Electronic Supplementary Material (ESI) for Organic Chemistry Frontiers.

Supporting Information

Bio-inspired Formal Total Synthesis of (±)-Bisabosqual A

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1. General Methods

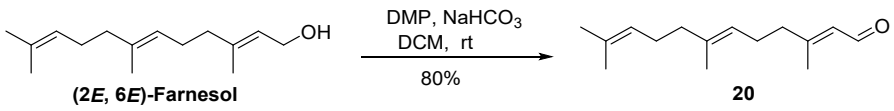
All reactions were carried out under an argon atmosphere with dry solvent under anhydrous conditions, unless otherwise noted. Dry dichloromethane (CH_2Cl_2) and tetrahydrofuran (THF) were obtained by passing commercially available pre-dried. Anhydrous acetone, dimethylformamide (DMF), ethyl acetate (EtOAc), and toluene were purchased from commercial suppliers and stored under argon. Yields refer to chromatographically and spectroscopically (^{1}H NMR) homogenous material, unless otherwise stated. Reagents were purchased at the highest commercial quality and used without further purification, unless otherwise noted.

Reactions were monitored by thin layer chromatography (TLC) carried out on 0.25 mm silica gel plates (GF254, Qingdao) using UV light as visualizing agent and an ethanolic solution of phosphomolybdic acid (PMA) or I_2 as developing agents. Silica gel (200-400 mesh, Qingdao) or neutral alumina (100-200 mesh) was used for column chromatography.

NMR spectra were recorded on Bruker AV 400, Agilent AV 500 or JEOL AV 400 instruments and calibrated using residual undeuterated solvent ($CDCl_3$, δ_H = 7.26 ppm, δ_C = 77.1 ppm; DMSO, δ_H = 2.50 ppm, δ_C = 39.6 ppm) as an internal reference. The information in parentheses report fine structures (s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, m = multiplet, br = broad), scalar coupling constants (*J*, given in Hz), relative integration of signals and the signal assignment. HRESIMS data were measured on UHD Accurate Mass Q-TOF LC/MS G6540A. Semi-preparative HPLC (Hitachi chromaster).

2. Experimental Procedures and Physical Data of Compounds

2.1 Synthesis of (2*E*, 6*E*)-3, 7, 11-trimethyldodeca-2, 6, 10-trienal (20)

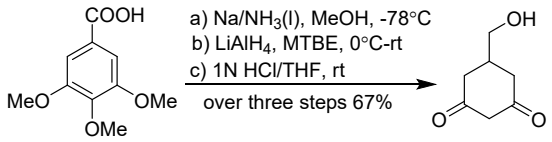


(2*E*, 6*E*)-Farnesol **20**

Aldehyde **20** was prepared in 80% accorting to the process reported in literature.[1]

To a solution of (2*E*, 6*E*)-farnesol (222.0 mg, 1.0 mmol, 1.0 eq) in dichloromethane (50 mL) was added $NaHCO_3$ (252.0 mg, 3.0 mmol, 3.0 eq), Dess-Martin periodinane (932.0 mg, 2.2 mmol, 1.2 eq) at 0 ºC. After being stirred for 1 h at room temperture, the reaction solvent was removed under vacuum. Saturated sodium bicarbonate aqueous solution (10 mL) and saturated sodium thiosulfate aqueous solution (5 mL) were added to the residue. The solution was extracted with dichloromethane (20 mL × 3). The combined organic phase was washed with brine (20 mL), dried over sodium sulfate, concentrated and purified by silica gel column chromatography (petroleum ether/ethyl acetate = 50:1) to give aldehyde **20** as a yellow oil (176.0 mg, 80%).

2.2 Synthesis of 5-(hydroxymethyl)cyclohexane-1, 3-dione (21)



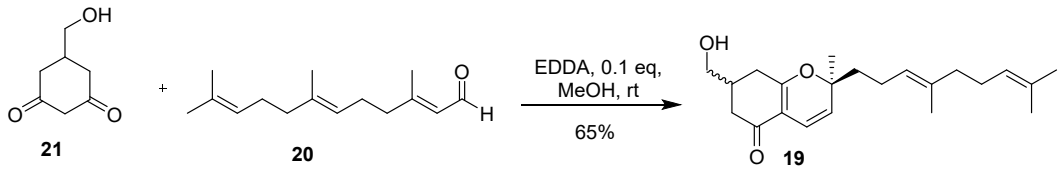
22 **21**

Hydroxydiketone **21** was prepared in 67% by 3 steps of the process reported in literature.[2, 3]

To a solution of compound **22** (50.0 g, 235.8 mmol, 1.0 eq) in methanol (300 mL) was added liquid ammonia (1000 mL) at -78 ºC, Sodium (30.0 g) was added in small pieces to a solution. When the addition was complete, ammonium chloride (125.0 g) was added, and the ammonia was allowed to evaporate at room temperature. The resulting solid was dissolved in ice-water, and the solution was acidified to congo-red with 2 N HCl at 0 ºC. The solution was extracted with methylene chloride. After drying, the methylene chloride was removed at room temperature giving crude 1, 4-dihydro-3, 5-dimethoxybenzoic acid. Crude product was added as a slurry in MTBE to a suspension of lithium aluminum hydride (17.0 g) in MTBE (500 mL) at 0 ºC. After stirring for 1h the excess hydride was quenched with saturated ammonium chloride aqueous solution and the mixture was filtered. Evaporation of the MTBE at room temperature gave the crude alcohol. A solution of alcohol (30.0 g, 176.0 mmol) in a mixture of THF (750 mL) and 1N HCl (150 mL) was stirred at room temperature for 8 hours and was then concentrated in vacuo, purified by neutral alumina column chromatography (DCM :

Methanol = 5:1) to give hydroxydiketone **21** as a yellow oil (22.4 g, 67%, 3 steps).

2.3 Synthesis of -2-((*E*)-4, 8-dimethylnona-3, 7-dien-1-yl)-7-(hydroxymethyl)-2-methyl-2, 6, 7, 8-tetrahydro-5*H*-chromene-5-one (19)

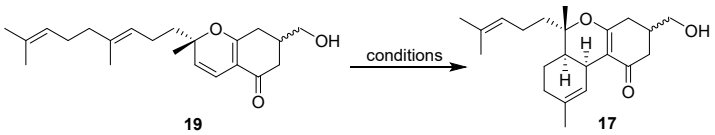


To a stirred solution of hydroxydiketone **21** (156.0 mg, 1.1 mmol, 1.1 eq) in dry MeOH (20 mL) was added freshly prepared EDDA (17.2 mg, 0.1 mmol, 0.1 eq) and (2*E*, 6*E*)-farnesal **20** (222.0 mg, 1.0 mmol, 1.0 eq) at room temperature. The resulting mixture was stirred about 1 h. The reaction mixture was concentrated under reduced pressure and was purified by flash column chromatography (silica gel, petrol ether : EtOAc = 10:1) to give pyran **19** as a yellow oil (223.6 mg, 65%).

19: R_f = 0.2 (petroleum ether : EtOAc = 1:1); IR (KBr): 3480, 3417, 2968, 2920, 1633, 1608, 1437, 1381, 1203, 1152, 1059, 830 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), two isomers, δ 6.43 (d, J = 10.1 Hz, 2H), 5.21 (d, J = 4.6 Hz, 1H), 5.18 (d, J = 4.6 Hz, 1H), 5.12 – 5.09 (m, 4H), 3.84 – 3.77 (m, 1H), 3.65–3.60 (m, 4H), 2.51 – 2.45 (m, 4H), 2.40 – 2.33 (m, 4H), 2.28 – 2.20 (m, 4H), 2.09 – 2.03 (m, 9H), 1.99 – 1.95 (m, 5H), 1.68 (s, 6H), 1.60 (s, 6H), 1.59 (s, 3H), 1.58 (s, 3H), 1.40 (s, 3H), 1.35 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 194.23, (194.15), 171.4, 171.3, 135.66, (135.66), 131.39, (131.39), 124.18, (124.18), 123.40, (123.36), 121.8, 121.7, 116.3, 116.2, 110.1, 109.9, 82.70, (82.66), 65.71, (65.68), 41.68, (41.68), 39.62, (39.62), 39.08, (39.05), 35.6, 35.5, 31.4, 31.3, 27.5, 27.3, 26.61, (26.61), 25.67, (25.67), 22.6, 22.2, 17.66, (17.66), 15.96, 15.95 ppm; HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{22}H_{33}O_3^+$ 345.2424; found 345.2426.

2.4 Synthesis of -3-(hydroxymethyl)-6, 9-dimethyl-6-(4-methylpent-3-en-1-yl)-2, 3, 4, 6, 6a, 7, 8, 10 a-octahydro-1*H*-benzo[c]chromene-1-one (17)

Table S1 Optimal conditions screened for the formation of 17 [a]



19 17

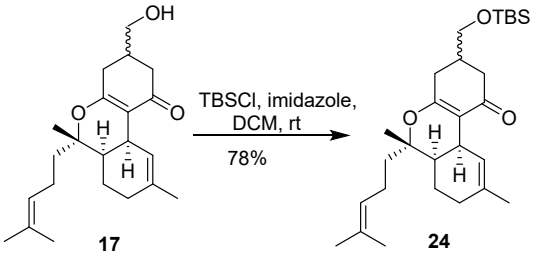
Entry	Reagent	Eq	Solvent	T(°C)	t (h)	Yield(%)[b]
1	$MgBr_2$	1	DCM	reflux	2	28
2	*p*-TSA	1	DCM	rt	2	45
3	$AlCl_3$	1	DCM	rt	2	14
4	$Zn(OTf)_3$	1	DCM	rt	2	No Reaction
5	$In(OTf)_3$	1	DCM	rt	2	34
6	**$FeCl_3$**	**1**	**DCM**	**rt**	**2**	**69(56[c])**
7	$Yb(OTf)_3$	1	DCM	rt	2	No Reaction
8	$FeCl_3$	1	Tol	rt	2	32
9	$FeCl_3$	1	DCM	rt	4	29

[a] Reactions were performed at the 0.1 mmol scale in solvent.
[b] Total yields were determined by ^1H NMR analysis of the crude reaction mixtures.
[c] Isolated yield.

To a stirred solution of compound **19** (1.0 g, 2.9 mmol, 1.0 eq) in dry DCM (0.1M, 29 mL) was added $FeCl_3$ (469.8 mg, 2.9 mmol, 1.0 eq) at room temperature. The resulting mixture was stirred about 2 h. The reaction mixture was concentrated under reduced pressure. The crude product was purified by flash column chromatography (neutral alumina, petrol ether : EtOAc = 15:1) to give product **17** as a yellow oil (558.7 mg, yield: 56%).

17: $\boldsymbol{R_f}$ = 0.3 (petroleum ether: EtOAc =1:1); IR (KBr): 3513, 3436, 2957, 2915, 1633, 1600, 1440, 1380, 1223, 1155, 1073, 667 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): two isomers, δ 6.09 (d, J = 4.2 Hz, 1H), 6.00 (d, J = 3.3 Hz, 1H), 5.06 – 5.00 (m, 2H), 3.62 – 3.52 (m, 4H), 3.13 (s, 2H), 2.46 – 2.28 (m, 7H), 2.26 – 2.19 (m, 1H), 2.15 – 2.04 (m, 3H), 2.01 – 1.88 (m, 7H), 1.84 – 1.76 (m, 5H), 1.75 – 1.69 (m, 3H), 1.65 (s, 9H), 1.63 (s, 3H), 1.58 (s, 3H), 1.56 (s, 3H), 1.54 (t, J = 3.0 Hz, 1H), 1.52 – 1.50 (m, 1H), 1.35 (s, 3H), 1.32 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.5, 197.2, 168.2, 167.4, 133.8, 133.6, 132.1, 132.0, 123.7, 123.6, 122.1, 122.0, 114.2, 113.5, 81.49, (81.47), 65.9, 65.6, 40.3, 40.1, 37.8, 37.4, 37.4, 36.8, 35.8, 34.9, 32.2, 31.6, 31.5, 30.2, 30.0, 29.8, 29.7, 29.6, 25.7, 23.54, (23.50), 22.7, 22.4, 22.3, 22.2, 20.4, 20.0, 17.6 ppm; HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{22}H_{33}O_3^+$ 345.2424; found 345.2427.

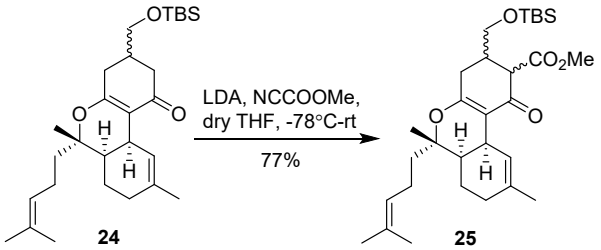
2.5 Synthesis of -3-(((*tert*-butyldimethylsilyl)oxy)methyl)-6, 9-dimethyl-6-(4-methy lpent-3-en-1-yl)-2, 3, 4, 6, 6a, 7, 8, 10a-octahydro-1*H*-benzo[c]chromene-1-one (24)



To a stirred solution of compound **17** (660.0 mg, 1.9 mmol, 1.0 eq) in dry DCM (50 mL) was added imidole (390.5 mg, 5.7 mmol, 3.0 eq) and TBSCl (573.8 mg, 3.8 mmol, 2.0 eq) at room temperature. The resulting mixture was stirred about 1 h. The mixture was quenched with H_2O (20 mL) and extracted with DCM (3 × 15 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (neutral alumina, petrol ether : EtOAc = 100:1) to give product **24** as a yellow oil (678.7 mg, yield: 78%).

24: $\boldsymbol{R_f}$ = 0.6 (petroleum ether : EtOAc = 5:1); IR (KBr): 3475, 2931, 2859, 1650, 1614, 1471, 1380, 1257, 1103, 979, 836, 667 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): two isomers, δ 6.07 (d, J = 4.2 Hz, 1H), 5.99 (d, J = 3.3 Hz, 1H), 5.02 – 4.97 (m, 2H), 3.52 – 3.42 (m, 4H), 3.10 (s, 2H), 2.35 – 2.21 (m, 7H), 2.12 – 2.02 (m, 5H), 1.99 – 1.84 (m, 9H), 1.81– 1.76 (m, 2H), 1.73 – 1.67 (m, 2H), 1.61 (s, 9H), 1.59 (s, 3H), 1.54 (s, 3H), 1.52 (s, 3H), 1.51 – 1.47 (m, 3H), 1.32 (s, 3H), 1.29 (s, 3H), 0.84 (s, 9H), 0.84 (s, 9H), -0.01 (s, 6H), -0.02 (s, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.8, 197.6, 168.3, 167.5, 133.6, 133.4, 132.0, 131.9, 123.7, 122.3, 122.2, 114.1, 114.1, 113.4, 81.32, (81.32), 66.0, 65.7, 40.5, 40.3, 37.89, (37.89), 37.5, 37.4, 36.74, (36.74), 36.06, (36.06), 35.02, (35.02), 32.24, (32.24), 31.62, (31.62), 30.11, (30.11), 29.84, (29.84), 29.69, (29.65), 26.0, 25.7, 23.6, 23.5, 22.8, 22.5, 22.4, 22.3, 20.4, 20.1, 18.4, 18.3, 17.64, (17.64), -5.4, -5.5 ppm; HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{28}H_{47}O_3Si^+$ 459.3289; found 459.3286.

