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Exploration of 1,3-dipolar cycloaddition reactions to construct the core skeleton of Calyciphylline A-type alkaloids

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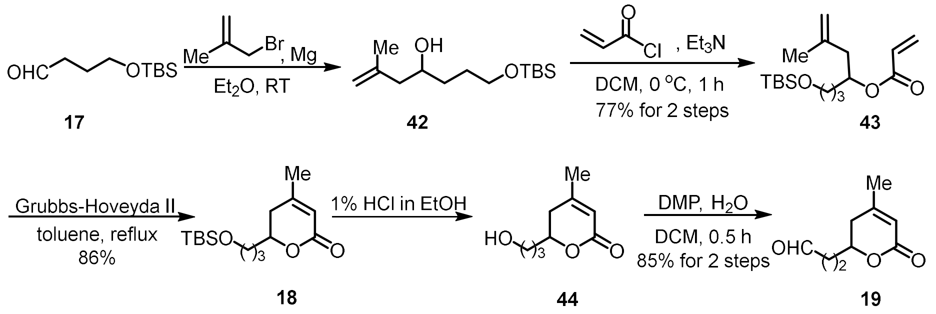
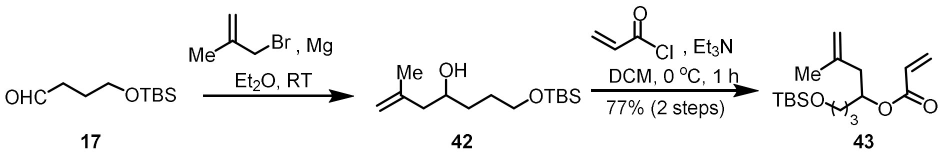
I. Experimental Procedures

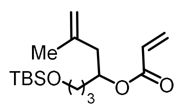
General Information:

Oxygen- and moisture-sensitive reactions were carried out under nitrogen atmosphere. Solvents were purified and dried by standard. All reactions were monitored by thin-layer chromatography with Huang Hai silica gel HSGF254 pre-coated plates (0.2 mm). Column chromatography was carried out on silica gel (200–300 mesh) purchased from *Silicycle* Silia Flash® P60. All commercially available reagents and catalysts were purchased from Sigma-Aldrich, TCI, Alfa Aesar, Strem Chemicals and J&K Chemical. ^{1}H and ^{13}C NMR spectra were recorded on Bruker-500, 400 spectrometers. Chemical shifts for ^{1}H and ^{13}C NMR spectra are reported in ppm (δ) relative to residue protium in the solvent (^{1}H, δ 7.26 ppm for $CDCl_3$; ^{13}C, δ 77.00 ppm for $CDCl_3$; the multiplicities are presented as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. High-resolution mass spectra (HRMS) were acquired on Waters Micromass GCT Premier or Bruker Daltonics Inc. APEXIII 7.0 TESLA FTMS. Mass spectra were acquired on Agilent 5975C. Specific rotation was performed on Rudolph Research Analytical Autopol VI Polarimeter (λ = 589 nm, T = 20 °C).

Experimental Procedures and Compound Characterization:



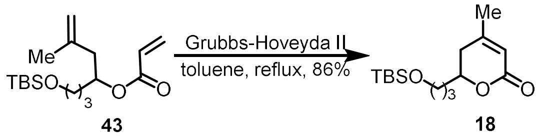


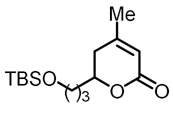


43

To a suspension of aldehyde **17** (4.0 g, 19.77 mmol, 1.0 equiv.) and magnesium chips (2.4 g, 98.83 mmol, 5.0 equiv.) in diethyl ether (200 mL) was added 3-bromo-2-methylpropene (13.34g，98.83 mmol, 5.0 equiv.) at room temperature during 10 min as the solution turned yellow, the mixture was stirred at room temperature for 2 hours, quenched by methanol (4 mL) and saturated NH_4Cl (aq.). Then the mixture was extracted with ethyl acetate (2×100 mL), the combined organic layer was washed with brine (3×50 mL), dried over Na_2SO_4, filtered and concentrated in vacuo to afford the crude product **42** (4.98 g), which was used directly for next step without further purification.

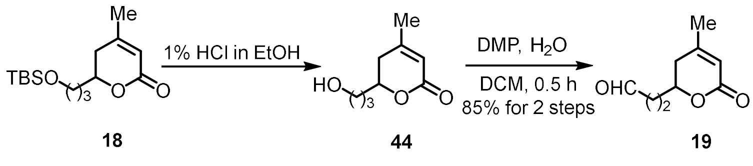
To a solution of crude product alcohol **42** (4.98 g) in dichloromethane (100 mL) was added triethylamine (3.9 g, 38.53 mmol, 2.0 equiv.) at 0 ºC, then acryloyl chloride (2.8 g, 38.53 mmol, 2.0 equiv.) was added dropwise during 10 min. The reaction was stirred at 0 ºC for 3 hours, then the mixture was poured into pre-ice cold saturated NH_4Cl (aq.) and extracted with ethyl acetate (300 mL). The combined organic layer was washed with brine (3×50 mL), dried over Na_2SO_4, filtered and concentrated in vacuo to afford the crude product, which was purified by silica gel column chromatography (2% to 4% ethyl acetate-petroleum ether) to give product **43** as a yellowish oil (4.66 g, 77% for 2 steps); R_f = 0.6 (7.5% ethyl acetate-petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.37 (d, J = 17.3 Hz, 1H), 6.09 (dd, J = 17.3, 10.4 Hz, 1H), 5.79 (d, J = 10.4 Hz, 1H), 5.13 (m, 1H), 4.74 (d, J = 17.2 Hz, 2H), 3.71 – 3.44 (m, 2H), 2.29 (dd, J = 21.6, 6.5 Hz, 2H), 1.75 (s, 3H), 1.59 – 1.49 (m, 2H), 1.31 (d, J = 14.7 Hz, 2H), 0.88 (s, 9H), 0.04 (s, 6H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.9, 141.6, 130.3, 128.8, 113.4, 72.2, 62.7, 42.9, 30.3, 28.6, 25.9, 22.5, 18.3, -5.3 ppm; IR ν_{max} 3734, 2361, 2342, 1722, 1275, 833 cm^{-1}; HRMS–EI (m/z): [M]$^+$ calcd for $C_{17}H_{32}O_3Si$, 312.2121; found, 312.2126.

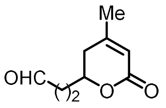




18

To a solution of diene **43** (320 mg, 1.02 mmol, 1.0 equiv.) in toluene (50 mL) was added Hoveyda-Grubbs II catalyst (19 mg, 0.03 mmol, 0.03 equiv.) in one potion. The mixture was heated to reflux and stirred for 3 hours. The reaction mixture was cooled to room temperature and concentrated in vacuo to afford the crude product, which was purified by silica gel column chromatography (4% to 10% ethyl acetate-petroleum ether) to give product **18** as dark oil (250 mg, 86%); R_f= 0.4 (20% ethyl acetate-petroleum ether; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.94 – 5.74 (m, 1H), 4.55 – 4.35 (m, 1H), 3.72 – 3.57 (m, 2H), 2.38 – 2.27 (m, 1H), 2.21 (dd, J = 17.8, 3.9 Hz, 1H), 1.97 (s, 3H), 1.87 – 1.56 (m, 4H), 0.89 (s, 9H), 0.04 (s, 6H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ165.4, 157.1, 116.5, 77.2, 62.6, 34.7, 31.4, 28.0, 25.9, 23.0, 18.3, -5.4 ppm; IR ν_{max} 3736, 2886, 1387, 1250, 775 cm^{-1}; HRMS–EI (m/z): [M]$^+$ calcd for $C_{15}H_{28}O_3Si$, 284.1808; found, 284.1805.

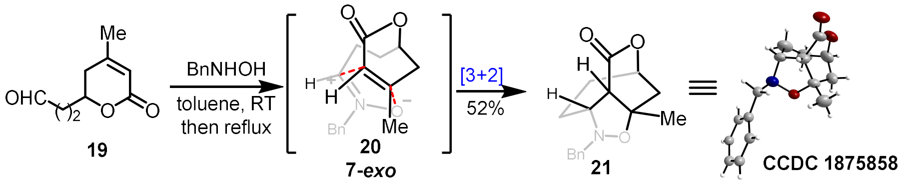


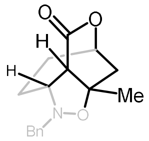


19

To a solution of lactone **18** (333 mg, 1.17 mmol, 1.0 equiv.) in ethanol (1 mL) was added hydrochloric acid (1% in ethanol, 12 mL) dropwise during 2 min. The mixture was stirred at room temperature for 10 min. Then saturated $NaHCO_3$ (aq.) was added to quench the reaction and concentrated in vacuo, diluted by ethyl acetate (50 mL) and washed with brine (3×10 mL), dried over Na_2SO_4, concentrated in vacuo to afford the crude product **44** (200 mg), which was used directly for next step without further purification.

To a stirred crude product solution of alcohol **44** (200 mg) in dichloromethane (15 mL) was added Dess-Martin periodinane (1.5 g, 3.53 mmol, 3.0 equiv.) in one potion, followed by an addition of water (60 μL) and the solution turned turbid and stirred at room temperature for 30 min. The reaction was quenched with saturated $NaHCO_3$ (aq., 5 mL) and saturated $Na_2S_2O_3$ (aq., 5 mL), extracted with ethyl acetate (3×20 mL). The combined organic layer was washed with brine (2×10 mL), dried over Na_2SO_4, filtered and concentrated in vacuo to afford the crude product, which was purified by silica gel column chromatography (50% to 70% ethyl acetate-petroleum ether) to give product **19** as colorless oil (167 mg, 85% for 2 steps); R_f = 0.7 (75% ethyl acetate-petroleum ether); ^1H NMR (400 MHz, $CDCl_3$) δ 9.83 (t, *J* = 0.7 Hz, 1H), 5.82 – 5.79 (m, 1H), 4.42 (ddt, *J* = 11.7, 8.9, 3.9 Hz, 1H), 2.76 (dt, *J* = 7.5, 3.9 Hz, 2H), 2.40 – 2.29 (m, 1H), 2.28 – 2.19 (m, 1H), 2.11 – 2.01 (m, 1H), 2.01 – 1.92 (m, 4H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 201.0, 164.8, 157.1, 116.4, 75.9, 39.2, 34.8, 26.9, 22.9 ppm; IR ν_{max} 3727, 2361, 2342, 1717, 1260, 748 cm^{-1}, HRMS–EI (m/z): $[M]^+$ calcd for $C_9H_{12}O_3$, 168.0786; found, 168.0787.





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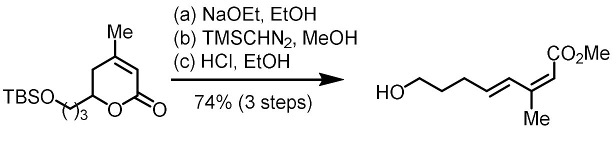
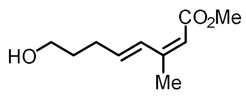
To a solution of aldehyde **19** (200 mg, 1.19 mmol, 1.0 equiv.) in toluene was added potassium carbonate (361 mg, 2.62 mmol, 2.2 equiv.) followed by *N*-benzylhydroxylamine hydrochloride (285 mg, 1.78 mmol, 1.5 equiv.) in one potion. The mixture was stirred at room temperature overnight until all the amine hydrochloride was dissolved to get a clarified solution. Then the solution was filtered and concentrated to obtain a greenish oil which was redissolved by toluene and heated to reflux at least 8 hours. The mixture was concentrated to afford the crude product, which was purified by silica gel column chromatography (10% to 20% ethyl acetate-petroleum ether) to give product **21** as yellowish powder (170 mg, 52%); R_f= 0.5 (20% ethyl acetate-petroleum ether); ^1H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.23 (m, 5H), 4.79 (ddd, *J* = 9.3 Hz, 1H), 4.20 (d, *J* = 12.7 Hz, 1H), 3.86 (d, *J* = 12.7 Hz, 1H), 3.73 (dd, *J* = 7.2 Hz, 1H), 3.62 (d, *J* = 7.8 Hz, 1H), 2.21 – 2.08 (m, 2H), 2.05 (dd, *J* = 14.9, 2.1 Hz, 1H), 1.91 (dd, *J* = 14.9, 4.4 Hz, 1H), 1.86 – 1.76 (m, 1H), 1.65 (ddd, *J* = 10.9, 8.6, 3.8 Hz, 1H), 1.59 (s, 3H) ppm; ^{13}C

NMR (101 MHz, $CDCl_3$) δ 170.5, 136.6, 128.9, 128.4, 127.6, 84.6, 75.2, 64.6, 62.9, 56.8, 41.9, 29.5, 26.8, 25.7 ppm; IR ν_{max} 2918, 1698, 1654, 1411, 1142 cm^{-1}; HRMS–EI (m/z): [M]$^+$ calcd for $C_{16}H_{19}NO_3$, 273.1365; found, 273.1363; Condition for culturing single crystal: 3 mg scale, dichloromethane : hexane = 1 : 4, static mixing, volatilization and crystallization at room temperature, CCDC 1875858.

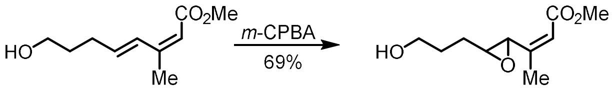


18 **24**

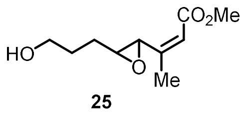


24

To a solution of lactone **18** (312 mg, 1.10 mmol, 1.0 equiv.) in ethanol (12 mL) was added sodium ethoxide (373.2 mg, 5.50 mmol, 5.0 equiv.) in one potion. The mixture was heated to reflux until NMR indicated there was no reactant left. Then the solvent was evaporated and diluted by ethyl acetate (20 mL), washed with brine (2×10 mL), dried over Na_2SO_4, filtered and concentrated in vacuo to afford the crude product, which was dissolved by methanol (10 mL). After that, (trimethylsilyl)diazomethane (636 mg, 5.52 mmol, 5.0 equiv.) was added dropwise in 10 min at 0 °C, the mixture was stirred for 3 hours and directly concentrated in vocuo to get a yellowish oil. The crude product was then dissolved in ethanol (10 mL) and HCl (1% in ethanol, 10 mL) was added dropwise at room temperature. The mixture was stirred for another 30 min and quench by saturated $NaHCO_3$ (5 mL), then it was extracted by ethyl acetate (80 mL), washed with brine (2×20 mL), dried over Na_2SO_4, filtered and concentrated in vacuo to afford the crude product, which was purified by silica gel column chromatography (10% to 30% ethyl acetate-petroleum ether) to give product **24** as colorless oil (150 mg, 74% for 3 steps); R_f = 0.4 (30% ethyl acetate-petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (dq, J = 16.1, 1.4 Hz, 1H), 6.16 (dt, J = 15.8, 6.9 Hz, 1H), 5.62 (s, 1H), 3.70 – 3.65 (m, 5H), 2.35 – 2.27 (m, 2H), 1.99 (d, J = 1.3 Hz, 3H), 1.73 (tt, J = 7.3, 6.5 Hz, 2H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.8, 151.3, 138.1, 128.2, 115.6, 62.3, 50.9, 31.9, 29.6, 21.1 ppm; IR ν_{max} 3499, 2951, 1645, 1373, 665 cm^{-1}; HRMS–EI (m/z): [M]$^+$ calcd for $C_{10}H_{16}O_3$, 184.1099; found, 184.1102.

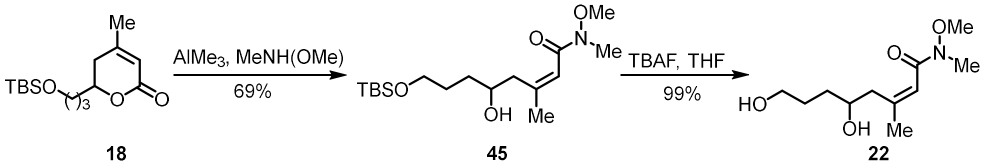


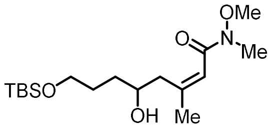
24 **25**



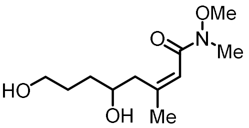
25

To a solution of diene **24** (102 mg, 0.55 mmol, 1.0 equiv.) in dichloromethane (1 mL) at 0 °C was added 3-chloroperoxybenzoic acid (280 mg, 1.22 mmol, 2.2 equiv.) in dichloromethane (5 mL) dropwise during 5 min. The mixture was moved to room temperature and stirred for another 4 hours. Then the reaction was quenched by statured $Na_2S_2O_3$ (2 mL), extracted by ethyl acetate (100 mL), washed with brine (2×20 mL), dried over Na_2SO_4, filtered and concentrated in vacuo to afford the crude product, which was purified by silica gel column chromatography (20% to 30% ethyl acetate-petroleum ether) to give product **25** as colorless oil (76 mg, 69%); $R_f = 0.3$ (30% ethyl acetate-petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.89 – 5.87 (m, 1H), 4.37 (d, $J = 0.7$ Hz, 1H), 3.73 – 3.65 (m, 5H), 2.93 (td, $J = 5.3$, 2.2 Hz, 1H), 1.84 – 1.74 (m, 4H), 1.73 (d, $J = 1.4$ Hz, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.7, 156.1, 119.0, 61.9, 58.0, 57.2, 51.3, 28.7, 28.6, 18.6 ppm; IR ν_{max} 3411, 2951, 1726, 1252, 1060, 596 cm^{-1}; HRMS–ESI (m/z): $[M+H]^+$ $C_{10}H_{17}O_4$, calcd for 201.1121; found, 201.1125.



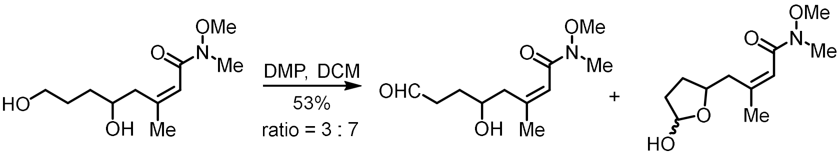

45

To a suspension of *N, O*-dimethylhydroxylamine hydrochloride (823 mg, 8.44 mmol, 5.0 equiv.) in dichloromethane (10 mL) was added trimethylaluminium (8.44 mL, 1 M in hexane, 5.0 equiv.) dropwise during 10 min at 0 ºC. The mixture was moved to room temperature and stirred for 30 min which was then cooling to 0 ºC and lactone **18** (480 mg, 1.69 mmol, 1.0 equiv.) in dichloromethane (10 mL) was added. The mixture was stirred for another 1 hour and saturated seignette salt solution (10 mL) was added to quench to reaction. Then the mixture was extracted by ethyl acetate (200 mL), washed with brine (2×30 mL), dried over Na_2SO_4, filtered and concentrated in vacuo to afford the crude product, which was purified by silica gel column chromatography (10% to 20% ethyl acetate-petroleum ether) to give product **45** as colorless oil (401 mg, 69%); $R_f = 0.2$ (30% ethyl acetate-petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.27 (s, 1H), 4.85 (d, $J = 6.3$ Hz, 1H), 3.80 – 3.70 (m, 1H), 3.68 (s, 3H), 3.67 – 3.59 (m, 2H), 3.21 (s, 3H), 2.99 (dd, $J = 12.3$, 10.5 Hz, 1H), 2.17 (dd, $J = 12.6$, 2.8 Hz, 1H), 1.96 (d, $J = 1.3$ Hz, 3H), 1.74 – 1.51 (m, 4H), 0.88 (s, 9H), 0.04 (s, 6H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.4, 154.1, 117.2, 69.7, 63.4, 61.4, 41.6, 35.6, 29.0, 26.0, 25.7, 18.4, -5.3 ppm; IR ν_{max} 3428, 2742, 1724, 1254, 836, 663 cm^{-1}; HRMS–EI (m/z): $[M]^+$ calcd for $C_{17}H_{35}NO_4Si$, 345.2335; found, 345.2333.

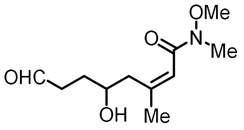

22

To a solution of siloxane **45** (179 mg, 0.52 mmol, 1.0 equiv.) in tetrahydrofuran (6 mL) was added tetrabutylammonium fluoride (0.78 mL, 1 M in tetrahydrofuran, 1.5 equiv.) dropwise during 2 min. The mixture was stirred at room temperature overnight and quenched with methanol. $CaCO_3$ (259 mg, 2.59 mmol, 5.0 equiv.) together with ion exchange resin (259 mg) was added sequentially and stirred for another 10 min. Then the solution was filtered and concentrated in vacuo to afford the crude product, which was purified by silica gel column chromatography (50% to 100% ethyl acetate-petroleum ether) to give product **22** as colorless oil (121 mg, quantitative); $R_f = 0.1$ (75% ethyl acetate-petroleum ether);

^{1}H NMR (400 MHz, CDCl$_3$) δ 6.29 (s, 1H), 5.53 (d, *J* = 5.2 Hz, 1H), 3.78 (s, 1H), 3.72 – 3.60 (m, 5H), 3.21 (s, 3H), 3.07 – 2.99 (m, 1H), 2.14 (dd, *J* = 12.6, 2.8 Hz, 1H), 1.97 (d, *J* = 1.3 Hz, 3H), 1.80 – 1.70 (m, 2H), 1.70 – 1.64 (m, 1H), 1.63 – 1.55 (m, 1H) ppm; ^{13}C NMR (101 MHz, CDCl$_3$) δ 168.4, 153.8, 117.4, 70.0, 63.0, 61.5, 41.9, 36.8, 32.2, 29.9, 25.7 ppm; IR ν_{max} 3458, 2853, 1648, 1456, 1057, 635 cm^{-1}; HRMS–EI (m/z): [M]$^+$ calcd for $C_{11}H_{21}NO_4$, 231.1471; found, 231.1475.



22 **23** **23'**



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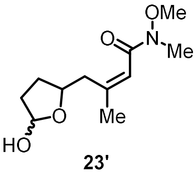
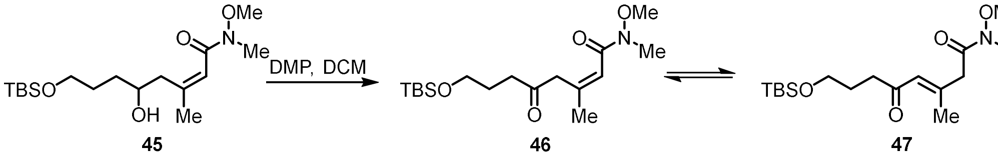
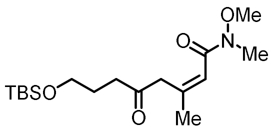


23'

To a solution of Weinreb amide **22** (19 mg, 0.082 mmol, 1.0 equiv.) in dichloromethane (2 mL) was added Dess-Martin periodinane (69.7 mg, 0.164 mmol, 2.0 equiv.) in one potion at room temperature. The mixture was stirred for another 30 min. Then the mixture was quenched by saturated $NaHCO_3$ (aq.) and $Na_2S_2O_3$ (aq.) and extracted with ethyl acetate (10 mL). The combined organic layer was washed with brine (3×5 mL), dried over Na_2SO_4, filtered and concentrated in vacuo to afford the crude product, which was purified by silica gel column chromatography 30% to 60% ethyl acetate-petroleum ether) to give product **23** and **23'** (mixture of aldehyde and hemiacetal, ratio = 3 : 7) as colorless oil (10 mg, 53%); R$_f$ = 0.4 (75% ethyl acetate-petroleum ether); ^{1}H NMR (500 MHz, CDCl$_3$) δ 9.82 (s, 0.3H), 6.33 – 6.04 (m, 1H), 5.80 (s, 0.3H), 5.49 – 5.18 (m, 0.7H), 4.50 – 4.16 (m, 1H), 3.71 – 3.63 (m, 3H), 3.23 – 3.14 (m, 3H), 2.76 (dd, *J* = 7.8, 6.4 Hz, 1H), 2.67 – 2.42 (m, 0H), 2.39 – 2.17 (m, 1H), 2.14 – 2.00 (m, 1H), 2.01 – 1.94 (m, 4H), 1.92 – 1.69 (m, 2H) ppm; ^{13}C NMR (126 MHz, CDCl$_3$) δ 201.1, 164.8, 157.0, 116.4, 100.2, 100.0, 80.6, 80.5, 61.4, 61.4, 41.1, 39.2, 38.7, 37.5, 34.8, 32.9, 31.8, 29.8, 29.2, 26.9, 23.0 ppm.



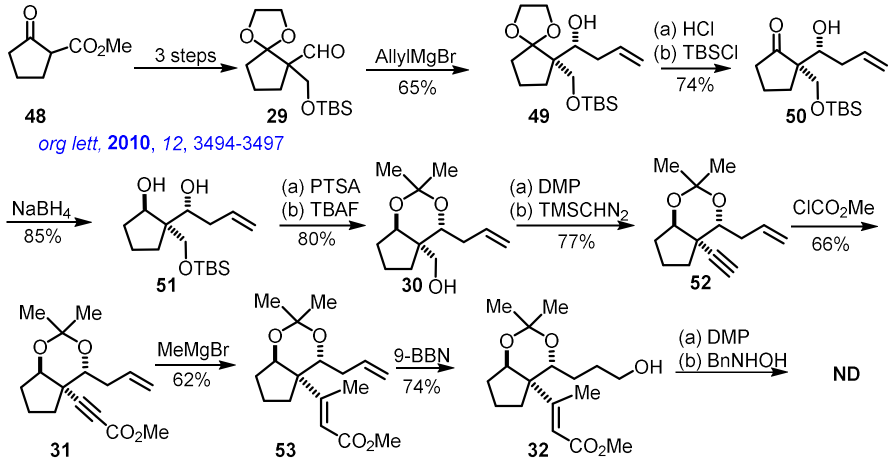
45 **46** **47**

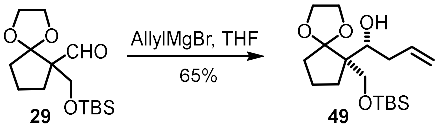


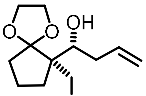
46

To a solution of alcohol **45** (800 mg, 2.32 mmol, 1.0 equiv.) in dichloromethane was added Dess-Martin periodinane (2.95 g, 6.95 mmol, 3.0 equiv.) in one potion followed by 50 μL water dropwise which the reaction turned into white turbidity and stirred for another 1 hour at room temperature. Then saturated $NaHCO_3$ (aq.) and $Na_2S_2O_3$ (aq.) was added to quench the reaction followed by extracted with ethyl acetate (80 mL), washed with brine (2×30 mL), dried over Na_2SO_4, filtered and concentrated in vacuo to afford the crude product, which was purified by silica gel column chromatography (5% to

10% ethyl acetate-petroleum ether) to give product **46** as colorless oil (395 mg, 50%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.32 (s, 1H), 3.80 (s, 2H), 3.68 (s, 3H), 3.60 (t, J = 6.3 Hz, 2H), 3.17 (s, 3H), 2.59 (t, J = 7.3 Hz, 2H), 1.93 (d, J = 1.5 Hz, 3H), 1.84 – 1.74 (m, 2H), 0.87 (s, 9H), 0.03 (s, 6H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 207.3, 167.1, 149.6, 116.3, 62.2, 61.5, 47.4, 39.0, 32.1, 26.7, 26.7, 25.9, 18.3, -5.4 ppm; IR ν_{max} 3798, 2361, 1657, 1258, 1098, 748 cm^{-1}; HRMS–EI (m/z): [M]$^+$ calcd for $C_{17}H_{33}NO_4Si$, 343.2179; found, 343.2173. Compounds **46** and **47** are isomerized interconversion between each other in solution.

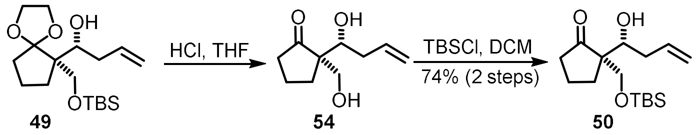


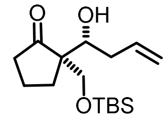




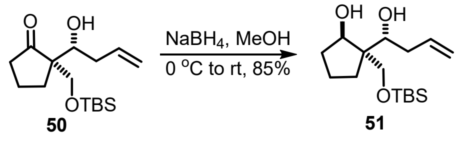
49

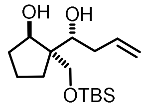
To a solution of aldehyde **29** (4.064 g, 13.53 mmol, 1.0 equiv.) in tetrahydrofuran (50 mL) was added allylmagnesium bromide (16.23 mL, 16.23 mmol, 1 M in tetrahydrofuran, 1.2 equiv.) dropwise at 0 °C during 30 min, the mixture was stirred at 0 °C for 2 hours. Then the reaction mixture was poured into pre-ice cold saturated NH_4Cl (aq.) and extracted with ethyl acetate (3×80 mL). The combined organic layer was washed with brine (3×100 mL), dried over Na_2SO_4, filtered and concentrated in vacuo to afford the crude product, which was purified by silica gel column chromatography (2% to 5% ethyl acetate-petroleum ether) to give product **49** as a yellowish oil (3 g, 65%); R_f = 0.3 (10% ethyl acetate-petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$) 5.94 (ddt, J = 17.0, 10.1, 6.9 Hz, 1H), 5.14 – 4.98 (m, 2H), 4.05 – 3.91 (m, 2H), 3.93 – 3.82 (m, 4H), 3.60 (d, J = 10.4 Hz, 1H), 3.14 (d, J = 6.5 Hz, 1H), 2.37 – 2.20 (m, 2H), 1.84 – 1.68 (m, 4H), 1.64 – 1.57 (m, 2H), 0.89 (s, 9H), 0.06 (s, 6H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ 137.6, 119.6, 115.9, 73.9, 64.3, 63.6, 63.5, 53.1, 38.0, 35.5, 29.7, 25.8, 19.0, 18.3, -5.6, -5.8 ppm; IR ν_{max} 2955, 1742, 1472, 1248, 837, 669 cm^{-1}; HRMS–ESI (m/z): [M+Na]$^+$ $C_{18}H_{34}O_4NaSi$, calcd for 365.2119; found, 365.2112.




50

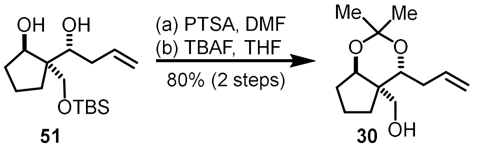
To a solution of ethylene glycol ketal **49** (1.55 g, 4.53 mmol, 1.0 equiv.) in tetrahydrofuran (15 mL) was added HCl (15 mL, 1 N in water) dropwise at 0 ºC during 5 min, the mixture was stirred at room temperature for 2 hours and quenched with saturated $NaHCO_3$ (aq.). The reaction mixture was extracted with ethyl acetate (2×50 mL), the combined organic layer was washed with brine (3×20 mL), dried over Na_2SO_4, filtered and concentrated in vacuo to afford the crude product, which was redissolved in dichloromethane (40 mL). Imidazole (926 mg, 13.6 mmol, 3.0 equiv.) was added in one potion followed by dimethylaminopyridine (55.4 mg, 0.45 mmol, 0.1 equiv.) and *tert*-butyldimethylsilyl chloride (1.02 g, 6.8 mmol, 1.5 equiv.). The mixture was stirred at room temperature overnight and quenched by water (10 mL). Then the solution was extracted with ethyl acetate (2×50 mL), the combined organic layer was washed with brine (3×20 mL), dried over Na_2SO_4, filtered and concentrated in vacuo to afford the crude product, which was purified by silica gel column chromatography (2% to 5% ethyl acetate-petroleum ether) to give product **50** as a yellowish oil (1 g, 74% for 2 steps); R_f = 0.8 (30% ethyl acetate-petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.90 – 5.76 (m, 1H), 5.18 – 5.03 (m, 2H), 3.86 – 3.70 (m, 3H), 3.40 (s, 1H), 2.34 – 2.12 (m, 4H), 2.11 – 1.99 (m, 2H), 1.99 – 1.86 (m, 2H), 0.87 (s, 9H), 0.04 (d, *J* = 7.0 Hz, 6H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 135.4, 117.4, 74.6, 66.4, 57.5, 39.9, 37.1, 28.6, 25.8, 19.5, 18.1, -5.7, -5.8 ppm; IR ν_{max} 3854, 2361, 1558, 1275, 837, 704 cm^{-1}; HRMS–ESI (m/z): $[M+H]^+$ $C_{16}H_{31}O_3Si$, calcd for 299.2037; found, 299.2034.

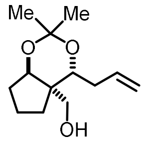



51

To a solution of ketone **50** (280 mg, 0.94 mmol, 1.0 equiv.) in methanol (10 mL) was added sodium borohydride (71 mg, 1.88 mmol, 2.0 equiv.) in batches. The mixture was then moved to room temperature and stirred for 2 hours. Water (5 mL) was added to quenched the reaction, after that the solution was extracted with ethyl acetate (2×30 mL), the combined organic layer was washed with brine (3×10 mL), dried over Na_2SO_4, filtered and concentrated in vacuo to afford the crude product, which was purified by silica gel column chromatography (2% to 5% ethyl acetate-petroleum ether) to give product **51** as a colorless oil (239 mg, 85%) ppm; R_f = 0.3 (10% ethyl acetate-petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.98 – 5.85 (m, 1H), 5.13 (dd, *J* = 12.3, 6.0 Hz, 2H), 4.32 (t, *J* = 5.7 Hz, 1H), 3.85 (dd, *J* = 50.6, 10.2 Hz, 2H), 3.54 – 3.45 (m, 1H), 2.90 – 2.78 (m, 2H), 2.42 – 2.28 (m, 1H), 2.28 – 2.18 (m, 1H), 2.06 – 1.92 (m, 1H), 1.76

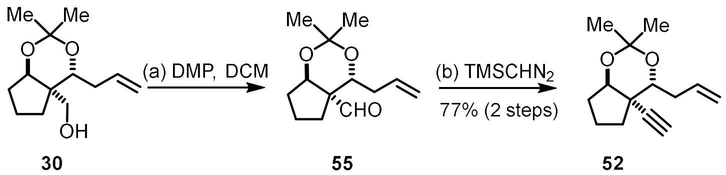
– 1.62 (m, 2H), 1.54 – 1.44 (m, 1H), 1.44 – 1.31 (m, 2H), 0.91 (s, 9H), 0.11 (d, *J* = 2.1 Hz, 6H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ 136.2, 117.3, 79.3, 77.9, 64.7, 51.9, 38.1, 33.7, 30.8, 25.8, 20.8, 18.0, -5.7, -5.8 ppm; IR ν_{max} 3690, 2928, 2342, 1541, 1256, 669 cm^{-1}; HRMS–ESI (m/z): $[M+H]^+$ $C_{16}H_{33}O_3Si$, calcd for 301.2193; found, 301.2190.

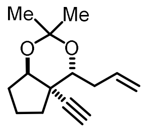




30

To a solution of the diol **51** (461 mg, 1.53 mmol, 1.0 equiv.) in dimethylformamide (15 mL) was added acetone dimethyl ketal (800 mg, 7.67 mmol, 5.0 equiv.) followed by *p*-toluene sulfonic acid monohydrate (15 mg, 0.08 mmol, 0.05 equiv.) in one potion. The mixture was stirred for 2 hours and quenched by saturated $NaHCO_3$ (aq.), extracted with ethyl acetate (2×30 mL), the combined organic layer was washed with brine (3×10 mL), dried over Na_2SO_4, filtered and concentrated in vacuo to afford the crude product, which was redissolved in tetrahydrofuran (20 mL) and tetrabutylammonium fluoride (480 mg, 1.84 mmol, 1.2 equiv.) was added dropwise during 2 min. The mixture was heated to 60 ºC and stirred for another 2 hours. Then the reaction was quenched by methanol and cooled to room temperature. $CaCO_3$ (767 mg, 7.66 mmol, 5.0 equiv.) and resin (767 mg) was added and stirred for another 15 min. The mixture was filtered and concentrated in vacuo to afford the crude product, which was purified by silica gel column chromatography (10% to 20% ethyl acetate-petroleum ether) to give product **30** as a yellowish oil (277 mg, 80% for 2 steps); R_f = 0.2 (20% ethyl acetate-petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.90 – 5.78 (m, 1H), 5.17 – 4.96 (m, 2H), 3.95 (d, *J* = 11.9 Hz, 1H), 3.82 – 3.72 (m, 2H), 3.63 (d, *J* = 11.9 Hz, 1H), 2.52 – 2.43 (m, 1H), 2.41 – 2.32 (m, 2H), 1.96 – 1.89 (m, 1H), 1.82 – 1.61 (m, 3H), 1.47 (d, *J* = 18.9 Hz, 6H), 1.12 – 1.03 (m, 1H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ 135.2, 116.6, 100.7, 81.9, 78.8, 61.0, 45.0, 36.8, 29.6, 26.5, 25.4, 19.5, 17.4 ppm; IR ν_{max} 3649, 3077, 2359, 1558, 1267, 831 cm^{-1}; HRMS–ESI (m/z): $[M+Na]^+$ $C_{13}H_{22}O_3Na$, calcd for 249.1461; found, 249.1458.



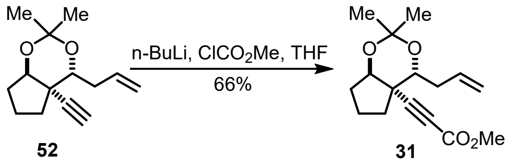


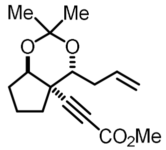
52

To a solution of acetonide **30** (797 mg, 3.52 mmol, 1.0 equiv.) in dichloromethane (30 mL) was added $NaHCO_3$ (1.48 g, 17.62 mmol, 5.0 equiv.) followed by Dess-Martin periodinane (1.79 g, 4.32 mmol, 1.2 equiv.) in one potion at room temperature. The mixture was stirred for another 30 min. Then the mixture was quenched by $Na_2S_2O_3$ (aq.)

and extracted with ethyl acetate (100 mL). The combined organic layer was washed with brine (2×50 mL), dried over Na_2SO_4, filtered and concentrated in vacuo to afford the crude product **55**, which was used directly for next step without further purification.

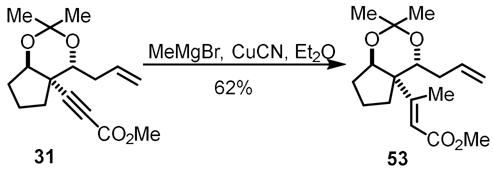
To a solution of (trimethylsilyl)diazomethane (5.28 mL, 2 M in hexane, 3.0 equiv.) in tetrahydrofuran (15 mL) was added *n*-butyllithium (3.52 mL, 2.5 M in hexane, 2.5 equiv.) dropwise during 10 min at -78 ºC. After stirring for another 10 min, the crude product of the aldehyde **55** in tetrahydrofuran (10 mL) was added dropwise during 5 min. The mixture was moved to room temperature after 15 min and stirred overnight. The reaction was quenched with saturated NH_4Cl (aq., 10 mL) and extracted with ethyl acetate (2×50 mL), the combined organic layer was washed with brine (3×10 mL), dried over Na_2SO_4, filtered and concentrated in vacuo to afford the crude product, which was purified by silica gel column chromatography (5% to 10% ethyl acetate-petroleum ether) to give product **52** as a yellowish oil (600 mg, 77% for 2 steps); $R_f = 0.5$ (10% ethyl acetate-petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.90 – 5.77 (m, 1H), 5.14 (ddd, $J = 17.2, 3.2, 1.7$ Hz, 1H), 5.05 (d, $J = 10.2$ Hz, 1H), 3.63 (dd, $J = 7.8, 5.4$ Hz, 1H), 3.55 (dd, $J = 11.0, 6.9$ Hz, 1H), 2.59 – 2.48 (m, 1H), 2.45 – 2.36 (m, 1H), 2.18 (s, 1H), 2.00 – 1.80 (m, 4H), 1.70 – 1.60 (m, 1H), 1.52 (s, 3H), 1.45 (s, 3H), 1.42 – 1.32 (m, 1H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ 134.5, 117.0, 100.5, 83.5, 78.6, 77.7, 72.6, 46.0, 37.3, 30.4, 29.7, 26.3, 19.8, 17.4 ppm; IR ν_{max} 3080, 2347, 1590, 1380, 1196, 841 cm^{-1};HRMS–ESI (m/z): $[M+H]^+$ $C_{14}H_{21}O_2$, calcd for 221.1536; found, 221.1533.

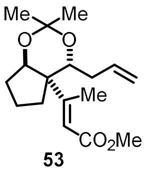




31

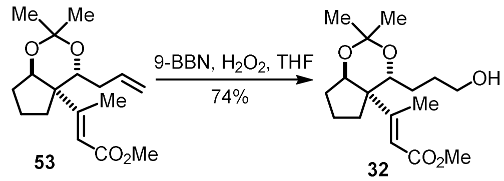
To a solution of alkyne **52** (600 mg, 2.72 mmol, 1.0 equiv.) in tetrahydrofuran (15 mL) was added *n*-butyllithium (4.36 mL, 2.5 M in hexane, 4.0 equiv.) dropwise during 5 min at -78 ºC. After 10 min, methylchloroformate (2.06 g, 21.79 mmol, 8.0 equiv) was added dropwise during 2 min. The mixture was stirred at -78 ºC for another 2 hours and quenched by saturated $NaHCO_3$ (aq.) and extracted with ethyl acetate (50 mL). The combined organic layer was washed with brine (3×10 mL), dried over Na_2SO_4, filtered and concentrated in vacuo to afford the crude product, which was purified by silica gel column chromatography (2% to 10% ethyl acetate-petroleum ether) to give product **31** as a colorless oil (500 mg, 66%); $R_f = 0.4$ (10% ethyl acetate-petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.84 (dddd, $J = 17.2, 10.2, 7.9, 5.9$ Hz, 1H), 5.17 (ddd, $J = 17.2, 3.1, 1.6$ Hz, 1H), 5.08 (d, $J = 10.0$ Hz, 1H), 3.78 (s, 3H), 3.69 (dd, $J = 7.9, 5.4$ Hz, 1H), 3.66 – 3.58 (m, 1H), 2.58 – 2.48 (m, 1H), 2.44 – 2.31 (m, 1H), 1.98 – 1.87 (m, 4H), 1.75 – 1.64 (m, 1H), 1.53 (s, 3H), 1.49 – 1.41 (m, 4H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ 154.1, 134.1, 117.3, 100.7, 88.8, 78.3, 77.9, 76.9, 52.5, 46.8, 37.4, 29.9, 29.6, 26.4, 19.7, 17.3 ppm; IR ν_{max} 3852, 2359, 2230, 1715, 1248, 835 cm^{-1}; HRMS–ESI (m/z): $[M+H]^+$ $C_{16}H_{23}O_4$, calcd for 279.1591; found, 279.1584.

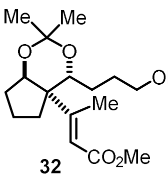




53

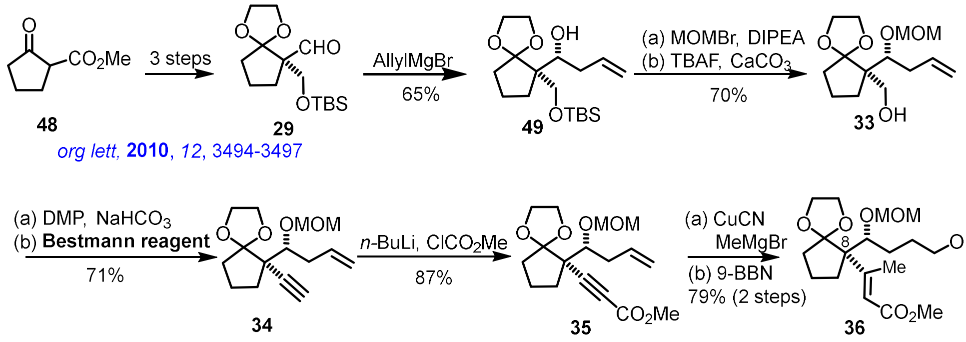
To a suspension of cuprous cyanide (334 mg, 3.73 mmol, 5.3 equiv.) in diethyl ether (5 mL) was added methyl magnesium bromide (2.35 mL, 3 M in diethyl ether, 10.0 equiv.) dropwise during 5 min at 0 ºC. After 10 min, the mixture was moved to -20 ºC and stirred for 10 min before methyl propiolate **31** (196 mg, 0.7 mmol, 1.0 equiv) in diethyl ether (4 mL) dropwise during 2 min. The reaction was stirred for another 2 hours and quenched by saturated NH_4Cl (aq.) at 0 ºC, then extracted with ethyl acetate (50 mL). The combined organic layer was washed with brine (3×10 mL), dried over Na_2SO_4, filtered and concentrated in vacuo to afford the crude product, which was purified by silica gel column chromatography (2% to 4% ethyl acetate-petroleum ether) to give product **53** as a colorless oil (129 mg, 62%); $R_f = 0.7$ (10% ethyl acetate-petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.46 (s, 1H), 5.79 (ddt, *J* = 17.0, 10.2, 6.7 Hz, 1H), 5.04 (ddt, *J* = 25.2, 16.5, 8.3 Hz, 2H), 3.78 – 3.72 (m, 2H), 3.69 (s, 3H), 2.32 (d, *J* = 0.9 Hz, 3H), 2.13 (dt, *J* = 14.3, 6.4 Hz, 2H), 2.02 (dd, *J* = 13.1, 8.1 Hz, 1H), 1.87 – 1.76 (m, 1H), 1.50 (d, *J* = 16.3 Hz, 6H), 1.44 – 1.36 (m, 2H), 1.34 – 1.23 (m, 2H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.5, 156.1, 135.1, 121.2, 116.7, 100.5, 81.3, 78.8, 50.8, 39.0, 37.2, 29.0, 25.7, 23.3, 19.3, 17.5, 14.1 ppm; IR ν_{max} 3883, 2932, 2361, 1466, 1192, 741 cm^{-1}; HRMS–ESI (m/z): $[M+Na]^+$ $C_{17}H_{26}O_4Na$, calcd for 317.1723; found, 317.1716.

