Supporting Information

A concise total synthesis of cochlearoid B

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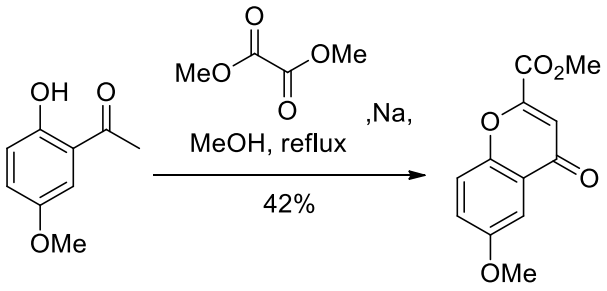
Contents:

1. General Information.

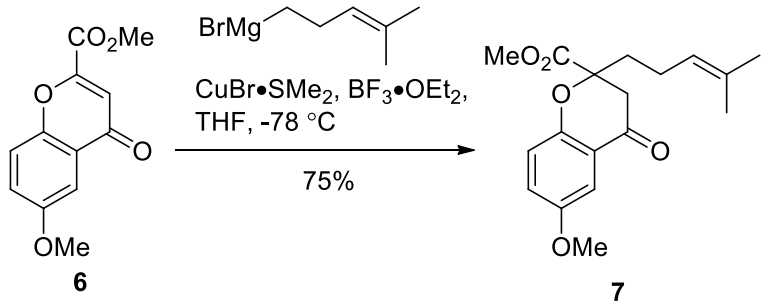
Dry THF, CH_2Cl_2, DMF were obtained by passing commercially available pre-dried, oxygen-free formulations through activated alumina columns. Oxygen- and moisture-sensitive reactions were carried out under argon atmosphere. All the commercially available reagents were used without further purification. Flash column chromatography was performed on SiliCycle silica gel (230-400 mesh). TLC was carried out using Merck 60 F_{254} which, after development, were visualized at 254/365 nm, and/or staining in CAM followed by heating. Melting points were determined with Shanghai Shenguang WRS-1B apparatus and were uncorrected. NMR spectra were recorded on (^{1}H at 300 MHz and 600 MHz, ^{13}C at 75 MHz and 150 MHz) Bruker spectrometers. Chemical shifts (δ) are given in ppm with reference to solvent signals and coupling constants (*J*) in Hz. HRMS were determined on Bruker micrOTOF-QII.

2. Experimental Procedures.



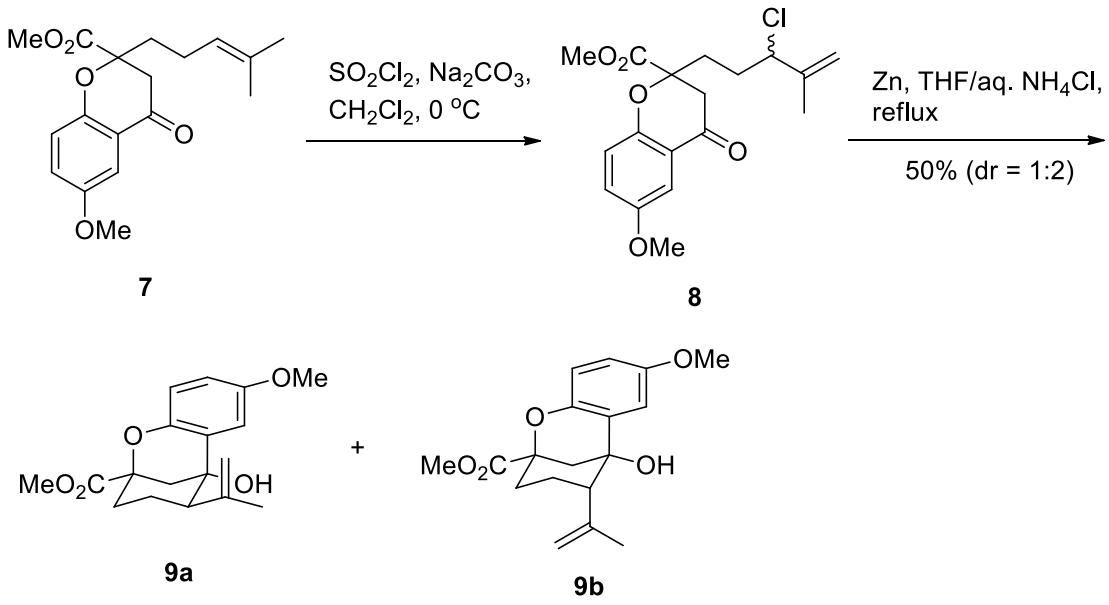
5 **6**

Acetylphenol **5** (21.0 g, 126 mmol) and dimethyl oxalate (74.0 g, 630 mmol) were added to MeONa/MeOH (freshly prepared by dissolving Na (14.5 g, 630 mmol) in MeOH (1 L)), the reaction was refluxed for 4 h. The reaction was cooled, conc. HCl (60 mL) was added, and the resulting mixture was refluxed for 1h again. The reaction mixture was poured into ice/water, the resulting solid was filtered, and dissolved in EtOAc, washed with sat. $NaHCO_3$ and brine, dried over $MgSO_4$, filtered and concentrated. The crude product was purified by silica gel chromatography (PE:EtOAc = 10:1 → 5:1) which afforded chromone **6** (12.3 g, 42%) as a light yellow solid. **6**: m.p. 145.4-145.9 °C; R_f = 0.30 (silica, PE:EtOAc = 2:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55 – 7.49 (m, 2H), 7.31 (dd, J = 9.1, 3.1 Hz, 1H), 7.08 (s, 1H), 4.00 (s, 3H), 3.88 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.29, 161.21, 157.59, 151.73, 150.87, 125.24, 125.16, 120.32, 114.09, 104.63, 56.08, 53.65; HRMS (ESI-TOF): $[M + Na]^+$ calcd for $C_{12}H_{10}O_5Na^+$ 257.0420, found 257.0432.



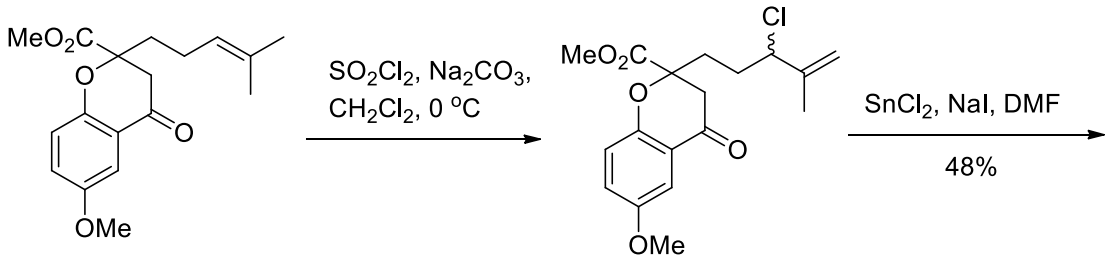
6 **7**

Homoprenylmagnesium bromide (5.3 mL, 0.6 M in THF, 3.2 mmol) was added dropwise to the suspension of $CuBr•SMe_2$ (658 mg, 3.2 mmol) in THF (13 mL) at 0 °C. The resulting black solution was stirred at the same temperature for 15 min, then was cooled to −78 °C, $BF_3•OEt_2$ (0.4 mL, 3.2 mmol) was added, after 5 min, chromone **6** (498 mg, 2.1 mmol) in THF (13 mL) was added dropwise, the mixture was warmed to rt overnight. The reaction was quenched with sat. NH_4Cl, extracted with Et_2O. The combined organic phase was washed with brine, dried over $MgSO_4$, filtered and concentrated. The crude product was purified by silica gel chromatography (PE:EtOAc = 5:1) to afford chromanone **7** (510 mg, 75%) as a light yellow oil. **7**: R_f = 0.27 (silica, PE:EtOAc = 5:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26 (d, 1H, overlap), 7.12 (dd, J = 8.9, 2.9 Hz, 1H), 7.03 (d, J = 9.0 Hz, 1H), 5.13 – 5.02 (m, 1H), 3.79 (s, 3H), 3.67 (s, 3H), 3.14 (d, J = 16.8 Hz, 1H), 2.89 (d, J = 16.8 Hz, 1H), 2.30 – 2.13 (m, 1H), 2.12 – 1.95 (m, 3H), 1.68 (s, 3H), 1.60 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 190.22, 171.82, 154.82, 154.26, 133.20, 125.61, 122.37, 120.33, 119.54, 107.03, 83.92, 55.72, 52.82, 44.24, 37.93, 25.73, 22.03, 17.69; HRMS (ESI-TOF): $[M + Na]^+$ calcd for $C_{18}H_{22}O_5Na^+$ 341.1359, found 341.1366.

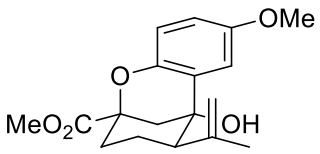


SO_2Cl_2 (1.7 mL, 20.7 mmol) was added dropwise to the suspension of chromanone **7** (6.0 g, 18.8 mmol), Na_2CO_3 (8.0 g, 75.4 mmol) in CH_2Cl_2 (190 mL) at 0 °C, after 10 min, the reaction was quenched with water, extracted with CH_2Cl_2. The combined organic phase was washed with brine, dried over $MgSO_4$, filtered and concentrated. The crude product **8** was used without further purification.

To a solution of the crude chloride **8** in THF (75 mL) was added 6% aq. NH_4Cl (15 mL) and freshly activated Zn (12.0 g, 188 mmol), the mixture was refluxed overnight. The reaction was cooled and filtered through Celite, the resulting solution was diluted with water, extracted with Et_2O. The combined organic phase was washed with brine, dried over $MgSO_4$, filtered and concentrated. The crude product was purified by silica gel chromatography (PE:EtOAc = 20:1 → 10:1) to afford alcohol **9a** (1.0 g, 17%) as a yellow solid and alcohol **9b** (2.0 g, 33%) as a light yellow oil. **9a**: m.p. 98.7-99.1 °C; R_f = 0.41 (silica, PE:EtOAc = 2:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.89 – 6.82 (m, 1H), 6.79 – 6.71 (m, 2H), 5.05 (s, 1H), 4.73 (s, 1H), 3.81 (s, 3H), 3.73 (s, 3H), 2.86 (s, 1H), 2.56 (dd, *J* = 12.9, 3.8 Hz, 1H), 2.34 – 2.17 (m, 3H), 1.95 (td, *J* = 13.5, 5.1 Hz, 1H), 1.81 – 1.53 (m, 2H), 1.49 (s, 3H)； ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.48, 153.09, 148.48, 144.56, 126.70, 116.06, 115.79, 115.05, 110.93, 80.16, 69.73, 56.00, 55.36, 52.91, 40.70, 35.53, 24.51, 22.14; HRMS (ESI-TOF): $[M + Na]^+$ calcd for $C_{18}H_{22}O_5Na^+$ 341.1359, found 341.1361; **9b**: R_f = 0.57 (silica, PE:EtOAc = 2:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.04 (d, *J* = 2.9 Hz, 1H), 6.83 (d, *J* = 8.9 Hz, 1H), 6.74 (dd, *J* = 8.9, 3.0 Hz, 1H), 5.15 (s, 1H), 5.10 (s, 1H), 3.81 (s, 3H), 3.77 (s, 3H), 2.58 – 2.46 (m, 3H), 2.15 – 2.04 (m, 2H), 1.97 (s, 3H), 1.84 – 1.64 (m, 2H)； ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.48, 153.81, 148.25, 145.62, 130.22, 116.13, 116.03, 115.14, 108.52, 80.35, 69.68, 55.84, 52.89, 52.00, 35.78, 31.79, 25.11, 23.65; HRMS (ESI-TOF): $[M + Na]^+$ calcd for $C_{18}H_{22}O_5Na^+$ 341.1359, found 341.1364.



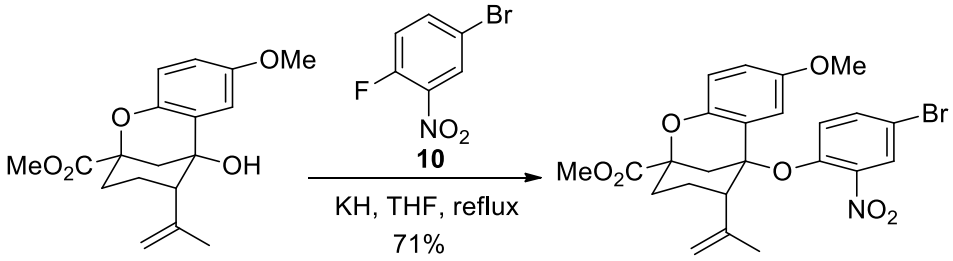
7 **8**



9a

SO_2Cl_2 (0.12 mL, 1.5 mmol) was added dropwise to the suspension of chromanone **7** (318 mg, 1.0 mmol), Na_2CO_3 (424 mg, 4.0 mmol) in CH_2Cl_2 (10 mL) at 0 °C, after 10 min, the reaction was quenched with water, extracted with CH_2Cl_2. The combined organic phase was washed with brine, dried over $MgSO_4$, filtered and concentrated. The crude product **8** was used without further purification.

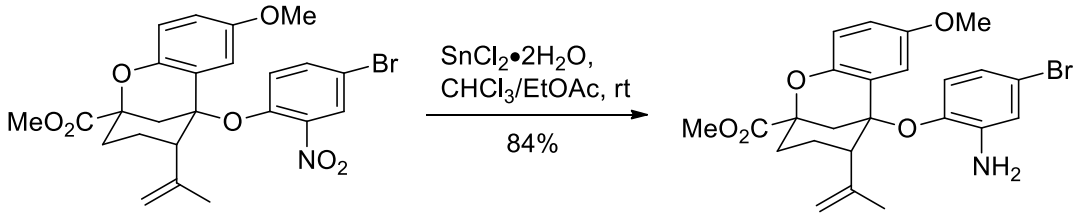
To a solution of the crude chloride **8** in DMF (5 mL) was added $SnCl_2$ (853 mg, 4.5 mmol) and NaI (1.3 g, 9 mmol), the mixture was heated at 90 °C in dark overnight. The reaction was cooled and quenched with sat. NH_4F, extracted with Et_2O. The combined organic phase was washed with water and brine, dried over $MgSO_4$, filtered and concentrated. The crude product was purified by silica gel chromatography (PE:EtOAc = 10:1 → 5:1) to afford alcohol **9a** (153 mg, 48%) as a yellow solid.



9b **11**

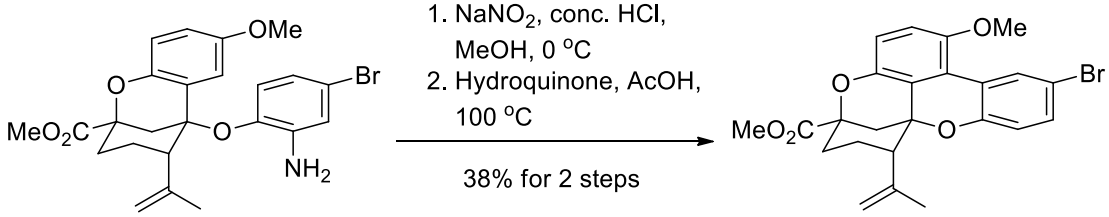
KH (24 mg, 0.6 mmol, freshly washed with hexane) was added to alcohol **9b** (96 mg, 0.3 mmol) in THF (1.5 mL) at 0 °C, after 10 min, 4-bromo-1-fluoro-2-nitrobenzene **10** (330 mg, 1.5 mmol) was added and the mixture was heated to reflux for 5 h. The reaction was cooled and quenched with water carefully, extracted with Et_2O. The combined organic phase was washed with brine, dried over $MgSO_4$, filtered and concentrated. The crude product was purified by silica gel chromatography (PE:EtOAc = 10:1) to afford **11** (111 mg, 71%) as a yellow solid. **11**: m.p. 211.0-220.4 °C (decomposition); R_f = 0.30 (silica, PE:EtOAc = 5:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.66 (d, J = 2.5 Hz, 1H), 7.22 (dd, J = 9.1, 2.5 Hz, 1H), 6.95 (d, J = 8.8 Hz, 1H), 6.88 – 6.78 (m, 2H), 6.41 (d, J = 9.1 Hz, 1H), 5.09 (s, 1H), 5.01 (s, 1H), 3.81 (s, 3H), 3.70 (s, 3H), 2.72 (d, J = 5.9 Hz, 1H), 2.63 (d, J = 13.0 Hz, 1H), 2.52 (d, J = 13.1 Hz, 1H), 2.27 (td, J = 14.3, 6.3 Hz, 1H), 2.08

(dd, J = 14.7, 5.6 Hz, 1H), 1.95 (s, 3H), 1.82 (dd, J = 14.8, 6.2 Hz, 1H), 1.73 – 1.58 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.79, 154.28, 148.03, 146.27, 145.59, 143.74, 134.69, 127.09, 125.73, 121.65, 117.50, 116.33, 114.29, 113.11, 109.10, 81.88, 80.64, 55.90, 53.16, 52.07, 31.86, 28.55, 27.07, 24.98; HRMS (ESI-TOF): $[M + Na]^+$ calcd for $C_{24}H_{24}BrNO_7Na^+$ 540.0628, found 540.0624.



