

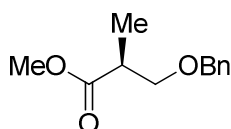
SUPPLEMENTARY INFORMATION FOR

Stereoselective Synthesis of the C15–C26 Fragment of the Antitumor Agent (–)-Dictyostatin

Leticia Ferreiro-Mederos, Silvia Vila-Gisbert, Antonio Urbano, M. Carmen Carreño, Françoise Colobert

Experimental Procedures

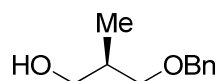
Methyl (*S*)-3-(benzyloxy)-2-methylpropionate



To a stirred solution of commercially available methyl (*S*)-3-hydroxy-2-methylpropanoate (5.0 g, 42.4 mmol) in a mixture of cyclohexane (100 mL) and CH₂Cl₂ (50 mL) at 0 °C, benzyl-2,2,2-trichloroacetimidate (10.3 mL, 59.2 mmol, 1.4 equiv) was slowly added, followed by the addition of triflic acid (110 μL, 1.2 mmol, 0.03 equiv). The reaction mixture was stirred at room temperature for 24 h, filtered and washed with a saturated solution of NaHCO₃ and brine. After workup and flash chromatography (EtOAc/hexane 1:10), the title compound was obtained as a colourless oil (8.37 g, 95% yield): R_f = 0.84 (EtOAc/hexane 1:2); [α]_D²⁰ = +11.6 (*c* 5.04, CHCl₃) {lit.¹ [α]_D²⁰ = +11.7 (*c* 5.04, CHCl₃)}; ¹H NMR δ 7.34-7.26 (m, 5H), 4.52 (s, 2H), 3.69 (s, 3H), 3.67 (dd, *J* = 7.3 and 9.1 Hz, 1H), 3.51 (dd, *J* = 5.9 and 9.1 Hz, 1H), 2.79 (m, 1H); 1.20 (d, *J* = 7.1 Hz, 3H); ¹³C NMR δ 175.4, 138.4, 128.5, 127.8, 73.3, 72.2, 51.9, 40.4, 14.2. HMRS (FAB+) calcd for C₁₂H₁₆O₃ [M + H]⁺ 209.1173, found 209.1178.

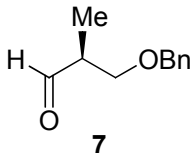
(1) G. E. Keck, A. Palani, S. F. McHardy, *J. Org. Chem.*, 1994, **59**, 3113.

(R)-3-(Benzyloxy)-2-methylpropan-1-ol



To a stirred suspension of LiAlH₄ (1.3 g, 35.2 mmol) in Et₂O (107 mL) at 0 °C, a solution of the above obtained methyl (*S*)-3-(benzyloxy)-2-methylpropionate (7.3 g, 35.2 mmol) in Et₂O (107 mL) was slowly added. After stirring for 1 h, the reaction was quenched by a very slow addition of water (5 mL) and a 15% solution of NaOH. The mixture was stirred for 15 min and enough MgSO₄ was added to dry the solution. After workup and flash chromatography (EtOAc/hexane 1:3), the title compound was obtained as a colourless oil (5.9 g, 94% yield): R_f = 0.48 (EtOAc/hexane 1:2); [α]_D²⁰ = +18.2 (*c* 1.47, CHCl₃) {lit.² [α]_D²⁰ = +10.4 (*c* 1.45, CHCl₃)}; ¹H NMR δ 7.36-7.27 (m, 5H), 4.44 (s, 2H), 3.51 (d, *J* = 5.9 Hz, 2H), 3.44 (dd, *J* = 5.1 and 9.1 Hz, 1H), 3.36 (dd, *J* = 7.6 and 9.1 Hz, 1H), 2.86 (s, 1H), 1.97 (m, 1H), 0.83 (d, *J* = 6.9 Hz, 3H); ¹³C NMR δ 138.3, 128.5, 127.8, 127.7, 74.9, 73.9, 67.1, 35.8, 13.7. HMRS (ES) calcd for C₁₁H₁₆O₂ (M + H)⁺ 180.1223, found 180.1223.

(S)-3-(Benzyloxy)-2-methylpropanal (7)

