

Stereoselective Synthesis of Thailandamide A Methyl Ester

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and Rajib Kumar Goswami**

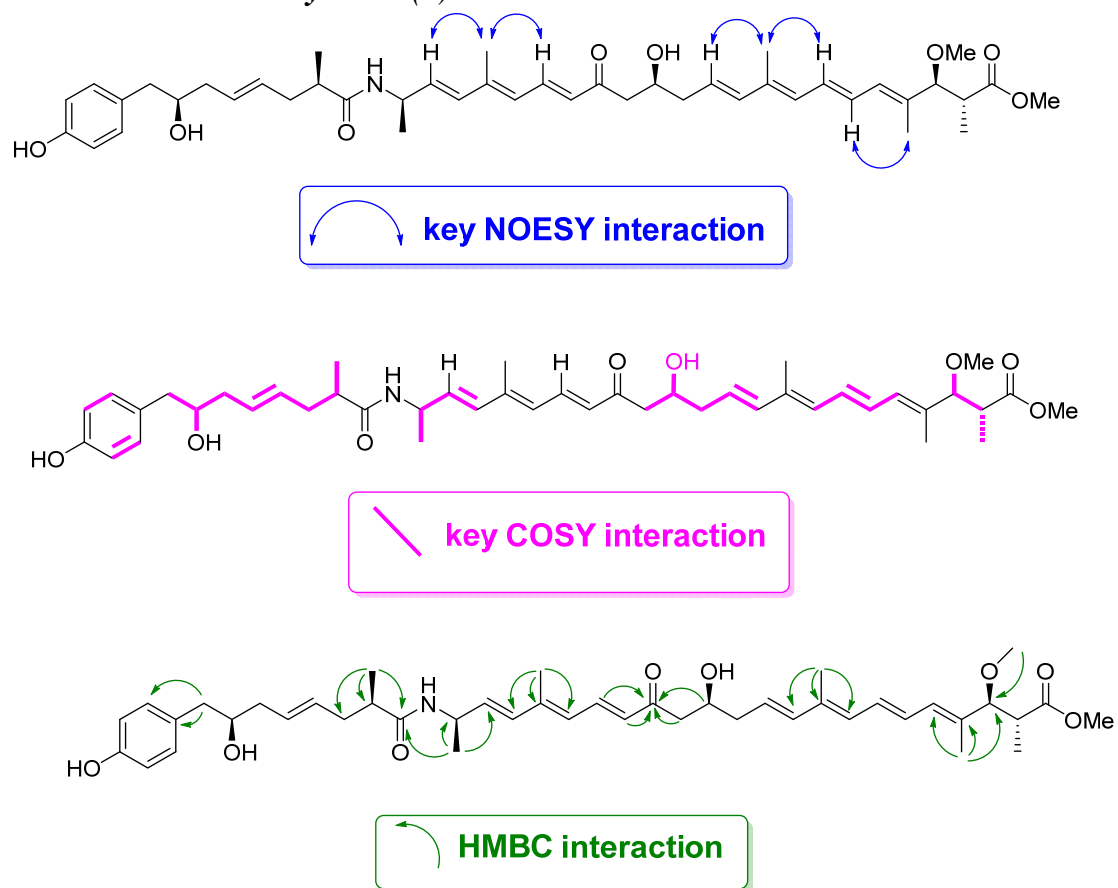
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Supporting Information

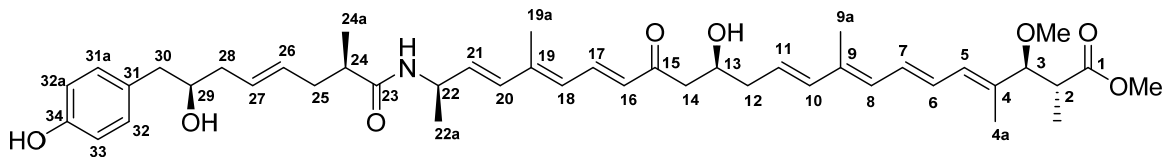
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1.1. Figure S1: Key 2D-NMR correlations and structural confirmation of thailandamide A methyl ester (4)



2.1. Table S-1. Comparison of the ¹H NMR spectra (MeOD-*d*₄) of synthetic methyl ester 4 and isolated acid 1¹



| Position | δ ¹ H [ppm] (Natural) (MeOD- <i>d</i> ₄) | δ ¹ H [ppm] (Synthetic) (500 MHz, MeOD- <i>d</i> ₄) | $\Delta\delta$ |
|-----------|--|--|----------------|
| 1 | | | |
| 2 | 2.57 (m) | 2.65-2.62 (m) | 0.06 |
| 3 | 3.66 (m) | 3.67 (d, 4.4) | 0.01 |
| 4 | | | |
| 5 | 6.18 (m) | 6.19 (d, 1.8) | 0.01 |
| 6 | 6.49 (dd 14.5, 11.1) | 6.50 (dd, 14.5, 11.1) | 0.01 |
| 7 | 6.63 (dd 14.5, 11.1) | 6.66-6.60 (m) | 0.0 |
| 8 | 6.10 (d 11.1) | 6.11 (d, 11.2) | 0.01 |
| 9 | | | |
| 10 | 6.19 (m) | 6.23-6.19 (m) | 0.02 |
| 11 | 5.80 (dt 15.4, 7.2) | 5.79 (dt, 15.3, 7.4) | 0.01 |
| 12 | 2.35 (m) | 2.38-2.34 (m) | 0.01 |
| 13 | 4.15 (m) | 4.16 (tdd, 11.7, 8.8, 5.8) | 0.01 |
| 14 | 2.75 (m) | 2.75 (dq, 9.0, 4.8, 4.2) | 0.0 |
| 15 | | | |
| 16 | 6.24 (d 15.1) | 6.25 (d, 9.5) | 0.01 |
| 17 | 7.62 (dd 15.1, 11.8) | 7.63 (dd, 15.1, 11.8) | 0.01 |
| 18 | 6.19 (m) | 6.23-6.19 (m) | 0.02 |
| 19 | | | |
| 20 | 6.26 (d 15.7) | 6.28 (d, 11.0) | 0.02 |
| 21 | 5.94 (dd 15.7, 6.0) | 5.93 (dd, 15.8, 6.1) | -0.01 |
| 22 | 4.54 (m) | 4.55 (td, 7.2, 3.5) | 0.01 |
| 23 | | | |
| 24 | 2.36 (m) | 2.41-2.37 (m) | 0.03 |

| | | | |
|--------------------------------|---------------------|---------------------------------|--------------|
| 25 | 2.08 (m), 2.29 (m) | 2.09-2.07 (m) , 2.3-2.26 (m) | 0.0, -0.01 |
| 26 | 5.43 (dt 15.2, 6.7) | 5.45-5.39 (m) | -0.01 |
| 27 | 5.53 (dt 15.2, 6.7) | 5.55-5.45 (m) | -0.03 |
| 28 | 2.06 (m), 2.12 (m) | 2.07-2.03 (m), 2.12-2.09 (m) | -0.01, -0.01 |
| 29 | 3.68 (m) | 3.67-3.64 (m) | -0.02 |
| 30 | 2.58 (m) | 2.59-2.56 (m) | -0.005 |
| 31 | | | |
| 32,32a | 6.98 (d 8.3) | 6.98 (8.4) | 0.0 |
| 33,33a | 6.69 (d 8.3) | 6.69 (d, 8.4) | 0.0 |
| 34 | | | |
| 2a | 0.94 (d 7.0) | 0.93 (d, 7.2) | -0.01 |
| 3a | 3.14 (s) | 3.12 (s) | -0.02 |
| 4a | 1.67 (s) | 1.67 (s) | 0.0 |
| 9a | 1.88 (s) | 1.89 (s) | 0.01 |
| 19a | 1.95 (s) | 1.95 (s) | 0.0 |
| 22a | 1.24 (d 6.7) | 1.24 (d, 6.9) | 0.0 |
| 24a | 1.09 (d 6.8) | 1.1 (d, 6.8) | 0.01 |
| NH | | | |
| CH₃ of ester | | 3.68 (s) | |

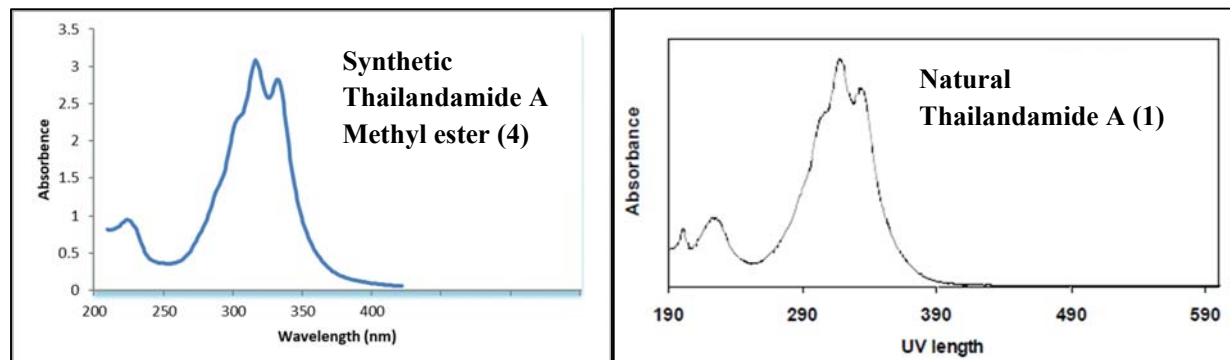
2.2. Table S-2. Comparison of the ¹³C NMR spectra (MeOD-*d*₄) of synthetic methyl ester 4 and isolated acid 1¹

| Position | δ ¹³C [ppm] (Natural) (MeOD-<i>d</i>₄) | δ ¹³C [ppm] (Synthetic) (500 MHz, MeOD-<i>d</i>₄) | Δδ | Δδ - 0.1ppm** |
|-----------------|---|--|-----------|--------------------------|
| 4a | 11.0 | 11.1 | 0.1 | 0.0 |
| 9a | 12.9 | 13.0 | 0.1 | 0.0 |
| 19a | 13.4 | 13.5 | 0.1 | 0.0 |
| 2a | 14.7 | 14.7 | 0.0 | -0.1 |
| 24a | 18.0 | 18.2 | 0.2 | 0.1 |
| 22a | 20.8 | 21.0 | 0.2 | 0.1 |
| 25 | 38.5 | 38.6 | 0.1 | 0.0 |
| 28 | 41.0 | 41.1 | 0.1 | 0.0 |
| 12 | 42.1 | 42.2 | 0.1 | 0.0 |
| 24 | 42.3 | 42.4 | 0.1 | 0.0 |

