Total Synthesis of (-)-Akaol A via Conformational Constraint Strategy

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Supporting Information

Table of Contents

General Information……..S1

Experimental details and characterization data for compounds…….....S2

Comparison of ^{1}H and ^{13}C NMR of akaol A with Literature……..……..S13

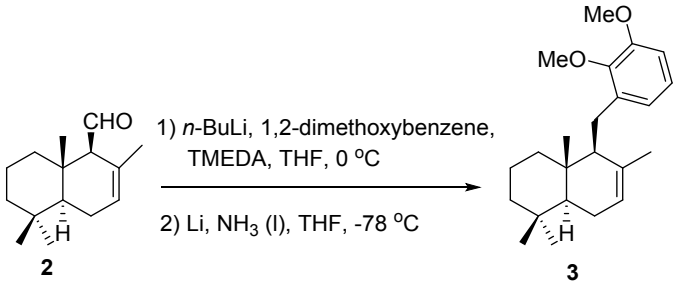
^{1}H and ^{13}C NMR spectra of products……S15-29

General Experimental Procedures: All reactions were performed with dry solvents under anhydrous conditions, unless otherwise noted. Dry tetrahydrofuran (THF) were obtained by distillation over sodium. Dichloromethane were obtained by distillation over calcium hydride. Reagents were used as received without further purification, unless otherwise stated. Silica gel (200-300 mesh, Qingdao Marine Chemical Ltd., China), light petroleum ether (bp 60–90 ºC) and ethyl acetate were used for product purification by flash column chromatography. Melting Point (MP) was determined with a X-4 Taike micro melting point apparatus and was uncorrected. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on Bruker Avance 400 spectrometer at 400 MHz. Carbon-13 nuclear magnetic resonance (^{13}C NMR) was recorded on Bruker Avance 400 and 600 spectrometer at 100 and 150 MHz. $CDCl_3$ was referenced to either TMS (0 ppm) or the solvent peaks (7.26 ppm and 77.0 ppm for ^{1}H and ^{13}C, respectively). CD_3OD was referenced to the solvent peaks (3.31 ppm and 49.0 ppm for ^{1}H and ^{13}C, respectively). .IR spectra were recorded on a Bruker Tensor 27 FT-IR spectrometer. Mass spectra were recorded on

a VG-Auto-Spec-3000 spectrometer. High-resolution mass spectral analysis (HRMS) data were recorded via electron impact mass spectrometry using a time of flight analyzer.

Experimental details and characterization data for compounds

(4aS,5S,8aS)-5-(2,3-dimethoxybenzyl)-1,1,4a,6-tetramethyl-1,2,3,4,4a,5,8,8a-octahydronaphthalene (3):

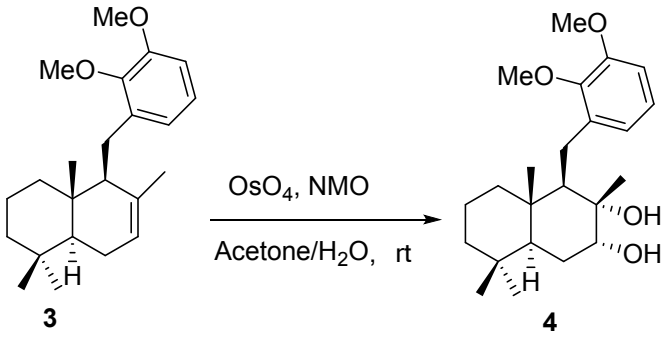


A flame-dried round-bottom flask charged with 1,2-dimethoxybenzene (1.88 g, 13.6 mmol) under nitrogen atmosphere in dry THF (18 mL) was added 2.5 M solution of *n*-BuLi in Hexane (7.08 ml, 17.7 mmol) in portions via syringe at 0 °C and at the same temperature TMEDA (2.65 ml, 17.7 mmol) was added dropwise via syringe. The reaction mixture was allowed to stand for continuous stirring for 60 min followed by dropwise addition of compound **2** (1.5 g, 6.8 mmol) in dry THF (6 ml). The stirring was continued till TLC showed complete consumption of starting materials. The reaction was quenched with saturated aqueous NH_4Cl (15 mL), extracted with EtOAc (3×15 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give the crude product as yellow oil.

To a stirred solution of liquid ammonia (30 mL) and THF (30 ml) at -78 °C, was added lithium (387 mg, 55.7 mmol) piece by piece, then added dropwise a solution of the crude product above in anhydrous THF(20 mL). The stirring was continued for 3 h at -78 °C, then a saturated aqueous solution of NH_4Cl (10 mL) was added to the residue. The aqueous layer was extracted with EtOAc (3×15 mL) and the combined organic layer was washed with water, brine and dried over Na_2SO_4 and concentrated in a rotary evaporator under vacuum. The crude product was purified by flash chromatography (PE/EtOAc = 50 : 1) to afford 1.62 g of compound **3** as yellow oil in 70% yield, R_f = 0.6 (5% EtOAc in PE); IR (KBr) ν_{max} 3442, 2944, 2846, 1582, 1477, 1303, 1270, 1222, 1079,

1010, 757; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.98 (t, *J* = 7.9 Hz, 1H), 6.88 (d, *J* = 7.6 Hz, 1H), 6.74 (d, *J* = 7.9 Hz, 1H), 5.36 (s, 1H), 3.85 (s, 3H), 3.80 (s, 3H), 2.73 (dd, *J* = 15.2, 9.1 Hz, 1H), 2.65 (dd, *J* = 15.1, 2.4 Hz, 1H), 2.38 (s, 1H), 2.07 – 1.76 (m, 3H), 1.59 – 1.53 (m, 1H), 1.47 –1.45 (m, 1H), 1.44 (s, 3H), 1.41 (d, *J* = 2.9 Hz, 1H), 1.28 (dd, *J* = 11.9, 5.0 Hz, 1H), 1.24 – 1.14 (m, 1H), 1.10 (dd, *J* = 13.1, 3.6 Hz, 1H), 0.91 (s, 3H), 0.90 (s, 3H), 0.87 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.7, 146.9, 137.9, 135.9, 123.5, 121.9, 121.4, 109.3, 60.4, 55.6, 54.6, 50.3, 42.3, 39.5, 36.9, 33.3, 33.1, 26.2, 23.8, 22.5, 22.0, 19.0, 13.9; HRMS (ESIMS) calcd for $C_{23}H_{34}O_2$ $[M]^+$: 342.2559, found 342.2568; $[\alpha]_{589}^{23.7\,°C}$ = -20.111 (c = 0.300, $CHCl_3$).

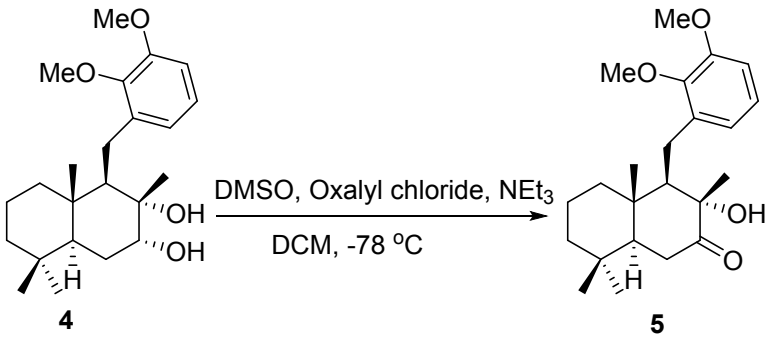
(1R,2S,3R,4aS,8aS)-1-(2,3-dimethoxybenzyl)-2,5,5,8a-tetramethyldecahydronaphthalene-2,3-diol (4)



A solution of OsO_4 (52 mg, 0.21 mmol) in water (2.6 mL) was added to a solution of compound **3** (700 mg, 2.05 mmol) and 4-methylmorpholine N-oxide (360 mg, 3.08 mmol) in acetone/H_2O (9/1) (7 mL), the reaction mixture was stirred at 25 °C for 40 h. The saturated aqueous $Na_2S_2O_3$ (10 mL) was added, then the mixture was stirred at the same temperature for 2 h. The mixture was extracted with EtOAc (3×10 mL) and the combined organic layers were washed with water, brine and dried over Na_2SO_4 and concentrated in a rotary evaporator under vacuum. The crude product was purified by column chromatography on silica gel (PE/EtOAc = 4:1) to afford 610 mg of pure diol **4** in 79% yield as colorless oil, R_f = 0.3 (35% EtOAc in PE); IR (KBr) ν_{max} 3437, 2932, 1583, 1475, 1398, 1272, 1080, 1009, 749; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.98 (t, *J* = 7.9 Hz, 1H), 6.85 (d, *J* = 7.5 Hz, 1H), 6.76 (d, *J* = 7.6 Hz, 1H), 3.88 (s, 3H), 3.85 (s, 3H), 3.65 (s, 2H), 2.91 (s, 1H), 2.81 (dd, *J* = 14.6, 5.1 Hz, 1H), 2.60 (dd, *J* = 14.6, 4.7 Hz, 1H), 1.91 (t, *J* = 4.9 Hz, 1H), 1.85 (dd, *J* = 11.7, 2.9 Hz, 1H), 1.77 (d, *J* = 12.6 Hz, 1H), 1.62 (d, *J* = 13.3 Hz, 1H), 1.57 (dd, *J* = 6.0, 2.5 Hz, 1H), 1.51 (s, 1H), 1.39 (ddd, *J* = 25.1, 14.2, 9.2 Hz, 3H), 1.27 (d, *J* = 11.4 Hz, 3H), 1.14 (td, *J*

= 13.4, 3.9 Hz, 1H), 0.91 (s, 3H), 0.86 (s, 3H), 0.80 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.5, 146.2, 137.6, 124.1, 122.9, 110.0, 74.9, 74.2, 60.7, 56.2, 55.7, 46.2, 41.7, 40.0, 39.1, 33.1, 32.7, 25.4, 24.9, 23.6, 21.6, 18.6, 14.9; HRMS (ESIMS) calcd for $C_{23}H_{36}O_4$ $[M]^+$: 376.2614, found 376.2617; $[\alpha]_{589}^{23.5\,^{\circ}C}$ = + 24.300 (c = 1.030, $CHCl_3$).

(3S,4R,4aS,8aS)-4-(2,3-dimethoxybenzyl)-3-hydroxy-3,4a,8,8-tetramethyloctahydronaphthalen-2(1H)-one (5)

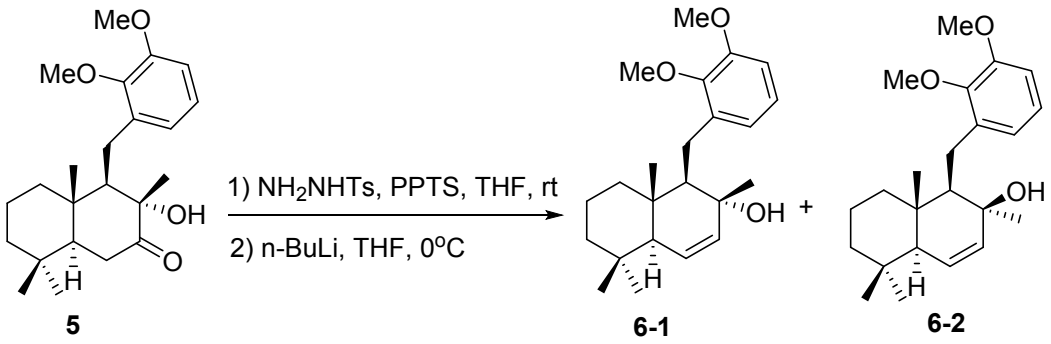


4 **5**

A solution of DMSO (0.38 mL, 5.3 mmol) in CH_2Cl_2 (3 mL) was added to a solution of oxalyl chloride (0.22 mL, 2.6 mmol) in CH_2Cl_2 (3 mL) at -78 °C. After 20 min diol **4** (500 mg, 1.33 mmol) in CH_2Cl_2 (8 mL) was added dropwise followed after 40 min by NEt_3 (1.10 mL, 8.0 mmol) at -78 °C. The reaction mixture was allowed to warm to room temperature for 30 min and concentrated in vacuo. The residue was dissolved in water and extracted with CH_2Cl_2 (3×10 mL). The combined organic extracts were washed with water, dried over anhydrous Na_2SO_4 and concentrated in vacuo. The crude material was purified by flash column chromatography on silica gel (PE/EtOAc = 20:1) to give hydroxyl ketone **5** (408 mg, 82%) as yellow oil, R_f = 0.6 (15% EtOAc in PE); IR (KBr) ν_{max} 3476, 2930, 1708, 1584, 1475, 1269, 1079, 1021, 749; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.00 – 6.92 (m, 2H), 6.72 (dd, *J* = 7.6, 1.7 Hz, 1H), 4.01 (s, 1H), 3.84 (s, 3H), 3.83 (s, 3H), 3.02 (dd, *J* = 14.7, 7.0 Hz, 1H), 2.82 (dd, *J* = 14.5, 3.2 Hz, 1H), 2.60 – 2.48 (m, 2H), 1.91 (dd, *J* = 6.9, 3.6 Hz, 1H), 1.69 – 1.63 (m, 1H), 1.51 (ddd, *J* = 13.8, 12.3, 7.0 Hz, 2H), 1.39 (s, 3H), 1.35 – 1.28 (m, 1H), 1.25 – 1.20 (m, 1H), 1.17 (s, 3H), 1.05 (td, *J* = 13.5, 4.6 Hz, 1H), 0.85 (s, 6H), 0.60 (td, *J* = 13.1, 3.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 214.4, 152.5, 146.5, 137.3, 123.7, 122.2, 109.3, 79.0, 63.5, 60.6, 55.9, 55.6, 41.3, 39.4, 39.1, 35.3, 33.9, 32.9, 23.5, 23.1, 21.1, 18.2, 14.6; HRMS (ESIMS) calcd for $C_{23}H_{34}O_4$ $[M]^+$: 374.2457, found 374.2465; $[\alpha]_{589}^{25.3\,^{\circ}C}$ = -

2.101 (c = 0.730, $CHCl_3$).