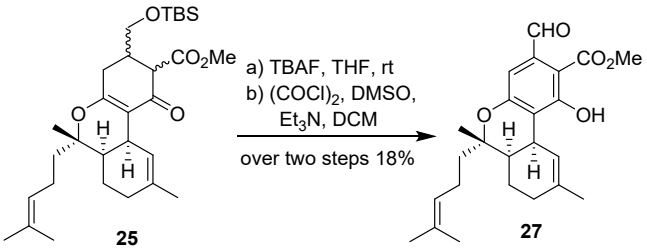
2.6 Synthesis of methyl-3-(((tert-butyldimethylsilyl)oxy)methyl)-6, 9-dimethyl-6-(4-methylpent-3-en-1-yl)-1-oxo-2, 3, 4, 6, 6a, 7, 8, 10a-octahydro-1*H*-benzo[c]chromene-2-carboxy late (25)



To a solution of compound **24** (4.58 g, 10.0 mmol, 1.0 eq) in anhydrous THF (250 mL) under Ar atmosphere at -78 ºC was added LDA (10.0 ml, 7.5 mmol, 1.5 eq) dropwise. The reaction was stirred at -78 ºC for 40 min and a solution of methyl cyanoformate (1.7 mL, 20.0 mmol, 2.0 eq) was added dropwise. The resultant mixture was stirred, then allowed to warm to rt. The mixture was quenched with saturated NH_4Cl solution (50 mL) and extracted with EtOAc (3 × 100 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (neutral alumina, petrol ether : EtOAc = 100:1) to give methyl ester product **25** as yellow oil (3.97 g, yield: 77%).

25: $\boldsymbol{R_f}$ = 0.55 (petroleum ether : EtOAc = 5:1); IR (KBr): 3471, 2954, 2929, 2857, 1743, 1650, 1606, 1429, 1384, 1257, 1158, 1105, 836, 669 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): two isomers, δ 6.05 (d, J = 4.1 Hz, 1H), 6.02 (d, J = 3.5 Hz, 1H), 5.05 – 5.00 (m, 2H), 3.76 (s, 3H), 3.75 (s, 3H), 3.66 – 3.63 (m, 1H), 3.52 – 3.50 (m, 4H), 3.46 (d, J = 10.5 Hz, 1H), 3.31(d, J = 12.3 Hz, 1H), 3.14 (bs, 1H), 3.09 (bs, 1H), 2.63 – 2.47 (m, 4H), 2.37 – 2.35 (m, 2H), 2.02 – 1.87 (m, 9H), 1.84 – 1.78 (m, 2H), 1.73 – 1.69 (m, 2H), 1.65 (s, 3H), 1.64 (s, 3H), 1.62 (s, 3H), 1.61 (s, 3H), 1.57 (s, 3H), 1.55(s, 3H) 1.52 –1.49 (m, 3H), 1.35 (s, 3H), 1.33 (s, 3H), 1.19 –1.18 (m, 1H), 0.86 (s, 18H), -0.02 – 0.01 (t, 12H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 193.13, (193.13), 192.63, (192.63), 171.1, 171.0, 168.3, 168.0, 133.7, 133.6, 132.1, 131.9, 123.6, 123.4, 121.8, 121.7, 113.10, (113.10), 112.41, (112.41), 81.83, (81.77), 64.2, 63.7, 55.53, (55.51), 51.92, (51.86), 38.8, 37.9, 37.5, 37.4, 37.0, 36.7, 31.0, 30.5, 29.96, (29.96), 29.71, (29.65), 25.82, (25.79), 25.62, (25.62), 23.43, (23.40), 22.6, 22.4, 22.3, 22.2, 20.3, 20.0, 18.3, 18.2, 17.58, (17.56), -5.62, (-5.64), -5.7, (-5.8) ppm; HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{30}H_{49}O_5Si^+$ 517.3344; found 517.3348.

2.7 Synthesis of methyl-3-formyl-1-hydroxy-6, 9-dimethyl-6-(4-methylpent-3-en-1-yl)-6a, 7, 8, 10a-tetrahydro-6*H*-benzo[c]chromene-2-carboxylate (27)



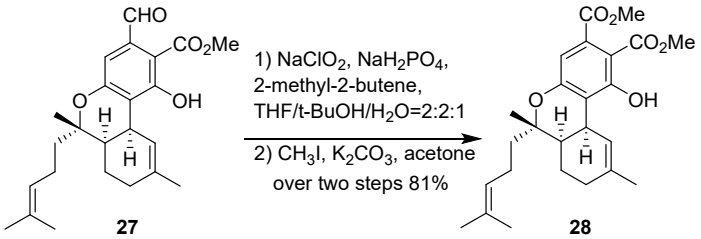
To a solution of compound **25** (2.82 g, 5.5 mmol, 1.0 eq) in anhydrous tetrahydrofuran (30 mL) was added tetrabutylammonium fluoride (1.0 M in tetrahydrofuran, 8.2 mL, 1.5 eq) under nitrogen. The mixture was stirred for 3 h at 27 ºC. The mixture was quenched with saturated NH_4Cl solution (50 mL) and extracted with EtOAc (3 × 100 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to afford the title compound as a pale yellow oil which was used without further purification.

To a solution of oxalyl chloride (5.79 mL, 44.8 mmol, 15.0 eq) in dry CH_2Cl_2 (100 mL) cooled to -78 ºC was added a solution of anhydrous dimethylsulfoxide (7.1 mL, 81.9 mmol, 22.0 eq) in dry CH_2Cl_2 (20 mL) keeping the internal temperature under -78 ºC. After 15 minutes, a solution of the crude product **26** (1.81 g, 4.5 mmol, 1.0 eq) in dry CH_2Cl_2 (10 mL) was added keeping the internal temperature under -78 ºC. After 1 h, anhydrous triethylamine (25.0 mL, 180.0 mmol, 40.0 eq) was added dropwise and the reaction mixture was warmed to room temperature over 30 minutes. Water was added and the aqueous phase extracted with DCM. The combined organic phases were washed with brine, dried over $MgSO_4$, filtrated and the filtrate concentrated under reduced pressure. The crude product. was purified by flash column chromatography flash chromatography on Et_3N-deactivated silica gel (petrol ether:EtOAc = 400:1) to give aromatization product **27** as yellow solid (393.4 mg, yield:18%, two steps).

27: $\boldsymbol{R_f}$ = 0.5 (petroleum ether : EtOAc = 10: 1); Mp: 74.4 ° C; IR (KBr): 2920, 2850, 1700, 1658, 1559, 1454, 1375, 1341, 1256, 1155, 963 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 11.85 (br, 1H), 10.39 (s, 1H), 6.75 (s, 1H), 6.28 (d, J = 3.6 Hz, 1H), 5.00 (t, J = 7.0 Hz, 1H), 3.96 (s, 3H), 3.60 (s, 1H), 2.08 – 1.88 (m, 7H), 1.69 (s, 3H), 1.63 (s, 3H), 1.55 (t, J = 8.7 Hz, 2H), 1.53 (s, 3H), 1.40 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 192.1, 170.8, 163.2, 158.2, 138.0, 135.1, 132.0, 123.6, 120.9, 117.3, 110.9, 103.1, 80.2,

52.5, 37.3, 37.0, 31.5, 29.5, 25.6, 23.6, 22.7, 22.2, 20.6, 17.6 ppm; HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{24}H_{31}O_5^+$ 399.2166; found 399.2167.

2.8 Synthesis of dimethyl-1-hydroxy-6, 9-dimethyl-6-(4-methylpent-3-en-1-yl)-6a, 7, 8, 10a-tetrahydro-6*H*-benzo[c]chromene-2, 3-dicarboxylate (28)

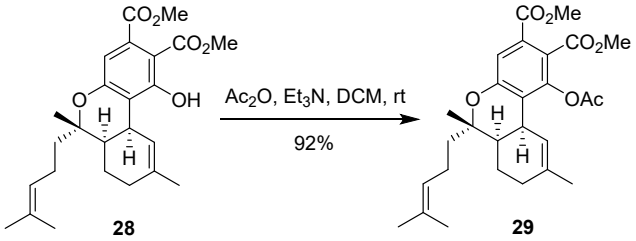


To a stirred solution of compound **27** (227.0 mg, 0.57 mmol, 1.0 eq) in THF/t-BuOH/H_2O = 2:2:1(20 mL) was added NaH_2PO_4 (205.2 mg, 1.71 mmol, 3.0 eq), 2-methyl-2-butene (0.18 ml, 1.71 mmol, 3.0 eq) at 0 ºC, finally, $NaClO_2$ (153.9 mg, 1.71mmol, 3.0 eq) was added. The resulting mixture was stirred about 1 h. The mixture was quenched with ice-water (30 mL) and extracted with EtOAc (3 × 50 mL). the combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to afford the title compound as a pale yellow oil which was used without further purification.

To a stirred solution of the above crude product in acetone (50 mL) was added K_2CO_3 (87.0 mg, 0.63 mmol, 1.1 eq) and CH_3I (0.05 mL, 0.63 mmol, 1.1 eq) at room temperature. The resulting mixture was stirred about 40min. The mixture was quenched with H_2O (100 mL) and extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, petrol ether : EtOAc = 50:1) to give dimethyl ester **28** as a yellow solid (197.6 mg, yield: 81%, two steps).

28: $\boldsymbol{R_f}$ = 0.3 (petroleum ether : EtOAc =10: 1); Mp: 80.9 ºC; IR (KBr): 3468, 2954, 2923, 2855, 1733, 1662, 1432, 1378, 1340, 1263, 1155, 912, 807, 644 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 11.57 (br, 1H), 6.39 (s, 1H), 6.26 (d, J =3.0 Hz, 1H), 5.01 (t, J = 7.1 Hz, 1H), 3.85 (s, 3H), 3.84 (s, 3H), 3.57 (brs, 1H), 2.03 – 1.86 (m, 7H), 1.68 (s, 3H), 1.63 (s, 3H), 1.56 – 1.58 (m, 2H), 1.54(s, 3H), 1.38 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.0, 169.5, 162.5, 158.0, 134.7, 134.3, 132.0, 123.7, 121.2, 114.4, 109.8, 101.7, 80.1, 52.5, 52.4, 37.2, 37.1, 31.2, 29.5, 25.6, 23.6, 22.7, 22.2, 20.5, 17.6 ppm; HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{25}H_{33}O_6^+$ 429.2272; found 429.2270.

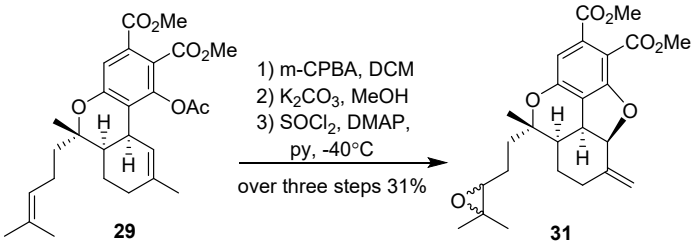
2.9 Synthesis of dimethyl -1-acetoxy-6, 9-dimethyl-6-(4-methylpent-3-en-1-yl)-6a, 7, 8, 10a-tetrahydro-6*H*-benzo[c]chromene-2, 3-dicarboxylate (29)



To a stirred solution of compound **28** (227.0 mg, 0.53 mmol, 1.0 eq) in DCM was added Et_3N (0.74 mL)，Ac_2O (0.53 mL), the resulting mixture was stirred about 3 h. The mixture was quenched with ice-water (20 mL) and extracted with DCM (3 × 50 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure.to afford the crude product. The crude product was purified by flash column chromatography (silica gel, petrol ether: EtOAc = 30:1) to give acetate ester **29** as a yellow oil (229.8 mg, yield: 92%).

29: R_f = 0.3 (petroleum ether : EtOAc = 5:1); IR (KBr): 3453, 2954, 2859, 1776, 1731, 1608, 1562, 1330, 1193, 1035, 979, 883, 792 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.25 (s, 1H), 5.77 (d, J = 3.9 Hz, 1H), 5.01 (t, J = 7.0 Hz, 1H), 3.86 (s, 3H), 3.83 (s, 3H), 3.44 (brs, 1H), 2.31 (s, 3H), 2.03 –1.90 (m, 6H), 1.85 –1.81(m, 1H), 1.66 (s, 3H), 1.62 (s, 3H), 1.59–1.54 (m, 2H), 1.52(s, 3H), 1.38 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 168.1, 166.9, 165.7, 154.7, 148.2, 136.4, 132.0, 128.4, 124.0, 123.5, 120.3, 119.5, 117.1, 79.7, 52.6, 52.5, 37.3, 36.9, 32.0, 29.5, 25.6, 23.7, 22.7, 22.2, 20.9, 20.3, 17.5; HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{27}H_{35}O_7^+$ 471.2377; found 471.2370.

2.10 Synthesis of dimethyl-9-(2-(3, 3-dimethyloxiran-2-yl) ethyl)-9-methyl-3-methylene-2, 3, 3a, 3a1, 9, 9a-hexahydro-1*H*-benzofuro[4, 3, 2-cde]chromene-5, 6-dicarboxylate (31)



To a stirred solution of acetyl ester **29** (127.0 mg, 0.27 mmol, 1.0 eq) in DCM (15 mL) was added *m*-CPBA(138.1 mg, 0.68 mmol, 2.5 eq) at 0 ºC. Then the resulting mixture was stirred about 1h at room temperature. The mixture was quenched with 5% $NaHCO_3$ solution (30 mL) and extracted with DCM

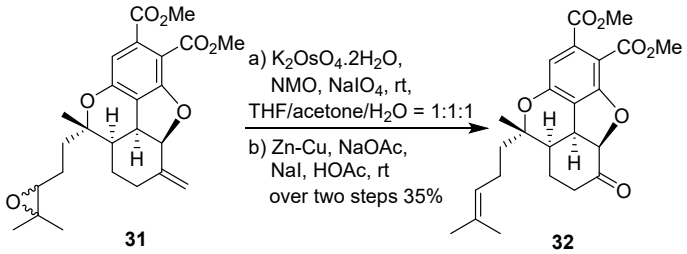
(3 × 30 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to afford the title bisepoxide compound as a yellow oil which was used without further purification.

To a stirred solution of the above crude product in MeOH (15 mL) was added K_2CO_3 (114.5 mg, 0.83 mmol, 3.0 eq) and the resulting mixture was stirred about 40min at room temperature. The mixture was quenched with saturated NH_4Cl solution (20 mL) and extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to afford the title tetracyclic alcohol **30** as a yellow oil which was used without further purification.