| | | | | |
|--------------------------------|-------|-------|------|------|
| 30 | 43.4 | 43.5 | 0.1 | 0.0 |
| 2 | 44.4 | 44.4 | 0.0 | -0.1 |
| 22 | 47.7 | 47.8 | 0.1 | 0.0 |
| 14 | 48.4 | 47.9 | -0.5 | -0.6 |
| 3a | 56.5 | 56.6 | 0.1 | 0.0 |
| 13 | 69.5 | 69.6 | 0.1 | 0.0 |
| 29 | 73.7 | 73.8 | 0.1 | 0.0 |
| 3 | 91.0 | 91.1 | 0.1 | 0.0 |
| 33,33a | 116.1 | 116.2 | 0.1 | 0.0 |
| 11 | 126.6 | 126.8 | 0.2 | 0.1 |
| 6 | 129.0 | 129.1 | 0.1 | 0.0 |
| 18 | 129.9 | 130.0 | 0.1 | 0.0 |
| 27 | 130.0 | 130.1 | 0.1 | 0.0 |
| 16 | 130.8 | 130.9 | 0.1 | 0.0 |
| 26 | 131.2 | 131.3 | 0.1 | 0.0 |
| 31 | 131.3 | 131.5 | 0.2 | 0.1 |
| 8 | 131.4 | 131.5 | 0.1 | 0.1 |
| 7 | 131.5 | 131.7 | 0.2 | 0.1 |
| 32,32a | 131.5 | 131.6 | 0.1 | 0.0 |
| 5 | 132.9 | 133.1 | 0.2 | 0.1 |
| 20 | 134.4 | 134.5 | 0.1 | 0.0 |
| 4 | 134.8 | 134.7 | -0.1 | -0.2 |
| 21 | 136.1 | 136.2 | 0.1 | 0.0 |
| 9 | 137.0 | 137.2 | 0.2 | 0.1 |
| 10 | 138.8 | 138.9 | 0.1 | 0.0 |
| 17 | 140.5 | 140.5 | 0.0 | -0.1 |
| 19 | 146.3 | 146.4 | 0.1 | 0.0 |
| 34 | 156.7 | 156.8 | 0.1 | 0.0 |
| 23 | 178.0 | 177.9 | -0.1 | -0.2 |
| 1 | 179.5 | 178.2 | -1.3 | -1.4 |
| 15 | 201.8 | 201.9 | 0.1 | 0.0 |
| CH₃ of ester | | 52.3 | | |

** Corrected for what seems to be a systematic drift of ca. – 0.1 ppm

Figure S2 : UV-VIS spectrum of synthetic thailandamide A methyl ester 4 and natural thailandamide A 1¹ in methanol:



3.1. Table S-3. Initial efforts towards the hydrolysis of methyl ester of thailandamide A :

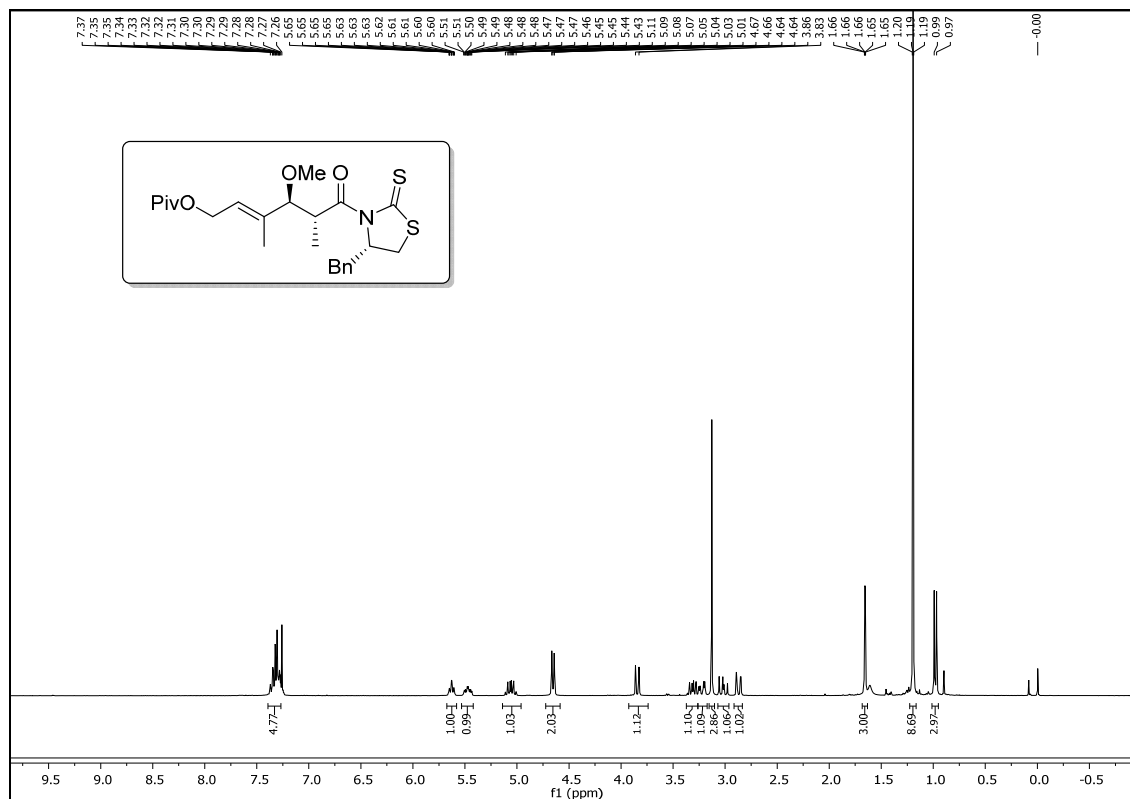
| Entry | Conditions | Result |
|-------|--|---------------------------------------|
| 1 | LiOH, THF:H ₂ O:MeOH(3:1:1), 0 °C, 30 min | Decomposed |
| 2 | Me ₃ SnOH, DCE, 60 °C, 6 h | Decomposed |
| 3 | TMSOK, THF, rt, 10 min | Trace (Product characterised by HRMS) |

Reference

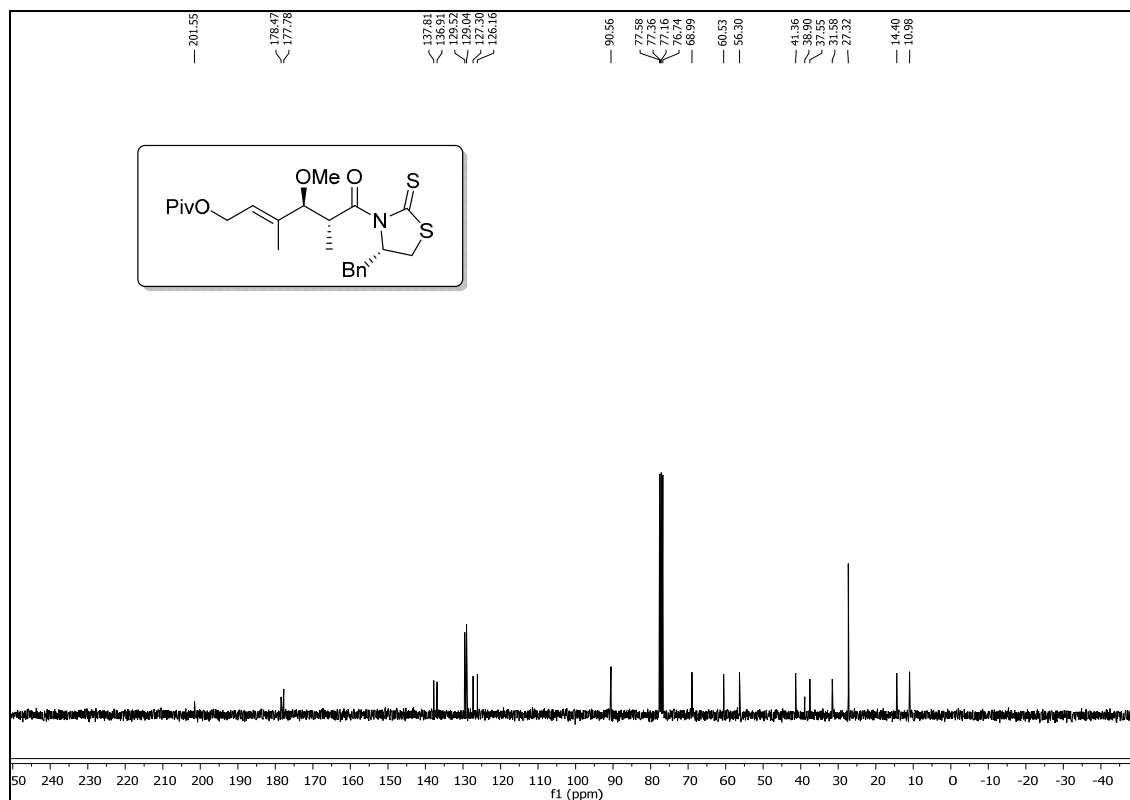
1. Nguyen, T.; Ishida, K.; Jenke-Kodama, H.; Dittmann, E.; Gurgui, C.; Hochmuth, T.; Taudien, S.; Platzer, M.; Hertweck, C.; Piel, J. Exploiting the mosaic structure of trans-acyltransferase polyketide synthases for natural product discovery and pathway dissection. *Nat. Biotechnol.* **2008**, *26*, 225-233.

