

Supporting Information
Total Synthesis of Nannocystin Ax

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Table of Contents	Page
General Methods	S02
Experimental Procedures	S03
NMR comparison to other samples	S30
References	S35
NMR Spectra	S36

General Methods

Unless otherwise noted all reactions were carried out under an argon atmosphere. Reactions were performed using glassware that was dried under vacuum (~0.3 mbar) using a heat gun. Air- and moisture-sensitive liquids and solutions were transferred via syringe or stainless steel cannula. All reagents were obtained commercially unless otherwise noted. Reactions were stirred with a magnetic stirrer. Temperatures for the reactions refer to bath temperatures.

Dry solvents: *Dichloromethane* was dried by heating under reflux over calcium hydride and subsequent distillation. *Triethylamine* was dried by heating under reflux over calcium hydride and subsequent distillation. *Toluene* was taken from M. Braun Solvent Purification System. *Diethylether*, *dimethylsulfoxide*, *N,N-dimethylformamide* and *tetrahydrofuran* were bought from Acros or Sigma Aldrich.

Flash column chromatography was performed on Merck silica (60M).

Thin layer chromatography: Reactions were monitored by TLC (0.2 mm, silica gel 60, F₂₅₄, aluminum-backed, Macherey-Nagel) with detection by UV light ($\lambda=254$ nm) and treatment with ceric ammonium molybdate-, anisaldehyde-, ninhydrin- and potassium permanganate-stain.

¹H-NMR: NMR spectra were recorded on a DPX-400 (Bruker), a AMX-400 (Bruker) and a DRX-500 (Bruker). Spectra were calibrated against the residual solvent peak: $\delta(\text{CDCl}_3) = 7.26$ ppm, $\delta(\text{benzol-}d_6) = 7.16$ ppm $\delta(\text{DMSO-}d_6) = 2.50$ ppm, $\delta(\text{CD}_3\text{OD}) = 3.31$ ppm, $\delta(\text{D}_2\text{O}) = 4.79$ ppm. Data are recorded as follows: chemical shift (δ , ppm), multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; bs, broad singlet; dd, doublet of doublets), coupling constant (Hz), and integration. Analysis was performed using MestReNova (Mestrelab Research).

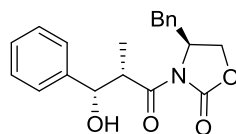
¹³C-NMR: NMR spectra were recorded on a DPX-400 (Bruker), a AMX-400 (Bruker) and a DRX-500 (Bruker) instrument. Spectra were calibrated against the residual solvent peak: $\delta(\text{CDCl}_3) = 77.16$ ppm, $\delta(\text{benzol-}d_6) = 128.06$ ppm $\delta(\text{DMSO-}d_6) = 39.52$ ppm, $\delta(\text{CD}_3\text{OD}) = 49.00$ ppm. Analysis was performed using MestReNova (Mestrelab Research).

High resolution mass spectrometry (HRMS): Electrospray (ESI-HRMS) mass spectra were obtained using an Applied Biosystems API 150EX LC/MS system.

Optical rotation $[\alpha]_D^{20}$: Optical rotations were recorded on a Perkin-Elmer 341 instrument under following standard conditions: Wavelength 589.3 nm (sodium D line), cell length 1 dm, solvent and sample concentration (in g/100 mL) are given with individual experiment.

Experimental Procedures

Evans aldol product **S1**¹



S1

C₂₀H₂₁NO₄
339,3910

N,N-Diisopropylethylamine (3.6 mL, 21.0 mmol, 1.2 equiv) and dibutylboryl trifluoromethanesulfonate (1M in dichloromethane, 18.9 mL, 19.0 mmol, 1.1 equiv) were added dropwise to a solution of (*S*)-(+)-4-benzyl-3-propionyl-2-oxazolidinone (4.0 g, 17.2 mmol, 1.0 equiv) in dichloromethane (170 mL) at -78 °C. The solution was stirred for 10 min at -78 °C and for 2 h at 0 °C. After cooling to -78 °C freshly distilled benzaldehyde (**5**) (2.3 mL, 22.3 mmol, 1.3 equiv) was added and the reaction mixture was stirred for additional 2 h at -78 °C and 1 h at 0 °C. Phosphate buffer (pH = 7, 45 mL), aqueous hydrogen peroxide solution (30%, 60 mL) and methanol (50 mL) were added at 0 °C and the solution was stirred for 1 h at this temperature. The layers were separated and the aqueous layer was extracted with dichloromethane (3 x 150 mL). The combined organic layers were dried over magnesium sulfate and concentrated *in vacuo*. The residue was purified by flash column chromatography (silica, 7:1 → 2:1 = petroleum ether : ethyl acetate) to provide Evans aldol product **S1** (5.63 g, 16.6 mmol, 96%).

¹H-NMR (400 MHz, CDCl₃) δ 7.42 – 7.25 (m, 8H), 7.22 – 7.16 (m, 2H), 5.09 (d, *J* = 4.0 Hz, 1H), 4.63 – 4.55 (m, 1H), 4.18 – 4.00 (m, 3H), 3.25 (dd, *J* = 13.6, 3.6 Hz, 1H), 3.09 (bs, 1H), 2.77 (dd, *J* = 13.2, 9.2 Hz, 1H), 1.23 (d, *J* = 7.2 Hz, 3H) ppm.

¹³C-NMR (100 MHz, CDCl₃) δ 176.9, 153.0, 141.4, 135.2, 129.6, 129.1, 128.4, 127.7, 127.6, 126.2, 74.0, 66.3, 55.4, 44.7, 37.9, 11.1 ppm.

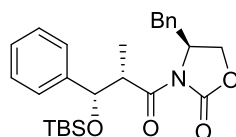
ESI-HRMS: *m/z* calc. for C₂₀H₂₁NO₄Na [M+Na]⁺: 362.1368, found: 362.1368.

[α]_D²⁰ = + 50.6 (c 1, CHCl₃).

R_f = 0.23 (4:1 = petroleum ether: ethyl acetate).

Analytical data are in accordance with the literature.¹

TBS ether **S2**¹



S2

C₂₆H₃₅NO₄Si
453,6540

tert-Butyldimethylsilyl trifluoromethanesulfonate (1.3 mL, 5.69 mmol, 1.50 equiv) was added dropwise to a solution of 2,6-dimethylpyridine (1.3 mL, 11.4 mmol, 3.0 equiv) and alcohol **S1** (1.29 g, 3.79 mmol, 1.0 equiv) in dichloromethane (76 mL) at -78 °C. After stirring for 1 h at 0 °C saturated aqueous sodium bicarbonate solution (50 mL) was added. The aqueous layer was extracted with dichloromethane (3 x 50 mL) and the combined organic layers were washed with saturated aqueous sodium chloride solution (30 mL), dried over magnesium sulfate and concentrated *in vacuo*. The residue was purified by flash column chromatography (silica, 15:1 = petroleum ether : ethyl acetate) to provide TBS-ether **S2** (1.59 g, 3.51 mmol, 93%).

¹H-NMR (400 MHz, CDCl₃) δ 7.39 – 7.20 (m, 8H), 7.19 – 7.15 (m, 2H), 4.83 (d, *J* = 7.2 Hz, 1H), 4.31 – 4.21 (m, 1H), 4.20 – 4.09 (m, 1H), 3.98 (dd, *J* = 8.8, 1.6 Hz, 1H), 3.77 – 3.53 (m, 1H), 3.20 (dd, *J* = 12.8, 3.2 Hz, 1H), 2.69 (dd, *J* = 13.6, 10.0 Hz, 1H), 1.29 (d, *J* = 6.8 Hz, 3H), 0.88 (s, 9H), 0.01 (s, 3H), -0.23 (s, 3H) ppm.

¹³C-NMR (100 MHz, CDCl₃) δ 174.8, 153.0, 143.0, 135.5, 129.6, 129.1, 128.0, 127.6, 127.4, 126.8, 76.7, 66.0, 55.9, 46.9, 37.9, 25.9, 18.3, 13.0, -4.5, -5.1 ppm.

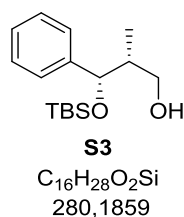
ESI-HRMS: *m/z* calc. for C₂₆H₃₅NO₄NaSi [M+Na]⁺: 476.2233, found: 476.2239.

[α]_D²⁰ = + 68.8 (c 1, CHCl₃).

R_f = 0.43 (10:1 = petroleum ether: ethyl acetate).

Analytical data are in accordance with the literature.¹

Alcohol **S3**¹



Lithium borohydride (4 M in tetrahydrofuran, 1.6 mL, 6.56 mmol, 2.0 equiv) was added dropwise to a solution of TBS-ether **S2** (1.49 g, 3.28 mmol, 1.0 equiv) and methanol (0.32 mL, 7.87 mmol, 2.4 equiv) in diethylether (22 mL) at -10 °C. The reaction mixture was warmed to 0 °C and stirred for 3 h at this temperature. Aqueous sodium hydroxide solution (2 M, 20 mL) was added and the aqueous layer was extracted with diethylether (3 x 20 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (20 mL), dried over magnesium sulfate and concentrated *in vacuo*. The residue was purified by flash column chromatography (silica, 10:1 → 5:1 = petroleum ether : ethyl acetate) to provide alcohol **S3** (0.71 g, 2.54 mmol, 77%).

¹H-NMR (400 MHz, CDCl₃) δ 7.36 – 7.22 (m, 5H), 4.83 (d, *J* = 4.4 Hz, 1H), 3.58 (dd, *J* = 10.8, 8.0 Hz, 1H), 3.44 (dd, *J* = 10.8, 4.8 Hz, 1H), 2.12 – 1.99 (m, 1H), 0.90 (s, 9H), 0.77 (d, *J* = 6.8 Hz, 3H), 0.05 (s, 3H), -0.18 (s, 3H) ppm.

¹³C-NMR (100 MHz, CDCl₃) δ 142.5, 127.9, 127.2, 126.9, 77.5, 65.6, 43.1, 26.0, 18.3, 12.0, -4.5, -5.2 ppm.

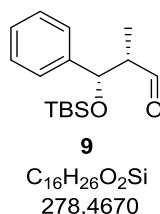
ESI-HRMS: *m/z* calc. for C₁₆H₂₈O₂NaSi [M+Na]⁺: 303.1756, found: 303.1758.

[α]_D²⁰ = -58.9 (c 1, CHCl₃).

R_f = 0.22 (10:1 = petroleum ether: ethyl acetate).

Analytical data are in accordance with the literature.¹

Aldehyde **9**¹



2-Iodoxybenzoic acid (1.08 g, 3.84 mmol, 2.5 equiv) was added to a solution of alcohol **S3** (0.54 g, 1.92 mmol, 1.0 equiv) in dimethyl sulfoxide (15 mL) at room temperature and the solution stirred for 3 h at this temperature. The reaction mixture was diluted with ethyl acetate (30 mL) and saturated aqueous sodium bicarbonate solution (15 mL) was added. The organic layer was successively washed with saturated aqueous sodium bicarbonate solution (15 mL), water (2 x 15 mL) and saturated aqueous sodium chloride solution (15 mL), dried over magnesium sulfate and concentrated *in vacuo*. This afforded aldehyde **9** (0.50 g, 1.81 mmol, 94%) which was immediately used in the next step without further purification.

¹H-NMR (400 MHz, CDCl₃) δ 9.76 (d, *J* = 1.2 Hz, 1H), 7.41 – 7.15 (m, 5H), 5.15 (d, *J* = 4.4 Hz, 1H), 2.65 - 2.50 (m, 1H), 1.04 (d, *J* = 7.2 Hz, 3H), 0.89 (s, 9H), 0.03 (s, 3H), -0.18 (s, 3H) ppm.

¹³C-NMR (100 MHz, CDCl₃) δ 204.5, 142.4, 128.3, 127.6, 126.4, 74.4, 54.9, 25.9, 18.3, 8.2, -4.4, -5.1 ppm.

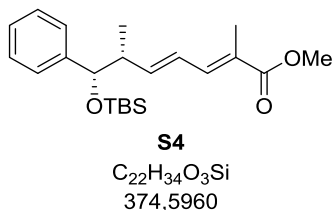
ESI-HRMS: not found.

[α]_D²⁰ = -34.4 (c 1, CHCl₃).

R_f = 0.50 (10:1 = petroleum ether: ethyl acetate).

Analytical data are in accordance with the literature.¹

Acrylic ester **S4**



n-Butyllithium (2.5 M in hexane, 2.8 mL, 7.09 mmol, 1.3 equiv) was added dropwise to a solution of phosphonate **12**² (1.78 g, 7.09 mmol, 1.3 equiv) in tetrahydrofuran (16 mL) at -78 °C. After 5 min at -78 °C the solution was warmed to 0 °C and stirred for 30 min at this temperature. Aldehyde **9** (1.50 g, 5.37 mmol, 1.0 equiv) in tetrahydrofuran (40 mL) was added over 5 min at room temperature and the reaction mixture stirred for 15 h at this temperature. Saturated aqueous ammonium chloride solution (30 mL) was added and the aqueous layer extracted with ethyl acetate (3 x 20 mL). The combined organic layers were successively washed with saturated aqueous sodium bicarbonate solution (15 mL) and saturated aqueous sodium chloride solution (15 mL), dried over magnesium sulfate and concentrated *in vacuo*. The residue was purified by flash column chromatography (silica, 40:1 = petroleum ether : ethyl acetate) to provide acrylic ester **S4** (1.93 g, 5.16 mmol, 96%, *E:Z* = 5.6:1).

¹H-NMR (400 MHz, CDCl₃) δ 7.32 – 7.20 (m, 5H), 7.10 (d, *J* = 11.2 Hz, 1H), 6.22 (ddd, *J* = 15.2, 11.2, 1.2 Hz, 1H), 5.97 (dd, *J* = 15.2, 7.6 Hz, 1H), 4.53 (d, *J* = 5.6 Hz, 1H), 3.74 (s, 3H), 2.61 – 2.50 (m, 1H), 1.88 (d, *J* = 1.2 Hz, 3H), 1.02 (d, *J* = 6.8 Hz, 3H), 0.89 (s, 9H), 0.01 (s, 3H), -0.22 (s, 3H) ppm.

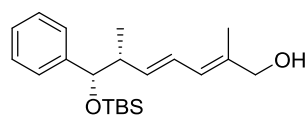
¹³C-NMR (100 MHz, CDCl₃) δ 169.3, 145.3, 143.4, 138.9, 127.9, 127.2, 126.8, 125.9, 125.4, 78.5, 51.9, 46.2, 26.0, 18.4, 14.8, 12.7, -4.5, -4.9 ppm.

ESI-HRMS: *m/z* calc. for C₂₂H₃₄O₃NaSi [M+Na]⁺: 397.2175, found: 397.2175.

[α]_D²⁰ = -22.3 (c 1, CHCl₃).

R_f = 0.51 (20:1 = petroleum ether: ethyl acetate).

Allylic alcohol **S5**



S5

C₂₁H₃₄O₂Si

346,5860

Diisobutylaluminum hydride (1 M in dichloromethane, 3.0 mL, 3.00 mmol, 2.0 equiv) was added dropwise to a solution of acrylic ester **S4** (0.56 g, 1.50 mmol, 1.0 equiv) in dichloromethane (7.5 mL) at -78 °C. After 1 h and 2 h additional diisobutylaluminum hydride (1 M in dichloromethane, 1.5 mL, 1.5 mmol, 1.0 equiv) was added at -78 °C. After 40 min at -78 °C the reaction mixture was diluted with diethyl ether (8 mL) and added to sodium potassium tartrate solution (40 mL) and stirred for 15 h. The aqueous layer was extracted with ethyl acetate (3 x 20 mL) and the combined organic layers were washed with saturated aqueous sodium chloride solution (20 mL), dried over magnesium sulfate and concentrated *in vacuo*. The residue was purified by flash column chromatography (silica, 8:1 → 5:1 = petroleum ether : ethyl acetate) to provide allylic alcohol **S5** (0.48 g, 1.38 mmol, 92%).

¹H-NMR (400 MHz, CDCl₃) δ 7.30 – 7.18 (m, 5H), 6.15 (ddd, *J* = 15.2, 10.8, 0.8 Hz, 1H), 5.96 (d, *J* = 10.8 Hz, 1H), 5.59 (dd, *J* = 15.2, 7.8 Hz, 1H), 4.51 (d, *J* = 5.2 Hz, 1H), 4.04 (s, 2H), 2.53 – 2.44 (m, 1H), 1.73 (s, 3H), 1.37 (bs, 1H), 1.00 (d, *J* = 6.8 Hz, 3H), 0.89 (s, 9H), 0.01 (s, 3H), -0.21 (s, 3H) ppm.

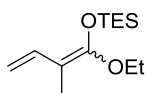
¹³C-NMR (100 MHz, CDCl₃) δ 143.9, 137.5, 135.3, 127.8, 127.0, 126.9, 125.7, 125.5, 78.9, 68.8, 45.8, 26.0, 18.4, 15.0, 14.2, -4.5, -4.9 ppm.

ESI-HRMS: *m/z* calc. for C₂₁H₃₄O₂NaSi [M+Na]⁺: 369.2226, found: 369.2230.

[α]_D²⁰ = -14.3 (c 1, CHCl₃).

R_f = 0.43 (5:1 = petroleum ether: ethyl acetate).

TES ketene acetal **13**



13

C₁₃H₂₆O₂Si
242,4340

n-Butyllithium (2.5 M in hexane, 3.7 mL, 9.36 mmol, 1.0 equiv) was added dropwise to a solution of diisopropylamine (1.4 mL, 10.1 mmol, 1.3 equiv) in tetrahydrofuran (16 mL) at 0 °C. After 20 min at this temperature the solution was cooled to -78 °C and *N,N'*-dimethylpropylene urea (1.4 mL, 11.7 mmol, 1.5 equiv) was added. After 15 min ethyl tiglate (1.1 mL, 7.8 mmol, 1.0 equiv) was added and after additional 15 min chlorotriethylsilane (1.7 mL, 10.0 mmol, 1.3 equiv) in tetrahydrofuran (1.6 mL) was added. The solution was stirred at -78 °C for 30 min and at room temperature for 2 h. The solution was diluted with pentane (20 mL) and filtered through Celite® (pentane, 50 mL). The filtrate was washed with saturated aqueous sodium chloride solution (2 x 25 mL), dried over magnesium sulfate and concentrated *in vacuo*. The residue was purified by vacuum distillation (1 mbar; bp.: 50-52 °C) to provide TES-ketene acetal **13** (1.44 g, 5.93 mmol, 76%; 1.2:1-mixture of C1-C2 (*E*)-(*Z*)-isomers). Analytical data are given for a 1.2:1-mixture of major (mj.)- and minor (mn.)-isomer:

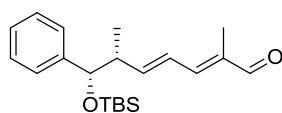
¹H-NMR (400 MHz, CDCl₃) δ 6.78 (dd, *J* = 17.6, 10.8 Hz, 1H, mj.), 6.70 (dd, *J* = 17.6, 10.8 Hz, 1H, mn.), 4.90 - 4.72 (m, 2H, mj. and mn.), 3.86 (q, *J* = 7.2 Hz, 2H, mn.), 3.85 (q, *J* = 7.2 Hz, 2H, mj.), 1.67 (s, 3H, mn.), 1.65 (s, 3H, mj.), 1.26 (t, *J* = 7.2 Hz, 3H, mj.), 1.25 (t, *J* = 7.2 Hz, 3H, mn.), 1.00 (t, *J* = 8.0 Hz, 9H, mj. and mn.), 0.71 (dt, *J* = 8.4, 4.0 Hz, 6H, mj. and mn.) ppm.

¹³C-NMR (100 MHz, CDCl₃) δ 152.6 (mj.), 152.2 (mn.), 134.8 (mn.), 134.7 (mj.), 107.8 (mn.), 107.3 (mj.), 98.0 (mj.), 97.4 (mn.), 65.9 (mj.), 65.2 (mn.), 15.0 (mn.), 14.9 (mj.), 10.9 (mj.), 10.4 (mn.), 6.72(3C, mn.), 6.70 (3C, mj.), 5.13 (3C, mj.), 5.06 (3C, mn.) ppm.

ESI-HRMS: not found.

Bp.: 50-52 °C (1 mbar).

Aldehyde **10**



10

C₂₁H₃₂O₂Si
344,5700

Manganese(IV) oxide (2.5 g, 29.4 mmol, 20.0 equiv) was added to a solution of allylic alcohol **S5** (0.51 g, 1.47 mmol, 1.0 equiv) in dichloromethane (29 mL) at room temperature and the mixture was stirred for 16 h. The reaction mixture was filtered through Celite® (dichloromethane, 300 mL) and the filtrate concentrated *in vacuo*. This provided aldehyde **10** which was immediately used in the next step.

¹H-NMR (400 MHz, CDCl₃) δ 9.40 (s, 1H), 7.37 – 7.17 (m, 5H), 6.76 (d, *J* = 11.2 Hz, 1H), 6.41 (ddd, *J* = 15.2, 11.2, 1.2 Hz, 1H), 6.13 (dd, *J* = 15.2, 7.6 Hz, 1H), 4.58 (d, *J* = 5.2 Hz, 1H), 2.72 – 2.55 (m, 1H), 1.79 (d, *J* = 1.2 Hz, 3H), 1.06 (d, *J* = 6.8 Hz, 3H), 0.90 (s, 9H), 0.02 (s, 3H), –0.20 (s, 3H) ppm.

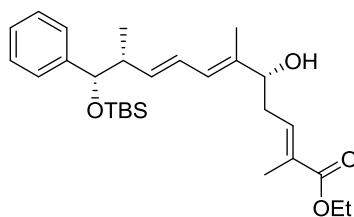
¹³C-NMR (100 MHz, CDCl₃) δ 195.2, 149.2, 147.8, 143.1, 136.5, 127.9, 127.3, 126.8, 125.8, 78.4, 46.3, 26.0, 18.3, 14.6, 9.5, –4.5, –4.9 ppm.

ESI-HRMS: *m/z* calc. for C₂₁H₃₂O₂NaSi [M+Na]⁺: 367.2069, found: 367.2071.

[α]_D²⁰ = –9.9 (c 1, CHCl₃).

R_f = 0.53 (10:1 = petroleum ether: ethyl acetate).

Alkohol **11**



11

C₂₈H₄₄O₄Si
472,7410

Dichlorophenylborane (0.19 mL, 1.47 mmol, 1.0 equiv) was added to *N*-Ts-L-tryptophane (0.53 g, 1.47 mmol, 1.0 equiv) in dichloromethane (7.4 mL) and stirred at room temperature for 2 h. The mixture was concentrated *in vacuo* and dried under high vacuum for 1 h. The residue was taken up in propionitrile (5.8 mL) and cooled to -78°C. Aldehyde **10** (0.51 g, 1.47 mmol, 1.0 equiv) in propionitrile (5.0 mL) was added dropwise and the solution turned orange. After 2 min TES-ketene acetal **13** (1.07 g, 4.41 mmol, 3.0 equiv) was added over a period of 2 min. After 3 h at -78 °C a mixture of tetrahydrofuran/ water/ hydrochloric acid (1 M) (36 mL/ 8.2 mL/ 1.7 mL) was added. The reaction mixture was warmed to room temperature and stirred for 1 h at this temperature before it was poured onto saturated aqueous sodium bicarbonate solution (40 mL). The aqueous layer was extracted with ethyl acetate (3 x 20 mL) and the combined organic layers were washed with saturated aqueous sodium chloride solution (20 mL), dried over magnesium sulfate and concentrated *in vacuo*. The residue was purified by flash column chromatography (silica, 10:1 → 5:1 = petroleum ether: ethyl acetate) to provide alcohol **11** (0.54 g, 1.14 mmol, 77% over 2 steps, *dr* 3.1:1).

¹H-NMR (400 MHz, CDCl₃) δ 7.35 – 7.11 (m, 5H), 6.75 (td, *J* = 7.2, 1.2 Hz, 1H), 6.13 (dd, *J* = 15.2, 10.8 Hz, 1H), 5.98 (d, *J* = 10.8 Hz, 1H), 5.60 (dd, *J* = 15.2, 7.6 Hz, 1H), 4.51 (d, *J* = 5.2 Hz, 1H), 4.18 (q, *J* = 7.2 Hz, 2H), 4.22 – 4.14 (m, 1H), 2.53 – 2.35 (m, 3H), 1.85 (d, *J* = 0.8 Hz, 3H), 1.71 (s, 3H), 1.62 (s, 1H), 1.28 (t, *J* = 7.2 Hz, 3H), 0.99 (d, *J* = 6.4 Hz, 3H), 0.89 (s, 9H), 0.00 (s, 3H), -0.22 (s, 3H) ppm.

¹³C-NMR (100 MHz, CDCl₃) δ 168.1, 143.8, 138.1, 137.9, 136.8, 129.9, 127.8 (2C), 127.0, 126.8 (2C), 126.2, 125.6, 78.8, 76.6, 60.6, 45.8, 34.8, 26.0 (3C), 18.4, 14.9, 14.4, 12.8, 12.3, -4.5, -4.9 ppm.

ESI-HRMS: *m/z* calc. for C₂₈H₄₄O₄NaSi [M+Na]⁺: 495.2907, found: 495.2903.

[α]_D²⁰ = +3.0 (c 1, CHCl₃).

R_f = 0.46 (5:1 = petroleum ether: ethyl acetate).

