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Total Synthesis of Antibacterial Polyketide Natural Product Thailandamide Lactone

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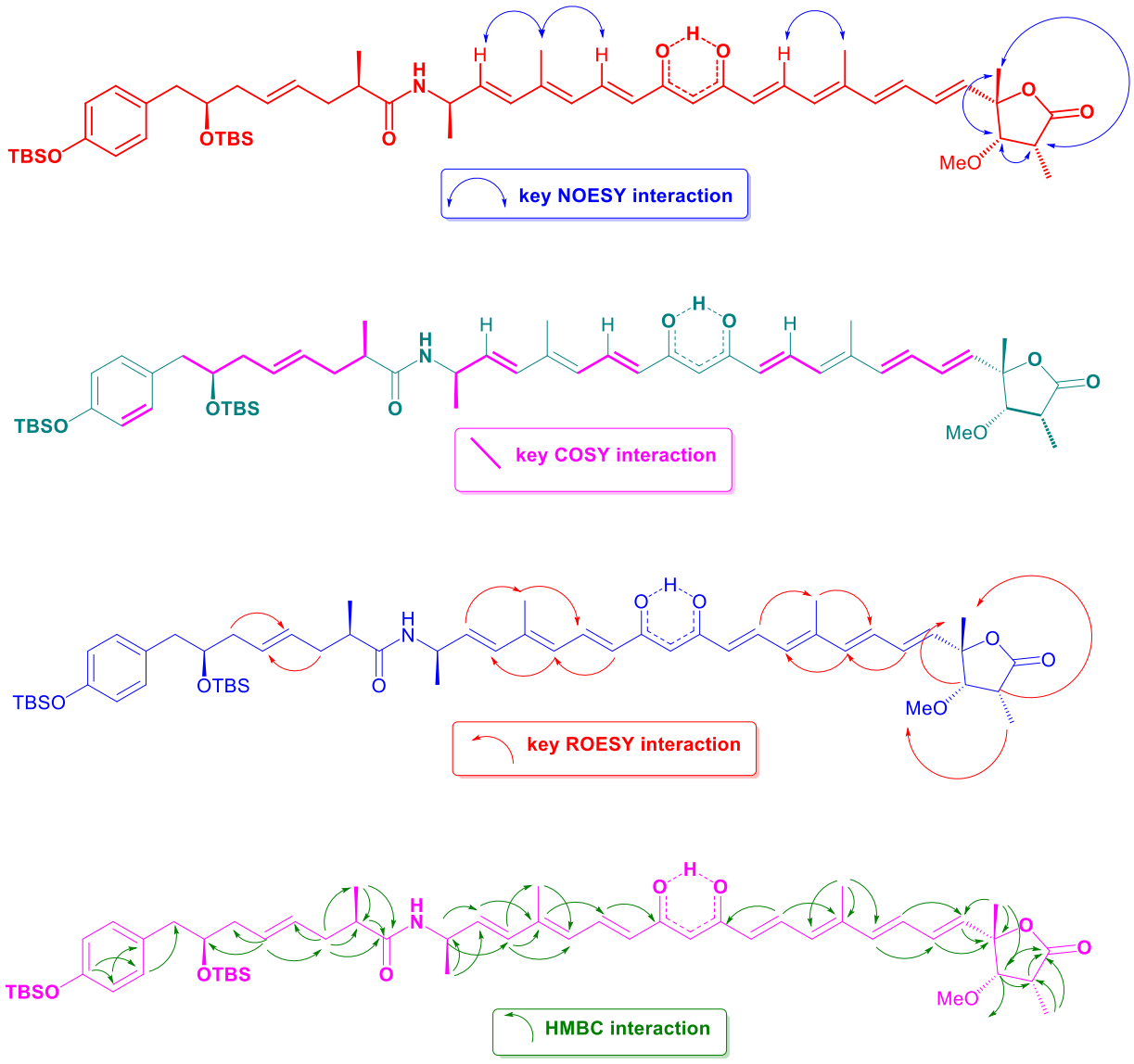
Supporting Information

Contents

1.1. General Experimental Procedure:

All moisture sensitive reactions were performed in oven or flame-dried glassware with Teflon coated magnetic stirring bar under argon atmosphere using dry, freshly distilled solvents, unless otherwise noted. Air- and moisture-sensitive liquids were transferred via a gastight syringe and a stainless-steel needle. Reactions were monitored by thin layer chromatography (TLC, Silica gel 60 F254) plates with UV light, ethanolic anisaldehyde (with 1% AcOH and 3.3% conc. H_2SO_4)-heat and aqueous $KMnO_4$ (with K_2CO_3 and 10% aqueous NaOH solution) as developing agents. All workup and purification procedures were carried out with reagent grade solvents under ambient atmosphere unless otherwise stated. Column chromatography was performed using silica gel 60-120 mesh, 100-200 mesh and 230-400 mesh. Yields mentioned as chromatographically and spectroscopically homogeneous materials unless otherwise stated. Optical rotations were measured using sodium (589, D line) lamp and are reported as follows: $[\alpha]_D^{28}$ (c = g/100 mL, solvent). Melting points of solids were measured in melting point apparatus. IR spectra were recorded as thin films (for liquids) or KBr matrix (for solids). HRMS were taken using Quadruple TOF (Q-TOF) micro MS system using electrospray ionisation (ESI) technique. ^{1}H NMR spectra were recorded on 300, 500 and 600 MHz spectrometers in appropriate solvents and calibrated using residual undeuterated solvent as an internal reference, and the chemical shifts are shown in δ ppm scales. Multiplicities of NMR signals are designated as s (singlet), d (doublet), t (triplet), q (quartet), br (broad), m (multiplet, for unresolved lines) etc. ^{13}C and 2D NMR spectra were recorded on 75, 151 MHz spectrometers.

1.2. Figure S1: Key 2D-NMR Correlations and Structure Confirmation of Protected Thailandamide Lactone (37).



1.3. Figure S2: Optimization Table for HWE Olefination for the Synthesis of Compound 9

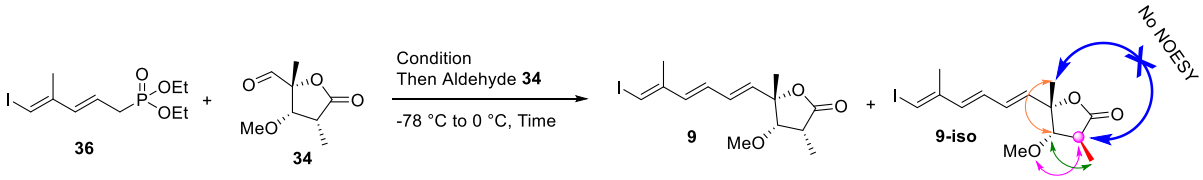
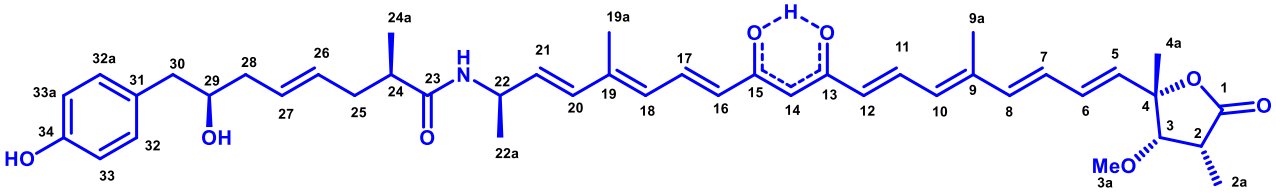


Table S1: Optimization Table for the Synthesis of 9

Entry	Condition	Time	*dr*. (**9**:**9-iso**)	Yield (%)
1	NaHMDS(2.0 equi.), THF, -78 ºC	8 h	Exclusively **9-iso**	89
2	NaHMDS(1.5 equi.), THF, -78 ºC	8 h	1:8	81
3	NaHMDS(1.1 equi.), THF, -78 ºC	8 h	1.1	80
4	NaHMDS(1.1 equi.), THF, -78 ºC	6 h	3:1	70
5	NaHMDS(1.1 equi.), THF, -78 ºC	4 h	Exclusively **9**	60 (brs)

1.4. Table S2. ^{1}H NMR (CD_3OD) Spectroscopic Data Comparison of Natural[1] and Synthetic Thailandamide Lactone (2)



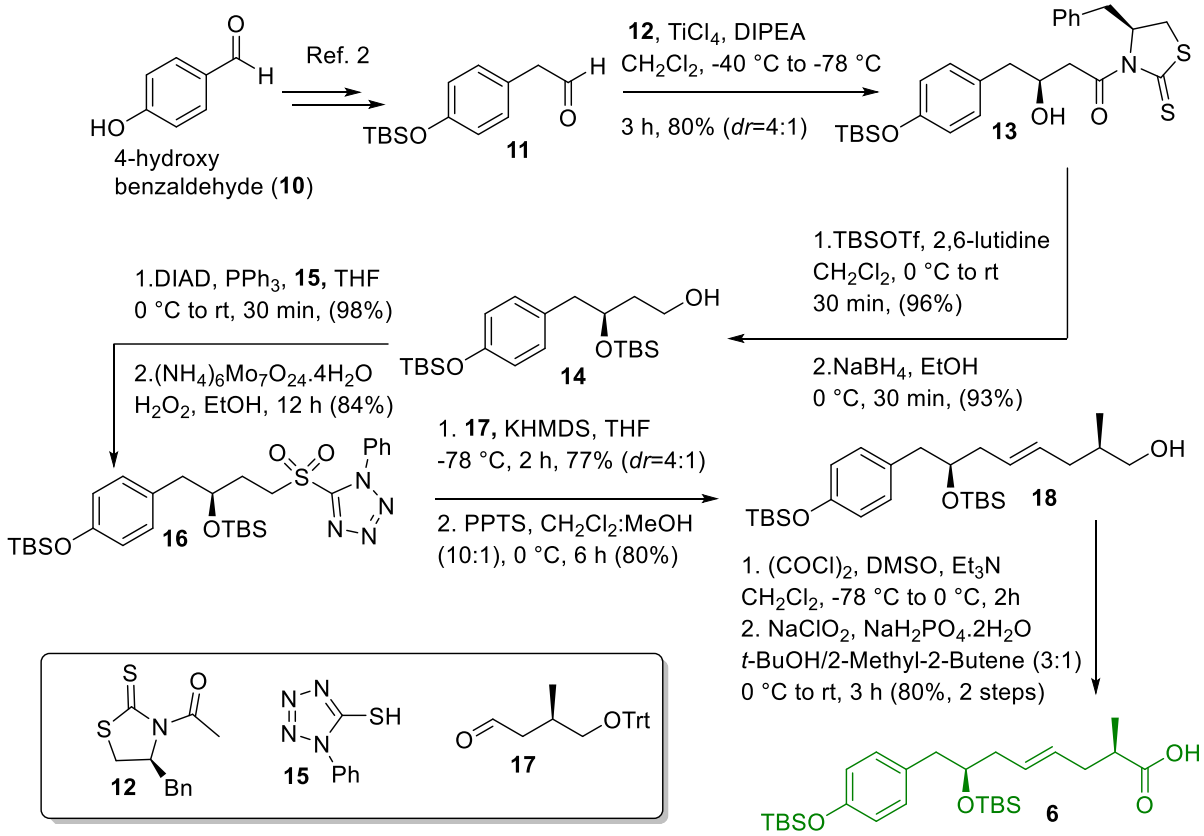
Position	δ ^{1}H [ppm, int, mult, J (Hz)] (Natural) (MeOD-d_4)	δ ^{1}H [ppm, int, mult, J (Hz)] (Synthetic) (500 MHz, MeOD-d_4)	δ ^{13}C [ppm] (Natural) (MeOD-d_4)	δ ^{13}C [ppm] 151 MHz (Synthetic) (151 MHz, MeOD-d_4)
1			180.1	180.94
2	3.13, 1H, dd, 6.1, 7.3	3.13, 1H, m	40.7	40.47
2a	1.17, 3H, d, 7.2	1.18, 1H, d, 7.4	9.1	8.87
3	3.78, 1H, d, 6.1	3.79, 1H, d, 6.2	87.3	86.48
3a	3.34, 3H, s	3.39, 3H, s	60.4	61.18
4			88.4	89.12
4a	1.50, 3H, s	1.50, 3H, s	23.9	23.89
5	6.04, 1H, d. 15.6	5.99, 1H, d, 15.4	134.9	134.82
6/8	6.48, 2H, m	6.43-6.54, 2H, m	132.1/138.8	132.54/139.18
7	6.63, 1H, dd, 10.4, 15.1	6.60, 1H, dd, 7.8, 15.0	132.3	131.33
9			145.1	147.1
9a	2.06, 3H, s	2.04, 3H, s	13.3	13.21
10	6.36, 1H, d, 11.8	6.37, 1H, d, 8.2	131.6	131.61
11/17	7.66, 2H, m	7.77-7.59, 2H, m	137.6/137.7	137.25/137.55
12/16	6.15, 2H, d, 15.6	6.16, 2H, d, 16.1	128.8/128.9	128.37/128.86
13			184.7	184.3
14	6.06, 1H, s	6.07, 1H, s	101.4	99.92
15			184.2	184.08
18	6.22, 1H, d, 11.2	6.22, 1H, d, 11.4	130.5	130.62
19			144.7	144.65
19a	1.95, 3H, s	1.96, 3H, s	13.3	13.45
20	6.27, 1H, d, 15.6	6.28, 1H, d, 12.8	134.6	134.05
21	5.90, 1H, dd, 6.1, 15.7	5.90, 1H, dd, 3.4, 18	135.6	135.71
22	4.54, 1H, td, 6.6, 6.6, 13.3		47.7	47.84
22a	1.24, 3H, d, 6.9	1.25, 3H, d, 6.9	20.9	21.1

23			178.0	178.15
24	2.38, 1H, m	2.39, 1H, m	42.4	42.5
24a	1.10, 3H, d, 6.8	1.11, 3H, d, 6.6	18.1	18.16
25	2.29/2.09, 2H, m	2.28/2.10, 2H, m	38.5	38.62
26	5.42, 1H, m	5.40-5.47, 1H, m	131.2	131.33
27	5.52, 1H, m	5.48-5.56, 1H, m	130.1	130.21
28	2.11-2.07, 2H, m	2.08-2.14, 2H, m	41.0	41.17
29	3.68, 1H, m	3.67-3.73, 1H, m	73.7	73.89
30	2.57/2.55, 2H, dd/dd, 5.8, 13.7, 7.1, 13.7	2.55-2.64, 2H, m	43.3	43.5
31			131.1	131.15
32/32a	6.98, 2H, d, 8.5	6.99, 2H, d, 7.9	131.5	131.57
33/33a	6.68, 2H, d, 8.5	6.69, 2H, d, 8.0	116.0	116.2
34			156.7	156.86

1.5. Experimental Procedure:

1.5.1. Synthesis of Intermediate 6:

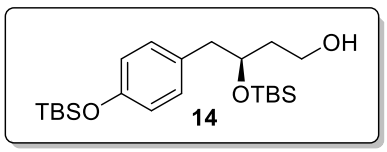
Scheme S1: *Synthesis of Intermediate* ***6***



(*S*)-1-((*S*)-4-Benzyl-2-thioxothiazolidin-3-yl)-4-(4-((tert-butyldimethylsilyl)oxy)phenyl)-3-hydroxybutan-1-one (13): Freshly distilled $TiCl_4$ (3.85 mL, 35.14 mmol, 1.1 equivalent) was added drop wise to a stirred solution of thiazolidinethione **12** (8.85 g, 35.14 mmol, 1.1 equivalent) dissolved in anhydrous CH_2Cl_2 (120 mL) at -40 °C under argon and stirring was continued further for 5 min. DIPEA (4.56 mL, 26.22 mmol, 1.1 equivalent) was then added to the reaction mixture in drop wise fashion and stirred for another 10 min. The reaction mixture was then cooled to −78 °C and the aldehyde **11**[2] (8.0 g, 31.94 mmol, dissolved in 30 mL

CH_2Cl_2: 1.0 equivalent) was cannulated into it. The reaction was continued further at −78 °C for 45 min prior to quench with saturated solution of NH_4Cl (15 mL). The resulting mixture was warmed to ambient temperature and extracted with EtOAc (2 × 100 mL), washed with water, brine, dried over Na_2SO_4, filtered and concentrated in vacuo. Purification of residue by column chromatography (SiO_2, 230−400 mesh, 15% EtOAc in hexane as eluent) resulted yellow crystal compound **13** as a major aldol product (10.25 g, 80%, *dr* = 4:1); mp: 93 - 97 °C; R_f = 0.37 (15% EtOAc in hexane); $[\alpha]_D^{28}$ = -157.3 (c 0.67, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35 – 7.25 (m, 5H), 7.18 – 7.04 (m, 2H), 6.88 – 6.73 (m, 2H), 5.38 (ddd, *J* = 10.6, 7.0, 3.9 Hz, 1H), 4.37 (dtd, *J* = 9.3, 6.6, 2.5 Hz, 1H), 3.61 (dd, *J* = 17.7, 2.5 Hz, 1H), 3.43 – 3.32 (m, 1H), 3.25 – 3.14 (m, 2H), 3.02 (dd, *J* = 13.2, 10.4 Hz, 1H), 2.90 – 2.76 (m, 3H), 1.00 (s, 9H), 0.21 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.30, 172.90, 154.39, 136.45, 130.48, 130.32, 129.46, 128.94, 127.28, 120.13, 77.58, 77.16, 76.74, 69.12, 68.34, 45.15, 42.14, 36.83, 32.10, 25.75, 18.23, -4.34; IR (neat) ν_{max} 3525, 2953, 2928, 2857, 1689, 1607, 1508, 1341, 1251, 1155, 1136, 1044; HRMS (ESI) m/z calculated for $C_{26}H_{35}NO_3S_2SiH$ $[M+H]^+$ 502.1906, found 502.1875.

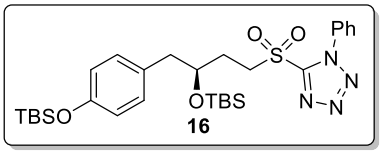
(*S*)-3-((*tert*-Butyldimethylsilyl)oxy)-4-(4-((tert-butyldimethylsilyl)oxy)phenyl)butan-1-ol



(14): To an ice-cold solution of **13** (9.5 g, 18.93 mmol, 1.0 equivalent) in anhydrous CH_2Cl_2 (100 mL) under argon, 2,6-lutidine (4.38 mL, 37.86 mmol, 2.0 equivalent) and TBSOTf (6.52 mL, 28.39 mmol, 1.5 equivalent) were added sequentially and the reaction mixture was stirred for 30 min before quenching with saturated solution of $NaHCO_3$ (12 mL). The reaction mixture was then extracted with CH_2Cl_2 (2 × 30), washed with aqueous solution of $CuSO_4$, water and brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification by column chromatography (SiO_2, 100−200 mesh, 2−5% EtOAc in hexane) furnished the corresponding TBS protected product as a yellow liquid (11.19 g, 96%): R_f = 0.15 (5% EtOAc in hexane);

$[\alpha]_D^{28}$ = -138.07 (c 0.52, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35 – 7.25 (m, 5H), 7.06 (d, *J* = 8.4 Hz, 2H), 6.76 (d, *J* = 8.4 Hz, 2H), 5.25 (ddd, *J* = 10.6, 7.0, 3.7 Hz, 1H), 4.48 (qd, *J* = 6.5, 4.1 Hz, 1H), 3.49 (dd, *J* = 17.0, 7.7 Hz, 1H), 3.33 (ddd, *J* = 11.5, 7.1, 1.0 Hz, 1H), 3.22 (dt, *J* = 17.0, 3.8 Hz, 2H), 3.01 (dd, *J* = 13.2, 10.6 Hz, 1H), 2.91 – 2.72 (m, 3H), 0.98 (s, 9H), 0.84 (s, 9H), 0.18 (s, 6H), 0.02 (s, 3H), -0.05 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.14, 172.35, 154.34, 136.76, 131.13, 130.74, 129.58, 129.05, 127.33, 120.11, 77.58, 77.16, 76.74, 71.04, 68.74, 45.87, 43.90, 36.70, 32.27, 26.00, 25.86, 18.35, 18.16, -4.29, -4.43, -4.67; IR (neat) ν_{max} 3028, 2953, 2928, 2886, 2856, 1697, 1607, 1508, 1462, 1340, 1251, 1136 cm^{-1}; HRMS (ESI) *m/z* calculated for $C_{32}H_{50}NO_3S_2Si_2H$ $[M+H]^+$ 616.2771, found 616.2734.

To a solution of above TBS protected alcohol (11.1 g, 18.01 mmol, 1.0 equivalent) in anhydrous EtOH (70 mL), $NaBH_4$ (3.40 g, 90.00 mmol, 5.0 equivalent) was added at 0 °C and the stirring was continued for 30 min at the same temperature. The reaction was then quenched with saturated aqueous NH_4Cl (30 mL). EtOH was removed under reduced pressure and extracted with EtOAc (3 ×50 mL), washed with brine, dried over Na_2SO_4 and concentrated in vacuo. Purification of the residue obtained by column chromatography (SiO_2, 100-200 mesh, 30% EtOAc in hexane eluent) afforded the corresponding alcohol **14** (6.86 g, 93%) as a thick colourless oil: R_f = 0.42 (20% EtOAc in hexane); $[\alpha]_D^{28}$ = -157.36 (c 0.51, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.00 (d, *J* = 8.4 Hz, 2H), 6.74 (d, *J* = 8.4 Hz, 2H), 4.06 (qd, *J* = 6.5, 4.2 Hz, 1H), 3.92 – 3.82 (m, 1H), 3.76 – 3.67 (m, 1H), 2.81 (dd, *J* = 13.5, 6.4 Hz, 1H), 2.69 (dd, *J* = 13.5, 7.0 Hz, 1H), 2.43 (s, 1H), 1.86 – 1.74 (m, 1H), 1.69 – 1.55 (m, 2H), 0.98 (s, 9H), 0.88 (s, 9H), 0.17 (s, 6H), 0.04 (s, 3H), -0.11 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.23, 131.52, 130.60, 120.08, 77.58, 77.16, 76.74, 73.55, 60.31, 42.95, 37.74, 26.01, 25.85, 18.35, 18.12, -4.30, -4.63, -4.72; IR (neat) ν_{max} 2954, 2929, 2857, 2886, 1609, 1509, 1472, 1251, 1088, 912, 833, 694 cm^{-1}; HRMS (ESI) *m/z* calculated for $C_{22}H_{42}O_3Si_2Na$ $[M+Na]^+$ 433.2570, found 433.2570.



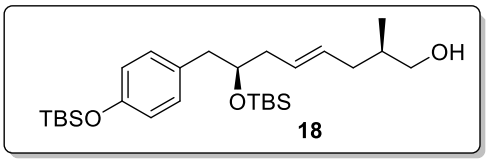
16

(*S*)-5-((3-((*tert*-Butyldimethylsilyl)oxy)-4-(4-((tert-butyldimethylsilyl)oxy)phenyl)butyl)sulfonyl)-1-phenyl-1H-tetrazole (16) : To a mixture of alcohol **14** (6.8 g, 16.55 mmol, 1.0 equivalent), PPh_3 (6.5 g, 24.83 mmol, 1.5 equivalent), and 1-phenyl-1H-tetrazol-5-thiol **15** (4.42 g, 24.83 mmol, 1.5 equivalent) in anhydrous THF (85 mL) at 0 °C, DIAD (4.88 mL, 24.83 mmol, 1.5 equivalent) was added in drop wise manner and stirred further for 2 h at the ambient temperature. The reaction mixture was then quenched with saturated aqueous $NaHCO_3$ (15 mL), extracted with EtOAc (2 × 50 mL), washed with brine, dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by column chromatography (SiO_2, 100-200 mesh, 8% EtOAc in hexane as eluent) to afford the corresponding sulfide (9.27 g, 98%) as a thick oil: R_f = 0.6 (10% EtOAc in hexane); $[\alpha]_D^{28}$ = -87.6 (c 0.22, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.59 – 7.50 (m, 5H), 7.03 – 6.96 (m, 2H), 6.77 – 6.71 (m, 2H), 3.95 (qd, J = 6.2, 4.7 Hz, 1H), 3.57 – 3.34 (m, 2H), 2.80 – 2.62 (m, 2H), 0.97 (s, 9H), 0.86 (s, 9H), 0.17 (s, 6H), -0.01 (s, 3H), -0.15 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.28, 133.89, 131.22, 130.66, 130.18, 129.89, 123.98, 120.09, 77.59, 77.16, 76.74, 72.58, 43.06, 36.09, 29.54, 26.03, 25.86, 18.35, 18.18, -4.30, -4.56; IR(neat): ν_{max} 2954, 2929, 2886, 2857, 1608, 1509, 1500, 1471, 1252, 912, 835, 751, 693 cm^{-1}; HRMS (ESI) *m/z* calculated for $C_{29}H_{46}N_4O_2SSi_2$ $[M+H]^+$ 571.2969, found 571.2958.

To an ice cold ethanolic solution (64 mL) of the above sulfide (9.2 g, 16.14 mmol, 1.1 equivalent), $(NH_4)_6Mo_7O_{24}.4H_2O$ (997 mg, 0.80 mmol, 0.05 equivalent) and 30% (w/w) aqueous H_2O_2 solution (16.14 mL, 1mL/mmol) were added sequentially. The reaction was stirred for 12 h at the room temperature. The reaction mixture was then diluted with saturated solution of $NaHCO_3$ (20 mL) and extracted with EtOAc (2 × 100 mL), washed with brine, dried over Na_2SO_4, filtered, and concentrated. The crude material was purified by column chromatography (SiO_2, 100-200 mesh, 10% EtOAc in hexane as eluent) to get sulfone **16** (8.17

g, 84%) as a colourless oil: R_f = 0.57 (10% EtOAc in hexane); $[\alpha]_D^{28}$ = -112 (c 0.67, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.71 – 7.64 (m, 2H), 7.64 – 7.55 (m, 3H), 7.01 (d, *J* = 8.4 Hz, 2H), 6.76 (d, *J* = 8.4 Hz, 2H), 4.10 – 3.96 (m, 1H), 3.93 – 3.72 (m, 2H), 2.80 – 2.57 (m, 2H), 2.15 – 1.94 (m, 2H), 0.98 (s, 9H), 0.88 (s, 9H), 0.18 (s, 6H), 0.02 (s, 3H), -0.14 (s, 3H^{13}C NMR (75 MHz, $CDCl_3$) δ 154.50, 153.58, 133.18, 131.55, 130.57, 130.53, 129.82, 125.20, 120.26, 77.58, 77.16, 76.74, 71.54, 52.49, 42.91, 28.64, 25.97, 25.84, 18.34, 18.14, -4.31, -4.65, -4.70 ; IR(neat): ν_{max} 2964, 2929, 2876, 2853, 1605, 1510, 1498, 1461, 1252, 912, 835, 751, 693 cm^{-1}; HRMS (ESI) *m/z* calculated for $C_{29}H_{46}N_4O_4SSi_2Na$ $[M+Na]^+$ 625.2676, found 625.2673.

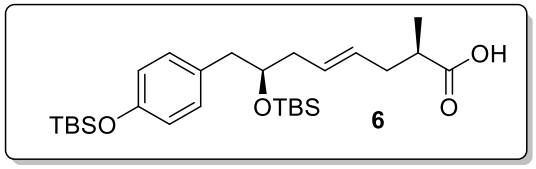
(2*R*,7*R*,*E*)-7-((*tert*-Butyldimethylsilyl)oxy)-8-(4-((tert-butyldimethylsilyl)oxy)phenyl)-2-methyloct-4-en-1-ol (18): To a stirred solution of sulfone **16** (1 g, 1.66 mmol, 1.0 equivalent) in anhydrous THF (10 mL) at -78 °C under argon, KHMDS (3.9 mL, 1.99 mmol, 0.5 M in toluene, 1.2 equivalent) was added and the reaction mixture was stirred for 30 min at the same temperature. A solution of the above aldehyde[3] **17** (742 mg, 2.1 mmol, 1.3 equivalent) dissolved in anhydrous THF (5 mL) was cannulated into the reaction mixture and stirred for another 2 h at the same temperature before quenching it with saturated solution NH_4Cl (3 mL). The resultant mixture was extracted with EtOAc (2 × 15 mL), washed with brine, dried over Na_2SO_4, filtered and concentrated in vacuo. Purification by column chromatography (SiO_2, 100-200 mesh, 3% EtOAc in hexane as eluent) furnished the corresponding pure E-olefin (736 mg, 77%, *E*:*Z* ~ 4:1), as a colourless liquid: R_f = 0.7 (5% EtOAc in hexane); $[\alpha]_D^{28}$ = -153 (c 0.5, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48 (dt, *J* = 6.4, 1.4 Hz, 6H), 7.37 – 7.20 (m, 10H), 7.01 (d, *J* = 8.4 Hz, 2H), 6.76 (d, *J* = 8.4 Hz, 2H), 5.38 (tq, *J* = 15.1, 7.6, 6.3 Hz, 2H), 3.80 – 3.69 (m, 1H), 3.02 – 2.89 (m, 2H), 2.67 (dd, *J* = 13.5, 4.8 Hz, 1H), 2.52 (dd, *J* = 13.5, 7.5 Hz, 1H), 2.28 – 2.08 (m, 3H), 1.88 (ddd, *J* = 23.5, 13.5, 6.7



Hz, 2H), 1.01 (d, *J* = 1.9 Hz, 9H), 0.97 (d, *J* = 6.6 Hz, 3H), 0.85 (d, *J* = 2.1 Hz, 9H), 0.20 (s, 6H), -0.07 (s, 3H), -0.23 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.97, 144.64, 132.54, 131.18, 130.80, 128.91, 128.01, 127.78, 126.92, 119.90, 119.86, 86.23, 77.58, 77.16, 76.74, 74.25, 68.01, 42.81, 40.87, 37.14, 34.43, 26.05, 25.90, 18.38, 18.25, 17.32, -4.29, -4.60, -4.82; IR(neat): ν_{max} 2955, 2928, 2857, 1509, 1253, 1068, 971, 835, 744, 705, 632 cm^{-1}; HRMS (ESI) *m/z* calculated for C46H64O3Si2Na $[M+Na]^+$ 743.4291, found 743.4291.

To an ice-cold solution of the above olefin (922 mg, 1.27 mmol, 1.0 equivalent) in anhydrous CH_2Cl_2/MeOH (10:1, 5 mL) under argon, CSA (15 mg, 0.06 mmol, 0.05 equivalent) was added. The reaction was continued for 4 h at 0 °C before quenching it with Et_3N (2 mL). The resultant mixture was concentrated and purified by column chromatography (SiO_2, 100-200 mesh, 15% EtOAc in hexane as eluent) to provide the required trityl deprotected alcohol **18** (486 mg, 80%) as a colourless oil: R_f = 0.4 (15% EtOAc in hexane); $[\alpha]_D^{28}$ = -162.3 (c 0.69, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.10 – 6.92 (m, 2H), 6.80 – 6.56 (m, 2H), 5.62 – 5.27 (m, 2H), 3.92 – 3.69 (m, 1H), 3.60 – 3.33 (m, 2H), 2.78 – 2.49 (m, 2H), 2.29 – 1.99 (m, 3H), 1.93 (dt, *J* = 13.1, 6.8 Hz, 1H), 1.70 (dt, *J* = 13.1, 6.5 Hz, 2H), 1.60 – 1.41 (m, 1H), 0.98 (s, 9H), 0.93 (d, *J* = 7.0 Hz, 3H), 0.84 (d, *J* = 0.9 Hz, 9H), 0.17 (s, 6H), -0.08 (d, *J* = 4.1 Hz, 3H), -0.24 (d, *J* = 2.9 Hz, 3H).; ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.00, 132.40, 131.06, 130.76, 129.58, 128.34, 127.38, 119.90, 100.11, 77.58, 77.16, 76.74, 74.15, 68.15, 42.84, 40.68, 36.95, 36.13, 26.04, 25.88, 18.36, 18.25, 16.70, -4.31, -4.62, -4.82; IR(neat): ν_{max} 3402, 2954, 2928, 2855, 1507, 1455, 1326, 1254, 9103, 833, 810, 775 cm^{-1}; HRMS (ESI) *m/z* calculated for $C_{27}H_{50}O_3Si_2Na$ $[M+Na]^+$ 501.3196, found 501.2674.

(2*R*,7*R*,*E*)-7-((*tert*-Butyldimethylsilyl)oxy)-8-(4-((tert-butyldimethylsilyl)oxy)phenyl)-2-methyloct-4-enoic acid (6) : To a stirred solution of $(COCl)_2$ (0.13 mL, 1.5 mmol, 1.5 equiv.) in anhydrous CH_2Cl_2 (10 mL) under argon at -78 °C, DMSO (0.21 mL, 3.00 mmol, 3.0 equivalent)



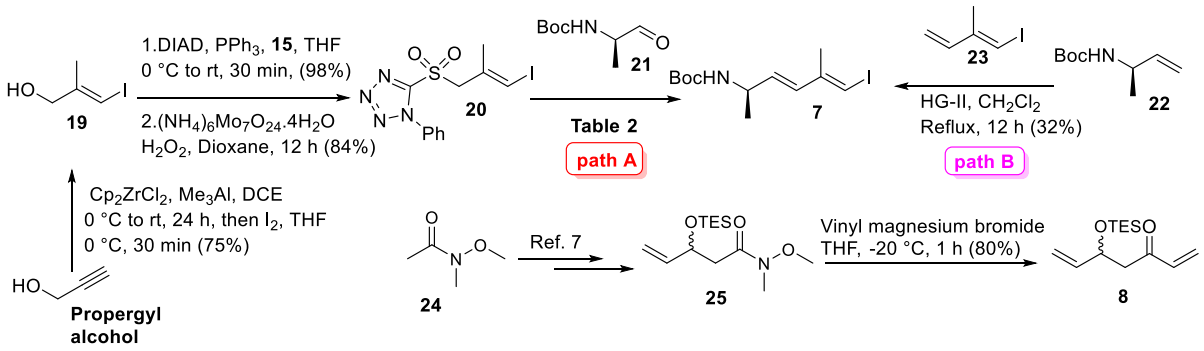
6

was added drop wise. After 15 min, a solution of compound **18** (480 mg, 1.00 mmol, dissolved in 5 mL anhydrous CH_2Cl_2, 1.0 equivalent) was cannulated into the reaction mixture and stirred further for 30 min at the same temperature. Et_3N (0.69 mL, 5.00 mmol, 5.0 equivalent) was then added and stirred further for 15 min at the same temperature. The reaction mixture was then warmed to 0 °C and quenched with saturated solution of NH_4Cl (2 mL). The resultant mixture was extracted with CH_2Cl_2 (2 × 20 mL), washed with water, brine, dried over Na_2SO_4 and concentrated in vacuo. Flash chromatography of the crude residue using a short pad of silica gave the corresponding aldehyde (quantitative) as a colourless liquid which was taken for the next step without further characterizations.

To a stirred solution of the above aldehyde in ^{t}BuOH/2-methyl-2-butene (3:1, 8 mL) at the room temperature, a freshly prepared mixture of aqueous solution of $NaClO_2$ (361 mg, 4.00 mmol, 4.0 equivalent) and $NaH_2PO_4.2H_2O$ (625 mg, 4.00 mmol, 4.0 equivalent) was added. The reaction was continued for 3 h at room temperature prior to extract with EtOAc (3 × 20 mL). The organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification of the crude residue by column chromatography (SiO_2, 60-120 mesh, 25% EtOAc in hexane as eluent) provided carboxylic acid **6** (394 mg, 80% over two steps) as a colourless oil: R_f = 0.3 (20% EtOAc in hexane); $[\alpha]_D^{28}$ = -1.3 (c 0.65, $CHCl_3$) ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.08 – 6.94 (m, 2H), 6.80 – 6.69 (m, 2H), 5.67 – 5.48 (m, 1H), 5.43 (t, *J* = 6.7 Hz, 1H), 3.78 (dq, *J* = 7.3, 5.3 Hz, 1H), 2.67 (dd, *J* = 13.5, 5.0 Hz, 1H), 2.62 – 2.47 (m, 2H), 2.41 (dt, *J* = 13.3, 6.6 Hz, 1H), 2.26 – 2.10 (m, 3H), 1.18 (d, *J* = 6.9 Hz, 3H), 0.98 (s, 9H), 0.84 (s, 9H), 0.18 (s, 6H), -0.08 (d, *J* = 2.7 Hz, 3H), -0.24 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 182.75, 154.01, 132.35, 130.78, 129.58, 129.23, 119.93, 119.89, 77.58, 77.16, 76.74, 74.02, 42.81, 40.65, 39.65, 36.63, 26.03, 25.89, 18.36, 18.23, 16.48, -4.30, -4.61, -4.82; IR(neat): ν_{max} 2954, 2929, 2857, 1706, 1609, 1509, 1471, 1362, 1251, 1168, 1099, 912, 833, 810, 694, cm^{-1}; HRMS (ESI) *m/z* calculated for $C_{27}H_{48}O_4Si_2Na$ $[M+Na]^+$ 515.2989, found 515.2977.

