Supporting Information

Fusarisetin A: Scalable Total Synthesis and Related Studies

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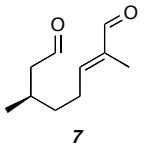
General Procedures

Unless indicated, all commercially available reagents and anhydrous solvents were purchased at the highest commercial quality and were used as received without further purification. All non-aqueous reactions were carried out under argon atmosphere using dry glassware that had been flame-dried under a stream of argon unless otherwise noted. Anhydrous tetrahydrofuran (THF) and dichloromethane (CH_2Cl_2) were obtained by passing commercially available pre-dried, oxygen-free formulations through activated alumina columns. Flash column chromatography was performed on silica gel (Merck Kieselgel 60, 230-400 mesh) using hexanes-EtOAc or CH_2Cl_2-MeOH mixtures of increasing polarity. The progress of all the reactions was monitored by thin-layer chromatography (TLC) using glass plates precoated with silica gel-60 F_{254} to a thickness of 0.5 mm (Merck), and compounds were visualized by irradiation with UV light and/or by treatment with a solution of ninhydrin stain or Ceric Ammonium Molybdate (CAM) stain followed by heating. ^{13}C NMR and ^{1}H NMR spectra were recorded on a 400 MHz, 500 MHz, 800 MHz Varian instrument or a 500 MHz JEOL instrument. $CDCl_3$ was treated with flame dried K_2CO_3, chemical shifts (δ) are quoted in parts per million (ppm) referenced to the appropriate residual solvent peak reference ($CDCl_3$ or CD_3OD), with the abbreviations s, br s, d, t, q, m, td, dt and qd denoting singlet, broad singlet, doublet, triplet, quartet, multiplet, quartet of doublets, triplet of doublets, doublet of triplets and quartet of doublets, respectively. *J* = coupling constants given in Hertz (Hz). High resolution Mass spectra (HRMS) were recorded on a trisector WG AutoSpecQ spectrometer. Optical rotation data were collected on a Jasco P-1010 polarimeter using HPLC grade anhydrous $CHCl_3$ or anhydrous MeOH. Microwave experiments were carried out in Biotage (model:Initiator) microwave reactor using high pressure vessels. Cell cultures were incubated in NABCO CO_2 6000 incubator and biological assays were performed in 24-well Falcon Multiwell (3047) cell dishes.

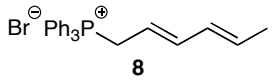


7

Di-aldehyde 7 (Method 1): To a solution of (*R*)-(+)-citronellal (**6**, 1.45 ml, 1.23 g, 8.0 mmol, purchased from TCI America) in CH_2Cl_2 (150 ml) was added methacrolein (1.32 ml, 16.0 mmol) and Grubbs catalyst (2nd generation, 340 mg, 0.4 mmol). The reaction mixture was refluxed for 24 hours under argon atmosphere. The reaction was allowed to cool to room temperature and concentrated. The residue was purified via silica column chromatography (hexanes:EtOAc, 100:1 to 10:1) to recover the (*R*)-(+)-citronellal (205 mg, 17%) and yield the di-aldehyde **7** (1.01 g, 75 %, 90% brsm) as a pale yellow oil. R_f = 0.5 (silica gel, hexanes:EtOAc, 2:1); $[\alpha]_D^{23}$ = +13.7 (*c* = 1.0 , $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.77 (d, *J* = 1.7 Hz, 1H), 9.39 (s, 1H), 6.46 (t, *J* = 5.8 Hz, 1H) 2.42-2.33 (m, 4H), 2.34 (m, 1H), 1.74 (s, 3H), 1.57 (m, 1H), 1.42 (m, 1H), 1.01 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.9, 194.9, 153.8, 139.2, 50.6, 34.9, 27.5, 26.1, 19.3, 8.9; HRMS (ESI) m/e 191.1042 [M+Na^+] calcd for $C_{10}H_{16}O_2Na^+$: 191.1043.

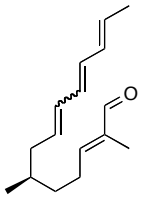
Di-aldehyde 7 (Method 2): To a solution of SeO_2 (416 mg, 3.7 mmol) and salicylic acid (1.99 g, 12.4 mmol) in CH_2Cl_2 (40 ml) was added *t*-butyl hydrogenperoxide slowly (70% in H_2O, 71.0 ml, 496 mmol). The mixture was stirred for 15 min then (*R*)-(+)-citronellal (**6**, 18.8 g, 122 mmol) was added. The reaction was stirred at room temperature for 96 hours. The reaction was diluted with benzene (100 ml) and concentrated. The residue was diluted with ether (400 ml) and washed with 10% NaOH (2 x 130 ml) and brine (120 ml). The organic layer was dried over $MgSO_4$, filtered, concentrated and purified through silica column chromatography (hexanes:EtOAc, 200:1 to 5:1) to recover the (*R*)-(+)-citronellal (1.0 g, 5%) and yield the di-aldehyde **7** (4 g, 20%) and corresponding allylic alcohol (10.2 g, 49%) as a clear oil. To a solution of this allylic alcohol (10.2 g, 60 mmol) in DMSO (220 ml) was added IBX (24 g, 85.7 mmol) in one portion at 0 ºC. The reaction was stirred for 1.5 hours at rt, then was diluted with water (500 ml) and filtered through Celite® to remove the precipitate and washed thoroughly with ether. The filtrate separated, and the aqueous phase was extracted with ether (5 x 500 ml). The combined organic layers were washed with brine (1000 ml) and 10% NaOH (2 x 500 ml), dried

over $MgSO_4$, filtered and concentrated to yield **7** (9.16 g, 90 %) as a pale yellow oil. The analytical data was identical with the one obtained from method 1.



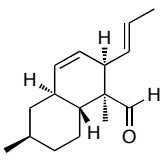
8

(2*E*,4*E*)-Hexa-2,4-dien-1-yltriphenylphosphonium bromide (**8**): To a stirred solution of (2*E*,4*E*)-hexadien-1-ol (9.80 g, 100 mmol) in CH_2Cl_2 (20 ml) at –10 ºC was slowly added a solution of phosphorus tribromide (9.20 g, 34.0 mmol) in CH_2Cl_2 (20 ml) dropwise via an additional funnel. After all the phosphorous tribromide was added, the reaction mixture was stirred for 3 hours before it was diluted with ether (150 ml) and quenched with a saturated $NaHCO_3$ (100 ml) solution. The mixture was separated with diethyl ether with the aid of brine. The aqueous phase was extracted with ether (2 x 100 ml). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford crude (2*E*,4*E*)-hexadienylbromide (10.4 g, 65%) as a brown oil. The crude (2*E*,4*E*)-hexadienylbromide was then dissolved in anhydrous toluene (90 ml), followed by the addition of triphenyl phosphine (18.9 g, 72.0 mmol). This reaction was then stirred for 72 hours at room temperature, and the resulting crystalline product was collected by suction filtration, rinsing the solids with a small amount of toluene. After pumping under high vacuum at room temperature for 12 hours, the phosphonium salt **8** were obtained (27.2 g, 99%, 64% from (2*E*,4*E*)-hexadien-l-ol). mp: 159-160 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.85-7.65 (m, 15H), 6.36 (m, 1H), 5.89 (m, 1H), 5.67 (m, 1H), 5.28 (m, 1H), 4.83 (dd, J = 15.5 Hz, 7.5 Hz, 2H), 1.68 (br d, J = 6.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 140.7, 140.6, 135.0, 135.0, 133.9, 133.8, 132.6, 132.6, 130.4, 130.3, 130.0, 129.9, 118.3, 117.6, 113.2 (d, J = 45.9 Hz), 28.2 (d, J = 195.8 Hz), 18.2; HRMS (ESI) m/e 343.1613 [M–Br$^-$] calcd for $C_{24}H_{24}P^+$: 343.1610.



5, (*E*:*Z* = 3:2)

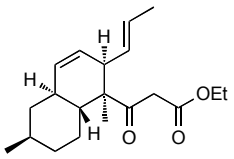
To a suspension of (2*E*,4*E*)-hexa-2,4-dien-1-yltriphenylphosphonium bromide **8** (41.2 g, 97.4 mmol) in THF (500 ml) was added dropwise *n*-BuLi (60.8 ml, 97.4 mmol, 1.6 M in hexane) via addition funnel at –78 ºC. The mixture was stirred for 1 h at –60 ºC then re-cooled to –78 ºC and transferred via cannula, slowly dropwise to a solution of the di-aldehyde **7** (16.4 g, 97.4 mmol) in THF (500 ml) at –78 ºC over 6 hours. After completion of addition the reaction mixture was stirred at this temperature for 10 min, quenched with saturated NH_4Cl solution (500 ml), diluted with ethyl ether (500 ml) and allowed to reach room temperature. The layers were separated and the aqueous layer was extracted with ether (2 x 500 ml). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, concentrated and purified through neutralized (Et_3N, 2%) silica column chromatography (pure hexanes, then hexanes:EtOAc, 500:1 to 50:1) to yield polyene **5** (13.7 g, 62%) as a pale yellow oil as an inseparable *E*/*Z* isomeric mixture (*E*:*Z* = ca. 3:2). R_f = 0.5 (silica gel, hexanes:EtOAc, 10:1); ^{1}H NMR (500 MHz, $CDCl_3$) (*E*:*Z* = ca. 3:2) δ 9.38 (s, 1H), 6.47 (t, *J* = 6.1 Hz, 1H), 6.36-6.01 (m, 4H), 5.75-5.36 (m, 2H), 2.35 (m, 2H), 2.22-1.96 (m, 2H), 1.77 and 1.76 (d, d, *J* = 13.8 Hz, 13.8 Hz, 3H), 1.74 (s, 3H), 1.56-1.49 (m, 2H), 1.35-1.28 (m, 1H), 0.93 and 0.91 (d, d, *J* = 6.9 Hz, 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) (*E*:*Z* = ca. 3:2) δ 195.3, 154.9, 139.1, 133.1, 132.1, 131.9, 131.6, 131.1, 130.2, 129.9, 129.8, 129.1, 125.5, 40.1, 34.9, 34.9, 34.8, 33.2, 33.0, 26.6, 26.6, 19.4, 19.3, 18.3, 18.2, 9.1; HRMS (ESI) m/e 255.1720 [M+Na^+] calcd for $C_{16}H_{24}ONa^+$: 255.1719.



9

To a solution of polyene **5** (13.7 g, 58.96 mmol) in CH_2Cl_2 (700 ml) was added dropwise a solution of I_2 (752 mg, 2.95 mmol) in CH_2Cl_2 (5 ml). The reaction mixture was

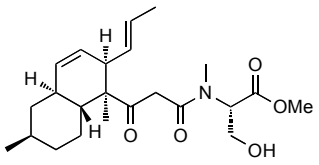
irradiated with visible light (sunlamp, visible light) for 5 minutes. (caution: keep the flask in a certain distance away from the light source to avoid the heat-induced IMDA reaction.) The mixture was then cooled down to –78 ºC, at which time Et_2AlCl (65.5 ml, 58.96 mmol, 0.9 M in toluene) was added dropwise. The reaction mixture was stirred for 24 hours at this temperature. The reaction was quenched with saturated $Na_2S_2O_3/NaHCO_3$ solution (500 ml, 1:1) and allowed to reach room temperature. The mixture was filtered through a Celite plug and the layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 300 ml). The combined organic layers were washed with brine (300 ml), dried over $MgSO_4$, filtered and concentrated under reduced pressure to obtain the *trans*-decalin aldehyde **9** as a clear viscous oil (11.28 g, 82%). This material can be used directly to the next step without further purification. An analytical sample of **9** was purified through preparative TLC (silica gel, hexanes:EtOAc, 20:1). R_f = 0.6 (silica gel, hexanes:EtOAc, 10:1); $[\alpha]_D^{23}$= +283.7 (*c* = 0.5, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ : 9.46 (s, 1H), 5.47-5.43 (m, 4H), 2.53 (m, 1H), 1.82-1.73 (m, 3H), 1.66 (m, 1H), 1.65 (d, *J* = 5.2 Hz, 3H), 1.48 (m, 1H), 1.38-1.35 (m, 1H), 1.12-1.02 (m, 2H) 1.00 (s, 3H), 0.92 (d, *J* = 6.3 Hz, 3H), 0.87 (q, *J* = 12.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 209.0, 130.9, 129.6, 128.6, 126.8, 50.3, 49.0, 41.7, 38.8, 37.5, 35.3, 33.2, 27.1, 22.6, 18.0, 13.7; HRMS (ESI) m/e 255.1717 [M+Na^+] calcd for $C_{16}H_{24}ONa^+$: 255.1719.



4

β-ketoester 4: To a solution of **9** (5.5 g, 23.7 mmol) in benzene (200 ml) was added ethyl bromoacetate (7.89 ml, 71.1 mmol) and activated zinc dust (7.76 g, 118.5 mmol). The reaction mixture was then refluxed for 45 minutes. The reaction mixture was allowed to cool to room temperature, acidified with 1 N HCl and extracted with EtOAc (3 x 300 ml). The combined organic layers were washed with saturated $NaHCO_3$ (300 ml), brine (300 ml), dried over $MgSO_4$ and concentrated to afford the corresponding isomeric alcohol mixture. The crude alcohols were then dissolved in CH_2Cl_2 (200 ml) and Dess-Martin periodinane (20.0 g, 47.2 mmol) was added portionwise at room temperature. The

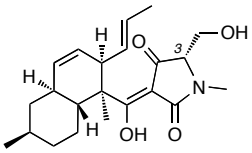
reaction mixture was then stirred for 2 hours. The reaction was quenched with with saturated $Na_2S_2O_3/NaHCO_3$ solution (500 ml, 1:1), filtered through Celite® (washed with 500 ml of ethyl ether) and the filtrate was extracted with ethyl ether (3 x 300 ml). The combined organic layers were washed with brine (300 ml), dried over $MgSO_4$ and concentrated to yield crude β-ketoester **4** (6.85 g, 92%) as a viscous yellow oil. This material can be used directly to the next step without further purification. An analytical sample of **4** was purified through preparative TLC (silica gel, hexanes:EtOAc, 10:1). R_f = 0.4 (silica gel, hexanes:EtOAc, 10:1); $[\alpha]_D^{23}$ = –146.9 (*c* = 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) (with minor amount of enol-form) δ: 5.42-5.35 (m, 3H), 5.16-5.07 (m, 1H), 4.19-4.14 (m, 2H), 3.49 (d, *J* = 15.8 Hz, 1H), 3.33 (d, *J* = 15.8 Hz, 1H), 2.54 (m, 1H), 1.80-1.62 (m, 5H), 1.60 (d, *J* = 6.2 Hz, 3H), 1.59 (m, 1H), 1.47 (m, 1H), 1.25 (t, *J* = 7.6 Hz, 3H), 1.17 (s, 3H), 0.90 (d, *J* = 6.9 Hz, 3H), 0.86 (q, *J* = 12.4 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 205.8, 167.8, 130.7, 130.4, 127.1, 126.4, 61.2, 53.4, 49.5, 46.5, 42.0, 39.6, 38.4, 35.6, 33.5, 27.1, 22.5, 17.9, 16.9, 14.2; HRMS (ESI) m/e 341.2088 [M+Na^+] calcd for $C_{20}H_{30}O_3Na^+$: 341.2087.



11

Ketoamide 11: To a solution of β-keto ester **4** (3.5 g, 11.2 mmol) in anhydrous EtOH (6.6 ml) was added the ethanolic KOH solution (3.5 g KOH in 35 ml EtOH), the reaction was then stirred at rt for 96 hrs before it was acidified with 2M HCl solution to pH = 2. The mixture was extracted with ether (3 x 200 ml), the combined organic layer was dried over $MgSO_4$ and concentrated in *vacuo*. This afforded acid was then dissolved in CH_2Cl_2 (20 ml) and transferred to a round bottom flask which contains the freshly prepared amine **18** (1.79 g, 13.4 mmol). To this solution was added DMF (4.4 ml), *O*-(7-azabenzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate (HATU, 4.68 g, 12.3 mmol) and cooled to 0 °C, followed by adding in the diisopropylethylamine (DIPEA, 5.93 ml, 33.6 mmol) dropwise. The reaction was stirred at rt for 2 hrs before it was acidified with 2M HCl solution to pH = 2. The mixture was then diluted with EtOAc

(500 ml), sequentially washed with 2M HCl solution (3 x 200 ml), $NaHCO_3$ (100 ml) and brine (2 x 200 ml). The organic layer was dried over $MgSO_4$ and concentrated in *vacuo* to afford the desired ketoamide **11** as a yellow oil (90%, 4.0 g). This ketoamide **11** was used directly to the next step without further purification. An analytical sample of **11** was purified with preparative TLC (EtOAc : Hexanes, 1:1 x 3). The ^{1}H NMR and ^{13}C NMR were complicated by the enol-keto tautomers and the amide rotamers. R_f = 0.4 (silica gel, CH_2Cl_2:MeOH, 20:1); $[\alpha]_D^{23}$ = –192.3 (*c* = 0.46, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 5.43-5.32 (m, 3H), 5.15 (m, 1H), 4.79 (m, minor), 4.07-3.99 (m, 2H), 3.74 (m, 3H), 3.54-3.47 (m, 1H), 2.96 (m, 3H), 2.57-2.51 (br m, 1H), 1.80-1.65 (m, 6H), 1.59 (m, 3H), 1.57-1.40 (m, 1H), 1.23 (s, 3H), 1.05 (m, 1H), 0.90 (m, 1H), 0.88 (d, *J* = 8.2 Hz, 3H) 0.84 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 207.9, 169.8, 168.7, 130.9, 130.5, 126.9, 126.4, 61.0, 60.0, 53.5, 52.3, 49.8, 46.3, 41.9, 39.8, 38.7, 38.4, 35.4, 33.4, 27.2, 22.4, 17.9, 17.3. HRMS (ESI) m/e 405.2519 [M+H$^+$] calcd for $C_{23}H_{35}O_5N^+$: 405.2517.



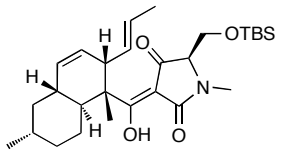
(–)-equisetin, 2

(–)-Equisetin (2) and C_3-*epi*-equisetin (C_3-*epi*-2): To a solution of ketoamide **11** (2.1 g, 5.11 mmol) in methanol (840 ml) was added methanolic sodium methoxide solution (51.1 ml, 0.5 M, 25.6 mmol) via syringe at rt. After 10 min the reaction was quenched with 1 N HCl (200 ml). To the mixture was added water (500 ml) and CH_2Cl_2 (1000 ml), the aqueous phase was extracted with CH_2Cl_2 (5 × 1000 ml). The combined organic phase was dried over $MgSO_4$ and concentrated in *vacuo* to give the (–)-equisetin **2** and C_3-*epi*-equisetin (C_3-*epi*-**2**) as a pale red oil (1.9 g, dr = 1:1, 100% overall). This crude material was used directly to the next step without further purification. Analytical samples of **2** and C_3-*epi*-**2** were purified with preparative TLC (CH_2Cl_2:MeOH:AcOH, 50:1:0.1, 3 times).

2: R_f = 0.45 (silica gel, CH_2Cl_2:MeOH:AcOH, 50:1:0.5, 2 times); $[\alpha]_D^{26}$ = –240.0 (*c* = 1.25, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.40 (m, 2H), 5.30-5.10 (m, 2H), 4.03 (dd, *J* = 11.5, 3.4 Hz, 1H) 3.88 (m, 1H), 3.63 (t, *J* = 4.6 Hz, 1H), 3.34 (br, 1H), 3.05 (s, 3H),

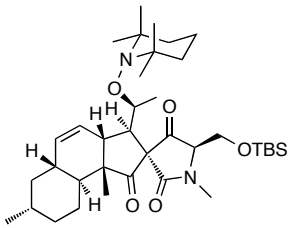
1.97 (m, 1H), 1.90-1.70 (m, 4H), 1.55 (d, J = 4.6 Hz, 3H), 1.60-1.40 (m, 3H), 1.17-1.00 (m, 3H), 0.92 (d, J = 6.9 Hz, 3H), 0.88 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 199.2, 190.6, 177.2, 131.0, 130.1, 127.1, 126,7, 100.0, 66.8, 60.5, 48.8, 45.1, 42.3, 40.0, 38.7, 35.8, 33.6, 28.3, 27.4, 22.5, 18.0, 14.0; HRMS (ESI) m/e 396.2141 [M+Na^+] calcd for $C_{22}H_{31}O_4NNa^+$: 396.2151.

C_3-*epi*-**2**: R_f = 0.5 (silica gel, CH_2Cl_2:MeOH:AcOH, 50:1:0.5, 2 times); $[\alpha]_D^{27}$ = –126.0 (*c* = 2.17, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.39 (m, 2H), 5.27-5.10 (m, 2H), 4.04 (m, 1H), 3.84 (dd, J = 4.6, 11.5 Hz, 1H), 3.66 (m, 1H), 3.34 (br, 1H), 3.04 (s, 3H), 1.95 (m, 1H), 1.85-1.70 (m, 4H), 1.52 (d, J = 5.5 Hz, 3H), 1.66-1.40 (m, 3H), 1.16-1.00 (m, 3H), 0.90 (d, J = 6.9 Hz, 3H), 0.87 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 199.1, 190.7, 177.1, 130.9, 130.0, 127.2, 126.7, 100.4, 66.4, 60.3, 48.9, 45.0, 42.4, 40.0, 38.6, 35.8, 33.6, 28.4, 27.3, 22.6, 18.0, 14.2; HRMS (ESI) m/e 396.2150 [M+Na^+] calcd for $C_{22}H_{31}O_4NNa^+$: 396.2151.



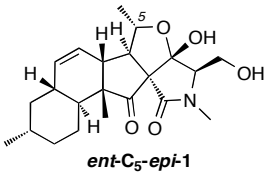
***ent*-12**

***ent*-12 (TBS-(+)-equisetin)**: To a solution of (+)-equisetin (*ent*-**2**, synthesized from (*S*)-(–)-citronellal, 37 mg, 0.1 mmol) in CH_2Cl_2 (1 ml) was added imidazole (13.6 mg, 0.2 mmol) and TBS-Cl (23 mg, 0.15 mmol). This reaction was stirred for 12 h before it was quenched with saturated NH_4Cl solution (5 ml). The mixture was extracted with CH_2Cl_2 (3 x 10 ml), dried over and concentrated. Purification *via* silica column chromatography (hexanes:EtOAc, 100:1 to 20:1) afforded *ent*-**12** as pale red oil (44 mg, 90%). R_f = 0.7 (silica gel, hexanes:EtOAc, 5:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.39 (m, 2H), 5.30-5.15 (m, 2H), 3.92 (m, 2H), 3.57 (m, 1H), 3.31 (br, 1H), 3.03 (s, 3H), 1.94 (m, 1H), 1.85-1.70 (m, 4H), 1.54 (d, J = 5.4 Hz, 3H), 1.42 (br s, 3H), 1.11 (m, 1H), 1.02 (m, 1H), 0.90 (d, J = 6.9 Hz, 3H), 0.86 (m, 1H), 0.81 (s, 9H), 0.02 (s, 3H), 0.00 (s, 3H); HRMS (ESI) m/e 510.3016 [M+Na^+] calcd for $C_{28}H_{45}NO_4SiNa^+$: 510.3010.



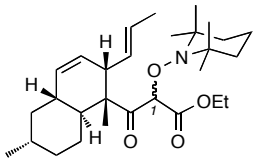
***ent*-14**

***ent*-14**: A solution in a sealed tube contains *ent*-**12** (24 mg, 50 μmol), TEMPO (23 mg, 0.15 mmol), ferrocenium hexafluorophosphate (**13**, 33 mg, 0.1 mmol) or Mn(III) acetate (27 mg, 0.1 mmol) in DMF (0.71 ml) was heated in a microwave at 100 °C for 10 min. The residue was directly purified via preparative TLC (hexanes:EtOAc, 20:1 x 2) to afford *ent*-**14** as a colorless oil (11 mg, 35%). R_f = 0.7 (silica gel, hexanes:EtOAc, 10:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.82 (ddd, *J* = 11.9, 5.0, 2.4 Hz, 1H), 5.52 (d, *J* = 12.5 Hz, 1H), 4.25 (m, 2H), 4.04 (m, 1H), 3.96 (m, 1H), 3.13 (s, 3H), 2.89 (t, *J* = 11.9 Hz, 1H), 2.43 (dd, *J* = 14.4, 6.3 Hz, 1H), 1.81-1.65 (m, 4H), 1.50 (m, 2H), 1.45 (d, *J* = 7.6 Hz, 3H), 1.38 (m, 6H), 1.07 (m, 1H), 1.02 (m, 1H), 1.00 (s, 6H), 0.97 (s, 3H), 0.94 (s, 3H), 0.91 (s, 9H), 0.90 (d, *J* = 6.9 Hz, 3H), 0.88 (s, 3H), 0.10 (s, 6H); HRMS (ESI) m/e 665.4318 [M+Na^+] calcd for $C_{37}H_{62}N_2O_5SiNa^+$: 665.4320.



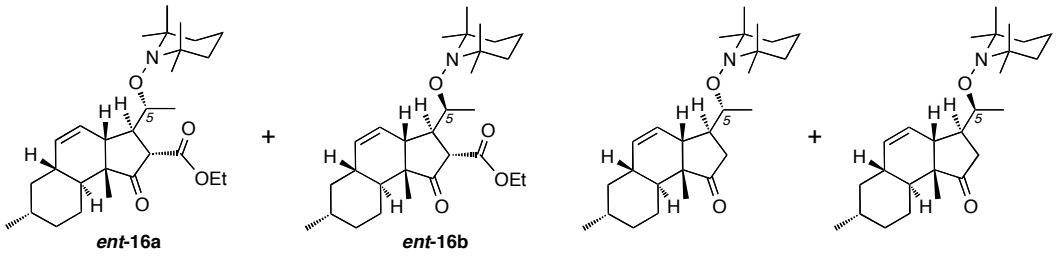
***ent*-C$_5$-*epi*-1**

***ent*-C$_5$-*epi*-1**: To a solution of *ent*-**14** (9.2 mg, 14.6 μmol) in THF (100 μl) and water (100 μl) was added acetic acid (300 μl) and activated zinc dust (95 mg, 1.46 mmol). The mixture was heated at 80 ºC for 3 hours and cooled to room temperature. To this mixture saturated solution of $NaHCO_3$ (1 ml) was slowly dropped in to neutralize the solution. The mixture was then diluted with ethyl acetate (100 ml), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified through preparative TLC (silica gel, hexanes:EtOAc, 1:1 x 5) to afford *ent*-C_5-*epi*-**1** as a white powder (1.7 mg, 30%). For the analytical data, see SI-20.