4.1. Copies of ^1H NMR, ^{13}C NMR, 2D NMR, UV-VIS and HRMS spectra

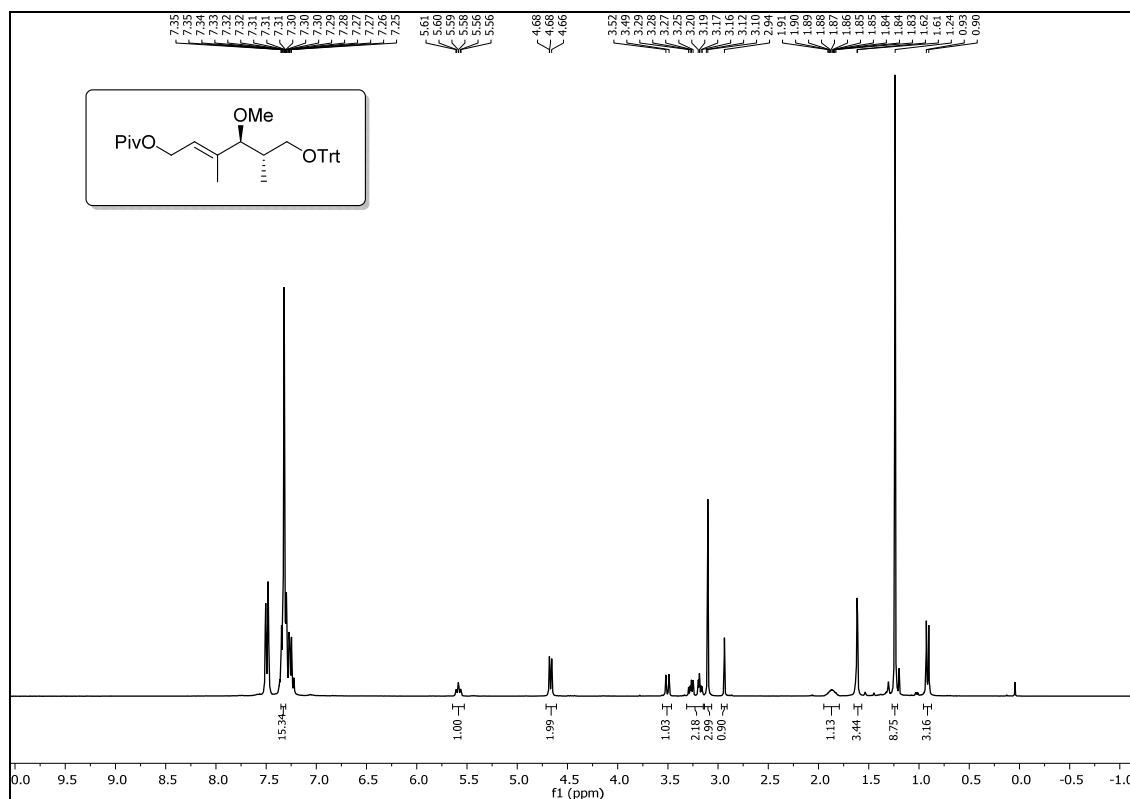
¹H NMR spectrum of compound 10 (300 MHz, CDCl₃):



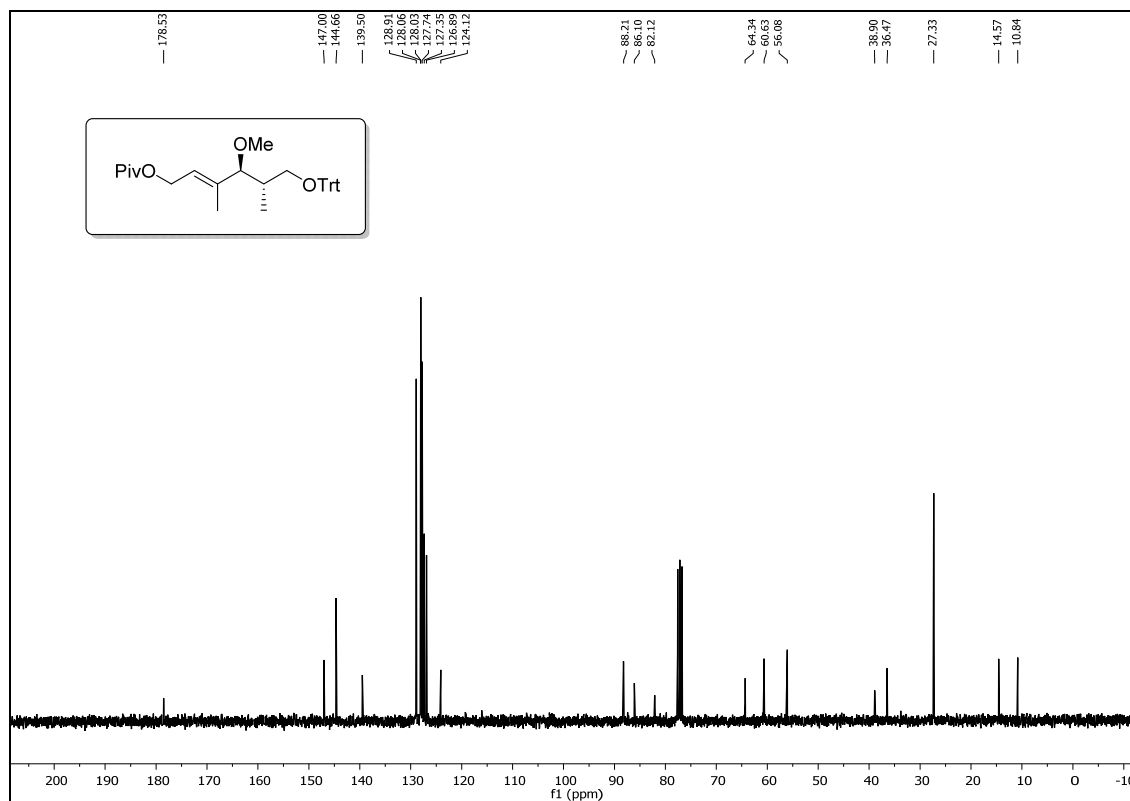
¹³C NMR spectrum of compound 10 (75 MHz, CDCl₃):



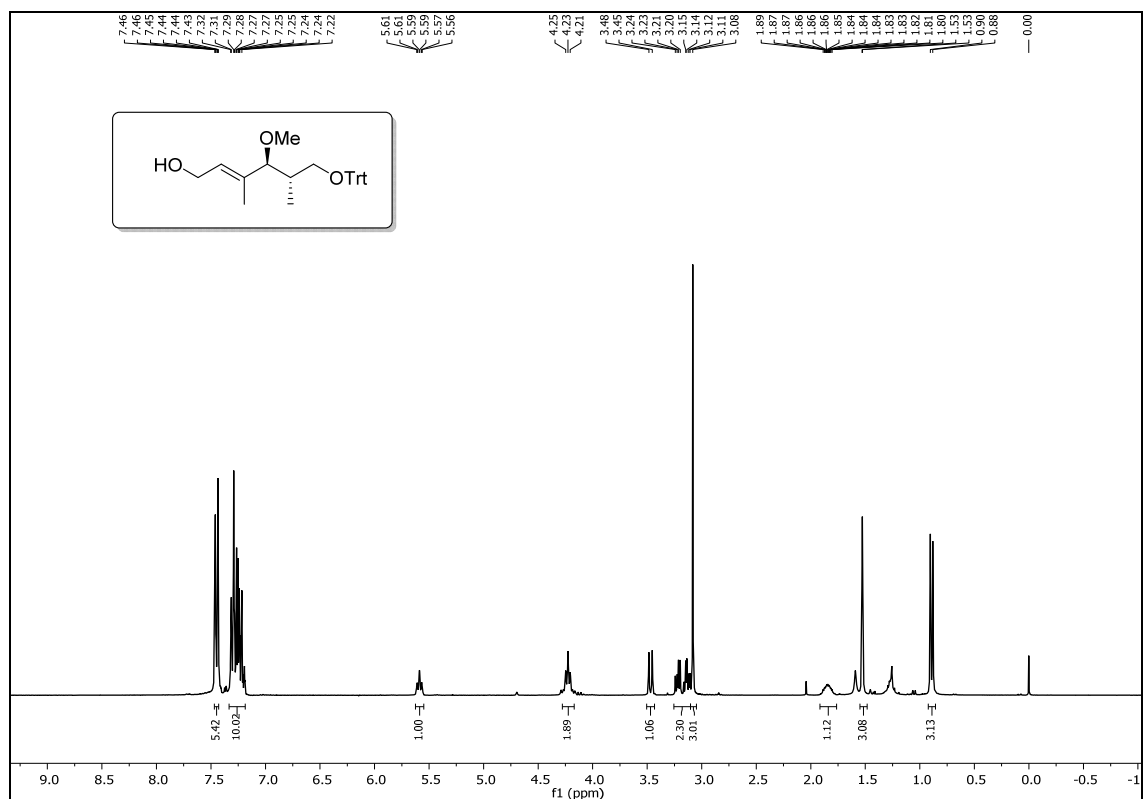
¹H NMR spectrum of compound 11 (300 MHz, CDCl₃):



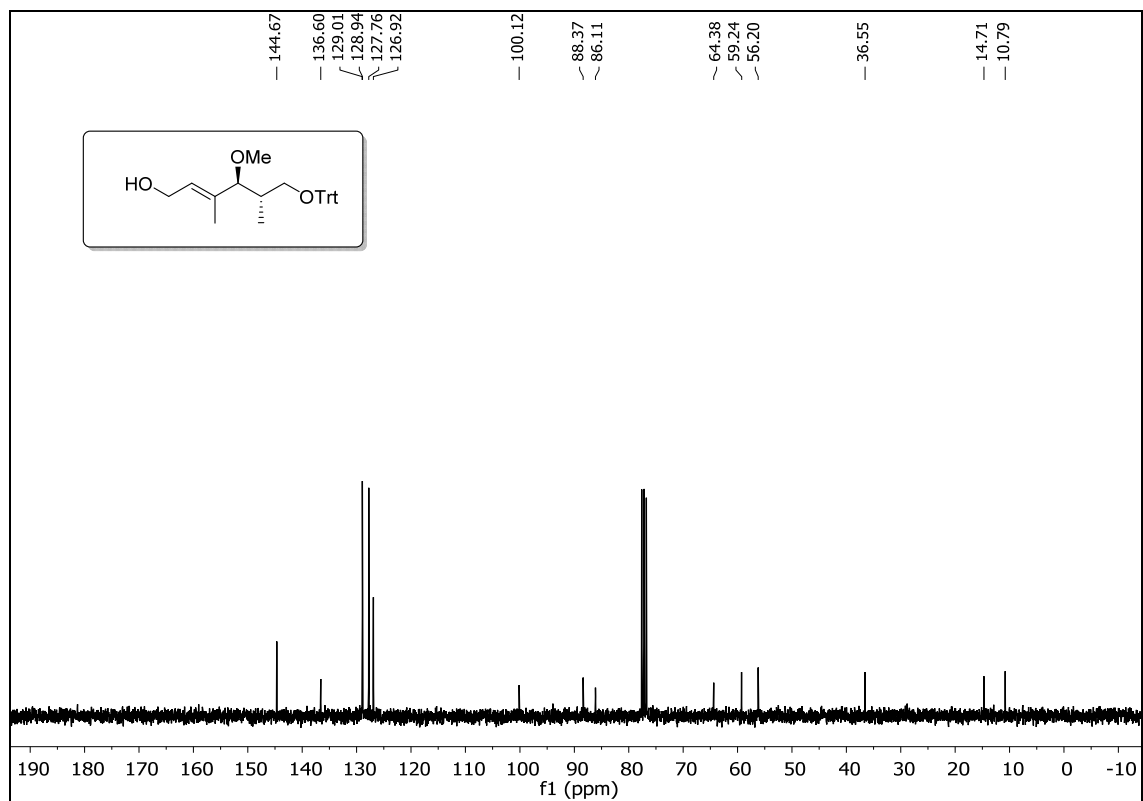
¹³C NMR spectrum of compound 11 (75 MHz, CDCl₃):