1.5.2. Synthesis of Intermediates 7 & 8:

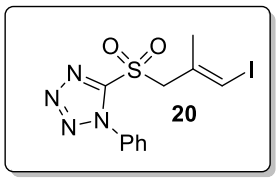
Scheme S2: *Synthesis of Intermediates 7 & 8*



(*E*)-3-Iodo-2-methylprop-2-en-1-ol (19) : Under argon atmosphere [Cp_2ZrCl_2] (1.03 g, 4.45 mmol, 0.5 equivalent) was dissolved in 50 mL of anhydrous dichloroethane and Me_3Al solution (13.3 mL, 26.7 mmol, 3.0 equivalent, 2.0 M in hexanes) was added. The stirred solution was then cooled to 0 °C and a solution of propargyl alcohol (0.5 mL, 8.9 mol, 1.0 equivalent) in 10 mL of anhydrous dichloroethane were added dropwise. The reaction mixture was allowed to warm to the room temperature and stirred further for 24 h. Next, the reaction mixture was cooled to -30 °C and a solution of iodine (3.38 g, 13.3 mmol, 1.5 equivalent) in 15 mL of anhydrous THF was added slowly and the mixture was stirred for another 1 h and quenched by careful addition of saturated solution $NaHCO_3$ (10 mL). The mixture was then diluted with $NaHCO_3$ solution. The resulting suspension was filtrated, the layers were separated and the aqueous layer was extracted Et_2O (3 × 50 mL). The combined organic layers were washed with saturated solution of $Na_2S_2O_3$, dried over Na_2SO_4 and the solvent was removed under reduced pressure. The resultant mixture was concentrated and purified by column chromatography (SiO_2, 100-200 mesh, 25% EtOAc in hexane as eluent) to provide the required iodo alcohol **19** (1.3 g, 75%) as a yellow oil: R_f = 0.3 (15% EtOAc in hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.19 (s, 1H), 4.02 (s, 2H), 1.77 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.1, 77.3, 66.8, 21.4; IR(neat): ν_{max} 3304, 2913, 2852, 1621, 1433, 1376,

1275, 1252, 1067, 1010, 773 cm^{-1}. HRMS (ESI) *m/z* calcd for C_4H_7IONa $[M+Na]^+$ 220.9439, found 220.9437.

(*E*)-5-((3-Iodo-2-methylallyl)sulfonyl)-1-phenyl-1H-tetrazole (20): To a solution of compound **15** (1.08 g, 5.4 mmol, 1.5 equivalent) in anhydrous THF at 0 °C , PPh_3 (2.15 g, 8.2 mmol, 1.5 equivalent), and 1-phenyl-1H-tetrazol-5-thiol **15** (1.46 g, 8.2 mmol, 1.5 equivalent), DIAD (1.62 mL, 8.2 mmol, 1.5 equivalent) was added subsequently and the reaction mixture was stirred for 2 h at the ambient temperature. The reaction mixture was then quenched with saturated solution of $NaHCO_3$ (10 mL), extracted with EtOAc (2 × 30 mL), washed with brine, dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by column chromatography (SiO_2, 100-200 mesh, 6% EtOAc in hexane as eluent) to afford the corresponding sulphide (1.89 g, 98%) as a white amorphous solid: R_f = 0.6 (25% EtOAc in hexane); ^1H NMR (300 MHz, $CDCl_3$) δ 7.65 – 7.47 (m, 5H), 6.52 (q, J = 1.0 Hz, 1H), 4.19 (d, J = 1.0 Hz, 2H), 1.93 (d, J = 1.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.50, 141.00, 133.63, 130.40, 129.97, 124.05, 82.52, 77.58, 77.16, 76.74, 40.67, 23.08; IR(neat): ν_{max} 3060, 2913, 1614, 1595, 1497, 1408, 1381, 1277, 1236, 1088, 1073, 1013, 684, 651, 553 cm^{-1}; HRMS (ESI) *m/z* calculated for $C_{11}H_{11}IN_4SNa$ $[M+Na]^+$ 380.9647, found 380.9638.

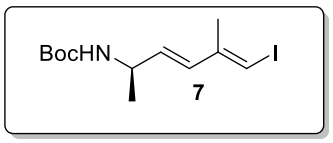


A solution of $(NH_4)_6Mo_7O_{24}.4H_2O$ (3.10 g, 2.51 mmol, 0.5 equivalent) in 30% w/w H_2O_2 (15.06 mL, 3 mL/mmol) was added to a stirring solution of above sulphide (1.8 g, 5.02 mmol, 1.0 equivalent) in dioxan (30 mL) at 0 °C and stirred further for 3 h at the same temperature prior to quench with saturated NH_4Cl solution (20 mL) and CH_2Cl_2 (30 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 50 mL), and the combined organic fractions were dried over Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography (SiO_2, 100-200 mesh, 10% EtOAc in hexane as eluent) to afford the corresponding sulfone **20** (1.89 g, 84%) as a white amorphous solid: R_f = 0.53 (25% EtOAc

in hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.71 – 7.48 (m, 5H), 6.67 (d, J = 1.1 Hz, 1H), 4.58 (d, J = 0.8 Hz, 2H), 2.01 (d, J = 1.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.13, 132.99, 132.50, 131.73, 129.80, 125.40, 89.75, 77.58, 77.16, 76.74, 63.84, 24.95; IR(neat): ν_{max} 3065, 2925, 1595, 1497, 1461, 1343, 1284, 1157, 1136, 1014, 761, 687, 636, 521, 478 cm^{-1}; HRMS (ESI) *m/z* calculated for $C_{11}H_{11}IN_4O_2SNa$ $[M+Na]^+$ 412.9545, found 412.9533.

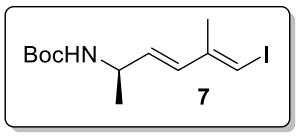
Path A

***tert*-Butyl ((*R*,*3E*,*5E*)-6-iodo-5-methylhexa-3,5-dien-2-yl)carbamate (7) :** To a stirred solution of sulfone **20** (50 mg, 0.12 mmol, 1.0 equivalent) in anhydrous DME (3 mL) at -60 °C under argon, KHMDS (0.30 mL, 0.15 mmol, 0.5 M in toluene, 1.25 equivalent) was added and the reaction mixture was stirred for 30 min at the same temperature. A solution of the above aldehyde[4] **21** (21 mg, 0.12 mmol, 1.0 equivalent) dissolved in anhydrous DME (2 mL) was cannulated into the reaction mixture and stirred for another 2 h at the same temperature before quenching it with saturated aqueous NH_4Cl solution (2 mL). The resultant mixture was extracted with EtOAc (2 × 20 mL), washed with brine, dried over Na_2SO_4, filtered and concentrated in *vacuo*. The crude product was purified by column chromatography (SiO_2, 100-200 mesh, 10% EtOAc in hexane as eluent) to yield iodo compound **7** along with its inseparable mixture of *Z*-isomer (21 mg, 68% yield, *3E:3Z* ~ 3:1) as a yellow liquid.



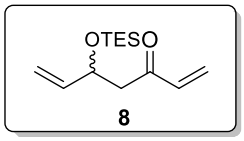
Path B

***tert*-Butyl ((*R*,*3E*,*5E*)-6-iodo-5-methylhexa-3,5-dien-2-yl)carbamate (7)** : To a solution of alkene[5] **22** (18 mg, 0.10 mmol, 1.0 equivalent) and diene[6] **23** (20 mg, 0.10 mmol, 1.0 equivalent) in degassed CH_2Cl_2 (2 mL) under argon, G-II catalyst (4 mg, 0.005 mmol, 0.05 equivalent) was added at the



room temperature. The reaction mixture was then refluxed for 12 h. The solvent was removed under reduced pressure, and the crude residue was purified by flash column chromatography (SiO_2, 240-400 mesh, 3-5% EtOAc in hexane as the eluent) to obtain the cross coupled product **7** (10.3 mg, 32% yield, *3E:3Z* ~ 10:1) as a colourless liquid. R_f = 0.4 (5% EtOAc in hexane); $[\alpha]_D^{28}$ = +88.2 (c 0.36, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.35 – 6.30 (m, 1H), 6.30 – 6.19 (m, 1H), 5.69 (dd, *J* = 15.6, 5.7 Hz, 1H), 4.45 (s, 1H), 4.25 (s, 1H), 1.94 (d, *J* = 1.0 Hz, 3H), 1.44 (s, 11H), 1.24 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.19, 144.65, 132.29, 130.44, 83.56, 77.58, 77.36, 77.16, 76.74, 29.85, 28.57, 21.21, 20.30; IR (neat) ν_{max} 3346, 2976, 2929, 1693, 1500, 1365, 1246, 1157, 1047, 1026, 960, 756 cm^{-1}; HRMS (ESI) *m/z* calculated for $C_{12}H_{20}INO_2Na$ $[M+Na]^+$ 360.0436, found 360.0435.

5-((Triethylsilyl)oxy)hepta-1,6-dien-3-one (8) : To a solution of known TES protected aldol



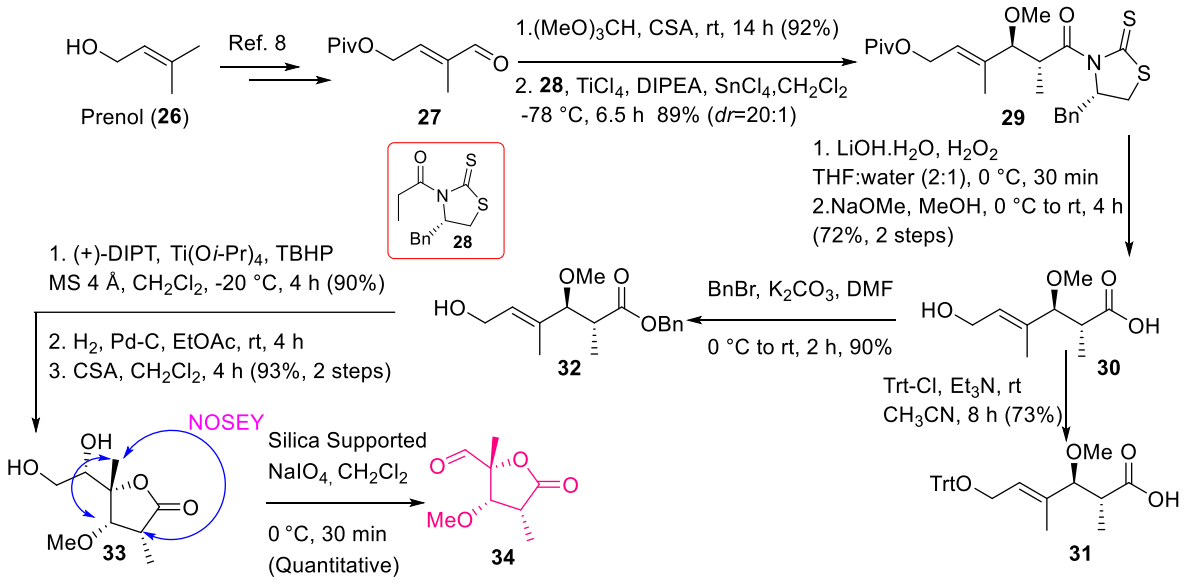
8

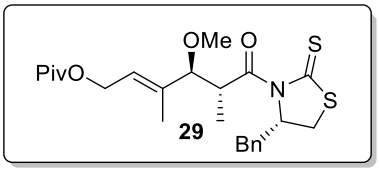
product[7] **25** (500 mg, 1.61 mmol, 1.0 equivalent) in anhydrous THF (10 mL) at -20 °C under argon, 1 (M) vinylmagnesium chloride in THF solution of (2.10 mL, 2.10 mmol, 1.5 equivalent) was added slowly. The reaction was stirred for 1 h and quenched by slow addition of saturated solution of NH_4Cl (3 mL). The mixture was then diluted with Et_2O and the aqueous phase was extracted with EtOAc (2 × 20 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification by column chromatography (SiO_2, 100-200 mesh, 3% EtOAc in hexane as eluent) furnished vinyl ketone **8** (309 mg, 80%) as a colourless liquid: R_f = 0.7 (5% EtOAc in hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.45 – 6.13 (m, 2H), 5.94 – 5.71 (m, 2H), 5.22 (dt, *J* = 17.2, 1.5 Hz, 1H), 5.04 (dt, *J* = 10.4, 1.4 Hz, 1H), 4.67 (dddd, *J* = 7.4, 6.2, 5.1, 1.2 Hz, 1H), 2.89 (ddd, *J* = 15.1, 7.5, 0.9 Hz, 1H), 2.60 (ddd, *J* = 15.1, 5.3, 1.0 Hz, 1H), 0.90 (t, *J* = 8.0 Hz, 9H), 0.56 (q, *J* = 7.9 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.94, 140.71, 137.52, 128.71, 114.37, 77.58, 77.16, 76.74, 70.44, 47.93, 6.87, 4.92; IR(neat): ν_{max} 2944, 2907, 1660, 1415,

1375, 1244 cm^{-1}; HRMS (ESI) *m/z* calculated for $C_{13}H_{24}O_2SiNa$ $[M+Na]^+$ 263.1443, found 263.1442.

1.5.3. Synthesis of Aldehyde 34:

Scheme S3: *Synthesis of Aldehyde* ***34***

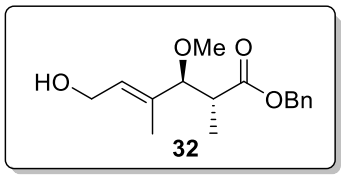




(*4R,5R,E*)-6-((*S*)-4-Benzyl-2-thioxothiazolidin-3-yl)-4-methoxy-5-methyl-6-oxohex-2-en-1-yl pivalate (29) : To an ice-cold solution of the known aldehyde[8] **27** (4 g, 21.4 mmol, 1.0 equivalent) in trimethylorthoformate (12 mL, 107 mmol, 5.0 equivalent), CSA (249 mg, 1.07 mmol, 0.05 equivalent) was added. The reaction mixture was stirred for 14 h at the room temperature and then quenched with saturated solution of $NaHCO_3$ (10 mL). The resultant mixture was extracted with EtOAc (2 × 40 mL), washed with water, brine, dried over Na_2SO_4, filtered and concentrated in vacuo. The crude product was then filtered through a short pad of Celite to provide the corresponding dimethyl acetal (4.53 g, 92%) as a colourless liquid (R_f = 0.5 in 5% EtOAc in hexane) which was used for next step without further characterizations.

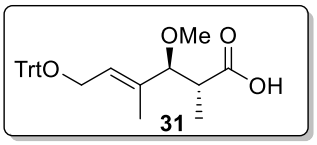
Freshly distilled $TiCl_4$ (2.37 mL, 21.65 mmol, 1.1 equivalent) was added drop wise to a stirred solution of auxiliary **28** (5.7 g, 21.65 mmol, 1.1 equivalent) dissolved in anhydrous CH_2Cl_2 (100 mL) under argon at 0 °C. The resultant yellow slurry was stirred for 10 min at 0 °C and then cooled to –78 °C. After 10 min, a solution of DIPEA (3.77 mL, 21.65 mmol, 1.1 equivalent) in anhydrous CH_2Cl_2 (10 mL) was added. A dark red solution was obtained which was stirred further for 1.5 h at the same temperature. Next, freshly distilled $SnCl_4$ (2.29 mL, 19.68 mmol, 1.1 equivalent) followed by dimethyl acetal (4.52 g, 19.68 mmol, 1.0 equivalent) dissolved in anhydrous CH_2Cl_2 (20 mL) were added drop wise into the reaction mixture. The reaction mixture was stirred for another 6.5 h at the same temperature and then quenched with saturated aqueous NH_4Cl (7 mL) solution. The resultant mixture was warmed to room temperature and extracted with CH_2Cl_2 (3 x 40 mL). The combined organic extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated in vacuo. Purification of the crude residue by flash column chromatography (SiO_2, 230-400, 4% EtOAc in hexane as eluent) provided pure major aldol adduct **29** (7.71 g, 89%, *dr* = 20:1) as a yellow oil. R_f = 0.45 (10% EtOAc in hexane); $[\alpha]_D^{28}$ = -81.2 (c 0.48, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39 – 7.27 (m, 5H), 5.67 – 5.58 (m, 1H), 5.47 (dddd, *J* = 10.5, 7.6, 3.6, 2.0 Hz, 1H), 5.06 (dq, *J* = 10.0, 6.9 Hz, 1H), 4.65 (dd, *J* = 6.6, 0.9 Hz, 2H), 3.84 (d, *J* = 10.0 Hz, 1H), 3.31 (ddd, *J* = 11.4, 7.6, 0.9 Hz, 1H), 3.22 (dd, *J* = 13.4, 3.5 Hz, 1H), 3.13 (s, 3H), 3.02 (dd, *J* = 13.4, 10.5 Hz, 1H), 2.87 (dd, *J* = 11.5, 2.0 Hz, 1H), 1.66 (dd, *J* = 1.5, 0.8 Hz, 3H), 1.19 (s, 9H), 0.98 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.55, 178.47, 177.78, 137.81, 136.91, 129.52, 129.04, 127.30, 126.16, 90.56, 77.58, 77.36, 77.16, 76.74, 68.99, 60.53, 56.30, 41.36, 38.90, 37.55, 31.58, 27.32, 14.40, 10.98; IR (neat) ν_{max} 2974, 2933, 2821, 1722, 1698, 1479, 1454, 1342, 1252, 1150, 1135, 1093, 1030, 946, 701, 749 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{24}H_{33}O_4NS_2Na$ $[M+Na]^+$ 486.1749, found 486.1749.

Benzyl (*2R,3S,E*)-6-hydroxy-3-methoxy-2,4-dimethylhex-4-enoate (32) : To a solution of compound **29** (8.0 g, 17.2 mmol, and 1.0 equivalent) in THF (90 mL) at 0 °C, lithium hydroxide solution (826 mg dissolved in 10 ml of water, 34.5 mmol, 2.0 equivalent) and 30% aqueous H_2O_2 solution (w/w 6.9 ml, 68.8 mmol, 4.0 equivalent) were added sequentially. The reaction mixture was warmed slowly to the room temperature in 30 min and extracted with EtOAc (3 × 50 mL). The organic extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification of the crude residue by flash column chromatography (SiO_2, 100-200 mesh, 15-25% EtOAc in hexane as the eluent) provided the corresponding acid (4.02 g, 86%) as a colourless liquid; R_f = 0.2 (20% EtOAc in hexane); $[\alpha]_D^{28}$ = -189.7 (c 0.67, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.59 (td, J = 6.8, 1.5 Hz, 1H), 4.73 – 4.53 (m, 2H), 3.62 (d, J = 10.1 Hz, 1H), 3.17 (s, 3H), 2.61 (dq, J = 10.2, 7.1 Hz, 1H), 1.61 (d, J = 1.3 Hz, 3H), 1.17 (s, 9H), 0.98 (d, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.7, 178.2, 94.5, 61.3, 57.2, 137.7, 120.5, 43.8, 38.9, , 27.9 12.8, , 12.3; IR (neat) ν_{max} 2922, 2913, 2822, 1727, 1588, 1412, 1399, 1320, 1202, 1188, 1098, 1093, 1031, 747 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{14}H_{24}O_5Na$ $[M+Na]^+$ 295.1521, found 295.1521.



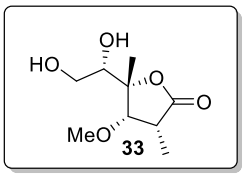
To an ice-cold solution of the above acid (3.9 g, 14.3 mmol, 1.0 equivalent) in anhydrous methanol (50 ml), NaOMe (46.8 ml, 200.46 mmol, 14.0 equivalent) was added. The reaction mixture was stirred for 4 h at the room temperature prior to removing methanol under reduced pressure. The resultant mixture was then quenched by 1(N) HCl and extracted with EtOAc (3 × 100), washed with water, brine, dried over Na_2SO_4, filtered and concentrated in vacuo. The crude product was then filtered through a short pad of Celite to provide acid-alcohol **30** as colourless liquid. R_f = 0.3 (EtOAc) which was used in the next reaction without further characterizations.

To an ice-cold solution of compound **30** (1.5 g, 7.9 mmol, 1.0 equivalent) in anhydrous DMF (20 mL) under argon, K_2CO_3 (2.20 g, 15.9 mmol, 2.0 equivalent) followed by BnBr (1.13 mL, 9.5 mmol, 1.2 equivalent) were added. The reaction was gradually warmed to the room temperature and the stirring was continued for 2 h at the same temperature. The resultant mixture was concentrated in vacuo. Purification of the crude residue by flash column chromatography (SiO_2, 100−200 mesh, 30% EtOAc in hexane as eluent) gave benzyl protected ester **32** (1.97 g, 90%) as a colourless oil; R_f = 0.4 (20% EtOAc in hexane as eluent); $[\alpha]_D^{28}$ = +110 (c 0.25, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39 – 7.27 (m, 5H), 5.70 – 5.58 (m, 1H), 5.28 – 5.06 (m, 2H), 4.33 – 4.15 (m, 2H), 3.64 (d, *J* = 10.1 Hz, 1H), 3.12 (s, 3H), 2.67 (dq, *J* = 10.2, 7.1 Hz, 1H), 1.83 (s, 1H), 1.58 – 1.50 (m, 3H), 0.98 (d, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.33, 136.27, 134.33, 131.04, 128.55, 128.14, 128.10, 89.08, 77.58, 77.16, 76.74, 66.28, 59.01, 56.29, 43.09, 14.21, 10.41; IR (neat) ν_{max} 3447, 2979, 2936, 2879, 2822, 1732, 1498, 1454. 1383, 1159, 1090, 1006, 822, 736, 599, 560 cm^{-1}; HRMS (ESI) *m/z* calculated for $C_{16}H_{22}O_4Na$ $[M+Na]^+$ 301.1416, found 301.1416.



(*2R,3S,E*)-3-Methoxy-2,4-dimethyl-6-(trityloxy)hex-4-enoic acid (31) : Et_3N (0.22 mL, 1.59 mmol, 3.0 equivalent) and trityl chloride (296 mg, 1.06 mmol, 2.0 equivalent) were added sequentially to a solution of compound **30** (100 mg, 0.53 mmol, 1.0 equivalent) in anhydrous acetonitrile (5 mL) under argon at 0 °C. After being stirred for 15 min at the same temperature, DMAP (3.24 mg, 0.26 mmol, 0.5 equivalent) was added and the reaction was continued for 8 h at the room temperature. The reaction mixture was quenched with saturated aqueous NH_4Cl (2 mL) and extracted with EtOAc (3×15 mL), washed with brine, dried over Na_2SO_4, filtered and concentrated in vacuo. Purification of the residue by column chromatography (SiO_2, 100-200 mesh, 20% EtOAc in hexane eluent) provided compound **31** (202 mg, 89%) as a white

crystalline solid; mp: 93 - 97 °C; R_f = 0.45 (20% EtOAc in hexane); $[\alpha]_D^{28}$ = +20.3 (c 0.53, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55 – 7.38 (m, 6H), 7.38 – 7.19 (m, 9H), 5.74 (td, *J* = 6.1, 1.5 Hz, 1H), 3.71 (t, *J* = 5.8 Hz, 2H), 3.65 (d, *J* = 10.2 Hz, 1H), 3.20 (s, 3H), 2.60 (dq, *J* = 10.1, 7.1 Hz, 1H), 1.38 (d, *J* = 1.2 Hz, 3H), 1.02 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 180.32, 144.29, 133.59, 129.66, 128.75, 127.95, 127.12, 88.96, 87.04, 77.58, 77.16, 76.74, 60.89, 56.35, 42.72, 14.09, 10.45; IR (neat) ν_{max} 3308, 2927, 2856, 2801, 1727, 1457, 1206, 1176, 1039, 753, 665, 614 cm^{-1}; HRMS (ESI) *m/z* calculated for $C_{28}H_{30}O_4Na$ $[M+Na]^+$ 453.2042, found 453.2042.



(*3R,4S,5S*)-5-((*R*)-1,2-Dihydroxyethyl)-4-methoxy-3,5-dimethyldihydrofuran-2(3H)-one (33) : To a suspension of powdered 4 Å MS (30 mg) in anhydrous CH_2Cl_2 (5 mL) at −20 °C under argon, (+)-DIPT (56 µL, 0.26 mmol, 0.25 equivalent) and Ti(O*i*-Pr)$_4$ (0.08 mL, 0.26 mmol, 0.25 equivalent) were added sequentially. After 15 min stirring at the same temperature, allylic alcohol **32** (300 mg, 1.07 mmol, dissolved in 5 mL anhydrous CH_2Cl_2, 1.0 equivalent) was cannulated into the reaction mixture. The reaction was continued for 15 min. TBHP (5.5 M solution in toluene, 0.43 mL, 2.37 mmol, 2.2 equivalent) was then added. The reaction mixture was stirred further at the same temperature for another 3 h and subsequently quenched with a saturated solution of tartaric acid (8 mL). The resultant mixture was stirred at the room temperature for 30 min. The mixture was extracted with CH_2Cl_2 (3 × 15 mL), washed with H_2O and brine, and dried over Na_2SO_4. The solvent was evaporated and the crude residue was purified by column chromatography (SiO_2, 100–200 mesh, 20-40% EtOAc in hexane as the eluent) to obtain the corresponding epoxide (284 mg, 90%) as a colourless oil; R_f = 0.5 in 40% EtOAc in hexane); $[\alpha]_D^{28}$ = +190.5 (c 0.85, $CHCl_3$; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39 – 7.28 (m, 5H), 5.15 (q, *J* = 12.4 Hz, 2H), 3.83 – 3.65 (m, 2H), 3.32 (s, 3H), 3.12 – 2.93 (m, 2H), 2.84

(dq, *J* = 8.9, 7.1 Hz, 1H), 2.10 (s, 1H), 1.26 (s, 3H), 1.22 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.51, 136.09, 128.61, 128.27, 128.20, 86.31, 77.58, 77.16, 76.74, 66.43, 61.21, 60.97, 58.99, 58.59, 43.41, 13.70, 12.00; IR (neat): ν_{max} 3442, 2890, 1705, 1478, 1455, 1253, 778, 586 cm−1; HRMS (ESI) *m/z* calculated for $C_{16}H_{22}O_5Na$ $[M+Na]^+$ 317.1365, found 317.1365.

A solution of the above epoxy ester (270 mg, 0.94 mmol, 1.0 equivalent) and 10% Pd/C (27 mg, 10 mol%) in distilled EtOAc (10 mL) was stirred under H_2 atmosphere (hydrogen balloon) at the room temperature for 4 h. The reaction mixture was filtered using a short Celite bed using CH_2Cl_2-MeOH (7:3) (2 × 50 mL), concentrated and this crude acid was directly used in next required step without further characterizations.

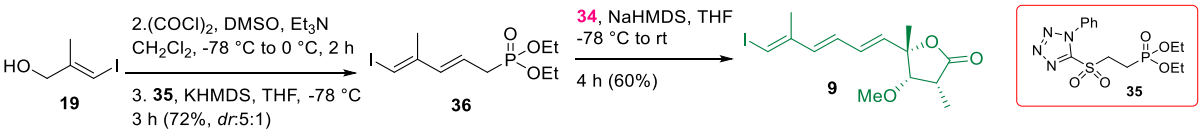
To an ice-cold solution of the above epoxide in anhydrous CH_2Cl_2 under argon, CSA (11 mg, 0.04 mmol, 0.05) was added. The reaction was continued for 4 h at 0 °C before quenching it with Et_3N (1 mL). The resultant mixture was concentrated and purified by column chromatography (SiO_2, 100-200 mesh, 60-100% EtOAc in hexane as eluent) to provide the required diol **33** (180 mg, 93%, 2 steps) as a white amorphous solid: R_f = 0.3 (60% EtOAc in hexane); $[\alpha]_D^{28}$ = +90.3 (c 0.57, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.06 (dd, *J* = 8.6, 2.9 Hz, 1H), 3.82 (dd, *J* = 11.2, 2.9 Hz, 1H), 3.75 (s, 1H), 3.70 – 3.58 (m, 2H), 3.47 (s, 3H), 2.90 (qd, *J* = 7.2, 5.6 Hz, 1H), 1.26 (s, 3H), 1.22 (d, *J* = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.90, 86.83, 84.98, 77.58, 77.16, 76.74, 71.37, 63.12, 60.86, 39.21, 18.38, 8.56; IR(neat): ν_{max} 3427, 2943, 1759, 1454, 1380, 1332, 1199, 1077, 1015, 754, 713, cm^{-1}; HRMS (ESI) *m/z* calculated for $C_9H_{16}O_5Na$ $[M+Na]^+$ 227.0895, found 227.0895.

To a vigorously stirred solution of diol **33** (88 mg, 0.43 mmol, 1.5 equivalent) in CH_2Cl_2 (8 mL) was added silica gel-supported $NaIO_4$ {872 mg, 2000 mg/ 1 mmol, prepared using 2.57 g $NaIO_4$ blended with 10g silica gel (240-400 mesh) } and the reaction was continued for 30 min. The mixture was then filtered through a sintered glass funnel, and the silica gel was

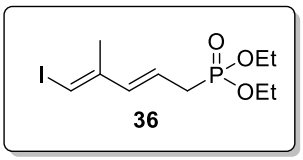
washed thoroughly with eluent (CH_2Cl_2/MeOH = 30:1). Organic solvents were removed under reduced pressure to afford the corresponding aldehyde which was taken for the next step without further characterizations.

1.5.4. Synthesis of Intermediate 9:

Scheme S4: *Synthesis of Intermediate* ***9***

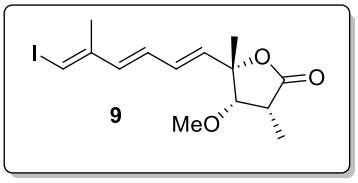


Diethyl ((*2E*,*4E*)-5-iodo-4-methylpenta-2,4-dien-1-yl)phosphonate (36) : To a stirred solution of $(COCl)_2$ (0.324 mL, 3.78 mmol, 1.5 equivalent) in anhydrous CH_2Cl_2 (20 mL) under argon at -78 °C, DMSO (0.53 mL, 7.57 mmol, 3.0 equivalent) was added drop wise. After 15 min, a solution of compound **19** (500 mg, 2.52 mmol, dissolved in 5 mL anhydrous CH_2Cl_2, 1.0 equivalent) was cannulated into the reaction mixture and stirred further for 30 min at the same temperature. Et_3N (1.75 mL, 12.62 mmol, 5.0 equivalent) was then added and stirred further for 15 min at the same temperature. The reaction mixture was then warmed to 0 °C and quenched with saturated aqueous solution of NH_4Cl (5 mL). The resultant mixture was extracted with CH_2Cl_2 (2 × 20 mL), washed with water, brine, dried over Na_2SO_4 and concentrated in vacuo. Flash chromatography of the crude residue using a short pad of silica gave the corresponding aldehyde (493 mg, quantitative) as a yellow liquid which was taken for the next step without further characterizations.



Sulfonylphosphonate **35** (847 mg, 2.26 mmol, 1 equivalent) was dissolved in anhydrous THF (12 mL) under argon and cooled to -78 °C. KHMDS (5.83 mL, 2.71 mmol, 1.2 equivalent, 0.5 M in THF) was added slowly. After 5 min, the above aldehyde (493 mg, 2.51 mmol, 1.0 equivalent) was added to the solution and stirred further for 20 min. The

reaction mixture was warmed to 0 °C and stirring was continued for 1 h prior to quench by addition of saturated solution of NH_4Cl (5 mL). The resultant mixture was extracted with EtOAc (2 × 20 mL), washed with brine, dried over Na_2SO_4, and then concentrated in vacuo. The reaction mixture was purified by column chromatography (SiO_2, 100-200 mesh, 8% acetone in hexane as eluent) to afford the required phosphonate **36** (521 mg, 72%, *dr*.5:1) as a colorless oil, R_f = 0.4 (20% acetone in hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.37 – 6.20 (m, 2H), 5.83 – 5.60 (m, 1H), 4.09 (dqd, *J* = 7.9, 7.0, 0.9 Hz, 4H), 2.59 (ddd, *J* = 22.4, 7.6, 1.3 Hz, 2H), 1.95 (t, *J* = 1.0 Hz, 3H), 1.30 (t, *J* = 7.1 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.74, 144.69, 135.94, 135.74, 119.56, 119.41, 83.77, 83.70, 77.58, 77.16, 76.74, 62.23, 62.14, 31.84, 29.98, 20.18, 16.63, 16.55; IR(neat): ν_{max} 2981, 2907, 1735, 1503, 1391, 1296, 1245, 1161, 1020, 959, 758, 676 cm^{-1}. HRMS (ES) *m/z* calculated for $C_{10}H_{18}IO_3P$ $[M+H]^+$ 345.0117, found 345.0078.



9

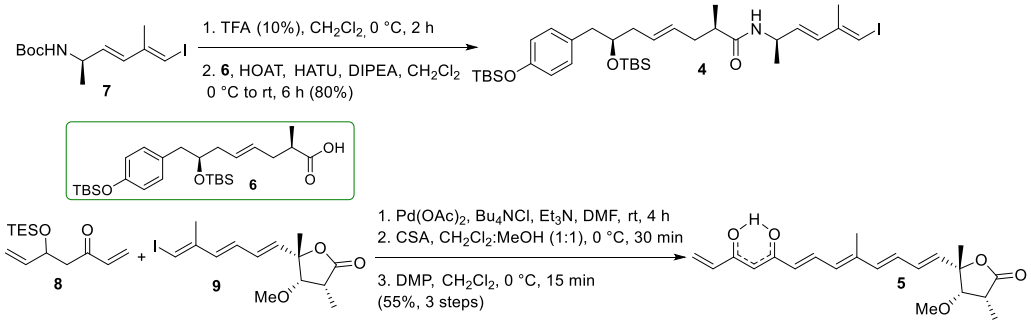
(*3R,4S,5S*)-5-((*1E,3E,5E*)-6-Iodo-5-methylhexa-1,3,5-trien-1-yl)-4-methoxy-3,5-dimethyldihydrofuran-2(3H)-one (9) :

Phosphonate (100 mg, 0.29 mmol, 1.0 equivalent) was dissolved in anhydrous THF (3 mL) and cooled to -78 °C. NaHMDS (0.29 mL, 1.1 equivalent, 1 M in hexanes) was added slowly. After 5 min, the above aldehyde (1.5 equivalent) was added into the reaction mixture and stirred for 15 minutes. The reaction mixture was warmed to the room temperature and stirred further for 4 h before quenching it with saturated solution NH_4Cl (2 mL). The resultant mixture was extracted with EtOAc (3 × 15 mL), washed with brine, dried over Na_2SO_4, filtered and concentrated in vacuo. Purification of the crude residue by column chromatography (SiO_2, 100-200 mesh, 10% EtOAc in hexane as eluent) furnished triene **9** (63 mg, 60%) as a colourless liquid: R_f = 0.4 (10% EtOAc in hexane); $[\alpha]_D^{28}$ = -125.9 (c 0.32, $CHCl_3$; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.47 – 6.28 (m, 4H), 6.03 – 5.88 (m,

1H), 3.65 (d, *J* = 6.5 Hz, 1H), 3.38 (s, 3H), 2.97 – 2.84 (m, 1H), 1.98 (d, *J* = 1.0 Hz, 3H), 1.49 (s, 3H), 1.22 (d, *J* = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.40, 144.13, 133.65, 131.79, 129.54, 127.35, 85.26, 85.22, 83.87, 76.59, 76.16, 75.74, 59.05, 38.39, 23.71, 19.08, 8.35; IR(neat): ν_{max} 2981, 2924, 2853, 1767, 1571, 1449, 1378, 1334, 1145, 1100, 1077, 1028, 932, 760, 688, 621 cm^{-1}; HRMS (ESI) *m/z* calculated for $C_{14}H_{19}IO_3Na$ $[M+Na]^+$ 385.0276, found 385.0276.

