**Electronic Supplementary Materials**

# Total synthesis of griseusins and elucidation of the griseusin mechanism of action

Yinan Zhang,[a,b,c,†] Qing Ye,[d,†] Larissa V. Ponomareva,[b,c] Yanan Cao,[d] Yang Liu,[b,c] Zheng Cui,[c] Steven G. Van Lanen,[c] S. Randal Voss,[e] Qing-Bai She,*[,d] Jon S. Thorson*[,b,c]

[a]Jiangsu Key Laboratory for Functional Substances of Chinese Medicine, School of Pharmacy, Nanjing University of Chinese Medicine, Nanjing, Jiangsu, 210023, China

[b]Center for Pharmaceutical Research and Innovation

[c]College of Pharmacy, University of Kentucky, Lexington, KY 40536, USA

[d]Markey Cancer Center and Department of Pharmacology and Nutritional Sciences, College of Medicine, University of Kentucky, Lexington, KY 40536, USA

[e]Department of Neuroscience, Spinal Cord and Brain Injury Research Center, Ambystoma Genetic Stock Center, University of Kentucky, Lexington, KY 40536, USA

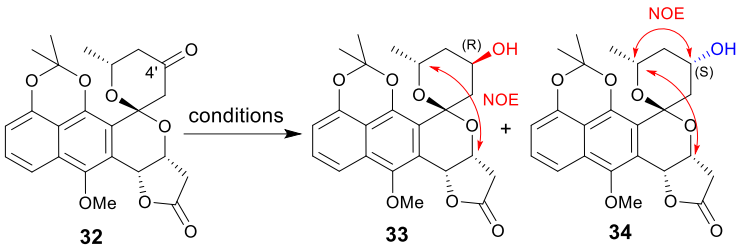
[†]These authors contribute equally to this work.

Correspondence to: Qing-Bai She, qing-bai.she@uky.edu; Jon S. Thorson, jsthorson@uky.edu

## Table of Contents

## Supplementary Tables and Figures

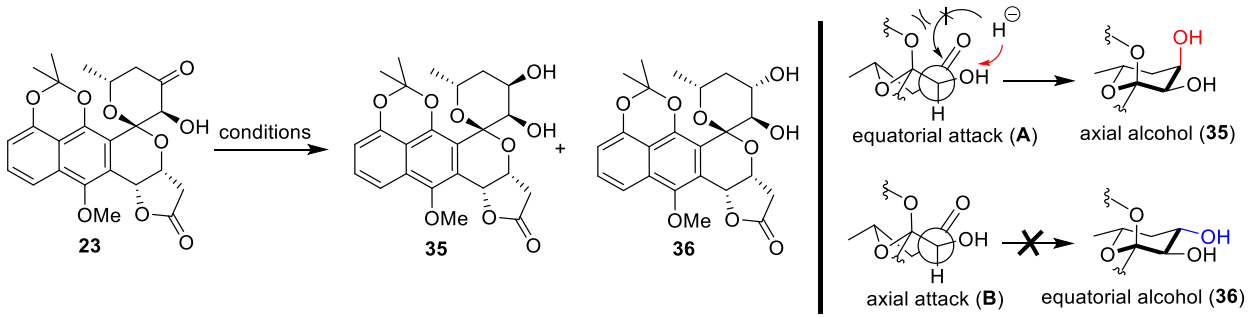
**Table S1.** Diastereoselective reduction of the precursor **32** 4-ketone.[a]




| entry | conditions | temp | time (h) | dr ratio[b] (**35:36**) | yields[c] (**35, 36**) |
|---|---|---|---|---|---|
| 1 | $NaBH_4$, MeOH | -78 ºC | 1 | 4:1 | -[d] |
| 2 | K-selectride, THF | -78 ºC | 2 | >10:1 | 94%, <5% |
| 3 | $BH_3 \cdot Me_2S$, THF | 0 ºC-rt | 2 | 1:2 | 30%, 62% |
| 4 | $BH_3 \cdot Me_3N$, HCl, THF | 0 ºC-rt | 16 | 1:2.5 | -[e] |
| 5 | $BH_3$·pyridine, HCl, THF | 0 ºC-rt | 16 | 1:3 | -[e] |
| 6 | $BH_3 \cdot tBuNH_2$, HCl, THF | 0 ºC-rt | 16 | 1:1 | -[e] |
| 7 | $BH_3$·2-picoline, HCl, THF | 0 ºC-rt | 16 | 1:5 | -[e] |
| 8 | $BH_3$·2-picoline, HCl, THF | -78 ºC-rt | 16 | 1:5 | -[e] |
| 9 | $BH_3$·2-picoline, AcOH, THF | 0 ºC-rt | 16 | -[d] | -[e] |
| 10 | $BH_3$·2-picoline, TsOH, THF | 0 ºC-rt | 16 | 1:4 | -[e] |
| 11 | $BH_3$·2-picoline, $(BnO)_2P(O)OH$, THF | 0 ºC-rt | 16 | 1:3 | -[e] |
| 12 | $BH_3$·2-picoline, HCl, DME | 0 ºC-rt | 16 | 1:10 | 6%, 62% |
| 13 | $BH_3$·2-picoline, HCl, tBuOMe | 0 ºC-rt | 16 | 1:8 | 9%, 71% |
| 14 | $BH_3$·2-picoline, HCl, dioxane | 0 ºC-rt | 16 | 1:10 | 5%, 52% |
| 15 | $BH_3$·2-picoline, HCl, ether | 0 ºC-rt | 16 | 1:10 | 8%, 75% |

[a]Key NOE crosspeaks are highlighted (red arrows). All reactions were carried out with substrate (0.05 mmol) under specified conditions and analyzed by analytical HPLC. [b]based on HPLC peak areas. [c]Isolated yields. [d]No reaction. [e]Not determined.

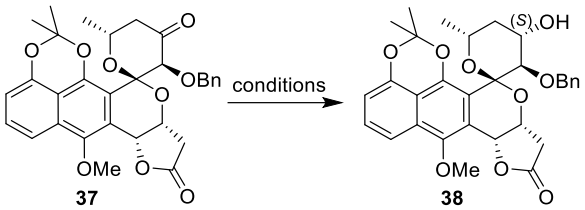
**Table S2.** Diastereoselective reduction of 4'-ketone of precursor **23**.[a]




| entry | conditions | temp | time (h) | dr ratio[b] (**35:36**) | yields[c] (**35, 36**) |
|---|---|---|---|---|---|
| 1 | 2 eq $NaBH_4$, 0.1 M MeOH | -78 °C | 1 | >10:1 | 80%, <5% |
| 2 | 2 eq K selectride, 0.1 M THF | -78 °C | 2 | >10:1 | 50%, <5% |
| 3 | 2 eq $NaCNBH_3$, 0.1 M MeOH | rt | 16 | -[d] | - |
| 4 | 2 eq $NaHB(OAc)_3$, 0.1 M THF | rt | 16 | -[d] | - |
| 5 | 2 eq $LiBH_4$, 0.1 M MeOH | -78 °C | 0.5 | >10:1 | 85%, <5% |
| 6 | 2 eq $LiHAl(OtBu)_3$, 0.1 M THF | rt | 16 | -[d] | - |
| 7 | 2 eq $NaBH_4$, 2 eq $CeCl_3$, 0.1 M MeOH | -78 °C-rt | 2 | >10:1 | - |
| 8 | 2 eq Red-Al, 0.1 M THF | -78 °c-rt | 2 | >10:1 | - |
| 9 | 2 eq $BH_3 \cdot Me_2S$, 0.1 M THF | 0 °C-rt | 2 | 10:1 | - |
| 10 | 2 eq $BH_3 \cdot Me_3N$, 4 eq HCl in dixoane, 0.1 M THF | 0 °C-rt | 16 | 5:1 | - |
| 11 | 2 eq $BH_3 \cdot$2-picoline, 4 eq HCl in dixoane, 0.1 M THF | 0 °C-rt | 16 | 10:1 | - |

[a]Reactions were carried out with 0.05 mmol **23** under specified conditions. Upon completion, a small portion of the reaction was analyzed by analytical HPLC and, where necessary, the reaction mixture purified on semi-preparative HPLC (products **35** and **36** could not be resolved via on normal phase chromatography). [b]HPLC peak area ratio. [c]Isolated yields. [d]No reaction.

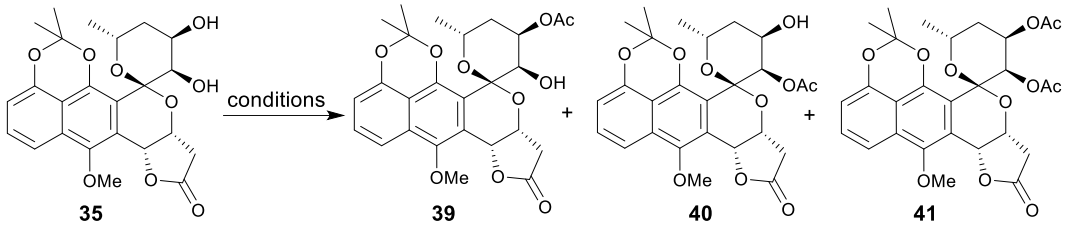
**Table S3.** Diastereoselective reduction of 4'-ketone of precursor **37**.[a]




| entry | conditions | time (h) | dr ratio[b] (*S:R*) | yield[c] (**38**) |
|---|---|---|---|---|
| 1 | 2 eq $BH_3 \cdot Me_2S$, 0.1 M THF, 0 °C-rt | 2 | 1:2 | - |
| 2 | 2 eq $BH_3 \cdot Me_3N$, 4 eq HCl in dixoane, 0.1 M THF, 0 °C-rt | 16 | 2:1 | - |
| 3 | 2 eq $BH_3 \cdot$pyridine, 4 eq HCl in dixoane, 0.1 M THF, 0 °C-rt | 16 | 1.3:1 | - |
| 4 | 2 eq $BH_3 \cdot Et_3N$, 4 eq HCl in dixoane, 0.1 M THF, 0 °C-rt | 16 | 1:1.8 | - |
| 5 | 2 eq $BH_3 \cdot$2-picoline, 4 eq HCl in dixoane, 0.1 M THF, 0 °C-rt | 16 | 1.5:1 | - |
| 6 | 2 eq $BH_3 \cdot Me_3N$, 4 eq HCl in dixoane, 0.1 M DME, 0 °C-rt | 16 | 2:1 | - |
| 7 | 2 eq $BH_3 \cdot Me_3N$, 4 eq HCl in dixoane, 0.1 M tBuOMe, 0 °C-rt | 16 | 4:1 | - |
| 8 | 2 eq $BH_3 \cdot Me_3N$, 4 eq HCl in dixoane, 0.1 M diglyme, 0 °C-rt | 16 | 2:1 | - |
| 9 | 2 eq $BH_3 \cdot Me_3N$, 4 eq HCl in dixoane, 0.1 M dioxane, 0 °C-rt | 16 | 1.2:1 | - |
| 10 | 2 eq $BH_3 \cdot Me_3N$, 4 eq HCl in dixoane, 0.1 M ether, 0 °C-rt | 16 | 3:1 | - |
| 11 | 2 eq $BH_3 \cdot Me_3N$, 4 eq TsOH, 0.1 M ether, 0 °C-rt | 16 | 1.5:1 | - |
| 12 | 2 eq $BH_3 \cdot Me_3N$, 4 eq $HClO_4$, 0.1 M ether, 0 °C-rt | 16 | 1:1.5 | - |
| 13 | 2 eq $BH_3 \cdot Me_3N$, 4 eq $F_2HCOOH$, 0.1 M ether, 0 °C-rt | 36 | 6:1 | 56% |
| 14 | 2 eq $BH_3 \cdot Me_3N$, 4 eq TFA, 0.1 M ether, 0 °C-rt | 16 | 9:1 | 65% |
| 15[d] | 2 eq $BH_3 \cdot Me_3N$, 4 eq TFA, 0.1 M ether, 0 °C-rt | 36 | 9:1 | 74% |

[a]Reactions were carried out with 0.02 mmol **37** under specified conditions. Upon completion, a small portion of the reaction was analyzed by analytical HPLC and, where necessary, the reaction mixture purified on semi-preparative HPLC. [b]HPLC peak area ratio. [c]Isolated yields. [d]0.5 mmol scale.

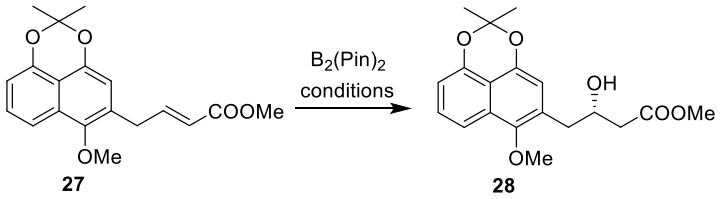
**Table S4.** Regioselective acetylation of precursor **35**.[a]




| entry | conditions | time (h) | yields[b] (**39, 40, 41, 35**) |
|---|---|---|---|
| 1 | 5 eq vinyl acetate, 10 mol% IMes[c], THF | 16 | 15%, 10%, 0%, 60% |
| 2 | 5 eq vinyl acetate, 5 mol% $PdCl_2$, 10mol% $CuCl_2$, toluene | 16 | 0%, 0%, 0%, >90% |
| 3 | 10 eq $Ac_2O$, 10 eq TEA, DCM | 16 | 44%, 15%, 0%, 32% |
| 4 | 10 eq $Ac_2O$, 10 eq DIPEA, DCM | 16 | 46%, 14%, 35%, <5% |
| 5 | 10 eq $Ac_2O$, 10 eq DIPEA, DCM | 40 | 61%[e], 24%, 5%, <5% |
| 6 | 10 eq $Ac_2O$, 10 eq DCHMA[d], DCM | 40 | 70%[e], 23%, <5%, <5% |
| 7 | 10 eq $Ac_2O$, 10 eq pyridine, DCM | 16 | <5%, 73%, 19%, <5% |
| 8 | 5 eq $Ac_2O$, 5 eq pyridine, DCM | 16 | <5%, 88%[e], <5%, <5% |
| 9 | 10 eq $Ac_2O$, 10 eq DABCO[f], DCM | 16 | <5%, <5%, 93%, <5% |

[a]Also see experimental details. [b]All reaction were carried out with substrate (0.02 mmol) under specified conditions and analyzed by $^1$H NMR analysis using 1-bromo-3,5-dichlorobenzene as an internal standard. [c]1,3-bis(2,4,6-trimethylphenyl)-imidazolium. [d]dicyclohexymethyl amine. [e]Isolated yields. [f]1,4-diazabicyclo[2.2.2]octane.

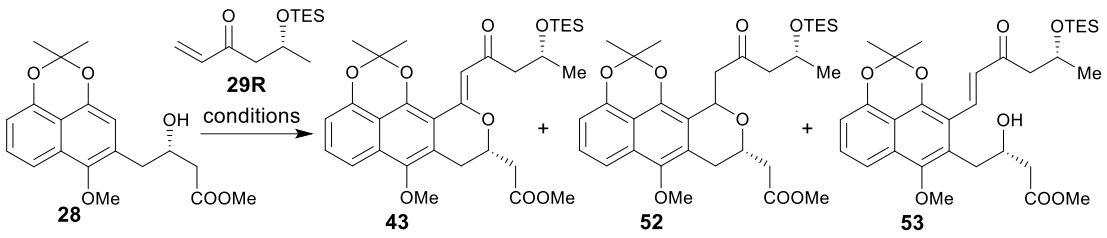
**Table S5.** Enantioselective β-conjugate addition of bis(pinacolato)diboron to precursor **27**.[a]




| entry | conditions | time (h) | yield[b] | ee[c] |
|---|---|---|---|---|
| 1 | 1 mol% Rh[(S,S)Phebox(OAc)$_2$], 5 mol% NaOtBu, toluene, 80 $^o$C | 3 | 37% | 75 |
| 2 | 1 mol% McQuade I, 5 mol% NaOtBu, MeOH (2 eq), toluene, -78 $^o$C-0 $^o$C | 3 | 56% | 37 |
| 3 | 1 mol% McQuade I, 5 mol% NaOtBu, MeOH (2 eq), THF, -78 $^o$C-0 $^o$C | 3 | 92% | 52 |
| 4 | 1.5 mol% CuCl, 3 mol% S-R$_p$-josiphos, 2.5 mol% NaOtBu, MeOH (2 eq), THF, rt | 3 | 93% | 86 |
| 5 | 1.5 mol% CuCl, 3 mol% S-R$_p$-josiphos, 2.5 mol% NaOtBu, MeOH (2 eq), toluene, rt | 16 | <5% | - |
| 6 | 1.5 mol% CuCl, 3 mol% S-R$_p$-josiphos, 2.5 mol% NaOtBu, MeOH (2 eq), THF, 0 $^o$C-rt | 16 | 87% | 90 |
| 7[d] | 1.5 mol% CuCl, 3 mol% S-R$_p$-josiphos, 2.5 mol% NaOtBu, MeOH (2 eq), THF, 0 $^o$C-rt | 16 | 91% | 90 |

[a]Reactions were carried out with 0.1 mmol **27** under specified conditions. Upon completion, 2 equivalent of $NaBO_3$ in water (1 mL) was added to the reaction and the resulting mixture was stirred at rt for 2 h. [b]Isolated yields. [c]Enantioselectivity were determined by NMR analysis of (*R*)-mosher esters obtained with intermediate **28** and its racemate **rac-28** (see Supplementary Methods for details).[1] [d]6 mmol scale.

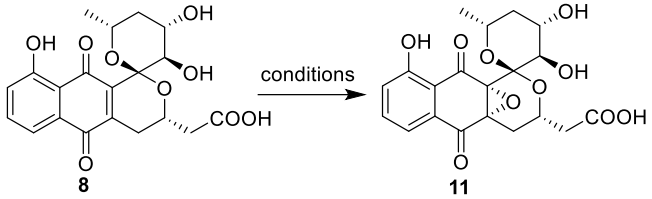
**Table S6.** C-H olefination of precursor **28**.[a]




| entry | conditions | solvent | yields[b] of **43, 52, 53, 28** |
|---|---|---|---|
| 1 | 20 mol% $Pd(OAc)_2$, 4 eq $Ag_2CO_3$ | DCE | 37%, 11%, <5%, 50% |
| 2 | 20 mol% $Pd(OAc)_2$, 4 eq $Ag_2CO_3$ | DCM | 25%, 16%, 13%, 40% |
| 3 | 20 mol% $Pd(OAc)_2$, 4 eq $Ag_2CO_3$ | $CHCl_3$ | 50%, 15%, <5%, 28% |
| 4 | 20 mol% $Pd(OAc)_2$, 4 eq $Ag_2CO_3$ | $CCl_4$ | <5%, <5%, <5%, 83% |
| 5 | 30 mol% $Pd(OAc)_2$, 4 eq $Ag_2CO_3$ | $CHCl_3$ | 61%, 12%, <5%, 22% |
| 6 | 40 mol% $Pd(OAc)_2$, 4 eq $Ag_2CO_3$ | $CHCl_3$ | 55%, 13%, 23%, 8% |
| 7 | 40 mol% $Pd(OAc)_2$, 2 eq $Ag_2CO_3$ | $CHCl_3$ | 66%, 18%, <5%, 10% |
| 8 | 50 mol% $Pd(OAc)_2$, 2 eq $Ag_2CO_3$ | $CHCl_3$ | 59%, 21%, <5%, 8% |
| 9[c] | 40 mol% $Pd(OAc)_2$, 2 eq $Ag_2CO_3$ | $CHCl_3$ | 63%[d], -%[e], -%, -% |

[a] Also see experimental details. [b]All reactions were carried out with **28** (0.05 mmol), **29*R*** (0.065 mmol), $Li_2CO_3$ (0.05 mmol), solvents (0.3 mL) at 80 °C for 16-24 h under specified conditions and analyzed by $^1H$ NMR using 1-bromo-3,5-dichlorobenzene as an internal standard. [c]4 mmol scale. [d]Isolated yields. [e]Not determined.

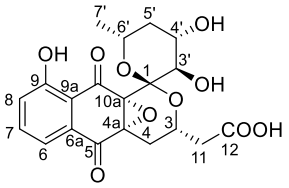
**Table S7.** Diastereoselective epoxidation of *epi*-deacetylgriseusin B (**8**) to 4a,10a-epoxy-*epi*-deacetylgriseusin B (**11**).[a]




| entry | conditions | time (h) | dr ratio[b] (**11**:*epi*-**11**) | yield[c] (**11**) |
|---|---|---|---|---|
| 1 | 2 eq $H_2O_2$, 0.1 M DCM, 0 °C-rt | 16 | - | <5% |
| 2 | 2 eq mCPBA, 0.1 M DCM, 0 °C-rt | 16 | - | <5% |
| 3 | 2 eq dimethyldioxirane, 0.1 M DCM, 0 °C-rt | 16 | - | <5% |
| 4 | 2 eq cumene oxide, 0.1 M DCM, 0 °C-rt | 16 | - | <5% |
| 5 | 2 eq tBuOOH, 0.1 M DCM, 0 °C-rt | 16 | - | <5% |
| 6 | 2 eq $H_2O_2$, 2 eq $NaHCO_3$, 0.1 M DCM, 0 °C-rt | 2 | 2:1 | 76% |
| 7 | 2 eq $H_2O_2$, 2 eq $Na_2CO_3$, 0.1 M DCM, 0 °C-rt | 2 | 3:1 | 90% |
| 8 | 2 eq $H_2O_2$, 2 eq KOtBu, 0.1 M DCM, 0 °C-rt | 2 | - | messy mixture |
| 9 | 2 eq $H_2O_2$, 2 eq TEA, 0.1 M DCM, 0 °C-rt | 2 | 6:1 | 87% |
| 10 | 2 eq $H_2O_2$, 2 eq DABCO, 0.1 M DCM, 0 °C-rt | 2 | 8:1 | 88% |
| 11 | 2 eq $H_2O_2$, 2 eq pyridine, 0.1 M DCM, 0 °C-rt | 16 | 3:1 | 83% |
| 12 | 2 eq $H_2O_2$, 2 eq DBU, 0.1 M DCM, 0 °C | 1 | 3:1 | 80% |
| 13 | 2 eq cumene oxide, 2 eq DABCO, 0.1 M DCM, 0 °C-rt | 16 | - | <5% |
| 14 | 2 eq tBuOOH, 2 eq DABCO, 0.1 M DCM, 0 °C-rt | 1 | - | messy mixture |
| 15 | 2 eq $H_2O_2$, 2 eq DABCO, 0.1 M DCM, -30 °C-0 °C | 2 | 8:1 | 82% |

[a]Reactions were carried out with 0.01 mmol **8** under specified conditions. Upon completion, dr ratio of the crude product was determined by $^1$H-NMR. Where necessary, the reaction mixture was subsequently purified on semi-preparative HPLC. [b]Determined $^1$H-NMR peak area ratio. [c]Isolated yields.

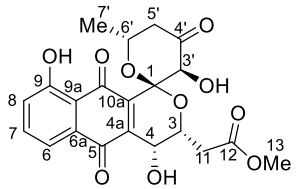
**Table S8.** Spectroscopic comparison of isolated[2] and synthetic **11**.



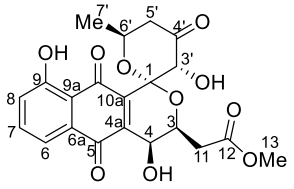

**11**

| position | Isolated **11** | | Synthesized **11** | |
|---|---|---|---|---|
| | $^{1}$H-NMR (ppm) | $^{13}$C-NMR (ppm) | $^{1}$H-NMR (ppm) | $^{13}$C-NMR (ppm) |
| 1 | | 97.1 | | 97.0 |
| 1-OH | 11.6 | | 11.6 | |
| 3 | 4.32 | 62.4 | 4.36 | 62.3 |
| 4 | 2.29, 2.48 | 27.5 | 2.33, 2.49 | 27.3 |
| 4a | | 63.9 | | 63.8 |
| 5 | | 189.4 | | 189.4 |
| 6a | | 131.1 | | 131.0 |
| 6 | 7.55 | 119.2 | 7.59 | 119.2 |
| 7 | 7.58 | 136.9 | 7.63 | 136.9 |
| 8 | 7.22 | 125.1 | 7.24 | 125.1 |
| 9 | | 162.7 | | 162.6 |
| 9-OH | | | | |
| 9a | | 114.4 | | 114.4 |
| 10 | | 193.1 | | 193.0 |
| 10a | | 62.9 | | 62.8 |
| 11 | 2.53, 2.64 | 38.8 | 2.59, 2.67 | 38.5 |
| 12 | | 174.1 | | 173.9 |
| 3’ | 4.44 | 74.3 | 4.46 | 74.3 |
| 4’ | 3.88 | 68.9 | 3.91 | 68.8 |
| 5’ | 1.54, 1.96 | 40.1 | 1.57,1.99 | 39.9 |
| 6’ | 4.03 | 66.3 | 4.03 | 66.3 |
| 7’ | 1.23 | 21.2 | 1.25 | 20.8 |
| $[\alpha]_D^{20}$ | +9$^o$ | | +11$^o$ | |

**Table S9.** Spectroscopic comparison of isolated griseusin D[3] and synthetic **12**.



isolated griseusin D



**12**

| position | griseusin D | | **12** | |
|---|---|---|---|---|
| | $^{1}$H-NMR (ppm) | $^{13}$C-NMR (ppm) | $^{1}$H-NMR (ppm) | $^{13}$C-NMR (ppm) |
| 1 | | 100.2 | | 100.2 |
| 1-OH | | | 11.84 | |
| 3 | 4.31 | 67.9 | 4.33 | 67.9 |
| 4 | 4.45 | 58.5 | 4.46 | 58.5 |
| 4a | | 136.8 | | 136.7 |
| 5 | | 182.0 | | 182.0 |
| 6a | | 131.5 | | 131.5 |
| 6 | 7.57 | 118.5 | 7.57 | 118.5 |
| 7 | 7.78 | 137.0 | 7.78 | 137.0 |
| 8 | 7.38 | 124.6 | 7.39 | 124.6 |
| 9 | | 160.5 | | 160.5 |
| 9-OH | | | | |
| 9a | | 114.9 | | 114.9 |
| 10 | | 187.8 | | 187.8 |
| 10a | | 145.3 | | 145.3 |
| 11 | 2.81, 2.69 | 34.7 | 2.80, 2.72 | 34.7 |
| 12 | | 171.0 | | 171.0 |
| 13 | 3.62 | 51.5 | 3.62 | 51.5 |
| 3’ | 5.13 | 76.3 | 5.13 | 76.3 |
| 4’ | | 203.7 | | 203.8 |
| 5’ | 2.42, 2.59 | 47.7 | 2.42, 2.59 | 47.7 |
| 6’ | 4.28 | 67.5 | 4.28 | 67.5 |
| 7’ | 1.25 | 21.1 | 1.25 | 21.1 |
| $[\alpha]_{D}^{20}$ | -67$^{o}$ | | +75$^{o}$ | |

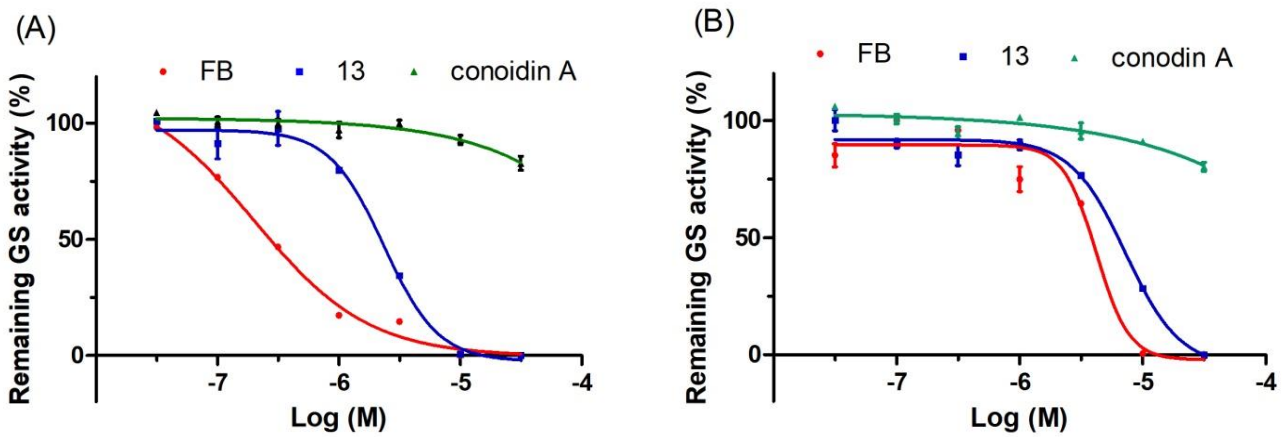



**Figure S1.** The inhibitory $IC_{50}$ of compound **13**, frenolicin B (FB), and conoidin A against peroxiredoxin 1 (A) and 2 (B) based on the glutamine synthase (GS) protection assay (see Supplementary Methods) under various concentrations (0.03-30 μM) in triplicate.

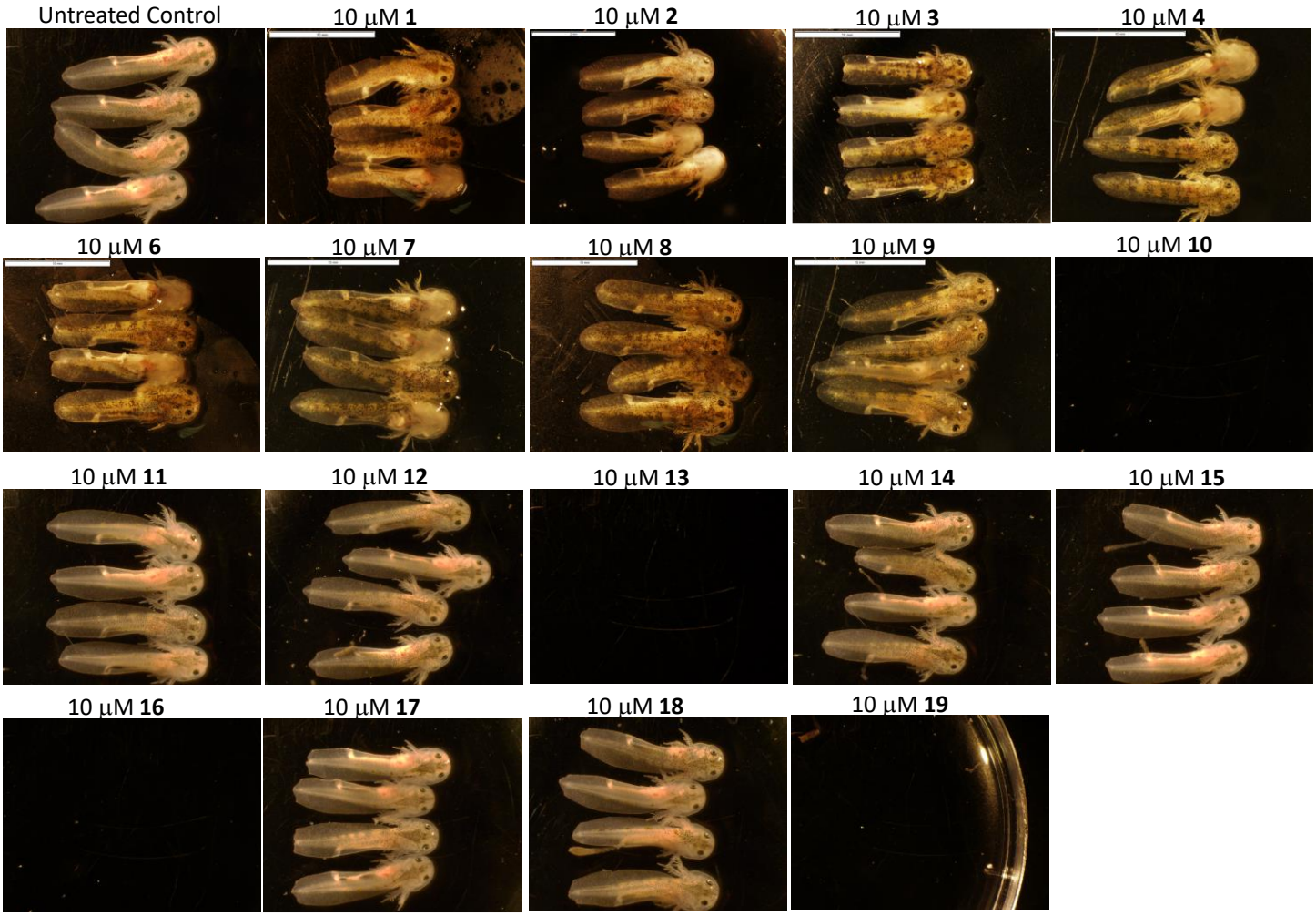
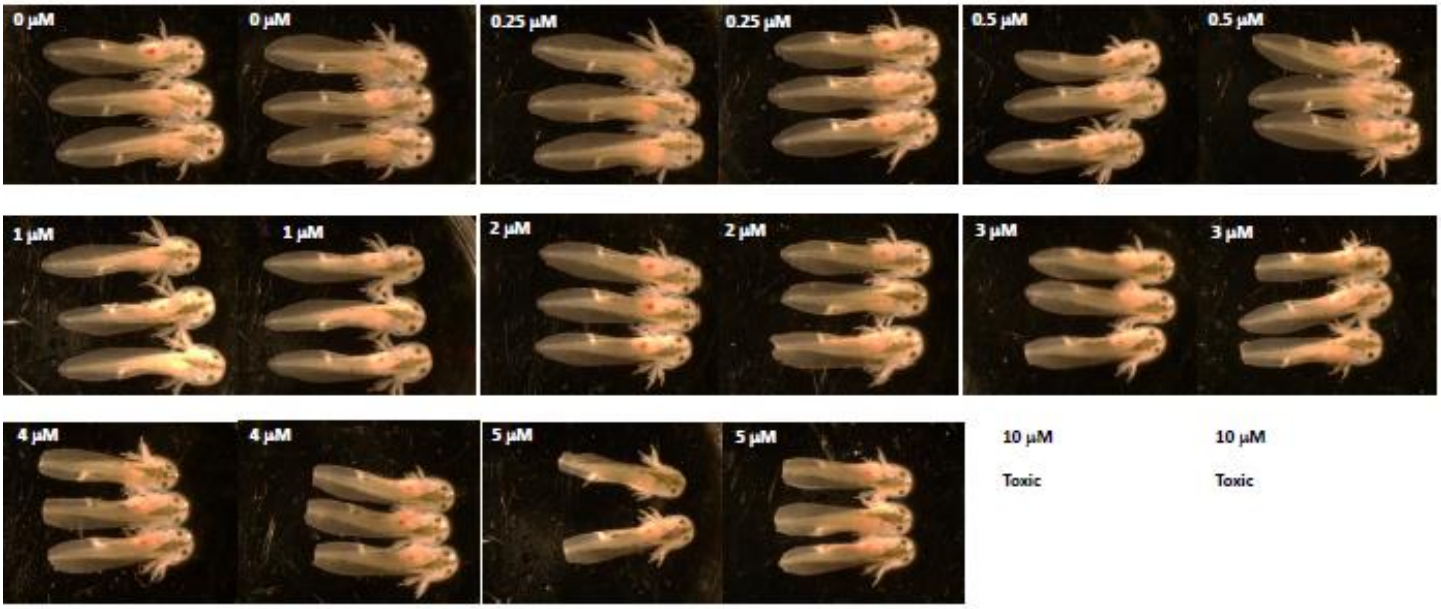



**Figure S2.** Single dose ETR assay of compounds (**1**-**4** and **6**-**19**) at 10 μM (see Supplementary Methods).



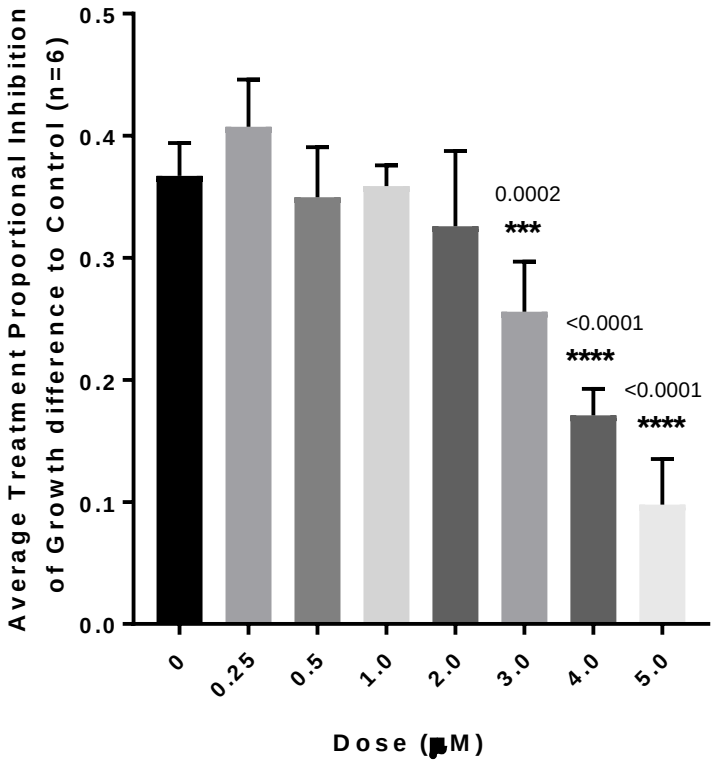




**Figure S3.** ETR assay dose response with compound **13** (***p< 0.005, ****p<0.0001, n=3; see Supplementary Methods).

## Supplementary Methods

**General Chemistry Methods.** $^{1}H$ (400 MHz) and $^{13}C$ (100 MHz) NMR spectra were recorded on a Varian Unity Inova 400 MHz instrument (Palo Alto, CA). The chemical shifts were reported in $\delta$ (ppm) using the $\delta$ 7.26 signal of $CDCl_3$, $\delta$ 1.94 signal of $CD_3CN$ and $\delta$ 2.50 signal of DMSO-$d_6$ ($^{1}H$ NMR), the $\delta$ 77.16 signal of $CDCl_3$, $\delta$ 1.32 signal of $CD_3CN$ and $\delta$ 39.52 signal of DMSO-$d_6$ ($^{13}C$ NMR) as internal standards. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. HR-ESI-MS experiments were carried out using AB SCIEX TripleTOF® 5600 System with internal standard (M = 510.3554) in the positive mode. HPLC analyses were performed using an Agilent 1260 system equipped with a DAD detector and a Phenomenex C18 column (4.6 × 150 mm, 0.5 μm, 1 mL/min, $CH_3CN$-$H_2O$ gradient as eluent). Semi-preparative HPLC separation was performed using a Varian Prostar 210 HPLC system equipped with a PDA detector 330 using a Supelco C18 column (25 × 21.2 mm, 10 μm 10 mL/min, $CH_3CN$-$H_2O$ gradient as eluent). All commercially available reagents were used without further purification, purchased from Sigma-Aldrich (St. Louis, MO), TCI America (Portland, OR) and Alfa-Aesar (Tewksbury, MA). The progress of the reactions was monitored by analytical thin-layer chromatography (TLC) from EMD Chemicals Inc. (Darmstadt, Germany) with fluorescence $F_{254}$ indicator. And Silica gel (230–400 mesh) for column chromatography was purchased from Silicycle (Quebec City, Canada).

**Cell Culture.** Human colon (HCT116, DLD-1), prostate (PC3) and lung (A549) cancer cell lines were obtained from the American Type Culture Collection (ATCC, Manassas, VA) and cultured as per ATCC recommendations. All the cell lines were confirmed to be free of mycoplasma contamination via PCR (e-Myco Plus kit; iNtRON Biotechnology). In addition, all the cell lines were routinely checked for morphologic and growth changes, to avoid cross-contamination or genetic drift. If observed, cell lines were re-authenticated using the short tandem repeat (STR) profiling service by ATCC.

**Antibodies and Chemicals.** Antibodies for phospho-AKT (Ser473) (#4060), phospho-p44/42 MAPK (Erk1/2) (Thr202/Tyr204) (#4370), phospho-p70S6 kinase (Thr389) (#9234), phospho-4E-BP1 (Thr37/46) (#2855), phospho-4E-BP1 (Ser65) (#13443) and phospho-4E-BP1 (Thr70) (#13396) were from purchased from Cell Signaling Technology (Danvers, MA). Peroxiredoxin 1 antibody (#ab15571) was from purchased from Abcam (Cambridge, MA), glutaredoxin 3 antibody (sc-100601) from Santa Cruz Biotechnology (Santa Cruz, CA) and β-actin antibody (#A5411) from Sigma (St. Louis, MO).

**Cell Viability Assay.** Cell growth was assessed as previously described.[4] Briefly, $5 \times 10^4$ cells/well were seeded in 6-well plates in triplicate. After 24 h, cells were treated with the indicated compounds for 3 days, and the number of viable cells was counted using the Vi-CELL XR 2.03 (Beckman Coulter).

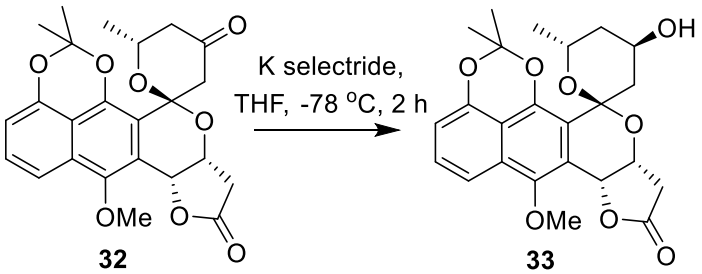
**Western Blot Analysis.** Cells were lysed in NP-40 lysis buffer (50 mM Tris-HCl, pH 7.5, 150 mM NaCl, 1 mM EDTA, 1% NP-40, 10% glycerol, protease and phosphatase inhibitor cocktail). Protein concentrations were measured using the BCA protein assay reagent (ThermoFisher Scientific, Waltham, MA). Equal amounts of protein were resolved by SDS-PAGE, transferred to PVDF membranes, immunoblotted with specific primary and secondary antibodies, and detected using chemiluminescence (GE Healthcare, Chicago, IL).

**Frenolicin B -Based Pulldown Competition Assay.** FB-based biotinylated active probe 1 and inactive probe 2 were synthesized and reported previously.[4] HCT116 cells were lysed in the NP-40 lysis buffer. The cell lysates (500 μg protein) were incubated with 1 μM probe 1 or probe 2 in the absence or presence of a ten-fold excess of compound **13** for 1 h, followed by pulldown with streptavidin agarose beads and Western blot analysis for the indicated proteins.

**Prx1/2 Inhibition Assay.** The Prx1/2 assay was conducted as previously described.[4b] Varying concentrations of FB, compound **13** and conoidin A (0.03-30 μM) were incubated with 0.2 μg DTT-reduced Prx1 or Prx2 in a total volume of 16 μL 100 mM HEPES buffer (pH 7.4) at room temperature for 15 min. Glutamine synthase (GS; 1 μl of 1 unit/μl stock in HEPES buffer, pH 7.4) and 3 μl of inactivation solution (50 mM DTT, 5 μM $FeCl_3$, 100 mM

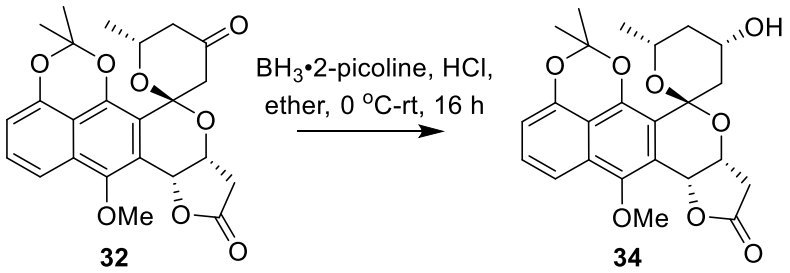
HEPES, pH 7.4) were added and the mixture was incubated at 30ºC for 20 min. Initiation solution (150 µl total; 100 mM HEPES, 10 mM $KH_2AsO_4$, 20 mM $NH_2OH{\cdot}HCl$, 0.4 mM ADP, 0.5 mM $MnCl_2$, 100 mM glutamine, pH 7.0) was subsequently added and the mixture incubated at 30ºC for an additional 30 min. Finally, the reaction was terminated by the addition of termination solution (80 µl total; 5.5% $FeCl_3{\cdot}6H_2O$, 2% TCA, 2% concentrated HCl), after which the absorption at 540 nm was measured and normalized to a corresponding blank lacking inhibitor. Assays were conducted in triplicate and the $IC_{50}$ values were calculated using Prism software. Using the described conditions, linear signal range was observed with assays containing 0.2-0.4 µg Prx1 and Prx2. FB and compound **13** were also confirmed to have no direct effect on GS activity (highest concentration tested 30 µM).

**Axolotl embryo tail regeneration assay.** The tail regeneration assay was conducted as previously described.[5] Mexican axolotl (*Ambystoma mexicanum*) embryos were obtained from the Ambystoma Genetic Stock Center at the University of Kentucky. Stage 42 embryos were manually hatched, administered benzocaine anesthesia (0.2 g in 10 mL EtOH stock diluted in 1L water), and photographed. For each test agent, 4-6 embryos were administered tail amputations. Additionally, control groups of embryos with tail amputations were reared in artificial pond water (43.25 g NaCl, 0.625 g KCl, 1.25 g $MgSO_4$, 2.5 g $NaHCO_3$ and 1.25 g CaCl per 50 L charcoal filtered municipal water). In administering amputations, the distal most 2 mm of tail tissue was removed with a sterile razor blade and photographs were taken to document the regeneration process. Images were captured using an Olympus microscope with 0.5× objective lens and DP400 camera. Embryos were reared at 18–19 ºC in 12-well microtiter plates, one embryo per well. Each well contained 2.0 mL of artificial pond water and 10 µM of chemical (or serial dilutions where noted). All chemicals were dissolved in DMSO and diluted to 0.1% final DMSO concentration. The solutions were changed on days 3 and 5 post-amputation (DPA), and experiments were terminated on 7 DPA. At 7 DPA, embryos were euthanized by prolonged exposure to 10× benzocaine (0.4 g in 10 mL EtOH stock diluted in 1L water) and imaged. The proportional increase in body length (day 7 body length – post-amputation body length / post-amputation body length) was compared between chemically treated and control embryos using Student's t-test. The use of pre-feeding stage axolotls does not require a protocol approved by the Institutional Animal Care and Use Committee (IACUC) at University of Kentucky. However, embryos used in this study were treated according to the same ethical standards that apply to feeding axolotls, which are cared for using standard axolotl husbandry methods approved under IACUC protocol 2017-2580. Embryos (RRID:AGSC_100E) were obtained from the Ambystoma Genetic Stock Center (RRID:SCR_006372).



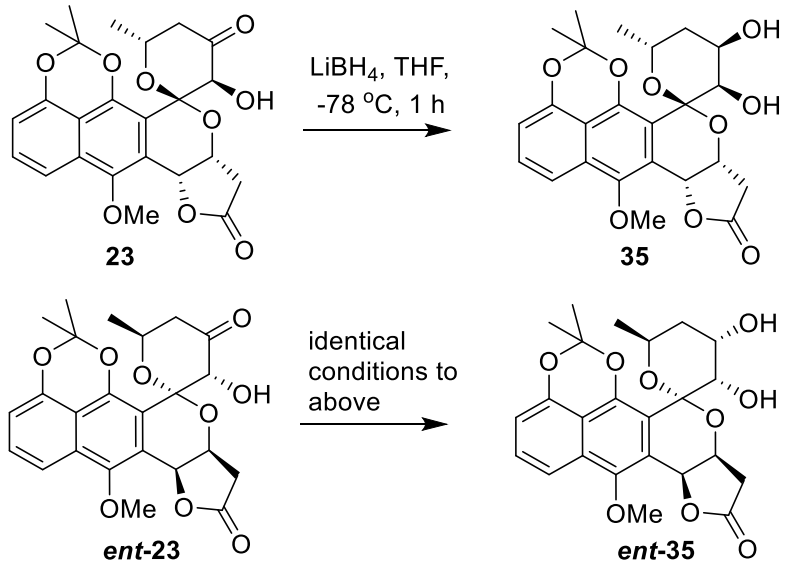

**(*4'R,6'R,7bR,10aR,12S*)-4'-Hydroxy-7-methoxy-2,2,6'-trimethyl-3',4',5',6',10,10a-hexahydrospiro[furo[2'',3'':5',6']pyrano[3',4':2,3]naphtho[1,8-de][1,3]dioxine-12,2'-pyran]-9(7b*H*)-one (33).** A solution of compound **32**[6] (44 mg, 0.1 mmol) in anhydrous THF (1 mL) was cooled to -78 ºC and then treated with K-selectride (0.2 mL, 0.2 mmol, 1 M in THF) in dropwise fashion with stirring. The reaction mixture was stirred for 2 h before the addition of saturated $NH_4Cl$ solution (2 mL). The mixture was warmed to room temperature and extracted with EtOAc (10 mL x 2) and the combined organic layers were washed with brine, dried over $Na_2SO_4$, filtered, and concentrated. The residue was purified by silica gel chromatography using 1:1 hexane/EtOAc to afford **33** as a colorless solid (41 mg, 94% yield). $R_f$ 0.40 (2:3 hexane/EtOAc); $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 7.64 (d, $J$ = 8.8 Hz, 1H), 7.47 (t, $J$ = 8.0 Hz, 1H), 6.92 (d, $J$ = 8.0 Hz, 1H), 5.59 (d, $J$ = 2.4 Hz,

1H), 4.81 (dd, *J* = 2.4, 4.4 Hz, 1H), 4.29 (m, 2H), 4.09 (s, 3H), 3.43 (br s, 1H), 3.18 (dd, *J* = 3.6, 14.4 Hz, 1H), 3.03 (dd, *J* = 4.4, 17.6 Hz, 1H), 2.75 (d, *J* = 17.6 Hz, 1H), 2.00 (d, *J* = 14.8 Hz, 1H), 1.93 (d, *J* = 14.0 Hz, 1H), 1.69 (s, 3H), 1.62 (s, 3H), 1.59 (m, 1H), 1.24 (d, *J* = 6.0 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ = 174.9, 150.9, 148.8, 128.5, 128.1, 118.9, 117.3, 115.3, 115.2, 111.0, 110.1, 101.9, 98.6, 72.3, 66.6, 65.2, 64.4, 62.4, 39.2, 37.8, 36.7, 25.5, 25.0, 21.7 ppm; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{24}H_{27}O_8$ 443.1706, found 443.1710.




**32** **34**

**(*4'S,6'R,7bR,10aR,12S*)-4'-Hydroxy-7-methoxy-2,2,6'-trimethyl-3',4',5',6',10,10a-hexahydrospiro[furo[2'',3'':5',6']pyrano[3',4':2,3]naphtho[1,8-de][1,3]dioxine-12,2'-pyran]-9(7b*H*)-one (34).** $BH_3$•2-picoline (21 mg, 0.2 mmol) and HCl (100 uL, 0.4 mmol, 4 M in dioxane) were added to a cooled solution of compound **33**[6] (44 mg, 0.1 mmol) in ether (2 mL) at 0 °C. The mixture was stirred for 16 h during which the temperature was allowed to equilibrate to room temp. The resulting solution was neutralized with saturated $NaHCO_3$ (2 mL) and extracted with EtOAc (10 mL x 2). The combined organic layers were washed with brine, dried over $Na_2SO_4$ and concentrated. The residue was purified using silica gel chromatography with 1:1 hexane/EtOAc to afford the product as a colorless solid (33 mg, 75% yield). $R_f$ 0.40 (2:3 hexane/EtOAc); $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 7.61 (d, *J* = 8.4 Hz, 1H), 7.46 (t, *J* = 7.6 Hz, 1H), 6.90 (d, *J* = 7.6 Hz, 1H), 5.57 (s, 1H), 4.66 (s, 1H), 4.33-4.27 (m, 1H), 4.07 (s, 3H), 4.93-3.99 (m, 2H), 2.96 (dd, *J* = 4.4, 17.2 Hz, 1H), 2.79-2.69 (m, 2H), 2.07-2.01 (m, 2H), 1.66 (s, 3H), 1.64 (s, 3H), 1.34 (q, *J* = 11.6 Hz, 1H), 1.22 (d, *J* = 6.0 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ = 176.0, 150.7, 148.8, 141.6, 128.4, 128.0, 119.2, 117.2, 115.3, 115.1, 110.8, 101.9, 97.8, 72.6, 66.7, 66.1, 65.1, 64.3, 41.7, 40.6, 37.6, 25.2, 25.1, 21.7 ppm; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{24}H_{27}O_8$ 443.1706, found 443.1688.

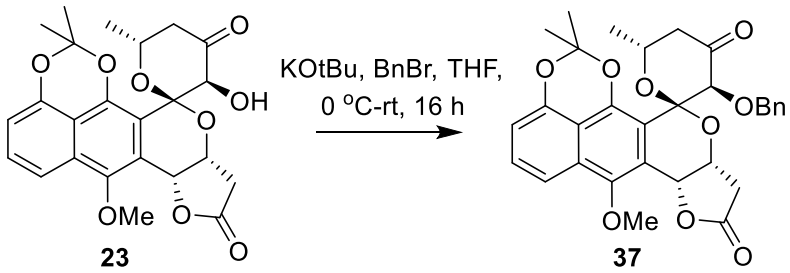



**23** **35**

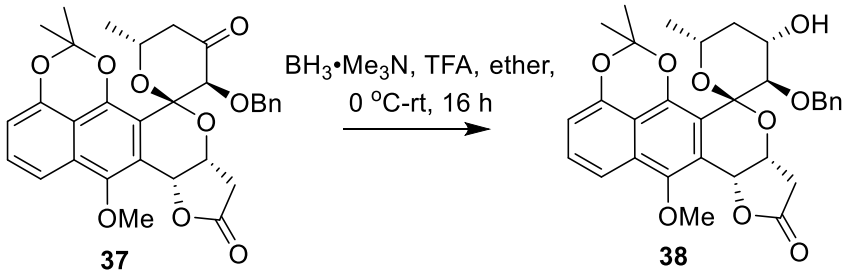
***ent*-23** ***ent*-35**

**(*3'R,4'R,6'R,7bR,10aR,12R*)-3',4'-dihydroxy-7-methoxy-2,2,6'-trimethyl-3',4',5',6',10,10a-hexahydrospiro[furo[2'',3'':5',6']pyrano[3',4':2,3]naphtho[1,8-de][1,3]dioxine-12,2'-pyran]-9(7bH)-one (35).** $LiBH_4$ (9 mg, 0.4 mmol) was added to a THF solution (2 mL) containing compound **23**[6] (90 mg, 0.2 mmol) at -78 °C. The resulting mixture was stirred for 1 h at -78 °C followed by the addition with $H_2O$ (1 mL). The

mixture was extracted with EtOAc (10 mL x 2) and the combined organic layers were washed with brine (5 mL), and dried over $Na_2SO_4$. After evaporating the volatiles, the residue was purified using silica gel chromatography with 1:2 hexane/EtOAc to obtain the product as a colorless solid (78 mg, 85% yield). $R_f$ 0.25 (2:3 hexane/EtOAc); $^1$H NMR ($CD_3OD$, 400 MHz): $\delta$ = 7.68 (d, $J$ = 8.0 Hz, 1H), 7.53 (t, $J$ = 8.0 Hz, 1H), 6.95 (d, $J$ = 8.0 Hz, 1H), 5.65 (s, 1H), 4.86 (br s, 1H), 4.79 (s, 1H), 4.32-4.28 (m, 1H), 4.15 (br s, 1H), 4.07 (s, 3H), 3.16 (dd, $J$ = 4.4, 17.6 Hz, 1H), 2.87 (d, $J$ = 17.6 Hz, 1H), 2.00 (d, $J$ = 14.0 Hz, 1H), 1.83-1.77 (m, 1H), 1.69 (s, 3H), 1.60 (s, 3H), 1.20 (d, $J$ = 6.0 Hz, 3H); $^{13}$C NMR ($CD_3OD$ , 100 MHz): $\delta$ = 178.1, 151.9, 150.1, 142.5, 129.5, 129.2, 121.6, 117.7, 116.2, 116.1, 111.8, 103.1, 100.5, 73.3, 69.7, 69.3, 68.1, 64.4, 62.9, 40.9, 38.0, 25.5, 25.1, 21.2 ppm; HRMS (ESI) m/z $[M + NH_4]^+$ calcd for $C_{24}H_{30}NO_9$ 476.1921, found 476.1912. The synthesis of ***ent*-35** followed the same protocol starting from ***ent*-23** and the corresponding characterization data was consistent with that of **35**.

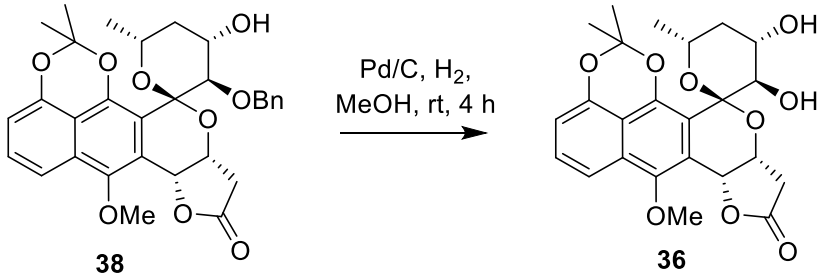



**(*3'R,6'R,7bR,10aR,12R*)-3'-(benzyloxy)-7-methoxy-2,2,6'-trimethyl-5',6',10,10a-tetrahydrospiro[furo[2'',3'':5',6']pyrano[3',4':2,3]naphtho[1,8-de][1,3]dioxine-12,2'-pyran]-4',9(3'H,7bH)-dione (37).** KOtBu (22 mg, 0.2 mmol) and benzyl bromide (23 μL, 0.2 mmol) were added to a THF solution (1 mL) containing compound **23**[6] (45 mg, 0.1 mmol) at 0 °C. The resulting mixture was allowed to equilibrate to room temperature with stirring overnight. The mixture was neutralized with saturated $NH_4Cl$ solution (2 mL), extracted with $CHCl_3$ (10 mL x 2) and the combined organic layers were washed with brine (5 mL), and dried over $Na_2SO_4$. After evaporating the volatiles, the residue was purified by silica gel chromatography using 4:1 hexane/EtOAc to obtain the product as a colorless solid (42 mg, 77% yield). $R_f$ 0.35 (2:1 hexane/EtOAc); $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ = 7.67 (d, $J$ = 8.4 Hz, 1H), 7.51 (t, $J$ = 8.0 Hz, 1H), 6.92-6.86 (m, 6H), 5.57 (d, $J$ = 2.4 Hz, 1H), 5.23 (s, 1H), 4.72-4.70 (m, 1H), 4.64 (d, $J$ = 13.2 Hz, 1H), 4.33 (d, $J$ = 13.2 Hz, 1H), 4.27-4.24 (m, 1H), 4.15 (s, 3H), 2.93 (dd, $J$ = 4.4, 17.6 Hz, 1H), 2.81 (d, $J$ = 17.6 Hz, 1H), 2.62 (dd, $J$ = 3.2, 14.0 Hz, 1H), 2.45 (dd, $J$ = 2.0, 14.0 Hz, 1H), 1.58 (s, 3H), 1.46 (s, 3H), 1.30 (d, $J$ = 6.0 Hz, 3H); HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{31}H_{31}O_9$ 547.1968, found 547.1981.



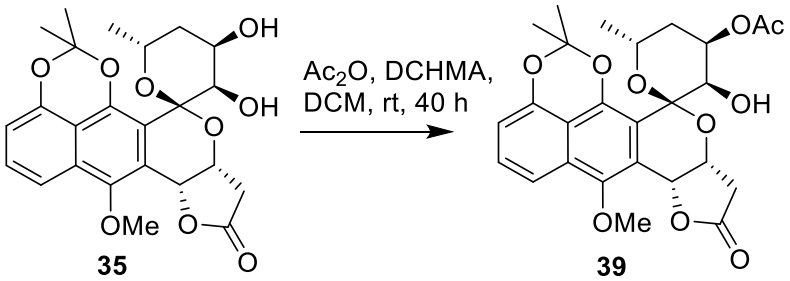

**(*3'R,4'S,6'R,7bR,10aR,12R*)-3'-(benzyloxy)-4'-hydroxy-7-methoxy-2,2,6'-trimethyl-3',4',5',6',10,10a-hexahydrospiro[furo[2'',3'':5',6']pyrano[3',4':2,3]naphtho[1,8-de][1,3]dioxine-12,2'-pyran]-9(7bH)-one (38).** $BH_3$•$Me_3N$ (9 mg, 0.15 mmol) and TFA (14 uL, 0.2 mmol) were added to a cooled solution of compound **37** (42 mg, 0.077 mmol) in ether (0.8 mL) at 0 °C. The mixture was stirred for 16 h during which the temperature was allowed to equilabrate to room temperature. The resulting solution was neutralized with saturated $NaHCO_3$ (2 mL) and extracted with EtOAc (10 mL x 2). The combined organic layers were washed with brine, dried over $Na_2SO_4$ and concentrated. The residue was purified by silica gel chromatography using 3:2 hexane/EtOAc to

afford the product as a colorless solid (33 mg, 75% yield). $R_f$ 0.40 (2:3 hexane/EtOAc); $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 7.64 (d, $J$ = 8.4 Hz, 1H), 7.48 (t, $J$ = 8.0 Hz, 1H), 7.11-7.00 (m, 5 H), 6.92 (d, $J$ = 7.2 Hz, 1H), 5.60 (d, $J$ = 2.4 Hz, 1H), 4.72 (t, $J$ = 3.2 Hz, 1H), 4.55 (d, $J$ = 8.8 Hz, 1H), 4.20-4.17 (m, 3H), 4.11(s, 3H), 4.06-4.02 (m, 1H), 2.98 (dd, $J$ = 4.4, 17.2 Hz, 1H), 2.82 (d, $J$ = 17.2 Hz, 1H), 2.09-2.07 (m, 2H), 1.82 (s, 3H), 1.60-1.54 (m, 1H), 1.52 (s, 3H), 1.22 (d, $J$ = 6.0 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ = 175.3, 150.9, 148.8, 141.7, 137.9, 128.6, 128.3 x 2, 128.2 x 2, 128.0, 127.6, 119.6, 116.1, 115.2, 114.8, 111.0, 102.2, 97.8, 82.2, 73.8, 71.9, 68.2, 66.6, 66.1, 64.7, 40.1, 37.7, 27.1, 23.6, 21.5 ppm; HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{31}H_{32}NaO_9$ 571.1944, found 571.1926.




38 36

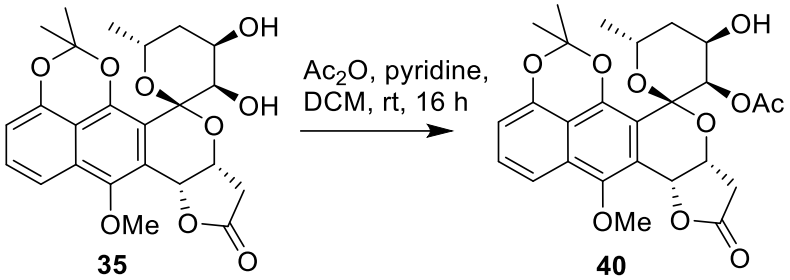
**(*3'R,4'S,6'R,7bR,10aR,12R*)-3',4'-dihydroxy-7-methoxy-2,2,6'-trimethyl-3',4',5',6',10,10a-hexahydrospiro[furo[2'',3'':5',6']pyrano[3',4':2,3]naphtho[1,8-de][1,3]dioxine-12,2'-pyran]-9(7bH)-one (36).** Solid 10% Pd/C (16 mg, 50% w/w) was added to a stirred solution of **36** (32 mg, 0.058 mmol) in MeOH (2 mL) under argon. The flask evacuated under vacuum and then quenched with $H_2$ (x 3). After 4 h under $H_2$, the reaction mixture was passed through a Celite pad, washed with MeOH and volatiles removed under vacuum to give the pure product without further purification (25 mg, 95% yield). $R_f$ 0.20 (2:3 hexane/EtOAc); $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 7.64 (d, $J$ = 8.4 Hz, 1H), 7.48 (t, $J$ = 8.0 Hz, 1H), 6.91 (d, $J$ = 7.6 Hz, 1H), 5.61 (d, $J$ = 1.6 Hz, 1H), 4.78 (s, 1H), 4.56 (d, $J$ = 8.8 Hz, 1H), 4.09 (s, 3H), 4.05-4.00 (m, 2H), 3.02 (dd, $J$ = 4.4, 17.6 Hz, 1H), 2.76 (d, $J$ = 17.6 Hz, 1H), 2.13-2.10 (m, 1H), 1.95 (br s, 2H), 1.70 (s, 3H), 1.66 (s, 3H), 1.60-1.57 (m, 1H), 1.25 (d, $J$ = 6.0 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ = 175.1, 150.9, 145.9, 141.8, 128.7, 128.4, 119.5, 115.3, 115.1, 114.5, 111.0, 102.1, 98.8, 77.3, 75.1, 72.2, 69.6, 66.7, 64.5, 40.0, 37.5, 25.3, 25.2, 21.3 ppm; HRMS (ESI) m/z $[M + NH_4]^+$ calcd for $C_{24}H_{30}NO_9$ 476.1921, found 476.1917.



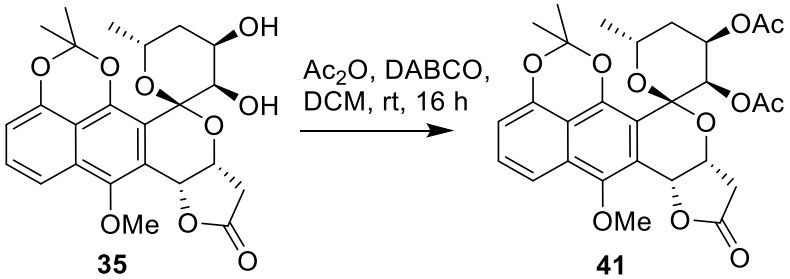

35 39

**(*3'R,4'R,6'R,7bR,10aR,12R*)-3'-hydroxy-7-methoxy-2,2,6'-trimethyl-9-oxo-3',4',5',6',7b,9,10,10a-octahydrospiro[furo[2'',3'':5',6']pyrano[3',4':2,3]naphtho[1,8-de][1,3]dioxine-12,2'-pyran]-4'-yl acetate (39).** Dicyclohexylmethylamine (128 μL, 0.6 mmol) and $Ac_2O$ (57 μL, 0.6 mmol) were added to a DCM solution (0.6 mL) of compound **35** (27 mg, 0.06 mmol). The resulting mixture was stirred for 40 h at room temperature and subsequently quenched with $H_2O$ (2 mL). The mixture then extracted with EtOAc (5 mL x 2) and the combined organic layers washed with brine (5 mL), and dried over $Na_2SO_4$. After evaporating the volatiles, the residue was purified by silica gel chromatography using 3:2 hexane/EtOAc to afford the product as a colorless solid (21 mg, 0.042 mmol, 70% yield). $R_f$ 0.60 (2:3 hexane/EtOAc); $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ = 7.64 (d, $J$ = 8.0 Hz, 1H), 7.48 (t, $J$ = 8.0 Hz, 1H), 6.92 (d, $J$ = 8.0 Hz, 1H), 5.62 (s, 1H), 5.32 (d, $J$ = 7.6 Hz, 1H), 4.95 (d, $J$ = 4.4 Hz, 1H), 4.81 (br s, 1H), 4.21-4.18 (m, 1H), 4.10 (s, 3H), 3.05 (dd, $J$ = 4.4, 17.6 Hz, 1H), 2.74 (d, $J$ = 17.6

Hz, 1H), 2.14 (s, 3H), 2.14-2.09 (m, 1H), 1.78-1.76 (m, 1H), 1.71 (s, 3H), 1.62 (s, 3H), 1.20 (d, *J* = 6.4 Hz, 3H); $^{13}$C NMR ($CDCl_3$ , 100 MHz): $\delta$ = 175.3, 170.8, 150.9, 148.8, 141.5, 128.5, 128.3, 119.8, 115.5, 115.2, 115.1, 111.0, 101.9, 98.1, 72.0, 70.4, 67.0, 66.5, 64.5, 62.2, 37.8, 36.7, 25.5, 25.0, 21.4, 20.9 ppm; HRMS (ESI) m/z [M + $NH_4$]$^+$ calcd for $C_{26}H_{32}NO_{10}$ 518.2026, found 518.2017.

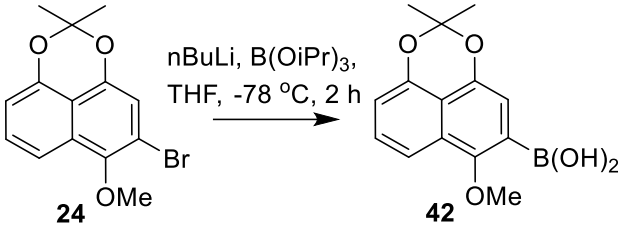



**(*3'R,4'R,6'R,7bR,10aR,12R*)-4'-hydroxy-7-methoxy-2,2,6'-trimethyl-9-oxo-3',4',5',6',7b,9,10,10a-octahydrospiro[furo[2'',3'':5',6']pyrano[3',4':2,3]naphtho[1,8-de][1,3]dioxine-12,2'-pyran]-3'-yl acetate (40).** Pyridine (20 μL, 0.25 mmol) and $Ac_2O$ (24 μL, 0.25 mmol) were added to a DCM solution (0.5 mL) of compound **35** (23 mg, 0.05 mmol). The resulting mixture was stirred for 16 h at room temperature and subsequently quenched with $H_2O$ (2 mL). The mixture was extracted with EtOAc (5 mL x 2) and the combined organic layers washed with brine (5 mL), and dried over $Na_2SO_4$. After evaporating the volatiles, the residue was purified by silica gel chromatography using 3:2 hexane/EtOAc to afford the product as a colorless solid (22 mg, 88% yield). $R_f$ 0.40 (2:3 hexane/EtOAc); $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ = 7.64 (d, *J* = 8.8 Hz, 1H), 7.48 (t, *J* = 8.0 Hz, 1H), 6.92 (d, *J* = 7.6 Hz, 1H), 5.98 (d, *J* = 3.6 Hz, 1H), 5.60 (d, *J* = 2.0 Hz, 1H), 4.81-4.80 (m, 1H), 4.40-4.37 (m, 2H), 4.08 (s, 3H), 3.41 (d, *J* = 7.6 Hz, 1H), 3.03 (dd, *J* = 4.4, 17.6 Hz, 1H), 2.79 (d, *J* = 17.6 Hz, 1H), 2.08-2.05 (m, 1H), 1.88 (s, 3H), 1.82-1.78 (m, 1H), 1.68 (s, 3H), 1.64 (s, 3H), 1.24 (d, *J* = 6.4 Hz, 3H); $^{13}$C NMR ($CDCl_3$ , 100 MHz): $\delta$ = 174.7, 170.2, 150.5, 148.9, 141.6, 128.8, 128.4, 119.2, 115.2, 115.1, 113.9, 111.1, 102.2, 98.6, 71.6, 70.2, 67.2, 66.3, 64.4, 62.5, 39.6, 38.0, 25.6, 24.6, 20.9, 20.9 ppm; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{26}H_{29}O_{10}$ 501.1761, found 501.1759.



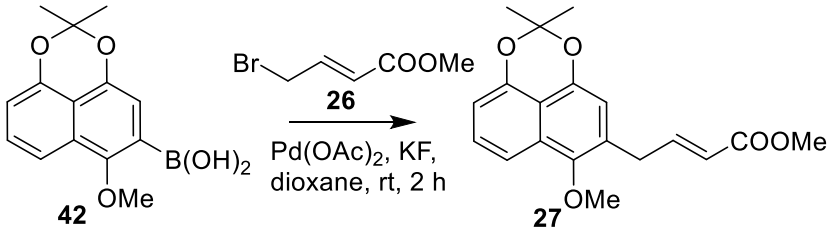

**(*3'R,4'R,6'R,7bR,10aR,12R*)-7-methoxy-2,2,6'-trimethyl-9-oxo-3',4',5',6',7b,9,10,10a-octahydrospiro[furo[2'',3'':5',6']pyrano[3',4':2,3]naphtho[1,8-de][1,3]dioxine-12,2'-pyran]-3',4'-diyl diacetate (41).** DABCO (22 mg, 0.2 mmol) and $Ac_2O$ (20 μL, 0.20 mmol) were added to a DCM solution (0.2 mL) of compound **35** (9 mg, 0.02 mmol). The resulting mixture was stirred for 16 h at room temperature and the reaction subsequently quenched with $H_2O$ (2 mL). The mixture then extracted with EtOAc (5 mL x 2) and the combined organic layers washed with brine (5 mL), and dried over $Na_2SO_4$. After evaporating the volatiles, the residue was purified by preparative TLC using 3:2 hexane/EtOAc to afford the product as a colorless solid (10 mg, 93% yield). $R_f$ 0.60 (2:3 hexane/EtOAc); $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ = 7.64 (d, *J* = 8.0 Hz, 1H), 7.46 (t, *J* = 8.0 Hz, 1H), 6.92 (d, *J* = 7.2 Hz, 1H), 6.02 (d, *J* = 4.0 Hz, 1H), 5.61 (m, 2H), 4.74 (dd, *J* = 2.0, 4.4 Hz, 1H), 4.42-4.40 (m, 1H), 4.07 (s, 3H), 3.01 (dd, *J* = 4.4, 16.8 Hz, 1H), 2.75 (d, *J* = 16.8 Hz, 1H), 2.04 (s, 3H), 1.97-1.91 (m, 2H), 1.78 (s, 3H), 1.72 (s, 3H), 1.64 (s, 3H), 1.23 (d, *J* = 6.4 Hz, 3H); $^{13}$C NMR ($CDCl_3$ , 100 MHz): $\delta$ = 175.4, 170.7, 170.4, 150.5, 148.9, 141.7, 128.7, 128.4, 119.8, 115.2, 115.1, 114.2, 111.0, 102.2, 96.6, 71.6, 68.7,

66.7, 66.6, 64.4, 62.7, 38.3, 36.7, 25.9, 24.5, 21.2, 21.0, 20.7 ppm; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{28}H_{31}O_{11}$ 543.1866, found 543.1870.



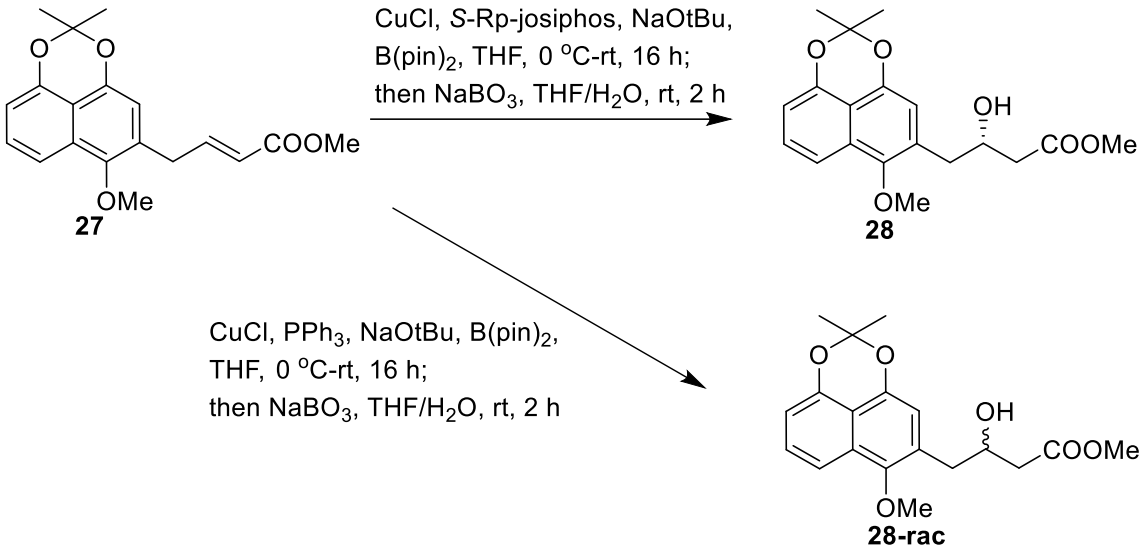
**24** **42**

**(6-Methoxy-2,2-dimethylnaphtho[1,8-de][1,3]dioxin-5-yl)boronic acid (42).** A solution of n-butyllithium (13 mL, 20 mmol, 1.6 M in hexane) was added in dropwise fashion to a solution of **24**[6] (4.0 g, 13 mmol) in anhydrous THF (40 mL) at -78 °C over 20 min. The resulting mixture was stirred for 30 min before the addition of $B(OiPr)_3$ (6 mL, 26 mmol). The reaction was allowed to equilibrate to room temperature with stirring for 2 h. The reaction was quenched with 1 M HCl solution (100 mL), stirred vigorously for 30 min and then extracted with EtOAc (100 mL x 2). The organic layers were washed with brine, dried over $Na_2SO_4$, filtered, and concentrated. The residue was purified by silica gel chromatography using a gradient of 10:1-4:1 hexane/EtOAc to provide the product as a colorless solid (2.85 g, 80%). $R_f$ 0.40 (2:1 hexane/EtOAc); $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ = 7.62 (d, $J$ = 8.4 Hz, 1H), 7.46 (t, $J$ = 8.0 Hz, 1H), 7.23 (s, 1H), 6.93 (d, $J$ = 8.0 Hz, 1H), 6.83 (br s, 2H), 4.01 (s, 3H), 1.65 (s, 6H); $^{13}$C NMR ($CDCl_3$ , 100 MHz): $\delta$ = 157.1, 148.7, 144.2, 127.6, 127.4, 116.4, 115.1, 115.0, 113.0, 110.6, 101.9, 63.8, 25.3 x 2 ppm; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{14}H_{16}BO_5$ 275.1091, found 275.1087.

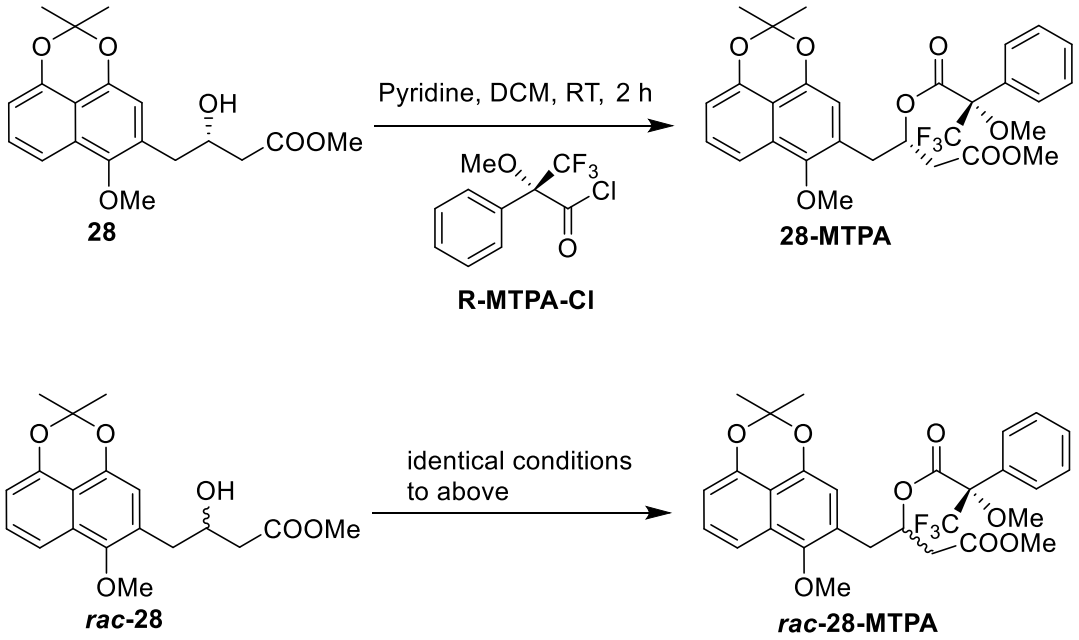


**42** **27**

**Methyl (*E*)-4-(6-methoxy-2,2-dimethylnaphtho[1,8-de][1,3]dioxin-5-yl)but-2-enoate (27).** A mixture of compound **42** (2.8 g, 10.2 mmol) and KF (2.7 g, 46 mmol) in 1,4-dioxane (100 mL) was stirred for 10 min followed by the addition of $Pd(OAc)_2$ (56 mg, 0.025 mmol) and compound **26** (1.48 mL, 11.2 mmol). The resulting mixture was stirred at room temperature for 2 h, filtered through Celite and washed with DCM (100 mL). After evaporating the volatiles, the residue was purified by silica gel chromatography using a gradient of (50:1-30:1 hexane/EtOAc to obtain the product as a colorless oil (2.47 g, 74%). $R_f$ 0.95 (2:1 hexane/EtOAc); $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ = 7.59 (d, $J$ = 8.8 Hz, 1H), 7.42 (t, $J$ = 8.0 Hz, 1H), 7.14 (dt, $J$ = 6.4, 15.6 Hz, 1H), 6.84 (d, $J$ = 7.2 Hz, 1H), 6.62 (s, 1H), 5.86 (dt, $J$ = 1.2, 15.2 Hz, 1H), 3.87 (s, 3H), 3.70 (s, 3H), 3.68 (dd, $J$ = 1.6, 6.8 Hz, 2H), 1.64 (s, 6H); $^{13}$C NMR ($CDCl_3$ , 100 MHz): $\delta$ = 166.8, 148.5, 147.6, 147.3, 144.2, 128.5, 127.7, 127.6, 122.5, 114.9, 113.5, 110.2, 109.1, 101.9, 62.3, 51.5, 32.6, 25.3 x 2 ppm; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{19}H_{21}O_5$ 329.1389, found 329.1380.

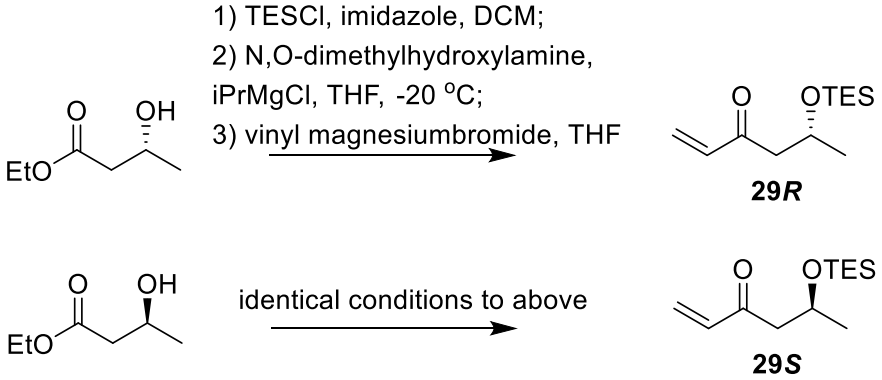



**Methyl (*S*)-3-hydroxy-4-(6-methoxy-2,2-dimethylnaphtho[1,8-de][1,3]dioxin-5-yl)butanoate (28).** CuCl (6 mg, 0.06 mmol), *S*-$R_p$-josiphos (77 mg, 0.12 mmol), and NaOtBu (8.6 mg, 0.09 mmol) were dissolved in THF (3 mL) and placed in an oven-dried Schlenk tube with a stirring bar under an argon atmosphere. The reaction mixture was stirred for 30 min at room temperature and bis(pinacolato)diboron (1.01 g, 4.0 mmol) in THF (2 mL) was added. The reaction mixture was stirred for another 10 min and then cooled to 0 °C. Compound **27** (1.18 g, 3.6 mmol) in THF (4 mL) was added to the resulting mixture followed by MeOH (288 uL, 7.2 mmol). The mixture was allowed to equilibrate to room temperature with stirring overnight. The reaction was quenched with $H_2O$ (10 mL) and $NaBO_3 \cdot 4H_2O$ (1.12 g, 7.2 mmol) and stirred for another 2 h at room temperature. The mixture was extracted with EtOAc (50 mL x 2) and the organic layers were combined, washed with brine, dried over $Na_2SO_4$ and concentrated. The residue was purified by silica gel using a gradient of (10:1-5:1) hexane/EtOAc to afford the product as a colorless oil (1.13 g, 91%). $R_f$ 0.40 (2:1 hexane/EtOAc); $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ = 7.58 (d, *J* = 8.4 Hz, 1H), 7.42 (t, *J* = 8.0 Hz, 1H), 6.83 (d, *J* = 7.2 Hz, 1H), 6.71 (s, 1H), 4.42-4.36 (m, 1 H), 3.90 (s, 3H), 3.68 (s, 3H), 3.23 (br s, 1H), 3.04 (dd, *J* = 6.8, 13.6 Hz, 1H), 2.94 (dd, *J* = 6.4, 13.2 Hz, 1H), 2.53-2.49 (m, 2H), 1.64 (s, 6H); $^{13}$C NMR ($CDCl_3$, 100 MHz): $\delta$ = 173.2, 148.5, 148.0, 144.2, 128.4, 127.9, 127.7, 114.9, 113.6, 110.9, 109.3, 101.9, 68.9, 62.0, 51.8, 40.7, 37.3, 25.4, 25.3 ppm; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{19}H_{23}O_6$ 347.1495, found 347.1488; ee, 90%; $[\alpha]_D^{20}$ +8.8° ($CHCl_3$, c = 1.0). Racemic **28-rac** was synthesized following the same protocol wherein *S*-$R_p$-josiphos was replaced by $PPh_3$. The corresponding characterization data for **28-rac** was consistent with that of **28.**




**28-MTPA and *rac*-28-MTPA.**[1] To a solution of **28** (11 mg, 0.03 mmol) and pyridine (8 μL, 0.1 mmol) in DCM (0.5 mL) at room temperature was added *R*-MTPA-Cl (10 μL, 0.06 mmol). The resulting mixture was allowed to stir for 2 h. After evaporating the volatiles, the residue was purified by silica gel chromatography using a gradient of 3:1-2:1 hexane/EtOAc to obtain the product **28-MTPA** as a colorless solid (16 mg, 88% yield). $R_f$: 0.90 (1:1 hexane/EtOAc); $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ = 7.53 (d, $J$ = 8.4 Hz, 1H), 7.43-7.37 (m, 3H), 7.22-7.19 (m, 3H), 6.86 (d, $J$ = 8.0 Hz, 1H), 6.64 (s, 1H), 5.87-5.82 (m, 1H), 3.87 (s, 0.16H), 3.80 (s, 3H), 3.63 (s, 3H), 3.58 (s, 0.16H), 3.49 (s, 3H), 3.23 (dd, $J$ = 6.8, 13.2 Hz, 1H), 2.96 (dd, $J$ = 6.8, 13.2 Hz, 1 H), 2.75-2.66 (m, 2H), 1.64 (s, 3H), 1.62 (s, 3H) ppm; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{29}H_{30}F_3O_8$ 563.1893, found 563.1890.

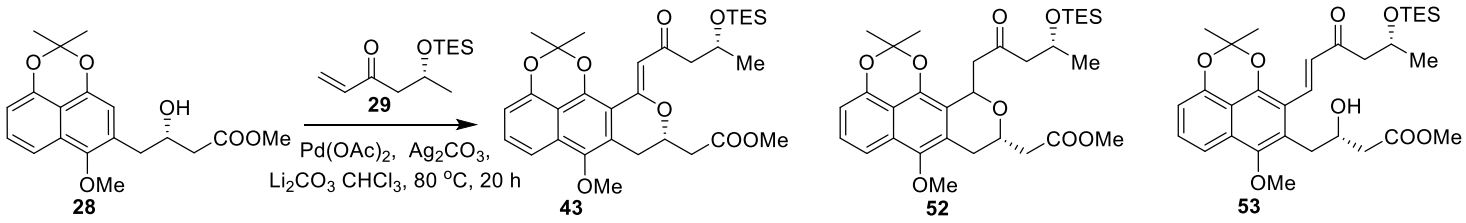
The ***rac*-28-MTPA** was synthesized following the same procedure. The comparison of proton NMR between **28-MTPA** and ***rac*-28-MTPA** revealed the key proton signals at δ 3.87 (*ent*-**28-MTPA**) and δ 3.80 (**28-MTPA**) to belong to the two enantiomers, respectively. Thus, ee values were determined by the ratio of areas of these two peaks. **28-MTPA** $R_f$: 0.90 (1:1 hexane/EtOAc); $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ = 7.53 (d, $J$ = 8.4 Hz, 1H), 7.43-7.37 (m, 3H), 7.22-7.19 (m, 3H), 6.86 (d, $J$ = 8.0 Hz, 1H), 6.64 (s, 1H), 5.87-5.82 (m, 1H), 3.87 (s, 0.16H), 3.80 (s, 3H), 3.63 (s, 3H), 3.58 (s, 0.16H), 3.49 (s, 3H), 3.23 (dd, $J$ = 6.8, 13.2 Hz, 1H), 2.96 (dd, $J$ = 6.8, 13.2 Hz, 1 H), 2.75-2.66 (m, 2H), 1.64 (s, 3H), 1.62 (s, 3H) ppm. ***rac*-28-MTPA** $R_f$: 0.90 (1:1 hexane/EtOAc); $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ = 7.53-7.17 (m, 14H), 6.89-6.84 (m, 2H), 6.74 (s, 1H), 6.64 (s, 1H), 5.87-5.82 (m, 2H), 3.87 (s, 3H), 3.80 (s, 3H), 3.63 (s, 3H), 3.58 (s, 3H), 3.49 (s, 3H), 3.41 (s, 3H), 3.27-3.25 (m, 2H), 3.23 (dd, $J$ = 6.8, 13.2 Hz, 1H), 2.96 (dd, $J$ = 6.8, 13.2 Hz, 1 H), 2.75-2.66 (m, 4H), 1.64 (s, 6H), 1.62 (s, 6H) ppm.



**(*R*)-5-(triethylsilyloxy)hex-1-en-3-one (29*R*). [Rxn 1]** Imidazole (5.1 g, 76 mmol) was added to a solution of ethyl (*R*)-3-hydroxybutyrate (5 g, 38 mmol) and TESCl (8.3 mL, 50 mmol) in $CH_2Cl_2$ (15 mL) at 0 °C. After stirring the thick suspension at room temperature overnight, $H_2O$ (50 mL) was added. The organic layers were separated and the aqueous layer was washed with $CH_2Cl_2$ (10 mL x 2). The combined organic layers were washed with $H_2O$ (20 mL) and brine (10 mL), dried over $Na_2SO_4$, filtered, and concentrated to give the crude product as a colorless oil.

**[Rxn 2]** The recovered crude product and *N*,*O*-dimethylhydroxylamine hydrochloride (5.5 g, 56 mmol) were subsequently dissolved in anhydrous THF (100 mL) at -20 °C. Isopropylmagnesium chloride in THF (55 mL, 110 mmol, 2M in THF) was added to the mixture in dropwise fashion over 30 min and the reaction was stirred at -20 °C for 2 h. The reaction was subsequently quenched by the addition of saturated $NH_4Cl$ solution (50 mL) and EtOAc (100 mL x 2). The combined organic layers were washed with $H_2O$ (100 mL) and brine (100 mL), dried over $Na_2SO_4$, filtered, and concentrated. The crude product was purified by silica gel chromatography using a gradient of 15:1-10:1 hexane/EtOAc to afford the desired product as a colorless oil (8.5 g).

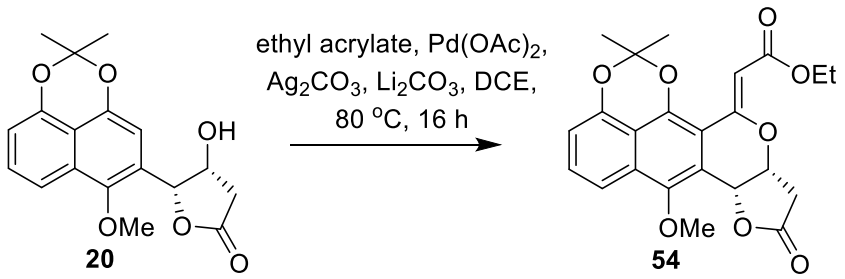
**[Rxn 3]** Vinylmagnesium bromide in THF (39 mL, 39 mmol, 1 M in THF) was added in dropwise fashion to a solution of the Rxn 2 product in THF (160 mL) at 0 °C over 20 min. The reaction mixture was stirred at 0 °C for 20 min and subsequently quenched by the addition of saturated $NH_4Cl$ solution (50 mL) and EtOAc (100 mL). The organic layers were separated and the aqueous layer was washed with EtOAc (100 mL). The combined organic layers were washed with $H_2O$ (100 mL) and brine (100 mL), dried over $Na_2SO_4$, filtered, and concentrated. The crude product was purified by silica gel chromatography using a gradient of 100:1-50:1 hexane/EtOAc to obtain the product **6** as a colorless oil (6.1 g, 71% three steps from ethyl (*R*)-3-hydroxybutyrate). $R_f$ : 0.95 (10:1 hexane/EtOAc); $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ = 6.35 (dd, *J* = 10.4, 18.0 Hz, 1H), 6.22 (d, *J* = 18.0 Hz, 1H), 5.83 (dt, *J* = 0.4, 10.4 Hz, 1H), 4.36-4.31 (m, 1H), 2.85 (dd, *J* = 6.4, 15.2 Hz, 1H), 2.57 (dd, *J* = 5.6, 15.2 Hz, 1 H), 1.20 (d, *J* = 6.0 Hz, 3H), 0.93 (t, *J* = 8.0 Hz, 9 H), 0.57 (q, *J* = 8.0 Hz, 6H); $^{13}$C NMR ($CDCl_3$, 100 MHz): $\delta$ = 199.7, 137.5, 128.6, 65.6, 49.3, 24.4, 6.9, 4.9 ppm. The synthesis of **29*S*** followed the same protocol starting from ethyl (*S*)-3-hydroxybutyrate and the corresponding characterization data was consistent with that of **29*R***.



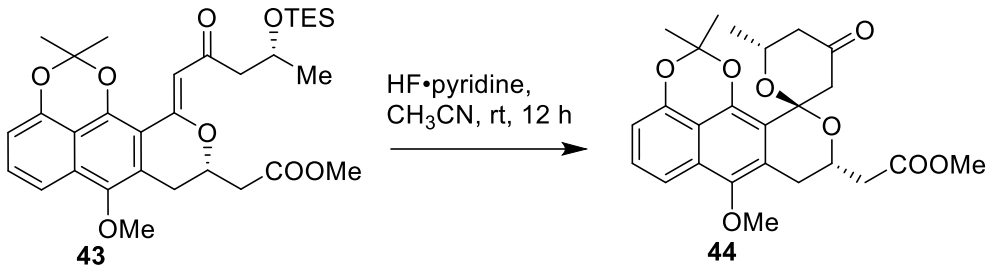

**Methyl 2-((*S*,*Z*)-11-((*R*)-4-((triethylsilyl)oxy)-2-oxopentylidene)-7-methoxy-2,2-dimethyl-8,11-dihydro-9H-pyrano[3',4':2,3]naphtho[1,8-de][1,3]dioxin-9-yl)acetate (43).** Compound **28** (1.4 g, 4 mmol), **29** (1.2 g, 5.2 mmol), $Pd(OAc)_2$ (356 mg, 1.6 mmol), $Li_2CO_3$ (326 mg, 4.4 mmol), and $Ag_2CO_3$ (2.2 g, 8 mmol) in a solution of $CHCl_3$ (24 mL) was added to a sealed tube equipped with a magnetic stir bar. The reaction mixture was stirred at 80 °C for 20 h, cooled and then filtered through a pad of Celite washed with 2:1 hexane/EtOAc. The filtrate was concentrated and then purified by silica gel chromatography using 6:1 hexane/EtOAc to obtain the desired product **43** as pale yellow oil (1.43 g, 63%). $R_f$ 0.60 (2:1 hexane/EtOAc); $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ = 7.59 (d, *J* = 8.0 Hz, 1H), 7.49 (t, *J* = 8.0 Hz, 1H), 6.88 (d, *J* = 7.6 Hz, 1H), 6.34 (s, 1H), 4.58-4.56 (m, 1 H), 4.45-4.40 (m, 1H), 3.87 (s, 3H), 3.77 (s, 3H), 3.41 (dd, *J* = 2.4, 15.2 Hz, 1H), 3.00-2.94 (m, 2H), 2.86-2.73 (m, 3H), 1.76 (s, 3H), 1.64 (s, 3H), 1.22 (d, *J* = 6.0 Hz, 3H), 0.93 (t, *J* = 8.0 Hz, 9 H), 0.60 (q, *J* = 8.0 Hz, 6H); $^{13}$C NMR ($CDCl_3$, 100 MHz): $\delta$ = 198.8, 170.6, 155.7, 149.1, 145.8, 143.9, 129.6, 128.7, 124.4, 114.8, 113.2, 110.4, 110.3, 110.2, 102.6, 72.4, 65.5, 62.0, 54.3, 52.2, 39.7, 28.6, 25.8, 24.7, 24.5, 7.0 x 3, 5.0 x 3 ppm; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{31}H_{43}O_8Si$ 571.2727, found 571.2713; $[\alpha]_D^{20}$ -191.0° ($CHCl_3$, c = 1.0).

**Methyl 2-((*9S*)-11-((*R*)-4-((triethylsilyl)oxy)-2-oxopentyl)-7-methoxy-2,2-dimethyl-8,11-dihydro-9H-pyrano[3',4':2,3]naphtho[1,8-de][1,3]dioxin-9-yl)acetate (52).** Compound **52** was isolated as a side product in the preparation of **43**. $R_f$ 0.40 (2:1 hexane/EtOAc); $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ = 7.57 (d, $J$ = 8.4 Hz, 1H), 7.37 (t, $J$ = 8.0 Hz, 1H), 6.80 (d, $J$ = 7.2 Hz, 1H), 5.68 (dd, $J$ = 2.8, 10.0 Hz, 0.4 H), 5.46 (dd, $J$ = 2.8, 9.2 Hz, 0.6H), 4.40-4.34 (m, 2H), 4.03-3.98 (m, 0.8H), 3.87 (s, 1.8H), 3.86 (s, 1.2H), 3.72 (s, 1.2H), 3.71 (s, 1.8H), 3.27 (dd, $J$ = 2.8, 15.2 Hz, 0.8H), 3.14 (d, $J$ = 16.0 Hz, 1.2H), 2.82-2.57 (m, 6H), 1.65 (s, 3H), 1.57 (s, 3H), 1.21 (d, $J$ = 6.0 Hz, 1.2 H), 1.17 (d, $J$ = 6.0 Hz, 1.8 H) 0.93 (t, $J$ = 8.0 Hz, 9 H), 0.60 (q, $J$ = 8.0 Hz, 6H); carbon signal was complicated due to diastereomeric mixture; HRMS (ESI) m/z $[M + NH_4]^+$ calcd for $C_{31}H_{48}NO_8Si$ 590.3149, found 590.3132.

**Methyl (*S*)-4-(4-((*R*,*E*)-5-((triethylsilyl)oxy)-3-oxohex-1-en-1-yl)-6-methoxy-2,2-dimethylnaphtho[1,8-de][1,3]dioxin-5-yl)-3-hydroxybutanoate (53).** Compound **53** was isolated as a side product in the preparation of **43**. $R_f$ 0.50 (2:1 hexane/EtOAc); $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ = 7.81 (d, $J$ = 12.8 Hz, 1H), 7.56 (d, $J$ = 6.0 Hz, 1H), 7.45 (t, $J$ = 6.0 Hz, 1H), 7.11 (d, $J$ = 12.8 Hz, 1H), 6.87 (d, $J$ = 5.4 Hz, 1H), 4.44-4.40 (m, 1H), 4.25-4.23 (m, 1H), 3.90 (s, 3H), 3.68 (s, 3H), 3.19 (t, $J$ = 5.2 Hz, 2H), 2.99-2.95 (m, 1H), 2.73-2.70 (m, 1H), 2.56 (t, $J$ = 6.0 Hz, 2H), 1.70 (s, 3H), 1.67 (s, 3H), 1.27 (d, $J$ = 4.8 Hz, 3 H), 0.94 (t, $J$ = 8.0 Hz, 9 H), 0.60 (q, $J$ = 8.0 Hz, 6H); $^{13}$C NMR ($CDCl_3$, 100 MHz): $\delta$ = 199.8, 173.1, 148.9, 148.4, 145.0, 136.0, 132.2, 129.0, 128.4, 127.8, 115.9, 115.3, 113.2, 110.0, 102.2, 68.8, 65.9, 61.9, 51.8, 50.9, 40.7, 33.7, 25.5, 25.2, 24.5, 7.0 x 3, 5.0 x 3 ppm; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{31}H_{45}O_8Si$ 573.2884, found 573.2874.

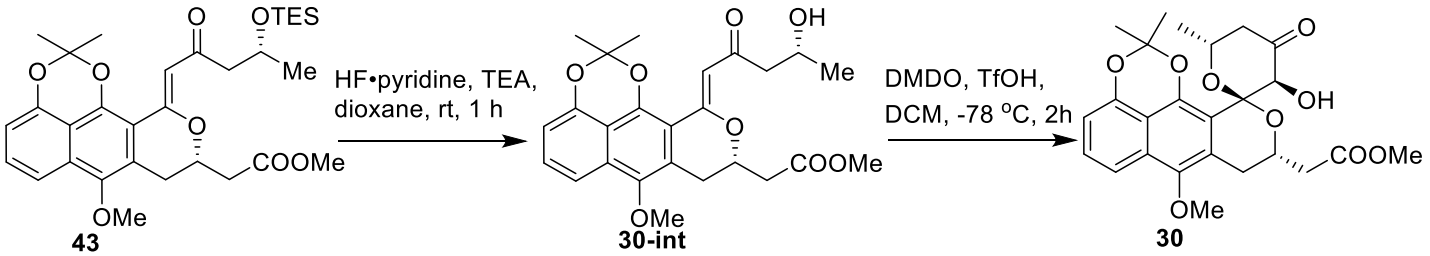



**Ethyl (*Z*)-2-((*7bR,10aR*)-7-methoxy-2,2-dimethyl-9-oxo-7b,9,10,10a-tetrahydro-12H-furo[2'',3'':5',6']pyrano[3',4':2,3]naphtho[1,8-de][1,3]dioxin-12-ylidene)acetate (54).** Compound **20**[6] (66 mg, 0.2 mmol), ethyl acrylate (28 μL, 0.26 mmol), $Pd(OAc)_2$ (9 mg, 0.04 mmol), $Li_2CO_3$ (16 mg, 0.22 mmol) and $Ag_2CO_3$ (220 mg, 0.8 mmol) in a solution of DCE (1.4 mL) were added to a sealed tube equipped with a magnetic stir bar. The reaction mixture was stirred at 80 °C for 16 h, cooled and then filtered through a pad of celite. The filtrate was concentrated and purified by silica gel chromatography using 3:1 hexane/EtOAc to provide the desired product **54** as pale yellow solid (69 mg, 81%). $R_f$ 0.30 (2:1 hexane/EtOAc); $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ = 7.68 (d, $J$ = 8.4 Hz, 1H), 7.55 (t, $J$ = 8.0 Hz, 1H), 6.98 (d, $J$ = 7.6 Hz, 1H), 6.52 (s, 1H), 5.84 (s, 1H), 4.86-4.85 (m, 1 H), 4.21 (q, $J$ = 6.4 Hz, 2H), 4.08 (s, 3H), 3.10 (d, $J$ = 17.6 Hz, 1H), 2.99 (dd, $J$ = 4.4, 17.6 Hz, 1H), 1.73 (s, 6H), 1.32 (t, $J$ = 7.2Hz, 3 H); $^{13}$C NMR ($CDCl_3$, 100 MHz): $\delta$ = 174.4, 166.0, 154.7, 150.4, 149.1, 143.7, 129.8, 128.5, 117.8, 115.6, 114.8, 111.9, 108.8, 103.2, 102.9, 73.8, 71.4, 64.5, 59.8, 38.2, 25.6, 25.1, 14.5 ppm; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{23}H_{23}O_8$ 427.1393, found 427.1381.



**43** **44**

**Methyl 2-((*2S,6R,9′S*)-7'-methoxy-2',2',6-trimethyl-4-oxo-3,4,5,6,8',9'-hexahydrospiro[pyran-2,11'-pyrano[3',4':2,3]naphtho[1,8-de][1,3]dioxin]-9'-yl)acetate (44).** HF·pyridine (52 μL, 2 mmol) was added in dropwise fashion to a $CH_3CN$ solution (2 mL) of **43** (114 mg, 0.2 mmol) in a polypropylene centrifuge vial. The resulting mixture was stirred for 16 h and then quenched with $H_2O$ (10 mL). The resulting mixture was extracted with EtOAc (20 mL x 2) and the combined organic layers were washed with 1N HCl (10 mL), saturated $NaHCO_3$ (10 mL), brine (10 mL), and dried over $Na_2SO_4$. After evaporating the volatiles, the residue was purified by silica gel chromatography using 7:1 hexane/EtOAc to obtain the product as a colorless oil (74 mg, 81%). $R_f$ 0.65 (2:1 hexane/EtOAc); $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ = 7.56 (d, *J* = 8.8 Hz, 1H), 7.41 (t, *J* = 8.0 Hz, 1H), 6.81 (d, *J* = 7.6 Hz, 1H), 4.64-4.59 (m, 1H), 4.44-4.40 (m, 1H), 3.86 (s, 3H), 3.73 (s, 3H), 3.43 (d, *J* = 16.0 Hz, 1H), 3.14 (dd, *J* = 2.8, 16.0 Hz, 1H), 2.74-2.70 (m, 4H), 2.48 (d, *J* = 16.0 Hz, 1H), 2.35 (dd, *J* = 11.6, 16.0 Hz, 1H), 1.65 (s, 3H), 1.62 (s, 3H), 1.35 (d, *J* = 6.0 Hz, 3H); $^{13}$C NMR ($CDCl_3$ , 100 MHz): $\delta$ = 206.9, 171.3, 148.6, 146.3, 141.5, 128.0, 127.9, 124.7, 118.4, 114.4, 113.1, 109.1, 102.1, 98.3, 65.6, 64.8, 61.3, 51.8, 50.4, 47.8, 40.5, 28.9, 25.3, 24.7, 21.7 ppm; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{25}H_{29}O_8$ 457.1862, found 457.1848; $[\alpha]_D^{20}$ -31.0° ($CHCl_3$, c = 1.0).

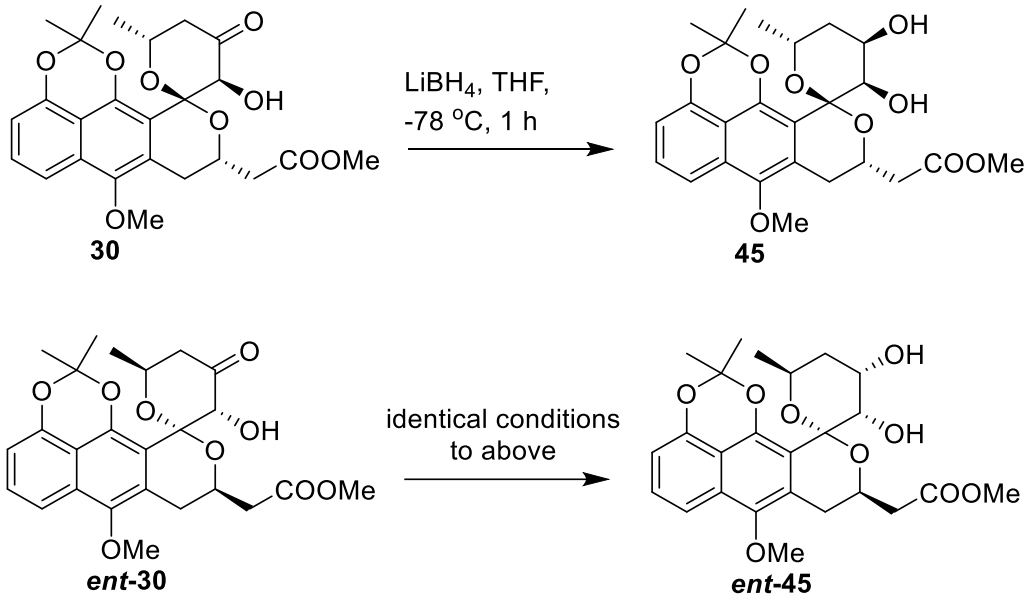


**43** **30-int** **30**

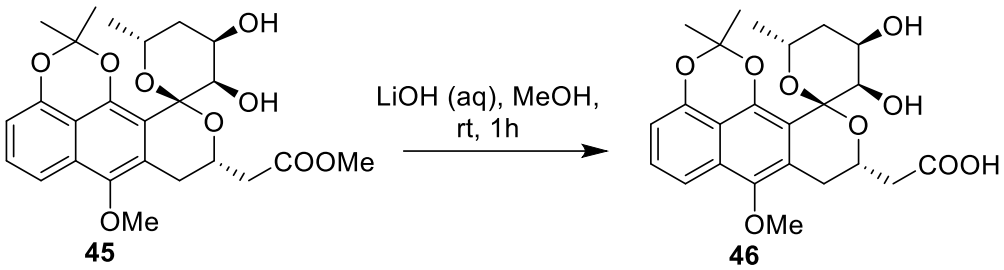
**Methyl 2-((*2R,3R,6R,9′S*)-3-hydroxy-7'-methoxy-2',2',6-trimethyl-4-oxo-3,4,5,6,8',9'-hexahydrospiro[pyran-2,11'-pyrano[3',4':2,3]naphtho[1,8-de][1,3]dioxin]-9'-yl)acetate (30).** HF·pyridine (400 μL, 16 mmol) in a solution of dixoane (1 mL) was added in dropwise fashion to a dioxane solution (16 mL) of compound **43** (912 mg, 1.6 mmol) and trimethylamine (450 μL, 3.2 mmol) in a in a polypropylene centrifuge vial at room temperature. The resulting mixture was stirred for 1 h before the addition with $H_2O$ (50 mL). The resulting mixture was extracted with EtOAc (20 mL x 2) and the combined organic layers were washed with 1N HCl (10 mL), saturated $NaHCO_3$ (10 mL), brine (10 mL), and dried over $Na_2SO_4$. After evaporating the volatiles, the residue was purified on silica gel using hexane/EtOAc (2/1-1/2) as eluent to obtain the product **30-int** as a yellow oil (638 mg, 88%). $R_f$ 0.10 (2:1 hexane/EtOAc); $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ = 7.60 (d, *J* = 8.0 Hz, 1H), 7.51 (t, *J* = 8.0 Hz, 1H), 6.89 (d, *J* = 7.6 Hz, 1H), 6.33 (s, 1H), 4.60-4.57 (m, 1H), 4.29-4.25 (m, 1H), 3.88-3.87 (m, 1H), 3.87 (s, 3H), 3.76 (s, 3H), 3.41 (d, *J* = 16.0 Hz, 1H), 3.03-3.75 (m, 5H), 1.77 (s, 3H), 1.64 (s, 3H), 1.22 (d, *J* = 6.0 Hz, 3H); $^{13}$C NMR ($CDCl_3$ , 100 MHz): $\delta$ = 201.8, 170.5, 157.4, 149.1, 145.8, 144.3, 129.9, 128.9, 124.2, 114.8, 113.2, 110.4, 110.0, 109.8, 102.7, 72.6, 64.4, 62.0, 52.2, 51.9, 39.8, 28.5, 25.8, 24.8, 22.3 ppm; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{25}H_{29}O_8$ 457.1862, found 457.1861; $[\alpha]_D^{20}$ -293.0° ($CHCl_3$, c = 1.0).

A precooled DMDO solution[7] (12 mL, 0.6 mmol, 0.05 M) in acetone was added to a solution of **30-int** (228 mg, 0.5 mmol) in DCM (10 mL) at -78 °C over 5 min. The reaction was stirred for 5 min at -78 °C followed by the addition of TfOH (22 μL, 0.25 mmol) in acetone (200 μL). The reaction was stirred for 2 h, during which the temperature was allowed to adjust to -20 °C. The reaction was neutralized by the addition of triethylamine (700

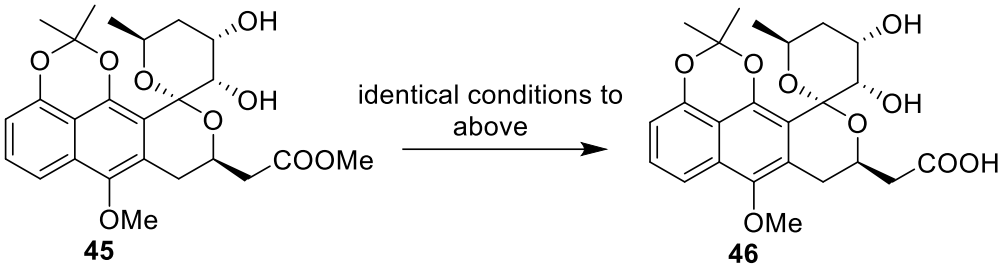
μL, 5 mmol) and partitioned between EtOAc (20 mL) and water (20 mL). The aqueous phase was extracted with EtOAc (20 mL) and the combined organic layers were washed with saturated aqueous $NaHCO_3$ solution (20 mL), brine, and dried over $Na_2SO_4$. After evaporating the volatiles, the residue was purified by silica gel chromatography using a gradient of 4:1-3:1 hexane/EtOAc to obtain the product **30** as a pale yellow foam (220 mg, 93%). $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ = 7.57 (d, $J$ = 8.4 Hz, 1H), 7.42 (t, $J$ = 8.0 Hz, 1H), 6.83 (d, $J$ = 7.6 Hz, 1H), 5.36 (d, $J$ = 8.4 Hz, 1H), 4.52-4.48 (m, 1H), 4.39-4.34 (m, 1H), 3.86 (s, 3H), 3.71 (s, 3H), 3.19-3.11 (m, 2H), 2.70-2.51 (m, 5H), 1.70 (s, 3H), 1.68 (s, 3H), 1.38 (d, $J$ = 6.0 Hz, 3H); $^{13}$C NMR ($CDCl_3$ , 100 MHz): $\delta$ = 205.7, 171.2, 148.8, 146.3, 142.0, 128.3, 128.2, 125.2, 114.8, 114.5, 113.3, 109.3, 102.1, 101.8, 76.8, 66.9, 65.4, 61.4, 51.9, 48.3, 40.3, 28.6, 25.6, 25.1, 22.0 ppm; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{25}H_{29}O_9$ 473.1812, found 473.1815; $[\alpha]_D^{20}$ +17.0$^o$ ($CHCl_3$, c = 1.0).




**Methyl 2-((*2R,3R,4R,6R,9'S*)-3,4-dihydroxy-7'-methoxy-2',2',6-trimethyl-3,4,5,6,8',9'-hexahydrospiro[pyran-2,11'-pyrano[3',4':2,3]naphtho[1,8-de][1,3]dioxin]-9'-yl)acetate (45).** $LiBH_4$ (11 mg, 0.5 mmol) was added to a THF solution (2.5 mL) of compound **30** (118 mg, 0.25 mmol) at -78 $^o$C. The resulting mixture was stirred for 1 h at -78 $^o$C and then quenched with $H_2O$ (1 mL). The mixture was extracted with EtOAc (10 mL x 2) and the combined organic layers were washed with brine (5 mL), and dried over $Na_2SO_4$. After evaporating the volatiles, the residue was purified by silica gel chromatography using 1:1 hexane/EtOAc to afford the product as a colorless solid (102 mg, 86% yield). $R_f$ 0.35 (2:3 hexane/EtOAc); $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ = 7.54 (dd, $J$ = 0.8, 8.4 Hz, 1H), 7.39 (dd, $J$ = 7.6, 8.4 Hz, 1H), 6.81 (dd, $J$ = 0.8, 7.6 Hz, 1H), 4.65 (dd, $J$ = 4.0, 11.2Hz, 1H), 4.52-4.47 (m, 1H), 4.20-4.12 (m, 2H), 3.85 (s, 3H), 3.76 (s, 3H), 3.53 (d, $J$ = 12.0 Hz, 1H), 3.16 (dd, $J$ = 2.4, 16.8 Hz, 1H), 2.79-2.69 (m, 4H), 2.11-2.06 (m, 1H), 1.78-1.74 (m, 1H), 1.72 (s, 3H), 1.60 (s, 3H), 1.23 (d, $J$ = 6.0 Hz, 3H); $^{13}$C NMR ($CDCl_3$ , 100 MHz): $\delta$ = 171.5, 148.8, 146.3, 141.7, 128.1, 128.0, 125.1, 116.2, 114.4, 113.4, 109.2, 101.6, 101.1, 69.4, 68.4, 65.6, 61.4, 60.9, 52.2, 40.7, 40.3, 29.1, 25.8, 24.8, 21.3 ppm; HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{25}H_{30}NaO_9$ 497.1778, found 497.1776; $[\alpha]_D^{20}$ -32.0$^o$ ($CHCl_3$, c = 1.0). The synthesis of ***ent*-45** followed the same protocol starting from ***ent*-30** and the corresponding characterization data was consistent with that of ***ent*-45**.

