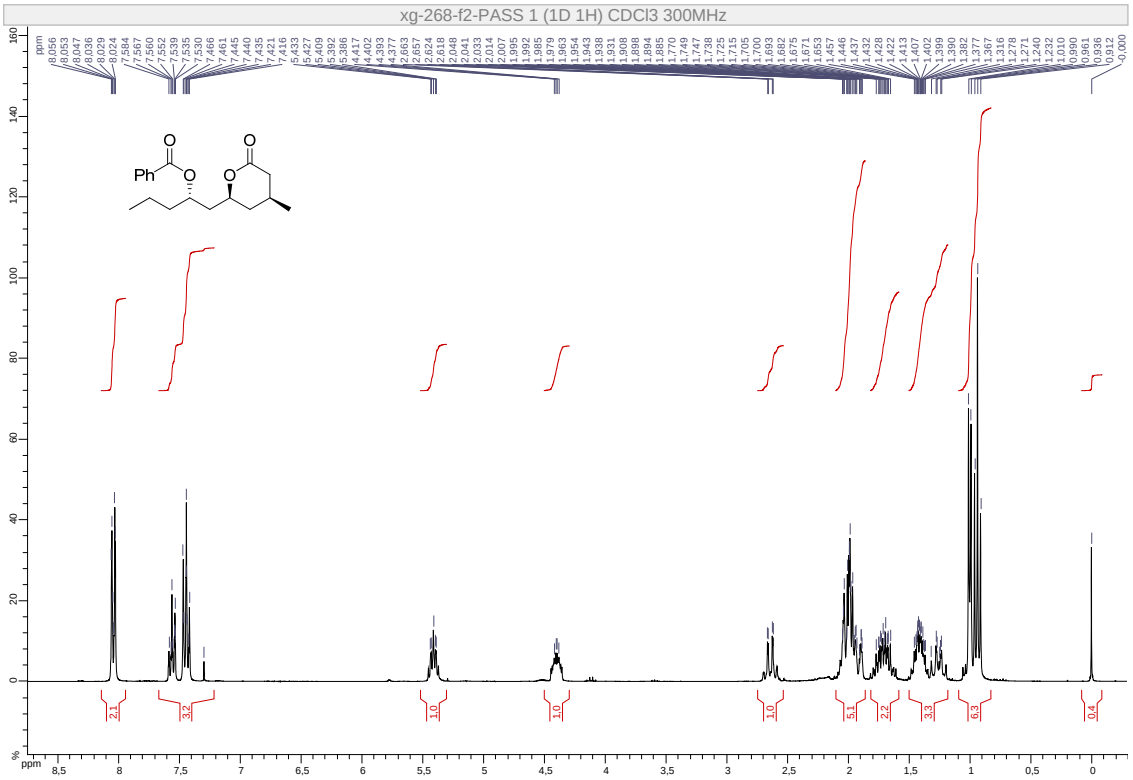


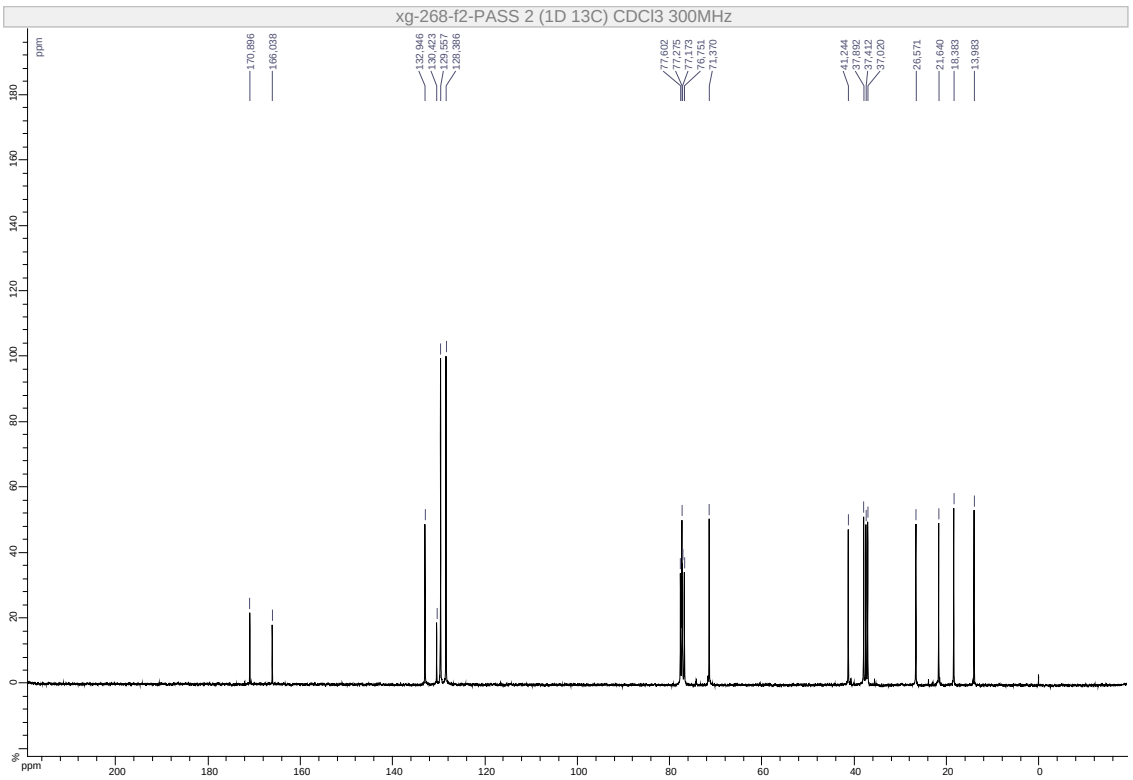
13, ^{1}H NMR (300 MHz, CD_3COCD_3) and ^{13}C NMR (75.5 MHz, CD_3COCD_3)



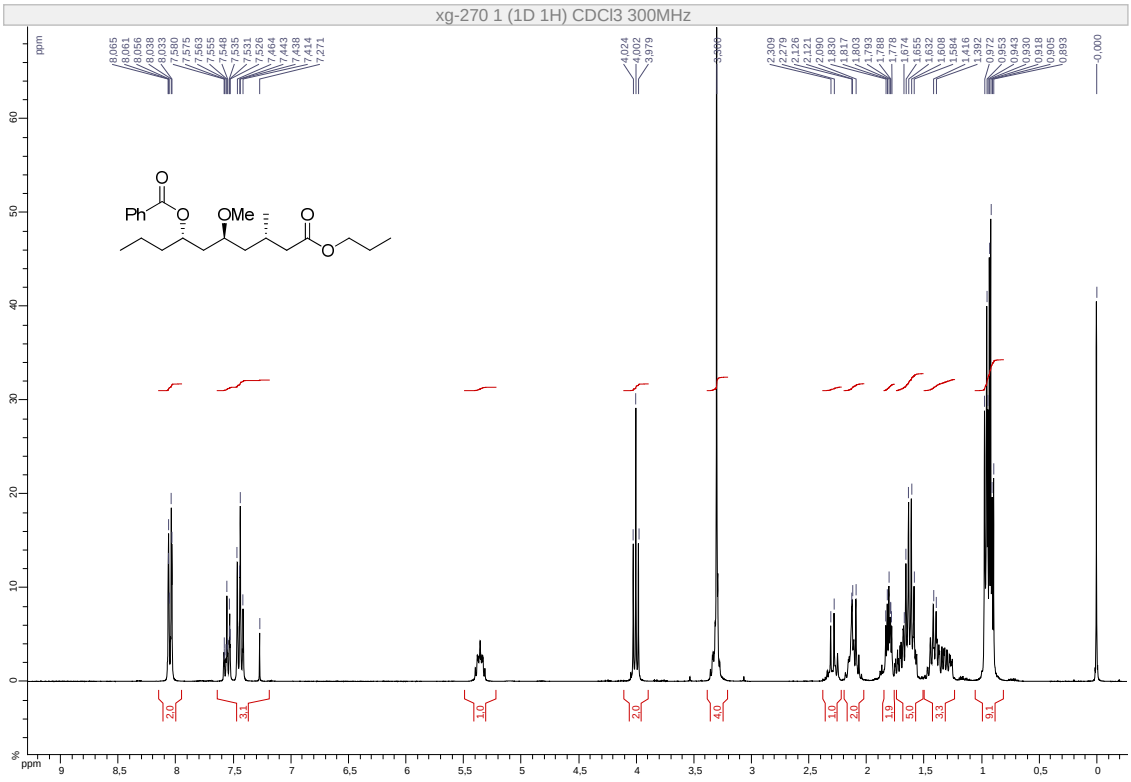


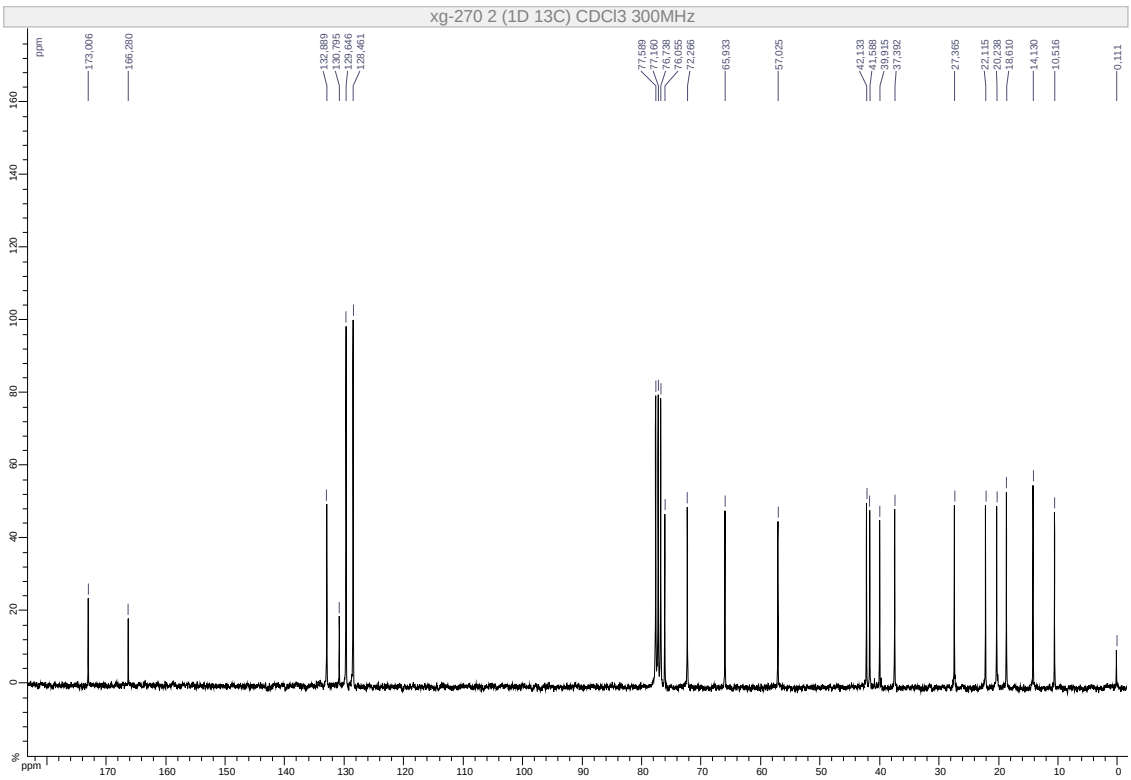
12, ^{1}H NMR (300 MHz, $CDCl_3$) and ^{13}C NMR (75.5 MHz, $CDCl_3$)



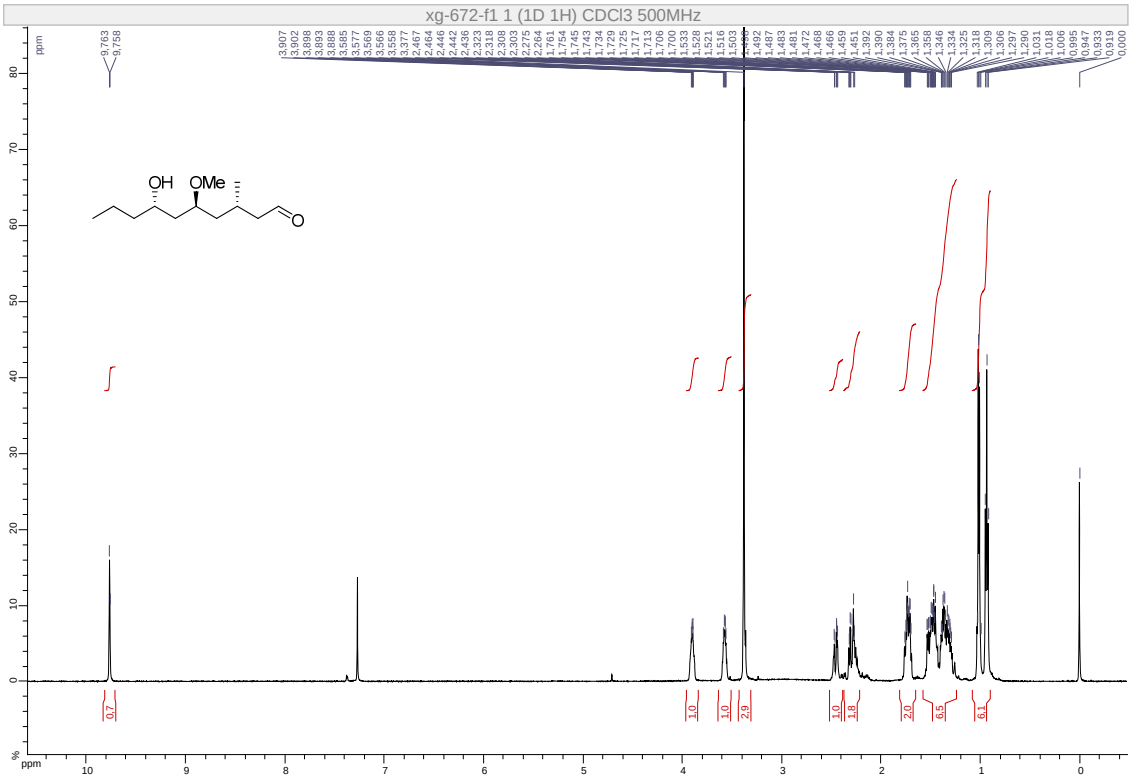


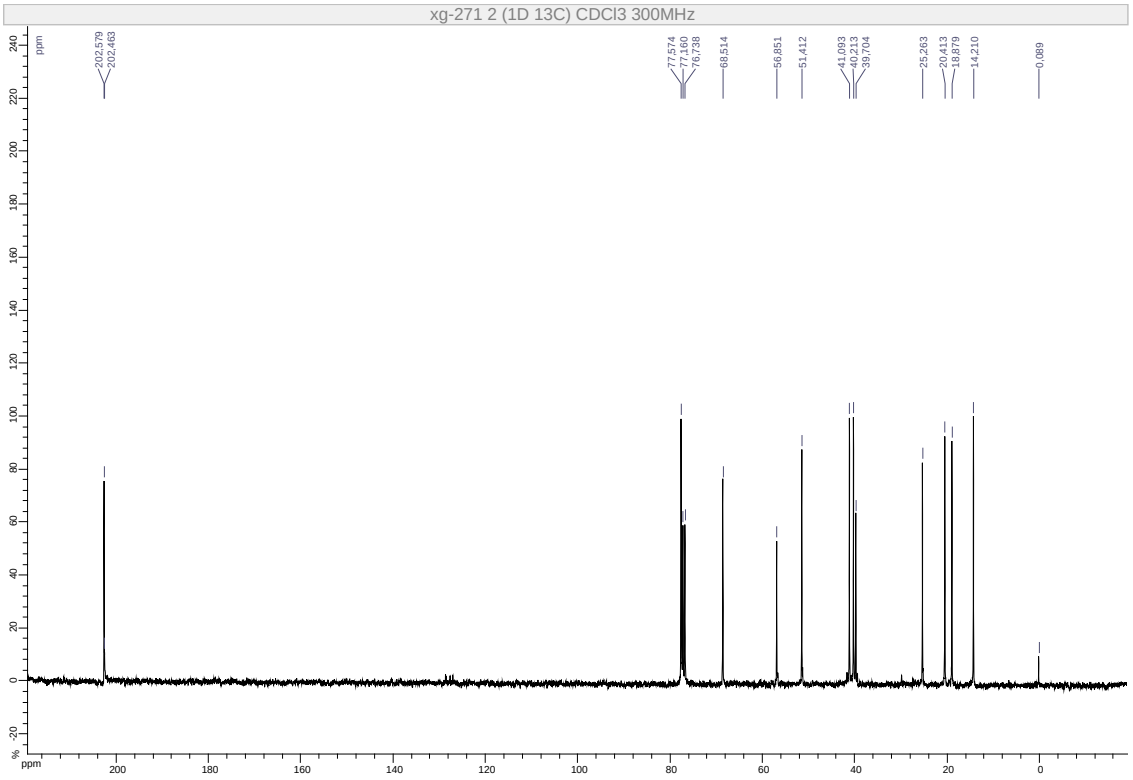
14, ^{1}H NMR (300 MHz, $CDCl_3$) and ^{13}C NMR (75.5 MHz, $CDCl_3$)



