Total Synthesis of Novel D-ring Modified Triptolide Analogues: Structure-activity Relationship Studies on D-ring of Triptolide

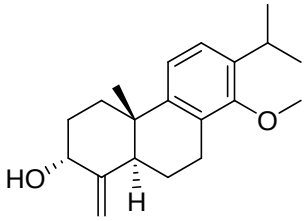
Bing Zhou, Xiaomei Li, Zehong Miao, Huanyu Tang, Huijin Feng, Yuanchao Li*

Shanghai Institute of Materia Medica, Chinese Academy of Sciences, 555 Road Zu Chong Zhi, Zhangjiang Hi-Tech Park, Shanghai 201203, PR China

ycli@mail.shcnc.ac.cn

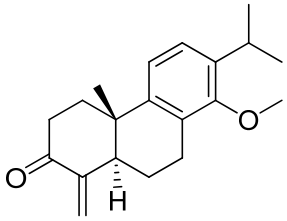
General

Mass spectra and high-resolution mass spectra were measured on a Finnigan MAT-95 mass spectrometer. Melting points were determined on a Buchi 510 melting point apparatus and are uncorrected. IR spectra were recorded on a Nicollet Magna FT-IR-750 spectrometer using KBr pellets. Optical rotations were recorded on a Jasco-Dip-181 polarimeter. ^{1}H and ^{13}C NMR spectra were determined on Bruker AM-300, Bruker AM-400 instruments using tetramethylsilane as internal reference. Data are presented as follows: chemical shift, multiplicity (s=singlet, br s=broad singlet, d=doublet, br d=broad doublet, t=triplet, m=multiplet), J=coupling constant in hertz (Hz). The signals of the ^{13}C NMR were assigned utilizing DEPT experiments and on the basis of literature data. Silica gel 60H (200-300 mesh) manufactured by Qingdao Haiyang Chemical Group Co. (China) was used for general chromatography.

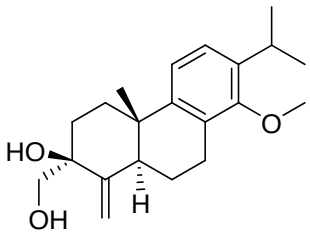


(2R,4aS,10aR)-7-isopropyl-8-methoxy-4a-methyl-1-methylene-1,2,3,4,4a,9,10,10a-octahydrophenanthren-2-ol (9). To a solution of compound **8** (13 g，0.045 mol) in CH_2Cl_2 (500 mL) were added t-BuOOH (70 wt% in water, 19.1 mL, 0.135 mol) and SeO_2 (2.5 g， 0.022mol). The mixture was stirred at room temperature overnight. $NaHSO_3$ (5 g) was added and the mixture was washed with brine. The organic phase was dried over Na_2SO_4 and concentrated to give a crude product, which was chromatographed on silica gel (5% EtOAc in cyclohexane) to give pure **9** (11.9 g,

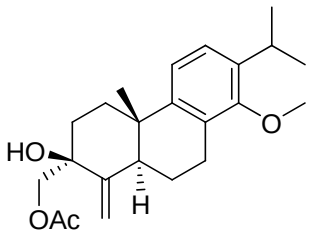
88%) as a colourless solid, mp 136-138 °C;^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.07 (s, 2 H), 5.08 (s, 1 H), 4.76 (t, J = 1.8 Hz, 1 H), 4.36 (s, 1 H), 3.73 (s, 3 H), 3.30 (sept, J = 3.0 Hz, 1 H), 3.14-3.04 (m, 1 H), 2.80-2.67 (m, 2 H), 2.08-1.60 (m, 7 H), 1.23 (d, J = 3.0 Hz, 3 H), 1.21 (d, J = 2.4 Hz, 3 H), 0.98 (s, 3 H);); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 154.8, 151.6, 145.7, 138.2, 128.4, 123.6, 121.3, 109.8, 72.7, 60.4, 41.1, 39.0, 32.4, 30.1, 26.0, 24.0, 23.9, 23.8, 21.8, 20.3; LRMS (EI, 70 eV) *m/z* (%) 300 (M^+, 10), 267 (100); HRMS (EI) calcd for $C_{20}H_{28}O_2$ (M^+): 300.2090, found 300.2086.



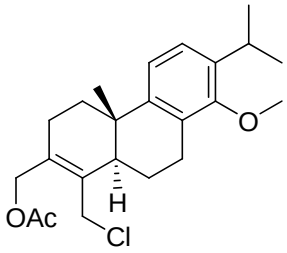
(4aS,10aR)-7-isopropyl-8-methoxy-4a-methyl-1-methylene-3,4,4a,9,10,10a-hexahydrophenanthren-2(1H)-one (10). To a solution of DMSO (7.1 mL) in CH_2Cl_2 (200 mL) were added $(COCl)_2$ (4.9 mL) at -78 °C under nitrogen and the mixture was stirred at -78 °C for 30 min. To the resultant solution was added **9** (15 g, 0.05mol) in CH_2Cl_2 (100 mL). The solution was stirred at -78 °C for 40 min and Et_3N (36 mL) was added dropwise. The solution was stirred for 30 min, warmed to room temperature, and water (20 mL) was added dropwise. The mixture was washed with water and brine. The organic phase was dried over Na_2SO_4 and concentrated to give a crude product, which was chromatographed on silica gel (2% EtOAc in cyclohexane) to give pure **10** (14 g, 94%) as a colourless solid, ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.11 (s, 2 H), 5.98 (s, 1 H), 5.23 (s, 1 H), 3.74 (s, 3 H), 3.31 (sept, J = 3.9 Hz, 1 H), 3.16 (dd, J = 18.0, 4.2 Hz, 1 H), 2.78-2.45 (m, 5 H), 2.14-1.90 (m, 2 H), 1.74-1.60 (m, 1 H), 1.24 (d, J = 3.9 Hz, 3 H), 1.21 (d, J = 3.9 Hz, 3 H), 1.13 (s, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 202.1, 154.8, 148.3, 144.0, 138.7, 128.4, 124.1, 121.7, 118.4, 60.5, 46.1, 37.2, 36.7, 36.1, 26.1, 24.0, 23.8, 23.8, 22.2, 20.3; LRMS (EI, 70 eV) *m/z* (%) 298 (M^+, 78), 241 (100); HRMS (EI) calcd for $C_{20}H_{26}O_2$ (M^+): 298.1932, found 298.1940.



(2S,4aS,10aR)-2-(hydroxymethyl)-7-isopropyl-8-methoxy-4a-methyl-1-methylene-1,2,3,4,4a,9,10,10a-octahydrophenanthren-2-ol (11). A solution of **10** (0.298 g, 1.0 mmol) in THF (6.0 mL) was added to the Grignard reagent [prepared from chloromethyldimethylisopropoxysilane (0.627 mL, 3.5 mmol), 1,2-dibromoethane (two drops), and Mg (0.096 g, 4.0 mmol) in THF (4.0 mL) according to the Tamao's procedure[28] under Ar atmosphere. After stirring at -30 °C for 55 min, the mixture was quenched with an aqueous NH_4Cl solution (10%) and extracted with EtOAc. The organic layer was washed with brine and dried over Na_2SO_4, and concentrated to give an single adduct as colorless oil. To a stirred mixture of colorless crude adduct, MeOH (5.0 mL), THF (5.0 mL), $KHCO_3$ (0.150 g, 1.5 mmol), and KF (0.282 g, 3.0 mmol) was added H_2O_2 (30%, 0.5 mL, 5.0 mmol) at room temperature. The mixture was stirred at room temperature until starting material disappeared. An aqueous $Na_2S_2O_3$ solution (50%) was added slowly to the mixture and stirred until a negative starch/iodide test was observed. The mixture was extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified via column chromatography (10% EtOAc in cyclohexane) to provide compound **11** (0.264 g, 80%) as a white solid, mp 158-160 °C; $[\alpha]_D^{25}$ +273 (c 0.15, CH_2Cl_2); IR (KBr) 3388, 2960, 2935, 2867, 1060, 1031 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.06 (m, 2 H), 5.38 (s, 1 H), 4.99 (s, 1 H), 3.76-3.72 (m, 4 H), 3.55 (d, J = 11.1 Hz, 1 H), 3.30 (sept, J = 3.0 Hz, 1 H), 3.15-3.06 (m, 1 H), 2.78-2.64 (m, 1 H), 2.46 (brs, 1 H), 2.26-2.19 (m, 2 H), 2.08-1.56 (m, 6 H), 1.23 (d, J = 2.7 Hz, 3 H), 1.21 (d, J = 3.0 Hz, 3 H), 1.02 (s, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 154.9, 151.1, 145.2, 138.5, 128.3, 123.9, 121.4, 108.6, 75.6, 66.8, 60.4, 44.5, 39.0, 35.6, 33.0, 26.0, 24.2, 23.8, 23.8, 22.3, 21.2 ; LRMS (EI, 70 eV) *m/z* (%) 330 (M^+, 15), 299 (100); HRMS (EI) calcd for $C_{21}H_{30}O_3$ (M^+): 330.2195, found 330.2187.

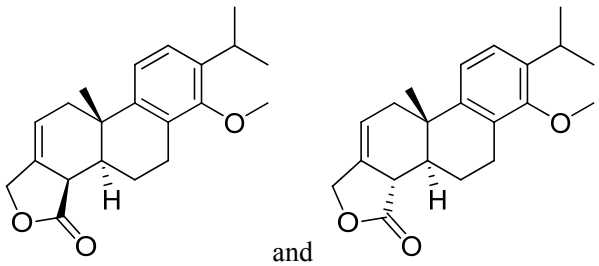


((2S,4aS,10aR)-2-hydroxy-7-isopropyl-8-methoxy-4a-methyl-1-methylene-1,2,3,4, 4a,9,10,10a-octahydrophenanthren-2-yl)methyl acetate (12). To a solution of compound **11** (4.2 g，0.013 mol) in pyridine (20 mL) was added Ac_2O (12 mL，0.13 mol). The mixture was stirred at room temperature for 3 h and CH_2Cl_2 was added. The organic layer was washed with 5% HCl and brine, dried over Na_2SO_4, and concentrated to give a crude product, which was chromatographed on silica gel (3% EtOAc in cyclohexane) to give pure **12** (4.7 g, 98%) as a colourless solid, mp 106-108 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.05 (m, 2 H), 5.36 (s, 1 H), 4.93 (s, 1 H), 4.34 (d, J = 11.7 Hz, 1 H), 4.15 (d, J = 11.1 Hz, 1 H), 3.73 (s, 3 H), 3.30 (sept, J = 3.6 Hz, 1 H), 3.10 (dd, J = 17.4, 5.7 Hz, 1 H), 2.80-2.65 (m, 2 H), 2.32-1.62 (m, 10 H), 1.23 (d, J = 3.6 Hz, 3 H), 1.21 (d, J = 3.6 Hz, 3 H), 1.01 (s, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.2, 154.9, 150.4, 145.2, 138.5, 128.3, 123.8, 121.4, 108.5, 74.8, 68.4, 60.4, 44.5, 38.9, 35.6, 32.9, 26.0, 24.3, 23.9, 23.8, 22.2, 21.2, 20.7; LRMS (EI, 70 eV) *m/z* (%) 372 (M^+, 27), 299 (100); HRMS (EI) calcd for $C_{23}H_{32}O_4$ (M^+): 372.2300, found 372.2302.



((4aS,10aR)-1-(chloromethyl)-7-isopropyl-8-methoxy-4a-methyl-3,4,4a,9,10,10a-h exahydrophenanthren-2-yl)methyl acetate (13). To a solution of compound **12** (70 mg，0.188 mmol) in Et_2O (10 mL) was added $SOCl_2$ (0.034 mL，0.47 mmol). The mixture was stirred at room temperature for 8 h and EtOAc was added. The organic layer was washed with 5% $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated to give a crude product, which was chromatographed on silica gel (0.5% EtOAc in

cyclohexane) to give pure **13** (36.0 mg, 50%) as a colourless oil, ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.08 (s, 2 H), 4.68 (m, 2 H), 4.29 (m, 2 H), 3.73 (s, 3 H), 3.30 (sept, J = 5.1 Hz, 1 H), 3.08 (ddd, J = 13.5, 4.8, 0.6 Hz, 1 H), 2.84 (m, 1 H), 2.50 (d, J = 9.6 Hz, 1 H), 2.33 (m, 4 H), 2.09 (s, 3 H), 1.70 (m, 2 H), 1.22 (d, J = 5.1 Hz, 6 H), 1.01 (s, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.0, 155.0, 145.3, 138.5, 134.3, 132.9, 128.4, 123.6, 120.3, 63.8, 60.4, 42.4, 41.0, 35.7, 33.3, 26.7, 26.0, 24.0, 23.9, 23.9, 22.3, 20.9, 19.9; LRMS (EI, 70 eV) *m/z* (%) 390 (M^+, 40), 279 (100); HRMS (EI) calcd for $C_{23}H_{31}ClO_3$ (M^+): 390.1962, found 390.1963.



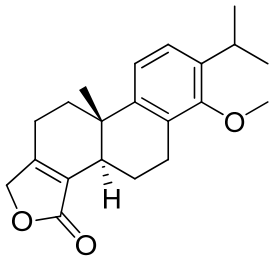
and

(3aR,3bS,9bS)-7-isopropyl-6-methoxy-9b-methyl-3a,3b,4,5,9b,10-hexahydrophenanthro[2,1-c]furan-3(1H)-one (16) and (3aS,3bS,9bS)-7-isopropyl-6-methoxy-9b-methyl-3a,3b,4,5,9b,10-hexahydrophenanthro[2,1-c]furan-3(1H)-one (17). To a solution of compound **13** (390 mg，1.0 mmol) in DMSO (10 mL) was added Me_3NO (300 mg, 4.0 mmol). The mixture was stirred at room temperature for 3 h, then AcOEt was added and the mixture was washed with brine. The organic layer was dried over Na_2SO_4 and concentrated to give a crude product, which without purification, was dissolved in MeOH (20 mL) and water (5 mL). K_2CO_3 (552 mg，4.0 mmol) was added in the solution and the mixture was stirred at room temperature for 3 h. The solvent was evaporated, then AcOEt was added and the mixture was washed with brine. The organic layer was dried over Na_2SO_4 and concentrated to give a crude product **14** and **15**. This crude product was dissolved in CH_2Cl_2 (10 mL) and pyridinium dichromate (676 mg, 1.8 mmol) was added. The mixture was stirred at room temperature overnight, diluted with ethyl acetate, and filtered through a pad of silica gel. The filtrate was concentrated under reduced pressure to give a crude product, which was chromatographed on silica gel (10% EtOAc in cyclohexane) to give pure **16** (94.5 mg, 29%) and **17** (114 mg, 35%)

as two colourless solid.

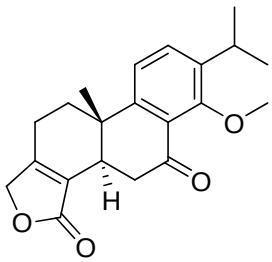
16: mp 206-208 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.10 (d, J = 8.1 Hz, 1 H), 7.04 (d, J = 8.1 Hz, 1 H); 5.80 (br s, 1 H), 4.74 (m, 2 H), 3.72 (s, 3 H), 3.31 (sept, J = 4.8 Hz, 1 H), 3.06 (dd, J = 17.4, 4.2 Hz, 1 H), 2.86-2.60 (m, 4 H), 2.26 (d, J = 18.3 Hz, 1 H), 1.86-1.77 (m, 1 H), 1.69-1.59 (m, 1 H), 1.23 (d, J = 4.8 Hz, 3 H), 1.21 (d, J = 4.8 Hz, 3 H), 1.18 (s, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 176.4, 154.7, 144.0, 138.6, 131.0, 128.9, 124.0, 121.9, 121.7, 69.9, 60.4, 40.7, 39.4, 39.3, 36.5, 26.0, 23.8, 23.7, 23.7, 23.5, 20.3; LRMS (EI, 70 eV) *m/z* (%) 326 (M^+, 100), 311 (68); HRMS (EI) calcd for $C_{21}H_{26}O_3$ (M^+): 326.1882, found 326.1873.

17: mp 204-206 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.09 (d, J = 8.1 Hz, 1 H), 7.03 (d, J = 8.1 Hz, 1 H), 5.80 (br s, 1 H), 4.74 (m, 2 H), 3.71 (s, 3 H), 3.30 (sept, J = 4.8 Hz, 1 H), 3.05 (dd, J = 17.7, 5.4 Hz, 1 H), 2.85-2.60 (m, 4 H), 2.26 (d, J = 18.0 Hz, 1 H), 1.81 (t, J = 12.6 Hz, 1 H), 1.64 (m, 1 H), 1.23 (d, J = 4.8 Hz, 3 H), 1.21 (d, J = 4.8 Hz, 3 H); 1.17 (s, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 176.5, 154.7, 144.0, 138.6, 131.0, 129.0, 124.0, 121.9, 121.8, 70.0, 60.5, 40.7, 39.4, 39.4, 36.5, 26.0, 23.9, 23.8, 23.8, 23.5, 20.4; LRMS (EI, 70 eV) *m/z* (%) 326 (M^+, 100), 311 (68); HRMS (EI) calcd for $C_{21}H_{26}O_3$ (M^+): 326.1882, found 326.1883.