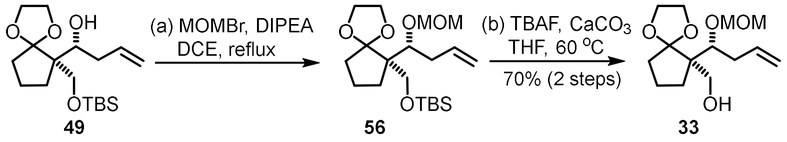


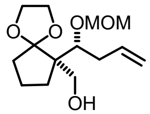


32

To the alkene **53** (100 mg, 0.34 mmol, 1.0 equiv.) was directly added was added 9-borabicyclo[3.3.1]nonane dimer (3.4 mL, 0.5 M in tetrahydrofuran, 1.70 mmol, 5.0 equiv.) dropwise at room temperature during 10 min. The mixture was stirred for another 5 hours. The solution was then moved to 0 ºC and quenched by methanol (2 mL), NaOH (1.13 mL 3 M in water, 10.0 equiv.) was added and followed by the addition of hydrogen peroxide (0.4 mL, 30% in water) dropwise during 20 min. The solution was warmed to room temperature and extracted with ethyl acetate (50 mL). The combined organic layer was washed with brine (3×10 mL), dried over Na_2SO_4, filtered and concentrated in vacuo to afford the crude product, which was purified by silica gel column chromatography (30% to 50% ethyl acetate-petroleum ether) to give product **32** as a colorless oil (78 mg, 74%); R_f = 0.3 (30% ethyl acetate-petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.45 (s, 1H), 3.75 (dd, *J* = 11.8, 7.3 Hz, 1H), 3.72 – 3.66 (m, 4H), 3.61 (t, *J* = 5.9 Hz, 2H), 2.30 (d, *J* = 0.9 Hz, 3H), 2.01 (dt, *J* = 16.0, 7.9 Hz, 1H), 1.87 – 1.78 (m, 1H), 1.71 – 1.54 (m, 6H), 1.50 (d, *J* = 10.7 Hz, 6H), 1.42 – 1.34 (m, 1H), 1.25 – 1.11 (m, 1H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.4, 156.0, 121.1, 100.6, 82.1, 78.8, 62.6, 51.0, 50.8, 29.9, 29.4, 29.0, 28.9, 24.9, 19.3, 19.2, 17.5 ppm; IR ν_{max} 3725, 2359, 1715, 1155, 1121, 1007 cm^{-1}; HRMS–ESI (m/z): $[M+Na]^+$ $C_{17}H_{28}O_5Na$, calcd for 335.1829; found, 335.1821.

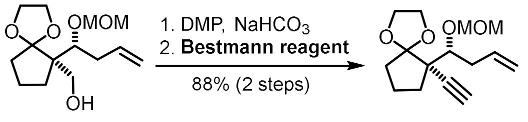





33

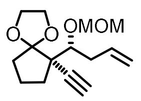
To a solution of alcohol **49** (1.77 g, 5.17 mmol, 1.0 equiv.) in 1,2-dichloroethane (40 mL) was added diisopropylethylamine (7.34 mL，41.34 mmol, 8.0 equiv.) dropwise at 0 °C during 10 min, followed by addition of methoxymethyl bromide (1.69 mL, 20.67 mmol, 4.0 equiv.). The mixture was stirred and heated to reflux for 4 hours. Then the reaction mixture was poured into pre-ice cold saturated $NaHCO_3$ (aq.) and extracted with ethyl acetate (200 mL). The combined organic layer was washed with brine (3×50 mL), dried over Na_2SO_4, filtered and concentrated in vacuo to afford the crude product **56** (2.0 g), which was used directly for next step without further purification.

To a solution of crude product **56** (2.0 g, crude product) in tetrahydrofuran (30 mL) was added tetrabutylammonium fluoride (7.76 mL, 1.0 M in tetrahydrofuran, 7.76 mmol, 1.5 equiv.) dropwise at room temperature during 10 min, the mixture was heated to 60 °C and stirred for 8 hours. Then methanol was added to quench the reaction followed by $CaCO_3$ and ion exchange resin. The mixture was stirred at room temperature for another 15 min. Then filtered and concentrated to afford the crude product, which was purified by silica gel column chromatography (10% to 30% ethyl acetate-petroleum ether) to give product **33** as a yellow oil (1.155 g, 82% for 2 steps). R_f = 0.3 (30% ethyl acetate-petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.96 (dddd, *J* = 16.6, 10.1, 7.7, 6.4 Hz, 1H), 5.10 (dq, *J* = 17.1, 1.7 Hz, 1H), 5.02 (ddd, *J* = 10.1, 2.3, 1.1 Hz, 1H), 4.70 (d, *J* = 6.5 Hz, 1H), 4.67 (d, *J* = 6.6 Hz, 1H), 4.05 – 3.91 (m, 2H), 3.94 – 3.84 (m, 2H), 3.83 (dd, *J* = 8.0, 3.0 Hz, 1H), 3.76 – 3.66 (m, 2H), 3.38 (s, 3H), 3.21 (t, *J* = 6.5 Hz, 1H), 2.56 (dddt, *J* = 14.5, 6.3, 3.0, 1.6 Hz, 1H), 2.36 (dtt, *J* = 14.5, 7.8, 1.2 Hz, 1H), 1.87 – 1.71 (m, 3H), 1.64 – 1.53 (m, 2H), 1.44 (dt, *J* = 13.4, 6.7 Hz, 1H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ 137.0, 119.4, 116.1, 98.3, 81.1, 65.3, 64.3, 64.1, 56.1, 54.1, 38.2, 36.5, 29.5, 20.1 ppm; IR ν_{max} 3055, 1717, 1636, 1271, 1034, 739 cm^{-1}; HRMS–ESI (m/z): $[M+Na]^+$ $C_{14}H_{24}O_5Na$ calcd for 295.1516; found, 295.1513.



33

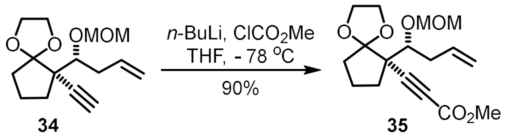
34

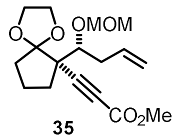


34

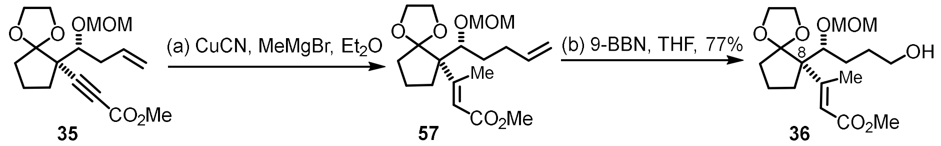
To a solution of MOM-protected alcohol **33** (1.155 g, 4.24 mmol, 1.0 equiv.) in dichloromethane (50 mL) was added $NaHCO_3$ (1.78 g, 21.21 mmol, 5.0 equiv.) followed by Dess-Martin periodinane (2.16 g, 5.09 mmol, 1.2 equiv.) in one potion at room temperature. The mixture was stirred for another 30 min. Then the mixture was quenched by $Na_2S_2O_3$ (aq.) and extracted with ethyl acetate (150 mL). The combined organic layer was washed with brine (3×50 mL), dried over Na_2SO_4, filtered and concentrated in vacuo to afford the crude product, which was used directly for next step without further purification.

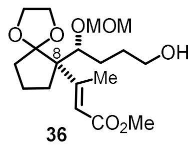
To the solution of crude product in methanol (20 mL) was added potassium carbonate (2.94 g, 21.27 mmol, 5.0 equiv.) followed by Bestmann reagent (1-diazoacetonylphosphonic acid dimethyl ester) (1.28 mL, 8.51 mmol, 2.0 equiv.) dropwise in 10 min. The mixture was stirred overnight at room temperature and turned into light blue. Then ethyl acetate (100 mL) was added and the combined organic layer was washed with brine (3×50 mL), dried over Na_2SO_4, filtered and concentrated in vacuo to afford the crude product, which was purified by silica gel column chromatography (10% to 20% ethyl acetate-petroleum ether) to give product **34** as a colorless oil (995 mg, 88%); R_f = 0.35 (20% ethyl acetate-petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.00 (ddt, *J* = 17.2, 10.1, 7.0 Hz, 1H), 5.10 (dq, *J* = 17.1, 1.7 Hz, 1H), 5.02 (ddt, *J* = 10.1, 2.2, 1.3 Hz, 1H), 4.75 (d, *J* = 6.7 Hz, 1H), 4.71 (d, *J* = 6.7 Hz, 1H), 4.11 – 3.90 (m, 4H), 3.82 (dd, *J* = 6.8, 4.6 Hz, 1H), 3.38 (s, 3H), 2.63 – 2.44 (m, 2H), 2.31 (s, 1H), 2.17 – 2.06 (m, 1H), 2.02 – 1.92 (m, 1H), 1.92 – 1.77 (m, 3H), 1.71 – 1.60 (m, 1H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ 136.4, 118.1, 116.1, 97.5, 85.3, 80.1, 72.3, 64.7, 64.2, 56.0, 52.2, 38.2, 35.8, 34.5, 18.2 ppm; IR ν_{max} 3744, 3279, 2359, 1653, 1032, 743 cm^{-1}; HRMS–EI (m/z): $[M]^+$ $C_{15}H_{22}O_4$, calcd for 266.1518; found 266.1520.




35

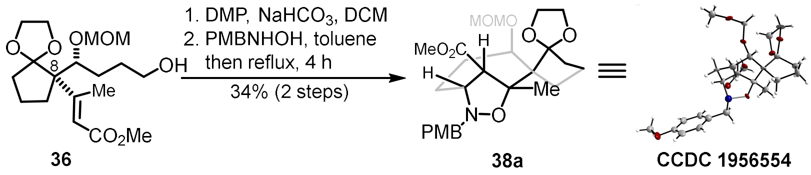
To a solution of alkyne **34** (100 mg, 0.375 mmol, 1.0 equiv.) in tetrahydrofuran (5 mL) was added *n*-butyllithium (0.75 mL, 2.5 M in hexane, 5.0 equiv.) at -78 °C dropwise during 5 min. After stirring for 10 min, methylchloroformate (355 mg, 3.75 mmol, 10.0 equiv.) was added dropwise during 2 min. The mixture was stirred at -78 °C for another 2 hours and quenched by saturated $NaHCO_3$ (aq.) and extracted with ethyl acetate (20 mL). The combined organic layer was washed with brine (3×10 mL), dried over Na_2SO_4, filtered and concentrated in vacuo to afford the crude product, which was purified by silica gel column chromatography (10% to 20% ethyl acetate-petroleum ether) to give product **35** as a colorless oil (110 mg, 90%); R_f = 0.4 (20% ethyl acetate-petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.99 (ddt, *J* = 17.1, 10.1, 7.0 Hz, 1H), 5.11 (ddd, *J* = 17.1, 3.3, 1.6 Hz, 1H), 5.05 (dd, *J* = 10.1, 1.8 Hz, 1H), 4.73 (dd, *J* = 20.0, 6.7 Hz, 2H), 4.09 – 4.01 (m, 2H), 3.99 – 3.91 (m, 2H), 3.81 (dd, *J* = 6.6, 4.5 Hz, 1H), 3.75 (s, 3H), 3.39 (s, 3H), 2.59 – 2.47 (m, 2H), 2.13 – 2.00 (m, 2H), 1.94 – 1.77 (m, 3H), 1.72 – 1.61 (m, 1H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ 154.2, 135.9, 118.1, 116.6, 97.5, 90.2, 80.0, 76.4, 64.9, 64.6, 56.1, 52.9, 52.5, 38.1, 35.3, 35.1, 18.6 ppm; IR ν_{max} 3725, 2342, 1717, 1267, 1038, 741 cm^{-1}; HRMS–ESI (m/z): $[M+Na]^+$ $C_{17}H_{24}O_6Na$ calcd for 347.1465; found, 347.1460.

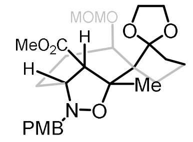



36

To a suspension of cuprous cyanide (803 mg, 8.97 mmol, 5.3 equiv.) in diethyl ether was added methyl magnesium bromide (5.64 mL, 3 M in diethyl ether, 10.0 equiv.) dropwise during 5 min at 0 °C. After stirring for 10 min, the mixture was moved to -20 °C and stirred for 10 min before methyl propiolate **35** (549 mg, 1.69 mmol, 1.0 equiv) in diethyl ether (5 mL) dropwise during 2 min. The reaction was stirred for another 2 hours and quenched by saturated NH_4Cl (aq.) at 0 °C, then diluted with ethyl acetate (50 mL). The combined organic layer was washed with brine (3×10 mL), dried over Na_2SO_4, filtered and concentrated in vacuo to afford the crude product **57** (600 mg), which was used to next step without further purification.

To the crude product **57** (600 mg) was directly added was added 9-borabicyclo[3.3.1]nonane dimer (16.9 mL, 0.5 M in tetrahydrofuran, 8.46 mmol, 5.0 equiv.) dropwise at room temperature during 10 min. The mixture was stirred for another 5 hours. The solution was then moved to 0 °C and quenched by methanol (3 mL), NaOH (5.6 mL 3 M in water, 10.0 equiv.) was added and followed by the addition of hydrogen peroxide (2 mL, 30% in water) dropwise during 20 min. The solution was warmed to room temperature and extracted with ethyl acetate (100 mL). The combined organic layer was washed with brine (3×20 mL), dried over Na_2SO_4, filtered and concentrated in vacuo to afford the crude product, which was purified by silica gel column chromatography (30% to 50% ethyl acetate-petroleum ether) to give product **36** as a colorless oil (465 mg, 77% for 2 steps); R_f = 0.4 (50% ethyl acetate-petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.92 (d, *J* = 0.9 Hz, 1H), 4.59 (dd, *J* = 28.3, 6.7 Hz, 2H), 3.98 (dd, *J* = 8.0, 3.5 Hz, 1H), 3.95 – 3.82 (m, 4H), 3.73 – 3.61 (m, 5H), 3.35 (s, 3H), 2.28 (d, *J* = 1.0 Hz, 3H), 2.06 (ddd, *J* = 9.1, 7.5, 4.6 Hz, 1H), 1.96 – 1.60 (m, 8H), 1.54 – 1.48 (m, 1H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.3, 161.2, 118.9, 117.4, 98.4, 82.2, 63.9, 63.4, 62.7, 60.9, 55.9, 50.8, 34.9, 30.9, 29.9, 29.5, 18.5, 18.3 ppm; IR ν_{max} 2359, 2342, 1717, 1150, 1030, 741cm^{-1}; HRMS–EI (m/z): $[M]^+$ calcd for $C_{18}H_{30}O_7$, 358.1992; found, 358.1995.

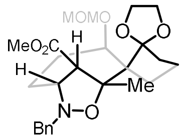




38a

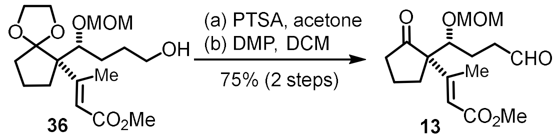
To a solution of α, β-unsaturated ester **36** (323 mg, 0.90 mmol, 1.0 equiv.) in dichloromethane (10 mL) was added $NaHCO_3$ (379 mg, 4.51 mmol, 5.0 equiv.) followed by Dess-Martin periodinane (459 mg, 1.08 mmol, 1.2 equiv.) in one potion at room temperature. The mixture was stirred for another 30 min. Then the mixture was quenched by $Na_2S_2O_3$ (aq, 10 mL) and extracted with Ethyl acetate (50 mL). The combined organic layer was washed with brine (3×20 mL), dried over Na_2SO_4, filtered and concentrated in vacuo to afford the crude product, which was used directly for next step without further purification.

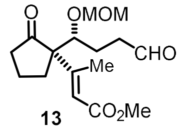
To a solution of crude product aldehyde in toluene was added Na_2SO_4 (386 mg, 2.72 mmol, 3.0 equiv.) followed by *N*-(4-methoxybenzyl)-hydroxylamine (278 mg, 1.81 mmol, 2.0 equiv.) in one potion. The mixture was stirred at room temperature overnight until all the amine hydrochloride was dissolved to get a clarified solution. Then the solution was filtered and concentrated as a yellowish oil which was redissolved by toluene (20 mL) and heated to reflux at least 8 hours. The mixture was concentrated to afford the crude product, which was purified by silica gel column chromatography (20% to 30% ethyl acetate-petroleum ether) to give product **38a** as yellowish powder (150 mg, 34% for 2 steps); R_f= 0.4 (30% ethyl acetate-petroleum ether); ^{1}H NMR (333K, 500 MHz, $CDCl_3$) δ 7.37 (d, *J* = 8.4 Hz, 2H), 6.84 (d, *J* = 8.6 Hz, 2H), 4.66 (s, 2H), 4.30 (d, *J* = 12.4 Hz, 1H), 4.18 (d, *J* = 12.4 Hz, 1H), 4.08 (s, 1H), 4.01 – 3.82 (m, 4H), 3.79 (s, 3H), 3.76 (d, *J* = 3.5 Hz, 1H), 3.74 (s, 3H), 2.30 – 2.14 (m, 2H), 2.10 – 2.00 (m, 2H), 1.83 – 1.67 (m, 4H), 1.65 (s, 4H), 1.63 – 1.48 (m, 5H) ppm; ^{13}C NMR (333K, 126 MHz, $CDCl_3$) δ 174.4, 158.8, 131.0, 130.3, 128.5, 119.9, 114.4, 113.7, 98.4, 83.9, 64.6, 64.1, 63.7, 60.8, 60.5, 56.6, 56.4, 55.4, 55.3, 51.5, 38.6, 33.3, 29.7, 26.8, 25.2, 21.0 ppm; IR ν_{max} 3734, 3055, 2461, 1541, 1623, 704 cm^{-1}; HRMS–EI (m/z): $[M]^+$ calcd for $C_{26}H_{37}NO_8$, 491.2519; found, 491.2524; Conditions for culturing single crystal: 3 mg scale, petroleum ether, static mixing, volatilization and crystallization at room temperature, CCDC 1956554.



38b

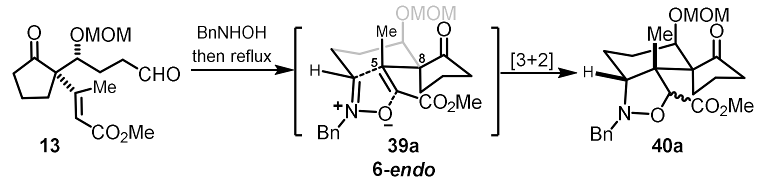
7-*endo* cycloadduct **38b** was synthesized through the conversion similar to **38a** in 30% yield for 2 steps. ^1H NMR (500 MHz, $CDCl_3$) δ 7.49 – 7.44 (m, 2H), 7.30 (t, *J* = 7.6 Hz, 2H), 7.26 – 7.19 (m, 1H), 4.74 – 4.59 (m, 2H), 4.37 (d, *J* = 12.6 Hz, 1H), 4.25 (d, *J* = 12.3 Hz, 1H), 4.01 – 3.91 (m, 2H), 3.91 – 3.81 (m, 3H), 3.76 (s, 1H), 3.74 (s, 3H), 3.39 (s, 3H), 2.30 – 2.13 (m, 2H), 2.10 – 1.96 (m, 1H), 1.84 – 1.68 (m, 4H), 1.68 – 1.48 (m, 7H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.4, 138.6, 129.1, 128.1, 126.8, 119.7, 98.3, 83.8, 63.7, 56.6, 56.2, 51.8, 42.8, 42.3, 38.6, 33.2, 26.8, 21.0 ppm; IR ν_{max} 3649, 2947, 1697, 1449, 912, 731 cm^{-1}; HRMS–EI (m/z): $[M]^+$ calcd for $C_{25}H_{35}NO_7$, 461.2414; found, 461.2419.

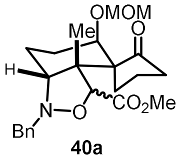




13

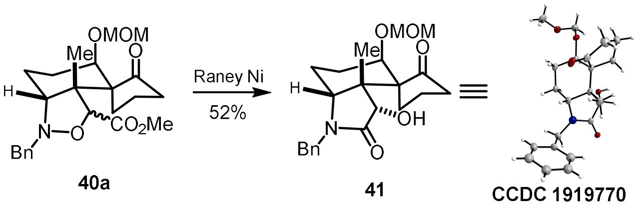
To a solution of ethylene α, β-unsaturated ester **36** (216 mg, 0.603 mmol, 1.0 equiv.) in acetone (5 mL) was added *p*-toluene sulfonic acid monohydrate (229 mg, 1.21 mmol, 2.0 equiv.) in one potion at room temperature. The mixture was stirred for 2 hours and quenched by saturated $NaHCO_3$ (aq.), extracted with ethyl acetate (20 mL), washed with brine (3×5 mL), dried over Na_2SO_4, filtered and concentrated in vacuo to afford the crude product, which was redissolved by dichloromethane (5 mL) followed by the addition of $NaHCO_3$ (253 mg, 3.01 mmol, 5.0 equiv.) and Dess-Martin periodinane (307 mg, 0.723 mmol, 1.2 equiv.) in one potion at room temperature. The mixture was stirred for another 30 min. Then the mixture was quenched by $Na_2S_2O_3$ (aq., 5 mL) and extracted with ethyl acetate (20 mL). The combined organic layer was washed with brine (3×5 mL), dried over Na_2SO_4, filtered and concentrated in vacuo to afford the crude product, which was purified by silica gel column chromatography (10% to 20% ethyl acetate-petroleum ether) to give product **13** as a colorless oil (141 mg, 75% for 2 steps); R_f = 0.5 (30% ethyl acetate-petroleum ether); ^1H NMR (500 MHz, $CDCl_3$) δ 9.75 (s, 1H), 5.83 (d, *J* = 1.1 Hz, 1H), 4.54 (dd, *J* = 17.1, 6.9 Hz, 2H), 3.81 (dd, *J* = 9.5, 2.5 Hz, 1H), 3.68 (s, 3H), 3.33 (s, 3H), 2.67 – 2.50 (m, 2H), 2.37 – 2.25 (m, 2H), 2.22 (d, *J* = 1.1 Hz, 3H), 2.21 – 2.12 (m, 2H), 2.10 – 1.99 (m, 1H), 1.94 (tdd, *J* = 12.3, 6.4, 3.0 Hz, 1H), 1.77 – 1.65 (m, 2H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ 216.9, 201.9, 166.6, 155.0, 118.8, 98.5, 82.9, 64.6, 56.1, 51.1, 40.9, 39.0, 30.5, 24.6, 18.8, 16.2 ppm; IR ν_{max} 3726, 2361, 1356, 1215, 1026 cm^{-1}; HRMS–ESI (m/z): $[M+Na]^+$ $C_{16}H_{24}O_6Na$ calcd for 335.1465; found, 335.1456.



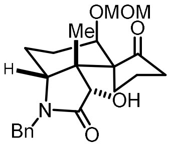


40a

To a solution of aldehyde **13** (34.5 mg, 0.11 mmol, 1.0 equiv.) in toluene (5 mL) was added NaHCO$_3$ (361 mg, 0.33 mmol, 3.0 equiv.) followed by *N*-benzylhydroxylamine hydrochloride (18.5 mg, 0.12 mmol, 1.1 equiv.) in one potion. The mixture was stirred at room temperature overnight until all the amine hydrochloride was dissolved to get a clarified solution. Then the solution was filtered and concentrated as a greenish oil which was redissolved by toluene (5 mL) and heated to reflux at least 8 hours. The mixture was concentrated to afford the crude product, which was purified by silica gel column chromatography (10% to 20% ethyl acetate-petroleum ether) to give product **40a** as yellowish powder (20 mg, 43%), a mixture of epimers, d.r = 3.4 : 1; R_f = 0.5 (30% ethyl acetate-petroleum ether); The major product: ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.50 – 7.30 (m, 5H), 4.75 (d, *J* = 7.0 Hz, 1H), 4.62 (d, *J* = 7.0 Hz, 1H), 4.42 (s, 1H), 4.16 (d, *J* = 14.3 Hz, 1H), 3.96 (d, *J* = 14.3 Hz, 1H), 3.93 – 3.82 (m, 1H), 3.78 (s, 3H), 3.40 (s, 3H), 2.60 (dt, *J* = 13.4, 9.0 Hz, 1H), 2.46 – 2.34 (m, 2H), 2.33 – 2.22 (m, 1H), 2.20 – 1.86 (m, 7H), 1.80 (s, 1H), 1.25 (s, 3H) ppm; ^{13}C NMR (126 MHz, CDCl$_3$) δ 173.9, 137.5, 128.8, 128.2, 127.9, 127.0, 126.9, 95.3, 62.0, 56.8, 56.4, 55.9, 51.9, 41.5, 32.8, 32.4, 28.5, 23.3, 20.2, 19.5 ppm; IR ν_{max} 3734, 2342, 1624, 1541, 1031, 748 cm^{-1}; HRMS–ESI (m/z): [M+H]$^+$ $C_{23}H_{32}O_6N$, calcd for 418.2224; found, 418.2213.



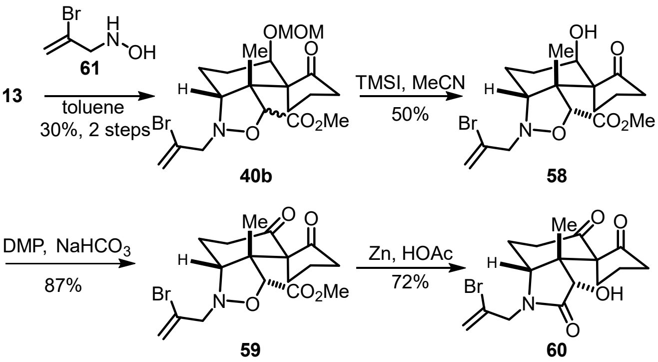
40a **41** **CCDC 1919770**



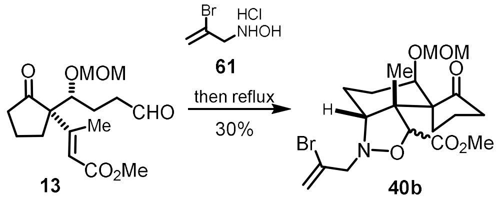
41

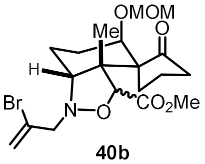
To a solution of isoxazolidine **40a** (38 mg) in methanol (5 mL) was added Raney Nickel (30 mg) in one potion. The mixture was protected by a hydrogen balloon and stirred at room temperature overnight. Then the solution was filtered and concentrated to afford the crude product, which was purified by silica gel column chromatography (30% to 50% ethyl acetate-petroleum ether) to give product **41** as white solid (18 mg, 52%); R_f = 0.1 (30% ethyl acetate-petroleum ether); ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.37 – 7.19 (m, 5H), 4.91 (d, *J* = 14.7 Hz, 1H), 4.69 – 4.59 (m, 2H), 4.28 (dd, *J* = 11.6, 4.5 Hz, 1H), 4.22 (d, *J* = 3.6 Hz, 1H), 3.99 (d, *J* = 14.7 Hz, 1H), 3.76 (d, *J* = 3.6 Hz, 1H), 3.42 – 3.25 (m, 4H), 2.51 – 2.39 (m, 1H), 2.38 – 2.20 (m, 2H), 2.19 – 1.97 (m, 4H), 1.90 (s, 1H), 1.84 – 1.75 (m, 1H), 0.75 (s, 3H) ppm; ^{13}C NMR (126 MHz, CDCl$_3$) δ 222.7, 173.7, 135.9, 128.7, 128.4, 127.8, 96.1, 82.9, 78.7, 61.6, 56.0, 55.7, 45.6, 44.7, 41.4, 32.3, 28.3, 24.1, 20.8, 20.6 ppm; IR ν_{max} 3737, 2361, 1730, 1653, 1032, 750 cm^{-1}; HRMS–EI (m/z): $[M]^+$ calcd for $C_{22}H_{29}NO_5$, 387.2046; found, 387.2049; Conditions for culturing single crystal: 4 mg scale, ethyl acetate : hexane = 1 : 4, static mixing, volatilization and crystallization at room temperature, CCDC 1919770.

Scheme 1. [3+2] cycloaddition of the alkenyl bromine substrate



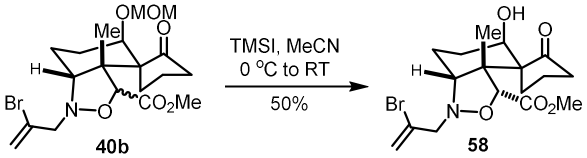
The N-alkenyl bromine substrate was also introduced to the [3+2] cycloaddition which would be a significative intermediate to construct the hydrogenated pyridine B ring. Aldehyde **13**, which condensed with hydroxylamine and heated to undergo 6-*endo* cycloaddition to generate **40b**. Removed the MOM-protecting group and oxidized by Dess-Martin Periodinane to generate the corresponding ketone in 87% yield. Reductive cleavage of the N-O bond of isoxazolidine **59** using Zn/HOAc furnished tricyclic product **60** which would be a highly effective product for the subsequent synthesis.

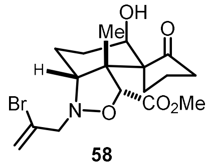



40b

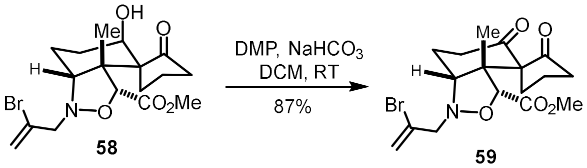
To a solution of aldehyde **13** (213 mg, 0.68 mmol, 1.0 equiv.) in toluene (10 mL) was added $NaHCO_3$ (172 mg, 2.05 mmol, 3.0 equiv.) followed by hydroxylamine hydrochloride **61** (154 mg, 0.82 mmol, 1.2 equiv.) in one potion. The mixture was stirred at room temperature overnight until all the amine hydrochloride was dissolved to get a clarified solution. Then the solution was filtered and concentrated as a yellowish oil which was redissolved by toluene (20 mL) and heated to reflux at least 8 hours. The mixture was concentrated to afford the crude product, which was purified by silica gel column chromatography (10% to 20% ethyl acetate-petroleum ether) to give product **40b** as yellowish powder (92 mg, 30%), a mixture of epimers, d.r = 2 : 1; R_f= 0.3 (10% ethyl acetate-petroleum ether); The major product: ^1H NMR (500

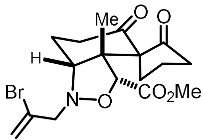
MHz, $CDCl_3$) δ 6.33 (s, 1H), 5.69 – 5.63 (m, 1H), 4.75 (d, *J* = 7.0 Hz, 1H), 4.61 (d, *J* = 7.0 Hz, 1H), 4.40 (s, 1H), 3.89 – 3.82 (m, 1H), 3.78 (s, 3H), 3.69 – 3.56 (m, 3H), 3.40 (s, 3H), 2.65 – 2.34 (m, 3H), 2.20 – 2.10 (m, 2H), 2.01 – 1.85 (m, 3H), 1.76 – 1.67 (m, 2H), 1.21 (s, 3H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ 221.5, 173.8, 130.0, 128.4, 127.0, 118.5, 96.4, 80.2, 66.0, 56.8, 56.3, 56.0, 52.0, 41.4, 32.6, 28.1, 23.1, 20.2, 19.5 ppm; IR ν_{max} 3726, 2953, 2342, 1251, 839, 781 cm^{-1}; HRMS–ESI (m/z): $[M+H]^+$ $C_{19}H_{29}BrNO_6$, calcd for 446.1173; found, 446.1167.



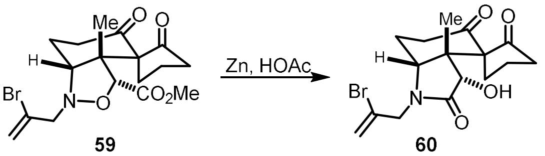

58

To a solution of isoxazolidine **40b** (129 mg, 0.29 mmol, 1.0 equiv.) in acetonitrile (5 mL) at 0 °C was added NaI (173 mg, 1.16 mmol, 4.0 equiv.) followed by trimethylchlorosilane (94 mg, 0.87 mmol, 3.0 equiv.) dropwise in 2 min. The mixture was warmed to room temperature after 10 min and stirred for another 2 hours. Then the solution was extracted by ethyl acetate (20 mL), washed by $Na_2S_2O_3$ (2×5 mL) and brine (2×5 mL), dried over Na_2SO_4, filtered and concentrated in vacuo to afford the crude product, which was purified by silica gel column chromatography (20% to 30% ethyl acetate-petroleum ether) to give product **59** as yellowish powder (58 mg, 50%); R_f= 0.4 (30% ethyl acetate-petroleum ether); ^1H NMR (500 MHz, $CDCl_3$) δ 6.30 (s, 1H), 5.63 (d, *J* = 1.5 Hz, 1H), 4.72 (d, *J* = 7.0 Hz, 1H), 4.59 (d, *J* = 7.0 Hz, 1H), 4.37 (s, 1H), 3.86 – 3.79 (m, 1H), 3.76 (s, 3H), 3.63 – 3.56 (m, 3H), 3.38 (s, 3H), 2.62 – 2.32 (m, 3H), 2.16 – 2.06 (m, 2H), 1.97 – 1.85 (m, 3H), 1.76 – 1.64 (m, 2H), 1.18 (s, 3H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.8, 118.2, 52.0, 41.2, 32.6, 19.6, 19.2, 18.1 ppm; The major product: IR ν_{max} 3736, 2926, 1460, 1248, 1045, 897 cm^{-1}; HRMS–ESI (m/z): $[M+H]^+$ $C_{17}H_{25}BrO_5N$, calcd for 402.0911; found, 402.0905.

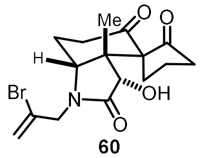



59

To a solution of isoxazolidine **58** (30 mg, 0.055 mmol, 1.0 equiv) in dichloromethane (5 mL) was added $NaHCO_3$ (23.3 mg, 0.277 mmol, 5.0 equiv.) and Dess-Martin periodinane (47 mg, 0.11 mmol, 2.0 equiv.) in one potion at room temperature. The mixture was stirred for another 30 min. Then the mixture was quenched by $Na_2S_2O_3$ (aq.) (5 mL) and extracted with ethyl acetate (20 mL). The combined organic layer was washed with brine (3×5 mL), dried over Na_2SO_4, filtered and concentrated in vacuo to afford the crude product, which was purified by silica gel column chromatography (10% to 20% ethyl acetate-petroleum ether) to give product **59** as a colorless oil (26 mg, 87%). R$_f$ = 0.5 (10% ethyl acetate-petroleum ether); ^{1}H NMR (400 MHz, CDCl$_3$) δ 5.98 (s, 1H), 5.59 (p, *J* = 1.0 Hz, 1H), 4.18 (s, 1H), 3.75 (s, 3H), 3.64 (s, 2H), 3.11 – 2.88 (m, 2H), 2.75 (ddt, *J* = 13.2, 6.6, 2.0 Hz, 1H), 2.57 (dd, *J* = 10.8, 7.3 Hz, 1H), 2.44 – 2.29 (m, 2H), 2.25 – 2.09 (m, 2H), 2.02 – 1.78 (m, 2H), 1.29 – 1.23 (m, 1H), 1.20 (s, 3H) ppm; ^{13}C NMR (126 MHz, CDCl$_3$) δ 213.3, 204.7, 169.4, 128.0, 118.8, 81.7, 71.5, 70.5, 62.2, 58.0, 52.2, 40.5, 33.5, 30.6, 20.4, 19.2, 18.7 ppm; IR ν_{max} 3099, 2953, 1740, 986, 741 cm^{-1}; HRMS–ESI (m/z): [M+H]$^+$ $C_{17}H_{23}BrO_5N$, calcd for 400.0754; found, 400.0750.



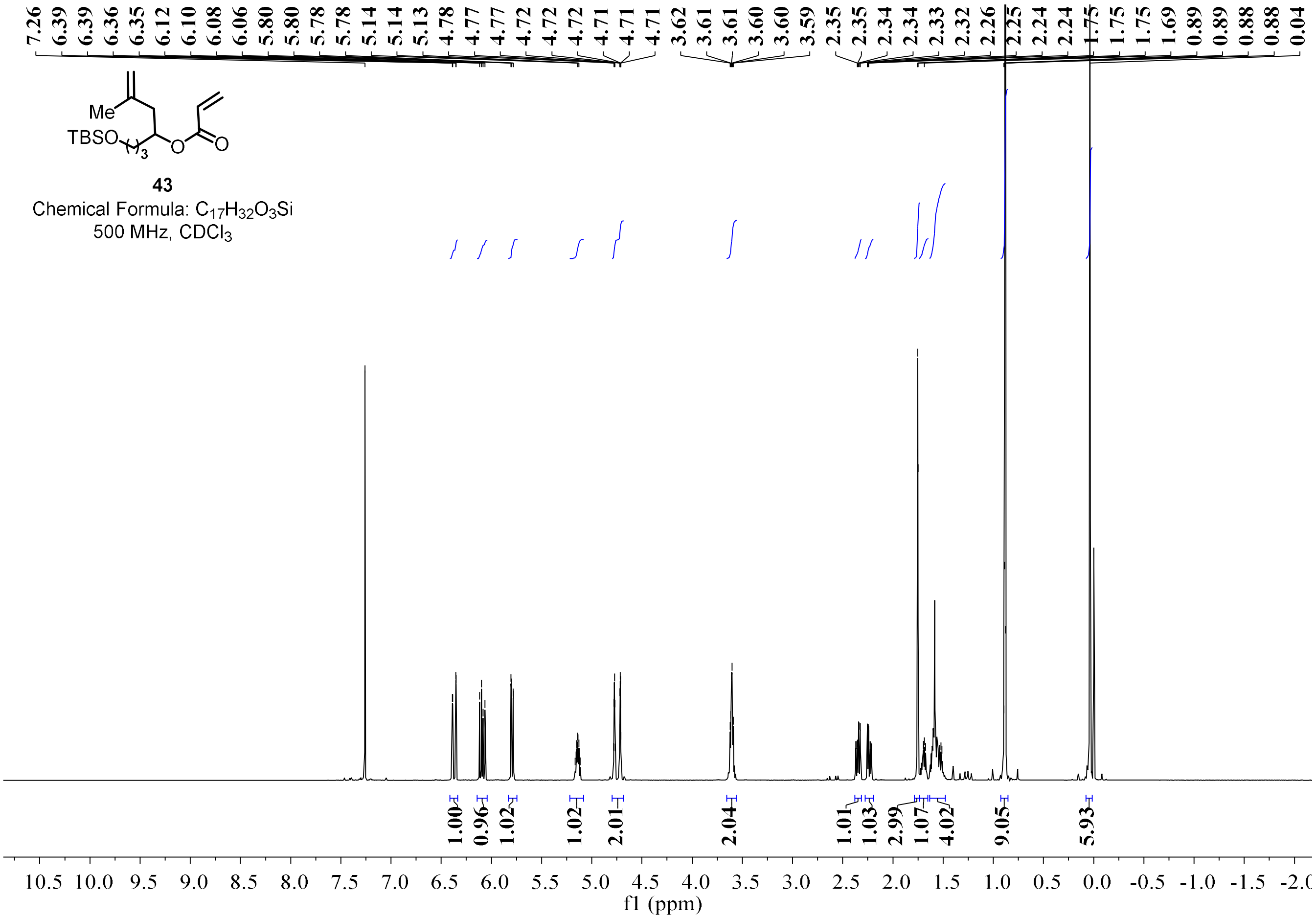
59 **60**



60

To a solution of isoxazolidine **59** (30 mg, 0.075 mmol, 1.0 equiv) in HOAc (5 mL) was added active zinc powder (245mg, 3.75 mmol, 50.0 equiv.) in one potion at room temperature. The mixture was heated to reflux for 8 hours. Then the mixture was filtered and concentrated in vacuo to afford the crude product, which was purified by silica gel column chromatography (20% to 40% ethyl acetate-petroleum ether) to give product **60** as a white solid (20 mg, 72%); R$_f$ = 0.4 (50% ethyl acetate-petroleum ether); ^{1}H NMR (500 MHz, CDCl$_3$) δ 5.89 (d, *J* = 1.8 Hz, 1H), 5.69 (d, *J* = 2.5 Hz, 1H), 4.66 (d, *J* = 15.2 Hz, 1H), 4.27 – 4.16 (m, 1H), 3.89 (t, *J* = 6.2 Hz, 1H), 3.82 – 3.72 (m, 2H), 2.99 (ddd, *J* = 11.2, 8.1, 6.5 Hz, 1H), 2.74 – 2.62 (m, 1H), 2.57 – 2.34 (m, 3H), 2.28 – 2.07 (m, 2H), 1.97 (tdt, *J* = 10.0, 5.3, 2.9 Hz, 3H), 1.14 (s, 3H) ppm; ^{13}C NMR (126 MHz, CDCl$_3$) δ 215.6, 204.0, 173.1, 126.9, 121.4, 77.5, 69.3, 60.9, 48.6, 47.8, 40.1, 34.4, 29.7, 25.2, 21.5, 20.2 ppm; IR ν_{max} 3728, 3059, 1659, 1267, 1013, 741 cm^{-1}; HRMS–ESI (m/z): [M+H]$^+$ $C_{16}H_{21}BrO_4N$, calcd for 370.0648; found, 370.0637.