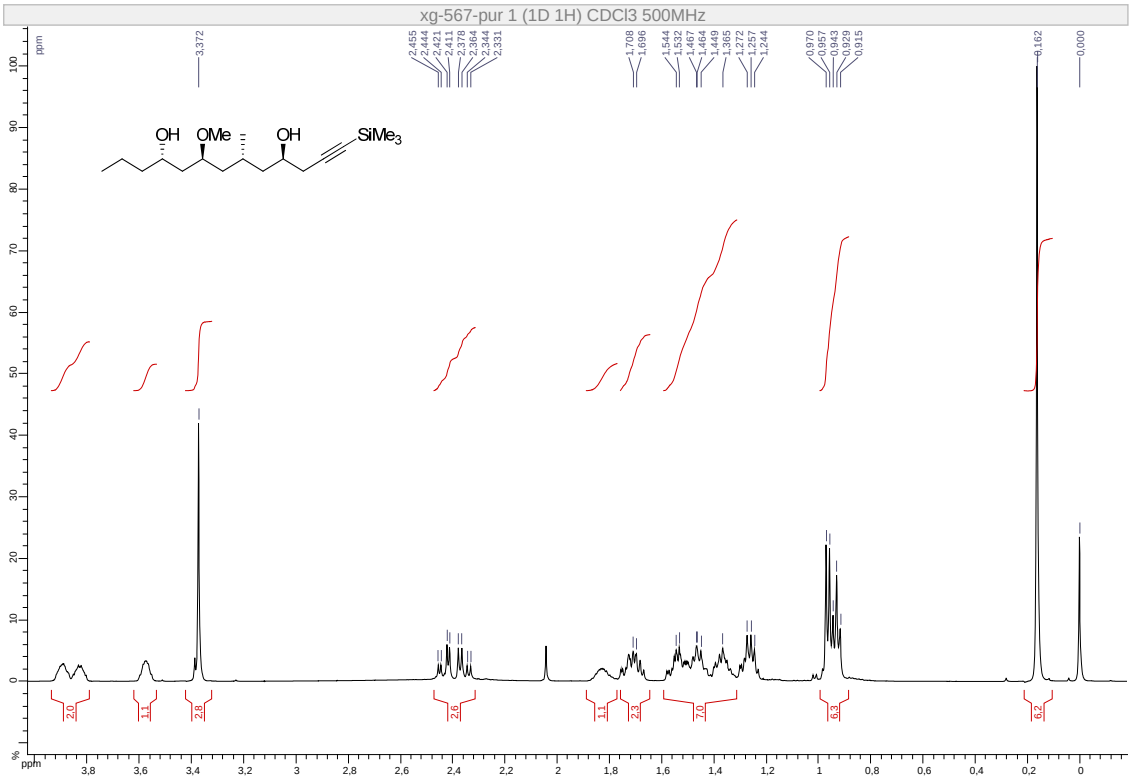


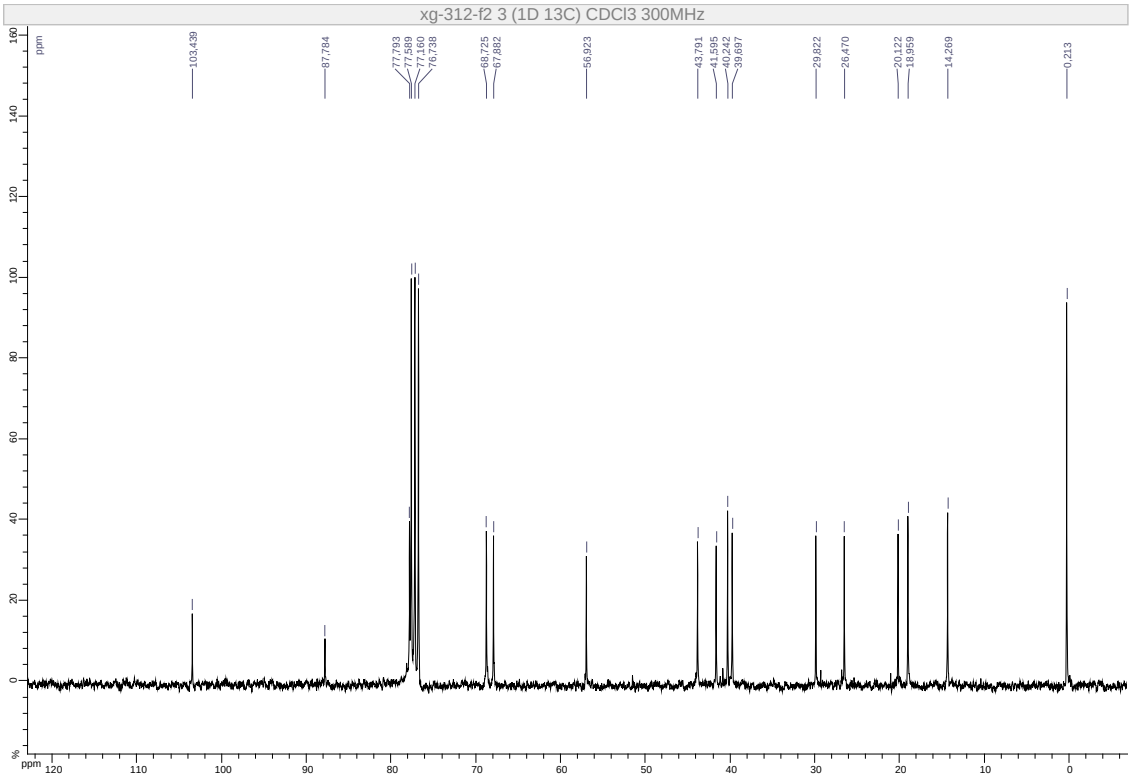
15, ^{1}H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (75.5 MHz, $CDCl_3$)



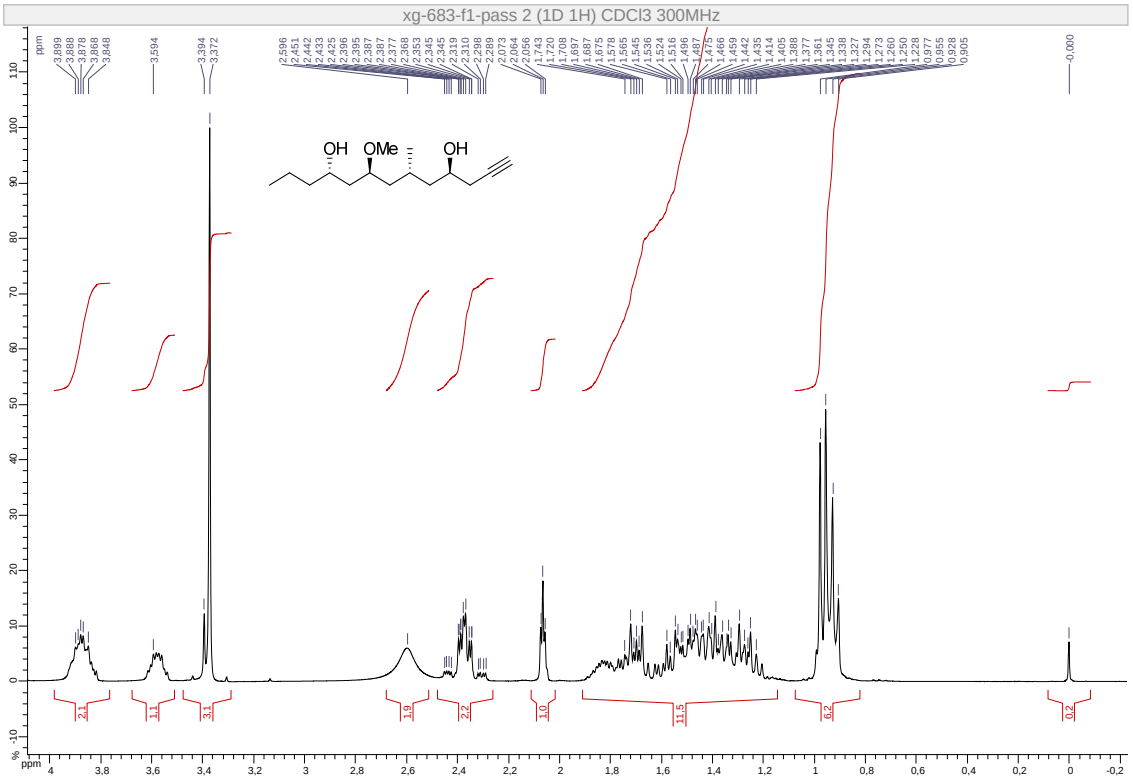


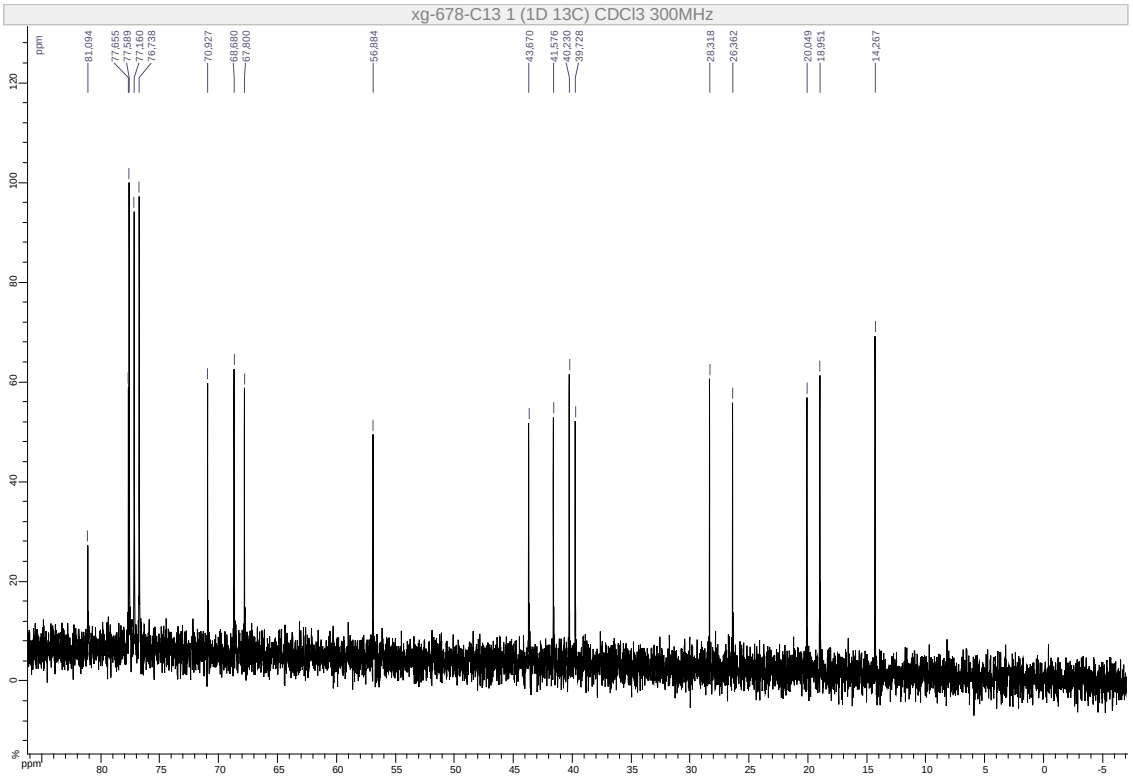
2, ^{1}H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (75.5 MHz, $CDCl_3$)