***ent*-15**

α-TEMPO-β-ketoester *ent*-15: To a solution of HMDS (0.57 ml, 2.70 mmol) in 1,2-dimethoxyethane (30 ml) at –78 ºC was added *n*-BuLi (1.6 ml, 2.60 mmol, 1.6 M in hexane) dropwise. The mixture was stirred at this temperature for 30 min. Then a solution of β-ketoester **4** (550 mg, 1.73 mmol) in 1,2-dimethoxyethane (30 ml) was added dropwise to the reaction mixture and the mixture was warmed up to –60 ºC and stirred for 30 min. The reaction was then raised to 0 ºC, TEMPO (283 mg, 1.80 mmol) was added in one portion, stirred for 5 min at this temperature, followed by addition of ferrocenium hexafluorophophate (850 mg, 2.6 mmol) in one portion. The dark blue mixture was stirred for 5 min at 0 ºC and quenched with 20 drops of saturated NH_4Cl solution. The reaction mixture was diluted with ether (120 ml) and filtered through a short silica pad. The filtrate was concentrated and purified through silica column chromatography (hexanes:EtOAc, 200:1 to 50:1) to yield α-TEMPO ester *ent*-**15** (785 mg, as an inseparable C-1 isomeric mixture, 99%) as a clear oil. R_f = 0.5 (silica gel, hexanes:EtOAc, 10:1); ^{1}H NMR (500 MHz, $CDCl_3$) (C-1 isomeric mixture, ca 3:1) δ: 5.42-5.25 (m, 3H), 5.25-5.10 (m, 2H), 4.28-4.07 (m, 2H), 2.56 and 2.47 (t, J = 5.9 Hz, 1H in total), 1.76-1.65 (m, 4H), 1.60 (d, J = 5.2 Hz, 1H), 1.58-1.53 (m, 5H), 1.40 (s, 3H), 1.38 (m, 1H), 1.31 (t, J = 7.4 Hz, 3H), 1.30-1.25 (m, 2H), 1.22 and 1.20 (s, 3H in total), 1.17 (s, 3H), 1.16-1.05 (m, 3H), 1.00 (s, 3H), 0.97 (s, 3H), 0.88 (d, J = 6.4 Hz, 3H), 0.84-0.80 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) (C-1 isomeric mixture) δ: 204.1, 203.7* (minor isomer), 167.4, 167.2*, 131.1*, 130.5, 130.1, 130.0*, 127.3*, 126.9, 126.4, 125.8*, 91.1, 89.8*, 61.3, 61.2*, 60.8, 59.7*, 59.6, 53.7, 53.4*, 49.2*, 48.2, 41.7, 40.8*, 40.4, 40.4*, 40.2, 40.2, 38.9*, 38.4, 38.2*, 35.6, 35.5*, 33.8*, 33.3*, 33.3, 33.1, 33.1, 32.9*, 26.9, 22.5, 20.5, 20.3, 18.6*, 18.2, 17.9*, 17.1, 16.4, 15.3*, 14.1, 14.0*; HRMS (ESI) m/e 474.3577 [M+H$^+$] calcd for $C_{29}H_{48}NO_4^+$: 474.3578.

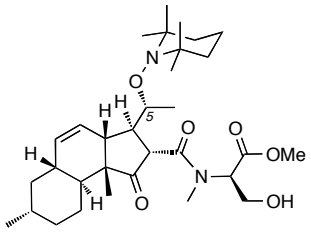


***ent*-16a, *ent*-16b and *ent*-17a+*ent*-17b:** A solution of *ent*-**15** (47 mg, 0.1 mmol) in toluene (1 ml) was heated at 90 °C for 3 h. The reaction was concentrated and purified via column chromatography (hexanes:EtOAc, 200:1 to 50:1) to yield the cyclized ester *ent*-**16a** (21 mg, 45%) and *ent*-**16b** (21 mg, 45%) along with the decarboxylated product *ent*-**17a**/*ent*-**17b** (inseparable C_5 isomeric mixtures, ca 1:1, 2 mg, 5%) all as clear oil.

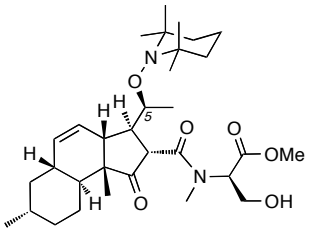
ent-**16a**: R_f = 0.68 (more polar, silica gel, hexanes:EtOAc, 10:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 5.80 (ddd, *J* = 10.4, 7.5, 2.9 Hz, 1H), 5.51 (d, *J* = 10.4 Hz, 1H), 4.17 (m, 3H), 3.23 (d, *J* = 10.3 Hz, 1H), 2.84 (td, *J* = 10.9, 4.6 Hz, 1H), 2.08 (dd, *J* = 11.5, 4.6 Hz, 1H), 1.83 (m, 2H), 1.72 (m, 1H), 1.52-1.39 (m, 8H), 1.29 (m, 2H), 1.26 (m, 7H), 1.13 (s, 3H), 1.11 (s, 3H), 1.10 (s, 3H), 0.98 (s, 3H), 0.96 (s, 3H), 0.90 (d, *J* = 6.3 Hz, 3H), 0.86 (m, 1H); HRMS (ESI) m/e 496.3394 [M+Na$^+$] calcd for $C_{29}H_{47}NO_4Na^+$: 496.3397.

ent-**16b**: R_f = 0.72 (less polar, silica gel, hexanes:EtOAc, 10:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 5.86 (ddd, *J* = 9.8, 6.5, 2.3 Hz, 1H), 5.52 (d, *J* = 9.8 Hz, 1H), 4.18 (m, 3H), 3.49 (d, *J* = 10.3 Hz, 1H), 2.60 (td, *J* = 10.3, 2.9 Hz, 1H), 2.46 (dd, *J* = 11.5, 5.2 Hz, 1H), 1.83 (m, 2H), 1.72 (m, 1H), 1.50-1.38 (m, 8H), 1.29 (m, 2H), 1.25 (m, 7H), 1.16 (s, 3H), 1.13 (s, 3H), 1.07 (s, 3H), 1.00 (s, 3H), 0.97 (s, 3H), 0.89 (d, *J* = 6.3 Hz, 3H), 0.84 (m, 1H); HRMS (ESI) m/e 496.3398 [M+Na$^+$] calcd for $C_{29}H_{47}NO_4Na^+$: 496.3397.

ent-**17a** and *ent*-**17b** (inseparable C_5 isomeric mixtures, ca 1:1): R_f = 0.8 (less polar, silica gel, hexanes:EtOAc, 10:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 5.95 (m, 1H), 5.87 (m, 1H), 5.49 (d, *J* = 10.3 Hz, 1H), 5.45 (d, *J* = 10.3 Hz, 1H), 4.19 (m, 1H), 4.02 (m, 1H), 2.54 (m, 2H), 2.49 (m, 2H), 2.21 (m, 1H), 2.15 (m, 1H), 2.09 (m, 2H), 1.82 (m, 4H), 1.75 (m, 2H), 1.50-1.35 (m, 12H), 1.30 (m, 6H), 1.24 (s, 3H), 1.23 (s, 3H), 1.22 (s, 3H), 1.21(s, 3H), 1.20 (s, 3H), 1.18 (s, 3H), 1.08 (m, 4H), 1.06 (s, 3H), 1.05 (m, 3H), 1.02 (s, 3H), 0.98 (m, 2H), 0.96 (s, 3H), 0.93 (s, 3H), 0.89 (d, *J* = 6.3 Hz, 3H), 0.88 (d, *J* = 6.3 Hz, 3H), 0.85 (m, 2H); HRMS (ESI) m/e 424.3188 [M+Na$^+$] calcd for $C_{26}H_{43}NO_2Na^+$: 424.3186.



19a

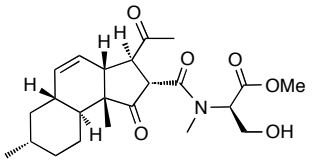


19b

Tricyclic β-ketoamide *ent*-19a and *ent*-19b: To a solution of **12** (20.0 mg, 42.2 μmol) in toluene (0.5 ml) was added 4-DMAP (10.3 mg, 84.4 μmol), freshly prepared amine **18** (28.1 mg, 0.21 mmol) and 4Å molecule seives (50 mg). The mixture was heated at 90˚C for 36 hours and then was allowed to cool to room temperature, concentrated and purified through preparative TLC (CH_2Cl_2:MeOH, 120:1 x 5) to yield tricyclic TEMPO adducts *ent*-**19a** (8.2 mg, 34%) and its C_5-epimer (*ent*-**19b**, 8.7 mg, 36%) as colorless oils.

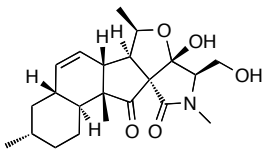
ent-**19a**: R_f = 0.2 (slightly less polar, silica gel, hexanes:EtOAc, 2:1); $[\alpha]_D^{23}$ = –59.2, (*c* = 0.1, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.87 (m, 1H), 5.48 (d, *J* = 10.3 Hz, 1H), 4.60 (t, *J* = 6.6 Hz, 1H), 4.13 (m, 2H), 3.77 (m, 1H), 3.72 (d, *J* = 11.5 Hz, 1H), 3.67 (s, 3H), 3.28 (s, 3H), 3.05 (td, *J* = 10.9 Hz, 4.6 Hz, 1H), 2.68 (t, *J* = 6.9 Hz, 1H), 2.23 (dd, *J* = 10.9 Hz, 4.6 Hz, 1H), 1.81-1.76 (m, 2H), 1.67-1.63 (m, 2H), 1.48-1.27 (m, 8H), 1.23 (s, 3H), 1.13 (br s, 6H), 1.10 (s, 3H), 1.04 (m, 1H), 1.01 (s, 3H), 0.95 (s, 3H), 0.87 (d, *J* = 6.3 Hz, 3H), 0.85-0.80 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 215.0, 170.9, 169.3, 131.9, 126.1, 78.6, 61.8, 61.1, 60.5, 59.0, 54.2, 52.8, 52.4, 48.8, 46.4, 41.6, 40.5, 40.2, 37.7, 36.8, 35.9, 35.3, 35.1, 34.8, 34.5, 29.9, 25.4, 22.8, 22.4, 21.2, 17.6, 15.3; HRMS (ESI) m/e 561.3896 [M+H$^+$] calcd for $C_{32}H_{53}N_2O_6^+$: 561.3898.

ent-**19b**: R_f = 0.2 (slightly more polar, silica gel, hexanes:EtOAc, 2:1); $[\alpha]_D^{23}$ = –39.8, (*c* = 0.42, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.86 (m, 1H), 5.51 (d, *J* = 9.8 Hz, 1H), 4.74 (t, *J* = 6.9 Hz, 1H), 4.25 (m, 1H), 4.11 (m, 1H), 4.04 (d, *J* = 9.7 Hz, 1H), 3.83 (m, 1H), 3.67 (s, 3H), 3.29 (s, 3H), 2.87 (td, *J* = 9.2 Hz, 2.3 Hz, 1H), 2.58 (m, 2H, overlapped with OH), 1.84-1.77 (m, 2H), 1.68-1.64 (m, 2H), 1.50-1.30 (m, 8H), 1.19 (s, 3H), 1.14 (br s, 6H), 1.07 (s, 3H), 1.04 (s, 3H), 1.02 (m, 1H), 0.98 (s, 3H), 0.86 (d, *J* = 6.9 Hz, 3H), 0.85-0.80 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 215.0, 170.8, 169.9, 132.5, 125.2, 74.6, 61.0, 60.5, 59.0, 52.4, 52.2, 52.1, 50.3, 45.0, 41.6, 40.6, 40.3, 37.5, 36.8, 35.3, 35.2, 34.7, 34.4, 33.0, 29.8, 25.2, 22.4, 20.9, 19.8, 17.3, 15.3, 14.2; HRMS (ESI) m/e 561.3895 [M+H$^+$] calcd for $C_{32}H_{53}N_2O_6^+$: 561.3898.



***ent*-20**

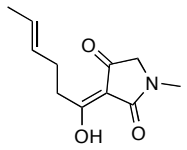
Tricyclic di-ketoamide *ent*-20: To a mixture of *ent*-**19a** and *ent*-**19b** (50 mg, 89 μmol) in CH_2Cl_2 (1 ml) at 0 °C was added a solution of 3-chloroperoxybenzoic acid (19 mg, 107 μmol) in CH_2Cl_2 (200 μl) dropwise. The reaction mixture was stirred for 15 min at the same temperature and then quenched with saturated $Na_2S_2O_3$ solution (0.5 ml) followed by adding saturated $NaHCO_3$ solution (0.5 ml). The mixture was vigorously stirred for 5 min at room temperature and was diluted with 200 ml of EtOAc, washed with NaOH solution (10%) and brine, dried over Na_2SO_4, filtrated and concentrated under reduced pressure. Purification of the crude product by silica column chromatography (hexane:ethyl acetate, 10:1 to 2:1) afforded ketone *ent*-**20** (35 mg, 95%) as a colorless oil. R_f = 0.3 (silica gel, hexanes:EtOAc, 1:1); $[\alpha]_D^{24}$ = –27.5, (*c* = 0.33, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.74 (m, 1 H), 5.60 (d, *J* = 10.3 Hz, 1 H), 4.90 (t, *J* = 5.9 Hz, 1 H), 4.10-4.05 (m, 2 H), 3.90-3.81 (m, 2 H), 3.70 (s, 3 H), 3.21 (s, 3 H), 2.37 (m, 1 H), 2.27 (s, 3 H), 1.86-1.81 (m, 2 H), 1.72-1.69 (m, 1H), 1.48-1.40 (m, 3H), 1.08 (m, 1 H), 0.98 (s, 3 H), 0.88 (d, *J* = 6.8 Hz, 3H), 0.85-0.80 (m, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 212.6, 209.5, 170.2, 168.7, 133.8, 123.7, 60.8, 60.5, 56.3, 55.7, 52.6, 52.1, 47.4, 41.6, 38.3, 37.0, 35.3, 34.7, 33.1, 32.0, 25.2, 22.4, 15.4; HRMS (ESI) m/e 420.2380 [M+H$^+$] calcd for $C_{23}H_{34}NO_6^+$: 420.2381.



(–)-fusarisetin A, ***ent*-1**

(–)-Fusarisetin A (*ent*-1): To a solution of tricyclic di-ketoamide *ent*-**20** (35 mg, 85 μmol) in MeOH (850 μl) was added $CeCl_3$•$7H_2O$ (48 mg, 128 μmol) and stirred at rt for 10 min. The reaction was then cooled to –20 °C and to this solution $NaBH_4$ (3.5 mg, 94 μmol) was added. This reaction was allowed to stir for 30 min at this temperature, then

saturated NH_4Cl solution (0.5 ml) was added in. The mixture was warmed up to room temperature and extracted with EtOAc (3 x 20 ml), the combined organic phase was washed with brine, dried over anhydrous $MgSO_4$ and concentrated in *vacuo*. The residue was purified by flash column chromatography (EtOAc:hexanes, 1:1 to 3:1) to give a ca. 4:1 mixture of tricyclic alcohols as a white foam. The obtained alcohol was dissolved in anhydrous MeOH (2 ml) and a solution of sodium methoxide (850 μl, 425 μmol, 0.5 M in MeOH) was dropped in at 0 ºC. This reaction was allowed to warm up to room temperature and stirred for 10 min and quenched by saturated NH_4Cl solution (1 ml). The mixture was then diluted with ethyl acetate (200 ml), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified through preparative TLC (EtOAc:hexanes, 1:1 x 5) to afford (–)-fusarisetin A (*ent*-**1**) as a white foam (11.2 mg, 34% from *ent*-**20**) and its C_5-epimer (*ent*-C_5-*epi*-**1**, 2.8 mg, 8%). *ent*-**1**: $[\alpha]_D^{23} = -86.3$, c = 0.065, MeOH; natural: $[\alpha]_D^{23} = +84.6$, c = 0.2, MeOH). Other analytical data are identical with the synthetic (+)-fusarisetin A, see page SI-19.

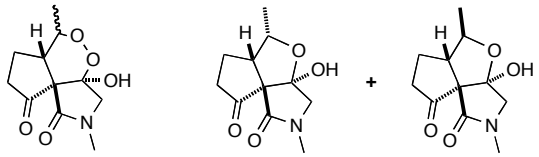


24

Synthesis of tetramic acid 24:

To a suspension of sodium hydride (6.05 g, 60% in mineral oil, 151 mmol) in THF (500 ml) was added ethyl acetoacetate **21** (17.55 ml, 137 mmol) dropwise at 0 °C and stirred for 10 min. Then *n*-BuLi (99.5 ml, 1.45 M in hexanes, 144 mmol) was added in dropwise at the same temperature. Upon completion of addition, this solution was stirred for another 10 min. Then a solution of crotyl bromide (15.1 ml, 147.6 mmol) in THF (200 ml) was slowly dropped into the previous solution over 15 min. The reaction was then allowed to warm up to rt and stirred for 2 hrs before it was quenched carefully with conc. HCl/H_2O (20 ml/200 ml). The mixture was extracted with ether (3 x 500 ml), and the combined organic phase was washed with water until the solution become neutral. Silica column chromatography (hexanes:EtOAc, 200:1 to 10:1) afforded the corresponding ketoester **22** (23.3 g, 92%). The ketoester **22** (7.5 g, 40.7 mmol), *N*-methyl glycine

methyl ester hydrochloride (11.3 g, 81.4 mmol), 4-DMAP (9.95 g, 81.4 mmol) and Et_3N (17.0 ml, 122.1 mmol) was refluxed in toluene (80 ml) for 12 hrs. The reaction was then cooled down and absorbed with silica gel. Following silica column chromatography (CH_2Cl_2:MeOH, 200:1 to 20:1) afforded the corresponding ketoamide **23** (4.9 g, 50%). The obtained ketoamide **7** (1.7 g, 7.0 mmol) was then dissolved in MeOH (210 ml) and the sodium methoxide solution (14 ml, 0.5 M in methanol) was added in. The reaction was stirred at rt for 2 hrs before it was quenched with 1N HCl (300 ml). The mixture was diluted with water (500 ml) and CH_2Cl_2 (500 ml) and separated, the aqueous layer was further extracted with CH_2Cl_2 (500 ml x 5). The combined organic phase was dried over $MgSO_4$ and concentrated in *vacuo* to yield the tetramic acid **24** as a dark red oil (1.43 g, 97%). R_f = 0.3 (CH_2Cl_2:MeOH, 20:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 5.50-5.35 (m, 2H), 3.68 (s, 2H), 2.98 (s, 3H), 2.83 (t, J = 7.4 Hz, 2H), 2.30 (m, 2H), 1.59 (d, J = 5.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 191.4, 186.8, 173.5, 128.8, 126.6, 101.8, 57.7, 32.8, 28.7, 28.5, 17.9; HRMS (ESI) m/e 208.0979 [M–H$^-$] calcd for $C_{11}H_{14}O_3N^-$: 208.0980.



25 **26a** **26b**

Oxidative radical cyclization (ORC) of 24 using CAN and molecular oxygen:

A solution of tetramic acid **24** (20.9 mg, 0.1 mmol) and ceric ammonium nitrate (CAN, 54.8 mg, 0.1 mmol) in acetic acid (0.5 ml) was stirred under oxygen atmosphere (1 atm) for 3 hrs. The reaction mixture was then diluted with CH_2Cl_2 (5 ml), passed through a short silica pad, washed with CH_2Cl_2/MeOH (20:1, 20 ml) and concentrated in *vacuo*. An analytical sample of **25a** and **25b** could be isolated as an inseparable C_5 diastereomeric mixture via preparative TLC (CH_2Cl_2:MeOH:AcOH, 30:1:0.15, 2 times, analytical data see below). The crude residue above was dissolved in anhydrous MeCN (0.5 ml), followed by the addition of CuCl (99 mg, 1 mmol). This reaction was stirred at rt for 2 hr, and was then concentrated in *vacuo* and purified via preparative TLC (CH_2Cl_2:MeOH: AcOH, 30:1:0.1, 3 times) to afford the tricyclic compound **26a** (5.1 mg, 32%) and **26b** (3.9 mg, 25%).

25a+25b (ca 2:1, as inseparable mixture): R_f = 0.25 (CH_2Cl_2:MeOH:AcOH, 50:1:0.5, 2 times); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 4.43 (**25a**, major, qd, *J* = 6.9, 2.9 Hz, 1H), 4.11* (**25b**, minor, qd, *J* = 6.9, 1.2 Hz, 1H), 3.71 (d, *J* = 10.9 Hz, 1H), 3.69* (d, *J* = 10.9 Hz, 1H), 3.18* (d, *J* = 10.9 Hz, 1H), 3.07 (d, *J* = 10.9 Hz, 1H), 2.94* (s, 3H), 2.92 (s, 3H), 2.80 (ddd, *J* = 9.7, 6.9, 2.9 Hz, 1H), 2.73* (ddd, *J* = 9.7, 6.9, 1.2 Hz, 1H), 2.57* (m, 1H), 2.53 (m, 1H), 2.37 and 2.37* (overlapped, 2H), 2.22 (m, 1H), 2.13* (m, 2H), 2.07 (m, 1H), 1.37* (d, *J* = 6.9 Hz, 3H), 1.20 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 211.9* (**25b**, minor), 211.5 (**25a**, major), 170.4*, 169.5, 101.0, 100.9*, 77.6*, 75.1, 62.3, 59.3*, 56.3*, 55.9, 39.0, 38.3*, 29.9, 29.8*, 25.1, 22.8*, 19.7, 18.5*, 14.8, 14.2*; HRMS (ESI) m/e 240.0873 [M–H$^-$] calcd for $C_{11}H_{14}O_5N^-$: 240.0877.

26a : R_f = 0.2 (slighly less polar than **26b**, CH_2Cl_2:MeOH:AcOH, 50:1:0.5, 2 times); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 4.35 (qd, *J* = 6.3, 6.3 Hz, 1H), 3.58 (d, *J* = 9.8 Hz, 1H), 3.50 (d, *J* = 10.3 Hz, 1H), 2.91 (s, 3H), 2.91 (m, 1H), 2.54 (m, 2H), 2.27 (m 1H), 1.80 (m, 1H), 1.33 (d, *J* = 5.8 Hz, 3H); ^{13}C NMR (200 MHz, $CDCl_3$) δ: 210.9, 170.2 107.5, 84.0, 73.5, 59.5, 53.3, 39.8, 32.1, 20.0, 14.3; HRMS (ESI) m/e 248.0894 [M+Na$^+$] calcd for $C_{11}H_{15}NO_4Na^+$: 248.0893.

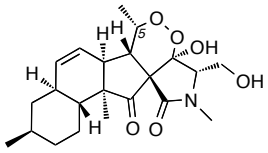
26b: R_f = 0.2 (slighly more polar than **26a**, CH_2Cl_2:MeOH:AcOH, 50:1:0.5, 2 times); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 4.31 (qd, *J* = 5.5, 5.5 Hz, 1H), 3.62 (d, *J* = 10.9 Hz, 1H), 3.51 (d, *J* = 10.3 Hz, 1H), 3.17 (m, 1H), 2.91 (s, 3H), 2.49 (m, 2H), 2.03 (m, 2H), 1.36 (d, *J* = 6.3 Hz, 3H) ^{13}C NMR (125 MHz, $CDCl_3$) δ: 211.0, 169.6, 107.5, 78.8, 73.7, 60.9, 49.9, 40.5, 29.8, 20.3, 16.0; HRMS (ESI) m/e 248.0892 [M+Na$^+$] calcd for $C_{11}H_{15}NO_4Na^+$: 248.0893.

Table 1. Studies of the oxidative radical cyclization (ORC) of 24

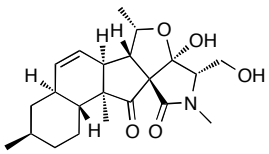
Oxidant	Equiv.	Solvent	Temp.	O_2	Time	Yield of 25	Reductant	Yield of 26
$Co(OAc)_2$	1.0	AcOH	70 °C	1 bar	5 min	20%	CuCl	80%
$Co(OAc)_2$	1.0	AcOH	70 °C	1 bar	5 min	20%	thiourea	n.r.
$Co(OAc)_2$	1.0	AcOH	25 °C	1 bar	4 h	10%	CuCl	79%
$Co(OAc)_2$	1.0	*i*-PrOH	25 °C	1 bar	12 h	n.r.	-	-

$Co(OAc)_2$	1.0	*i*-PrOH	50 °C	1 bar	12 h	decomp.	-	-
$CoCl_2$	1.0	AcOH	25 °C	1 bar	12 h	n.r.	-	-
$CeCl_3$	1.0	AcOH	25 °C	1 bar	12 h	trace	-	-
$CeSO_4$	1.0	AcOH	25 °C	1 bar	12 h	n.r.	-	-
$Mn(OAc)_3$	1.0	AcOH	25 °C	1 bar	12 h	5%	-	-
MnO_2	1.0	AcOH	25 °C	1 bar	12 h	n.r.	-	-
$Mn(OAc)_2$ (0.2 eq) $Co(OAc)_2$ (0.1 eq)	1.0	AcOH	25 °C	1 bar	12 h	7%	-	-
$CrCl_2$	1.0	AcOH	25 °C	1 bar	12 h	trace	-	-
$BiO(NO)_3$	1.0	AcOH	25 °C	1 bar	12 h	n.r.	-	-
VCl_3	1.0	AcOH	25 °C	1 bar	12 h	trace	-	-
$V(acac)_3$	1.0	AcOH	25 °C	1 bar	12 h	n.r.	-	-
$PhI(OAc)_2$	1.0	AcOH	25 °C	1 bar	12 h	trace	-	-
$CuCl_2$	1.0	AcOH	25 °C	1 bar	12 h	trace	-	-
PbO_2	1.0	AcOH	25 °C	1 bar	12 h	trace	-	-
$Pb(NO_3)_2$	1.0	AcOH	25 °C	1 bar	12 h	n.r.	-	-
$Pd(OAc)_2$	1.0	AcOH	25 °C	1 bar	12 h	trace	-	-
$Pd(OAc)_2$/BQ	0.1	AcOH	25 °C	1 bar	12 h	n.r.	-	-
$InCl_3$	1.0	AcOH	25 °C	1 bar	12 h	n.r.	-	-
$[Fe(C_5H_5)_2]PF_6$	1.0	AcOH	25 °C	1 bar	12 h	15%	CuCl	81%
$Fe(acac)_3$	1.0	AcOH	25 °C	1 bar	12 h	n.r.	-	-
Fe(*S*,*S*-PDP)	1.0	AcOH	25 °C	1 bar	12 h	n.r.	-	-
AgO	1.0	AcOH	25 °C	1 bar	12 h	n.r.	-	-
$AgNO_3$	1.0	AcOH	25 °C	1 bar	12 h	n.r.	-	-

CAN	1.0	AcOH	25 °C	1 bar	3 h	57%	CuCl	82%
CAN	1.0	MeCN	25 °C	1 bar	3 h	56%	CuCl	80%
CAN	1.0	AcOH	–20 °C	1 bar	18 h	57%	CuCl	79%
CAN	1.0	AcOH	70 °C	1 bar	5 min	20%	-	-
CAN	0.1	AcOH	25 °C	1 bar	6 h	40%	CuCl	80%
CAN	1.0	AcOH	70 °C	air	1 h	30%	CuCl	81%



peroxy-fusarisetin A, **27** (dr = 1.3 : 1)



(+)-fusarisetin A, **1**

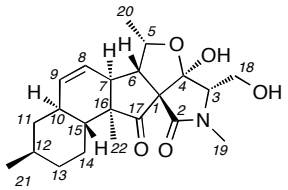
Peroxy-fusarisetin A (27) and (+)-Fusarisetin A (1): A solution of crude equisetin (**2**, 1.1 g, ~50% purity, 2.95 mmol) in acetic acid (14 ml) was degassed with an oxygen balloon for 5 minutes, ceric ammonium nitrate (CAN, 1.62 g, 2.95 mmol) was added in and this reaction was stirred at rt under oxygen atmosphere (1 atm, balloon) for 3 hrs. The reaction was diluted with CH_2Cl_2 (200 ml), passed through a short silica pad, washed with CH_2Cl_2/MeOH (20:1, 500 ml) and concentrated in *vacuo*. Analytical amount of peroxy-fusarisetin A (**27**) and C_5-*epi*-peroxy-fusarisetin A (C_5-*epi*-**27**) can be isolated as an inseparable mixture via preparative TLC (hexanes:EtOAc, 1:1 x 3, analytical data see below). The residue obtained above was then dissolved in anhydrous MeOH (30 ml), followed by the addition of thiourea (2.2 g, 29.5 mmol). This reaction was refluxed for 1 hr, and then was allowed to cool to rt and was concentrated in *vacuo*. The crude product was purified via silica column chromatography (slow gradient, hexanes:EtOAc, 50:1 to 1:1) to afford (+)-fusarisetin A (**1**, 201 mg, 35%) as white foam and C_5-*epi*-(+)-fusarisetin A (C_5-*epi*-**1**, 155 mg, 27%, contaminated with ca 15% minor isomers, analytical sample of C_5-*epi*-**1** was purified via preparative TLC (hexanes:EtOAc, 3:1 x 8) as a white foam.