11 **12**

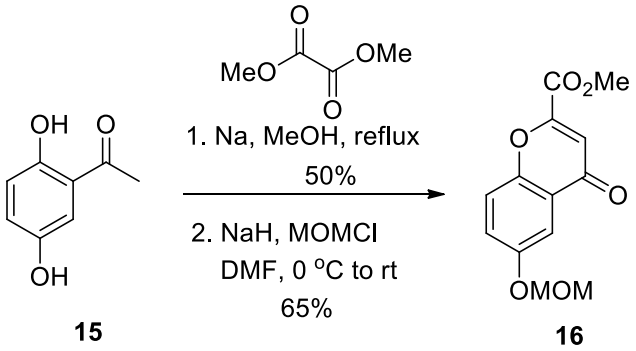
$SnCl_2$•$2H_2O$ (552 mg, 2 mmol) was added to nitrobromide **11** (111 mg, 0.2 mmol) in $CHCl_3$ (0.5 mL) and EtOAc (1 mL), the suspension was stirred at rt for 36 h. The reaction was quenched with 2 M NaOH, extracted with CH_2Cl_2. The combined organic phase was washed with brine, dried over $MgSO_4$, filtered and concentrated. The crude product was purified by silica gel chromatography (PE:EtOAc = 5:1) to afford **12** (88 mg, 84%) as a white foam. **12**: R_f = 0.24 (silica, PE:EtOAc = 5:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.06 (d, J = 2.9 Hz, 1H), 6.88 (d, J = 8.9 Hz, 1H), 6.79 (dd, J = 9.0, 2.9 Hz, 1H), 6.74 (d, J = 2.3 Hz, 1H), 6.40 (dd, J = 8.6, 2.3 Hz, 1H), 6.21 (d, J = 8.6 Hz, 1H), 5.14 (s, 1H), 5.13 (s, 1H), 4.11 (s, 2H), 3.74 (s, 3H), 3.71 (s, 3H), 2.78 (d, J = 5.2 Hz, 1H), 2.39 (s, 2H), 2.23 (td, J = 14.1, 6.4 Hz, 1H), 2.06 (s, 4H), 1.83 – 1.60 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.02, 153.77, 148.11, 147.35, 141.74, 140.13, 127.63, 121.02, 119.71, 117.76, 116.74, 115.82, 115.63, 114.39, 109.28, 80.14, 79.33, 55.69, 52.83, 52.10, 31.87, 28.36, 26.82, 24.14; HRMS (ESI-TOF): $[M + H]^+$ calcd for $C_{24}H_{27}BrNO_5^+$ 488.1067, found 488.1062.



12 **13**

To a solution of aminobromide **12** (41 mg, 0.084 mmol) in MeOH (0.5 mL) at 0 °C was added $NaNO_2$ (11 mg, 0.168 mmol), conc. HCl (0.1 mL, 1.2 mmol), the reaction was stirred at the same temperature for 30 min. The mixture was concentrated *in vacuo* and dissolved in AcOH (1 mL), and hydroquinone (9 mg, 0.084 mmol) was added, the reaction was heated at 100 °C for 1.5 h. The reaction mixture was quenched with water, extracted with Et_2O. The combined organic phase was washed with sat. $NaHCO_3$ and brine, dried over $MgSO_4$, filtered and concentrated. The crude product was purified by silica gel chromatography (PE:EtOAc = 10:1) to afford **13** (15 mg, 38%) as a white solid. **13**: m.p. 169.7-171.8 °C (decomposition); R_f = 0.37 (silica, PE:EtOAc = 5:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.53 (d, J = 2.4 Hz, 1H), 7.28 (dd, J = 8.6, 2.5 Hz, 1H), 6.93 (d, J = 9.0 Hz, 1H), 6.89 (d, J = 9.1 Hz, 1H), 6.79 (d, J = 8.6 Hz, 1H), 5.12 (s, 1H), 5.03 (s, 1H), 3.89 (s, 3H), 3.85 (s, 3H), 3.01 (d, J = 12.9 Hz, 1H), 2.66 (d, J = 5.1 Hz, 1H), 2.36 (dt, J = 12.9, 1.5 Hz, 1H), 2.11 – 2.02 (m, 2H), 1.76 (s, 3H), 1.75 – 1.65 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.09,

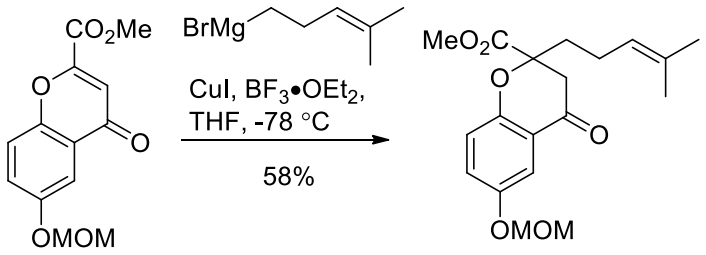
150.67, 150.51, 146.73, 142.93, 131.48, 131.14, 123.49, 122.50, 119.97, 115.98, 115.33, 115.10, 114.15, 113.17, 80.21, 74.88, 56.29, 53.07, 44.95, 33.22, 31.78, 24.90, 23.68; HRMS (ESI-TOF): $[M + Na]^+$ calcd for $C_{24}H_{23}BrO_5Na^+$ 493.0621, found 493.0613.



15 **16**

Acetylphenol **15** (30.4 g, 200 mmol) and dimethyl oxalate (118.0 g, 1000 mmol) were added to MeONa/MeOH (freshly prepared by dissolving Na (23.0 g, 1000 mmol) in MeOH (1 L)), the reaction was refluxed for 4 h. The reaction was cooled, conc. HCl (100 mL) was added, and the resulting mixture was refluxed for 1h again. The reaction mixture was poured into ice/water, the resulting solid was filtered, and washed with cold MeOH, dried in oven at 120 °C which afforded the crude chromone (21.7 g, 50%) as a grey solid. The crude chromone was used without further purification.

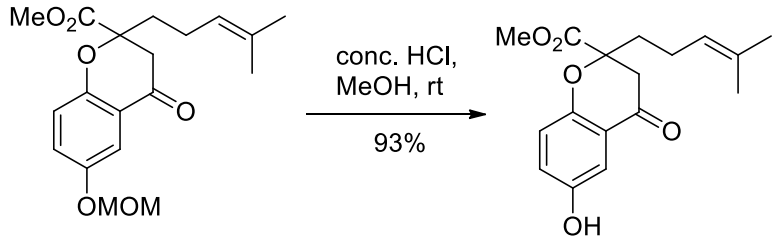
To the crude chromone (21.7 g, 100 mmol) in DMF (200 mL), 60% NaH (6.0 g, 150 mmol) was added at 0 °C, after 15 min, MOMCl (11.4 mL, 150 mmol) was added dropwise, the mixture was stirred at rt overnight. The reaction was quenched with water carefully, extracted with Et_2O. The combined organic phase was washed with water and brine, dried over $MgSO_4$, filtered and concentrated. The crude product was purified by silica gel chromatography (PE:EtOAc = 5:1) to afford chromanone **16** (17.3 g, 65%) as a light yellow solid. **16**: m.p. 97.6-98.2 °C; R_f = 0.35 (silica, PE:EtOAc = 2:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.75 (s, 1H), 7.55 (d, J = 9.1 Hz, 1H), 7.42 (d, J = 8.7 Hz, 1H), 7.08 (s, 1H), 5.19 (s, 2H), 4.01 (s, 3H), 3.49 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.14, 161.20, 155.01, 151.80, 151.31, 125.41, 125.33, 120.25, 114.13, 109.32, 94.78, 56.40, 53.62; HRMS (ESI-TOF): $[M + H]^+$ calcd for $C_{13}H_{13}O_6^+$ 265.0707, found 265.0701.



16 **17**

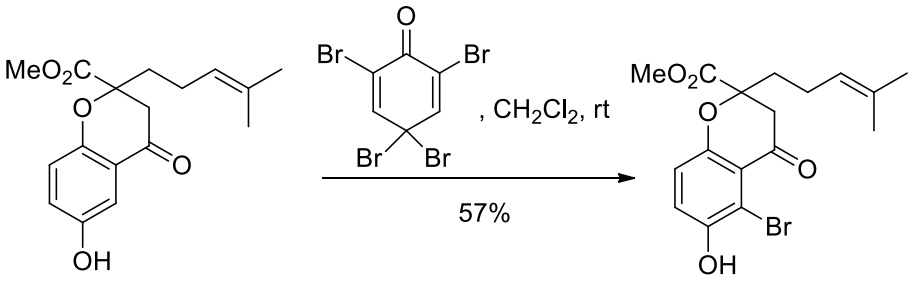
Homoprenylmagnesium bromide (13.5 mL, 0.7 M in THF, 9.4 mmol) was added dropwise to the suspension of CuI (1.8 g, 9.4 mmol) in THF (25 mL) at 0 °C. The resulting black solution was stirred at the same temperature for 15 min, then was cooled to −78 °C, BF_3•OEt_2 (1.2 mL, 9.4 mmol) was added, after 5 min, chromone **16** (1.7 g, 6.3 mmol) in THF (25 mL) was added dropwise, the mixture was warmed up to rt overnight. The reaction was quenched with sat. NH_4Cl, extracted with Et_2O. The combined organic phase was washed with brine, dried over $MgSO_4$, filtered and concentrated. The crude product was purified by silica gel chromatography

(PE:EtOAc = 5:1) to afford chromanone **17** (1.3 g, 58%) as a light yellow oil. **17**: R_f = 0.62 (silica, PE:EtOAc = 2:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43 (d, *J* = 3.0 Hz, 1H), 7.19 (dd, *J* = 9.0, 3.0 Hz, 1H), 7.01 (d, *J* = 8.9 Hz, 1H), 5.11 (s, 2H), 5.05 (t, *J* = 6.2 Hz, 1H), 3.65 (s, 3H), 3.44 (s, 3H), 3.12 (d, *J* = 16.8 Hz, 1H), 2.87 (d, *J* = 16.8 Hz, 1H), 2.28 – 2.11 (m, 1H), 2.10 – 1.94 (m, 3H), 1.66 (s, 3H), 1.58 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 190.07, 171.81, 155.45, 151.83, 133.29, 126.56, 122.39, 120.66, 119.43, 111.90, 94.99, 83.93, 77.58, 77.16, 76.74, 56.16, 52.91, 44.28, 37.96, 25.77, 22.07, 17.74; HRMS (ESI-TOF): $[M + Na]^+$ calcd for $C_{19}H_{24}O_6Na^+$ 371.1465, found 371.1453.



17 **18**

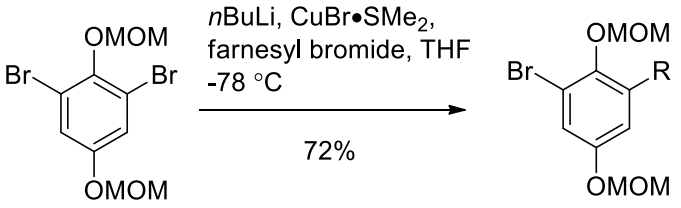
To a solution of chromanone **17** (11.6 g, 33.3 mmol) in MeOH (160 mL), conc. HCl (8 mL, 96.0 mmol) was added, the mixture was stirred at rt overnight. The reaction was quenched with sat. $NaHCO_3$, then concentrated, and extracted with CH_2Cl_2. The combined organic phase was washed with brine, dried over $MgSO_4$, filtered and concentrated. The crude product was purified by silica gel chromatography (PE:EtOAc = 5:1) to afford chromanone **18** (9.4 g, 93%) as a light yellow solid. **18**: m.p. 78.4-78.8 °C; R_f = 0.46 (silica, PE:EtOAc = 2:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32 (d, *J* = 3.0 Hz, 1H), 7.07 (dd, *J* = 8.9, 3.0 Hz, 1H), 6.97 (d, *J* = 8.9 Hz, 1H), 6.91 (s, 1H), 5.05 (t, *J* = 6.9 Hz, 1H), 3.66 (s, 3H), 3.14 (d, *J* = 16.9 Hz, 1H), 2.90 (d, *J* = 17.0 Hz, 1H), 2.26 – 2.12 (m, 1H), 2.10 – 1.93 (m, 3H), 1.66 (s, 3H), 1.58 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 191.54, 172.18, 154.54, 150.95, 133.36, 125.68, 122.34, 120.44, 119.60, 110.97, 83.91, 53.05, 44.26, 37.92, 25.78, 22.07, 17.75; HRMS (ESI-TOF): $[M + H]^+$ calcd for $C_{17}H_{21}O_5^+$ 305.1384, found 305.1385.



18 **19**

To a solution of chromanone **18** (2.5 g, 8.2 mmol) in CH_2Cl_2 (40 mL), TBCO (3.7 g, 9.0 mmol) was added at 0 °C, the mixture was stirred at rt for 30 min. The reaction was quenched with sat. $Na_2S_2O_3$, extracted with CH_2Cl_2. The combined organic phase was washed with brine, dried over $MgSO_4$, filtered and concentrated. The crude product was purified by silica gel chromatography (PE:EtOAc = 10:1) to afford bromide **19** (1.8 g, 57%) as a light yellow oil. **19**: R_f = 0.53 (silica, PE:EtOAc = 2:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.23 (d, *J* = 9.1 Hz, 1H), 7.05 (d, *J* = 9.0 Hz, 1H), 5.94 (s, 1H), 5.16 – 4.95 (m, 1H), 3.68 (s, 3H), 3.15 (d, *J* = 16.5 Hz, 1H), 2.93 (d, *J* = 16.5 Hz, 1H), 2.28 – 2.14 (m, 1H), 2.09 – 1.94 (m, 3H), 1.67 (s, 3H), 1.59 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 188.52, 171.50, 155.75, 148.24, 133.46, 123.24, 122.28, 119.21, 117.66, 106.88, 83.61, 77.58,

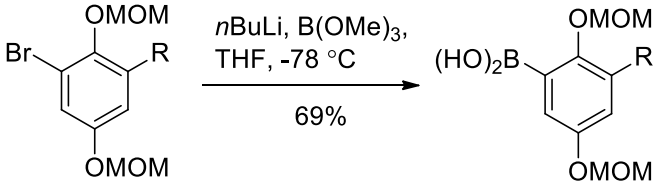
77.16, 76.74, 53.03, 45.08, 37.88, 25.81, 22.00, 17.79; HRMS (ESI-TOF): $[M + Na]^+$ calcd for $C_{17}H_{19}BrO_5Na^+$ 405.0308, found 405.0307.



20 **21**

R = farnesyl

Dibromide **20** (1.0 g, 2.9 mmol) was dissolved in THF (10 mL), the solution was cooled to −78 °C, *n*BuLi (1.1 mL, 2.6 M in hexane, 2.9 mmol) was added dropwise, after 15 min, $CuBr•SMe_2$ (596 mg, 2.9 mmol) was added, the mixture was stirred at the same temperature for 30 min before farnesyl bromide (1.1 g, 4.0 mmol) was added, the reaction was warmed to rt and stirred overnight. The reaction was quenched with sat. NH_4Cl, extracted with Et_2O. The combined organic phase was washed with brine, dried over $MgSO_4$, filtered and concentrated. The crude product was purified by silica gel chromatography (PE:EtOAc = 100:1) to afford bromide **21** (969 mg, 72%) as a light yellow oil. **21**: R_f = 0.50 (silica, PE:EtOAc = 10:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.12 (d, *J* = 2.9 Hz, 1H), 6.79 (d, *J* = 2.9 Hz, 1H), 5.29 (t, *J* = 6.8 Hz, 1H), 5.17 – 5.05 (m, 4H), 5.03 (s, 2H), 3.64 (s, 3H), 3.49 – 3.40 (m, 5H), 2.18 – 1.93 (m, 8H), 1.69 (s, 3H), 1.67 (s, 3H), 1.60 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.10, 147.50, 137.96, 137.51, 135.32, 131.41, 124.50, 124.12, 121.79, 118.31, 117.42, 117.37, 100.01, 94.91, 57.95, 56.17, 39.83, 29.09, 26.86, 26.70, 25.85, 17.82, 16.36, 16.15; HRMS (ESI-TOF): $[M + Na]^+$ calcd for $C_{25}H_{37}BrO_4Na^+$ 503.1767, found 503.1758.

