Electronic Supplementary Material (ESI) for Organic & Biomolecular Chemistry.

Supporting Information

A divergent strategy to gabosines featuring a switchable two-way aldol cyclization

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Experimental Section

General: Flash chromatography was performed using silica gel (200–300 mesh). Reactions were monitored by thin layer chromatography (TLC). Visualization was achieved under a UV lamp (254 nm), IR spectra were recorded on a commercial spectrophotometer. Optical rotations were reported as follows: $[\alpha]_D^T$ (*c* g/100 mL, in solvent). ^1H and ^{13}C NMR were recorded on commercial instruments (400 MHz) with TMS as the internal standard and were calibrated using residual undertreated solvent as an internal reference ($CDCl_3$: ^1H NMR = 7.26, ^{13}C NMR = 77.16; CD_3OD: ^1H NMR = 3.31, ^{13}C NMR = 49.00; C_2D_6SO: ^1H NMR = 2.50, ^{13}C NMR = 39.96). Coupling constants (*J*) are reported in Hertz (Hz). HRMS spectra were recorded by using a commercial apparatus and methanol or dichloromethane were used to dissolve the sample.

All air sensitive manipulations were carried out under dry argon. Solvents for reaction were distilled prior to use: dichloromethane (DCM), $PhCH_3$ and MeCN from CaH_2, tetrahydrofuran (THF) from Na. Methanol was distilled from magnesium, acetone from Potassium carbonate, and other reagents were obtained from commercial suppliers unless otherwise stated. Drying of organic extracts during the work-up of reactions was performed over anhydrous Na_2SO_4.

(1R)-1-((*tert*-butyldimethylsilyl)oxy)-1-((4S,4'R)-2,2,2',2'-tetramethyl-[4,4'-bi(1,3-dioxolan)]-5-yl)propan-2-one (6):

To a solution of compound **5** (290 mg, 0.72 mmol) and MeNHOMe·HCl (88 mg, 0.90 mmol) in THF (7 mL) at –5 °C was added dropwise MeMgBr (3M in THF, 1.44 mL, 4.30 mmol). The mixture was stirred at –5 °C for 90 min, and then allowed to warm slowly to room temperature in the low-temperature reactor. The reaction was stirred for 10 h at room temperature before saturated aqueous NH_4Cl (1.5 mL) and EtOAc (5 mL) were slowly added. The phases were separated and the aqueous phase was extracted with EtOAc (3×15 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (petroleum ether/EtOAc,16:1) to give ketone **6** (274 mg, 90%)as a colorless crystal solid. m.p.51–52℃; $[\alpha]_D^{18}$ +73.5 (*c* 1.62, $CHCl_3$); IR (neat) ν_{max}: 2931, 1719, 1375, 1254, 1149, 1074, 846cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.17 – 4.12 (m, 2H), 4.09 (d, *J* = 2.4 Hz, 1H), 4.04 – 3.92 (m, 2H), 3.78 (dd, *J* = 8.4, 6.8 Hz, 1H), 2.22 (s, 3H), 1.40 (s, 3H), 1.37 (s, 3H), 1.32 (s, 6H), 0.94 (s, 9H), 0.08 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.8,110.4, 109.7, 82.4, 78.6, 77.4, 76.7, 68.3, 27.5, 27.1, 26.8, 26.4, 25.8, 25.2, 18.2, –4.7,–4.9; HRMS (ESI - TOF) m/z[M + Na]$^+$calcdfor $C_{19}H_{36}NaO_6Si$: 411.2179; Found: 411.2178.

(1R)-1-((*tert*-butyldimethylsilyl)oxy)-1-((5S)-5-((R)-1,2-dihydroxyethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)propan-2-one (7):

$CuCl_2·2H_2O$ (369 mg, 2.17 mmol) was added the solution of compound **6** (840 mg, 2.17 mmol) in CH_3CN (4 mL) at 0 °C. The violently stirred mixture was kept at same temperature for 45min. The reaction was quenched with saturated aqueous $NaHCO_3$ (1 mL).The mixture was filtered and the filtrate was extracted with EtOAc (3 × 10 mL). Then the organic phase was dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by silica gel column chromatography (petroleum ether/EtOAc,8:1) to yield diol **7** (301 mg, 91%) as a white solid. m.p. 51–52℃; $[\alpha]_D^{19}$ +36.7 (*c*1.31, $CHCl_3$); IR (neat) ν_{max}: 3448, 2933, 2860, 1713, 1467, 1374, 1254, 1139, 1079, 930, 842, 779 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.23 (d, *J* = 2.4 Hz, 1H), 4.16 (dd, *J* = 7.6, 2.8 Hz, 1H), 3.95 (t, *J* = 7.4 Hz, 1H), 3.81 (d, *J* = 10.8 Hz, 1H), 3.70 (dt, *J* = 12.8, 3.6 Hz, 1H), 3.61 (m, 1H), 3.36 (s, 1H),2.77 (s, 1H), 2.22 (s, 3H), 1.39 (s, 3H), 1.33 (s, 3H), 0.93 (s, 9H), 0.07 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.3, 110.0, 81.7, 78.3, 76.2, 73.3, 64.3,

27.6, 27.3, 26.8, 25.9, 18.3, –4.8, –5.0; HRMS (ESI - TOF) m/z [M + Na]$^+$calcd for $C_{16}H_{32}NaO_6Si$: 371.1866; Found: 371.1867.

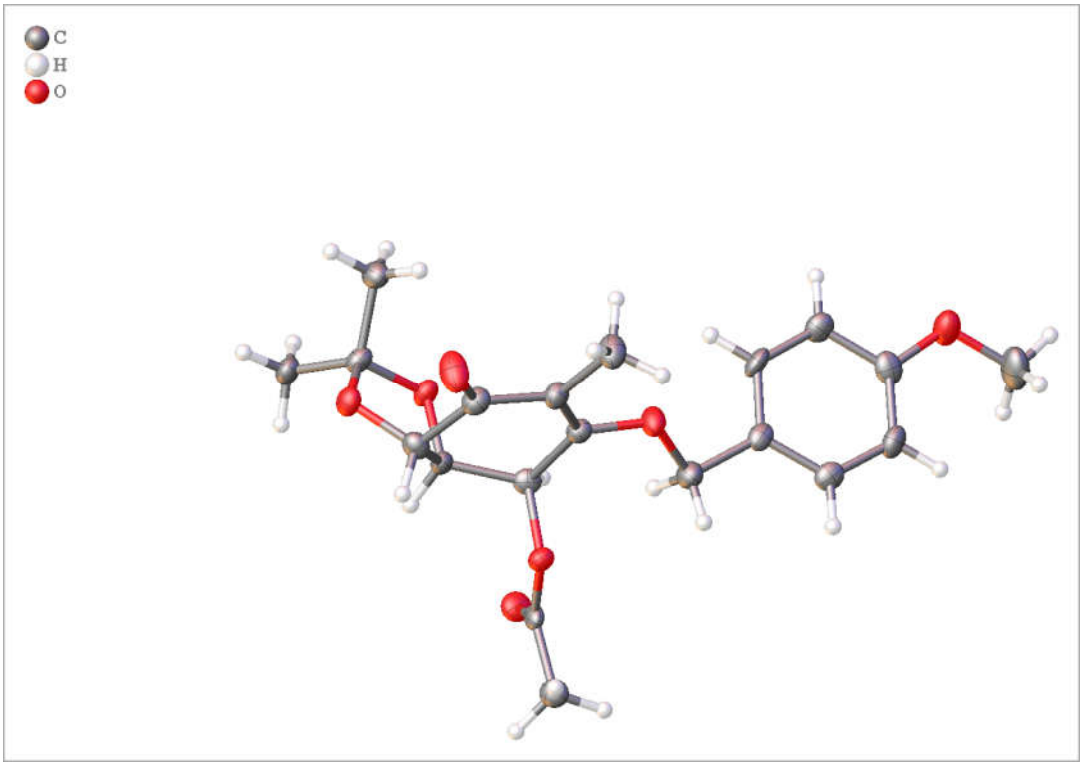
(1R)-1-((*tert*-butyldimethylsilyl)oxy)-1-((5S)-5-((R)-1-hydroxy-2-((4-methoxybenzyl)oxy)ethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)propan-2-one (8):

To a solution of compound **7**(235 mg, 0.68 mmol) in DCM (6 mL) was added PPTS (17 mg, 0.068 mmol) and PMBTCA (4-methoxybenzyl 2,2,2-trichloroethanimidoate) (210 mg, 0.74 mmol). The mixture was stirred at room temperature for 2 h, and then evaporated under reduced pressure and purified by flash column chromatography (petroleum ether/EtOAc, 8:1) on silica gel to afford the desired product **8** (294 mg, 93%) as a slight yellow oil. $[\alpha]_D^{19}$ +43.0 (*c*0.54, $CHCl_3$); IR (neat) ν_{max}: 3447, 2932, 2859, 1714, 1613, 1514, 1465, 1372, 1302, 1250, 1137, 1077, 929, 881, 840, 779, 678, 565, 512 cm^{-1};^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 – 7.22 (m, 2H), 6.90 – 6.82 (m, 2H), 4.53 – 4.46 (m, 2H), 4.22 (dd, *J* = 7.2, 2.4 Hz, 1H), 4.16 (d, *J* = 2.8Hz, 1H), 4.01 (t, *J* = 7.8 Hz, 1H), 3.80 (s, 3H), 3.79 – 3.74 (m, 1H), 3.70 (dd, *J* = 9.6, 3.2 Hz, 1H), 3.51 (dd, *J* = 9.6, 6.0Hz, 1H), 2.51 (d, *J* = 4.4 Hz, 1H), 2.21 (s, 3H), 1.40 (s, 3H), 1.32 (s,3H), 0.94 (s, 9H), 0.05 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.9, 159.5, 130.0, 129.6, 114.0, 110.1, 81.9, 78.7, 75.5, 73.3, 72.6, 71.6, 55.4, 27.4, 27.3, 26.9, 25.9, 18.3, -4.7, -4.5; HRMS (ESI - TOF) m/z [M + Na]$^+$calcd for $C_{24}H_{40}NaO_7Si$: 491.2441; Found: 491.2439.

(1R)-1-((*tert*-butyldimethylsilyl)oxy)-1-((5S)-5-((R)-1-hydroxy-2-((4-methoxybenzyl)oxy)ethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)propan-2-one (2):

To stirred solution of $(COCl)_2$ (106 µL, 1.21 mmol) in DCM (10 mL) was added DMSO (171 µL, 2.42 mmol) in DCM (0.20 mL) at -78 ^{o}C under argon. After 40 min, a solution of **8** (378 mg, 0.81 mmol) in DCM (2 mL) was added dropwise slowly to the reaction mixture at -78 ^{o}C under argon. After 60 min, Et_3N (675 µL, 4.84 mmol) was added dropwise to the above mixture. Then the mixture was allowed to warm slowly to room temperature by removing low-temperature reactor. The reaction mixture was poured into appropriate saturated aqueous $NaHCO_3$ solution, extracted with DCM (3 × 15 mL), dried over anhydrous Na_2SO_4.The evaporated residue was purified by silica gel column chromatography (petroleum ether/EtOAc, 8:1) to givediketone**2** (365 mg, 97%) as a slight yellow oil.$[\alpha]_D^{19}$ +80.0 (*c*0.17, $CHCl_3$); IR (neat) ν_{max}: 2932, 2858, 1732, 1613, 1514, 1465, 1379, 1302, 1251, 1138, 1093, 1037, 839, 780, 576 cm^{-1};^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 – 7.26 (m, 2H), 6.90 – 6.84 (m, 2H), 4.52 (s, 2H), 4.49 – 4.33 (m, 3H), 4.25 (dd, *J* = 7.6, 3.2 Hz, 1H), 4.13 (d, *J* = 3.2 Hz, 1H), 3.79 (s, 3H), 2.21 (s, 3H), 1.42 (s, 3H), 1.31 (s, 3H), 0.93 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.2, 206.2, 159.6, 129.9, 129.1, 114.0, 111.6, 79.8, 79.3, 78.2, 73.1, 72.4, 55.4, 27.2, 26.6, 25.8, 18.2, –4.8, –5.1; HRMS (ESI - TOF) m/z [M + Na]$^+$calcd for $C_{24}H_{38}NaO_7Si$: 489.2284; Found: 489.2280.

X-Ray Crystallographic Data for compound 11



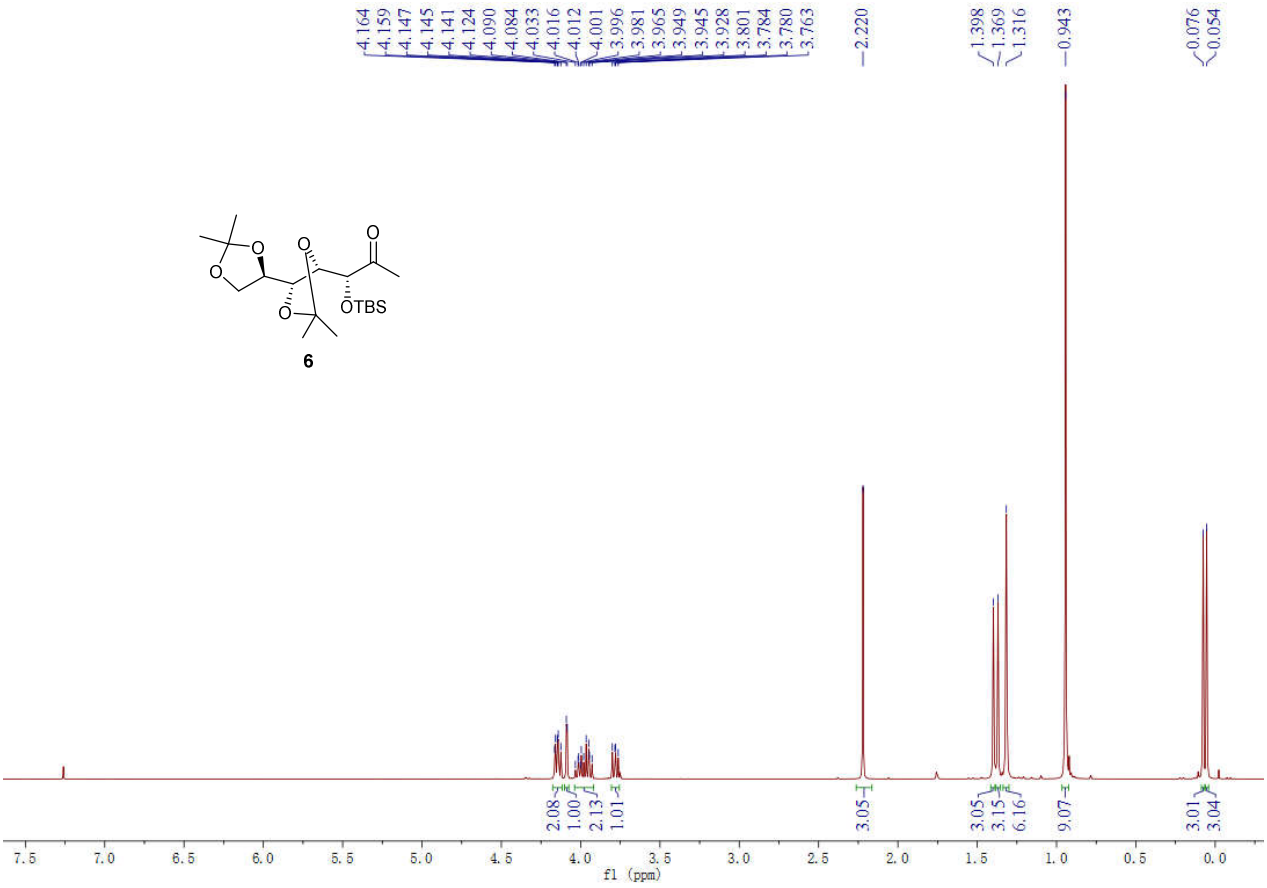
Structure deposited at the Cambridge Crystallographic Data Centre (CCDC 1540899)

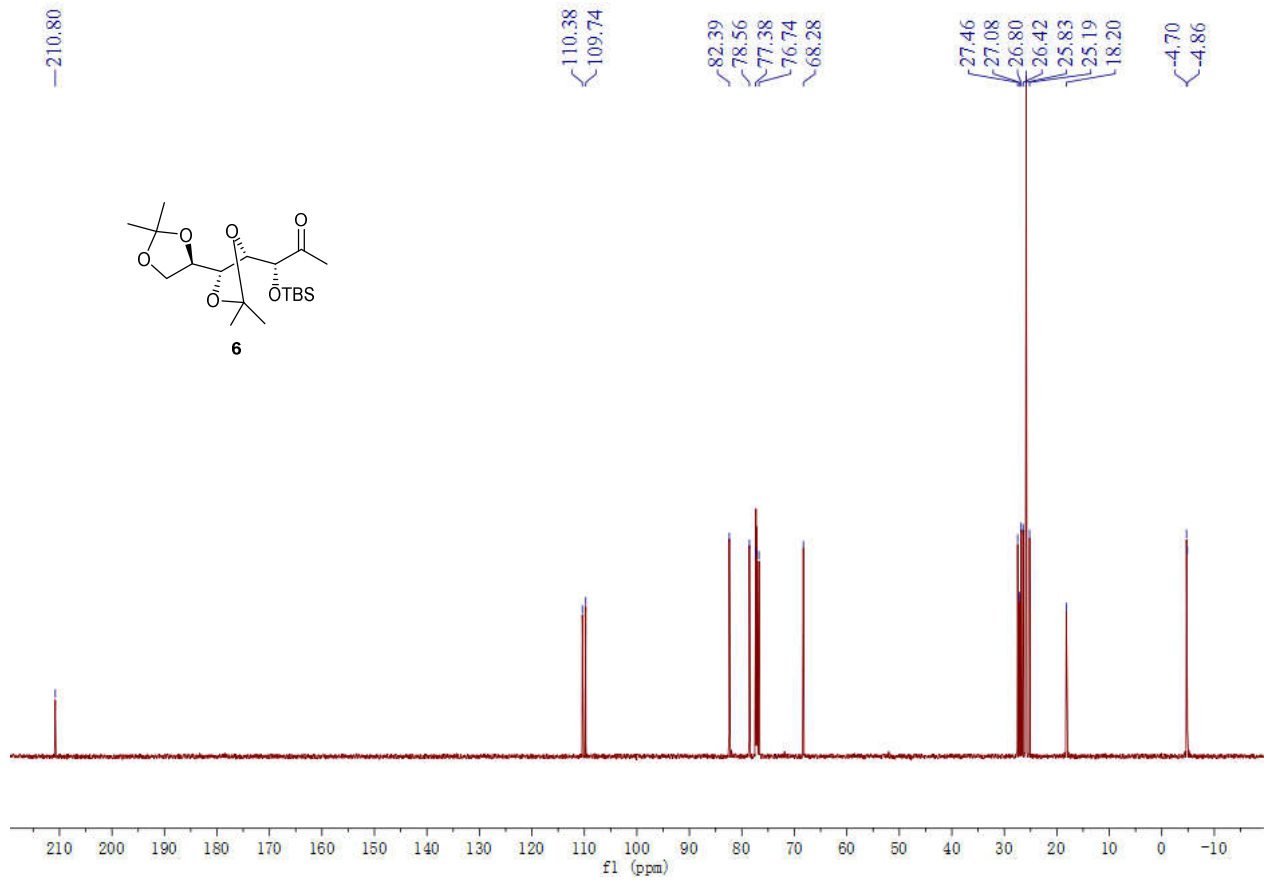
Crystal data and structure refinement for CCDC 1540899.