Confirmation of the absolute stereochemistry (at C11) of alcohol 11:

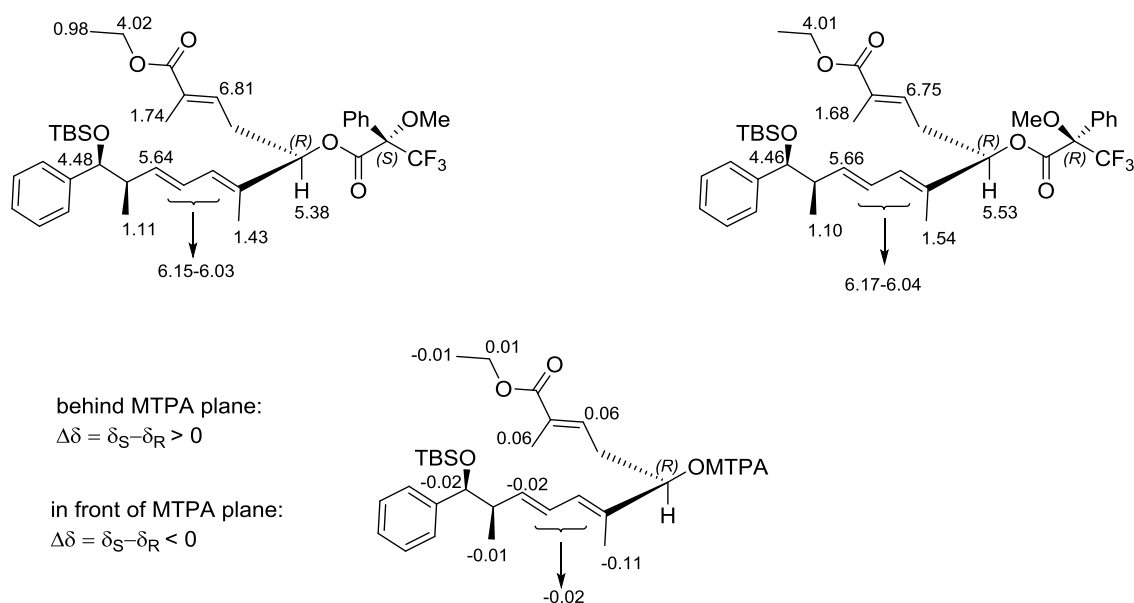
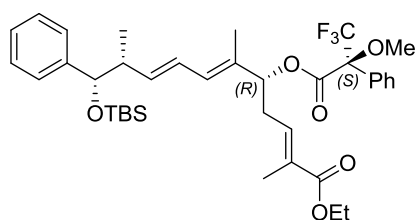


Figure 1: Analysis of Mosher ester (*R*)-S6 und (*S*)-S6.

To confirm the stereochemistry of the secondary alcohol at C11 (*S*)- and (*R*)-Mosher ester (*R*)-S6 and (*S*)-S6 have been synthesized. Analysis of the results showed an (*R*)-configuration for the newly formed stereocenter. Additionally the diastereoselectivity of the VMAR has been determined as 3.1:1.

Mosher ester (*S*)-S6



(*S*)-S6

$C_{38}H_{51}F_3O_6Si$
 688,9002

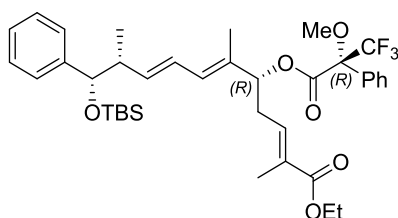
Triethylamine (24 μ L, 0.17 mmol, 8.0 eq.), 4-(dimethylamino)-pyridine (4 mg, 30 μ mol, 1.4 equiv) and (*R*)-(-)- α -methoxy- α -(trifluoromethyl)phenylacetyl chloride (16 μ L, 85 μ mol, 4.0 equiv) were successively added to a solution of alcohol 11 (10 mg, 21 μ mol, 1.0 equiv) in dichloromethane (1.1 mL) and the solution stirred at room temperature for 15 h. The solution was diluted with ethyl acetate and washed with saturated aqueous sodium bisulfate solution (3 mL), aqueous sodium hydroxide solution (1 M, 3 mL) and saturated aqueous sodium chloride solution (3 mL), dried over magnesium sulfate and concentrated *in vacuo*. The residue was purified by flash column

chromatography (silica, 30:1 = petroleum ether: ethyl acetate) to provide mosher ester (**S**)-**S6** (15 mg, 21 μ mol, quant; 3.1:1-mixture with the C11-diastereomer).

¹H-NMR (400 MHz, benzol-*d*₆) δ 7.67 (m, 2H), 7.28 – 7.03 (m, 8H), 6.81 (td, *J* = 7.6, 1.2 Hz, 1H), 6.15 – 6.03 (m, 2H), 5.64 (dd, *J* = 13.6, 7.6 Hz, 1H), 5.38 (dd, *J* = 8.8, 5.2 Hz, 1H), 4.48 (d, *J* = 5.6 Hz, 1H), 4.02 (q, *J* = 7.2 Hz, 2H), 3.50 (d, *J* = 0.8 Hz, 3H), 2.57 – 2.47 (m, 1H), 2.45 – 2.31 (m, 1H), 2.18 – 2.04 (m, 1H), 1.74 (d, *J* = 1.2 Hz, 3H), 1.43 (s, 3H), 1.11 (d, *J* = 6.8 Hz, 3H), 0.99 (s, 9H), 0.98 (t, *J* = 7.7 Hz, 3H), 0.05 (s, 3H), –0.15 (s, 3H) ppm.

R_f = 0.42 (10:1 = petroleum ether: ethyl acetate).

Mosher ester (**R**)-**S6**



(R)-S6

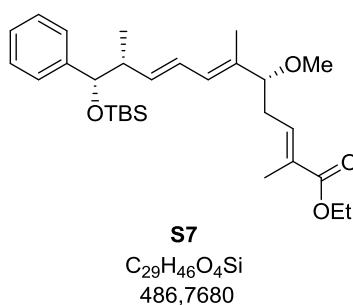
C₃₈H₅₁F₃O₆Si
688,9002

Triethylamine (24 μ L, 0.17 mmol, 8.0 eq.), 4-(dimethylamino)-pyridine (4 mg, 30 μ mol, 1.4 equiv) and (S)-(+)- α -methoxy- α -(trifluoromethyl)phenylacetyl chloride (16 μ L, 85 μ mol, 4.0 equiv) were successively added to a solution of alcohol **11** (10 mg, 21 μ mol, 1.0 equiv) in dichloromethane (1.1 mL) and the solution stirred at room temperature for 15 h. The solution was diluted with ethyl acetate and washed with saturated aqueous sodium bisulfate solution (3 mL), aqueous sodium hydroxide solution (1 M, 3 mL) and saturated aqueous sodium chloride solution (3 mL), dried over magnesium sulfate and concentrated *in vacuo*. The residue was purified by flash column chromatography (silica, 30:1 = petroleum ether: ethyl acetate) to provide mosher ester (**R**)-**S6** (15 mg, 21 μ mol, quant; 3.1:1-mixture with the C11-diastereomer).

¹H-NMR (400 MHz, benzol-*d*₆) δ 7.68 (m, 2H), 7.26 – 7.02 (m, 8H), 6.75 (td, *J* = 7.6, 1.2 Hz, 1H), 6.17 – 6.04 (m, 2H), 5.66 (dd, *J* = 14.4, 7.6 Hz, 1H), 5.53 (dd, *J* = 8.0, 6.0 Hz, 1H), 4.46 (d, *J* = 6.0 Hz, 1H), 4.01 (q, *J* = 7.2 Hz, 2H), 3.44 (d, *J* = 0.8 Hz, 3H), 2.56 – 2.47 (m, 1H), 2.44 – 2.34 (m, 1H), 2.18 – 2.04 (m, 1H), 1.69 (d, *J* = 1.2 Hz, 3H), 1.53 (s, 3H), 1.10 (d, *J* = 6.8 Hz, 3H), 1.02 – 0.95 (m, 3H), 0.98 (s, 9H), 0.04 (s, 3H), –0.15 (s, 3H) ppm.

R_f = 0.36 (10:1 = petroleum ether: ethyl acetate).

Methyl ether **S7**



Trimethyloxonium tetrafluoroborate (0.86 g, 5.79 mmol, 6.2 equiv) was weighed in the glovebox, washed with dichloromethane (3 x 1 mL) under an argon atmosphere and dried under high vacuum. 1,8-bis(dimethylamino)naphthalene (1.54 g, 7.18 mmol, 7.7 equiv) was also weighed in the glovebox. To this dry trimethyloxonium tetrafluoroborate and dichloromethane (46 mL) were added. Alcohol **11** (0.44 g, 0.93 mmol, 1.0 equiv) in dichloromethane (9.3 mL) was added over a period of 5 min and the reaction mixture stirred for 20 h. Saturated aqueous sodium bicarbonate solution (20 mL) and dichloromethane (50 mL) were added. The organic layer was washed with aqueous potassium bisulfate solution (1 M, 3 x 30 mL) and saturated aqueous sodium chloride solution (30 mL), dried over magnesium sulfate and concentrated *in vacuo*. The residue was purified by flash column chromatography (silica, 30:1 = petroleum ether: ethyl acetate) to provide methyl ether **S7** (0.42 g, 0.87 mmol, 93%).

¹H-NMR (400 MHz, CDCl₃) δ 7.37 – 7.11 (m, 5H), 6.72 (td, J = 6.8, 1.2 Hz, 1H), 6.15 (dd, J = 15.2, 10.8 Hz, 1H), 5.92 (d, J = 10.8 Hz, 1H), 5.62 (dd, J = 15.2, 7.2 Hz, 1H), 4.53 (d, J = 5.2 Hz, 1H), 4.18 (q, J = 7.2 Hz, 2H), 3.58 (t, J = 6.8 Hz, 1H), 3.17 (s, 3H), 2.54 – 2.42 (m, 2H), 2.41 – 2.28 (m, 1H), 1.82 (d, J = 1.2 Hz, 3H), 1.63 (s, 3H), 1.28 (t, J = 7.2 Hz, 3H), 0.99 (d, J = 6.8 Hz, 3H), 0.89 (s, 9H), 0.00 (s, 3H), –0.21 (s, 3H) ppm.

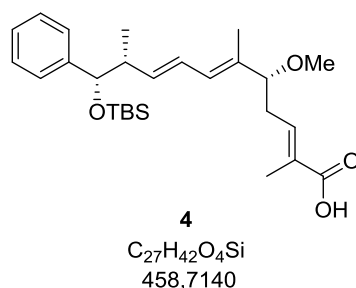
¹³C-NMR (100 MHz, CDCl₃) δ 168.1, 143.9, 138.0, 138.0, 134.2, 129.2, 128.6, 127.7, 127.0, 126.8, 125.6, 86.1, 78.8, 60.5, 56.1, 45.7, 33.7, 26.0, 18.4, 14.4, 12.8, 11.3, –4.5, –4.9 ppm.

ESI-HRMS: m/z calc. for C₂₉H₄₆O₄NaSi [M+Na]⁺: 509.3063, found: 509.3062.

$[\alpha]_D^{20}$ = +6.5 (c 1, CHCl₃).

R_f = 0.46 (20:1 = petroleum ether: ethyl acetate).

Carboxylic acid **4** (northern fragment)



Lithium hydroxide (0.44 g, 14.6 mmol, 20.0 equiv) was added to a solution of ethyl ester **S7** (0.36 g, 0.73 mmol, 1.0 equiv) in tetrahydrofuran/ methanol/ water (5.2 mL/ 1.3 mL/ 1.3 mL) at 0 °C. After 15 min at 0 °C the mixture was stirred at room temperature for 15 h. The reaction mixture was diluted with ethyl acetate (10 mL) and water (5 mL). The aqueous phase was adjusted to pH = 3-4 with aqueous hydrogen chloride solution (1 M) and extracted with ethyl acetate (3 x 10 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (5 mL), dried over sodium sulfate and concentrated *in vacuo*. Carboxylic acid **4** (0.33 g, 0.73 mmol, quant) was obtained and immediately submitted to the next step without further purification

¹H-NMR (400 MHz, CDCl₃) δ 7.33 – 7.15 (m, 5H), 6.90 – 6.81 (m, 1H), 6.15 (ddd, *J* = 15.2, 10.8, 1.2 Hz, 1H), 5.93 (d, *J* = 10.8 Hz, 1H), 5.63 (dd, *J* = 15.2, 7.6 Hz, 1H), 4.54 (d, *J* = 4.8 Hz, 1H), 3.58 (t, *J* = 6.8 Hz, 1H), 3.17 (s, 3H), 2.57 – 2.45 (m, 2H), 2.41 – 2.32 (m, 1H), 1.83 (d, *J* = 0.8 Hz, 3H), 1.63 (s, 3H), 1.00 (d, *J* = 6.8 Hz, 3H), 0.89 (s, 9H), 0.00 (s, 3H), -0.21 (s, 3H) ppm.

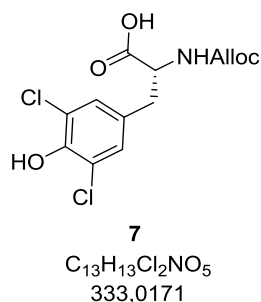
¹³C-NMR (100 MHz, CDCl₃) δ 173.2, 143.9, 141.3, 138.2, 134.0, 128.8, 128.4, 127.8, 127.0, 126.8, 125.5, 85.9, 78.8, 56.1, 45.6, 33.9, 26.0, 18.4, 14.4, 12.4, 11.3, -4.5, -4.9 ppm.

ESI-HRMS: *m/z* calc. for C₂₇H₄₂O₄NaSi [M+Na]⁺: 481.2750, found: 481.2750.

[α]_D²⁰ = +7.5 (c 1, CHCl₃).

R_f = 0.55 (5:1 = petroleum ether: ethyl acetate).

***N*-Alloc-3,5-dichloro-D-tyrosine (7)**



Sodium carbonate (1.30 g, 12.2 mmol, 3.5 equiv) and allyl chloroformate (0.37 mL, 3.49 mmol, 1.0 equiv) were successively added to a solution of 3,5-dichloro-D-tyrosine (**18**) (1.00 g, 3.49 mmol, 1.0 equiv) in tetrahydrofuran (17.5 mL) and water (17.5 mL) and the solution stirred at room temperature for 20 h. Tetrahydrofuran was removed *in vacuo* and the residue washed with methyl *tert*-butyl ether (10 mL). The aqueous layer was acidified to pH = 2 with aqueous hydrochloric acid (1 M) and extracted with ethyl acetate (3 x 15 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (15 mL), dried over sodium sulfate and concentrated *in vacuo*. The residue was purified by flash column chromatography (silica, 8:1 = petroleum ether: ethyl acetate + 1vol% acetic acid) to provide *N*-Alloc-3,5-dichloro-D-tyrosine (**7**) (1.07 g, 3.20 mmol, 91 %).

¹H NMR (400 MHz, DMSO-*d*₆) δ 12.71 (bs, 1H), 9.92 (bs, 1H), 7.58 (d, *J* = 8.5 Hz, 1H), 7.25 (s, *J* = 11.9 Hz, 2H), 5.94 – 5.75 (m, 1H), 5.21 (dd, *J* = 17.2, 1.5 Hz, 1H), 5.13 (dd, *J* = 10.5, 1.0 Hz, 1H), 4.42 (d, *J* = 5.2 Hz, 2H), 4.20 – 4.04 (m, 1H), 2.98 (dd, *J* = 13.8, 4.3 Hz, 1H), 2.72 (dd, *J* = 13.8, 10.7 Hz, 1H) ppm.

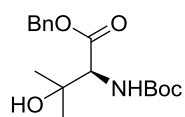
¹³C NMR (100 MHz, DMSO-*d*₆) δ 173.0, 155.8, 147.5, 133.5, 130.9, 129.2, 121.9, 116.9, 79.2, 64.4, 35.0 ppm.

ESI-HRMS: *m/z* calc. for C₁₃H₁₂NO₅Cl₂ [M-H]⁻: 332.0093, found: 332.0095.

[α]_D²⁰ = -10.1 (c 1, CH₃OH).

R_f = 0.25 (1:1 = petroleum ether: ethyl acetate).

Benzyl ester **S8**



S8

C₁₇H₂₅NO₅
323,1733

Benzyl bromide (1.8 mL, 15.4 mmol, 2.0 equiv) was added to a solution of *N*-Boc-L-β-hydroxyvaline (**16**)³ (1.80 g, 7.72 mmol, 1.0 equiv) and sodium carbonate (2.45 g, 23.2 mmol, 3.0 equiv) in *N,N*-dimethylformamide (24 mL) at 0 °C over a period of 5 min. The solution was stirred at 0 °C for another 5 min and then at room temperature for 15 h before saturated aqueous ammonium chloride solution (10 mL) was added. The mixture was diluted with ethyl acetate and the aqueous layer extracted with ethyl acetate (3 x 10 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (2 x 15 mL), dried over sodium sulfate and concentrated *in vacuo*. The residue was purified by flash column chromatography (silica, 5:1 = petroleum ether: ethyl acetate) to provide benzyl ester **S8** (2.41 g, 7.47 mmol, 96%).

¹H NMR (400 MHz, CDCl₃) δ 7.41 – 7.31 (m, 5H), 5.40 (bs, 1H), 5.24 (d, *J* = 12.2 Hz, 1H), 5.17 (d, *J* = 12.2 Hz, 1H), 4.24 (d, *J* = 8.6 Hz, 1H), 2.40 (bs, 1H), 1.43 (s, 9H), 1.22 (d, *J* = 10.6 Hz, 6H) ppm.

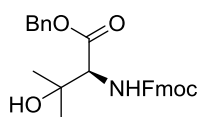
¹³C NMR (100 MHz, CDCl₃) δ 171.9, 155.9, 135.2, 128.8, 128.7, 128.6, 80.3, 72.1, 67.3, 61.4, 28.4, 27.0, 26.5 ppm.

ESI-HRMS: *m/z* calc. for C₁₇H₂₅NO₅Na [M+Na]⁺: 346.1630, found: 346.1631.

[α]_D²⁰ = -11.6 (c 1, CHCl₃).

R_f = 0.25 (5:1 = petroleum ether: ethyl acetate).

Fmoc-carbamate **17**



17

C₂₇H₂₇NO₅
445,1889

Hydrochloric acid (4 M in 1,4-dioxane, 14 mL, 57.6 mmol, 15.0 equiv) was added to a solution of benzyl ester **S8** (1.24 g, 3.84 mmol, 1.0 equiv) in 1,4-dioxane (14 mL) and stirred at room temperature for 14 h. The reaction mixture was concentrated *in vacuo*, coevaporated with methanol (2 x 5 mL) and dried on high vacuum to furnish amine **S9** which was directly submitted to the next reaction.

N-(9-Fluorenylmethoxycarbonyloxy)succinimide (1.30 g, 3.84 mmol, 1.0 equiv) in 1,4-dioxane (7.7 mL) was added to a solution of amine **S9** and sodium bicarbonate (1.13 g, 13.4 mmol, 3.5 equiv) in water (7.7 mL) at 0 °C over a period of 20 min. The reaction mixture was stirred at 0 °C for 5 min and at room temperature for 20 h. Ethyl acetate (10 mL) and water (10 mL) were added and the aqueous layer was extracted with ethyl acetate (3 x 10 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (15 mL), dried over sodium sulfate and concentrated *in vacuo*. The residue was purified by flash column chromatography (silica, 3:1 = petroleum ether: ethyl acetate) to provide Fmoc-carbamate **17** (1.65 g, 3.71 mmol, 97% over 2 steps).

¹H NMR (400 MHz, CDCl₃) δ 7.79 – 7.74 (m, 2H), 7.62 – 7.55 (m, 2H), 7.46 – 7.28 (m, 9H), 5.65 (d, *J* = 8.8 Hz, 1H), 5.25 (d, *J* = 12.2 Hz, 1H), 5.18 (d, *J* = 12.2 Hz, 1H), 4.46 – 4.39 (m, 2H), 4.32 (d, *J* = 8.8 Hz, 1H), 4.22 (t, *J* = 6.8 Hz, 1H), 2.25 – 1.75 (bs, 1H), 1.24 (s, 3H), 1.23 (s, 3H) ppm.

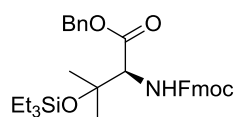
¹³C NMR (101 MHz, CDCl₃) δ 171.6, 156.5, 143.9, 143.8, 141.5, 135.0, 128.8, 128.8, 128.6, 127.9, 127.2, 125.2, 120.2, 120.1, 72.1, 67.5, 67.4, 61.7, 47.3, 27.0, 26.5 ppm.

ESI-HRMS: *m/z* calc. for C₂₇H₂₇NO₅Na [M+Na]⁺: 468.1787, found: 468.1784.

[α]_D²⁰ = -2.4 (c 1, CHCl₃).

R_f = 0.30 (3:1 = petroleum ether: ethyl acetate).

TES ether **S10**



2,6-Lutidine (0.97 mL, 8.32 mmol, 4.0 equiv) and triethylsilyltrifluoromethanesulfonate (0.94 mL, 4.16 mmol, 2.0 equiv) were added sequentially to a solution of alcohol **17** (0.93 g, 2.08 mmol, 1.0 equiv) in dichloromethane (20 mL) at -78 °C. The reaction mixture was stirred at -78 °C for additional 5 min and at 0 °C for 1 h. Saturated aqueous sodium bicarbonate solution (10 mL) was added and the aqueous layer was extracted with dichloromethane (3 x 10 mL). The combined organic layers were washed with aqueous potassium bisulfate solution (1M, 10 mL) and saturated aqueous sodium chloride solution (10 mL), dried over sodium sulfate and concentrated *in vacuo*. The residue was purified by flash column chromatography (silica, 10:1 = petroleum ether: ethyl acetate) to provide TES ether **S10** (1.15 g, 2.05 mmol, 99%).

¹H NMR (400 MHz, CDCl₃) δ 7.81 – 7.74 (m, 2H), 7.64 – 7.56 (m, 2H), 7.44 – 7.27 (m, 9H), 5.63 (d, *J* = 9.6 Hz, 1H), 5.20 (d, *J* = 12.2 Hz, 1H), 5.14 (d, *J* = 12.2 Hz, 1H), 4.41 – 4.36 (m, 2H), 4.27 – 4.18 (m, 2H), 1.35 (s, 3H), 1.29 (s, 3H), 0.94 (t, *J* = 7.9 Hz, 9H), 0.57 (q, *J* = 7.9 Hz, 6H) ppm.

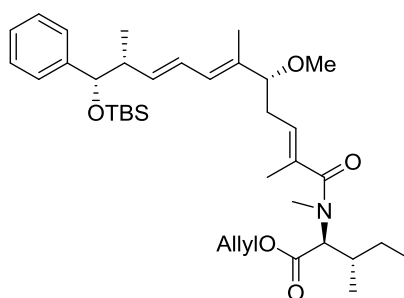
¹³C NMR (100 MHz, CDCl₃) δ 170.4, 156.3, 144.2, 143.9, 141.5, 141.4, 135.5, 128.7, 128.6, 128.5, 127.8, 127.8, 127.2, 125.3, 125.3, 120.1, 74.9, 67.2, 67.1, 63.4, 47.3, 28.2, 28.0, 7.1, 6.7 ppm.

ESI-HRMS: *m/z* calc. for C₃₃H₄₁NO₅NaSi[M+Na]⁺: 582.2652, found: 582.2650.

[α]_D²⁰ = -14.9 (c 1, CHCl₃).

R_f = 0.27 (10:1 = petroleum ether: ethyl acetate).

Amide **S11**



S11
C₃₇H₅₉NO₅Si
625,4163

Hydrochloric acid (4 M in 1,4-dioxane, 5.5 mL, 21.9 mmol, 15.0 equiv) was added to a solution of allyl *N*-(*tert*-butoxycarbonyl)-*N*-methyl-L-isoleucinate (0.42 g, 1.46 mmol, 1.0 equiv) in 1,4-dioxane (5.5 mL) and stirred at room temperature for 14 h. The reaction mixture was concentrated *in vacuo*, coevaporated with methanol (2 x 5 mL) and dried on high vacuum to furnish amine **8** which was directly submitted to the next reaction.

Diisopropylethylamine (0.15 mL, 0.88 mmol, 1.2 equiv) and COMU[®] (0.38 g, 0.88 mmol, 1.2 equiv) were added sequentially to a solution of carboxylic acid **4** (0.33 g, 0.73 mmol, 1.0 equiv) in *N,N*-dimethylformamide (7.5 mL) at 0 °C. After 5 min amine **8** (0.32 g, 1.46 mmol, 2.0 equiv) in *N,N*-dimethylformamide (7.5 mL) was added over a period of 5 min and additional diisopropylethylamine (0.25 mL, 1.46 mmol, 2.0 equiv) was added. The solution was stirred at 0 °C for additional 5 min and then at room temperature for 14 h. Ethyl acetate (20 mL) and water (15 mL) were added and the aqueous layer was extracted with ethyl acetate (3 x 15 mL). The combined organic layers were washed successively with aqueous hydrochloric acid (1 M, 10 mL), saturated aqueous sodium bicarbonate solution (10 mL) and saturated aqueous sodium chloride solution (15 mL), dried over sodium sulfate and concentrated *in vacuo*. The residue was purified by flash column chromatography (silica, 5:1 = petroleum ether: ethyl acetate) to provide amide **S11** (0.37 g, 0.60 mmol, 82%).

¹H NMR (400 MHz, benzol-*d*₆) δ 7.29 – 7.24 (m, 2H), 7.21 – 7.15 (m, 3H), 7.10 – 7.04 (m, 1H), 6.23 (ddd, *J* = 15.2, 10.8, 0.9 Hz, 1H), 5.93 (d, *J* = 10.2 Hz, 1H), 5.71 – 5.60 (m, 3H), 5.11 (d, *J* = 17.2 Hz, 1H), 4.95 (dd, *J* = 10.4, 1.4 Hz, 1H), 4.52 (d, *J* = 5.6 Hz, 1H), 4.42 – 4.37 (m, 2H), 3.38 (s, 1H), 3.00 (s, 3H), 2.93 (s, 3H), 2.61 – 2.51 (m, 1H), 2.46 – 2.34 (m, 1H), 2.24 – 2.15 (m, 1H), 2.02 (bs, 1H), 1.82 (bs, 3H), 1.58 (s, 3H), 1.43 - 1.32 (m, 1H), 1.12 (d, *J* = 6.8 Hz, 3H), 0.98 (s, 9H), 0.99 – 0.96 (m, 1H), 0.89 (bs, 3H), 0.78 (bs, 3H), 0.05 (s, 3H), -0.15 (s, 3H) ppm.