To a stirred solution of the above crude product tetracyclic alcohol **30** in pyridine (10 mL) was added DMAP（36.9 mg, 0.19 mmol, 1.0 eq) at -40 ºC, then $SOCl_2$ (55 μL, 0.48mmol, 2.5 eq) was added. The resulting mixture was stirred about 30min at same temperature. The mixture was quenched with ice-water (10 mL) and extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with brine, saturated $CuSO_4$ solution (20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to afford the title crude product. The crude product was purified by flash column chromatography Flash chromatography on Et_3N-deactivated silica gel (silica gel, petrol ether : EtOAc =10:1-4:1) to give a 1:1 mixture of diastereomers exocyclic alkene **31** as white solid (37.9 mg, yield: 31%, three steps).

31: $\boldsymbol{R_f}$ = 0.4 (petroleum ether : EtOAc = 2:1); Mp: 216.6 ºC; IR (KBr): 3448, 2954, 2923, 2847, 1723, 1625, 1429, 1372, 1293, 1262, 1228, 1138, 1011, 726 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): two isomers, δ 6.69 (s, 1H), 6.68 (s, 1H), 5.53–5.50 (m, 2H), 5.11 (s, 2H), 4.81 (s, 2H), 3.89 (s, 6H), 3.85 (s, 6H), 3.73 (t, J = 7.3 Hz, 1H), 3.68 (t, J = 7.2 Hz, 1H), 2.67 (t, J = 6.2 Hz, 1H), 2.63 (t, J = 5.2 Hz, 1H), 2.28–2.26 (m, 2H), 2.17 – 2.12 (m, 2H), 1.87 – 1.82 (m, 6H), 1.61 – 1.58 (m, 8H), 1.40 (s, 3H), 1.37 (s, 3H), 1.28 (s, 6H), 1.25 (s, 6H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.28, (168.28), 165.64, (165.61), 160.1, 160.0, 153.8, 153.7, 143.04, (142.97), 134.7, 134.6, 113.4, 113.3, 111.4, 111.3, 110.0, 109.9, 107.81, (107.77), 88.14, (88.09), 82.2, 82.1, 64.0, 63.6, 58.5, 58.4, 52.61, (52.61), 52.29, (52.29), 37.5, 37.1, 36.18, (36.16), 34.9, 34.7, 31.4, 31.3, 24.78, (24.76), 23.74, (23.68), 23.6, 23.4, 22.4, 22.0, 18.7, 18.6 ppm; HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{25}H_{30}NaO_7^+$ 465.1884, found 465.1881.

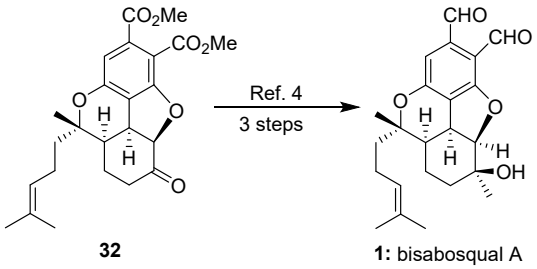
2.11 Synthesis of dimethyl-9-methyl-9-(4-methylpent-3-en-1-yl)-3-oxo-2, 3, 3a, 3a1, 9, 9a-hexahydro-1*H*-benzofuro[4, 3, 2-cde]chromene-5, 6-dicarboxylate (32)



To a stirred solution of the product exocyclic alkene **31** (27.0 mg, 0.06 mmol, 1.0 eq) in THF/ace tone/H_2O = 1:1:1 (15 mL) was added $K_2OsO_4 \cdot 2H_2O$ (4.3 mg, 0.11 mmol, 0.2 eq), NMO (10.5 mg, 0.09 mmol, 1.5 eq), $NaIO_4$ (49.9 mg, 0.23 mmol, 4.0 eq) and the resulting mixture was stirred about 4h at room temperature. The mixture was quenched with ice-water (20 mL) and extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to afford the title ketone which was used without further purification.

To a stirred solution of the above crude product ketone in acetic acid (2 mL) was added NaOAc (4.2 mg, 0.05 mmol, 1.1 eq), NaI (13.4 mg, 0.09 mmol, 2.0 eq), Zn-Cu reagent (11.7 mg, 0.18 mmol, 4.0 eq) at room temperature. The resulting mixture was stirred about 30 min at same temperature. The mixture was quenched with 5%$NaHCO_3$ solution (10 mL) and extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to afford the title crude product. The crude product was purified by flash column chromatography Flash chromatography on silica gel, (petrol ether : EtOAc = 5:4) to give the title product alkenyl ketone **32** as white solid (8.0 mg, yield: 35%, two steps).

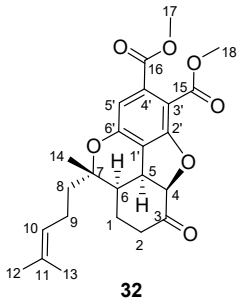
32: $\boldsymbol{R_f}$ = 0.2 (petroleum ether : EtOAc = 5:4); Mp: 112.7 ºC; ^{1}H NMR (500 MHz, $CDCl_3$), δ 6.69 (s, 1H), 5.21 (d, J = 8.6 Hz, 1H), 5.03 (t, J = 7.0 Hz, 1H), 4.08 (t, J = 7.2 Hz, 1H), 3.90 (s, 3H), 3.84 (s, 3H), 2.44 – 2.27 (m, 3H), 2.16 – 2.02 (m, 3H), 1.73 –1.62 (m, 1H), 1.65 (s, 3H), 1.59 (s, 3H), 1.44 (s, 3H), 1.30 – 1.15 (m, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 205.3, 168.0, 165.0, 159.9, 153.3, 135.7, 132.7, 122.8, 111.0, 110.1, 107.4, 88.2, 82.4, 52.6, 52.5, 38.5, 38.5, 36.3, 25.6, 22.6, 22.5, 22.2, 17.6 ppm; HRMS (ESI) m/z: $[M+Na]^+$ calcd for $C_{24}H_{28}NaO_7^+$ 451.1727, found 451.1722.



The formal total synthesis of bisabosqual A (**1**) could be achieved using the known procedure developed by Parker's group through three steps. [4]

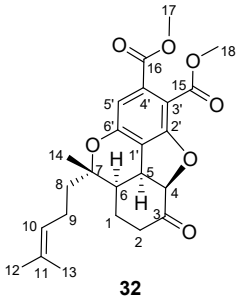
2.12 Intermediate Product Spectral Comparisons

Table S2 Comparison of ^{1}H NMR spectroscopic data of Parker's synthetic **32**[4] with our synthetic **32:**



No.	**Parker's synthetic** δ ^{1}H [ppm; mult; J (Hz)] $CDCl_3$, 400 MHz	**Our synthetic** δ ^{1}H [ppm; mult; J (Hz)] $CDCl_3$, 500 MHz	**Deviation** $\Delta\delta$ (ppm)
5′	6.68 (s, 1H)	6.69 (s, 1H)	0.01
4	5.22 (d, J = 8.6 Hz, 1H)	5.21 (d, J = 8.6 Hz, 1H)	-0.01
10	5.03 (t, J = 7.0 Hz, 1H)	5.03 (t, J = 7.0 Hz, 1H)	0.00
5	4.08 (t, J = 6.8 Hz, 1H)	4.08 (t, J = 7.2 Hz, 1H)	0.00
17	3.89 (s, 3H)	3.90 (s, 3H)	-0.01
18	3.84 (s, 3H),	3.84 (s, 3H),	0.00
6/2	2.47 – 2.25 (m, 3H)	2.44 – 2.27 (m, 3H)	-
9/1	2.16 – 2.02 (m, 3H)	2.16 – 2.02 (m, 3H)	-
1	1.73 –1.62 (m, 1H)	1.73 –1.62 (m, 1H)	-
12	1.65 (s, 3H),	1.65 (s, 3H),	0.00
14	1.59 (s, 3H),	1.59 (s, 3H),	0.00
13	1.44 (s, 3H),	1.44 (s, 3H),	0.00
8	1.30 – 1.16 (m, 2H)	1.30 – 1.15 (m, 2H)	-

Table S3 Comparison of ^{13}C NMR spectroscopic data of Parker's synthetic **32**[4] with our synthetic **32**:



32

No.	**Parker's synthetic** δ ^{13}C [ppm]; $CDCl_3$, 100 MHz	**Our synthetic** δ ^{13}C [ppm] $CDCl_3$, 125 MHz	**Deviation** $\Delta\delta$ (ppm)
3	205.4	205.3	-0.1
16	168.0	168.0	0.0
15	165.0	165.0	0.0
2′	159.9	159.9	0.0
6′	153.4	153.3	-0.1
4′	135.6	135.7	0.1
11	132.6	132.7	0.1
10	122.8	122.8	0.0
1′	111.1	111.0	-0.1
5′	110.1	110.1	0.0
3′	107.4	107.4	0.0
4	88.3	88.2	-0.1
7	82.4	82.4	0.0
18	52.6	52.6	0.0
17	52.5	52.5	0.0
2	38.5	38.5	0.0
6	38.5	38.5	0.0
8	38.5	38.5	0.0
5	36.3	36.3	0.0
12	25.6	25.6	0.0
1	22.6	22.6	0.0
14	22.5	22.5	0.0
9	22.2	22.2	0.0
13	17.6	17.6	0.0

3. References

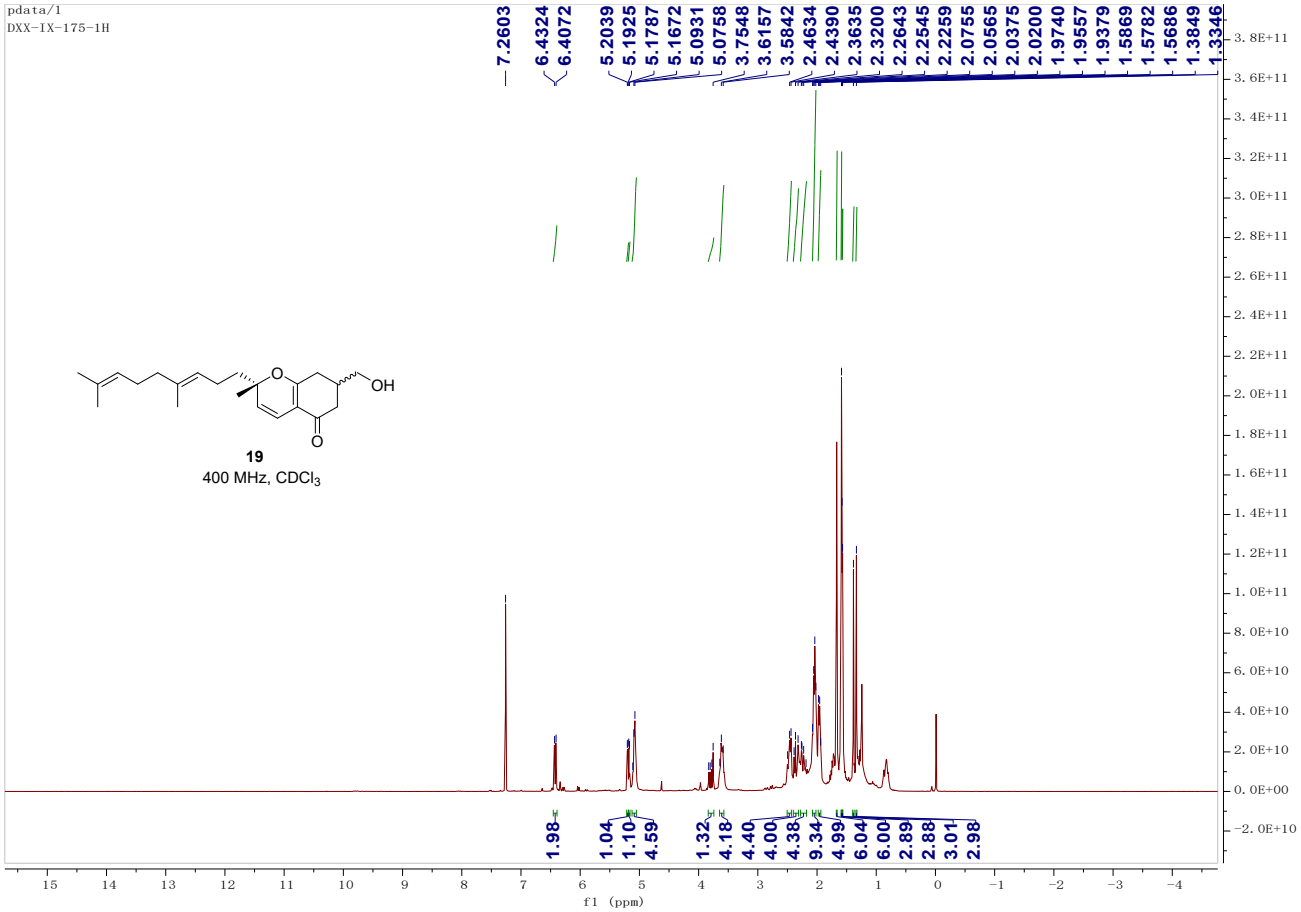
[1] J. H. Chen, Y.Y. Li, Z. M. Xiao, H. B. He, S. H. Gao, Asymmetric Synthesis of Rugulotrosin A, *Org. Lett*., 2020, **22**, 1485–1489.