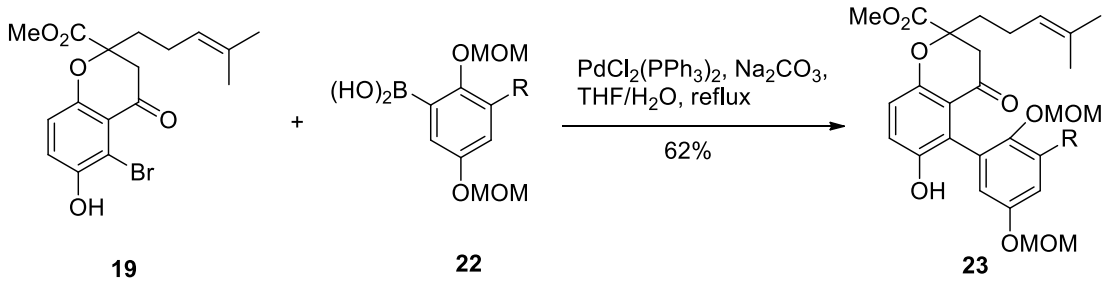


21 **22**

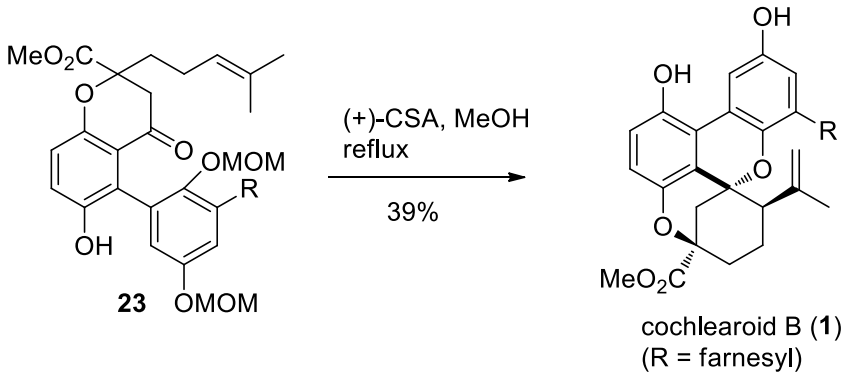
R = farnesyl

Bromide **21** (719 mg, 1.5 mmol) was dissolved in THF (7 mL), the solution was cooled to −78 °C, *n*BuLi (0.7 mL, 2.6 M in hexane, 1.8 mmol) was added dropwise, after 15 min, $B(OMe)_3$ (0.34 mL, 3.0 mmol) was added, the mixture was warmed to rt and stirred for 3 h. The reaction was quenched with sat. NH_4Cl, extracted with Et_2O. The combined organic phase was washed with brine, dried over $MgSO_4$, filtered and concentrated. The crude product was purified by silica gel chromatography (PE:EtOAc = 1:1) to afford boronic acid **22** (460 mg, 69%) as a light yellow oil. **22**: R_f = 0.19 (silica, PE:EtOAc = 2:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38 – 7.28 (m, 1H), 7.01 – 6.90 (m, 1H), 6.32 (s, 1H), 5.37 – 5.17 (m, 2H), 5.16 – 5.05 (m, 4H), 4.99 (s, 1H), 3.58 – 3.49 (m, 3H), 3.51 – 3.41 (m, 4H), 3.32 (d, *J* = 6.9 Hz, 1H), 2.20 – 1.92 (m, 9H), 1.71 (s, 3H), 1.67 (s, 3H), 1.60 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.09, 154.03, 137.31, 135.35, 135.26, 131.41, 124.48, 124.09, 122.16, 121.71, 120.42, 100.90, 94.82, 58.14, 56.14, 39.83, 28.56, 26.86, 26.71, 25.82, 17.80, 16.42, 16.13; HRMS (ESI-TOF): $[M + Na]^+$ calcd for $C_{25}H_{39}BO_6Na^+$ 469.2732,

found 469.2727.



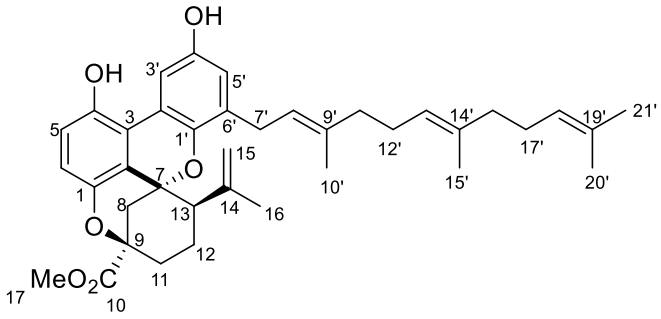
To a solution of boronic acid **22** (45 mg, 0.1 mmol) in THF/H_2O (0.2/0.05 mL), bromide **19** (19 mg, 0.05 mmol), $PdCl_2(PPh_3)_2$ (3.5 mg, 0.005 mmol), Na_2CO_3 (16 mg, 0.15 mmol) was added in sequence, the mixture was heated to reflux overnight. The reaction was quenched with water, extracted with Et_2O. The combined organic phase was washed with brine, dried over $MgSO_4$, filtered and concentrated. The crude product was purified by silica gel chromatography (PE:EtOAc = 5:1) to afford **23** (22 mg, 62%) as a yellow oil. **23**: inseparable atropisomers; R_f = 0.26 (silica, PE:EtOAc = 5:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.21 (d, *J* = 2.4 Hz, 0.5H), 7.18 (d, *J* = 2.4 Hz, 0.5H), 7.09 (d, *J* = 4.1 Hz, 0.5H), 7.06 (d, *J* = 4.1 Hz, 0.5H), 6.92 (d, *J* = 3.0 Hz, 0.5H), 6.91 (d, *J* = 3.1 Hz, 0.5H), 6.57 (d, *J* = 3.0 Hz, 0.5H), 6.52 (d, *J* = 3.0 Hz, 0.5H), 5.50 (s, 0.5H), 5.35 (t, *J* = 6.2 Hz, 1H), 5.21 – 5.01 (m, 5H), 4.67 (d, *J* = 5.7 Hz, 0.5H), 4.61 (d, *J* = 5.8 Hz, 0.5H), 4.58 (d, *J* = 5.8 Hz, 0.5H), 4.48 (d, *J* = 5.7 Hz, 0.5H), 3.71 (s, 1.5H), 3.67 (s, 1.5H), 3.51 – 3.37 (m, 5H), 3.13 (s, 1.5H), 3.10 – 2.94 (m, 2.5H), 2.90 – 2.76 (m, 1H), 2.26 – 1.93 (m, 12H), 1.72 (s, 3H), 1.68 (s, 6H), 1.60 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 189.59, 189.50, 172.12, 155.64, 155.16, 154.38, 148.24, 148.18, 147.73, 147.14, 137.30, 137.07, 136.82, 135.52, 135.29, 133.31, 131.41, 129.92, 129.51, 124.84, 124.55, 124.25, 124.18, 124.11, 123.53, 122.51, 122.20, 122.13, 119.48, 119.39, 119.01, 118.19, 116.20, 115.42, 99.77, 99.37, 95.02, 83.67, 57.15, 56.90, 56.17, 56.08, 52.94, 52.74, 45.54, 45.36, 39.91, 39.86, 37.84, 37.68, 28.62, 26.90, 26.83, 25.86, 22.13, 17.84, 17.80, 16.41, 16.16; HRMS (ESI-TOF): $[M + Na]^+$ calcd for $C_{42}H_{56}O_9Na^+$ 727.3817, found 727.3813.



To a solution of **23** (22 mg, 0.03 mmol) in MeOH (0.2 mL) was added (+)-CSA (7 mg, 0.03 mmol), the solution was heated to reflux for 10 min. The reaction mixture was cooled to rt, and directly purified by silica gel chromatography (PE:EtOAc = 2:1) to afford **1** (7 mg, 39%) as a light yellow oil. **1**: R_f = 0.34 (silica, PE:EtOAc = 2:1); ^{1}H NMR (600 MHz, MeOD) δ 7.86 (d, *J* = 3.0 Hz, 1H), 6.76 (d, *J* = 8.8 Hz, 1H), 6.72 (d, *J* = 8.8 Hz, 1H), 6.45 (d, *J* = 2.9 Hz, 1H), 5.30 (t, *J* = 7.4 Hz,

1H), 5.13 (t, *J* = 6.9 Hz, 1H), 5.07 (t, *J* = 7.0 Hz, 1H), 4.46 (s, 1H), 4.27 (s, 1H), 3.81 (s, 3H), 3.36 (dd, *J* = 15.6, 7.5 Hz, 1H), 3.19 (dd, *J* = 15.7, 7.6 Hz, 1H), 2.63 (dd, *J* = 12.9, 3.2 Hz, 1H), 2.47 (d, *J* = 12.5 Hz, 1H), 2.35 (dd, *J* = 12.5, 2.2 Hz, 1H), 2.15 – 2.12 (m, 2H), 2.12 – 2.09 (m, 1H), 2.09 – 2.05 (m, 2H), 2.05 – 2.01 (m, 2H), 2.00 – 1.96 (m, 1H), 1.94 (t, *J* = 7.6 Hz, 2H), 1.73 (s, 3H), 1.72 – 1.67 (m, 1H), 1.65 (s, 3H), 1.59 (s, 3H), 1.58 (s, 3H), 1.52 – 1.46 (m, 1H), 1.25 (s, 3H); ^{13}C NMR (151 MHz, MeOD) δ 173.95, 151.18, 149.06, 147.18, 146.25, 145.77, 136.80, 135.99, 131.95, 130.03, 125.53, 125.41, 123.85, 122.93, 119.40, 118.36, 117.73, 116.23, 116.07, 113.94, 113.45, 80.97, 75.98, 58.37, 53.18, 41.88, 40.90, 40.79, 36.42, 29.47, 27.79, 27.56, 26.78, 25.90, 17.76, 16.37, 16.15; HRMS (ESI-TOF): $[M + Na]^+$ calcd for $C_{38}H_{46}O_6Na^+$ 621.3187, found 621.3175.

Table 1 ^{1}H NMR comparison of Synthetic and Natural cochlearoid B



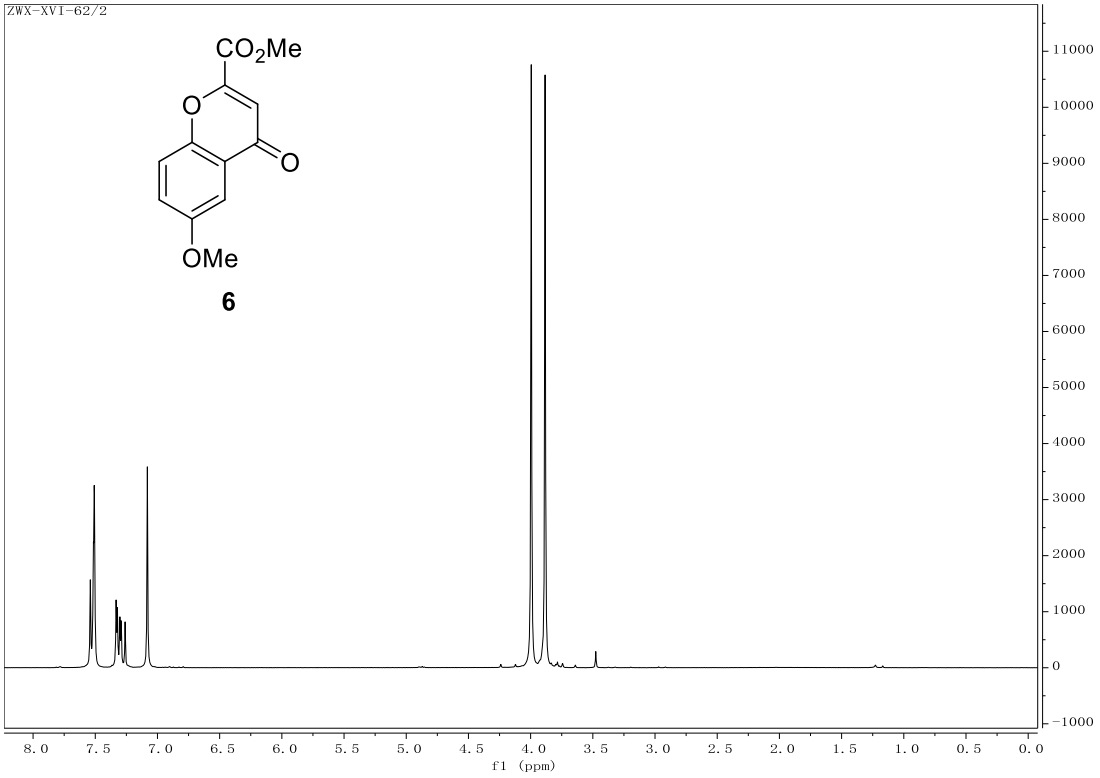
cochlearoid B (**1-1**)

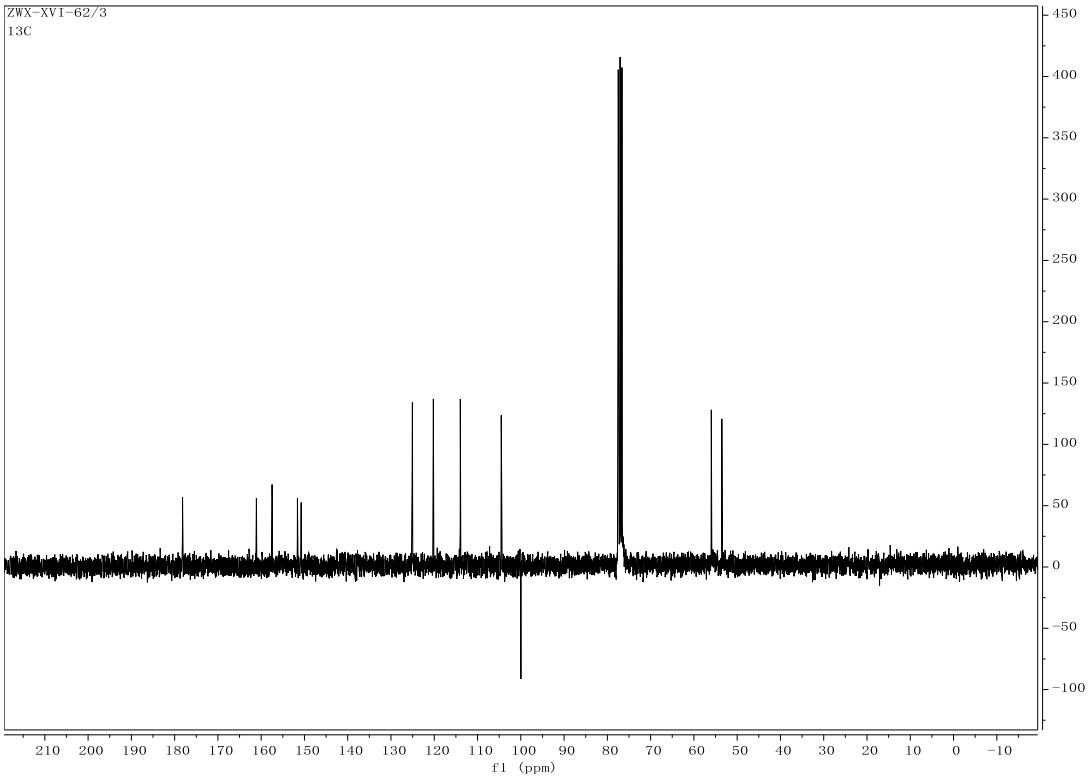
position	**Natural** δ_H (ppm, mult, *J* in Hz)	**Synthetic** δ_H (ppm, mult, *J* in Hz)
5	6.72 (d, 8.8)	6.72 (d, 8.8)
6	6.76 (d, 8.8)	6.76 (d, 8.8)
8a	2.47 (d, 12.5)	2.47 (d, 12.5)
8b	2.35 (dd, 12.5, 2.1)	2.35 (dd, 12.5, 2.2)
11a	2.10 (m)	2.12 - 2.09 (m)
11b	1.98 (m)	2.00 - 1.96 (m)
12a	1.68 (m)	1.72 - 1.67 (m)
12b	1.49 (m)	1.52 - 1.46 (m)
13	2.69 (brd, 14.0)	2.63 (dd, 12.9, 3.2)
15a	4.47 (brs)	4.46 (s)
15b	4.27 (brs)	4.27 (s)
16	1.25 (s)	1.25 (s)
17	3.81 (s)	3.81 (s)
3’	7.86 (d, 2.9)	7.86 (d, 3.0)
5’	6.44 (d, 2.9)	6.45 (d, 2.9)
7’a	3.36 (dd, 15.7, 7.5)	3.36 (dd, 15.6, 7.5)
7’b	3.19 (dd, 15.7, 7.5)	3.19 (dd, 15.7, 7.6)
8’	5.29 (t-like, 7.5)	5.30 (t, 7.4)
10’	1.73 (s)	1.73 (s)
11’	1.94 (t, 7.5)	1.94 (t, 7.6)
12’	2.13 (m)	2.15 - 2.12 (m)
13’	5.12 (t, 6.5)	5.13 (t, 6.9)
15’	1.65 (s)	1.65 (s)
16’	2.06 (t, 7.0)	2.09 - 2.05 (m)
17’	2.03 (m)	2.05 - 2.01 (m)
18’	5.06 (t, 7.0)	5.07 (t, 7.0)
20’	1.59 (s)	1.59 (s)
21’	1.57 (s)	1.58 (s)