Empirical formula	$C_{20}H_{24}O_7$
Formula weight	376.39
Temperature/K	297.71(10)
Crystal system	tetragonal
Space group	$P4_12_12$
a/Å	8.84318(16)
b/Å	8.84318(16)
c/Å	47.4590(11)
α/°	90
β/°	90
γ/°	90
Volume/Å^3	3711.37(16)
Z	8
ρ_{calc}g/cm^3	1.347
μ/mm^{-1}	0.850
F(000)	1600.0
Crystal size/mm^3	0.8 × 0.8 × 0.35
Radiation	CuKα (λ = 1.54184)
2Θ range for data collection/°	10.176 to 134.046
Index ranges	-6 ≤ h ≤ 9, -10 ≤ k ≤ 10, -43 ≤ l ≤ 56

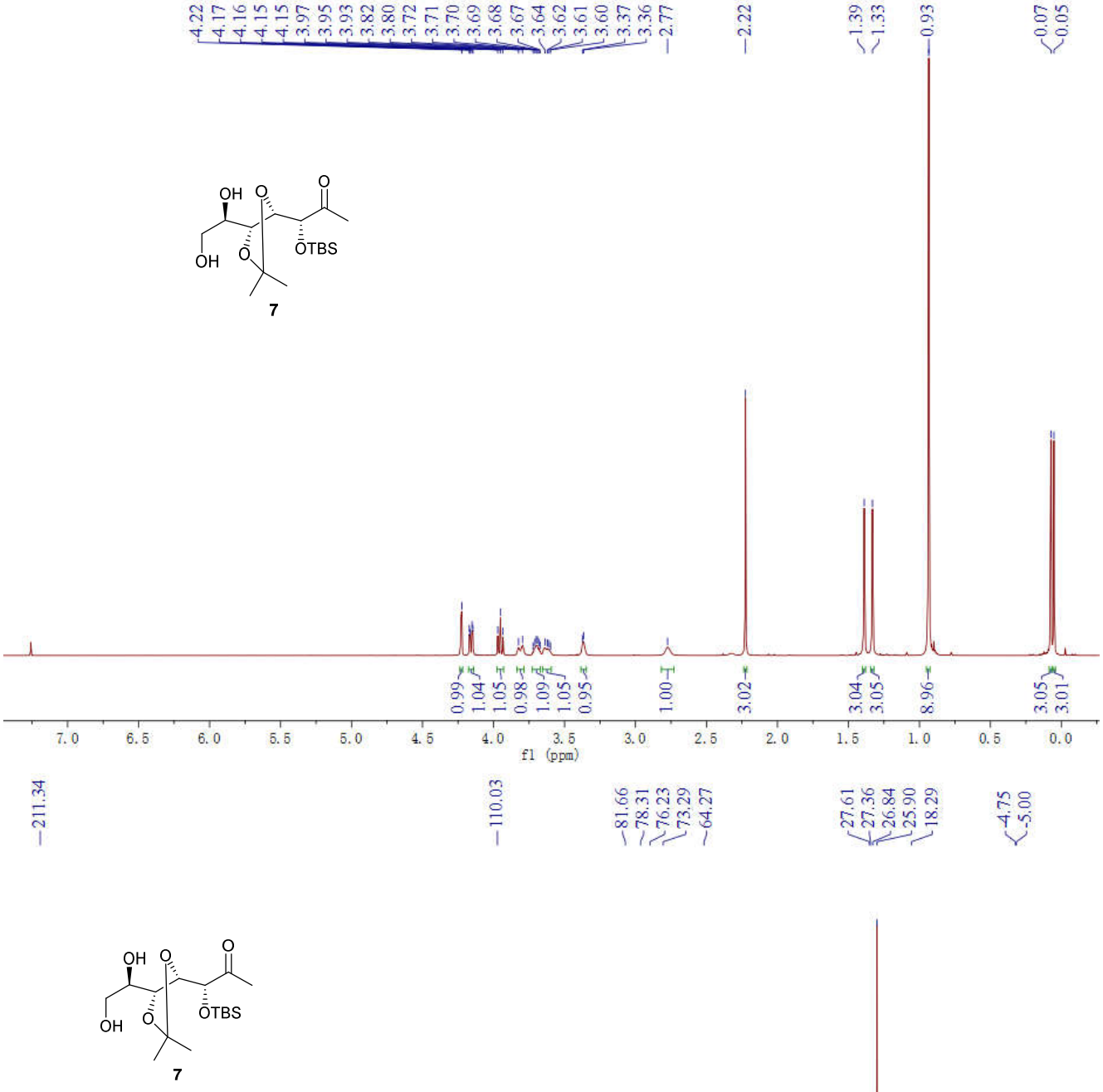
Reflections collected	14623
Independent reflections	3307 [R_{int} = 0.0422, R_{sigma} = 0.0361]
Data/restraints/parameters	3307/0/249
Goodness-of-fit on F^2	1.115
Final R indexes [I>=2σ (I)]	R_1 = 0.0745, wR_2 = 0.1895
Final R indexes [all data]	R_1 = 0.0780, wR_2 = 0.1909
Largest diff. peak/hole / e $Å^{-3}$	0.35/-0.49
Flack parameter	0.17(12)

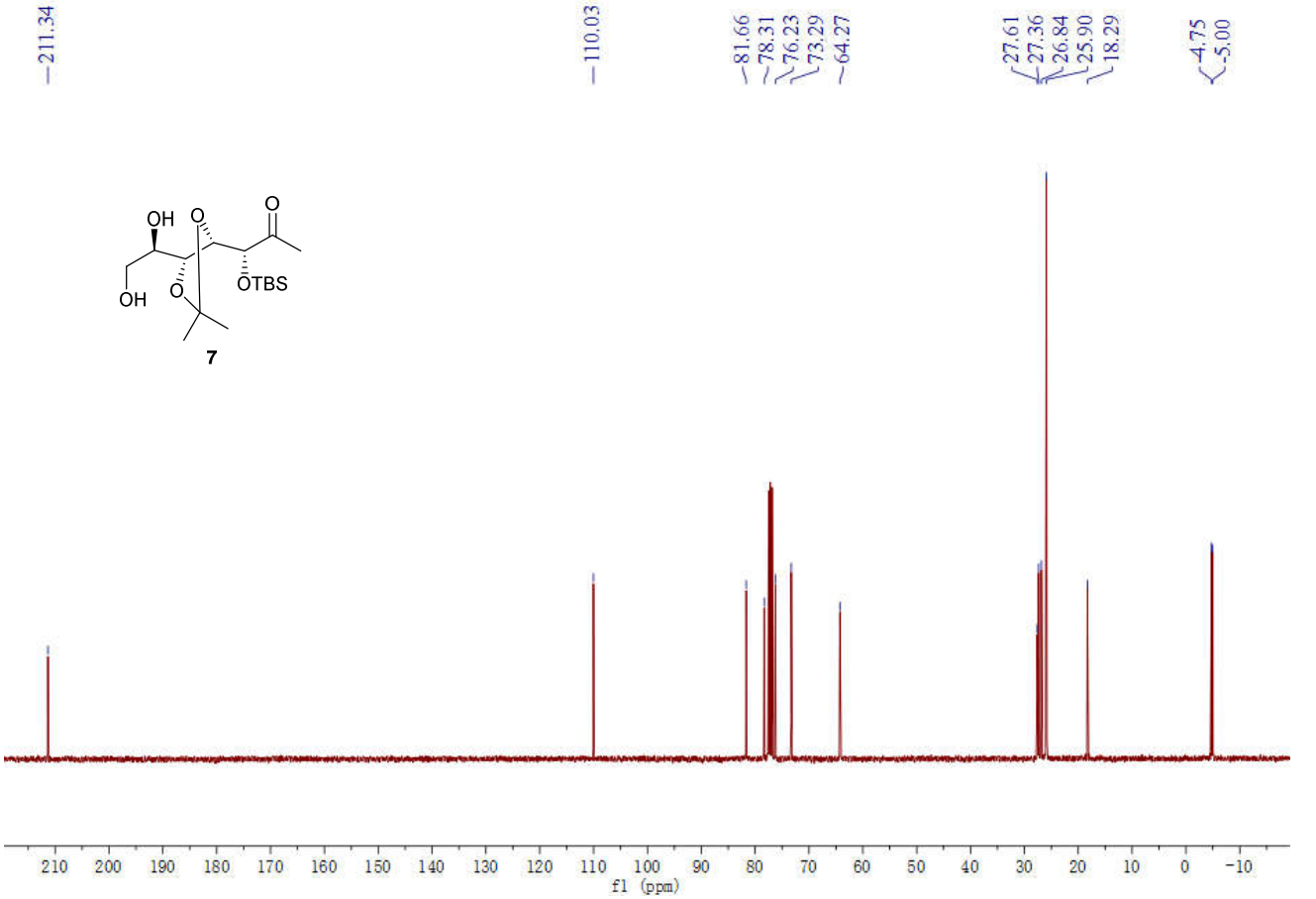
^{1}H NMR (400 MHz, $CDCl_3$/TMS) and ^{13}C NMR (100 MHz, $CDCl_3$) of compound **6**



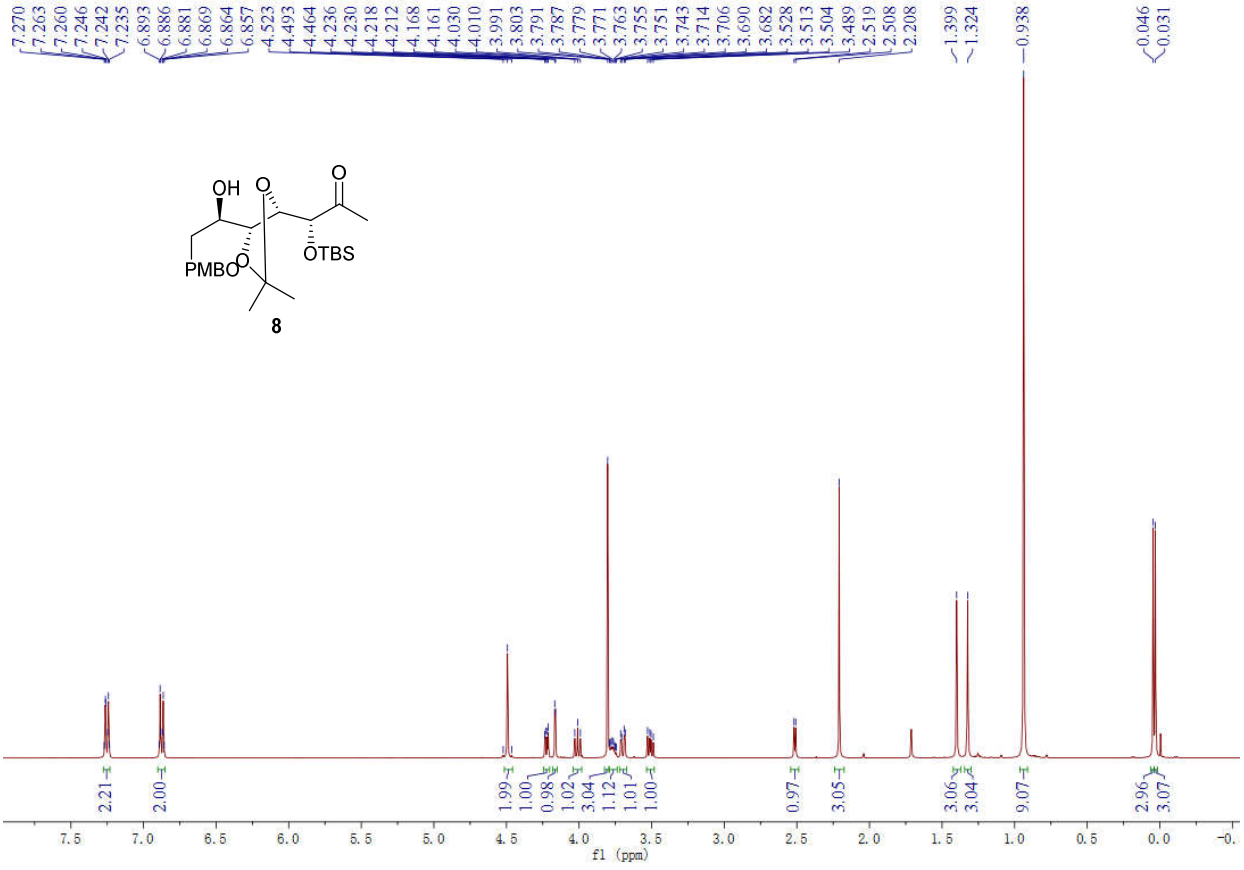


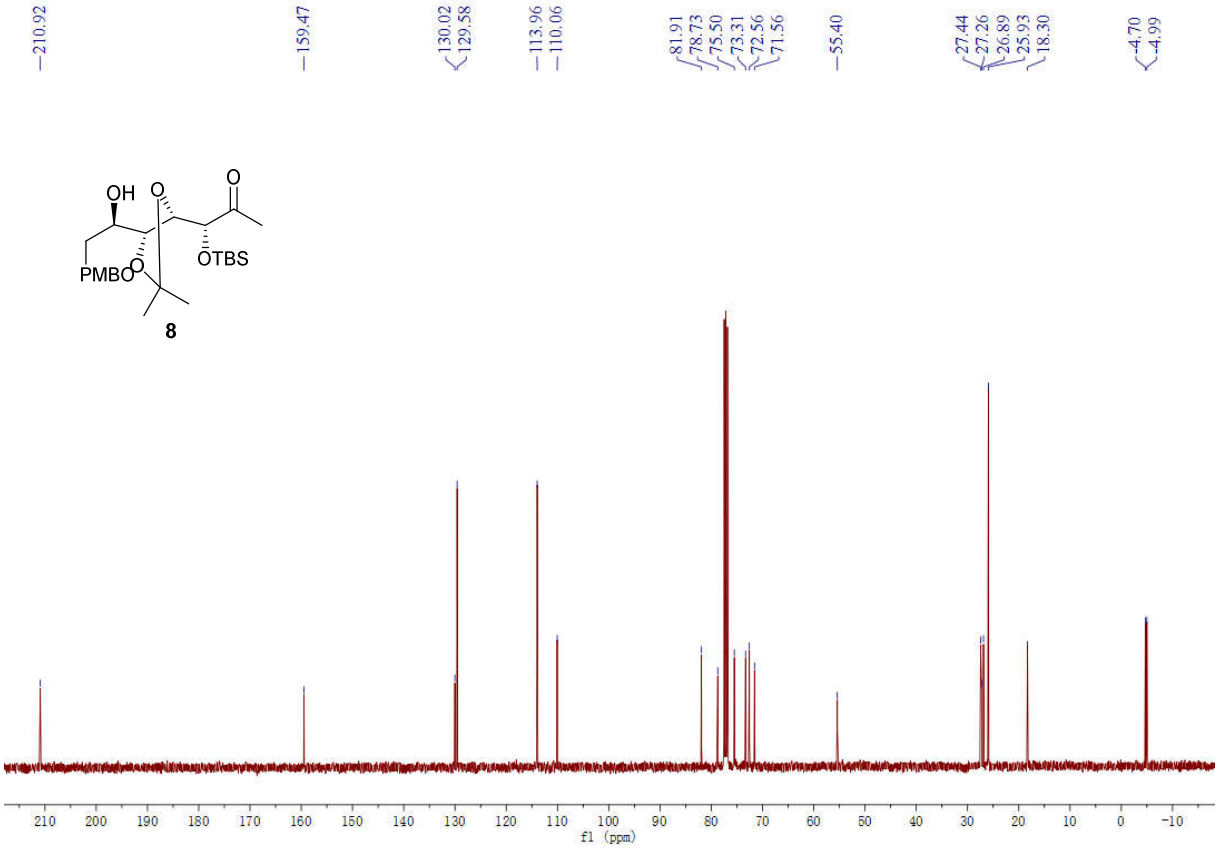
^{1}H NMR (400 MHz, $CDCl_3$/TMS) and ^{13}C NMR (100 MHz, $CDCl_3$) of compound **7**



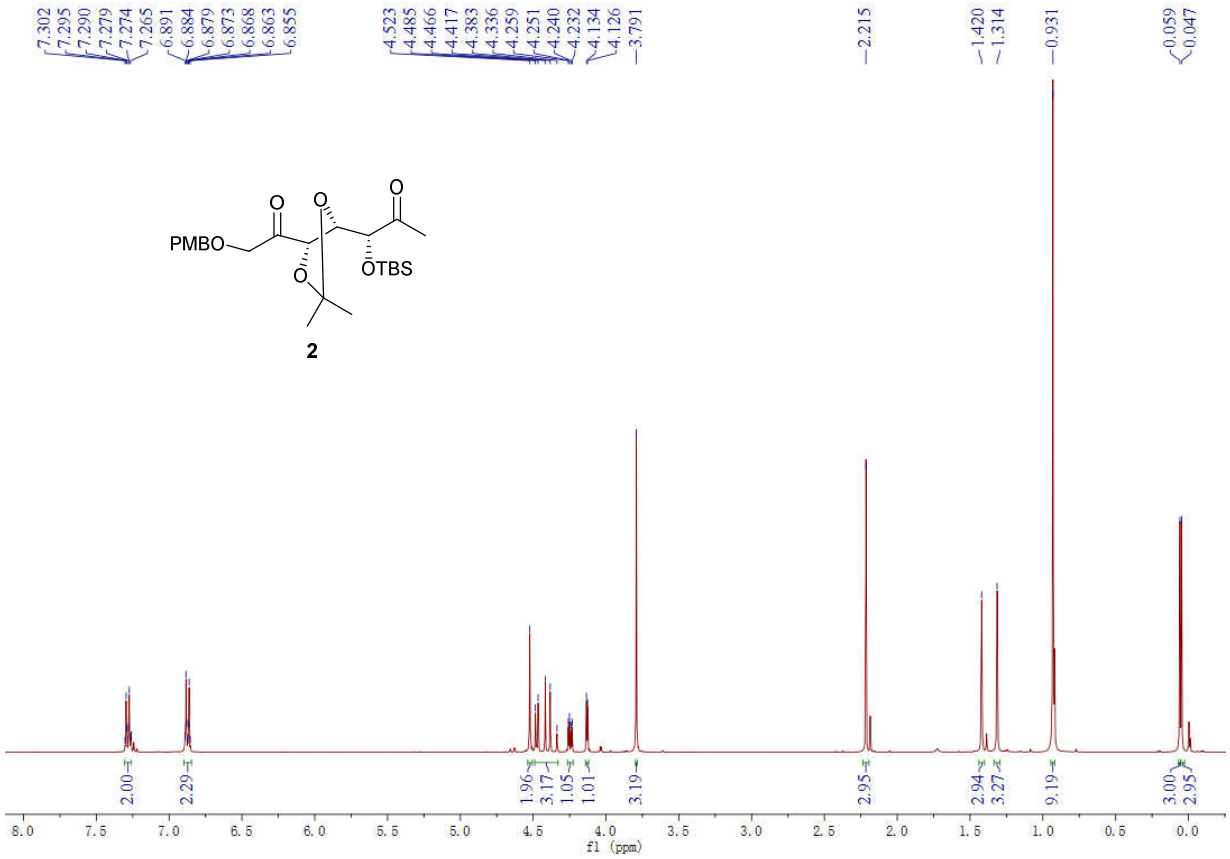


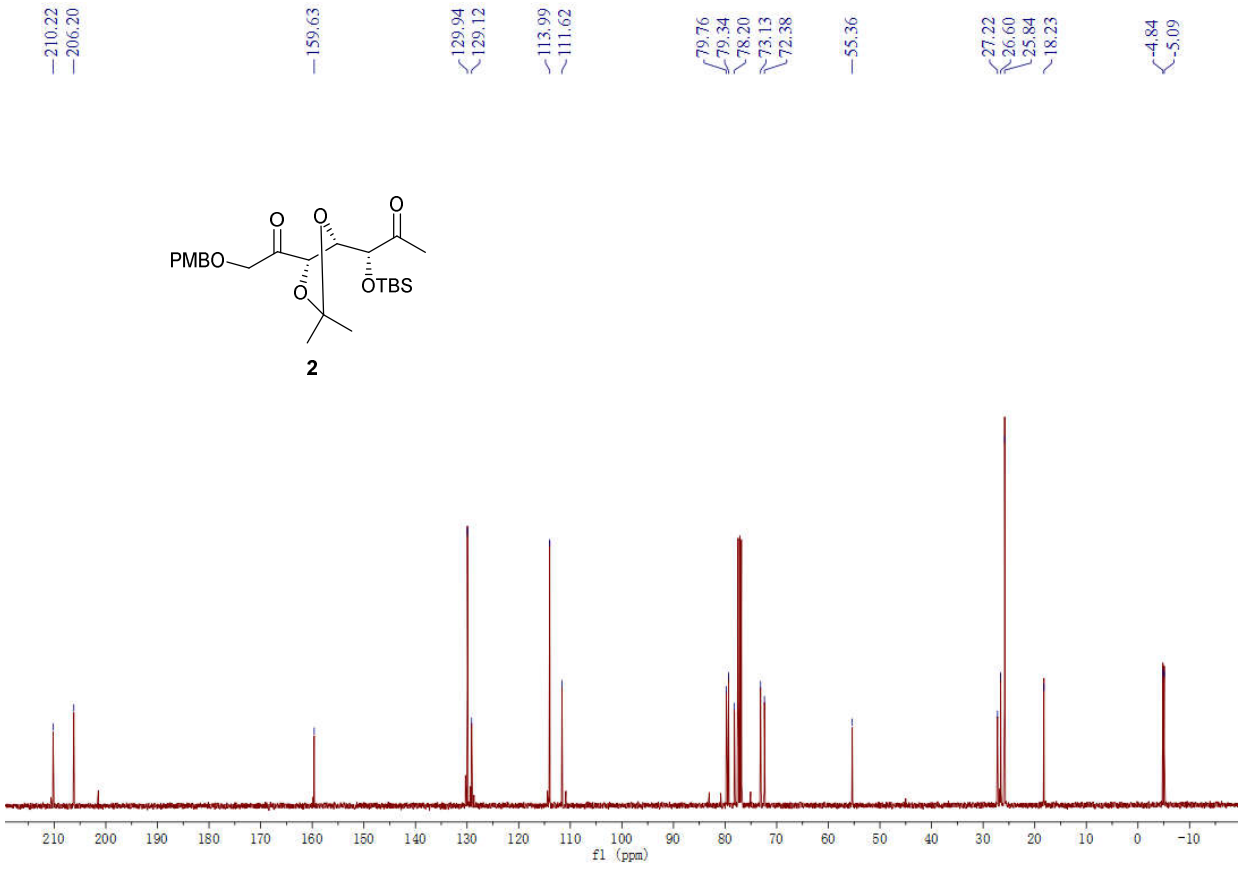
^{1}H NMR (400 MHz, $CDCl_3$/TMS) and ^{13}C NMR (100 MHz, $CDCl_3$) of compound **8**