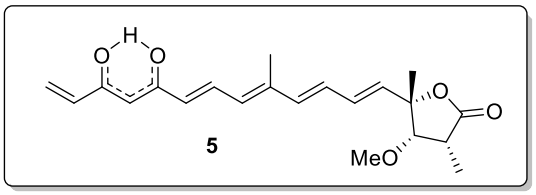
1.5.5. Synthesis of Coupling Partners 4 and 5:

Scheme S5*: Synthesis of Coupling Partners 4 and 5*



(*2R,7R,E*)-7-((*tert*-Butyldimethylsilyl)oxy)-8-(4-((tert-butyldimethylsilyl)oxy)phenyl)-N-((*R,3E,5E*)-6-iodo-5-methylhexa-3,5-dien-2-yl)-2-methyloct-4-enamide (4) : To a solution of compound **7** (62 mg, 0.183 mmol, 1.0 equivalent) in anhydrous CH_2Cl_2 (2.7 mL) under argon, 10% TFA (0.3 mL) was added. After being stirred at the room temperature for 30 min, the reaction mixture was concentrated in vacuo. The residue was azeotroped with anhydrous toluene (3 × 1 mL), dissolved in anhydrous CH_2Cl_2 (3 mL) and transferred via cannula under argon atmosphere into a stirred mixture of acid **6** (90 mg, 0.183 mmol, 1.0 equivalent), DIPEA (0.16 mL, 0.919 mmol, 5.0 equivalent), HOAt (30 mg, 0.22 mmol, 1.2 equivalent) and HATU (83.9 mg, 0.22 mmol, 1.2 equivalent) in anhydrous CH_2Cl_2 (3 mL) at the room temperature. After being stirred for 12 h at the same

temperature, the reaction mixture was concentrated in vacuo. The residue was purified by flash chromatography (SiO_2, 100-200 mesh, 8 to 15% EtOAc in hexane as eluent) to give iodide **4** (104 mg, 80% in 2 steps) as a colourless liquid; R_f = 0.4 (20% EtOAc in hexane); $[\alpha]_D^{28}$ = +111.3 (c 0.66, $CHCl_3$; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.06 – 6.95 (m, 2H), 6.77 – 6.67 (m, 2H), 6.31 (s, 1H), 6.21 (ddd, *J* = 15.6, 1.6, 0.6 Hz, 1H), 5.68 (ddd, *J* = 15.6, 5.7, 0.6 Hz, 1H), 5.52 (dt, *J* = 14.4, 6.8 Hz, 1H), 5.43 – 5.27 (m, 2H), 4.59 (dq, *J* = 13.8, 6.6 Hz, 1H), 3.76 (dq, *J* = 7.4, 5.6 Hz, 1H), 2.72 – 2.46 (m, 2H), 2.34 (dd, *J* = 12.9, 6.7 Hz, 1H), 2.26 – 2.06 (m, 4H), 1.91 (d, *J* = 1.0 Hz, 3H), 1.24 (d, *J* = 6.8 Hz, 3H), 1.15 (d, *J* = 6.6 Hz, 3H), 0.97 (s, 9H), 0.83 (s, 9H), 0.16 (d, *J* = 0.8 Hz, 6H), -0.09 (s, 3H), -0.25 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.03, 154.04, 144.50, 132.26, 131.58, 130.87, 130.77, 129.86, 129.43, 119.91, 83.96, 77.58, 77.16, 76.74, 73.97, 46.01, 42.98, 41.89, 40.78, 37.55, 26.05, 25.88, 20.77, 20.26, 18.37, 18.24, 17.54, -4.29, -4.55, -4.79; IR (neat): ν_{max} 3287, 2955, 2927, 2855, 1645, 1509, 1462, 1252, 1167, 1099, 965, 775 cm−1; HRMS (ESI) *m/z* calculated for $C_{34}H_{58}INO_3Si_2Na$ $[M+Na]^+$ 734.2898, found 734.2898.



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(*3R,4S,5S*)-5-((*1E,3E,5E,7E,9Z*)-9-Hydroxy-5-methyl-11-oxotrideca-1,3,5,7,9,12-hexaen-1-yl)-4-methoxy-3,5-dimethyldihydrofuran-2(3H)-one (5) : To a solution of compounds **8** (39 mg, 0.16 mmol, 2.0 equivalent) and **9** (30 mg, 0.08 mmol, 1.0 equivalent) in anhydrous and degassed DMF (2 mL), $Pd(OAc)_2$ (0.18 mg, 0.0008 mmol, 0.01 equivalent), Bu_4NCl (45 mg, 0.16 mmol, 2.0 equivalent) and Et_3N (0.04 mL, 0.33 mmol, 4.0 equivalent) were added. The reaction mixture was stirred for 1 h at the room temperature. The mixture was filtered through a celite pad. The filtrate was quenched by saturated solution of NH_4Cl (1 mL) and extracted by Et_2O (2 × 15 mL). The solvent was evaporated under reduced pressure and the crude residue was purified by column chromatography (SiO_2, 230-400 mesh, 20% EtOAc in hexane as eluent) to give the

corresponding keto compound (34 mg, 90%) as a yellow oil: R_f = 0.43 (20% EtOAc in hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.64 – 7.44 (m, 1H), 6.57 – 6.30 (m, 3H), 6.31 – 5.78 (m, 4H), 5.23 (dt, *J* = 17.2, 1.6 Hz, 1H), 5.05 (dt, *J* = 10.4, 1.5 Hz, 1H), 4.73 – 4.57 (m, 1H), 3.67 (d, *J* = 6.5 Hz, 1H), 3.39 (s, 3H), 3.00 – 2.78 (m, 2H), 2.70 – 2.55 (m, 1H), 2.01 (d, *J* = 2.6 Hz, 3H), 1.50 (s, 3H), 1.22 (d, *J* = 7.4 Hz, 3H), 0.91 (t, *J* = 7.9 Hz, 9H), 0.57 (q, *J* = 8.2 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.55, 177.30, 144.75, 143.47, 140.86, 138.52, 137.73, 137.36, 134.29, 133.66, 131.82, 131.09, 130.95, 130.75, 130.55, 130.17, 130.00, 129.83, 128.63, 114.26, 86.44, 86.30, 86.15, 86.10, 77.58, 77.36, 77.16, 76.74, 70.81, 60.08, 60.05, 49.50, 39.42, 39.37, 29.81, 24.85, 24.50, 21.02, 13.27, 9.37, 9.33, 6.91, 4.93; IR (neat): ν_{max} 2924, 2854, 1773, 1670, 1577, 1457, 1378, 1195, 1079, 1029, 990, 743 cm−1; HRMS (ESI) *m/z* calculated for $C_{27}H_{42}O_5SiNa$ $[M+Na]^+$ 497.2699, found 497.2698.

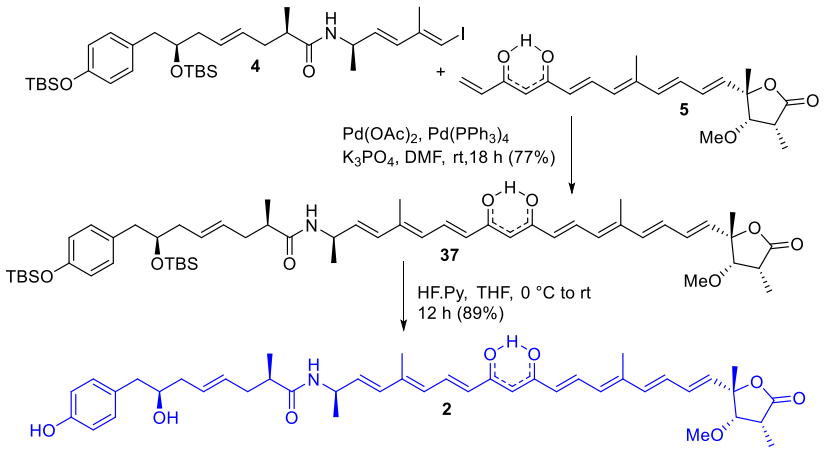
To an ice-cold solution of the above compound (30 mg, 0.063 mmol, 1.0 equivalent) in anhydrous CH_2Cl_2/MeOH (1:1, 3 mL) under argon, CSA (1 mg, 0.0006 mmol, 0.01) was added. The reaction was continued for 30 min at 0 °C and then concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, 100-200 mesh, 15% EtOAc in hexane as eluent) to provide the corresponding secondary alcohol (19 mg, 85%) as a yellow oil: R_f = 0.3(30% EtOAc in hexane), ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60 (dd, *J* = 15.1, 11.8 Hz, 1H), 6.62 – 6.31 (m, 3H), 6.31 – 6.12 (m, 2H), 6.12 – 5.81 (m, 2H), 5.31 (dt, *J* = 17.2, 1.5 Hz, 1H), 5.14 (dt, *J* = 10.5, 1.4 Hz, 1H), 4.63 (s, 1H), 3.68 (dd, *J* = 6.6, 2.2 Hz, 1H), 3.39 (s, 3H), 3.34 – 3.20 (m, 1H), 2.99 – 2.84 (m, 1H), 2.84 – 2.70 (m, 2H), 2.04 (d, *J* = 0.9 Hz, 4H), 1.50 (s, 3H), 1.23 (d, *J* = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.13, 177.29, 145.67, 139.34, 139.12, 137.54, 134.61, 134.05, 132.25, 131.47, 130.90, 130.65, 129.79, 129.59, 129.29, 128.27, 115.16, 115.10, 86.38, 86.30, 86.13, 86.10, 77.58, 77.36, 77.16, 76.74, 69.13, 60.06, 47.02, 46.99, 39.36, 29.83, 24.91, 21.08, 14.33, 13.34, 9.40; IR(neat): ν_{max} 3433,

2924, 2853, 1772, 1665, 1453, 1382, 1079, 1025, 996, 941 cm^{-1}; HRMS (ESI) *m/z* calculated for $C_{21}H_{29}O_5$ $[M+H]^+$ 361.2015, found 361.2015.

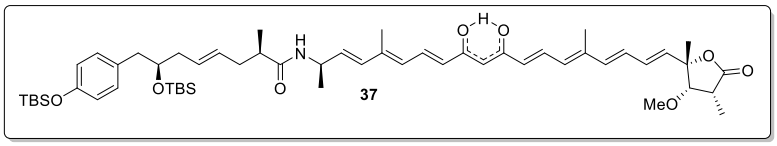
To an ice-cold solution of above secondary alcohol (19 mg, 0.052 mmol, 1.0 equivalent) in anhydrous CH_2Cl_2 under argon, DMP (33 mg, 0.079 mmol, 1.5 equivalent) was added. The reaction was continued for 1 h at 0 °C. The resultant mixture was immediately concentrated and purified by column chromatography (SiO_2, 100-200 mesh, 25% EtOAc in hexane as eluent) to provide the required 1,3-dicarbonyl compound **5** (13.6 mg, 73%) as a bright yellow oil: R_f = 0.5(30% EtOAc in hexane); $[\alpha]_D^{28}$ = +156.3 (c 0.5, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 15.61 (s, 1H), 7.67 (dd, *J* = 14.9, 11.9 Hz, 1H), 6.56 – 6.43 (m, 2H), 6.43 – 6.34 (m, 1H), 6.31 – 6.22 (m, 2H), 6.14 – 6.03 (m, 1H), 3.67 (dd, *J* = 6.6, 1.7 Hz, 1H), 3.40 (s, 3H), 2.99 – 2.85 (m, 1H), 2.04 (s, 3H), 1.50 (s, 3H), 1.23 (d, *J* = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 183.86, 183.04, 177.33, 143.88, 137.90, 136.85, 134.12, 133.50, 130.85, 130.82, 130.52, 127.62, 125.98, 101.13, 86.32, 86.19, 77.58, 77.36, 77.16, 76.74, 60.10, 60.07, 39.45, 39.38, 29.84, 24.95, 13.28, 9.41; IR(neat): ν_{max} 3477, 2925, 2854, 1771, 1577, 1612, 1453, 1271, 1246, 1197, 1132, 1100, 1029, 1077, 988, 937 cm^{-1}; HRMS (ESI) *m/z* calculated for $C_{21}H_{27}O_5$ $[M+H]^+$ 359.1858, found 359.1858.

1.5.6. Completion of the Total Synthesis of Thailandandamide Lactone (2):

Scheme S6: *Completion of the Synthesis of Thailandandamide Lactone* ***2***



(*2R,7R,E*)-7-((*tert*-Butyldimethylsilyl)oxy)-8-(4-((tert-butyldimethylsilyl)oxy)phenyl)-N-((*R,3E,5E,7E,10Z,12E,14E,16E,18E*)-11-hydroxy-19-((*2S,3S,4R*)-3-methoxy-2,4-dimethyl-5-oxotetrahydrofuran-2-yl)-5,15-dimethyl-9-oxononadeca-3,5,7,10,12,14,16,18-octaen-2-yl)-2-methyloct-4-enamide (37) : To a solution of compound **5** (2.5 mg, 0.0065

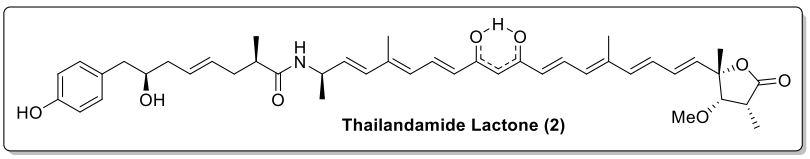


37

mmol) and compound **4** (4.96 mg, 0.0065 mmol) in anhydrous and degassed DMF (1.0 mL), $Pd(OAc)_2$ (0.01 mg, 0.000065 mmol), $Pd(PPh_3)_4$ (0.08 mg, 0.000065 mmol) and K_3PO_4 (1.65 mg, 0.007 mmol) were added. The reaction mixture was stirred for 18 h at room temperature. The mixture was filtered through a celite pad. The filtrate was quenched by NH_4Cl then extracted by diethyl ether. Purified by column chromatography (SiO_2, 230-400 mesh, 30% EtOAc in hexane as eluant) to give corresponding TBS protected thailandamide lactone **37** (4.5 mg, 77%) as a yellow oil: R_f = 0.25 (30% EtOAc in hexane); $[\alpha]_D^{28}$ = -26.3 (c 0.26, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 15.91 (s, 1H), 7.84 – 7.56 (m, 2H), 7.03 – 6.93 (m, 2H), 6.76 – 6.66 (m, 2H), 6.54 – 6.32 (m, 3H), 6.32 – 6.14 (m, 3H), 6.14 – 6.03 (m, 2H), 5.97 (dd, J = 14.8, 5.9 Hz, 1H), 5.89 – 5.73 (m, 1H), 5.72 – 5.60 (m, 1H), 5.53 (dt, J = 14.6, 7.1 Hz, 1H), 5.38 (dt, J = 20.0, 6.3 Hz, 2H), 4.78 – 4.58 (m, 1H), 3.76 (t, J = 6.3 Hz, 1H), 3.67 (t, J = 5.4 Hz, 1H), 3.40 (s, 3H), 2.93 (td, J = 6.9, 3.1 Hz, 1H), 2.71 – 2.46 (m, 2H), 2.35 (dd, J = 10.6, 6.2 Hz, 2H), 2.21 (dt, J = 7.0, 3.0 Hz, 1H), 2.13 (dq, J = 13.5, 6.0 Hz, 3H), 2.04 (d, J = 2.7 Hz, 3H), 1.96 (s, 3H), 1.51 (s, 3H), 1.29 (s, 3H), 1.22 (s, 3H), 1.16 (d, J = 6.7 Hz, 3H), 0.97 (s, 9H), 0.82 (s, 9H), 0.11 (d, J = 37.2 Hz, 6H), -0.10 (s, 3H), -0.26 (s, 3H) ; ^{13}C NMR (151 MHz, $CDCl_3$) δ 183.09, 182.87, 177.42, 175.11, 154.07, 143.57, 138.02, 136.39, 134.00, 133.34, 132.28, 130.88, 130.78, 129.89, 129.83, 129.42, 127.95, 119.93, 114.21, 102.49, 77.37, 77.16, 76.95, 73.98, 60.08, 46.32, 42.93, 41.89, 40.81, 39.39, 37.55, 33.98, 32.35, 32.08, 31.77, 31.74, 29.85, 29.81, 29.77, 29.66, 29.51, 29.31, 29.10, 27.36, 26.04, 25.88, 24.94, 23.58, 22.84, 22.80, 20.87, 18.37, 18.25, 17.51, 14.27, 13.44, 13.27, 9.43, 1.17,

0.14, -4.31, -4.59, -4.81.; IR (neat): ν_{max} 3299, 2970, 2926, 2855, 1773, 1729, 1605, 1509, 1462, 1254, 1129, 1123, 971, 914, 837, 777 cm−1; HRMS (ESI) *m/z* calculated for $C_{55}H_{83}NO_8Si_2Na$ $[M+H]^+$ 942.5735, found 942.5703.

(*2R,7R,E*)-7-Hydroxy-N-*((R,3E,5E,7E,10Z,12E,14E,16E,18E*)-11-hydroxy-19-((*2S,3S,4R*)-3-methoxy-2,4-dimethyl-5-oxotetrahydrofuran-2-yl)-5,15-dimethyl-9-oxononadeca-3,5,7,10,12,14,16,18-octaen-2-yl)-8-(4-hydroxyphenyl)-2-methyloct-4-enamide (2) : A solution of compound **37** (4.0 mg, 4.24 µmmol) in THF (2 mL) was placed



Thailandamide Lactone (2)

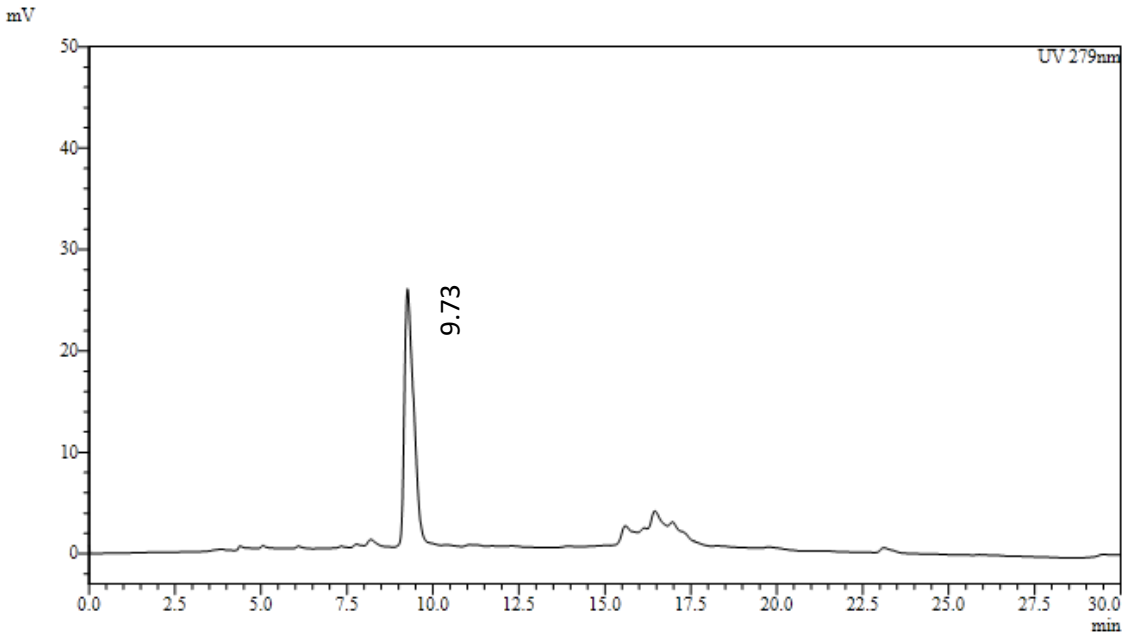
in a plastic vial and cooled to 0 °C. HF-pyridine (70% in pyridine 100 µL) was added and the mixture stirred for 12 h at the room temperature. The reaction mixture was diluted with cold water. The resultant mixture was extracted with diethyl ether (3 × 15 mL), washed repeatedly with plenty of water (15 × 5 mL), brine, dried (Na_2SO_4), filtered, and concentrated in vacuum. The crude mixture was then purified using HPLC (Xbridge RP18, 10 mm I.D x 250 mm) to furnish the title compound **2** (2.6 mg, 89%) as a yellow liquid. R_f = 0.4 (40% EtOAc in hexane); $[\alpha]_D^{28}$ = -43.2 (c 0.37, MeOH); ^{1}H NMR (500 MHz, CD_3OD) δ 7.77 – 7.59 (m, 2H), 6.99 (d, *J* = 7.9 Hz, 2H), 6.69 (d, *J* = 8.0 Hz, 2H), 6.60 (dd, *J* = 15.0, 7.8 Hz, 1H), 6.54 – 6.43 (m, 2H), 6.37 (d, *J* = 8.2 Hz, 1H), 6.28 (d, *J* = 12.8 Hz, 1H), 6.22 (d, *J* = 11.4 Hz, 1H), 6.16 (d, *J* = 16.1 Hz, 2H), 6.07 (s, 1H), 5.99 (d, *J* = 15.4 Hz, 1H), 5.90 (dd, *J* = 18.0, 3.4 Hz, 1H), 5.56 – 5.48 (m, 1H), 5.47 – 5.40 (m, 1H), 3.79 (d, *J* = 6.2 Hz, 1H), 3.73 – 3.67 (m, 1H), 3.39 (s, 3H), 3.13 (s, 1H), 2.64 – 2.55 (m, 2H), 2.39 – 2.28 (m, 2H), 2.14 – 2.08 (m, 2H), 2.04 (s, 3H), 1.96 (s, 3H), 1.50 (s, 3H), 1.25 (d, *J* = 6.9 Hz, 3H), 1.18 (d, *J* = 7.4 Hz, 3H), 1.11 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR (101 MHz, MeOD) δ 184.30, 184.08, 180.94, 178.15, 156.86, 147.10, 144.65, 135.71, 134.82, 134.05, 132.33, 131.61, 131.57, 131.33, 131.15, 130.62, 130.21, 116.20, 99.92, 89.12, 86.48, 73.89, 61.18, 47.84, 43.50, 42.50, 41.17, 40.47,

38.62, 23.86, 21.10, 18.16, 13.45, 13.21, 8.87; IR (neat): ν_{max} 3450, 3299, 2950, 2982, 2867, 1772, 1725, 1604, 1502, 1452, 1274, 1139, 1013, 981 cm−1; HRMS (ESI) *m/z* calculated for $C_{43}H_{55}NO_8$ $[M+H]^+$ 714.4006, found 714.4008.

Note: The global deprotection was tricky. HF-Py was found only the condition to function efficiently and water can only be used for washing during work up. No NH_4Cl or $NaHCO_3$ solution could be used during work up as the final product decomposed rapidly. Moreover, trace amount of HF in presence of silica gel or even in glass wares decomposed completely the title compound **2**. Thus, plastic container was used for the handling of this synthesized compound.

1.6. HPLC Analysis of Thailandamide Lactone (2):

HPLC analysis of compound **2** (coupling time 30 minutes): Reverse phase C18 column (Xbridge RP18, 10 mm I.D x 250 mm); MeCN/H_2O 70/33 for 5 min, to MeCN/H_2O 99/1 in 20 min] and a flow rate of 2 mL min^{-1}, R_t = 9.73 min.



2.0. Materials and Methods for Evaluation of Antibacterial property of Thailandamide Lactone (2):

Media and Growth Conditions of Bacteria

Bacillus subtilis (PY79), Bacillus megaterium (2G), Staphylococcus aureus, Vibrio cholerae (N16961), Escherichia coli (MC1061) and Enteropathogenic Escherichia coli (EPEC e2348/69) were grown in LB medium aerobically at 37 °C/ 250 rpm.[9a,b] Bacteria were harvested at the logarithmic growth phase with optical densities from 0.6 to 1 at 600 nm. Bacterial strains were maintained at −80 °C in LB containing 10% DMSO. All the bacterial strains were minimally sub-cultured, and before every experiment they were directly inoculated from −80 °C stock.

Minimum Inhibitory Concentration (MIC) Determination

The MIC of Thailandamide was determined by broth dilution assay.[10] A stock solution of Thailandamide (1.0 mg/mL) was prepared by dissolving it in ethanol. Different dilutions from the stock solution were done for screening different concentrations of the compound in LB broth. The final volume was 1ml and 10 μL bacterial solutions (1:100) were added to each test tubes. The test tubes were incubated at 37 °C overnight under shaking conditions at 250 rpm. The MIC was taken as the lowest concentration of the compounds for which there were no visible growth of bacteria. Broth containing only cells and ethanol were used as negative control. All experiments were performed in triplicate.

Table S3: Antibacterial Activities of Thailandamide Lactone Against Selected Strains

Gram Negative Bacteria										
Strain	Concentration (*μM)*									
	25	50	60	70	75	80	85	90	100	125
V. cholerae (N16961)	+	+	+	+	+	+	+	+	-	-
EPEC (e2348/69)	+	+	+	+	+	+	+	+	-	-
Non-pathogenic E. coli (MC1061)	+	+	+	+	-	-	-	-	-	-

Gram Positive Bacteria										
Strain	Concentration (μM)									
	5	10	25	50	75	80	85	100	125	150
B. subtilis (PY79)	+	+	+	+	+	-	-	-	-	-
B. megaterium (2G)	+	+	+	+	-	-	-	-	-	-
S. aureus	+	+	+	+	+	+	+	+	-	-

(+) refers to bacterial growth in the LB containing indicated concentration of the Thailandamide lactone i.e., MIC not reached.

(-) refers to no bacterial growth i.e., MIC reached.

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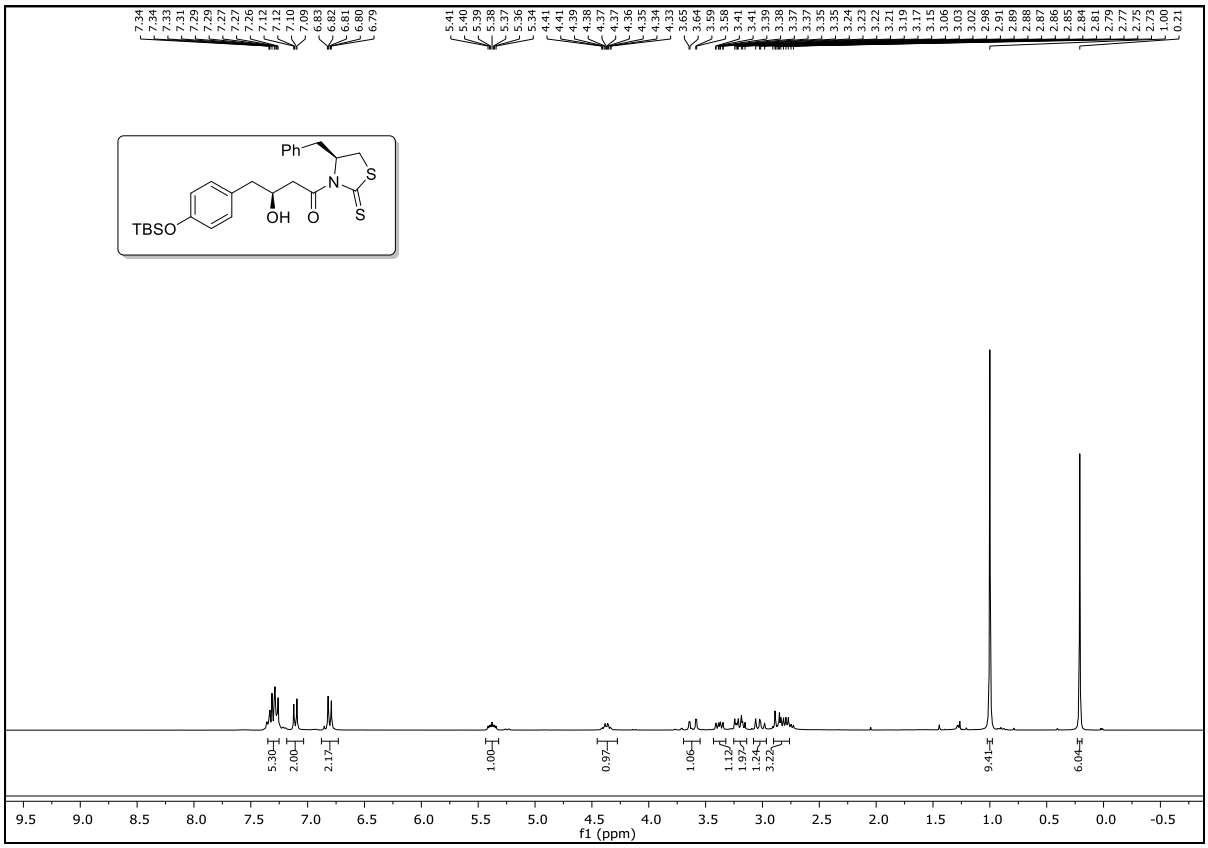
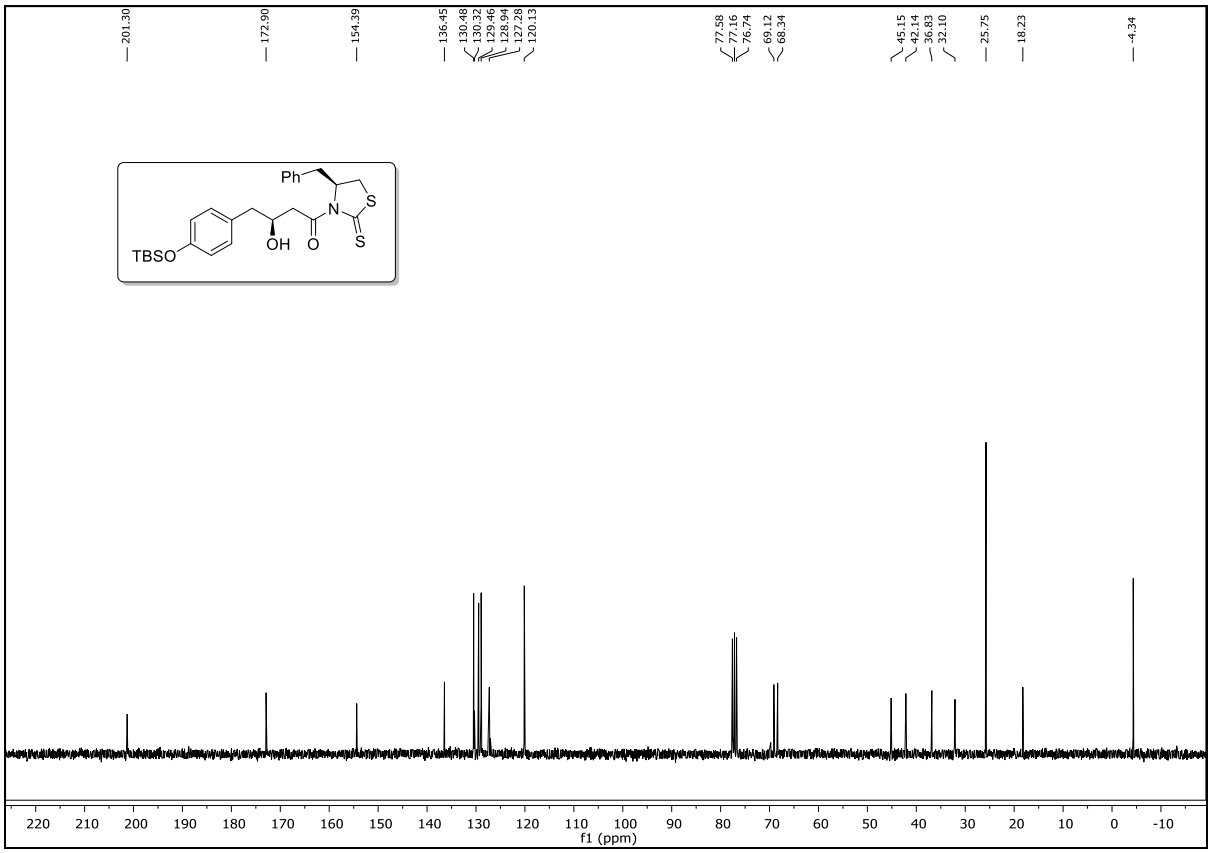
3.0. Copies of ^{1}H NMR, ^{13}C NMR, 2D NMR, FT-IR, UV-Visible and HRMS Spectra

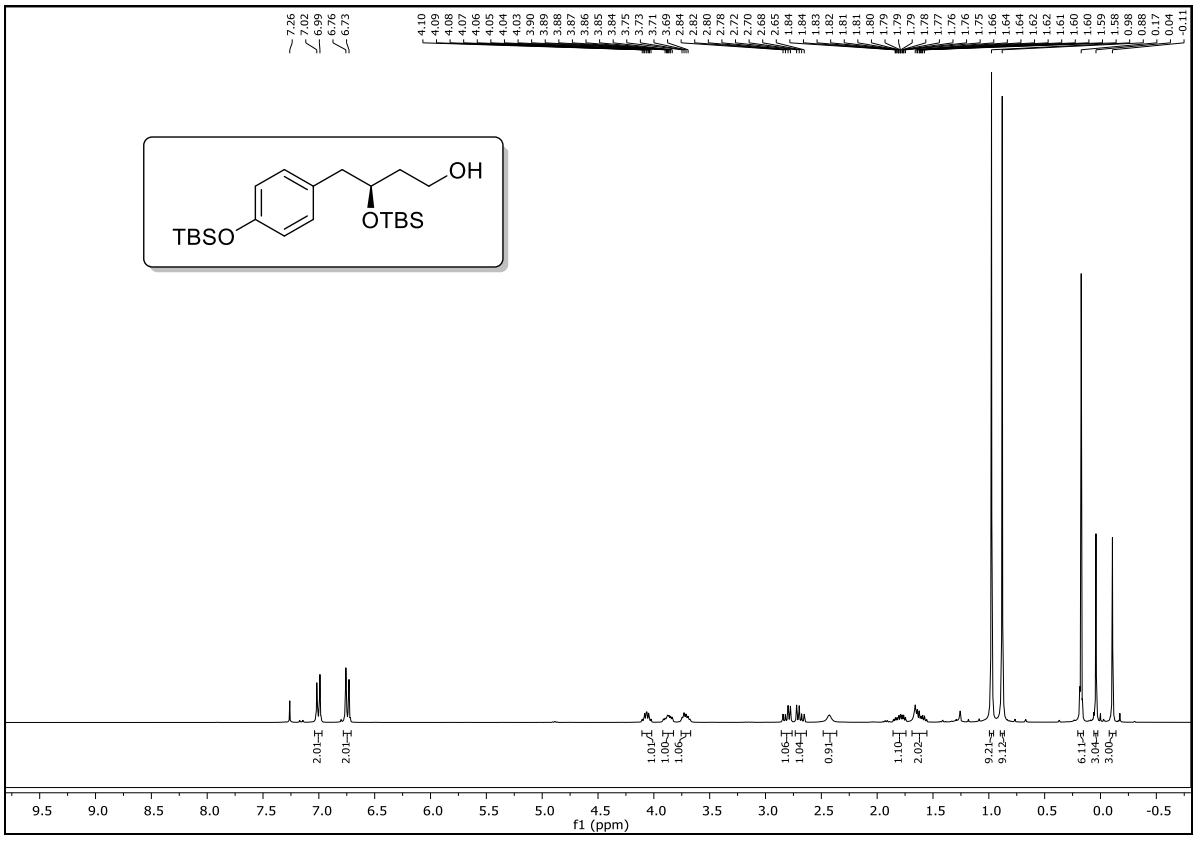
^{1}H NMR spectrum of compound 13 (300 MHz, $CDCl_3$):



