Supporting Information

Nickel-Catalyzed Regiodivergent Approach to Macrolide Motifs

Abdur-Rafay Shareef, David H. Sherman, John Montgomery**

Life Science Institute and Departments of Chemistry, Medicinal Chemistry, and Microbiology & Immunology, University of Michigan, Ann Arbor, MI, 48109

davidhs@umich.edu; jmontg@umich.edu

Materials and Methods. Unless stated otherwise, all reactions were performed in flame-dried glassware under a nitrogen or argon atmosphere. All solvents were purified under nitrogen using a solvent purification system unless specified (Innovative Technology, Inc., Model # SPS-400-3 and PS-400-3 or MBraun-MB-SPS # 08-113). All other commercially obtained reagents were used as received, unless otherwise stated. $Ni(COD)_2$ (Strem Chemicals, Inc., used as received), potassium *tert*-butoxide (Aldrich), *N*-heterocyclic carbene salt (IMES-HCl), and [(±)-DP-IPr-BF_4], were stored and weighed in an inert atmosphere glovebox. Reaction temperatures were controlled by a JKEM Scientific (Model 210) temperature modulator or IKA RET Control Visc (Serial RS 232 C). Analytical thin-layer chromatography (TLC) was conducted with Kieselgel 60 F254 pre-coated glass plates (0.25 mm) and visualized using a combination of UV (256 nm), *p*-anisaldehyde (20.5 mL, H_2SO_4, 530 mL EtOH, 28.0 mL H_2O, 6.20 mL AcOH, 15.0 mL *p*-anisaldehyde) and $KMnO_4$ (3.00 g $KMnO_4$, 20.0 g K_2CO_3, 5.00 mL 5% NaOH (aq.), 300 mL H_2O). Flash column chromatography was performed using Kieselgel 60 (230-400 mesh) silica gel. ^1H NMR spectra were recorded on a Varian Mercury 400, Varian Inova 500, Varian vnmrs 500, or Varian vnmrs 700, and are reported relative to residual solvent peaks ($CDCl_3$, δ 7.24). Data for ^1H NMR spectra is reported as follows: chemical shift (δ ppm), multiplicity, coupling constant (Hz), and integration. ^{13}C NMR spectra were recorded on a Varian Inova 400 (at 101 MHz) or Varian vnmrs 500 (at 126 MHz) and are reported relative to residual solvent peaks ($CDCl_3$, δ 77.0). Data for ^{13}C NMR spectra is reported in terms of chemical shift. High-resolution mass spectra (HRMS) were obtained on a VG-70-250-s spectrometer manufactured by Micromass Corp. (Manchester UK) at the University of Michigan Mass Spectrometry Laboratory. Compound names are generated from ChemBioDraw Ultra, Version 12.0.

List of reagents prepared or purified

Ammonia•borane was dried under vacuum for several hours prior to use.

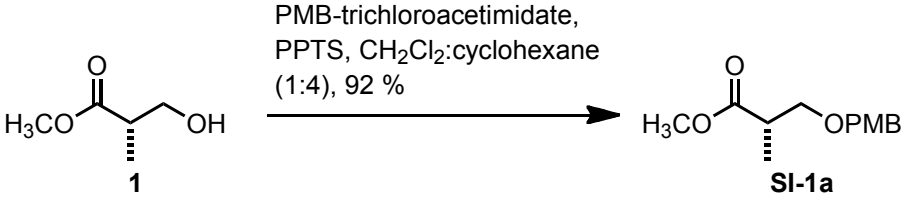
Butyl lithium was titrated with diphenyl acetic acid three times, and the average was taken as molarity.

Dess Martin Periodinane was prepared as described by Schreiber, S.L.[1]

Dibutylboron Trifluoromethanesulfonate was prepared as described by Evans, D.A.[2]

4-(Dimethylamino)pyridine was dried under vacuum prior to use

Diisopropylamine, was distilled over CaH_2.
N,N-Diisopropylethylamine *N*,*N*-Diisopropylethylamine was distilled over CaH_2.
Lithium Chloride was dried under vacuum overnight under oil bath heating at 50°C and flame dried prior to use.
2,6-Lutidine was distilled over CaH_2.
Manganese dioxide was prepared as described by Taylor, R.K.[3]
Propanol was distilled from drierite (no indicator)
Pseudoephedrinepropionamide were prepared as described by Myers, A.G.[4]
Triethylsilane was filtered through a plug of basic alumina and degassed.
tert-Butyldimethylsilyl trifluoromethanesulfonate was distilled at 60°C, at 0.993 mmHg.

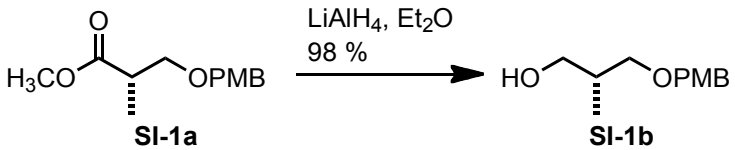


1 **SI-1a**

(S)-methyl 3-((4-methoxybenzyl)oxy)-2-methylpropanoate

To a stirred solution of NaH (0.24 g, 0.010 mmol) in MTBE (75 mL) was added PMB-OH (12 mL, 101. mmol) (neat and dropwise) and stirred at rt for 90 min. Subsequently re-cooled to 0°C, and trichloroacetonitrile (10.2 mL, 101.6 mmol) was added dropwise. The reaction was stirred for 90 min at 0°C, and 30 min at rt. Solvents were removed under reduced pressure. To the resulting crude mixture, a solution of 0.5 mL of MeOH in 250 mL of hexanes was added slowly. Filtered through Celite, solvents were removed under reduced pressure, and used directly without further purification.

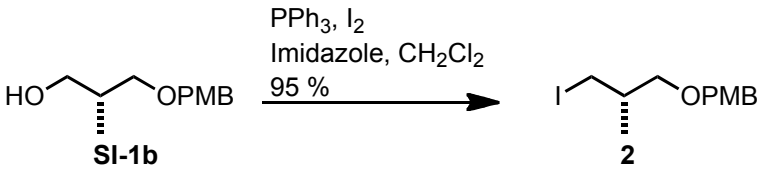
1 (8.0 g, 68 mmol) was dissolved in 100 mL of cyclohexane, and PPTS (1.7 g, 6.8 mmol) was added at rt. Imidate prepared in previous step was dissolved in CH_2Cl_2 (25 mL) and added via cannula. The resulting solution was stirred overnight, and TLC indicated an incomplete reaction; therefore, additional PPTS (1.7 g, 6.8 mmol) was added and stirred for 12 h. An additional portion of PPTS was added (1.7 g, 6.8 mmol) and stirred for 2 h. TLC indicated completion, and crude reaction mixture was filtered through Celite:Silica gel bed with 1:5 EtOAc:hexanes, and concentrated under reduced pressure. The residue was purified by flash chromatography (1:20 EtOAc:hexanes) to afford the title compound (15 g, 92 %) as a colorless oil. Matched all data as previously reported by Boger and colleagues[5], please see page **16** for ^{1}H and ^{13}C spectrum.



SI-1a **SI-1b**

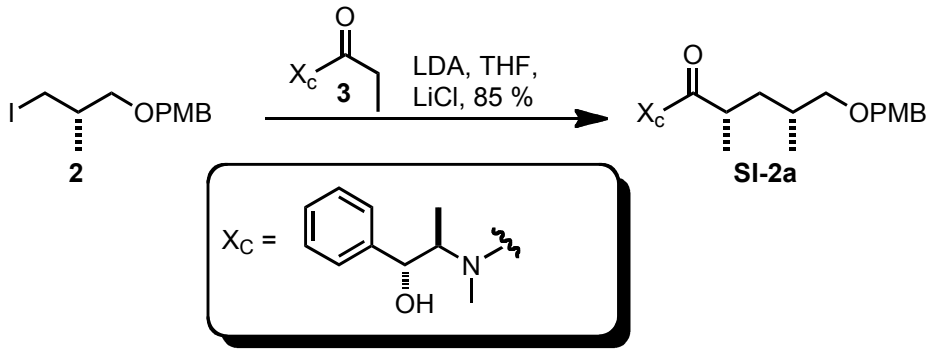
(S)-3-((4-methoxybenzyl)oxy)-2-methylpropan-1-ol

To a suspension of $LAlH_4$ (4.0 g, 0.11 mol) in Et_2O (50 mL) at 0°C was added a solution of **SI-1a** (10 g, 44 mmol) in Et_2O (50 mL) via cannula. The resulting solution was warmed to rt, and stirred for 18 h. The solution was cooled to 0°C, and reaction was terminated by slow addition of H_2O (25 mL), followed by 1N NaOH (25 mL), during which grey $LiAlH_4$ was converted into white $Al(OH)_3$, and removed via filtration, washed with Et_2O (~300 mL), H_2O (100 mL) was added, and extracted with EtO_2, dried with $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash chromatography (2.5:10 EtOAc:hexanes) to afford the title compound (7.83 g, 98 %) as a colorless oil. Matched all data as previously reported by Boger and colleagues[5], please see page **17** for ^1H and ^{13}C spectrum.



(S)-1-((3-iodo-2-methylpropoxy)methyl)-4-methoxybenzene

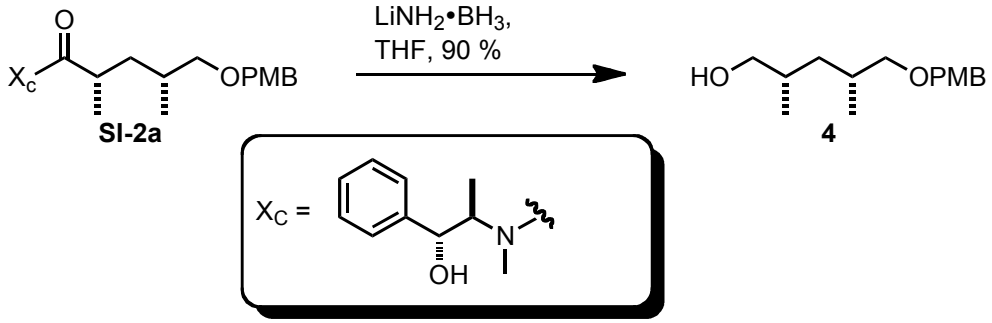
To a stirred solution of **SI-1b** (5.4 g, 30 mmol) in CH_2Cl_2 (150 mL) was added imidazole (5.1 g, 75 mmol), PPh_3 (20 g, 75 mmol), and I_2 (15 g, 60 mmol) at 0°C, and stirred for 10 minutes, allowed to warm to rt, and stirred for 6 h. The reaction was terminated by addition of half saturated $Na_2S_2O_3$, extracted with ethyl acetate, washed with water, dried with $MgSO_4$, and concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2 and purified by flash chromatography (1:15 EtOAc:hexanes) to afford the title compound (8.27 g, 95 %) as a colorless oil. Matched all data as previously reported by Carter and colleagues[6], please see page **18** for ^1H and ^{13}C spectrum.



(2S,4R)-5-((4-methoxybenzyl)oxy)-N,2,4-trimethyl-N-((2R,3R)-3-phenylbutan-2-yl)pentanamide

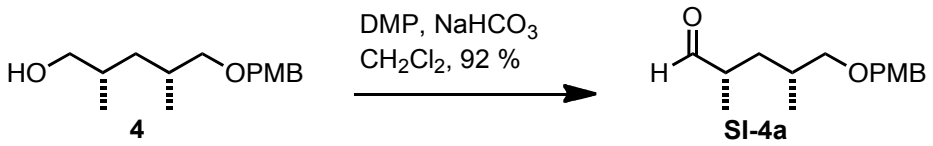
A solution of BuLi (42 mL, 2.5 M) was added to LiCl (11 g, 0.27 mol) and *i*-pr_2NH (15 mL, 0.11 mol in THF (10 mL) at -78°C. The resulting solution was warmed to 0°C, and stirred for 15 min, re-cooled to -78°C to which an ice cooled solution of **3** (12 g, 53 mmol) in THF (50 mL) was added via cannula (slowly dripped down side of flask). The mixture was stirred for 1 h at -78°C, 0°C for 15 min, rt for 5 min; after which the flask is

re-cooled to 0°C. A solution of **2** (7.7 g, 26 mmol) in THF (10 mL) is added via cannula, stirred for 30 min at 0°C, warmed to rt and stirred for 18 h. The flask was cooled to 0°C and half saturated ammonium chloride was added, extracted with ethyl acetate, washed with water, dried with $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash chromatography (gradient elution from 1:5 EtOAc:hexanes to 2:3 EtOAc:hexanes) to afford the title compound (9.4 g, 85 %) as a colorless oil. Matched all data as previously reported by Carter and colleagues,[6] please see page **19** for ^{1}H and ^{13}C spectrum.



(2S,4R)-5-((4-methoxybenzyl)oxy)-2,4-dimethylpentan-1-ol

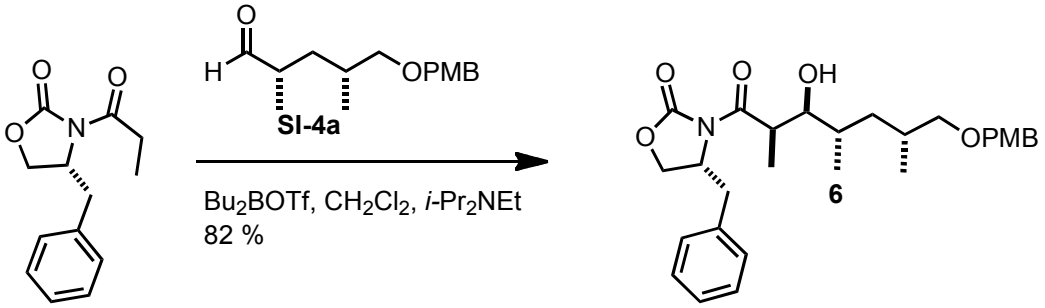
A solution of BuLi (17 mL, 2.5M) was added to a stirred solution of THF (5 mL) and *i*-pr_2NH (6.1 mL, 44 mmol) at -78°C, and stirred at -78°C for 10 min, 0°C for 5 min, and re-cooled to -78°C. A separate flask was charged with $BH_3•NH_3$ (1.4 g, 44 mmol) and cooled to -78°C, and previously prepared solution of LDA was added via cannula. The resulting solution was warmed to 0°C and stirred for 20 min. The cooling bath was removed, and resulting solution was warmed to rt, and stirred for 20 min during which the solution became easy to stir, and was re-cooled to 0°C, and **SI-2a** (4.5 g, 11 mmol) in THF (25 mL) was added via cannula, stirred for 20 minutes at 0°C, the cooling bath was removed and stirred at rt for 2 h. The reaction was terminated by addition of 3N HCl (added slowly), extracted with EtOAc, washed combined organic extracts with 2N NaOH, water, dried with MgSO4, and concentrated under reduced pressure. The residue was purified by flash chromatography (1:5 EtOAc:hexanes) to afford the title compound (2.5 g, 90 %) as a colorless oil. Matched all data as previously reported by Sherman and colleagues,[7] please see page **20** for ^{1}H and ^{13}C spectrum.



(2*S*,4*R*)-5-((4-methoxybenzyl)oxy)-2,4-dimethylpentanal

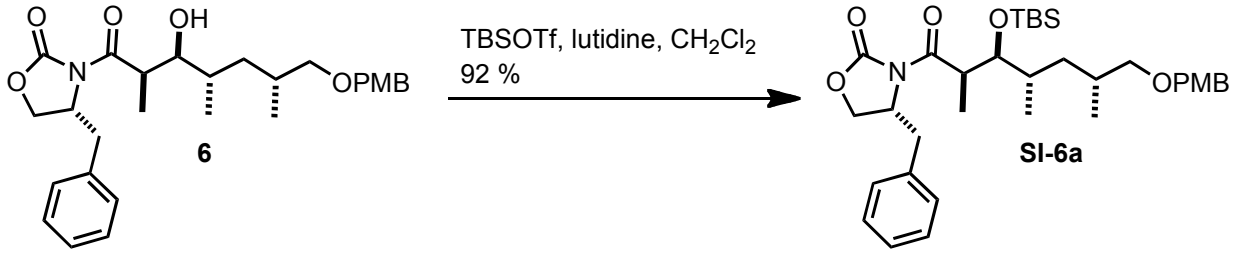
A solution of **4** (1.4 g, 5.6 mmol) and $NaHCO_3$ (2.4 g, 29 mmol) in CH_2Cl_2 (70 mL, non anhydrous) was cooled to 0 °C, and DMP (3.0 g, 8.4 mmol) was added slowly and stirred for 3 h. The reaction was terminated by addition of a 1:1 solution of half-saturated aqueous $Na_2S_2O_3$ and half-saturated aqueous $NaHCO_3$ and vigorously stirred

for 0.5 h, extracted with CH_2Cl_2, washed with half-saturated aqueous $NaHCO_3$, half-saturated NaCl, water, dried with $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash chromatography (1:5 EtOAc:hexanes) to afford the title compound (1.3 g, 92 %) as a colorless oil. Matched all data as previously reported by Kang and colleagues,[8] please see page **21** for ^1H and ^{13}C spectrum.



(*R*)-4-benzyl-3-((2*R*,3*S*,4*S*,6*R*)-3-hydroxy-7-((4-methoxybenzyl)oxy)-2,4,6-trimethylheptanoyl)oxazolidin-2-one

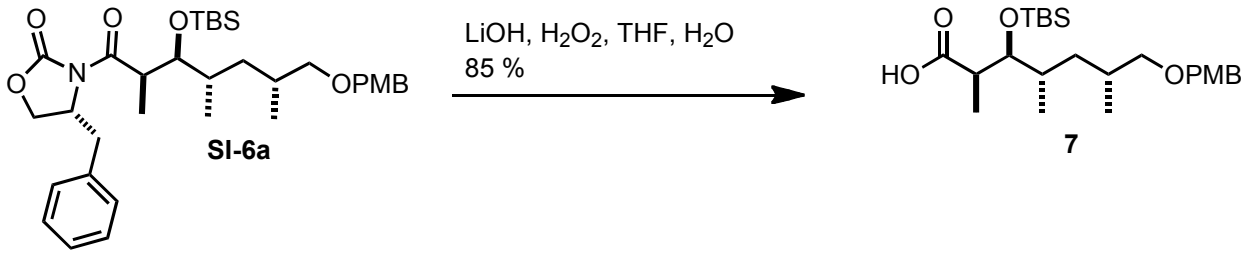
To a solution of **5** (1.6 g, 6.84 mmol) in CH_2Cl_2 (30 mL) at 0 °C, was added neat dibutylboron triflate (2.3 mL, 9.10 mmol), and stirred for 15 min. The solution was cooled to -78 °C, i-Pr_2NEt (1.6 mL, 9.1 mmol) was added drop-wise, stirred for 15 min, warmed to 0 °C, and stirred for 1 h, followed by cooling to -78 °C. An ice-cooled solution of **SI-4a** (1.1 g, 4.6 mmol) in CH_2Cl_2 (5 mL) was added drop-wise (dripped down side of flask). The solution was stirred at -78 °C for 2 h, at -20 °C for 1 h, and was terminated by addition of pH = 7 phosphate buffer. To this cloudy solution was added 50 mL of (1:3) 30% hydrogen peroxide:MeOH solution, the reaction vessel was removed from cooling bath and stirred for 3 h at rt, extracted with CH_2Cl_2, washed with half-saturated NaCl solution, water, dried with $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash chromatography (3.5:10 EtOAc:hexanes) to afford the title compound (1.8 g, 82 %) as a colorless oil. Matched data as previously reported by Kang and colleagues,[8] please see page **22** for ^1H and ^{13}C spectrum.



(*R*)-4-benzyl-3-((2*R*,3*S*,4*S*,6*R*)-3-((*tert*-butyldimethylsilyl)oxy)-7-((4-methoxybenzyl)oxy)-2,4,6-trimethylheptanoyl)oxazolidin-2-one

To a solution of **6** (1.5 g, 3.1 mmol) in CH_2Cl_2 (40 mL) at 0 °C was added 2,6-lutidine (0.69 mL, 5.9 mmol) and TBSOTf (1.1 mL, 4.7 mmol). The reaction mixture was stirred at 0 °C for 4 h, terminated by addition of half-saturated aqueous $NaHCO_3$, and allowed

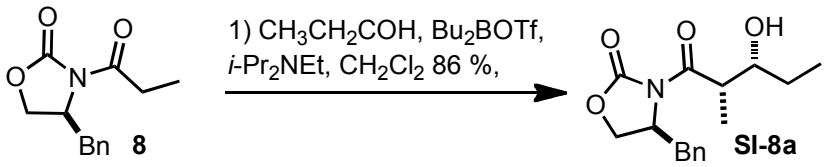
to warm to rt. Extracted with CH_2Cl_2, washed with half-saturated aqueous $NaHCO_3$, half-saturated NaCl solution, water, dried with $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash chromatography (1:10 EtOAc:hexanes) to afford the title compound (1.7 g, 92 %) as a colorless oil. Matched data as previously reported by Kang and colleagues,[8] please see page **23** for ^1H and ^{13}C spectrum.



SI-6a **7**

(2*R*,3*S*,4*S*,6*R*)-3-((*tert*-butyldimethylsilyl)oxy)-7-((4-methoxybenzyl)oxy)-2,4,6-trimethylheptanoic acid

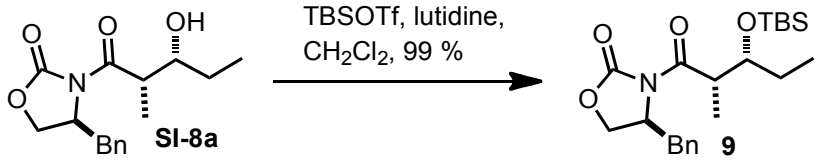
To a solution of **SI-6c** (0.71 g, 1.2 mmol) in (4:1) THF:water (2 mL) to was added 30% H_2O_2 (600 μL) and 0.8M LiOH (0.08 g, 1.9 mmol) at 0 °C and stirred for 5 h, quenched by adding aqueous Na_2SO_3 (1.3 M, 3 mL) and half-saturated aqueous NH_4Cl (4 mL). Extracted with ethyl acetate, dried with $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash chromatography (2.5:10 EtOAc:hexanes) to afford the title compound (0.44 g, 85 %) as a colorless oil. Matched data as previously reported by Kang and colleagues,[8] please see page **24** for ^1H and ^{13}C spectrum.