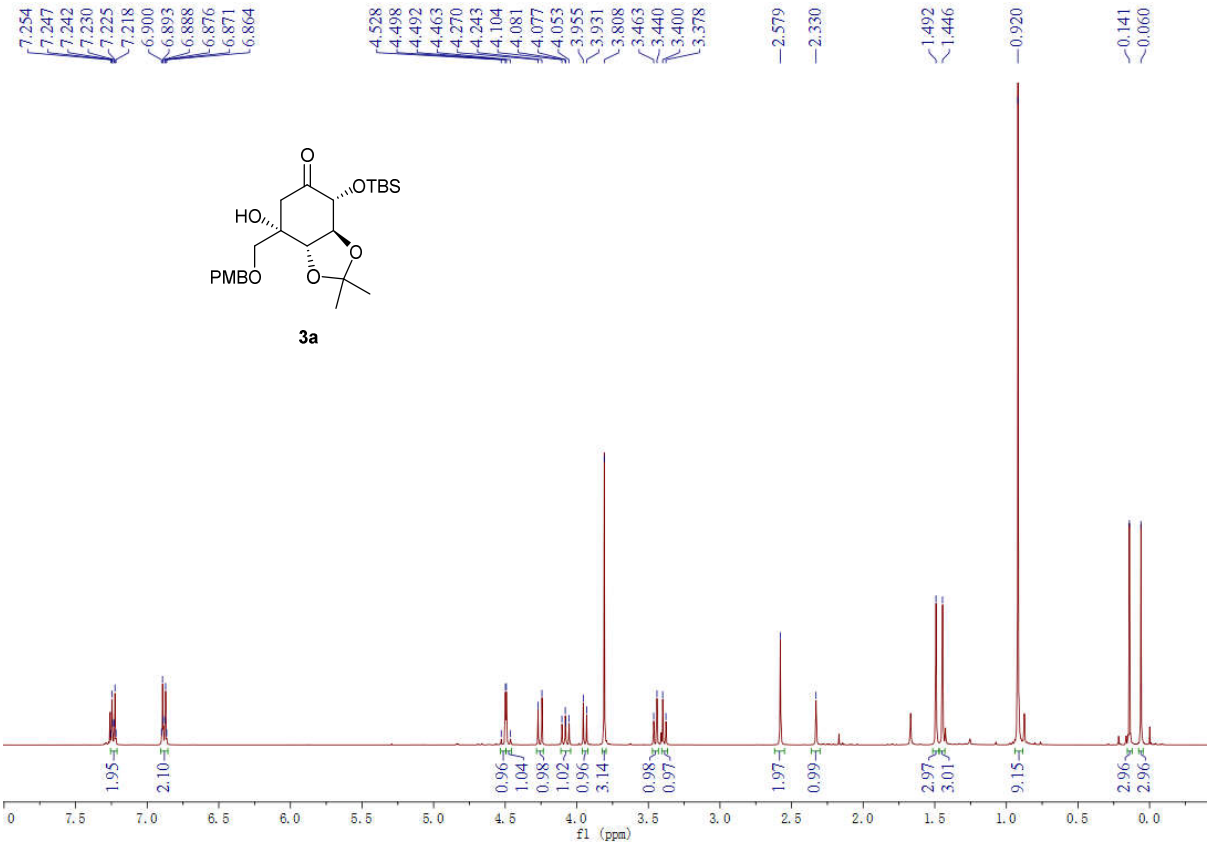


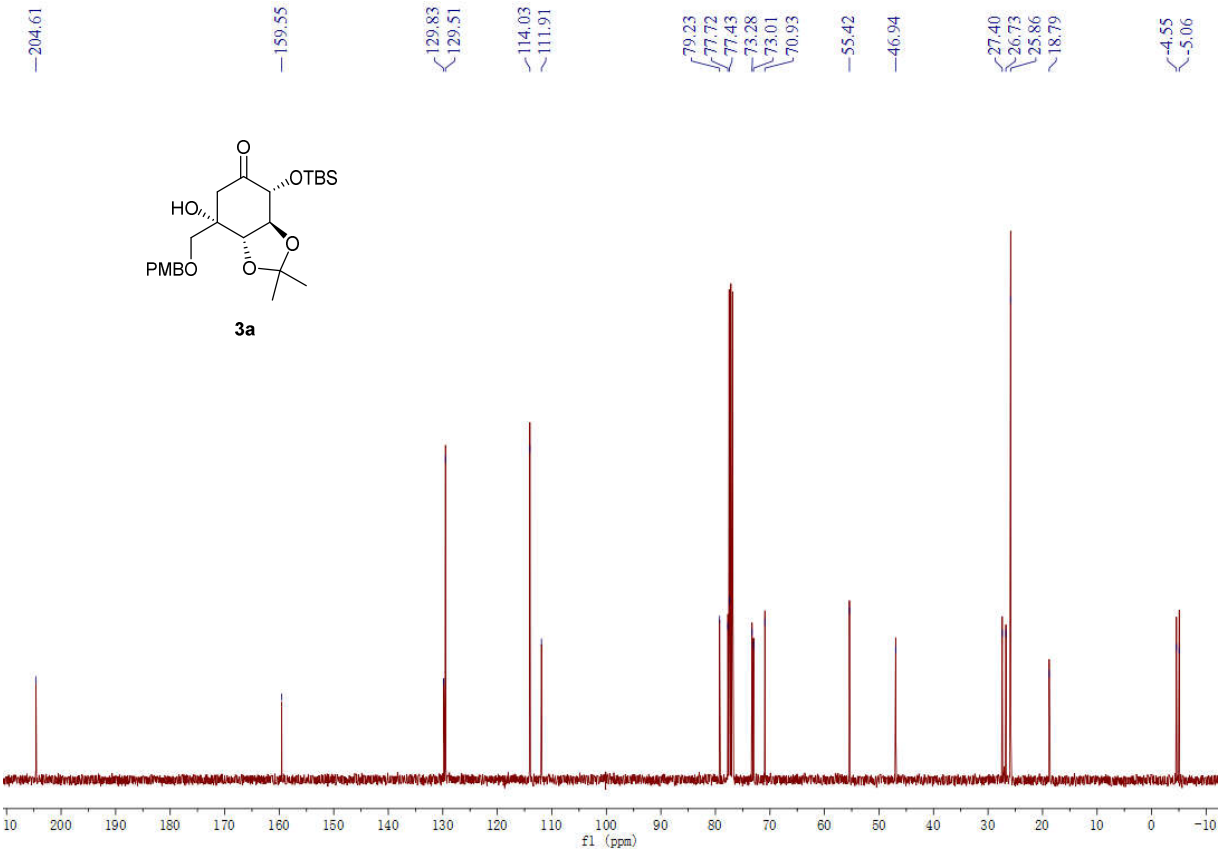
^{1}H NMR (400 MHz, $CDCl_3$/TMS) and ^{13}C NMR (100 MHz, $CDCl_3$) of compound **2**



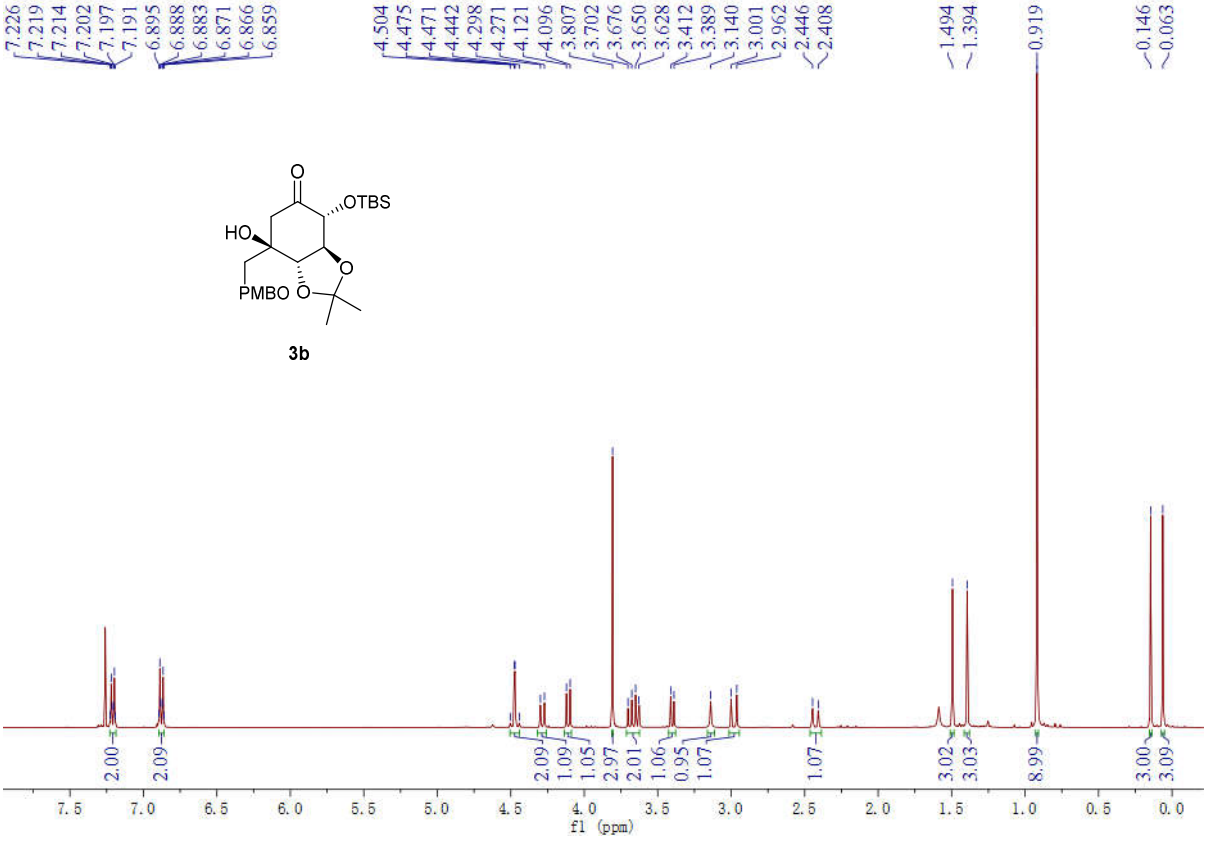


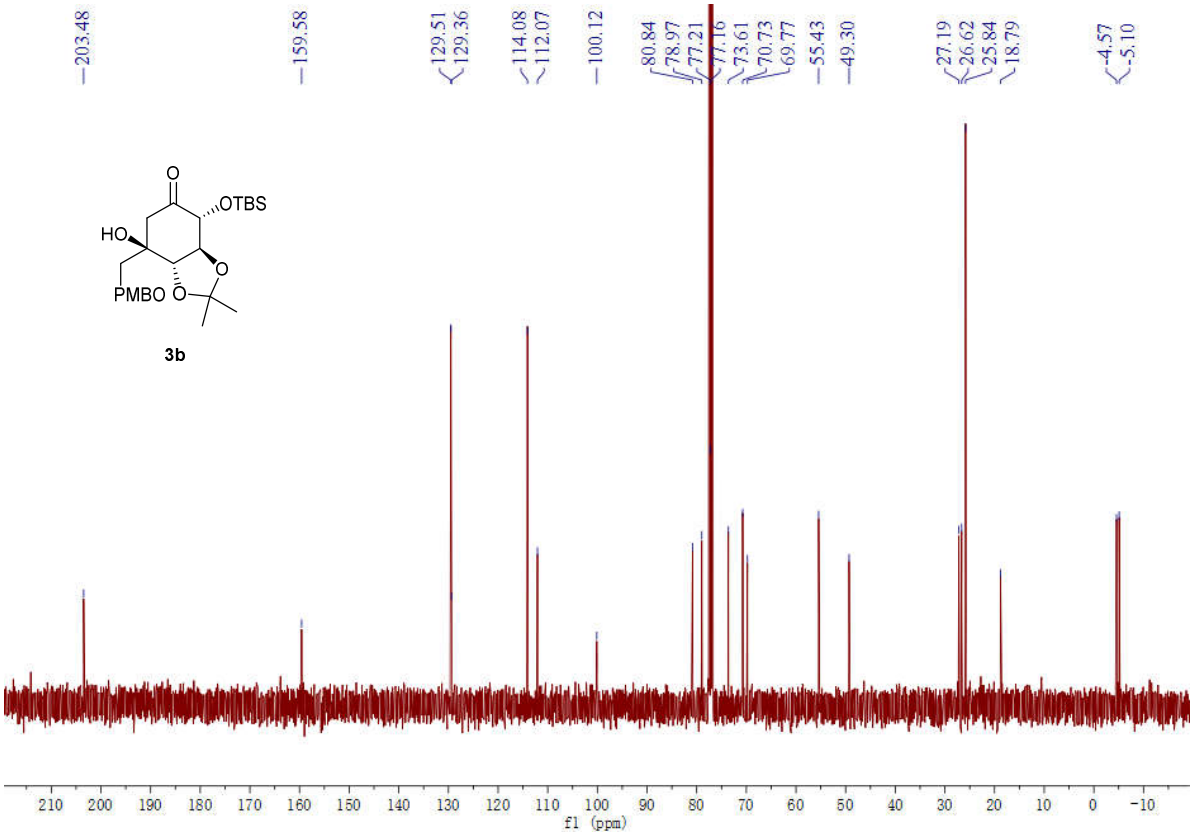
^{1}H NMR (400 MHz, $CDCl_3$/TMS) and ^{13}C NMR (100 MHz, $CDCl_3$) of compound **3a**



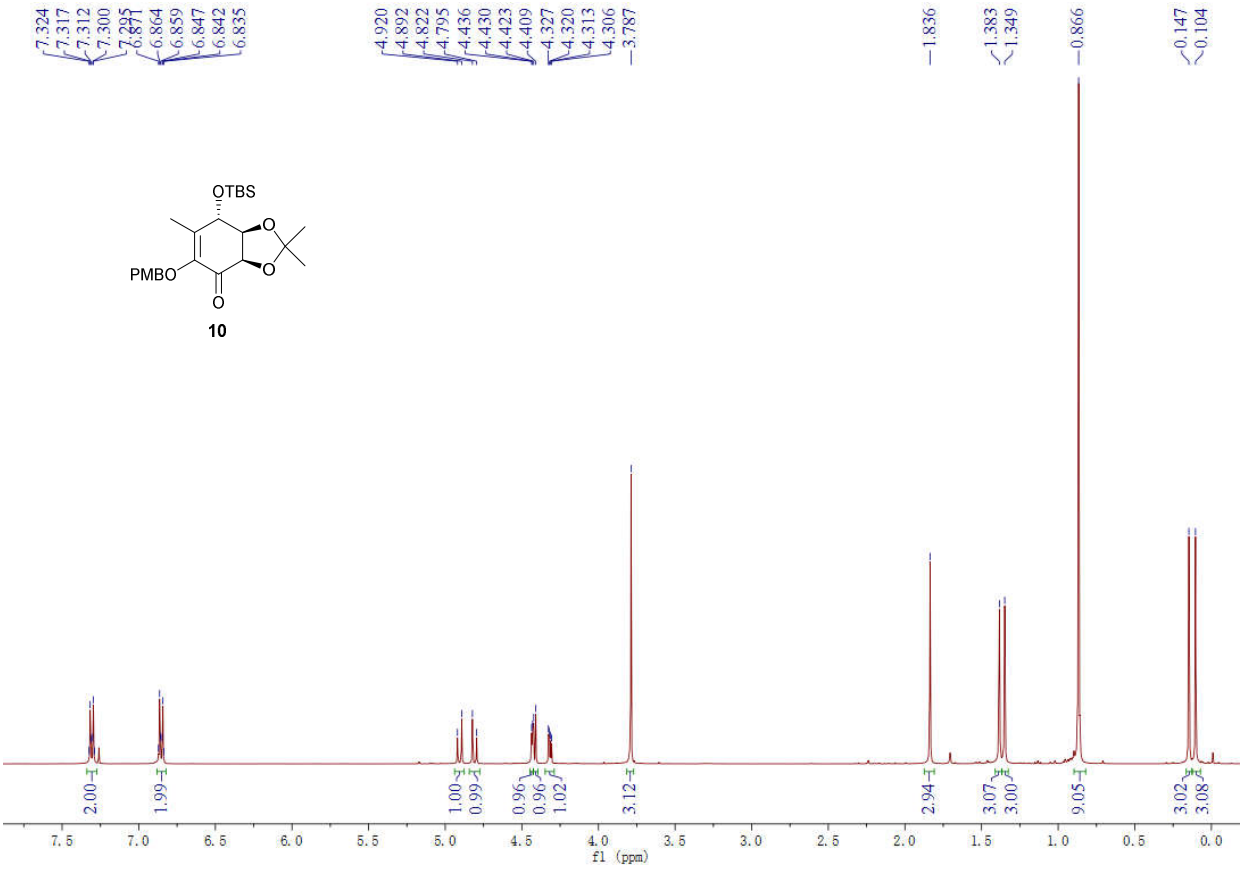


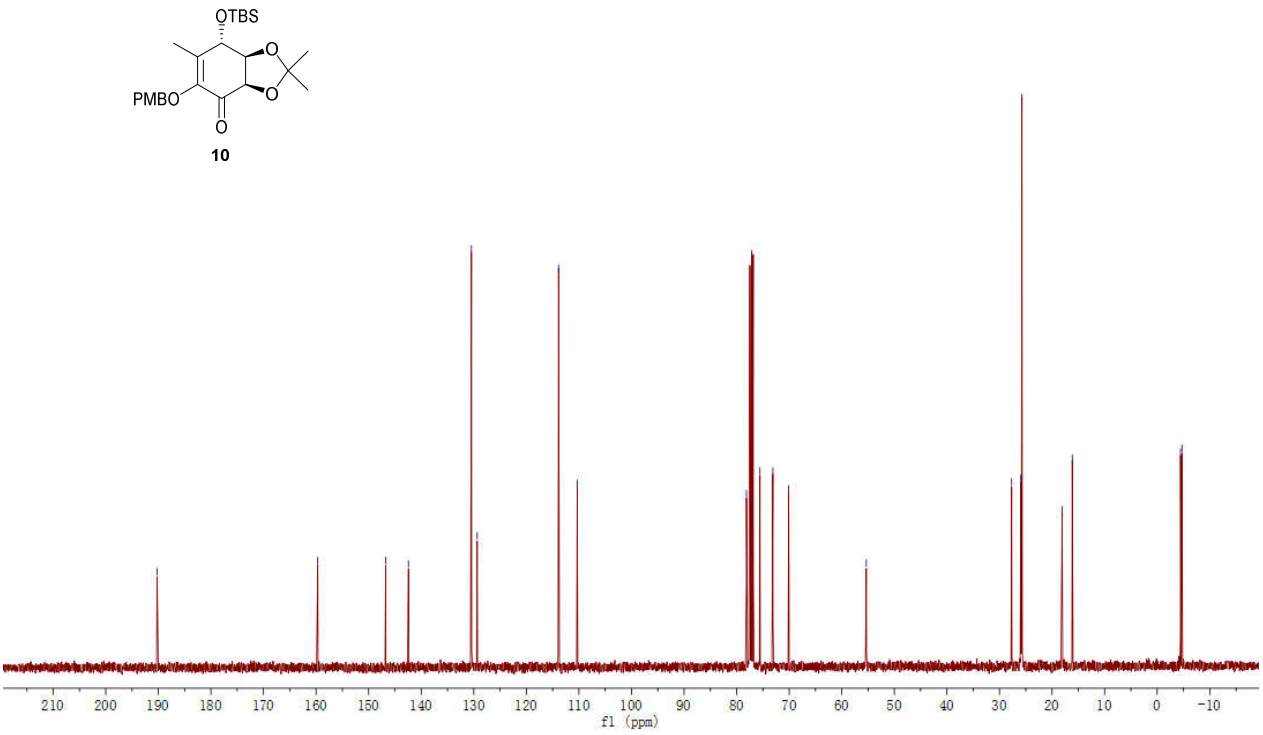
^{1}H NMR (400 MHz, $CDCl_3$/TMS) and ^{13}C NMR (100 MHz, $CDCl_3$) of compound **3b**



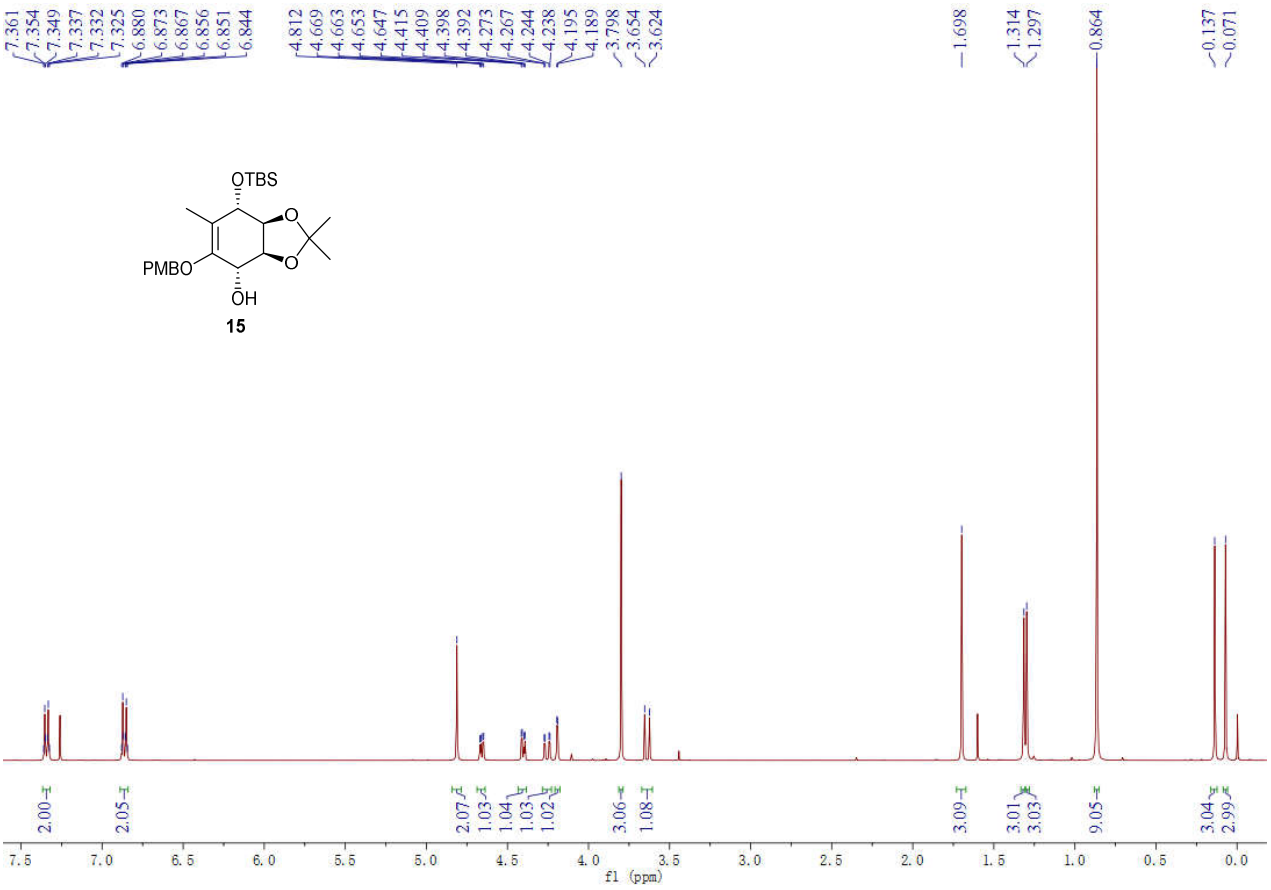


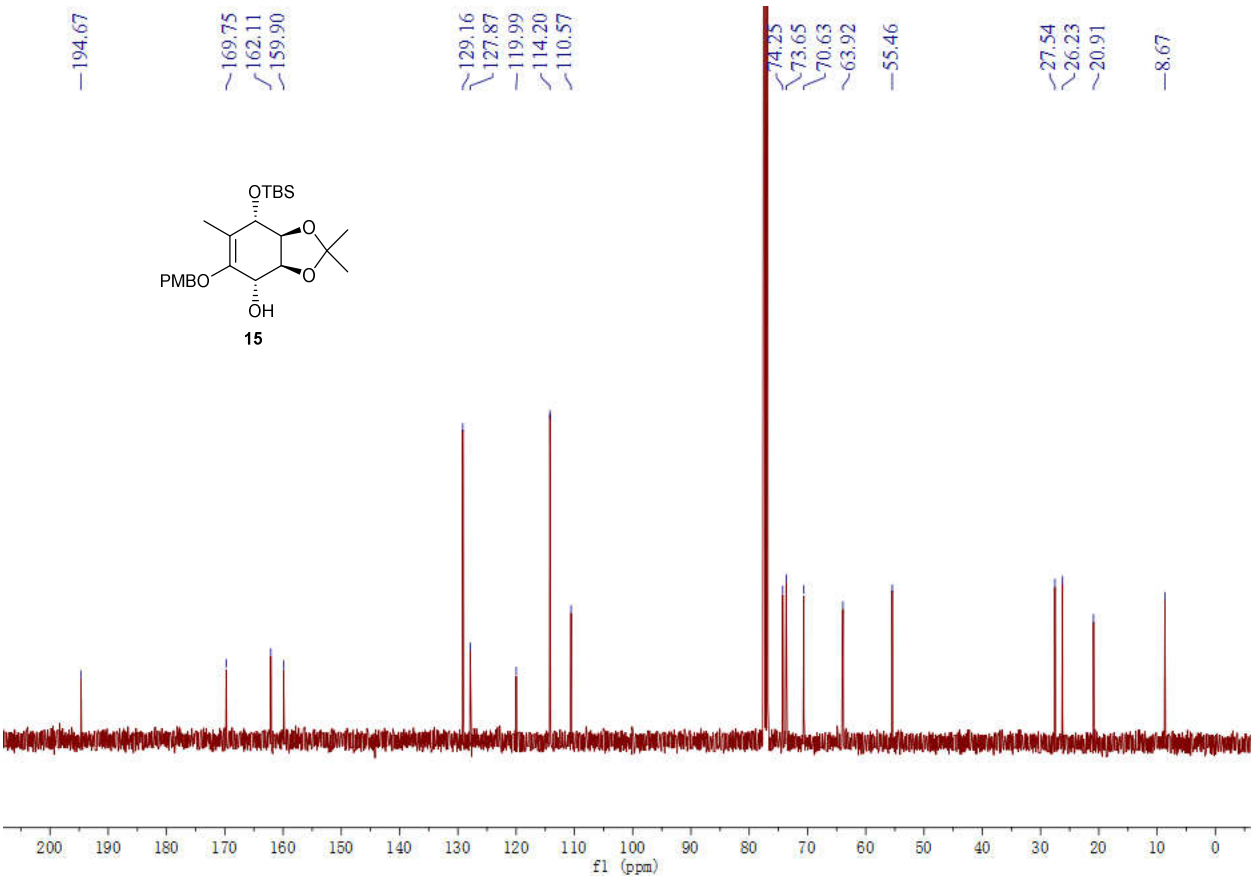
^{1}H NMR (400 MHz, $CDCl_3$/TMS) and ^{13}C NMR (100 MHz, $CDCl_3$) of compound **10**



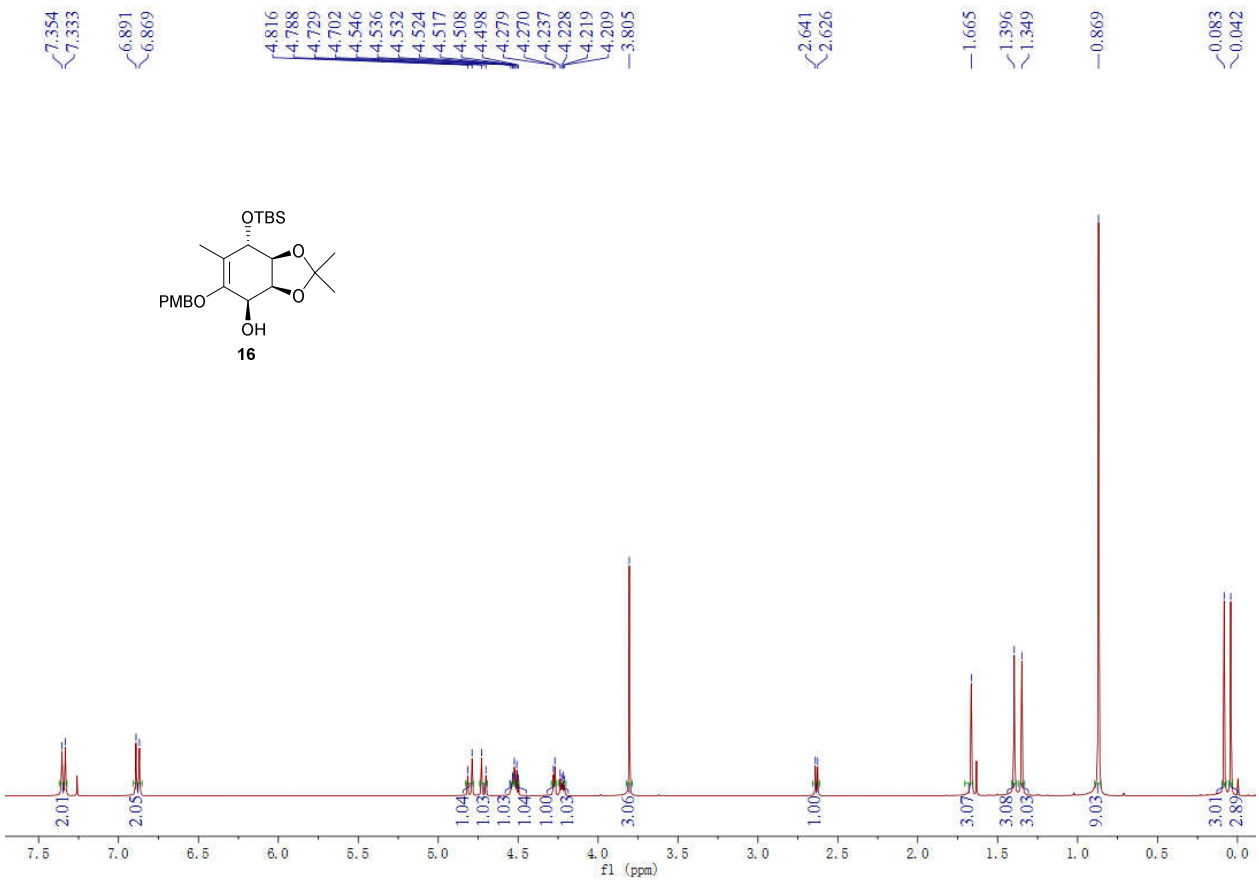


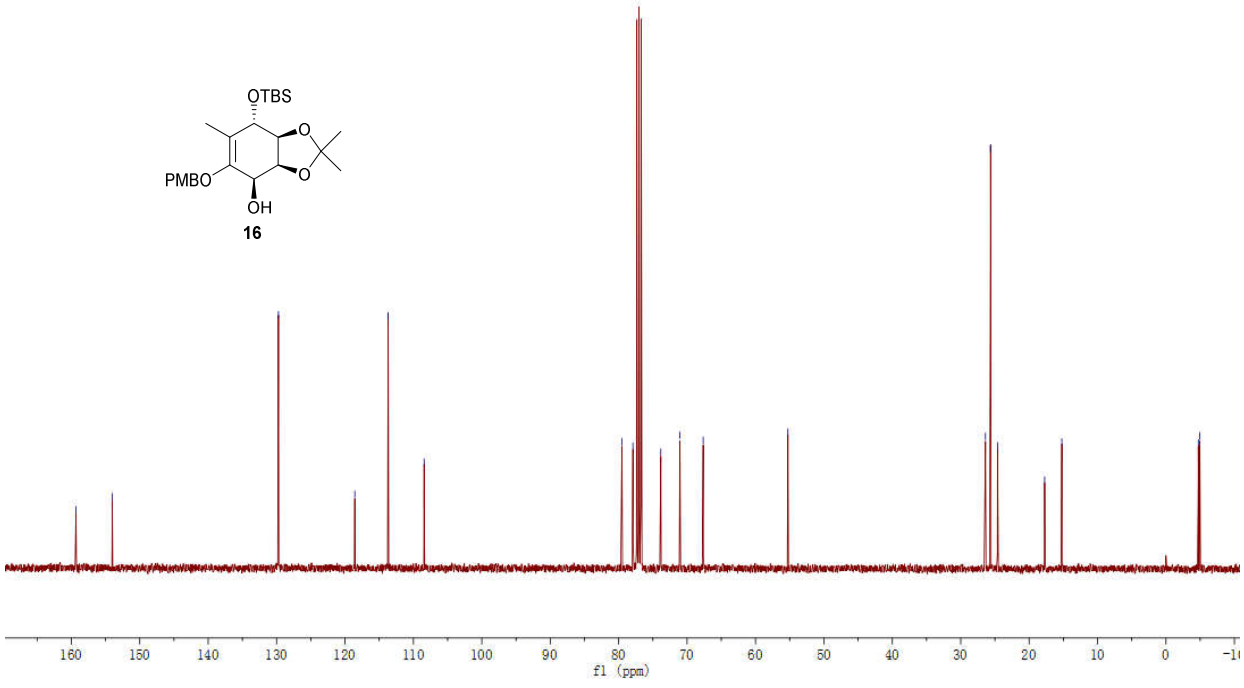
^{1}H NMR (400 MHz, $CDCl_3$/TMS) and ^{13}C NMR (100 MHz, $CDCl_3$) of compound **15**



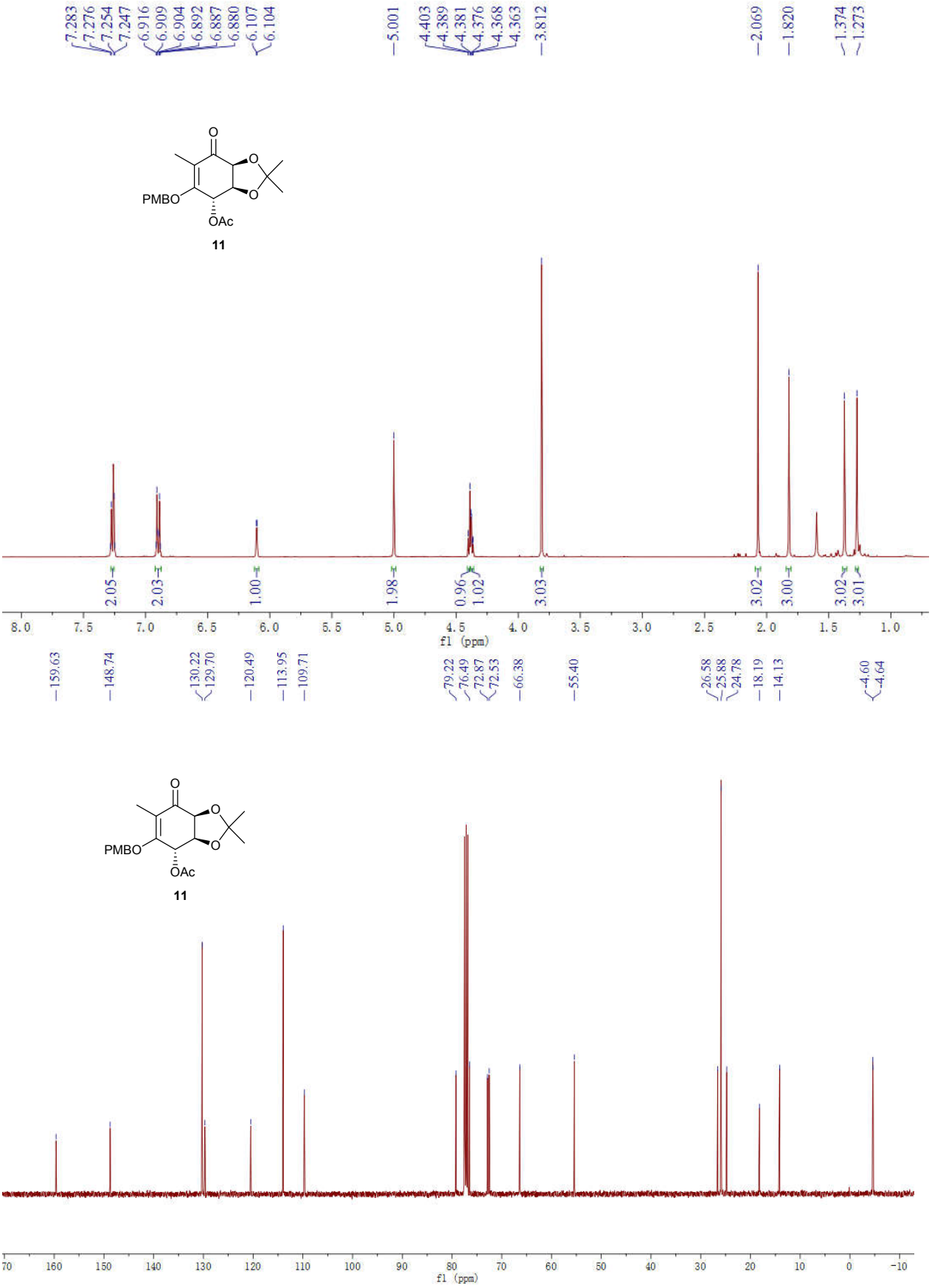


^{1}H NMR (400 MHz, $CDCl_3$/TMS) and ^{13}C NMR (100 MHz, $CDCl_3$) of compound **16**

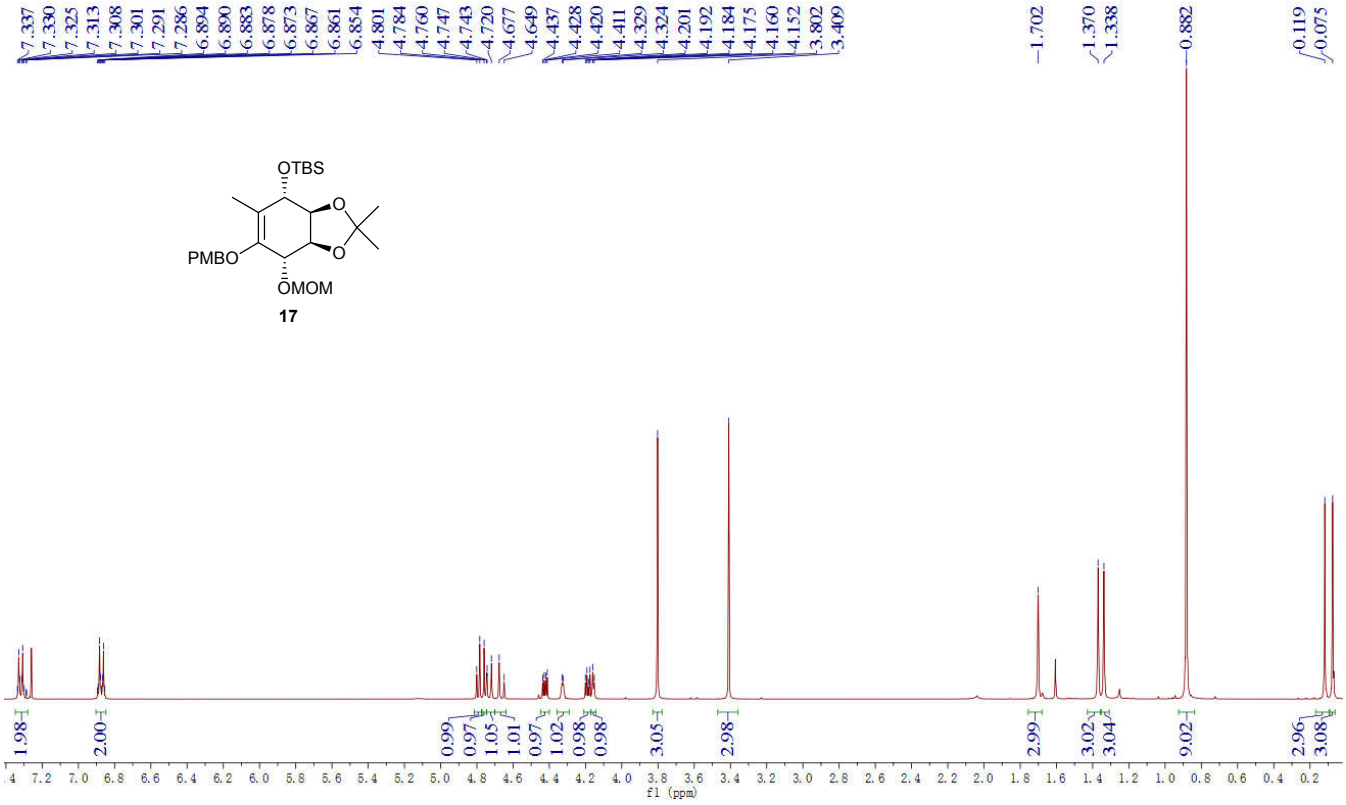


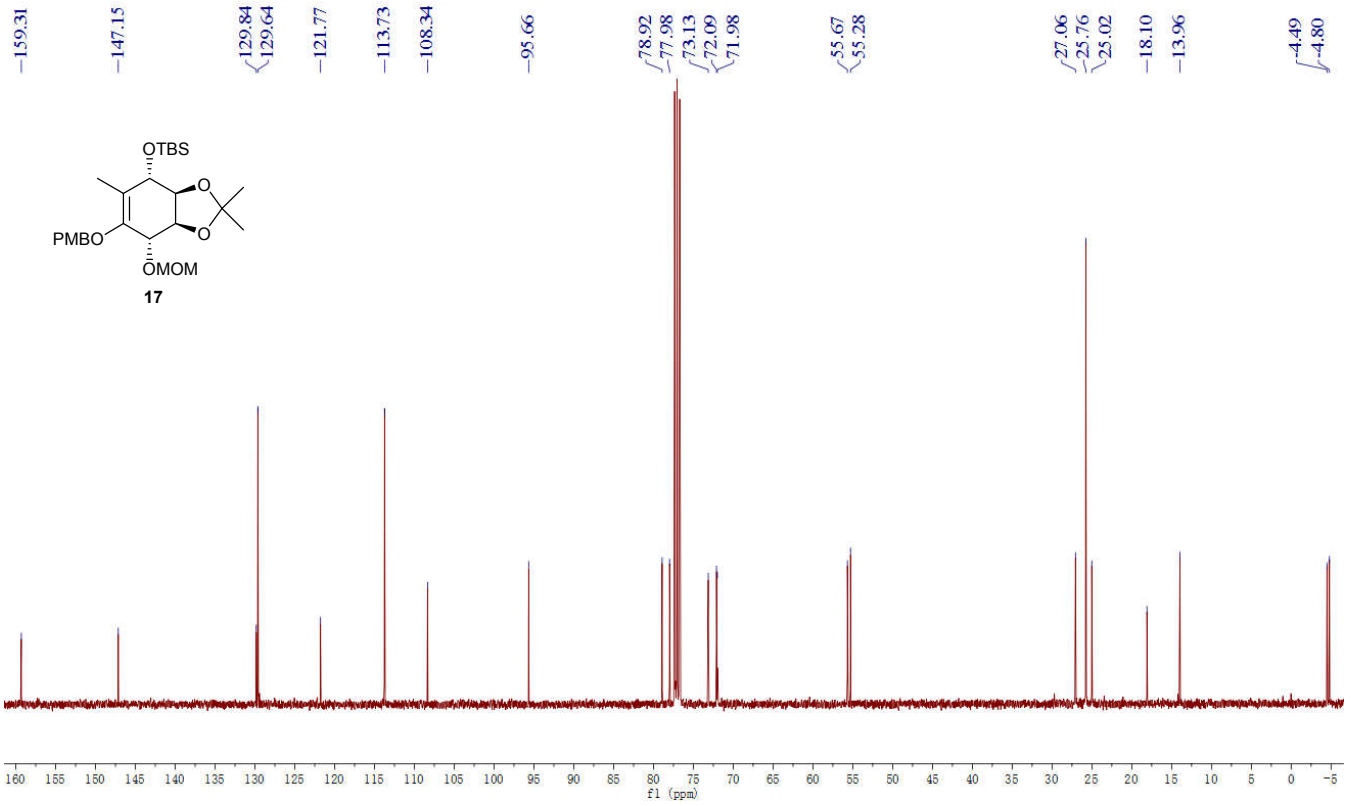


^{1}H NMR (400 MHz, $CDCl_3$/TMS) and ^{13}C NMR (100 MHz, $CDCl_3$) of compound **11**