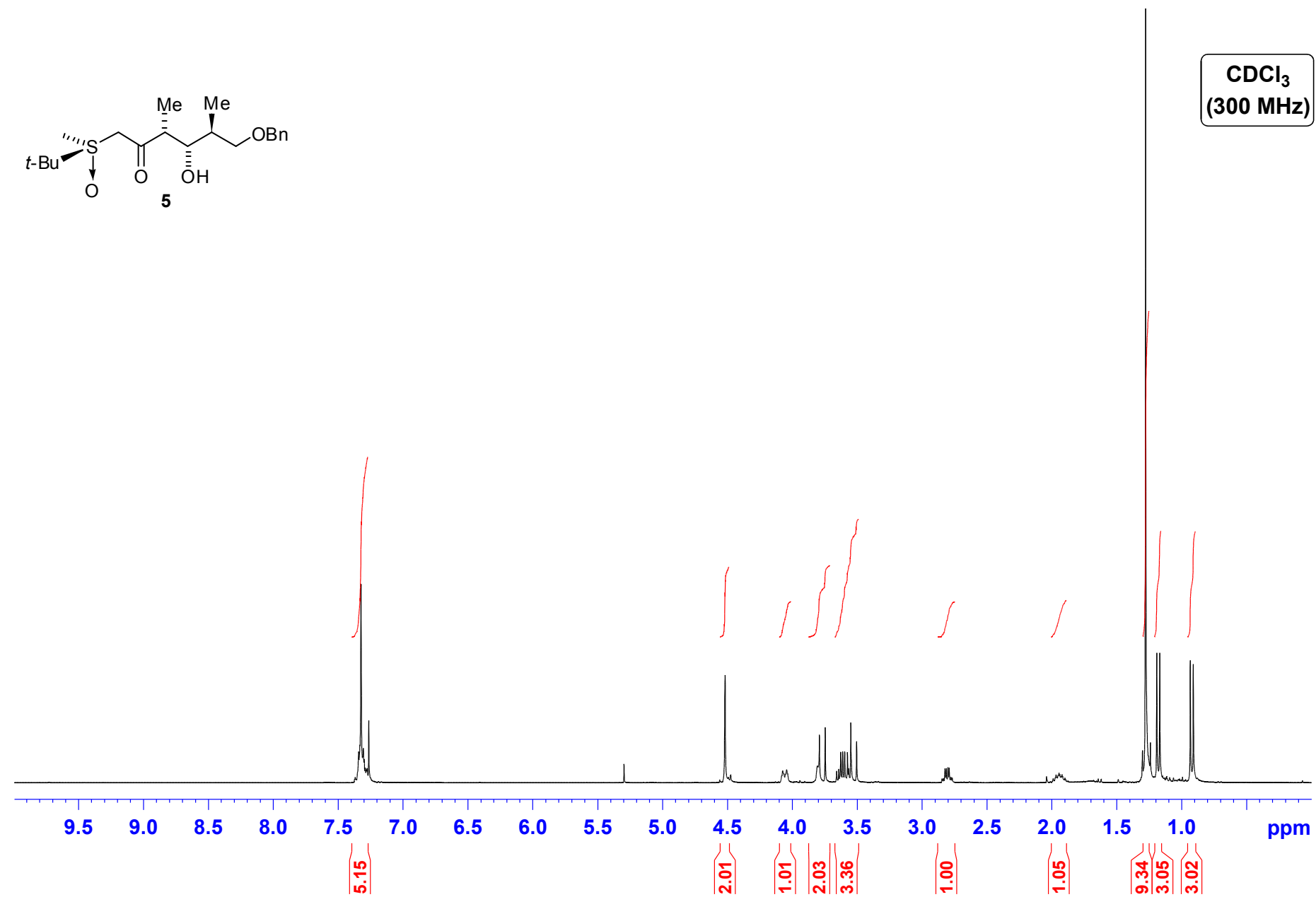


To a solution of the above obtained (*R*)-3-(benzyloxy)-2-methylpropan-1-ol (1.5 g, 8.4 mmol) in CH₂Cl₂ (34 mL) and DMSO (17 mL) at -15 °C, iPr₂EtNH (4.4 mL, 25.3 mmol, 3 equiv) was added. The mixture was cooled to -78 °C and a solution of the SO₃•pyr complex (3.2 g, 25.3 mmol, 3 equiv) in DMSO (17 mL) was slowly added. After stirring for 1 h at -78 °C, the reaction mixture was diluted with Et₂O (100 mL) and washed successively with brine (2 x 50 mL), H₂O (50 mL), NaHCO₃ (50 mL) and CuSO₄ (2 x 50 mL). After workup, aldehyde (*S*)-7 was obtained as a yellow oil (1.14 g, 96% yield) and used without further purification: R_f = 0.53 (EtOAc/hexane 1:3); [α]_D²⁰ = +21.1 (*c* 4.9, CHCl₃) {lit.³ [α]_D²⁰ = +27.6 (*c* 4.9, CHCl₃)}; ¹H NMR δ 9.73 (d, *J* = 1.6 Hz, 1H), 7.36-7.27 (m, 5H), 4.53 (s, 2H), 3.69 (dd, *J* = 6.2 and 9.0 Hz, 1H), 3.64 (dd, *J* = 4.9 and 9.0 Hz, 1H), 2.67 (m, 1H), 1.14 (d, *J* = 7.1 Hz, 3H); ¹³C NMR δ 203.9, 138.1, 128.5, 127.9, 127.8, 73.4, 70.3, 46.9, 10.9. HRMS (ES) calcd for C₁₁H₁₄O₂ (M + H)⁺ 179.1066, found 179.1058.

(2) J. Marshall, J. D. Trometer, B. E. Blough, T. D. Crute, *J. Org. Chem.*, 1988, **53**, 4274.