(1R,2R,4aS,8aS)-1-(2,3-dimethoxybenzyl)-2,5,5,8a-tetramethyl-1,2,4a,5,6,7,8,8a-octahydronaphthalen-2-ol (6-1) and (6-2)

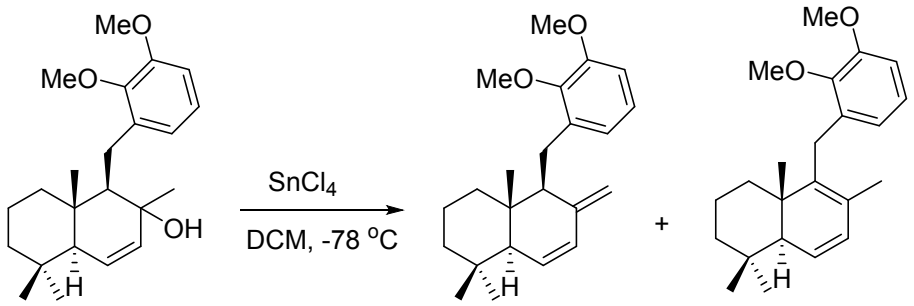


To a solution of ketone **5** (220 mg, 0.59 mmol) in THF (4 mL) at room temperature was added 4-methylbenzenesulfonhydrazide (110 mg, 0.59 mmol), followed by a catalytic amount (ca. 7 mg) of PPTS, the mixture was stirred at 25 °C for 12 h. The reaction was quenched with water (3 mL), extracted with EtOAc (3×3 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give the crude product as yellow solid. This was immediately dissolved in dry THF (4 mL) under argon. To the solution, at 0 °C, was added 2.5 M solution of n-BuLi in Hexane (0.71 ml, 1.76 mmol) in portions via syringe. The mixture was stirred for 5 h with gradual warming to room temperature and sat. aq. NH_4Cl (5 ml) was added. The aqueous layers were extracted with EtOAc (3×3 mL) and the combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was chromatographed on silica gel (PE/EtOAc = 30:1) to give allyl alcohol **6-1** (56.4 mg, 27%) as colorless oil, R_f = 0.5 (20% EtOAc in PE) and allyl alcohol **6-2** (67.8 mg, 32%) as colorless oil, R_f = 0.6 (20% EtOAc in PE); Compound **6-1**: IR (KBr) ν_{max} 3428, 2928, 1707, 1587, 1474, 1380, 1272, 1222, 1081, 1012, 750; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.97 (t, *J* = 7.9 Hz, 1H), 6.90 (d, *J* = 6.8 Hz, 1H), 6.81 – 6.68 (m, 1H), 5.70 (dd, *J* = 10.2, 1.3 Hz, 1H), 5.54 (dd, *J* = 10.2, 3.1 Hz, 1H), 3.85 (s, 3H), 3.84 (s, 3H), 2.81 (dd, *J* = 14.3, 5.6 Hz, 1H), 2.75 (dd, *J* = 14.3, 6.3 Hz, 1H), 2.16 (t, *J* = 5.9 Hz, 1H), 1.97 (s, 1H), 1.87 (s, 1H), 1.66 (d, *J* = 13.4 Hz, 1H), 1.63 – 1.59 (m, 1H), 1.44 – 1.36 (m, 2H), 1.34 (s, 3H), 1.13 – 1.02 (m, 1H), 0.91 (s, 3H), 0.88 (s,

3H), 0.87 – 0.83 (m, 1H), 0.82 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.8, 146.9, 137.3, 134.5, 127.4, 123.7, 122.8, 109.9, 73.4, 60.6, 60.5, 55.7, 55.1, 40.9(two singles), 37.5, 32.7(two singles), 25.3, 24.7, 21.6, 18.5, 14.8; HRMS (ESIMS) calcd for $C_{23}H_{34}O_3$ $[M]^+$: 358.2508, found 358.2516; $[\alpha]_{589}^{23.8\,°C}$ = -15.833 (c = 0.500, $CHCl_3$).

Compound **6-2**: IR (KBr) ν_{max} 3447, 2928, 1586, 1474, 1379, 1271, 1080, 1012, 750; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.01 (t, *J* = 7.9 Hz, 1H), 6.86 (d, *J* = 7.0 Hz, 1H), 6.76 (d, *J* = 8.0 Hz, 1H), 5.81 – 5.46 (m, 2H), 3.87 (d, *J* = 4.2 Hz, 6H), 2.93 (dd, *J* = 14.4, 8.1 Hz, 1H), 2.82 (dd, *J* = 14.4, 4.2 Hz, 1H), 2.54 (s, 1H), 1.84 (d, *J* = 12.8 Hz, 1H), 1.71 – 1.66 (m, 1H), 1.64 – 1.59 (m, 2H), 1.52 – 1.35 (m, 2H), 1.12 (td, *J* = 13.6, 4.1 Hz, 1H), 0.98 (s, 3H), 0.93 (d, *J* = 3.6 Hz, 1H), 0.91 (s, 3H), 0.90 (s, 3H), 0.87 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.8, 146.5, 137.9, 135.2, 126.5, 124.2, 122.5, 109.6, 70.3, 60.8, 59.6, 55.7, 54.3, 41.1, 37.7, 37.6, 32.9, 32.7, 30.9, 23.5, 21.8, 18.6, 14.2; HRMS (ESIMS) calcd for $C_{23}H_{34}O_3$ $[M]^+$: 358.2508, found 358.2509; $[\alpha]_{589}^{23.8\,°C}$ = -48.083 (c = 0.400, $CHCl_3$).

(4aR,5S,8aS)-5-(2,3-dimethoxybenzyl)-1,1,4a-trimethyl-6-methylene-1,2,3,4,4a,5,6,8a-octahydronaphthalene (7a) and (4aS,8aS)-5-(2,3-dimethoxybenzyl)-1,1,4a,6-tetramethyl-1,2,3,4,4a,8a-hexahydronaphthalene (7b):

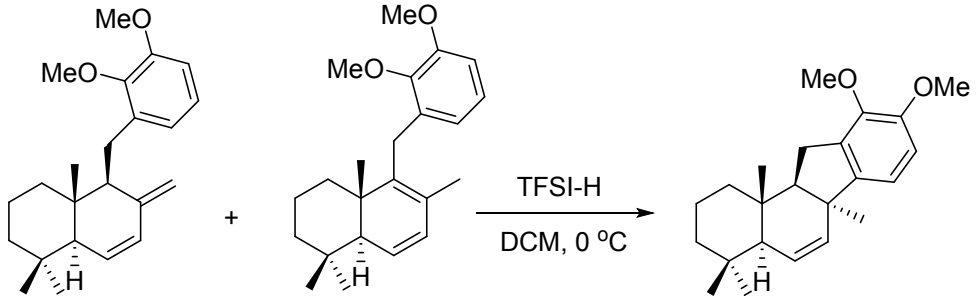


6-1 and 6-2 **7a** **7b**

A dried round-bottom flask charged with the mixture of compounds **6-1** and **6-2** (200 mg, 0.56 mmol) in dry CH_2Cl_2 (4 ml) under nitrogen atmosphere was added tin tetrachloride (20 mg, 0.056 mmol) in dry CH_2Cl_2 (0.2 ml) at - 78 ºC. The round-bottom flask was stirred at this temperature for 0.5 h. The mixture was quenched by saturated $NaHCO_3$ solution (2 ml). The mixture was extracted with CH_2Cl_2 (3×3 mL) and the combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was chromatographed on silica gel (PE/EtOAc = 50:1) to afford the mixture 144 mg as colorless oil in 76% yield, R_f =

0.6 (5% EtOAc in PE); Compound **7a**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.96 (d, *J* = 8.0 Hz, 1H), 6.84 (d, *J* = 7.8 Hz, 1H), 6.75 (d, *J* = 8.0 Hz, 1H), 6.14 (dd, *J* = 9.9, 3.0 Hz, 1H), 5.73 (d, *J* = 9.9 Hz, 1H), 4.87 (d, *J* = 13.9 Hz, 2H), 3.85 (s, 3H), 3.83 (s, 3H), 2.92 (dd, *J* = 15.9, 2.0 Hz, 1H), 2.80 (dd, *J* = 15.7, 9.1 Hz, 1H), 2.57 (d, *J* = 8.2 Hz, 1H), 2.07 (s, 1H), 1.87 (d, *J* = 12.6 Hz, 1H), 1.68 (d, *J* = 10.2 Hz, 1H), 1.45 (d, *J* = 13.3 Hz, 1H), 1.38 – 1.23 (m, 2H), 1.19 (dd, *J* = 14.1, 4.0 Hz, 1H), 0.96 (s, 3H), 0.87 (s, 3H), 0.82 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 152.7, 146.9, 146.7, 136.4, 131.4, 128.9, 123.7, 120.9, 112.5, 109.5, 60.3, 56.0, 55.6, 53.2, 41.2, 38.9, 37.4, 33.1, 32.7, 24.3, 21.7, 19.2, 13.8. Compound **7b**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.98 (t, *J* = 8.0 Hz, 1H), 6.86 (d, *J* = 8.2 Hz, 1H), 6.75 (d, *J* = 8.0 Hz, 1H), 5.83 (d, *J* = 5.6 Hz, 1H), 5.67 (s, 1H), 3.85 (s, 3H), 3.82 (s, 3H), 2.98 (dd, *J* = 15.8, 10.3 Hz, 1H), 2.71 (t, *J* = 12.2 Hz, 2H), 2.03 (dd, *J* = 19.7, 10.3 Hz, 1H), 1.68 (d, *J* = 11.0 Hz, 1H), 1.66 (d, *J* = 8.2 Hz, 1H), 1.43 (t, *J* = 18.9 Hz, 1H), 1.38 – 1.22 (m, 2H), 1.15 (s, 3H), 1.12 (s, 3H), 0.96 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.7, 152.1, 146.9, 137.3, 136.6, 123.6, 121.1, 120.9, 117.6, 109.5, 60.3, 55.7, 50.7, 40.1, 40.0, 38.6, 35.3, 31.9, 31.8, 23.7, 21.6, 18.9, 16.4.

(4aS,6aS,11aR,11bR)-9,10-dimethoxy-4,4,6a,11b-tetramethyl-2,3,4,4a,6a,11,11a,11b-octahydro-1H-benzo[a]fluorene (8)

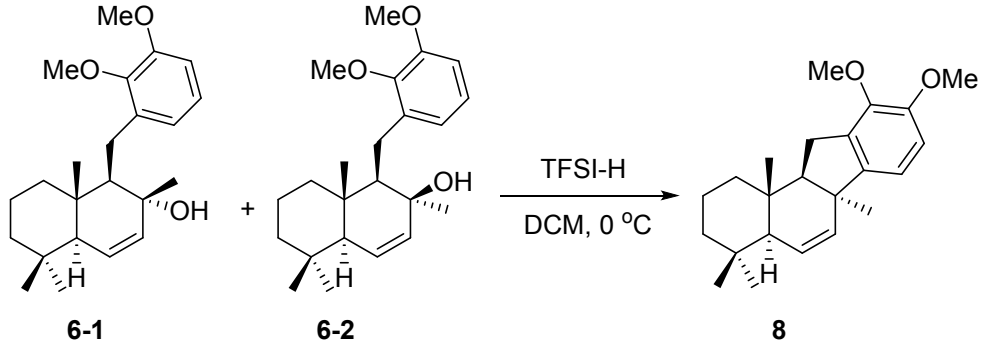


7a **7b** **8**

A dried round-bottom flask charged with the mixture of compounds **7a** and **7b** (200 mg, 0.58 mmol) in CH_2Cl_2 (4 ml) under nitrogen atmosphere was added bistrifluoromethanesulfonimide (23 mg, 0.087 mmol) in CH_2Cl_2 (0.2 ml) at 0 ºC. The round-bottom flask was stirred for 1 h at 0 ºC. Upon completion of the reaction, the mixture was quenched by saturated $NaHCO_3$ solution and it was extracted with CH_2Cl_2 (3×3 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was chromatographed on silica gel (PE/EtOAc = 50:1) to afford 171 mg Friedel-crafts alkylation product **8** as colorless

solid in 87% yield, R_f = 0.5 (5% EtOAc in PE).

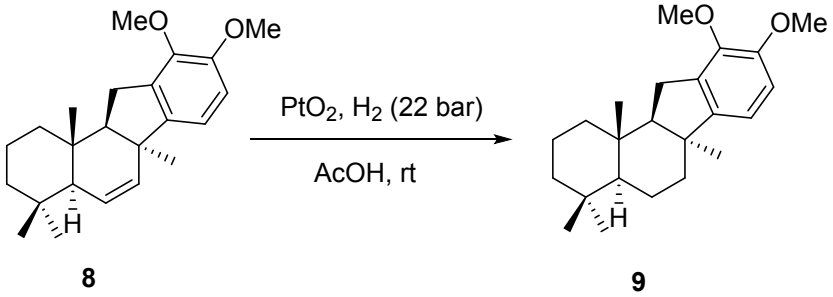
(4aS,6aS,11aR,11bR)-9,10-dimethoxy-4,4,6a,11b-tetramethyl-2,3,4,4a,6a,11,11a,11b-octahydro-1H-benzo[a]fluorene (8)



6-1 **6-2** **8**

A dried round-bottom flask charged with the mixture of compounds **6-1** and **6-2** (200 mg, 0.56 mmol) in CH_2Cl_2 (4 ml) under nitrogen atmosphere was added bistrifluoromethanesulfonimide (24 mg, 0.084 mmol) in CH_2Cl_2 (0.2 ml) at 0 ºC. The round-bottom flask was stirred for 1 h at 0 ºC. Upon completion of the reaction, the mixture was quenched by saturated $NaHCO_3$ solution and it was extracted with CH_2Cl_2 (3×3 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was chromatographed on silica gel (PE/EtOAc = 50:1) to afford 163 mg Friedel-crafts alkylation product **8** as colorless solid in 86% yield, R_f = 0.5 (5% EtOAc in PE); Mp 104 – 105 ºC; IR (KBr) ν_{max} 3429, 2925, 1631, 1484, 1385, 1217, 1076, 1028, 802, 585; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.75 (dd, *J* = 20.4, 8.1 Hz, 2H), 6.09 (dd, *J* = 9.9, 2.9 Hz, 1H), 5.68 (dd, *J* = 9.9, 1.9 Hz, 1H), 3.85(s, 3H), 3.82(s, 3H), 3.05 – 2.86 (m, 2H), 1.98 (d, *J* = 7.3 Hz, 1H), 1.82 (d, *J* = 12.3 Hz, 1H), 1.74 (s, 1H), 1.61 – 1.51 (m, 2H), 1.47 – 1.42 (m, 2H), 1.19 (s, 3H), 1.18-1.17 (m,1H), 0.95 (s, 3H), 0.82 (s, 3H), 0.38 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.8, 144.8, 144.4, 135.2, 133.1, 125.8, 116.1, 111.0, 61.0, 60.0, 56.0, 52.0, 48.1, 41.5, 38.2, 37.6, 33.0, 32.5, 31.9, 27.4, 21.7, 18.4, 13.8; HRMS (ESIMS) calcd for $C_{23}H_{32}O_2$ $[M]^+$: 340.2402, found 340.2398; $[\alpha]_{589}^{25.1ºC}$ = -6.405 (c = 0.510, $CHCl_3$).