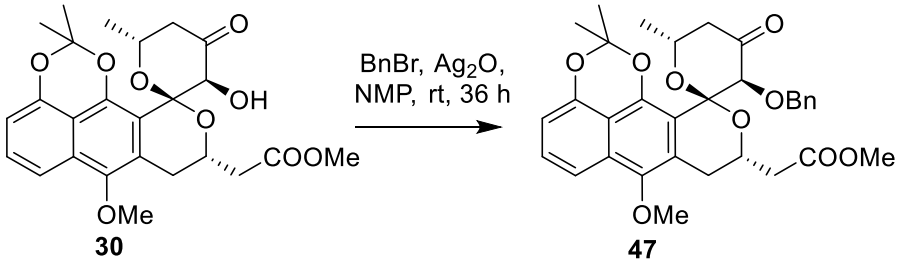



**45** **46**




**45** **46**

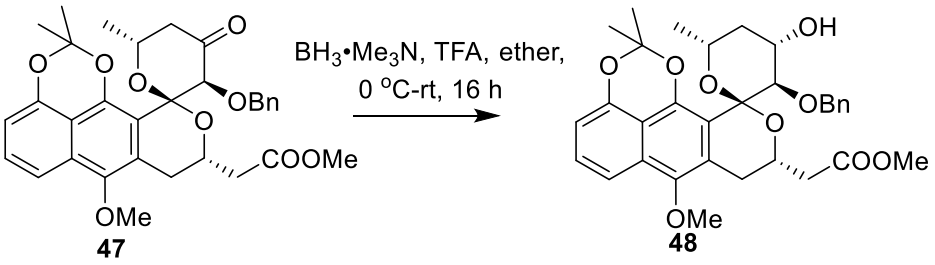
**2-((*2R,3R,4R,6R,9'S*)-3,4-dihydroxy-7'-methoxy-2',2',6-trimethyl-3,4,5,6,8',9'-hexahydrospiro[pyran-2,11'-pyrano[3',4':2,3]naphtho[1,8-de][1,3]dioxin]-9'-yl)acetic acid (46).** Aqueous 1 N LiOH (0.3 mL) was added to a stirred solution of **45** (28 mg, 0.06 mmol) in MeOH (0.6 mL) and the resulting mixture was stirred for 1 h at room temperature. Upon completion, the resulting mixture was neutralized with 2N HCl (0.2 mL) and extracted with EtOAc (3 mL x 2). The organic layers were combined and washed with brine, dried over $Na_2SO_4$ and concentrated to give the crude product without further purification. $R_f$ 0.10 (2:3 hexane/EtOAc); $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ = 7.54 (d, $J$ = 8.4 Hz, 1H), 7.40 (t, $J$ = 8.0 Hz, 1H), 6.81 (d, $J$ = 7.2 Hz, 1H), 4.68 (d, $J$ = 3.2Hz, 1H), 4.56-4.51 (m, 1H), 4.33-4.22 (m, 2H), 3.86 (s, 3H), 3.16 (d, $J$ = 14.8 Hz, 1H), 2.81-2.75 (m, 3H), 2.13-2.10 (m, 1H), 1.76-1.73 (m, 1H), 1.69 (s, 3H), 1.60 (s, 3H), 1.22 (d, $J$ = 6.0 Hz, 3H), hydroxyl and carboxylic proton signals did not appear; $^{13}$C NMR ($CDCl_3$ , 100 MHz): $\delta$ = 174.0, 148.8, 146.3, 141.7, 128.1, 128.0, 125.2, 116.0, 114.4, 113.3, 109.2, 101.6, 101.0, 69.9, 68.4, 65.5, 61.4, 61.1, 40.5, 40.0, 28.9, 25.8, 24.8, 21.2 ppm; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{24}H_{29}O_9$ 461.1812, found 461.1807. The synthesis of ***ent*-46** followed the same protocol starting from *ent*-**45** and the corresponding characterization data was consistent with that of ***ent*-46**.




**30** **47**

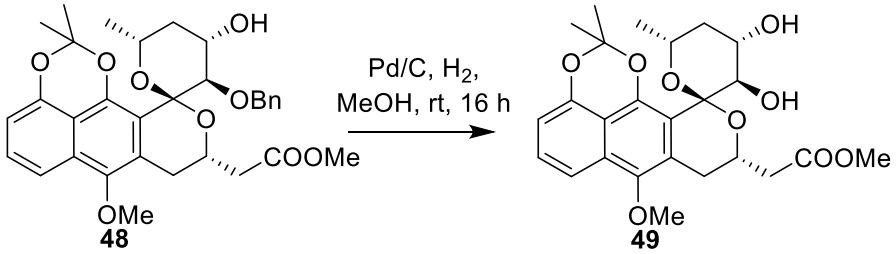
**Methyl 2-((*2R,3R,6R,9'S*)-3-(benzyloxy)-7'-methoxy-2',2',6-trimethyl-4-oxo-3,4,5,6,8',9'-hexahydrospiro[pyran-2,11'-pyrano[3',4':2,3]naphtho[1,8-de][1,3]dioxin]-9'-yl)acetate (47).** $Ag_2O$ (1.83 g, 8.0 mmol) and BnBr (970 μL, 8.0 mmol) were added to an *N*-methyl-2-pyrrolidone (NMP) solution (10 mL) of compound **30** (470 mg, 1 mmol) and the resulting mixture stirred at room temperature for 36 h. The mixture was filtered, washed with EtOAc (50 mL) and partitioned between EtOAc (50 mL) and water (50 mL). The organic layer was recovered, washed with brine (20 mL), and dried over $Na_2SO_4$. After evaporating the volatiles, the residue was purified by silica gel chromatrography using 5:1 hexane/EtOAc to obtain the product as a colorless oil (427 mg, 76% yield). $R_f$ 0.40 (2:1 hexane/EtOAc); $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ = 7.59 (dd, $J$ = 0.4, 8.4 Hz,

1H), 7.44 (dd, *J* = 7.6, 8.4 Hz, 1H), 6.94 (t, *J* = 7.6 Hz, 1H), 6.81-6.71 (m, 5H), 5.03 (s, 1H), 4.63 (d, *J* = 12.4 Hz, 1H), 4.50-4.40 (m, 2H), 4.25 (d, *J* = 12.4 Hz, 1H), 3.89 (s, 3H), 3.67 (s, 3H), 3.11 (dd, *J* = 4.4, 16.0 Hz, 1H), 2.87 (dd, *J* = 8.0, 16.0 Hz, 1H), 2.75-2.66 (m, 2H), 2.55 (dd, *J* = 2.4, 13.6 Hz, 1H), 2.41 (dd, *J* = 8.0, 12.0 Hz, 1H), 1.55 (s, 3H), 1.46 (s, 3H), 1.31 (d, *J* = 6.0 Hz, 3H); $^{13}$C NMR ($CDCl_3$ , 100 MHz): $\delta$ = 204.2, 171.4, 148.8, 146.1, 141.7, 137.4, 128.1, 128.0, 127.7 x 2, 127.6, 127.5 x 2, 126.0, 115.6, 114.3, 113.0, 109.0, 101.8, 101.5, 82.1, 73.0, 66.4, 65.8, 61.5, 51.8, 49.4, 39.9, 28.7, 27.1, 23.3, 21.9 ppm HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{32}H_{35}O_9$ 563.2281, found 563.2256.



**47** **48**

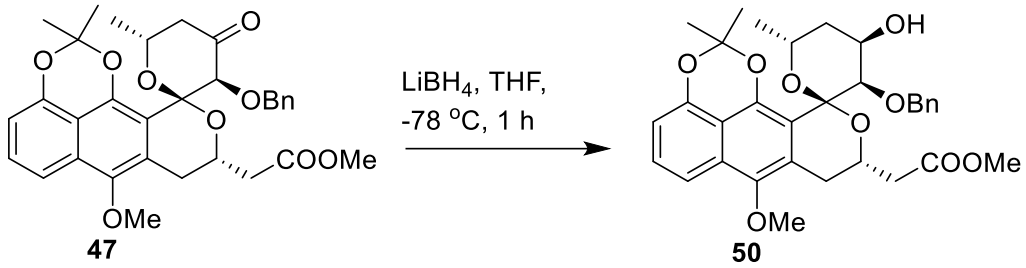
**Methyl 2-((*2R,3R,4S,6R,9'S*)-3-(benzyloxy)-4-hydroxy-7'-methoxy-2',2',6-trimethyl-3,4,5,6,8',9'-hexahydrospiro[pyran-2,11'-pyrano[3',4':2,3]naphtho[1,8-de][1,3]dioxin]-9'-yl)acetate (48).** $BH_3$•$Me_3N$ (90 mg, 1.5 mmol) and TFA (140 μL, 2 mmol) were added to a cooled solution of compound **47** (280 mg, 0.5 mmol) in ether (5 mL) at 0 °C. The mixture was stirred for 16 h during which the temperature was allowed to equilibrate to room temperature. The resulting solution was neutralized with saturated $NaHCO_3$ (10 mL) and extracted with EtOAc (20 mL x 2). The combined organic layers were washed with brine, dried over $Na_2SO_4$, concentrated and the recovered residue purified by silica gel chromatography using 2:1 hexane/EtOAc to afford the product as a colorless solid (216 mg, 77% yield). $R_f$ 0.20 (2:1 hexane/EtOAc); $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 7.57 (d, *J* = 8.4 Hz, 1H), 7.42 (t, *J* = 8.0 Hz, 1H), 7.09-7.07 (m, 3H), 6.95-6.93 (m, 2H), 6.82 (d, *J* = 7.2 Hz, 1H), 4.47-4.44 (m, 1H), 4.39 (d, *J* = 9.2 Hz, 1H), 4.17-4.13 (m, 4H), 3.87 (s, 3H), 3.71 (s, 3H), 3.15 (dd, *J* = 2.0, 16.0 Hz, 1H), 2.85 (dd, *J* = 4.4, 16.0 Hz, 1H), 2.75-2.73 (m, 2H), 2.07-2.06 (br s, 2H), 1.80 (s, 3H), 1.53 (s, 3H), 1.53-1.52 (m, 1H), 1.22 (d, *J* = 6.0 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ = 171.5, 148.9, 146.3, 142.0, 138.0, 128.2 x 2, 128.1, 128.0, 127.9 x 2, 127.8, 126.2, 117.1, 114.4, 113.1, 109.1, 101.8, 98.9, 82.7, 74.1, 68.3, 65.2, 65.0, 61.5, 51.8, 40.7, 40.5, 29.2, 27.3, 23.5, 21.5 ppm; HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{32}H_{36}NaO_9$ 587.2257, found 587.2213.



**48** **49**

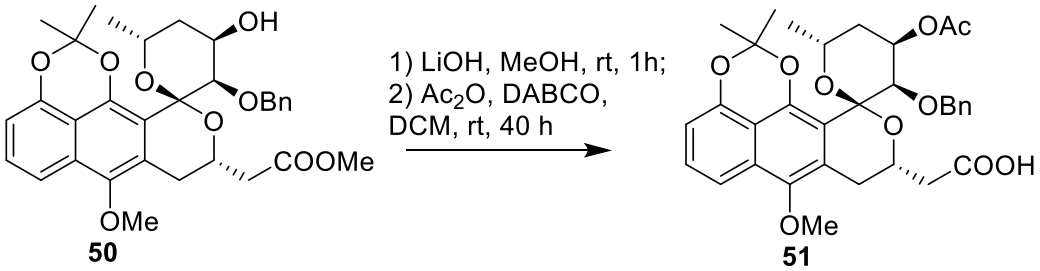
**Methyl 2-((*2R,3R,4S,6R,9'S*)-3,4-dihydroxy-7'-methoxy-2',2',6-trimethyl-3,4,5,6,8',9'-hexahydrospiro[pyran-2,11'-pyrano[3',4':2,3]naphtho[1,8-de][1,3]dioxin]-9'-yl)acetate (49).** Solid 10% Pd/C (29 mg, 50% w/w) was added to a stirred solution of **36** (58 mg, 0.1 mmol) in MeOH (1 mL) under argon. The flask was evacuated under vacuum and filled with $H_2$ (x 3) and then stirred for 16 h under $H_2$. The reaction mixture was subsequently filtered through a celite pad, washed with MeOH and recovered organics concentrated to give the pure product without further purification (44 mg, 93% yield). $R_f$ 0.40 (2:1 hexane/EtOAc); $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 7.53 (dd, *J* = 0.4, 8.4 Hz, 1H), 7.39 (dd, *J* = 7.6, 8.4 Hz, 1H), 6.81 (d, *J* = 7.2 Hz, 1H), 4.54-4.50 (m, 1H), 4.37 (d, *J* = 9.2 Hz, 1H), 4.01-4.06 (m, 1H), 4.04-3.96 (m, 1H), 3.84 (s, 3H), 3.70 (s, 3H), 3.15 (dd, *J* = 2.4, 16.4 Hz, 1H), 2.75-2.74 (m, 2H), 2.65 (dd, *J* = 3.6, 16.4 Hz, 1H), 2.40-2.25 (br s, 2H), 2.07-2.02 (m,

1H), 1.70 (s, 3H), 1.62 (s, 3H), 1.56-1.53 (m, 1H), 1.24 (d, $J$ = 6.0 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ = 171.2, 148.9, 146.2, 141.9, 128.1, 128.0, 125.5, 115.9, 114.3, 113.4, 109.1, 101.7, 99.5, 75.5, 70.0, 65.6, 65.0, 61.3, 51.9, 40.6, 40.1, 29.0, 25.8, 24.8, 21.4 ppm; HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{25}H_{30}NaO_9$ 497.1788, found 497.1777; $[\alpha]_D^{20}$ -25.0° ($CHCl_3$, c = 1.0).




**47** **50**

**Methyl 2-((2R,3R,4R,6R,9'S)-3-(benzyloxy)-4-hydroxy-7'-methoxy-2',2',6-trimethyl-3,4,5,6,8',9'-hexahydrospiro[pyran-2,11'-pyrano[3',4':2,3]naphtho[1,8-de][1,3]dioxin]-9'-yl)acetate (50).** $LiBH_4$ (4.4 mg, 0.2 mmol) was added to a THF solution (1 mL) of compound **47** (56 mg, 0.1 mmol) at -78 °C. The resulting mixture was stirred for 1 h at -78 °C and then quenched with the addition with $H_2O$ (1 mL). The mixture was extracted with EtOAc (10 mL x 2) and the combined organic layers were washed with brine (5 mL), and dried over $Na_2SO_4$. After evaporating the volatiles, the residue was purified by silica gel chromatography using 2:1 hexane/EtOAc to obtain the product as a colorless solid (54 mg, 96% yield). $R_f$ 0.40 (2:3 hexane/EtOAc); $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ = 7.57 (d, $J$ = 8.4 Hz, 1H), 7.42 (t, $J$ = 8.4 Hz, 1H), 7.01-6.97 (m, 1H), 6.93-6.79 (m, 5H), 4.53-4.42 (m, 3H), 4.36-4.24 (m 3H), 3.89 (s, 3H), 3.83-3.81 (m, 1H), 3.75 (s, 3H), 3.12 (dd, $J$ = 2.4, 16.4 Hz, 1H), 2.90-2.74 (m, 3H), 2.04-2.00 (m, 1H), 1.59-1.58 (m, 1H), 1.57 (s, 3H), 1.44 (s, 3H), 1.19 (d, $J$ = 6.0 Hz, 3H); $^{13}$C NMR ($CDCl_3$ , 100 MHz): $\delta$ = 171.4, 148.8, 146.1, 141.5, 138.0, 127.9 x 2, 127.8 x 2, 127.6, 127.4, 126.0, 117.1, 114.3, 113.1, 108.9, 101.4, 100.2, 74.6, 70.8, 66.2, 65.9, 61.5, 61.2, 52.0, 40.6, 40.5, 29.8, 29.1, 27.0, 23.4, 21.3 ppm; HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{32}H_{36}NaO_9$ 587.2257, found 587.2237.

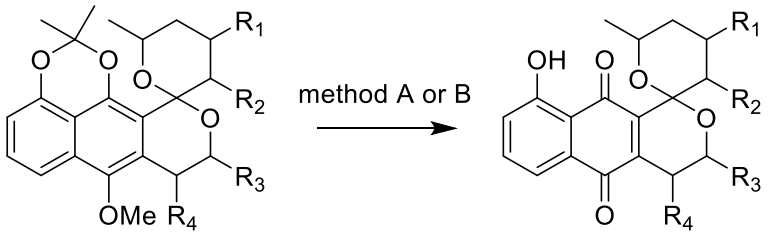



**50** **51**

**2-((*2R,3R,4R,6R,9'S*)-4-acetoxy-3-(benzyloxy)-7'-methoxy-2',2',6-trimethyl-3,4,5,6,8',9'-hexahydrospiro[pyran-2,11'-pyrano[3',4':2,3]naphtho[1,8-de][1,3]dioxin]-9'-yl)acetic acid (51). [Rxn 1]** Aqueous 0.5 N LiOH (0.6 mL, 0.3 mmol) was added to a stirred solution of **50** (46 mg, 0.1 mmol) in MeOH (1 mL) and the resulting mixture stirred for 1 h at room temperature. Upon completion, the resulting mixture was neutralized with 1N HCl (0.3 mL) and extracted with EtOAc (5 mL x 2). The organic layers were combined and washed with brine, dried over $Na_2SO_4$ and concentrated to give the crude product without further purification.

**[Rxn 2]** DABCO (122 mg, 1.0 mmol) and $Ac_2O$ (0.1 mL, 1.0 mmol) were added to a DCM solution (1 mL) of the Rxn 1 crude product and the resulting mixture stirred for 40 h at room temperature The reaction was quenched with $H_2O$ (0.5 mL) and then extracted with DCM (5 mL x 2). The combined organic layers were washed with brine (5 mL), and dried over $Na_2SO_4$. After evaporating the volatiles, the residue was purified by silica gel using a gradient of 70:30:1-50:50:1 hexane/EtOAc/AcOH to afford the product as a colorless solid. $R_f$ 0.70 (2:3:0.1 hexane/EtOAc/AcOH); $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ = 7.57 (dd, $J$ = 0.8, 8.4 Hz, 1H), 7.43 (t, $J$ = 8.4 Hz, 1H), 6.89-6.86 (m, 1H), 6.80-6.73 (m, 5H), 5.57-5.54 (m, 1H), 4.46-4.436 (m, 4H), 4.21 (d, $J$ =12.8 Hz, 1H), 3.89 (s, 3H), 3.15 (dd, $J$ = 2.4, 16.0 Hz, 1H), 2.94-2.92 (m, 2H), 2.81 (dd, $J$ = 4.4, 16.0 Hz, 1H), 2.18 (s, 3H), 2.00-1.96

(m, 1H), 1.68-1.65 (m, 1H), 1.55 (s, 3H), 1.40 (s, 3H), 1.16 (d, $J$ = 6.0 Hz, 3H), carboxylic proton signals did not appear; $^{13}$C NMR ($CDCl_3$ , 100 MHz): $\delta$ = 171.2, 170.3, 148.8, 146.1, 141.5, 137.1, 128.0, 127.9 x 2, 127.8 x 2, 127.7, 127.6, 125.4, 116.5, 114.2, 113.1, 109.3, 101.3, 98.6, 72.6, 71.1, 66.5, 65.0, 61.7, 61.5, 40.4, 36.9, 28.3, 27.0, 23.3, 21.4, 21.2 ppm; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{33}H_{37}O_{10}$ 593.2387, found 593.2370.




**General method A for the deprotection of acetonide and methyl ether.** AgO (0.25 mmol) and 6N $HNO_3$ (82 μL, 0.5 mmol) were added in succession to a stirred solution of substrate (0.05 mmol) in THF (1 mL) at 0 ºC. After stirring for 10 min, the mixture was filtered through celite. The filtrate was partitioned between EtOAc (5 mL) and $H_2O$ (5 mL), and the aqueous layer was extracted with EtOAc (5 mL). The combined extracts were washed with brine (5 mL), dried over $Na_2SO_4$, and evaporated. The residue was purified on silica gel using hexane/EtOAc to access the product as an orange solid.

**General method B for the deprotection of acetonide and methyl ether.** AgO (0.11 mmol) and 3N $HNO_3$ (100 μL, 0.3 mmol) were added in succession to a stirred solution of substrate (0.05 mmol) in THF (1 mL) at -10 ºC. After stirring for 30 min the mixture was filtered through celite. The filtrate was partitioned between EtOAc (5 mL) and $H_2O$ (5 mL), and the aqueous layer was extracted with EtOAc (5 mL). The combined extracts were washed with brine (5 mL), dried over $Na_2SO_4$, and evaporated. The residue was purified by semi-preparative reverse-phase HPLC using a $CH_3CN$/water gradient and then lyophilized to access the product as an orange solid.

**Griseusin A (1).** Compound **39** was deprotected by general method A to give **1** in 81% yield. $R_f$ 0.45 (2:3 hexane/EtOAc); $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ = 11.89 (s, 1H), 7.64-7.63 (m, 2H), 7.29-7.28 (m, 1H), 5.28-5.26 (m, 2H), 4.91 (d, $J$ = 4.0 Hz, 1H), 4.78 (t, $J$ = 4.0 Hz, 1H), 4.19-4.10 (m, 1H), 3.06 (dd, $J$ = 4.8, 17.6 Hz, 1H), 2.72 (d, $J$ = 17.6 Hz, 1H), 2.10 (s, 3H), 2.10-2.04 (m, 1H), 1.92-1.86 (m, 1H), 1.22 (d, $J$ = 6.4 Hz, 3H); $^{13}$C NMR ($CDCl_3$, 100 MHz): $\delta$ = 187.7, 181.9, 174.0, 169.0, 162.1, 143.3, 138.8, 137.1, 131.2, 125.5, 119.6, 115.4, 96.8, 69.8, 68.6, 66.9, 66.0, 63.1, 36.6, 36.1, 21.4, 20.6 ppm; HRMS (ESI) m/z $[M + NH_4]^+$ calcd for $C_{22}H_{24}NO_{10}$ 462.1400, found 462.1401; $[\alpha]_D^{20}$ -153º ($CHCl_3$, c = 1.0). The characterization data is consistent to that of the isolated natural product.[8]

**4'-Deacetyl griseusin A (2)**. Compound **35** was deprotected by general method A to give **2** in 85% yield. $R_f$ 0.10 (2:3 hexane/EtOAc); $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ = 11.89 (s, 1H), 7.63-7.61 (m, 2H), 7.28-7.26 (m, 1H), 5.27 (s, 1H), 4.80-4.76 (m, 2H), 4.22-4.17 (m, 2H), 3.05 (dd, $J$ = 4.4, 17.6 Hz, 1H), 2.83 (d, $J$ = 17.6 Hz, 1H), 2.04 (d, $J$ = 14.4 Hz, 1H), 1.91-1.85 (m, 1H), 1.25 (d, $J$ = 6.0 Hz, 3H); $^{13}$C NMR ($CDCl_3$, 100 MHz): $\delta$ = 187.4, 181.9, 173.9, 162.1, 143.1, 138.4, 137.0, 131.2, 125.5, 119.5, 115.4, 98.7, 68.6, 68.4, 68.1, 66.5, 62.7, 39.2, 36.5, 20.7 ppm; HRMS (ESI) m/z $[M + NH_4]^+$ calcd for $C_{20}H_{22}NO_9$ 420.1295, found 420.1298; $[\alpha]_D^{20}$ -202º ($CHCl_3$, c = 1.0). The characterization data is consistent to that of the isolated natural product.[9]

**Griseusin C (3).** Compound **23**[6] was deprotected by general method A to give **3** in 63% yield. $R_f$ 0.20 (2:3 hexane/EtOAc); $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ = 11.91 (s, 1H), 7.70-7.68 (m, 2H), 7.33 (dd, $J$ = 2.4, 7.6 Hz, 1H), 5.50 (d, $J$ = 7.6 Hz, 1H), 5.29 (d, $J$ = 2.8 Hz, 1H), 4.69 (dd, $J$ = 2.8, 4.8 Hz, 1H), 4.25-4.20 (m, 1H), 3.19 (d, $J$ = 8.4 Hz, 1H), 2.95 (dd, $J$ = 4.8, 18.0 Hz, 1H), 2.72-2.68 (m, 3H), 1.41 (d, $J$ = 6.0 Hz, 3H); $^{13}$C NMR ($CDCl_3$, 100 MHz): $\delta$ = 203.1, 187.4, 181.7, 173.1, 162.4, 140.6, 138.6, 137.3, 131.3, 125.7, 119.8, 115.3, 99.5, 76.0, 69.6,

68.2, 66.8, 47.7, 36.1, 21.6 ppm; HRMS (ESI) m/z $[M + NH_4]^+$ calcd for $C_{20}H_{20}NO_9$ 418.1138, found 418.1132; $[\alpha]_D^{20}$ -100° (MeOH, c = 1.0). The characterization data is consistent to that of the isolated natural product.[10]

***epi*-4'-Deacetylgriseusin A (4).** Compound **36** was deprotected by general method A to give **4** in 62% yield. $R_f$ 0.10 (2:3 hexane/EtOAc); $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ = 11.92 (s, 1H), 7.64-7.62 (m, 2H), 7.29-7.28 (m, 1H), 5.29 (s, 1H), 4.75 (s, 1H), 4.53 (d, *J* = 9.2 Hz, 1H), 4.04-3.99 (m, 2H), 3.02 (dd, *J* = 4.4, 17.6 Hz, 1H), 2.77 (d, *J* = 17.6 Hz, 1H), 2.73-2.14 (brs, 2H), 2.13-2.09 (m, 1H), 1.74-1.67 (m, 1H), 1.27 (d, *J* = 6.0 Hz, 3H); $^{13}$C NMR ($CDCl_3$, 100 MHz): $\delta$ = 187.2, 181.9, 162.1, 148.8, 142.6, 138.5, 137.0, 130.7, 125.6, 122.1, 119.5, 97.4, 74.8, 69.1, 68.9, 67.9, 66.3, 39.7, 36.3, 21.0 ppm; HRMS (ESI) m/z $[M + NH_4]^+$ calcd for $C_{20}H_{22}NO_9$ 420.1295, found 420.1289; $[\alpha]_D^{20}$ -107° ($CHCl_3$, c = 1.0). The characterization data is consistent to that of the isolated natural product.[2]

***ent*-4'-deacetyl-griseusin A (5).** Compound *ent*-**35** was deprotected by general method A to give **5** in 77% yield. $R_f$ 0.10 (2:3 hexane/EtOAc); $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ = 11.88 (s, 1H), 7.65-7.62 (m, 2H), 7.30-7.28 (m, 1H), 5.27 (s, 1H), 4.81-4.79 (m, 2H), 4.19-4.15 (m, 2H), 3.05 (dd, *J* = 4.4, 17.6 Hz, 1H), 2.80 (d, *J* = 17.6 Hz, 1H), 2.06 (d, *J* = 14.4 Hz, 1H), 1.93-1.86 (m, 1H), 1.26 (d, *J* = 6.0 Hz, 3H); $^{13}$C NMR ($CDCl_3$, 100 MHz): $\delta$ = 187.5, 181.9, 173.9, 162.1, 143.1, 138.4, 137.0, 131.3, 125.5, 119.6, 115.4, 98.8, 68.7, 68.4, 68.1, 66.6, 62.8, 39.2, 36.6, 20.8 ppm; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{20}H_{19}O_9$ 403.1029, found 403.1025; $[\alpha]_D^{20}$ 190° ($CHCl_3$, c = 1.0). The characterization data is consistent to that of the isolated natural product.[11]

**Griseusin B (6).** Compound **51** was deprotected by general method B to give **6** in 54% yield. $R_f$ 0.2 (2:3:0.2 hexane/EtOAc/AcOH); $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ = 12.16 (s, 1H), 7.62-7.59 (m, 2H), 7.28-7.26 (m, 1H), 5.27 (d, *J* = 3.6 Hz, 1H), 4.78 (d, *J* = 4.4 Hz, 1H), 4.54-4.51 (m, 1H), 4.28-4.24 (m, 1H), 2.94-2.73 (m, 3H), 2.42 (dd, *J* = 11.2, 18.8 Hz, 1H), 2.10 (s, 3H), 2.06-2.02 (m, 1H), 1.92-1.88 (m, 1H), 1.20 (d, *J* = 6.4 Hz, 3H), hydroxyl and carboxylic proton signals did not appear; $^{13}$C NMR ($CDCl_3$, 100 MHz): $\delta$ = 187.9, 183.2, 173.7, 171.0, 162.1, 147.0, 139.9, 136.3, 131.5, 125.3, 119.1, 115.3, 97.6, 70.3, 67.1, 63.3, 62.0, 39.7, 36.1, 28.0, 21.2, 20.6 ppm; HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{22}H_{22}NaO_{10}$ 469.1111, found 469.1114; $[\alpha]_D^{20}$ -189° ($CHCl_3$, c = 1.0). The characterization data is consistent to that of the isolated natural product.[8]

**4'-Deacetyl-griseusin B (7).** Compound **46** was deprotected by general method B to give **7** in 68% yield. $R_f$ 0.1 (2:3:0.2 hexane/EtOAc/AcOH); $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ = 12.10 (s, 1H), 7.56-7.54 (m, 2H), 7.24-7.21 (m, 1H), 4.70 (s, 1H), 4.44-4.31 (m, 5H), 4.18-4.17 (m, 1H), 2.87-2.79 (m, 2H), 2.71-2.67 (m, 1H), 2.52 (dd, *J* = 11.2, 19.2 Hz, 1H), 2.10-2.07 (m, 1H), 1.90-1.86 (m, 1H), 1.23 (d, *J* = 6.4 Hz, 3H); $^{13}$C NMR ($CDCl_3$, 100 MHz): $\delta$ = 187.7, 183.1, 173.2, 161.9, 146.7, 139.4, 136.2, 131.4, 125.2, 119.1, 115.2, 99.3, 69.3, 68.2, 63.7, 61.6, 39.6, 39.3, 28.1, 20.8 ppm; HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{20}H_{20}NaO_9$ 427.1005, found 427.0998; $[\alpha]_D^{20}$ -200° (MeOH, c = 1.0). The characterization data is consistent to that of the isolated natural product.[9]

***epi*-4'-Deacetyl-griseusin B (8).** Compound **49** was deprotected by general method B to give **8** in 56% yield. $R_f$ 0.1 (2:3:0.2 hexane/EtOAc/AcOH); $^1$H NMR ($CD_3OD$, 400 MHz): $\delta$ = 7.67-7.58 (m, 2H), 7.27 (dd, *J* = 1.2, 8.0 Hz, 1H), 4.44-4.40 (m, 1H), 4.37 (d, *J* = 9.2 Hz, 1H), 4.29-4.25 (m, 1H), 3.98-3.92 (m, 1H), 2.84 (dd, *J* = 2.8, 19.2 Hz, 1H), 2.78-2.70 (m, 2H), 2.38 (dd, *J* = 11.2, 19.2 Hz, 1H), 2.02-1.98 (m, 1H), 1.54 (q, *J* = 12.0 Hz, 1H), 1.20 (d, *J* = 6.4 Hz, 3H); $^{13}$C NMR ($CD_3OD$, 100 MHz): $\delta$ = 189.3, 184.4, 174.5, 162.8, 148.9, 140.7, 137.2, 133.0, 125.5, 119.5, 116.4, 99.6, 75.8, 69.4, 67.0, 64.8, 42.2, 40.6, 29.1, 21.3 ppm; HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{20}H_{20}NaO_9$ 427.1005, found 427.0996; $[\alpha]_D^{20}$ -152° (MeOH, c = 1.0). The characterization data is consistent to that of the isolated natural product.[2]

***ent*-4'-Deacetyl-griseusin B (9).** Compound *ent*-**45** was deprotected by general method B to give **9** in 55% yield. $R_f$ 0.1 (2:3:0.2 hexane/EtOAc/AcOH); $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ = 12.11 (s, 1H), 7.57-7.55 (m, 2H), 7.24-7.22 (m, 1H), 4.71 (s, 1H), 4.44-4.31 (m, 5H), 4.18-4.17 (m, 1H), 2.89-2.79 (m, 2H), 2.71-2.68 (m, 1H), 2.52 (dd,

*J* = 11.2, 19.2 Hz, 1H), 2.11-2.08 (m, 1H), 1.91-1.84 (m, 1H), 1.23 (d, *J* = 6.4 Hz, 3H); $^{13}$C NMR ($CDCl_3$, 100 MHz): $\delta$ = 187.7, 183.2, 173.2, 161.9, 146.7, 139.5, 136.3, 131.4, 125.3, 119.2, 115.3, 99.3, 69.3, 68.2, 63.8, 61.7, 39.6, 39.3, 28.2, 20.9 ppm; HRMS (ESI) m/z $[M-H]^-$ calcd for $C_{20}H_{19}O_9$ 403.1029, found 403.1037; $[\alpha]_D^{20}$ 198º (MeOH, c = 1.0). The characterization data is consistent to that of the isolated natural product.[11]

***ent*-4'-Deacetyl-griseusin B methyl ester (10).** Compound *ent*-**46** was deprotected by general method A to give **10** in 79% yield. $R_f$ 0.3 (2:3 hexane/EtOAc); $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ = 12.14 (s, 1H), 7.61-7.57 (m, 2H), 7.24 (d, *J* = 8.0 Hz, 1H), 4.66 (dd, *J* = 4.0, 11.2 Hz, 1H), 4.46-4.40 (m, 1H), 4.25-4.22 (m, 1H), 4.12-4.08 (m, 1H), 3.75 (s, 3H), 3.34 (d, *J* = 12.0 Hz, 1H), 2.90-2.71 (m, 4H), 2.40 (dd, *J* = 11.2, 19.2 Hz, 1H), 2.09-2.04 (m, 1H), 1.91-1.85 (m, 1H), 1.25 (d, *J* = 6.4 Hz, 3H); $^{13}$C NMR ($CDCl_3$, 100 MHz): $\delta$ = 187.7, 183.2, 171.2, 162.0, 146.4, 139.7, 136.3, 131.4, 125.2, 119.1, 115.3, 99.4, 68.8, 68.2, 63.7, 61.5, 52.3, 39.8, 39.6, 28.4, 20.9 ppm; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{21}H_{23}O_9$ 419.1342, found 419.1330; $[\alpha]_D^{20}$ 176º (MeOH, c = 1.0). The characterization data is consistent to that of the isolated natural product.[11]

**3'-Dehydroxyl griseusin C (13).** Compound **32**[6] was deprotected by general method A to give **13** in 73% yield. $R_f$ 0.60 (2:3 hexane/EtOAc); $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ = 11.77 (s, 1H), 7.68-7.66 (m, 2H), 7.32 (dd, *J* = 2.8, 6.8 Hz, 1H), 5.27 (d, *J* = 2.8 Hz, 1H), 4.80 (t, *J* = 2.8 Hz, 1H), 4.40-4.36 (m, 1H), 3.39 (d, *J* = 17.6 Hz, 1H), 2.97 (dd, *J* = 5.2, 17.6 Hz, 1H), 2.76-2.52 (m, 4H), 1.35 (d, *J* = 6.4 Hz, 3H); $^{13}$C NMR ($CDCl_3$, 100 MHz): $\delta$ = 203.1, 187.5, 182.1, 173.6, 162.2, 143.0, 137.4, 136.7, 131.2, 125.6, 119.8, 115.1, 96.0, 68.5, 67.8, 66.7, 47.6, 46.7, 36.3, 21.3 ppm; HRMS (ESI) m/z $[M + NH_4]^+$ calcd for $C_{20}H_{20}NO_8$ 402.1189, found 402.1188; $[\alpha]_D^{20}$ -163º ($CHCl_3$, c = 1.0).

**1,3'-*epi*-Griseusin C (14).** Compound 1,3'-*epi*-**23**[6] was deprotected by general method A to give **14** in 63% yield. $R_f$ 0.20 (2:3 hexane/EtOAc); $^1$H NMR ($CD_3OD$, 400 MHz): $\delta$ = 7.76 (t, *J* = 8.0 Hz, 1H), 7.69 (d, *J* = 8.0 Hz, 1H), 7.37 (d, *J* = 8.0 Hz, 1H), 5.56 (s, 1H), 5.42 (d, *J* = 4.0 Hz, 1H), 5.25 (t, *J* = 4.0 Hz, 1H), 5.00-4.97 (m, 1H), 3.01 (dd, *J* = 5.2, 17.6 Hz, 1H), 2.74-2.55 (m, 3H), 1.39 (d, *J* = 6.0 Hz, 3H); $^{13}$C NMR ($CD_3OD$, 100 MHz): $\delta$ = 206.6, 189.4, 182.9, 176.9, 163.0, 143.0, 140.0, 138.2, 132.8, 126.0, 120.2, 100.0, 78.8, 73.3, 70.0, 69.6, 49.8, 46.2, 38.4, 21.7 ppm; HRMS (ESI) m/z $[M + NH_4]^+$ calcd for $C_{20}H_{20}NO_9$ 418.1138, found 418.1133; $[\alpha]_D^{20}$ -14º (MeOH, c = 1.0).

**3'-Acetyl-4'-deacetyl-griseusin A (15).** Compound **40** was deprotected by general method A to give **15** in 75% yield. $R_f$ 0.35 (2:3 hexane/EtOAc); $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ = 11.92 (s, 1H), 7.68-7.62 (m, 2H), 7.32 (dd, *J* = 2.0, 7.6 Hz, 1H), 5.82 (d, *J* = 4.4 Hz, 1H), 5.26 (d, *J* = 2.8 Hz, 1H), 4.78-4.77 (m, 1H), 4.42-4.39 (m, 1H), 4.30-4.29 (m, 1H), 3.01 (dd, *J* = 4.8, 17.6 Hz, 1H), 2.78 (d, *J* = 17.6 Hz, 1H), 2.06-2.04 (m, 1H), 1.96 (s, 3H), 1.93-1.92 (m, 1H), 1.27 (d, *J* = 6.4 Hz, 3H), hydroxyl proton signals did not appear; $^{13}$C NMR ($CDCl_3$, 100 MHz): $\delta$ = 187.1, 182.0, 173.5, 170.6, 162.1, 142.5, 136.8, 136.4, 131.2, 125.6, 119.6, 115.4, 96.5, 69.8, 68.0, 66.6, 66.2, 62.8, 38.5, 36.9, 20.7, 20.6 ppm; HRMS (ESI) m/z $[M + NH_4]^+$ calcd for $C_{22}H_{24}NO_{10}$ 462.1400, found 462.1395; $[\alpha]_D^{20}$ -205º ($CHCl_3$, c = 1.0).

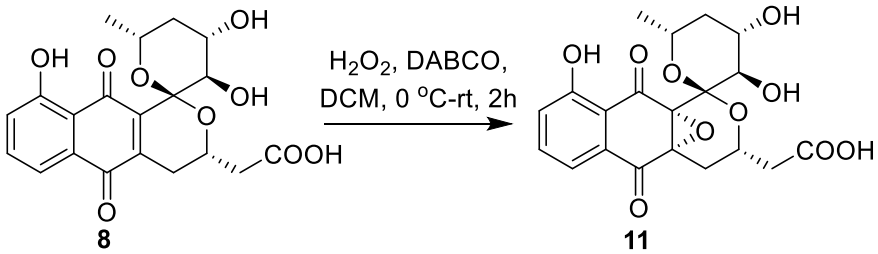
**3'-Dehydroxy-4'-deacetyl-griseusin A (16).** Compound **33** was deprotected by general method A to give **16** in 78% yield. $R_f$ 0.40 (2:3 hexane/EtOAc); $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ = 11.91 (s, 1H), 7.66-7.65 (m, 2H), 7.30 (dd, *J* = 2.8, 6.8 Hz, 1H), 5.26 (d, *J* = 2.8 Hz, 1H), 4.79 (dd, *J* = 2.8, 4.8 Hz, 1H), 4.28-4.25 (m, 2H), 3.20 (br s, 1H), 3.06-3.00 (m, 2H), 2.73 (d, *J* = 18.0 Hz, 1H), 1.90-1.78 (m, 2H), 1.75-1.72 (m, 1H), 1.26 (d, *J* = 6.0 Hz, 3H); $^{13}$C NMR ($CDCl_3$, 100 MHz): $\delta$ = 187.5, 182.5, 173.5, 162.1, 143.9, 137.2, 137.1, 131.2, 125.5, 119.6, 115.4, 97.0, 68.8, 66.2, 64.0, 63.1, 38.5, 36.6, 36.1, 21.4 ppm; HRMS (ESI) m/z $[M + NH_4]^+$ calcd for $C_{20}H_{22}NO_8$ 404.1345, found 404.1355; $[\alpha]_D^{20}$ -135º ($CHCl_3$, c = 1.0).

**3'-Dehydroxy-*epi*-4'-deacetyl-griseusin A (17).** Compound **34** was deprotected by general method A to give **17** in 75% yield. $R_f$ 0.40 (2:3 hexane/EtOAc); $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ = 11.96 (s, 1H), 7.65-7.64 (m, 2H),

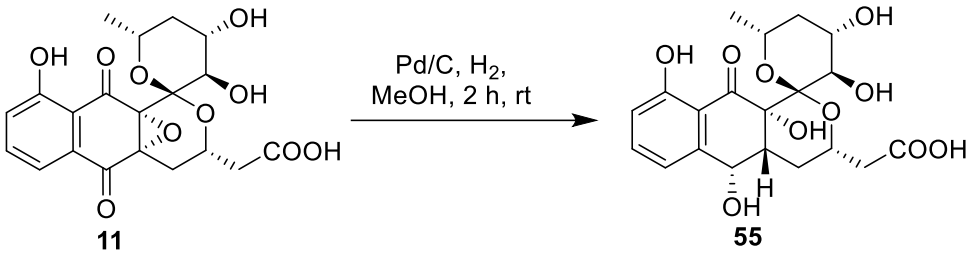
7.30 (dd, *J* = 2.8, 6.8 Hz, 1H), 5.25 (s, 1H), 4.66-4.64 (m, 1H), 4.25-4.22 (m, 1H), 3.97-3.94 (m, 1H), 2.95 (dd, *J* = 4.8, 17.6 Hz, 1H), 2.71-2.61 (m, 2H), 2.07-2.01 (m, 2H), 1.67 (br s, 1H), 1.55-1.49 (m, 1H), 1.27 (d, *J* = 6.0 Hz, 3H); $^{13}$C NMR ($CDCl_3$, 100 MHz): $\delta$ = 187.5, 182.4, 174.0, 162.1, 143.8, 137.1, 137.0, 131.3, 125.4, 119.5, 115.5, 96.5, 69.1, 67.9, 65.7, 64.5, 41.5, 40.0, 36.4, 21.5 ppm; HRMS (ESI) m/z $[M + NH_4]^+$ calcd for $C_{20}H_{22}NO_8$ 404.1345, found 404.1341; $[\alpha]_D^{20}$ -146$^o$ ($CHCl_3$, c = 1.0).

***ent*-Griseusin C (18).** Compound **25** was deprotected by general method A to give **18** in 63% yield. $R_f$ 0.20 (2:3 hexane/EtOAc); $^1$H NMR ($CD_3OD$, 400 MHz): $\delta$ = 7.77-7.72 (m, 1H), 7.66 (dd, *J* = 1.2, 7.6 Hz, 1H), 7.35 (dd, *J* = 1.2, 7.6 Hz, 1H), 5.53 (s, 1H), 5.36 (d, *J* = 3.2 Hz, 1H), 4.79 (dd, *J* = 2.8, 4.8 Hz, 1H), 4.31-4.26 (m, 1H), 3.12 (dd, *J* = 5.2, 18.0 Hz, 1H), 2.74-2.71 (m, 1H), 2.68-2.56 (m, 2H), 1.36 (d, *J* = 6.4 Hz, 3H); $^{13}$C NMR ($CD_3OD$, 100 MHz): $\delta$ = 204.9, 189.1, 183.2, 176.6, 163.1, 142.2, 140.3, 138.2, 132.9, 126.1, 120.1, 116.6, 100.8, 77.3, 70.3, 70.2, 68.3, 36.7, 21.6, 14.5 ppm; HRMS (ESI) m/z $[M + NH_4]^+$ calcd for $C_{20}H_{20}NO_9$ 418.1138, found 418.1126; $[\alpha]_D^{20}$ 102$^o$ (MeOH, c = 1.0); $[\alpha]_D^{20}$ 198$^o$ (MeOH, c = 1.0).

**3'-Dehydroxy-4'-oxo-griseusin B (19).** Compound **44** was deprotected by general method B to give **19** in 52% yield. $R_f$ 0.40 (1:1:0.2 hexane/EtOAc/AcOH); $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ = 12.01 (s, 1H), 7.62-7.60 (m, 2H), 7.29-7.26 (m, 1H), 4.55-4.49 (m, 1H), 4.48-4.44 (m, 1H), 3.39 (d, *J* = 15.6 Hz, 1H), 2.87 (d, *J* = 2.8 Hz, 1H), 2.75-2.74 (m, 2H), 2.58-2.42 (m, 4H), 1.34 (d, *J* = 6.4 Hz, 3H), carboxylic proton signals did not appear; $^{13}$C NMR ($CDCl_3$, 100 MHz): $\delta$ = 205.7, 187.8, 183.5, 175.4, 162.0, 145.1, 140.4, 136.5, 131.5, 125.3, 119.3, 115.0, 96.9, 66.9, 63.2, 48.3, 47.2, 39.4, 28.1, 21.3 ppm; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{20}H_{19}O_8$ 387.1080, found 387.1081; $[\alpha]_D^{20}$ -228$^o$ ($CHCl_3$, c = 1.0).

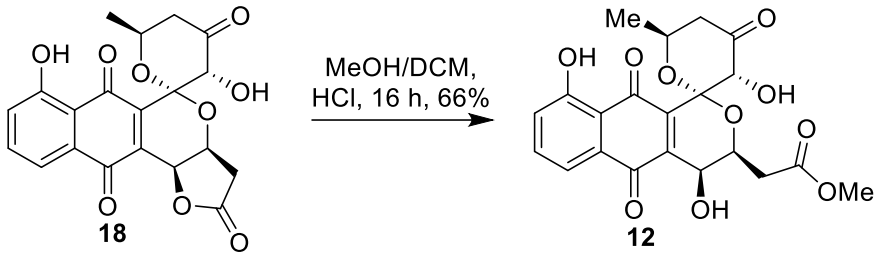



***4a,10a*-Epoxy-*epi*-4'-deacetyl-griseusin B (11).** Aqueous 30% $H_2O_2$ (10 uL, 0.08 mmol) was added to a precooled solution of **8** (17 mg, 0.04 mmol) and DABCO (9 mg, 0.08 mmol) in DCM (0.4 mL) at 0 $^o$C. The reaction was stirred for 2 h during which the temperature was allowed to equilibrate to room temperature. The resulting mixture was partitioned between EtOAc (1 mL) and water (1 mL) and the organic phase collected and concentrated. The recovered residue was dissolved in $CH_3CN$ and purified by semi-preparative reverse-phase HPLC (10 mL/min, 30%-40% $CH_3CN/H_2O$) to afford the product as colorless solid (15 mg, 88%). $R_f$ 0.1 (2:3:0.2 hexane/EtOAc/AcOH); $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ = 11.60 (s, 1H), 7.63-7.59 (m, 2H), 7.24-7.22 (m, 1H), 4.46 (d, *J* = 9.2 Hz, 1H), 4.36-4.32 (m, 1H), 4.01-4.05 (m, 1H), 3.94-3.87 (m, 1H), 3.67 (br s, 3H), 2.67 (dd, *J* = 4.0, 15.6 Hz, 1H), 2.59-2.49 (m, 2H), 2.33 (dd, *J* = 11.6, 14.4 Hz, 1H), 2.01-1.97 (m, 1H), 1.59-1.54 (m, 1H), 1.25 (d, *J* = 5.6 Hz, 3H); $^{13}$C NMR ($CD_3OD$, 100 MHz): $\delta$ = 193.0, 189.4, 173.9, 162.6, 136.9, 131.0, 125.1, 119.2, 114.4, 97.0, 74.3, 68.8, 66.3, 63.8, 62.8, 62.3, 39.9, 38.5, 27.3, 20.8 ppm; HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{20}H_{20}NaO_{10}$ 443.0954, found 443.0958; $[\alpha]_D^{20}$ +11$^o$ (MeOH, c = 1.0). The characterization data is consistent to that of the isolated natural product.[2]




11 55

**2-((*1S,3S,3'R,4aR,4'S,5S,6'R,10aR*)-3',4',5,9,10a-pentahydroxy-6'-methyl-10-oxo-3,3',4,4a,4',5,5',6',10,10a-decahydrospiro[benzo[g]isochromene-1,2'-pyran]-3-yl)acetic acid (55).** The reaction flask containing a solution of **11** (13 mg, 0.03 mmol) and Pd/C (6 mg, 10% w/w) in MeOH (3 mL) was evacuated under vacuum and quenched with $H_2$ (x 3) and then the reaction was stirred at room temperature for 2 h under with $H_2$. The reaction mixture was subsequently filtered via a 0.45 μM syringe filter, washed with MeOH (1 mL), concetrated and purified by semi-preparative reverse-phase HPLC (10 mL/min, 15%-40% $CH_3CN/H_2O$) to get the product as colorless solid (5.3 mg, 42%). $^1$H NMR (DMSO-$d_6$, 400 MHz): $\delta$ = 12.13 (br s, 1H), 11.44 (s, 1H), 7.61 (t, *J* = 8.0 Hz, 1H), 7.09 (d, *J* = 8.0 Hz, 1H), 6.87 (d, *J* = 8.0 Hz, 1H), 6.17 (s, 1H), 5.79 (d, *J* = 5.6 Hz, 1H), 5.69 (s, 1H), 5.13 (t, *J* = 5.6 Hz, 1H), 4.70 (d, *J* = 4.0 Hz, 1H), 4.05-3.99 (m, 1H), 3.91-3.88 (m, 1H), 3.68 (d, *J* = 8.0 Hz, 1H), 3.64-3.60 (m, 1H), 3.20-3.16 (m, 1H), 2.36 (dd, *J* = 4.4, 16.0 Hz, 1H), 2.18 (dd, *J* = 8.8, 16.0 Hz, 1H), 1.89-1.84 (m, 1H), 1.79-1.75 (m, 1H), 1.27-1.24 (m, 1H), 1.20 (d, *J* = 6.4 Hz, 3H), 0.85-0.75 (m, 1H); $^{13}$C NMR (DMSO-$d_6$, 100 MHz): $\delta$ = 201.7, 171.9, 162.2, 146.1, 137.5, 117.0, 116.1, 114.4, 99.6, 78.8, 70.3, 69.0, 66.2, 64.0, 63.3, 43.3, 39.9, 39.5, 27.7, 20.7 ppm; HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{20}H_{24}NaO_{10}$ 447.1267, found 447.1270; $[\alpha]_D^{20}$ +39$^o$ (MeOH, c = 1.0).




18 12

**Griseusin D (12).** Concentrated HCl (6 μL, 0.07 mmol) was added to a stirred solution of **18** (14 mg, 0.035 mmol) in MeOH (5 mL) and DCM (1 mL) at room temperature and the reaction progress monitored by analytical reverse phase HPLC with gradient $CH_3CN$-$H_2O$ as eluent. Upon completion (~18 h, based on consumption of starting material), the mixture was concentrated to 1 mL and purified by semi-preparative HPLC (10 mL/min, 40%-50% $CH_3CN/H_2O$) to afford the product as an orange solid (10 mg, 66%). $R_f$ 0.2 (2:3 hexane/EtOAc); $^1$H NMR (DMSO-$d_6$, 400 MHz): $\delta$ = 11.84 (s, 1H), 7.78 (dd, *J* =7.2, 8.4 Hz, 1H), 7.57 (dd, *J* = 1.2, 7.2 Hz, 1H), 7.39 (dd, *J* = 1.2, 8.4 Hz, 1H), 5.14-5.12 (m, 2H), 4.96 (d, *J* = 9.2 Hz, 1H), 4.46-4.44 (m, 1H), 4.33-4.28 (m, 2H), 3.62 (s, 3H), 2.80 (dd, *J* = 4.4, 16.4 Hz, 1H), 2.72-2.56 (m, 2H), 2.42 (dd, *J* = 3.2, 14.0 Hz, 1H), 1.25 (d, *J* = 6.4 Hz, 3H); $^{13}$C NMR (DMSO-$d_6$, 100 MHz): $\delta$ = 203.8, 187.8, 182.0, 171.0, 160.5, 145.3, 137.0, 136.7, 131.5, 124.6, 118.5, 114.9, 100.2, 76.3, 67.9, 67.5, 58.5, 51.5, 47.7, 34.7, 21.1 ppm; HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{21}H_{20}NaO_{10}$ 455.0954, found 455.0945; $[\alpha]_D^{20}$ 75$^o$ (MeOH, c = 1.0). The characterization data is consistent to that of the isolated natural product.[3]

## Supplementary References


1. T. M. Hoye, C. S. Jeffrey, and F.Shao, *Nat. Protoc.* 2007, **2**, 2451.
2. J. He, E. Roemer, C. Lange, X. Huang, A. Maier, G. Kelter, Y. Jiang, L. H. Xu, K. D. Menzel, S. Grabley, H. H. Fiebig, C. L. Jiang, and I. Sattler, *J. Med. Chem.* 2007, **50**, 5168.
3. Y. Q. Li, M. G. Li, W. Li, J. Y. Zhao, Z. G. Ding, X. L. Cui, and M. L. Wen, *J. Antibiot.* 2007, **60**, 757.
4. a) Q.-B. She, E. Halilovic, Q. Ye, W. Zhen, S. Shirasawa, T. Sasazuki, D. B. Solit, and N. Rosen, *Cancer Cell* 2010, **18**, 39. b) Q. Ye, Y. Zhang, Y. Cao, X. Wang, Y. Guo, J. Chen, J. Horn, L. V. Ponomareva, L. Chaiswing, K. A. Shaaban, Q. Wei, B. D. Anderson, D. St Clair, H. Zhu, M. Leggas, J. S. Thorson, and Q.-B. She, *Cell Chem. Biol.* 2019, **26**, 366.
5. L. V. Ponomareva, A. Athippozhy, S. R. Voss, and J. S. Thorson, *Comp. Biochem. Physiol. C Toxicol. Pharmacol.*, 2015, **178**, 128.
6. Y. Zhang, Q. Ye, X. Wang, Q.-B. She, and J. S. Thorson *Angew. Chem. Int. Ed.* 2015, **54**, 11219.
7. D. F. Taber, P. W. DeMatteo, and R. A. Hassan, *Org. Synth.* 2013, **90**, 350.
8. N. Tsuji, M. Kobayashi, Y. Terui, and K. Tori, *Tetrahedron* 1976, **32,** 2207.
9. M. Igarashi, W. Chen, T. Tsuchida, M. Umekita, T. Sawa, H. Naganawa, M. Hamada and T. Takeuchi, *J. Antibiot.* 1995, **48**, 1502.
10. X. Li, Y. Zheng, I. Sattler, and W. Lin, *Arch. Pharm. Res.* 2006, **29**, 942.
11. M. S. Abdelfattah, T. Kazufumi, and M. Ishibashi, *J. Antibiot.* 2011, **64**, 729.

