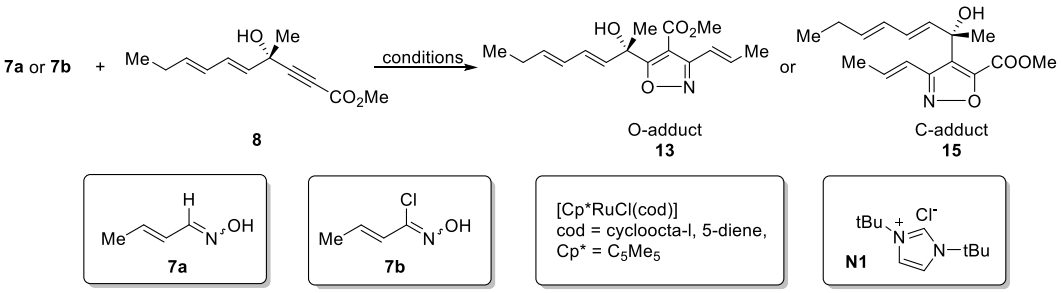
Scalable Synthesis of (±)-Gregatin A via 1, 3-dipolar Cycloaddition Strategy

Yiming Ding, [‡,a,b] Xiaoli Zhao, [‡,a] Chunlei Qu, [a] Xianwen Long, [a] Yaqiu Zhao,[c] Jun Deng*[,a]

[a] State Key Laboratory and Institute of Elemento-Organic Chemistry, Frontiers Science Center for New Organic Matter, College of Chemistry, Nankai University, Tianjin 300071, China.
[b] Key Laboratory of Medicinal Chemistry for Natural Resources, Ministry of Education; Yunnan Provincial Center for Research & Development of Natural Products; School of Chemical Science and Technology, Yunnan University, Kunming, 650091
[c] State Key Laboratory for Quality Ensurance and Sustainable Use of Dao-di Herbs，National Resource Center for Chinese Materia Medica, China Academy of Chinese Medical Sciences，Beijng，100700，P. R. China;

I Conditions screened for the 1, 3-dipolar cycloaddition

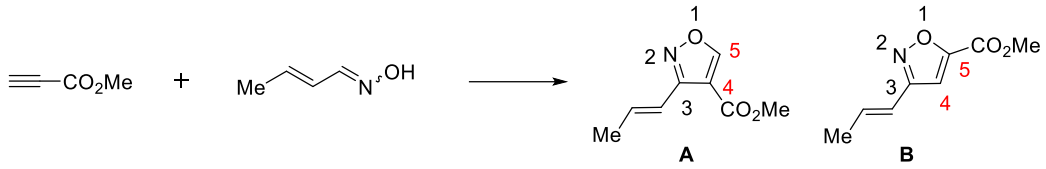
Table S1. Optimization of the 1, 3-dipolar cycloaddition.



Entry	Conditions	Yield of **13**
1	**7a** (7.0 eq), Oxone (7.0 eq), KCl (7.0 eq), H_2O, 35°C, 40 min	29% (brsm 40%)
2	**7a** (14.0 eq), 20% aq. NaClO (15.0 eq), Et_3N (15.0 eq), Toluene, 80°C, 10 min	31% (brsm 68%)
3	**7a** (5.0 eq), Chloramine-T (5.5 eq), $CuSO_4 \cdot 5H_2O$/Cu (0.2 eq), tBuOH/H_2O, 35°C, 40 min	12% (brsm 43%)
4	**7a** (5.0 eq), PIDA (5.0 eq), MeOH, 35°C, 40 min	NR
5	**7a** (5.0 eq), PhIOH(OTs) (5.0 eq), DCM, 35°C, 40 min	NR
6	**7b** (4.0 eq), AgOTf (1.5 eq), DCM, 35°C, 10 min	ND
7	**7b** (7.0 eq), Et_3N (7.0 eq), DMF, 35°C, 40 min	7% (brsm 57%)
8	**7b** (7.0 eq), [Cp*RuCl(cod)] (0.1 eq), Et_3N (7.0 eq), DCE, 50°C, 40 min	22% (brsm 40%)
9	**7b** (7.0 eq), [Cp*RuCl(cod)] (0.1 eq), Et_3N (7.0 eq), Toluene, 80°C, 40 min	30% (brsm 42%)
10	**7b** (7.0 eq), [Cp*RuCl(cod)] (0.1 eq), 4Å MS, Toluene, 80°C, 40 min	25% (brsm 44%)
11	**7b** (7.0 eq), [Cp*RuCl(PPh_3)$_2$] (0.1 eq), Et_3N (7.0 eq), Toluene, 80°C, 40 min	26% (brsm 41%)
12	**7b** (5.0 eq), Et_3N (5.4 eq), **N1** (0.2 eq), DCM, 35°C, 40 min	21% (brsm 73%)
13	**7b** (5.0 eq), Et_3N (5.4 eq), **N1** (0.2 eq), Toluene, 80°C, 10 min	32% (brsm 86%)
14	**7b** (5.0 eq), Et_3N (6.0 eq), **N1** (1.0 eq),	27% (brsm 66%)

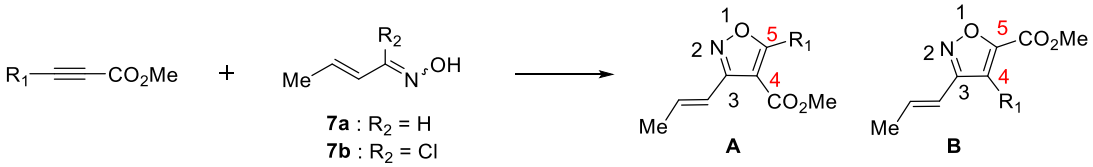
	Toluene, 80℃, 10 min	
15	**7b** (5.0 eq), Cs_2CO_3 (3.0 eq), **N1** (0.2 eq), Toluene, 80℃, 10 min	Decomposed

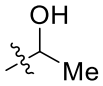
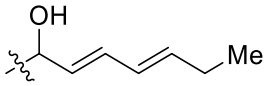
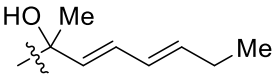
Table S2. The regioselectivity of 1, 3-dipolar cycloaddition for simple alkyne.



Entry	Conditions	Temp. (℃)	Yield (%)	A: B
1	PIDA (2.0 eq), MeCN: H_2O = 2:1	25	75	1:5
2	Et_3N (2.0 eq), NaClO (2.0 eq), Toluene	25	74	1:5
3	PIFA (4.0 eq), MeOH: H_2O = 5:1	25	58	1:8.5
4	PIDA (2.0 eq), MeCN: H_2O = 2:1	80	78	1:2
5	Et_3N (2.0 eq), NaClO (2.0 eq), Toluene	80	75	1:2
6	Et_3N (2.0 eq), NaClO (2.0 eq), H_2O	80	70	1:1.5

Table S3. The regioselectivity of 1, 3-dipolar cycloaddition for internal alkynes.



Entry	R_1	Conditions	Temp. (℃)	Yield (%)	A: B
1	Br	Et_3N (2.0 eq), THF	80	trace	1:4
2	TMS	Et_3N (4.0 eq), Toluene ,	80	trace	1:4
3		**7b** (2.5 eq), TEA (4.0 eq), Toluene,	80	44	2:1
4		**7a (**2.0 eq), PIDA (2.0 eq), MeCN:H_2O = 2:1	80	30	>5:1
5		**7a** (14.0 eq), NaClO (15.0 eq), Et_3N (15.0 eq) Toluene	80	31	A

II Experimental Procedures and Spectroscopic Data of Compounds

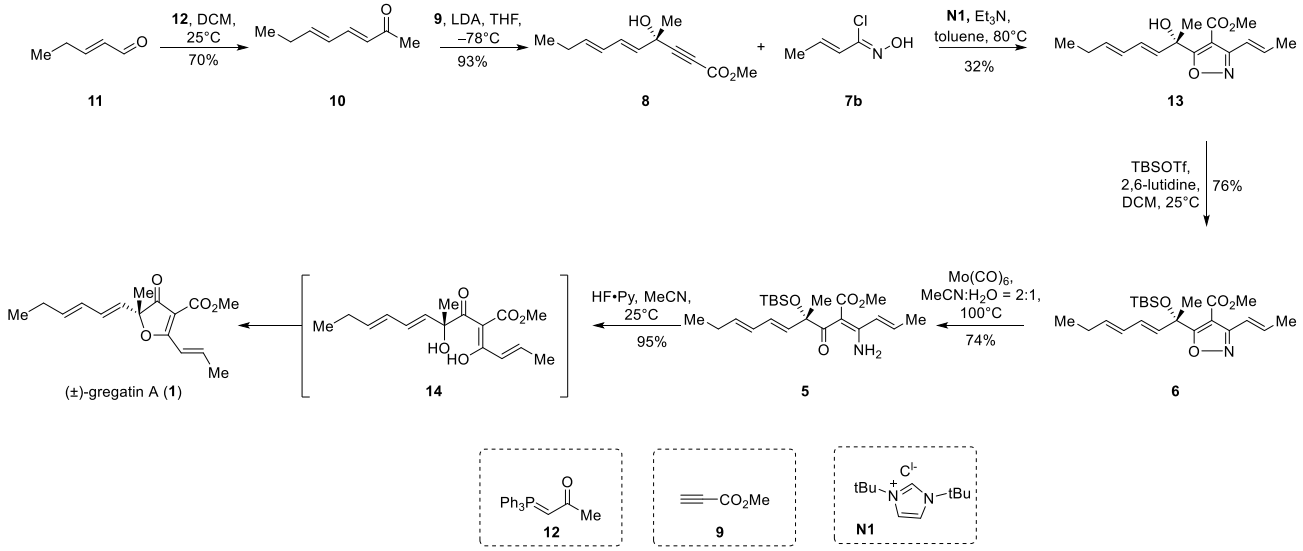
1. General Procedures

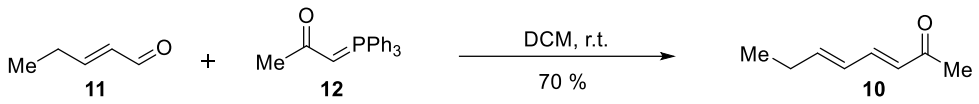
All reactions were carried out under an argon atmosphere with dry solvents under anhydrous conditions, unless otherwise noted. Tetrahydrofuran (THF) and Toluene were distilled immediately before use from sodium-benzophenoneketyl. Methylene chloride (CH_2Cl_2), *N*,*N*-Dimethylformamide (DMF) were distilled from calcium hydride and stored under an argon atmosphere. Reagents were purchased at the highest commercial quality and used without further purification, unless otherwise stated. Solvents for chromatography were used as supplied by Titan chemical. Reactions were monitored by thin layer chromatography (TLC) carried out on 0.2 mm Huanghai gel plates (60F-254) using UV light as visualizing agent and aqueous ammonium cerium nitrate/ammonium molybdate or basic aqueous potassium permanganate as developing agent. Huanghai silica gel (60, particle size 0.040–0.063 mm) was used for flash column chromatography. For the reactions require heating, dimethicone was used as the heat source.

NMR spectra were recorded on Bruker AV III 400, 500 or 600, The spectra were calibrated by using residual undeuterated solvents (for ^{1}H NMR) and deuterated solvents (for ^{13}C NMR) as internal references: chloroform (δ_H = 7.26 ppm) and $CDCl_3$ (δ_C = 77.16 ppm); acetone (δ_H = 2.05 ppm) and acetone-d_6 (δ_C = 29.84, 206.26 ppm); The following abbreviations are used to designate multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, quint = quintet, br = broad. IR spectra were recorded on a BRUKER Tensor-27 FT-IR spectrometer. High-resolution mass spectra (HRMS) were recorded on Agilent G6230 ESI-FT and the analyzer type was TOF.

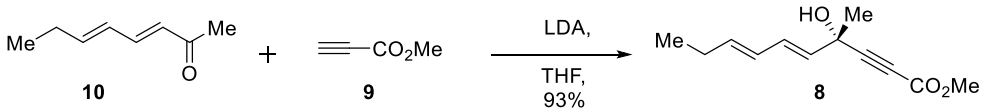
2. Synthetic Procedures

Scheme 1. Total synthesis of (±)-gregatin A



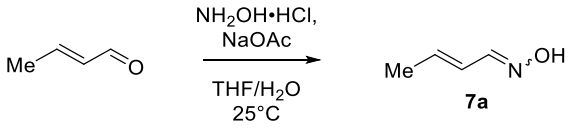


According to the reported literature[1] : to a stirred solution of **11** (20.0 g, 237.76 mmol) in DCM (115.0 mL) were added triphenylphosphoranylidene-2-propanon (98.4 g, 309.09 mmol) at room temperature. The mixture was allowed to stir at room temperature for 5 days before concentration under vacuum. The resultant mixture was allowed to wash with petroleum ether until the products in the filter cake couldn't be detected by TLC. Then the combined organic phases were concentrated under vacuum. The residue was purified by flash column chromatography with petroleum ether:EtOAc (30:1) to give **10** (20.8 g, 70%) as a pale yellow liquid. **10**: R_f = 0.4 (silica, petroleum ether:EtOAc = 30:1); ^{1}H NMR (400 MHz, $CDCl_3$) : δ = 7.24 – 7.04 (m, 1H), 6.27 – 6.12 (m, 2H), 6.05 (d, *J* = 15.6 Hz, 1H), 2.25 (s, 3H), 2.23 – 2.17 (m, 2H), 1.04 (t, *J* = 7.4 Hz, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) : δ = 198.9, 147.2, 144.2, 128.9, 128.0, 27.3, 26.2, 13.0 ppm.

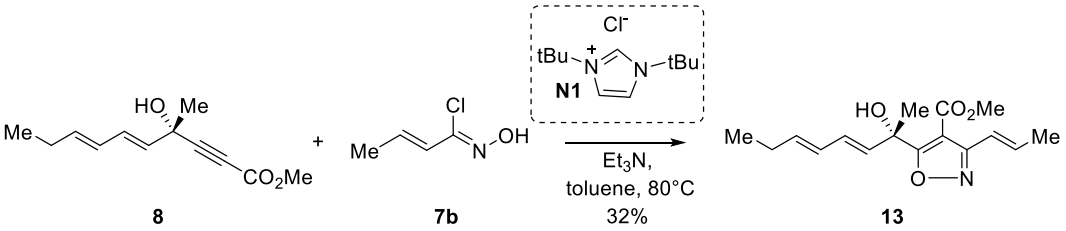


To a stirred solution of *i*-Pr_2NH (3.0 mL, 21.4 mmol) in THF (36.0 mL) were added *n*-BuLi (8.7 mL, 2.4 M in hexane, 20.90 mmol) at 0 ℃. The mixture was allowed to stir for 20 min at 0 ℃, before the temperature was changed to −78℃. Methyl propiolate (2.15 mL, 24.16 mmol) was added to the mixture at −78 ℃ and the mixture was allowed to stir for 1 h. Compound **10** (2.0 g, 16.11 mmol) was added at −78 ℃. The mixture was stirred at −78 ℃ for another 30 min before it was quenched with aq. NH_4Cl (15 mL). The mixture obtained was extracted with EtOAc (3 × 40

mL), and combined organic phases were washed with brine (50 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under vacuum. The residue was purified by flash column chromatography with petroleum ether: EtOAc (8:1) to give **8**, (3.2 g, 93%) as a pale yellow liquid. **8 :** R_f = 0.45 (silica, petroleum ether:EtOAc = 8:1). IR (film) : ν_{max} = 3320, 2965, 2934, 2236, 1719, 1436, 1264, 1063, 991, 752 cm^{-1} ; ^1H NMR (400 MHz, $CDCl_3$) : δ = 6.43 (dd, *J* = 15.3, 10.3 Hz, 1H), 6.01 (dd, J = 15.3, 10.3 Hz, 1H), 5.85 (dt, *J* = 15.2, 6.5 Hz, 1H), 5.63 (d, *J* = 15.3, 1H), 3.78 (s, 3H), 2.50 (s, 1H), 2.25 – 2.01 (m, 2H), 1.60 (s, 3H), 1.00 (t, *J* = 7.5 Hz, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) : δ = 154.0, 139.4, 132.2, 130.9, 127.6, 89.2, 76.0, 67.8, 52.9, 29.7, 25.8, 13.4 ppm; HRMS (m/z) : $[M+Na]^+$ calcd for $C_{12}H_{16}O_3Na^+$ 231.0997, found 231.0990.

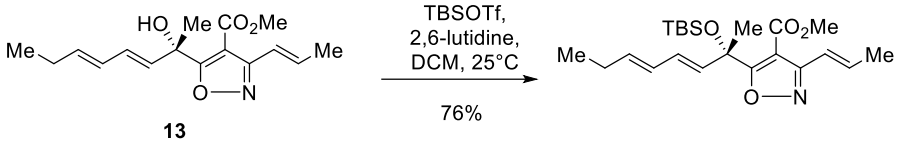


According to the reported literature[2] : a solution of hydroxylamine hydrochloride (7.4 g, 107.00 mmol) and sodium acetate (11.7 g, 142.67 mmol) in water (70 mL) were added to a stirred solution of crotonaldehyde (5.0 g, 71.34 mmol) in THF (143 mL). The mixture was allowed to stir at 25 °C for 30 min before the resultant mixture was quenched with aq. $NaHCO_3$ (100 mL). THF was removed in a rotary evaporator under reduced pressure. The aqueous solution was extracted with EtOAc (3 × 70 mL). The combined organic phases were washed with brine (100 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under vacuum. The residue was purified by flash column chromatography with petroleum ether:EtOAc (5:1) to give **7a** (5.5 g, 91%) as an white solid. R_f = 0.43 (silica, petroleum ether:EtOAc = 5:1).



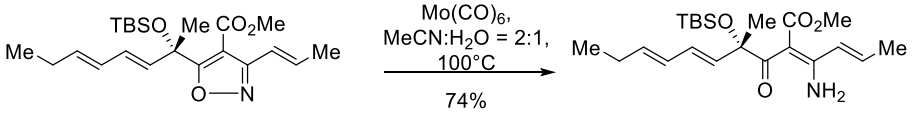
To a stirred suspension of **8** (1.2 g, 5.76 mmol) and NHC precursor **N1** (249 mg, 1.15 mmol) in toluene (23 mL) were added Et_3N (4.3 mL, 31.1 mmol) at room temperature. The reaction mixture was heated to 80°C and a solution of chlorooximes **7b** (28.8 mmol), generated in situ by the treatment of oximes **7a** (2.45 g, 28.8 mmol) with tBuOCl (3.26 mL, 28.8 mmol) in toluene (28.8 mL), was added dropwise to this reaction mixture. The mixture was allowed to stir for 10 min at 80°C before the resultant mixture was filtered. The solvent was evaporated under vacuum and the residue was purified by flash column chromatography with petroleum ether:EtOAc (30:1) to (8:1) to give **13** (540.0 mg, 32%) and the alkynes **8** (750 mg) respectively. **13** : R_f = 0.45 (silica, petroleum ether:EtOAc = 8 : 1); IR

(film) : ν_{max} = 3412, 2964, 1693, 1575, 1451, 1319, 1118, 966, 991, 616 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) : δ = 6.67 (dq, *J* = 15.9, 6.6 Hz, 1H), 6.58 – 6.45 (m, 1H), 6.32 – 6.12 (m, 2H), 6.10 – 5.94 (m, 1H), 5.89 – 5.68 (m, 2H), 3.92 (s, 3H), 2.16 – 2.02 (m, 2H), 1.93 (dd, *J* = 6.6, 1.7 Hz, 3H), 1.73 (s, 3H), 0.99 (t, *J* = 7.5 Hz, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) : δ = 182.20, 164.89, 159.62, 138.41, 135.67, 132.80, 129.44, 128.11, 117.65, 106.90, 72.25, 52.88, 25.99, 25.81, 19.05, 13.45 ppm; HRMS (m/z) : $[M+Na]^+$ calcd for $C_{16}H_{21}NO_4Na^+$ 314.1369, found 314.1360.



13 **6**

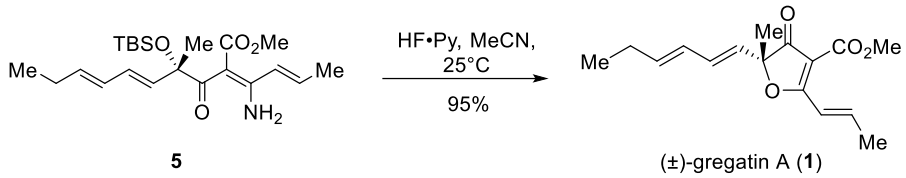
To a stirred solution of **13** (1.50 g, 5.15 mmol) in DCM (23 mL) were added 2,6-lutidine (3.78 mL, 32.4 mmol) at 0 °C. The mixture was allowed to stir at 0 °C for 10 min before TBSOTf (7.10 mL, 30.9 mmol) was added. The resultant mixture was allowed to stir at 25 °C for 1 h before it was quenched with saturated $NaHCO_3$ (40 mL). The mixture so obtained was extracted with EtOAc (3 × 40 mL). The combined organic phases were washed with brine (50 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under vacuum. The residue was purified by flash column chromatography with petroleum ether:EtOAc (50:1) to give **6** (1.60 g, 76%) as a pale yellow liquid. **6** : R_f = 0.68 (silica, petroleum ether:EtOAc = 30:1); IR (film) : ν_{max} = 3436, 2958, 2932, 2858, 1727, 1257, 1102, 994, 837, 778 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) : δ = 6.60 (dq, J = 16.0, 6.6 Hz, 1H), 6.45 (dd, J = 15.9, 1.7 Hz, 1H), 6.27 (dd, J = 15.3, 10.4 Hz, 1H), 6.02 (dd, J = 15.1, 10.6 Hz, 1H), 5.88 (d, J = 15.3 Hz, 1H), 5.77 (dt, J = 15.1, 6.5 Hz, 1H), 3.79 (s, 3H), 2.15 – 2.05 (m, 2H), 1.89 (dd, J = 6.6, 1.7 Hz, 3H), 1.79 (s, 3H), 1.00 (t, J = 7.5 Hz, 3H), 0.89 (s, 9H), 0.07 (s, 3H), 0.01 (s, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) : δ = 177.60, 162.81, 159.96, 138.14, 134.94, 133.31, 130.33, 128.34, 117.68, 107.24, 74.54, 52.07, 26.87, 25.92, 25.83, 19.01, 18.42, 13.52, -2.21, -2.65 ppm; HRMS (m/z) : $[M+H]^+$ calcd for $C_{22}H_{36}NO_4Si^+$ 406.2413, found 406.2414.



6 **5**

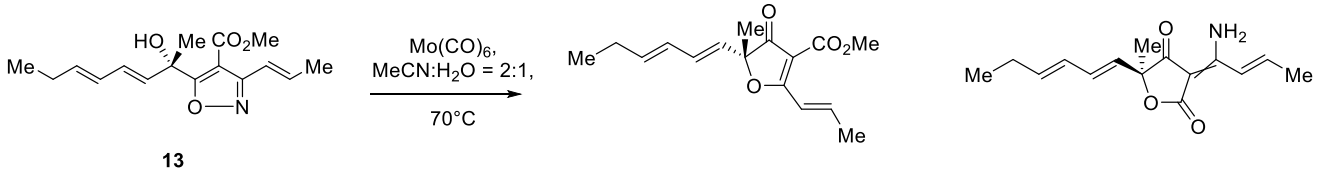
To a stirred solution of **6** (1.60 g, 3.94 mmol) in MeCN (16.0 mL) and H_2O (8.0 mL) were added $Mo(CO)_6$ (2.17 g, 8.20 mmol) at 25 °C. The mixture was allowed to stir at 100 °C for 3 h before the resultant mixture was quenched with H_2O (20 mL). The mixture so obtained was extracted with EtOAc (3 × 30 mL). The combined organic phases were washed with brine (30 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under vacuum. The residue was purified by flash column chromatography with petroleum ether:EtOAc (5:1) to give **5** (1.20 g, 74%) as an pale yellow liquid. **5** : R_f = 0.31 (silica, petroleum ether:EtOAc = 5:1); IR (film) : ν_{max} = 3390, 3178, 2958,

2392, 2857, 1733, 1594, 1254, 993, 837 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) : δ = 6.27 – 6.12 (m, 2H), 6.05 – 5.87 (m, 2H), 5.78 – 5.57 (m, 2H), 3.64 (s, 3H), 2.08 (p, J = 7.2 Hz, 2H), 1.77 (d, J = 6.3 Hz, 3H), 1.56 (s, 3H), 0.99 (t, J = 7.4 Hz, 3H), 0.85 (s, 9H), 0.04 (d, J = 1.7 Hz, 6H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) : δ = 209.93, 168.30, 153.99, 137.02, 135.14, 132.38, 130.40, 128.66, 126.45, 100.61, 83.65, 50.66, 26.83, 25.98, 25.79, 18.59, 18.35, 13.58, -1.96, -2.06 ppm; HRMS (m/z) : $[M-H]^-$ calcd for $C_{22}H_{36}NO_4Si^-$ 406.2414, found 406.2421.



5 (±)-gregatin A (**1**)

To a stirred solution of **22** (2.0 g, 4.91 mmol) in MeCN (23 mL) were added HF•Py (4.42 mL, 49.1 mmol) at 0 ℃，The mixture was allowed to stir at 25 °C for 30 min before the resultant mixture was quenched with aq. $NaHCO_3$ (160 mL). The mixture so obtained was extracted with EtOAc (3 × 80 mL). The combined organic phases were washed with brine (80 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under vacuum. The residue was purified by flash column chromatography with petroleum ether:EtOAc (5:1) to give (±)-gregatin A (**1**) (1.3 g, 95%) as a pale-yellow liquid. (±)-gregatin A (**1**) : R_f = 0.50 (silica, petroleum ether: EtOAc = 5:1); IR (film) : νmax = 3439, 2963, 2931, 1710, 1644, 1557, 1441, 1398, 1204, 1053 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) : δ = 7.33 (dd, J = 15.8, 1.6 Hz, 1H), 7.19 (dq, J = 15.8, 6.7 Hz, 1H), 6.26 (dd, J = 15.5, 10.3 Hz, 1H), 5.97 (dd, J = 15.1, 10.4 Hz, 1H), 5.80 (dt, J = 15.1, 6.5 Hz, 1H), 5.56 (d, J = 15.4 Hz, 1H), 3.83 (s, 3H), 2.12 – 2.06 (m, 2H), 2.05 (dd, J = 6.8, 1.5 Hz, 3H), 1.53 (s, 3H), 0.98 (t, J = 7.4 Hz, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) : δ = 198.47, 185.35, 163.61, 144.88, 139.42, 131.62, 127.91, 126.29, 120.92, 103.83, 90.57, 51.76, 25.82, 22.65, 19.50, 13.45 ppm; ^1H NMR (400 MHz, Acetone-d_6) : δ = 7.34 – 7.17 (m, 2H), 6.31 (dd, J = 15.4, 10.4 Hz, 1H), 6.06 (dd, J = 15.2, 10.4 Hz, 1H), 5.84 (dt, J = 15.2, 6.6 Hz, 1H), 5.59 (d, J = 15.4 Hz, 1H), 3.73 (s, 3H), 2.20 – 1.94 (m, 5H), 1.49 (s, 3H), 0.97 (t, J = 7.5 Hz, 3H) ppm; ^{13}C NMR (101 MHz, Acetone-d_6) : δ = 197.60, 185.33, 163.67, 145.37, 139.54, 132.09, 128.97, 127.66, 121.21, 104.33, 90.67, 51.38, 26.25, 22.40, 19.39, 13.66; HRMS (m/z) : $[M+H]^+$ calcd for $C_{16}H_{21}O_4^+$ 277.1440, found 277.1435.

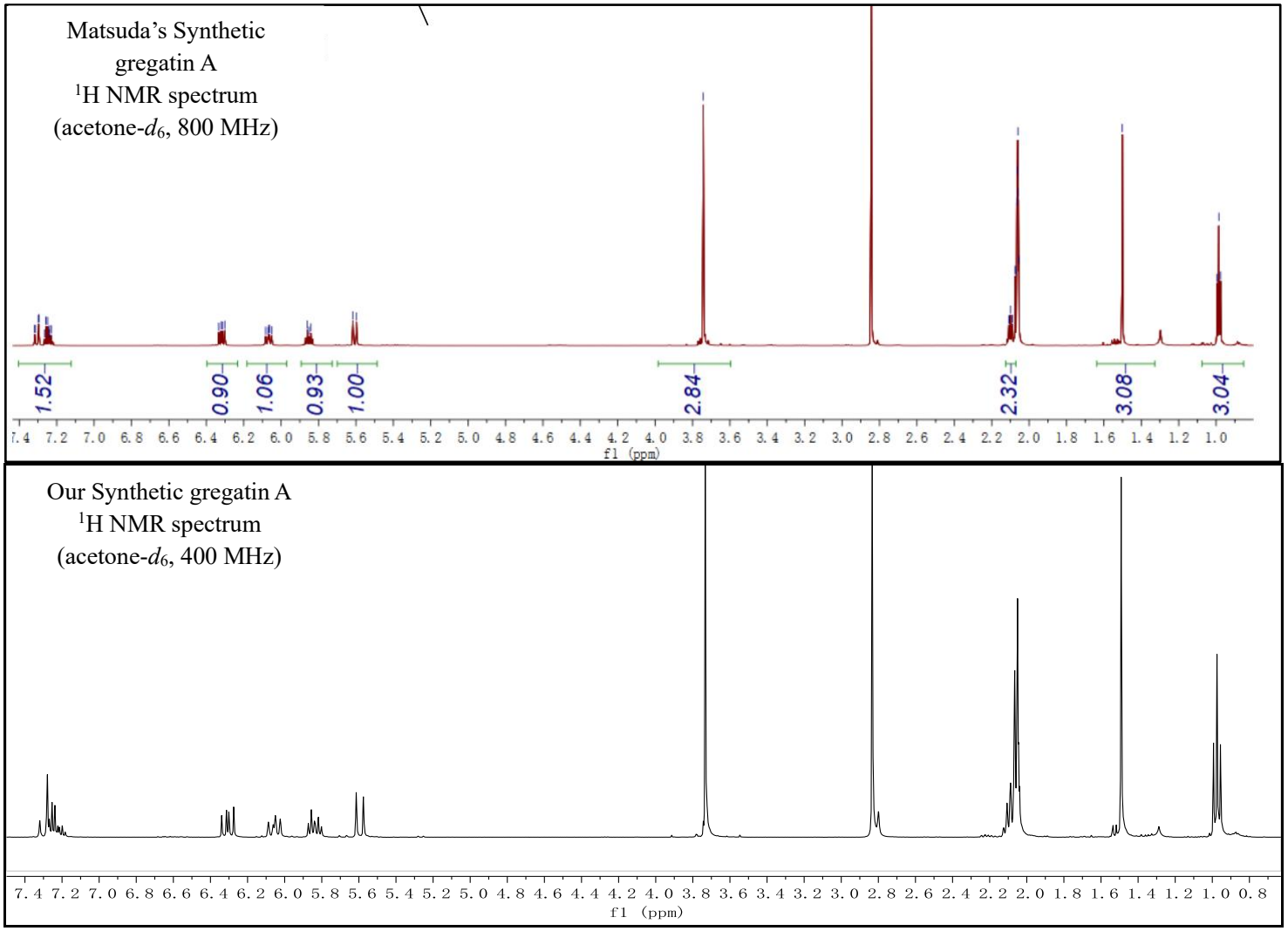


13 (±)-gregatin A (**1**), 19% **16**. 53%

To a stirred solution of **13** (40.0 mg, 0.14 mmol) in MeCN (0.6 mL) and H_2O (0.3 mL) were added $Mo(CO)_6$ (181.0 mg, 0.69 mmol) at 25 °C. The mixture was allowed to stir at 70 °C for 2 h before the resultant mixture was

quenched with H_2O (1 mL). The mixture so obtained was extracted with EtOAc (3 × 2 mL). The combined organic phases were washed with brine (3 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under vacuum. The residue was purified by flash column chromatography with petroleum ether:EtOAc (5:1 → 3:1) to give (±)-gregatin A (**1**) (7 mg, 19%) as a pale yellow liquid and **16** (19 mg, 53%) as a white solid. **16** : R_f = 0.30 (silica, petroleum ether:EtOAc = 3:1); IR (film) : ν_{max} = 3330, 3198, 2965, 2934, 1710, 1655, 1515, 1326, 1062, 988 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) : δ = 9.90, 9.24 (brs, 1H), 7.42 – 7.29 (m, 1H), 6.86 – 6.78 (overlap, 1H), 6.77 (dq, *J* = 16.2, 6.7 Hz, 1H), 6.34 (ddd, *J* = 14.9, 10.3, 4.0 Hz, 1H), 5.98 (dd, *J* = 15.3, 10.4 Hz, 1H), 5.78 (dt, *J* = 14.7, 6.6 Hz, 1H), 5.63 (d, *J* = 15.4 Hz, 1H), 2.07 (p, *J* = 8.2, 7.4 Hz, 2H), 2.01 (dt, *J* = 6.1, 3.0 Hz, 3H), 1.52 (d, *J* = 3.3 Hz, 3H), 0.97 (t, *J* = 7.4 Hz, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) : δ = 200.88, 196.90, 174.44, 170.66, 164.56, 164.21, 141.31, 141.05, 138.77, 138.63, 130.97, 130.74, 128.21, 128.15, 128.08, 128.02, 123.19, 123.01, 89.50, 88.47, 87.38, 85.72, 25.79, 23.07, 19.24, 19.18, 13.45 ppm; HRMS (m/z) : $[M+Na]^+$ calcd for $C_{15}H_{19}NO_3Na^+$ 284.1263, found 284.1262.

III Comparison of the Spectra and Data of Matsuda's[3] and Our Synthetic gregatin A



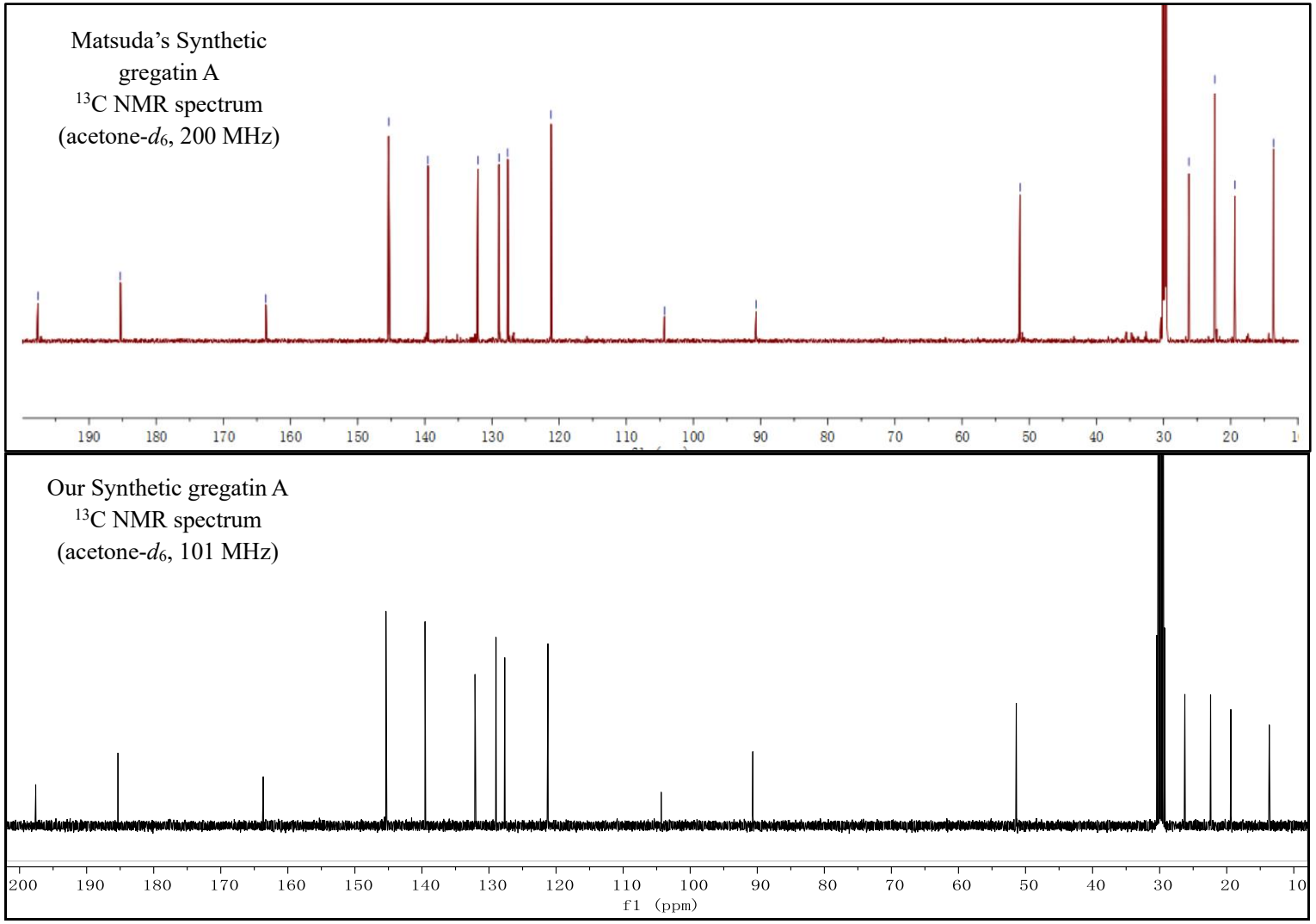
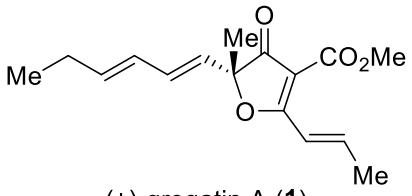

Matsuda's Synthetic
gregatin A
^{13}C NMR spectrum
(acetone-d_6, 200 MHz)
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20
Our Synthetic gregatin A
^{13}C NMR spectrum
(acetone-d_6, 101 MHz)
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)

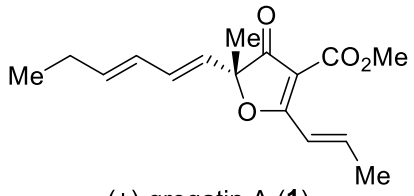
Table S4. Comparison of the ^{1}H NMR spectroscopic data (acetone-d_6) of Matsuda's and our synthetic gregatin A



(±)-gregatin A (**1**)

Matsuda's Synthetic δ_H [ppm, mult, *J* (Hz)] 800 MHz	**Our Synthetic δ_H [ppm, mult, *J* (Hz)] 400 MHz**	**Err (Matsuda's Synthetic – Our Synthetic) $\Delta\delta_H$ (ppm)**
7.31 1 H, dq, 15.8, 1.5	7.34 – 7.17 2 H, m	–
7.24 1 H, dq, 15.8, 6.7		–
6.32 1 H, dd, 15.5, 10.5	6.31 1 H, dd, 15.4, 10.4	+0.01
6.07 1 H, dd, 15.2, 10.5	6.06 1 H, dd, 15.2, 10.4	+0.01
5.85 1 H, dt, 15.2, 6.6	5.84 1 H, dt, 15.2, 6.6	+0.01
5.61 1 H, d, 15.5	5.59 1 H, d, 15.4	+0.02
3.74 3 H, s	3.73 3 H, s	+0.01
2.10 2H, overlapped	2.20 – 1.94 5 H, overlapped	–
2.06 3H, overlapped		–
1.50 3H, s	1.49 3H, s	+0.01
0.99 3H, t, 7.5	0.97 3H, t, 7.5	+0.02

Table S5. Comparison of the ^{13}C NMR spectroscopic data (acetone-d_6) of Matsuda's and our synthetic gregatin A



(±)-gregatin A (**1**)

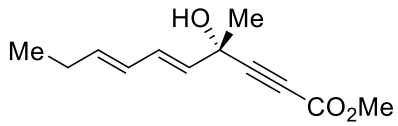
Matsuda's Synthetic δ_C (ppm) 200 MHz	**Our Synthetic δ_C (ppm) 101 MHz**	**Err (Matsuda's Synthetic – Our Synthetic) $\Delta\delta_C$ (ppm)**
197.6	197.6	0
185.3	185.3	0
162.7	163.6	−0.9
145.4	145.4	0
139.5	139.5	0
132.1	132.1	0
129.0	129.0	0
127.7	127.7	0
121.2	121.2	0
104.3	104.3	0
90.7	90.7	0
51.4	51.4	0
26.2	26.2	0
22.4	22.4	0
19.4	19.4	0
13.6	13.7	−0.1

Reference:

1. Burghart-Stoll, H.; Brückner, R. Total syntheses of the gregatins A-D and aspertetronin A: Structure revisions of these compounds and of aspertetronin B, together with plausible structure revisions of gregatin E, cyclogregatin, graminin A, the penicilliols A and B, and the huaspenones A and B. *Eur. J. Org. Chem*. **2012**, 3978-4017.
2. Mabasa, T. F.; Mabasa, J.; Simelane, M.; Vatsha, B.; Makhubela, B. C. E.; Kinfe, H. H. Acetic Anhydride–Acetic Acid as a New Dehydrating Agent of Aldoximes for the Preparation of Nitriles: Preparation of 2-Cyanoglycals. *Synlett*, **2020**, *31*, 991-996.
3. Wang, W.-G.; Wang, H.; Du, L.-Q.; Li, M.; Chen, L.; Yu, J.; Cheng, G.-G.; Zhan, M.-T.; Hu, Q.-F.; Zhang, L.; Yao, M.; Matsuda, Y. Molecular basis for the biosynthesis of an unusual chain-fused polyketide, gregatin A. *J. Am. Chem. Soc*. **2020**, *142*, 8464−8472.

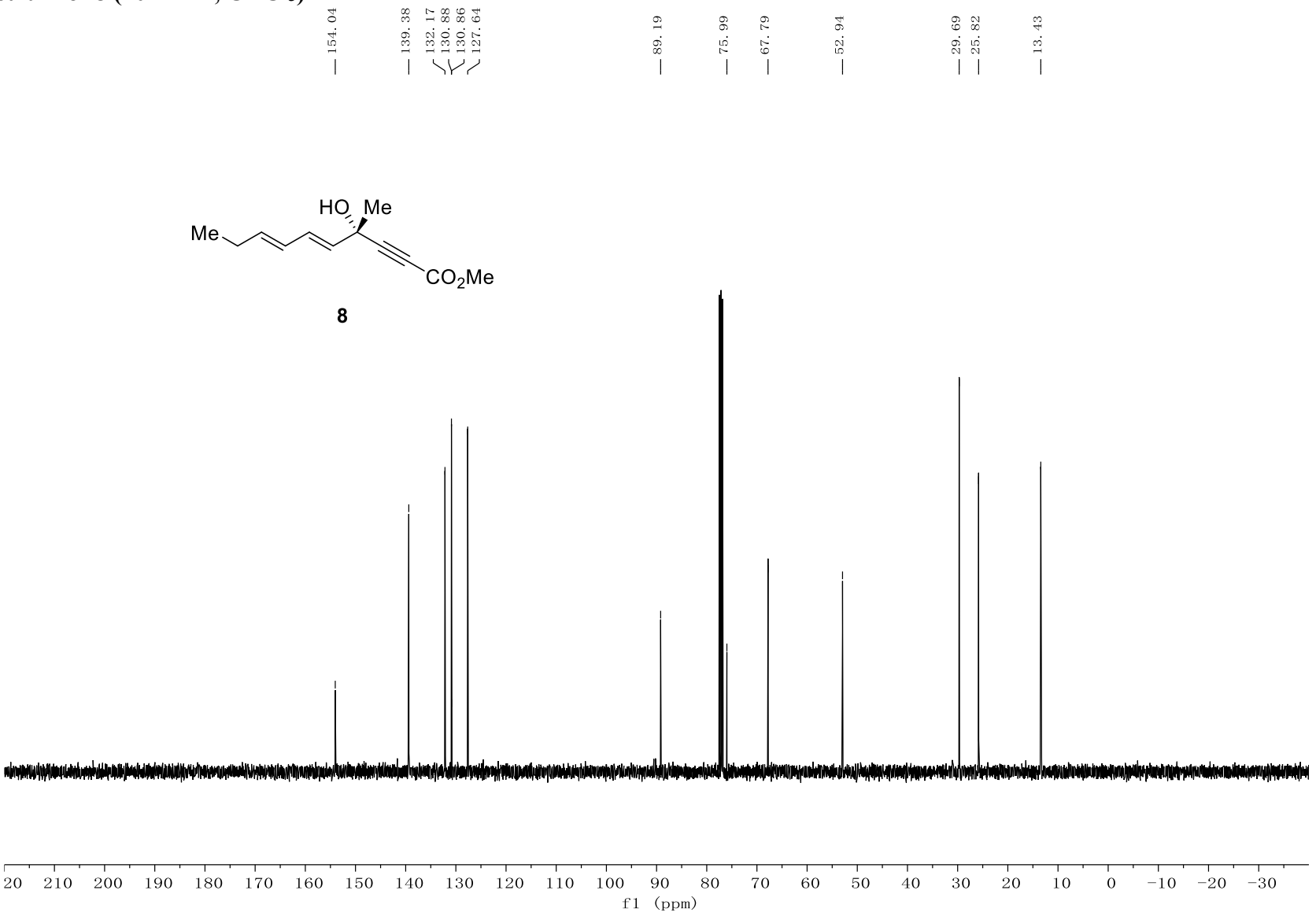
IV ^{1}H and ^{13}C NMR Spectra of Compounds

^{1}H NMR Spectrum of 8 (400 MHz, $CDCl_3$)

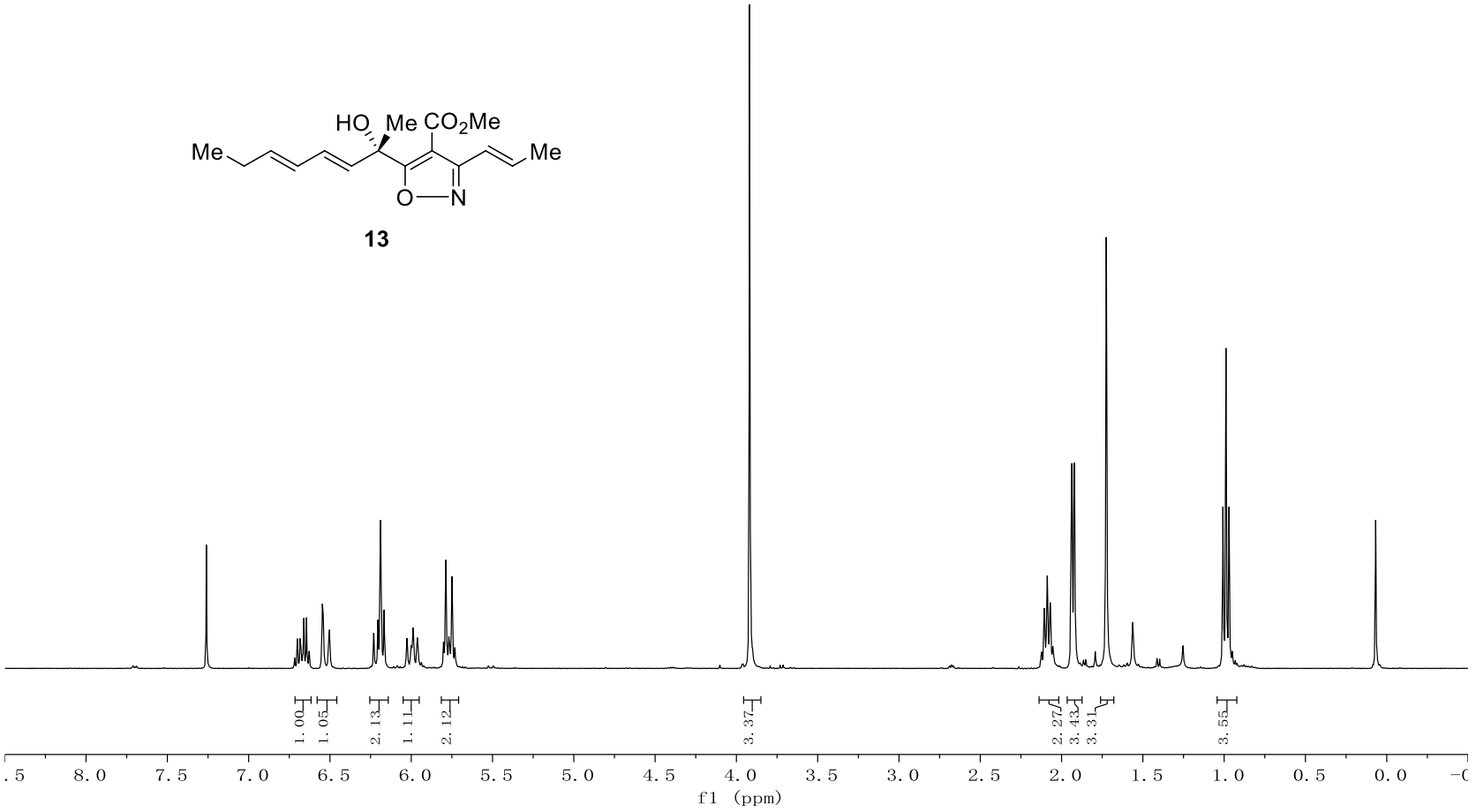


8

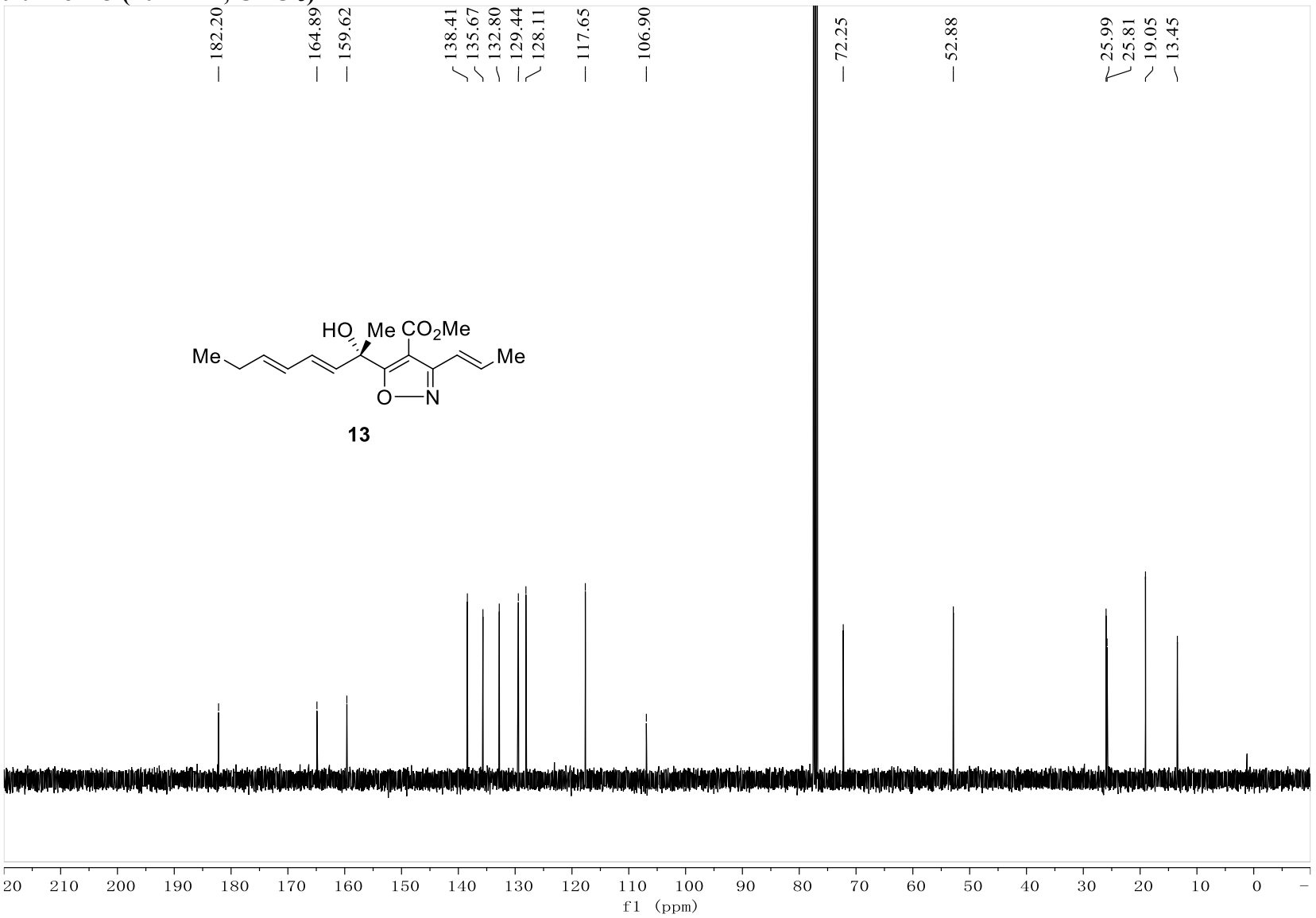
^{13}C NMR Spectrum of 8 (101MHz, $CDCl_3$)



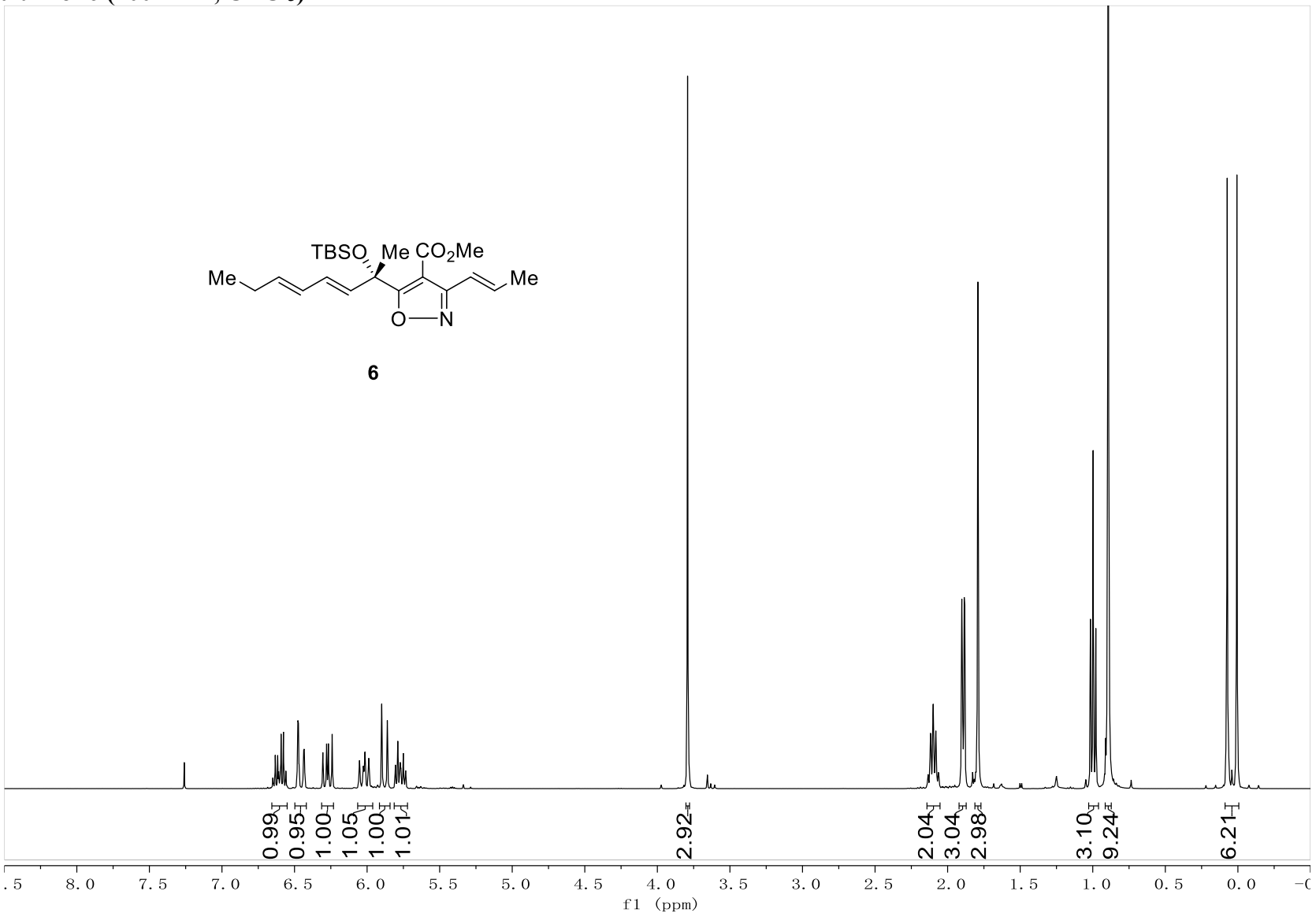
^{1}H NMR Spectrum of 13 (400 MHz, $CDCl_3$)



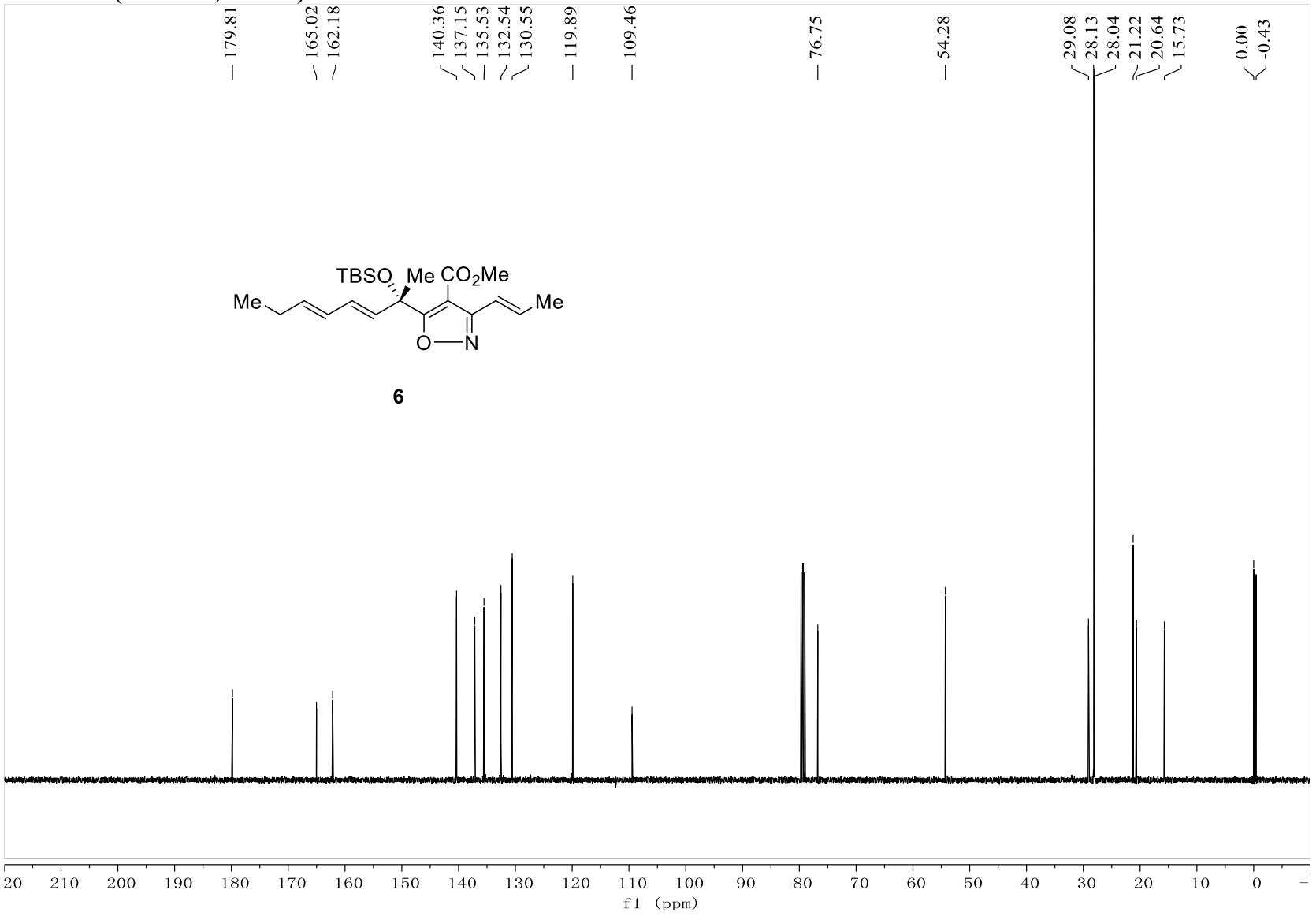
^{13}C NMR Spectrum of 13 (101MHz, $CDCl_3$)



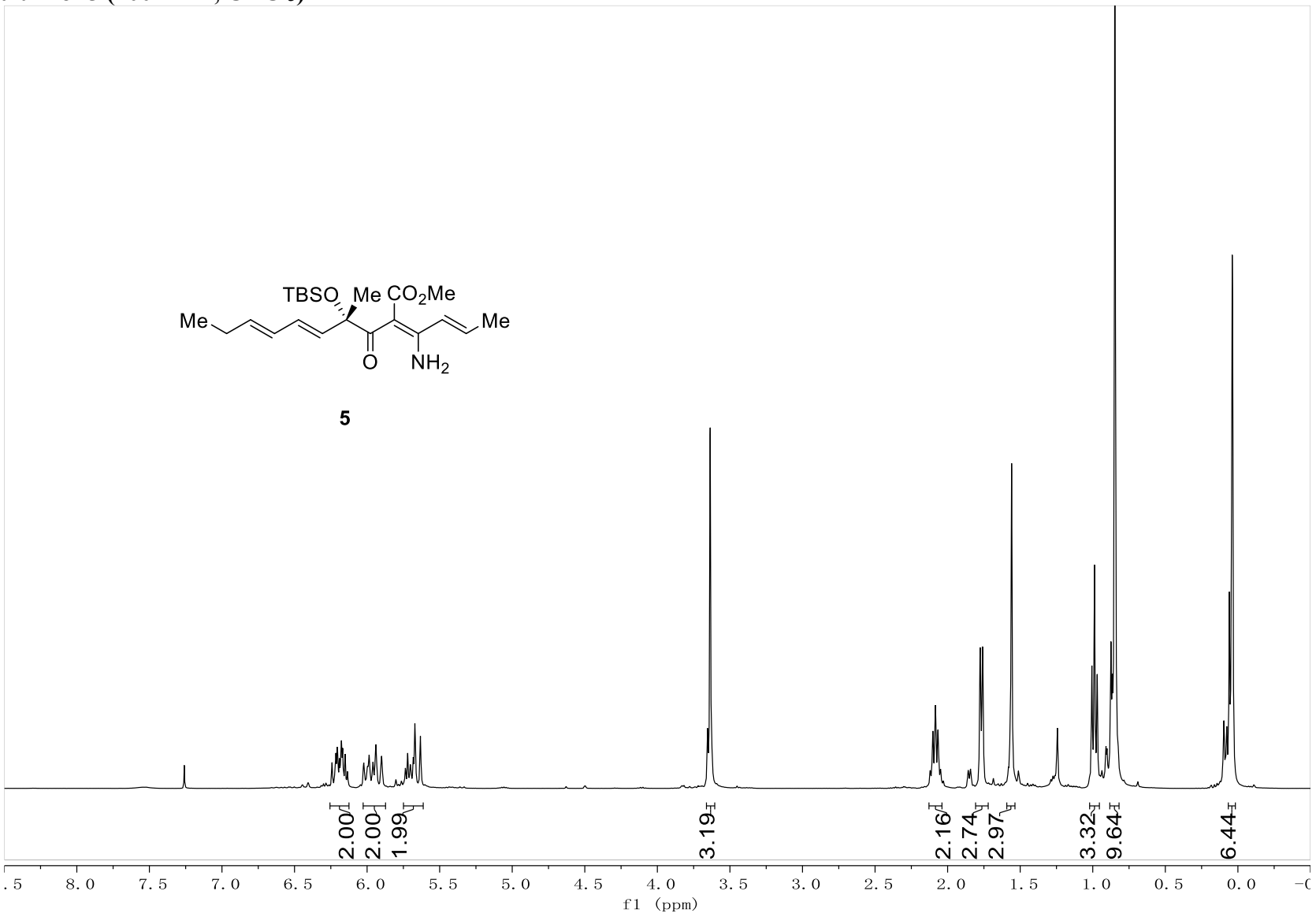
^{1}H NMR Spectrum of 6 (400 MHz, $CDCl_3$)



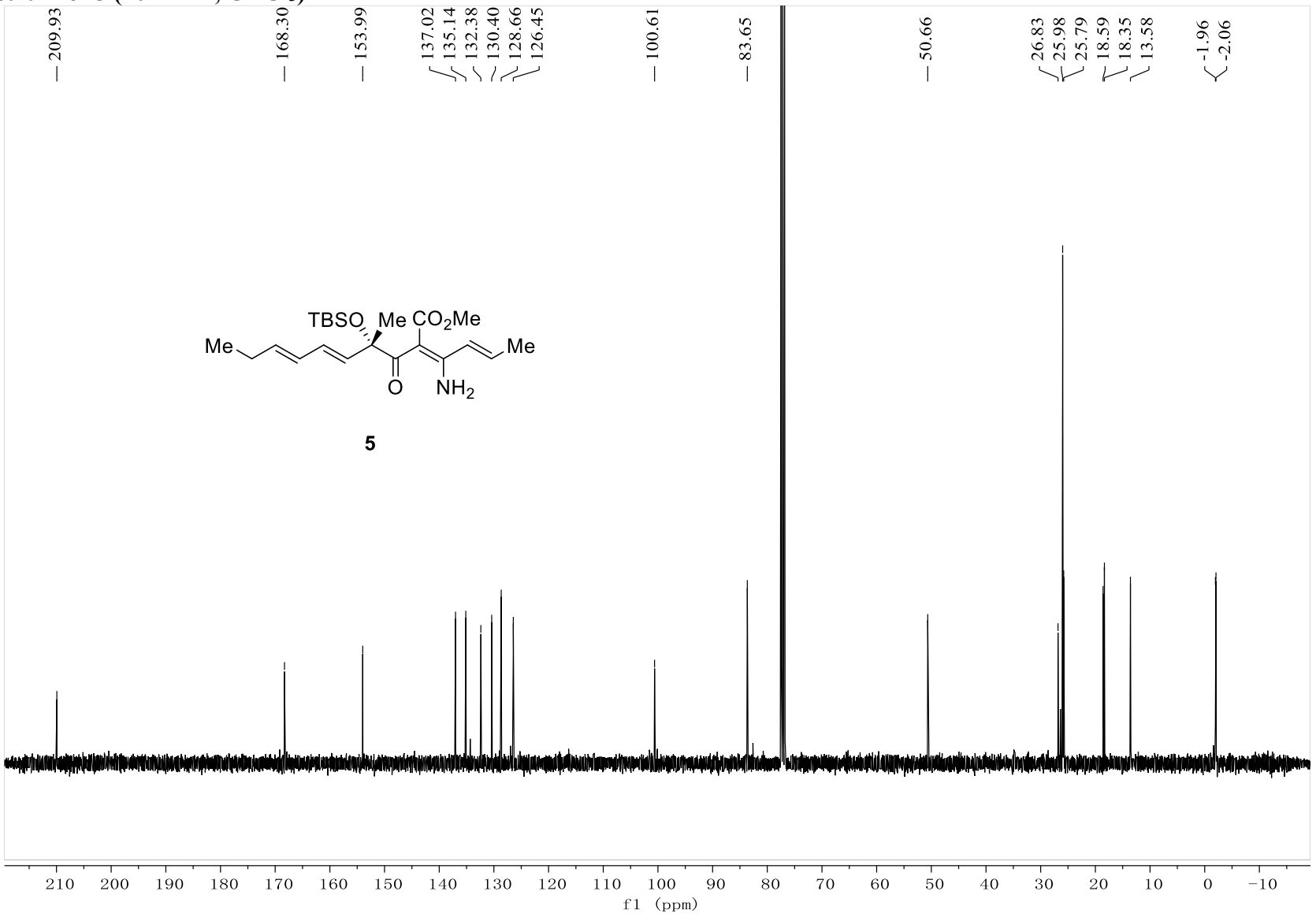
^{13}C NMR Spectrum of 6 (101MHz, $CDCl_3$)



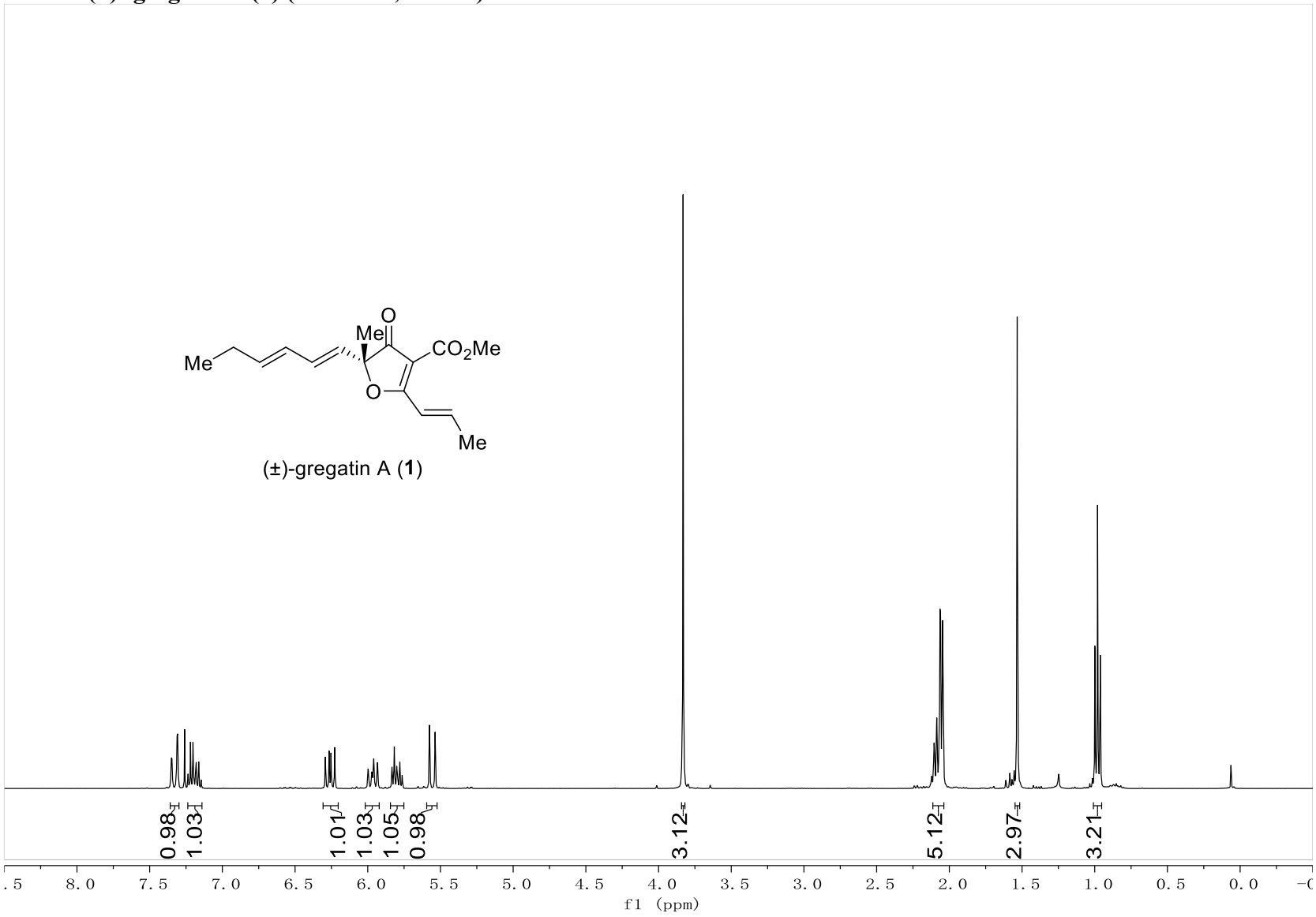
^{1}H NMR Spectrum of 5 (400 MHz, $CDCl_3$)



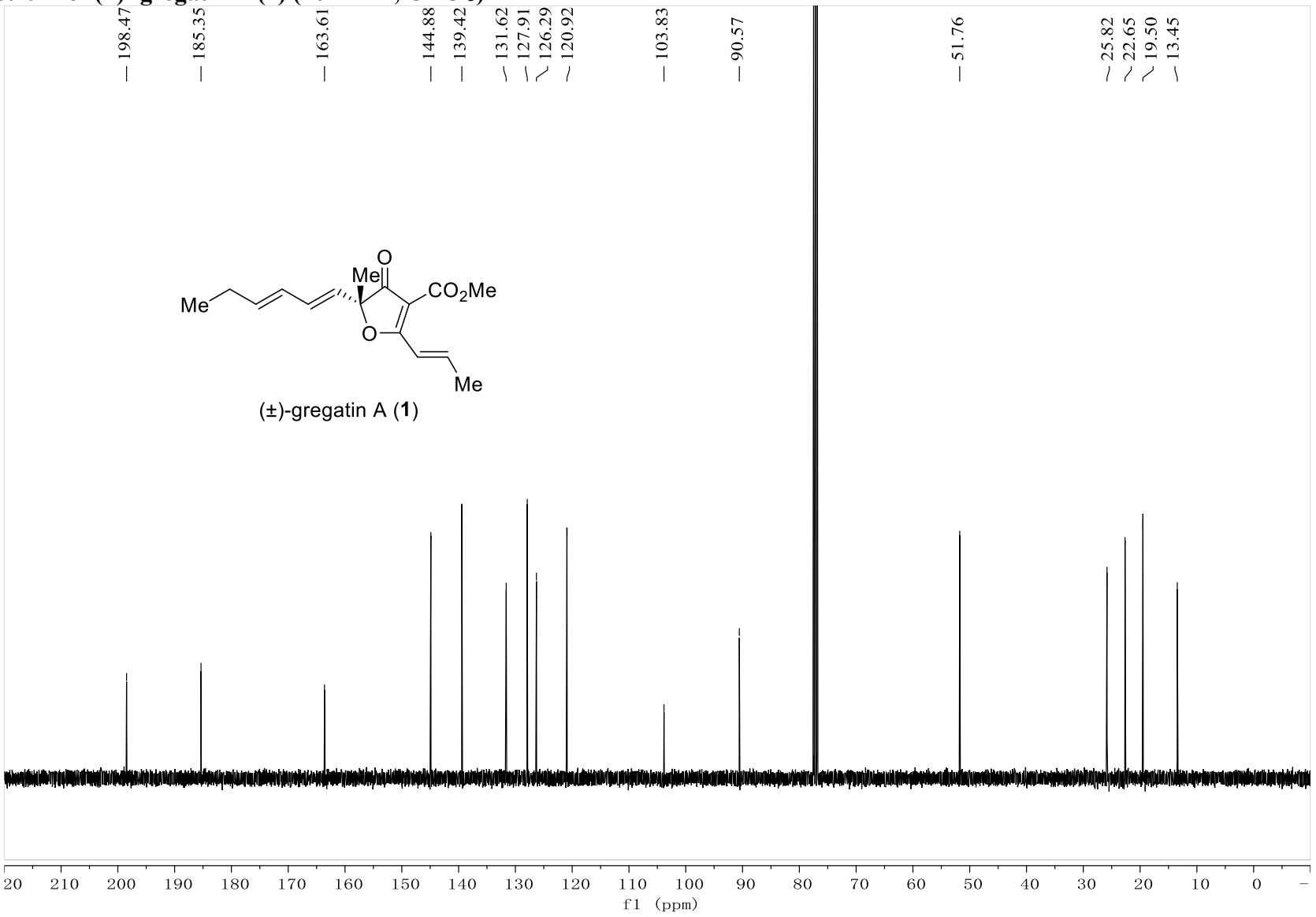
^{13}C NMR Spectrum of 5 (101MHz, $CDCl_3$)