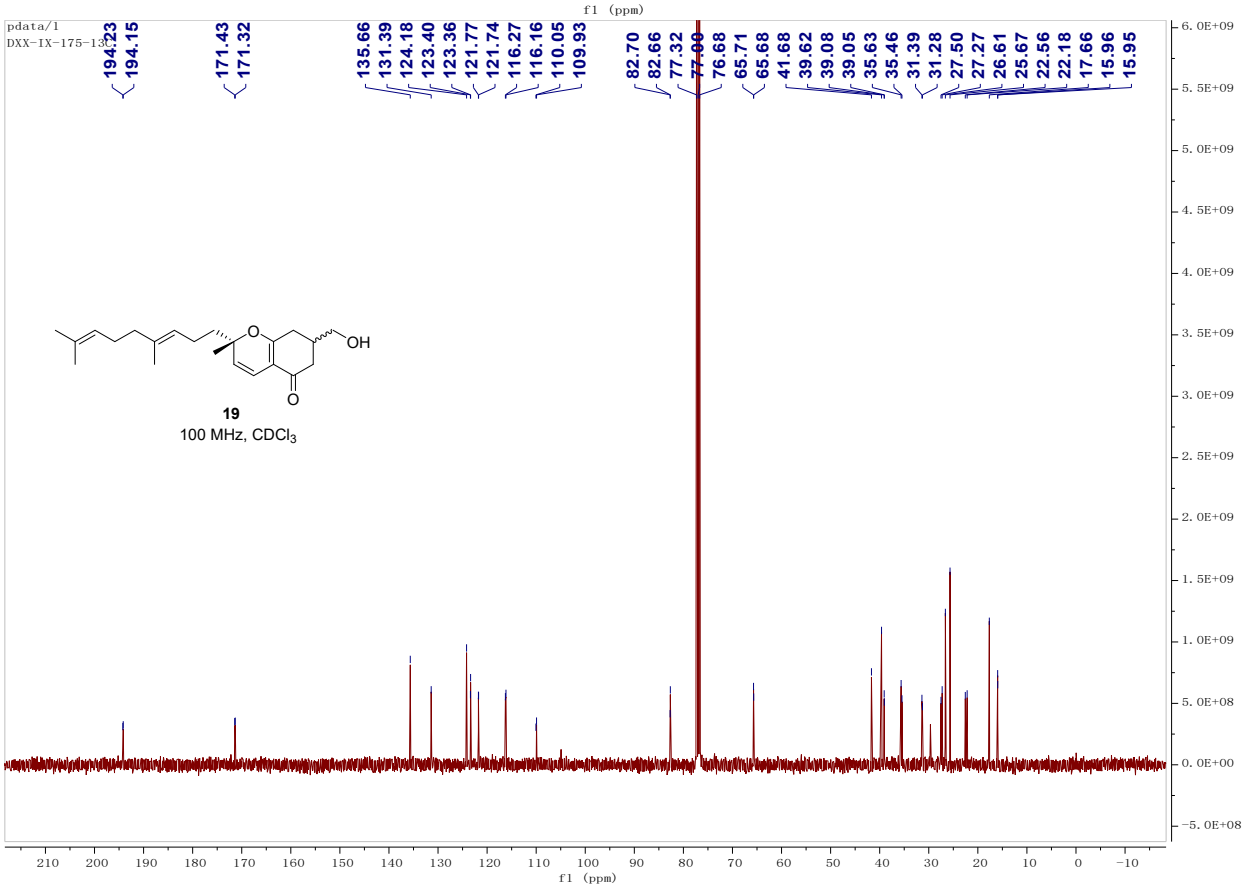
[2] O. L. Chapman, P. A. Fitton, General Synthesis of the Troponoid System Based on Solvolysis of 1, 4-Dihydrobenzyl Tosylates, *J. Am. Chem. Soc*., 1963, **85**, 41–47.

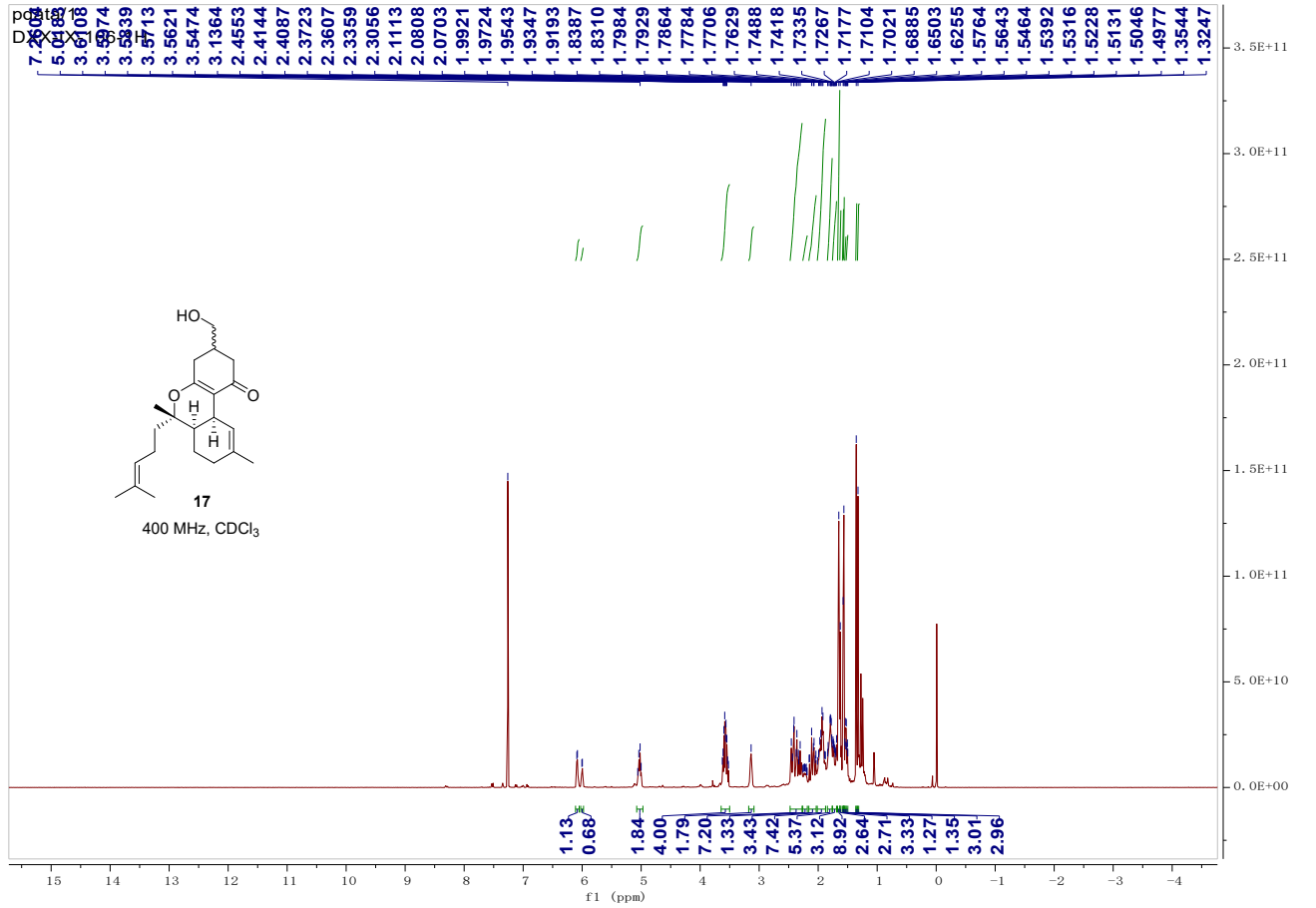
[3] R. Aranda, K. Villalba, E. Raviña, C. F. Masaguer, J. Brea, F. Areias, E. Domínguez, J. Selent, L. López, F. Sanz, M. Pastor, M. I. Loza, Synthesis, Binding Affinity, and Molecular Docking Analysis of New Benzofuranone Derivatives as Potential Antipsychotics, *J. Med. Chem*., 2008, **51**, 6085–6094.

[4] C.W. am Ende, Z. Zhou, K. A. Parker, Total Synthesis of (±)-Bisabosqual A, *J. Am. Chem. Soc*., 2013, **135***,* 582–585.