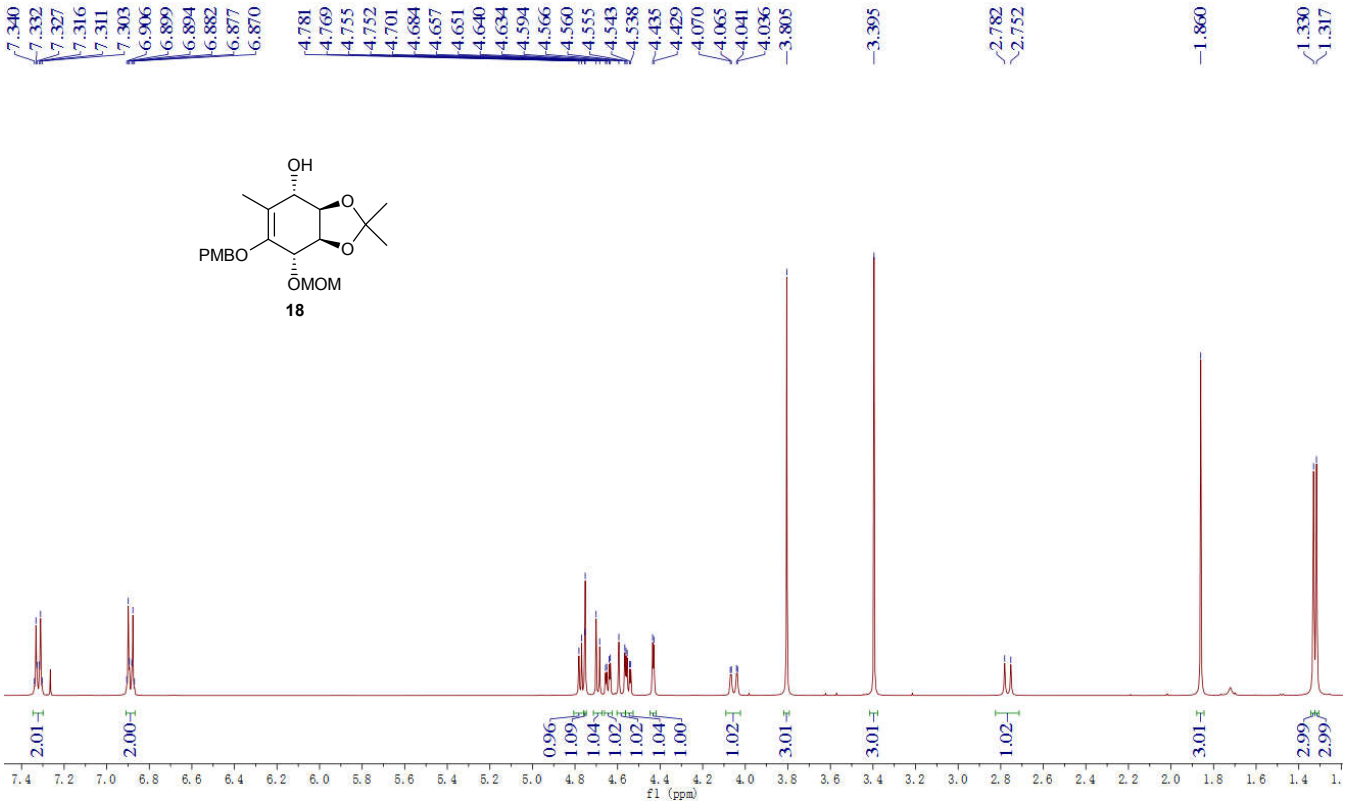


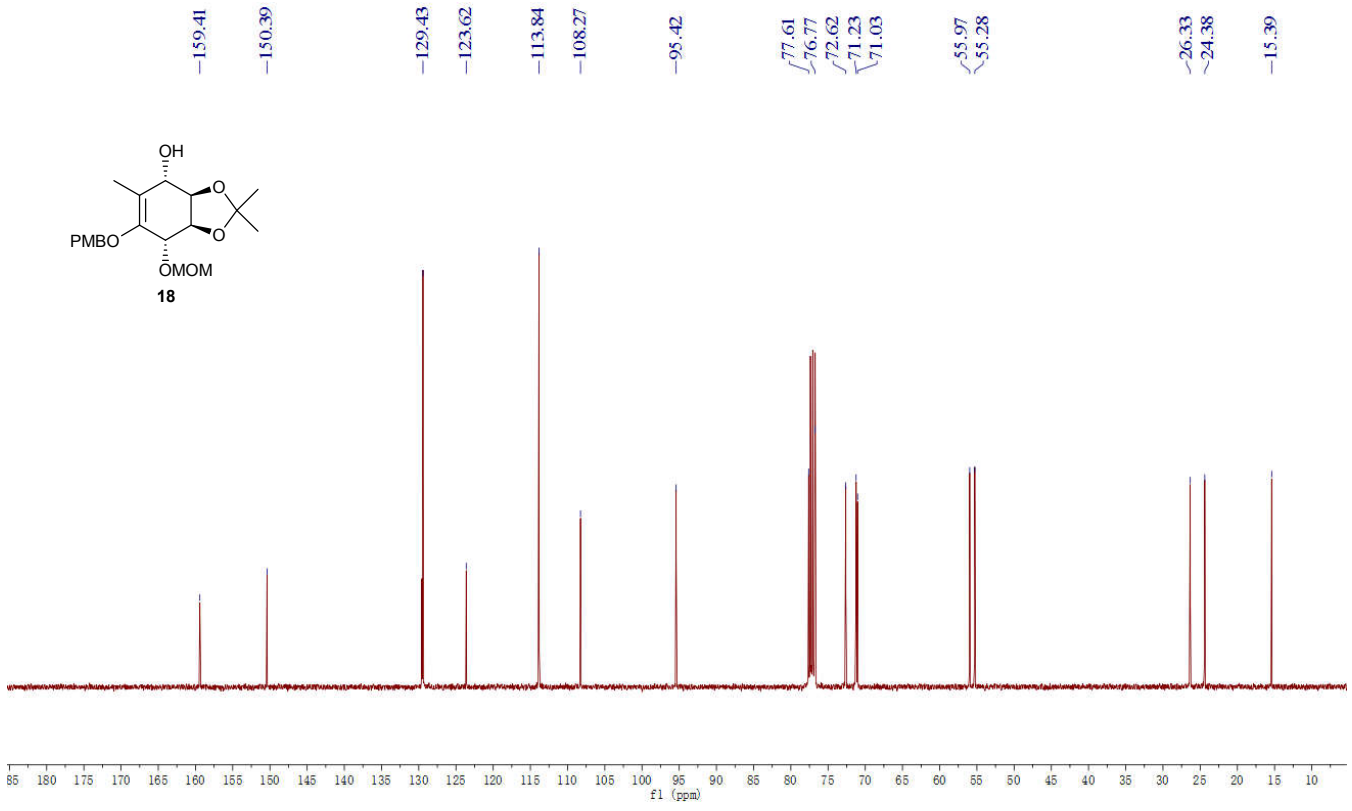
^{1}H NMR (400 MHz, $CDCl_3$/TMS) and ^{13}C NMR (100 MHz, $CDCl_3$) of compound **17**



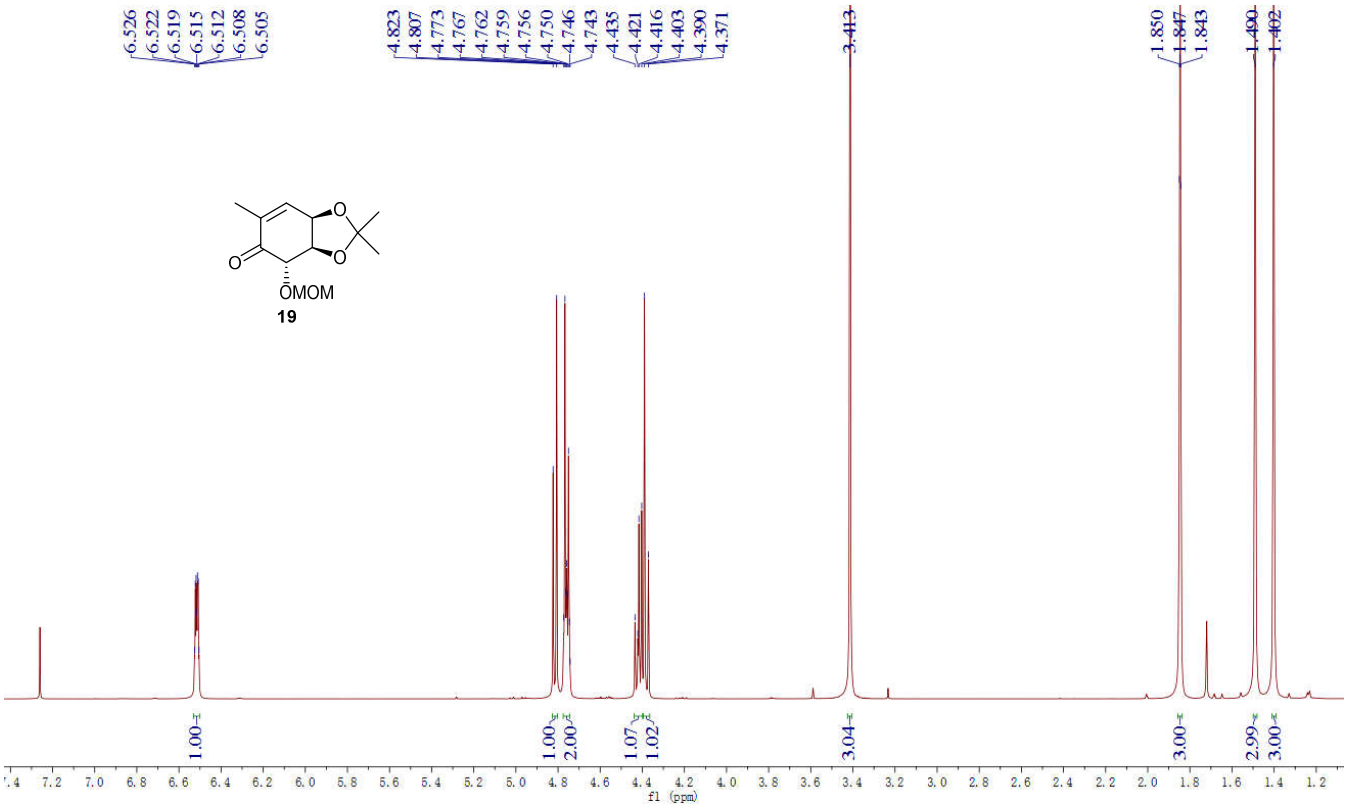


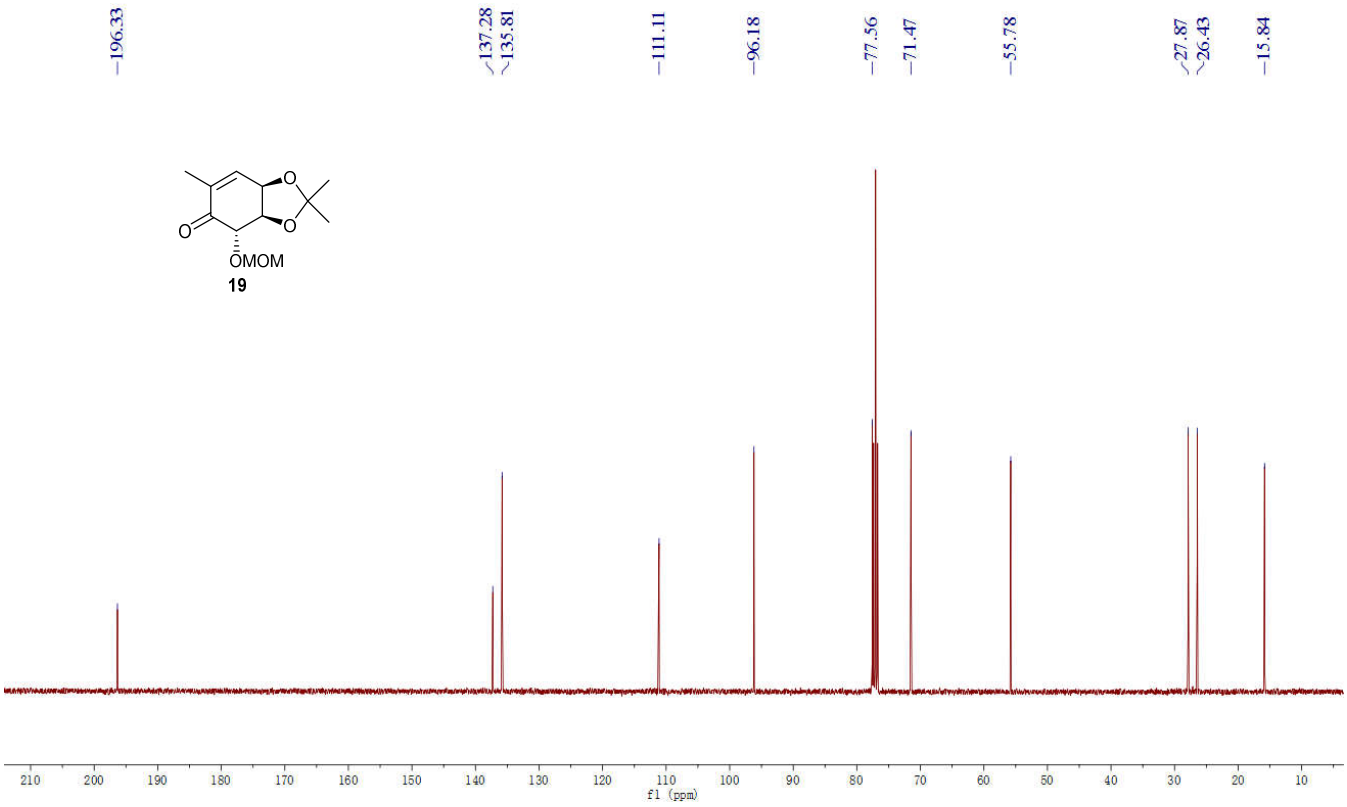
^{1}H NMR (400 MHz, $CDCl_3$/TMS) and ^{13}C NMR (100 MHz, $CDCl_3$) of compound **18**



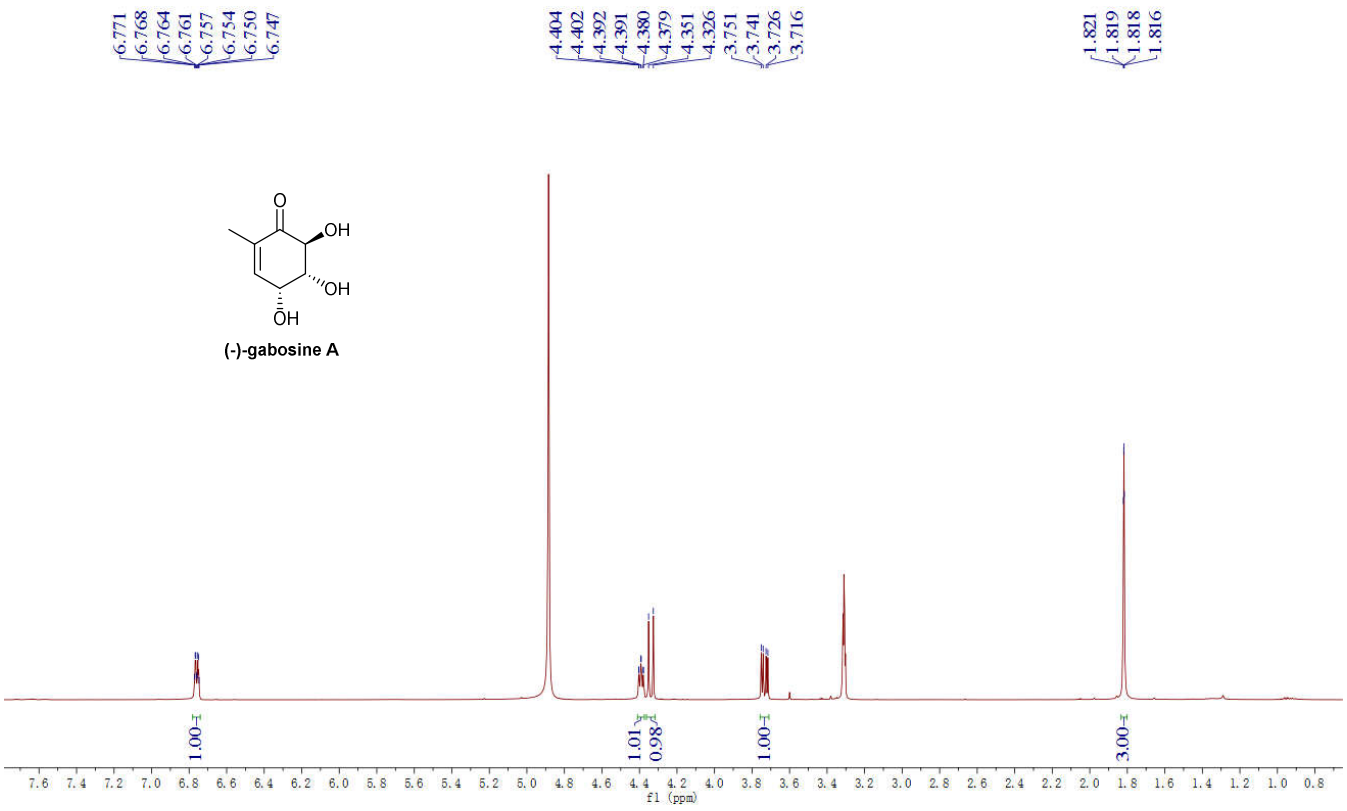


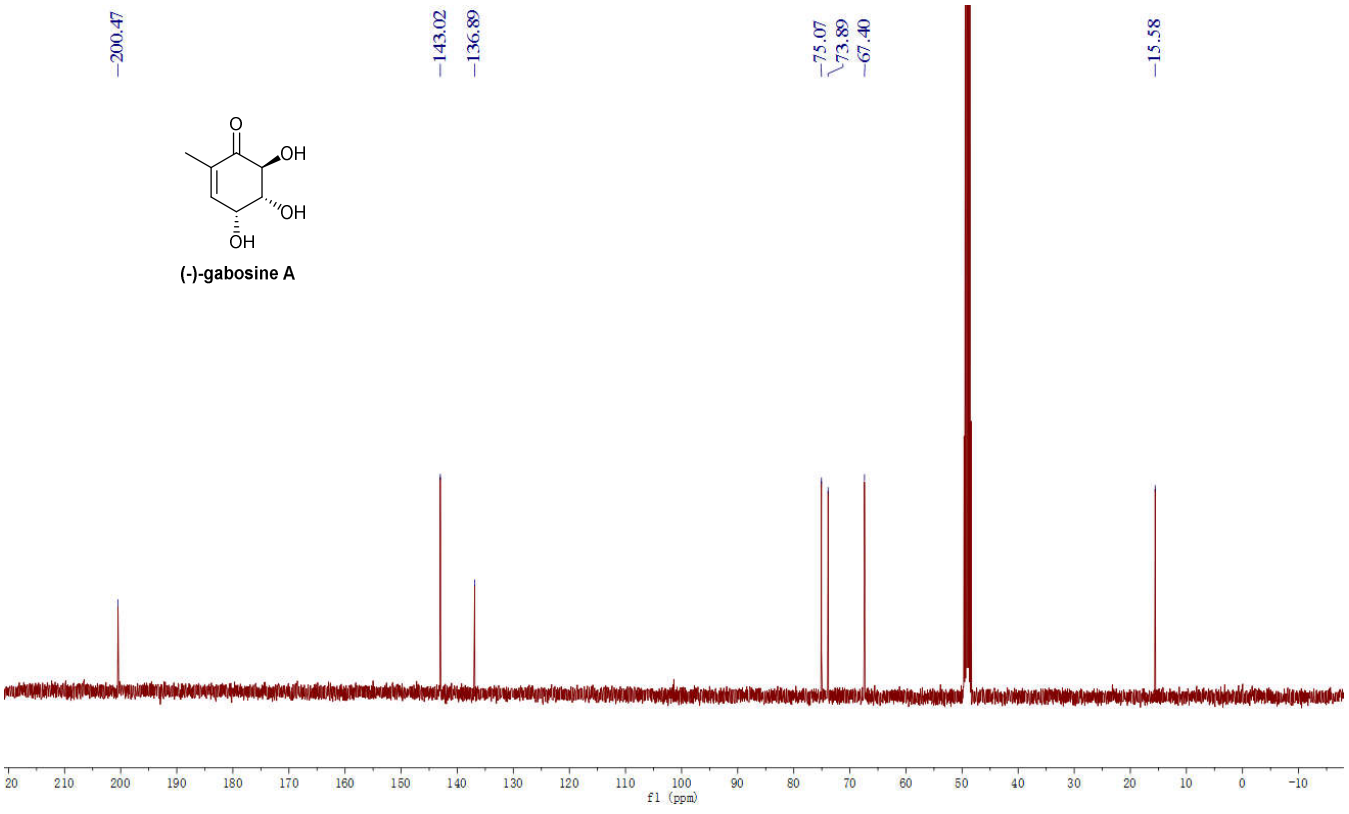
^{1}H NMR (400 MHz, $CDCl_3$/TMS) and ^{13}C NMR (100 MHz, $CDCl_3$) of compound **19**