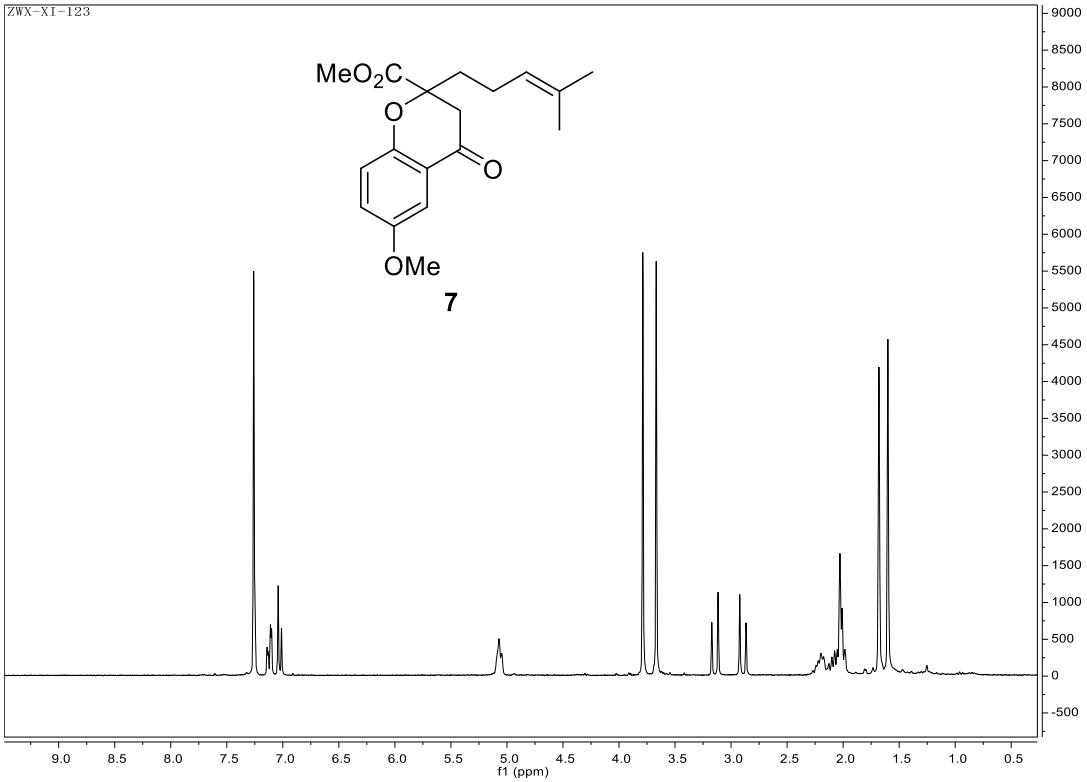
Table 2 ^{13}C NMR comparison of Synthetic and Natural cochlearoid B

position	**Natural** δ_C (ppm)	**Synthetic** δ_C (ppm)
1	147.1	147.18
2	119.4	119.40
3	117.7	117.73
4	149.1	149.06
5	118.3	118.36
6	116.2	116.23
7	76.0	75.98
8	41.8	41.88
9	81.0	80.97
10	174.0	173.95
11	36.5	36.42
12	26.7	26.78
13	58.3	58.37
14	145.8	145.77
15	114.0	113.94
17	53.3	53.18
1’	146.3	146.25
2’	130.0	130.03
3’	113.3	113.45
4’	151.2	151.18
5’	116.1	116.07
6’	123.0	122.93
7’	29.5	29.47
8’	123.8	123.85
9’	132.1	131.95
10’	16.2	16.15
11’	41.0	40.90
12’	27.8	27.79
13’	125.5	125.53
14’	136.8	136.80
15’	16.4	16.37
16’	40.8	40.79
17’	27.6	27.56
18’	125.4	125.41
19’	136.0	135.99
20’	26.0	25.90
21’	17.8	17.76

3. NMR Spectra.



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O
OMe
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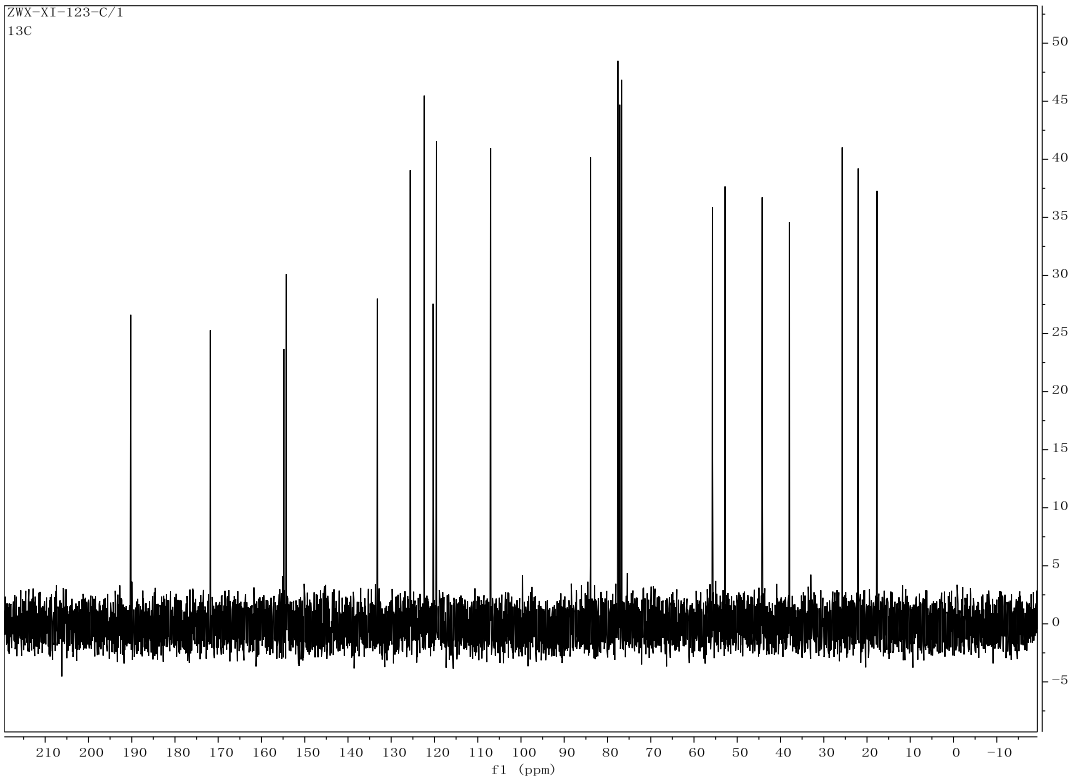
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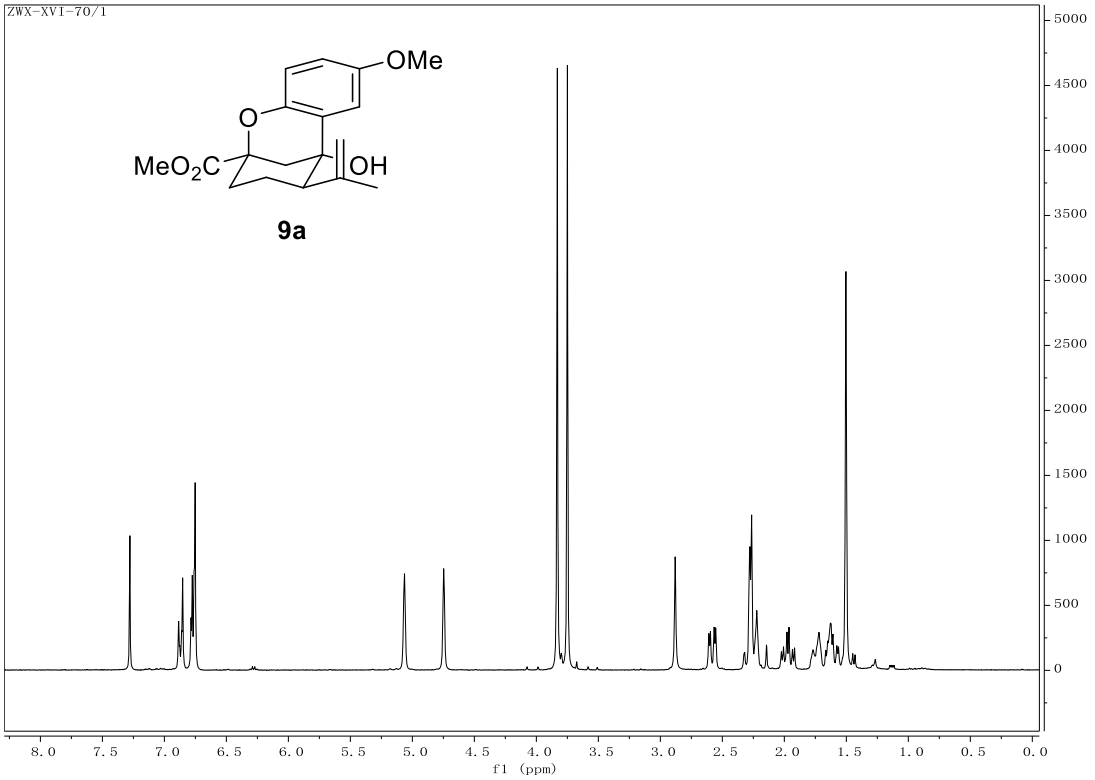
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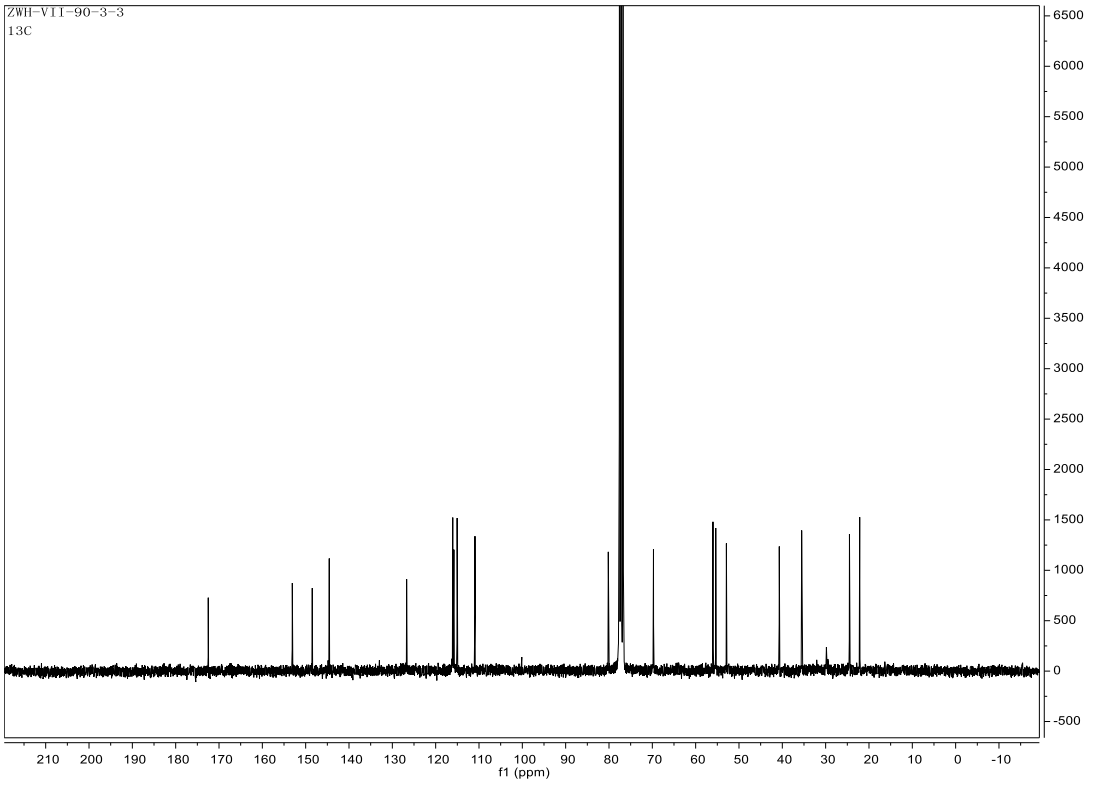
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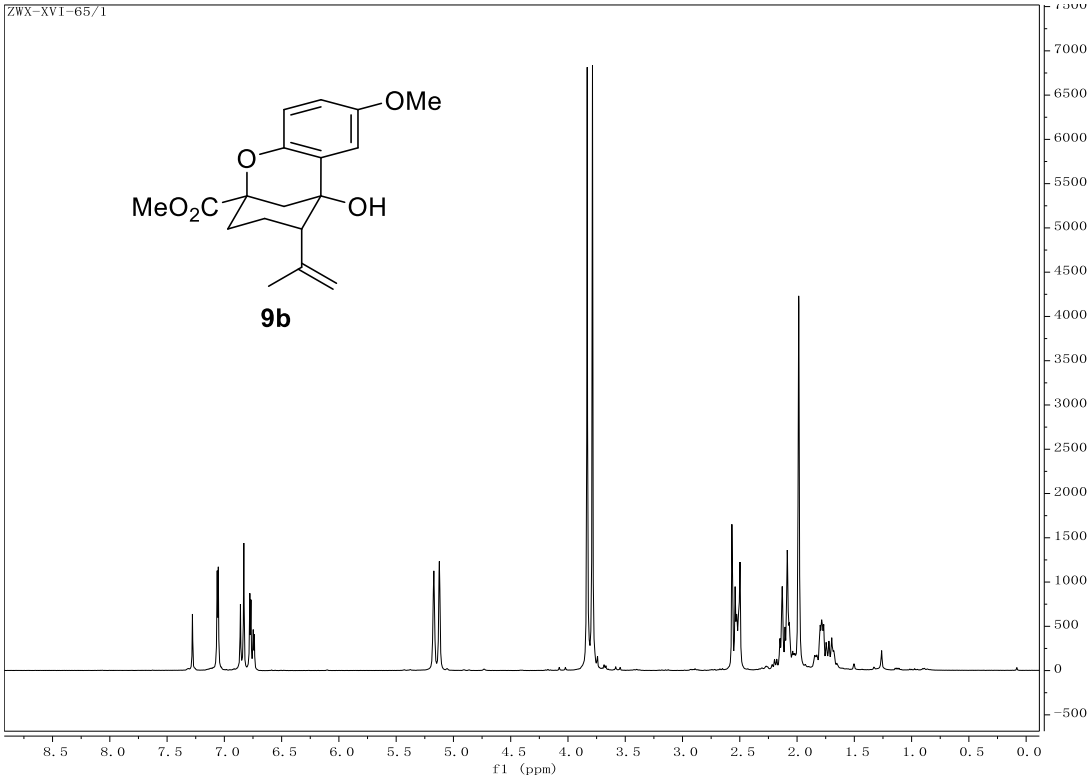
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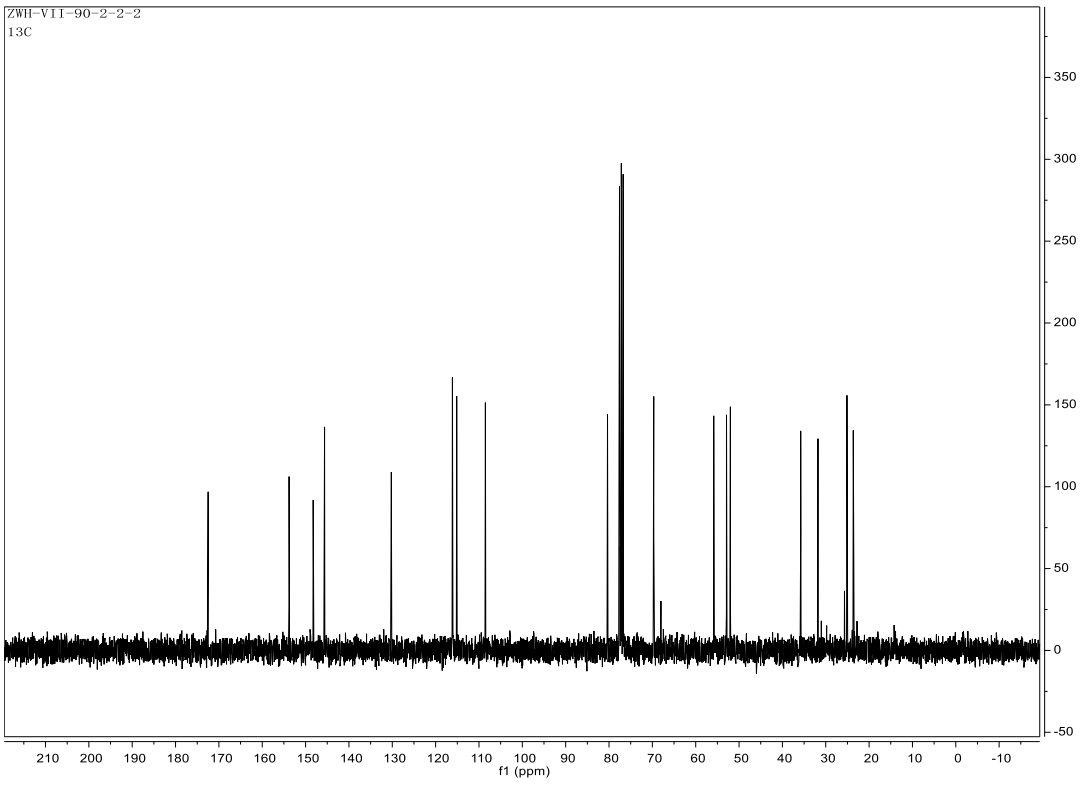
f1 (ppm)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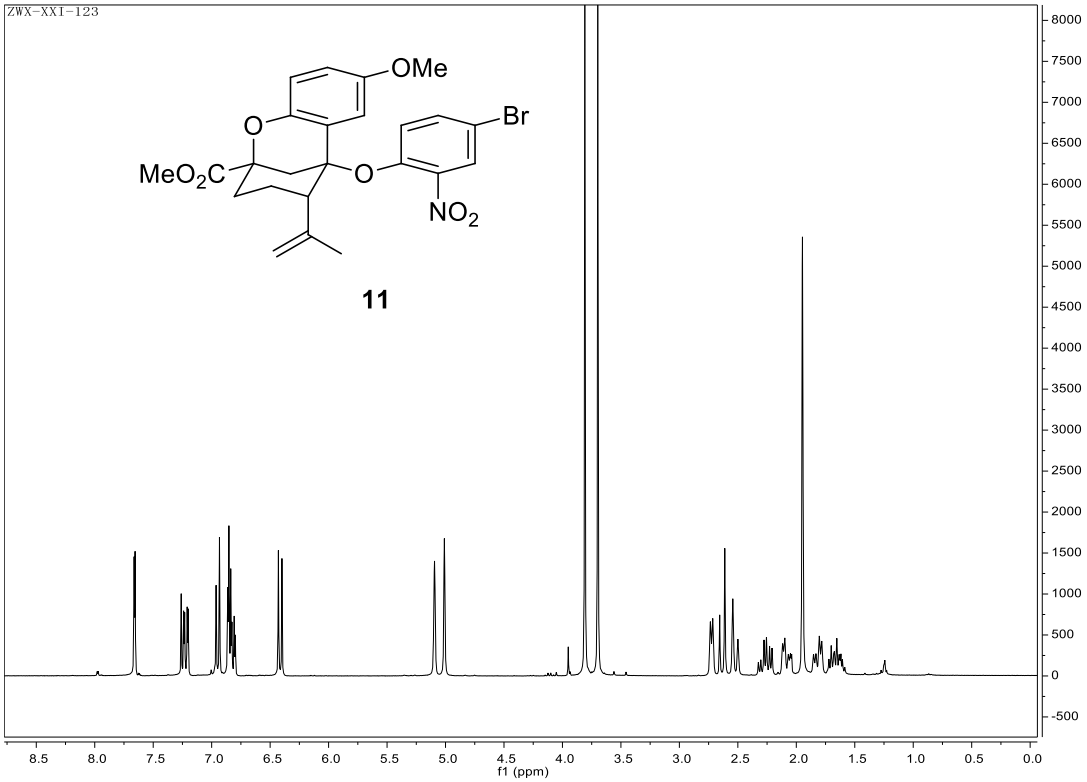
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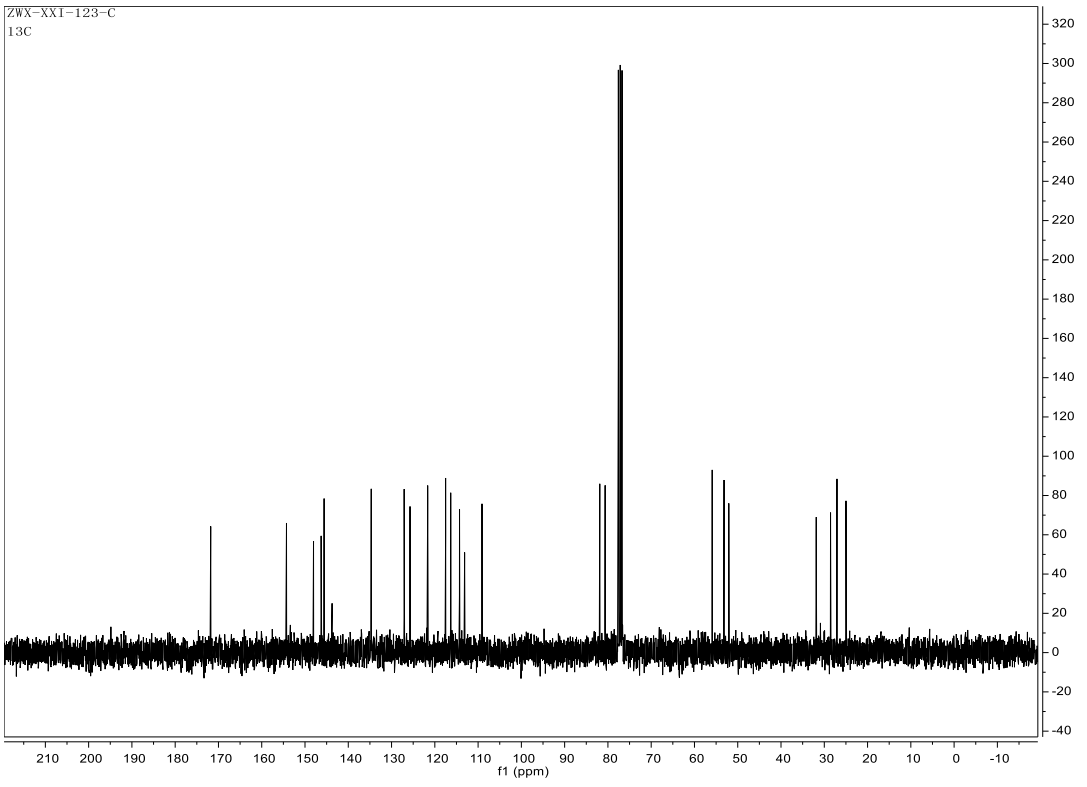
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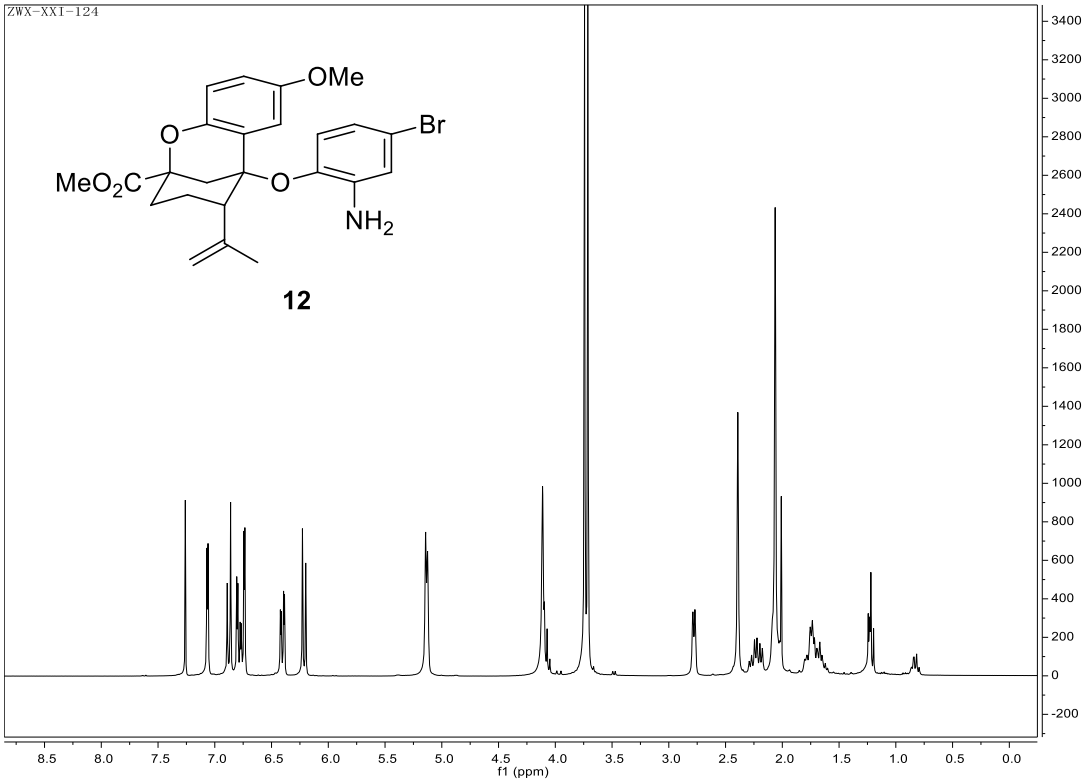
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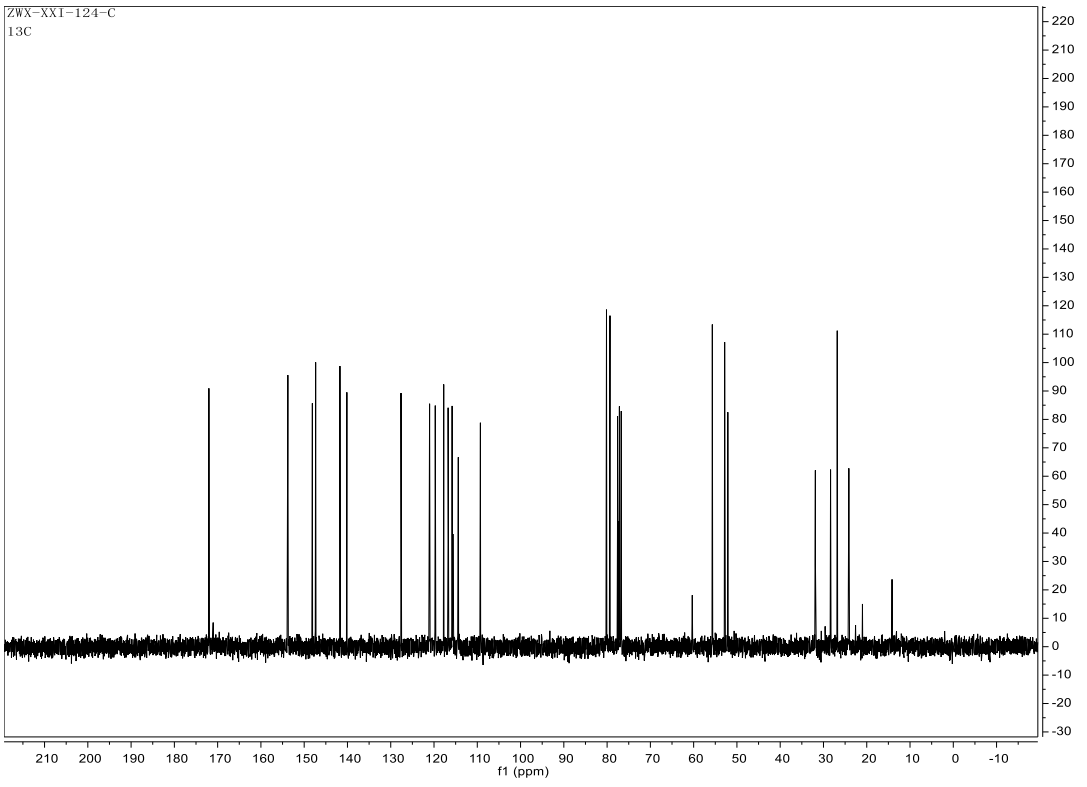
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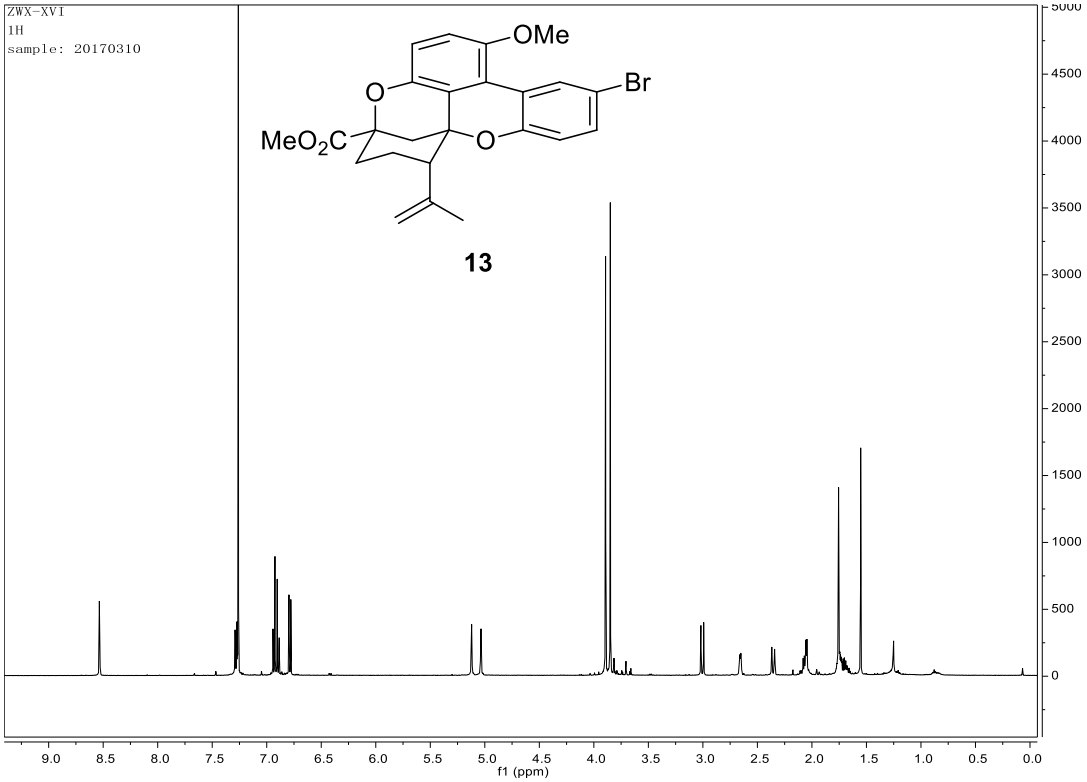
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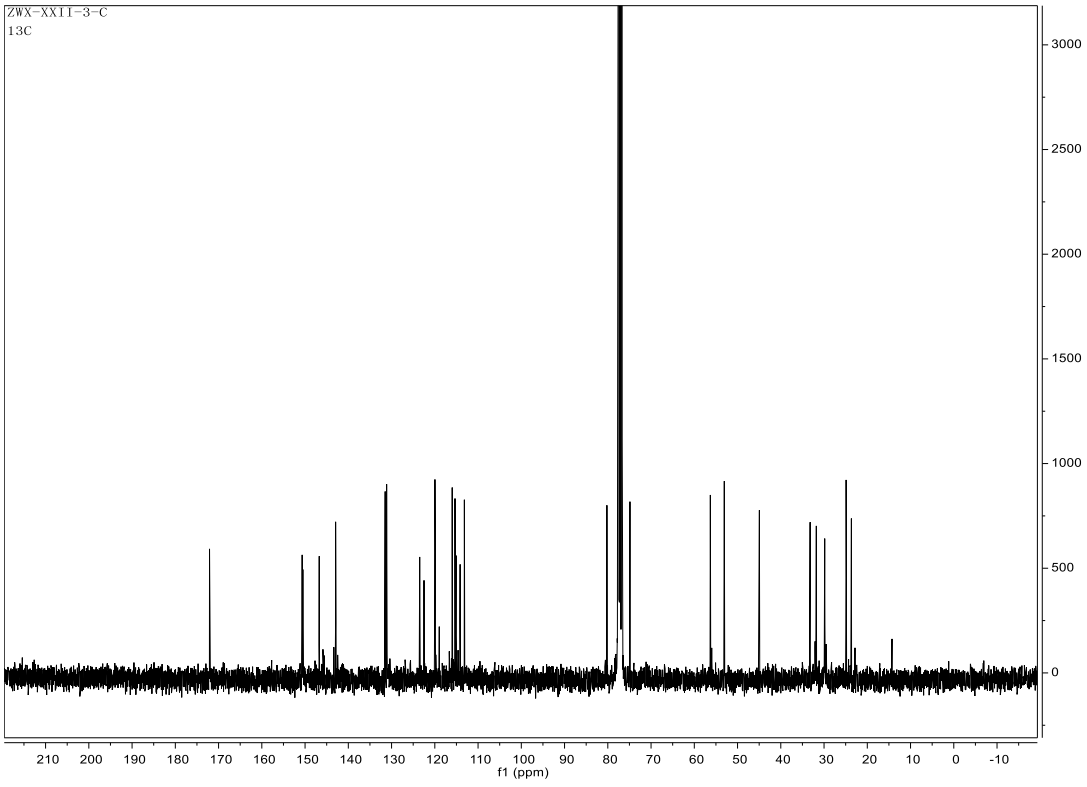
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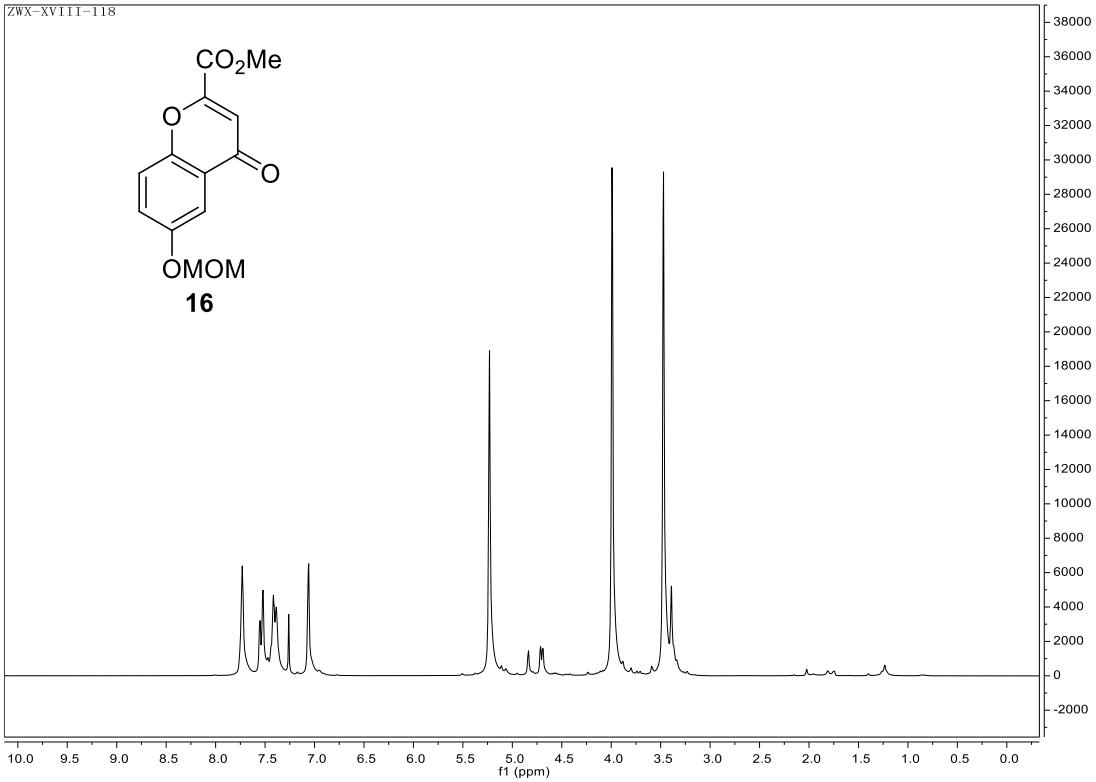
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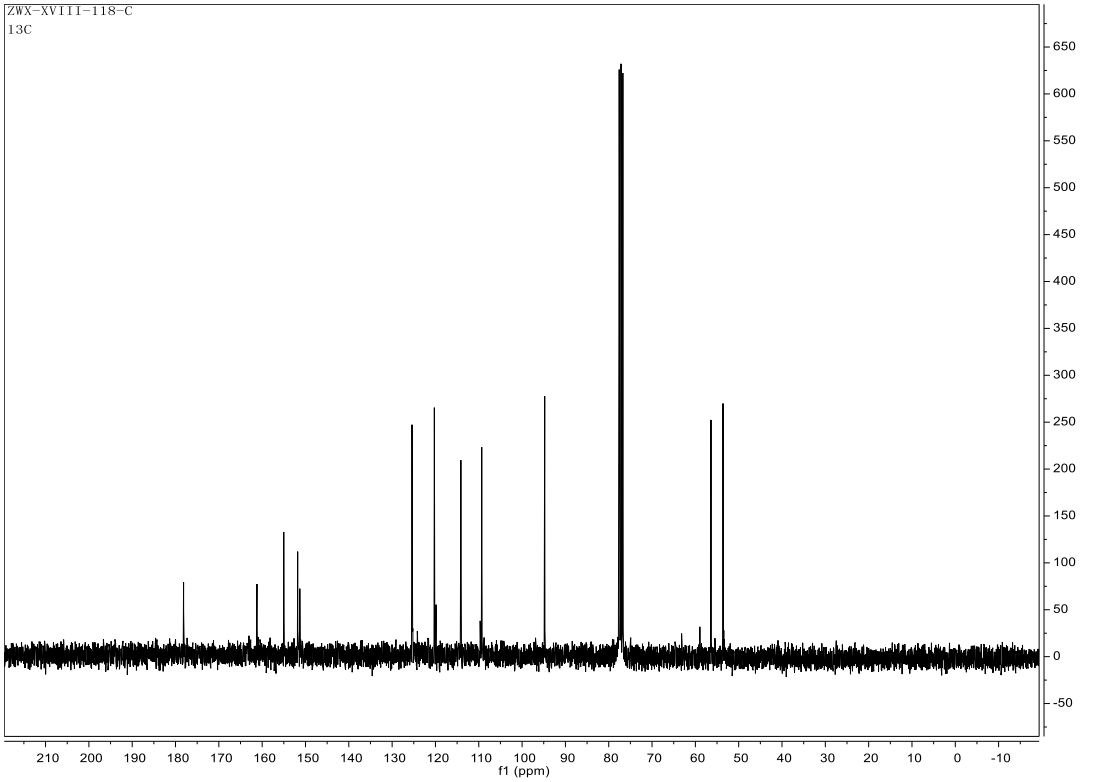
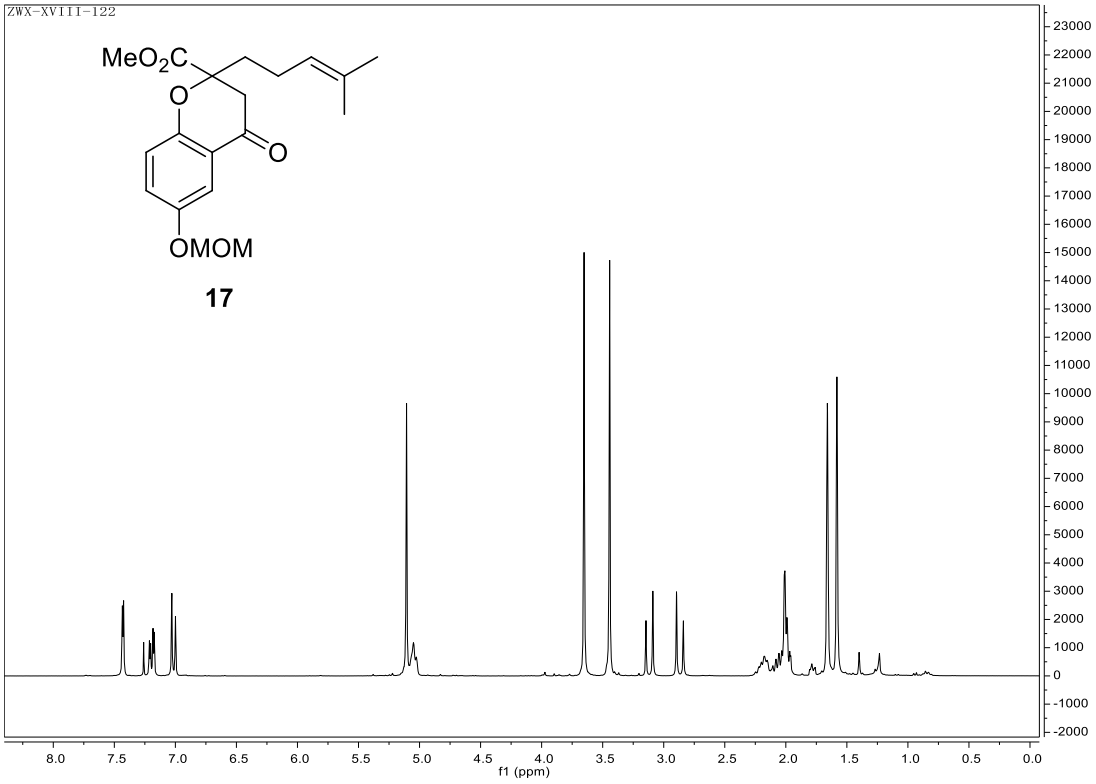
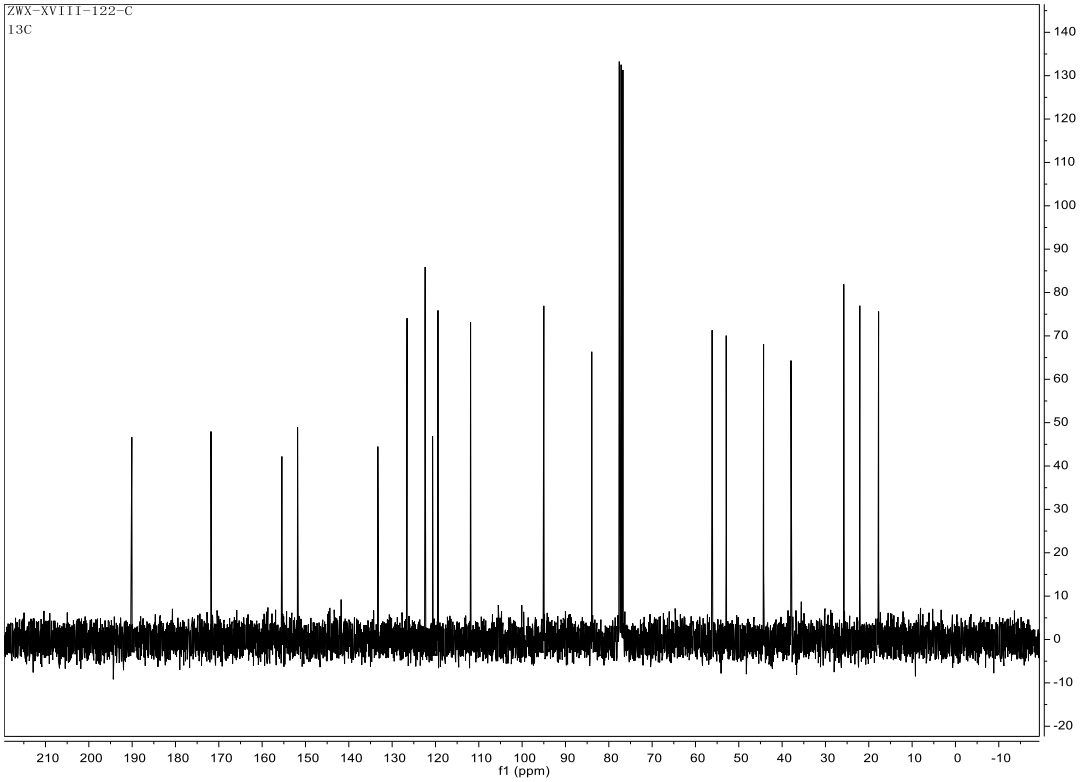
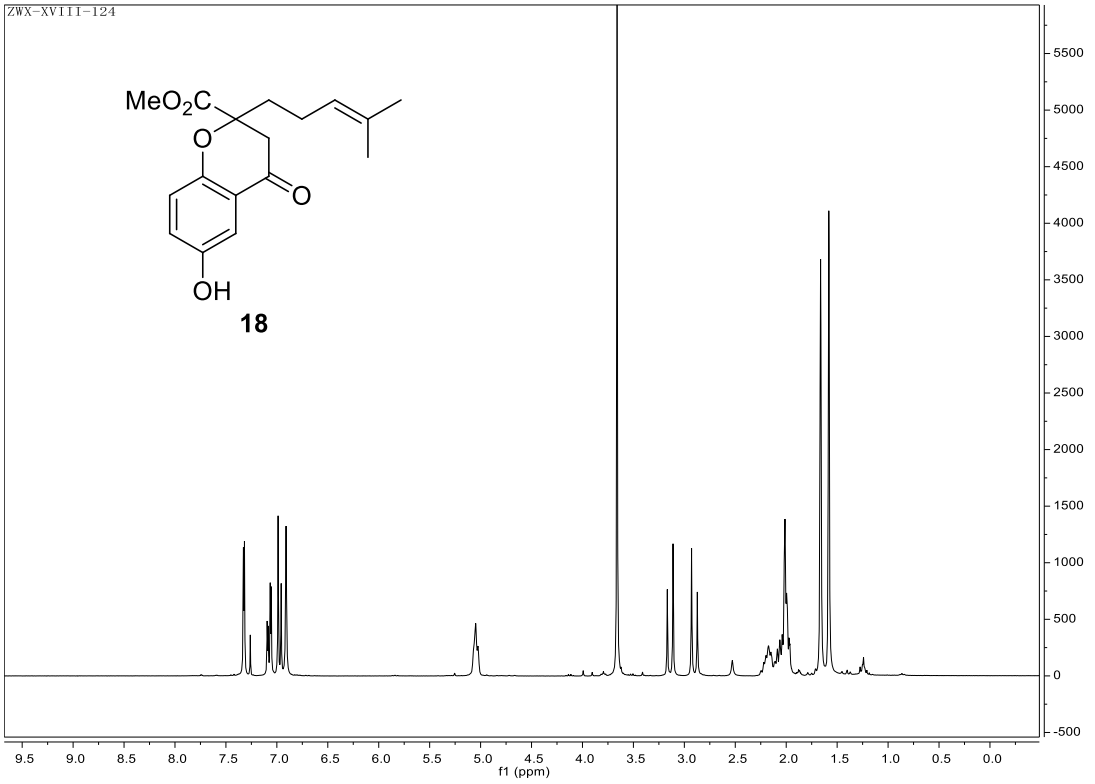
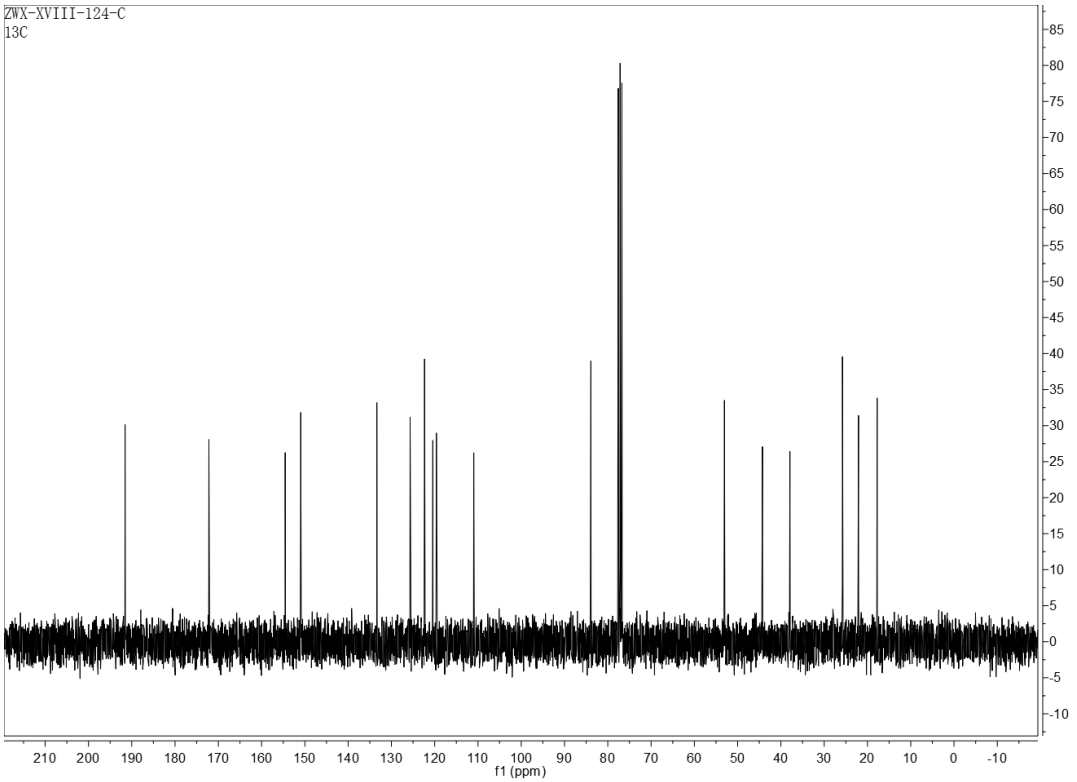
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