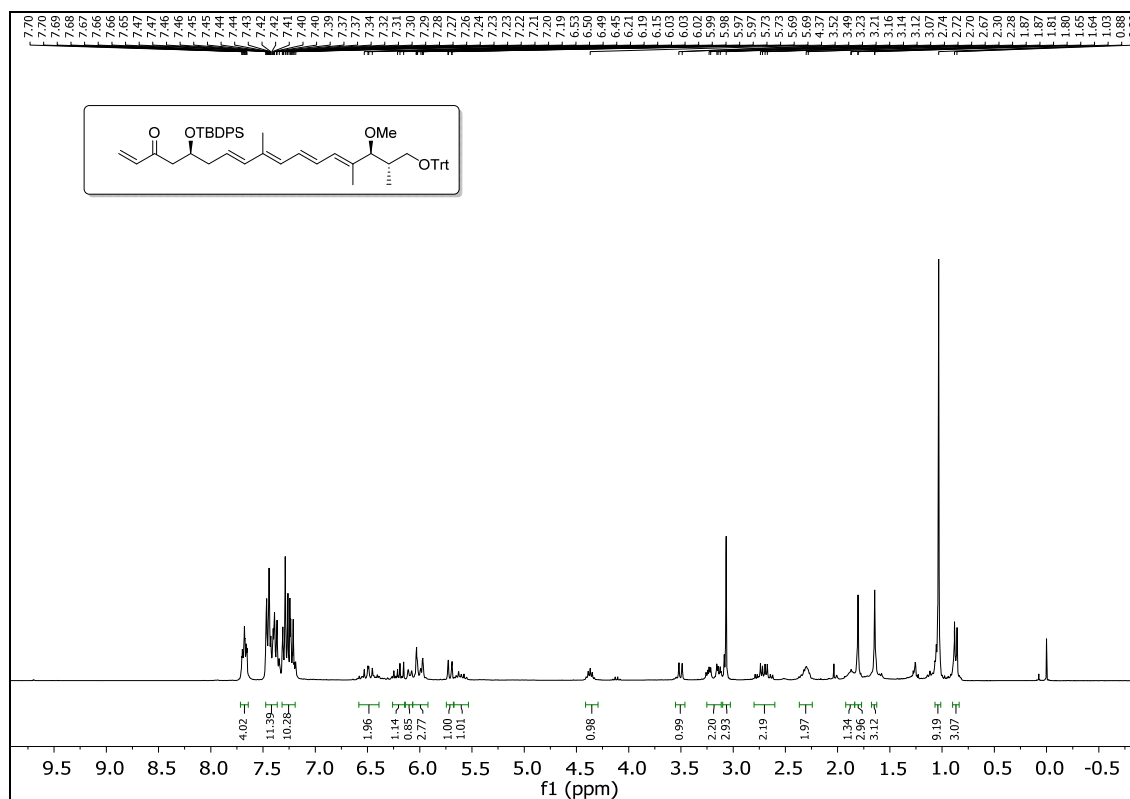
¹H NMR spectrum of pivaloyl deprotected product of compound 11 (300 MHz, CDCl₃):



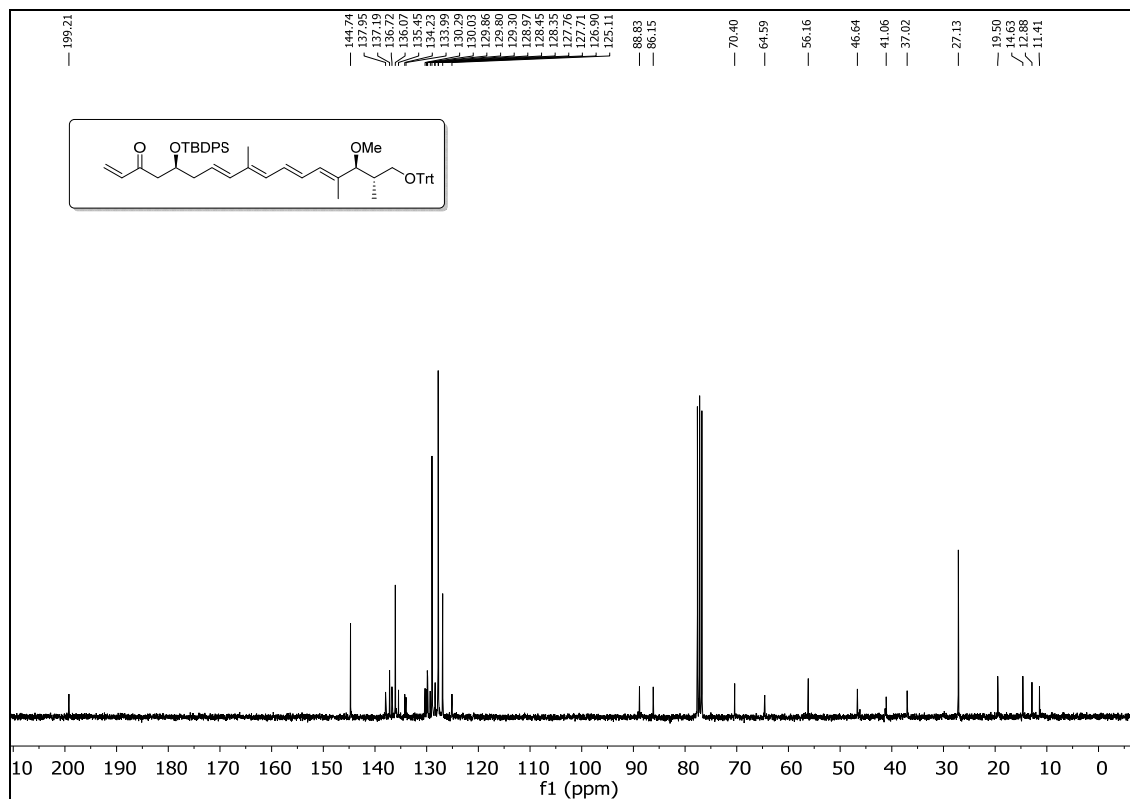
¹³C NMR spectrum of pivaloyl deprotected product of compound 11 (75 MHz, CDCl₃):



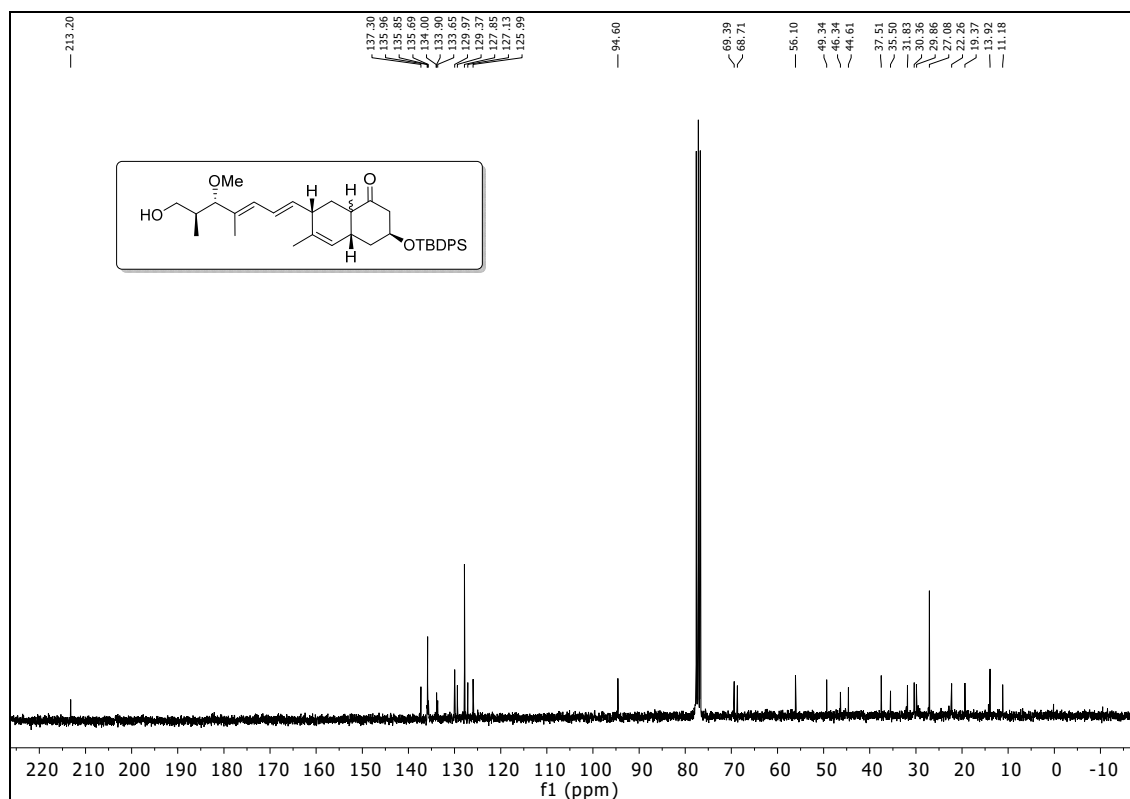
¹H NMR spectrum of compound 18 (300 MHz, CDCl₃):