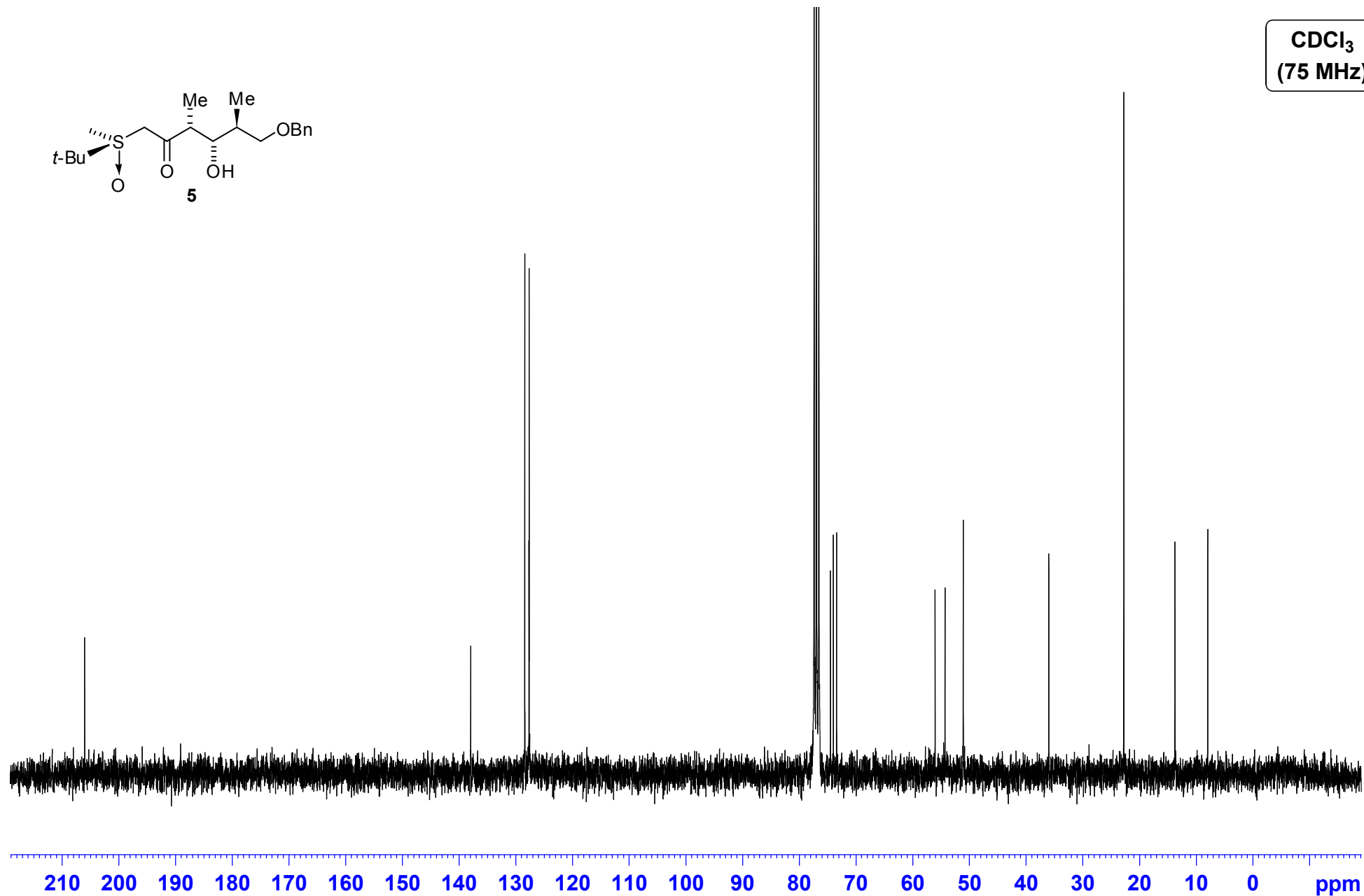
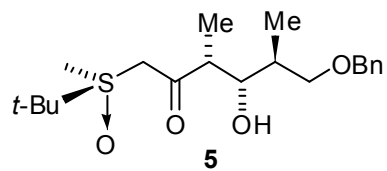
(3) C. H. Heathcock, S. D. Young, J. P.; Hagen, P. Pilli, U. Badertscherad, *J. Org. Chem.*, 1985, **50**, 2095.

S-3

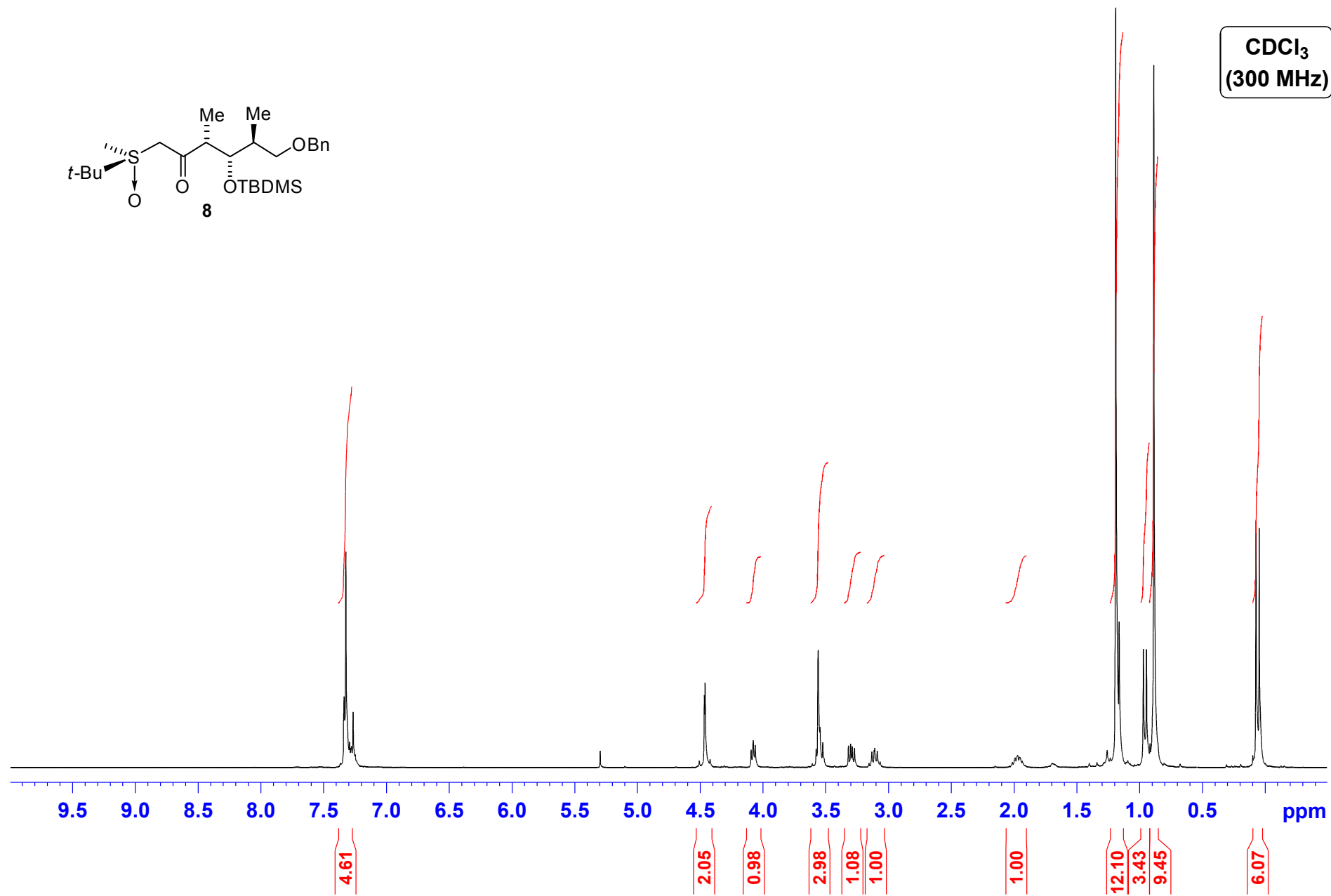
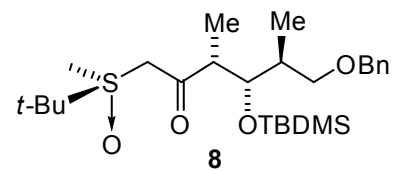