4. NMR Spectra



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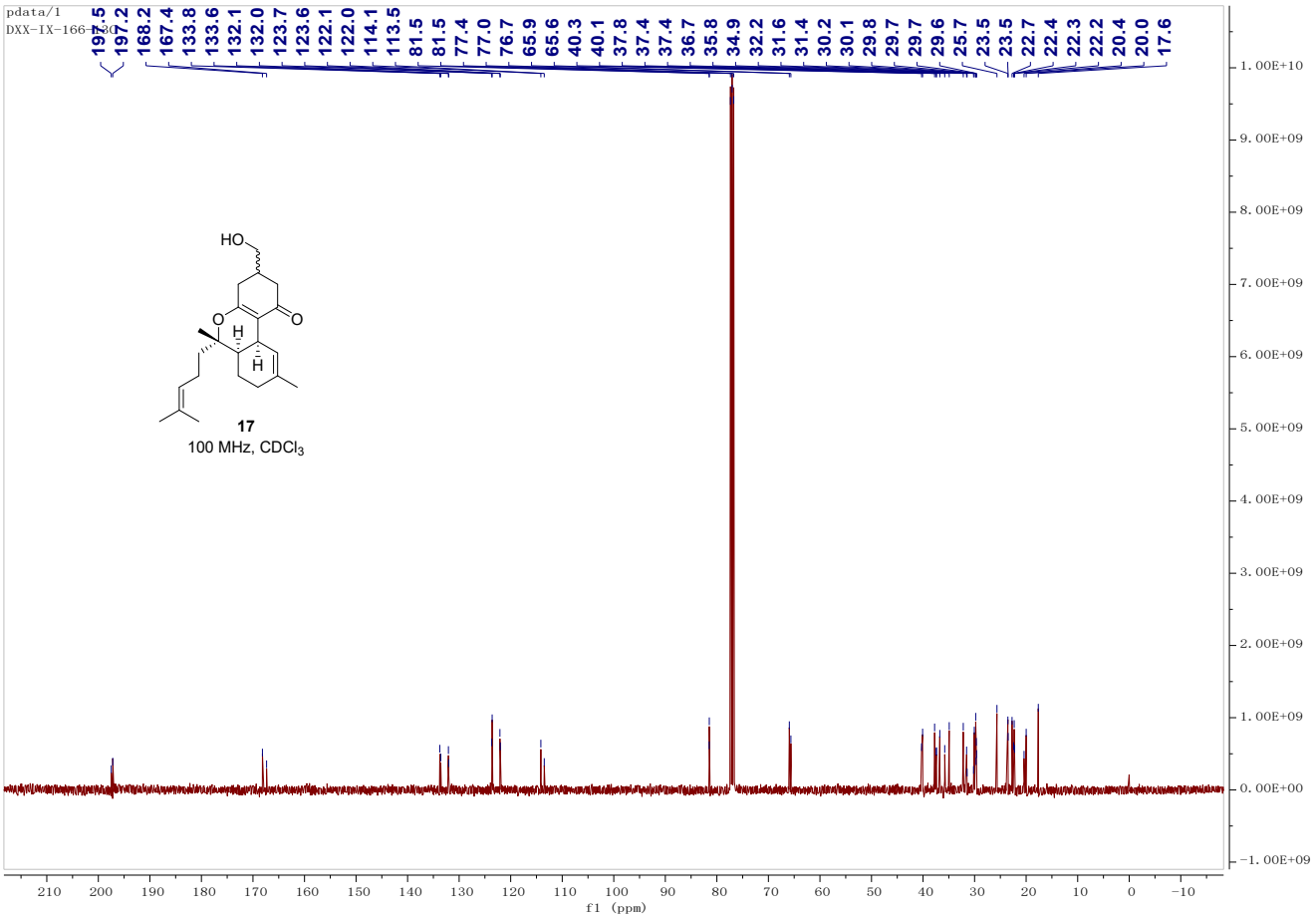
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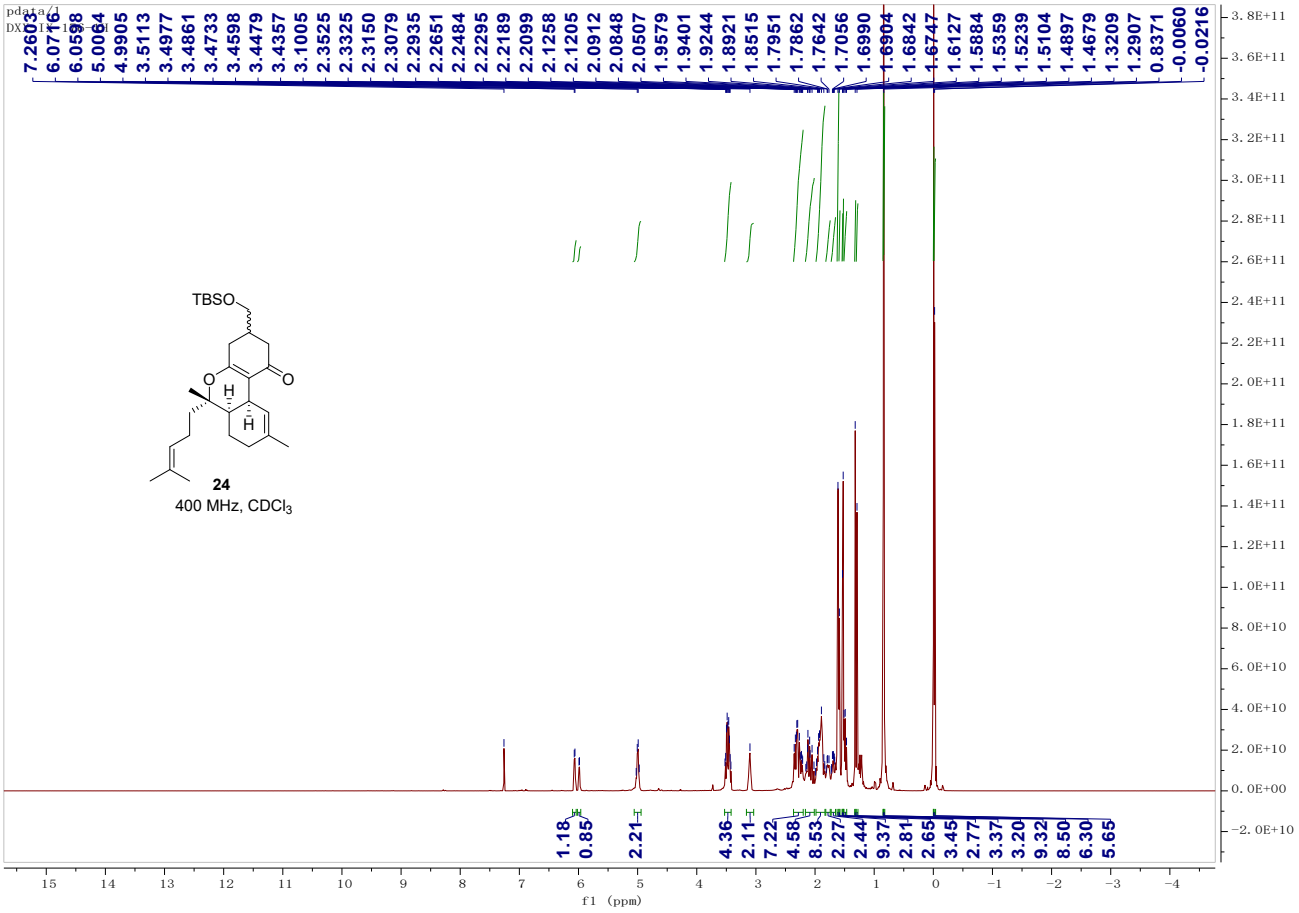
f1 (ppm)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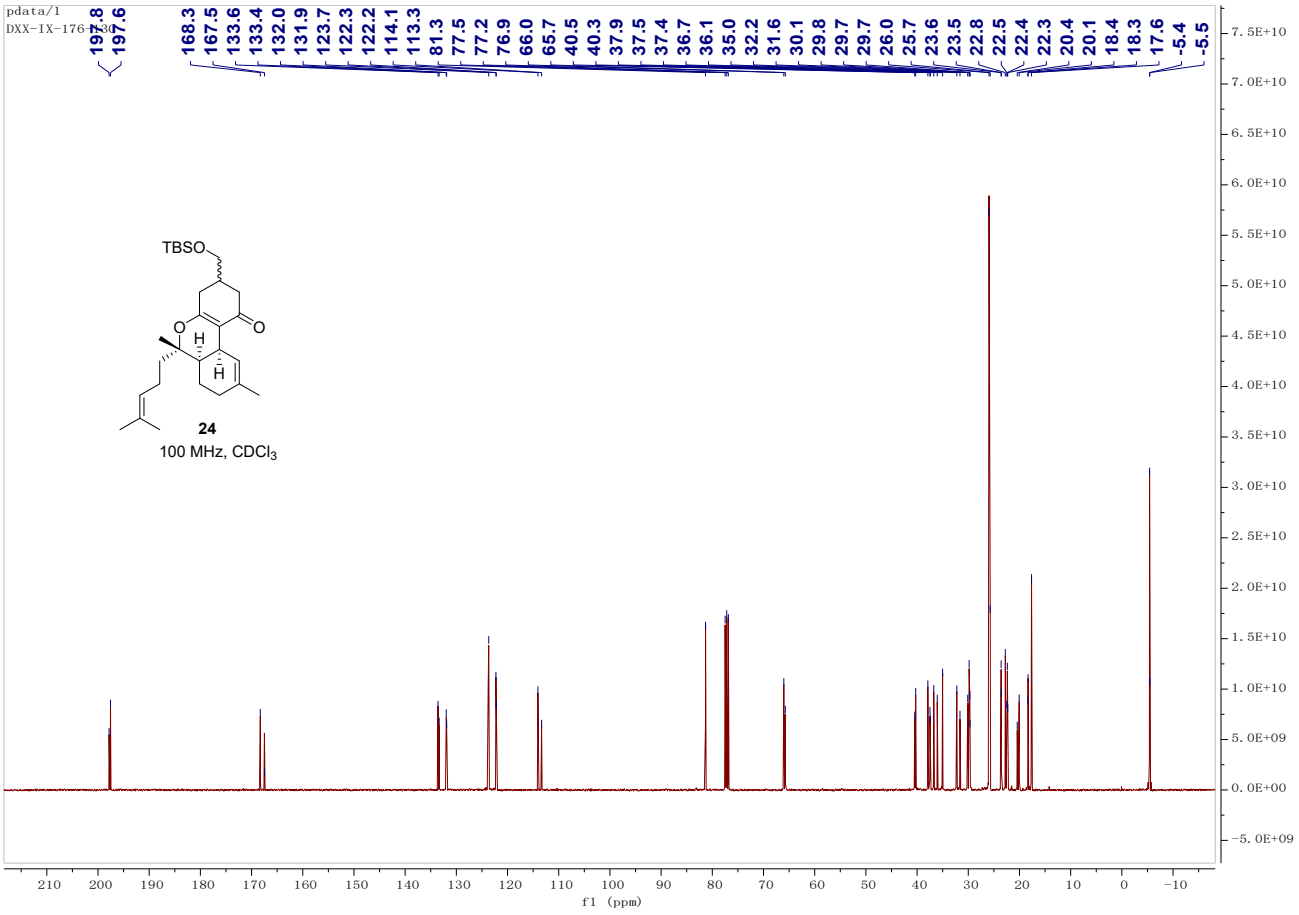
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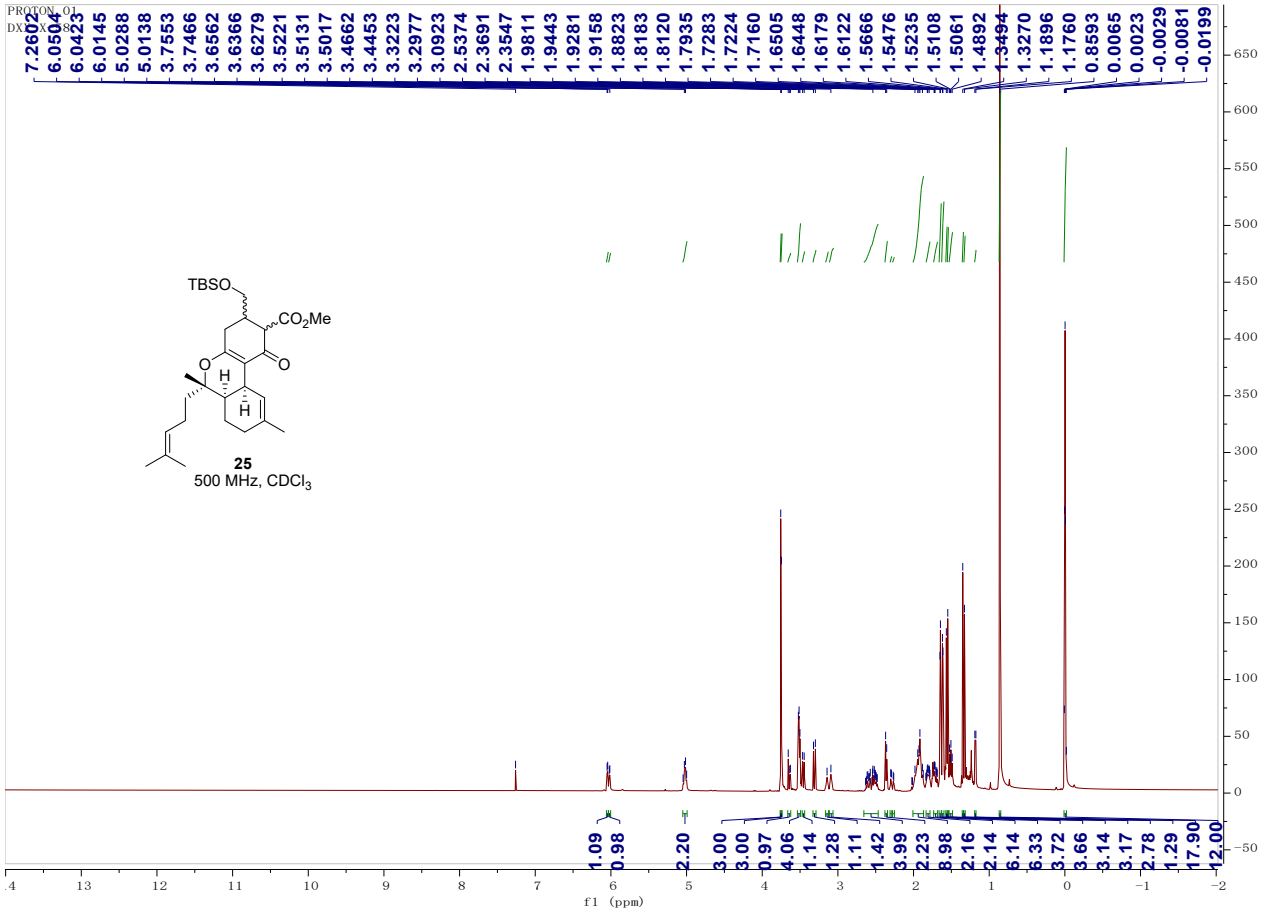