27 and C_5-*epi*-**27** (dr = 1.3 : 1, inseparable mixture): an analytical sample of 0.7:1 mixture of **27** and C_5-*epi*-**27** was used for characterization; R_f = 0.25 (silica gel, hexanes:EtOAc, 1:2); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 5.82* (**27**, minor, m, 1H), 5.77 (C_5-

epi-**27**, major, m, 1H), 5.59 (d, *J* = 9.8 Hz, 1H), 5.57* (d, *J* = 10.4 Hz, 1H), 4.47* (qd, *J* = 4.6, 2.3 Hz, 1H), 4.31 (qd, *J* = 6.9, 0.6 Hz, 1H), 4.27* (dd, *J* = 10.3, 9.2 Hz, 1H), 4.20 (dd, *J* = 10.9, 9.2 Hz, 1H), 3.99 and 3.99* (m, 2H, overlapped), 3.26 (dd, *J* = 9.2, 3.4 Hz, 1H), 3.15* (dd, *J* = 9.2, 3.5 Hz, 1H), 2.97 (s, 3H), 2.95* (s, 3H), 2.75 and 2.75* (m, 2H, overlapped), 2.66* (dd, *J* = 12.1, 4.6 Hz, 1H), 2.49 (d, *J* = 12.0 Hz, 1H), 1.88-1.79 (m, 4H, overlapped), 1.70-1.40 (m, 6H, overlapped), 1.37 (d, *J* = 6.9 Hz, 3H), 1.35* (d, *J* = 6.9 Hz, 3H), 1.10 (m, 2H, overlapped), 1.02 and 1.02* (d, *J* = 5.2 Hz, 6H, overlapped), 0.90 (m, 2H, overlapped), 0.90 (m, 2H, overlapped), 0.88 (d, *J* = 6.3 Hz, 6H), 0.83 (m, 2H, overlapped); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 213.9, 213.4*, 169.6, 168.7*, 133.7, 133.3*, 126.1*, 123.6, 102.3*, 101.8, 76.0*, 74.6, 65.7, 65.5*, 63.7, 61.1*, 60.4*, 59.5, 52.4*, 51.3, 46.3, 44.7*, 44.1, 43.5*, 41.7, 41.6*, 38.3*, 38.2, 37.0*, 37.0, 35.3*, 35.3, 32.9, 32.9*, 29.3*, 29.2, 25.1*, 25.0, 22.4, 19.1*, 17.2*, 15.1, 14.7, 14.2*; HRMS (ESI) m/e 428.2047 [M+Na$^+$] calcd for $C_{22}H_{31}NO_6Na^+$: 428.2044.

1: R_f = 0.2 (silica gel, hexanes:EtOAc, 1:2); $[\alpha]_D^{25}$ = +85.3, *c* = 0.2, MeOH; natural: $[\alpha]_D^{23}$ = +84.6, *c* = 0.2, MeOH); ^{1}H NMR (500 MHz, CD_3OD) δ 5.80 (ddd, *J* = 10.1, 4.8, 2.6 Hz, 1H), 5.55 (d, *J* = 10.1 Hz, 1H), 4.34 (q, *J* = 6.4 Hz, 1H), 3.86 (dd, *J* = 12.0, 5.6 Hz, 1H), 3.82 (dd, *J* = 12.0, 5.6 Hz, 1H), 3.57 (t, *J* = 5.2 Hz, 1H), 2.95 (s, 3H), 2.85 (dd, *J* = 11.2, 5.8 Hz, 1H), 2.66 (dd, *J* = 11.2, 4.9 Hz, 1H), 1.89 (m, 2H), 1.75 (br d, *J* = 12.7 Hz, 1H), 1.56-1.48 (m, 3H), 1.44 (d, *J* = 6.5 Hz, 3H), 1.10 (qd, *J* = 12.2, 3.2 Hz, 1H), 0.99 (m, 1H), 0.96 (s, 3H), 0.91 (d, *J* = 6.6 Hz, 3H), 0.83 (q, *J* = 12.5 Hz, 1H); ^{13}C NMR (125 MHz, CD_3OD): δ 214.0, 171.9, 133.5, 126.8, 109.5, 79.5, 76.3, 71.6, 61.7, 56.3, 55.2, 44.5, 43.2, 38.9, 37.9, 36.4, 34.2, 29.8, 26.4, 22.8, 17.7, 14.3; HRMS (ESI) m/e 412.2092 [M+Na$^+$] calcd for $C_{22}H_{31}NO_5Na^+$: 412.2094.

C_5-*epi*-**1**: R_f = 0.25 (silica gel, hexanes:EtOAc, 1:2); $[\alpha]_D^{22}$ = +51.2 (*c* = 0.15, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 5.72 (m, 1H), 5.52 (d, *J* = 10.4 Hz, 1H), 4.56 (qd, *J* = 6.3, 3.5 Hz, 1H), 3.97 (m, 2H), 3.52 (dd, *J* = 6.9, 2.9 Hz, 1H), 2.92 (s, 3H), 2.73 (dd, *J* = 10.3, 4.0 Hz, 1H), 2.37 (dd, *J* = 9.8, 4.6 Hz, 1H), 1.89-1.78 (m, 2H), 1.75-1.65 (m, 2H), 1.49-1.30 (m, 2H), 1.26 (d, *J* = 6.4 Hz, 3H), 1.05 (m, 2H), 0.96 (s, 3H), 0.89 (d, *J* = 6.3 Hz, 3H), 0.85 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 213.1, 169.9, 132.5, 124.6, 109.3, 83.7, 74.8, 67.4, 59.2, 57.7, 55.4, 50.3, 41.7, 36.8, 36.5, 35.2, 33.0, 29.1, 25.4, 22.5, 22.4, 14.2; HRMS (ESI) m/e 412.2093 [M+Na$^+$] calcd for $C_{22}H_{31}O_5NNa^+$: 412.2094.



1: (+)-fusarisetin A

Table 1. ^{1}H NMR and ^{13}C NMR datum comparison of synthetic 1 with natural (+)-fusarisetin A (data from ref. 13). Errors are due to different NMR reference value.

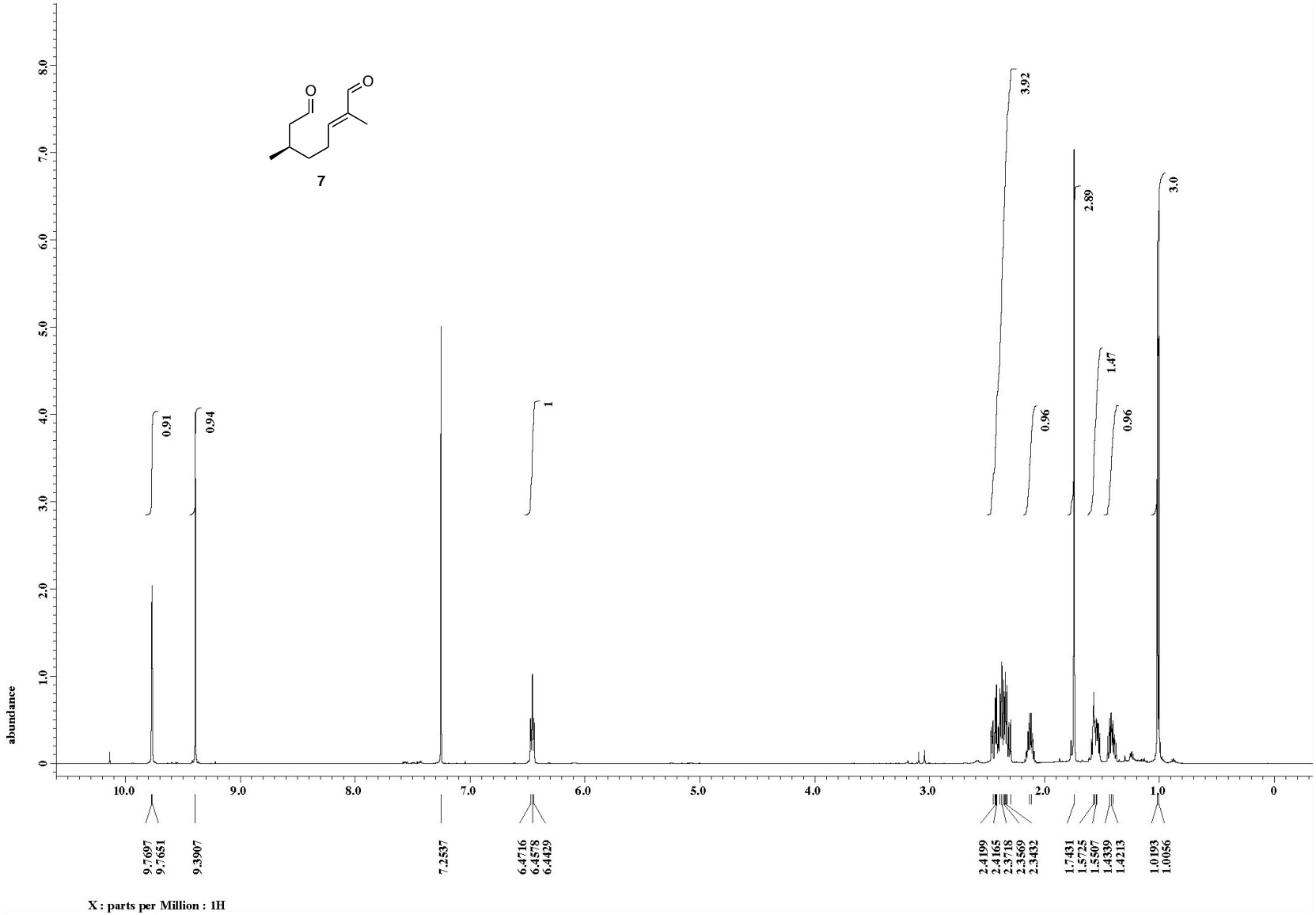
Position	δ ^{1}H (natural) (CD_3OD)	δ ^{1}H (synthetic) (CD_3OD)	Δ	δ ^{13}C (natural)	δ ^{13}C (synthetic)	Δ
1				75.3	76.3	1.0
2				170.9	171.9	1.0
3	3.60, dd, 5.0, 2.5	3.57, t, 5.2	0.03	70.5	71.6	1.1
4				108.5	109.5	1.0
5	4.37, q, 6.3	4.34, q, 6.4	0.03	78.5	79.5	1.0
6	2.87, dd, 11.0, 5.8	2.85, dd, 11.2, 5.8	0.02	54.2	55.2	1.0
7	2.69, dd, 11.0, 4.8	2.66, dd, 11.2, 4.9	0.03	43.5	44.5	1.0
8	5.83, ddd, 2.5, 4.8, 10.0	5.80, ddd, 2.6, 4.8, 10.1	0.03	125.7	126.8	1.1
9	5.58, d, 10.0	5.55, d, 10.1	0.03	132.5	133.5	1.0
10	1.90, m	1.89, m	0.01	36.8	37.9	1.2
11	1.87, m; 0.85, q, 12.8	1.86, m; 0.83, q, 12.5	0.01 0.02	42.1	43.2	1.1
12	1.51, m	1.48, m	0.03	33.1	34.2	1.1
13	1.76, br d, 12.8; 0.99, m	1.75, br d, 12.7 0.99, m	0.01 0.00	35.3	36.4	1.1
14	1.56, m; 1.13, ddd, 12.8, 9.6, 3.2	1.54, m 1.10, qd, 12.2, 3.2	0.02 0.02	25.4	26.4	1.0
15	1.53, m	1.52, m	0.01	37.9	38.9	1.0
16				55.2	56.3	1.1
17				212.9	214.0	1.1
18	3.89, dd, 12.0, 5.0 3.84, dd, 12.0, 5.0	3.86, dd, 12.0, 5.6 3.82, dd, 12.0, 5.6	0.03 0.02	60.6	61.7	1.1
19	2.97, s	2.95, s	0.02	28.8	29.8	1.0
20	1.47, d, 6.5	1.44, d, 6.5	0.03	16.6	17.7	1.1
21	0.94, d, 6.5	0.91, d, 6.6	0.03	21.7	22.8	1.1
22	0.98, s	0.96, s	0.02	13.2	14.3	1.1

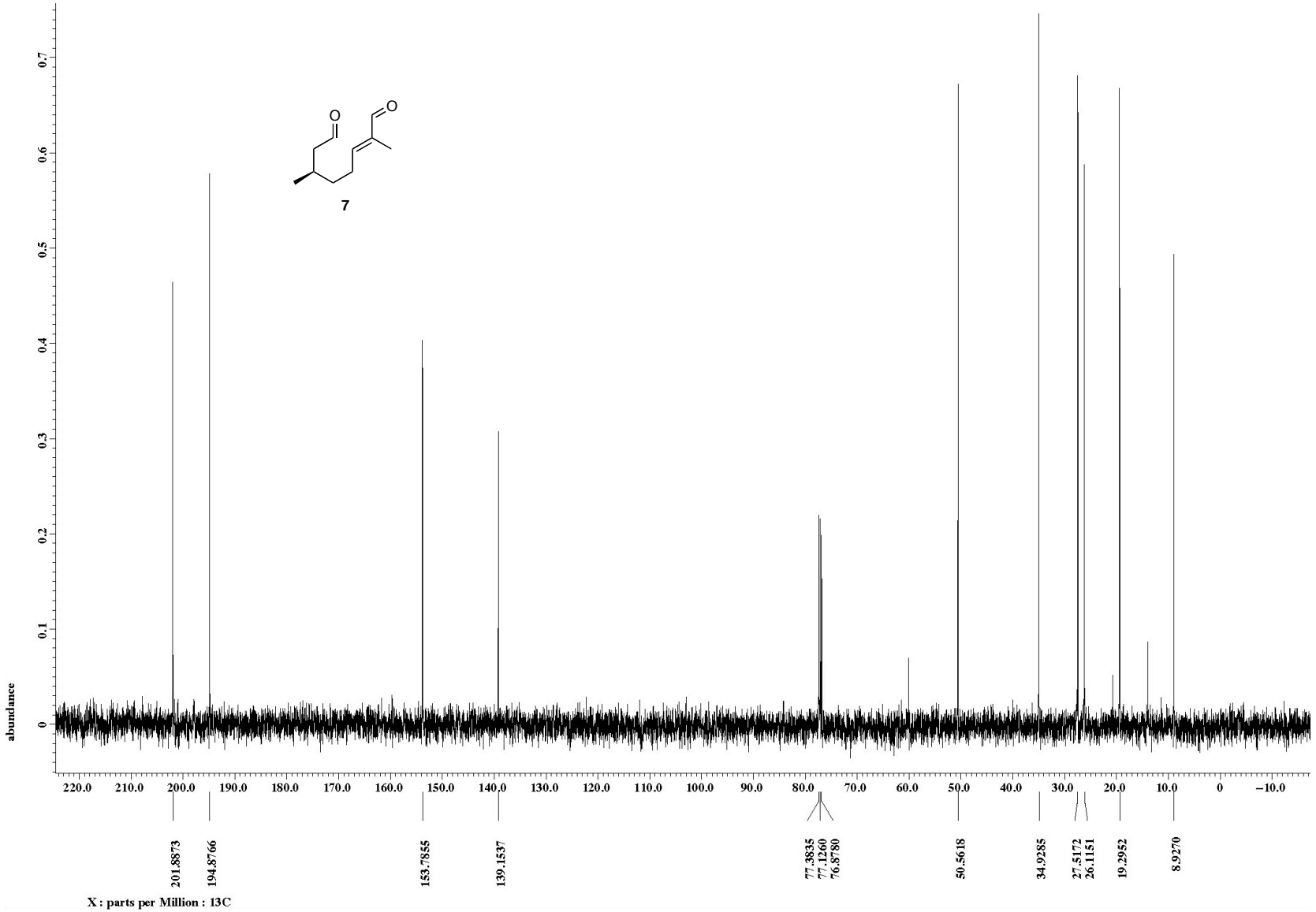
Biological Experiments

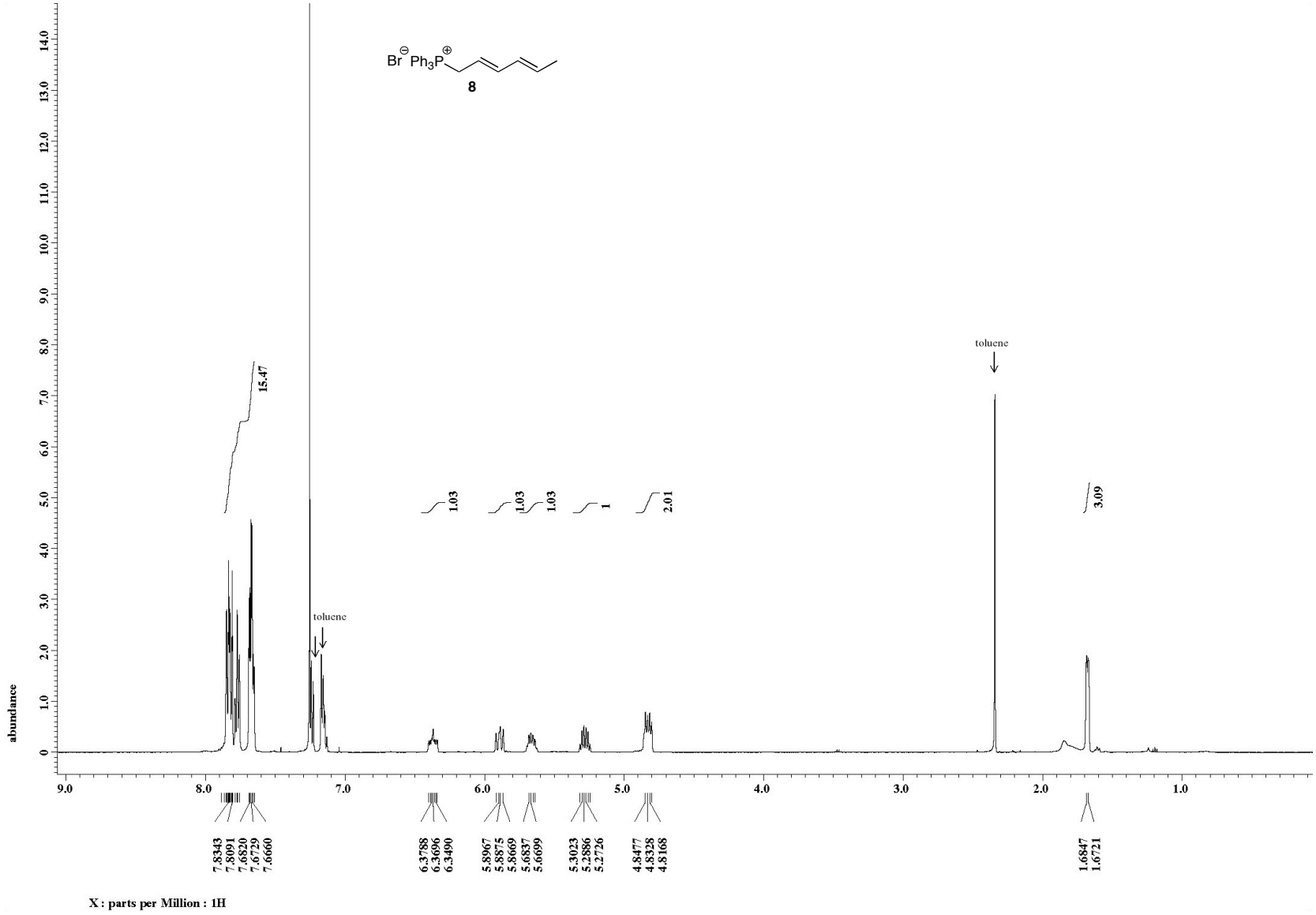
Scratch wound assay: MDA-MB-231 cells (5 x10^5 cells/24-well plate) were plated in dishes, and after 24 h of incubation at 37 °C in 5% CO_2 in Dulbecco's Modified Eagle's Medium (DMEM) containing 10% fetal bovine serum (FBS), the confluent monolayer of cells was scratched with a pipette tip twice (in the shape of a cross, forming 4 quarter-circle quadrants) to create a cell-free zone in each well. The medium was aspirated and each well washed with 10% Phosphate-buffered Saline (PBS) solution to remove any detached cells. The PBS was aspirated and replaced with fresh DMEM medium (500 μL) in the presence or absence of appropriate concentrations compound. The scratch-wounds (cell-free zones) were photographed (4 pictures per well; top, bottom, right and left) under a microscope (10x magnification). After 48 h, migrated cells were photographed (4 pictures per well; top, bottom, right and left) under a microscope (10x magnification). Values are the means ± SD for quadruplicate (n = 4) samples of the ratio (original wound area/area occupied by migrated cells) standardized to DMSO controls for each concentration.

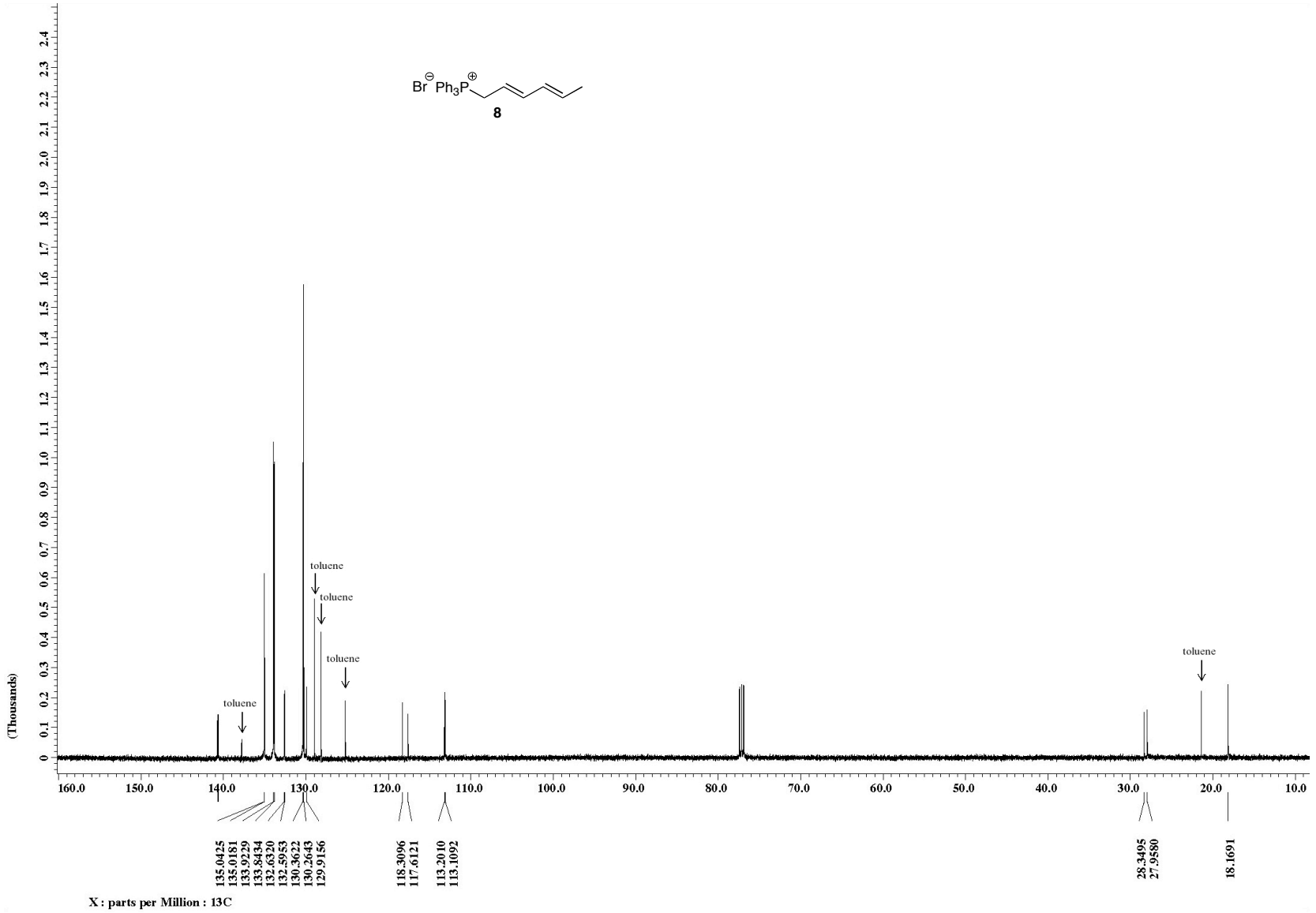
Boyden-Chamber Transwell assay: Transwell cell migration assays were carried out using Transwell membrane filter inserts (BioExpress Transwell PC well insert, 6.5mm diameter) in a 24-well tissue-culture plate. The Transwell filter has 8 μm pore-size membranes. MDA-MB-231 cells (5x10^5 cells/well) suspended in serum free DMEM medium with diverse concentrations of fusarisetin A were added to the upper chambers, and DMEM medium containing 10% FBS was placed in the lower well, then incubated for 24 h at 37 °C in 5% CO_2. Non-invading cells on the upper surface of the membrane were removed by wiping them out with a cotton swab, and migrated cells on the lower surface were fixed with 4% formaldehyde solution and stained with Crystal Violet staining solution. The number of invaded cells per membrane was counted under a light microscope at 10x magnification. Values are the means ± SD for triplicate samples as a ratio of migrated cells with (+)-**1** : migrated with corresponding concentration of DMSO.