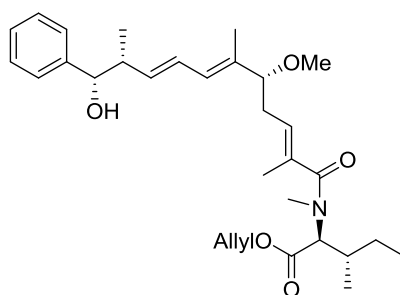
¹³C NMR (101 MHz, benzol-*d*₆) δ 173.9, 170.7, 144.1, 137.5, 135.3, 133.4, 132.4, 128.5, 128.2, 127.5, 127.1, 126.2, 118.2, 86.5, 79.5, 79.3, 65.2, 55.8, 46.1, 33.9, 32.8, 26.1, 25.4, 18.5, 16.1, 15.3, 14.8, 11.3, -4.4, -4.8 ppm.

ESI-HRMS: *m/z* calc. for C₃₇H₅₉NO₅SiNa [M+Na]⁺: 648.4060, found: 648.4054.

[α]_D²⁰ = -44.4 (c 1, CHCl₃).

R_f = 0.36 (4:1 = petroleum ether: ethyl acetate).

Alkohol **18**



18

C₃₁H₄₅NO₅
511,3298

Tetrabutylammonium fluoride (1 M in tetrahydrofuran, 2.3 mL, 2.29 mmol, 4.0 equiv) was added to a solution of TBS ether **S11** (0.36 g, 0.57 mmol, 1.0 equiv) in tetrahydrofuran (2.9 mL) over a period of 5 min and the solution stirred at room temperature for 19 h. The reaction mixture was diluted with ethyl acetate (5 mL) and water (5 mL) and the aqueous layer extracted with ethyl acetate (3 x 5 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (10 mL), dried over sodium sulfate and concentrated *in vacuo*. The residue was purified by flash column chromatography (silica, 3:1 → 2:1 = petroleum ether: ethyl acetate) to provide alcohol **18** (0.24 g, 0.47 mmol, 83%).

¹H NMR (400 MHz, benzol-*d*₆) δ 7.34 – 7.28 (m, 2H), 7.24 – 7.16 (m, 3H), 7.12 – 7.06 (m, 1H), 6.34 – 6.23 (m, 1H), 5.91 (d, *J* = 9.6 Hz, 1H), 5.78 – 5.55 (m, 3H), 5.10 (d, *J* = 17.2 Hz, 1H), 4.99 – 4.93 (m, 1H), 4.53 (t, *J* = 5.0 Hz, 1H), 4.44 – 4.35 (m, 2H), 3.38 (bs, 1H), 3.00 (s, 3H), 2.89 (bs, 3H), 2.66 – 2.57 (m, 1H), 2.42 – 2.33 (m, 1H), 2.23 – 2.12 (m, 1H), 2.00 (s, 1H), 1.79 (bs, 3H), 1.57 (d, *J* = 3.6 Hz, 3H), 1.34 (bs, 1H), 1.11 (d, *J* = 6.8 Hz, 3H), 0.87 (bs, 3H), 0.93 – 0.71 (m, 1H), 0.77 (bs, 3H) ppm.

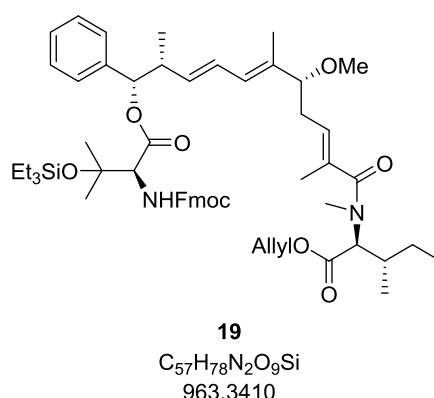
¹³C NMR (101 MHz, benzol-*d*₆) δ 174.3, 171.0, 144.1, 136.9, 135.1, 133.3, 132.3, 128.5, 128.2, 127.3, 127.0, 126.2, 118.3, 86.5, 77.6, 65.2, 55.8, 44.9, 33.9, 32.6, 25.4, 16.1, 16.1, 15.0, 14.9, 11.3, 11.1 ppm.

ESI-HRMS: *m/z* calc. for C₃₁H₄₅NO₅Na[M+Na]⁺: 534.3195, found: 534.3192.

[α]_D²⁰ = -54.3 (c 1, CHCl₃).

R_f = 0.29 (3:1 = petroleum ether: ethyl acetate).

Ester **19**



Hydrogen was bubbled through a suspension of palladium on activated charcoal (10% Pd basis, 0.11 g, 0.1 mmol, 0.1 equiv) and benzyl ester **10** (0.56 g, 1.0 mmol, 1.0 equiv) in ethyl acetate (10 mL) for 5 min. The reaction mixture was then stirred under an atmosphere of hydrogen for 1 h and afterwards filtered through Celite® (ethyl acetate, 250 mL). The filtrate was concentrated *in vacuo* and obtained carboxylic acid **6** (0.47 g, 1.0 mmol, quant) directly submitted to the next step.

N-(3-Dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride (0.19 g, 1.00 mmol, 2.5 equiv) and 4-(dimethylamino)pyridine (49 mg, 0.40 mmol, 1.0 equiv) were successively added to a solution of alcohol **18** (0.20 g, 0.40 mmol, 1.0 equiv) and carboxylic acid **6** (0.47 g, 1.0 mmol, 2.5 equiv) in dichloromethane (4 mL) at 0 °C. The resulting solution was stirred at 0 °C for 5 min and at room temperature for 14 h and diluted with dichloromethane (4 mL) and water (4 mL). The aqueous layer was extracted with dichloromethane (3 x 5 mL) and the combined organic layers washed with saturated aqueous sodium chloride solution (5 mL), dried over sodium sulfate and concentrated *in vacuo*. The residue was purified by flash column chromatography (silica, 5:1 → 2:1 = petroleum ether: ethyl acetate) to provide ester **19** (0.23 g, 0.24 mmol, 60% (98% brsm)). Not converted alcohol **18** (78 mg, 0.15 mmol, 38%) was recovered after the reaction.

¹H NMR (400 MHz, CDCl₃): δ 7.81 – 7.72 (m, 2H), 7.67 – 7.54 (m, 2H), 7.47 – 7.37 (m, 2H), 7.35 – 7.23 (m, 7H), 6.11 (dd, *J* = 14.9, 11.0 Hz, 1H), 5.93 – 5.78 (m, 2H), 5.64 (d, *J* = 8.2 Hz, 2H), 5.44 (bs, 1H), 5.39 (dd, *J* = 15.2, 7.8 Hz, 1H), 5.31 (dd, *J* = 17.2, 1.4 Hz, 1H), 5.23 (d, *J* = 9.7 Hz, 1H), 4.60 (d, *J* = 4.6 Hz, 2H), 4.45 – 4.15 (m, 5H), 3.49 – 3.42 (m, 1H), 3.09 (s, 3H), 2.87 (s, 3H), 2.94 – 2.80 (m, 1H), 2.44 - 2.31 (m, 1H), 2.29 – 2.17 (m, 1H), 2.08 - 1.94 (m, 1H), 1.80 (s, 3H), 1.57 (s, 3H), 1.44 – 1.32 (m, 2H), 1.26 (s, 3H), 1.22 (s, 3H), 1.13 (d, *J* = 6.7 Hz, 3H), 0.88 (m, 15H), 0.49 (q, *J* = 8.0 Hz, 6H) ppm.

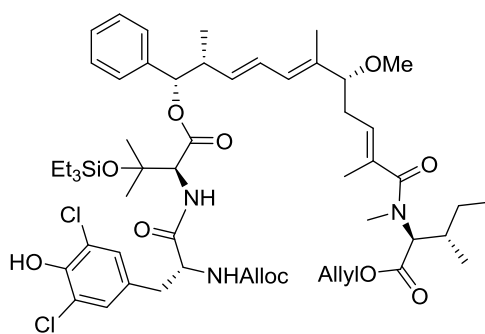
¹³C NMR (101 MHz, CDCl₃) δ 174.5 (HMBC-correlation), 169.9, 163.1 (HMBC-correlation), 156.3, 144.1, 143.9, 141.4, 138.3, 134.6, 128.2, 127.9, 127.8, 127.2, 125.3, 120.1, 86.2, 80.7, 74.9, 67.2, 63.3, 56.1, 47.3, 42.2, 28.6, 27.8, 25.2, 16.0, 11.2, 7.1, 6.6 ppm.

ESI-HRMS: m/z calc. for $C_{57}H_{78}N_2O_9SiNa$ $[M+Na]^+$: 985.5374, found: 985.5377.

$[\alpha]_D^{20} = -47.5$ (c 0.8, $CHCl_3$).

$R_f = 0.42$ (2:1 = petroleum ether: ethyl acetate).

Amide **20**



20

C₅₅H₇₉Cl₂N₃O₁₁Si
1057,2320

Piperidine (40 μ L, 20 vol % in dichloromethane) in dichloromethane (0.2 mL) was added dropwise to Fmoc-amine **19** (18.7 mg, 19.7 μ mol, 1.0 equiv) at 0 °C and stirred for 2.5 h at this temperature. The mixture was concentrated *in vacuo* and the residue was purified by flash column chromatography (silica, 4:1 \rightarrow 1:1 = petroleum ether: ethyl acetate) to provide amine **S12** (10.5 mg, 14.4 μ mol, 73%), which was directly submitted to the next step.

1-Hydroxybenzotriazole hydrate (12% H₂O, 4.6 mg, 28.8 μ mol, 2.0 equiv), N-(3-Dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (5.5 mg, 28.8 μ mol, 2.0 equiv) and diisopropylethylamine (4.9 μ L, 28.8 μ mol, 2.0 equiv) were sequentially added to a solution of amine **S12** (10.5 mg, 14.4 μ mol, 1.0 equiv) and carboxylic acid **7** (9.6 mg, 28.8 μ mol, 2.0 equiv) in dichloromethane (0.1 mL) and *N,N*-dimethylformamide (0.1 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 5 min and at room temperature for 20 h. Dichloromethane (1 mL) and water (1 mL) were added and the aqueous layer extracted with dichloromethane (3 x 2 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (2 x 2 mL), dried over sodium sulfate and concentrated *in vacuo*. The residue was purified by flash column chromatography (silica, 5:1 \rightarrow 3:1 = petroleum ether : acetone) to provide amide **20** (11.7 mg, 11.1 μ mol, 77%).

¹H NMR (400 MHz, CDCl₃) δ 7.32 – 7.23 (m, 5H), 7.10 (s, 2H), 6.73 (d, *J* = 8.7 Hz, 1H), 6.12 (dd, *J* = 15.1, 10.8 Hz, 1H), 5.95 – 5.79 (m, 3H), 5.60 (d, *J* = 8.1 Hz, 1H), 5.39 (dd, *J* = 15.2, 7.7 Hz, 1H), 5.50 - 5.17 (m, 7H), 4.65 – 4.49 (m, 5H), 4.46 – 4.38 (m, 1H), 4.31 (d, *J* = 8.6 Hz, 1H), 3.49 – 3.41 (m, 1H), 3.09 (s, 3H), 2.99 (d, *J* = 5.9 Hz, 2H), 2.87 (s, 3H), 2.91 – 2.81 (m, 1H), 2.41 – 2.32 (m, 1H), 2.29 - 2.19 (m, 1H), 2.05 – 1.93 (m, 1H), 1.80 (s, 3H), 1.58 (s, 3H), 1.43 – 1.26 (m, 2H), 1.16 (d, *J* = 1.2 Hz, 3H), 1.14 (d, *J* = 6.7 Hz, 3H), 1.10 (s, 3H), 0.93 – 0.84 (m, 6H), 0.79 (t, *J* = 7.9 Hz, 9H), 0.40 (q, *J* = 8.0 Hz, 6H) ppm.

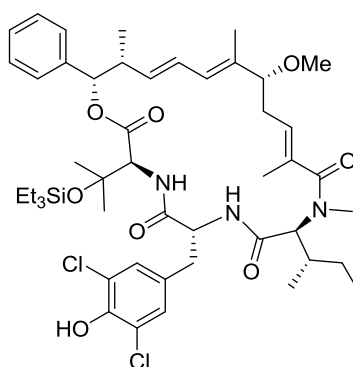
¹³C NMR (101 MHz, CDCl₃) δ 170.4, 169.3, 155.8, 147.2, 138.3, 135.5, 134.5, 132.4, 131.8, 129.9, 129.3, 128.3, 128.2, 128.0, 127.5, 127.0, 121.4, 118.4, 86.2, 80.9, 74.4, 66.3, 61.7, 60.3, 56.2, 56.1, 42.1, 37.2, 34.2, 33.4, 32.4, 29.8, 28.7, 27.7, 26.6, 25.2, 16.8, 16.0, 11.2, 7.0, 6.5 ppm.

ESI-HRMS: *m/z* calc. for C₅₅H₇₉N₃O₁₁Cl₂SiNa [M+Na]⁺: 1078.4759, found: 1078.4755.

[α]_D²⁰ = -34.7 (c 1, CHCl₃).

R_f = 0.25 (3:1 = petroleum ether: acetone).

Macrolactone **S13**



S13

C₄₈H₆₉Cl₂N₃O₈Si
913,4231

Phenylsilane (11.7 μ l, 94.6 μ mol, 4.0 equiv) and tetrakis(triphenylphosphine)palladium(0) (2.5 mg, 2.4 μ mol, 0.1 equiv) were successively added to a solution of ally ester **20** (25 mg, 23.7 μ mol, 1.0 equiv) in dichloromethane (0.47 mL) and the mixture stirred for 1 h. Filtration through Celite[®] (dichloromethane, 10 mL) and concentration *in vacuo* provided amino acid **S14** which was directly submitted to the next step.

COMU[®] (10.0 mg, 23.7 μ mol, 1.0 equiv) in *N,N*-dimethylformamide (0.4 mL) was added to a solution of amino acid **S14** and diisopropylamine (16 μ l, 94.6 μ mol, 4.0 equiv) in *N,N*-dimethylformamide (2.0 mL) over a period of 2 h using a syringe pump. The reaction mixture was stirred at room temperature for 13 h and at 80 °C for 3 d. After cooling to room temperature ethyl acetate (2 mL) and water (2 mL) were added and the aqueous layer was extracted with ethyl acetate (3x 2 mL). The combined organic layers were washed with aqueous hydrochloric acid (1 M, 5 mL) saturated aqueous sodium bicarbonate solution (5 mL) and saturated aqueous sodium chloride solution (10 mL), dried over sodium sulfate and concentrated *in vacuo*. The residue was purified by flash column chromatography (silica, 5:1 = petroleum ether: acetone) to provide macrolactone **S13** (14.7 mg, 15.7 μ mol, 66% over 2 steps).

¹H NMR (400 MHz, CDCl₃) δ 7.34 – 7.21 (m, 5H), 7.15 (s, 2H), 6.94 (d, *J* = 8.9 Hz, 1H), 6.73 (d, *J* = 8.7 Hz, 1H), 6.30 (ddd, *J* = 15.4, 10.6, 1.7 Hz, 1H), 5.93 (d, *J* = 1.5 Hz, 1H), 5.85 (d, *J* = 10.7 Hz, 1H), 5.75 (b, *J* = 15.3, 5.4 Hz, 1H), 5.75 (dd, *J* = 15.3, 5.4 Hz, 1H), 5.45 – 5.37 (m, 1H), 4.63 (d, *J* = 11.5 Hz, 1H), 4.47 (td, *J* = 10.2, 5.2 Hz, 1H), 4.39 (d, *J* = 8.7 Hz, 1H), 3.60 (dd, *J* = 10.7, 3.2 Hz, 1H), 3.22 (s, 3H), 3.05 (dd, *J* = 13.3, 10.2 Hz, 1H), 2.74 (dd, *J* = 13.2, 4.9 Hz, 1H), 2.61 (s, 3H), 2.64 – 2.55 (m, 2H), 2.42 - 2.34 (m, 1H), 2.22 – 2.12 (m, 1H), 1.82 (s, 3H), 1.76 (s, 3H), 1.38 (s, 3H), 1.42 – 1.29 (m, 2H), 1.09 (d, *J* = 6.9 Hz, 3H), 0.94 – 0.87 (m, 9H), 0.75 (t, *J* = 7.9 Hz, 9H), 0.36 (q, *J* = 7.9 Hz, 6H) ppm.

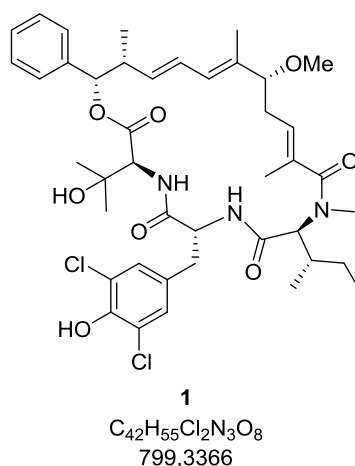
¹³C NMR (101 MHz, CDCl₃) δ 175.9, 170.5, 169.6, 169.5, 146.9, 139.2, 136.7, 135.5, 133.6, 130.2, 129.5, 128.5, 128.1, 127.7, 127.6, 126.8, 125.6, 121.1, 85.8, 79.9, 75.7, 61.0, 60.0, 56.1, 55.1, 42.2, 35.9, 32.3, 31.9, 30.4, 28.5, 27.5, 24.6, 16.1, 14.5, 11.5, 10.6, 10.5, 7.0, 6.6 ppm.

ESI-HRMS: *m/z* calc. for C₄₈H₆₉N₃O₈NaCl₂Si [M+Na]⁺: 936.4129, found: 936.4131.

[α]_D²⁰ = -40.7 (c 0.7, CHCl₃).

R_f = 0.28 (3:1 = petroleum ether: acetone).

Nannocystin Ax (1)



Tetrabutylammonium fluoride (1 M in tetrahydrofuran, 26 μ L, 26 μ mol, 10 equiv) was added to a solution of TES ether **S13** (2.4 mg, 2.6 μ mol, 1.0 equiv) in tetrahydrofuran (0.2 mL) at 0 °C. The solution was stirred at 0 °C for 1 h, diluted with ethyl acetate (5 mL) and water (5 mL) and the aqueous layer extracted with ethyl acetate (3 x 3 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (2 mL), dried over sodium sulfate and concentrated *in vacuo*. The residue was purified by flash column chromatography (silica, 5:1 \rightarrow 2:1 = petroleum ether: acetone) to provide Nannocystin Ax (**1**) (1.7mg, 2.1 μ mol, 82%).

¹H NMR (500 MHz, DMSO-*d*₆) δ 8.49 (d, *J* = 9.9 Hz, 1H), 7.86 (d, *J* = 9.4 Hz, 1H), 7.53 (d, *J* = 7.6 Hz, 2H), 7.37 (s, 2H), 7.32 (t, *J* = 7.6 Hz, 2H), 7.25 (t, *J* = 7.2 Hz, 1H), 6.38 – 6.32 (m, 1H), 6.04 (d, *J* = 10.8 Hz, 1H), 5.99 (dd, *J* = 15.3, 4.6 Hz, 1H), 5.88 (bs, 1H), 5.14 (t, *J* = 6.4 Hz, 1H), 5.09 (s, 1H), 4.76 - 4.69 (m, 1H), 4.62 (d, *J* = 9.9 Hz, 1H), 4.52 (d, *J* = 11.2 Hz, 1H), 3.59 – 3.52 (m, 1H), 3.08 (s, 3H), 2.82 – 2.77 (m, 1H), 2.73 (s, 3H), 2.68 – 2.62 (m, 1H), 2.62 – 2.55 (m, 1H), 2.39 – 2.34 (m, 2H), 1.77 - 1.74 (m, 1H), 1.72 (s, 3H), 1.66 (s, 3H), 1.24-1.20 (m, 1H), 1.10 (s, 3H), 1.02 (s, 3H), 0.93 (d, *J* = 6.8 Hz, 3H), 0.88 (m, 1 H), 0.76 (t, *J* = 7.3 Hz, 3H), 0.43 (d, *J* = 6.5 Hz, 3H) ppm.

¹³C NMR (125 MHz, DMSO-*d*₆) δ 173.3, 171.2, 171.0, 169.6, 147.8, 140.2, 137.8, 134.4, 134.0, 131.3, 130.1, 128.9, 128.3, 127.5, 126.5, 125.6, 125.3, 122.0, 85.4, 79.3, 72.2, 59.7, 59.4, 55.5, 53.4, 42.1, 37.0, 32.2, 31.8, 30.9, 28.6, 25.0, 24.5, 14.9, 14.4, 11.6, 10.7, 10.5 ppm.

ESI-HRMS: *m/z* calc. für C₄₂H₅₅N₃O₈NaCl₂ [M+Na]⁺: 822.3264 , gefunden: 822.3265.

[α]_D²⁰ = -70.8 (c 0.3, CH₃OH); lit.: -67.4 (c 0.3, CH₃OH)⁵.

R_f = 0.38 (2:1 = petroleum ether: acetone).

The analytical data are in accordance with the literature.^{4,5}

NMR comparison to natural sample⁴ and synthetic sample by Liu⁵

The recorded ¹H- and ¹³C-NMR data for our synthetic Nannocystin Ax (**1**) are compared to the natural sample by Hoepfner *et. al.*⁴ and the synthetic sample by Liu *et. al.*⁵:

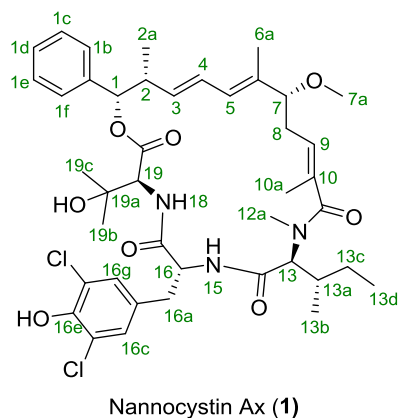


Table 1: Comparison of ¹H-NMR Data.

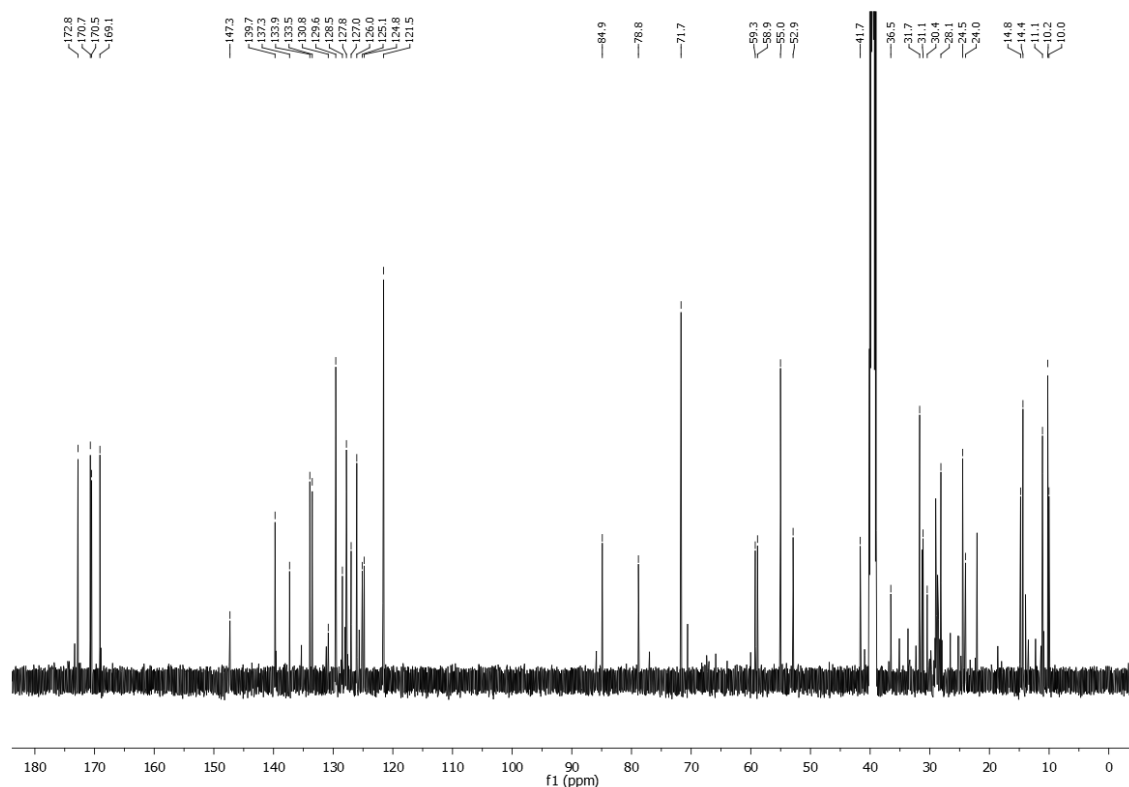
position	Natural sample δ_H , mult (J in Hz)	Synthetic sample by Liu δ_H , mult (J in Hz)	Synthetic sample (this work) δ_H , mult (J in Hz)
1	5.89, br	5.89, br	5.88, bs
1b	7.54, d (7.6)	7.54, d (7.6)	7.53, d (7.6)
1c	7.32, t (7.6)	7.32, t (7.6)	7.32, t (7.6)
1d	7.25, t (7.6)	7.25, t (7.3)	7.25, t (7.2)
1e	7.32, t (7.6)	7.32, t (7.6)	7.32, t (7.6)
1f	7.54, d (7.6)	7.54, d (7.6)	7.53, d (7.6)
2	2.65, m	2.65, m	2.68-2.62, m
2a	0.93, d (6.7)	0.93, d, (6.8)	0.93, d (3H)
3	6.01, m	6.00, m	5.99, dd (15.3, 4.6)
4	6.35, m	6.35, m	6.38-6.32, m
5	6.02, m	6.05, m	6.04, d (10.8)
6a	1.65, s	1.65, s	1.66, s
7	3.53, m	3.54, m	3.59-3.52, m
7a	3.07, s	3.08, s	3.08, s
8	2.36, m	2.35, m	2.39-2.34, m
9	5.13, m	5.14, m	5.14, t (6.4)
10a	1.71, s	1.72, s	1.72, s
12a	2.74, s	2.74, s	2.73, s

13	4.51, d (11.1)	4.52, d (11.2)	4.52, d (11.2)
13a	1.74, m	1.73, m	1.77-1.74, m
13b	0.41, d (6.6)	0.42, d (6.5)	0.43, d (6.5)
13c	0.89, m	0.89, m	0.90-0.86, m
	1.22, m	1.22, m	1.24-1.20, m
13d	0.76, t (7.2)	0.76, t, (7.3)	0.76, t (7.3)
15	7.92, d (9.6)	7.90, d (9.5)	7.86, d (9.4)
16	4.70, m	4.72, m	4.76-4.69, m
16a	2.59, m	2.59, m	2.62-2.55, m
	2.80, m	2.80, m	2.82-2.77, m
16c	7.38, s	7.38, s	7.37, s
16e-OH	n.d.	9.81, s	n.d.
16g	7.38, s	7.38, s	7.37, s
18	8.53, d (10.0)	8.52, d (9.9)	8.49, d (9.9)
19	4.63, m	4.63, m	4.62, d (9.9)
19a-OH	5.14, s	5.11, s	5.09, s
19b	1.10, s	1.11, s	1.10, s
19c	1.02, s	1.02, s	1.02, s

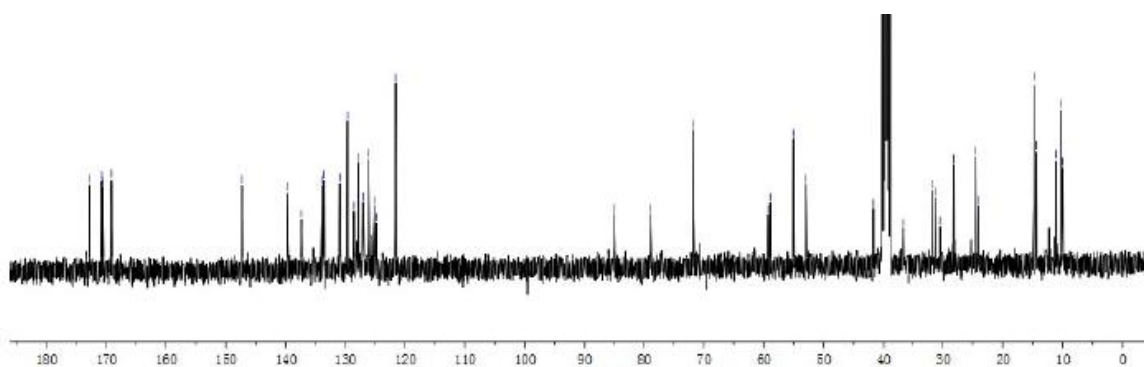
Table 2: Comparison of ^{13}C NMR data (no ^{13}C NMR data available for natural sample).