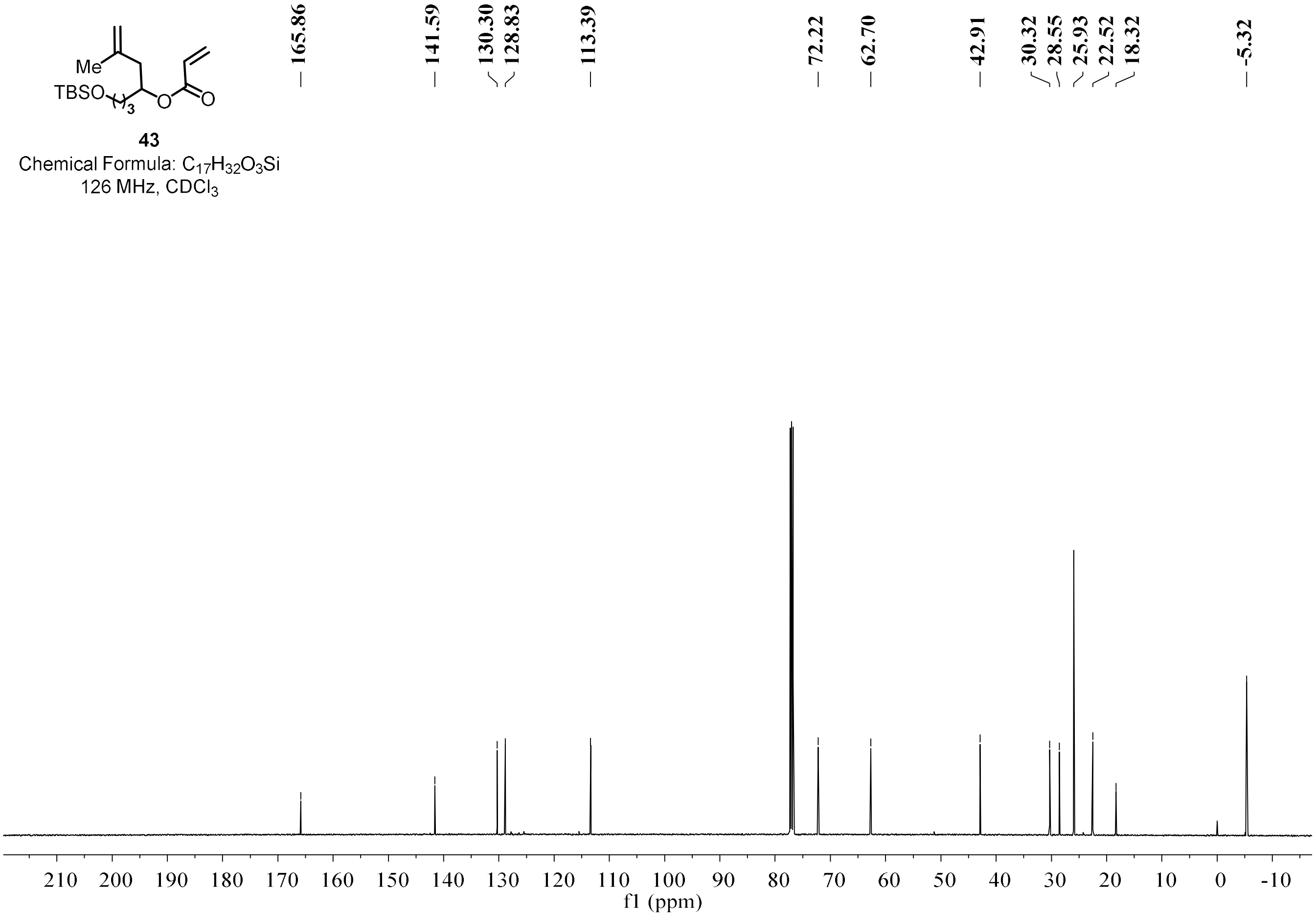
II. ^{1}H and ^{13}C NMR Spectra



43

Chemical Formula: $C_{17}H_{32}O_3Si$

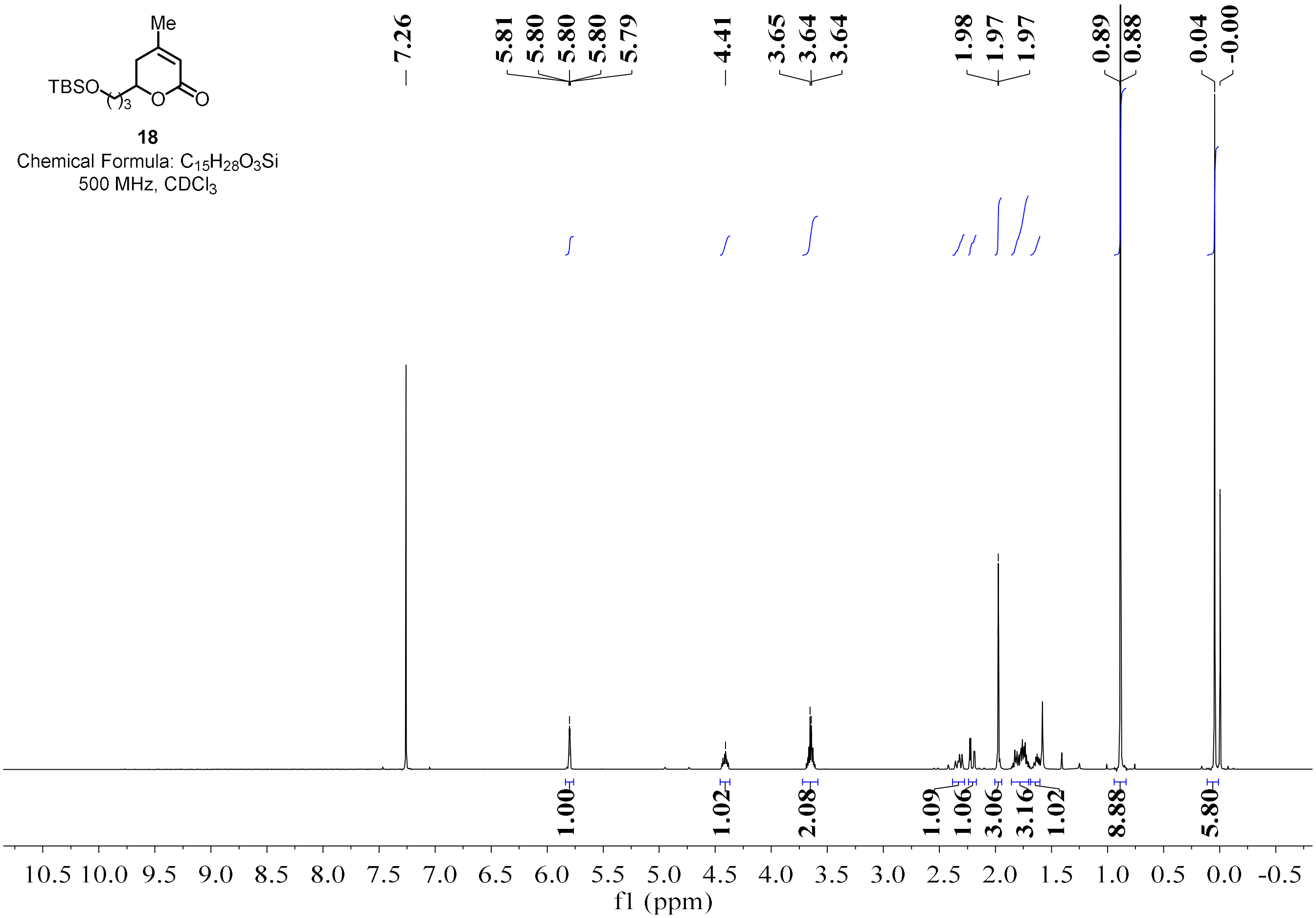
500 MHz, $CDCl_3$



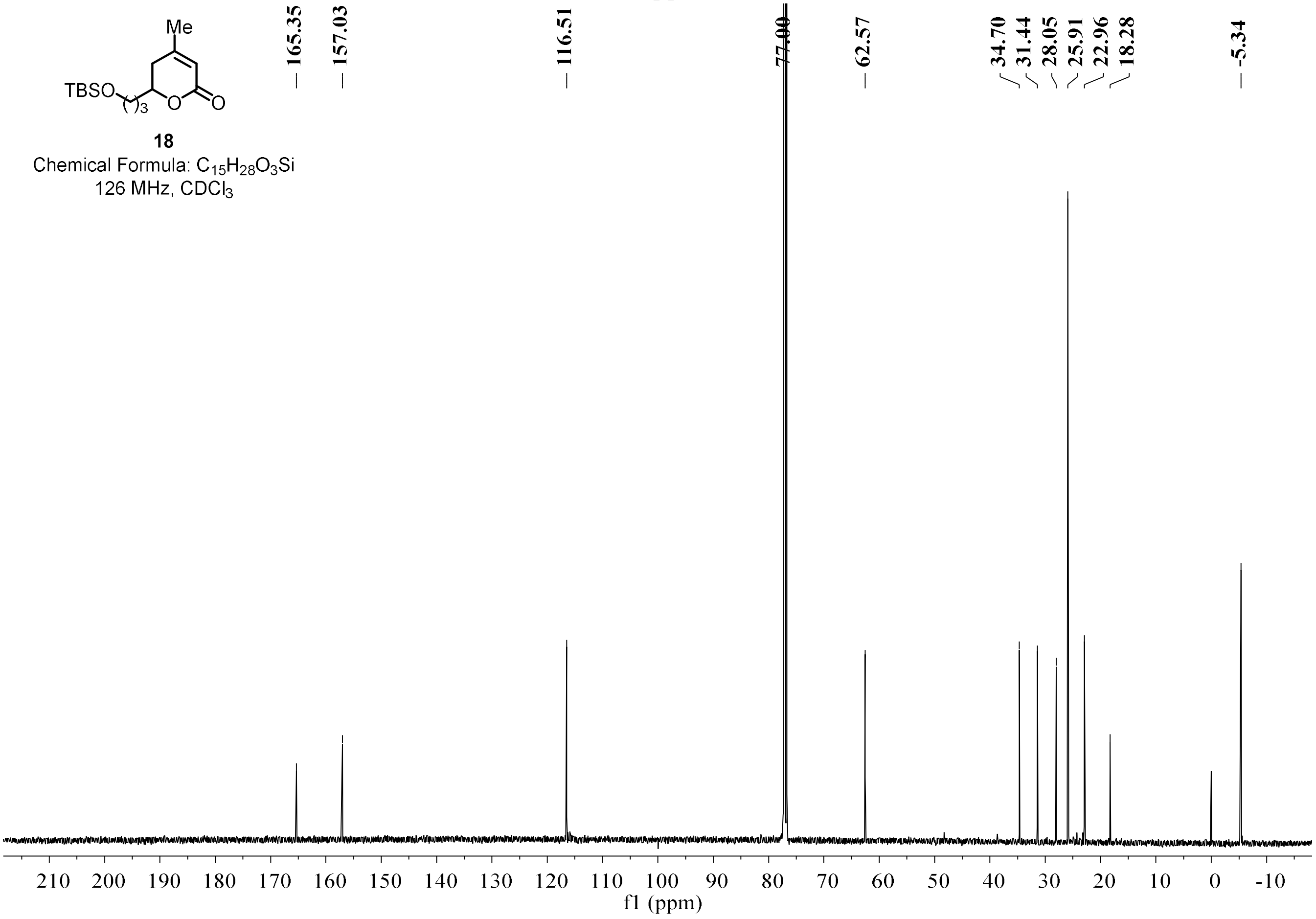
43

Chemical Formula: $C_{17}H_{32}O_3Si$

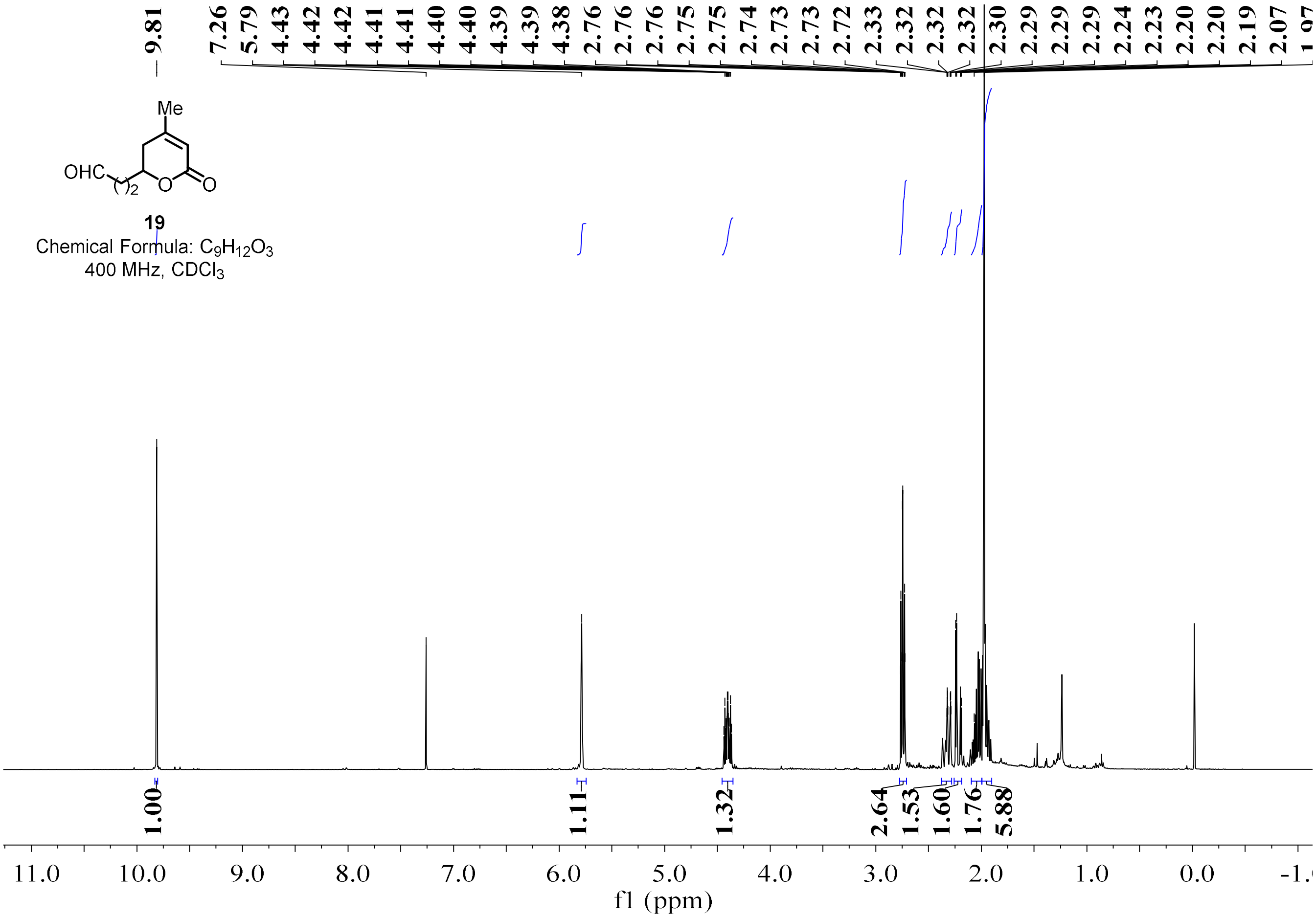
126 MHz, $CDCl_3$

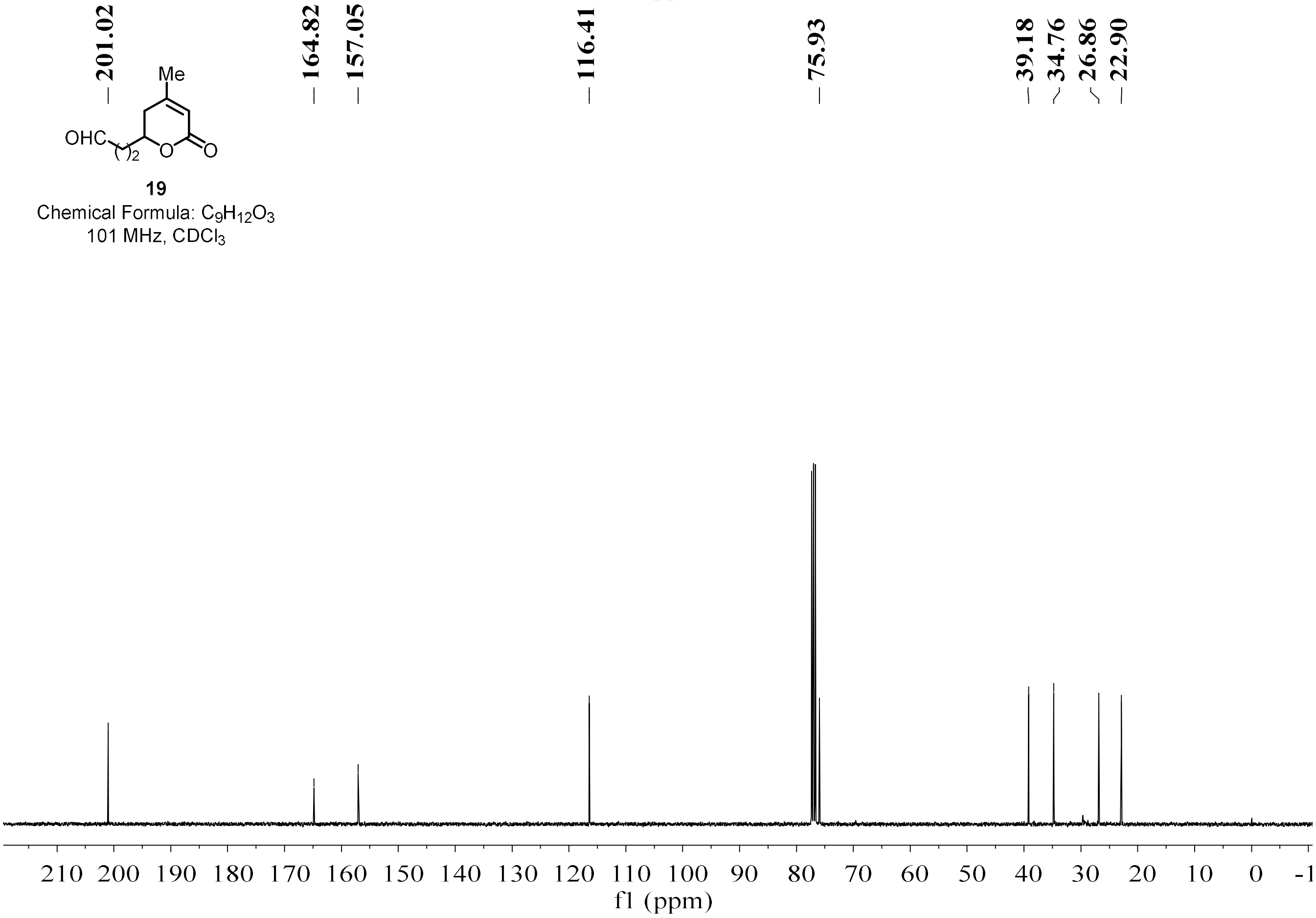


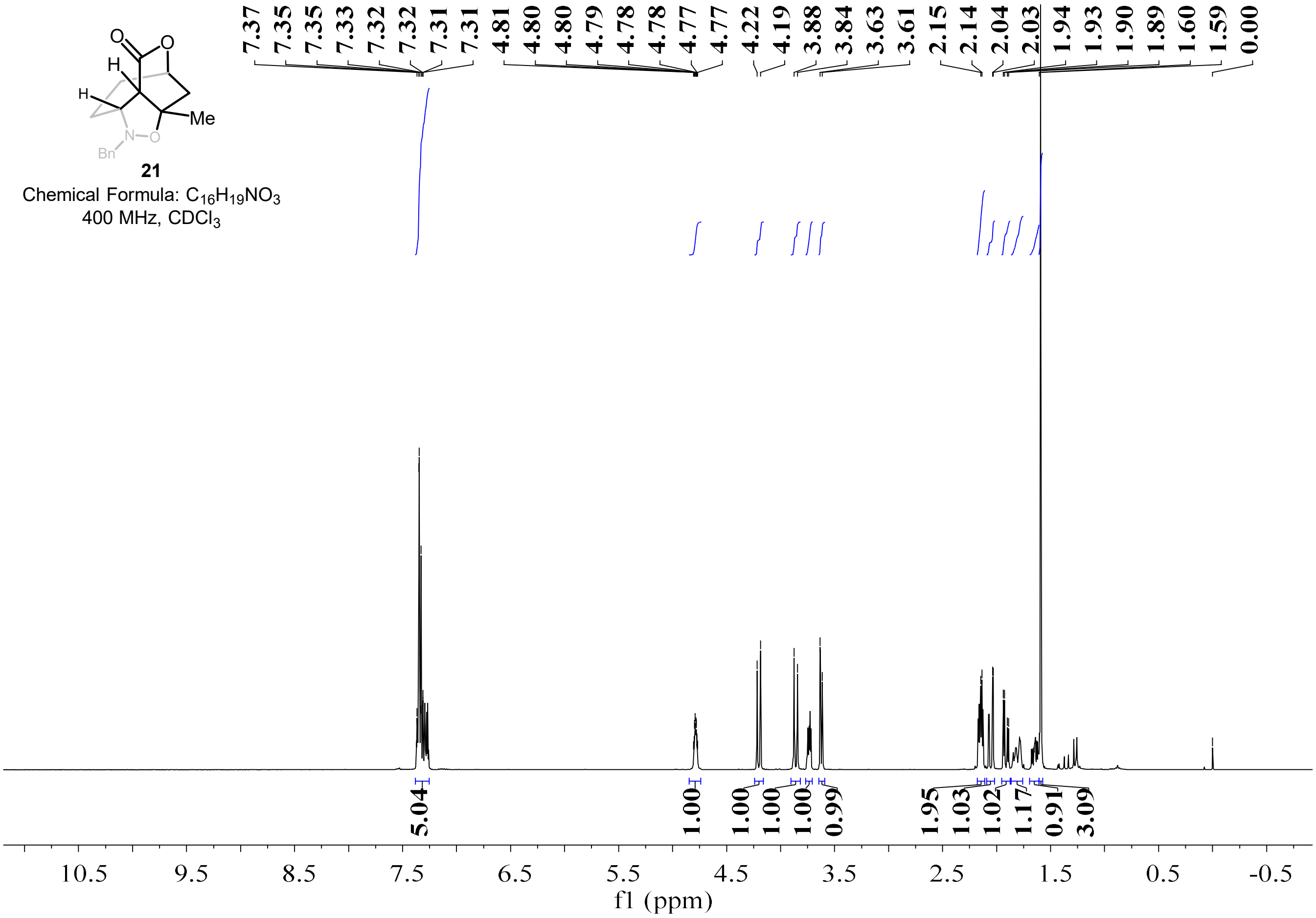
18
Chemical Formula: $C_{15}H_{28}O_3Si$
500 MHz, $CDCl_3$



18
Chemical Formula: $C_{15}H_{28}O_3Si$
126 MHz, $CDCl_3$


9.81
7.26
5.79
4.43
4.42
4.42
4.41
4.41
4.40
4.40
4.39
4.39
4.38
2.76
2.76
2.76
2.75
2.75
2.74
2.73
2.73
2.72
2.33
2.32
2.32
2.32
2.30
2.29
2.29
2.29
2.24
2.23
2.20
2.20
2.19
2.07
Me
OHC
2
O
O
19
Chemical Formula: $C_9H_{12}O_3$
400 MHz, $CDCl_3$
1.00
1.11
1.32
2.64
1.53
1.60
1.76
5.88
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
f1 (ppm)

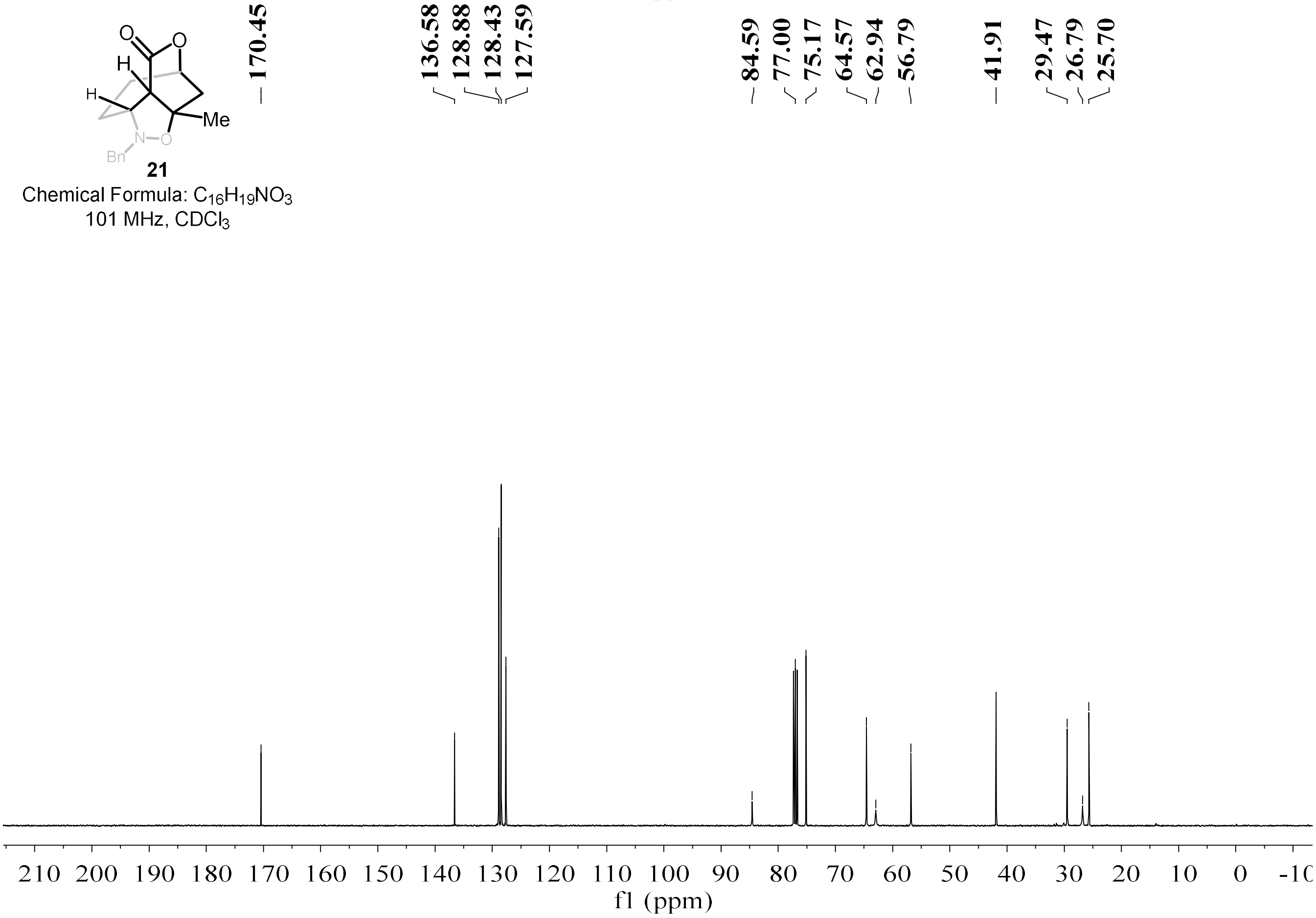

201.02
164.82
157.05
116.41
75.93
39.18
34.76
26.86
22.90
Me
OHC
2
O
O
19
Chemical Formula: $C_9H_{12}O_3$
101 MHz, $CDCl_3$
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)



21

Chemical Formula: $C_{16}H_{19}NO_3$

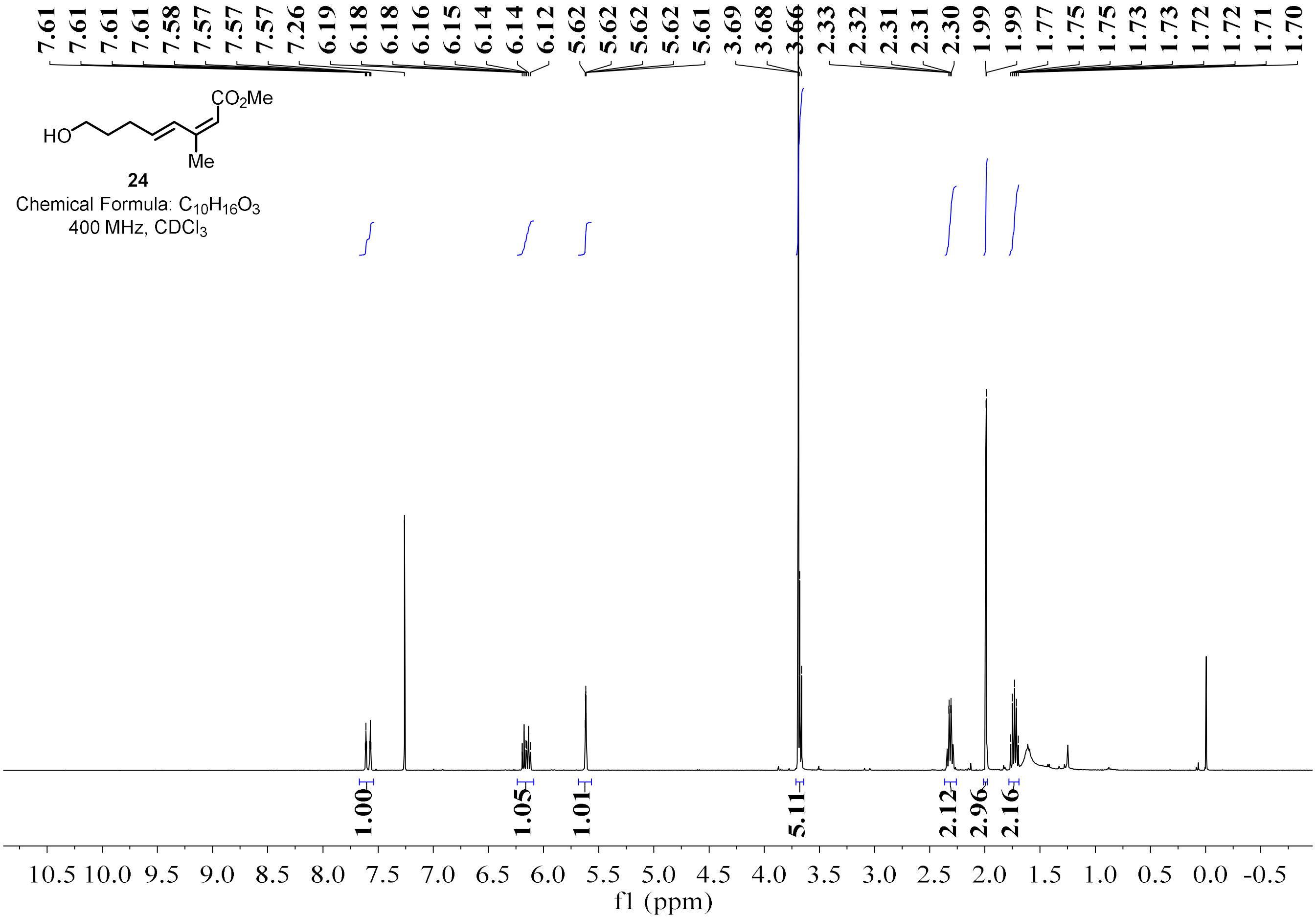
400 MHz, $CDCl_3$

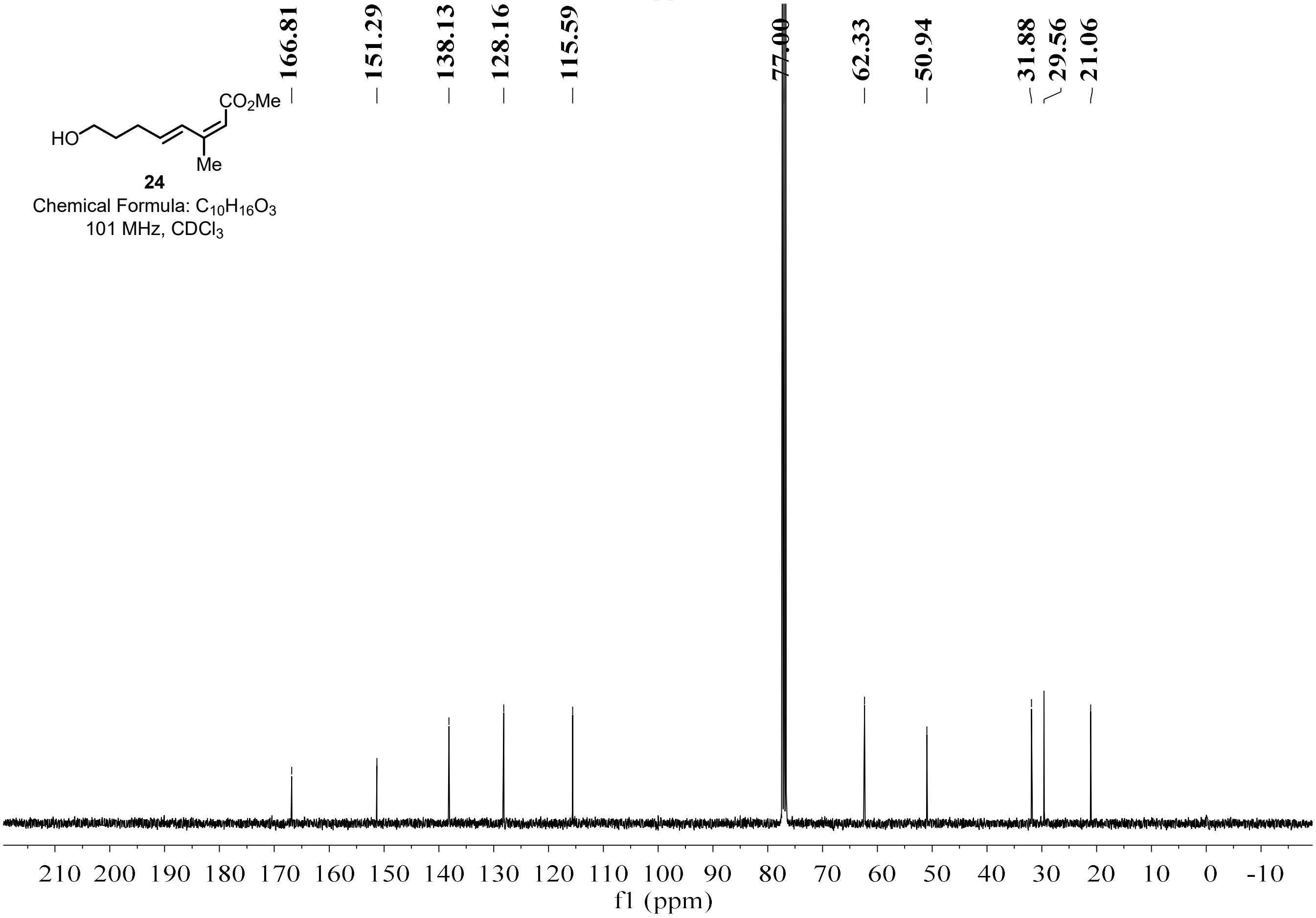


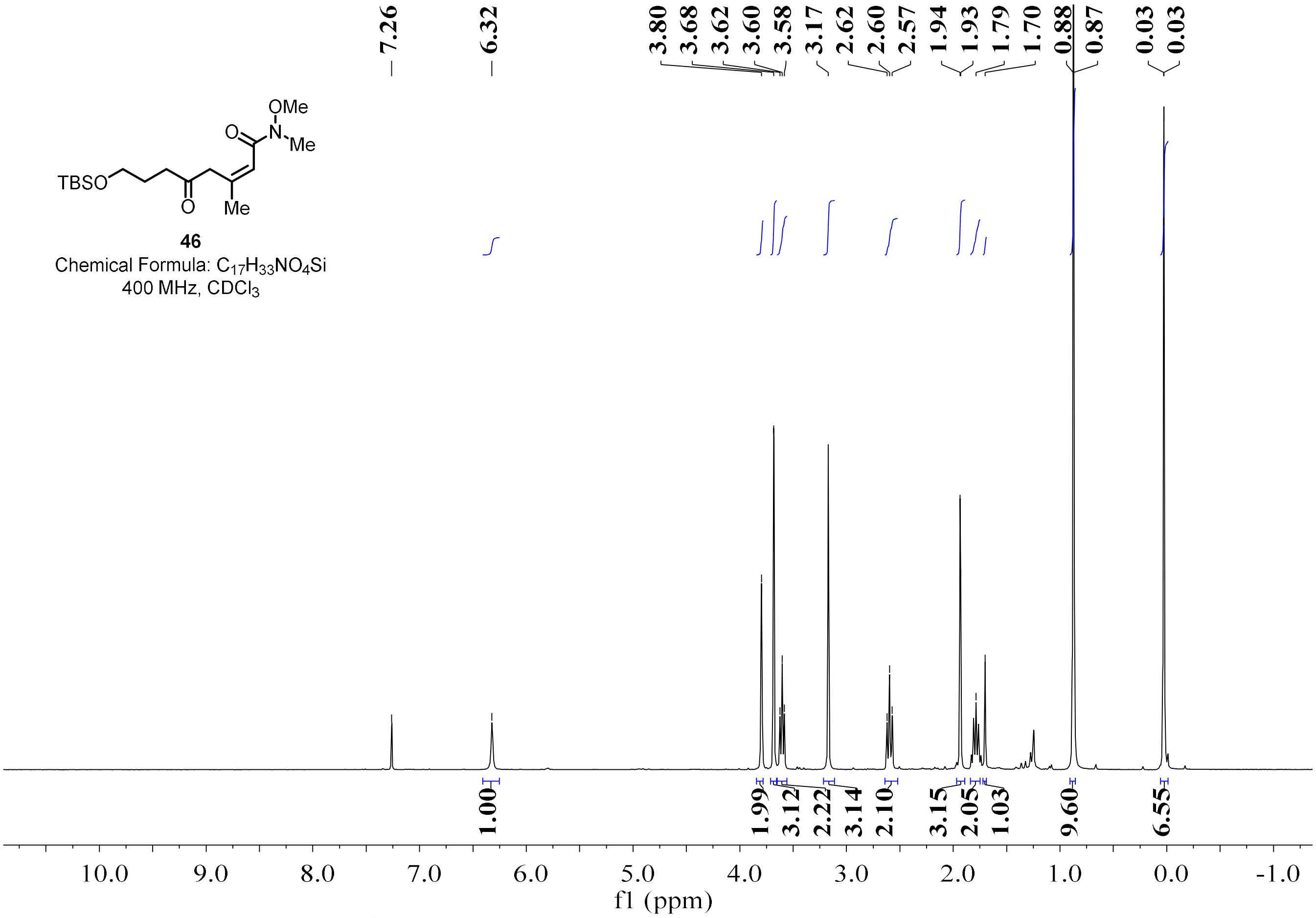
21

Chemical Formula: $C_{16}H_{19}NO_3$

101 MHz, $CDCl_3$


7.61
7.61
7.61
7.61
7.58
7.57
7.57
7.57
7.26
6.19
6.18
6.18
6.16
6.15
6.14
6.14
6.12
5.62
5.62
5.62
5.62
5.61
3.69
3.68
3.66
2.33
2.32
2.31
2.31
2.30
1.99
1.99
1.77
1.75
1.75
1.73
1.73
1.72
1.72
1.71
1.70
CO2Me
HO
Me
24
Chemical Formula: C10H16O3
400 MHz, CDCl3
1.00
1.05
1.01
5.11
2.12
2.96
2.16
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

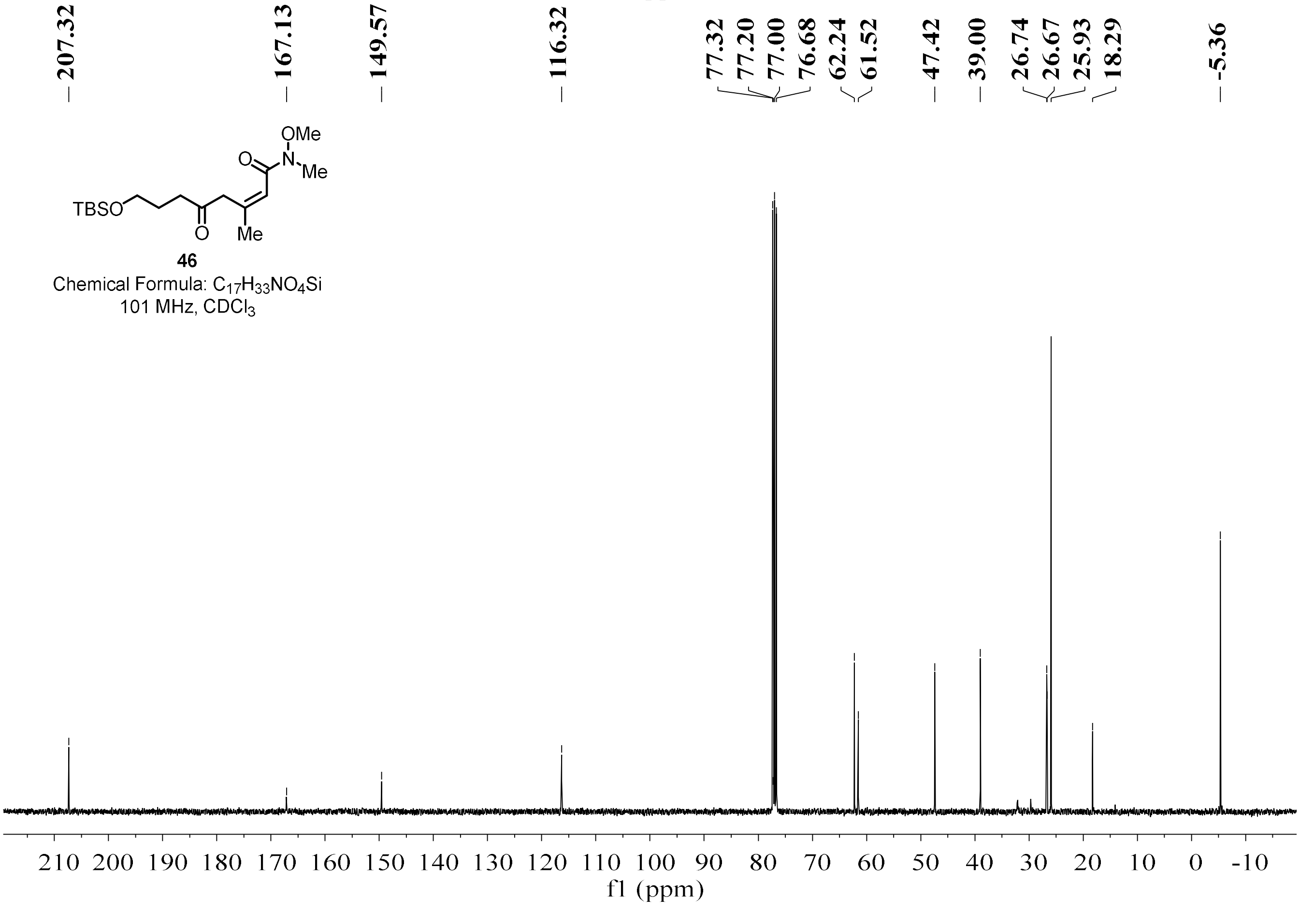

166.81
151.29
138.13
128.16
115.59
77.00
62.33
50.94
31.88
29.56
21.06
CO2Me
HO
Me
24
Chemical Formula: C10H16O3
101 MHz, CDCl3
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)