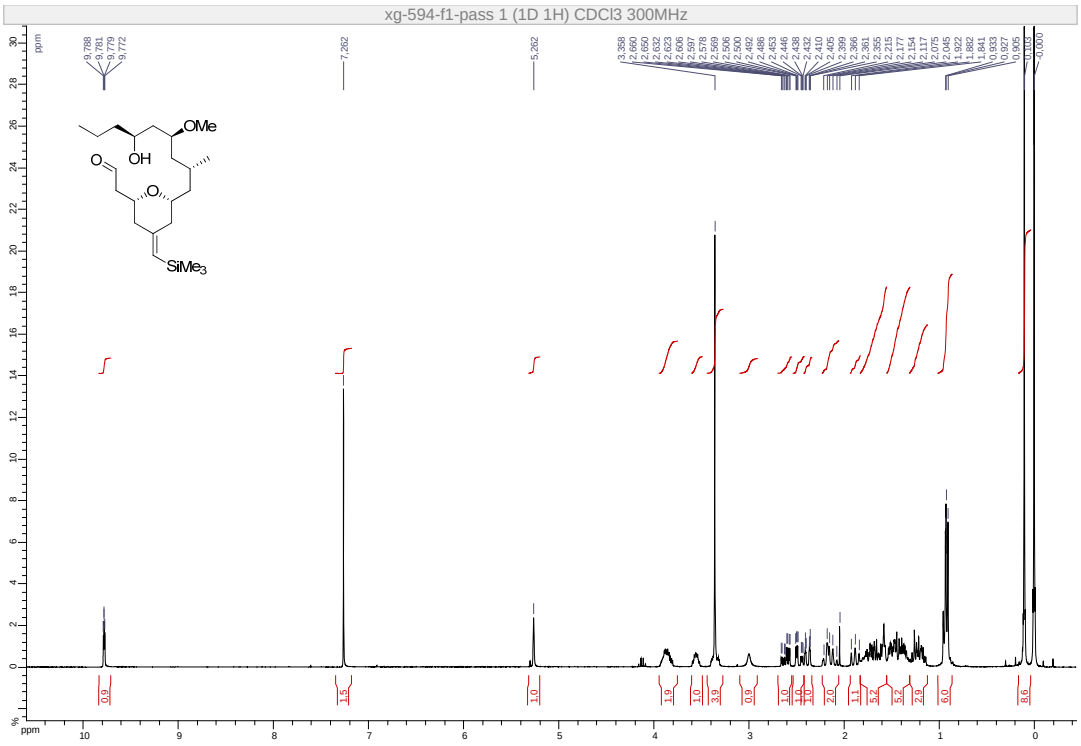


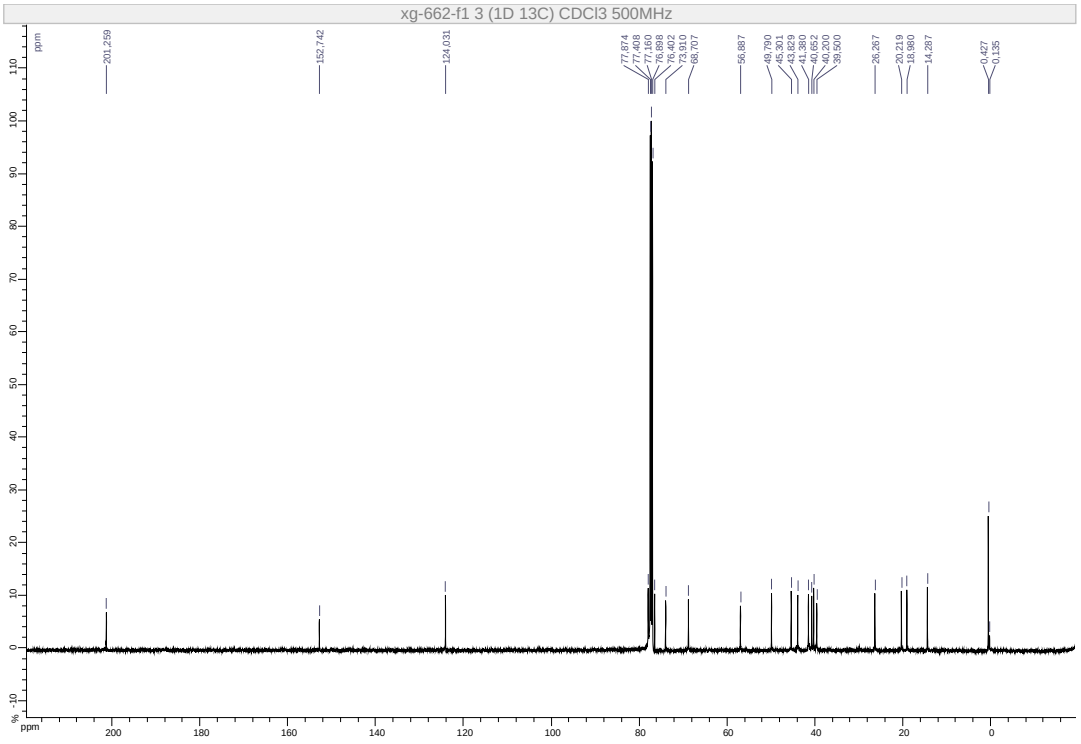
18, ^{1}H NMR (300 MHz, $CDCl_3$) and ^{13}C NMR (75.5 MHz, $CDCl_3$)

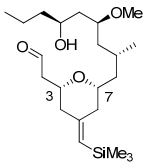




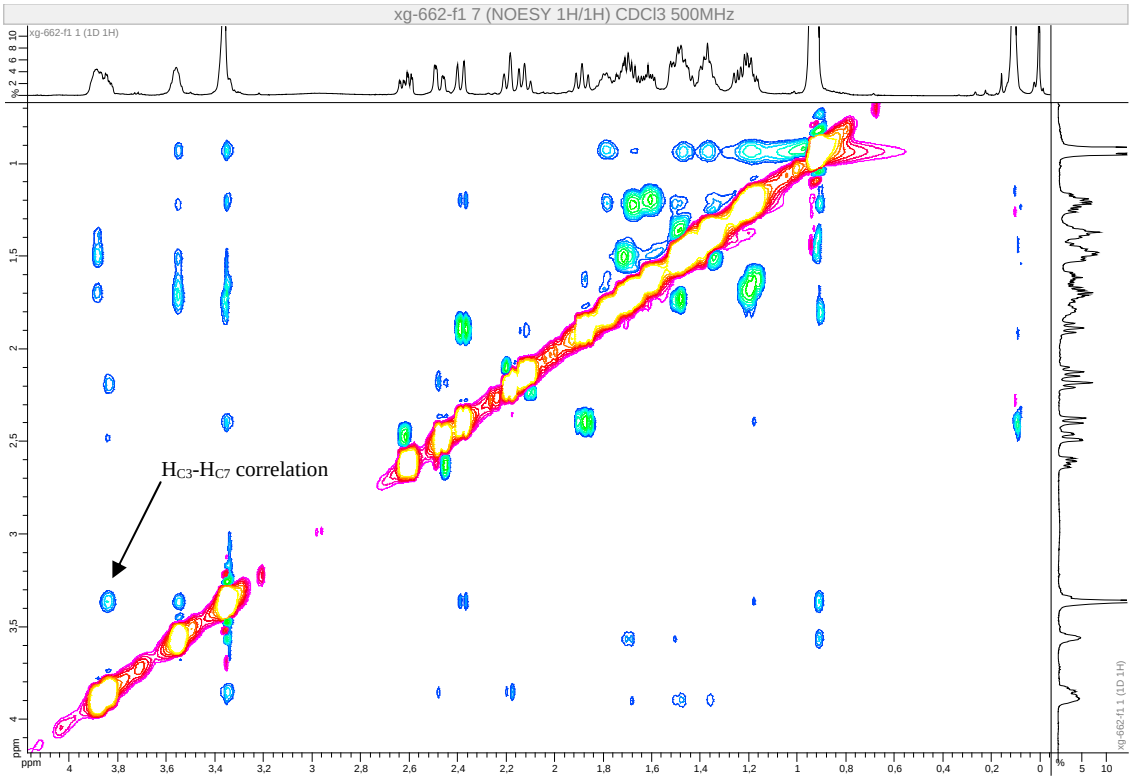
17, ^{1}H NMR (300 MHz, $CDCl_3$) and ^{13}C NMR (125.5 MHz, $CDCl_3$)



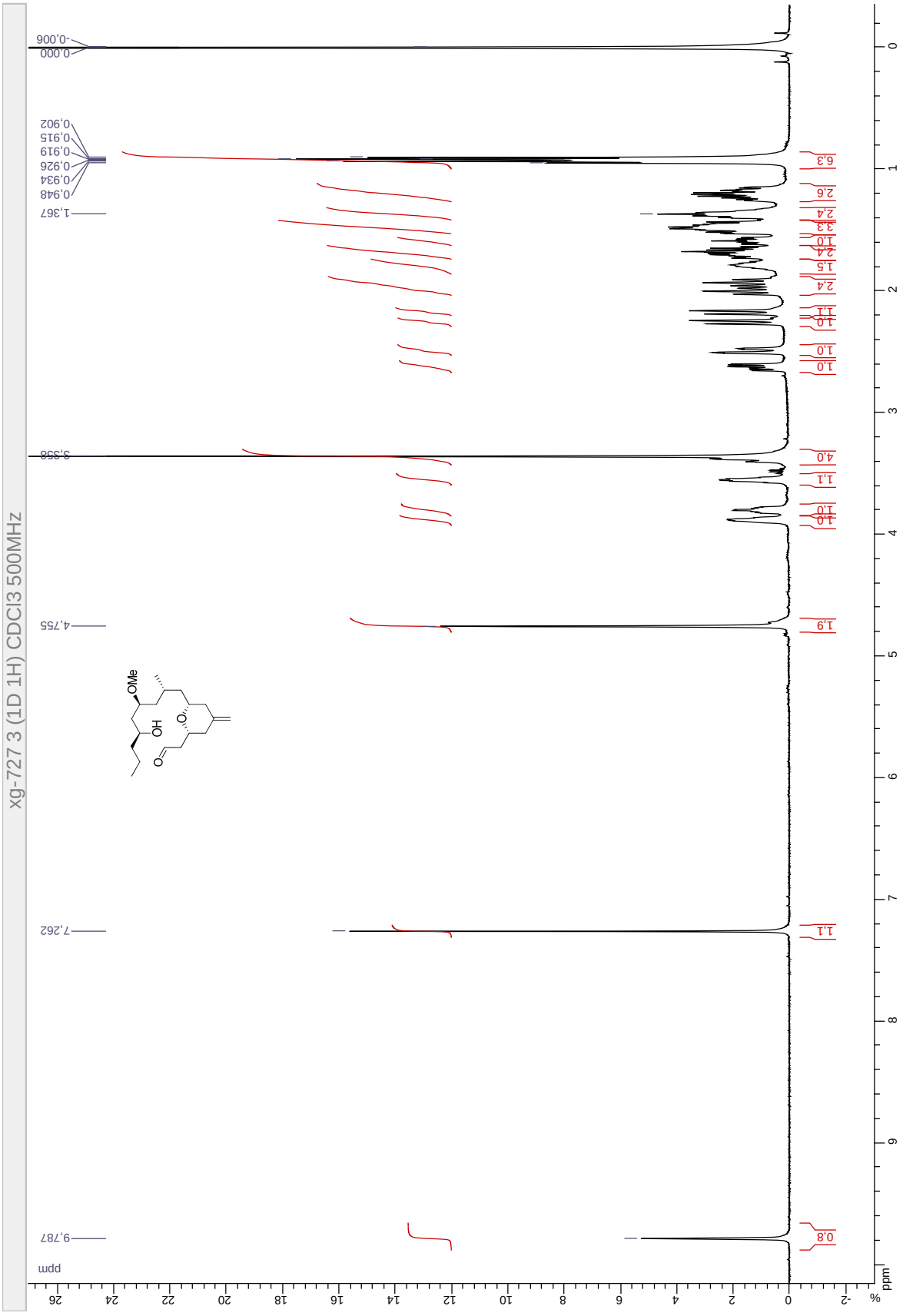




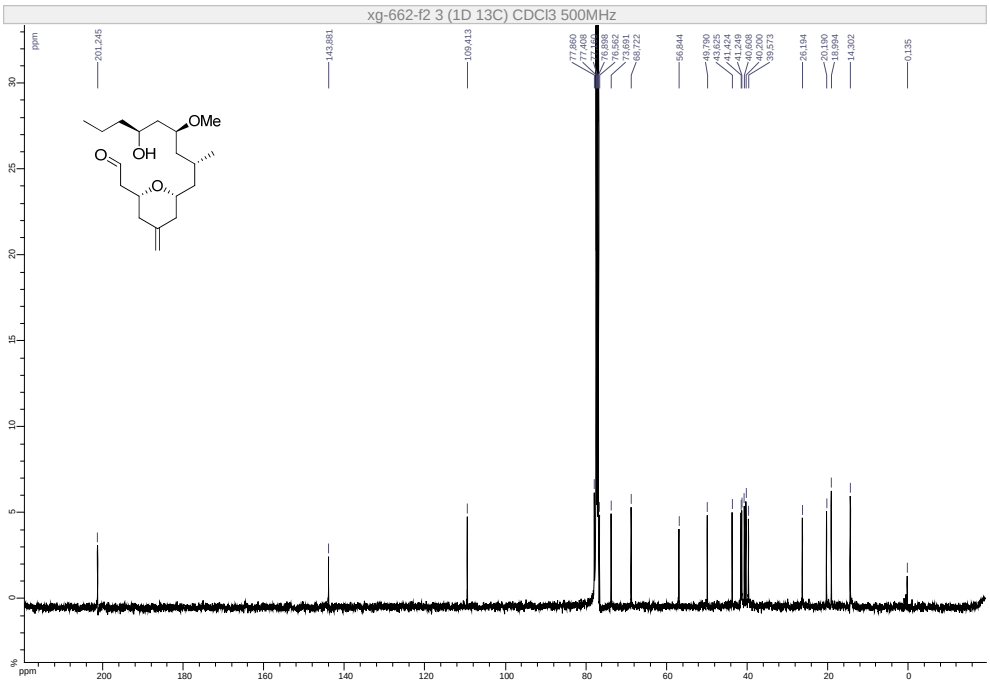
17, NOESY $^{1}H/^{1}H$ NMR (500 MHz, $CDCl_3$)



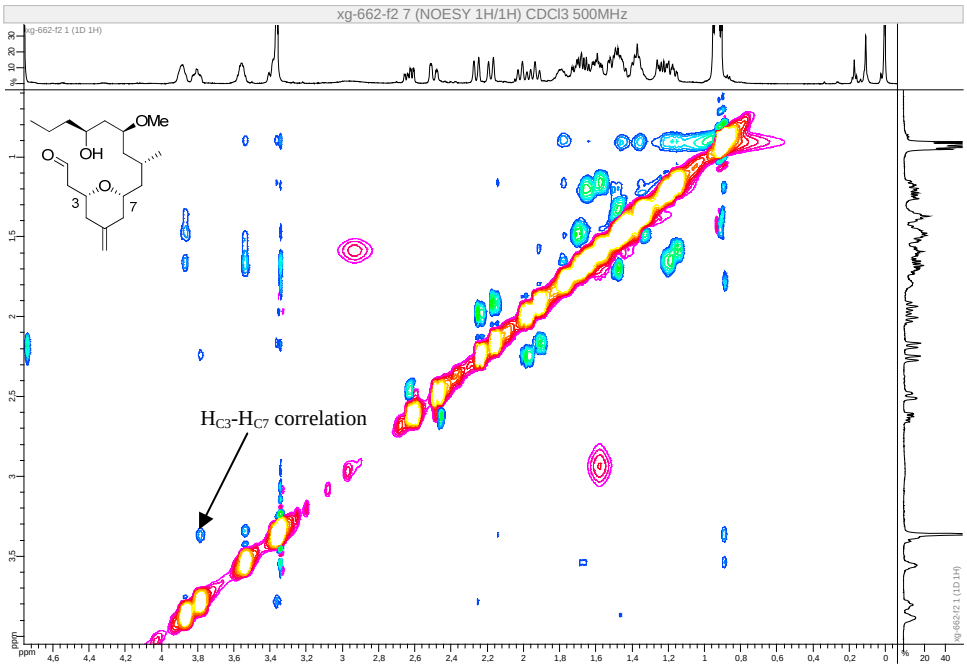
19, ^{1}H NMR (500 MHz, $CDCl_3$)



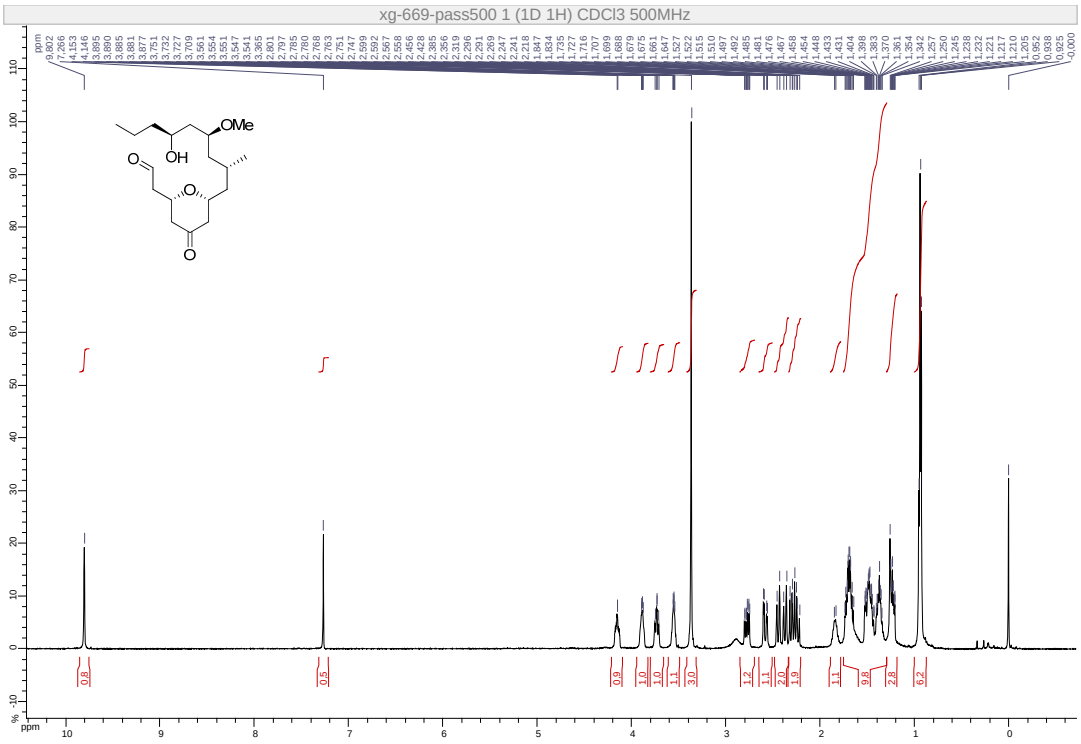
^{13}C NMR (125.5 MHz, $CDCl_3$)