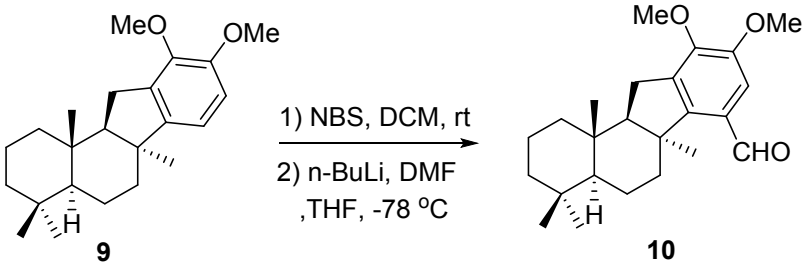
(4aS,6aS,11aR,11bS)-9,10-dimethoxy-4,4,6a,11b-tetramethyl-2,3,4,4a,5,6,6a,11,11a,11b-decahydro-1H-benzo[a]fluorene (9)



8 **9**

A dried round-bottom flask charged with compound **8** (100 mg, 0.29 mmol) under nitrogen atmosphere in acetic acid glacial (1.5 mL) was added PtO_2 (6.8 mg, 0.030 mmol), then the air of the device was replaced with hydrogen at 22 bar. The reaction mixture was stirred at 25 °C for the period of 12 h. The mixture was filtered through celite filtere and concentrated using rotator evaporator under vaccum. The crude products were purified by flash chromatography (PE/EtOAc = 50:1) to afford 96 mg of compound **9** in 96% yield as colorless oil, R_f = 0.5 (5% EtOAc in PE); IR (KBr) ν_{max} 3422, 2929, 1604, 1484, 1460, 1383, 1262, 1222, 1081, 1035, 798; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.71 (s, 2H), 3.85 (s, 3H), 3.83 (s, 3H), 2.93 (dd, *J* = 16.6, 6.9 Hz, 1H), 2.78 (d, *J* = 16.6 Hz, 1H), 2.38 – 2.25 (m, 1H), 1.74 (t, *J* = 9.3 Hz, 2H), 1.62 – 1.57 (m, 1H), 1.48 (ddd, *J* = 13.5, 8.2, 2.8 Hz, 2H), 1.41 – 1.34 (m, 2H), 1.15 (dd, *J* = 12.4, 4.2 Hz, 2H), 1.07 (s, 3H), 0.93 (d, *J* = 11.1 Hz, 1H), 0.89 (s, 4H), 0.84 (d, *J* = 4.5 Hz, 1H), 0.74 (s, 3H), 0.33 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.8, 145.8, 144.9, 136.4, 114.9, 110.2, 62.3, 59.9, 55.9, 52.9, 45.9, 42.1, 41.2, 37.0, 35.1, 34.0, 33.7, 33.0, 28.7, 22.2, 19.5, 18.4, 15.2; HRMS (ESIMS) calcd for $C_{23}H_{34}O_2$ $[M]^+$: 342.2559, found 342.2549; $[\alpha]_{589}^{25.1\,^{\circ}C}$ = -13.974 (c = 0.520, $CHCl_3$).

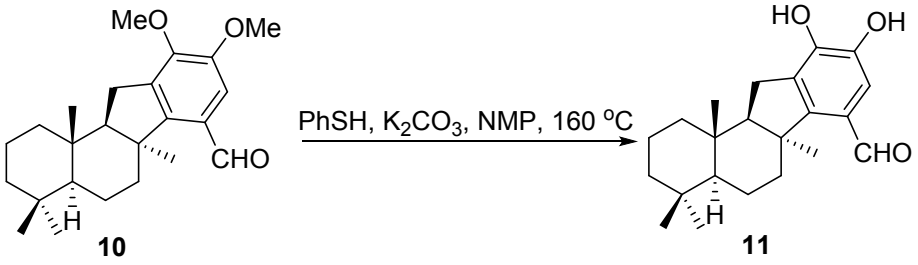
(4aS,6aS,11aR,11bS)-9,10-dimethoxy-4,4,6a,11b-tetramethyl-2,3,4,4a,5,6,6a,11,11a,11b-decahydro-1H-benzo[a]fluorene-7-carbaldehyde (10)



9 **10**

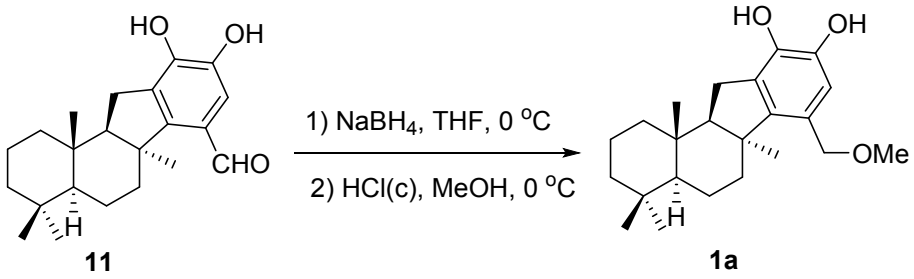
In a dry round-bottom flask charged with compound **9** (200 mg, 0.58 mmol) in CH_2Cl_2 (2 mL) was added N-bromosuccinamide (105 mg, 0.59 mmol). The reaction mixture was allowed to stand on continuous stirring for 1 h at room temperature. Reaction mixture was treated with saturated aq. solution of sodium thiosulphate, then organic layer was extracted with CH_2Cl_2 (3×5 mL). The combined CH_2Cl_2 extracts were dried over anhydrous Na_2SO_4, filtered and concentrated using rotator evaporator under vacuum. The crude product was taken in flame-dried round-bottom flask under nitrogen atmosphere in dry THF (2 mL) and cooled to -78 ºC. The n-butyl lithium solution [0.70 mL (2.5 M in Hexane), 1.74 mmol] was added dropwise to the reaction mixture by a syringe and allowed to stirred for 20 min followed by dropwise addition of DMF (0.14 mL, 1.74 mmol) at -78ºC. The stirring was continued till TLC showed complete consumption of starting materials. The reaction mixture was quenched by saturated NH_4Cl (2 mL), extracted with EtOAc (3×3 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude products were purified by flash chromatography (PE/EtOAc = 50:1) to afford 163 mg of compound **10** as colorless oil in 75% yield, R_f = 0.5 (15% EtOAc in PE); IR (KBr) ν_{max} 3085, 3006, 2938, 2866, 1704, 1413, 1255, 1225, 1151, 926, 912; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.48 (s, 1H), 7.30 (s, 1H), 3.93 (s, 3H), 3.87 (s, 3H), 2.97 (dd, *J* = 17.3, 8.3 Hz, 1H), 2.85 (dd, *J* = 17.2, 1.6 Hz, 1H), 2.58 – 2.30 (m, 1H), 1.94 (ddd, *J* = 14.3, 7.7, 6.6 Hz, 1H), 1.81 – 1.65 (m, 3H), 1.55 – 1.45 (m, 1H), 1.41 (d, *J* = 7.1 Hz, 1H), 1.40 (s, 3H), 1.37 – 1.32 (m, 2H), 1.21 – 1.09 (m, 1H), 1.04 (dd, *J* = 11.0, 5.4 Hz, 1H), 0.95 – 0.90 (m, 1H), 0.87 (s, 3H), 0.80 (s, 3H), 0.49 (s, 3H).^{13}C NMR (100 MHz, $CDCl_3$): δ 189.9, 150.9, 149.9, 149.6, 137.7, 127.7, 109.9, 62.8, 60.1, 55.9, 51.5, 49.4, 42.0, 41.1, 37.3, 37.0, 33.7, 33.3, 33.1, 28.8, 21.6, 19.3, 18.4, 15.6.

(4aS,6aS,11aR,11bS)-9,10-dimethoxy-4,4,6a,11b-tetramethyl-2,3,4,4a,5,6,6a,11,11a,11b-decahydro-1H-benzo[a]fluorene-7-carbaldehyde (11)



In a dry round-bottom flask charged with compound **10** (50 mg, 0.14 mmo) in dry NMP (0.6 mL) was added dry K_2CO_3 (38 mg, 0.28 mmol) and thiophenol (31 μL, 0.30 mmol). The reaction mixture was allowed to stand on continuous stirring for 1 h at 160 ºC, then cooled to room temperature. Reaction was extracted with EtOAc (3×3 mL). The combined EtOAc extracts were dried over anhydrous Na_2SO_4, filtered and concentrated using rotator evaporator under vacuum. The crude product was purified by flash chromatography (PE/EtOAc = 5:2) to afford 39 mg of compound **11** in 83% yield as colorless solid, R_f = 0.6 (50% EtOAc in PE); ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.34 (s, 1H), 7.39 (s, 1H), 6.33 (s, 1H), 4.88 (s, 1H), 3.00 – 2.85 (m, 1H), 2.80 (d, *J* = 16.4 Hz, 1H), 2.48 – 2.31 (m, 1H), 1.98 – 1.91 (m, 1H), 1.79 – 1.65 (m, 4H), 1.56 – 1.44 (m, 2H), 1.39 (s, 3H), 1.35 – 1.33 (m, 1H), 1.20 – 1.11 (m, 1H), 1.06 (dd, *J* = 10.7, 6.0 Hz, 1H), 0.97 – 0.90 (m, 1H), 0.87 (s, 3H), 0.81 (s, 3H), 0.53 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 190.3, 151.3, 146.4, 142.1, 130.3, 124.8, 113.1, 63.1, 51.1, 49.6, 42.1, 41.3, 37.3, 36.6, 33.7, 33.4, 32.9, 28.1, 21.5, 19.3, 18.5, 15.6.

Akaol A (**1**)



In a dry round-bottom flask charged with compound **11** (30 mg, 0.088 mmol) in THF (0.8 mL) was added sodium borohydride (3.4 mg, 0.088 mmol). The reaction mixture was allowed to stand on continuous stirring for 3 h at 0 °C. Reaction was quenched by using methanol and concentrated using rotator evaporator under vacuum. The crude product was dissolved in methanol followed by dropwise addition of concentrated HCl at 0 °C for 20 min. Reaction mixture was diluted with water and extracted with 50% EtOAc in hexane solution. The combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated using rotator evaporator under vacuum. The crude products were purified by flash chromatography (PE/EtOAc = 4/1) to afford 25 mg of compound **1a (Akaol A)** in 78% yield as colorless solid, R_f = 0.5 (40% EtOAc in PE); Mp 135 –

136 ºC; IR (KBr) ν_{max} 3418, 2997, 2967, 2925, 2855, 1461, 1369, 1112, 1026, 932, 897, 742, 693; ^{1}H NMR (400 MHz, CD_3OD): δ 6.57 (s, 1H), 4.92 (s, 2H), 4.50 (d, *J* = 10.9 Hz, 1H), 4.34 (d, *J* = 10.9 Hz, 1H), 3.37 (s, 3H), 2.83 (dd, *J* = 16.5, 6.9 Hz, 1H), 2.74 (d, *J* = 16.4 Hz, 1H), 2.70 – 2.58 (m, 1H), 1.82 (d, *J* = 12.6 Hz, 1H), 1.71 – 1.55 (m, 4H), 1.49 – 1.22 (m, 4H), 1.20 (s, 3H), 1.04 (dd, *J* = 11.5, 2.5 Hz, 1H), 1.01 – 0.97 (m, 1H), 0.95 (s, 3H), 0.84 (s, 3H), 0.44 (s, 3H); ^{13}C NMR (100 MHz, CD_3OD): δ 143.9, 142.9, 141.9, 132.2, 124.1, 117.4, 73.7, 64.5, 57.5, 54.9, 50.0, 43.3, 42.0, 38.6, 36.6, 34.1, 34.0, 33.3, 28.8, 22.5, 21.0, 19.5, 15.8; HRMS (ESIMS) calcd for $C_{23}H_{34}O_3$ $[M]^+$: 358.2508, found 358.2509; $[\alpha]_{589}^{24.3\ ºC}$ = -10.387 (c = 0.690, MeOH).

Comparison of ^{1}H NMR Data:

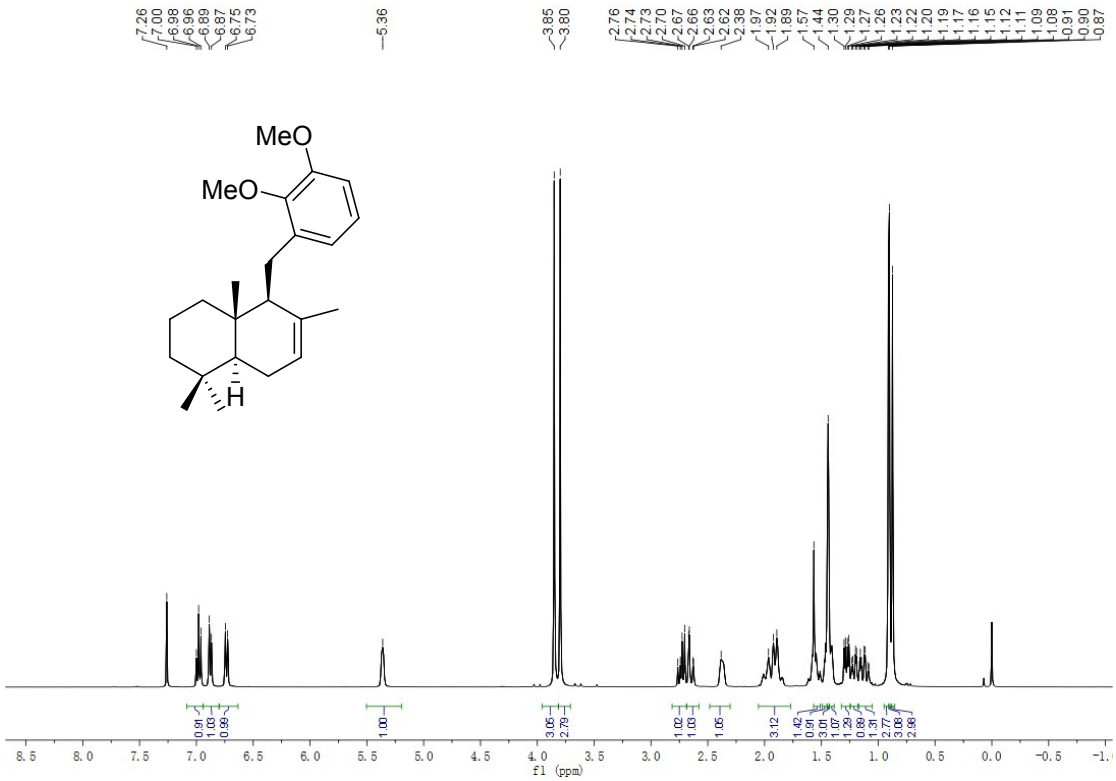
Alvarez-Manzaneda's report Akaol A (^{1}H NMR, 500 MHz, CD_3OD)				**This report Akaol A (^{1}H NMR, 400 MHz, CD_3OD)**				**Error (Manzaneda's report - This report) Δδ (ppm)**
δ (ppm)	**Int.**	**mult.**	***J* (Hz)**	**δ (ppm)**	**Int.**	**mult.**	***J* (Hz)**	
6.58	1H	s	-	6.57	1H	s	-	0.01
4.87	2H (-OH)	s	-	4.92	2H (-OH)	s	-	-0.05
4.50	1 H	d	11.0	4.50	1 H	d	10.9	0.00
4.34	1 H	d	11.0	4.34	1 H	d	10.9	0.00
3.37	3 H	s	-	3.37	3 H	s	-	0.00
2.83	1 H	dd	16.4,7.1	2.83	1 H	dd	16.5, 6.9	0.00
2.75	1 H	d	16.4	2.74	1 H	d	16.4	0.01
2.67	1 H	m	-	2.67	1 H	m	-	0.00
1.82	1 H	br d	12.6	1.82	1 H	d	12.6	0.00
1.71-1.55	4 H	m	-	1.71-1.55	4 H	m	-	0.00
1.49-1.22	4 H	m	-	1.49 - 1.22	4 H	m	-	0.00
1.21	3 H	s	-	1.20	3 H	s	-	0.01
1.04	1 H	dd	11.5, 2.4	1.04	1 H	dd	11.5, 2.5	0.00
0.98	1 H	ddd	13.1, 13.1, 3.4	0.98	1 H	m	-	0.00
0.95	3 H	s	-	0.95	3 H	s	-	0.00
0.84	3 H	s	-	0.84	3 H	s	-	0.00