## Spectroscopic Data

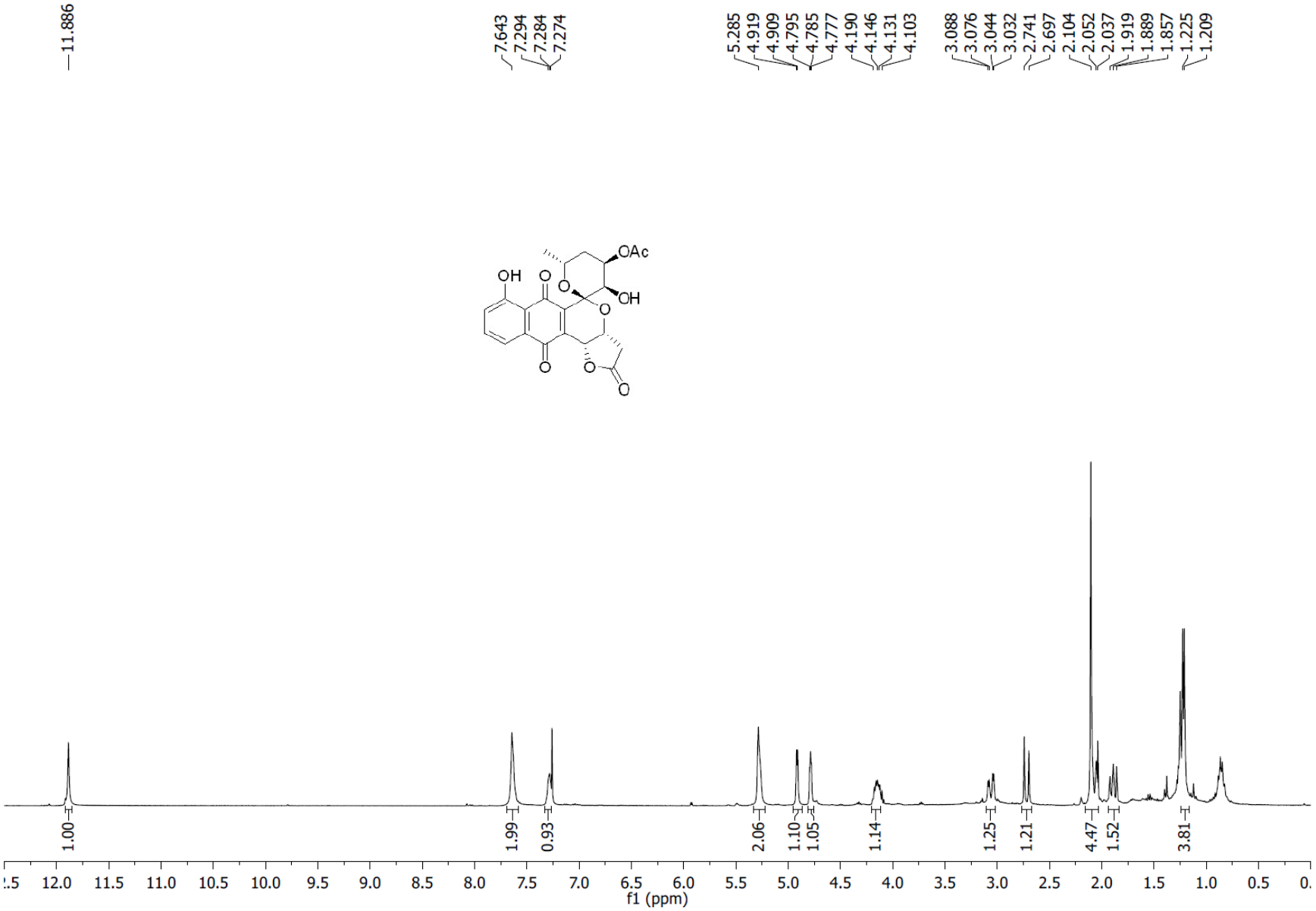



**Figure S4.** $^{1}$H-NMR ($CDCl_3$, 400 MHz) of **1.**

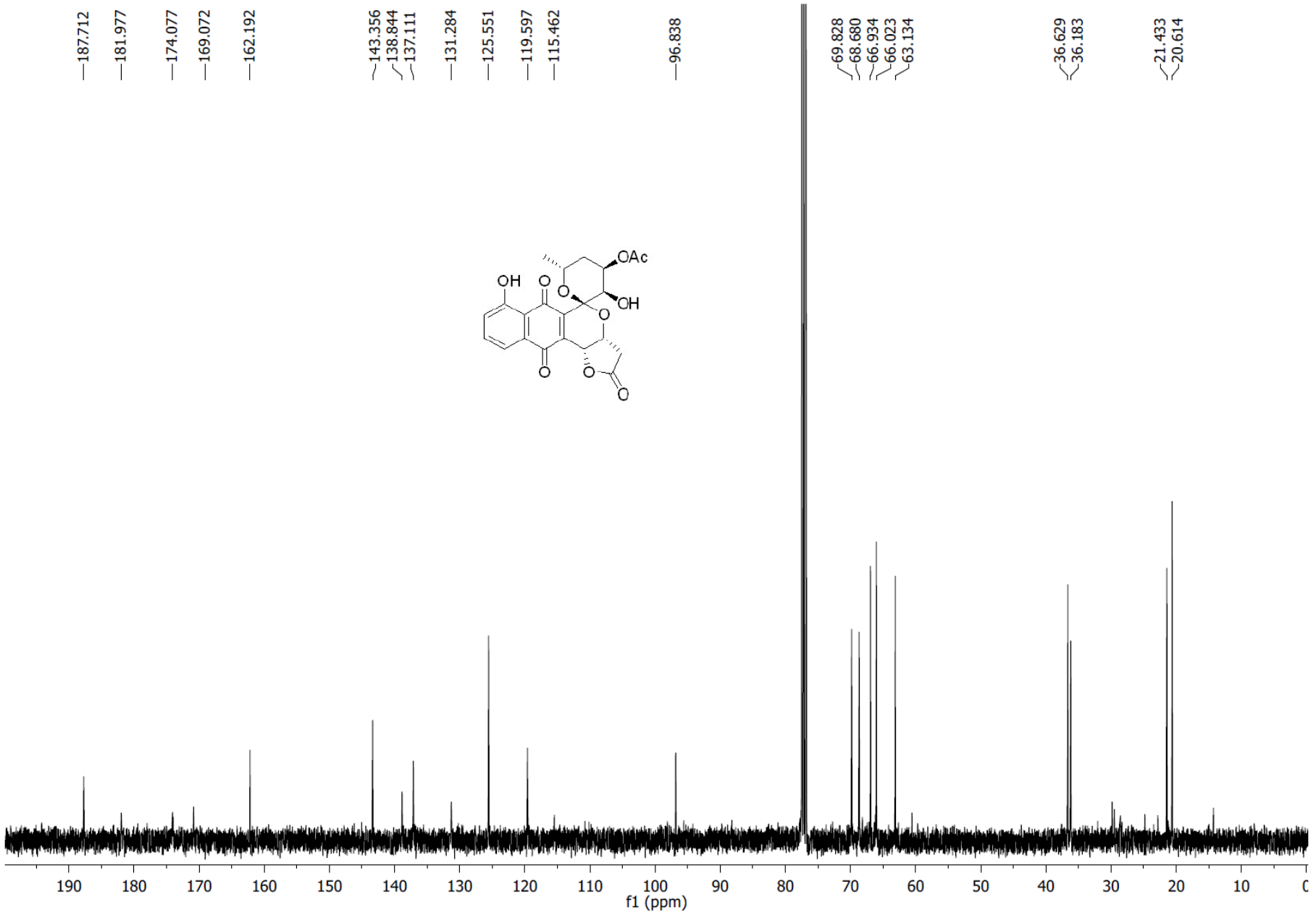



**Figure S5.** $^{13}$C-NMR ($CDCl_3$, 100 MHz) of **1.**

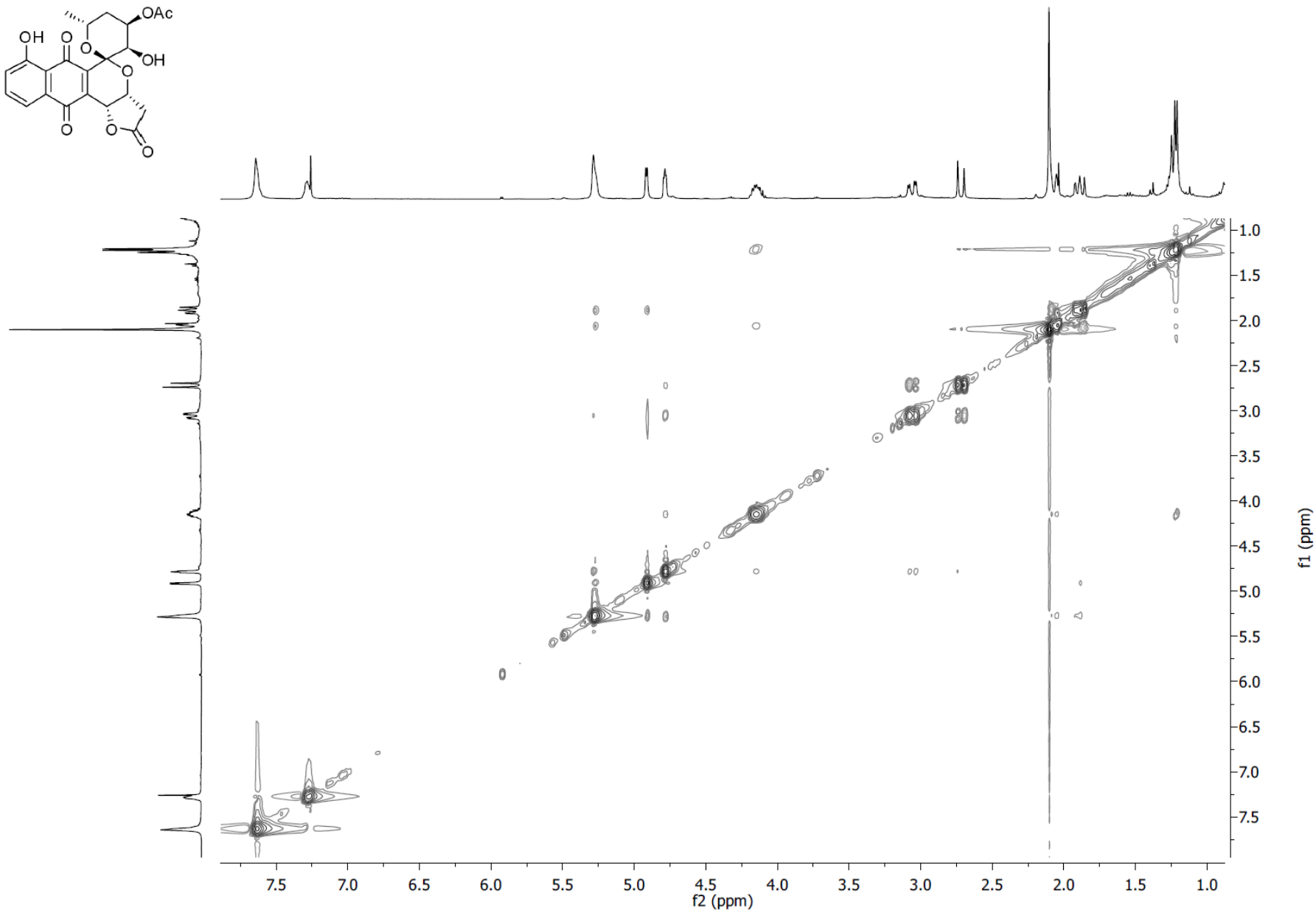



**Figure S6.** NOESY spectrum ($CDCl_3$, 400 MHz) of **1.**

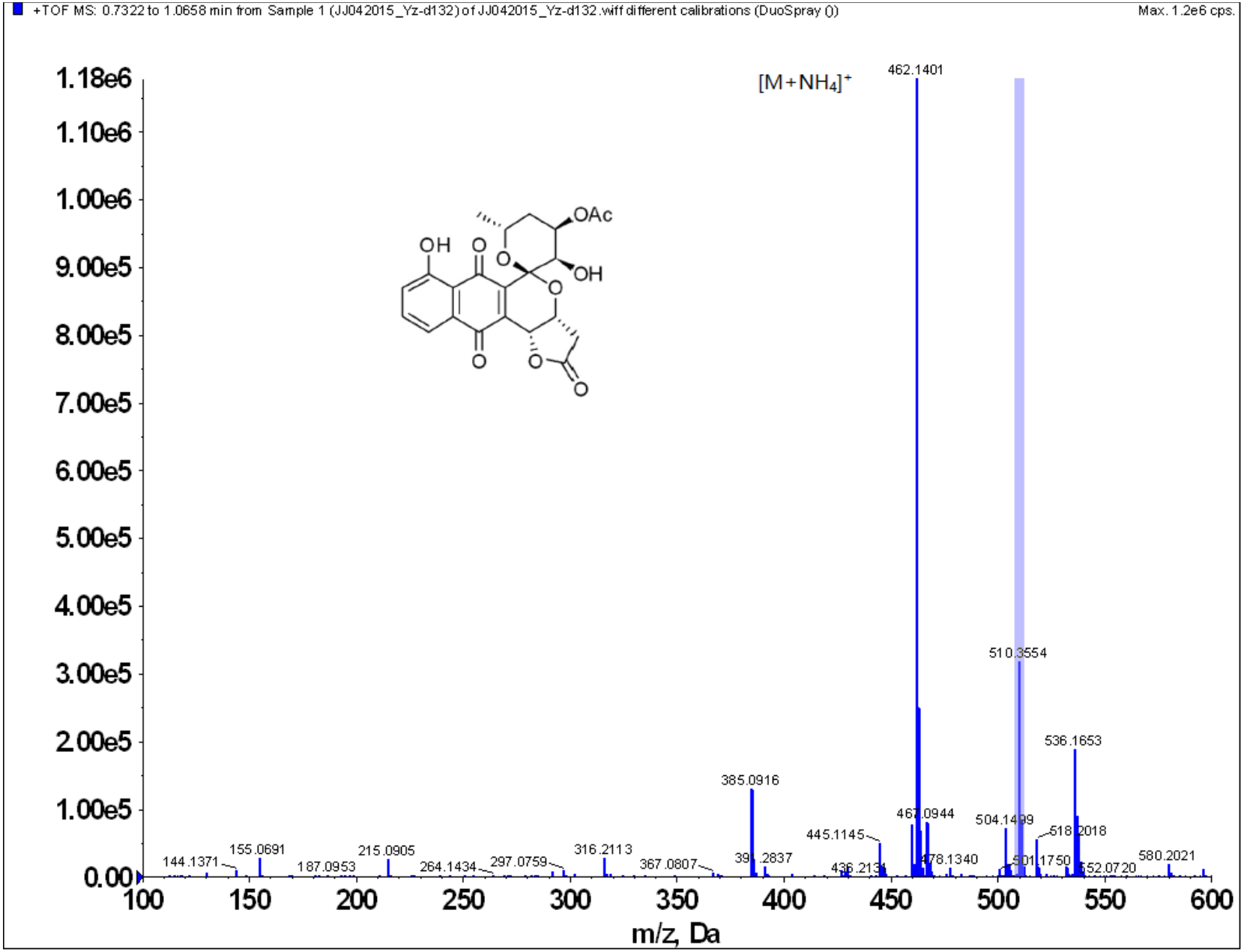



**Figure S7.** (+)-HRESI-MS spectrum of **1.**

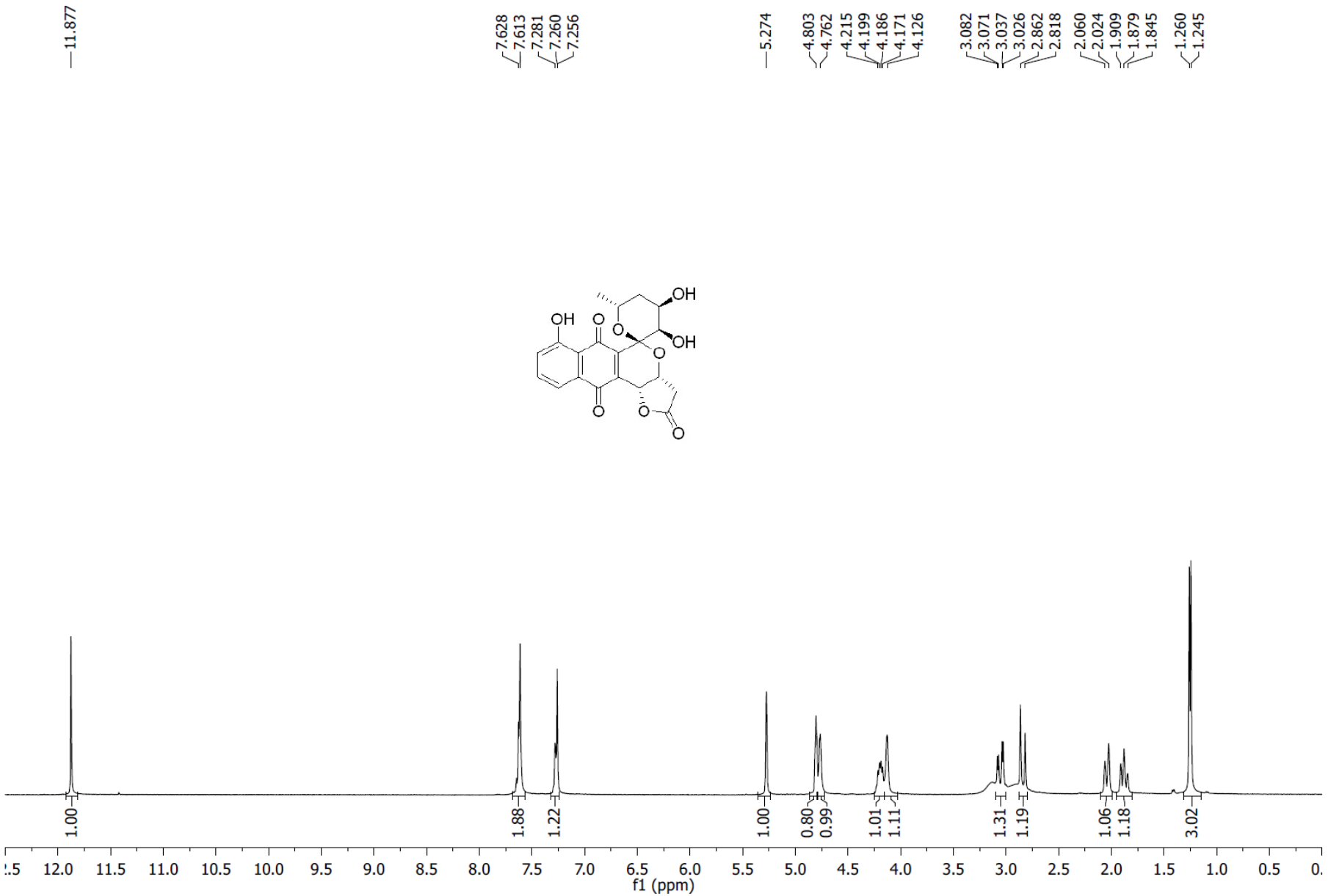



**Figure S8.** $^{1}$H-NMR ($CDCl_3$, 400 MHz) of **2.**

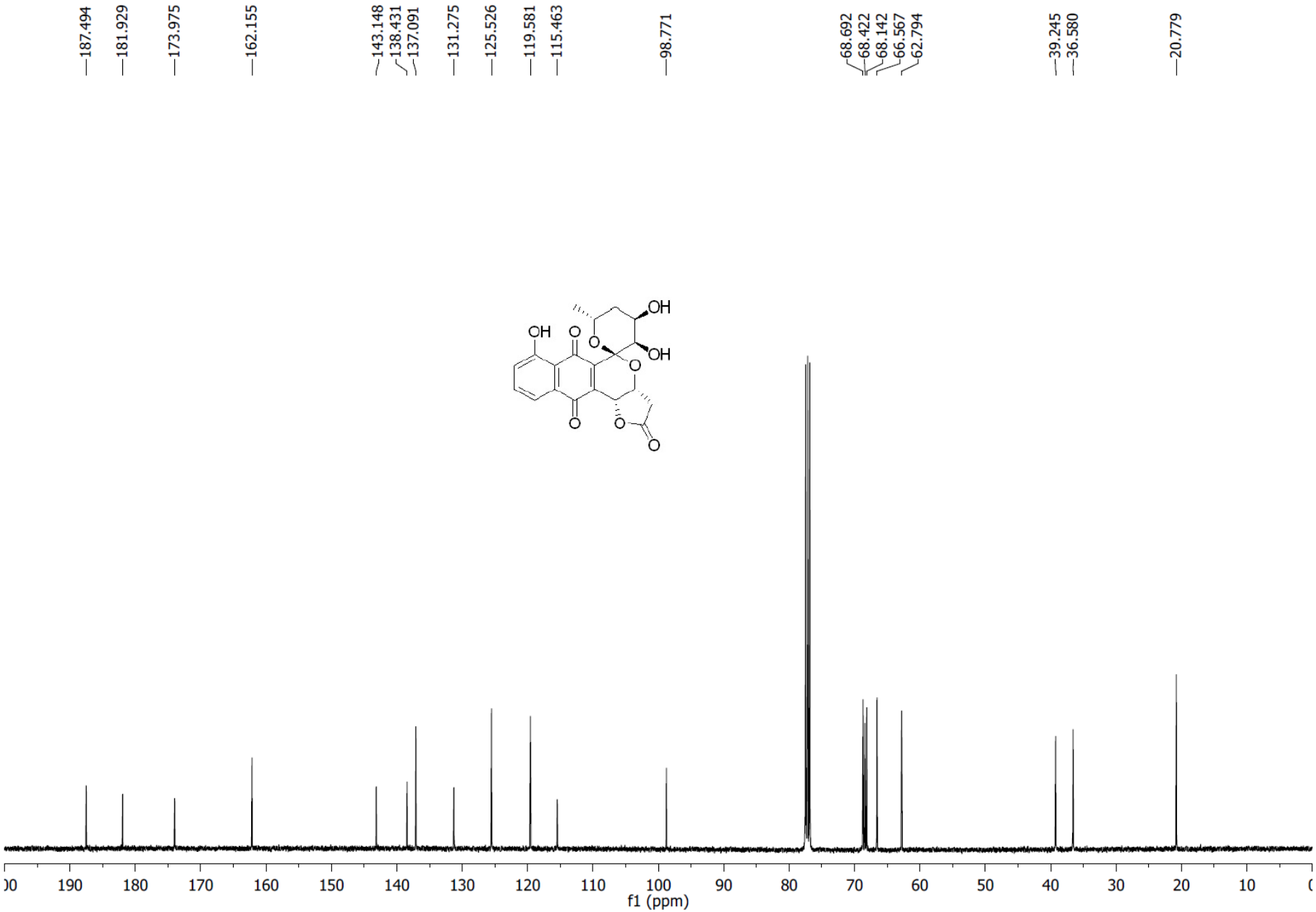



**Figure S9.** $^{13}$C-NMR ($CDCl_3$, 100 MHz) of **2.**

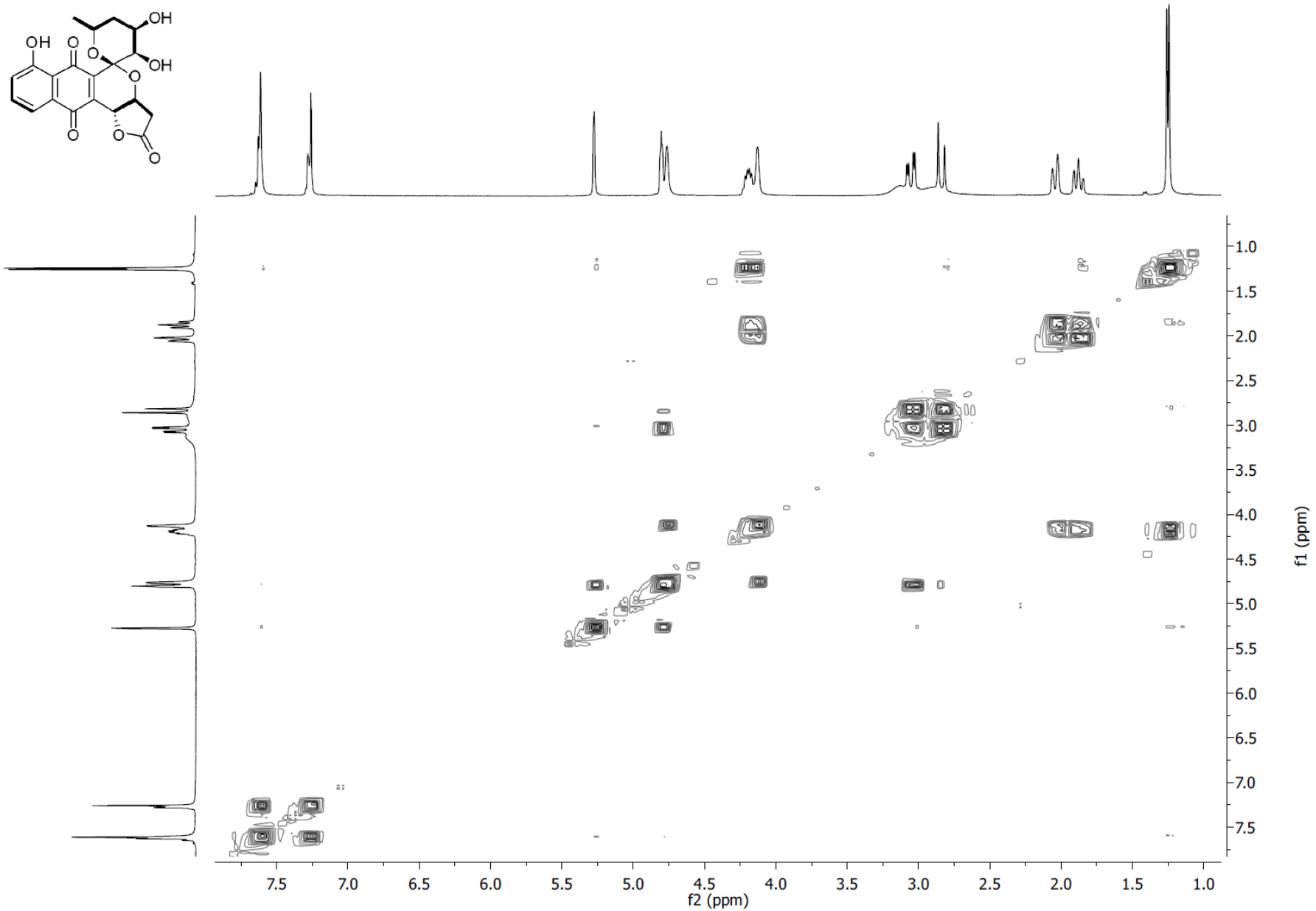



**Figure S10.** $^{1}$H-$^{1}$H COSY ($CDCl_3$, 400 MHz) of **2.**

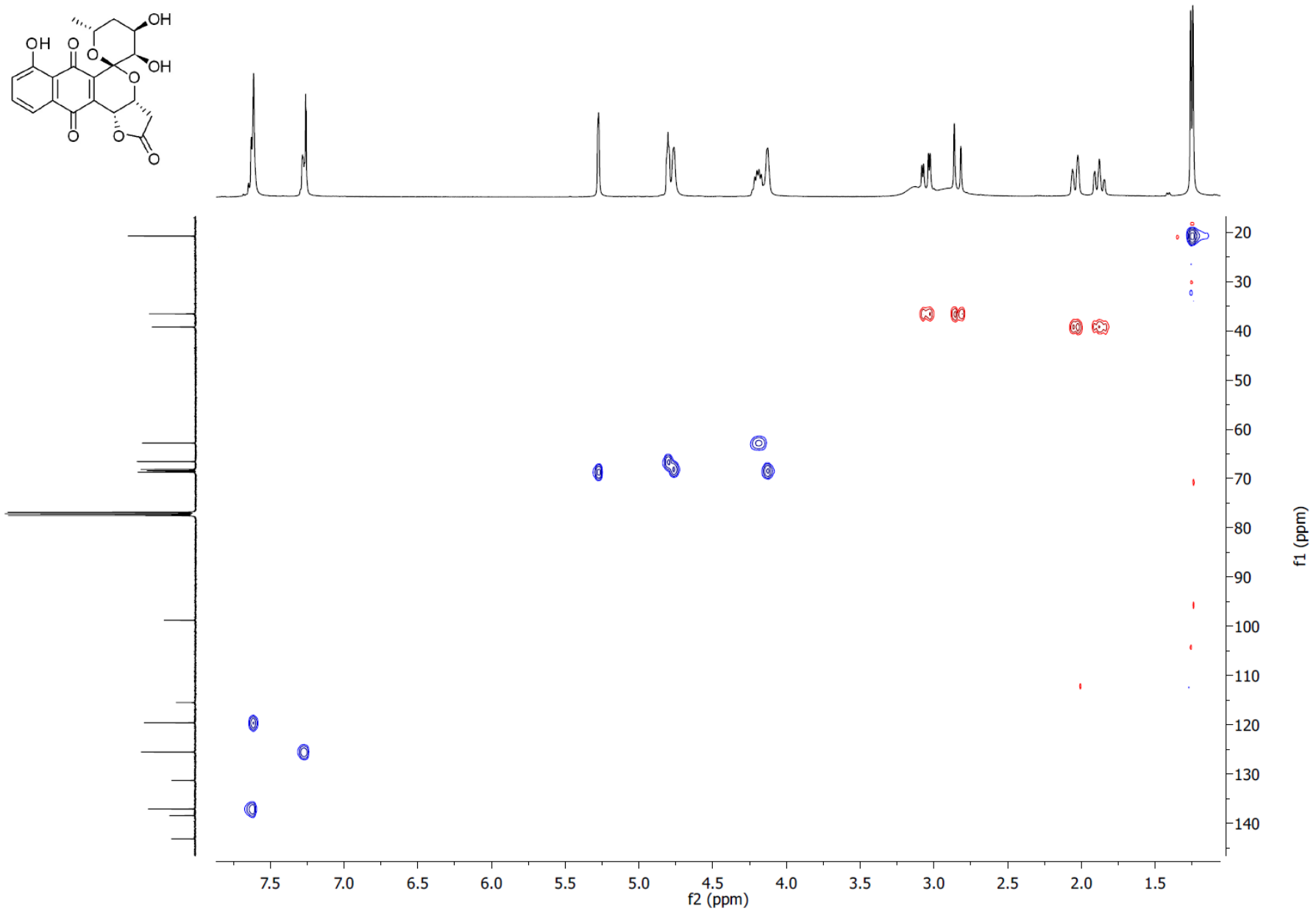



**Figure S11.** HSQC ($CDCl_3$, 400 MHz) of **2.**

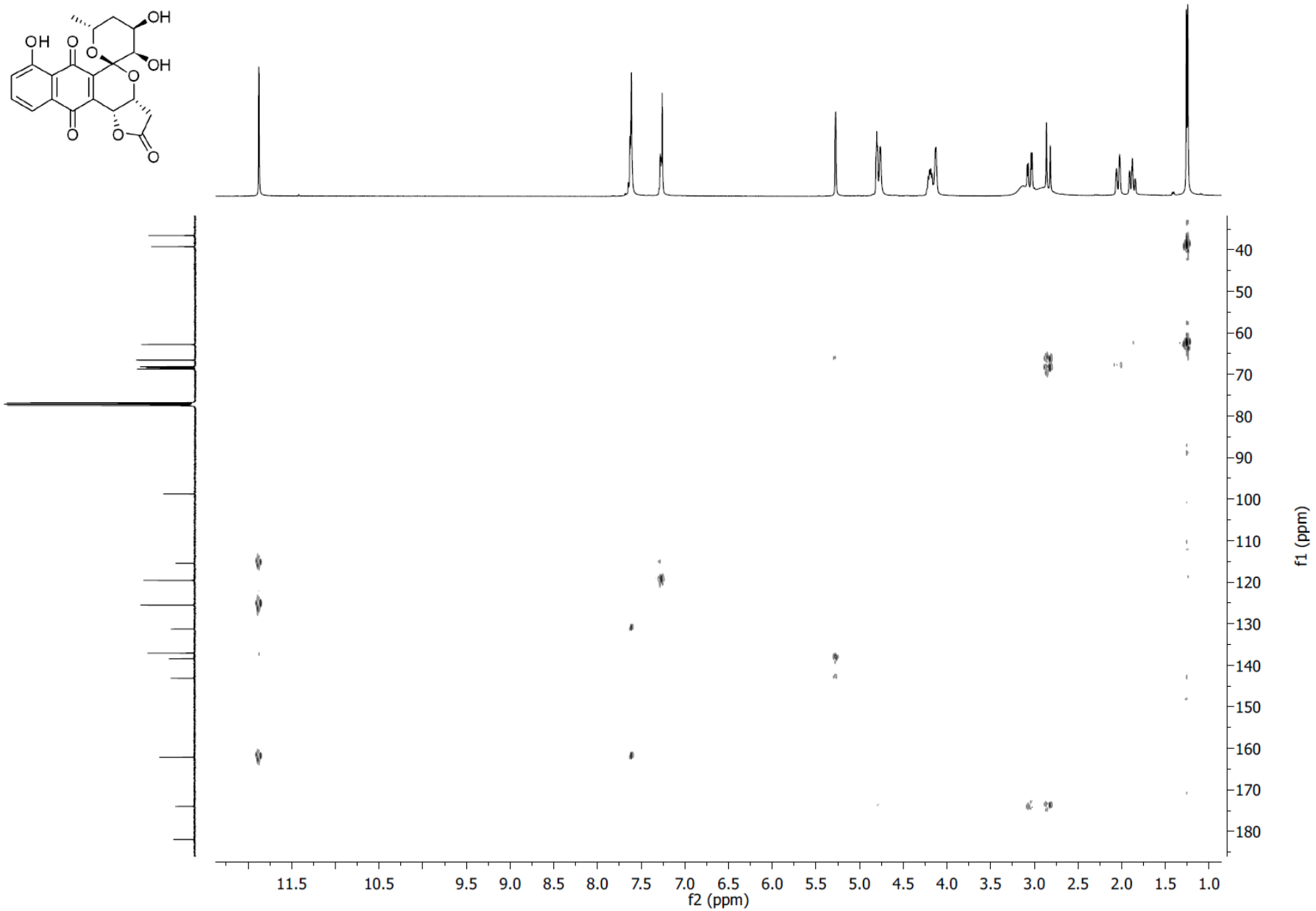



**Figure S12.** HMBC ($CDCl_3$, 400 MHz) of **2.**

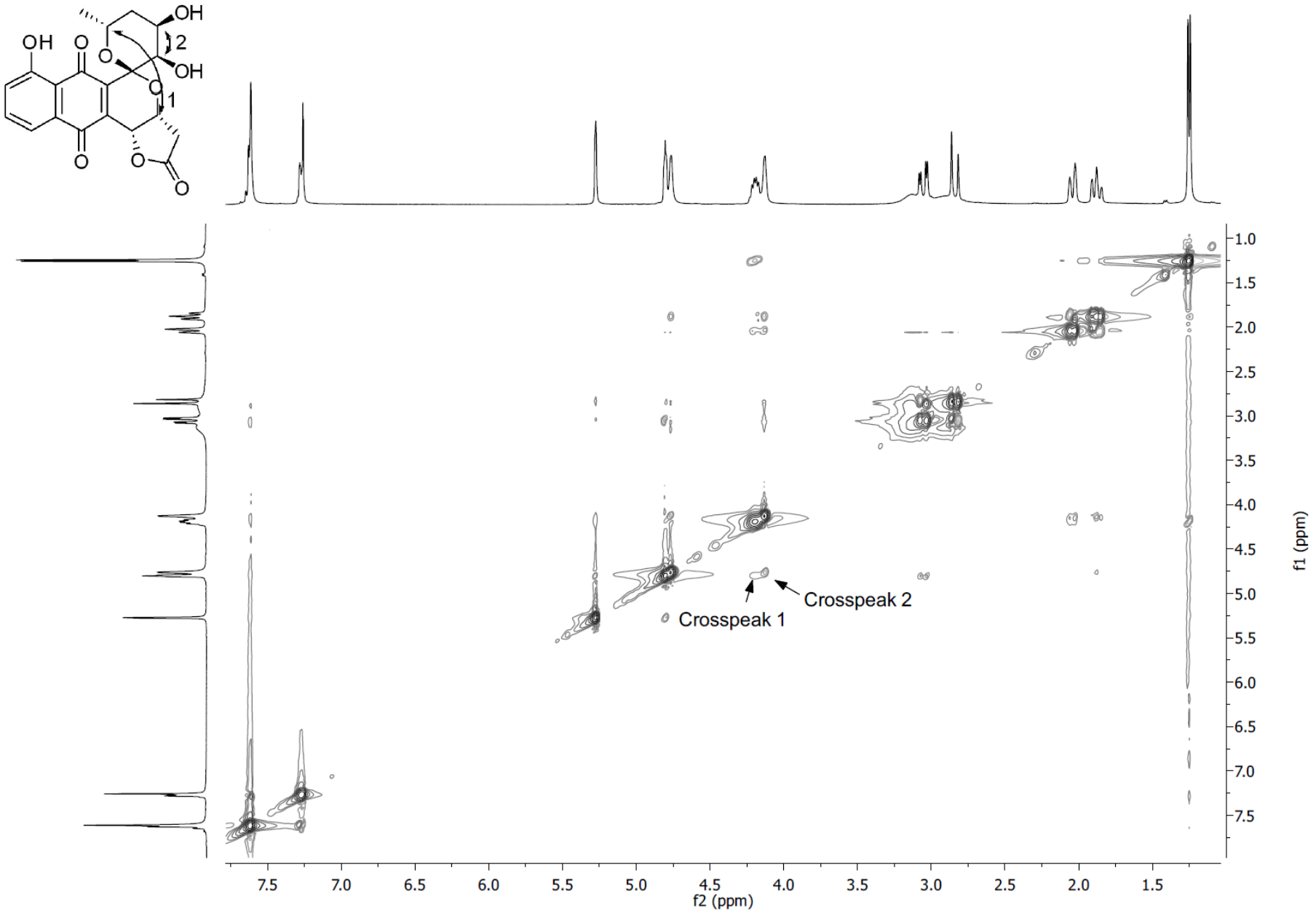



**Figure S13.** NOESY ($CDCl_3$, 400 MHz) of **2.**

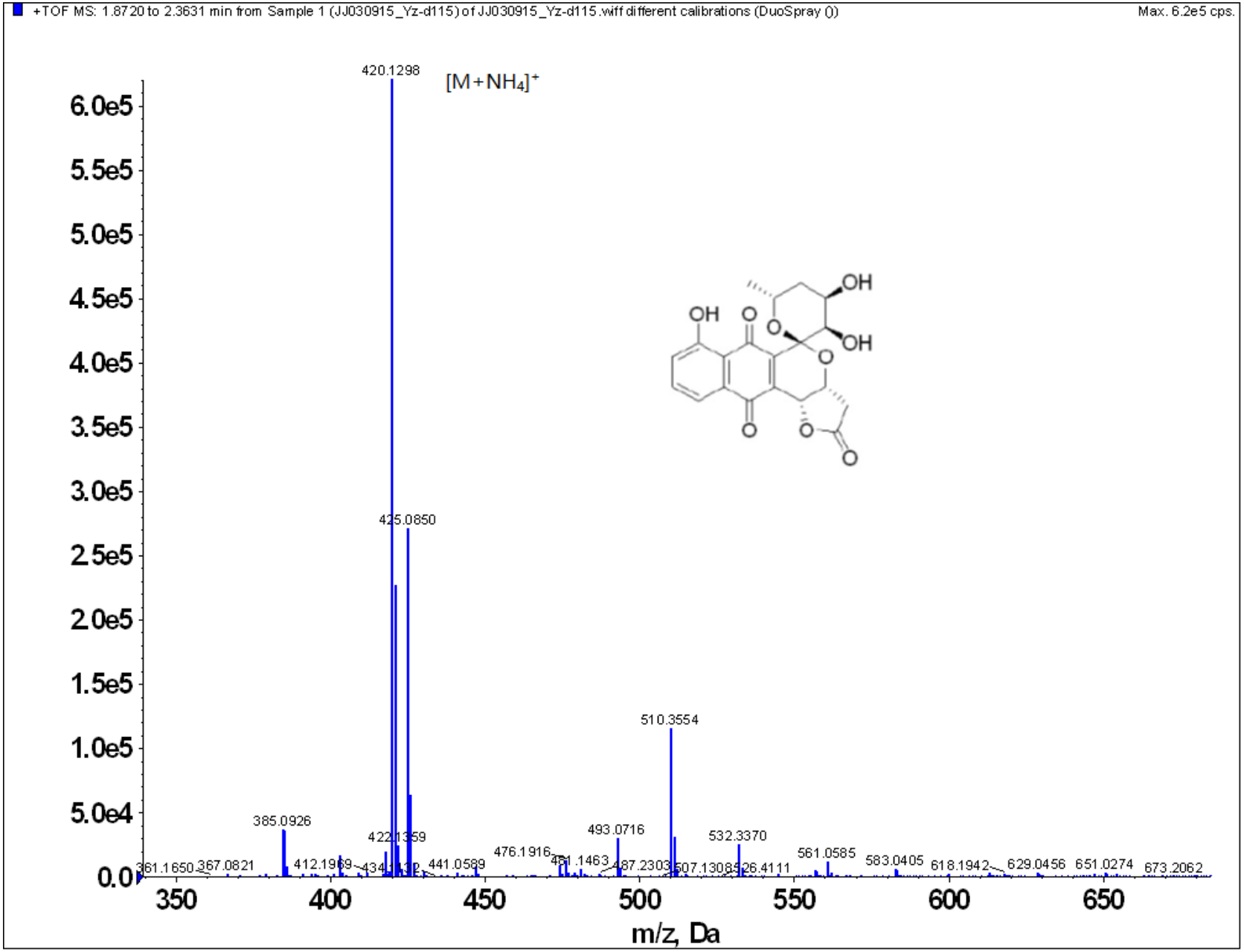



**Figure S14.** (+)-HRESI-MS spectrum of **2.**

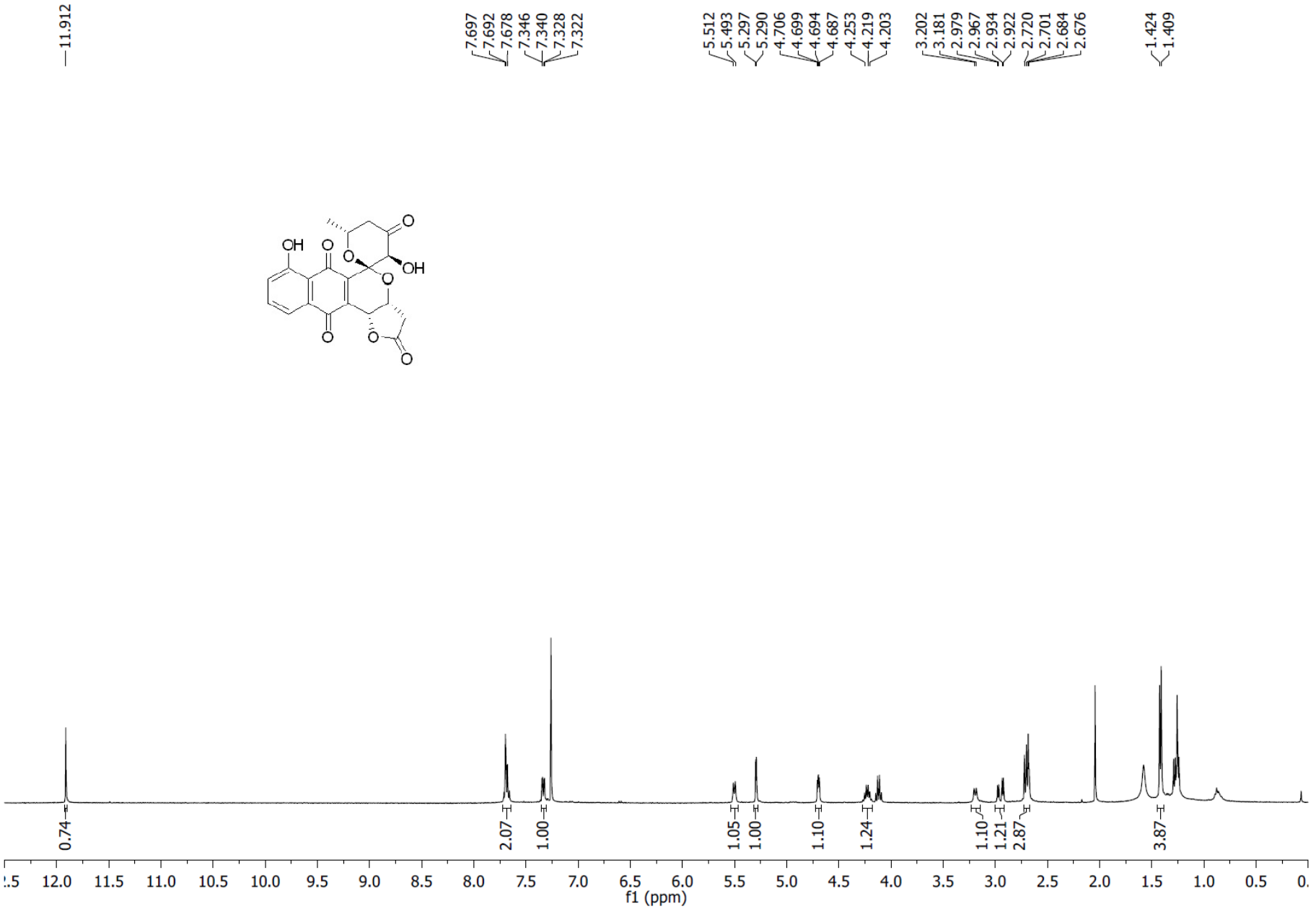



**Figure S15.** $^{1}$H-NMR ($CDCl_3$, 400 MHz) of **3.**

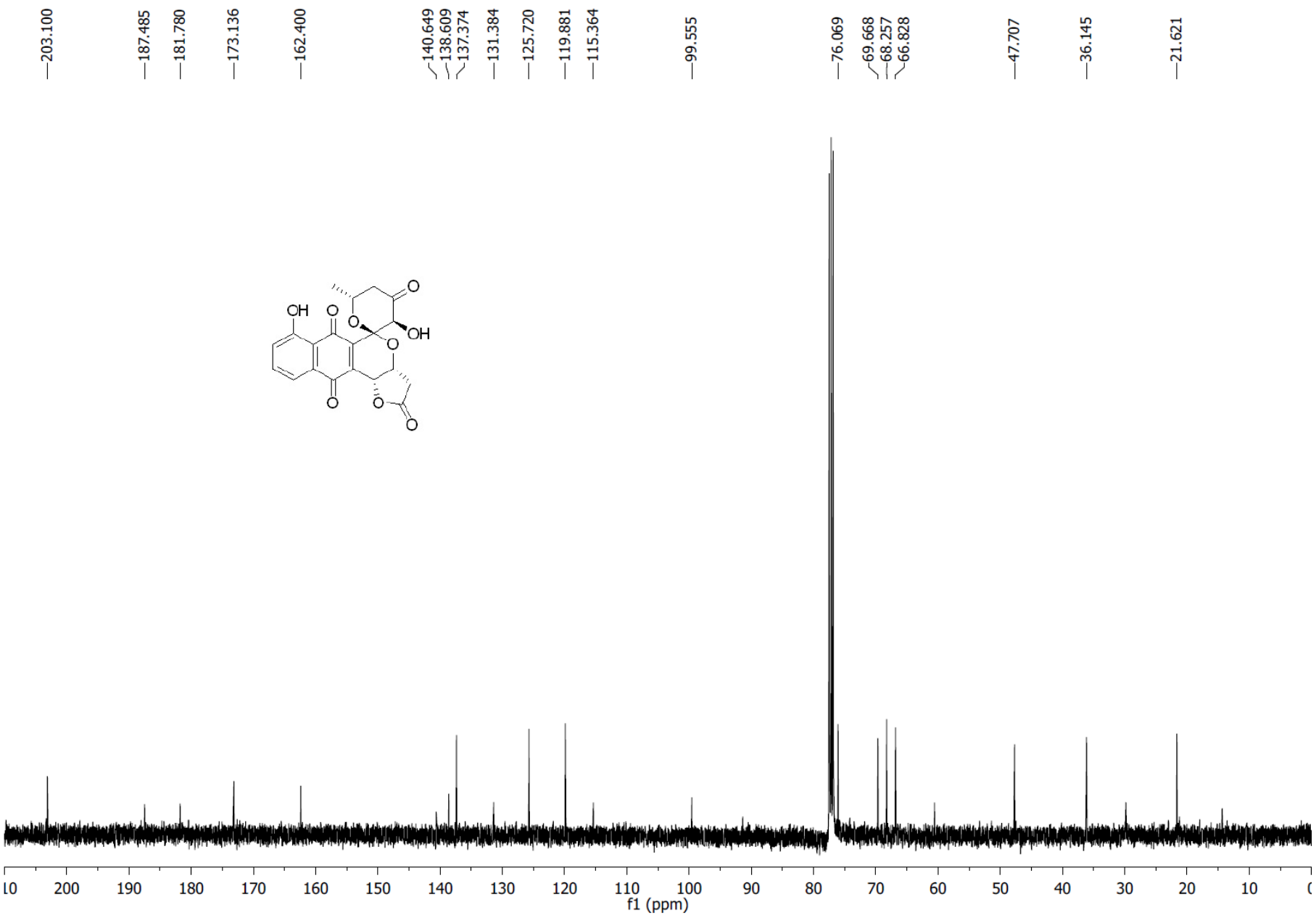



**Figure S16.** $^{13}$C-NMR ($CDCl_3$, 100 MHz) of **3.**

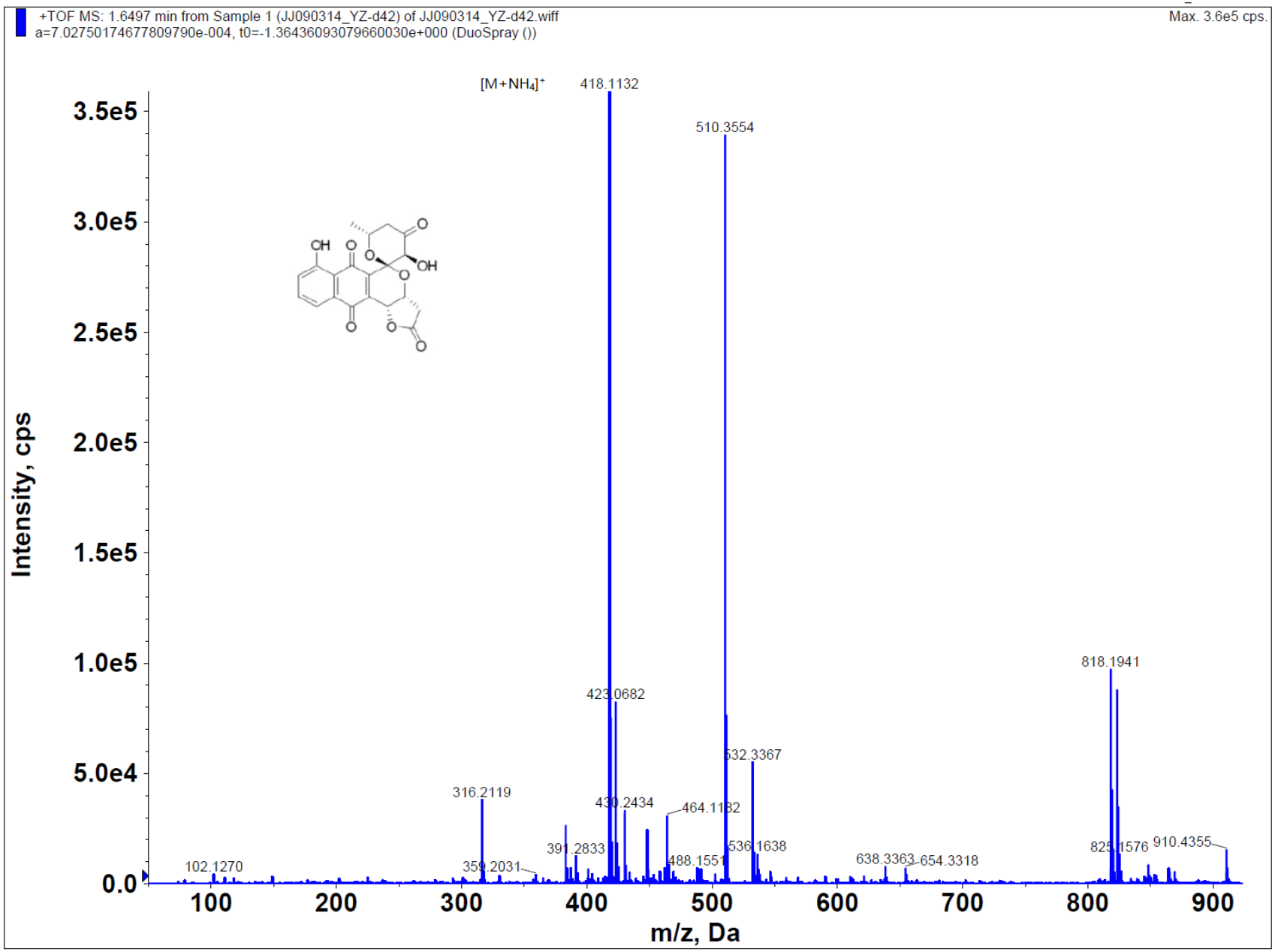



**Figure S17.** (+)-HRESI-MS spectrum of **3.**

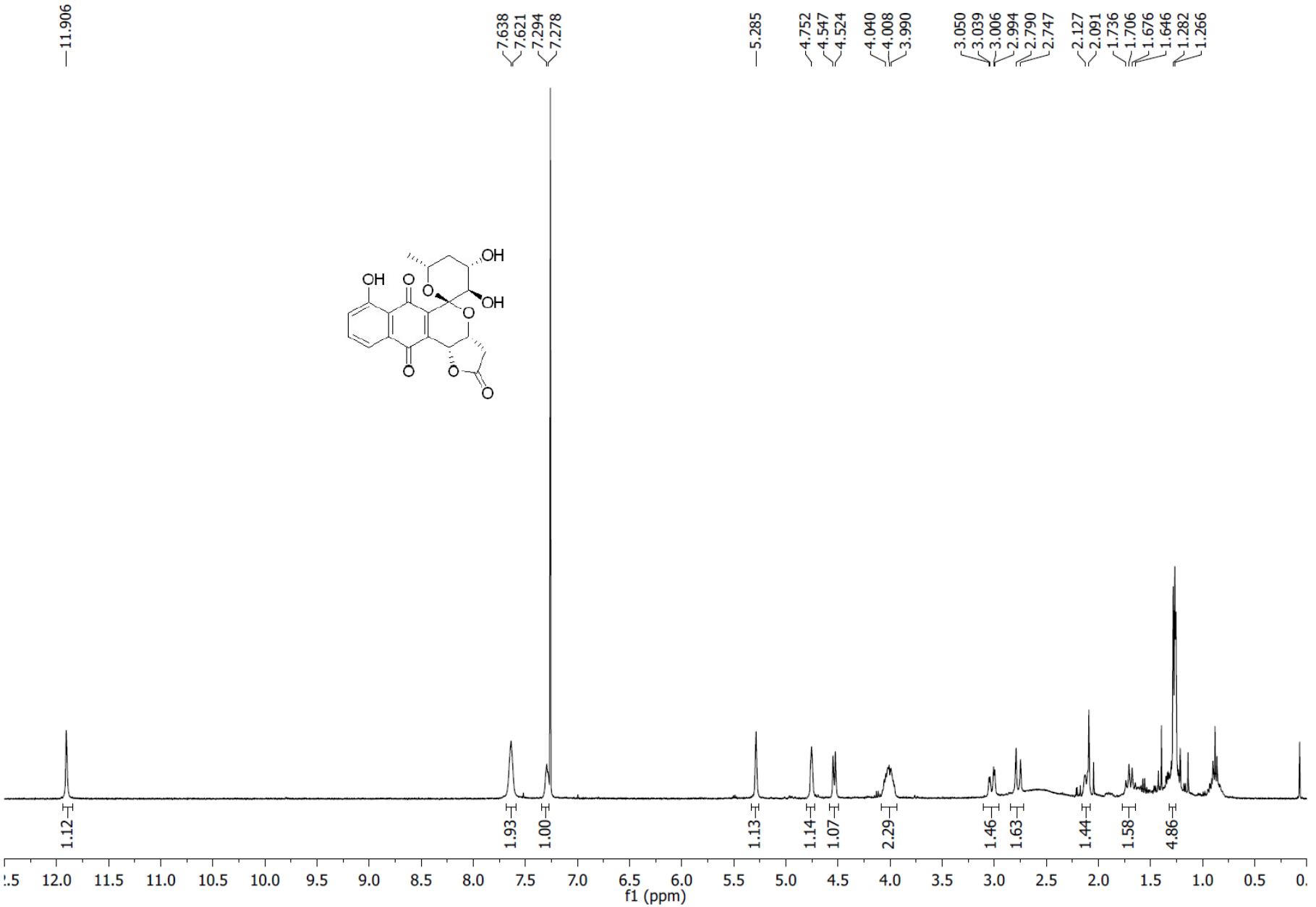



**Figure S18.** $^{1}$H-NMR ($CDCl_3$, 400 MHz) of **4.**

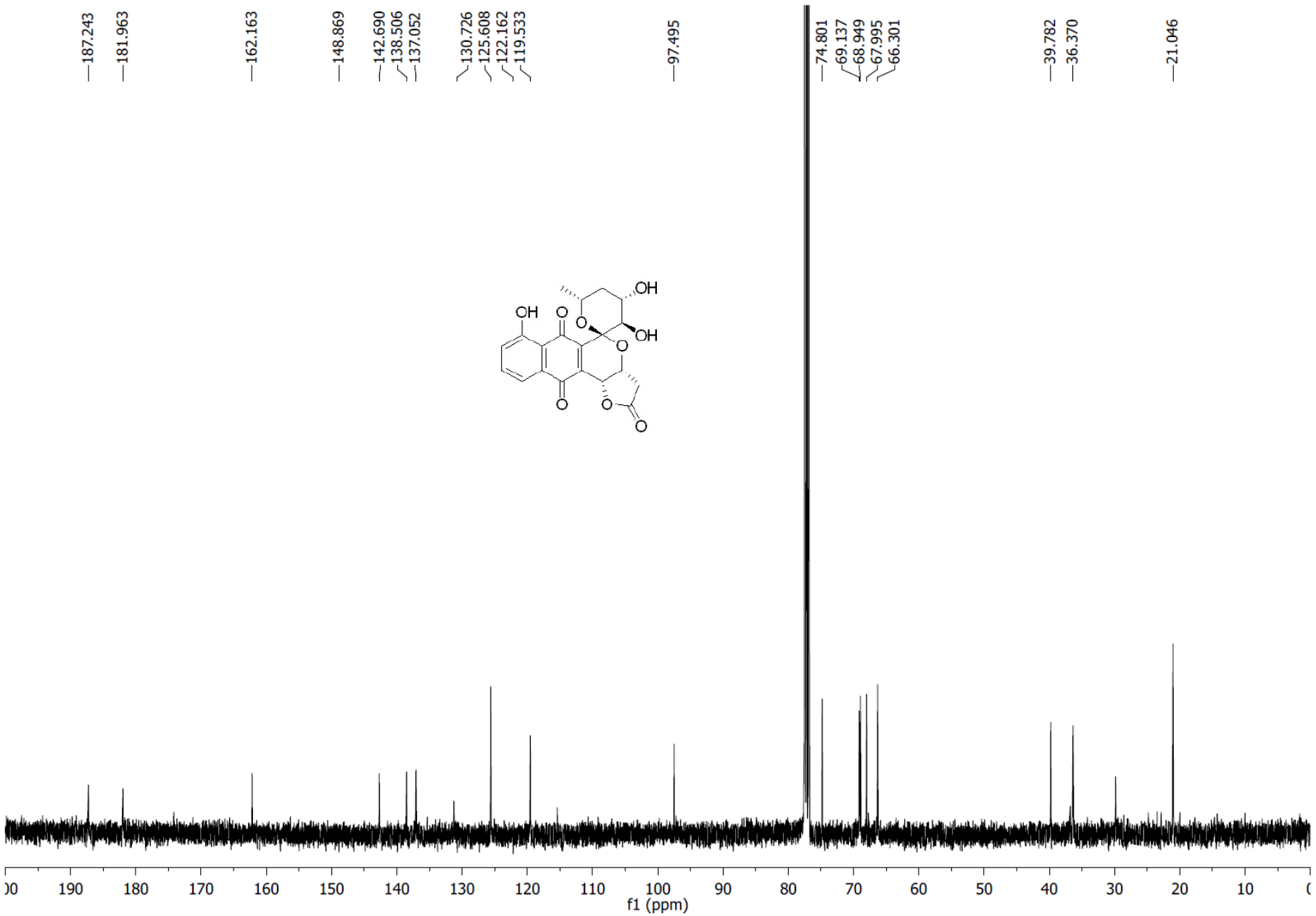



**Figure S19.** $^{13}$C-NMR ($CDCl_3$, 100 MHz) of **4.**

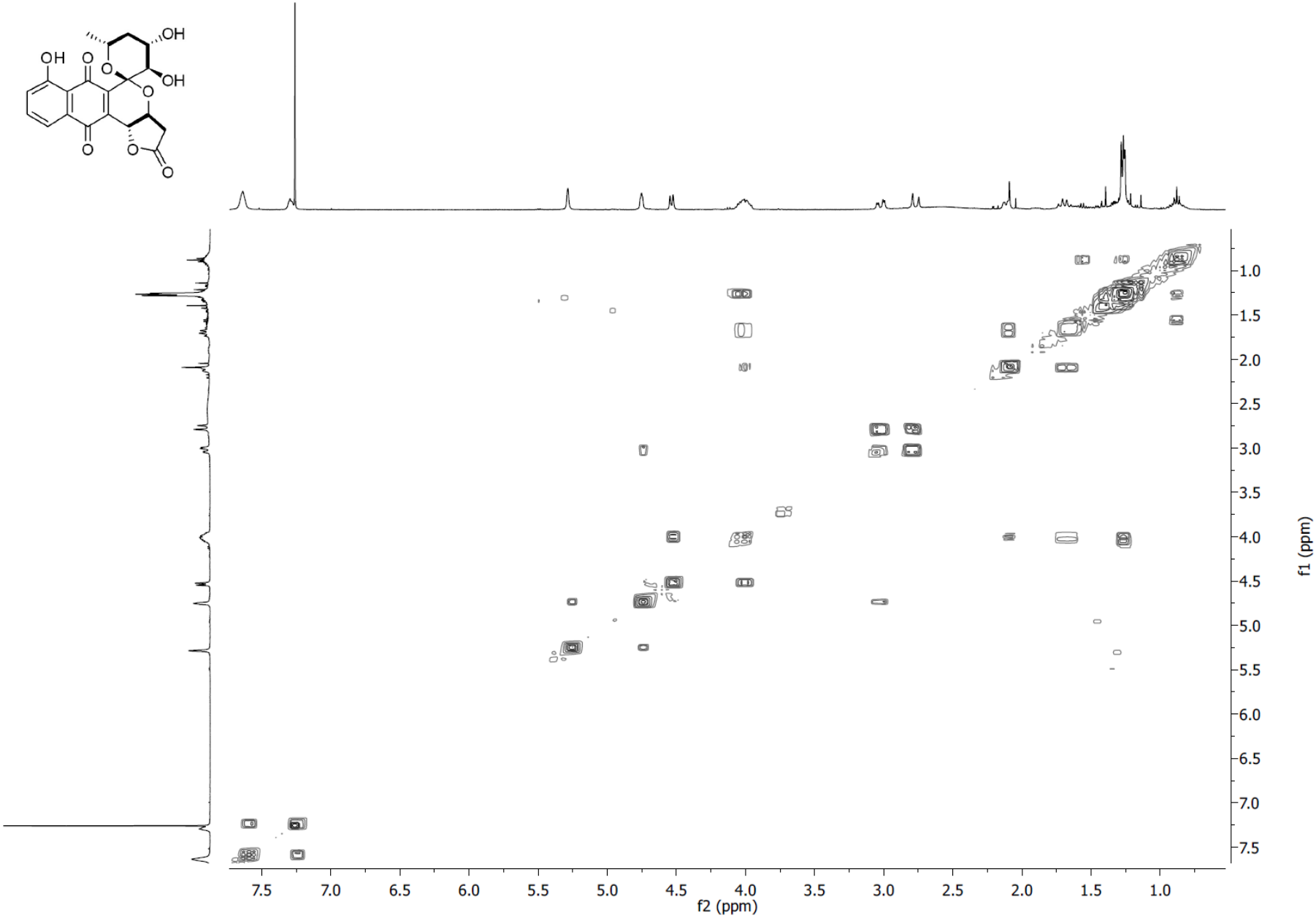



**Figure S20.** $^{1}H$-$^{1}H$ COSY ($CDCl_3$, 400 MHz) of **4.**

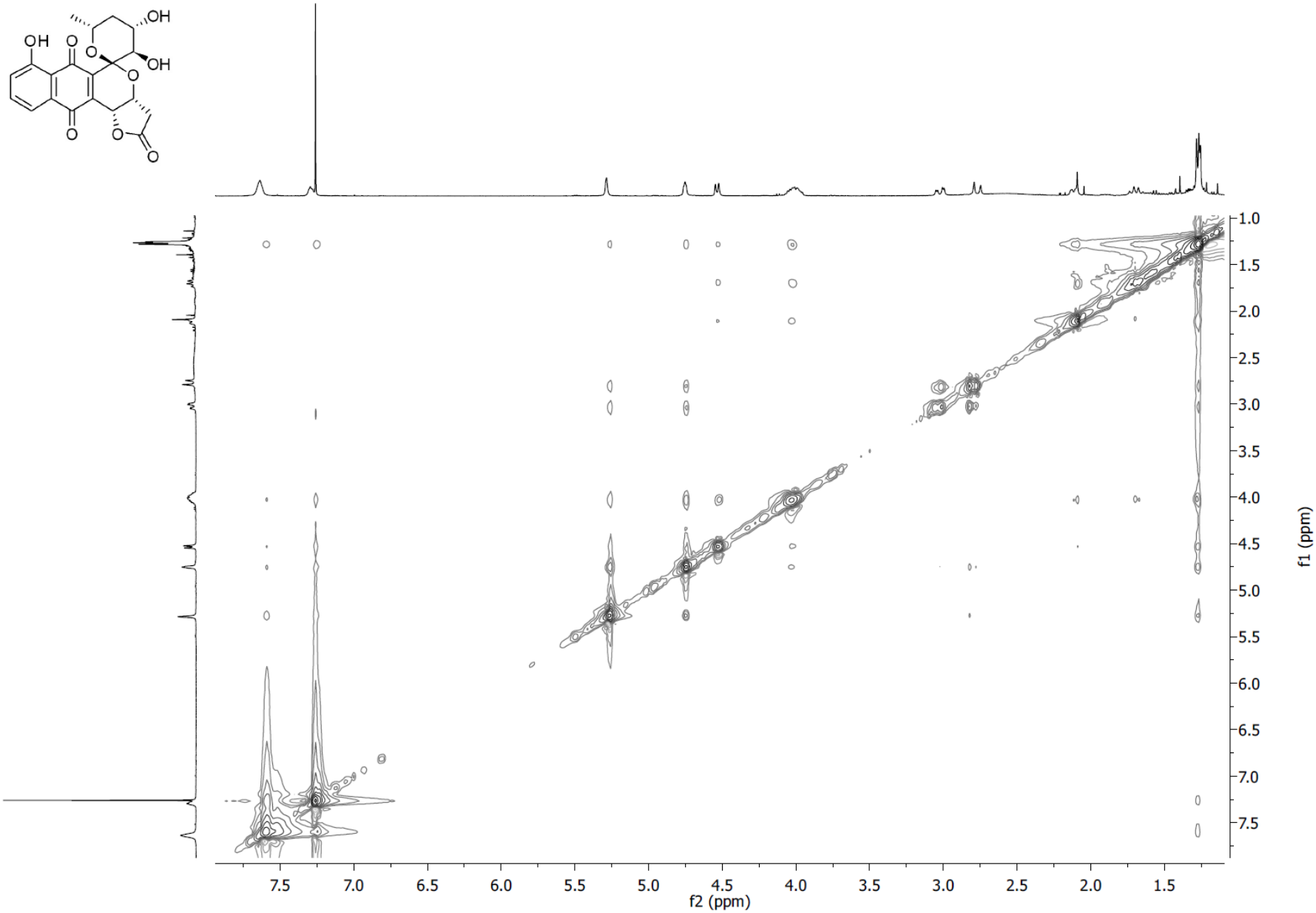



**Figure S21.** NOESY ($CDCl_3$, 400 MHz) of **4.**

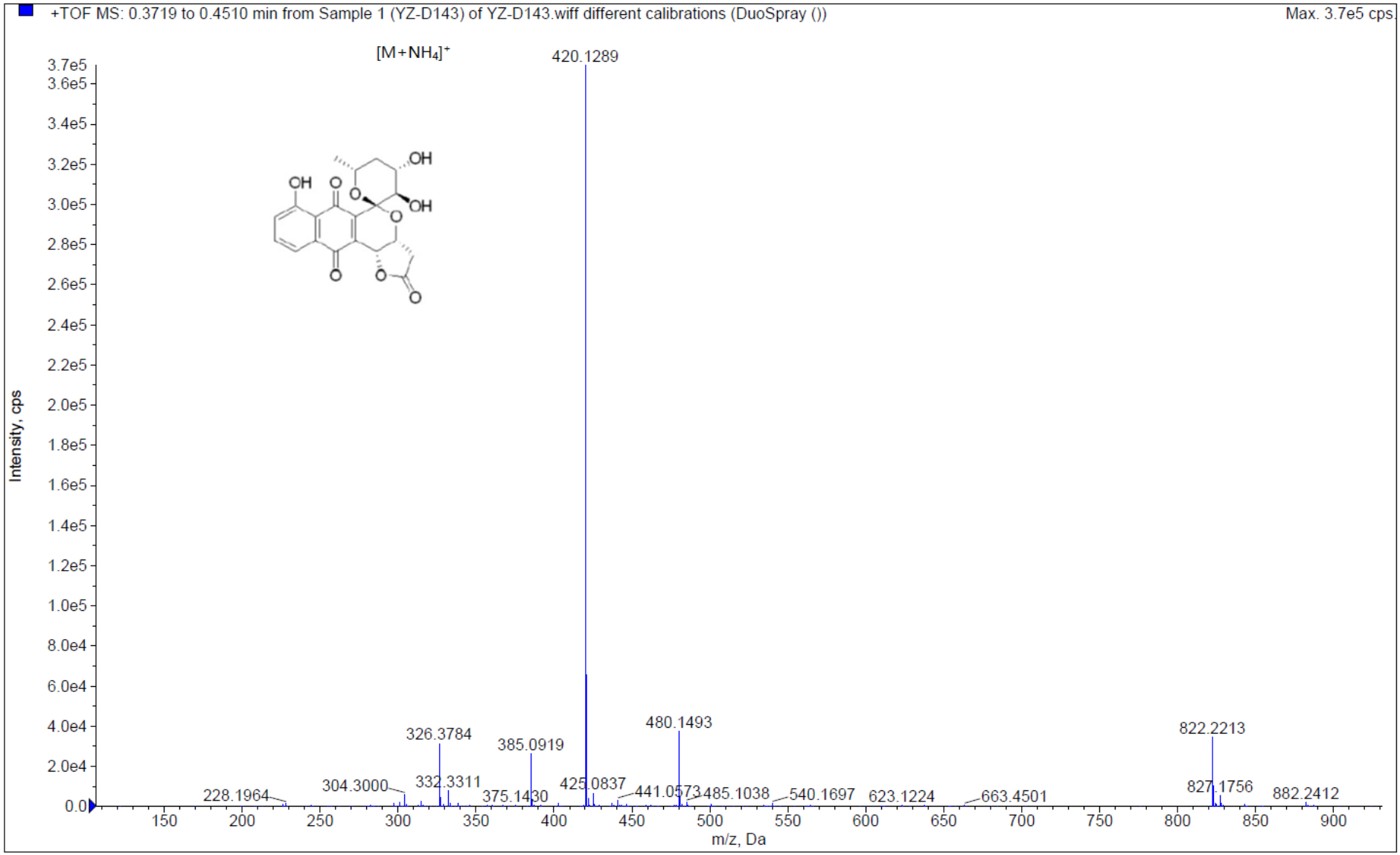



**Figure S22.** (+)-HRESI-MS spectrum of **4.**

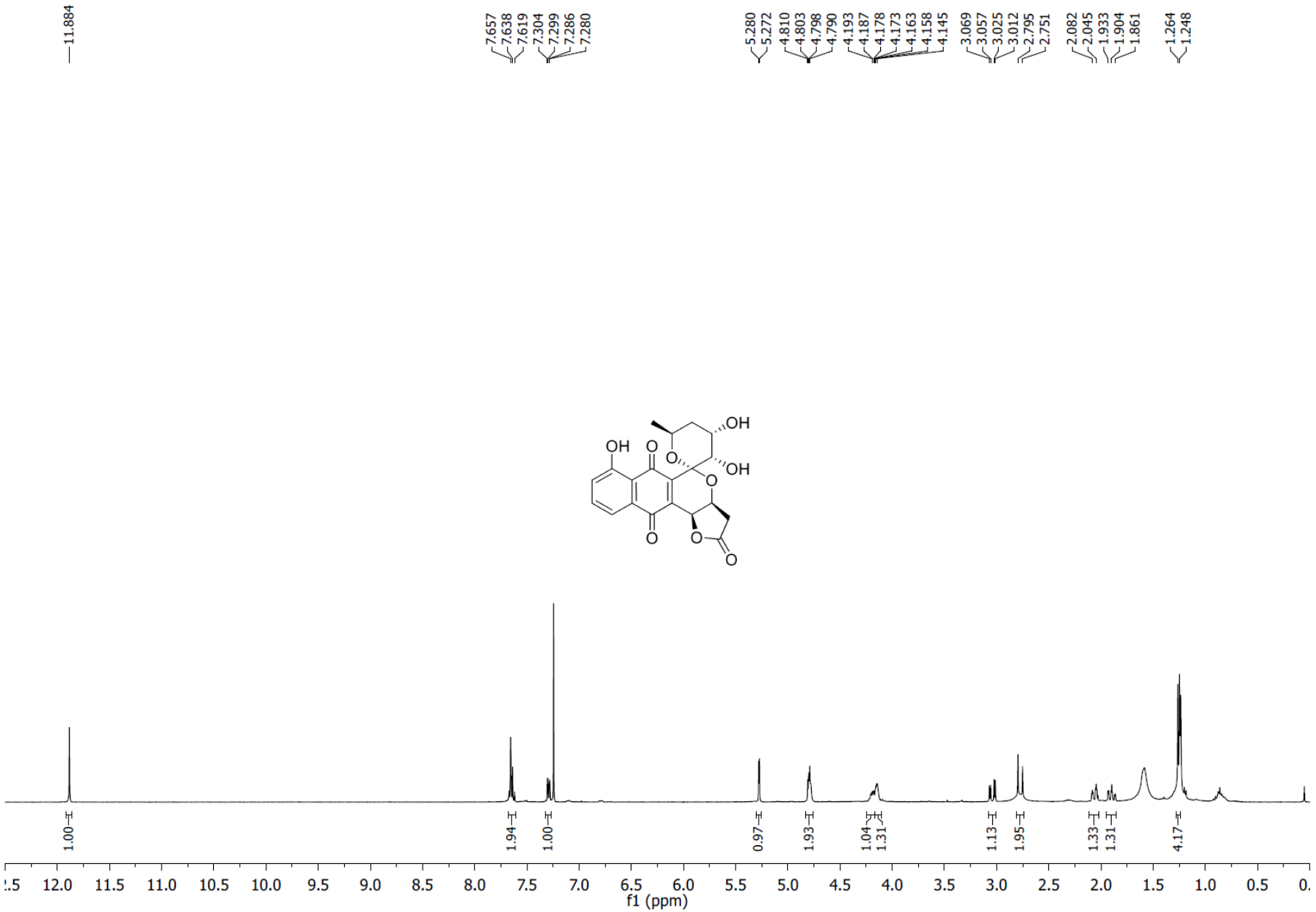



**Figure S23.** $^{1}$H-NMR ($CDCl_3$, 400 MHz) of **5.**

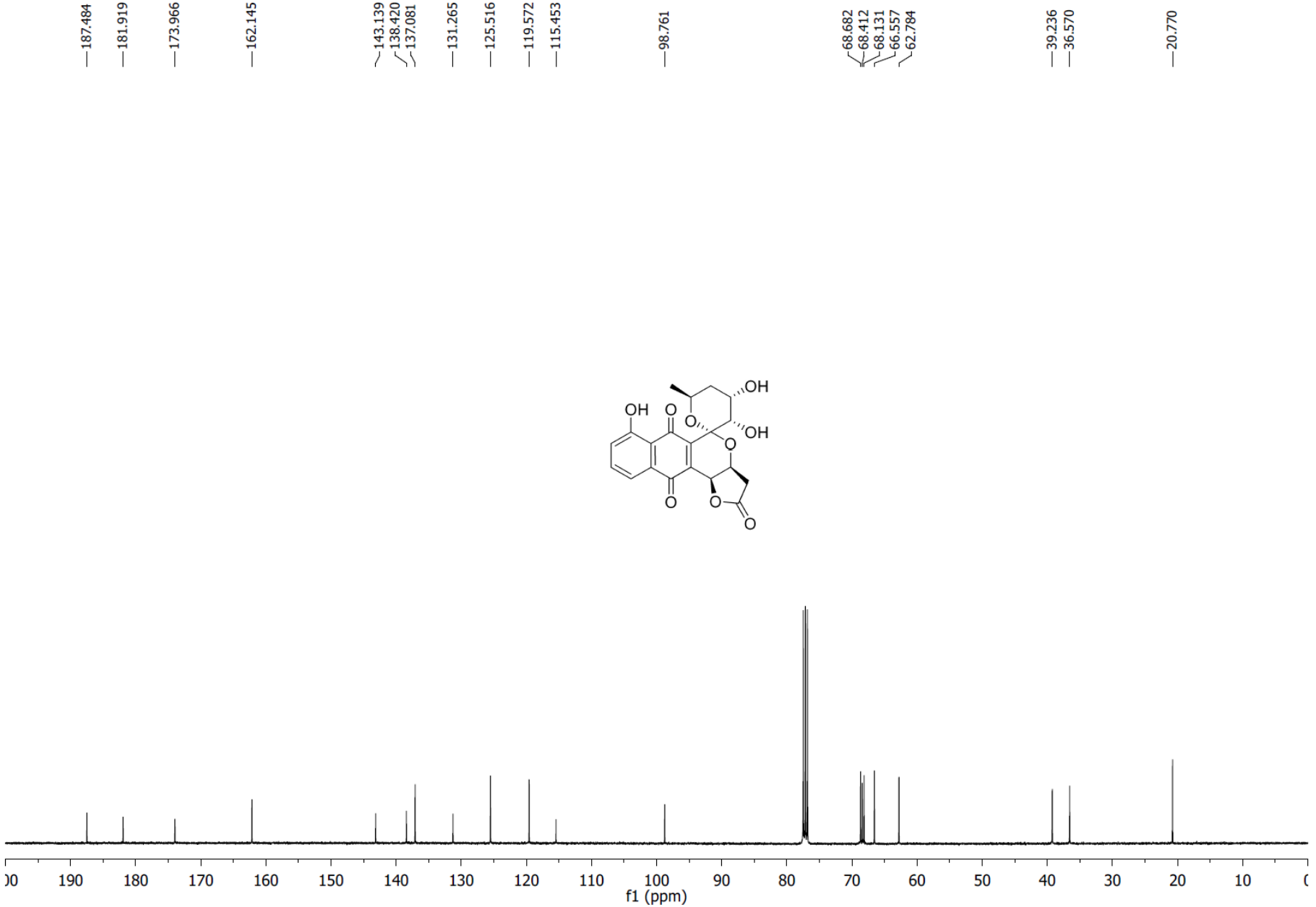



**Figure S24.** $^{13}$C-NMR ($CDCl_3$, 100 MHz) of **5.**

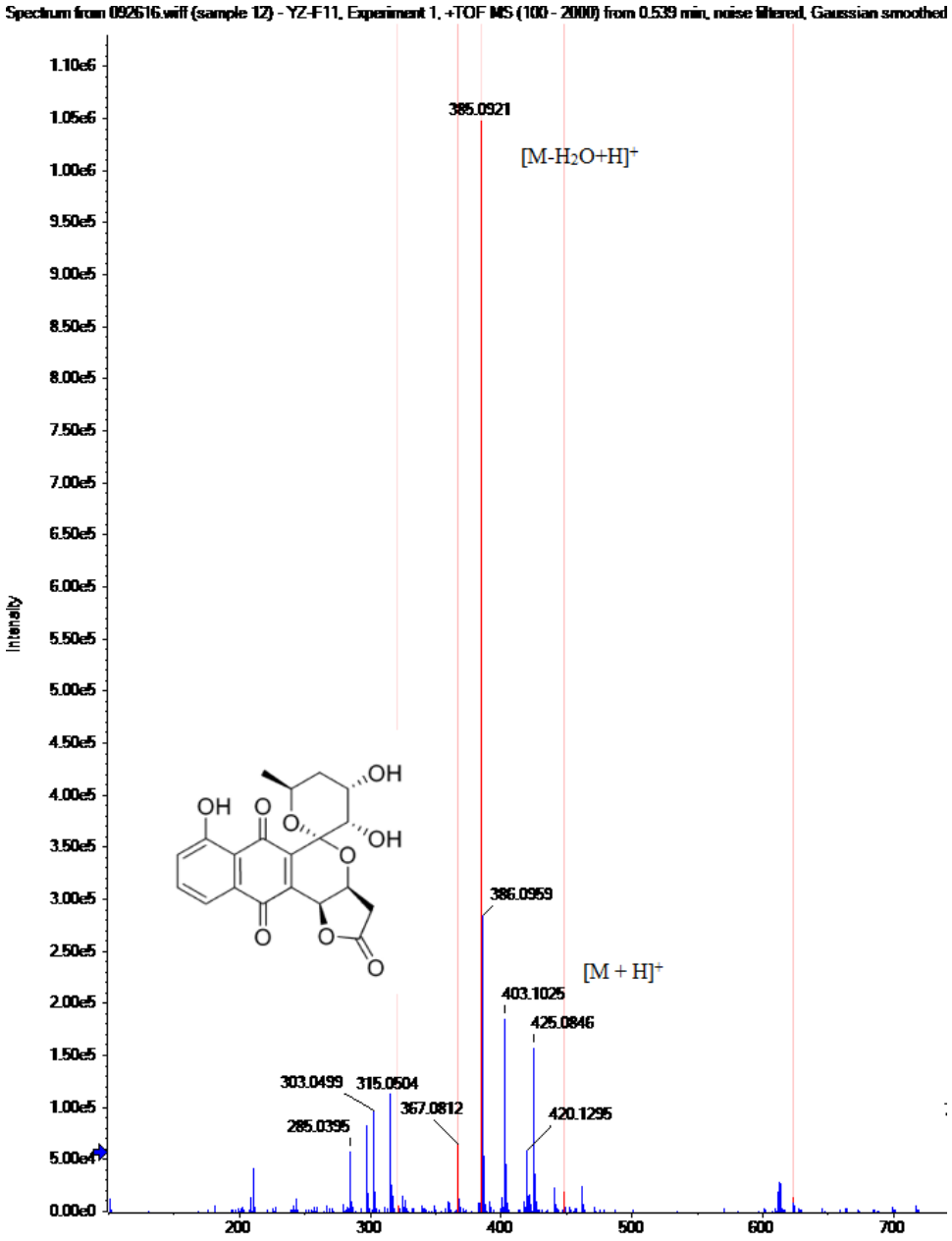



**Figure S25.** (+)-HRESI-MS spectrum of **5.**

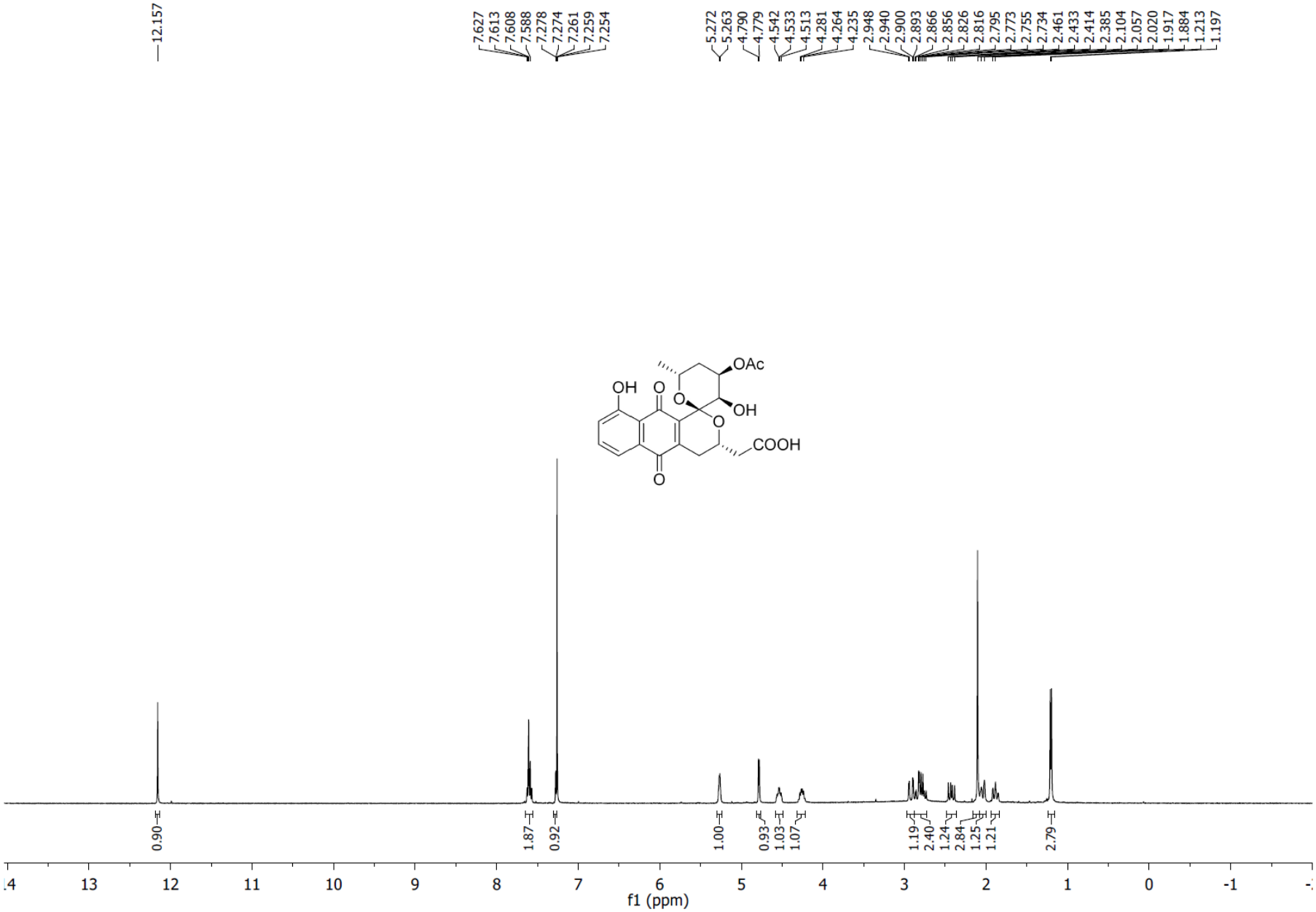



**Figure S26.** $^{1}$H-NMR ($CDCl_3$, 400 MHz) of **6.**

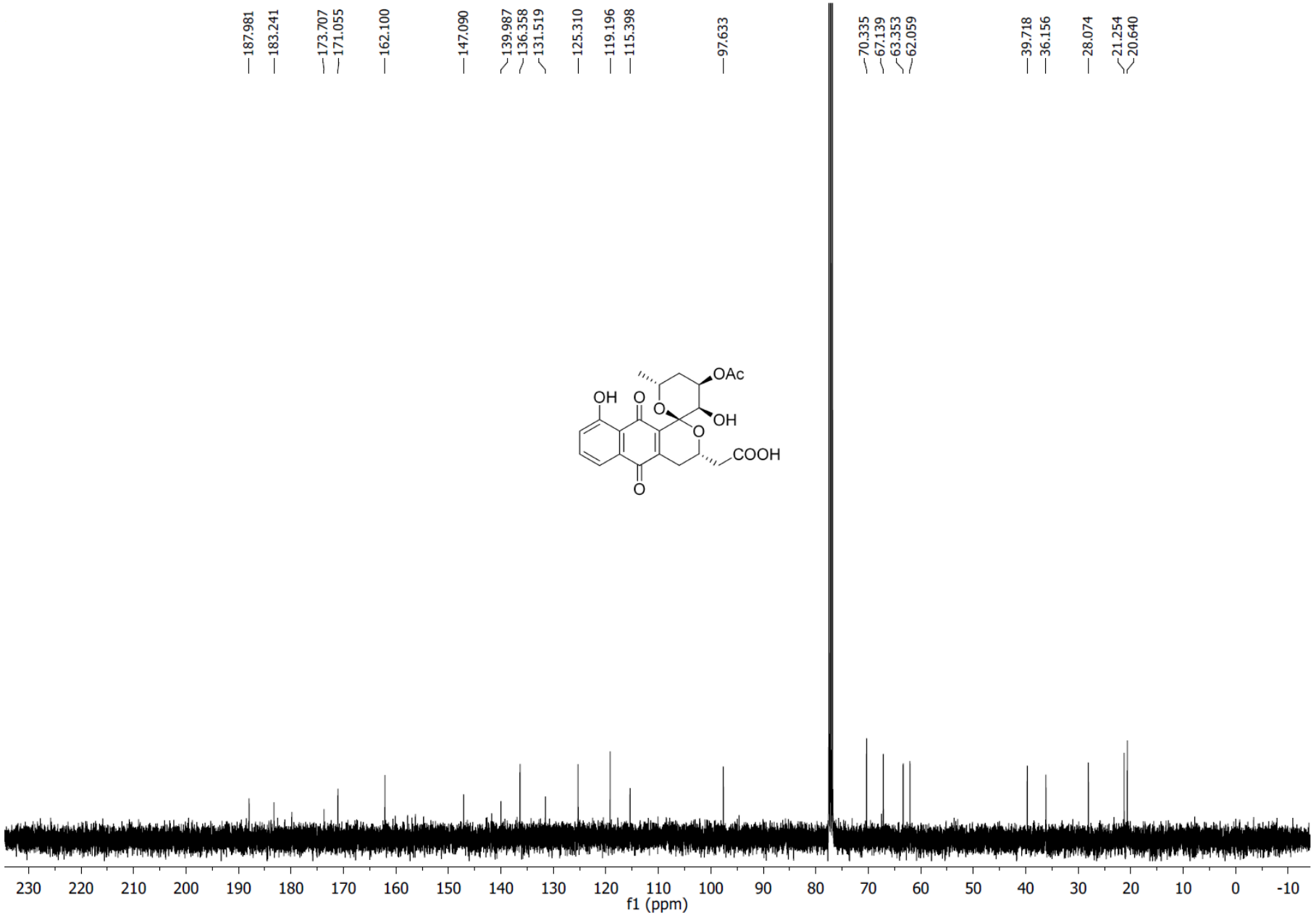



**Figure S27.** $^{13}$C-NMR ($CDCl_3$, 100 MHz) of **6.**

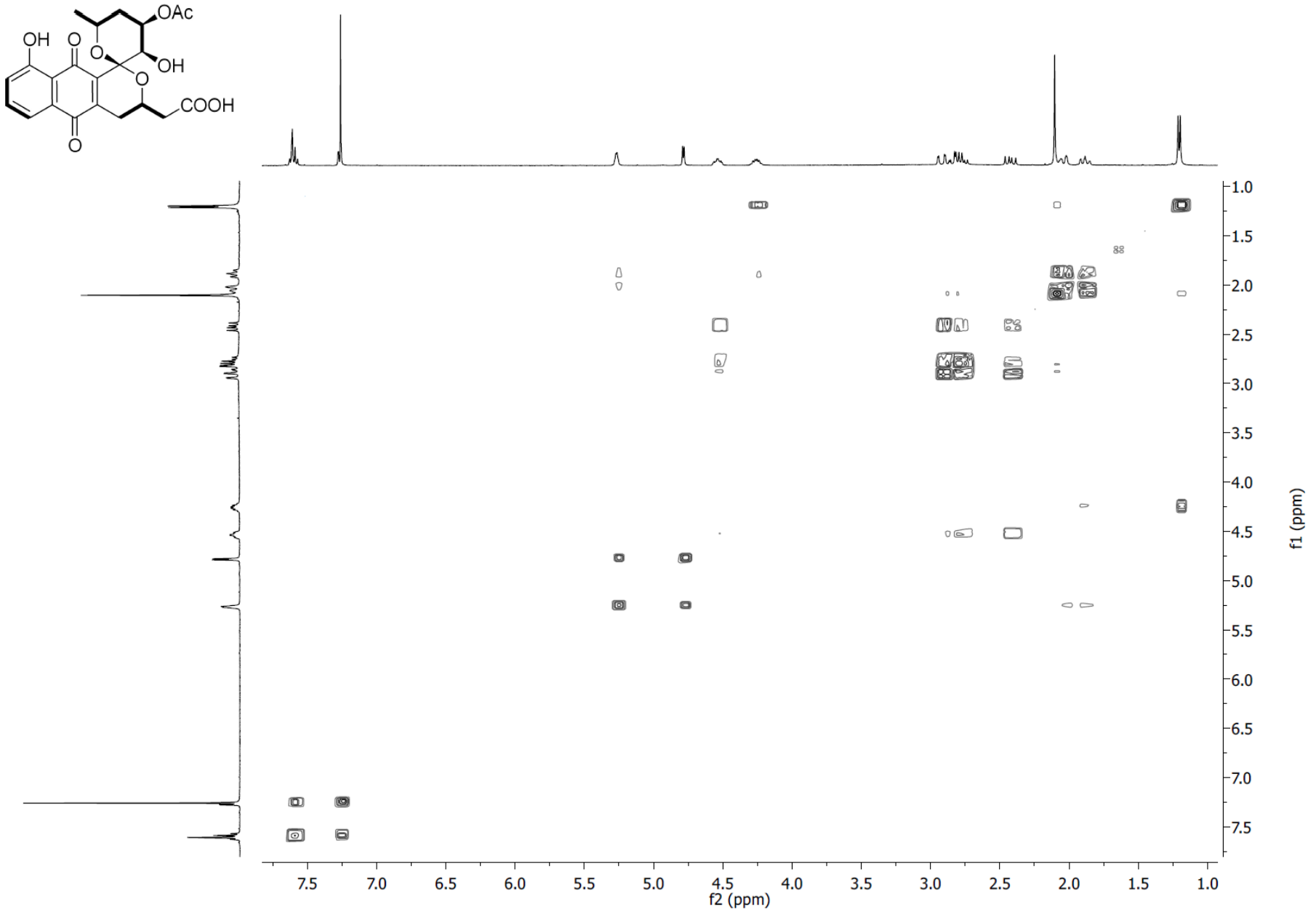



**Figure S28.** $^{1}$H-$^{1}$H COSY ($CDCl_3$, 400 MHz) of **6.**

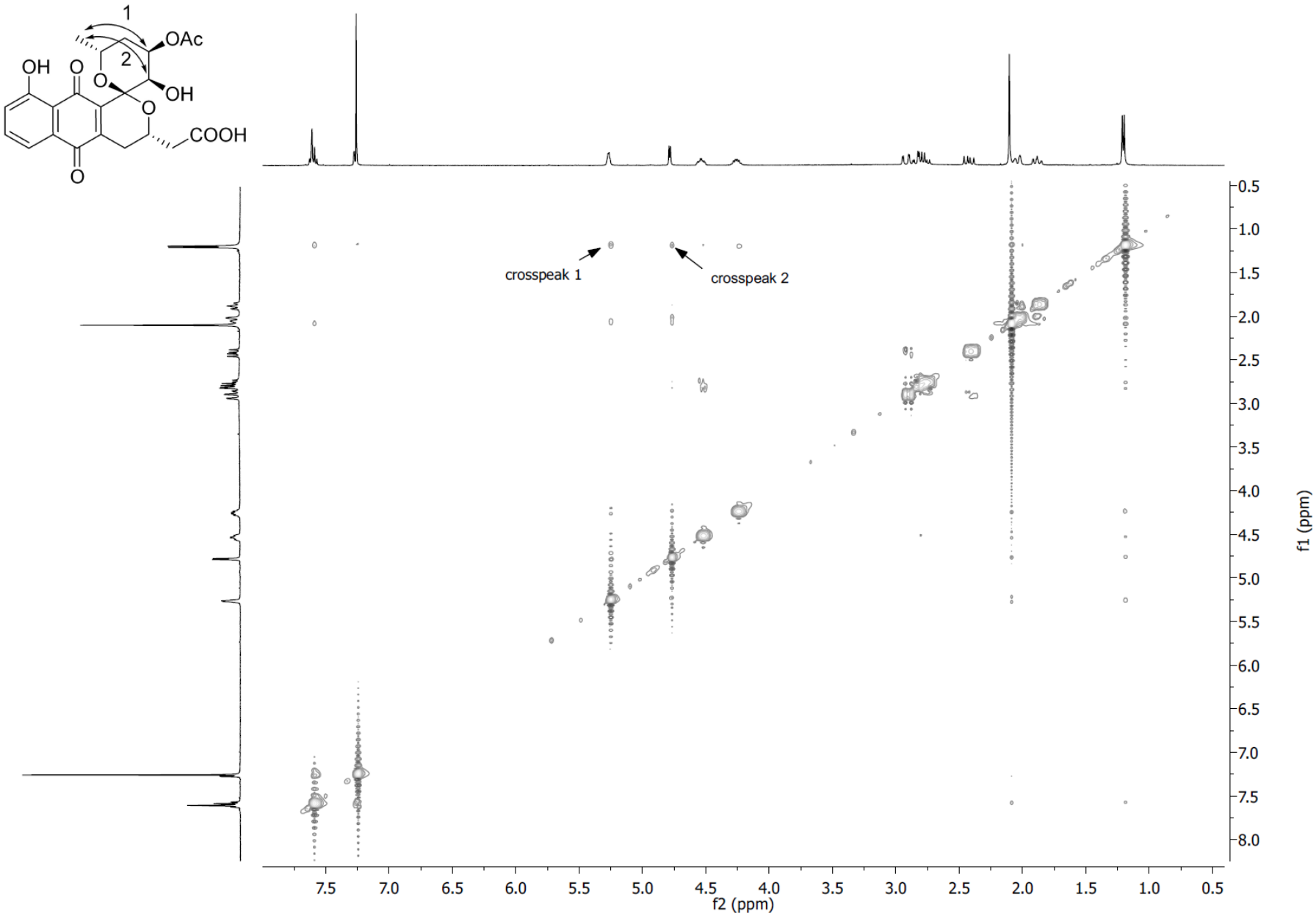



**Figure S29.** NOESY ($CDCl_3$, 400 MHz) of **6.**

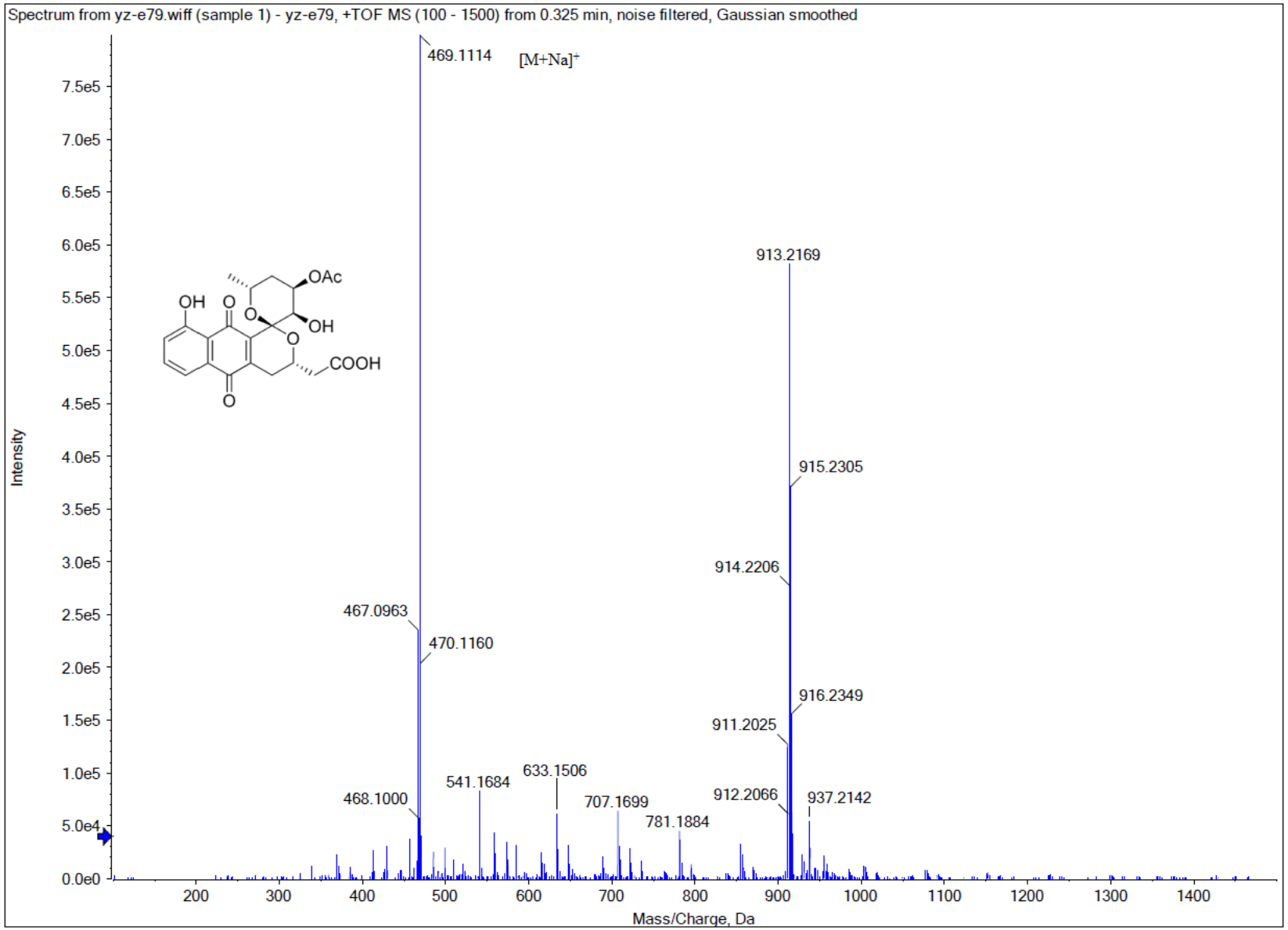



**Figure S30.** (+)-HRESI-MS of **6.**

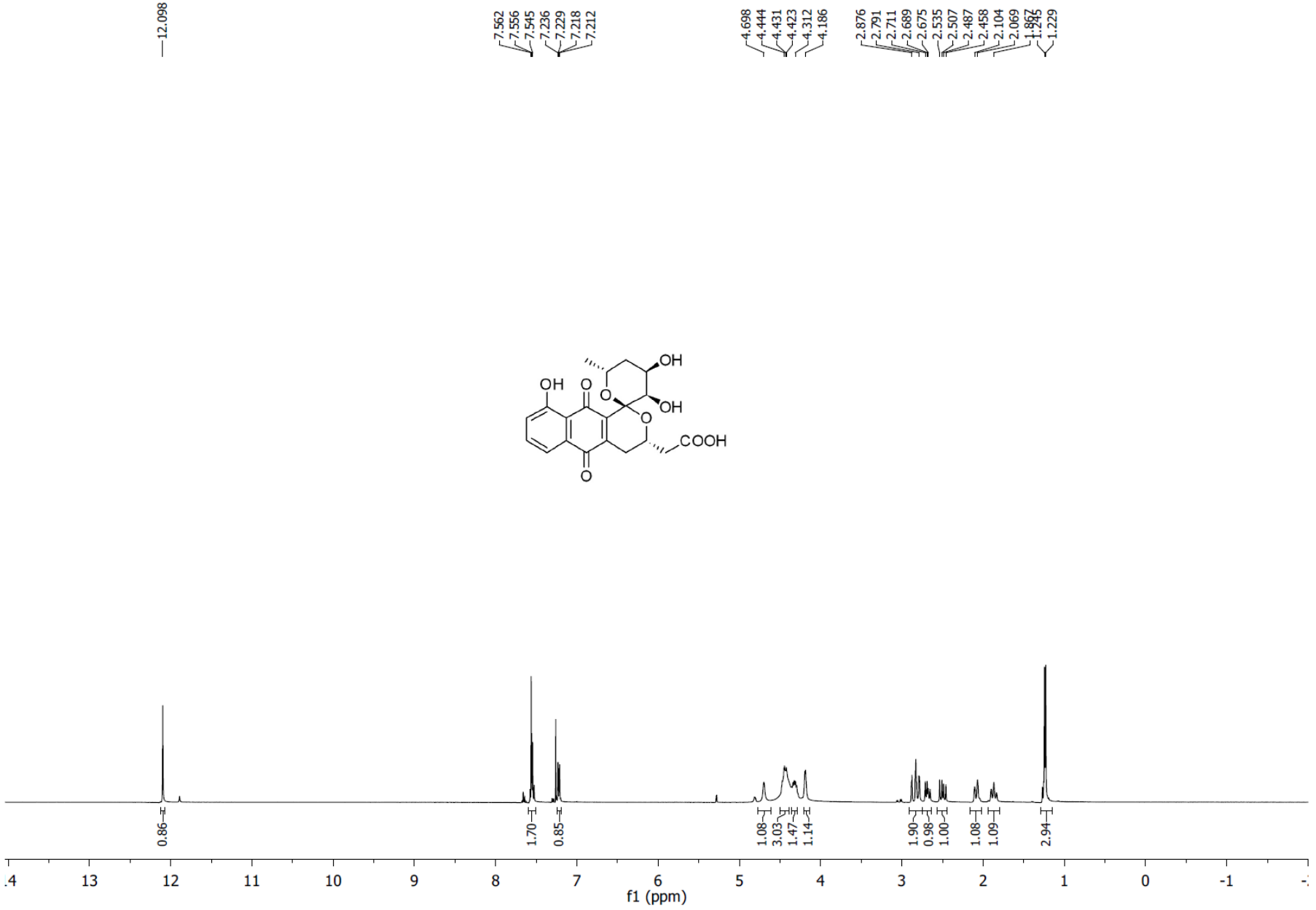



**Figure S31.** $^{1}$H-NMR ($CDCl_3$, 400 MHz) of **7.**

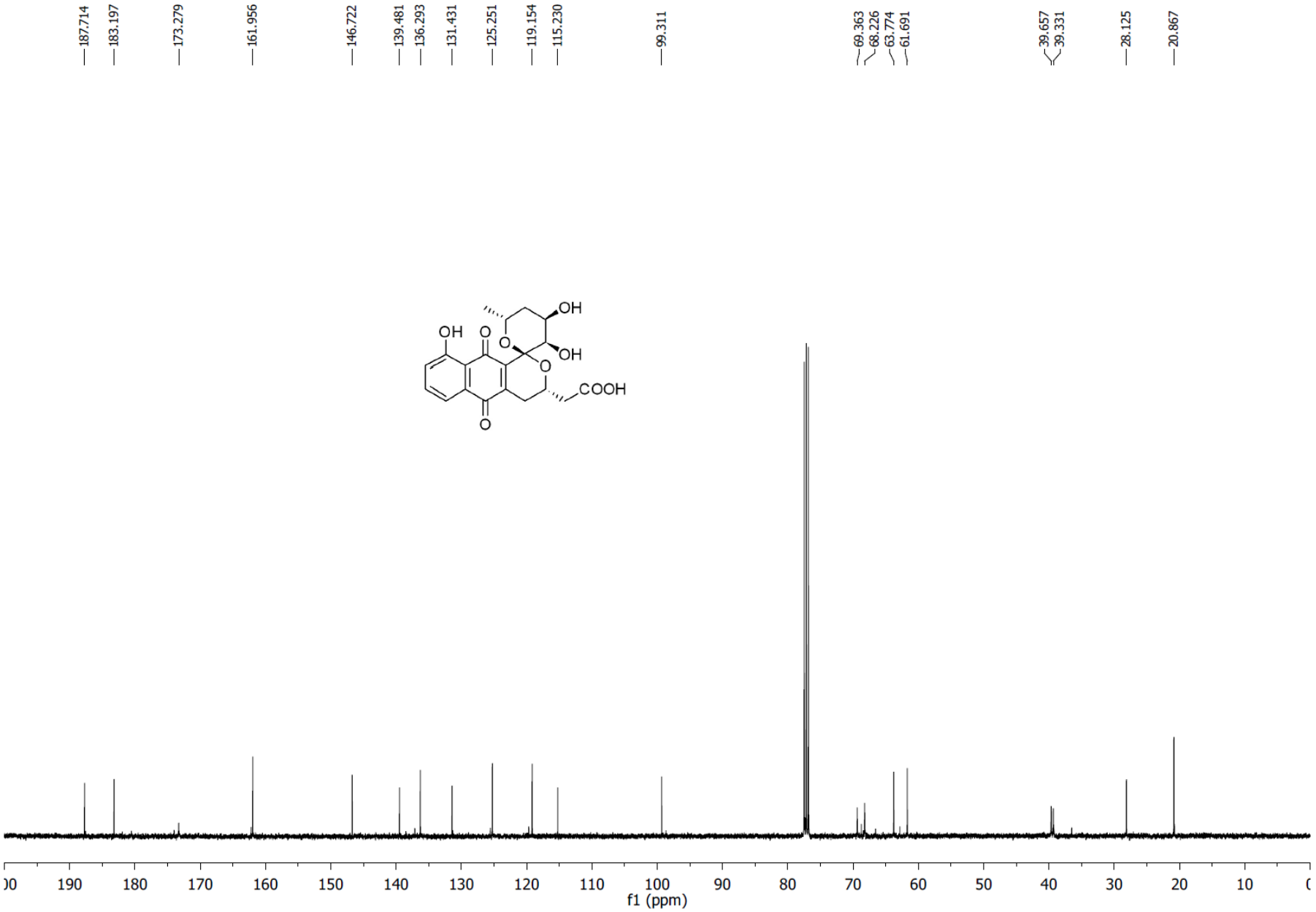



**Figure S32.** $^{13}$C-NMR ($CDCl_3$, 100 MHz) of **7.**

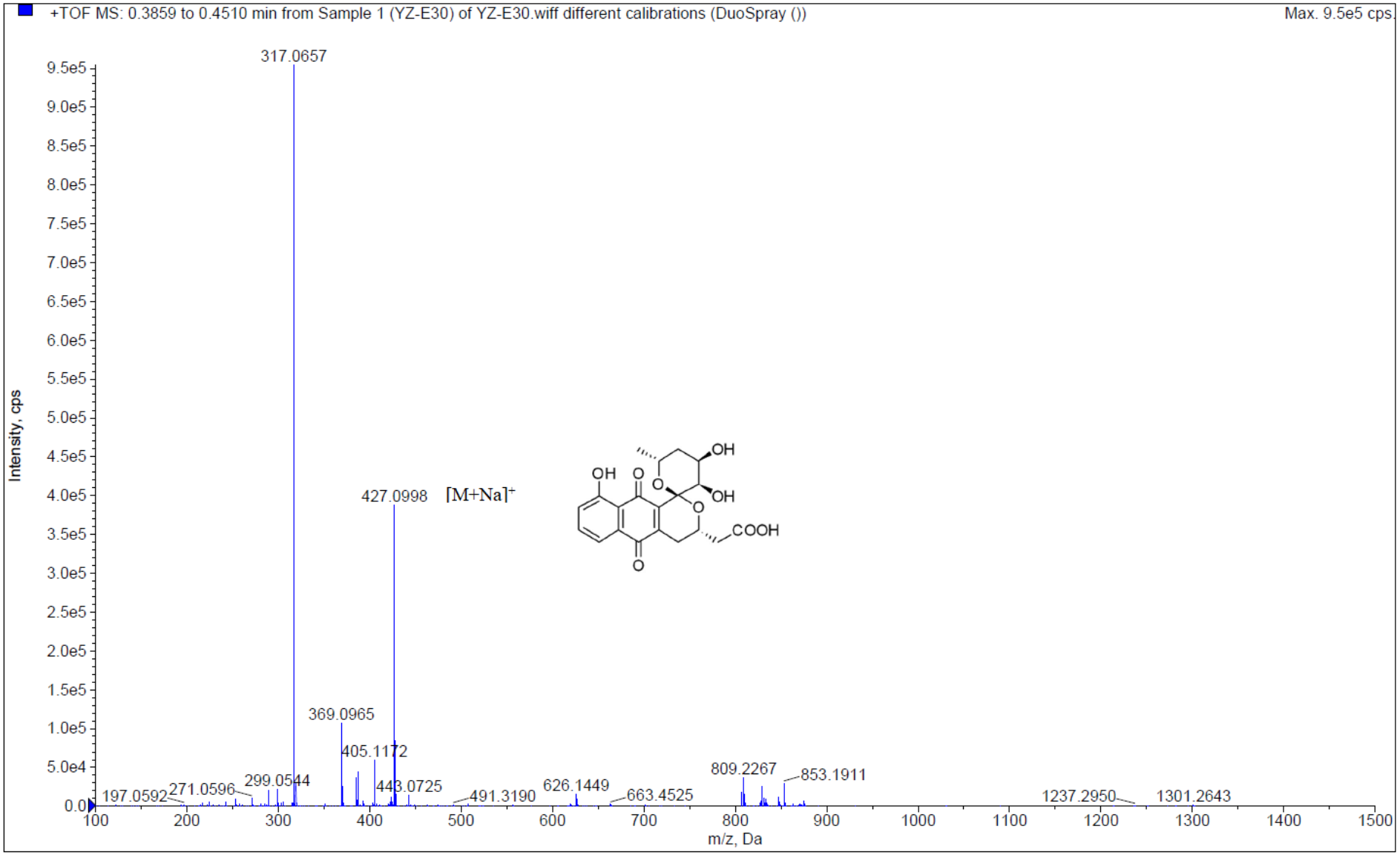



**Figure S33.** (+)-HRESI-MS of **7.**

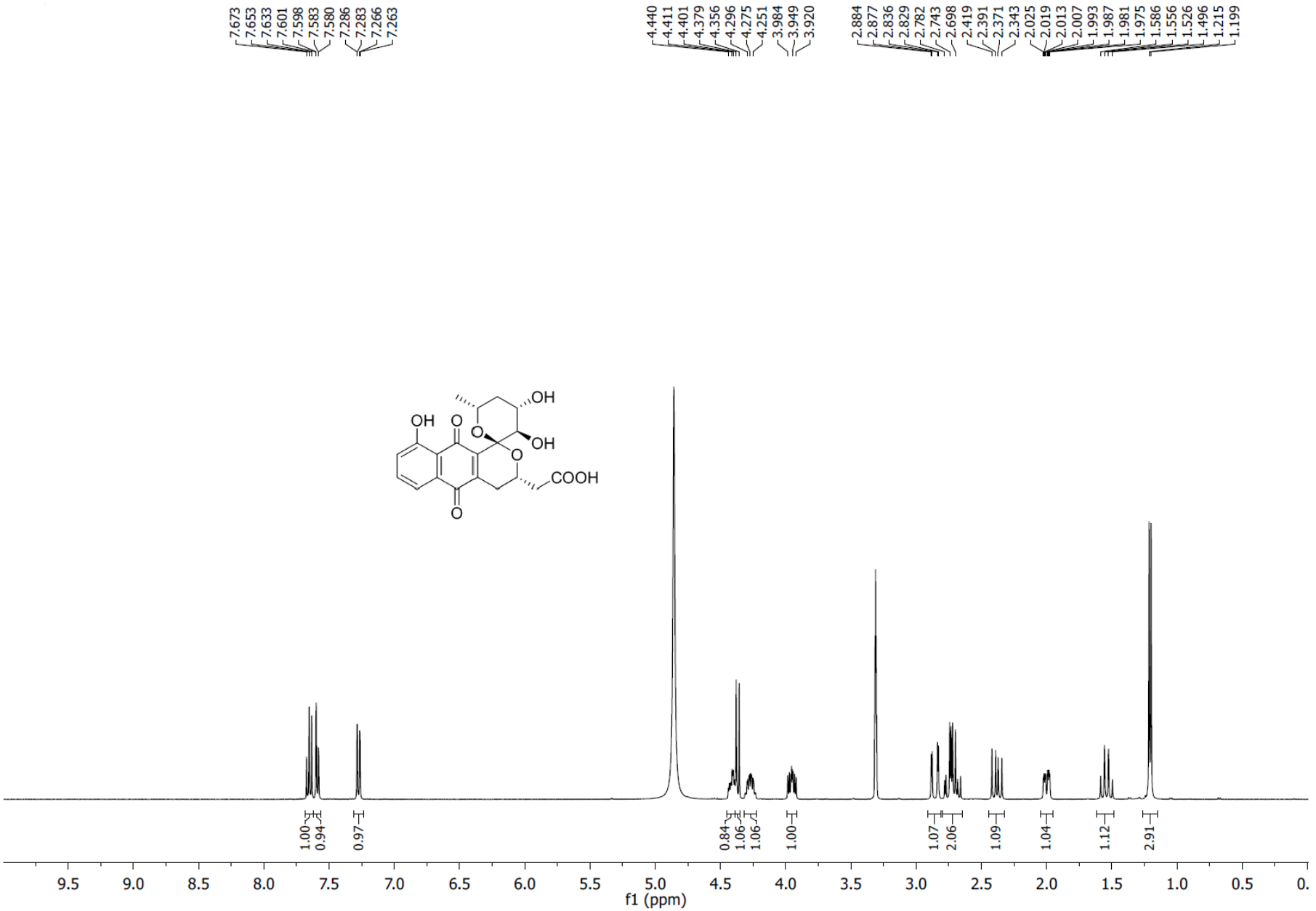



**Figure S34.** $^{1}$H-NMR ($CDCl_3$, 400 MHz) of **8.**

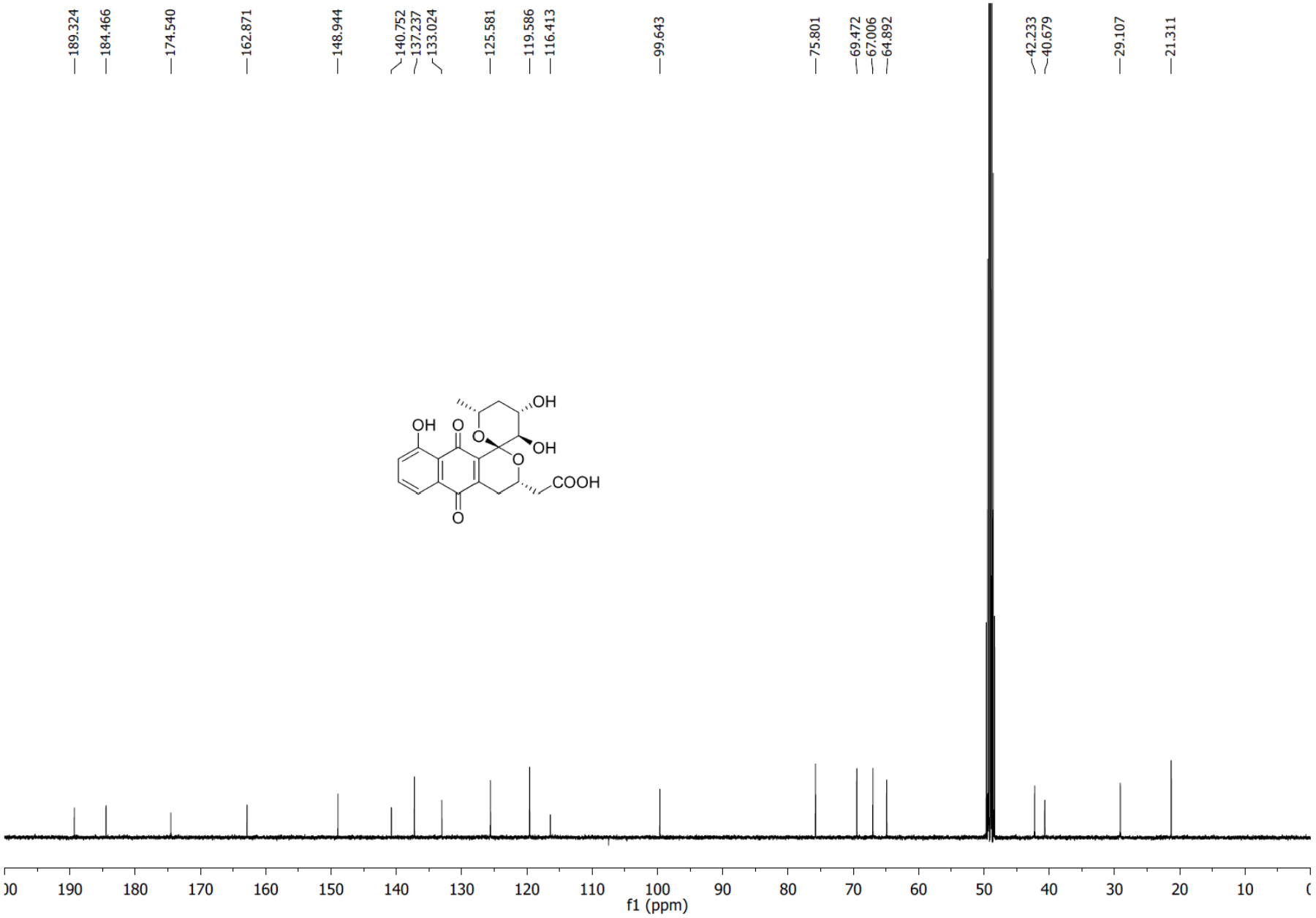



**Figure S35.** $^{13}$C-NMR ($CDCl_3$, 100 MHz) of **8.**

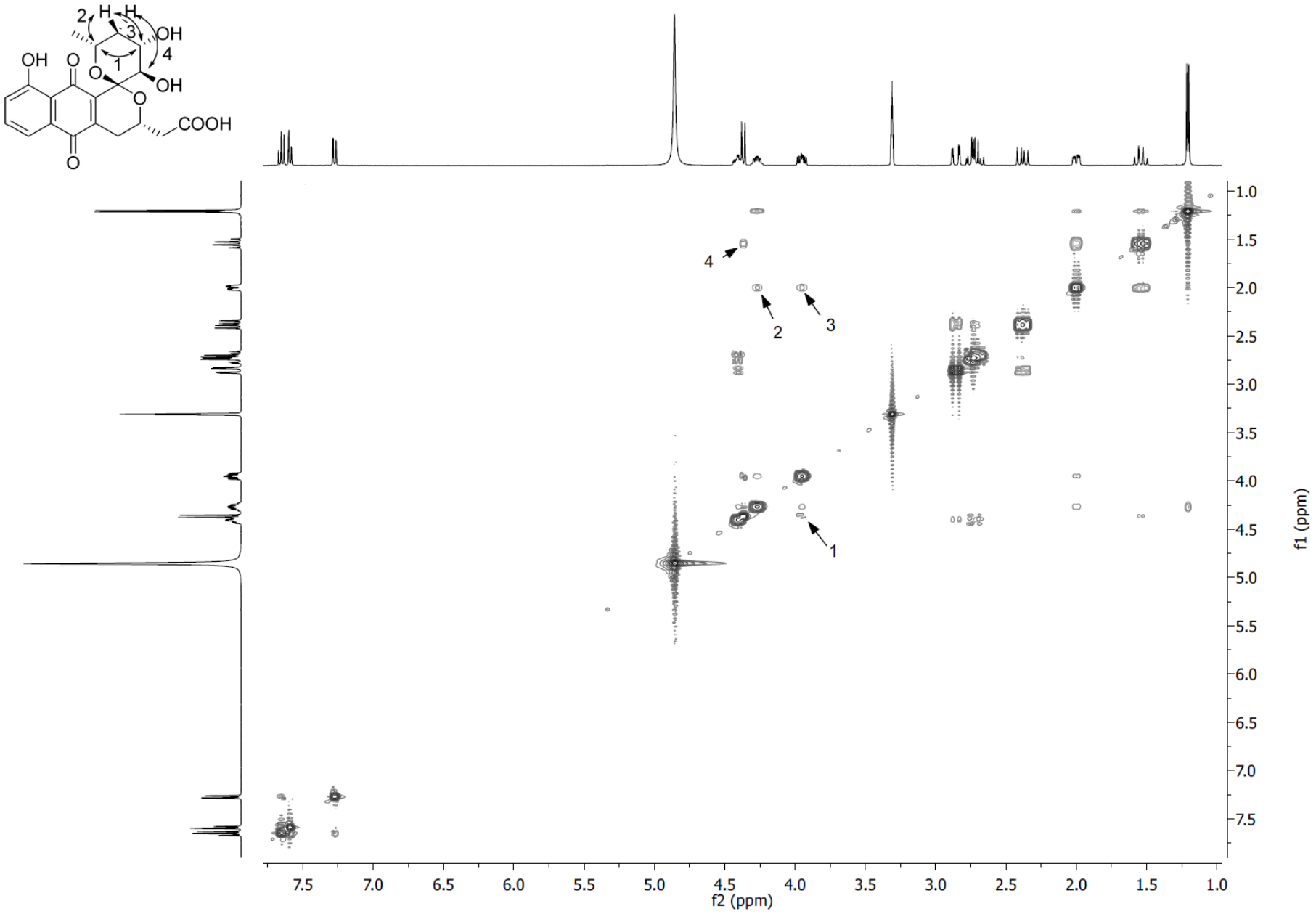



**Figure S36.** NOESY ($CDCl_3$, 400 MHz) of **8.**

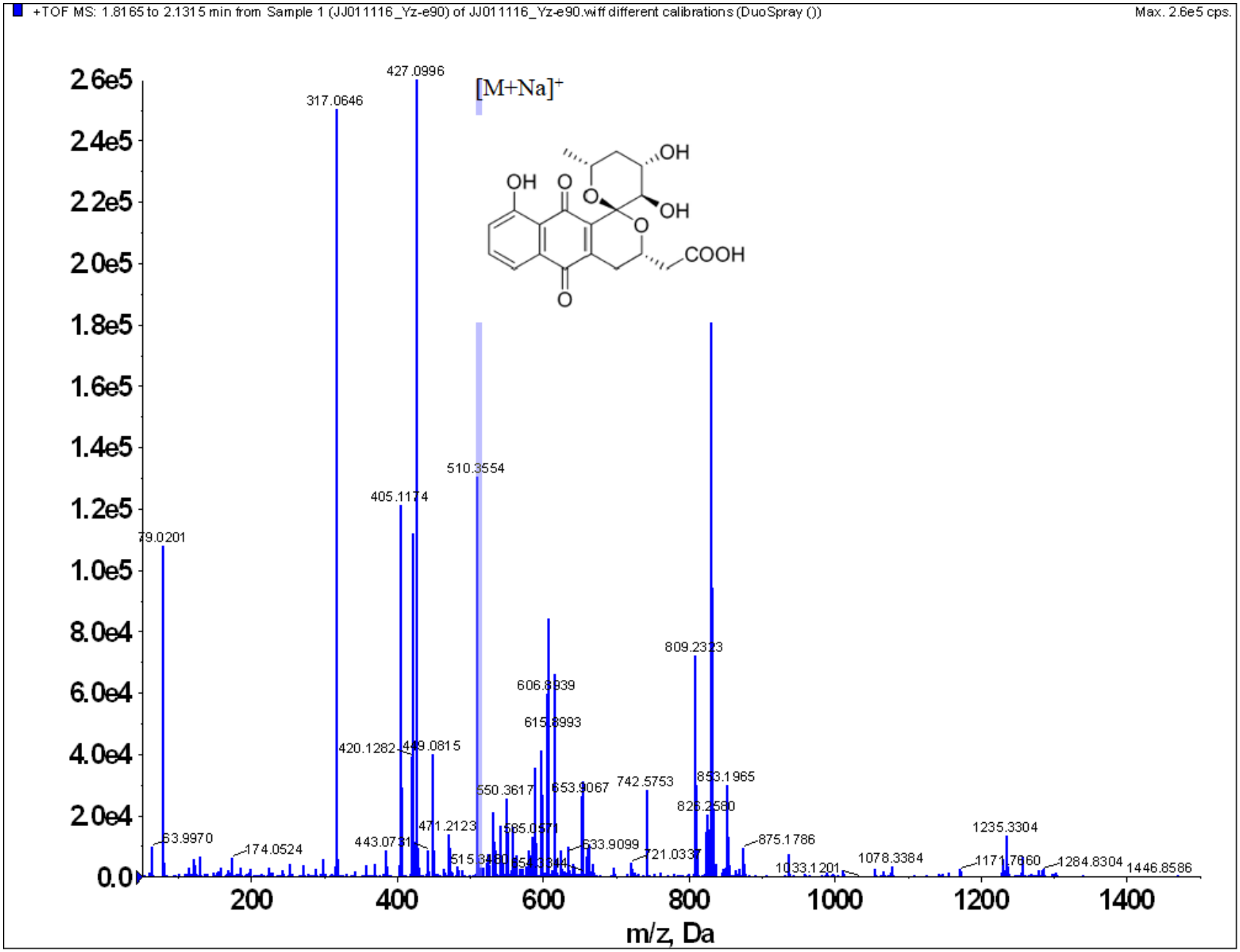



