A Highly Stereocontrolled Total Synthesis of (–)-Neodysiherbaine A

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Supporting Information

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General Experimental. All reactions were performed under argon atmosphere, except for DDQ oxidation of **19** and $NaIO_4$ oxidation of **28**. All extracts were dried over $MgSO_4$ and concentrated by rotary evaporation below 30 °C at 25 Toor unless otherwise noted. Commercial reagents and solvents were used as supplied with following exceptions. Dichloromethane (CH_2Cl_2), triethylamine (Et_3N), dimethyl sulfoxide (DMSO), *N*,*N*-dimethylformamide (DMF), *N*,*N*-dimethylacetoamide (DMA), *N*,*N*,*N*,*N'*,*N'*,*N'*-hexamethylphosphoramide (HMPA), benzene, acetonitrile (MeCN) were distilled from CaH_2. Methanol (MeOH) was distilled from sodium. Analytical thin-layer chromatography (TLC) was performed using glass-packed silica gel plates (0.2 mm thickness). Column chromatography was performed using silica gel (particle size 100-210 μ). Optical rotations were recorded on a digital polarimeter at ambient temperature. Infrared spectra were measured on a Fourier transform infrared spectrometer. ^{1}H NMR (400 and 500 MHz) and ^{13}C NMR (100 MHz) spectra were measured using $CDCl_3$, CD_3OD, or D_2O as solvent, and chemical shifts are reported as δ values in ppm based on internal $CHCl_3$ (7.26 ppm, ^{1}H; 77.0 ppm, ^{13}C), H_2O (4.65 ppm, ^{1}H), or MeOH (49.9 ppm, ^{13}C). HRMS spectra were taken in EI or FAB mode.

(3a*R*,6*R*,7*R*,7a*R*)-Tetrahydro-(7-(*tert*-butyldimethylsilyl)oxy-2,2-dimethyl-3a*H*-[1,3]dioxolo[4,5-*c*]pyran-6-yl)methanol (14). To a stirred solution of tri-*O*-acetyl-D-glucal (**9**) (71 g, 261 mmol) in CH_2Cl_2 (600 ml) at 0 °C were added triethylsilane (73 g, 522 mmol) and $BF_3{\cdot}OEt_2$ (54 g, 470 mmol). After stirring at 0 °C for 2 h, the reaction was quenched with saturated $NaHCO_3$ (300 ml). The reaction mixture was extracted with $CHCl_3$, washed with brine and concentrated to give ((2*R*,3*S*)-3,6-dihydro-3-acetoxy-2*H*-pyran-2-yl)methyl acetate (60 g) as a colorless oil, which was used for the next reaction without purification.

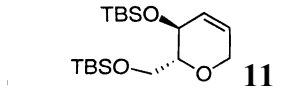
Crude ((2*R*,3*S*)-3,6-dihydro-3-acetoxy-2*H*-pyran-2-yl)methyl acetate (60 g) was dissolved into MeOH (300ml) and NaOMe (4.2g, 78.3 mmol) was added. After being stirred for 2 h at room temperature, the reaction mixture was neutralized with Dowex 50, filtrated, and evaporated to give **10** (40 g) as a colorless solid, which was used for the next reaction without purification.

Crude **10** (40 g) was dissolved into DMF (300 ml), and the mixture was cooled to 0 °C. Imidazole (106 g, 1570 mmol) and *tert*-butyldimethylsilyl chloride (100g, 666 mmol) were added and the mixture was stirred at room temperature for 10 h. MeOH (20 ml) was added and the mixture was stirred for 10 mim. The reaction mixture was diluted with Et_2O, washed with water and brine, and concentrated to give **11** (96 g) as a pale yellow oil, which was used for the next reaction without purification. Pure **11**, a colorless oil, obtained by silica gel column chromatography (hexane/AcOEt = 10/1-4/1) showed the following spectral and analytical data: $[\alpha]^{25}_D$ +53.7° (*c* 1.20, $CHCl_3$); FTIR (neat) 2939, 2858, 1462, 1251, 1089 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.76 (dd, *J* = 2.0, 10.4 Hz, 1H), 5.70 (d, *J* = 10.4 Hz, 1H), 4.15 (m, 3H), 3.89 (dd, *J* = 2.0, 11.2 Hz, 1H), 3.72 (dd, *J* = 4.4, 11.2 Hz, 1H), 3.29 (t, *J* = 5.6 Hz, 1H), 0.91 (s, 9H), 0.90 (s, 9H), 0.10 (s, 3H), 0.10 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 129.3, 127.0, 79.9, 65.5, 64.9, 63.4, 26.1, 25.8, 18.6, 18.0, –4.1, –4.7, –5.0, –5.1; HRMS (EI) calcd for $C_{18}H_{38}O_3Si_2$ (M^+) 358.2360, found 358.2347.

Crude **11** (96 g) was dissolved into acetone (522 ml) and water (130 ml). *N*-methylmolpholine oxide (NMO) (61 g, 522 mmol) and OsO_4 (1.5 M in water, 8.7 ml, 1.35 mmol) were added, and the mixture was stirred for 15 h. The reaction mixture was diluted with Et_2O, washed with 10% $Na_2S_2O_3$, water, and brine, dried, concentrated, and filtrated thorough SiO_2 (500 g) with hexane/EtOAc (3:1) to give **12** (90 g) as a pale yellow solid, which was used for the next reaction without purification. Pure **12**, a colorless solid, obtained by silica gel column chromatography (hexane/AcOEt = 4/1-2/1) showed the following spectral and analytical data: $[\alpha]^{24}_D$ +2.8° (*c* 1.34, $CHCl_3$); FTIR (neat) 3428, 2942, 2859, 1463,

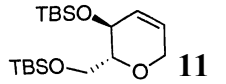
1251, 1103 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.00 (dd, *J* = 2.2, 12.4 Hz, 1H), 3.86 (dd, *J* = 2.0, 11.2 Hz, 1H), 3.86 (m, 1H), 3.75 (dd, *J* = 4.9, 11.2 Hz, 1H), 3.67 (t, *J* = 9.0 Hz, 1H), 3.52 (dd, *J* = 1.0, 12.4 Hz, 1H), 3.47 (td, *J* = 9.0, 3.5 Hz, 1H), 3.10 (ddd, *J* = 2.0, 4.9, 9.0 Hz, 1H), 2.38 (d, *J* = 9.0 Hz, 1H, exchangeable with D_2O), 2.19 (d, *J* = 7.1 Hz, 1H, exchangeable with D_2O), 0.40 (s, 18H), 0.16 (s, 3H), 0.11 (s, 3H), 0.08 (s, 3H), 0.07 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 81.8, 75.3, 69.9, 69.8, 62.8, 26.0, 18.5, 18.3, –3.9, –4.8, –5.0, –5.2; HRMS (EI) calcd for $C_{17}H_{37}O_5Si_2$ [$(M\text{-}Me)^+$] 377.2180, found 377.2173.

To an ice-cooled solution of crude **12** (90 g) in CH_2Cl_2 (500 ml) were added 2,2-dimetoxypropane (72 g, 690 mmol) and *p*-toluenesulfonic acid monohydrate (2.2 g, 11.5 mmol), and the mixture was stirred at 0 °C for 4 h. After disappearance of **12** on TLC, MeOH (11g, 345 mmol) was added and stirring was continued at room temperature for 10 h. The reaction mixture was diluted with Et_2O, washed with saturated $NaHCO_3$ and brine, and concentrated. Recrystallization of the residue from hexane and column chromatography (SiO_2 400g, hexane/AcOEt = 8/1) of the mother liqor gave **14** (45.0 g, 54 % from **9**): $[\alpha]^{25}_D$ –40.9° (*c* 1.92, $CHCl_3$); FTIR (neat) 3460, 2943, 2860, 1458, 1378, 1315, 1249, 1134 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.25 (d, *J* = 13.4 Hz, 1H), 4.17 (dd, *J* = 6.2, 2.0 Hz, 1 H), 3.96 (t, *J* = 6.2 Hz 1H), 3.84 (dd, *J* = 2.9, 11.7 Hz, 1H), 3.73 (dd, *J* = 2.2, 13.4 Hz, 1H), 3.61 (dd, *J* = 6.36, 11.7 Hz, 1H), 3.59 (dd, *J* = 6.2, 9.5 Hz), 3.11 (ddd, *J* = 3.0, 6.4, 9.3 Hz, 1H), 2.08 (brs, 1H), 1.52 (s, 3H), 1.35 (s, 3H), 0.87 (s, 9H), 0.15 (s, 3H), 0.82 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 109.2, 79.7, 79.5, 74.0, 71.3, 66.6, 62.7, 28.1, 26.4, 25.9, 18.1, –4.0, –5.1; HRMS (FAB) calcd for $C_{15}H_3O_5Si$ [$(M+H)^+$] 319.1941, found 319.1950.



11

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



11

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

129.302
126.975
79.904
77.322
77.000
76.687
65.467
64.048
63.413
26.092
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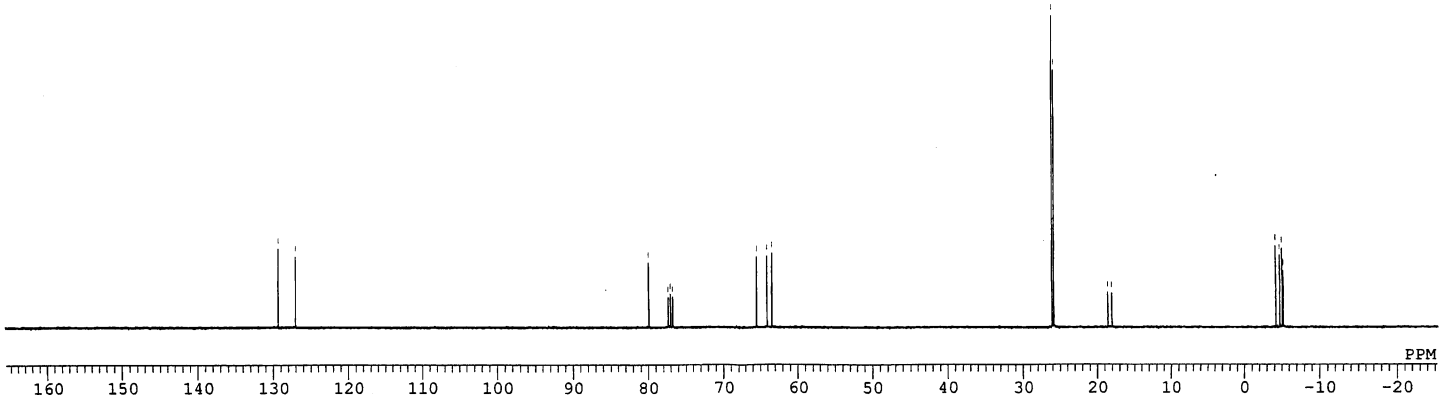
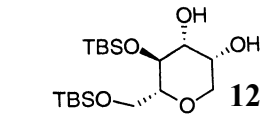
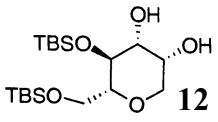
18.049
-4.101
-4.653
-4.975
-5.082