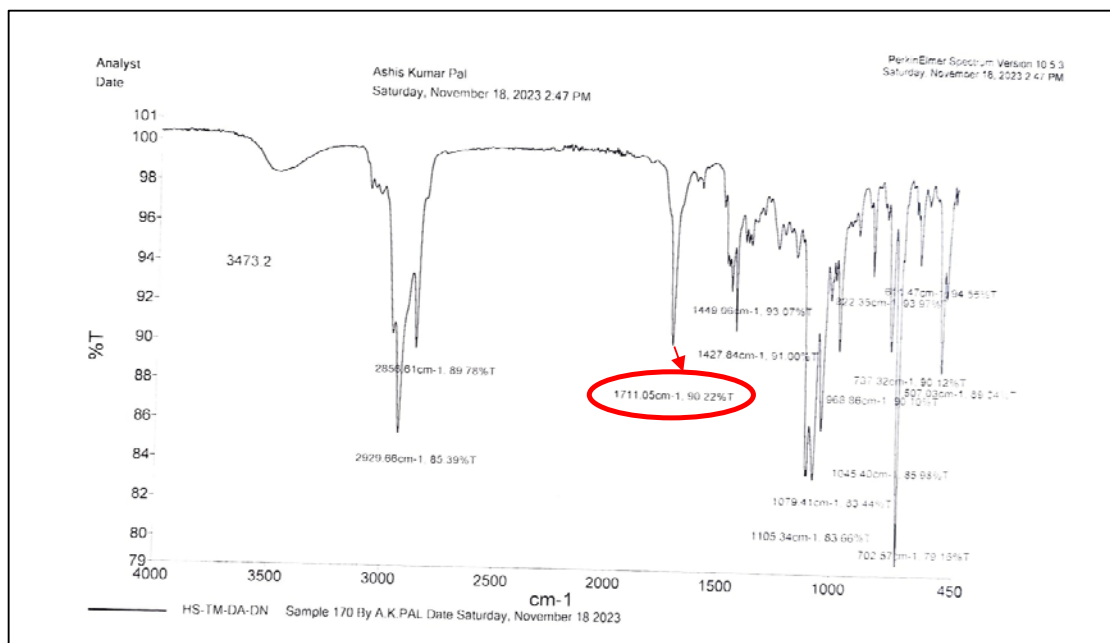
¹³C NMR spectrum of compound 18 (75 MHz, CDCl₃):



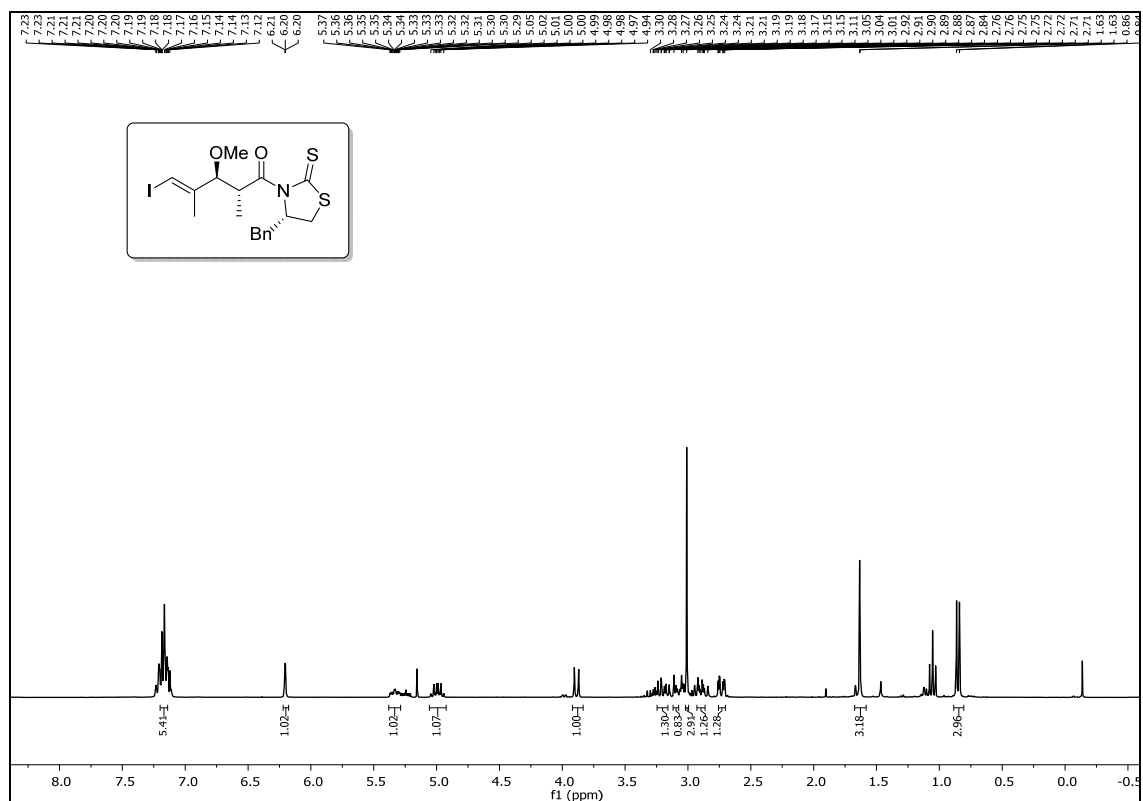
^{13}C NMR spectrum of compound 19 (75 MHz, CDCl_3):



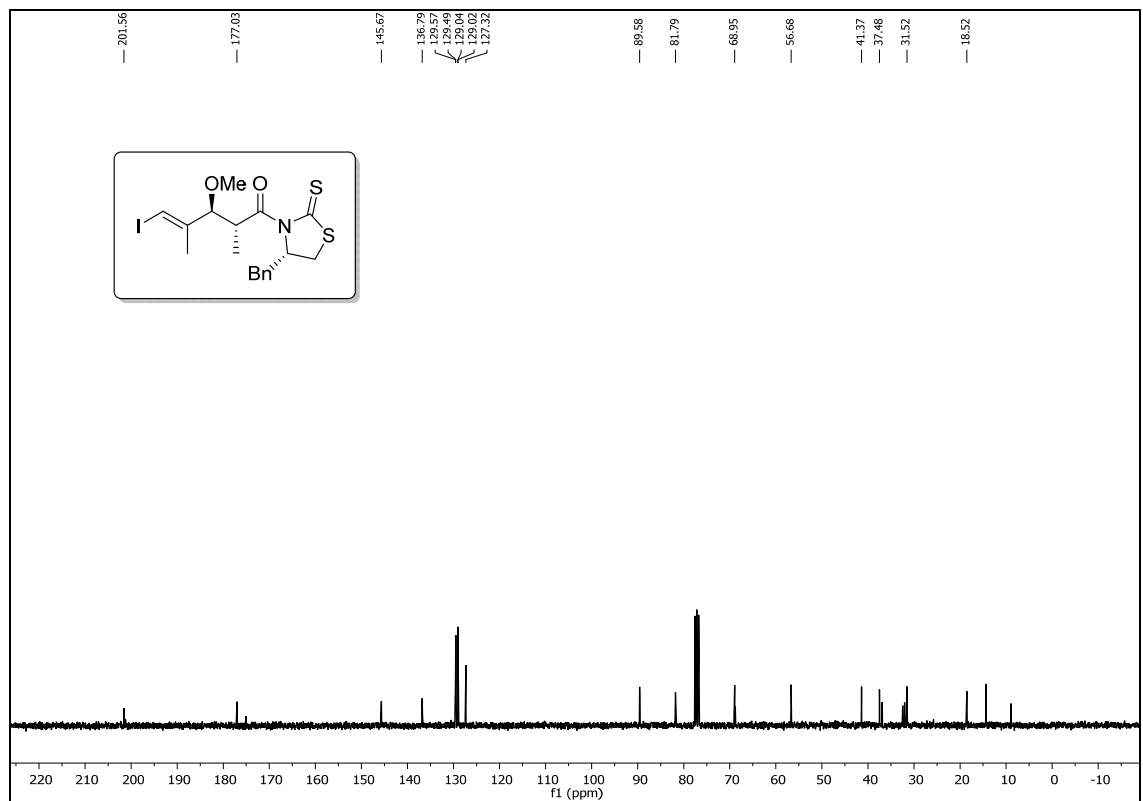
FT-IR spectrum of compound 19 :



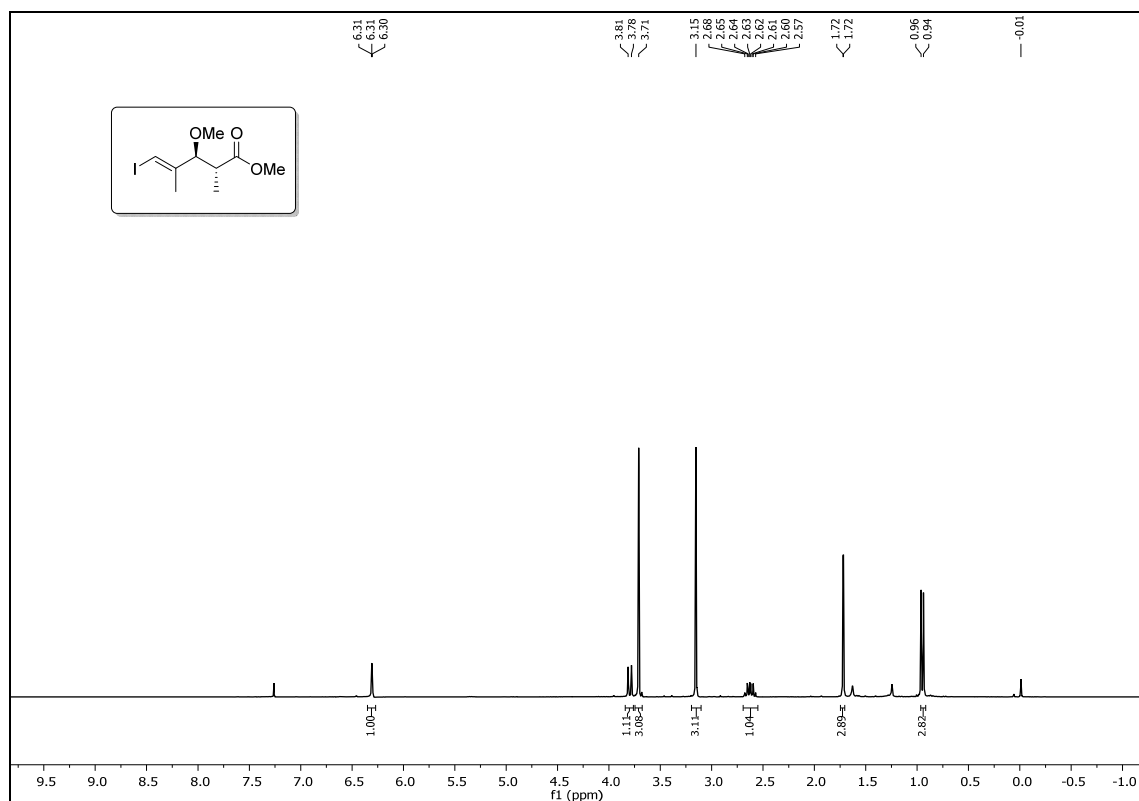
¹H NMR spectrum of compound 24 (300 MHz, CDCl₃):