**Figure S37.** (+)-HRESI-MS of **8.**

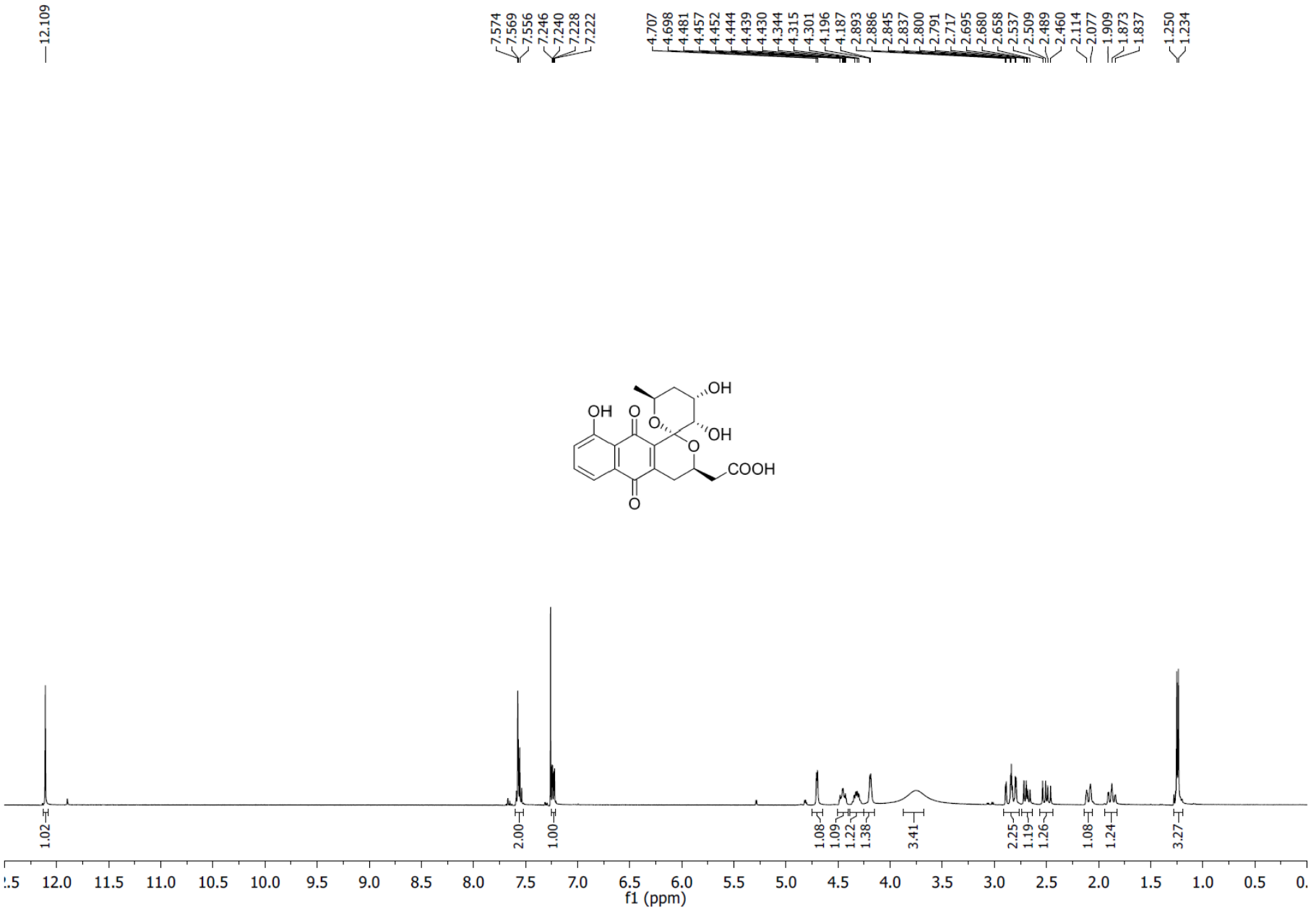



**Figure S38.** $^{1}$H-NMR ($CDCl_3$, 400 MHz) of **9.**

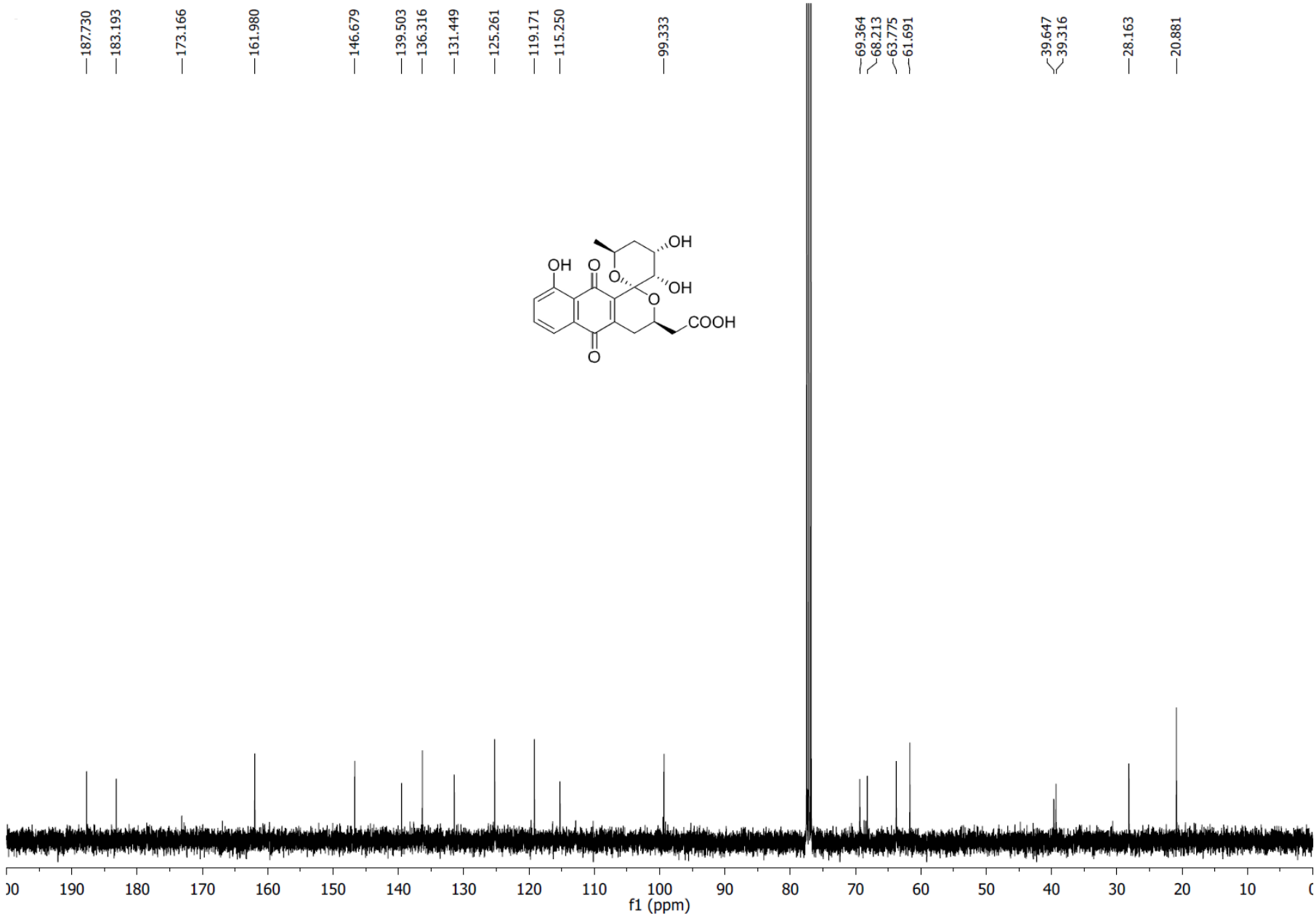



**Figure S39.** $^{13}$C-NMR ($CDCl_3$, 100 MHz) of **9.**

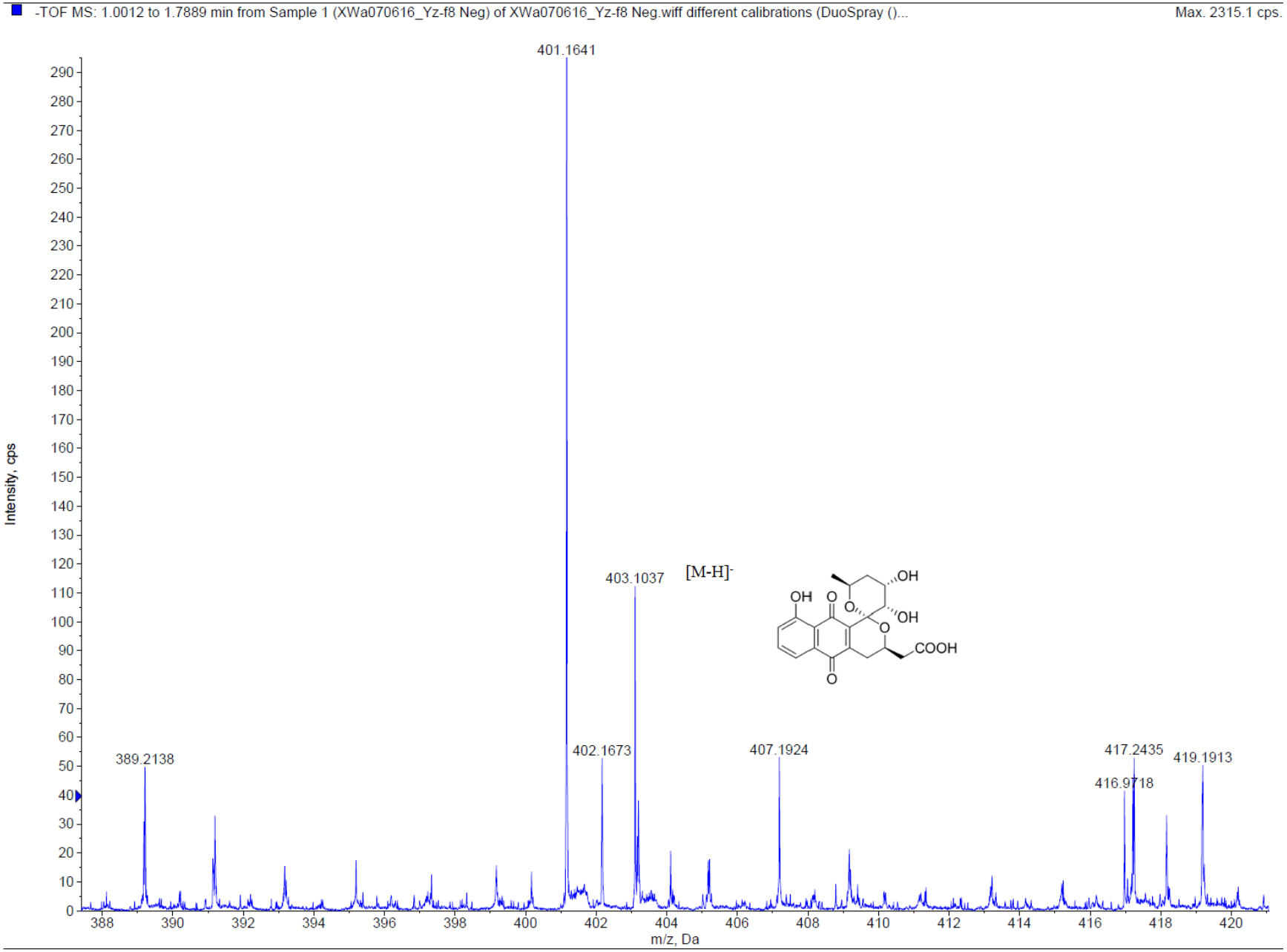



**Figure S40.** (-)-HRESI-MS of **9.**

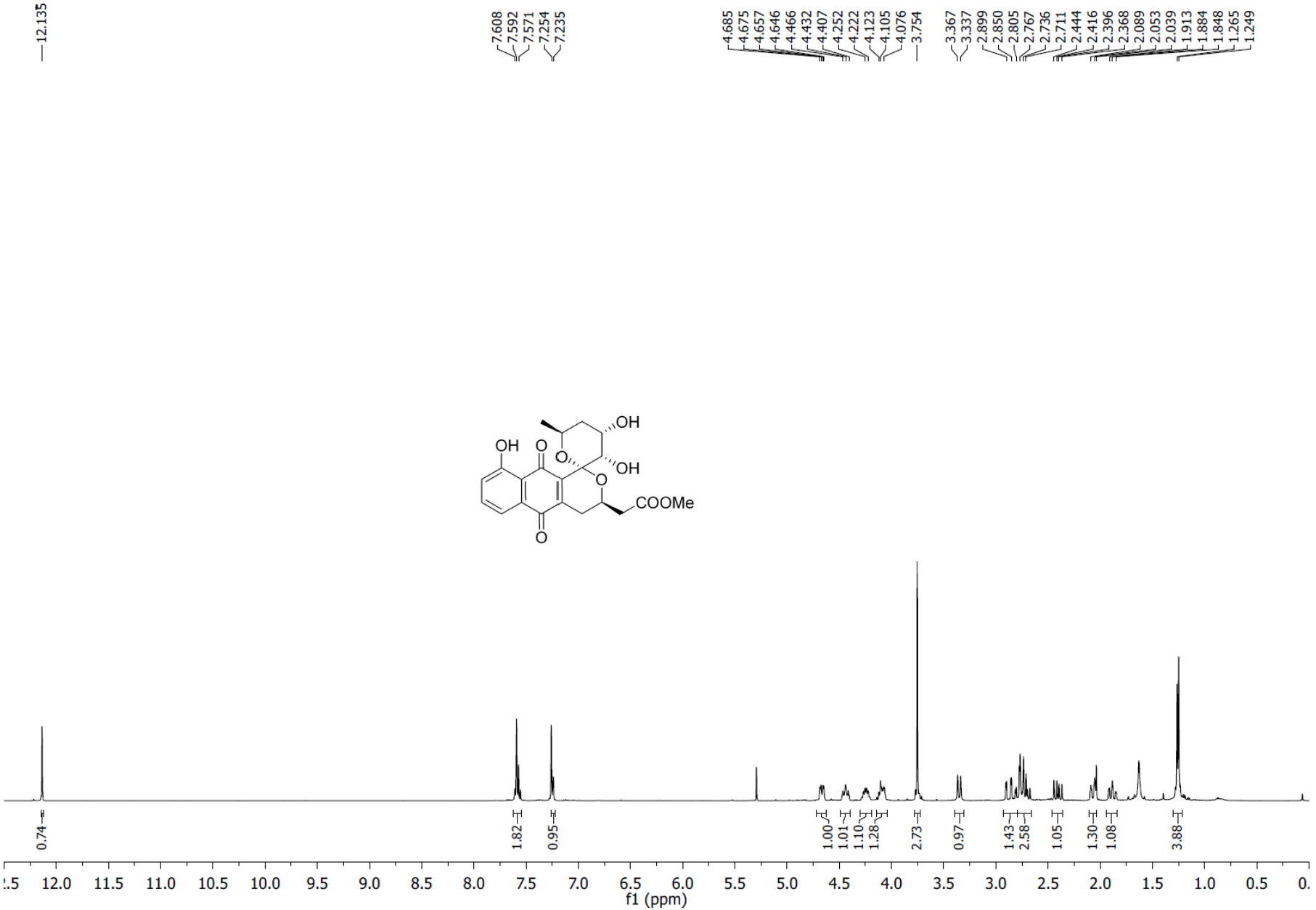



**Figure S41.** $^{1}$H-NMR ($CDCl_3$, 400 MHz) of **10.**

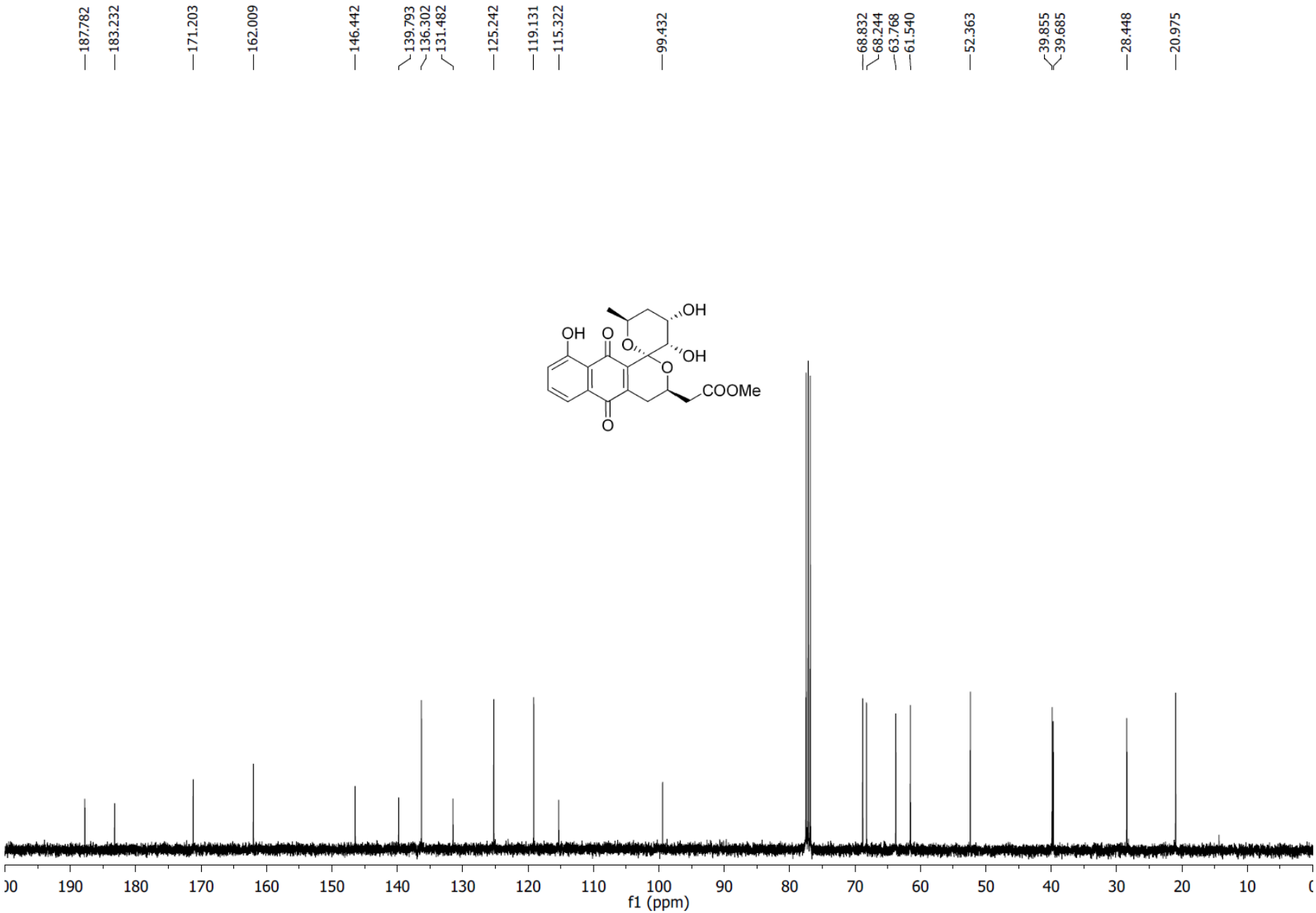



**Figure S42.** $^{13}$C-NMR ($CDCl_3$, 100 MHz) of **10.**

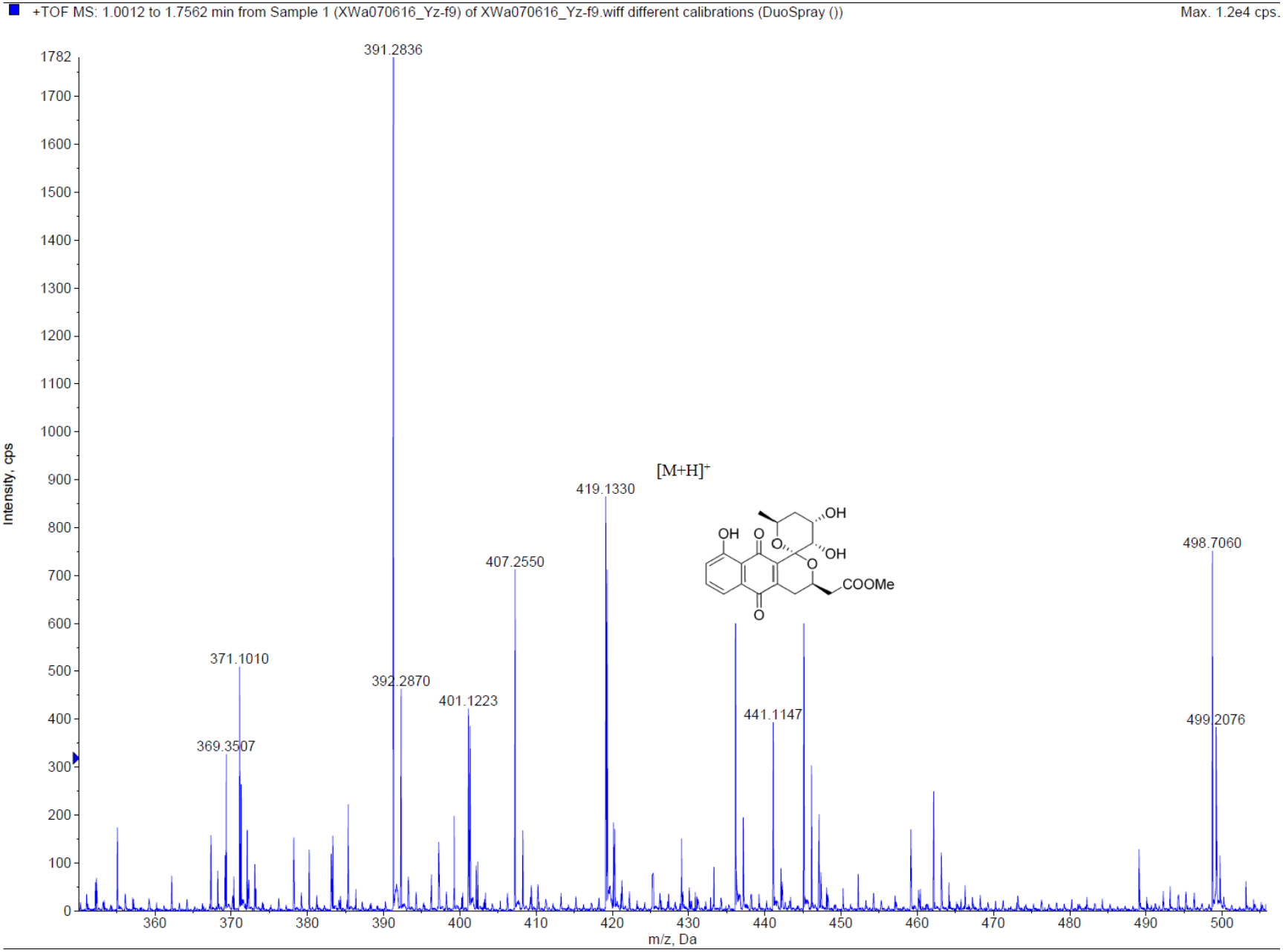



**Figure S43.** (+)-HRESI-MS of **10.**

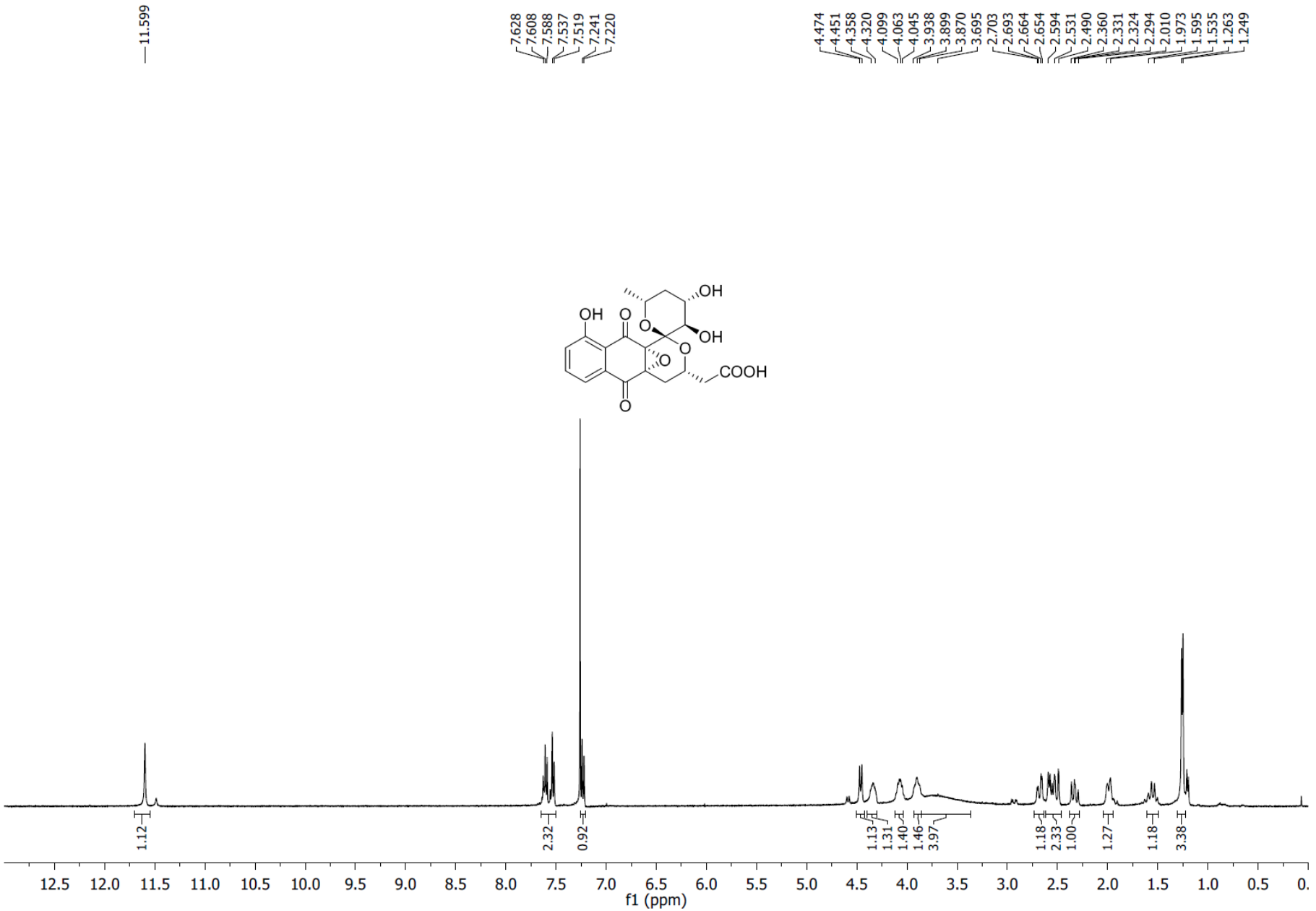



**Figure S44.** $^{1}$H-NMR ($CDCl_3$, 400 MHz) of **11.**

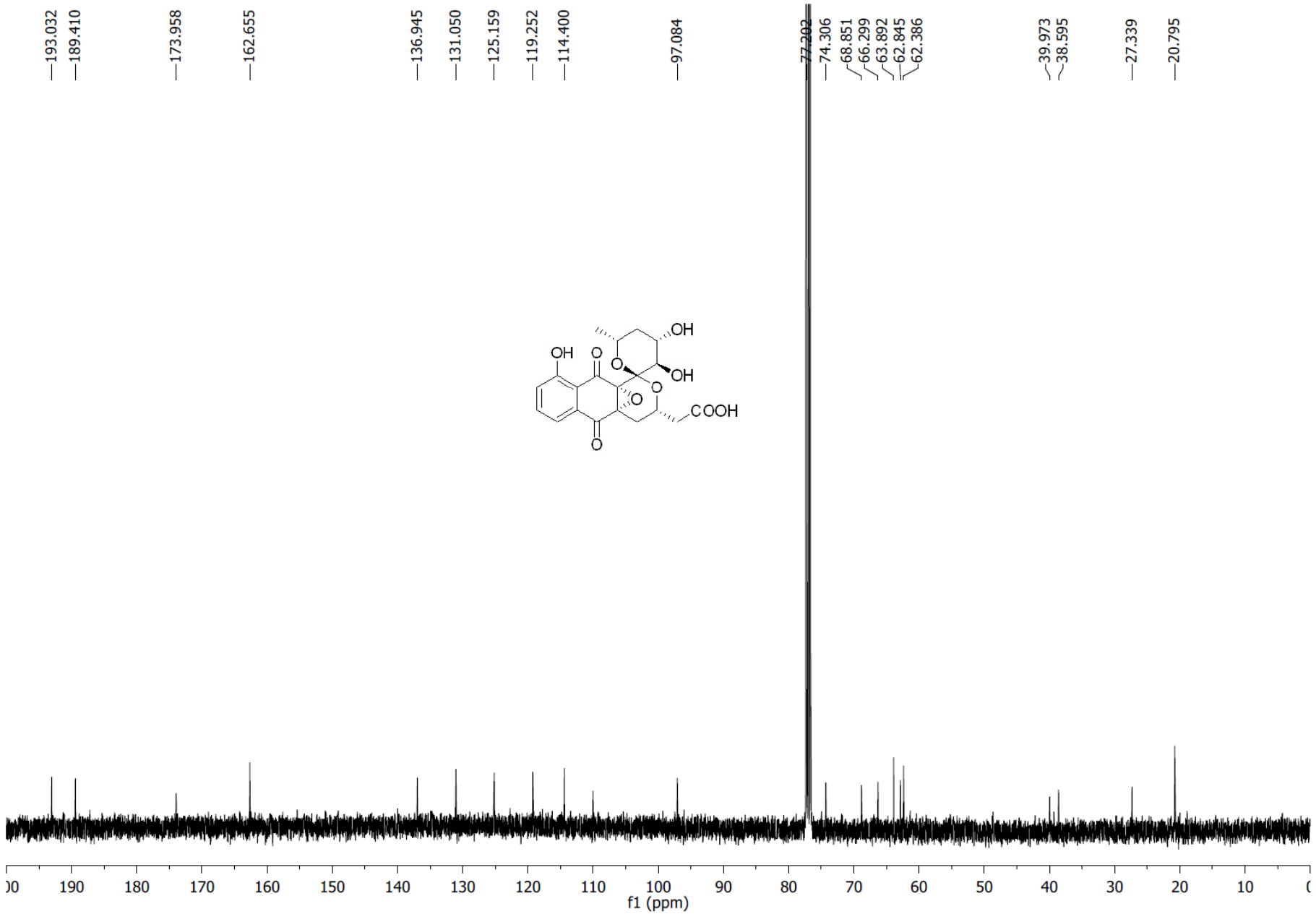



**Figure S45.** $^{13}$C-NMR ($CDCl_3$, 100 MHz) of **11.**

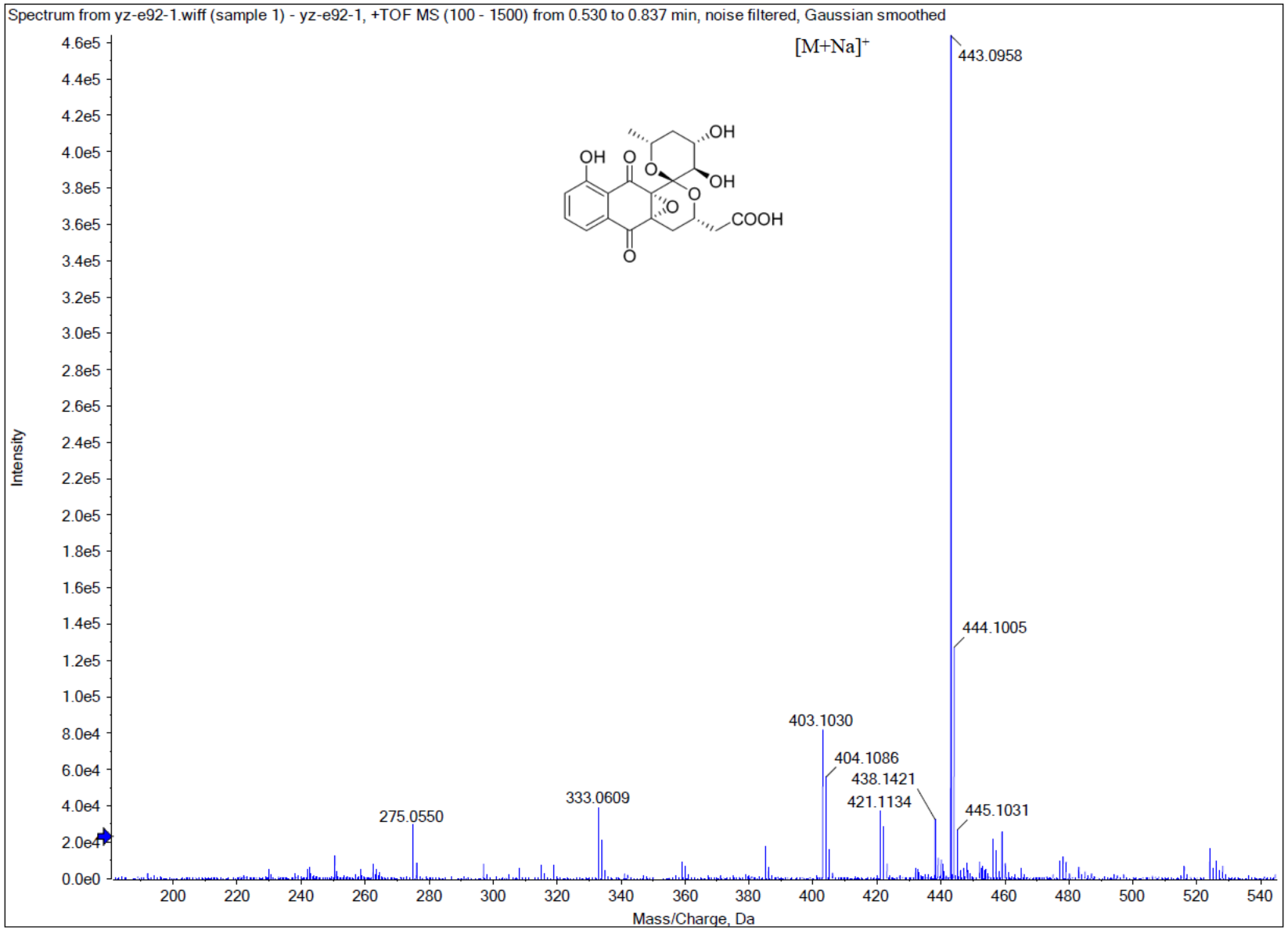



**Figure S46.** (+)-HRESI-MS of **11.**

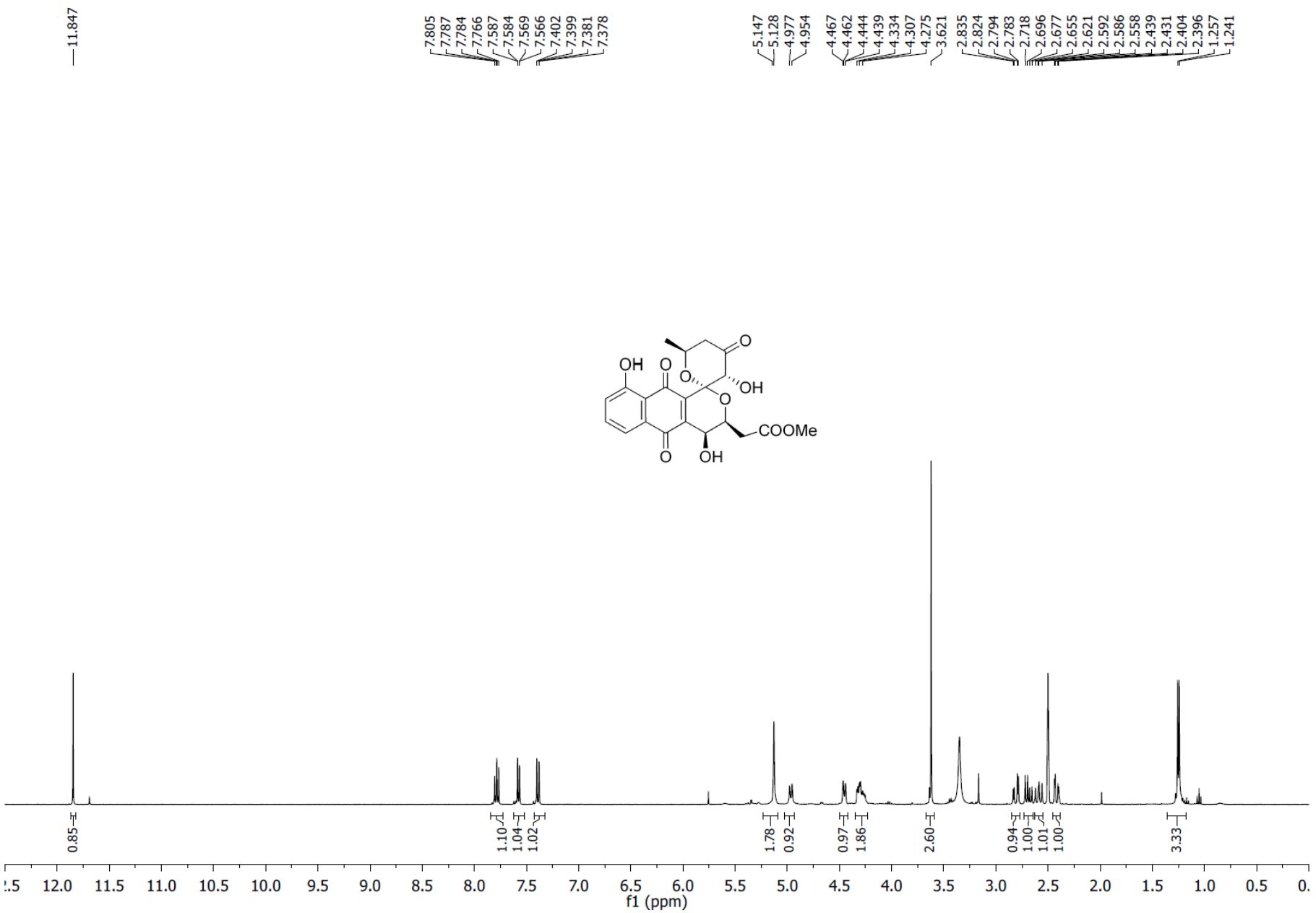



**Figure S47.** $^{1}$H-NMR (DMSO-$d_6$, 400 MHz) of **12.**

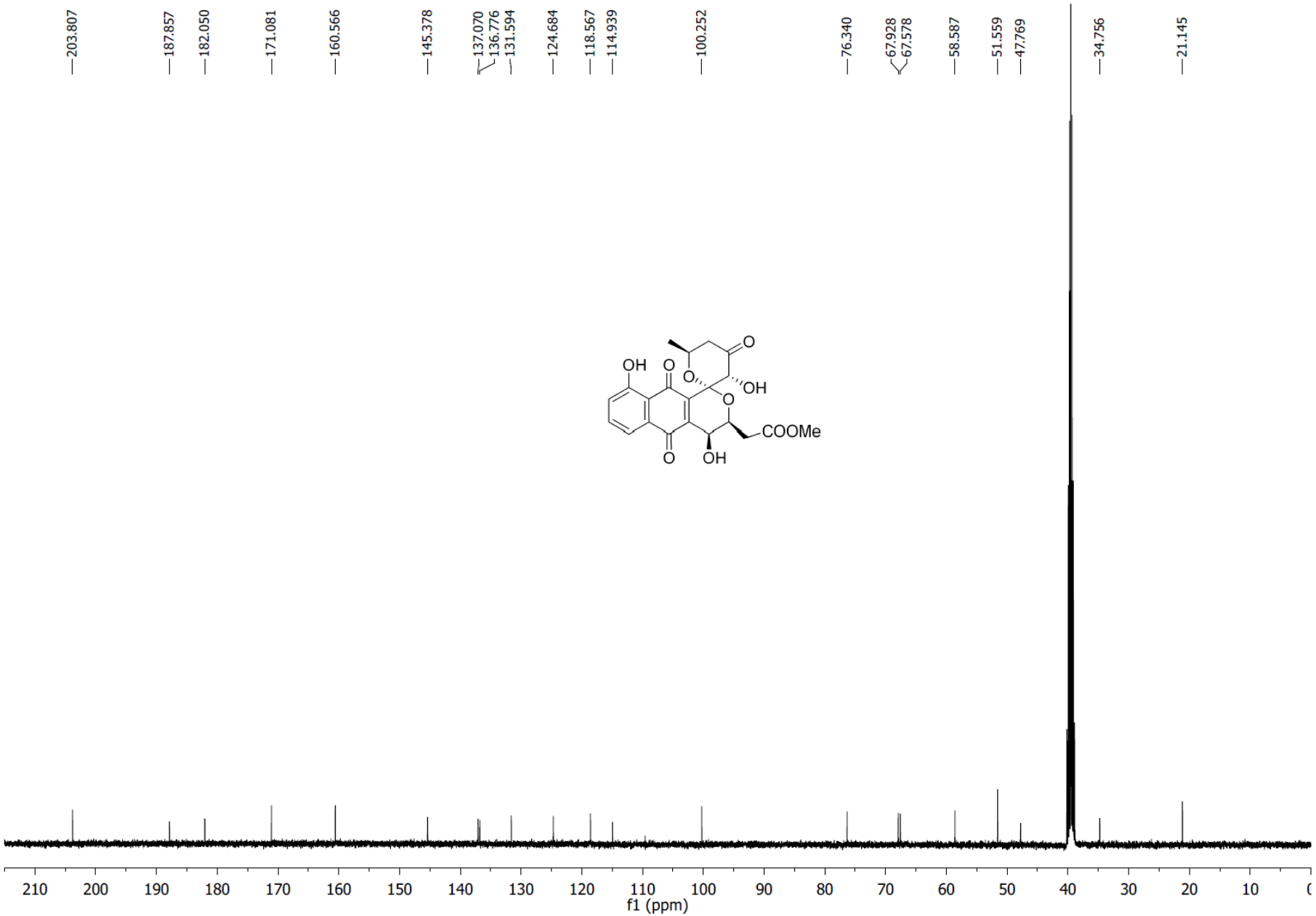



**Figure S48.** $^{13}$C-NMR (DMSO-$d_6$, 100 MHz) of **12.**

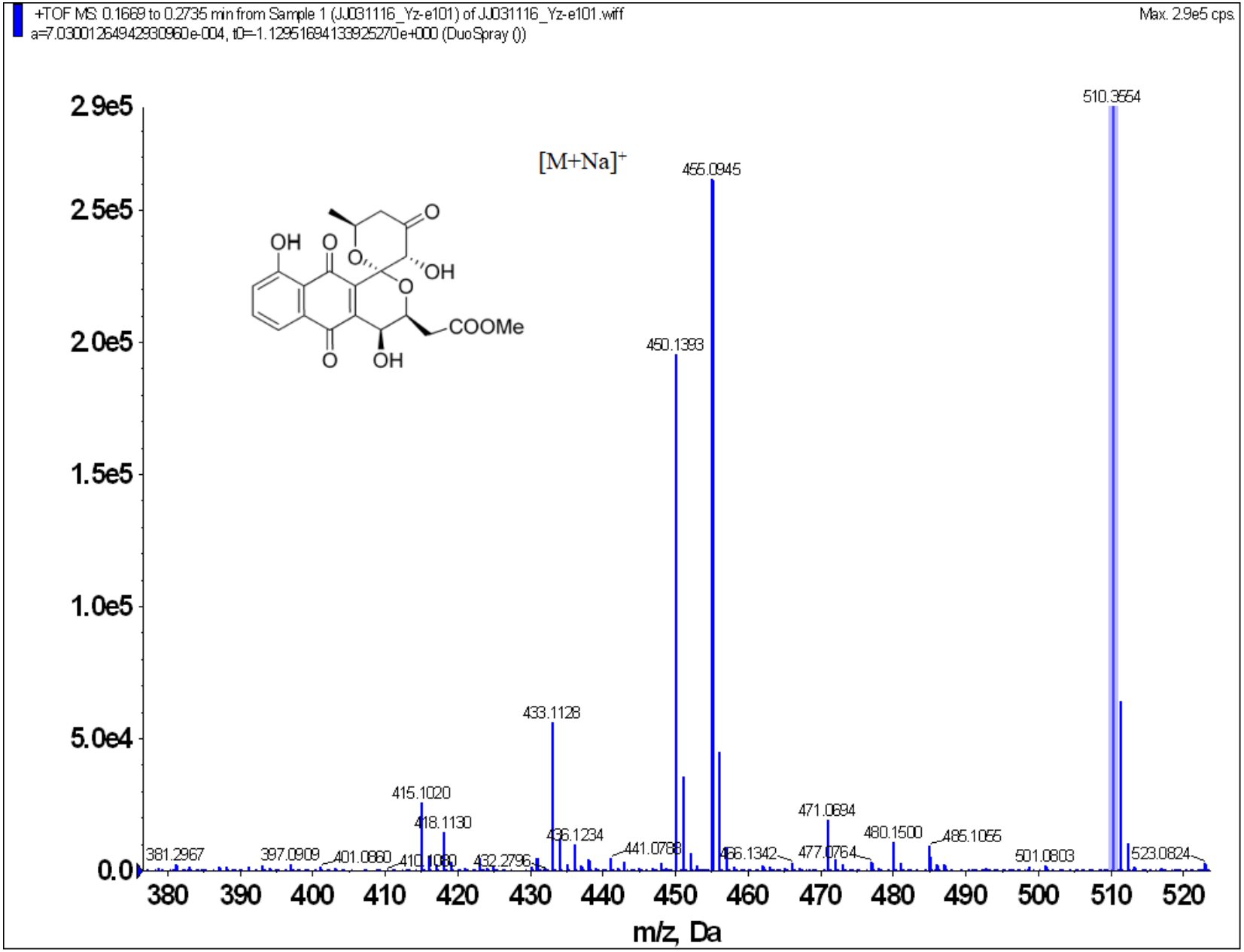



**Figure S49.** (+)-HRESI-MS of **12.**

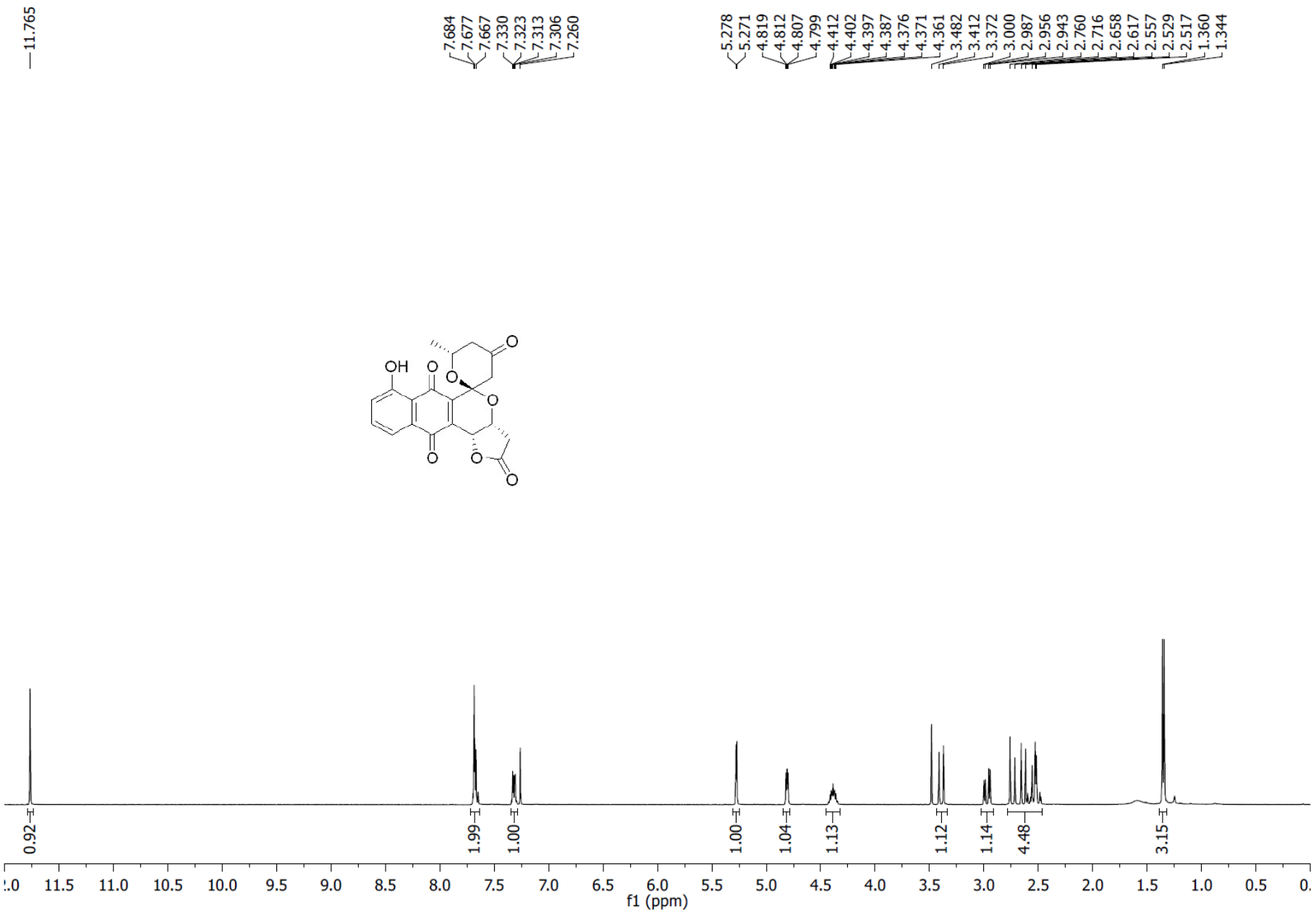



**Figure S50.** $^{1}$H-NMR ($CDCl_3$, 400 MHz) of **13.**

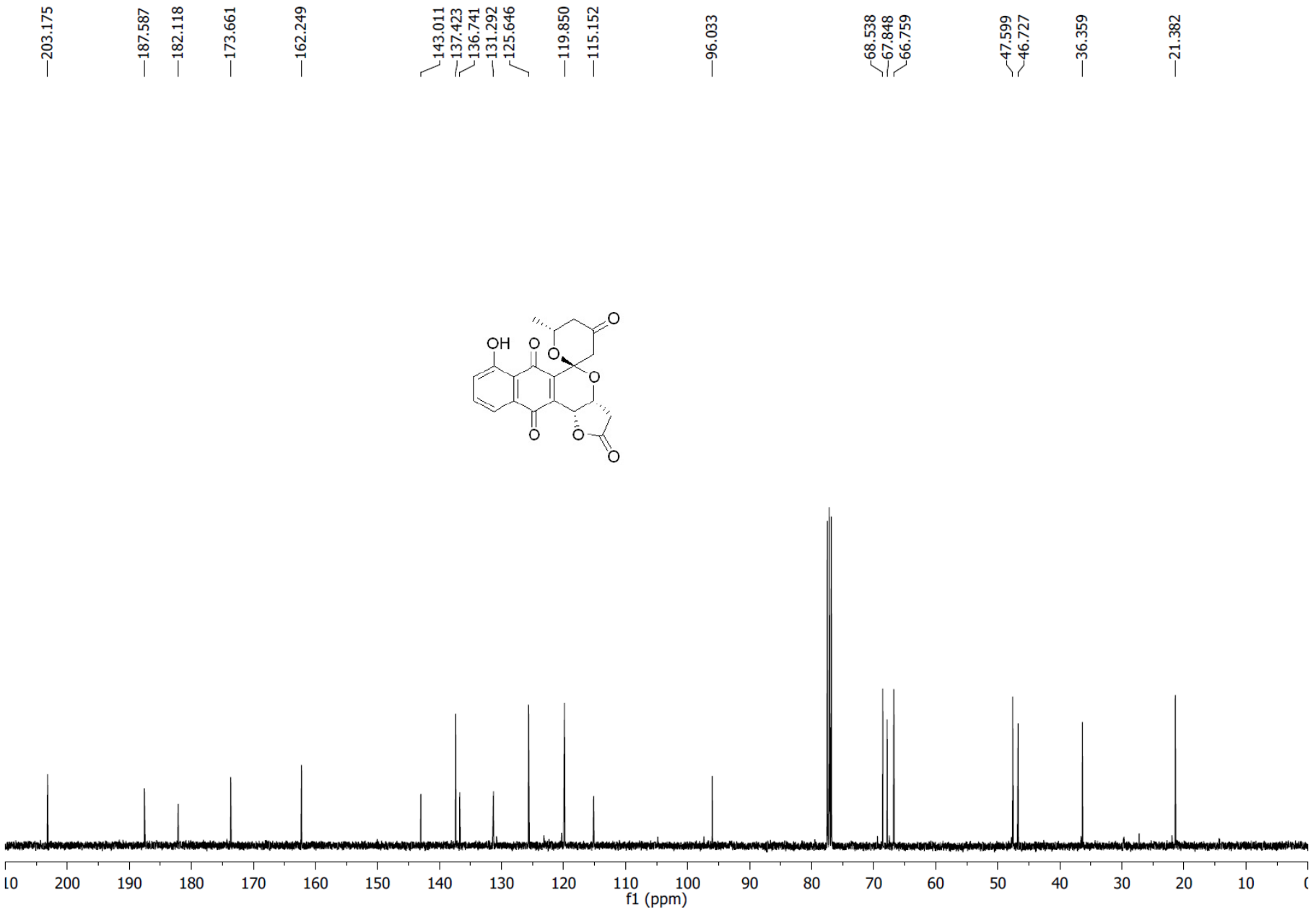



**Figure S51.** $^{13}$C-NMR ($CDCl_3$, 100 MHz) of **13.**

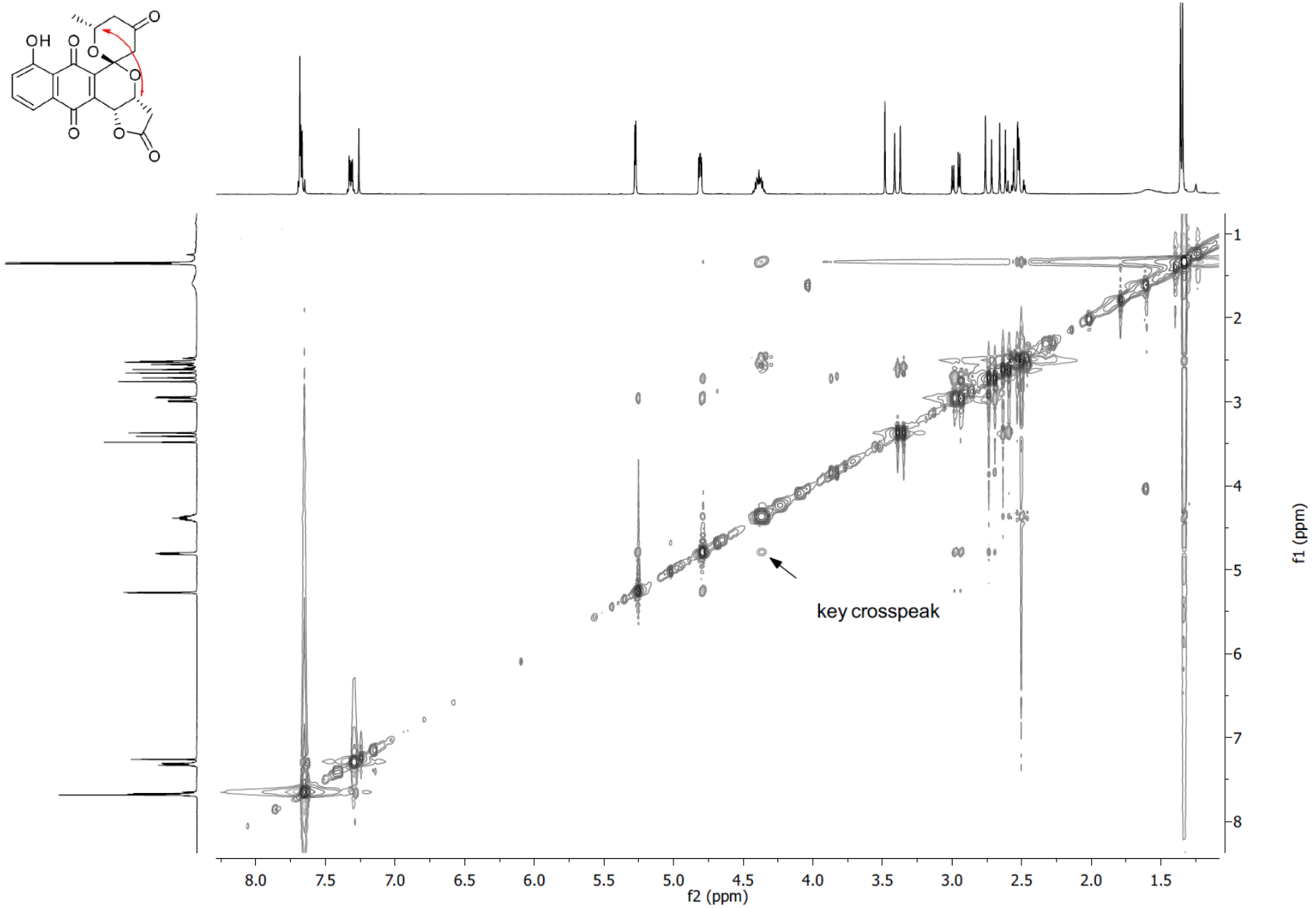



**Figure S52.** NOESY ($CDCl_3$, 400 MHz) of **13.**

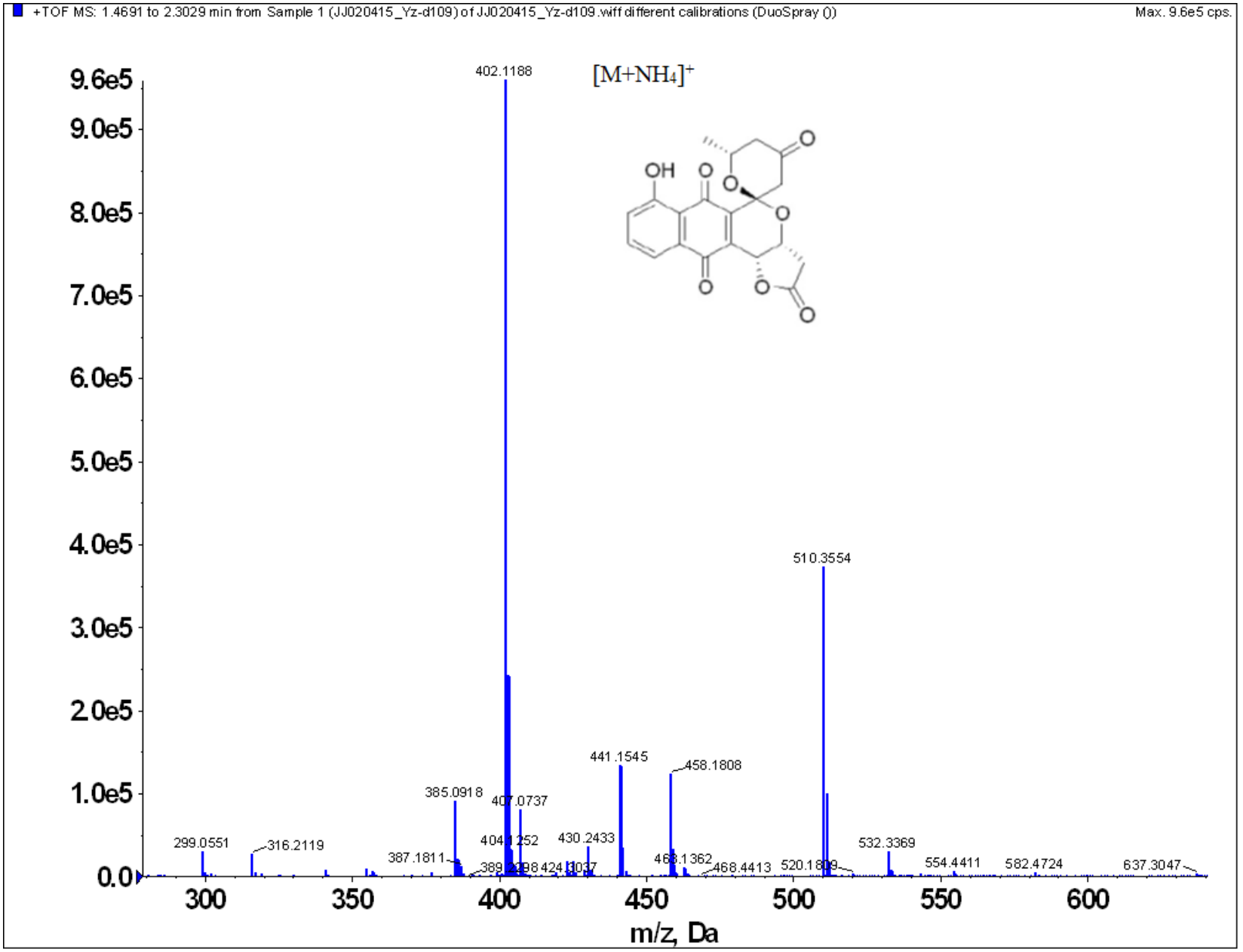



**Figure S53.** (+)-HRESI-MS of **13.**

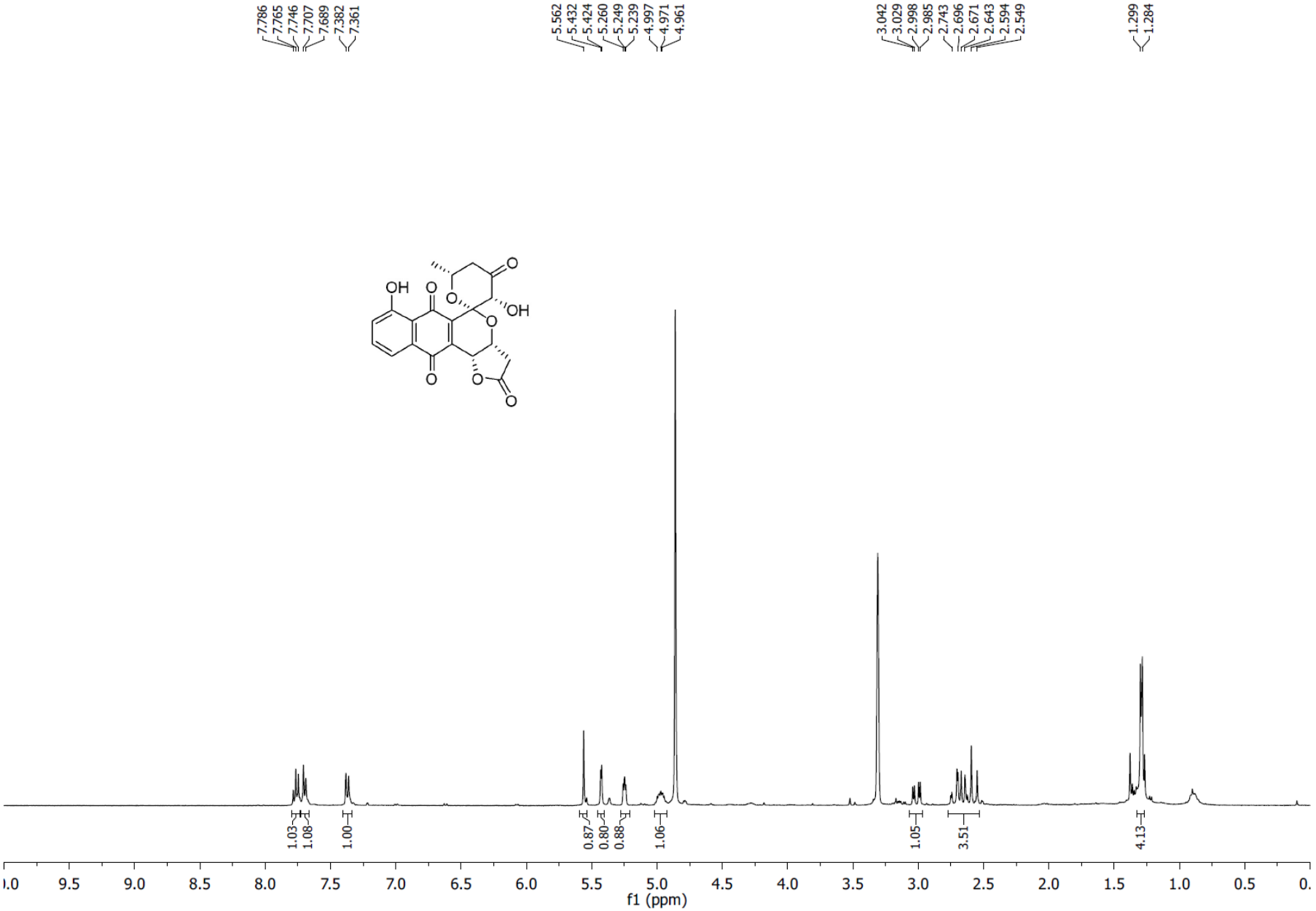



**Figure S54.** $^{1}$H-NMR ($CD_3OD$, 400 MHz) of **14.**

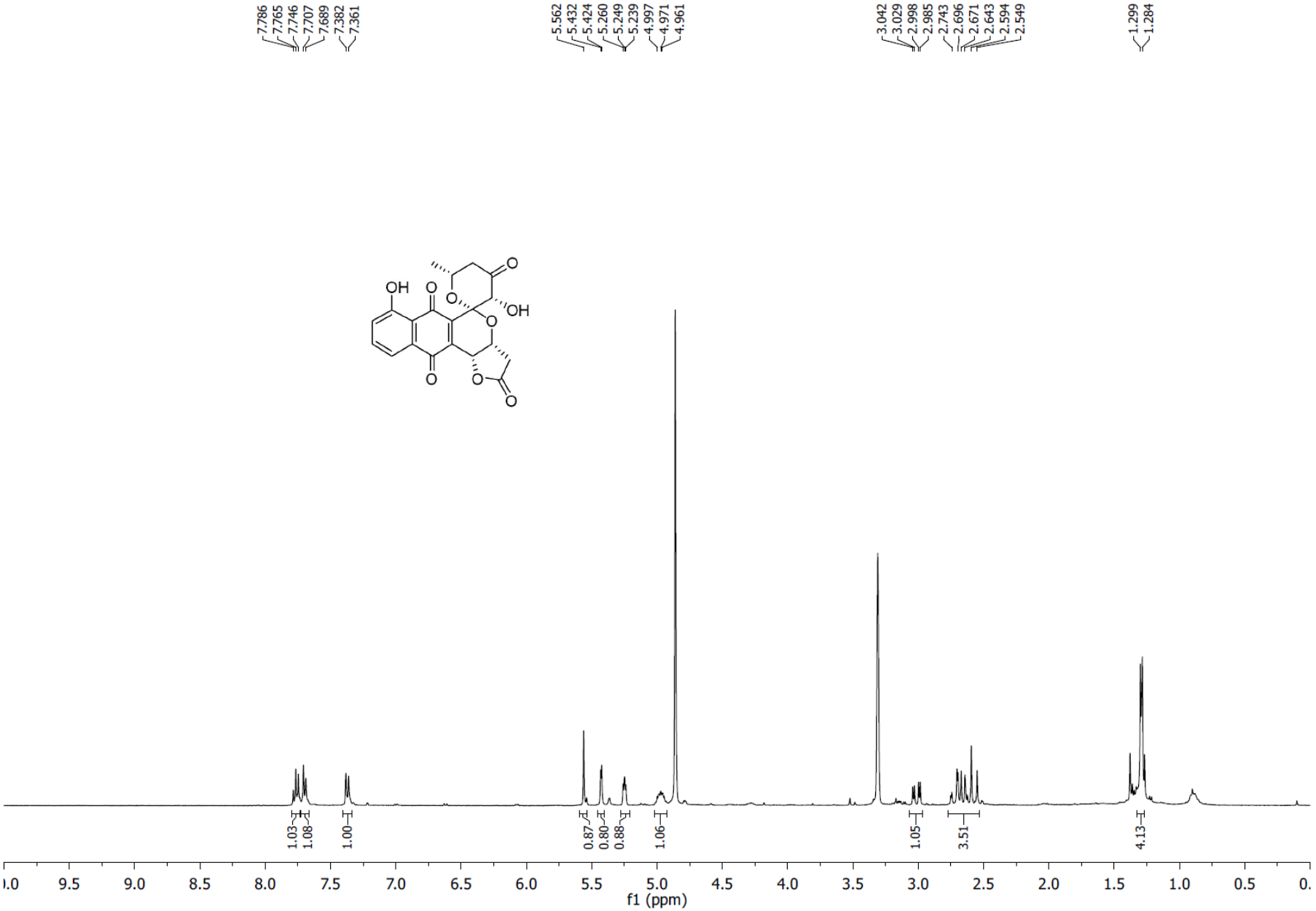



**Figure S55.** $^{1}$H-NMR ($CD_3OD$, 400 MHz) of **14.**

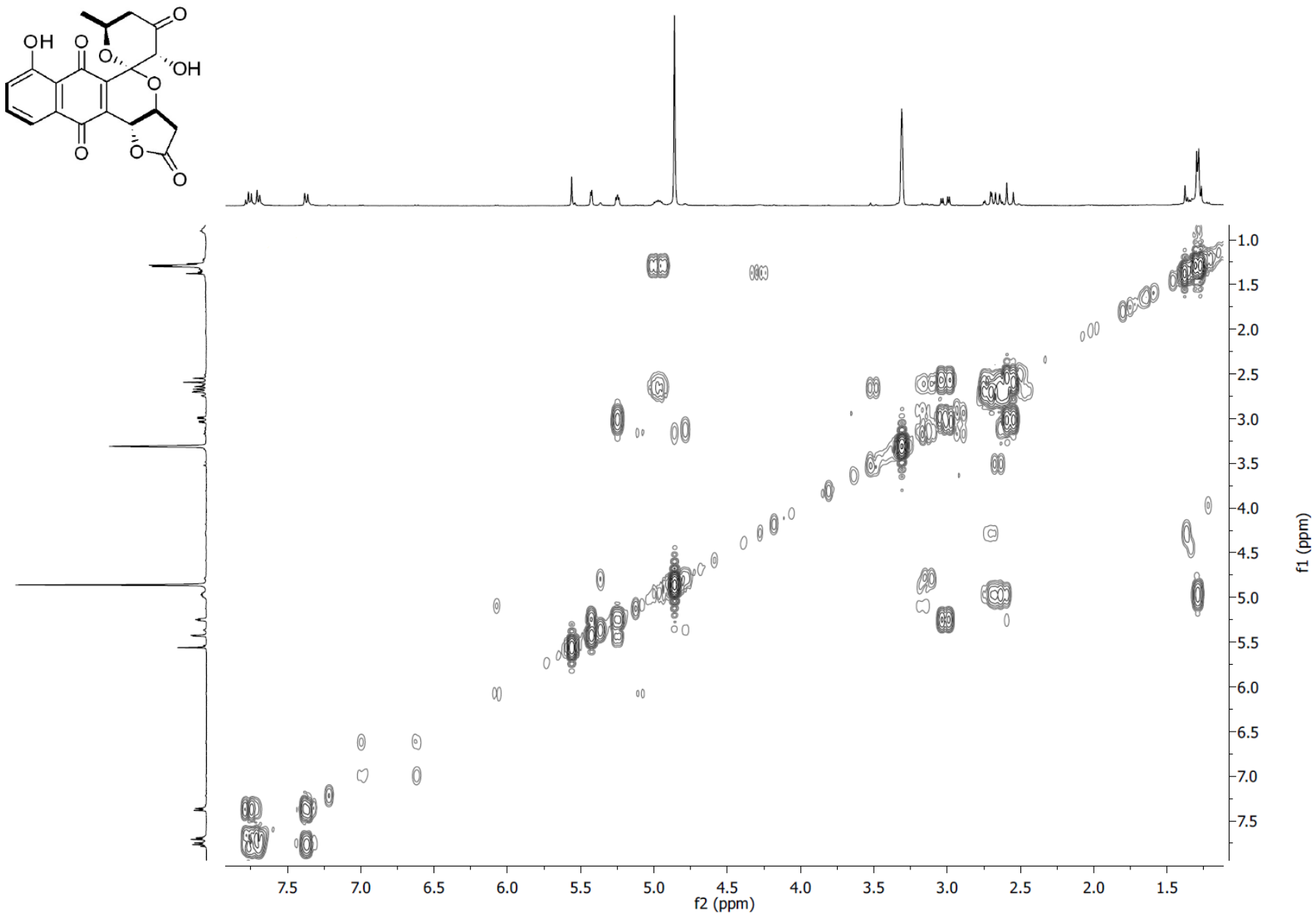



**Figure S56.** $^{1}$H-$^{1}$H COSY ($CD_3OD$, 400 MHz) of **14.**

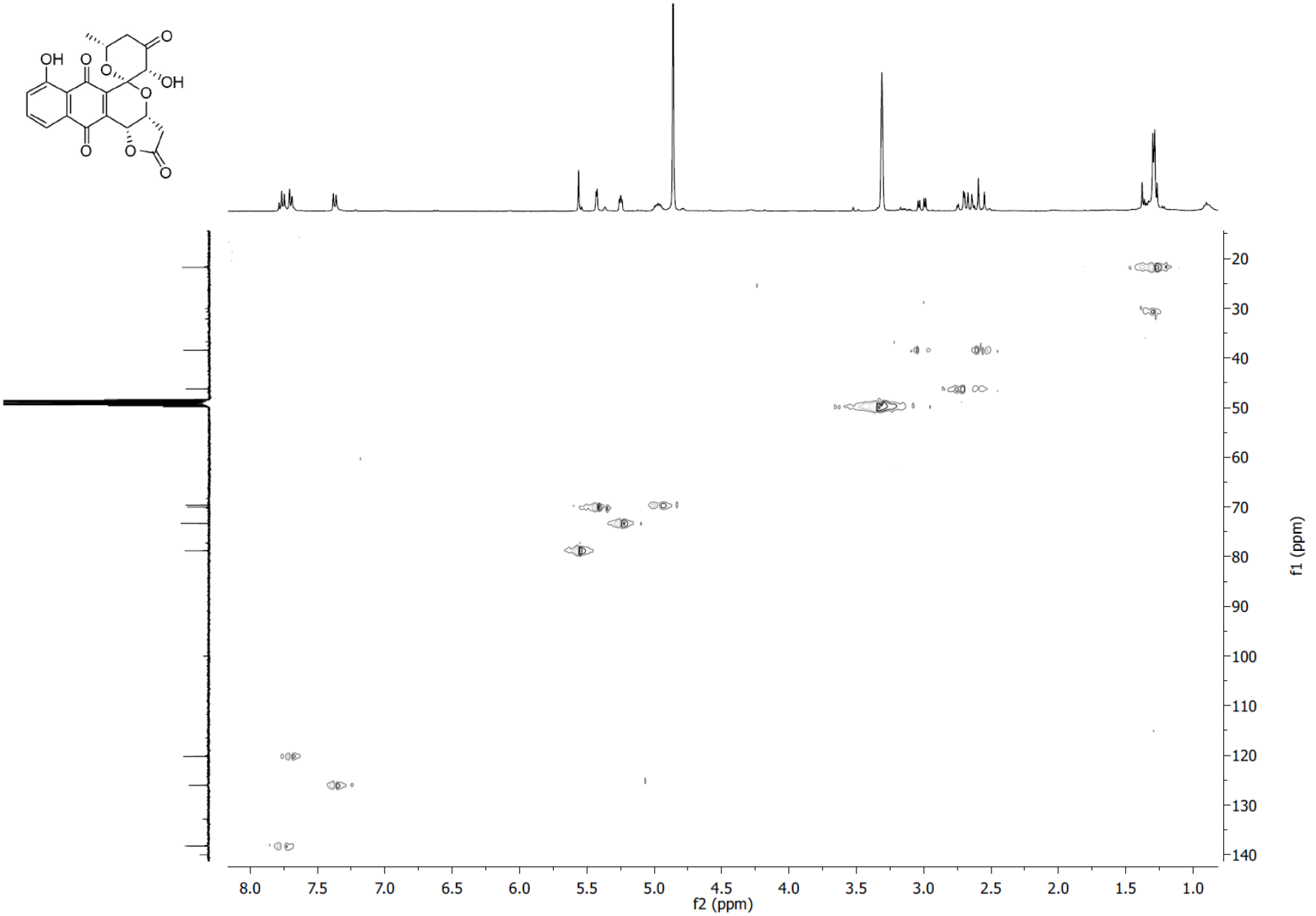



**Figure S57.** HSQC ($CD_3OD$, 400 MHz) of **14.**

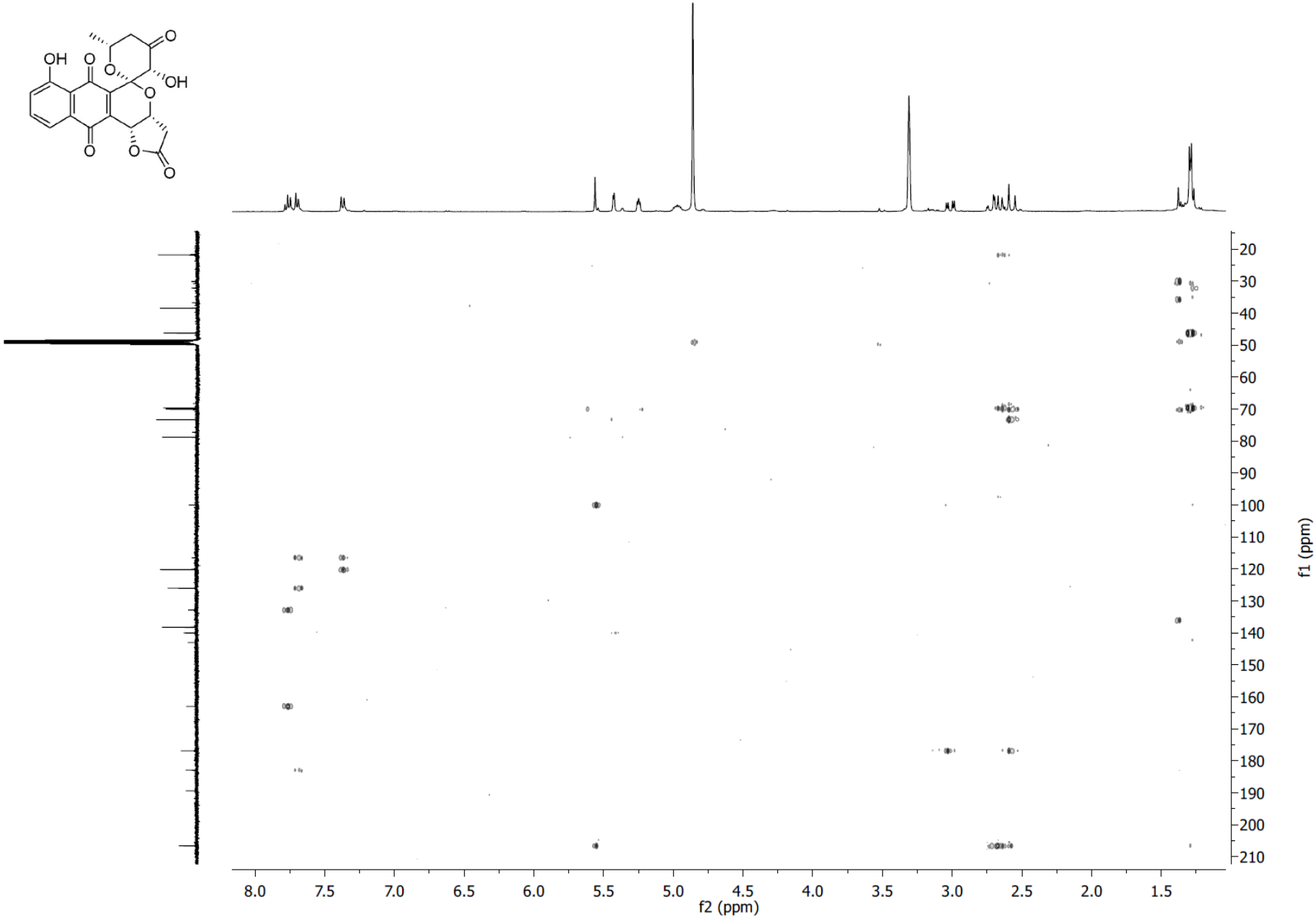



**Figure S58.** HMBC ($CD_3OD$, 400 MHz) of **14.**

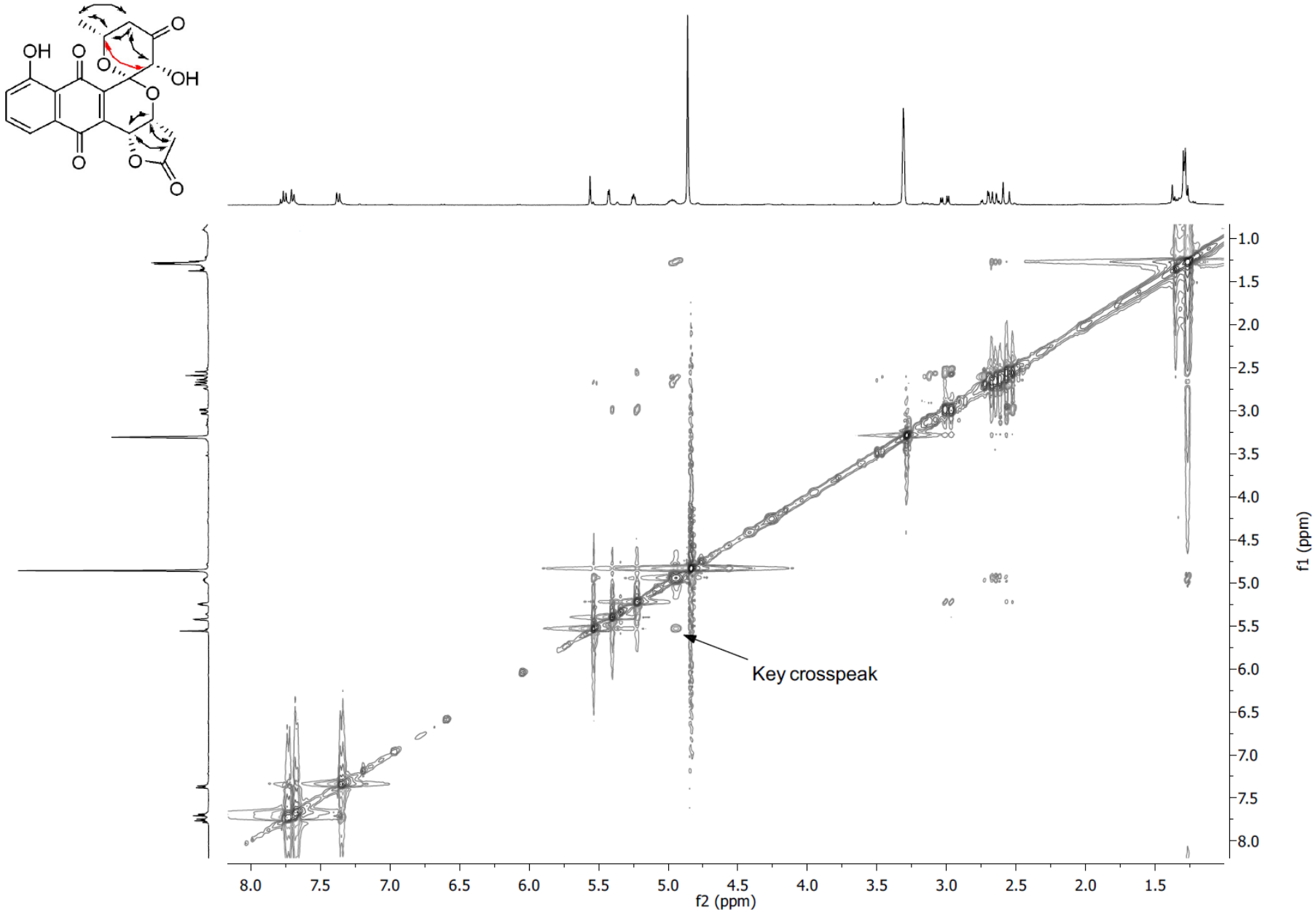



**Figure S59.** NOESY ($CD_3OD$, 400 MHz) of **14.**

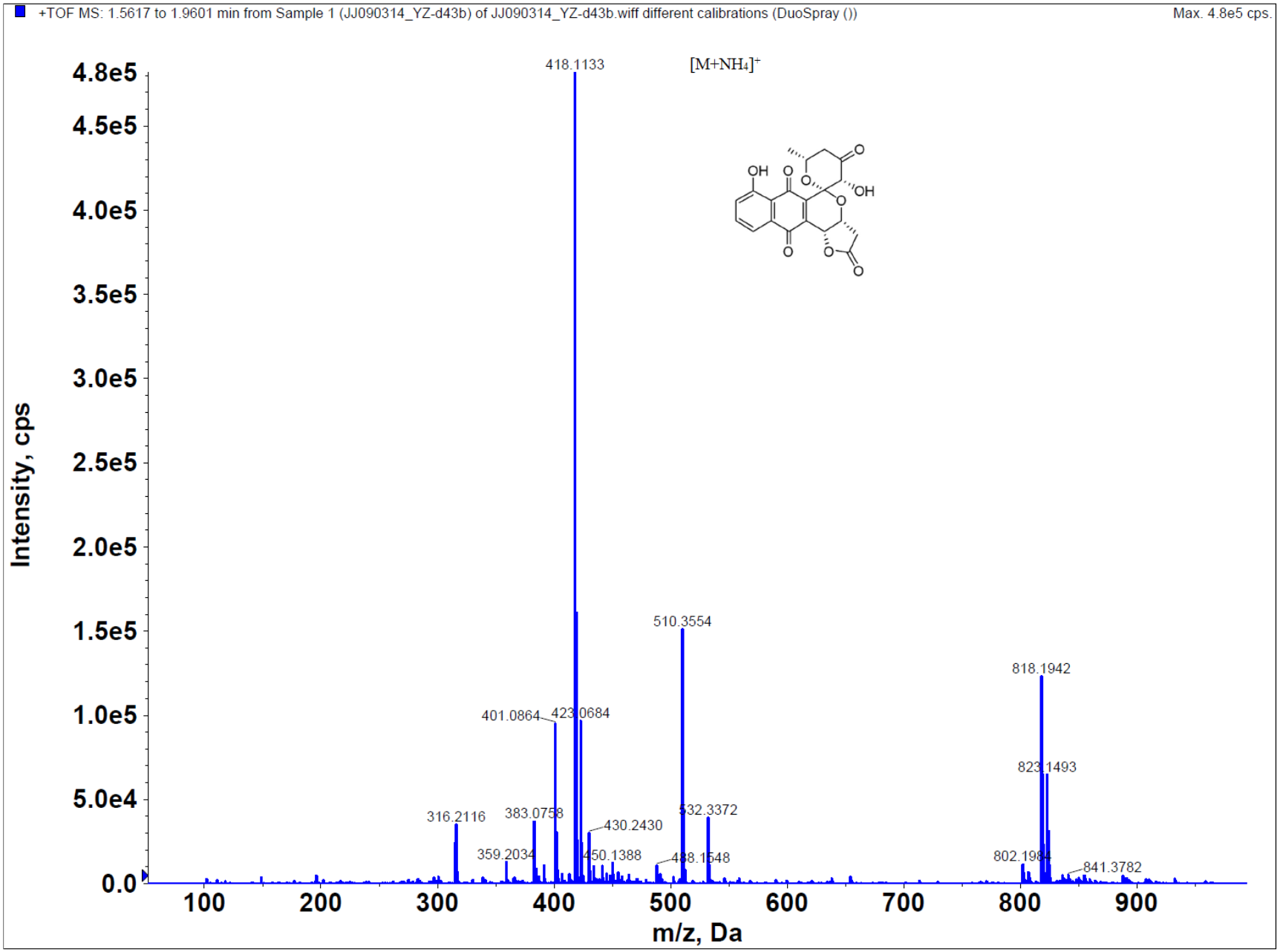



**Figure S60.** (+)-HRESI-MS of **14.**

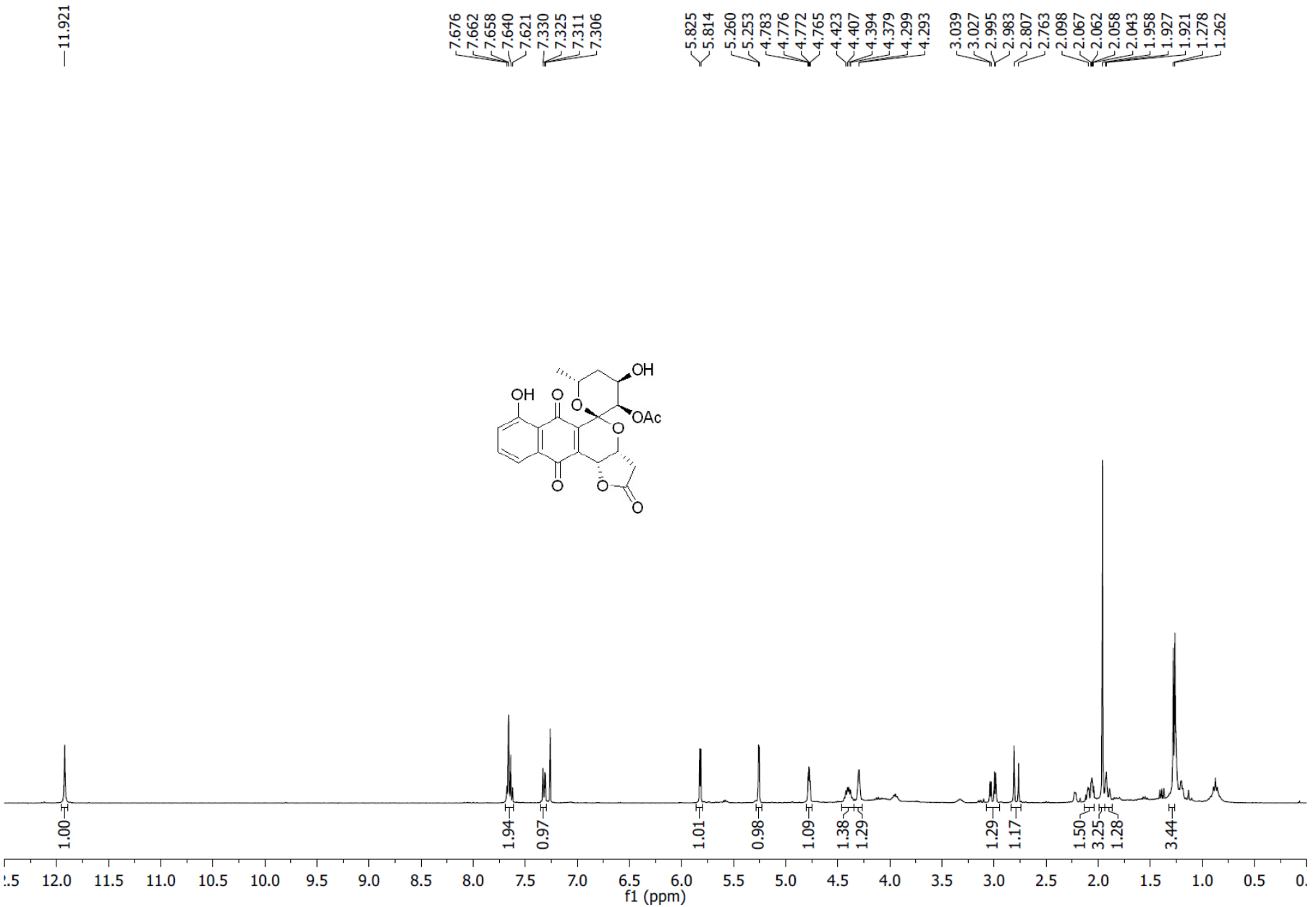



**Figure S61.** $^{1}$H-NMR ($CDCl_3$, 400 MHz) of **15.**

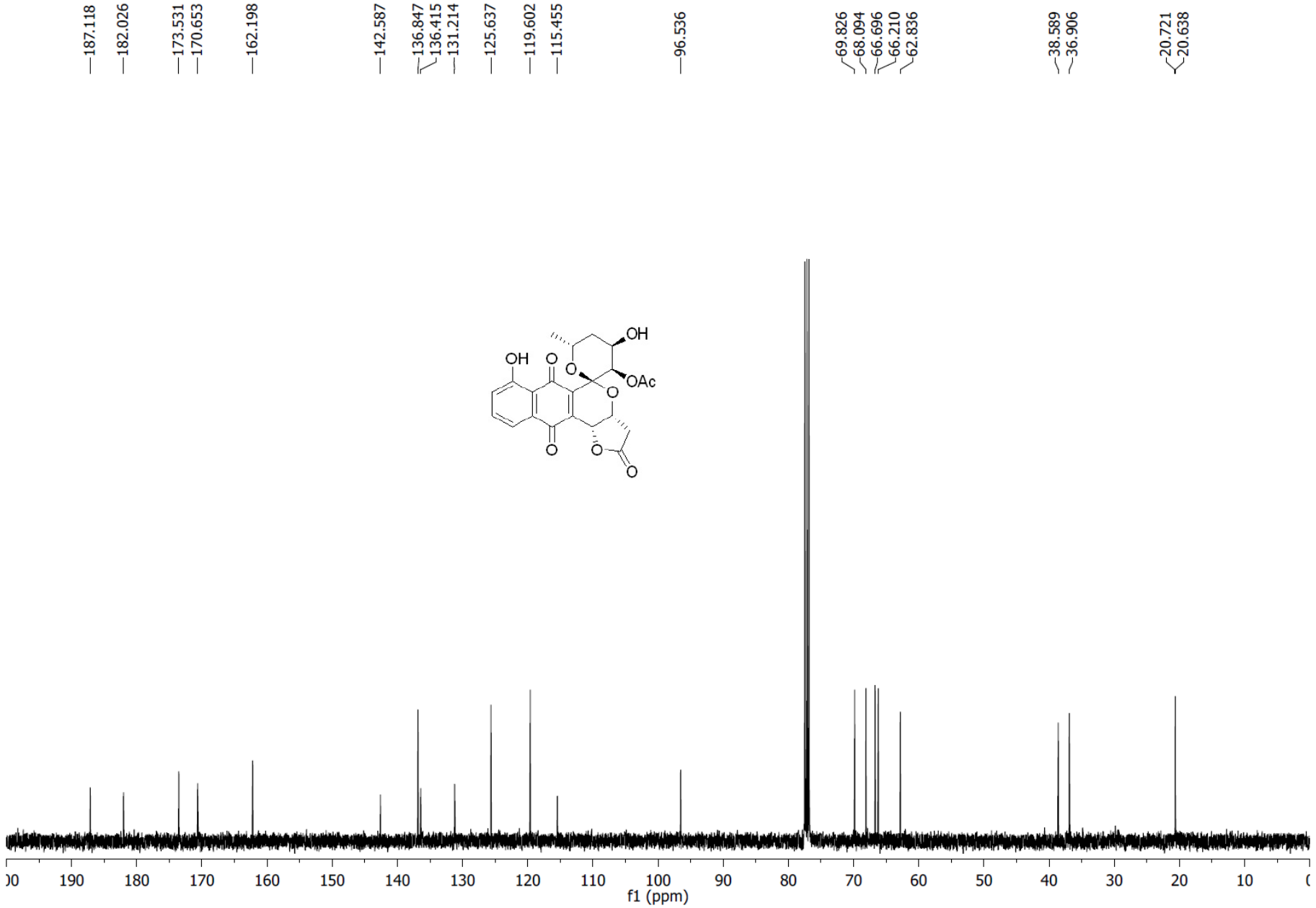



**Figure S62.** $^{13}$C-NMR ($CDCl_3$, 100 MHz) of **15.**

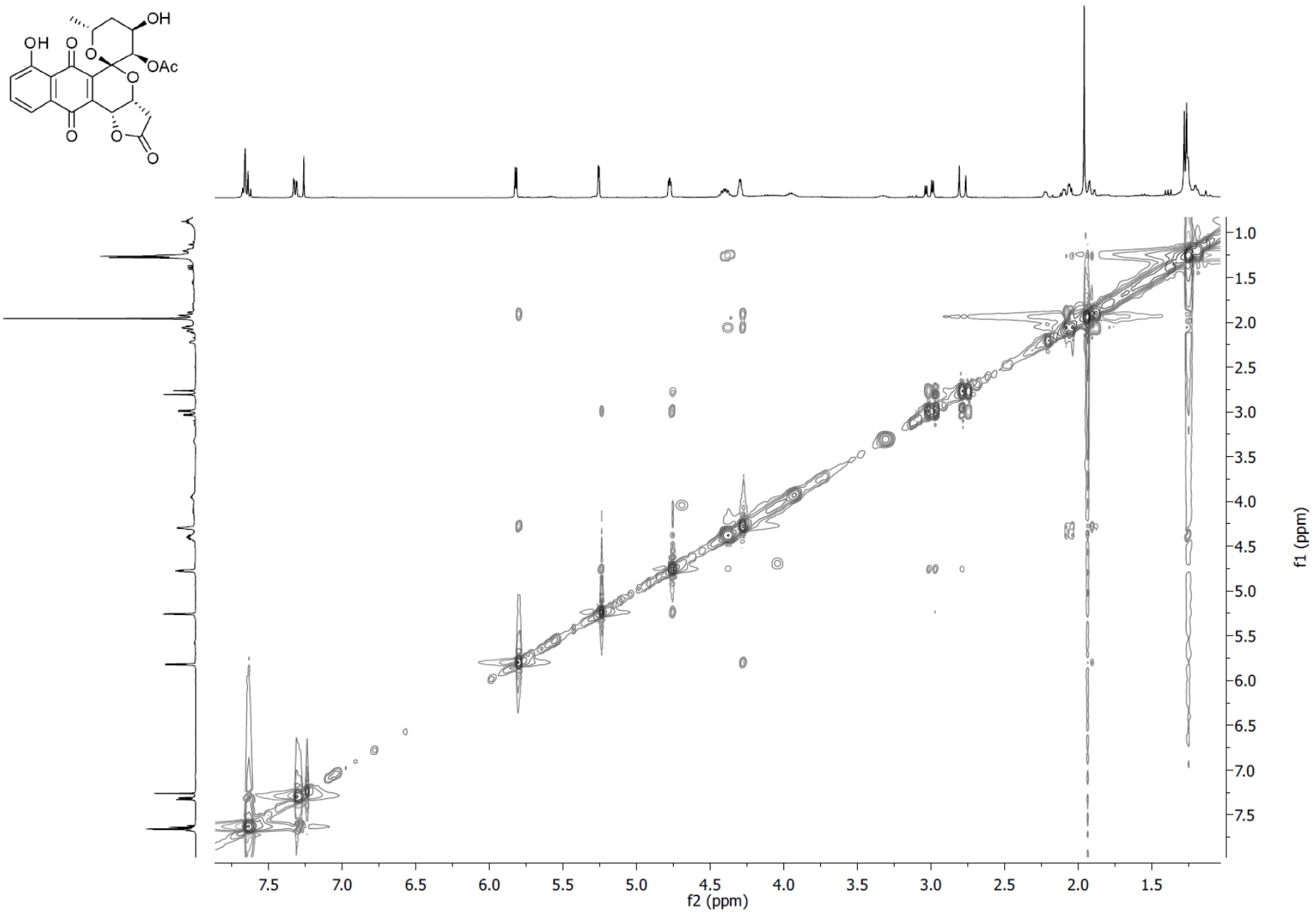



**Figure S63.** NOESY ($CDCl_3$, 400 MHz) of **15.**

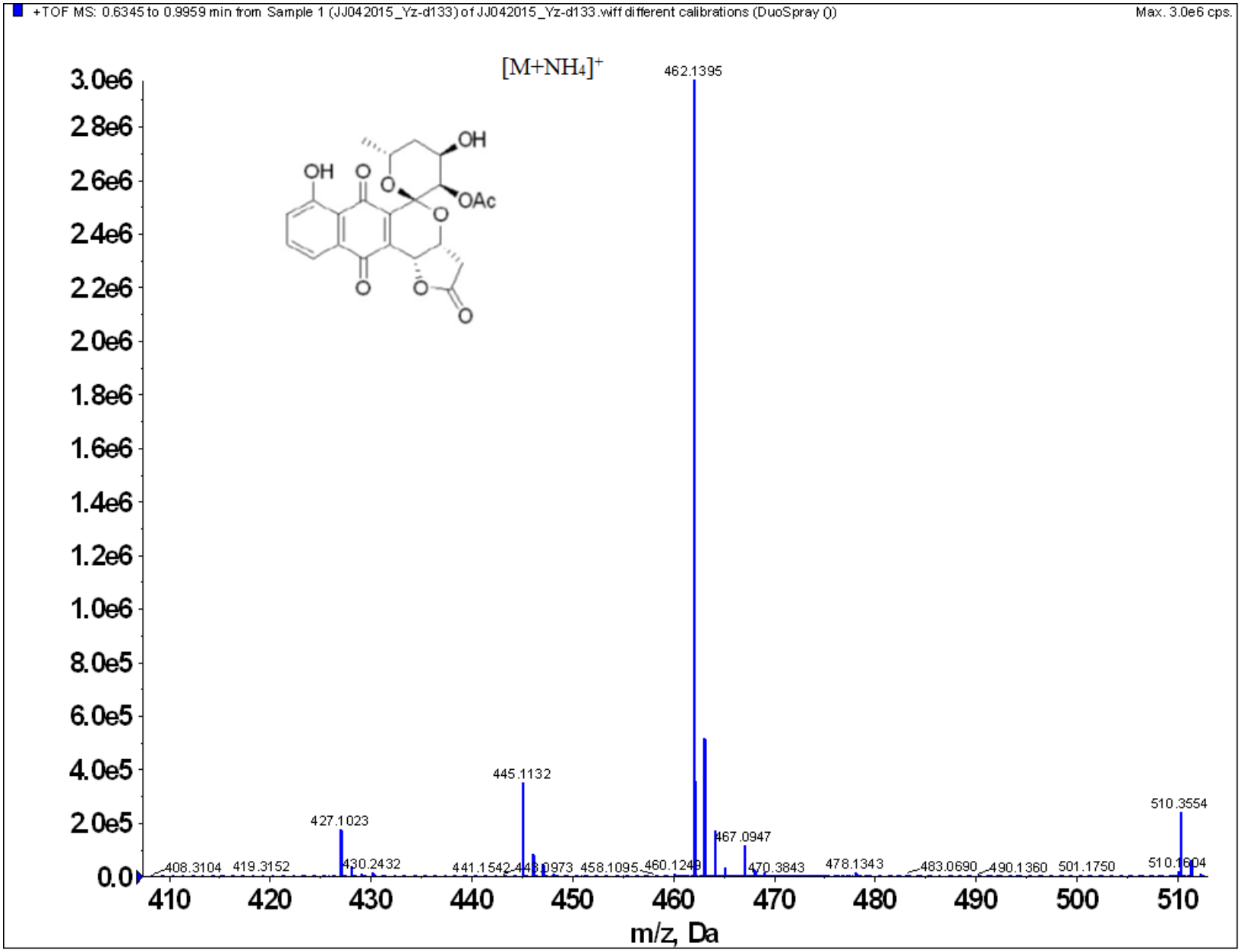



**Figure S64.** (+)-HRESI-MS of **15.**

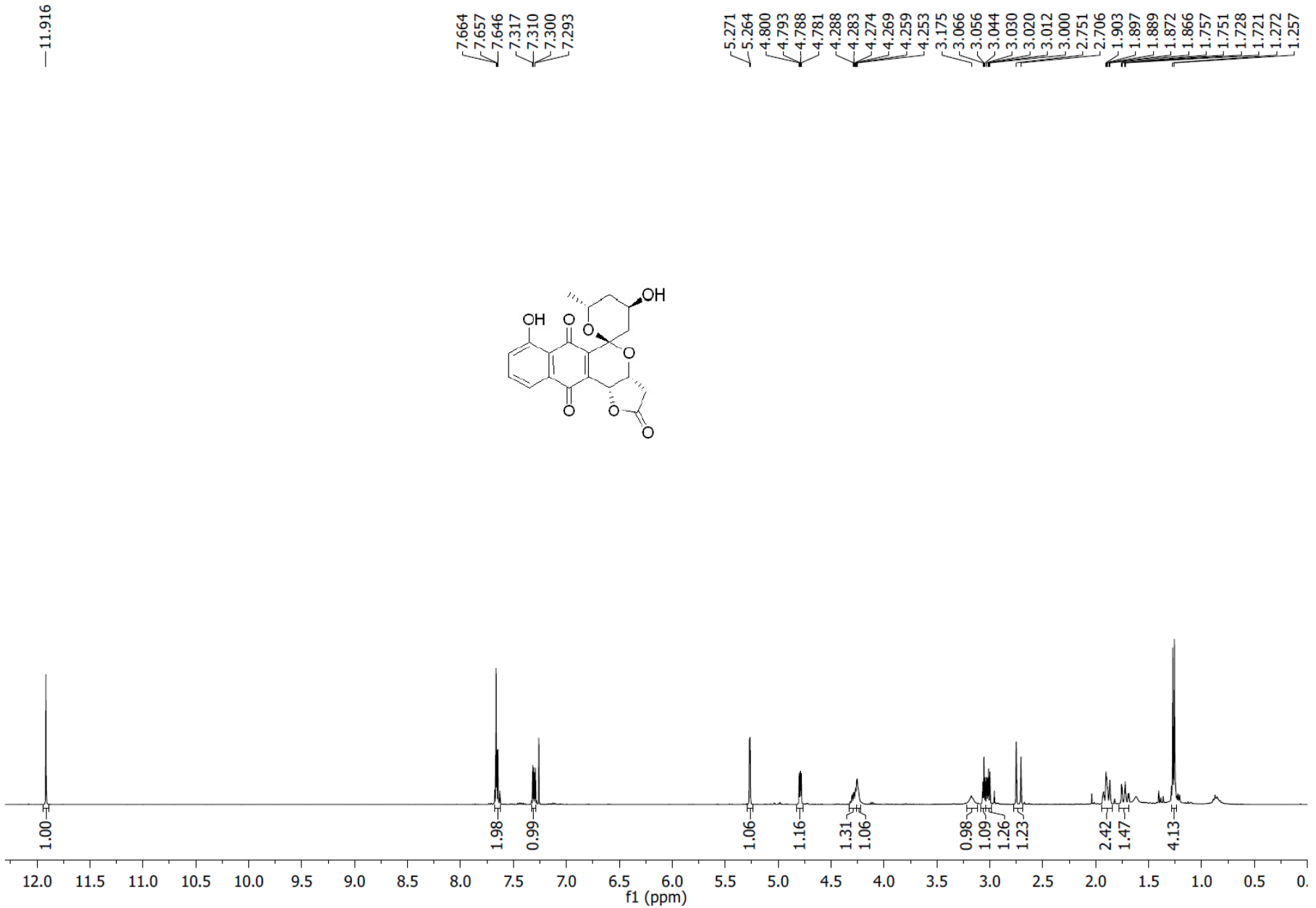



**Figure S65.** $^{1}$H-NMR ($CDCl_3$, 400 MHz) of **16.**

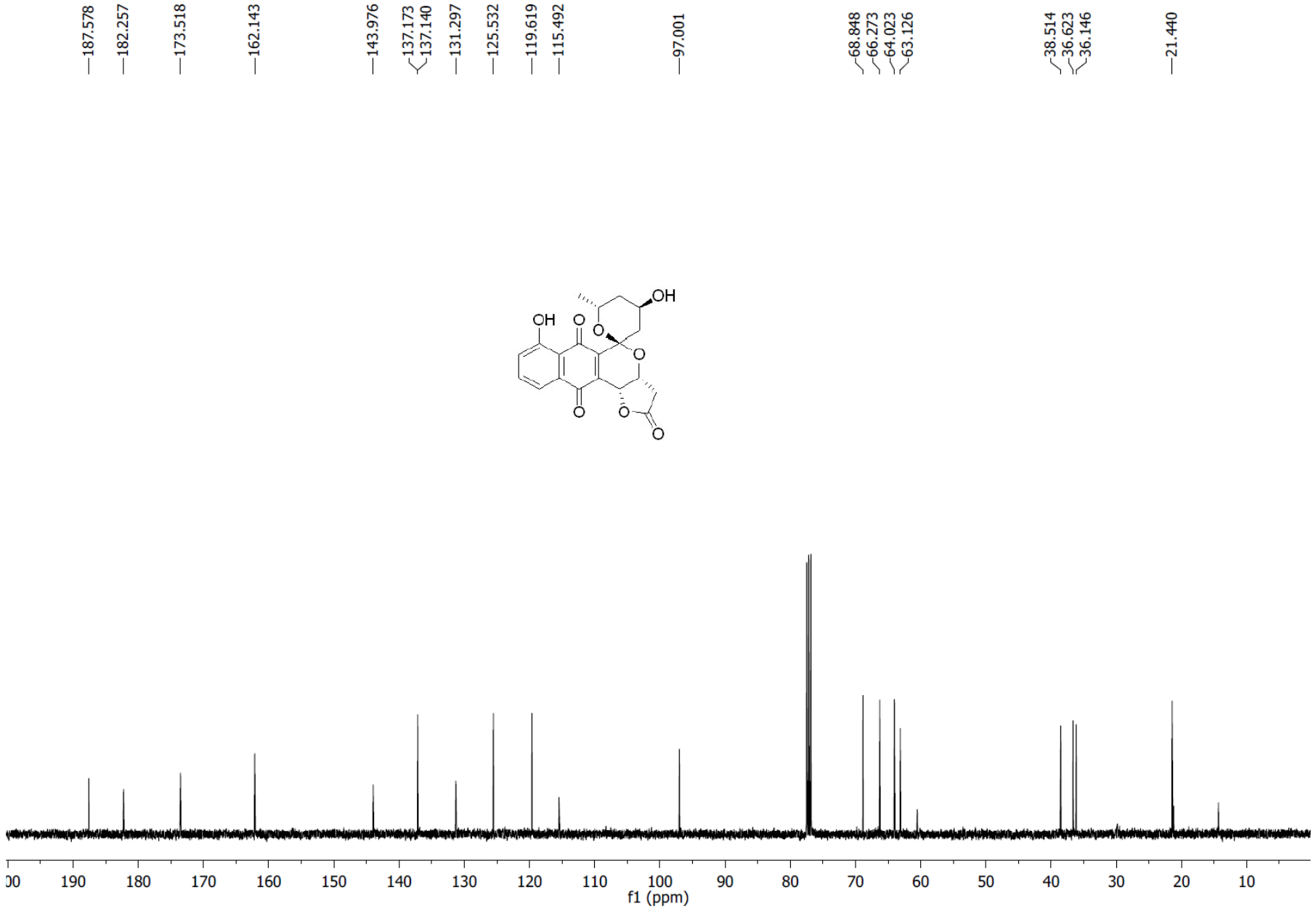



**Figure S66.** $^{13}$C-NMR ($CDCl_3$, 100 MHz) of **16.**

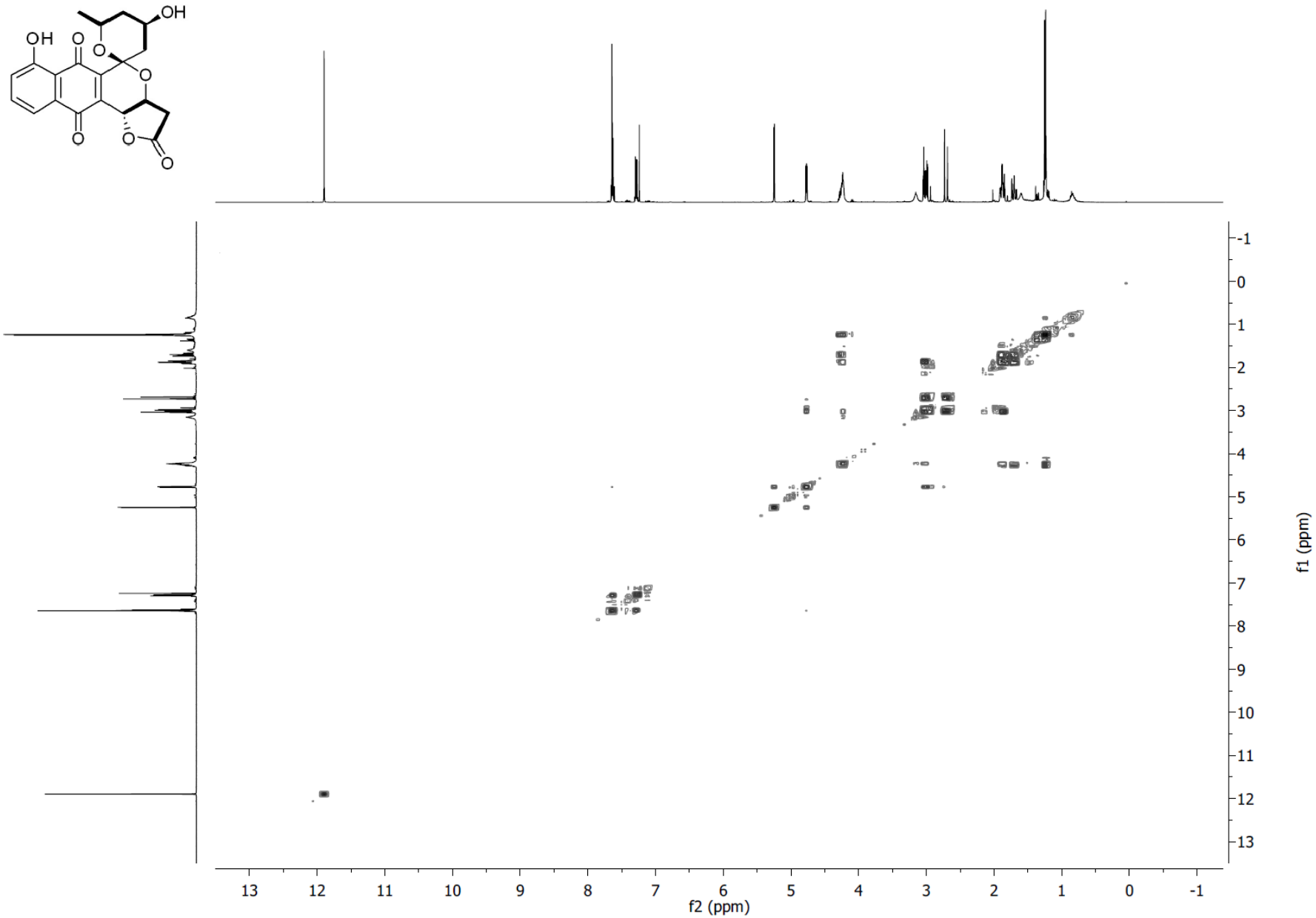



**Figure S67.** $^{1}$H-$^{1}$H COSY ($CDCl_3$, 400 MHz) of **16.**

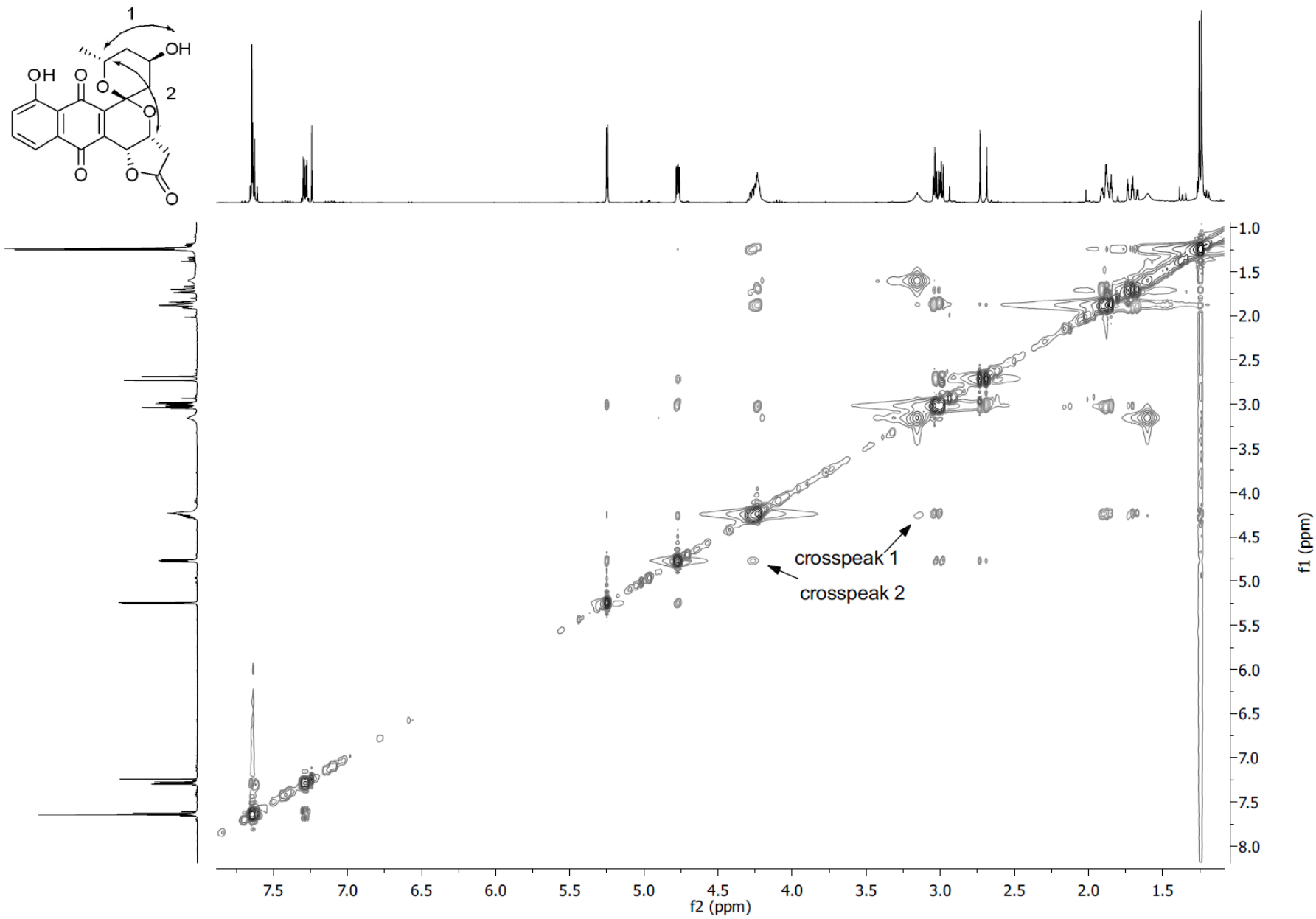



**Figure S68.** NOESY ($CDCl_3$, 400 MHz) of **16.**

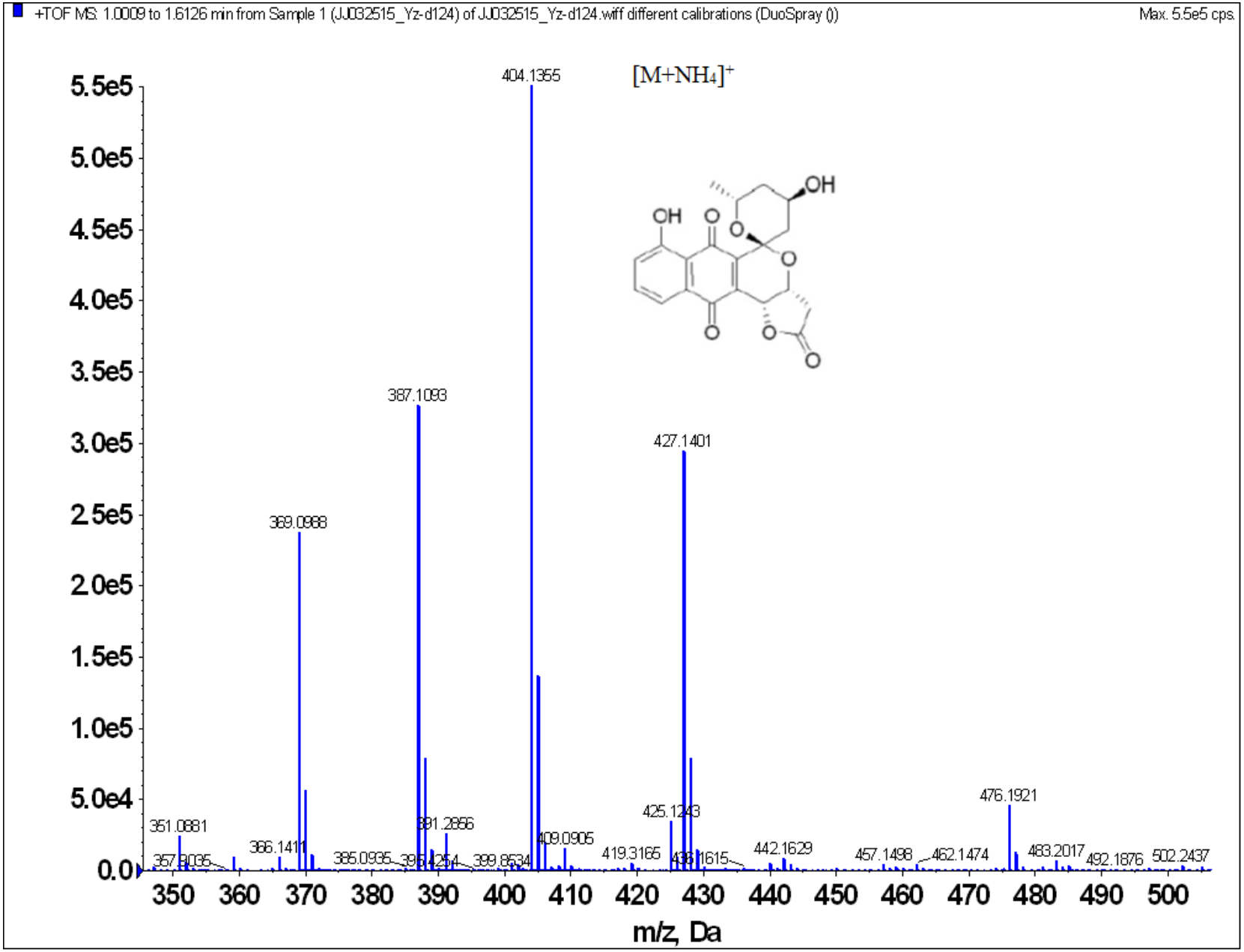



**Figure S69.** (+)-HRESI-MS of **16.**

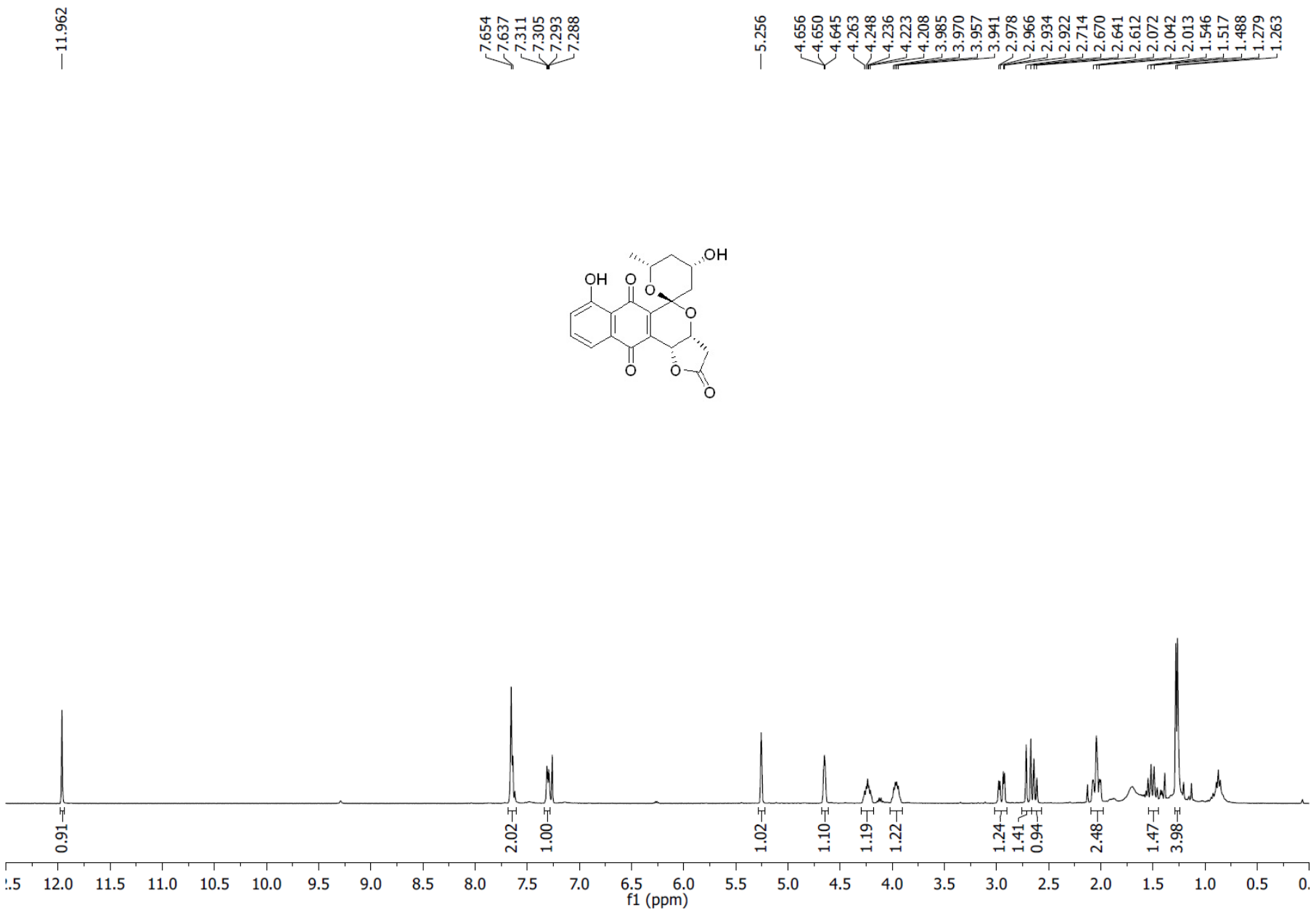



**Figure S70.** $^{1}$H-NMR ($CDCl_3$, 400 MHz) of **17.**

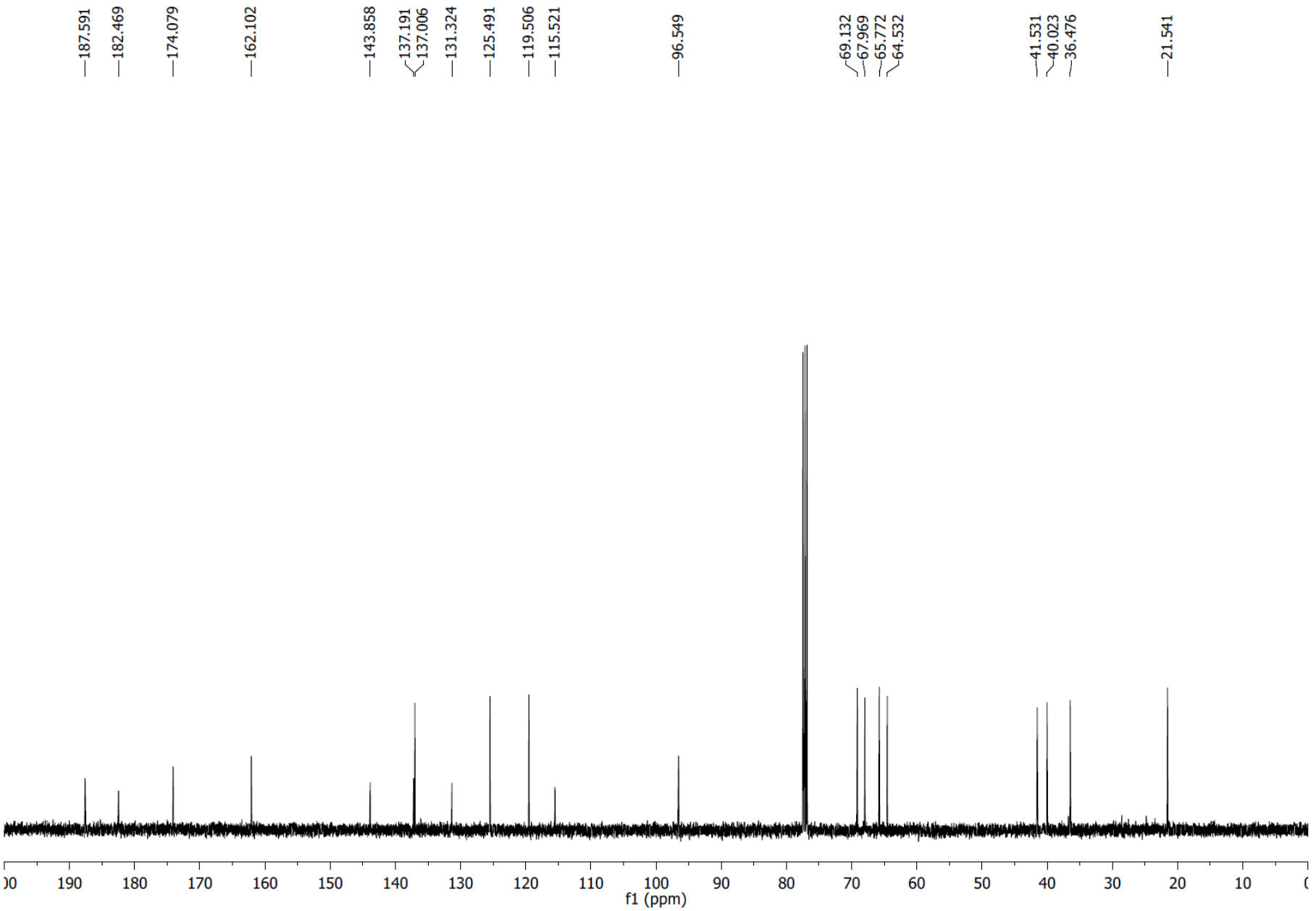