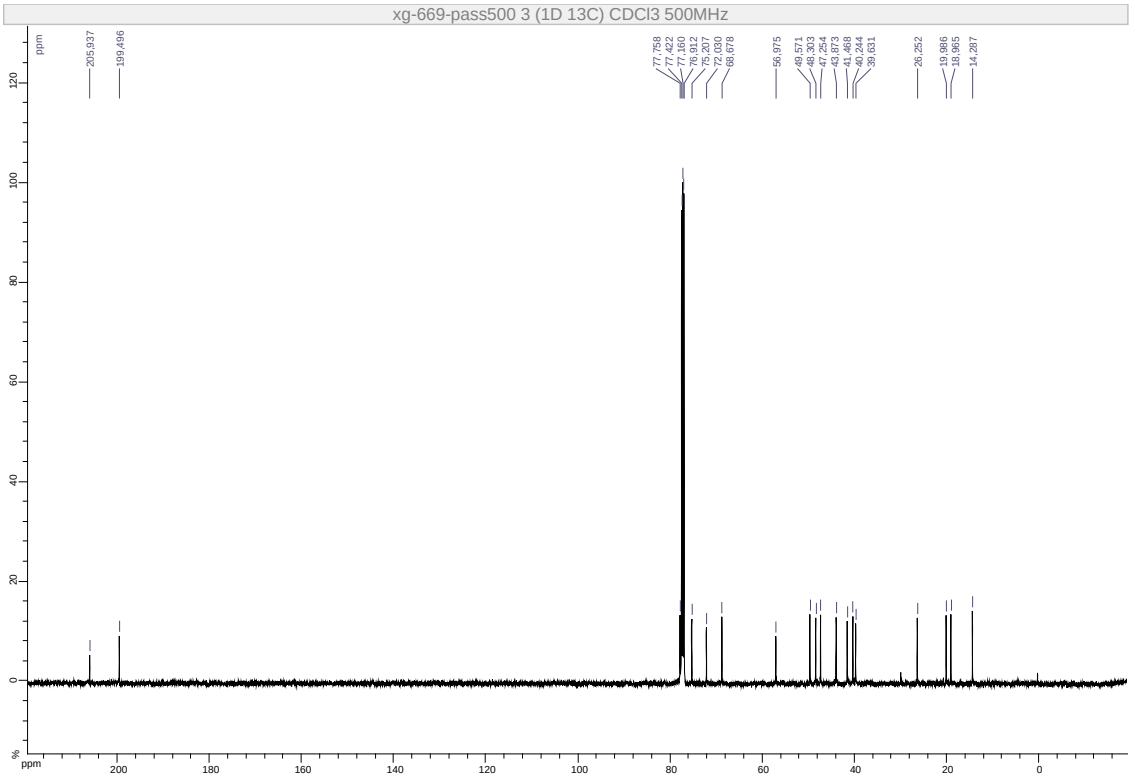


19, NOESY ^{1}H/^{1}H NMR (500 MHz, $CDCl_3$)

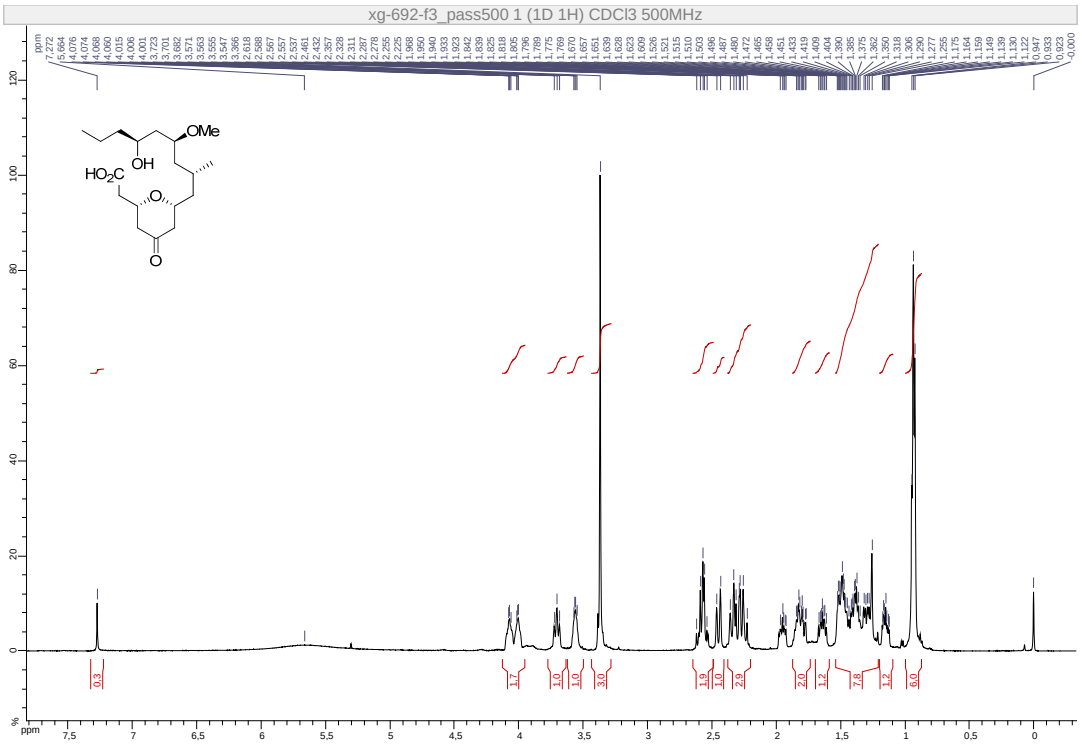


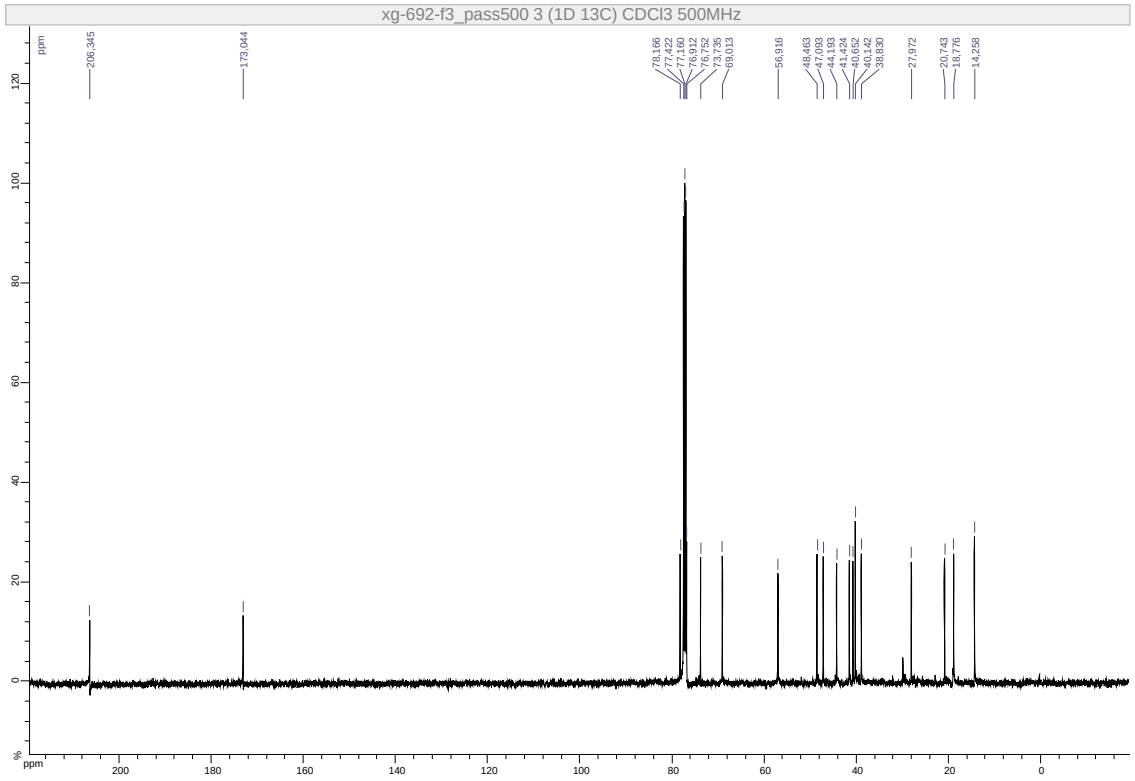
20, ^{1}H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (125.5 MHz, $CDCl_3$)



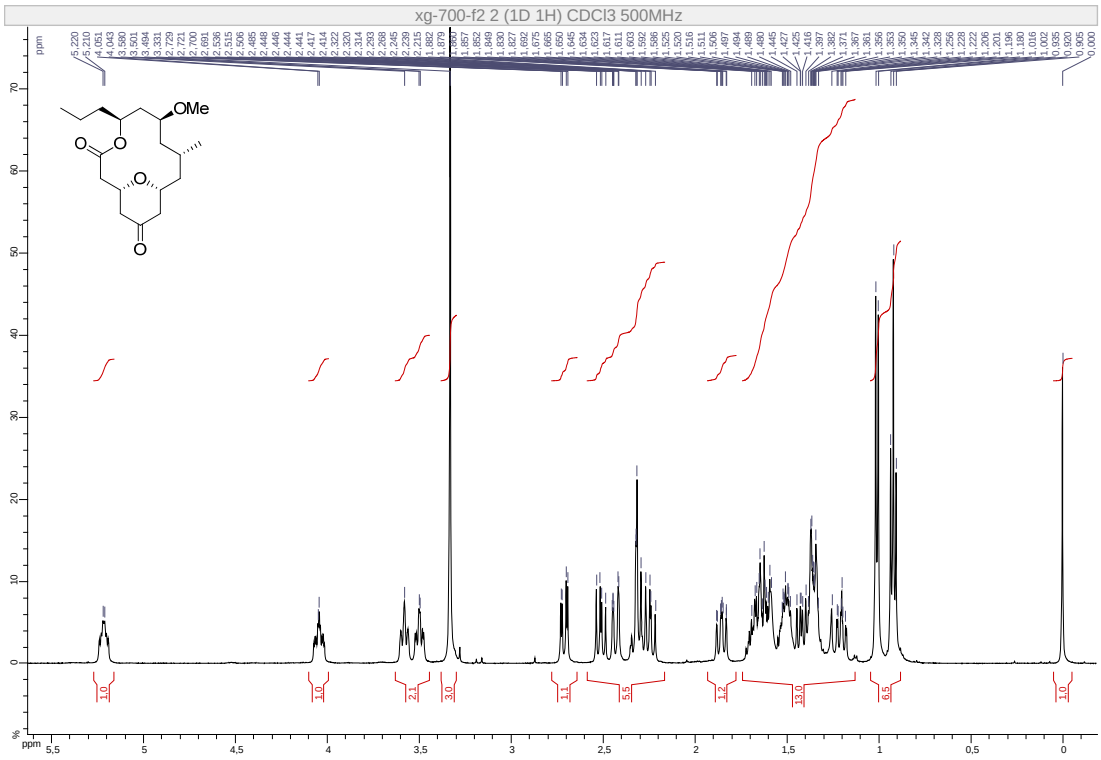


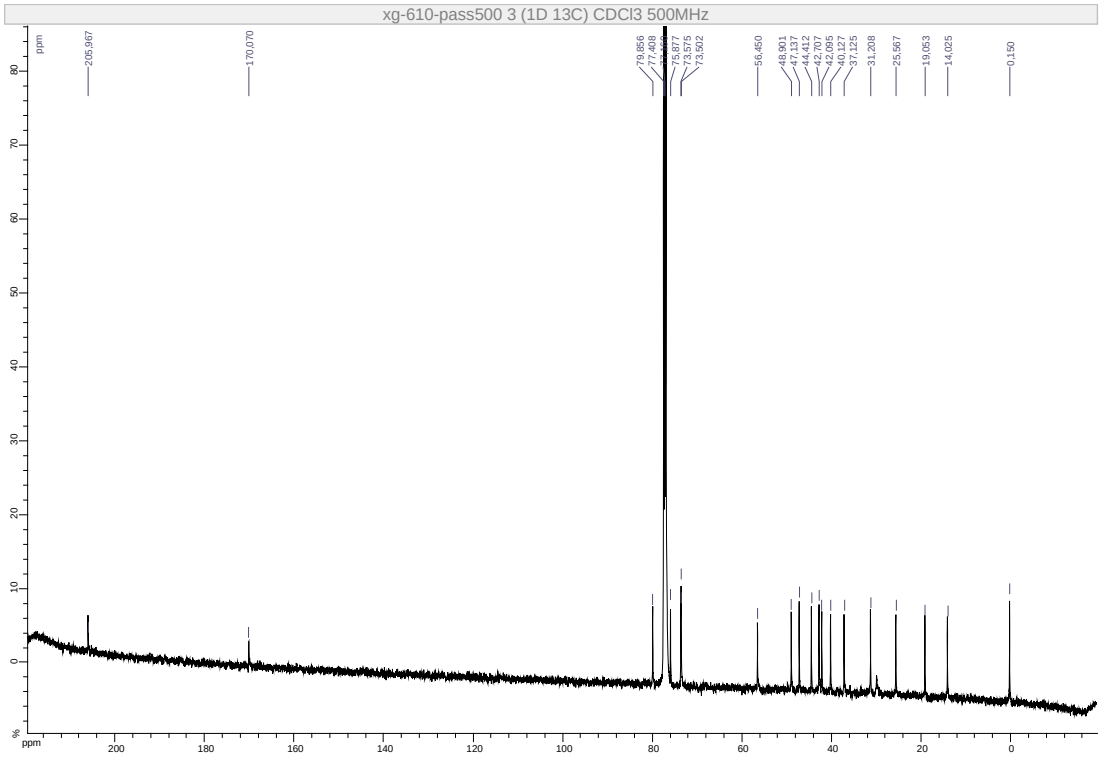
21, ^{1}H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (125.5 MHz, $CDCl_3$)