S-4

CDCl₃
(75 MHz)

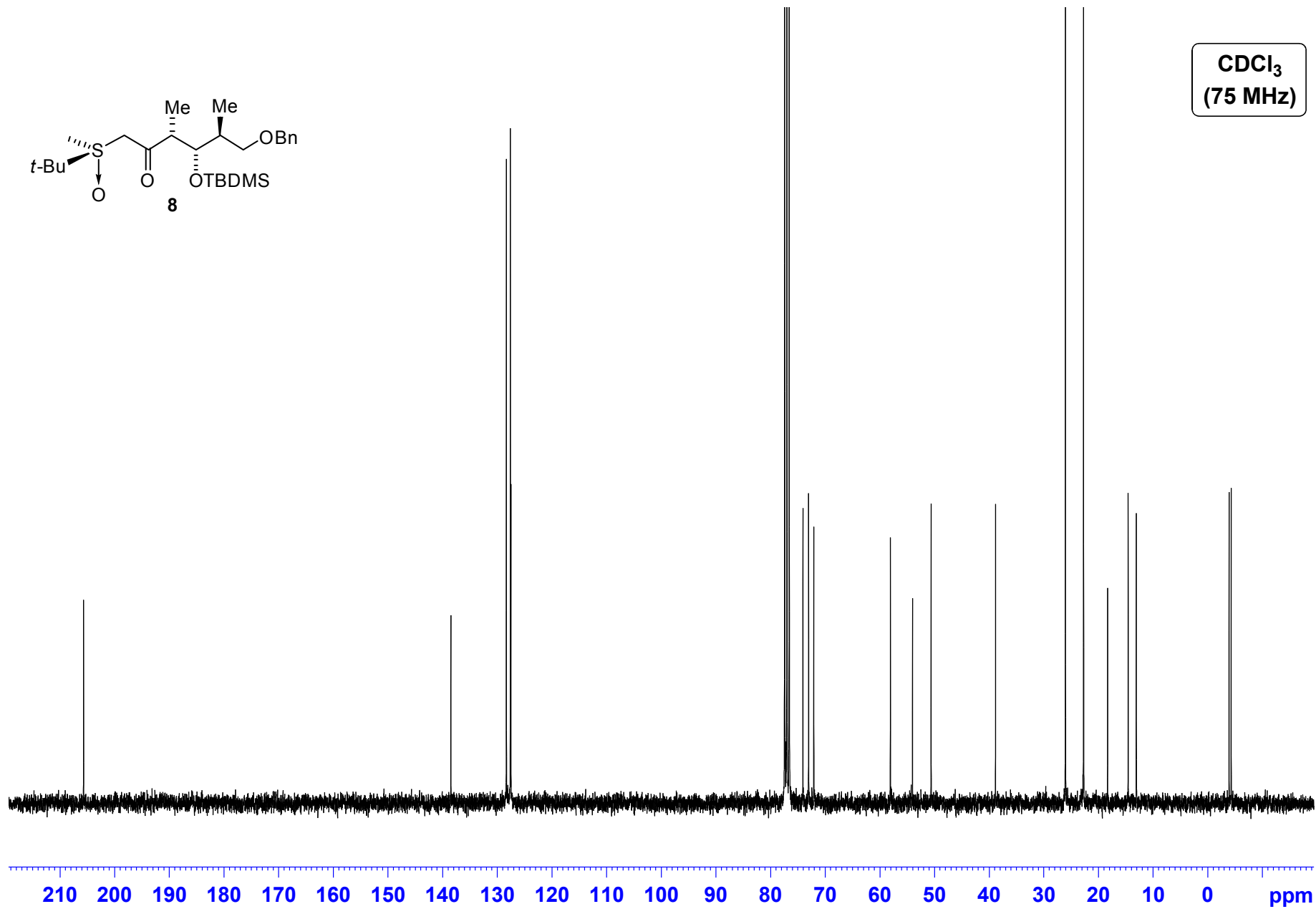
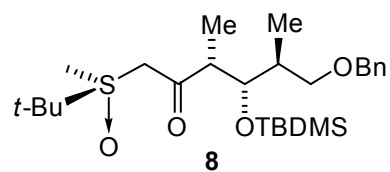


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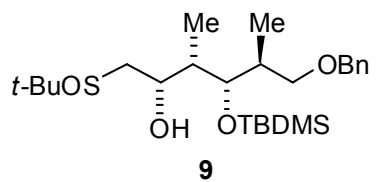