SI-8a

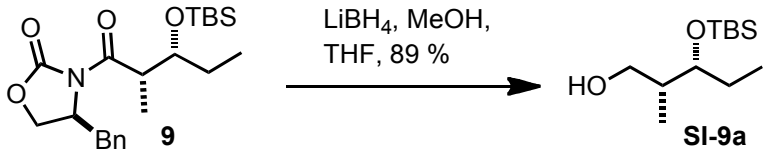
(S)-4-benzyl-3-((2S,3R)-3-hydroxy-2-methylpentanoyl)oxazolidin-2-one

To a solution of **8** (12 g, 52 mmol) in CH_2Cl_2 (75 mL) at 0°C was added Bu_2BOTf (20 mL, 78 mmol), and stirred for 5 min, followed by slow addition of *i*-Pr_2NEt (18 mL, 0.10 mol). The resulting mixture was stirred at 0°C for 30 min followed by cooling to -78°C. A solution of propanal (7.6 mL, 0.10 mol) in CH_2Cl_2 (5 mL) was added slowly (dripped down side of flask), and stirred at -78°C for 30 min, and 1 h at 0°C. Reaction was terminated by addition of pH = 7 phosphate buffer, followed by slow addition of a 30% H_2O_2:MeOH (1:3, 40 mL), and stirred at rt for 3 h, extracted with ethyl acetate, washed with half-saturated aqueous NaCl, dried with $MgSO_4$, and solvents were removed under reduced pressure. The crude solid was recrystallized using EtOAc:hexanes (1:2) solvents were removed from mother liquor and the residue was purified by flash chromatography (3:20 EtOAc:hexanes) to afford title compound as a colorless solid, (13 g, 86%). Matched data as reported by Evans and colleagues.[9] Please see page **25** for ^1H and ^{13}C spectrum.



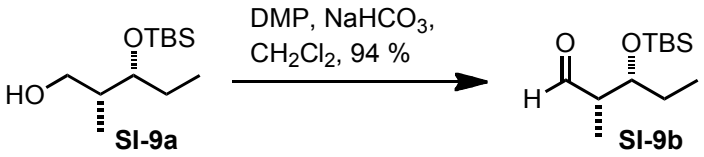
(S)-4-benzyl-3-((2S,3R)-3-((tert-butyldimethylsilyl)oxy)-2-methylpentanoyl)oxazolidin-2-one

To a solution of **SI-8a** (9.2 g, 32 mmol) in CH_2Cl_2 (115 mL) at 0°C was added 2,6-lutidine (7.4 mL, 64 mmol) and TBSOTf (16 mL, 64 mmol). The reaction mixture was stirred at 0°C for 4 h, quenched with half-saturated aqueous $NaHCO_3$, and allowed to warm to rt. Extracted with CH_2Cl_2, washed with half-saturated aqueous $NaHCO_3$, half-saturated NaCl solution, water, dried with $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash chromatography (1:5 EtOAc:hexanes) to afford the title compound (13 g, 99 %) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35-7.21, (m, 5H), 4.60 (ddd, *J* = 3, 6.5, 9.5 Hz, 1H), 4.18-4.14 (m, 2H), 3.96 (app. q, J = 5.5, 11 Hz, 1H), 3.89 (app. q, J = 6.5, 11Hz, 1H), 3.31 (dd, *J* = 3, 13.5 Hz, 1H), 2.77 (dd, *J* = 9.5, 13 Hz, 1H), 1.61-1.53 (m, 2H), 1.21 (d, *J* = 7.0 Hz, 3H), 0.91-0.88 (m, 12H), 0.03 (s, 3H), 0.01 (s, 3H)^{13}C NMR (126 MHz, $CDCl_3$) δ 175.59, 153.27, 135.61, 129.67, 129.15, 127.53, 73.98, 66.19, 56.03, 42.44, 37.82, 28.35, 26.02, 18.26, 11.67, 9.58, -3.94, -4.66. Also reported by Liu, H.-W and colleagues.[10] Please see pag **26** for ^{1}H and ^{13}C spectrum.



(2R,3R)-3-((tert-butyldimethylsilyl)oxy)-2-methylpentan-1-ol

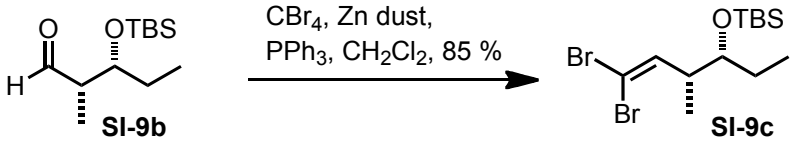
To a stirred solution of **9** (4 g, 9.9 mmol) in THF at 0°C was added MeOH (1.2 mL, 30 mmol) followed by slow addition of $LiBH_4$ (15 mL, 30 mmol), during which evolution of gas was observed. The resulting mixture was stirred at 0°C for 10 min, and stirred at rt for 2 h. The reaction was terminated by addition of 1N NaOH (30 mL), poured into water (30 mL), extracted with ethyl acetate, washed with half-saturated aqueous $NaHCO_3$, half-saturated NaCl solution, water, dried with $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash chromatography (1:5 EtOAc:hexanes) to afford the title compound (2.0 g, 89 %) as a colorless oil. Matched data as previously reported by Das, P and colleagues,[11] please see page **27** for ^{1}H and ^{13}C spectrum.



SI-9a **SI-9b**

(2S,3R)-3-((tert-butyldimethylsilyl)oxy)-2-methylpentanal

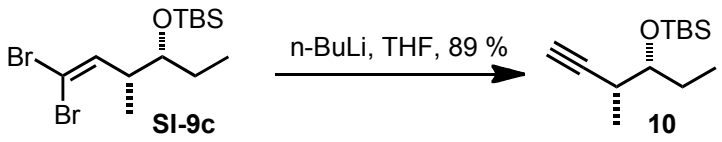
To a solution of **SI-9a** (1.1 g, 4.7 mmol) and $NaHCO_3$ (1.9 g, 24 mmol) in CH_2Cl_2 (30 mL, non anhydrous) cooled to 0°C, was added DMP (3.2 g, 7.5 mmol) (slowly added portion wise) and stirred for 3 h. The reaction was terminated by addition of a 1:1 solution of half-saturated aqueous $Na_2S_2O_3$ and half-saturated aqueous $NaHCO_3$ and vigorously stirred for 0.5 h, extracted with CH_2Cl_2, washed with half-saturated aqueous $NaHCO_3$, half-saturated NaCl, water, dried with $MgSO_4$, and concentrated under reduced pressure. The residue was filtered through a plug of silica gel (1:5 EtOAc:hexanes) to afford the title compound (1.0 g, 94%) as a colorless oil. The title compound was used immediately.



SI-9b **SI-9c**

tert-butyl((3R,4R)-6,6-dibromo-4-methylhex-5-en-3-yloxy)dimethylsilane

To a solution of PPh_3 (2.3 g, 8.2 mmol) and Zn dust (0.54 g, 8.2 mmol) in 50 mL of CH_2Cl_2 was added CBr_4 (2.7 g, 4.1 mmol) and stirred for 15 min at rt. A solution of **SI-9b** (0.94 g, 4.1 mmol) in 10 mL of CH_2Cl_2 was added drop-wise, and stirred for 18 h, poured into hexanes, filtered through Celite and purified by flash chromatography (100% hexanes) to afford title compound as a colorless oil (1.3 g, 85%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.30 (d, *J* = 9.5 Hz, 1H), 3.53 (app. q, J = 5.5, 1H), 2.54 (dquint., *J* = 2.5, 7.0 Hz, 1H), 1.45 (m, 2H), 0.95 (d, *J* = 6.5 Hz, 3H), 0.89 – 0.85 (m, 12H), 0.03 (s, *3*H), 0.02 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 142.7, 87.6, 75.4, 42.4, 27.7, 26.1, 18.3, 13.3, 9.7, -4.0, -4.5. HMRS calcd for $C_{13}H_{26}Br_2OSi$ $[M - H]^+$ 383.0052, found 383.0041.

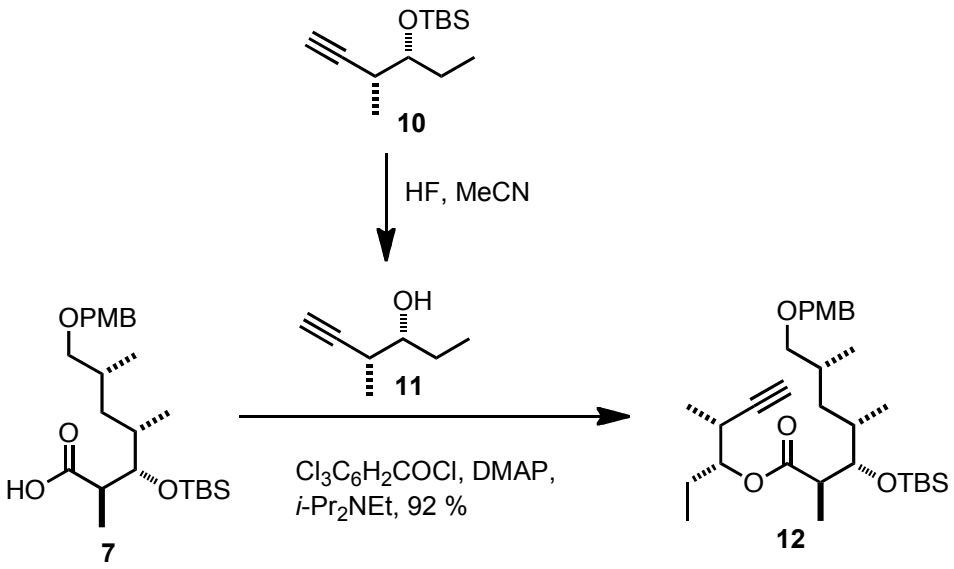


SI-9c **10**

***tert*-butyldimethyl(((3*R*,4*R*)-4-methylhex-5-yn-3-yl)oxy)silane**

To a solution of **SI-9c** (1.60 g, 4.1 mmol) in THF (40 mL) cooled to -78 °C was added butyl lithium (7.0 mL, 2.4M) drop-wise. Reaction was stirred at -78 °C for 3 h and 0 °C for 3 h, terminated by addition water, extracted with ethyl acetate, washed with half-saturated NaCl, water, dried with $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash chromatography (1:20 EtOAc:hexanes) to afford the

title compound (0.89 g, 89%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) 3.58 (app. q, J = 5.5, 11 Hz) 2.56 (dquint., *J* = 2.0, 5.6 Hz, 1H), 2.04 (d, *J* = 2.4 Hz, 1H), 1.74 (m, 1H), 1.58 (m, 1H), 1.17 (d, *J* = 7.0 Hz, 3H), 0.92 (m, 12H), 0.09 (s, 3H), 0.07 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 87.58, 76.26, 69.64, 31.58, 27.41, 26.27, 18.54, 17.41, 9.05, -3.95, -4.14. HMRS calcd for $C_{13}H_{26}OSi$ [M – ^{t}Bu]$^+$ 169.1049, found 169.1052.

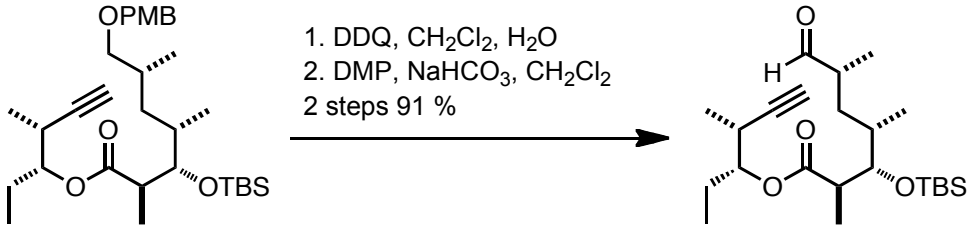


(2*R*,3*S*,4*S*,6*R*)-(3*R*,4*R*)-4-methylhex-5-yn-3-yl 3-((*tert*-butyldimethylsilyl)oxy)-7-((4-methoxybenzyl)oxy)-2,4,6-trimethylheptanoate

To a solution of 48% HF (3.2 mL), MeCN (5 mL), and water (2 mL) at 0 °C was added **10** (0.64 g, 2.8 mmol), in MeCN (10 mL). The resulting solution was removed from ice bath and stirred at rt for 3 h, and carefully transferred to a separatory funnel, washed with half-saturated aqueous $NaHCO_3$, extracted with diethyl ether, dried with $MgSO_4$, and concentrated under reduced pressure while cooling flask in an ice bath (CAUTION: resulting alkyne was volatile, caution must be exercised when removing solvents). The residue is dissolved in THF, dried with molecular sieves, and used without characterization.

To a solution of **7** (0.22 g, 0.50 mmol) in THF (2 mL) at rt was added *i*-Pr_2NEt (96 μL, 0.55 mmol), trichlorobenzoyl chloride (78 μL, 0.5 mmol) and stirred for 1 h. A separate flask was charged with **11** and DMAP (0.122 g, 1.0 mmol) in THF (1.5 mL) and was added via cannula to activated acid. The resulting solution was stirred for 18 h, quenched with aqueous half-saturated NH_4Cl, extracted with EtOAc, washed with half-saturated aqueous NaCl, dried with $MgSO_4$, and solvents were removed under reduced pressure. The residue was purified by flash chromatography (1:10 EtOAc:hexanes) to afford the title compound (0.24 g, 92 %) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (d, *J* = 8.8 Hz, 2H), 6.85 (d, *J* = 8.4 Hz, 2H), 4.71 (app. q, J = 6.0, 1H), 4.39 (s, 2H), 3.88 (dd, *J* = 6.0, 3.2 Hz, 1H), 3.78 (s, 3H), 3.31 (dd, *J* = 9.2, 4.8 Hz, 1H), 3.10 (app. t, *J* = 7.4 Hz, 1H), 2.73 (dquint., *J* = 2.4, 6.8 Hz, 1H), 2.59 (quint., *J* = 6.8 Hz, 1H), 2.03 (d, *J* = 2.8 Hz, 1H), 1.86-1.76 (m, 2H), 1.74-1.69 (m, 3H), 1.39 (ddd, *J* = 4.8, 8.0, 13.4 Hz, 1H), 1.14 (d, *J* = 8 Hz, 6H), 0.95 – 0.9 (m, 9H), 0.87-0.86 (m, 9H), 0.034 (s, 3H), 0.026 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.7, 159.0, 131.0, 129.1, 113.8, 85.1, 76.8,

76.0, 75.4, 72.7, 70.3, 55.3, 42.6, 36.9, 36.5, 31.1, 29.7, 26.1, 23.7, 18.9, 18.4, 17.2, 16.4, 14.6, 9.6, -4.06, -4.08. HMRS calcd for $[C_{31}H_{52}O_5SiNa]^+$ 555.3476, found 555.3476.

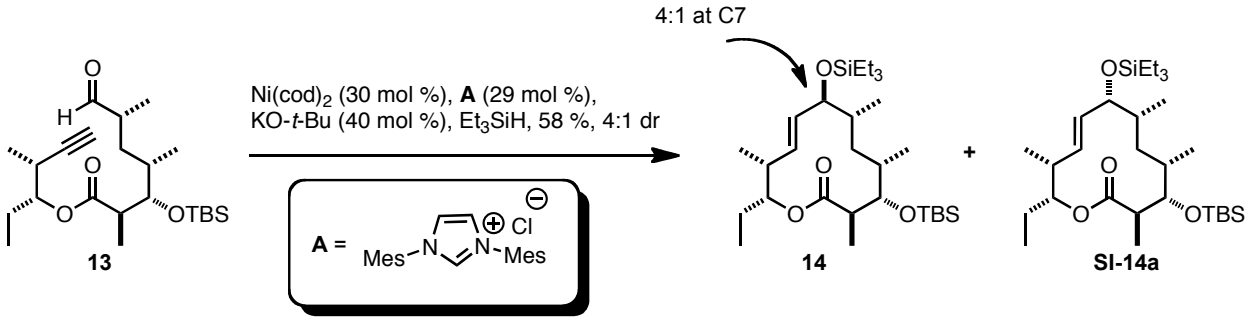


12 **13**

(2*R*,3*S*,4*S*,6*R*)-(3*R*,4*R*)-4-methylhex-5-yn-3-yl 3-((*tert*-butyldimethylsilyl)oxy)-2,4,6-trimethyl-7-oxoheptanoate

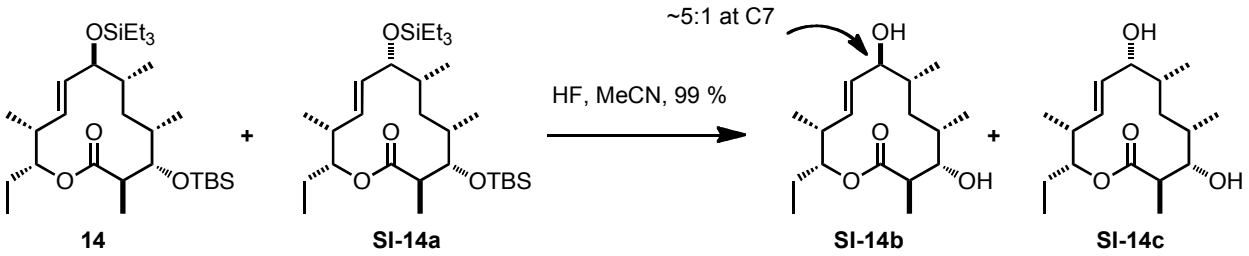
To a solution of **12** (0.12 g, 0.22 mmol) in water (0.5 mL), and CH_2Cl_2 (5 mL) at rt was added DDQ (0.10 g, 0.45 mmol), the biphasic mixture was stirred for 4 h, diluted with CH_2Cl_2 (5 mL), and washed with aqueous half-saturated $NaHCO_3$, extracted with CH_2Cl_2, washed with water, dried with $MgSO_4$, and solvents were removed under reduced pressure. The residue was purified by flash chromatography (1:20 hexanes:EtOAC); however, desired compound co-eluted with anisaldehyde and contaminated material was carried forward.

To a solution of previously prepared mixture in CH_2Cl_2 (10 mL, non-anhydrous) and $NaHCO_3$ (0.092 g, 1.1 mmol), at 0 °C was added DMP (0.168 g, 0.40 mmol) in one portion, and was stirred at 0 °C for 4 hours. The reaction was quenched by addition a 1:1 solution of half-saturated $Na_2S_2O_3$ and half-saturated $NaHCO_3$ (5 mL) and then vigorously stirred for 0.5 h, extracted with CH_2Cl_2, washed with half-saturated $NaHCO_3$, half-saturated NaCl, water, dried with $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash chromatography (1:20 EtOAc:hexanes) to afford the title compound (0.082 g, 91 %) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.52 (d, *J* = 2.4 Hz, 1H), 4.69 (ddd, *J* = 4.8, 6.0, 7.6 Hz, 1H), 3.87 (dd, *J* = 7.2, 4.0 Hz, 1H), 2.75 (ddq, *J* = 2.4, 6.9, 13.0, 1H), 2.62 (quint., *J* = 7.0 Hz, 1H), 2.42 (m, 1H), 2.04 (d, *J* = 2.8 Hz, 1H), 1.84 (ddd, *J* = 4.0, 8.8, 13.6 Hz, 1H), 1.72- 1.60 (m, 4H), 1.17-1.14 (m, 6H), 1.08 (d, *J* = 7.2 Hz, 3H), 0.93 – 0.87 (m, 15H), 0.05 (s, 3H), 0.04 (s, 3H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 205.3, 175.6, 85.1, 77.2, 76.4, 70.4, 44.3, 43.2, 36.8, 33.2, 29.8, 26.3, 23.7, 18.6, 17.2, 16.6, 15.0, 14.8, 9.88, -3.79, -3.84. HMRS calcd for $[C_{23}H_{42}O_4SiNa]^+$ 433.2745, found 433.2746.



(3*R*,4*S*,5*S*,7*R*,11*R*,12*R*,*E*)-4-((*tert*-butyldimethylsilyl)oxy)-12-ethyl-3,5,7,11-tetramethyl-8-((triethylsilyl)oxy)oxacyclododec-9-en-2-one

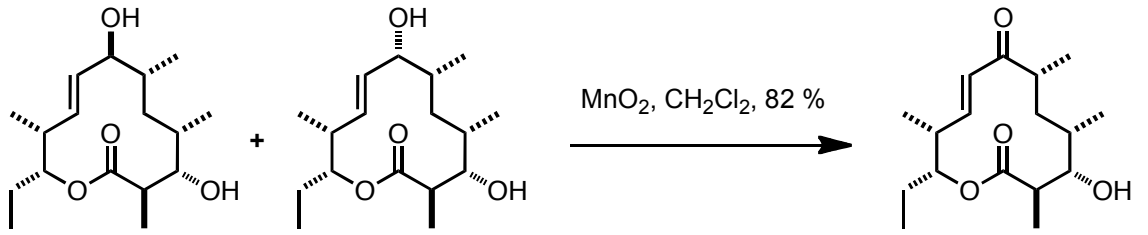
In a glovebox $Ni(cod)_2$ (0.007 g, 30 mol %), **A** (IMes-HCl) (0.008 g, 29 mol %), and KO-*t*-Bu (0.004 g, 40 mol %), were charged to a round-bottom flask, removed from the glovebox, THF (9 mL) was added and stirred for 10 min at rt. Neat triethylsilane (27 μL, 0.17 mmol) was added, followed by syringe drive addition of **13** (0.035 g, 0.085 mmol) in THF (1 mL) over three hours, the reaction was stirred for 12 h at rt. The septum was removed from the round bottom, stirred for 1 h in open atmosphere. Solvents were concentrated, and the residue was purified by flash chromatography (1:50 EtOAc:hexanes) to afford the title compound {a 4:1 mixture of C7 diastereomers as judged by comparing integration of the signals at 5.00 (major) 5.05 (minor)} (0.026 g, 58 %) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.66 (dd, *J* = 15.4, 4.2 Hz, 1H), 5.41 (dd, *J* = 15.6, 1.8 Hz, 1H), 5.01 – 4.97 (m, 1H), 4.00 (m, 1H), 3.63 (d, *J* = 9.6 Hz, 1H), 2.58 – 2.41 (m, 2H), 1.89-1.85 (m, 1H), 1.80 – 1.76 (m, 2H), 1.67 – 1.48 (m, 5H), 1.34–1.24 (m, 3H), 1.03 –1.01 (m, 4H), 0.96 – 0.94 (m, 3H), 0.93-0.92 (m, 8H), 0.91-0.89 (m, 8H), 0.88-0.86 (m, 16H), 0.62 – 0.45 (m, 9H), 0.05-0.04 (m, 9H). Combined integrals for major and minor isomers are reported in regions where resolution is poor. ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.2, 131.5, 128.6, 79.5, 77.4, 75.6, 44.1, 37.8, 36.5, 33.6, 32.8, 26.5, 26.47, 24.9, 20.6, 18.8, 18.4, 17.6, 10.8, 10.6, 7.2, 7.1, 5.22, 5.08, -2.98, -3.09. Diagnostic signals for the minor diastereomer include the following: 5.51-5.48 (m, 2H) and 5.10 (m, 1H), and for major diastereomer include 5.66 (dd, *J* = 15.6, 4.2 Hz, 1H), 5.41 (dd, *J* = 15.5, 1.6 Hz, 1H), and 5.01-4.97 (m, 1H). All resolved carbon signals for the major and minor diastereomers are reported, and unless noted, integrations refer to mixture of C7 diastereomers. HMRS calcd for : $C_{29}H_{58}O_4Si_2$ 526.3874 found 526.3866.



(3*R*,4*S*,5*S*,7*R*,11*R*,12*R*,*E*)-12-ethyl-4,8-dihydroxy-3,5,7,11-tetramethyloxacyclododec-9-en-2-one

To a solution of 48% HF (0.3 mL), MeCN (0.5 mL), and water (0.2 mL) at 0 °C, was added **14 and SI-14a** (0.022 g, 0.042 mmol) in MeCN (0.5 mL). Reaction was removed from cooling bath, and stirred at rt for 3 h. Diluted with MeCN (5 mL), carefully transferred to a separatory funnel, washed with half-saturated aqueous $NaHCO_3$, extracted with CH_2Cl_2, washed with half-saturated NaCl solution, water, dried with $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash chromatography (3:10 EtOAc:hexanes) to afford the title compound {a 5:1 mixture of C7 diastereomers as judged by comparing integration of the signals at 4.99 (major) 5.09 (minor)} (0.012 g, 99%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.71- 5.66 (m, 1H), 5.50-5.46 (m, 1H), 4.99 (ddd, *J* = 3.5, 5.0, 8.8 Hz, 1H), 4.14-4.11 (m, 1H), 3.55-3.51 (m, 1H), 2.59-2.55 (m, 1H), 2.54-2.47 (m, 1H), 1.95-1.87 (m, 2H), 1.69-1.51 (m, 7H), 1.29-1.21 (m, 8H), 1.05-1.00 (m, 7H), 0.98-0.96 (m, 6H), 0.91-0.84 (m, 5H). Combined integrals for major and minor isomers are reported in regions where resolution is poor. ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.5, 131.2, 128.6, 79.1, 77.4, 76.2, 43.9, 38.0, 35.6, 32.8, 32.1, 24.6, 20.8, 17.4, 16.7, 11.1, 10.6. Diagnostic signal for the minor diastereomer: 5.09 (ddd, *J* = 3.0, 5.5, 8.8, 1H) and for major diastereomer is 4.99 (ddd, *J* = 3.5, 5.0, 8.3 Hz, 1H). Please see page **33** for ^{1}H and ^{13}C spectrum.

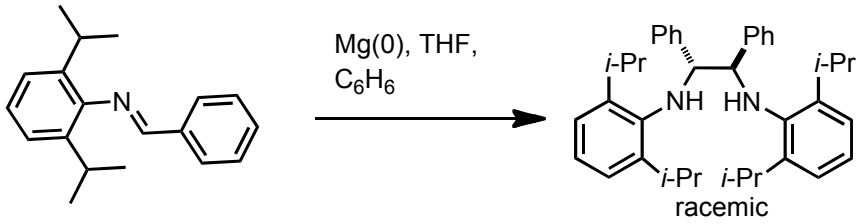
Assignment of stereochemistry at C7 was done by correlation with known compound from the Sherman and colleagues [7] and from Cane and colleagues.[12]



SI-14b **SI-14c** **10-deoxymethynolide**

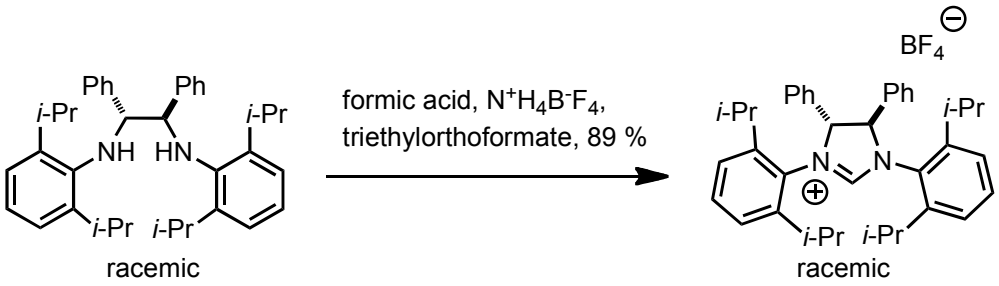
(3*R*,4*S*,5*S*,7*S*,11*R*,12*R*,*E*)-12-ethyl-4-hydroxy-3,5,7,11-tetramethyloxacyclododec-9-ene-2,8-dione

To a solution of **SI-14b and SI-14c** (0.008 g, 0.027 mmol) in CH_2Cl_2, was added MnO_2 (0.047g, 0.54 mmol), and stirred at rt for 2 h. Filtered through a pad of Celite, dried with $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash chromatography (2.5:10 EtOAc:hexanes) to afford the title compound (0.0066 g, 82%) as a colorless oil. Matched data as previously reported by Pilli and colleagues,[13] please see page **34** for ^1H and ^{13}C spectrum.



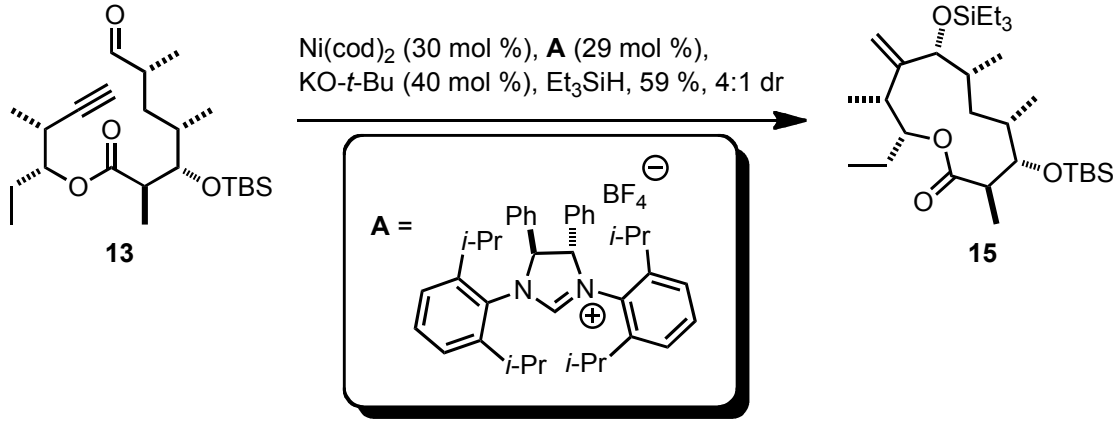
(+/-)-(1R,2R)-N1,N2-bis(2,6-diisopropylphenyl)-1,2-diphenylethane-1,2-diamine

N-Benzylidene-2,6-diisopropylaniline[1] (10.0 g, 37.7 mmol), magnesium powder (Aldrich reagent plus 99.5% purity, 2.75 g, 113 mmol) and of benzene (120 mL) were combined in 1.0 L flame dried round-bottom flask with a stir bar under nitrogen. Trifluoroacetic acid (17.4 mL, 226 mmol) was then dispensed by syringe drive over 1 h and stirred overnight at ambient temperature. The reaction was terminated with sat. $NaHCO_3$ (250 mL) and stirred for 1 h. The two layers were separated, and the aqueous layer was extracted with EtOAc (3 x 100 mL). The combined organics were then dried with Na_2SO_4 and concentrated under reduced pressure to yield crude brown colored oil. The oil was then dissolved in methanol (40 mL) and placed in a freezer (-20 °C) overnight. The solvent was then decanted from the precipitate, affording 7.0 g as a mixture of racemic and meso products. The precipitate was then dissolved in refluxing methanol (250 mL) and undissolved solids remaining after 1 h were removed by filtration. The filtered methanol solution cooled overnight at room temperature. The solvent was then decanted from the resulting 2.5 g of white crystalline solid (meso isomer). The mother liquor was then concentrated to 125 mL and heated to reflux until all solids dissolved. The solution was then cooled to RT and placed in a -20 °C freezer overnight. The solvent was decanted to afford 3.2 g of white solid (>98:2 racemic:meso). Matched data as previously reported by Sigman and colleagues.[14]



(±)-(4R,5R)-1,3-Bis(2,6-diisopropylphenyl)-4,5-diphenyl-4,5-dihydro-1H-imidazol-3-ium tetrafluoroborate (DP-IPr)

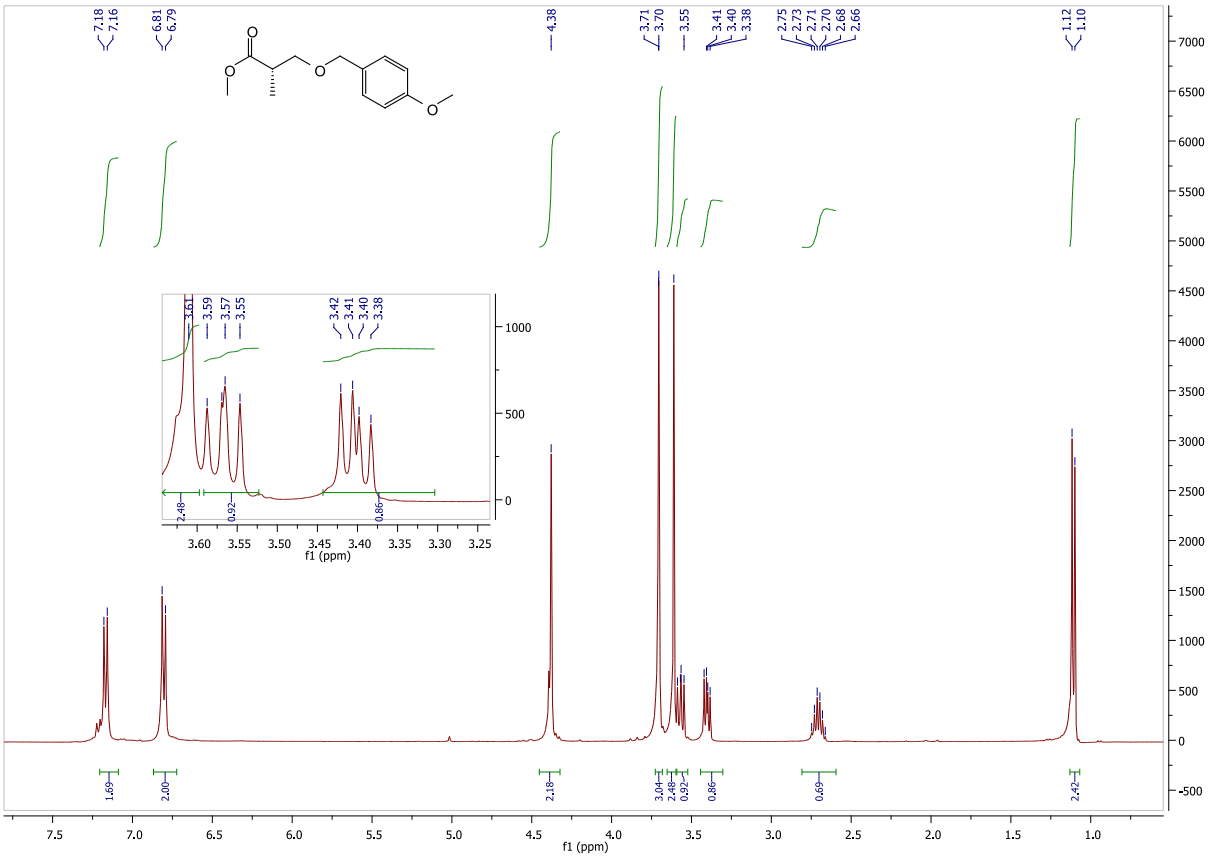
(±)-(1R, 2R)-N1, N2-Bis(2,6-diisopropylphenyl)-1,2-diphenylethane-1,2-diamine (0.580 g, 0.940 mmol), ammonium tetrafluoroborate (98 mg, 0.94 mmol), triethylorthoformate (1.11 g, 7.52 mmol), and formic acid (1 drop) were combined in a dry 25 mL round-bottom flask with a reflux condenser under nitrogen. The reaction was then heated to 120 °C with stirring for 24 h. The reaction mixture cooled to room temperature and was then concentrated under high vacuum. The reaction mixture was purified by flash column chromatography (SiO_2, 80% v/v EtOAc/Hexanes, R_f = 0.2) to afford title compound (0.530 g, 0.84 mmol, 89% yield) as a pale yellow solid. This material was then heated at 40 °C overnight, under reduced pressure. Matched data as previously reported by Montgomery and colleagues.[15]



(3R,4S,5S,7R,8S,10R,11R)-4-((tert-butyldimethylsilyl)oxy)-11-ethyl-3,5,7,10-tetramethyl-9-methylene-8-((triethylsilyl)oxy)oxacycloundecan-2-one

In a glovebox $Ni(cod)_2$ (0.0085 g, 30 mol %), **A** (0.018 g, 29 mol %), and KO-*t*-Bu (0.004g, 39 mol %), were charged to a round-bottom flask, the flask was removed from the glovebox, THF (8 mL) was added and stirred for 10 min at rt. Neat triethylsilane (33 μL, 0.21 mmol) was added, followed by syringe drive addition of **13** (0.042 g, 0.103 mmol) in THF (2 mL) over three hours, the reaction was stirred for 12 h at rt. The septum was removed from the round bottom, stirred for 1 h in open atmosphere. Solvents were concentrated, and the residue was purified by flash chromatography