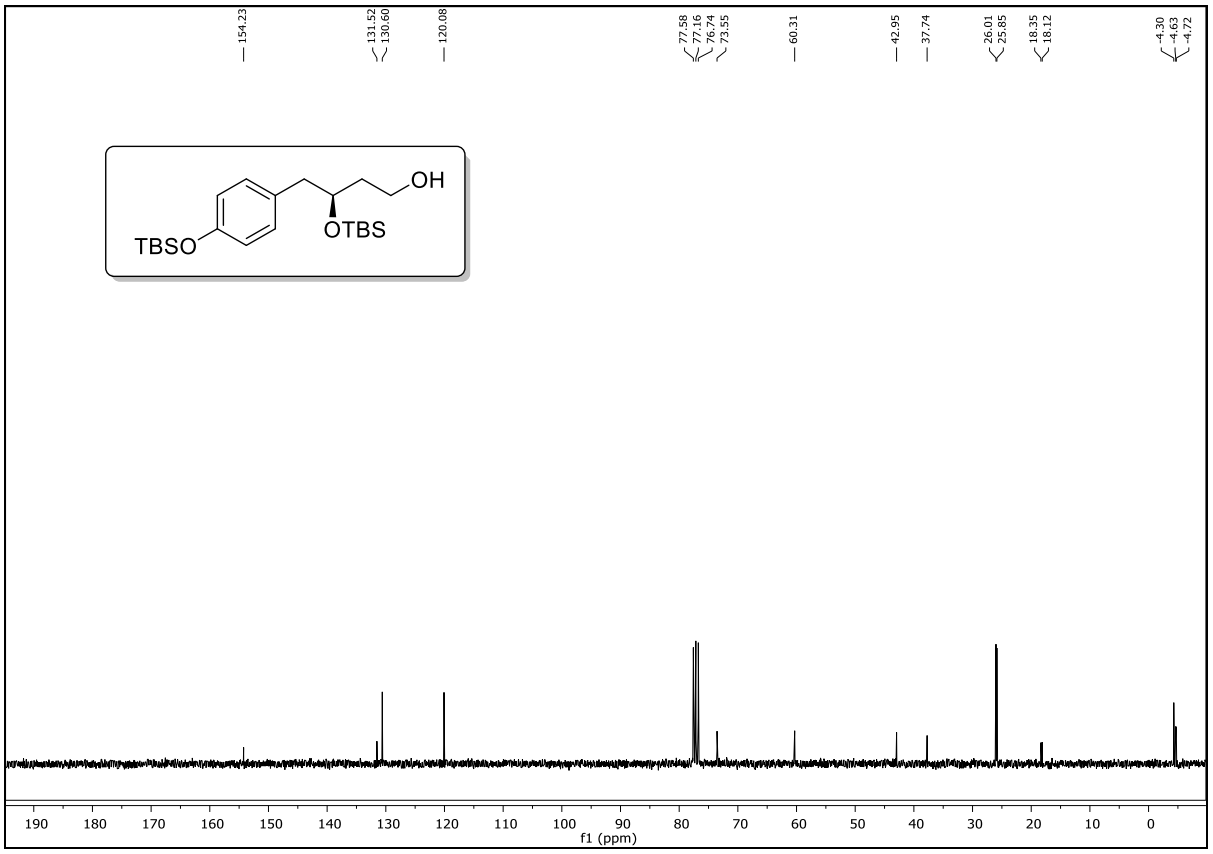
^{13}C NMR spectrum of compound 13 (75 MHz, $CDCl_3$):



^{1}H NMR spectrum of compound 14 (300 MHz, $CDCl_3$):

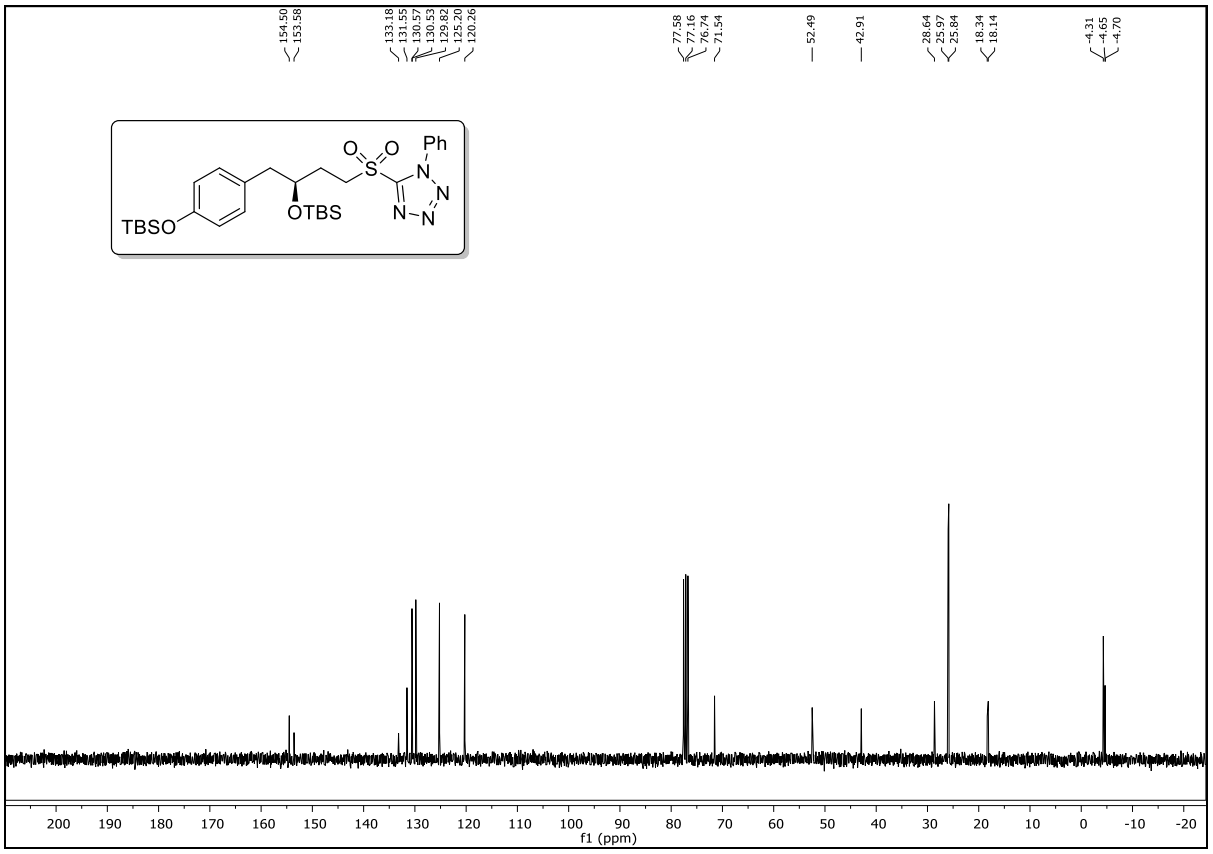


^{13}C NMR spectrum of compound 14 (75 MHz, $CDCl_3$):

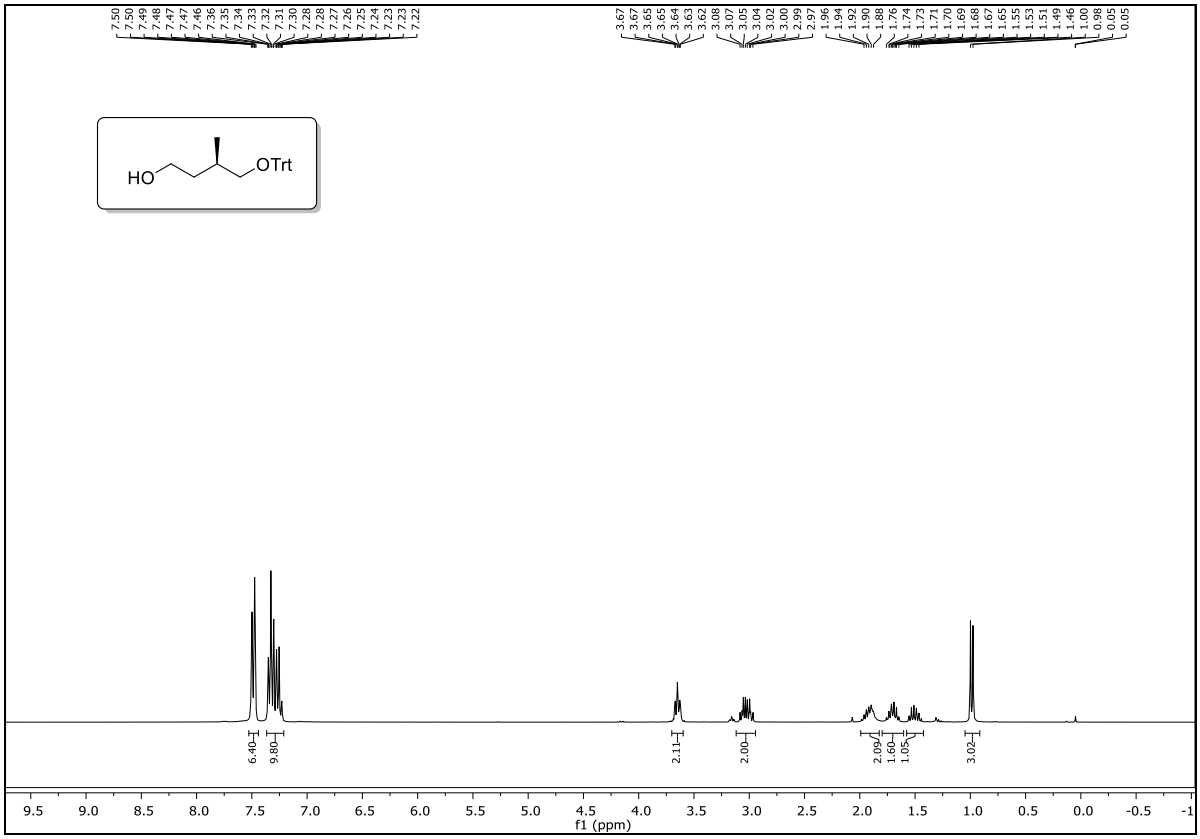


^{1}H NMR spectrum of compound 16 (300 MHz, $CDCl_3$):

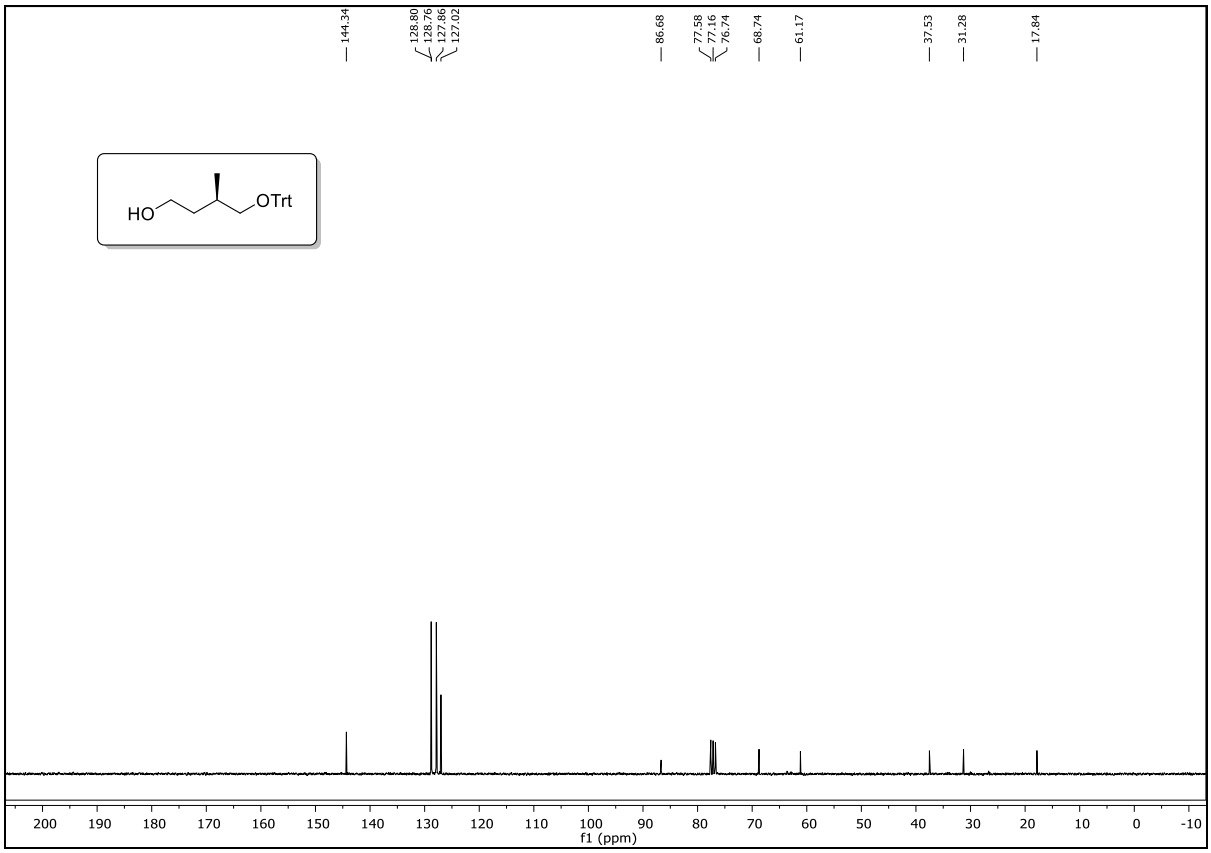
^{13}C NMR spectrum of compound 16 (75 MHz, $CDCl_3$):



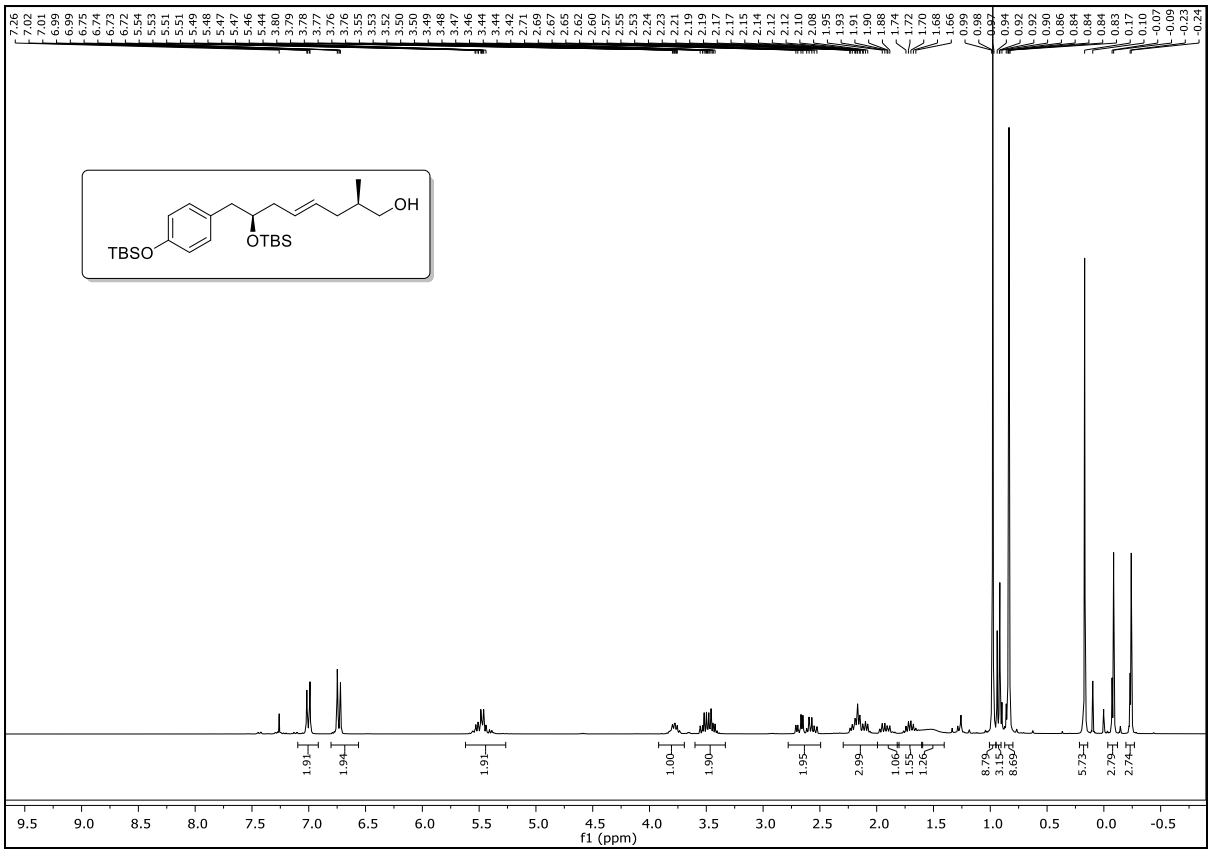
^{1}H NMR spectrum of compound 17a (300 MHz, $CDCl_3$):



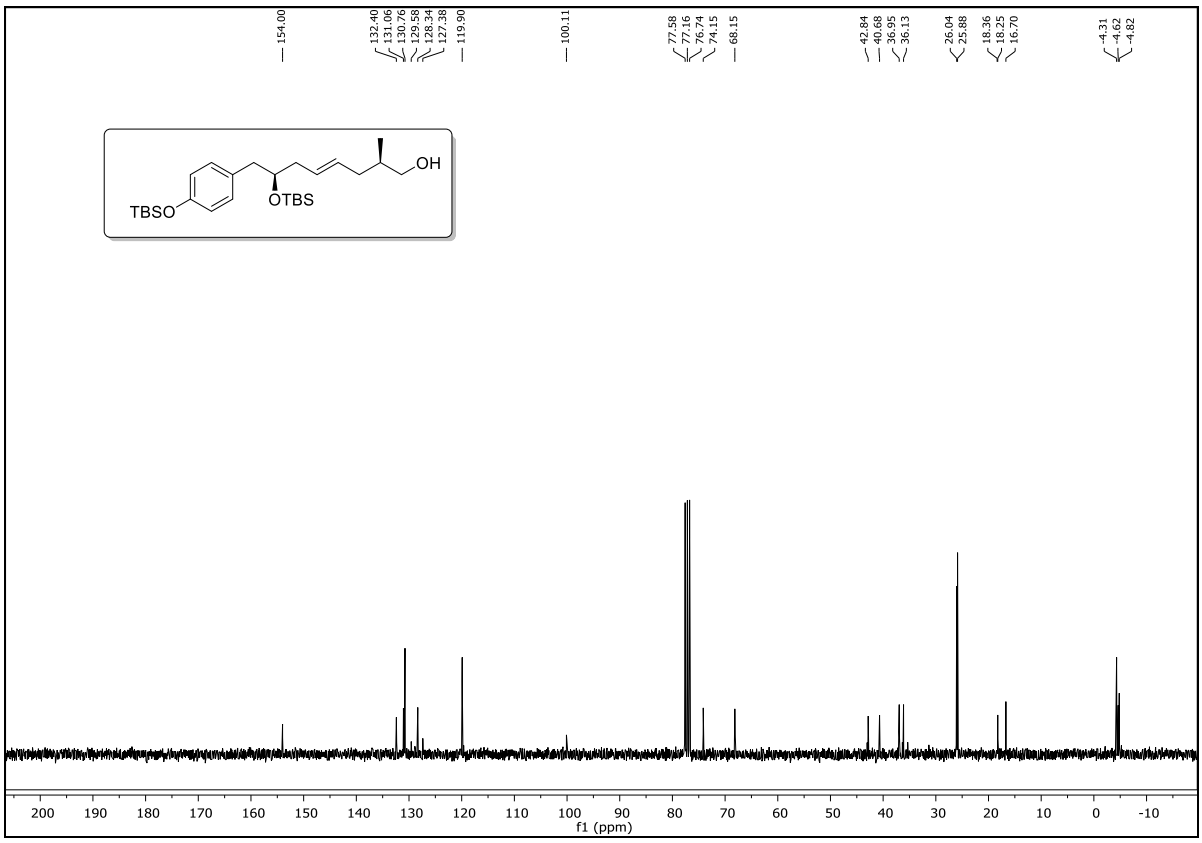
^{13}C NMR spectrum of compound 17a (75 MHz, $CDCl_3$):



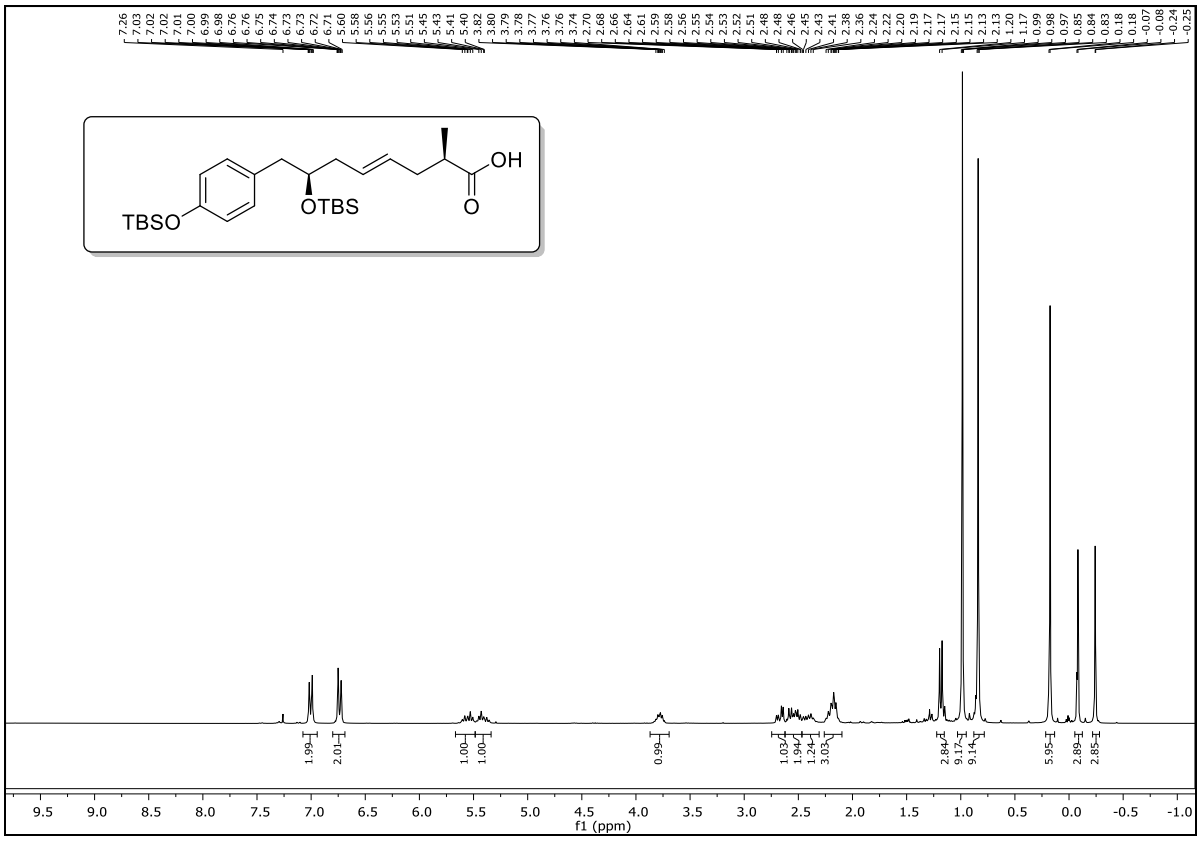
^{1}H NMR spectrum of compound 18 (300 MHz, $CDCl_3$):



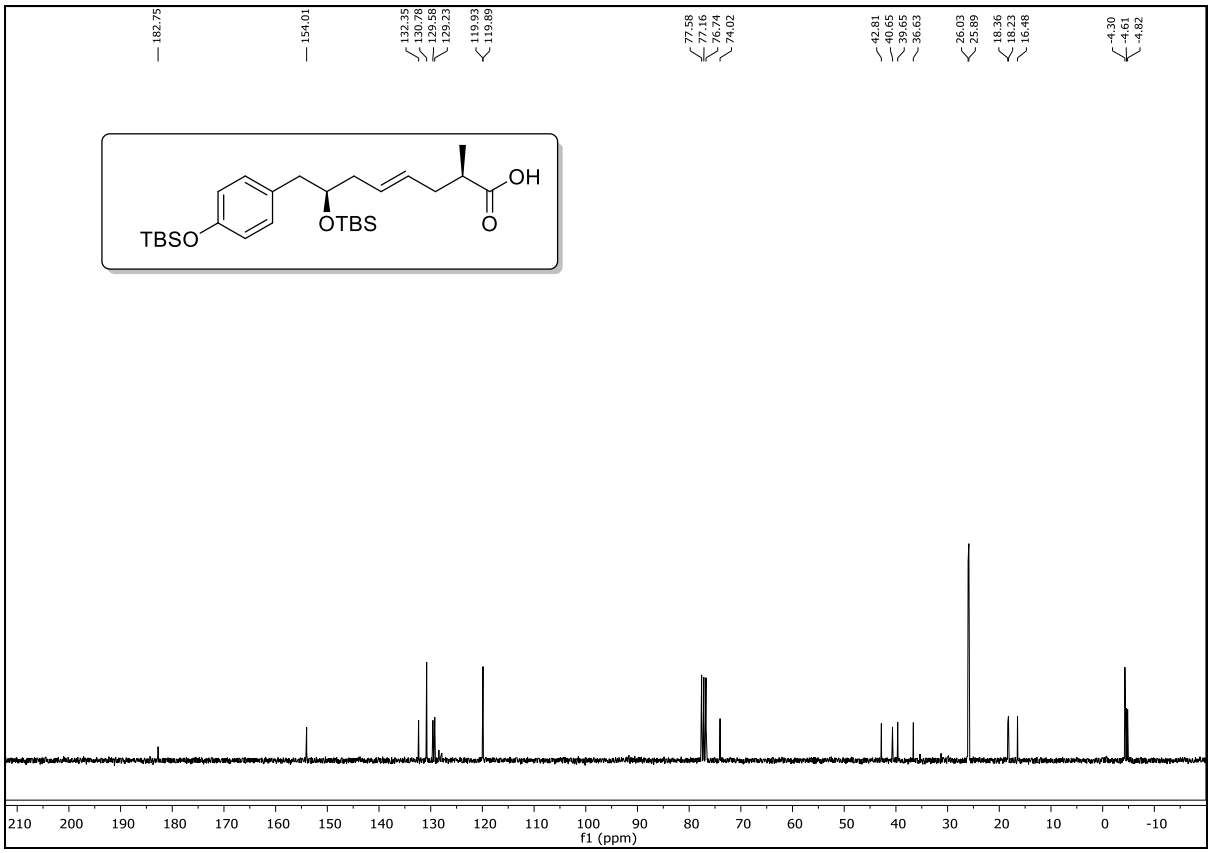
^{13}C NMR spectrum of compound 18 (75 MHz, $CDCl_3$):



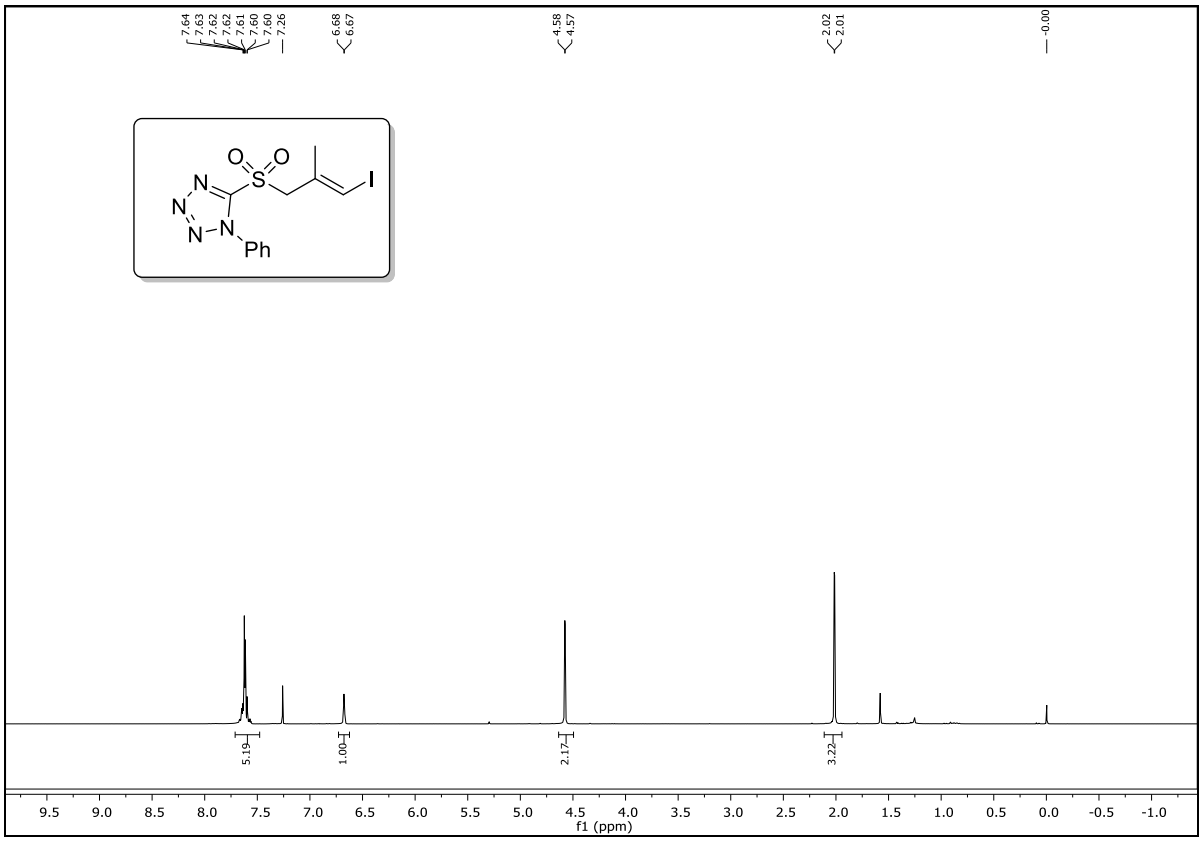
^{1}H NMR spectrum of compound 6 (300 MHz, $CDCl_3$):



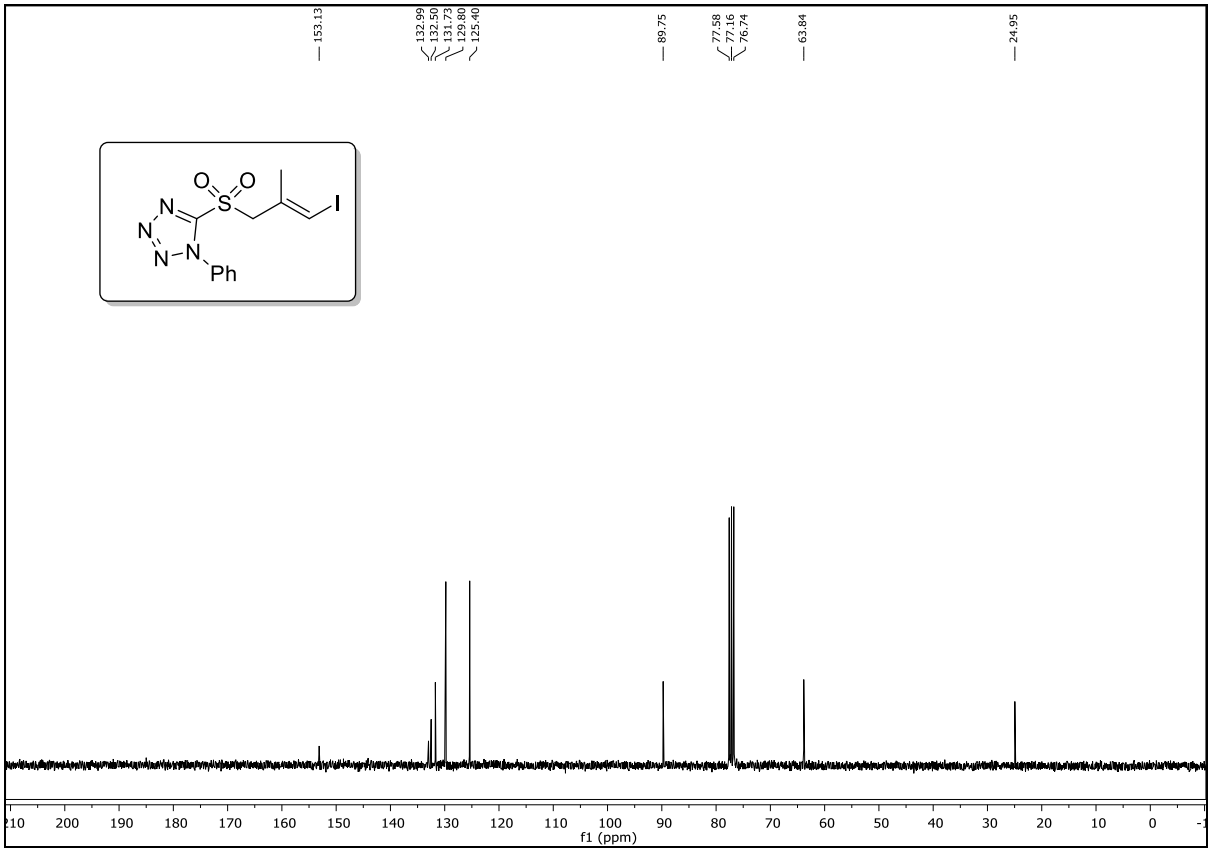
^{13}C NMR spectrum of compound 6 (75 MHz, $CDCl_3$):



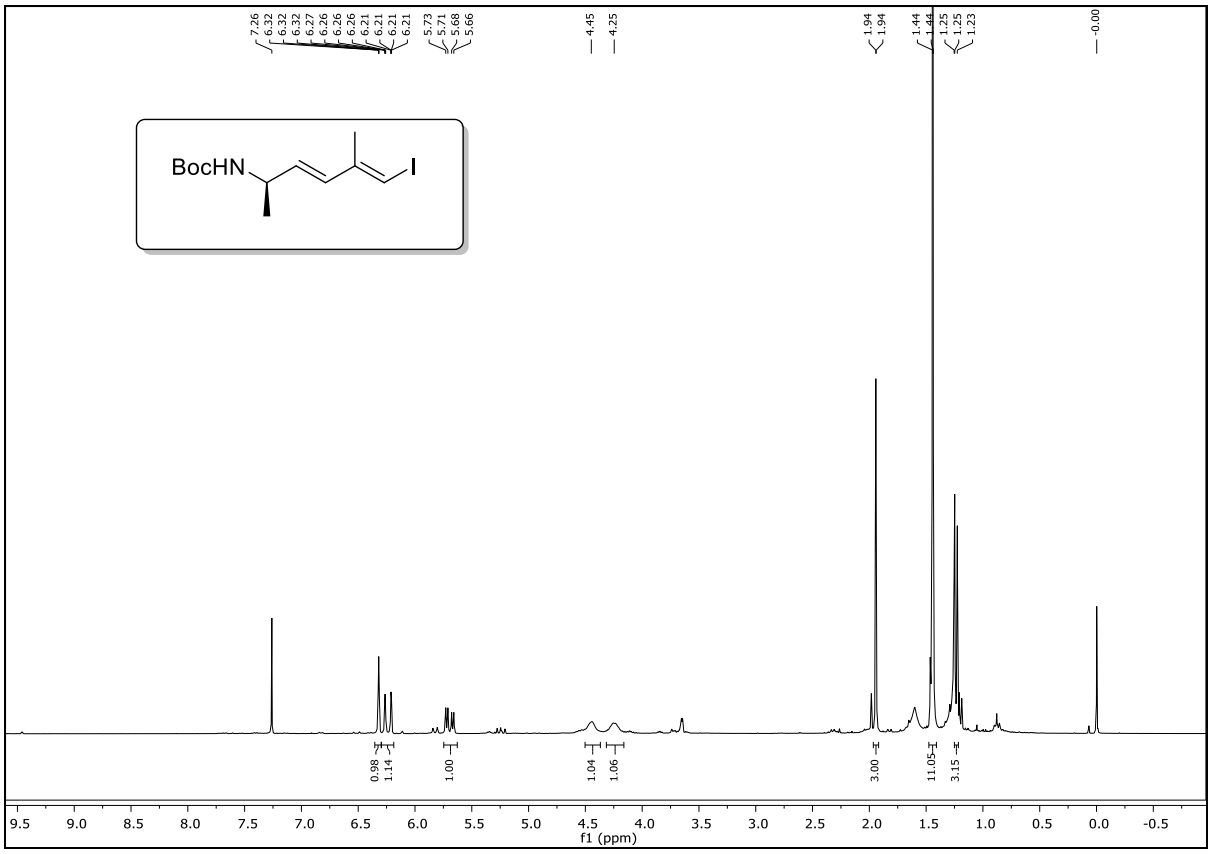
^{1}H NMR spectrum of compound 20 (300 MHz, $CDCl_3$):



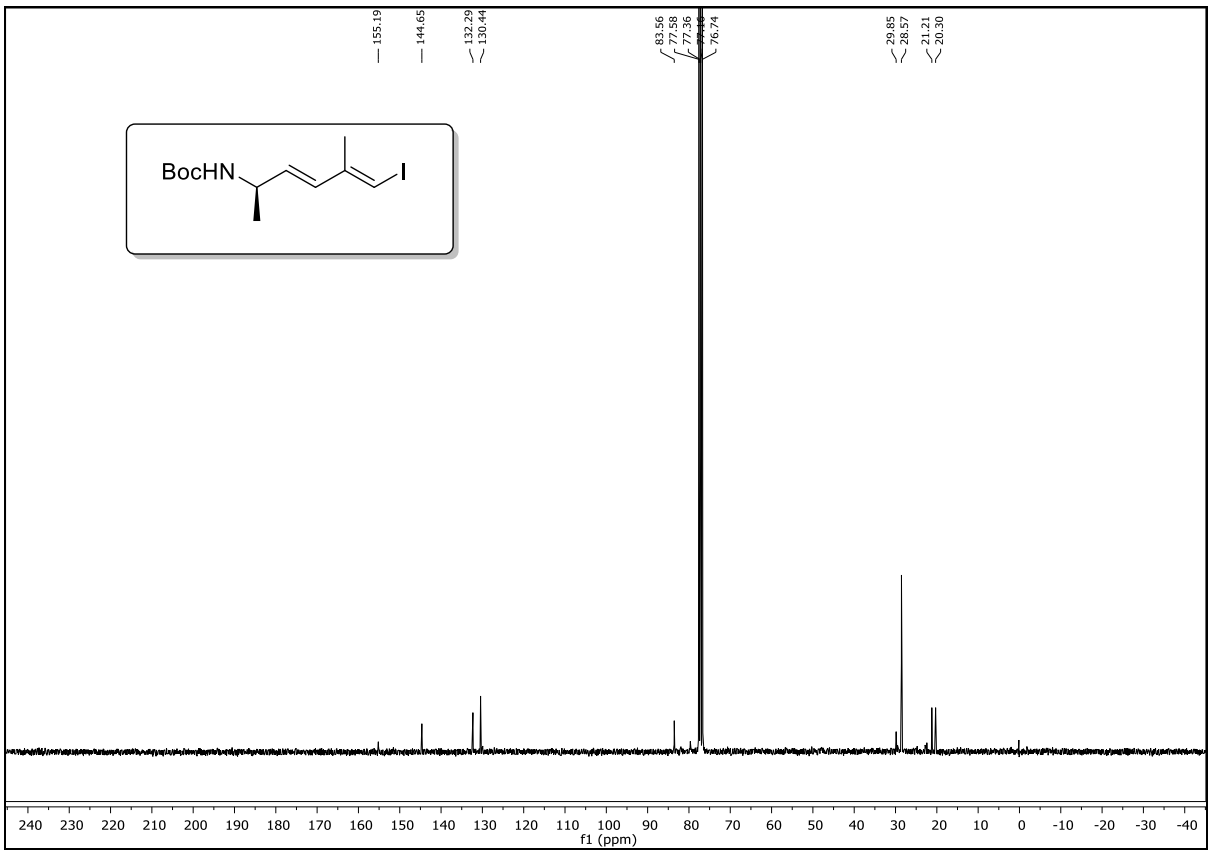
^{13}C NMR spectrum of compound 20 (75 MHz, $CDCl_3$):



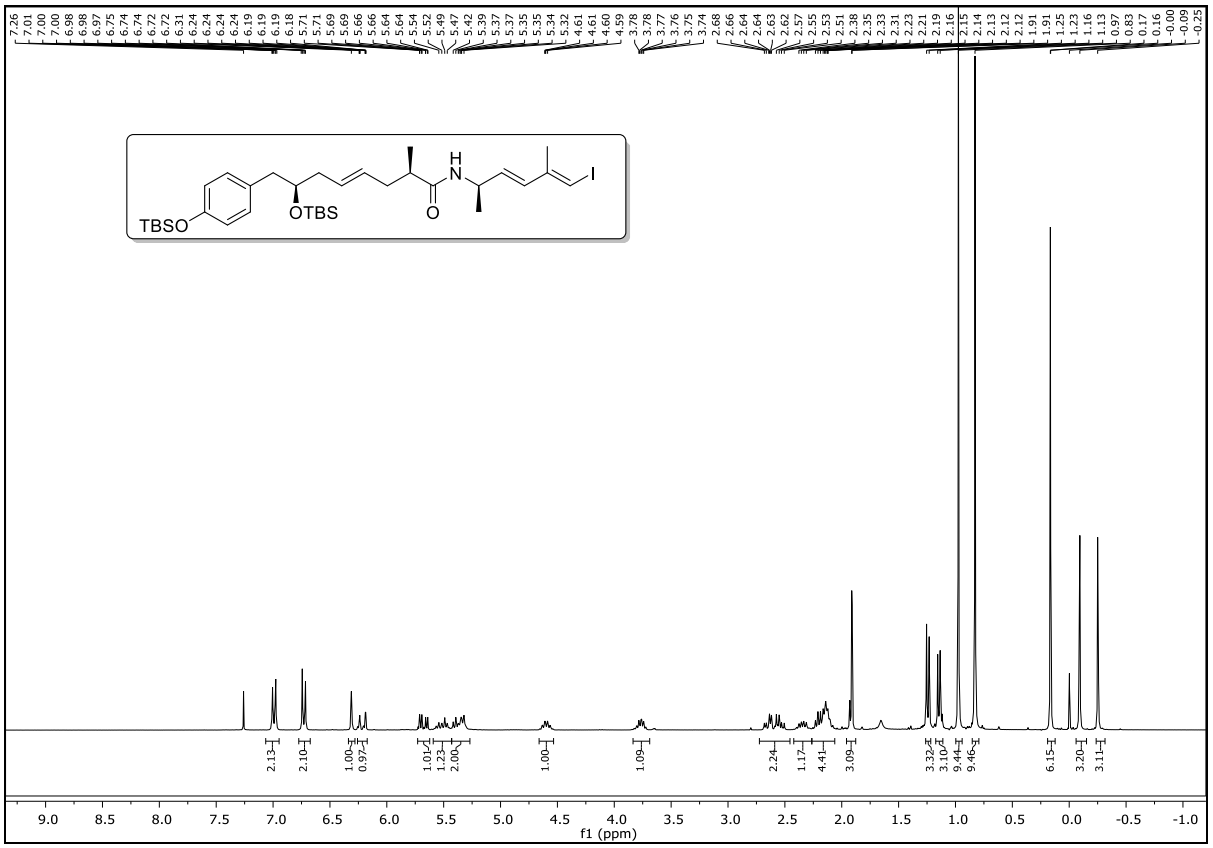
^{1}H NMR spectrum of compound 7 (300 MHz, $CDCl_3$):



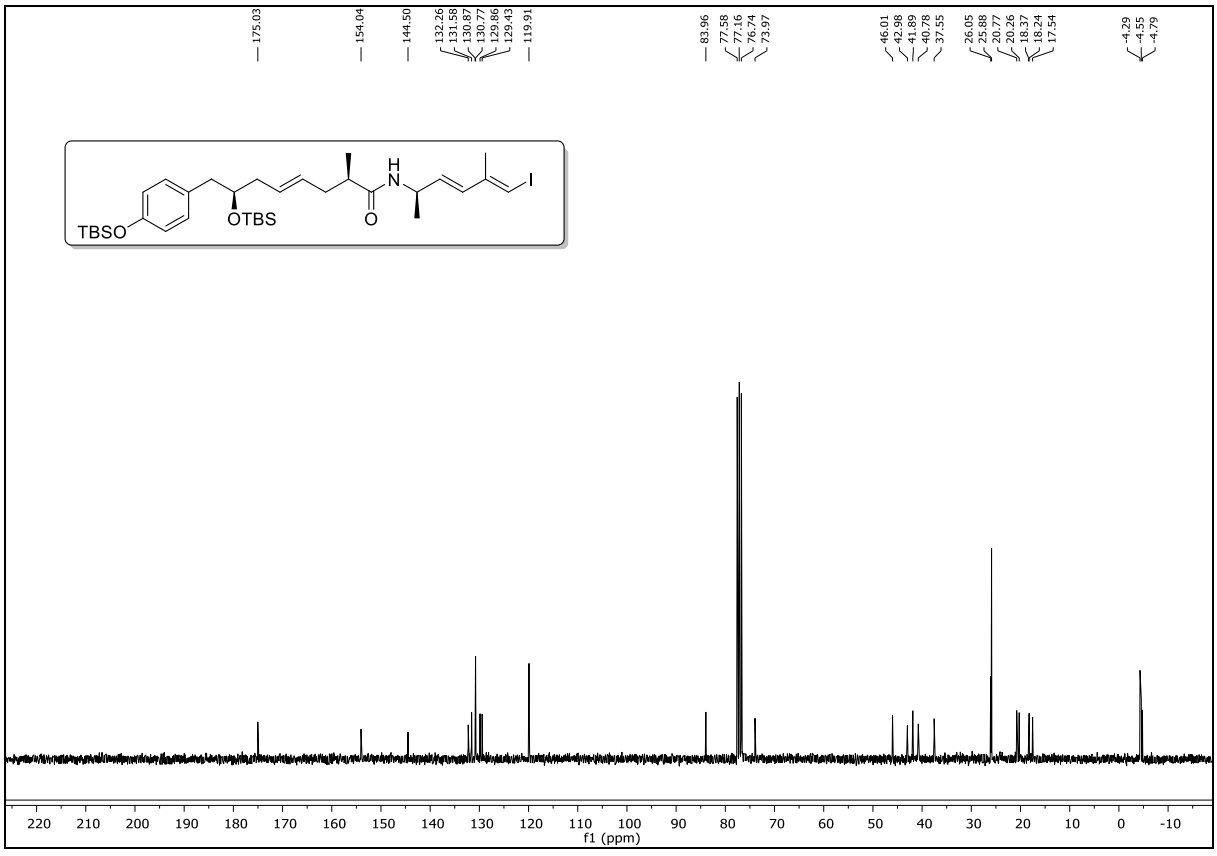
^{13}C NMR spectrum of compound 7 (75 MHz, $CDCl_3$):



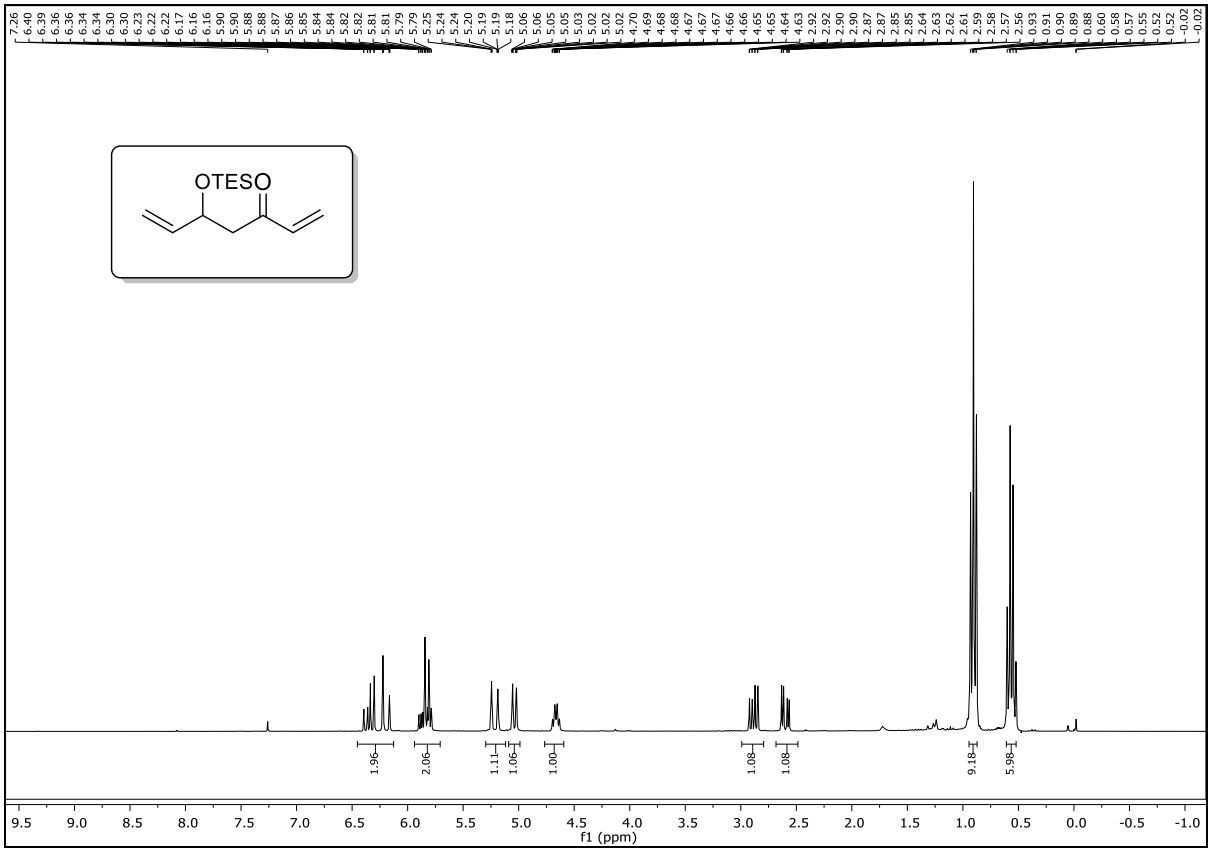
^{1}H NMR spectrum of compound 4 (300 MHz, $CDCl_3$):



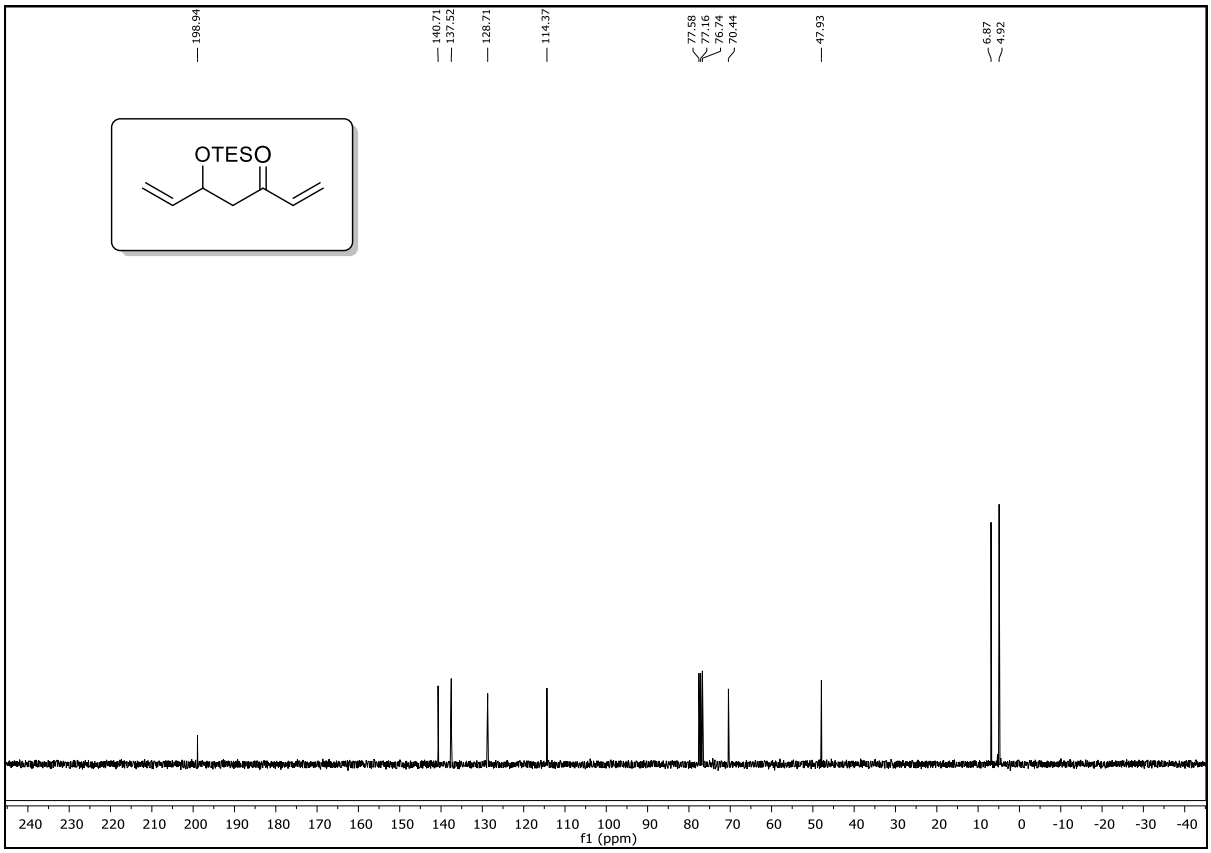
^{13}C NMR spectrum of compound 4 (75 MHz, $CDCl_3$):



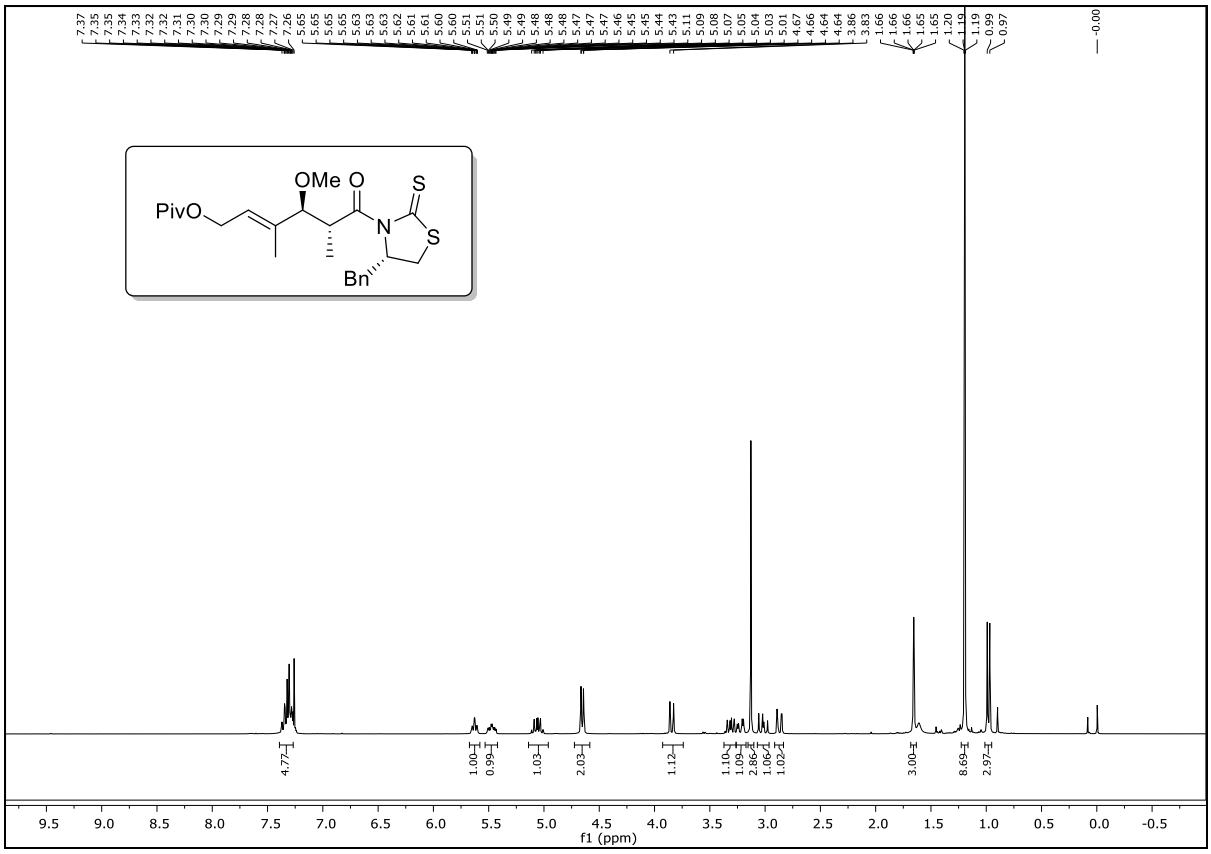
^{1}H NMR spectrum of compound 8 (300 MHz, $CDCl_3$):



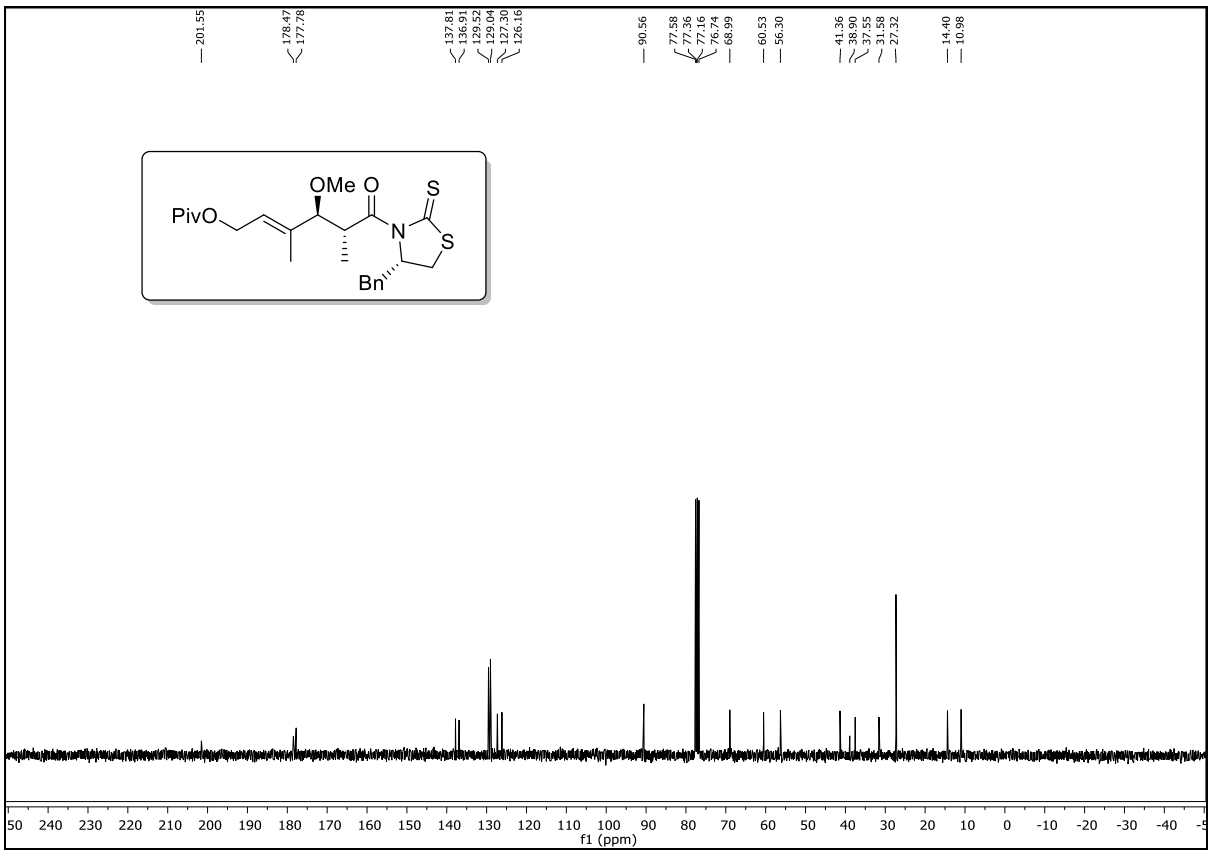
^{13}C NMR spectrum of compound 8 (75 MHz, $CDCl_3$):



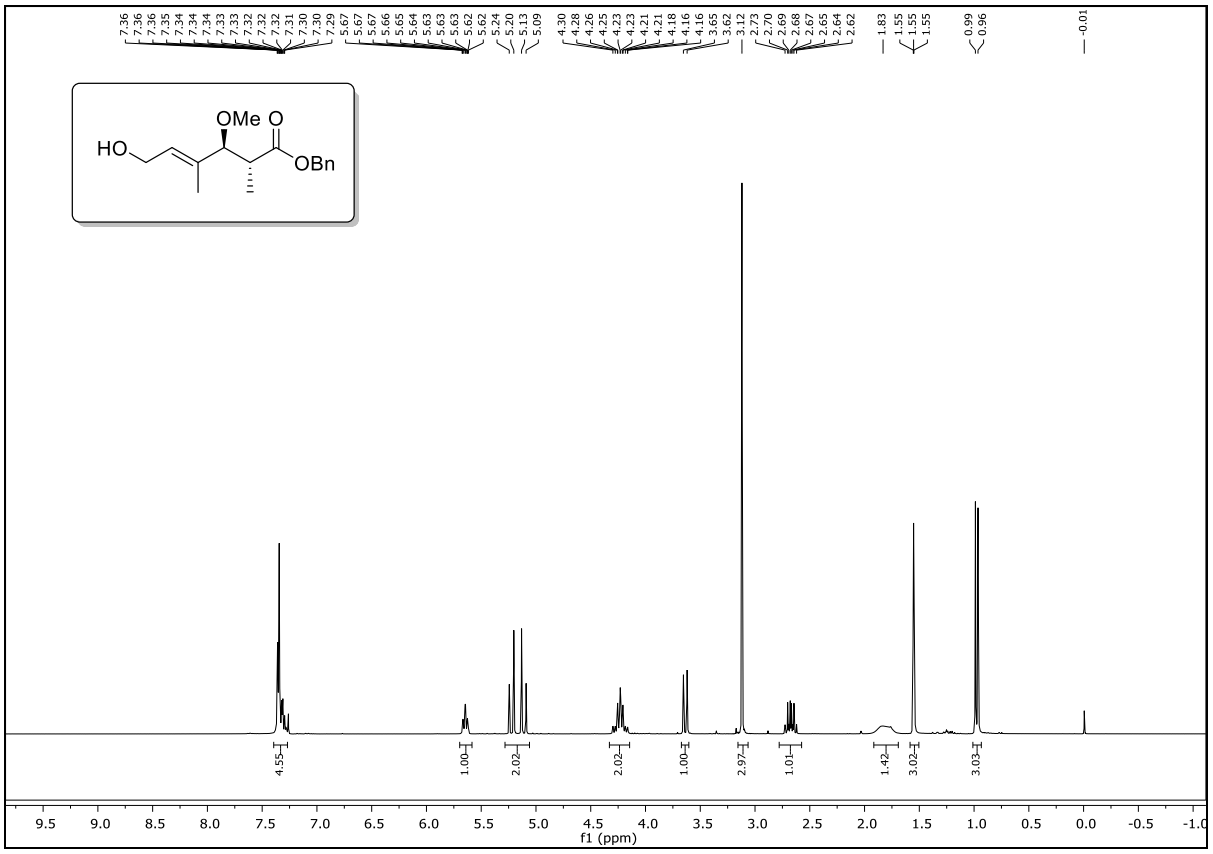
^{1}H NMR spectrum of compound 29 (300 MHz, $CDCl_3$):



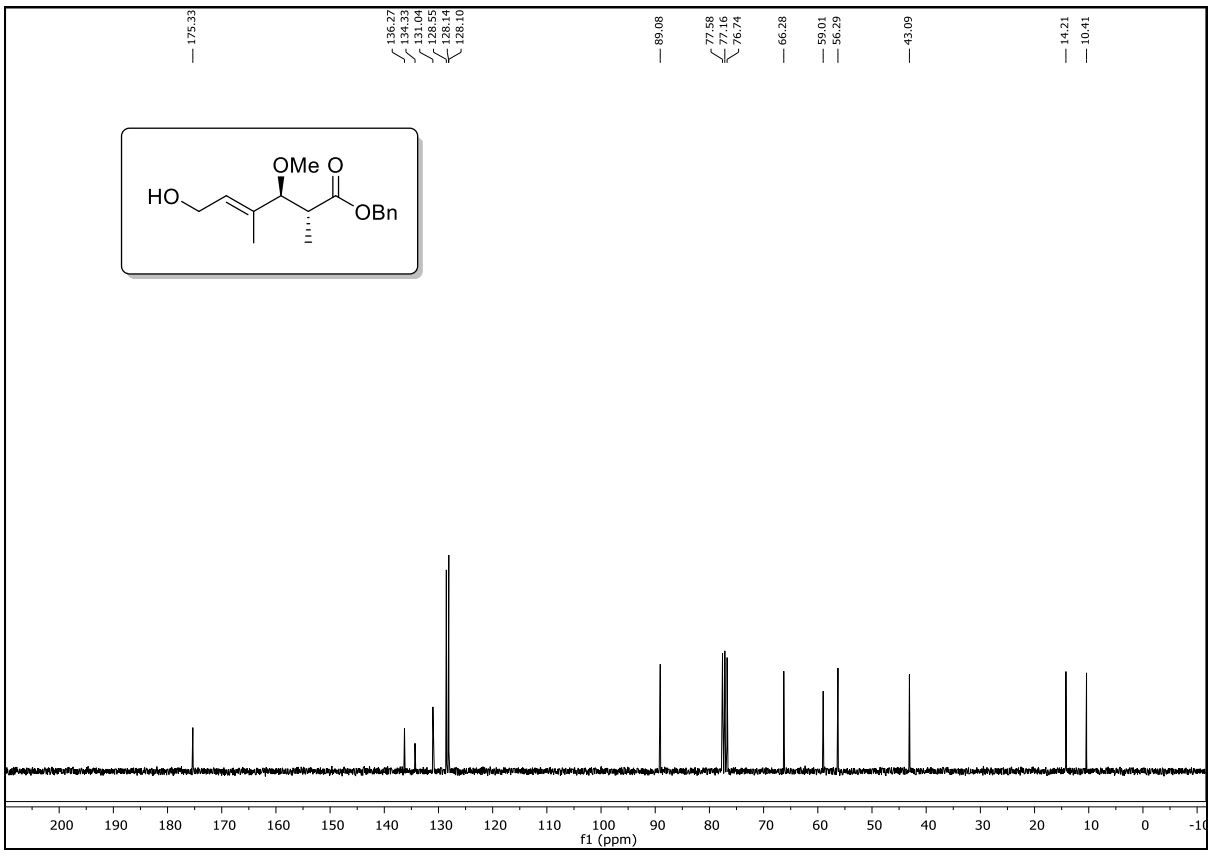
^{13}C NMR spectrum of compound 29 (75 MHz, $CDCl_3$):



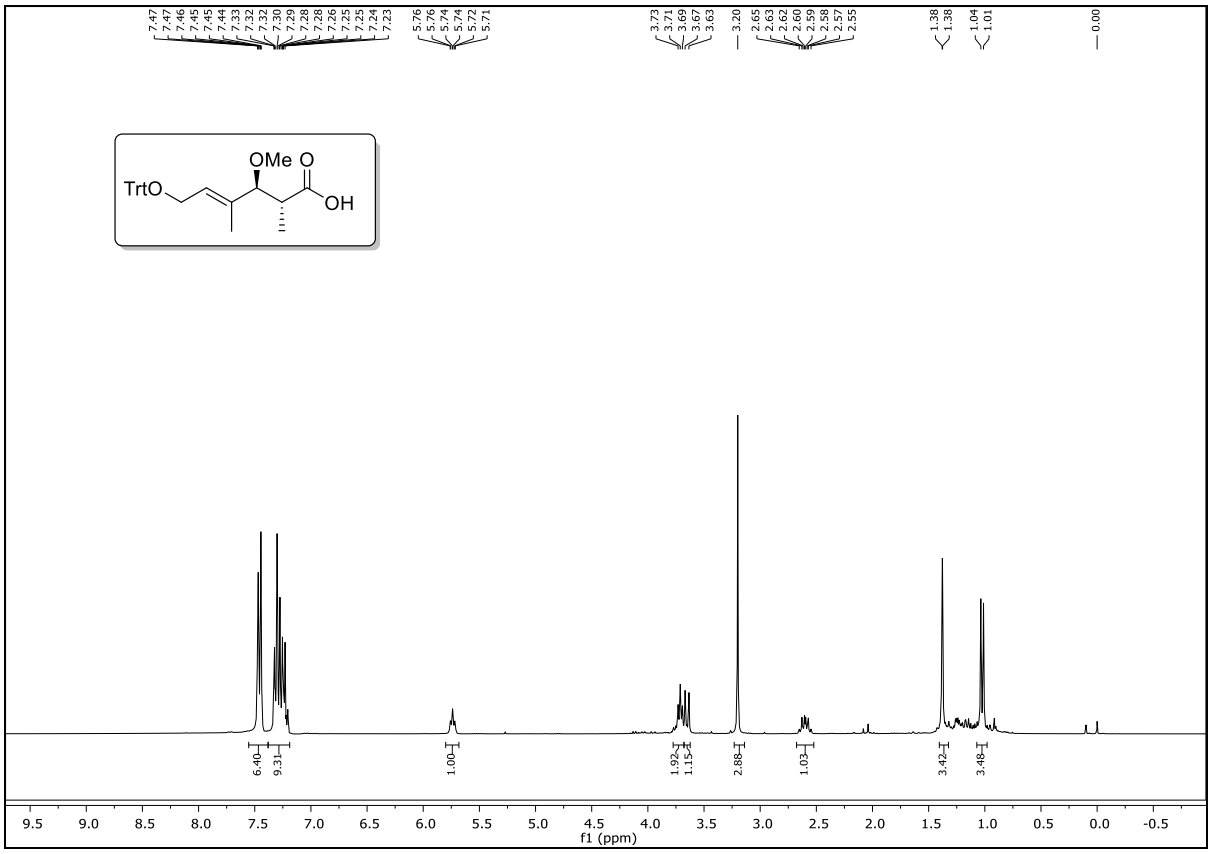
^{1}H NMR spectrum of compound 32 (300 MHz, $CDCl_3$) :



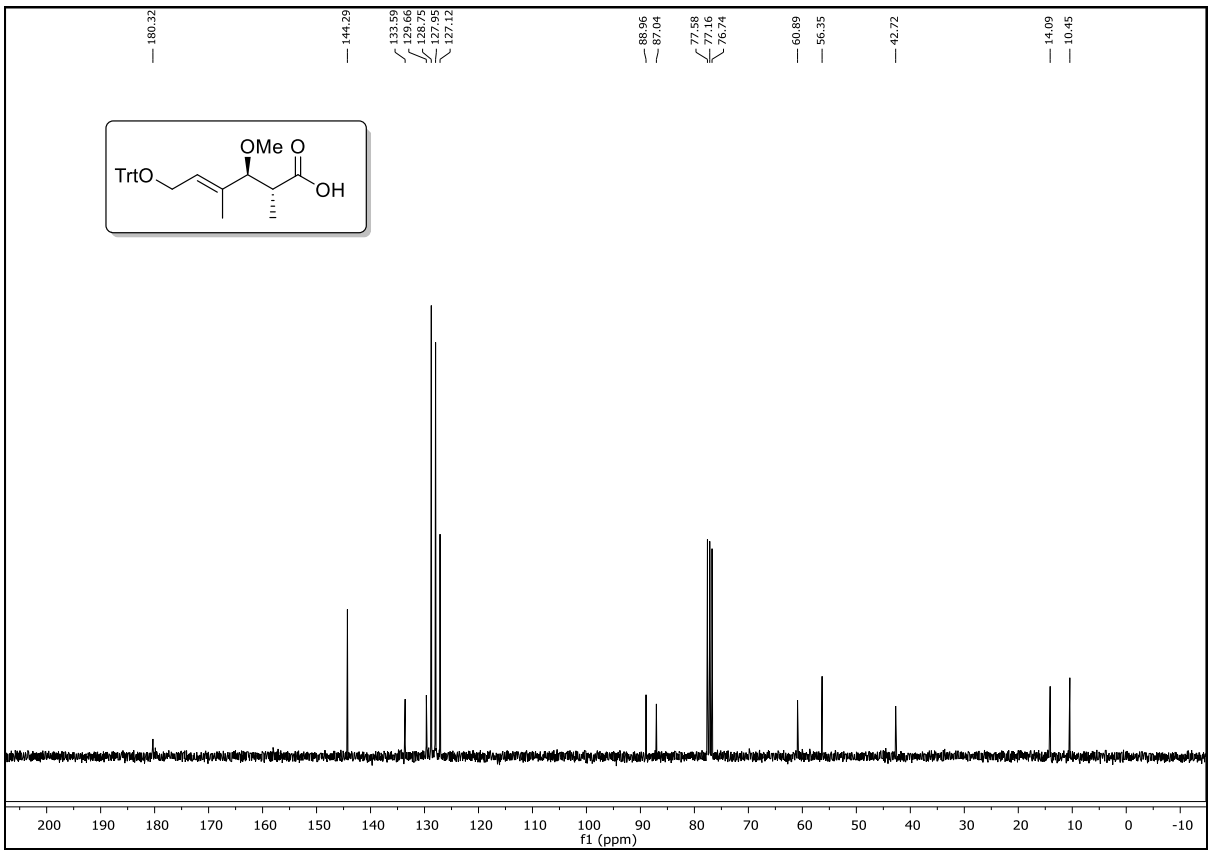
^{13}C NMR spectrum of compound 32 (75 MHz, $CDCl_3$):



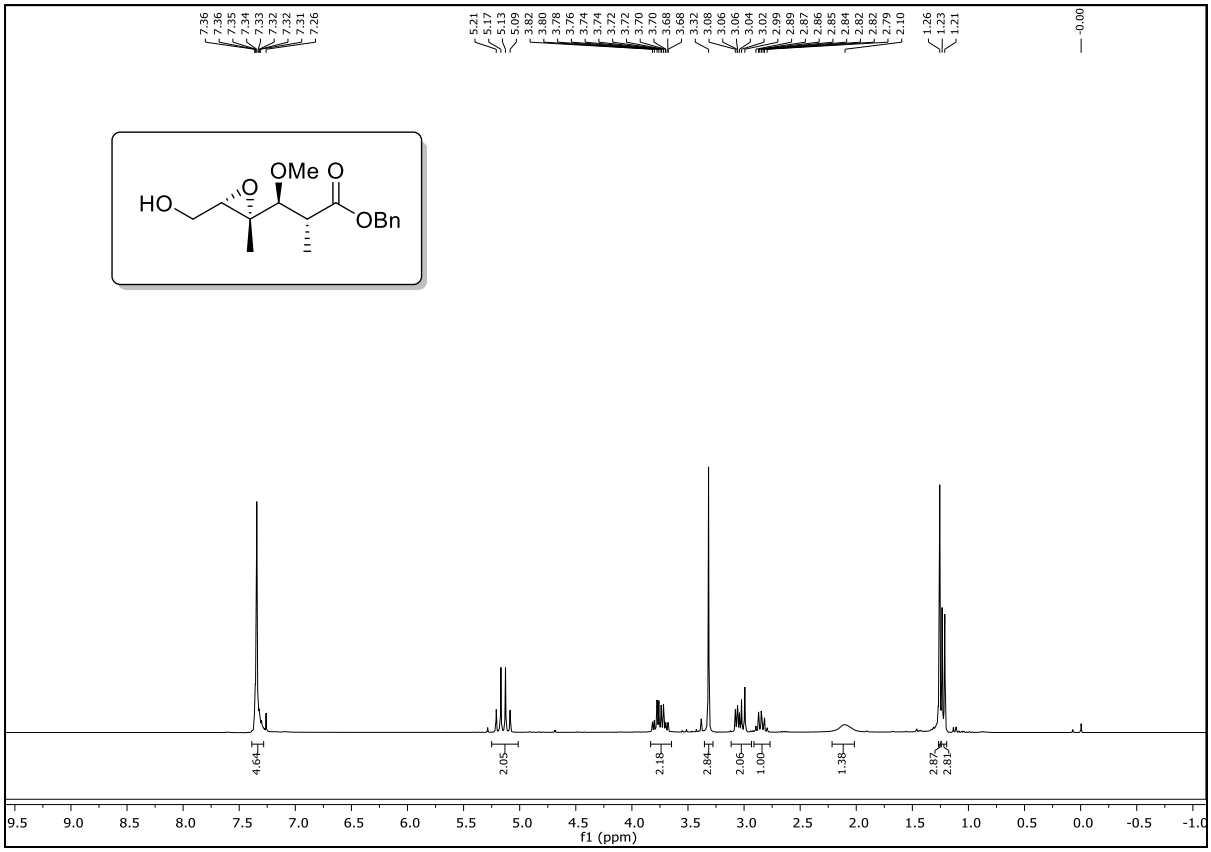
^{1}H NMR spectrum of compound 31 (300 MHz, $CDCl_3$):



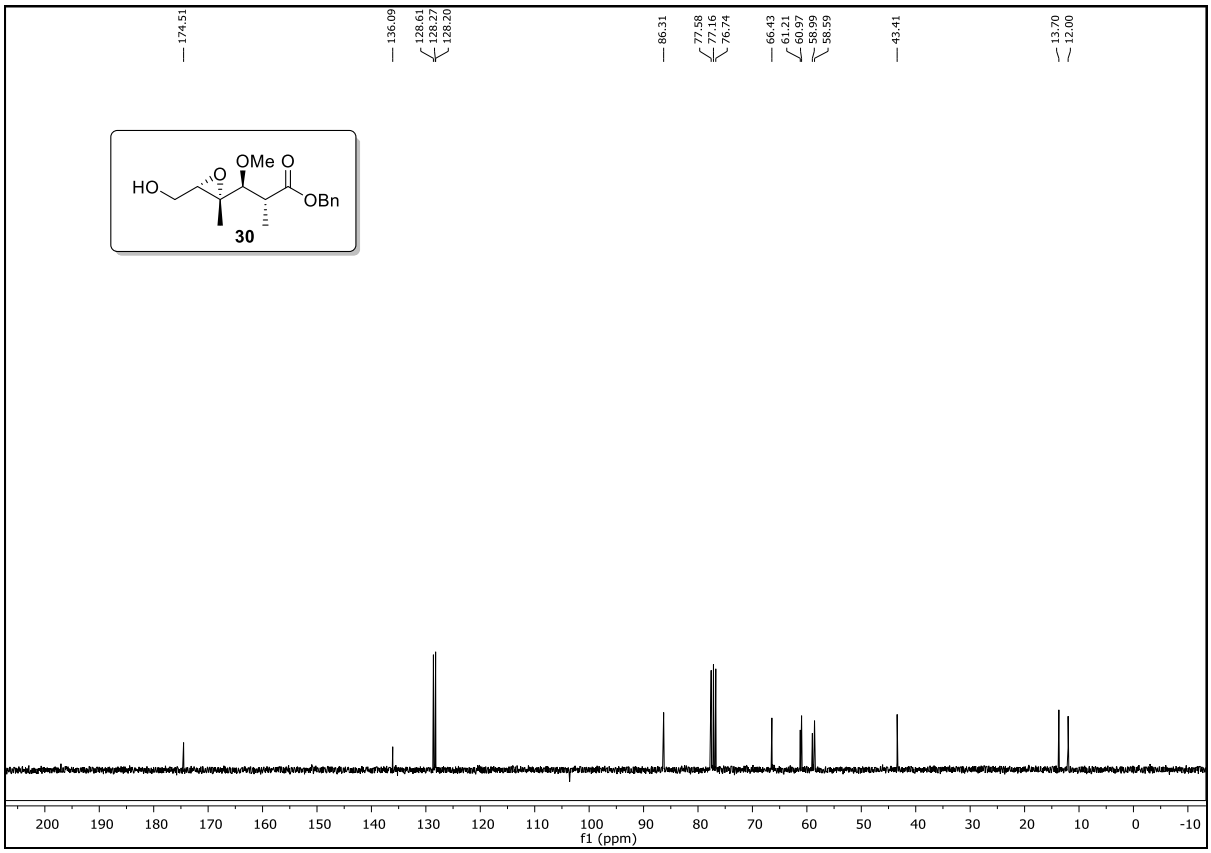
^{13}C NMR spectrum of compound 31 (75 MHz, $CDCl_3$):



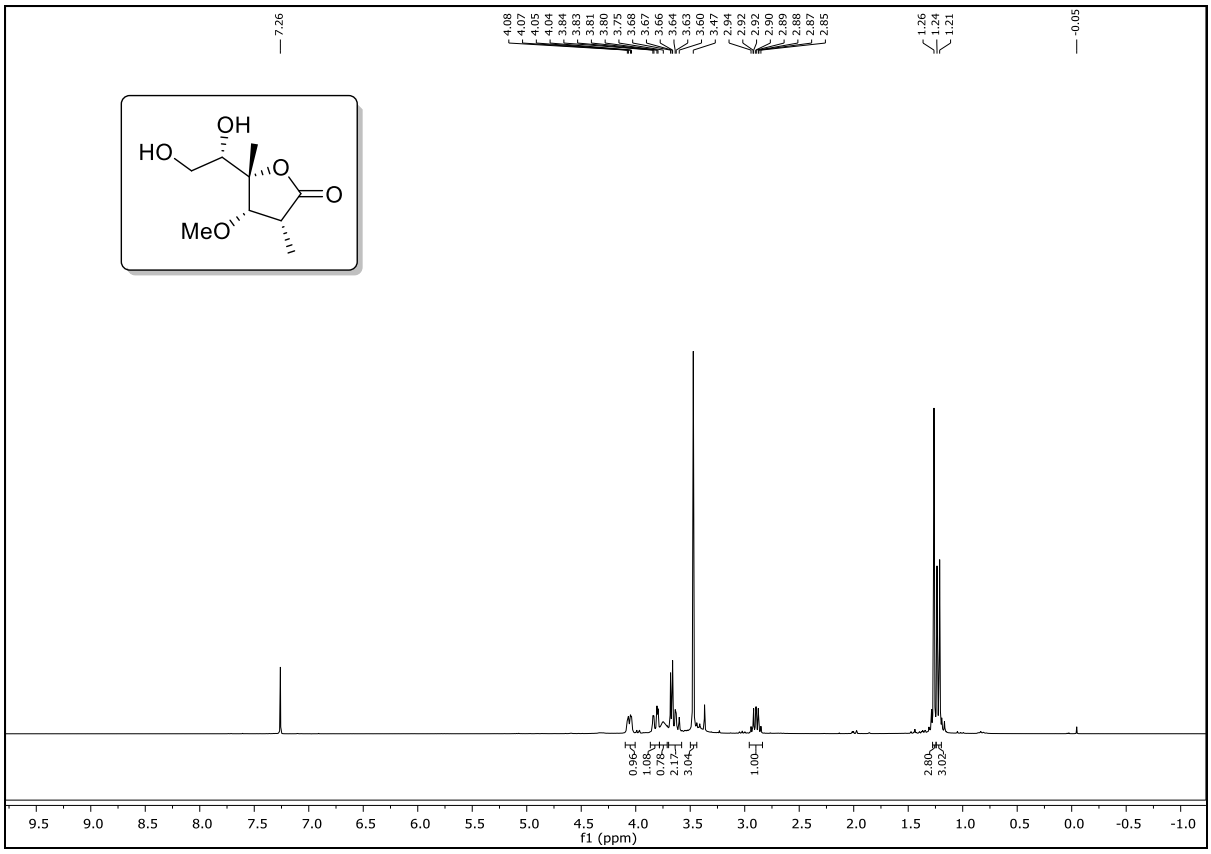
^{1}H NMR spectrum of epoxide corresponding product of 32 (300 MHz, $CDCl_3$):



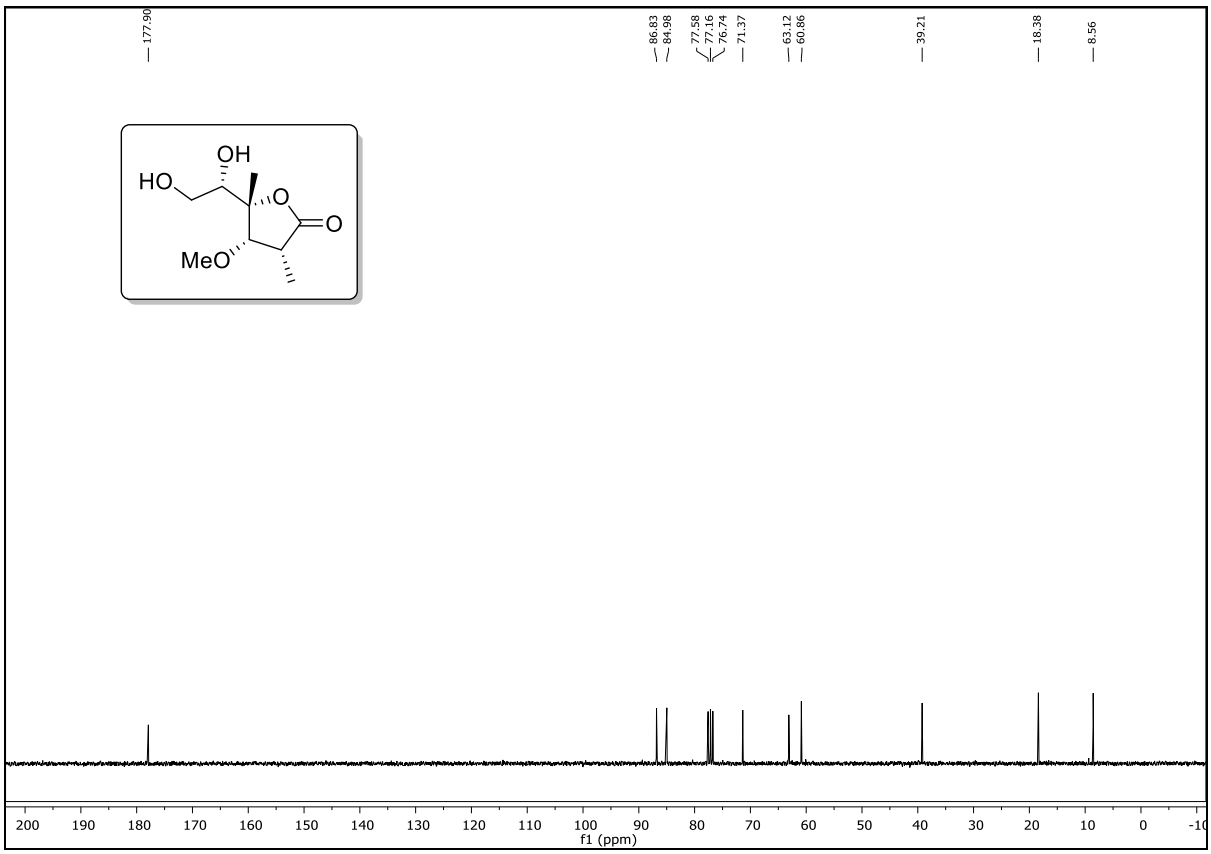
^{13}C NMR spectrum of epoxide corresponding product of 32 (75 MHz, $CDCl_3$):



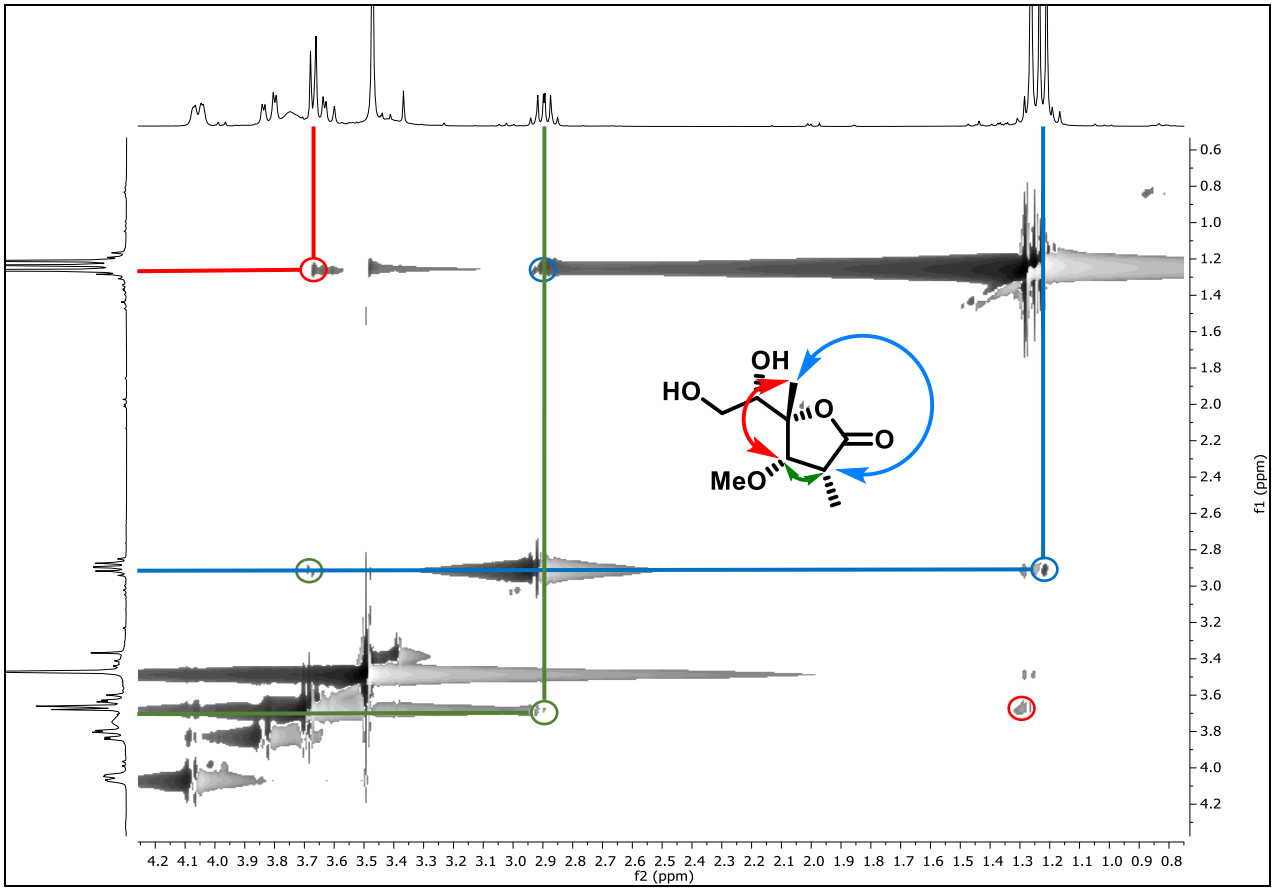
^{1}H NMR spectrum of compound 33 (300 MHz, $CDCl_3$):



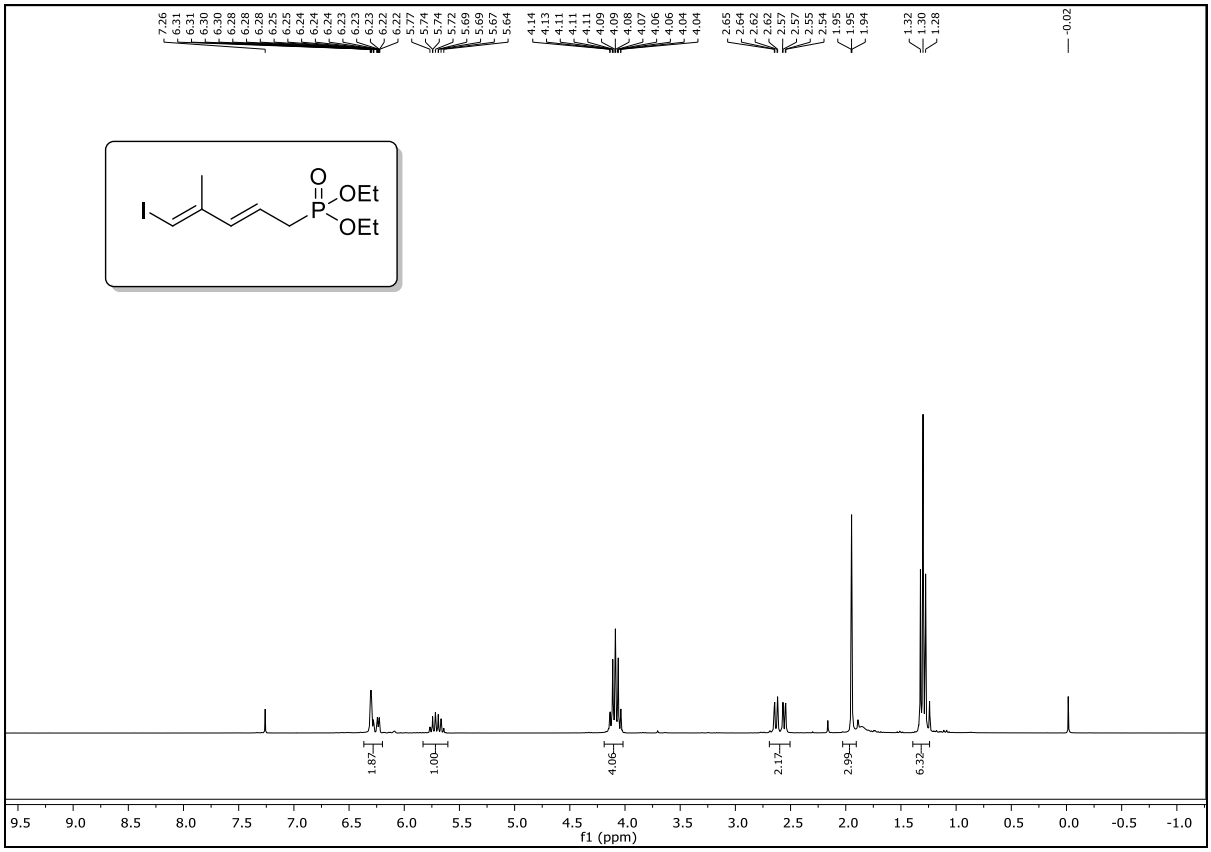
^{13}C NMR spectrum of compound 33 (75 MHz, $CDCl_3$):



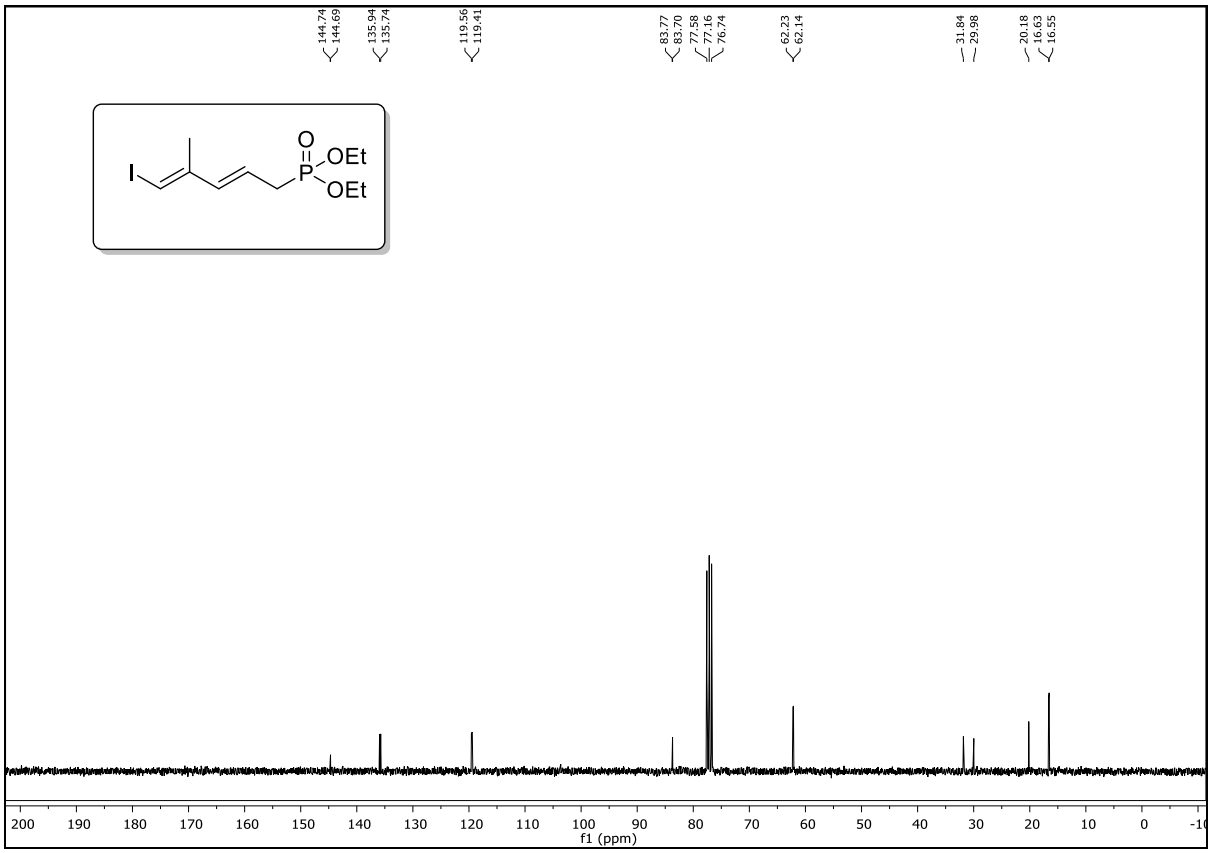
NOSEY spectrum of compound 33 (300 MHz, $CDCl_3$):



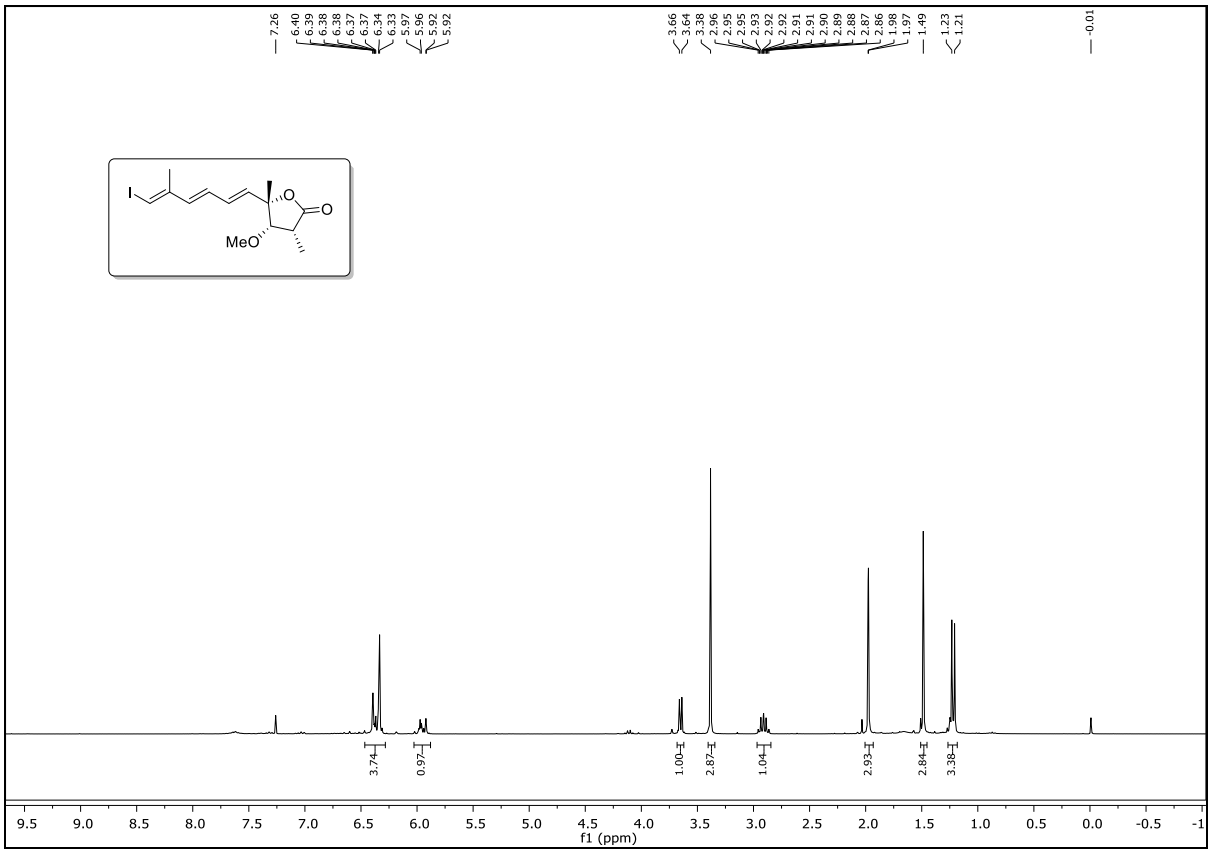
^{1}H NMR spectrum of compound 36 (300 MHz, $CDCl_3$):



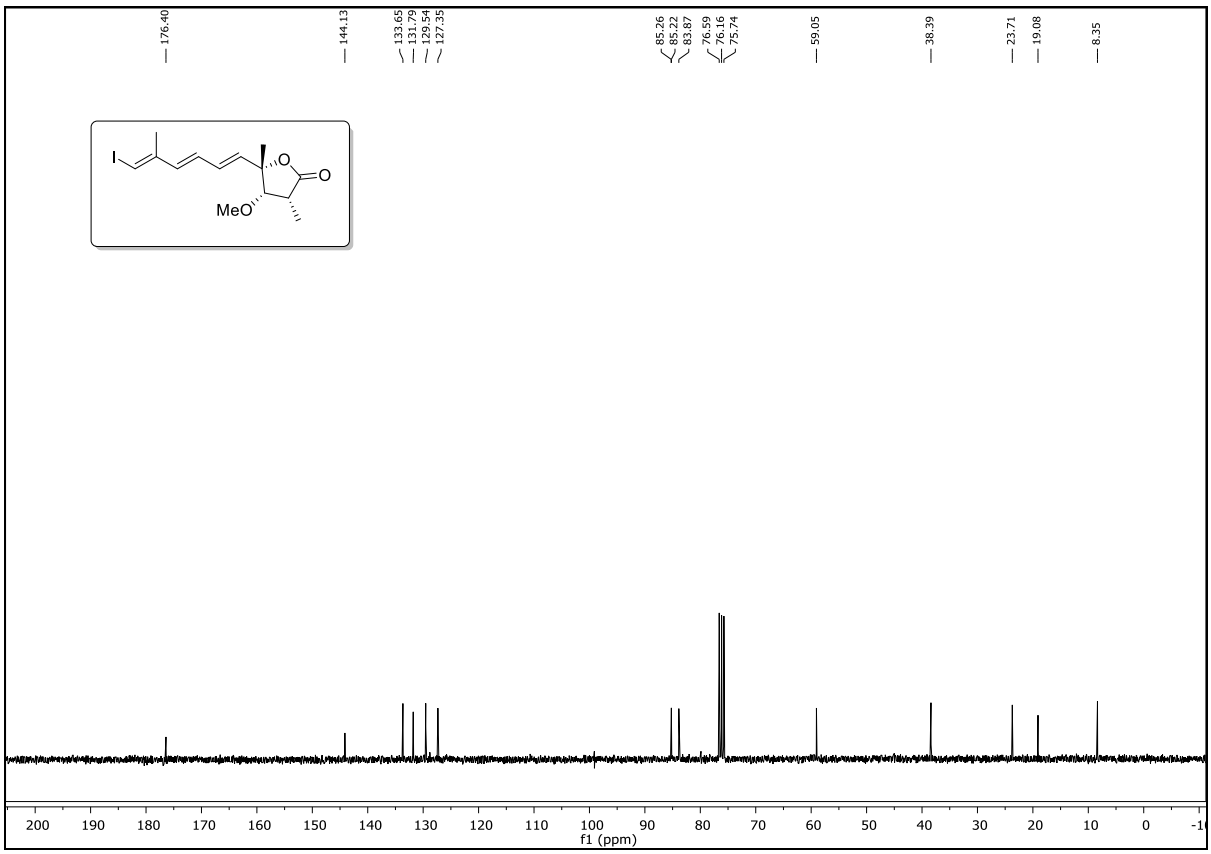
^{13}C NMR spectrum of compound 36 (75 MHz, $CDCl_3$):



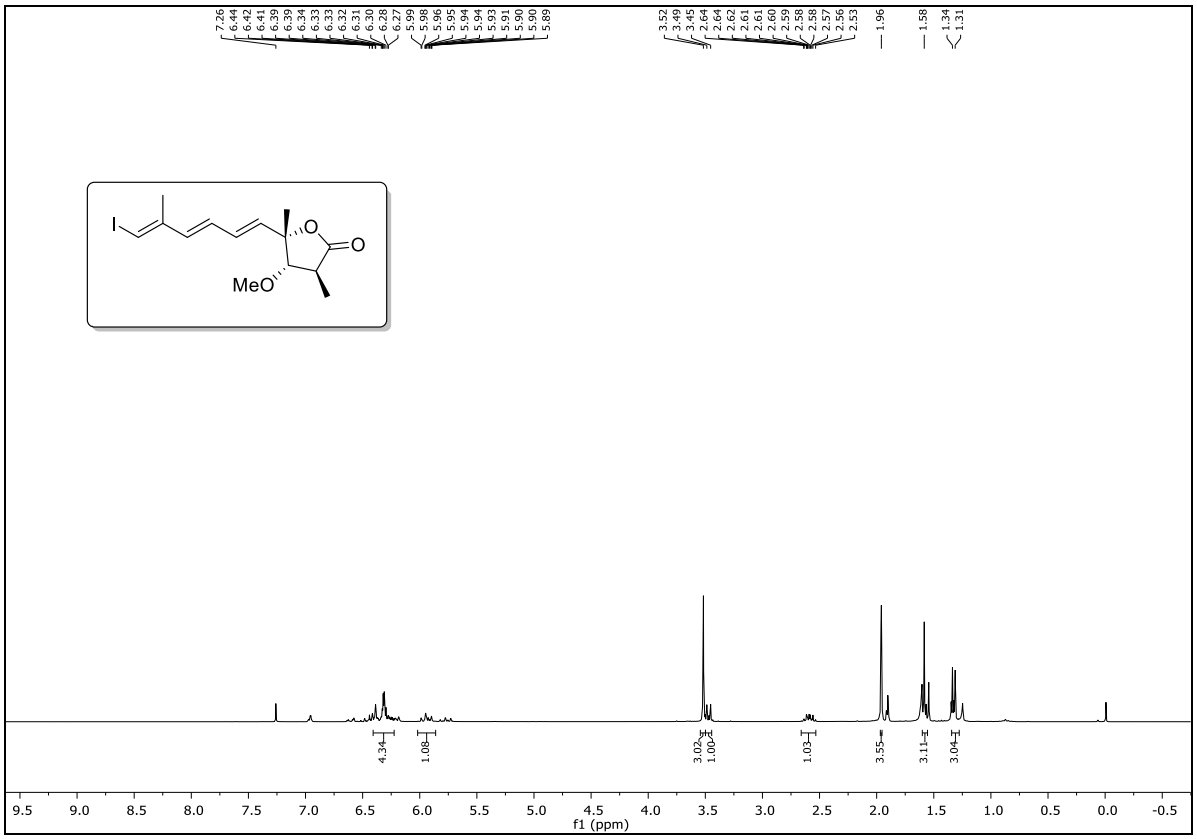
^{1}H NMR spectrum of compound 9 (300 MHz, $CDCl_3$):



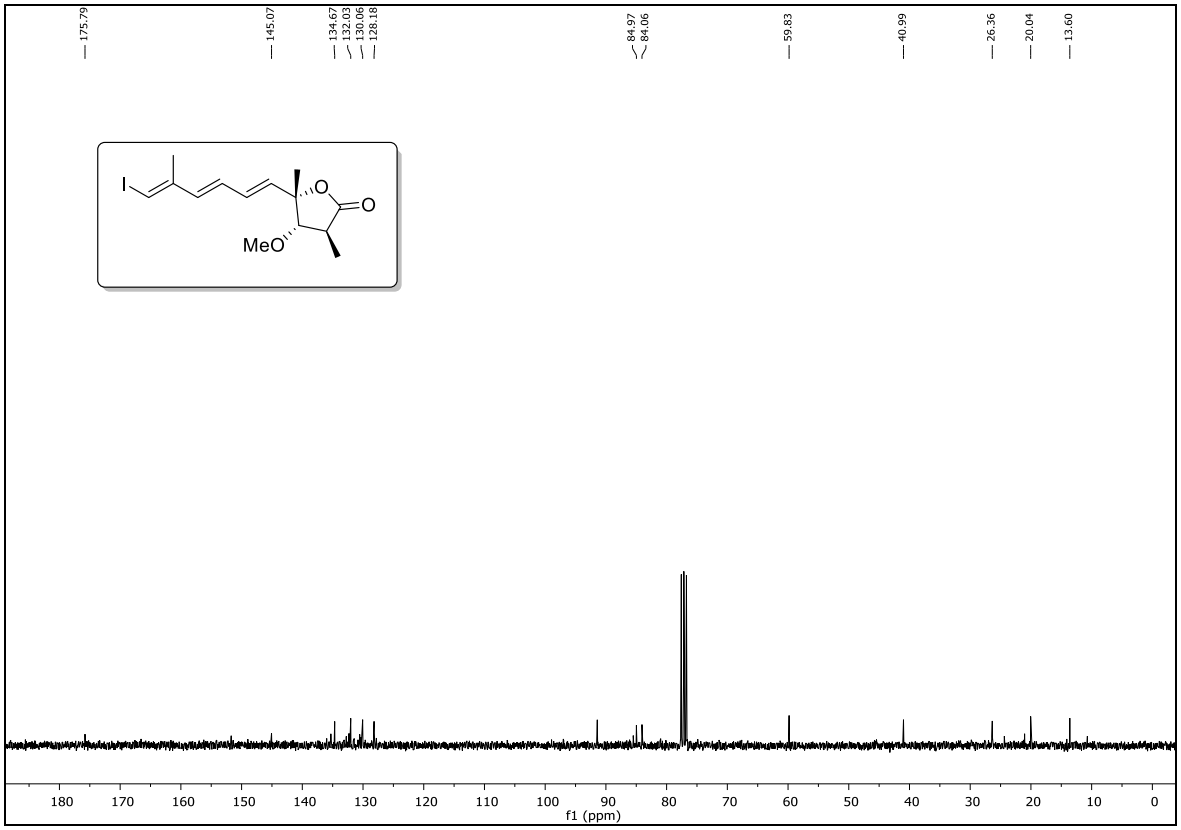
^{13}C NMR spectrum of compound 9 (75 MHz, $CDCl_3$):



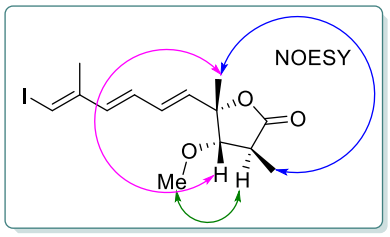
^{1}H NMR spectrum of compound 9-iso (300 MHz, $CDCl_3$):

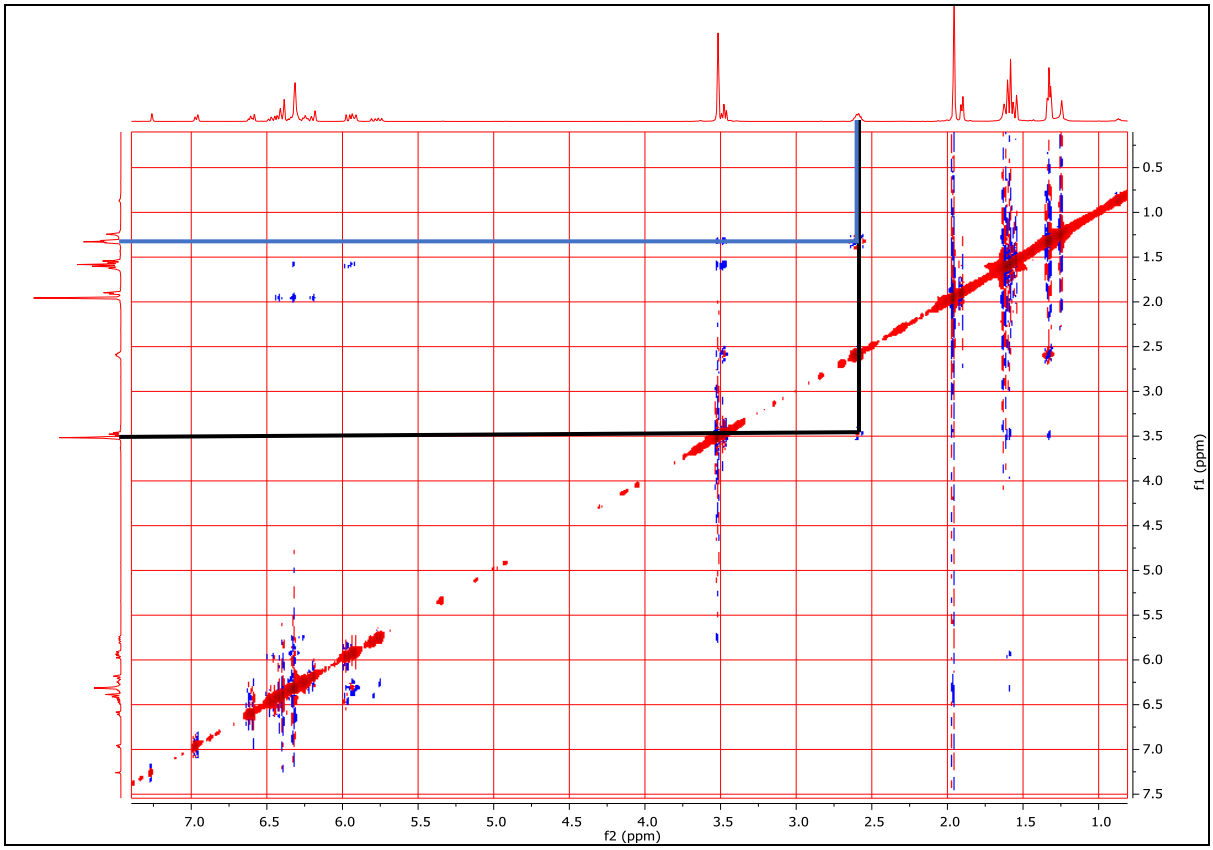


^{13}C NMR spectrum of compound 9-iso (75 MHz, $CDCl_3$):

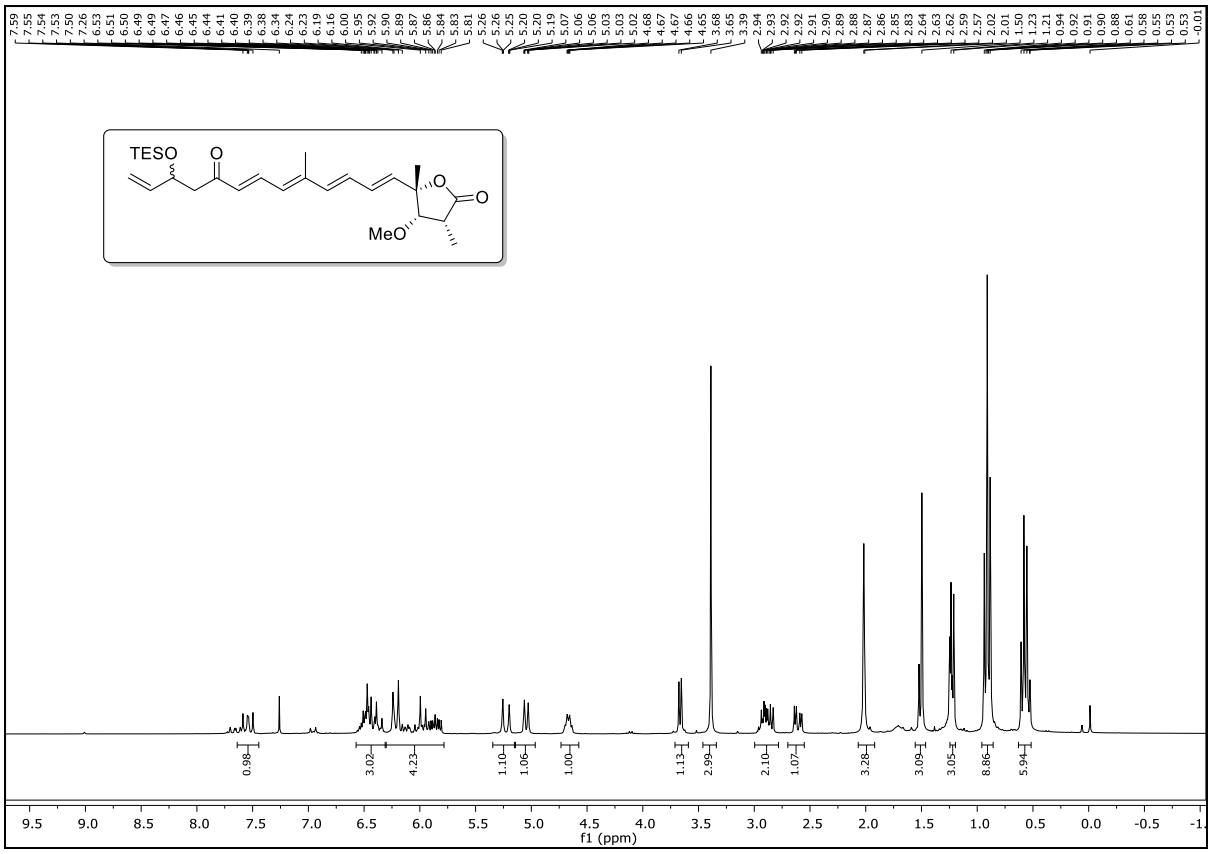


NOSEY spectrum of 9-iso (600 MHz, $CDCl_3$):

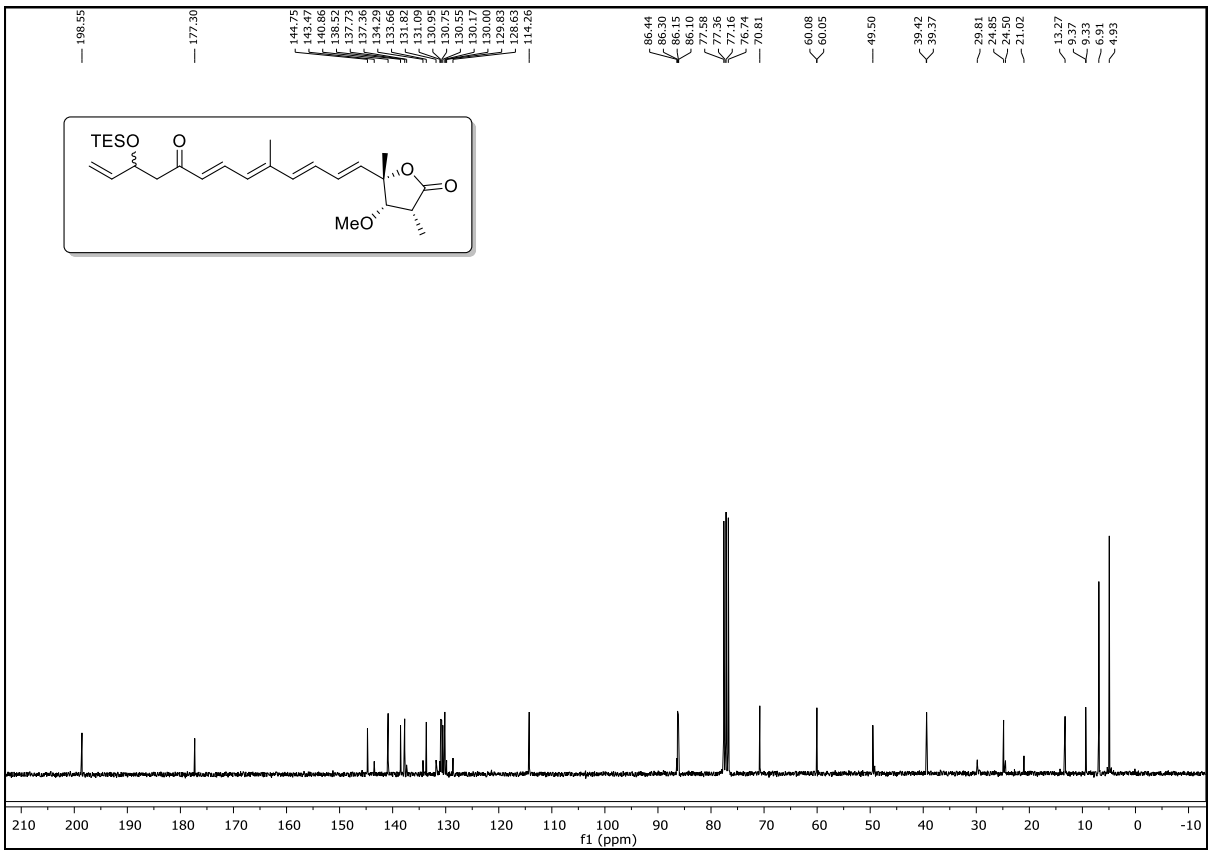




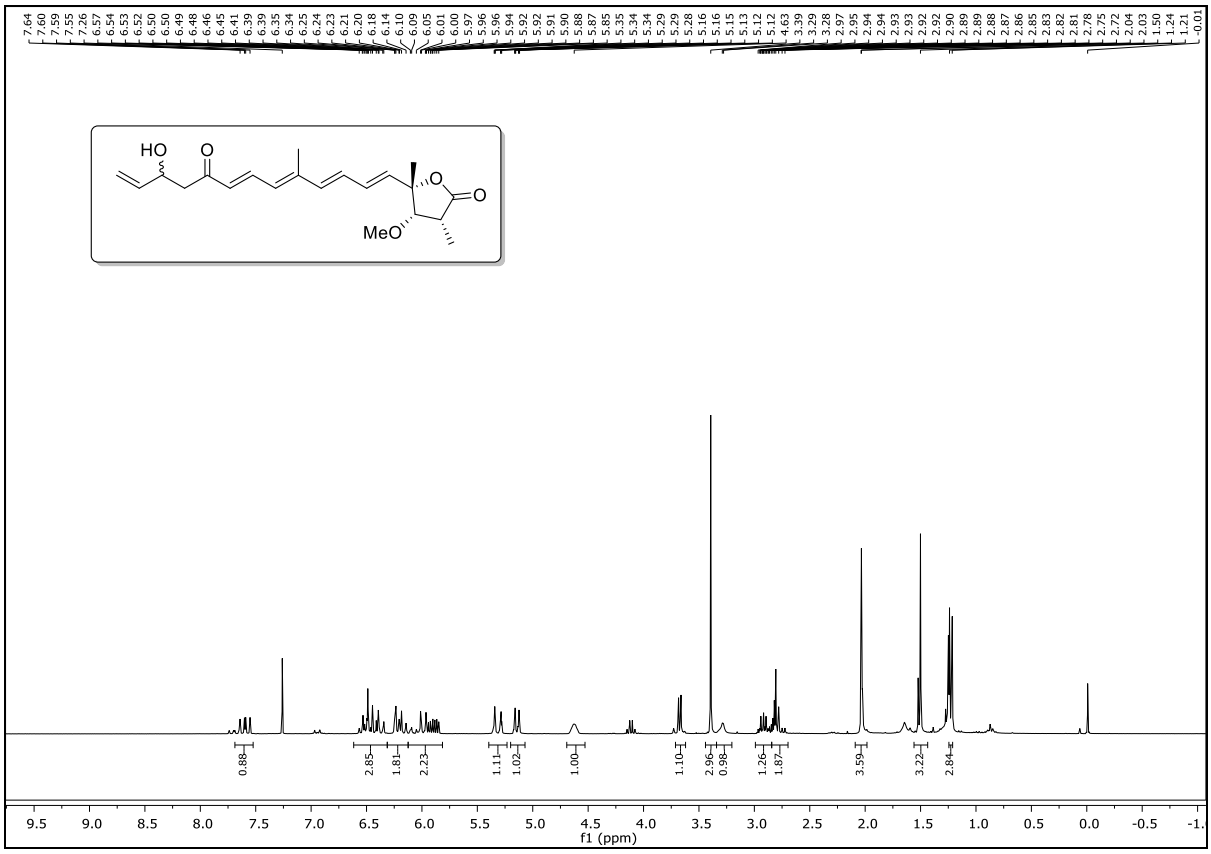
^{1}H NMR spectrum of Heck couple product of 8 and 9 (300 MHz, $CDCl_3$):



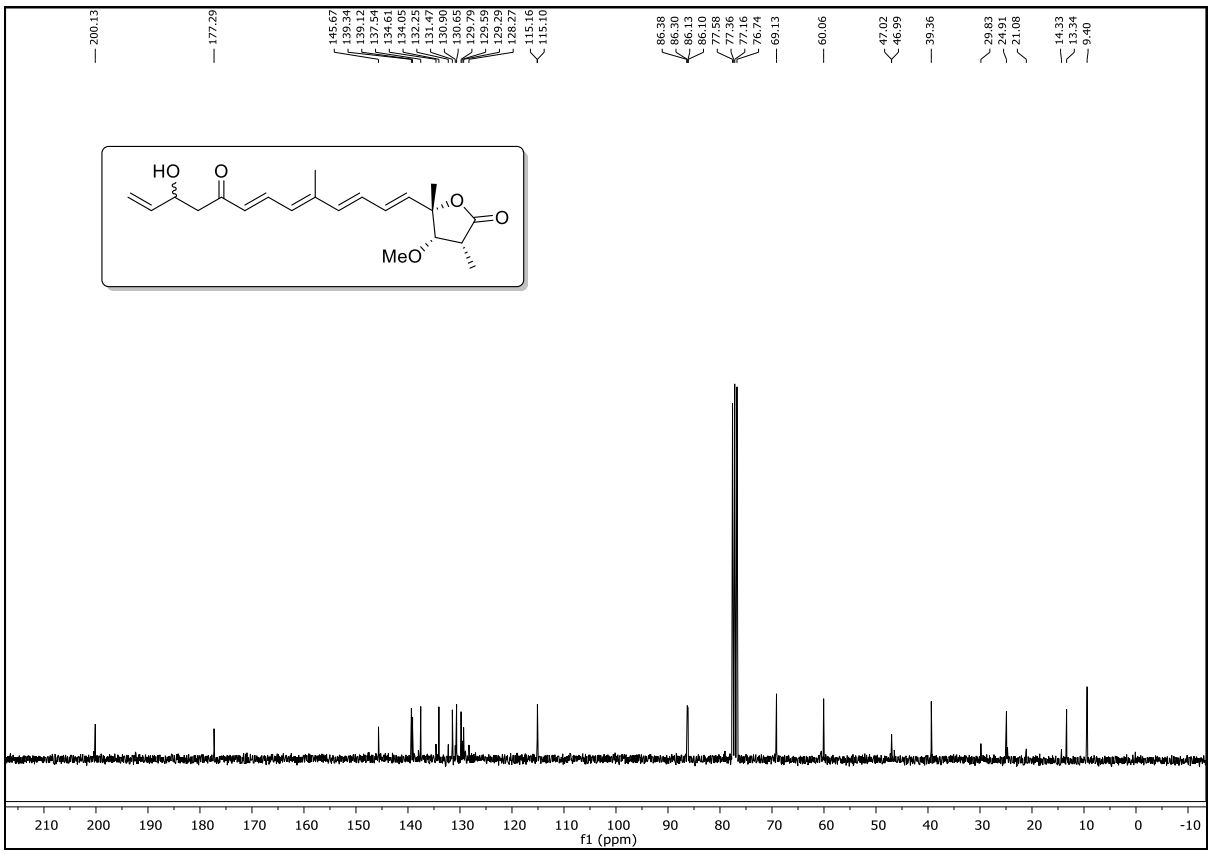
^{13}C NMR spectrum of Heck couple product of 8 and 9 (75 MHz, $CDCl_3$):



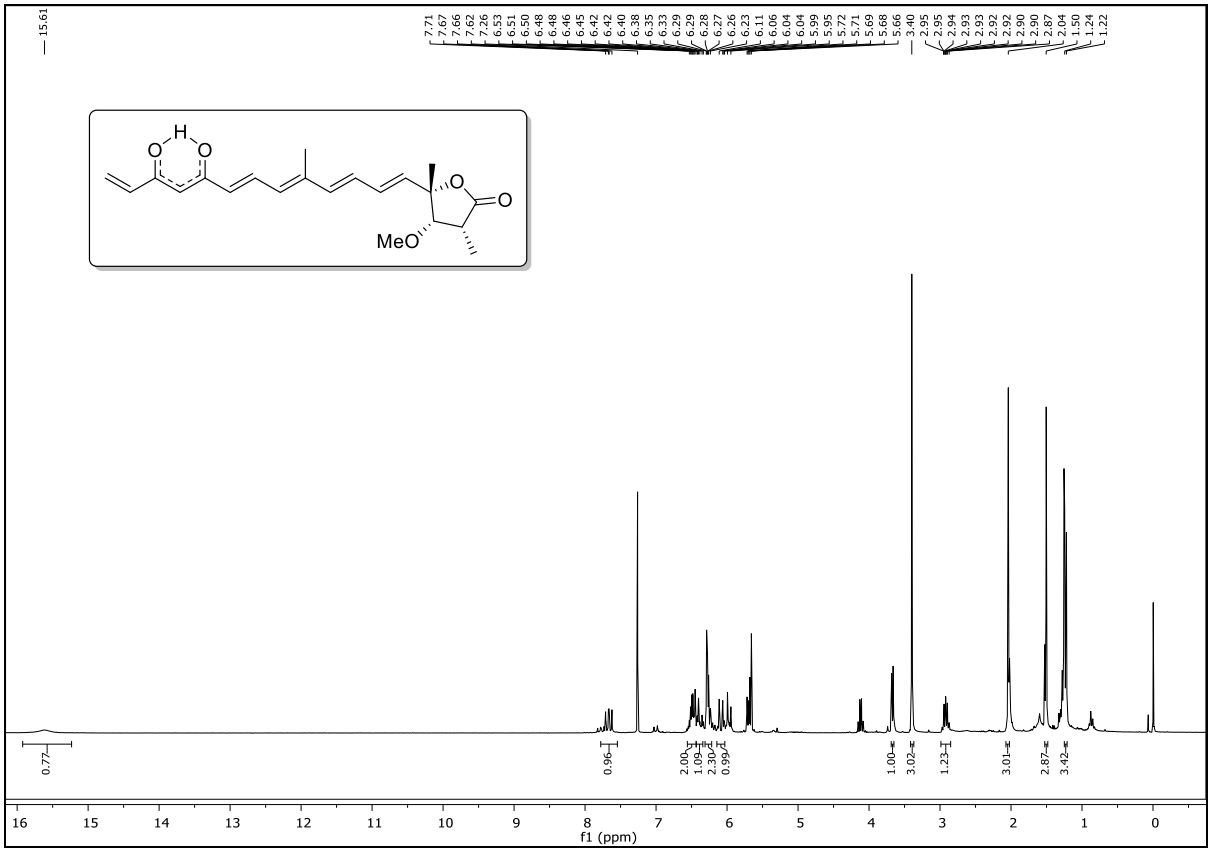
^{1}H NMR spectrum of TES deprotected couple product of 8 & 9 (300 MHz, $CDCl_3$):



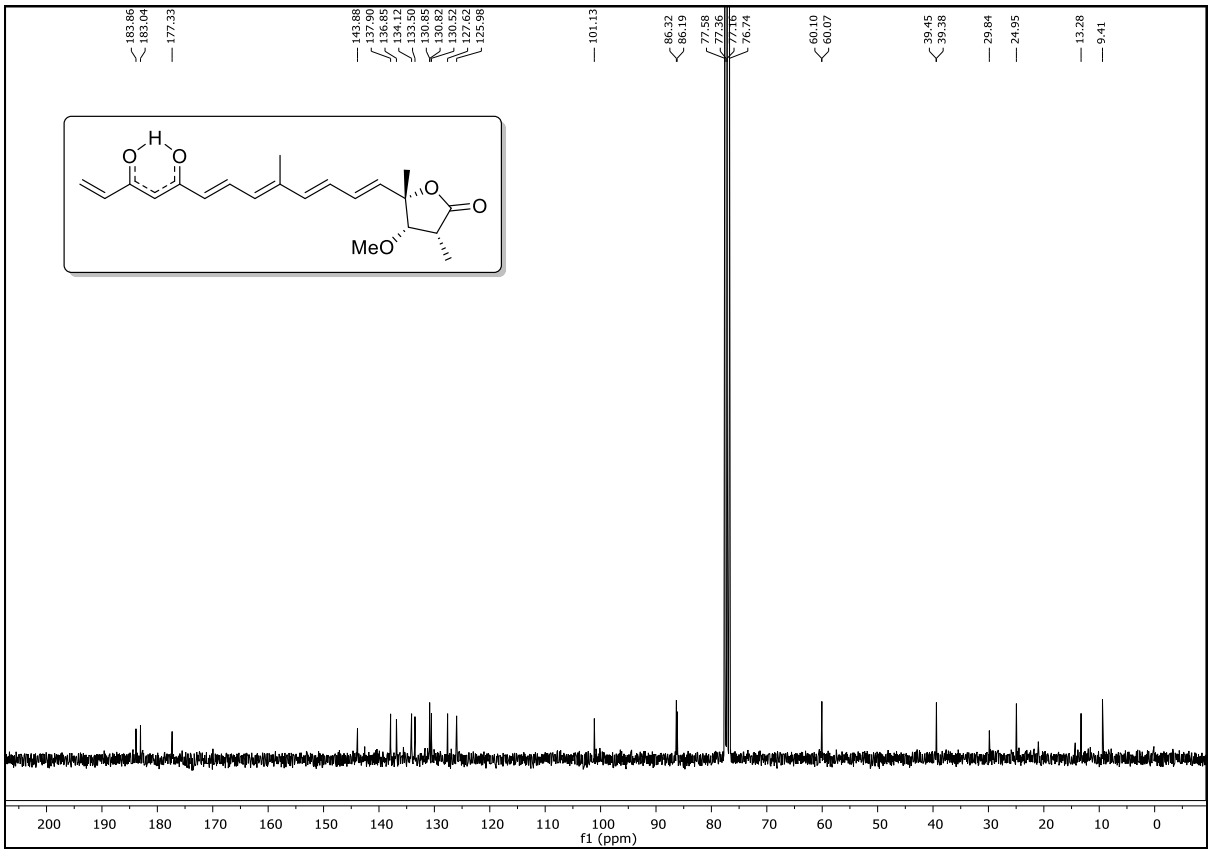
^{13}C NMR spectrum of TES deprotected couple product of 8 & 9 (75 MHz, $CDCl_3$):



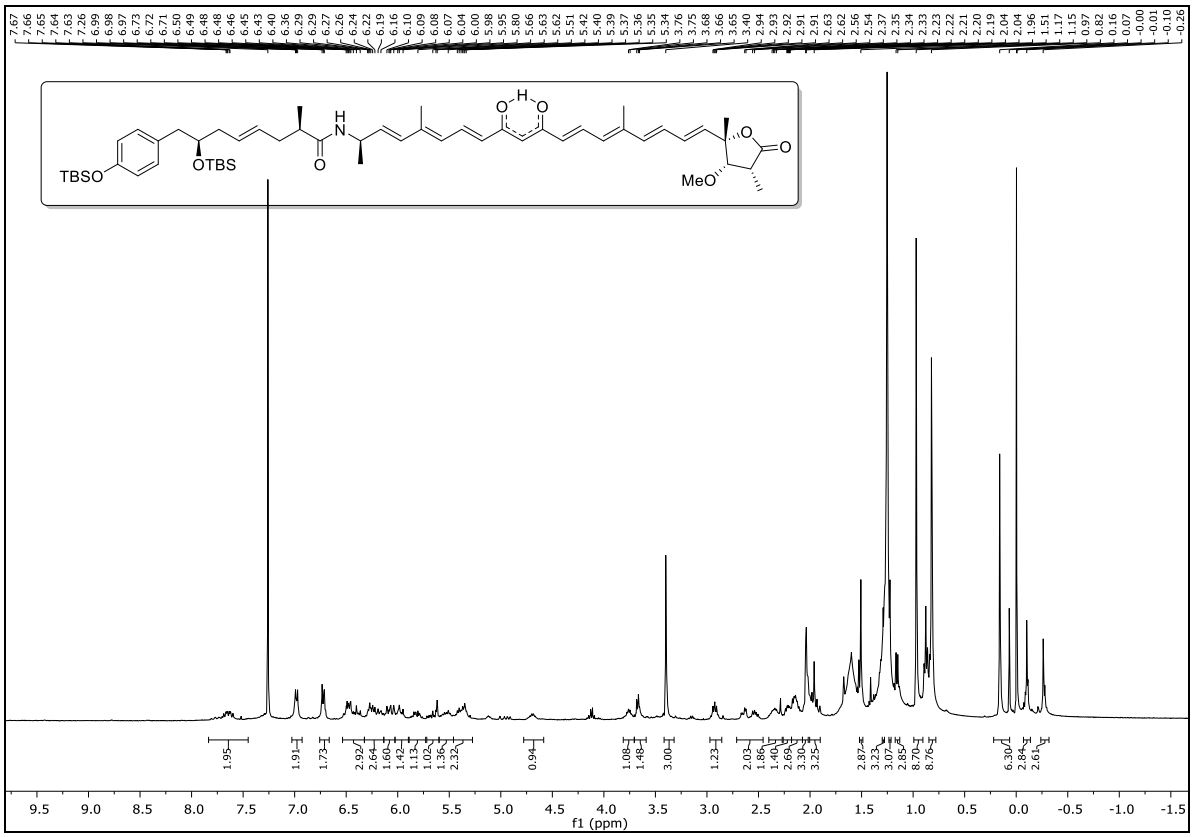
^{1}H NMR spectrum of compound 5 (300 MHz, $CDCl_3$):



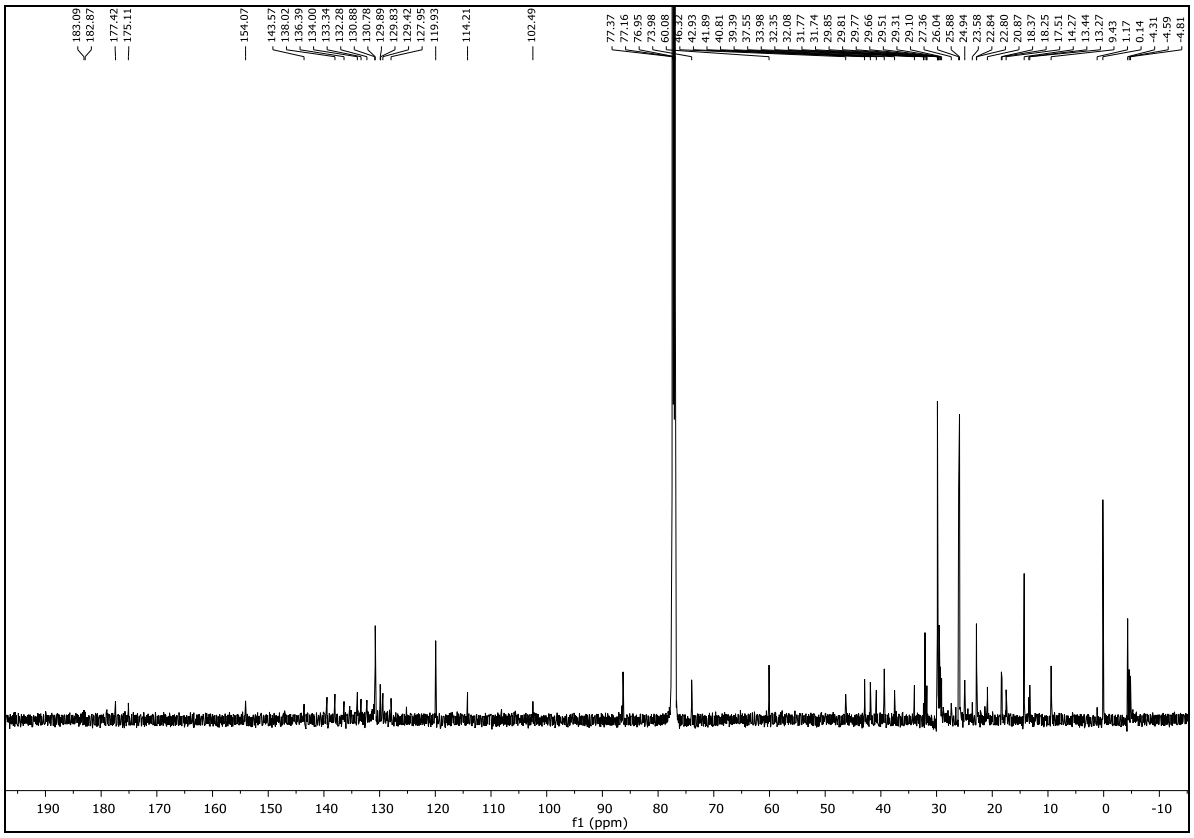
^{13}C NMR spectrum of compound 5 (75 MHz, $CDCl_3$):



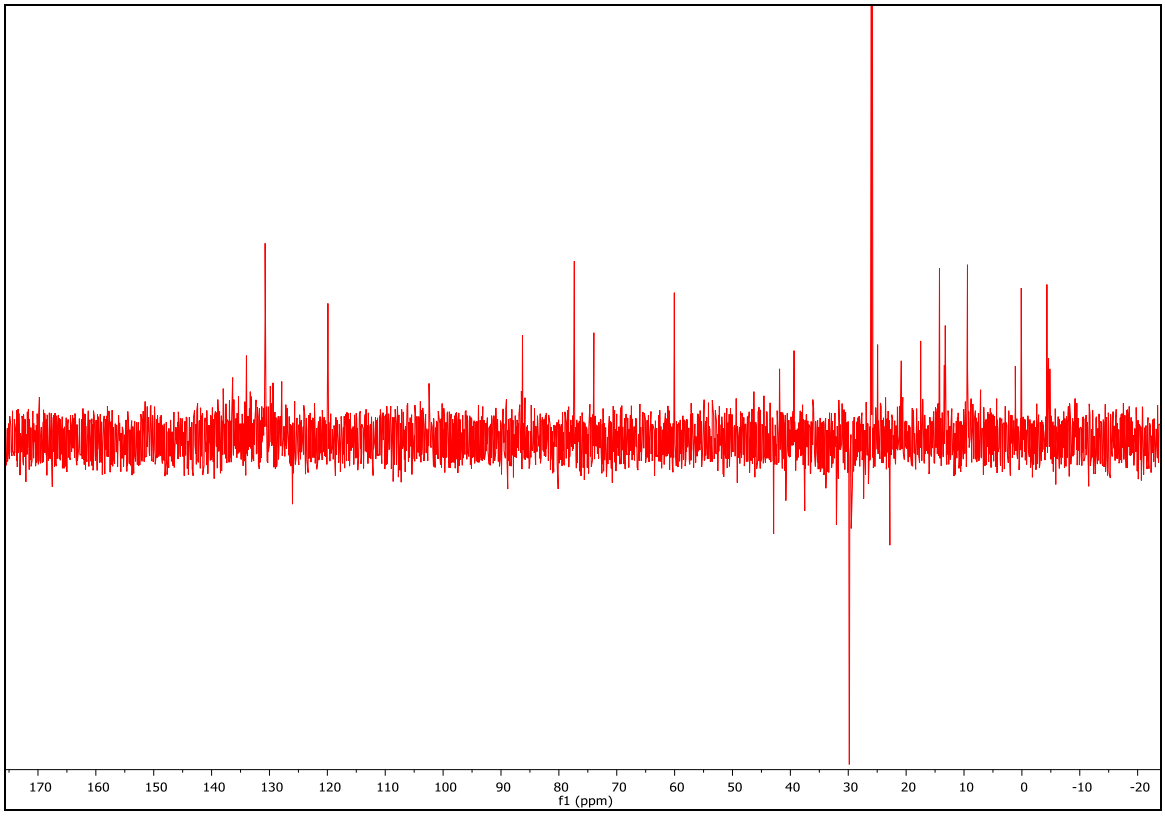
^{1}H NMR spectrum of compound 37 (400 MHz, $CDCl_3$):



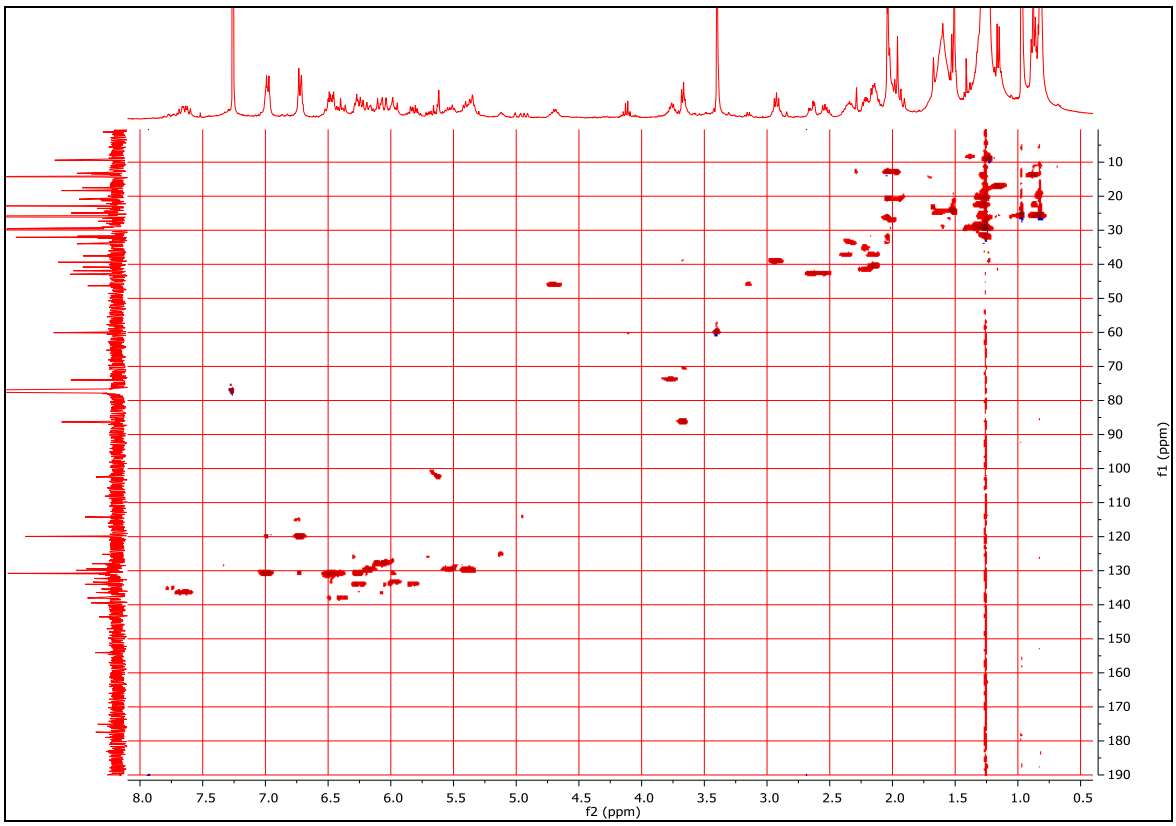
^{13}C NMR spectrum of compound 37 (151 MHz, $CDCl_3$):