12

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



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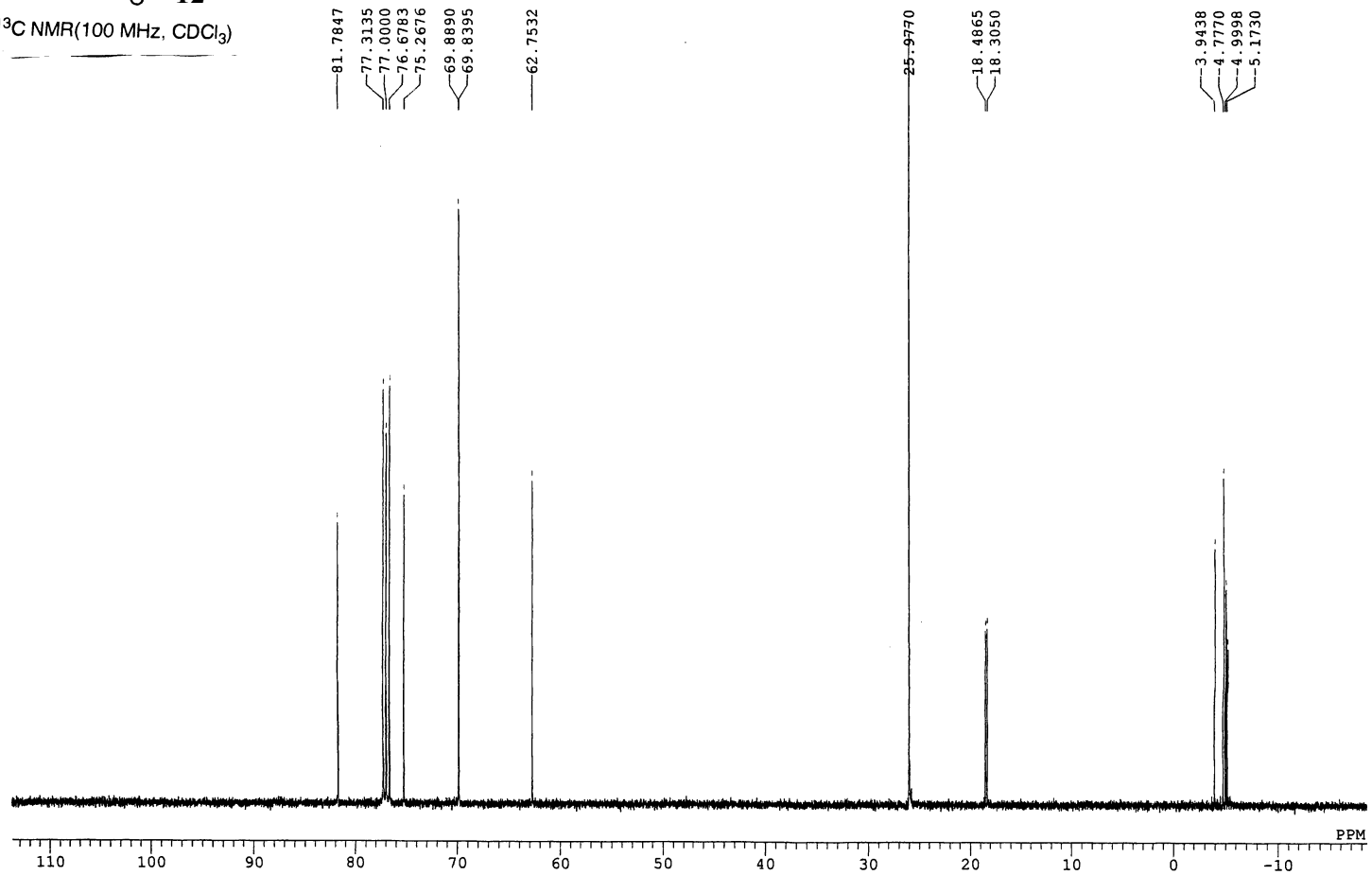
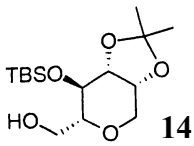
^{13}C NMR(100 MHz, $CDCl_3$)





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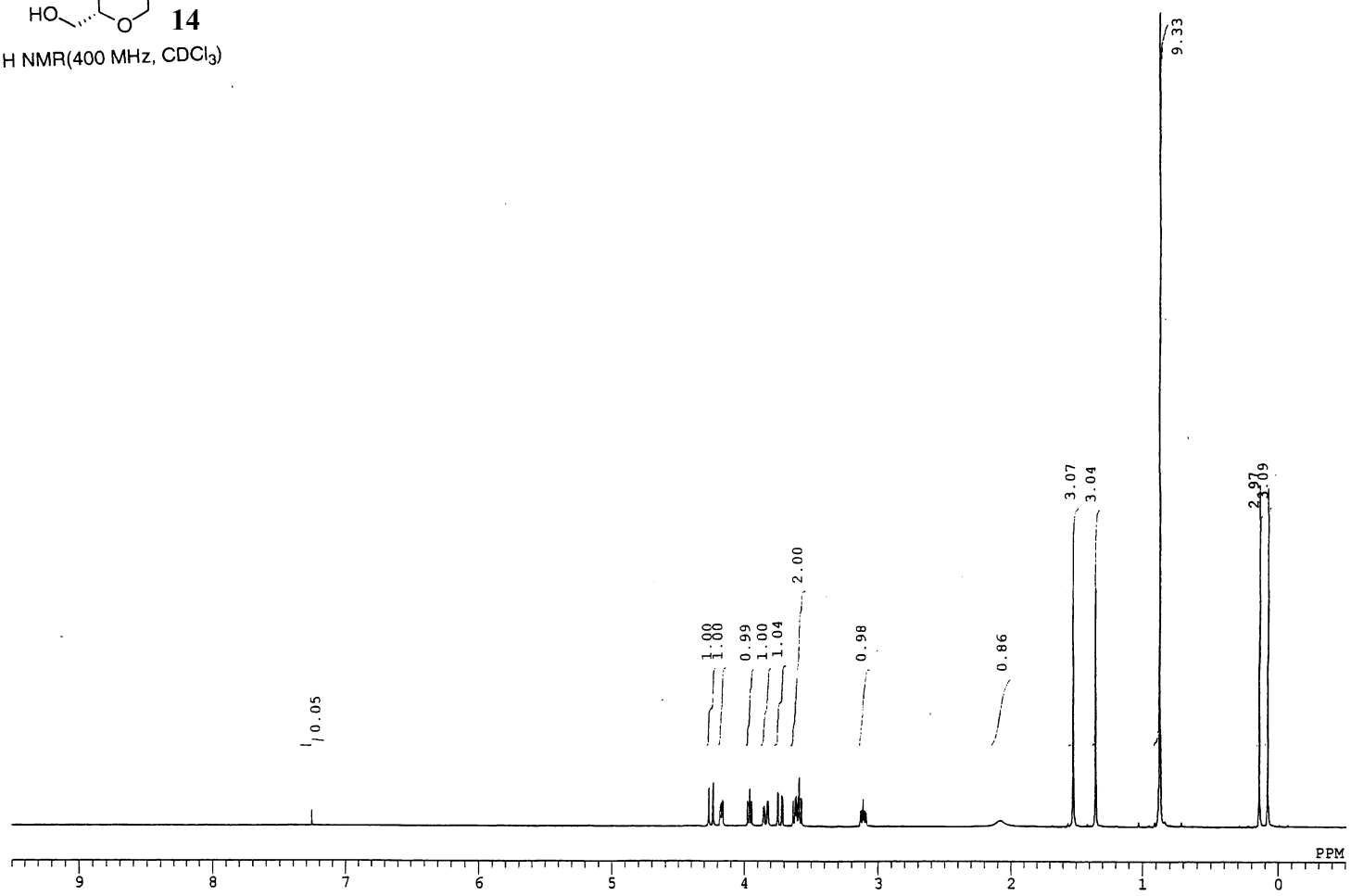
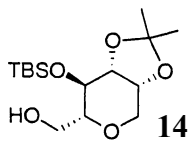
^{1}H NMR(400 MHz, $CDCl_3$)





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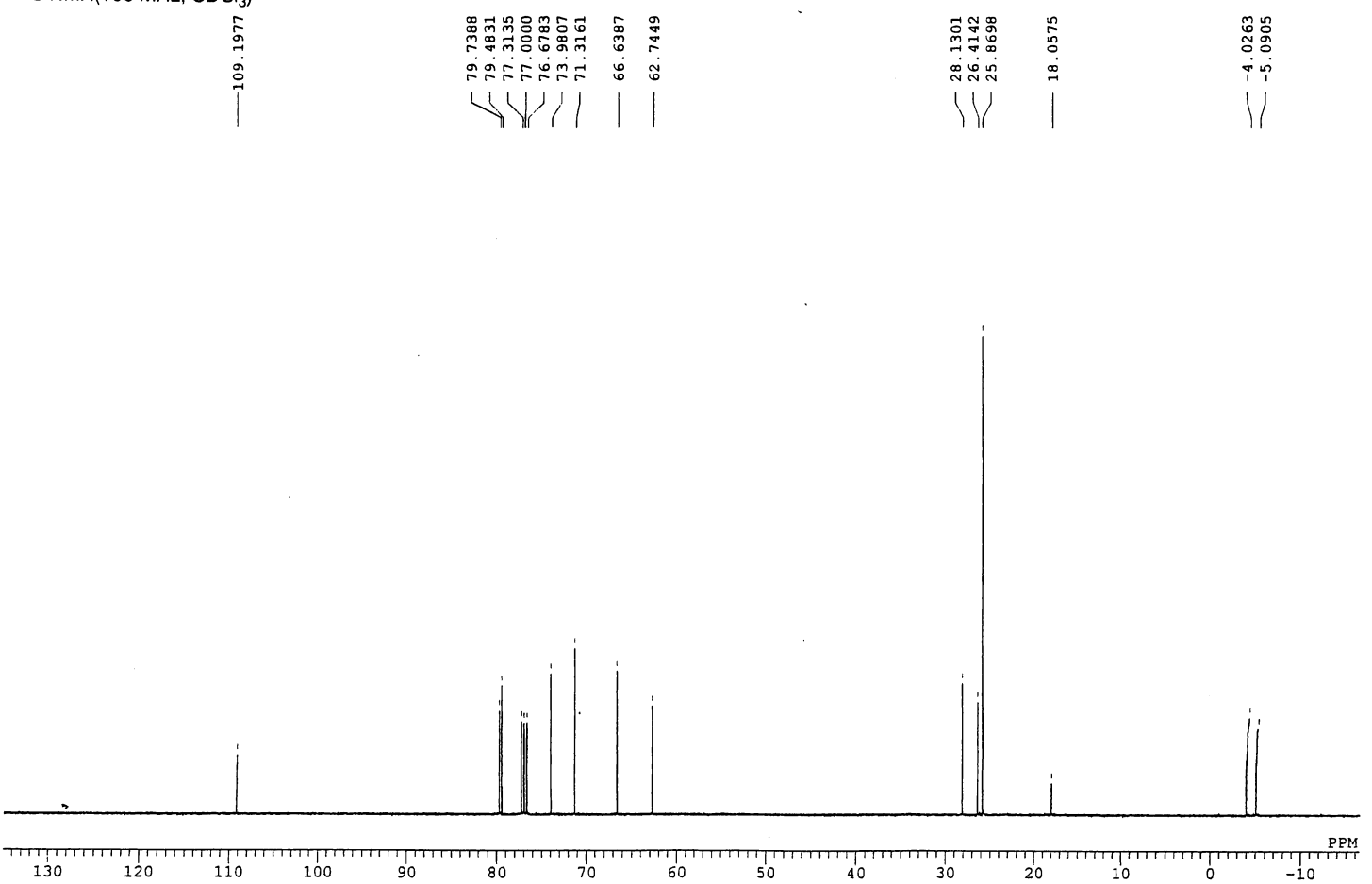