Synthetic sample by Liu	Synthetic sample (this work)
δ_{C}	δ_{C}
172.8	173.3
170.7	171.2
170.5	171.0
169.1	169.6
147.3	147.8
139.8	140.2
137.4	137.8
133.9	134.4
133.5	134.0
130.9	131.3
129.6	130.1
128.5	128.9
127.8	128.3
127.0	127.5
126.1	126.5
125.1	125.6
124.8	125.3
121.6	122.0
84.9	85.4
78.9	79.3
71.7	72.2
59.3	59.7
58.9	59.4
55.0	55.5
52.9	53.4
41.7	42.1
36.6	37.0
31.7	32.2
31.2	31.8
30.5	30.9
28.2	28.6

24.5	25.0
24.0	24.0
14.8	14.9
14.4	14.4
11.1	11.6
10.2	10.7
10.0	10.5



This work
125 MHz, DMSO- d_6



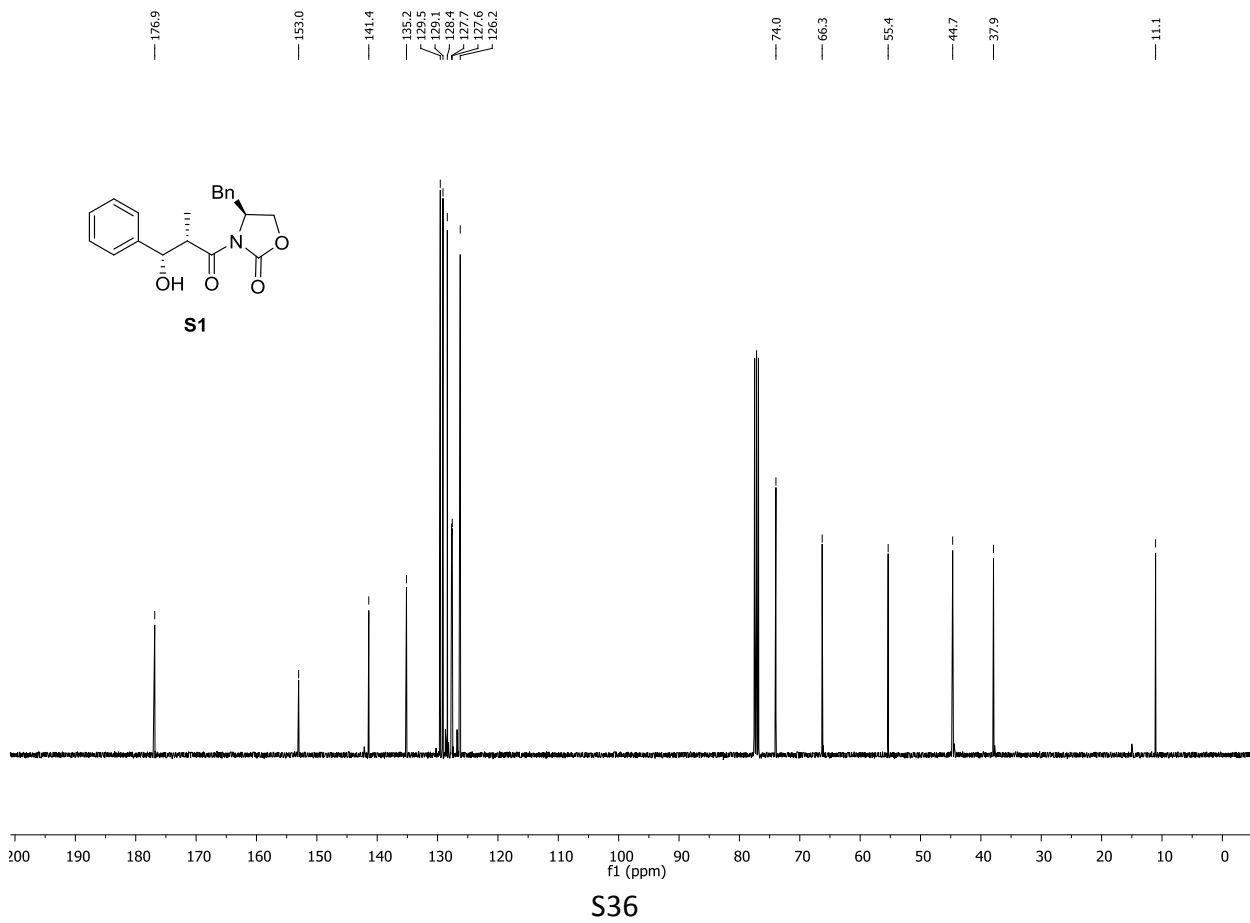
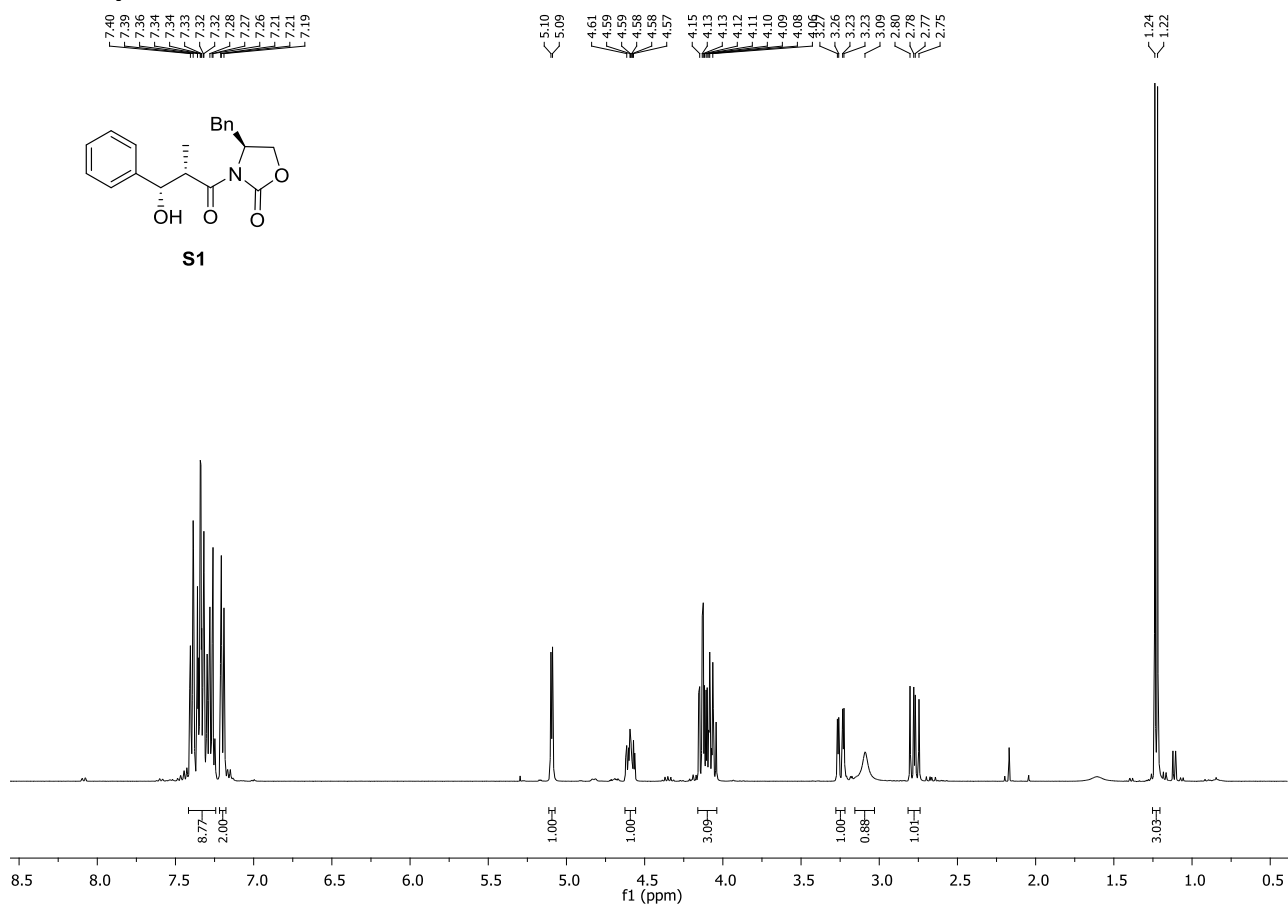
Liu, B., et. al.
100 MHz, DMSO- d_6

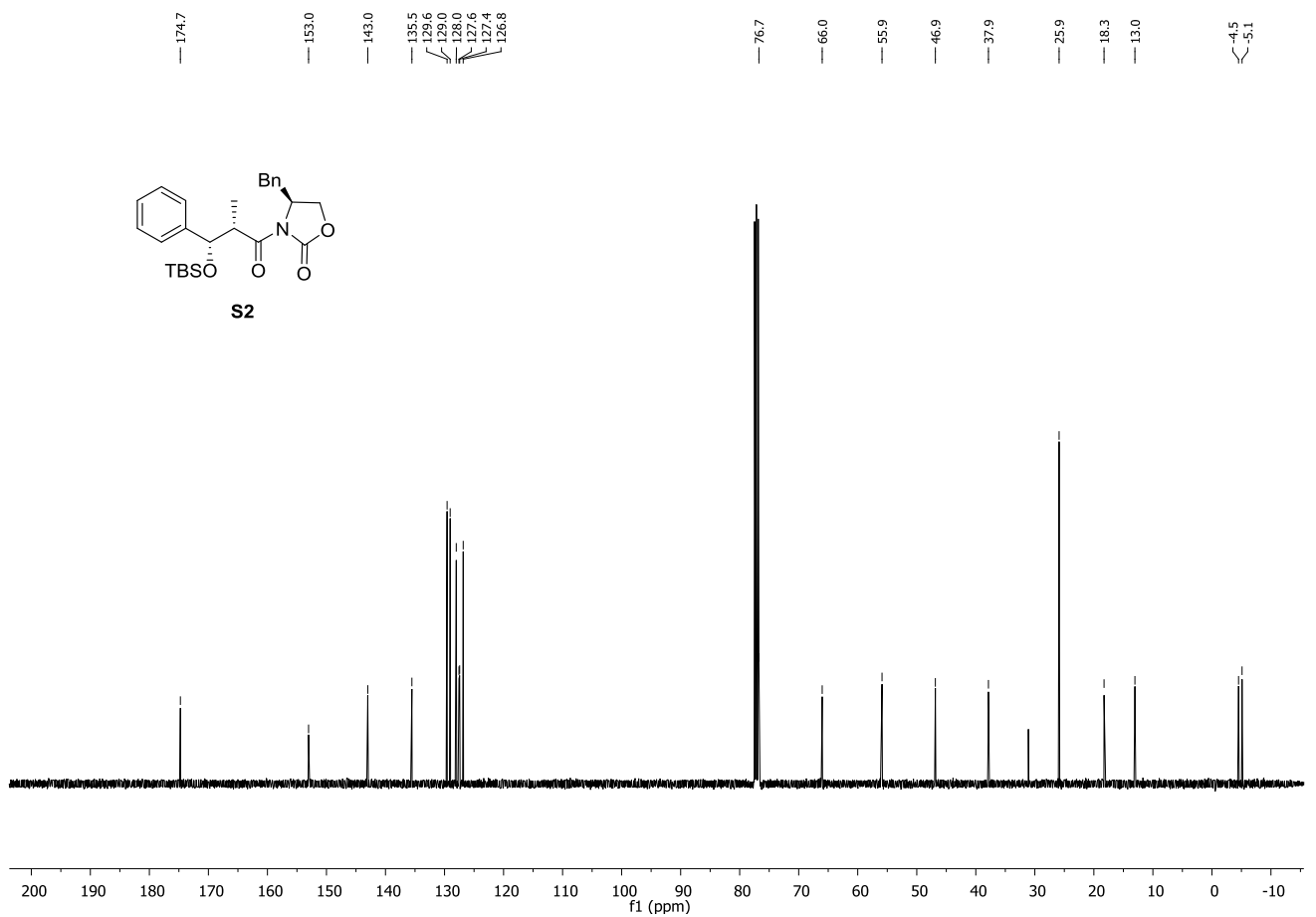
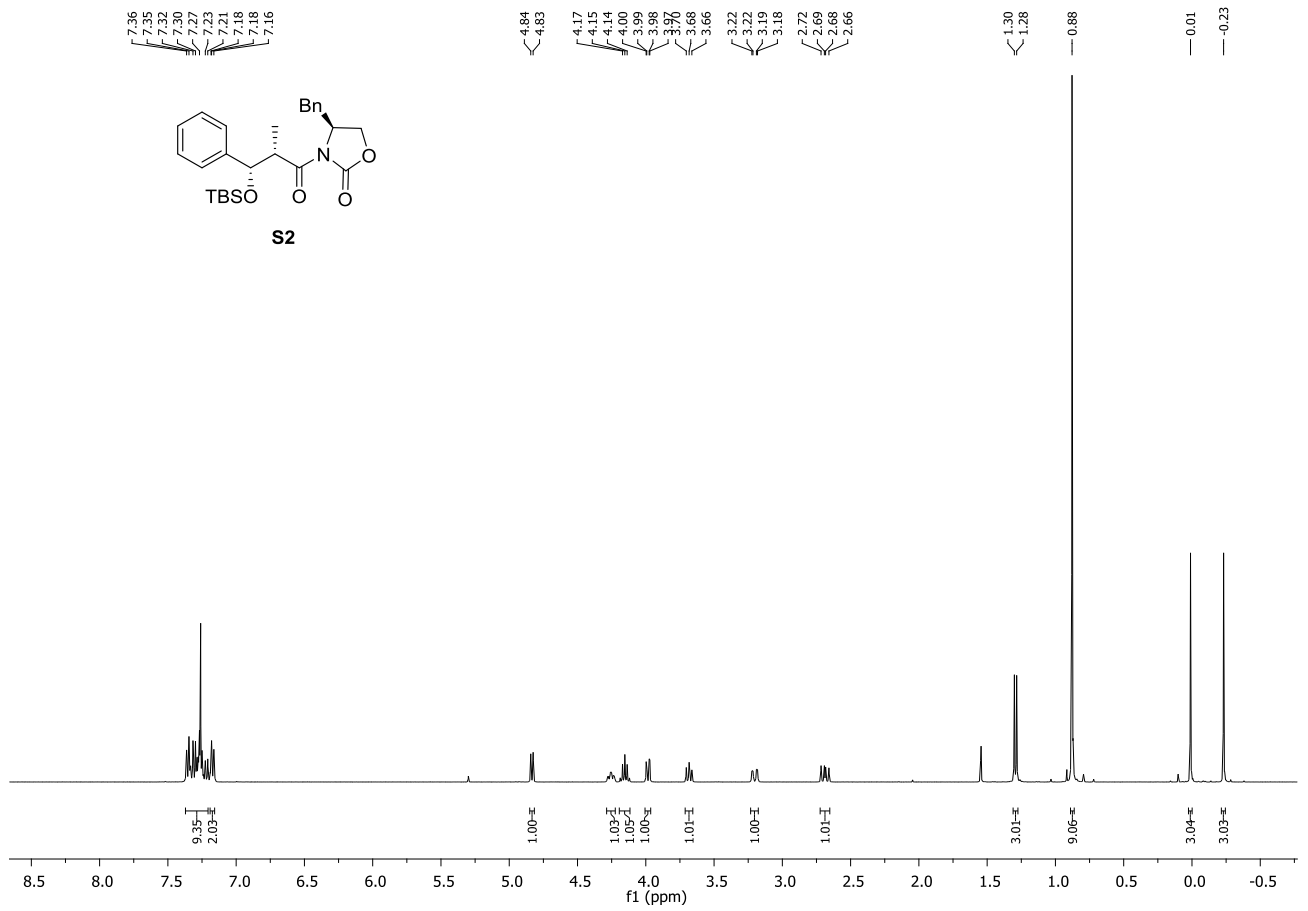
Figure 3: Comparison of ^{13}C -NMR spectra.

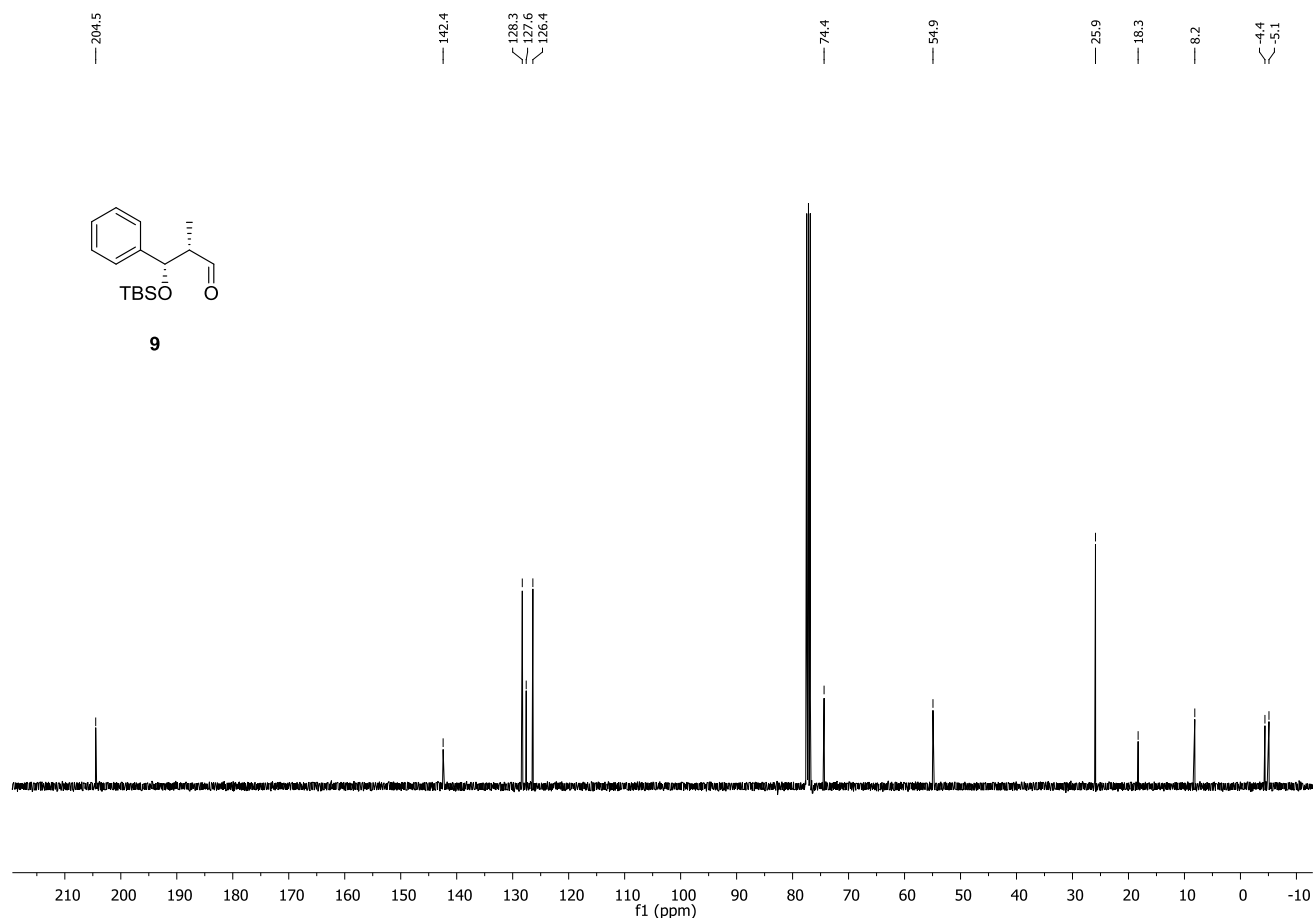
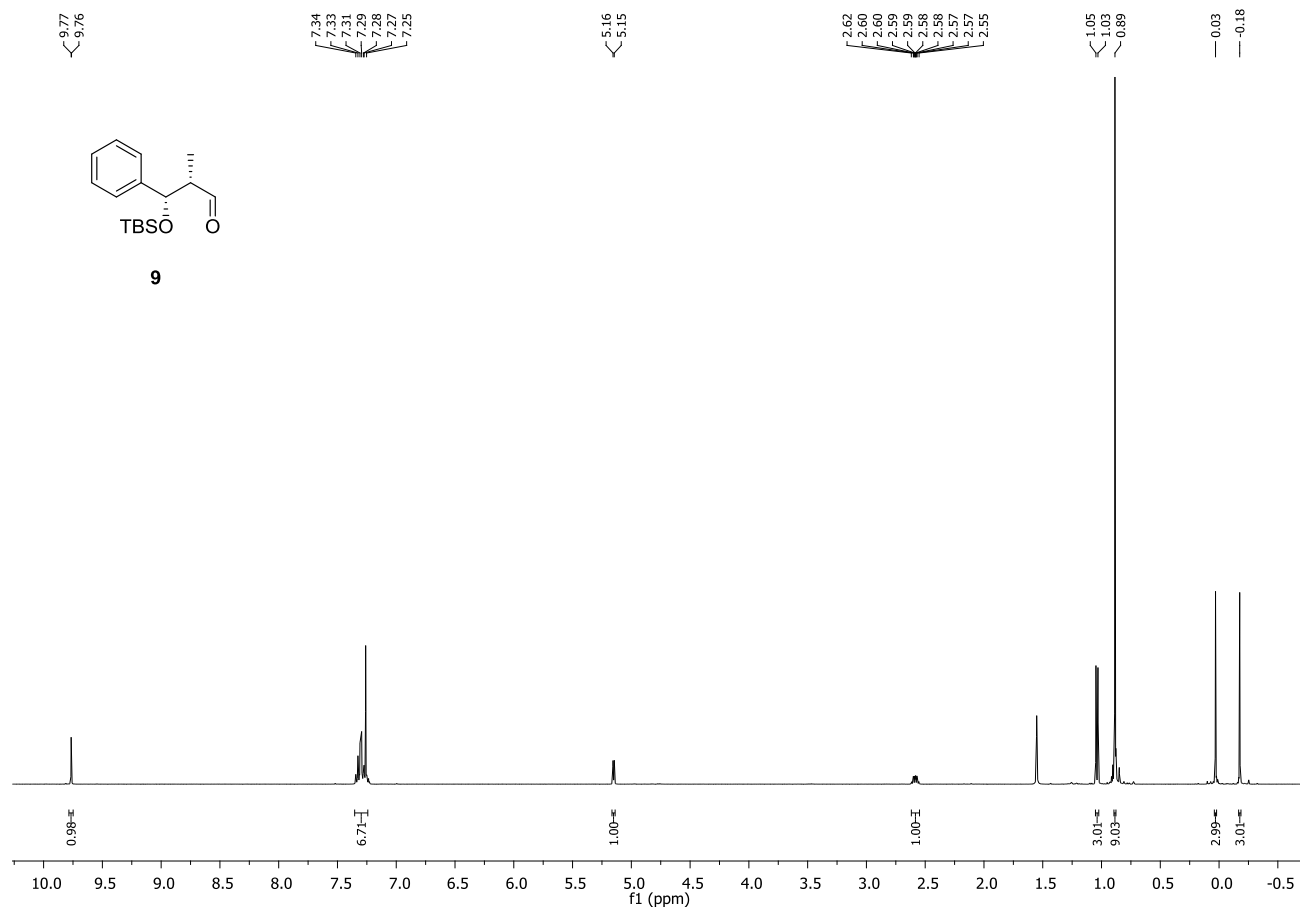
References