0.45	3 H	s	-	0.44	3 H	s	-	0.01

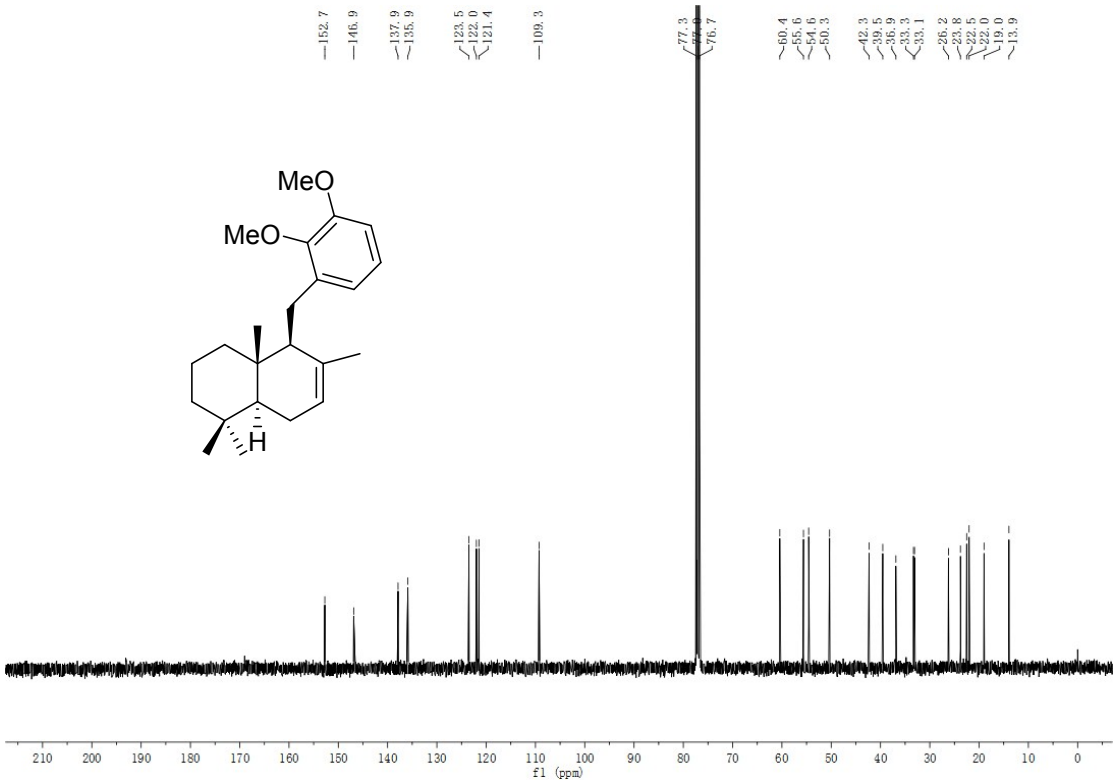
Comparison of ^{13}C NMR Data:

Alvarez-Manzaneda's report Akaol A (^{13}C NMR, 125 MHz, CD_3OD)	**This report Akaol A (^{13}C NMR, 100 MHz, CD_3OD)**	**Error (Manzaneda's report - This report) Δδ (ppm)**
144.0	143.9	0.1
142.9	142.9	0.0
141.9	141.9	0.0
132.2	132.2	0.0
124.1	124.1	0.0
117.4	117.4	0.0
73.7	73.7	0.0
64.5	64.5	0.0
57.5	57.5	0.0
54.9	54.9	0.0
50.1	50.0	0.1
43.3	43.3	0.0
42.1	42.0	0.1
38.6	38.6	0.0
36.6	36.6	0.0
34.1	34.1	0.0
34.0	34.0	0.0
33.3	33.3	0.0
28.8	28.8	0.0
22.5	22.5	0.0
21.0	21.0	0.0
19.6	19.5	0.1
15.8	15.8	0.0

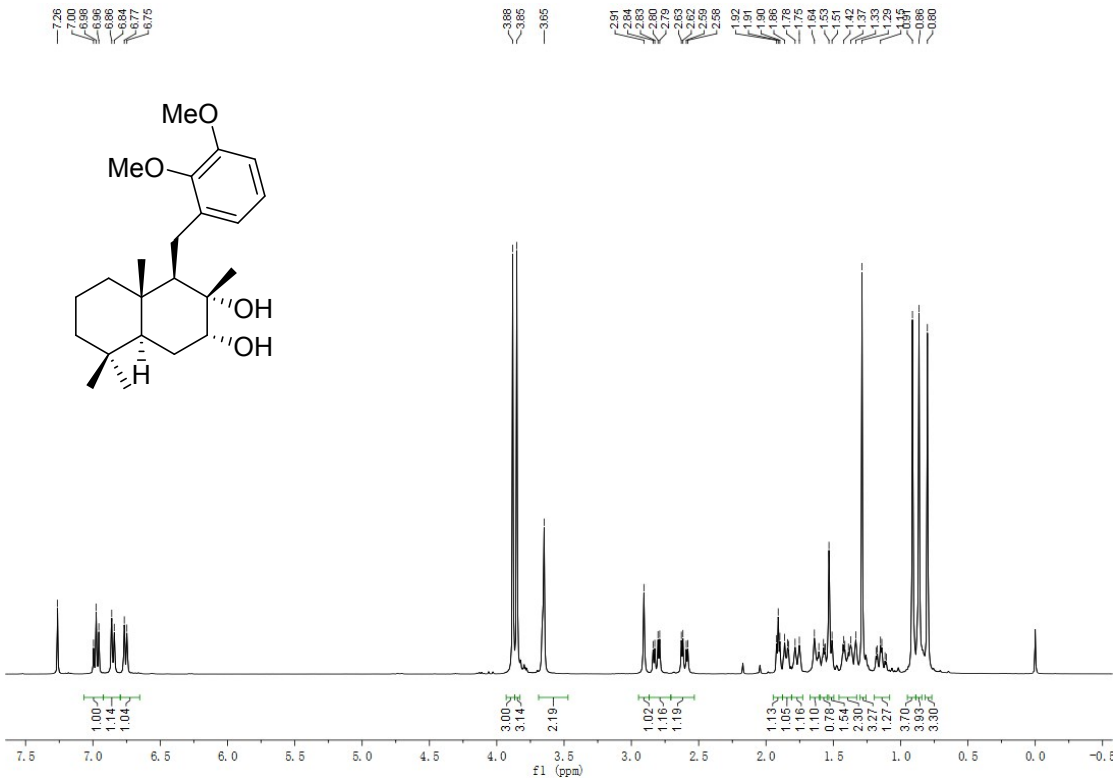
^{1}H and ^{13}C NMR spectra of intermediates



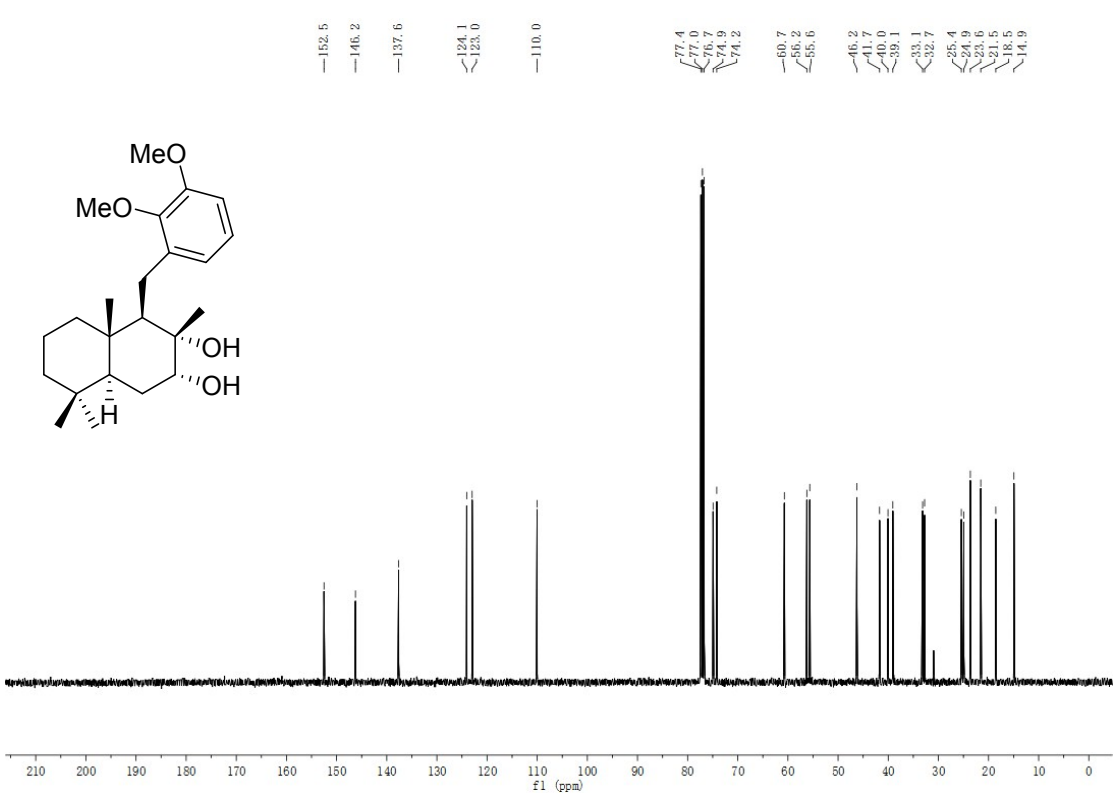
^{1}H NMR (400 MHz, $CDCl_3$) of compound 3



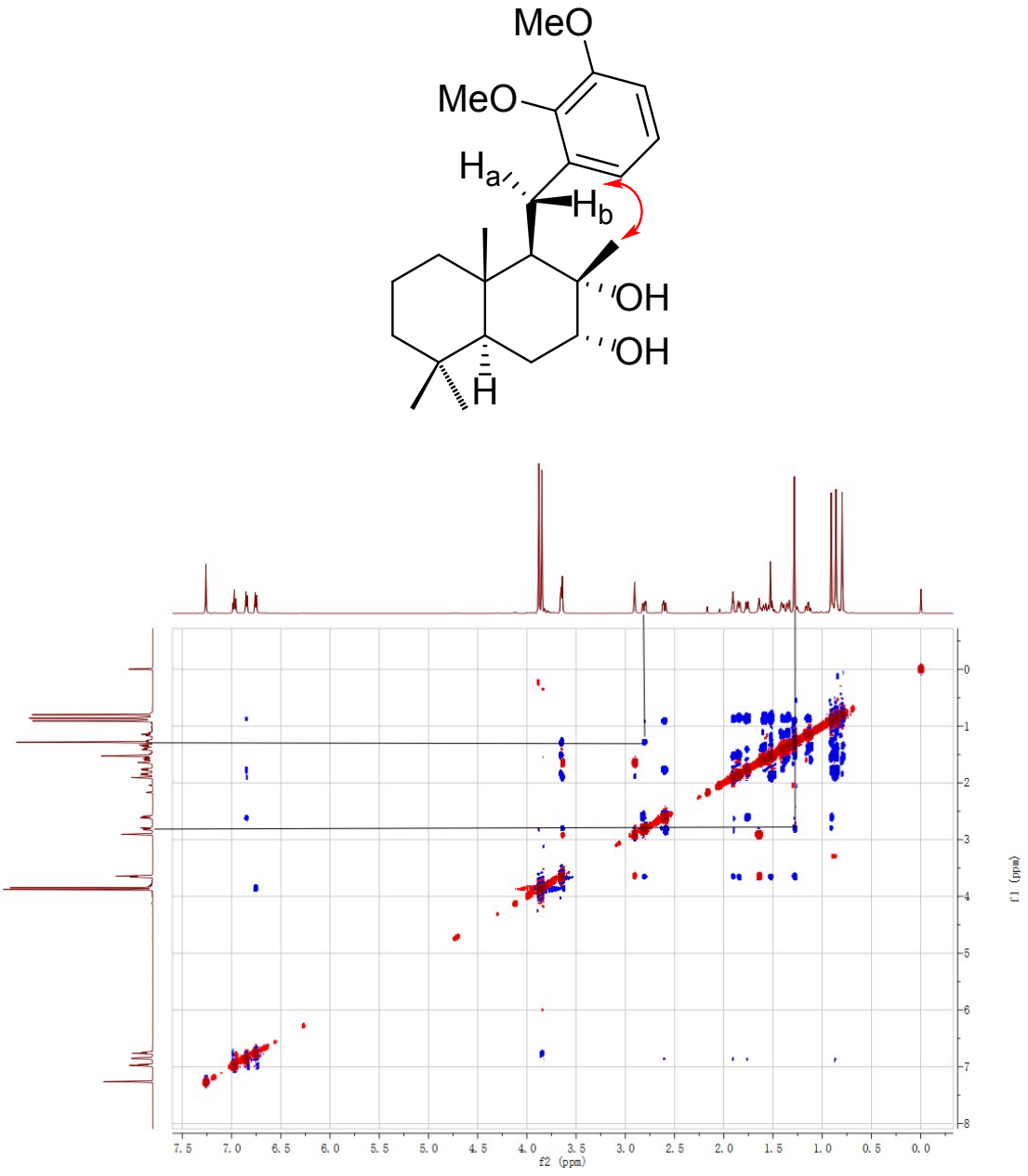
^{13}C NMR (100 MHz, $CDCl_3$) of compound 3



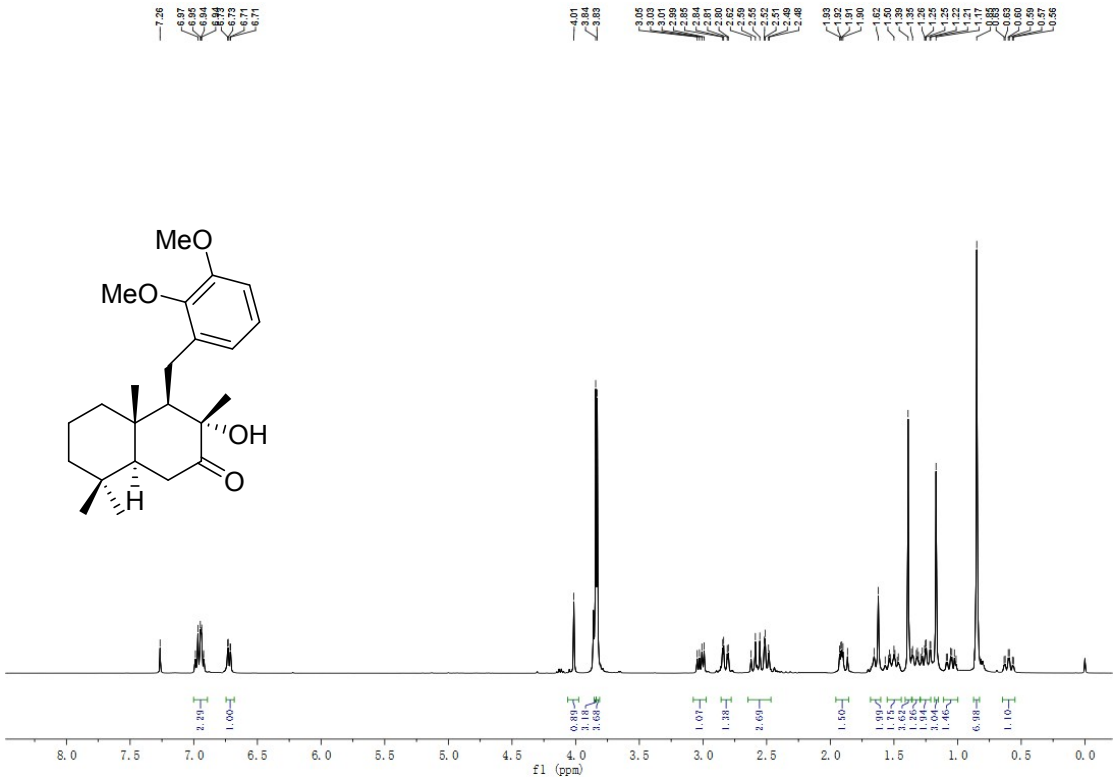
^{1}H NMR (400 MHz, $CDCl_3$) of compound 4