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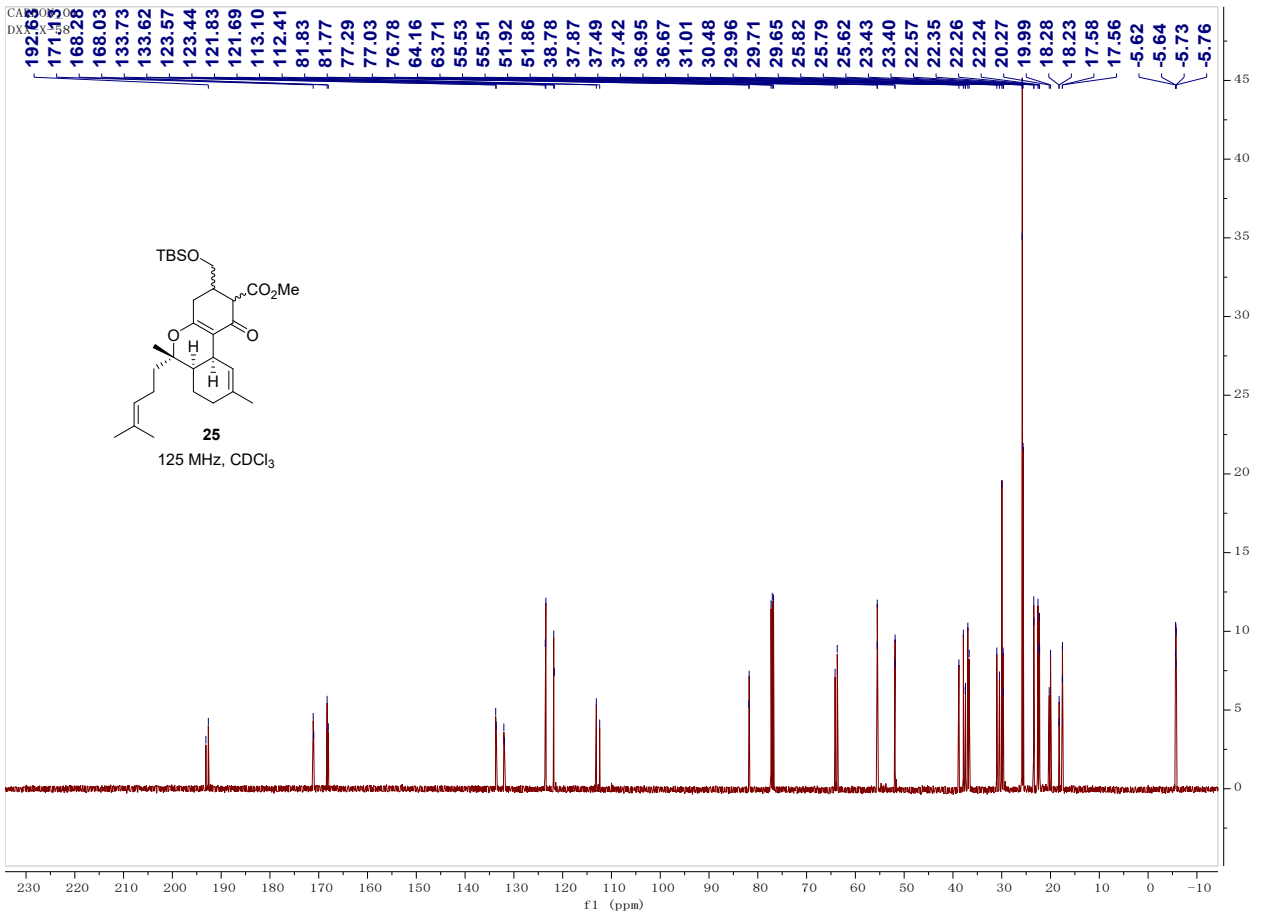
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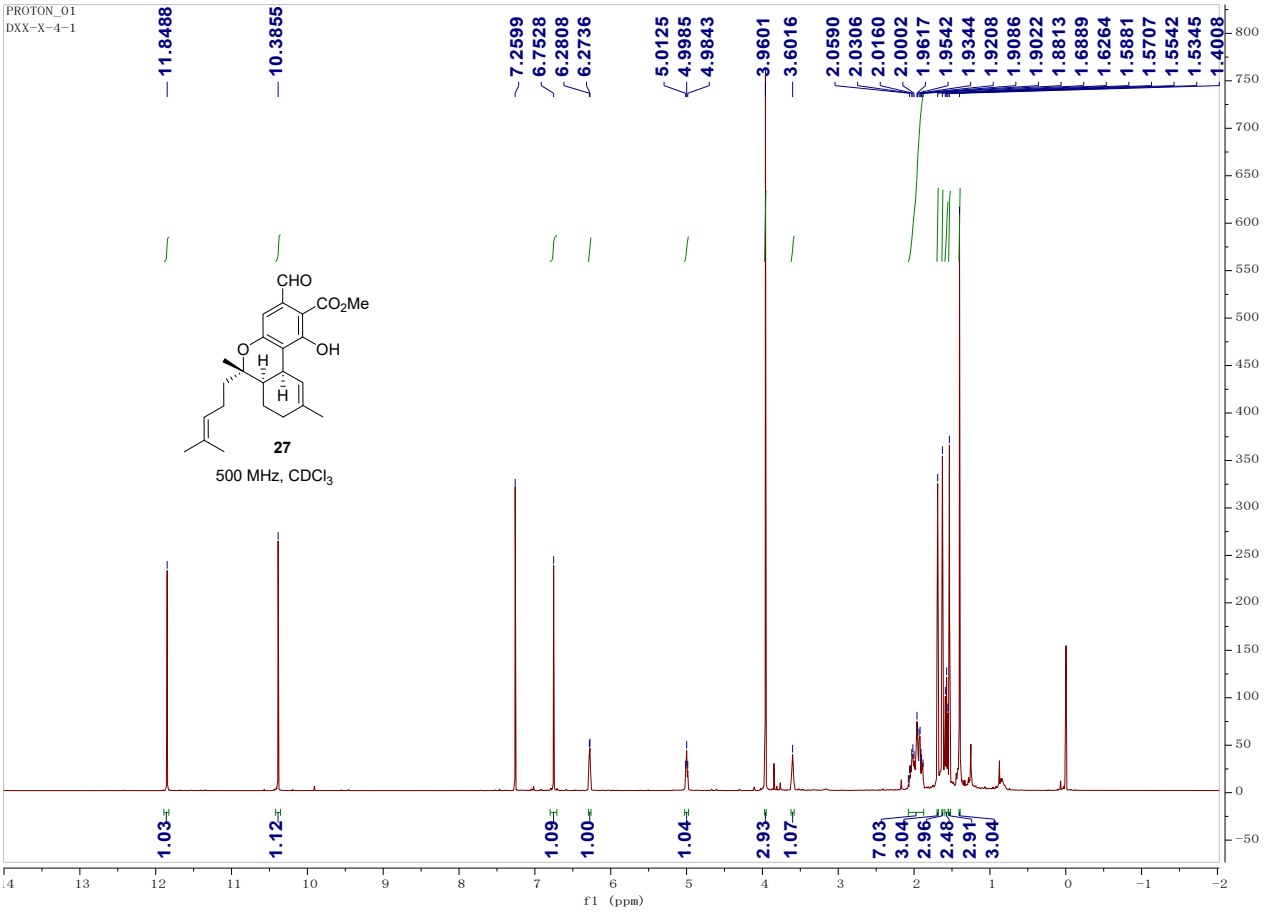
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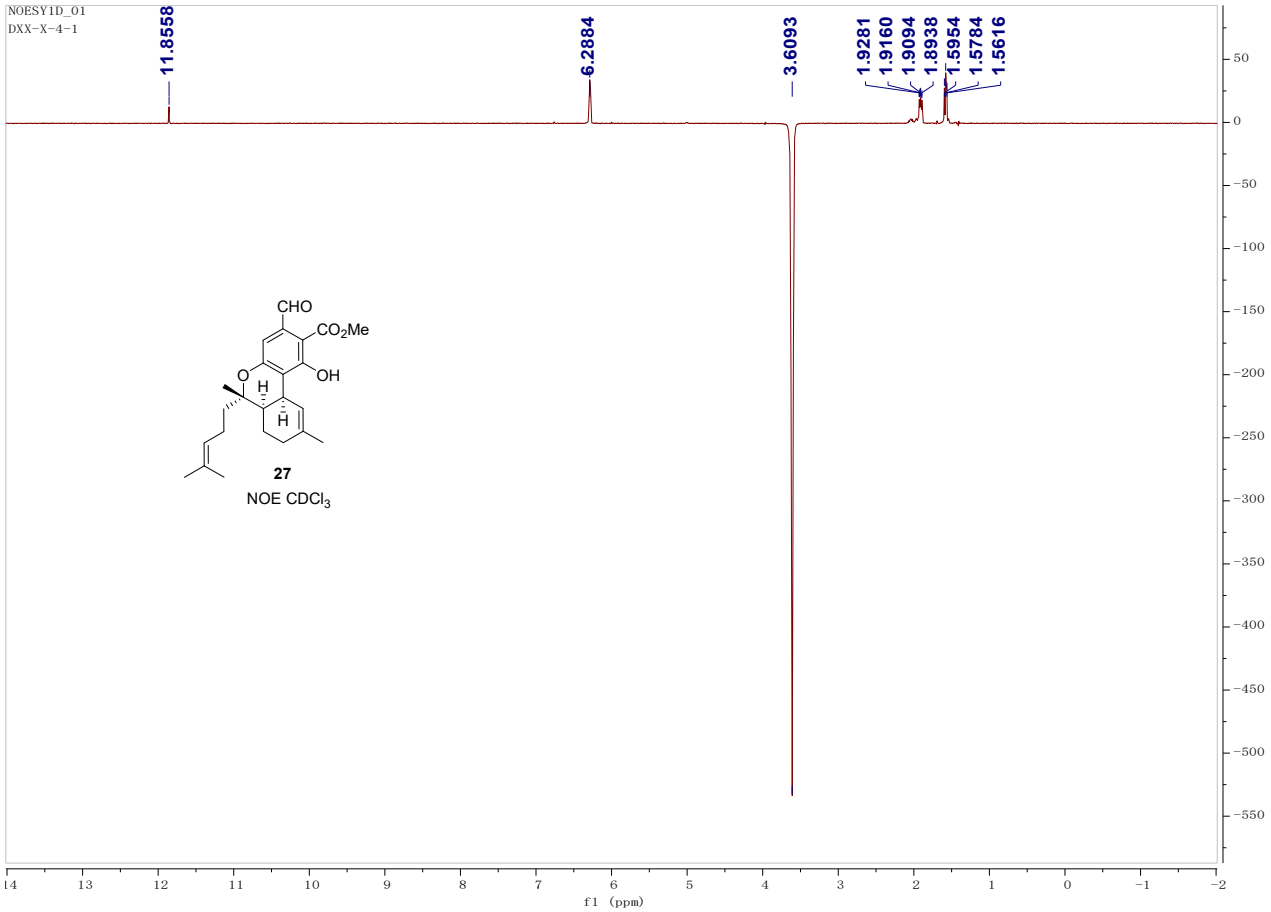
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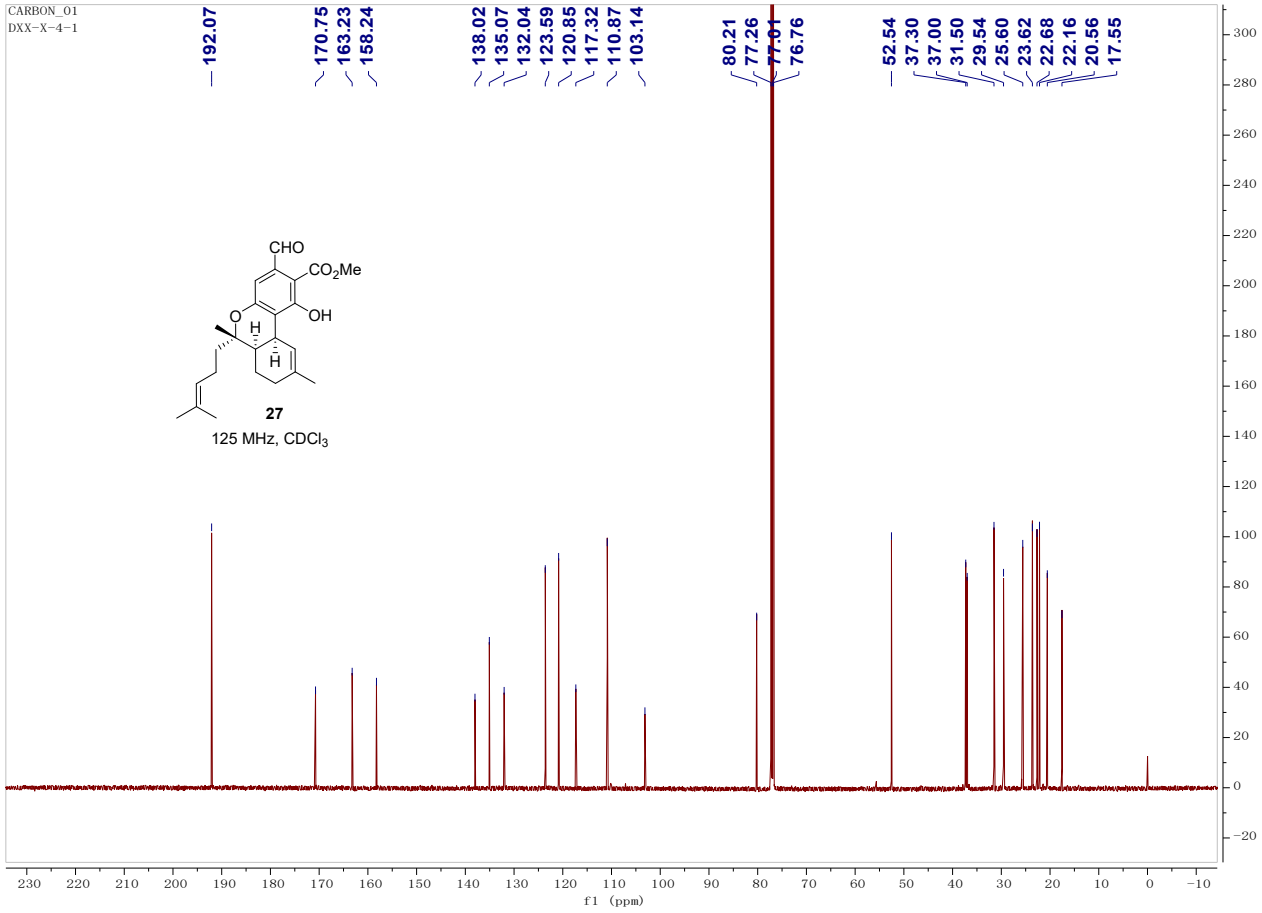