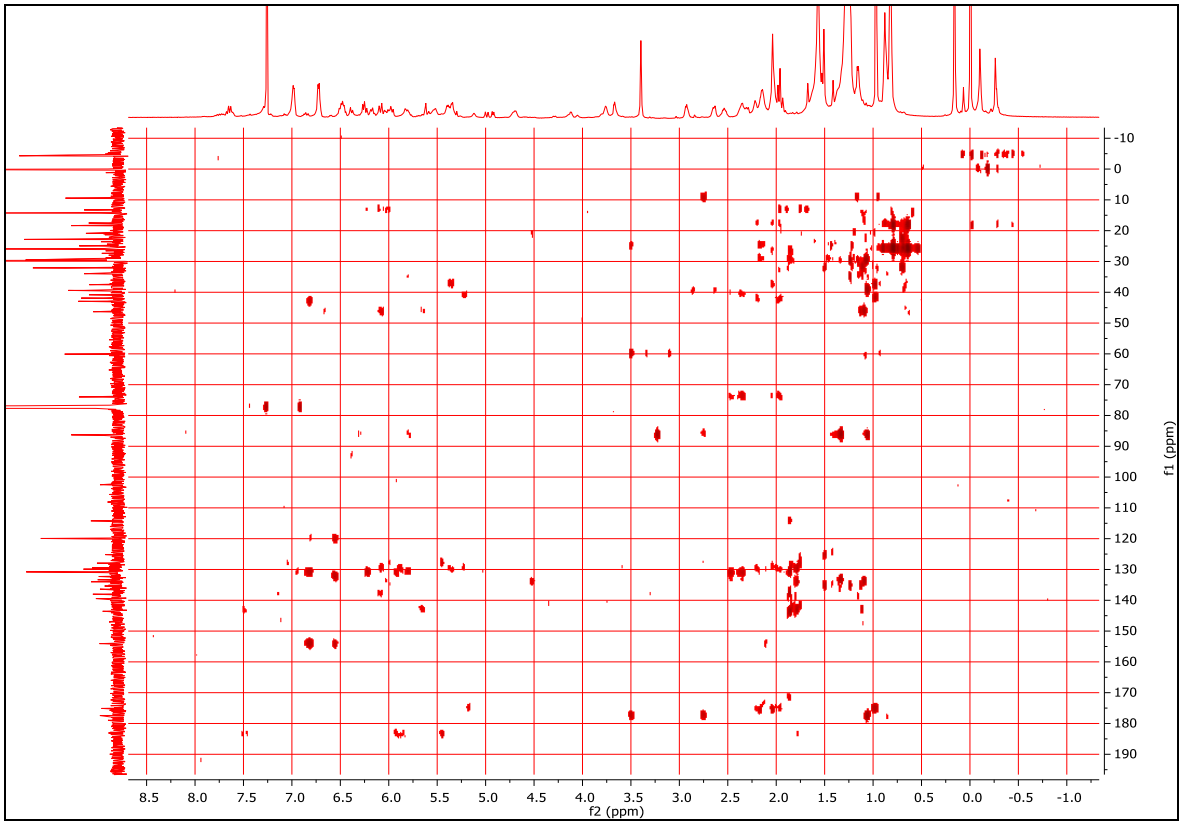
DEPT 135 spectrum of compound 37 (75 MHz, $CDCl_3$):



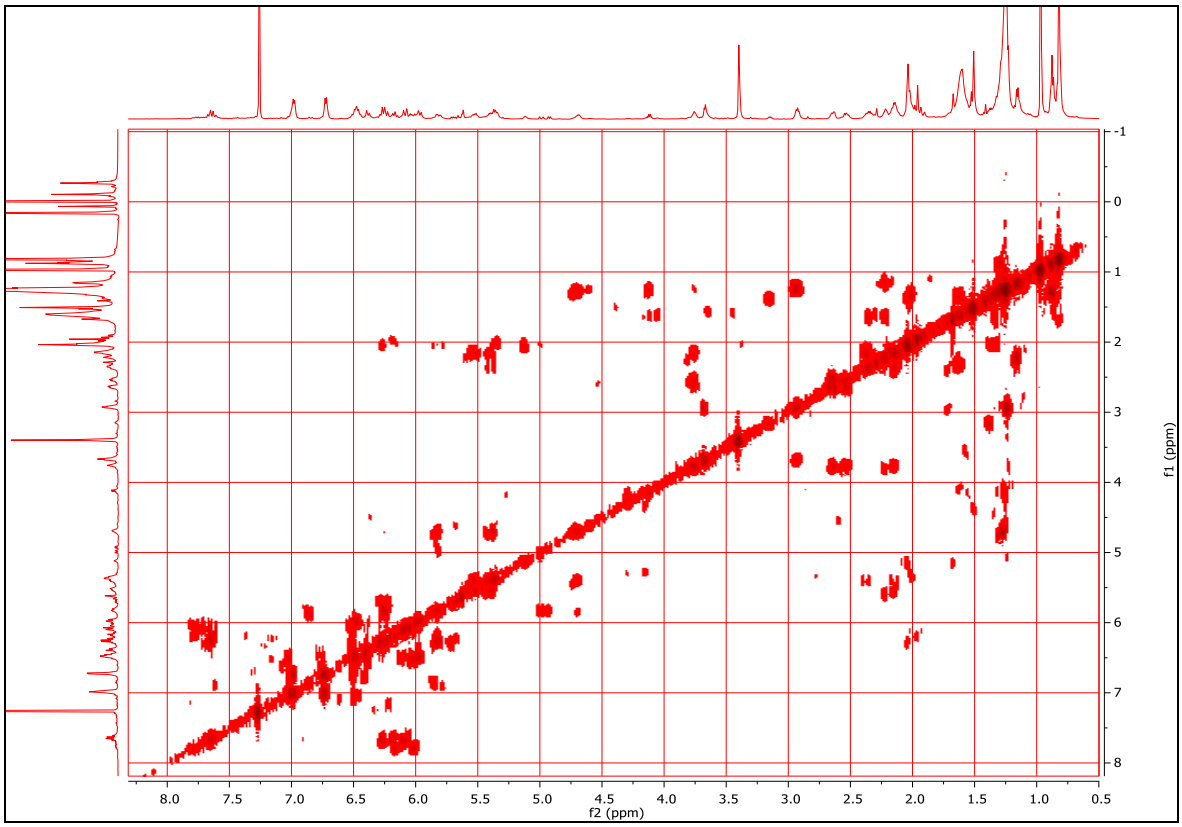
HSQC NMR spectrum of compound 37 (75 MHz, $CDCl_3$):



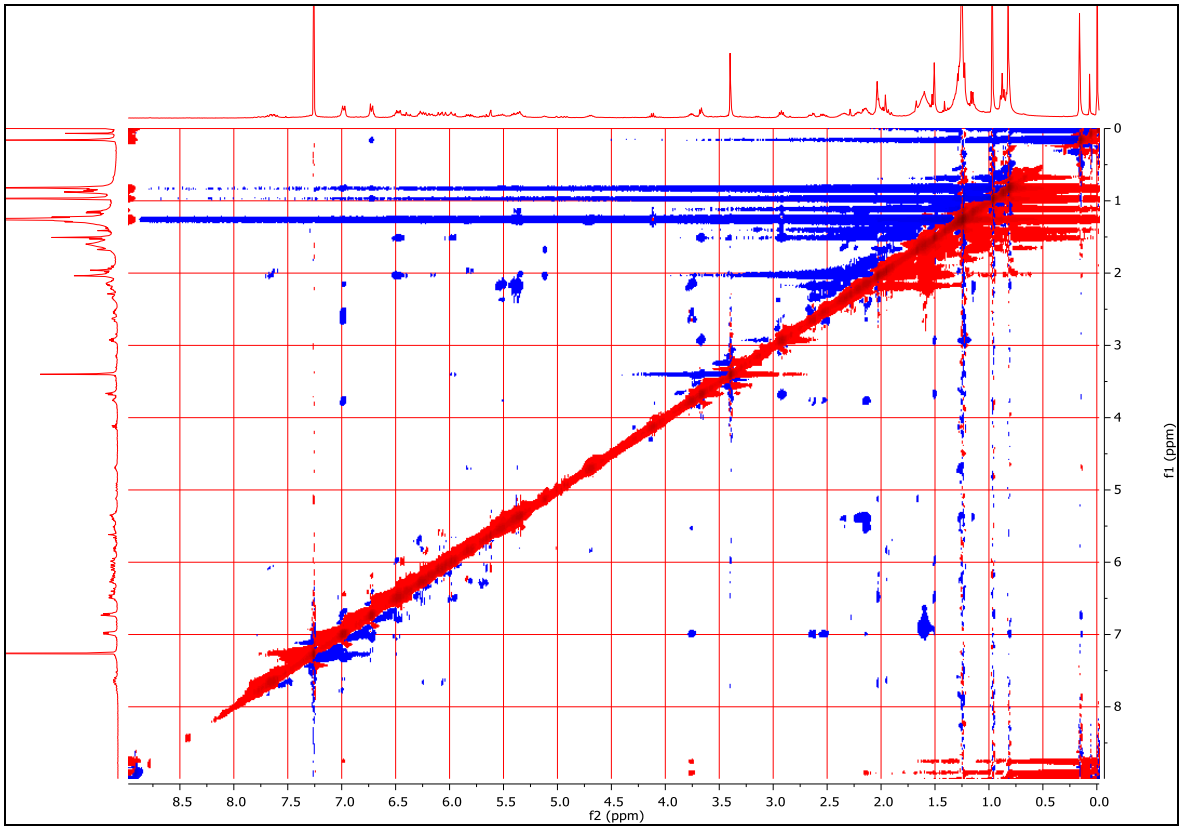
HMBC NMR spectrum of compound 37 (151 MHz, $CDCl_3$):



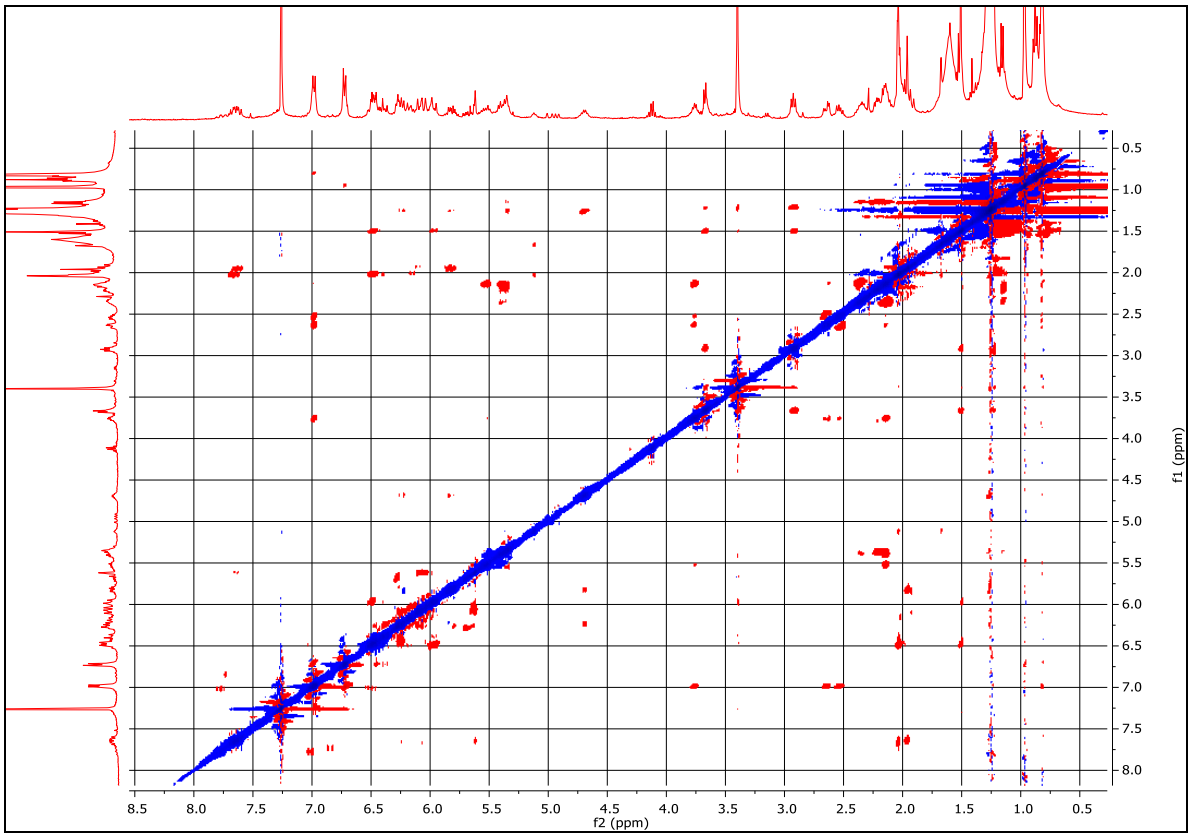
COSY NMR spectrum of compound 37 (600 MHz, $CDCl_3$):



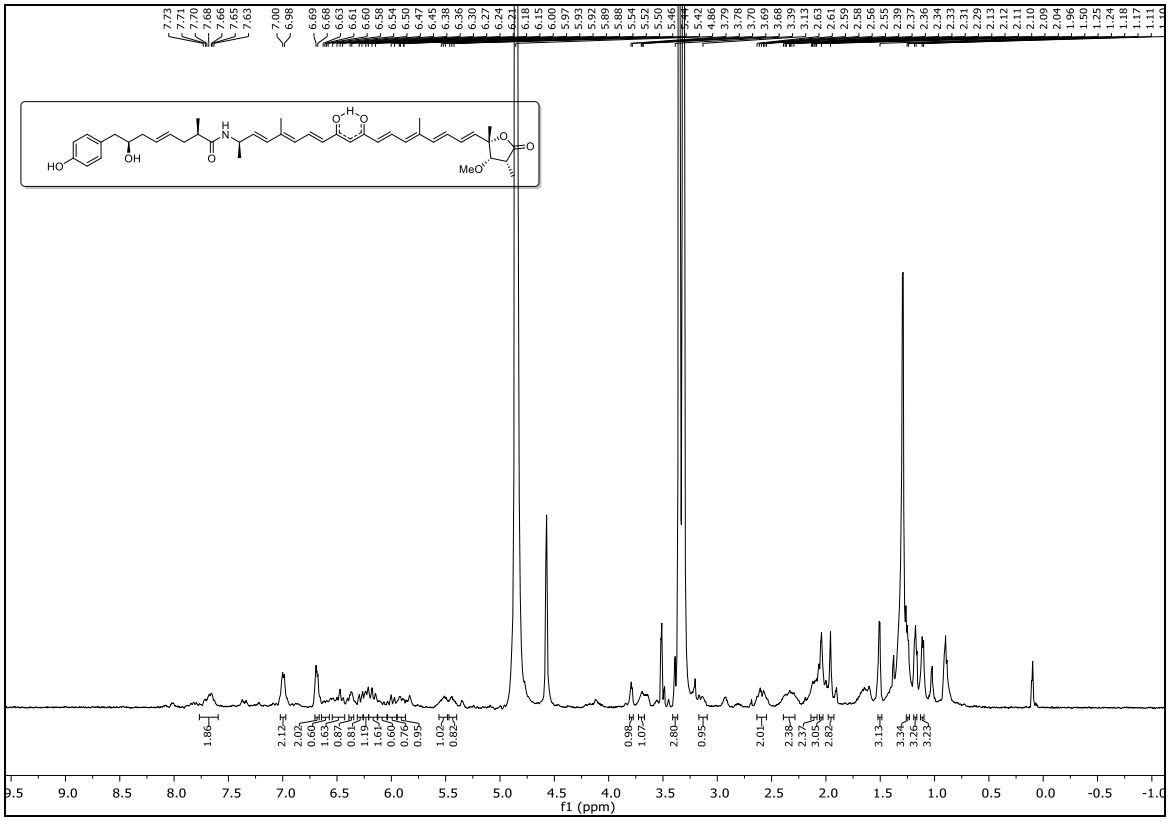
NOESY NMR spectrum of compound 37 (400 MHz, $CDCl_3$):



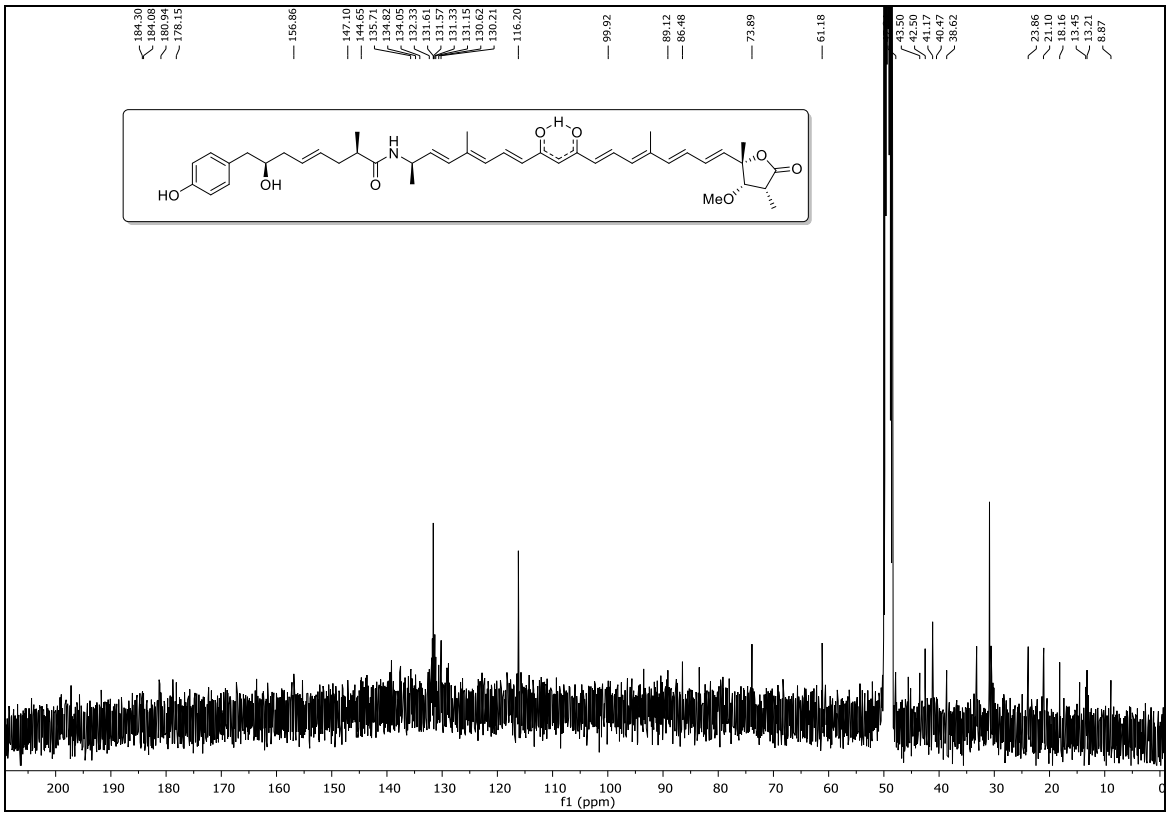
ROESY NMR spectrum of compound 37 (400 MHz, $CDCl_3$):



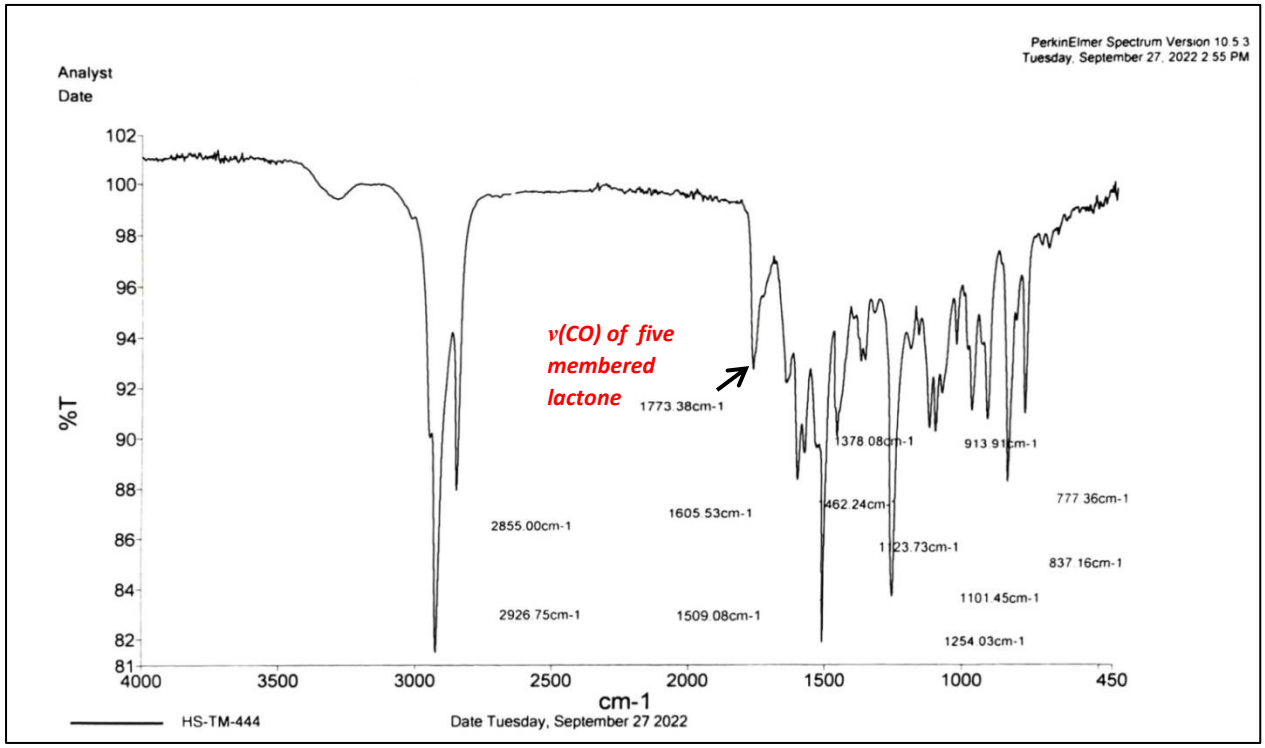
^{1}H NMR spectrum of compound 2 (500 MHz, CD_3OD):



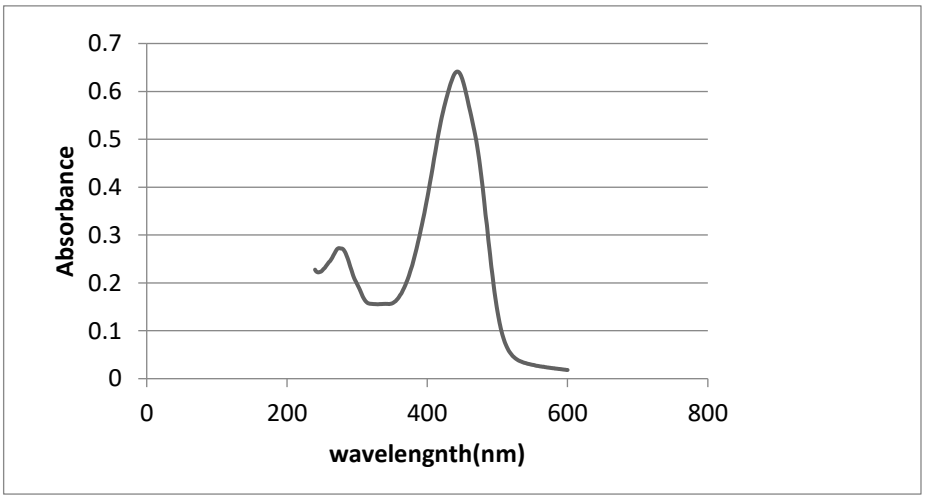
^{13}C NMR spectrum of compound 2 (151 MHz, CD_3OD):



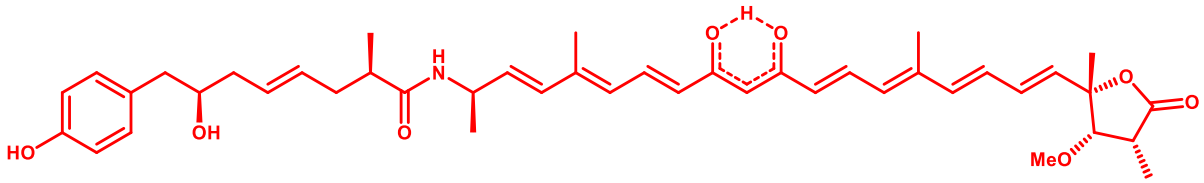
FT-IR spectrum of compound 2:

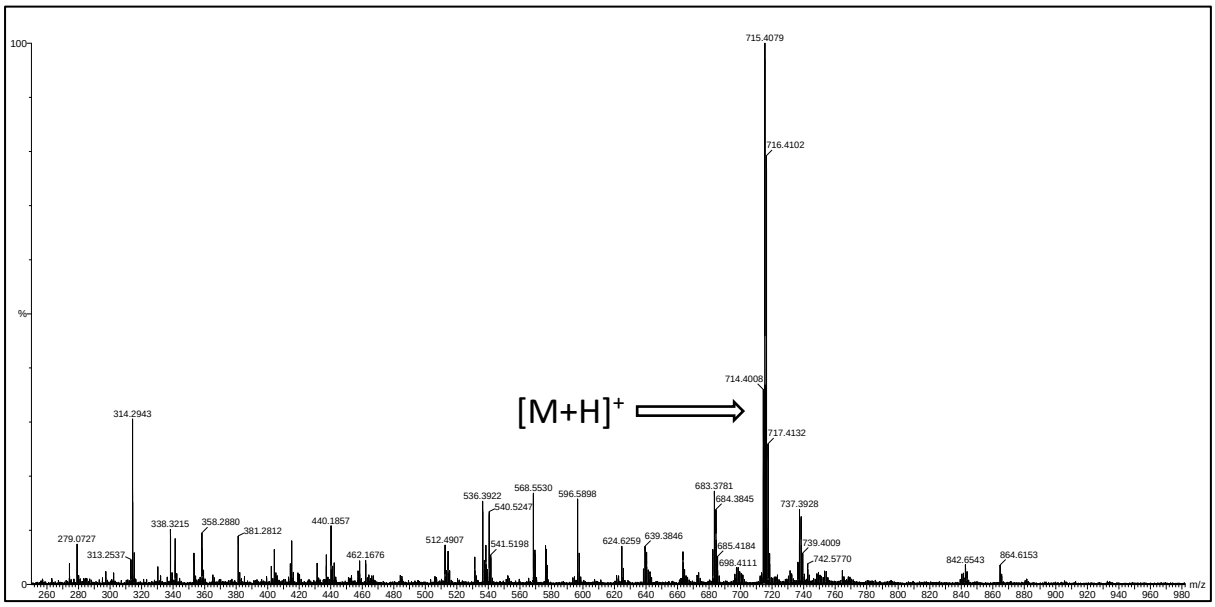


UV-VIS spectrum of compound 2 in methanol:



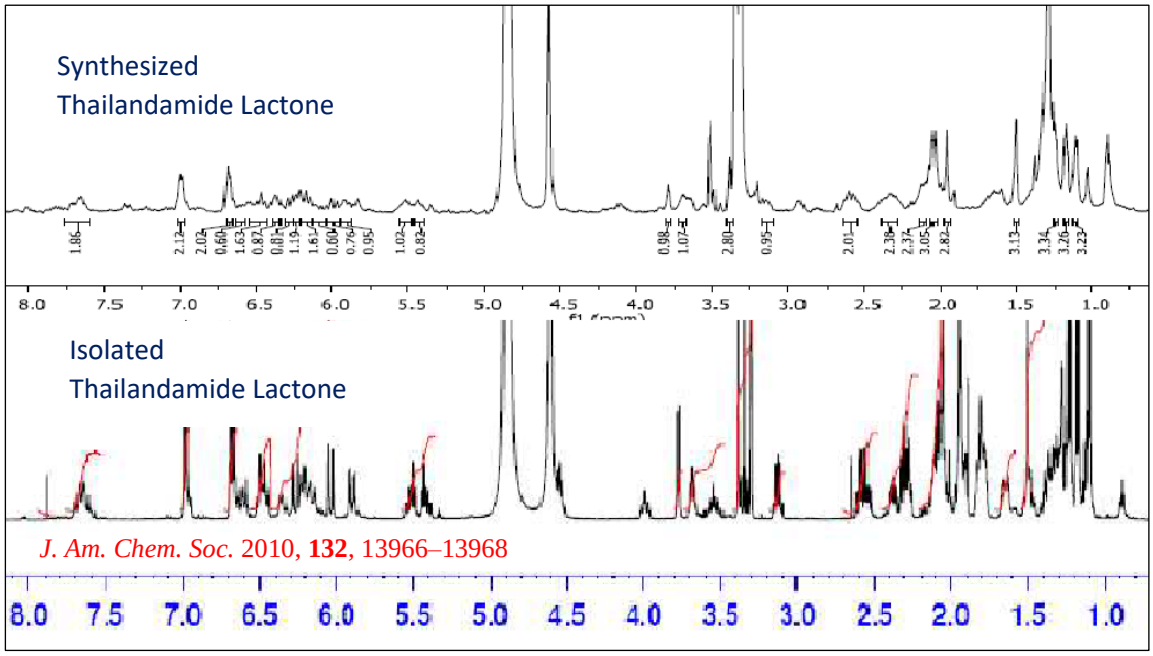
HRMS spectrum of Thailandamide Lactone (2):

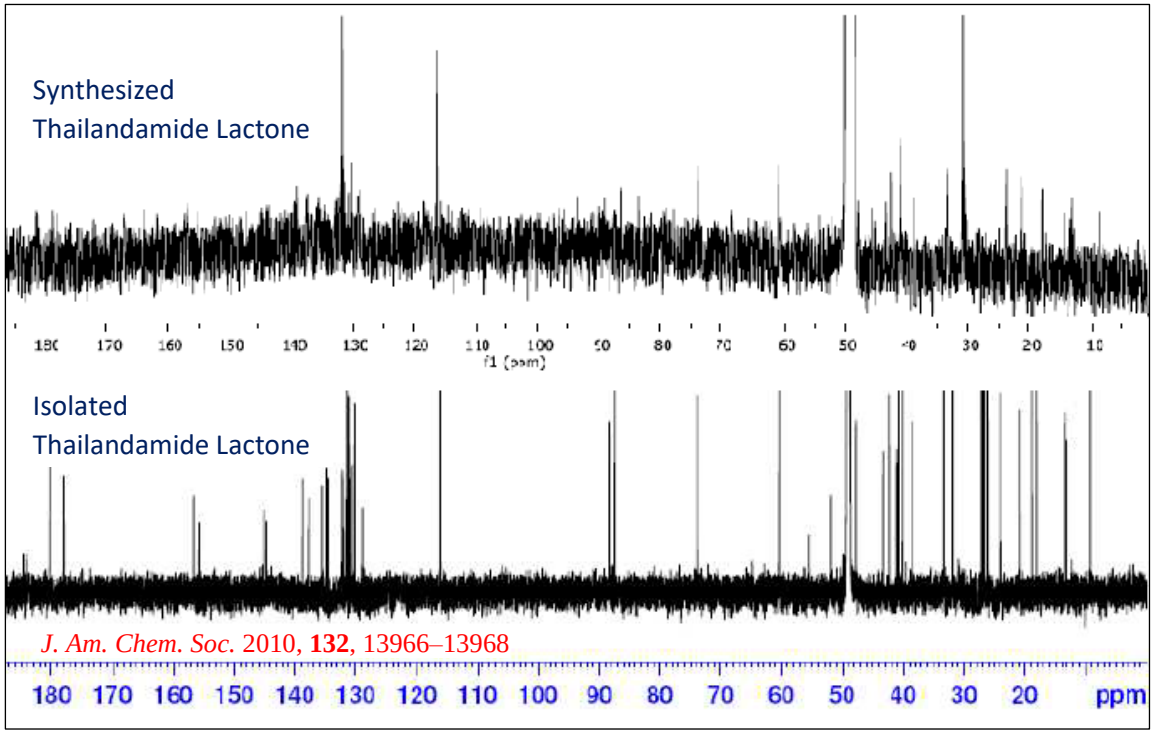




HRMS (ESI) *m/z* calculated for $C_{43}H_{55}NO_8$ $[M+H]^+$ 714.4006, found 714.4008.

4.0. Figure S3: ^{1}H and ^{13}C Spectral Comparison of the Synthesized and isolated Thailandamide Lactone

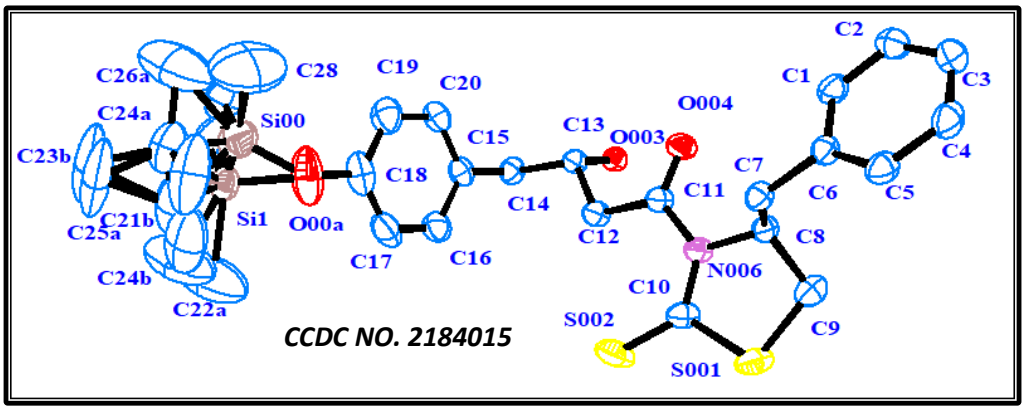




4.1. X-Ray Crystallographic Data for Compound 13

Table S3 Crystal Data and Structure Refinement for Compound 13:

Identification code	**HS-TM-6**
Empirical formula	$C_{26}H_{35}NO_3S_2Si$
Formula weight	501.76
Temperature/K	298
Crystal system	trigonal
Space group	$P3_1$
a/Å	18.235(3)
b/Å	18.235(3)
c/Å	7.1321(9)
α/°	90
β/°	90
γ/°	120
Volume/Å^3	2053.9(6)
Z	3
ρ_{calc}g/cm^3	1.217
μ/mm^{-1}	0.265
F(000)	804.0
Crystal size/mm^3	0.45 × 0.1 × 0.1
Radiation	MoKα (λ = 0.71073)
2Θ range for data collection/°	4.468 to 53.422
Index ranges	$-23 \le h \le 19$, $-23 \le k \le 23$, $-9 \le l \le 8$
Reflections collected	22774
Independent reflections	5650 [R_{int} = 0.0691, R_{sigma} = 0.0610]
Data/restraints/parameters	5650/1/356
Goodness-of-fit on F^2	1.071
Final R indexes [I>=2σ (I)]	R_1 = 0.0439, wR_2 = 0.0923
Final R indexes [all data]	R_1 = 0.0624, wR_2 = 0.1057
Largest diff. peak/hole / e Å^{-3}	0.34/-0.38
Flack parameter	-0.03(4)



4.2. X-Ray Crystallographic Data for Compound 31

Table S4 Crystal Data and Structure Refinement for Compound 31 :

Identification code	**HS-TM-233**
Empirical formula	$C_{28}H_{29}O_4$
Formula weight	430.52
Temperature/K	105.33
Crystal system	tetragonal
Space group	$P4_12_12$
a/Å	9.6794(11)
b/Å	9.6794(11)
c/Å	49.548(8)
α/°	90
β/°	90
γ/°	90
Volume/Å^3	4642.2(13)
Z	8
ρ_{calc}g/cm^3	1.232
μ/mm^{-1}	0.081
F(000)	1840.0
Crystal size/mm^3	0.32 × 0.32 × 0.09
Radiation	MoKα (λ = 0.71073)
2Θ range for data collection/°	4.518 to 50.172
Index ranges	$-11 \le h \le 11$, $-11 \le k \le 11$, $-59 \le l \le 59$
Reflections collected	44343
Independent reflections	4139 [R_{int} = 0.1132, R_{sigma} = 0.0519]
Data/restraints/parameters	4139/0/292
Goodness-of-fit on F^2	1.155
Final R indexes [I>=2σ (I)]	R_1 = 0.0512, wR_2 = 0.1149
Final R indexes [all data]	R_1 = 0.0731, wR_2 = 0.1280
Largest diff. peak/hole / e Å^{-3}	0.34/-0.26
Flack parameter	0.5(10)