(1:50 EtOAc:hexanes) to afford the title compound (0.031 g, 59%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.23 (s, 1H), 5.11 (s, 1H), 4.66-4.61 (m, 1H), 3.89 (dd, *J* = 4.4, 8.0 Hz, 1H), 3.76 (s, 1H), 2.56 (quintet, *J* = 7.2 Hz, 2H), 1.87-1.78 (m, 3H), 1.57-1.49 (m, 1H), 1.42-1.34 (m, 1H), 1.24-1.13 (m, 2H), 1.05-1.00 (m, 5H), 0.94-0.87 (m, 25H), 0.84-0.83, (m, 2H), 0.58-0.52 (m, 6H), 0.1 (s, 3H), 0.05 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 178.8, 152.3, 111.2, 80.3, 80.1, 72.2, 40.0, 36.6, 36.1, 30.9, 30.8, 26.1, 21.7, 19.9, 18.5, 18.3, 16.1, 14.4, 11.7, 7.3, 5.1, -4.4, -4.5. HMRS calcd for : $C_{29}H_{58}O_4Si_2$ 526.3874, found 526.3877.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1.12
1.10
3.61
3.59
3.57
3.55
3.42
3.41
3.40
3.38
2.48
0.92
0.86
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0.86
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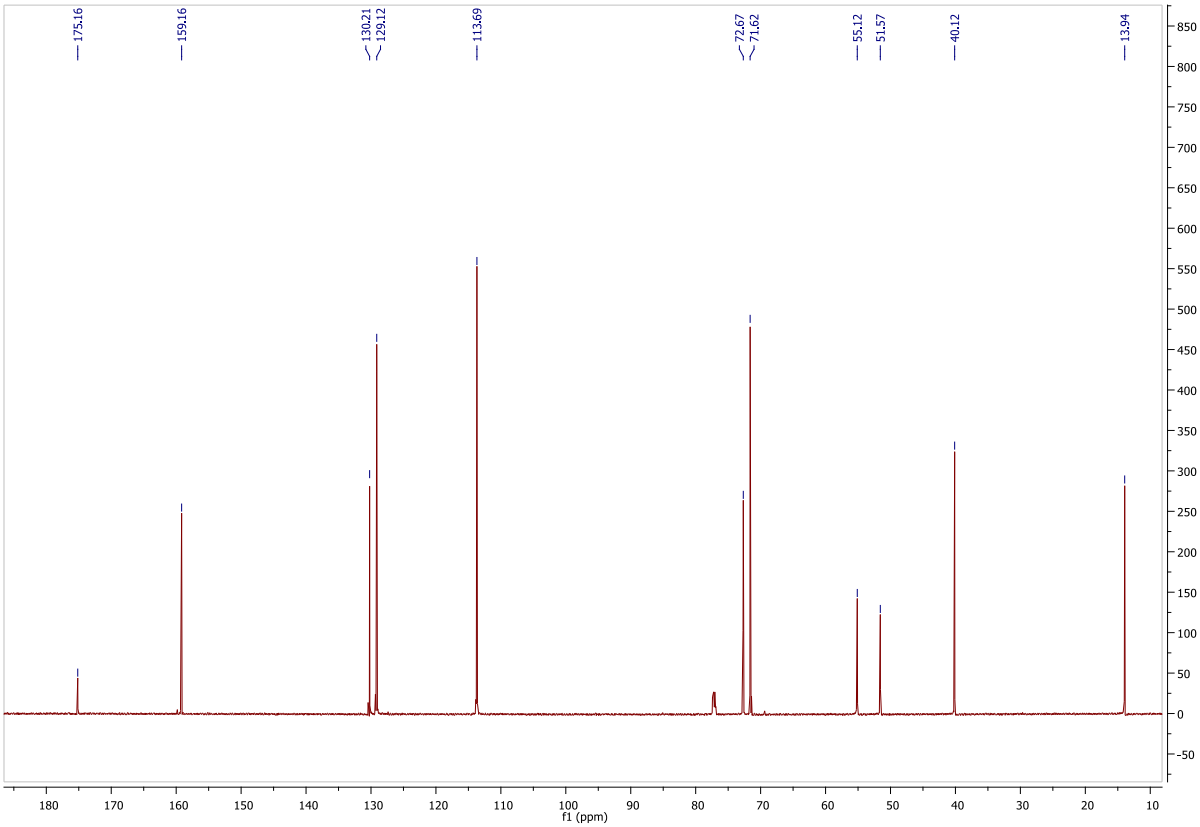
2.42
f1 (ppm)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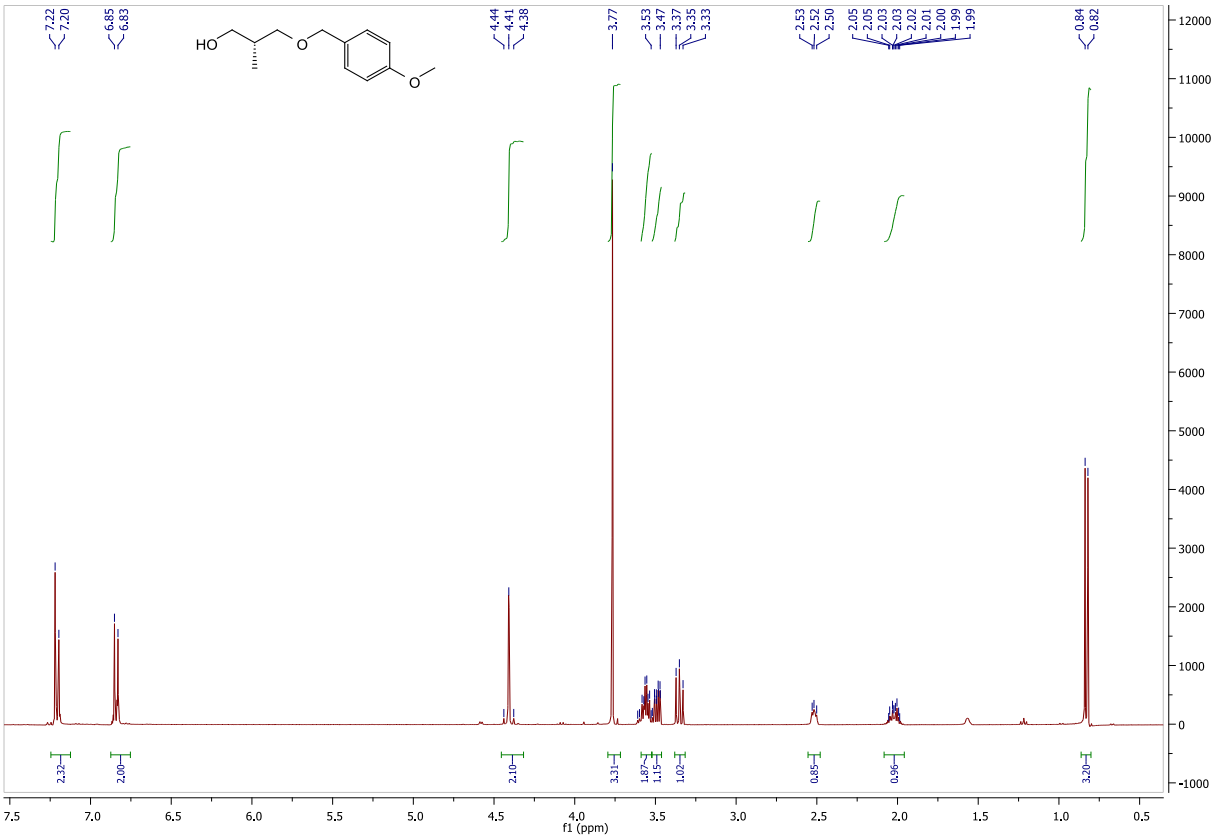
f1 (ppm)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2.50
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2.03
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2.02
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2.00
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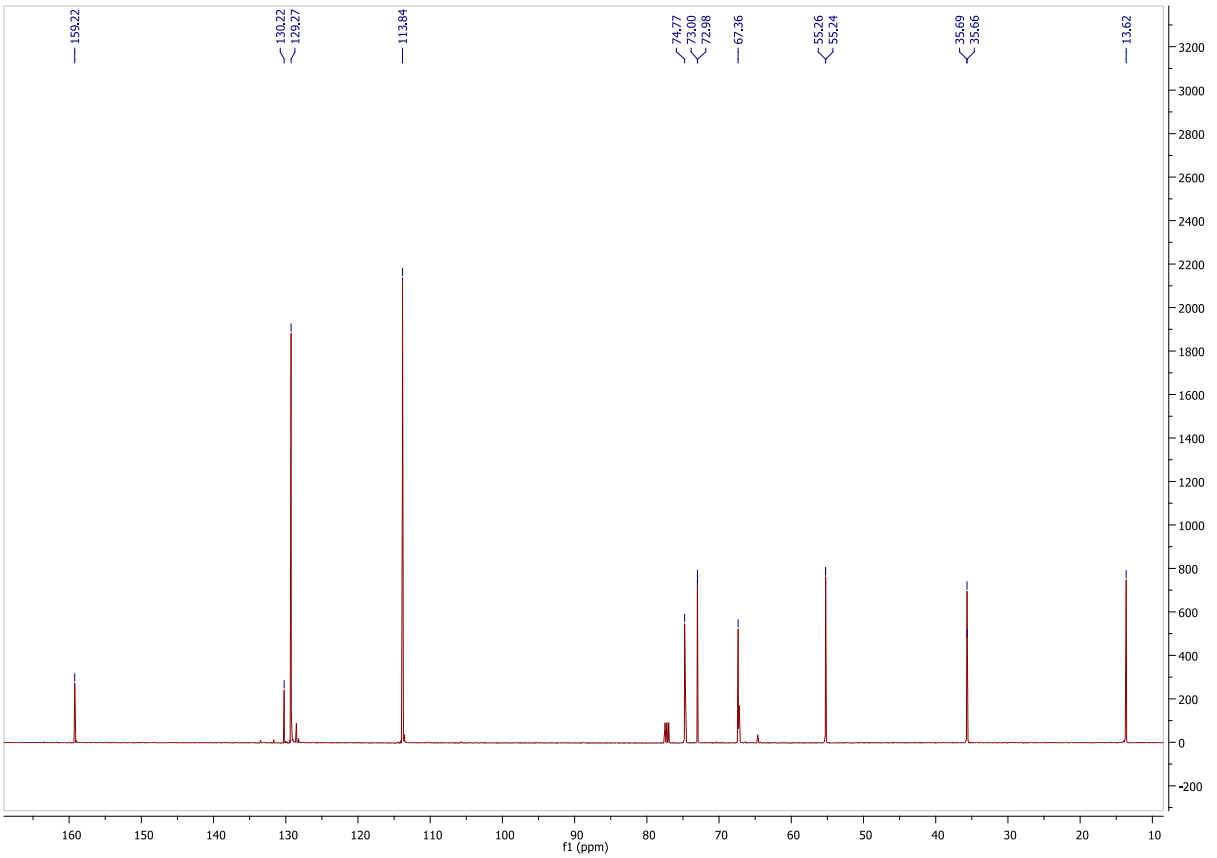
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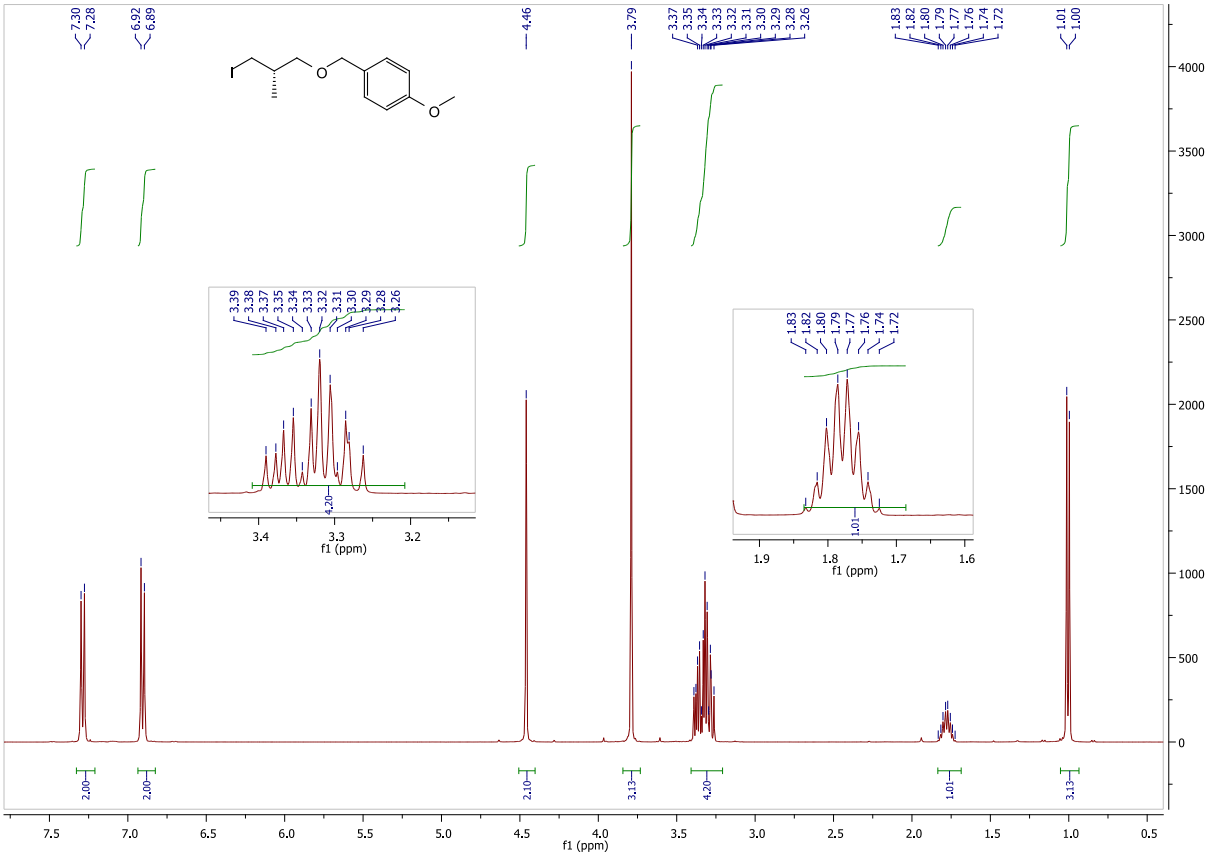
f1 (ppm)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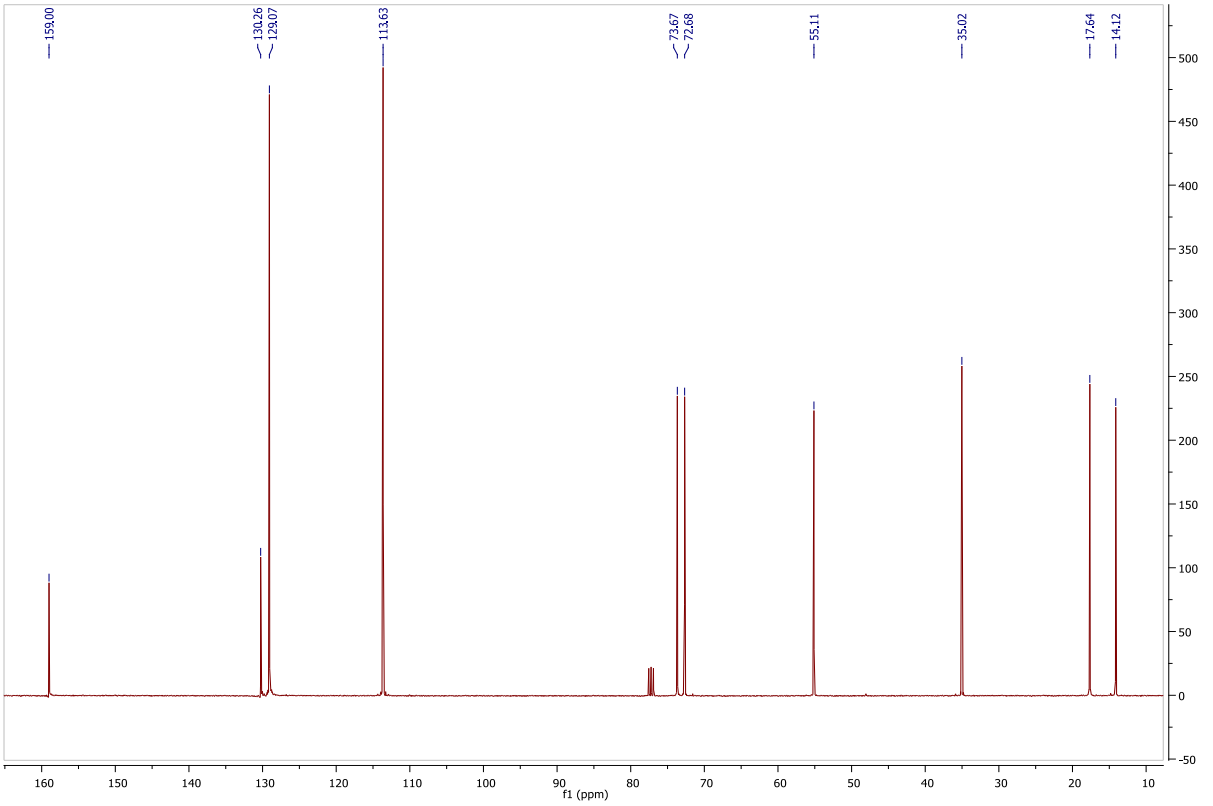
1.01
3.13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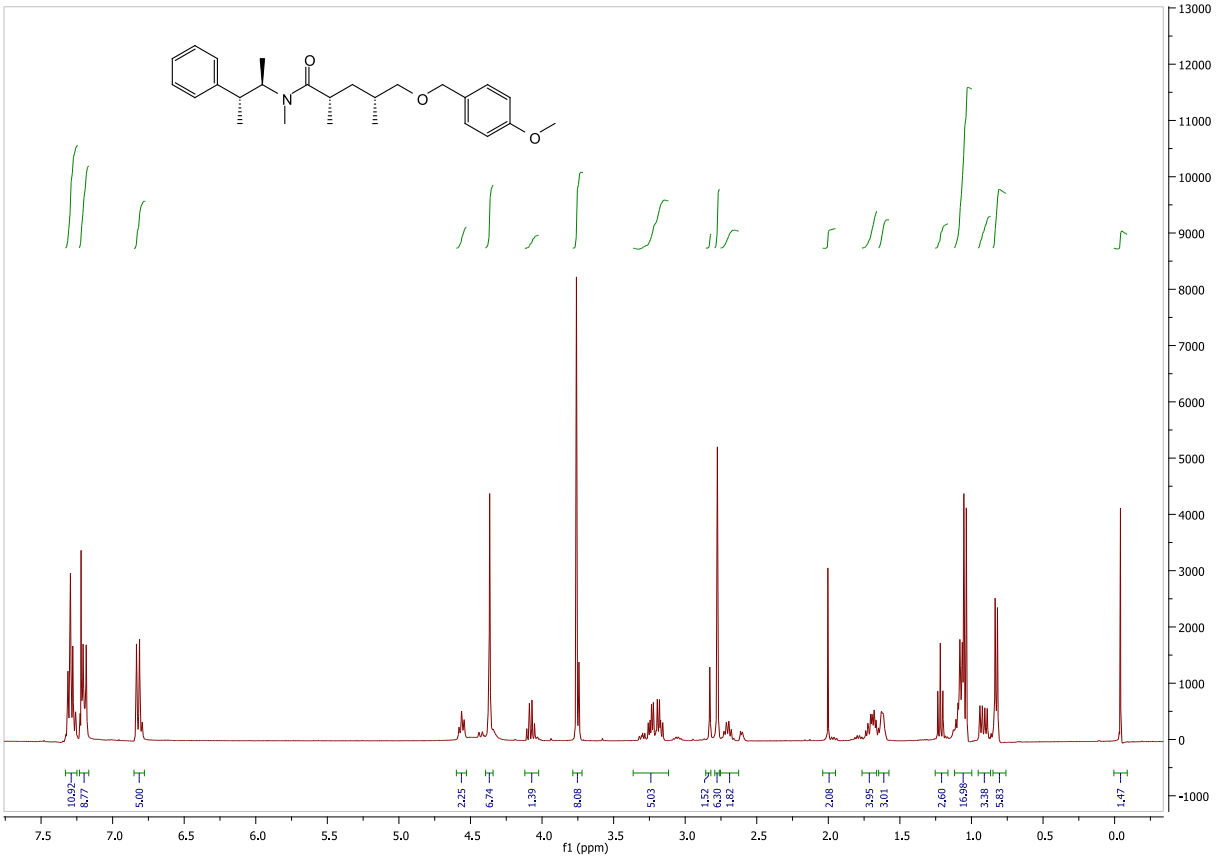
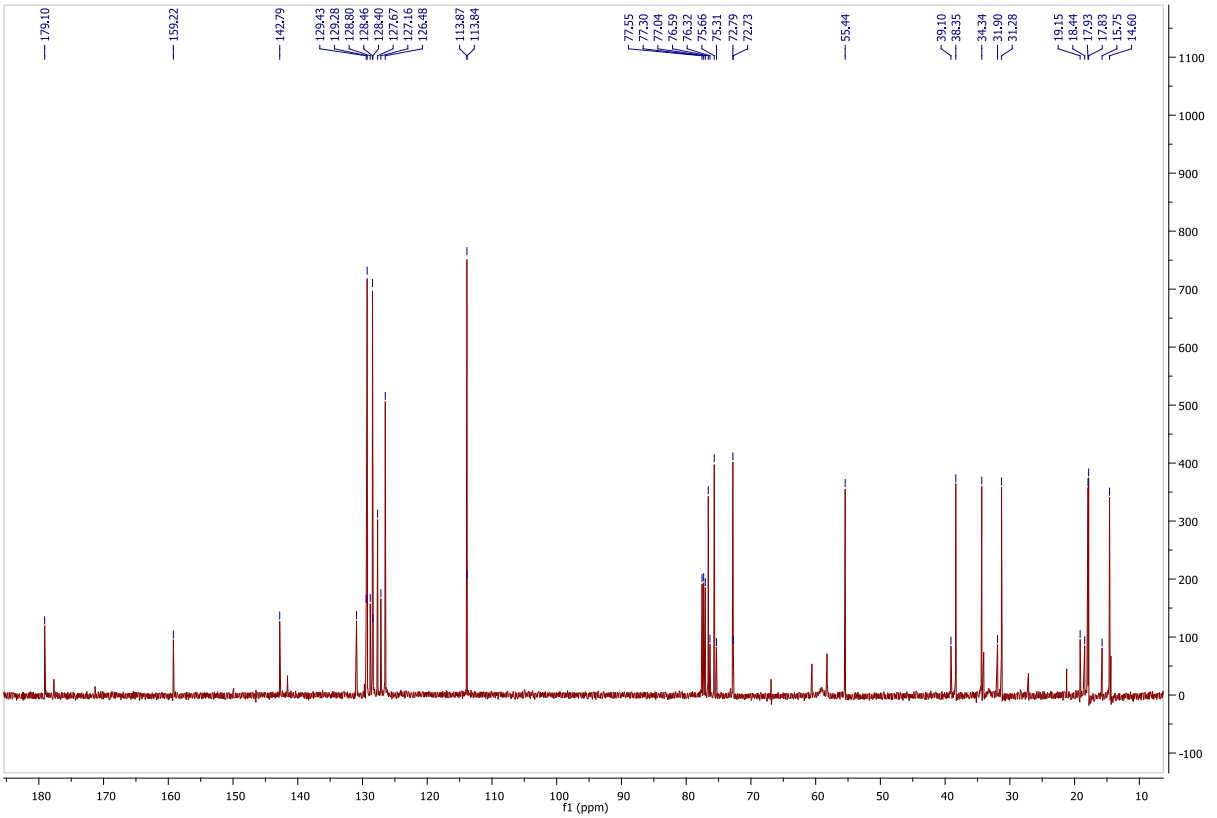
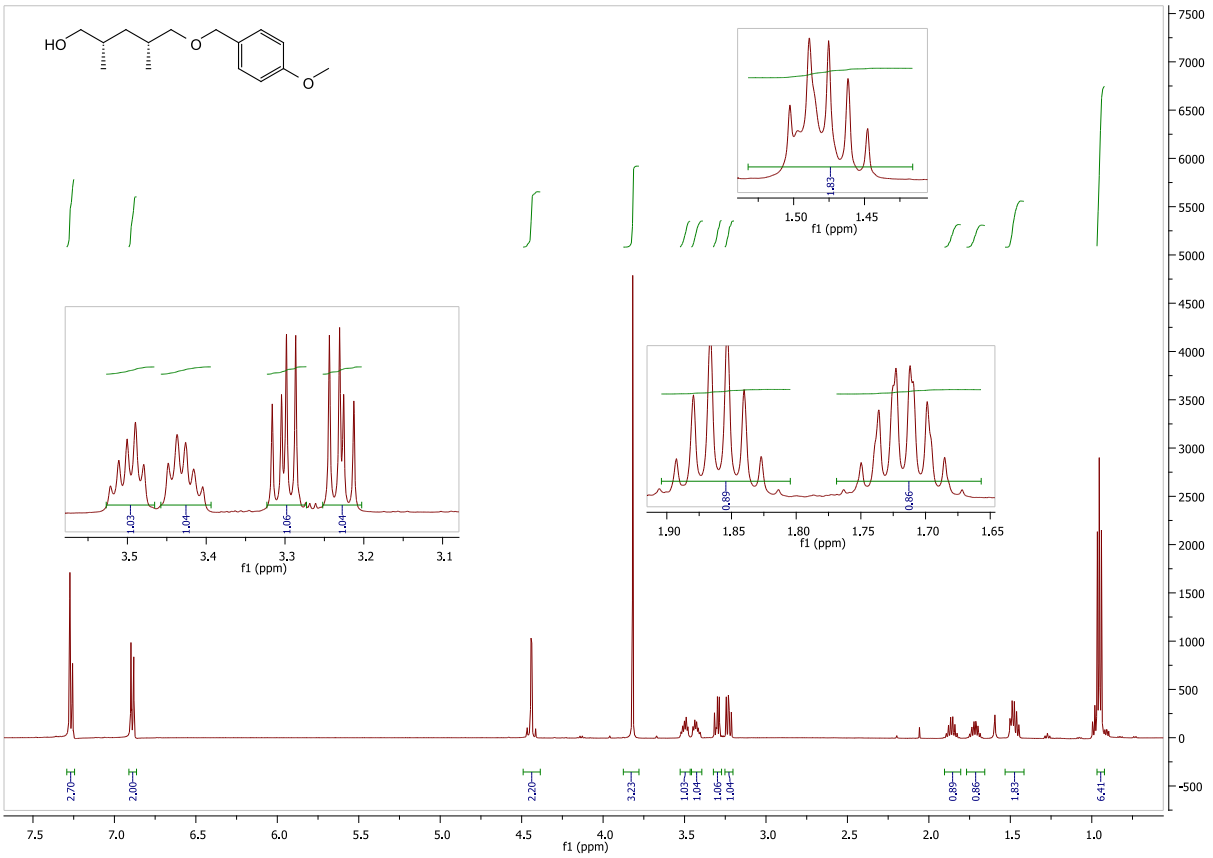
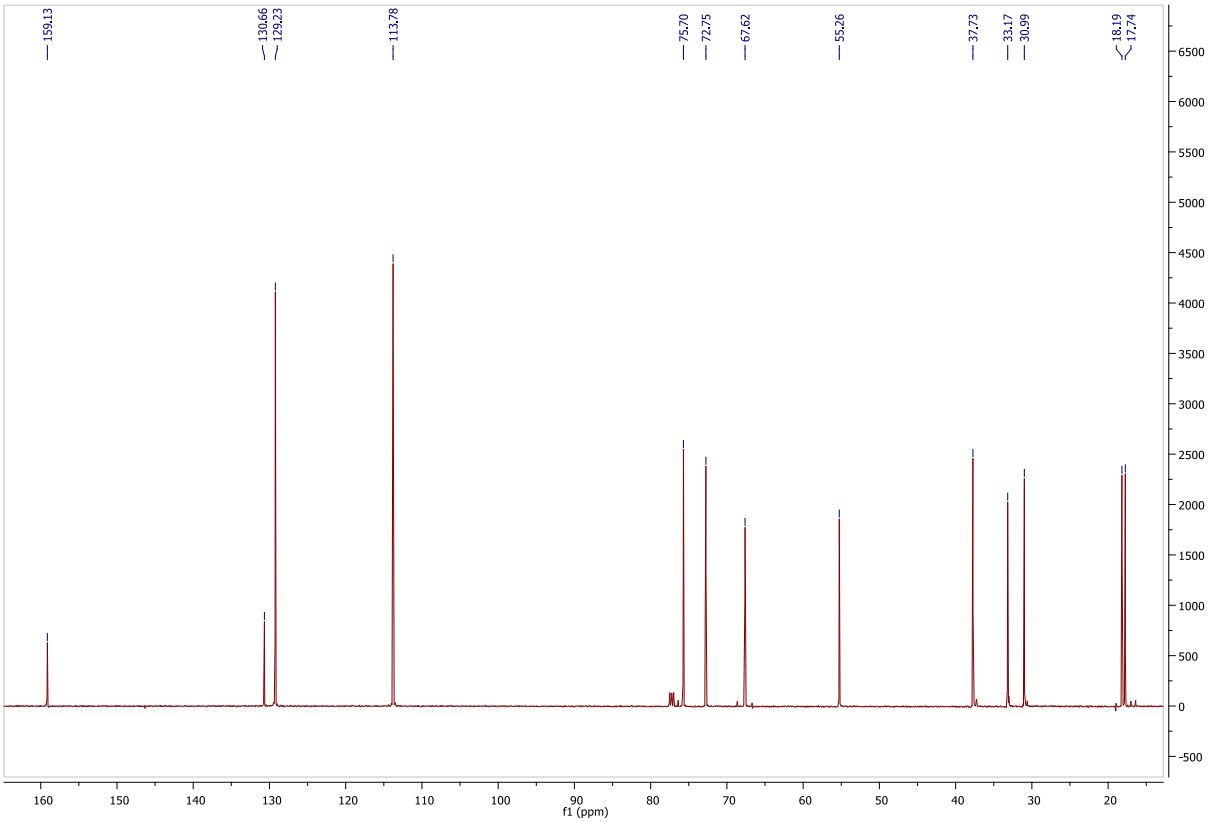
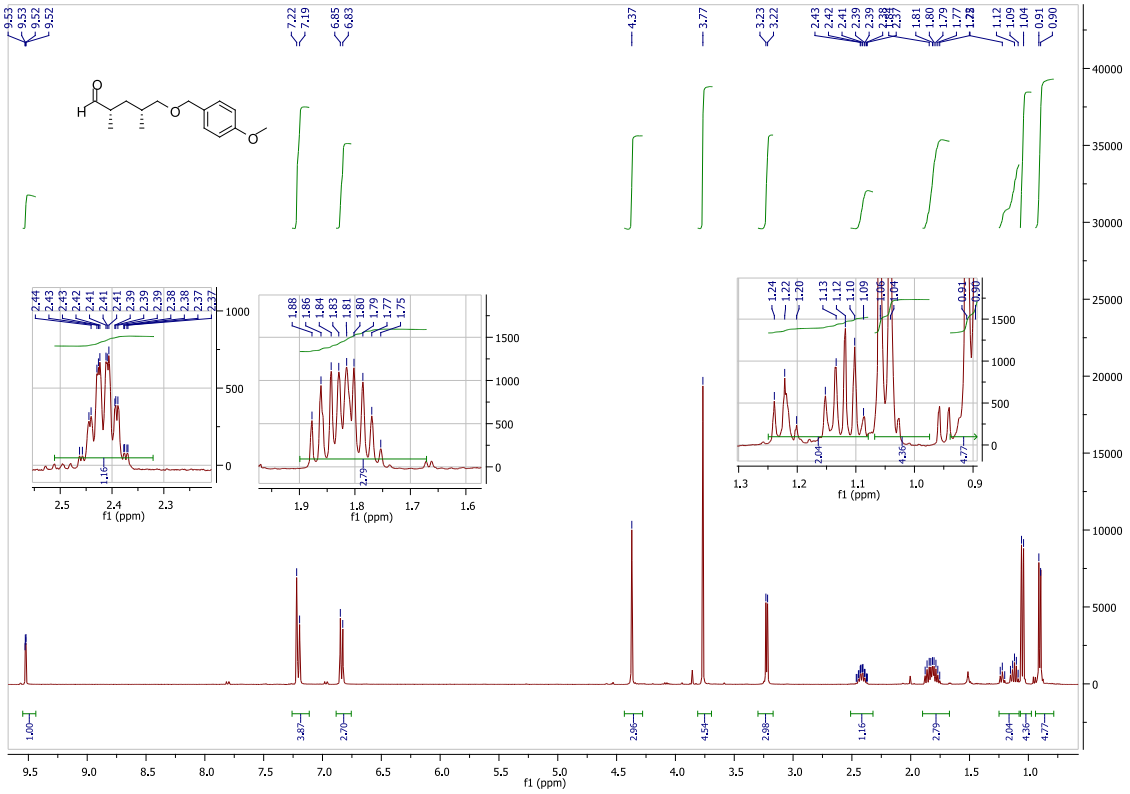
f1 (ppm)