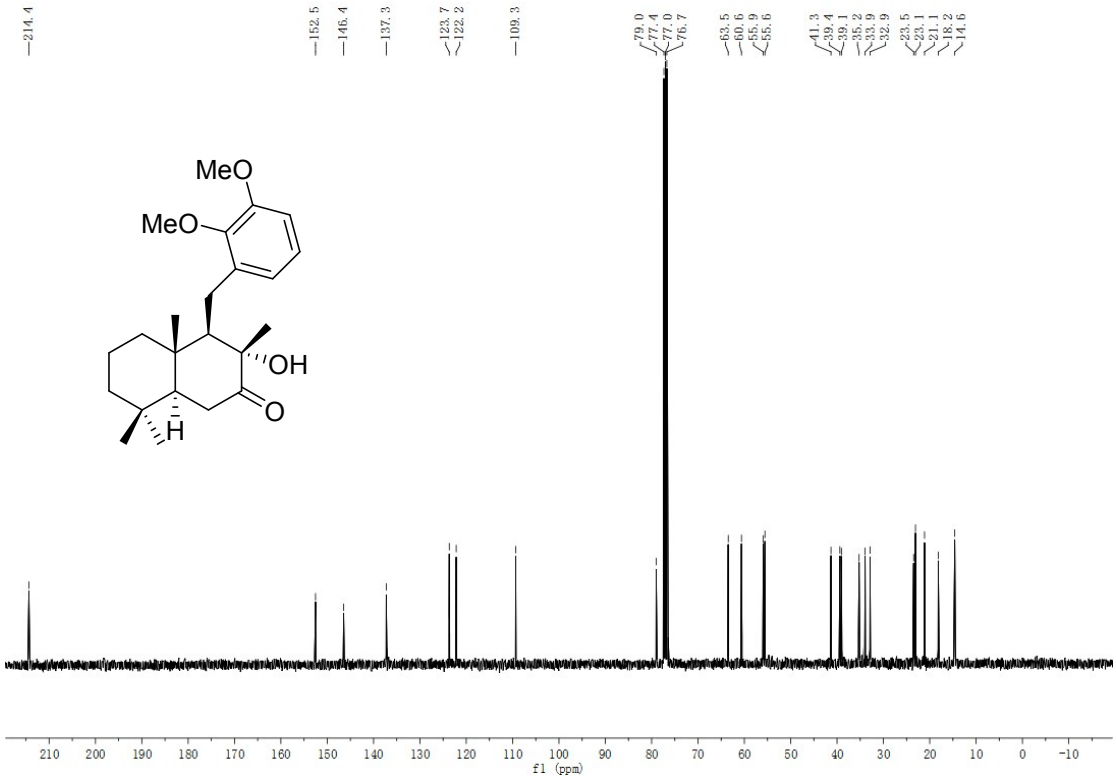
^{13}C NMR (100 MHz, $CDCl_3$) of compound 4



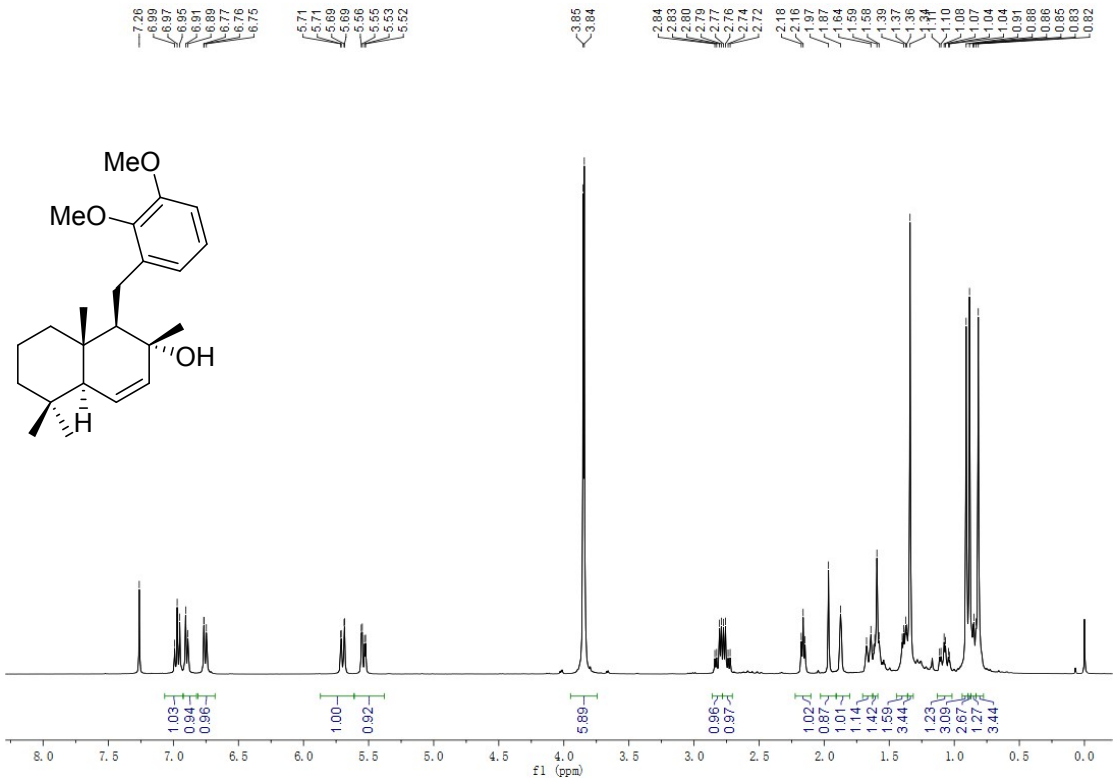
ROESY of compound 4 (600 MHz, $CDCl_3$)



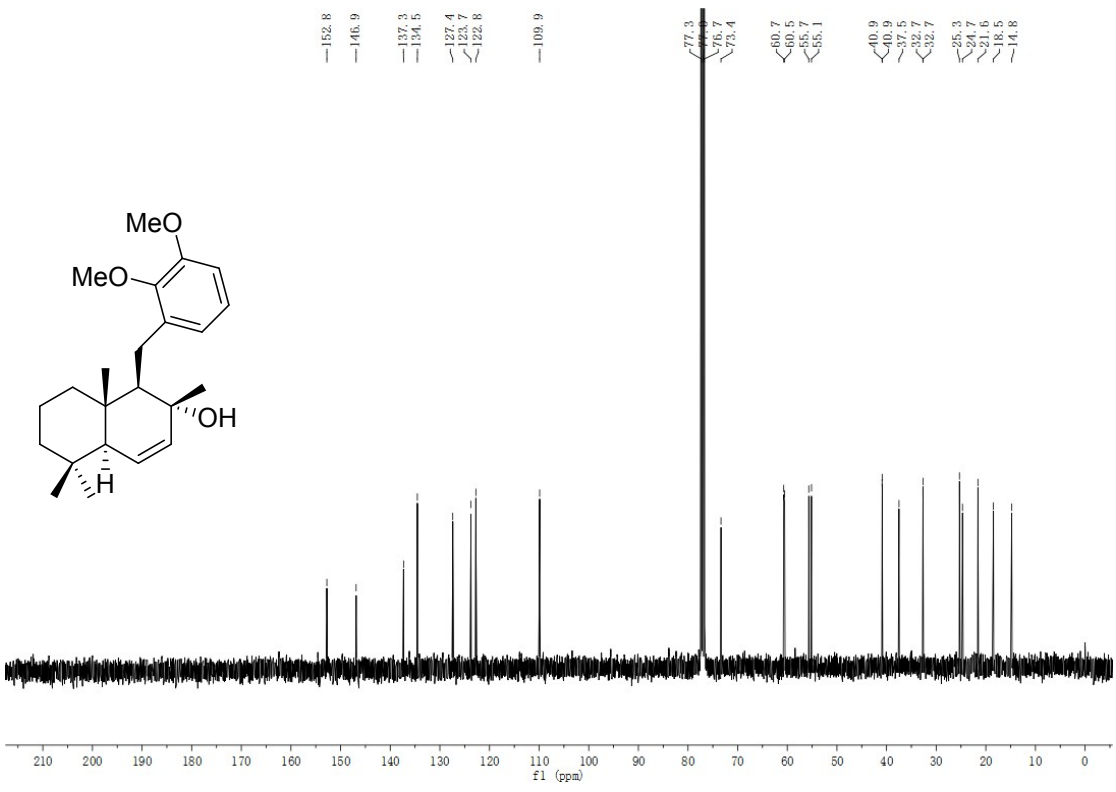
^{1}H NMR (400 MHz, $CDCl_3$) of compound 5



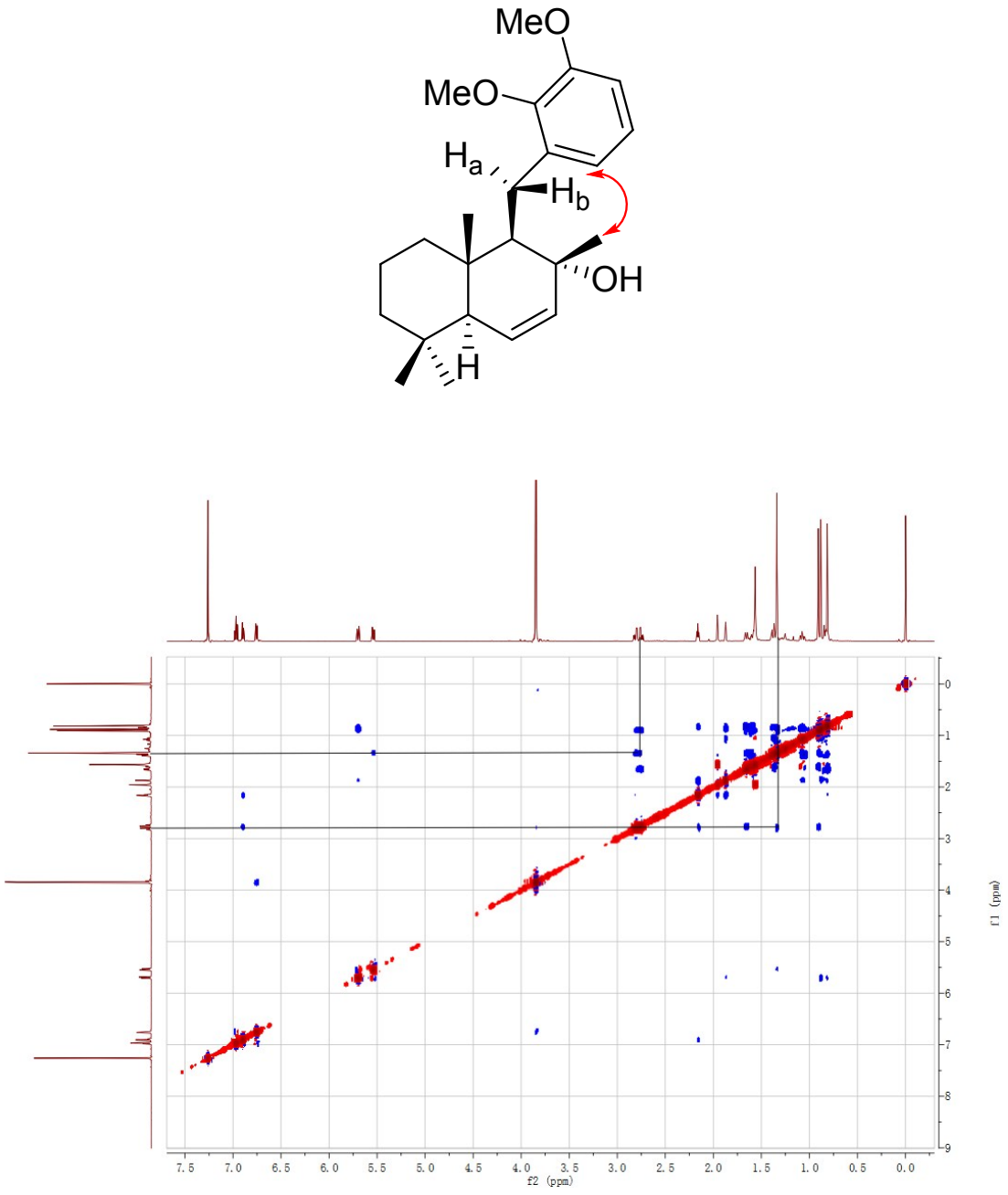
^{13}C NMR (100 MHz, $CDCl_3$) of compound 5



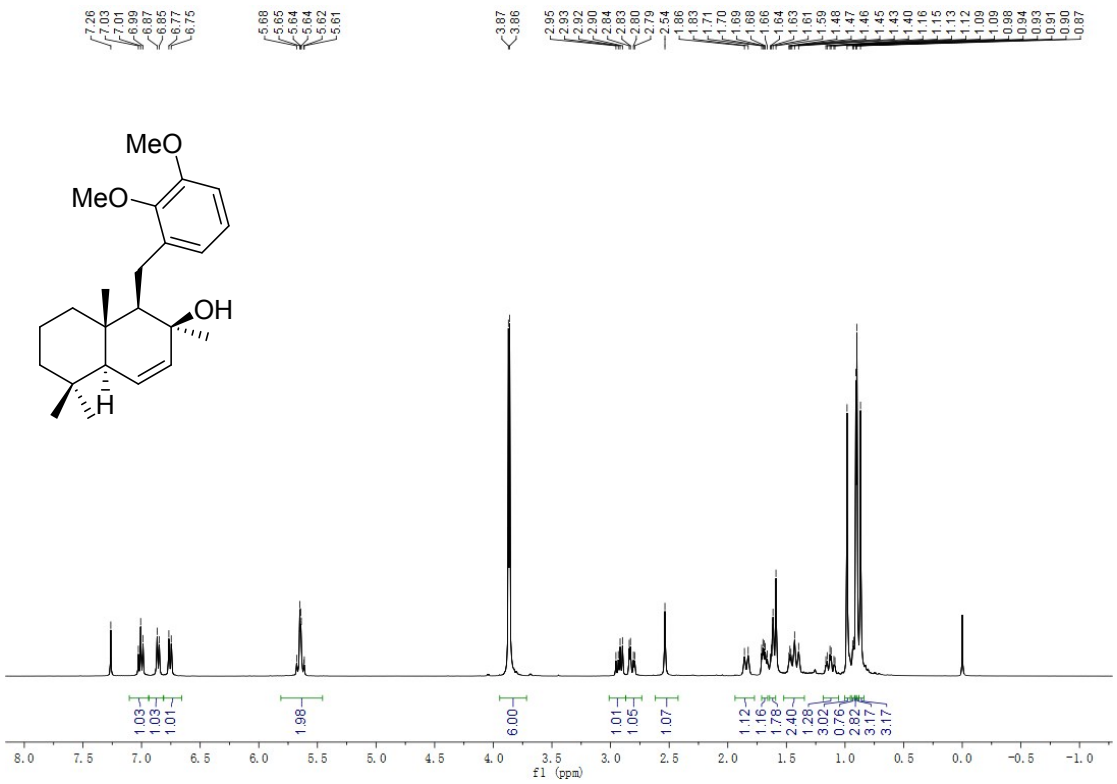
^{1}H NMR (400 MHz, $CDCl_3$) of compound 6-1