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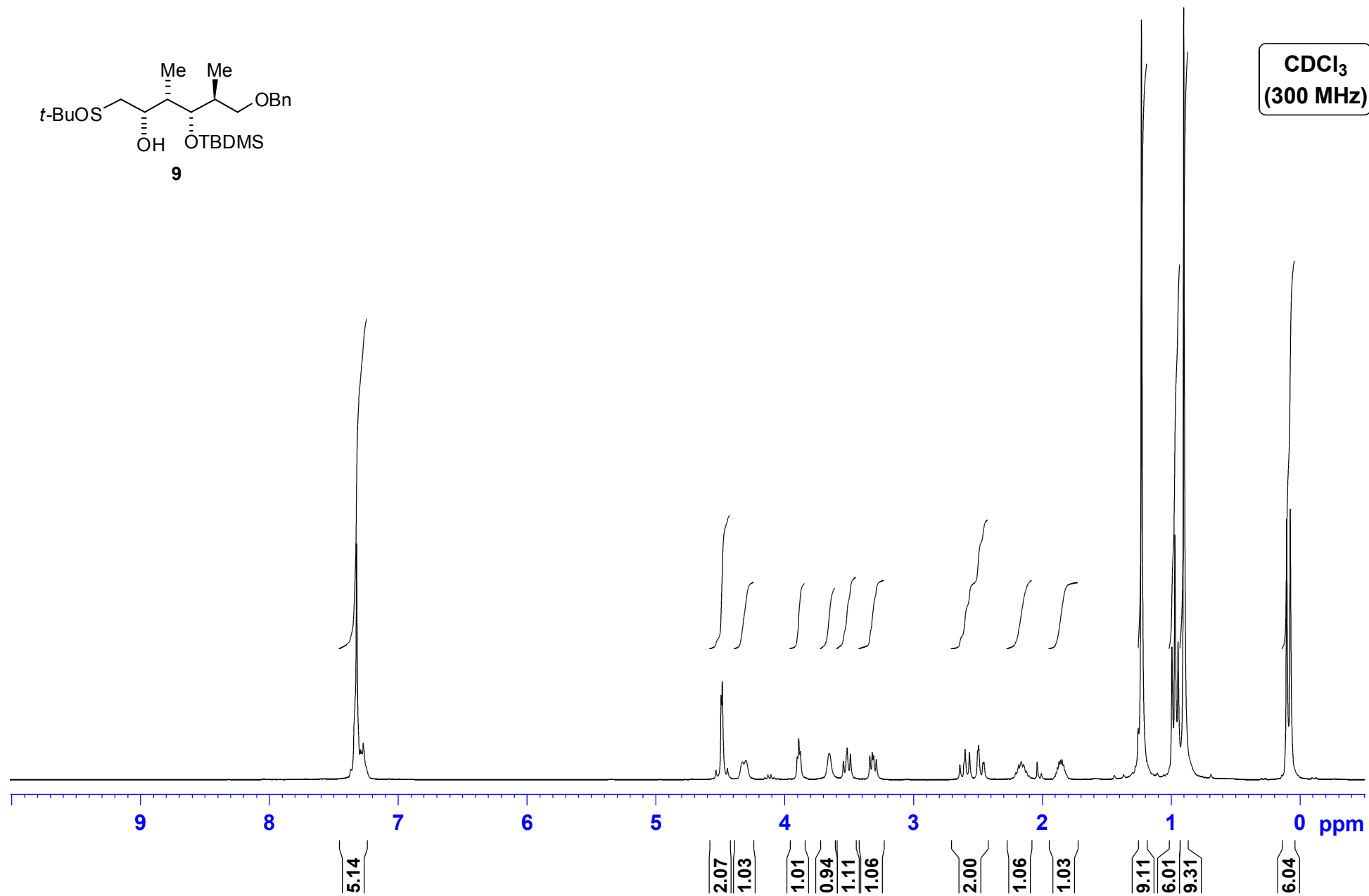
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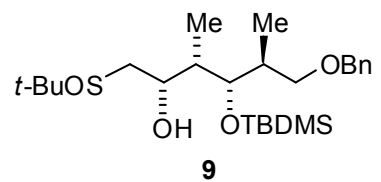