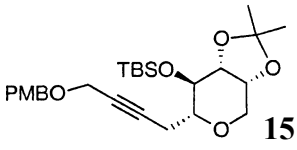

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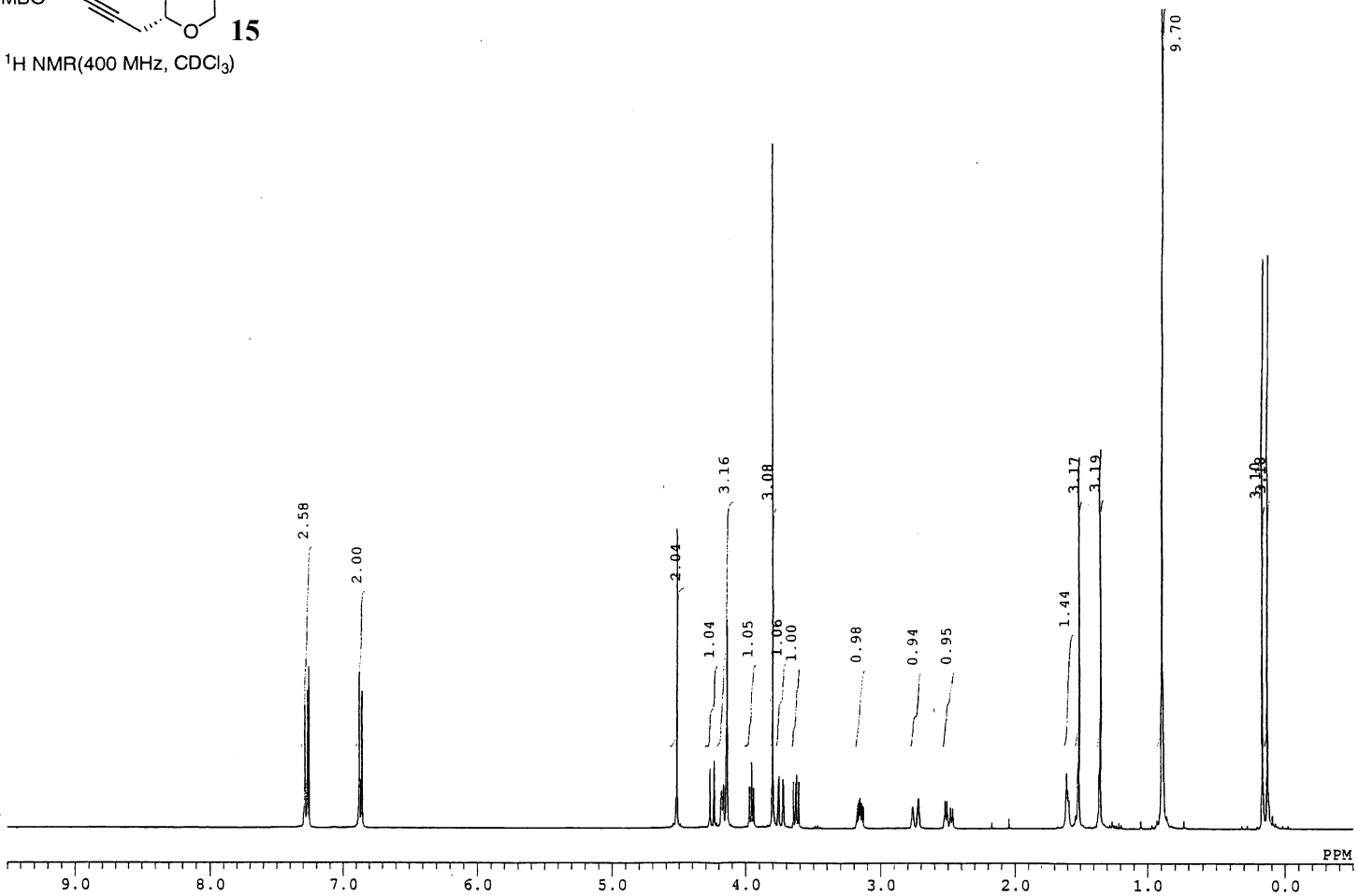

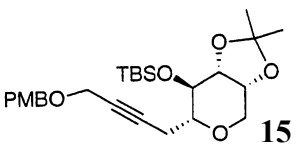

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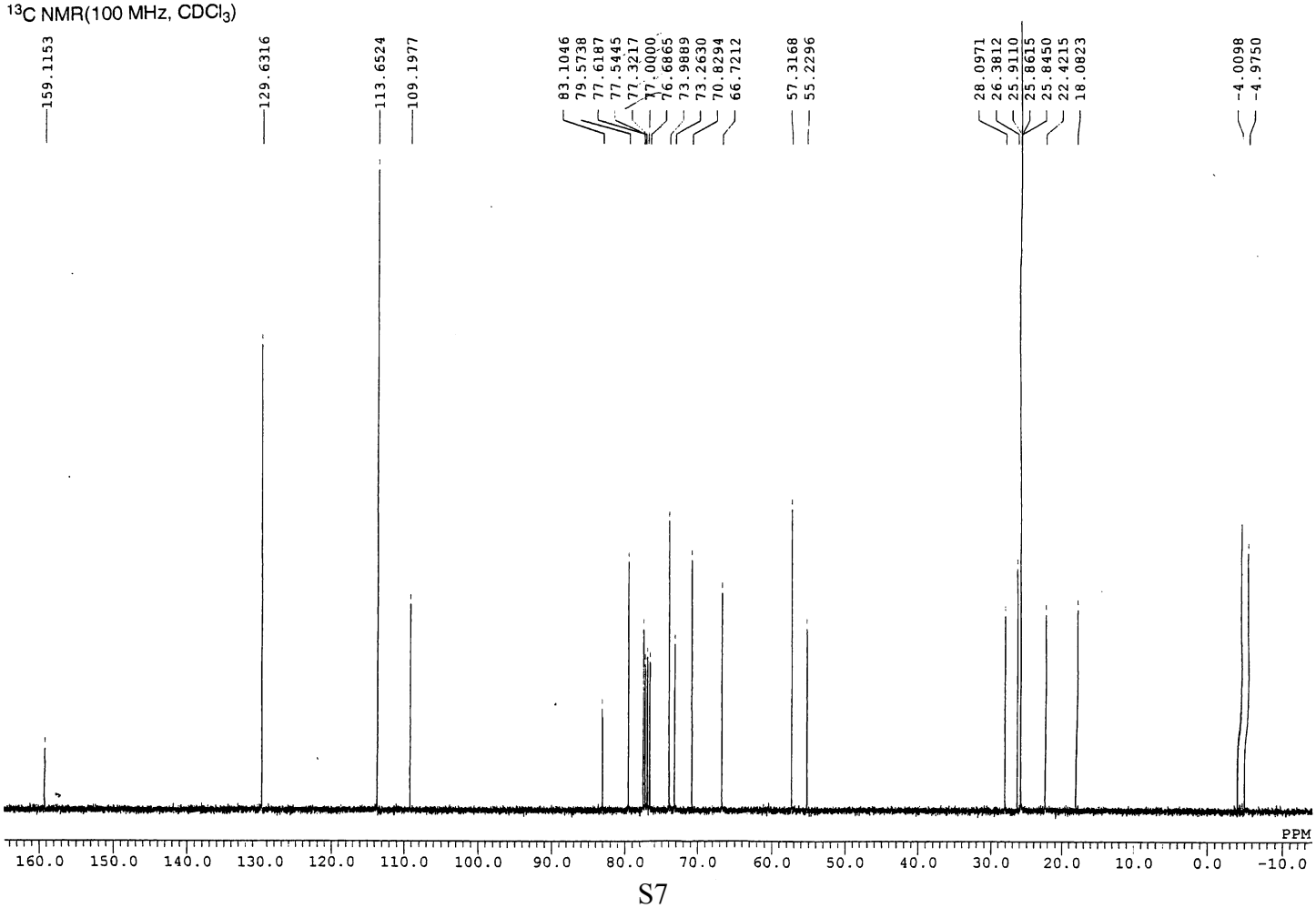
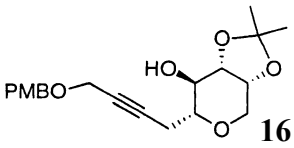
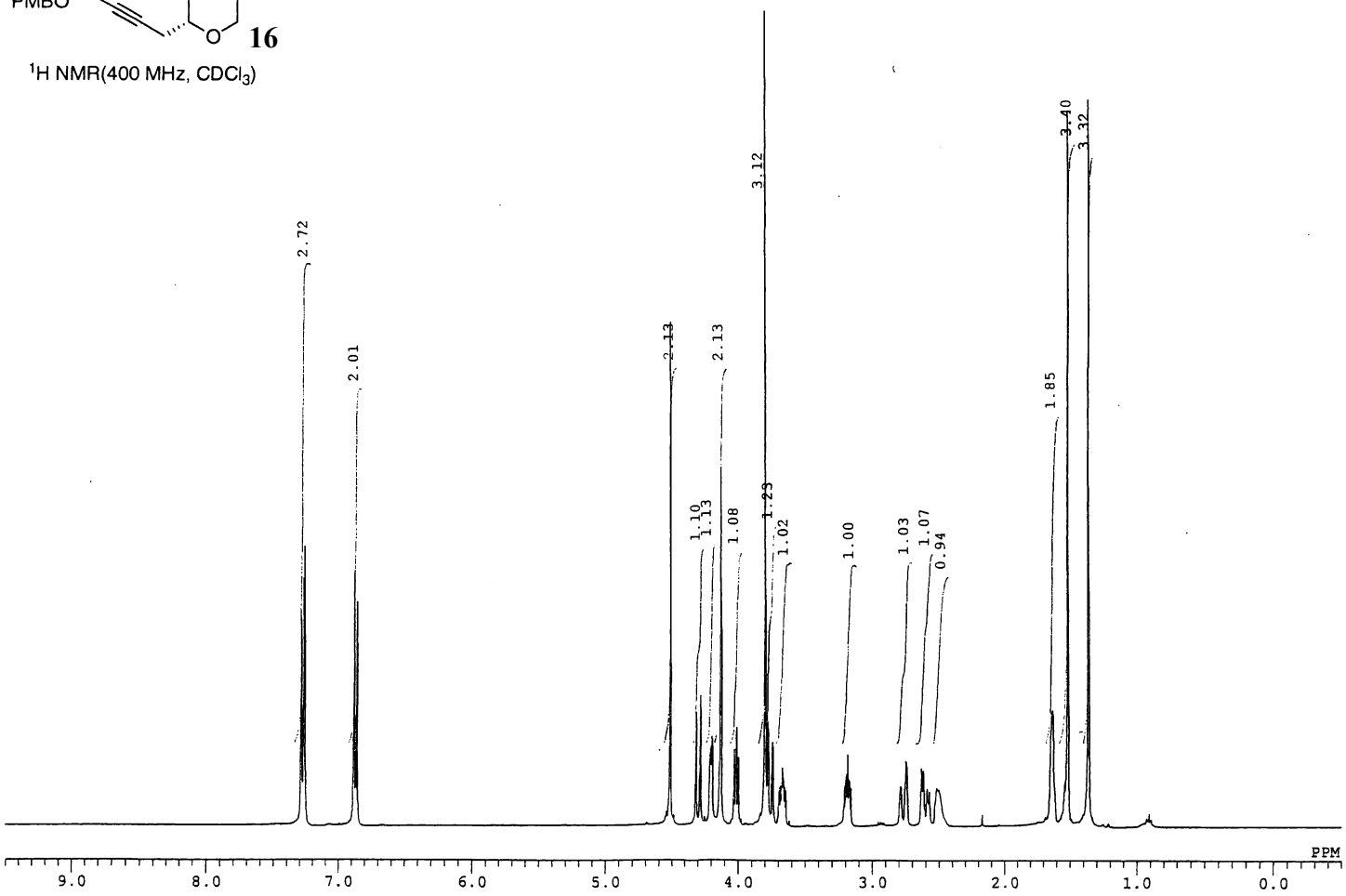
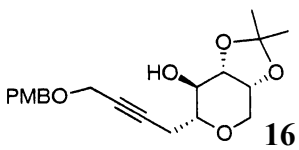