46

Chemical Formula: $C_{17}H_{33}NO_4Si$

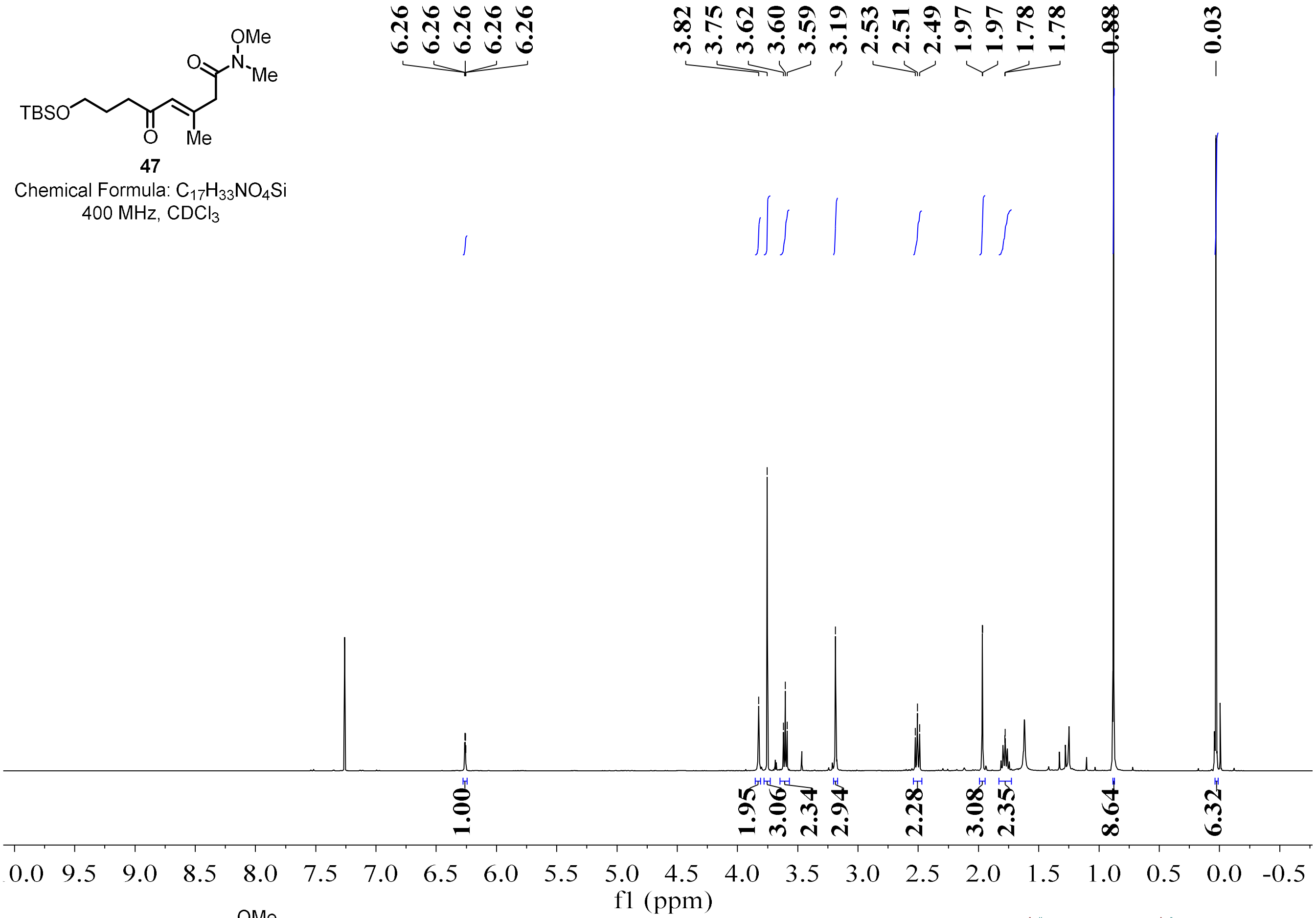
400 MHz, $CDCl_3$

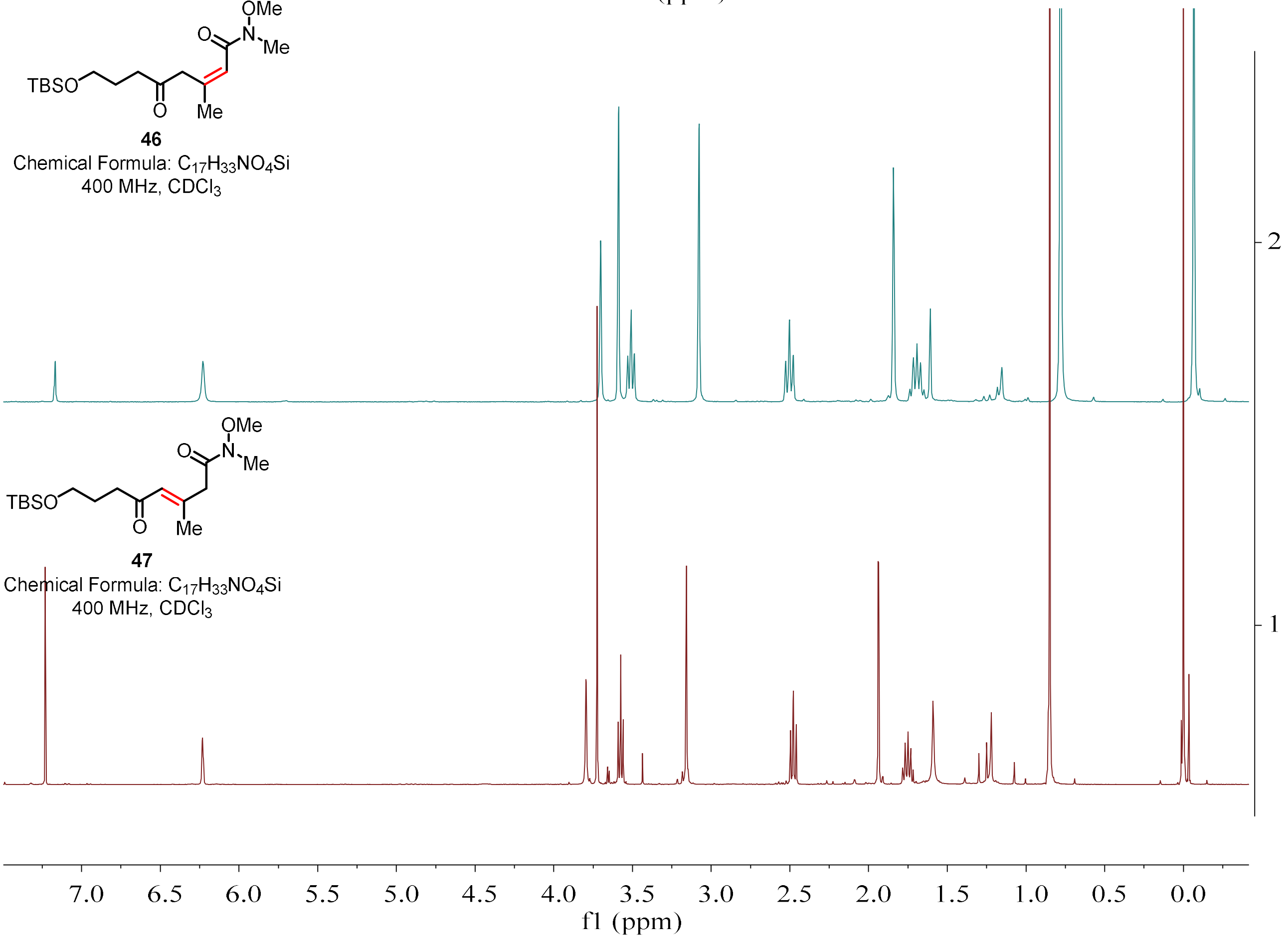


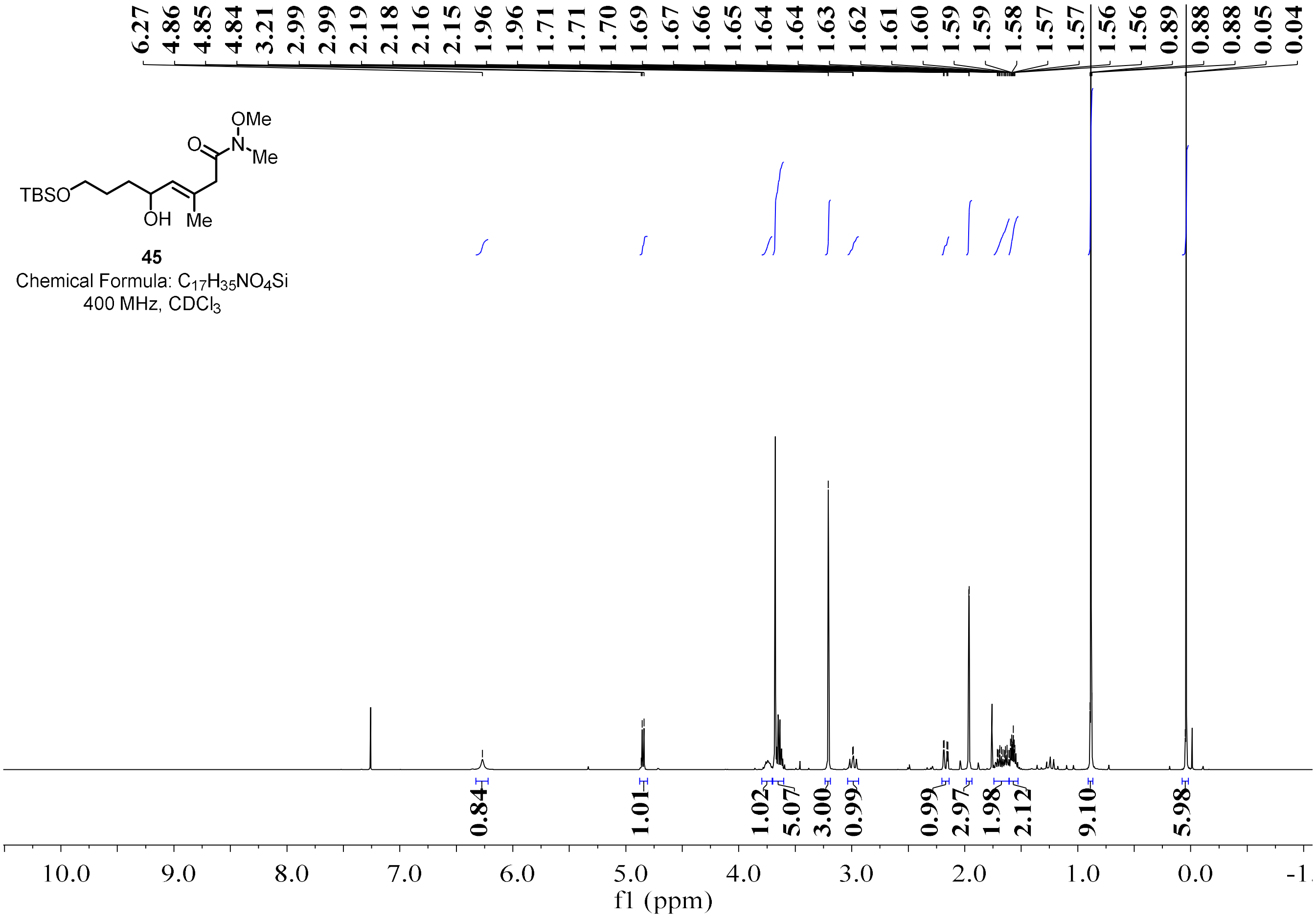
46

Chemical Formula: $C_{17}H_{33}NO_4Si$

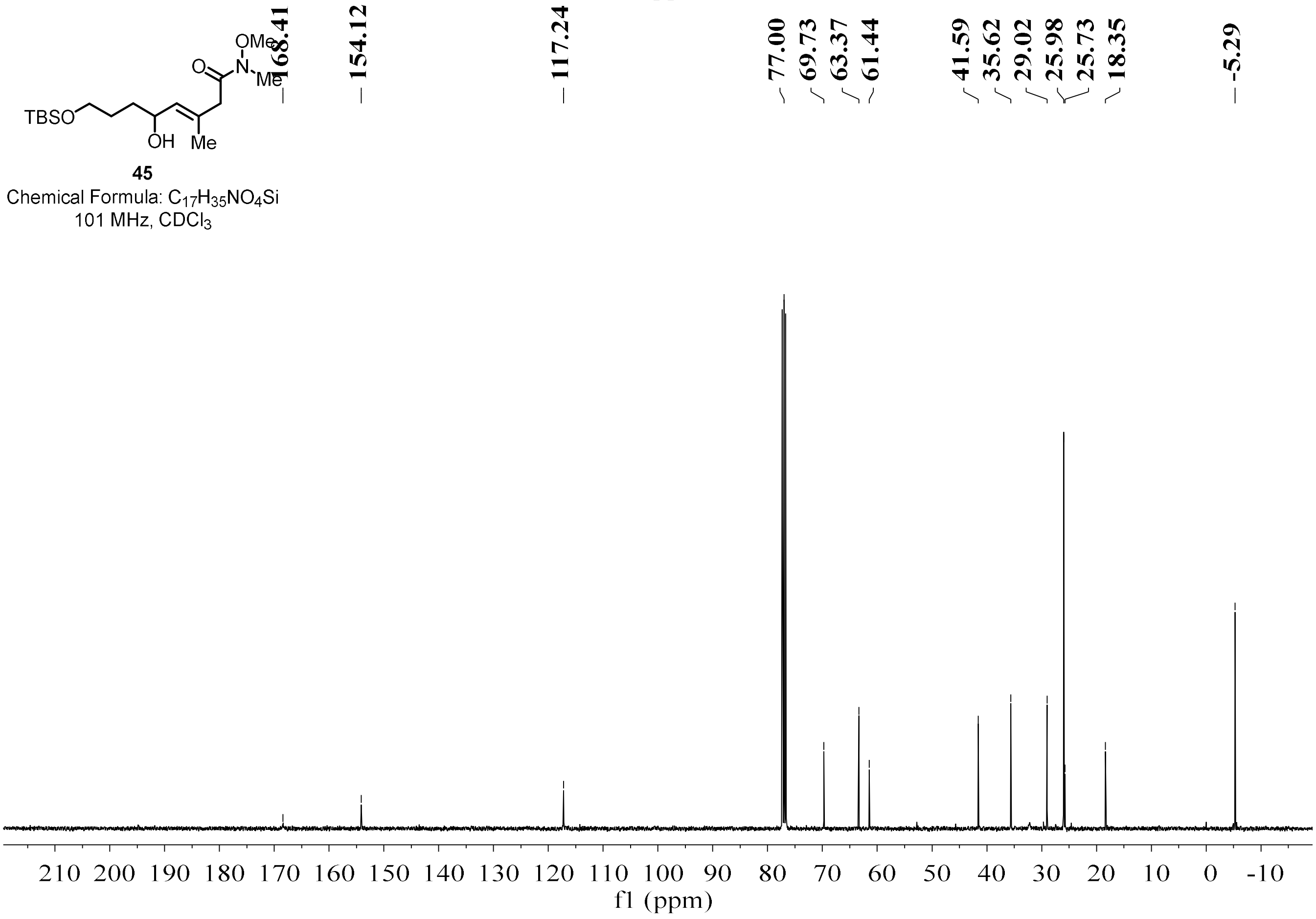
101 MHz, $CDCl_3$


6.26
6.26
6.26
6.26
6.26
3.82
3.75
3.62
3.60
3.59
3.19
2.53
2.51
2.49
1.97
1.97
1.78
1.78
0.88
0.03
OMe
N
Me
O
TBSO
O
Me
47
Chemical Formula: C17H33NO4Si
400 MHz, CDCl3
1.00
1.95
3.06
2.34
2.94
2.28
3.08
2.35
8.64
6.32
0.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

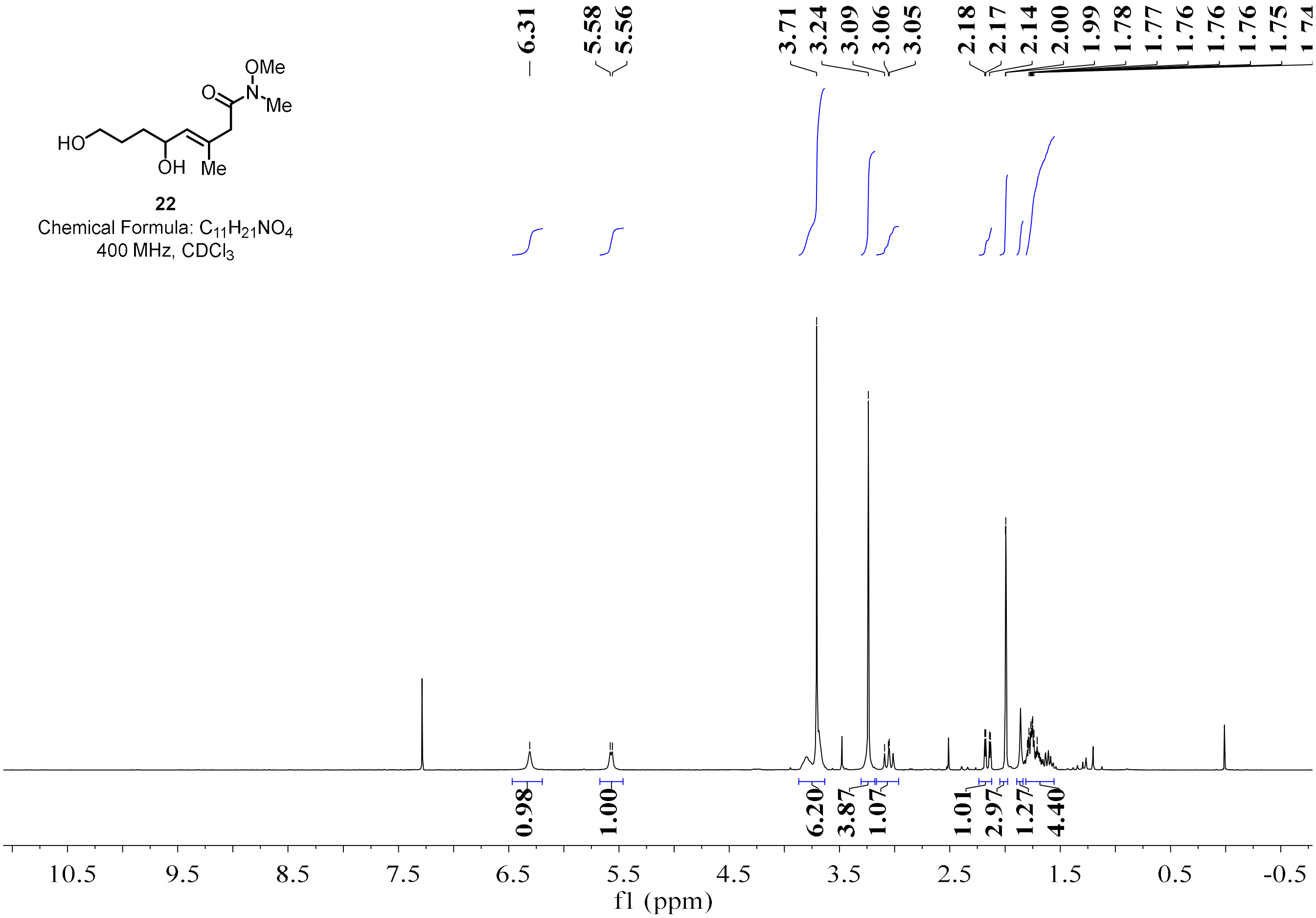

OMe
N
Me
O
TBSO
O
Me
46
Chemical Formula: C17H33NO4Si
400 MHz, CDCl3
OMe
N
Me
O
TBSO
O
Me
47
Chemical Formula: C17H33NO4Si
400 MHz, CDCl3
2
1
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)



45
Chemical Formula: $C_{17}H_{35}NO_4Si$
400 MHz, $CDCl_3$

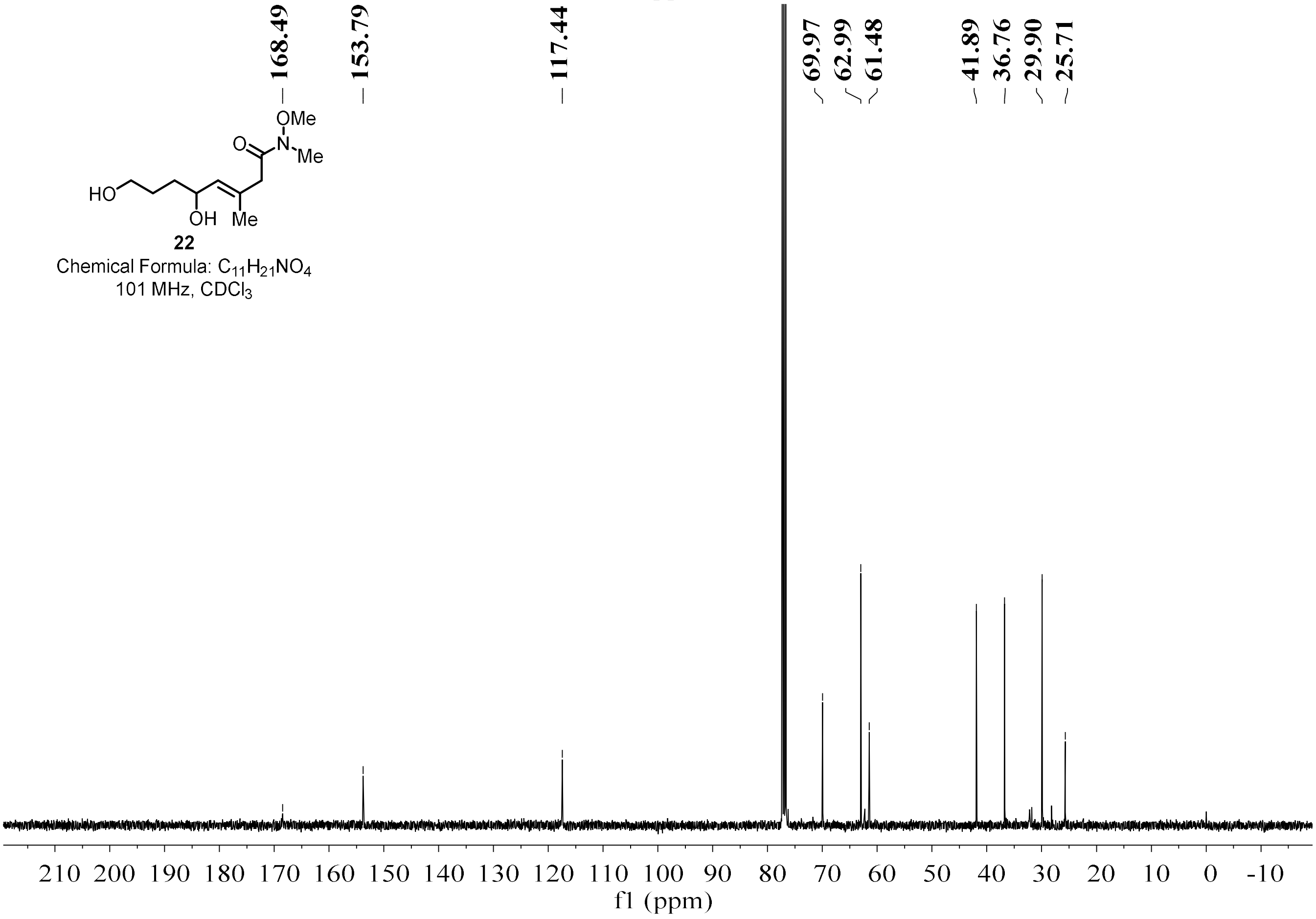


45
Chemical Formula: $C_{17}H_{35}NO_4Si$
101 MHz, $CDCl_3$


22

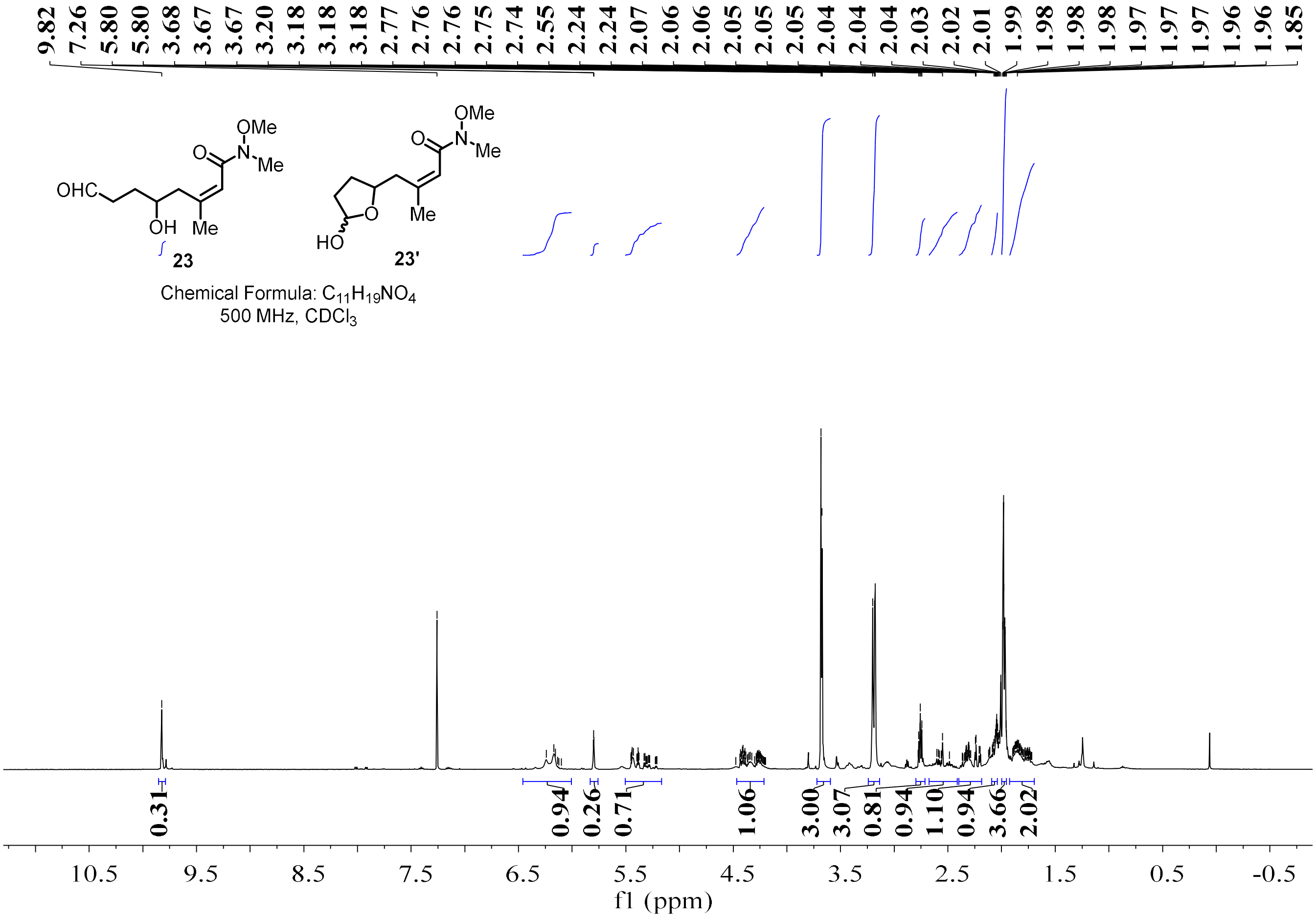
Chemical Formula: $C_{11}H_{21}NO_4$

400 MHz, $CDCl_3$


22

Chemical Formula: $C_{11}H_{21}NO_4$

101 MHz, $CDCl_3$


9.82
7.26
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5.80
3.68
3.67
3.67
3.20
3.18
3.18
3.18
2.77
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2.76
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2.04
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2.02
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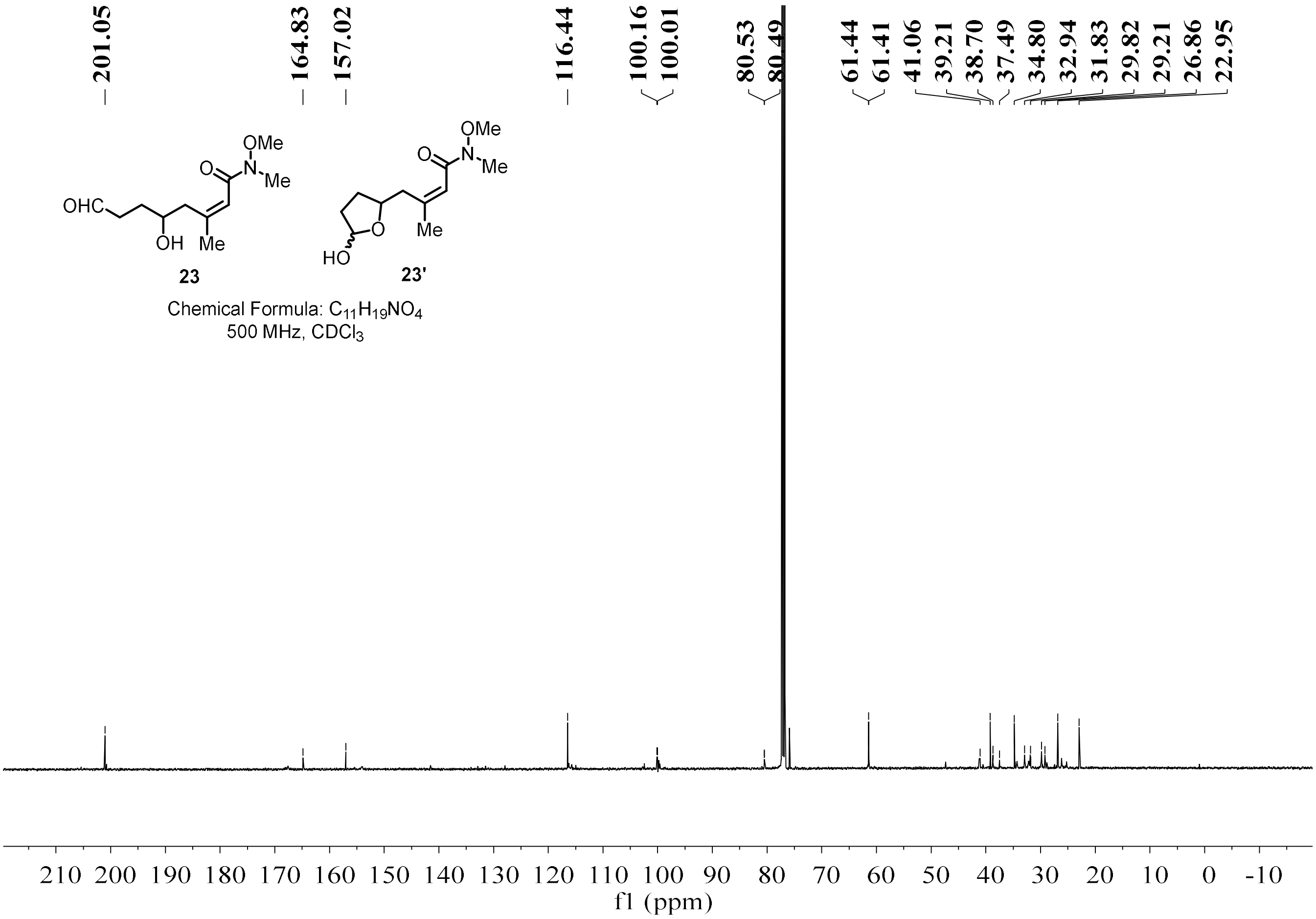
1.98
1.98
1.98
1.97
1.97
1.97
1.96
1.96
1.85
OMe
O
N
Me
OHC
OH
Me
23
OMe
O
N
Me
O
Me
HO
23'
Chemical Formula: C11H19NO4
500 MHz, CDCl3
0.31
0.94
0.26
0.71
1.06
3.00
3.07
0.81
0.94
1.10
0.94
3.66
2.02
10.5
9.5
8.5
7.5
6.5
5.5
4.5
3.5
2.5
1.5
0.5
-0.5
f1 (ppm)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164.83
157.02
116.44
100.16
100.01
80.53
80.49
61.44
61.41
41.06
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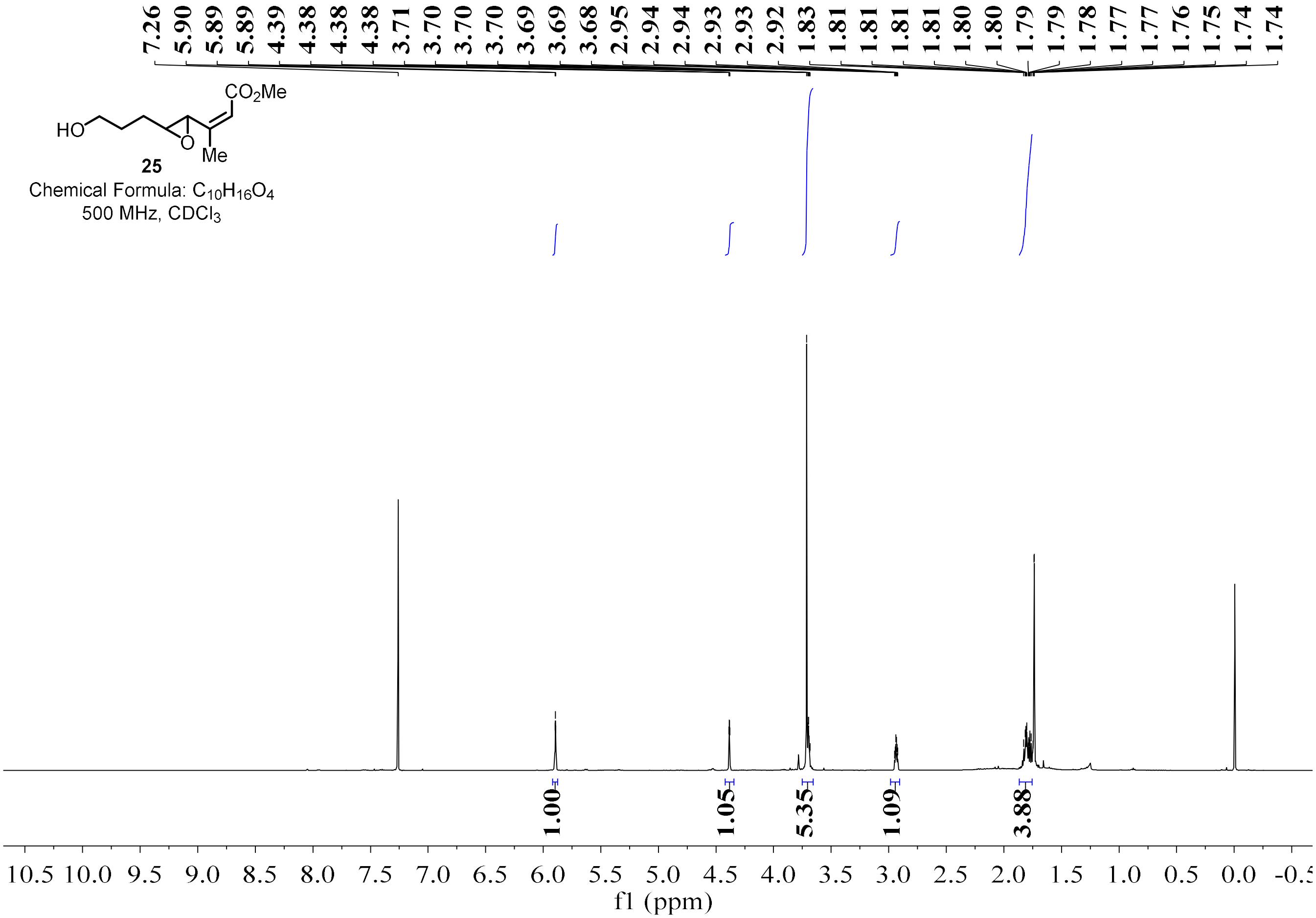
37.49
34.80
32.94
31.83
29.82
29.21
26.86
22.95
OMe
O
N
Me
OHC
OH
Me
23
OMe
O
N
Me
O
Me
HO
23'
Chemical Formula: C11H19NO4
500 MHz, CDCl3
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)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5.89
4.39
4.38
4.38
4.38
3.71
3.70
3.70
3.70
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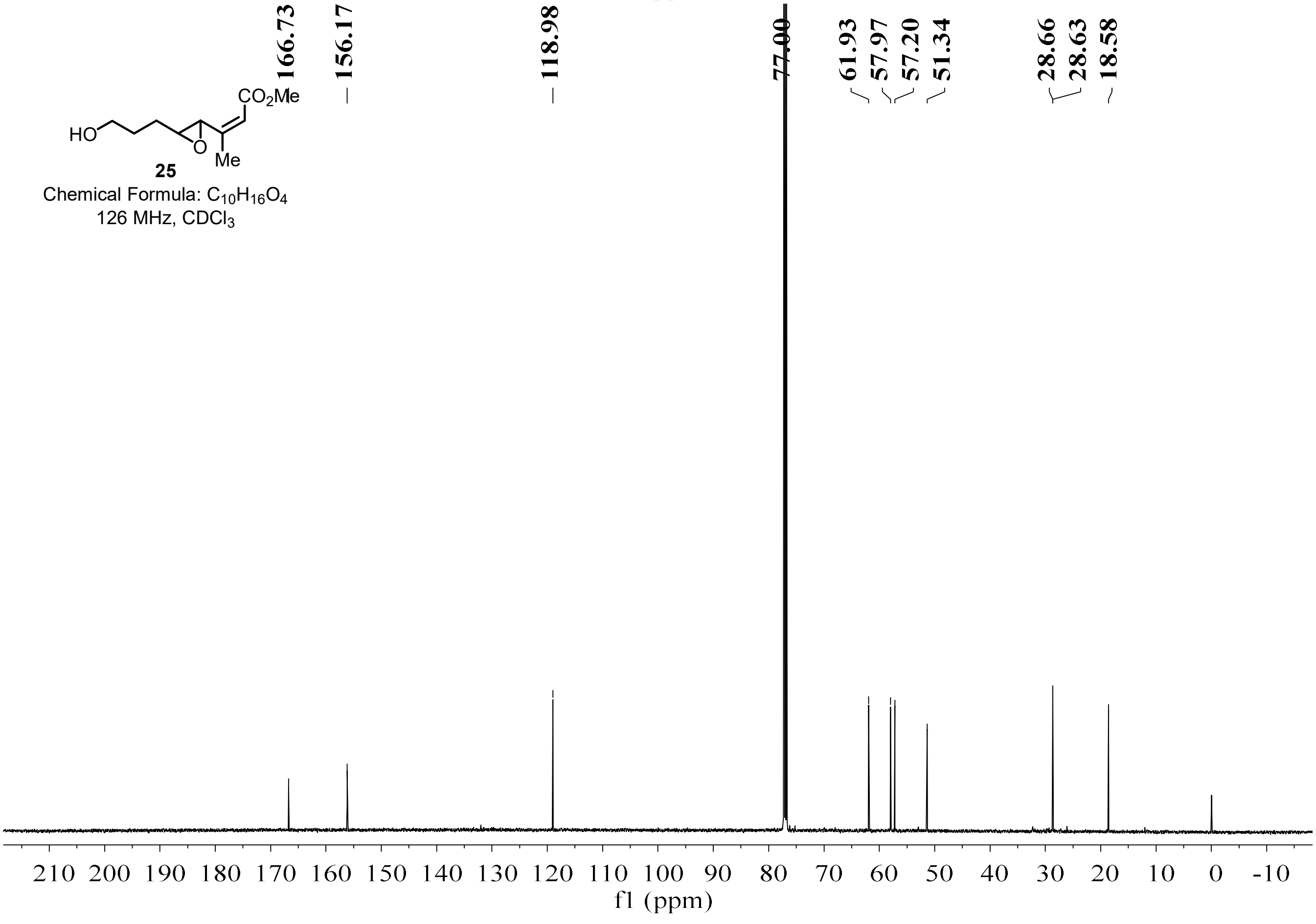
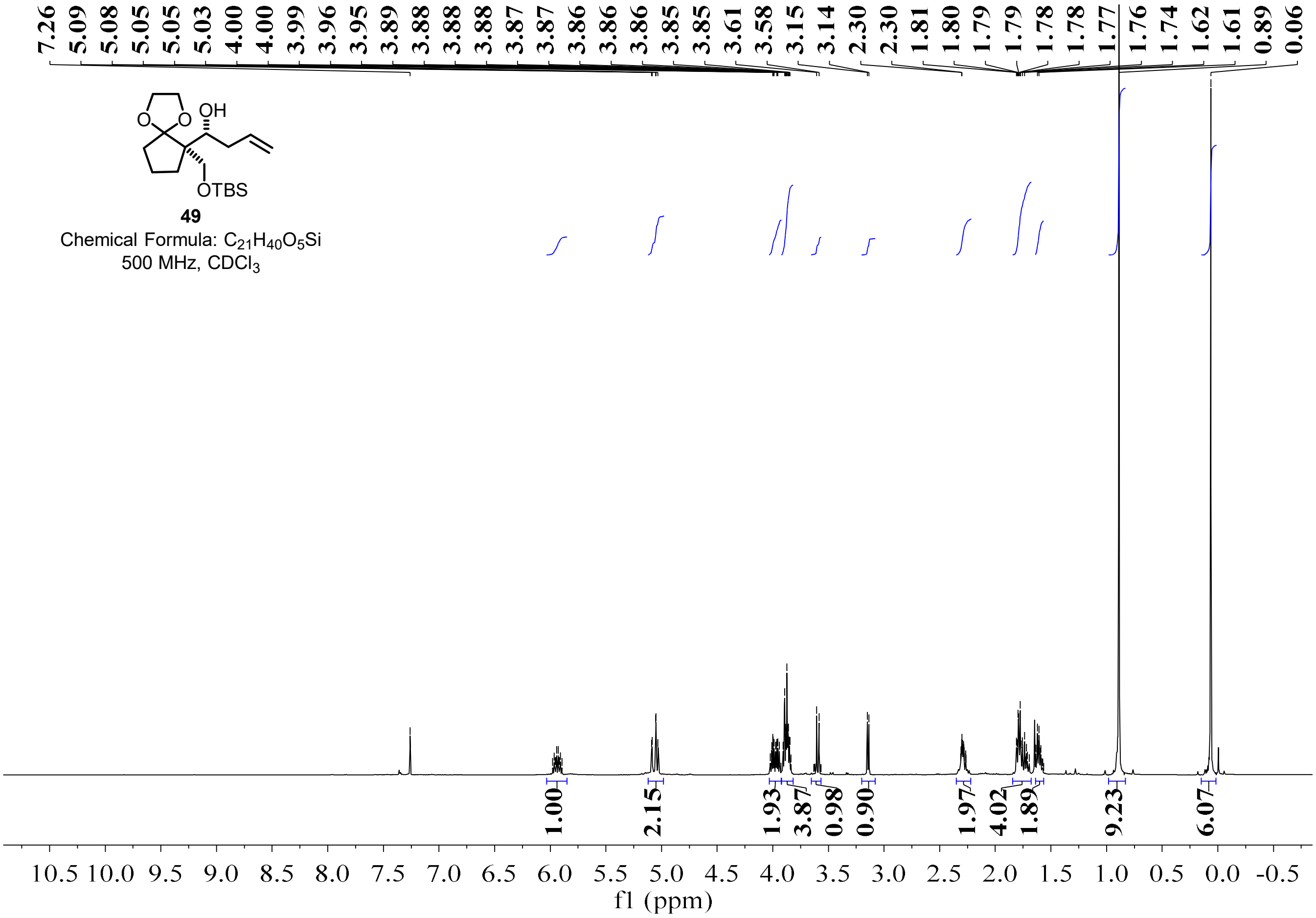
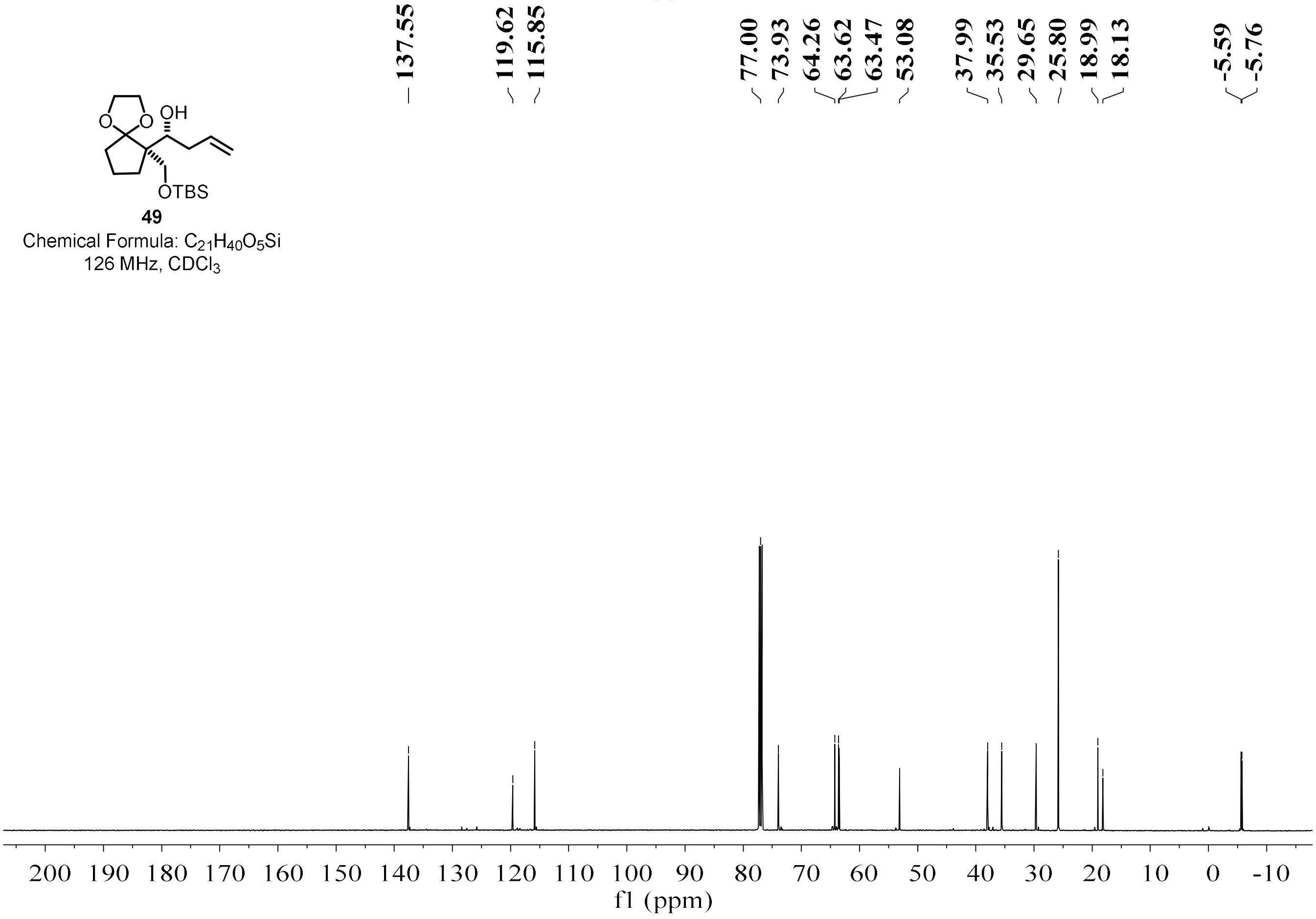
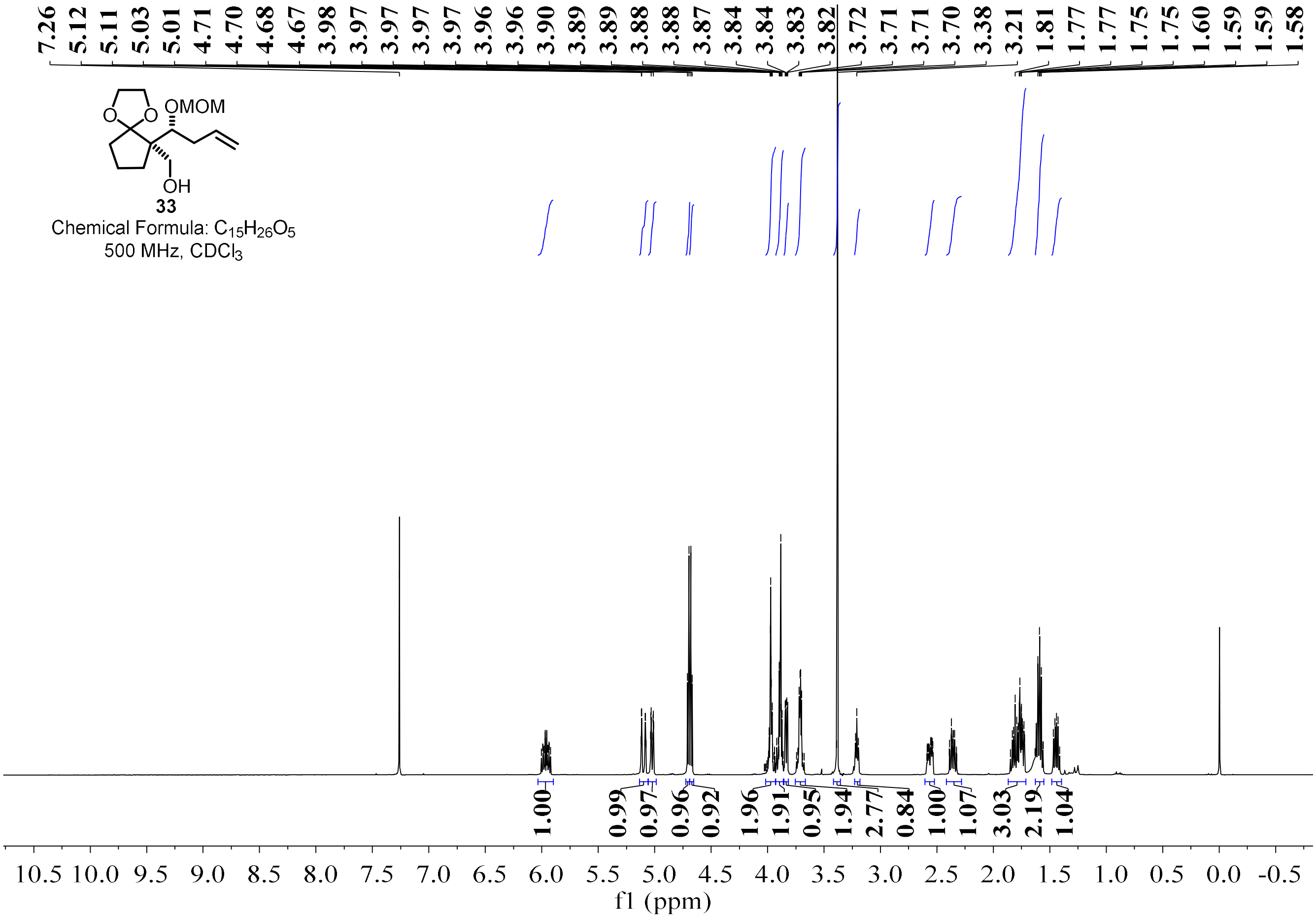
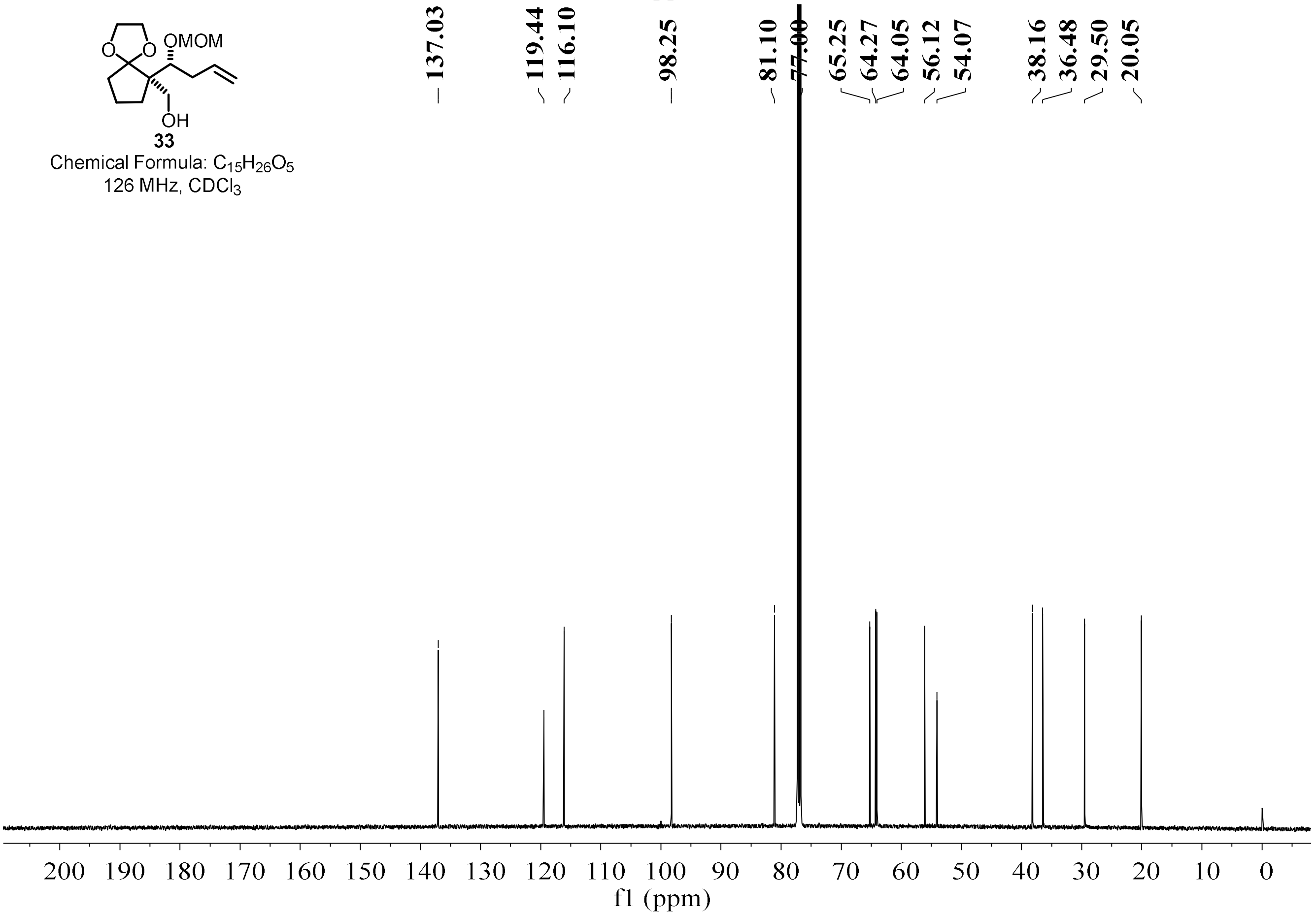
3.69
3.68
2.95
2.94
2.94
2.93
2.93
2.92
1.83
1.81
1.81
1.81
1.81
1.80
1.80
1.79
1.79
1.78
1.77
1.77
1.76
1.75
1.74
1.74
CO2Me
HO
O
Me
25
Chemical Formula: $C_{10}H_{16}O_4$
500 MHz, $CDCl_3$
1.00
1.05
5.35
1.09
3.88
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