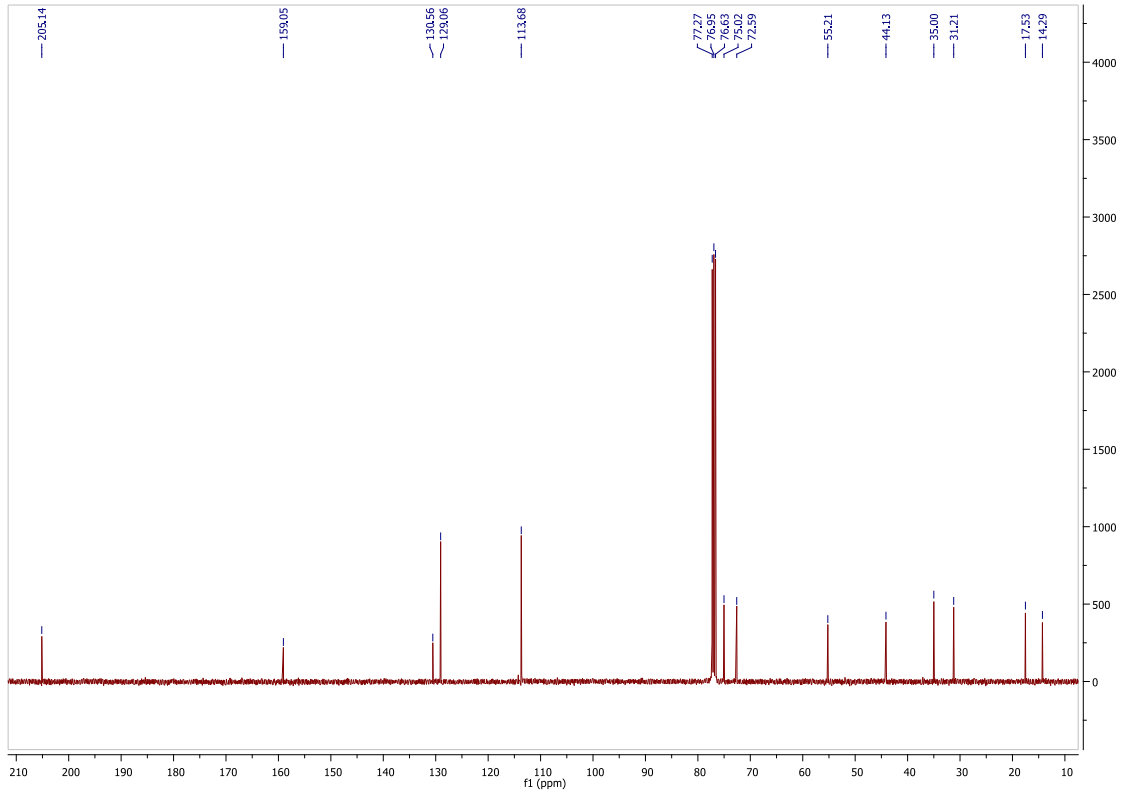


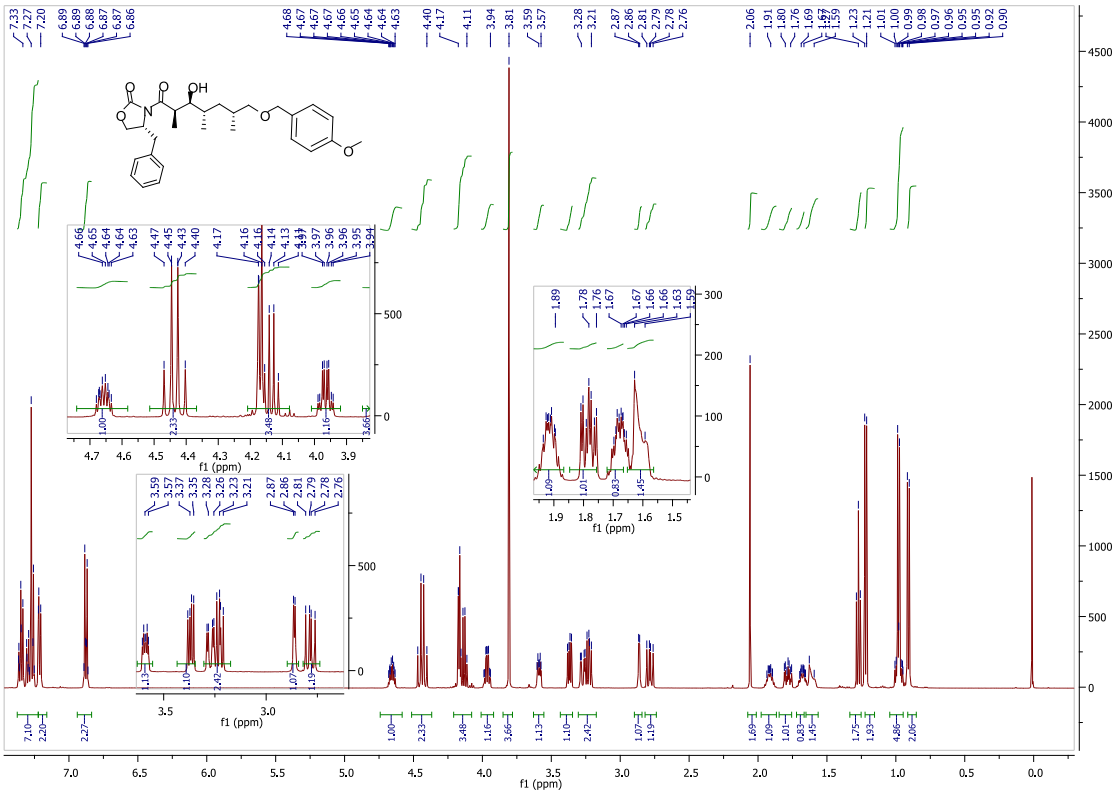


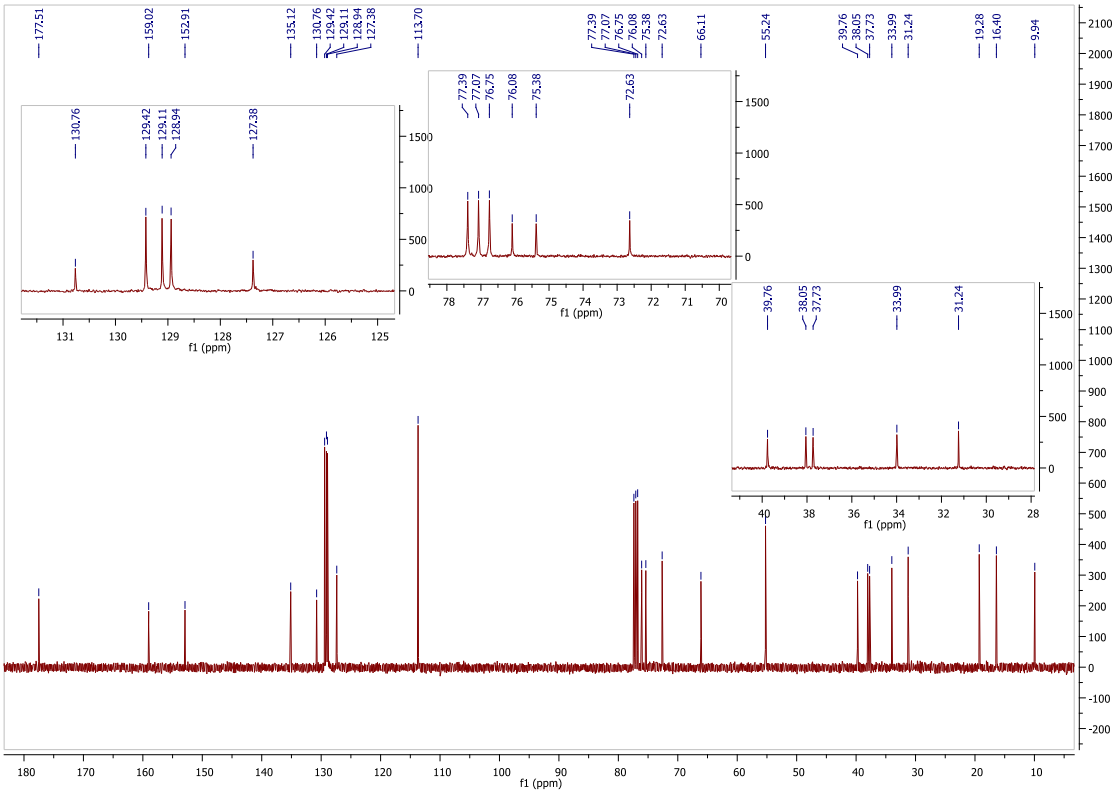

HO
O
O
f1 (ppm)

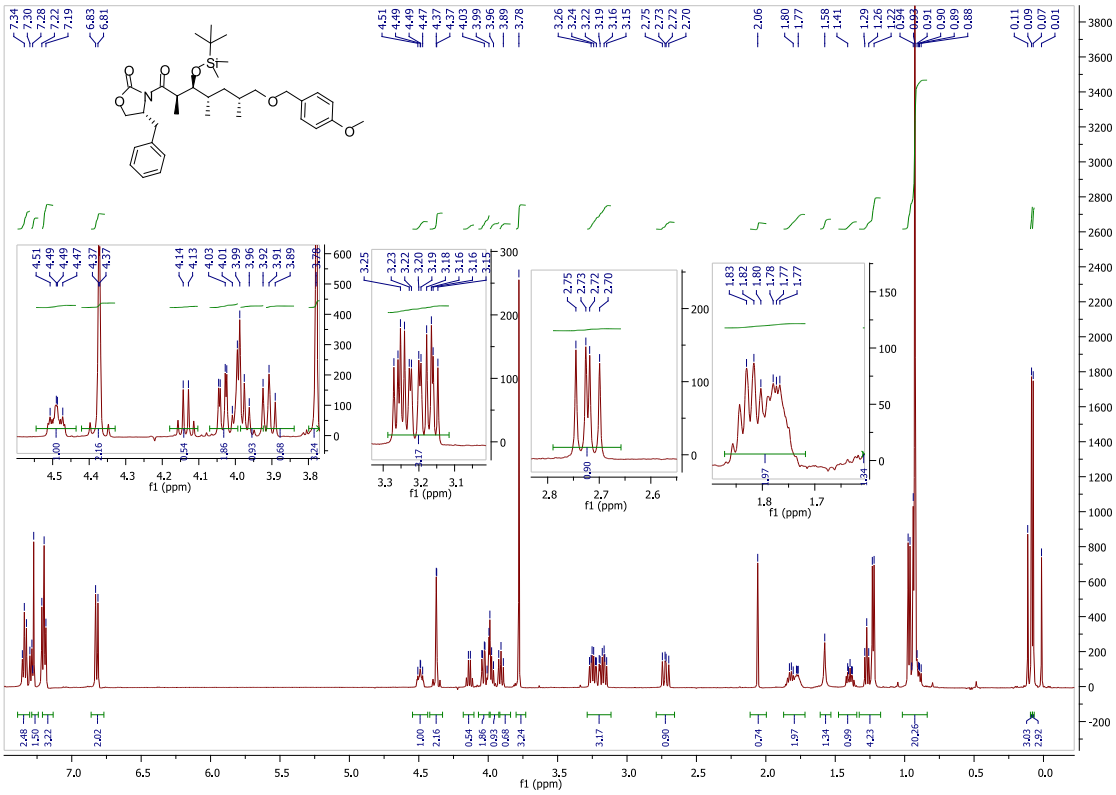

159.13
130.66
129.23
113.78
75.70
72.75
67.62
55.26
37.73
33.17
30.99
18.19
17.74
f1 (ppm)