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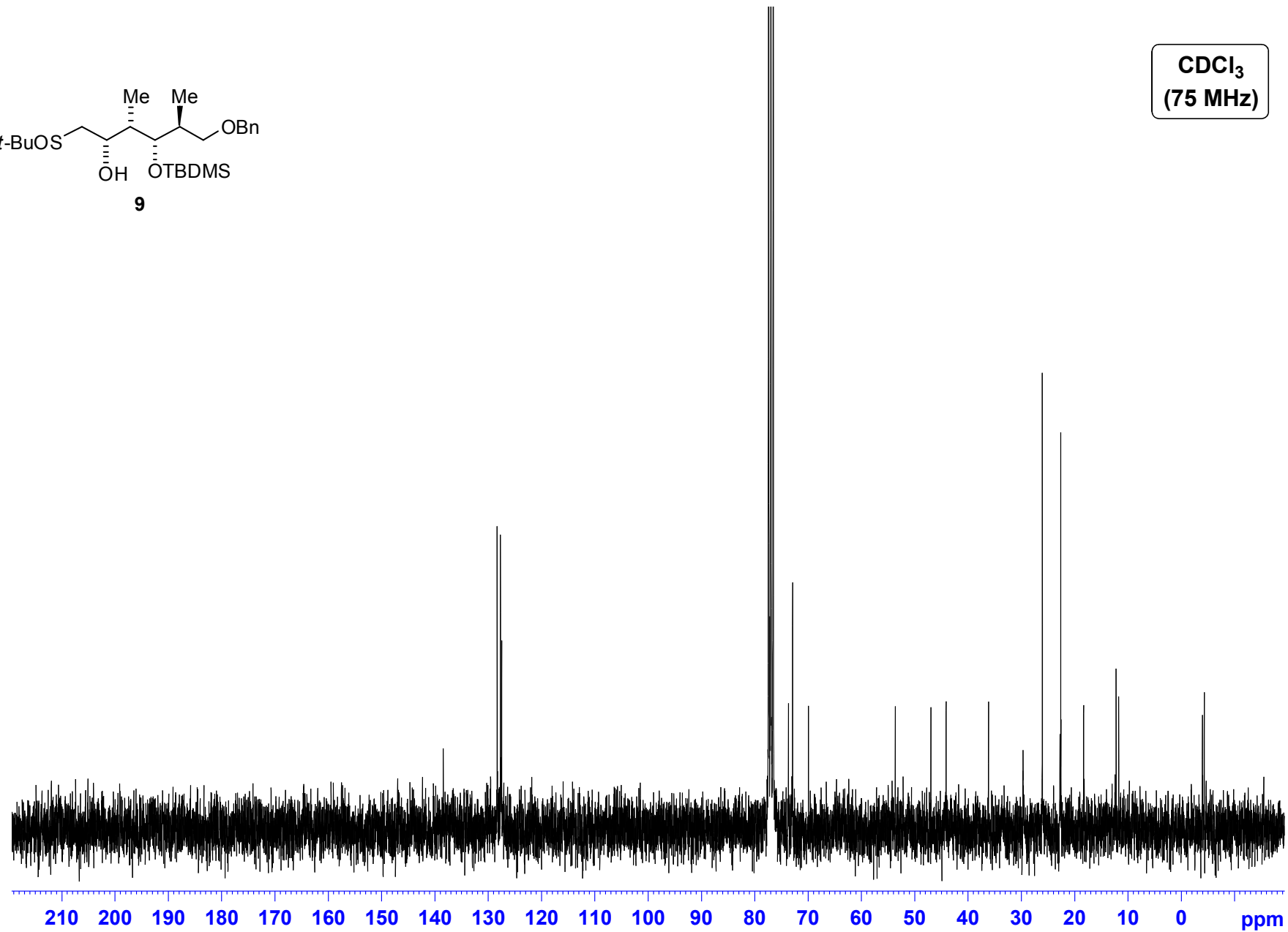
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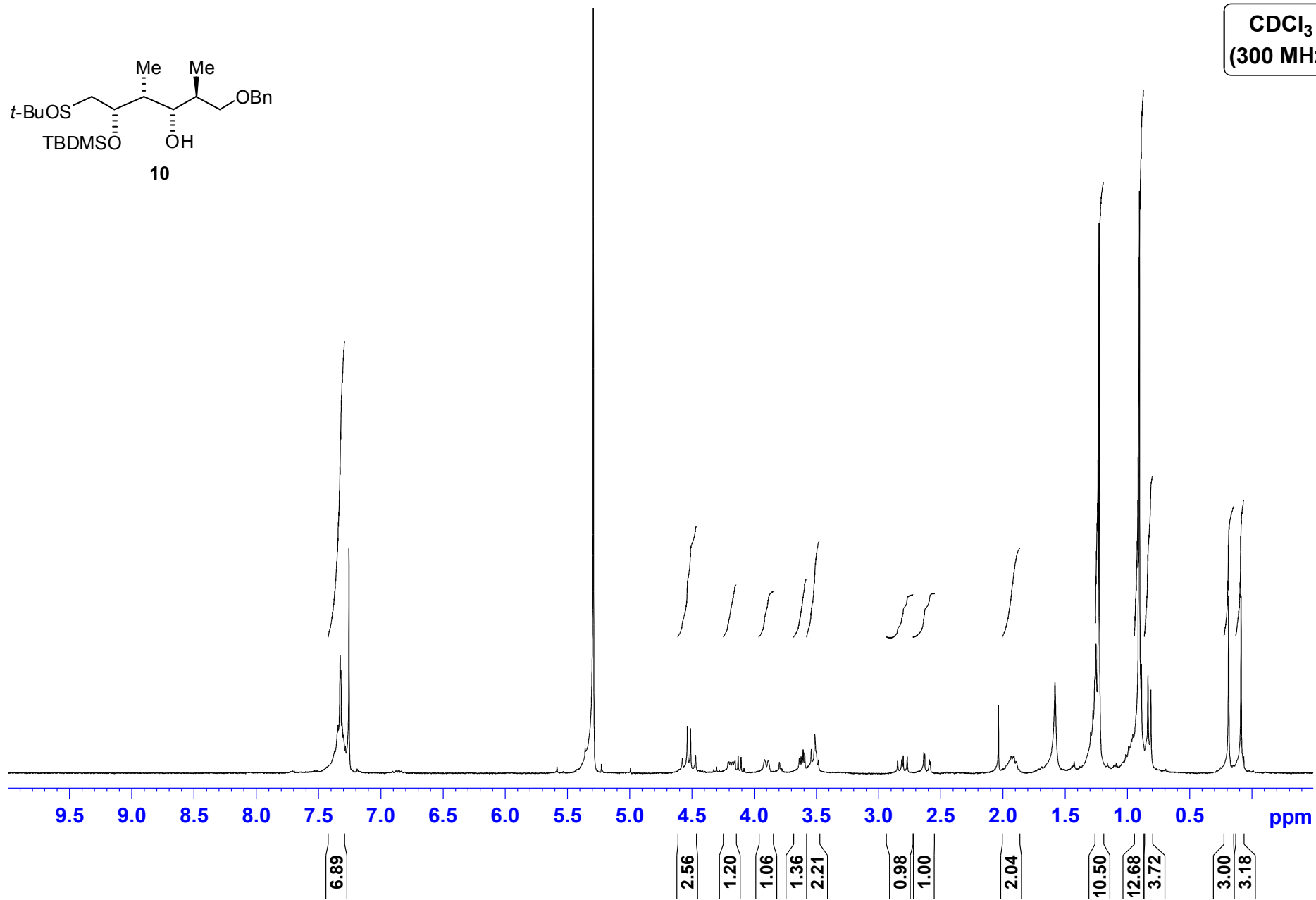
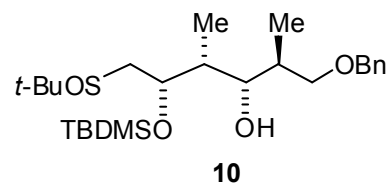


