Total Synthesis and Structure Revision of Gonioheptenolactone

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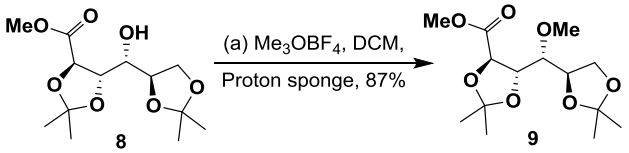
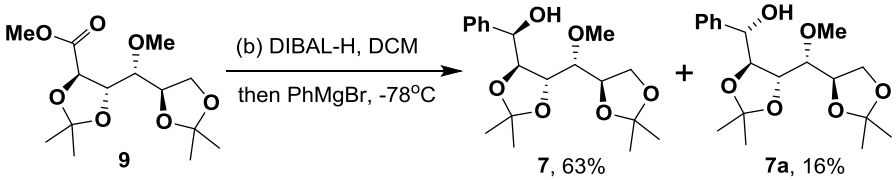
1. Experimental procedure

The chemicals and solvents used in this work were purchased from commercial suppliers and applied without further purification if no further claims in our procedures. The required solvents were dried according to standard procedures, and the reaction process was monitored by thin-layer chromatography (TLC). THF was freshly distilled from sodium/benzophenone under nitrogen. Dichloromethane and pyridine were distilled from calcium hydride. Other reagents were purchased from commercial suppliers and were used without purification. The crude products were purified by flash chromatography using 100-200 mesh silica gel. The optical rotation data were measured by polarimeter at 20 ℃. High-resolution mass spectrometry (HRMS) experiments were recorded by Fourier-transform mass spectrometry (FT-ICR-MS) in electrospray ionization positive (ESI^+) mode. The solvent was chromatographic pure methanol. ^1H NMR and ^{13}C NMR data were obtained by 400 MHz or 100 MHz nuclear magnetic resonance spectrometer. Chemical shift (δ) was expressed in ppm relative to the residual solvent, including chloroform-d. The coupling constant (J) is in Hz. s means singlet state, d means doublet state, t means triplet state, q means quartet state, m means multiplet state.



Synthesis of compound 9:

To a solution of compound **8** (5.30 g, 18.28 mmol) in anhydrous DCM (80 ml) was added trimethyloxonium tetrafluoroborate (5.5 g, 37 mmol) and 1,8-bis(dimethylamino)naphthalene (1.2 g, 5.3 mmol) under N_2 atmosphere at 0 ^oC. The reaction mixture was stirred for 2 h and distilled under reduced pressure to give the crude product. The mixture was diluted with brine and extracted with DCM. The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Purification of the residue by flash chromatography on silica gel (petroleum ether / EtOAc 3:1) provided compound **9** (4.83 g, 87%) as colorless oil. $[\alpha]^{25}_D = -9.6$ (*c* 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 4.50 (dd, J = 8.0, 2.4 Hz, 1H), 4.26-4.23 (m, 1H), 4.16 (dd, J = 6.0, 2.8 Hz, 1H), 4.06-3.96 (m, 2H), 3.78 (d, J = 2.8 Hz, 3H), 3.57 (d, J = 2.8 Hz, 3H), 3.49-3.47 (m, 1H), 1.43 (s, 3H), 1.40 (s, 3H×2), 1.32 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.9, 111.1, 108.7, 79.6, 79.5, 76.6, 74.9, 66.0, 61.4, 52.3, 26.5 (×2), 25.9, 25.3; HRMS (ESI): calcd. for $C_{14}H_{24}O_7Na^+$ $[M + Na]^+$, 327.1415; found 327.1411.

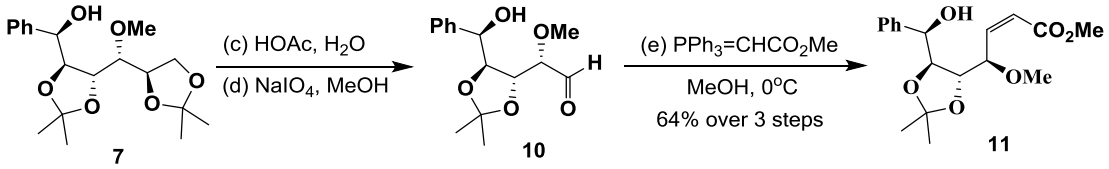


Synthesis of compounds 7 and 7a:

To a solution of compound **9** (2.78 g, 9.1 mmol) in anhydrous DCM (30 mL) was added DIBAL-H (1.0 M in hexane, 11.7 mL, 11.7 mmol) via syringe at −78 ℃ under N_2 atmosphere. After 15 min, phenylmagnesium bromide (1.0 M in THF, 16 mL, 16 mmol) was added into the

mixture via syringe at −78 ℃. The solution was then warmed to room temperature and stirred overnight. The reaction was quenched by the slow addition of a saturated solution of K/Na tartrate (40 mL). The aqueous layer was extracted with DCM (3 × 50 mL). The combined organic phase was washed with brine, dried over Na_2SO_4, and concentrated under vacuum. Purification of the residue by flash chromatography on silica gel (petroleum ether / EtOAc = 6:1 and 4:1) provided compound **7** (2.03 g, 63%) as a yellowish oil and compound **7a** (0.515 g, 16%) as a white amorphous solid. For compound **7**: $[\alpha]^{25}_{D} = -14.0$ (*c* 0.7, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.40-7.30 (m, 5H), 4.67 (dd, *J* = 6.8, 3.6 Hz, 1H), 4.24 (dd, *J* = 7.6, 7.2 Hz, 1H), 4.01 (dd, *J* = 11.6, 6.4 Hz, 1H), 3.96-3.91 (m, 2H), 3.81 (dd, *J* = 8.4, 6.8 Hz, 1H), 3.26 (s, 3H), 2.94 (d, *J* = 3.6 Hz, 1H), 2.46 (dd, *J* = 5.2, 2.4 Hz, 1 H), 1.43 (s, 3H), 1.40 (s, 3H), 1.32 (s, 3H), 1.29 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.6, 128.7 (×2), 128.6, 127.1 (×2), 109.7, 108.5, 80.5, 79.6, 78.7, 76.8, 75.8, 65.9, 61.2, 27.4, 26.7, 26.4, 25.3; HRMS (ESI): calcd. for $C_{19}H_{28}O_6Na^+$ $[M + Na]^+$, 375.1779; found 375.1786.

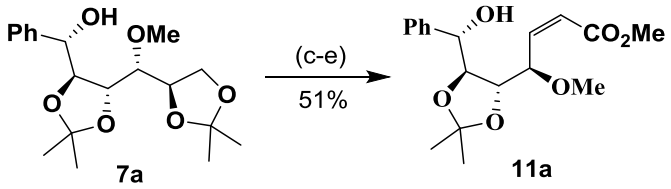
For compound **7a**: $[\alpha]^{25}_{D} = +16.8$ (*c* 1.4, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.40-7.28 (m, 5H), 5.04 (d, *J* = 3.2 Hz, 1H), 4.30 (dd, *J* = 8.0, 4.0 Hz, 1H), 4.17 (dd, *J* = 8.0, 2.0 Hz, 1 H), 4.07 (dd, *J* = 11.2, 6.4 Hz, 1H), 3.94 (dd, *J* = 8.4, 6.8 Hz, 1H), 3.84 (dd, *J* = 11.2, 8.4 Hz, 1 H), 3.20 (s, 3H), 2.75 (*br* s, 1H), 2.45 (dd, *J* = 4.4, 2.0 Hz, 1H), 1.43 (s, 3H), 1.38 (s, 3H), 1.35 (s, 3H), 1.30 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.1, 128.6 (×2), 128.0, 125.9 (×2), 109.1, 108.3, 79.7, 79.6, 77.3, 76.6, 72.2, 65.7, 61.1, 27.3, 26.6, 26.4, 25.2; HRMS calculated for $C_{19}H_{28}O_6Na^+$ $[M+Na]^+$ 375.1779, found 375.1778.



Synthesis of compound 11:

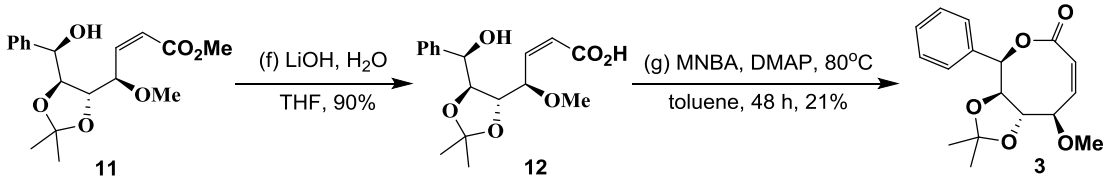
To a solution of **7** (270 mg, 0.77 mmol) in THF (5 mL) was added 70% acetic acid (AcOH) (12 mL) at room temperature. The mixture was stirred for 24 h and concentrated with toluene under vacuum. The yellow residue was directly subjected to the next step without further purification. To a solution of the crude triol in MeOH (20 mL) was added solid $NaIO_4$ (250 mg, 1.15 mmol) at room temperature. After stirring for 15 min, the mixture was filtered through a pad of Celite, and the pad was washed with MeOH (10 mL). To the resulting solution was added (methoxycarbonylmethylene) triphenylphosphorane (271 mg, 0.78 mmol) at 0 ℃. After stirring at 0 ℃ for 12 h, the reaction mixture was concentrated under vacuum. The crude residue was purified by flash column chromatography (petroleum ether / EtOAc 3:1) to give compound **11** as as colorless oil (166 mg, 64% for 3 steps). $[\alpha]^{25}_{D} = -35.5$ (*c* 0.9, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.40-7.31 (m, 5H), 5.87-5.78 (m, 2H), 4.65-4.61 (m, 2H), 4.30 (dd, *J* = 6.4, 6.0 Hz, 1 H), 4.05 (dd, *J* = 6.4, 6.0 Hz, 1H), 3.71 (s, 3H), 3.18 (s, 3H), 2.89 (d, *J* = 4.8 Hz, 1H), 1.48 (s, 3H), 1.45 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.0, 146.1, 140.0, 128.5 (×2), 128.2, 127.1 (×2),

123.0, 110.2, 80.4, 79.7, 76.2, 74.4, 57.3, 51.6, 27.5, 27.1; HRMS (ESI): calcd. for $C_{18}H_{24}O_6Na^+$ $[M + Na]^+$, 359.1466; found 359.1466.



Synthesis of compound 11a:

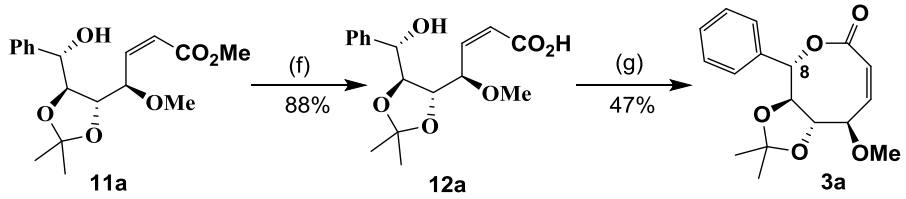
Compound **11a** was obtained in 79 mg (51% yield) as a white amorphous solid from **7a** following the same procedures as described above in the synthesis of compound **11**. $[\alpha]^{25}_D = -49$ (*c* 0.4, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.42-7.29 (m, 5H), 5.89-5.79 (m, 2H), 4.89 (*br* s, 1H), 4.60 (dd, *J* = 8.0, 4.0 Hz, 1H), 4.31 (dd, *J* = 6.8, 5.2 Hz, 1H), 4.18 (dd, *J* = 7.2, 4.0 Hz, 1H), 3.71 (s, 3H), 3.16 (s, 3H), 2.98 (d, *J* = 1.6 Hz, 1H), 1.43 (s, 3H), 1.41 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.2, 146.8, 139.5, 128.3 (×2), 127.8, 126.6 (×2), 122.4, 109.5, 79.9, 79.4, 76.3, 73.5, 57.4, 51.5, 27.2, 26.7; HRMS (ESI): calcd. for $C_{18}H_{24}O_6Na^+$ $[M + Na]^+$, 359.1466; found 359.1465.



Synthesis of compounds 12 and 3:

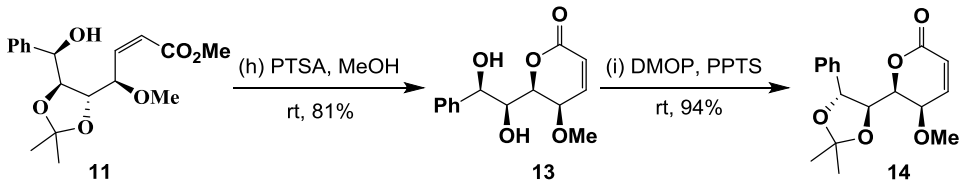
To a solution of ester **11** (72 mg, 0.21 mmol) in THF/H_2O (3 : 2, 10 mL) was treated with solid LiOH (13 mg, 0.31 mmol). The reaction mixture was stirred at room temperature for 8 h. After completion of the reaction (monitored by TLC), the reaction mixture was acidified with 0.5 N HCl until pH ~ 3 and then extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude acid **12** was used for the next step without further purification. A small sample was purified on a silica gel column (petroleum ether / EtOAc 1:3) to get the yield (90%) and physical data. $[\alpha]^{25}_D = -35.6$ (*c* 0.2, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.37-7.30 (m, 5H), 6.03 (t, *J* = 11.6 Hz, 1H), 5.88 (d, *J* = 11.6 Hz, 1H), 4.64 (d, *J* = 6.0 Hz, 1H), 4.37-4.29 (m, 2H), 4.01 (*br* s, 1H), 3.12 (s, 3H), 1.46 (s, 3H), 1.44 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4, 149.0, 139.4, 128.6 (×2), 128.5, 127.2 (×2), 122.4, 110.0, 80.2, 79.6, 75.6, 75.1, 57.4, 27.4, 26.9; HRMS (ESI): calcd. for $C_{17}H_{22}O_6Na^+$ $[M + Na]^+$, 345.1309; found 345.1308. To a solution of the crude acid **12** in anhydrous toluene (35 mL) was slowly added a solution of MNBA (130 mg, 0.39 mmol) and DMAP (108 mg, 0.88 mmol) in anhydrous toluene (25 mL) at 80 ℃ with a mechanically driven syringe over an 4 h period under a nitrogen atmosphere. After completion of reaction, the mixture cooled to room temperature and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (petroleum ether/EtOAc 6:1) to give lactone **3** as colorless oil (14 mg, 21%). $[\alpha]^{25}_D = -32.8$ (*c* 0.05, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.53 (d, *J* = 7.2 Hz, 2H), 7.40-7.33 (m, 3H), 6.50 (dd, *J* = 11.6, 8.4 Hz, 1H), 6.15 (dd, *J* = 11.6, 0.8 Hz, 1H), 6.12 (*br* s, 1H),

5.18 (d, *J* = 8.4 Hz, 1H), 4.46 (dd, *J* = 8.4, 1.2 Hz, 1H), 3.73 (dd, *J* = 8.4, 0.8 Hz, 1H), 3.39 (s, 3H), 1.46 (s, 3H), 1.42 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.3, 150.3, 137.3, 128.4 (×2), 128.3, 127.7 (×2), 122.0, 110.0, 80.3, 78.5, 73.5, 71.3, 58.2, 26.9, 26.7; HRMS (ESI): calcd. for $C_{17}H_{20}O_5Na^+$ $[M + Na]^+$, 327.1203; found 327.1203.



Synthesis of compounds 12a and 3a:

Compound **12a** was obtained in 46 mg as colorless oil from **11a** following the same procedures as described above for the synthesis of compound **12**. The crude acid **12a** was used for the next step without further purification. A small sample was purified on a silica gel column (petroleum ether / EtOAc 1:3) to get the yield (88%) and physical data. $[\alpha]^{25}_D$ = + 9.8 (*c* 0.1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.41-7.29 (m, 5H), 6.06 (dd, *J* = 12.0, 8.0 Hz, 1H), 5.90 (d, *J* = 12.0 Hz, 1H), 4.96 (d, *J* = 4.8 Hz, 1H), 4.38 (dd, *J* = 6.8, 4.8 Hz, 1H), 4.23-4.18 (m, 2H), 3.10 (s, 3H), 2.97 (*br* s, 1H), 1.43 (s, 3H), 1.42 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.7, 148.9, 139.1, 128.6 (×2), 128.1, 126.4 (×2), 122.3, 109.5, 79.7, 78.5, 76.2, 72.8, 57.7, 27.4, 26.8; HRMS (ESI): calcd. for $C_{17}H_{22}O_6Na^+$ $[M + Na]^+$, 345.1309; found 345.1310. Compound **3a** was obtained in 29 mg as colorless oil from **12a** following the same procedures as described above for the synthesis of compound **3**. $[\alpha]^{25}_D$ = + 2.8 (*c* 0.43, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.46-7.34 (m, 5H), 6.43 (dd, *J* = 12.0, 2.0 Hz, 1H), 6.02 (dd, *J* = 12.0, 2.4 Hz, 1H), 5.56 (d, *J* = 8.8 Hz, 1H), 4.40 (td, *J* = 8.4, 1.2 Hz, 1H), 4.20 (t, *J* = 8.4 Hz, 1H), 3.95 (t, *J* = 8.4, 1H), 3.55 (s, 3H), 1.45 (s, 3H), 1.43 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.0, 147.8, 136.5, 128.8, 128.5 (×2), 126.8 (×2), 121.7, 110.2, 84.6, 81.2, 81.0, 78.9, 59.1, 26.8, 26.6; HRMS (ESI): calcd. for $C_{17}H_{20}O_5Na^+$ $[M + Na]^+$, 327.1203; found 327.1202.

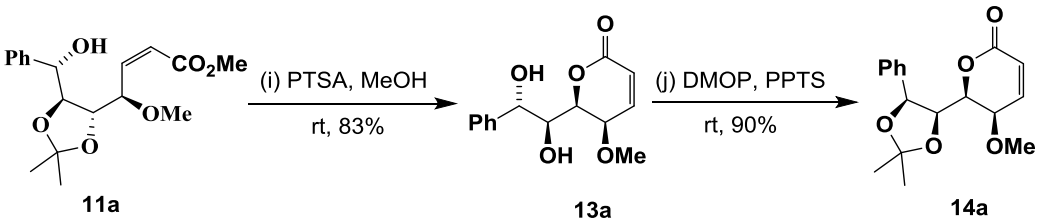


Synthesis of compounds 13 and 14:

To a solution of α, β-unsaturated ester **11** (62 mg, 0.185 mmol) in MeOH (15 mL) was added PTSA H_2O (3.6 mg, 0.019 mmol) at room temperature. After stirring at room temperature for 24 h, the mixture was quenched with Et_3N (1 mL) and concentrated under reduced pressure. A small sample was purified on a silica gel column (petroleum ether / EtOAc 1:3) to get the yield (81%) and physical data. $[\alpha]^{25}_D$ = + 17.8 (*c* 0.2, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.43-7.31 (m, 5H), 7.01 (dd, *J* = 10.0, 5.2 Hz, 1H), 6.22 (d, *J* = 10.0 Hz, 1H), 4.93 (d, *J* = 5.2 Hz, 1H), 4.28 (t, *J* = 3.6 Hz, 1H), 4.16 (t, *J* = 4.8 Hz, 1H), 3.98 (dd, *J* = 4.8, 3.2 Hz, 1H), 3.41 (s, 3H), 3.10 (*br* s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.3, 141.1, 140.1, 128.6 (×2), 128.2, 126.7 (×2), 124.8, 78.4, 74.9,

73.1, 69.5, 56.7; HRMS (ESI): calcd. for $C_{14}H_{16}O_5Na^+$ $[M + Na]^+$, 287.0890; found 287.0890.

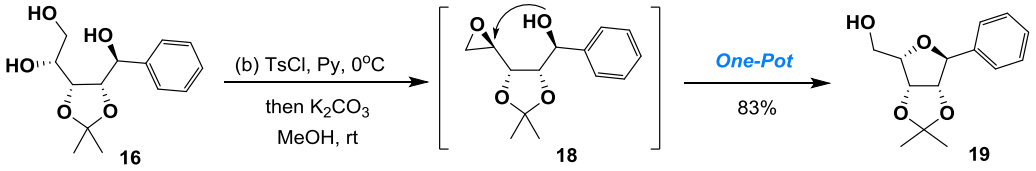
To the above lactone **13** (36 mg, 0.136 mmol) in anhydrous acetone (10 mL) were added 2, 2-dimethoxypropane (DMOP) (0.63 mL, 5.1 mmol) and PPTS (18 mg, 0.07 mmol). The mixture was stirred at room temperature for 10 h and concentrated under reduced pressure. The residue was purified by silica gel chromatography (petroleum ether / EtOAc 1: 1) to afford compound **14** as a white amorphous solid (39 mg, 94%):$[\alpha]^{25}_D$ = – 26.7 (*c* 0.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.43-7.35 (m, 5H), 6.82 (dd, *J* = 10.0, 3.6 Hz, 1H), 6.08 (dd, *J* = 10.0, 1.2 Hz, 1H), 4.96 (d, *J* = 8.8 Hz, 1H), 4.49 (dd, *J* = 4.4, 4.0 Hz, 1H), 4.28 (dd, *J* = 8.8, 4.0 Hz, 1H), 3.99 (dd, *J* = 4.8, 1.2 Hz, 1H), 2.97 (s, 3H), 1.58 (s, 3H), 1.48 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.2, 142.2, 136.7, 128.9 (×2), 128.8, 127.6 (×2), 122.9, 110.3, 80.0, 79.4, 76.2, 69.6, 56.6, 27.4, 26.7; HRMS (ESI): calcd. for $C_{17}H_{20}O_5Na^+$ $[M + Na]^+$, 327.1203; found 327.1201.



Synthesis of compounds 13a and 14a:

Compound **13a** was obtained in 22 mg (83%) as colorless oil from **11a** following the same procedures as described above for the synthesis of compound **13**. $[\alpha]^{25}_D$ = + 35.2 (*c* 0.2, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.47 (d, *J* = 7.6 Hz, 2H), 7.40-7.30 (m, 3H), 7.01 (dd, *J* = 10.0, 5.2 Hz, 1H), 6.21 (d, *J* = 10.0 Hz, 1H), 4.98 (d, *J* = 7.2 Hz, 1H), 4.74 (t, *J* = 3.2 Hz, 1H), 4.21 (dd, *J* = 7.2, 3.2 Hz, 1H), 3.83 (dd, *J* = 5.2, 3.2 Hz, 1H), 3.29 (s, 3H), 2.62 (*br* s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.8, 141.5, 141.0, 128.7 (×2), 128.3, 127.0 (×2), 125.0, 74.6, 73.0, 70.8, 70.7, 56.8; HRMS (ESI): calcd. for $C_{14}H_{16}O_5Na^+$ $[M + Na]^+$, 287.0890; found 287.0892.

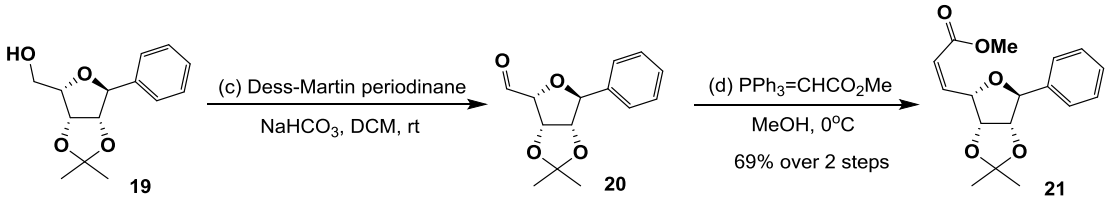
Compound **14a** was obtained as a white amorphous solid (17 mg, 90%) from **13a** following the same procedures as described above for the synthesis of compound **14**. $[\alpha]^{25}_D$ = – 46.5 (*c* 0.1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.43-7.34 (m, 5H), 6.64 (dd, *J* = 10.0, 5.2 Hz, 1H), 6.08 (d, *J* = 10.0 Hz, 1H), 5.24 (d, *J* = 6.8 Hz, 1H), 4.84 (t, *J* = 7.2 Hz, 1H), 4.17 (dd, *J* = 7.6, 4.0 Hz, 1H), 3.23 (s, 3H), 2.90 (t, *J* = 4.4 Hz, 1H), 1.66 (s, 3H), 1.51 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.0, 141.1, 137.6, 129.0, 128.9 (×2), 127.9 (×2), 124.6, 109.6, 79.0, 78.9, 66.7 (×2), 56.0, 27.1, 24.9; HRMS (ESI): calcd. for $C_{17}H_{20}O_5Na^+$ $[M + Na]^+$, 327.1203; found 327.1203.



Synthesis of compound 19:

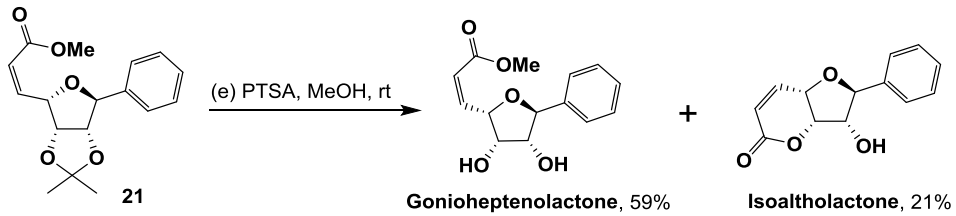
To a solution of the known triol **16** [20] (1.93 g, 7.2 mmol) in anhydrous pyridine (40 mL) was added solid TsCl (1.4 g, 7.3 mmol) in three portions at 0 ℃. After 10 min, the solution was

warmed to room temperature and stirred for a further 2-4 h. To the mixture was added K_2CO_3 (1.77 g, 12.8 mmol) in MeOH (30 mL).The resulting solution was stirred for 4 h at room temperature before water (25 mL) was added. The solution was concentrated with toluene and poured into saturated aqueous $CuSO_4$ (50 mL) and then extracted with DCM (3× 50 mL). The combined organic phase was washed with brine, dried over Na_2SO_4, and concentrated under vacuum. The crude residue was purified by flash column chromatography (petroleum ether / EtOAc 1: 1) to give known compound **19** as yellowish oil (1.50 g, 83%).$[\alpha]^{25}_D$ = + 26.6 (*c* 0.3, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.38-7.27 (m, 5H), 5.23 (s, 1H), 4.96 (dd, *J* = 6.0, 1.2 Hz, 1H), 4.80 (dd, *J* = 6.0, 4.0 Hz, 1H), 4.10 (dd, *J* = 12.0, 5.6 Hz, 1H), 4.05-3.95 (m, 2H), 2.24 (*br* s, 1H),1.59 (s, 3H), 1.37 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.5, 128.7 (×2), 127.6, 125.6 (×2), 113.2, 87.6, 84.6, 81.7, 80.4, 61.5, 26.2, 24.8; HRMS (ESI): calcd. for $C_{14}H_{18}O_4Na^+$ $[M + Na]^+$, 273.1100; found 273.1102. The physical data were consistent with the literature reports. [21]



Synthesis of compound 21:

To a solution of **19** (251 mg, 1 mmol) in 20 mL of wet DCM (with 0.1% V/V H_2O) was added $NaHCO_3$ (350 mg, 4 mmol) and Dess-Martin periodinane (900 mg, 2 mmol) at 0 ℃. The mixture was stirred at room temperature for 1 h and quenched with saturated $NaHCO_3$ aqueous solution. The mixture was extracted with DCM, dried over Na_2SO_4 and evaporated under reduced pressure. The crude aldehyde **20** was used for the next step without further purification. To the resulting solution was added (methoxycarbonylmethylene) triphenylphosphorane (550 mg, 1.6 mmol) at 0 ℃. After stirring at 0 ℃ for 4 h, the reaction mixture was concentrated under vacuum. The crude residue was purified by flash column chromatography (petroleum ether / EtOAc 4:1) to give compound **21** as as colorless oil (210 mg, 69% for two steps). $[\alpha]^{25}_D$ = + 7.5 (*c* 0.1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.37-7.27 (m, 5H), 6.48 (dd, *J* = 11.6, 6.4 Hz, 1H), 6.02 (dd, J = 11.6, 1.6 Hz, 1H), 5.40 (ddd, *J* = 7.6, 4.0, 1.2 Hz, 1H), 5.27 (*br* s, 1H), 5.04 (dd, J = 6.0, 4.0 Hz, 1H), 5.00 (dd, *J* = 6.0, 0.8 Hz, 1H), 3.70 (s, 3H), 1.57 (s, 3H), 1.35 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.1, 145.9, 138.5, 128.7 (×2), 127.5, 125.5 (×2), 120.4, 112.7, 87.4, 85.1, 83.0, 78.3, 51.5, 26.3, 25.0; HRMS (ESI): calcd. for $C_{17}H_{20}O_5Na^+$ $[M + Na]^+$, 327.1203; found 327.1202.

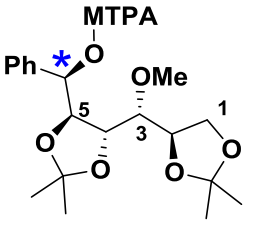


Synthesis of gonioheptenolactone (2) and isoaltholactone (4):

To a solution of α, β-unsaturated ester **21** (34 mg, 0.11 mmol) in MeOH (12 mL) was added PTSA H_2O (3.6 mg, 0.019 mmol) at room temperature. After stirring at room temperature for 6 h, the mixture was quenched with Et_3N (1 mL) and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (petroleum ether/EtOAc 2:3) to give gonioheptenolactone (**2**) (17.5 mg, 59%) and isoaltholactone (**4**) (5.5 mg, 21%) as colorless oil. For gonioheptenolactone (**2**): $[\alpha]^{25}_D$ = + 22.9 (*c* 1.0, EtOH); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.40-7.29 (m, 5H), 6.49 (dd, *J* = 11.6, 6.4 Hz, 1H), 6.02 (dd, *J* = 11.6, 1.6 Hz, 1H), 5.66 (ddd, *J* = 6.4, 5.2, 1.6 Hz, 1H), 5.00 (d, *J* = 6.0 Hz, 1H), 4.61 (t, *J* = 5.2 Hz, 1H), 4.17 (dd, *J* = 6.0, 4.8 Hz, 1H), 3.76 (s, 3H), 2.98 (*br* s, 1H), 2.64 (*br* s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.6, 148.8, 140.2, 128.7, 128.0, 125.7, 120.5, 84.0, 79.0, 78.8, 73.7, 51.9; HRMS (ESI): calcd. for $C_{14}H_{16}O_5Na^+$ $[M + Na]^+$, 287.0890; found 287.0891.

For isoaltholactone (**4**): $[\alpha]^{25}_D$ = + 18.6 (*c* 0.2, EtOH); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.41-7.33 (m, 5H), 6.89 (dd, *J* = 10.0, 4.4 Hz, 1H), 6.22 (d, *J* = 10.0 Hz, 1H), 5.07 (t, *J* = 5.2 Hz, 1H), 4.89 (t, *J* = 5.2 Hz, 1H), 4.78 (d, *J* = 7.6 Hz, 1H), 4.29 (dd, *J* = 7.2, 5.2 Hz, 1H), 2.66 (*br* s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.7, 141.8, 138.5, 128.8 (×2), 128.5, 125.8 (×2), 123.1, 83.4, 78.7, 78.6, 67.8; HRMS (ESI): calcd. for $C_{13}H_{12}O_4Na^+$ $[M + Na]^+$, 255.0628; found 255.0630. The physical data were consistent with the literature reports. [5]

2. $\Delta\delta$ values (δ^S-δ^R) for the protons of **(*S*)-MTPA-7** and **(*R*)-MTPA-7 (Table S1**)



6-*R*

H	*S*-Mosher-7	*R*-Mosher-7	*ΔS-ΔR*
Ph	7.522-7.327	7.474-7.287	+0.020
H-5	4.424	4.422	-0.070
H-4	3.898-3.873	3.962-3.928	-0.064
H-3	2.452	2.225	-0.227
OCH_3	3.562	3.499	-0.142

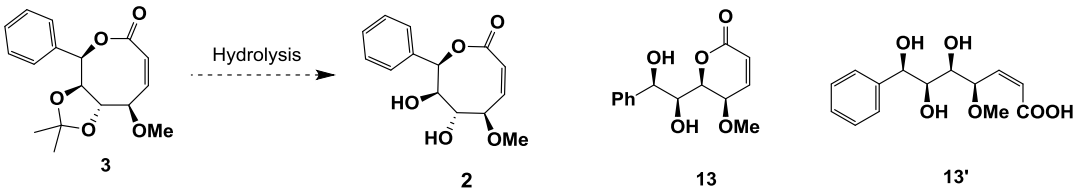
3. Comparison of ^{1}H NMR data of acetonide derivative (3) [a] and synthetic 3/3a [b] (**Table S2**)

No	Reported Acetonide derivative **3**	Synthetic **3**	Synthetic **3a**
3	6.01 (dd, 1H, *J*=11.6, 1.6)	6.15 (d, 1H, *J* = 11.6)	6.02 (dd, 1H, *J* = 12.0, 2.4)
4	6.47 (dd, 1H, *J*=11.6, 6.6)	6.50 (dd, 1H, *J* = 11.6, 8.4)	6.43 (dd, 1H, *J* = 12.0, 2.0)
5	5.40 (ddd, 1H, *J*=7.0, 4.0, 1.6)	5.18 (d, 1H, *J* = 8.4)	4.40 (dd, 1H, *J* = 8.4, 1.2)
6	5.04 (dd, 1H, *J*=6.0, 4.0)	3.73 (d, 1H, *J* = 8.4)	3.95 (dd, 1H, *J* = 8.4, 8.0)
7	5.00 (dd, 1H, *J*=6.0, 1.0)	4.46 (dd, 1H, *J* = 8.4, 1.2)	4.18 (t, 1H, *J* = 8.4)
8	5.28 (*br* s, 1H)	6.12 (d, 1H, *J* = 1.2)	5.56 (d, 1H, *J* = 8.8)
OMe	3.70 (s, 3H)	3.39 (s, 3H)	3.55 (s, 3H)
Ph	7.26–7.37 (m, 5H)	7.53 (d, *J* = 7.2 Hz, 2H), 7.40-7.33 (m, 3H)	7.47–7.34 (m, 5H)
13,14	1.36, 1.57 (s, 3H×2)	1.46, 1.42 (s, 3H×2)	1.45, 1.43 (s, 3H×2)

[a] Spectra were recorded at 500 MHz (^{1}H NMR) in $CDCl_3$.[4]

[b] Spectra were recorded at 400 MHz (^{1}H NMR) in $CDCl_3$.

4. Removal of the isopropylidene group in lactone **3** under various conditions **(Table S3)**



3 2 13 13'

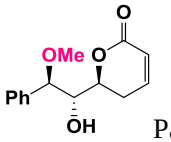
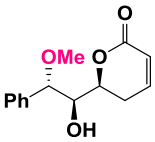
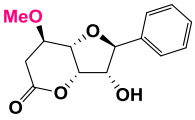
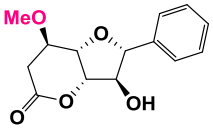
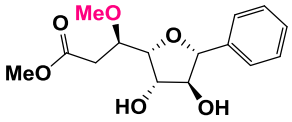
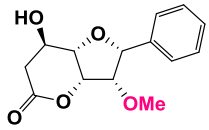
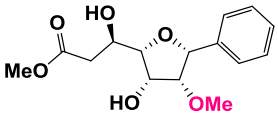
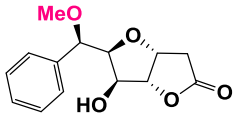
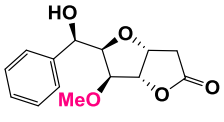
	Conditions	Temperature	Time	Result
1	CSA (0.05 to 0.5 eq), MeOH	r.t.	6 h	**13** (>50%)
2	PTSA (0.1 to 0.5 eq), MeOH	0 ℃ to r.t.	8 h	**13** (>60%)
3	PPTS (0.2 to 1.0 eq), MeOH	0 ℃ to r.t.	24 h	No Reaction [a]
4	IR-120 resin, MeOH	r.t.	12 h	**13** (>50%)
5	TfOH (0.1 eq), CH_2Cl_2	0 ℃ to r.t.	2 h	Decomposition [b]
6	AcOH (60%)	r.t. to 80 ℃	24 h	Decomposition [c]
7	TFA / CH_2Cl_2 (1:2)	0 ℃ to r.t.	45 min	**13'** (>20%) [b]
8	$BF_3 \cdot OEt_2$, CH_2Cl_2	0 ℃ to r.t.	2 h	Decomposition [b]
9	$PdCl_2(CH_3CN)_2$ in acetonitrile/water	0 ℃ to r.t.	2 h	No Reaction [a]
10	$TiCl_4$, CH_2Cl_2	-78 ℃	12 h	No Reaction [a]
11	$TiCl_4$, CH_2Cl_2	0 ℃ to r.t.	2 h	Decomposition [b]
12	1.5% HCl in MeOH	0 ℃ to r.t.	30 min	No reaction [a]
13	4 N HCl, EtOAc	r.t.	10 h	**13** (>50%)
14	TFA/CH_2Cl_2 = 1:10	0 ℃ to r.t.	2 h	**13'** (>35%)

[a] TLC monitoring confirmed no reaction occurred, and the starting materials were recovered.

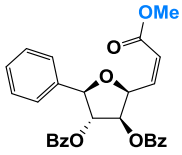
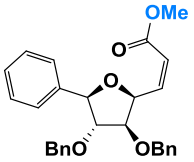
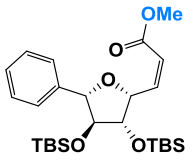
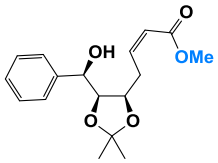
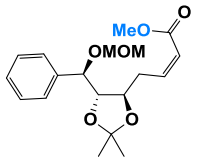
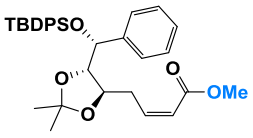
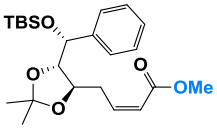
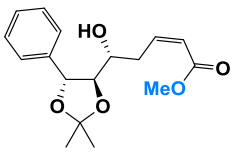
[b] Significant decomposition was observed with increased temperature or extended reaction time, and prolonged exposure at low temperature also led to decomposition.

[c] Under room temperature, the starting materials were recovered without any target product formation; decomposition occurred upon increasing the temperature.

5. Reported NMR data of aliphatic methoxy groups in the styryllactones (**Table S4)**

No	Structures	Chemical shifts (ppm, in $CDCl_3$) of methyl ester	Reference
1	 Parvistone B	δ_H 3.24 (s, 3H) δ_C 56.8	Wu, Y. C., *J. Nat. Prod.* **2014**, 77, 2626
2	 Parvistone C	δ_H 3.22 (s, 3H) δ_C 56.7	Wu, Y. C., *J. Nat. Prod.* **2014**, 77, 2626
3	 Goniotortilactone	δ_H 3.47 (s, 3H) δ_C 57.3	Laphookhieo, S. *J. Nat. Prod.* **2025**, 10.1021/acs.jnatprod.4c00933.
4	 Derivative of almuheptolide A	δ_H 3.46 (s, 3H) δ_C 57.3	Cortes, D. *J. Med. Chem.*, **1998**, 41, 5158.
5	 Goniothalesacetate	δ_H 3.55 (s, 3H) δ_C 51.8	Sabitha, G, *Org. Biomol. Chem.*, **2015**, 13, 10487.
6	 4-*epi*-Methoxy-goniofupyron	δ_H 3.03 (s, 3H) δ_C 60.6	Enders, D., *Synlett* **2012**, 44, 3483.
7	 4-*epi*-Methoxy-gonioheptolide	δ_H 3.02 (s, 3H) δ_C 51.7	Enders, D., *Synlett* **2012**, 44, 3483.
8	 7-O-Methyl-goniofufurone	δ_H 3.35 (s, 3H) δ_C 57.9	Popsavin, V., *Med. Chem. Commun.*, **2018**, 9, 2017.
9	 5-O-Methylgoniofufurone	δ_H 3.48 (s, 3H) δ_C 58.3	Popsavin, V., *Med. Chem. Commun.*, **2018**, 9, 2017.

6. Reported data of (Z)-α, β-unsaturated methyl ester in the styryllactones **(Table S5)**

No	Structures	Chemical shifts (ppm, in $CDCl_3$) of methyl ester	Reference
1	 Intermediate **18** of altholactone.	δ_H 3.76 (s, 3H) δ_C NA	Gesson, J. P, *Tetrahedron*, **1989**, 45, 2627.
2	 Intermediate **14** of goniothalesdiol.	δ_H 3.64 (s, 3H) δ_C 52.4	Carreno, M. C.; *Org. Lett.* **2002**, 7, 5517.
3	 Intermediate **12b** of altholactone.	δ_H 3.71 (s, 3H) δ_C 51.3	Yadav, J. S.; *Tetrahedron: Asymmetry*, **2005**, 16, 3283.
4	 Intermediate **5** of 7-*epi*-goniodiol.	δ_H 3.67 (s, 3H) δ_C 51.4	Wang, D, *J. Chem. Res.*, **2016**, 40, 330.
5	 Intermediate **2** of goniodiol,	δ_H 3.69 (s, 3H) δ_C 51.0	Sabitha, G, *Synthesis* **2011**, 821.
6	 Intermediate **2** of goniodiol,	δ_H 3.68 (s, 3H) δ_C 50.9	Yadav, J. S.; *Tetrahedron: Asymmetry*, **2010**, 21, 2443.
7	 Intermediate **8** of goniodiol.	δ_H 3.65 (s, 3H) δ_C 51.1	Yadav, J. S.; *Synthesis* **2010**, 3004.
8	 Intermediate **10** of 7-*epi*-goniodiol.	δ_H 3.69 (s, 3H) δ_C 50.8	Yadav, J. S.; *Synthesis* **2007**, 385.

7. Computational details

To predict the product of the acid hydrolysis of **3** and **3a**, computational calculation were carried out. Structures of **3** and **3a** and their possible hydrolysis products (**3**, **13,** and **13'; 3a**, **13a,** and **13a'**) were optimized with B3LYP/6-31+G(d,p), [1-4] and frequency analyses were performed at the same level. To get more precise thermodynamic parameters, single point energies were calculated with M062X/6-311++G(d,p) [5-7] and SMD [8] solvation model on optimized structures. The structure generated with *CYLview* software. [9]

1. C. Lee, W. Yang and R. G. Parr, Development of the Colle-Salvetti correlation-energy formula into a functional of the electron density. *Phys. Rev. B.*, 1988, **37**, 785–789.

2. A. D. Becke, Density‐functional thermochemistry. III. The role of exact exchange. *J. Chem. Phys.*, 1993, **98**, 5648–5652.

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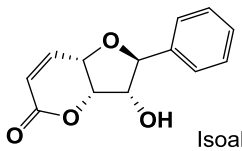
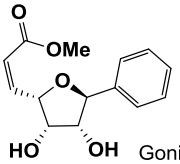
8. A. V. Marenich, C. J. Cramer and D. G. Truhlar, Universal solvation model based on solute electron density and on a continuum model of the solvent defined by the bulk dielectric constant and atomic surface tensions. *J. Phys. Chem. B*, 2009, **113**, 6378–6396.

9. C. Y. Legault, CYLview. 1.0b ed.; Université de Sherbrooke, 2009.

8. In vitro cytotoxicity [a, b] of gonioheptenolactone (**2**) and isoaltholactone (**4**) **(Table S6)** [c, d]

Cell lines \ Compounds	 Isoaltholactone, **4**			 Gonioheptenolactone, **2**		
	30 μM	10 μM	3 μM	30 μM	10 μM	3 μM
Jurkat	77.63%±2.15%	5.34%±1.63%	-10.16%±2.48%	57.39%±6.91%	12.67%±1.98%	5.02%±4.81%
OCI-LY3	62.95%±6.10%	29.74%±7.07%	7.88%±2.66%	64.60%±1.87%	25.54%±1.35%	19.29%±6.45%
HCT116	29.37%±6.25%	-0.03%±3.79%	9.97%±7.90%	12.65%±7.99%	-21.09%±5.33%	-9.96%±6.93%
MDA-MB-231	30.10%±1.53%	3.39%±3.76%	-5.60%±1.63%	25.18%±2.64%	1.47%±3.48%	0.05%±2.83%
Hela	28.64%±1.20%	10.79%±5.46%	8.24%±3.34%	18.16%±1.57%	3.51%±4.59%	3.19%±3.29%
HepG2	51.21%±0.66%	-1.79%±1.94%	-6.37%±5.34%	40.22%±1.75%	8.54%±5.57%	5.54%±4.20%

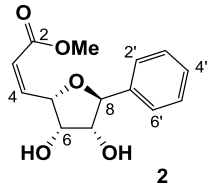
[a] The cells were continuously treated with each sample for 72 h, and the cell growth was evaluated using the MTT reduction assay.

[b] Data are mean values of three experiments performed in triplicate.

[c] Data are expressed as mean ± standard deviation (SD).

[d] IC_{50} value of each compound was calculated using GraphPad Prism 9.0 (GraphPad Software, Inc., US).

9. The comparisons of ^{1}H and ^{13}C NMR data of natural and synthetic gonioheptenolactone **(Table S7)**



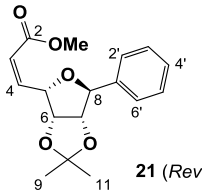
2

No	^{1}H-Natural [a]	^{1}H-synthetic	$\Delta\delta = \delta_a-\delta_b$	^{13}C [a]	^{13}C [b]	$\Delta\delta = \delta_a-\delta_b$
2	-	-	-	167.7	167.6	0.1
3	6.02 (dd, 1H, *J*=10.5, 1.7)	6.02 (dd, 1H, *J*=11.6, 1.6)	0	120.5	120.5	0
4	6.49 (dd, 1H, *J*=10.5, 6.5)	6.49 (dd, 1H, *J*=11.6, 6.4)	0	148.8	148.8	0
5	5.66 (ddd, 1H, *J*=6.5, 5.2, 1.7)	5.66 (ddd, 1H, *J*=6.4, 5.2, 1.6)	0	78.7	78.8	-0.1
6	4.61 (t, 1H, *J*=5.2)	4.61 (t, 1H, *J*=5.2)	0	73.6	73.7	-0.1
7	4.17 (dd, 1H, *J*=6.0, 4.7)	4.17 (dd, 1H, *J*=6.0, 4.8)	0	79.0	79.0	0
8	5.00 (d, 1H, *J*=6.0)	5.00 (d, 1H, *J*=6.0)	0	84.0	84.0	0
OMe	3.76 (s, 3H)	3.76 (s, 3H)	0	51.8	51.9	-0.1
1’				140.2	140.2	0
2’,6’	7.28–7.40 (m, 5H)	7.29–7.40 (m, 5H)	-	125.7	125.7	0
3’,5’				127.9	128.0	-0.1
4’				128.7	128.7	0
OH	3.52 (*br* s, 2H)	2.98 (*br* s, 1H), 2.64 (*br* s, 1H)	-			

[a] Spectra were recorded at 500 MHz (^{1}H NMR) and 125 MHz (^{13}C NMR) in $CDCl_3$. [4]

[b] Spectra were recorded at 400 MHz (^{1}H NMR) and 100 MHz (^{13}C NMR) in $CDCl_3$.

10. The comparisons of ^{1}H NMR data of natural and synthetic **3** **(Table S8)**



21 (*Revised* **3**)

No	^{1}H-Natural [a, b] (*J* in Hz)	^{1}H-synthetic [c] (*J* in Hz)	Δδ = δ_a-δ_b
2	-	-	-
3	6.01 (dd, 1H, *J* = 11.6, 1.6)	6.02 (dd, 1H, *J* = 11.6, 1.6)	-0.01
4	6.47 (dd, 1H, *J* = 11.6, 6.6)	6.48 (dd, 1H, *J* = 11.6, 6.4)	-0.01
5	5.40 (ddd, 1H, *J* = 7.0, 4.0, 1.6)	5.40 (ddd, 1H, *J* = 7.6, 4.0, 1.2)	0
6	5.04 (dd, 1H, *J* = 6.0, 4.0)	5.04 (dd, 1H, *J* = 6.0, 4.0)	0
7	5.00 (dd, 1H, *J* = 6.0, 1.0)	5.00 (dd, 1H, *J* = 6.0, 0.8)	0
8	5.28 (*br* s, 1H)	5.27 (*br* s, 1H)	+0.01
OMe	3.70 (s, 3H)	3.70 (s, 3H)	0
1’			
2’,6’	7.36–7.37 (m, 5H) [d]	7.26–7.37 (m, 5H)	-
3’,5’			
4’			
9-Me	1.36 (s, 3H)	1.35 (s, 3H)	+0.01
11-Me	1.57 (s, 3H)	1.57 (s, 3H)	0

[a] Spectra were recorded at 500 MHz (^{1}H NMR) in $CDCl_3$. [4]

[b] The ^{13}C NMR data of **3** was not recorded in the isolation paper. [4]

[c] Spectra were recorded at 400 MHz (^{1}H NMR) in $CDCl_3$.

[d] We recorded these aromatic protons at 7.26–7.37 ppm and attributed the discrepancy to a typographical error in the isolation paper.

11. Copies of NMR spectra

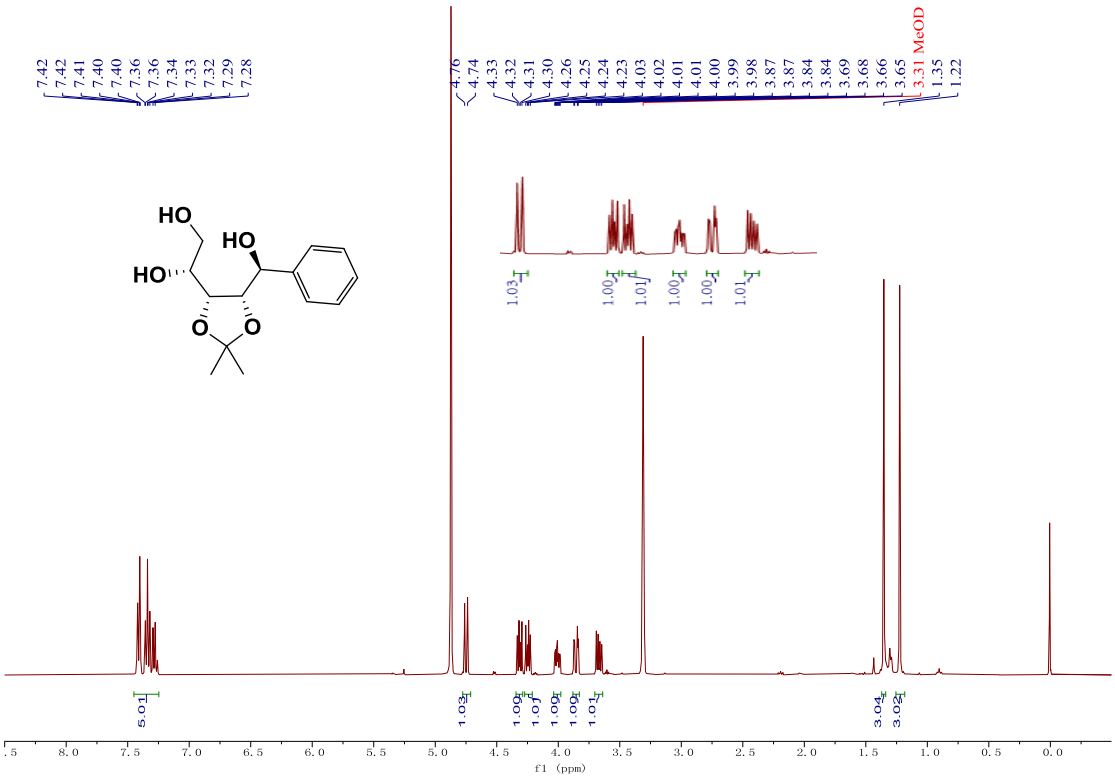


Figure 1. ^{1}H NMR (400 MHz, CD_3OD) spectrum of compound **16**

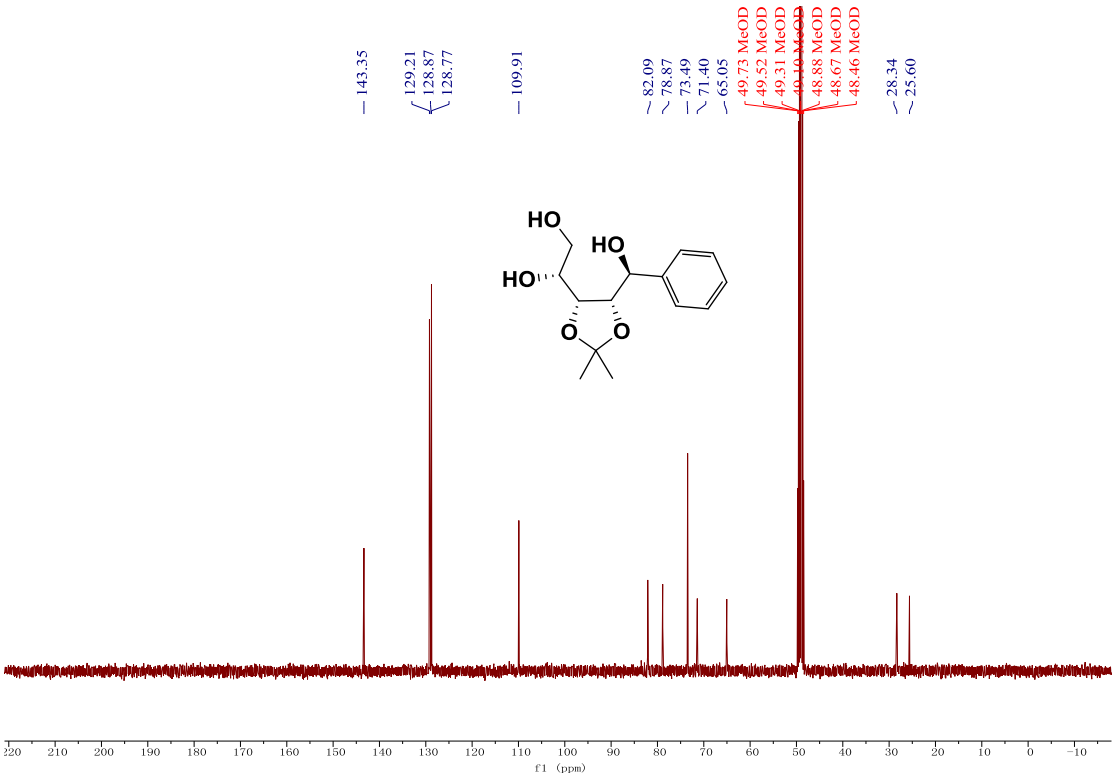


Figure 2. ^{13}C NMR (100 MHz, CD_3OD) spectrum of compound **16**

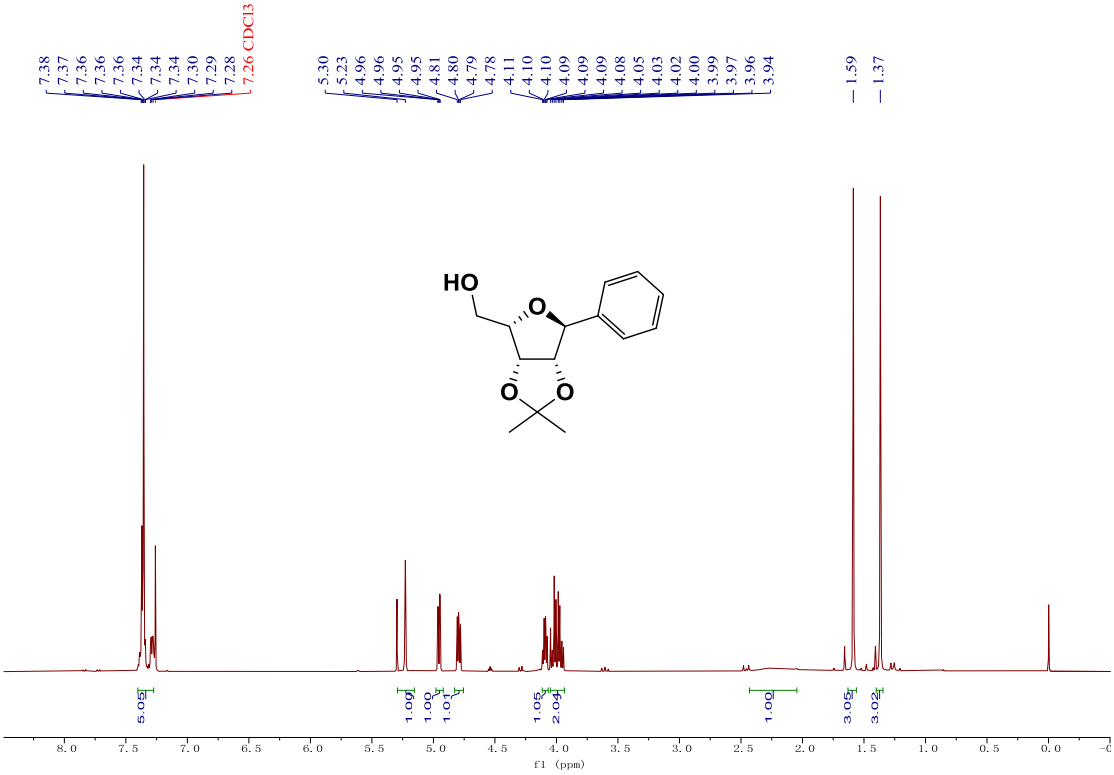


Figure 3. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **19**

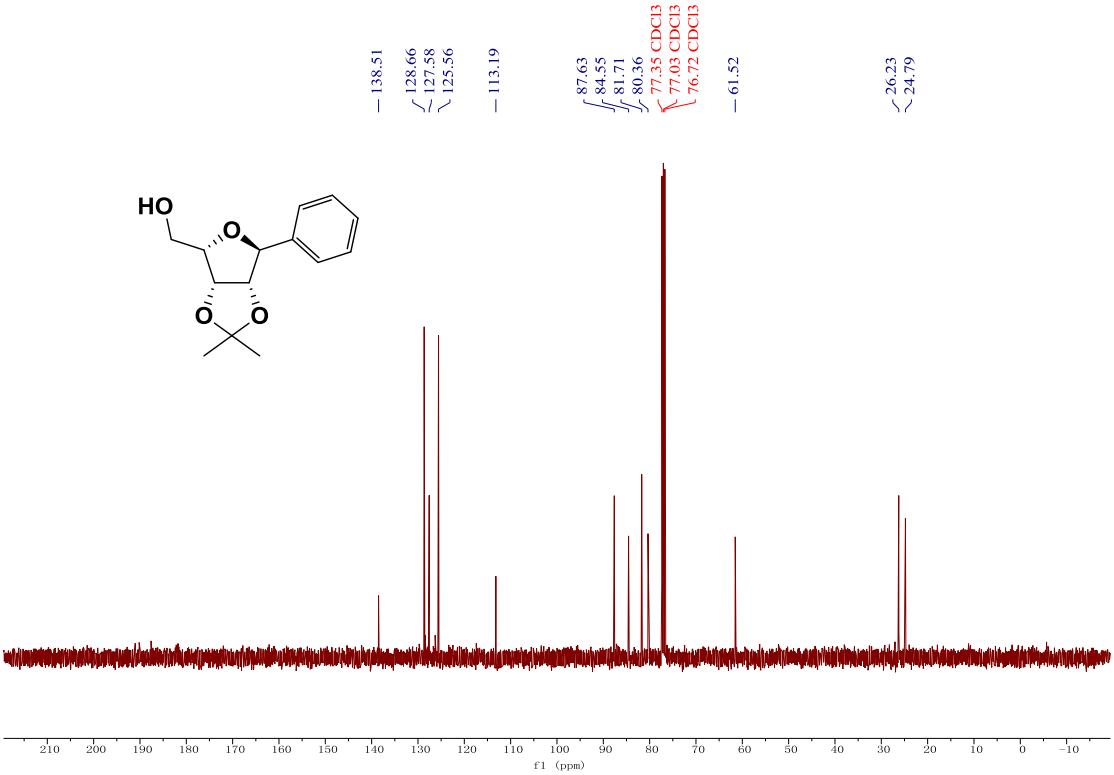


Figure 4. ^{13}C NMR (100 MHz, $CDCl_3$) spectrum of compound **19**

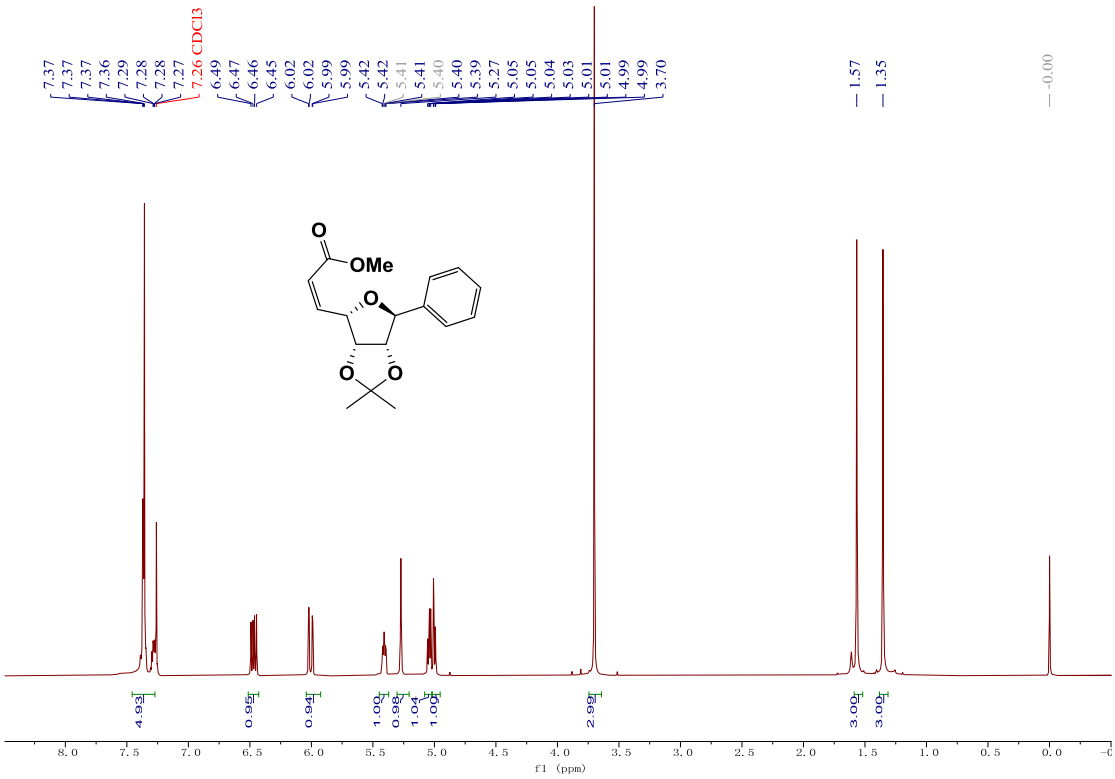


Figure 5. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **21**

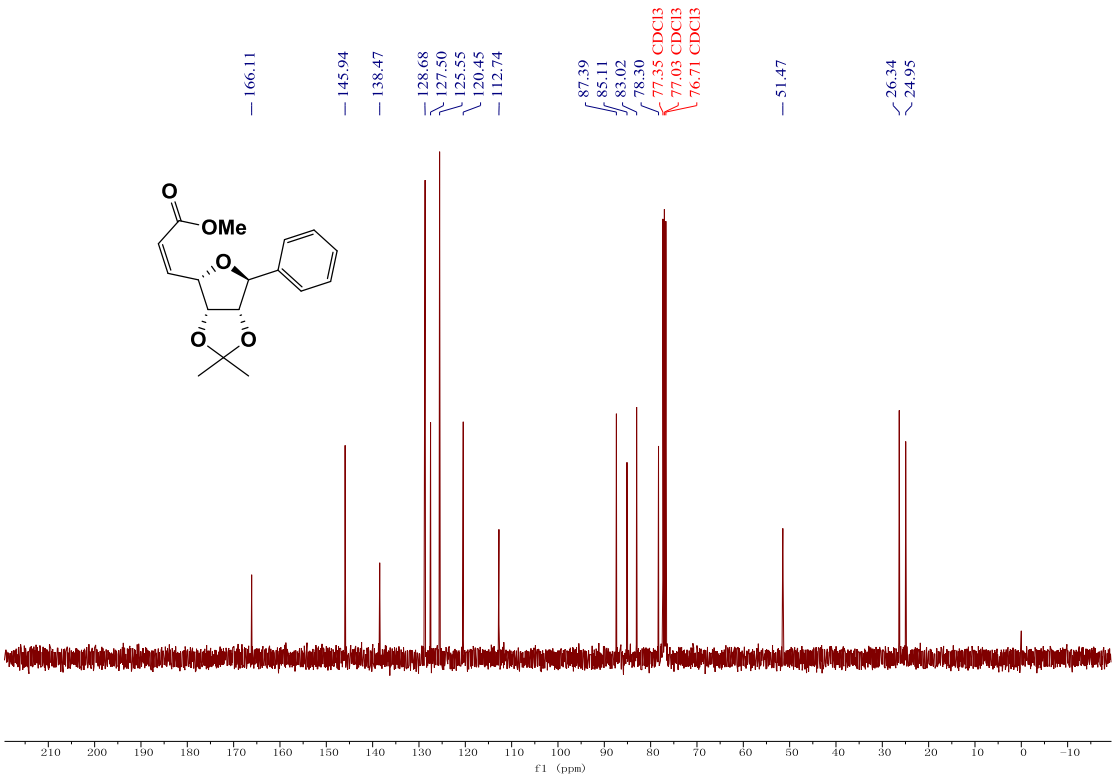


Figure 6. ^{13}C NMR (100 MHz, $CDCl_3$) spectrum of compound **21**

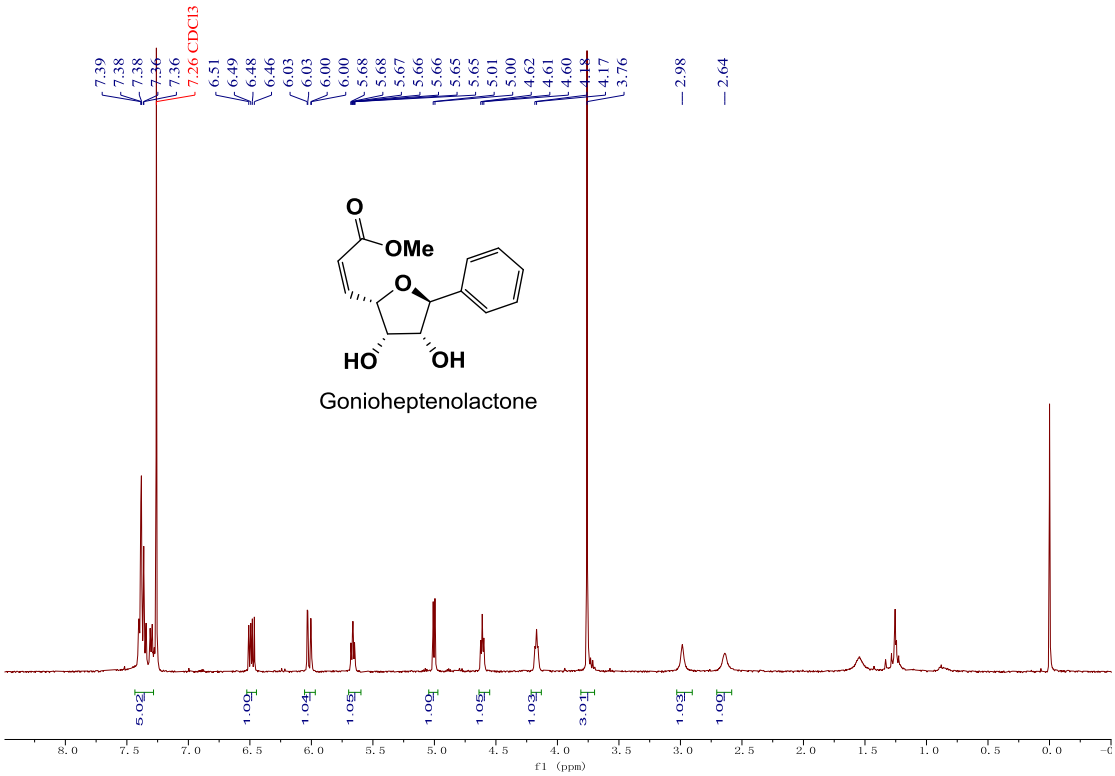


Figure 7. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **2**

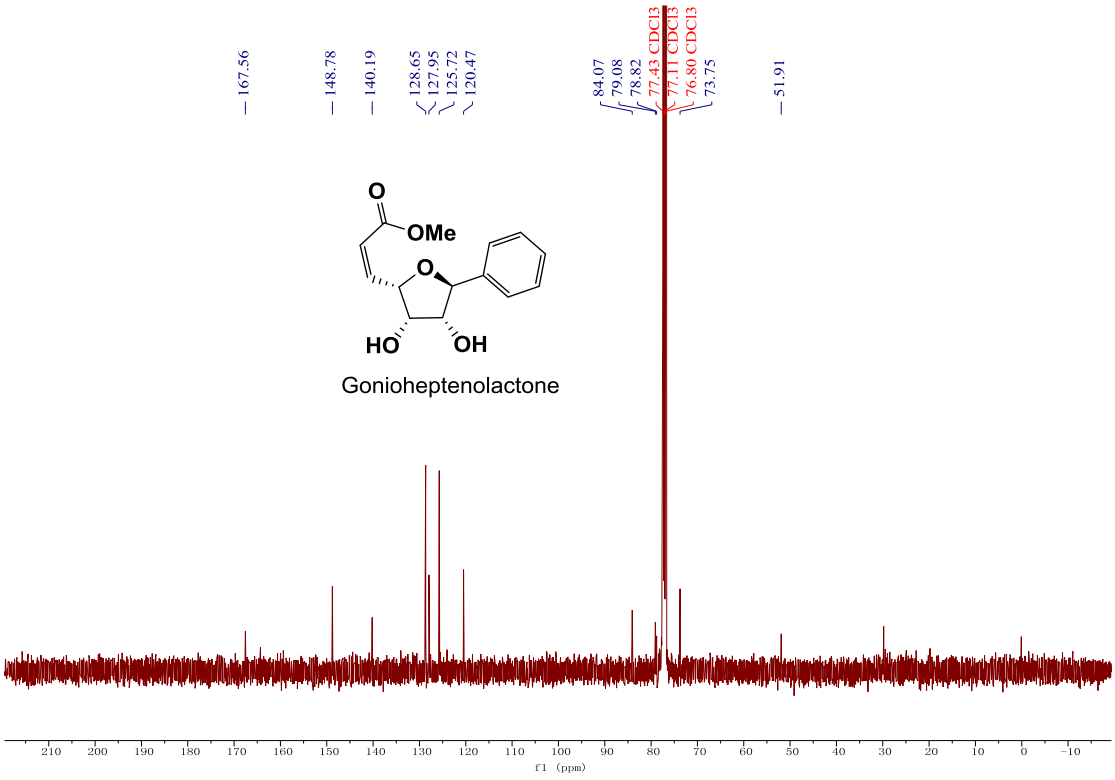


Figure 8. ^{13}C NMR (100 MHz, $CDCl_3$) spectrum of compound **2**

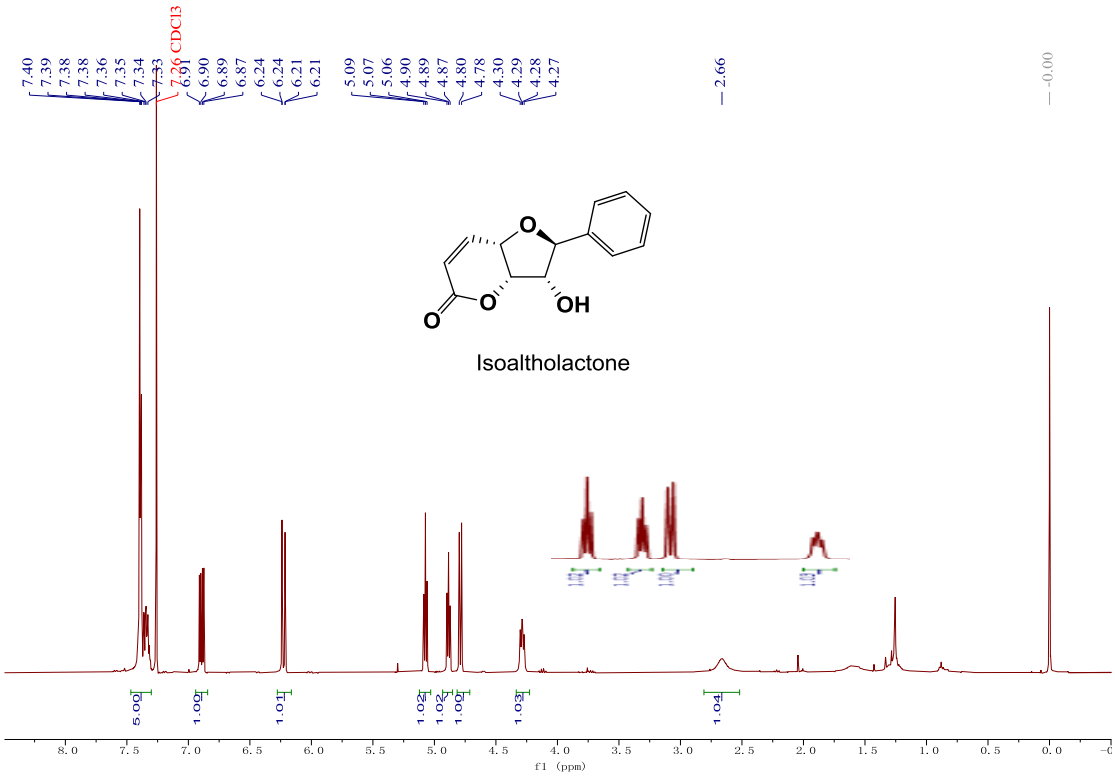


Figure 9. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **4**

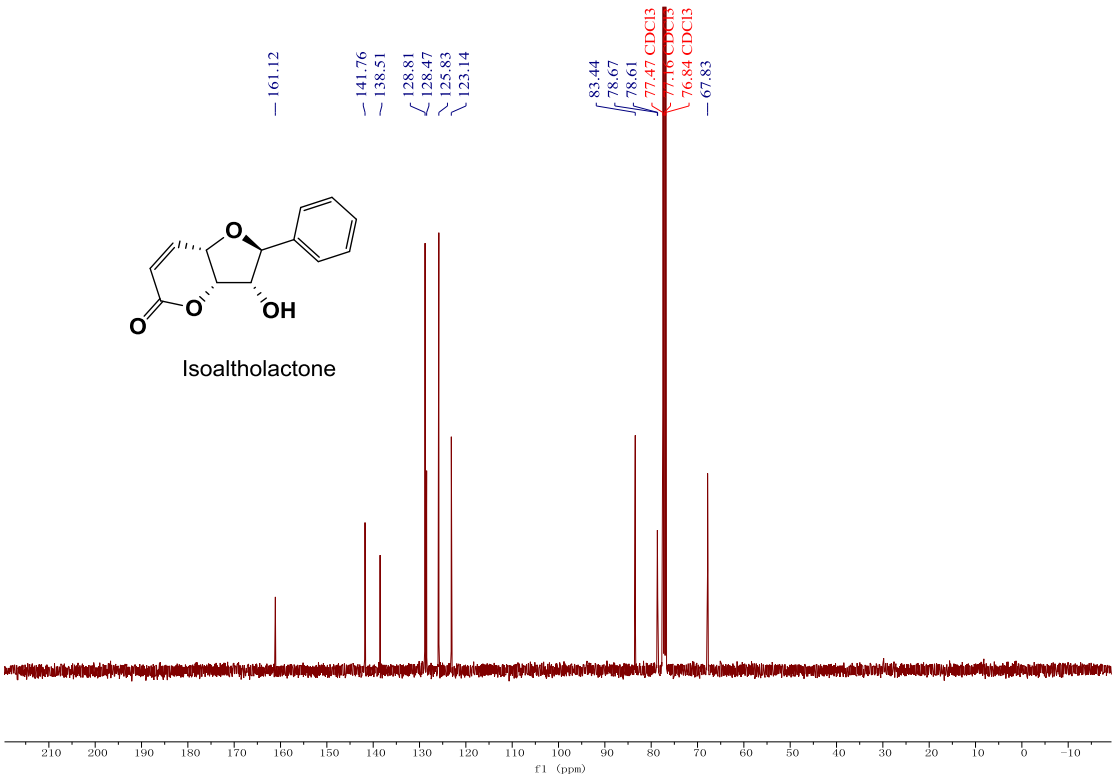


Figure 10. ^{13}C NMR (100 MHz, $CDCl_3$) spectrum of compound **4**

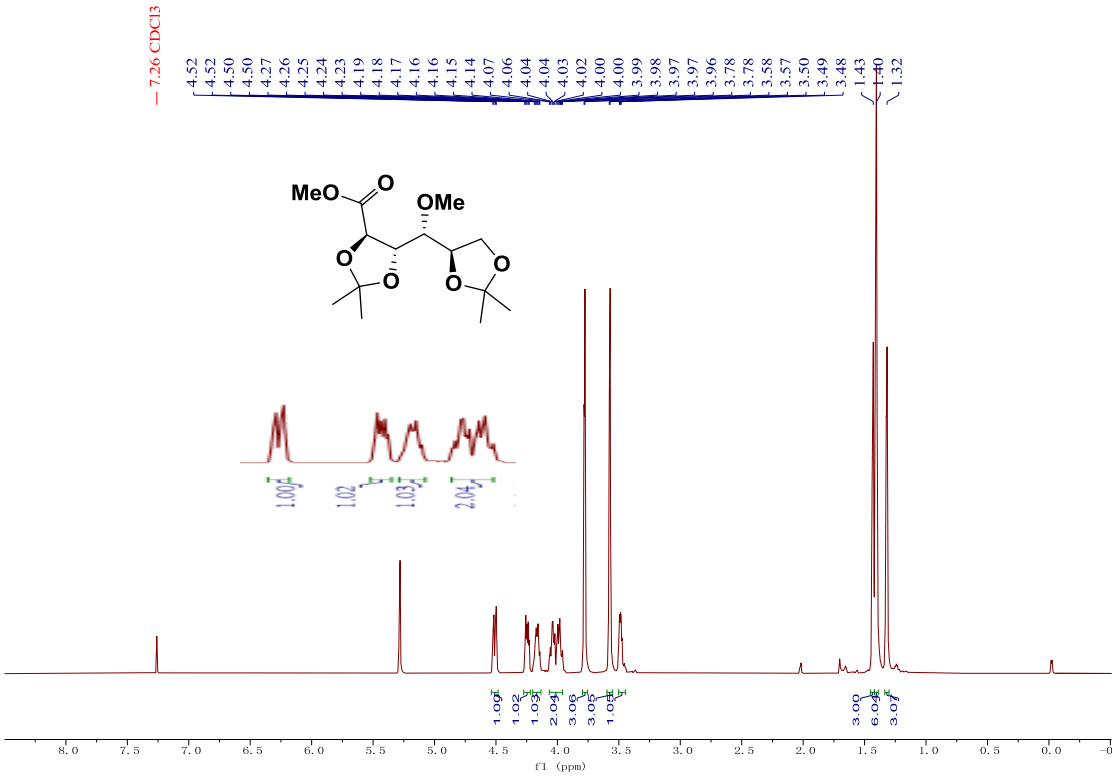


Figure 11. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **9**

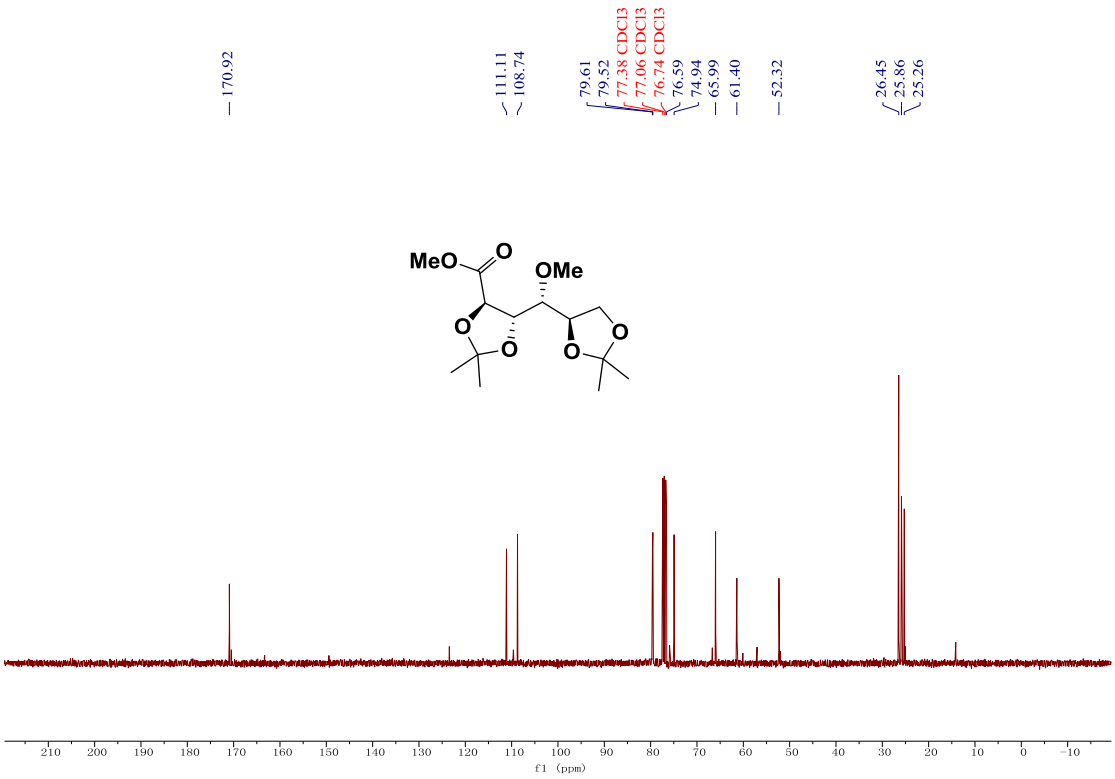


Figure 12. ^{13}C NMR (100 MHz, $CDCl_3$) spectrum of compound **9**

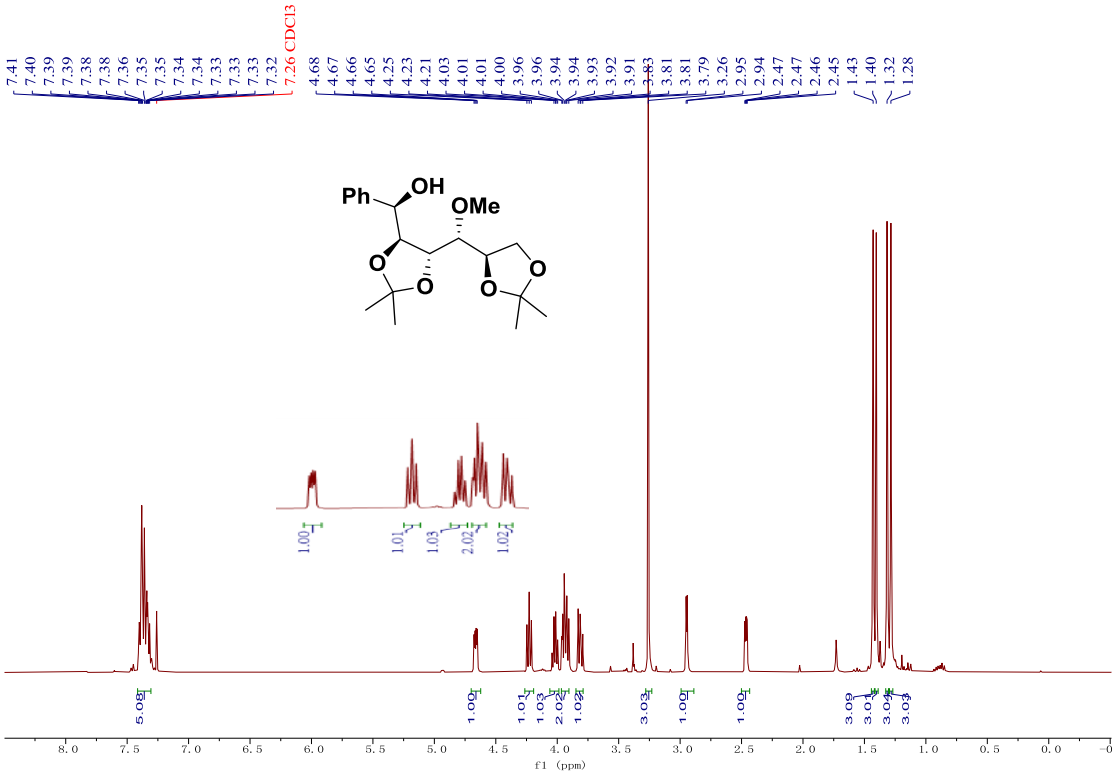


Figure 13. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **7**

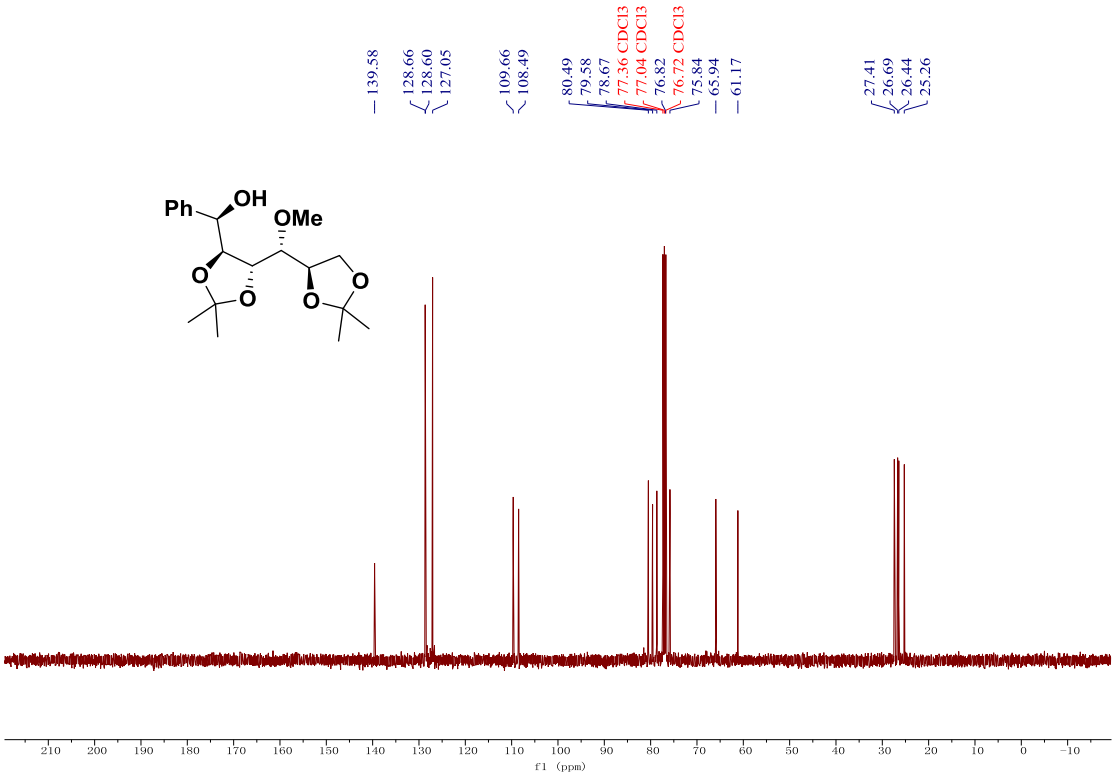


Figure 14. ^{13}C NMR (100 MHz, $CDCl_3$) spectrum of compound **7**

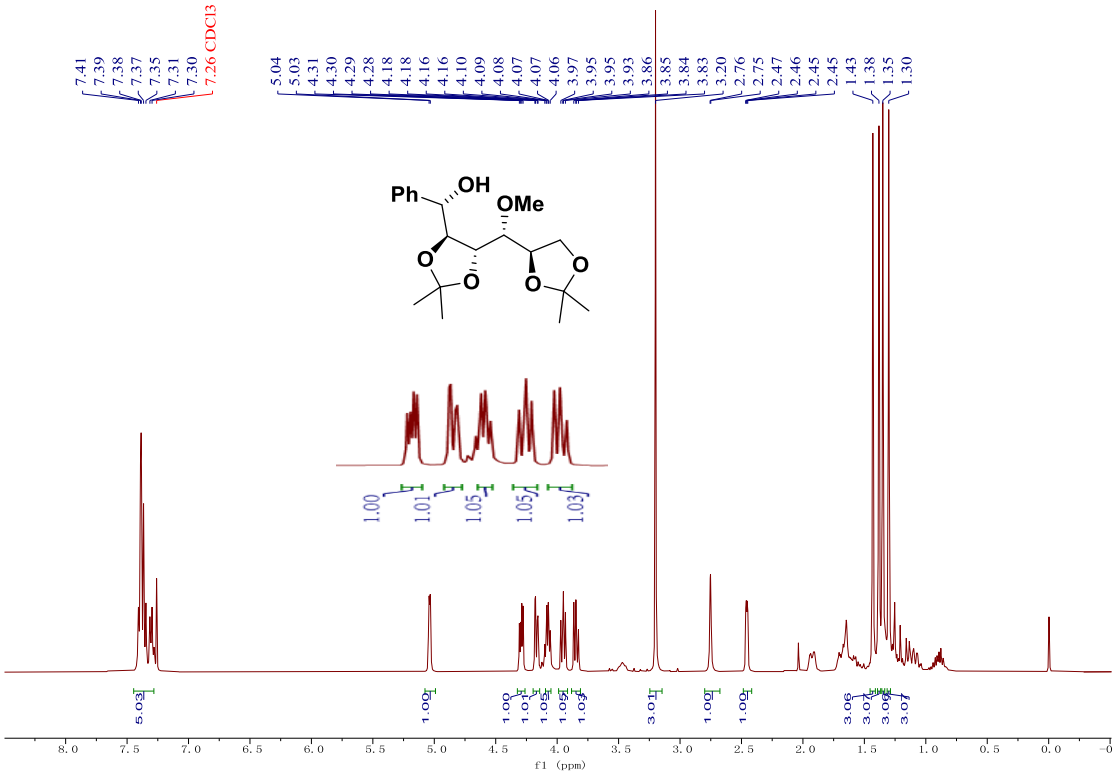


Figure 15. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **7a**

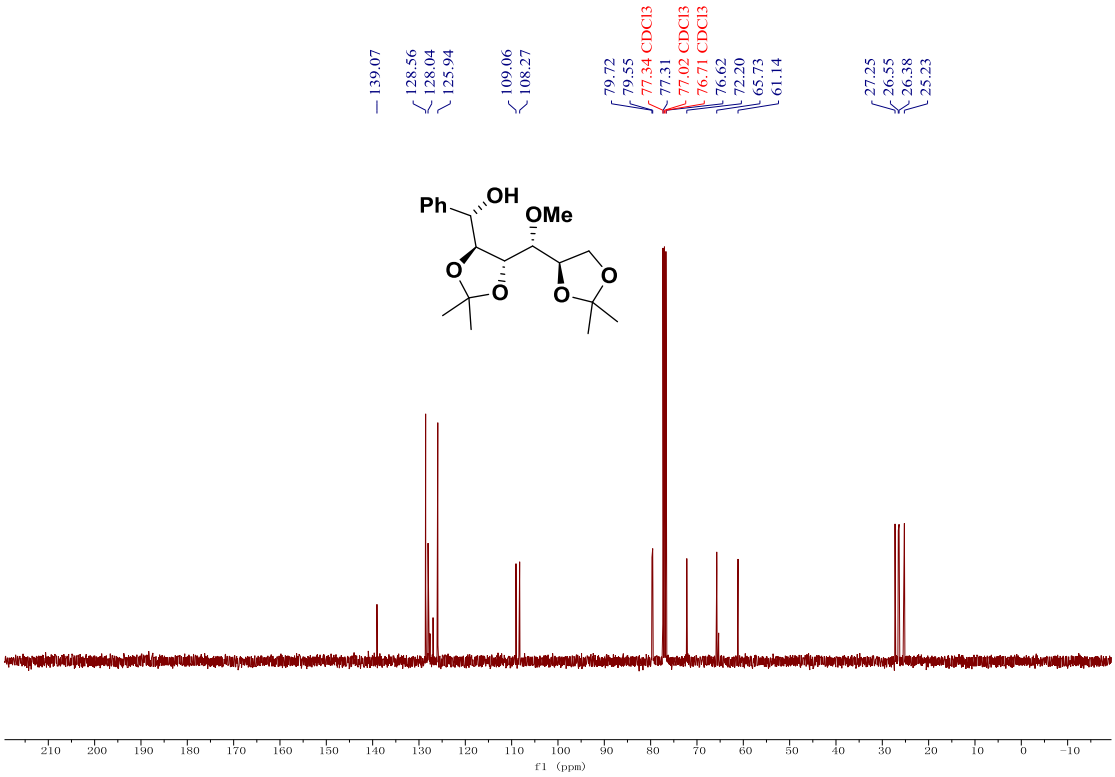


Figure 16. ^{13}C NMR (100 MHz, $CDCl_3$) spectrum of compound **7a**

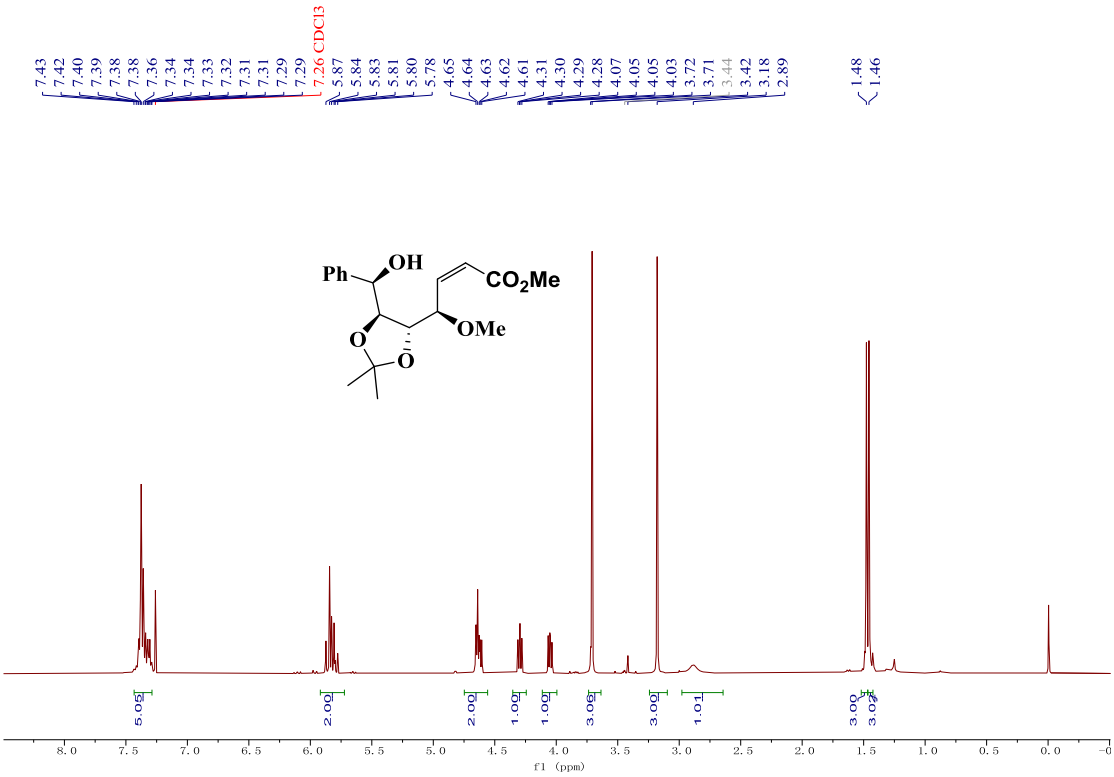


Figure 17. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **11**

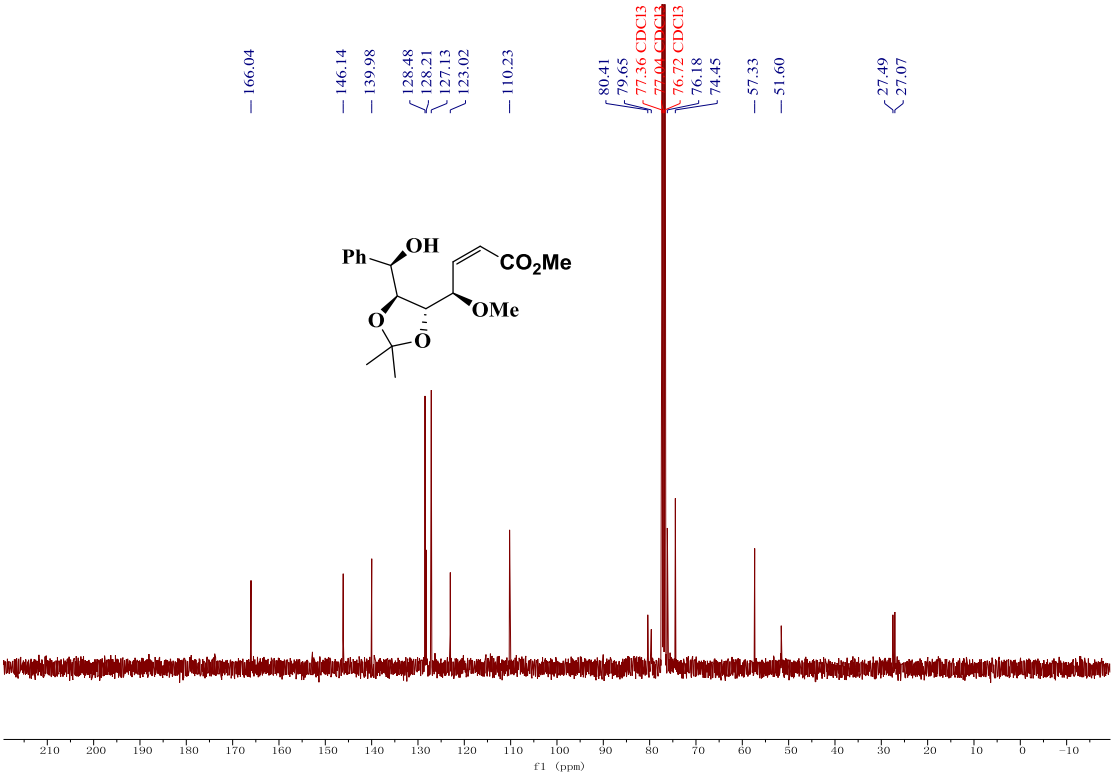


Figure 18. ^{13}C NMR (100 MHz, $CDCl_3$) spectrum of compound **11**

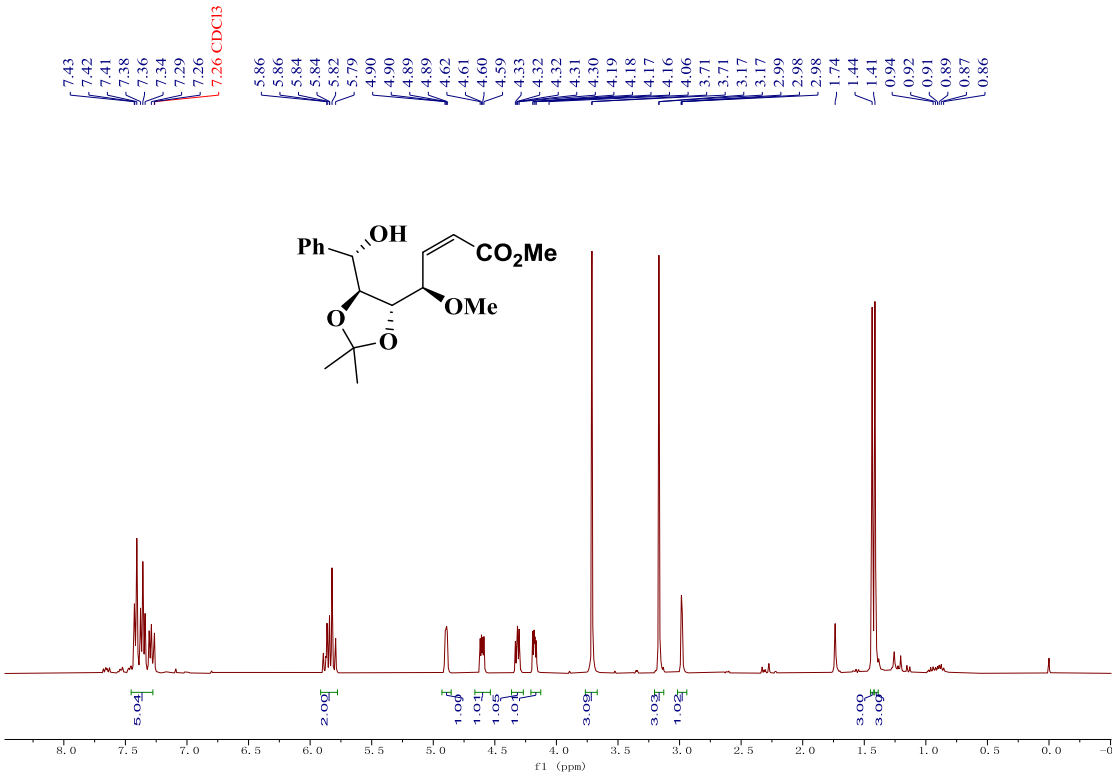


Figure 19. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **11a**

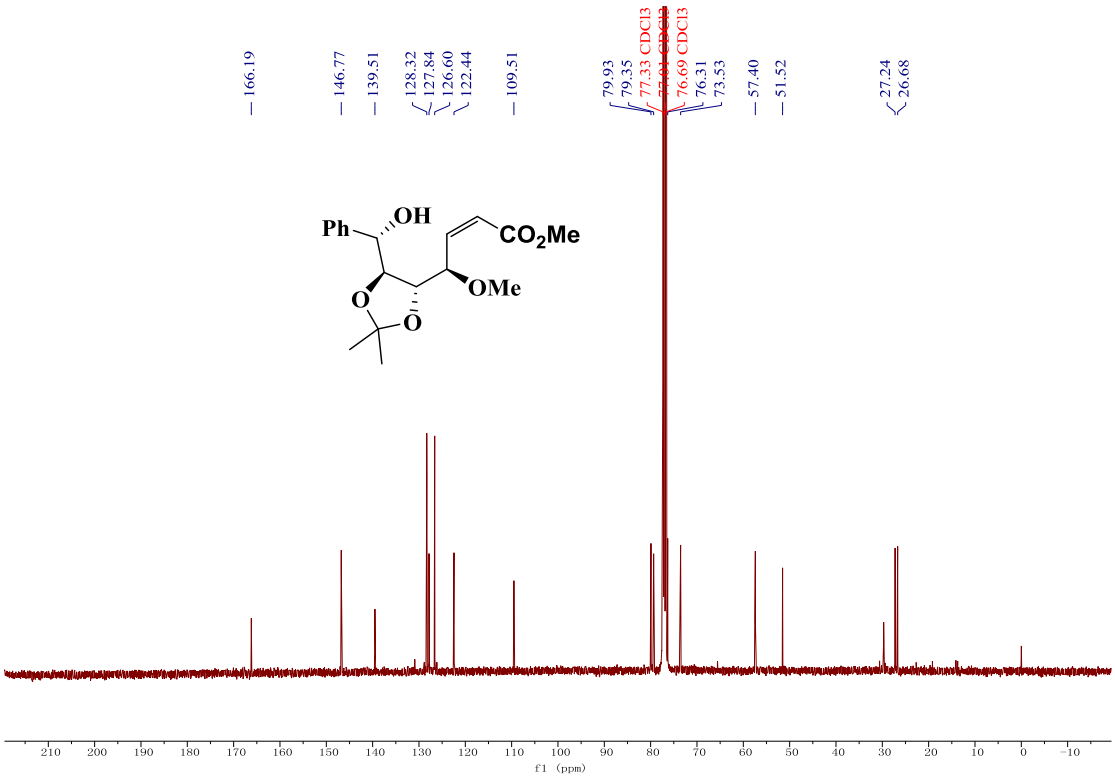


Figure 20. ^{13}C NMR (100 MHz, $CDCl_3$) spectrum of compound **11a**

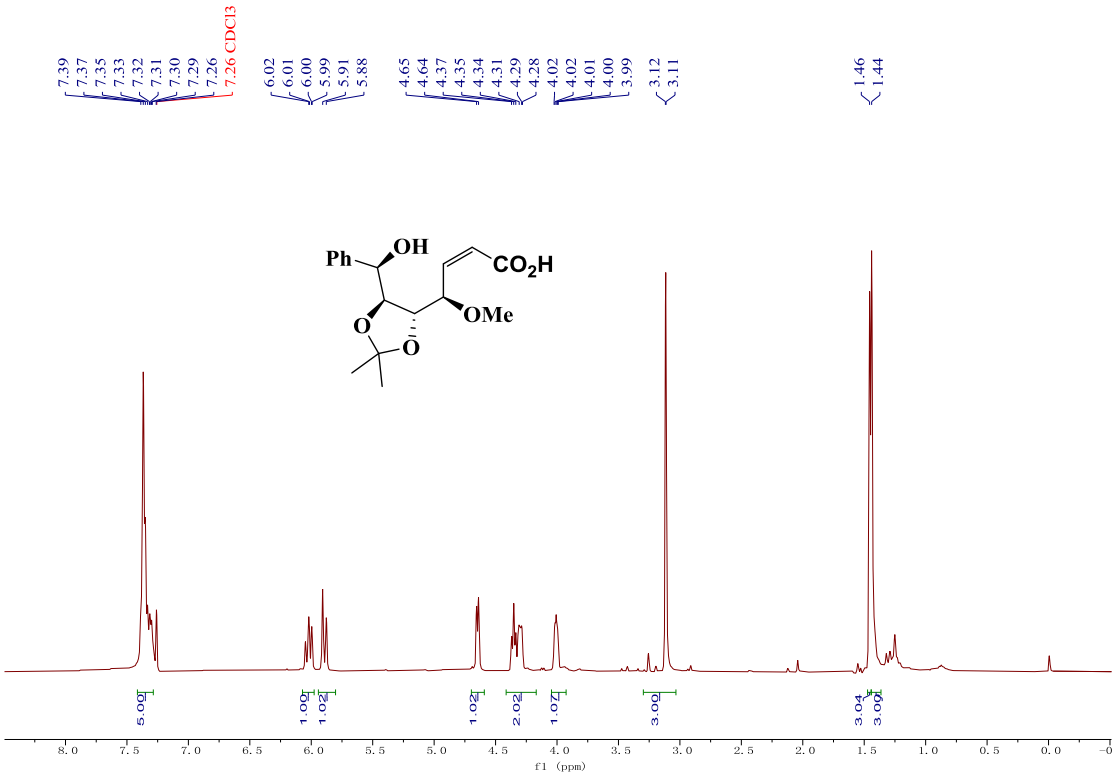


Figure 21. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **12**

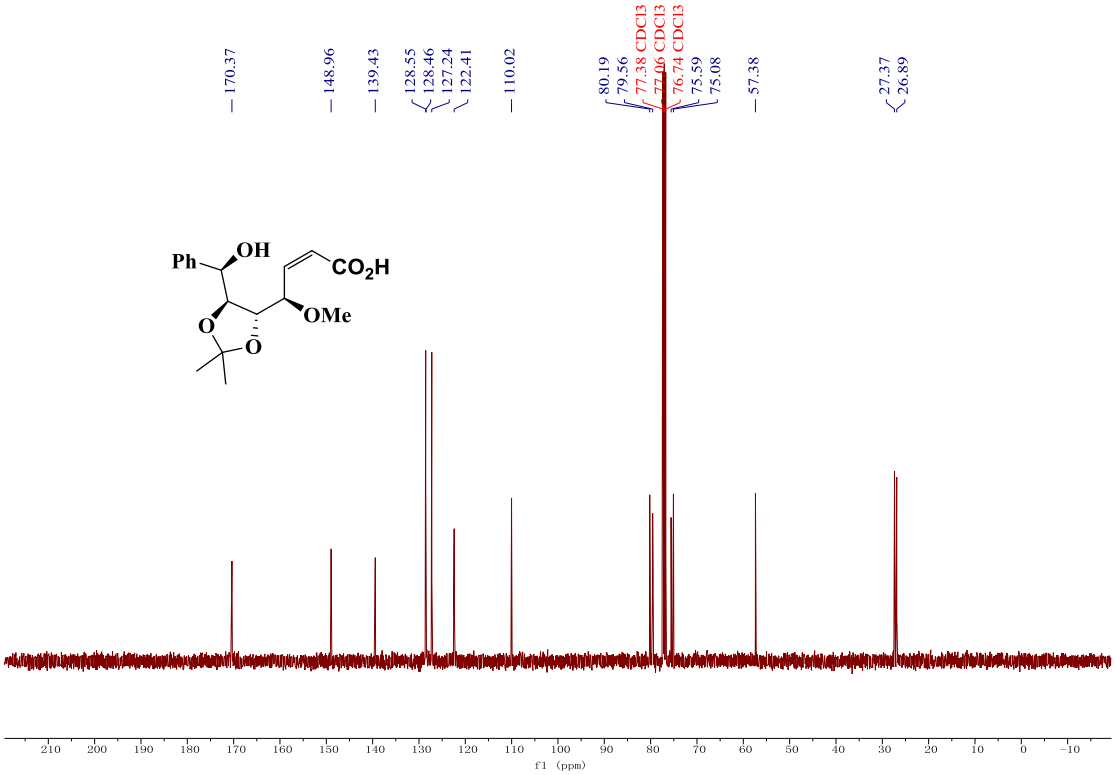


Figure 22. ^{13}C NMR (100 MHz, $CDCl_3$) spectrum of compound **12**

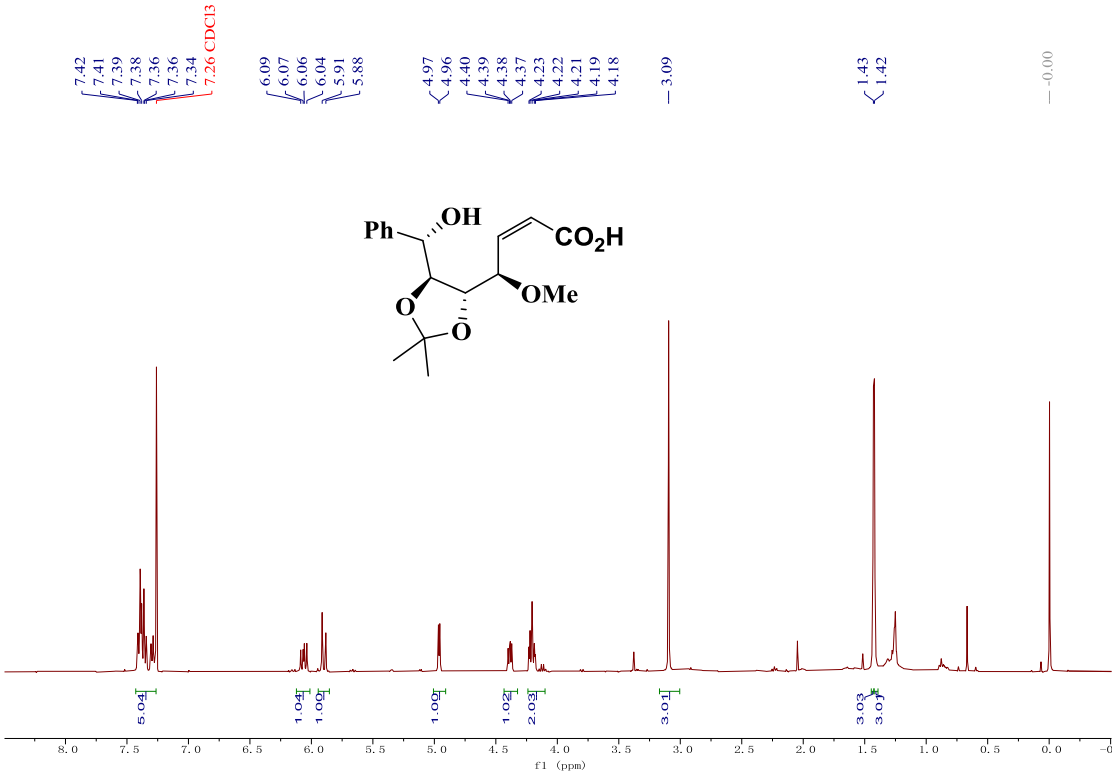


Figure 23. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **12a**

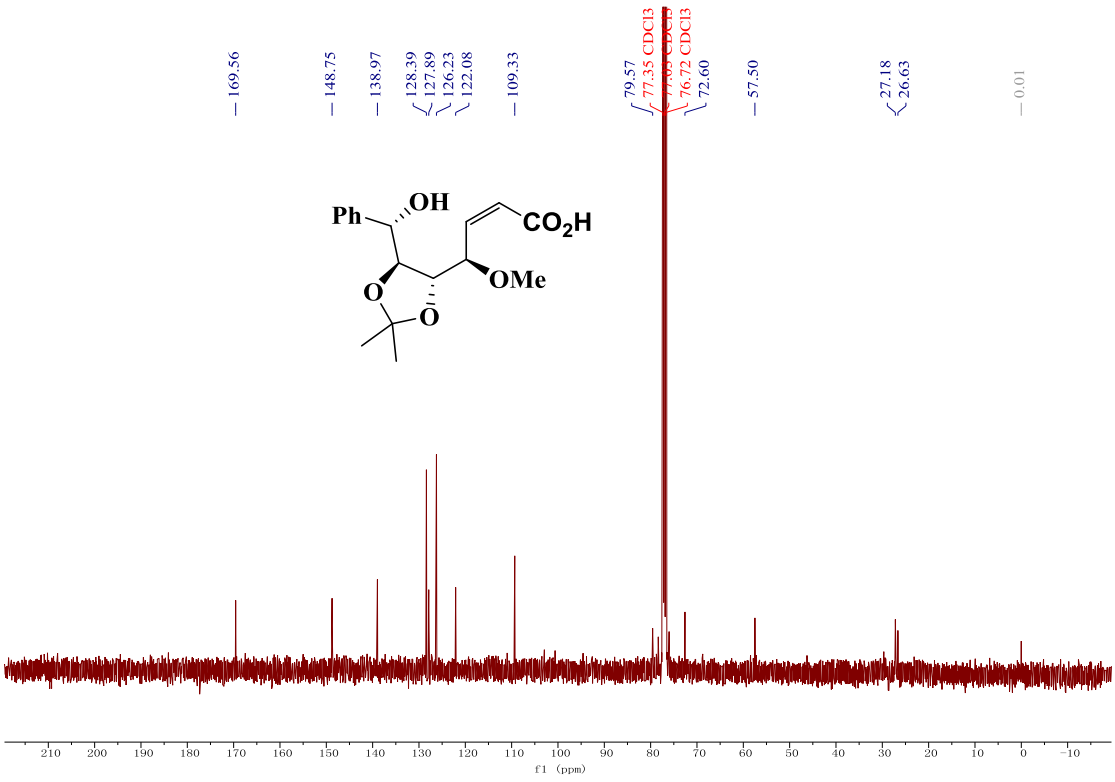


Figure 24. ^{13}C NMR (100 MHz, $CDCl_3$) spectrum of compound **12a**

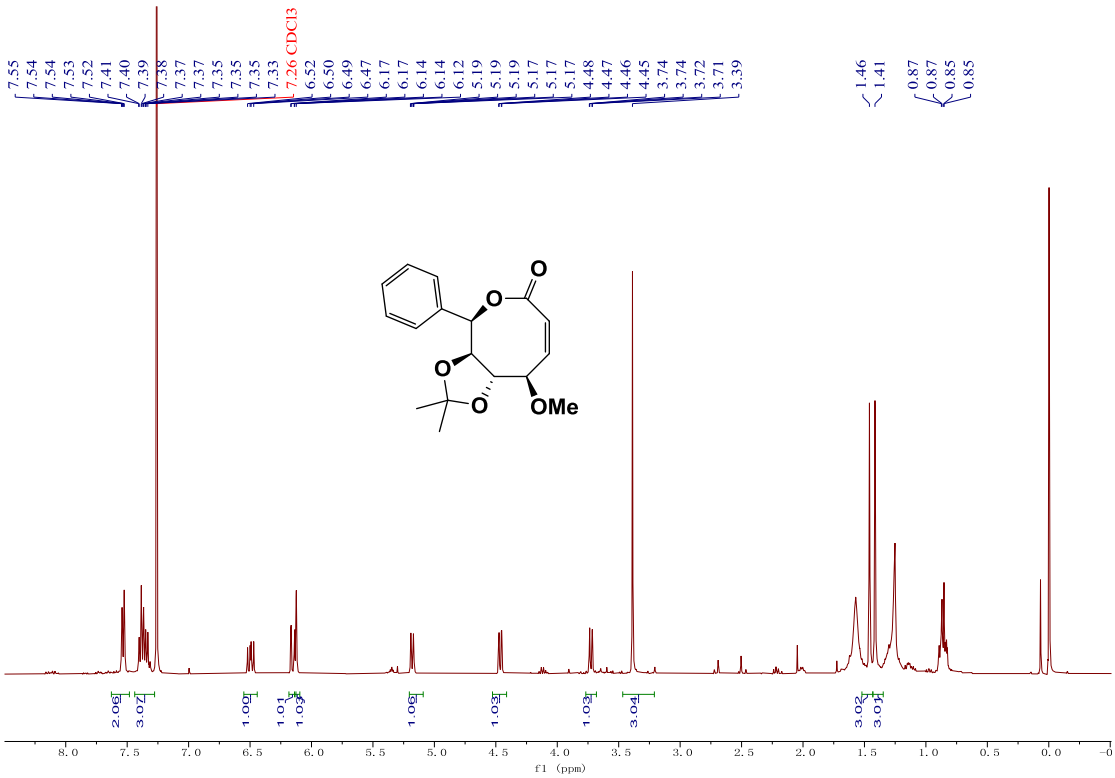


Figure 25. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **3**

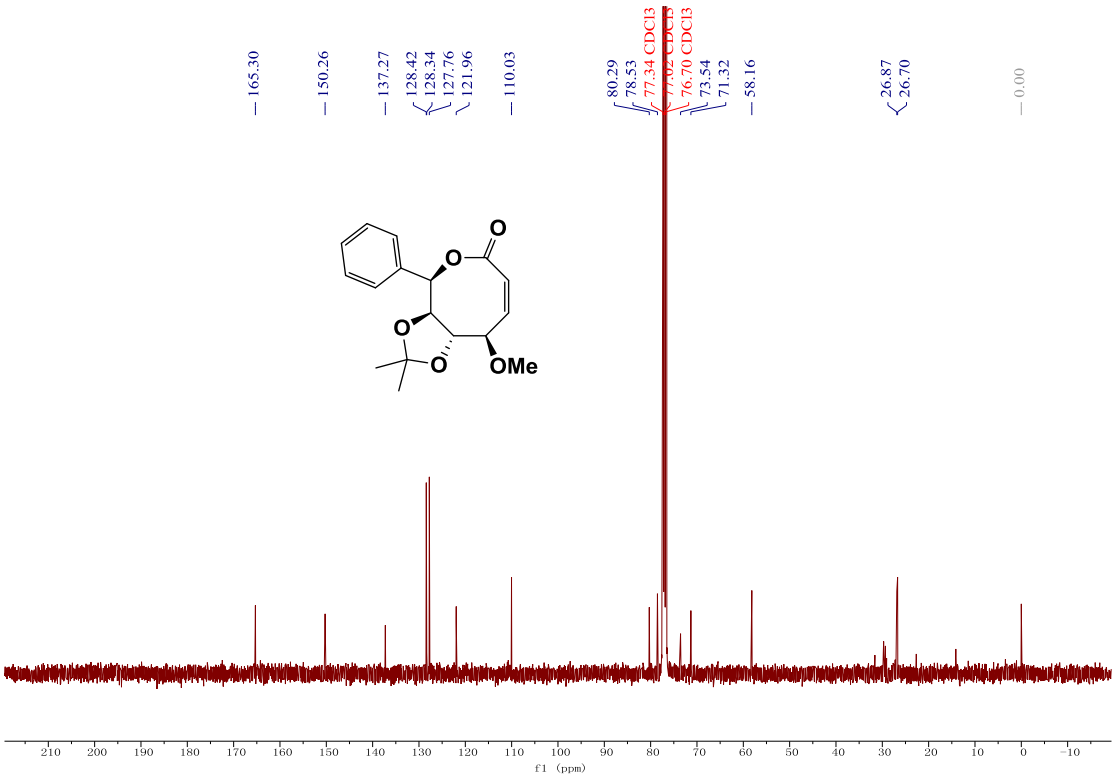


Figure 26. ^{13}C NMR (100 MHz, $CDCl_3$) spectrum of compound **3**

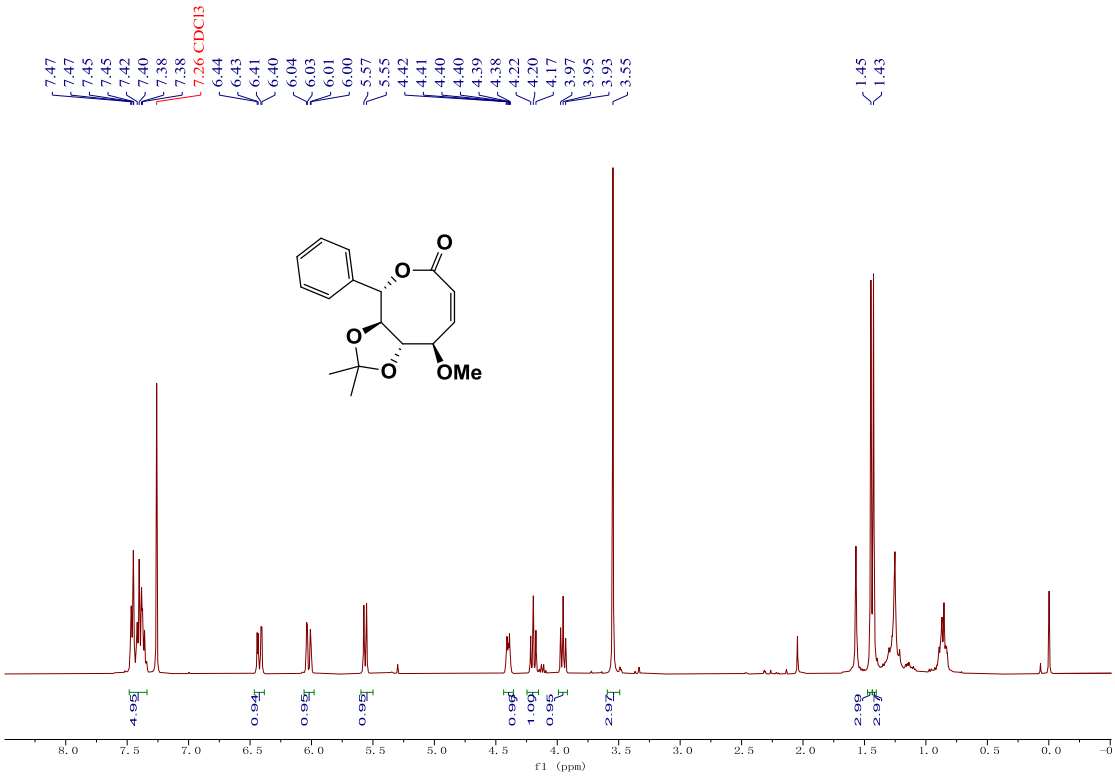


Figure 27. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **3a**

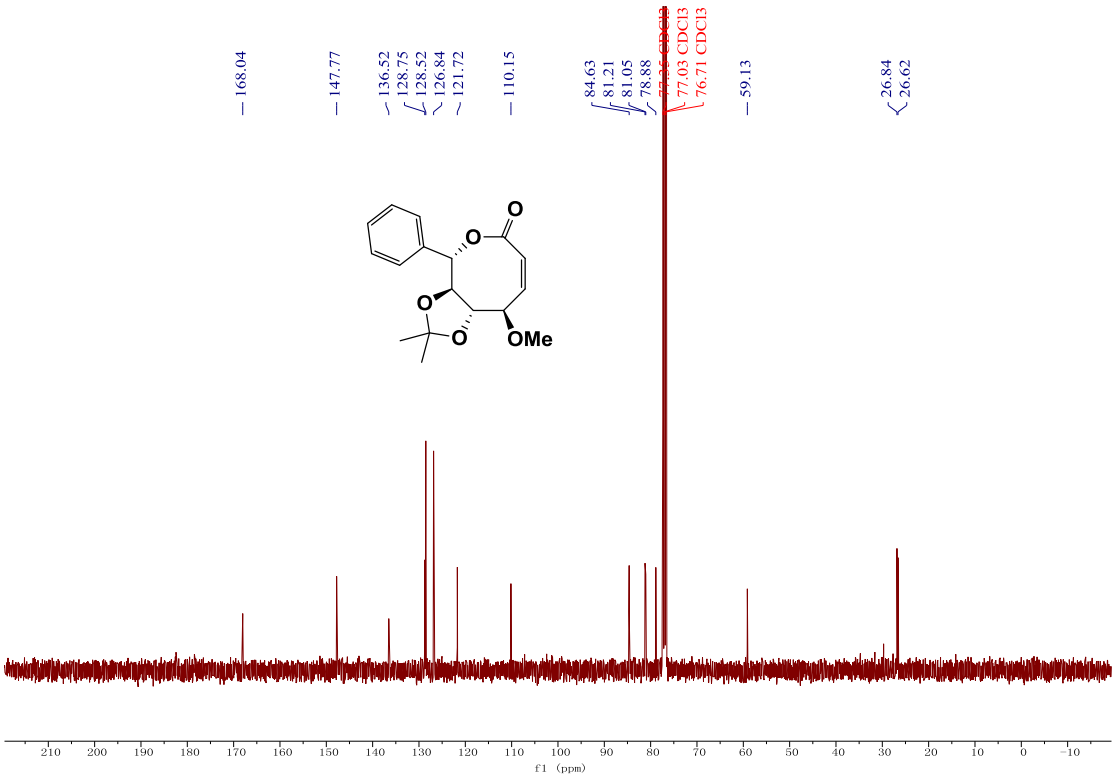


Figure 28. ^{13}C NMR (100 MHz, $CDCl_3$) spectrum of compound **3a**

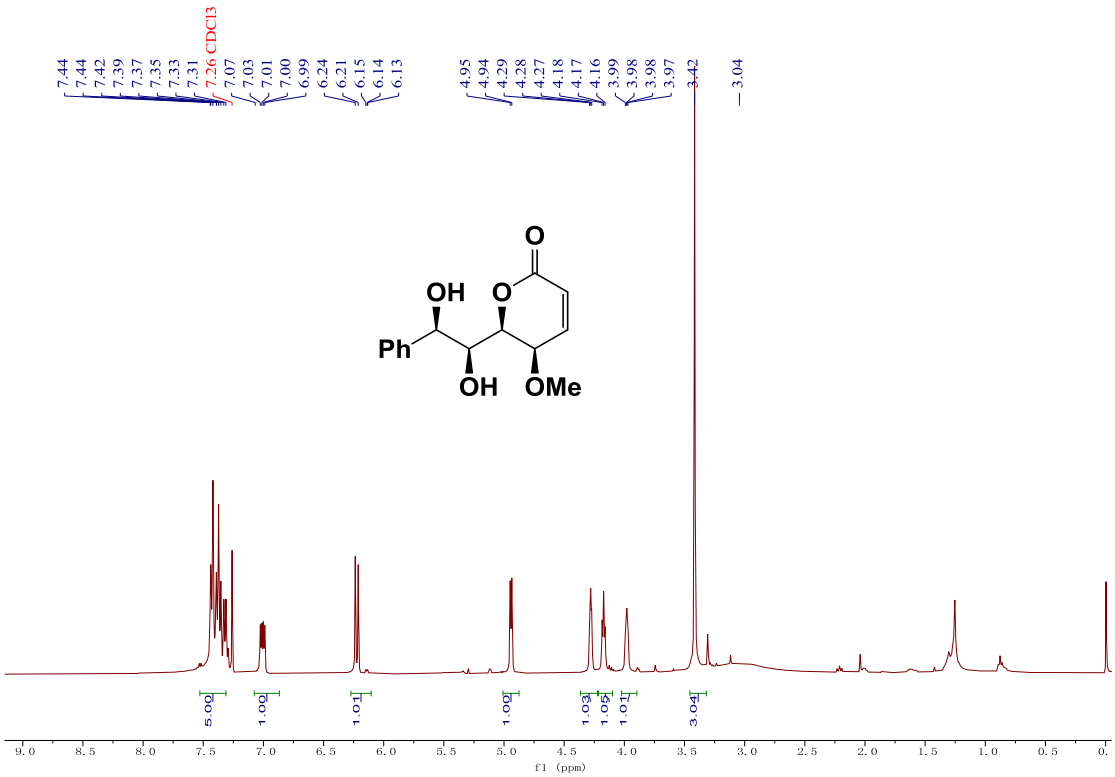


Figure 29. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **13**

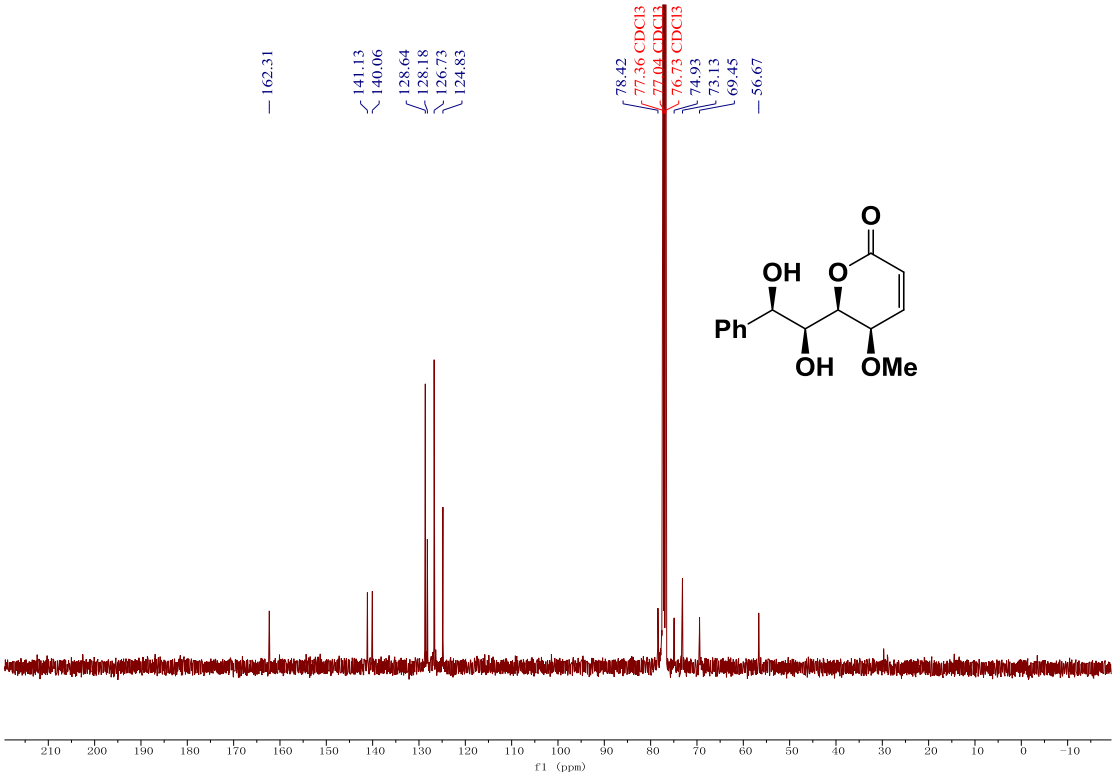


Figure 30. ^{13}C NMR (100 MHz, $CDCl_3$) spectrum of compound **13**

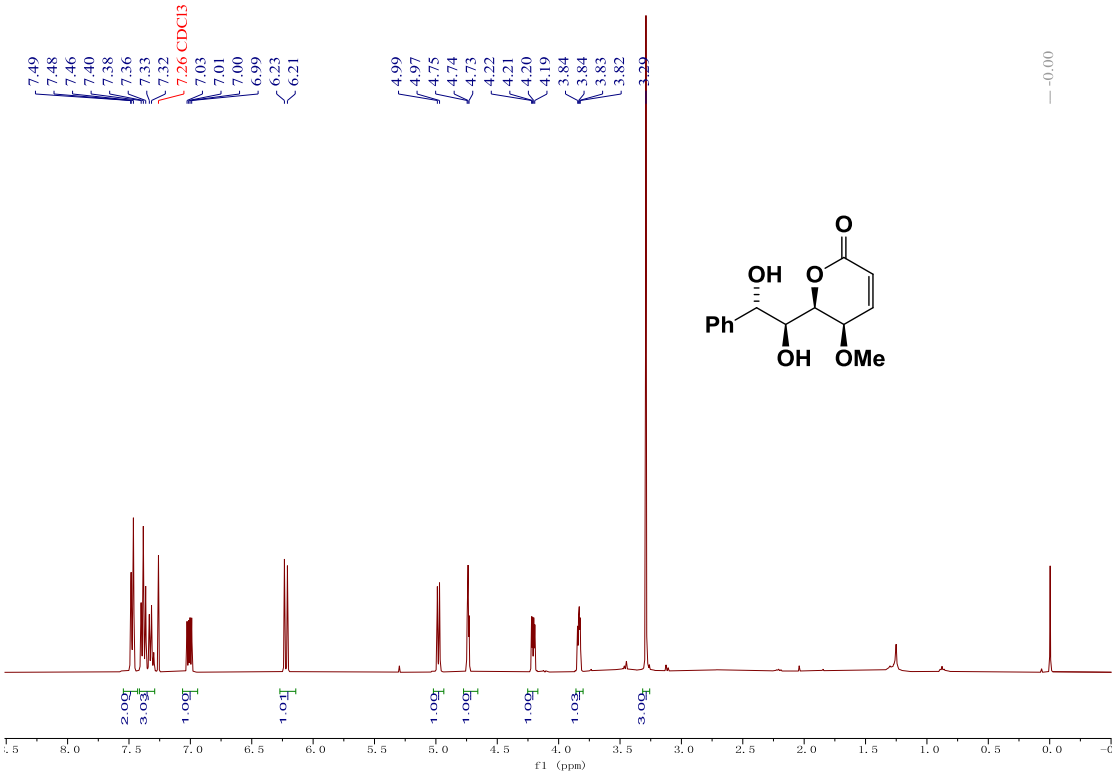


Figure 31. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **13a**

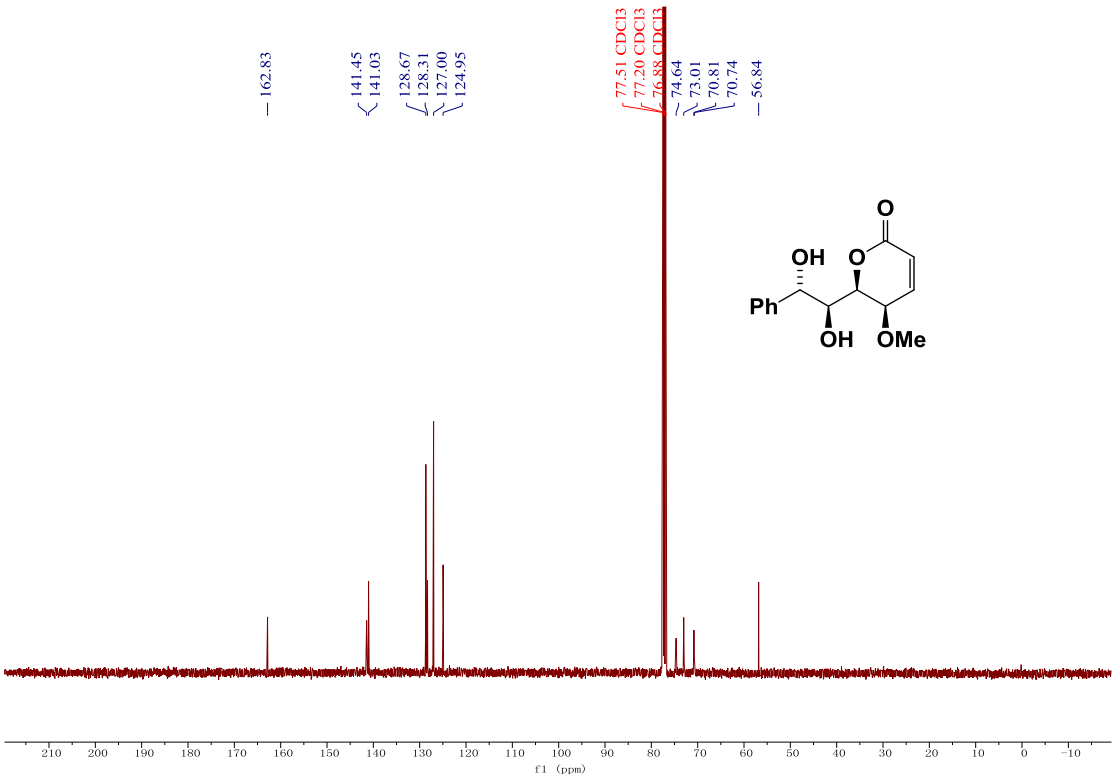


Figure 32. ^{13}C NMR (100 MHz, $CDCl_3$) spectrum of compound **13a**

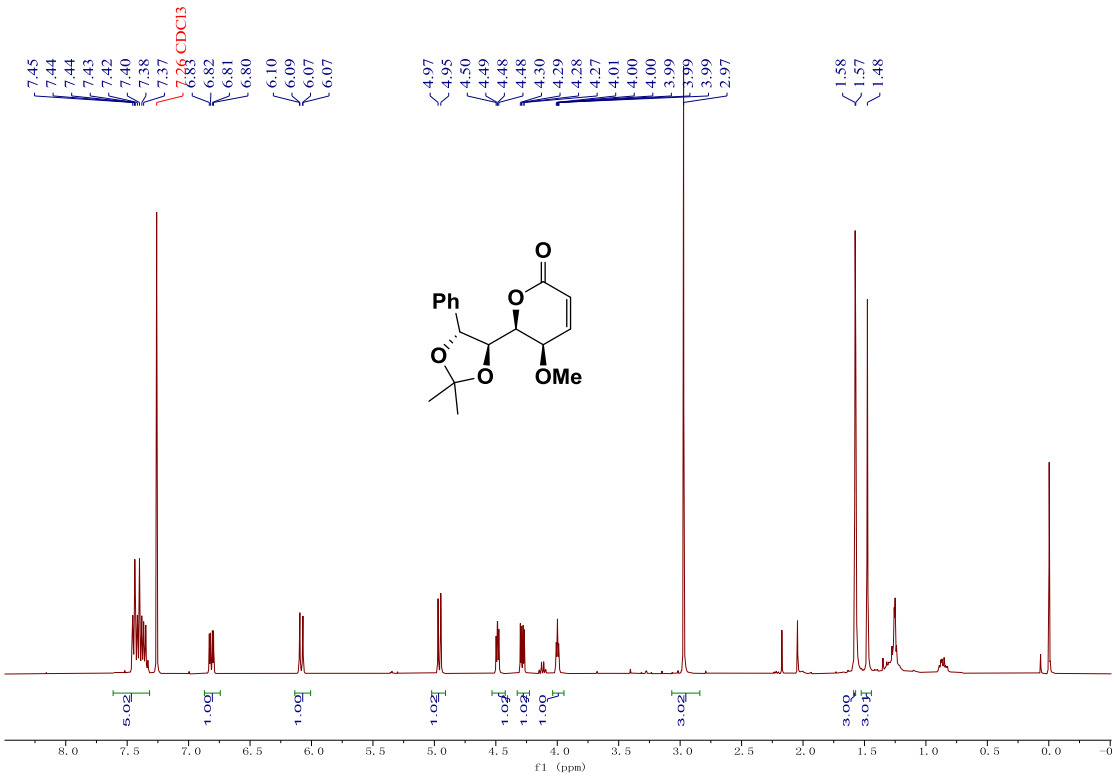


Figure 33. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **14**

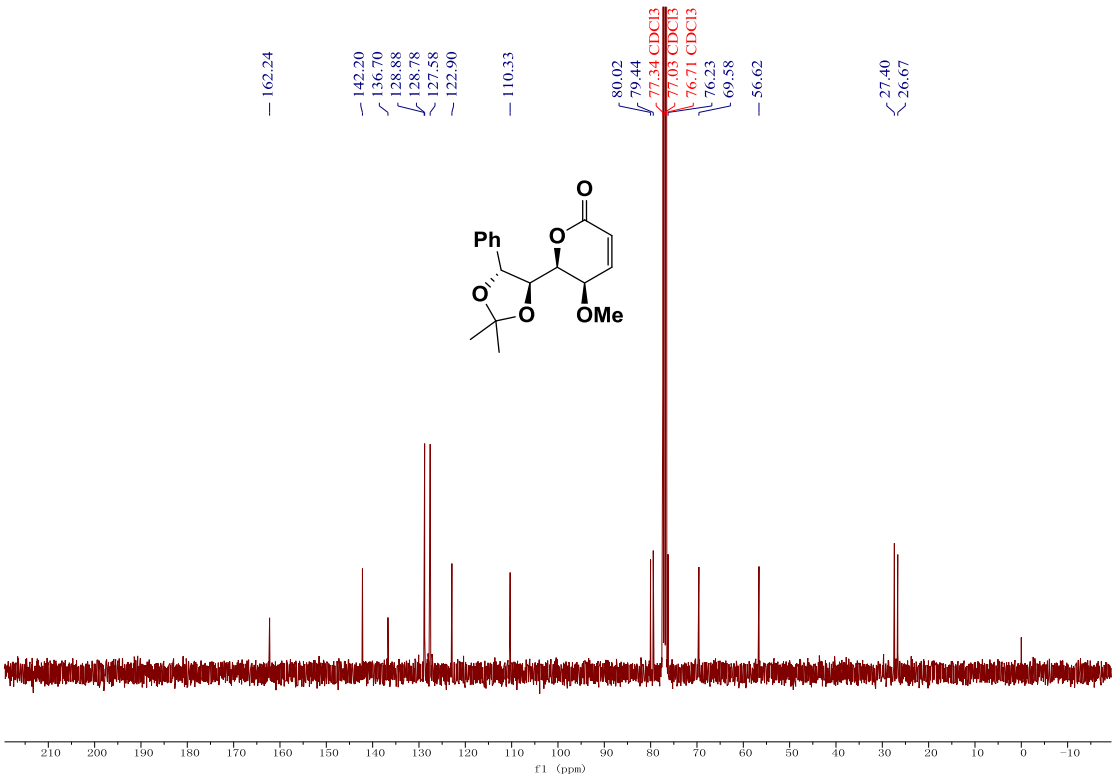


Figure 34. ^{13}C NMR (100 MHz, $CDCl_3$) spectrum of compound **14**

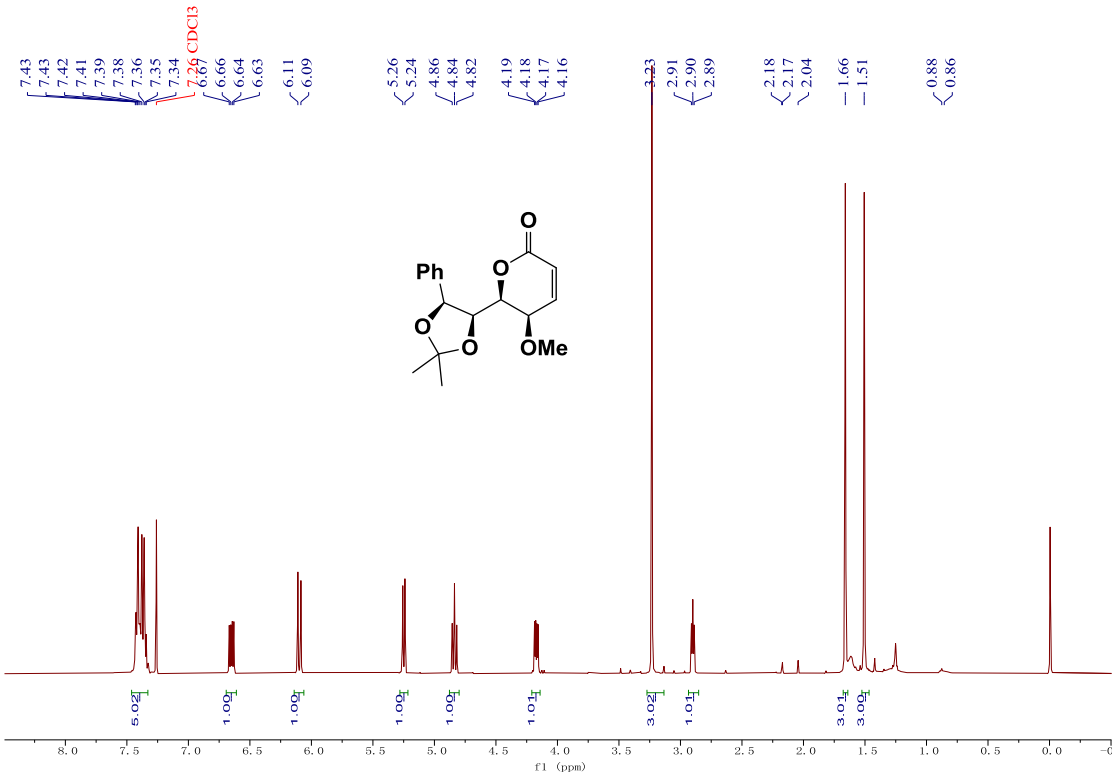


Figure 35. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **14a**

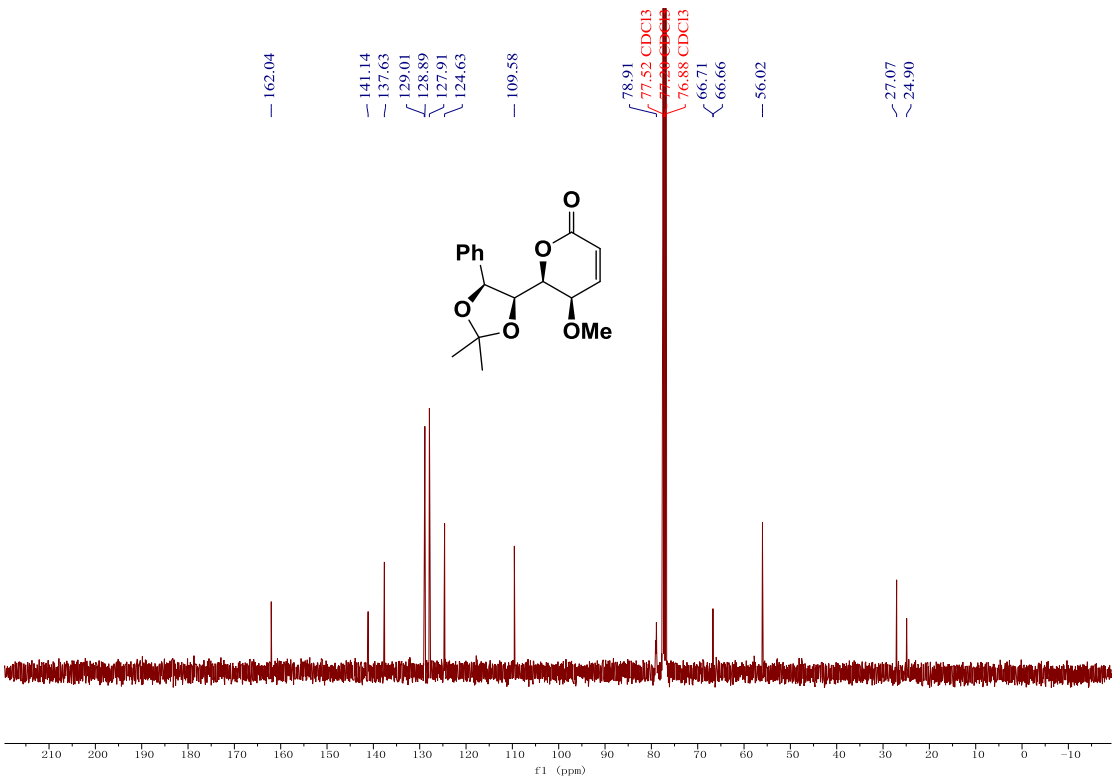


Figure 36. ^{13}C NMR (100 MHz, $CDCl_3$) spectrum of compound **14a**

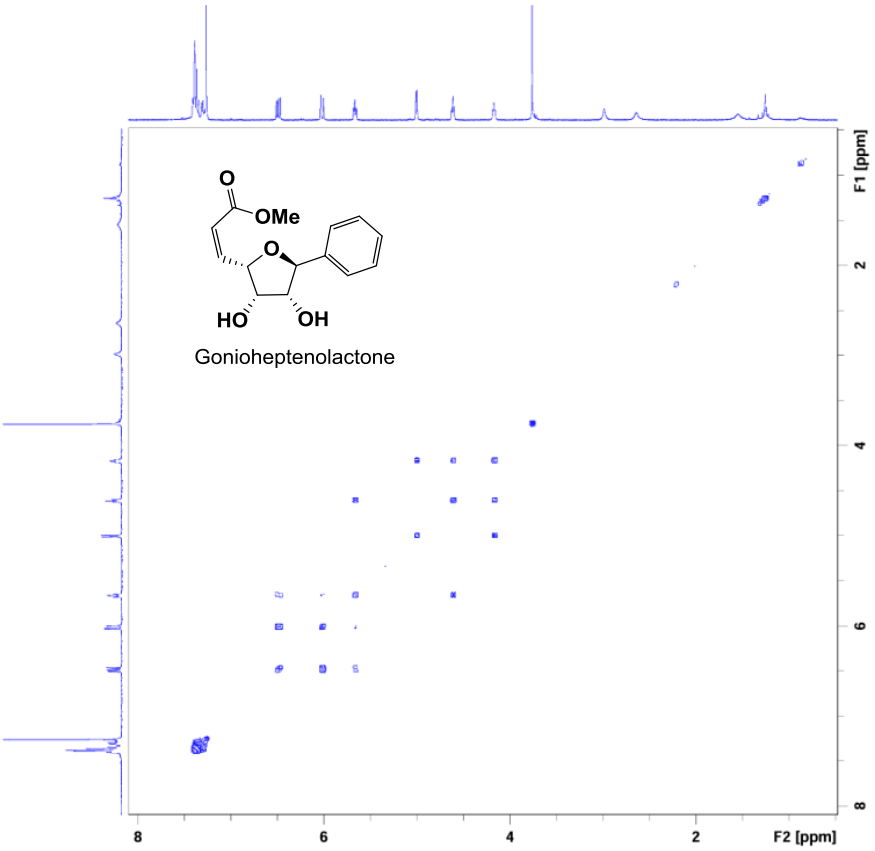


Figure 37. ^{1}H-^{1}H COSY (400 MHz, $CDCl_3$) spectrum of compound **2**

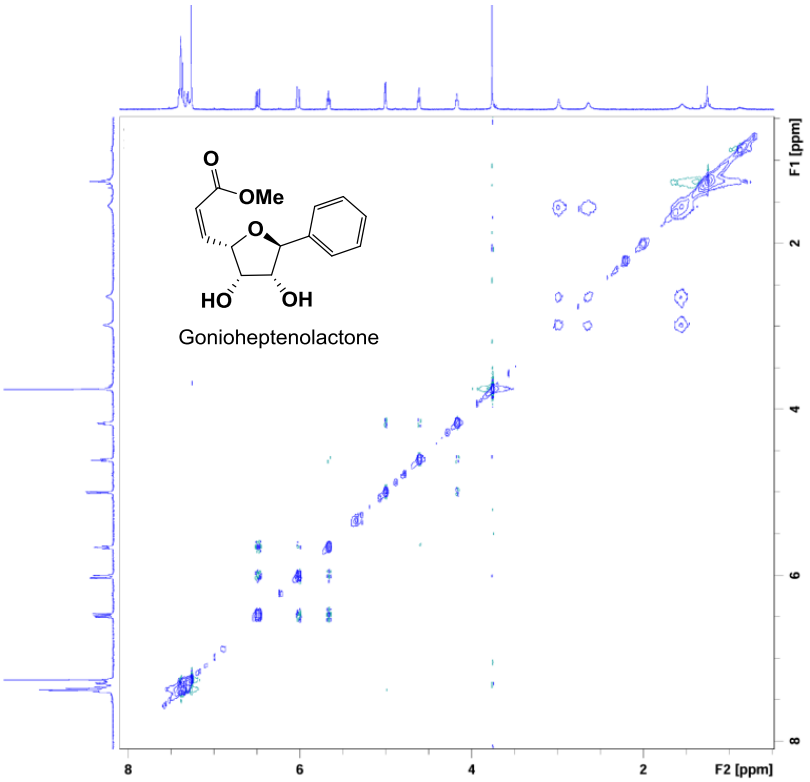


Figure 38. NOESY (400 MHz, $CDCl_3$) spectrum of compound **2**