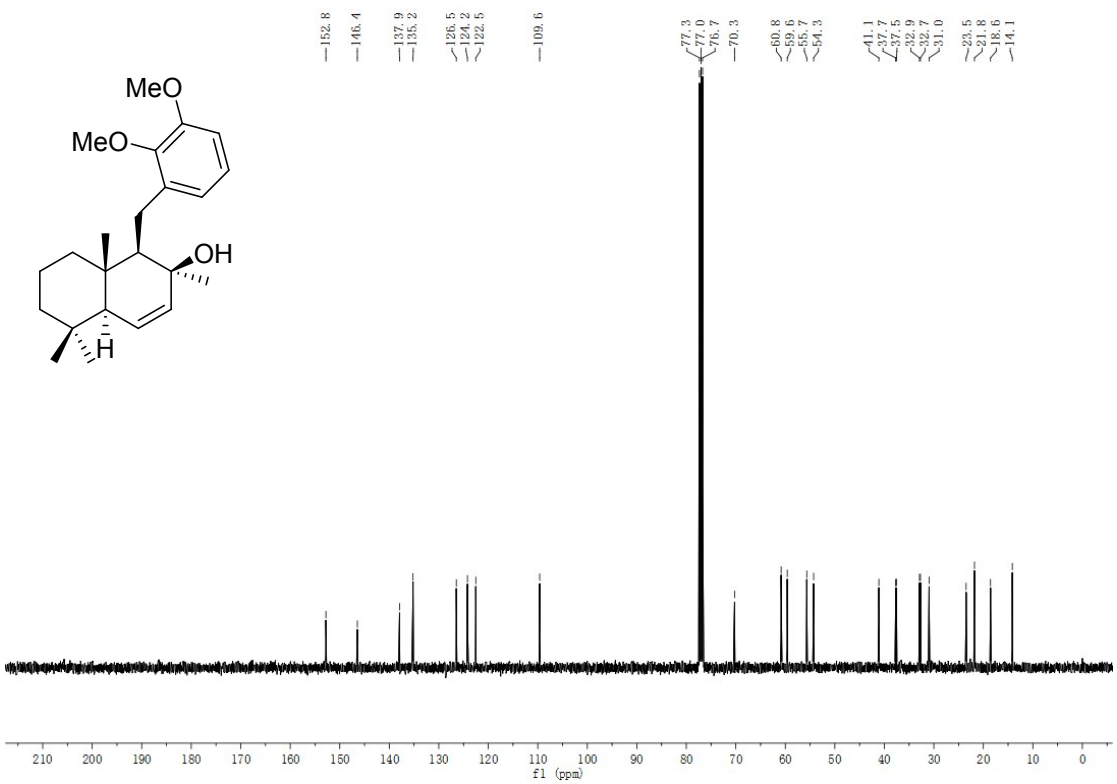
^{13}C NMR (100 MHz, $CDCl_3$) of compound 6-1



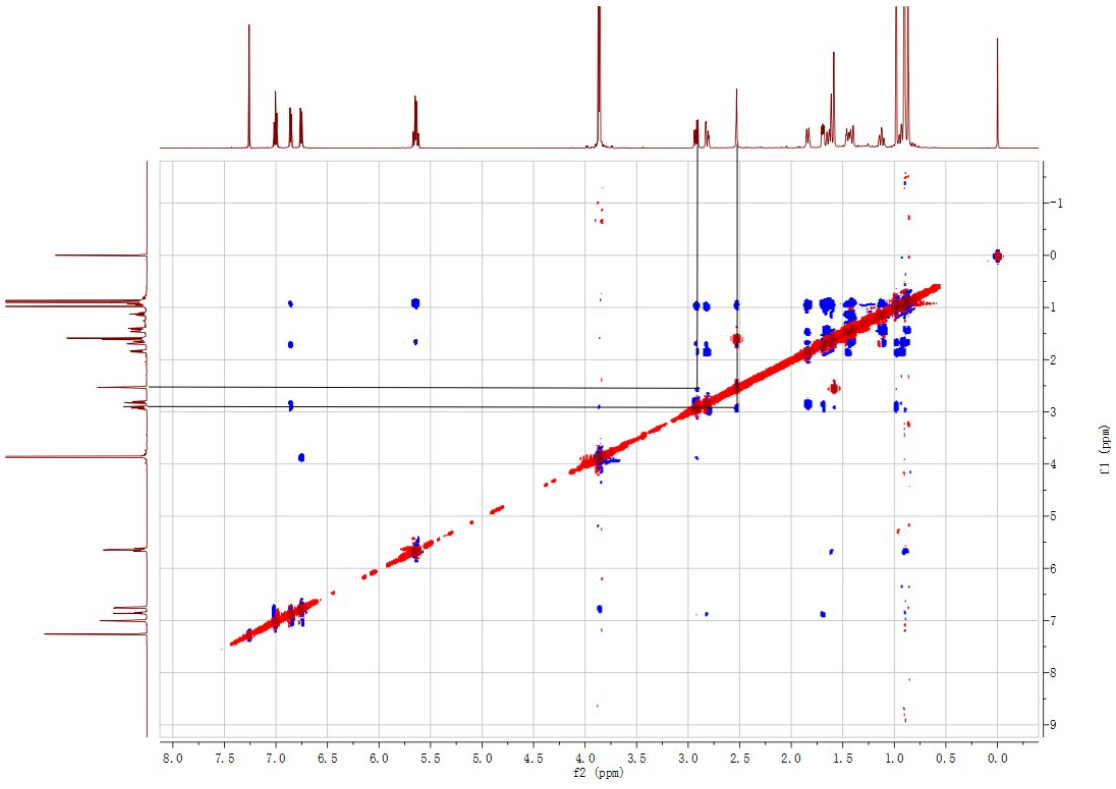
ROESY of compound 6-1 (600 MHz, $CDCl_3$)



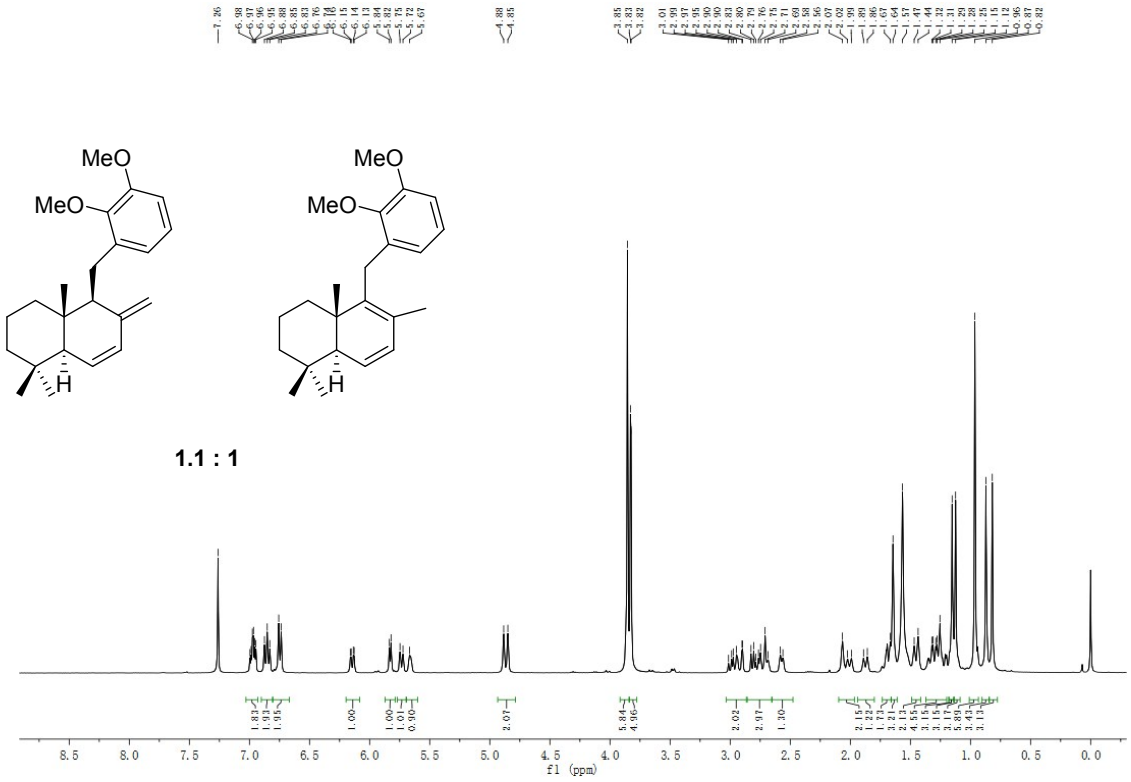
^{1}H NMR (400 MHz, $CDCl_3$) of compound 6-2



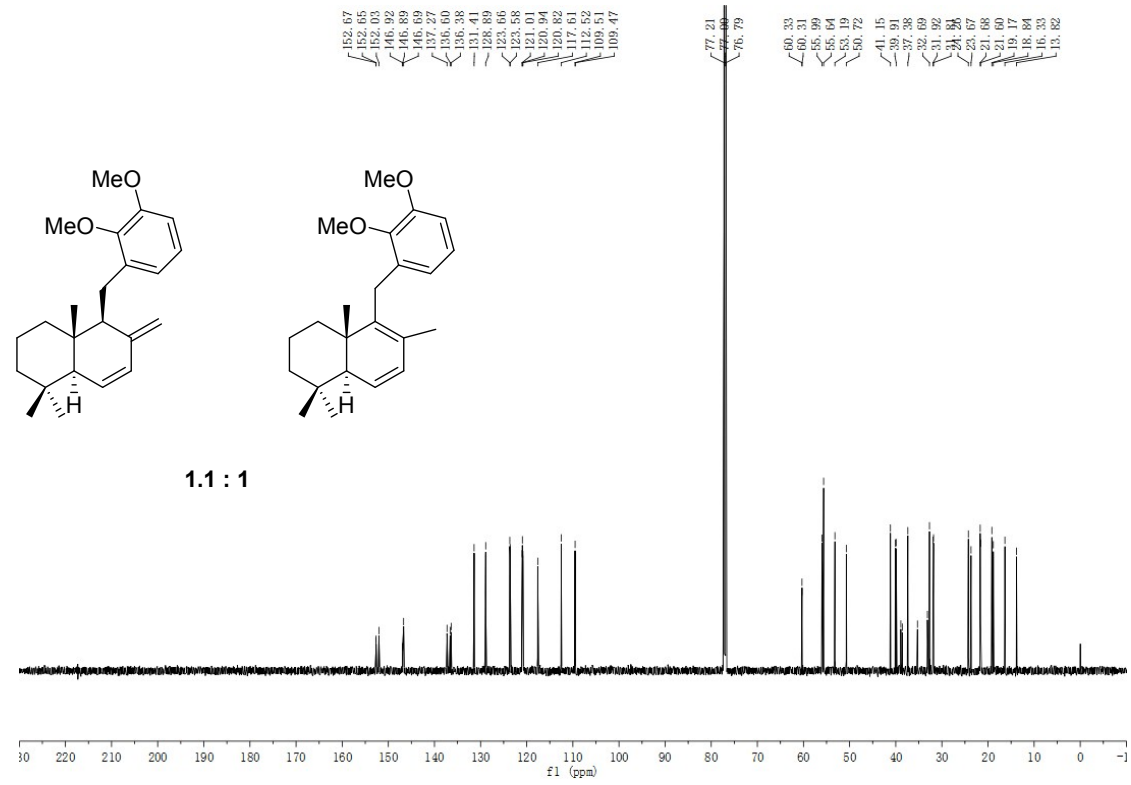
^{13}C NMR (100 MHz, $CDCl_3$) of compound 6-2



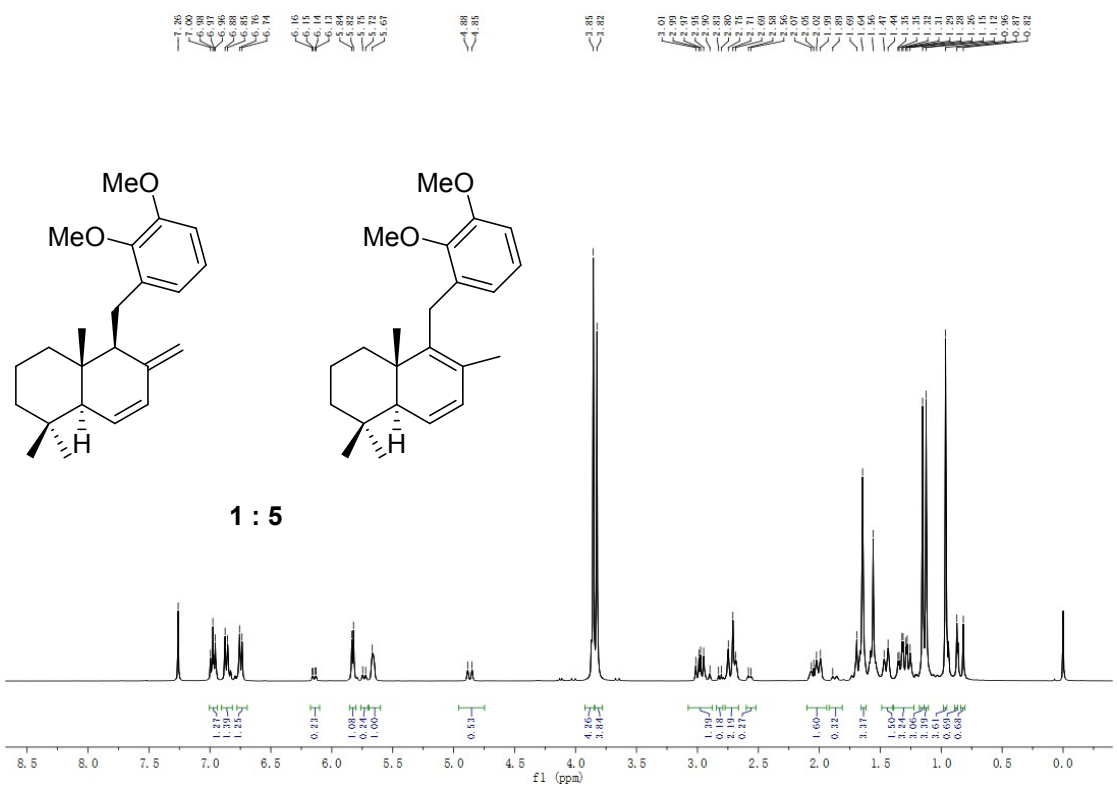
ROESY of compound 6-2 (600 MHz, $CDCl_3$)