CDCl₃
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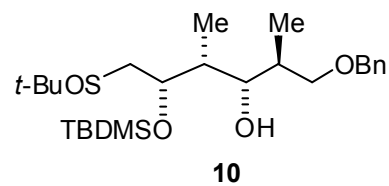


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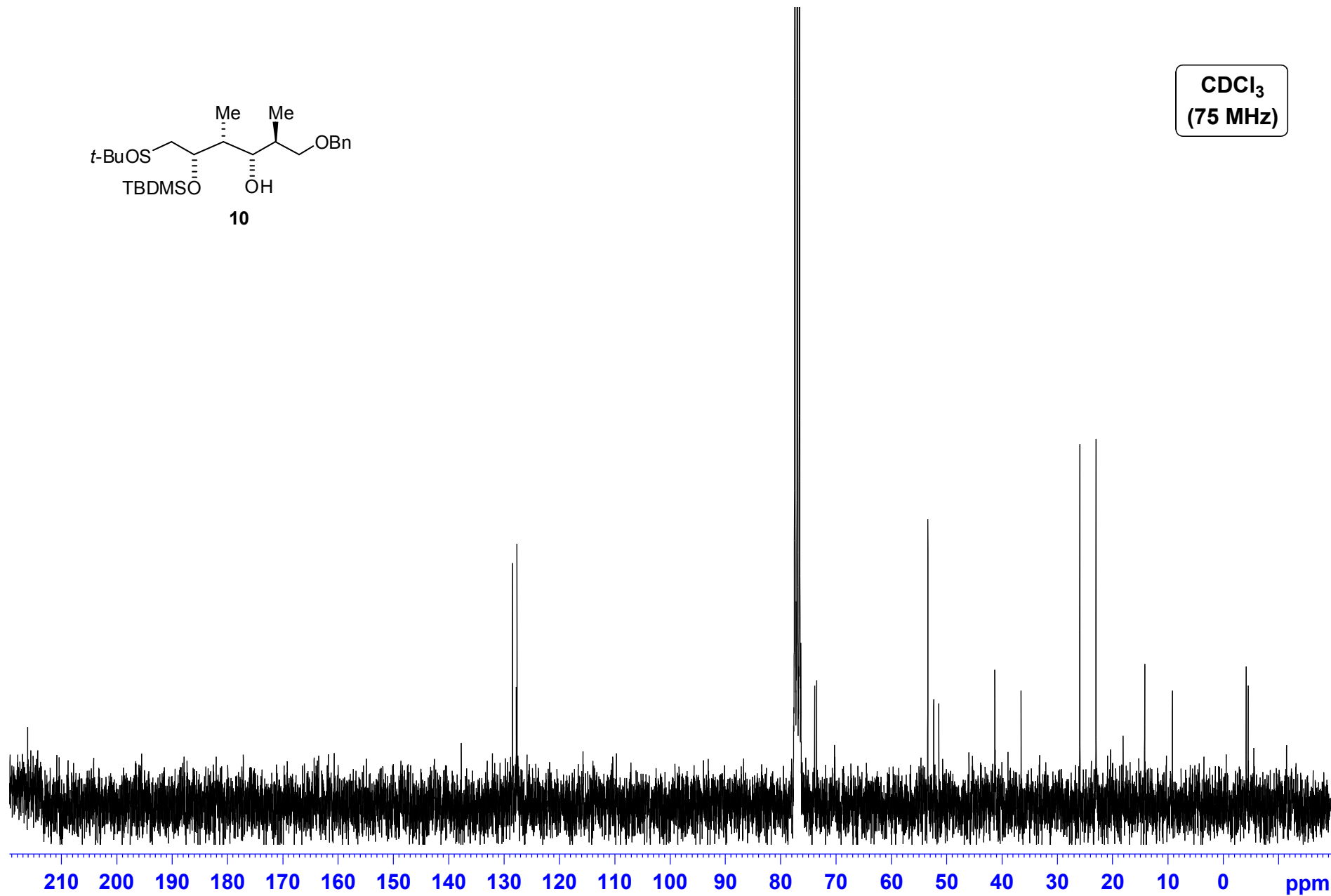
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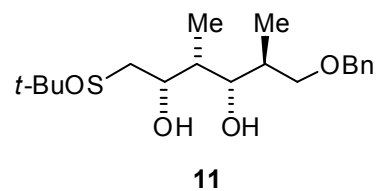
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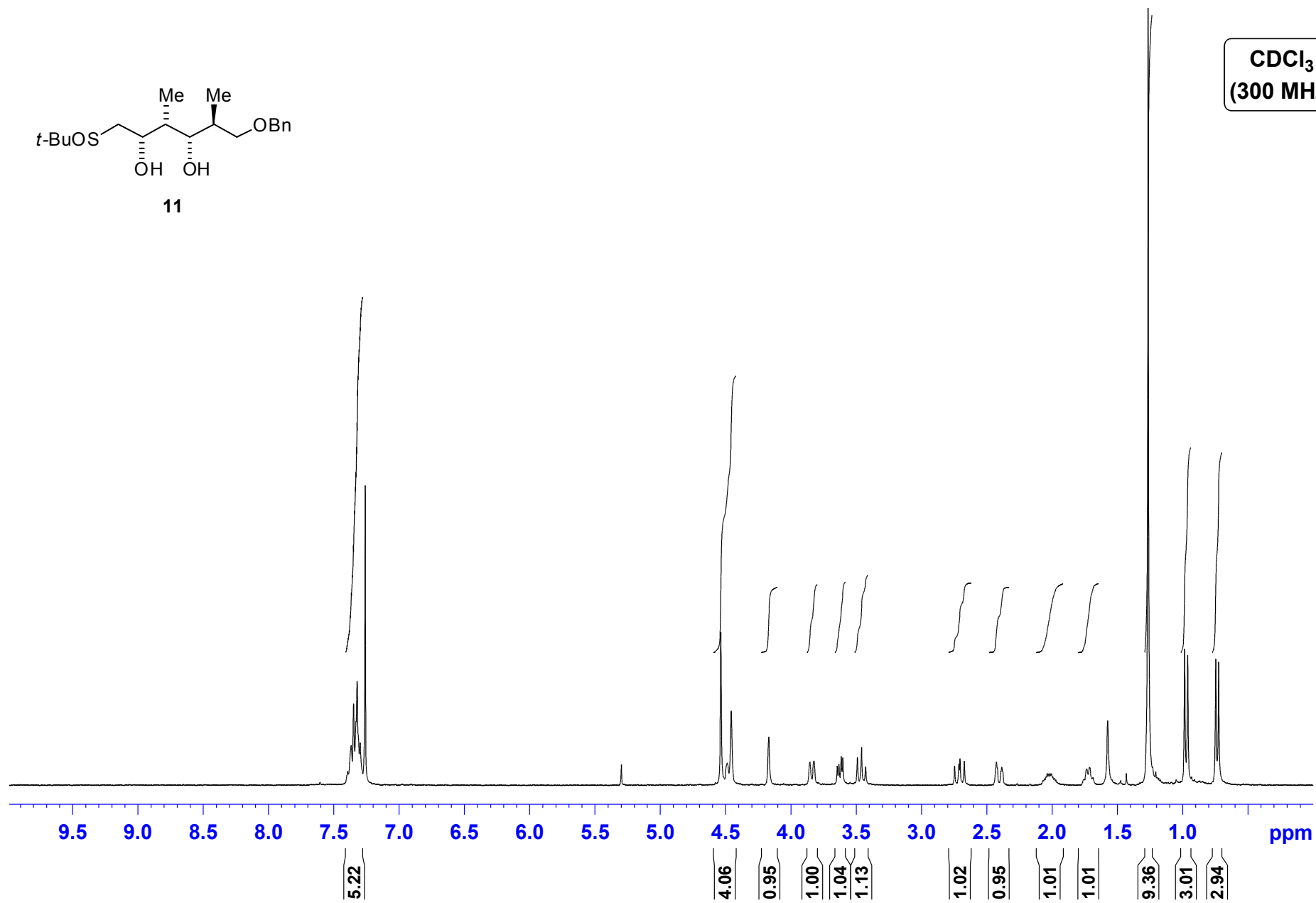