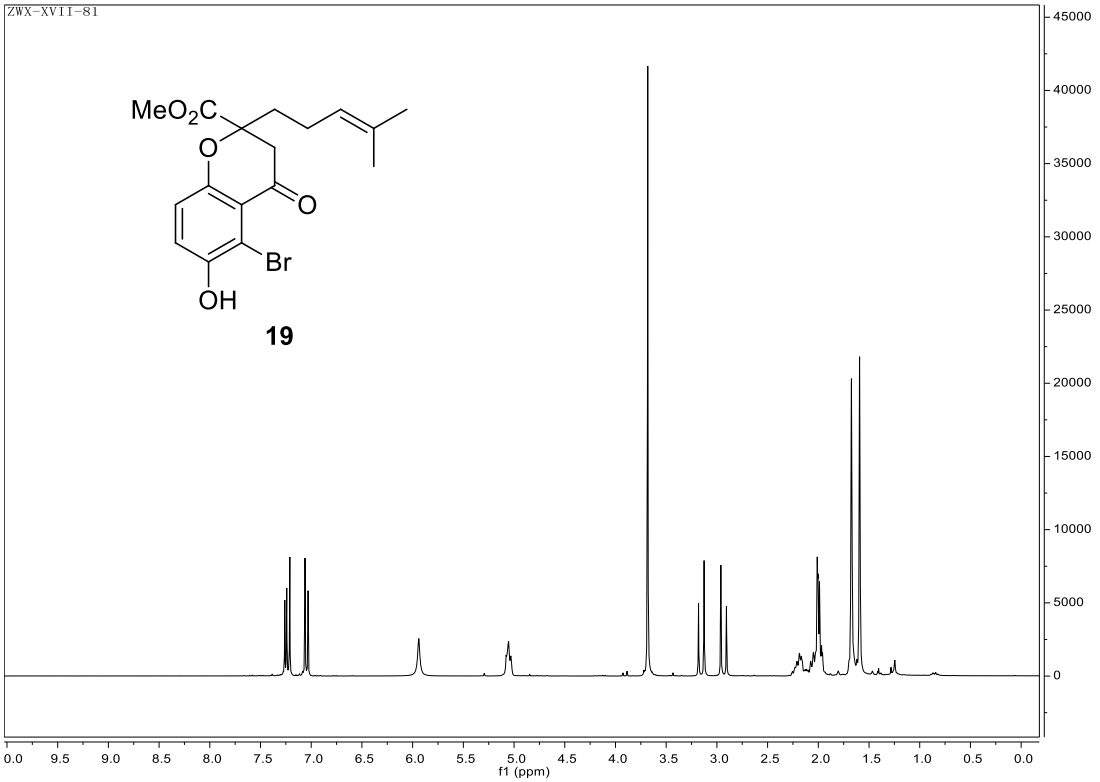

ZWX-XVIII-118-C
13C
650
600
550
500
450
400
350
300
250
200
150
100
50
0
-50
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