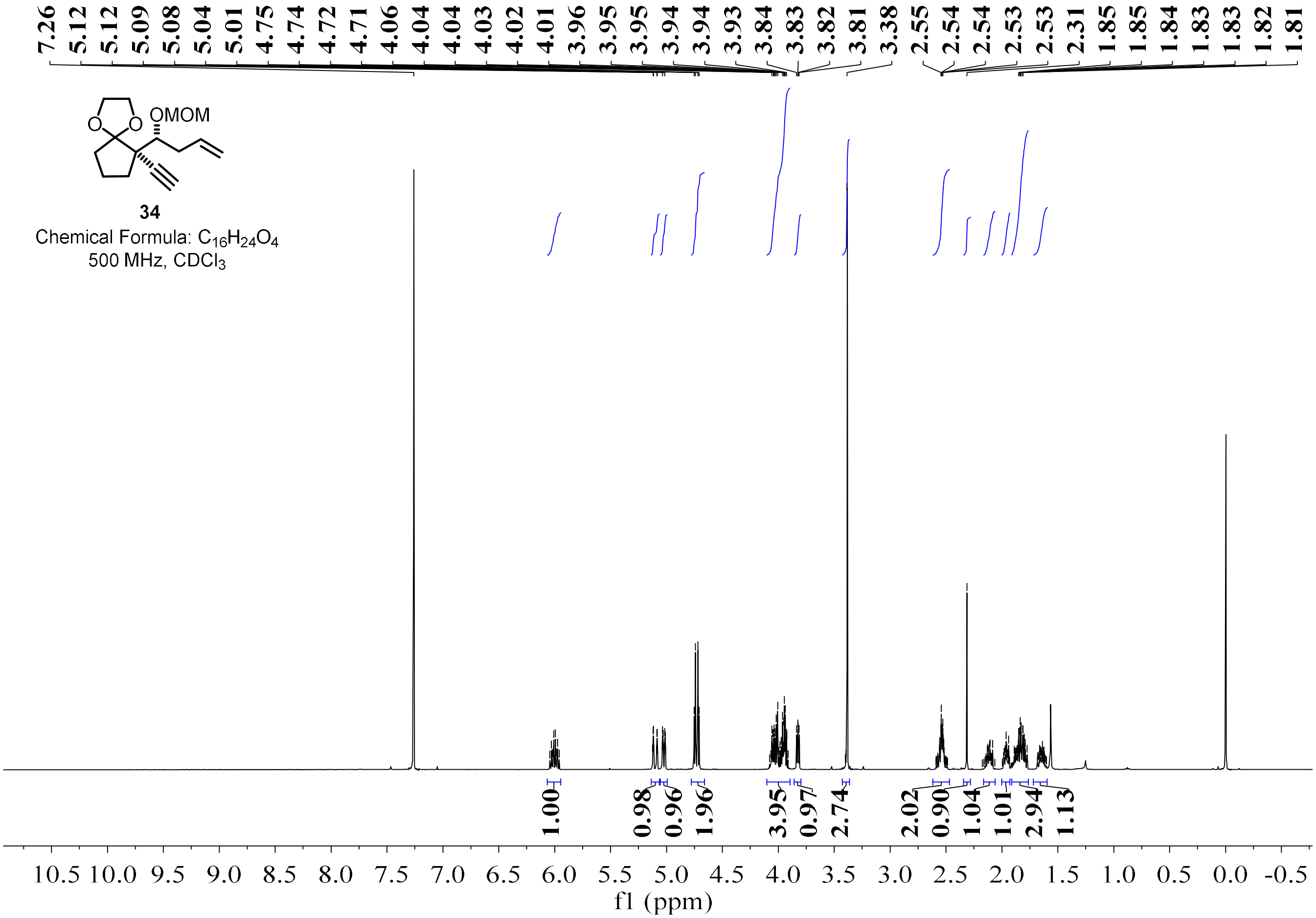

166.73
156.17
118.98
77.00
61.93
57.97
57.20
51.34
28.66
28.63
18.58
CO2Me
HO
O
Me
25
Chemical Formula: $C_{10}H_{16}O_4$
126 MHz, $CDCl_3$
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


7.26
5.09
5.08
5.05
5.05
5.03
4.00
4.00
3.99
3.96
3.95
3.89
3.88
3.88
3.88
3.87
3.87
3.86
3.86
3.86
3.85
3.85
3.61
3.58
3.15
3.14
2.30
2.30
1.81
1.80
1.79
1.79
1.78
1.78
1.77
1.76
1.74
1.62
1.61
0.89
0.06
OH
O
O
OTBS
49
Chemical Formula: $C_{21}H_{40}O_5Si$
500 MHz, $CDCl_3$
1.00
2.15
1.93
3.87
0.98
0.90
1.97
4.02
1.89
9.23
6.07
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)


137.55
119.62
115.85
77.00
73.93
64.26
63.62
63.47
53.08
37.99
35.53
29.65
25.80
18.99
18.13
-5.59
-5.76
OH
O
O
OTBS
49
Chemical Formula: $C_{21}H_{40}O_5Si$
126 MHz, $CDCl_3$
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


7.26 5.12 5.11 5.03 5.01 4.71 4.70 4.68 4.67 3.98 3.97 3.97 3.97 3.97 3.96 3.96 3.90 3.89 3.89 3.88 3.88 3.87 3.84 3.84 3.83 3.82 3.72 3.71 3.71 3.70 3.38 3.21 1.81 1.77 1.77 1.75 1.75 1.60 1.59 1.59 1.58
OMOM
OH
33
Chemical Formula: $C_{15}H_{26}O_5$
500 MHz, $CDCl_3$
1.00 0.99 0.97 0.96 0.92 1.96 1.91 0.95 1.94 2.77 0.84 1.00 1.07 3.03 2.19 1.04
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

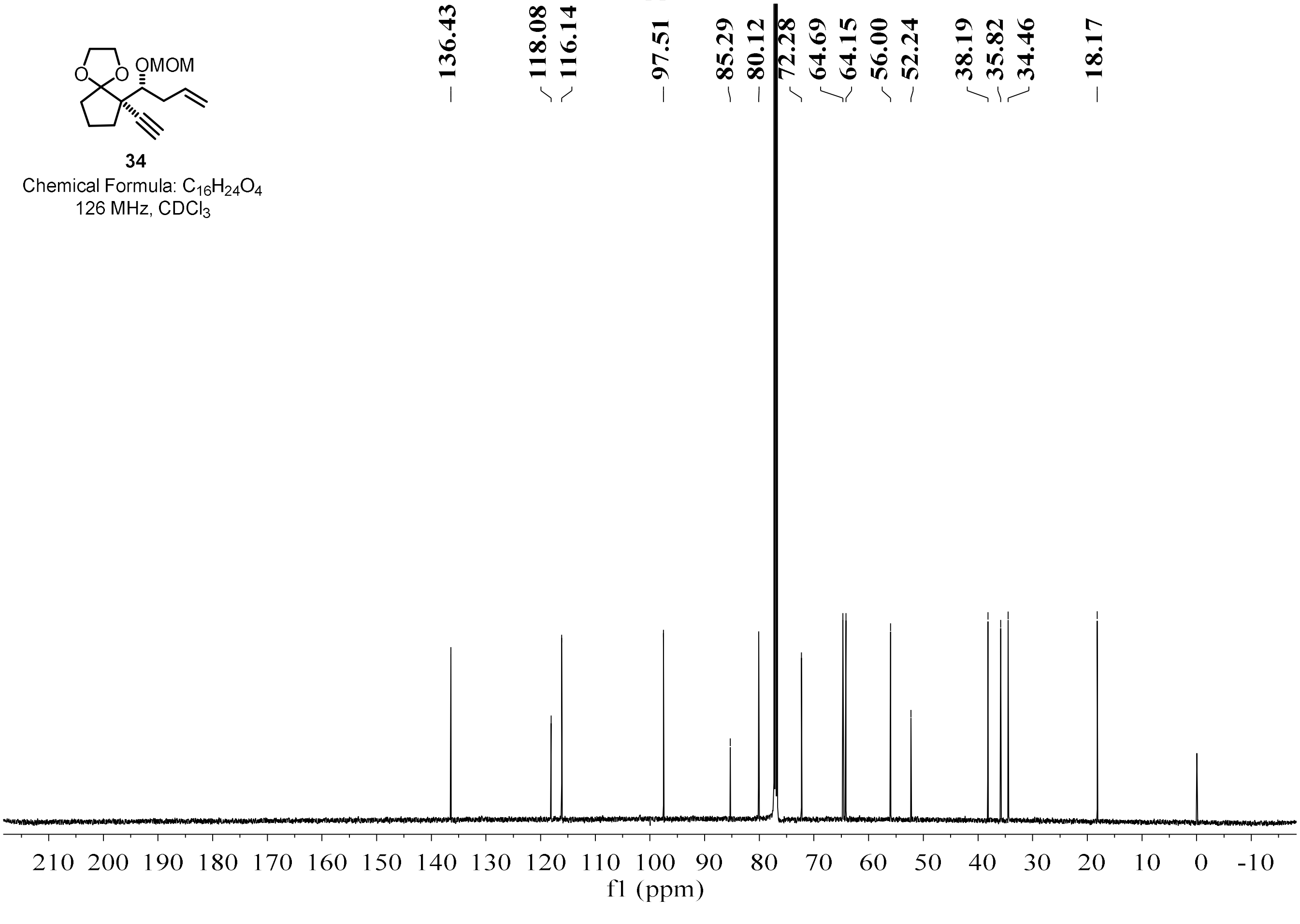

137.03 119.44 116.10 98.25 81.10 77.00 65.25 64.27 64.05 56.12 54.07 38.16 36.48 29.50 20.05
OMOM
OH
33
Chemical Formula: $C_{15}H_{26}O_5$
126 MHz, $CDCl_3$
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)



34

Chemical Formula: $C_{16}H_{24}O_4$

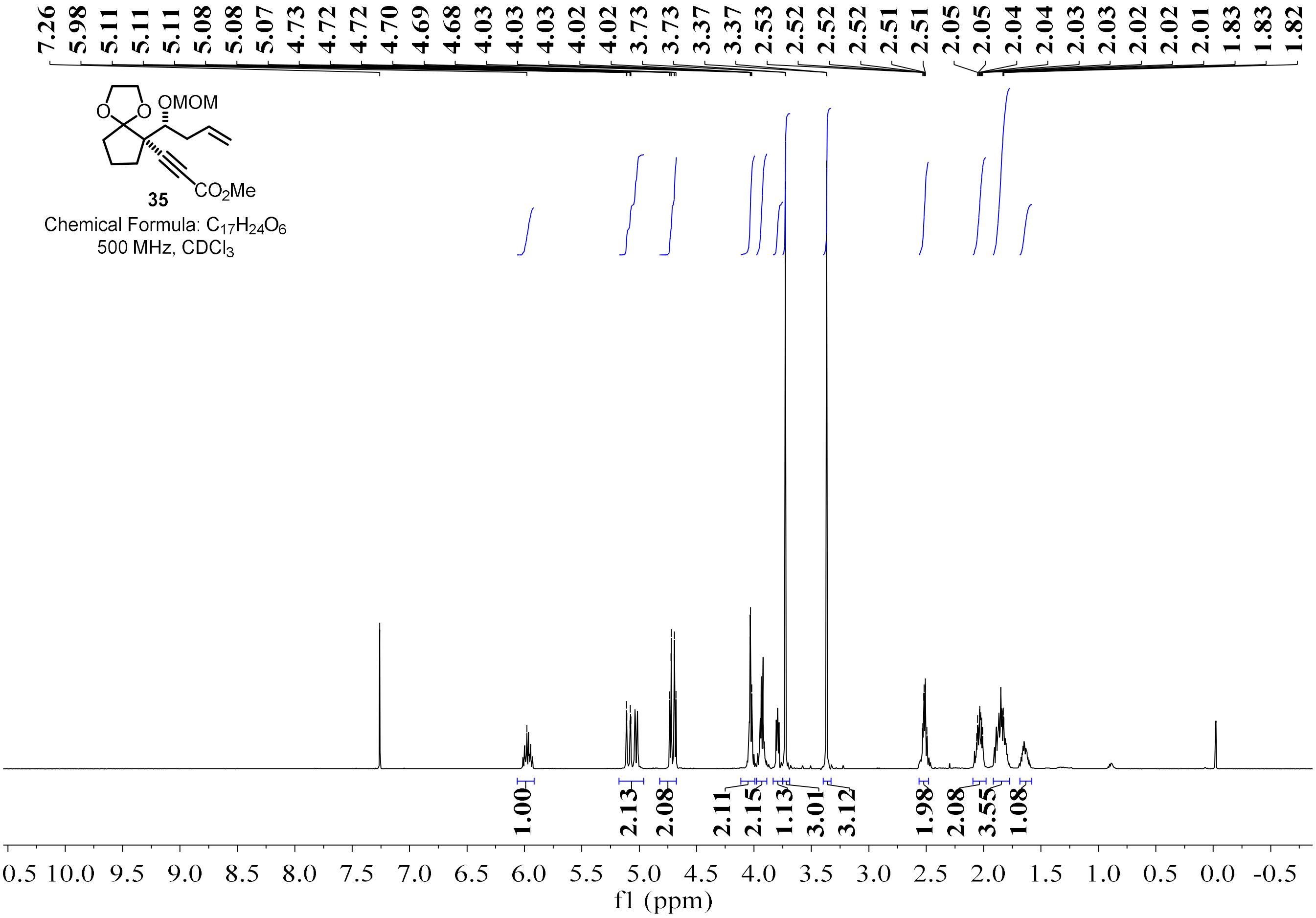
500 MHz, $CDCl_3$



34

Chemical Formula: $C_{16}H_{24}O_4$

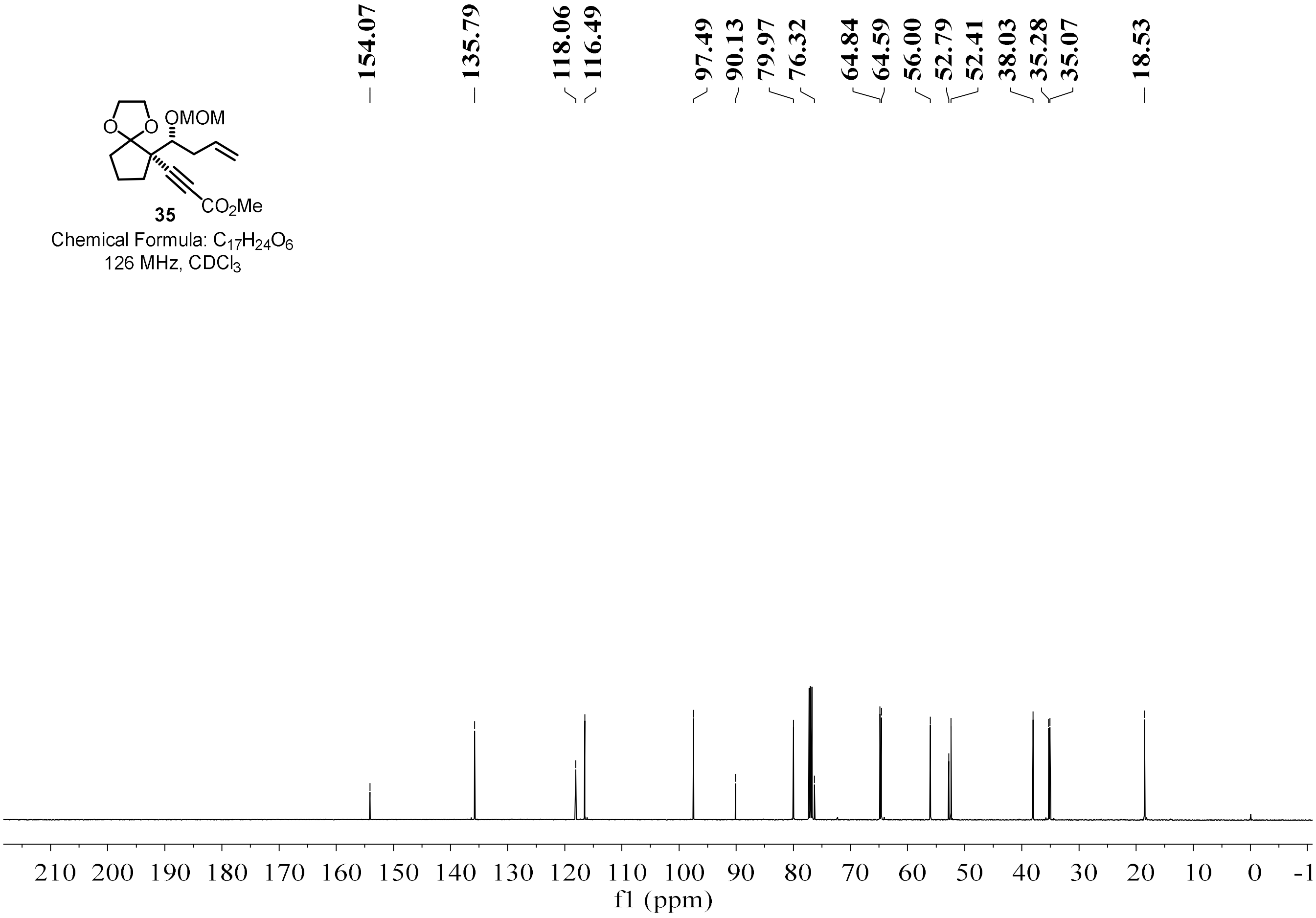
126 MHz, $CDCl_3$



35

Chemical Formula: $C_{17}H_{24}O_6$

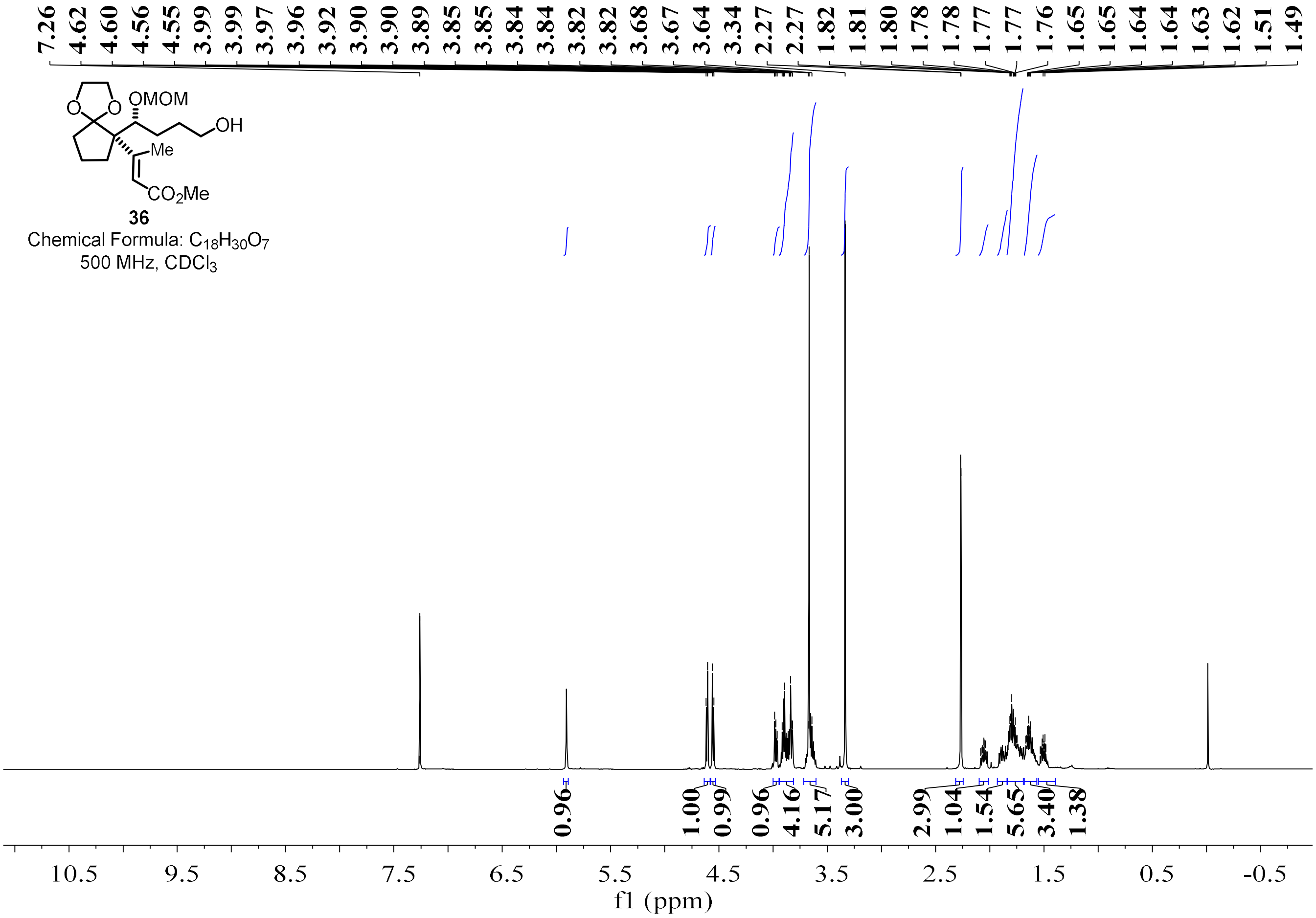
500 MHz, $CDCl_3$



35

Chemical Formula: $C_{17}H_{24}O_6$

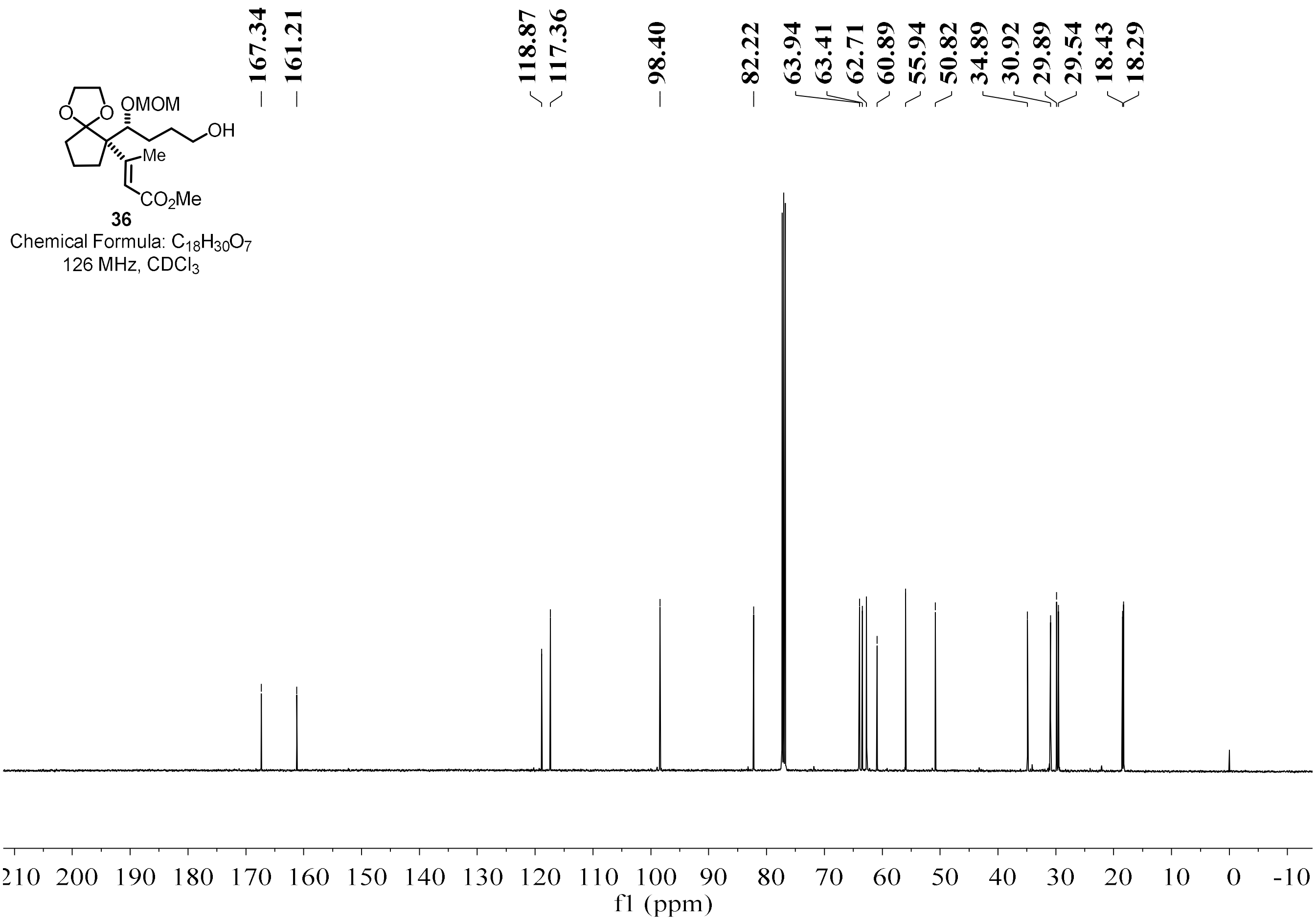
126 MHz, $CDCl_3$



36

Chemical Formula: $C_{18}H_{30}O_7$

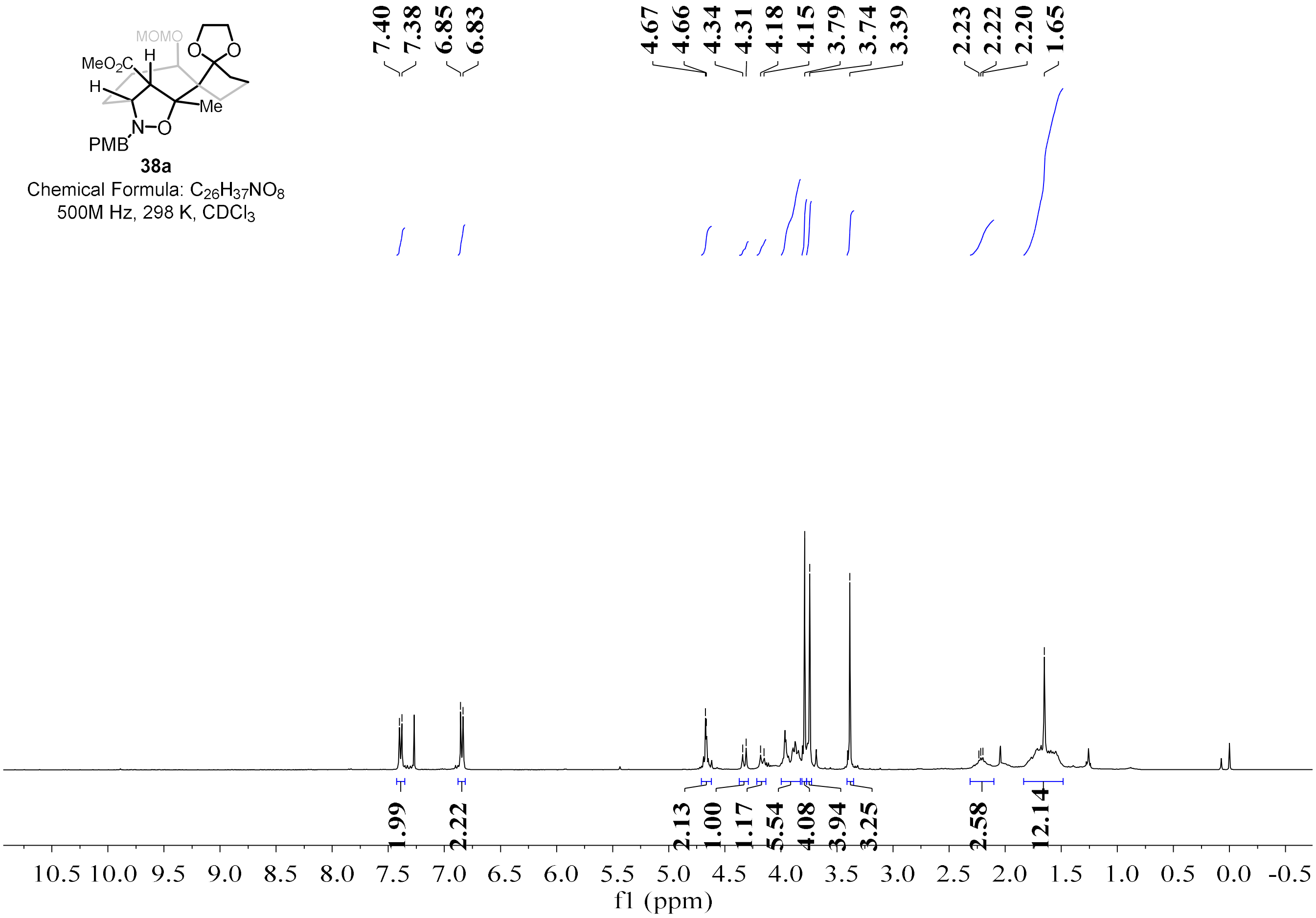
500 MHz, $CDCl_3$

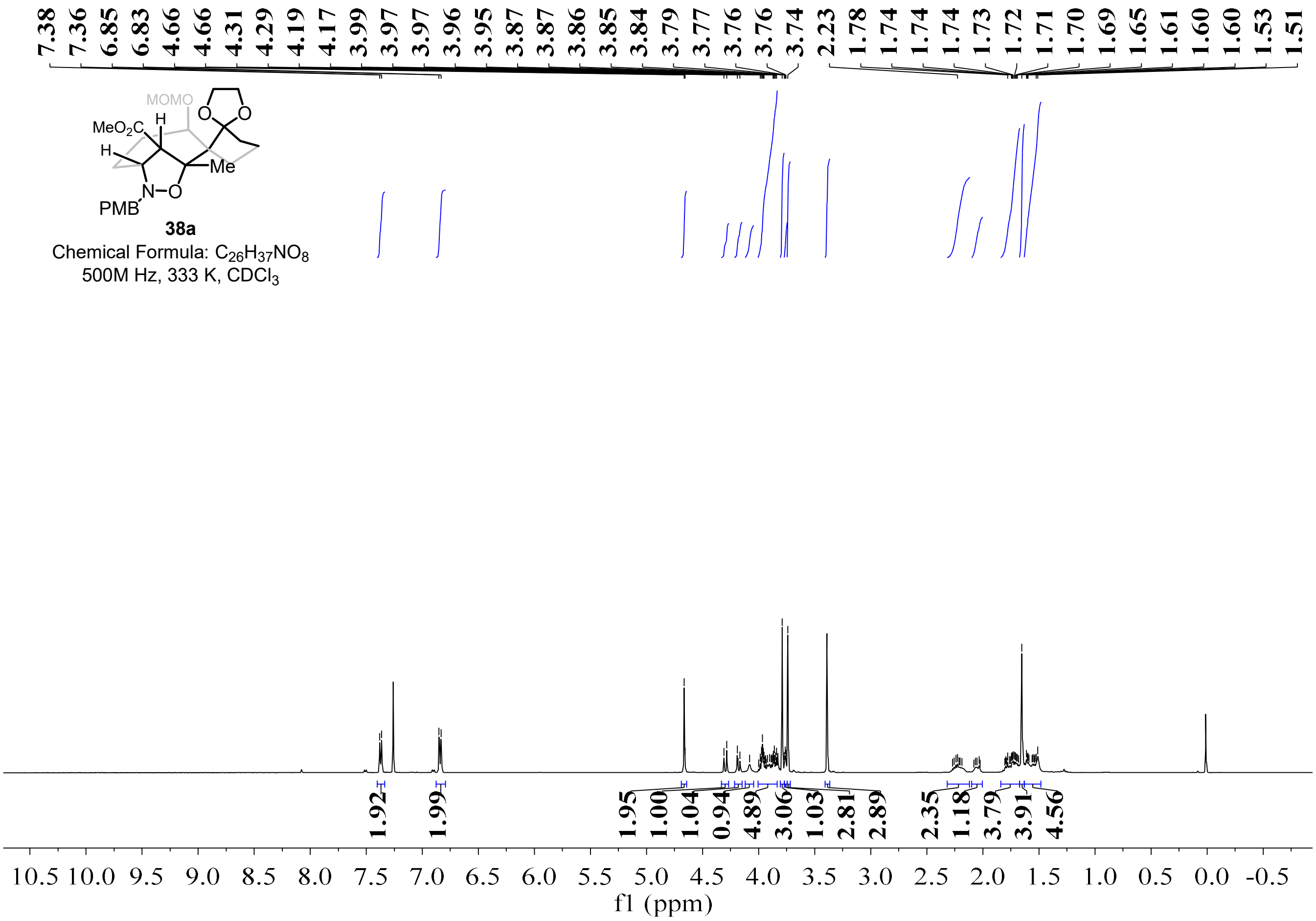


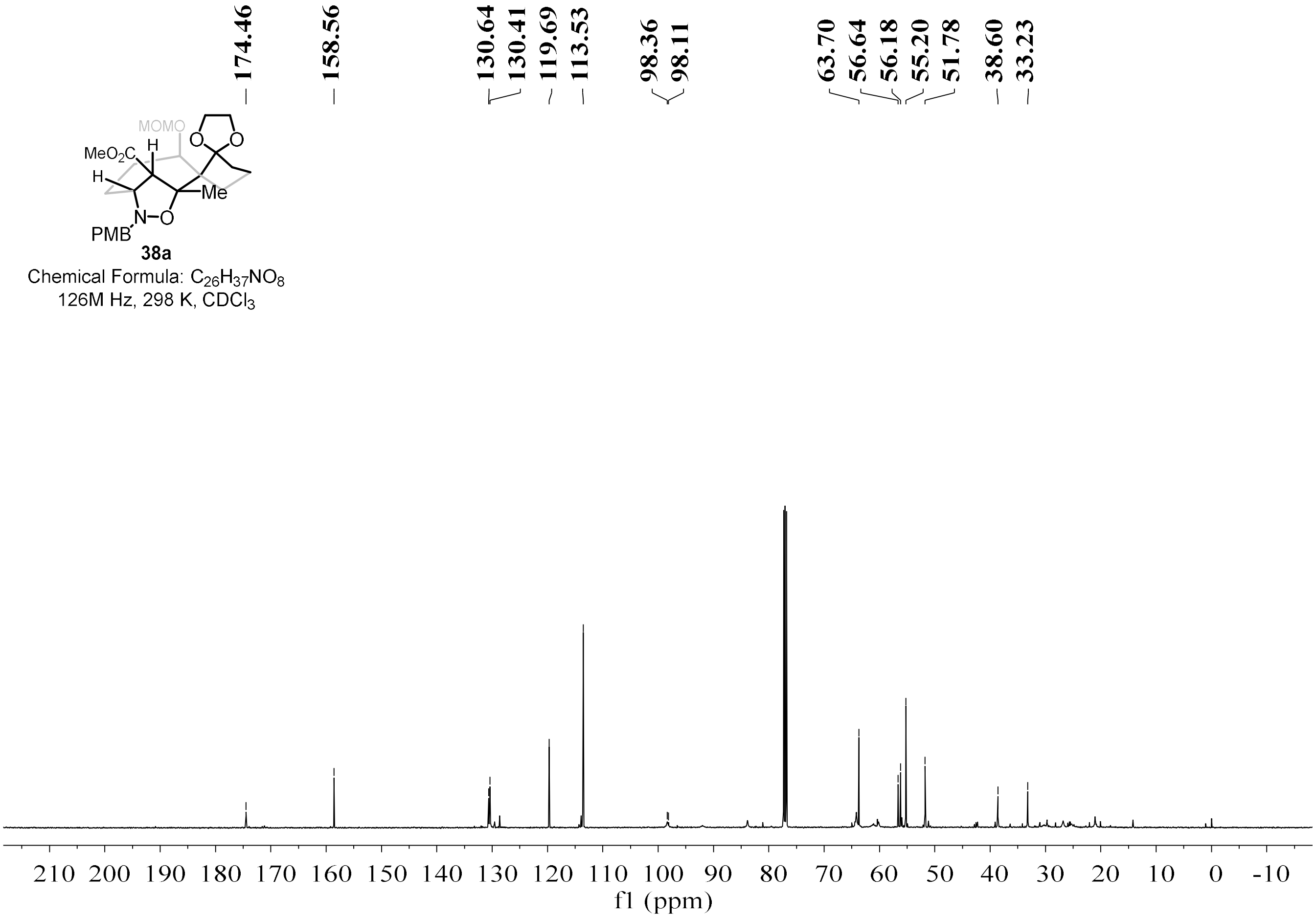
36

Chemical Formula: $C_{18}H_{30}O_7$

126 MHz, $CDCl_3$


MOMO
MeO2C
H
H
O
O
Me
N–O
PMB
38a
Chemical Formula: C26H37NO8
500M Hz, 298 K, CDCl3
7.40
7.38
6.85
6.83
4.67
4.66
4.34
4.31
4.18
4.15
3.79
3.74
3.39
2.23
2.22
2.20
1.65
1.99
2.22
2.13
1.00
1.17
5.54
4.08
3.94
3.25
2.58
12.14
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

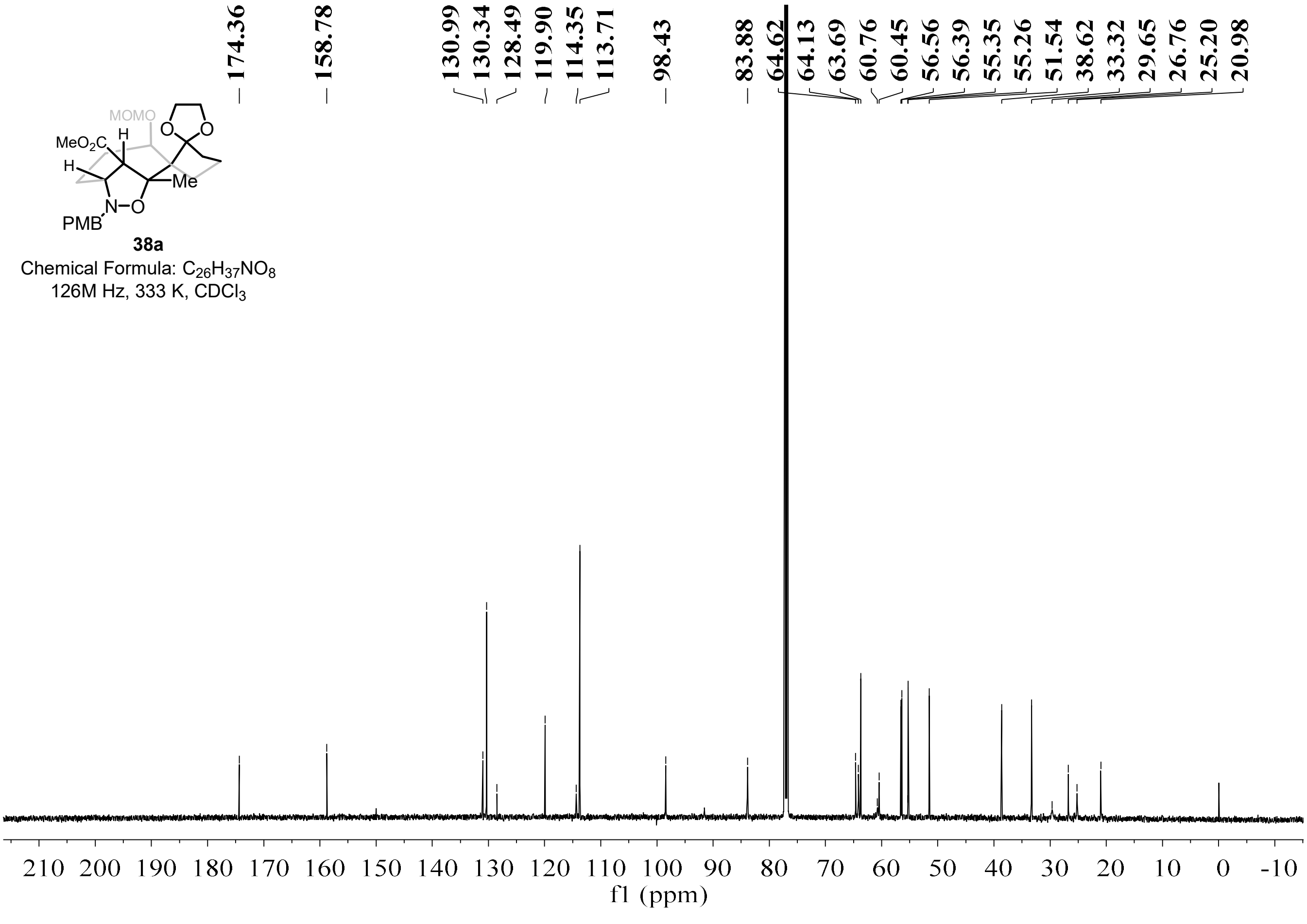

7.38
7.36
6.85
6.83
4.66
4.66
4.31
4.29
4.19
4.17
3.99
3.97
3.97
3.96
3.95
3.87
3.87
3.86
3.85
3.84
3.79
3.77
3.76
3.76
3.74
2.23
1.78
1.74
1.74
1.74
1.73
1.72
1.71
1.70
1.69
1.65
1.61
1.60
1.60
1.53
1.51
MOMO
MeO2C
H
H
O
O
Me
N–O
PMB
38a
Chemical Formula: C26H37NO8
500M Hz, 333 K, CDCl3
1.92
1.99
1.95
1.00
1.04
0.94
4.89
3.06
1.03
2.81
2.89
2.35
1.18
3.79
3.91
4.56
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)