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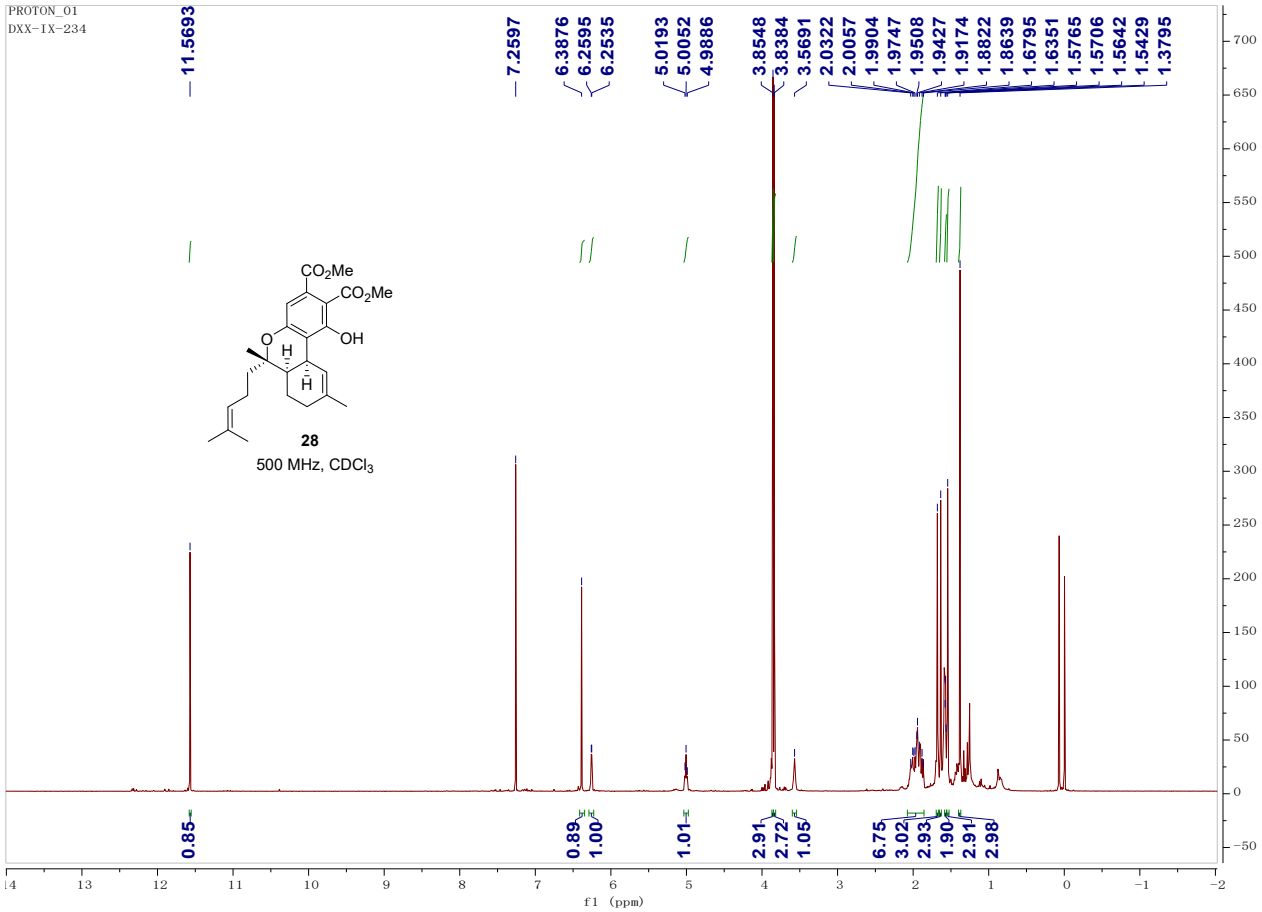
f1 (ppm)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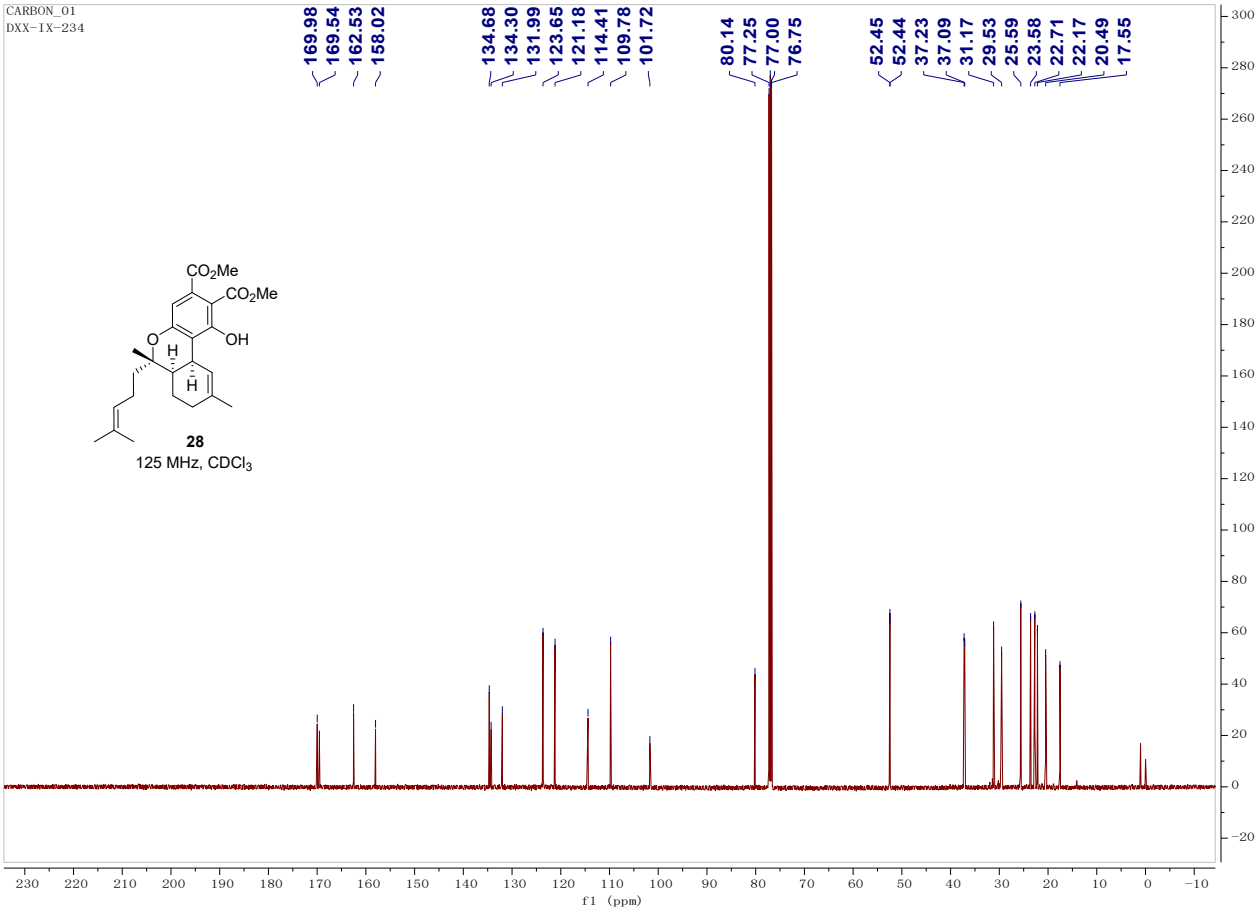
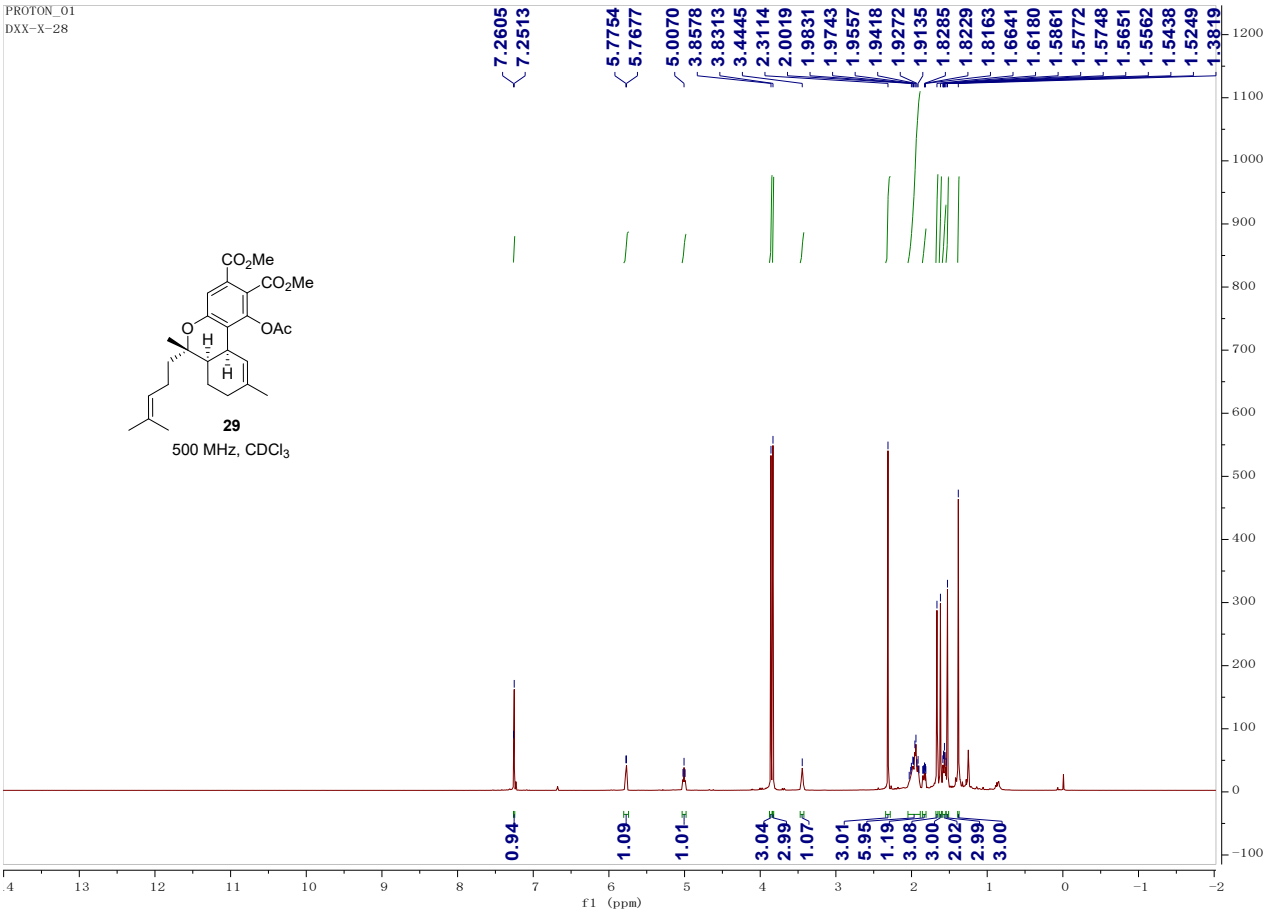
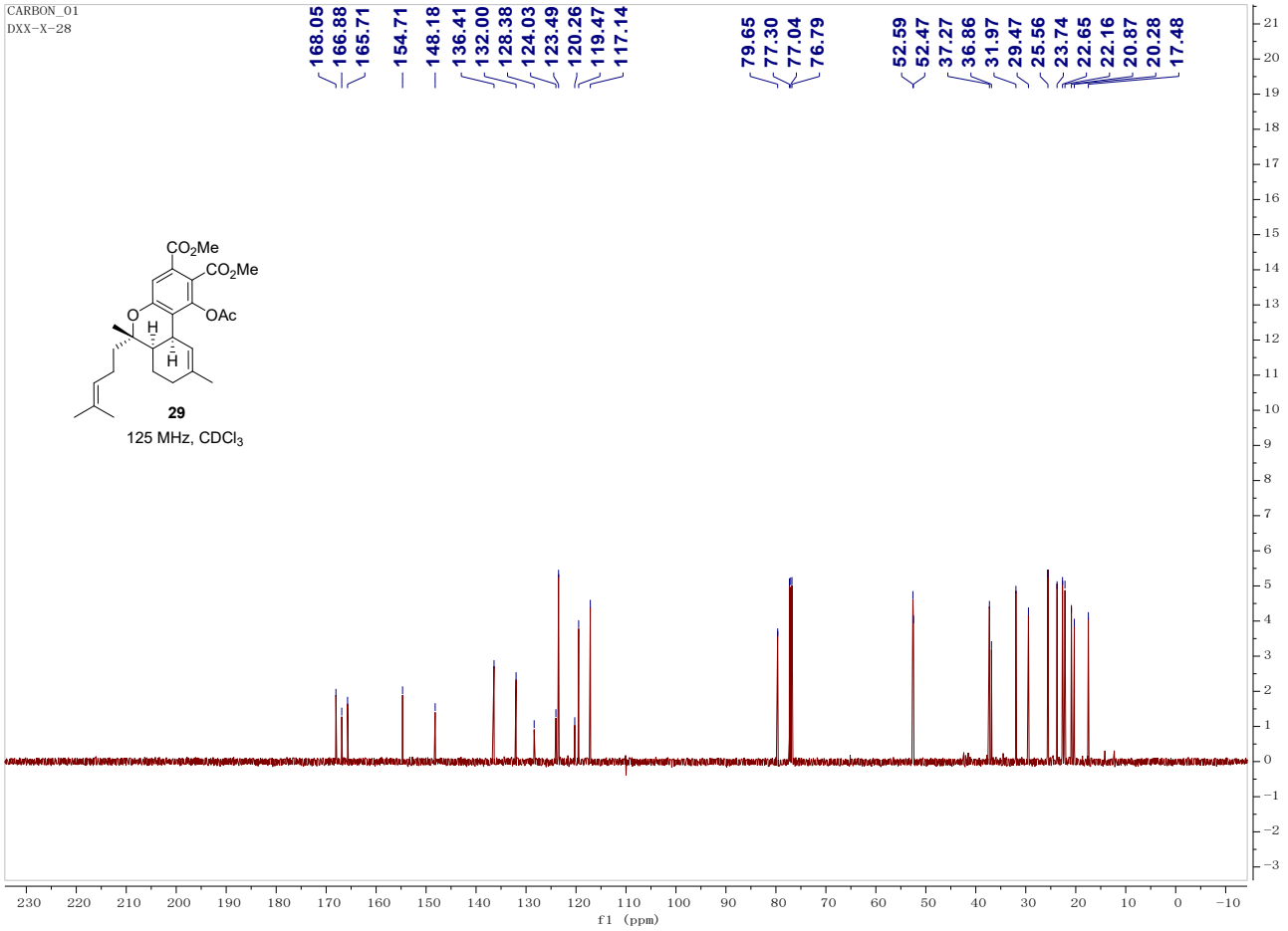
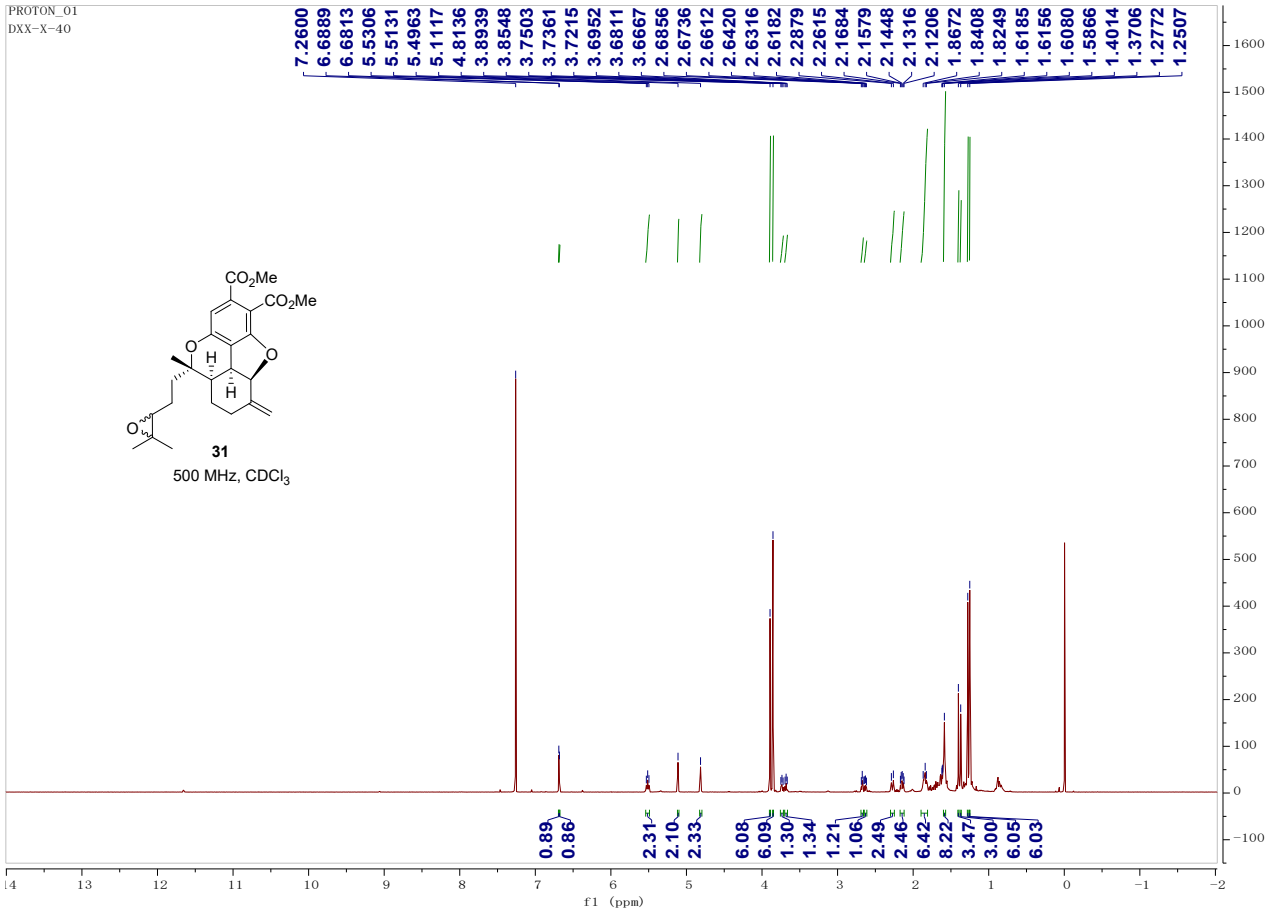
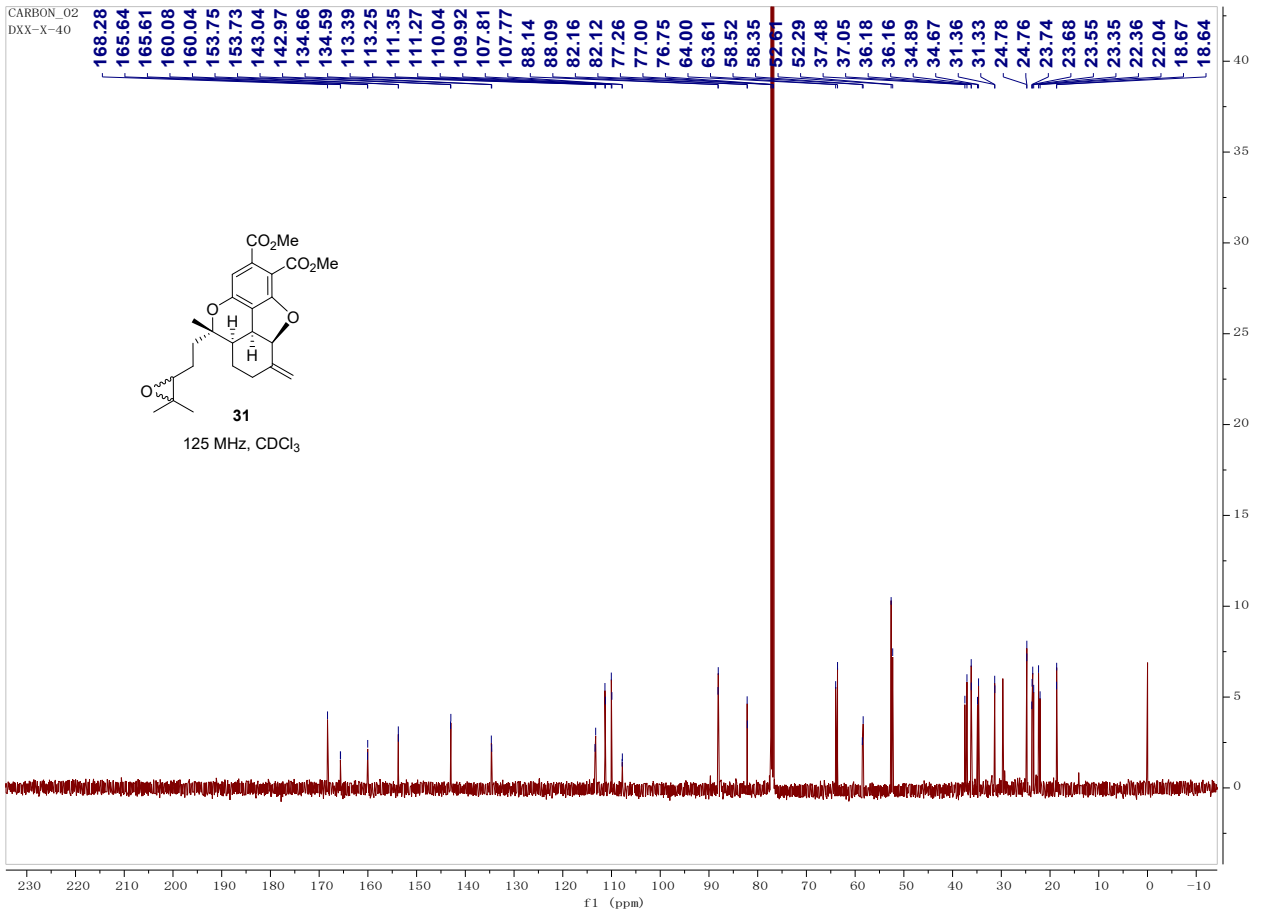
2.72
1.05
6.75
3.02
2.93
1.90
2.91
2.98
f1 (ppm)