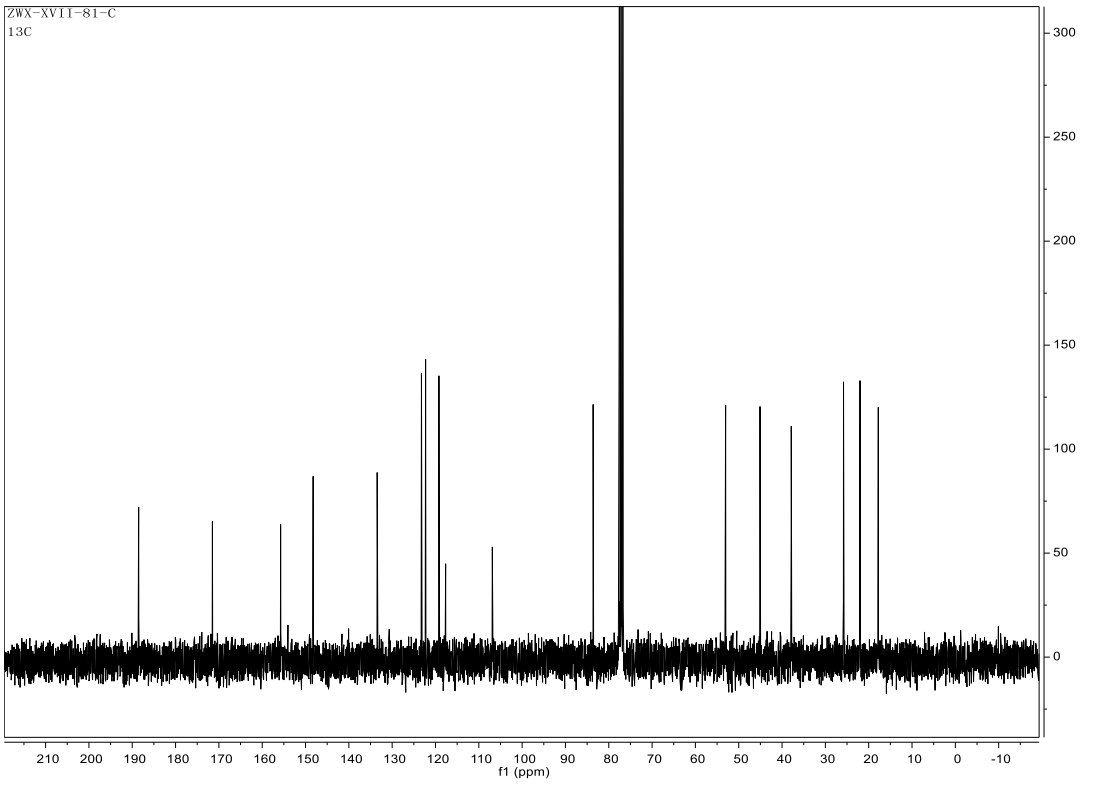

ZWX-XVIII-122
MeO2C
O
O
OMOM
17
f1 (ppm)

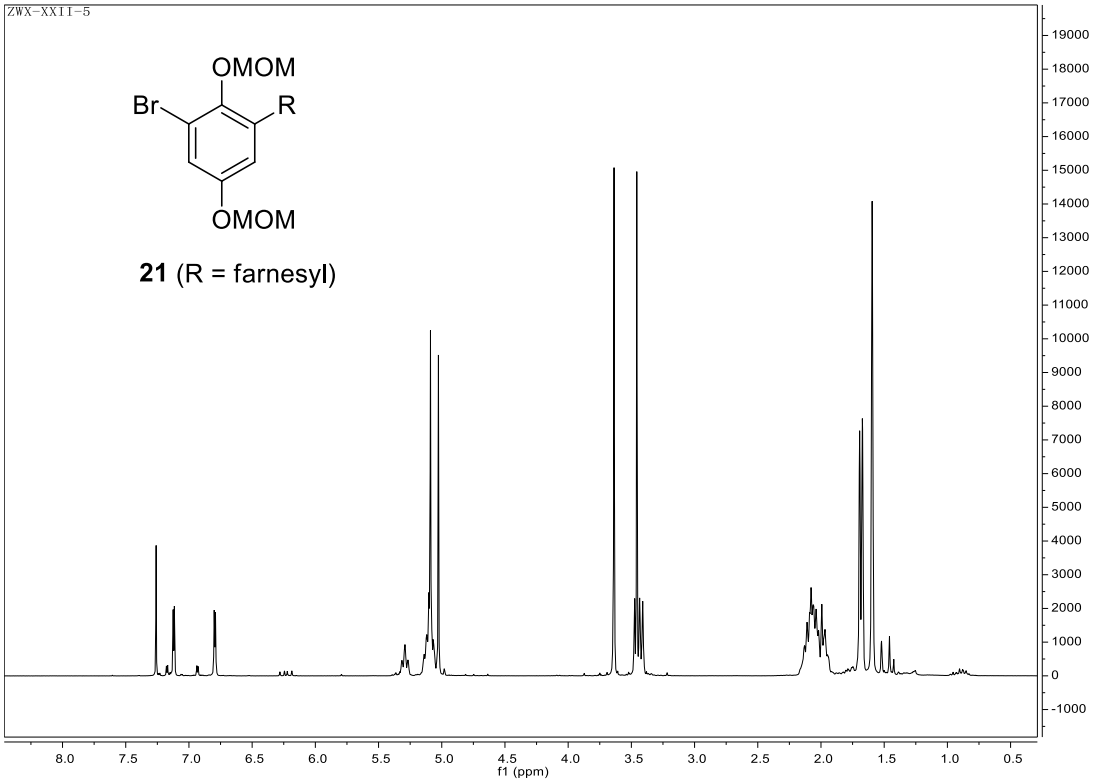

ZWX-XVIII-122-C
13C
f1 (ppm)

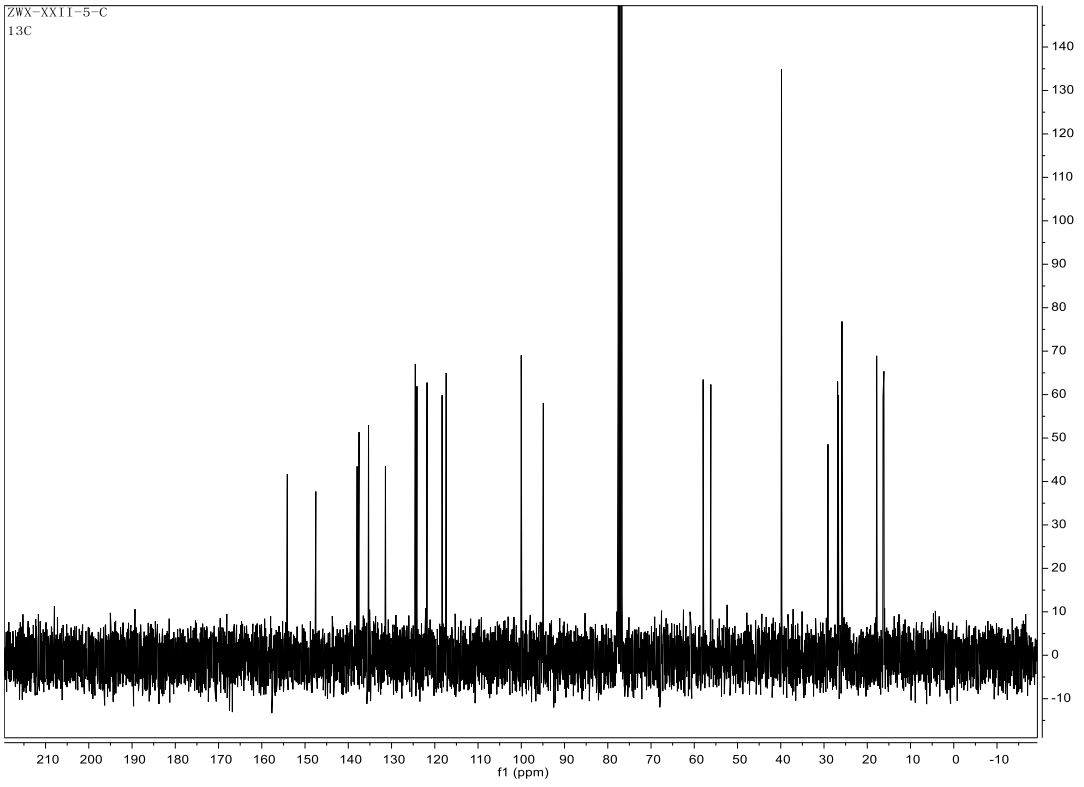

ZWX-XVIII-124
MeO2C
O
O
OH
18
f1 (ppm)

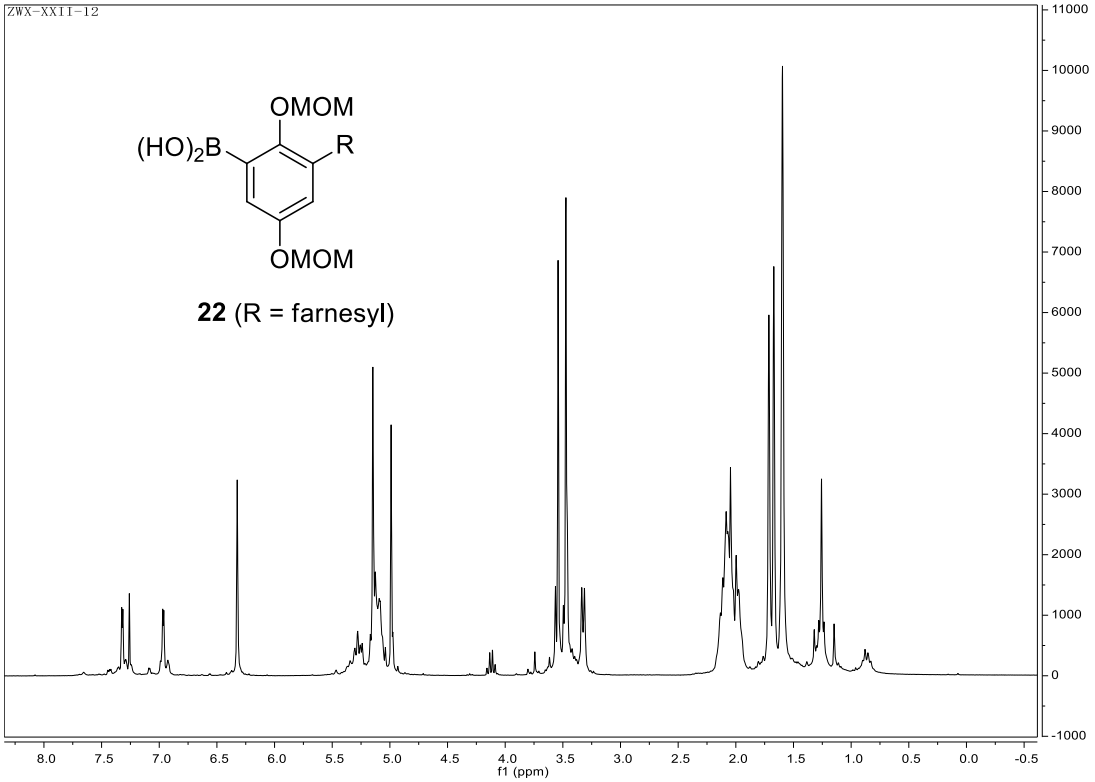

ZWX-XVIII-124-C
13C
f1 (ppm)

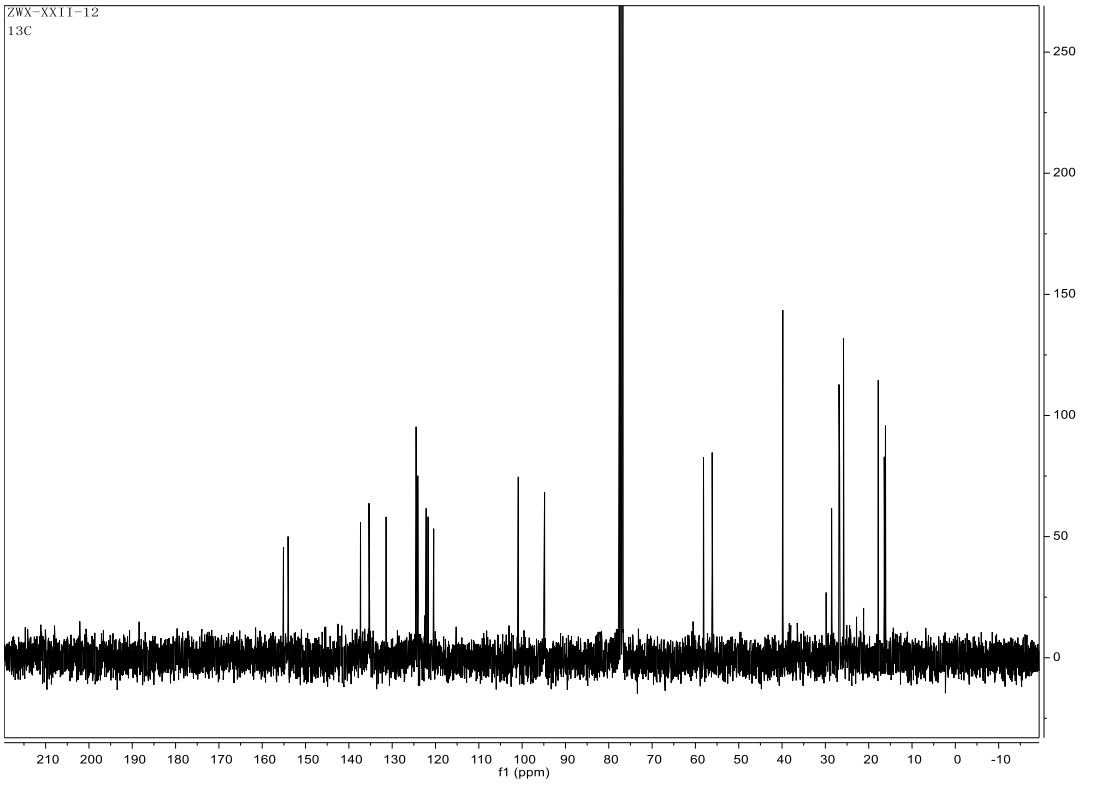

ZWX-XVII-81
MeO2C
O
O
Br
OH
19
f1 (ppm)

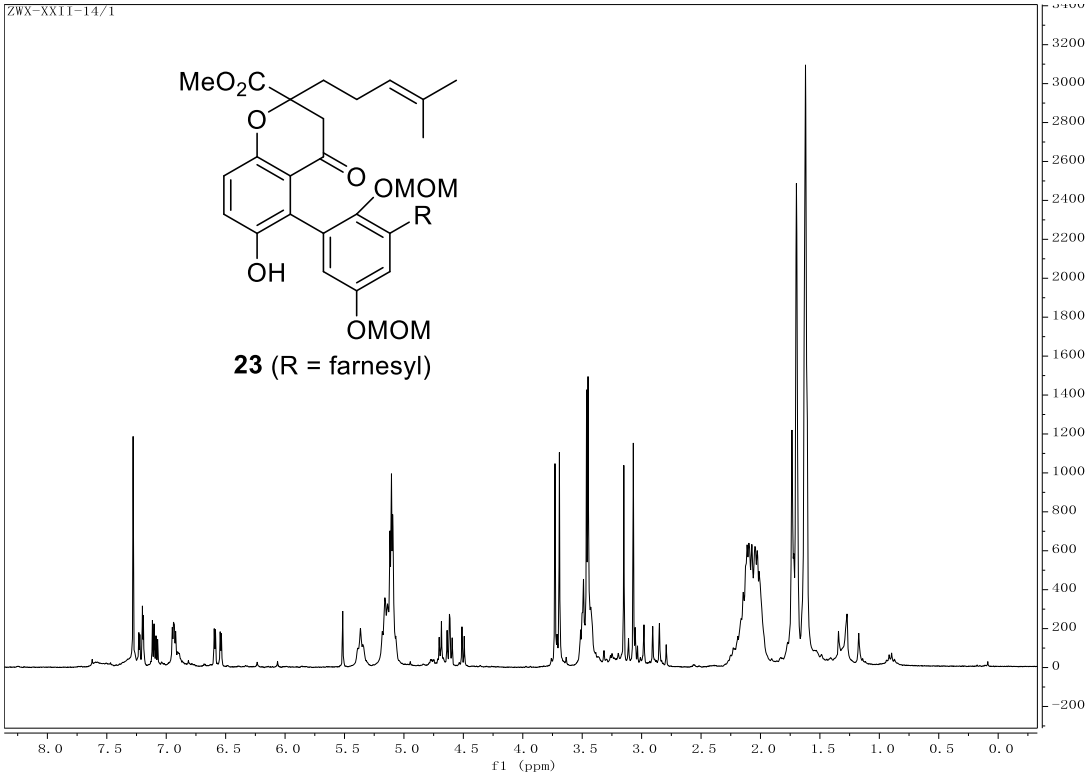

ZWX-XVII-81-C
13C
f1 (ppm)