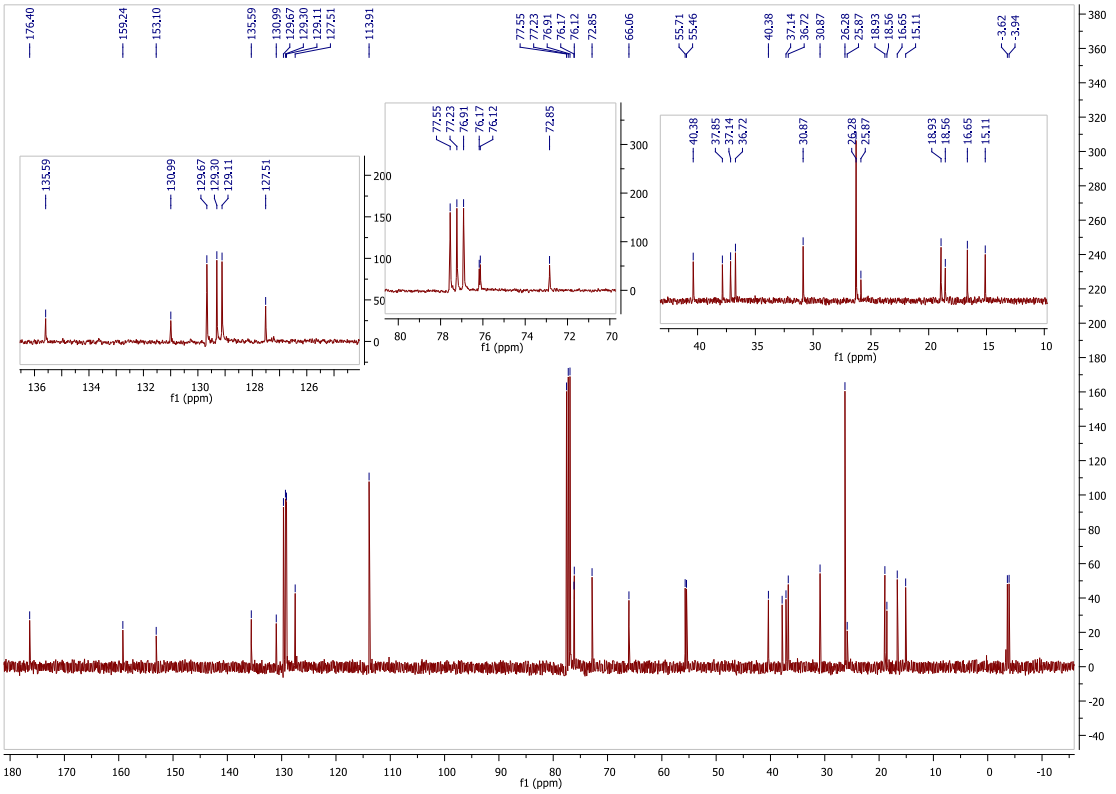


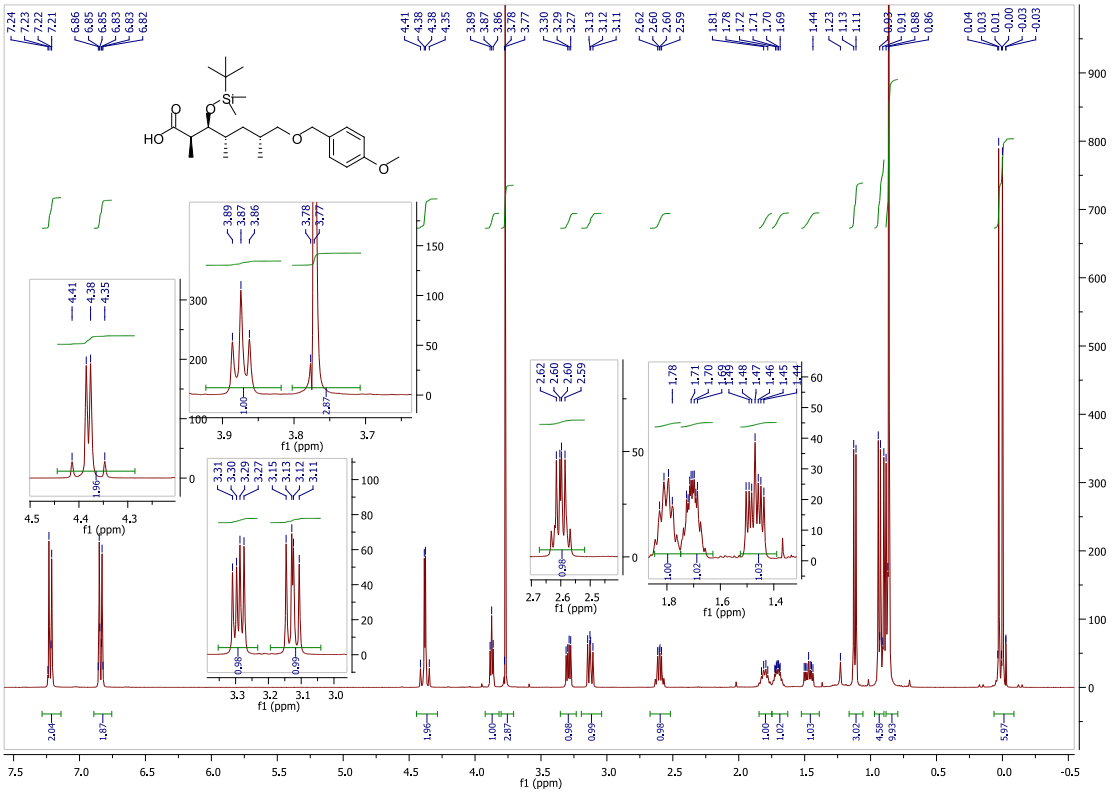


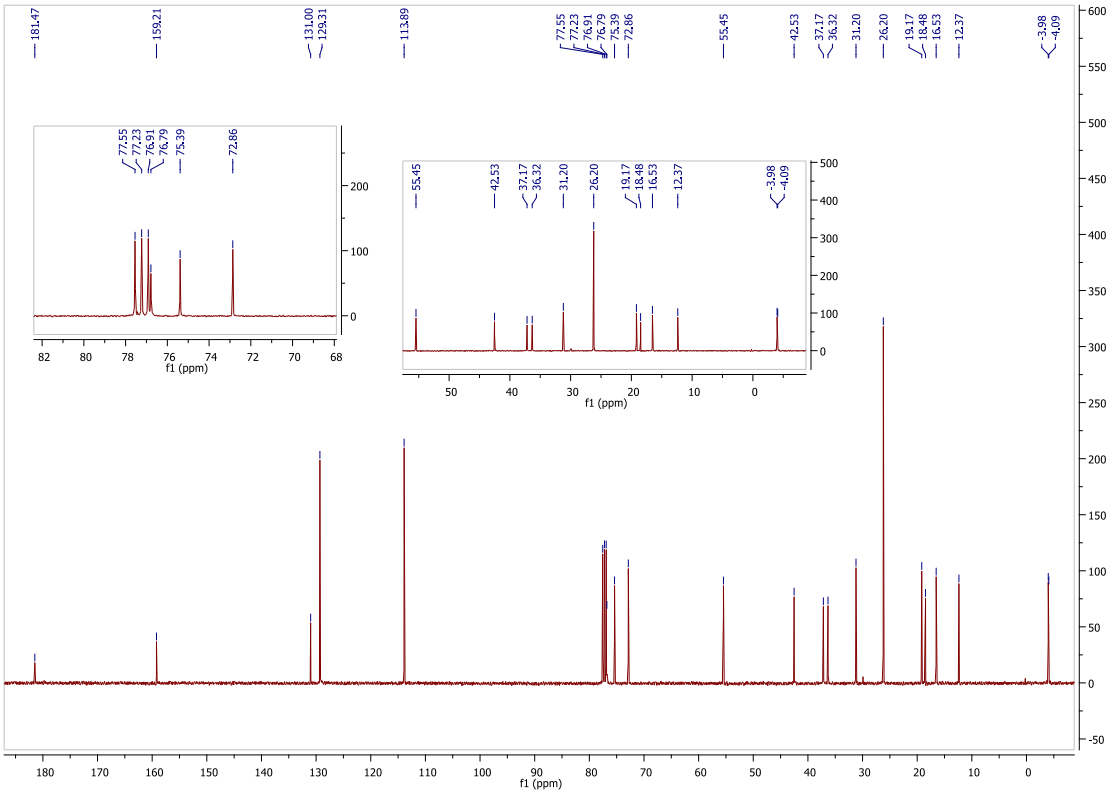


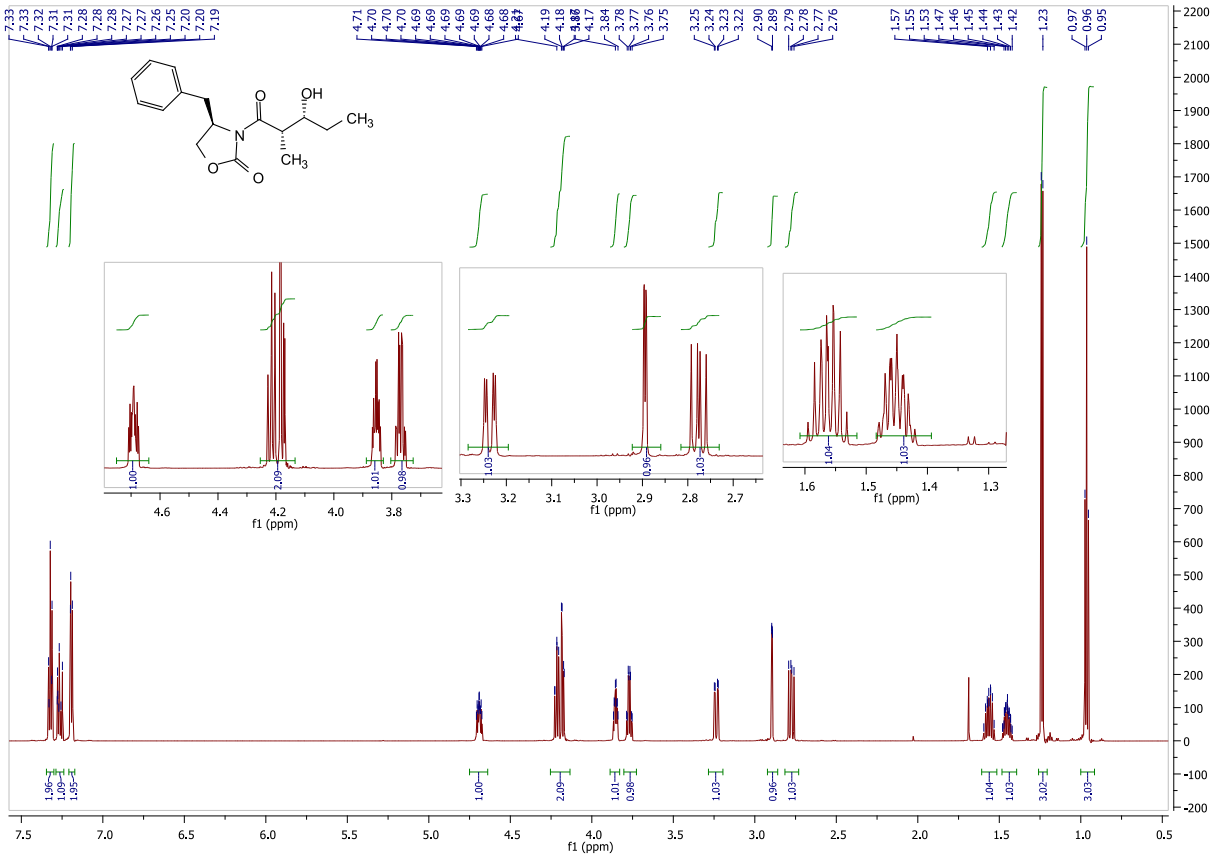


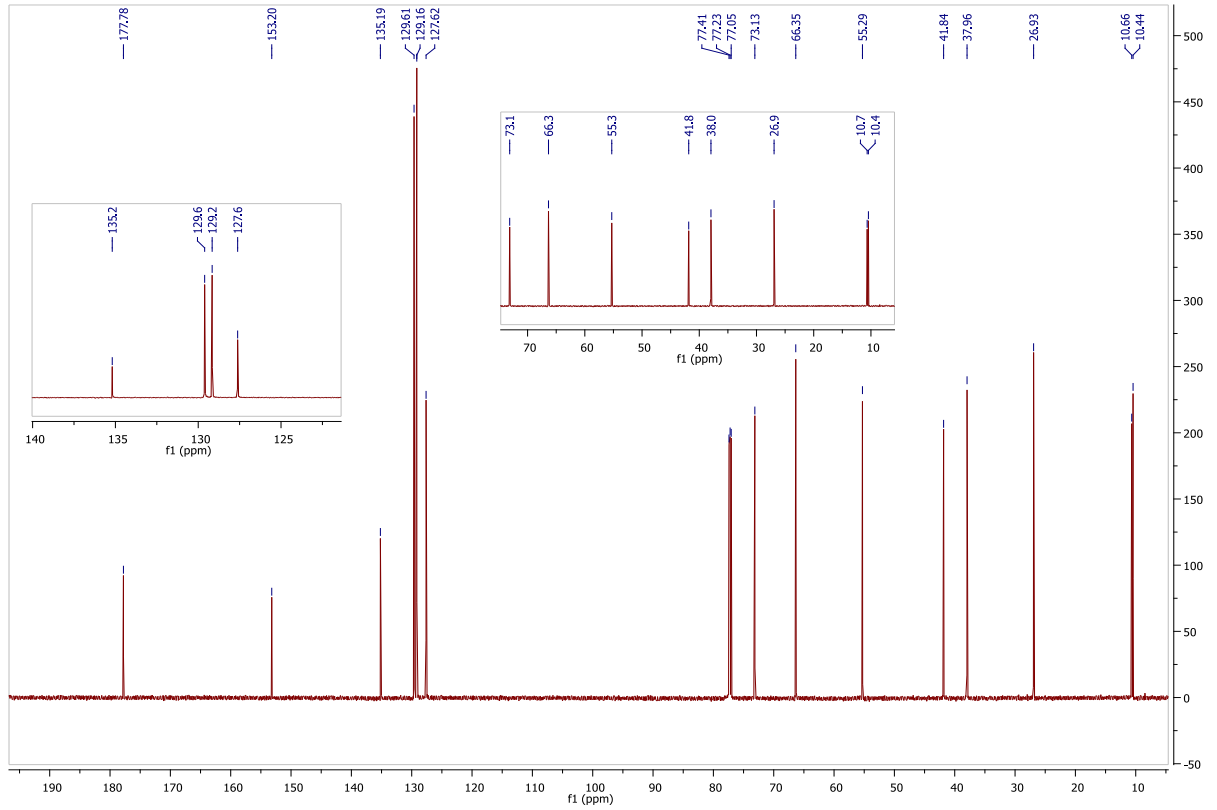


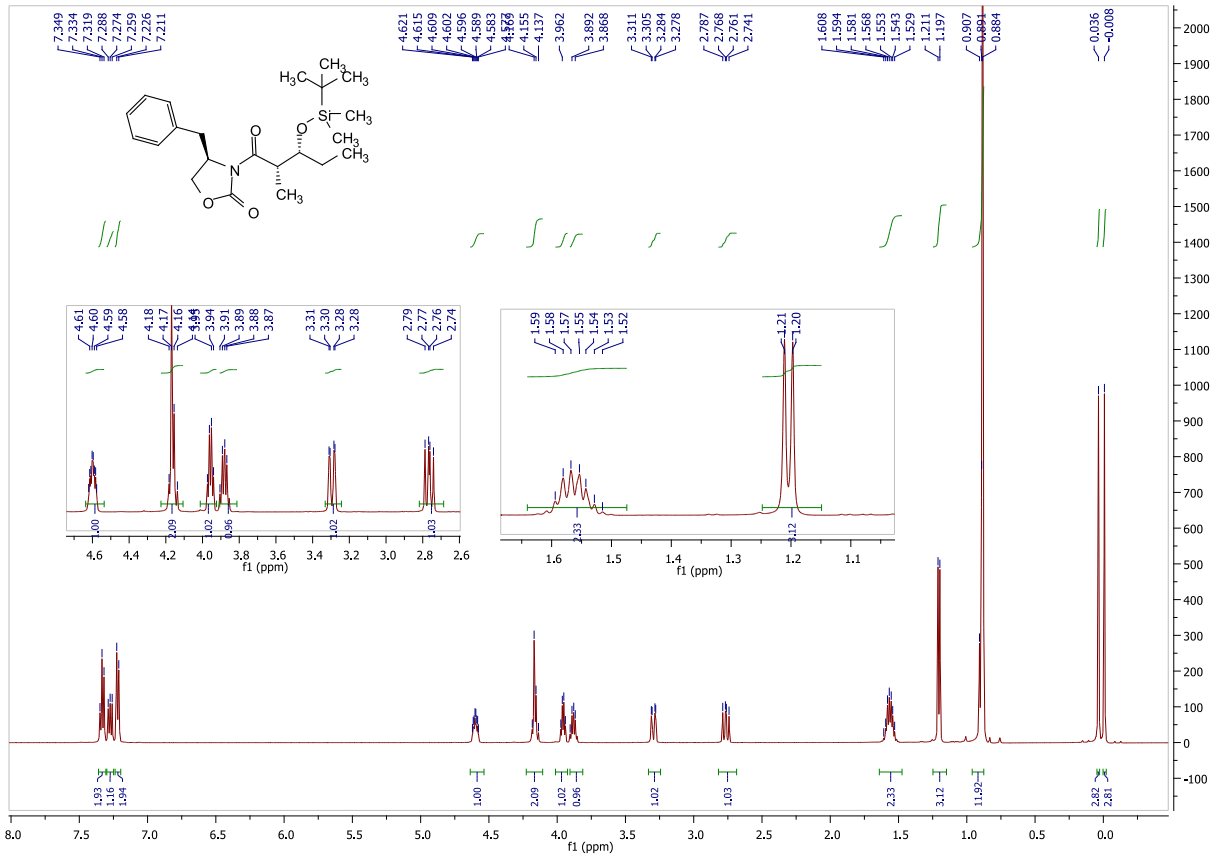


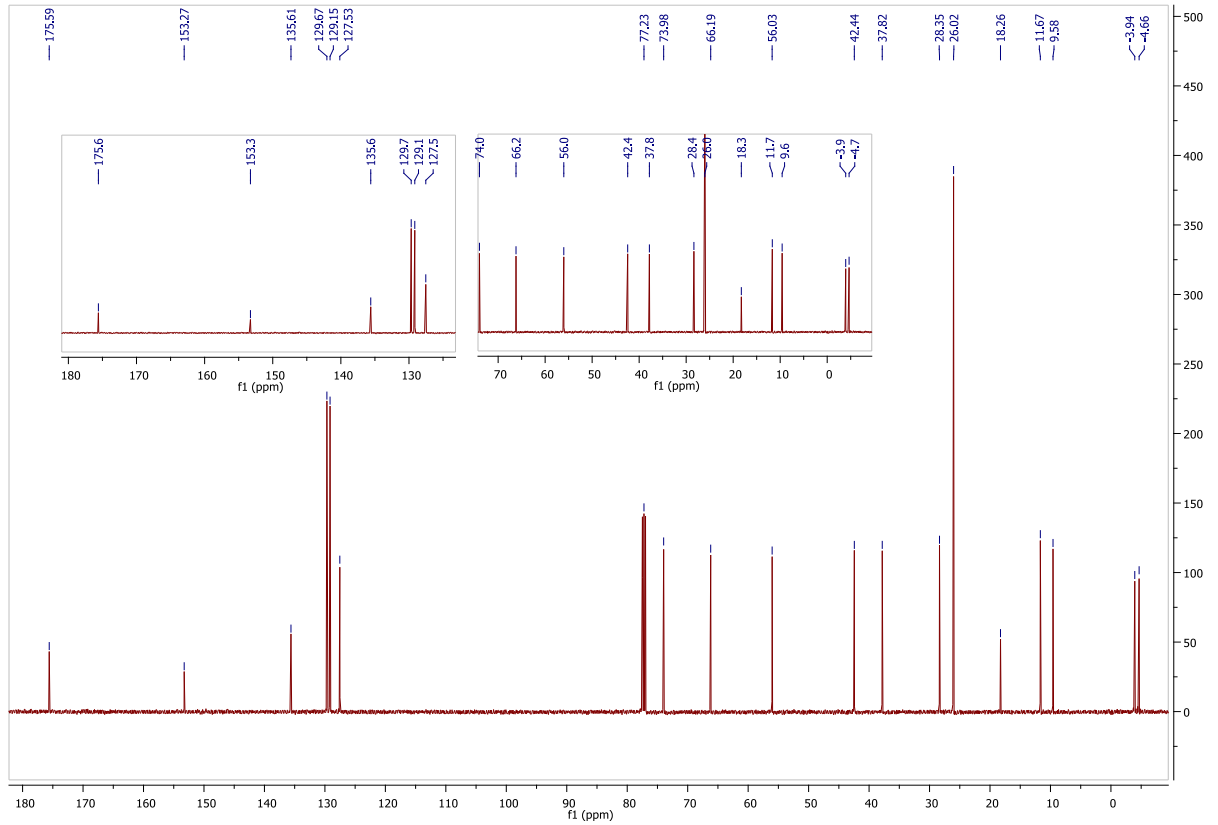


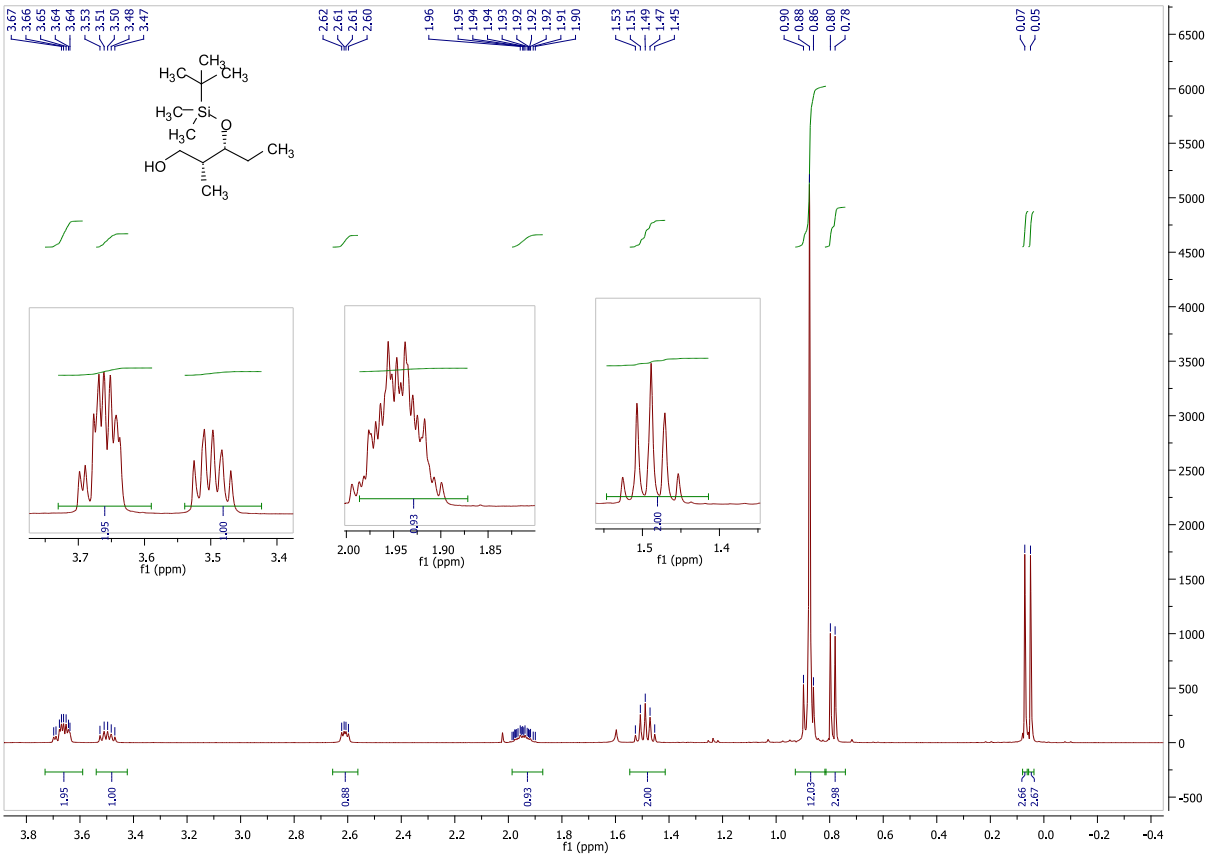


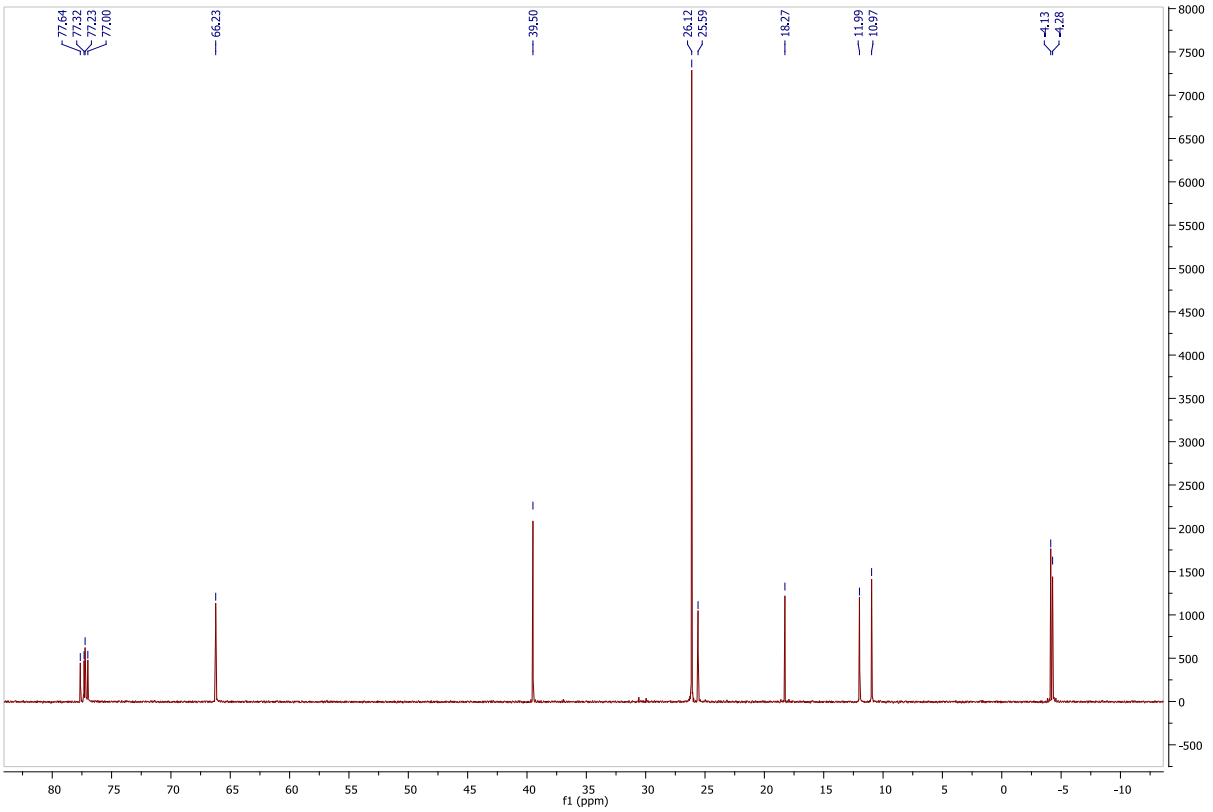

OH
CH3
CH3
O
N
O
O
f1 (ppm)

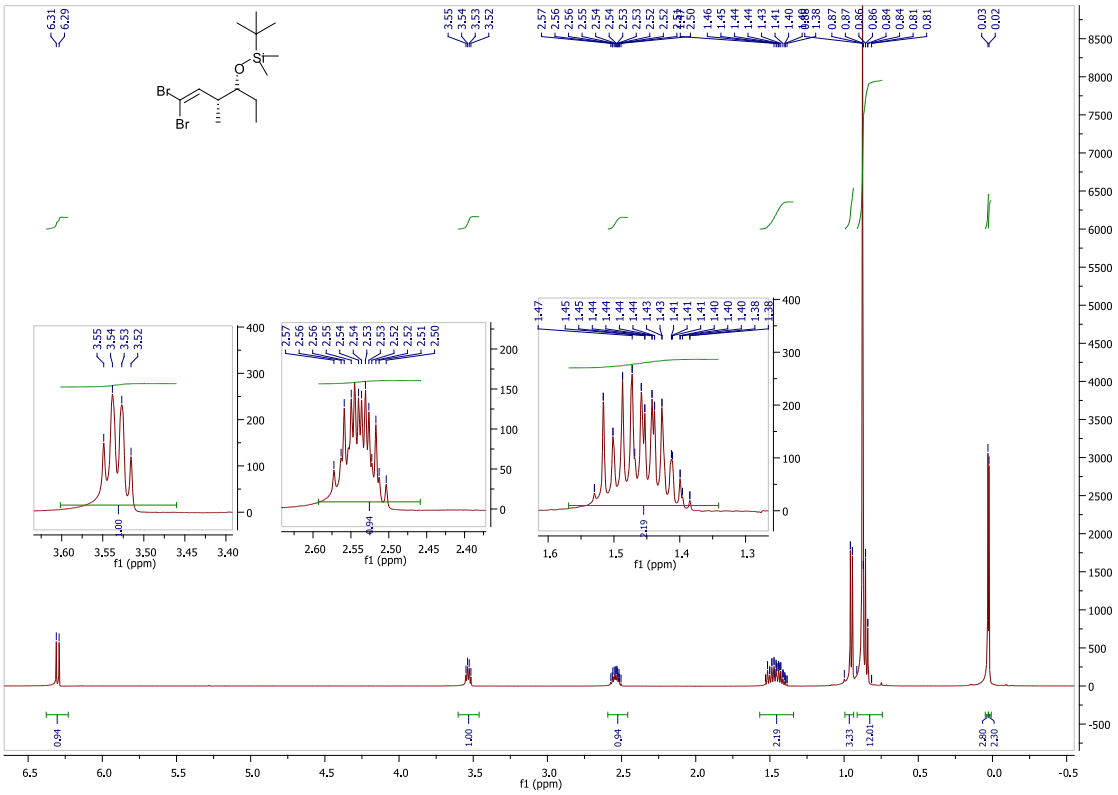

177.78
153.20
135.19
129.61
129.16
127.62
77.41
77.23
77.05
73.13
66.35
55.29
41.84
37.96
26.93
10.66
10.44
135.2
129.6
129.2
127.6
73.1
66.3
55.3
41.8
38.0
26.9
10.7
10.4
f1 (ppm)