**Figure S71.** $^{13}$C-NMR ($CDCl_3$, 100 MHz) of **17.**

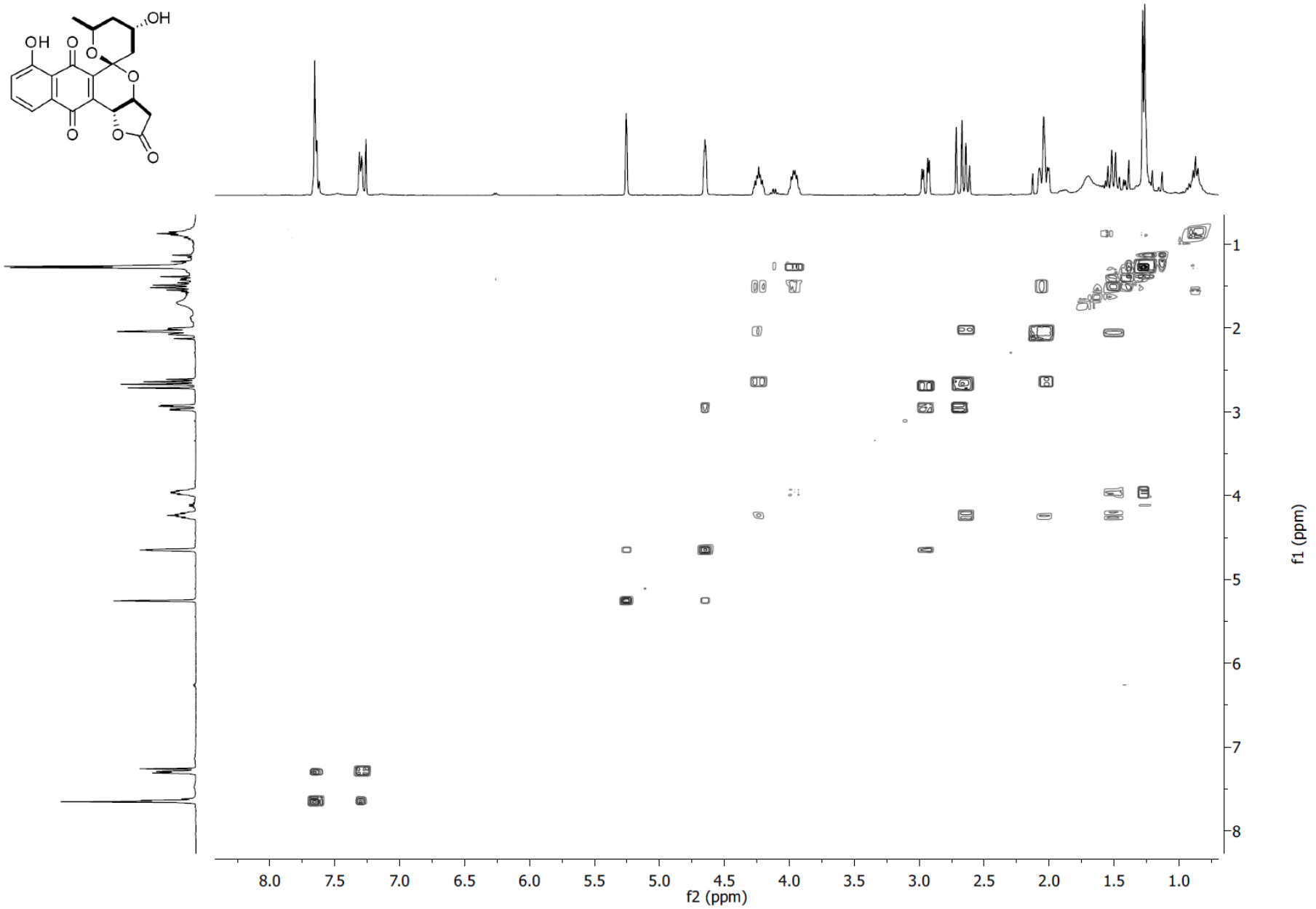



**Figure S72.** $^{1}$H-$^{1}$H COSY ($CDCl_3$, 400 MHz) of **17.**

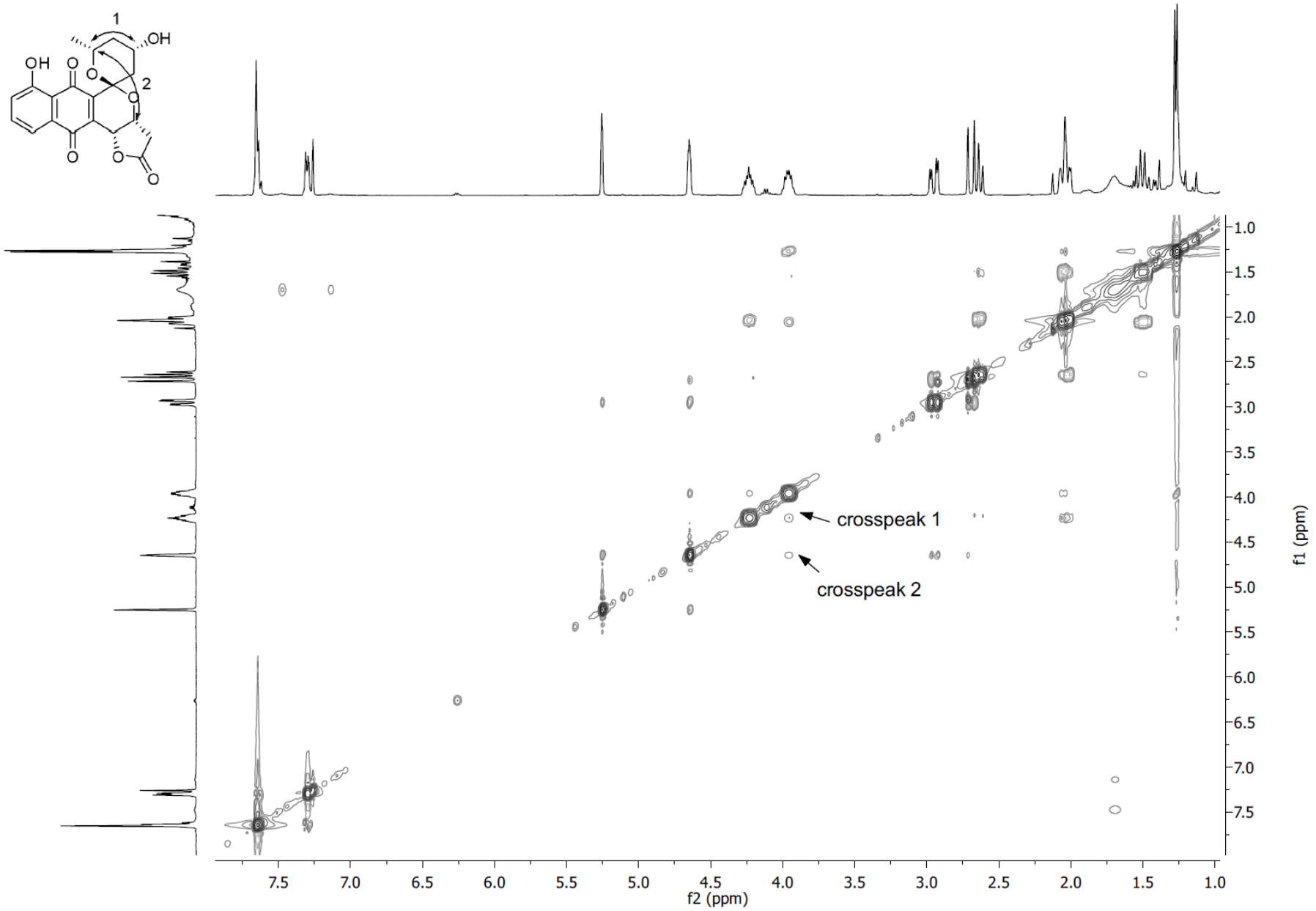



**Figure S73.** NOESY ($CDCl_3$, 400 MHz) of **17.**

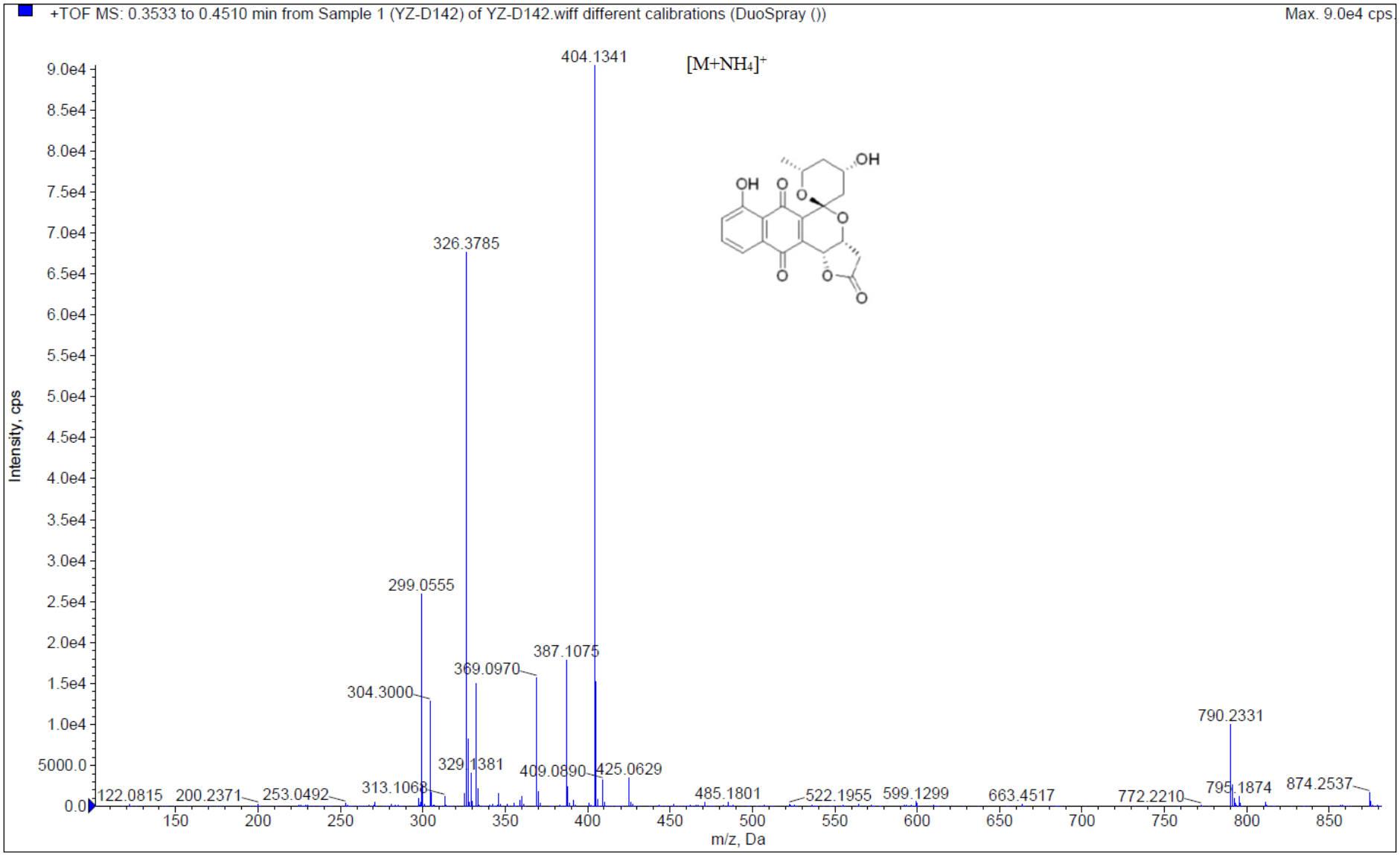



**Figure S74.** (+)-HRESI-MS of **17.**

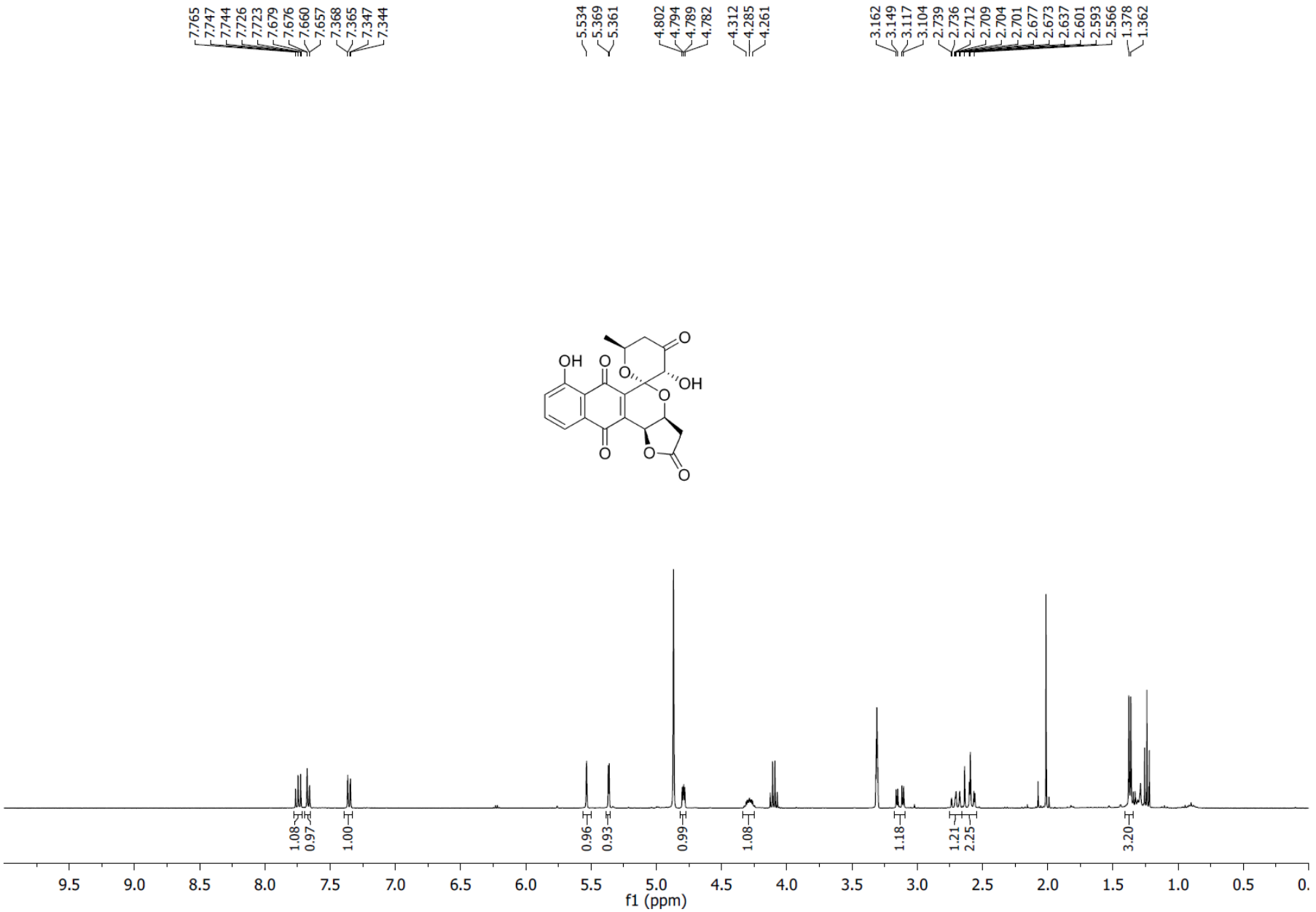



**Figure S75.** $^{1}$H-NMR ($CD_3OD$, 400 MHz) of **18.**

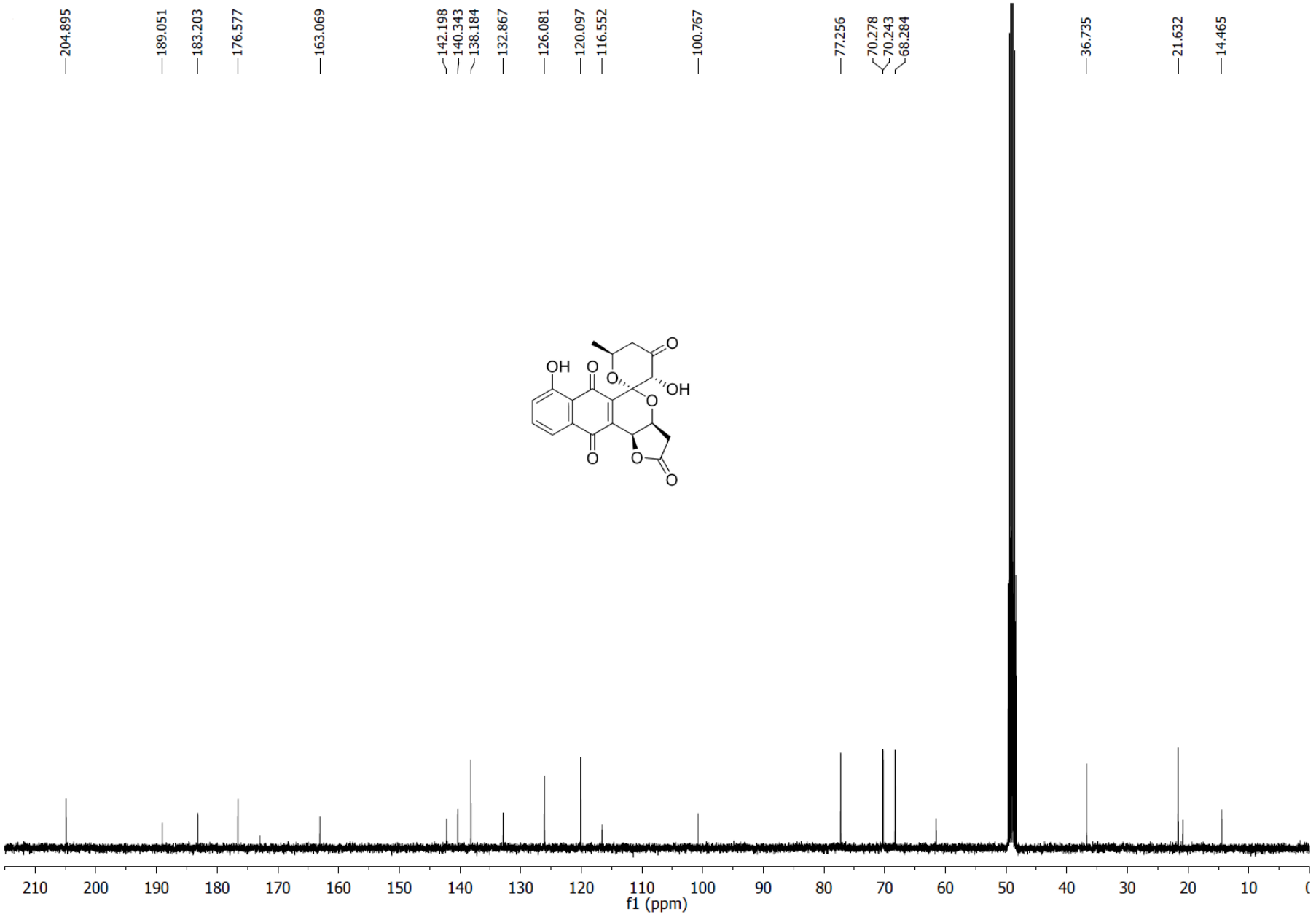



**Figure S76.** $^{13}$C-NMR ($CD_3OD$, 100 MHz) of **18.**

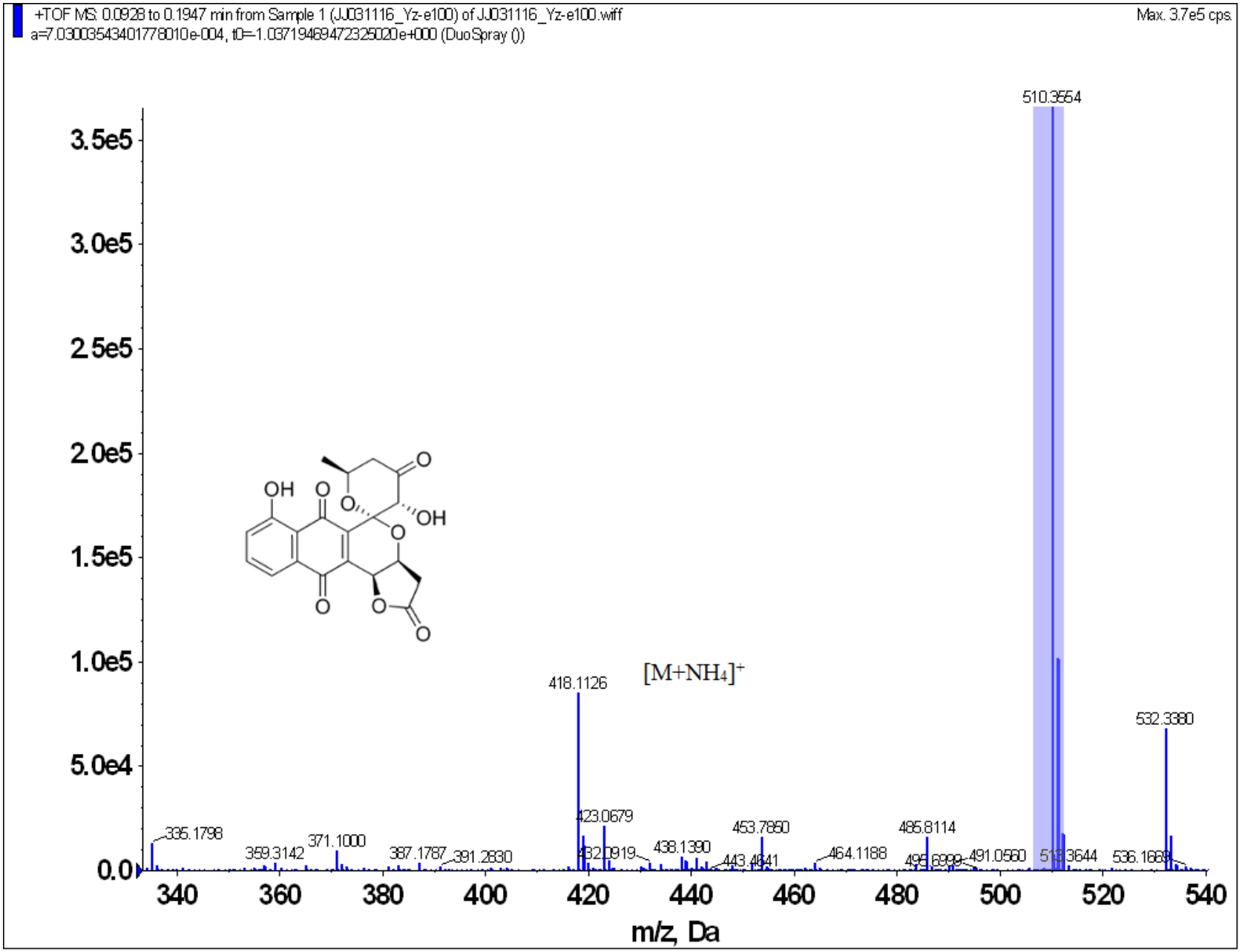



**Figure S77.** (+)-HRESI-MS of **18.**

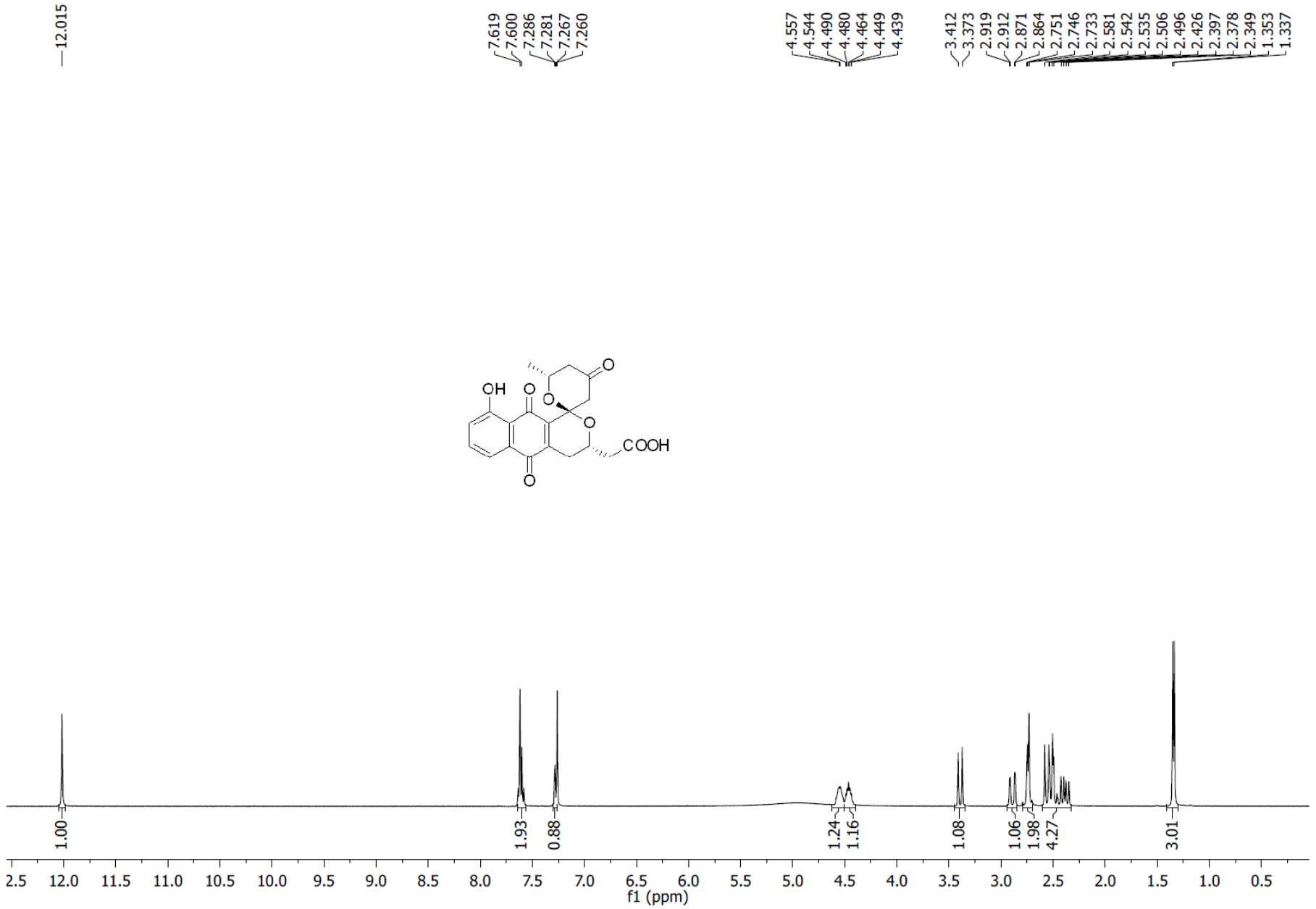



**Figure S78.** $^{1}$H-NMR ($CDCl_3$, 400 MHz) of **19.**

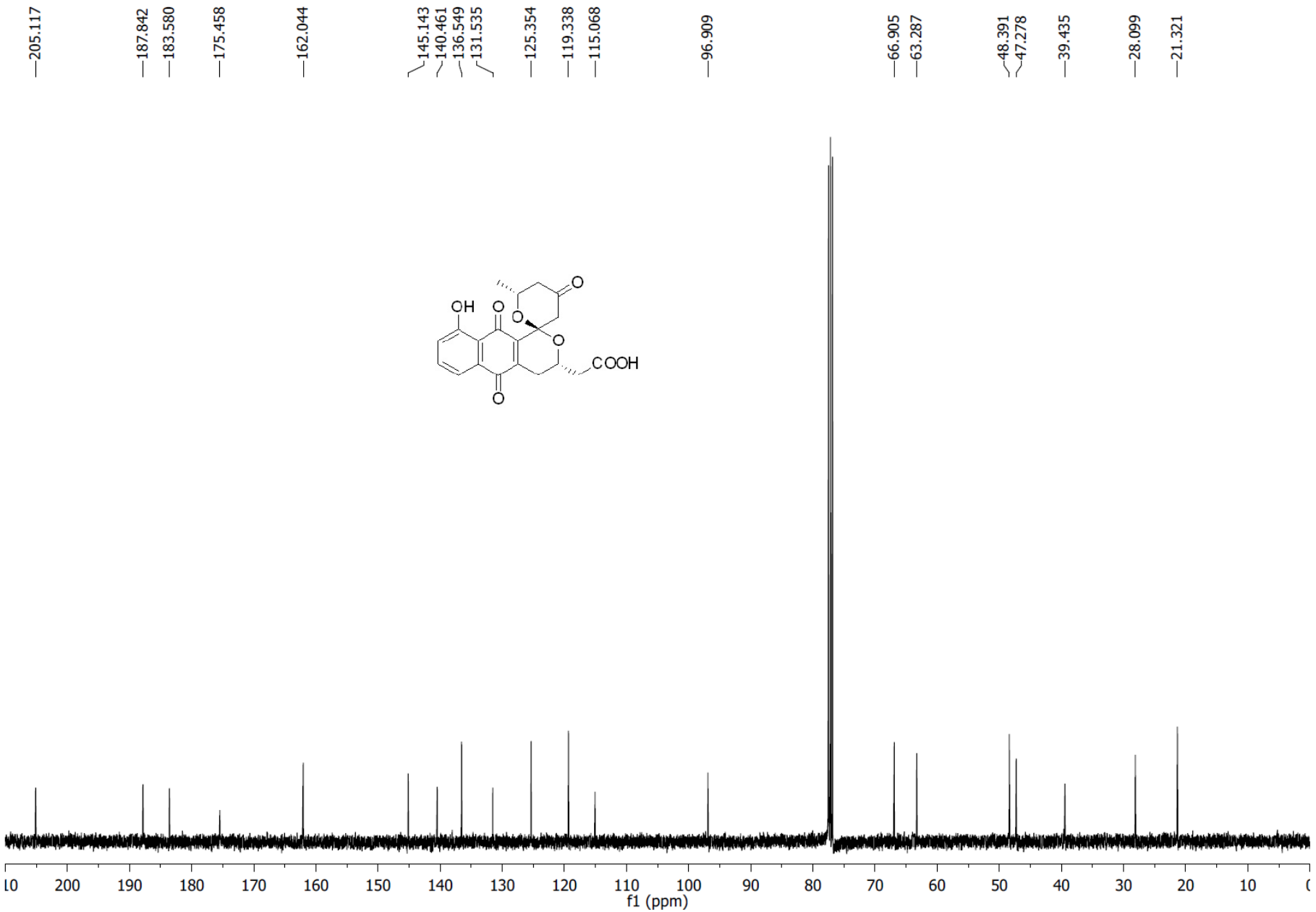



**Figure S79.** $^{13}$C-NMR ($CDCl_3$, 100 MHz) of **19.**

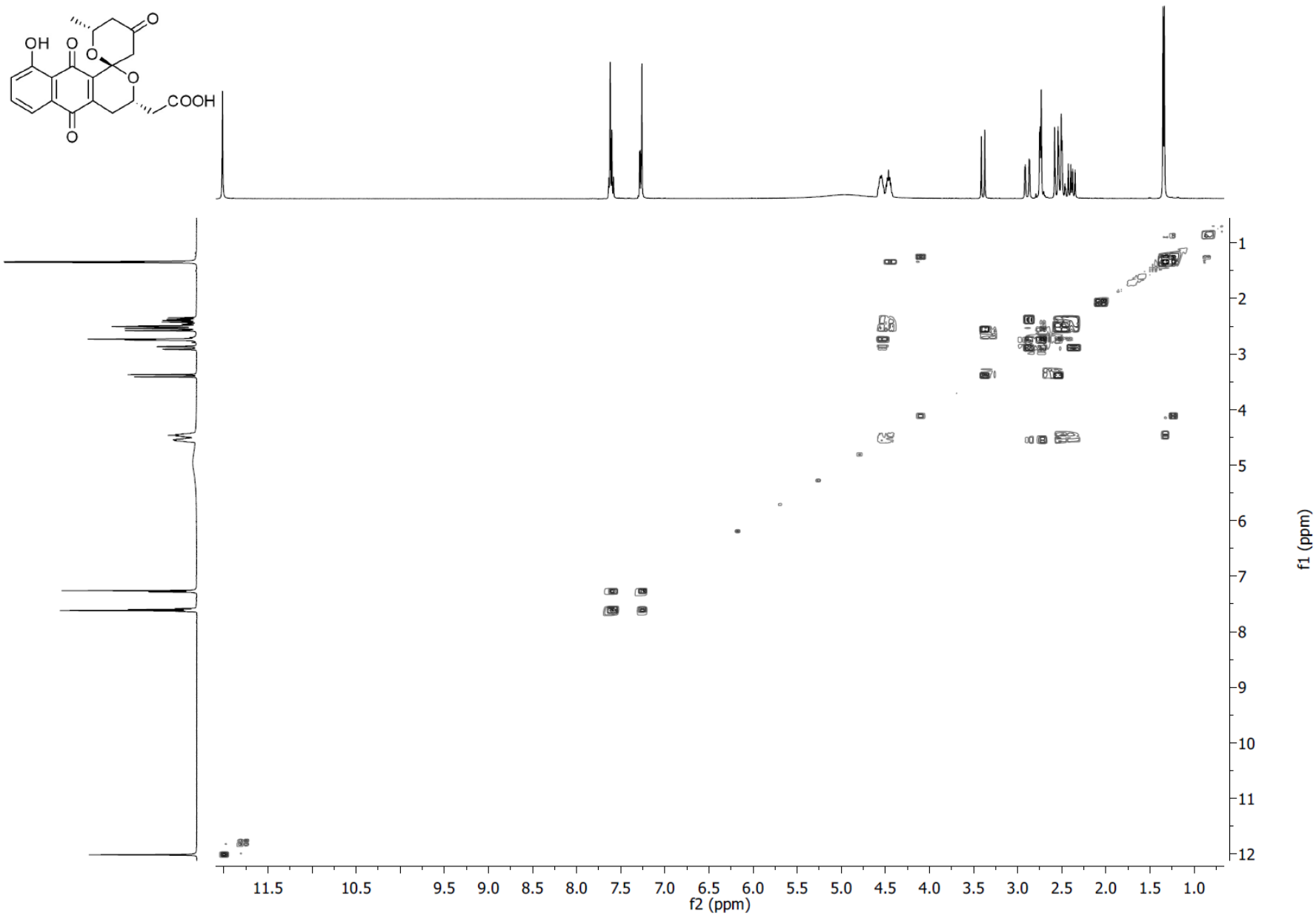



**Figure S80.** $^{1}$H-$^{1}$H COSY ($CDCl_3$, 400 MHz) of **19.**

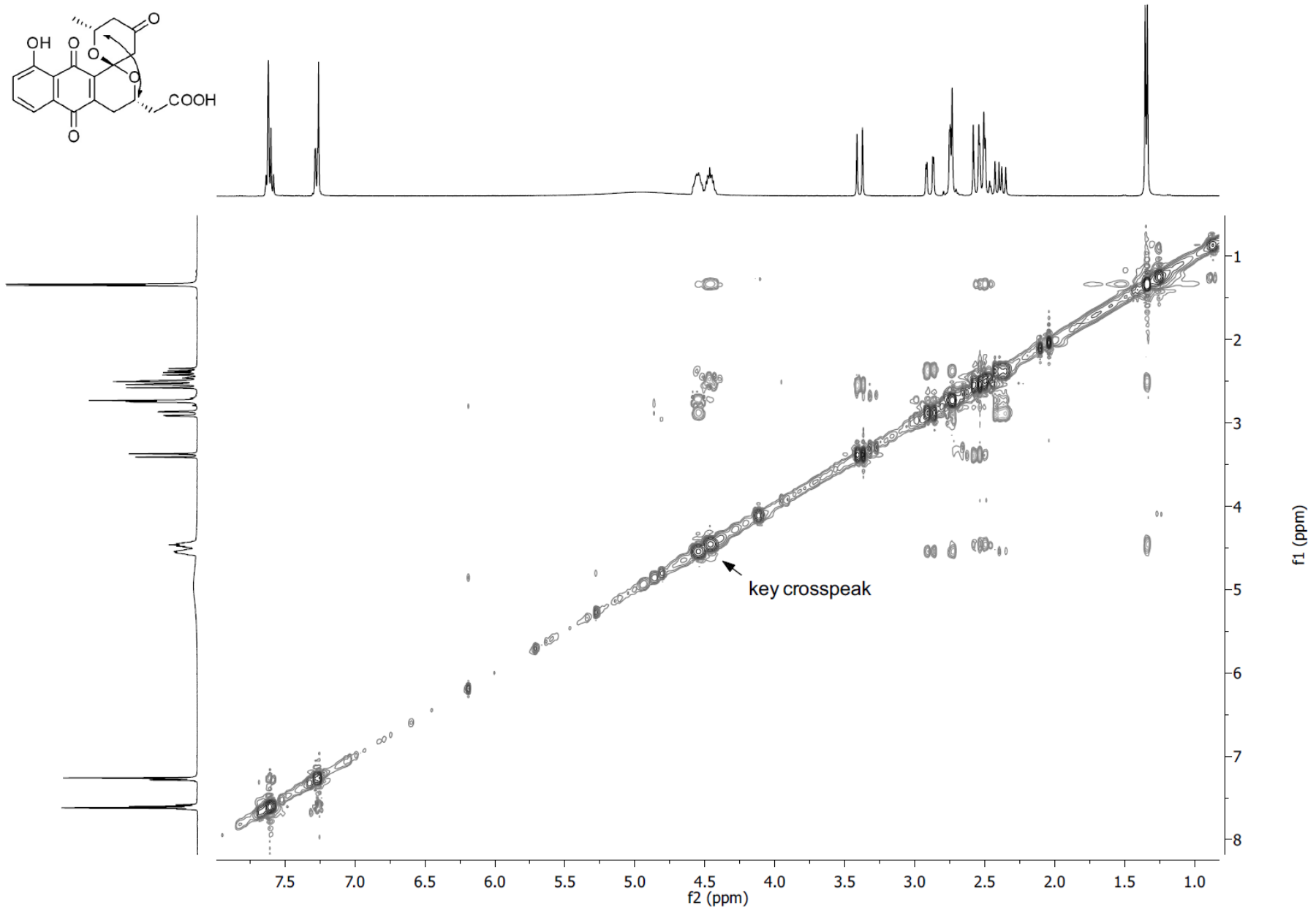



**Figure S81.** NOESY ($CDCl_3$, 400 MHz) of **19.**

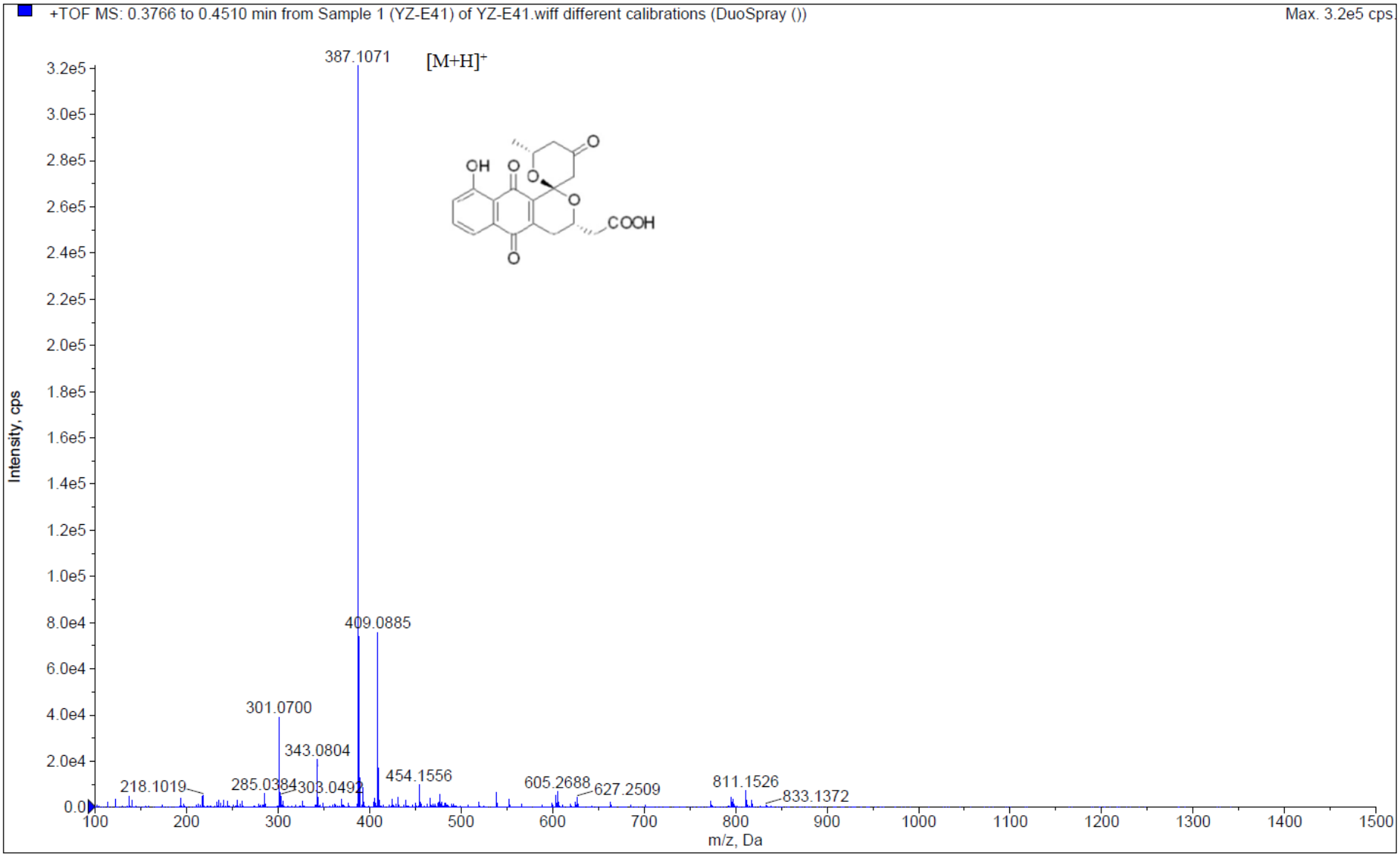



**Figure S82.** (+)-HRESI-MS of **19.**

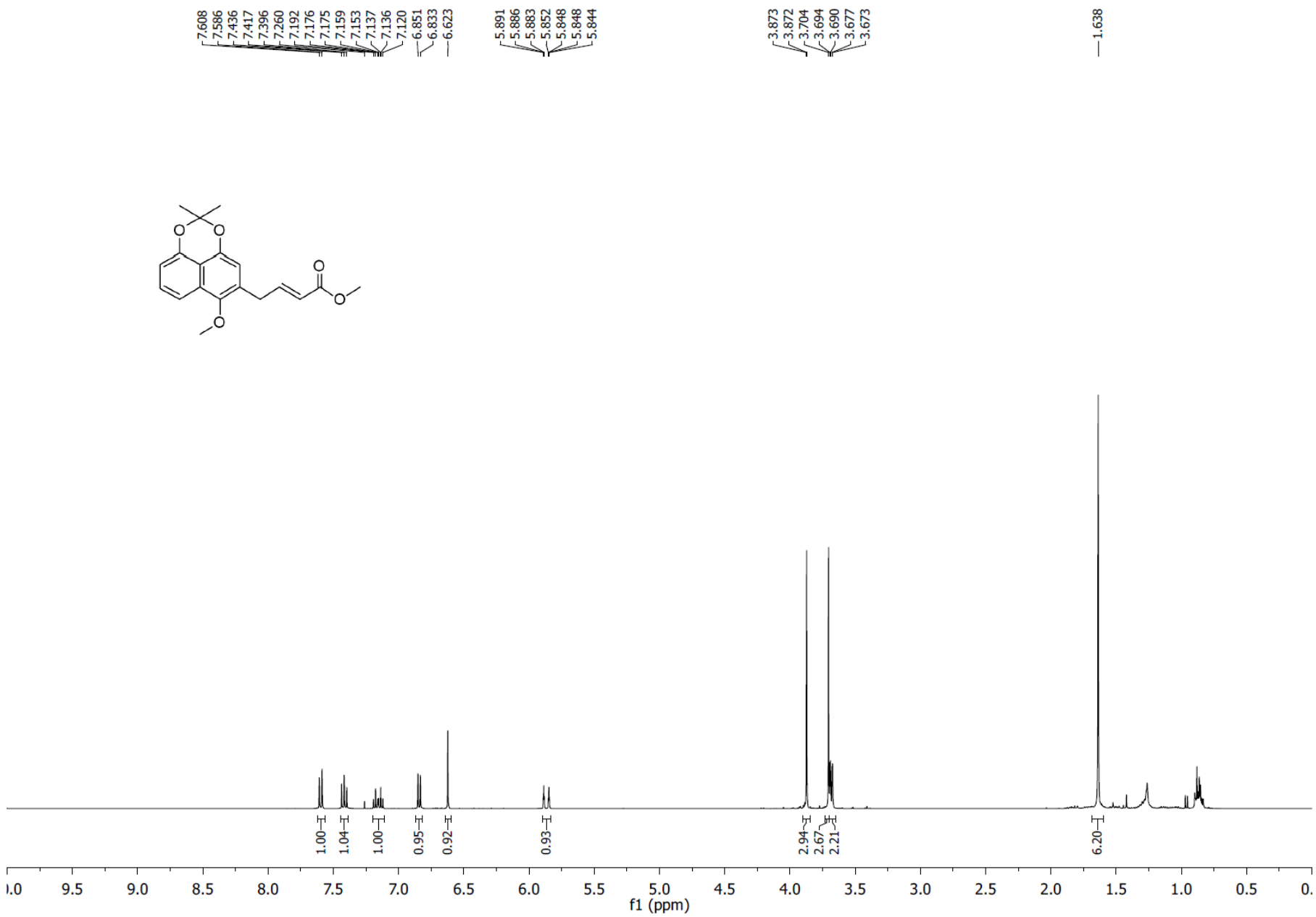



**Figure S83.** $^{1}$H-NMR ($CDCl_3$, 400 MHz) of **27.**

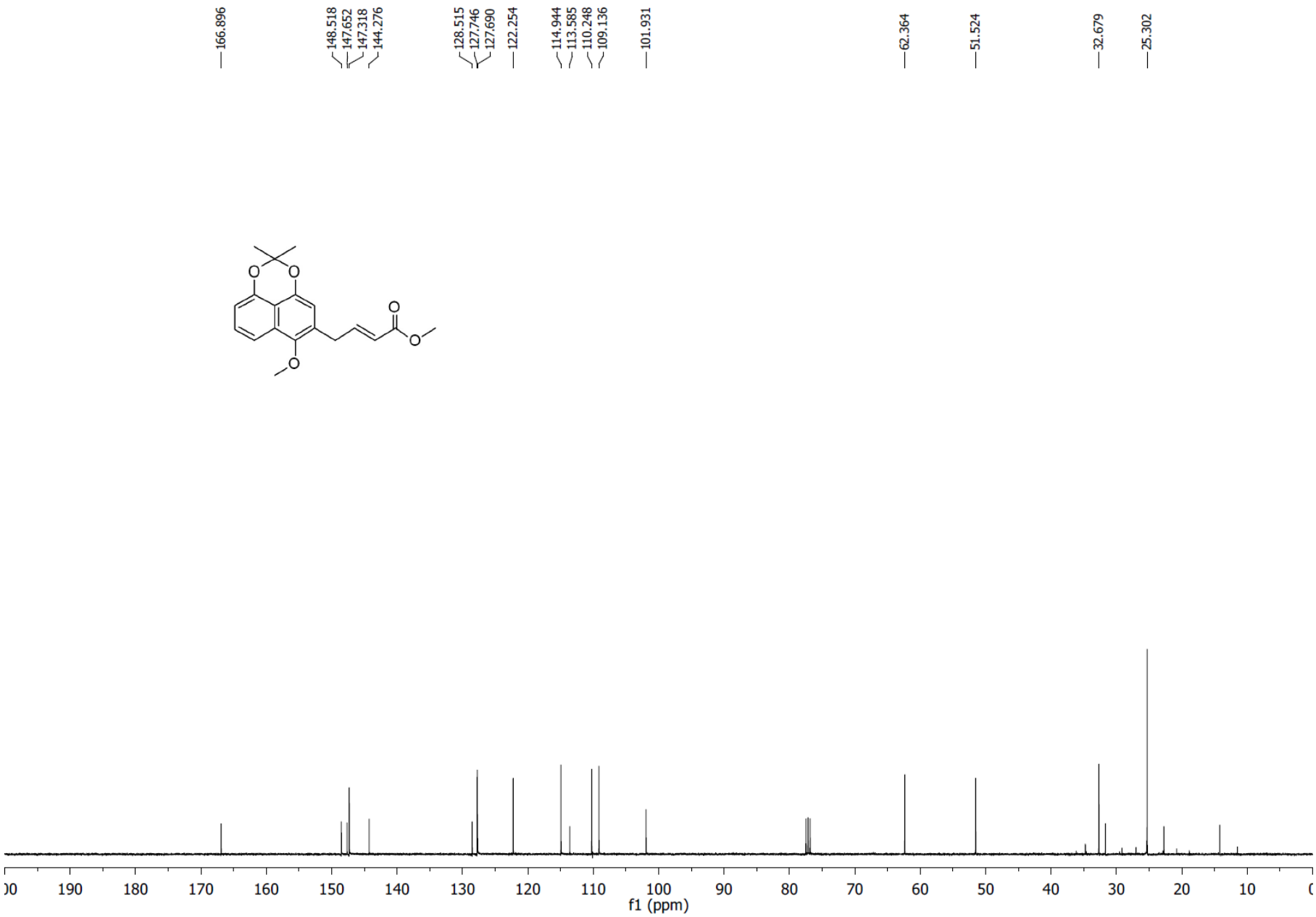



**Figure S84.** $^{13}$C-NMR ($CDCl_3$, 100 MHz) of **27.**

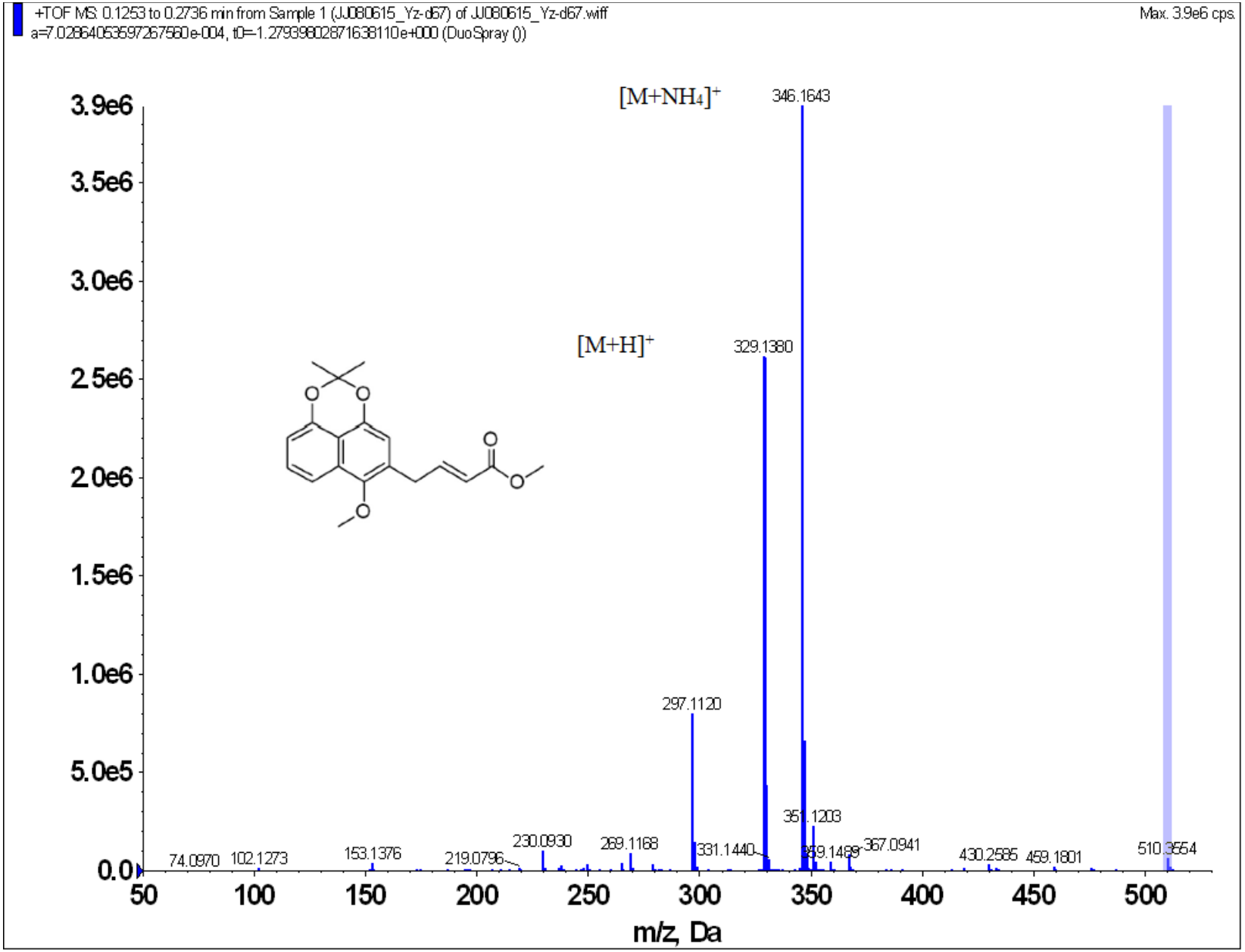



**Figure S85.** (+)-HRESI-MS of **27.**

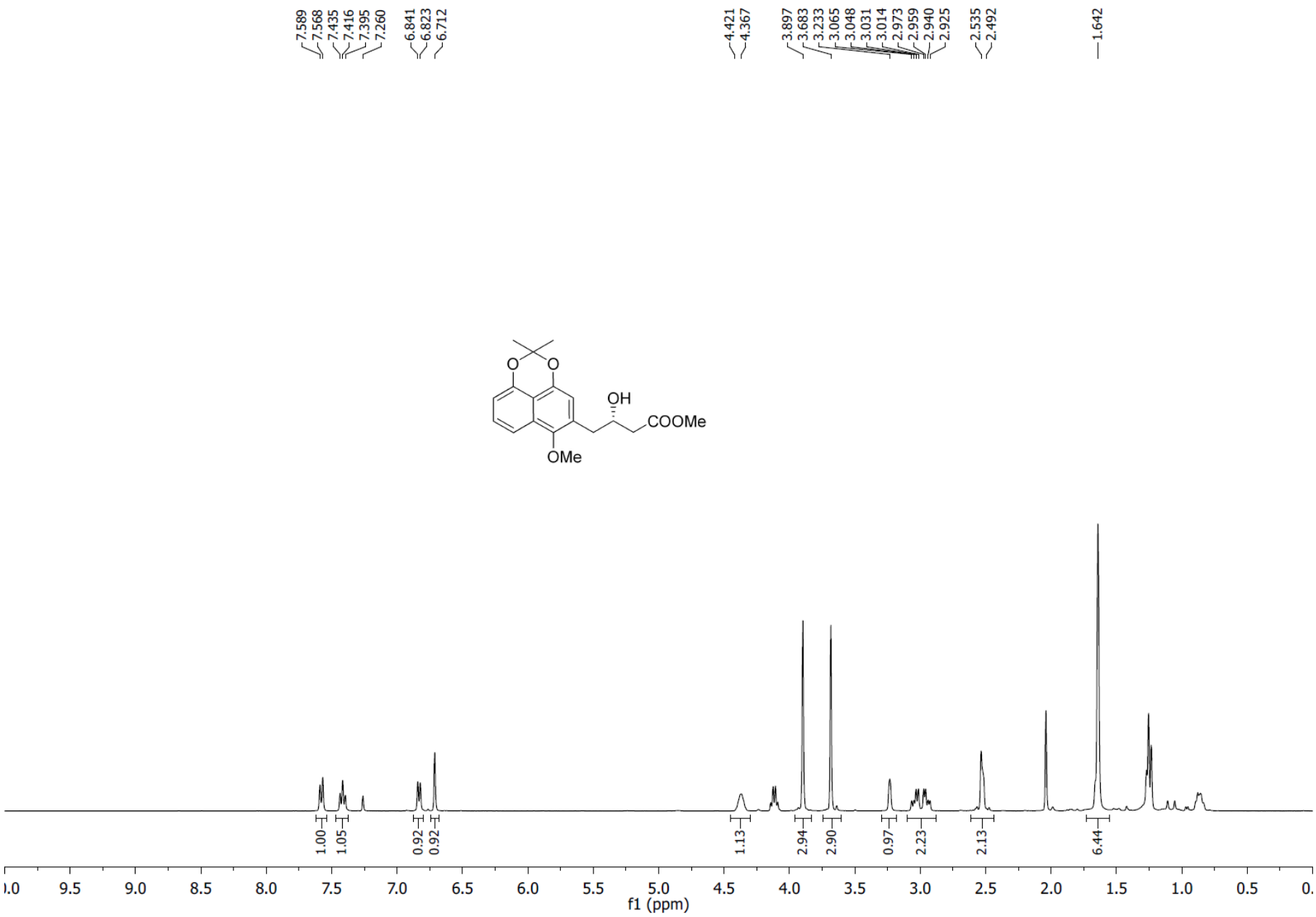



**Figure S86.** $^{1}$H-NMR ($CDCl_3$, 400 MHz) of **28.**

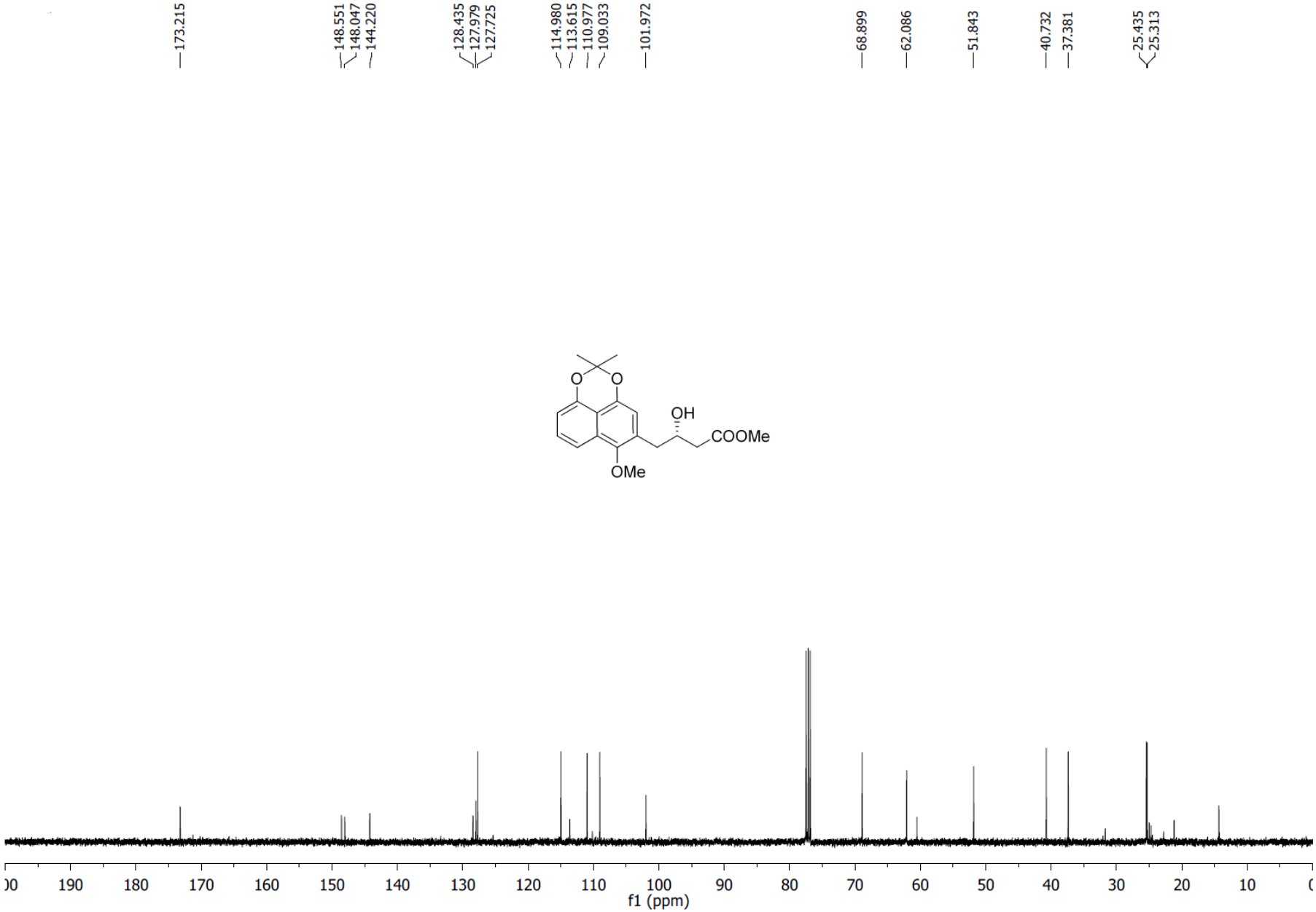



**Figure S87.** $^{13}$C-NMR ($CDCl_3$, 100 MHz) of **28.**

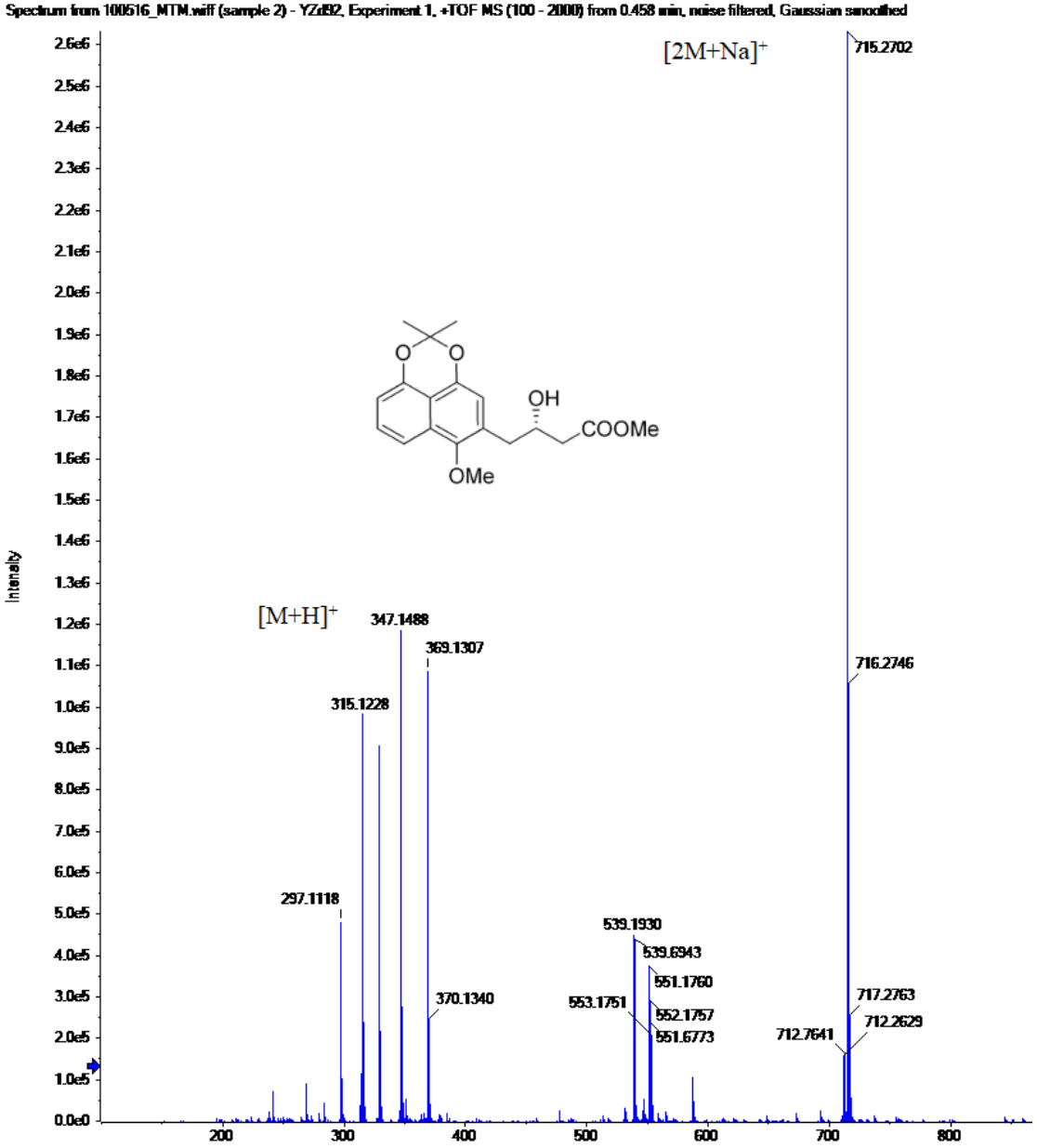



**Figure S88.** (+)-HRESI-MS of **28.**

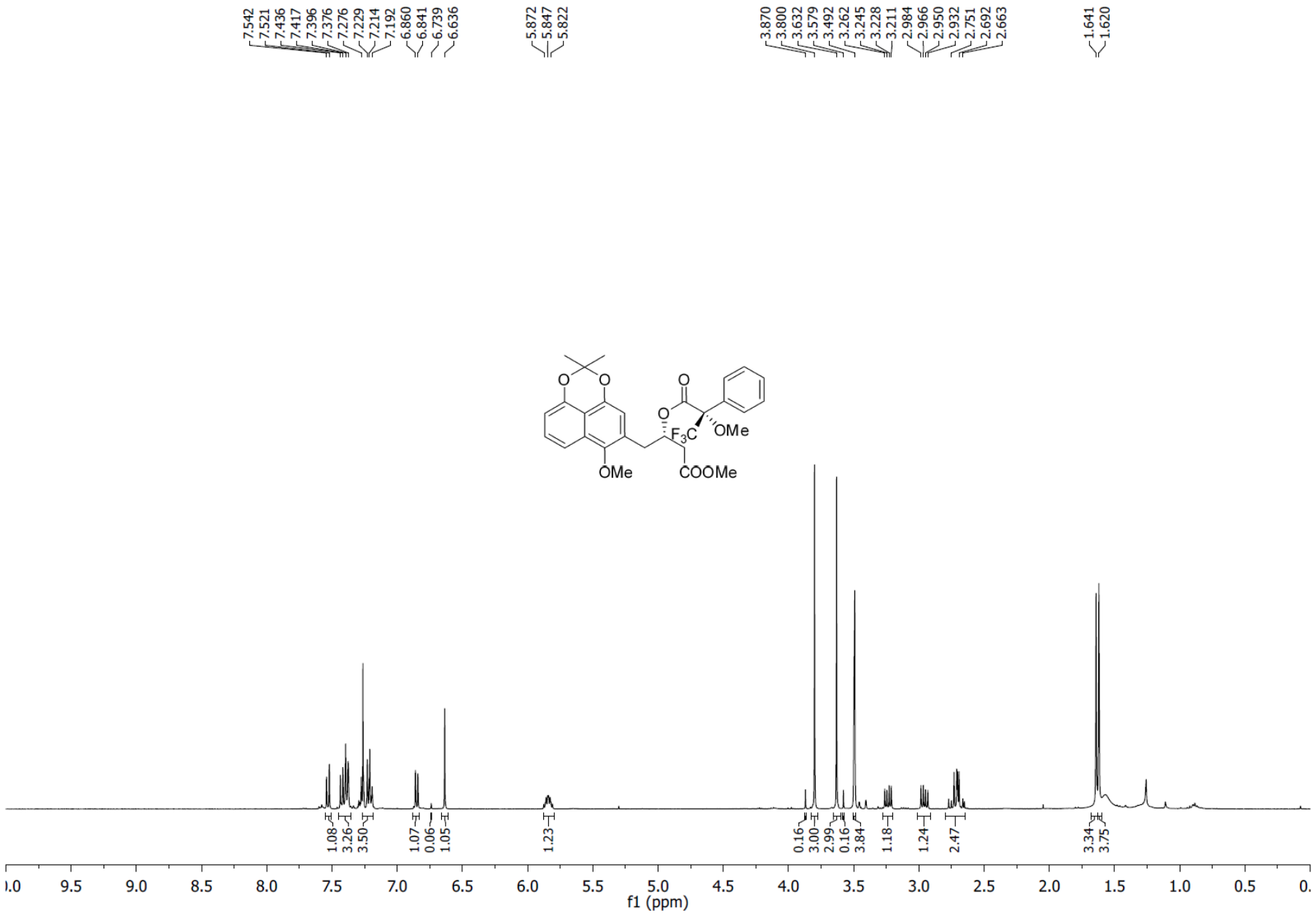



**Figure S89.** $^{1}$H-NMR ($CDCl_3$, 400 MHz) of **28-MTPA.**

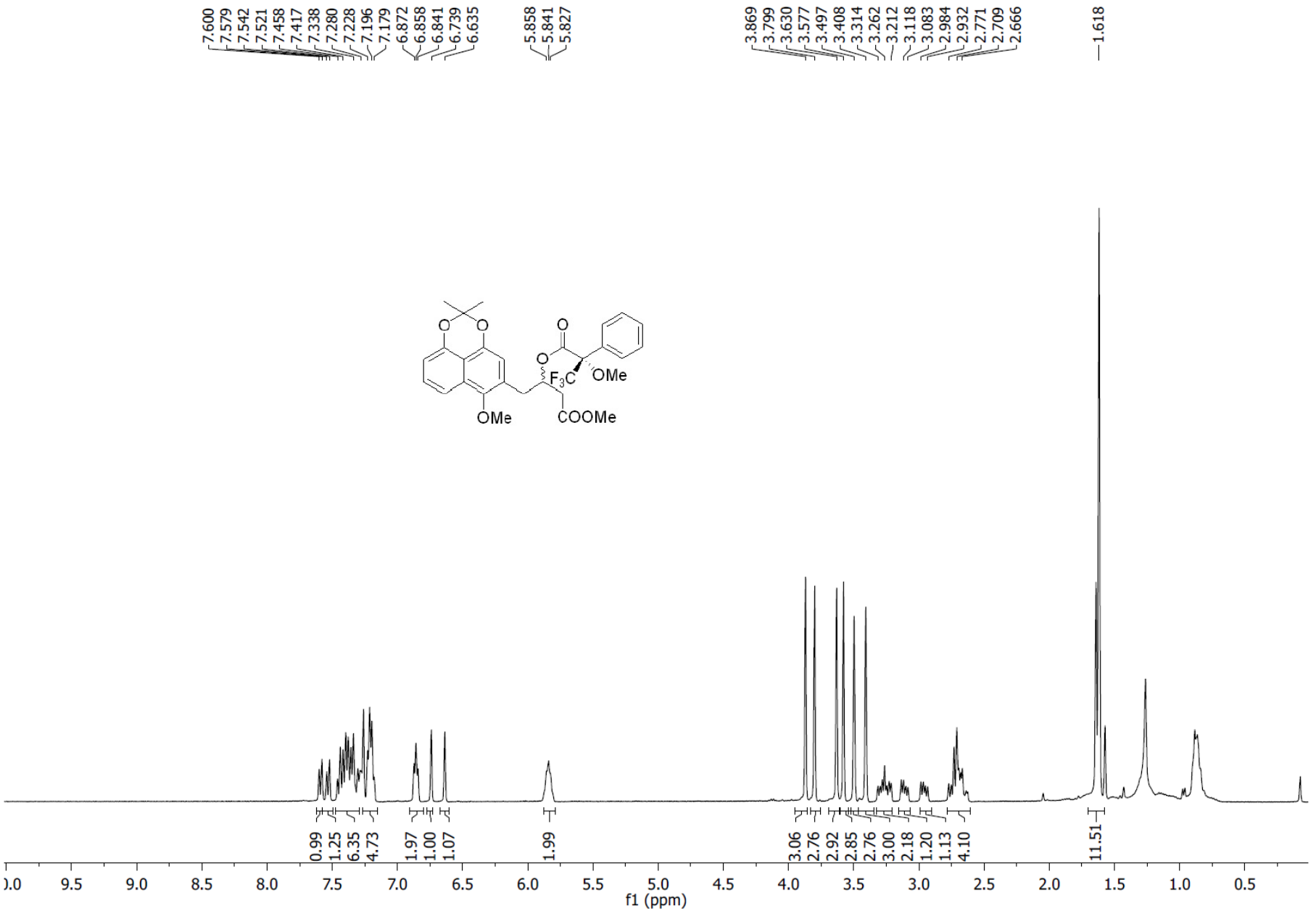



**Figure S90.** $^{1}$H-NMR ($CDCl_3$, 400 MHz) of **rac-28-MTPA.**

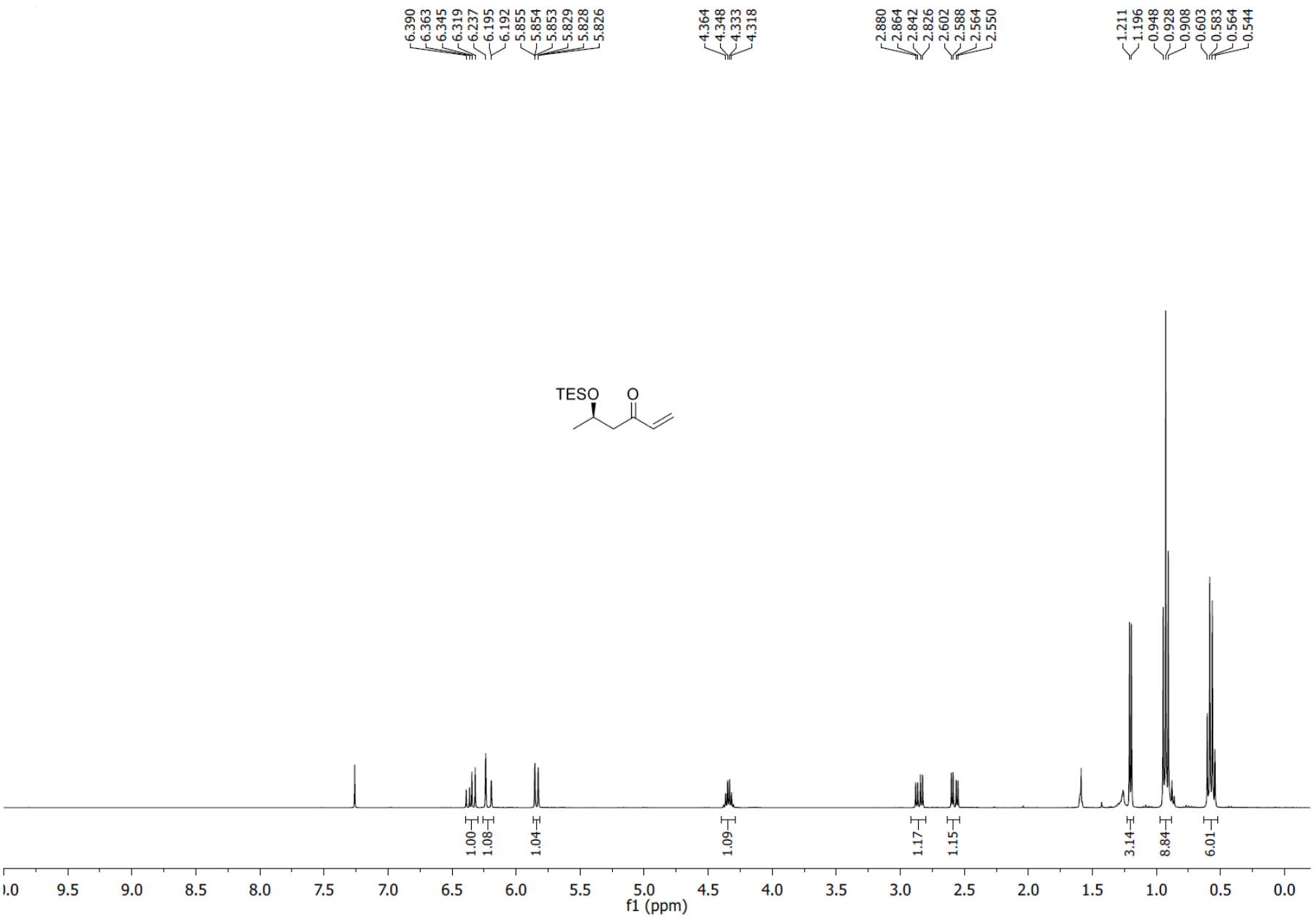



**Figure S91.** $^{1}$H-NMR ($CDCl_3$, 400 MHz) of **29*R*.**

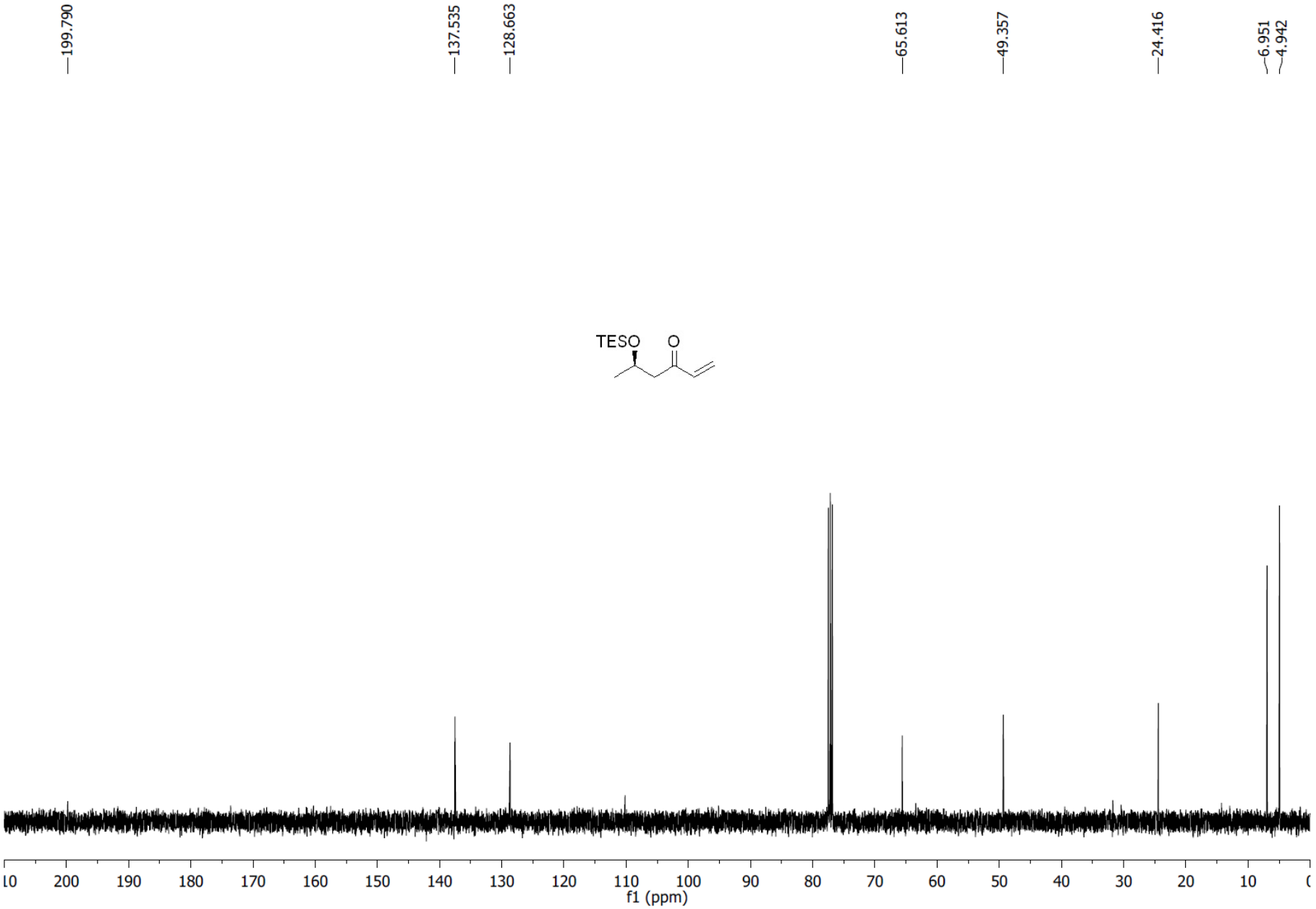



**Figure S92.** $^{13}$C-NMR ($CDCl_3$, 100 MHz) of **29*R*.**

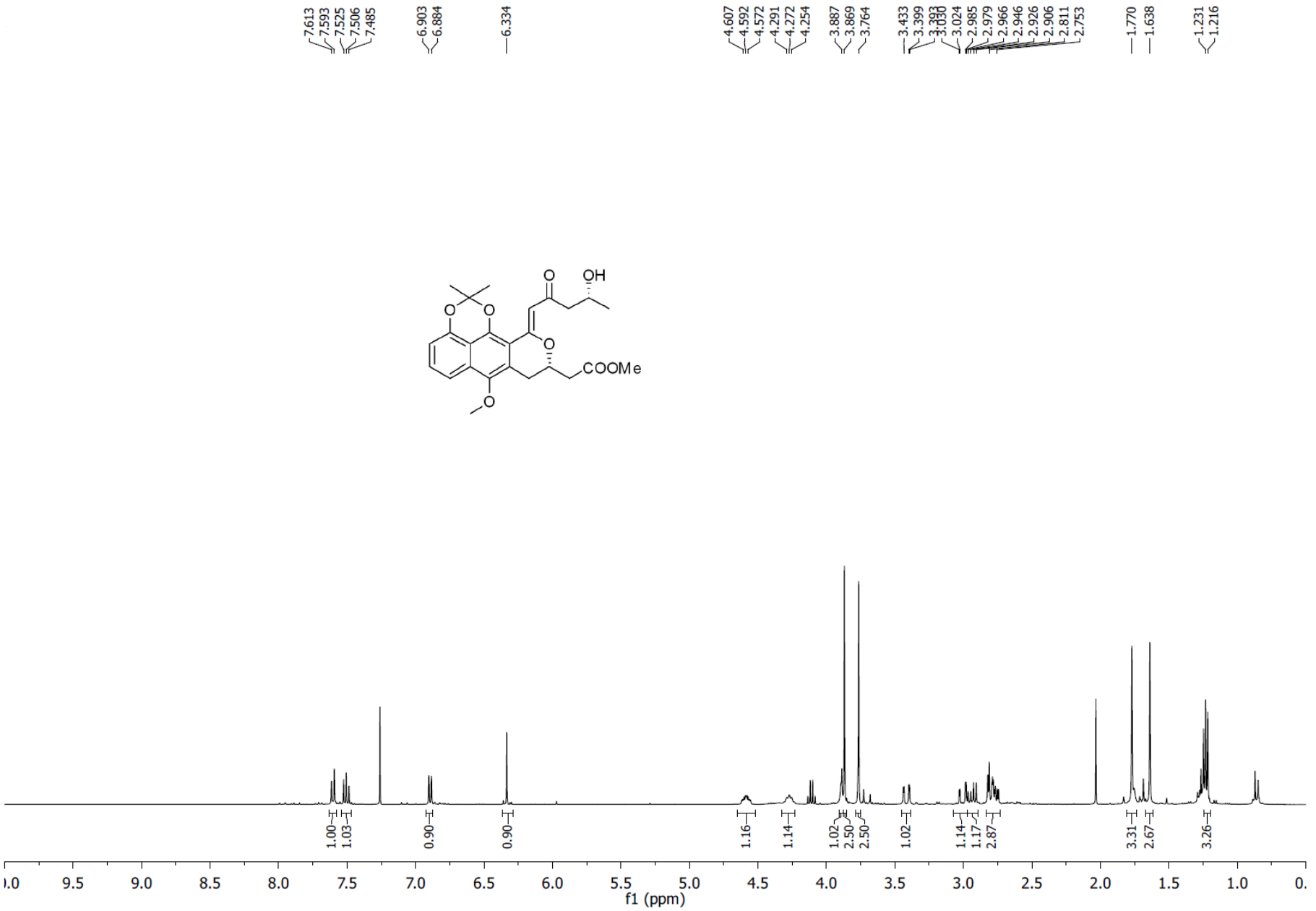



**Figure S93.** $^{1}$H-NMR ($CDCl_3$, 400 MHz) of **30-int.**

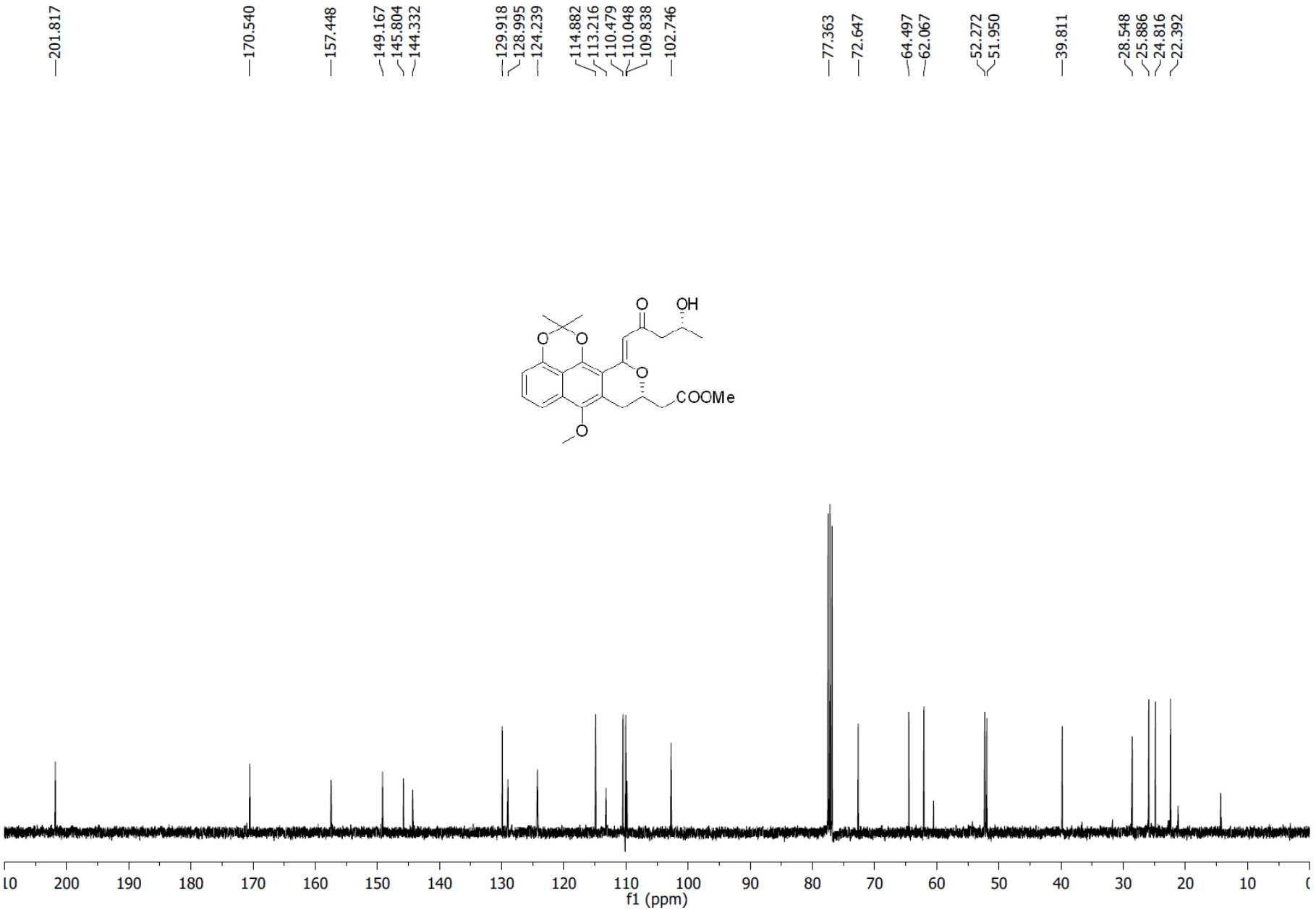



**Figure S94.** $^{13}$C-NMR ($CDCl_3$, 100 MHz) of **30-int.**

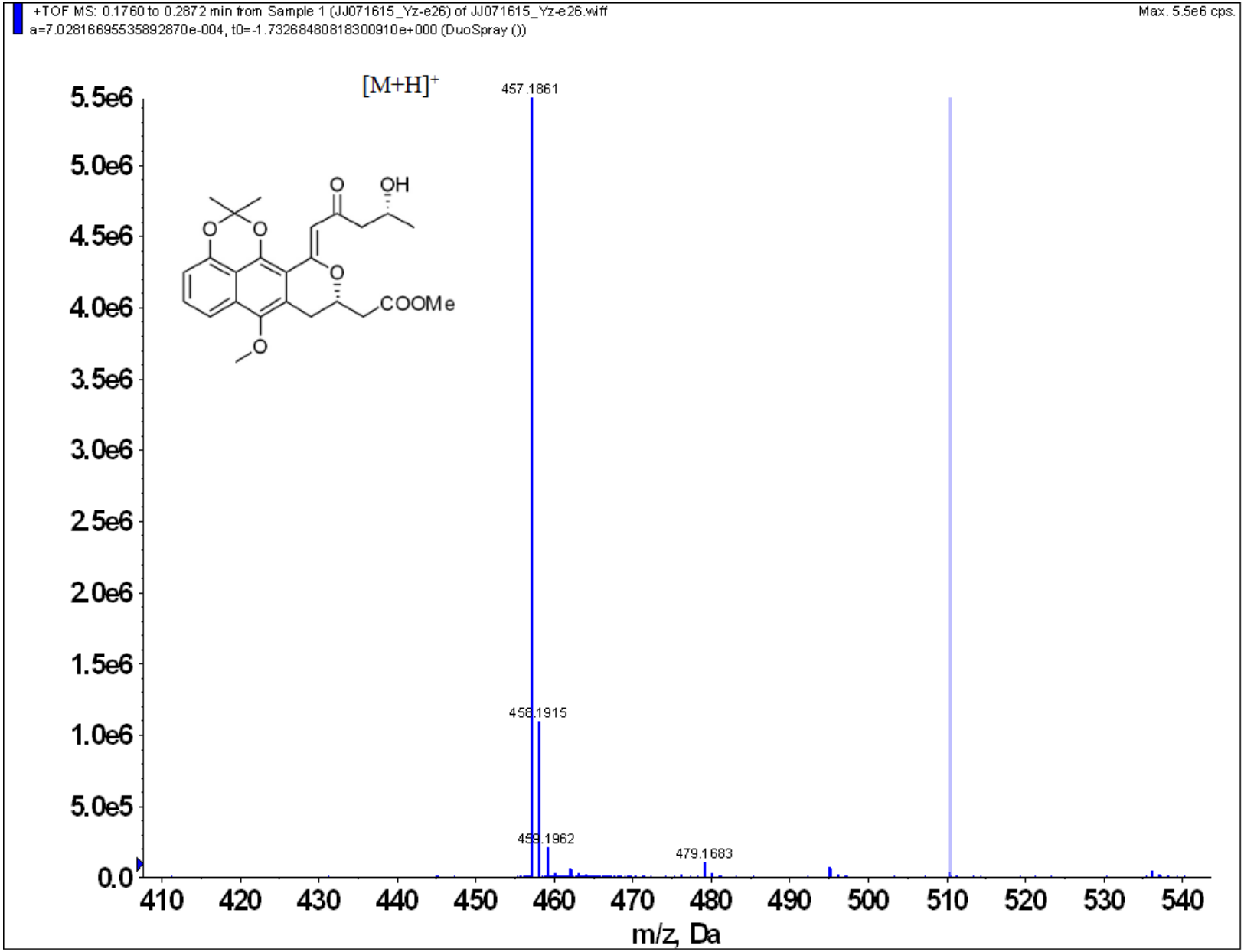



**Figure S95.** (+)-HRESI-MS of **30-int.**

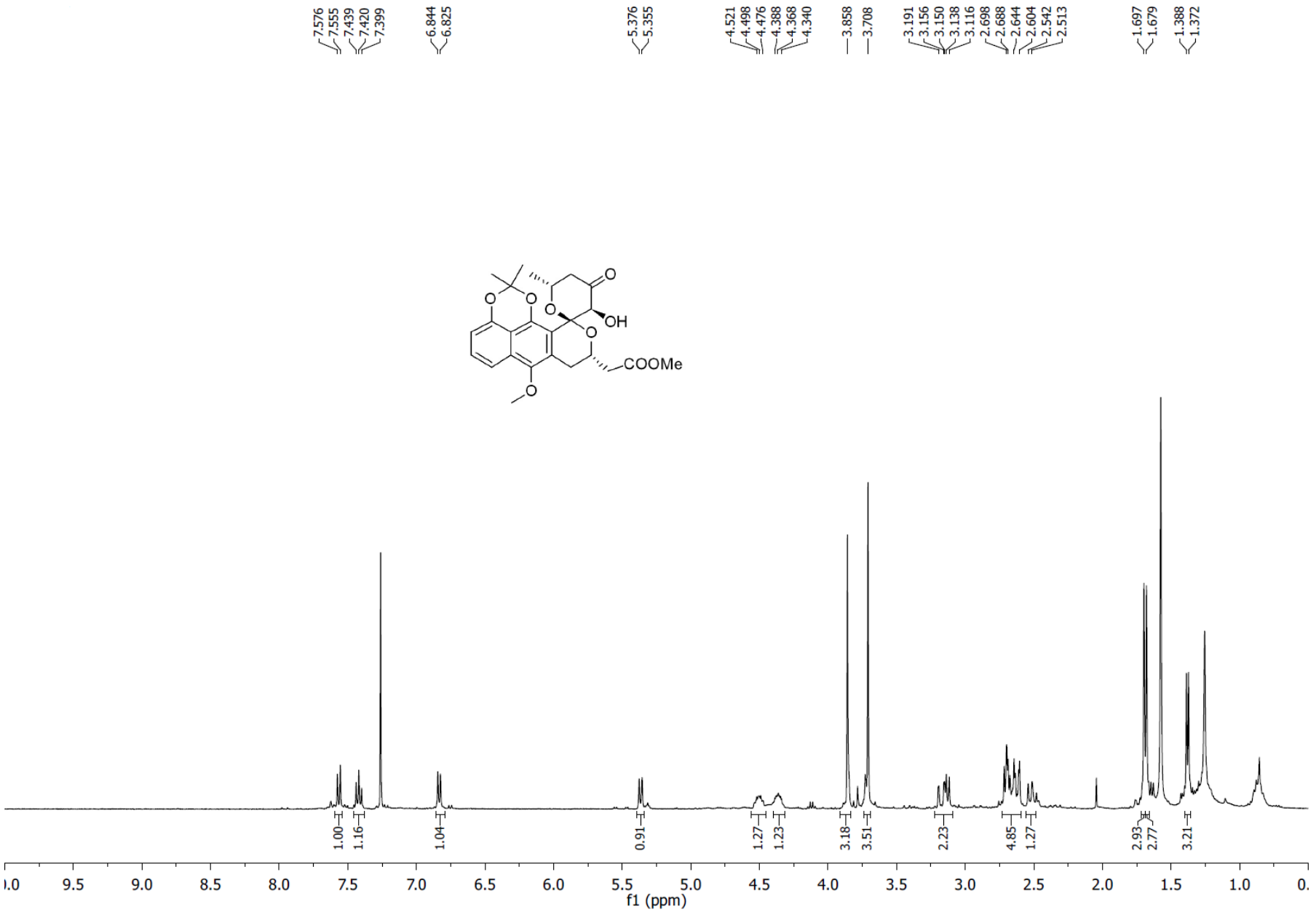



**Figure S96.** $^{1}$H-NMR ($CDCl_3$, 400 MHz) of **30.**

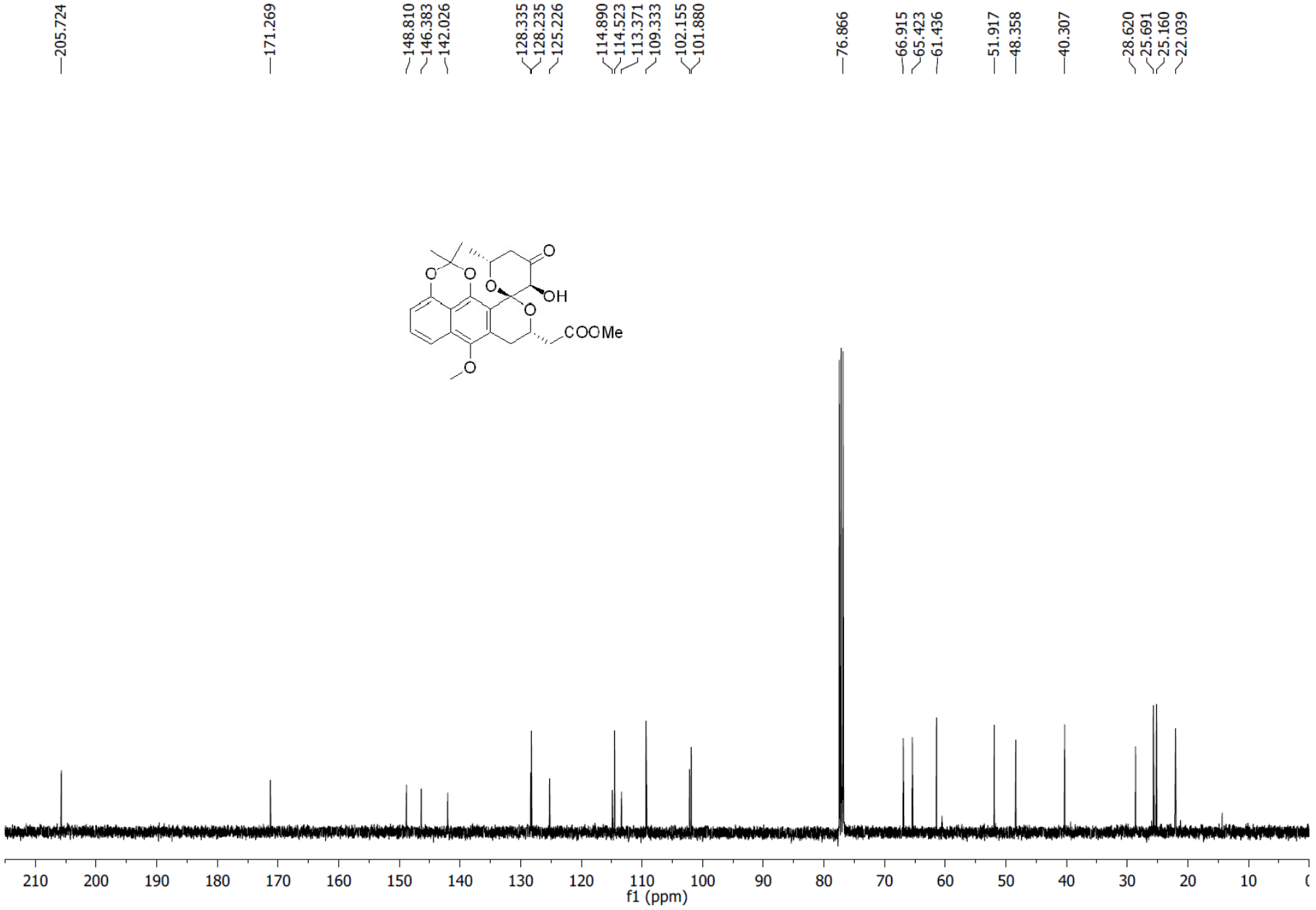



**Figure S97.** $^{13}$C-NMR ($CDCl_3$, 100 MHz) of **30.**

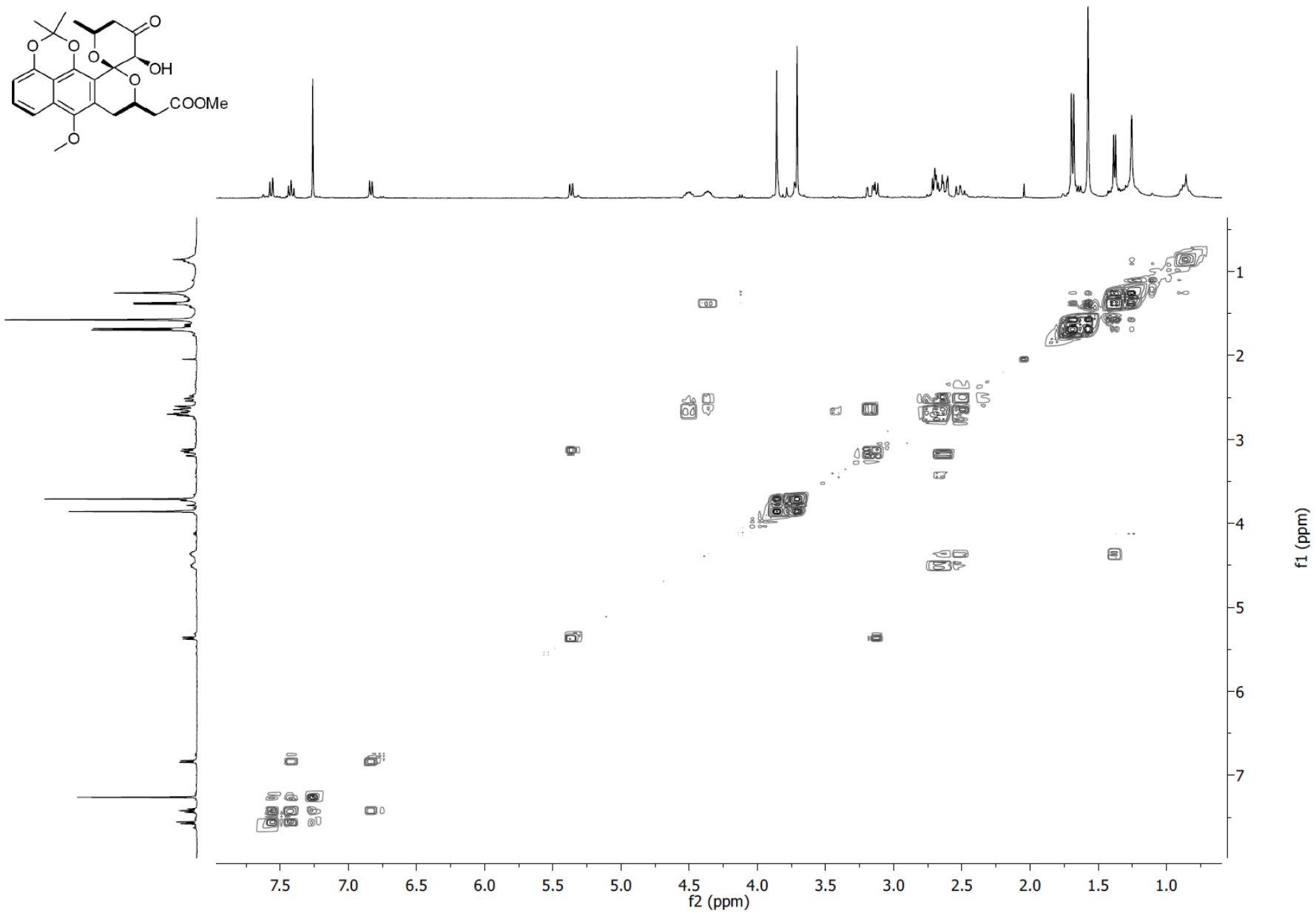



**Figure S98.** $^{1}$H-$^{1}$H COSY ($CDCl_3$, 400 MHz) of **30.**

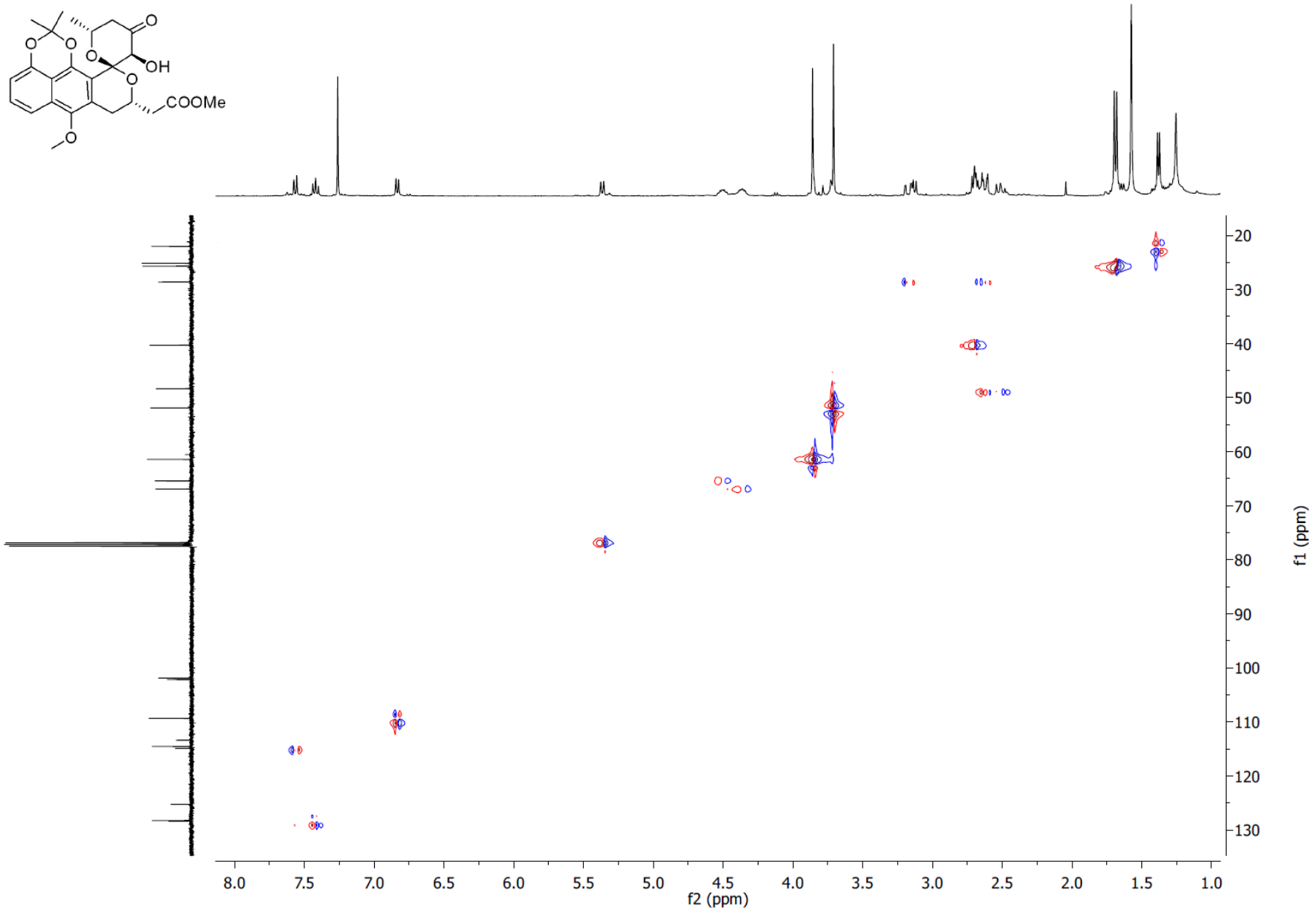



**Figure S99.** HSQC ($CDCl_3$, 400 MHz) of **30.**

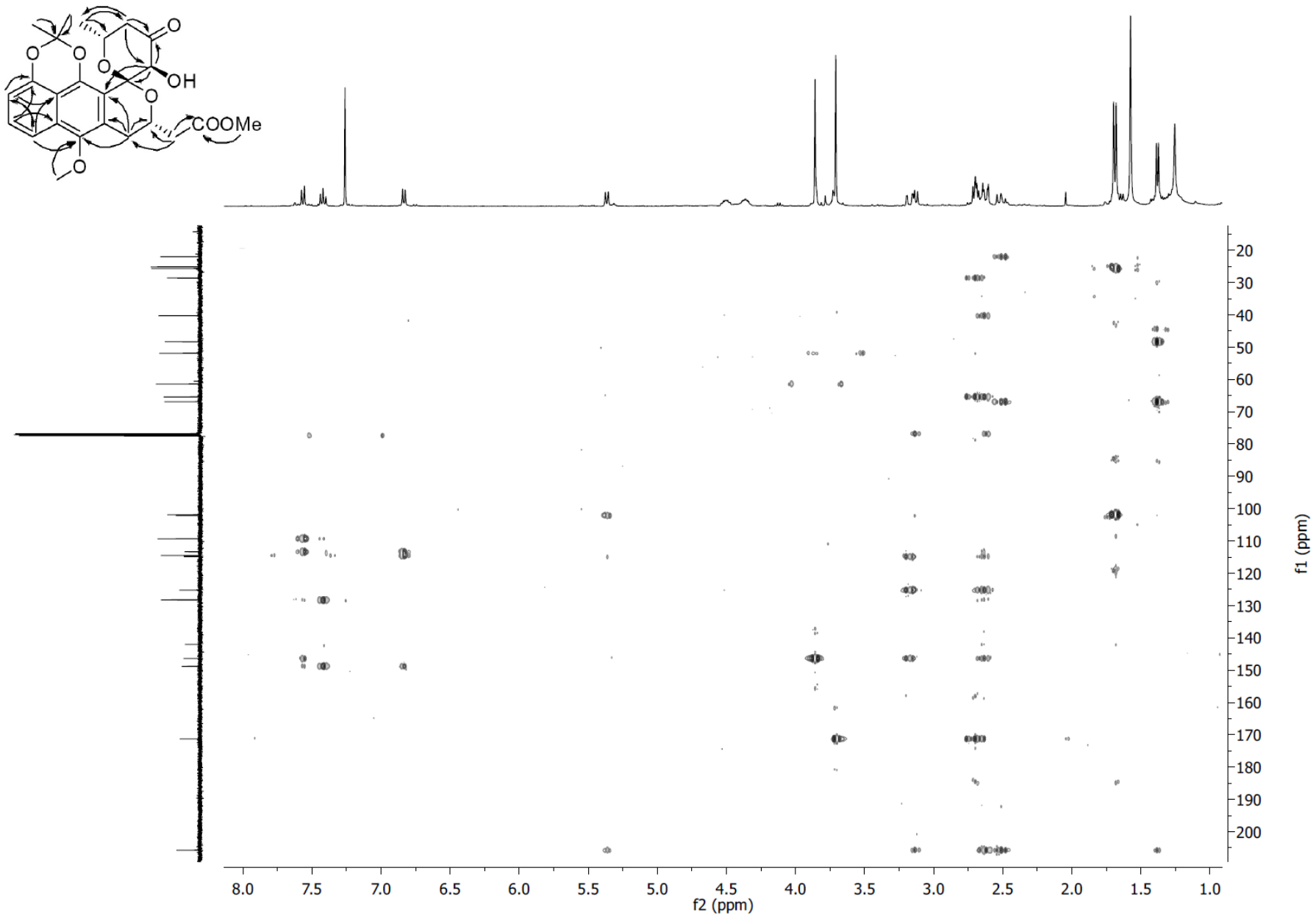



**Figure S100.** HMBC ($CDCl_3$, 400 MHz) of **30.**

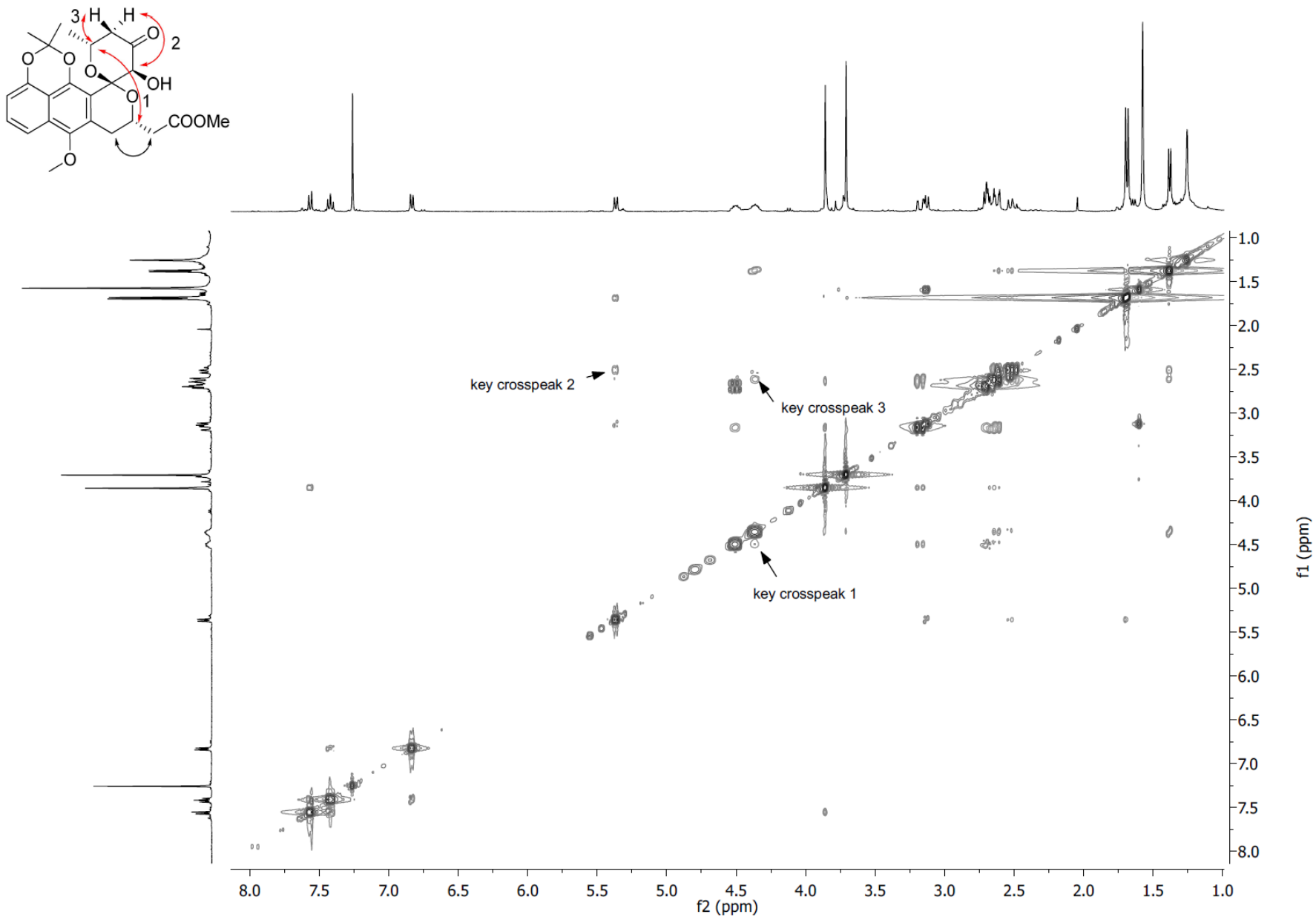



**Figure S101.** NOESY ($CDCl_3$, 400 MHz) of **30.**

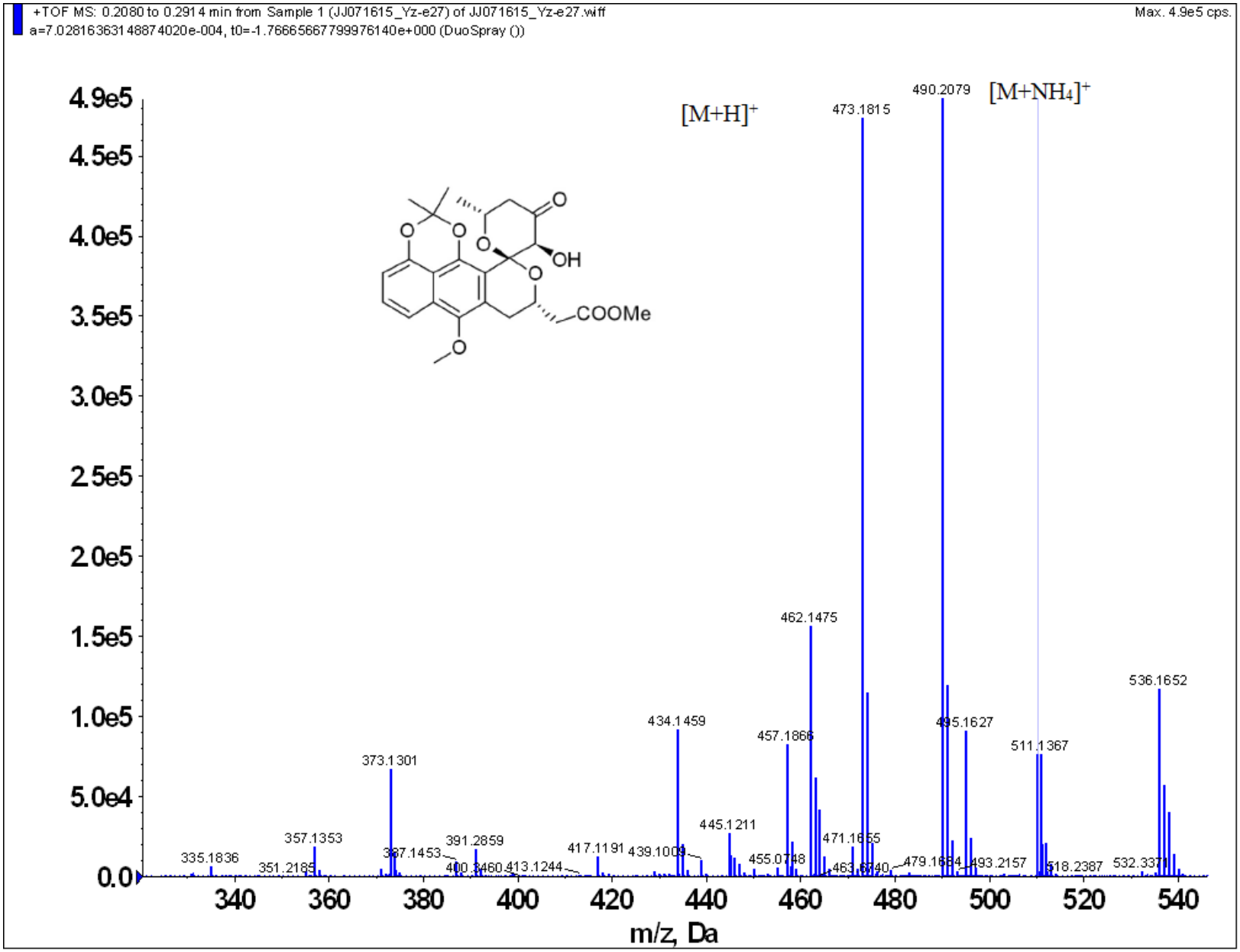



**Figure S102.** (+)-HRESI-MS of **30.**

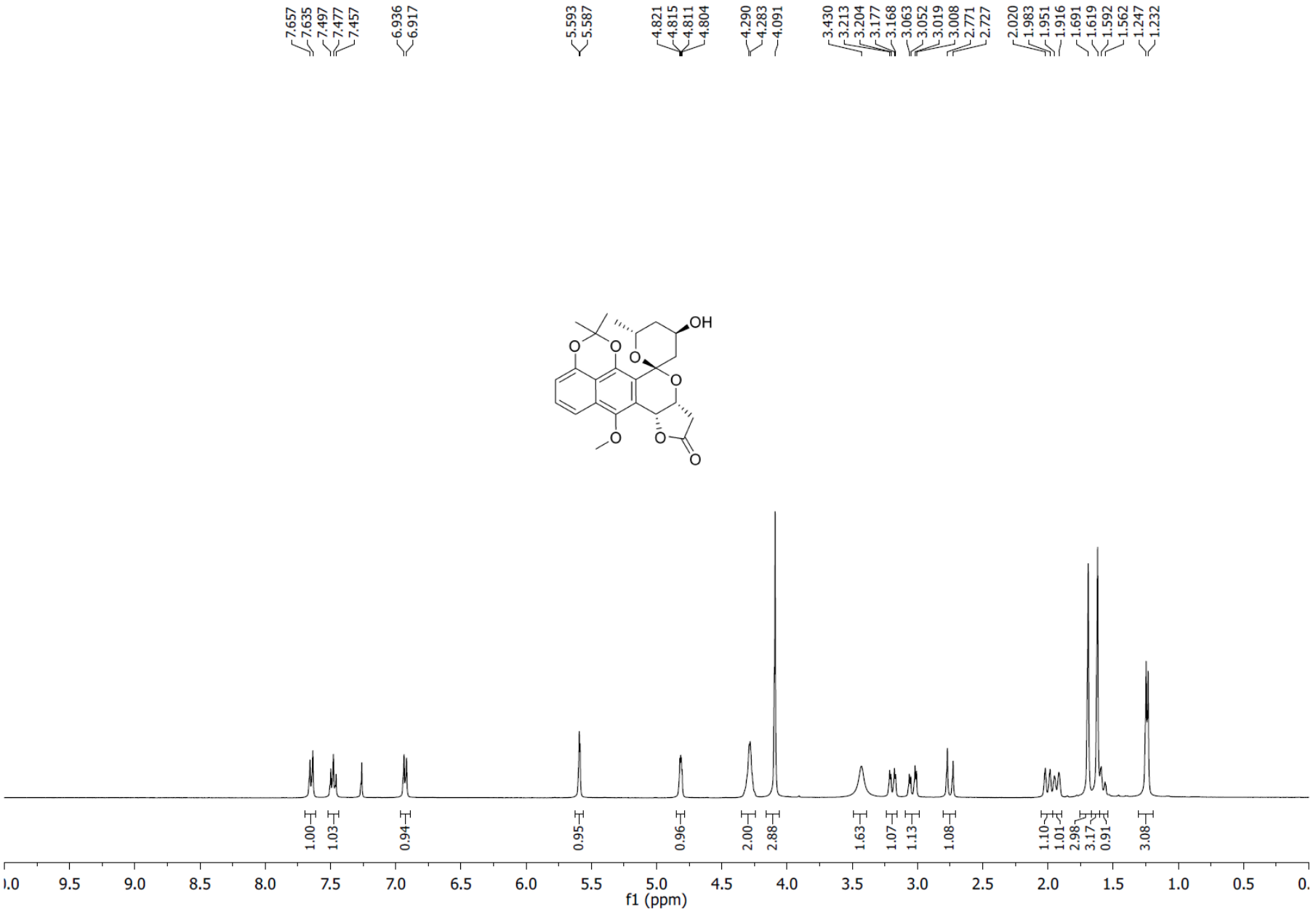



**Figure S103.** $^{1}$H-NMR ($CDCl_3$, 400 MHz) of **33.**

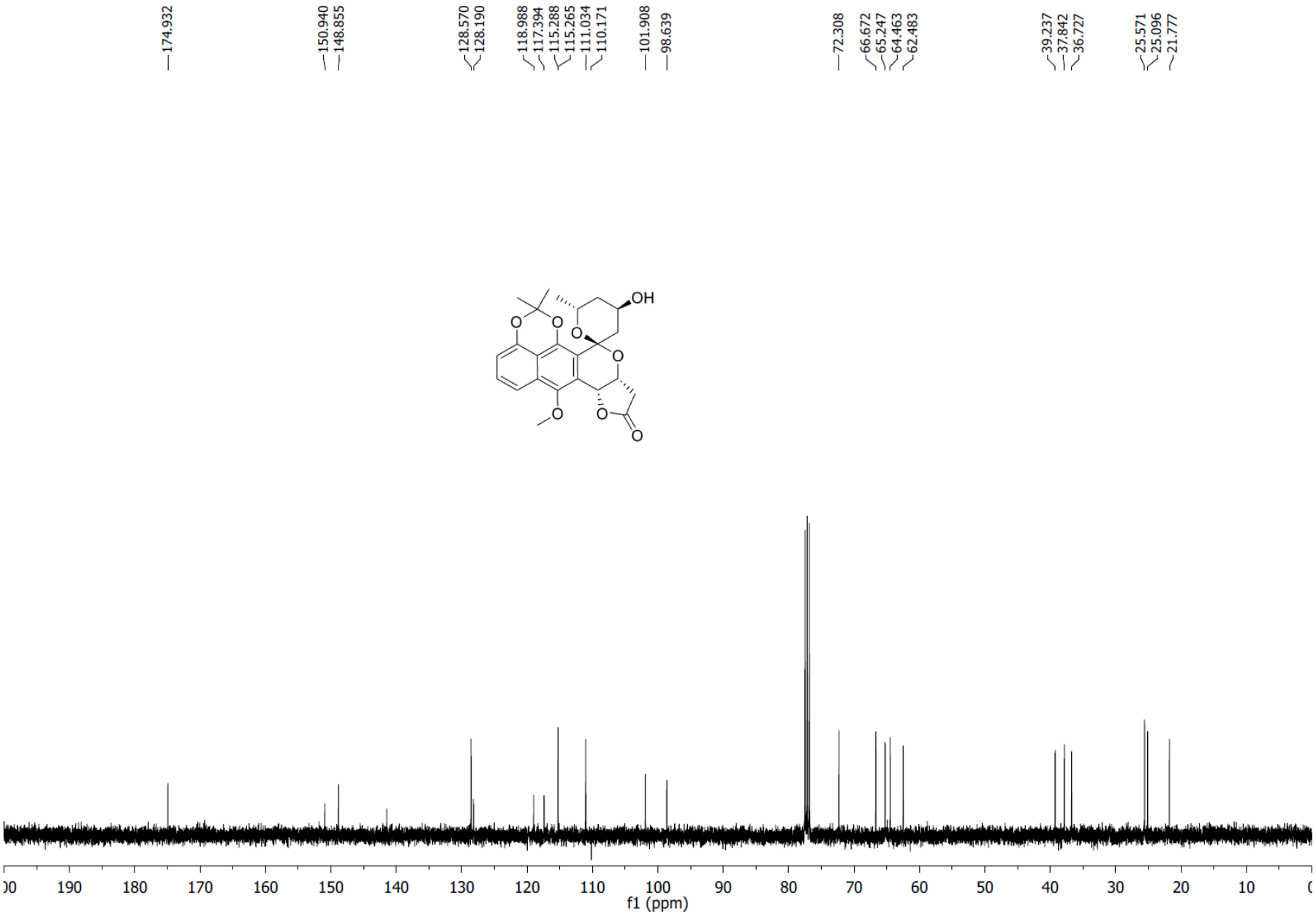



**Figure S104.** $^{13}$C-NMR ($CDCl_3$, 100 MHz) of **33.**

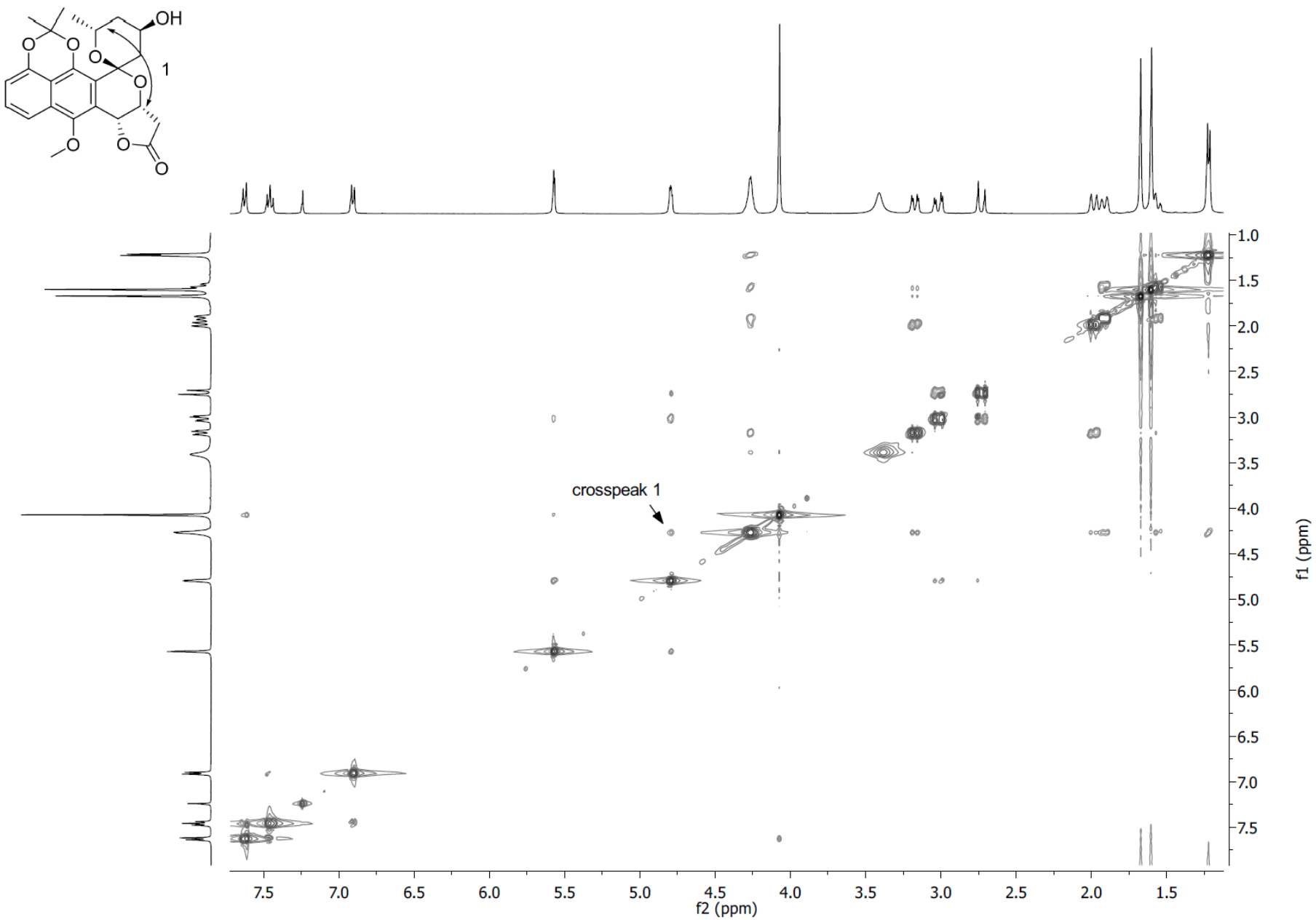