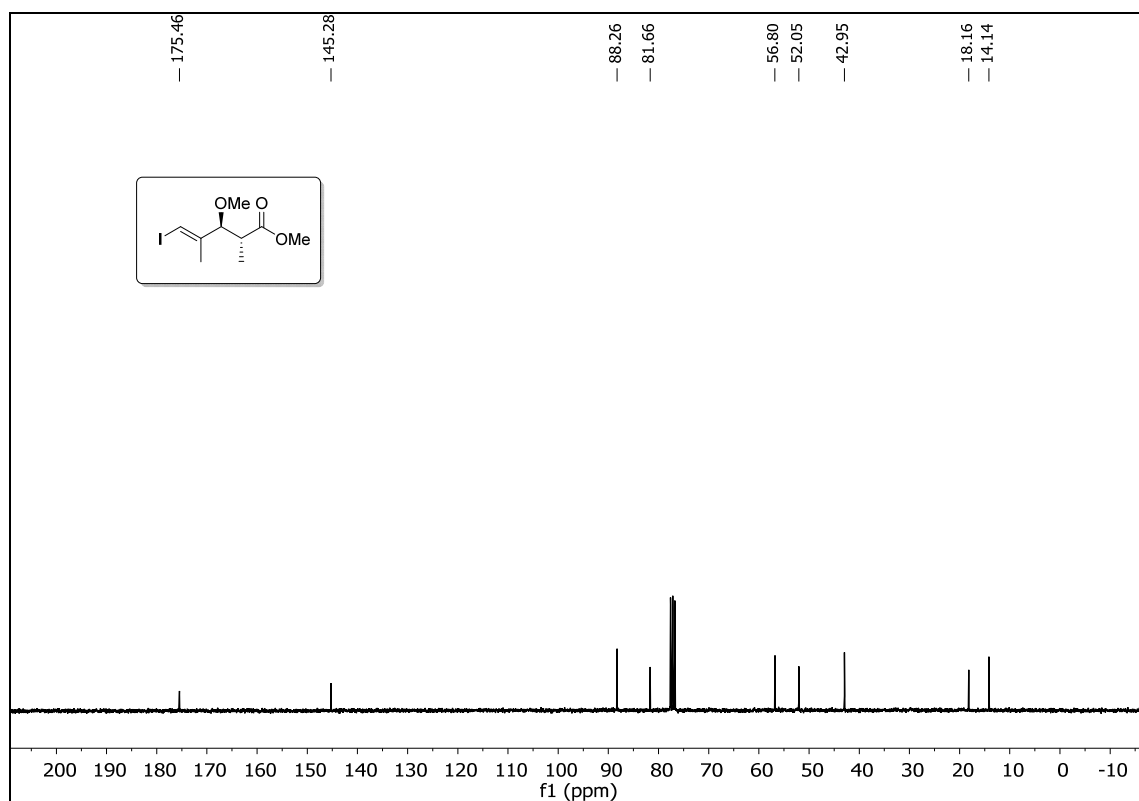
¹³C NMR spectrum of compound 24 (75 MHz, CDCl₃):



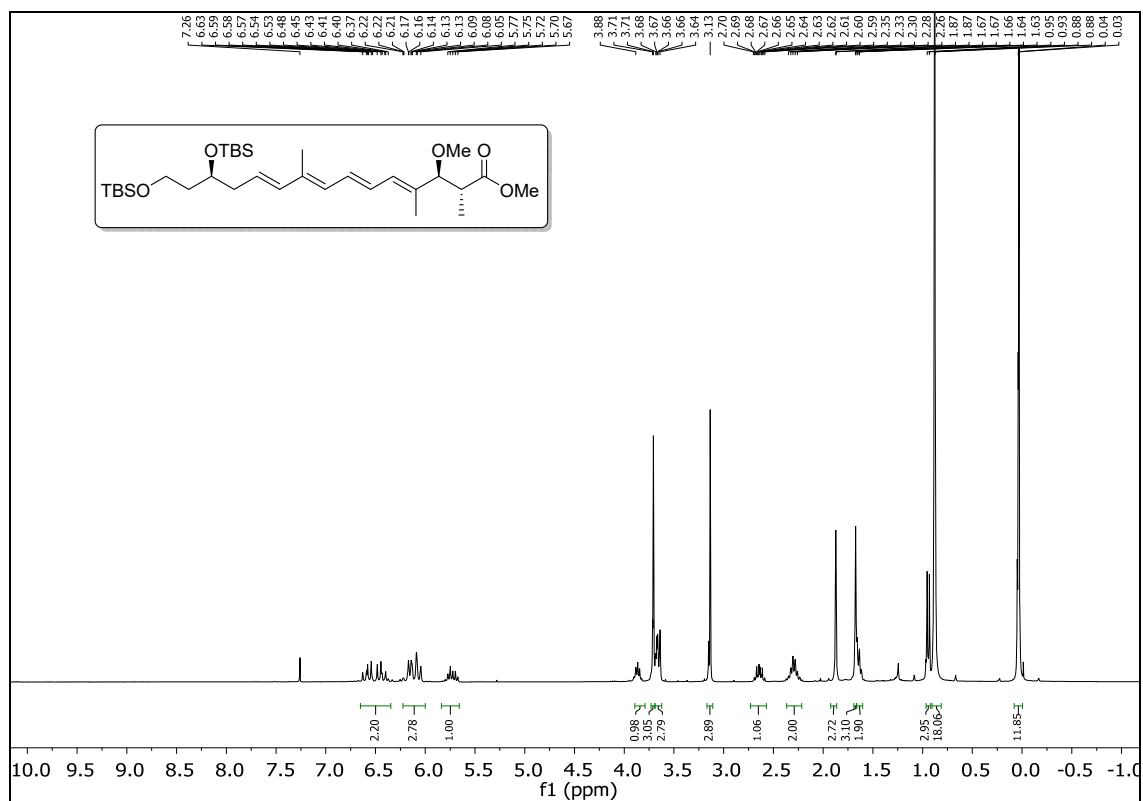
¹H NMR spectrum of compound 20 (300 MHz, CDCl₃):



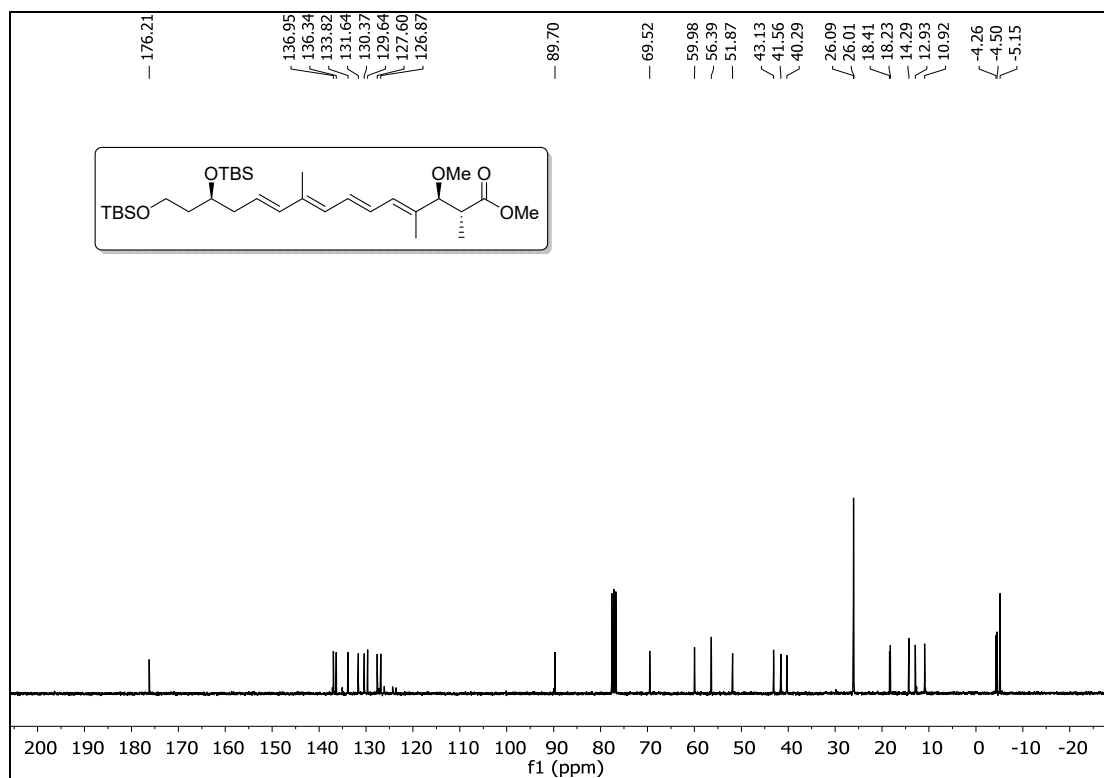
¹³C NMR spectrum of compound 20 (75 MHz, CDCl₃):