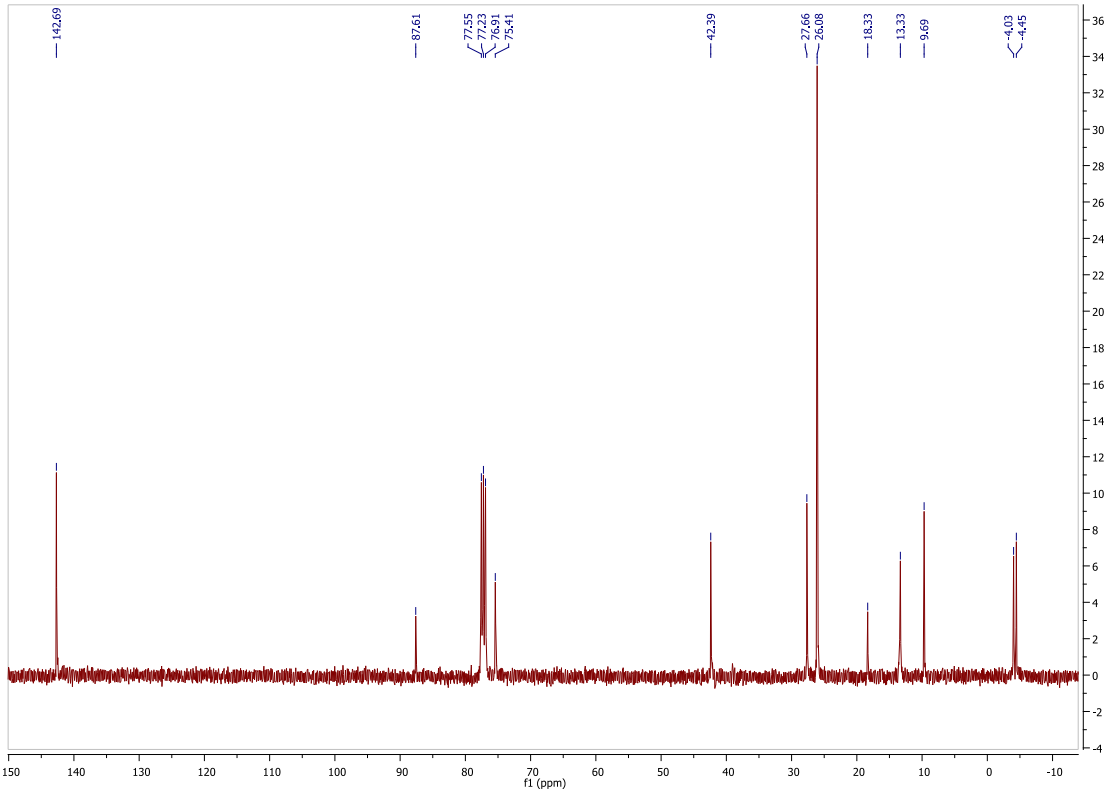


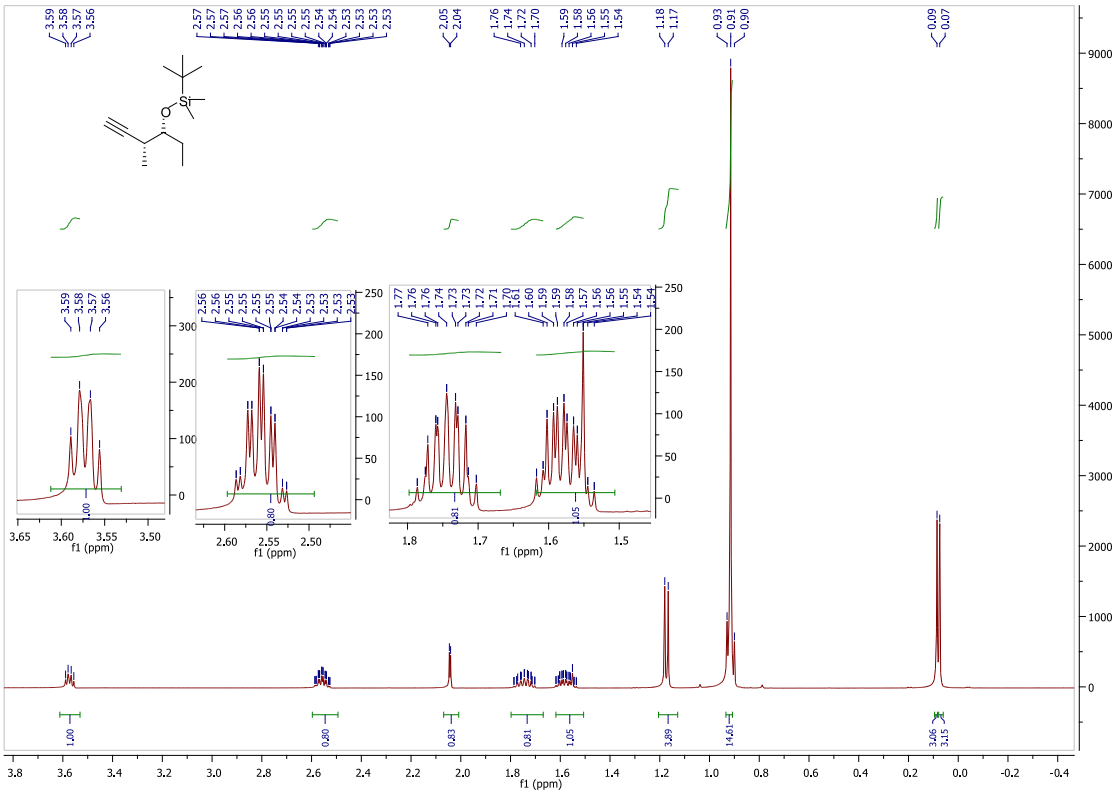


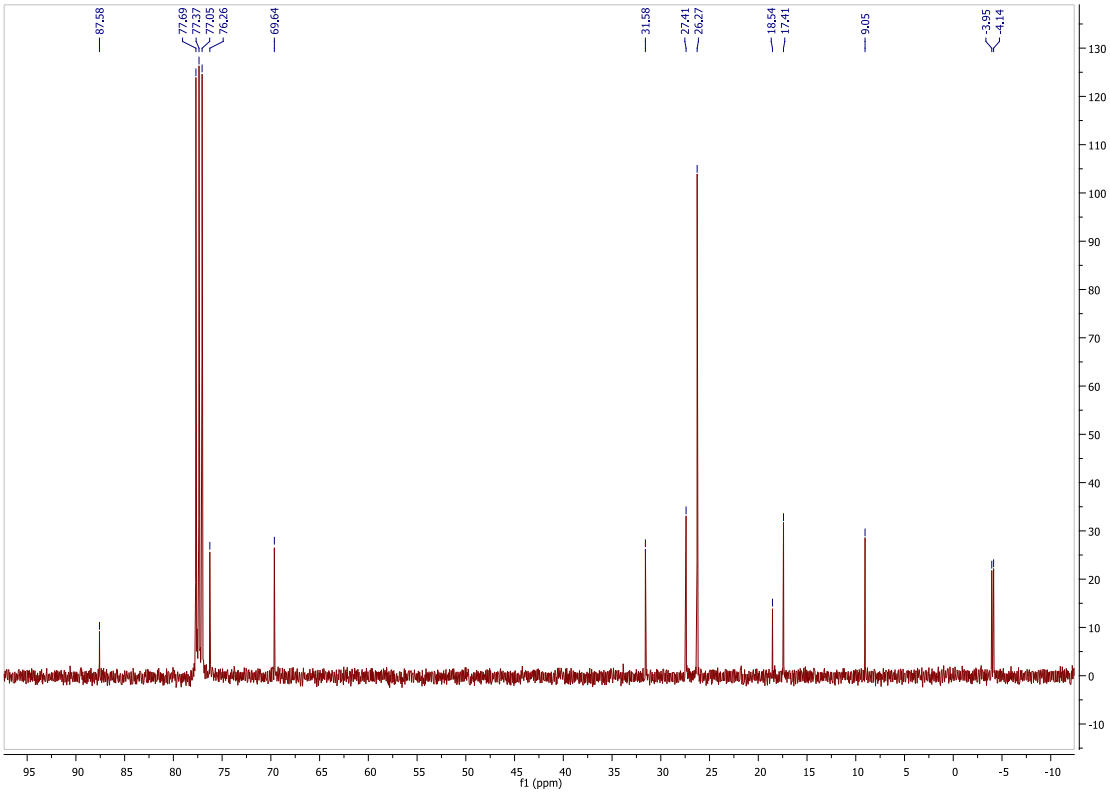

3.67
3.66
3.65
3.64
3.64
3.53
3.51
3.50
3.48
3.47
2.62
2.61
2.61
2.60
1.96
1.95
1.94
1.94
1.93
1.92
1.92
1.91
1.90
1.53
1.51
1.49
1.47
1.45
0.90
0.88
0.86
0.80
0.78
0.07
0.05
f1 (ppm)

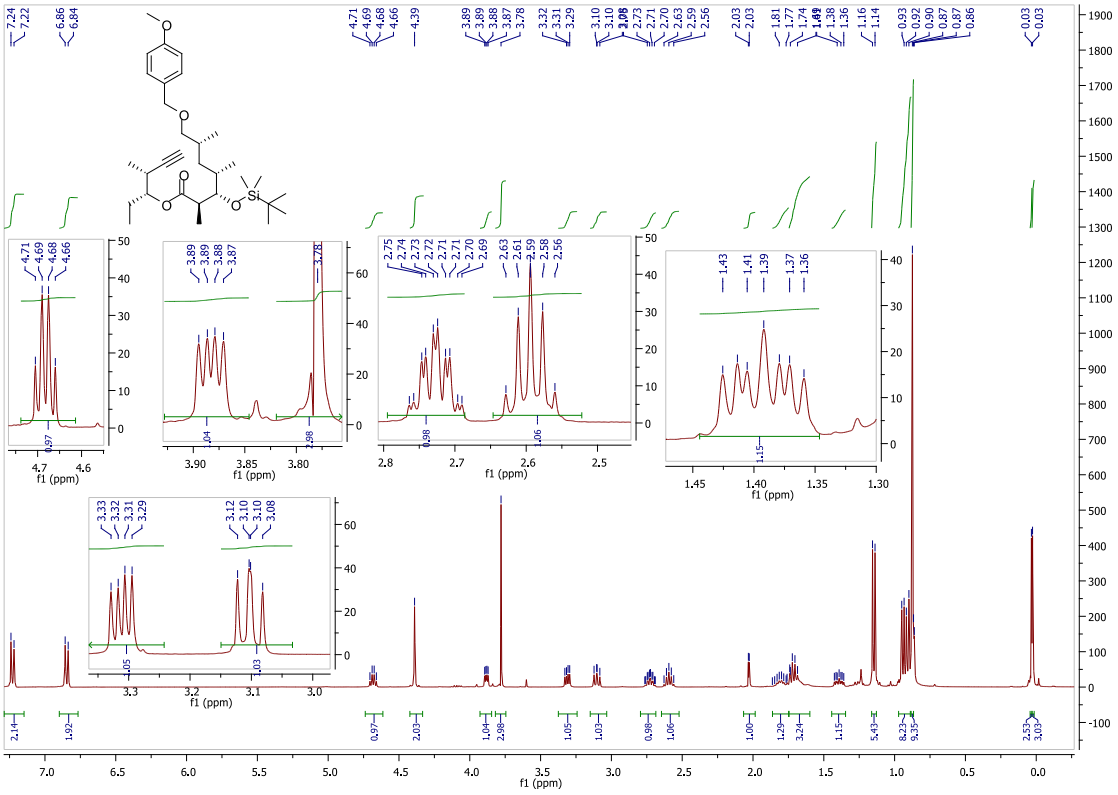

77.64
77.32
77.23
77.00
66.23
39.50
26.12
25.59
18.27
11.99
10.97
-4.13
-4.28
f1 (ppm)

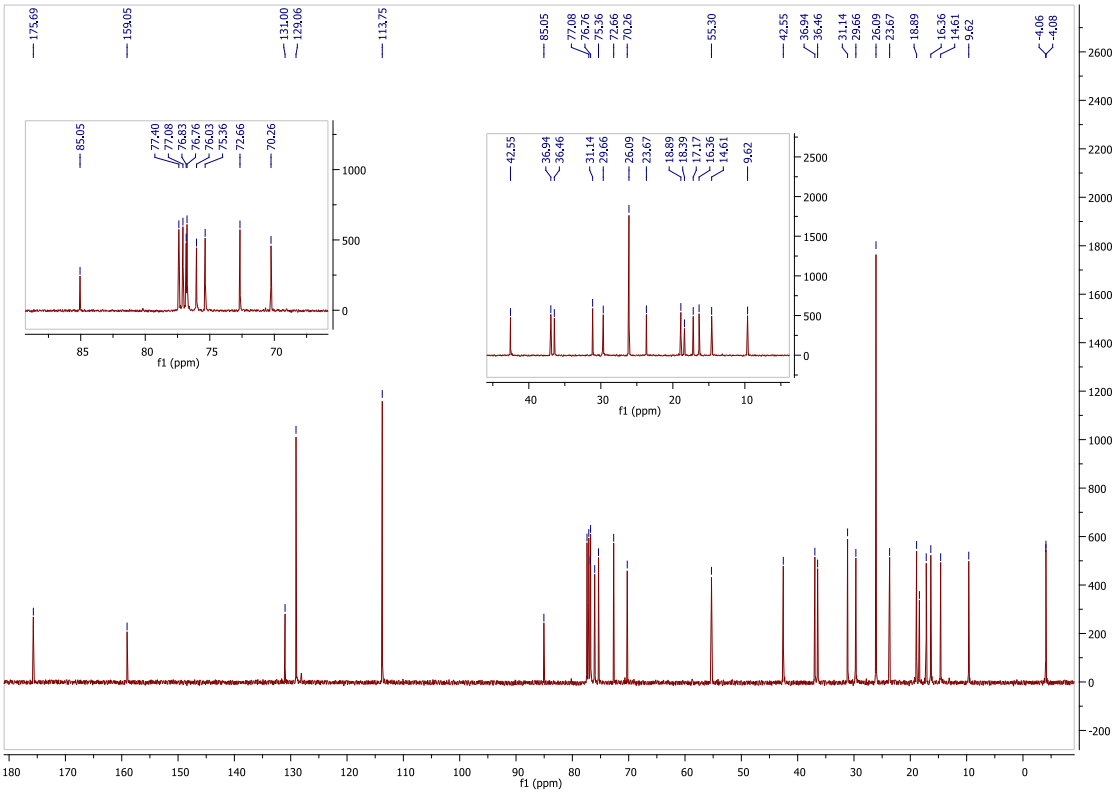

Br
Br
O
Si
f1 (ppm)

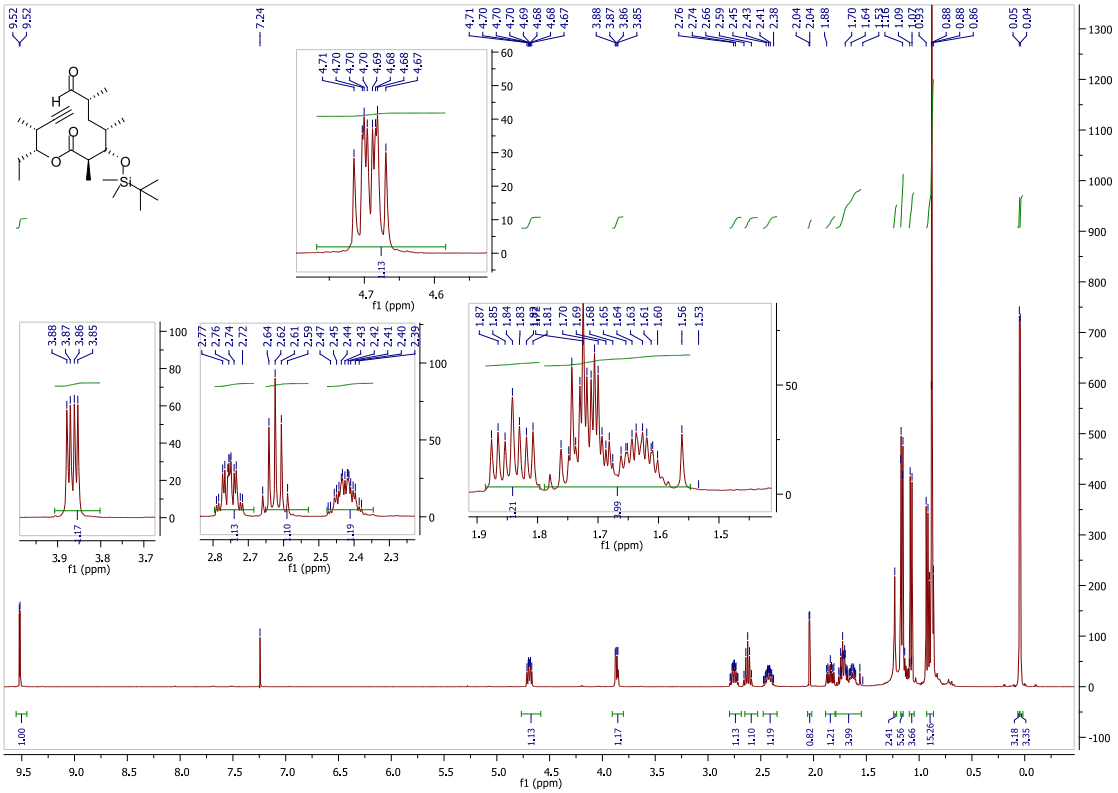

f1 (ppm)