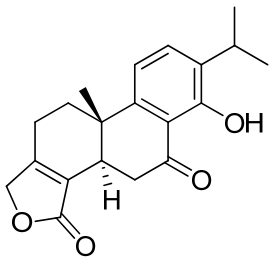


(3bR,9bS)-7-isopropyl-6-methoxy-9b-methyl-3b,4,5,9b,10,11-hexahydrophenanthro[2,1-c]furan-3(1H)-one (18). To a solution of compound **16** or **17** (326 mg，1.0 mmol) in CH_3OH (20 mL) was added CH_3ONa (10.8 mg, 0.2 mmol). The mixture was stirred at room temperature for 15 min, then AcOEt was added and the mixture was washed with brine. The organic layer was dried over Na_2SO_4 and concentrated to give a crude product, which was chromatographed on silica gel (10% EtOAc in cyclohexane) to give pure **18** (326 mg, 100%) as a colourless solid, mp 172-174 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.08 (s, 2 H), 4.70 (s, 2 H), 3.73 (s, 3 H), 3.30 (sept, J

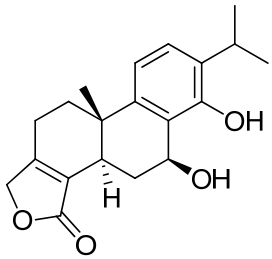
= 1.5 Hz, 1 H), 2.97 (m, 3 H), 2.53 (m, 4 H), 1.72 (m, 2 H), 1.23 (d, *J* = 1.5 Hz, 3 H), 1.21 (d, *J* = 1.5 Hz, 3 H), 1.01 (s, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 173.5, 160.8, 155.5, 144.2, 139.1, 128.9, 127.0, 123.6, 119.8, 70.7, 60.5, 38.5, 36.4, 32.5, 26.1, 23.9, 23.8, 22.7, 22.1, 21.9, 17.5; LRMS (EI, 70 eV) *m/z* (%) 326 (M^+, 80), 311 (100); HRMS (EI) calcd for $C_{21}H_{26}O_3$ (M^+): 326.1882, found 326.1881.



(3bR,9bS)-7-isopropyl-6-methoxy-9b-methyl-3b,4,10,11-tetrahydrophenanthro[2, 1-c]furan-3,5(1H,9bH)-dione (19). To a solution of **18** (32.6 mg, 0.1 mmol) in acetonitrile (2 mL) and water (2 mL), was added ammonium ceric nitrate (109 mg, 0.2 mmol) and the mixture was stirred at room temperature for 5 h. The solvent was evaporated, then CH_2Cl_2 was added and the mixture was washed with water and brine. The organic phase was dried over Na_2SO_4 and concentrated to give a crude product, which without purification, was dissolved in CH_2Cl_2 (5 mL) and pyridinium dichromate (67.6 mg, 0.18 mmol) was added. The mixture was stirred at room temperature overnight, diluted with ethyl acetate, and filtered through a pad of silica gel. The filtrate was concentrated under reduced pressure to give a crude product, which was chromatographed on silica gel (20% EtOAc in cyclohexane) to give pure **19** (30.0 mg, 88%) as a colourless solid, ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.42 (d, *J* = 8.4 Hz, 1 H), 7.13 (d, *J* = 8.4 Hz, 1 H), 4.77 (m, 2 H), 3.81 (s, 3 H), 3.66 (dd, *J* = 19.6, 6.0 Hz, 1 H), 3.42 (sept, *J* = 6.8 Hz, 1 H), 3.02 (m, 1 H), 2.62-2.49 (m, 4 H), 1.86 (m, 1 H), 1.25 (d, *J* = 6.8 Hz, 3 H), 1.21 (d, *J* = 6.8 Hz, 3 H), 1.10 (s, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 196.8, 172.6, 160.6, 158.2, 150.5, 141.7, 131.2, 125.8, 125.1, 118.0, 71.1, 62.6, 37.4, 37.0, 36.4, 31.7, 25.9, 23.7, 23.1, 21.3, 21.2; LRMS (EI, 70 eV) *m/z* (%) 340 (M^+, 36), 325 (100); HRMS (EI) calcd for $C_{21}H_{24}O_4$ (M^+): 340.1674, found 340.1680.

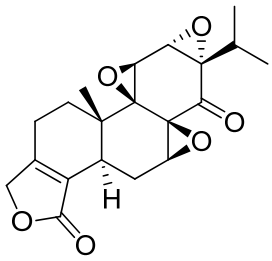


(3bR,9bS)-6-hydroxy-7-isopropyl-9b-methyl-3b,4,10,11-tetrahydrophenanthro[2,1-c]furan-3,5(1H,9bH)-dione (20). To a solution of **19** (21.1 mg, 0.062 mmol) in dichloromethane (2 mL), under nitrogen at -78 °C, was added BBr_3 (0.018 mL, 0.186 mol) and the mixture was stirred at -78 °C for 1 h and warmed to room temperature. An aqueous $NaHCO_3$ solution (10%) was added and the extracts were washed with brine. The organic phase was dried over Na_2SO_4 and concentrated to give a crude product which was chromatographed on silica gel (20% EtOAc in cyclohexane) to give pure **20** (19.5 mg, 96.5%) as a white solid, mp 84-86 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 13.2 (s, 1 H), 7.38 (d, J = 7.6 Hz, 1 H), 6.83 (d, J = 7.6 Hz, 1 H), 4.76 (m, 2 H), 3.78 (dd, J = 18.8, 4.4 Hz, 1 H), 3.35 (sept, J = 6.8 Hz, 1 H), 3.08-3.01 (m, 1 H), 2.60 (m, 4 H), 1.85 (m, 1 H), 1.24 (d, J = 6.8 Hz, 3 H), 1.22 (d, J = 6.8 Hz, 3 H), 1.13 (s, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 203.9, 172.5, 161.5, 161.1, 149.1, 135.8, 133.0, 125.3, 114.8, 113.0, 71.0, 37.7, 36.2, 35.4, 31.4, 26.1, 22.2, 22.1, 21.5, 21.4; LRMS (EI, 70 eV) *m/z* (%) 326 (M^+, 40), 311 (100); HRMS (EI) calcd for $C_{20}H_{22}O_4$ (M^+): 326.1518, found 326.1510.



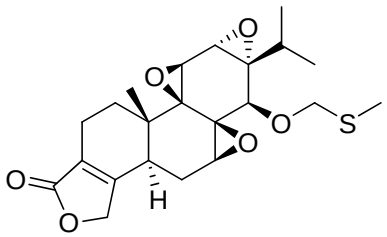
(3bR,5S,9bS)-5,6-dihydroxy-7-isopropyl-9b-methyl-3b,4,5,9b,10,11-hexahydrophenanthro[2,1-c]furan-3(1H)-one (21). To a solution of **20** (28.7 mg, 0.088 mmol) in methanol (2 mL) at 0 °C was added sodium borohydride (3.3 mg, 0.088 mmol) in three portions. After stirring at 0 °C for 30 min, the mixture was quenched with an aqueous NH_4Cl solution (10%) and extracted with EtOAc. The organic layer was

washed with brine and dried over Na_2SO_4, and concentrated to give a crude product which was chromatographed on silica gel (40% EtOAc in cyclohexane) to give pure **21** (24.2 mg, 84%) as a white solid, mp 160-162 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.70 (s, 1 H), 7.13 (d, J = 8.0 Hz, 1 H), 6.83 (d, J = 8.0 Hz, 1 H), 5.28 (m, 1 H), 4.73 (m, 2 H), 3.50 (m, 2 H), 3.34 (sept, J = 6.8 Hz, 1 H), 2.67 (m, 1 H), 2.56-2.46 (m, 3 H), 1.89-1.71 (m, 2 H), 1.25 (d, J=6.8 Hz, 3 H), 1.22 (d, J=6.8 Hz, 3 H); 1.12 (s, 3 H);); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 173.6, 161.9, 154.6, 143.2, 133.9, 125.7, 125.6, 121.0, 115.0, 70.9, 69.5, 37.6, 36.6, 32.4, 28.0, 26.4, 23.1, 22.6, 22.4, 21.7; LRMS (EI, 70 eV) *m/z* (%) 328 (M^+, 8), 310 (100); HRMS (EI) calcd for $C_{20}H_{24}O_4$ (M^+): 328.1675, found 328.1684.

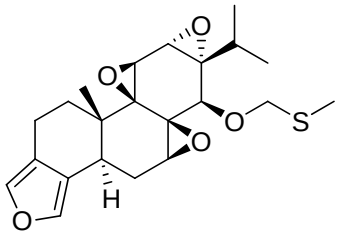


(7,8)β,(9,11)β,(12,13)α-tris(epoxy)-18-hydroxy-14-oxo-l8(4 → 3) abeo-abieta-3-en-19-oic acid lactone (3). To a solution of compound **21** (30.1 mg, 0.092 mmol) in MeOH (3 mL) was added a solution of $NaIO_4$ (19.8 mg, 0.092 mmol) in water (1 mL) at 0 °C. After stirring at 0 °C for 50 min, the mixture was extracted with EtOAc. The organic layer was washed with brine and dried over Na_2SO_4, and concentrated to give a crude product **22** which was dissolved in acetonitrile (2 mL) and was added an aqueous Na_2(EDTA) solution (4×10^{-4} M, 2 mL). The resulting homogeneous solution was cooled to 0 °C, followed by addition of 1,1,1-trifluoroacetone (0.1 mL) via a precooled syringe. To this homogeneous solution was added in portions a mixture of sodium bicarbonate (22.7 mg, 0.27 mmol) and Oxone (115.3 mg, 0.18 mmol) in a period of 1 h (pH 7-7.5). The reaction was monitored by TLC. The mixture was poured into water and extracted with dichloromethane. The extracts were dried (Na_2SO_4), filtered, and concentrated to give a crude product which was dissolved in MeOH (2 mL) and was added H_2O_2 (30%, 0.1 mL, 1.0 mmol) at room temperature. After stirring for 1 h, the mixture was extracted

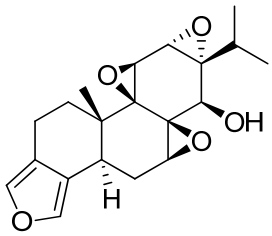
with EtOAc. The organic layer was washed with brine and dried over Na_2SO_4, and concentrated to give a crude product which was chromatographed on silica gel (40% EtOAc in cyclohexane) to give pure **3** (20.4 mg, 62%) as a white solid, mp 224-226 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.68 (m, 2 H), 4.00 (d, J = 3.0 Hz, 1 H), 3.81 (d, J = 3.0 Hz, 1 H), 3.42 (d, J = 5.4 Hz, 1 H), 3.18 (m, 1 H), 2.69 (m, 1 H), 2.47-2.33 (m, 3 H), 2.02 (m, 1 H), 1.85 (dd, J = 15.6, 13.5 Hz, 1 H), 1.31 (m, 1 H), 1.08 (s, 3 H), 0.98 (d, J = 6.9 Hz, 3 H), 0.89 (d, J = 6.9 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 197.2, 172.5, 160.5, 125.6, 70.9, 66.4, 65.3, 61.3, 60.8, 58.7, 55.9, 38.1, 35.3, 30.2, 25.7, 22.0, 20.7, 18.0, 16.3, 13.7; LRMS (EI, 70 eV) *m/z* (%) 358 (M^+, 52), 329 (28), 287 (40), 175 (100); HRMS (EI) calcd for $C_{20}H_{22}O_6$ (M^+): 358.1417, found 358.1422.



Triptolide methylthiomethy ether (23). To a solution of compound **1** (50 mg, 0.139 mmol) in DMSO (0.4 mL) was added Ac_2O (0.28 mL) and AcOH (0.05 mL). After stirring overnight, the mixture was extracted with EtOAc. The organic layer was washed with brine and dried over Na_2SO_4, and concentrated to give a crude product which was chromatographed on silica gel (20% EtOAc in cyclohexane) to give pure **23** (32.1 mg, 55%) as a white solid, ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.00 (m, 2 H), 4.66 (m, 2 H), 3.78 (d, J = 3.0 Hz, 1 H), 3.67 (s, 1 H), 3.50 (d, J = 2.7 Hz, 1 H), 3.23 (d, J = 5.4 Hz, 1 H), 2.70 (m, 1 H), 2.37-2.26 (m, 2 H), 2.21-2.12 (m, 5 H), 1.92 (t, J = 13.5 Hz, 1 H), 1.60 (m, 1 H), 1.20 (m, 1 H), 1.08 (s, 3 H), 1.00 (d, J = 6.9 Hz, 3 H), 0.82 (d, J = 6.9 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 173.2, 160.1, 125.5, 76.7, 75.8, 69.9, 64.5, 63.9, 61.4, 58.0, 55.0, 54.6, 40.4, 35.8, 29.5, 26.3, 23.4, 17.1, 17.0, 16.8, 14.8, 13.6; LRMS (EI, 70 eV) *m/z* (%) 421 (M+1, 2), 377 (4), 273 (40), 61 (100); HRMS (EI) calcd for $C_{22}H_{29}SO_6$ (M+1): 421.1685, found 421.1672.

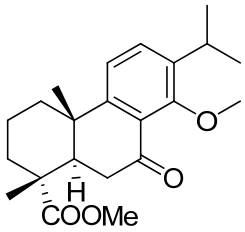


Preparation of compound 24. To a solution of compound **23** (42.0 mg, 0.1mmol) in CH_2Cl_2 (5 mL) was added a solution of DIBAL (0.15 mL, 1.0 M in n-hexane) at -78 °C. After stirring at -78 °C for 50 min, water (0.1mL) was added slowly and the mixture was extracted with EtOAc. The organic layer was washed with brine and dried over Na_2SO_4, and concentrated to give a crude product which was dissolved in $CDCl_3$ (2 mL) and silica gel (100 mg) was added. The mixture stirred overnight and was extracted with CH_2Cl_2. The organic layer was washed with brine and dried over Na_2SO_4, and concentrated to give a crude product which was chromatographed on silica gel (5% EtOAc in cyclohexane) to give pure **24** (30.3 mg, 75%) as a white oil, ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.12 (s, 2 H), 5.02 (m, 2 H), 3.79 (d, J = 3.3 Hz, 1 H), 3.66 (s, 1 H), 3.50 (d, J = 2.4 Hz, 1 H), 3.20 (d, J = 5.4 Hz, 1 H), 2.71 (dd, J = 12.3, 6.6 Hz, 1 H), 2.58 (dd, J = 16.5, 4.8 Hz, 1 H), 2.48-2.30 (m, 3 H), 2.18 (s, 3 H), 1.95 (dd, J = 15.3, 12.3 Hz, 1 H), 1.53 (m, 1 H), 1.19 (m, 1 H), 1.06 (s, 3 H), 1.02 (d, J = 6.9 Hz, 3 H), 0.83 (d, J = 6.9 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 137.5, 137.2, 124.6, 119.1, 76.6, 76.2, 64.4, 64.3, 61.3, 58.6, 55.0, 54.8, 37.6, 35.9, 30.7, 26.3, 25.9, 17.1, 16.9, 15.5, 14.8, 12.9; LRMS (EI, 70 eV) *m/z* (%) 404 (M^+, 2), 327 (20), 61 (100); HRMS (EI) calcd for $C_{22}H_{28}SO_5$ (M^+): 404.1658, found 404.1675.

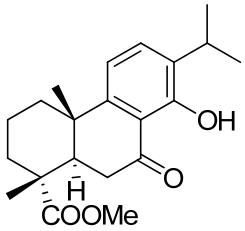


Preparation of compound 4. To a solution of compound **24** (10 mg, 0.025 mmol) in CH_3CN (1 mL) and water (0.25 mL)was added $HgCl_2$ (54.2 mg, 0.2 mmol). After stirring overnight, the mixture was extracted with EtOAc. The organic layer was washed with brine and dried over Na_2SO_4, and concentrated to give a crude product which was chromatographed on silica gel (20% EtOAc in cyclohexane) to give pure **4**

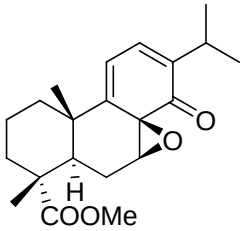
(7.3 mg, 85%) as a white oil, ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.12 (s, 2 H), 3.93 (d, J = 3.2 Hz, 1 H), 3.52 (d, J = 2.8 Hz, 1 H), 3.45 (d, J = 10.8 Hz, 1 H), 3.39 (d, J = 5.2 Hz, 1 H), 2.88 (d, J = 10.8 Hz, 1 H), 2.72 (dd, J = 11.2, 6.0 Hz, 1 H), 2.61 (dd, J = 16.8, 6.0 Hz, 1 H), 2.44 (m, 2 H), 2.25 (sept, J = 7.2 Hz, 1 H), 2.00 (dd, J = 15.2, 12.4 Hz, 1 H), 1.48 (dd, J = 12.0, 5.6 Hz, 1 H), 1.21 (m, 1 H), 1.09 (s, 3 H), 1.02 (d, J=7.2 Hz, 3 H), 0.89 (d, J=7.2 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 137.6, 137.3, 124.2, 118.8, 73.6, 66.9, 65.5, 60.9, 60.7, 56.9, 54.6, 37.5, 35.7, 30.9, 28.0, 26.0, 17.7, 16.8, 15.5, 12.9; LRMS (EI, 70 eV) *m/z* (%) 344 (M^+, 100); HRMS (EI) calcd for $C_{20}H_{24}O_5$ (M^+): 344.1624, found 344.1627.