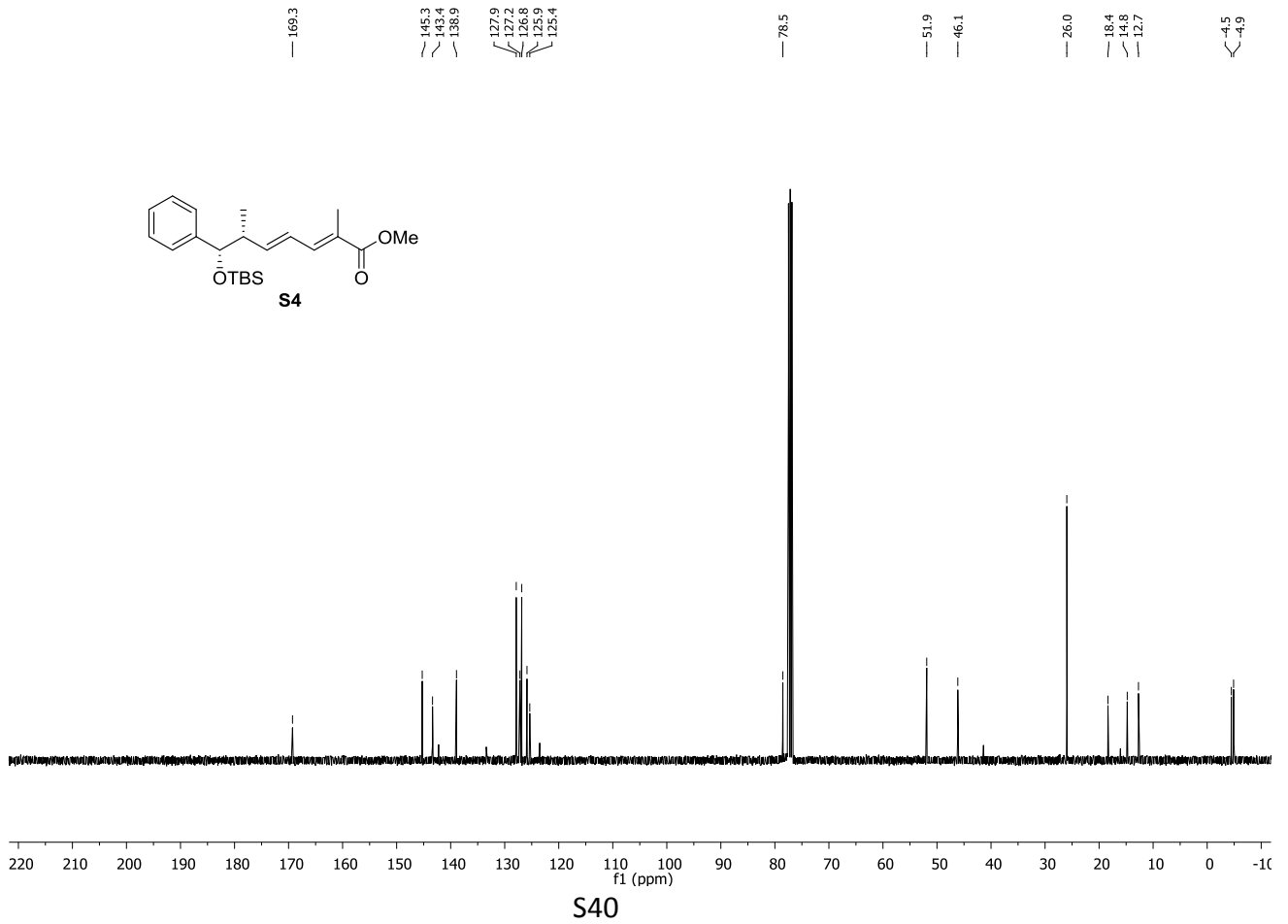
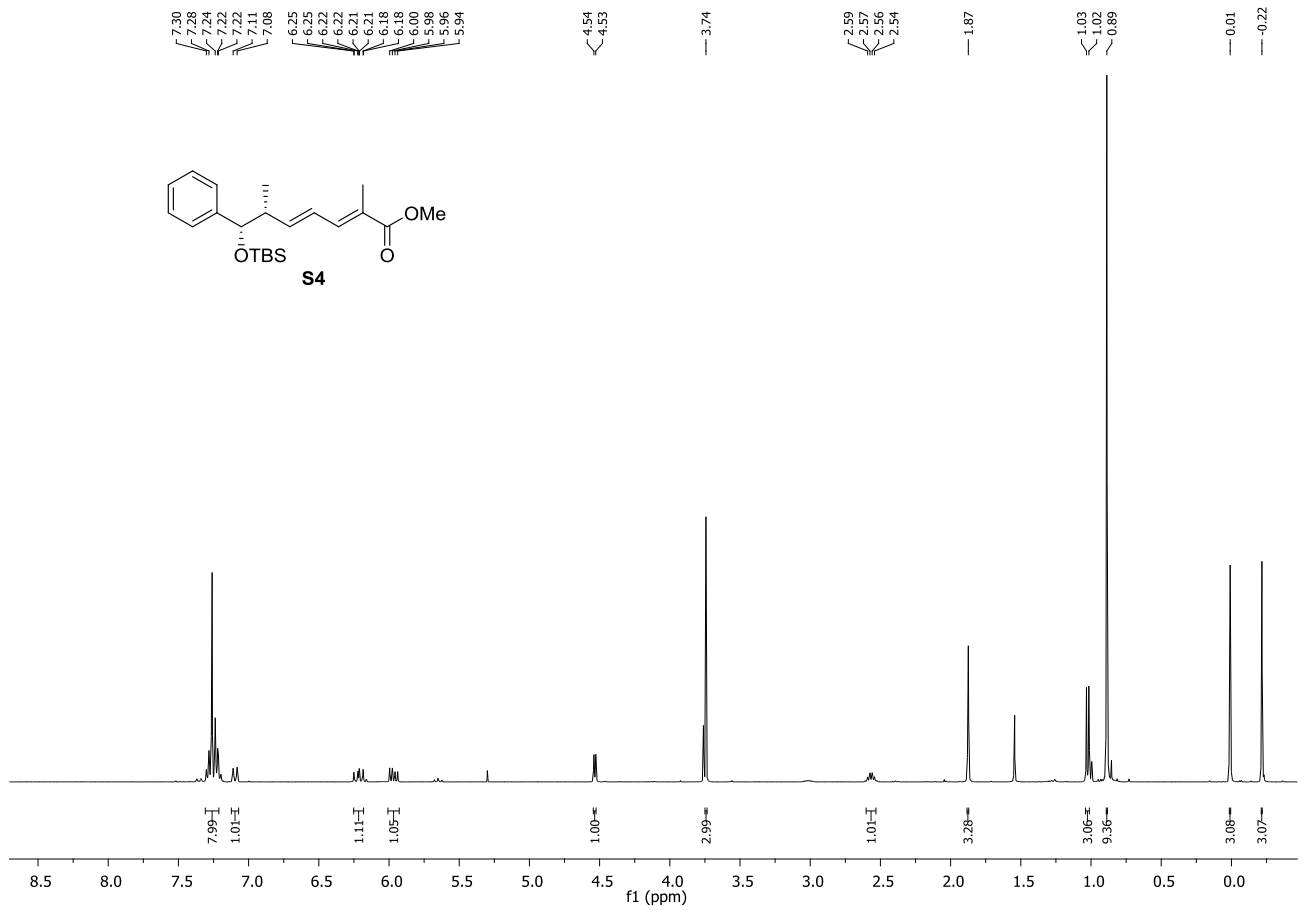
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- (5) Zhang, Y.-H.; Liu, R.; Liu, B.; *Chem. Comm.* **2017**, *53*, 5549 - 5552.

NMR Spectra

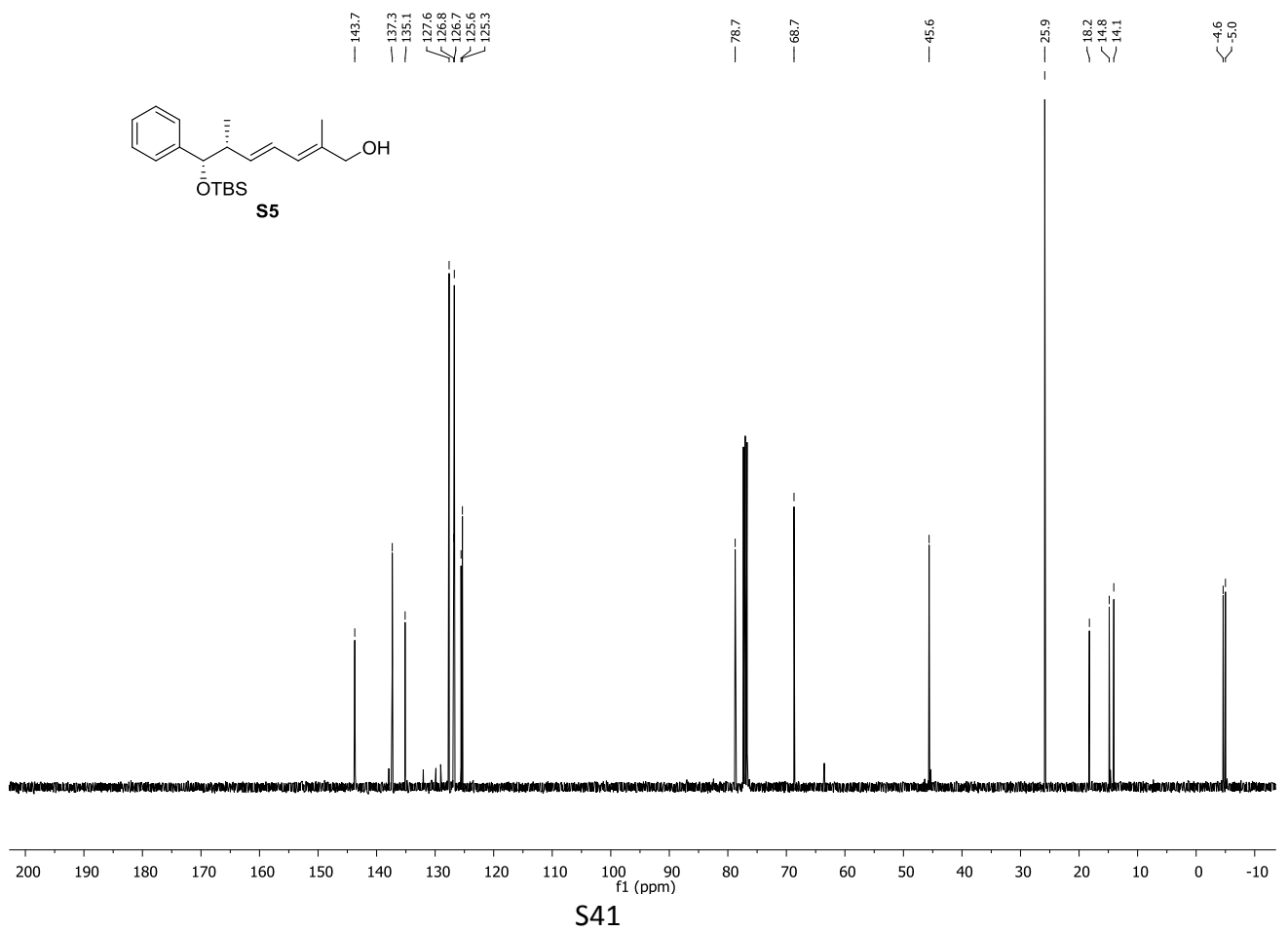
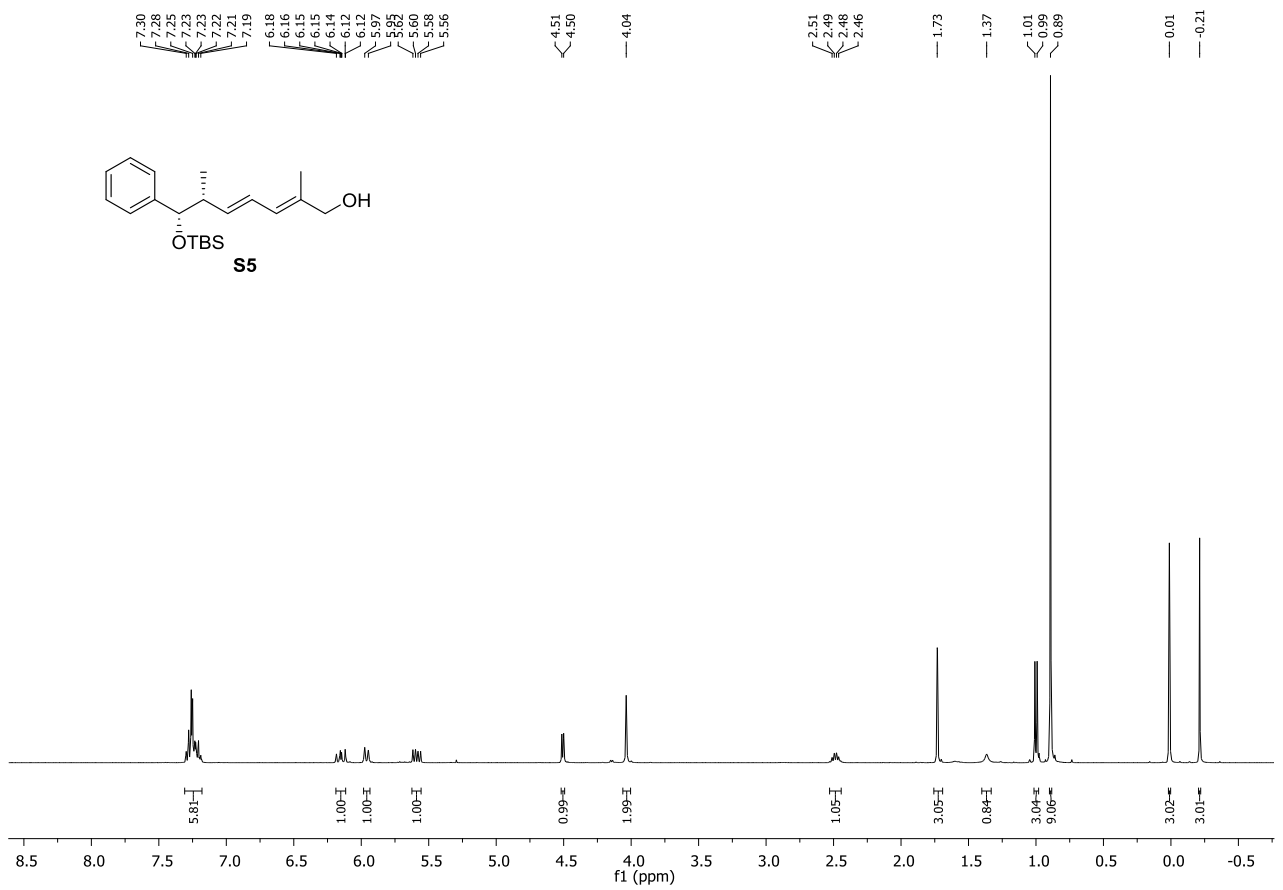


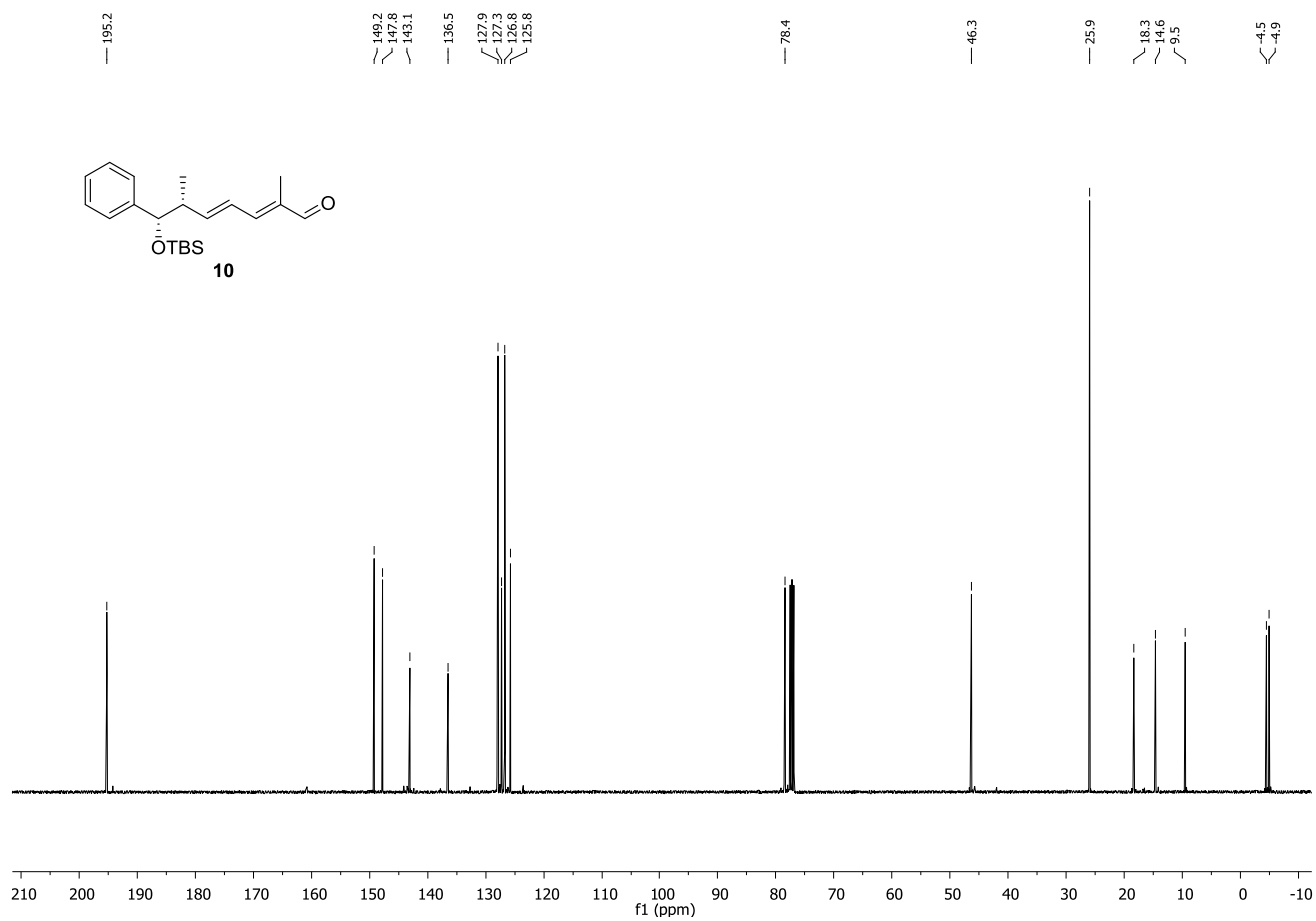
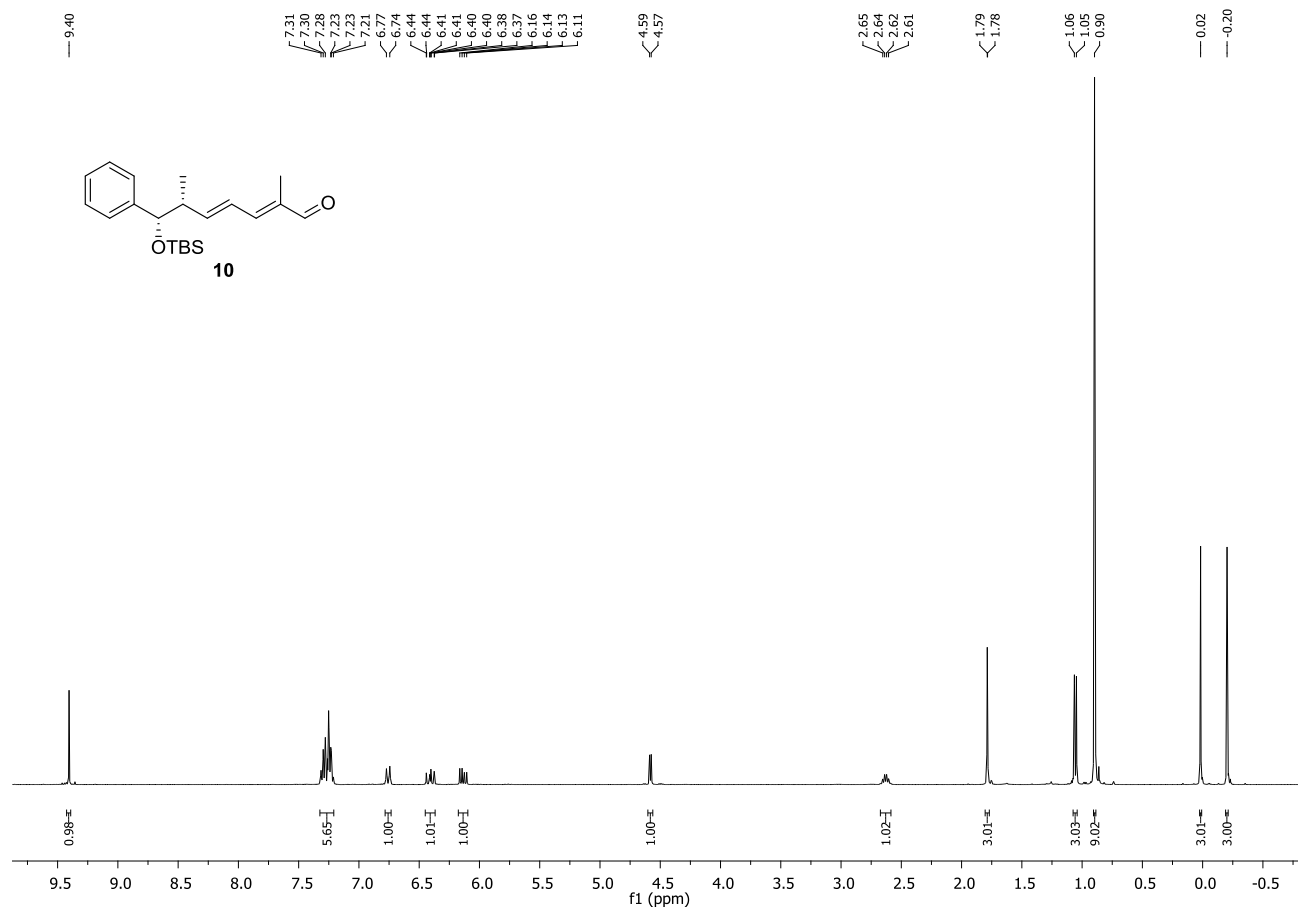