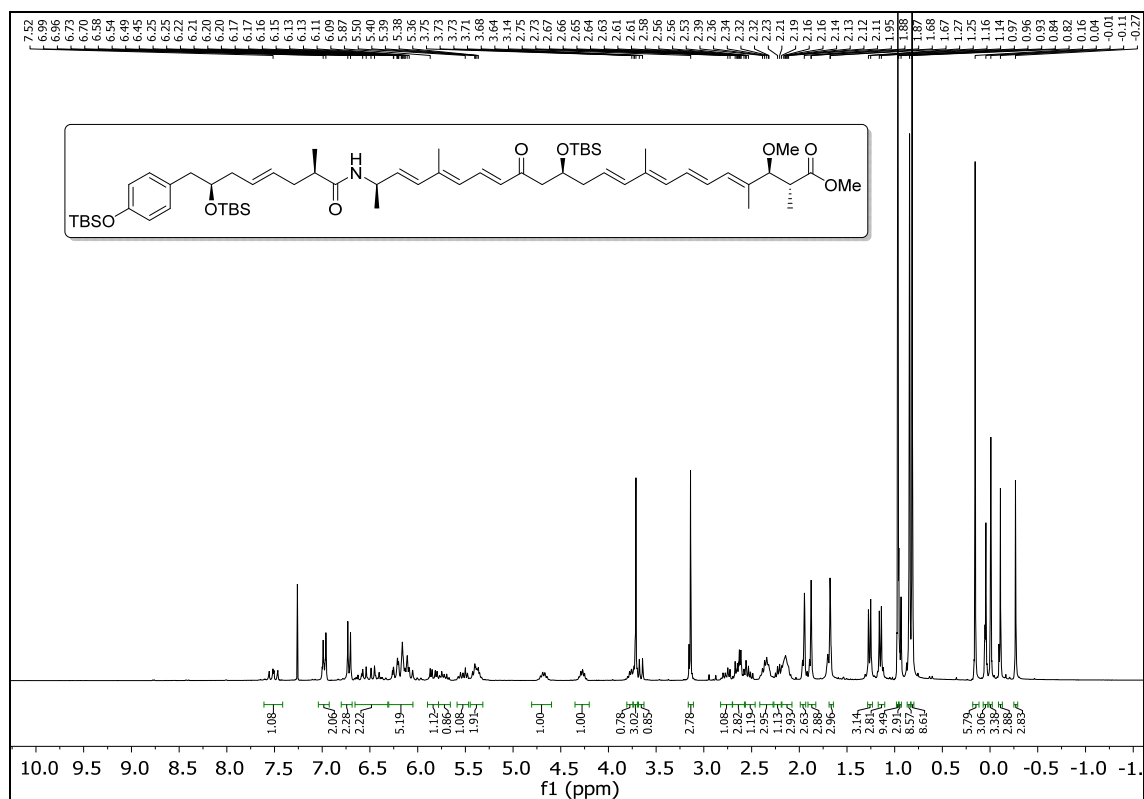
¹H NMR spectrum of compound 27 (300 MHz, CDCl₃):



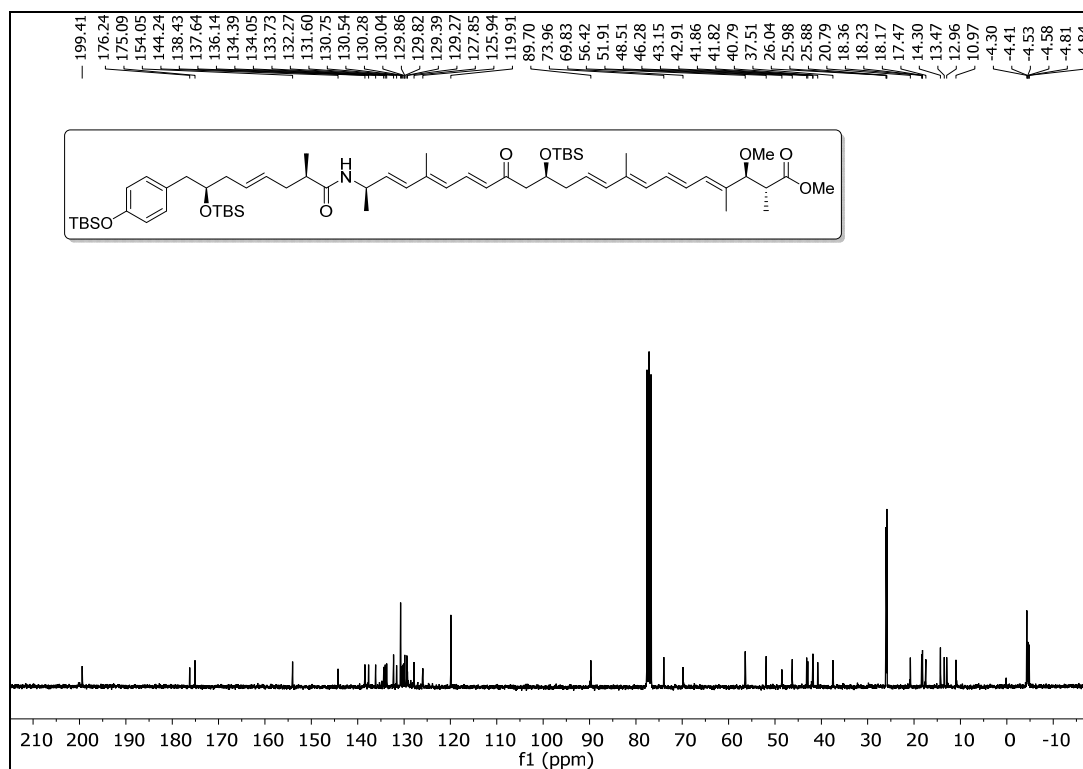
¹³C NMR spectrum of compound 27 (75 MHz, CDCl₃):



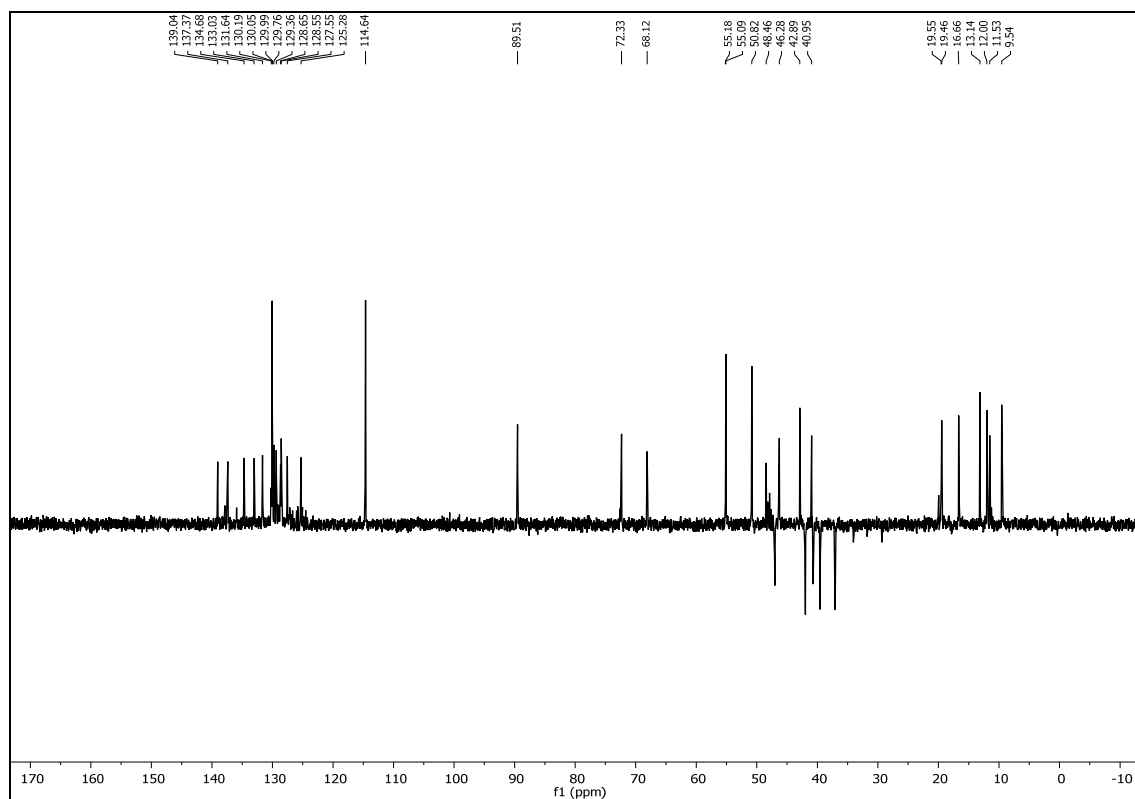
¹H NMR spectrum of compound 28 (300 MHz, CDCl₃):



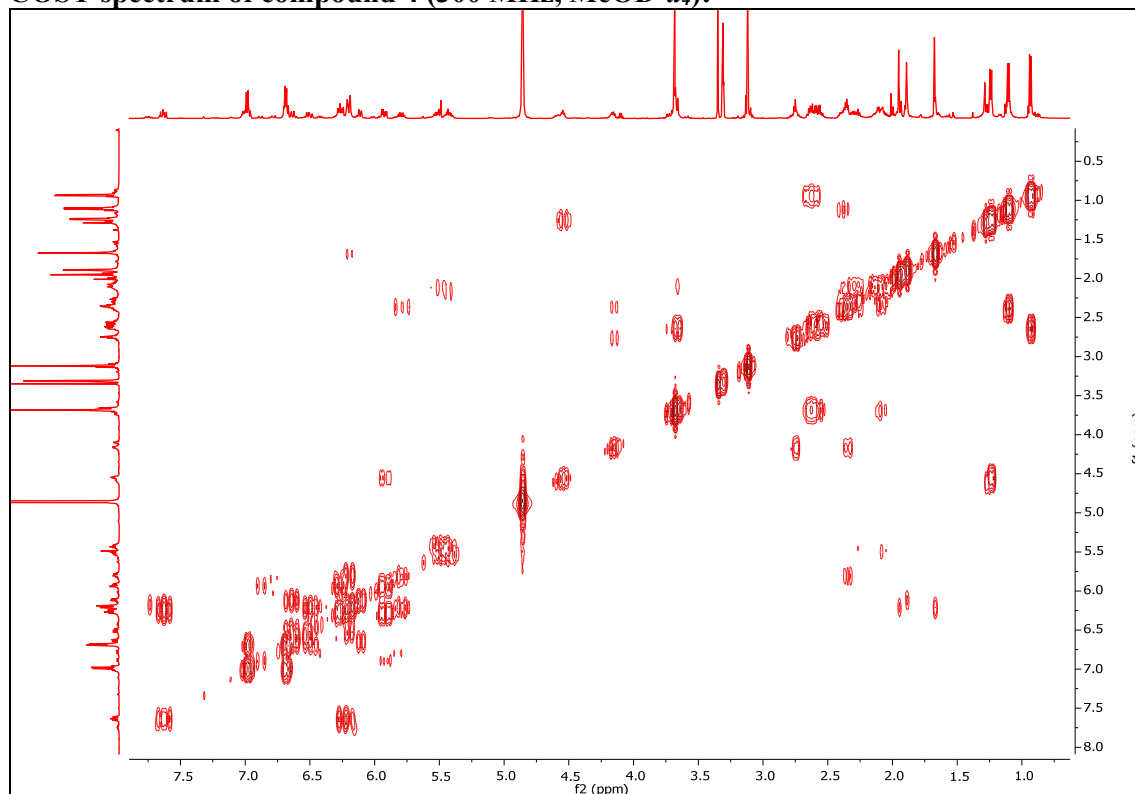
¹³C NMR spectrum of compound 28 (75 MHz, CDCl₃):