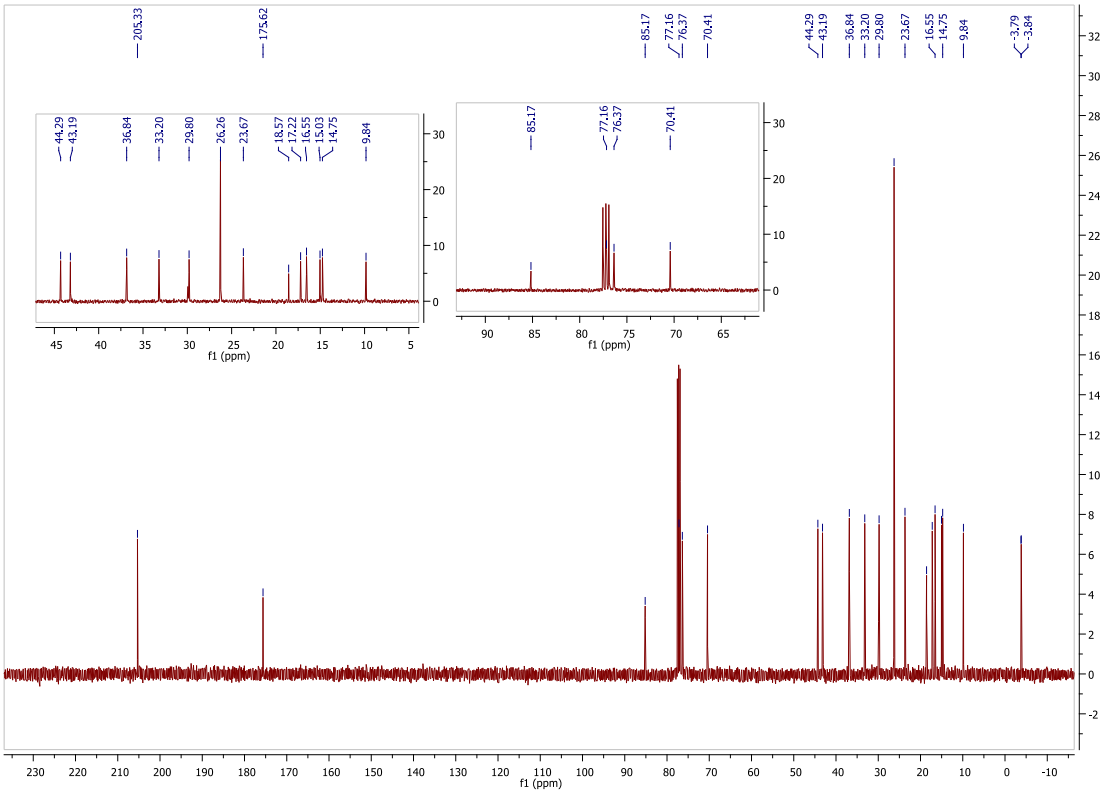


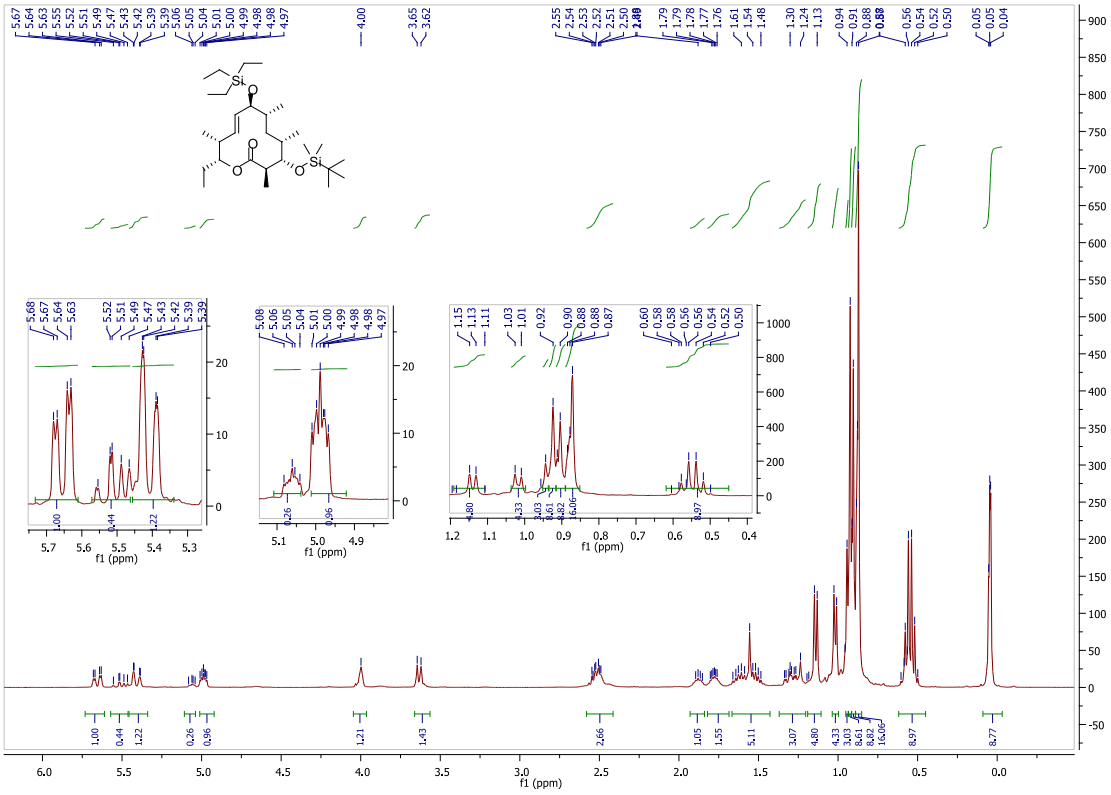


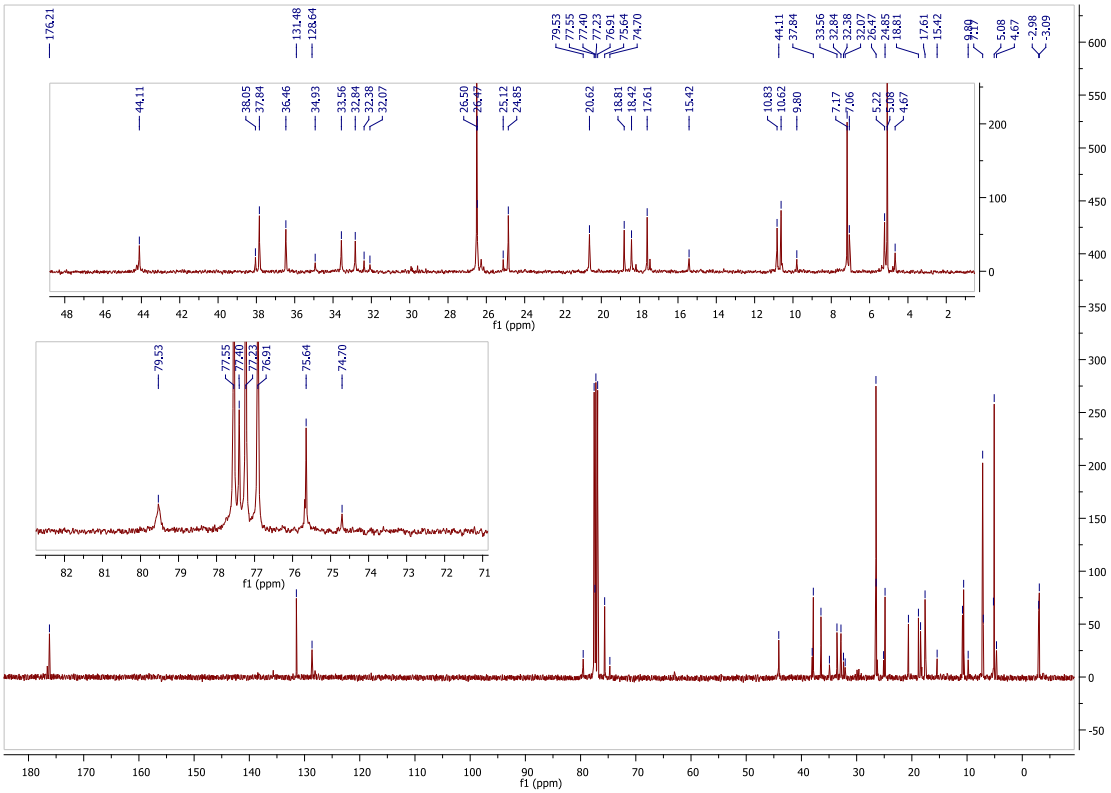


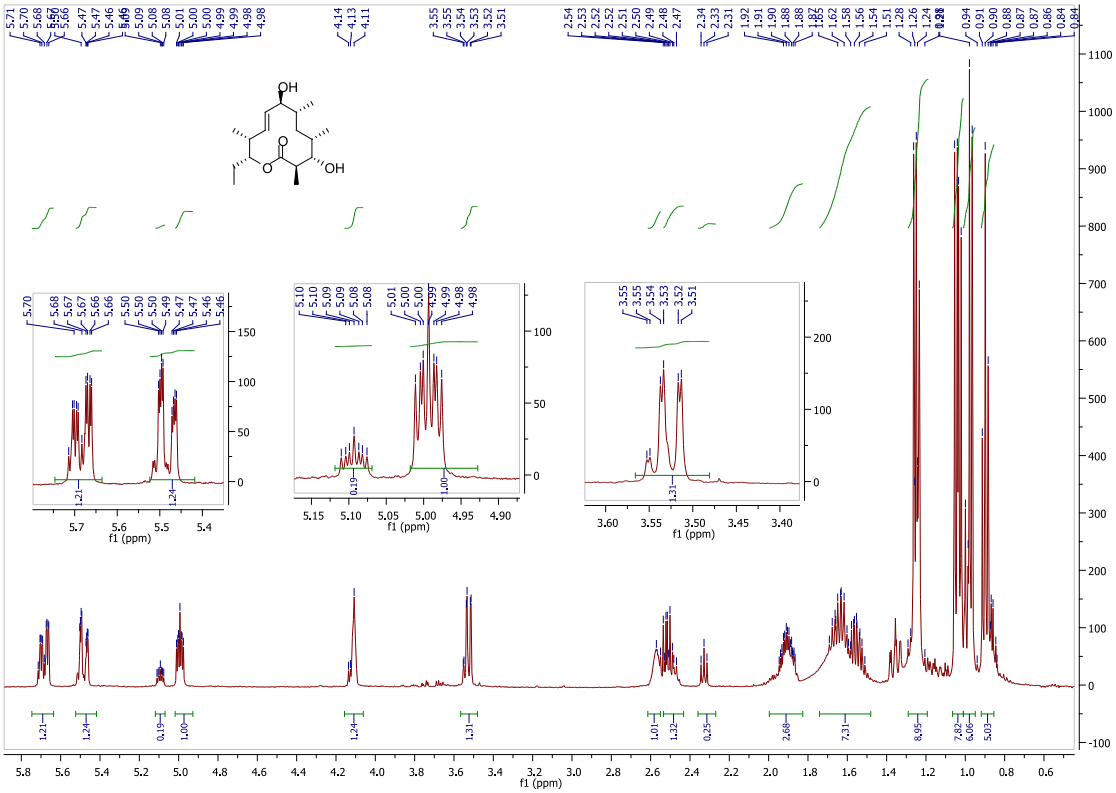


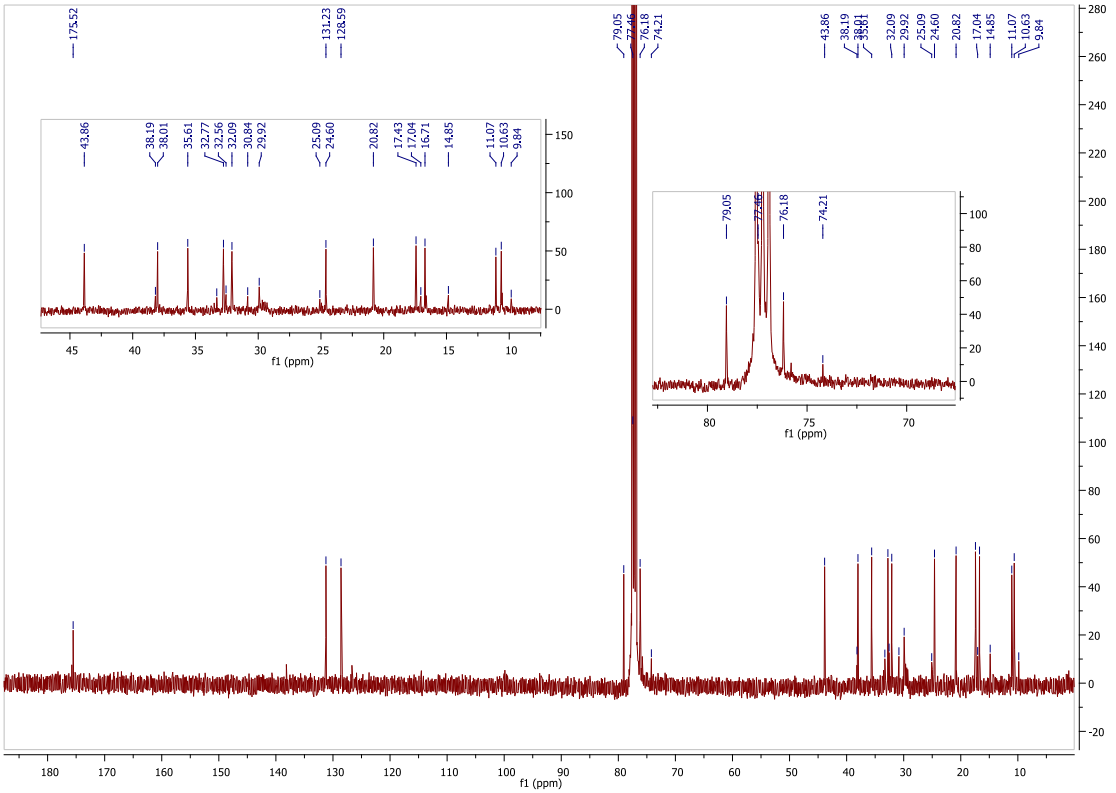









OH
O
O
OH
f1 (ppm)


175.52
131.23
128.59
79.05
77.46
76.18
74.21
43.86
38.19
38.01
35.61
32.77
32.56
32.09
30.84
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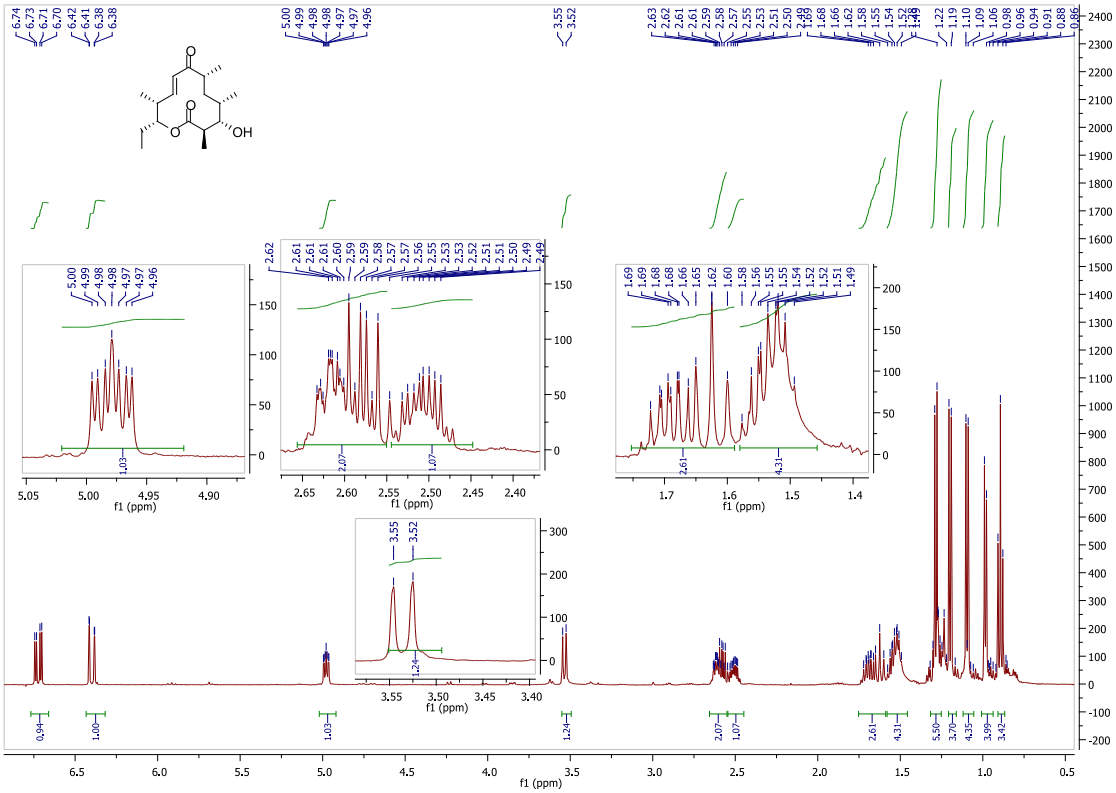
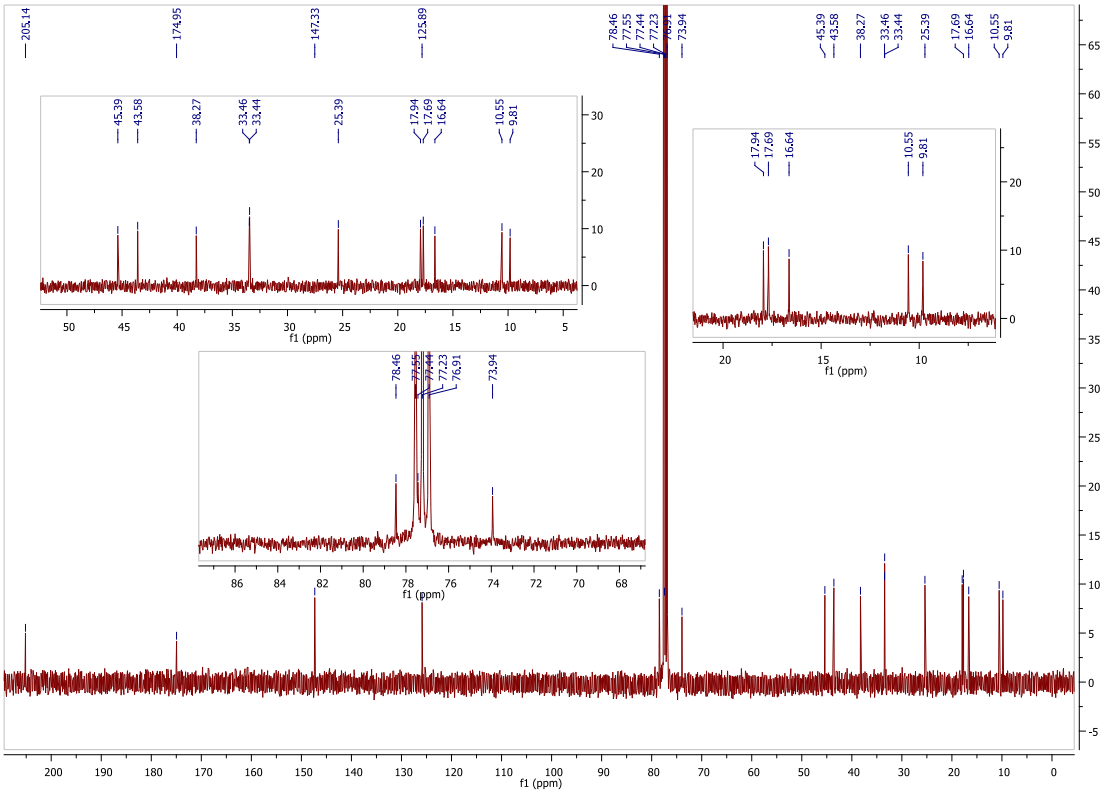
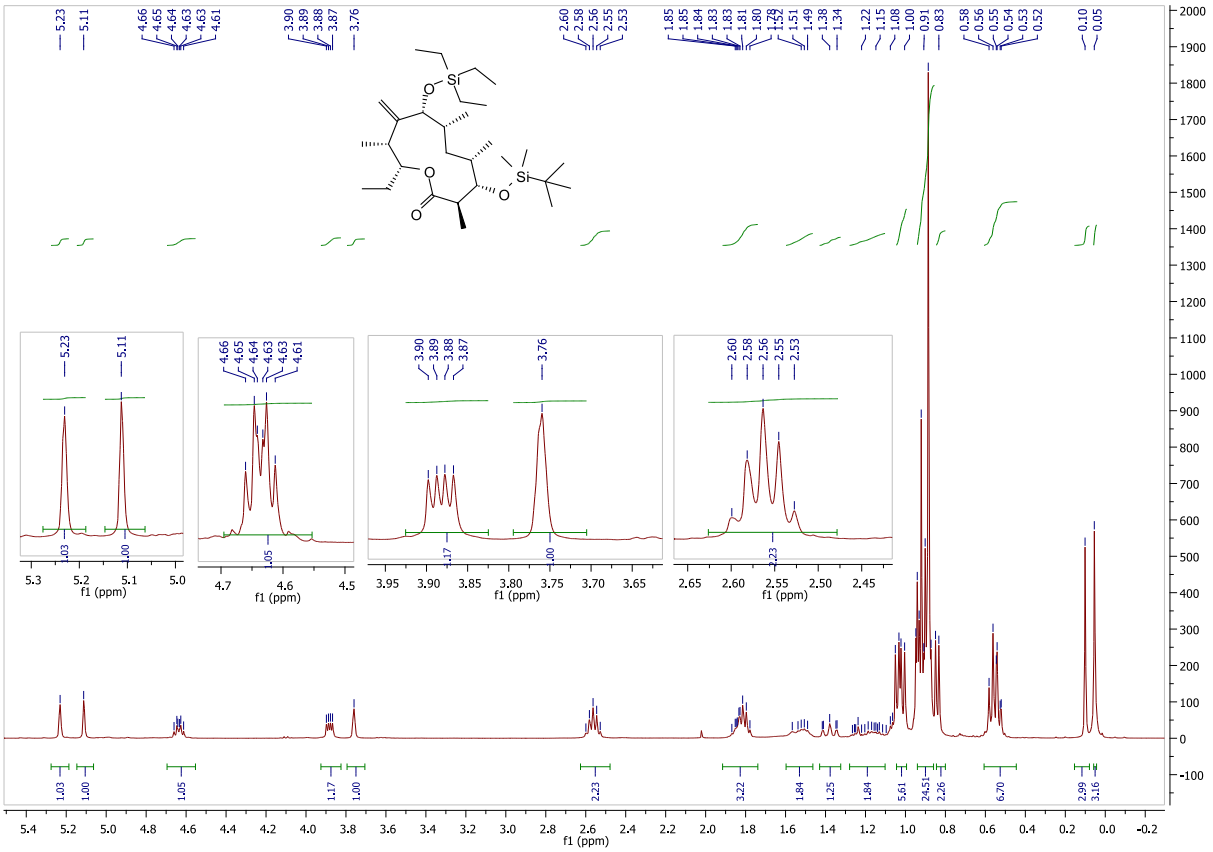
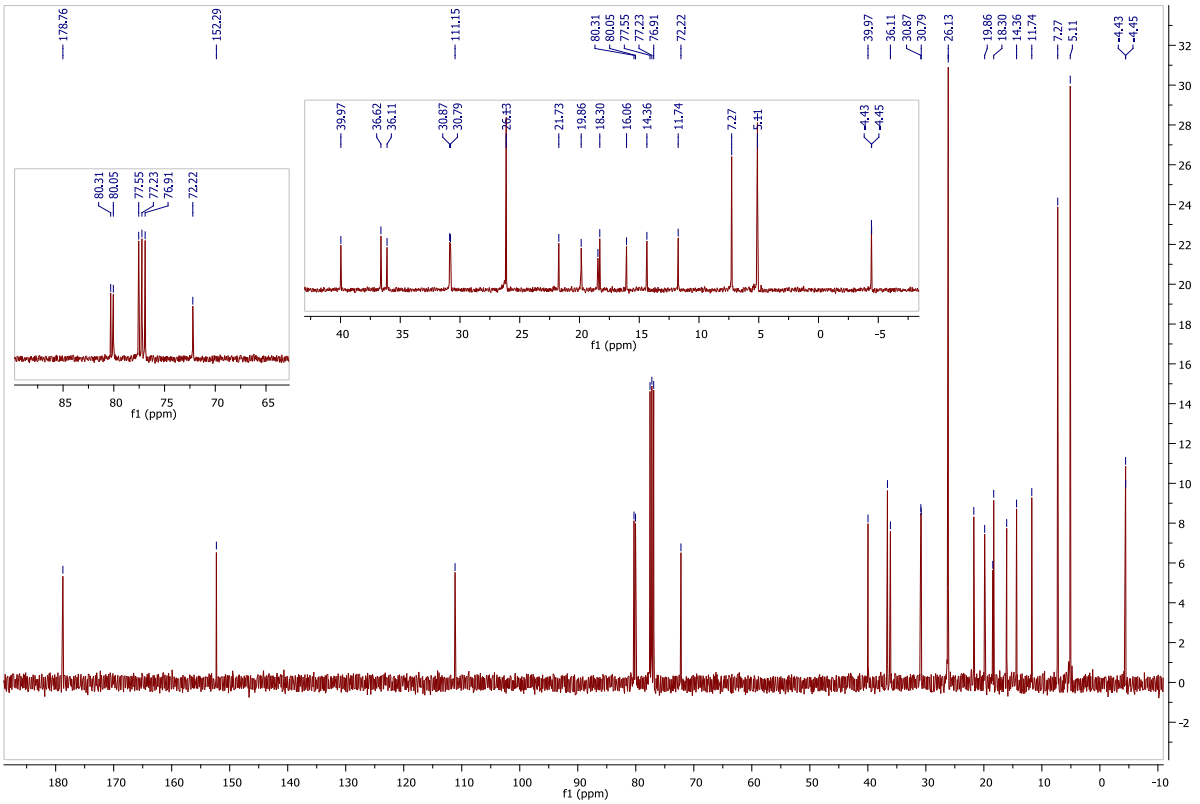
17.43
17.04
16.71
14.85
11.07
10.63
9.84
f1 (ppm)


OH
f1 (ppm)


f1 (ppm)





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