**Figure S105.** NOESY ($CDCl_3$, 400 MHz) of **33.**

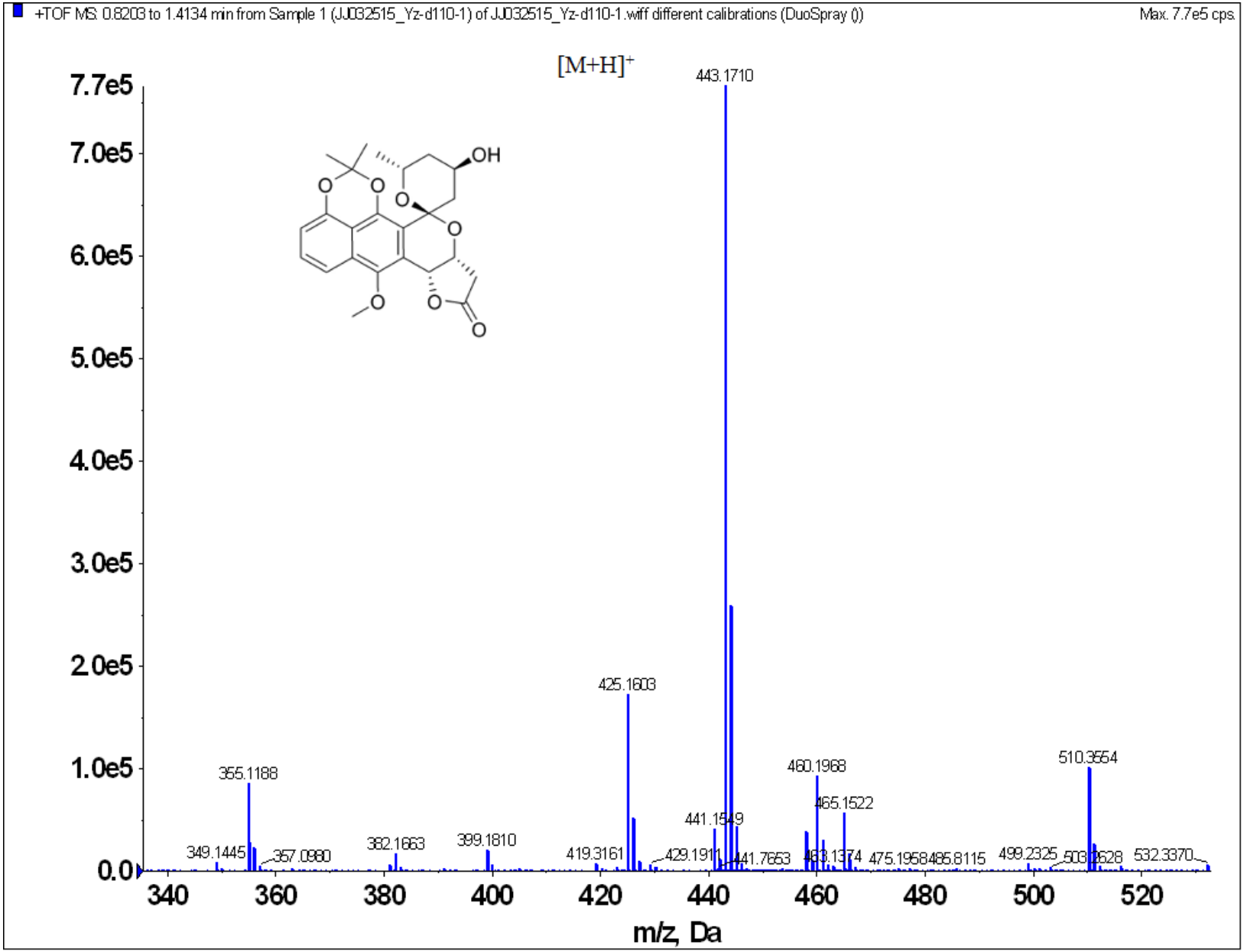



**Figure S106.** (+)-HRESI-MS of **33.**

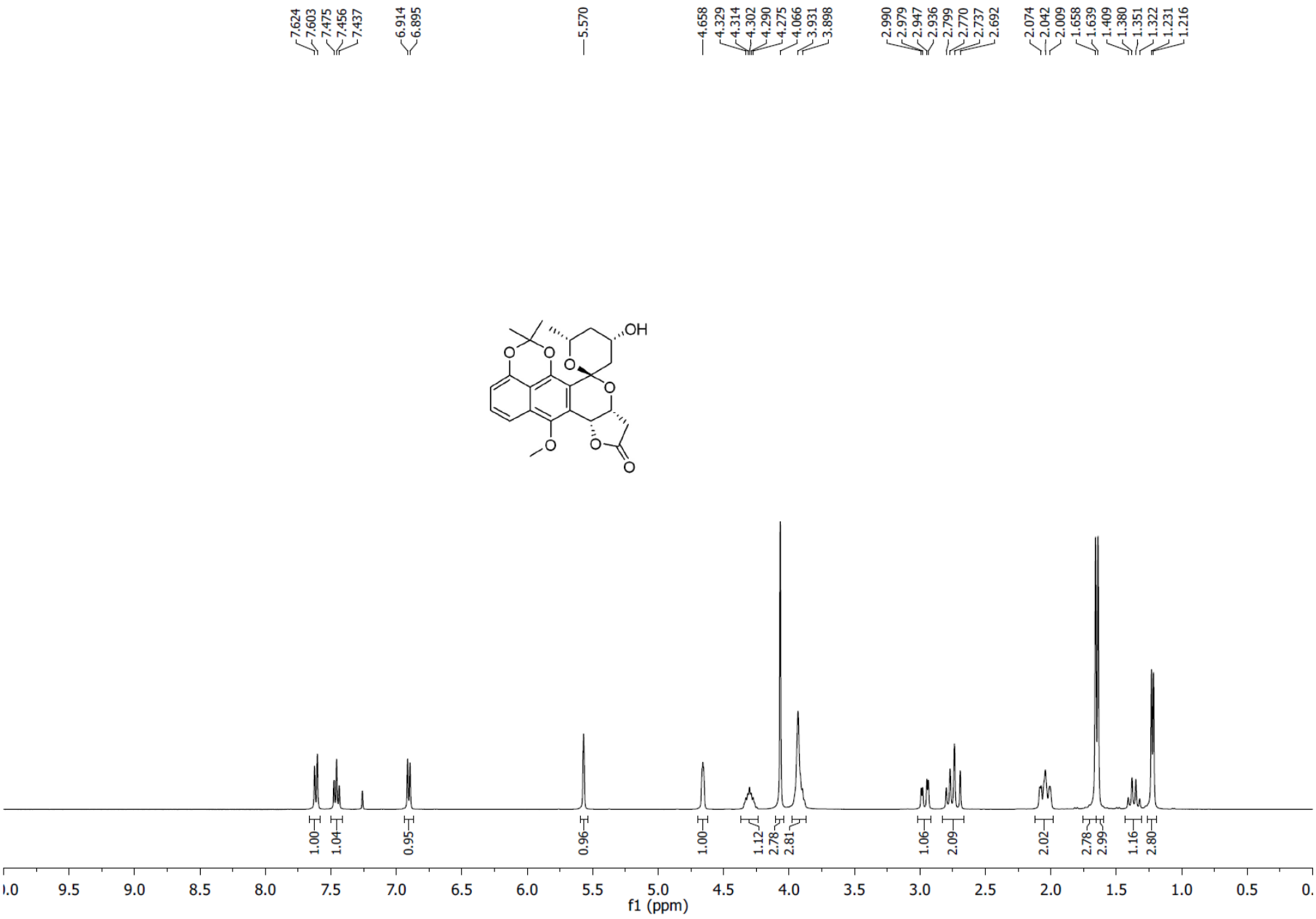



**Figure S107.** $^{1}$H-NMR ($CDCl_3$, 400 MHz) of **34.**

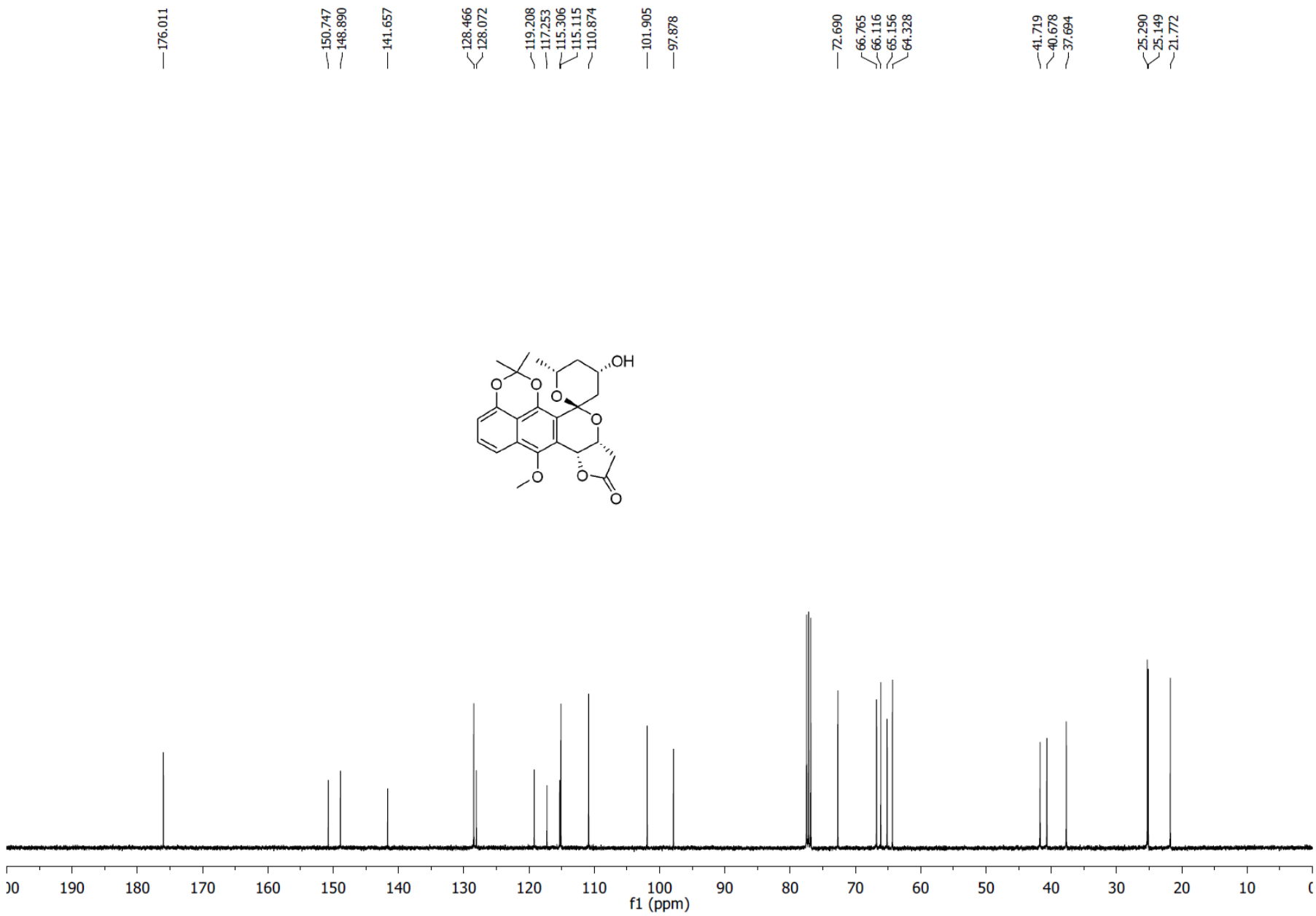



**Figure S108.** $^{13}$C-NMR ($CDCl_3$, 100 MHz) of **34.**

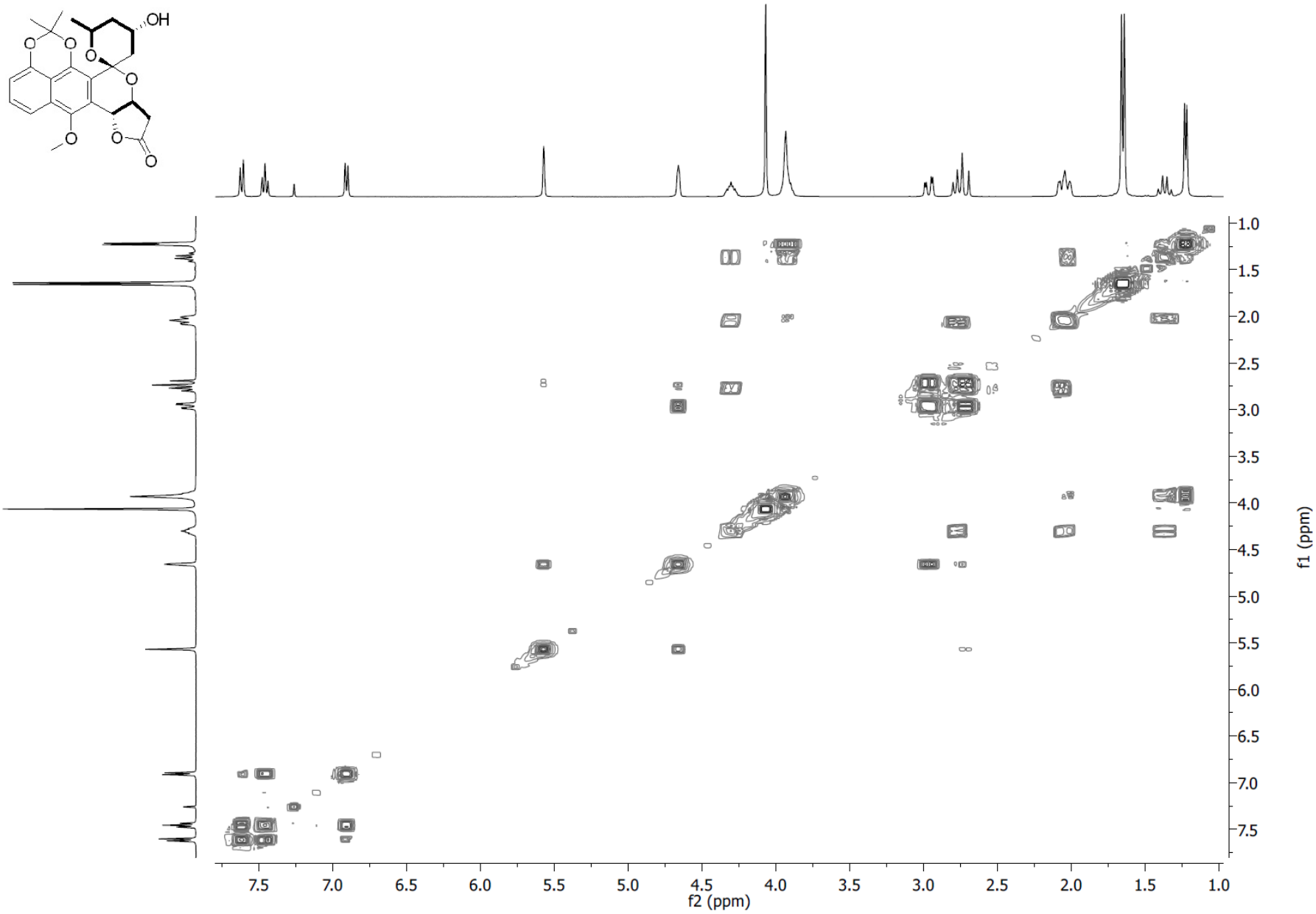



**Figure S109.** $^{1}$H-$^{1}$H COSY ($CDCl_3$, 400 MHz) of **34.**

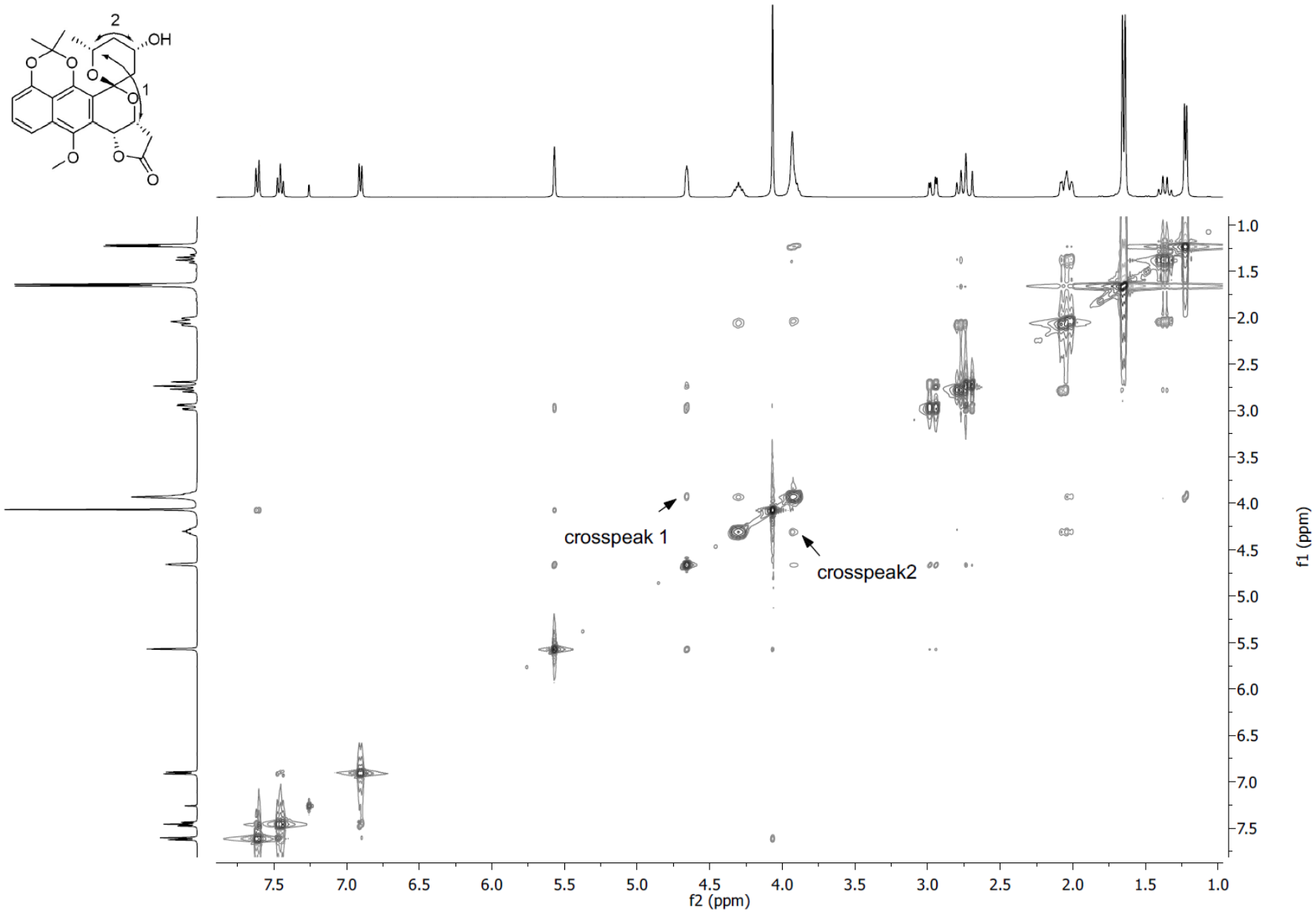



**Figure S110.** NOESY ($CDCl_3$, 400 MHz) of **34.**

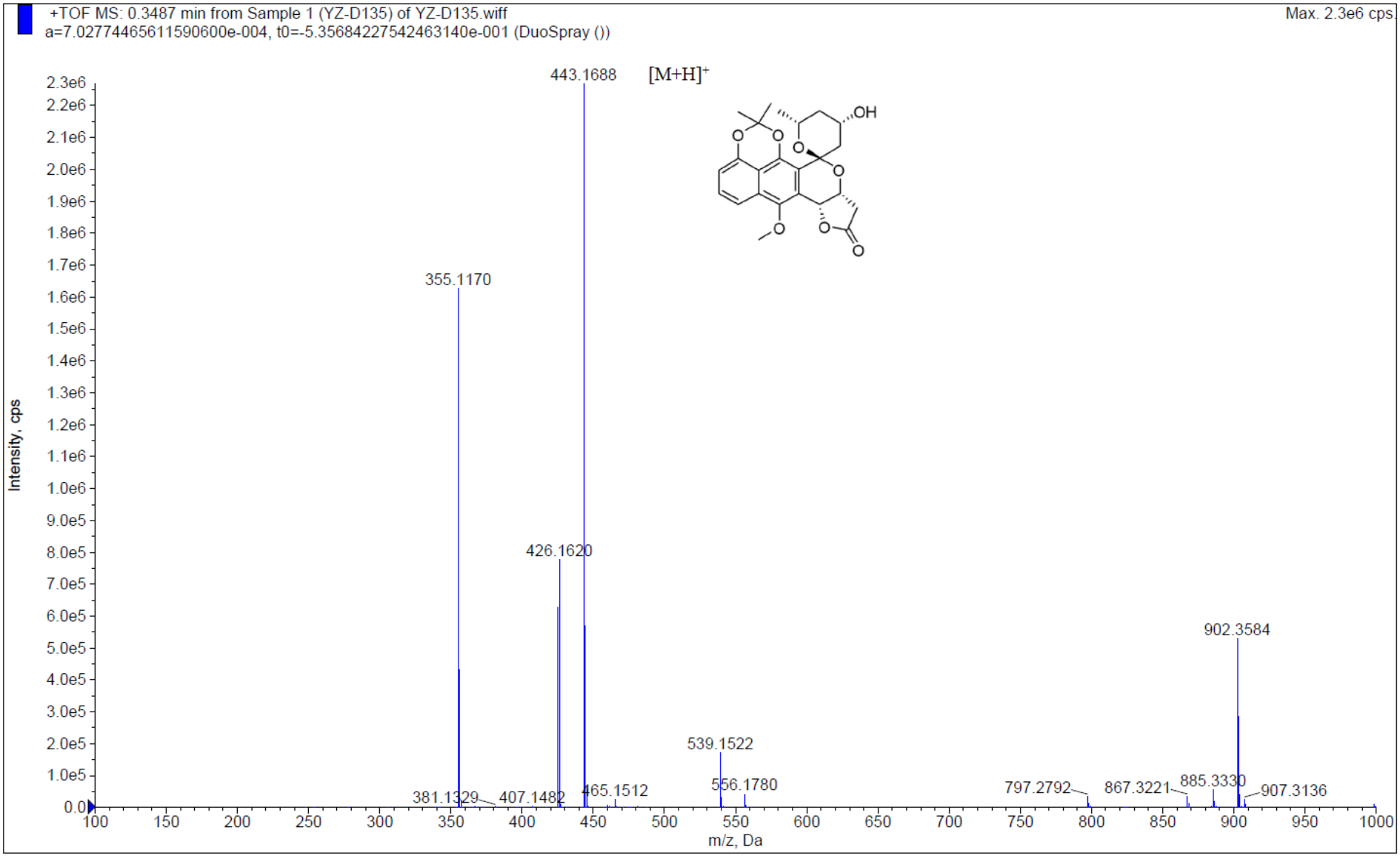



**Figure S111.** (+)-HRESI-MS of **34.**

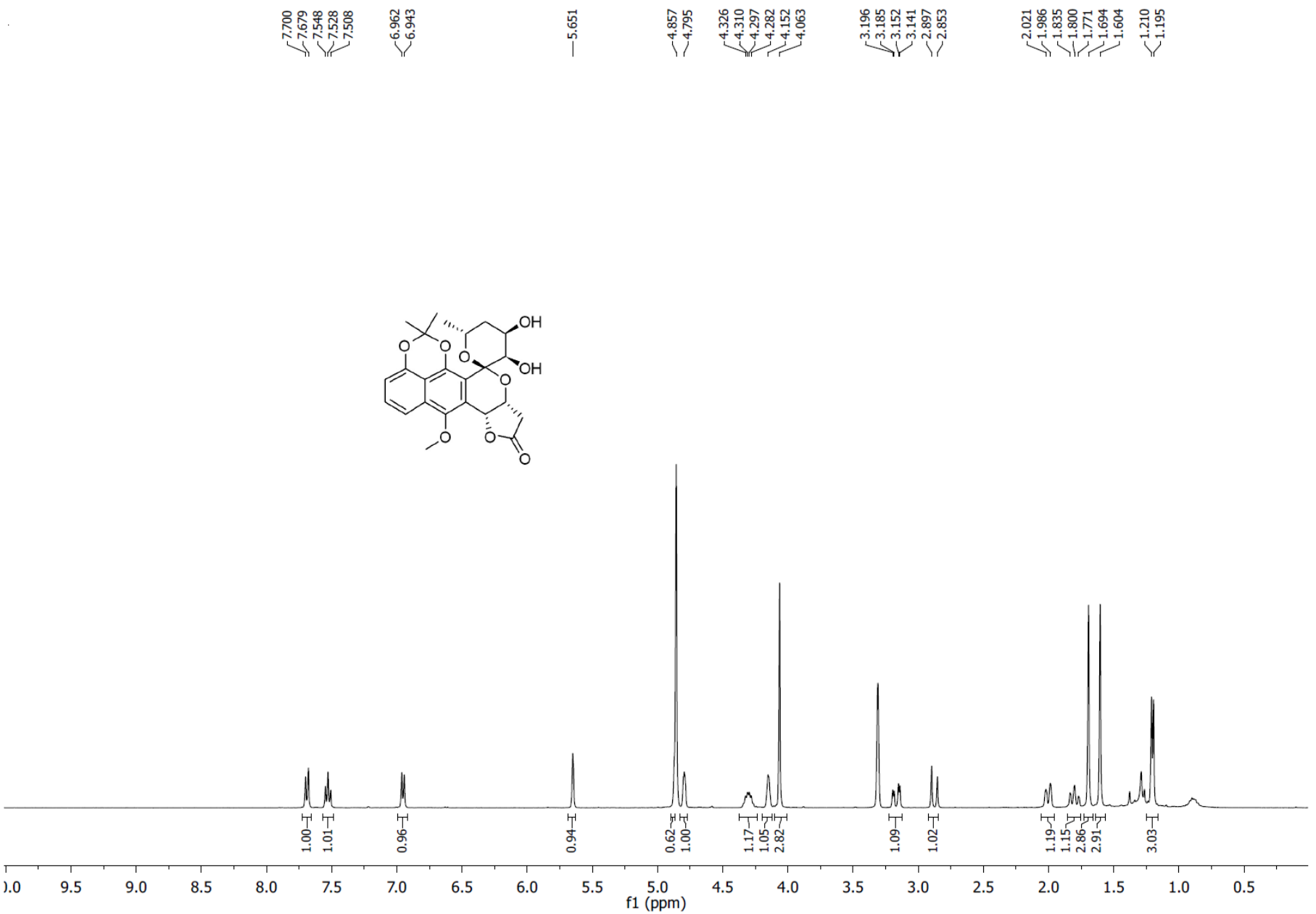



**Figure S112.** $^{1}$H-NMR ($CD_3OD$, 400 MHz) of **35.**

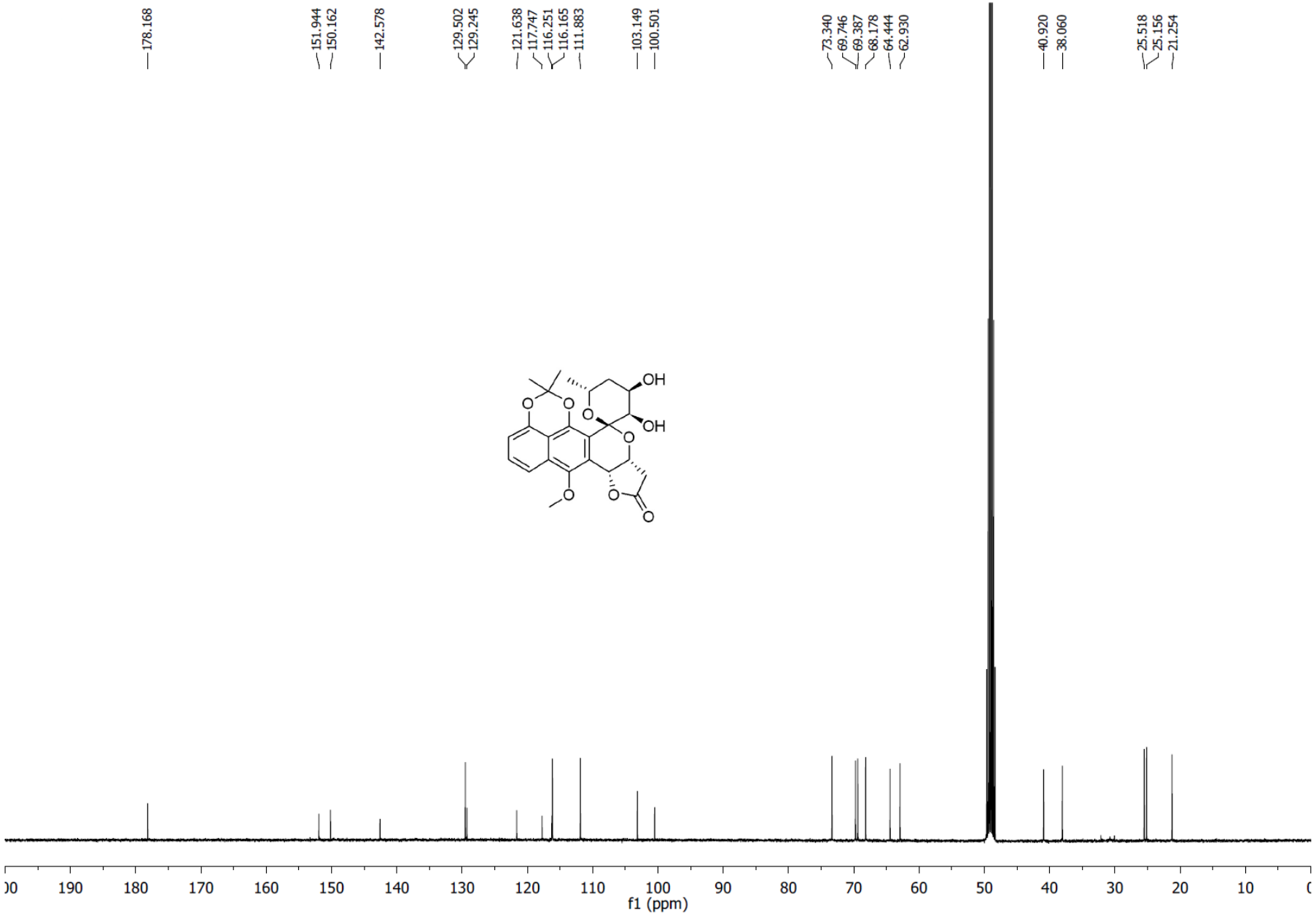



**Figure S113.** $^{13}$C-NMR ($CD_3OD$, 100 MHz) of **35.**

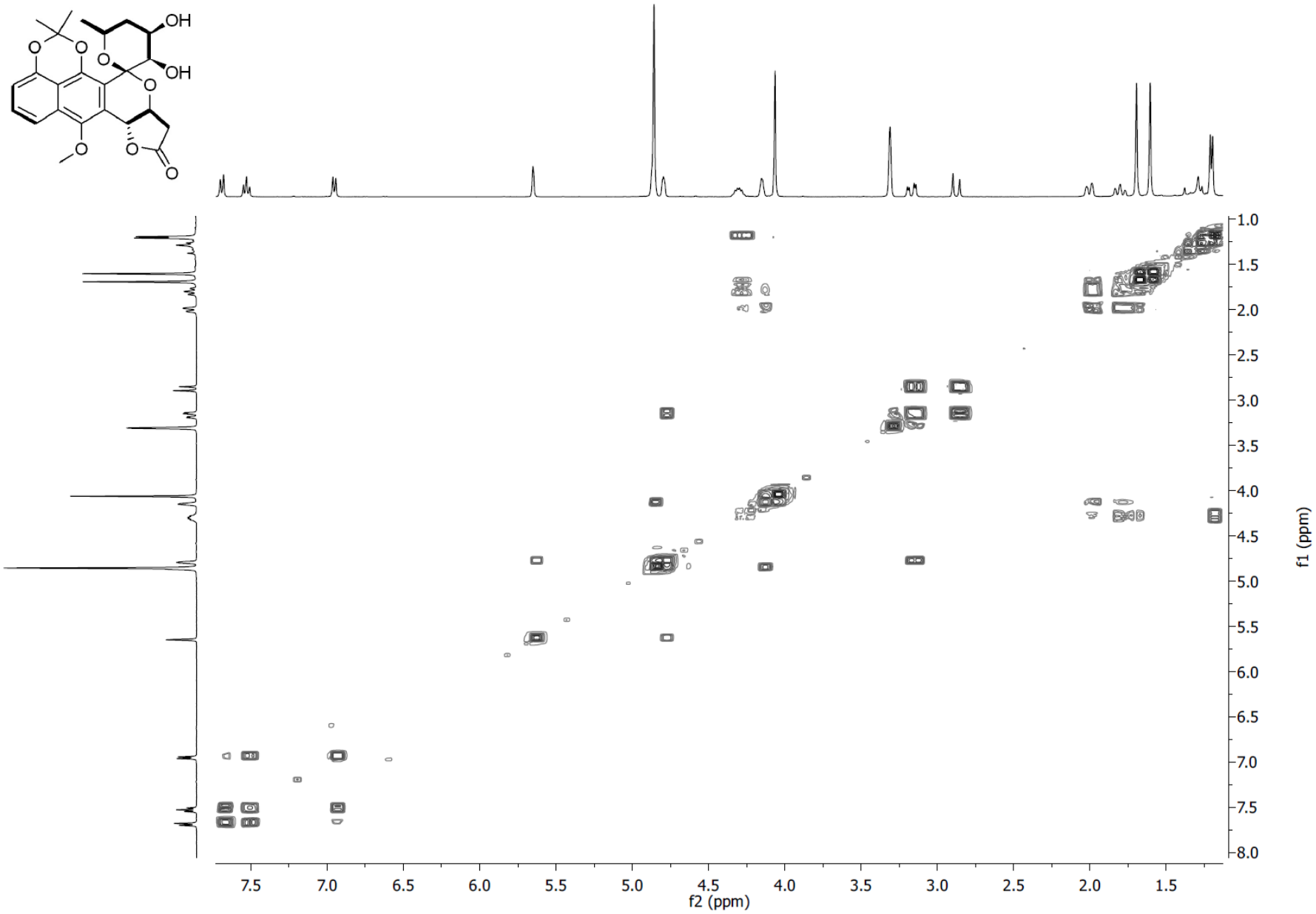



**Figure S114.** $^{1}$H-$^{1}$H COSY ($CD_3OD$, 400 MHz) of **35.**

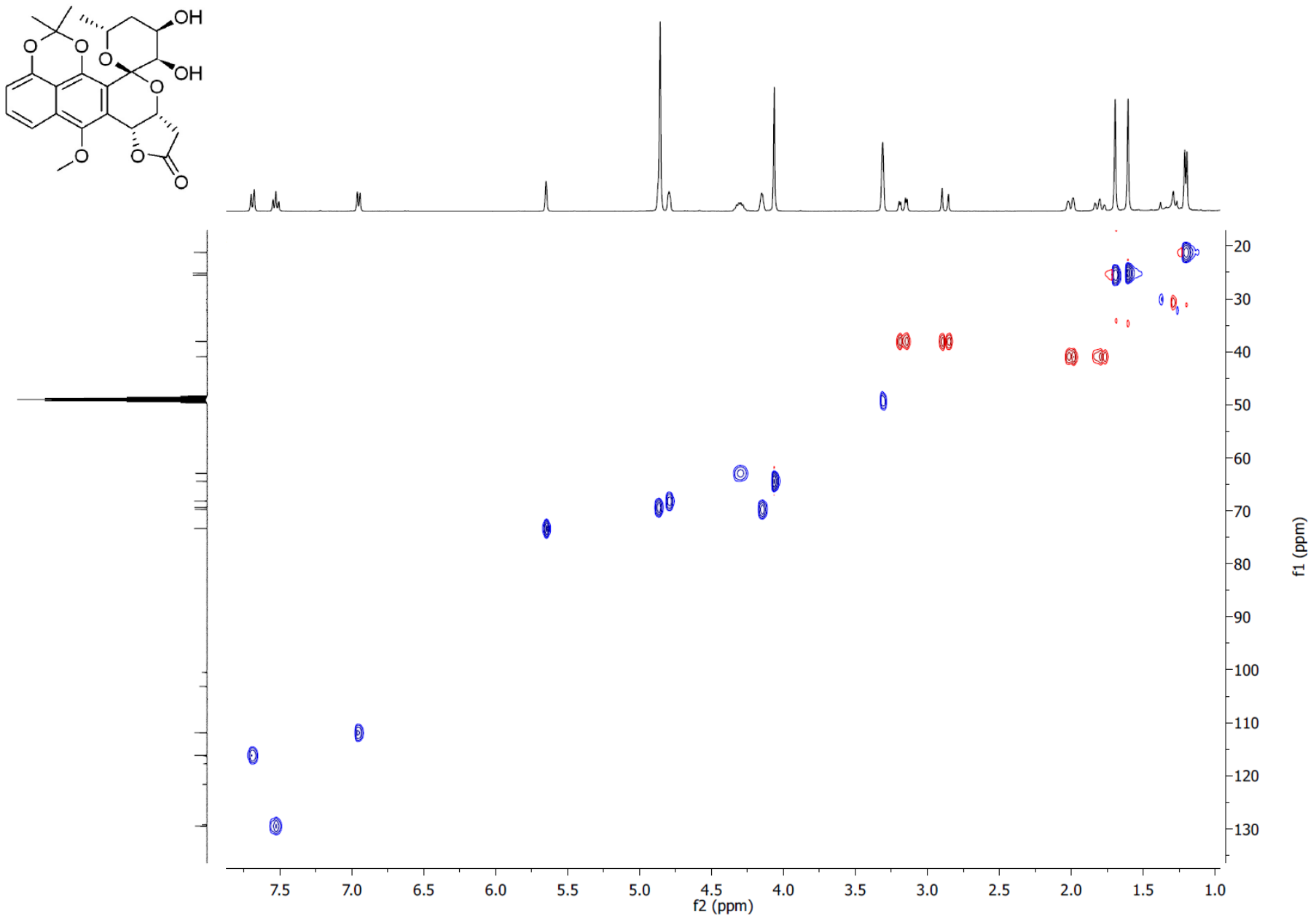



**Figure S115.** HSQC ($CD_3OD$, 400 MHz) of **35.**

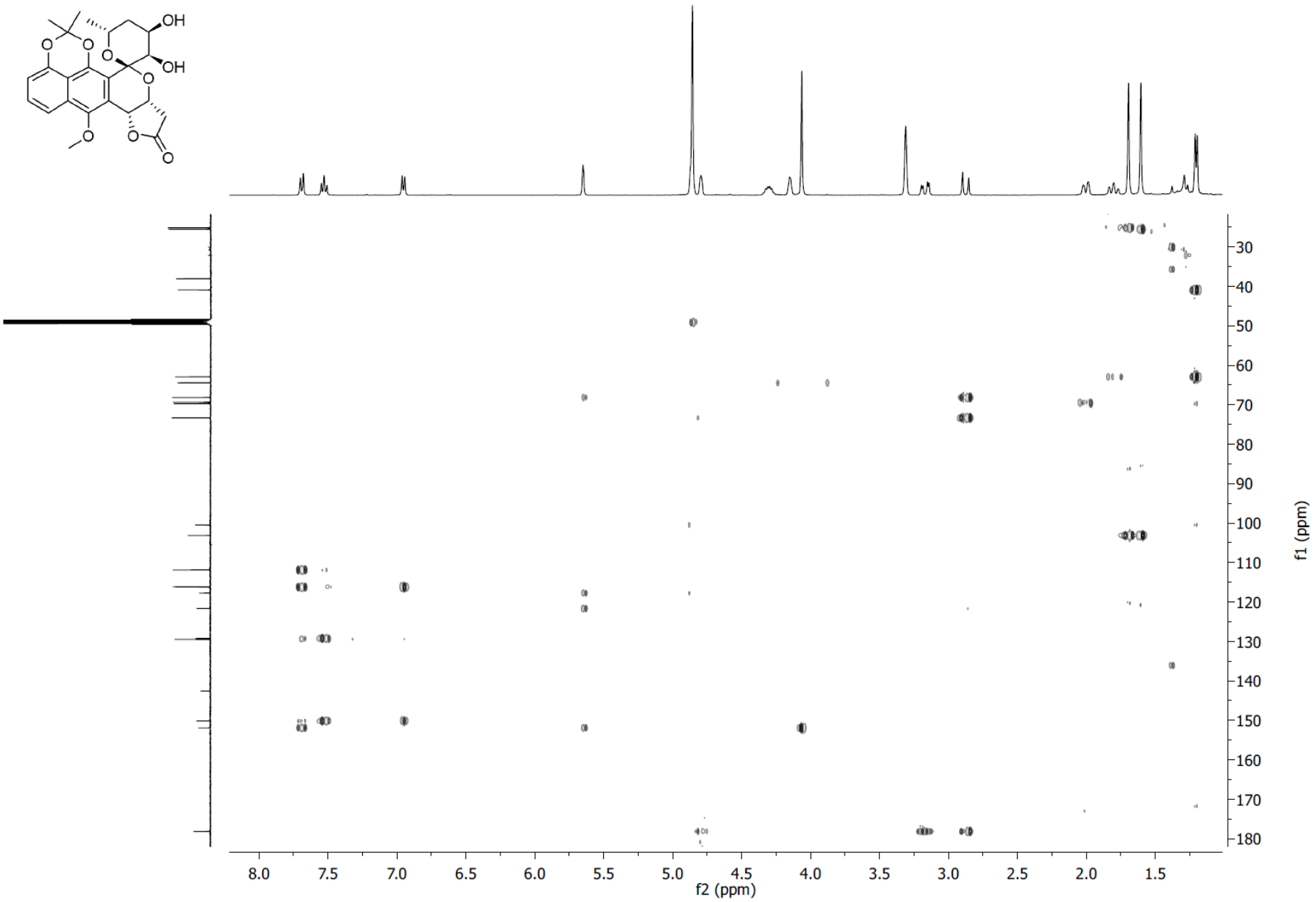



**Figure S116.** HMBC ($CD_3OD$, 400 MHz) of **35.**

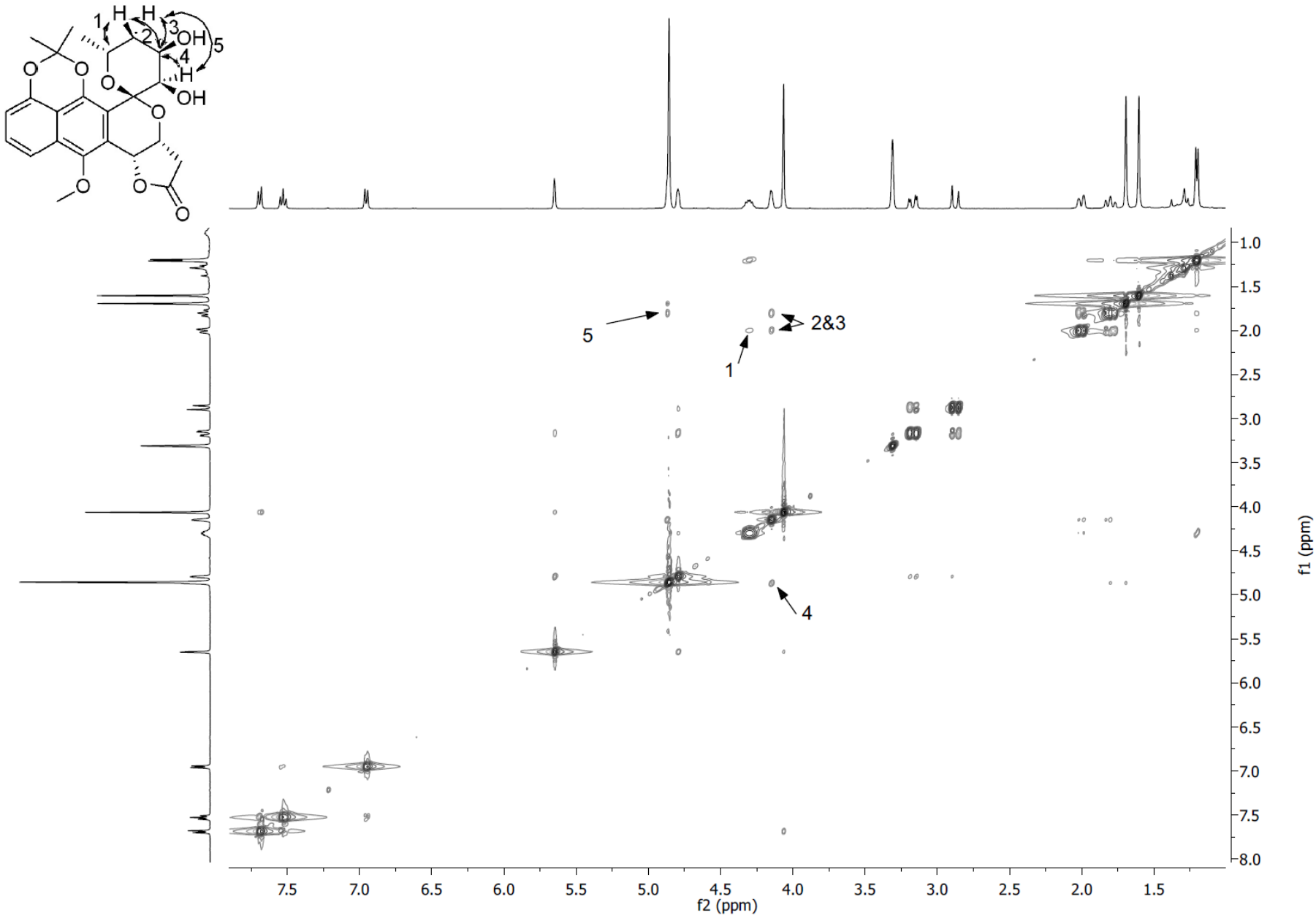



**Figure S117.** NOESY ($CD_3OD$, 400 MHz) of **35.**

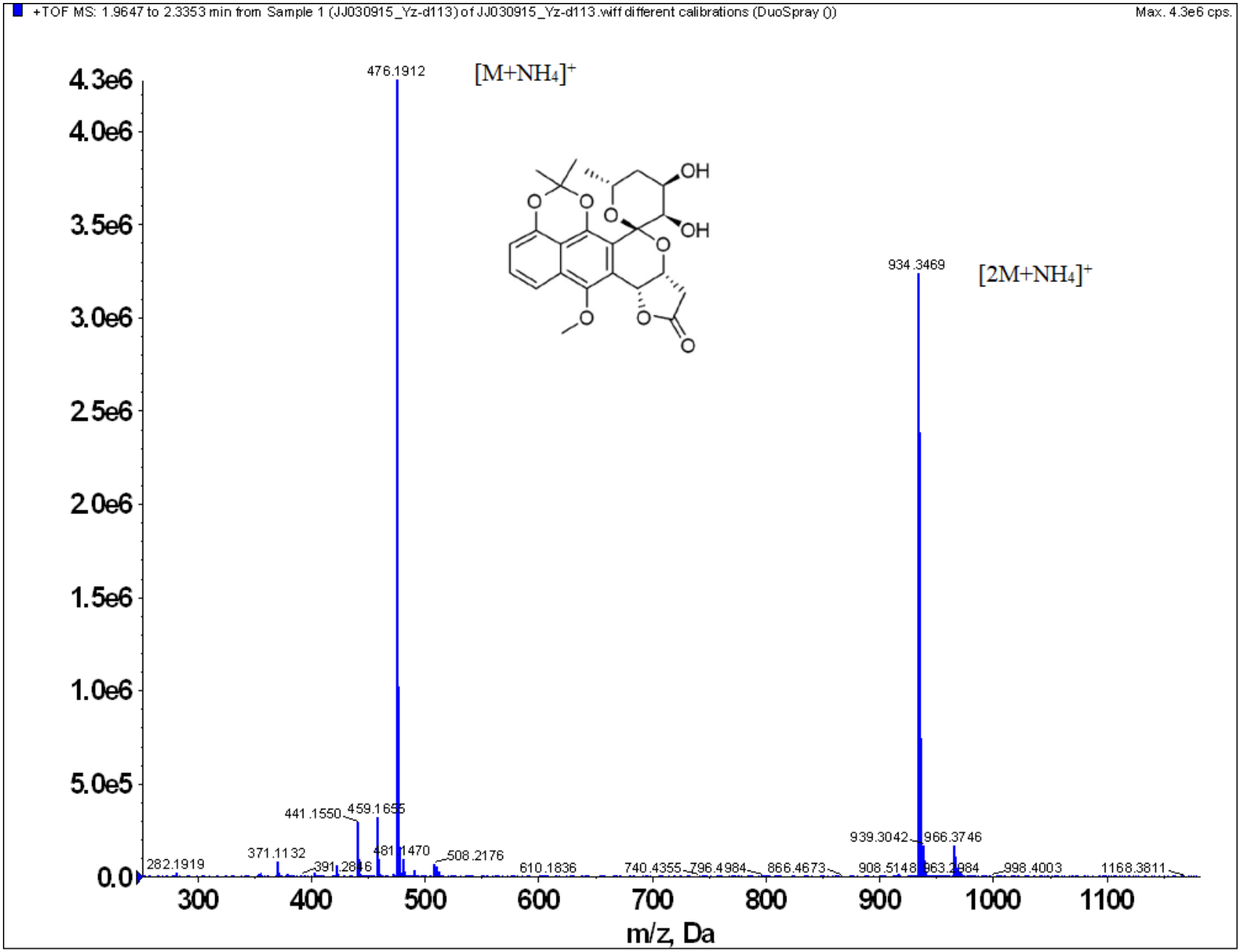



**Figure S118.** (+)-HRESI-MS of **35.**

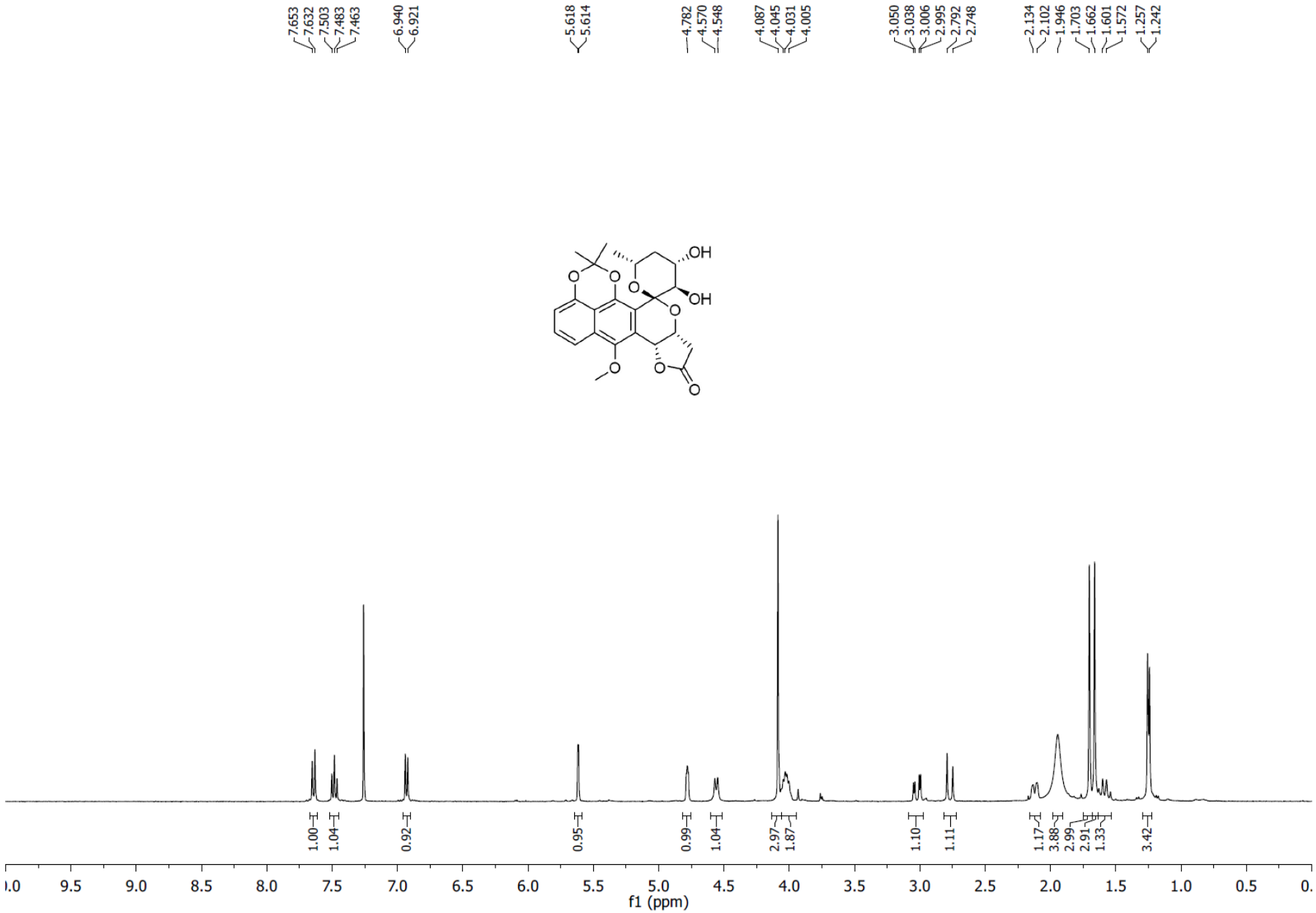



**Figure S119.** $^{1}$H-NMR ($CDCl_3$, 400 MHz) of **36.**

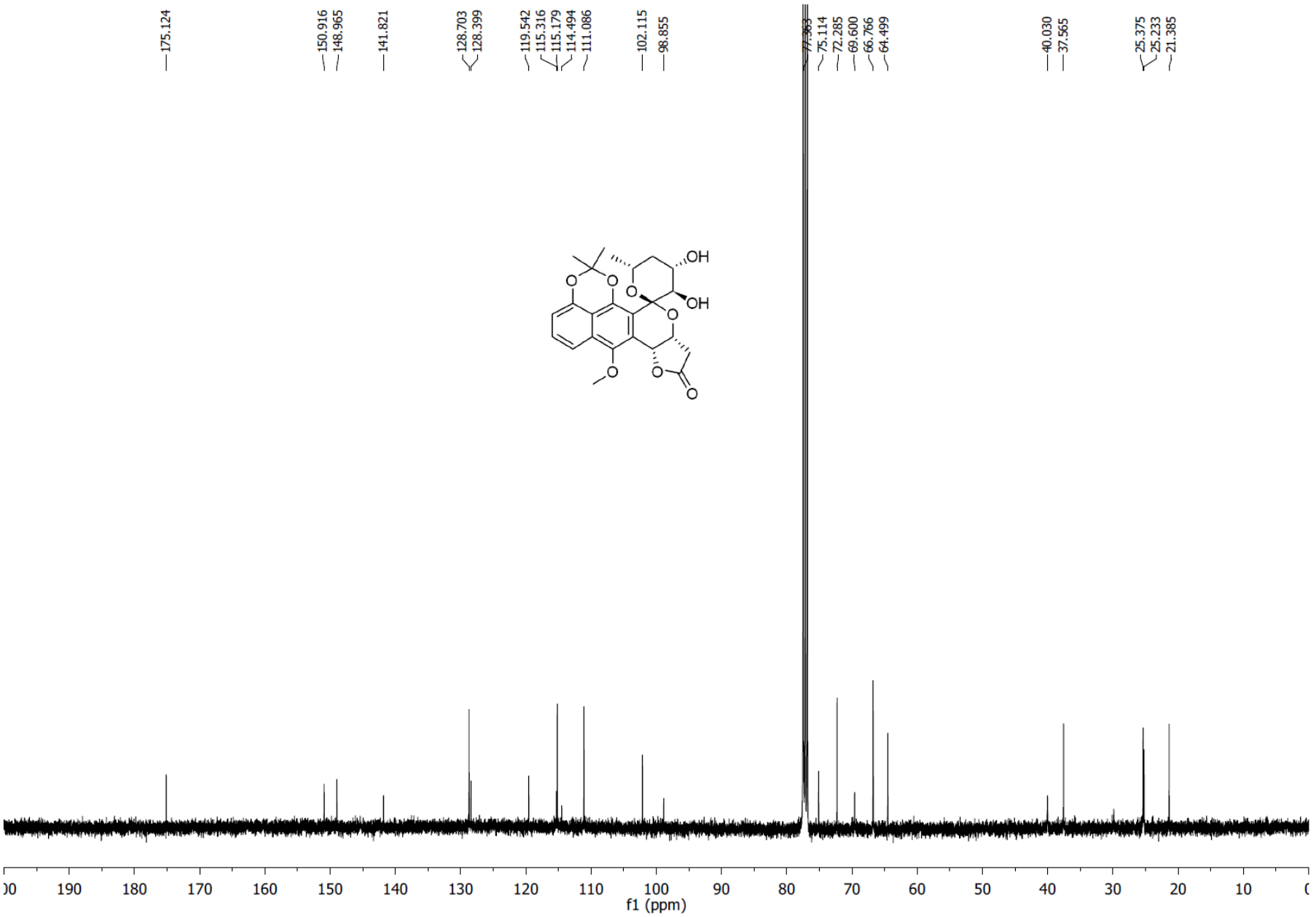



**Figure S120.** $^{13}$C-NMR ($CDCl_3$, 100 MHz) of **36.**

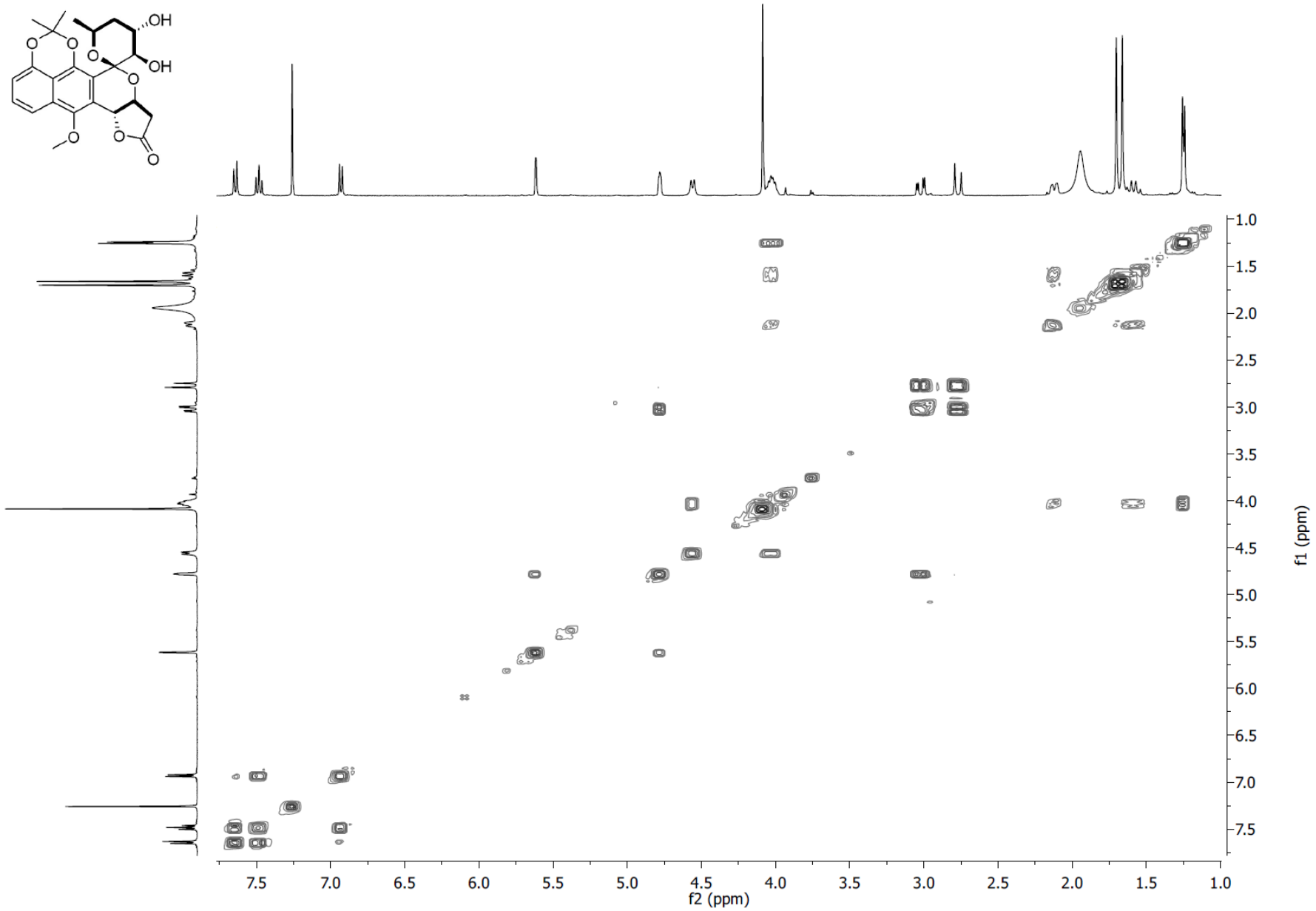



**Figure S121.** $^{1}$H-$^{1}$H COSY ($CDCl_3$, 400 MHz) of **36.**

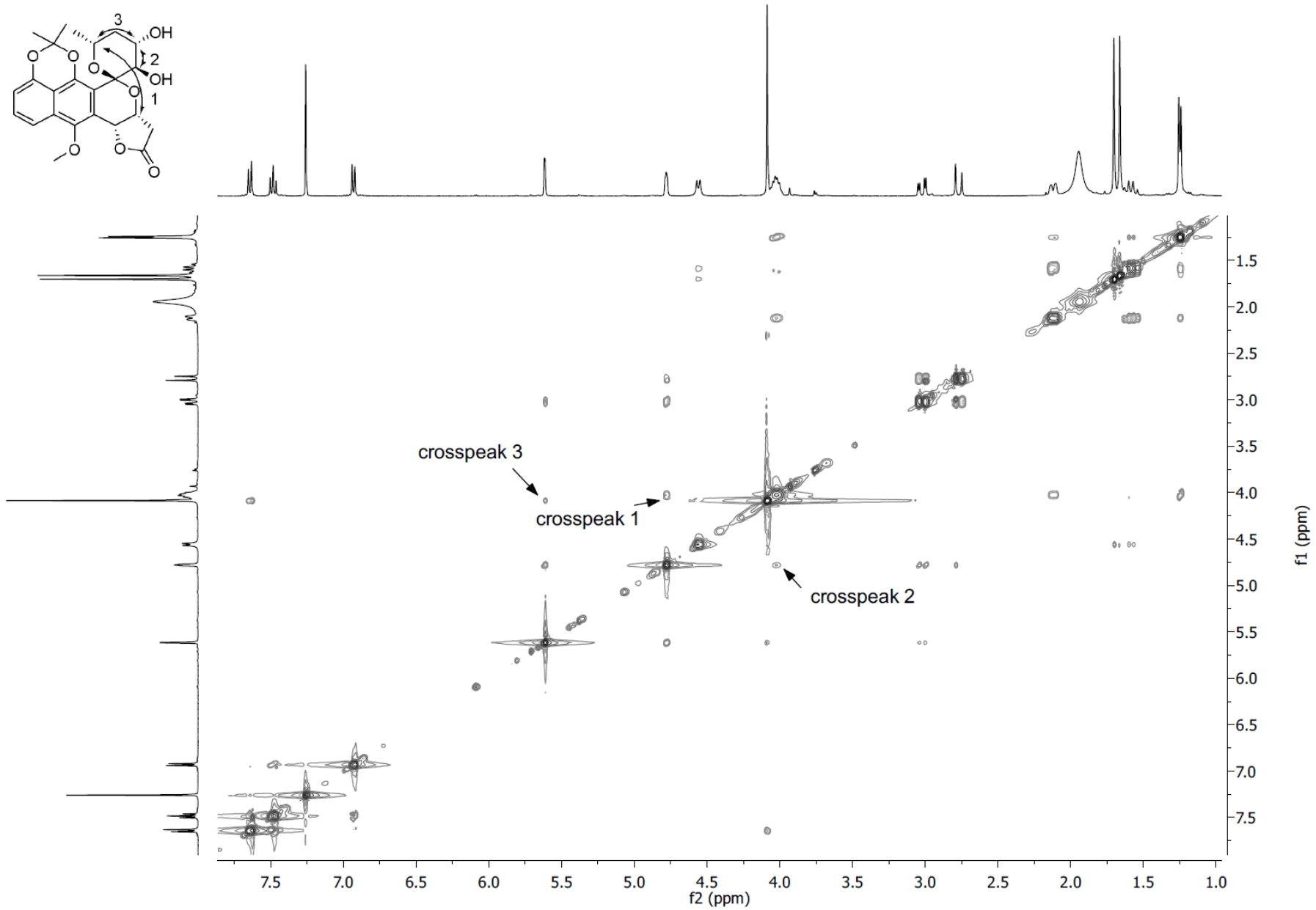



**Figure S122.** NOESY ($CDCl_3$, 400 MHz) of **36.**

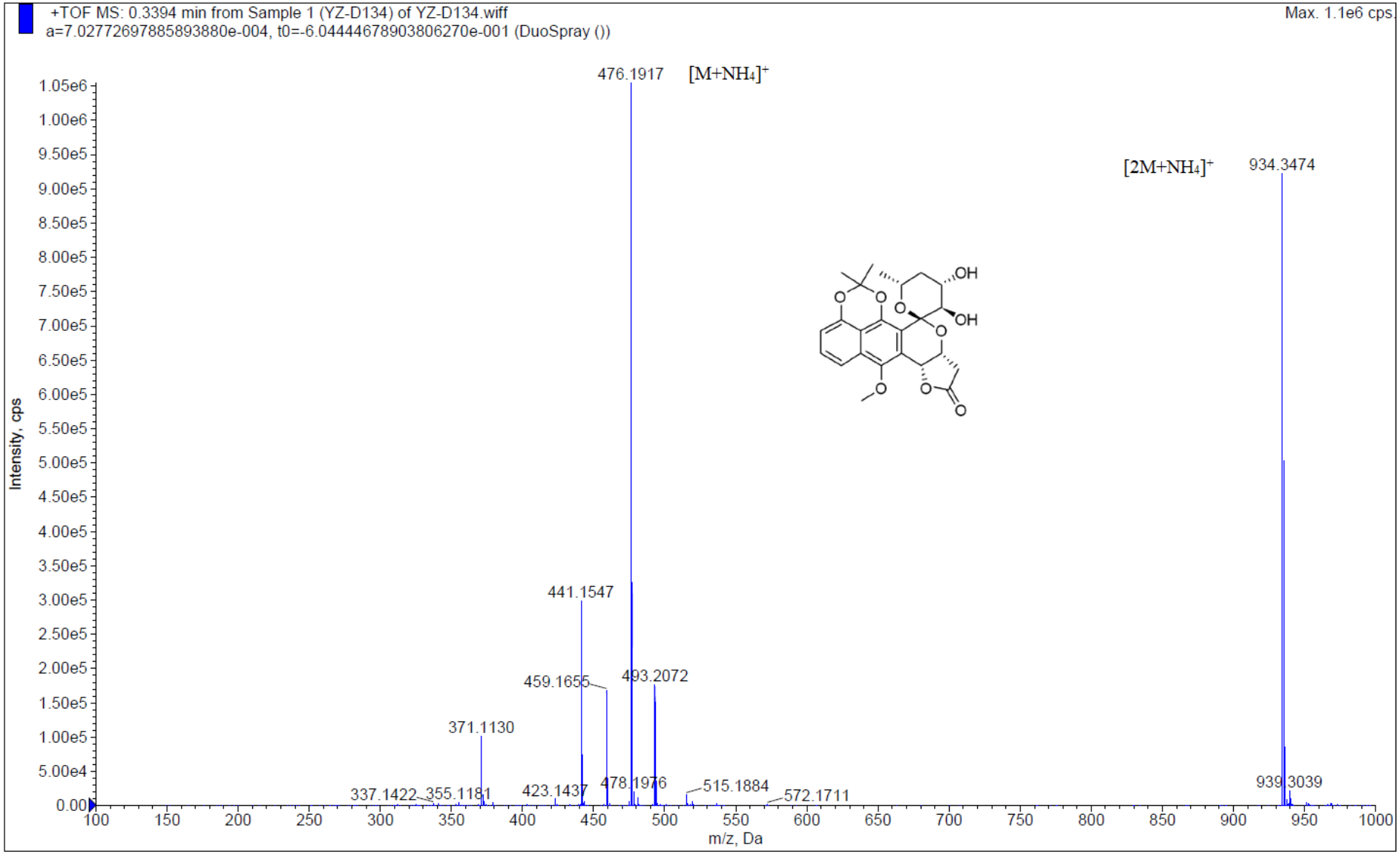



**Figure S123.** (+)-HRESI-MS of **36.**

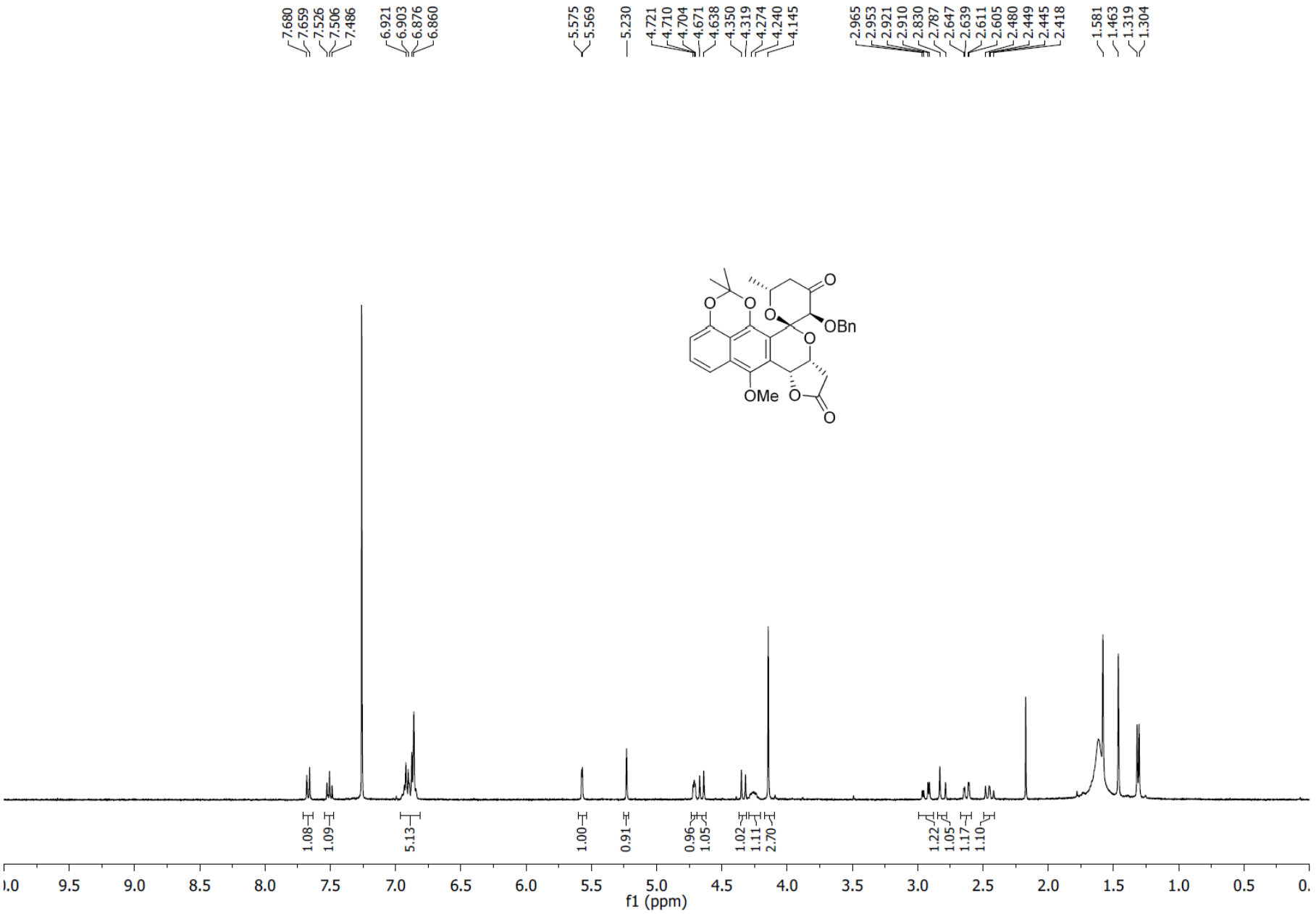



**Figure S124.** $^{1}$H-NMR ($CDCl_3$, 400 MHz) of **37.**

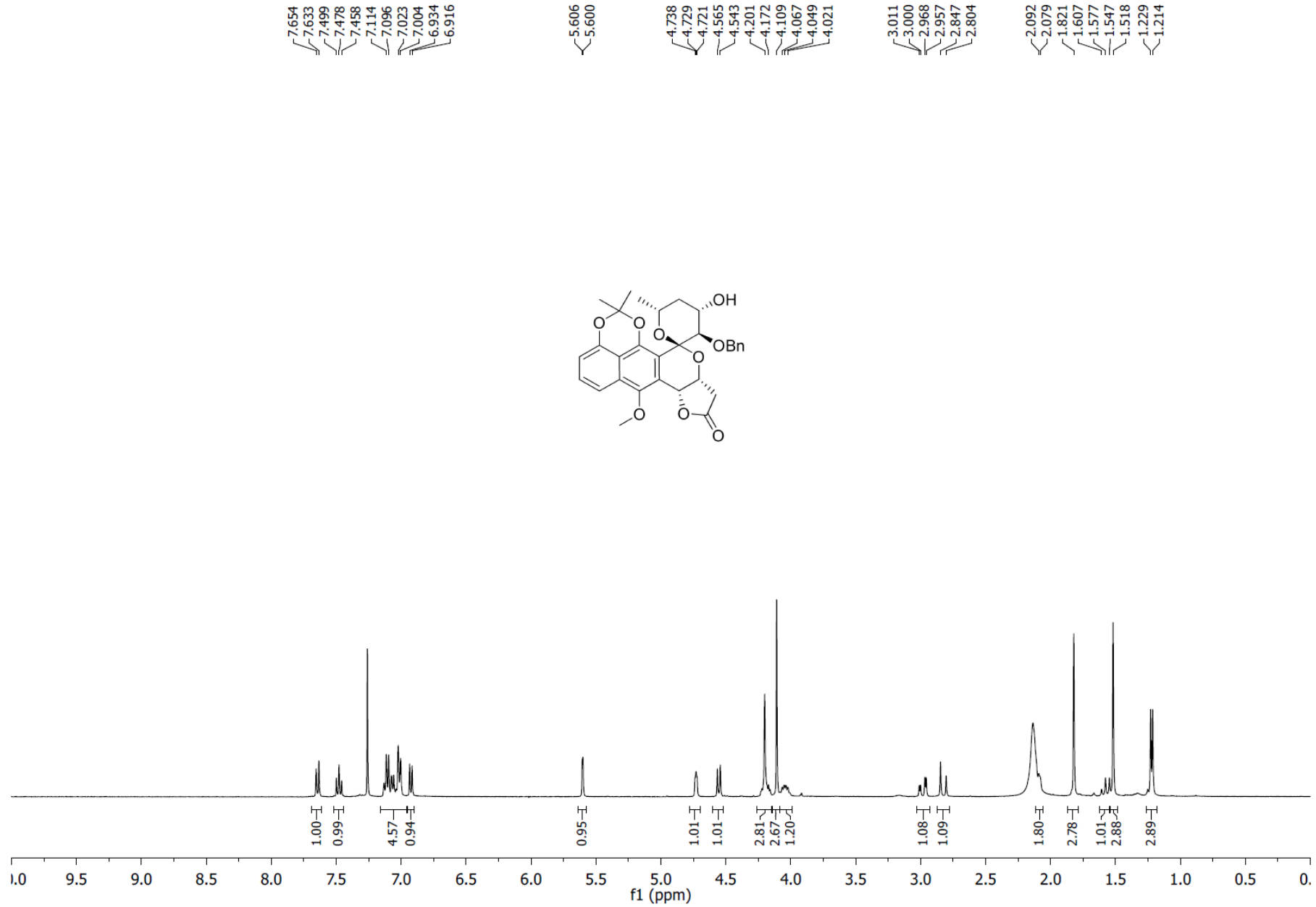



**Figure S125.** $^{1}$H-NMR ($CDCl_3$, 400 MHz) of **38.**

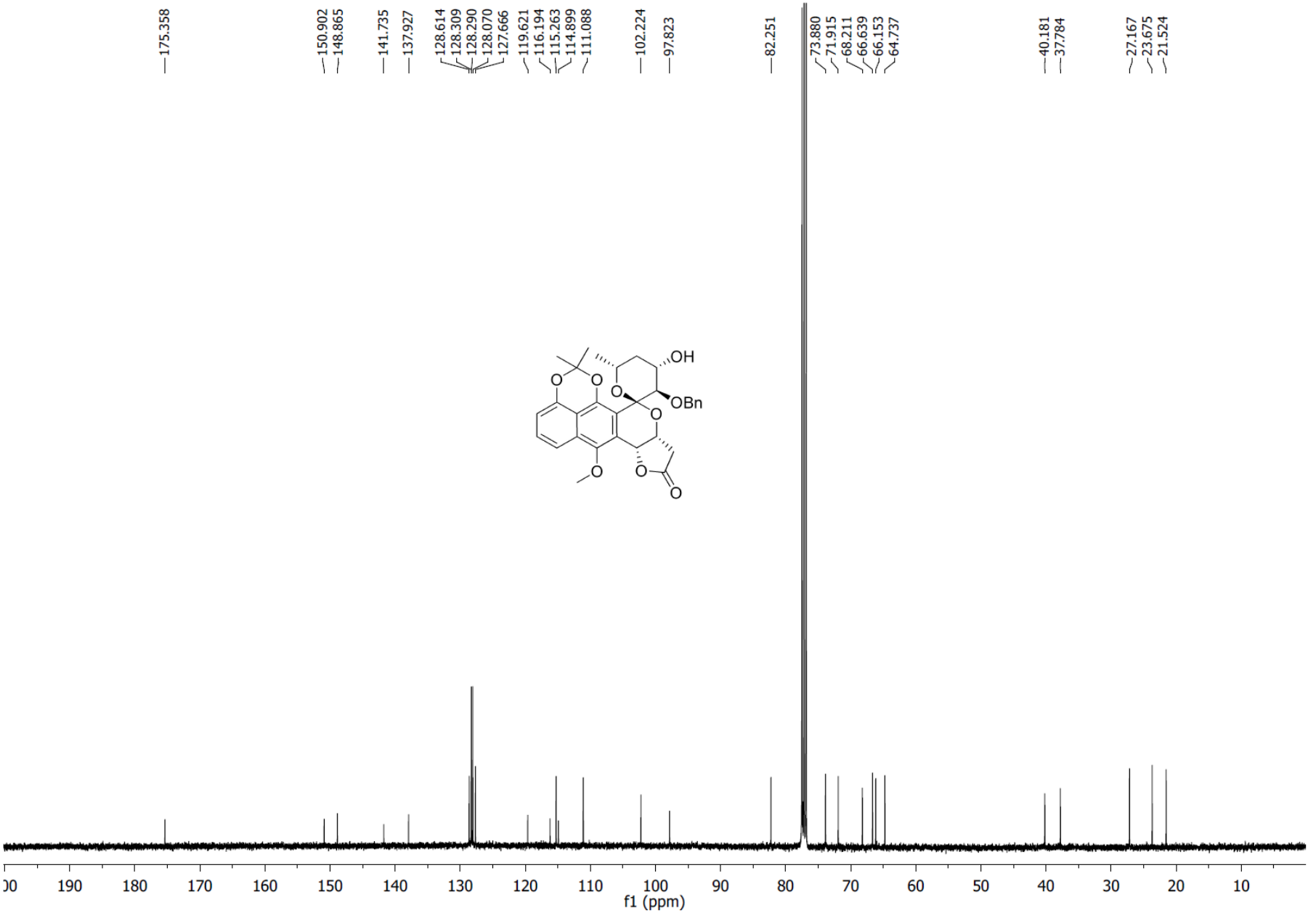



**Figure S126.** $^{13}$C-NMR ($CDCl_3$, 100 MHz) of **38.**

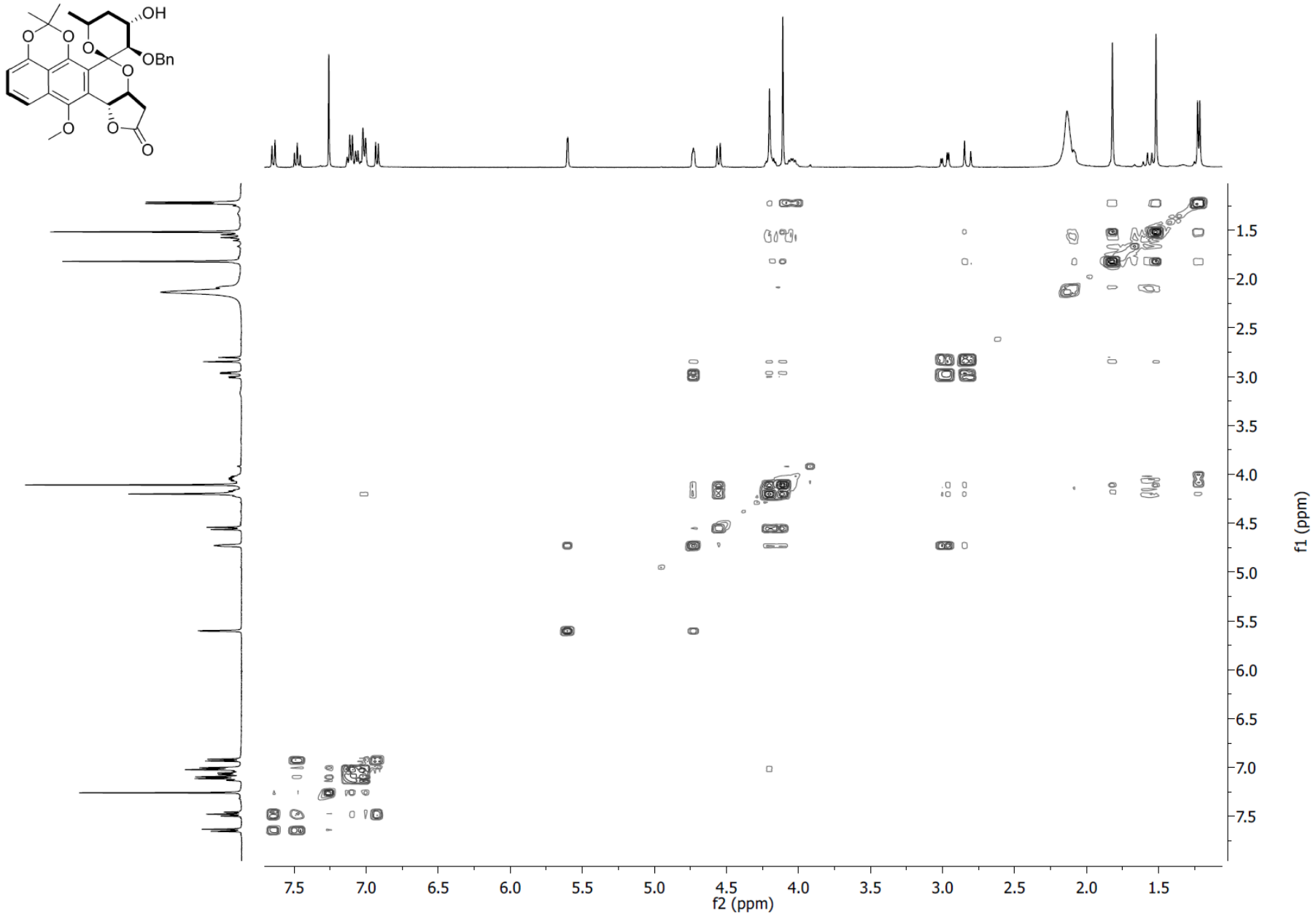



**Figure S127.** $^{1}$H-$^{1}$H COSY ($CDCl_3$, 400 MHz) of **38.**

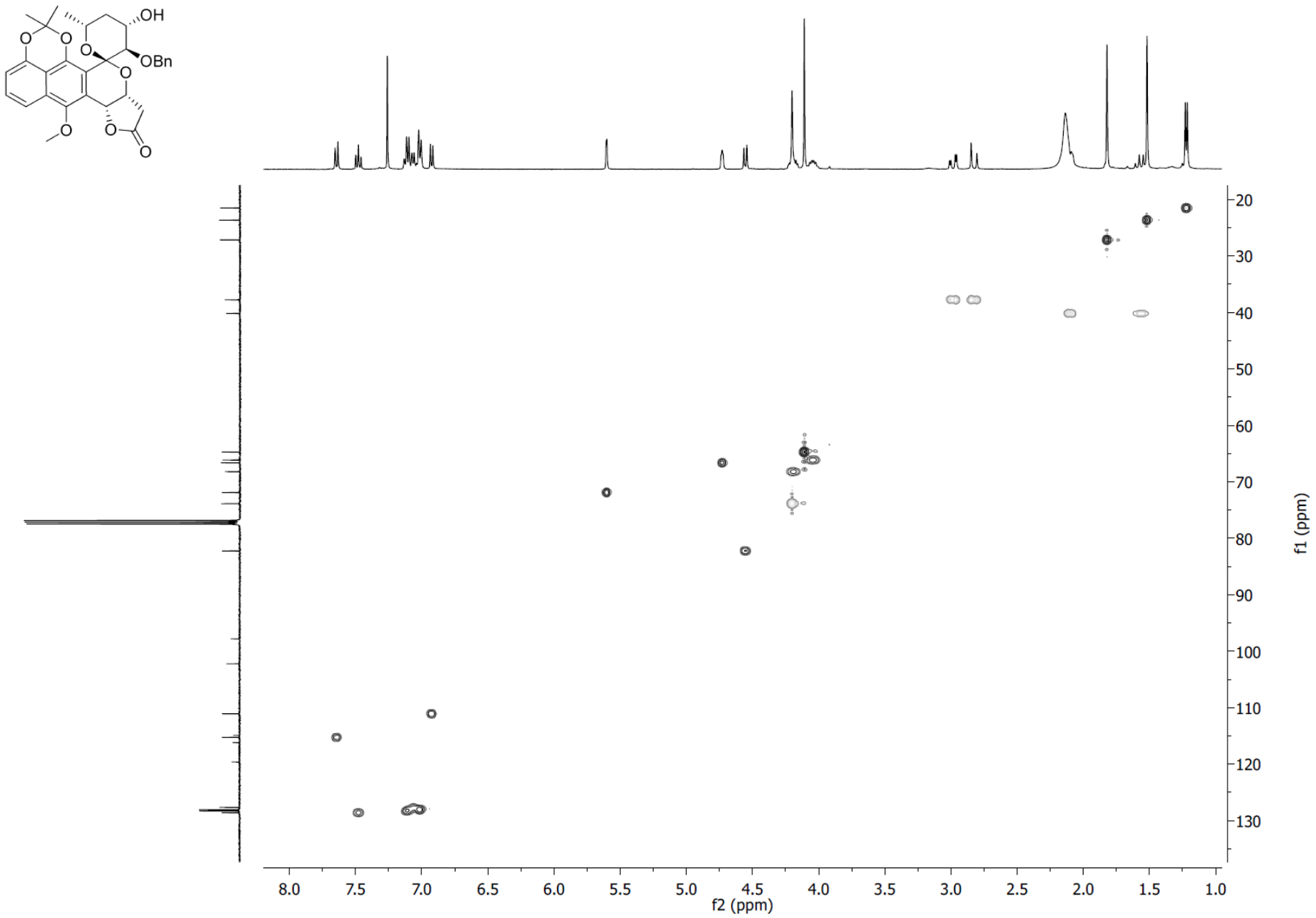



**Figure S128.** HSQC ($CDCl_3$, 400 MHz) of **38.**

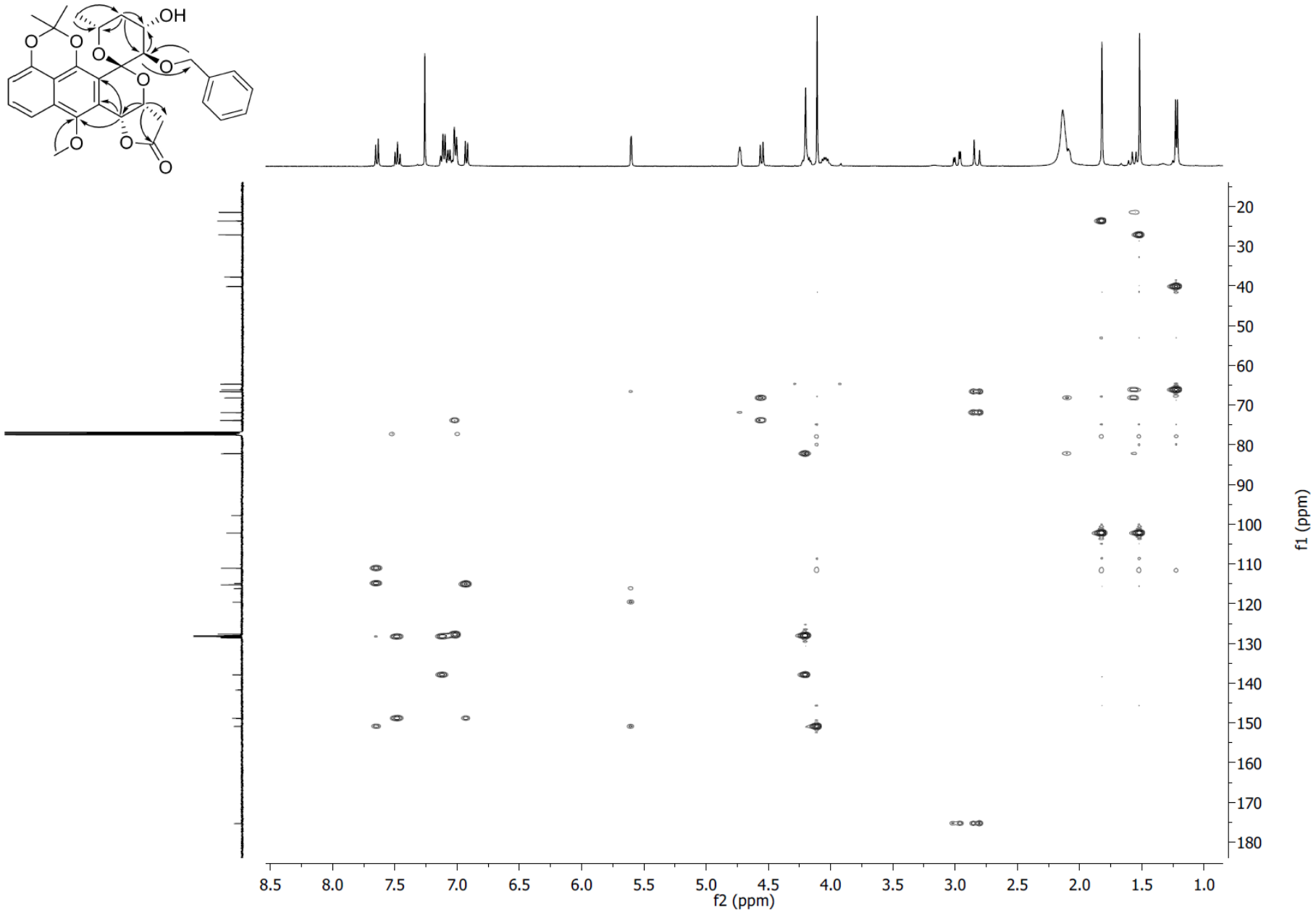



**Figure S129.** HMBC ($CDCl_3$, 400 MHz) of **38.**

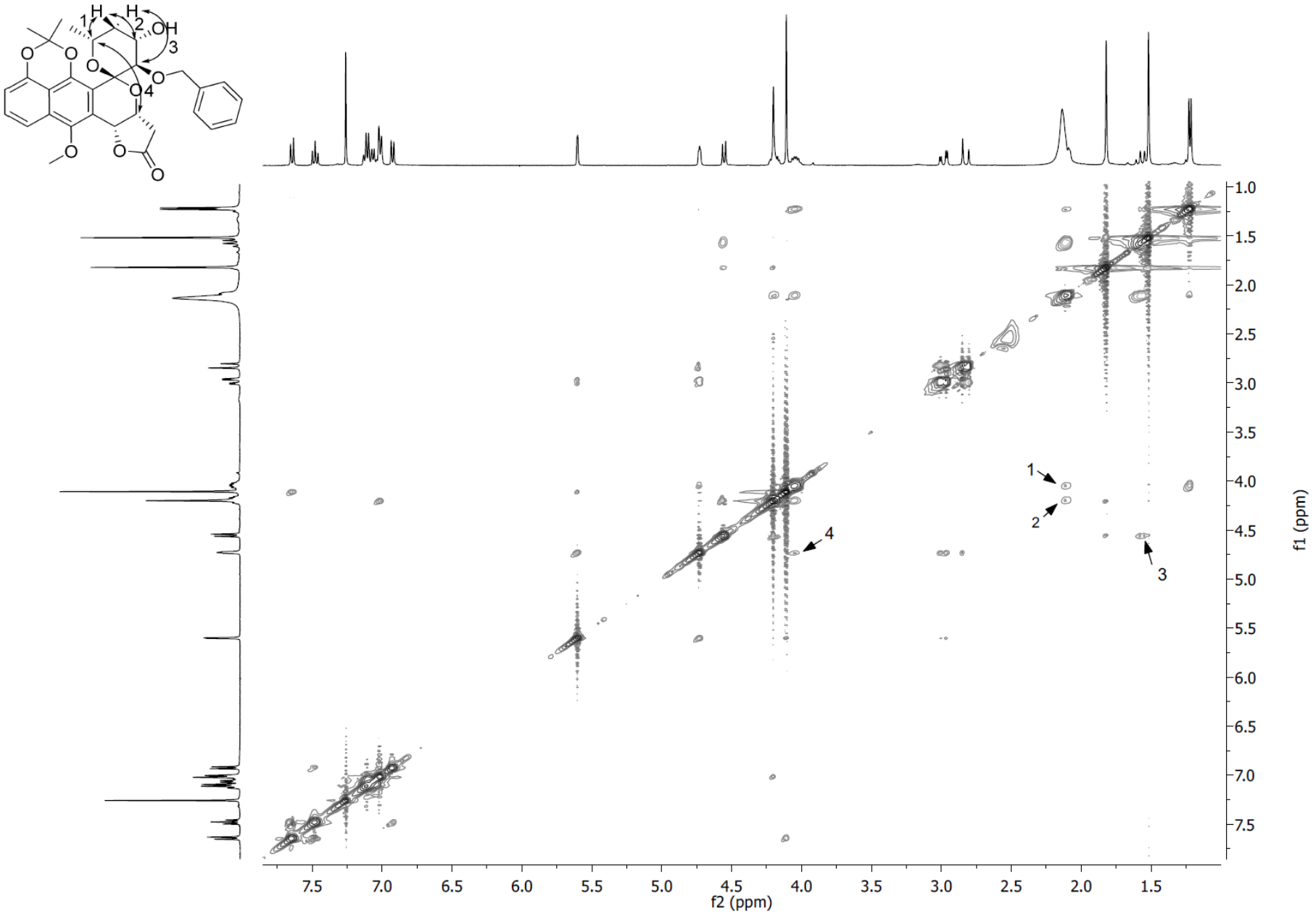



**Figure S130.** NOESY ($CDCl_3$, 400 MHz) of **38.**

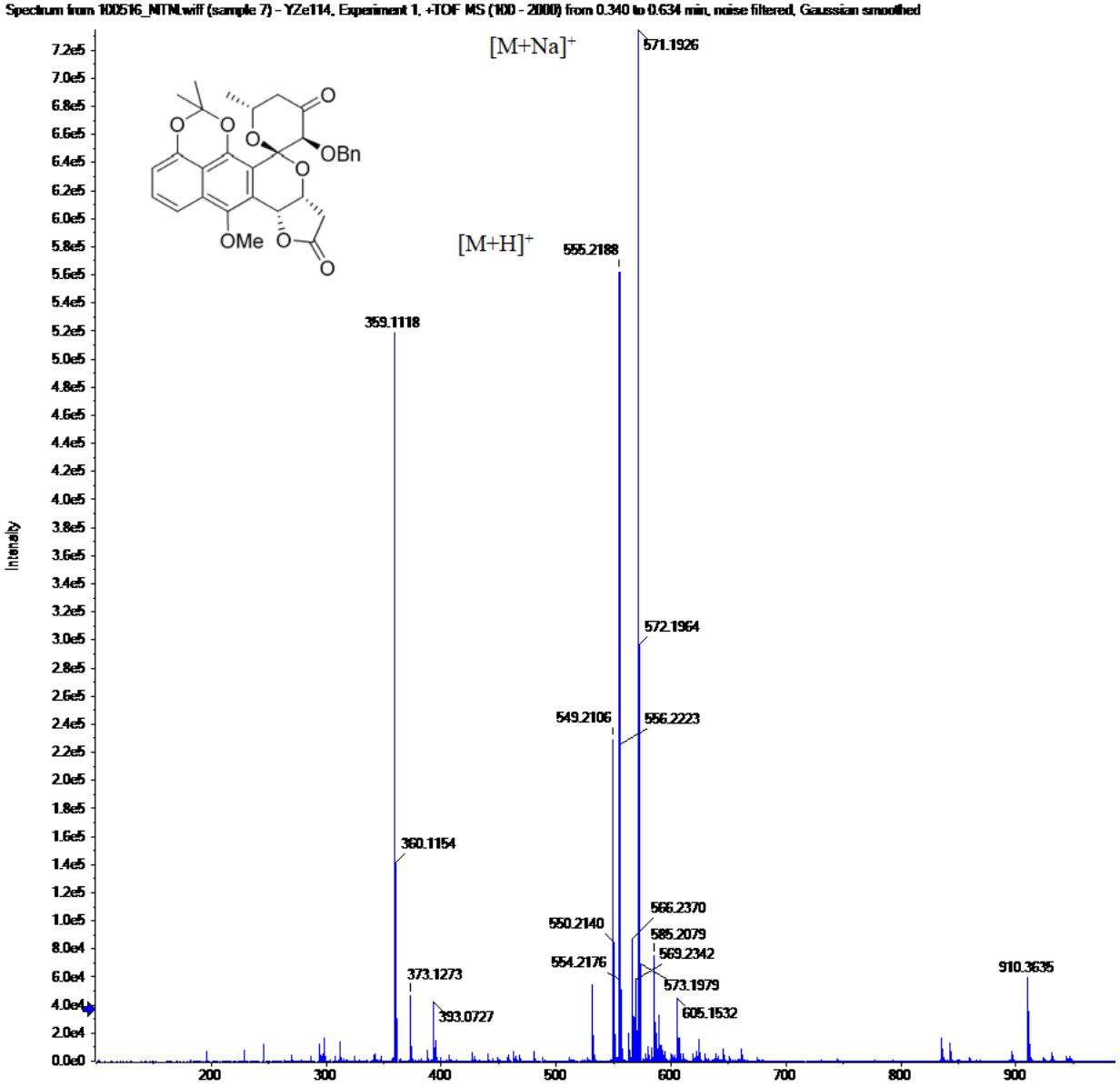



**Figure S131.** (+)-HRESI-MS of **38.**

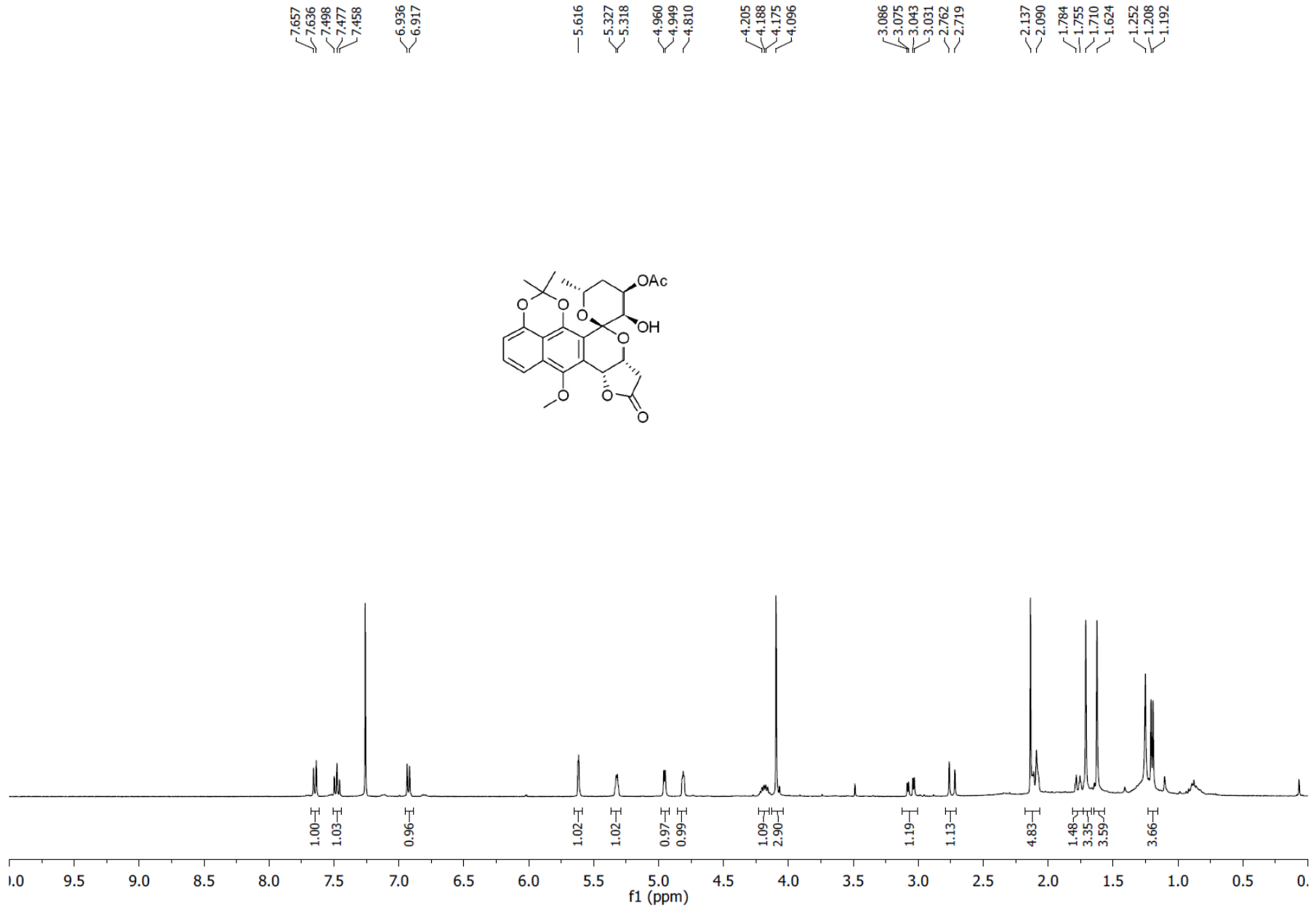



**Figure S132.** $^{1}$H-NMR ($CDCl_3$, 400 MHz) of **39.**

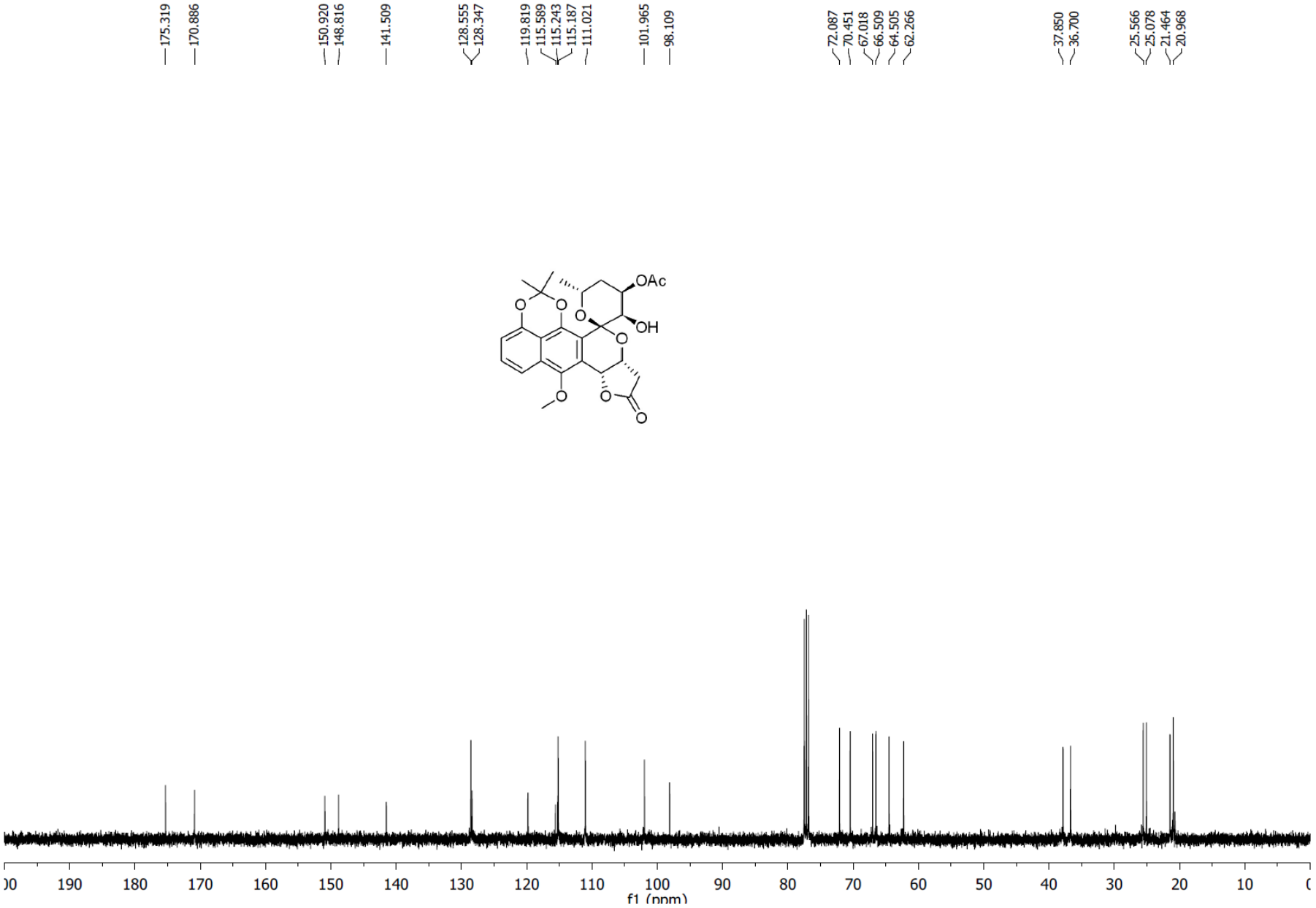



**Figure S133.** $^{13}$C-NMR ($CDCl_3$, 100 MHz) of **39.**

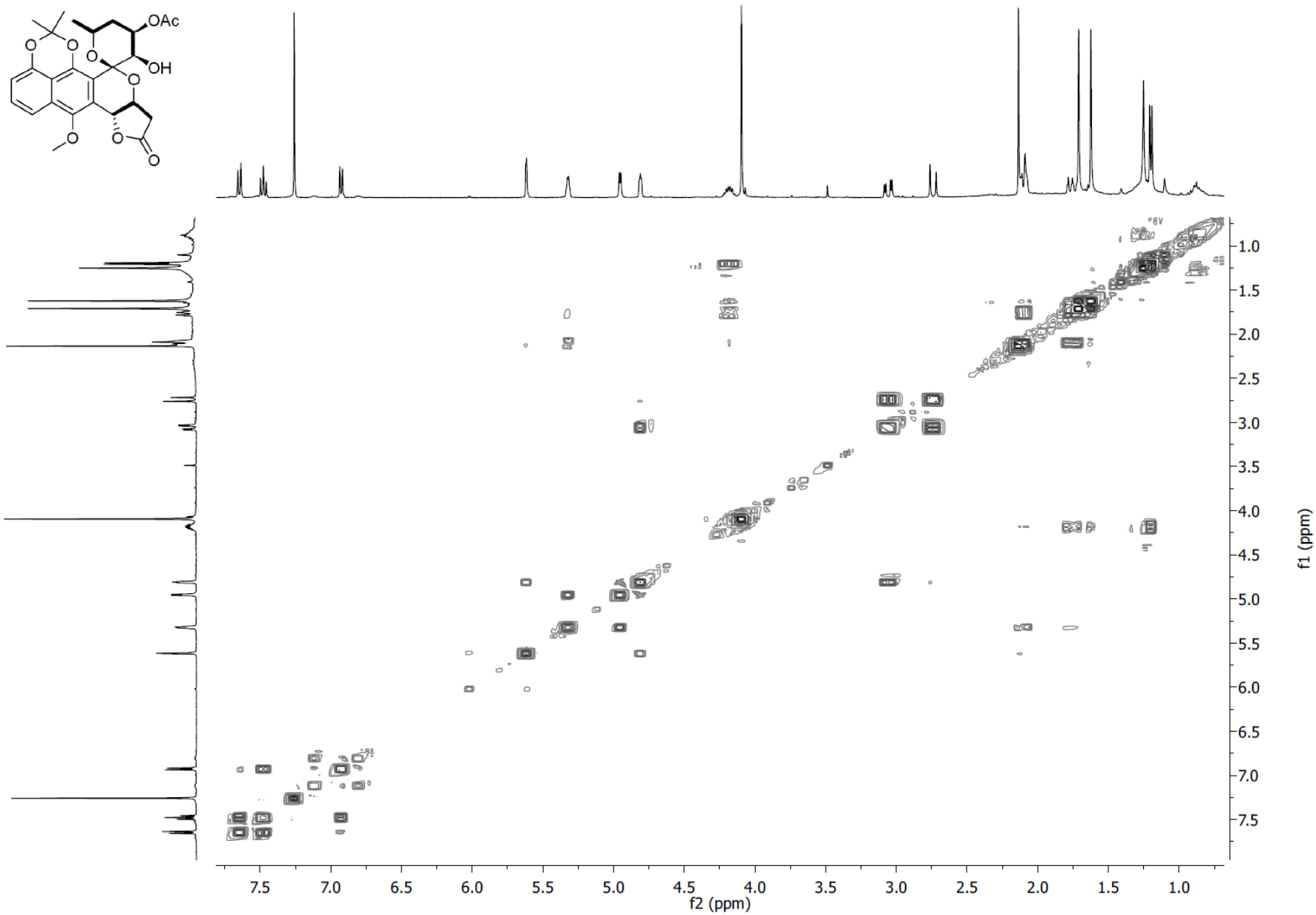



**Figure S134.** $^{1}H$-$^{1}H$ COSY ($CDCl_3$, 400 MHz) of **39.**

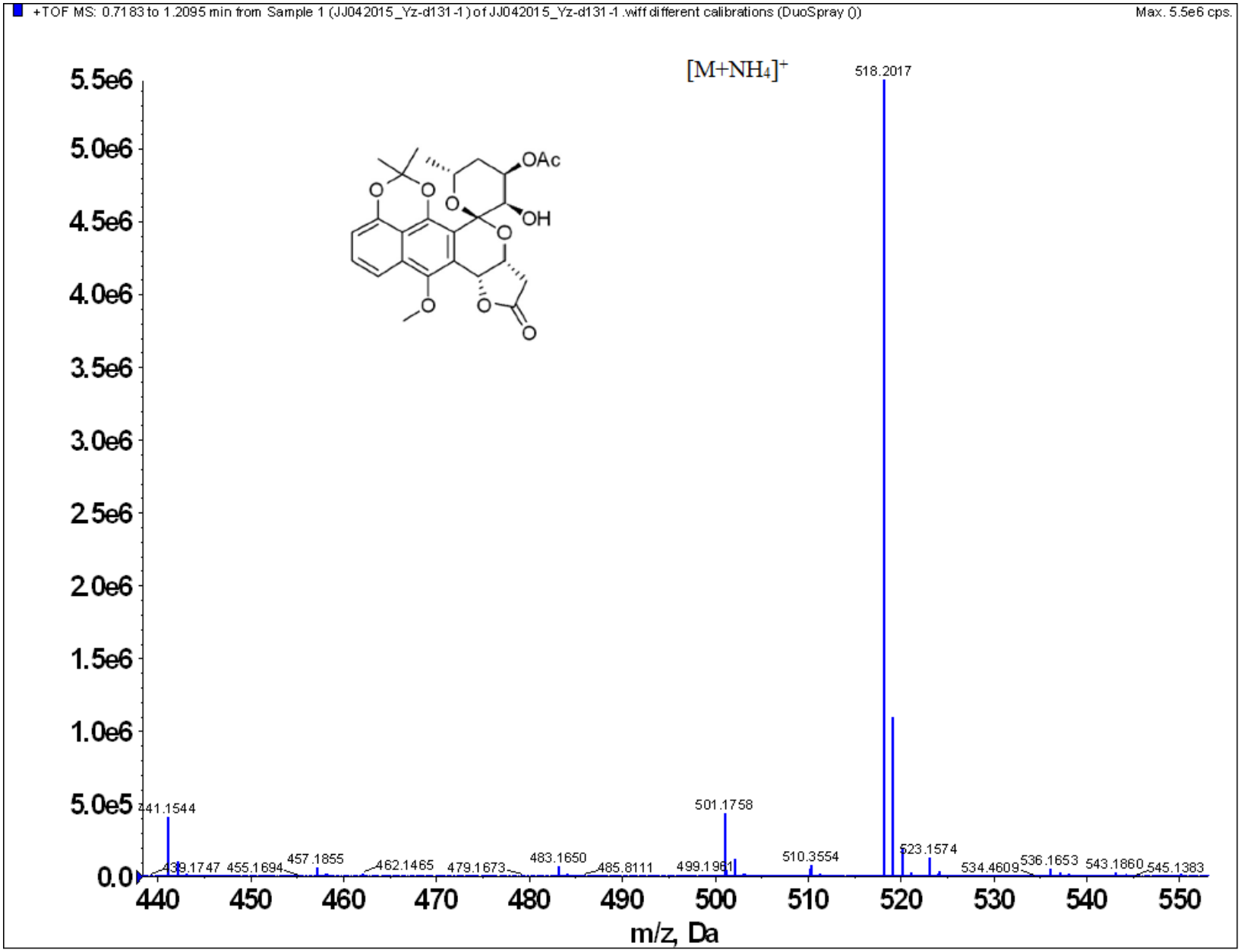



**Figure S135.** (+)-HRESI-MS of **39.**

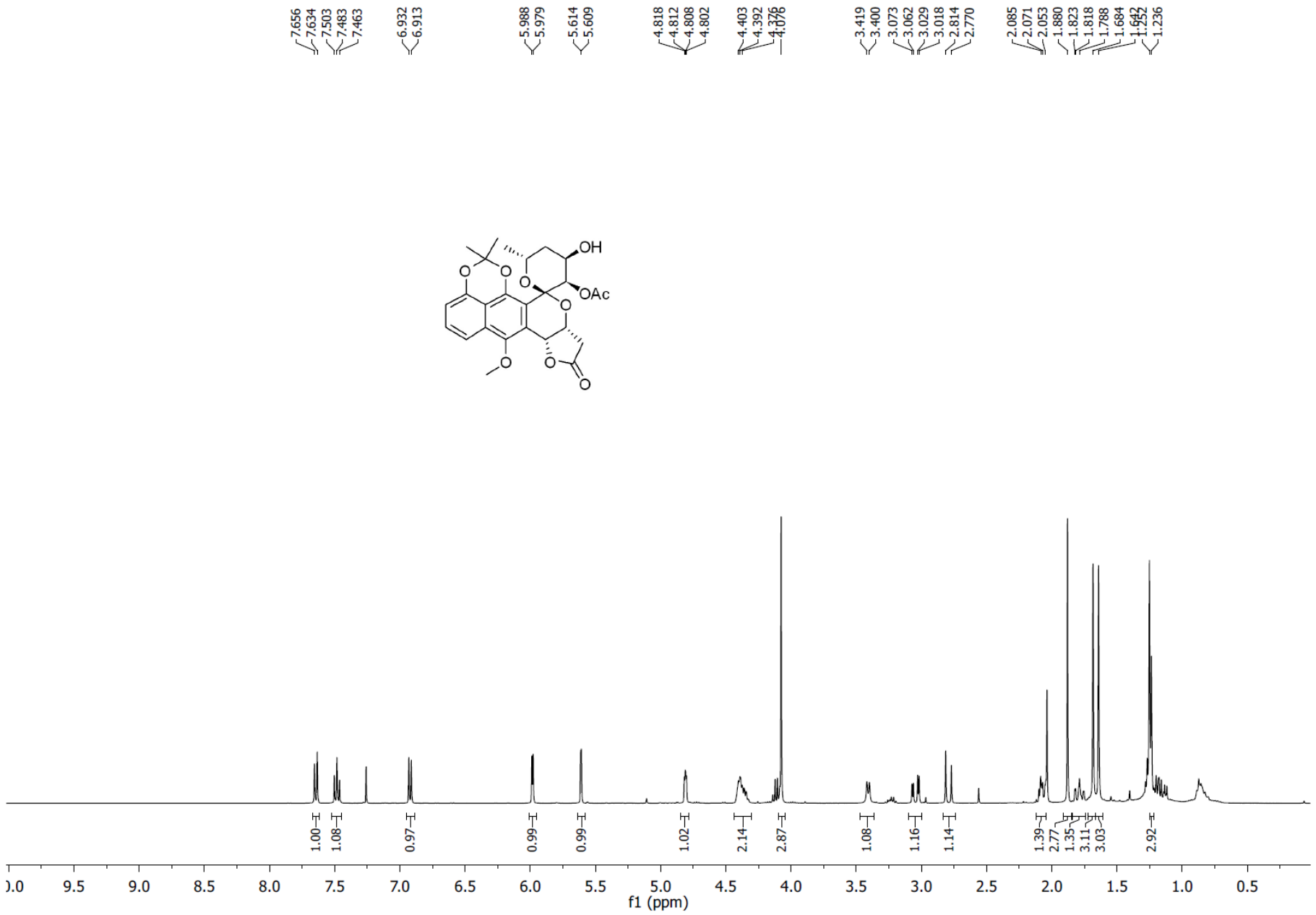



**Figure S136.** $^{1}$H-NMR ($CDCl_3$, 400 MHz) of **40.**

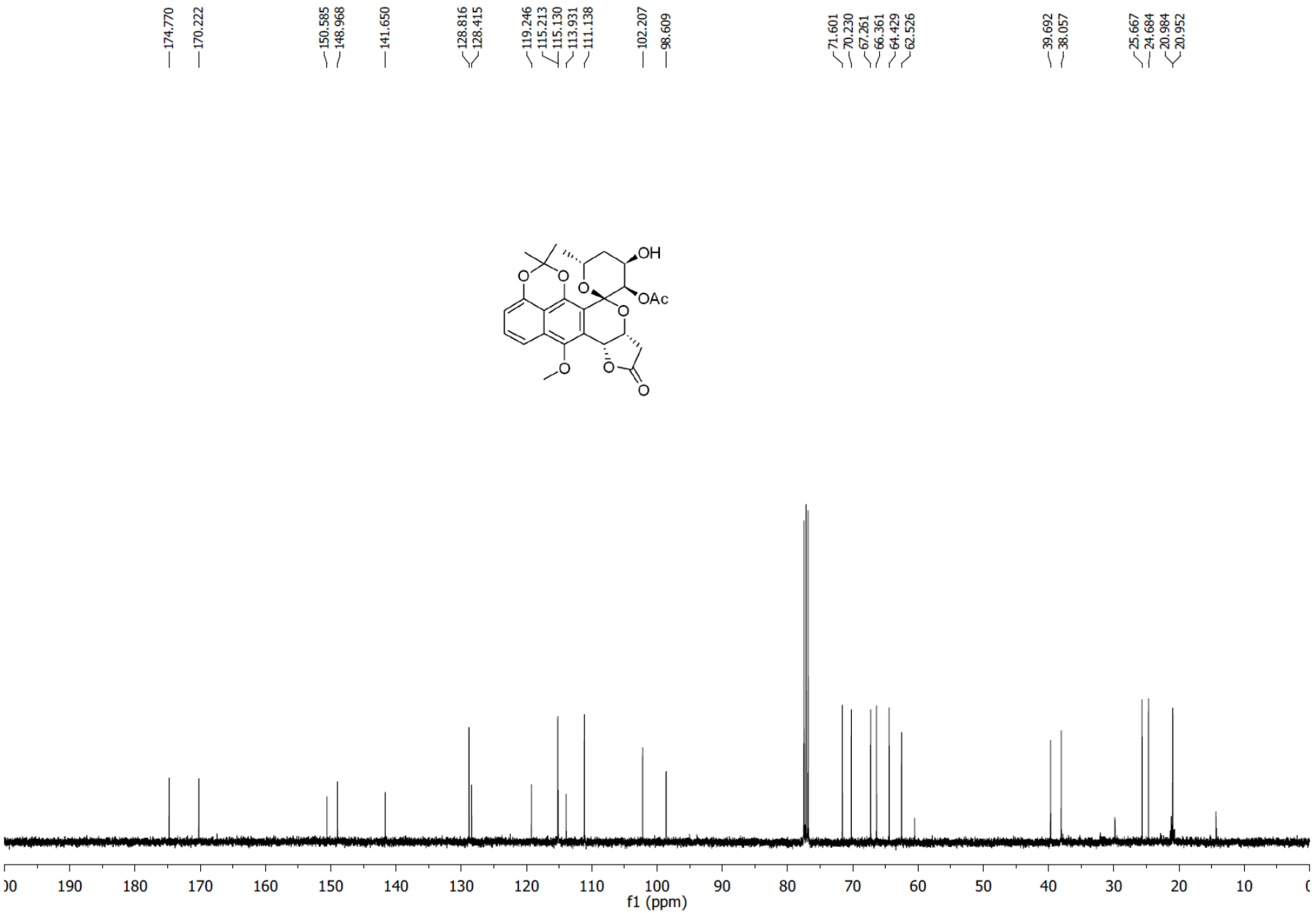



**Figure S137.** $^{13}$C-NMR ($CDCl_3$, 100 MHz) of **40.**

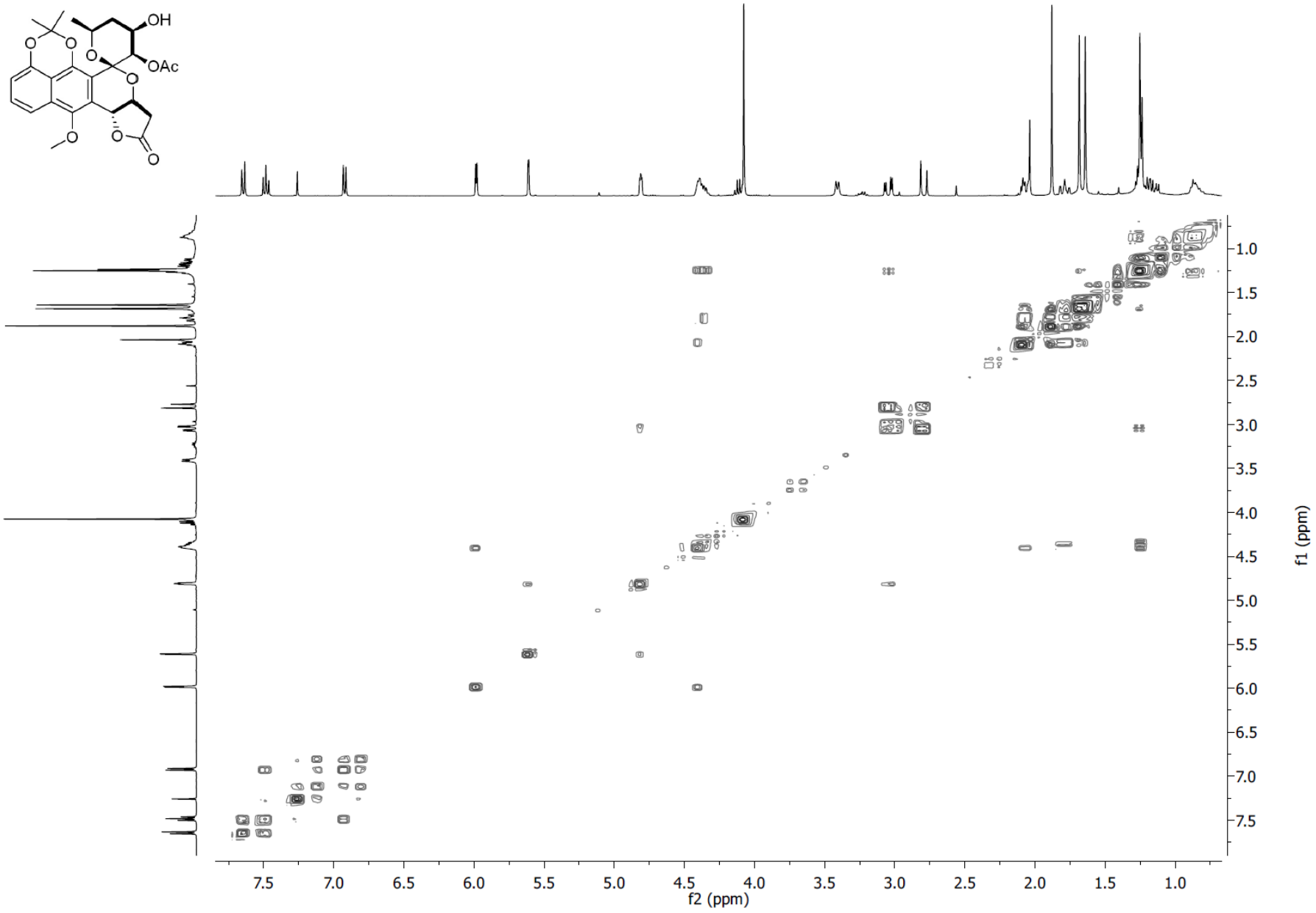