16

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





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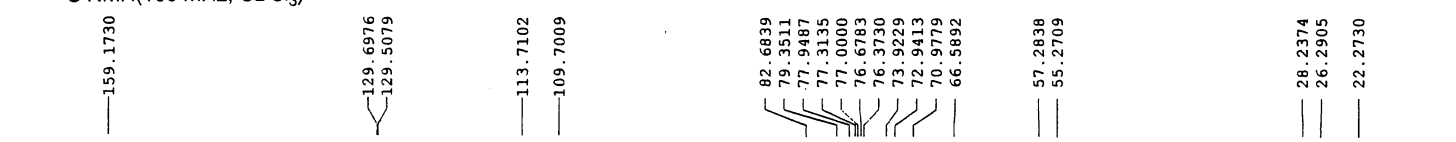
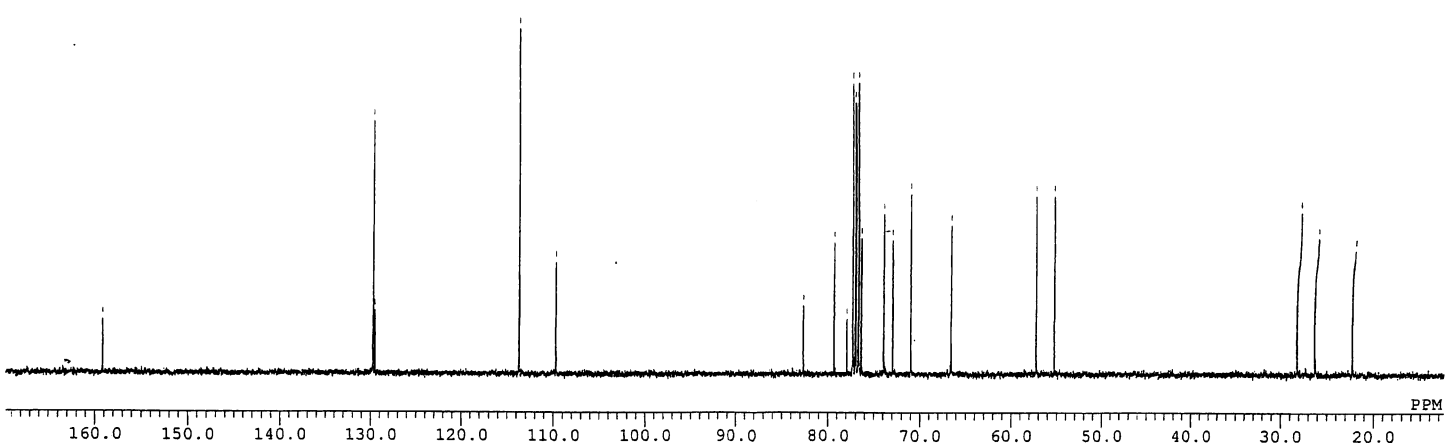
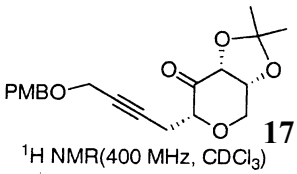
^{13}C NMR(100 MHz, $CDCl_3$)

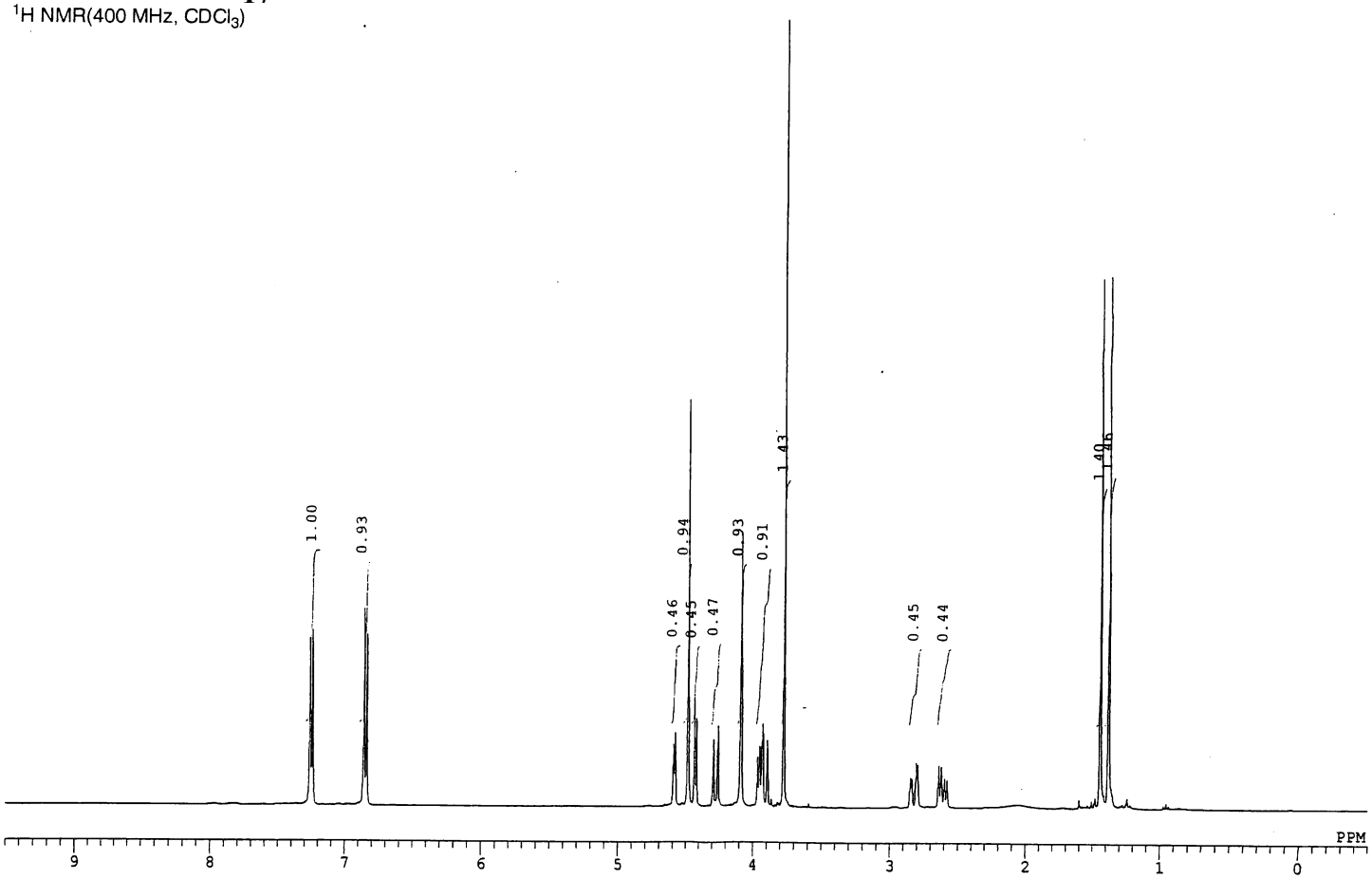


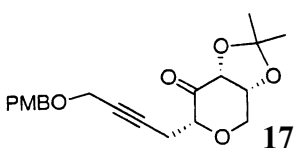




17

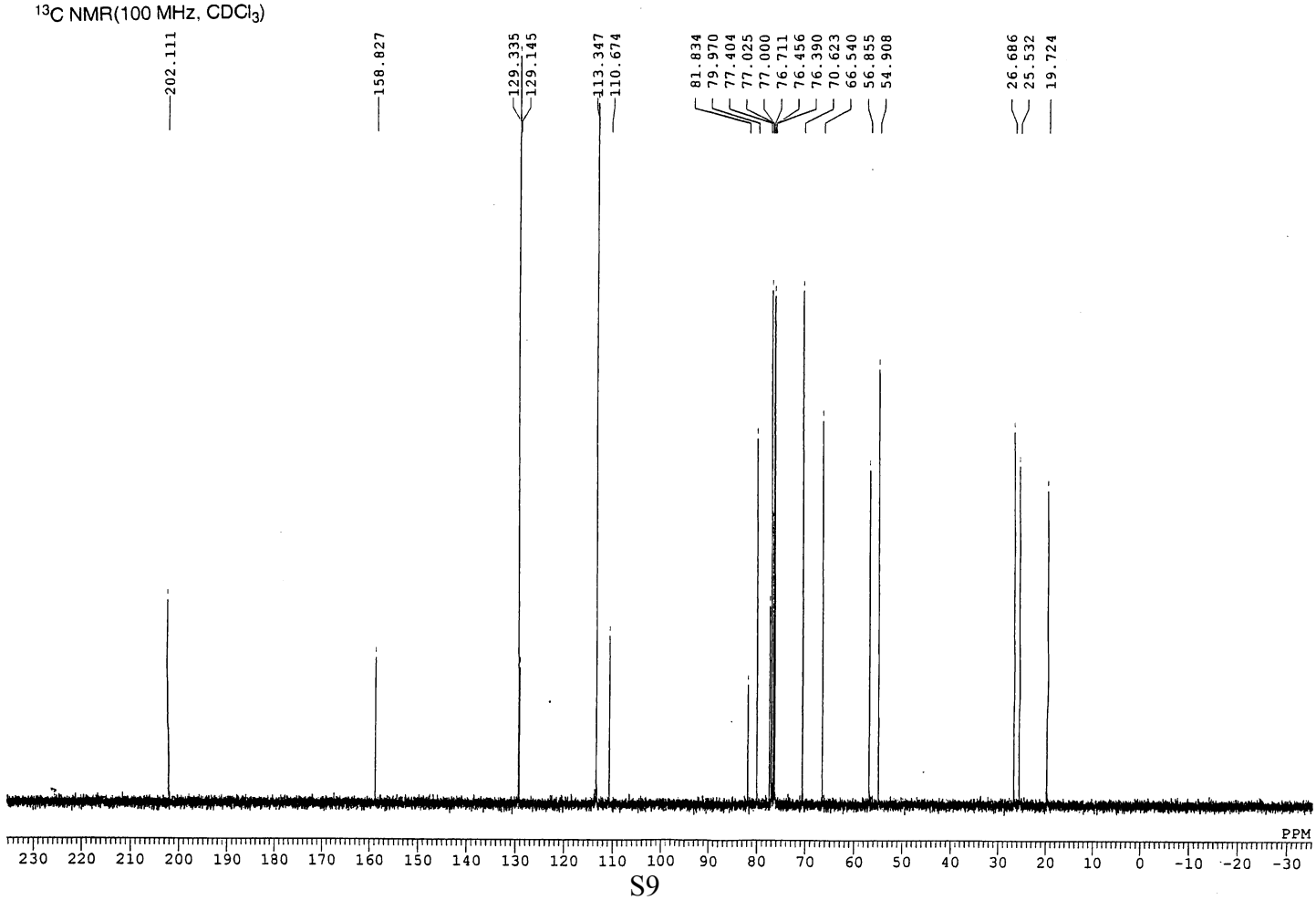
^{1}H NMR(400 MHz, $CDCl_3$)

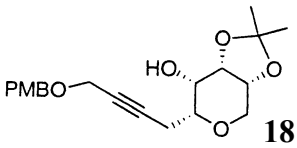




17

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





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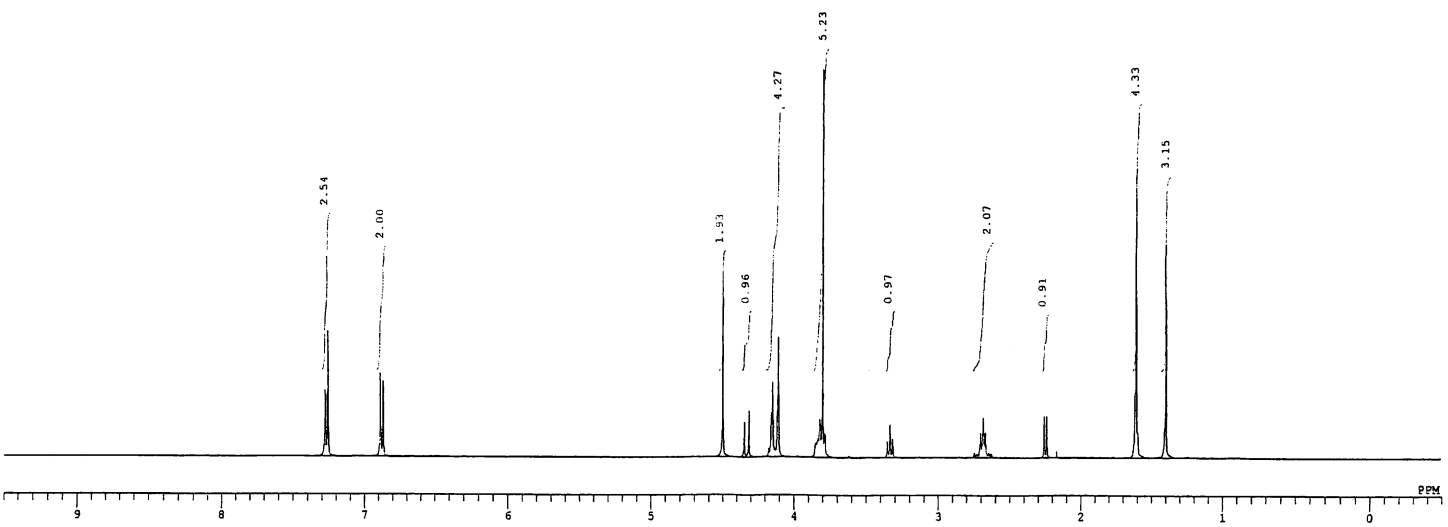
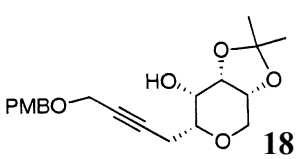
^{1}H NMR(400 MHz, $CDCl_3$)





18

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

159.091
129.516
129.376
113.611
109.189
82.478
77.652
77.322
77.000
76.687
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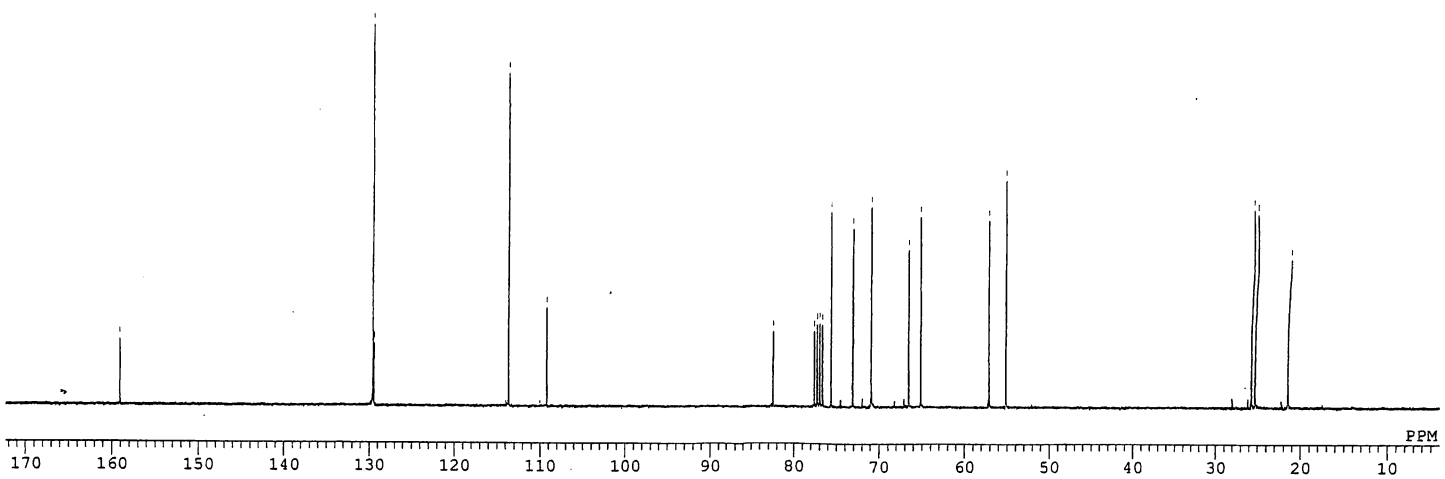
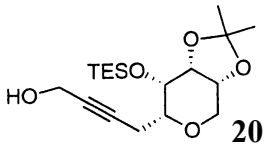
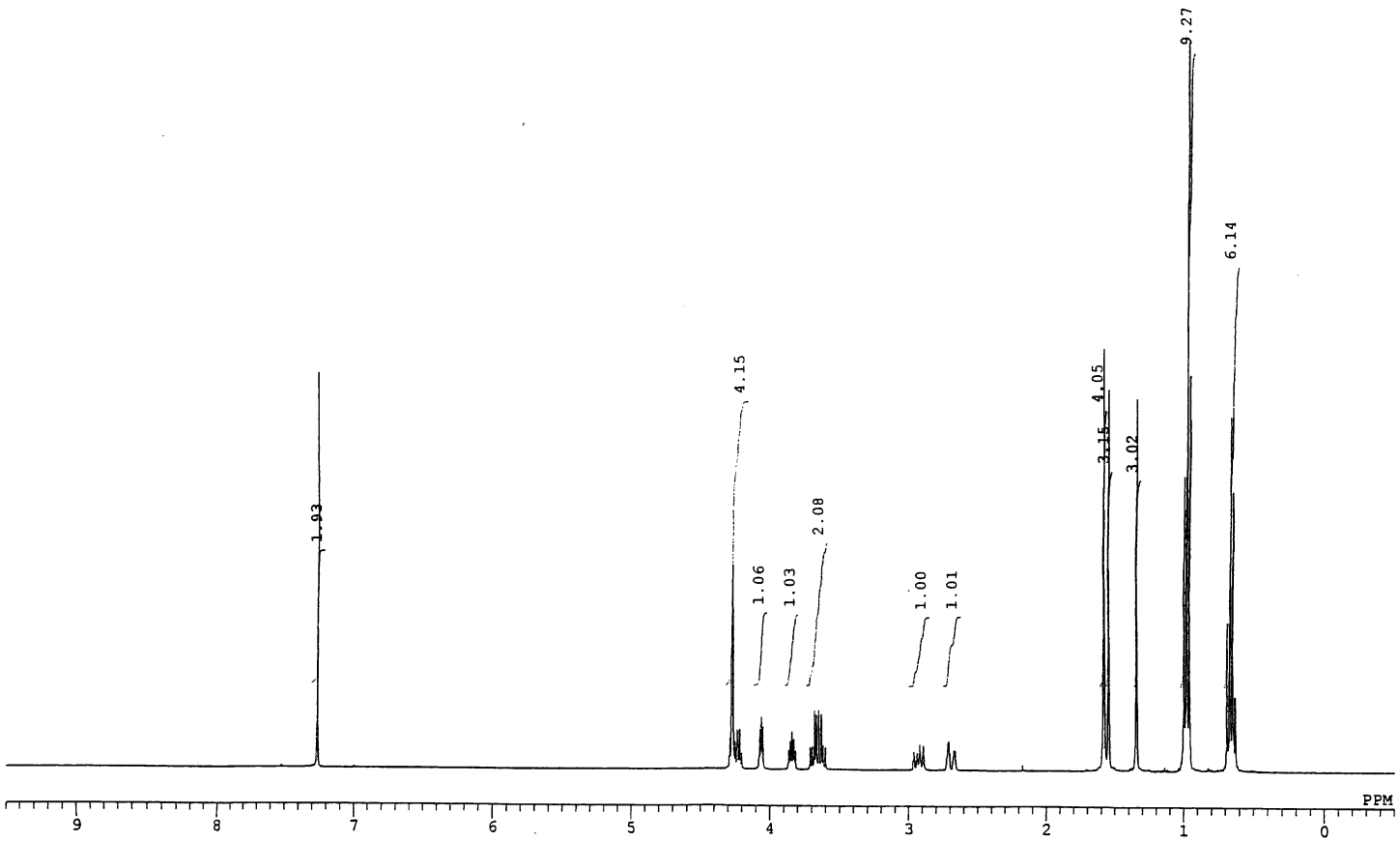
57.152
55.147
25.787
25.325
21.506

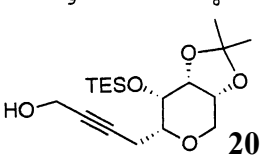




20

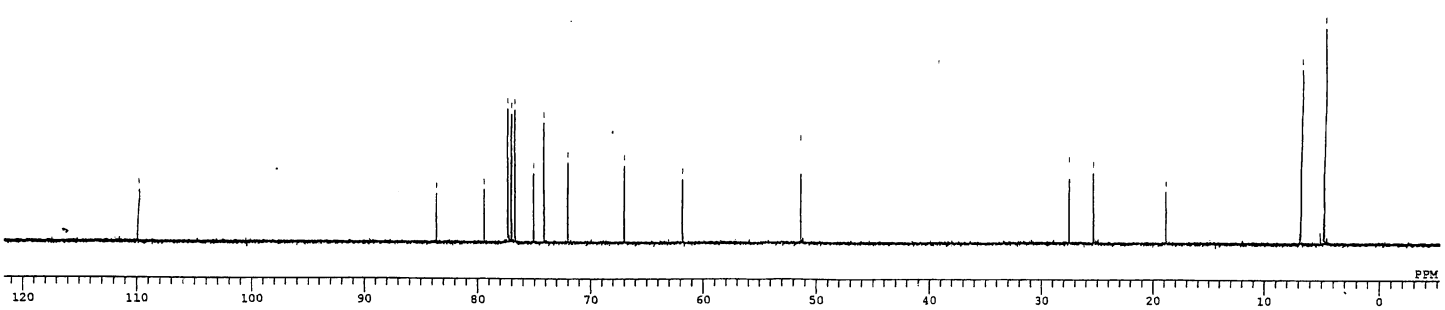
^{1}H NMR(400 MHz, $CDCl_3$)

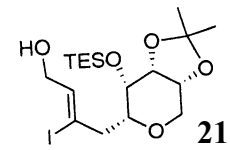




20

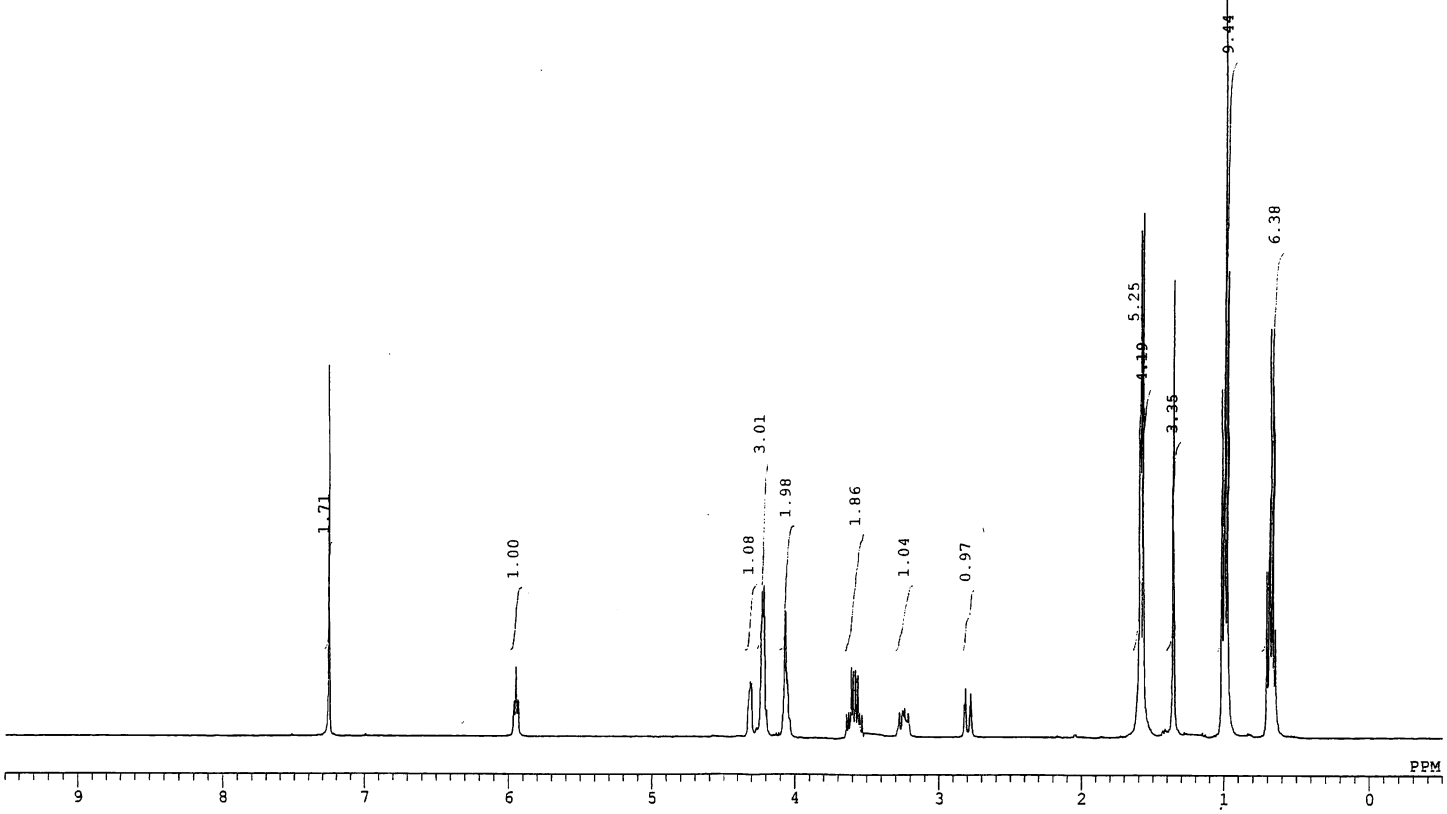
^{13}C NMR(100 MHz, $CDCl_3$)

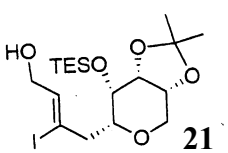




21

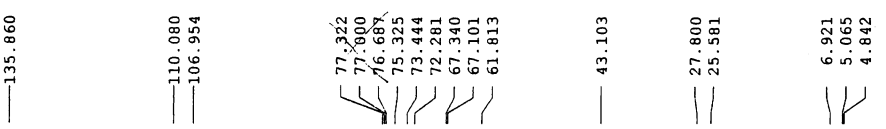
^{1}H NMR(400 MHz, $CDCl_3$)

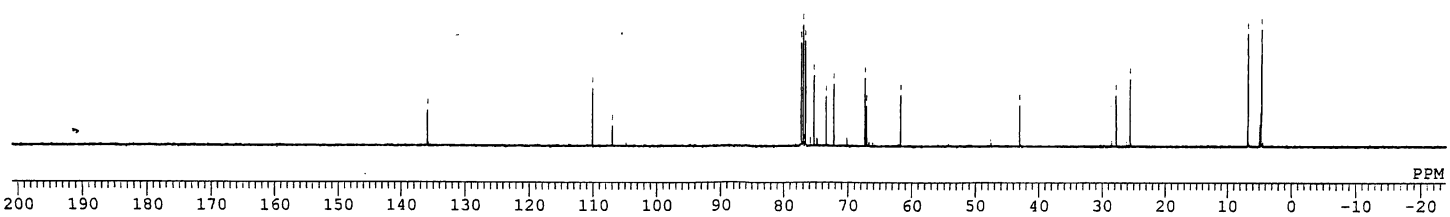


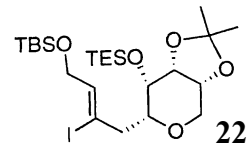


21

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

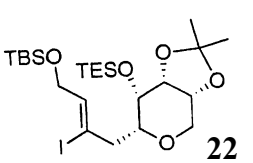






22

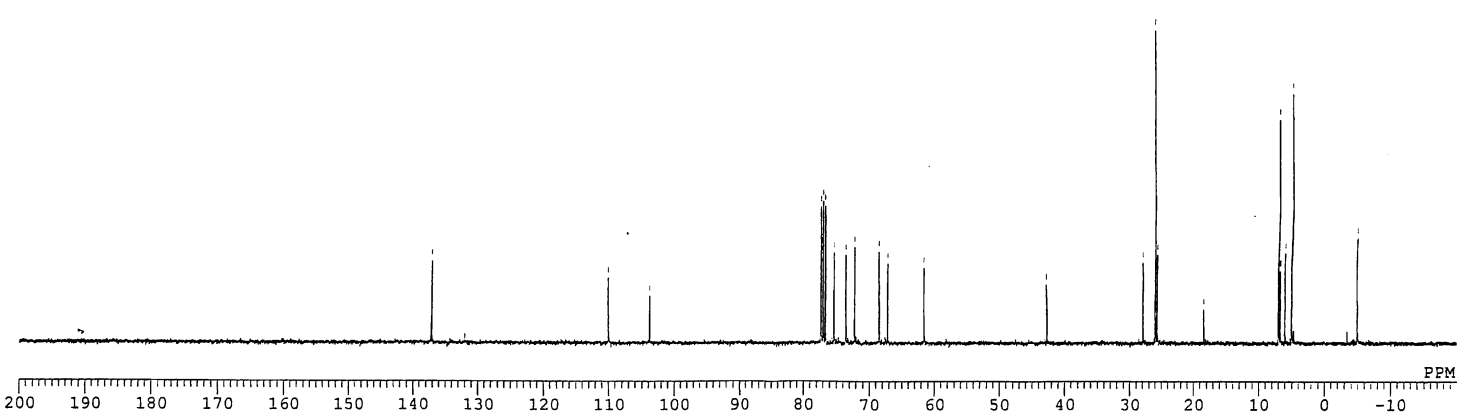
^{1}H NMR(400 MHz, $CDCl_3$)

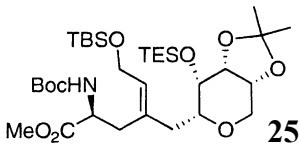


22

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

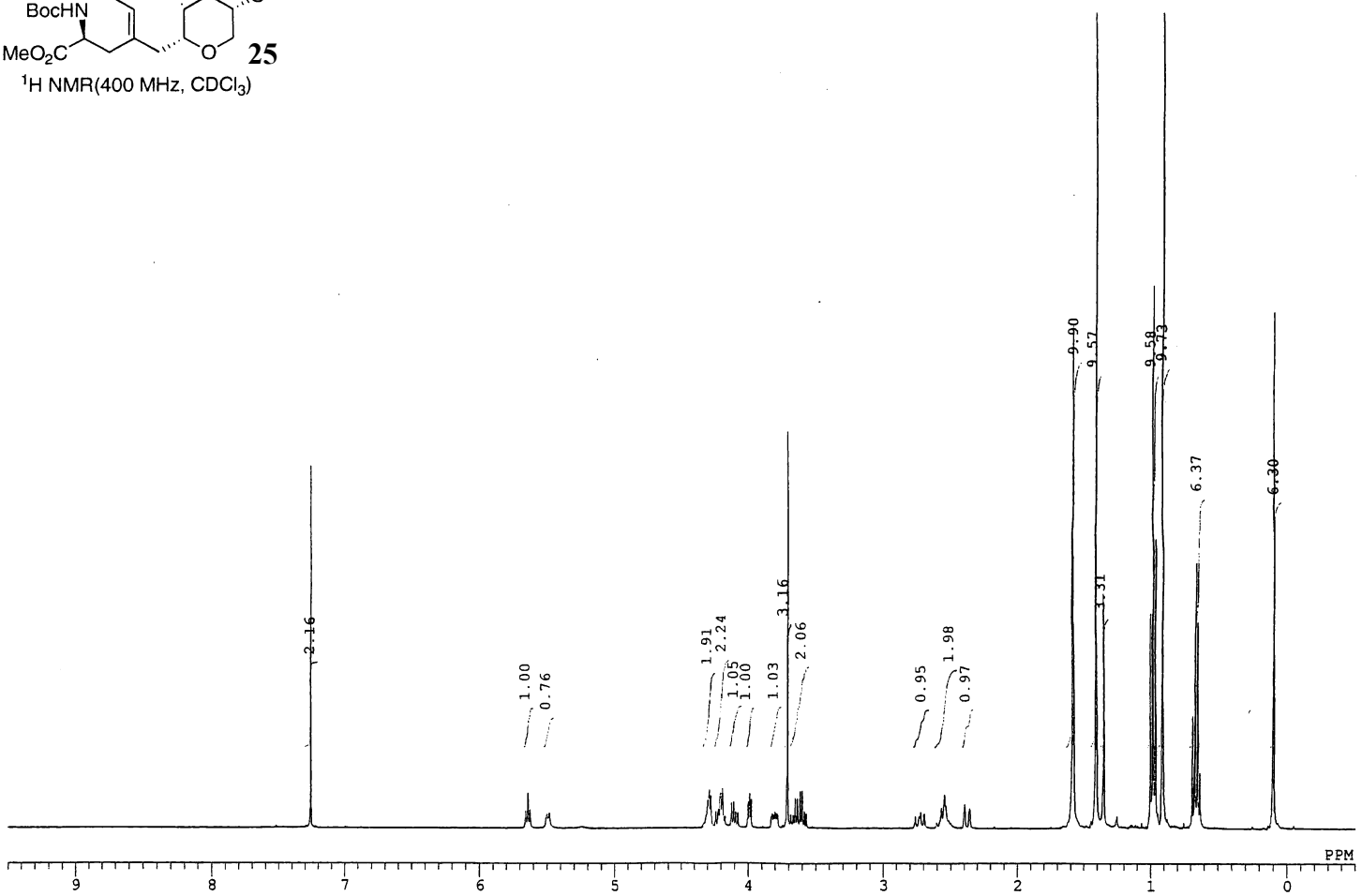
137.015
110.047
103.778
77.322
77.000
76.687
75.408
73.576
72.257
68.528
67.241
61.648
42.756
27.866
25.969
25.919
25.697
25.664
18.346
6.912
6.648
5.898
4.875
-5.008

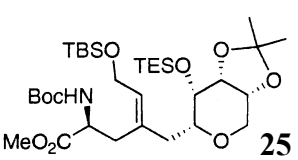




25

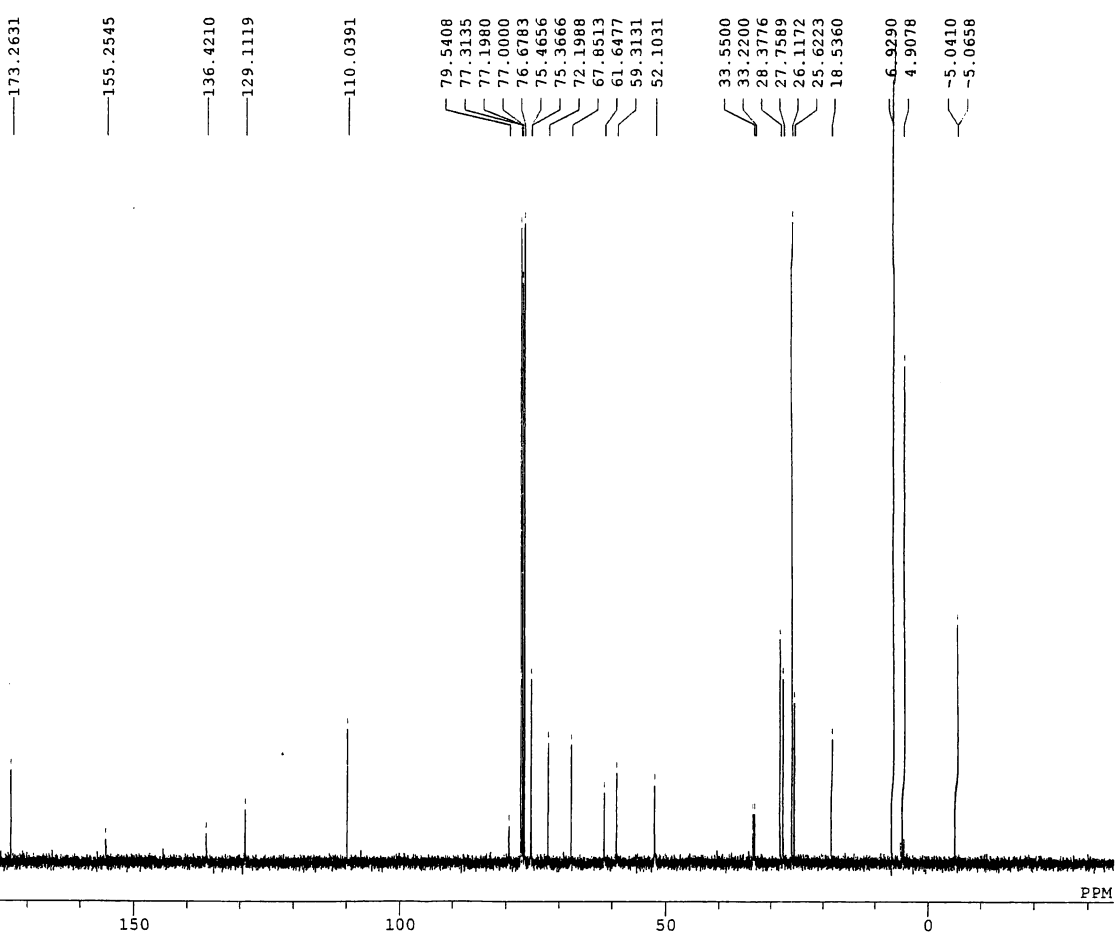
^{1}H NMR(400 MHz, $CDCl_3$)

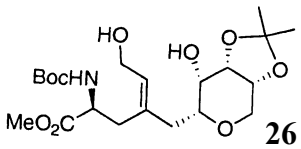




25

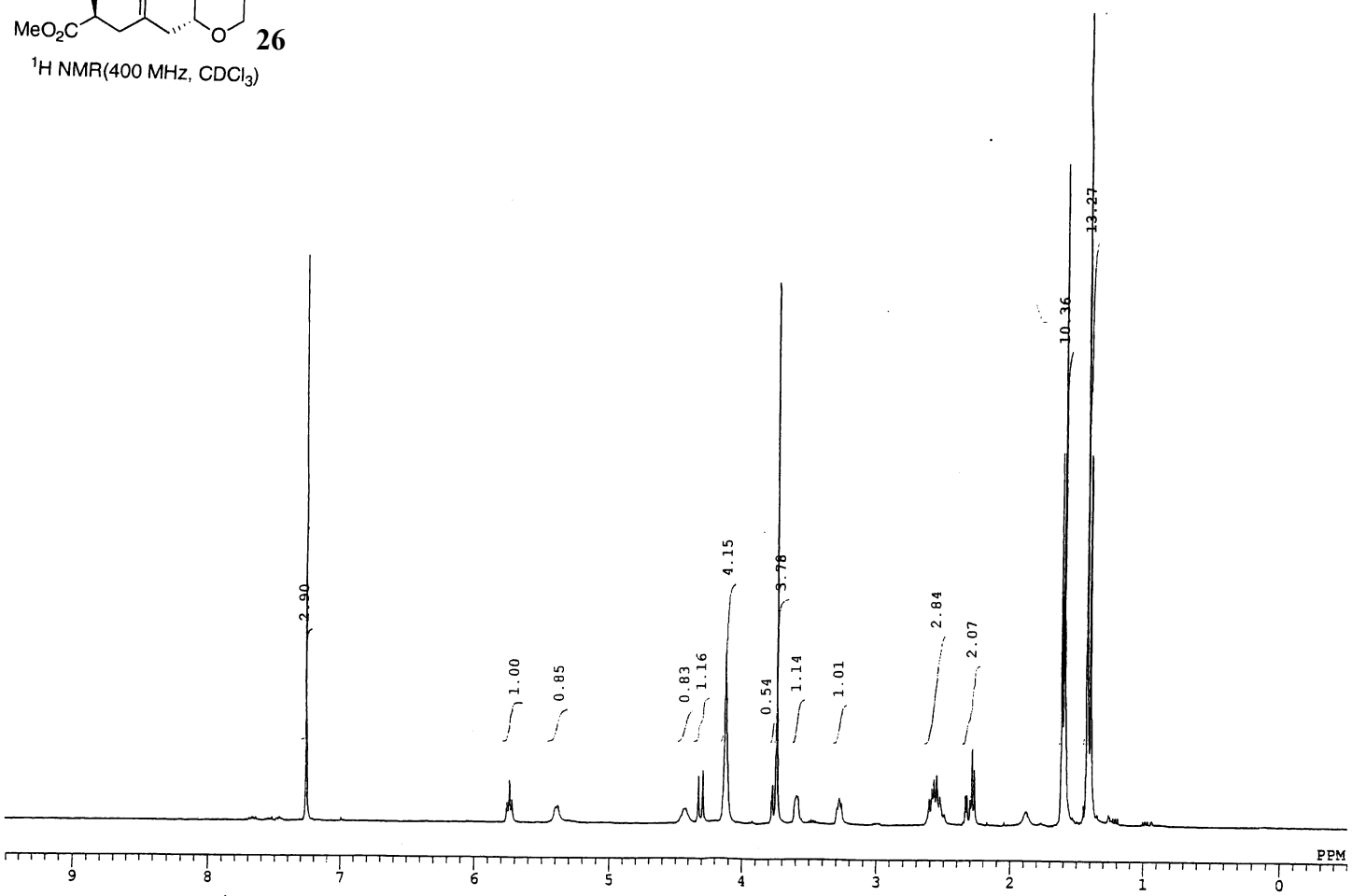
^{13}C NMR(100 MHz, $CDCl_3$)

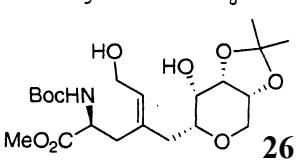




26

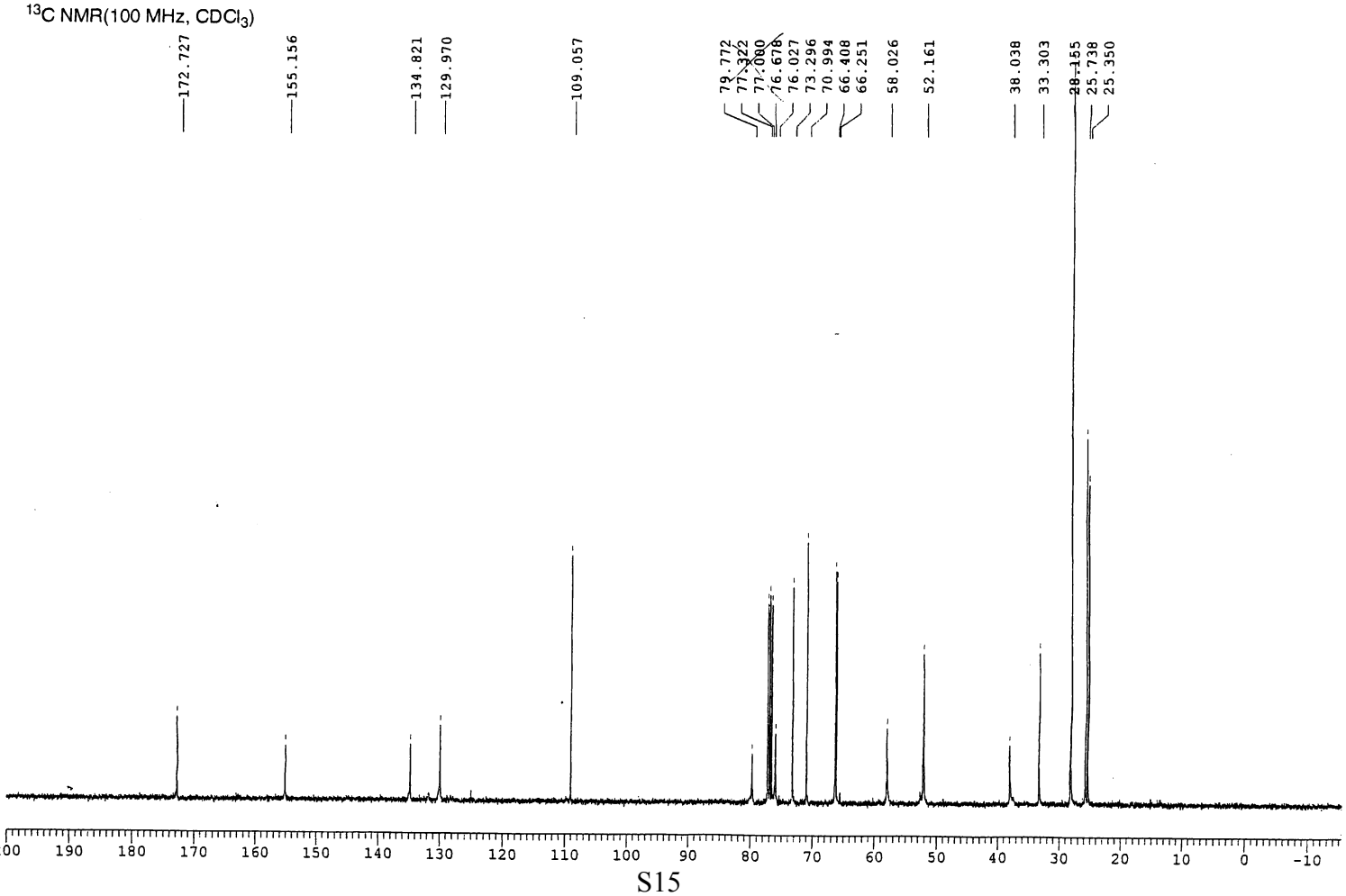
^{1}H NMR(400 MHz, $CDCl_3$)

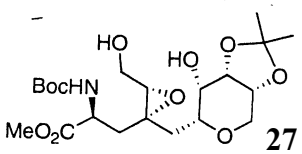




26

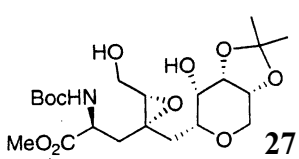
^{13}C NMR(100 MHz, $CDCl_3$)