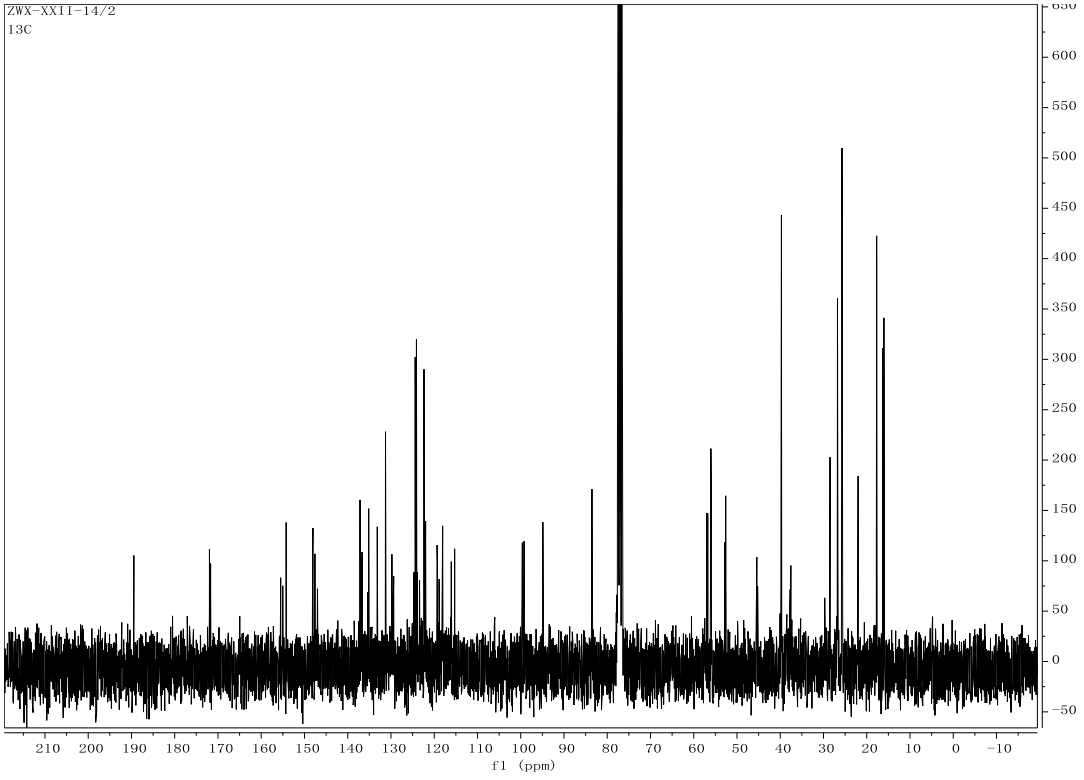

ZWX-XXII-5
OMOM
Br
R
OMOM
21 (R = farnesyl)
f1 (ppm)

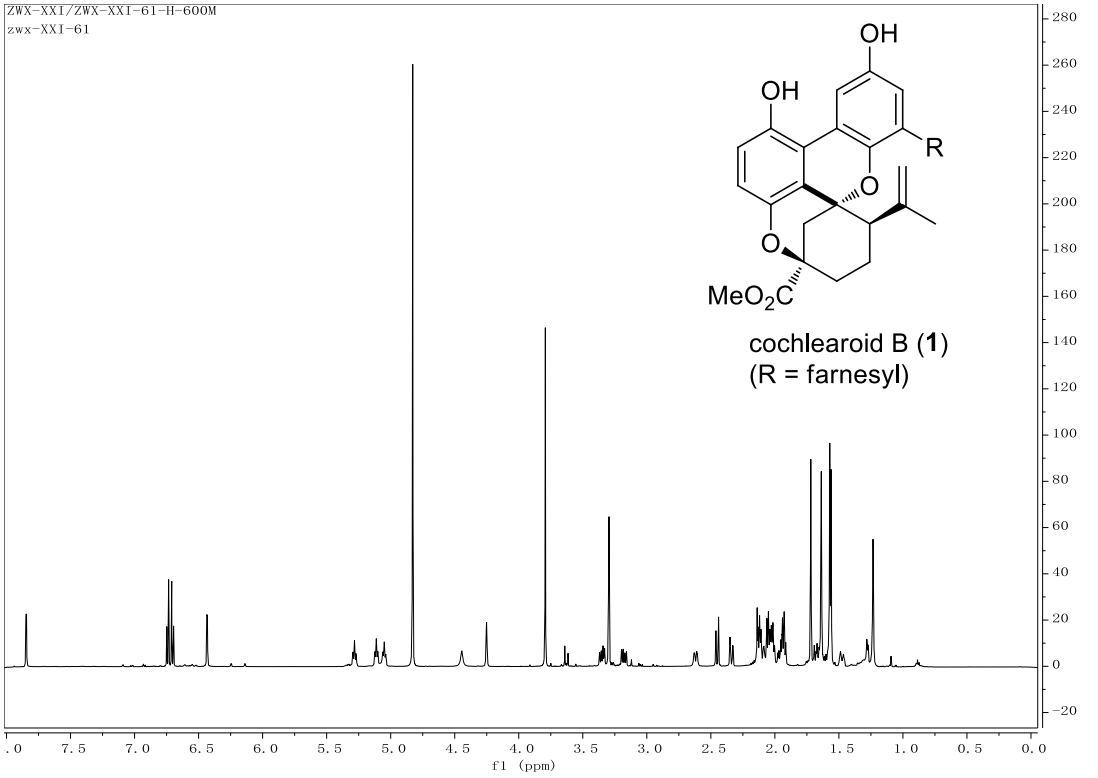

ZWX-XXII-5-C
13C
f1 (ppm)

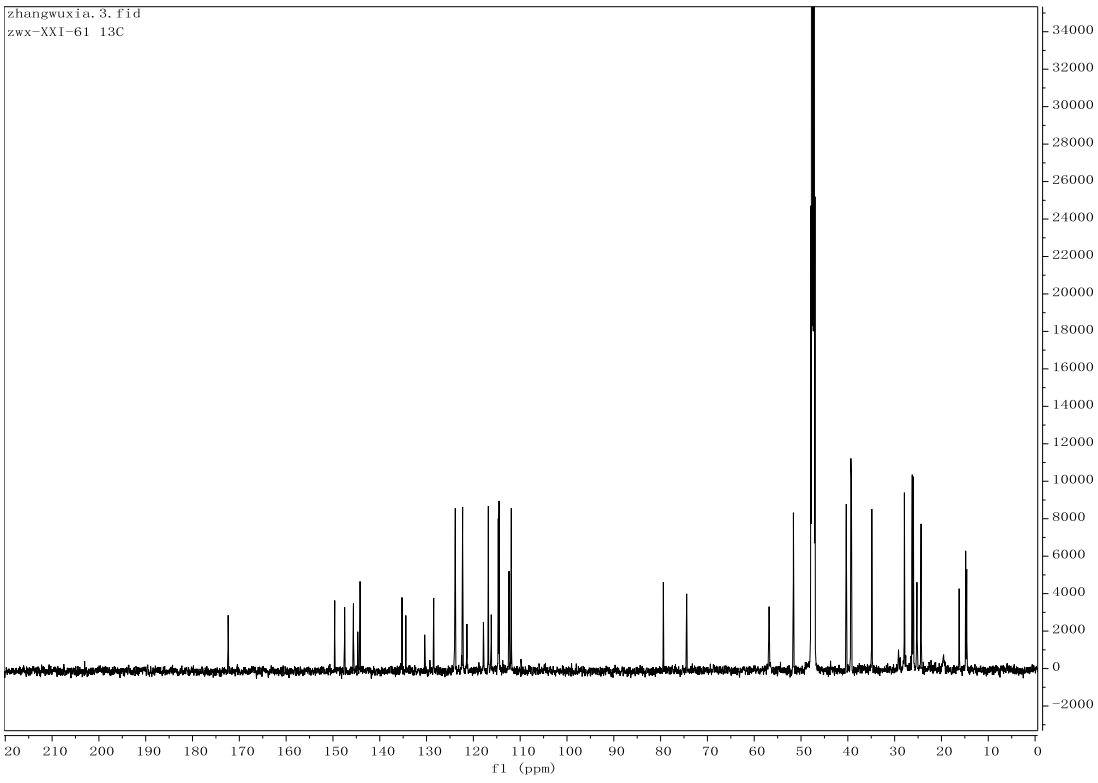

ZWX-XXII-12
OMOM
(HO)2B
R
OMOM
22 (R = farnesyl)
f1 (ppm)


ZWX-XXII-12
13C
f1 (ppm)

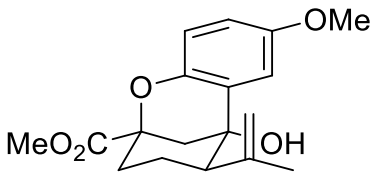

ZWX-XXII-14/1
MeO2C
O
O
OMOM
R
OH
OMOM
23 (R = farnesyl)
f1 (ppm)


ZWX-XXII-14/2
13C
f1 (ppm)

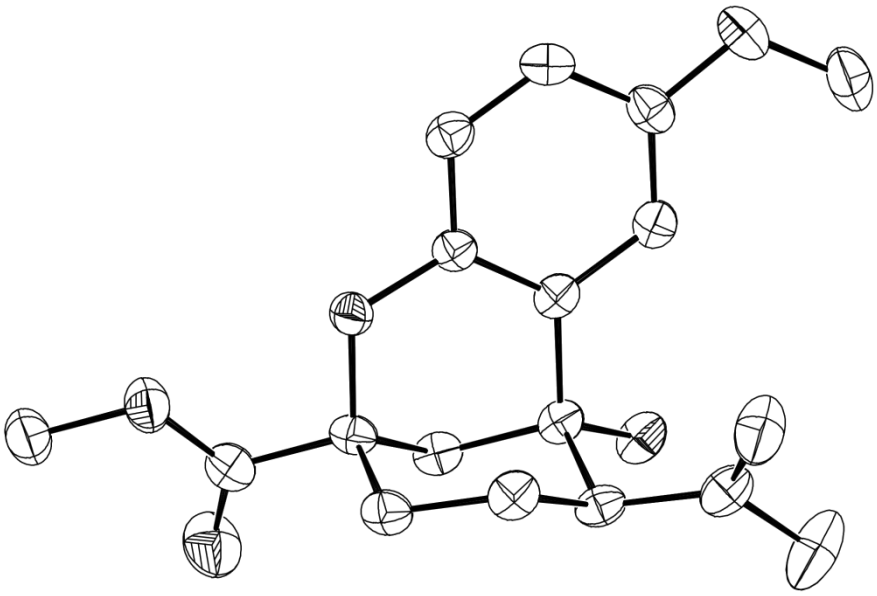

ZWX-XXI/ZWX-XXI-61-H-600M
zwx-XXI-61
OH
OH
R
O
O
MeO2C
cochlearoid B (1)
(R = farnesyl)
f1 (ppm)


zhangwuxia.3.fid
zwx-XXI-61 13C
f1 (ppm)

4. X-ray data.



9a



Crystal Data and Details of the Structure Determination

for: C101 P b c a R = 0.06

Crystal Data

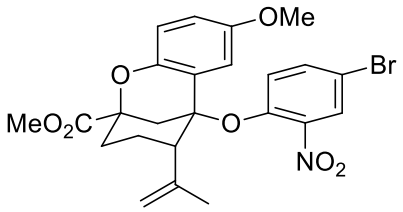
Formula			C18 H22 O5
Formula Weight			318.36
Crystal System			orthorhombic
Space group		Pbca	(No. 61)
a, b, c [Angstrom]	13.248(8)	11.319(7)	21.558(12)
V [Ang**3]			3233(3)
Z			8
D(calc) [g/cm**3]			1.308
Mu(MoKa) [/mm]			0.095
F(000)			1360
Crystal Size [mm]		0.13 x	0.15 x 0.16

Data Collection

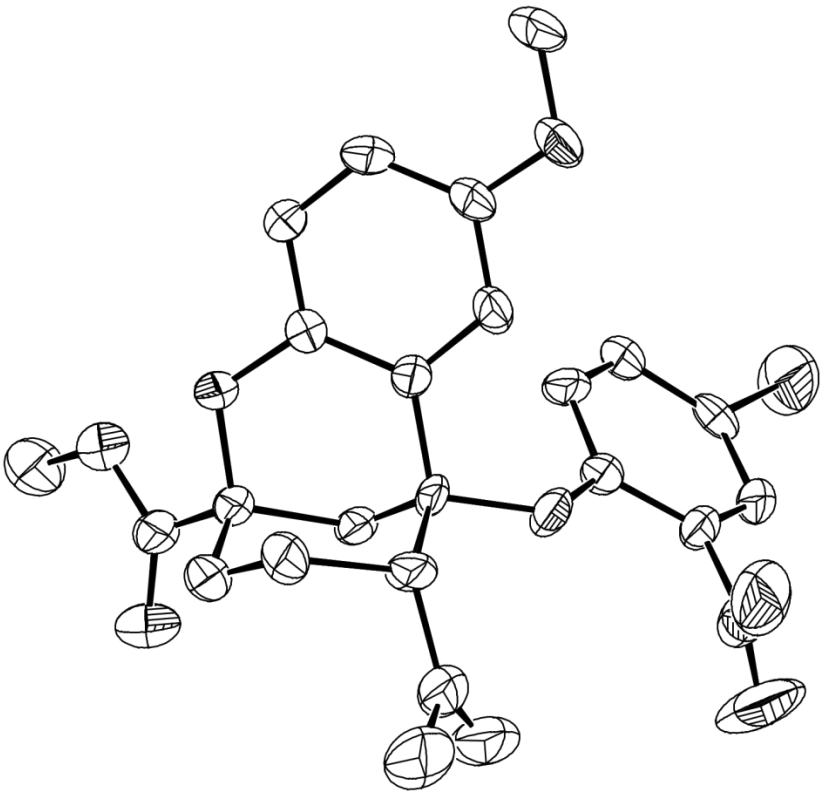
Temperature (K)		296
Radiation [Angstrom]	MoKa	0.71073
Theta Min-Max [Deg]		1.9, 26.4
Dataset	-16: 15 ;	-7: 14 ; -26: 26
Tot., Uniq. Data, R(int)	17621,	3322, 0.124
Observed data [I > 2.0 sigma(I)]		2258

Refinement

Nref, Npar	3322, 212
R, wR2, S	0.0631, 0.1671, 0.99
w = ^2^(FO^2^)+(0.0897P)^2^] WHERE P=(FO^2^+2FC^2^)/3'	
Max. and Av. Shift/Error	0.00, 0.00
Min. and Max. Resd. Dens. [e/Ang^3]	-0.22, 0.73



11



Crystal Data and Details of the Structure Determination

for: aaaaa P -1 R = 0.05

Crystal Data

Formula			C24 H24 Br N O7
Formula Weight			518.35
Crystal System			triclinic
Space group		P-1	(No. 2)
a, b, c [Angstrom]	8.5808(17)	10.449(2)	27.944(6)

alpha, beta, gamma [deg]	83.51(3)	88.58(3)	66.94(3)
V [Ang**3]			2290.0(10)
Z			4
D(calc) [g/cm**3]			1.503
Mu(MoKa) [/mm]			1.841
F(000)			1064
Crystal Size [mm]		0.16 x	0.18 x 0.20

Data Collection

Temperature (K)		296
Radiation [Angstrom]	MoKa	0.71073
Theta Min-Max [Deg]		2.1, 25.1
Dataset	-10: 7 ; -12: 12 ; -32: 33	
Tot., Uniq. Data, R(int)	11905,	8000, 0.027
Observed Data [I > 0.0 sigma(I)]		4907

Refinement

Nref, Npar	8000, 620
R, wR2, S	0.0532, 0.1359, 1.01
w = ^2^(FO^2^)+(0.0631P)^2^] WHERE P=(FO^2^+2FC^2^)/3'	
Max. and Av. Shift/Error	0.00, 0.00
Min. and Max. Resd. Dens. [e/Ang^3]	-0.24, 0.40