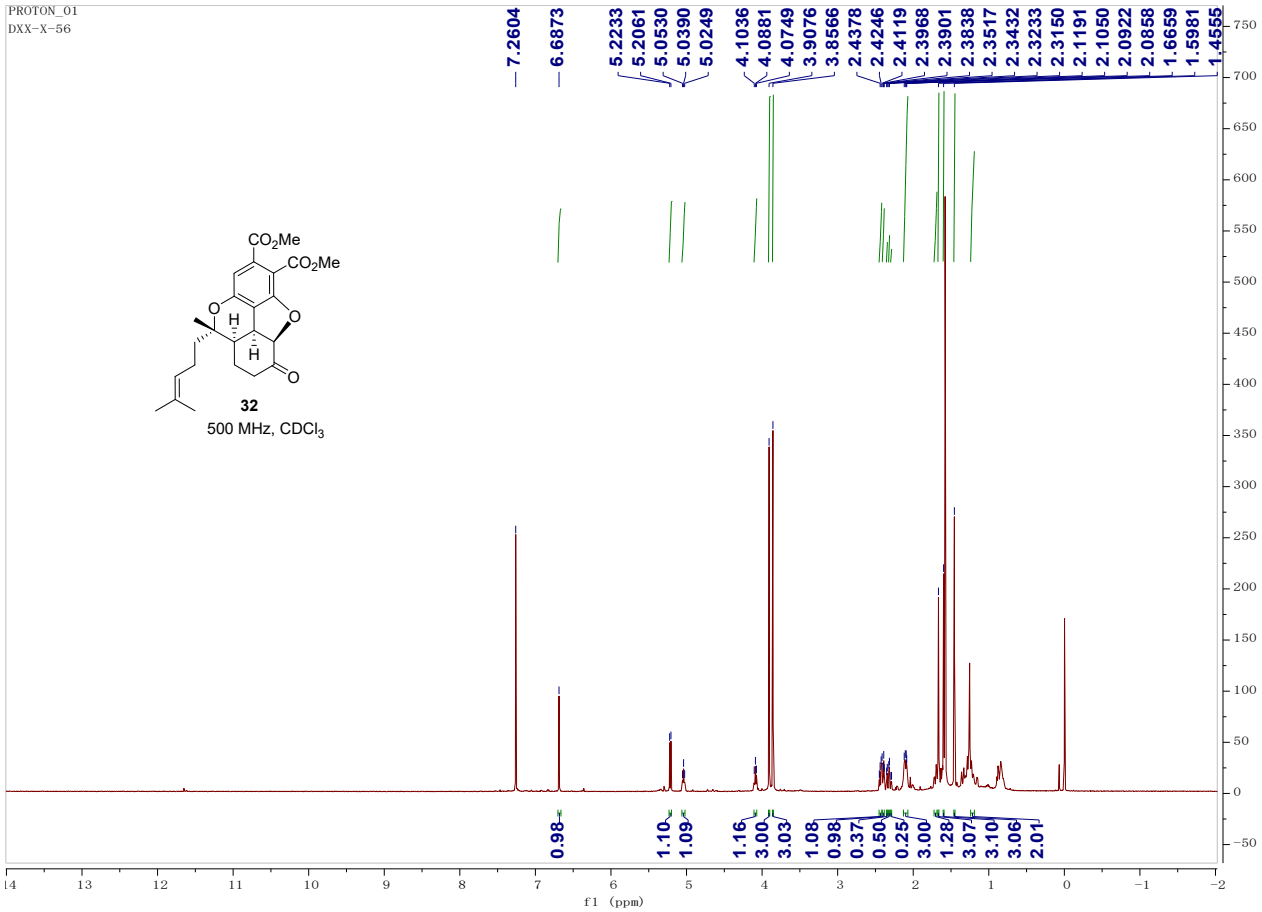

CARBON_01
DXX-IX-234
169.98
169.54
162.53
158.02
134.68
134.30
131.99
123.65
121.18
114.41
109.78
101.72
80.14
77.25
77.00
76.75
52.45
52.44
37.23
37.09
31.17
29.53
25.59
23.58
22.71
22.17
20.49
17.55
CO2Me
CO2Me
OH
O
H
H
28
125 MHz, CDCl3
f1 (ppm)

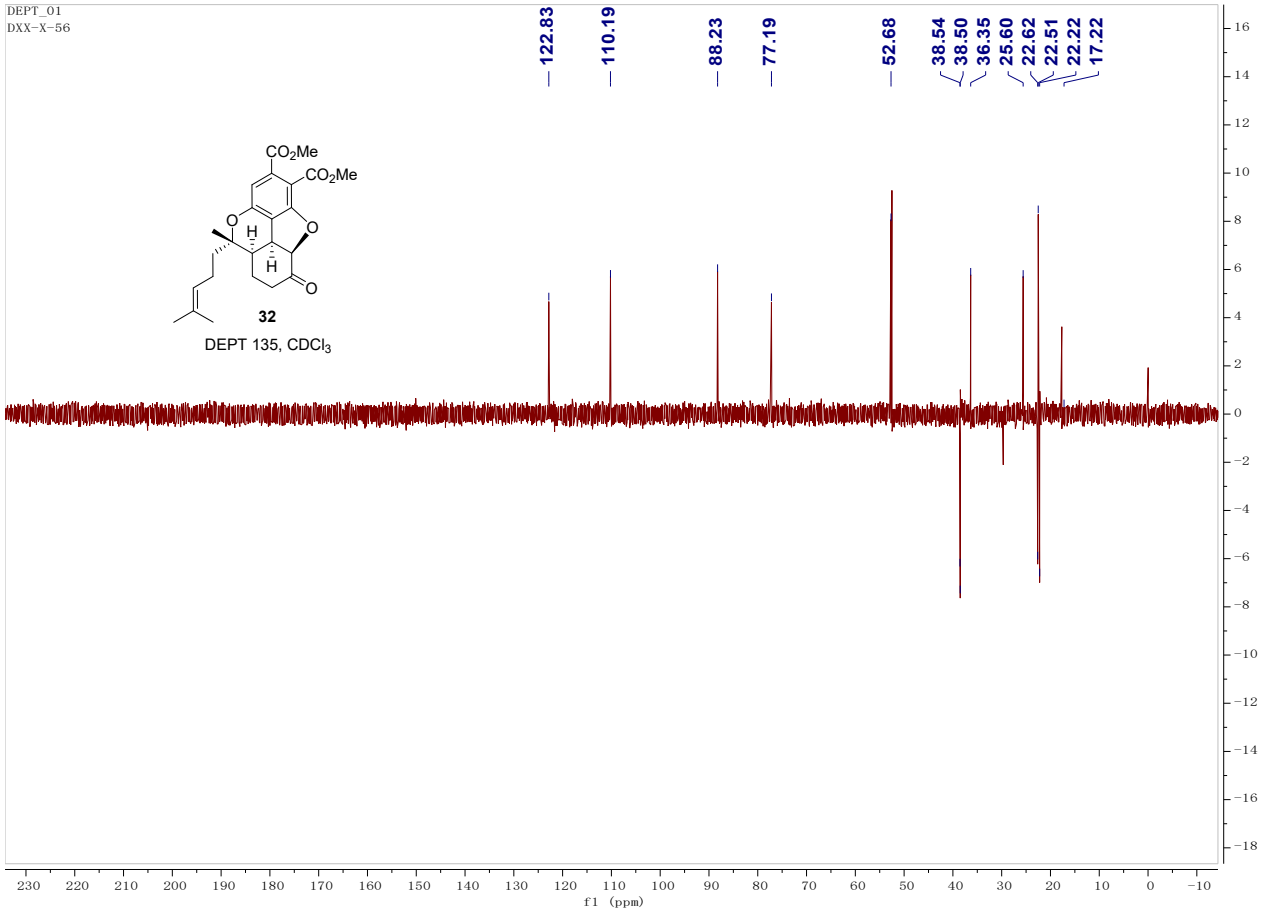

PROTON_01
DXX-X-28
7.2605
7.2513
5.7754
5.7677
5.0070
3.8578
3.8313
3.4445
2.3114
2.0019
1.9831
1.9743
1.9557
1.9418
1.9272
1.9135
1.8285
1.8229
1.8163
1.6641
1.6180
1.5861
1.5772
1.5748
1.5651
1.5562
1.5438
1.5249
1.3819
CO2Me
CO2Me
OAc
O
H
H
29
500 MHz, CDCl3
0.94
1.09
1.01
3.04
2.99
1.07
3.01
5.95
1.19
3.08
3.00
2.02
2.99
3.00
f1 (ppm)

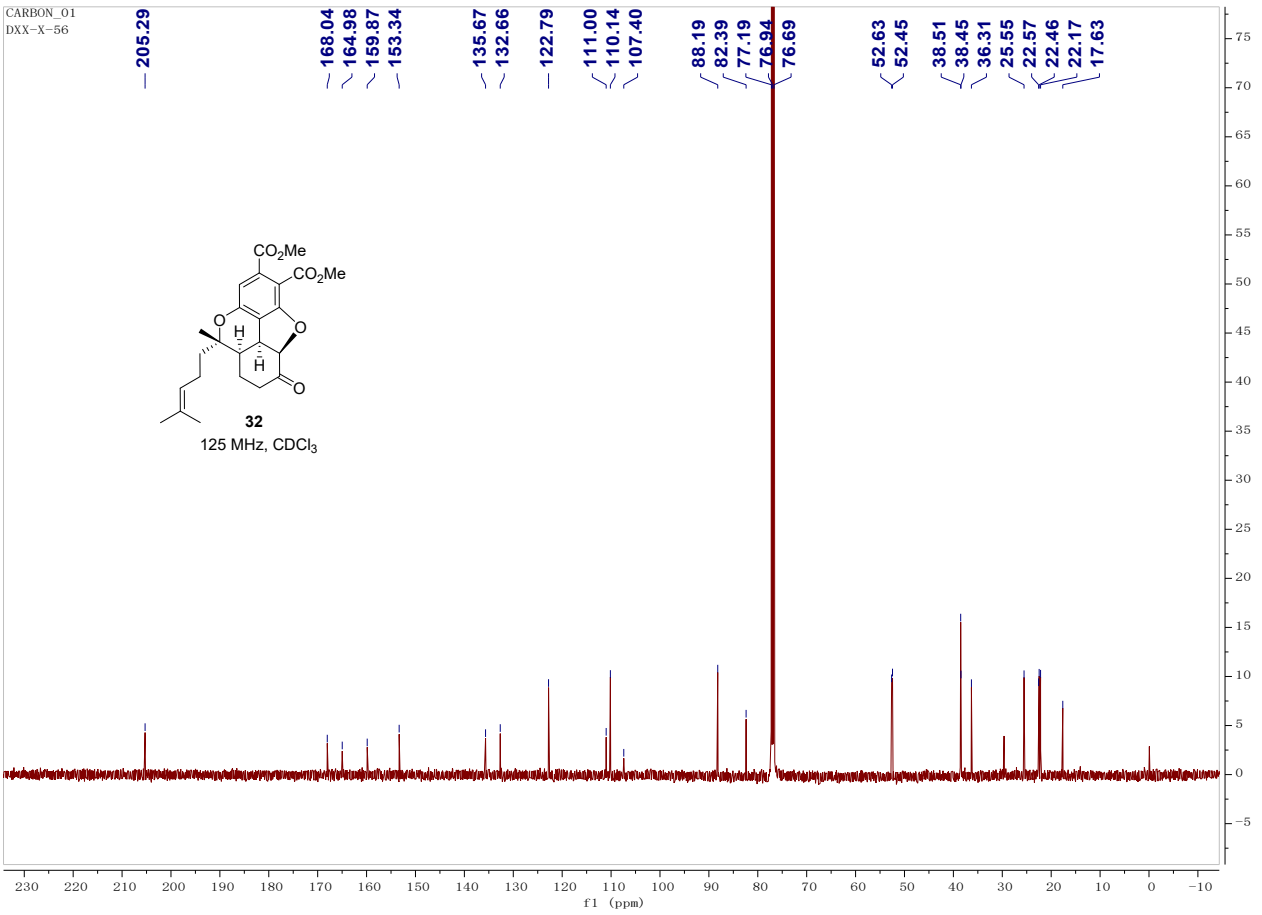

CARBON_01
DXX-X-28
168.05
166.88
165.71
154.71
148.18
136.41
132.00
128.38
124.03
123.49
120.26
119.47
117.14
79.65
77.30
77.04
76.79
52.59
52.47
37.27
36.86
31.97
29.47
25.56
23.74
22.65
22.16
20.87
20.28
17.48
CO2Me
CO2Me
OAc
O
H
H
29
125 MHz, CDCl3
f1 (ppm)


PROTON_01
DXX-X-40
7.2600
6.6889
6.6813
5.5306
5.5131
5.4963
5.1117
4.8136
3.8939
3.8548
3.7503
3.7361
3.7215
3.6952
3.6811
3.6667
2.6856
2.6736
2.6612
2.6420
2.6316
2.6182
2.2879
2.2615
2.1684
2.1579
2.1448
2.1316
2.1206
1.8672
1.8408
1.8249
1.6185
1.6156
1.6080
1.5866
1.4014
1.3706
1.2772
1.2507
CO2Me
CO2Me
O
H
O
H
O
31
500 MHz, CDCl3
0.89
0.86
2.31
2.10
2.33
6.08
6.09
1.30
1.34
1.21
1.06
2.49
2.46
6.42
8.22
3.47
3.00
6.05
6.03
f1 (ppm)


CARBON_02
DXX-X-40
168.28 165.64 165.61 160.08 160.04 153.75 153.73 143.04 142.97 134.66 134.59 113.39 113.25 111.35 111.27 110.04 109.92 107.81 107.77 88.14 88.09 82.16 82.12 77.26 77.00 76.75 64.00 63.61 58.52 58.35 52.61 52.29 37.48 37.05 36.18 36.16 34.89 34.67 31.36 31.33 24.78 24.76 23.74 23.68 23.55 23.35 22.36 22.04 18.67 18.64
CO2Me
CO2Me
31
125 MHz, CDCl3
f1 (ppm)


PROTON_01
DXX-X-56
7.2604 6.6873 5.2233 5.2061 5.0530 5.0390 5.0249 4.1036 4.0881 4.0749 3.9076 3.8566 2.4378 2.4246 2.4119 2.3968 2.3901 2.3838 2.3517 2.3432 2.3233 2.3150 2.1191 2.1050 2.0922 2.0858 1.6659 1.5981 1.4555
0.98 1.10 1.09 1.16 3.00 3.03 1.08 0.98 0.37 0.50 0.25 3.00 1.28 3.07 3.10 3.06 2.01
CO2Me
CO2Me
32
500 MHz, CDCl3
f1 (ppm)


DEPT_01
DXX-X-56
122.83
110.19
88.23
77.19
52.68
38.54
38.50
36.35
25.60
22.62
22.51
22.22
17.22
CO2Me
CO2Me
O
H
O
H
O
32
DEPT 135, CDCl3
f1 (ppm)


CARBON_01
DXX-X-56
205.29
168.04
164.98
159.87
153.34
135.67
132.66
122.79
111.00
110.14
107.40
88.19
82.39
77.19
76.94
76.69
52.63
52.45
38.51
38.45
36.31
25.55
22.57
22.46
22.17
17.63
CO2Me
CO2Me
O
H
O
H
O
32
125 MHz, CDCl3
f1 (ppm)