38a

Chemical Formula: $C_{26}H_{37}NO_8$

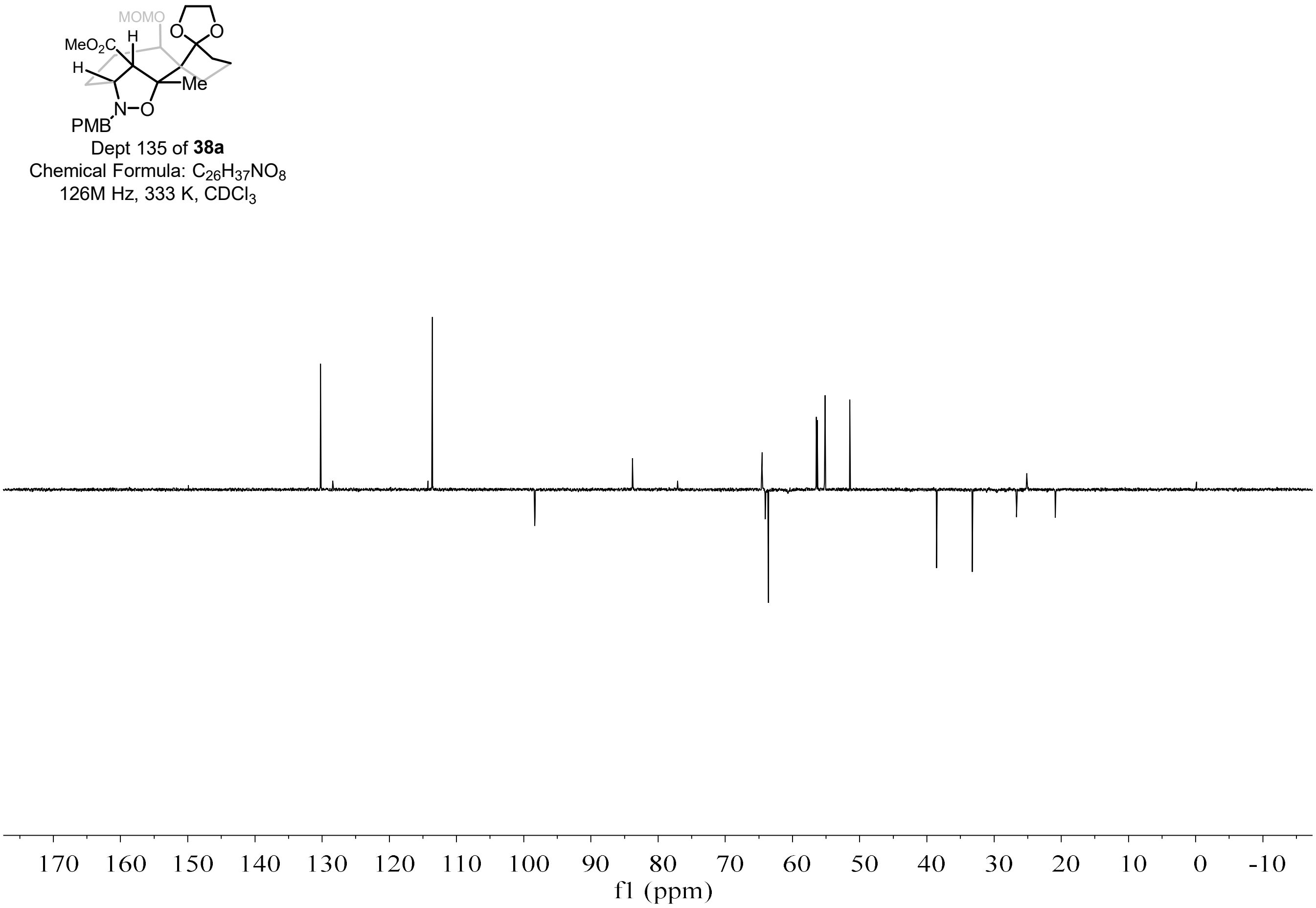
126M Hz, 298 K, $CDCl_3$

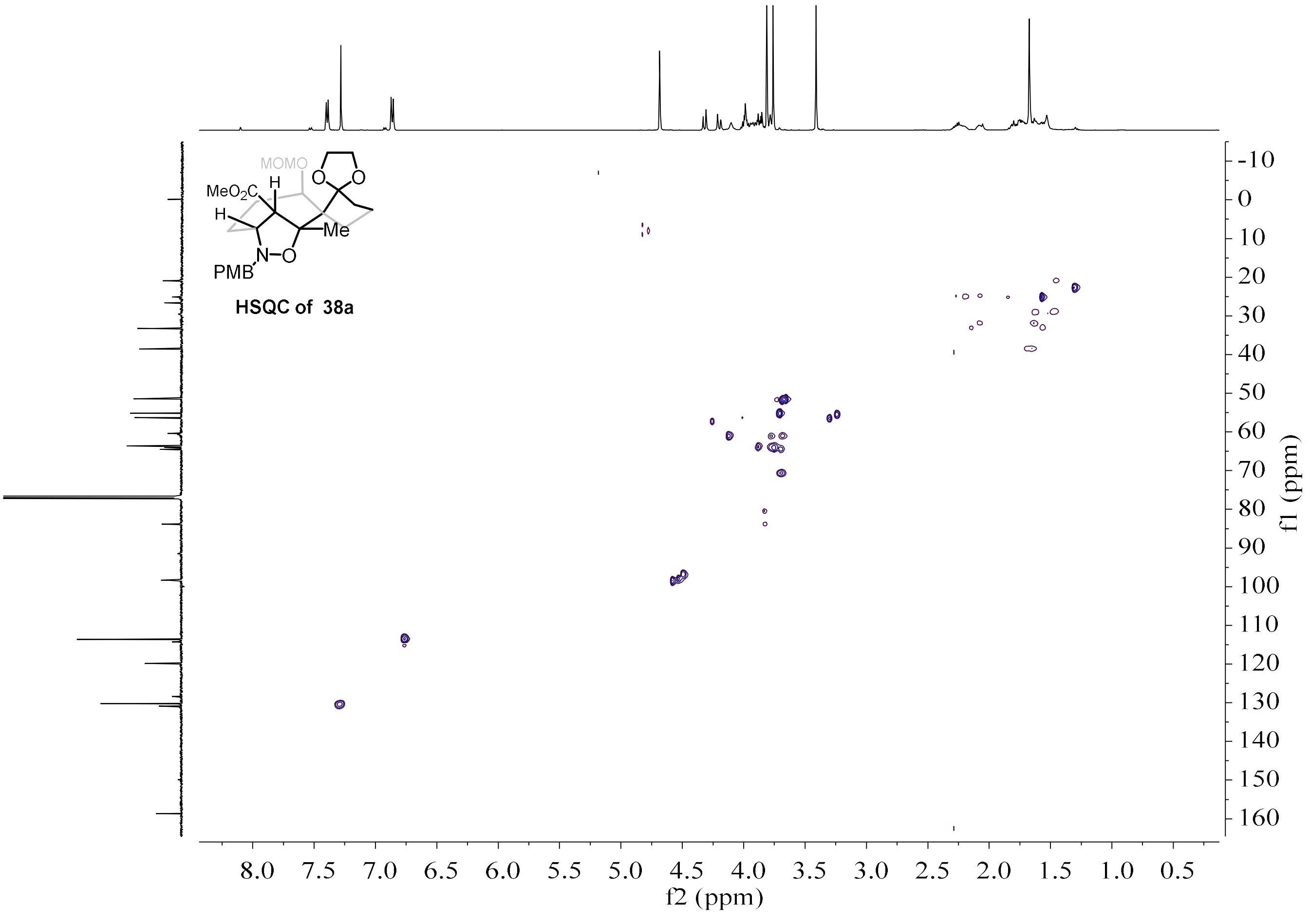


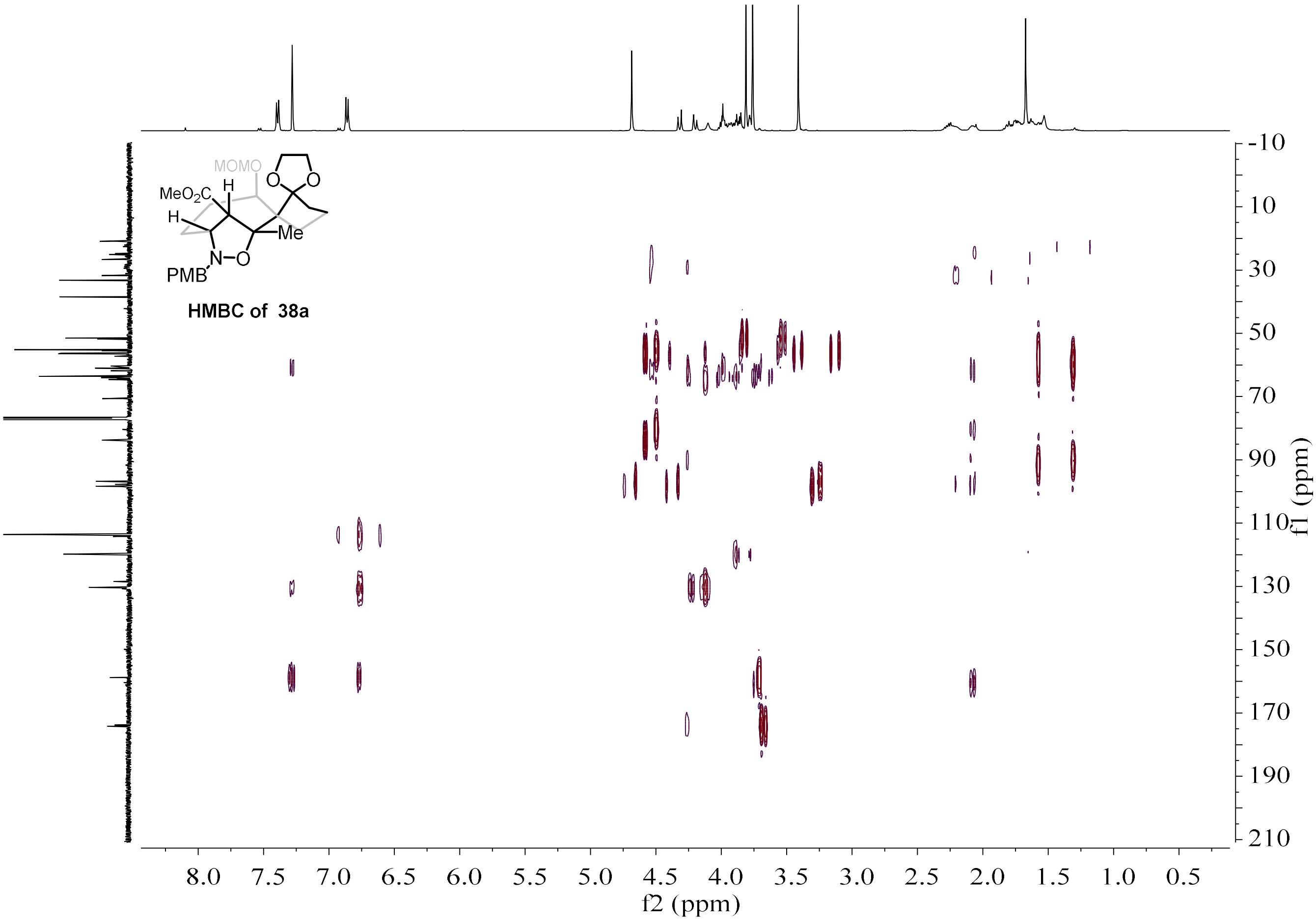
38a

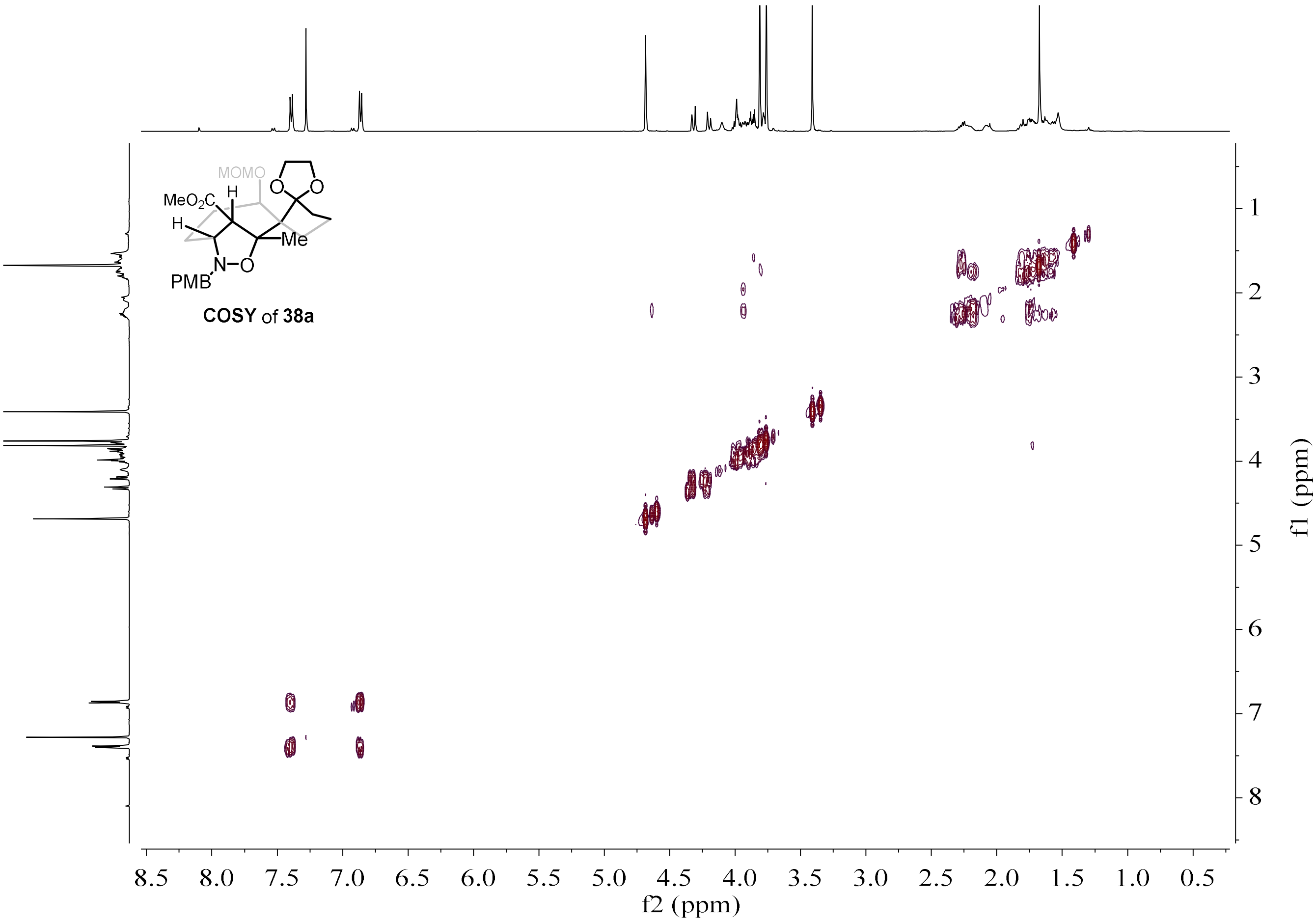
Chemical Formula: $C_{26}H_{37}NO_8$

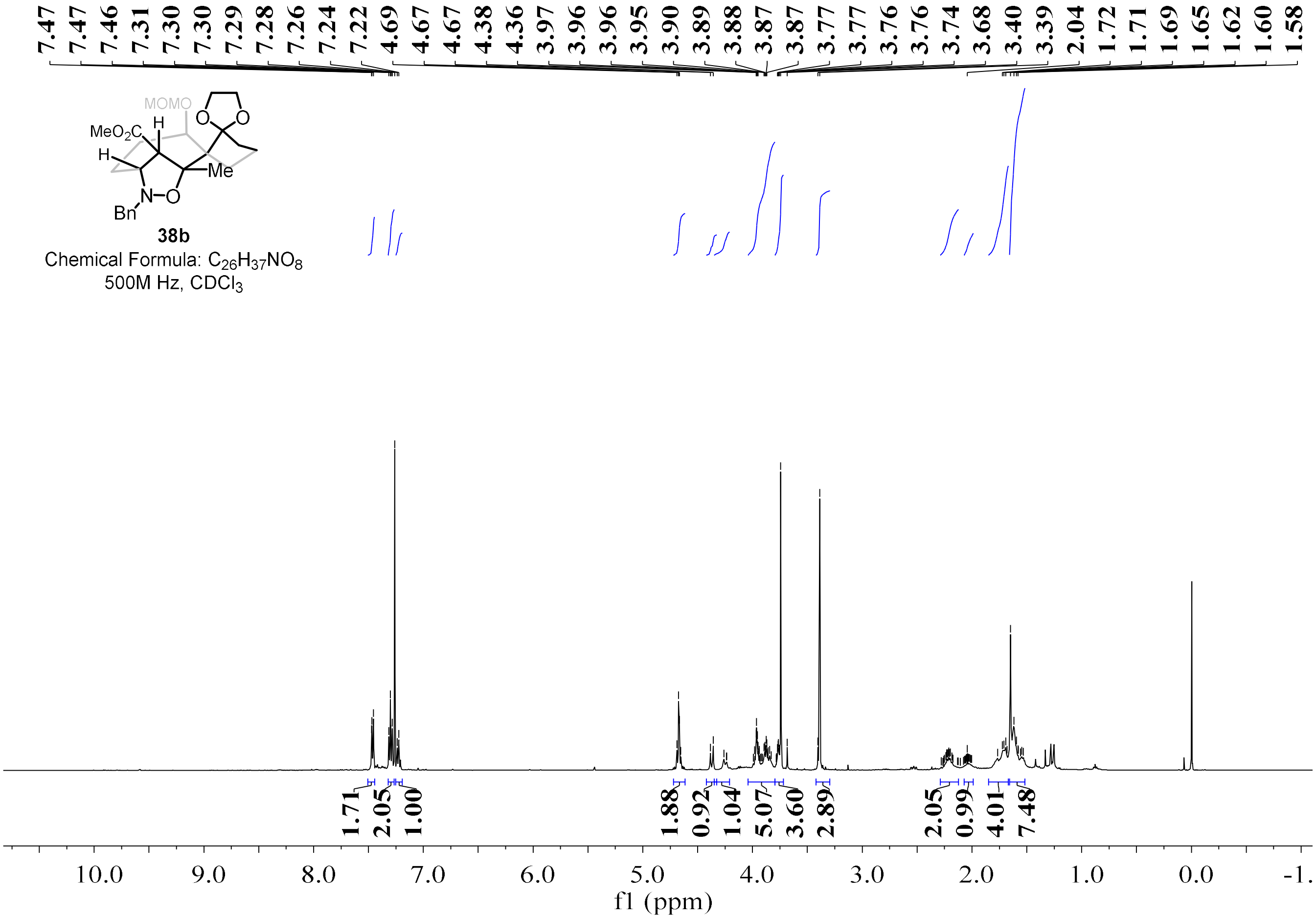
126M Hz, 333 K, $CDCl_3$


Dept 135 of **38a**
Chemical Formula: $C_{26}H_{37}NO_8$
126M Hz, 333 K, $CDCl_3$




MOMO
MeO2C
H
H
Me
N–O
PMB
O
O
HMBC of 38a
-10
10
30
50
70
90
110
130
150
170
190
210
f1 (ppm)
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f2 (ppm)

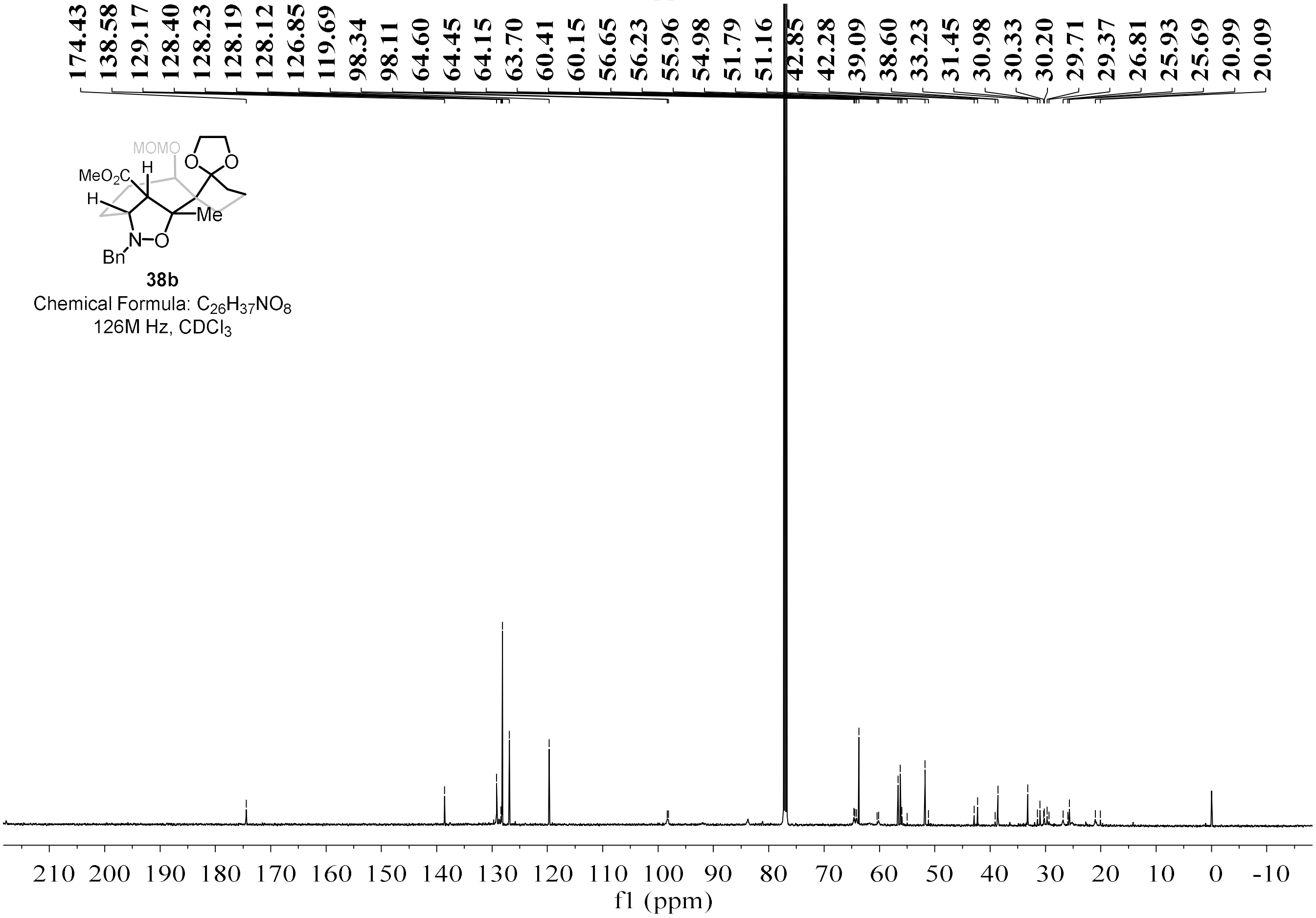

MOMO
MeO2C
H
H
Me
N–O
PMB
O
O
COSY of 38a
1
2
3
4
5
6
7
8
f1 (ppm)
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f2 (ppm)



38b

Chemical Formula: $C_{26}H_{37}NO_8$

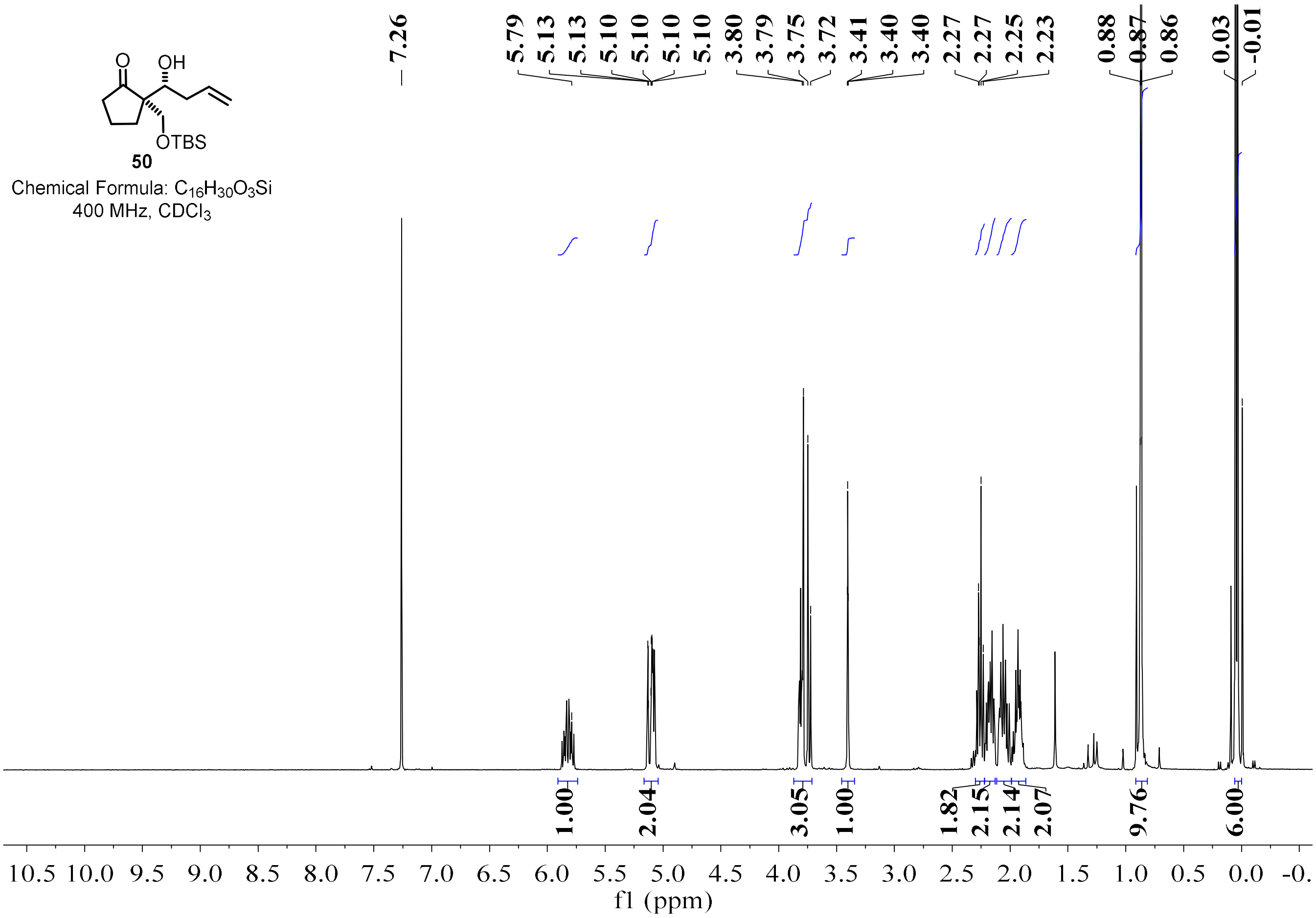
500M Hz, $CDCl_3$



38b

Chemical Formula: $C_{26}H_{37}NO_8$

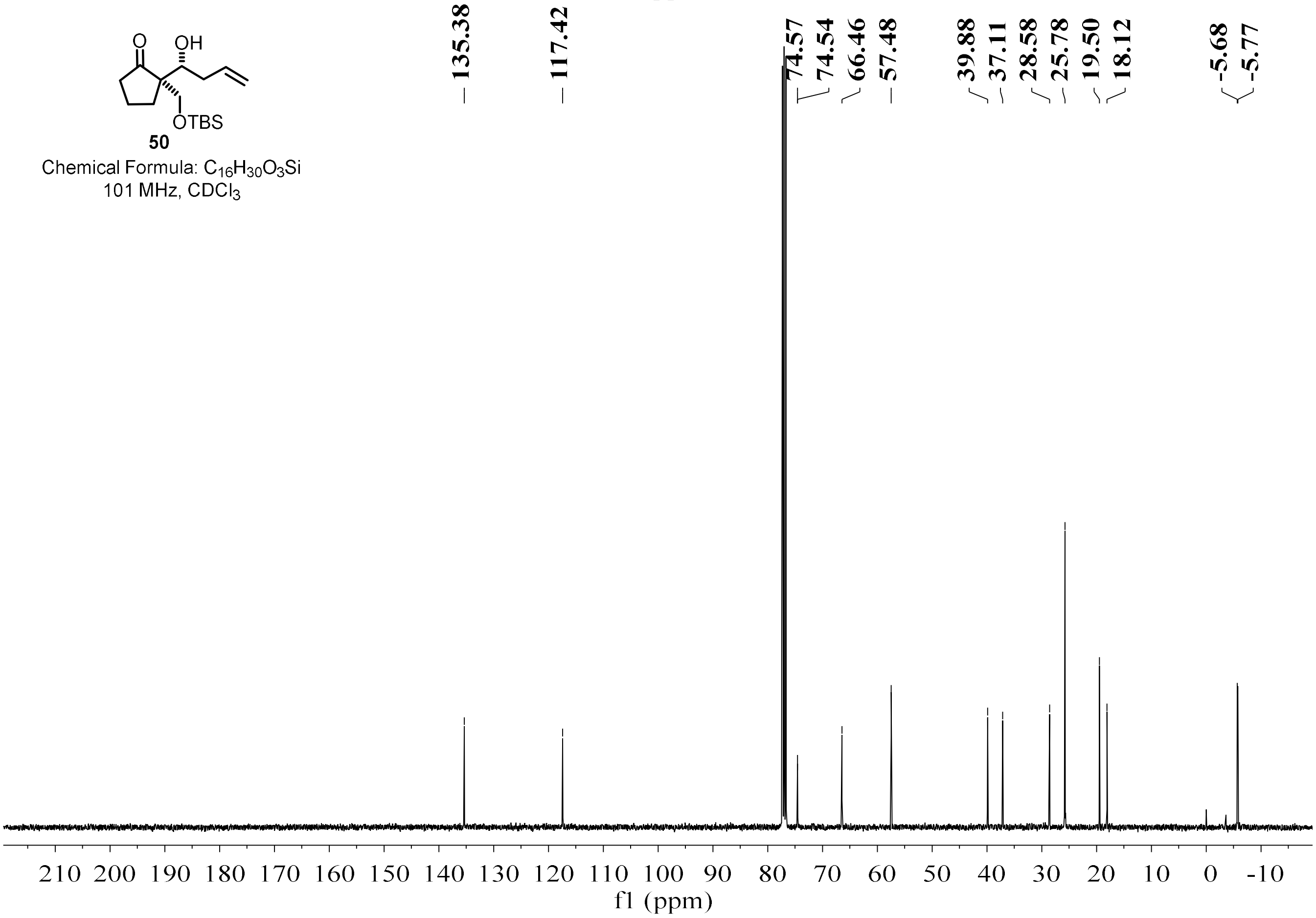
126M Hz, $CDCl_3$



50

Chemical Formula: $C_{16}H_{30}O_3Si$

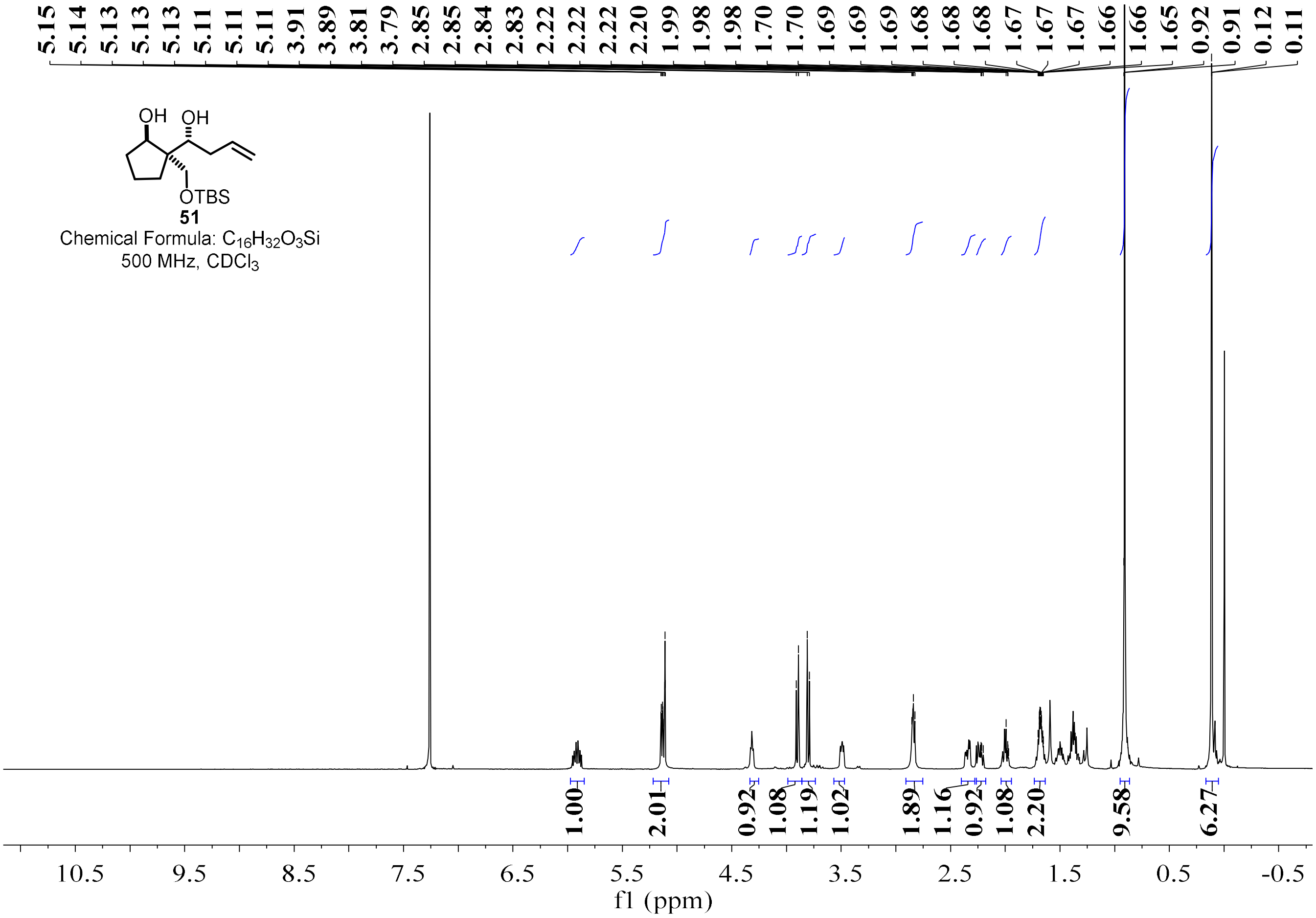
400 MHz, $CDCl_3$



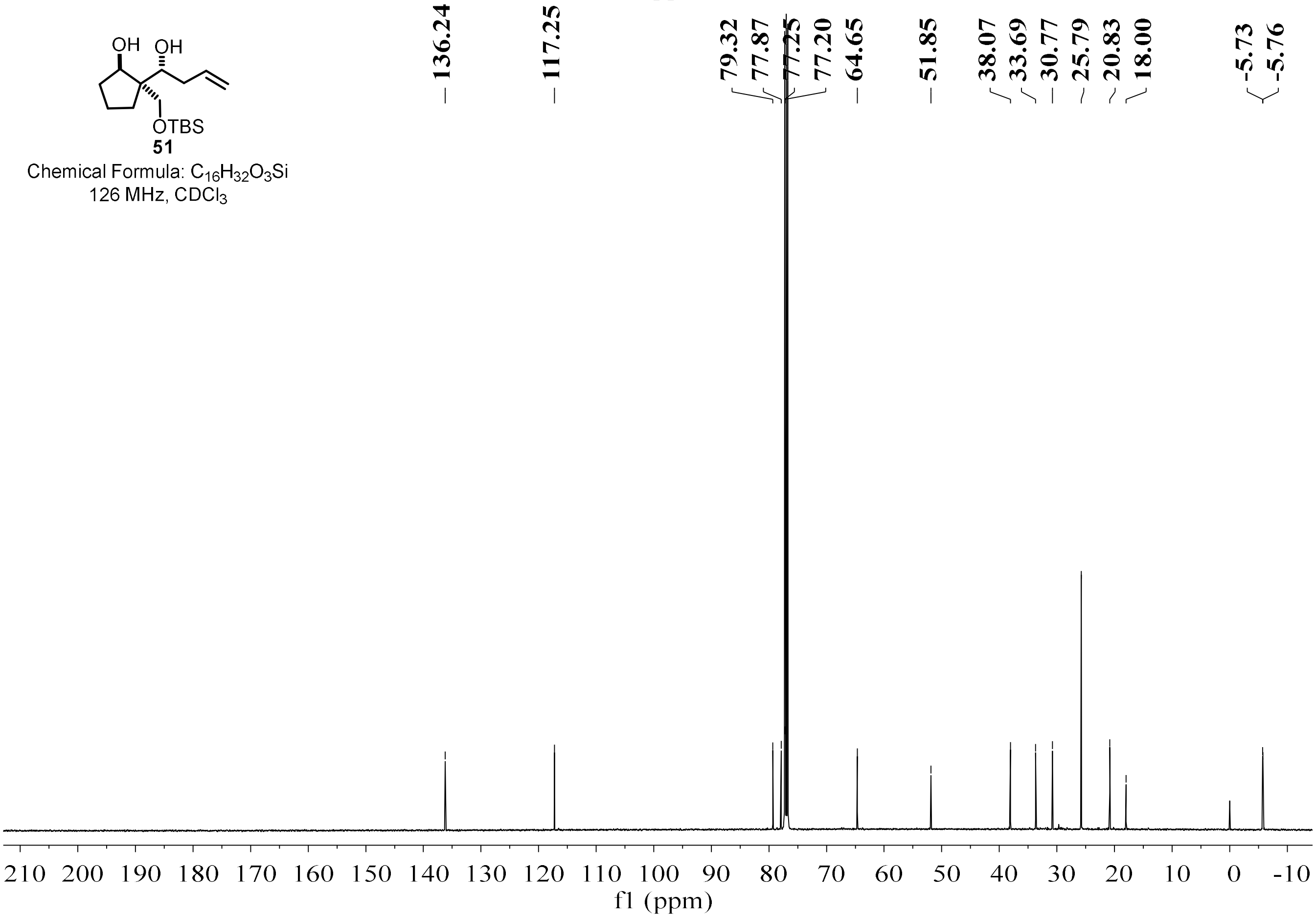
50

Chemical Formula: $C_{16}H_{30}O_3Si$

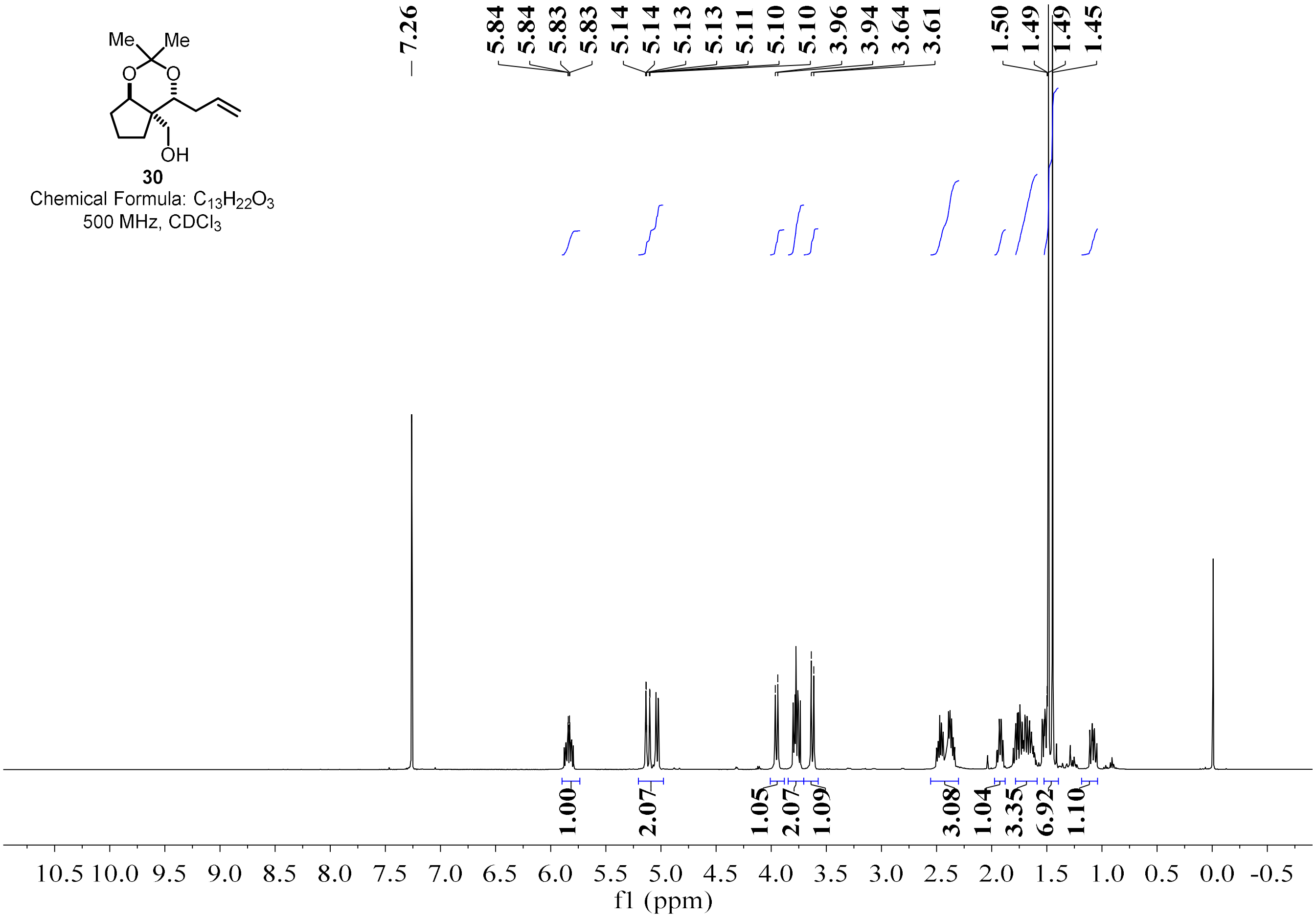
101 MHz, $CDCl_3$



OTBS
51
Chemical Formula: $C_{16}H_{32}O_3Si$
500 MHz, $CDCl_3$



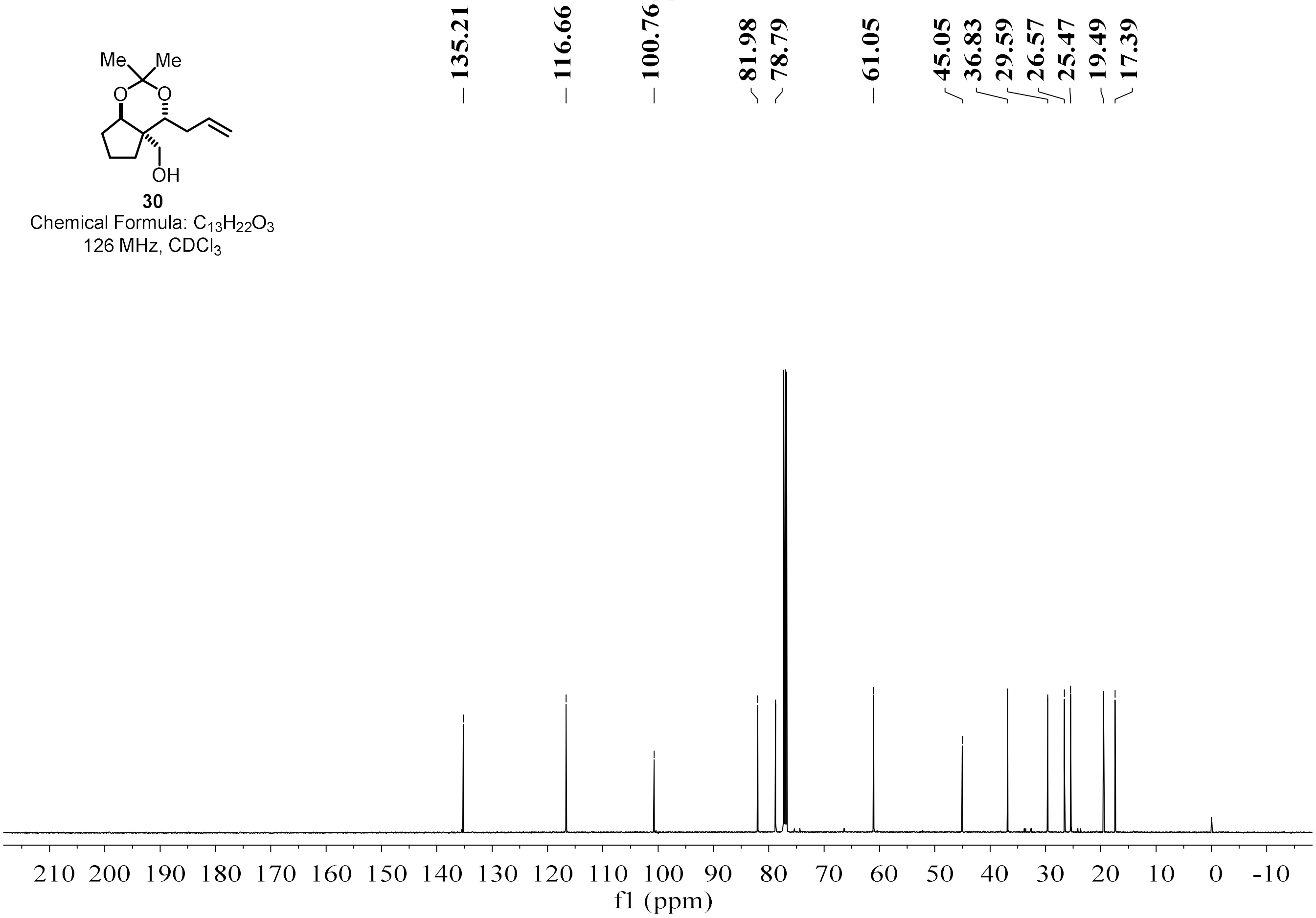
OTBS
51
Chemical Formula: $C_{16}H_{32}O_3Si$
126 MHz, $CDCl_3$



30

Chemical Formula: $C_{13}H_{22}O_3$

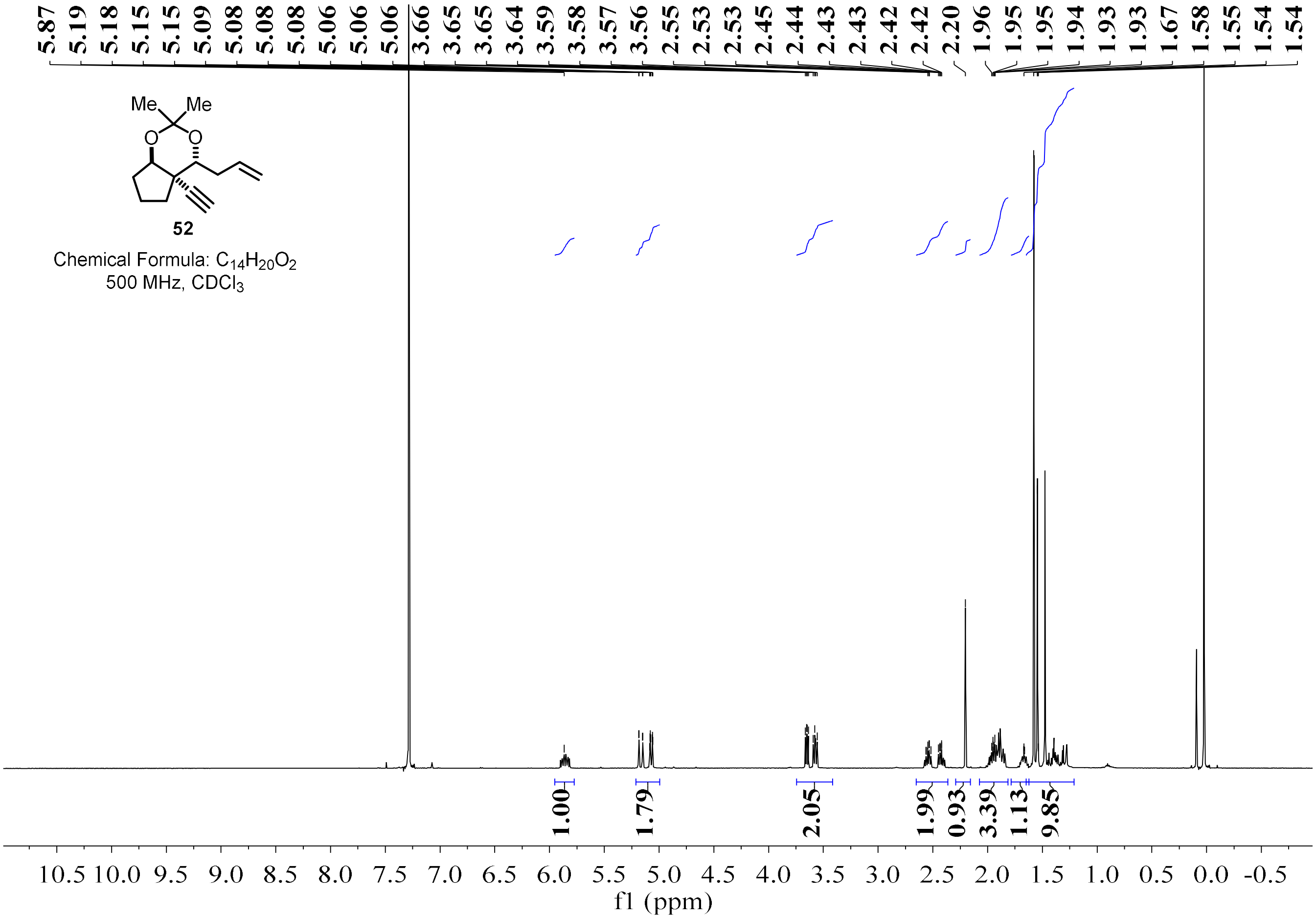
500 MHz, $CDCl_3$

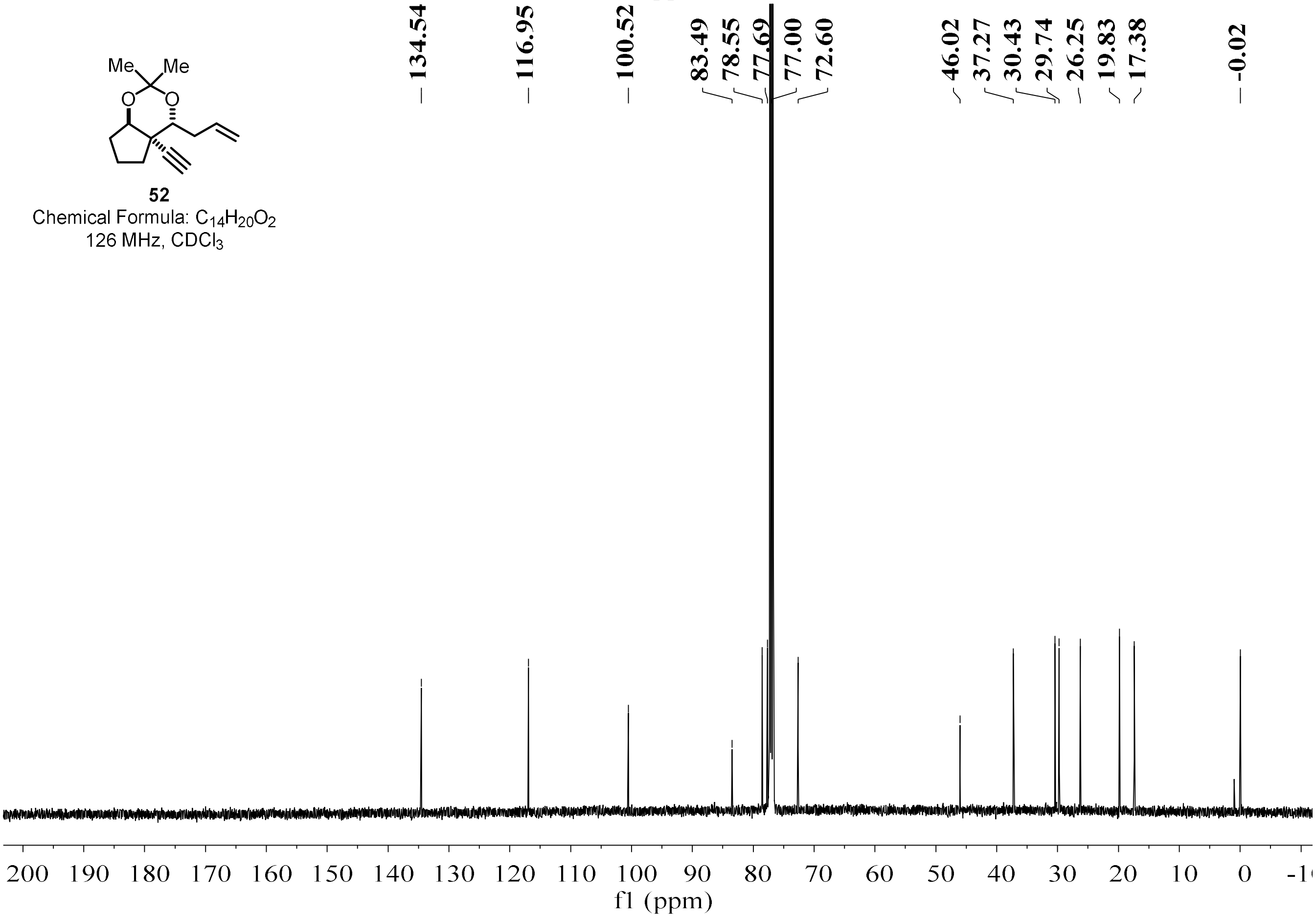


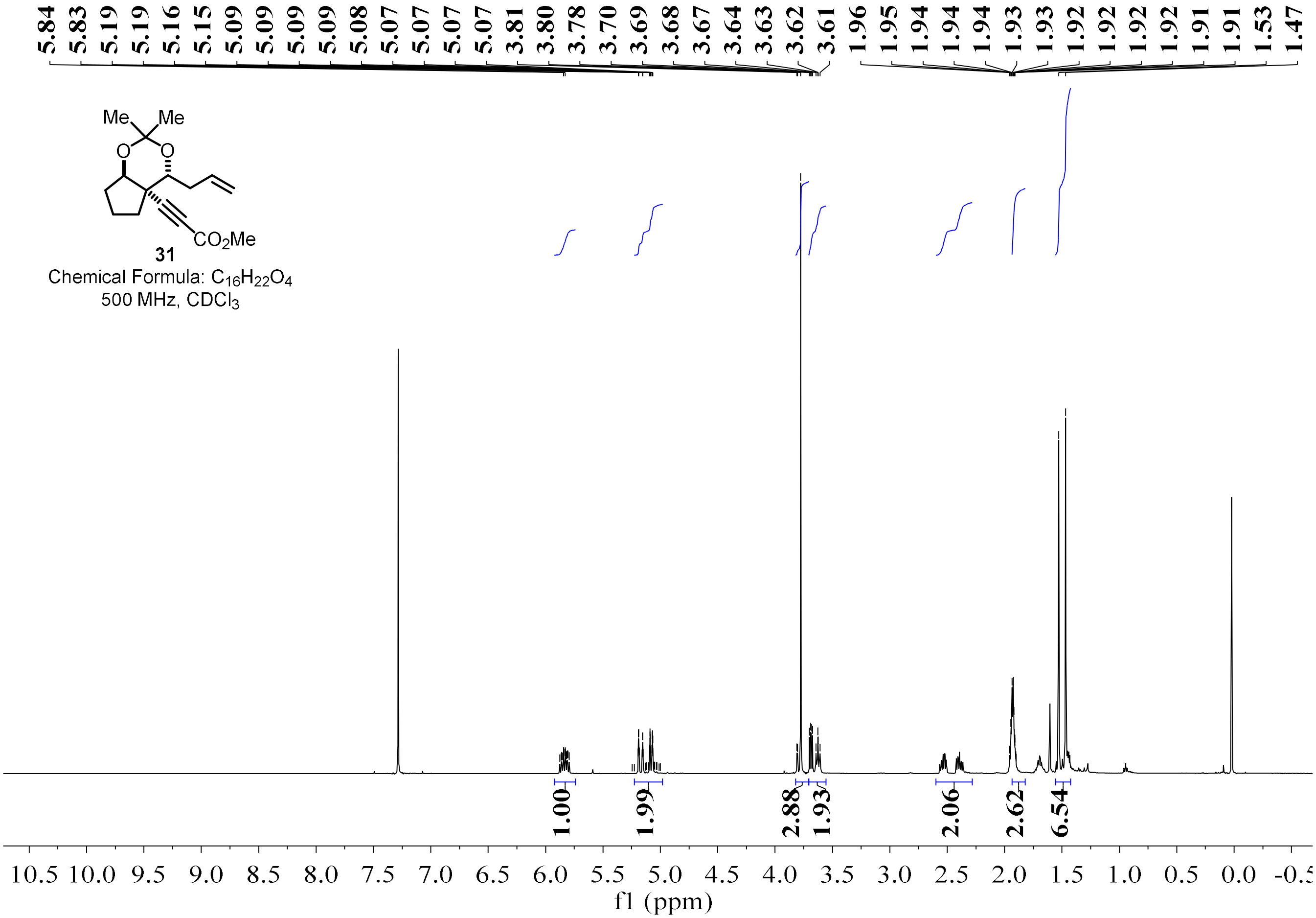
30

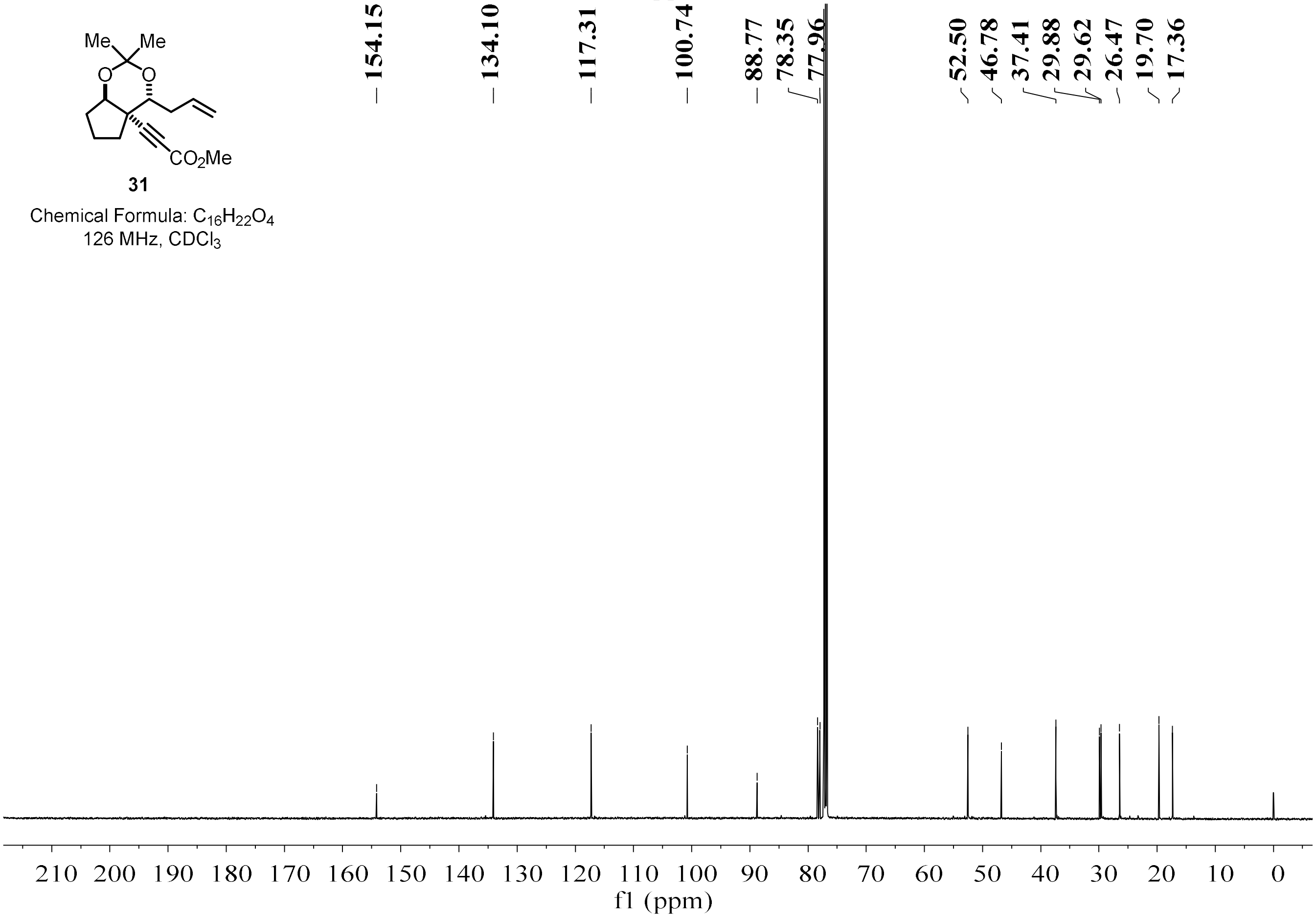
Chemical Formula: $C_{13}H_{22}O_3$

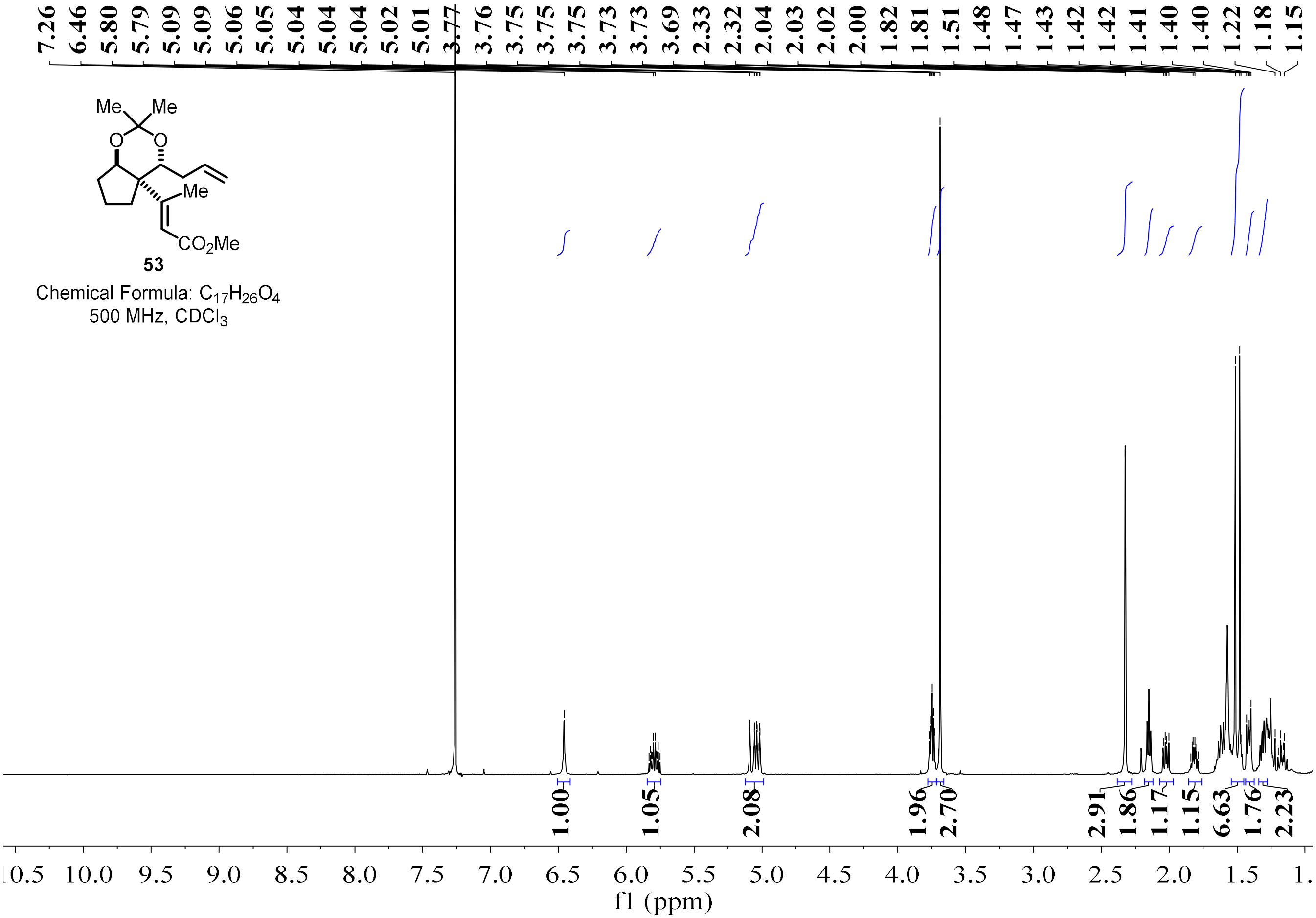
126 MHz, $CDCl_3$


5.87
5.19
5.18
5.15
5.15
5.09
5.08
5.08
5.08
5.06
5.06
5.06
3.66
3.65
3.65
3.64
3.59
3.58
3.57
3.56
2.55
2.53
2.53
2.45
2.44
2.43
2.43
2.42
2.42
2.20
1.96
1.95
1.95
1.94
1.93
1.93
1.67
1.58
1.55
1.54
1.54
Me
Me
O
O
52
Chemical Formula: C14H20O2
500 MHz, CDCl3
1.00
1.79
2.05
1.99
0.93
3.39
1.13
9.85
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)


134.54
116.95
100.52
83.49
78.55
77.69
77.00
72.60
46.02
37.27
30.43
29.74
26.25
19.83
17.38
-0.02
Me
Me
O
O
52
Chemical Formula: C14H20O2
126 MHz, CDCl3
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-1
f1 (ppm)

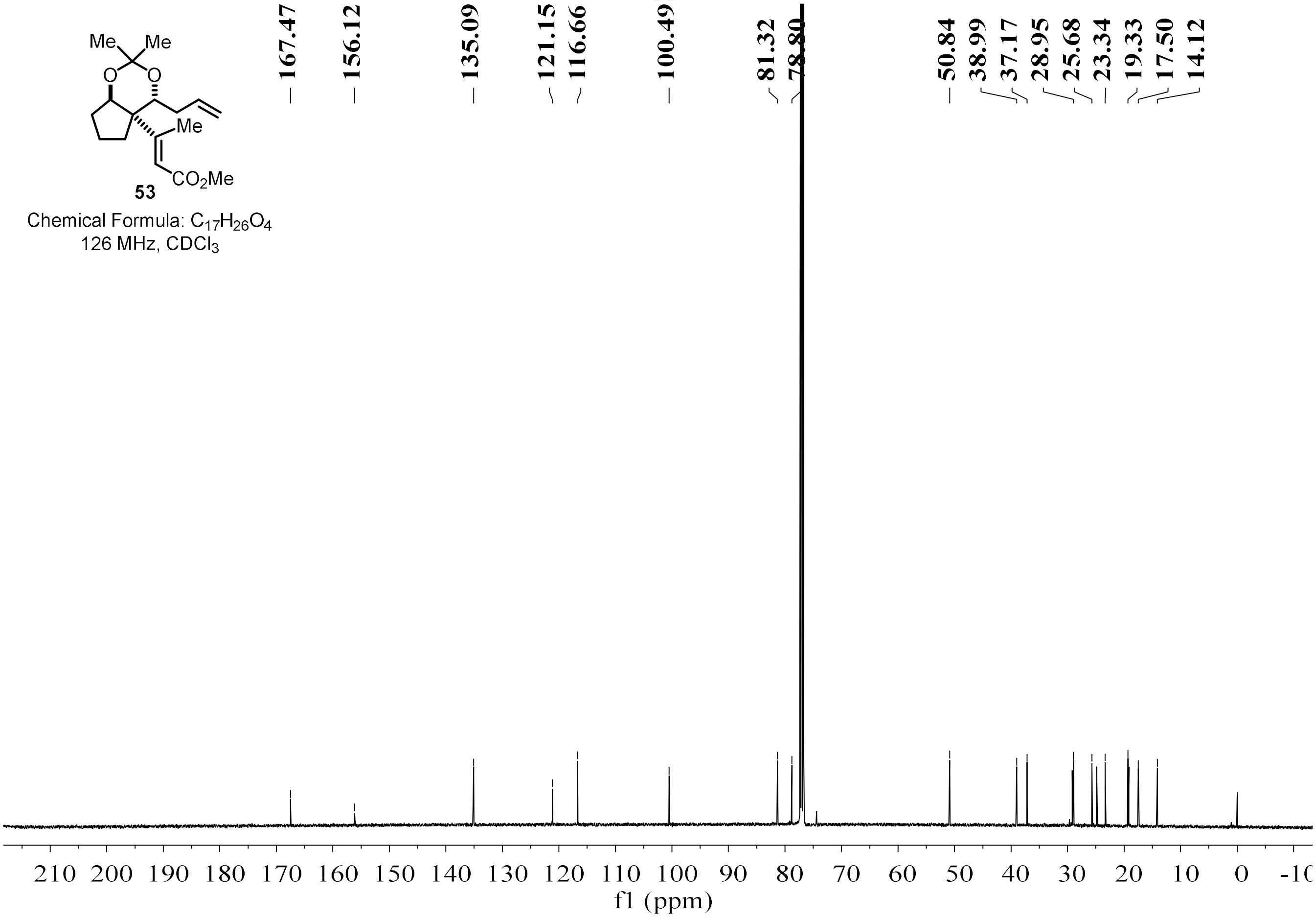

5.84 5.83 5.19 5.19 5.16 5.15 5.09 5.09 5.09 5.09 5.08 5.07 5.07 5.07 5.07 3.81 3.80 3.78 3.70 3.69 3.68 3.67 3.64 3.63 3.62 3.61 1.96 1.95 1.94 1.94 1.94 1.93 1.93 1.92 1.92 1.92 1.92 1.91 1.91 1.53 1.47
Me
Me
O
O
CO$_2$Me
31
Chemical Formula: $C_{16}H_{22}O_4$
500 MHz, $CDCl_3$
1.00
1.99
2.88
1.93
2.06
2.62
6.54
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)


154.15
134.10
117.31
100.74
88.77
78.35
77.96
52.50
46.78
37.41
29.88
29.62
26.47
19.70
17.36
Me
Me
O
O
CO$_2$Me
31
Chemical Formula: $C_{16}H_{22}O_4$
126 MHz, $CDCl_3$
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


53

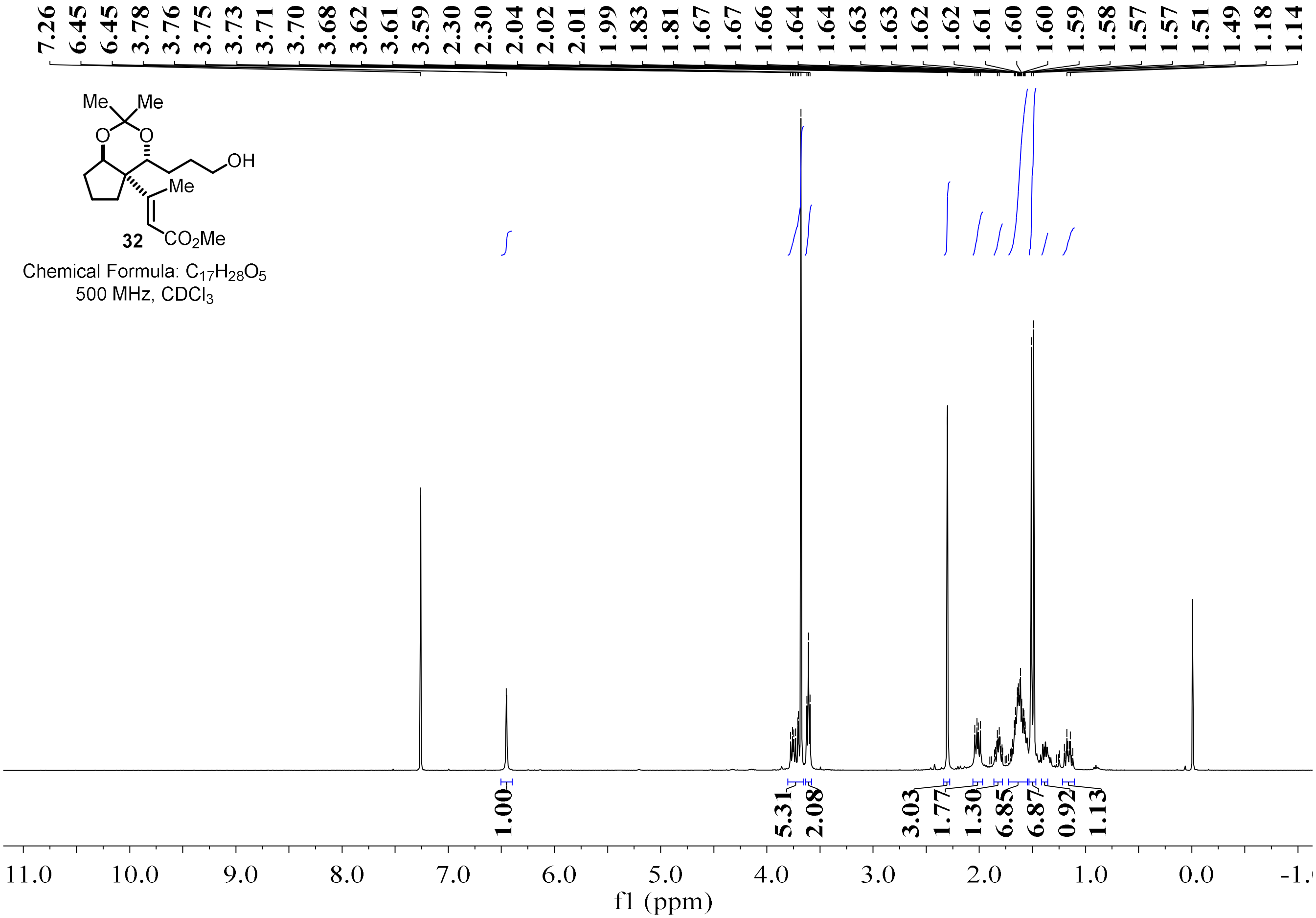
Chemical Formula: $C_{17}H_{26}O_4$

500 MHz, $CDCl_3$


53

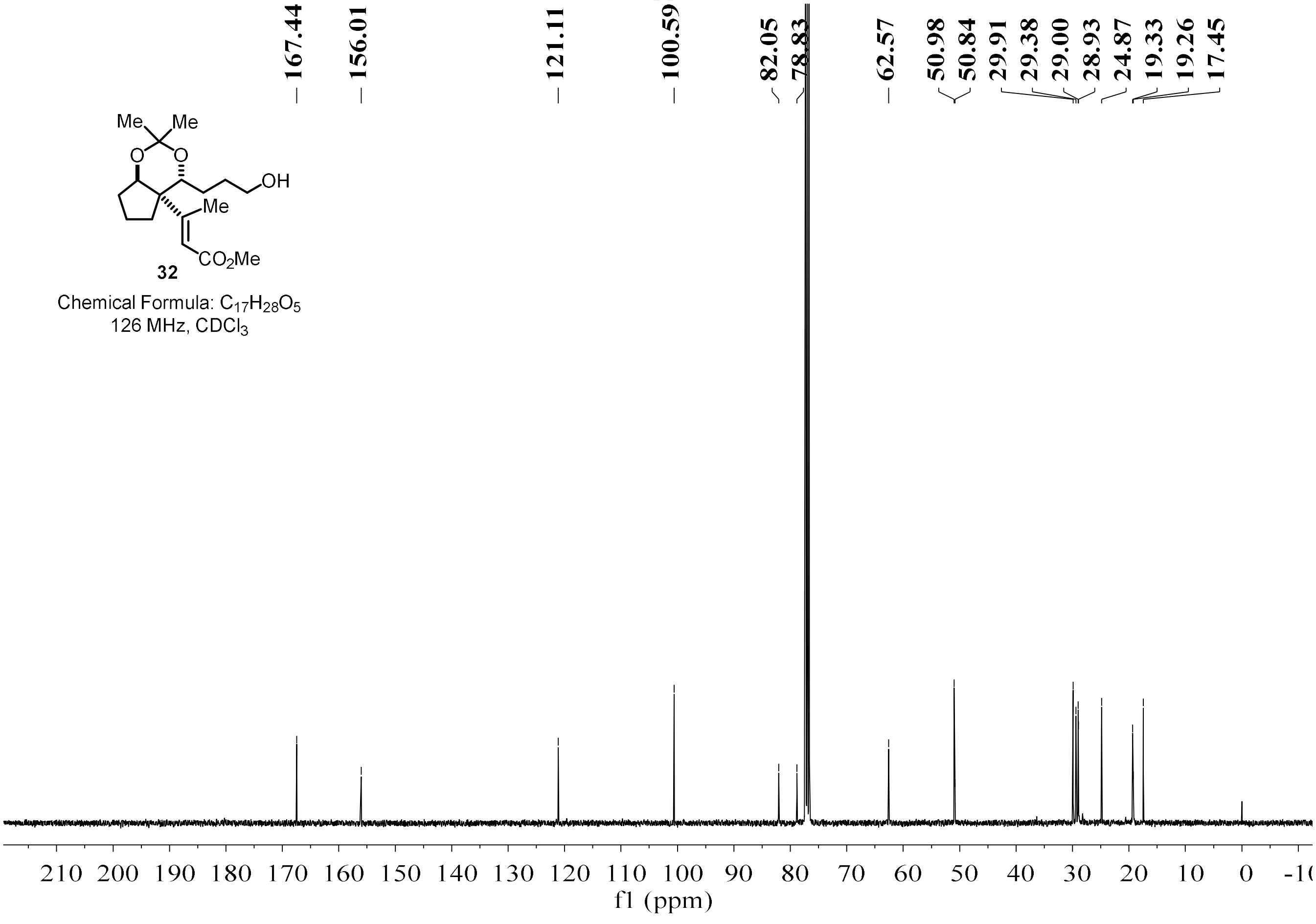
Chemical Formula: $C_{17}H_{26}O_4$

126 MHz, $CDCl_3$



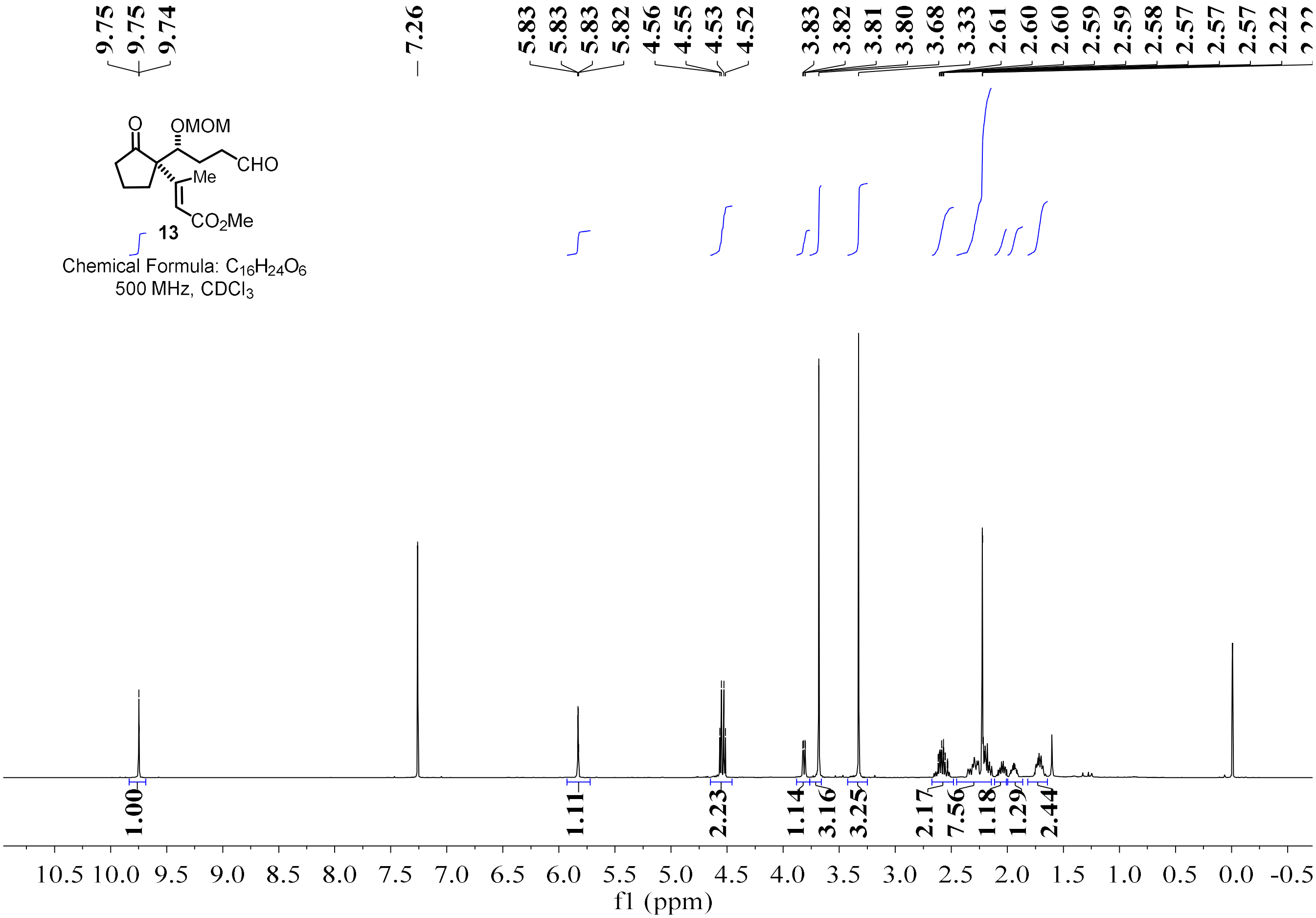
32

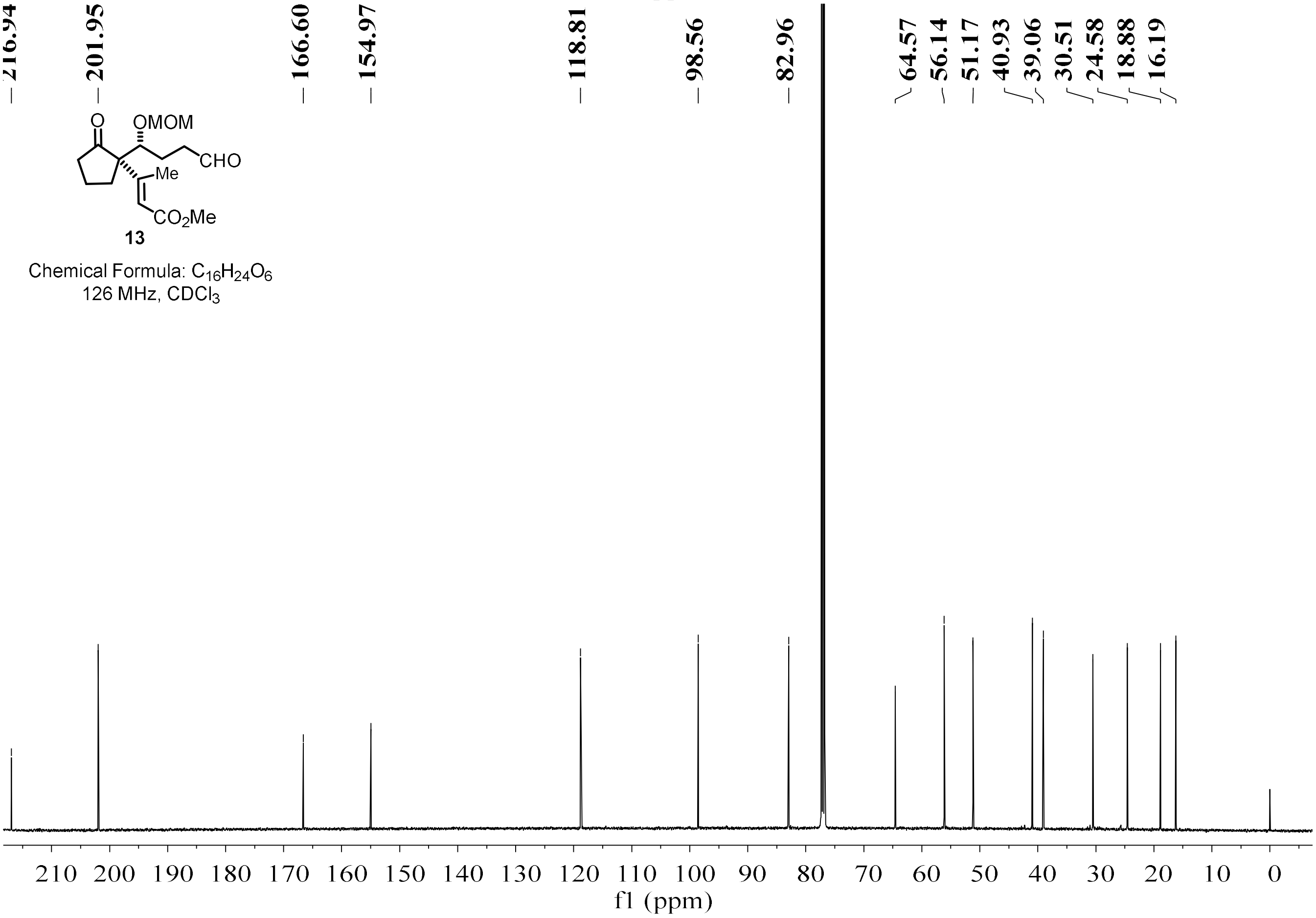
Chemical Formula: $C_{17}H_{28}O_5$
500 MHz, $CDCl_3$