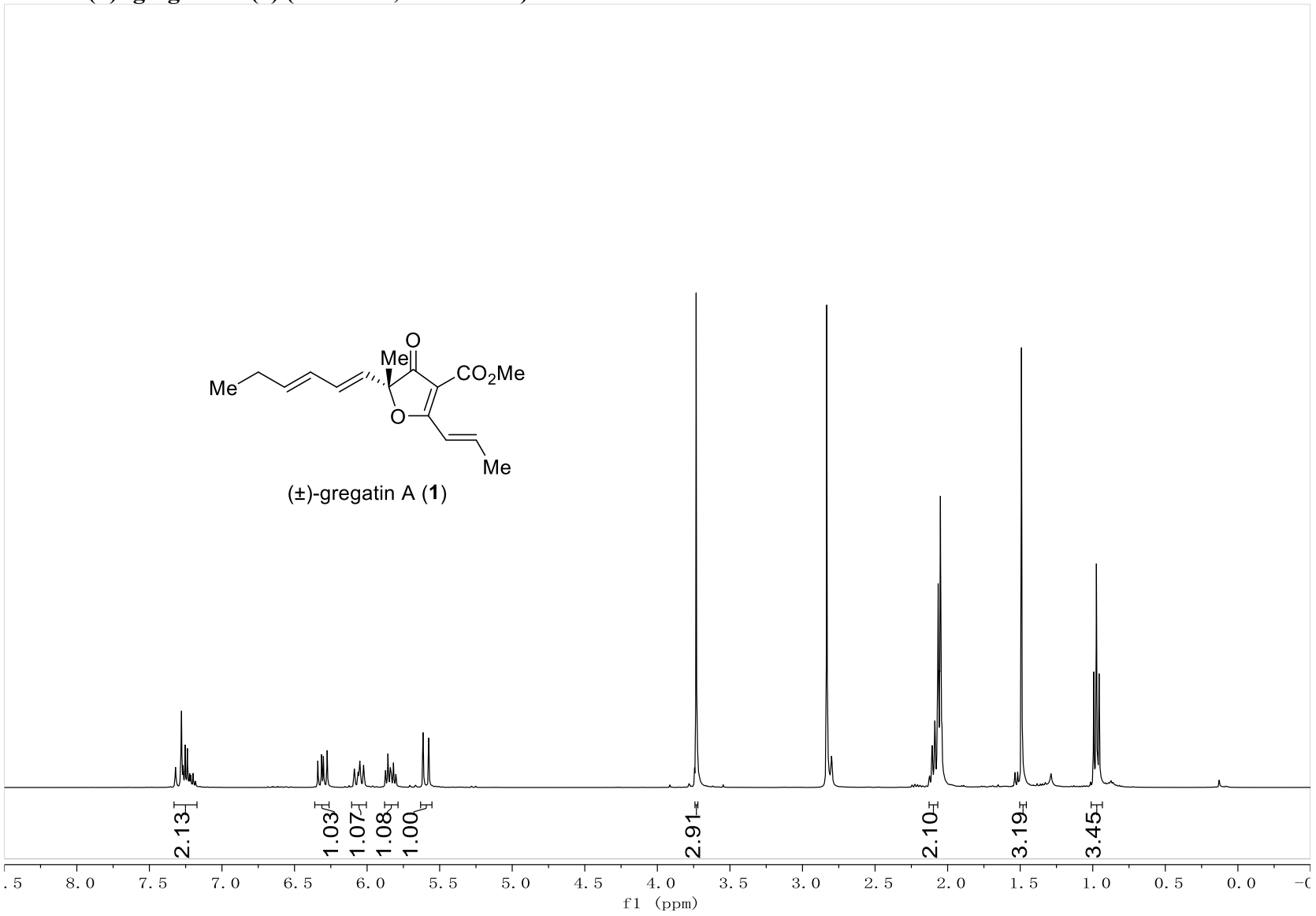
^{1}H NMR Spectrum of (±)- gregatin A (1) (400 MHz, $CDCl_3$)



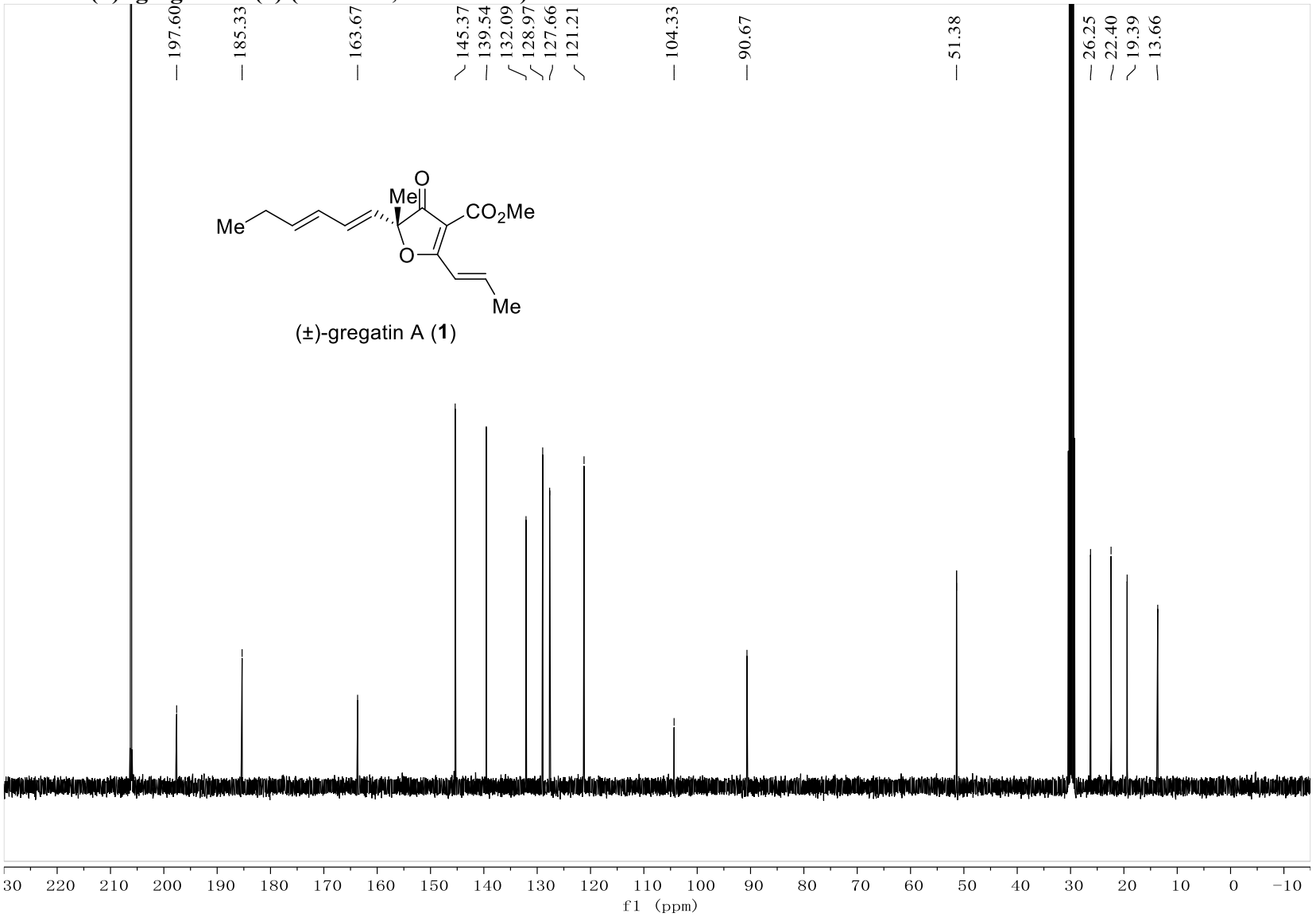
^{13}C NMR Spectrum of (±)- gregatin A (1) (101MHz, $CDCl_3$)



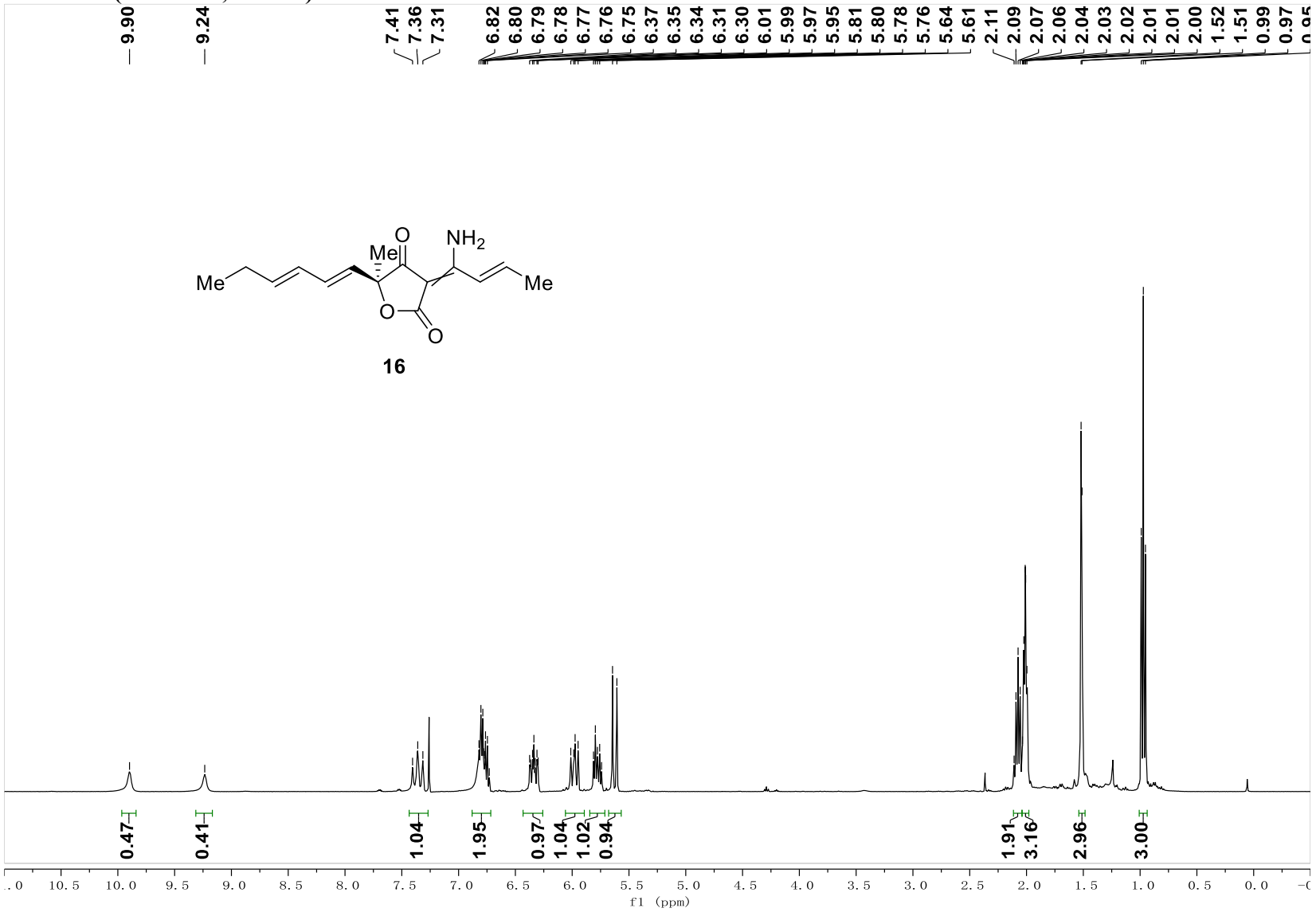
^{1}H NMR Spectrum of (±)- gregatin A (1) (400 MHz, Acetone-d_6)



^{13}C NMR Spectrum of (±)- gregatin A (1) (101MHz, Acetone-d_6)



^{1}H NMR Spectrum of 16 (400 MHz, $CDCl_3$)



^{13}C NMR Spectrum of 16 (101 MHz, $CDCl_3$)