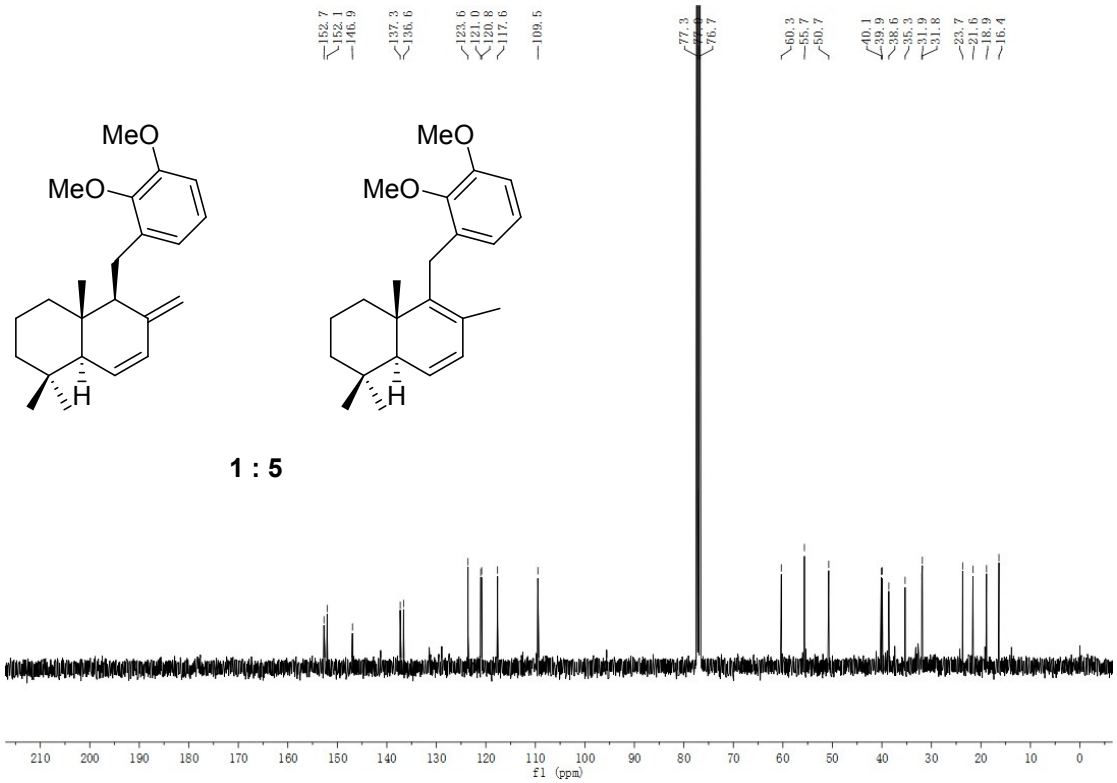
^{1}H NMR (400 MHz, $CDCl_3$) of compound 7a and 7b



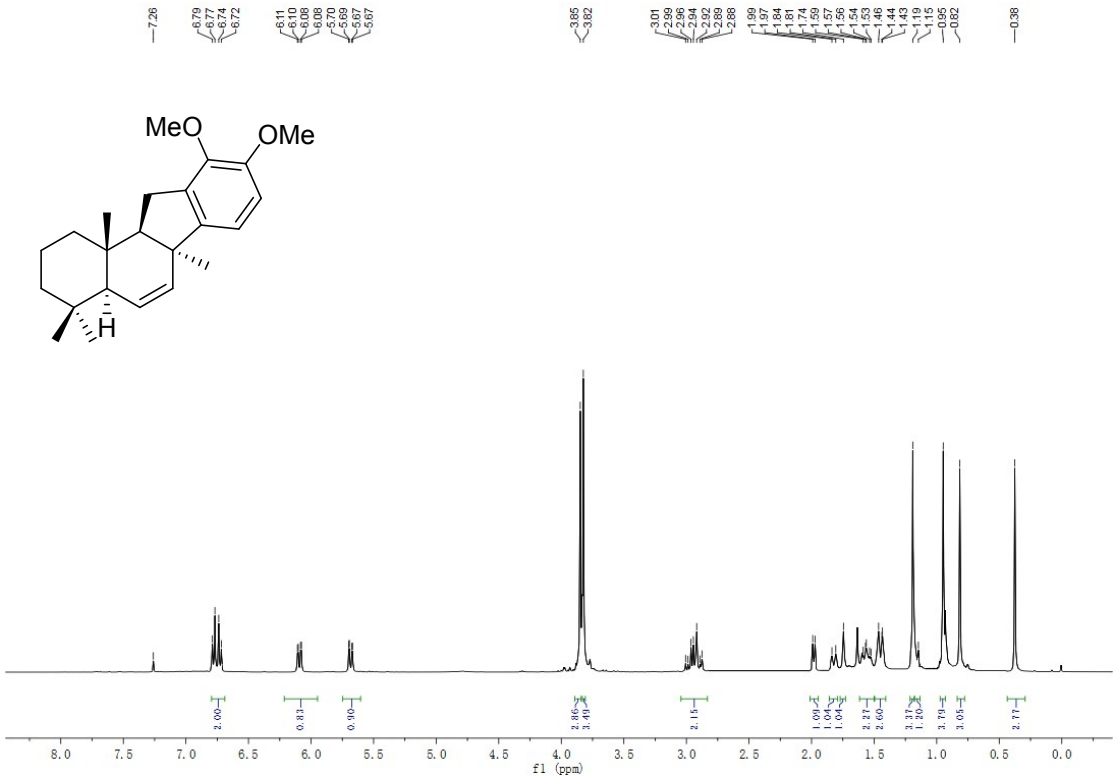
^{13}C NMR (150 MHz, $CDCl_3$) of compound 7a and 7b



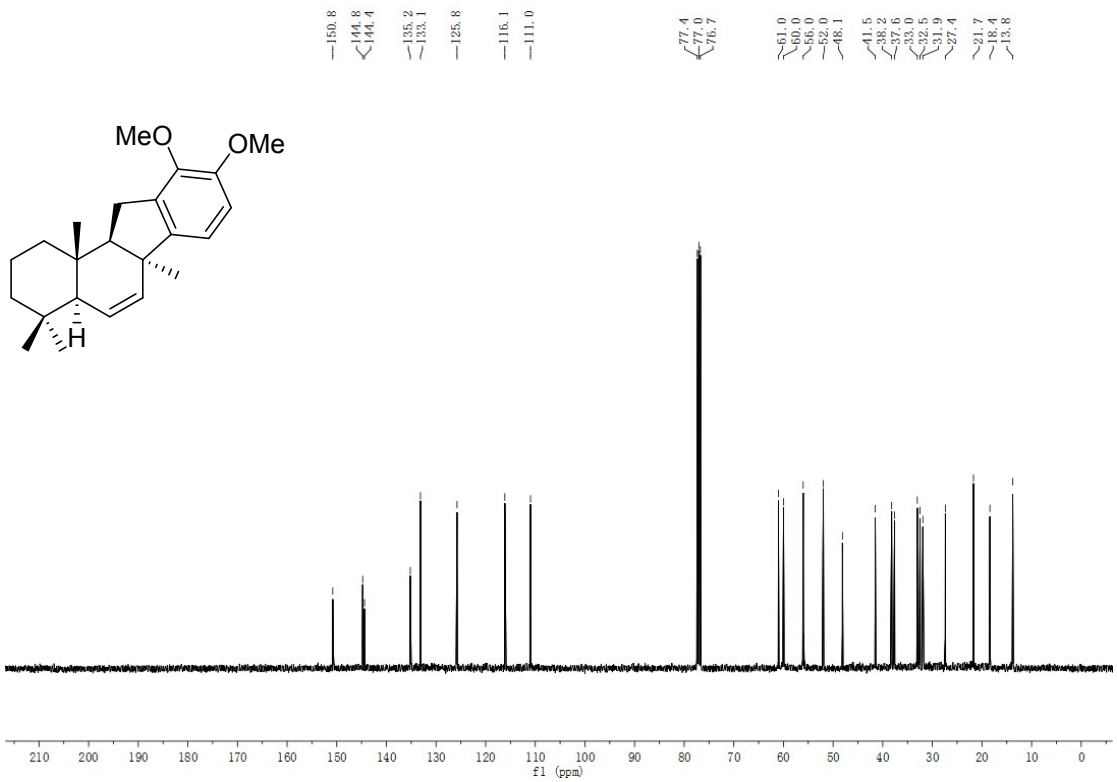
^{1}H NMR (400 MHz, $CDCl_3$) of compound 7a and 7b



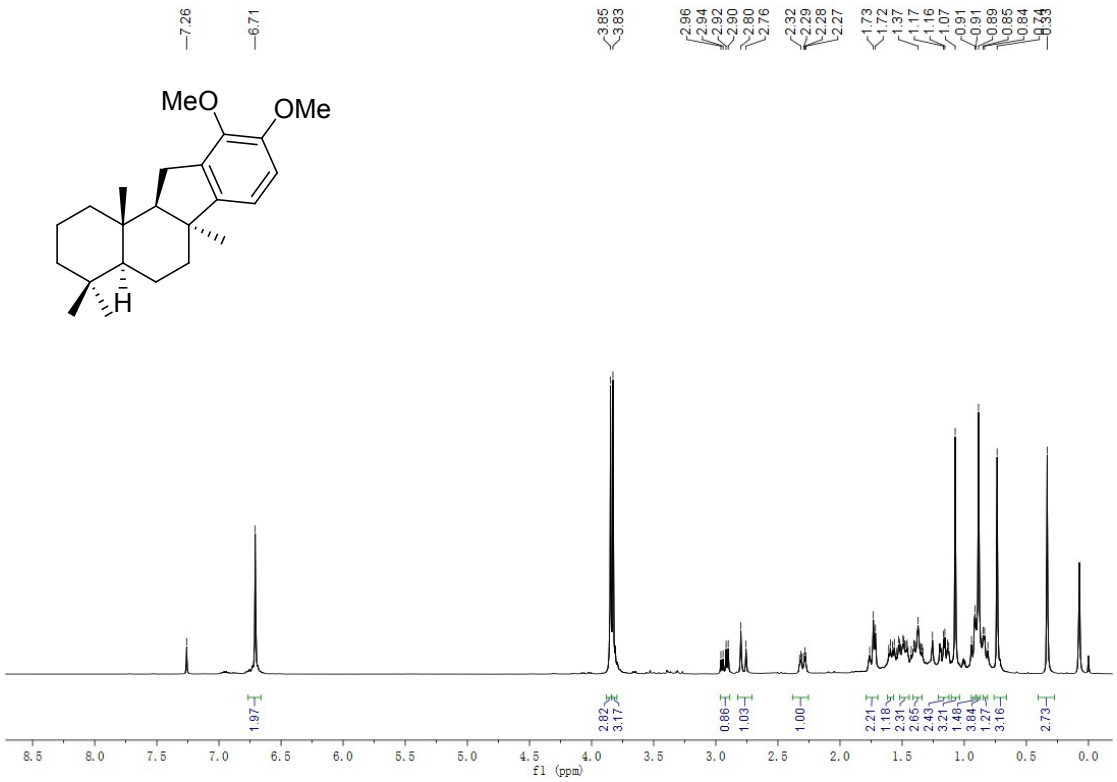
^{13}C NMR (100 MHz, $CDCl_3$) of compound 7a and 7b



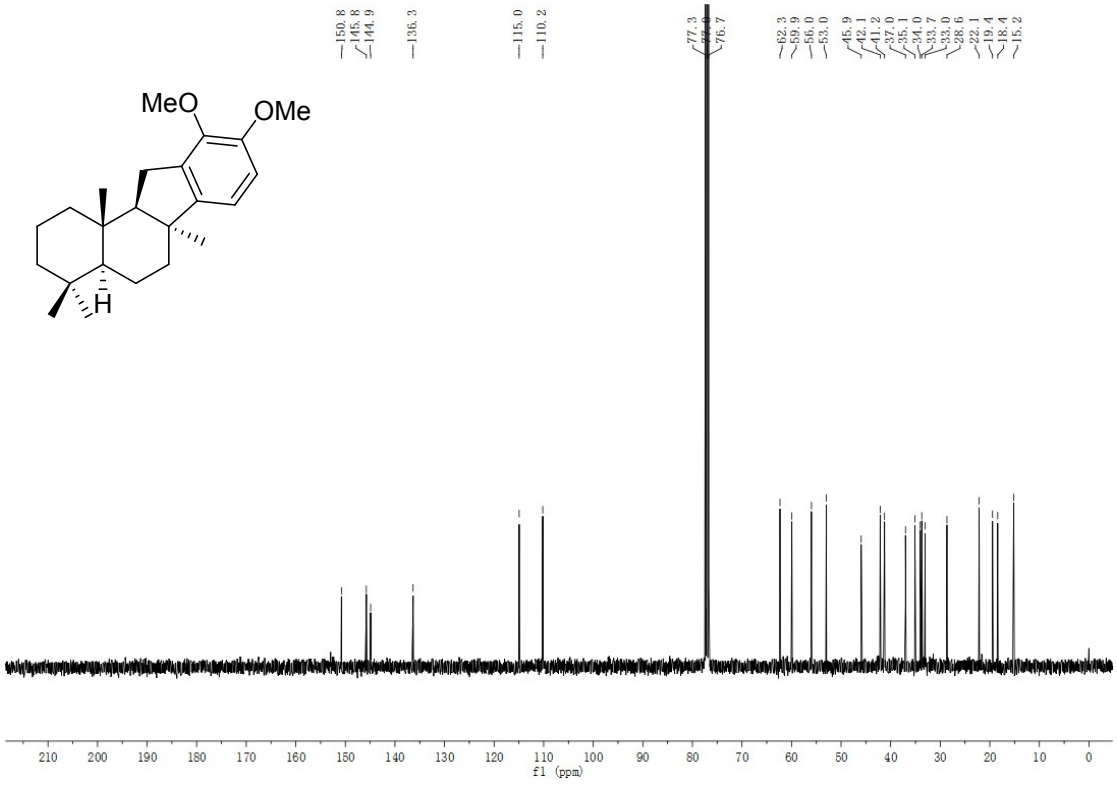
^{1}H NMR (400 MHz, $CDCl_3$) of compound 8



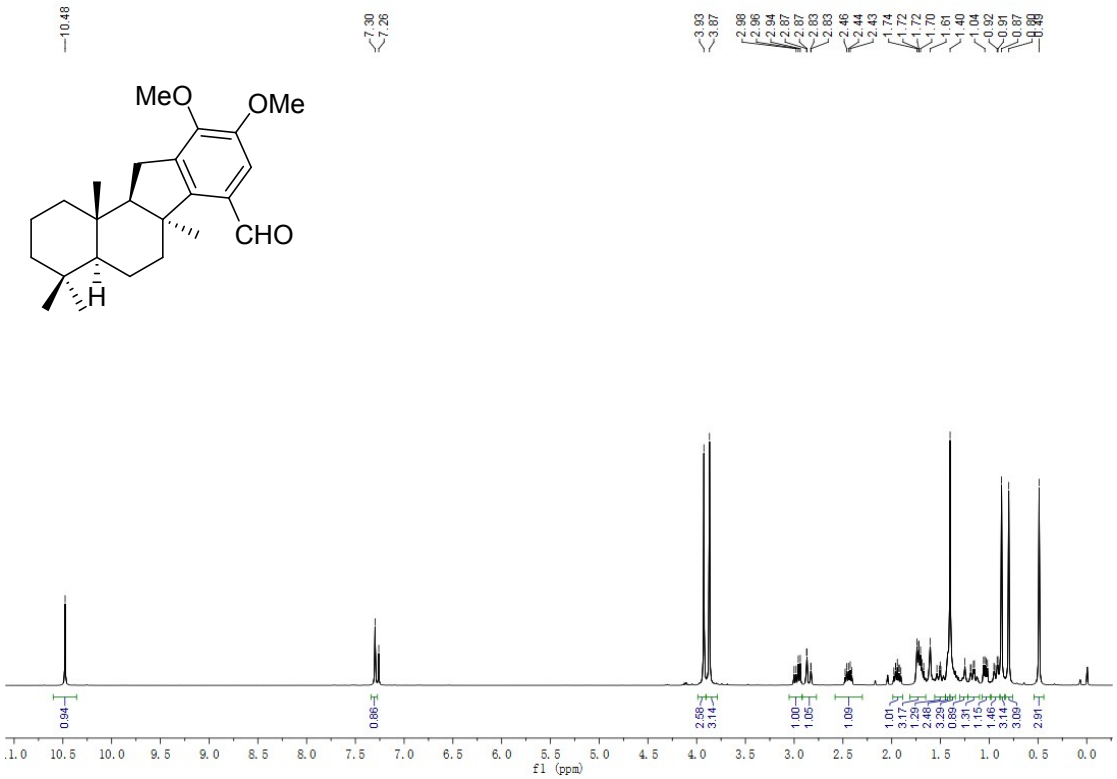
^{13}C NMR (100 MHz, $CDCl_3$) of compound 8