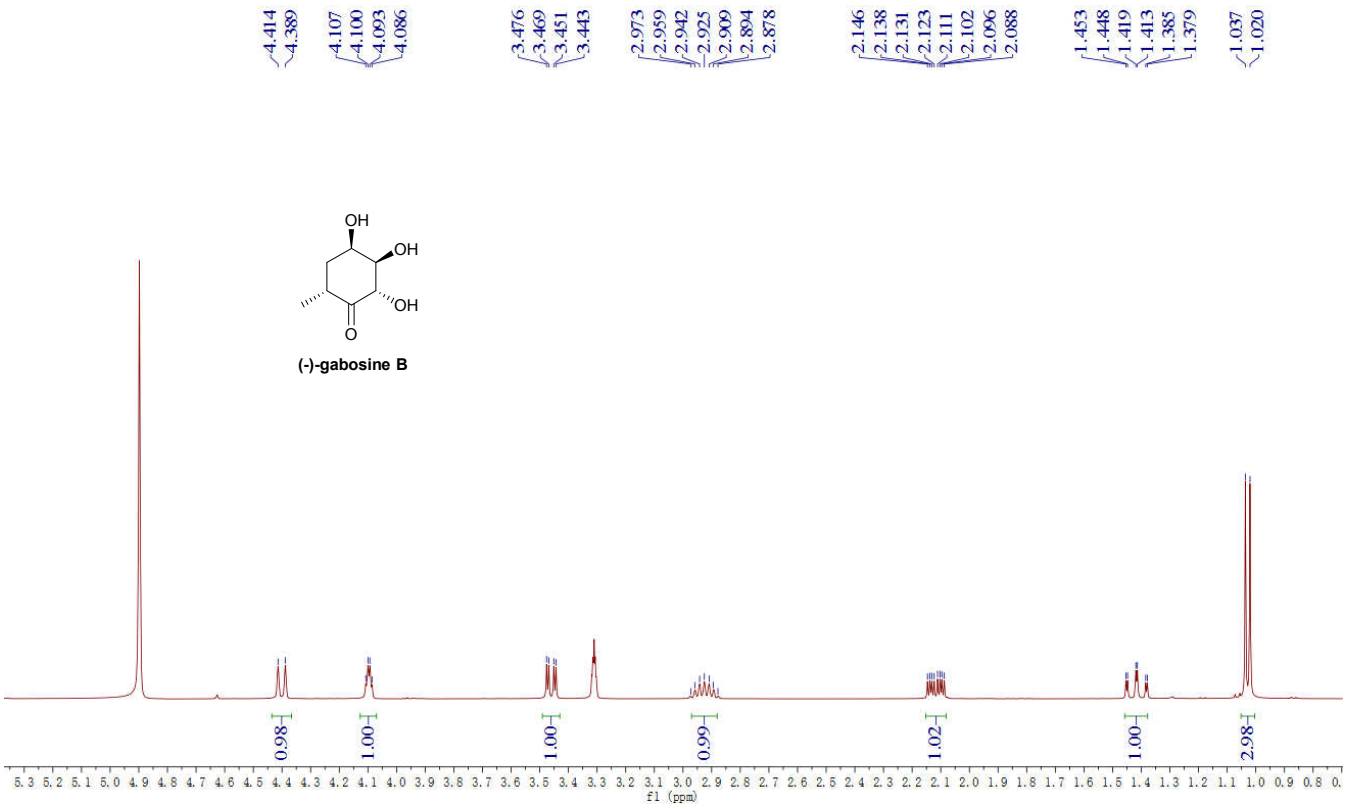


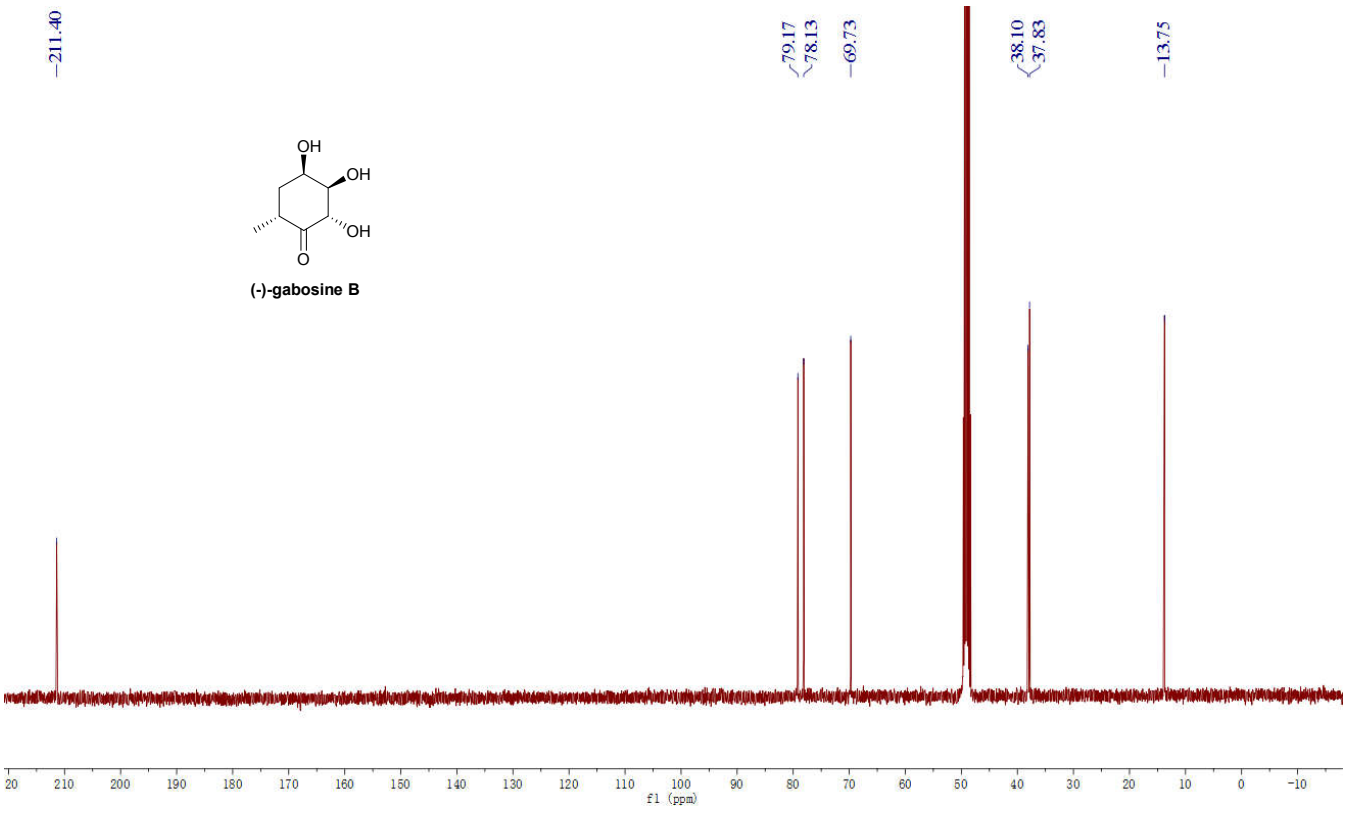
^{1}H NMR (400 MHz, CD_3OD/TMS) and ^{13}C NMR (100 MHz, CD_3OD) of **(–)-Gabosine A**



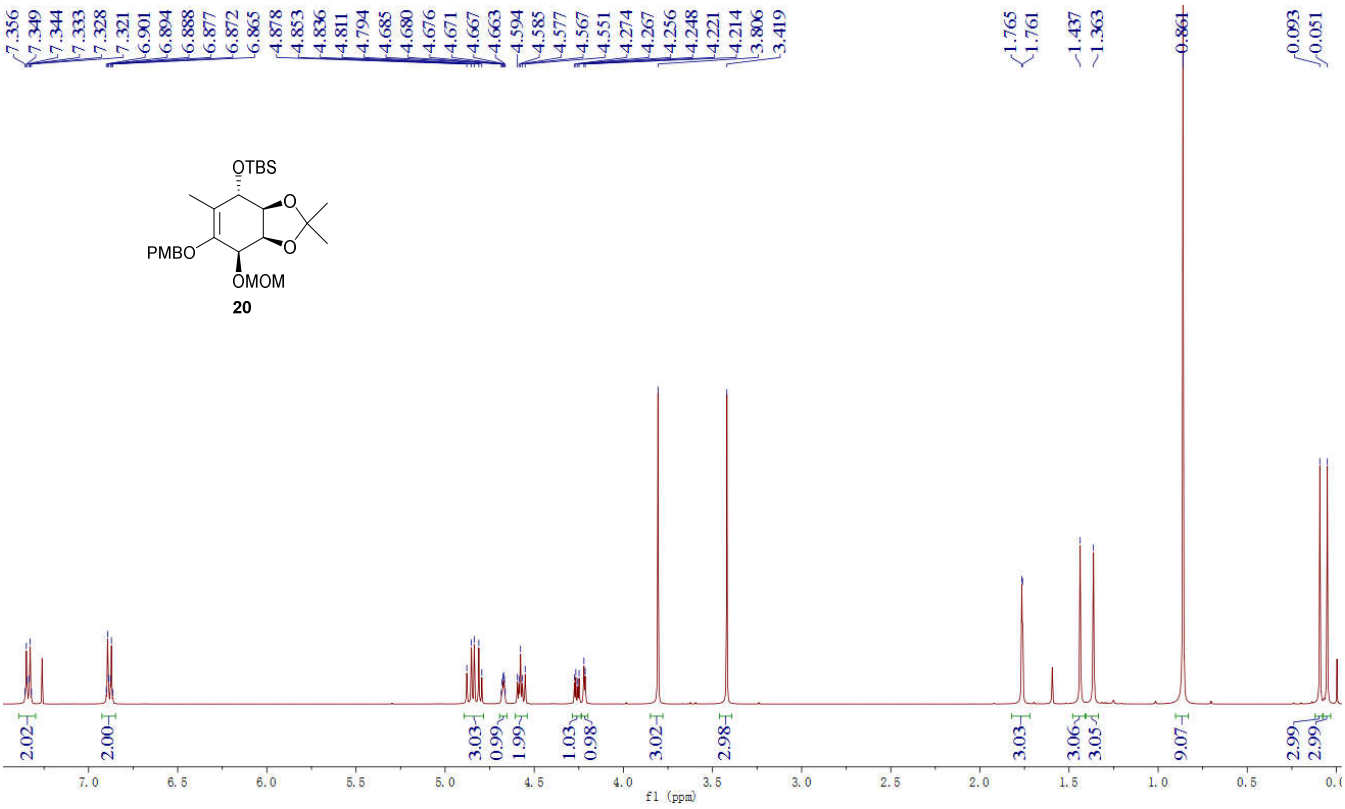


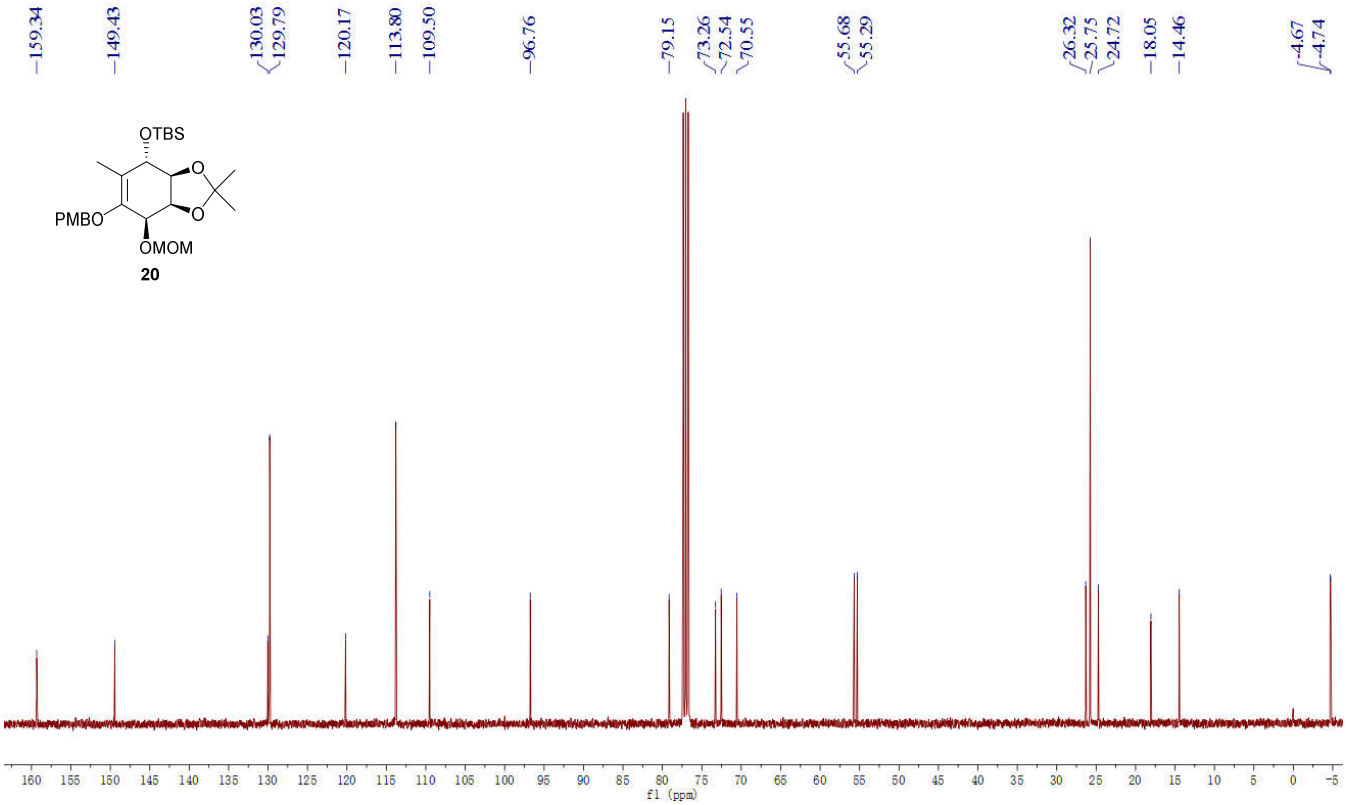
^{1}H NMR (400 MHz, CD_3OD /TMS) and ^{13}C NMR (100 MHz, CD_3OD) of **(–)-Gabosine B**



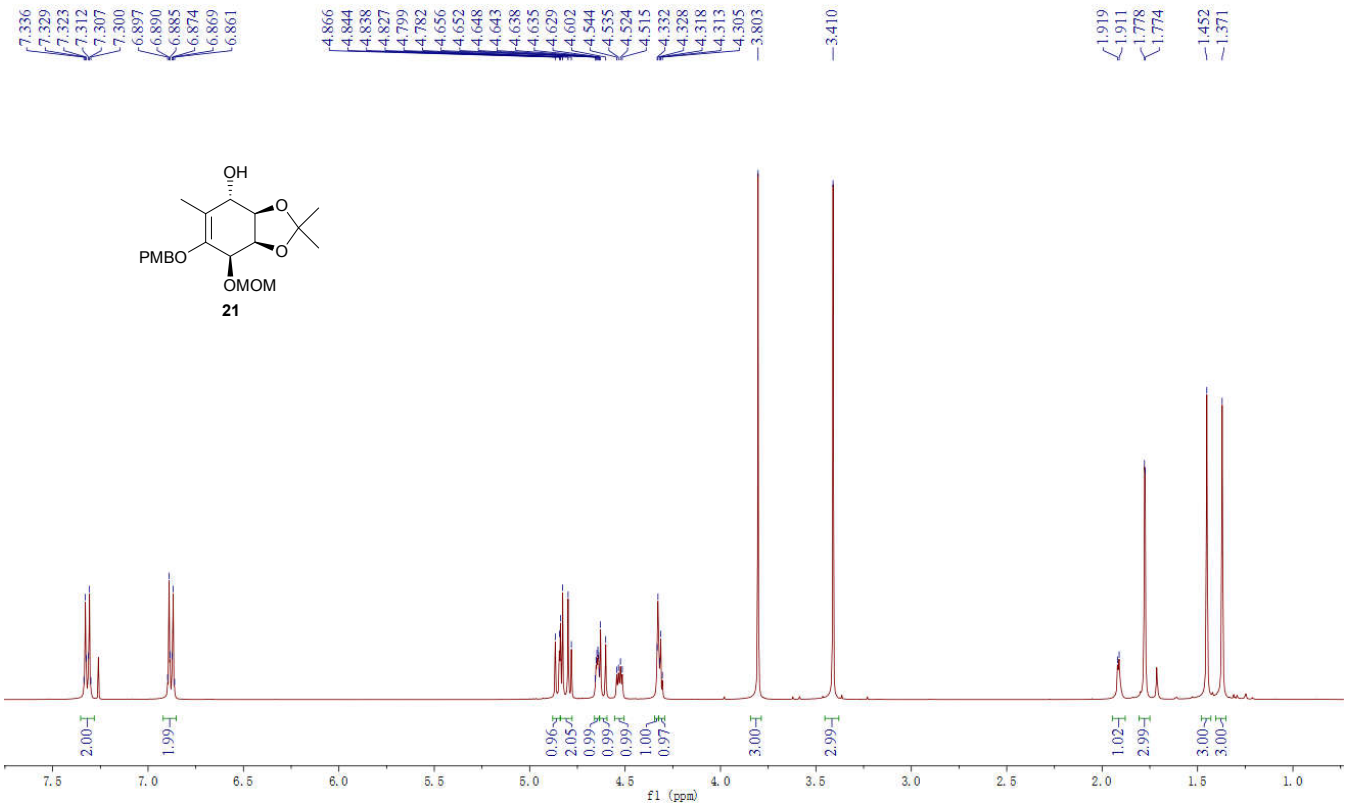


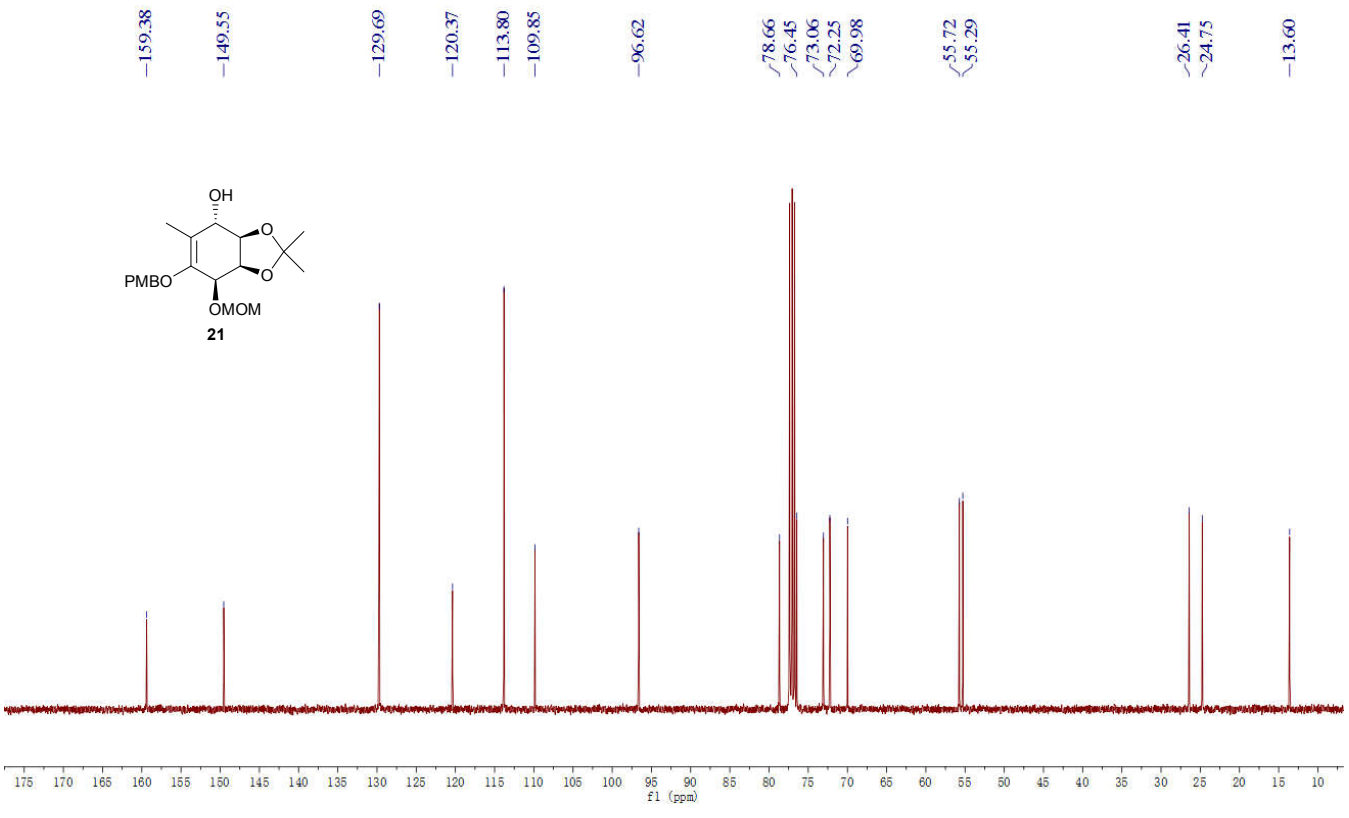
^{1}H NMR (400 MHz, $CDCl_3$/TMS) and ^{13}C NMR (100 MHz, $CDCl_3$) of compound **20**