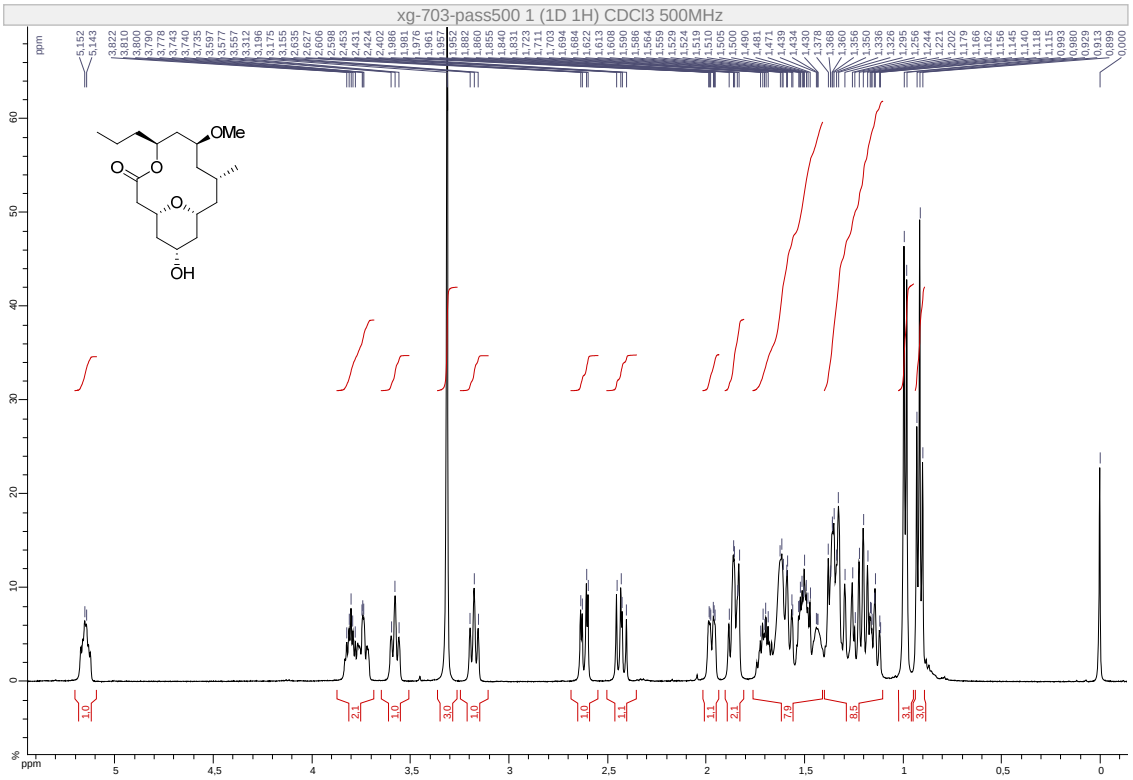


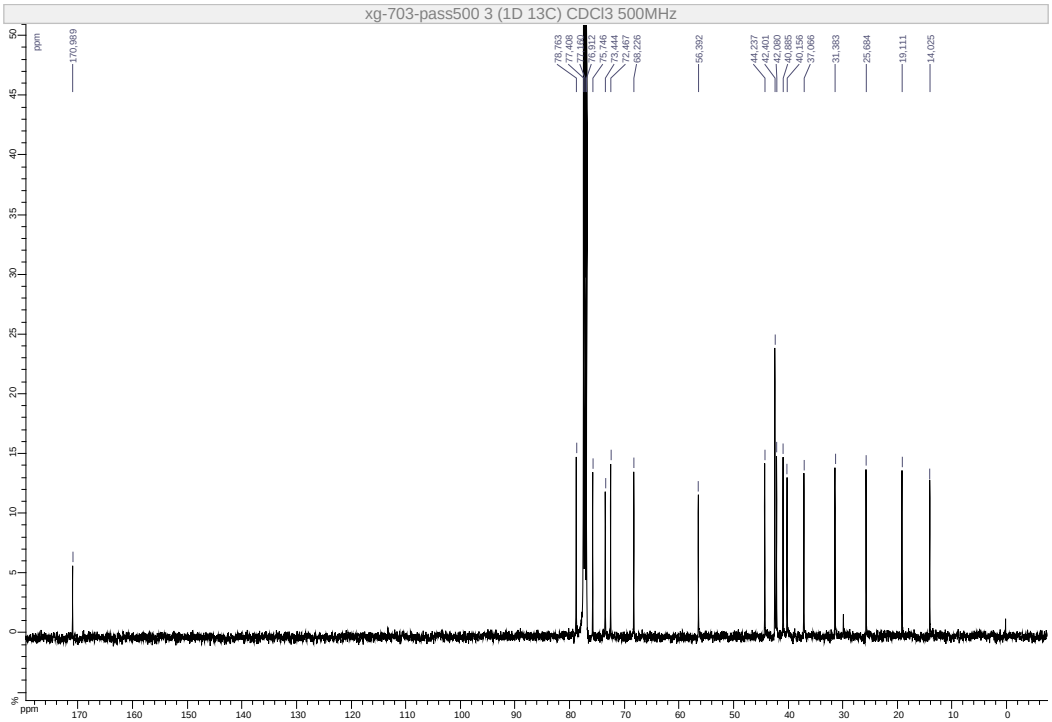
22, ^{1}H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (125.5 MHz, $CDCl_3$)

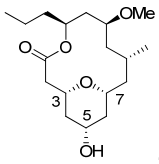




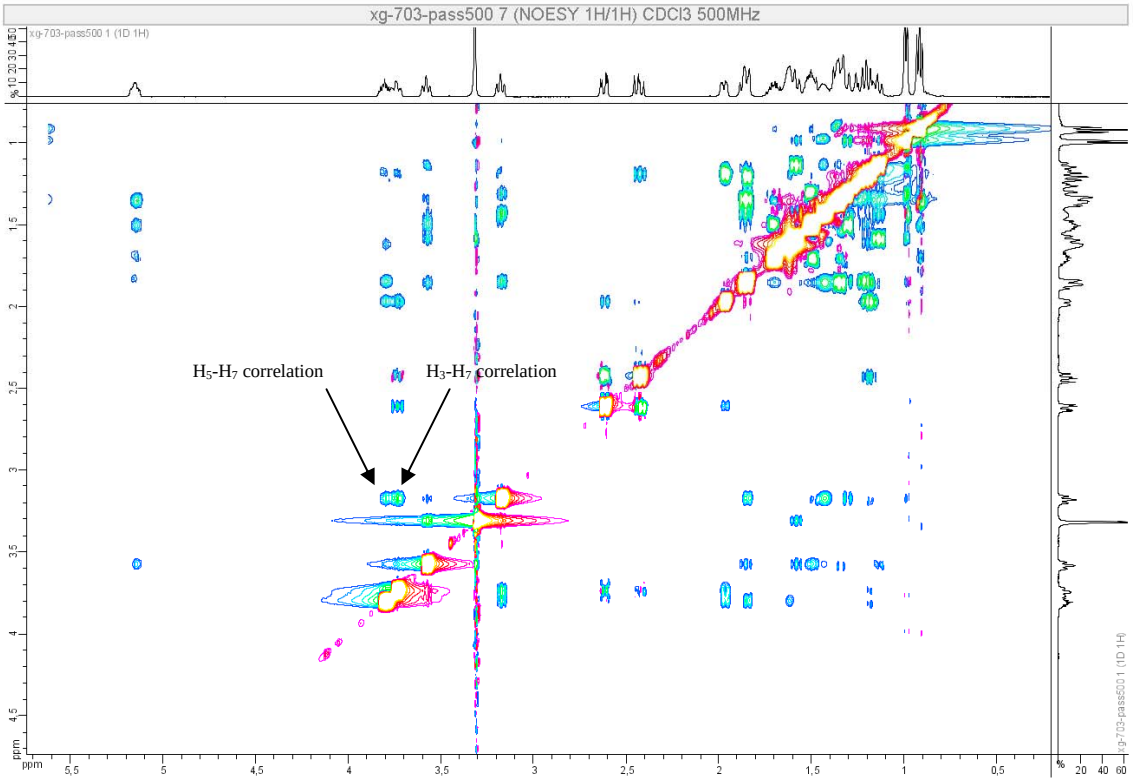
23, ^{1}H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (125.5 MHz, $CDCl_3$)



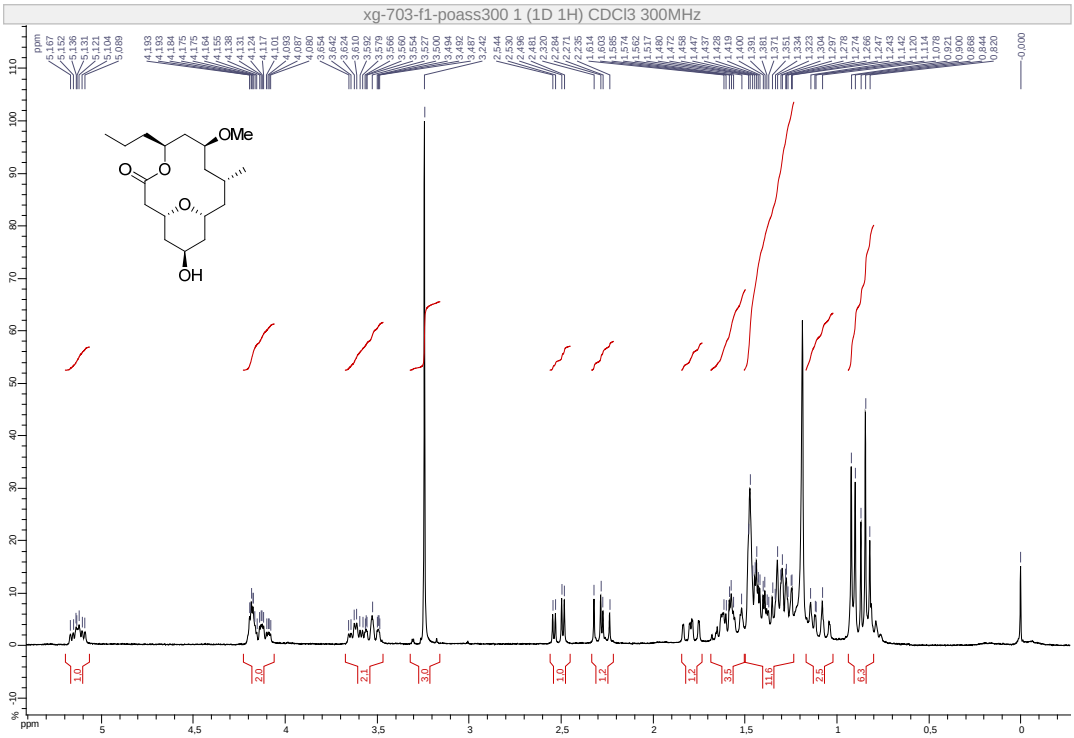


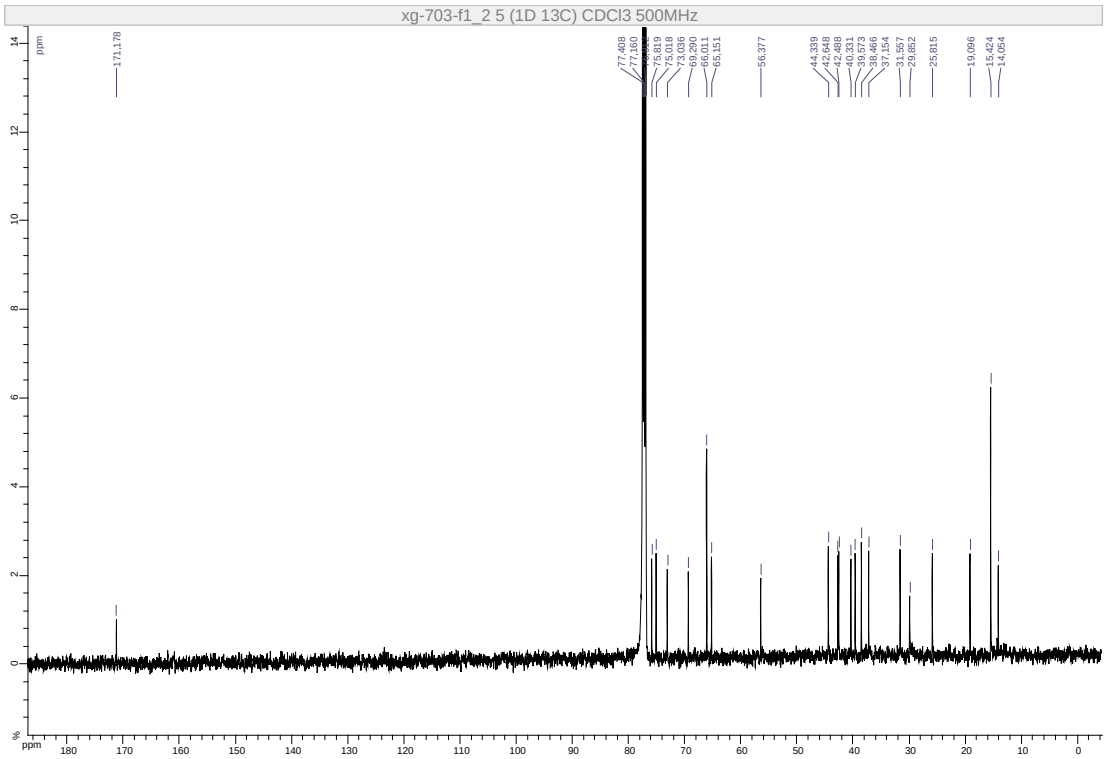


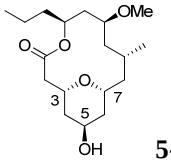
23, $^{1}H/^{1}H$ NOESY NMR (500 MHz, $CDCl_3$)



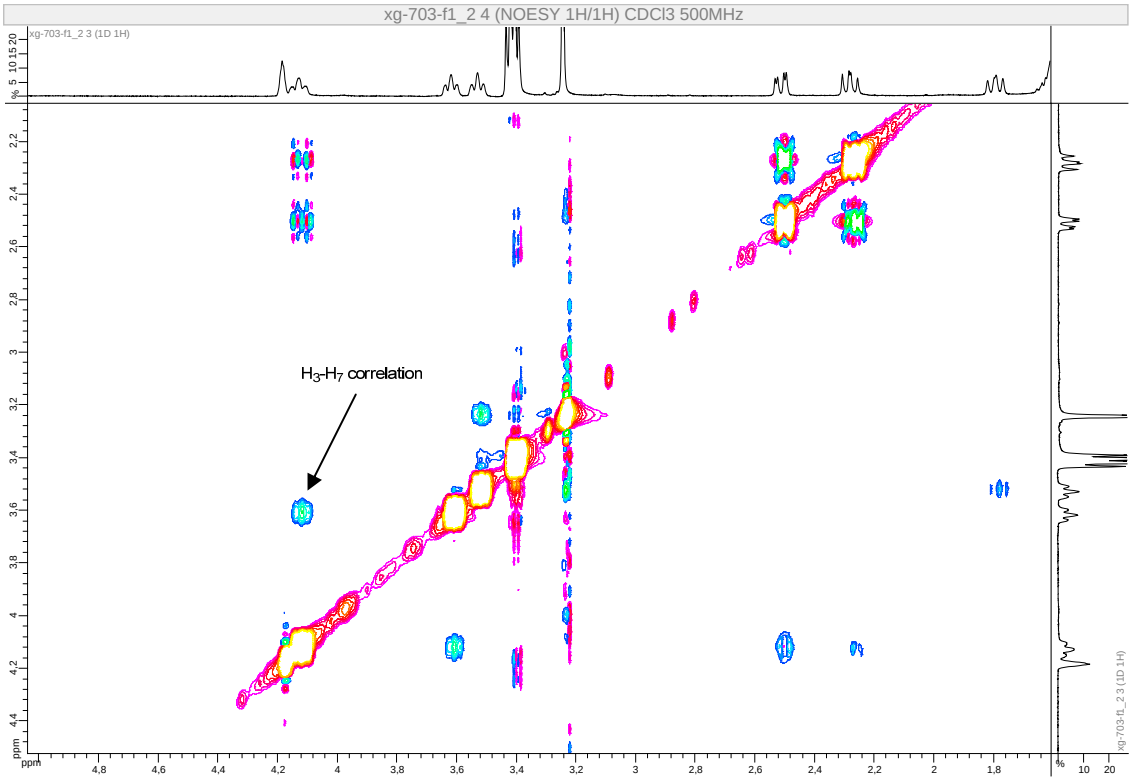
5-*epi*-23, ^{1}H NMR (300 MHz, $CDCl_3$) and ^{13}C NMR (125.5 MHz, $CDCl_3$)



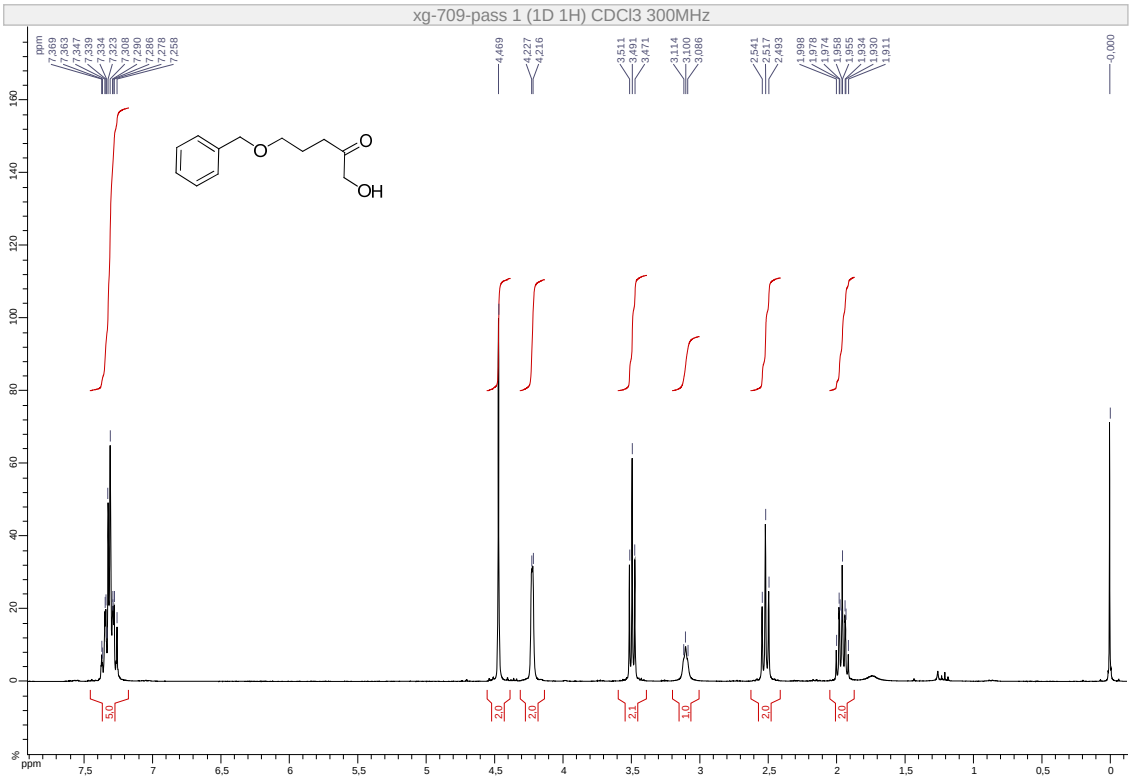


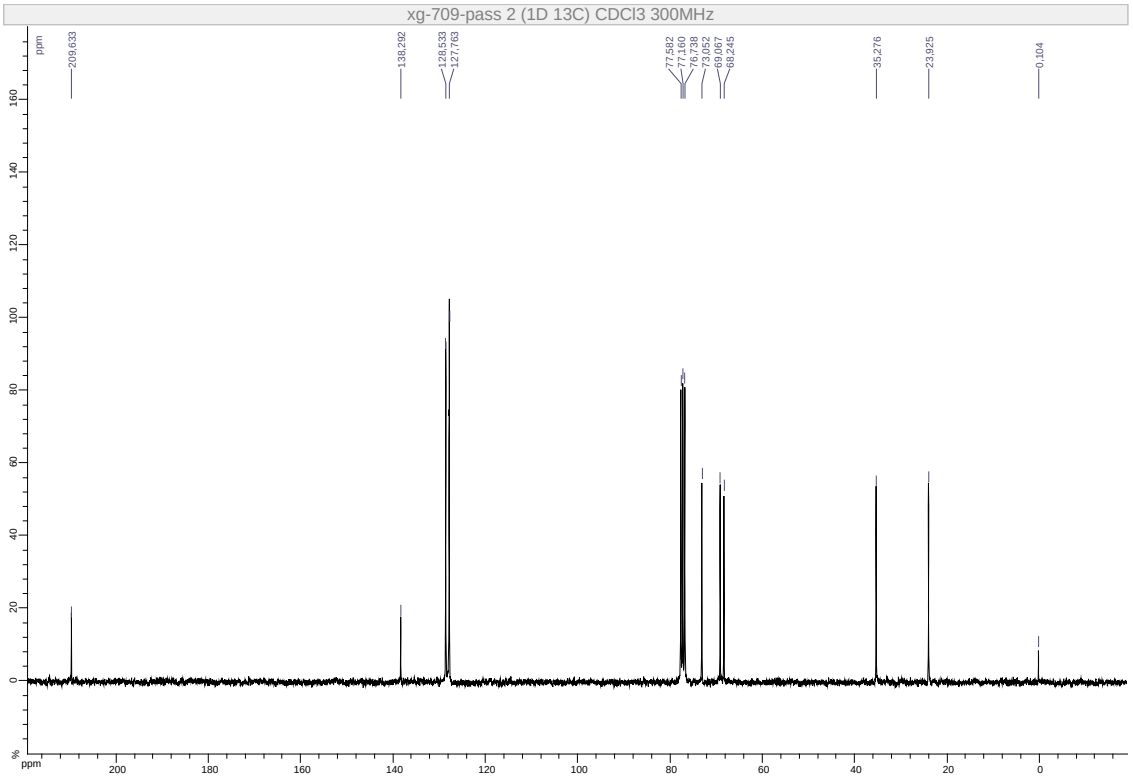


5-*epi*-23, $^{1}H/^{1}H$ NOESY NMR (500 MHz, $CDCl_3$)

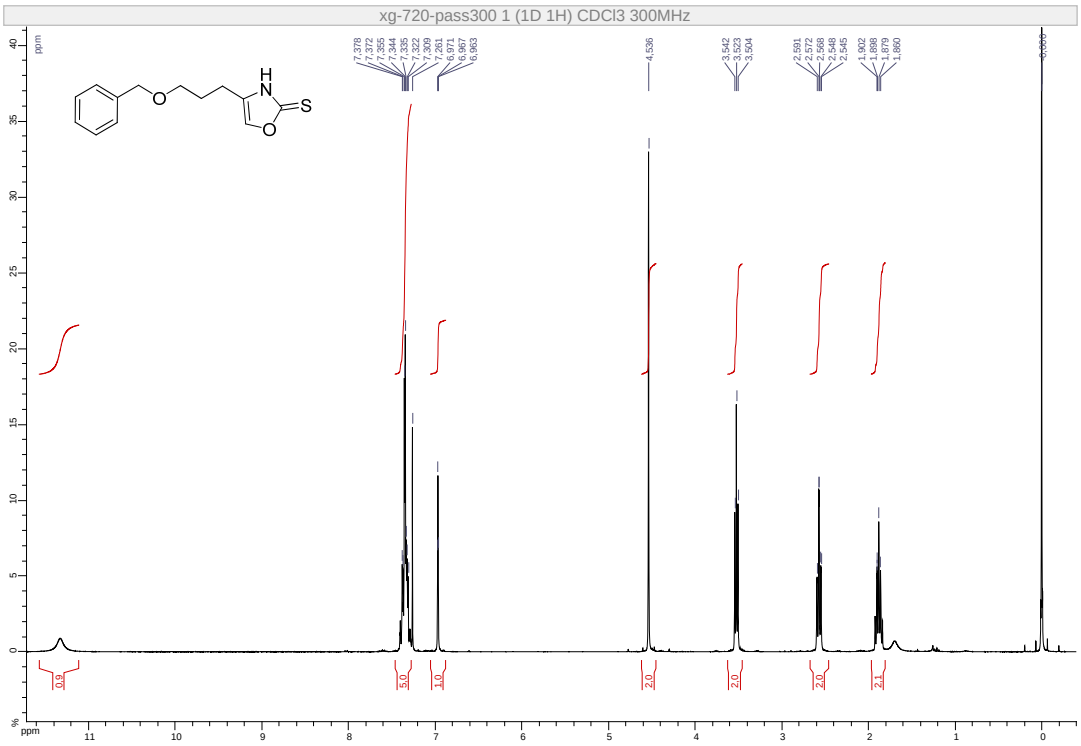


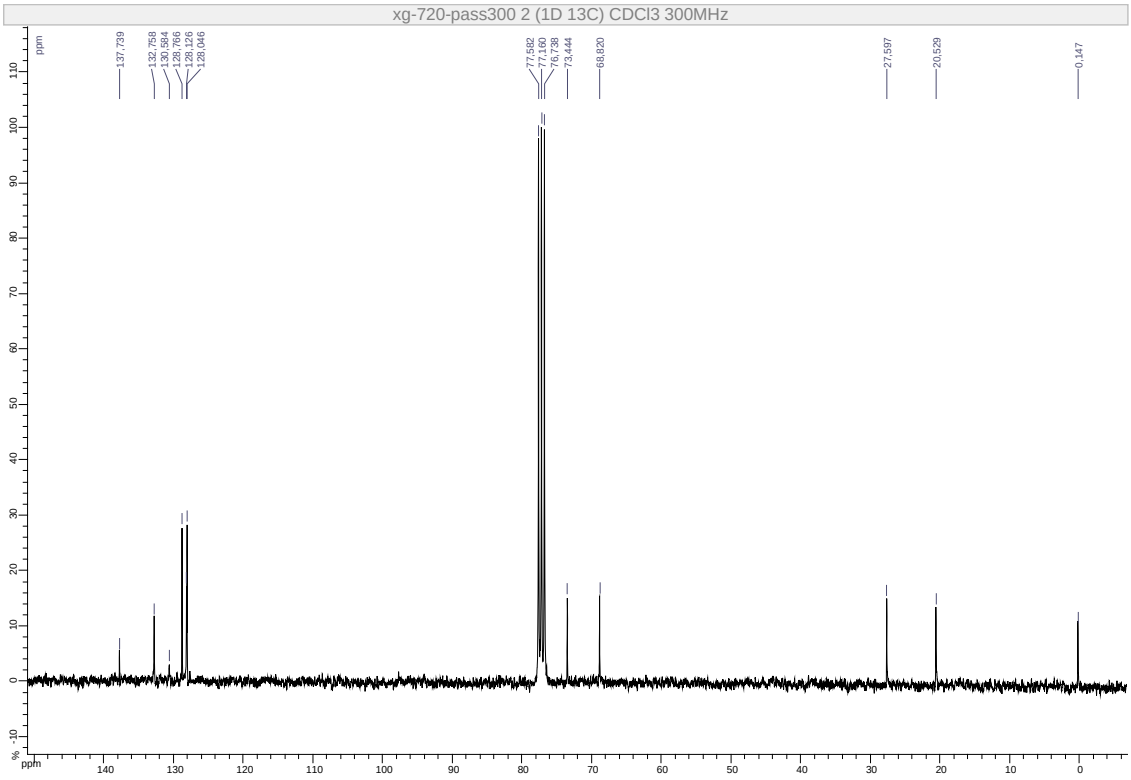
24, ^{1}H NMR (300 MHz, $CDCl_3$) and ^{13}C NMR (75.5 MHz, $CDCl_3$)



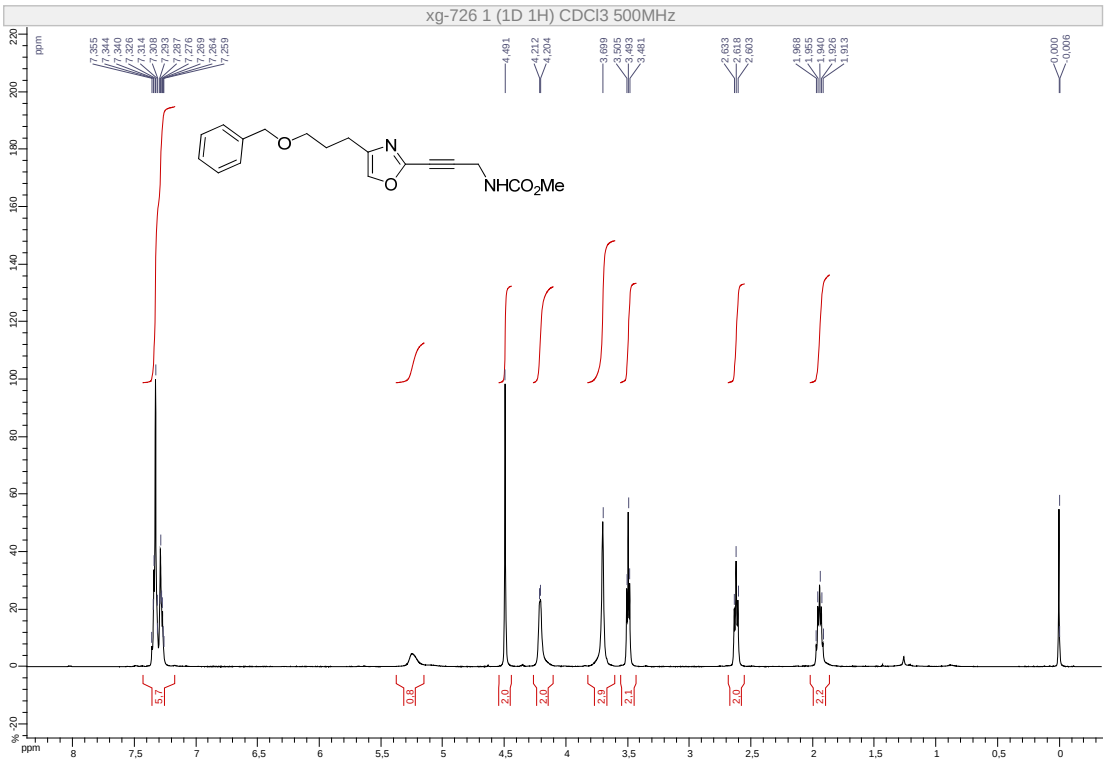


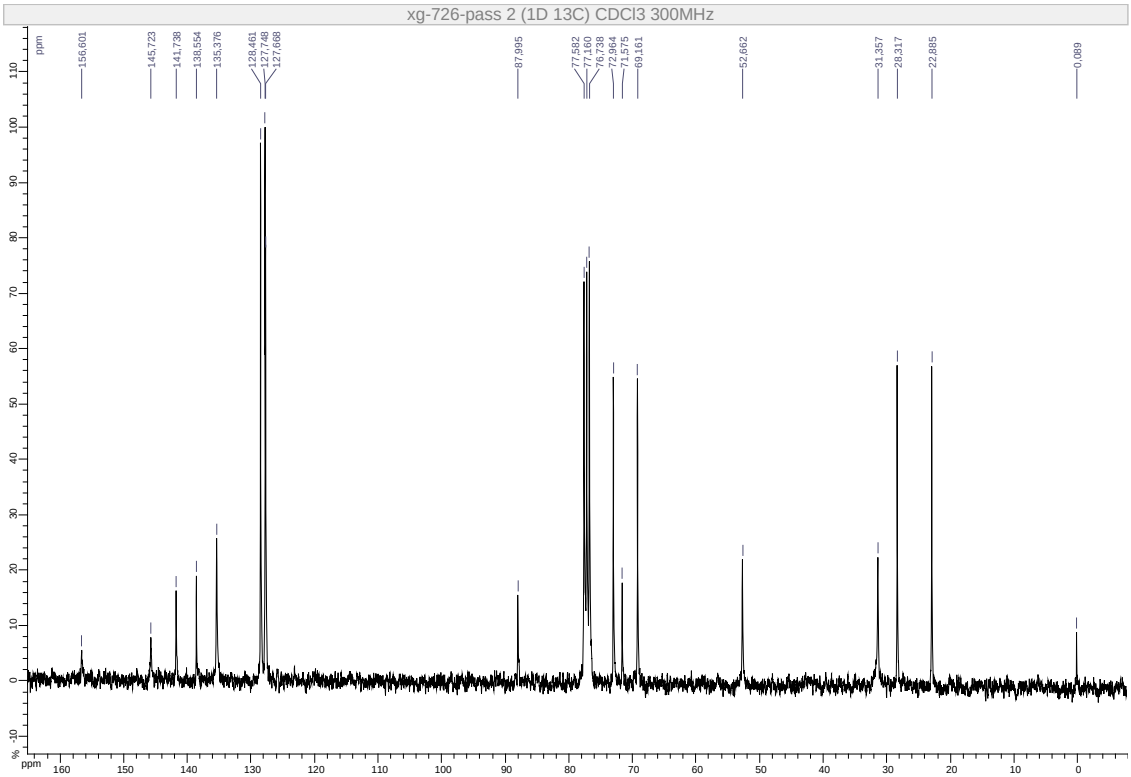
3, ^{1}H NMR (300 MHz, $CDCl_3$) and ^{13}C NMR (75.5 MHz, $CDCl_3$)



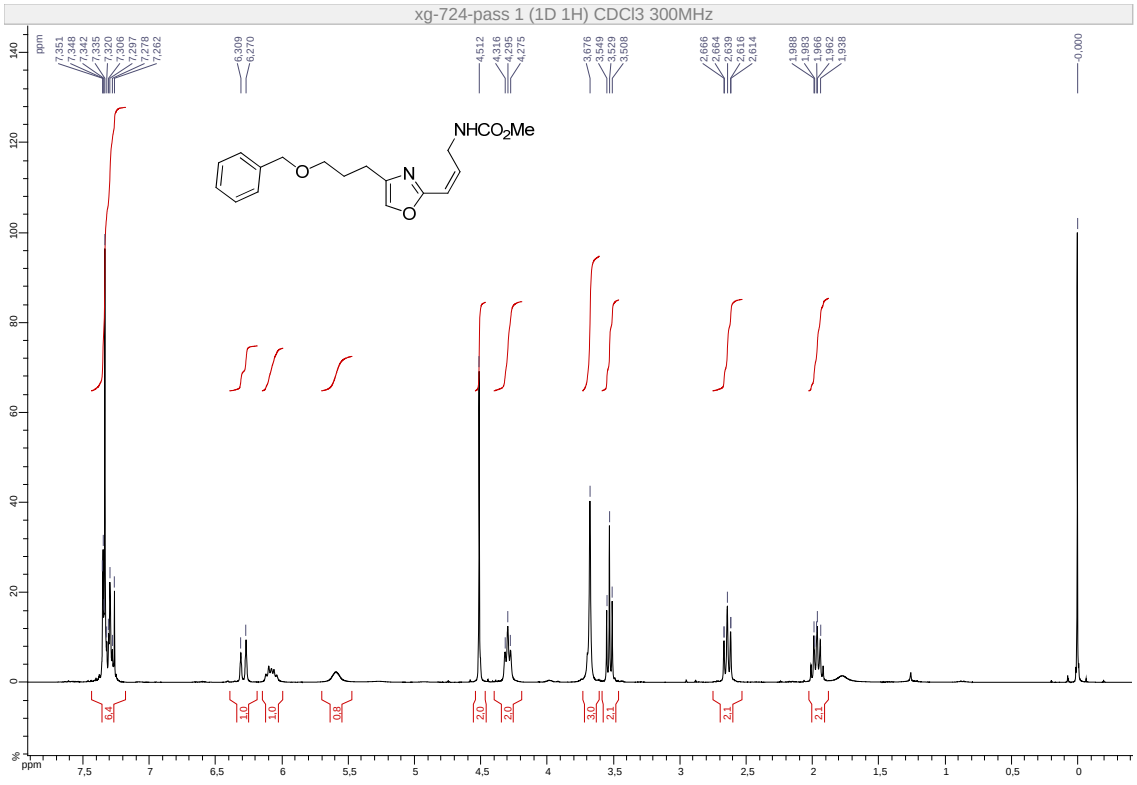


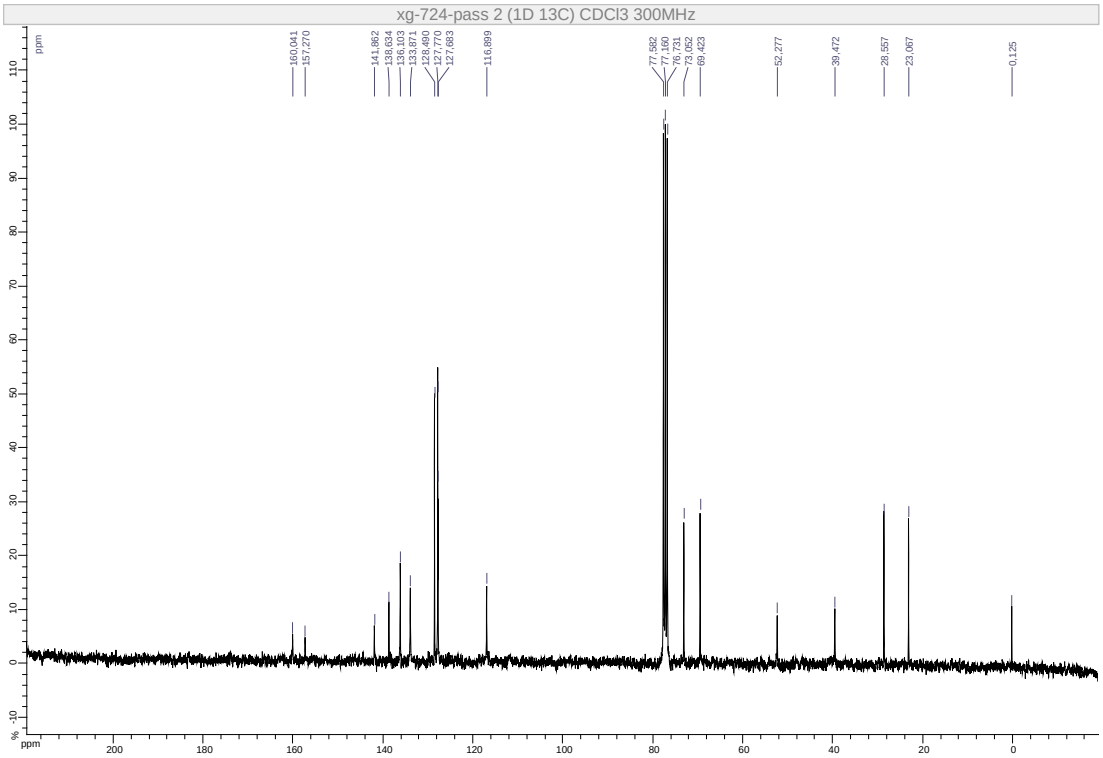
25, ^{1}H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (75.5 MHz, $CDCl_3$)



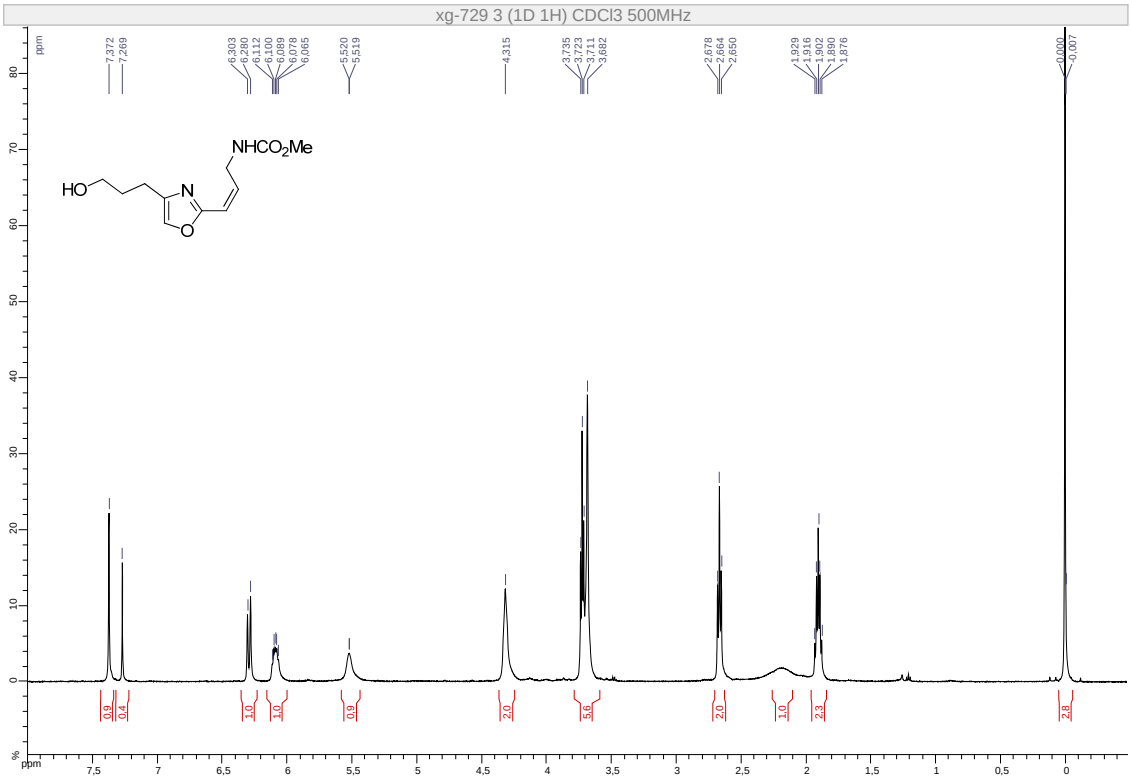


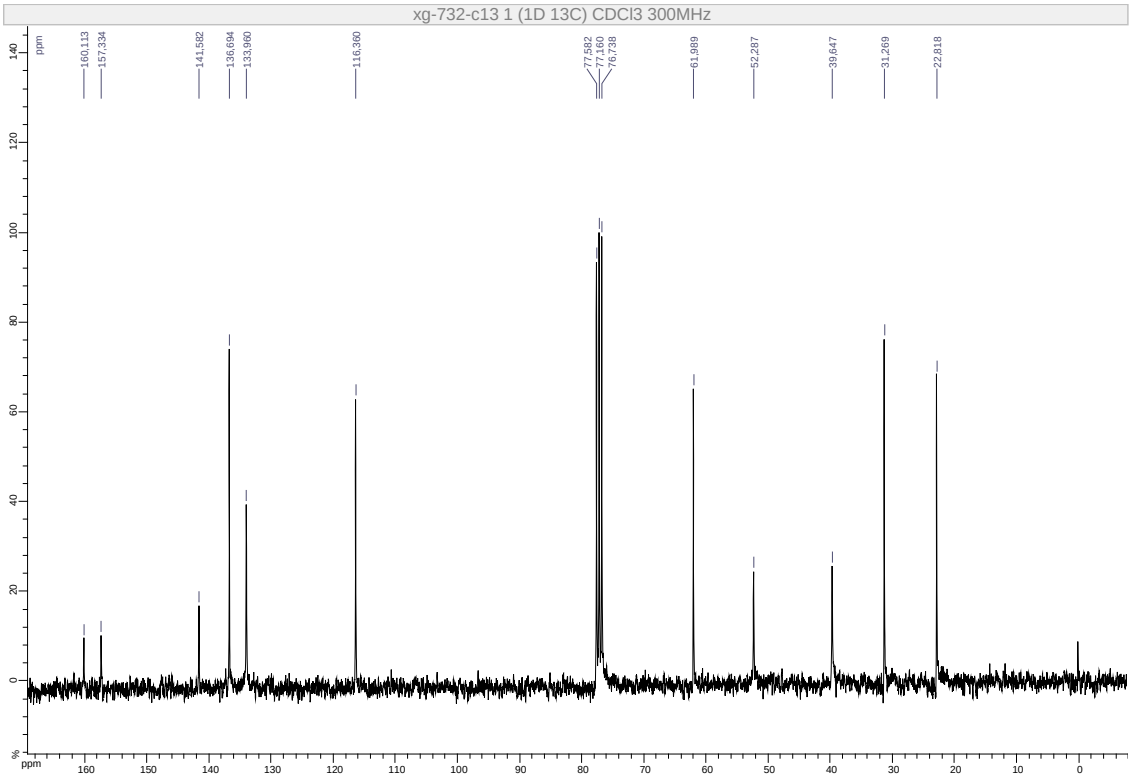
26, ^{1}H NMR (300 MHz, $CDCl_3$) and ^{13}C NMR (75.5 MHz, $CDCl_3$)



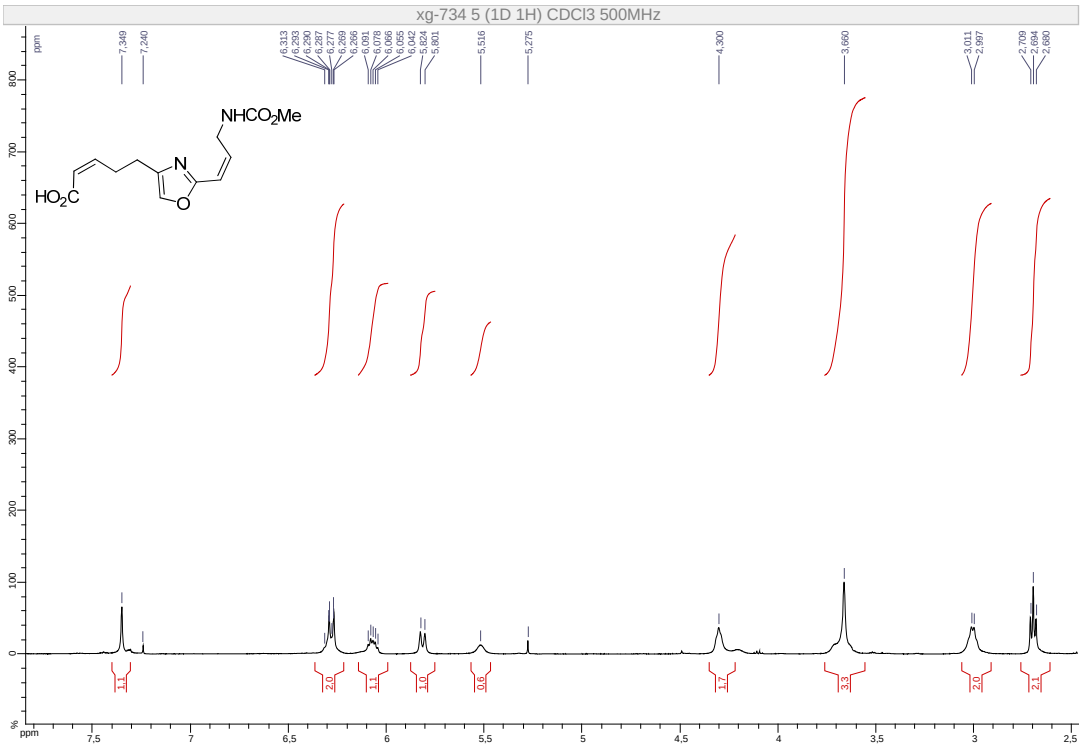


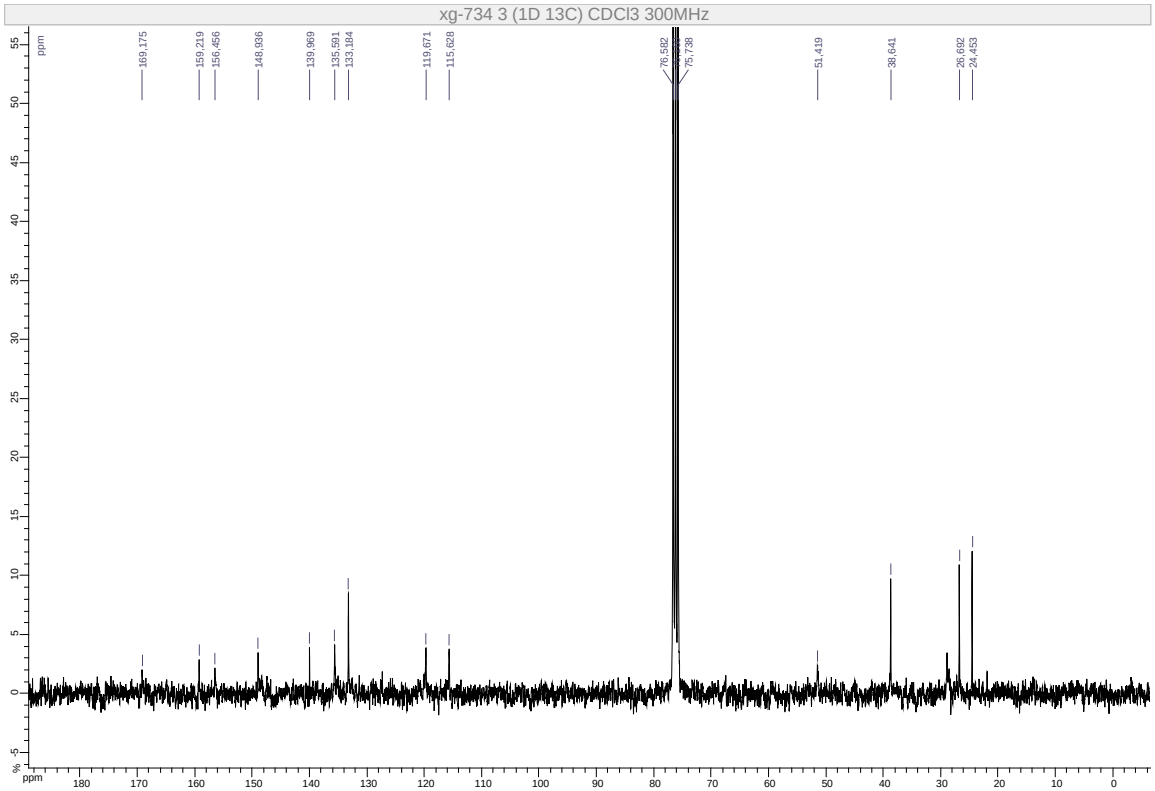
27, ^{1}H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (75.5 MHz, $CDCl_3$)



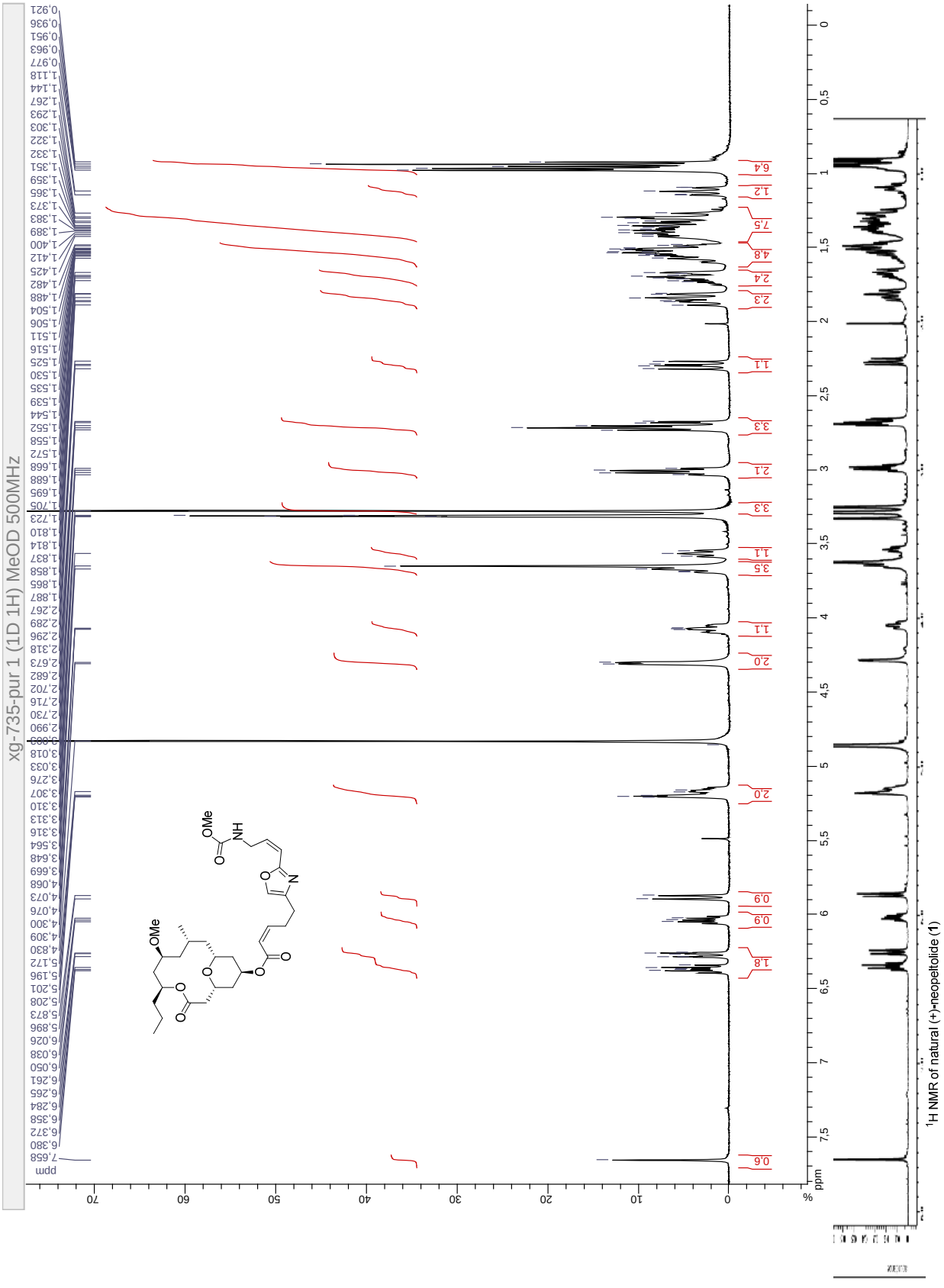


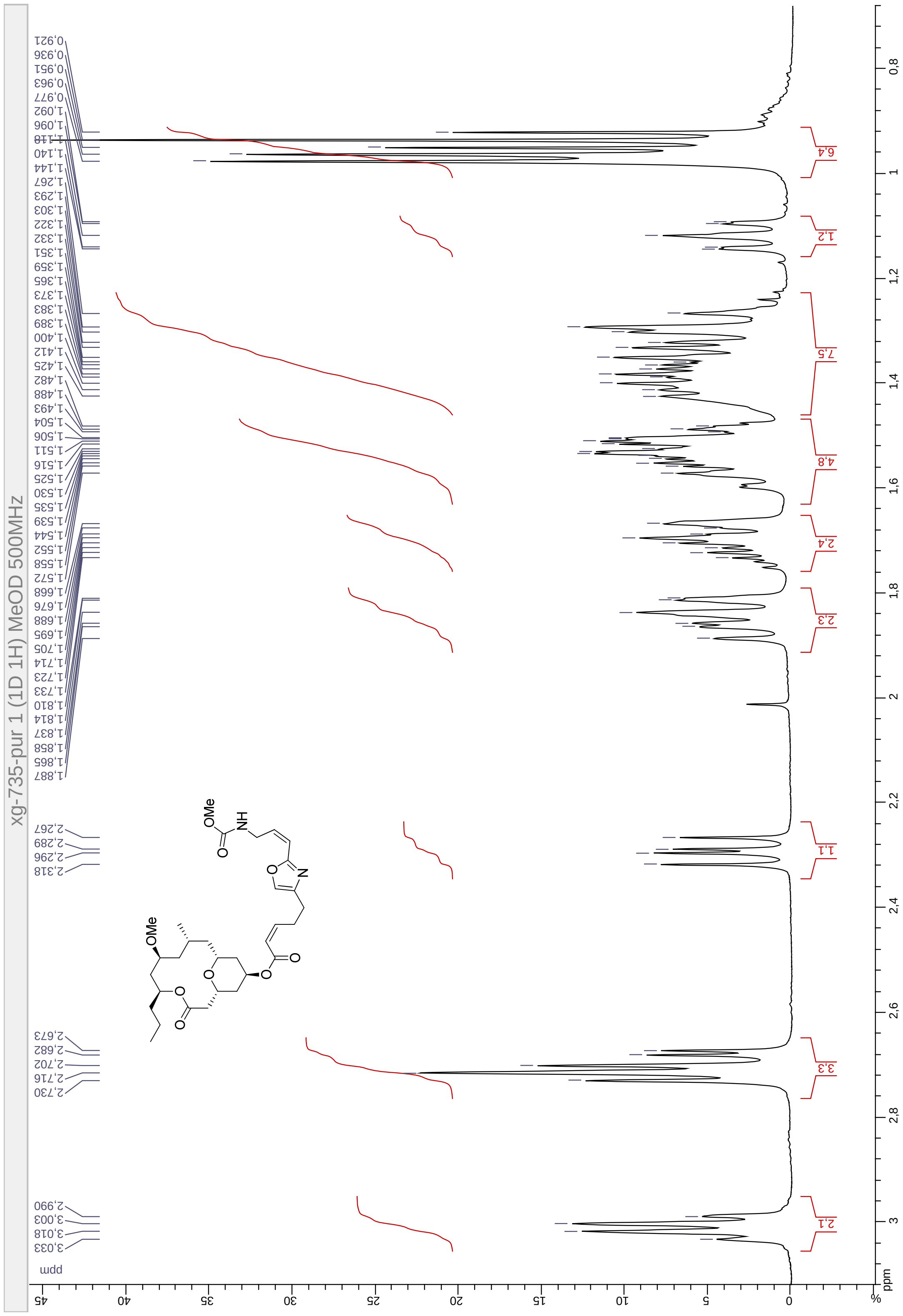
28, ^{1}H NMR (300 MHz, $CDCl_3$) and ^{13}C NMR (75.5 MHz, $CDCl_3$, D_1= 1.2 s)

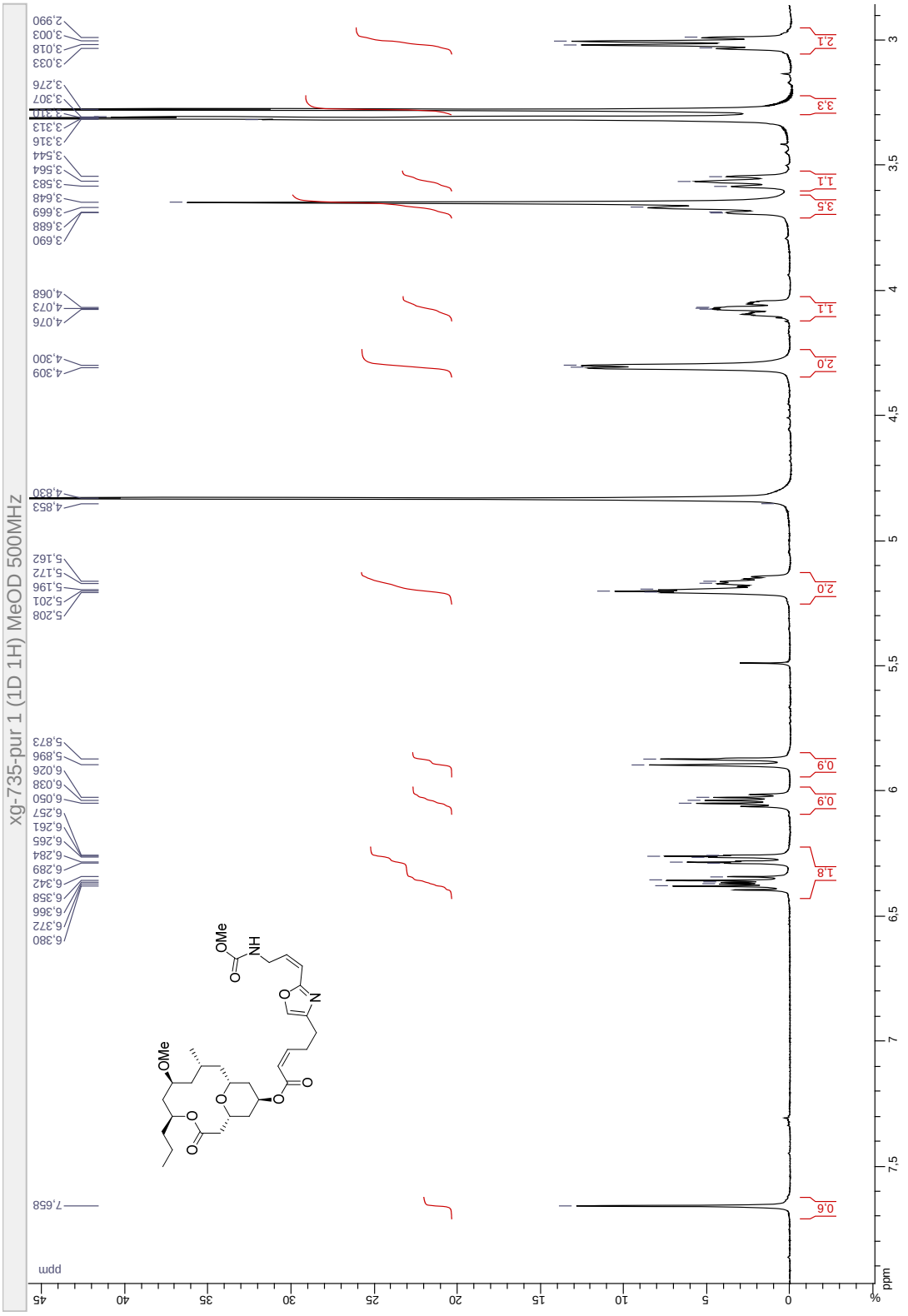




(+)-neopeltolide (**1**), ^{1}H NMR (500 MHz, CD_3OD)




xg-735-pur 1 (1D 1H) MeOD 500MHz


xg-735-pur 1 (1D 1H) MeOD 500MHz
ppm
OMe
NH
OMe
O
N
O

(+)-neopeltolide (**1**), ^{13}C NMR (125 MHz, CD_3OD) and DEPT 135