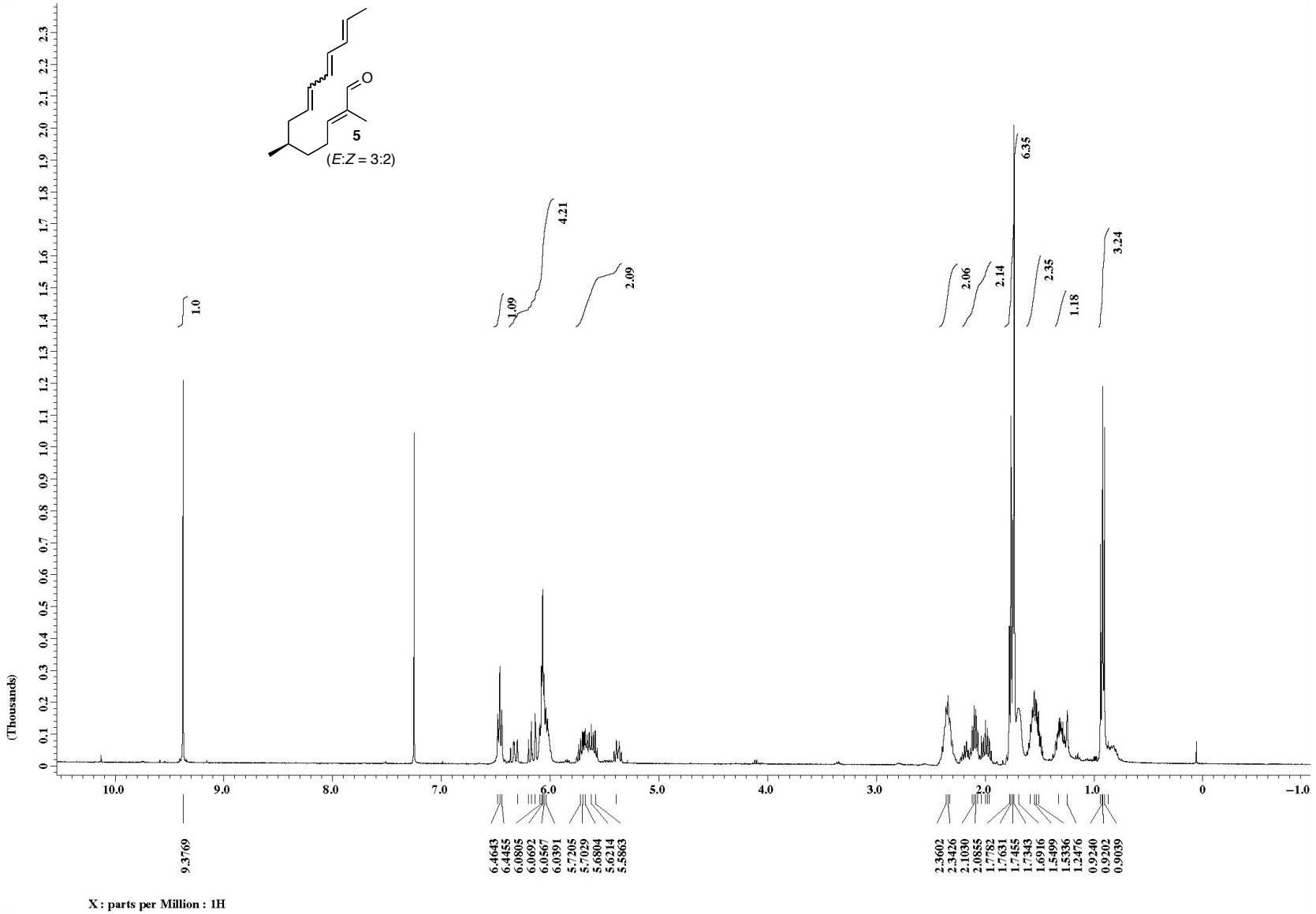
***ex-vivo* Mice skin assay**: Mice skin explants (5mm) were plated in a tissue culture dish and incubated (37°C at 5% CO_2 atmosphere) with DMEM growth media containing 10 μg/ml of (+)-**1** or corresponding amount of DMSO. After 5 days of incubation the explants were photographed under a microscope (10x).

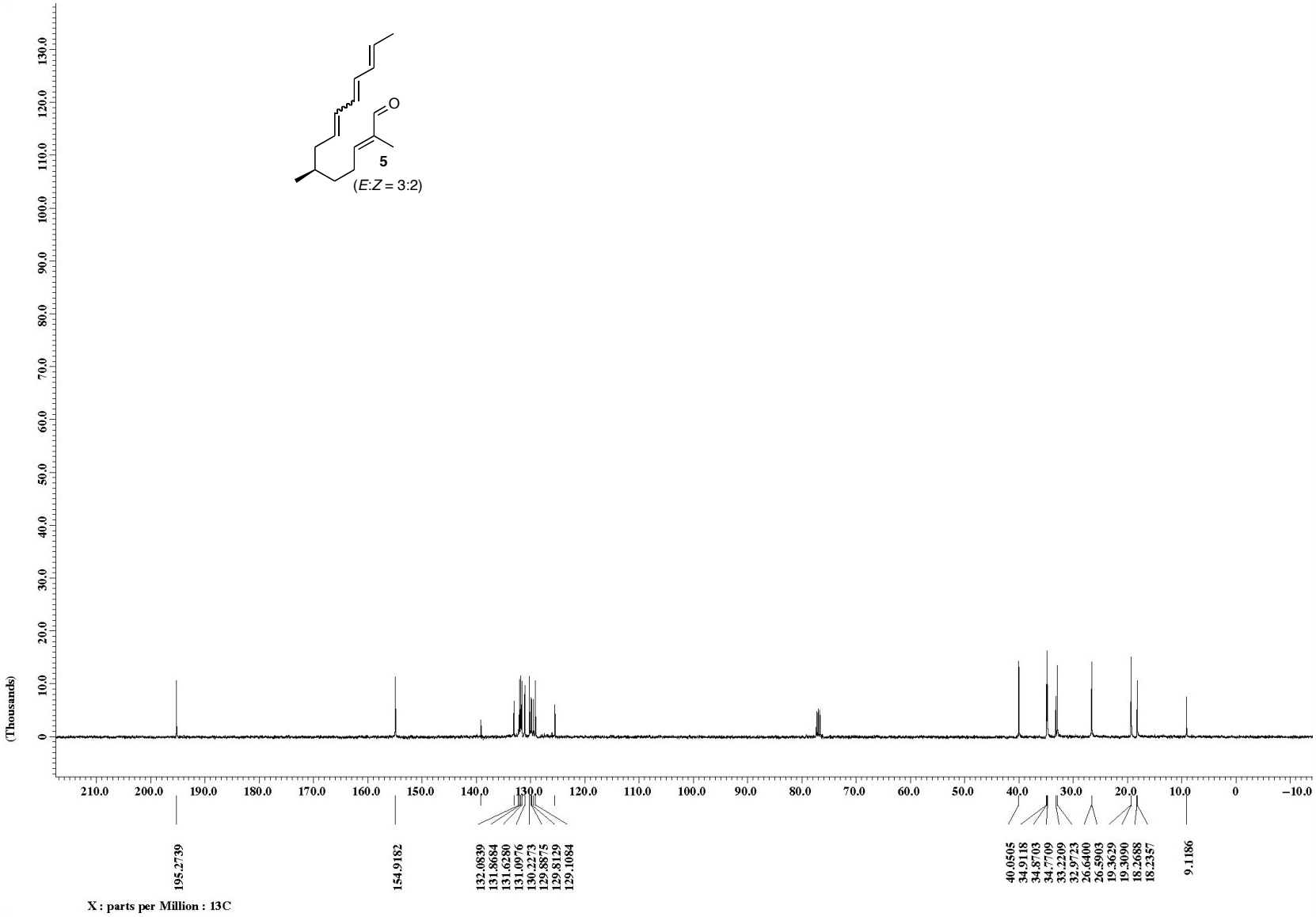


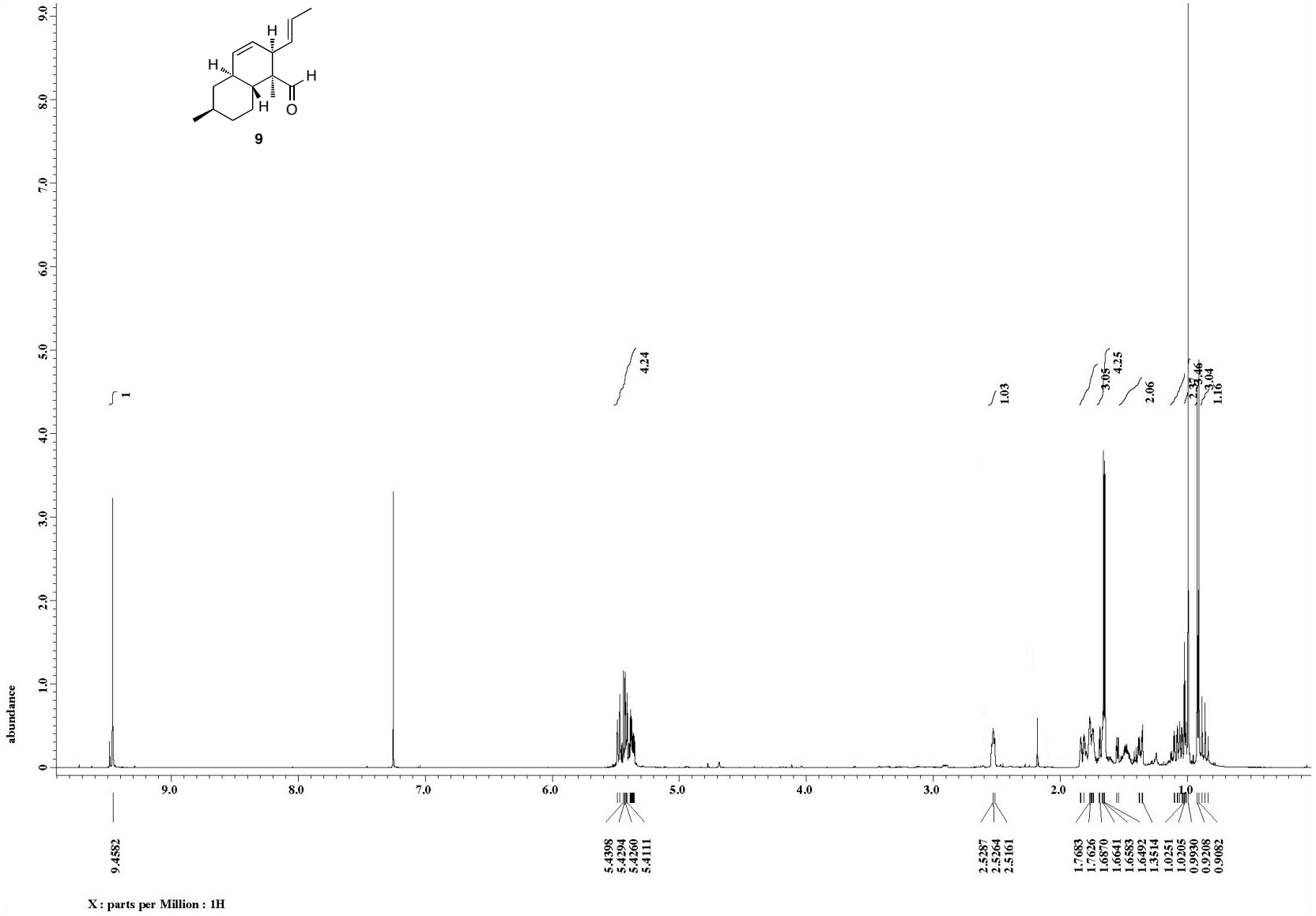


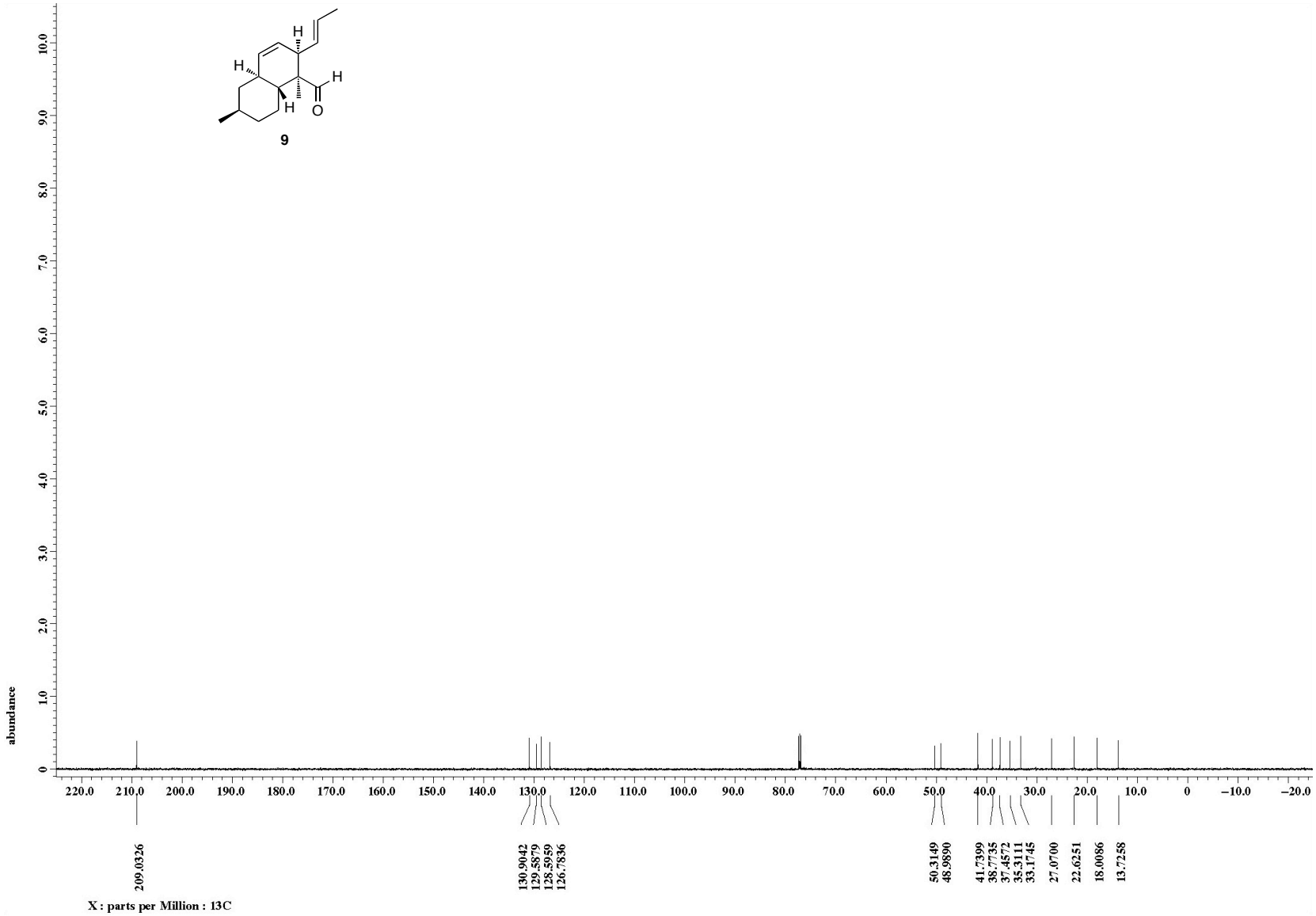


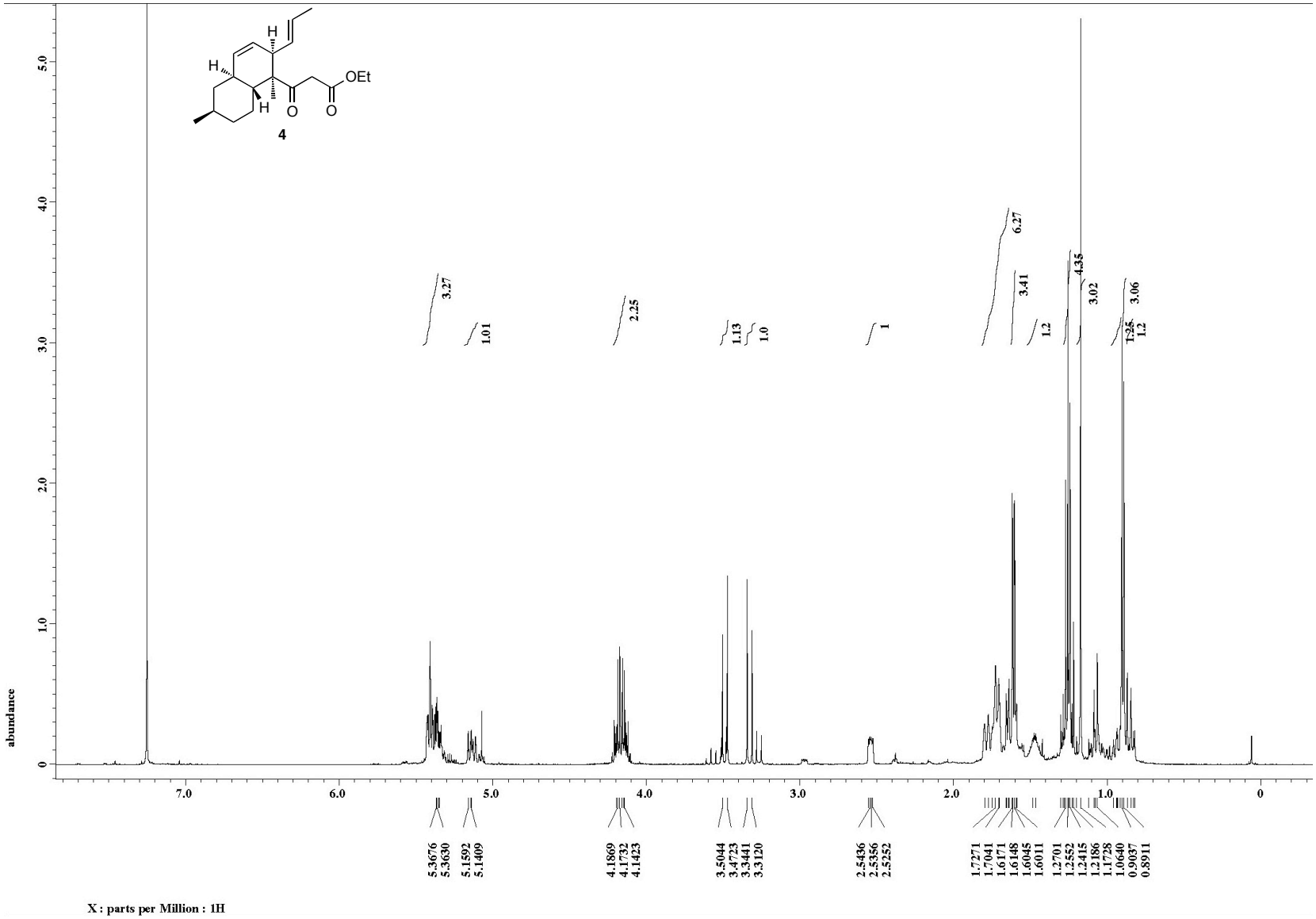


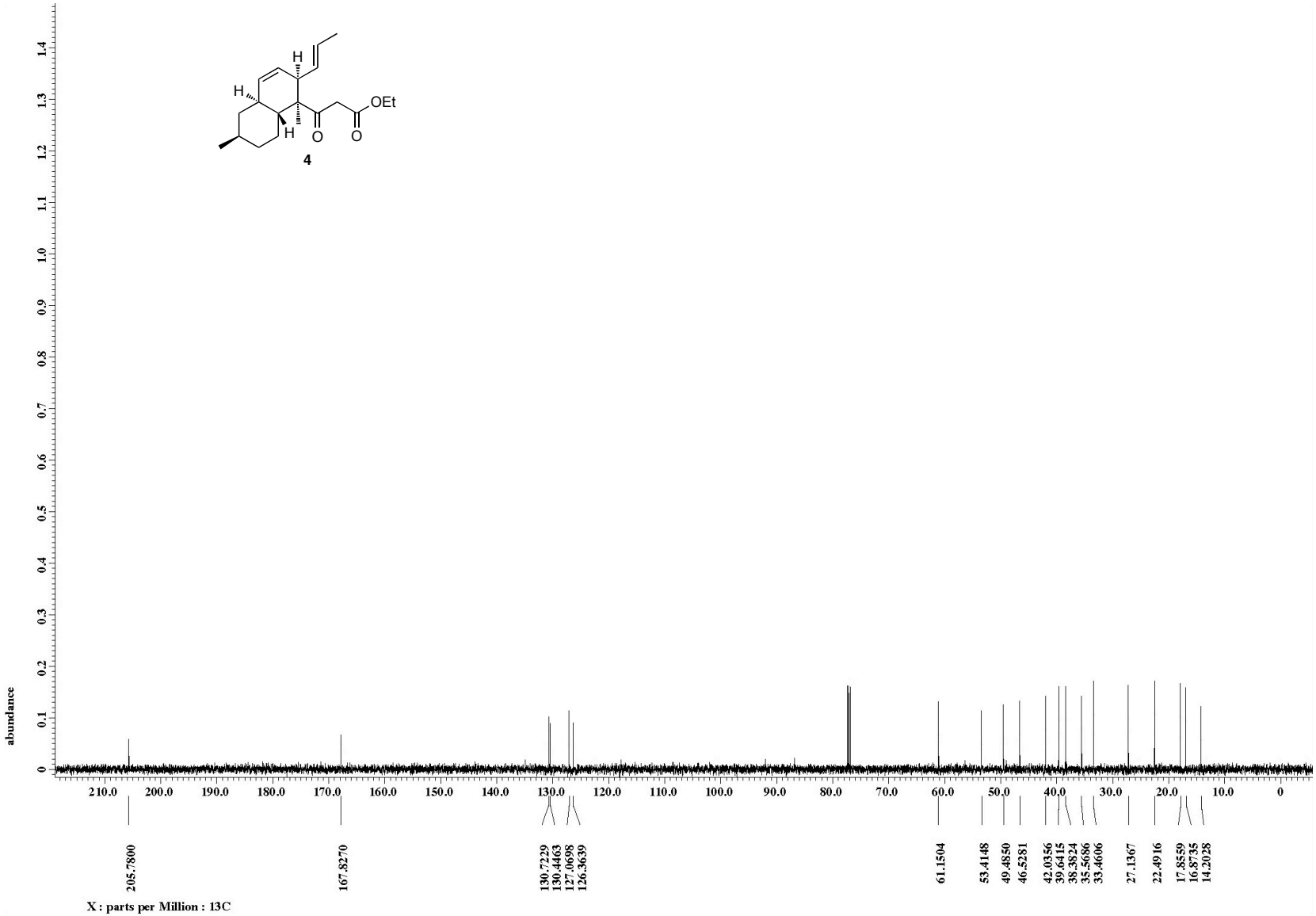


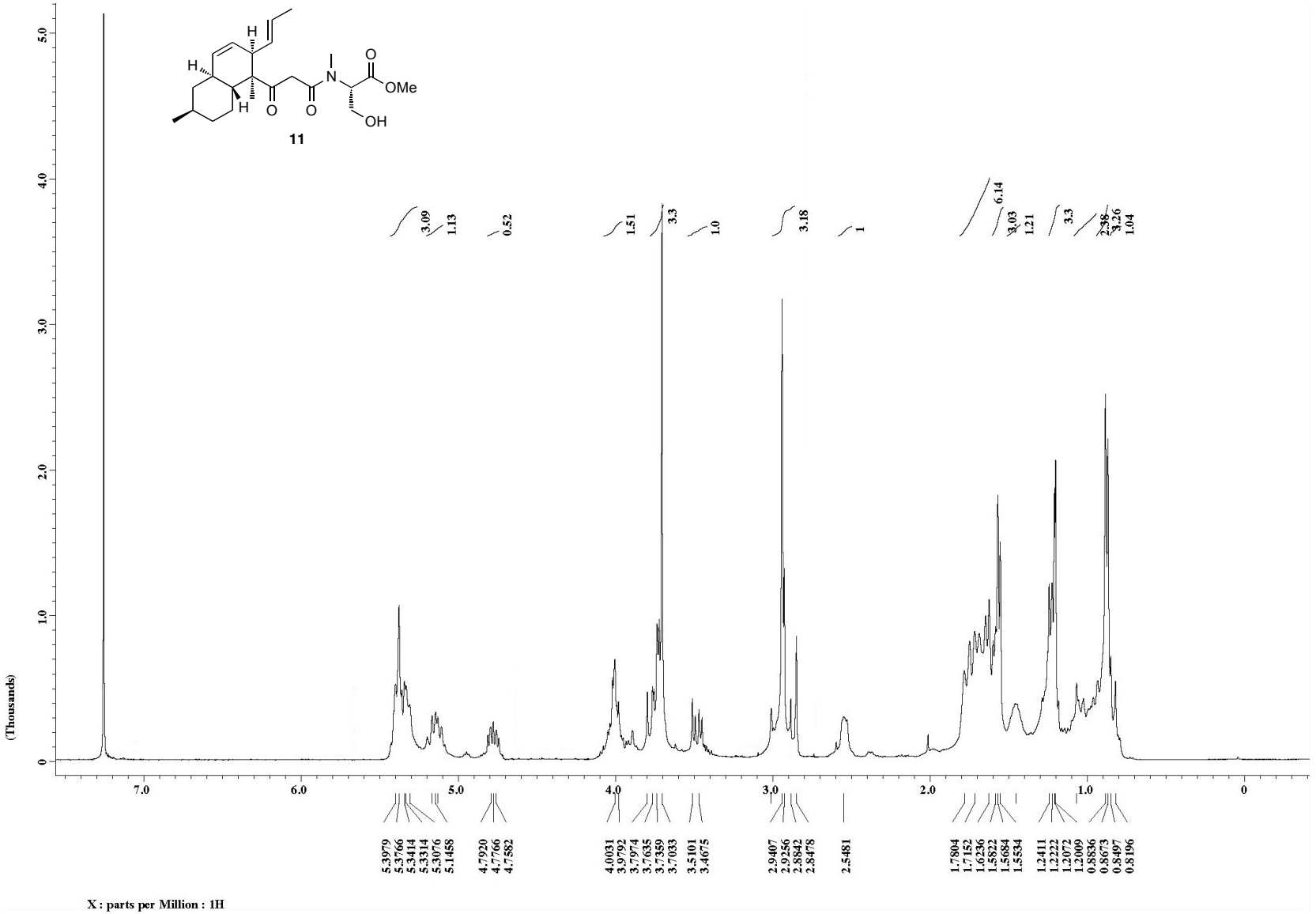


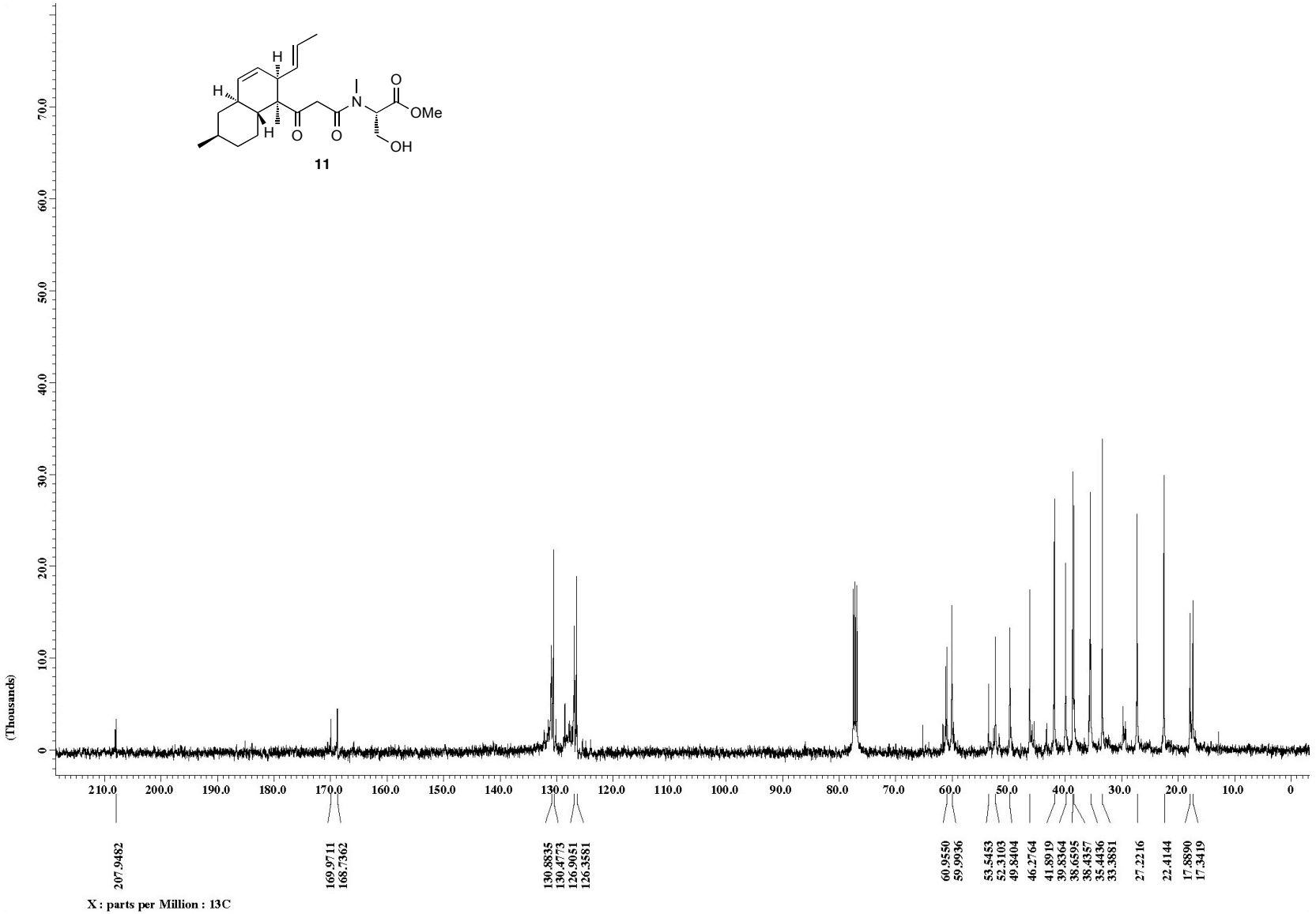


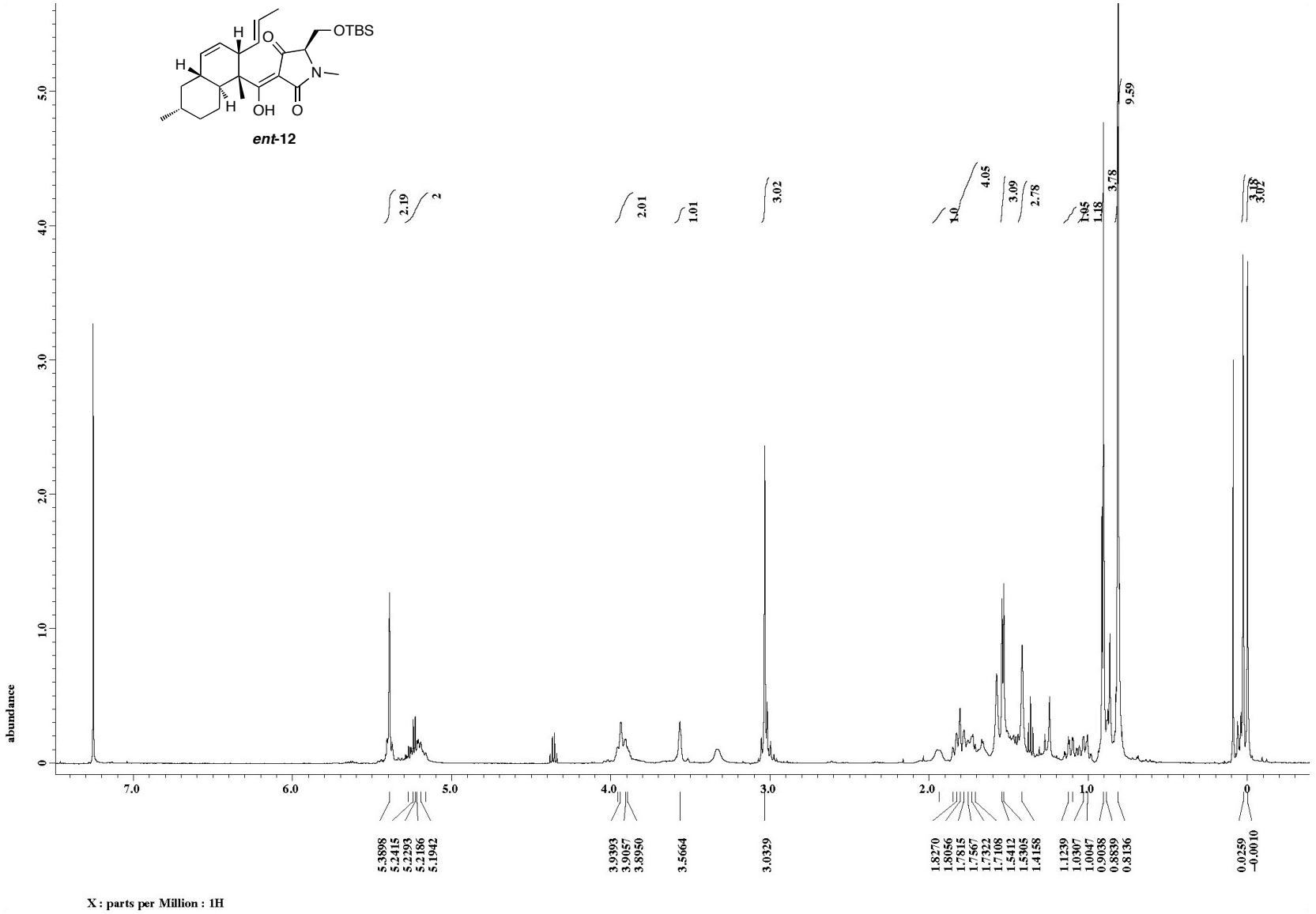


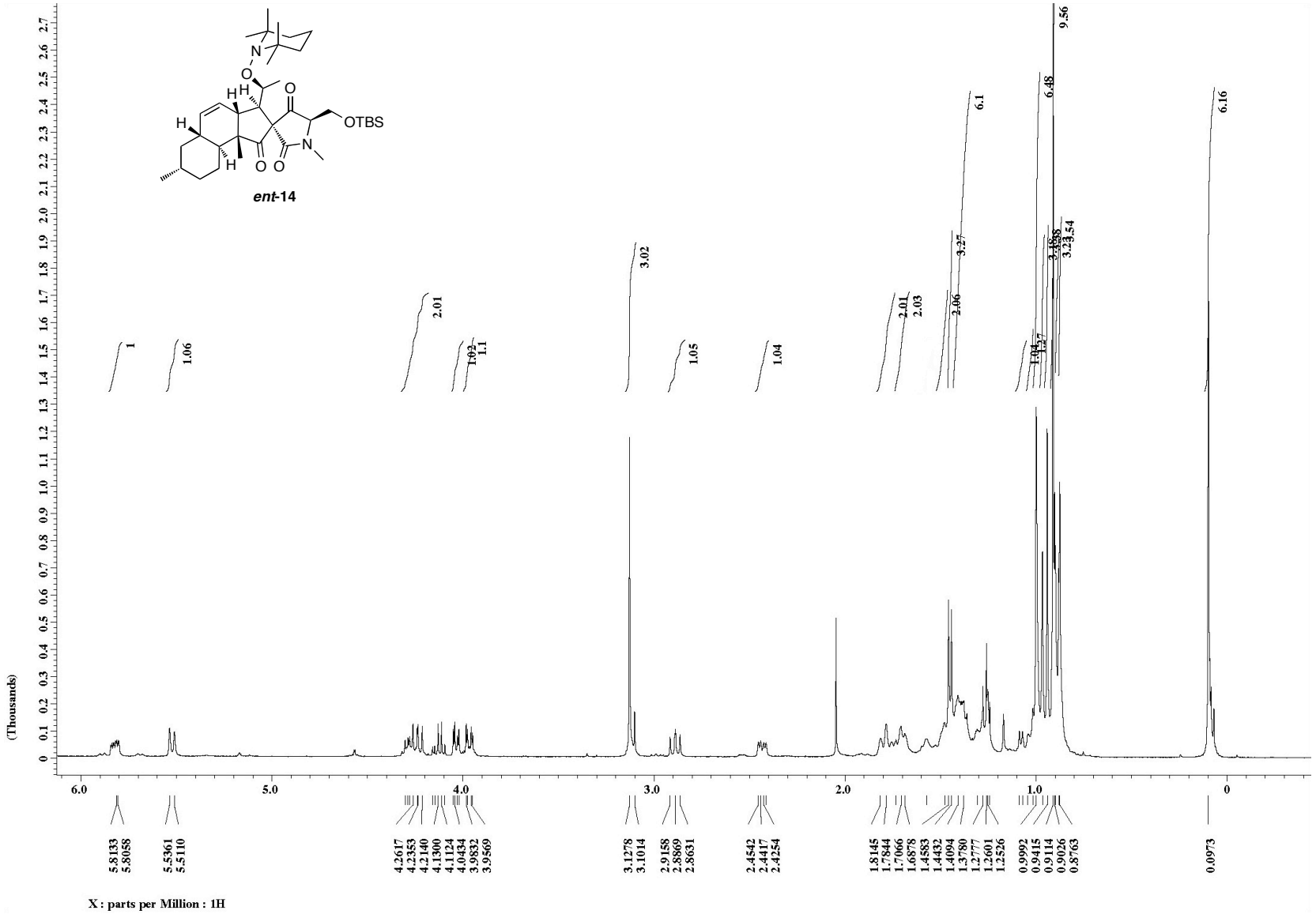


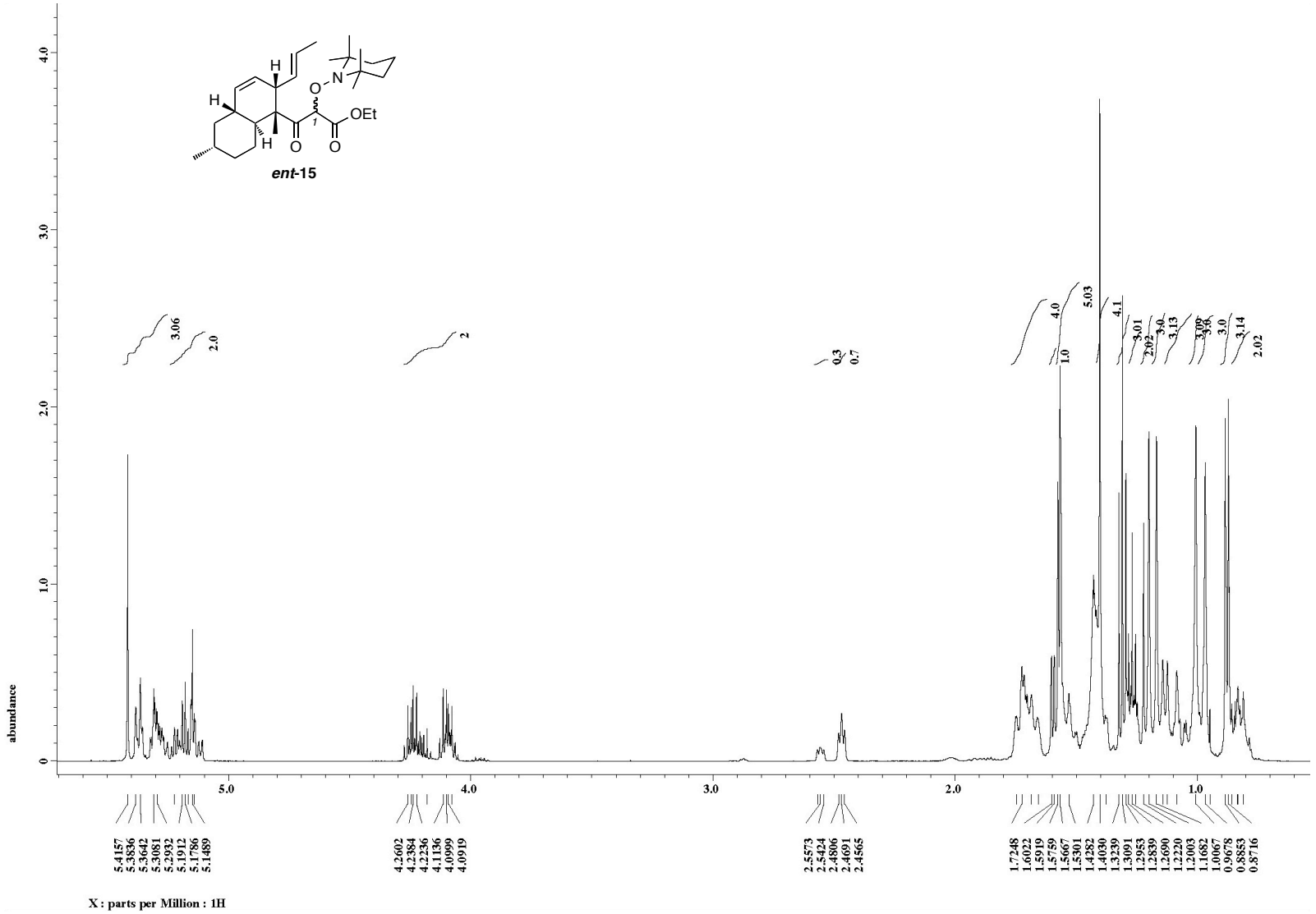


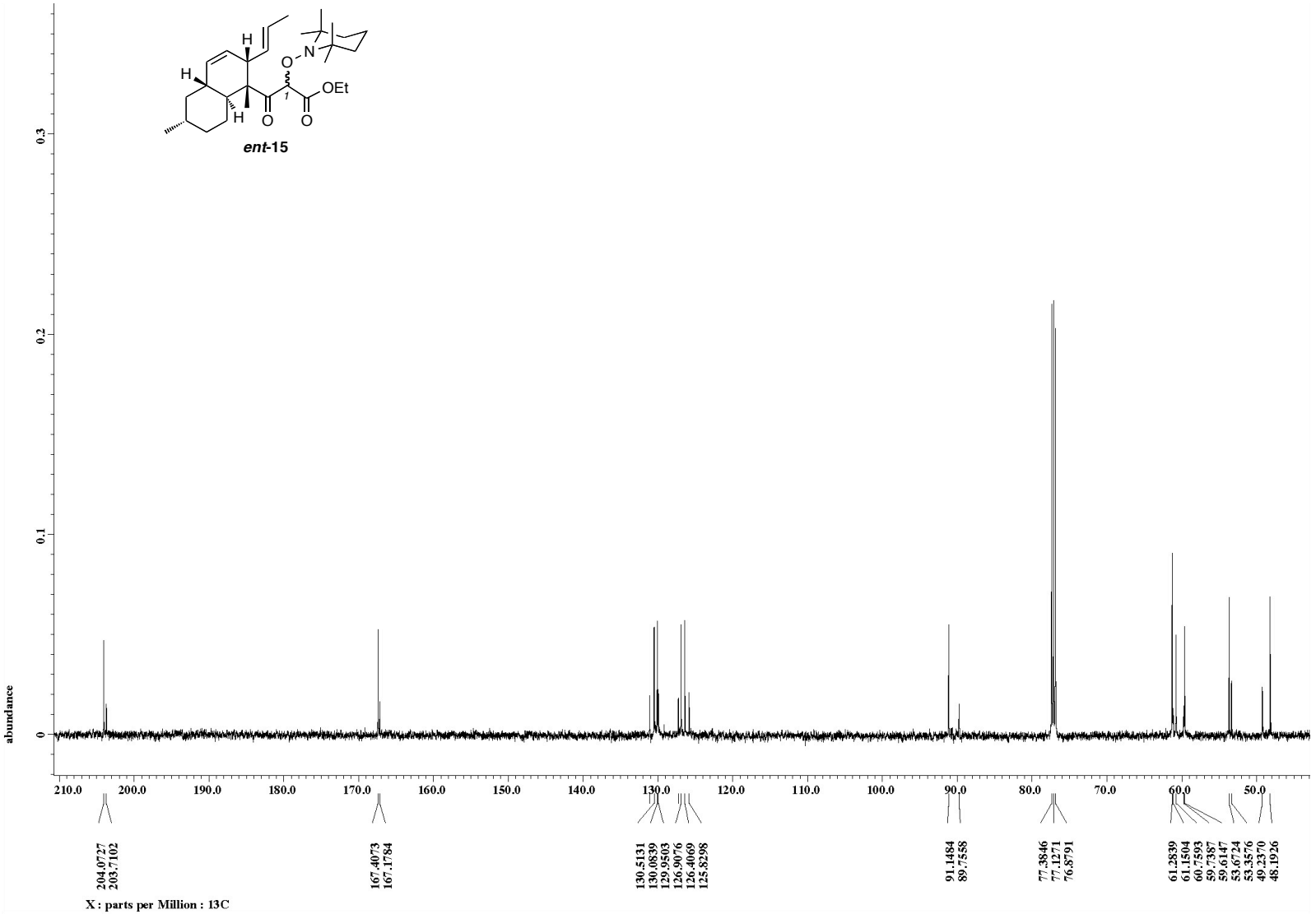


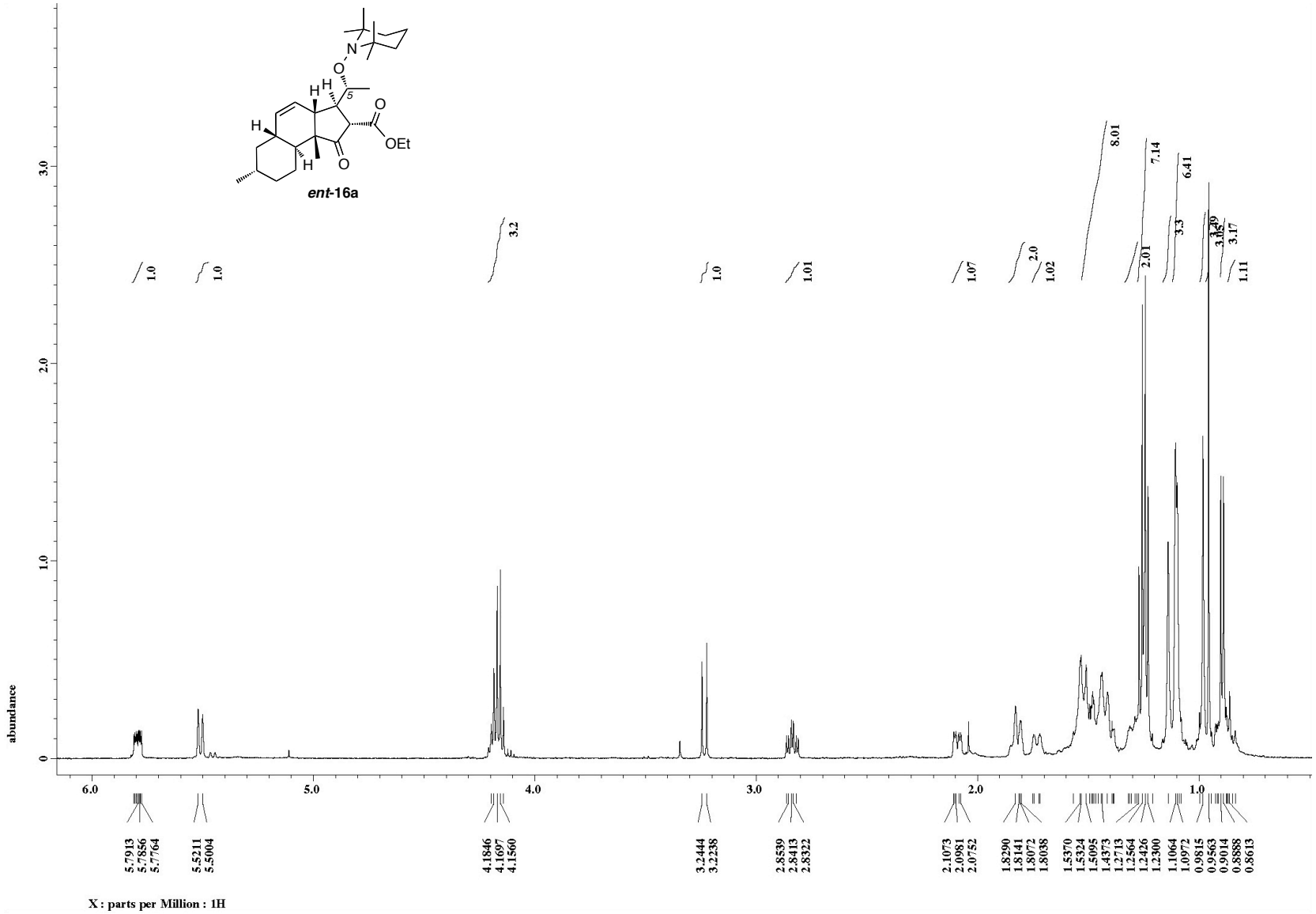


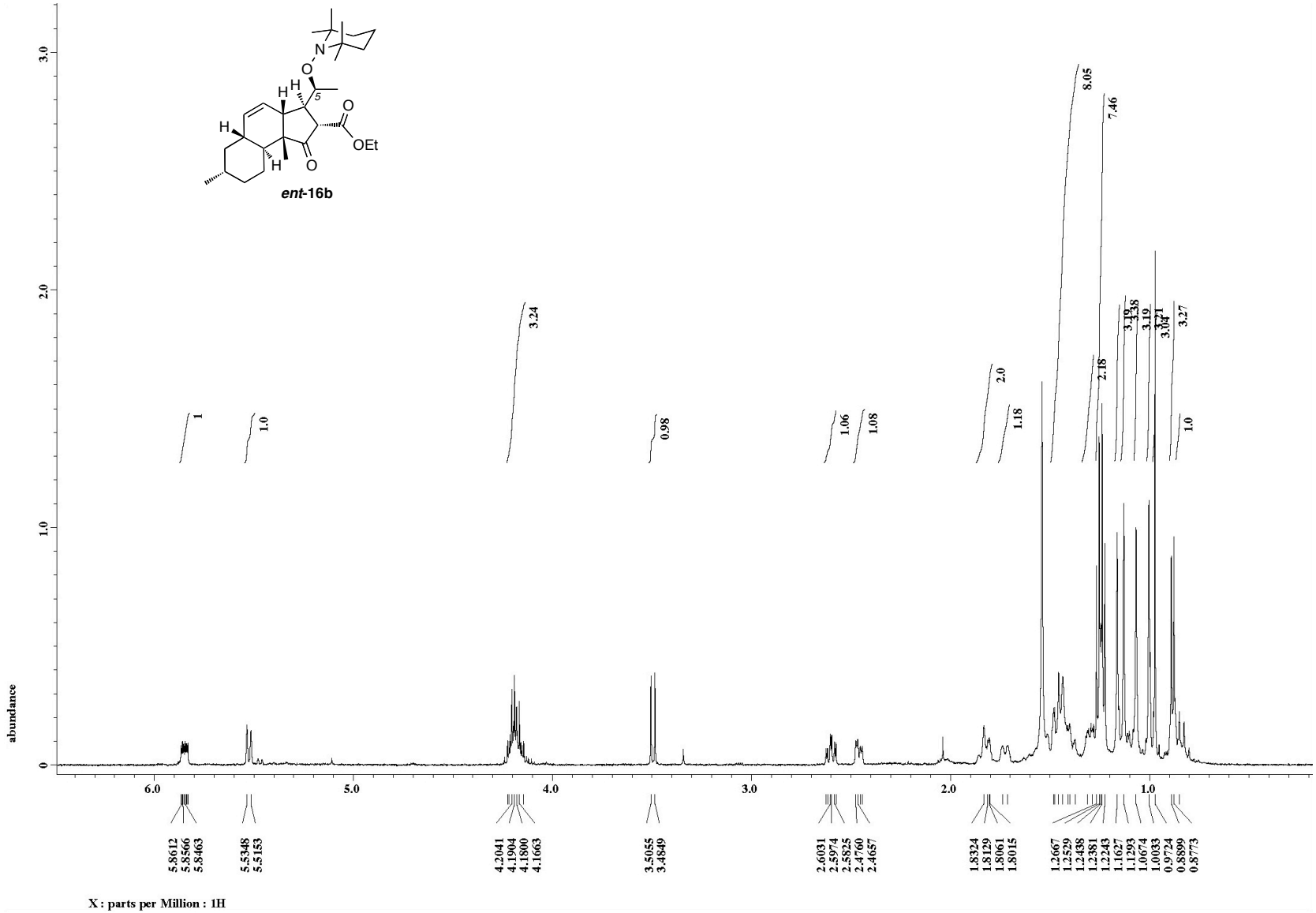


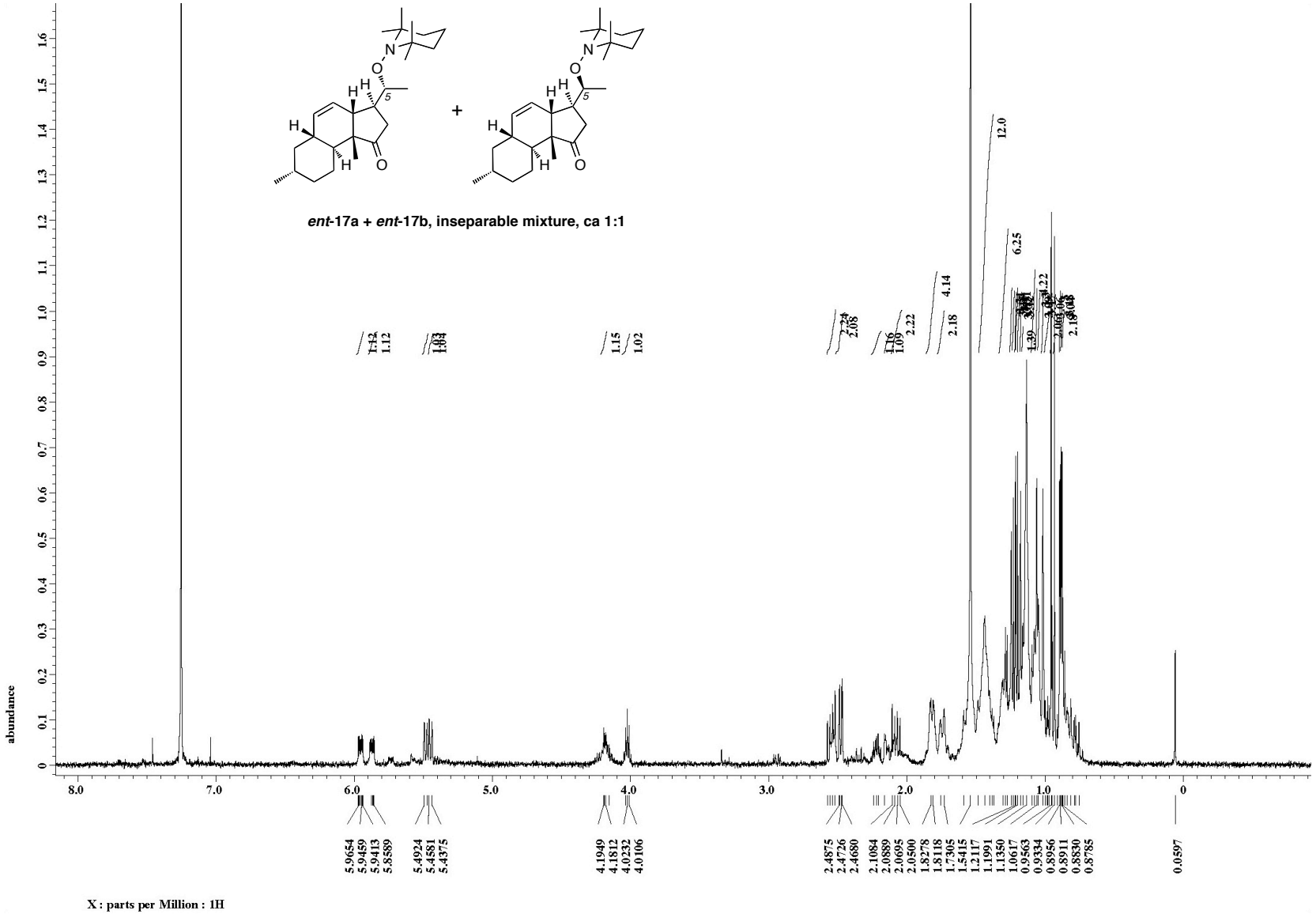


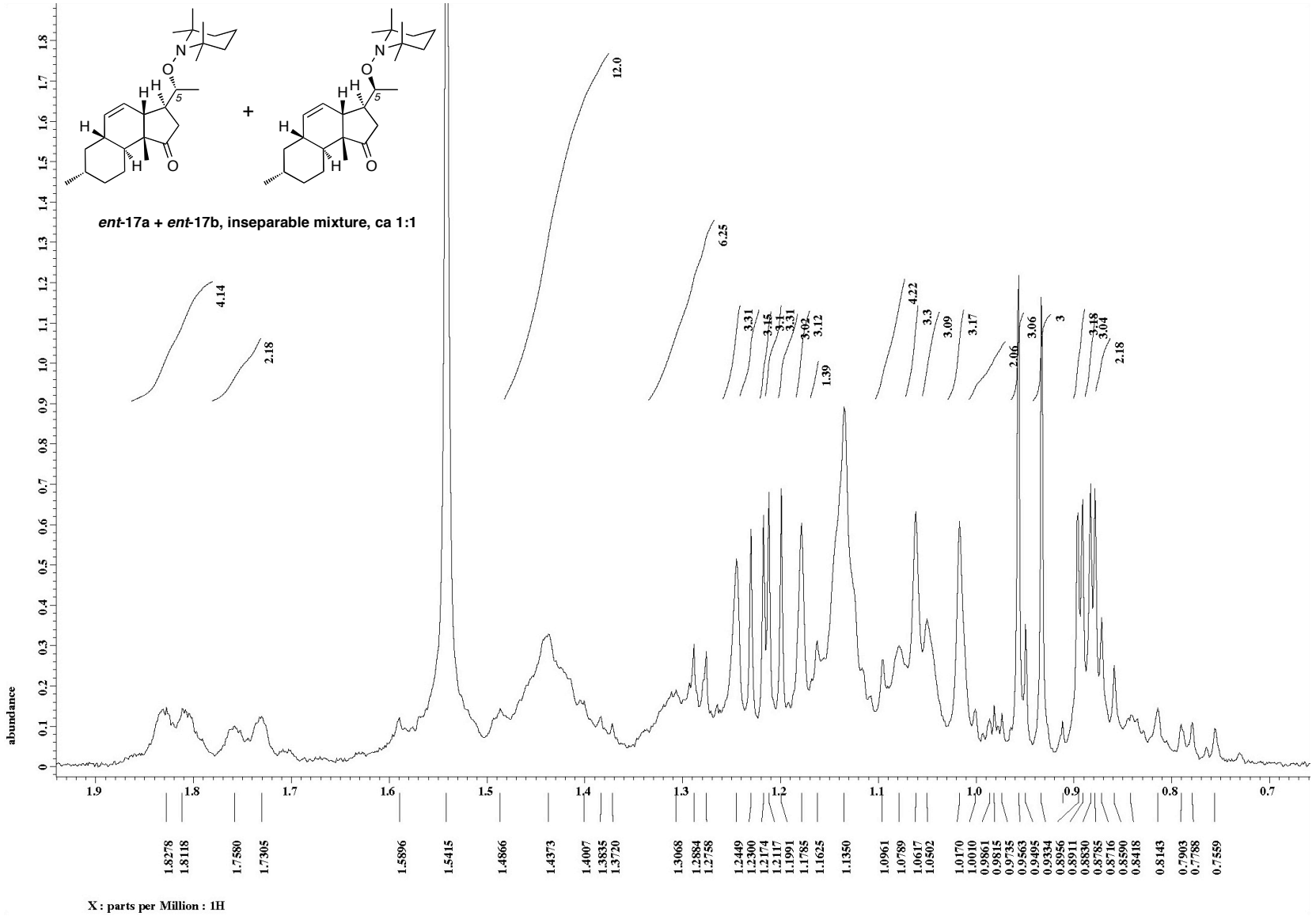


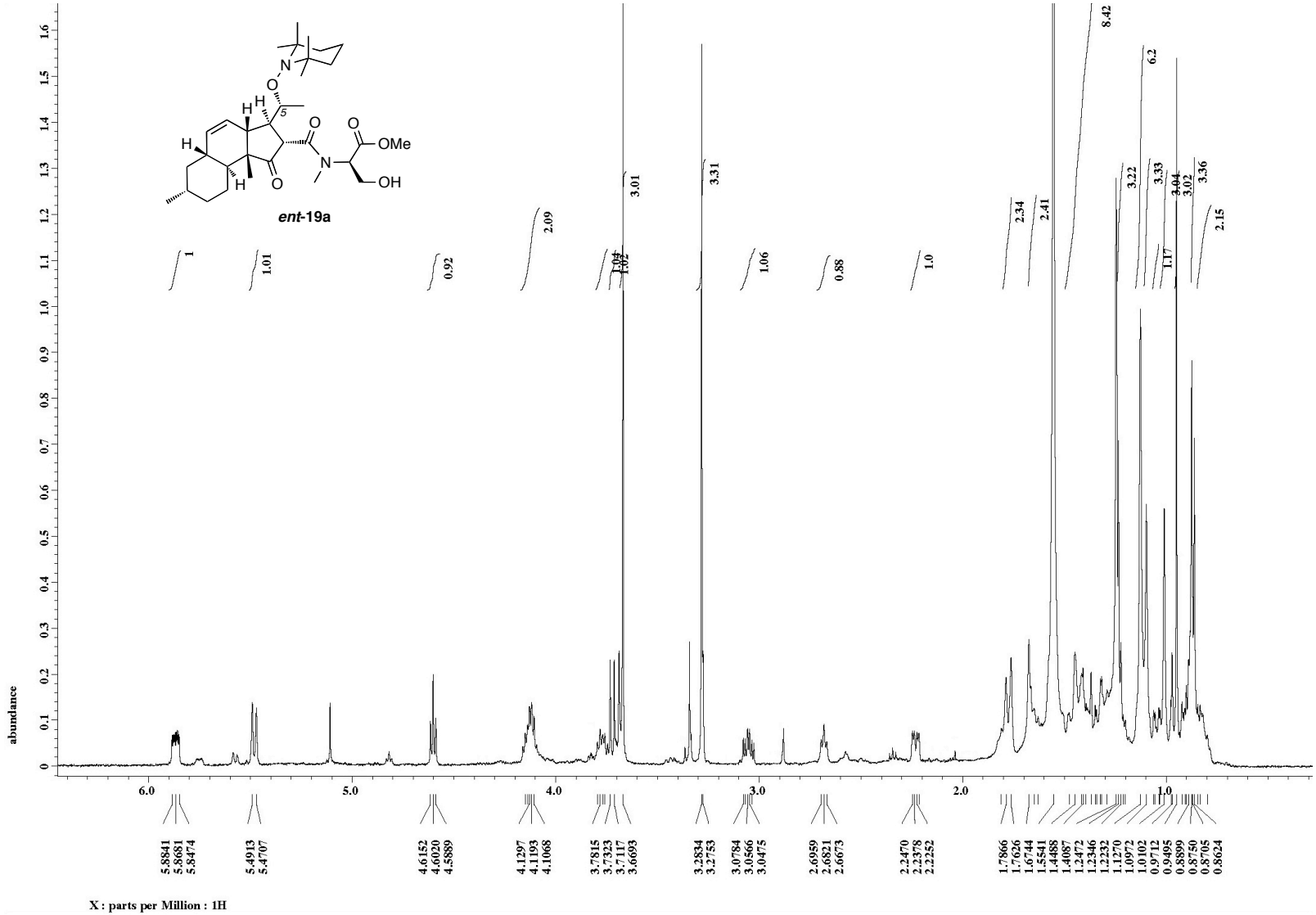


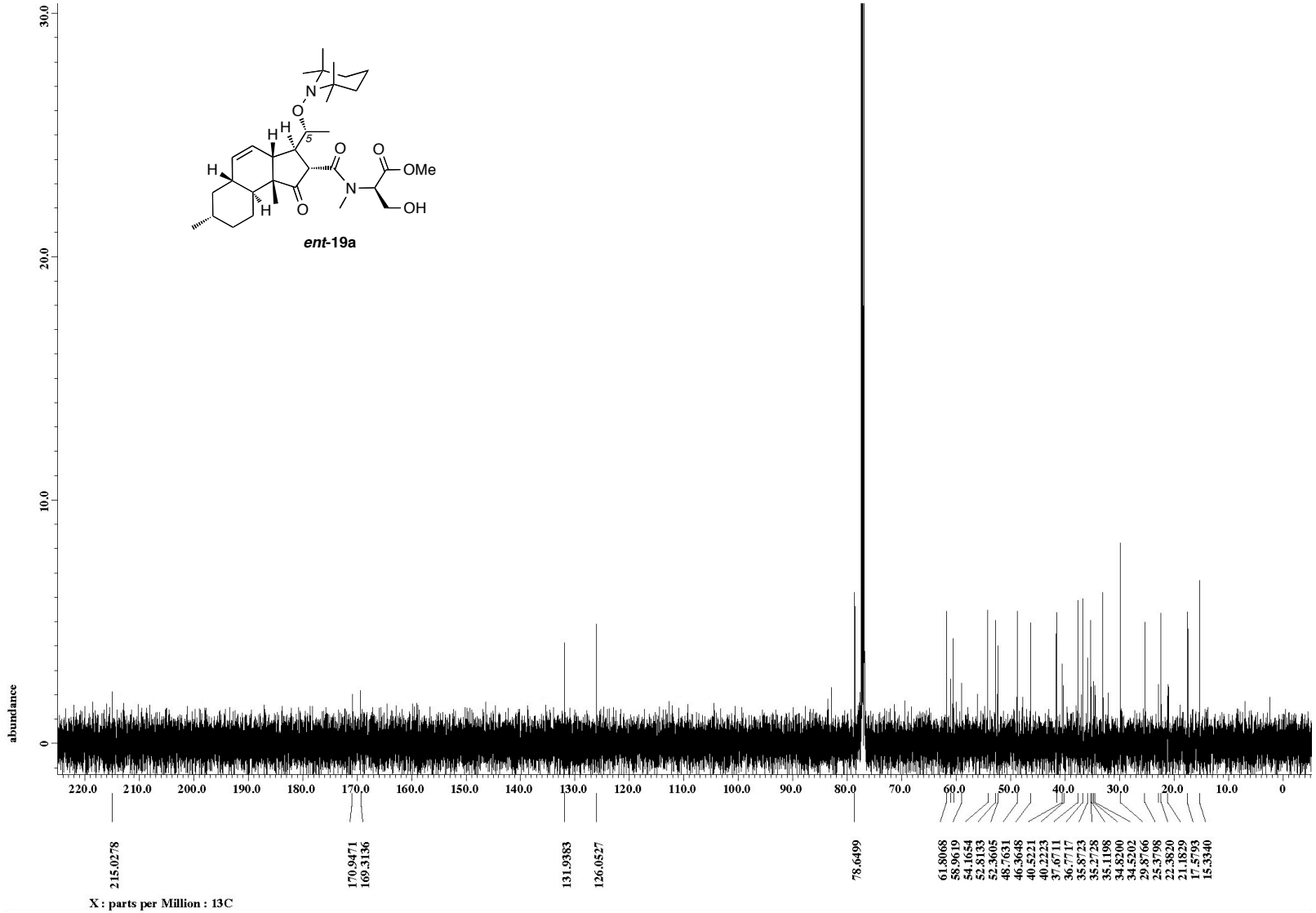


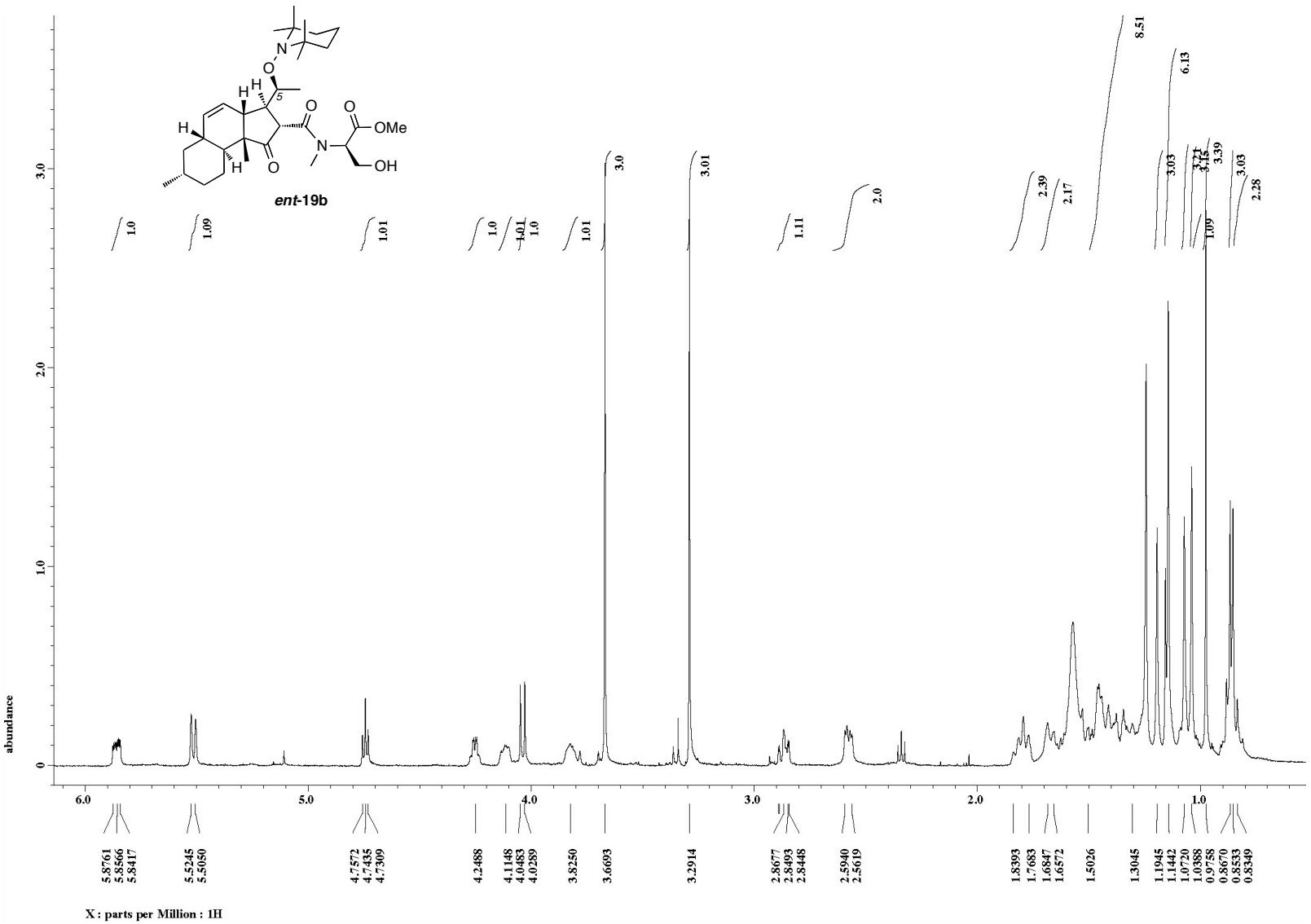


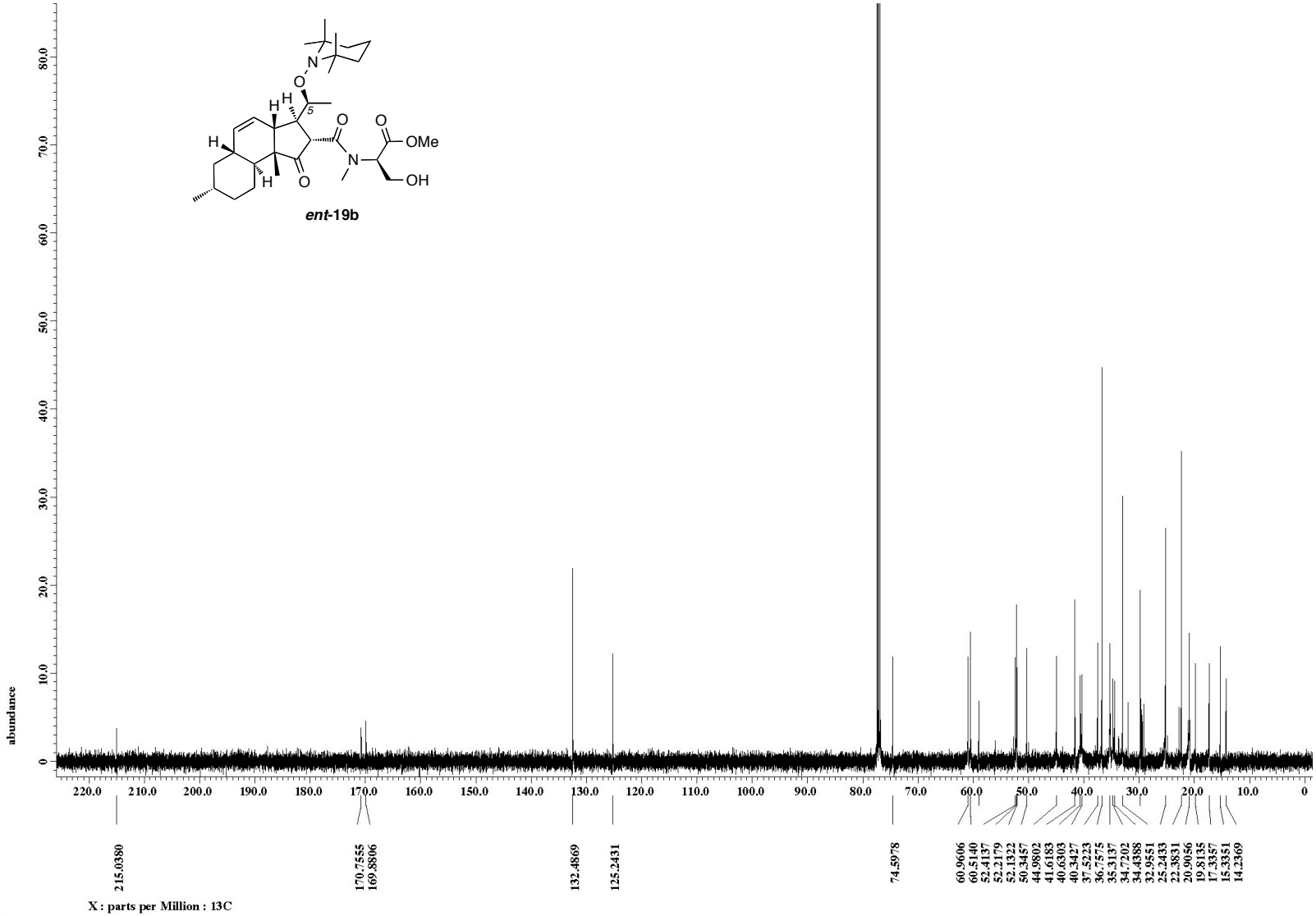


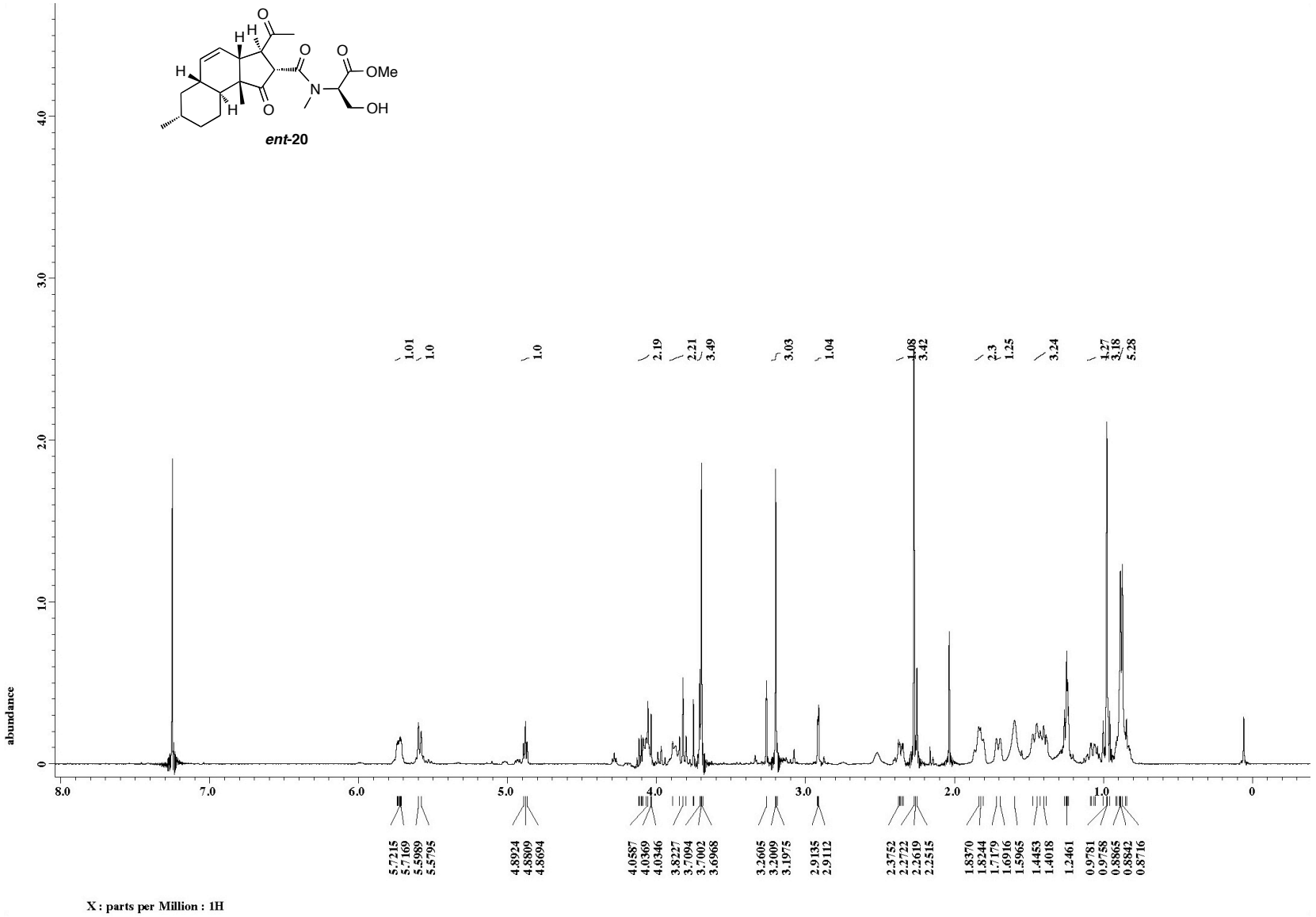


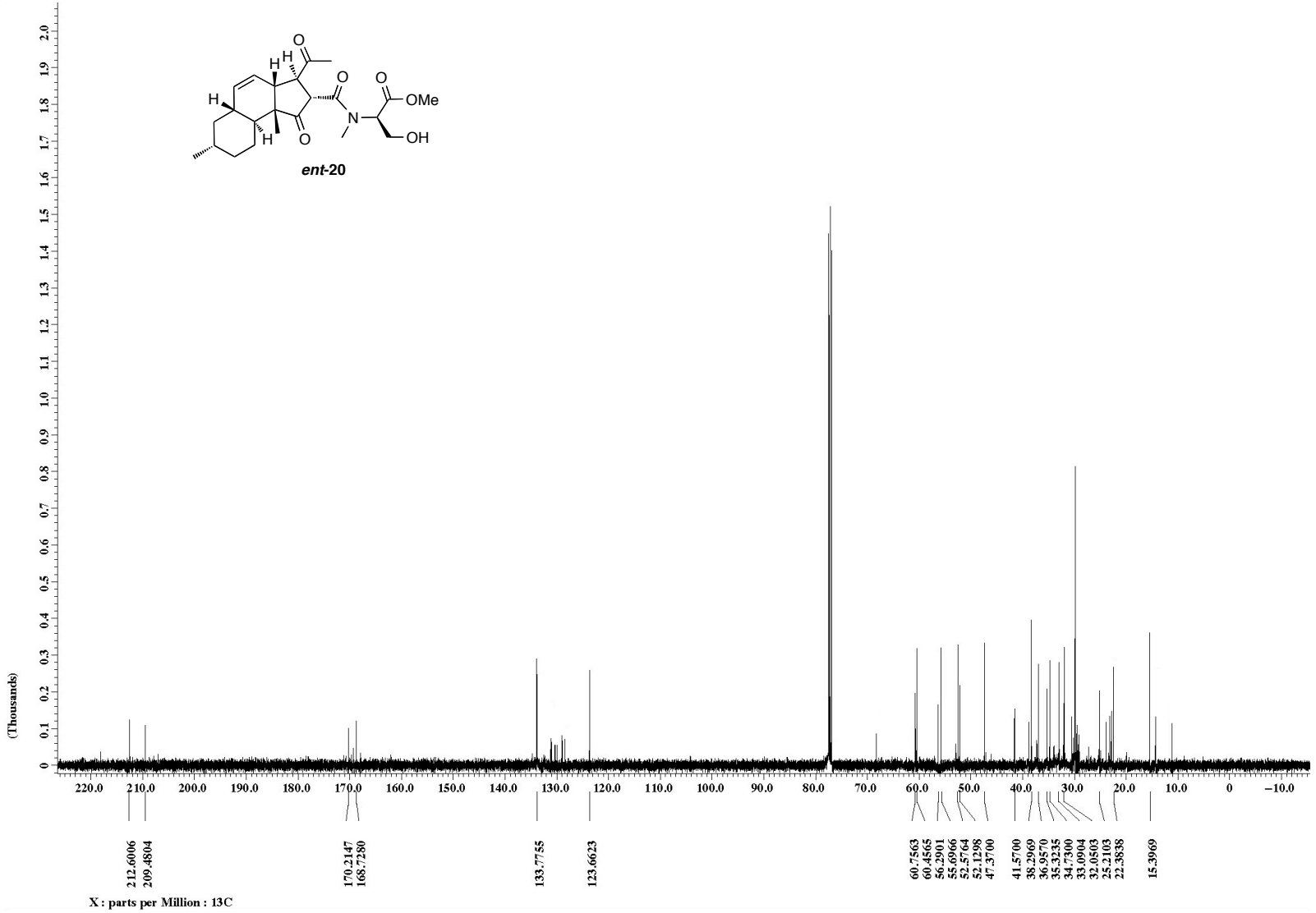


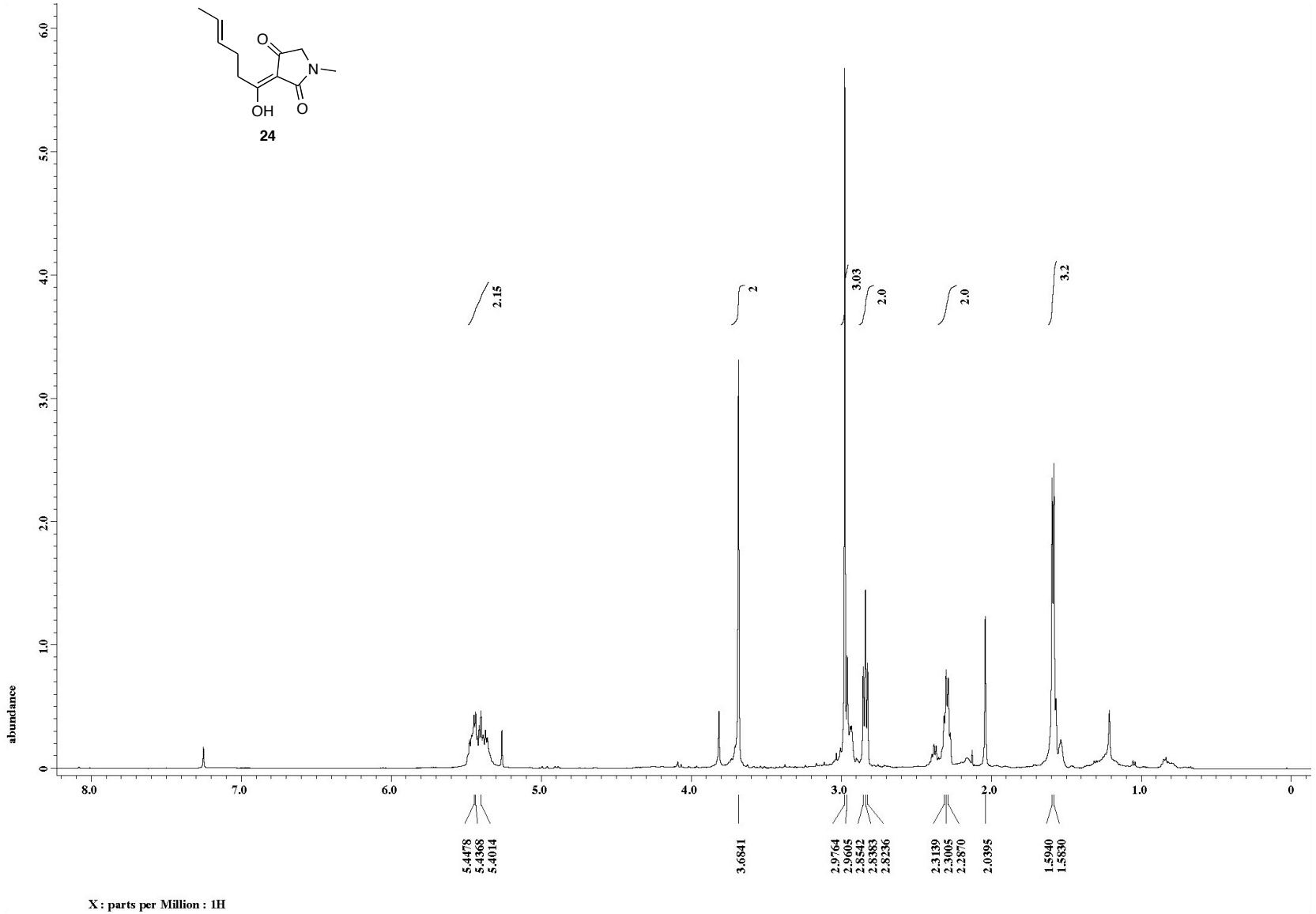


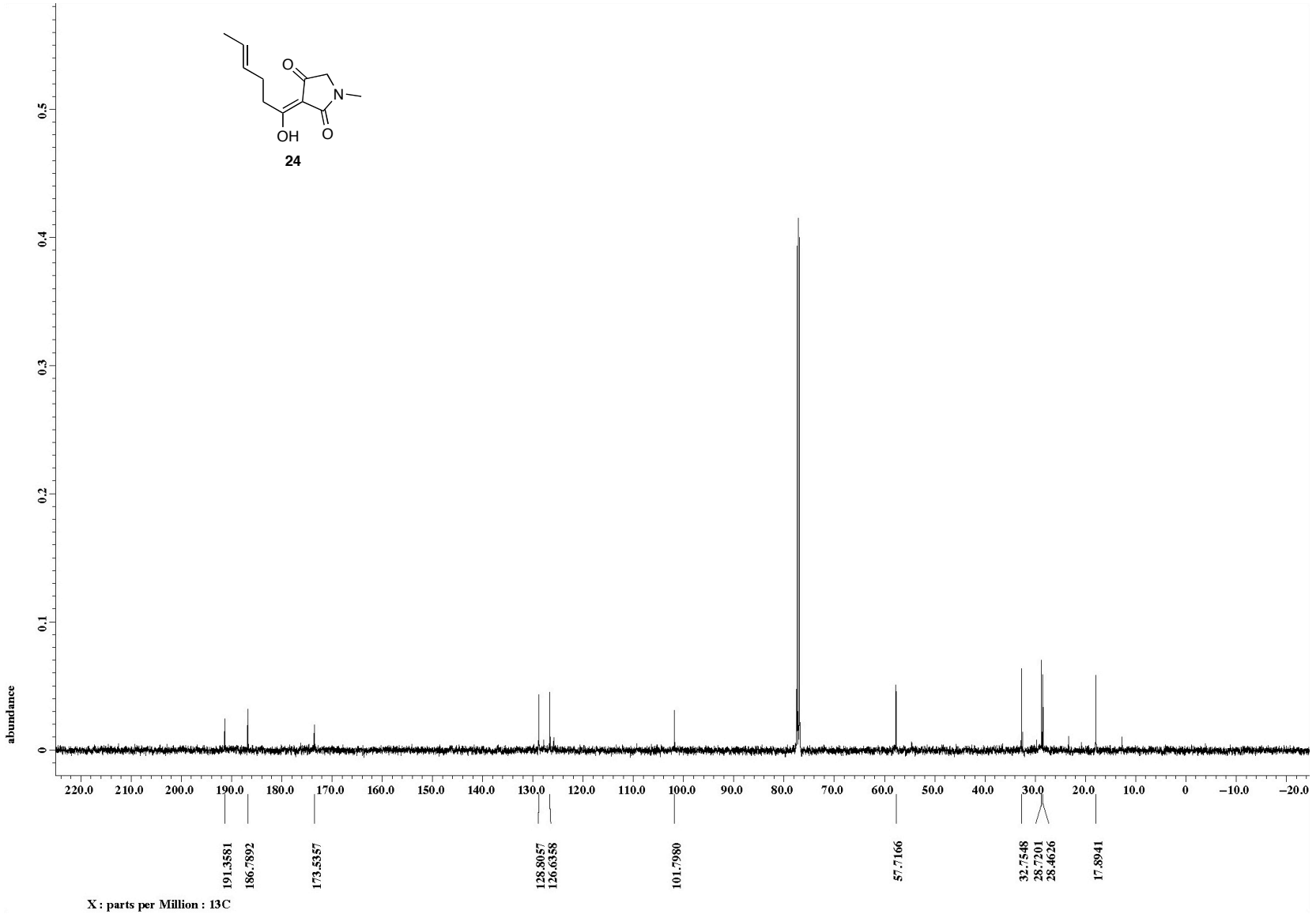


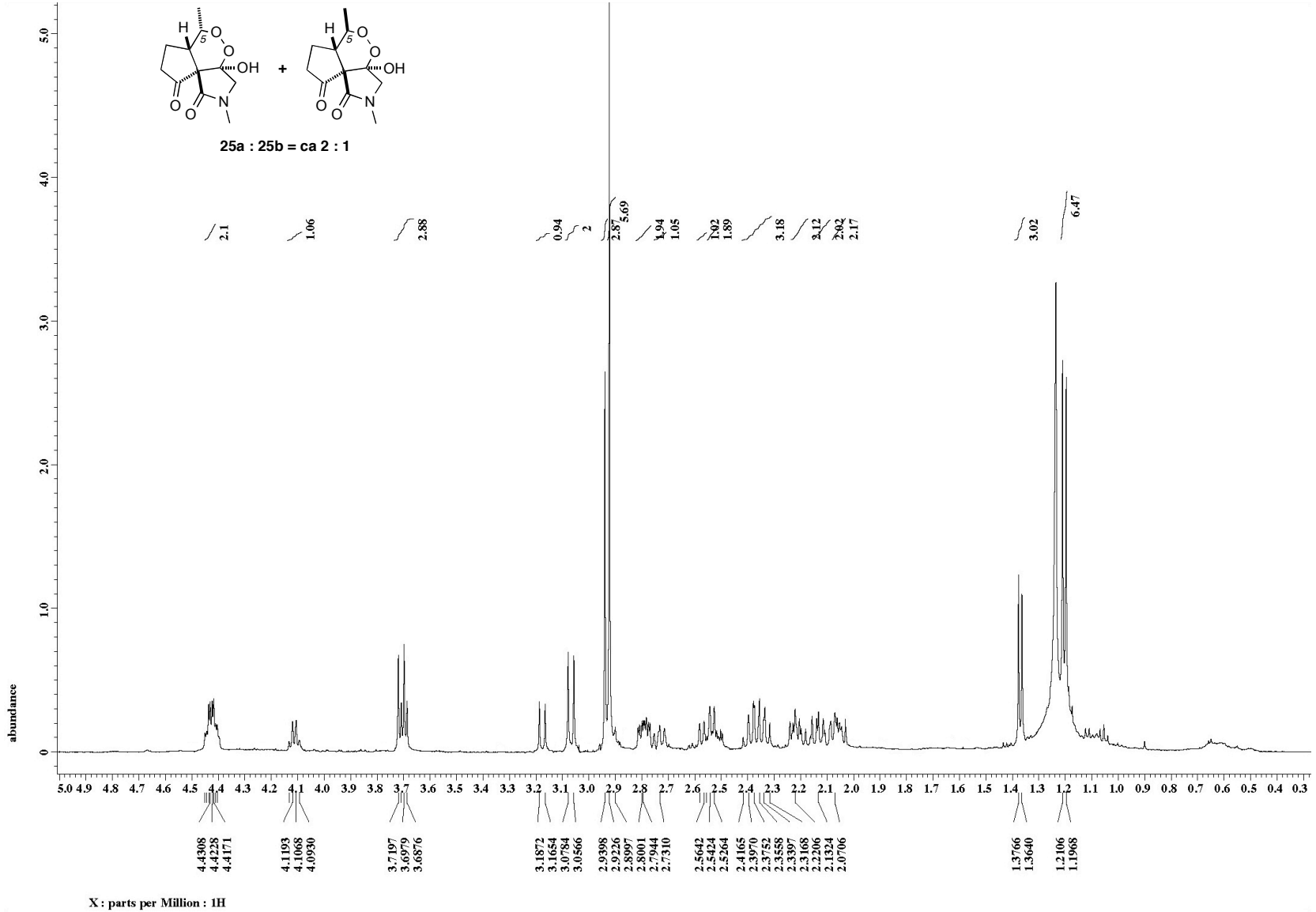


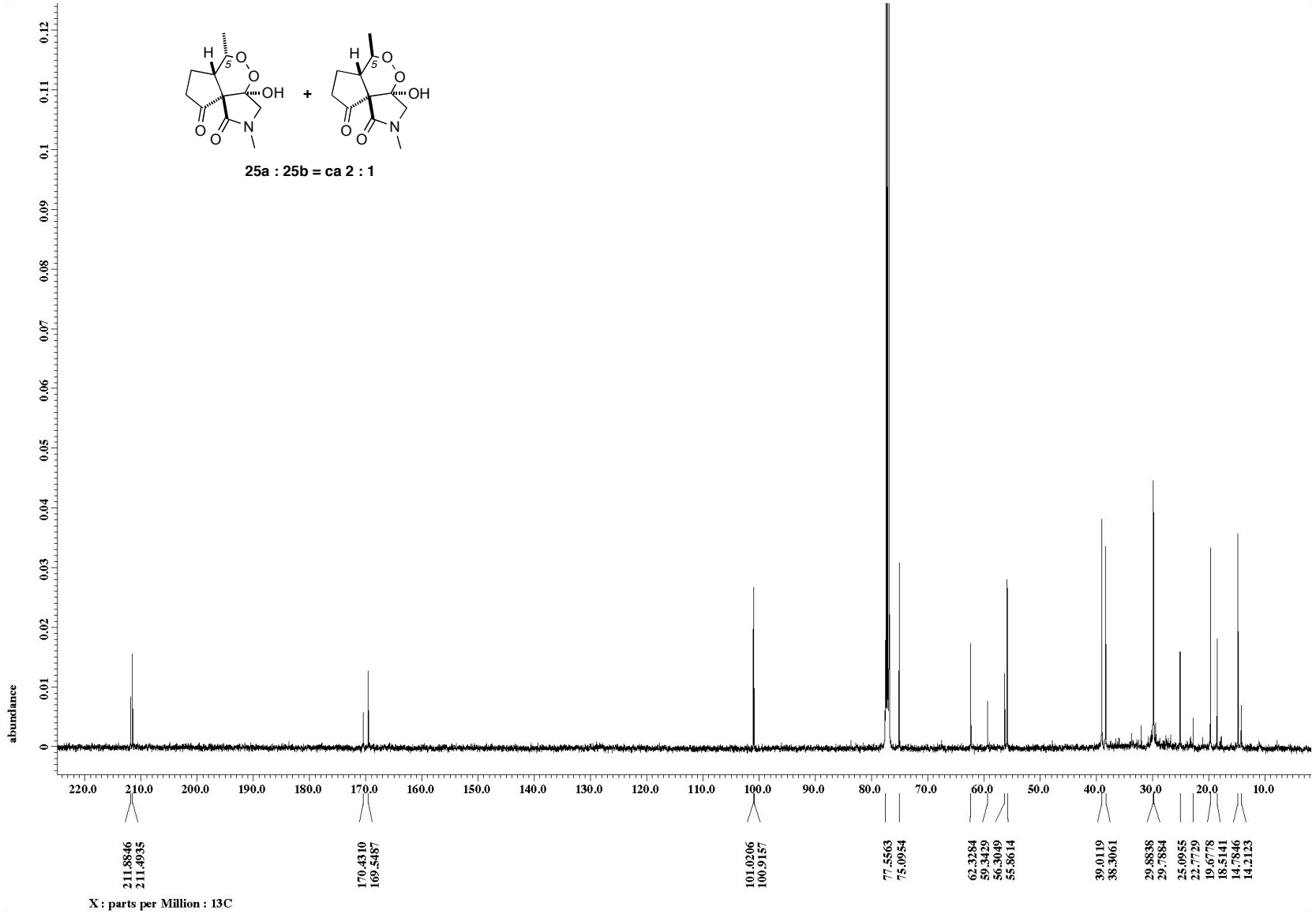


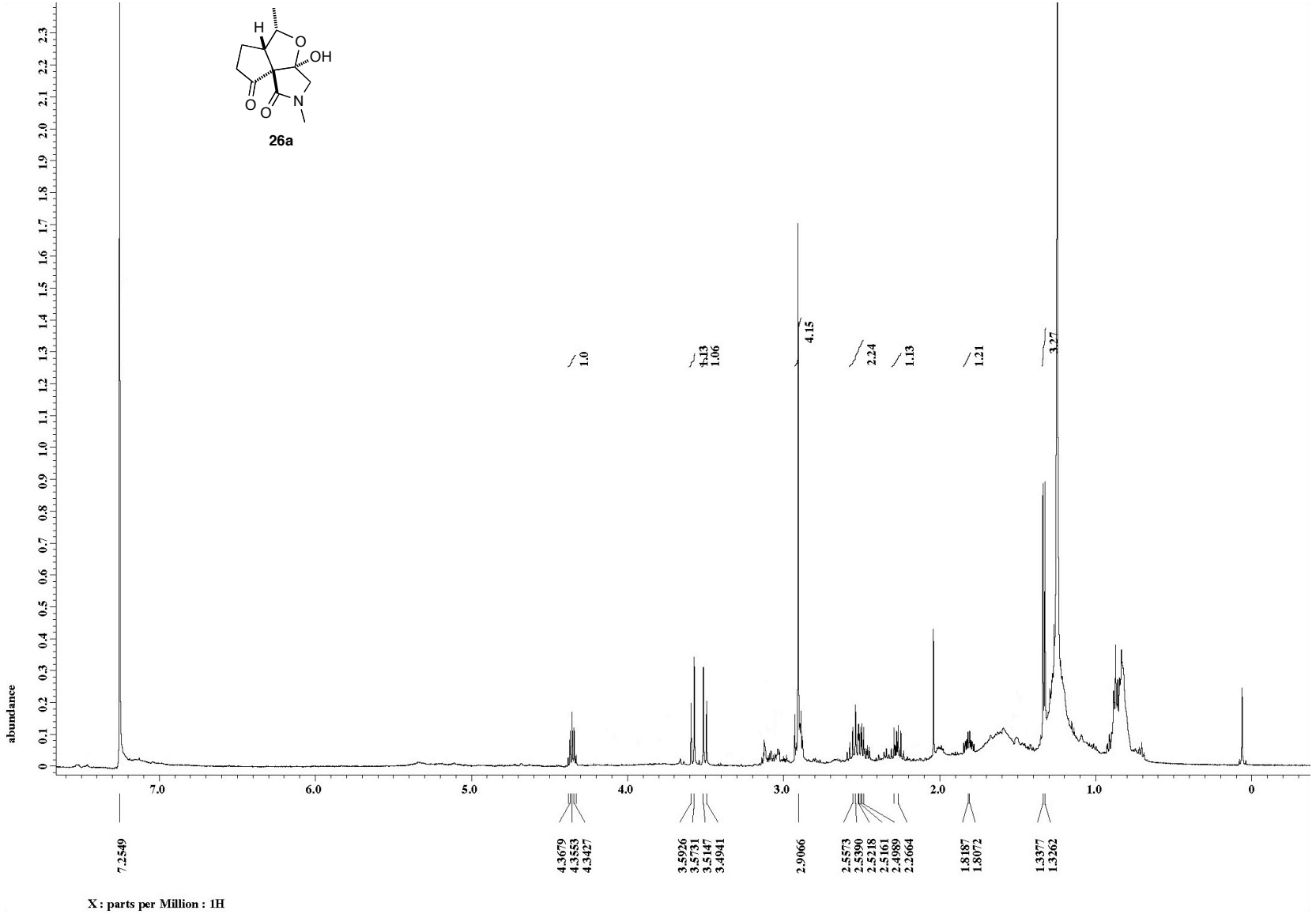


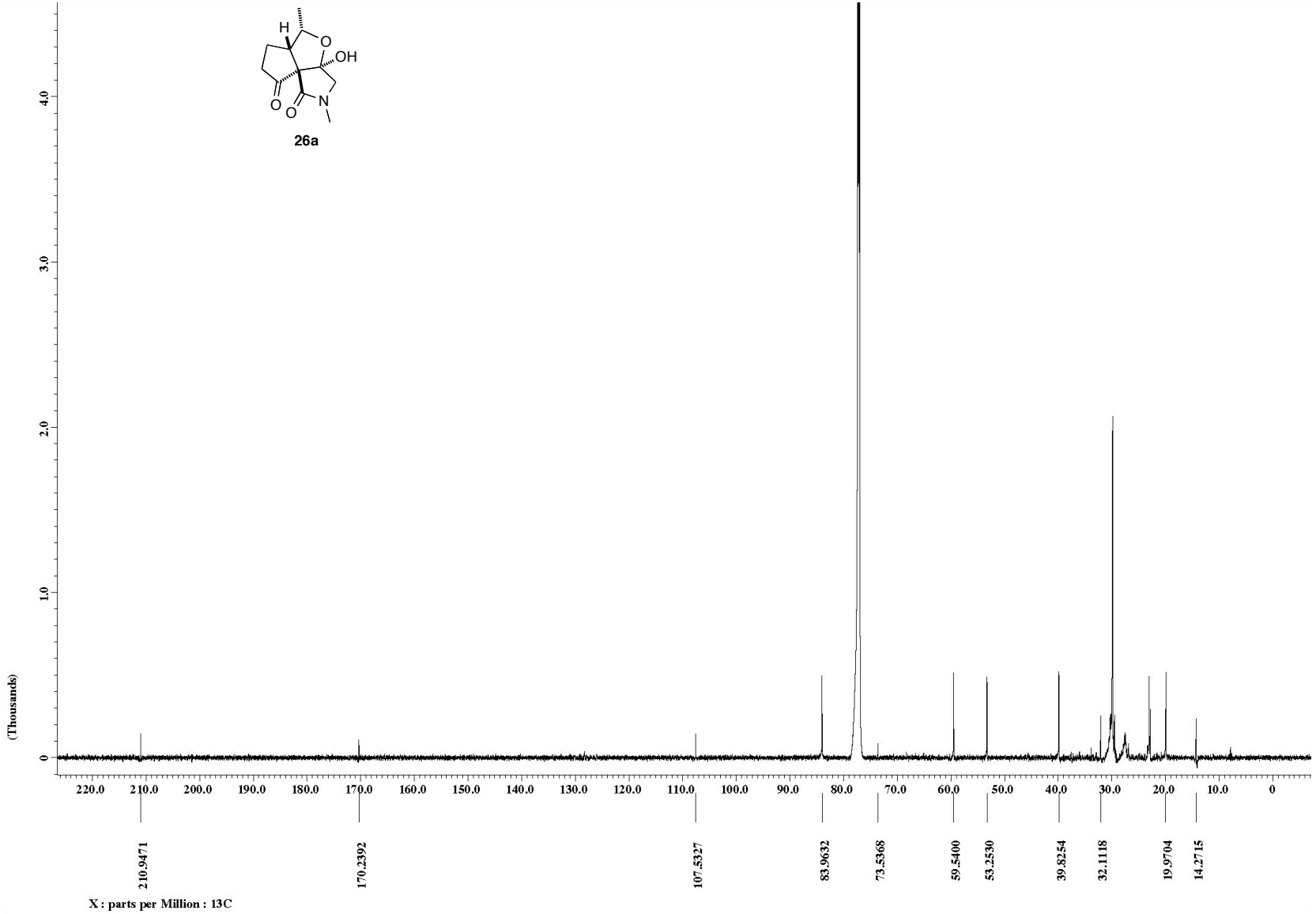


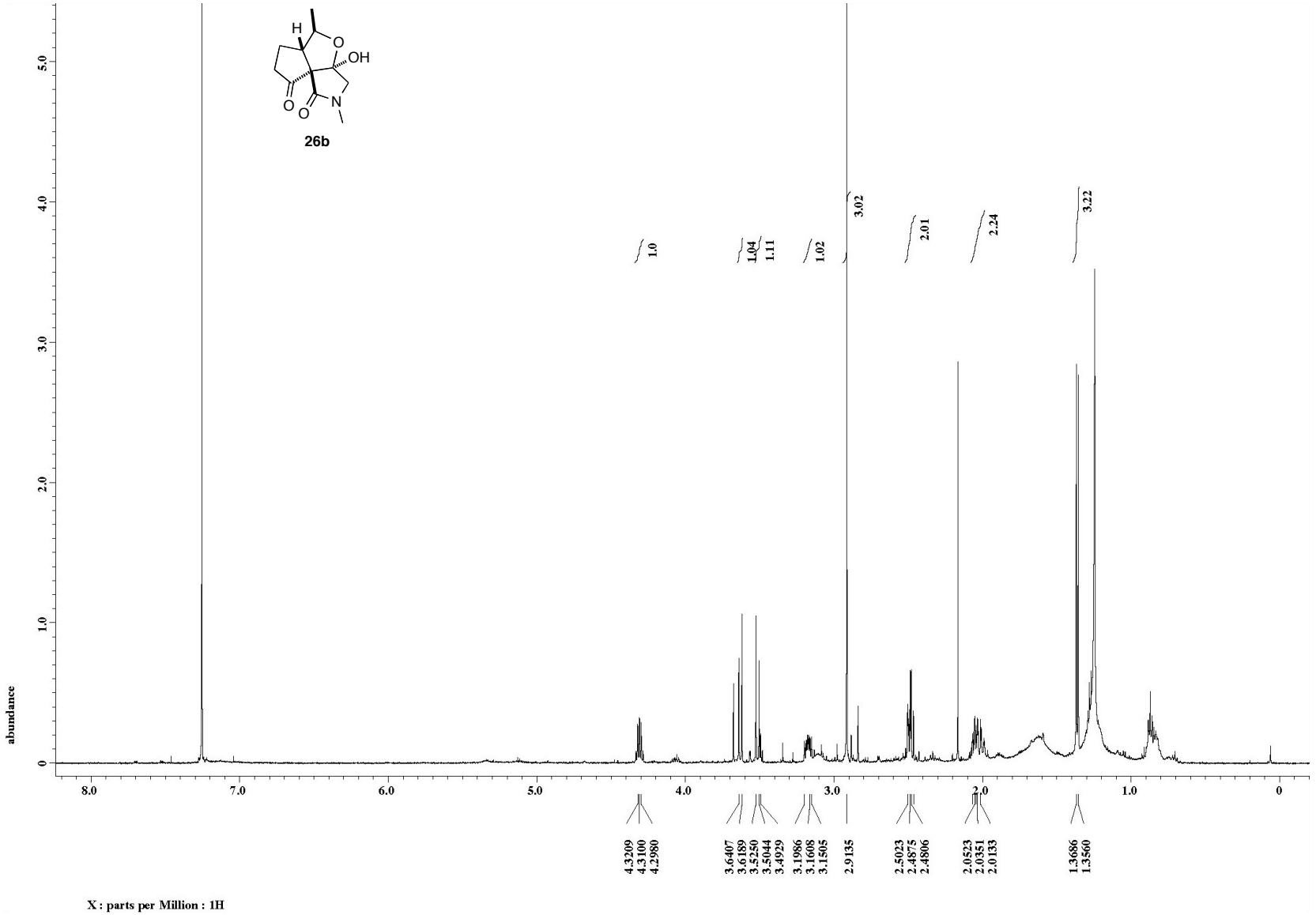


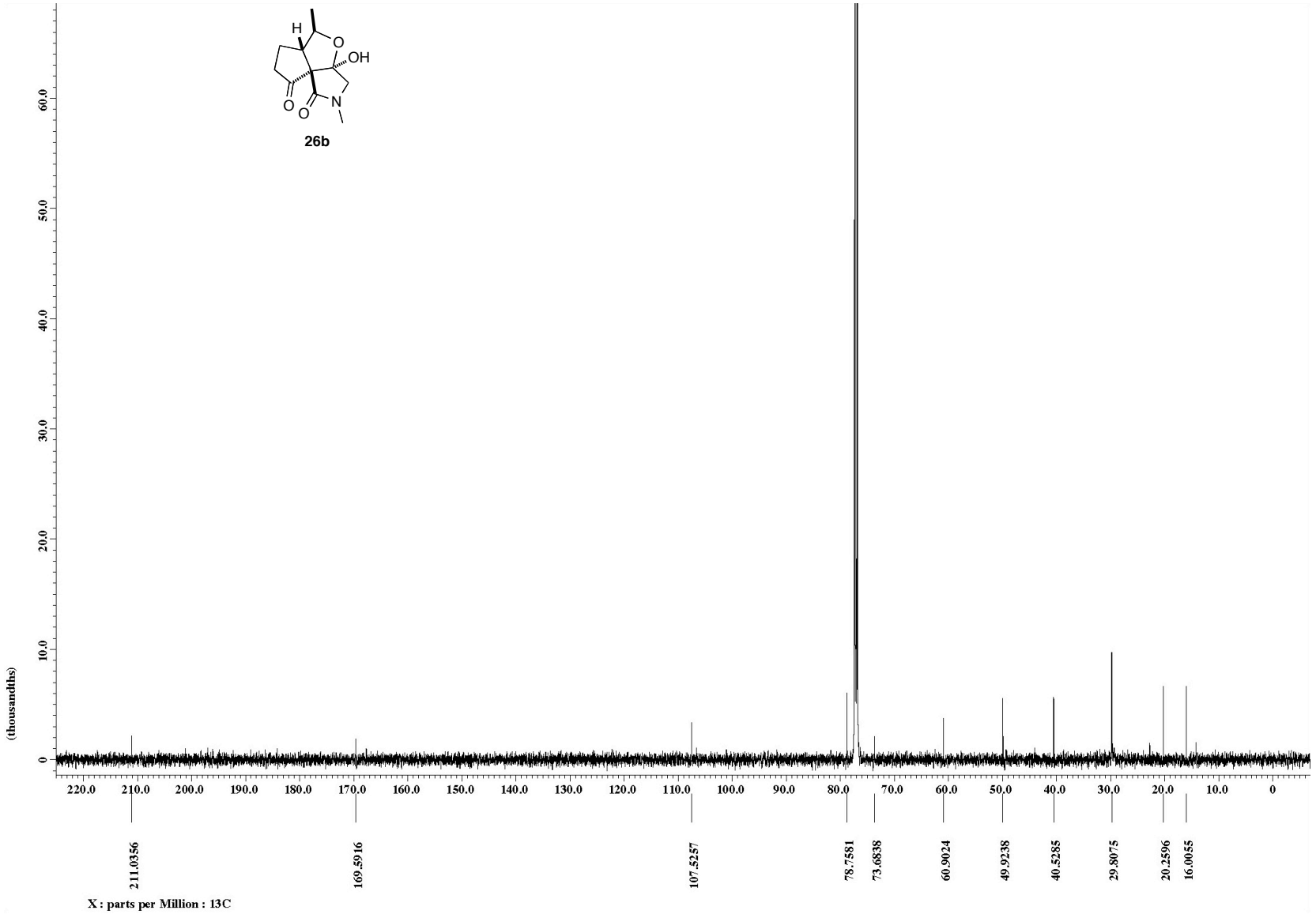


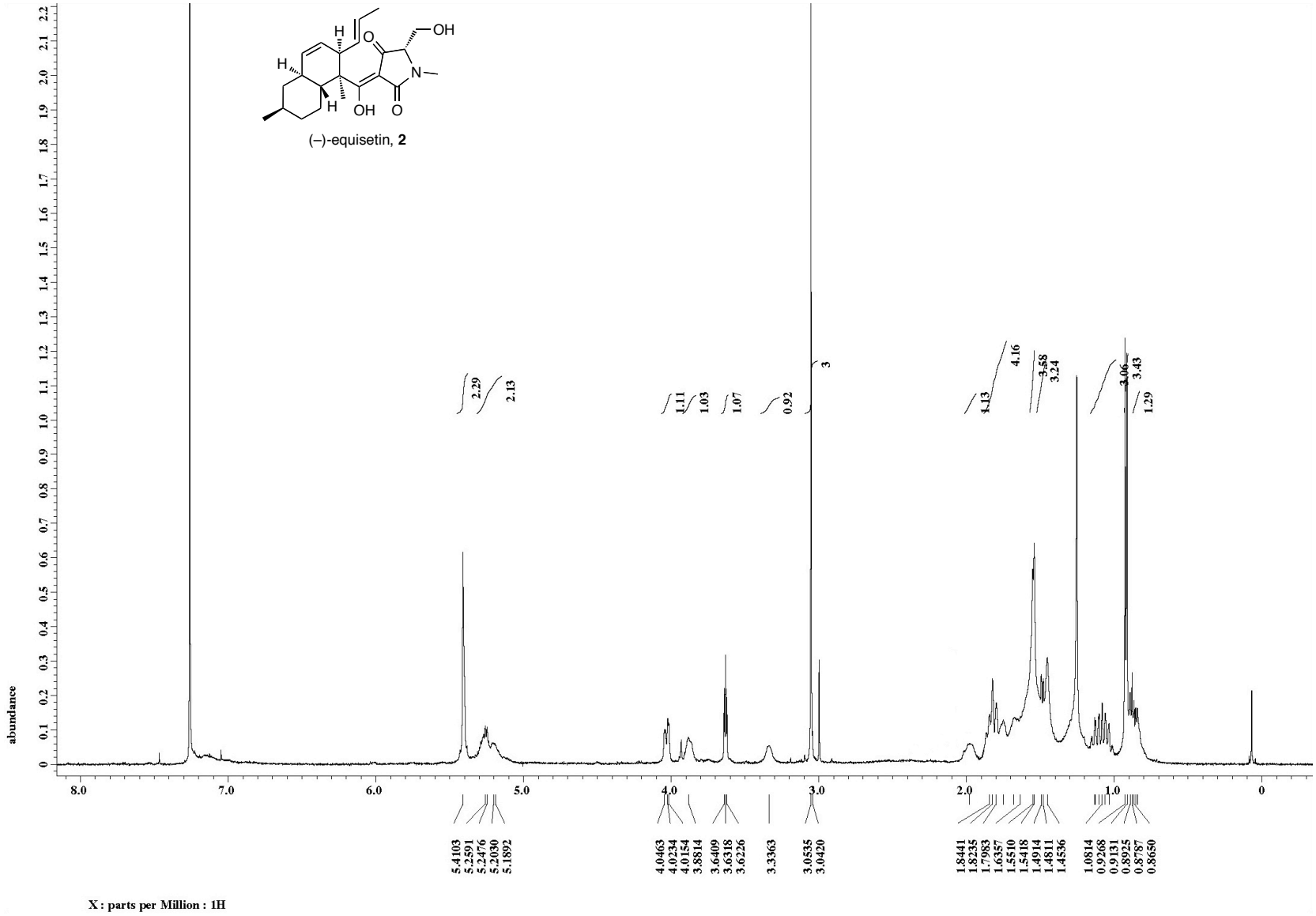


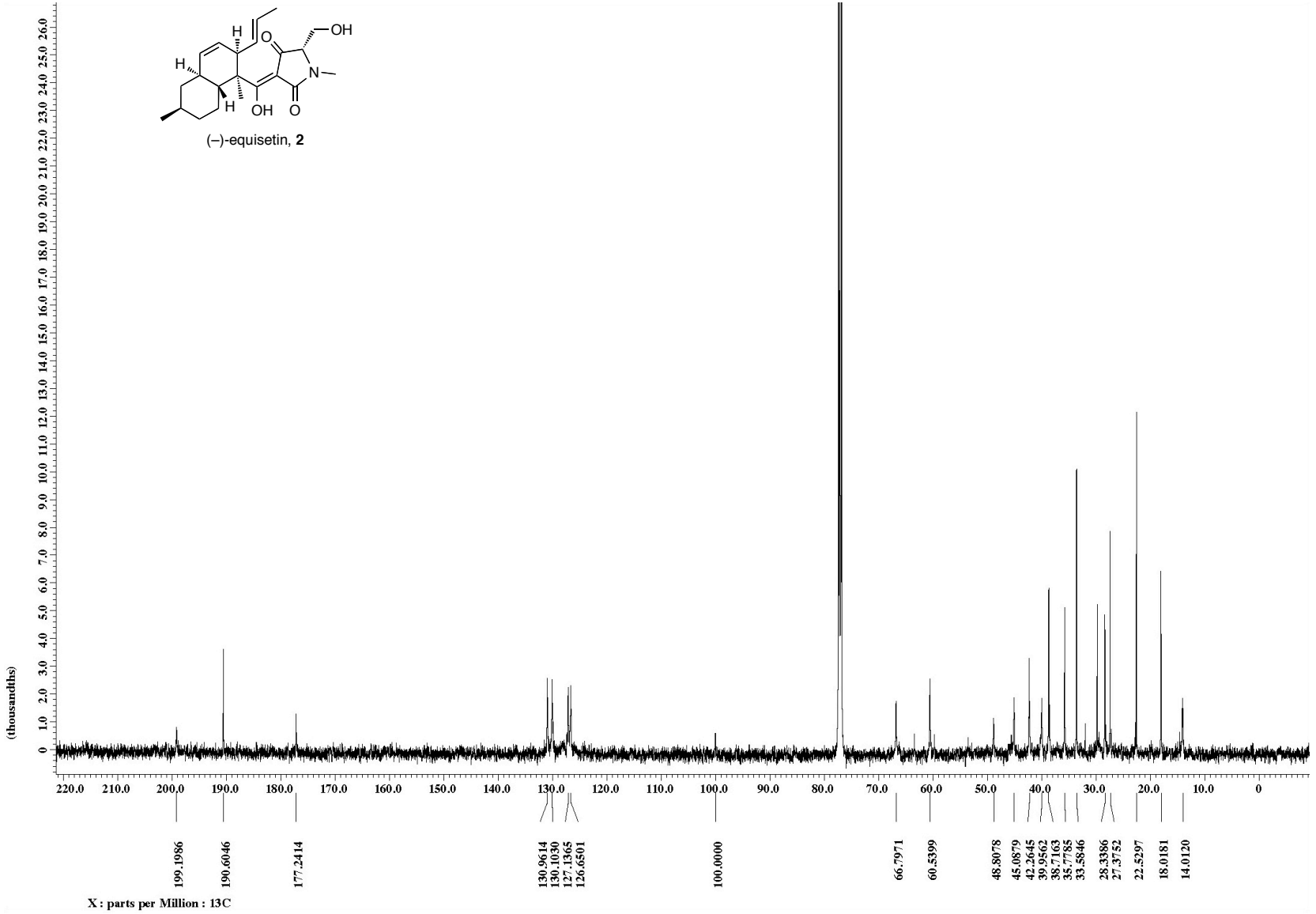


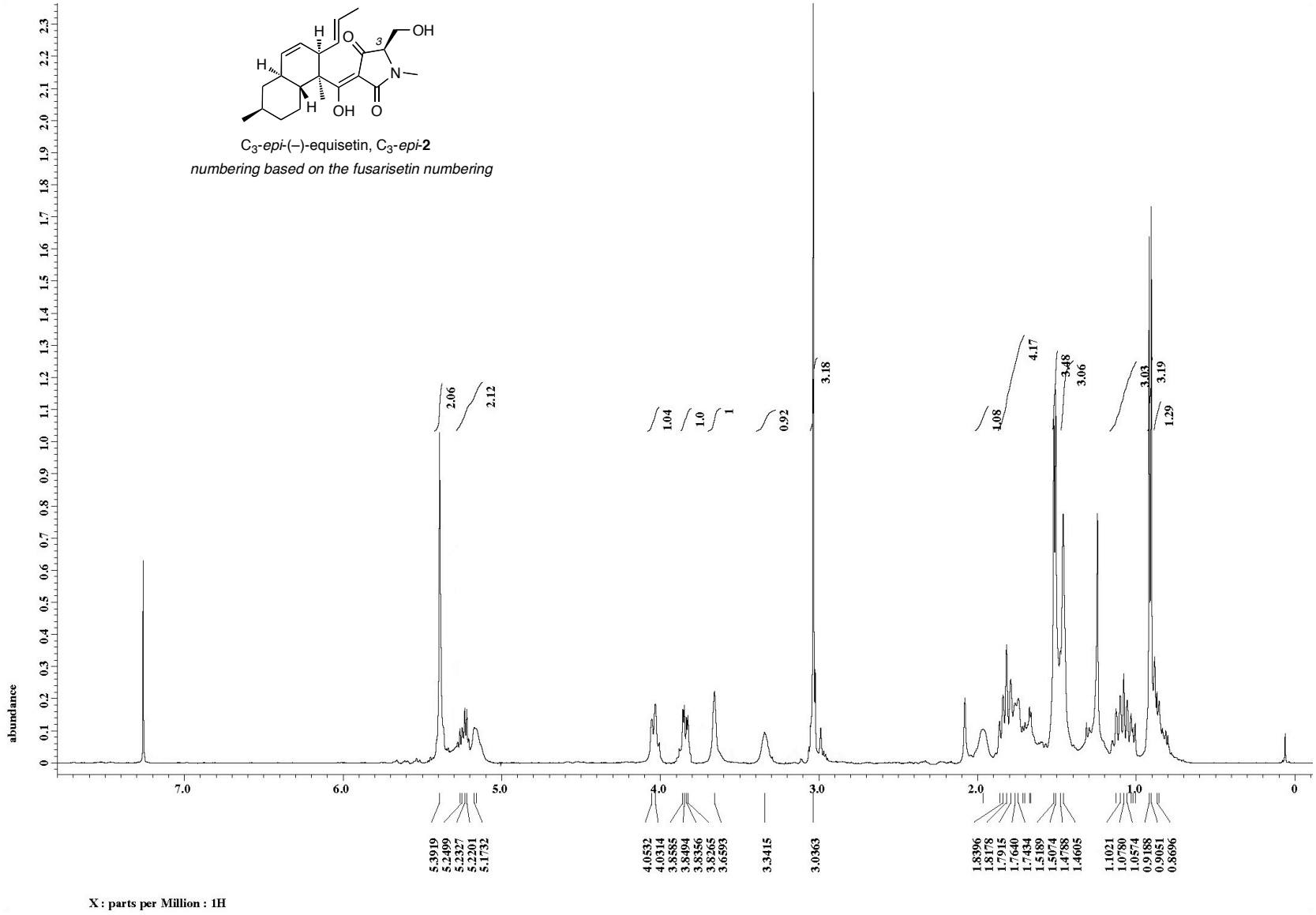


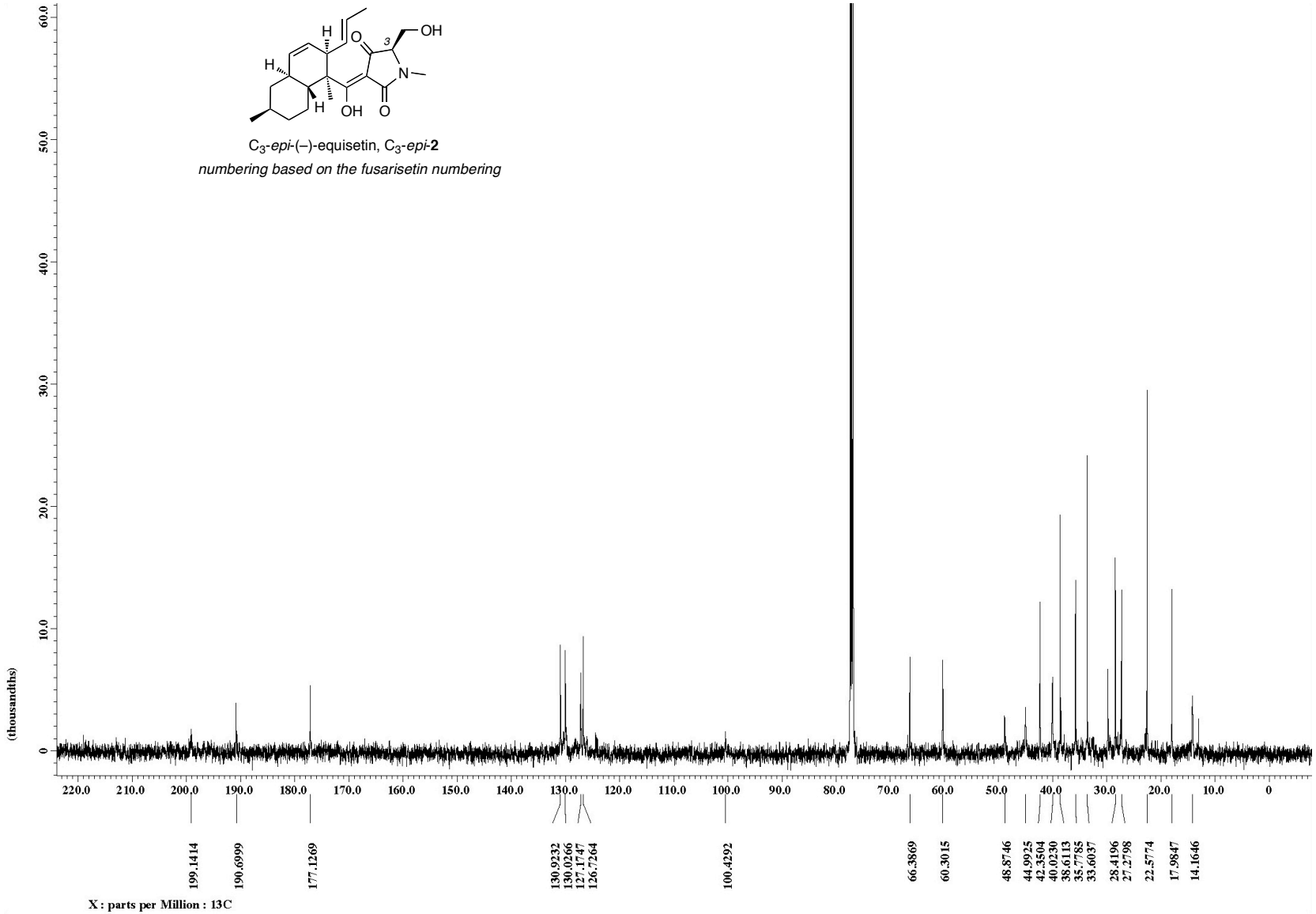


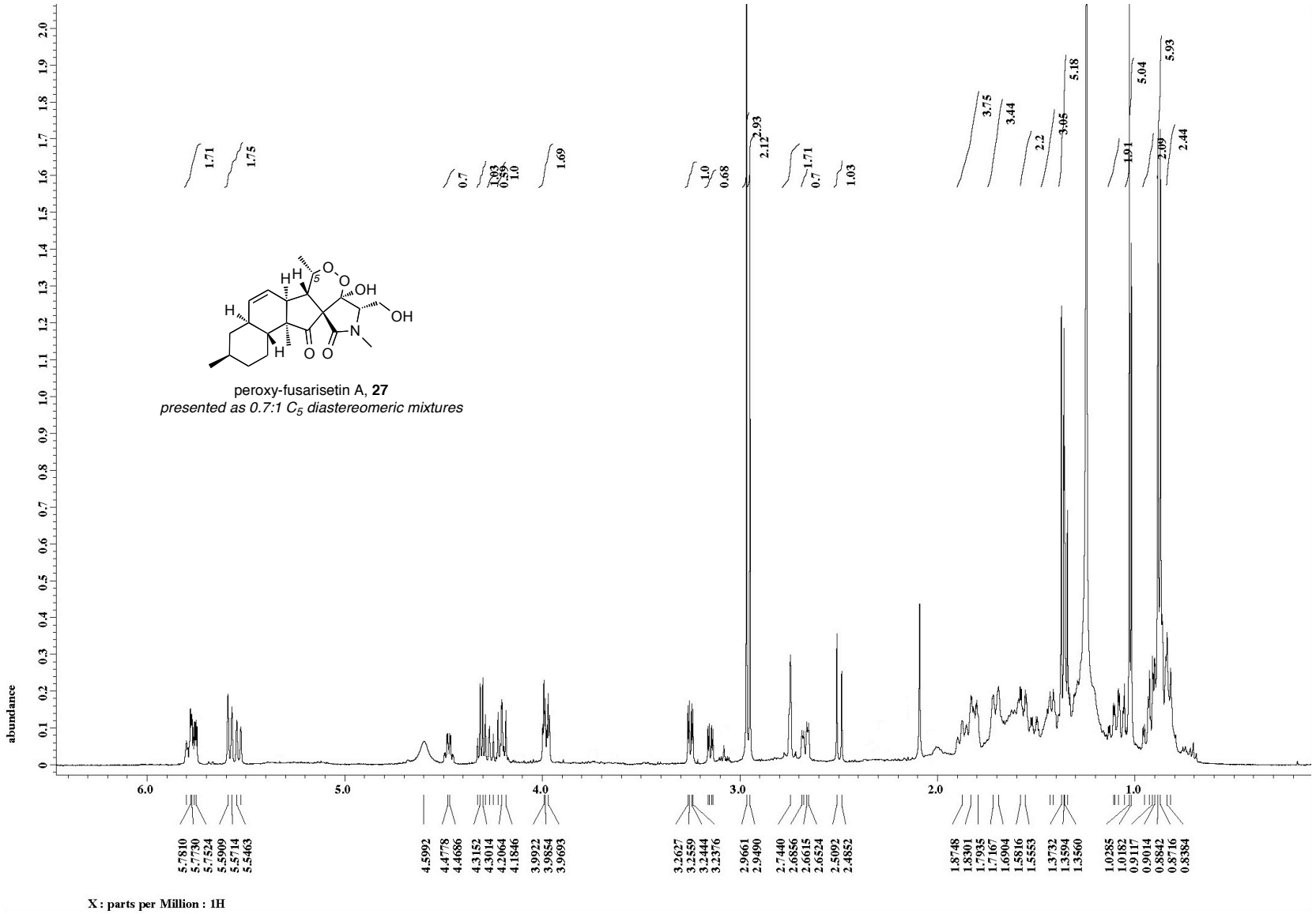












peroxy-fusarisetin A, **27**
presented as 0.7:1 C_5 diastereomeric mixtures