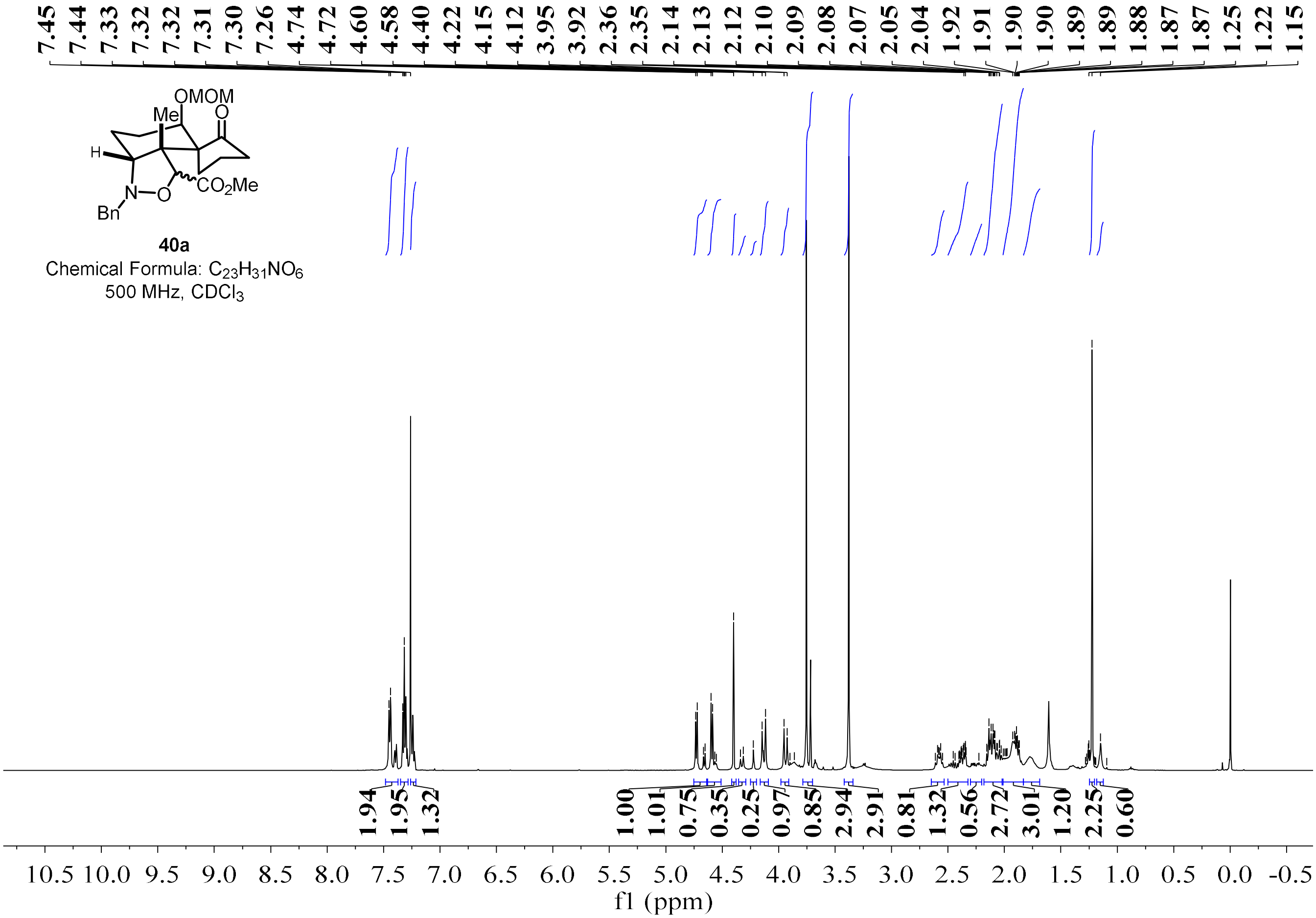


32

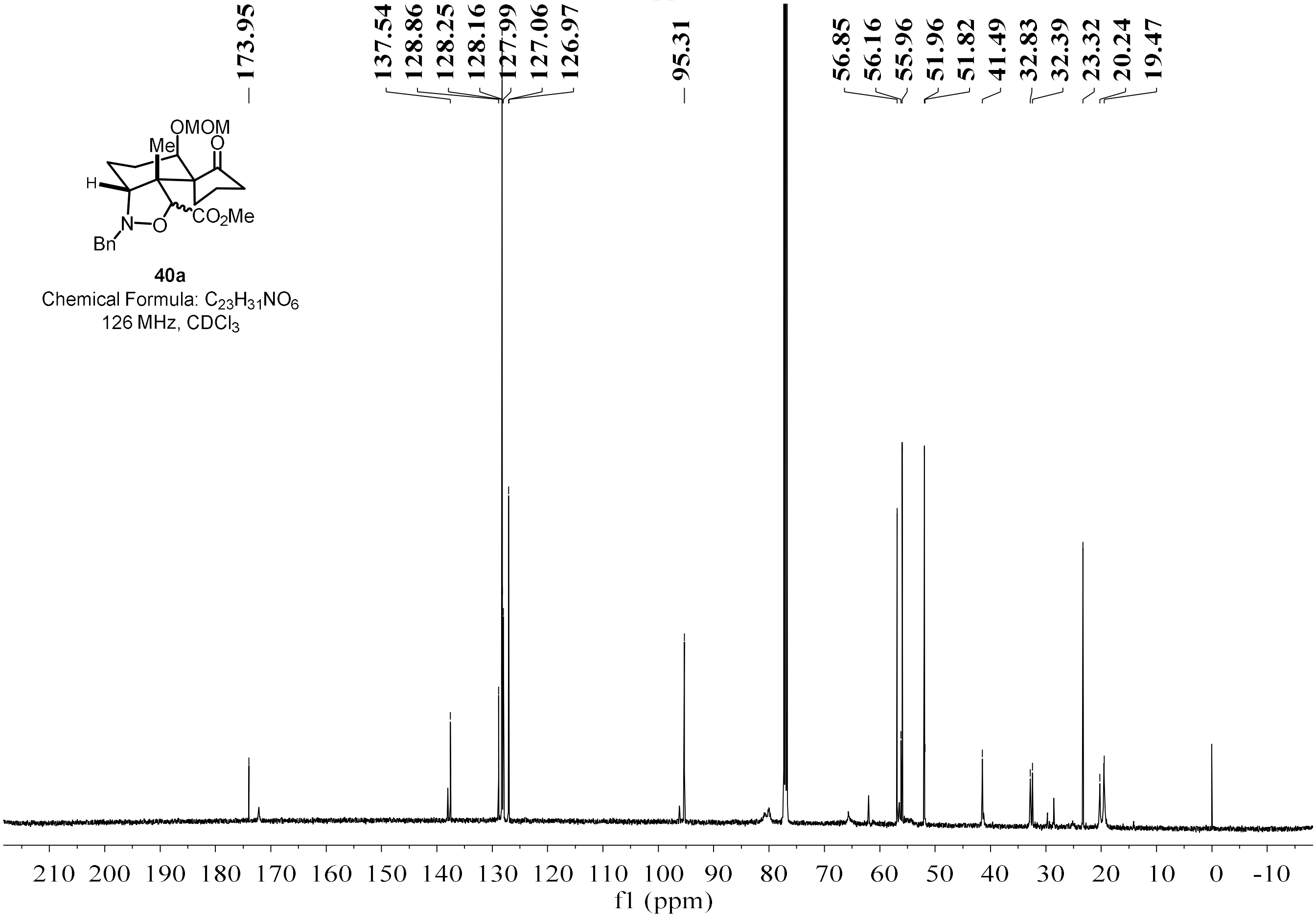
Chemical Formula: $C_{17}H_{28}O_5$
126 MHz, $CDCl_3$


9.75
9.75
9.74
7.26
5.83
5.83
5.83
5.82
4.56
4.55
4.53
4.52
3.83
3.82
3.81
3.80
3.68
3.33
2.61
2.60
2.60
2.59
2.59
2.58
2.57
2.57
2.57
2.22
O
OMOM
CHO
Me
CO2Me
13
Chemical Formula: C16H24O6
500 MHz, CDCl3
1.00
1.11
2.23
1.14
3.16
3.25
2.17
7.56
1.18
1.29
2.44
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

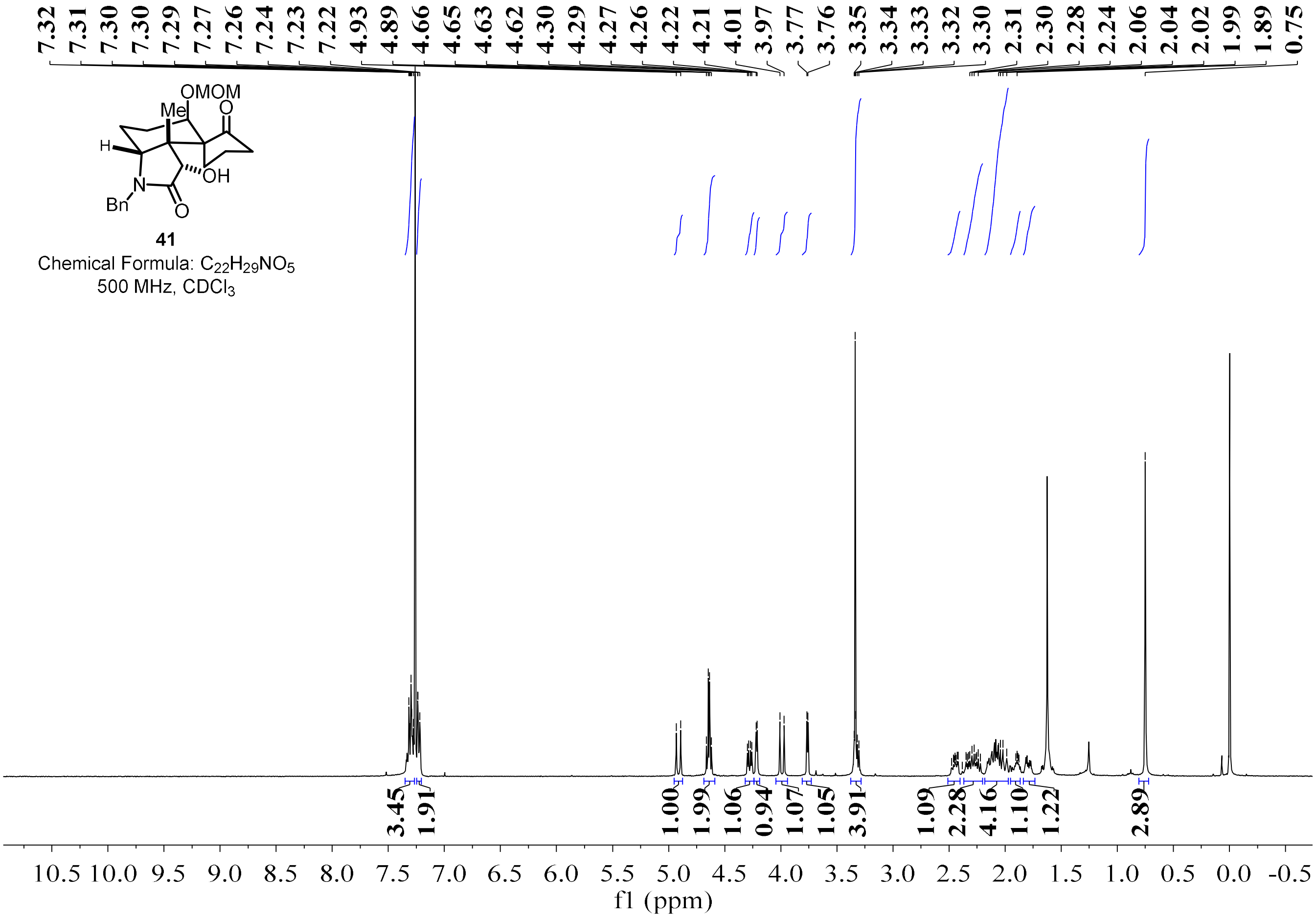

216.94
201.95
166.60
154.97
118.81
98.56
82.96
64.57
56.14
51.17
40.93
39.06
30.51
24.58
18.88
16.19
O
OMOM
CHO
Me
CO2Me
13
Chemical Formula: C16H24O6
126 MHz, CDCl3
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

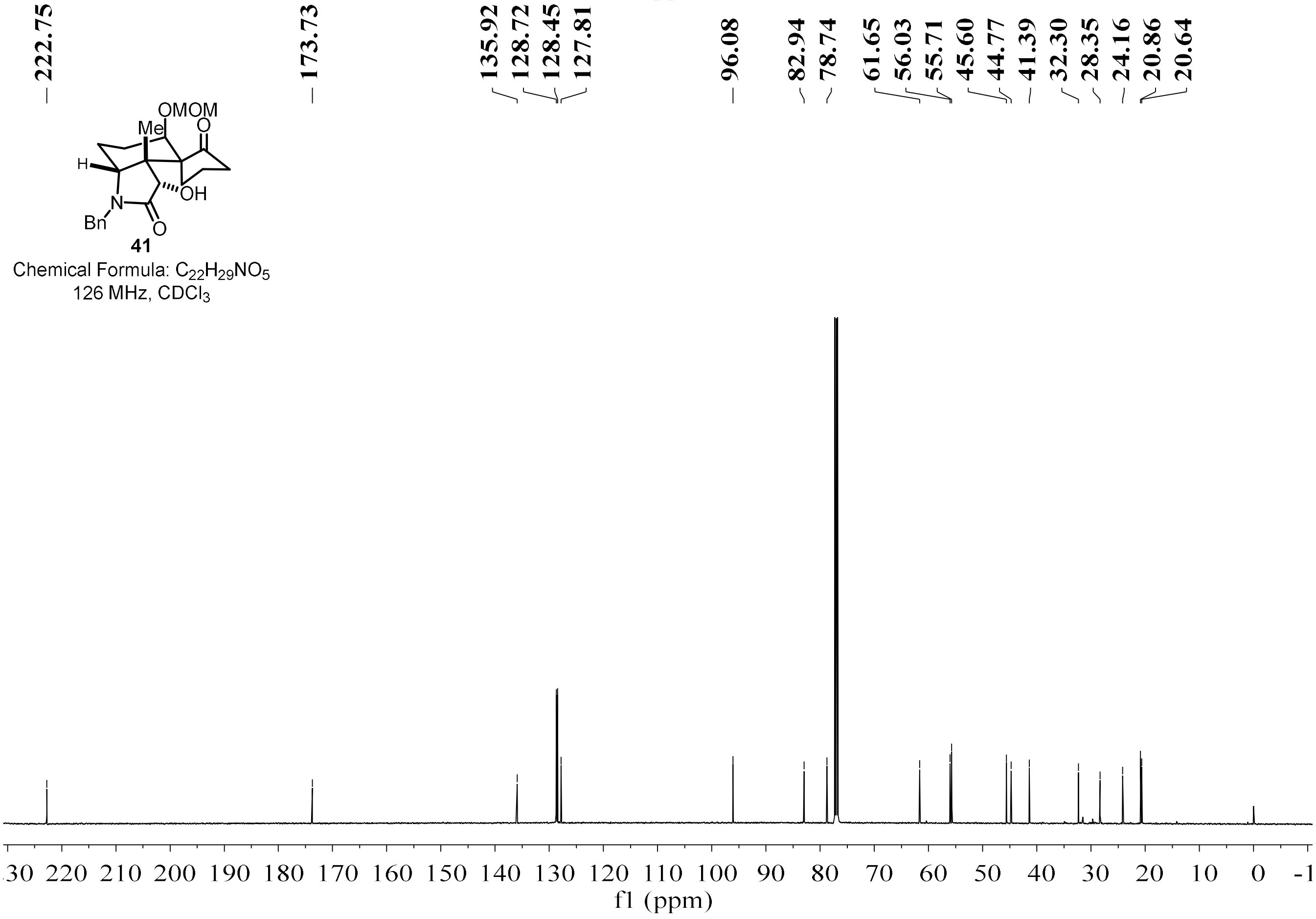


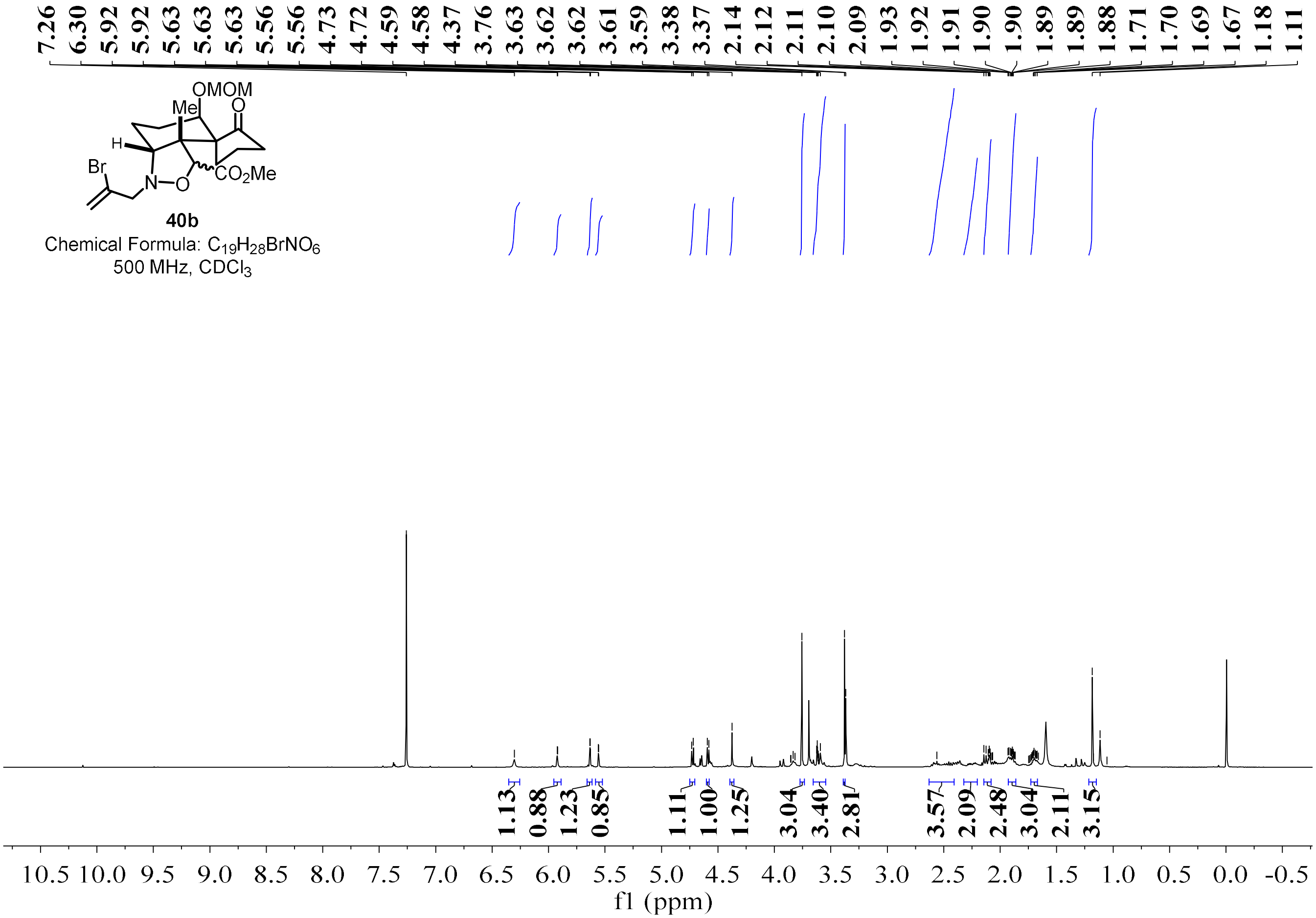
40a
Chemical Formula: $C_{23}H_{31}NO_6$
500 MHz, $CDCl_3$



40a
Chemical Formula: $C_{23}H_{31}NO_6$
126 MHz, $CDCl_3$


7.32 7.31 7.30 7.30 7.29 7.27 7.26 7.24 7.23 7.22 4.93 4.89 4.66 4.65 4.63 4.62 4.30 4.29 4.27 4.26 4.22 4.21 4.01 3.97 3.77 3.76 3.35 3.34 3.33 3.32 3.30 2.31 2.30 2.28 2.24 2.06 2.04 2.02 1.99 1.89 0.75
OMOM
Me
O
H
N
OH
Bn
O
41
Chemical Formula: C22H29NO5
500 MHz, CDCl3
3.45 1.91 1.00 1.99 1.06 0.94 1.07 1.05 3.91 1.09 2.28 4.16 1.10 1.22 2.89
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

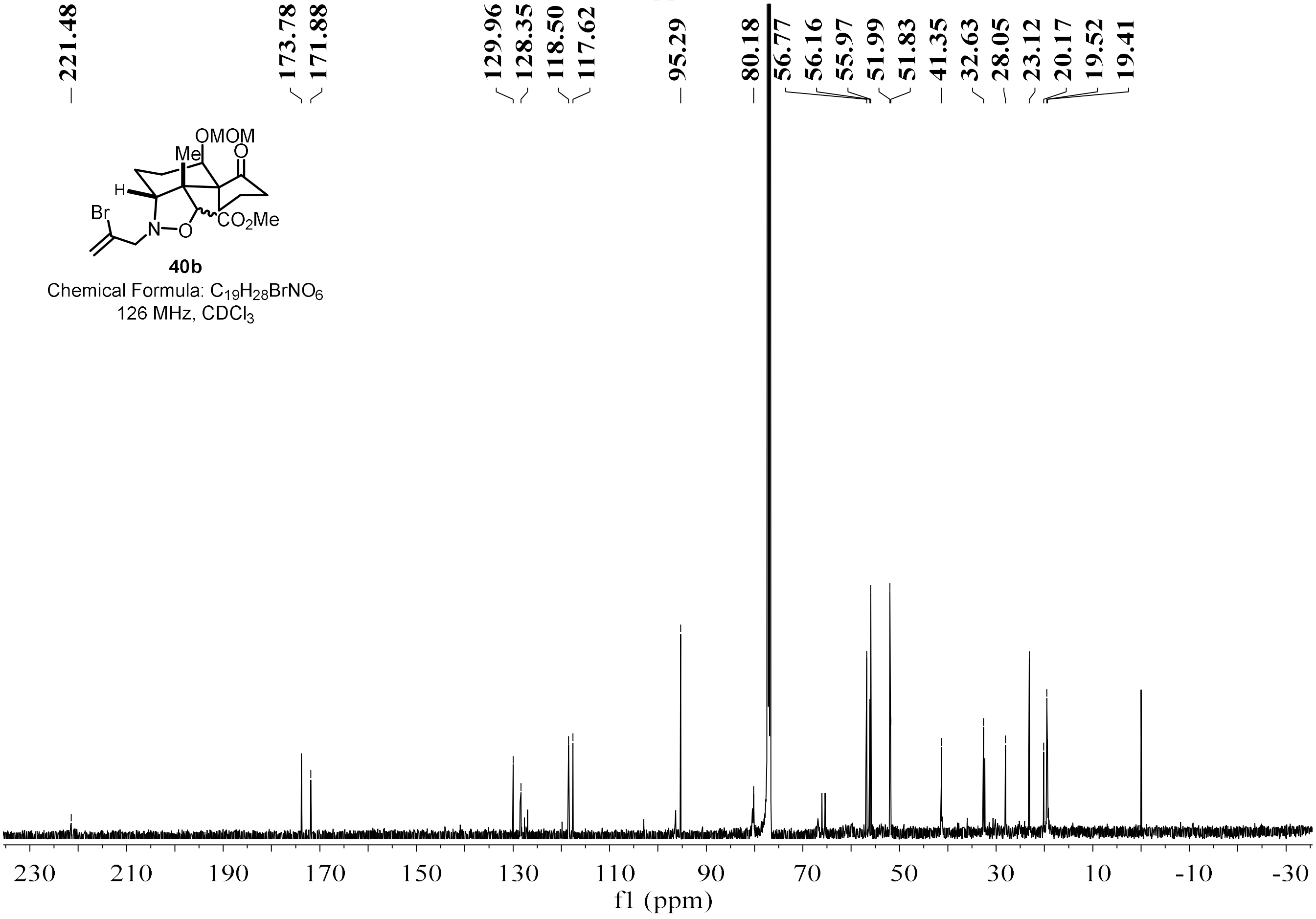

222.75
173.73
135.92 128.72 128.45 127.81
96.08
82.94 78.74
61.65 56.03 55.71 45.60 44.77 41.39 32.30 28.35 24.16 20.86 20.64
OMOM
Me
O
H
OH
N
Bn
O
41
Chemical Formula: C22H29NO5
126 MHz, CDCl3
30 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -1
f1 (ppm)



40b

Chemical Formula: $C_{19}H_{28}BrNO_6$

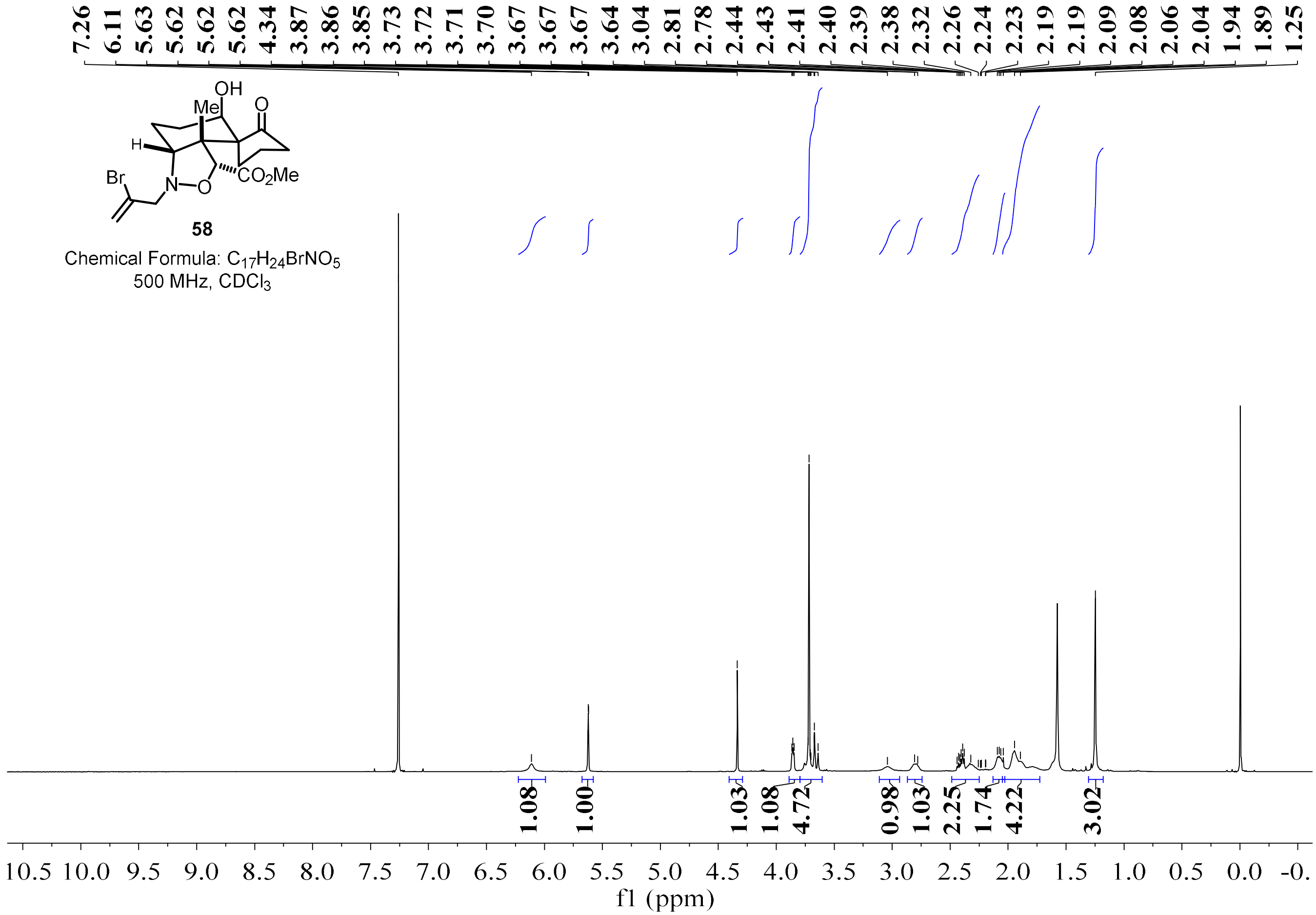
500 MHz, $CDCl_3$

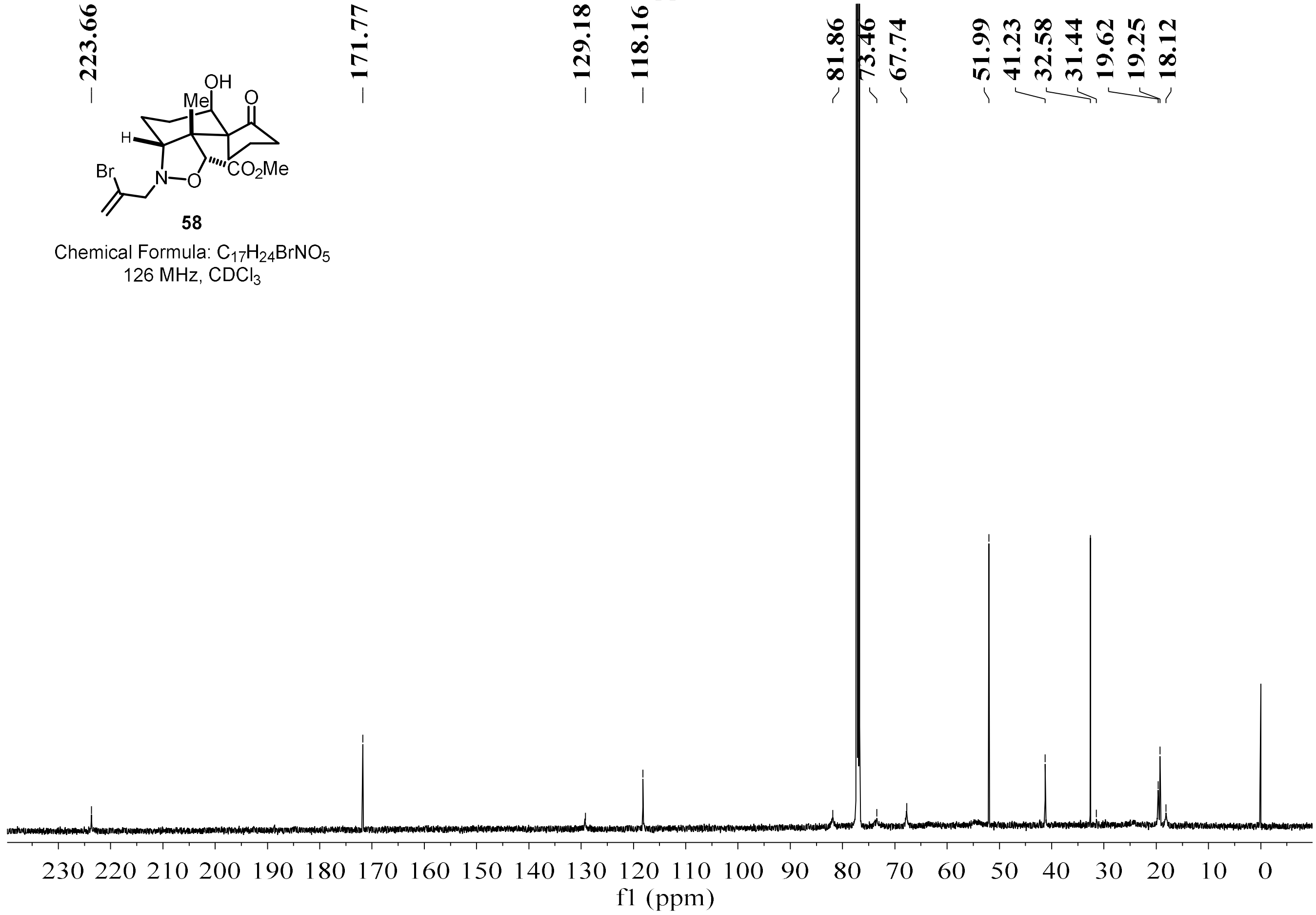


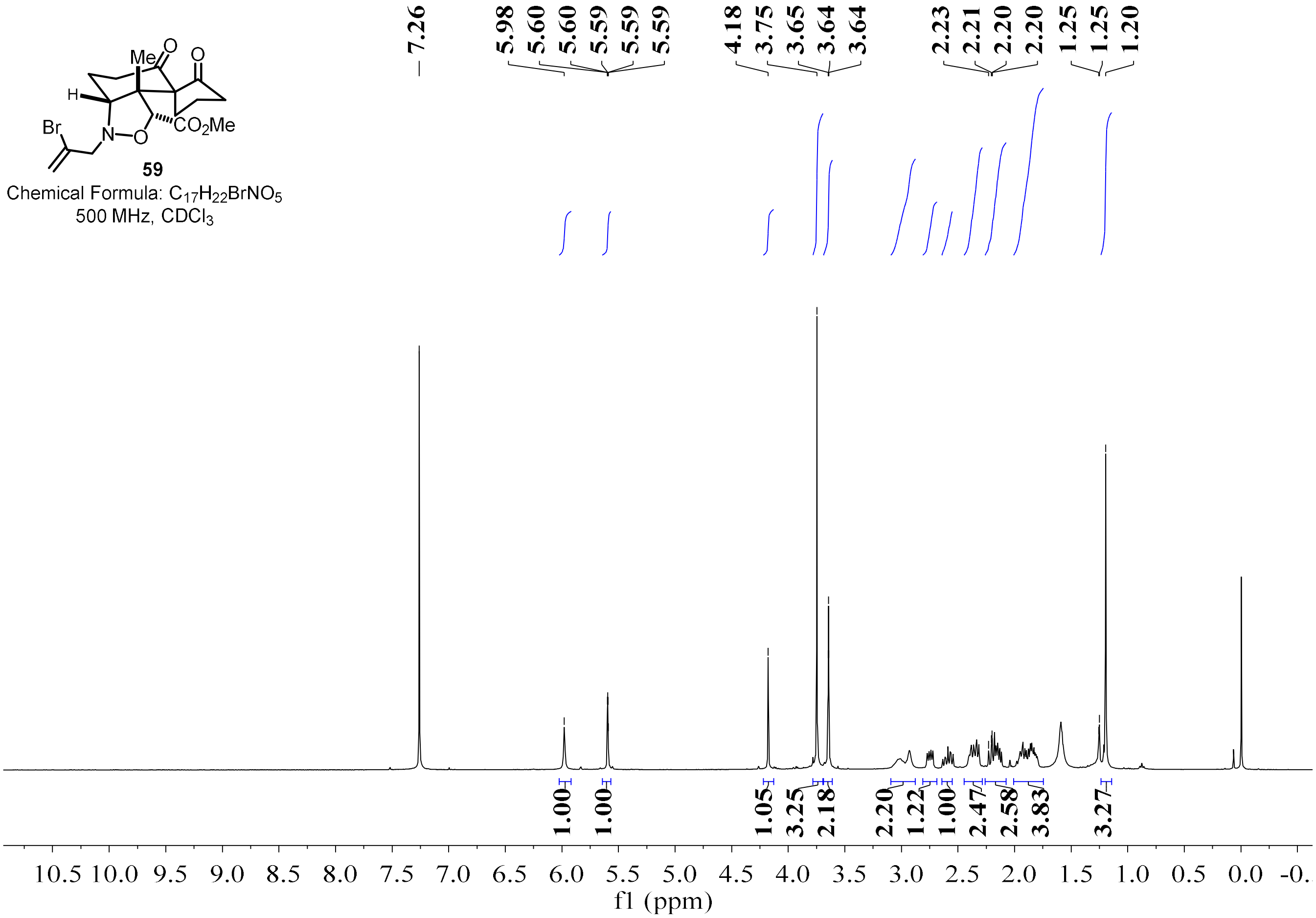
40b

Chemical Formula: $C_{19}H_{28}BrNO_6$

126 MHz, $CDCl_3$


7.26 6.11 5.63 5.62 5.62 5.62 4.34 3.87 3.86 3.85 3.73 3.72 3.71 3.70 3.67 3.67 3.67 3.64 3.04 2.81 2.78 2.44 2.43 2.41 2.40 2.39 2.38 2.32 2.26 2.24 2.23 2.19 2.19 2.09 2.08 2.06 2.04 1.94 1.89 1.25
OH
Me
O
H
Br
N–O
CO2Me
58
Chemical Formula: C17H24BrNO5
500 MHz, CDCl3
1.08 1.00 1.03 1.08 4.72 0.98 1.03 2.25 1.74 4.22 3.02
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.
f1 (ppm)

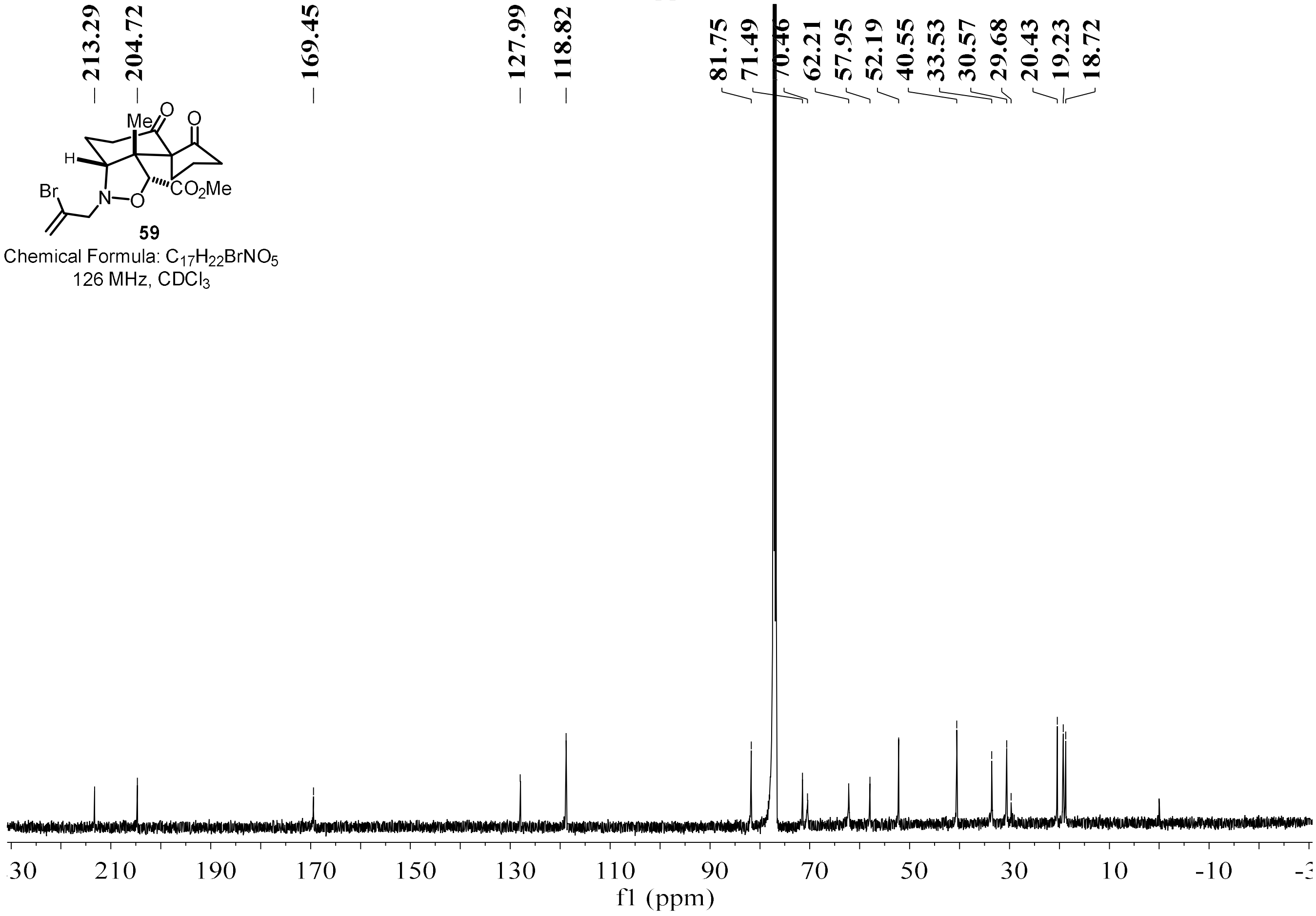

223.66 171.77 129.18 118.16 81.86 73.46 67.74 51.99 41.23 32.58 31.44 19.62 19.25 18.12
OH
Me
O
H
Br
N–O
CO2Me
58
Chemical Formula: C17H24BrNO5
126 MHz, CDCl3
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)



59

Chemical Formula: $C_{17}H_{22}BrNO_5$

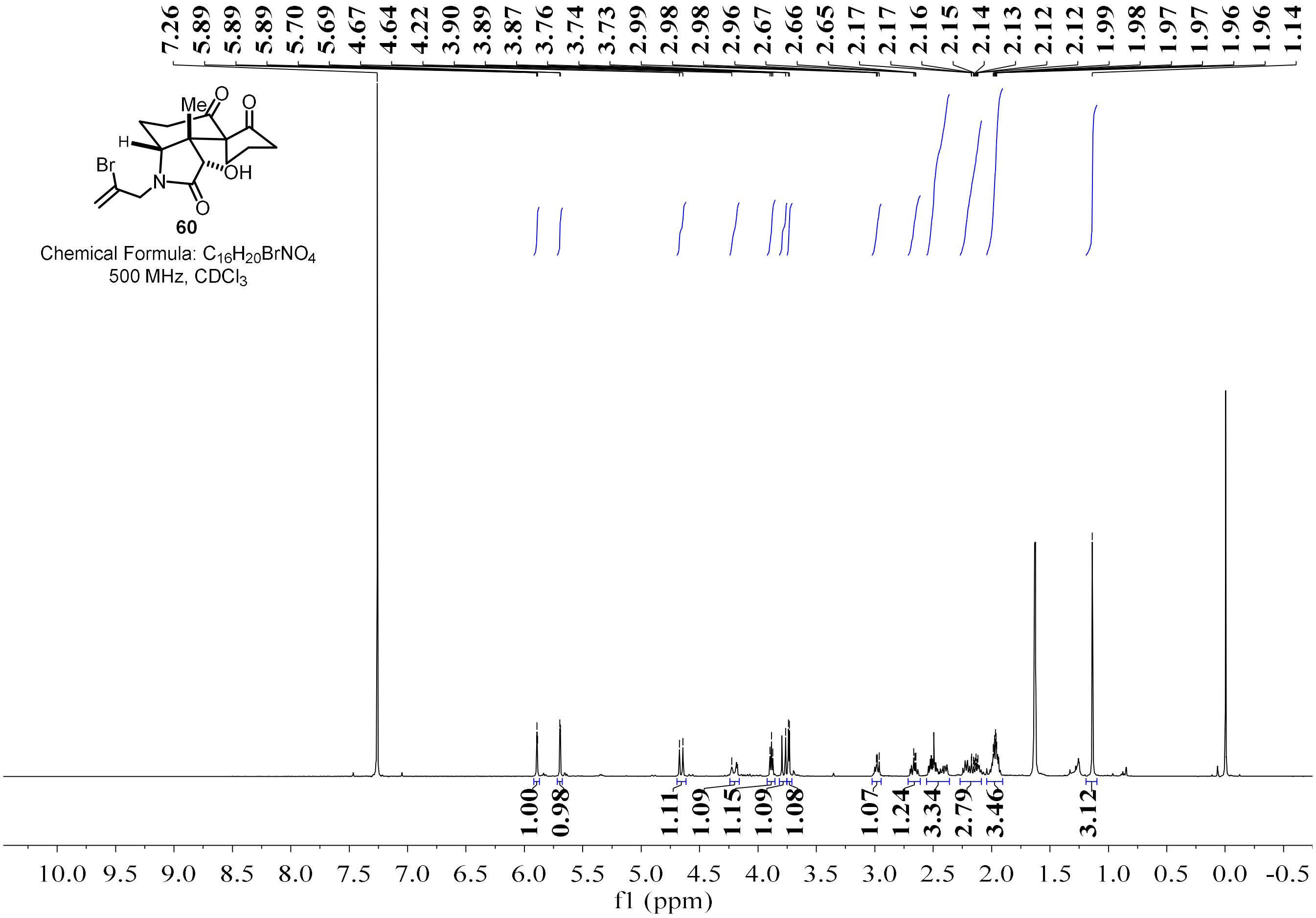
500 MHz, $CDCl_3$



59

Chemical Formula: $C_{17}H_{22}BrNO_5$

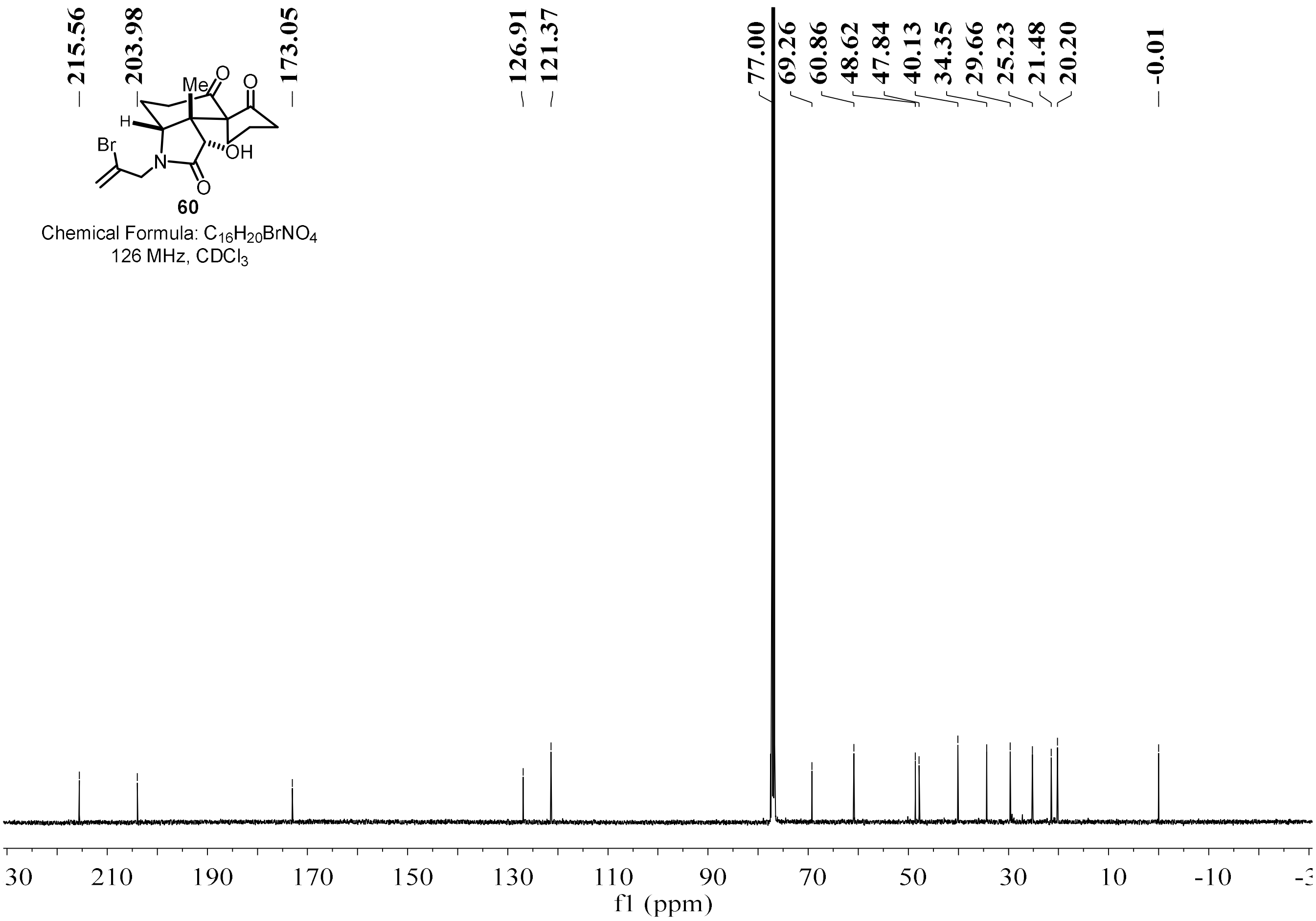
126 MHz, $CDCl_3$



60

Chemical Formula: $C_{16}H_{20}BrNO_4$

500 MHz, $CDCl_3$



60

Chemical Formula: $C_{16}H_{20}BrNO_4$

126 MHz, $CDCl_3$

According to the 2 D spectra (HSQC and NOESY of compound **33**), H_a and H_b have no correlation in steric configuration at all, which proves the the [5,6] rings possess a *cis* configuration, the two C-O side chains are *trans* configuration.