**Figure S138.** $^{1}$H-$^{1}$H COSY ($CDCl_3$, 400 MHz) of **40.**

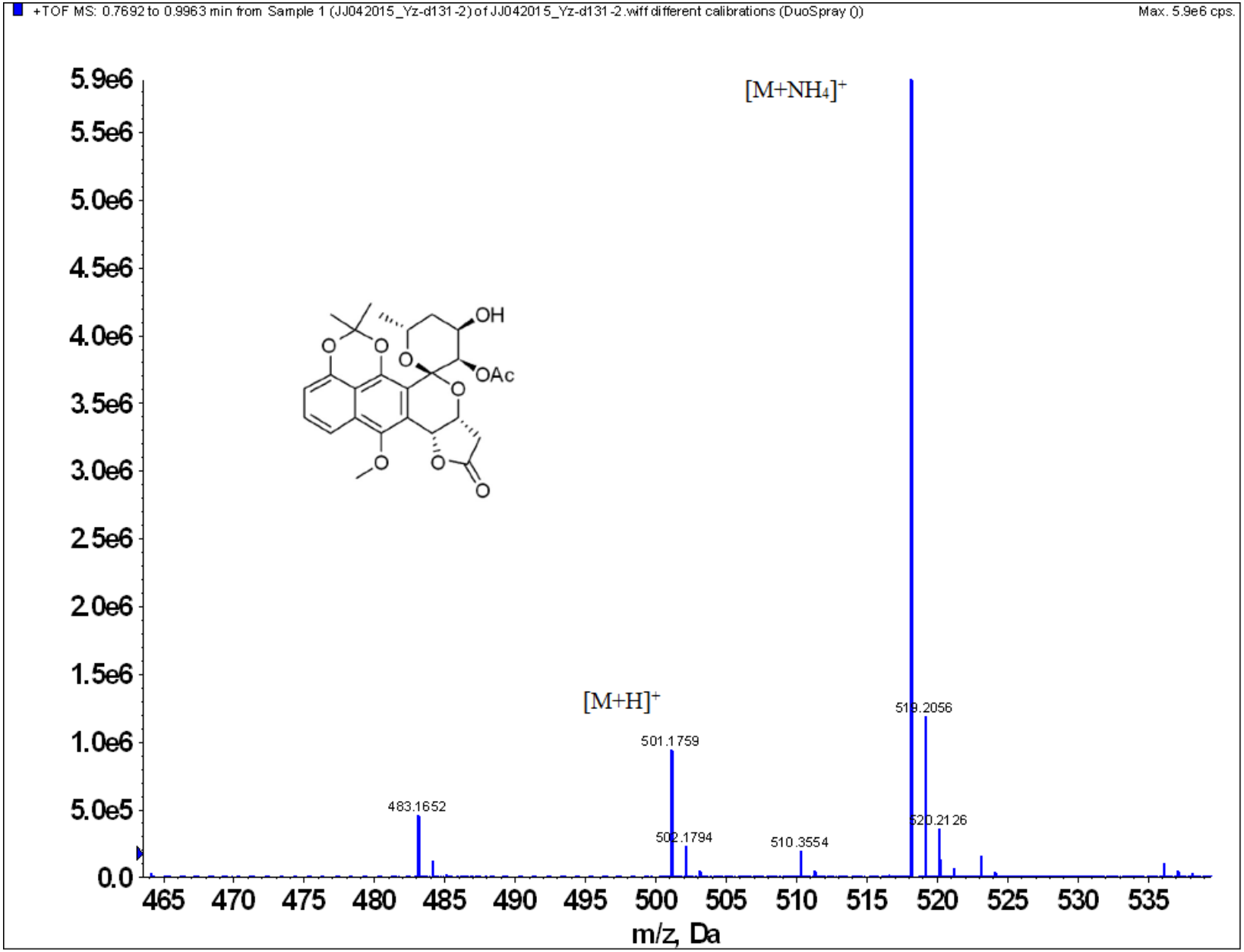



**Figure S139.** (+)-HRESI-MS of **40.**

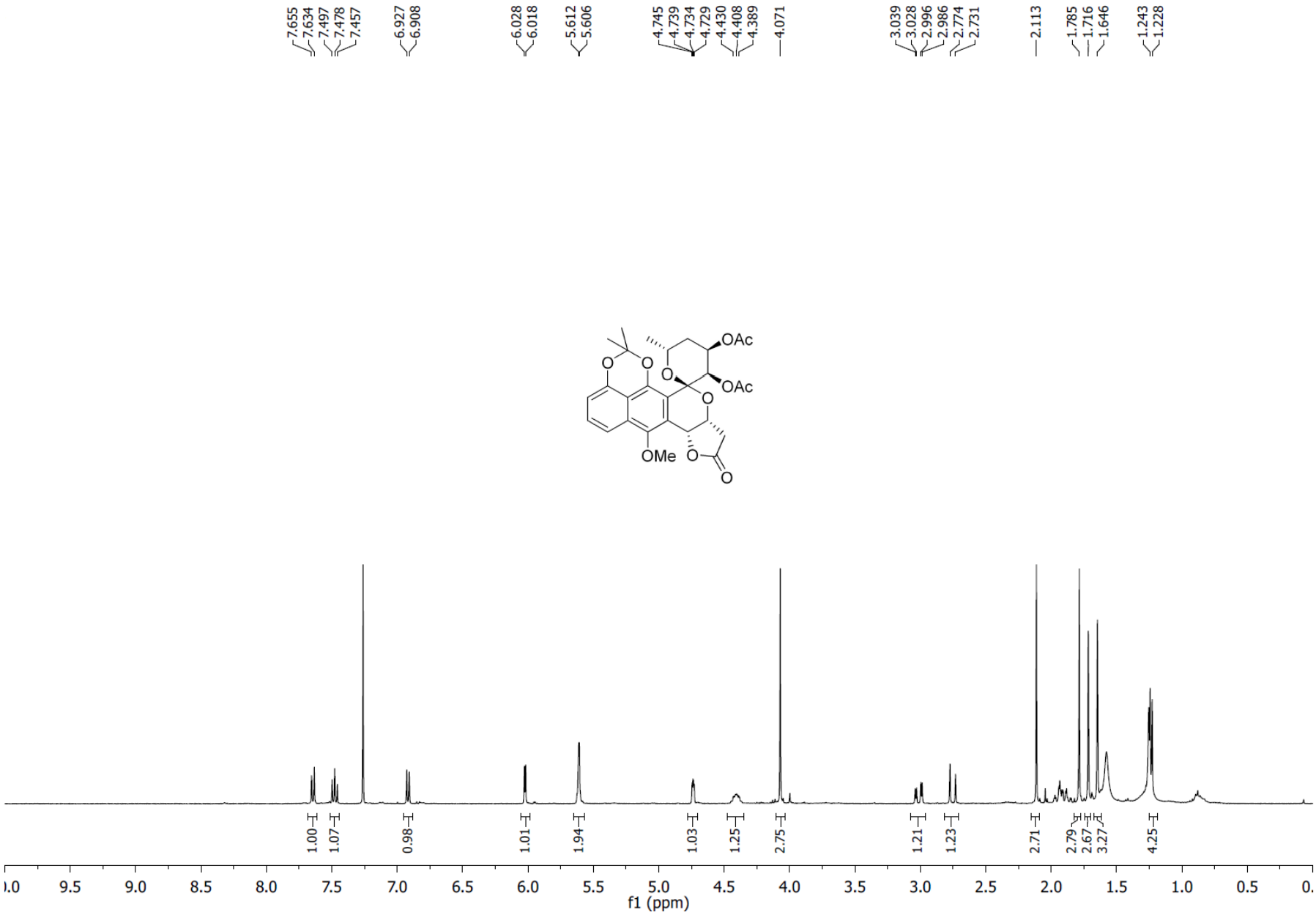



**Figure S140.** $^{1}$H-NMR ($CDCl_3$, 400 MHz) of **41.**

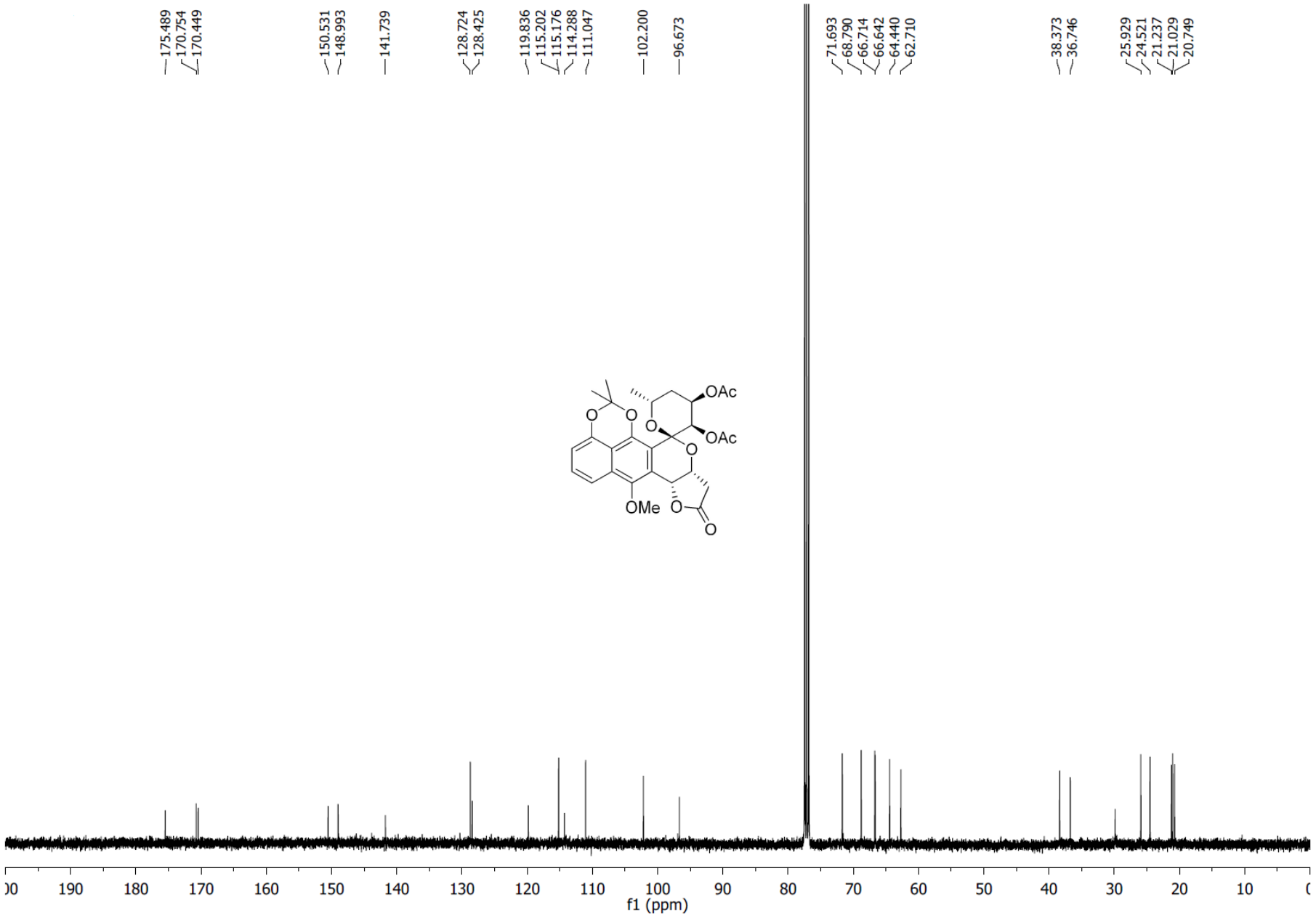



**Figure S141.** $^{13}$C-NMR ($CDCl_3$, 100 MHz) of **41.**

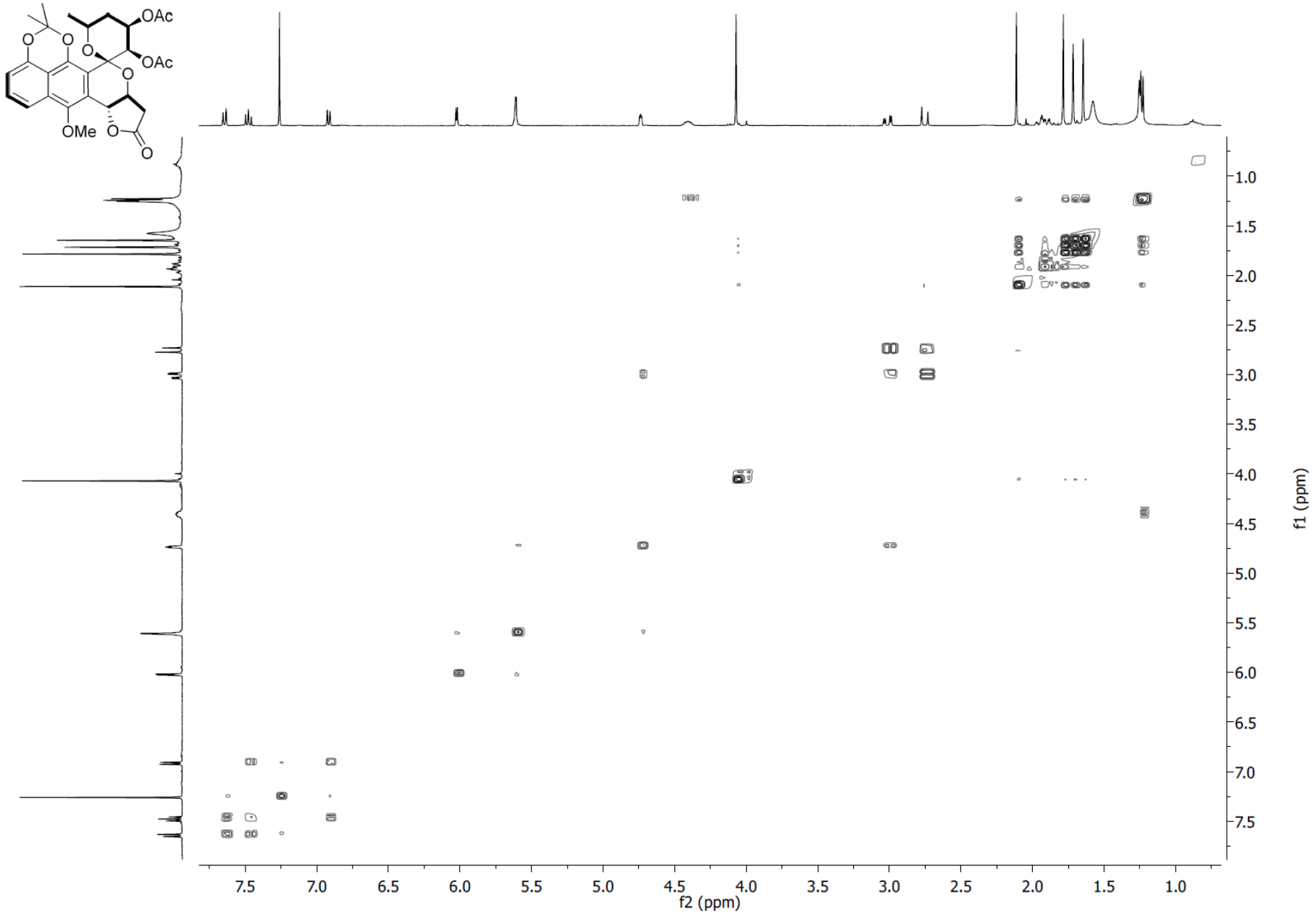



**Figure S142.** $^{1}$H-$^{1}$H COSY ($CDCl_3$, 400 MHz) of **41.**

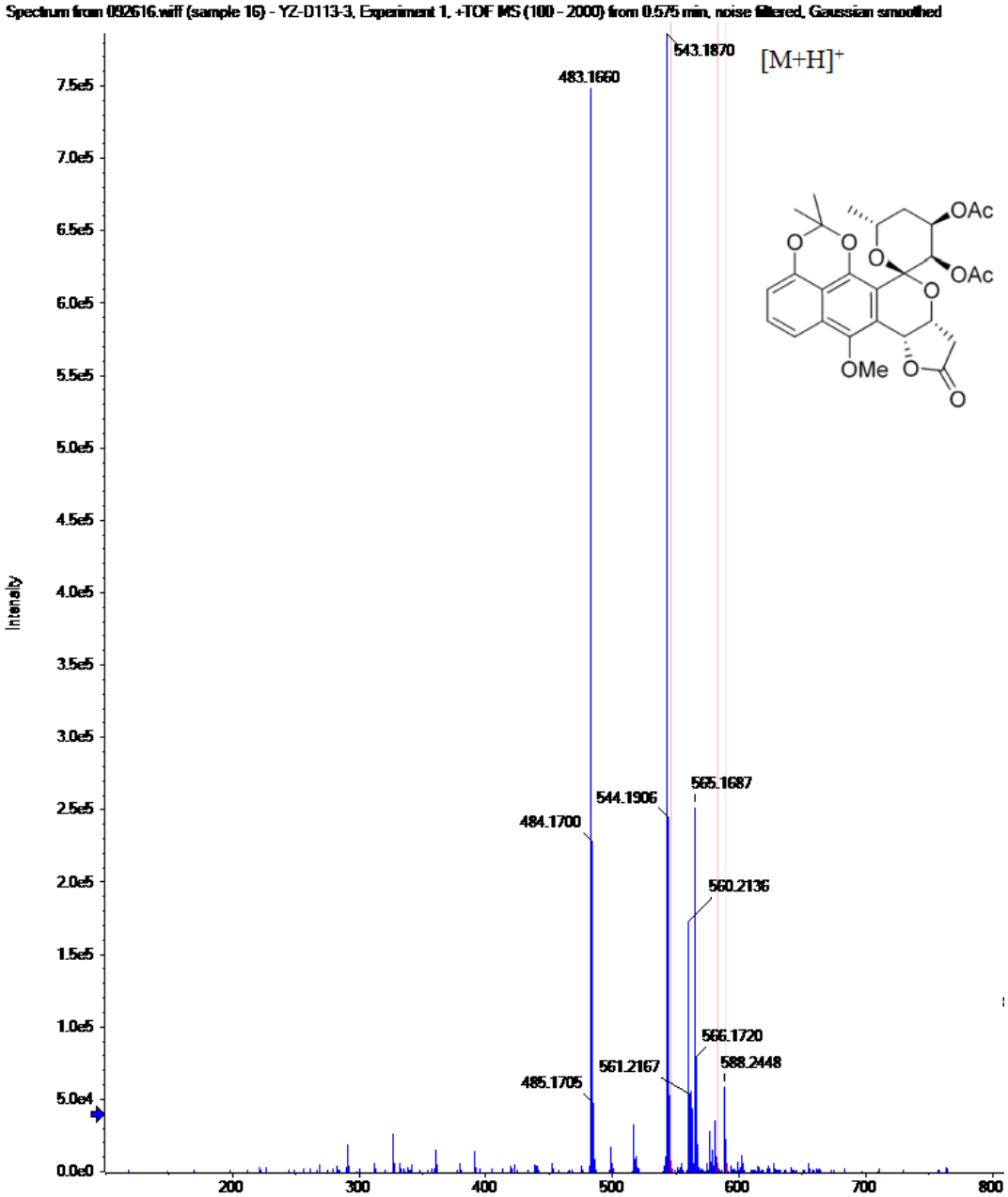



**Figure S143.** (+)-HRESI-MS of **41.**

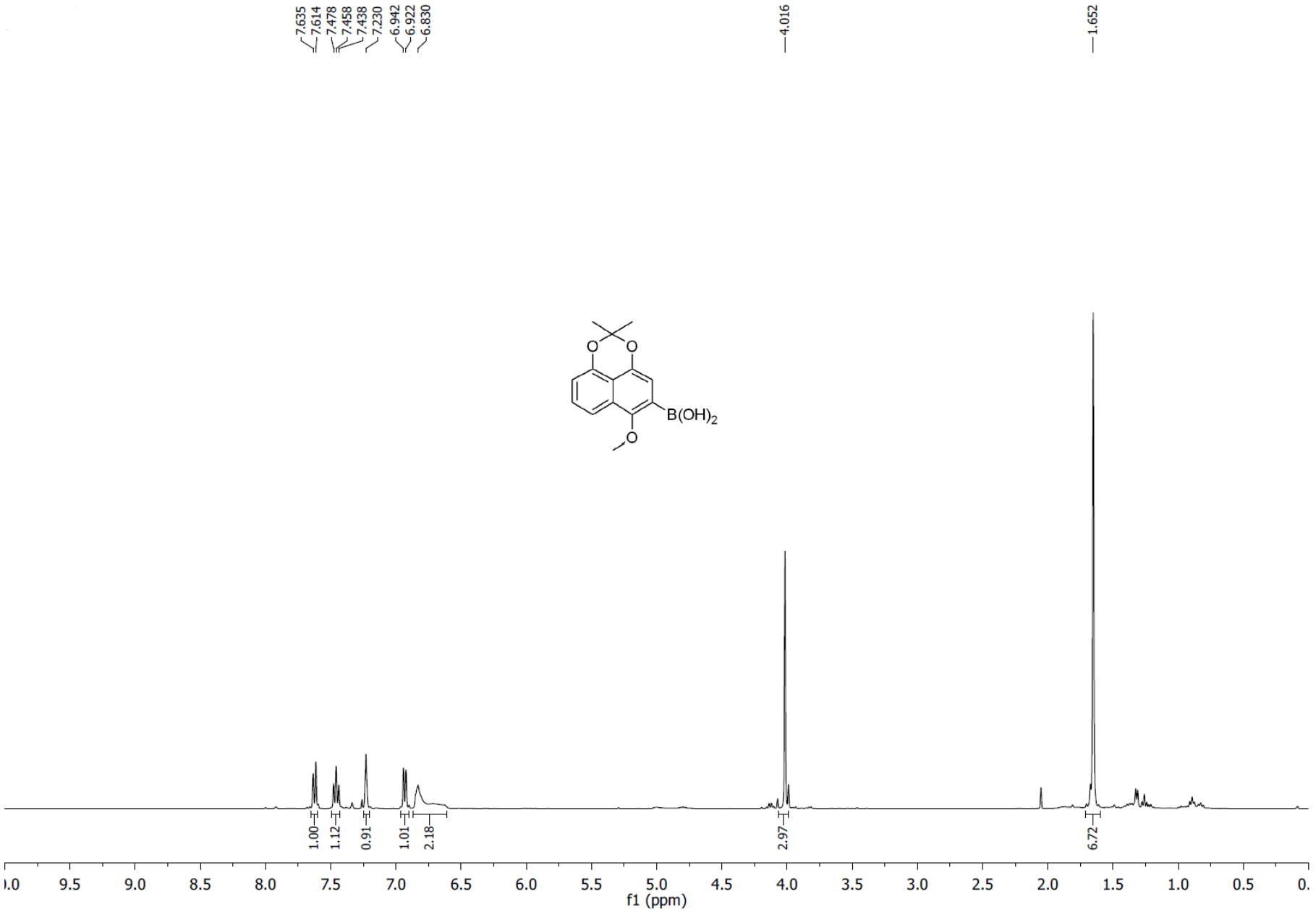



**Figure S144.** $^{1}$H-NMR ($CDCl_3$, 400 MHz) of **42.**

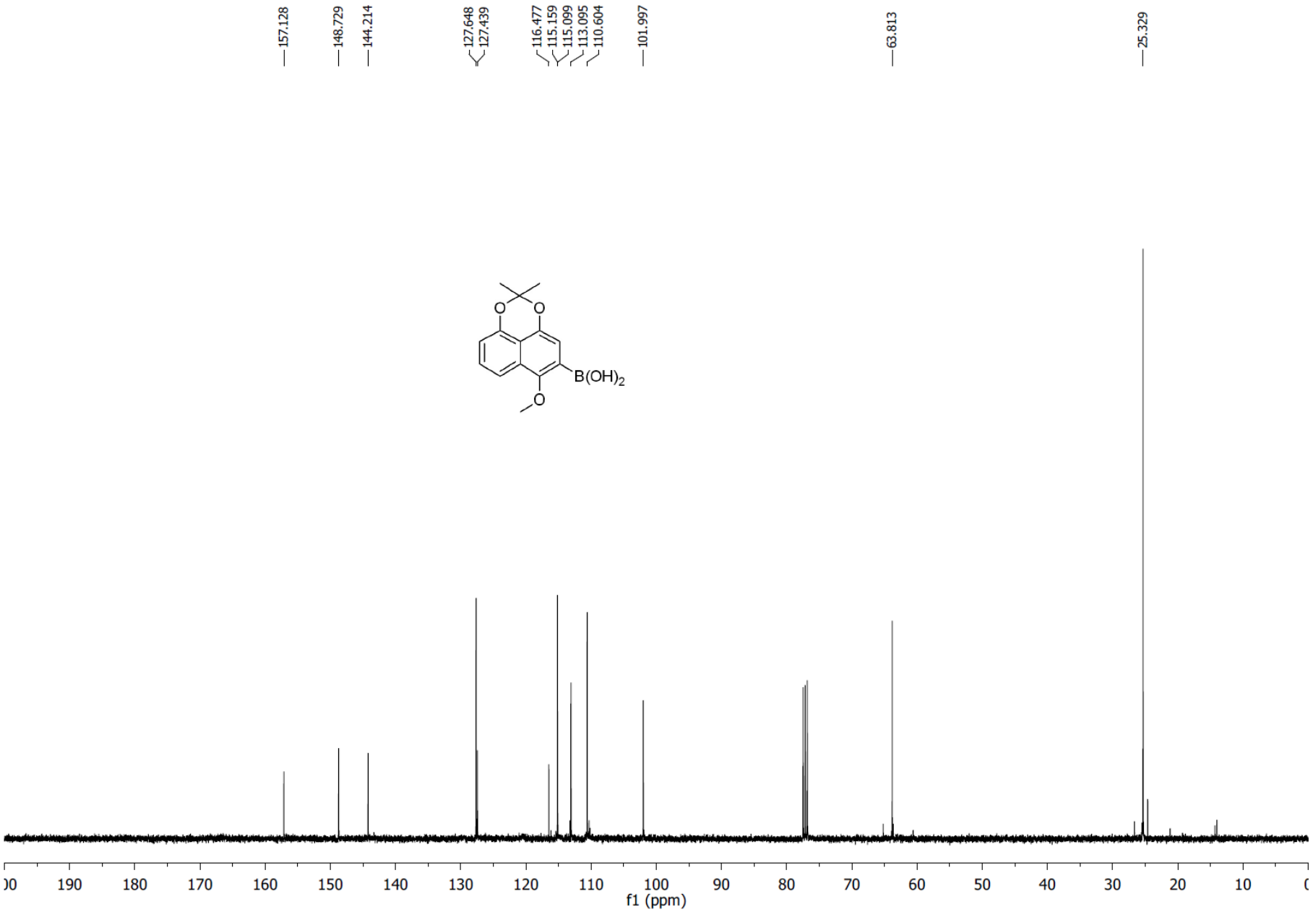



**Figure S145.** $^{13}$C-NMR ($CDCl_3$, 100 MHz) of **42.**

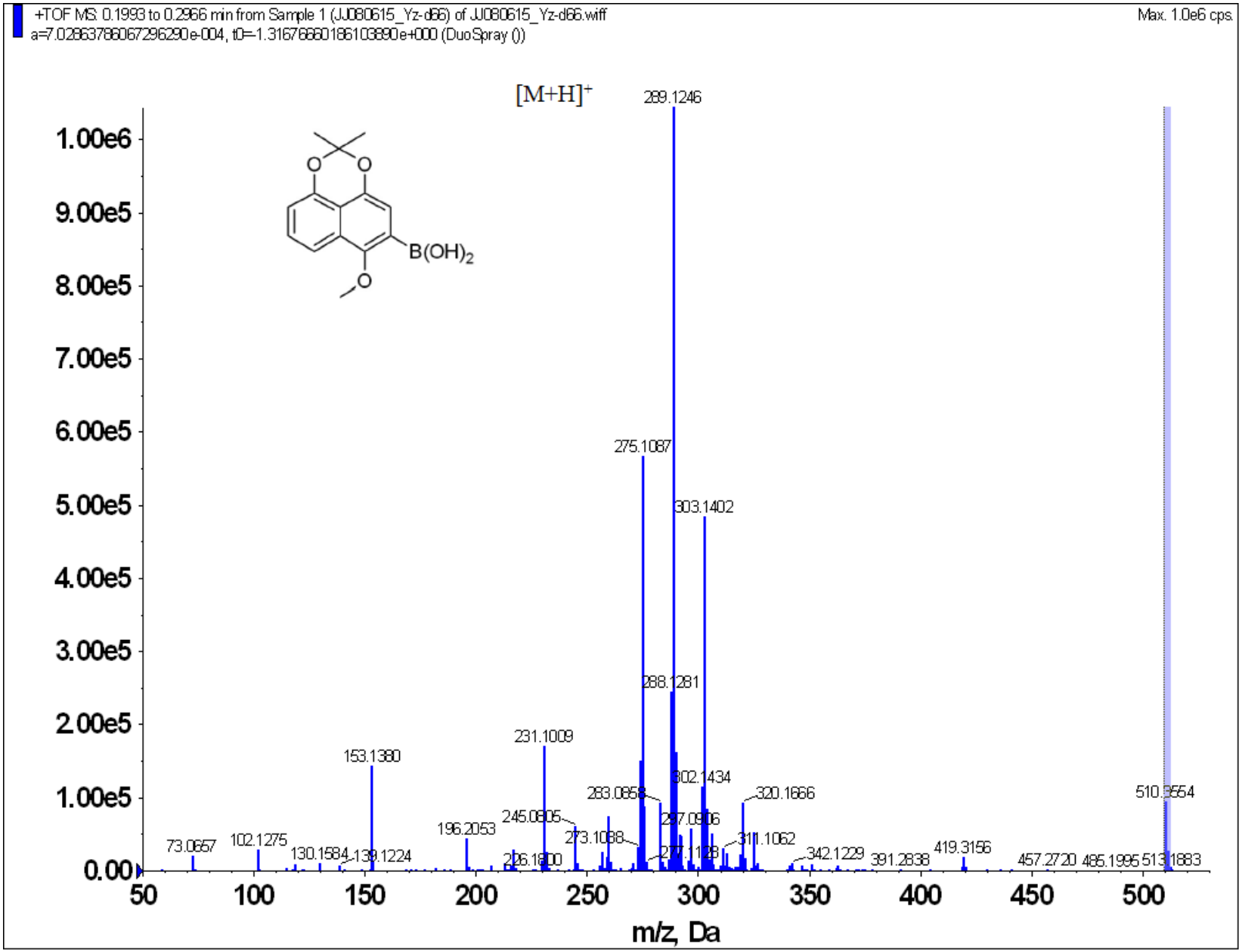



**Figure S146.** (+)-HRESI-MS of **42.**

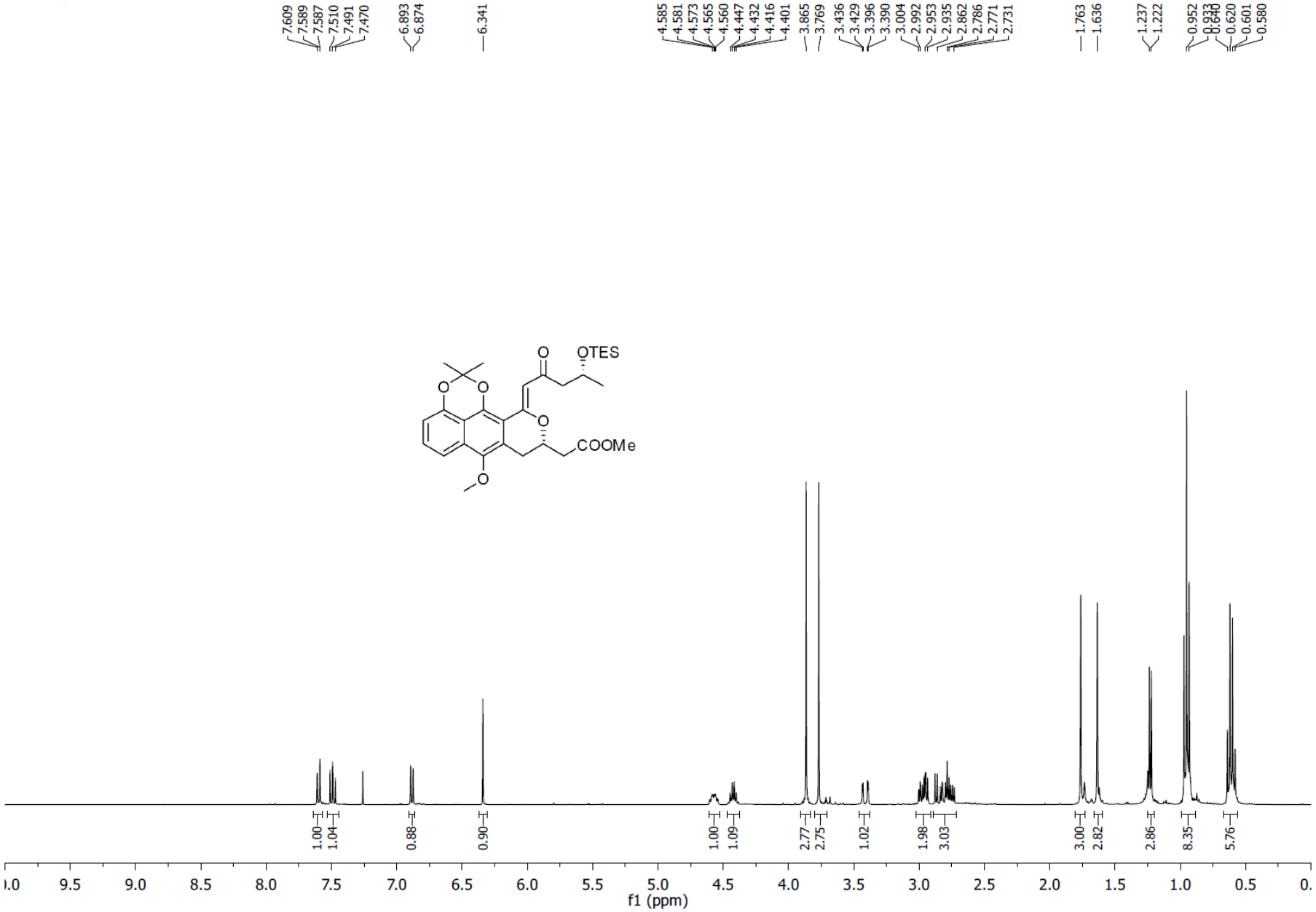



**Figure S147.** $^{1}$H-NMR ($CDCl_3$, 400 MHz) of **43.**

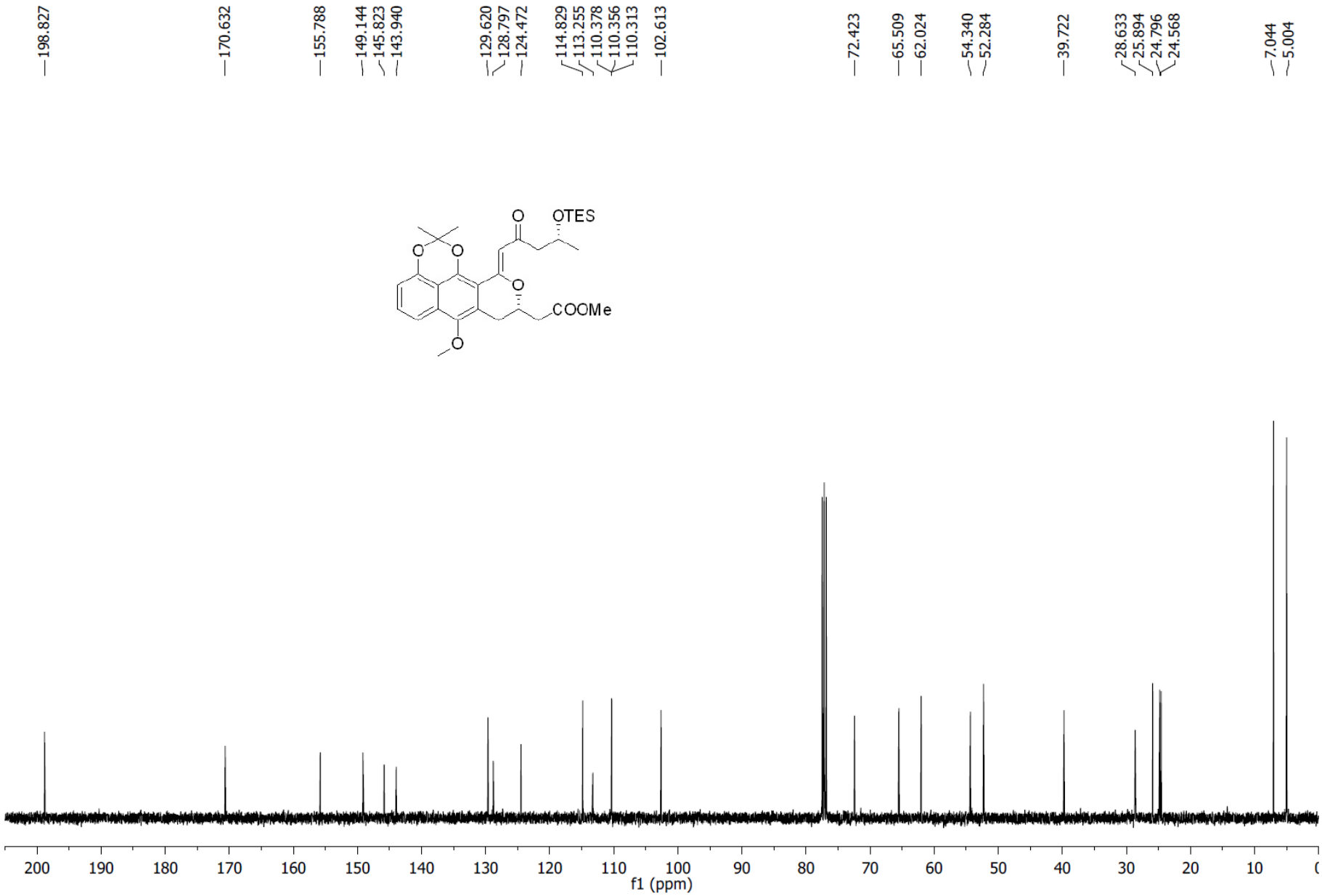



**Figure S148.** $^{13}$C-NMR ($CDCl_3$, 100 MHz) of **43.**

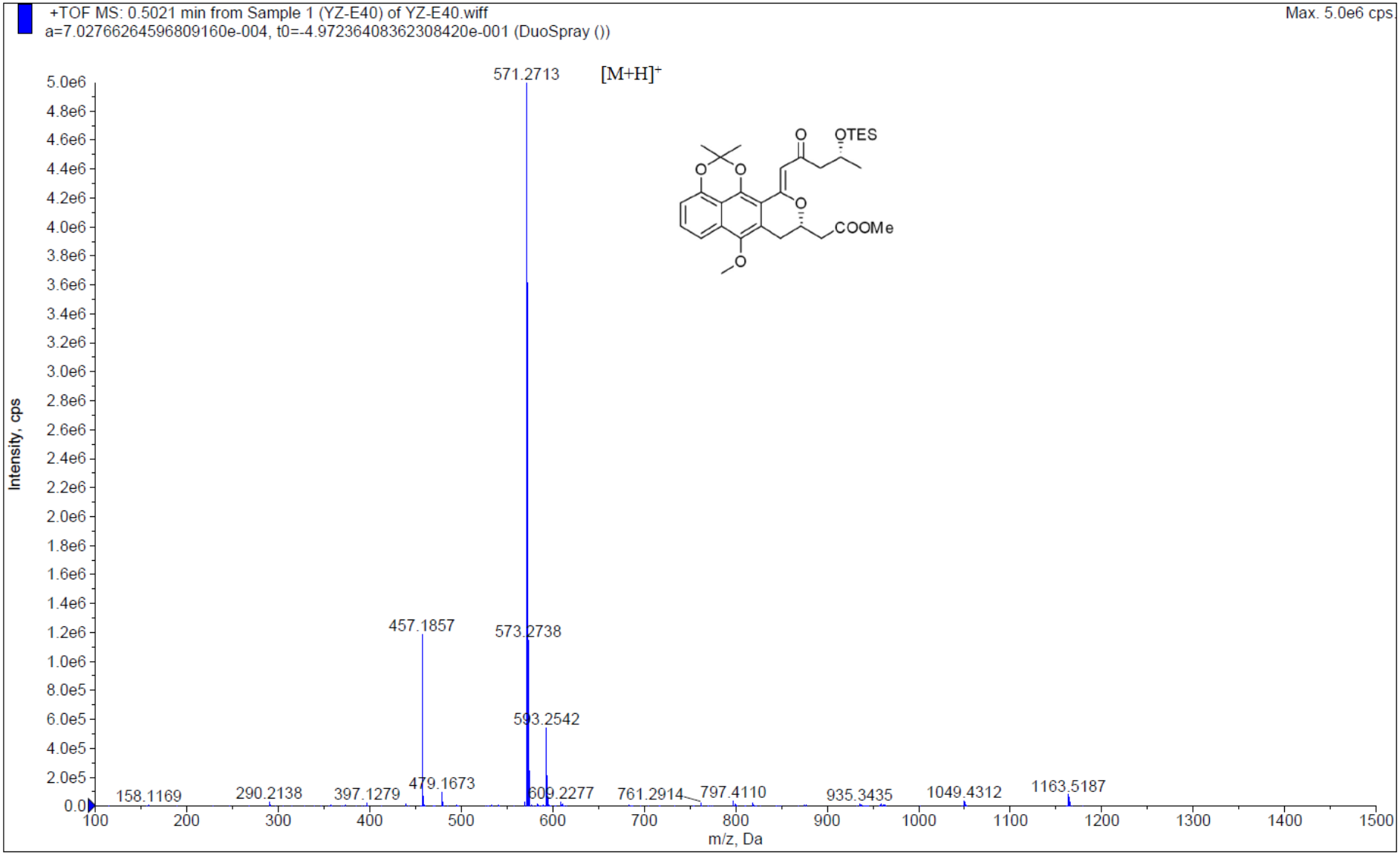



**Figure S149.** (+)-HRESI-MS of **43.**

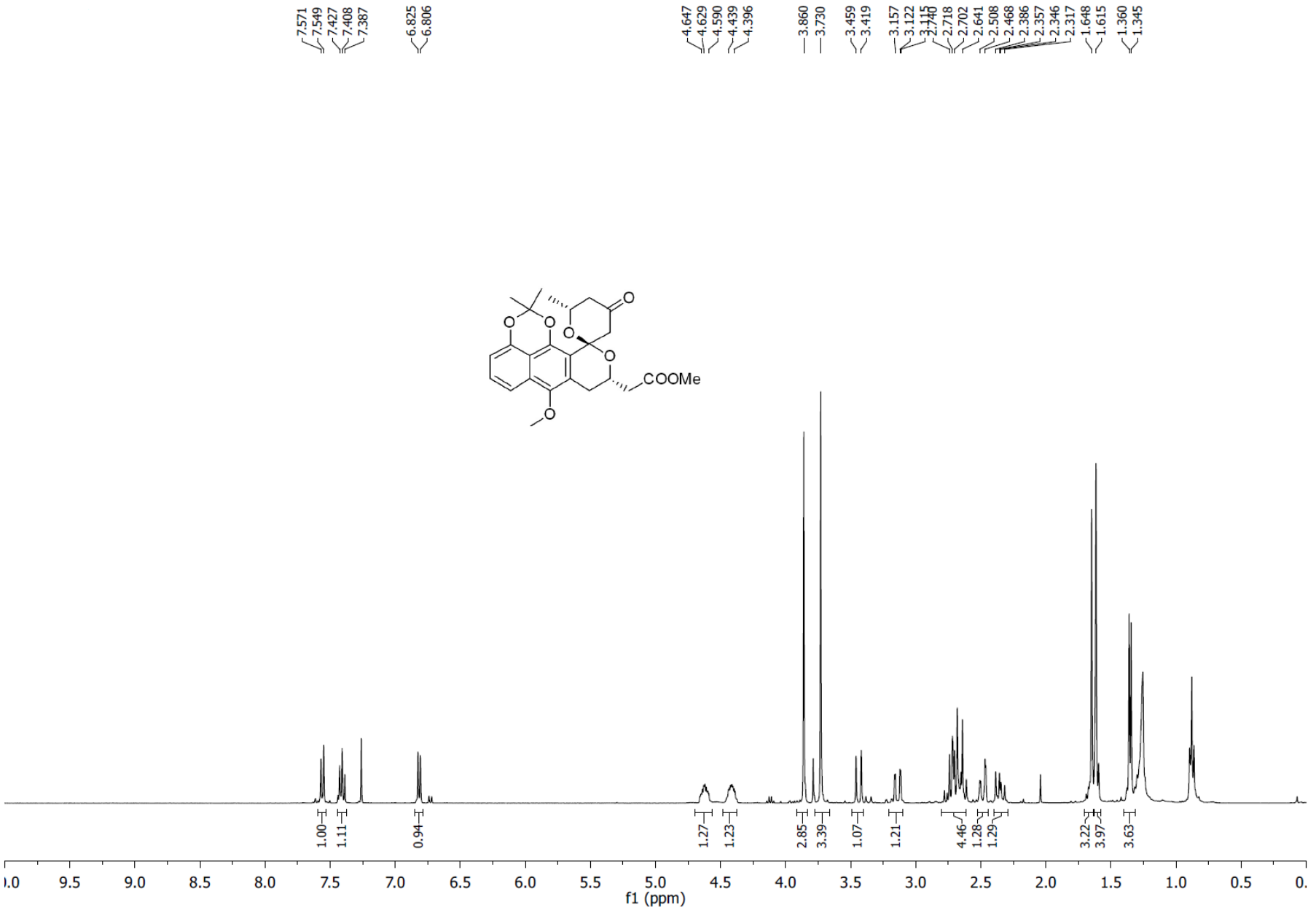



**Figure S150.** $^{1}$H-NMR ($CDCl_3$, 400 MHz) of **44.**

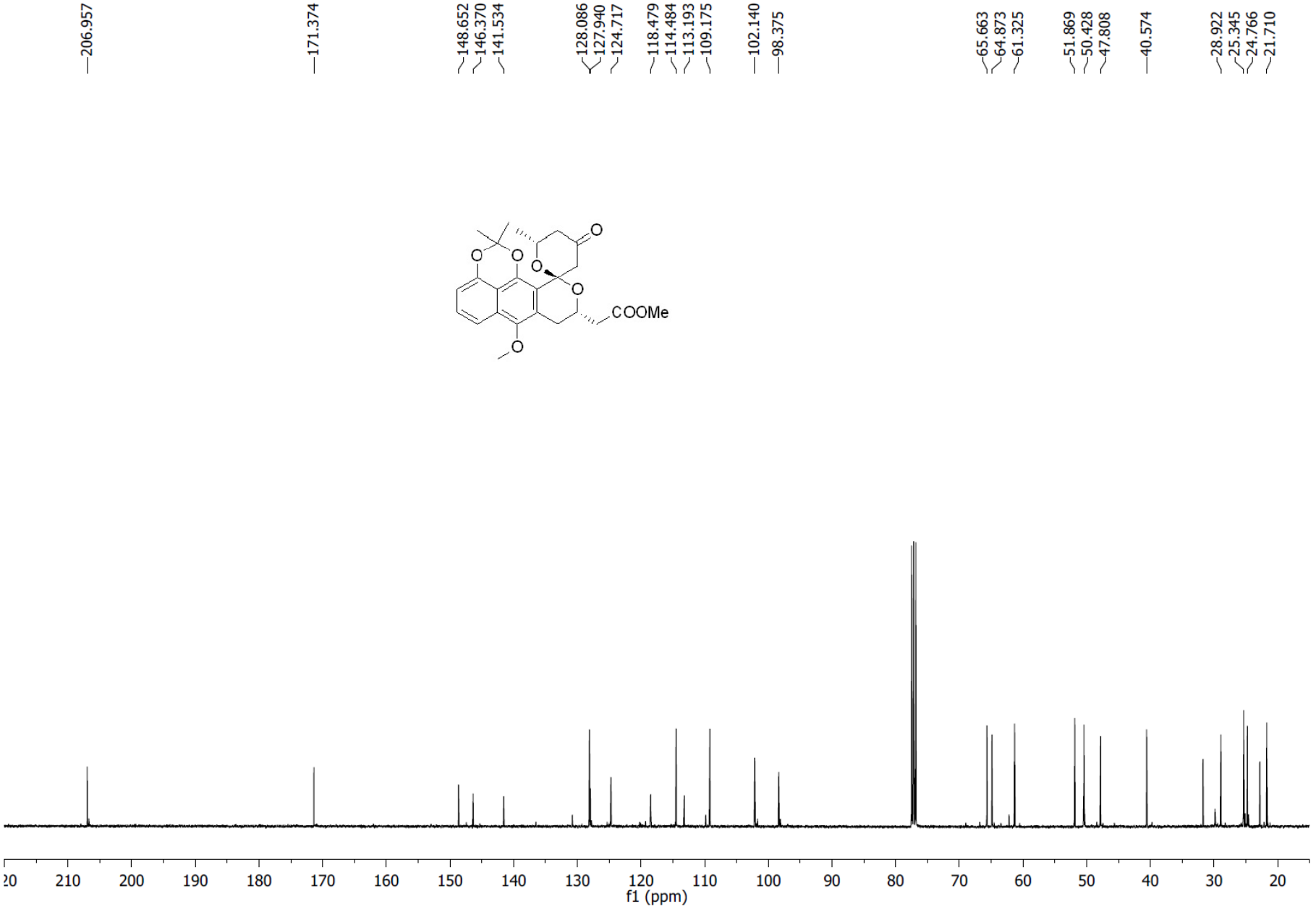



**Figure S151.** $^{13}$C-NMR ($CDCl_3$, 100 MHz) of **44.**

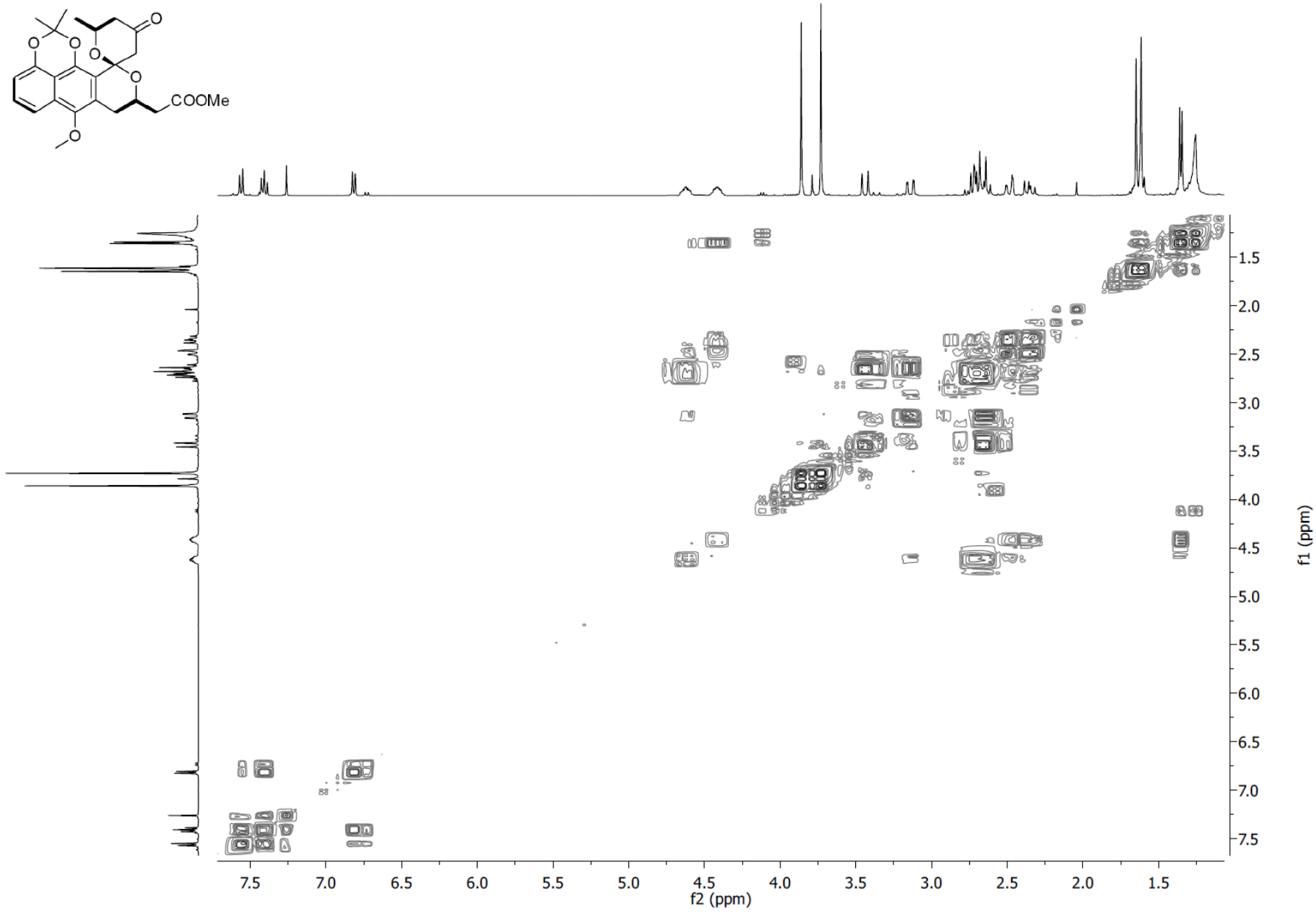



**Figure S152.** $^{1}H$-$^{1}H$ COSY ($CDCl_3$, 400 MHz) of **44.**

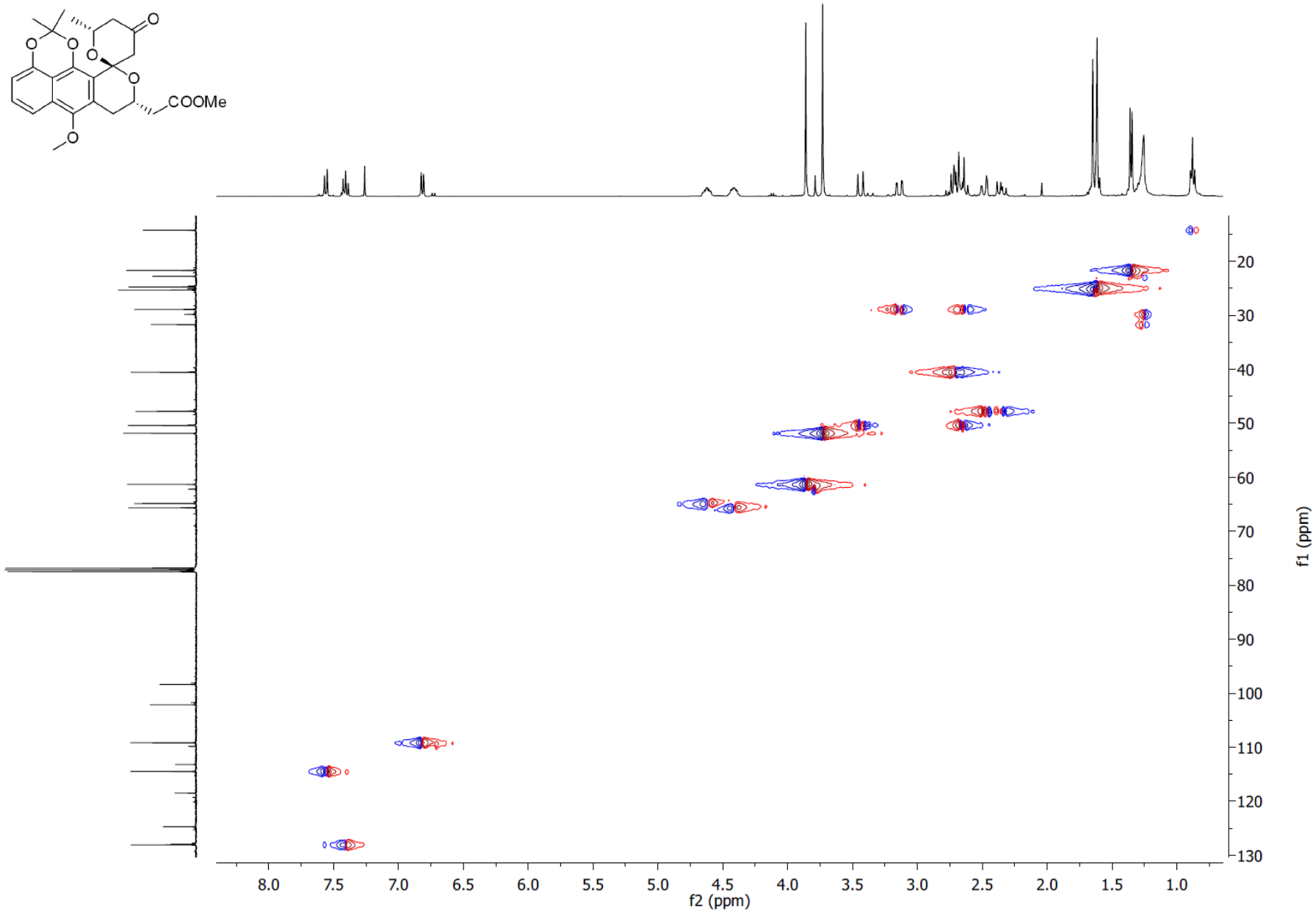



**Figure S153.** HSQC ($CDCl_3$, 400 MHz) of **44.**

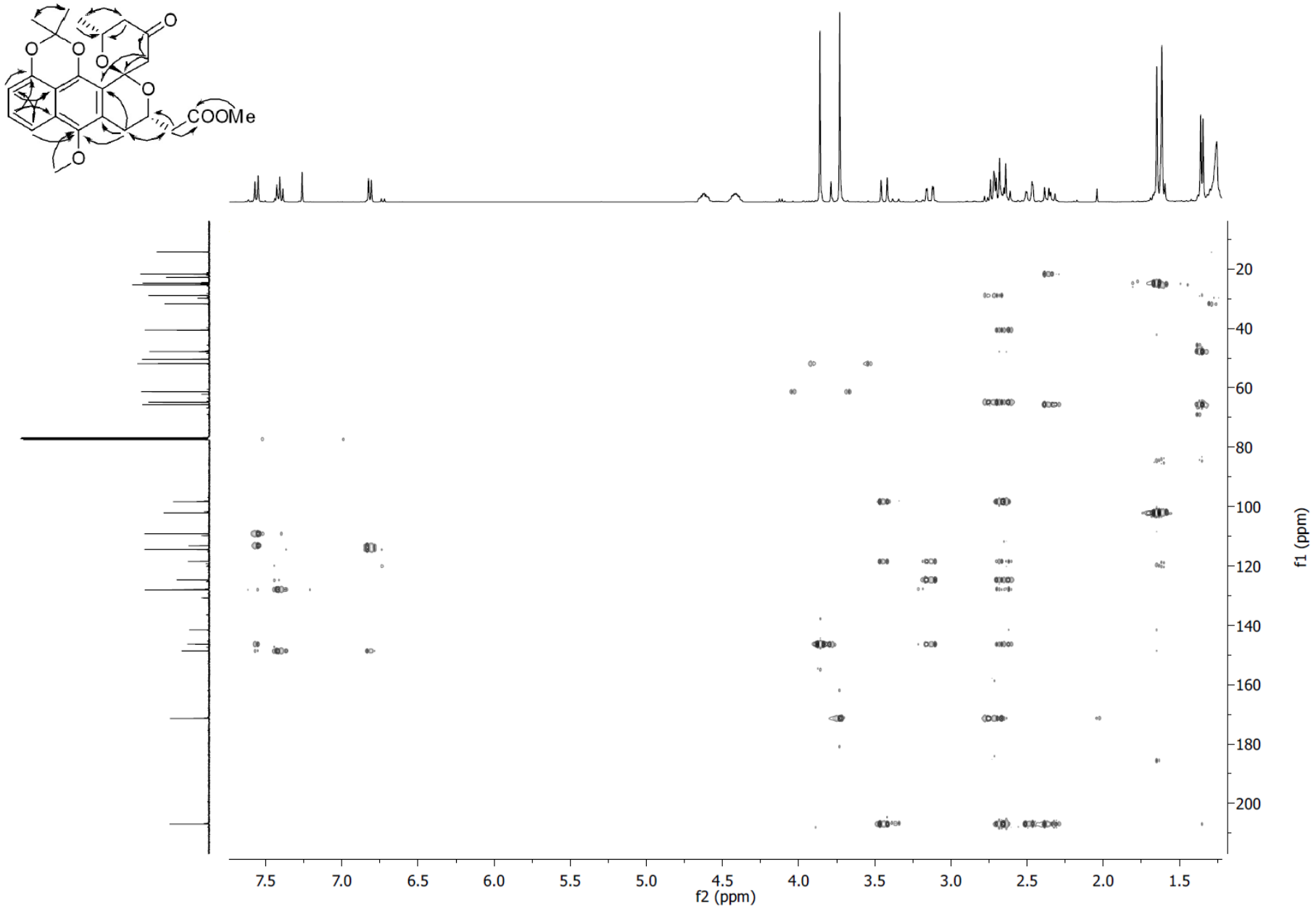



**Figure S154.** HMBC ($CDCl_3$, 400 MHz) of **44.**

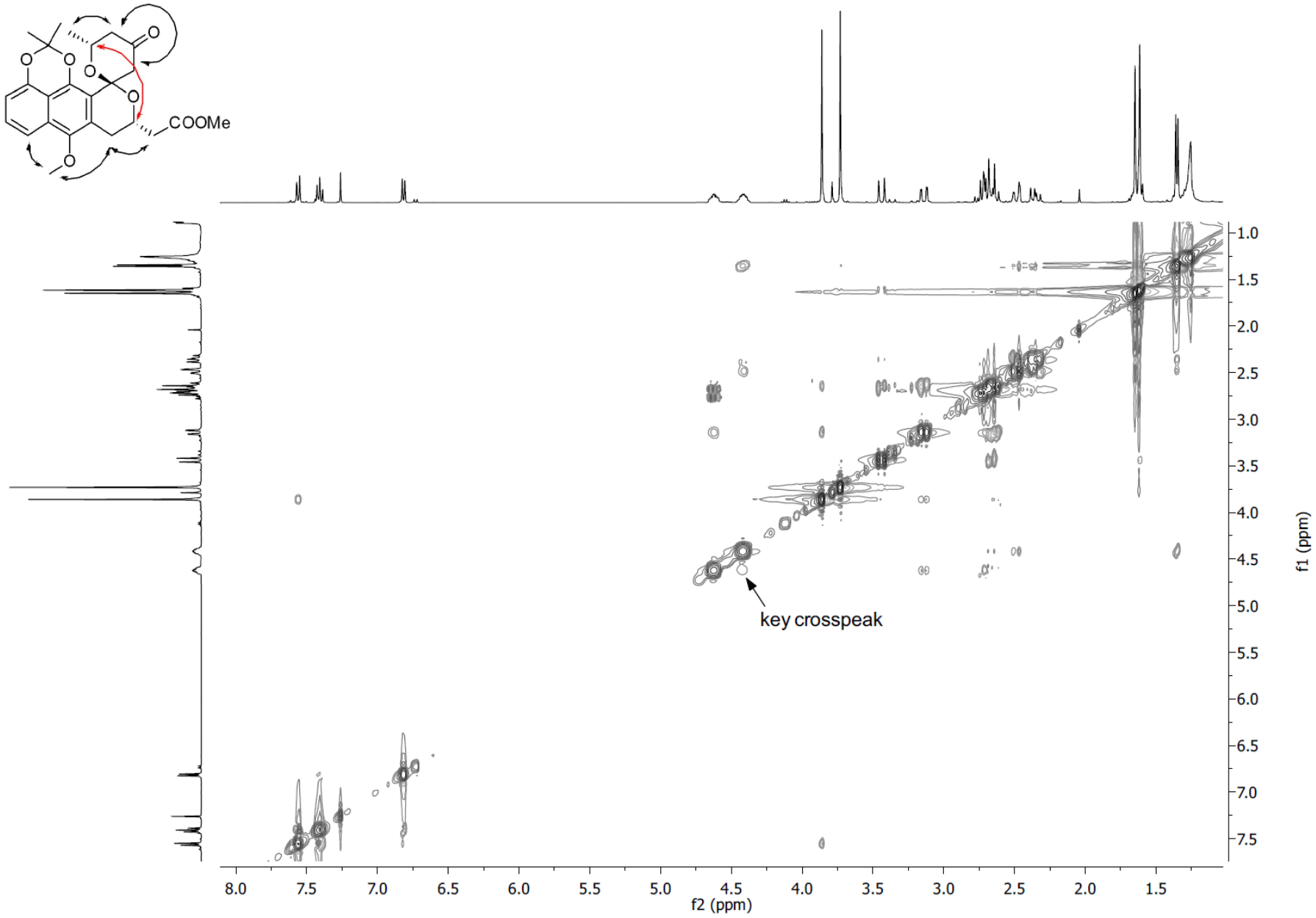



**Figure S155.** NOESY ($CDCl_3$, 400 MHz) of **44.**

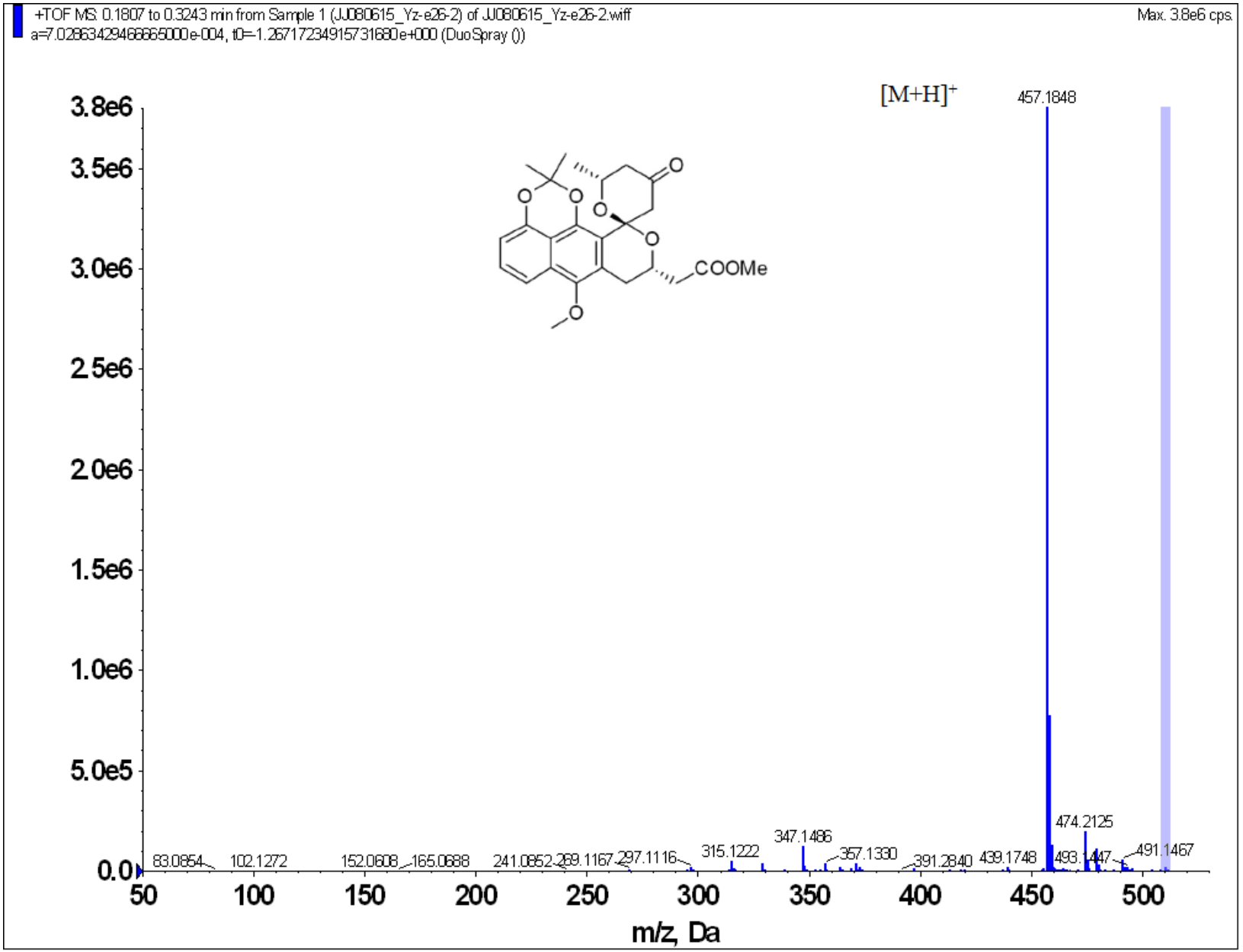



**Figure S156.** (+)-HRESI-MS of **44.**

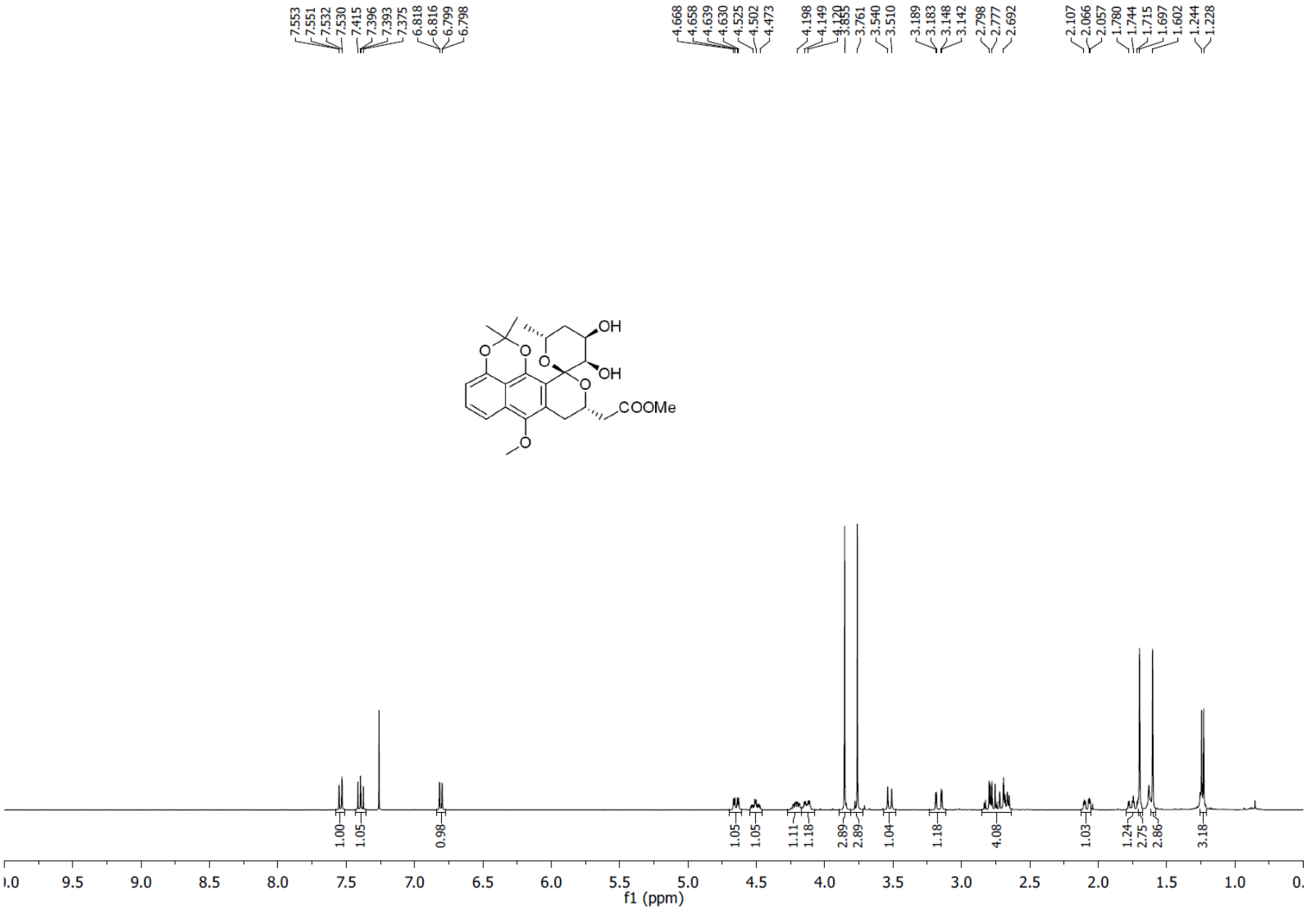



**Figure S157.** $^{1}$H-NMR ($CDCl_3$, 400 MHz) of **45.**

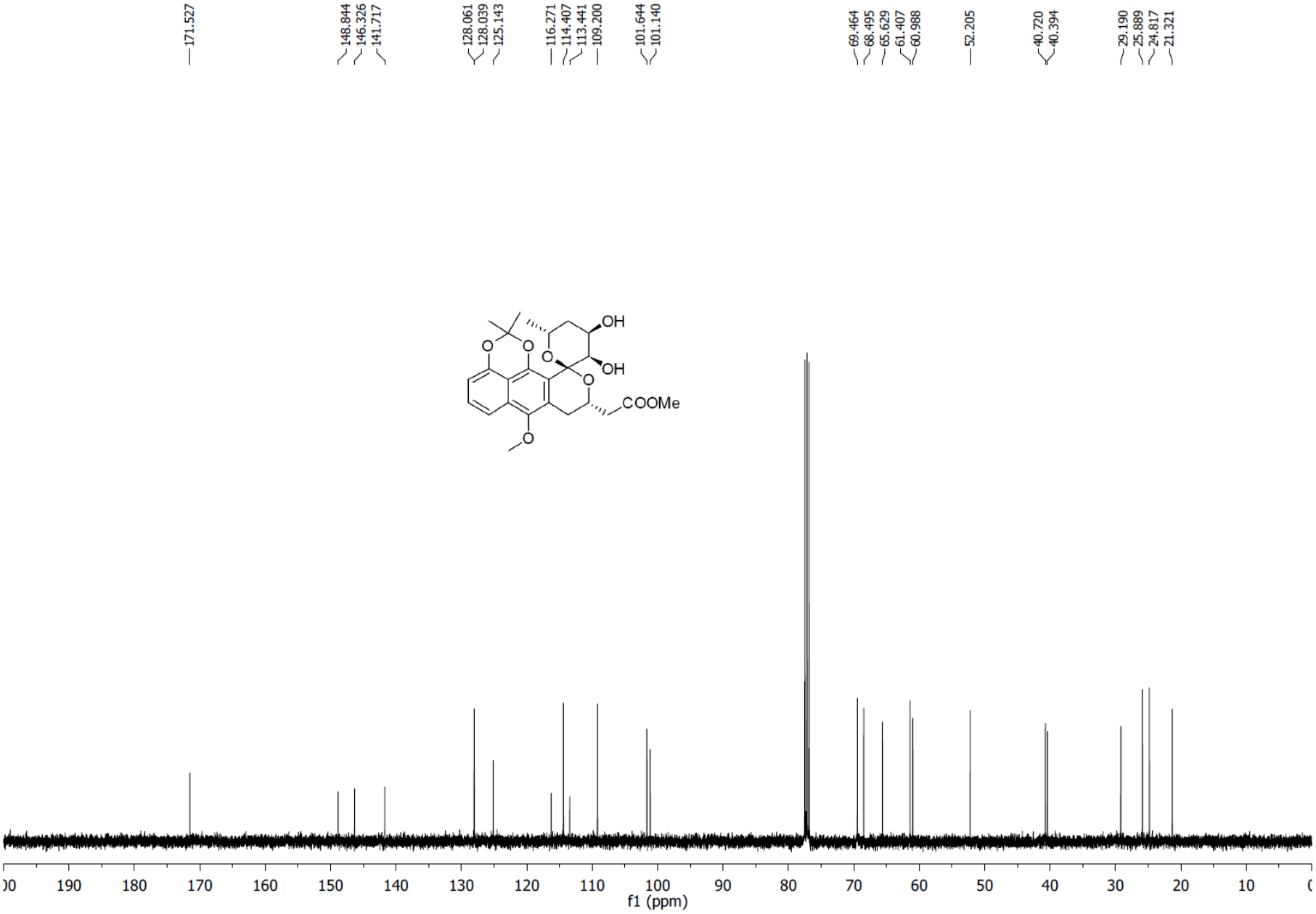



**Figure S158.** $^{13}$C-NMR ($CDCl_3$, 100 MHz) of **45.**

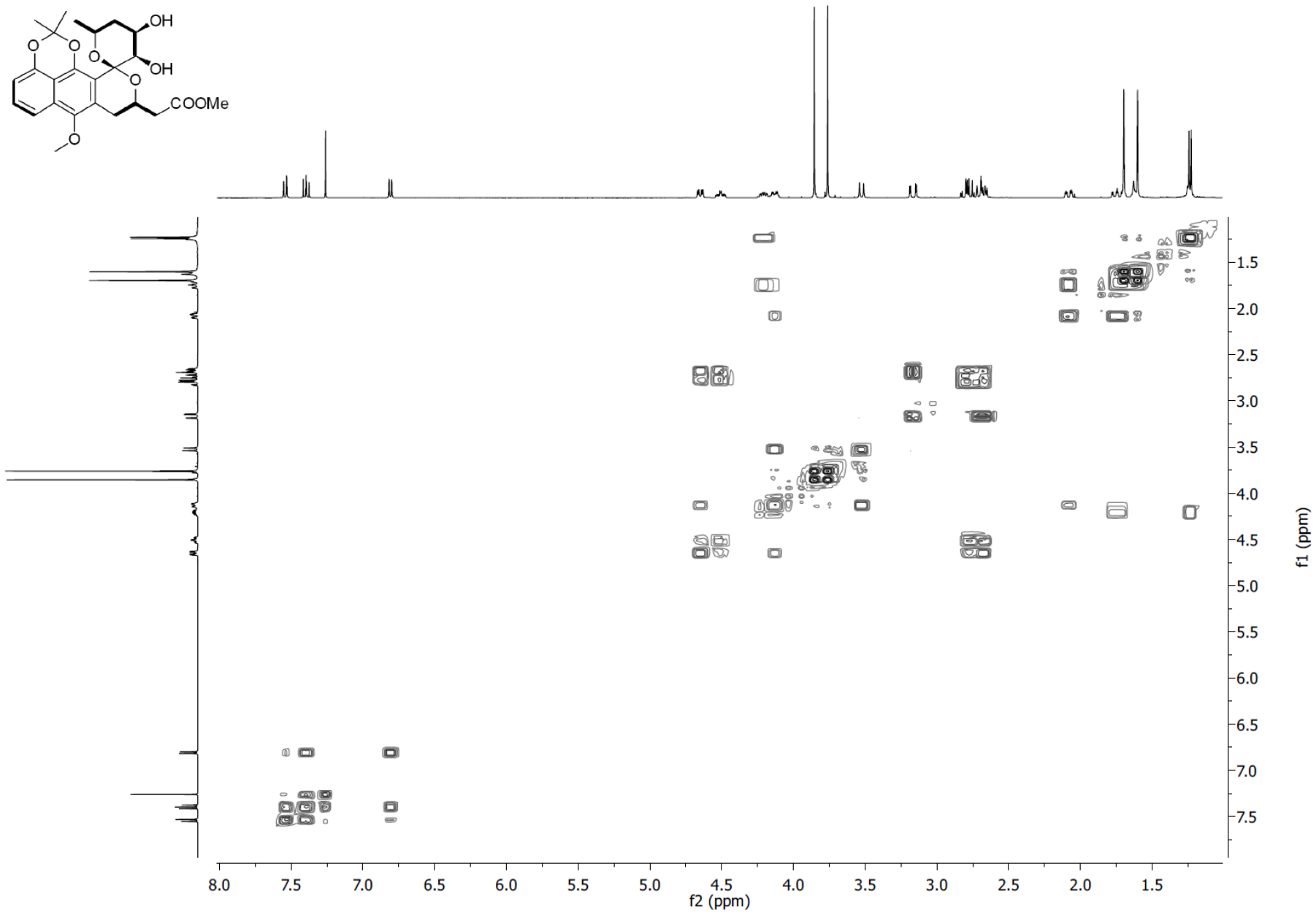



**Figure S159.** $^{1}H$-$^{1}H$ COSY ($CDCl_3$, 400 MHz) of **45.**

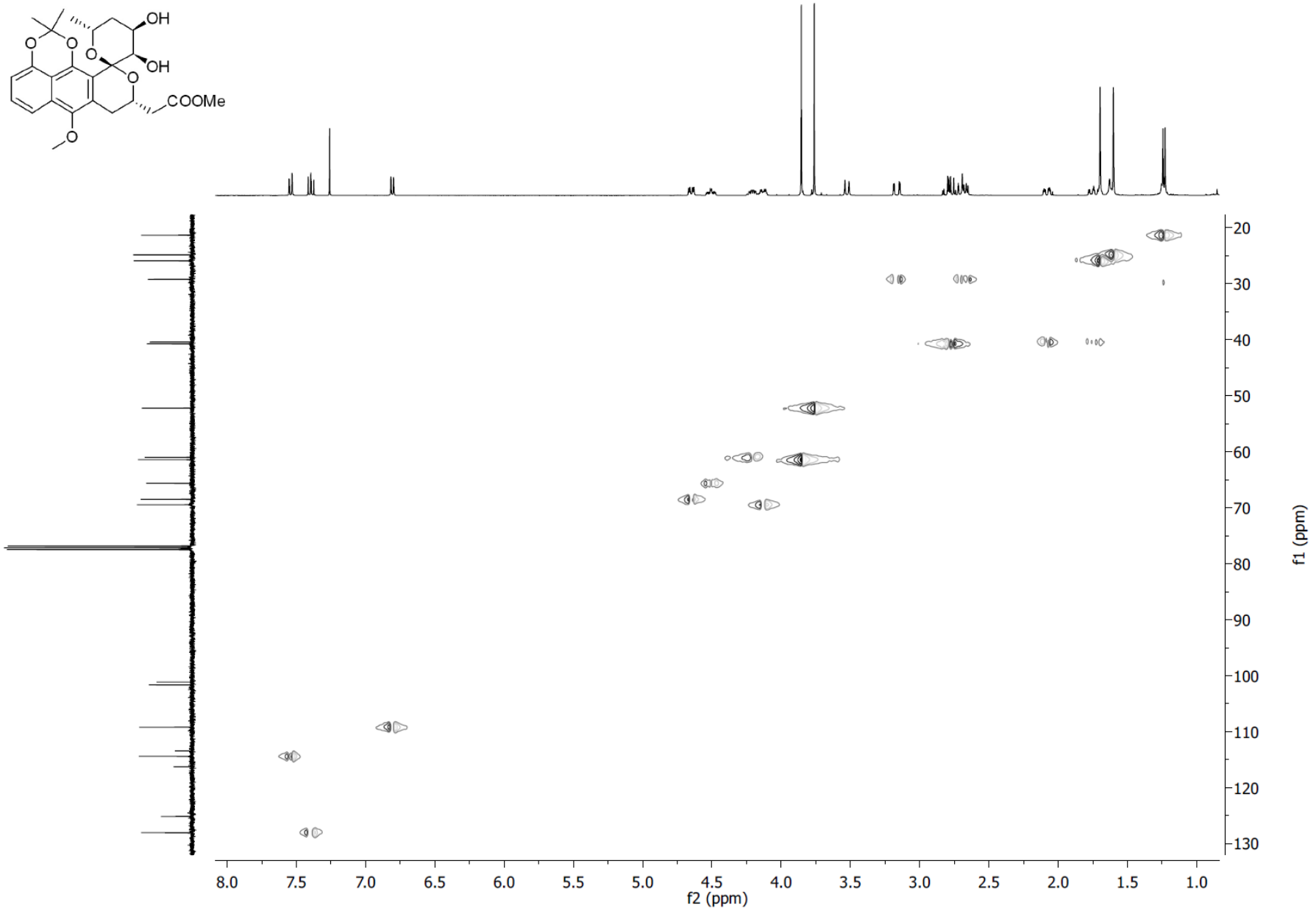



**Figure S160.** HSQC ($CDCl_3$, 400 MHz) of **45.**

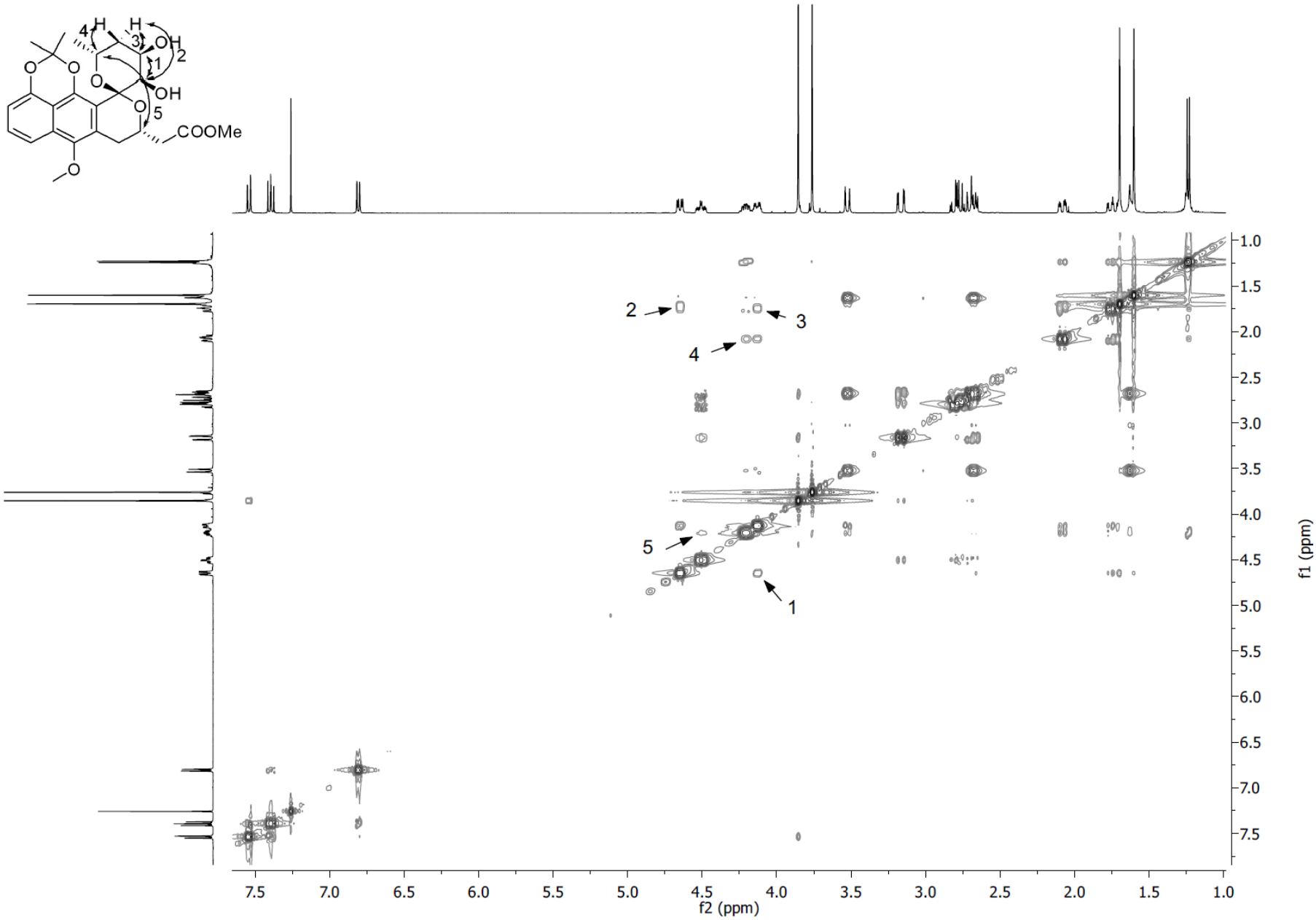



**Figure S161.** NOESY ($CDCl_3$, 400 MHz) of **45.**

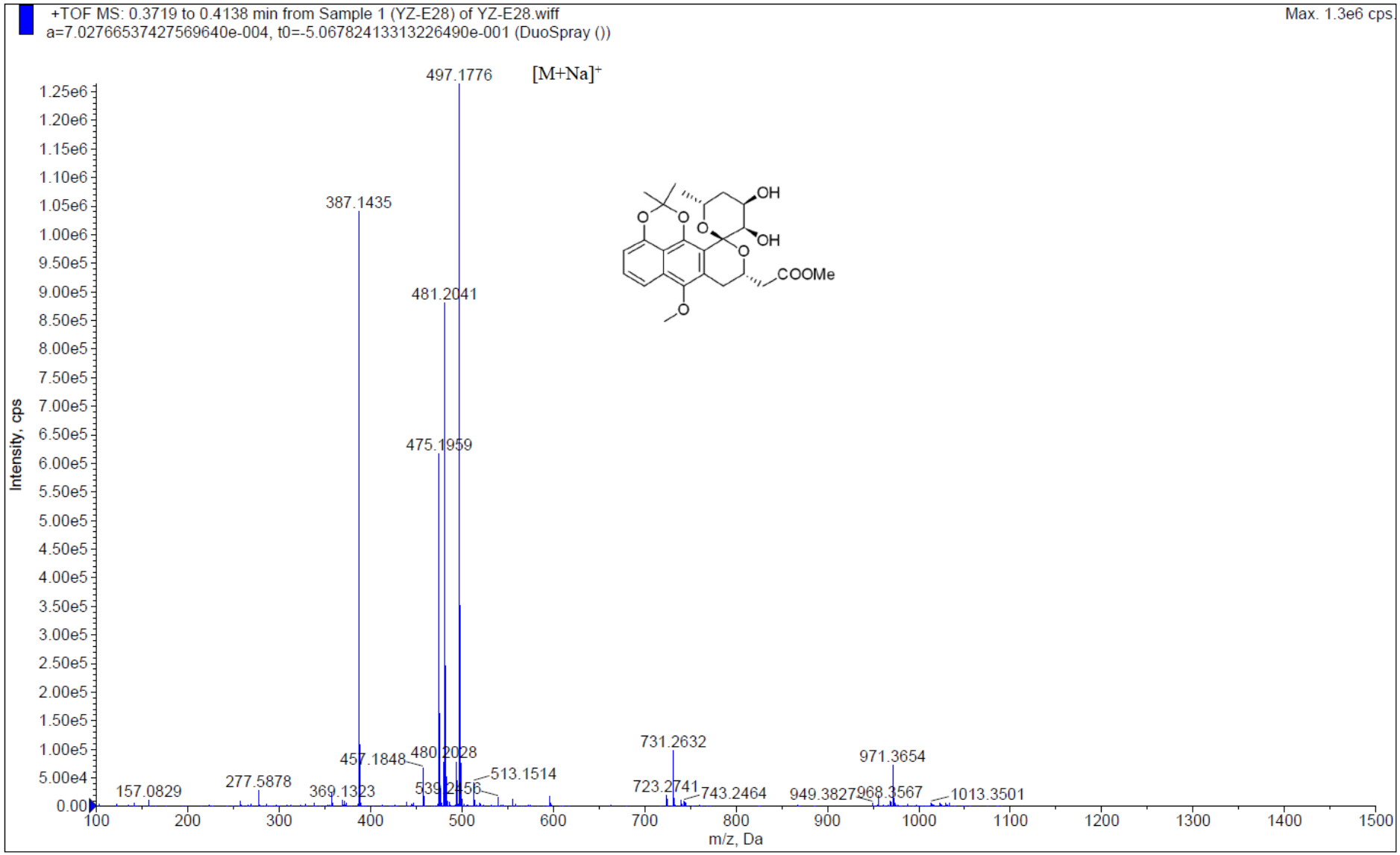



**Figure S162.** (+)-HRESI-MS of **45.**

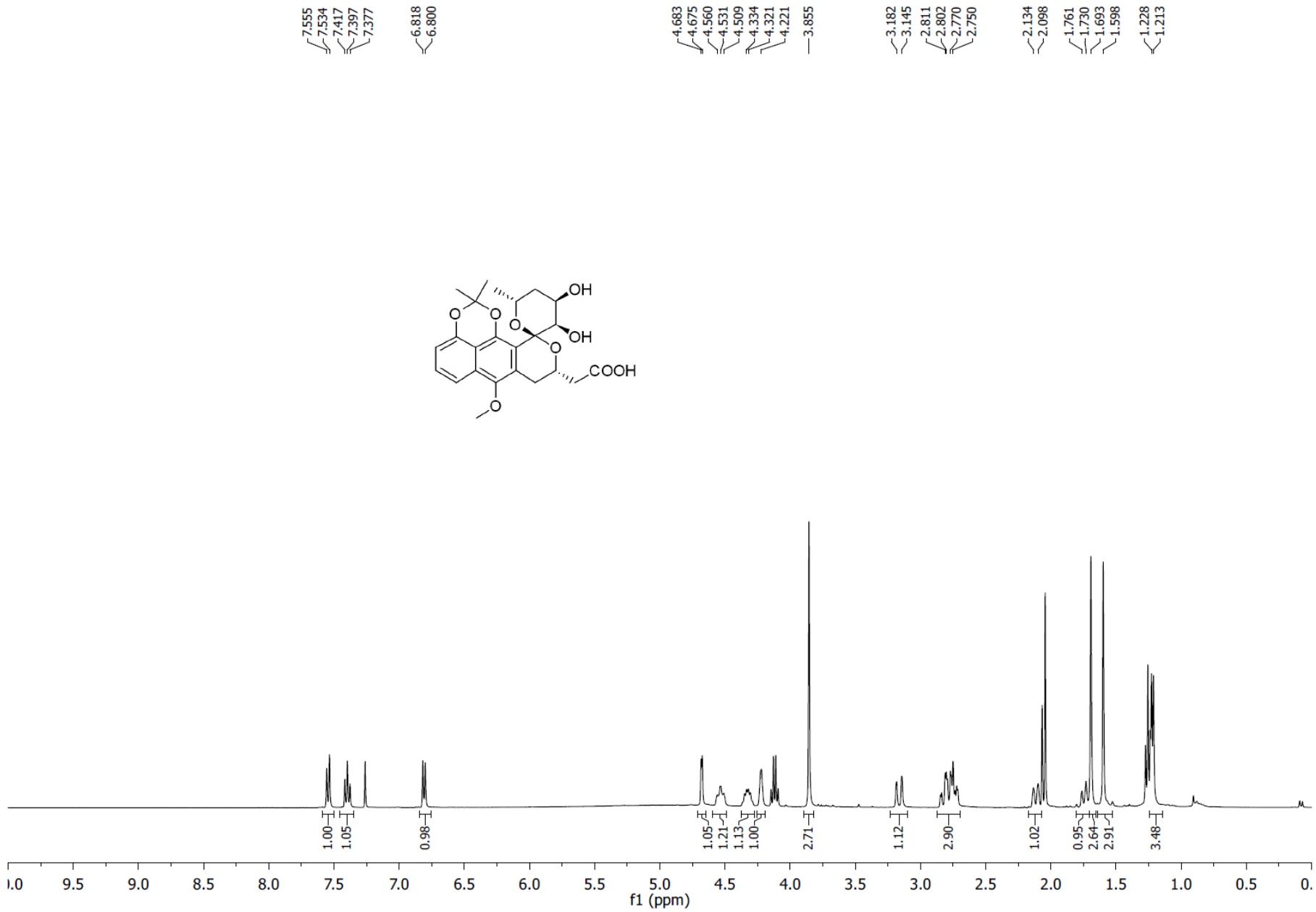



**Figure S163.** $^{1}$H-NMR ($CDCl_3$, 400 MHz) of **46.**

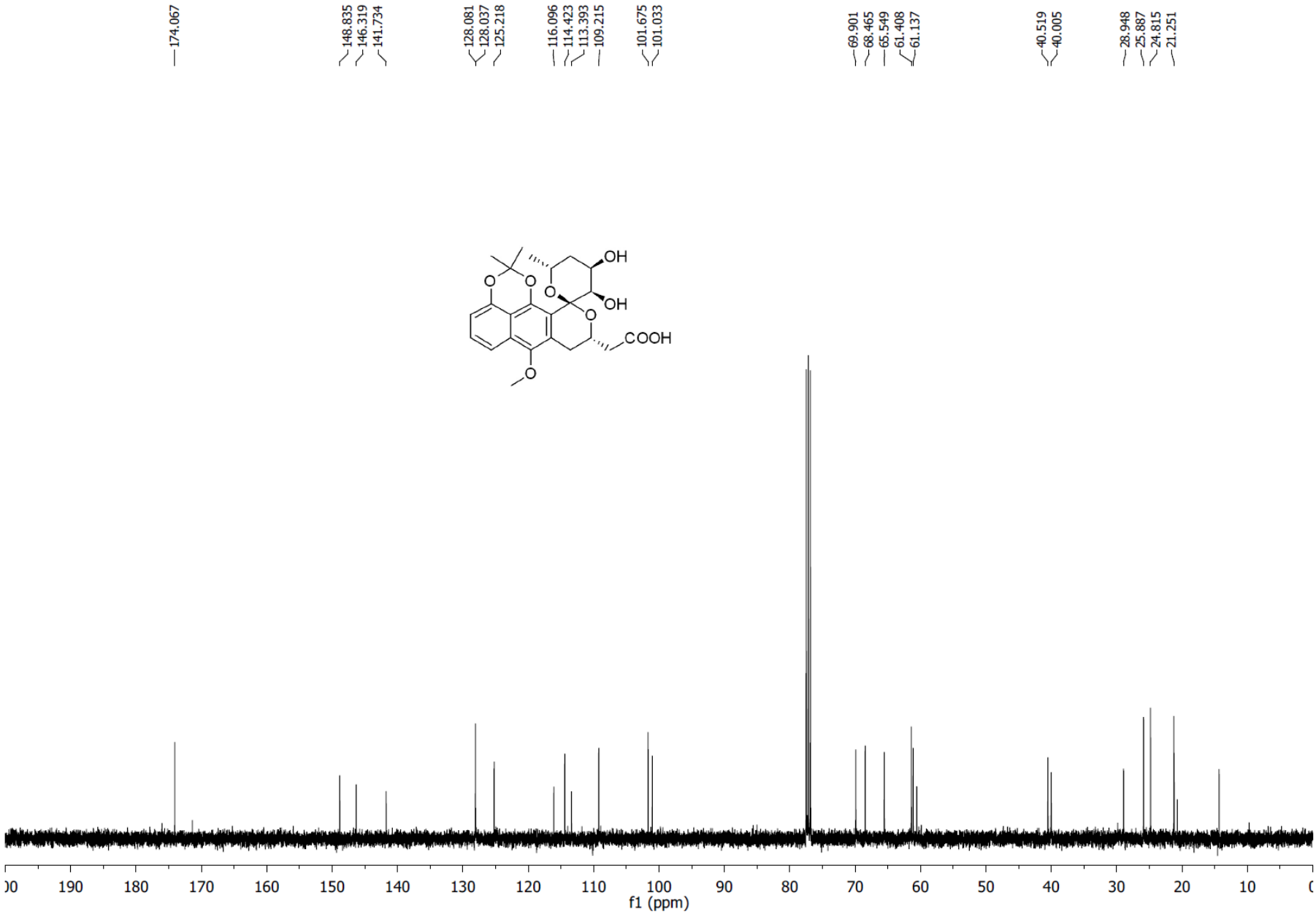



**Figure S164.** $^{13}$C-NMR ($CDCl_3$, 100 MHz) of **46.**

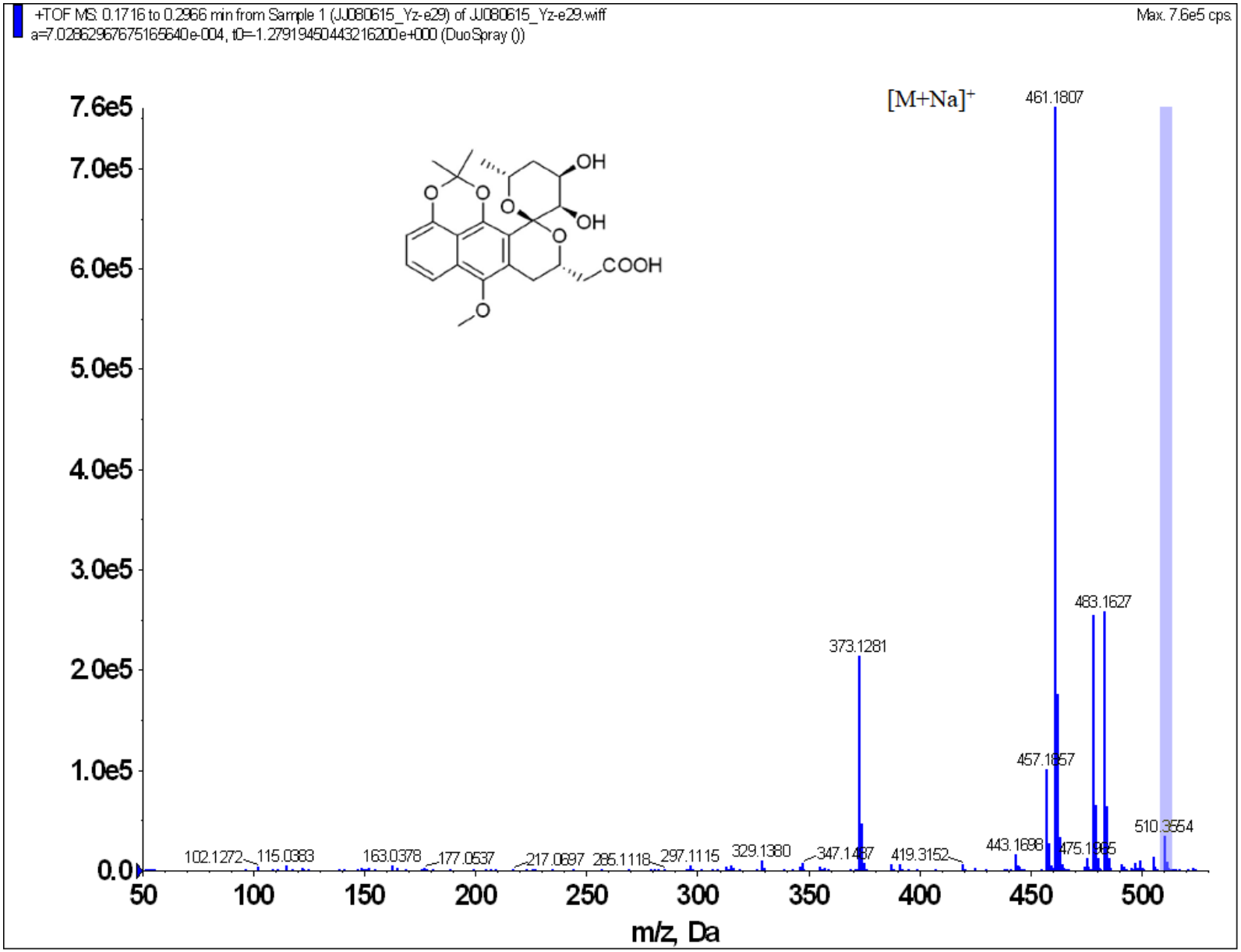



**Figure S165.** (+)-HRESI-MS of **46.**

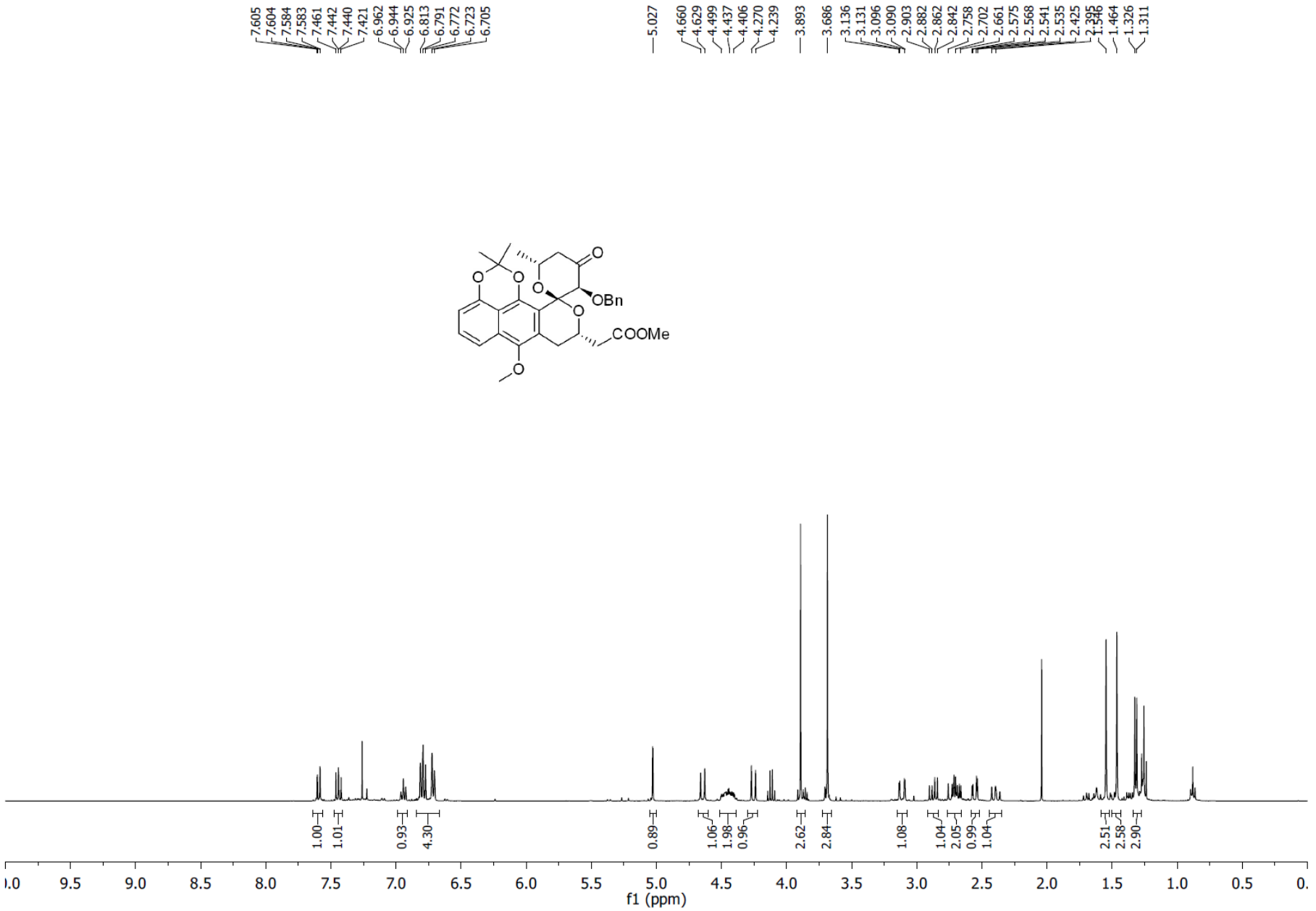



**Figure S166.** $^{1}$H-NMR ($CDCl_3$, 400 MHz) of **47.**

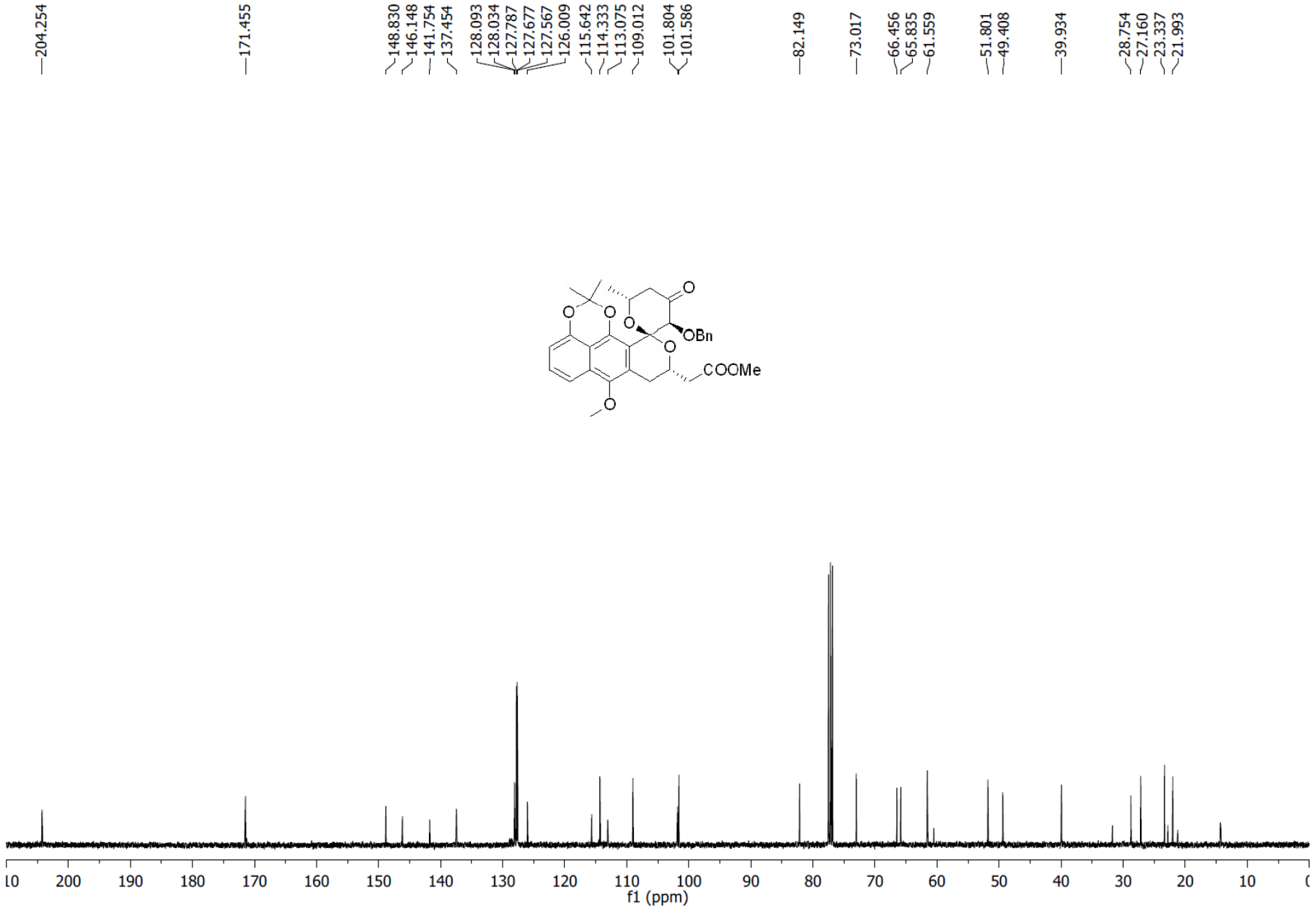



**Figure S167.** $^{13}$C-NMR ($CDCl_3$, 100 MHz) of **47.**

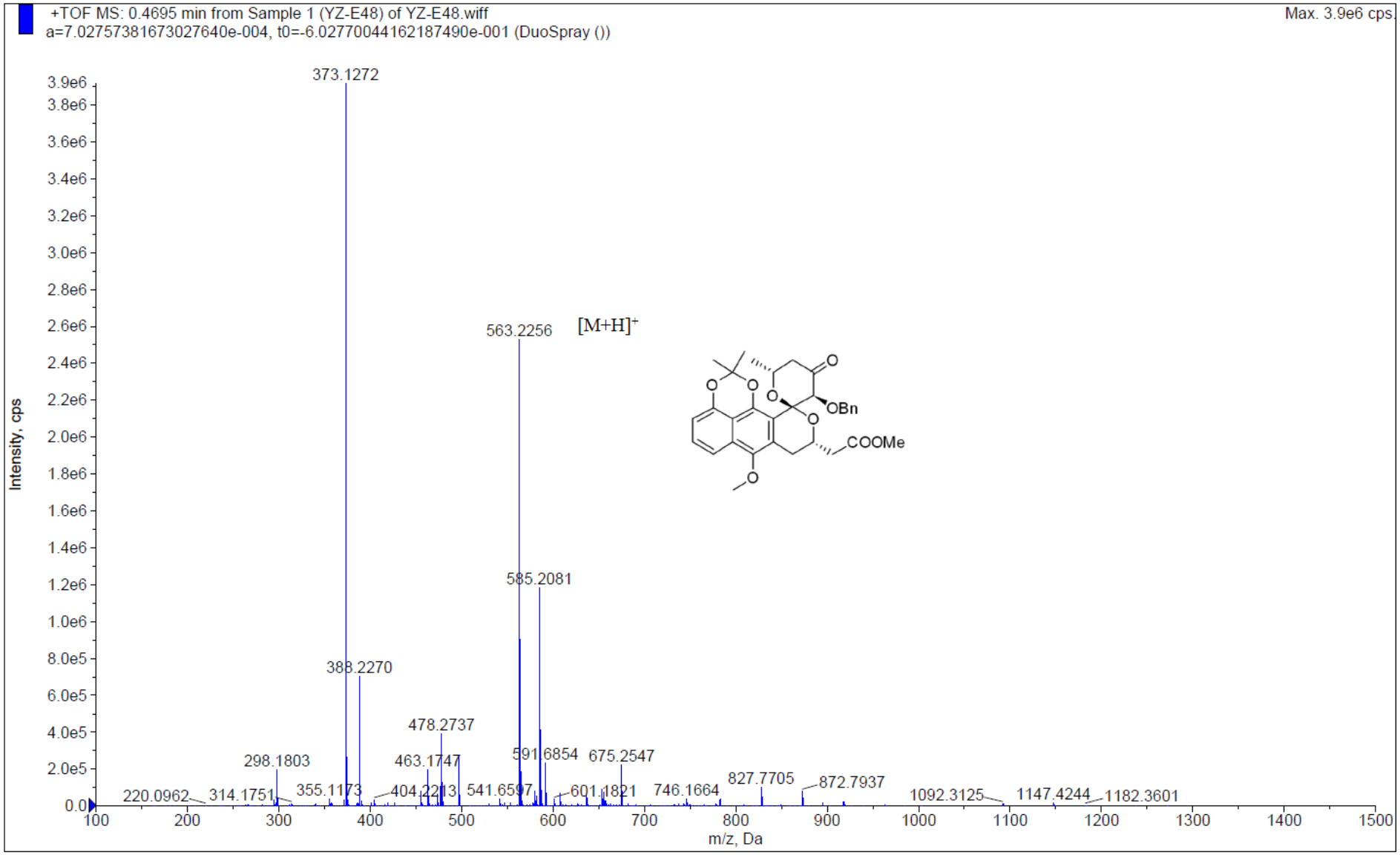



**Figure S168.** (+)-HRESI-MS of **47.**

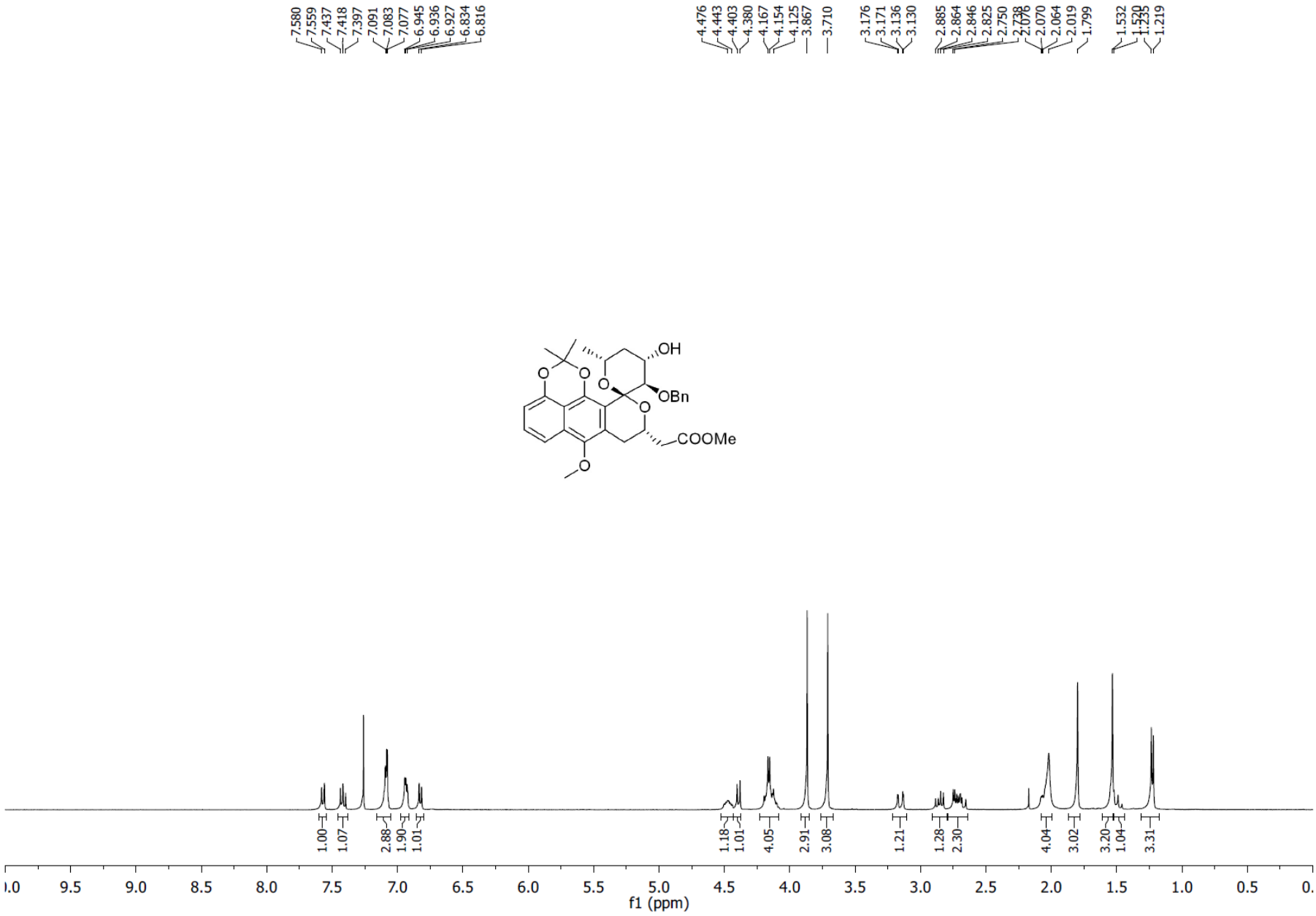



**Figure S169.** $^{1}$H-NMR ($CDCl_3$, 400 MHz) of **48.**

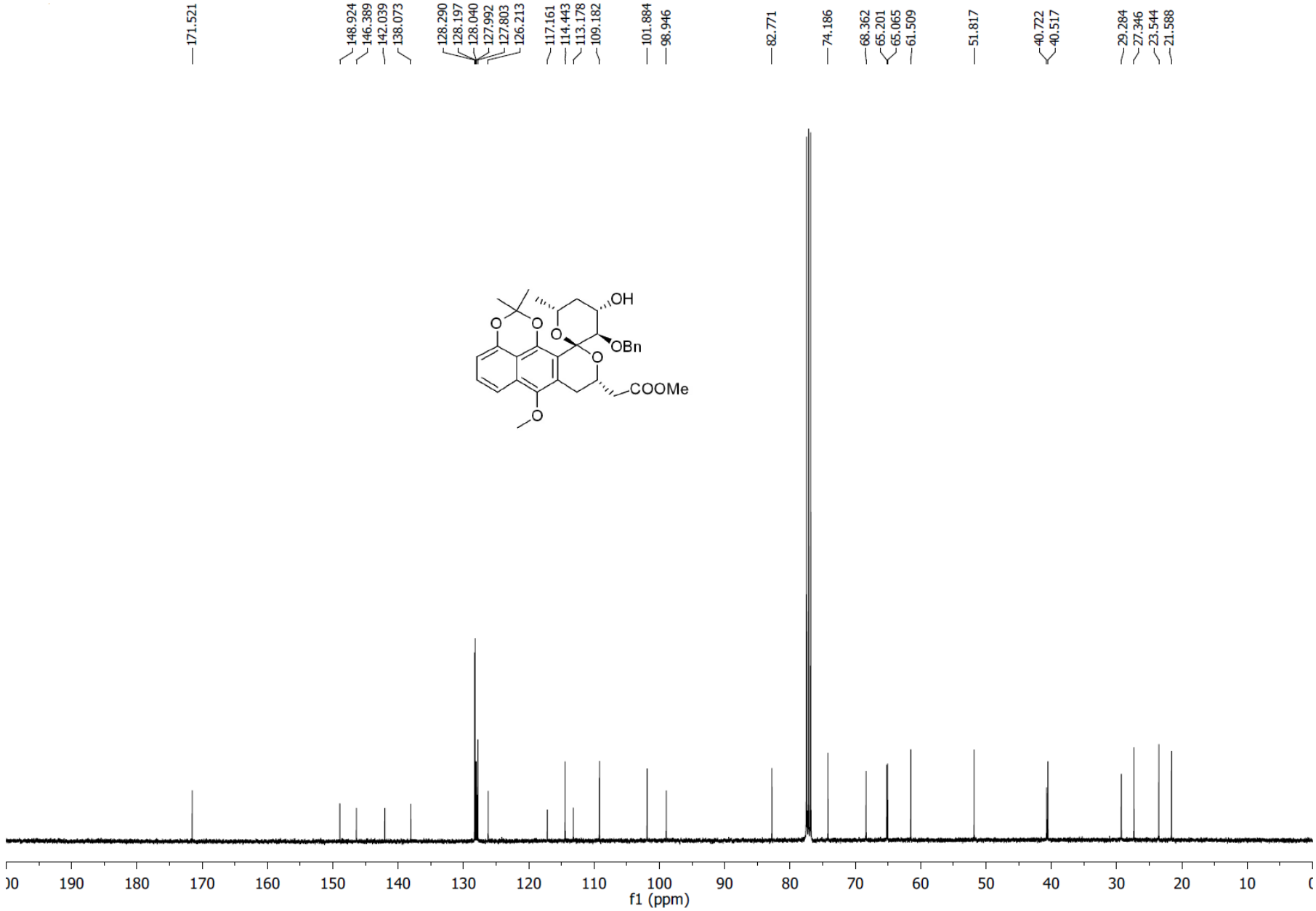



**Figure S170.** $^{13}$C-NMR ($CDCl_3$, 100 MHz) of **48.**

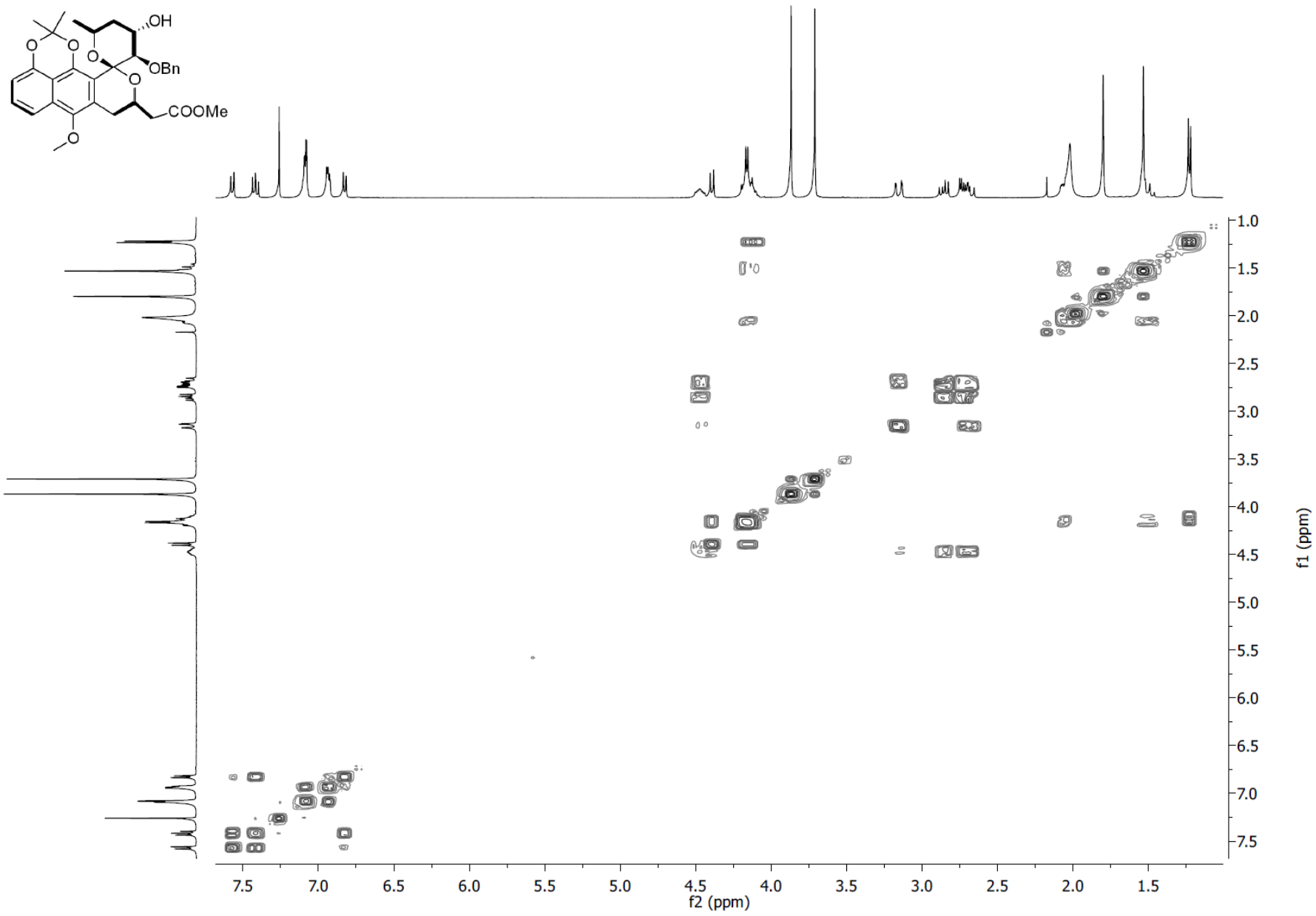



**Figure S171.** $^{1}H$-$^{1}H$ COSY ($CDCl_3$, 400 MHz) of **48.**

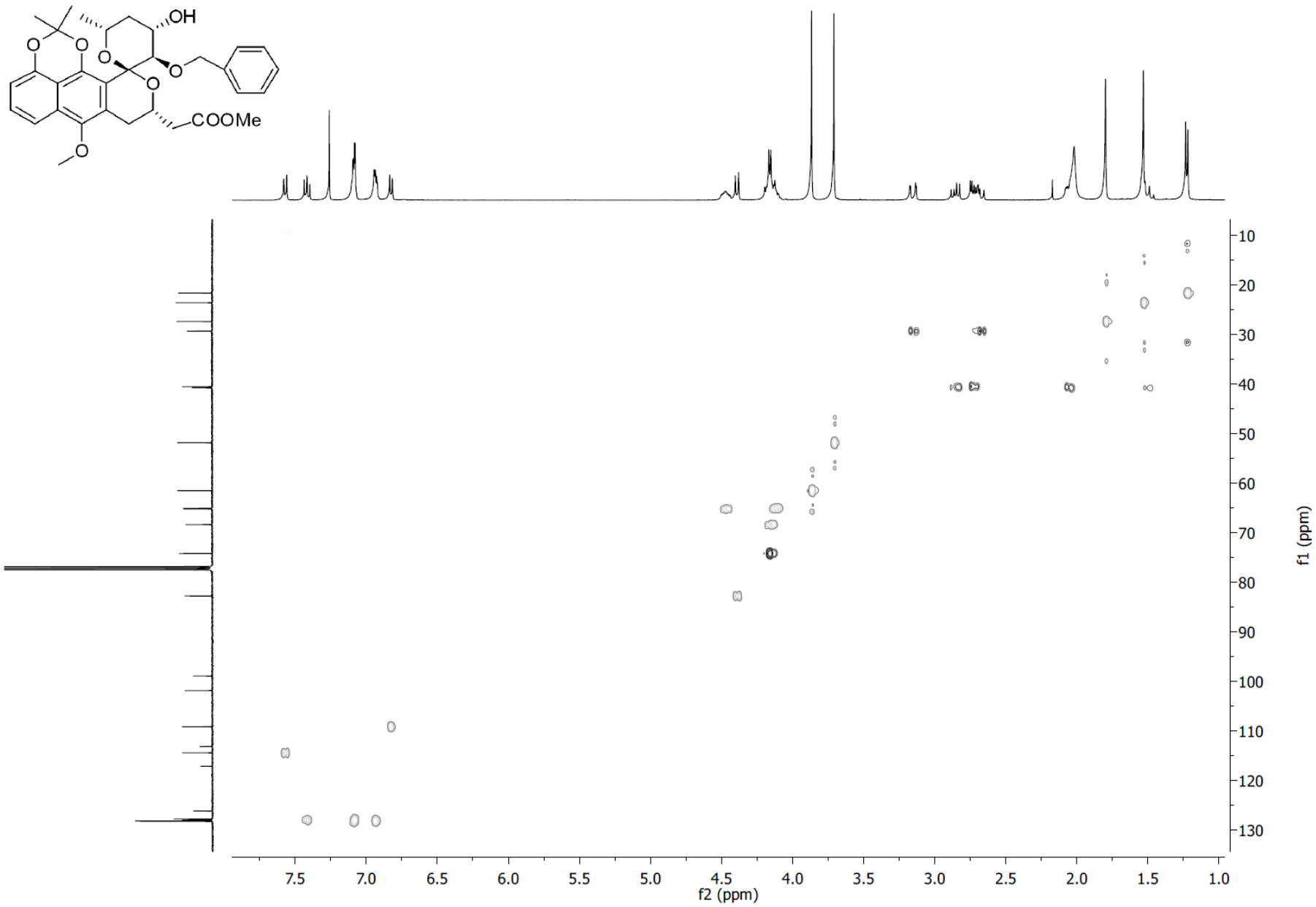