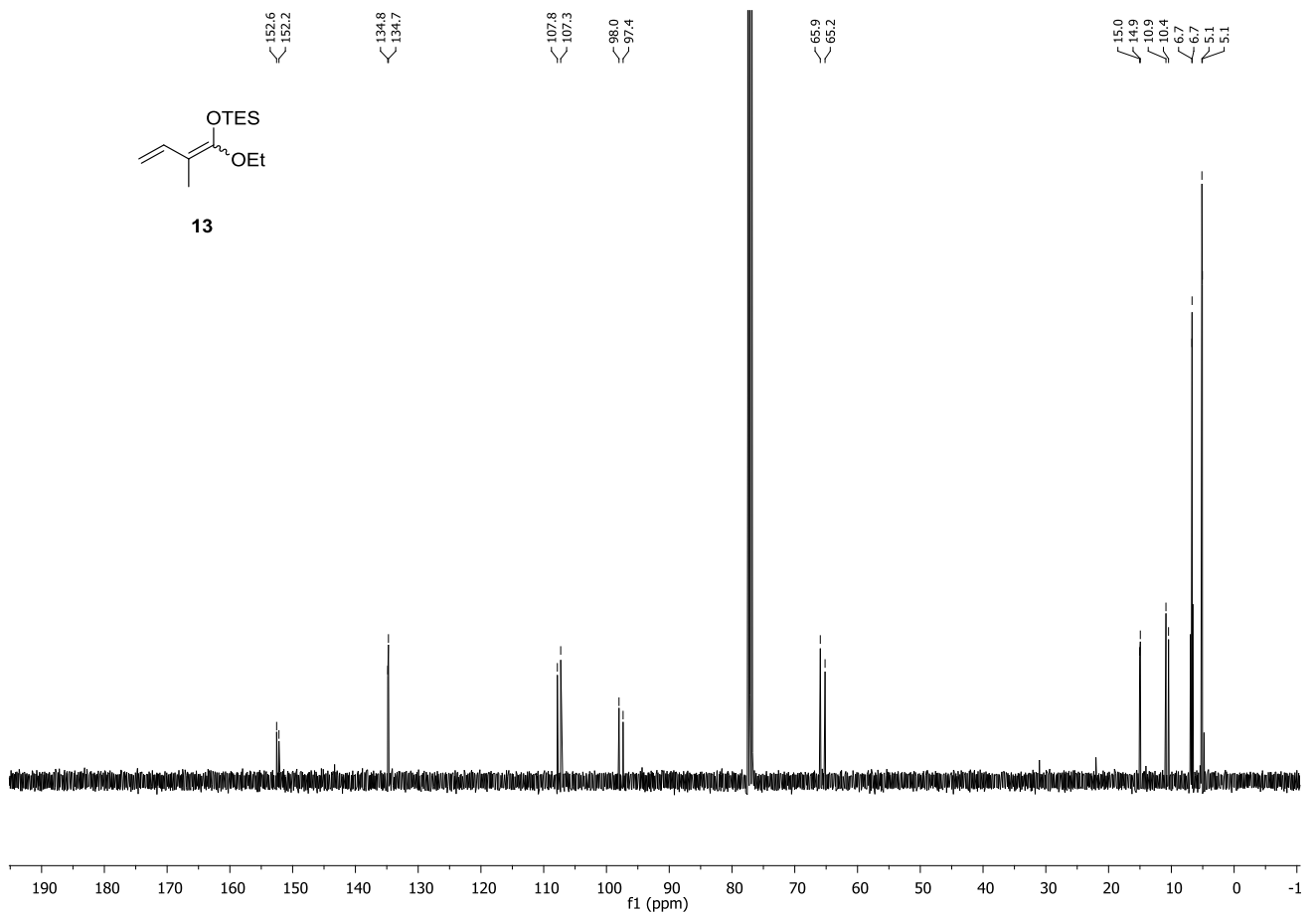
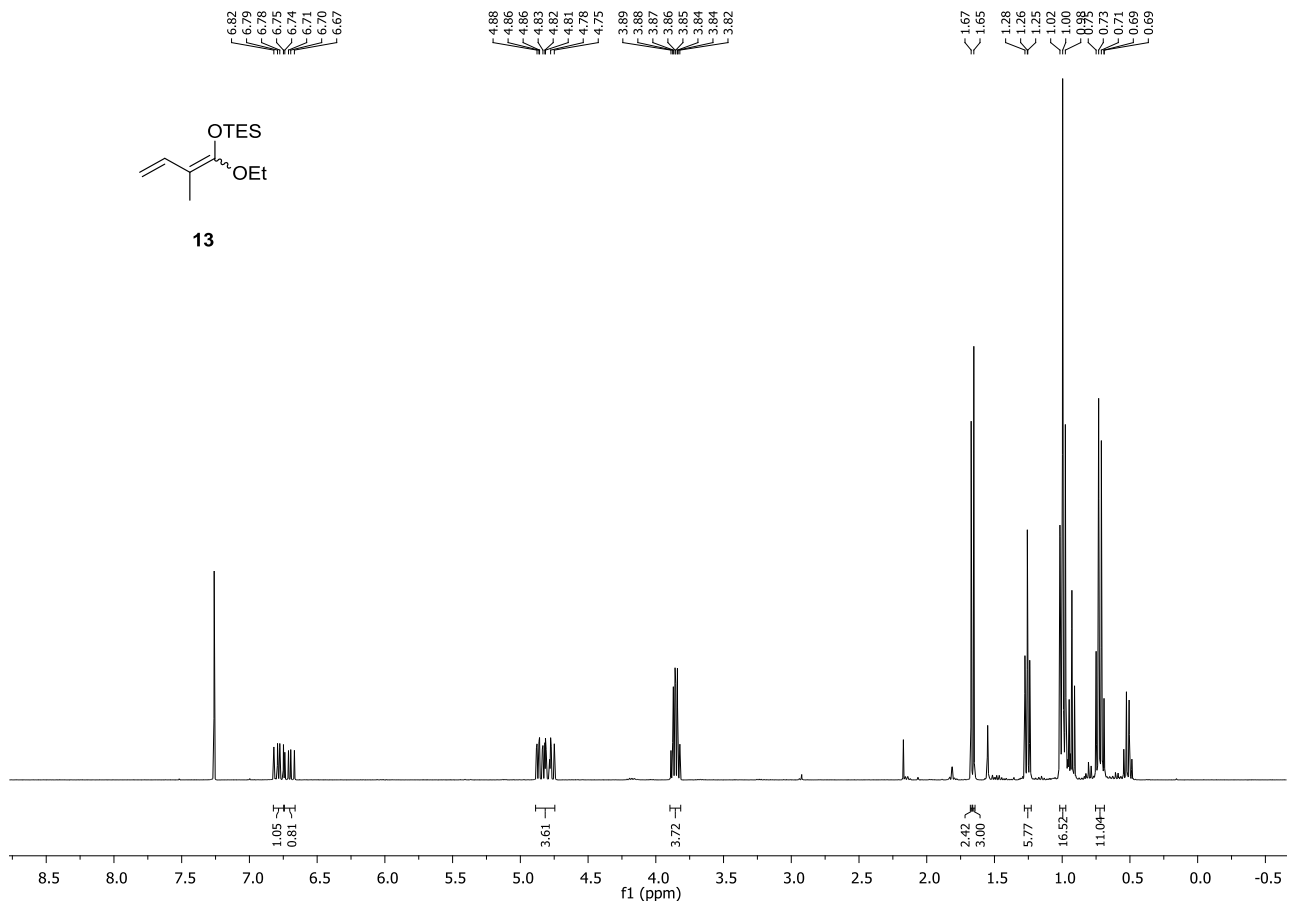


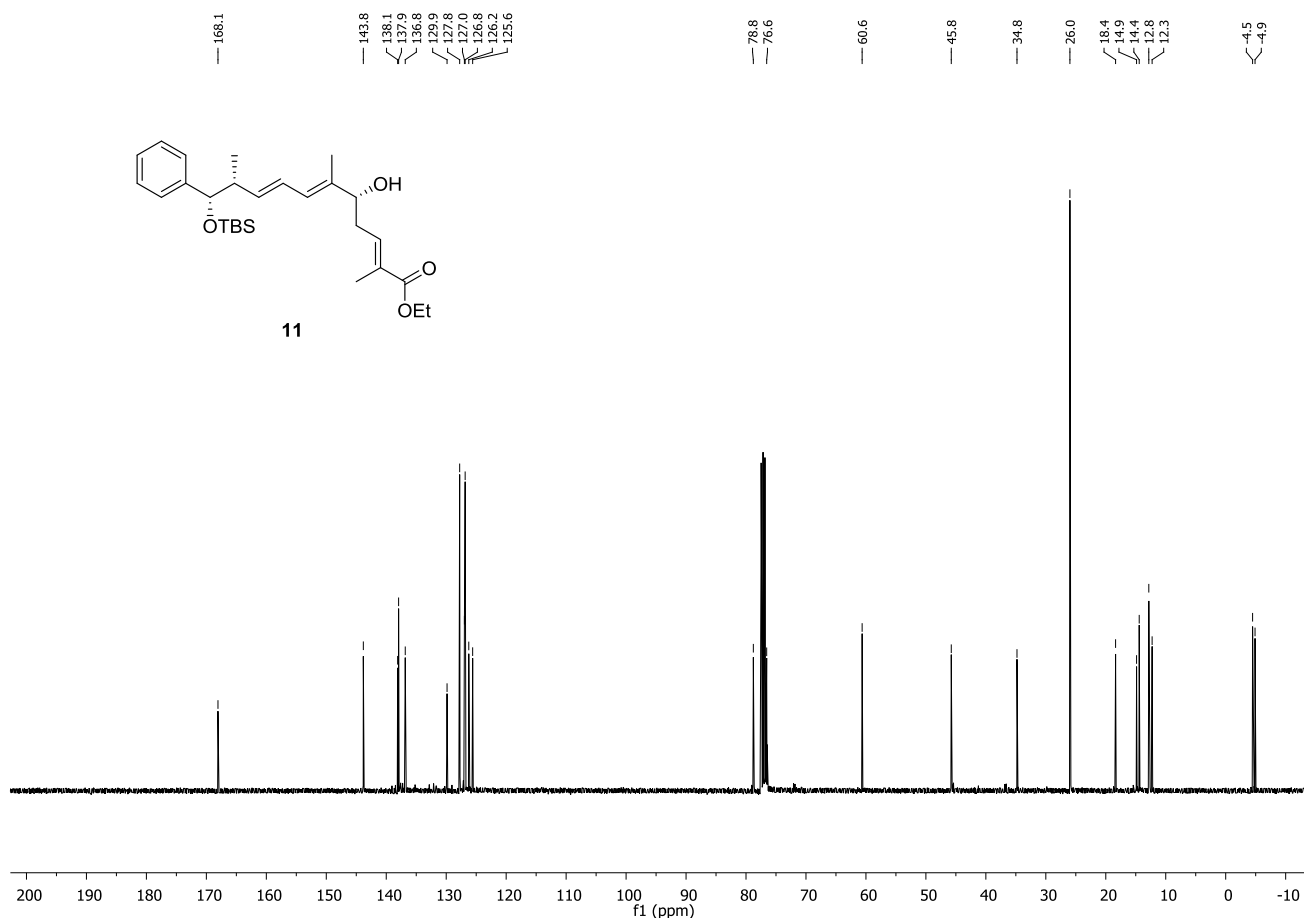
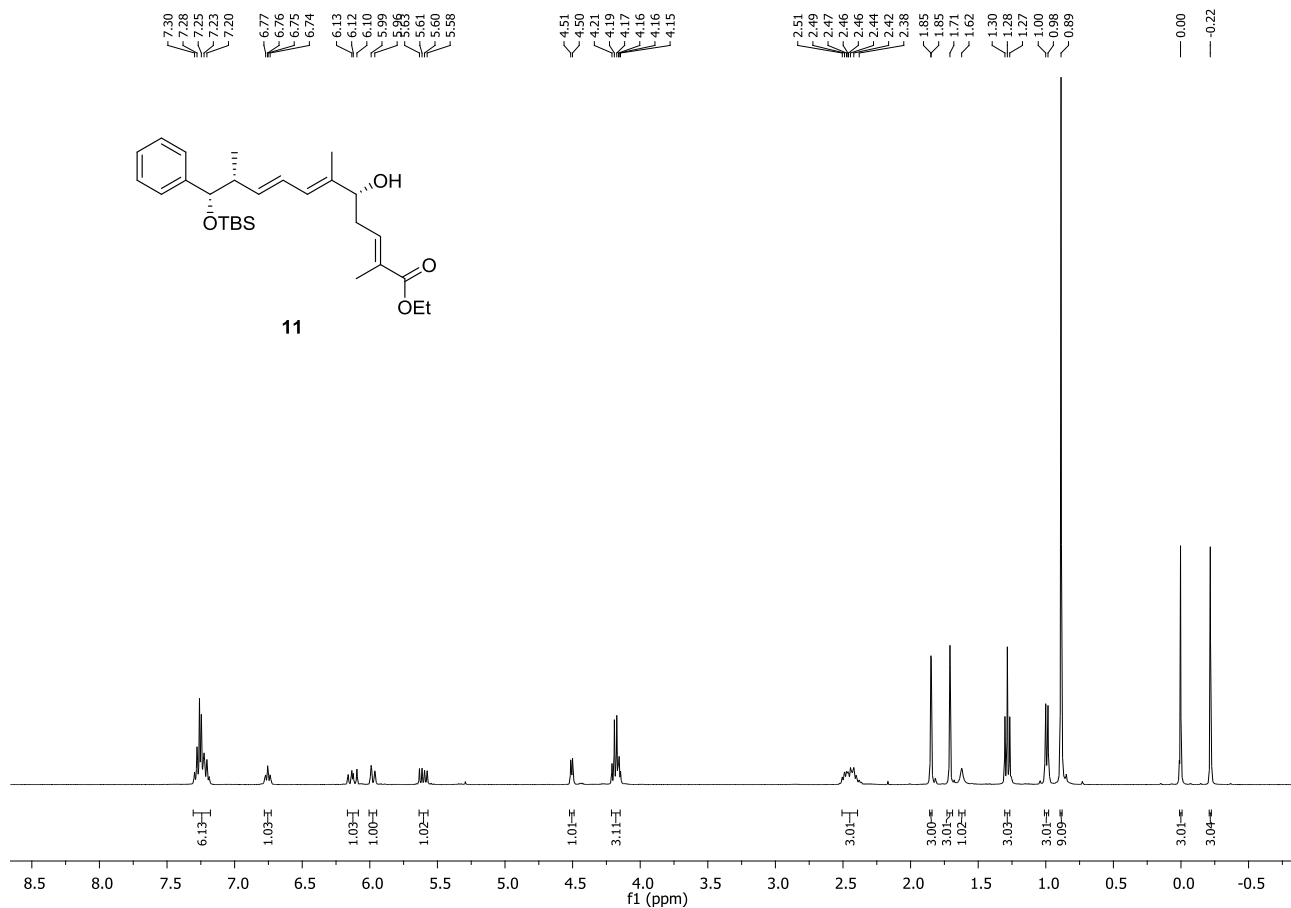


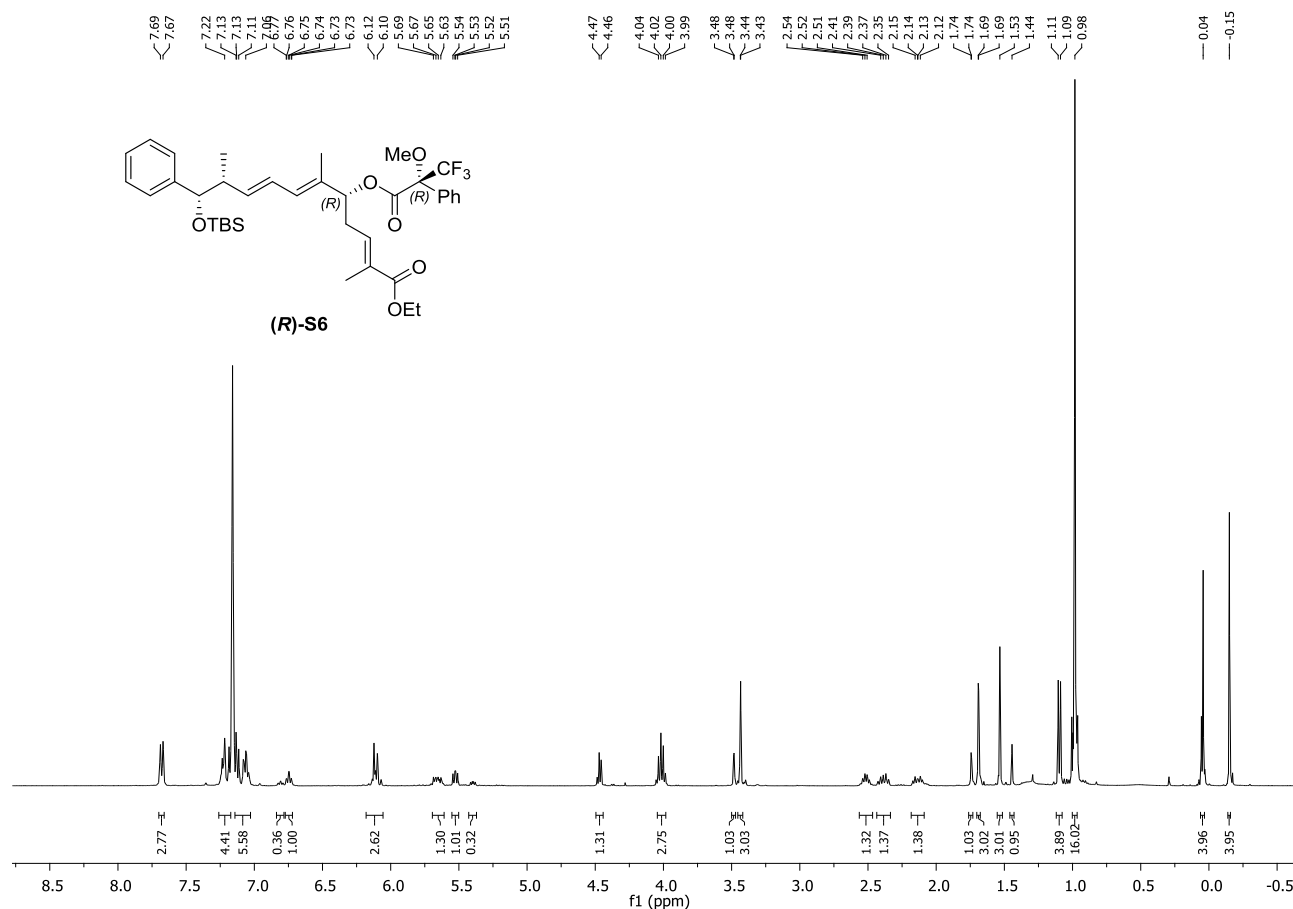
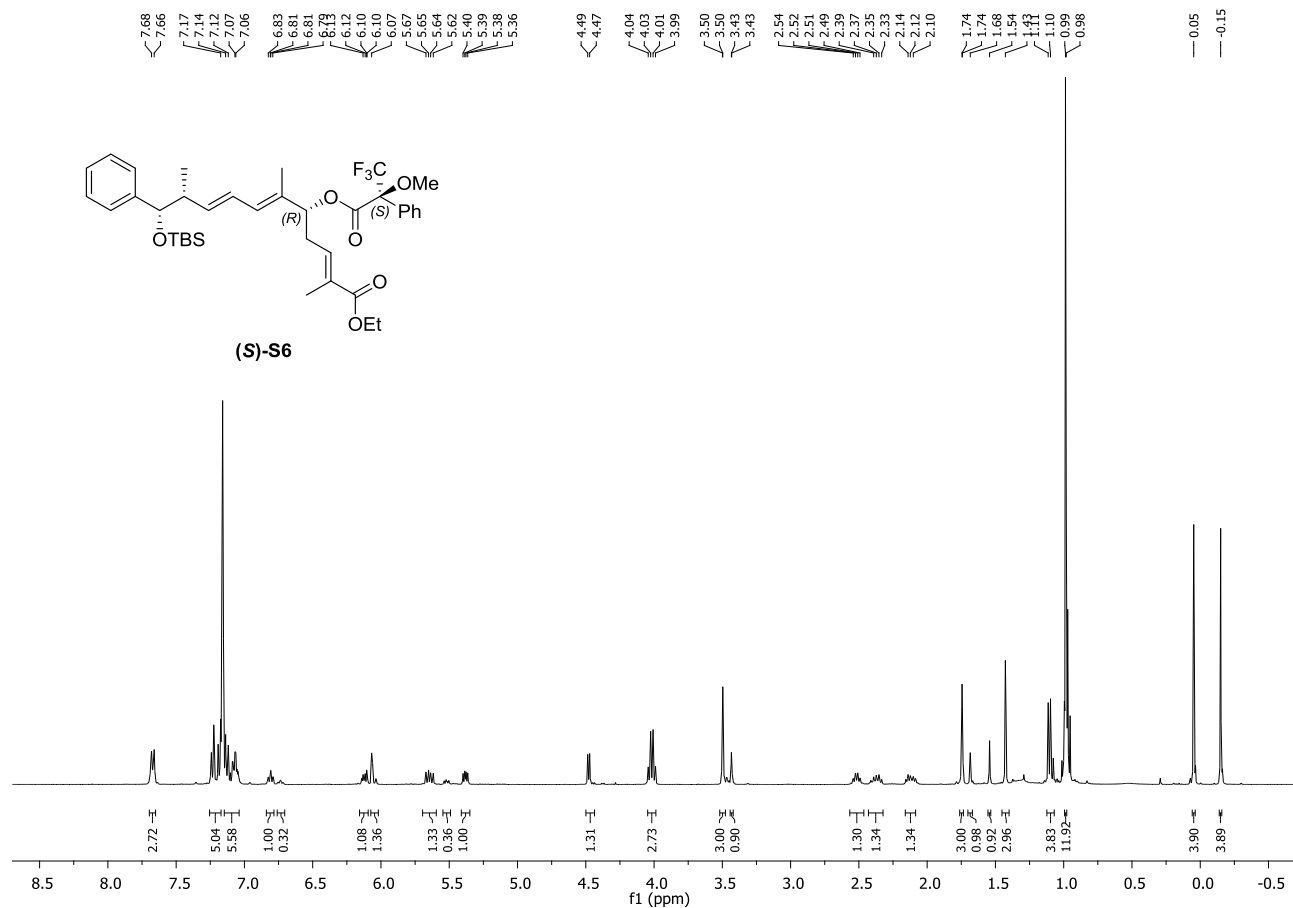
S40

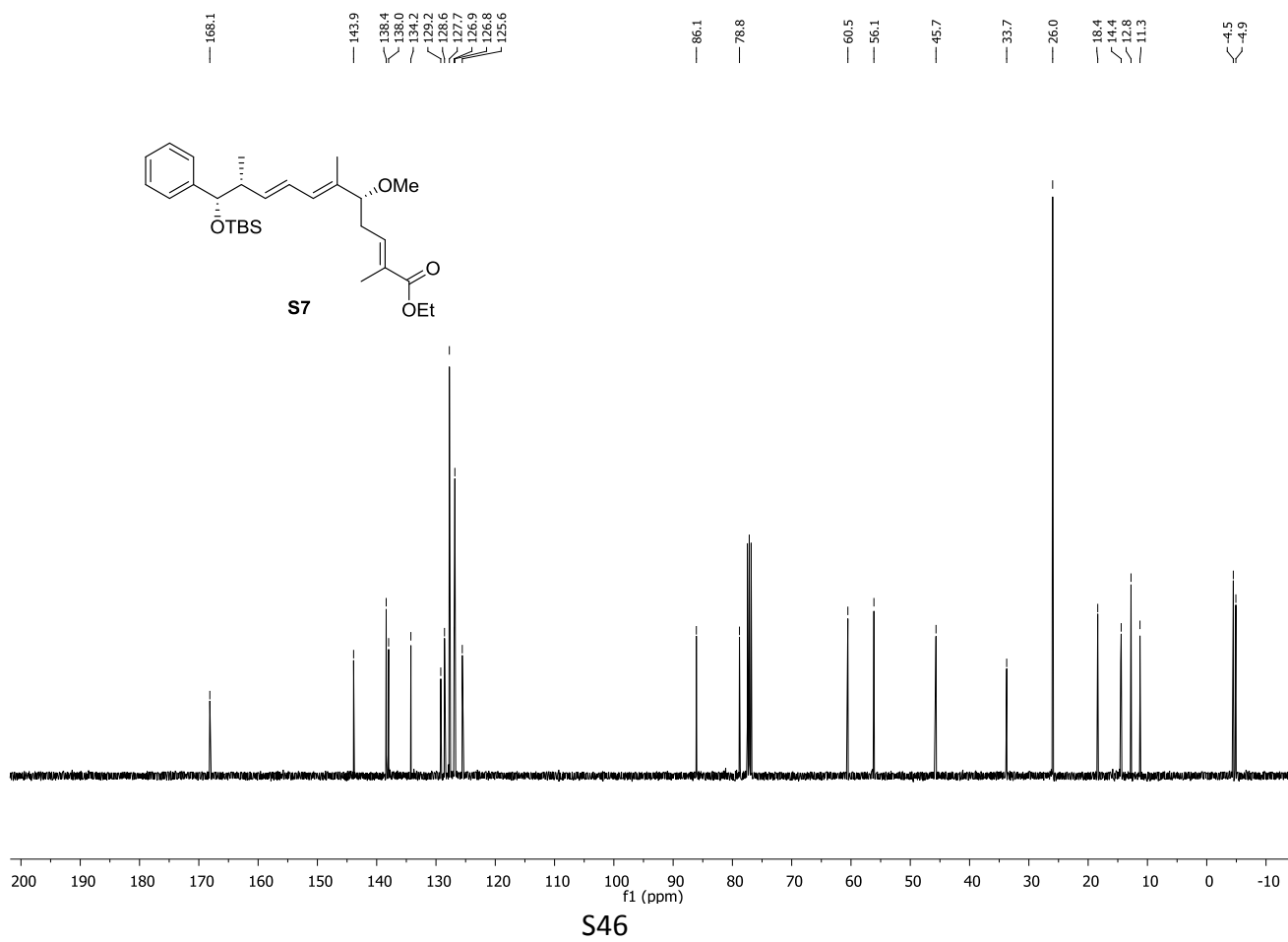
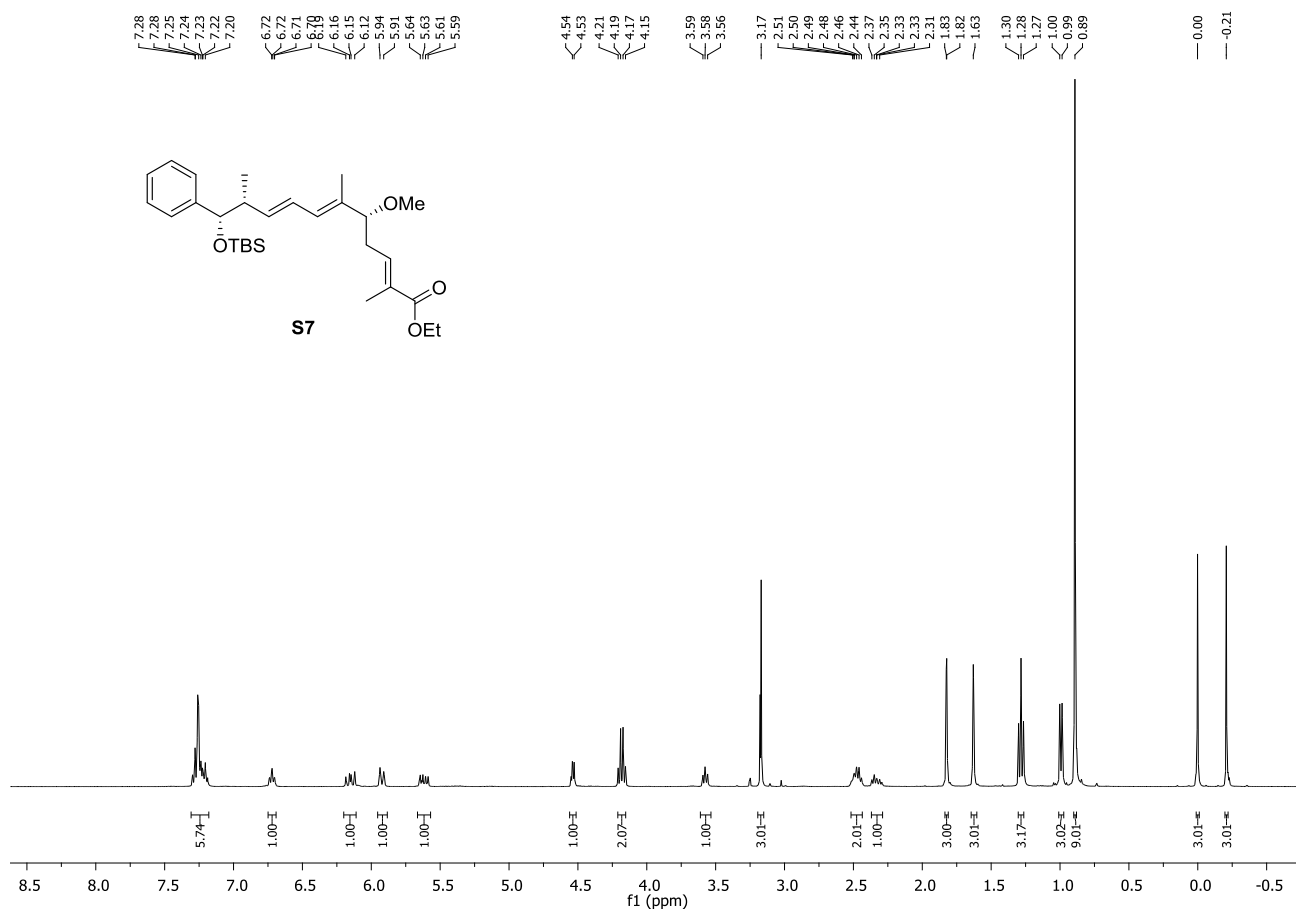