(1R,4aS,10aR)-methyl 7-isopropyl-8-methoxy-1,4a-dimethyl-9-oxo-1,2,3,4,4a,9,10,10a-octahydrophenanthrene-1-carboxylate (26). To a solution of compound **25** (3 g, 6.2 mmol) in acetone (100 mL)was added $Na_2Cr_2O_7$ (3.68 g, 12.3 mmol) and N-hydroxyphthalimide (4.03 g, 24.7 mmol). The mixture was stirred at room temperature overnight, diluted with ethyl acetate, and filtered through a pad of silica gel. The filtrate was concentrated under reduced pressure to give a crude product, which was chromatographed on silica gel (5% EtOAc in cyclohexane) to give pure **26** (1.85 g, 81.6%) as a colourless oil, $[\alpha]_D^{25}$ +67.9 (c 0.98, $CHCl_3$); IR (KBr) 2958, 1720, 1679, 1471, 1228, 1037, 840 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.40 (d, J = 8.3 Hz, 1 H), 7.09 (d, J = 8.2 Hz, 1 H), 3.78 (*s*, 3 H), 3.65 (s, 3 H), 3.39 (sept, J = 7.2 Hz, 1 H), 2.64 (m, 2 H), 2.42 (m, 1 H), 2.28 (d, J = 11.4 Hz, 1 H), 1.80-1.23 (m, 5 H), 1.33 (s, 3 H), 1.22 (d, J = 7.2 Hz, 3 H), 1.20 (s, 3 H) , 1.18 (d, J = 7.2 Hz, 3 H); ^{13}C NMR (100MHz, $CDCl_3$) δ 197.7, 177.8, 157.4, 154.7, 140.8, 131.6, 124.6, 118.5, 62.4, 52.0, 46.1, 42.6, 38.9, 37.5, 37.5, 36.5, 25.8, 23.7, 23.4, 23.1, 18.0, 16.4; LRMS (EI, 70 eV) *m/z* (%) 358 (M^+, 40), 343 (100).

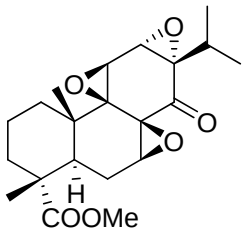


(1R,4aS,10aR)-methyl 8-hydroxy-7-isopropyl-1,4a-dimethyl-9-oxo-1,2,3,4,4a,9,10,10a-octahydrophenanthrene-1-carboxylate (27). To a solution of **26** (22.2 mg, 0.062 mmol) in dichloromethane (2 mL), under nitrogen at -78 °C, was added BBr_3 (0.018 mL, 0.186 mol) and the mixture was stirred at -78 °C for 1 h and warmed to room temperature. An aqueous $NaHCO_3$ solution (10%) was added and the extracts were washed with brine. The organic phase was dried over Na_2SO_4 and concentrated to give a crude product which was chromatographed on silica gel (5% EtOAc in cyclohexane) to give pure **27** (18.7 mg, 88%) as a white oil, IR (KBr) 3432, 2954, 1727, 1625, 1429, 1351, 1249, 1122, 821 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 13.09 (s, 1 H), 7.36 (d, J = 8.0 Hz, 1 H), 6.77 (d, J = 8.0 Hz, 1 H), 3.66 (s, 3 H), 3.32 (sept, J = 6.8 Hz, 1 H), 2.72 (m, 2 H), 2.32 (m, 2 H), 1.74-1.23 (m, 5 H), 1.33 (s, 3 H), 1.24 (s, 3 H), 1.21 (d, J = 6.8 Hz, 6 H); ^{13}C NMR (100MHz, $CDCl_3$) δ 205.0, 177.6, 160.6, 153.6, 134.7, 133.3, 114.6, 113.0, 52.2, 46.5, 43.3, 37.7, 37.4, 37.0, 36.4, 26.0, 23.6, 22.3, 22.1, 18.1, 16.4; LRMS (EI, 70 eV) *m/z* (%) 344 (M^+, 72), 329 (100).



(41R,5aS,6aR,7R,10aS)-methyl 3-isopropyl-7,10a-dimethyl-4-oxo-5a,6,6a,7,8,9,10,10a-octahydro-4H-phenanthro[9-b]oxirene-7-carboxylate (29). To a solution of **27** (30.3 mg, 0.088 mmol) in methanol (2 mL) at 0 °C was added sodium borohydride (3.3 mg, 0.088 mmol) in three portions. After stirring at 0 °C for 30 min, the mixture was quenched with an aqueous NH_4Cl solution (10%) and extracted with EtOAc. The organic layer was washed with brine and dried over Na_2SO_4, and concentrated to give a crude product

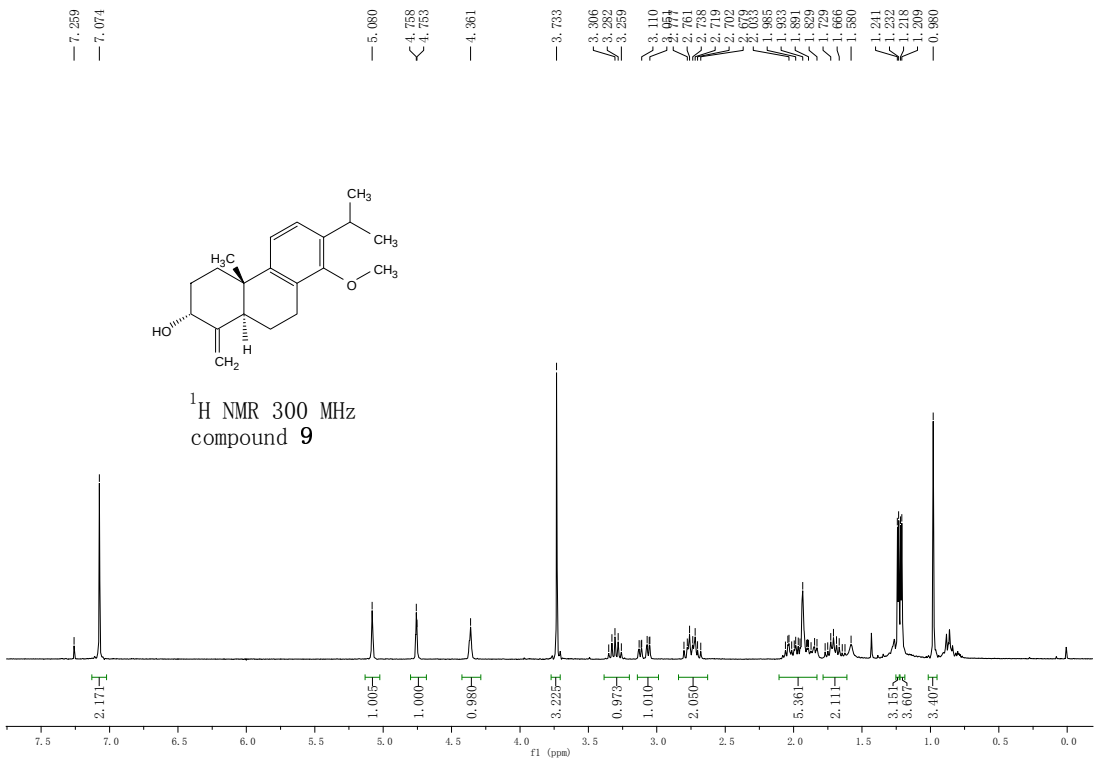
which was dissolved in MeOH (3 mL) and $NaIO_4$ (18.8 mg, 0.088 mmol) in H_2O (1 mL) was added at 0 °C. After stirring at 0 °C for 50 min, the mixture was extracted with EtOAc. The organic layer was washed with brine and dried over Na_2SO_4, and concentrated to give a crude product product which was chromatographed on silica gel (5% EtOAc in cyclohexane) to give pure **29** (19.0 mg, 63%) as a white oil, ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.93 (dd, J = 6.7, 1.0 Hz, 1 H), 6.28 (d, J = 6.8 Hz, 1 H), 3.93 (d, J = 5.5 Hz, 1 H), 3.63 (s, 3 H), 2.80 (sept, J = 6.9 Hz, 1 H), 2.17-1.98 (m, 2H), 1.83-1.56 (m, 6 H), 1.24 (s, 3 H), 1.21 (s, 3 H), 1.08 (d, J = 2.1 Hz, 3 H), 1.06 (d, J = 2.1 Hz, 3 H); ^{13}C NMR (100MHz, $CDCl_3$) δ 194.6, 178.1, 155.5, 141.5, 135.7, 118.9, 68.6, 57.2, 52.1, 47.3, 47.0, 38.5, 37.5, 37.4, 26.1, 24.3, 21.8, 21.5, 20.5, 17.6, 16.6; LRMS (EI, 70 eV) *m/z* (%) 344 (M^+, 68), 329 (100).



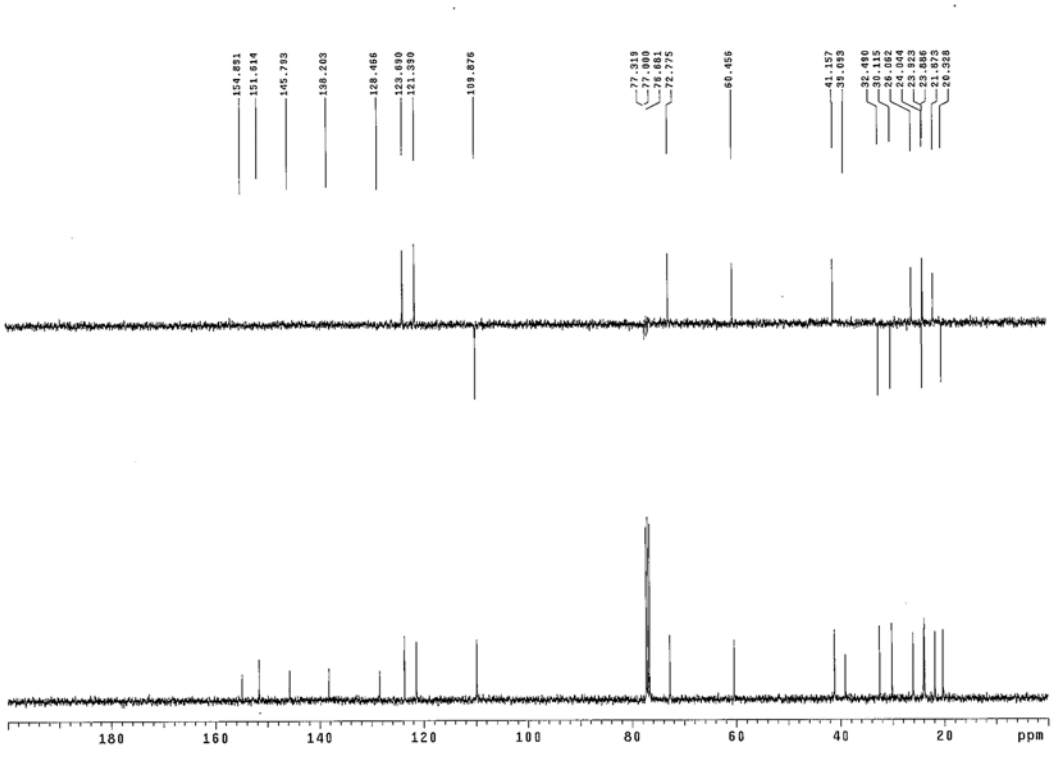
(7,8)β,(9,11)β,(12,13)α-tris(epoxy)-14-oxo-abieta-19α-oic acid methyl ester (5). To a solution of **29** (31.0 mg, 0.09 mmol) in acetonitrile (2 mL) and was added an aqueous Na_2(EDTA) solution (4×10^{-4} M, 2 mL). The resulting homogeneous solution was cooled to 0 °C, followed by addition of 1,1,1-trifluoroacetone (0.1 mL) via a precooled syringe. To this homogeneous solution was added in portions a mixture of sodium bicarbonate (22.7 mg, 0.27 mmol) and Oxone (115.3 mg, 0.18 mmol) in a period of 1 h (pH 7-7.5). The reaction was monitored by TLC. The mixture was poured into water and extracted with dichloromethane. The extracts were dried (Na_2SO_4), filtered, and concentrated to give a crude product which was dissolved in MeOH (2 mL) and was added H_2O_2 (30%, 0.1 mL, 1.0 mmol) at room temperature. After stirring for 1 h, the mixture was extracted with EtOAc. The organic layer was washed with brine and dried over Na_2SO_4, and concentrated to give a crude product which was chromatographed on silica gel (8% EtOAc in cyclohexane) to give pure **5** (22.0 mg, 65%) as a white oil, $[\alpha]_D^{25}$ -50.2 (c 0.45, $CHCl_3$); IR (KBr) 3430, 2950,

2877, 1724, 1434, 1240, 1191, 947, 891 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.18 (d, J = 2.7 Hz, 1 H), 3.80 (d, J = 2.7 Hz, 1 H), 3.67 (s, 3 H), 3.26 (d, J = 5.4 Hz, 1 H), 2.39 (sept, J = 6.9 Hz, 1 H), 2.22 (dd, J = 12.5, 5.8 Hz, 1 H), 2.00 (dd, J = 15.1, 12.7Hz, 1 H), 1.75-1.55 (6H, m), 1.20 (s, 3 H), 1.14 (m, 1 H), 1.13 (s, 3 H), 0.97 (d, J = 6.5 Hz, 3 H), 0.87 (d, J = 6.3 Hz, 3 H); ^{13}C NMR (100MHz, $CDCl_3$) δ 197.8, 177.8, 68.0, 66.2, 61.3, 60.8, 59.1, 57.2, 52.2, 46.6, 43.6, 37.3, 35.9, 33.9, 25.6, 23.0, 18.0, 17.0, 16.8, 16.3; LRMS (EI, 70 eV) *m/z* (%) 376 (M^+, 20), 273 (100); HRMS (EI) calcd for $C_{21}H_{28}O_6$ (M^+): 376.1784, found 376.1886.

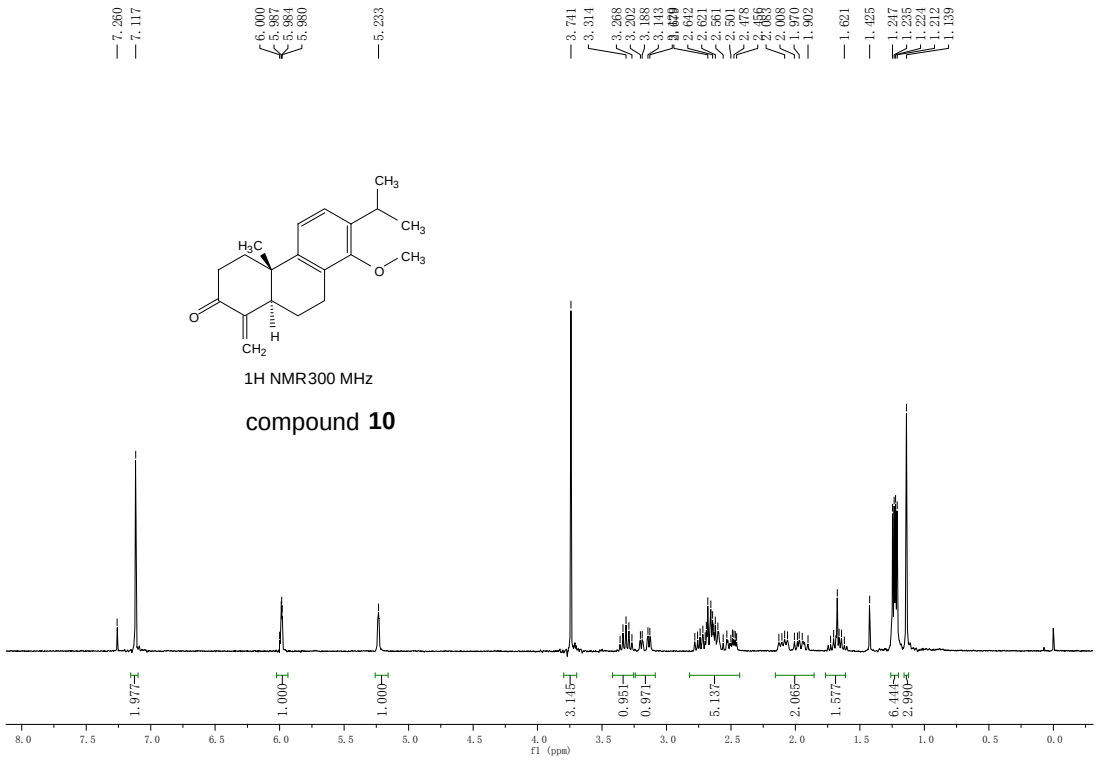
^{1}H NMR of compound **9**:



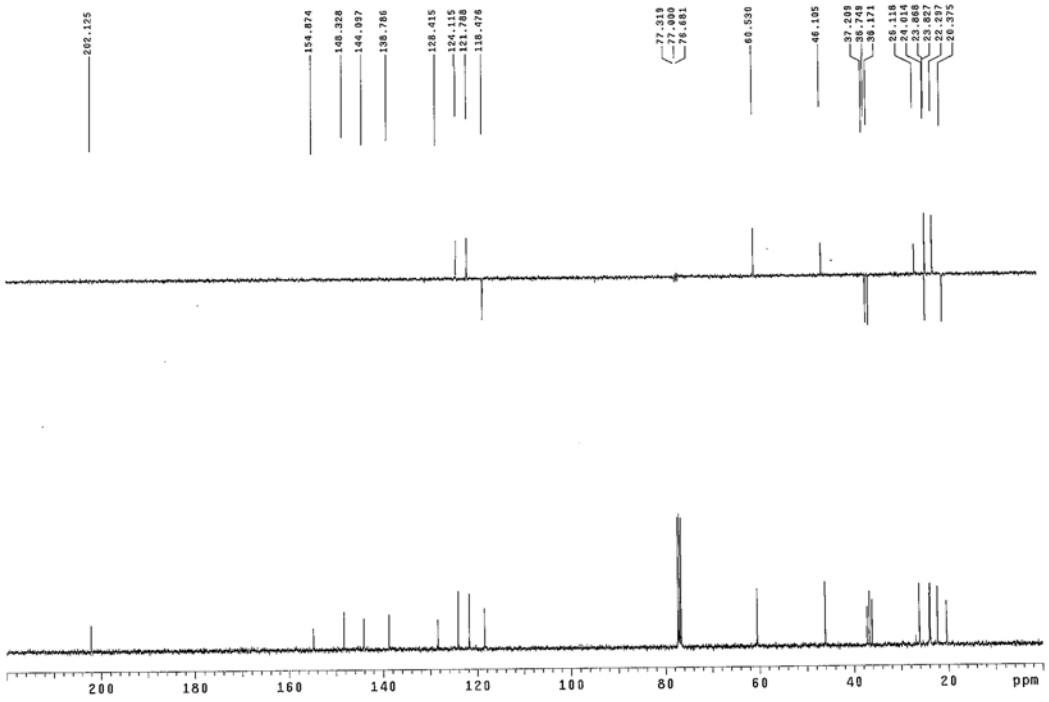
^{13}C NMR of compound **9**:



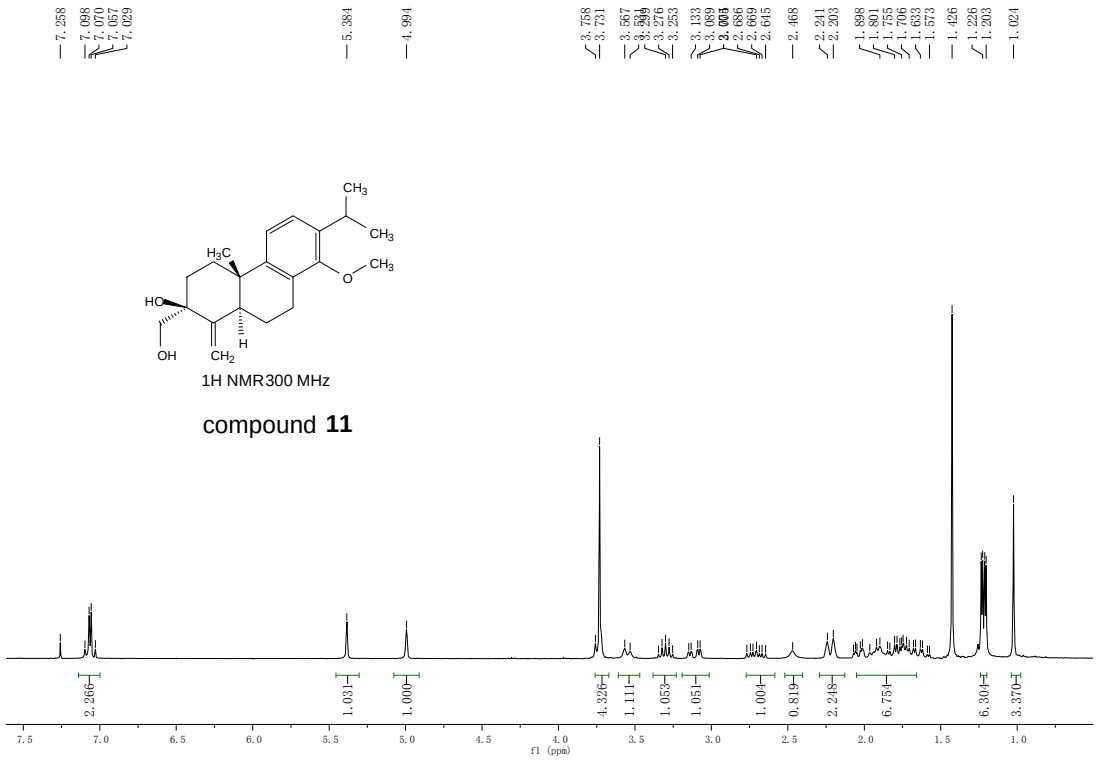
^{1}H NMR of compound **10**:



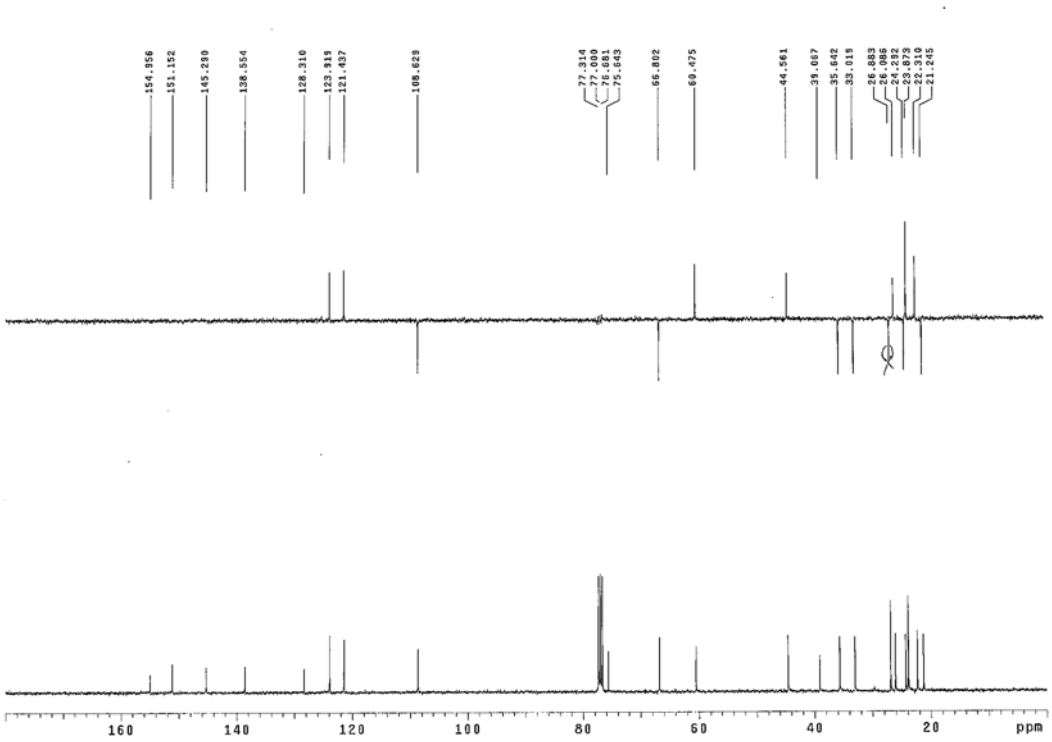
^{13}C NMR of compound **10**:



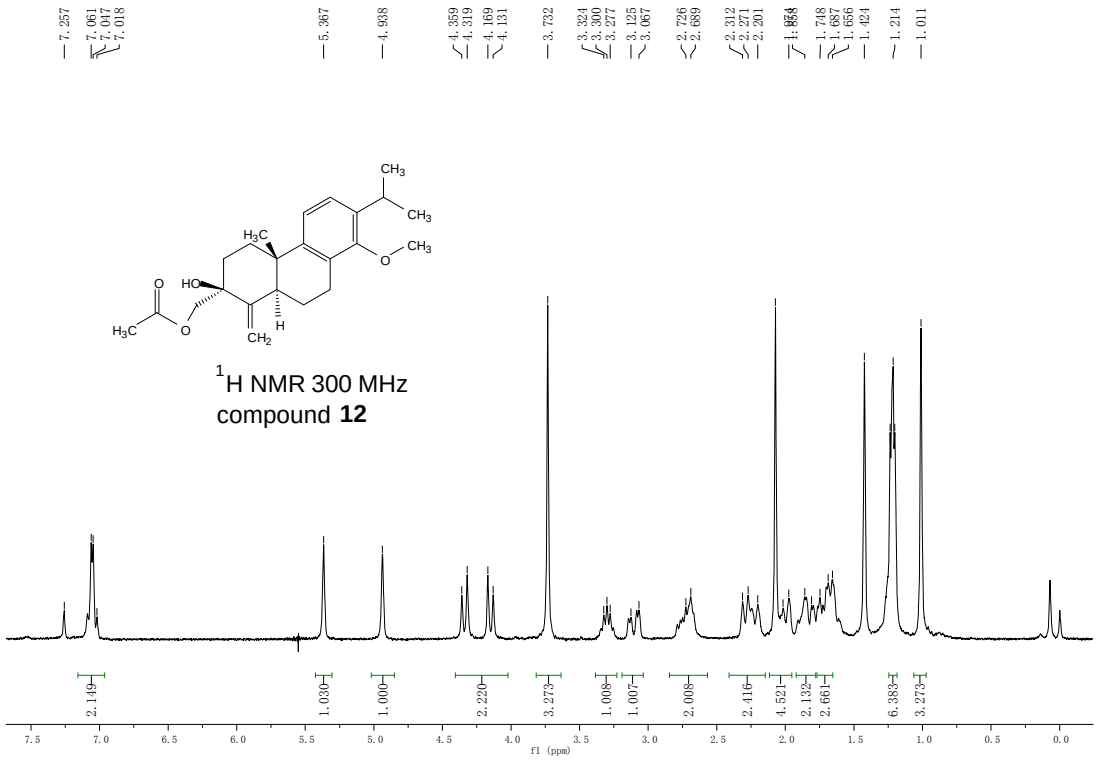
^{1}H NMR of compound **11**:



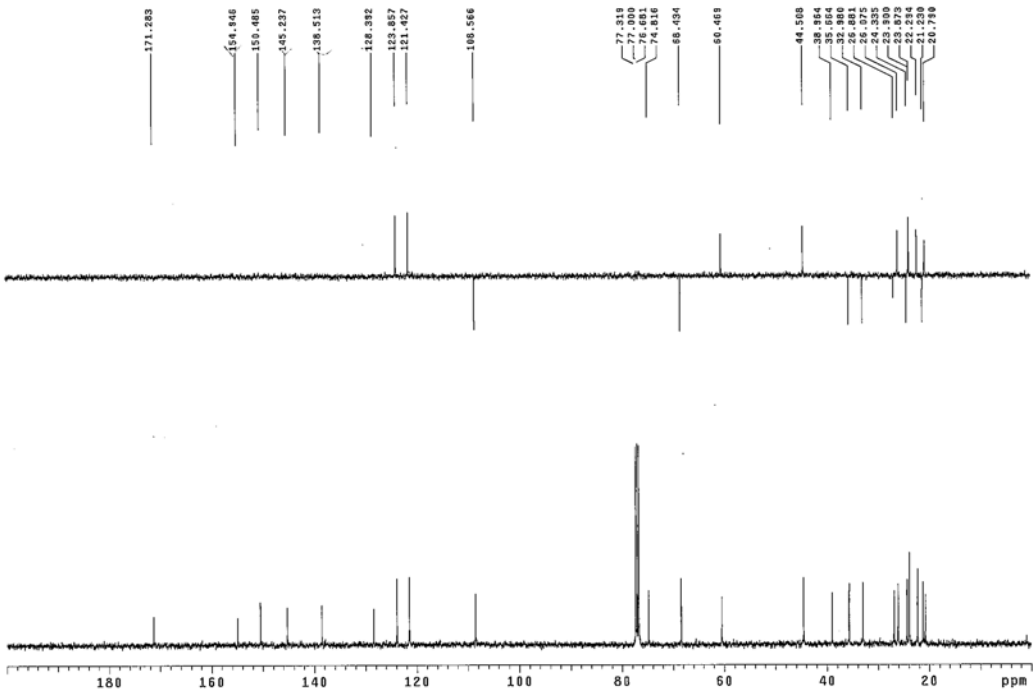
^{13}C NMR of compound **11**:



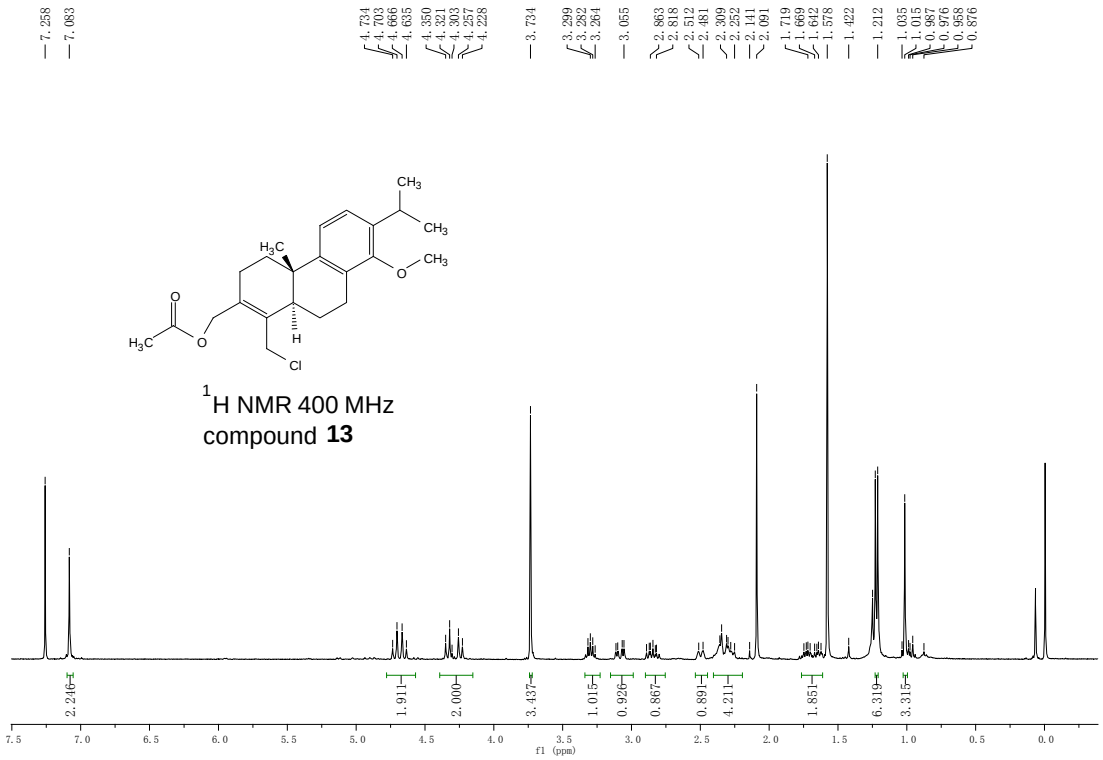
^{1}H NMR of compound **12**:



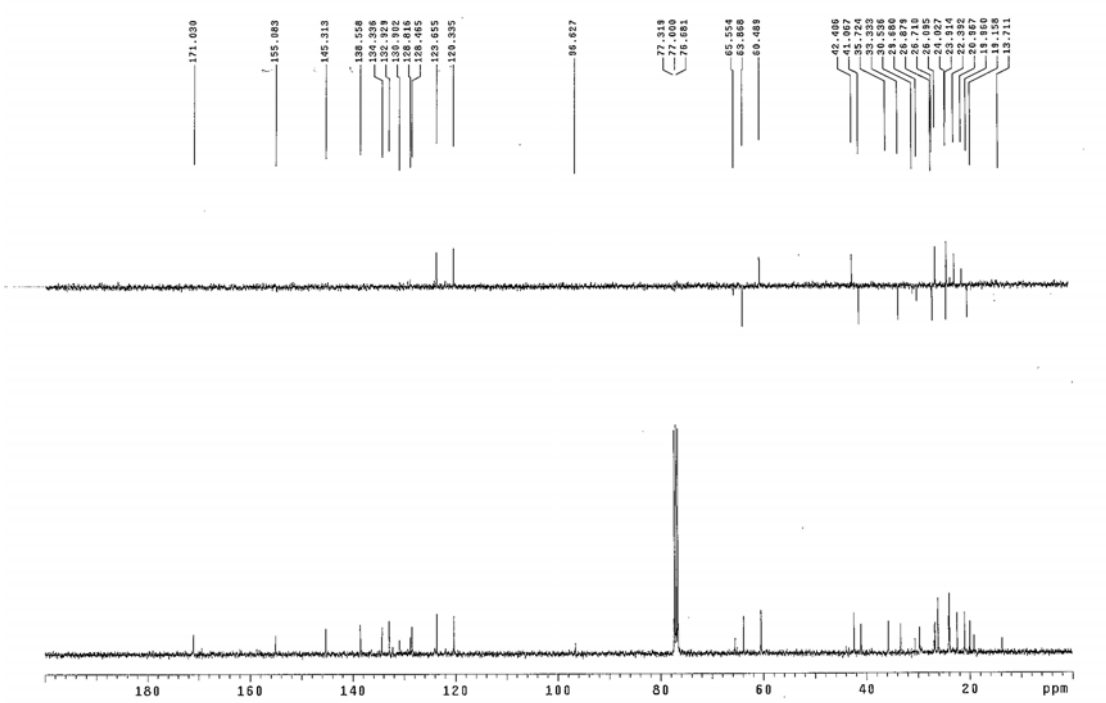
^{13}C NMR of compound **12**:



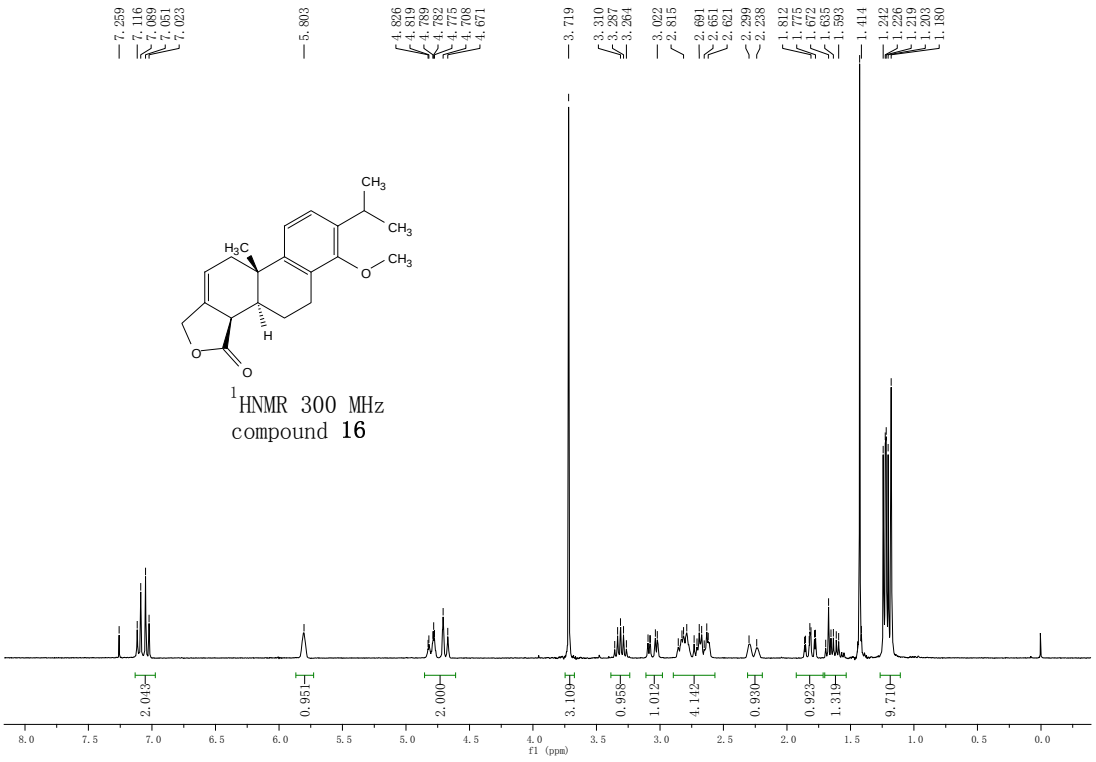
^{1}H NMR of compound **13**:



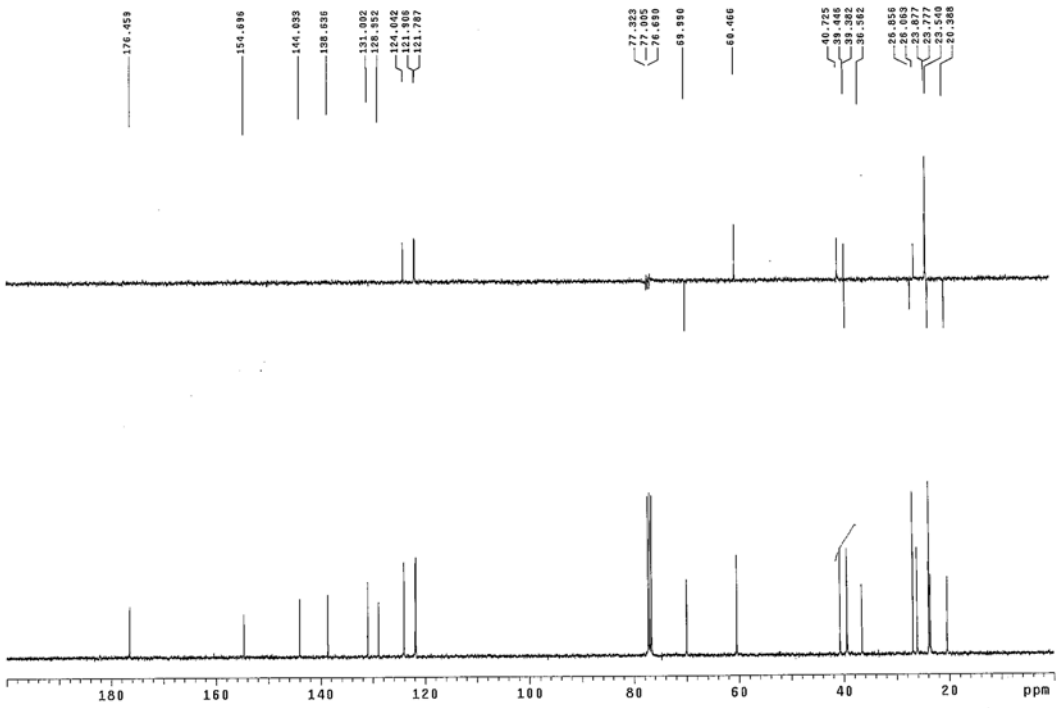
^{13}C NMR of compound **13**:



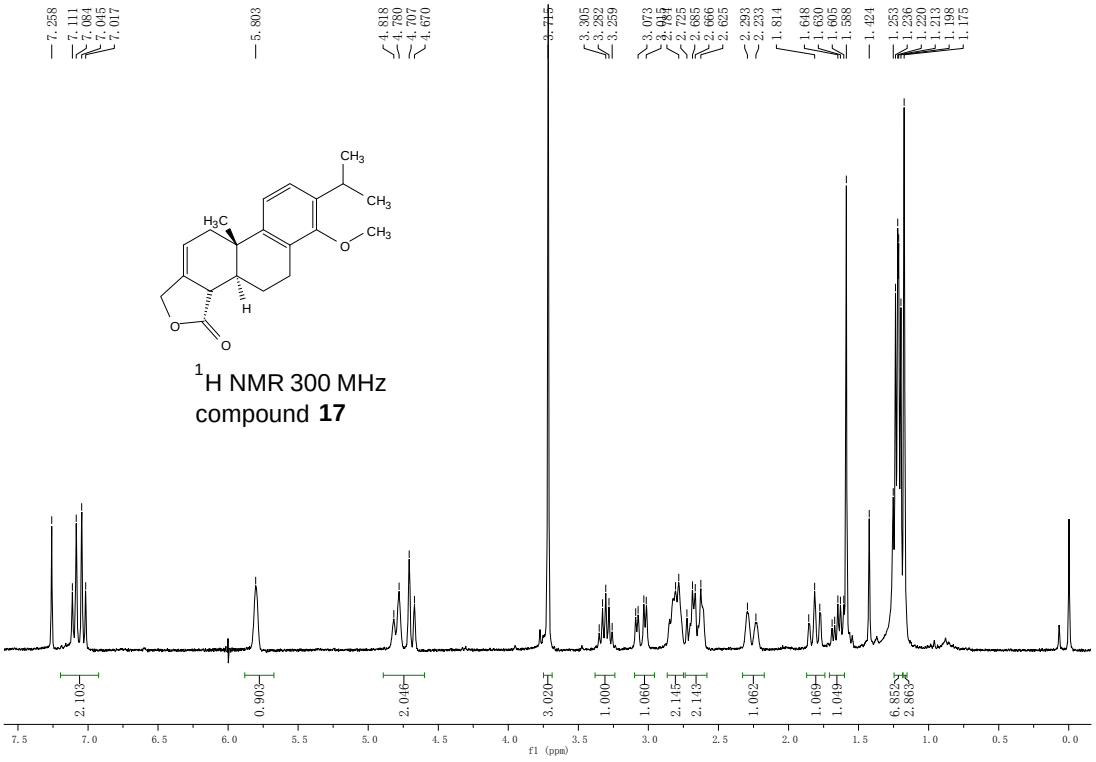
^{1}H NMR of compound **16**:



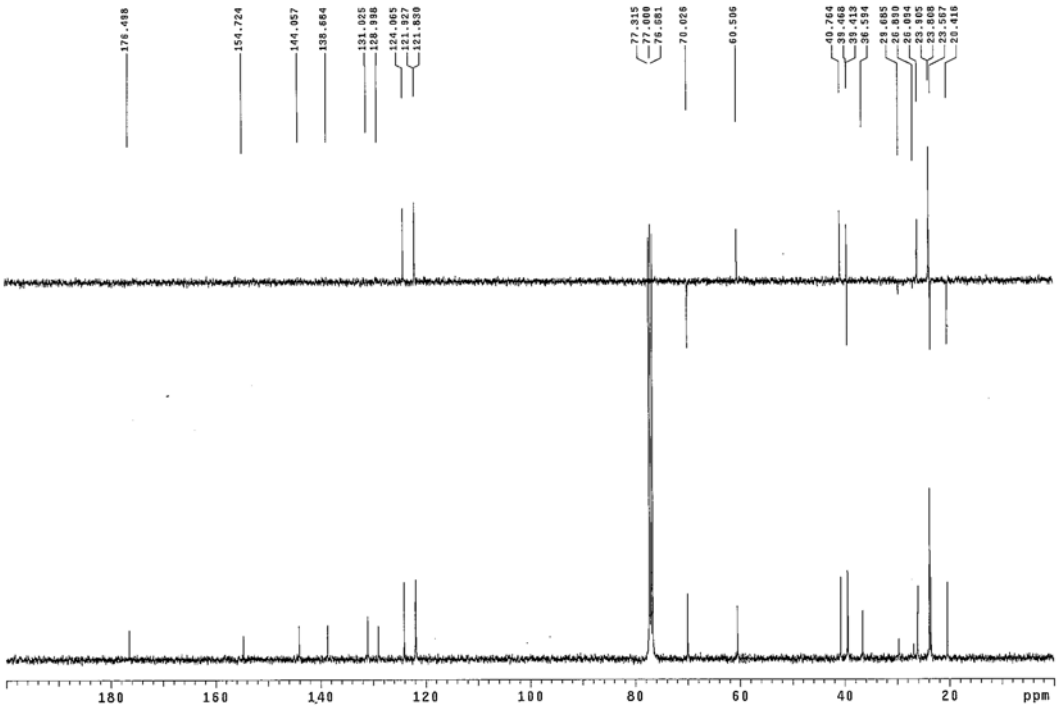
^{13}C NMR of compound **16**:



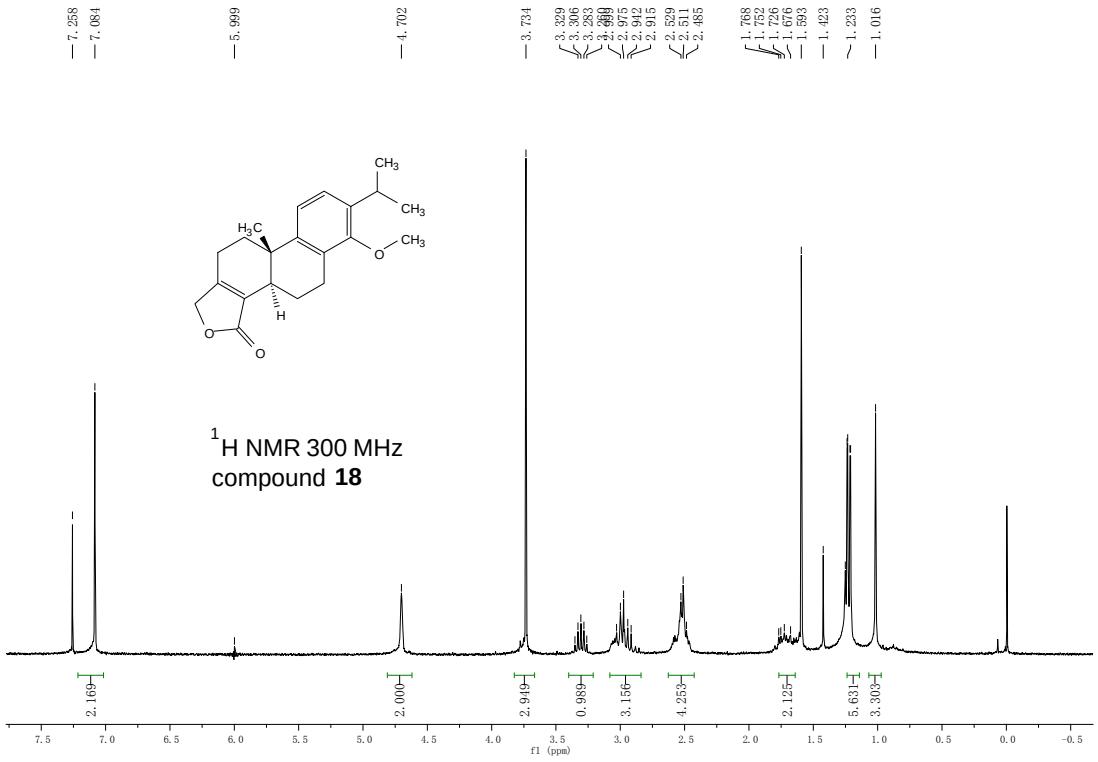
^{1}H NMR of compound **17**:



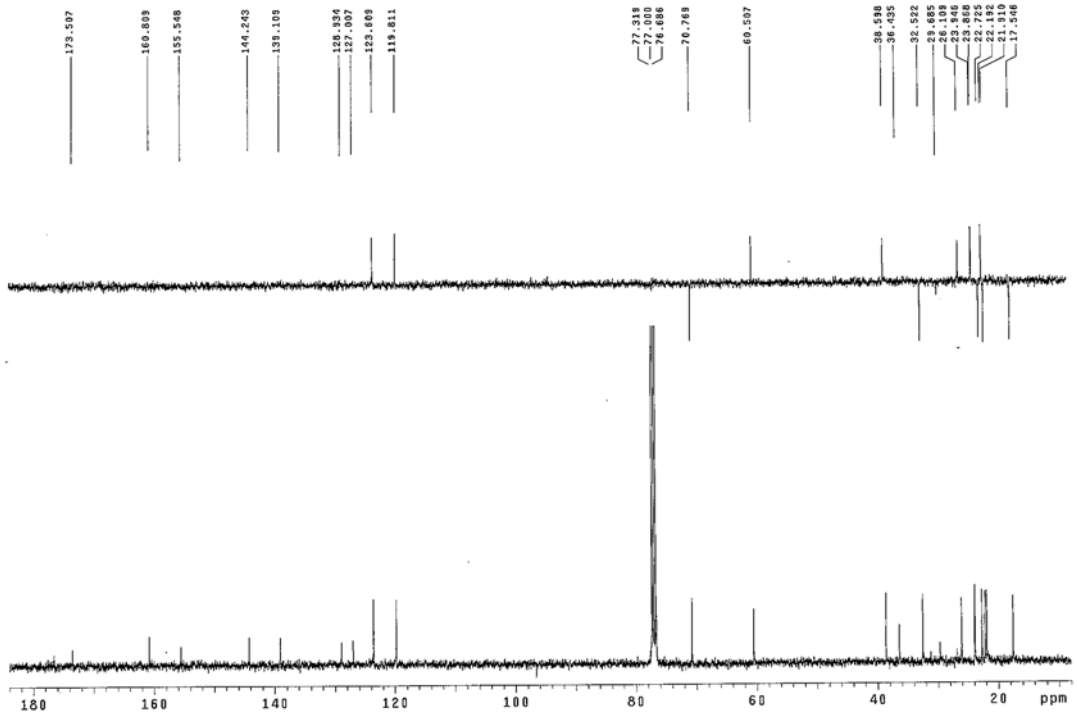
^{13}C NMR of compound **17**:



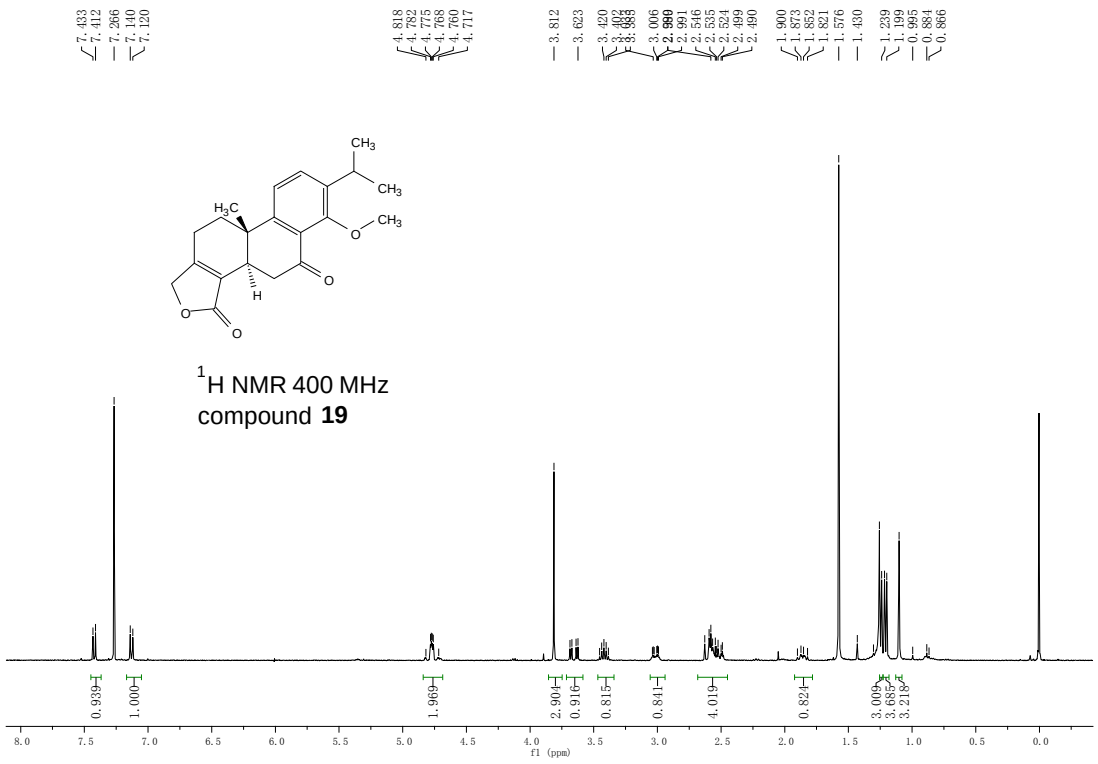
^{1}H NMR of compound **18**:



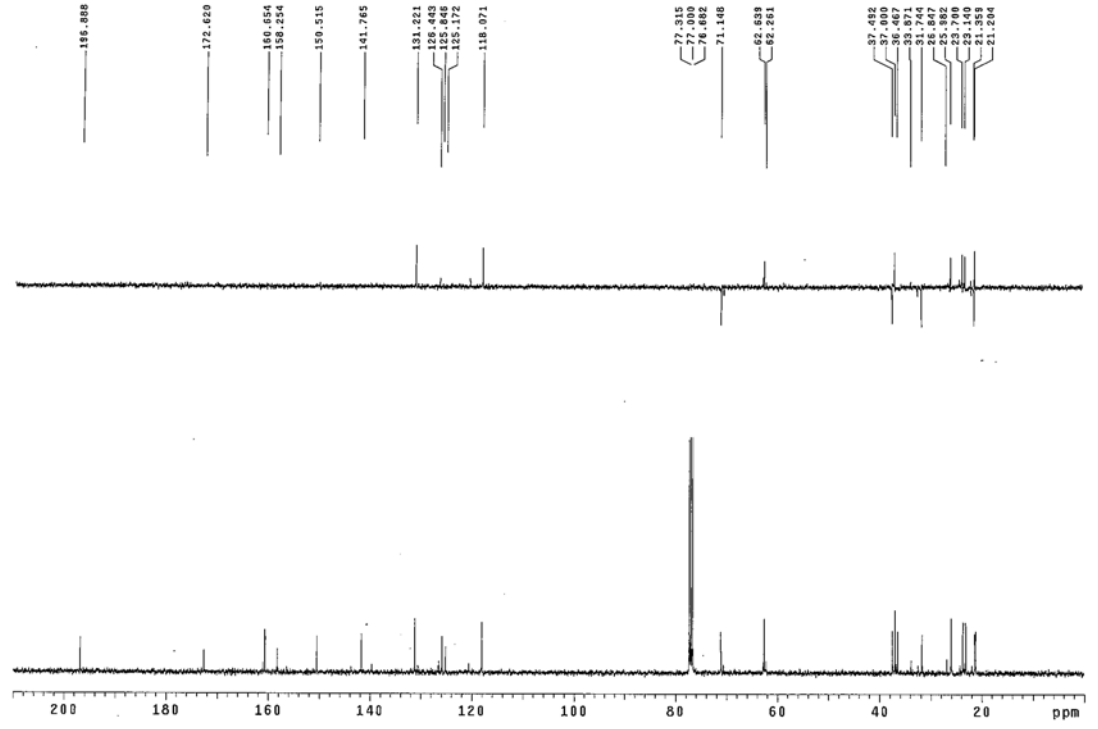
^{13}C NMR of compound **18**:



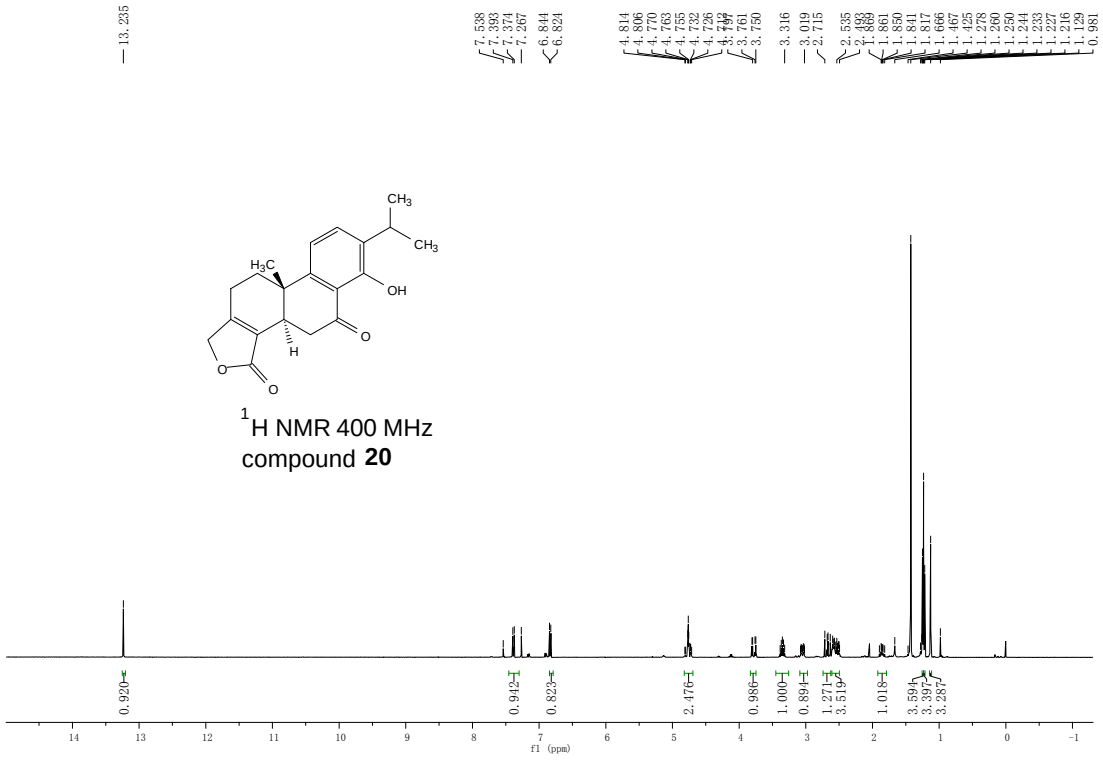
^{1}H NMR of compound **19**:



^{13}C NMR of compound **19**:

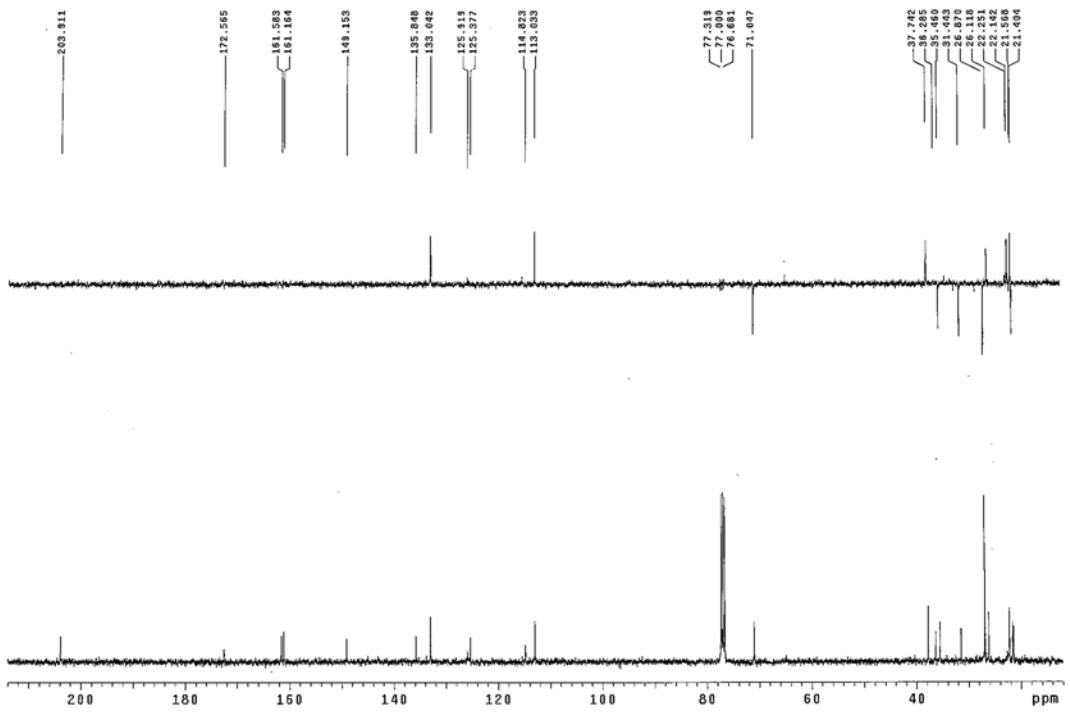


^{1}H NMR of compound **20**:

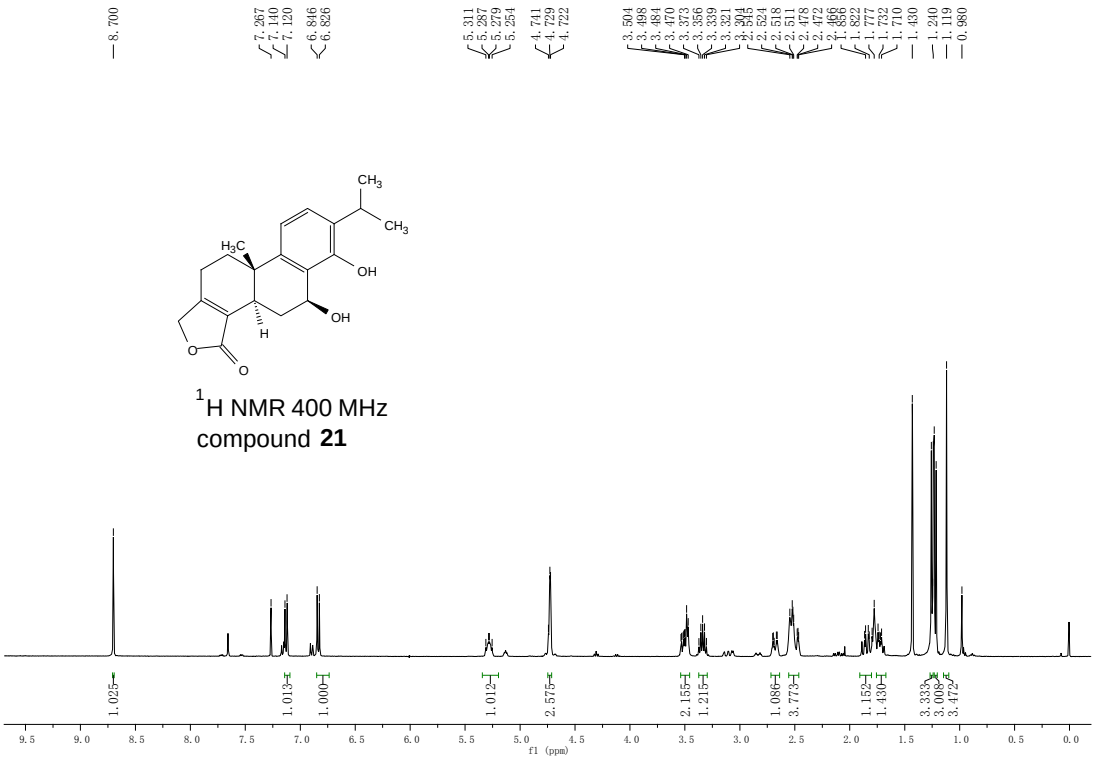


^{1}H NMR 400 MHz
compound **20**

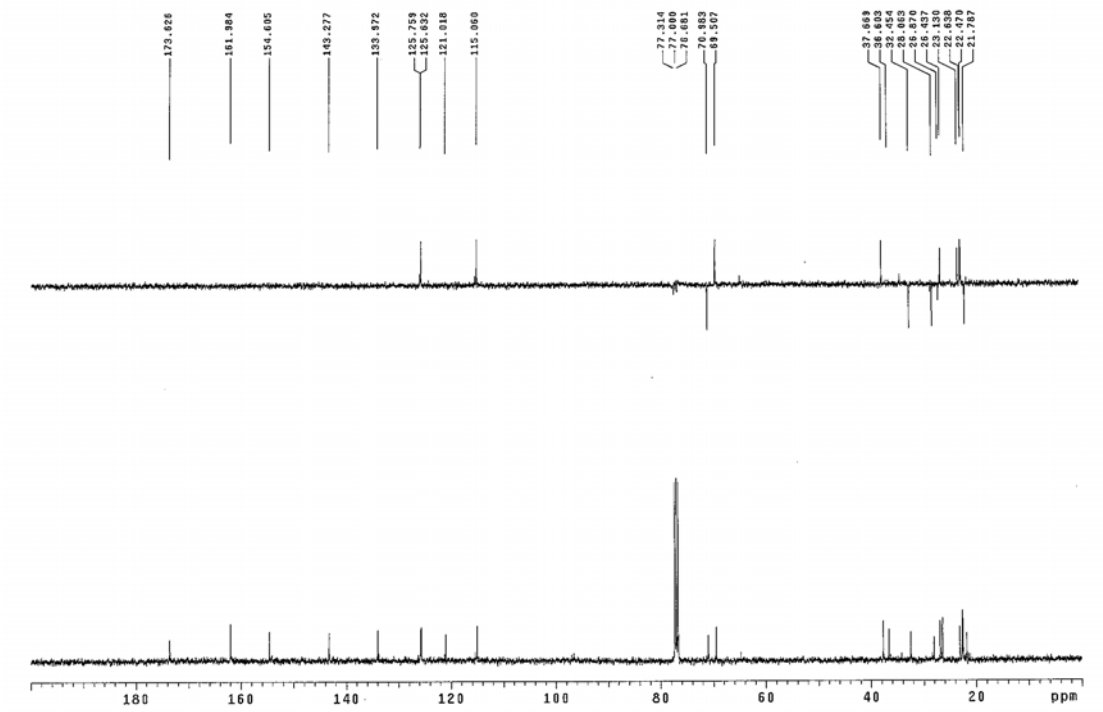
^{13}C NMR of compound **20**:



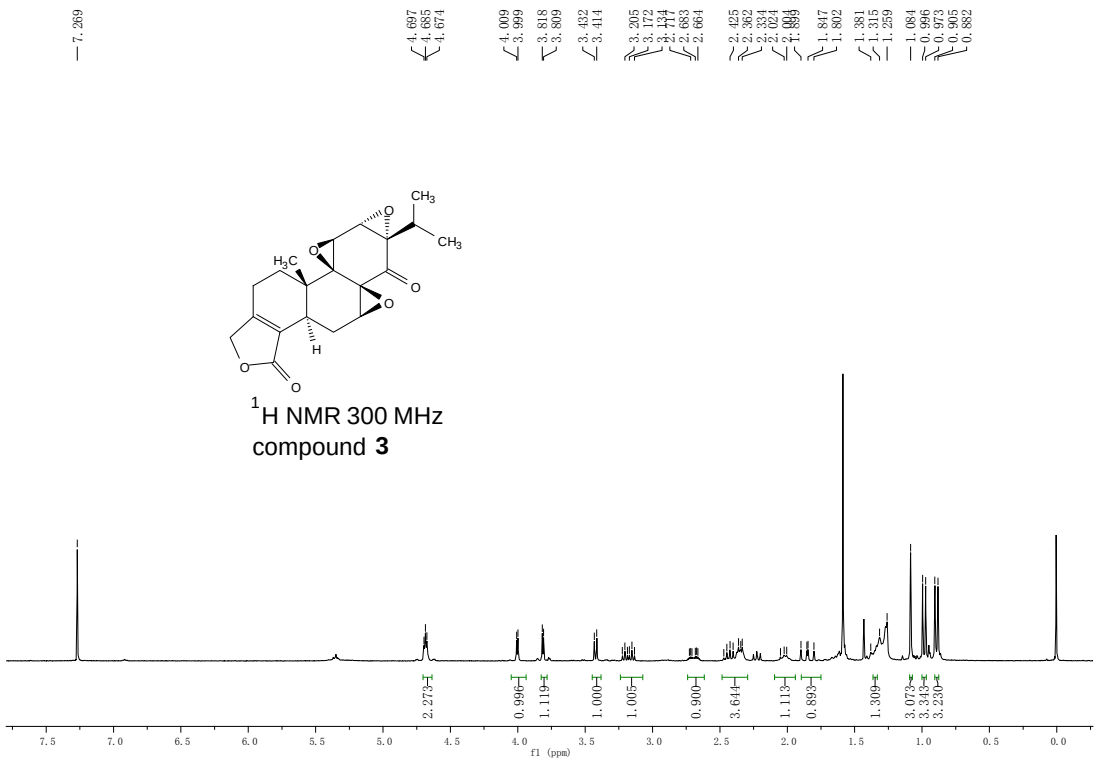
^{1}H NMR of compound **21**:



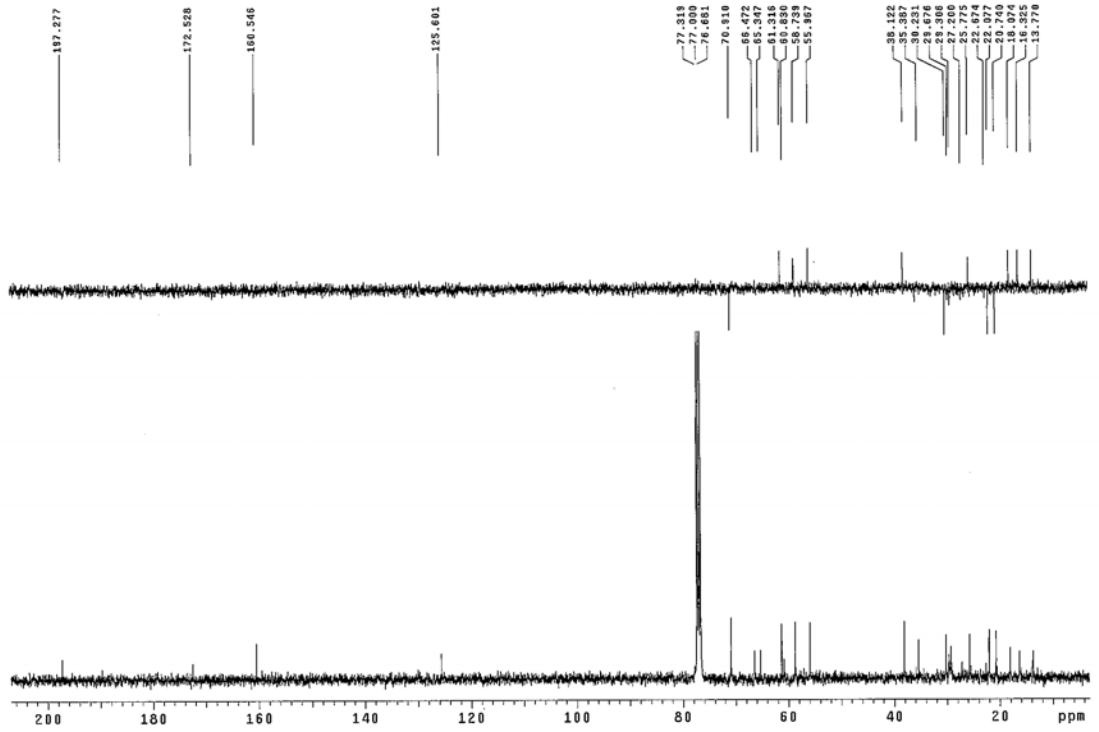
^{13}C NMR of compound **21**:



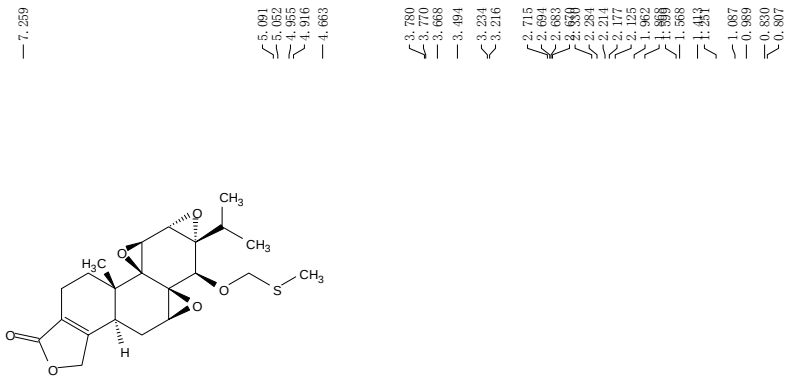
^{1}H NMR of compound **3**:



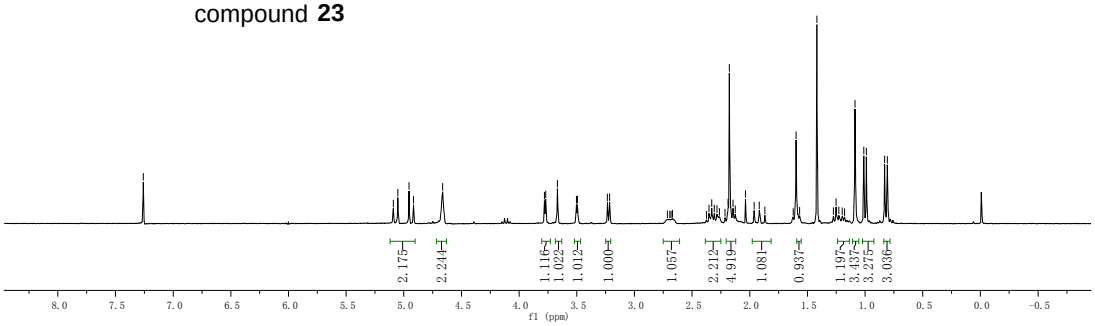
^{13}C NMR of compound **3**:



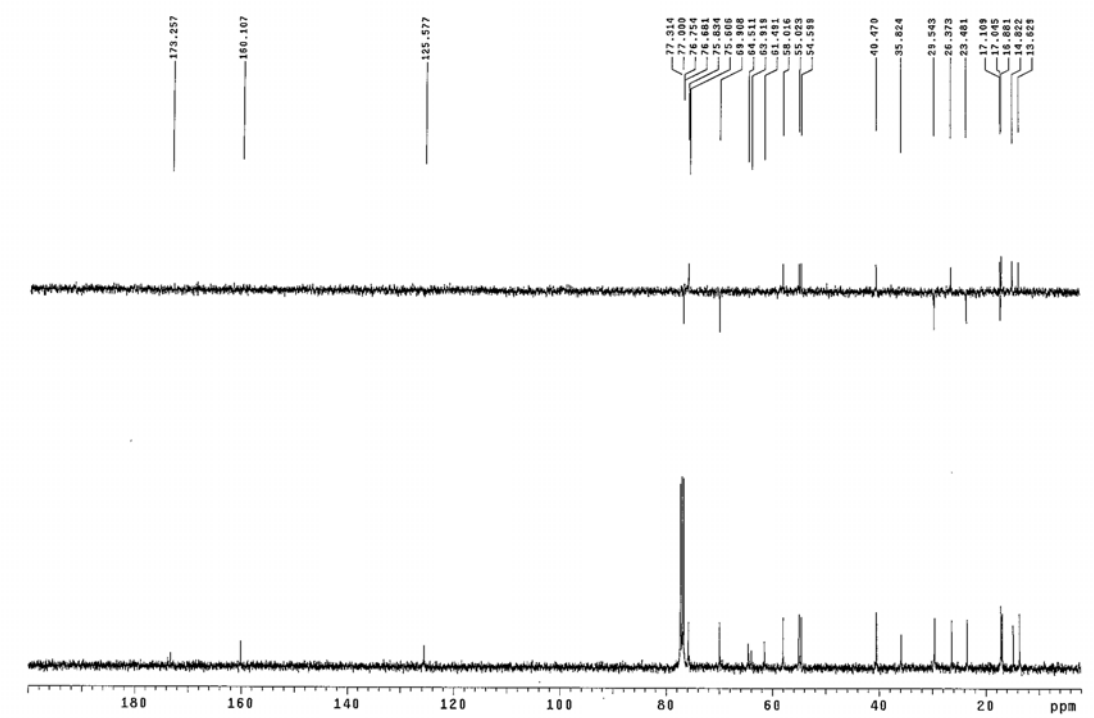
^{1}H NMR of compound **23**:



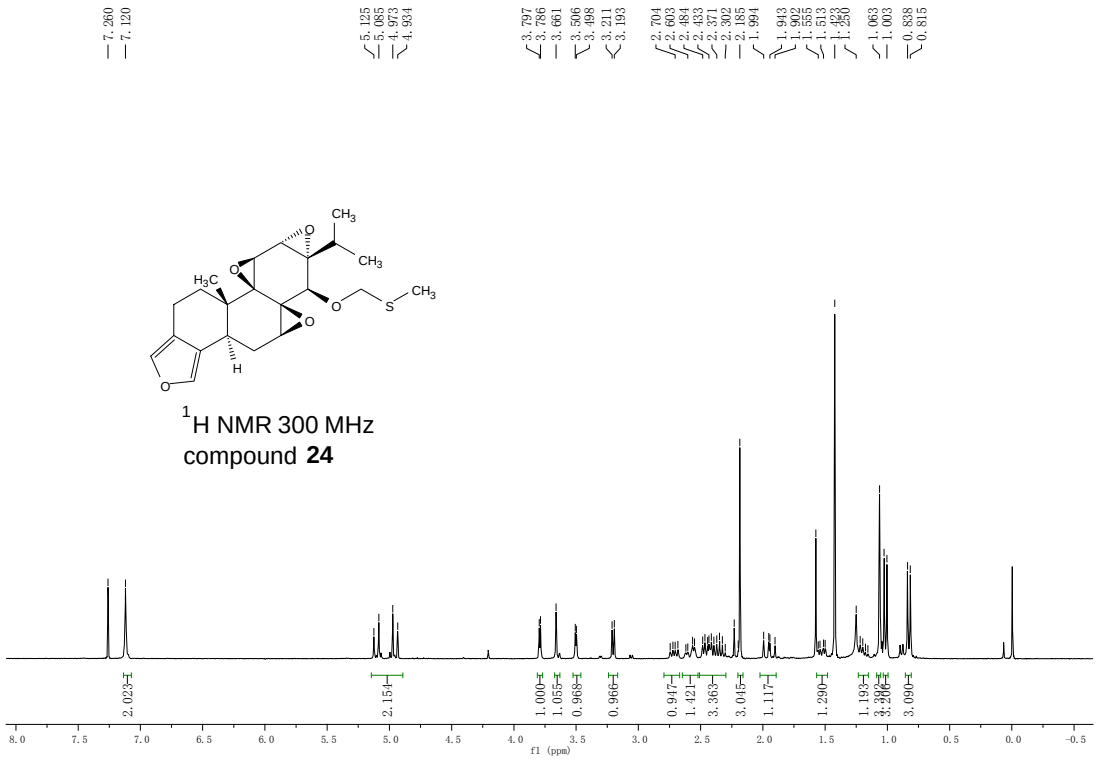
^{1}H NMR 300 MHz
compound **23**



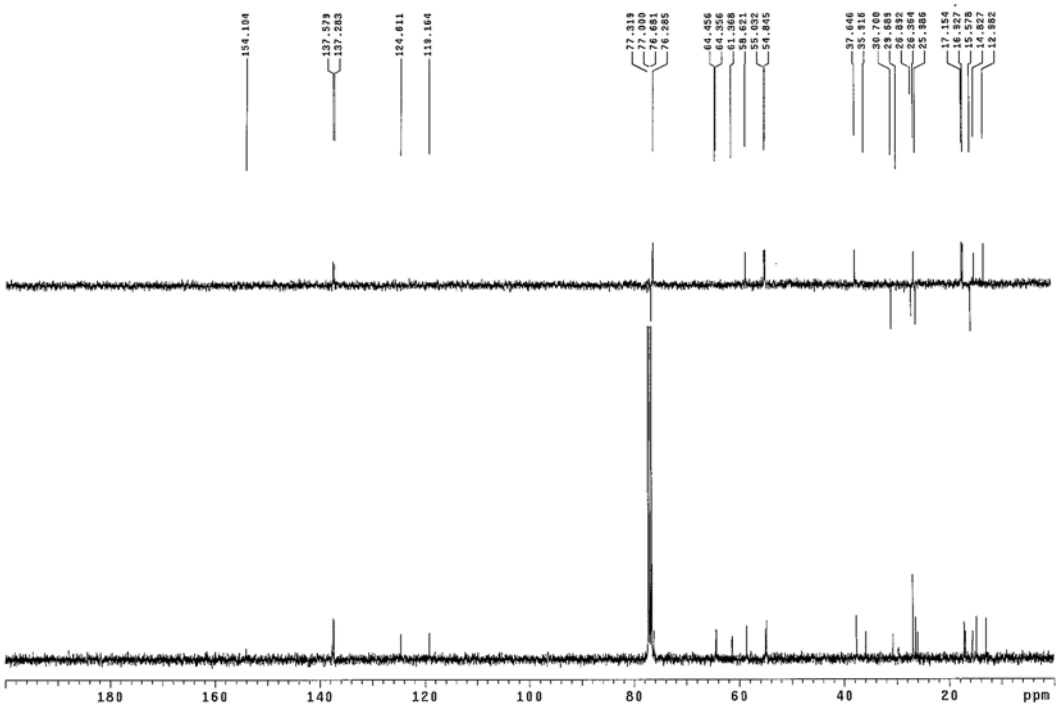
^{13}C NMR of compound **23**:



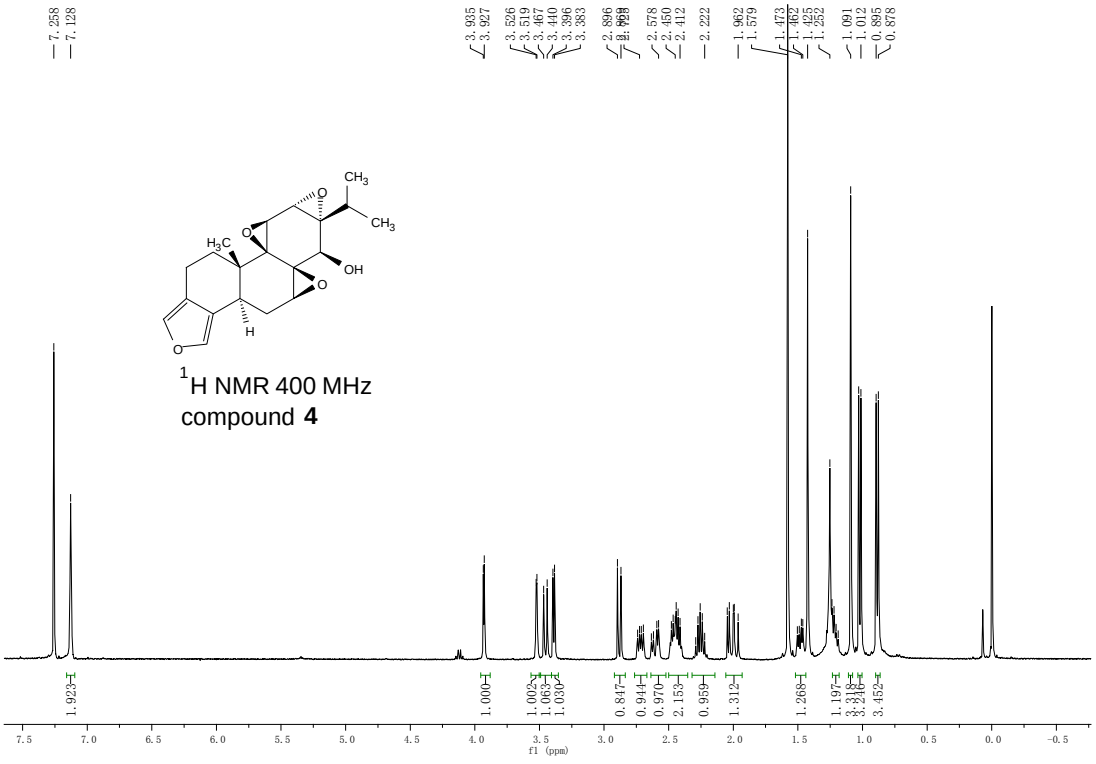
^{1}H NMR of compound **24**:



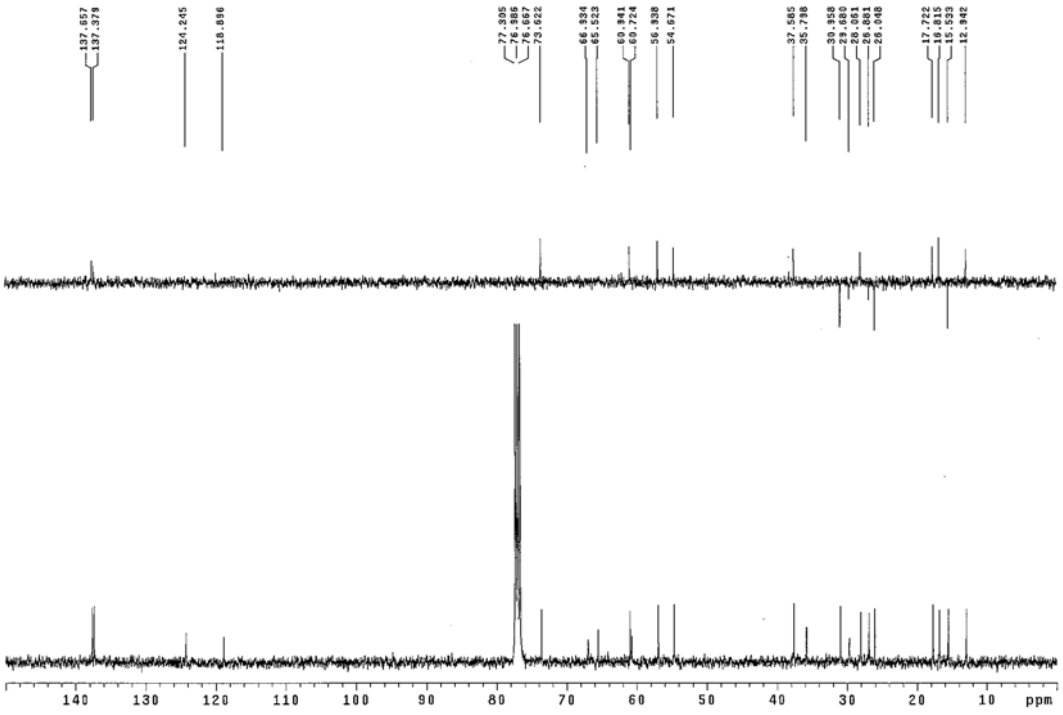
^{13}C NMR of compound **24**:



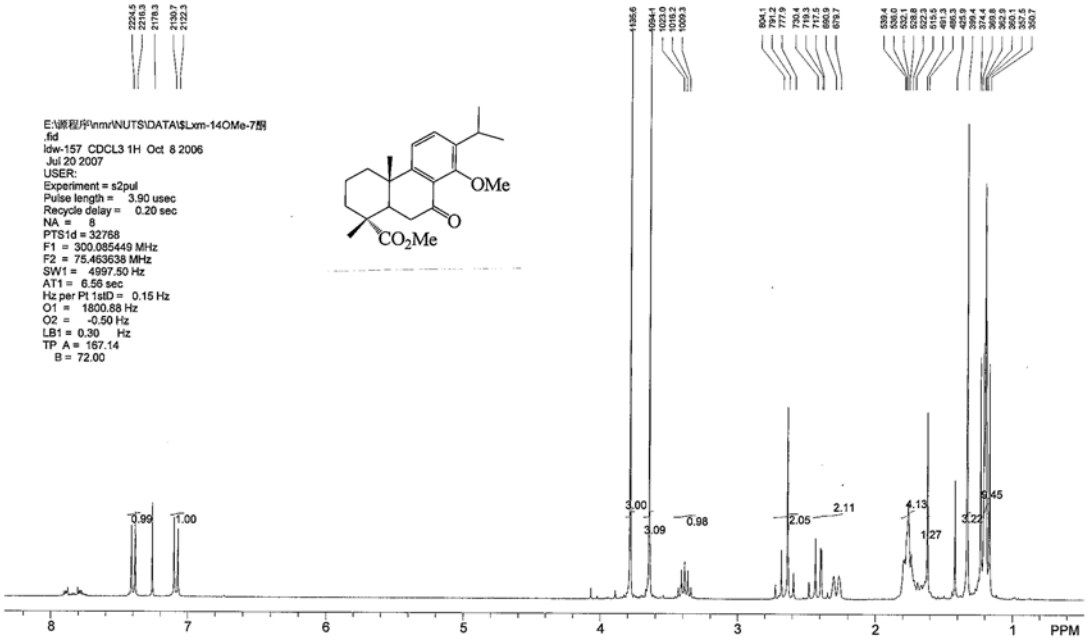
^{1}H NMR of compound **4**:



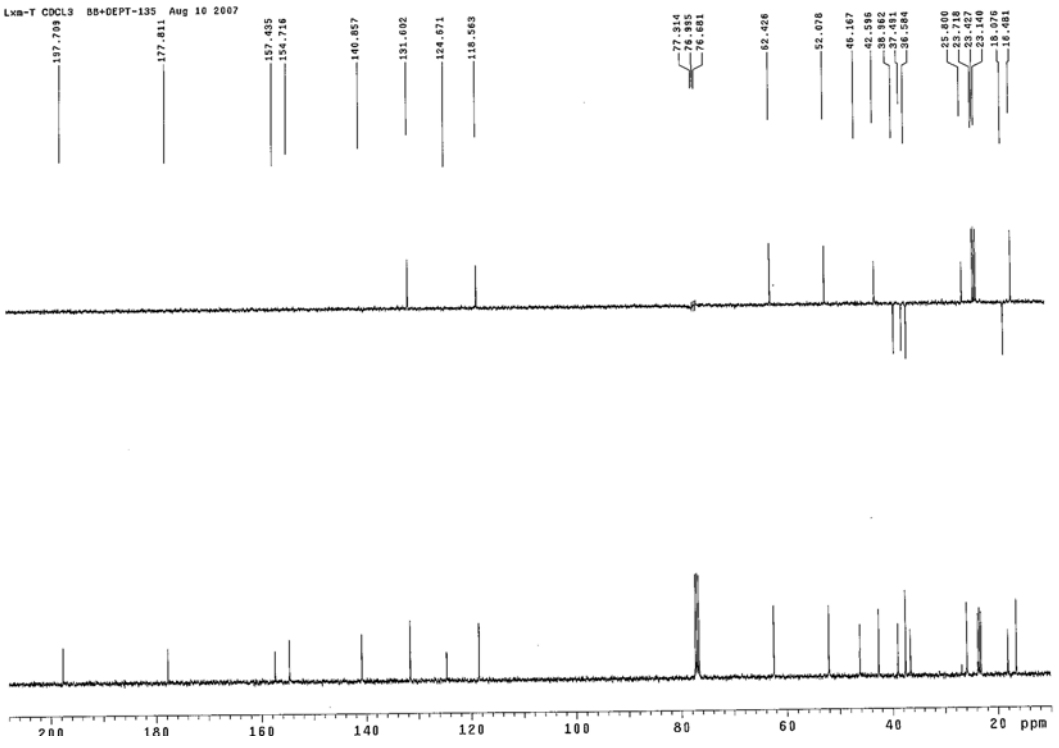
^{13}C NMR of compound **4**:



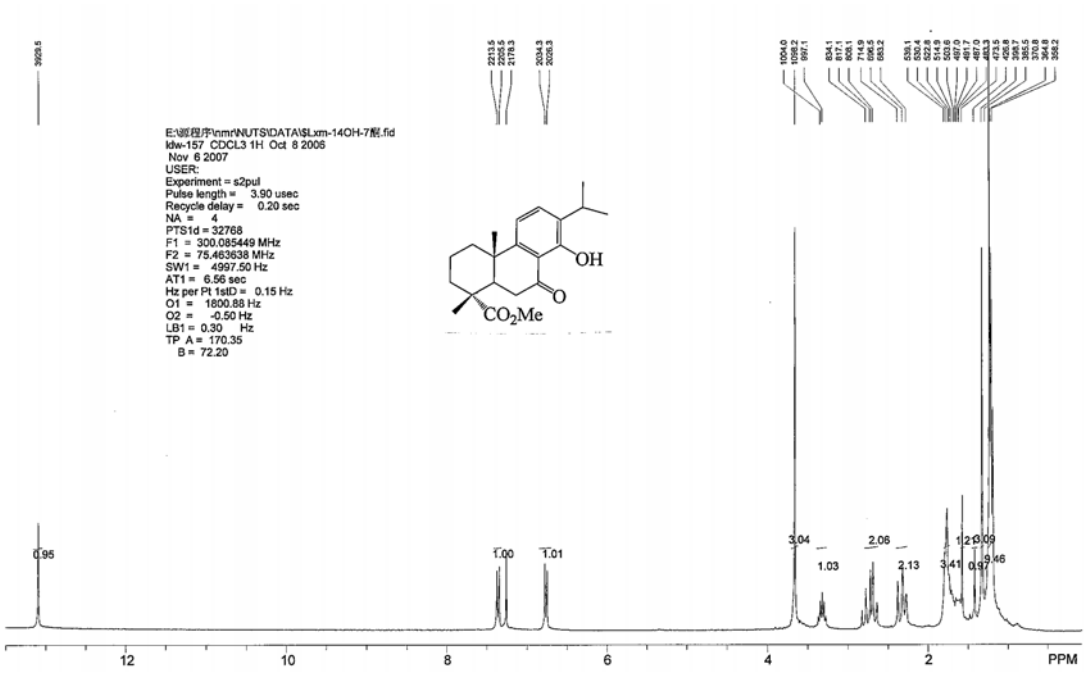
^{1}H NMR of compound **26**:



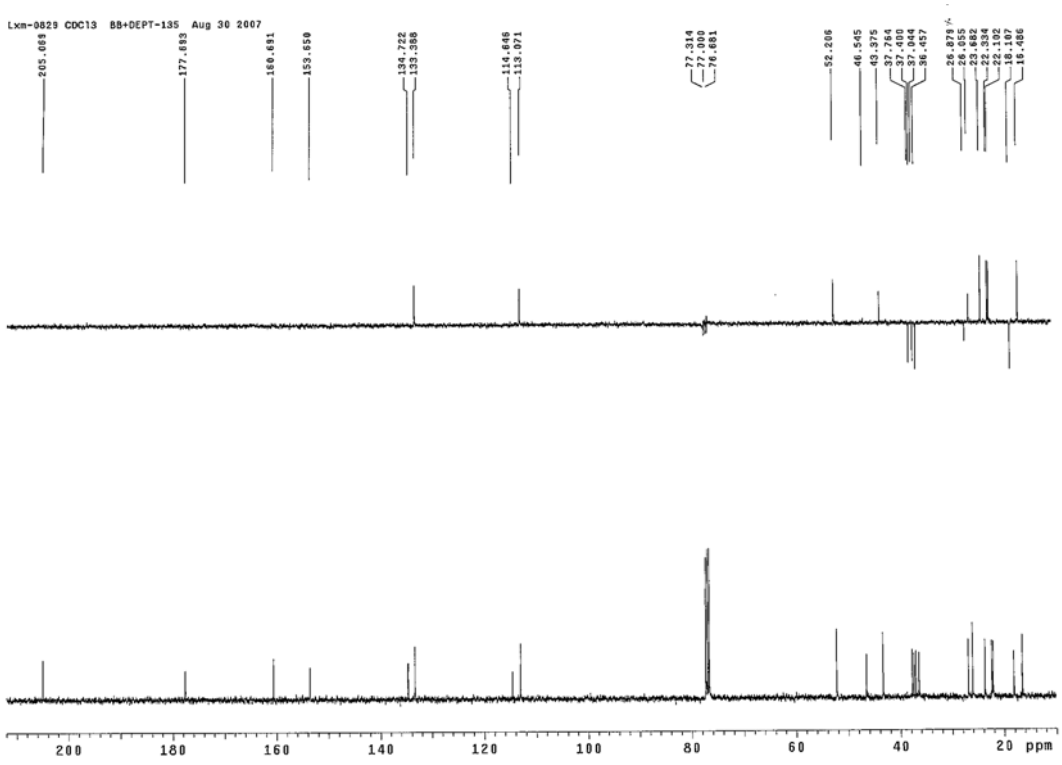
^{13}C NMR of compound **26**:



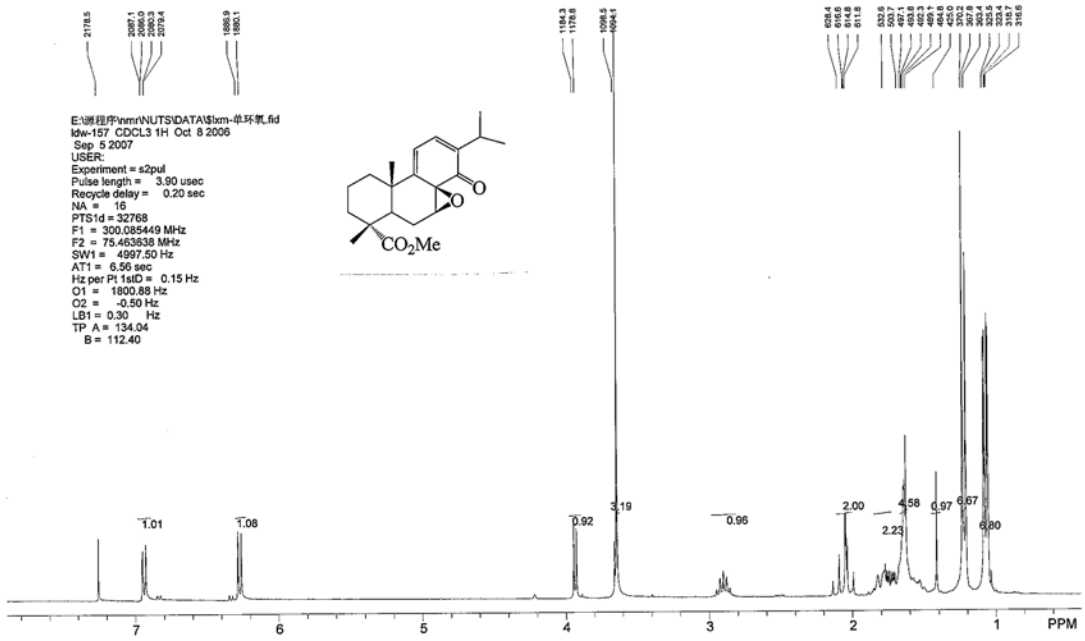
^{1}H NMR of compound **27**:



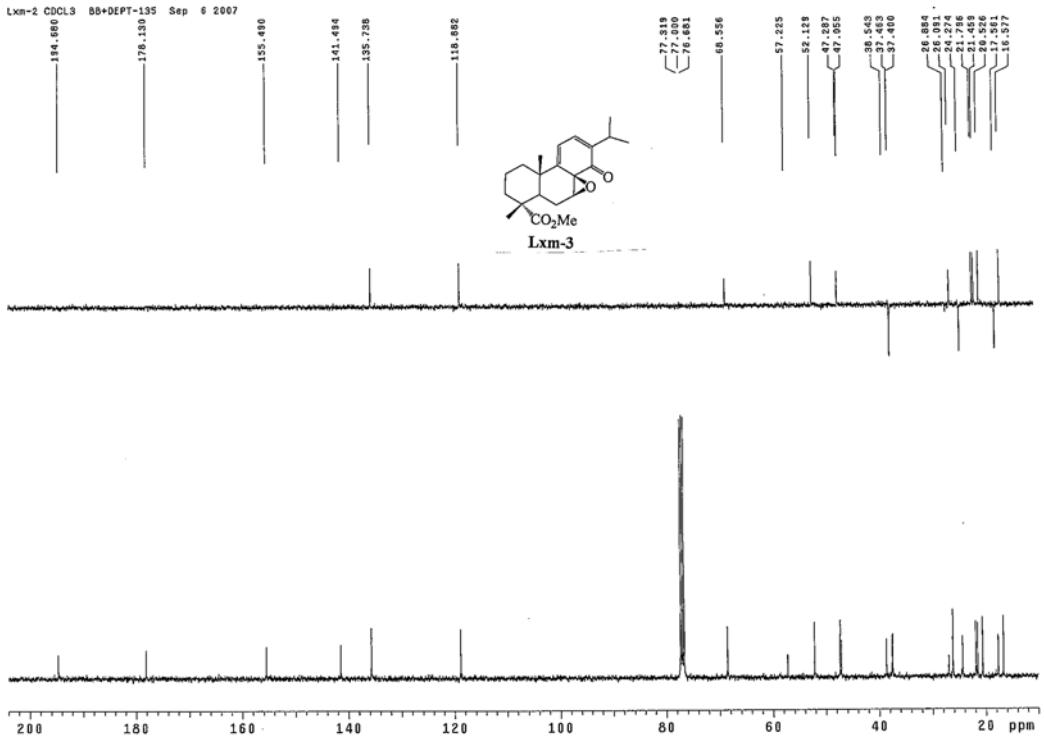
^{13}C NMR of compound **27**:



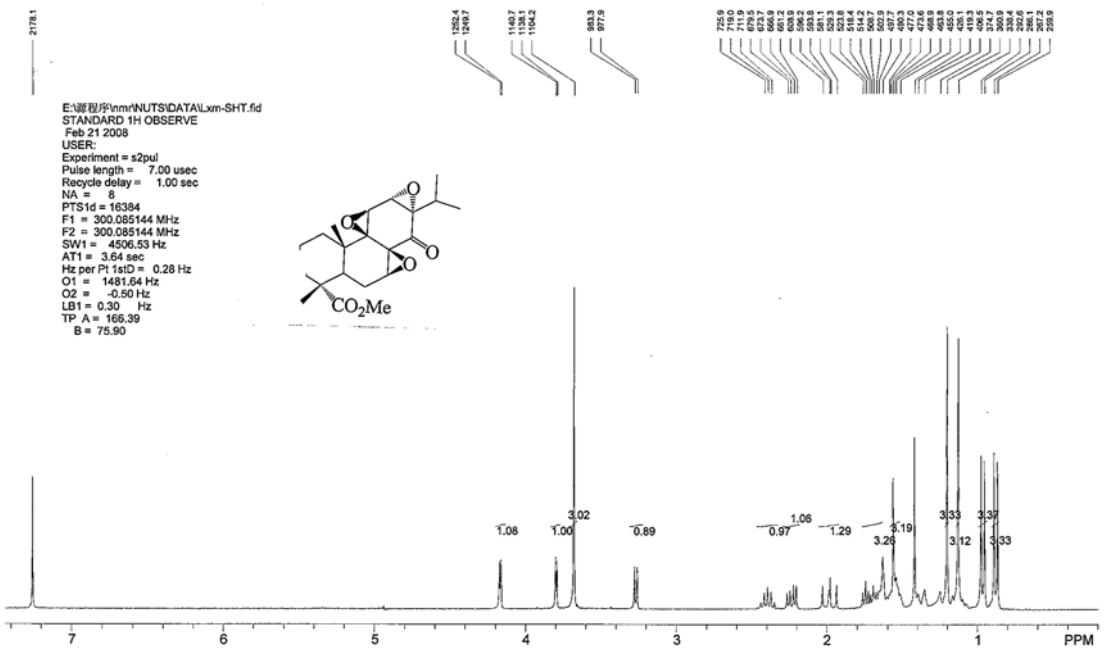
^{1}H NMR of compound **29**:



^{13}C NMR of compound **29**:



^{1}H NMR of compound **5**:



^{13}C NMR of compound **5**: