Supporting Information

Scalable, Efficient Total Synthesis of (+)-Mupirocin H

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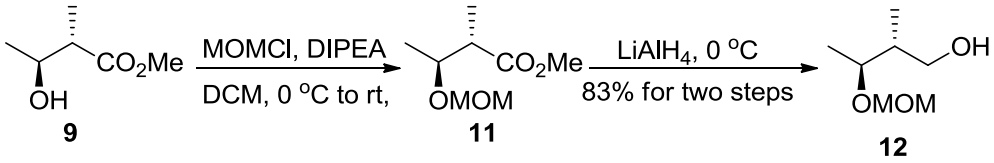
Table of Contents

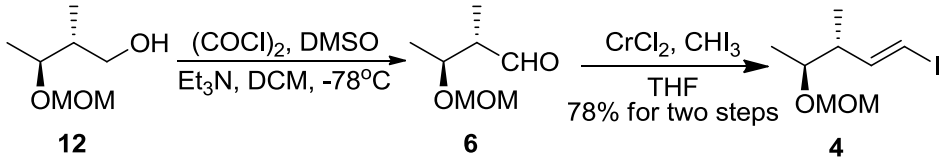
General Information.

Oxygen and moisture-sensitive reaction were carried out under argon atmosphere. Solvents were purified and dried by standardmethods prior to use. All commercially available reagents were used without further purification unless otherwise noted. Column chromatography was performed on silica gel (200-300 mesh). Optical rotations were measured on a precision automated polarimeter. Infrared spectra were recorded on a 670 FT-IR spectrometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on a 400 MHz spectrometers. Chemical shifts are reported as δ values relative to internal chloroform (δ7.27 for ^{1}H NMR and 77.0 for ^{13}C NMR)

Experimental Procedures.

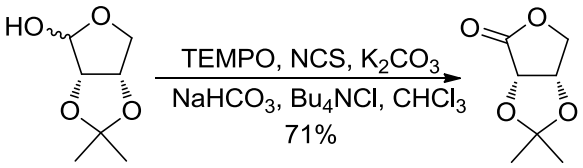


Synthesis of (2R,3S)-3-(methoxymethoxy)-2-methylbutan-1-ol (12) To a solution of the alcohol **9** (5.28 g, 40.0 mmol) and diisopropylethylamine (DIPEA, 10.4 g, 80.0 mmol) dissolved in 150 mL of DCM was added MOMCl (4.8 g, 60.0 mmol) and DMAP (0.49 g, 4.0 mmol) at 0 ^{o}C, and then the mixture was allowed to warm gradually to room temperature and stirred at the same temperature for 12 h. To the reaction mixture was added saturated $NaHCO_3$ and the aqueous layer was extracted with DCM (3×50 mL). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude ester was redissolved in ether (200 mL). To this new solution was slowly added $LiAlH_4$ (2.0 g, 52 mmol) at 0 ^{o}C, then the mixture was stirred at this temperature for 45 min. Saturate $NaHCO_3$ (14 mL) aqueous solution was added. The solid formed was filtered and washed with EtOAc for several times. The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated. Purification of the residue by silica gel column chromatography (5:1 petroleum/EtOAc) gave alcohol **12** (4.9 g, 83% yield for two steps) as a colorless oil: $[\alpha]^{20}_{D}$ = 73.0 (*c* = 1.0, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.66 (d, *J* = 6.8 Hz, 1H), 4.55 (d, *J* = 6.8 Hz, 1H), 3.61 (dd, *J* = 12.5, 6.0 Hz, 2H), 3.51 (t, *J* = 6.0 Hz, 1H), 3.33 (s, 3H), 2.90 (s, 1H), 1.72 – 1.66 (m, 1H), 1.12 (d, *J* = 6.0 Hz, 3H), 0.88 (d, *J* = 6.8 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 94.9, 77.3, 65.5, 55.4, 41.0, 17.5, 13.3; **IR** (KBr) ν_{max} 3438, 2972, 1451, 1378, 1148, 1104, 1039, 918 cm^{-1}; **HRMS** (ESI): *m/z*: calculated for $C_7H_{16}NaO_3$: $[M + Na]^+$ 171.0997, found: 171.1002.



Synthesis of (E,3R,4S)-1-iodo-4-(methoxymethoxy)-3-methylpent-1-ene (4) To a 150 mL oven-dried round-bottom flask under argon was added 50 mL of dichloromethane dried over CaH_2. Freshly distilled oxalyl chloride (1.27 g, 10 mmol) was added, and the solution was chilled to -78 ^{o}C. Then dimethyl sulfoxide (1.56 g, 20 mmol) was added over 5 min dropwise in 20 mL of dry dichloromethane with stirring. The resulting clear solution was stirred for an additional 15 min, and then **12** (740 mg, 5.0 mmol) in 20 mL of dry dichloromethane was added dropwise with stirring. During this time the solution acquired a white slushy appearance and stirring was

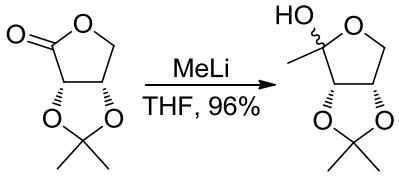
continued for an additional 40 min at -78 °C. Then Et_3N (4.04 g, 40.0 mmol) was added dropwise over 5 min and the reaction flask was removed from the cold bath and allowed to warm gradually to room temperature with stirring over 30 min. This was followed by the addition of water (20 mL) and stirring for another 10 min. The organic layer was separated and the aqueous layer was extracted with DCM (3×50 mL). The combined organic extracts were washed with water and brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. To a well-stirred solution of CHI_3 (4.33 g, 11 mmol) and $CrCl_2$ (5.36 g, 35 mmol) in dried THF (5 mL) was added dropwise a solution of compound **6** in THF (10 mL) at 0 ℃. After stirred for 20 min, the ice-bath was removed, and the mixture was stirred for another 2 h until the starting material had disappeared completely. The reaction was quenched with addition of a saturated solution of $Na_2S_2O_3$ (50 mL) and then stirred for another 0.5 h. The aqueous layer was extracted with Et_2O (3×50 mL), and the combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under the reduced pressure. Purification of the residue by flash column chromatography on silica gel (petroleum/EtOAc 20:1) gave compound **4** (0.7 g, 78% for two steps) as a colorless oil: $[\alpha]^{20}_D$ = 18.0 (*c* = 1.0, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.50 (dd, *J* = 14.4, 8.4 Hz, 1H), 6.04 (d, *J* = 14.8 Hz, 1H), 4.67 (d, *J* = 7.2 Hz, 1H), 4.57 (d, *J* = 7.2 Hz, 1H), 3.60 – 3.54 (m, 1H), 3.37 (s, 3H), 2.39 – 2.27 (m, 1H), 1.11 (d, *J* = 6.4 Hz, 3H), 1.03 (d, *J* = 6.8 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 148.4, 95.1, 77.6, 75.2, 55.4, 46.2, 17.4, 15.3; **IR** (KBr) ν_{max} 2969, 2929, 1148, 1102, 1037 cm^{-1}; **HRMS** (ESI) calculated for $C_8H_{15}INaO_2$ $[M+Na]^+$ 293.0014, found: 293.0010.



10 **13**

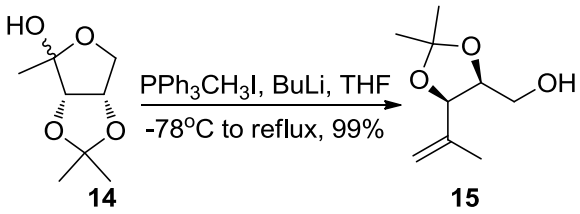
Synthesis of (3aS,6aS)-dihydro-2,2-dimethylfuro[3,4-d][1,3]dioxol-4(3aH)-one (13) To a solution of the alcohol **10** (14.3 g, 89 mmol) in $CHCl_3$ (400 mL) was added Bu_4NCl (2.29 g), TEMPO (1.27 g), and $NaHCO_3$ (11 g, 130 mmol), K_2CO_3 (1.86 g, 13.5 mmol) in H_2O (240 mL) was added, then NCS (21.1 g, 160 mmol) was added. After the mixture was stirred for 24 h, the reaction was quenched with addition of a saturated solution of $Na_2S_2O_3$, the aqueous layer was extracted with EtOAc (3×100 mL), and the combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under the reduced pressure. Purification of the residue by flash column chromatography on silica gel (petroleum/EtOAc 2:1) gave compound **13** (10 g, 71 %) as a white solid: mp. 60-62 ℃; $[\alpha]^{20}_D$ = 118.0 (*c* = 1.0, $CHCl_3$); **^{1}H NMR** (400 MHz,

$CDCl_3$) δ 4.88 – 4.85 (m, 1H), 4.72 (d, J = 5.6 Hz, 1H), 4.40 (d, J = 2.4 Hz, 2H), 1.43 (s, 3H), 1.35 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 174.2, 113.7, 75.4, 74.5, 70.1, 26.6, 25.4; **IR** (KBr) ν_{max} 3417, 2996, 1766, 1384, 1215, 1196, 1066, 996, 852 cm^{-1}; **HRMS** (ESI) calculated for $C_7H_{10}NaO_4$ $[M+Na]^+$ 181.0477, found: 181.0476.



13 **14**

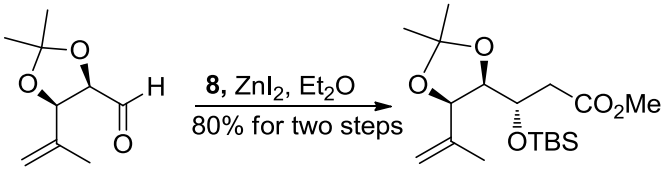
Synthesis of protected 1-deoxy ribulose (14) To a solution of the **13** (5.4 g, 31.5 mmol) in THF (90 mL) was added MeLi (1.8 M in Et_2O, 19.3 mL, 35 mmol) at -78 ^{o}C. After the mixture was stirred for 3 h at the same temperature, saturated NH_4Cl was added, the aqueous layer was extracted with EtOAc (3×50 mL), and the combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under the reduced pressure. Purification of the residue by flash column chromatography on silica gel (petroleum/EtOAc 2:1) gave compound **14** (5.2 g, 95 %) as a white solid: mp. 82-85 ℃; $[\alpha]^{20}_D$ = 65.0 (c = 1.0, $CHCl_3$); **^{1}H NMR** (400 MHz,$CDCl_3$) δ 4.86 (dd, J = 5.6 4.0 Hz, 1H), 4.15 (d, J = 6.0 Hz, 1H), 4.01 (dd, J = 10.0, 3.6 Hz, 1H), 3.93 (dd,J = 10.0, 3.0 Hz, 1H), 2.39 (s, 1H), 1.54 (s, 3H), 1.44 (s, 3H), 1.38 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 112.4, 106.0, 85.0, 80.9, 71.0, 26.3, 24.9, 22.4; **IR** (KBr) ν_{max} 3233, 2986, 2940, 1384, 1184, 1072, 863 cm^{-1}; **HRMS** (ESI): *m/z*: calculated for $C_8H_{14}NaO_4$ $[M + Na]^+$: 197.0790, found: 197.0792.



14 **15**

Synthesis of ((4S,5R)-2,2-dimethyl-5-(prop-1-en-2-yl)-1,3-dioxolan-4-yl)methanol (15) To a suspension of methyltriphenylphophonium iodide (36.4 g, 90 mmol) in dry THF (150 mL) at -78 ^{o}C was added n-BuLi (2.5 M in hexane, 37.2 mL, 93 mmol) slowly. After being stirred at 0 ^{o}C for 30 min, the mixture was cooled to -78 ^{o}C, and to this was added slowly the **14** (5.22 g, 30 mmol) in dry THF (25 mL). The mixture was stirred at the same temperature for 1 h, then gradually warmed to 70 ^{o}C, and stirred for 24 h. Water was added to the mixture, which was extracted with EtOAc (3×50 mL), washed with brine, dried over anhydrous Na_2SO_4 and concentrated under the reduced pressure. Purification of the residue by flash column

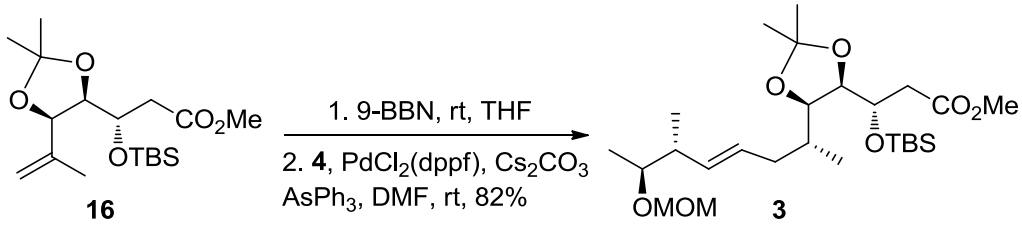
chromatography on silica gel (petroleum/EtOAc 3:1) gave compound **15** (5.16 g, 99 %) as a colorless oil: $[\alpha]^{20}_{D}$ = -86.0 (*c* = 1.0, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.09 (s, 1H), 4.93 (d, *J* = 0.8 Hz, 1H), 4.58 (d, *J* = 6.4 Hz, 1H), 4.28 – 4.23 (m, 1H), 3.49 – 3.40 (m, 2H), 2.23 (s, 1H), 1.72 (s, 3H), 1.49 (s, 3H), 1.37 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 139.6, 112.1, 108.6, 79.1, 77.7, 62.0, 27.6, 25.3, 20.0; **IR** (KBr) ν_{max} 3452, 2989, 2937, 1378, 1243, 1164, 1037, 898 cm^{-1}; **HRMS** (ESI) calculated for $C_9H_{16}NaO_3$ $[M+Na]^+$ 195.0097, found: 195.0094.



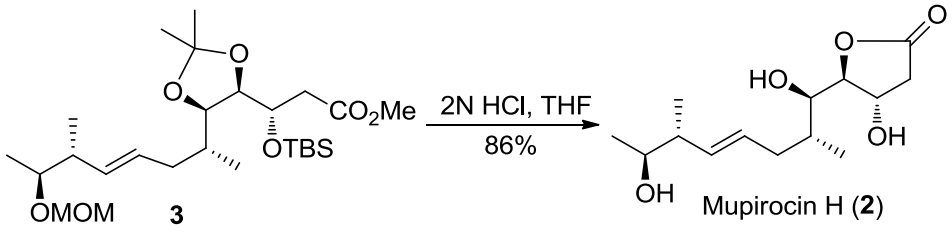
7 **16**

Synthesis of 16: To a 250 mL oven-dried round-bottomed flask under argon was added 100 mL of dichloromethane dried over CaH_2. Freshly distilled oxalyl chloride (5.08 g, 40 mmol) was added, and the solution was chilled to -78 ^{o}C. Then dimethyl sulfoxide (6.04 g, 80 mmol) was added over 10 min dropwise in 40 mL of dry dichloromethane with stirring. The resulting clear solution was stirred for an additional 15 min, and then **7** (3.44 g, 20 mmol) in 40 mL of dry dichloromethane was added dropwise with stirring. During this time the solution acquired a white slushy appearance and stirring was continued for an additional 40 min at -78 ^{o}C. Then DIPEA (20.7 g, 160.0 mmol) was added dropwise over 5 min and the reaction flask was removed from the cold bath and allowed to warm gradually to room temperature with stirring over 30 min. This was followed by the addition of water (20 mL) and stirring for another 10 min. The organic layer was separated and the aqueous layer was extracted with Et_2O (3×50 mL). The combined organic extracts were washed with water and brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude aldehyde **7** was dissolved in Et_2O (20 mL) and flushed with argon. To this new solution was slowly added **8** (5.13 g, 30 mmol) and ZnI_2 (338 mg, 1 mmol). After the mixture was stirred at the room temperature for 48 h, pyridine (158 mg, 2 mmol) was added and the mixture was then concentrated under reduced pressure. The residue was purified by flash column chromatography (hexanes/EtOAc = 30/1) to provide **16** (5.73 g, 80% for two steps) as a colorless oil: $[\alpha]^{20}_{D}$ = -44.0 (c = 1.0, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.11 (s, 1H), 4.99 (s, 1H), 4.62 (d, J = 7.2 Hz 1H), 4.25 (dd, *J* = 7.2, 4.0 Hz 1H), 4.17 – 4.13 (m, 1H), 3.64 (s, 3H), 2.61 – 2.50 (m, 2H), 1.80 (s, 3H), 1.49 (s, 3H), 1.37 (s, 1H), 0.85 (s, 9H), 0.06 (s, 3H), 0.03 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 172.1, 139.6, 113.4, 108.0, 81.0, 79.7, 68.9, 51.3, 39.3, 26.2, 25.8, 24.7, 20.2, 18.0, -4.3, -4.4; **IR** (KBr) ν_{max} 2950, 2929, 2856, 1741, 1381,

1253, 1086, 836 cm^{-1}; **HRMS** (ESI) calculated for $C_{18}H_{34}NaO_5Si$ $[M+Na]^+$ 381.2073, found: 381.2077.

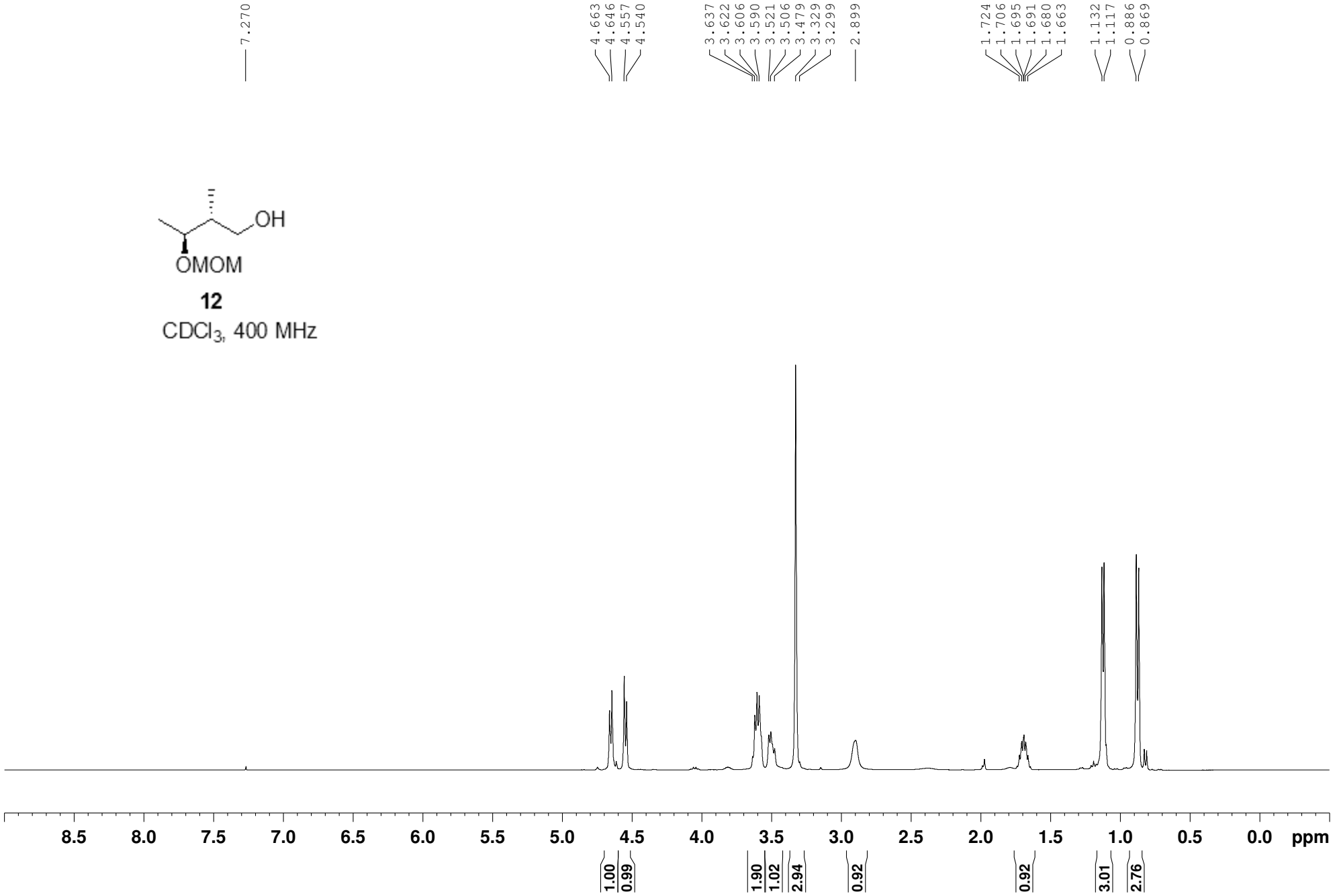


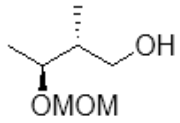
Synthesis of 3: To a solution of compound **16** (2.14 g, 6 mmol) was added dropwise a solution of 9-BBN (24 mL, 0.5 M in THF) at -78 ℃ under the argon atmosphere, the mixture was allowed to warm to room temperature over 1 h, and then stirred for 3 h at room temperature. The reaction was quenched with degassed H_2O, and then stirred for another 1 h. To a solution of iodine **4** (1.4 g, 5 mmol) in degassed DMF (30 mL) was added Cs_2CO_3 (5.3 g, 18 mmol), $Pd(dppf)Cl_2$ (984 mg, 1.2 mmol), $AsPh_3$ (366 mg, 1.2 mmol), the mixture was stirred for 10 min under the argon atmosphere, and the above resulting B-alkyl solution was then added dropwise to these mixtures. The reaction was stirred for 8 h, and the water was added. The aqueous layer was extracted with Et_2O (3×100 mL), and the combined organic phase was washed with brine, dried with anhydrous Na_2SO_4 and concentrated in vacuum. The residue was purified on silica gel (petroleum/EtOAc = 20:1) to afford compound **3** (2.4 g, 82%) as a colorless oil: $[\alpha]^{20}_D$ = -21.0 (c = 1.0, $CHCl_3$); **^{1}H NMR** (400 MHz, CDCl3) δ 5.41 (d, *J* = 3.6 Hz, 2H), 4.66 (d, *J* = 6.8 Hz, 1H), 4.60 (d, *J* = 6.8 Hz, 1H), 4.32 – 4.29 (m, 1H), 4.10 (t, *J* = 6.0 Hz, 1H), 3.84 (dd, *J* = 8.4, 2.0 Hz, 1H), 3.65 (s, 3H), 3.62 – 3.57 (m, 1H), 3.35 (s, 3H), 2.65 – 2.52 (m, 2H), 2.35 – 2.28 (m, 2H), 1.94 – 1.76 (m, 2H), 1.41 (s, 3H), 1.31 (s, 3H), 1.08 (d, *J* = 6.0 Hz, 3H), 1.00 (d, *J* = 6.8 Hz, 3H), 1.94 (d, *J* = 7.2 Hz, 3H), 0.84 (s, 9H), 0.07 (s, 3H), 0.04 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 172.2, 134.6, 127.6, 107.5, 95.2, 81.0, 80.6, 68.9, 55.2, 51.2, 42.2, 40.1, 36.6, 32.0, 26.3, 25.8, 25.0, 18.0, 16.9, 16.7, 15.7, -4.3, -4.4; **IR** (KBr) ν_{max} 2956, 2929, 1741, 1256, 1039, 886 cm^{-1}; **HRMS** (ESI) calculated for $C_{26}H_{50}NaO_7Si$ $[M+Na]^+$ 525.3224, found: 525.3231.



Synthesis of Mupirocin H (2): To the ester **3** (1.2 g, 2.4 mmol) in THF (120 mL) was added 2N HCl (24 mL, 48 mmol). The resulting solution was stirred at 70 ℃ for 3 h. After the reaction

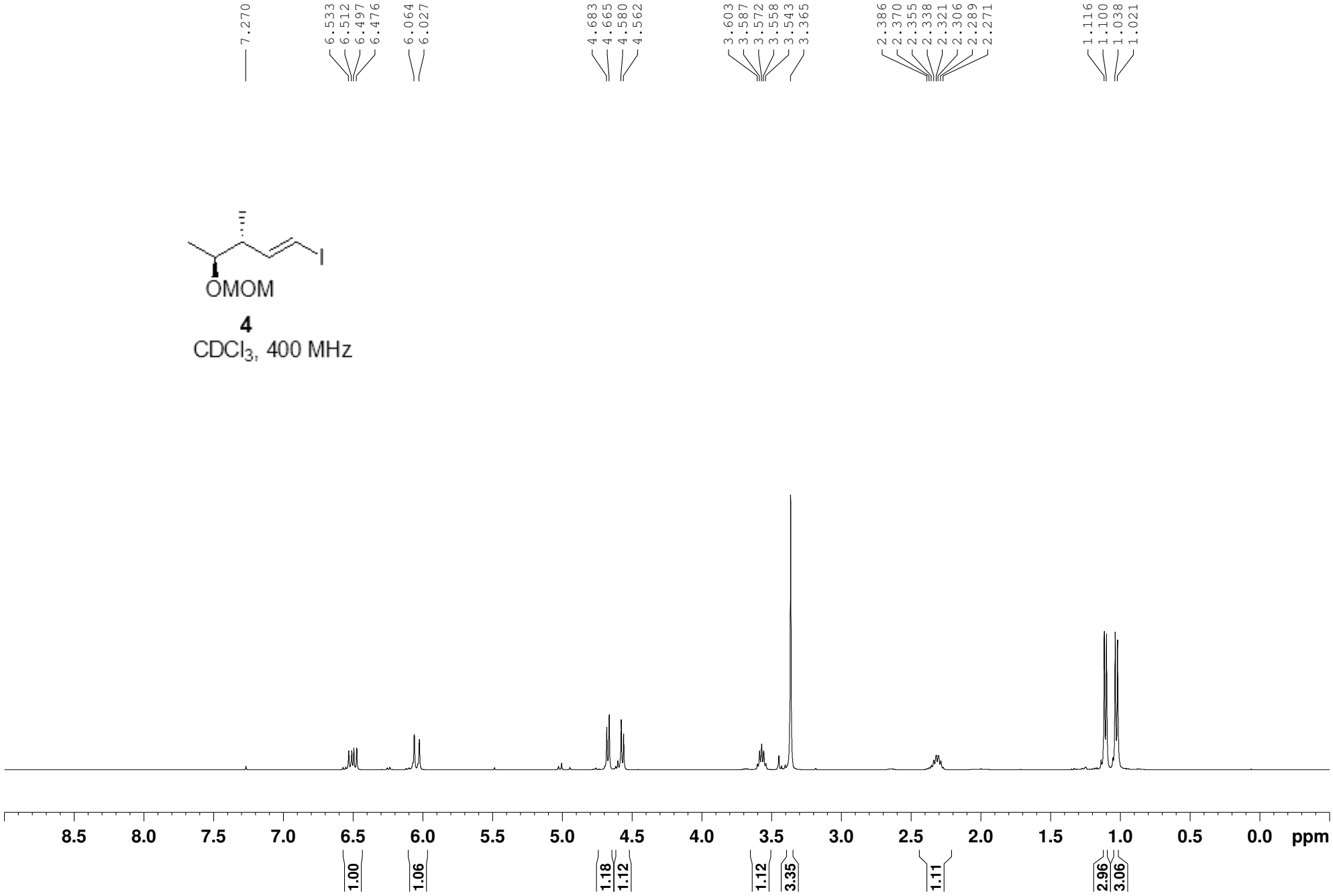
mixture was cooled to rt, the aqueous layer was extracted with DCM (3×100 mL), and the combined organic phase was washed with brine, dried with anhydrous Na_2SO_4 and concentrated in vacuum. The residue was purified on silica gel (chloroform/MeOH = 20:1 to 10:1) to afford Mupirocin H (**2**) (560 mg, 86%) as a colorless oil: $[\alpha]^{20}_D$ = 30.5 (c = 1.3, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.60 (ddd, *J* = 14.8, 8.0, 6.8 Hz, 1H), 5.38 (dd, *J* = 15.2, 8.8 Hz, 1H), 4.60 – 4.57 (m, 1H), 4.44 (dd, *J* = 5.2, 2.8 Hz, 1H), 3.57 (dd, *J* = 6.4, 6.0 Hz, 1H), 3.52 – 3.48 (m, 1H), 2.93 (dd, *J* = 18.4, 7.6 Hz, 1H), 2.52 (dd, *J* = 18.4, 3.6 Hz, 1H), 2.29 – 2.19 (m, 2H), 2.11 – 2.02 (m, 1H), 1.93 – 1.86 (m, 2H), 1.18 (d, J = 6.4 Hz, 3H), 1.04 (d, *J* = 7.2 Hz, 3H), 0.98 (d, *J* = 6.8 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 176.5, 134.7, 129.5, 88.2, 75.0, 71.6, 68.3, 45.2, 38.4, 35.4, 34.8, 20.6, 17.0, 16.0; **IR** (KBr) ν_{max} 3382, 2967, 2929, 1769, 1457, 771 cm^{-1}; **HRMS** (ESI) calculated for $C_{14}H_{24}NaO_5$ $[M+Na]^+$ 295.1521, found: 295.1516.





12

$CDCl_3$, 100 MHz



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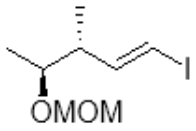

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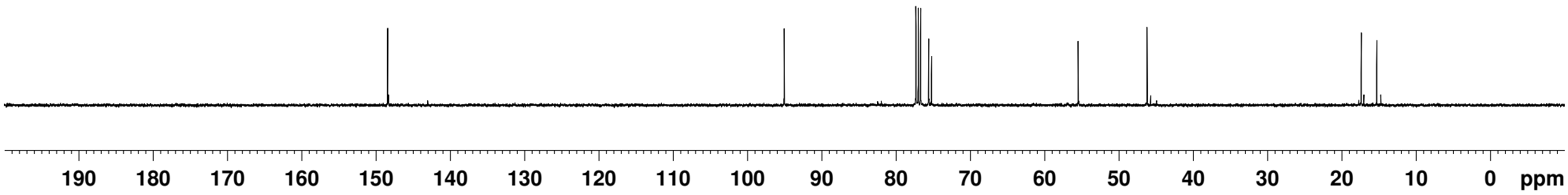

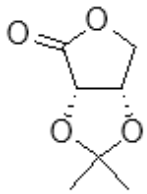

13

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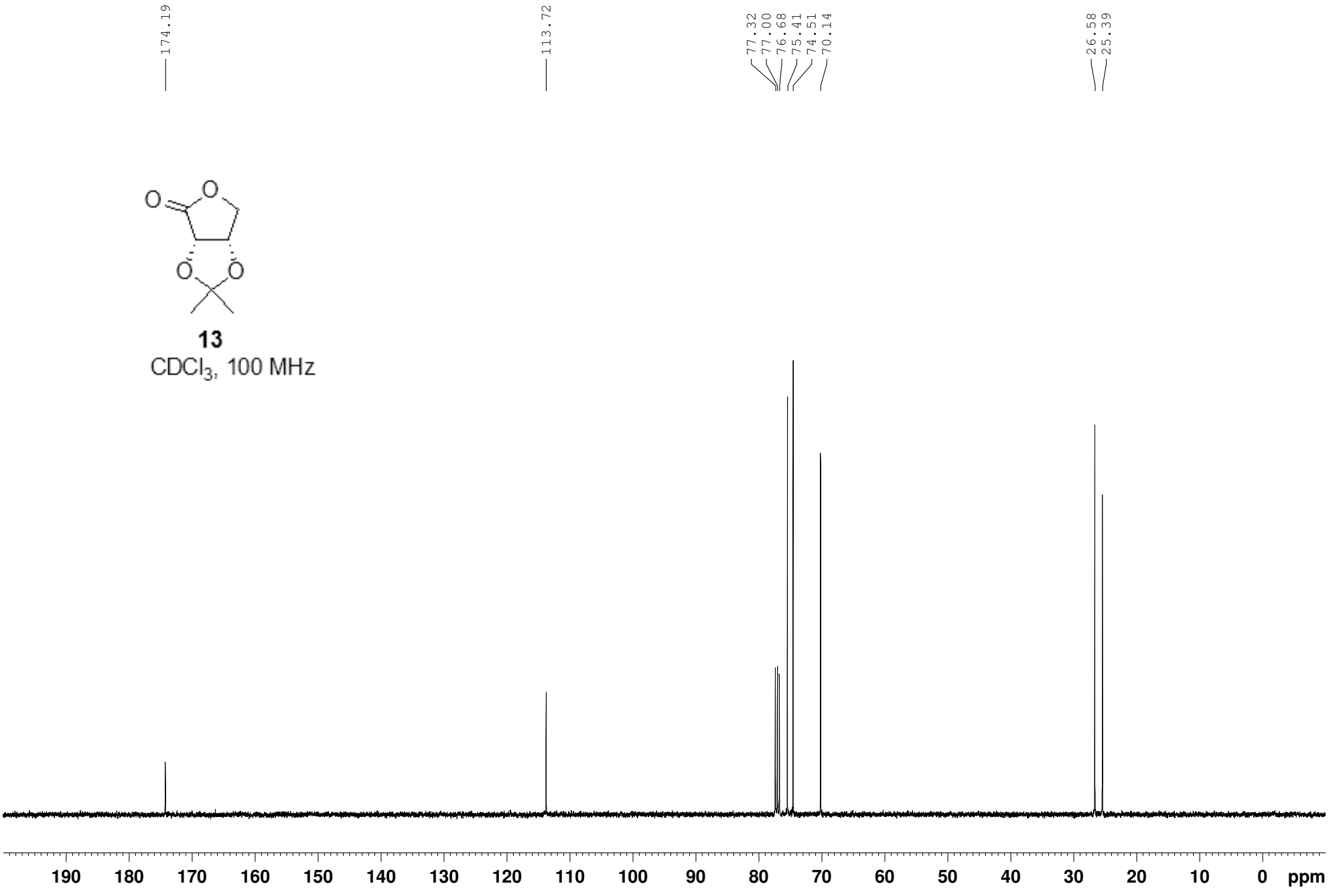
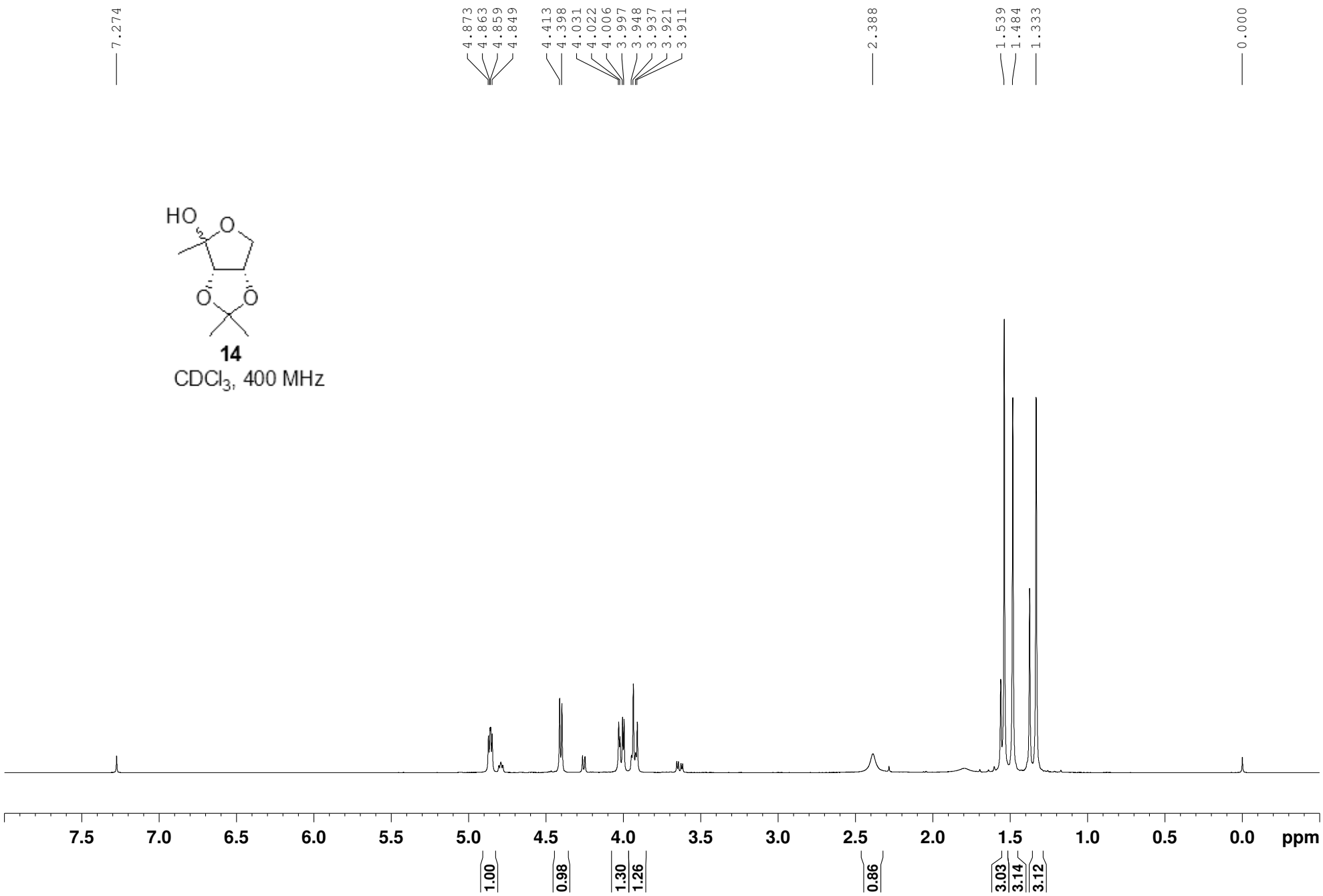
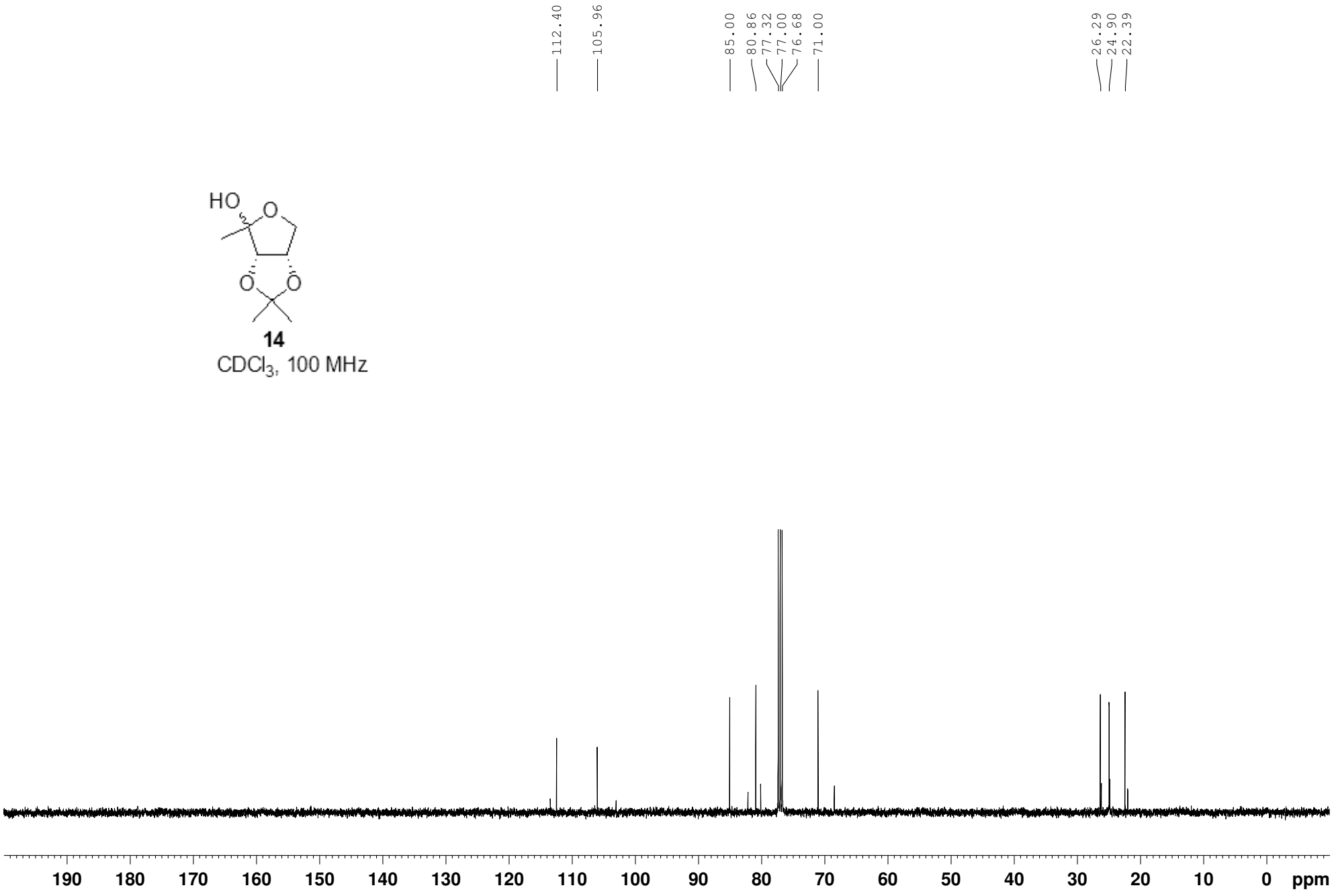
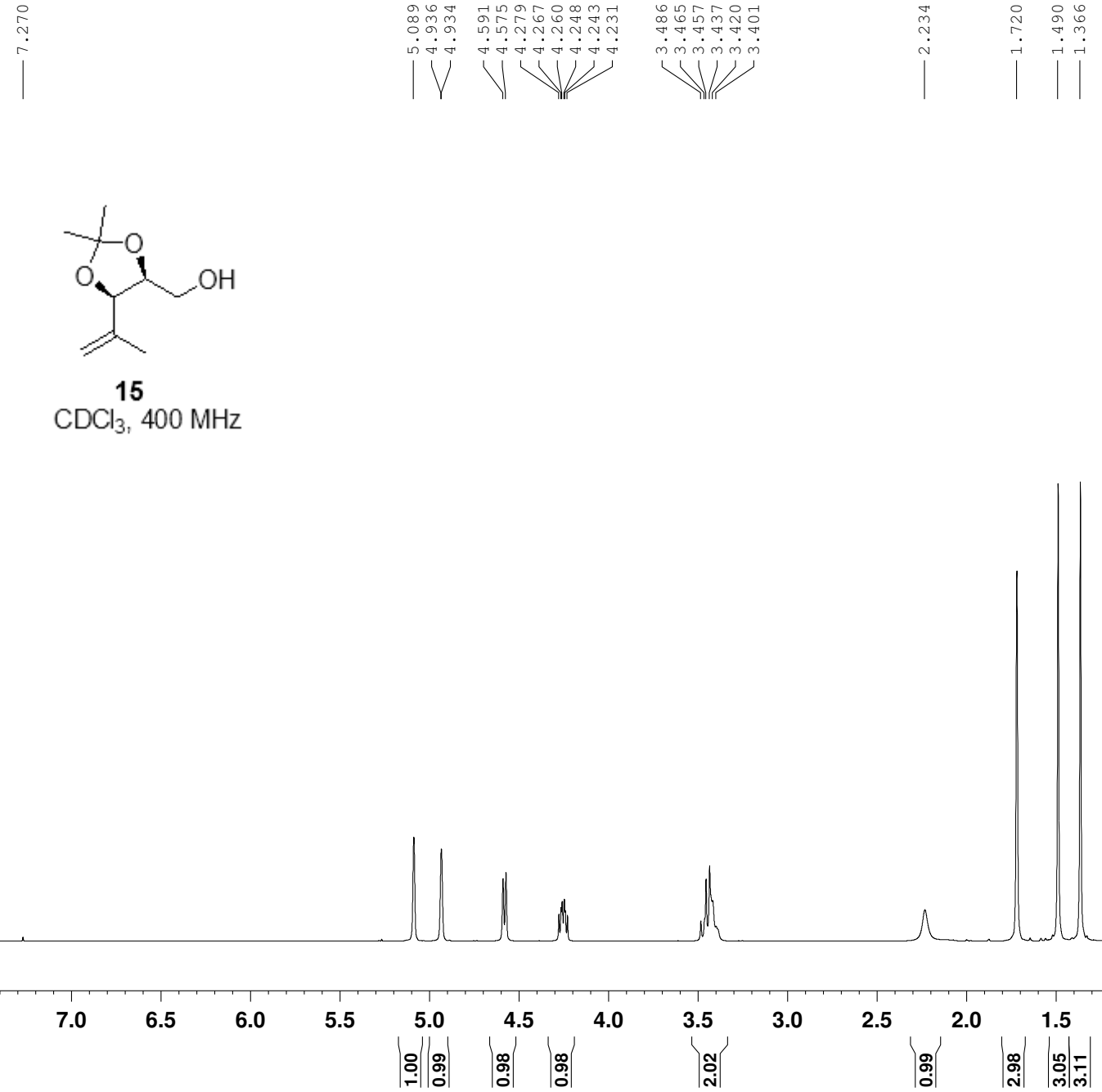
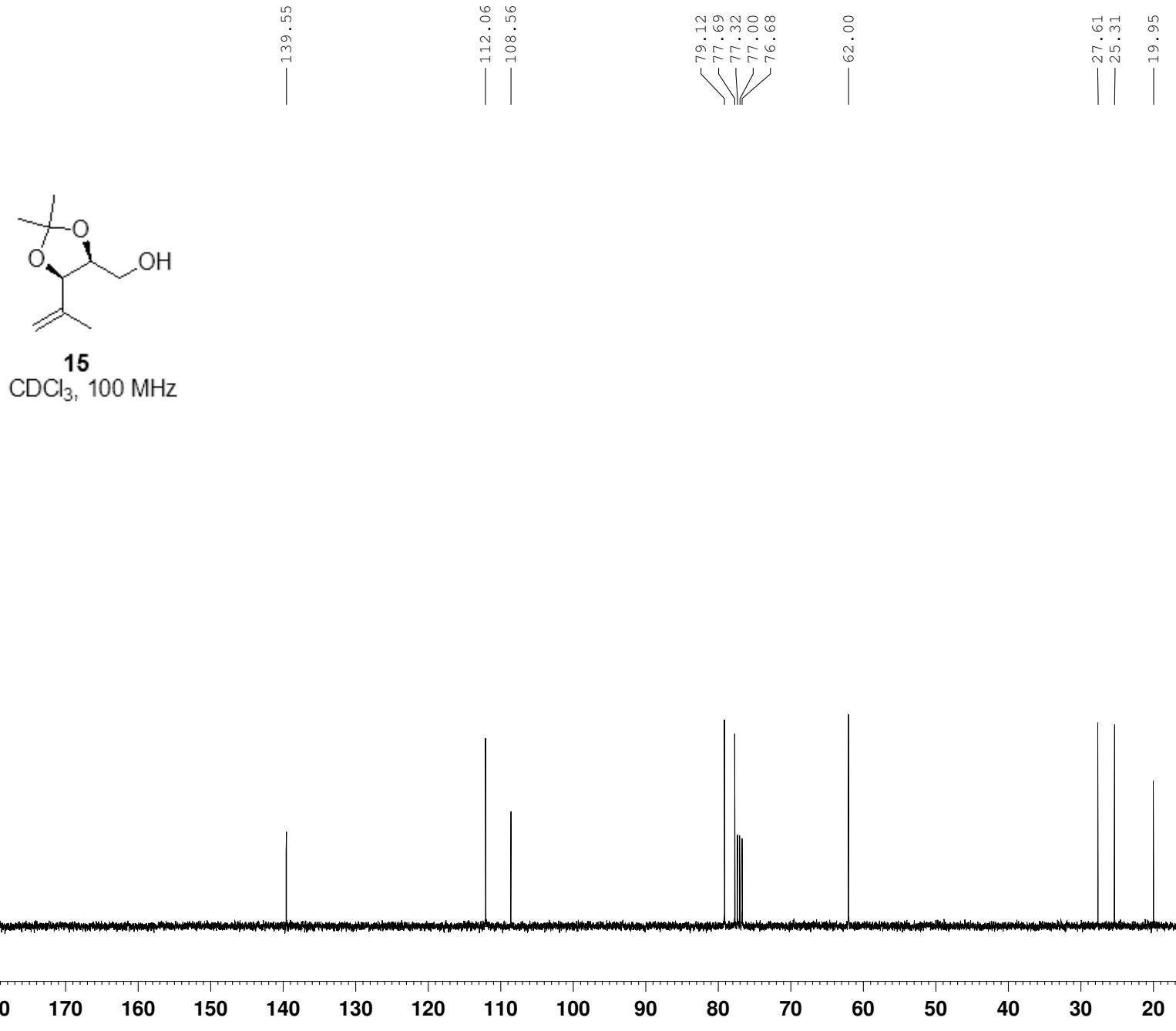




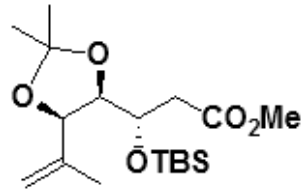






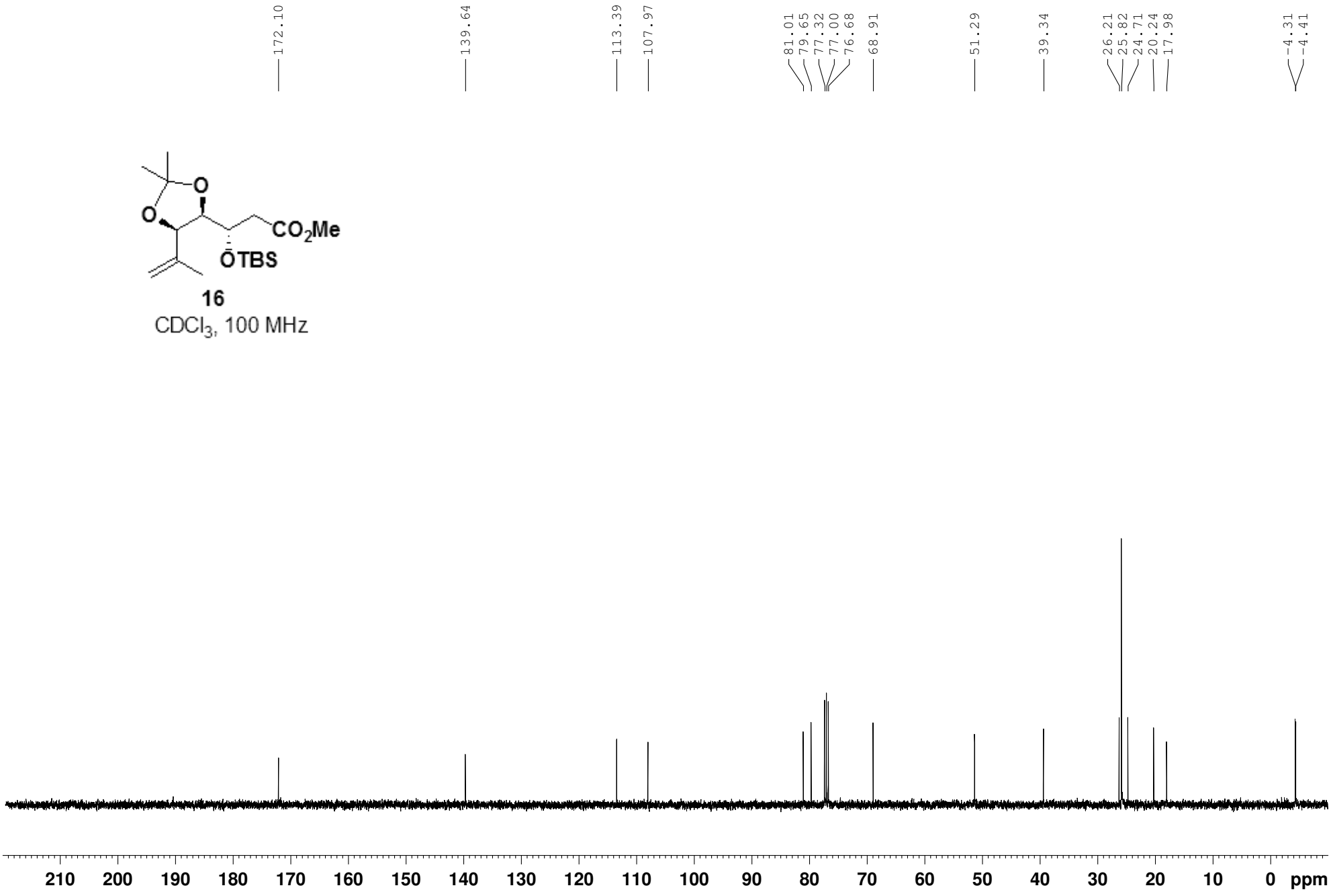
15

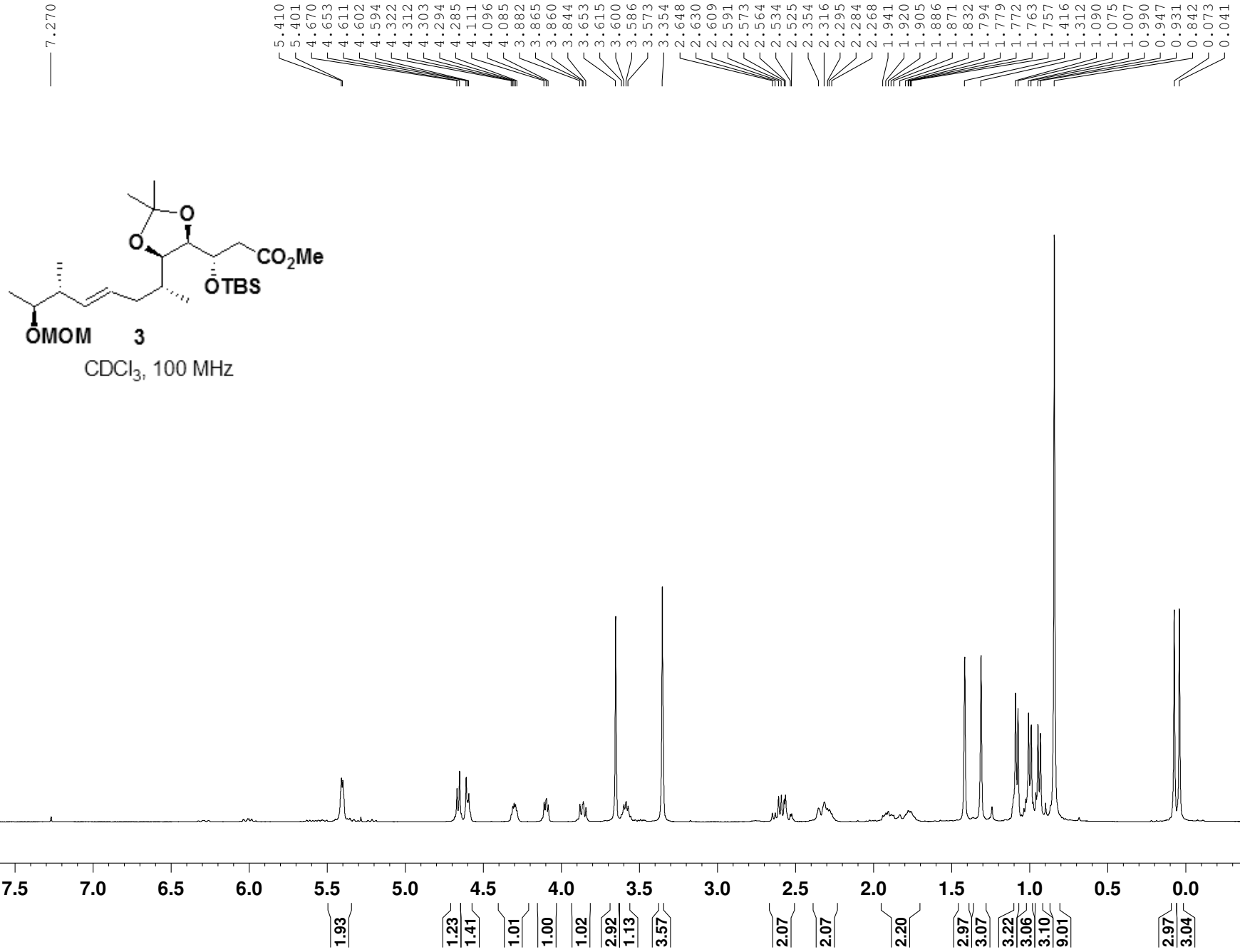
$CDCl_3$, 100 MHz

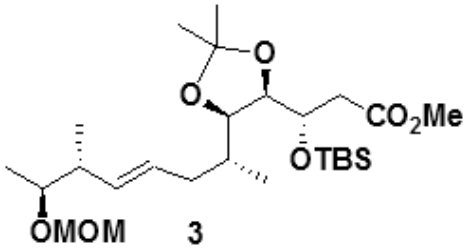


16

$CDCl_3$, 400 MHz







3

$CDCl_3$, 400 MHz