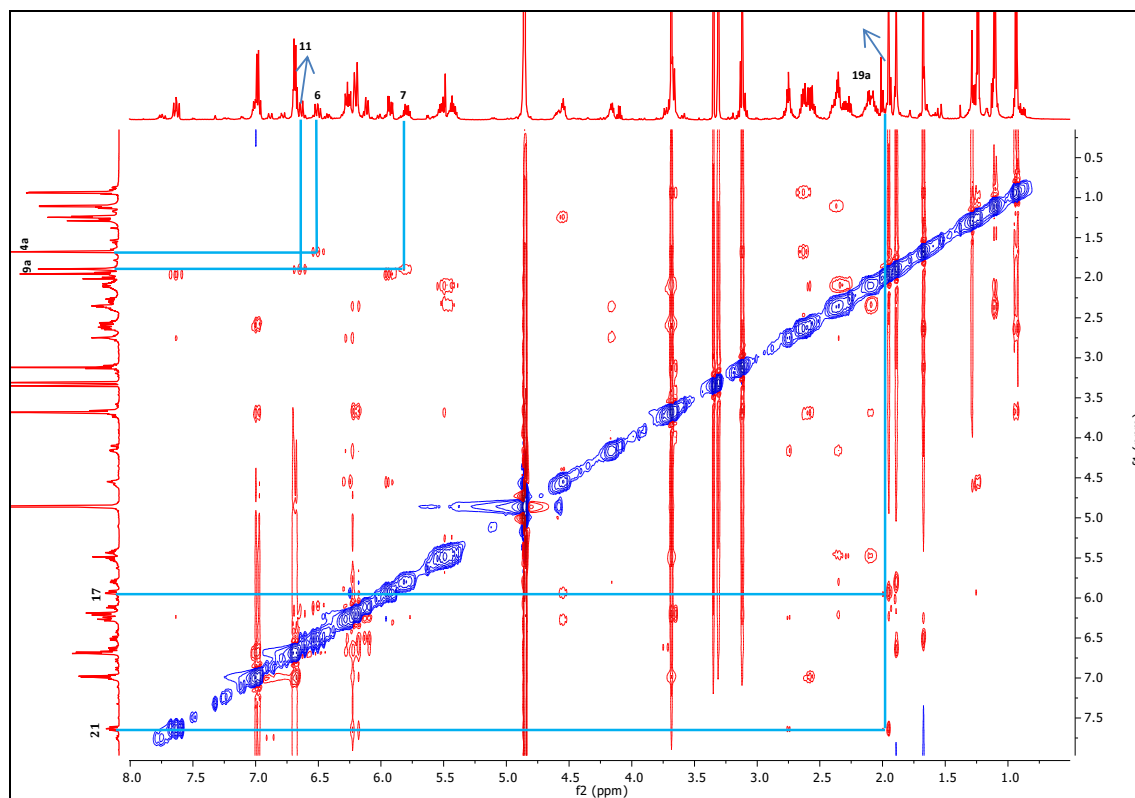
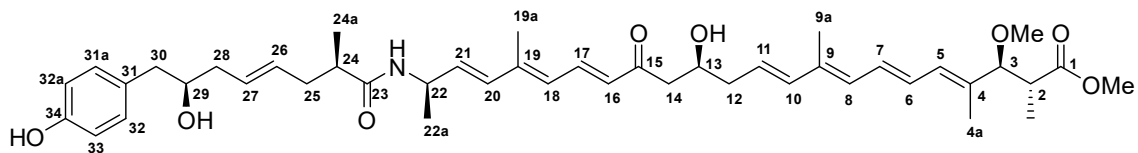
DEPT spectrum of compound 4 (75 MHz, MeOD-*d*₄):



COSY spectrum of compound 4 (300 MHz, MeOD-*d*₄):

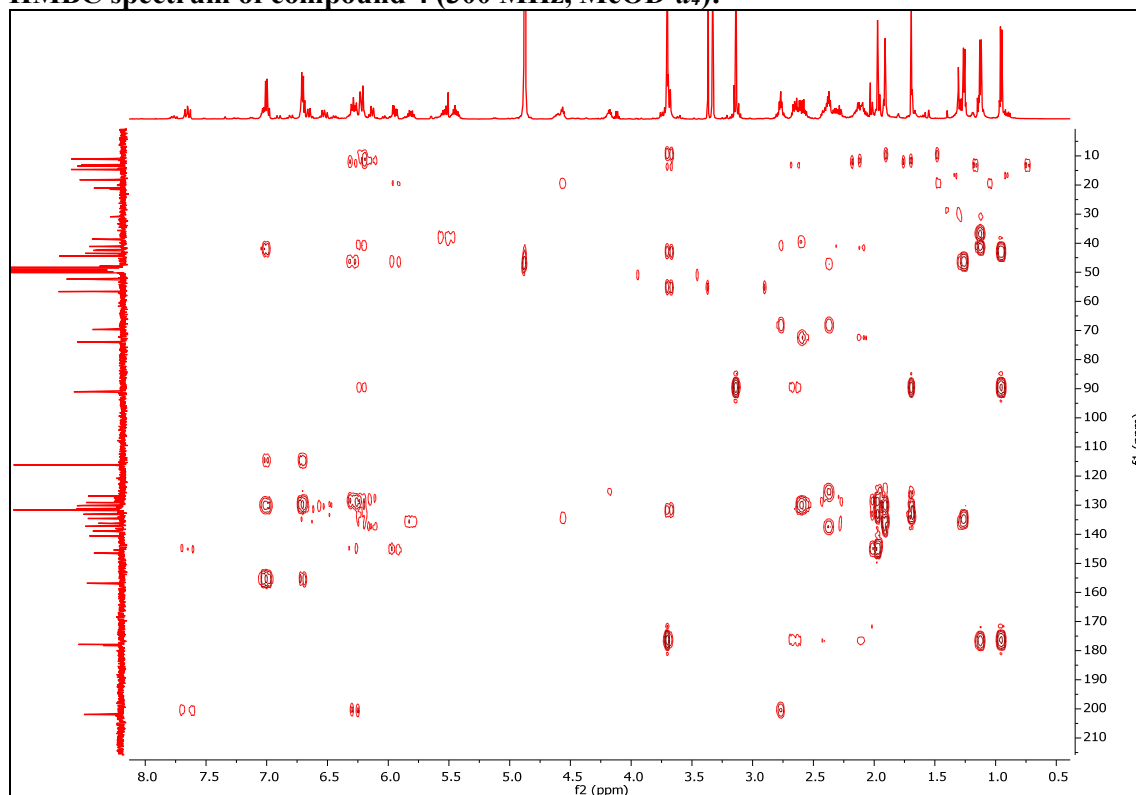


NOESY spectrum of compound 4 (300 MHz, MeOD-*d*₄):

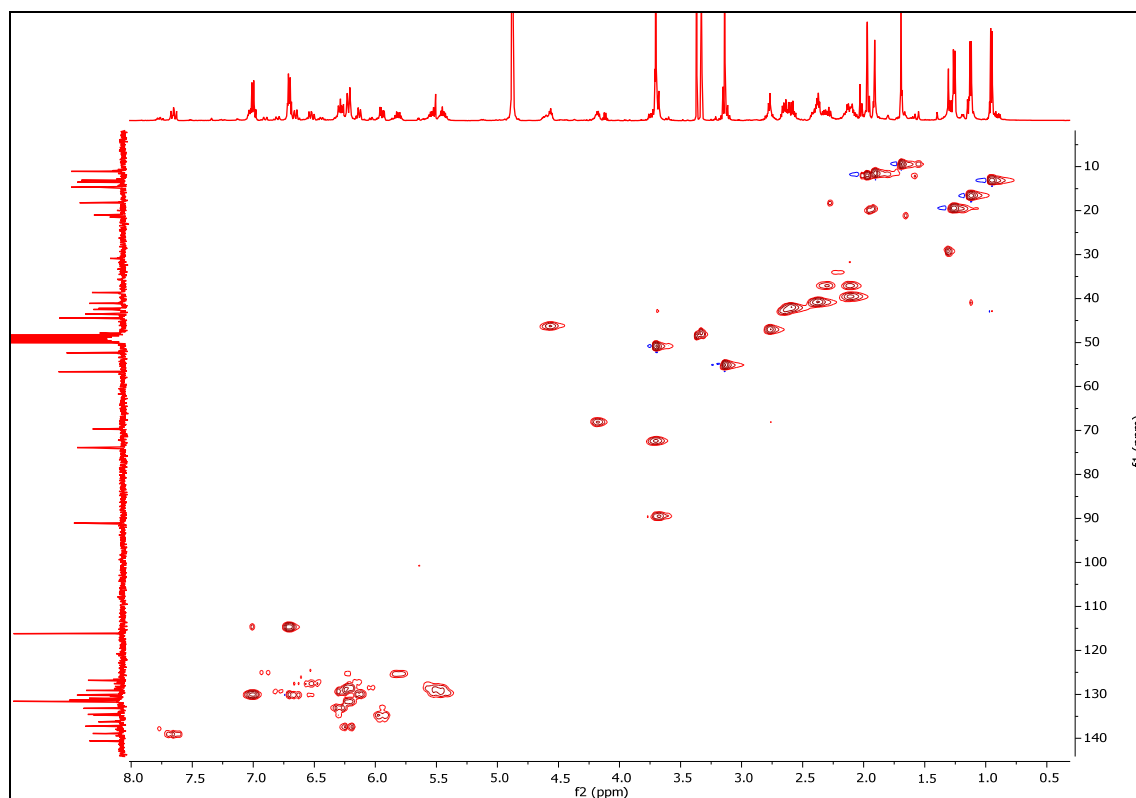


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HMBC spectrum of compound 4 (300 MHz, MeOD-*d*₄):



HSQC spectrum of compound 4 (300 MHz, MeOD-*d*₄):



HRMS spectrum of Thailandamide A Methyl Ester (4):