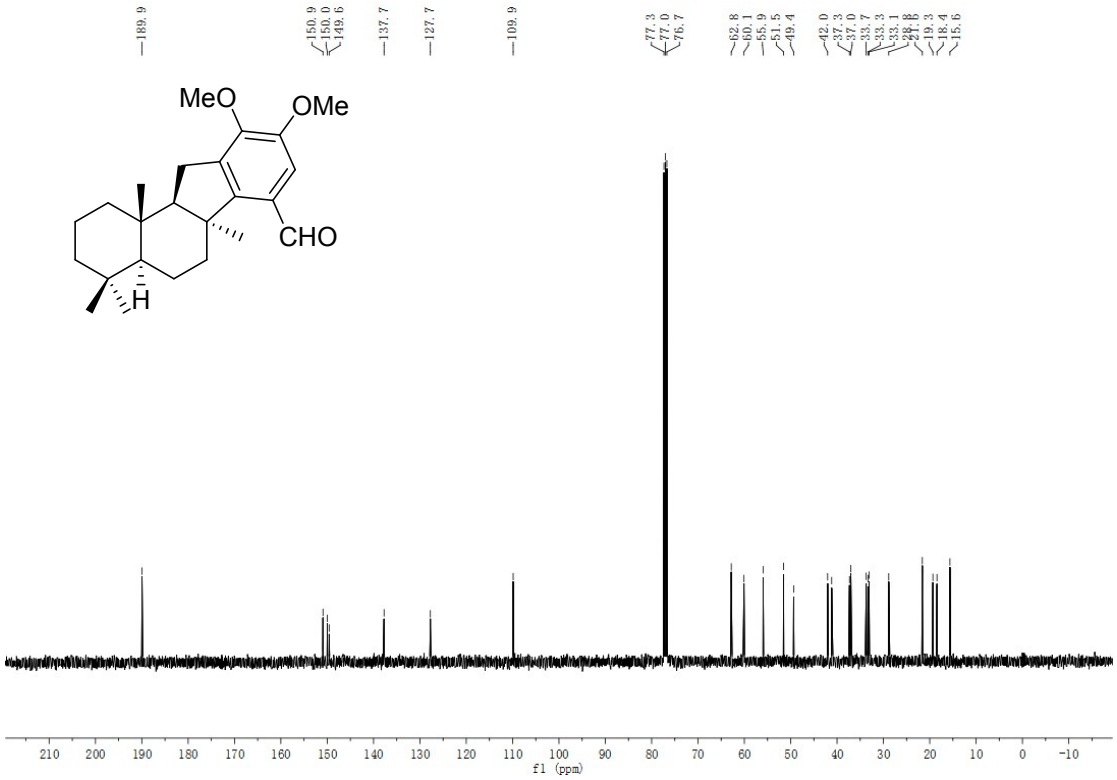
^{1}H NMR (400 MHz, $CDCl_3$) of compound 9



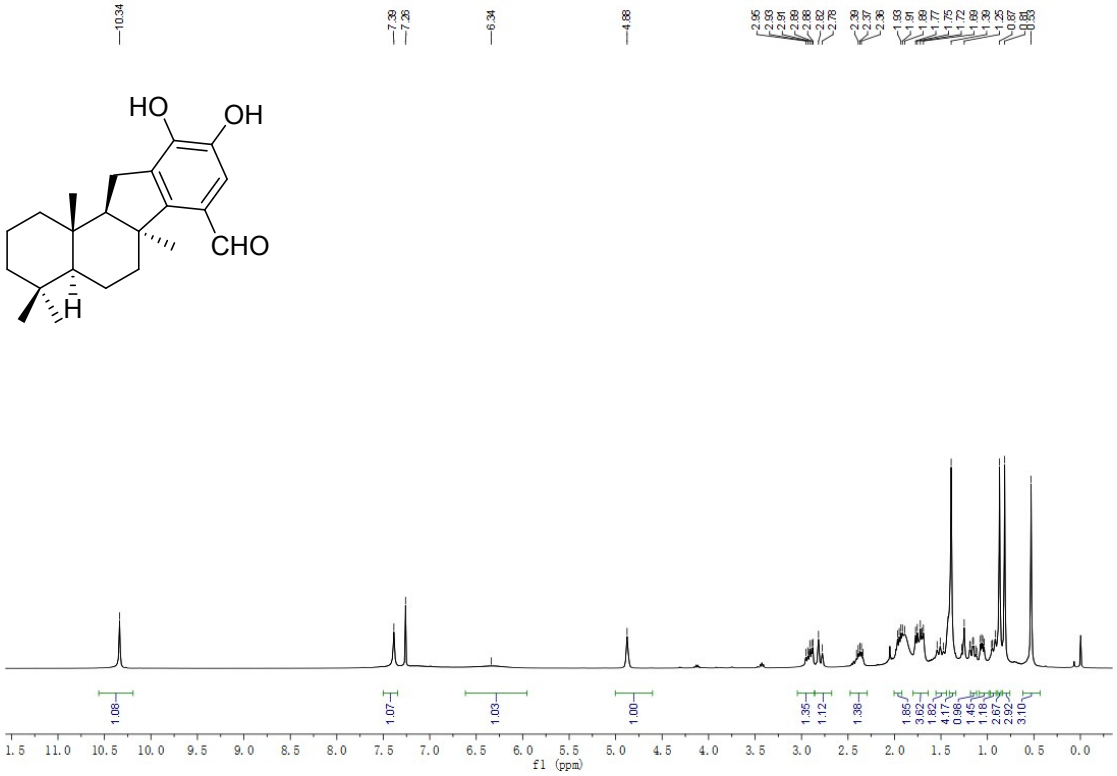
^{13}C NMR (100 MHz, $CDCl_3$) of compound 9



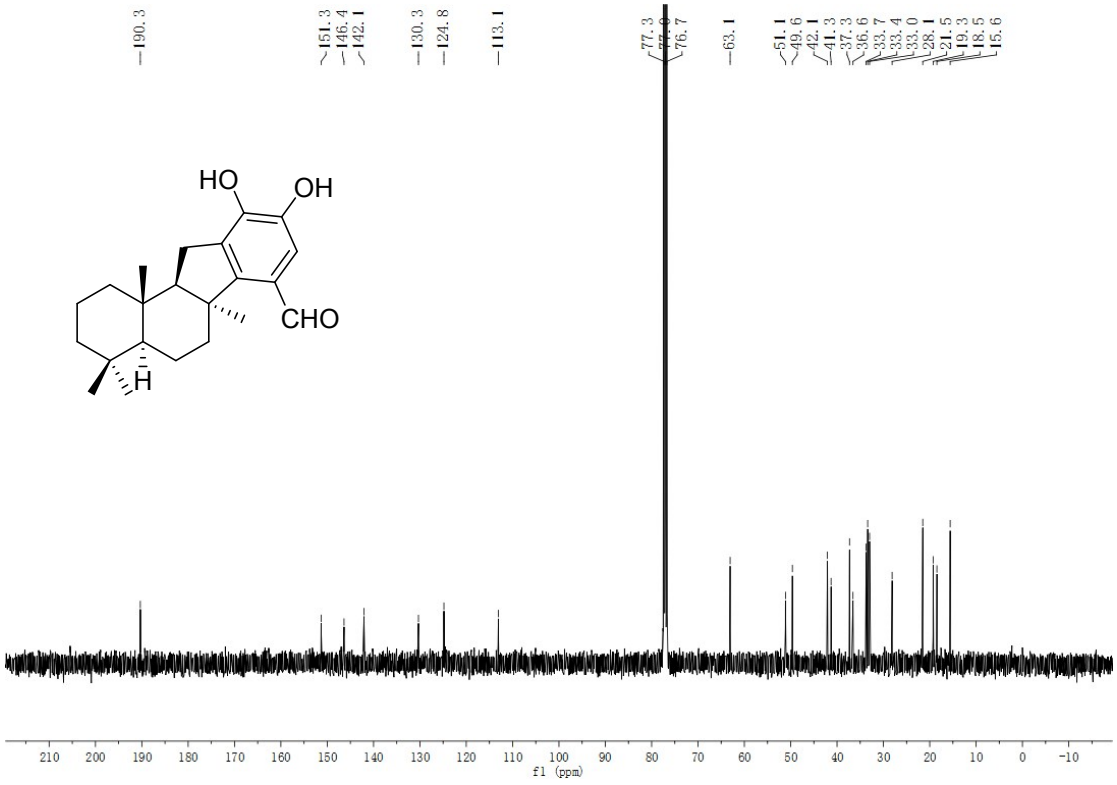
^{1}H NMR (400 MHz, $CDCl_3$) of compound 10



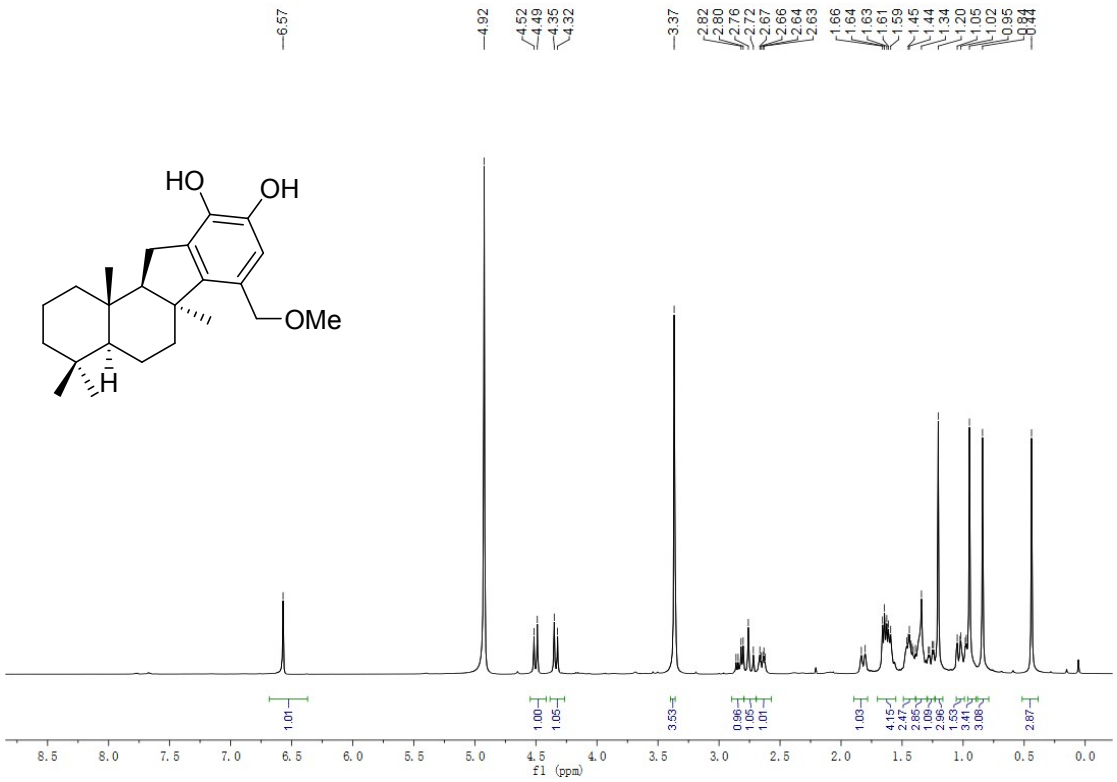
^{13}C NMR (100 MHz, $CDCl_3$) of compound 10



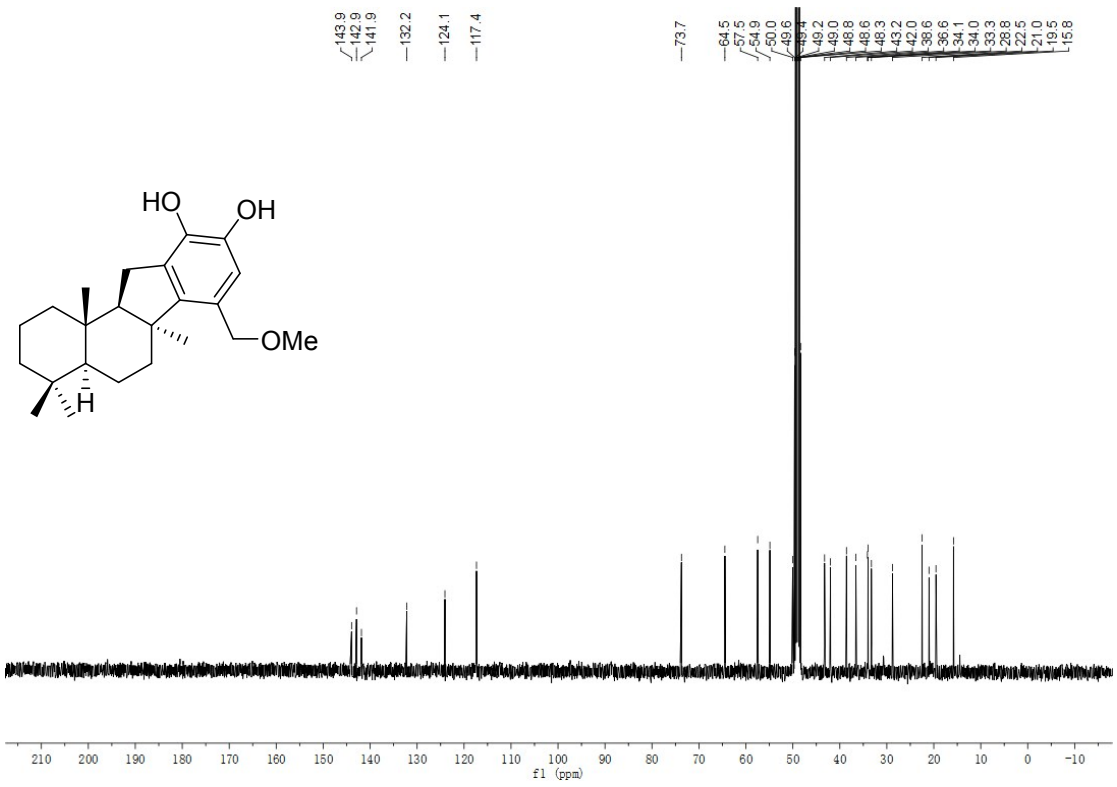
^{1}H NMR (400 MHz, $CDCl_3$) of compound 11



^{13}C NMR (100 MHz, $CDCl_3$) of compound 11



^{1}H NMR (400 MHz, CD_3OD) of compound 1a (Akaol A)



^{13}C NMR (100 MHz, CD_3OD) of compound 1a (Akaol A)