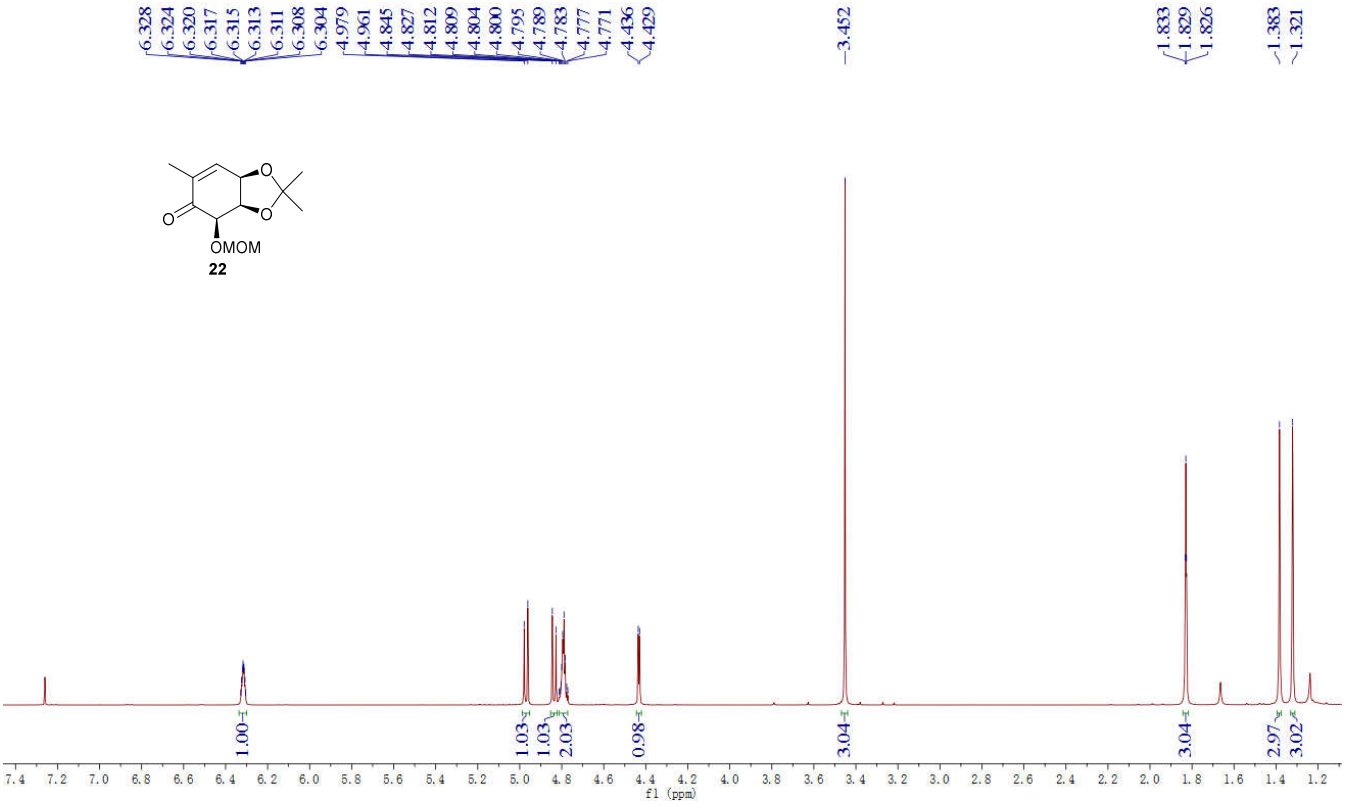


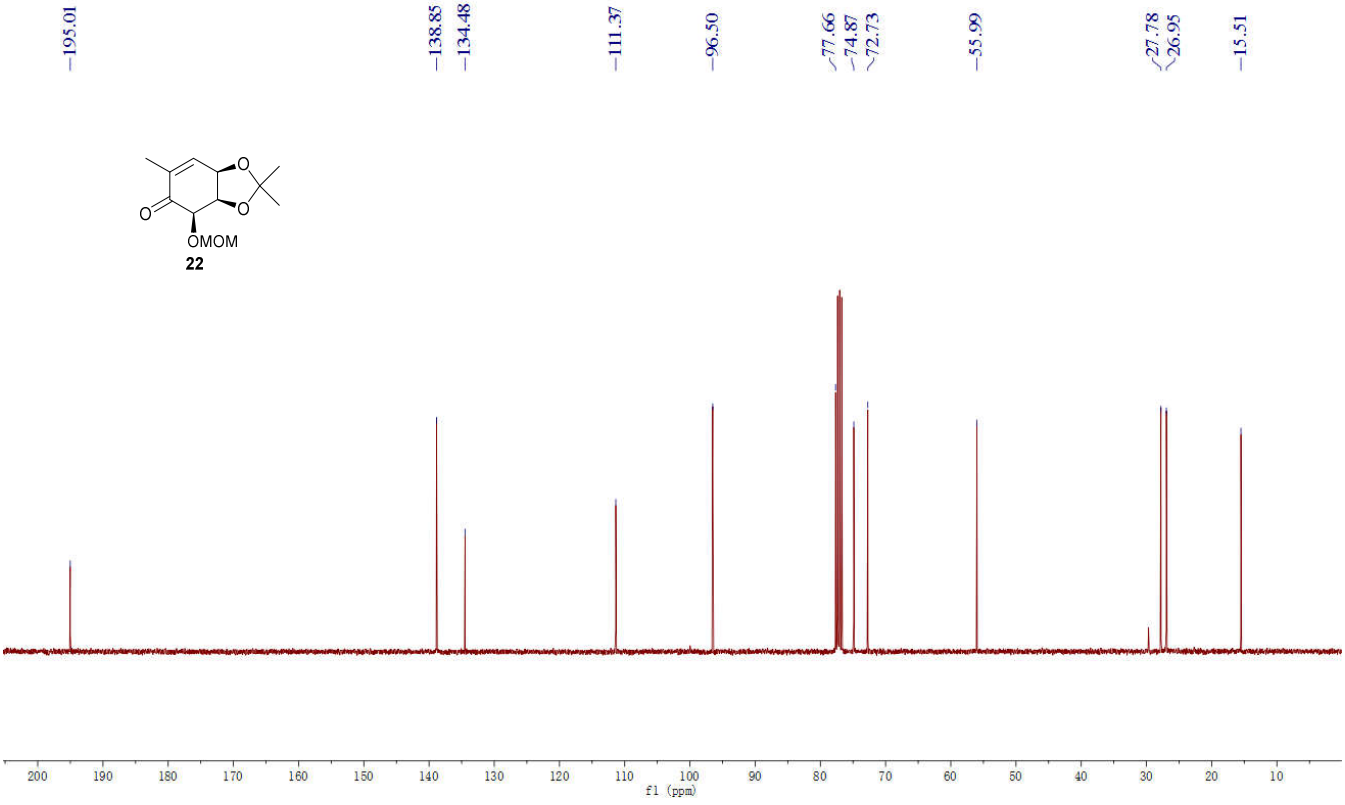
^{1}H NMR (400 MHz, $CDCl_3$/TMS) and ^{13}C NMR (100 MHz, $CDCl_3$) of compound **21**



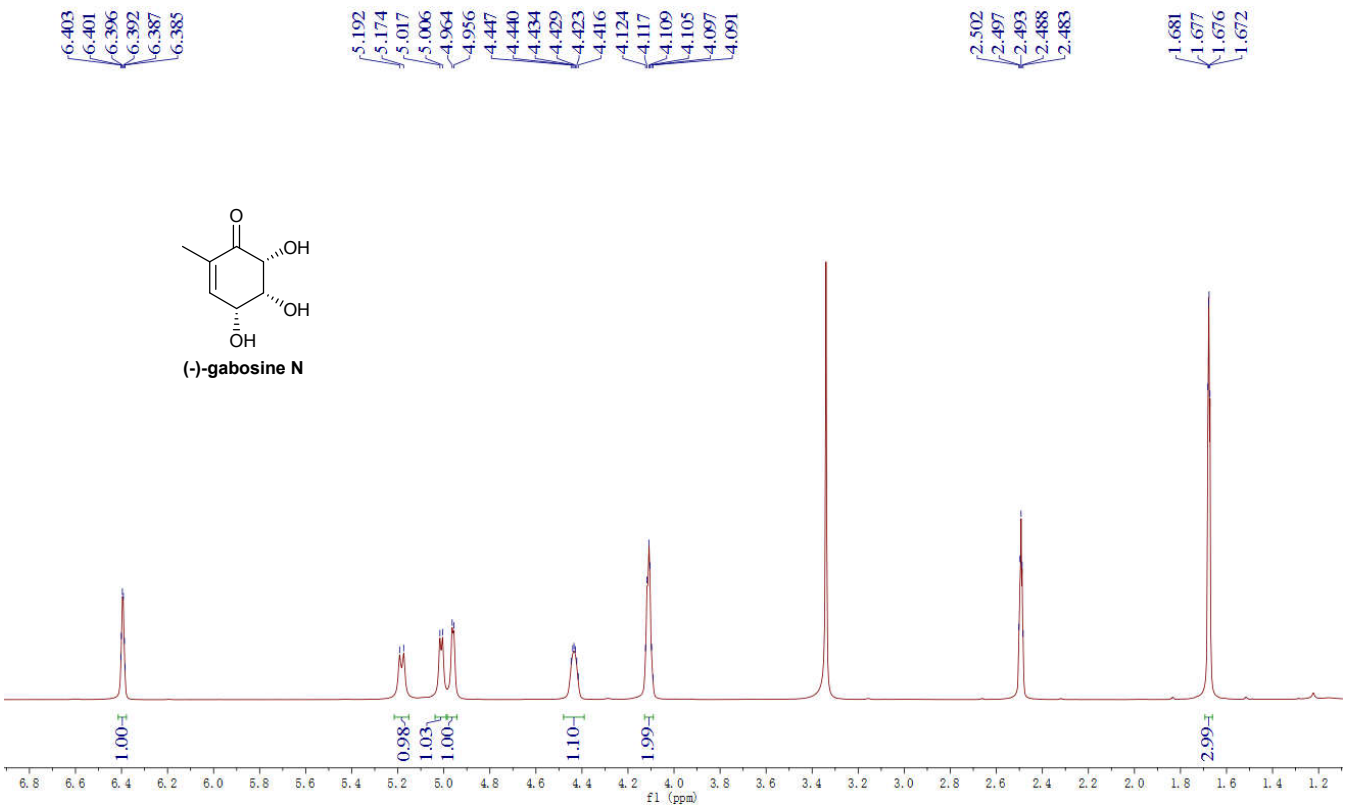


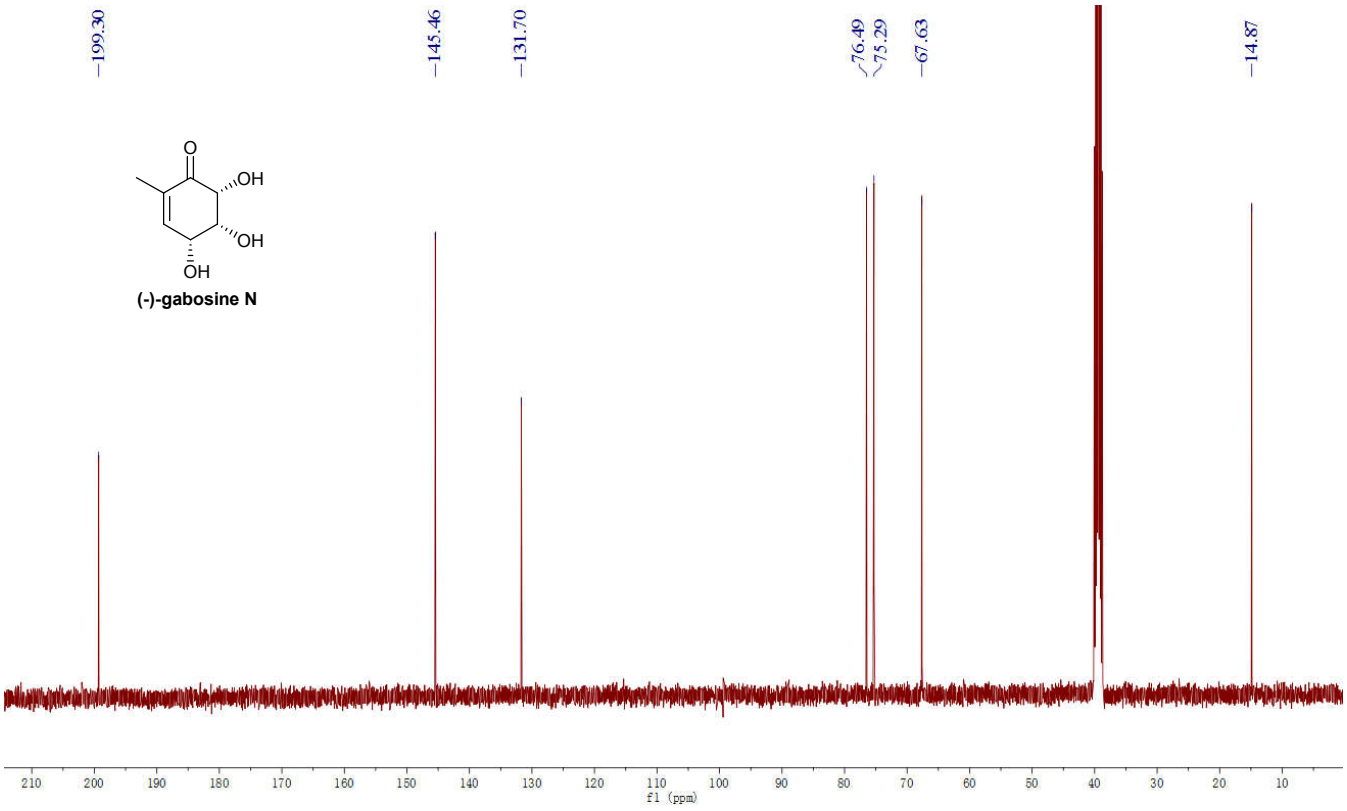
^{1}H NMR (400 MHz, $CDCl_3$/TMS) and ^{13}C NMR (100 MHz, $CDCl_3$) of compound **22**



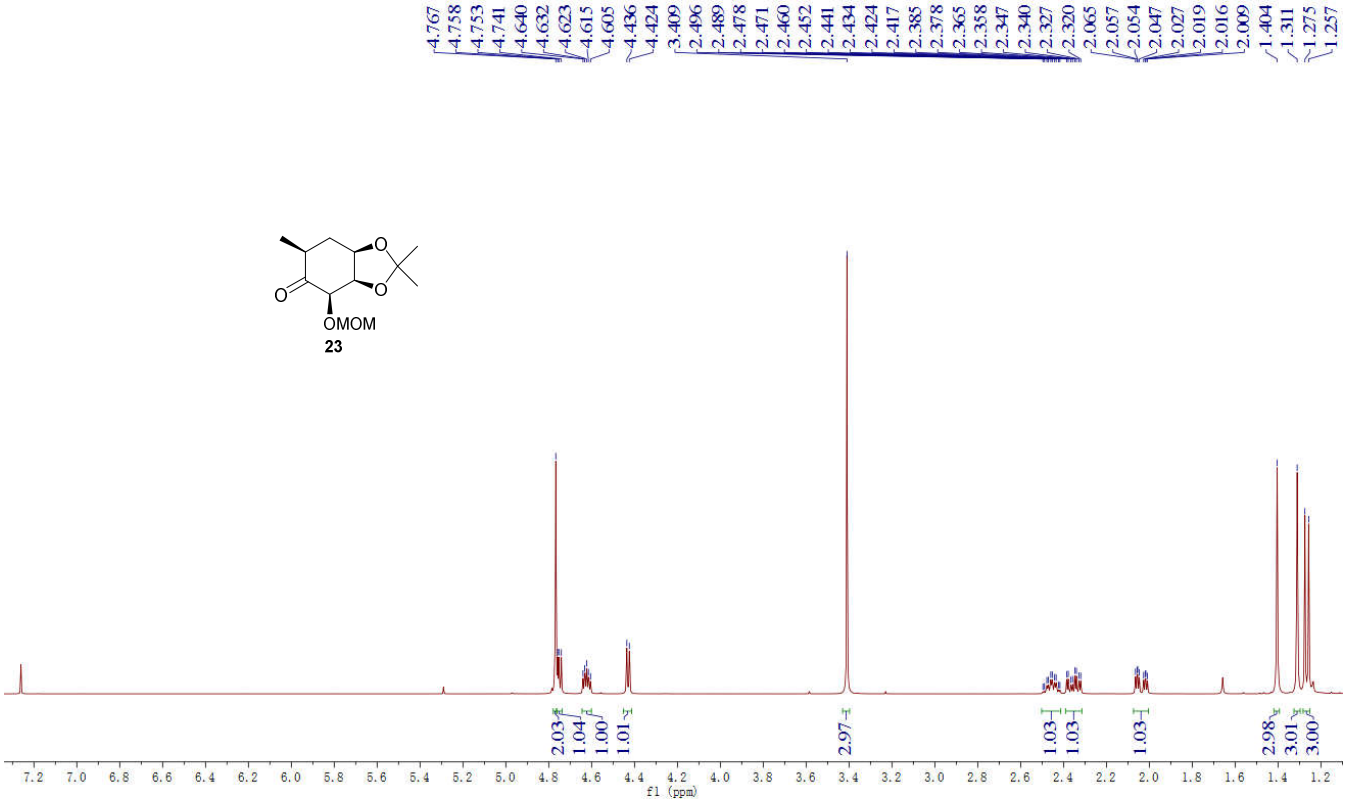


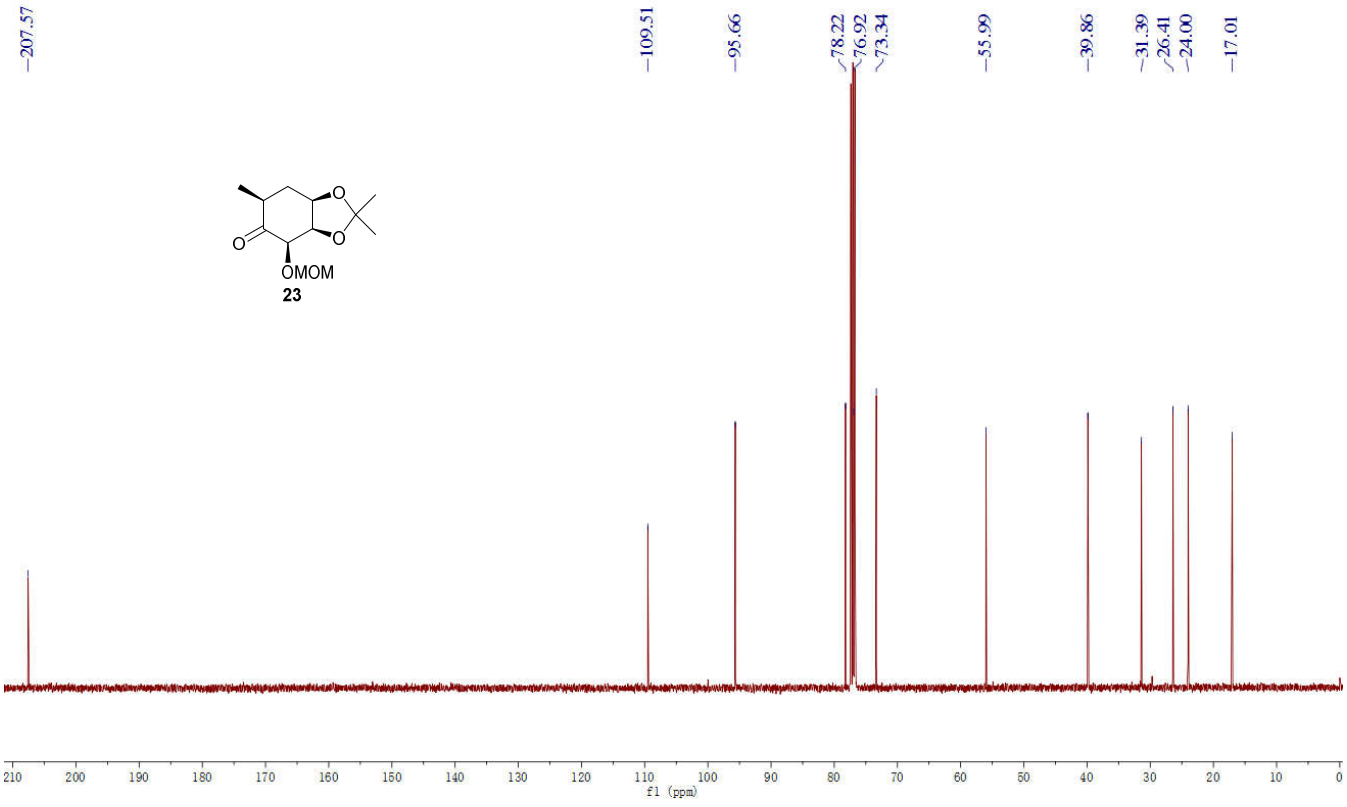
^{1}H NMR (400 MHz, C_2D_6SO/TMS) and ^{13}C NMR (100 MHz, C_2D_6SO) of **(–)-Gabosine N**