**Figure S172.** HSQC ($CDCl_3$, 400 MHz) of **48.**

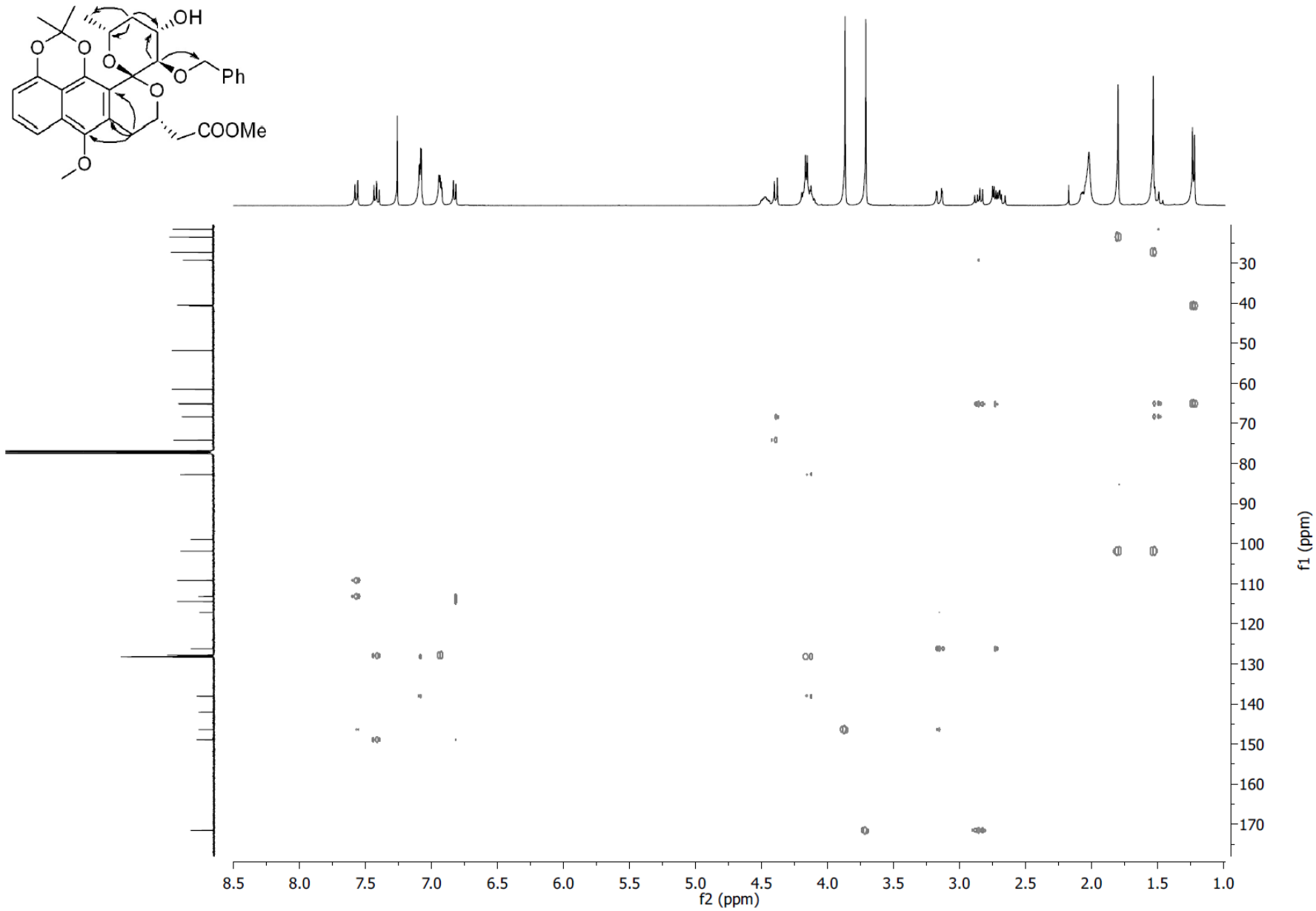



**Figure S173.** HMBC ($CDCl_3$, 400 MHz) of **48.**

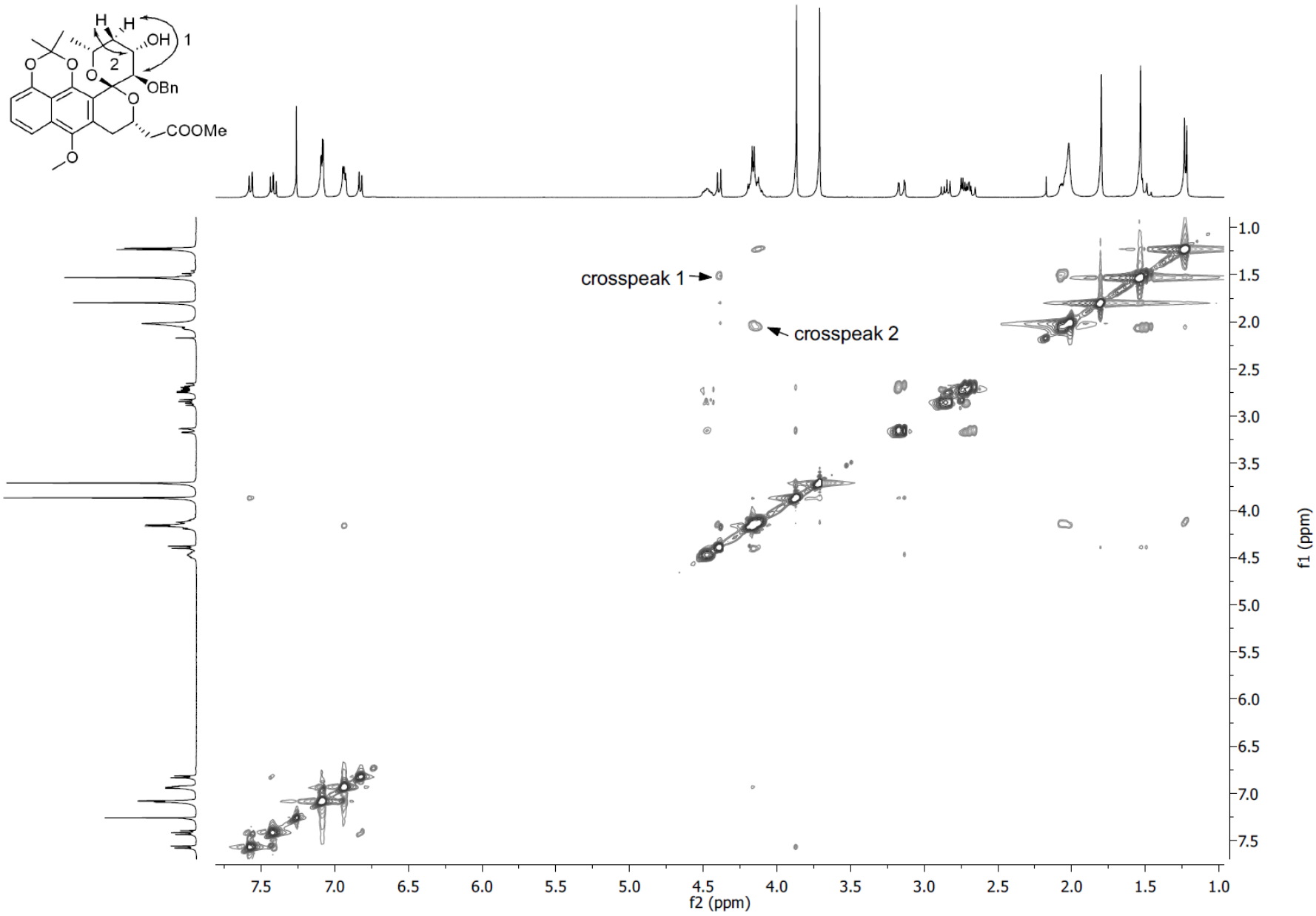



**Figure S174.** NOESY ($CDCl_3$, 400 MHz) of **48.**

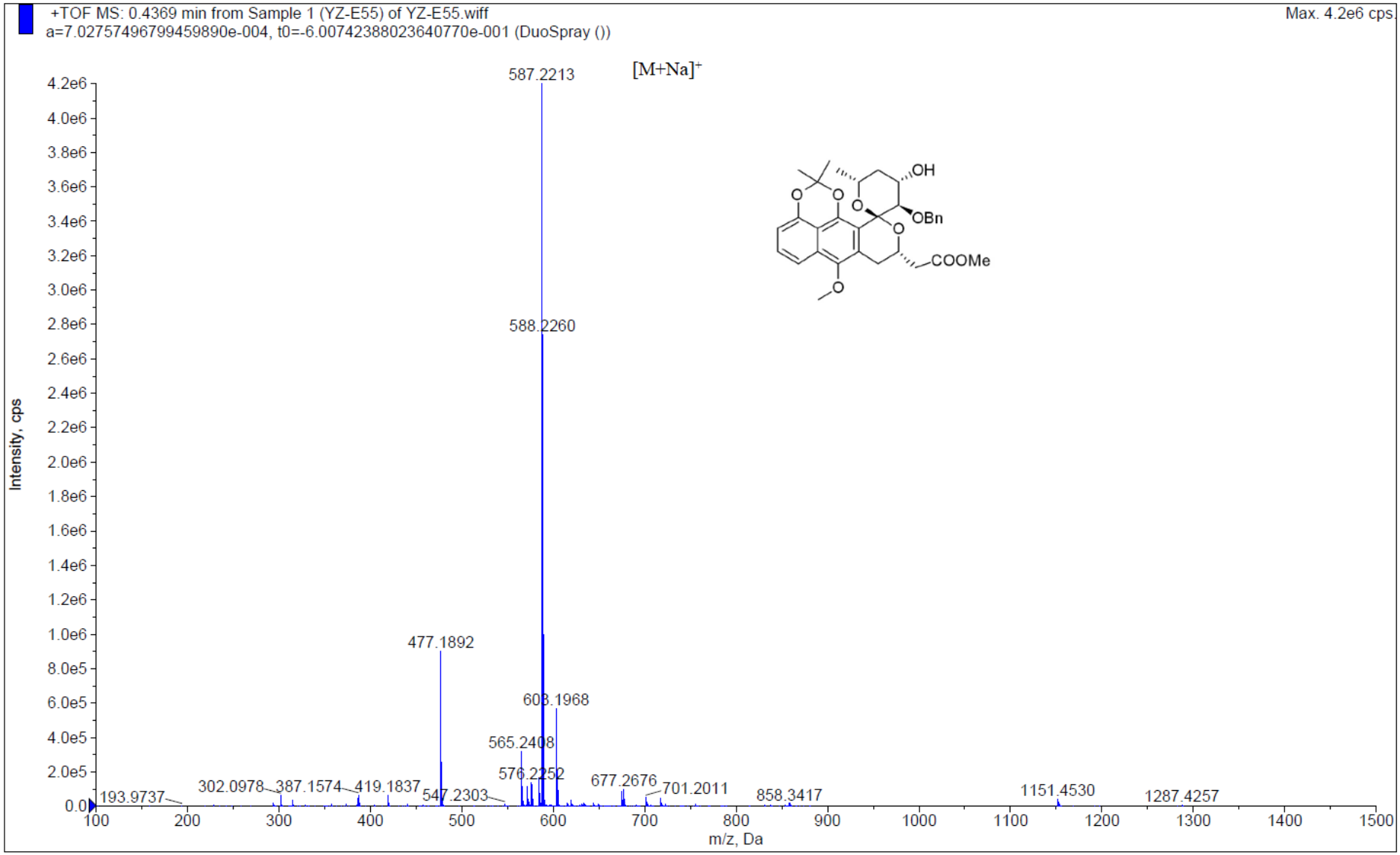



**Figure S175.** (+)-HRESI-MS of **48.**

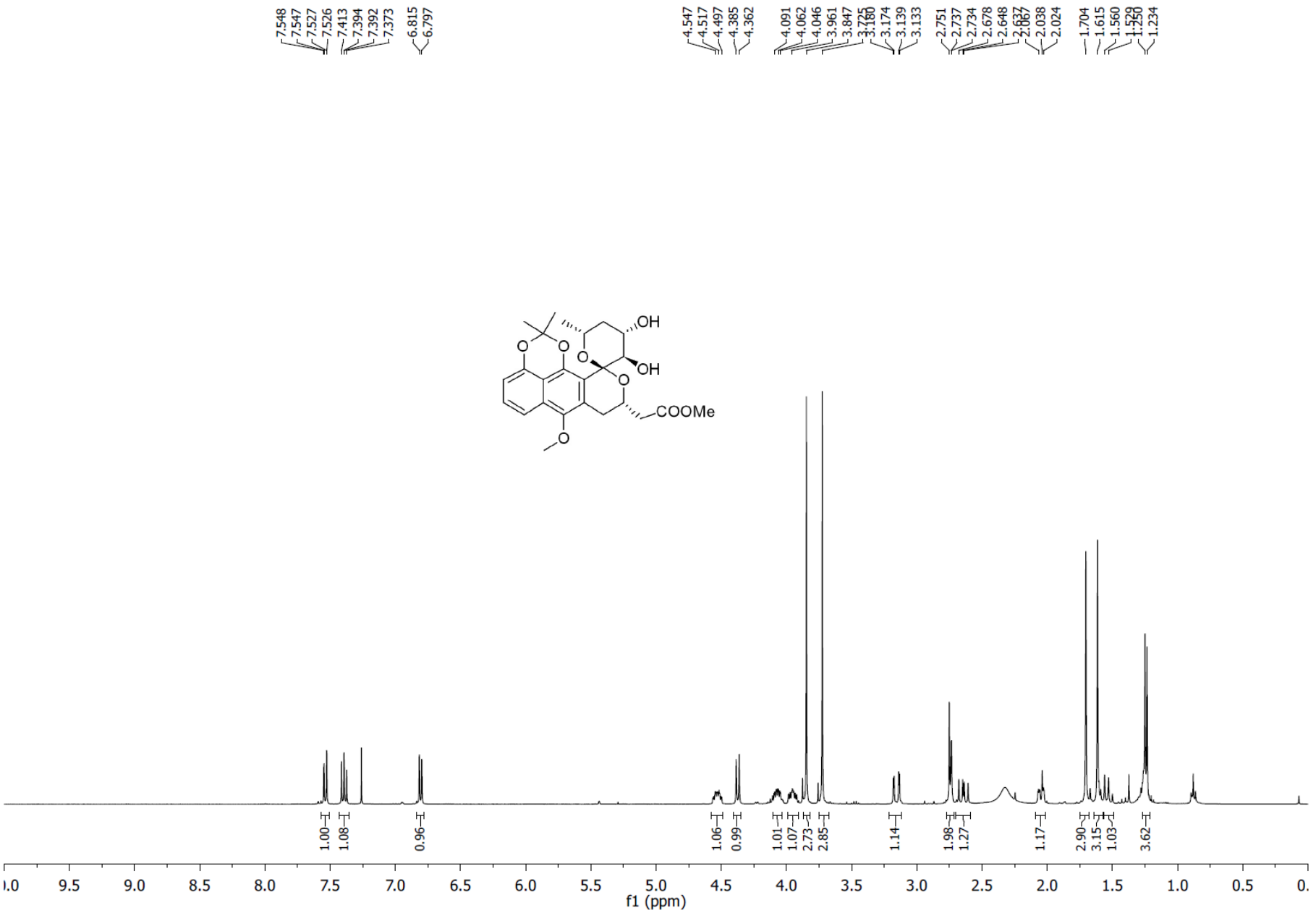



**Figure S176.** $^{1}$H-NMR ($CDCl_3$, 400 MHz) of **49.**

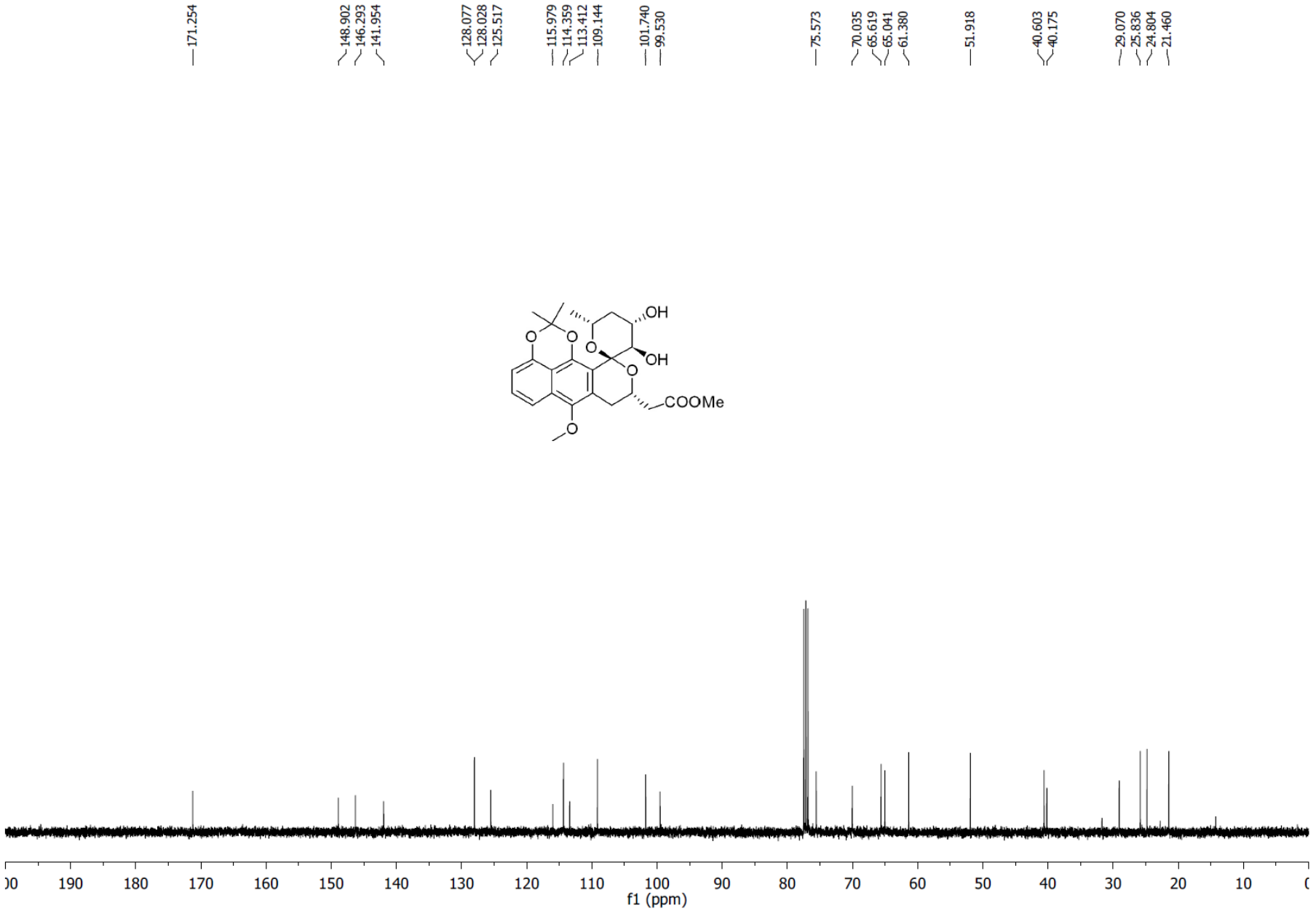



**Figure S177.** $^{13}$C-NMR ($CDCl_3$, 100 MHz) of **49.**

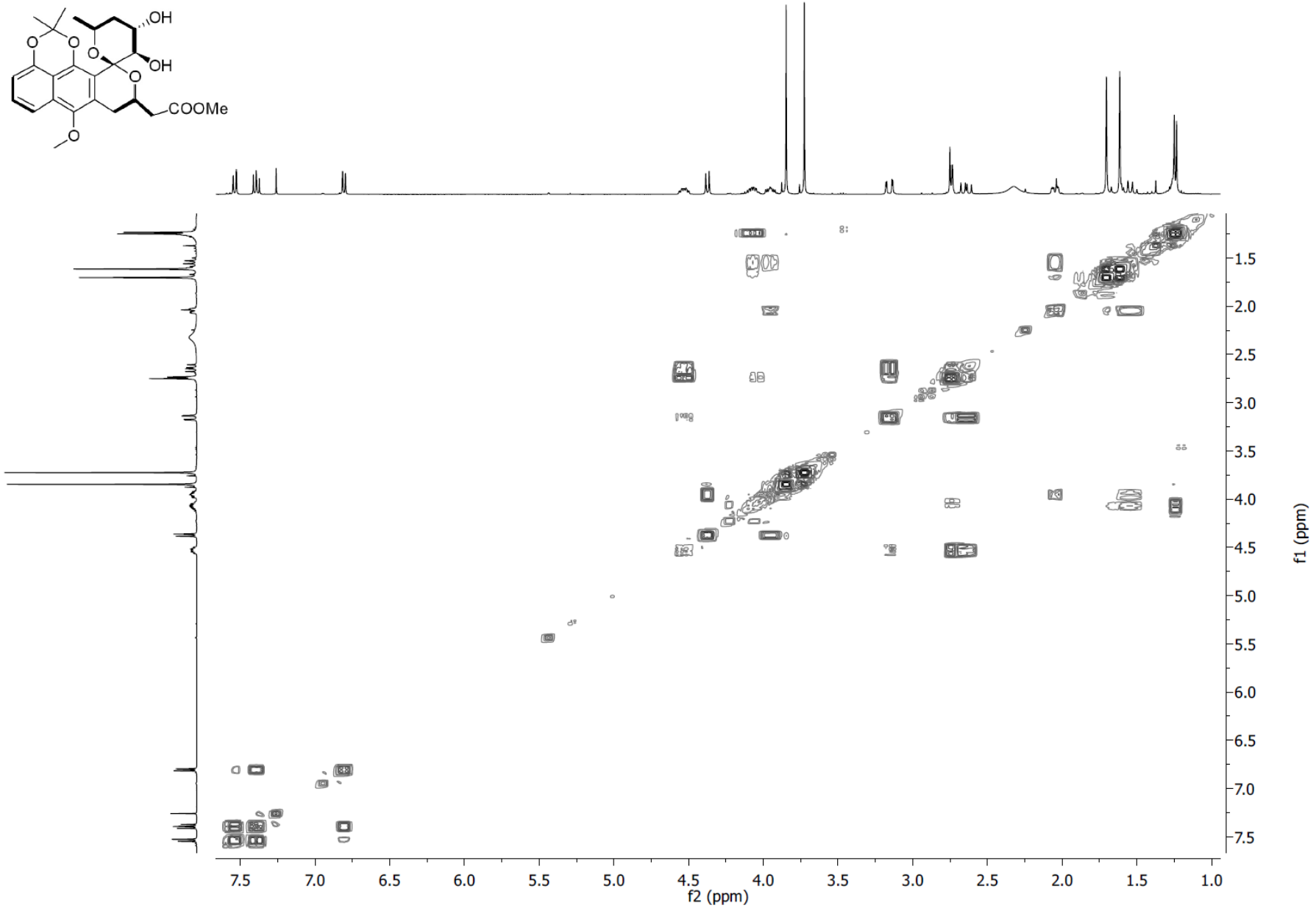



**Figure S178.** $^{1}$H-$^{1}$H COSY ($CDCl_3$, 400 MHz) of **49.**

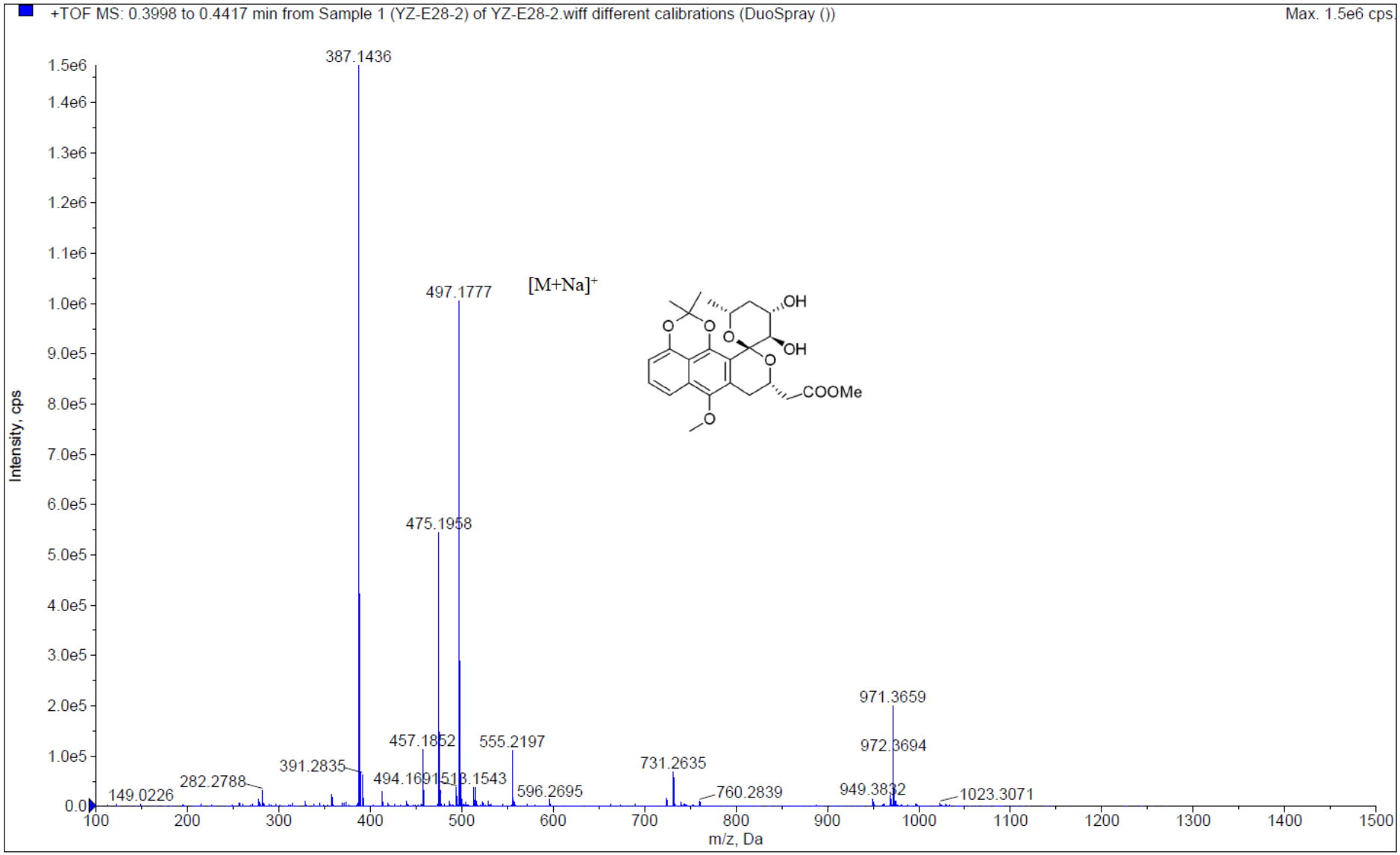



**Figure S179.** (+)-HRESI-MS of **49.**

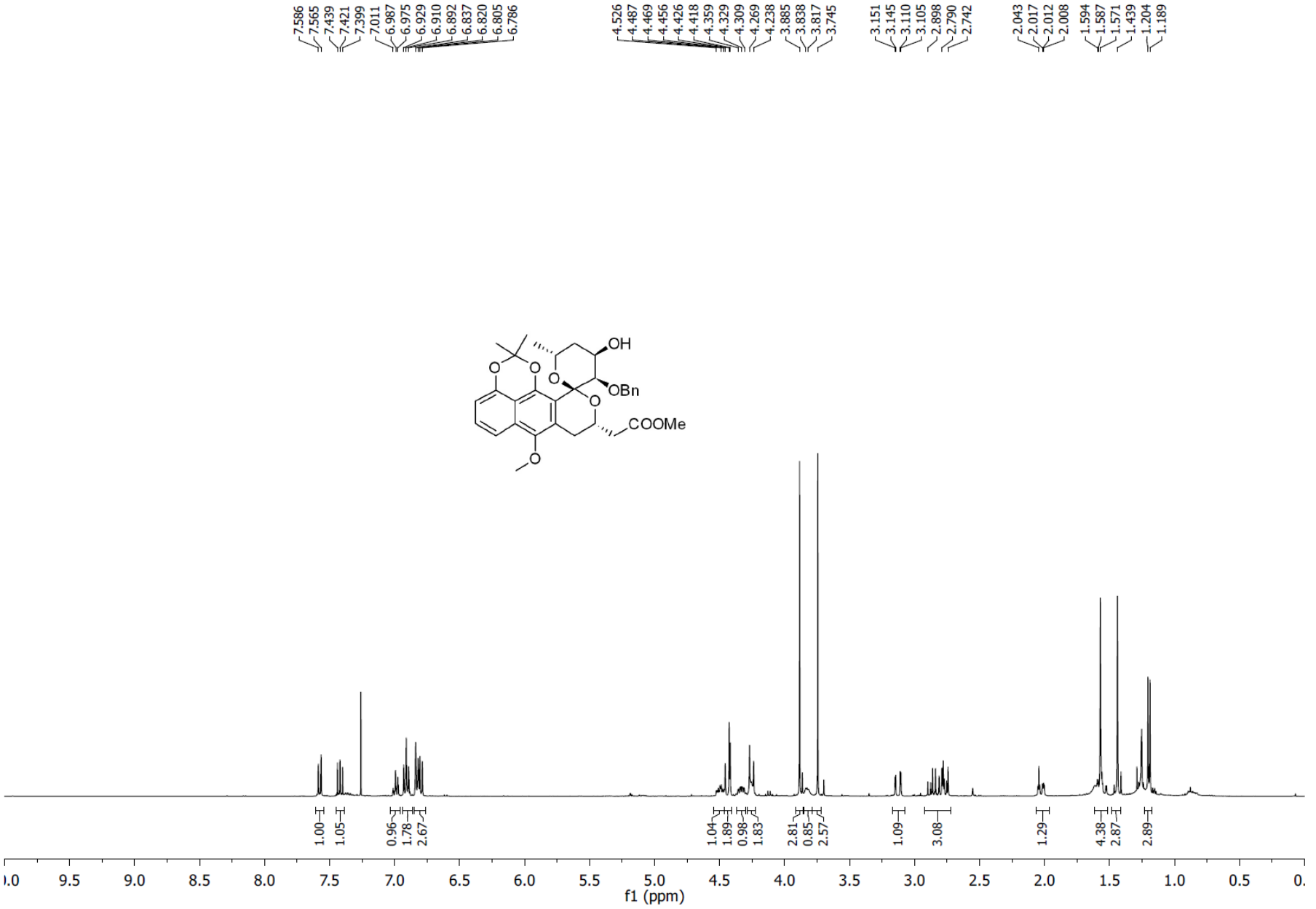



**Figure S180.** $^{1}$H-NMR ($CDCl_3$, 400 MHz) of **50.**

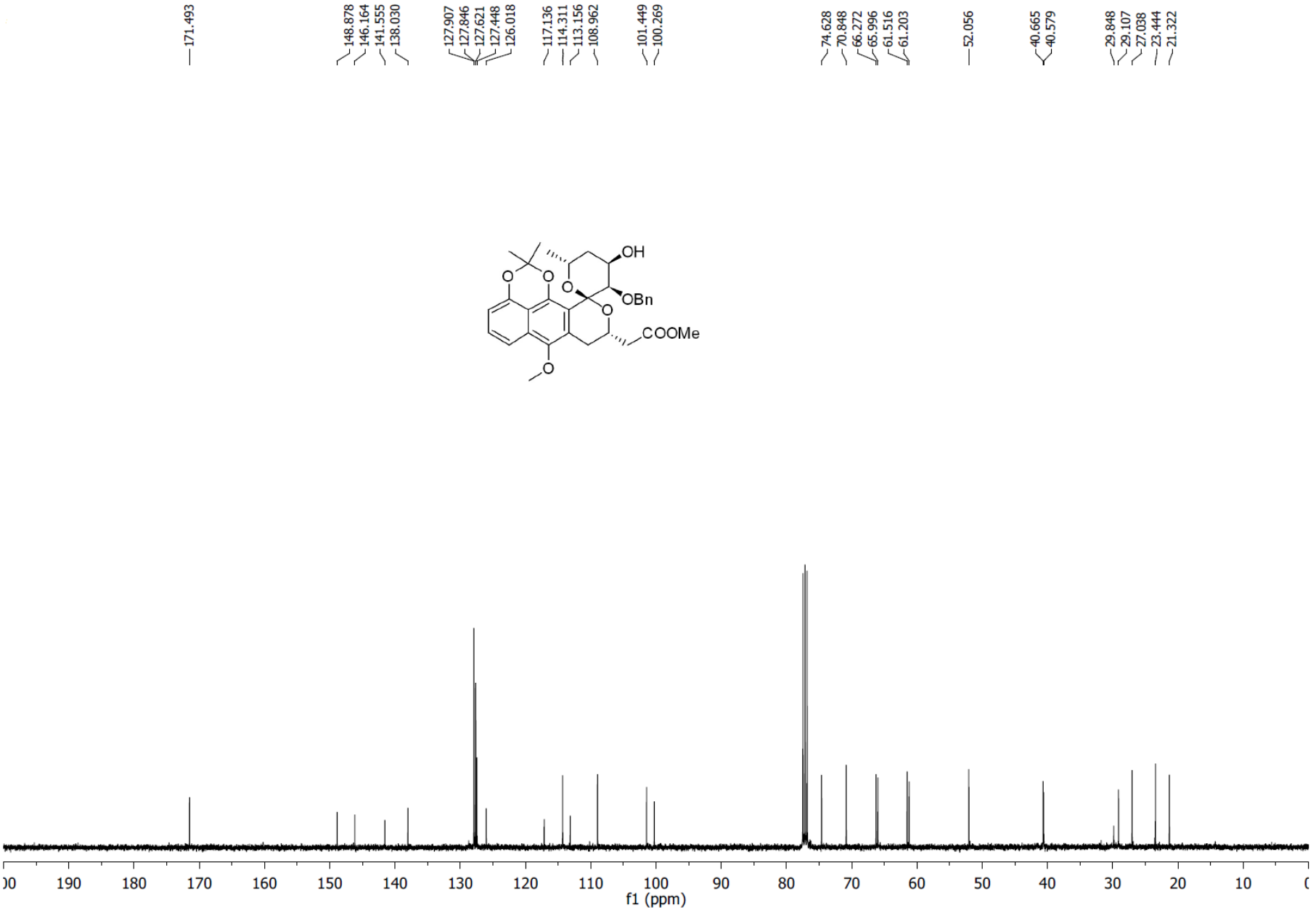



**Figure S181.** $^{13}$C-NMR ($CDCl_3$, 100 MHz) of **50.**

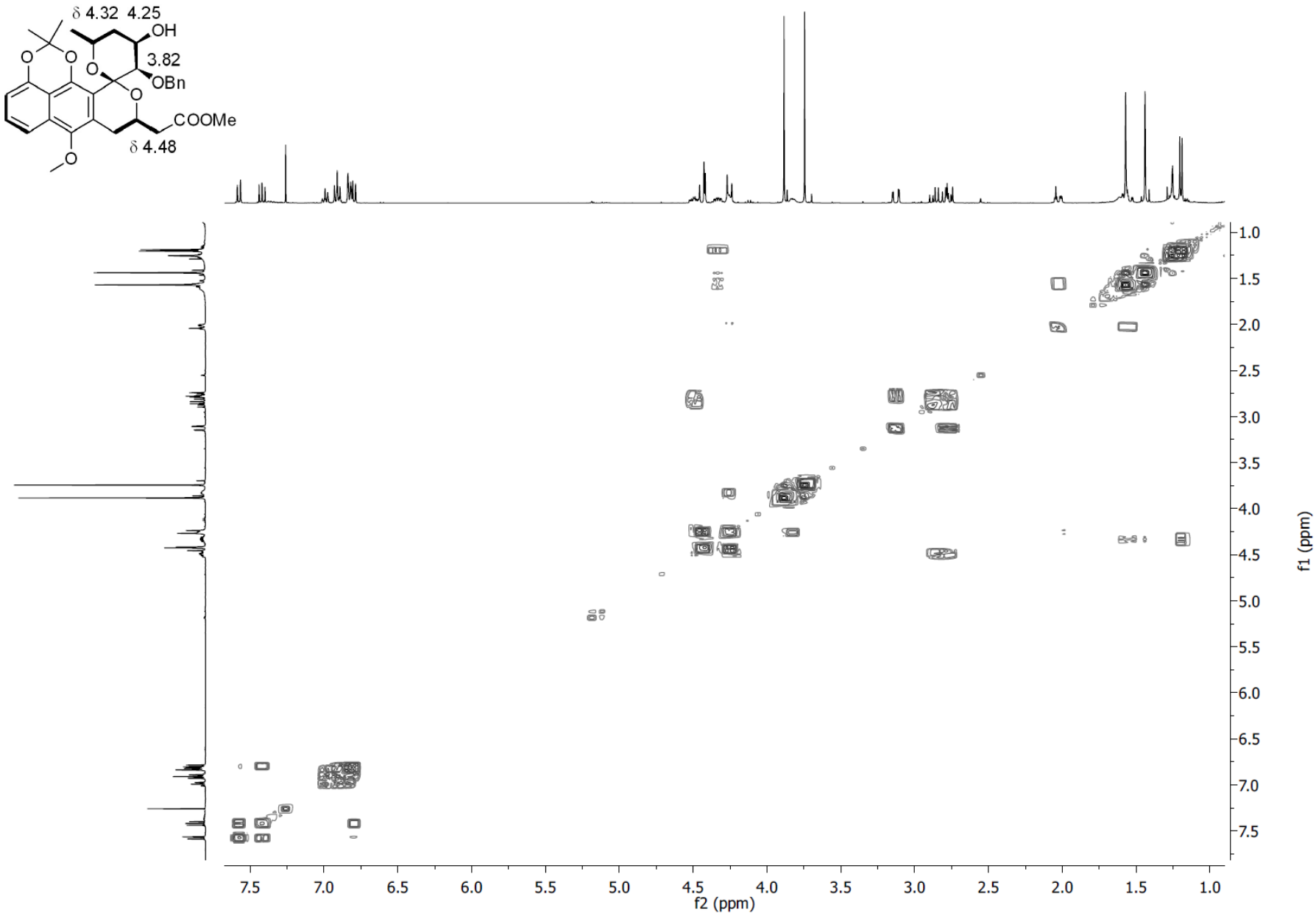



**Figure S182.** $^{1}$H-$^{1}$H COSY ($CDCl_3$, 400 MHz) of **50.**

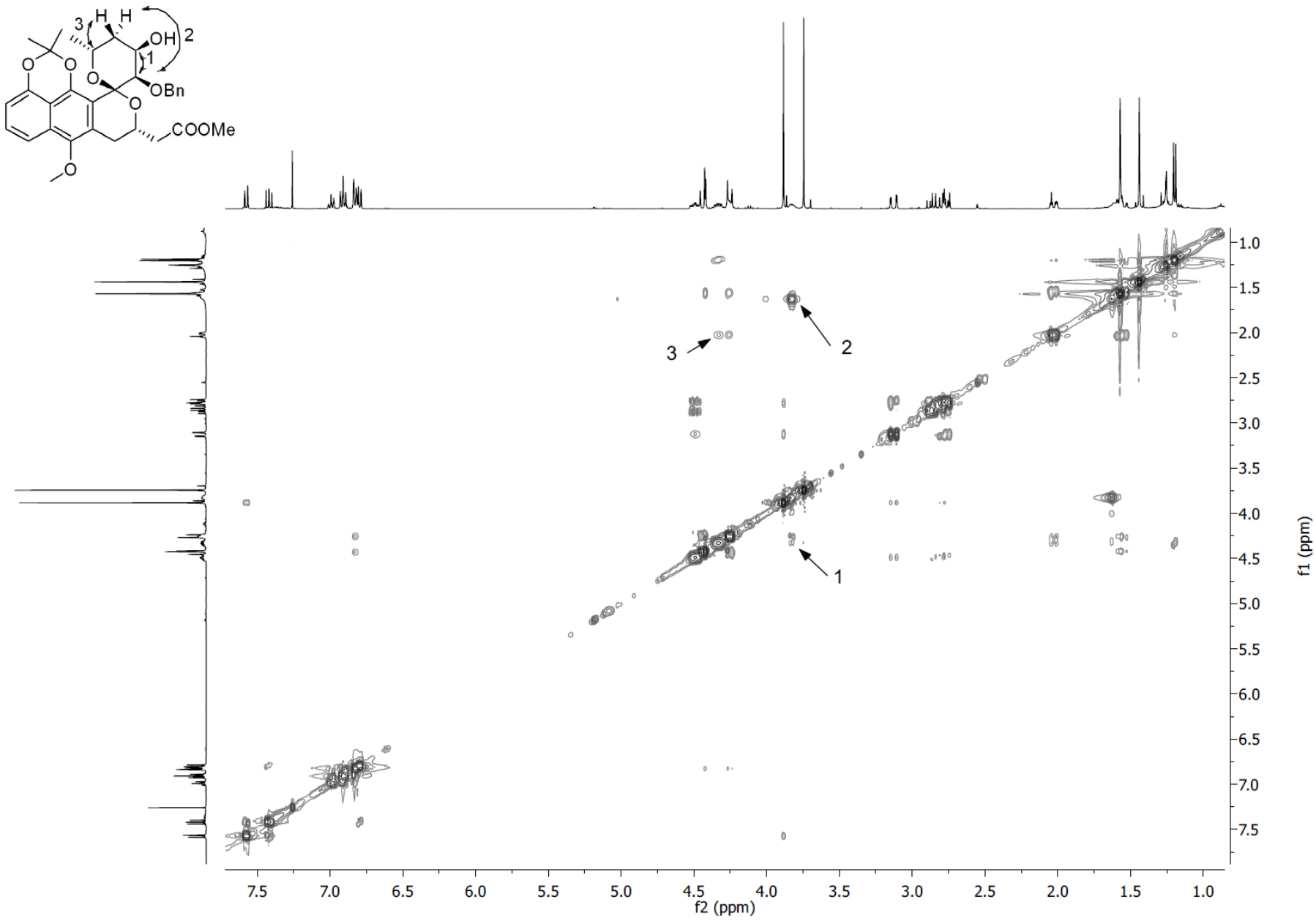



**Figure S183.** NOESY ($CDCl_3$, 400 MHz) of **50.**

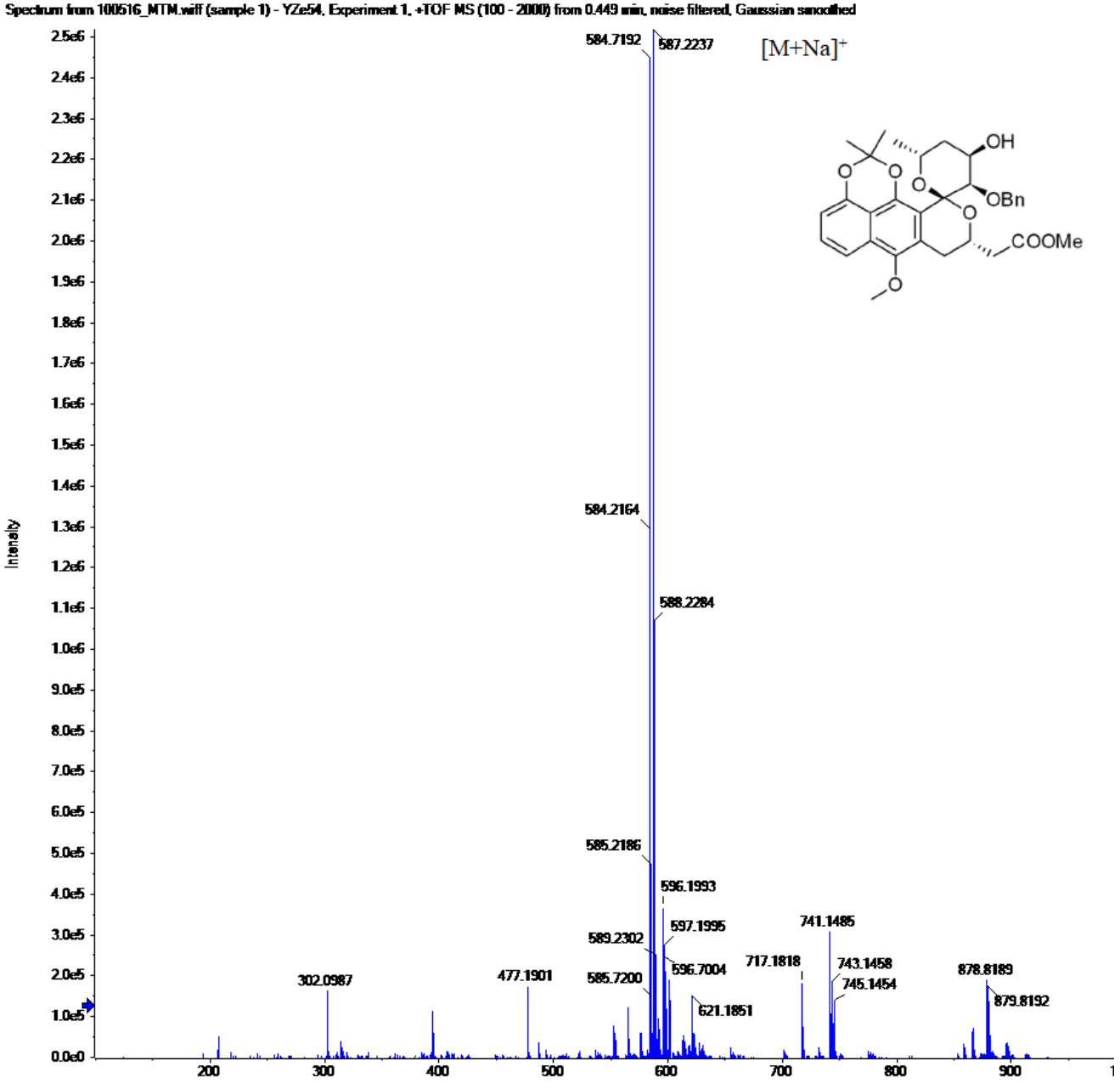



**Figure S184.** (+)-HRESI-MS of **50.**

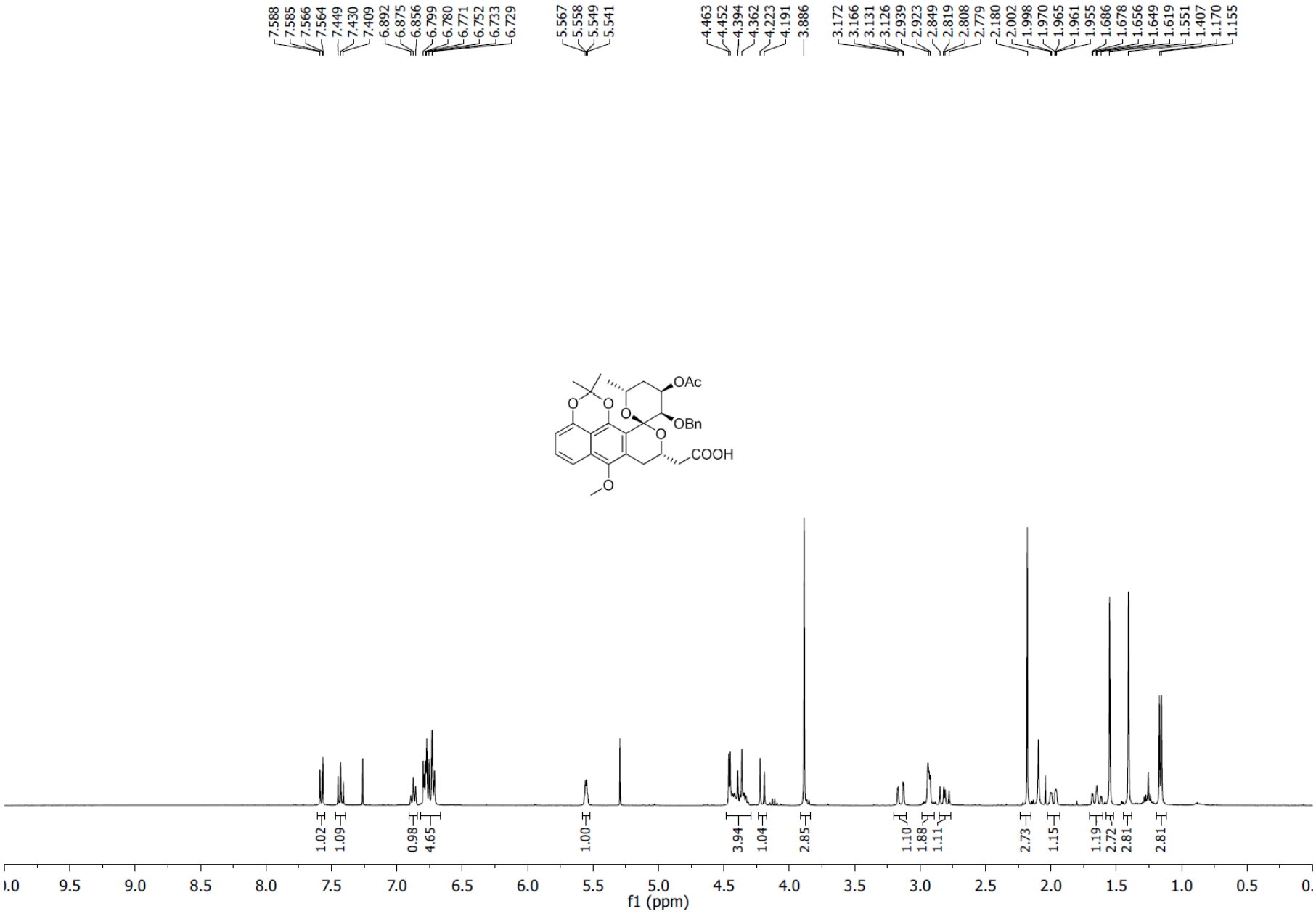



**Figure S185.** $^{1}$H-NMR ($CDCl_3$, 400 MHz) of **51.**

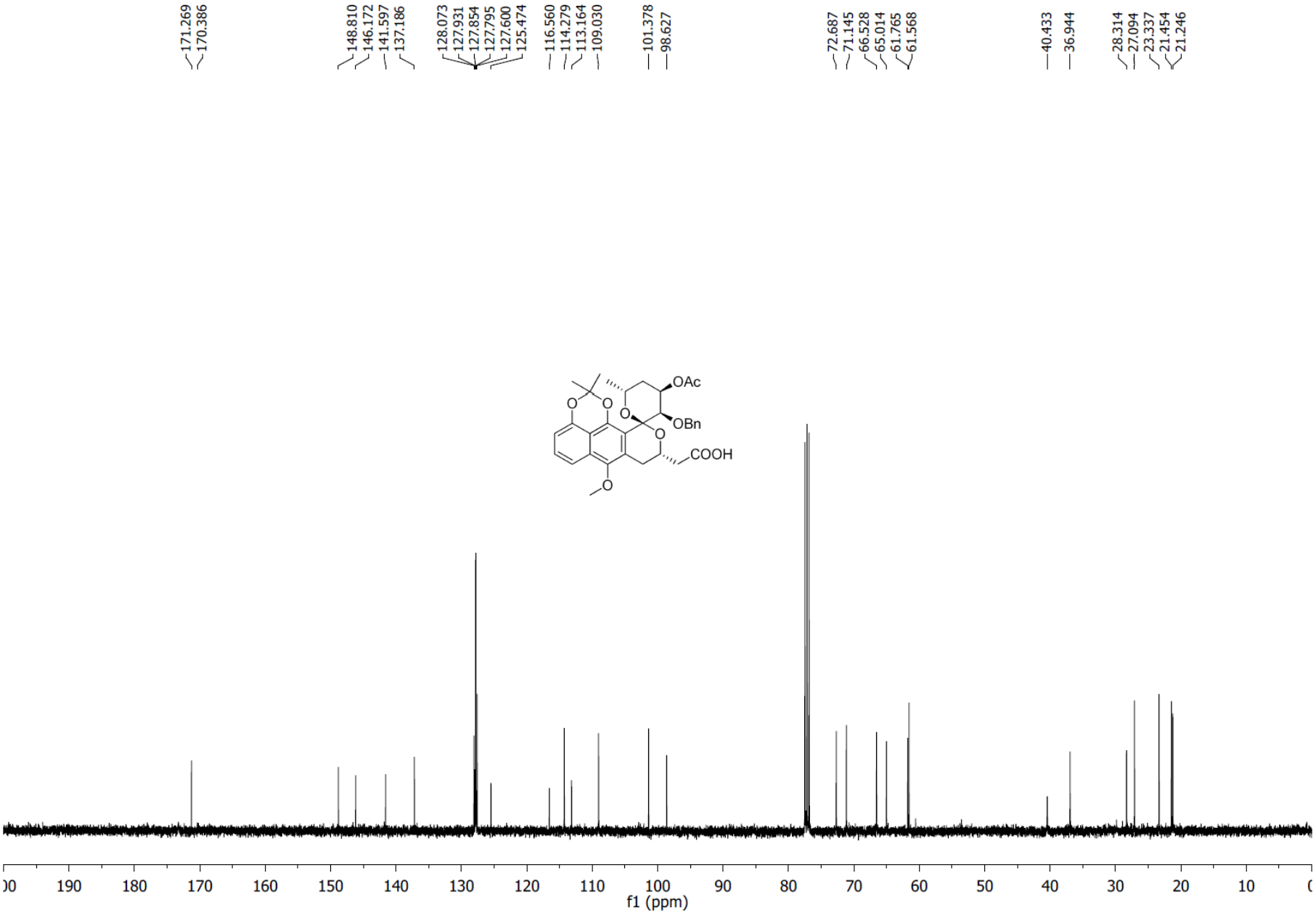



**Figure S186.** $^{13}$C-NMR ($CDCl_3$, 100 MHz) of **51.**

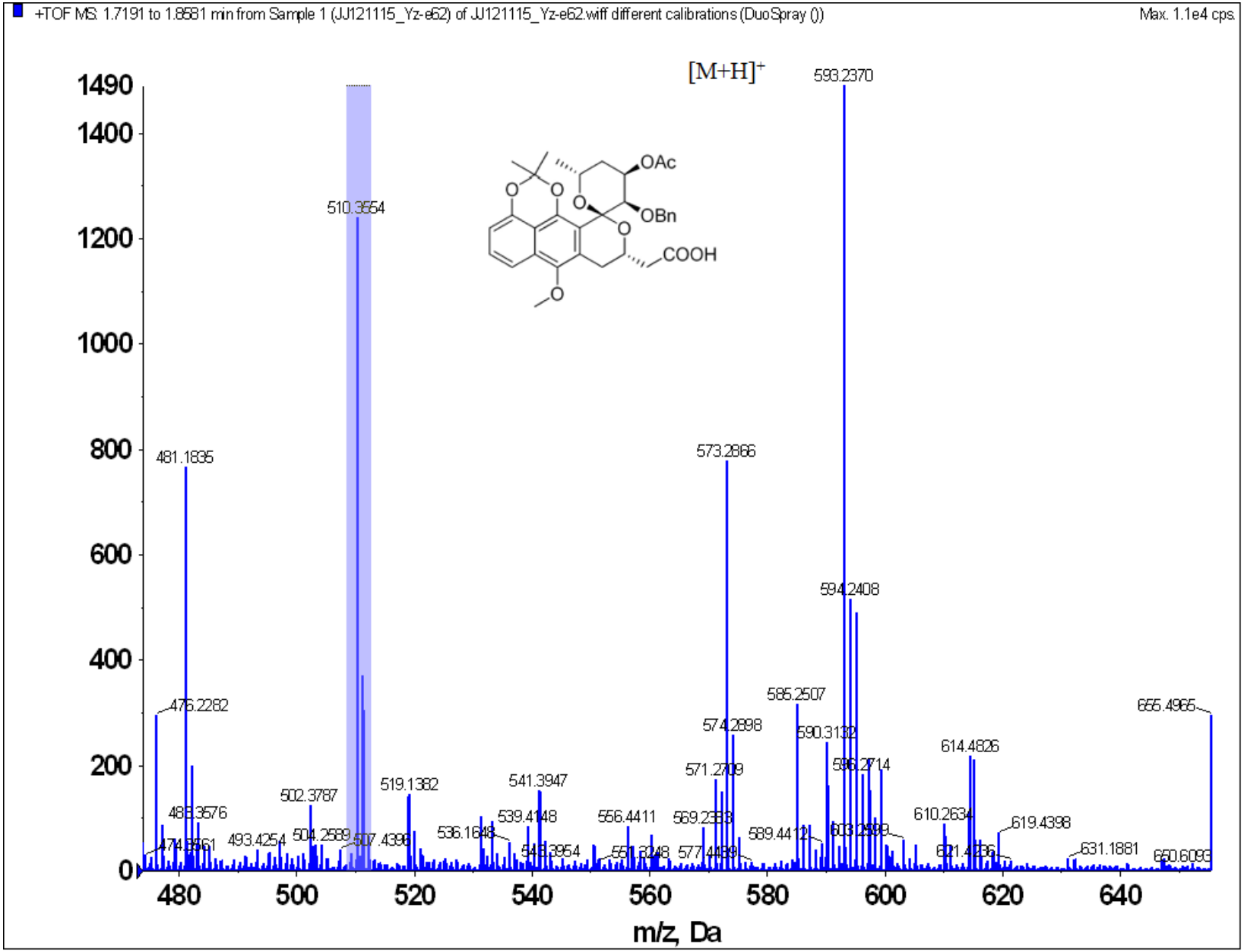



**Figure S187.** (+)-HRESI-MS of **51.**

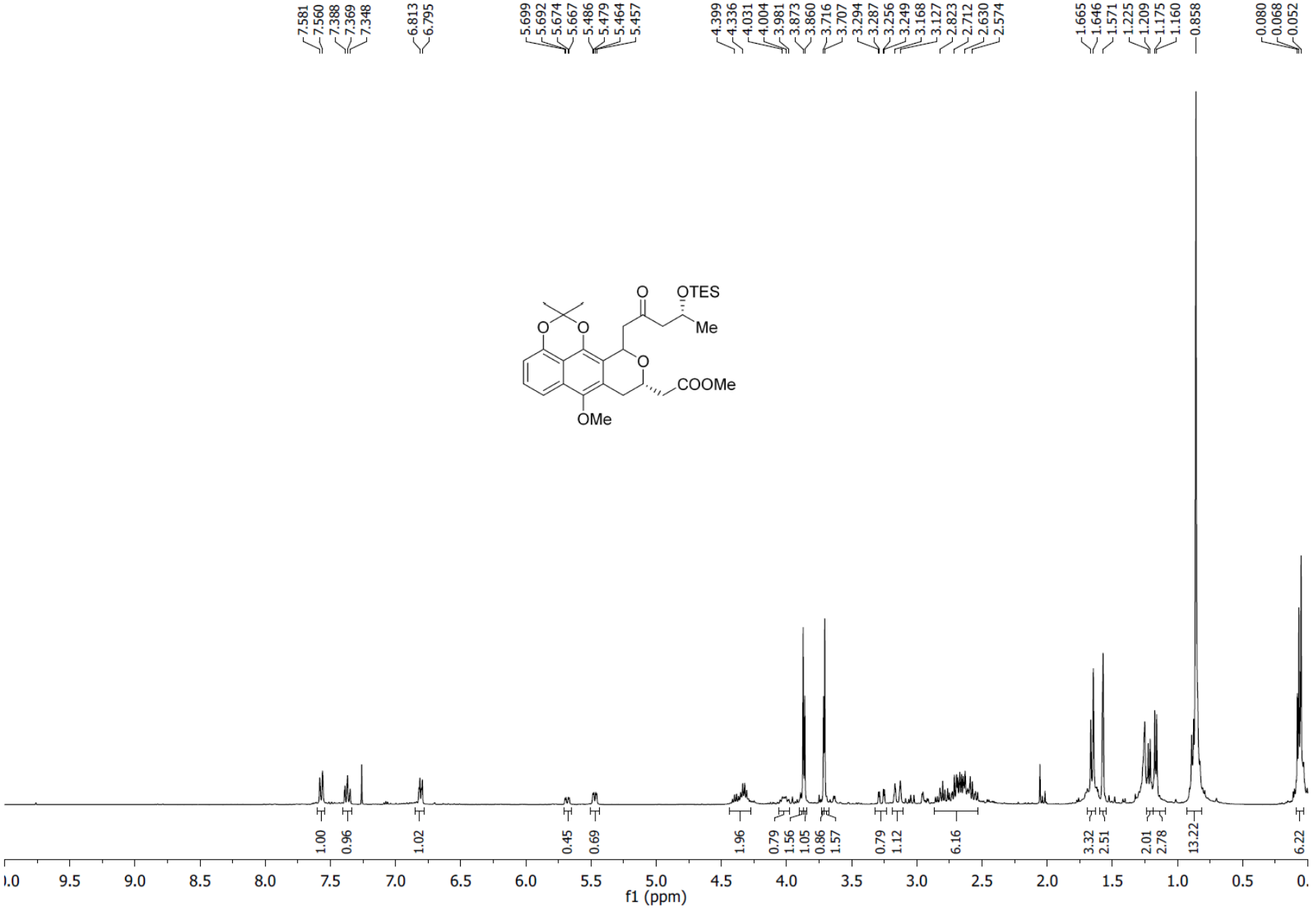



**Figure S188.** $^{1}$H-NMR ($CDCl_3$, 400 MHz) of **52.**

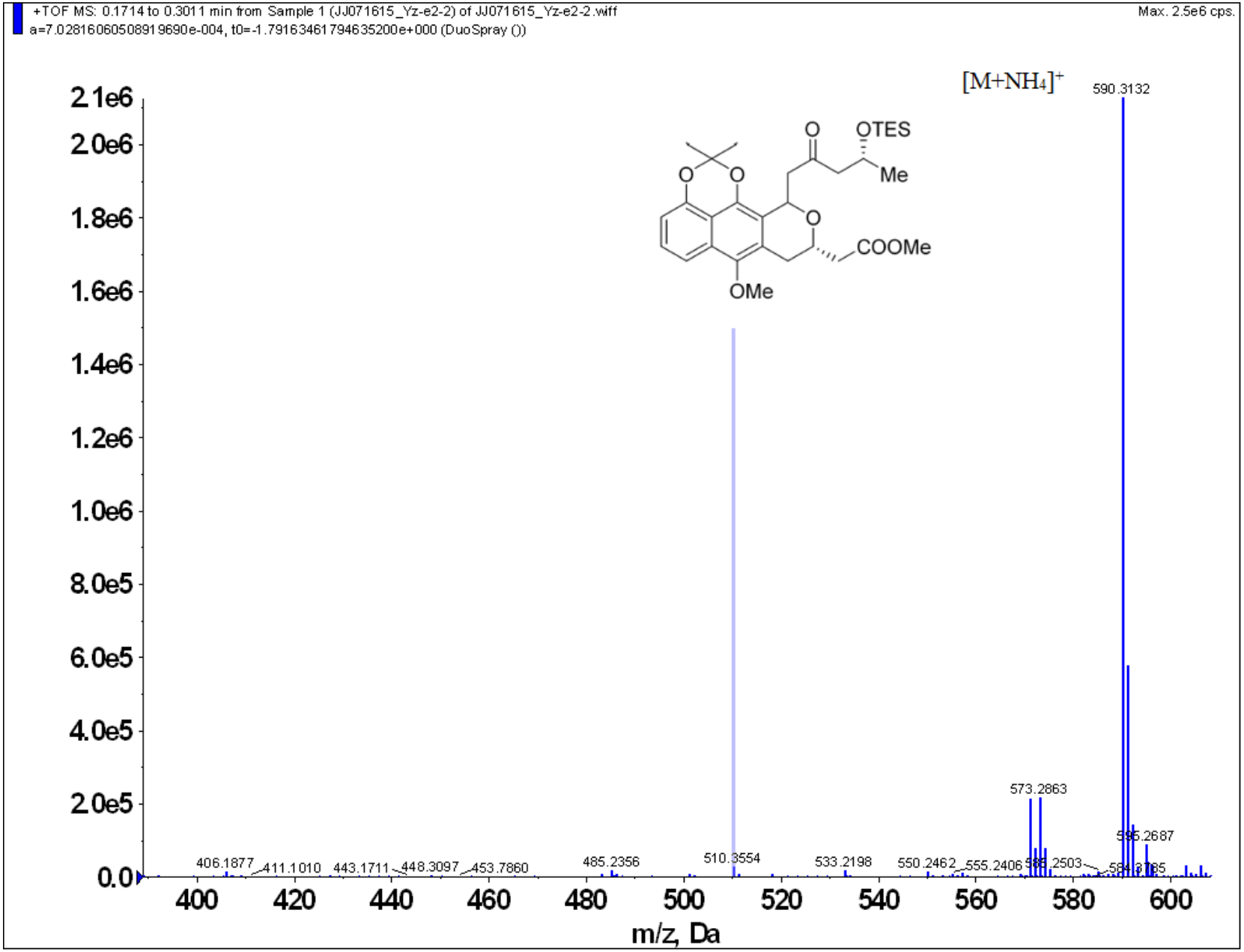



**Figure S189.** (+)-HRESI-MS of **52.**

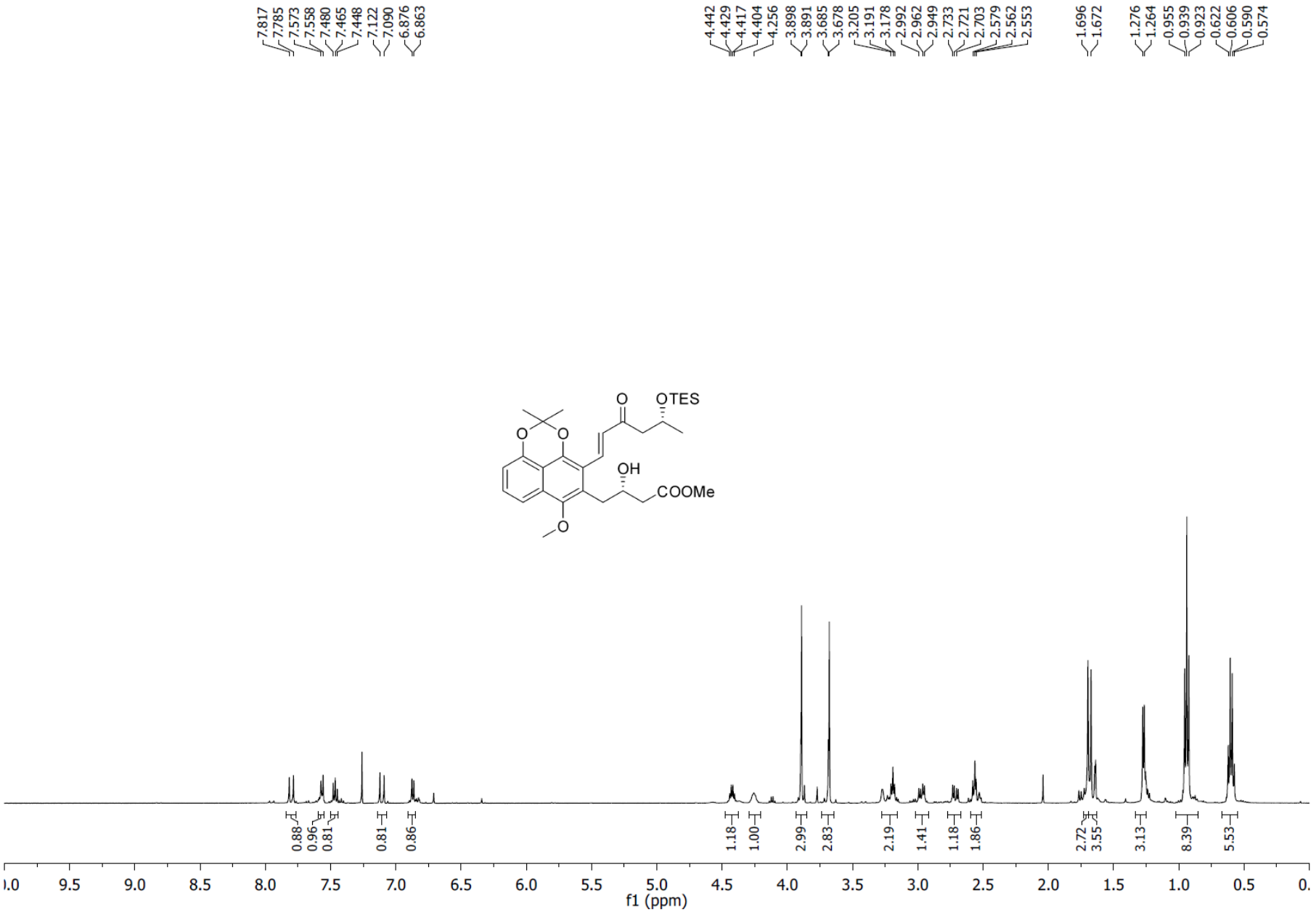



**Figure S190.** $^{1}$H-NMR ($CDCl_3$, 400 MHz) of **53.**

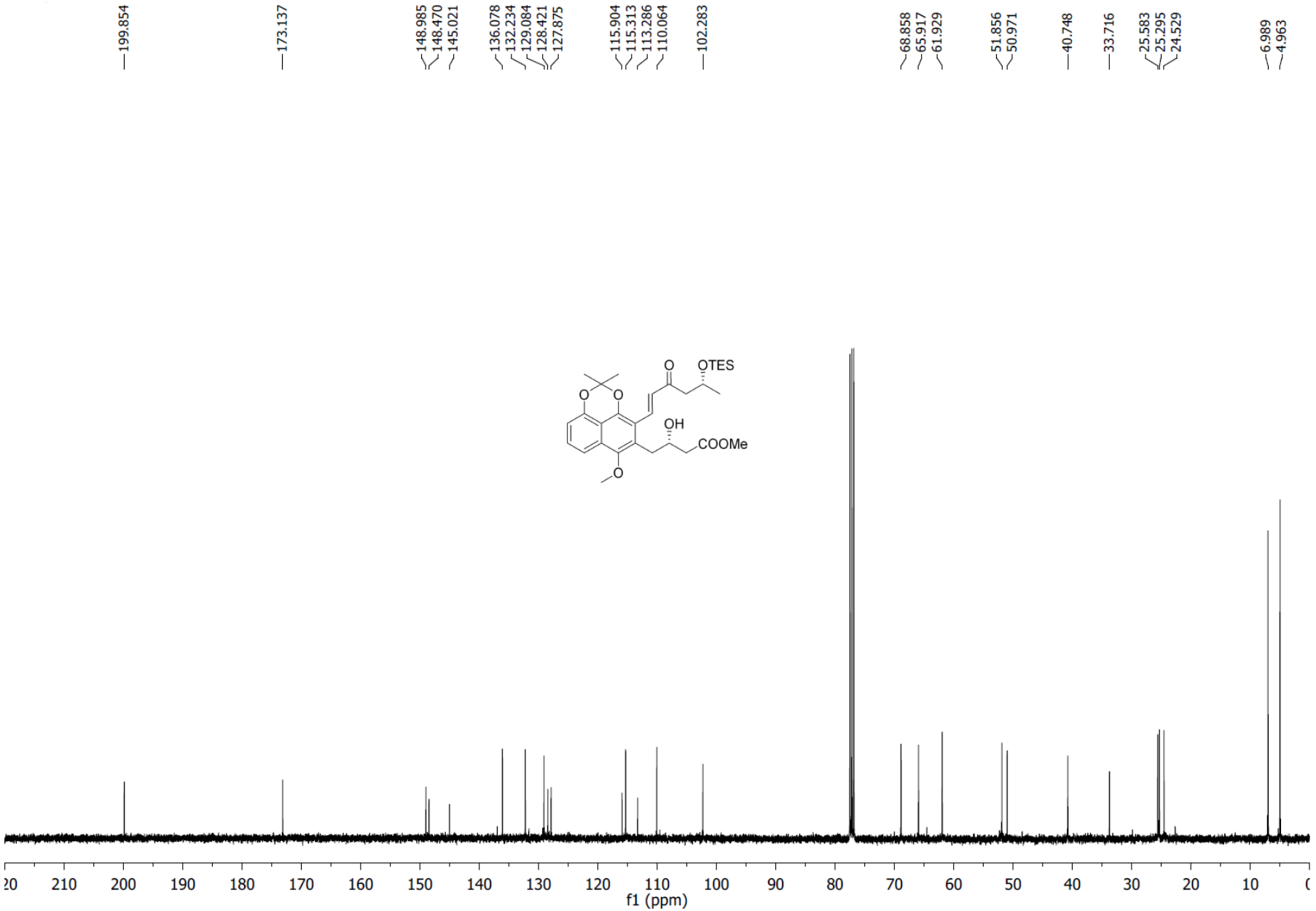



**Figure S191.** $^{13}$C-NMR ($CDCl_3$, 100 MHz) of **53.**

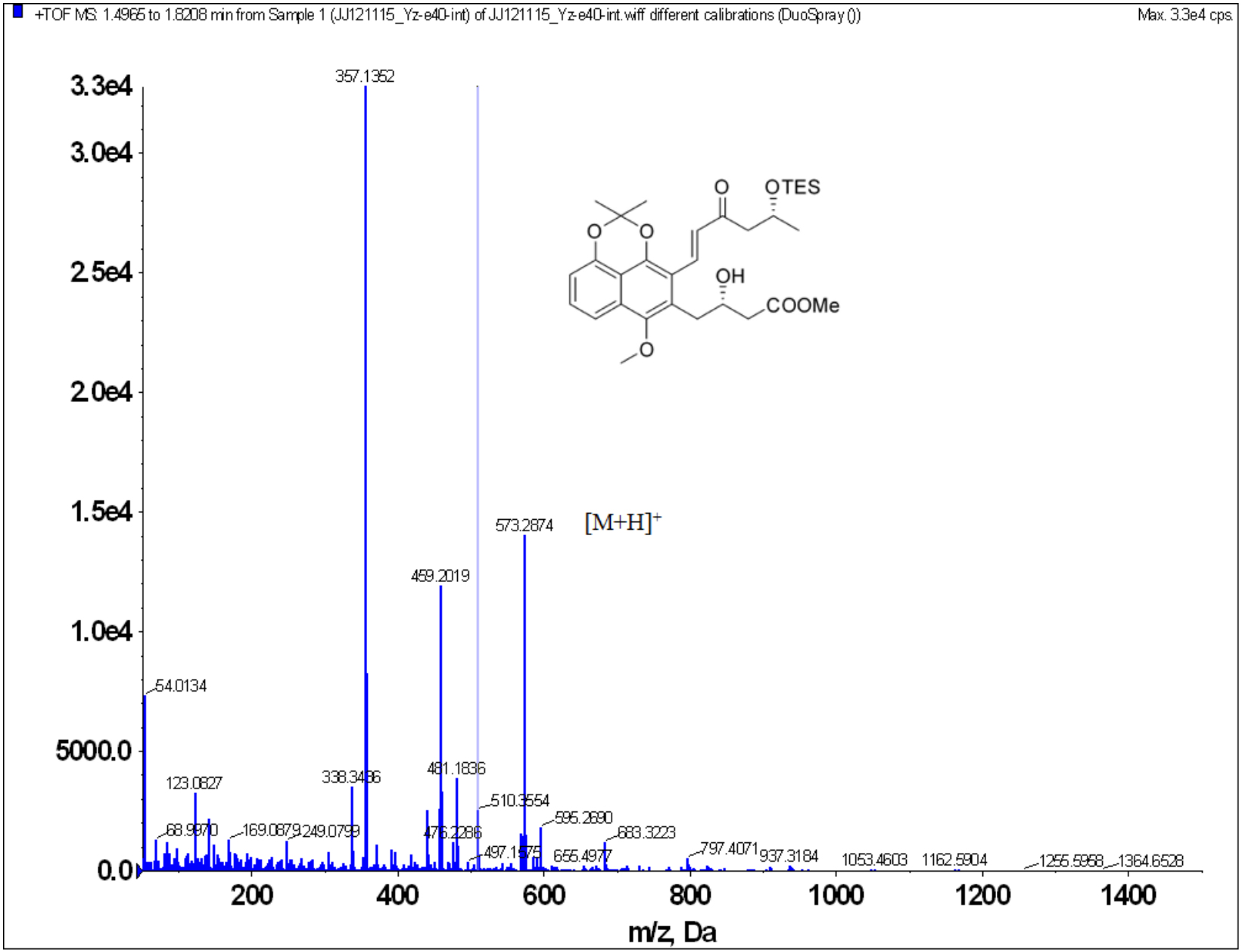



**Figure S192.** (+)-HRESI-MS of **53.**

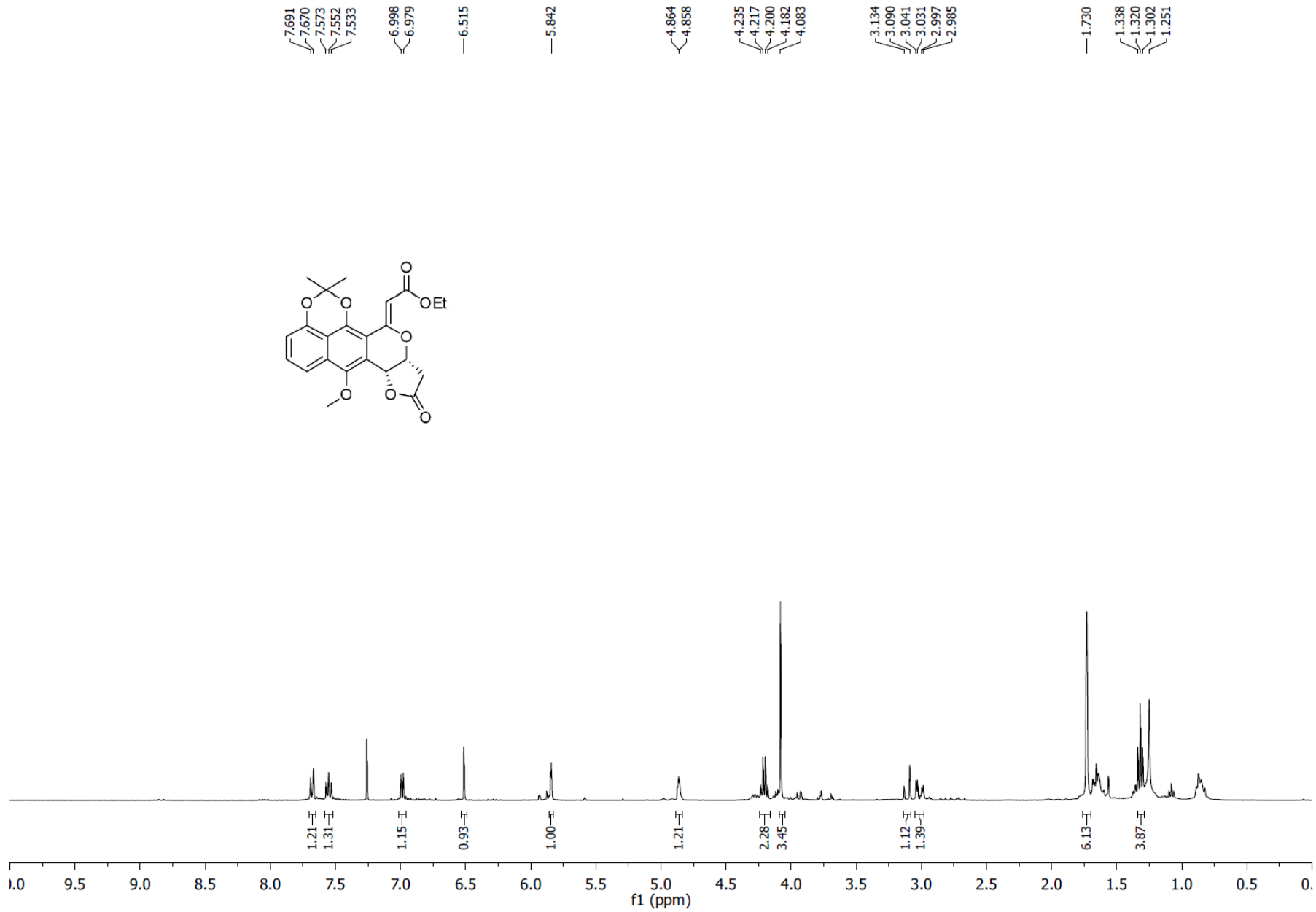



**Figure S193.** $^{1}$H-NMR ($CDCl_3$, 400 MHz) of **54.**

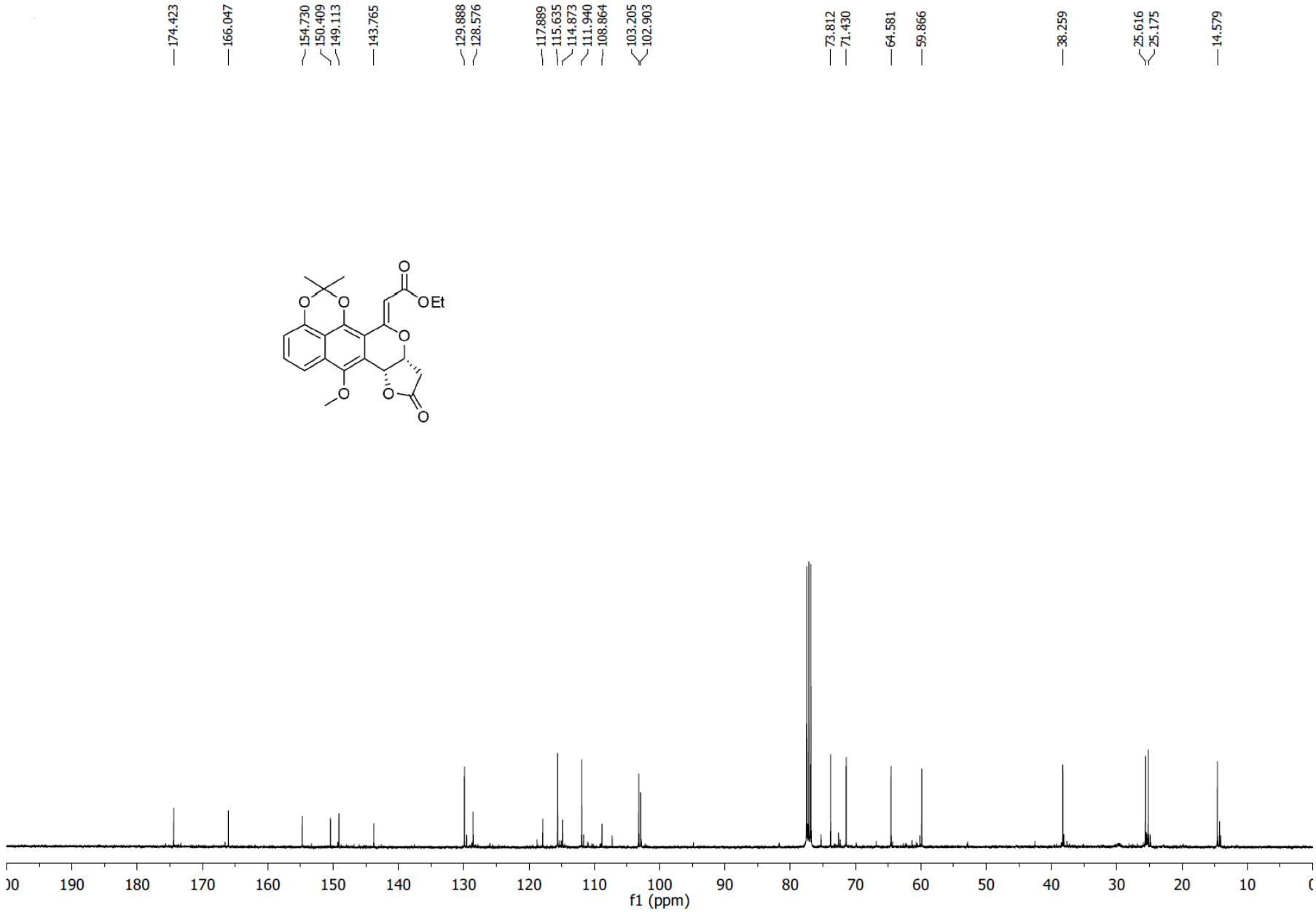



**Figure S194.** $^{13}$C-NMR ($CDCl_3$, 100 MHz) of **54.**

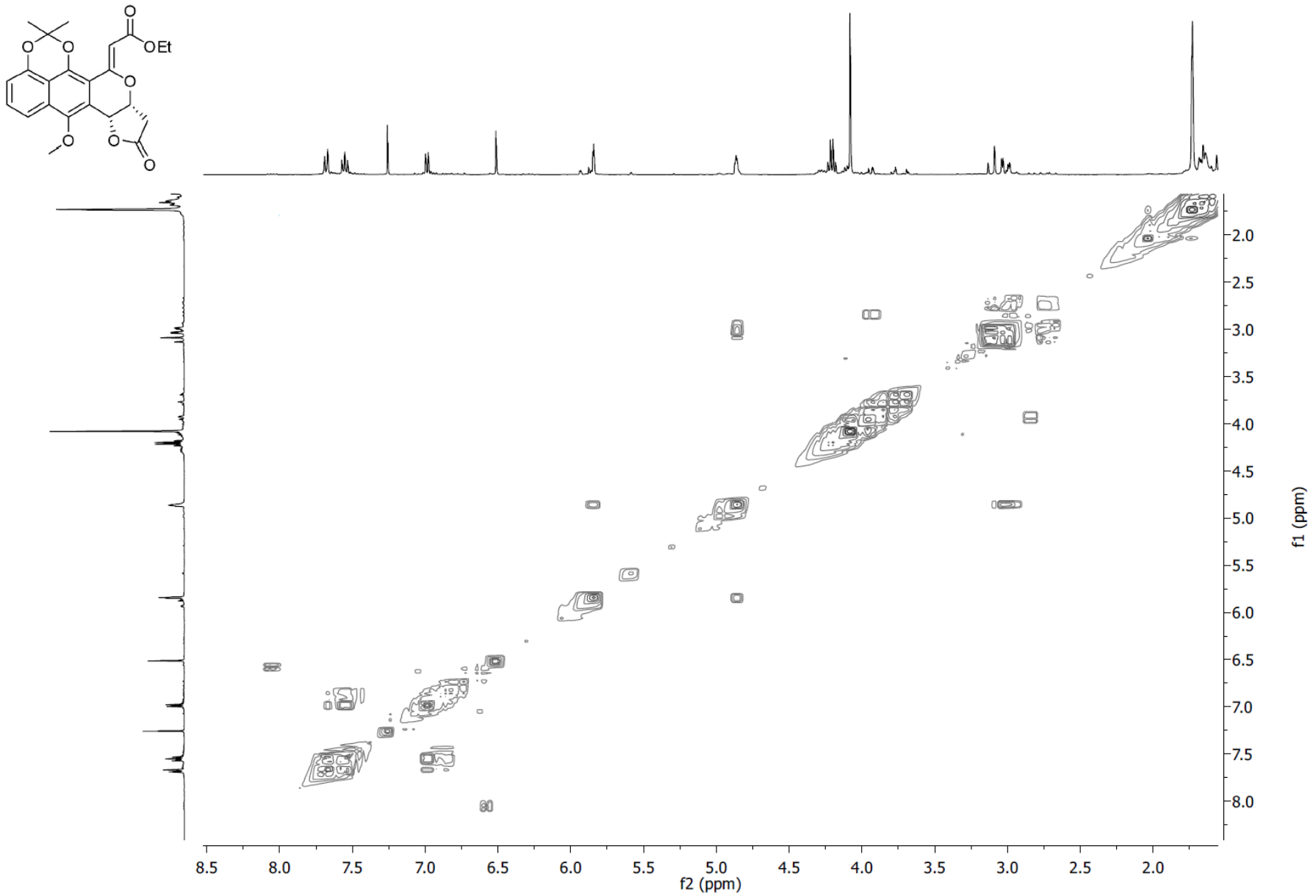



**Figure S195.** $^{1}$H-$^{1}$H COSY ($CDCl_3$, 400 MHz) of **54.**

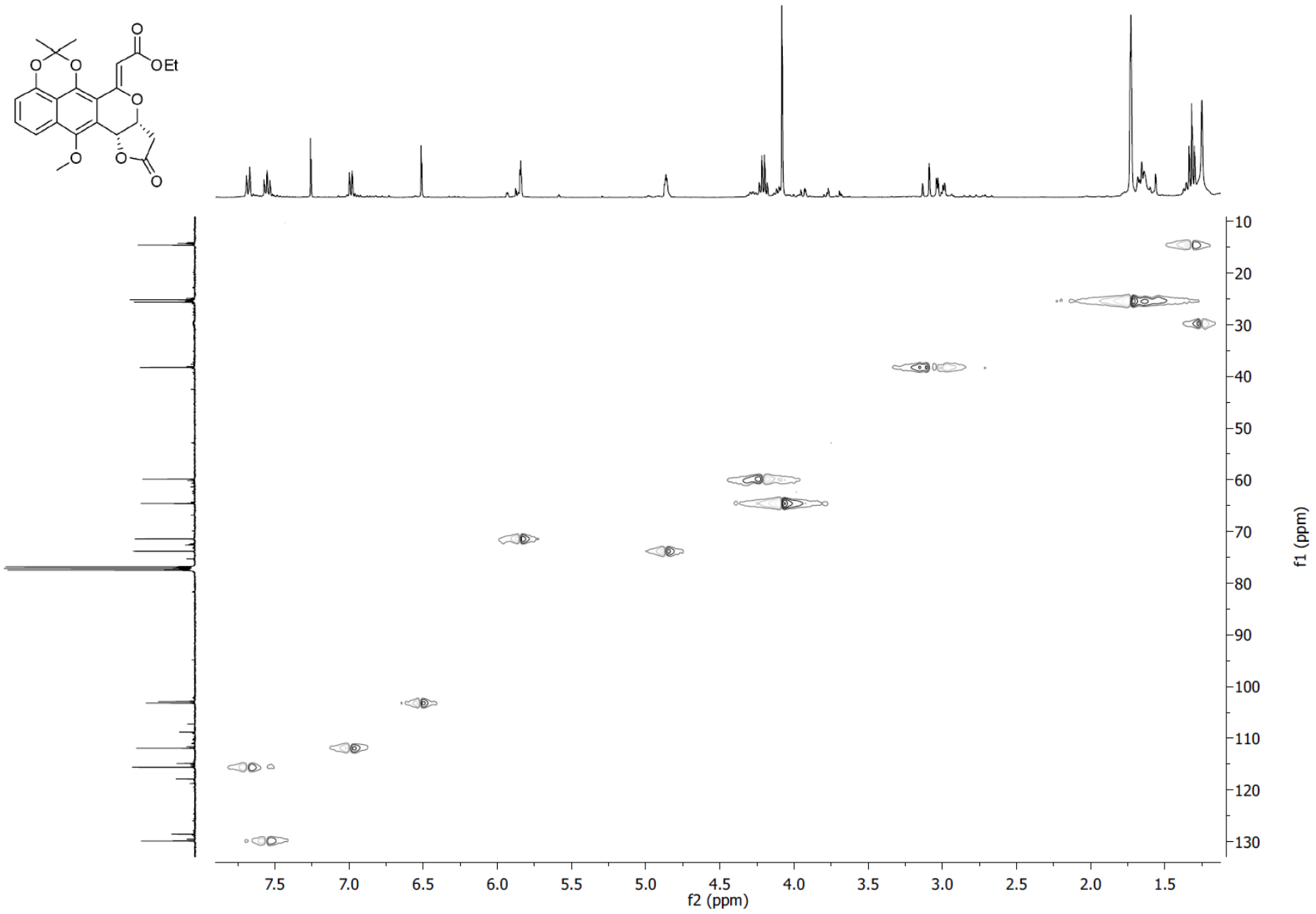



**Figure S196.** HSQC ($CDCl_3$, 400 MHz) of **54.**

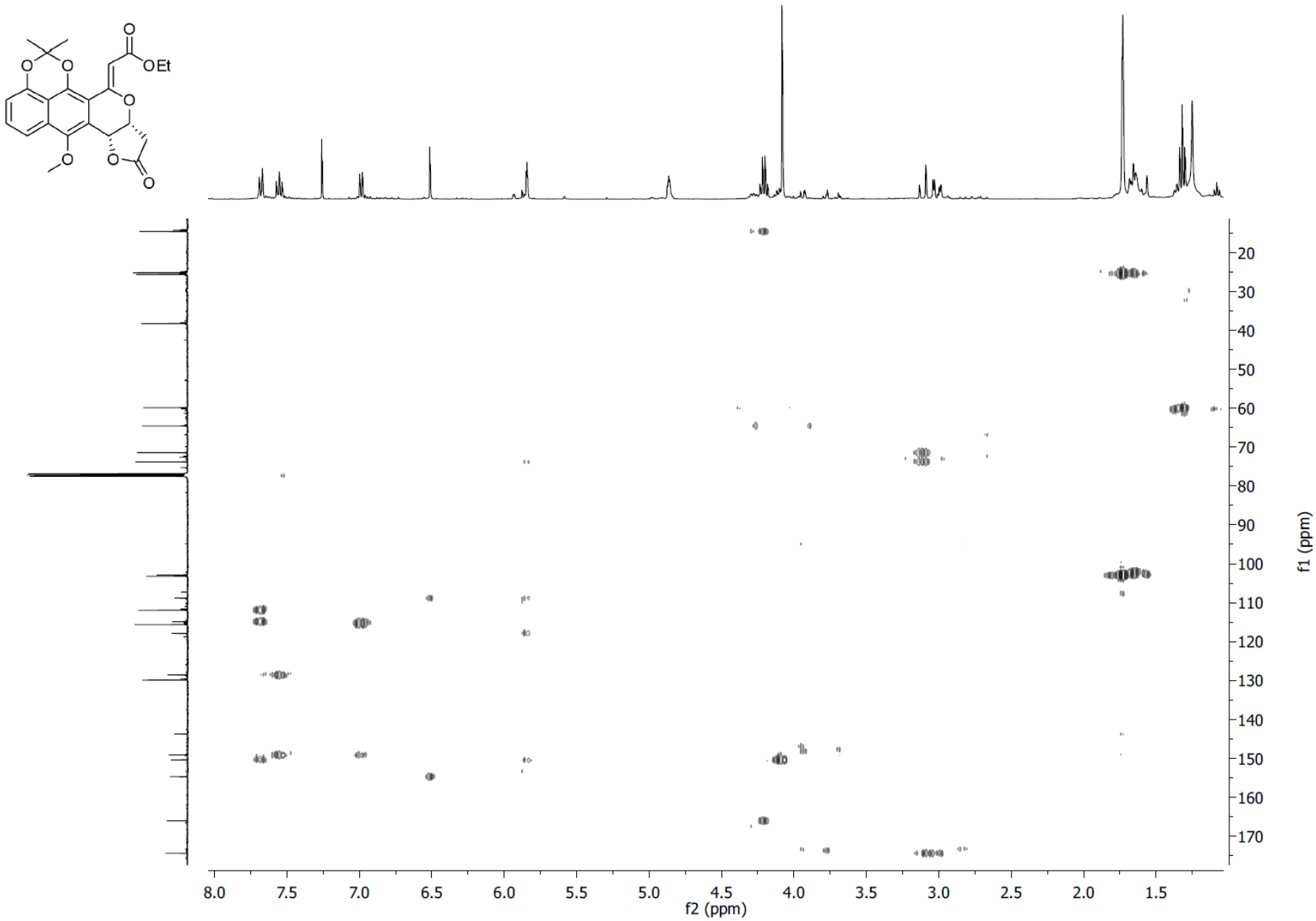



**Figure S197.** HMBC ($CDCl_3$, 400 MHz) of **54.**

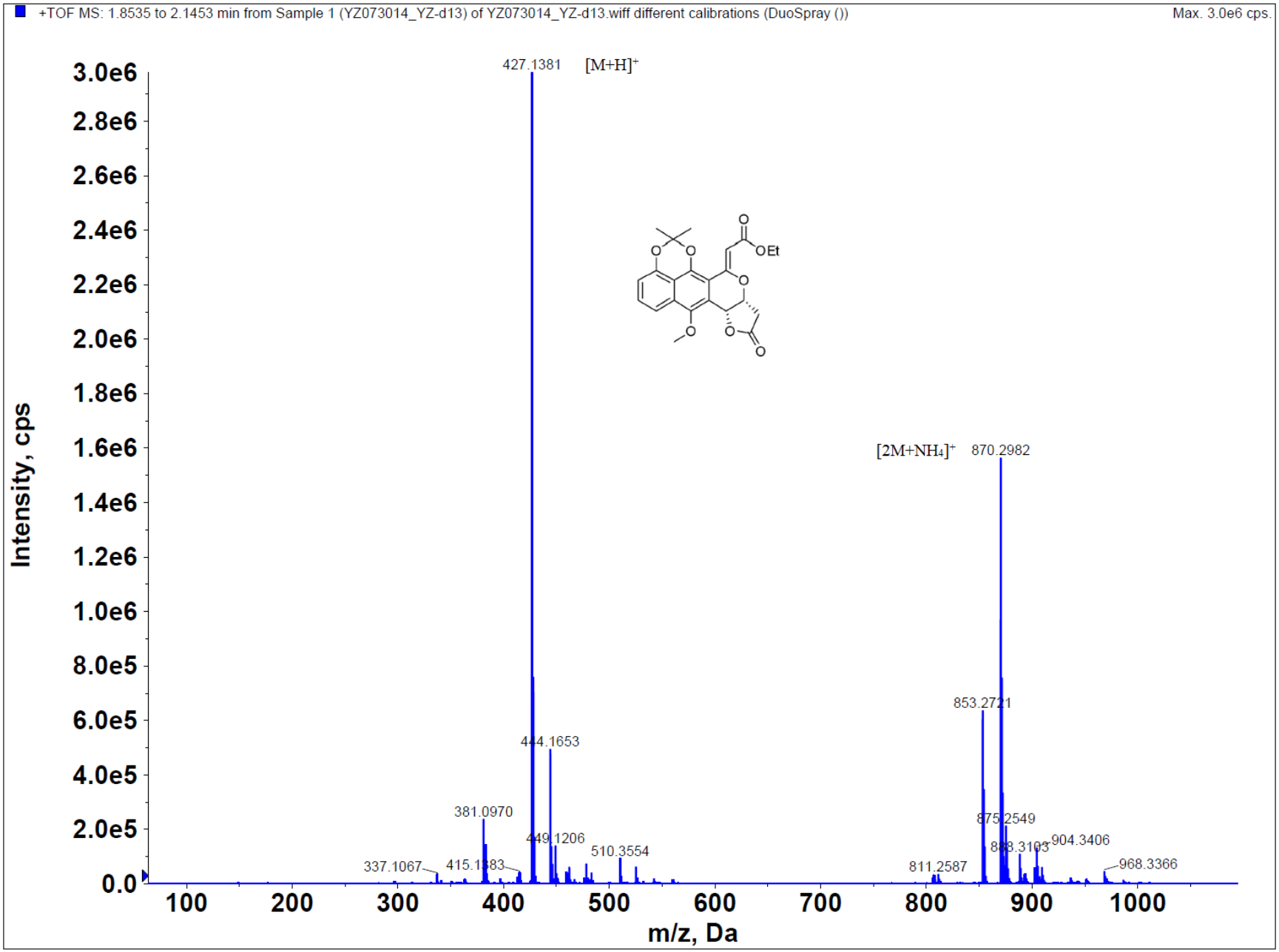



**Figure S198.** (+)-HRESI-MS of **54.**

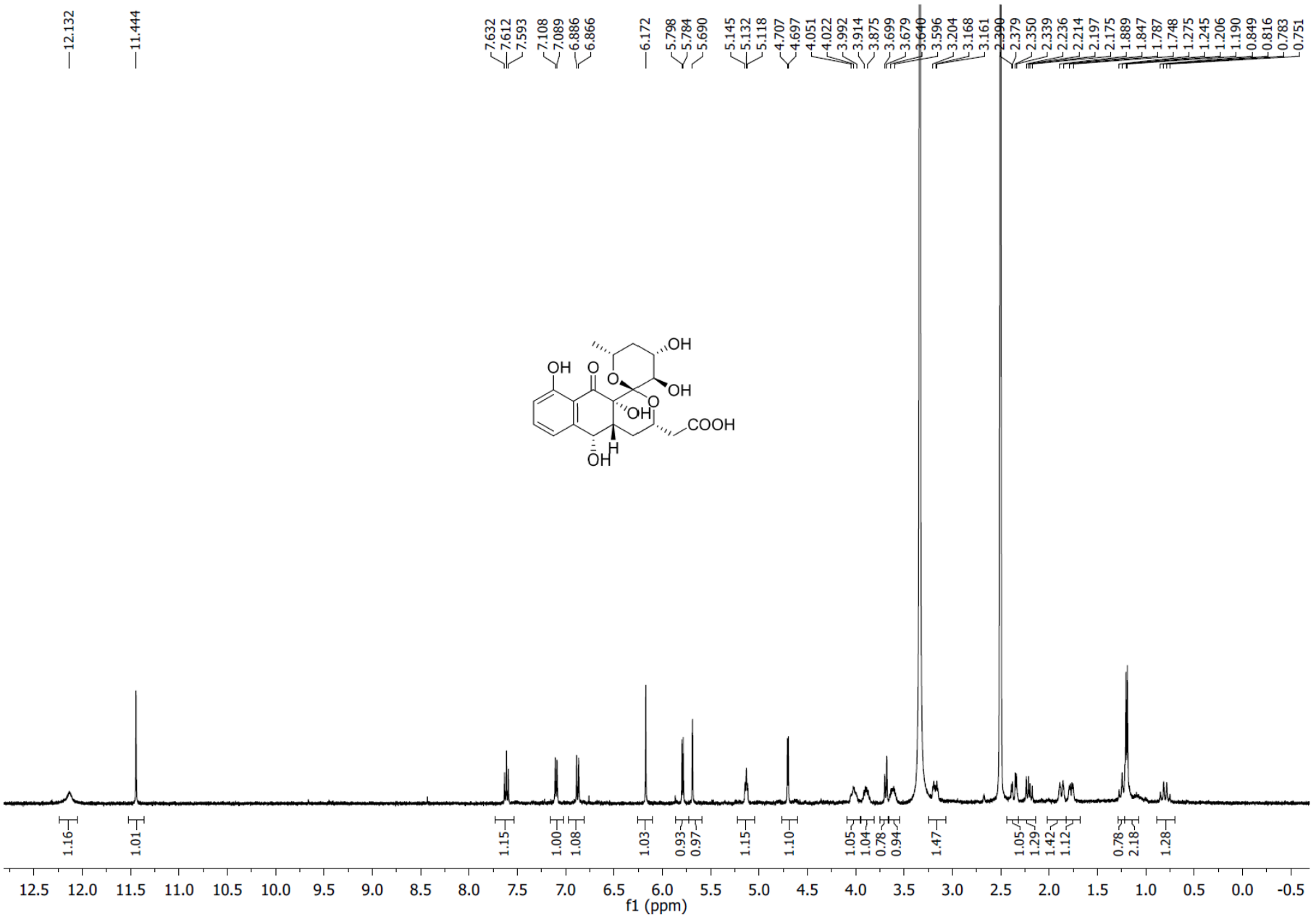



**Figure S199.** $^{1}$H-NMR (DMSO-$d_6$, 400 MHz) of **55.**

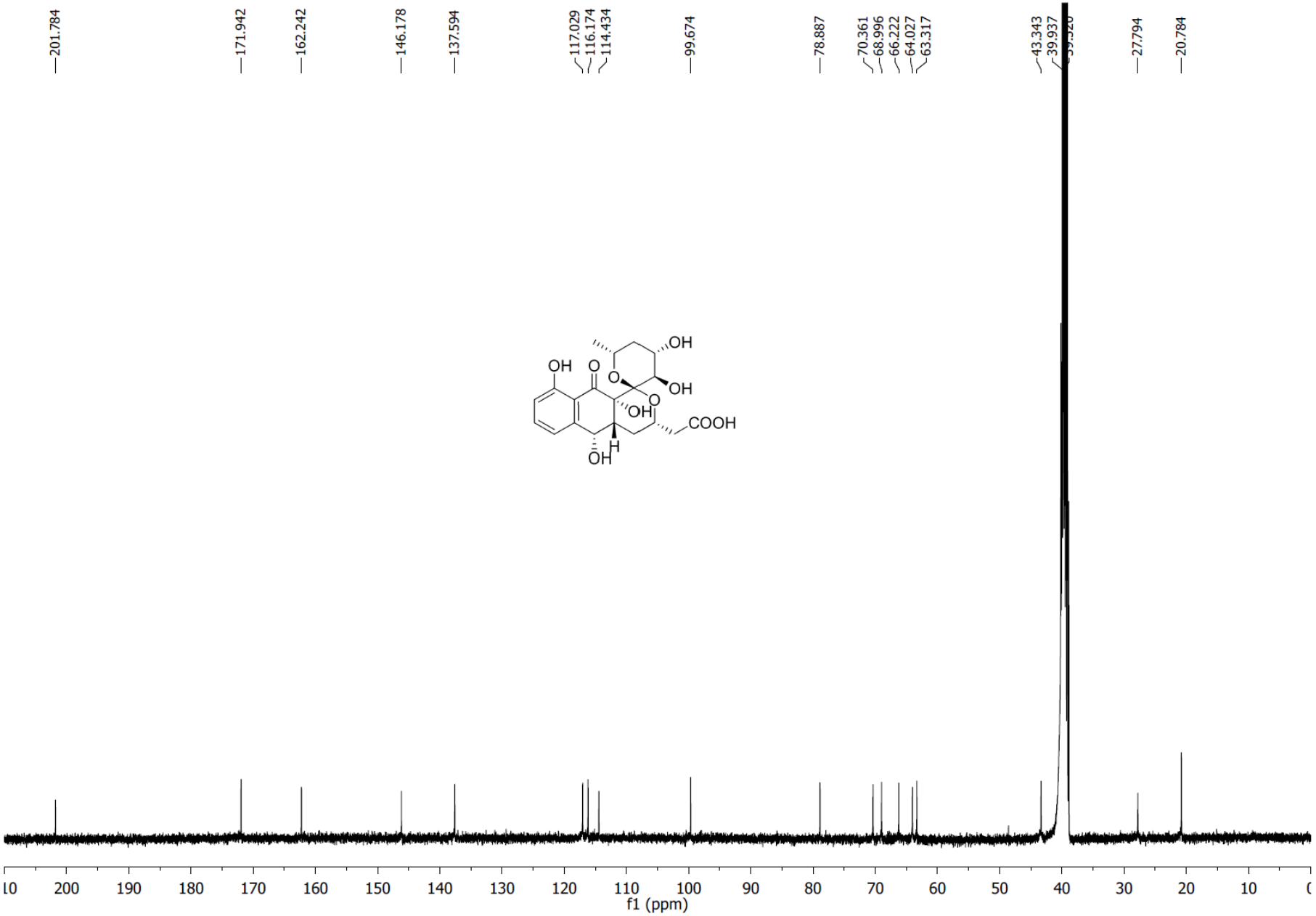



**Figure S200.** $^{13}$C-NMR (DMSO-$d_6$, 100 MHz) of **55.**

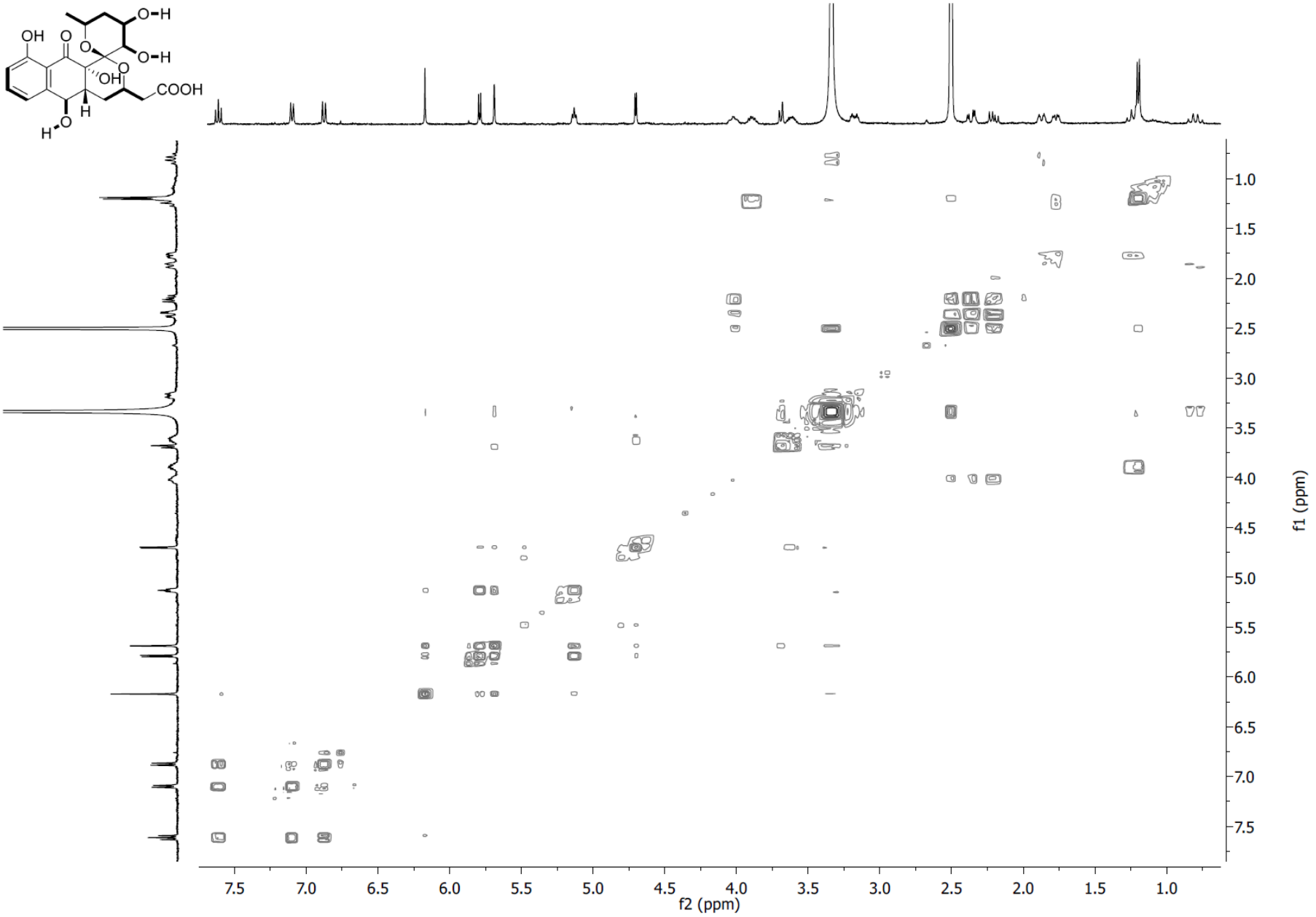



**Figure S201.** $^{1}$H-$^{1}$H COSY (DMSO-$d_6$, 400 MHz) of **55.**

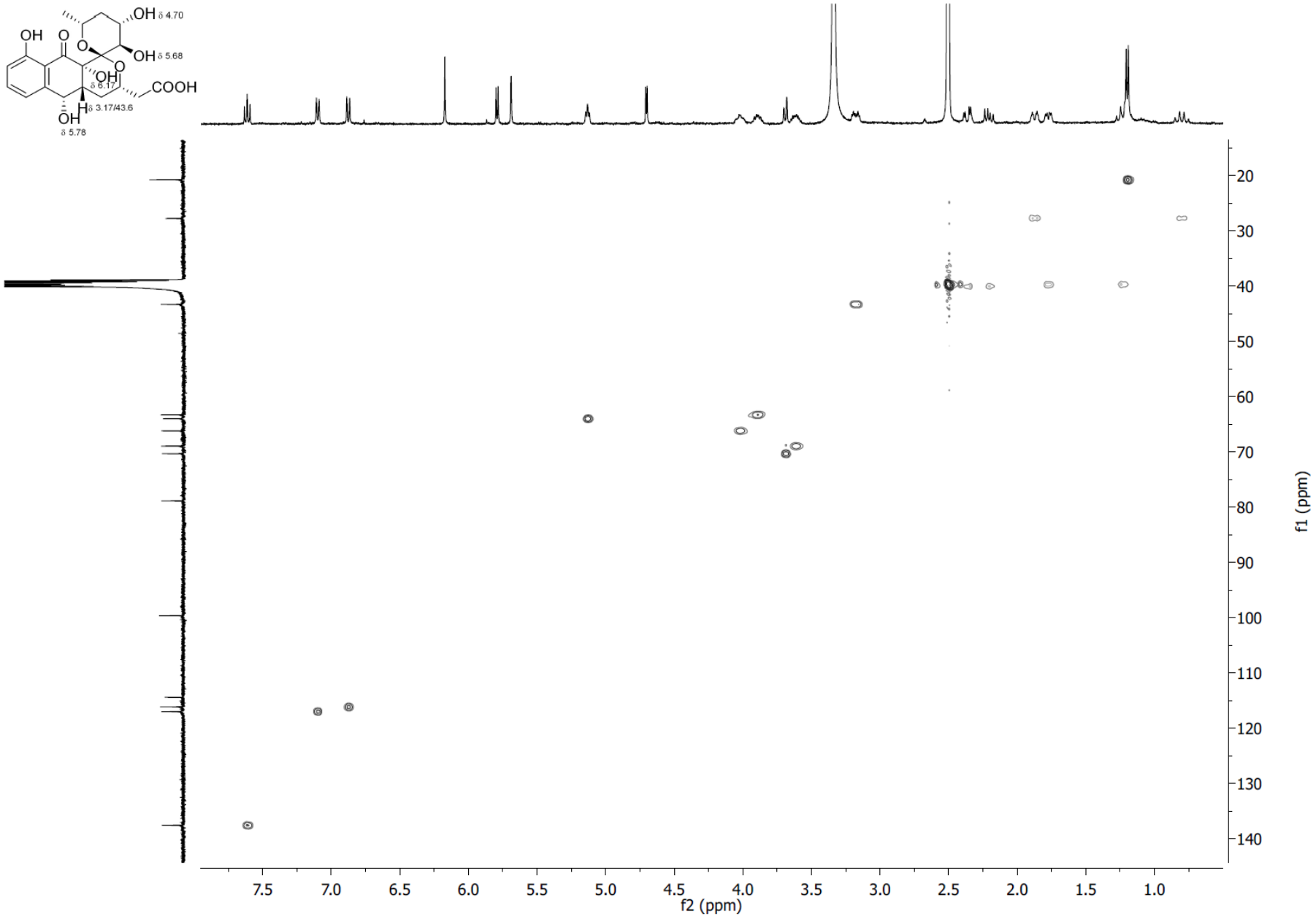



**Figure S202.** HSQC (DMSO-$d_6$, 400 MHz) of **55.**

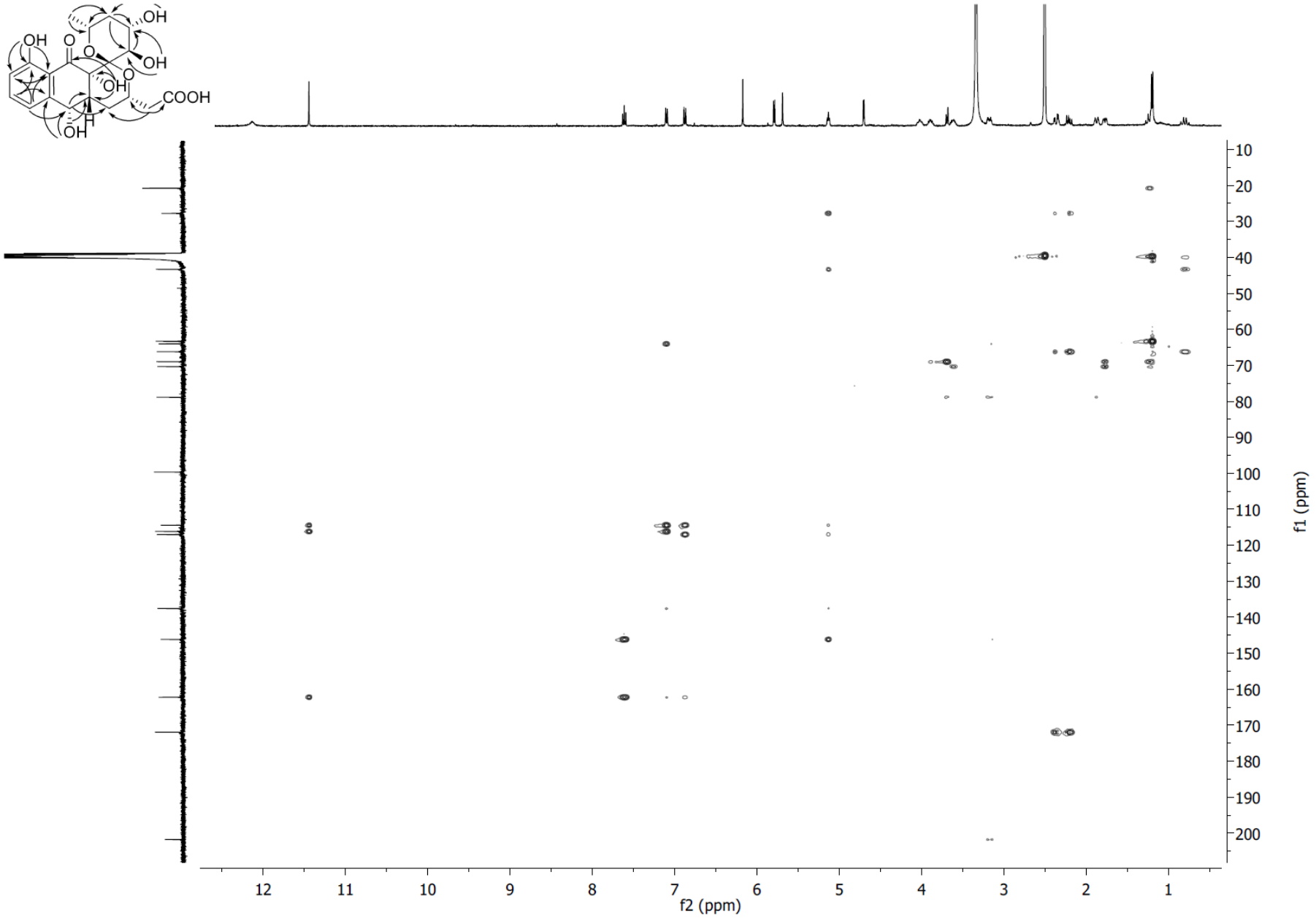



**Figure S203.** HMBC (DMSO-$d_6$, 400 MHz) of **55.**

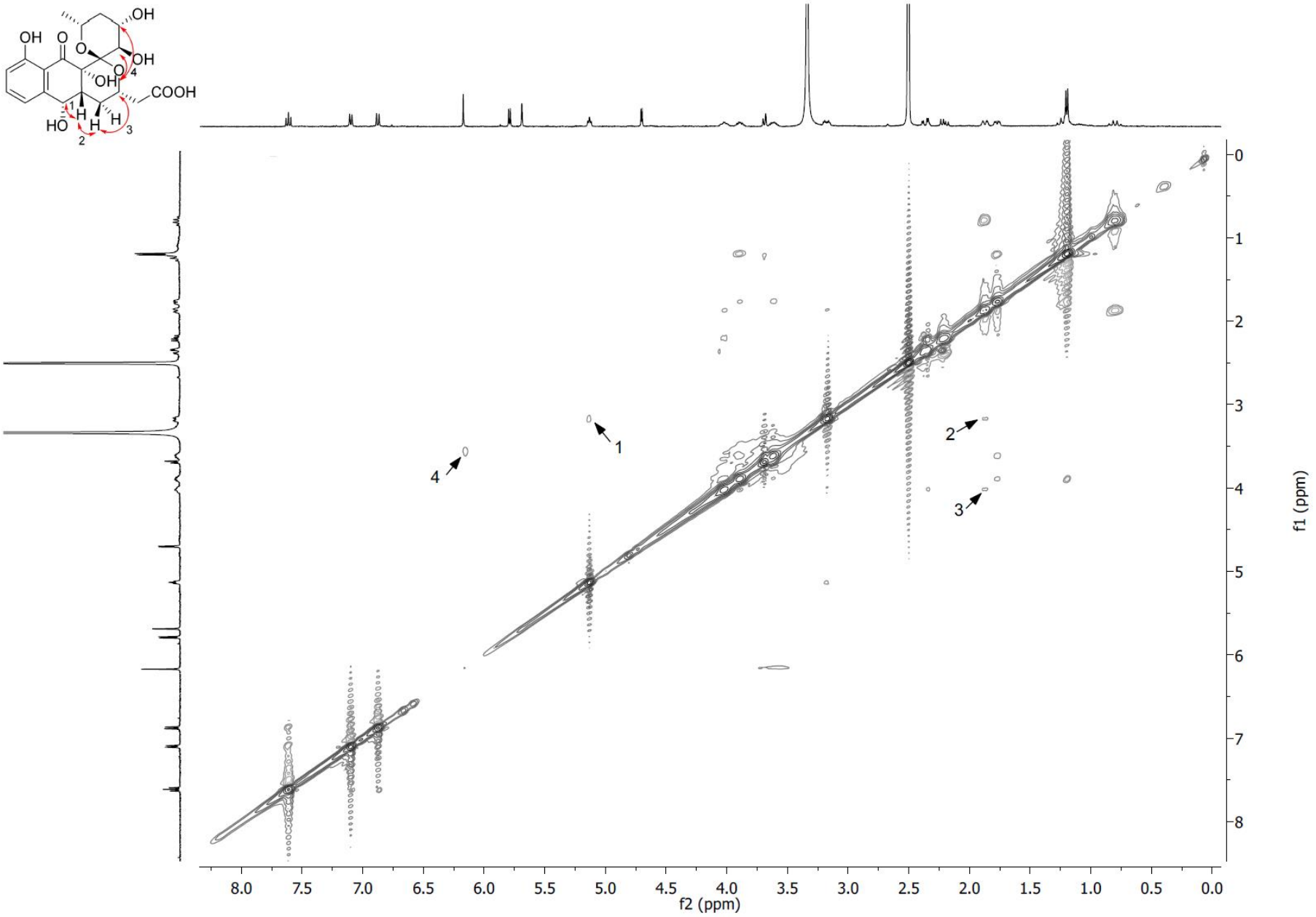



**Figure S204.** NOESY (DMSO-$d_6$, 400 MHz) of **55.**

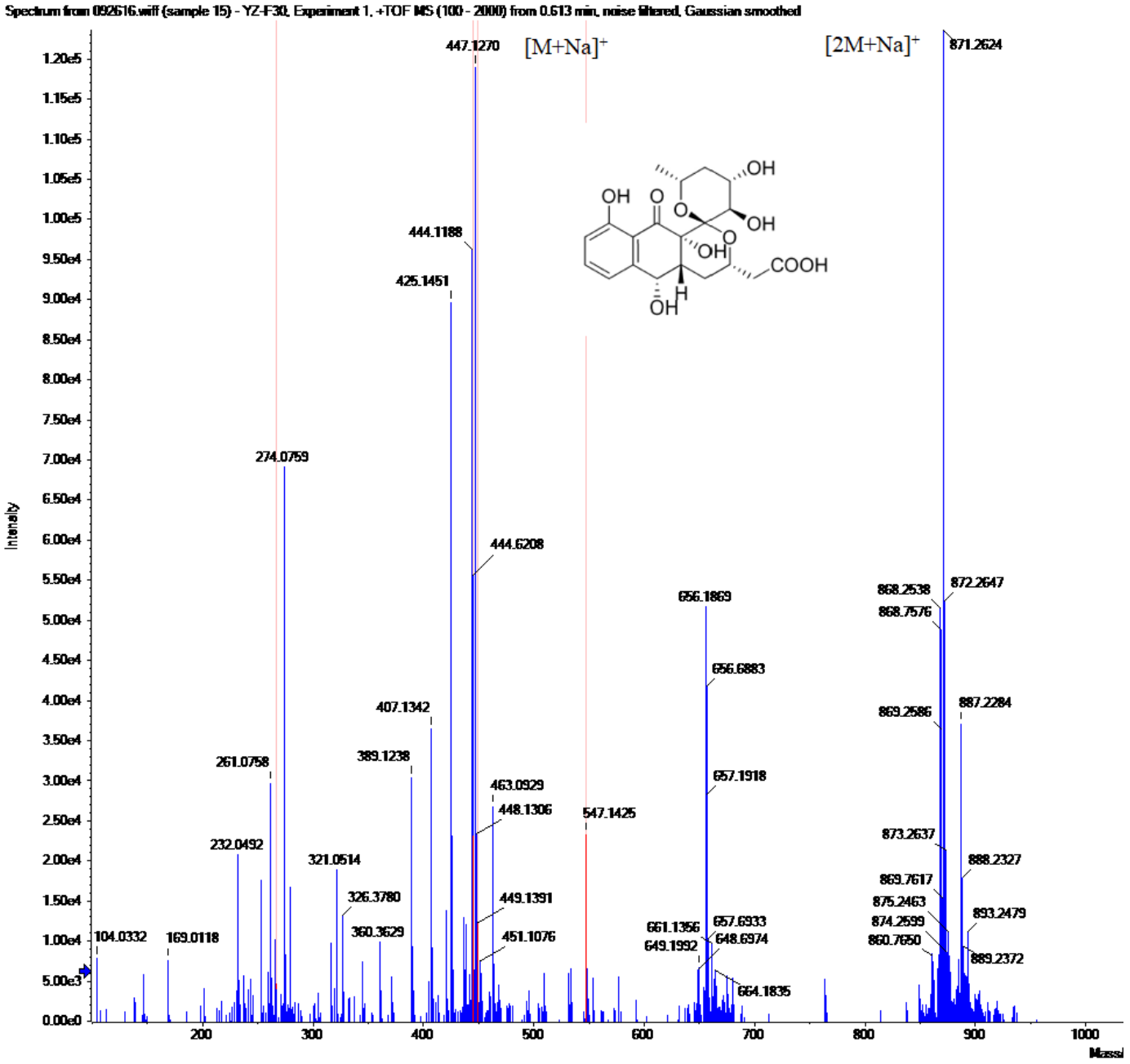



**Figure S205.** (+)-HRESI-MS of **55.**