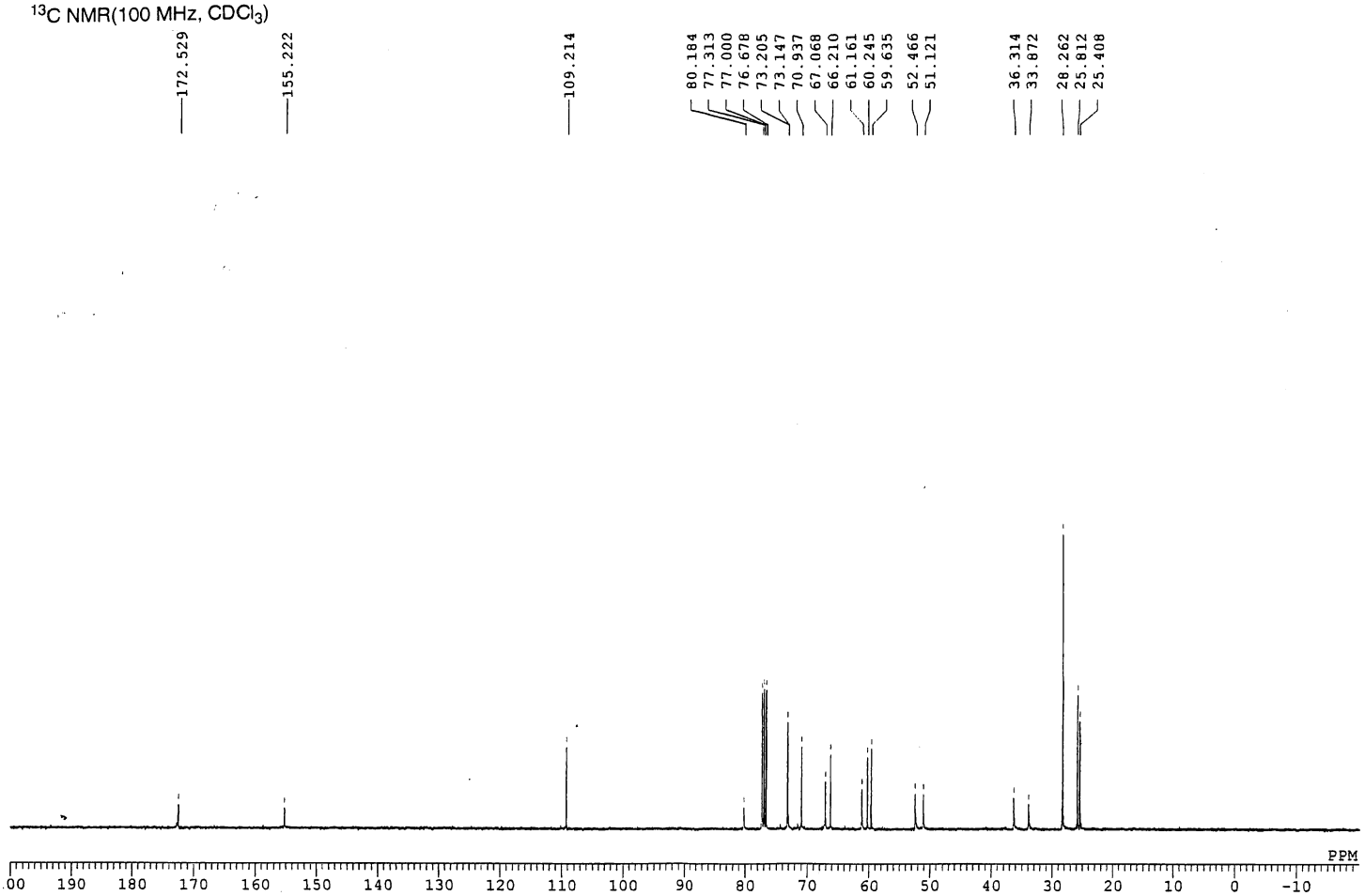
27

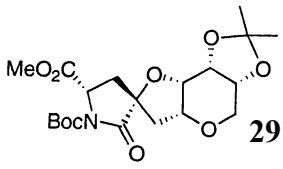
^{1}H NMR(400 MHz, $CDCl_3$)



27

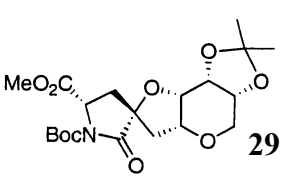
^{13}C NMR(100 MHz, $CDCl_3$)





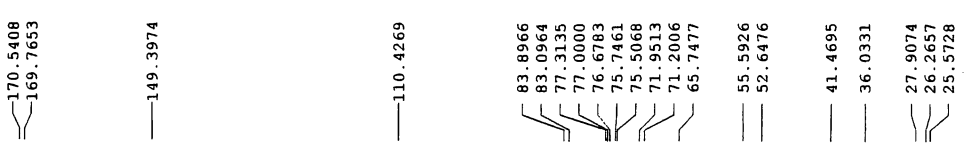
29

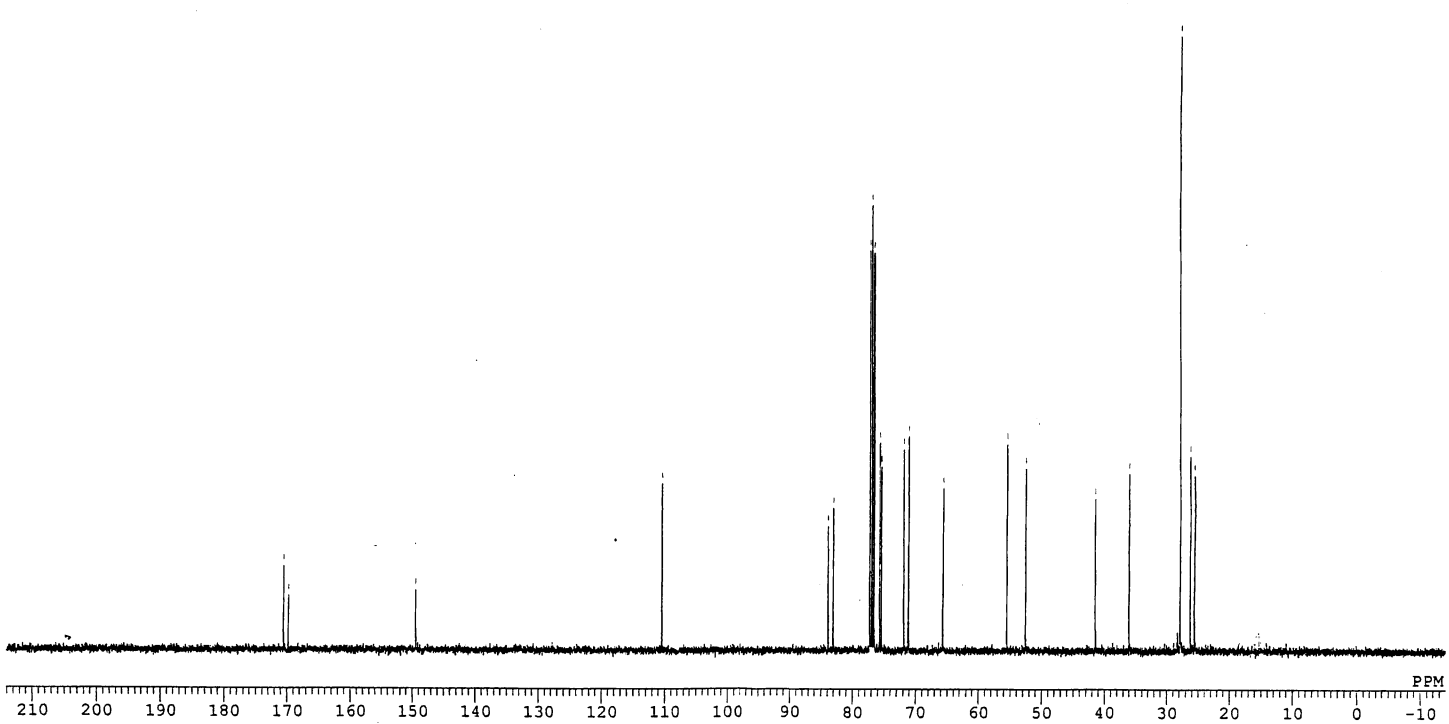
^{1}H NMR(500 MHz, C_6D_6)

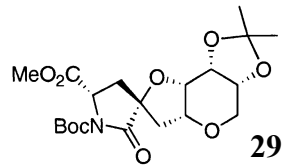


29

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

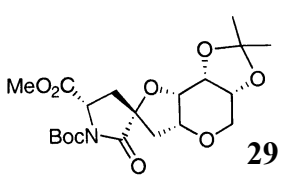






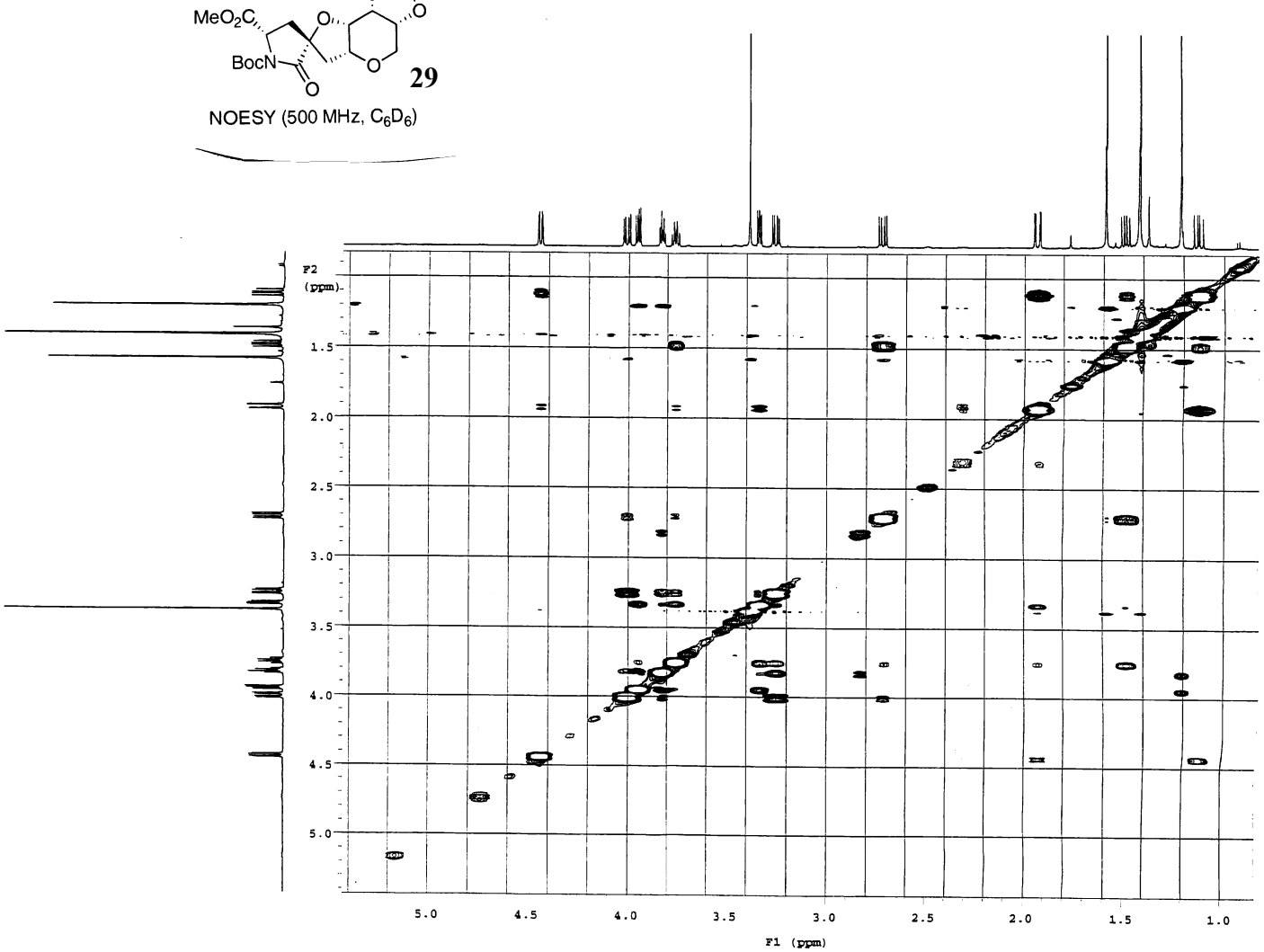
29

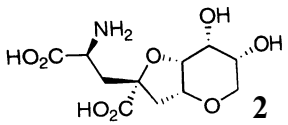
COSY (500 MHz, C_6D_6)



29

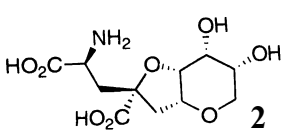
NOESY (500 MHz, C_6D_6)





2

^{1}H NMR(500 MHz, D_2O)



2

^{13}C NMR(100 MHz, D_2O +CD_3OD)