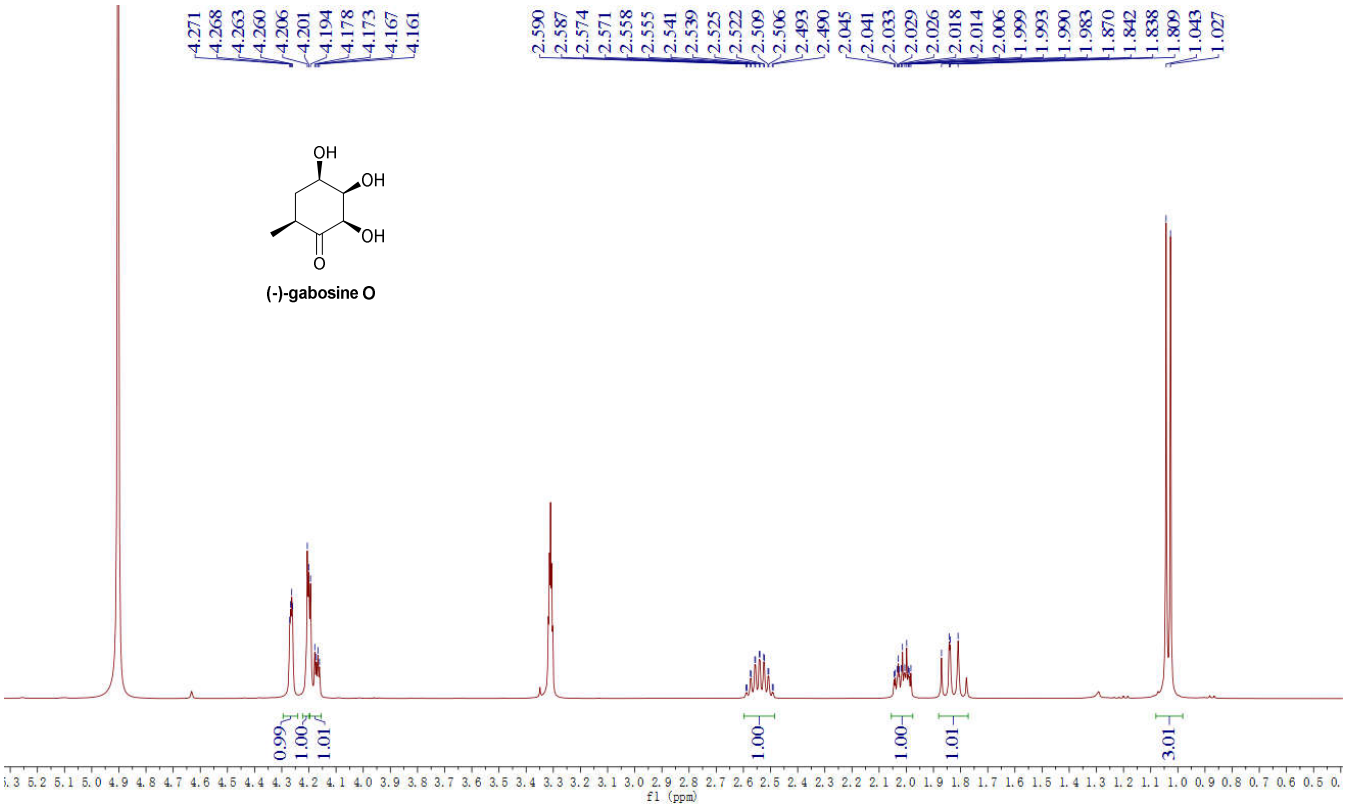


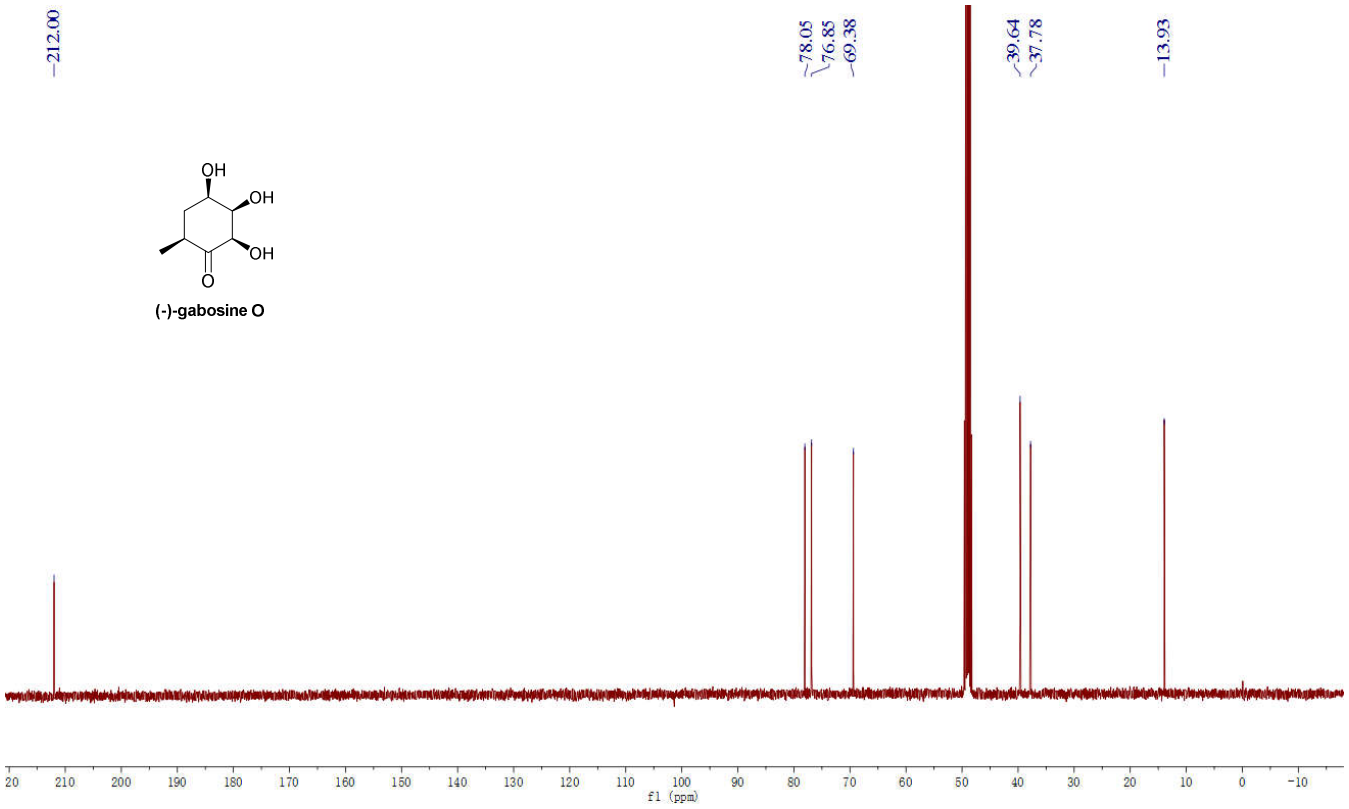
^{1}H NMR (400 MHz, $CDCl_3$/TMS) and ^{13}C NMR (100 MHz, $CDCl_3$) of compound **23**



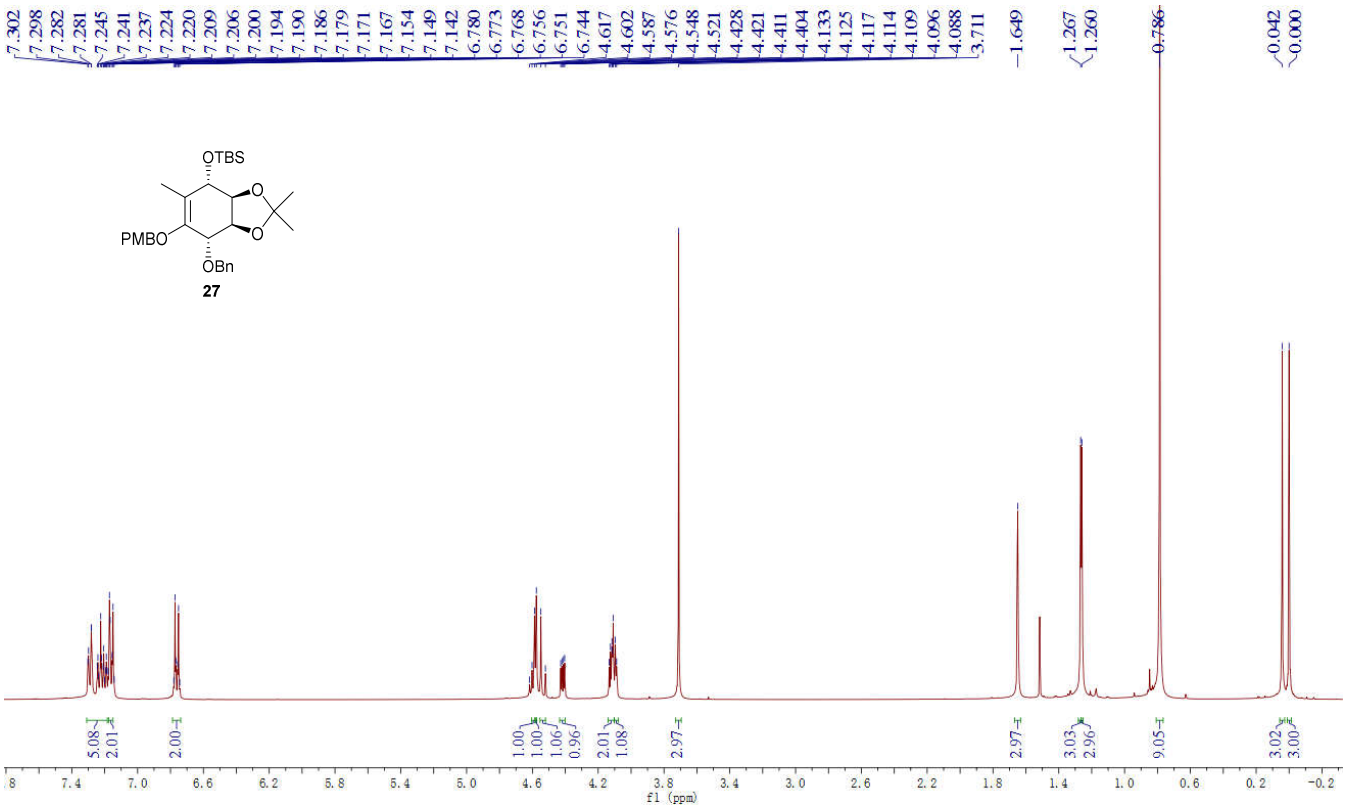


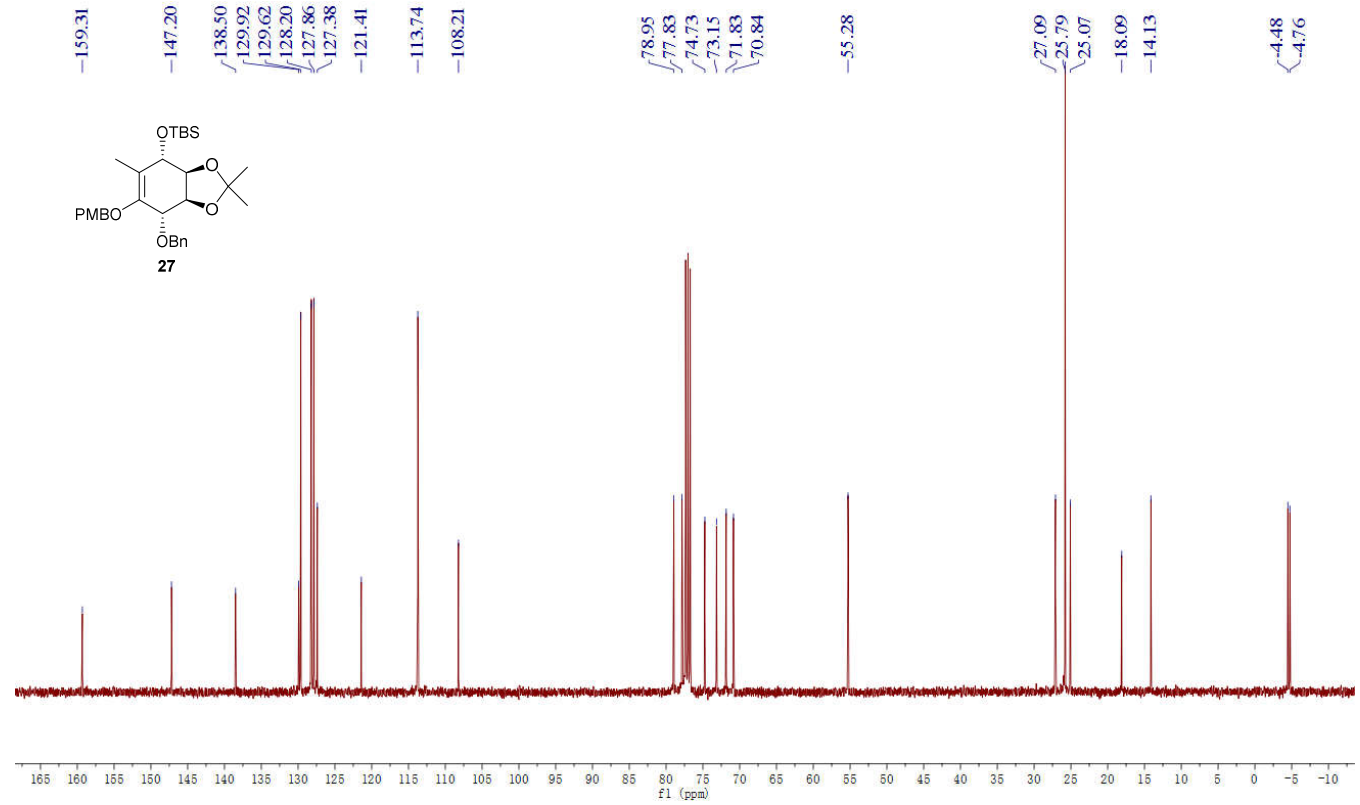
^{1}H NMR (400 MHz, CD_3OD/TMS) and ^{13}C NMR (100 MHz, CD_3OD) of **(–)-Gabosine O**



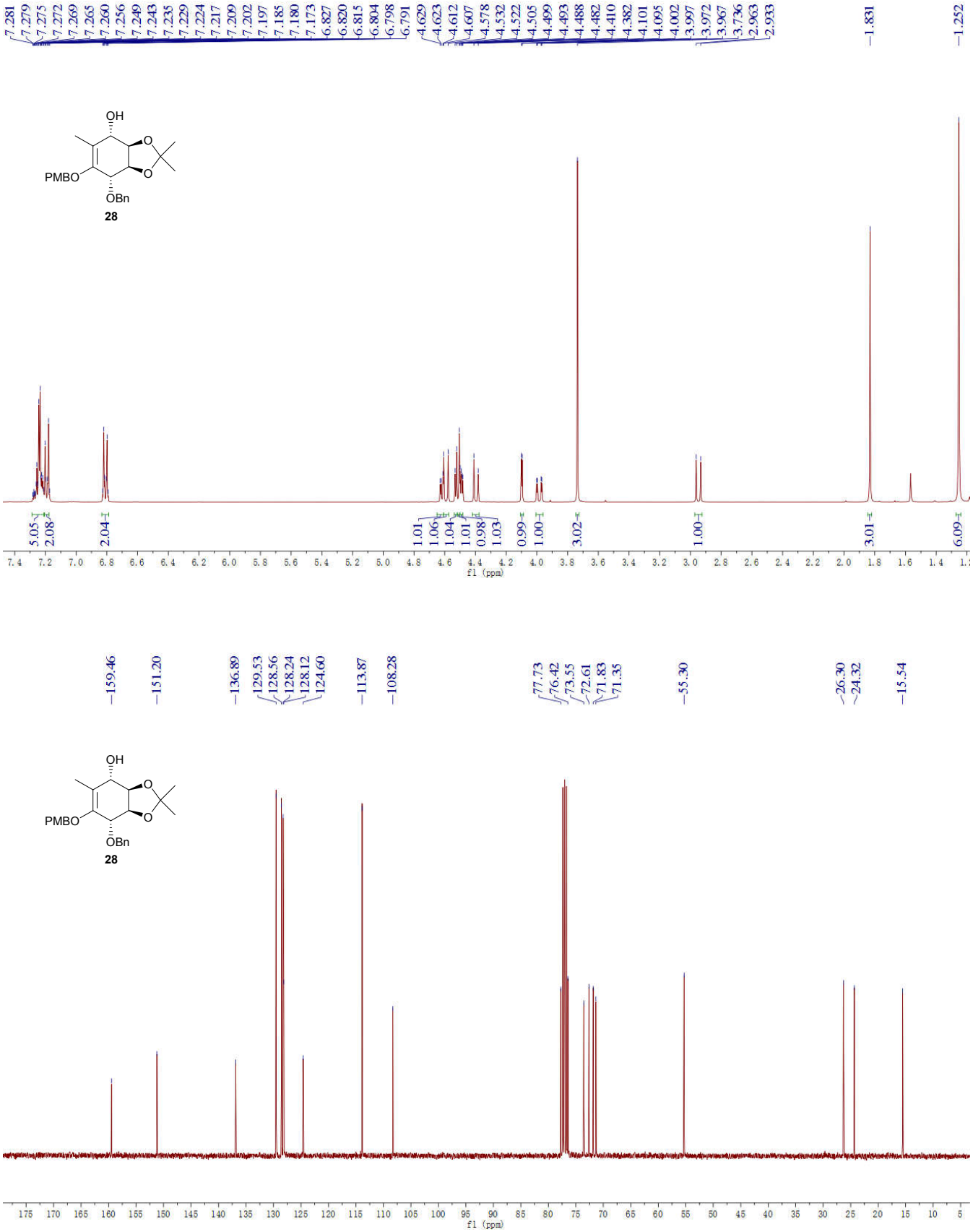


^{1}H NMR (400 MHz, $CDCl_3$/TMS) and ^{13}C NMR (100 MHz, $CDCl_3$) of compound **27**

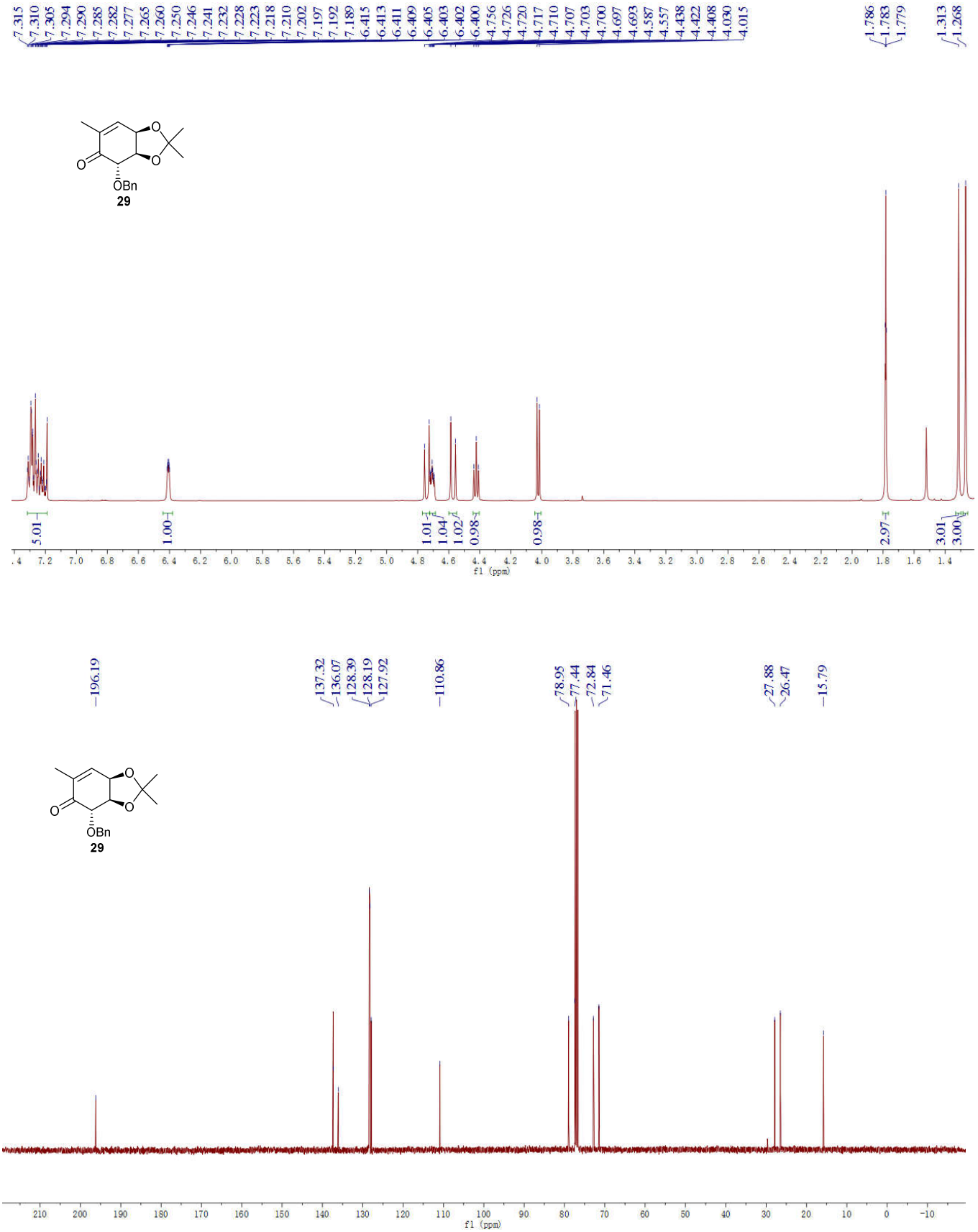




^{1}H NMR (400 MHz, $CDCl_3$/TMS) and ^{13}C NMR (100 MHz, $CDCl_3$) of compound **28**



^{1}H NMR (400 MHz, $CDCl_3$/TMS) and ^{13}C NMR (100 MHz, $CDCl_3$) of compound **29**



^{1}H NMR (400 MHz, CD_3OD/TMS) and ^{13}C NMR (100 MHz, CD_3OD) of **(–)-Gabosine L**