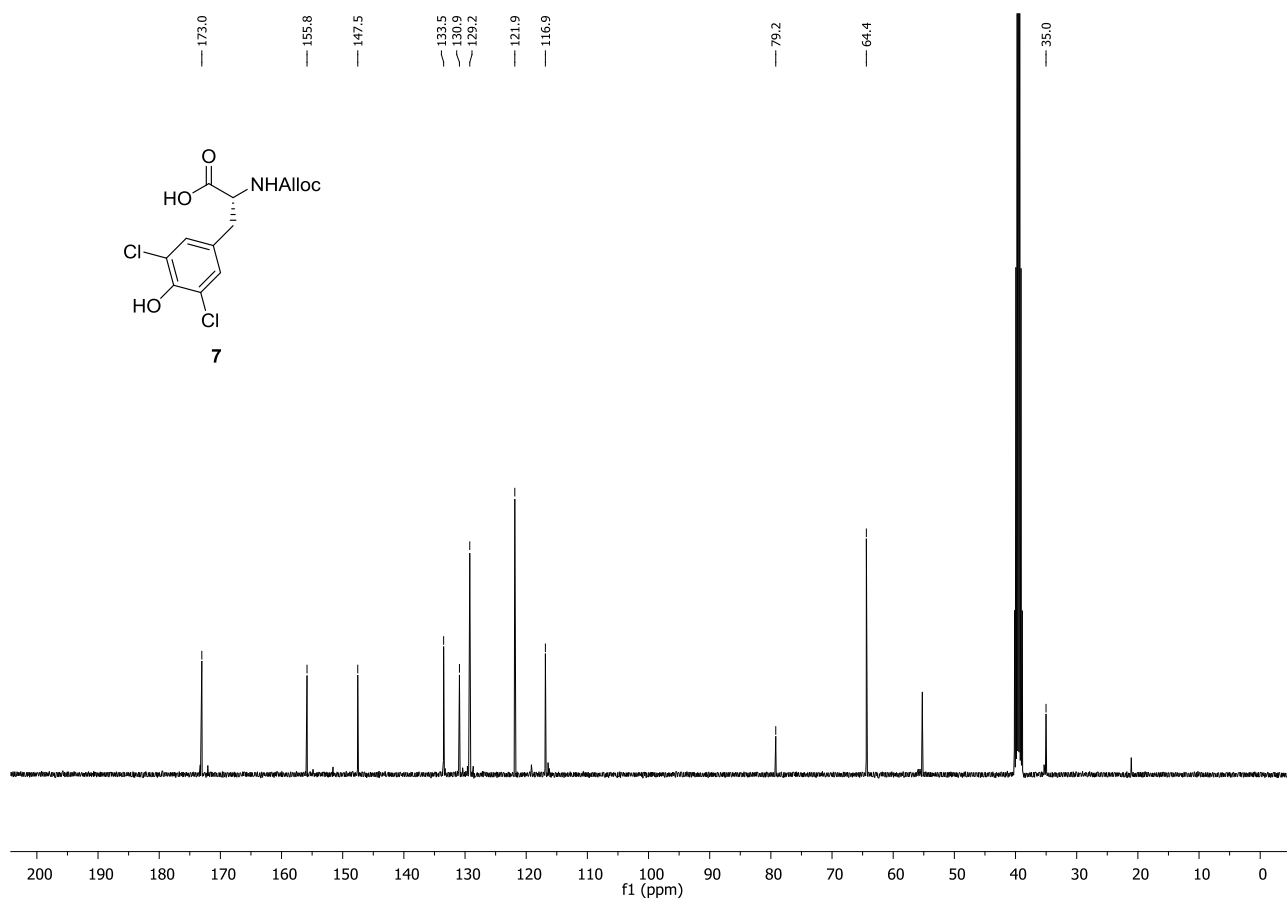
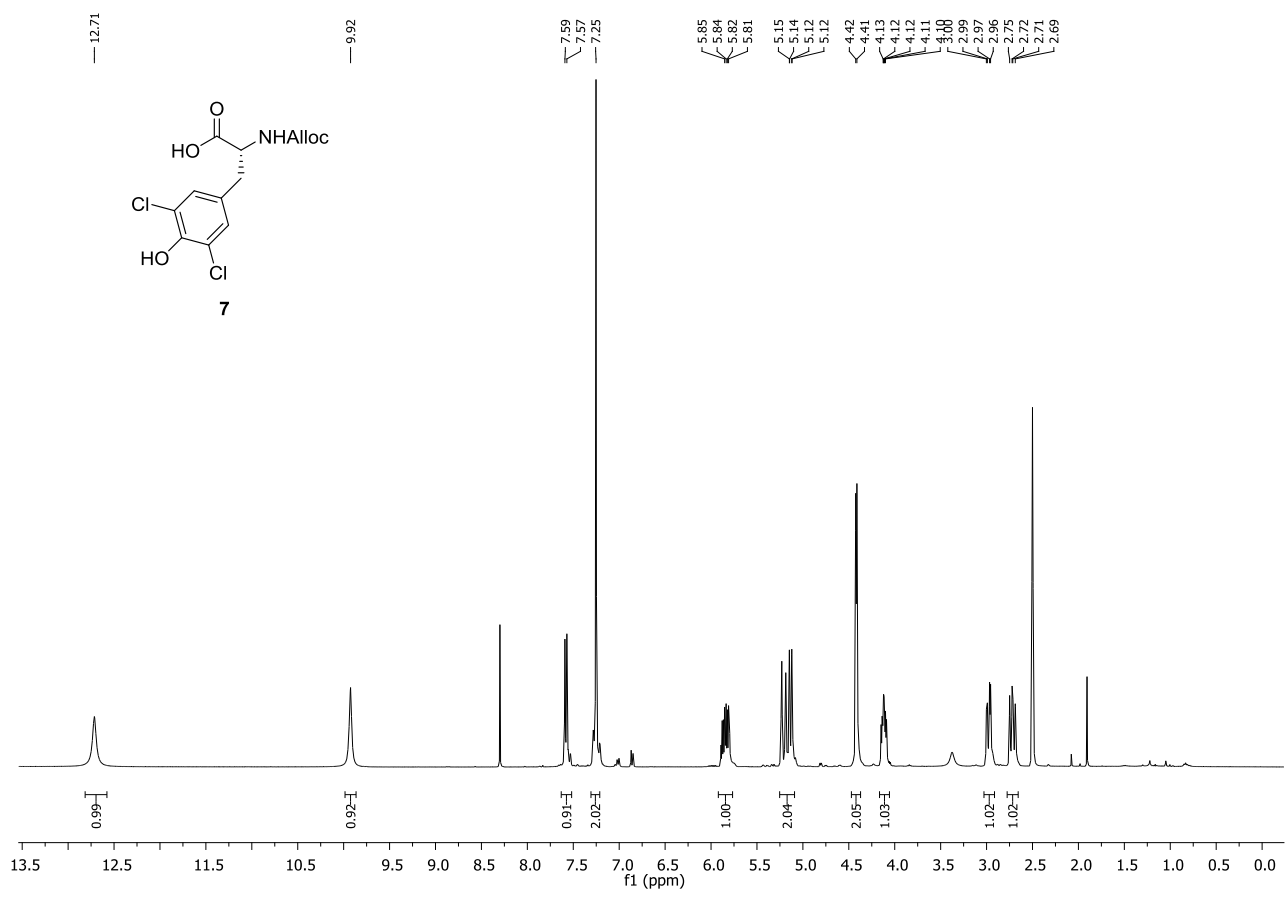


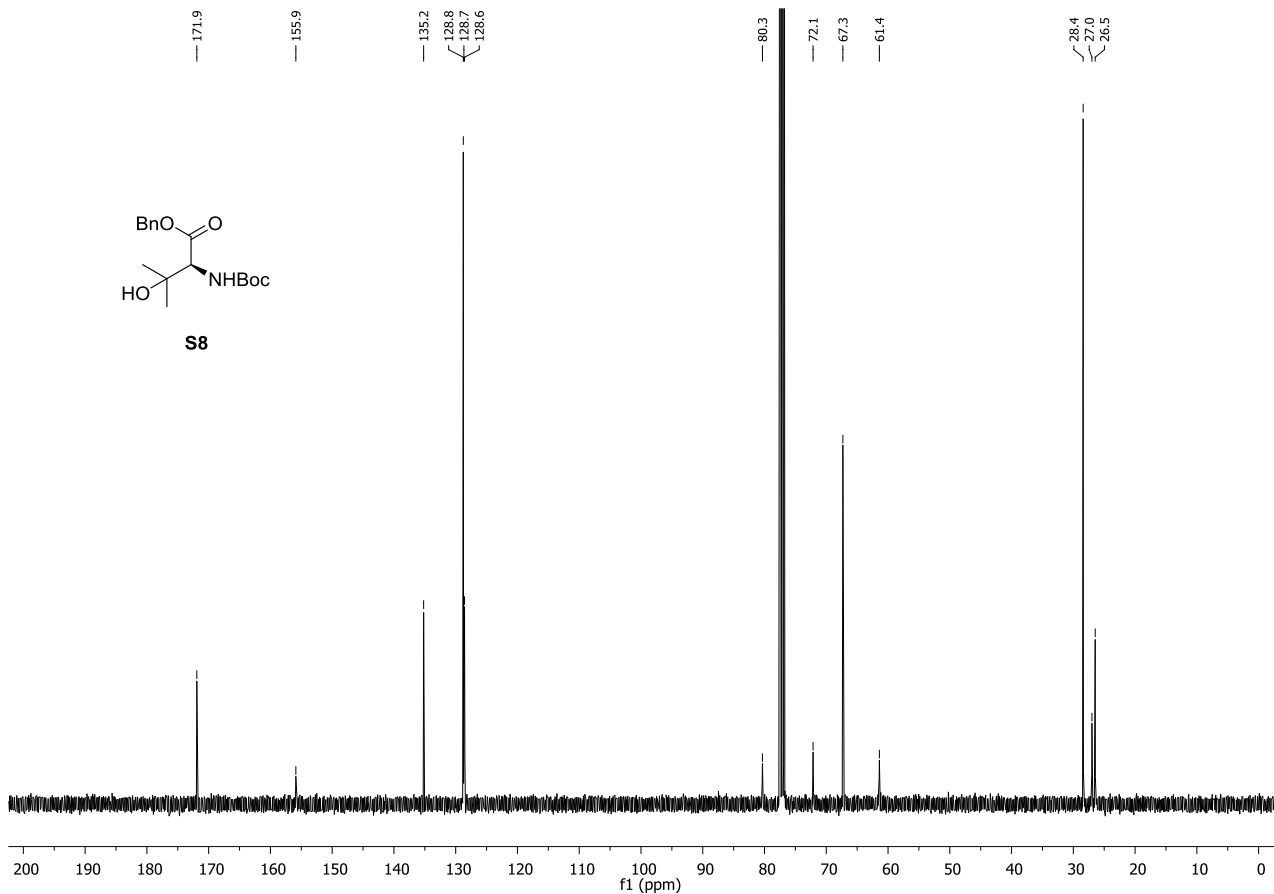
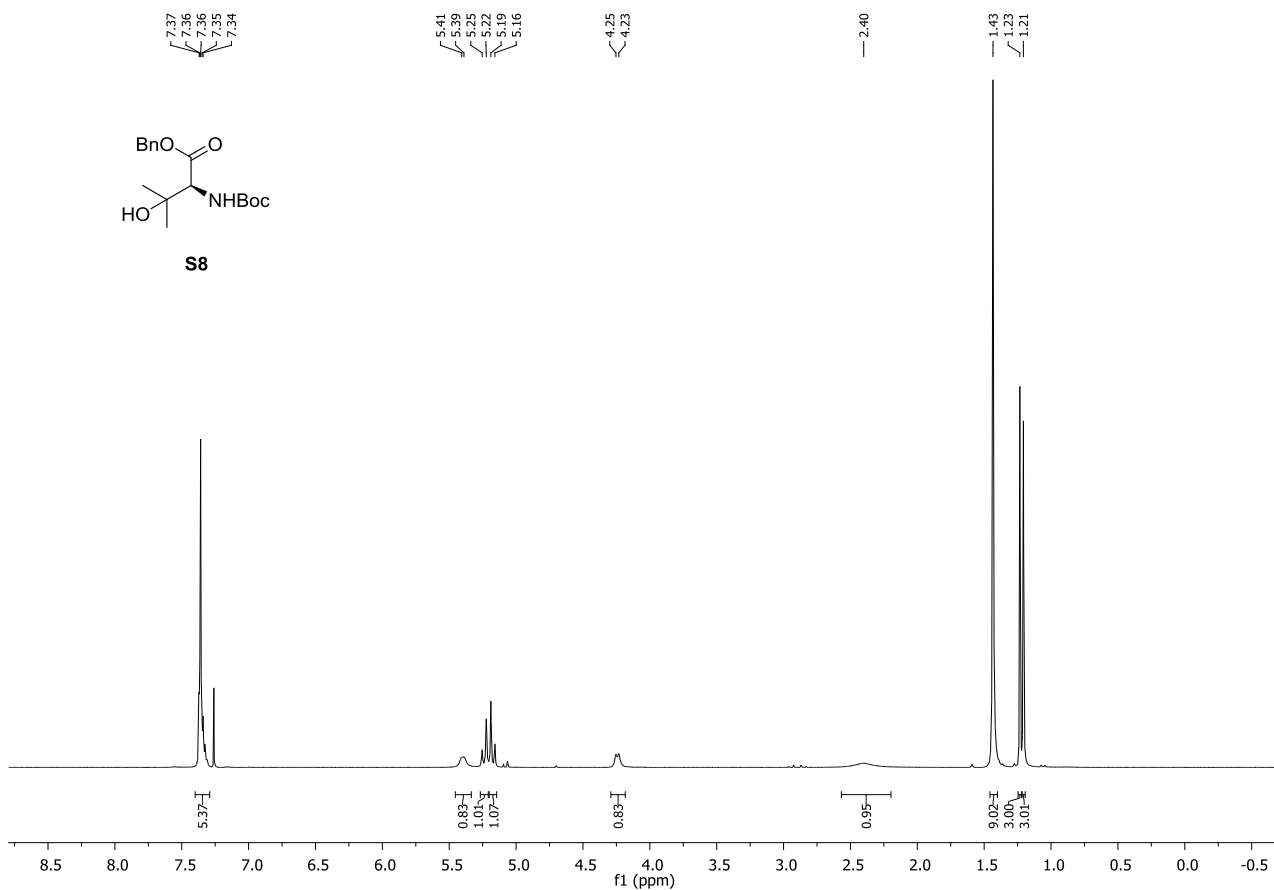


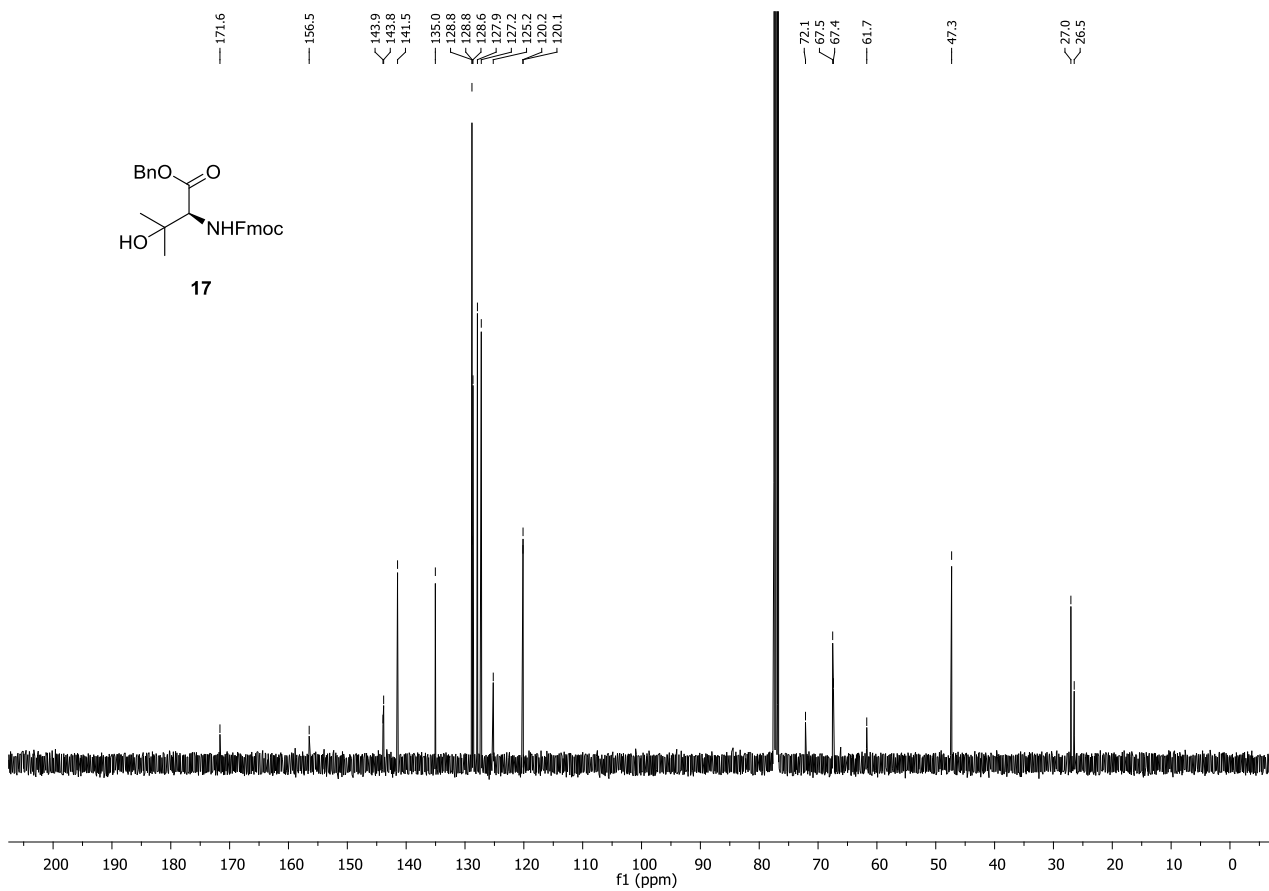
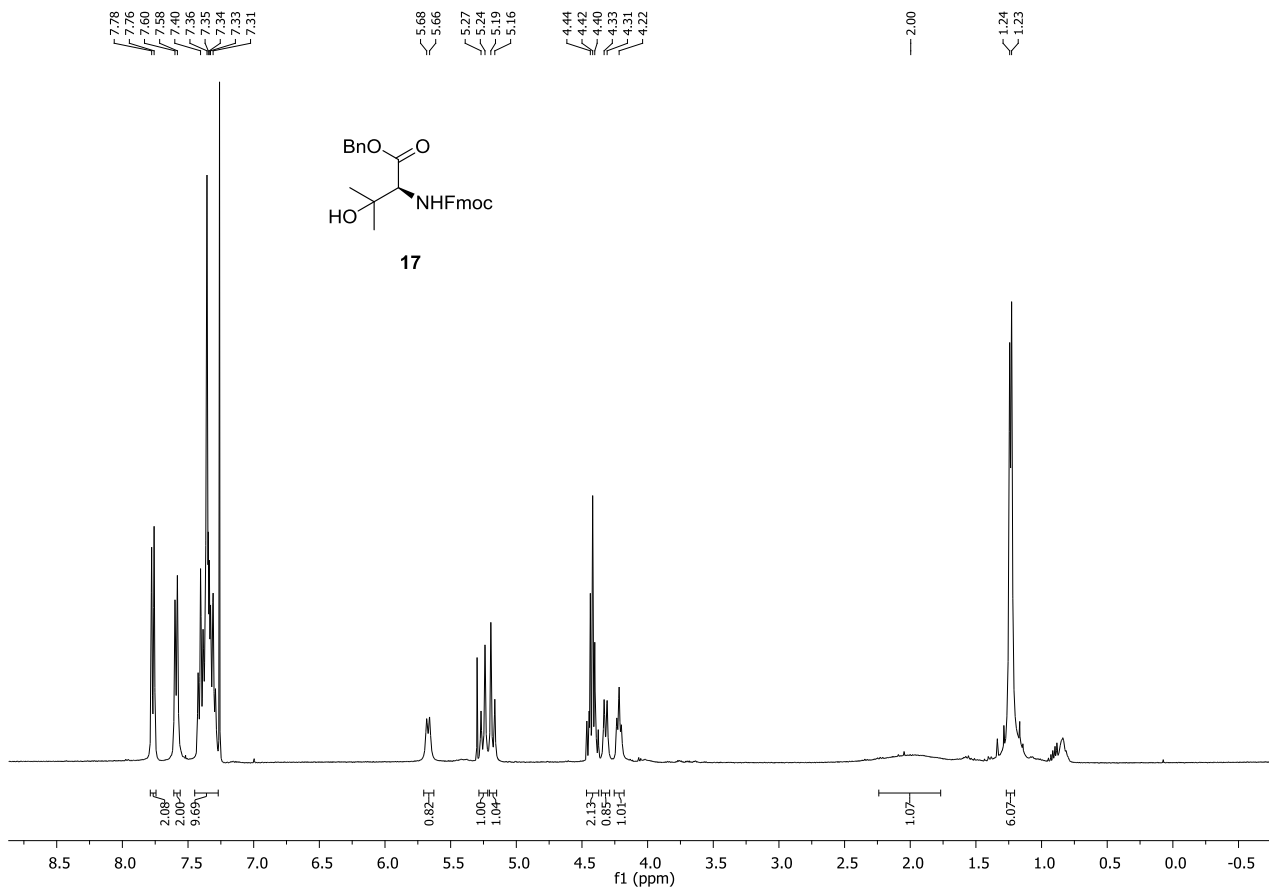


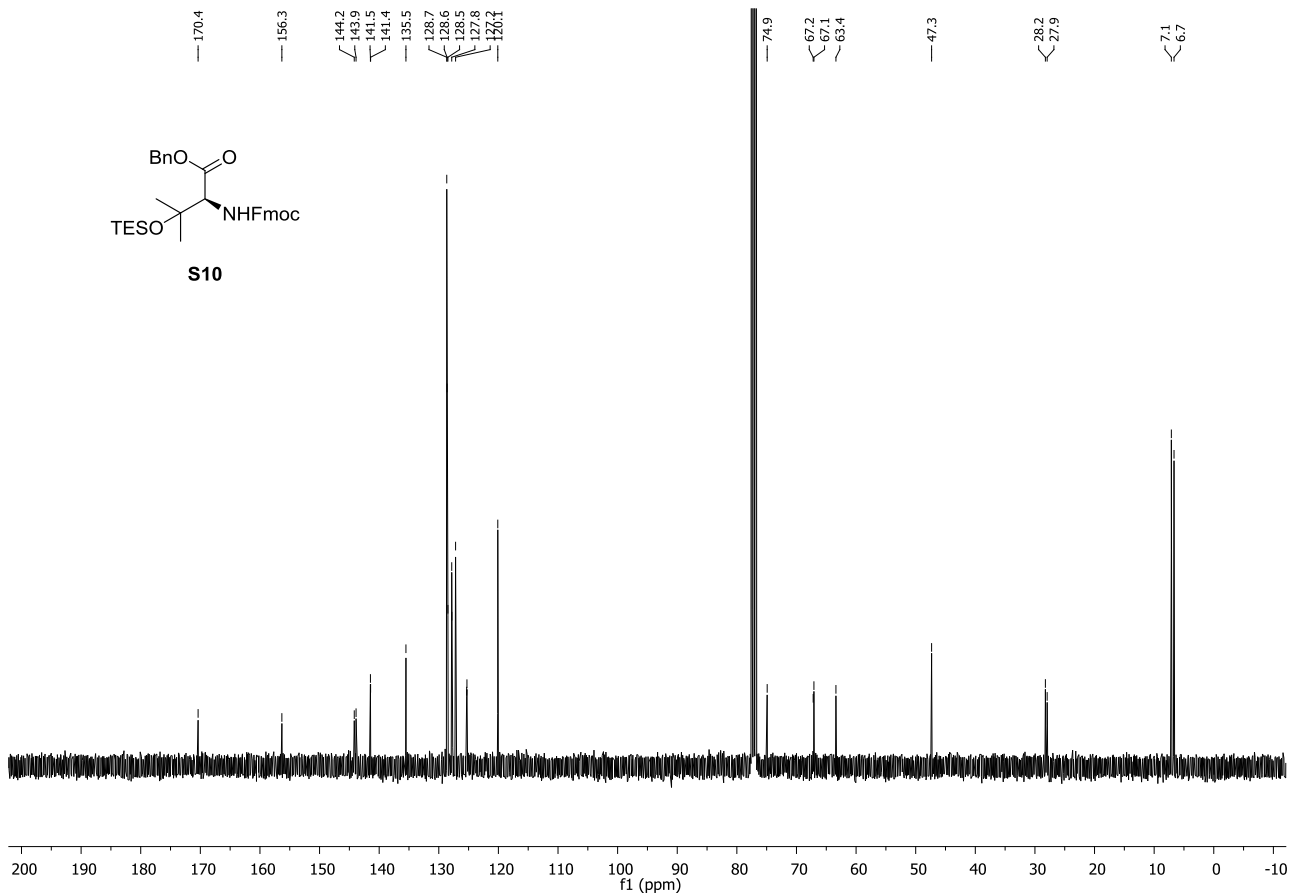
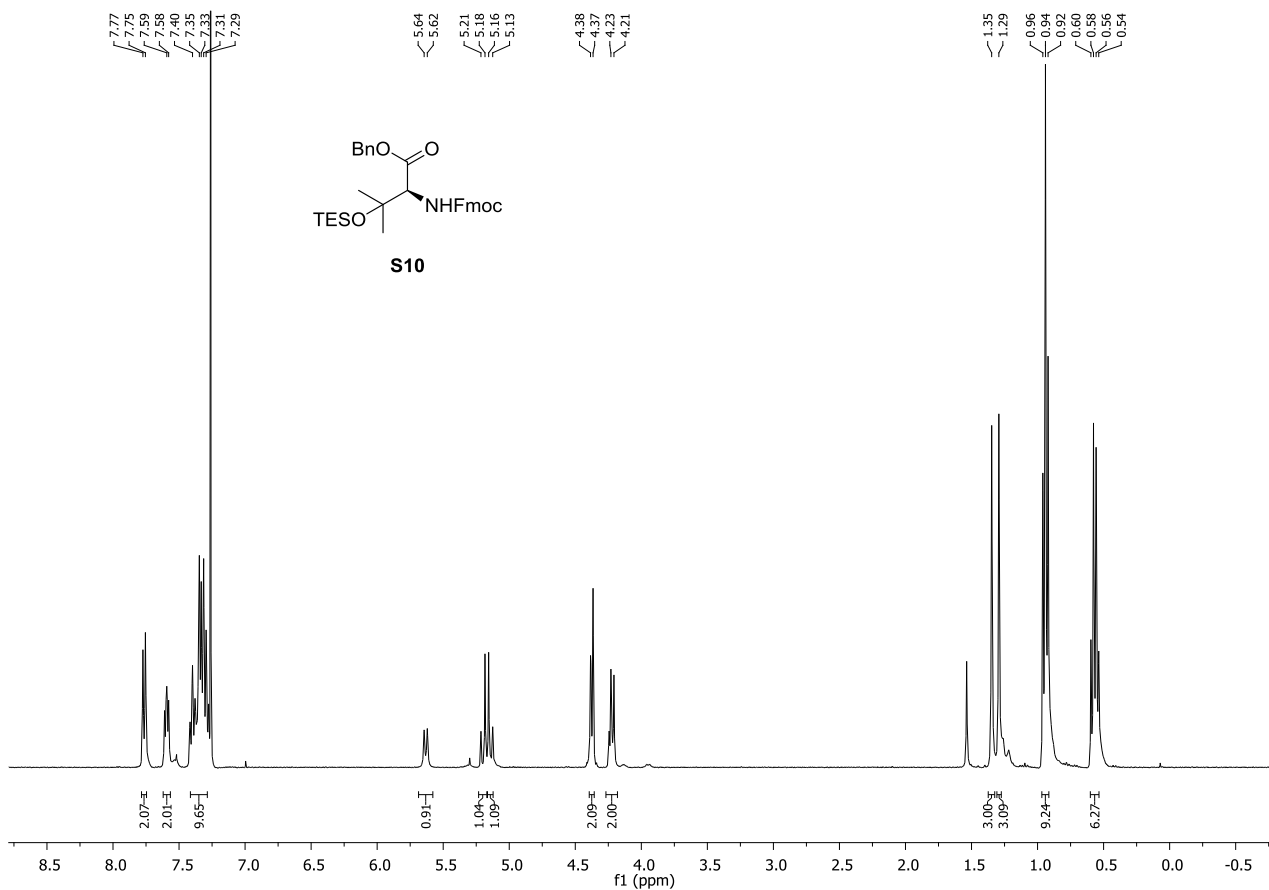




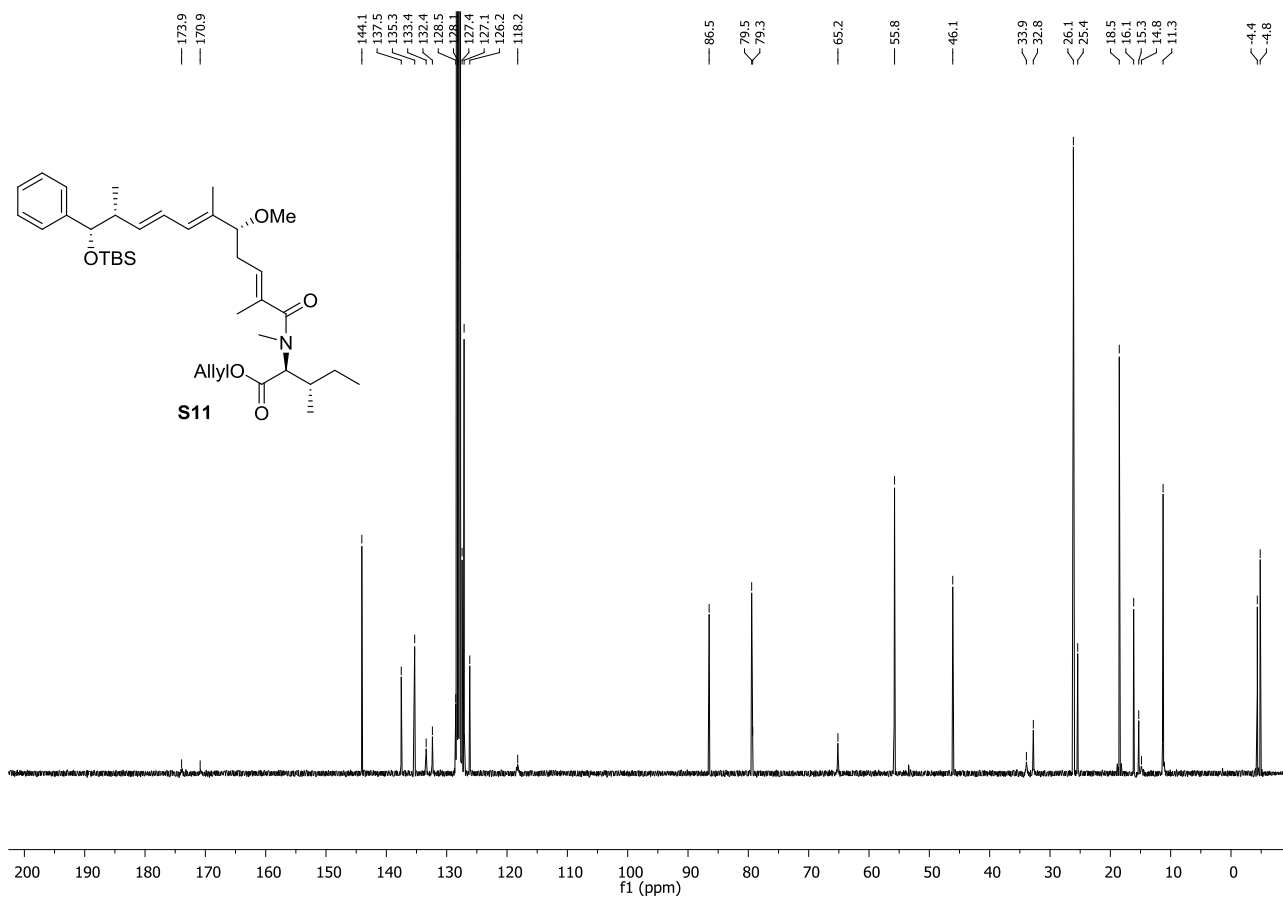
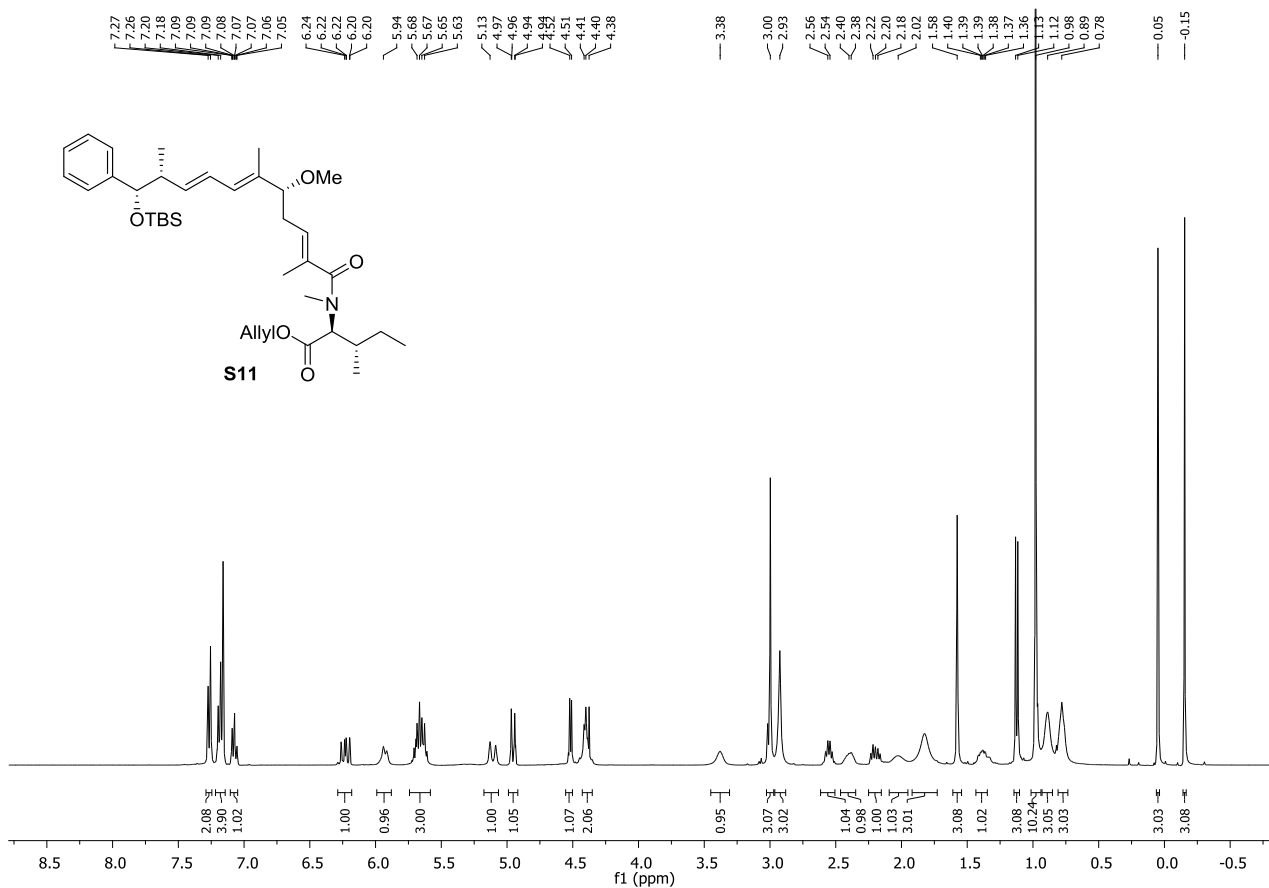


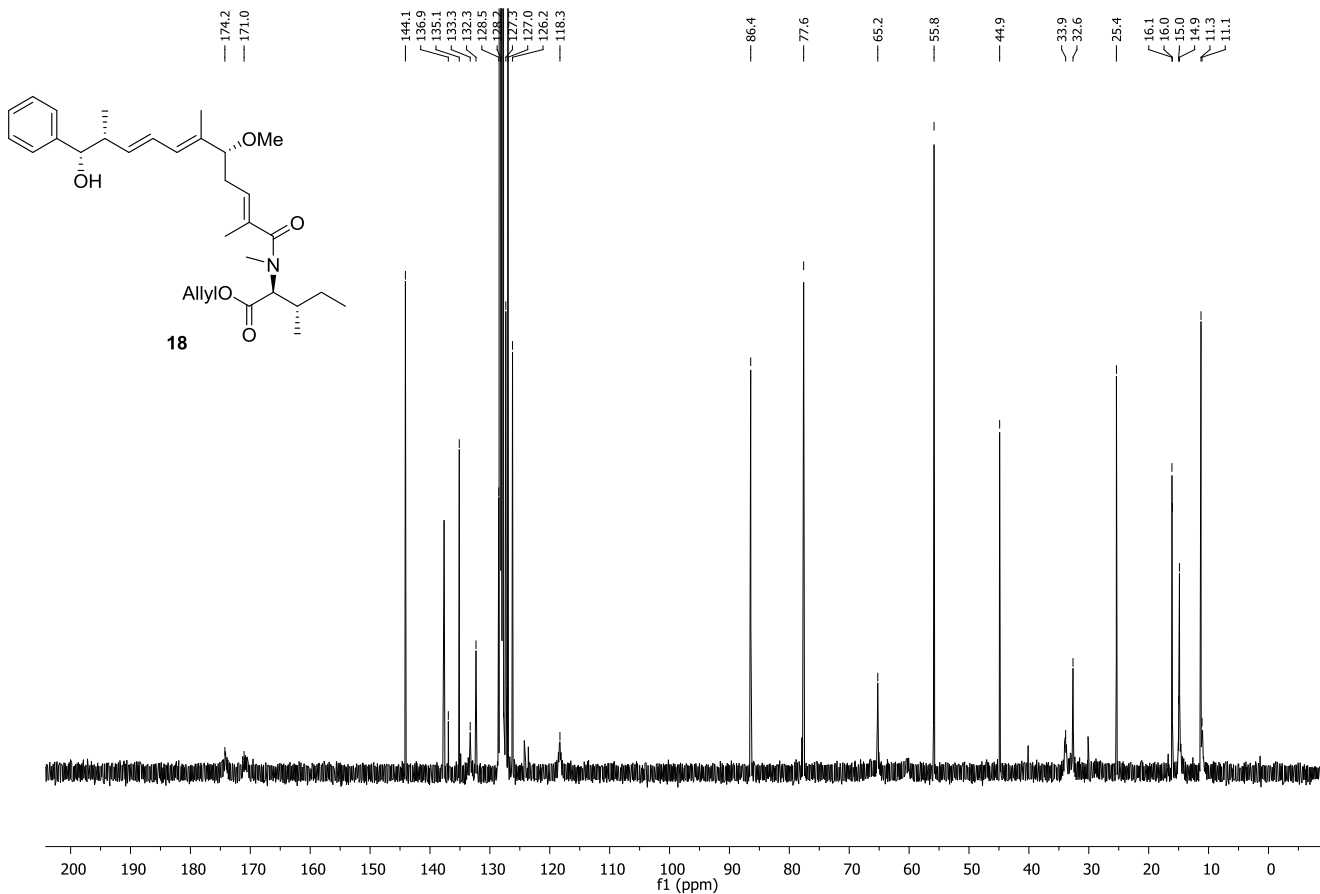
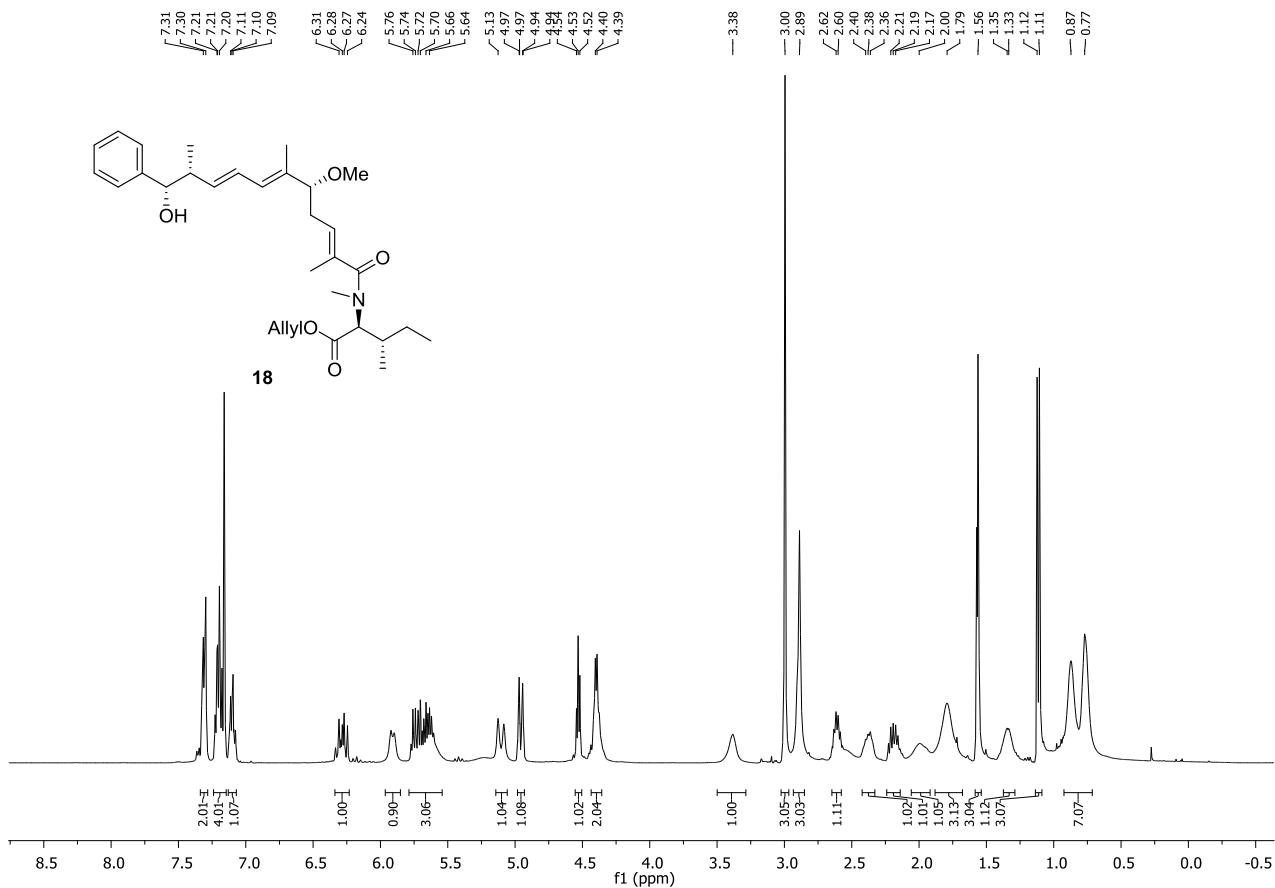


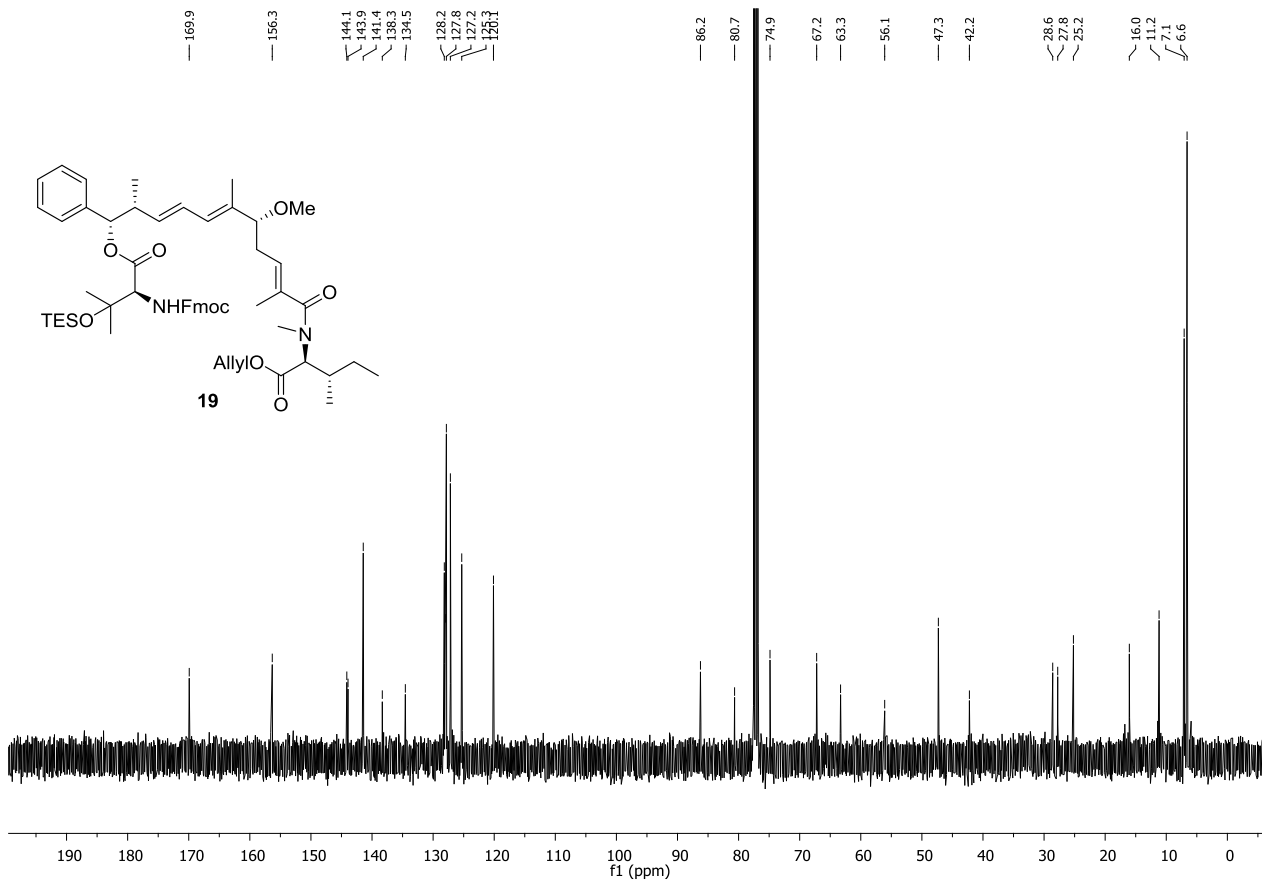
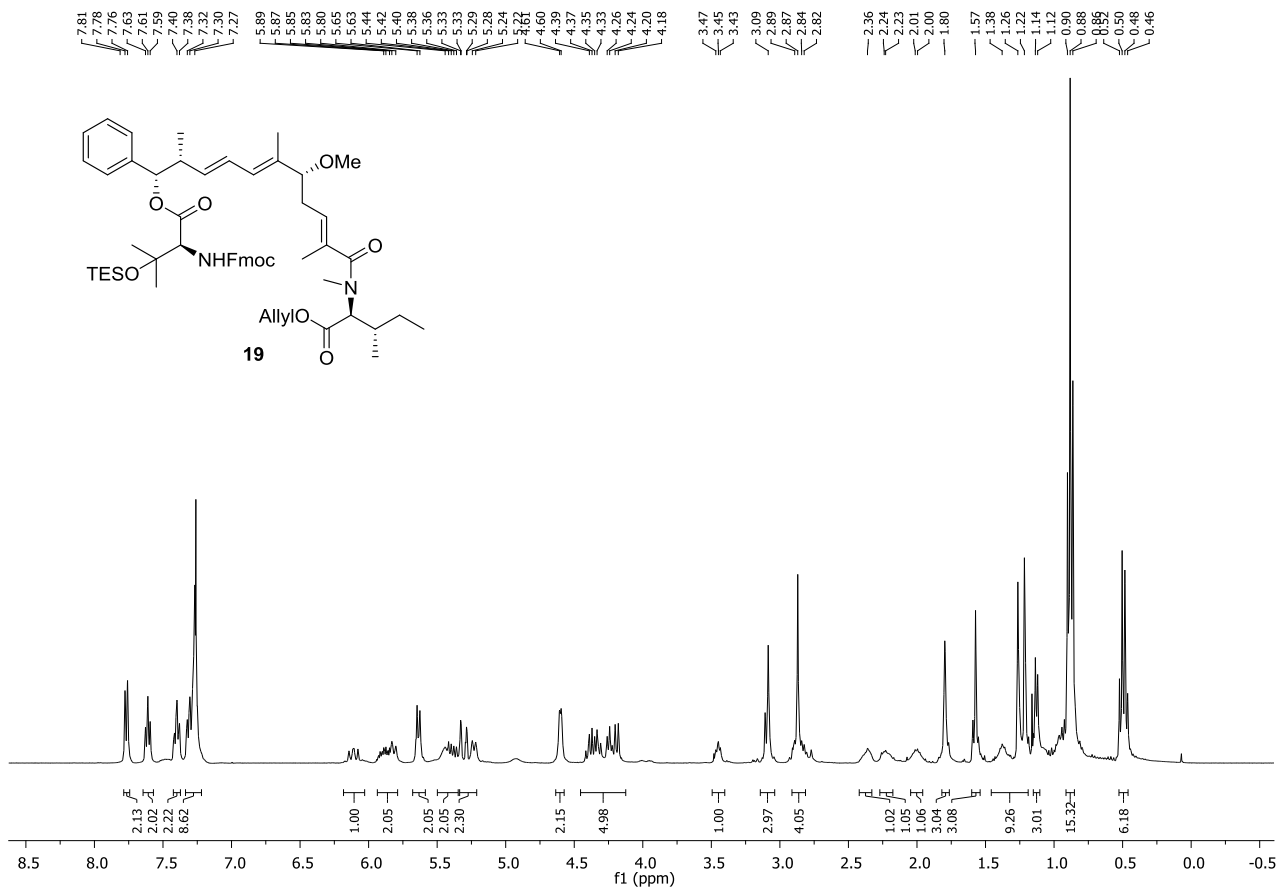




S51







HMBC of compound 19