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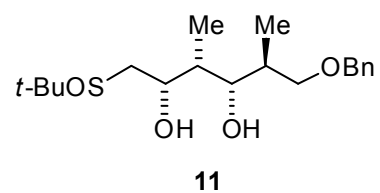
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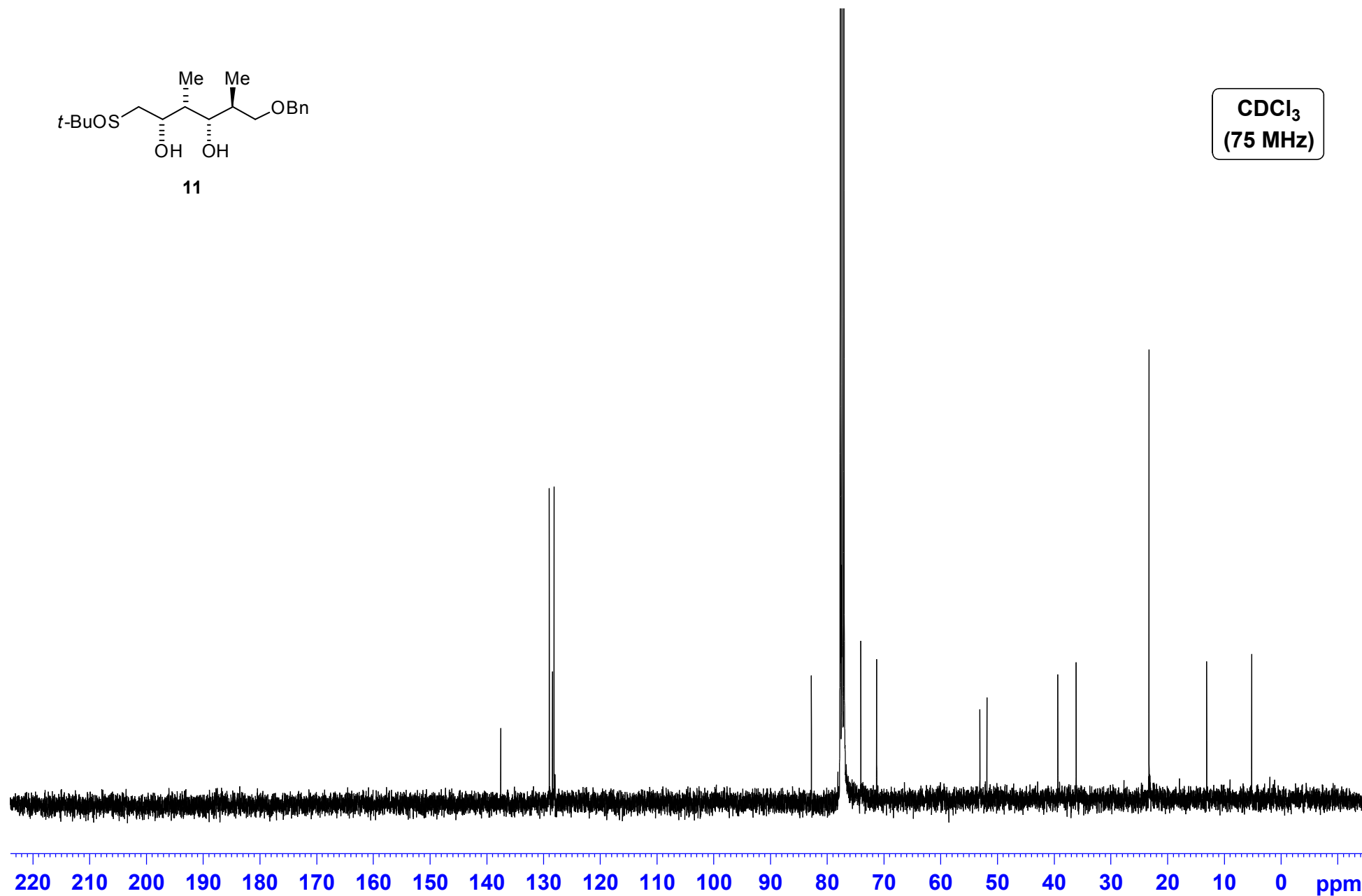
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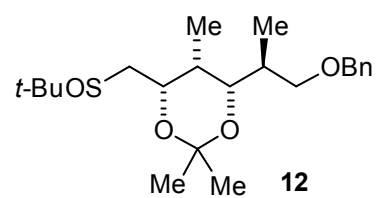
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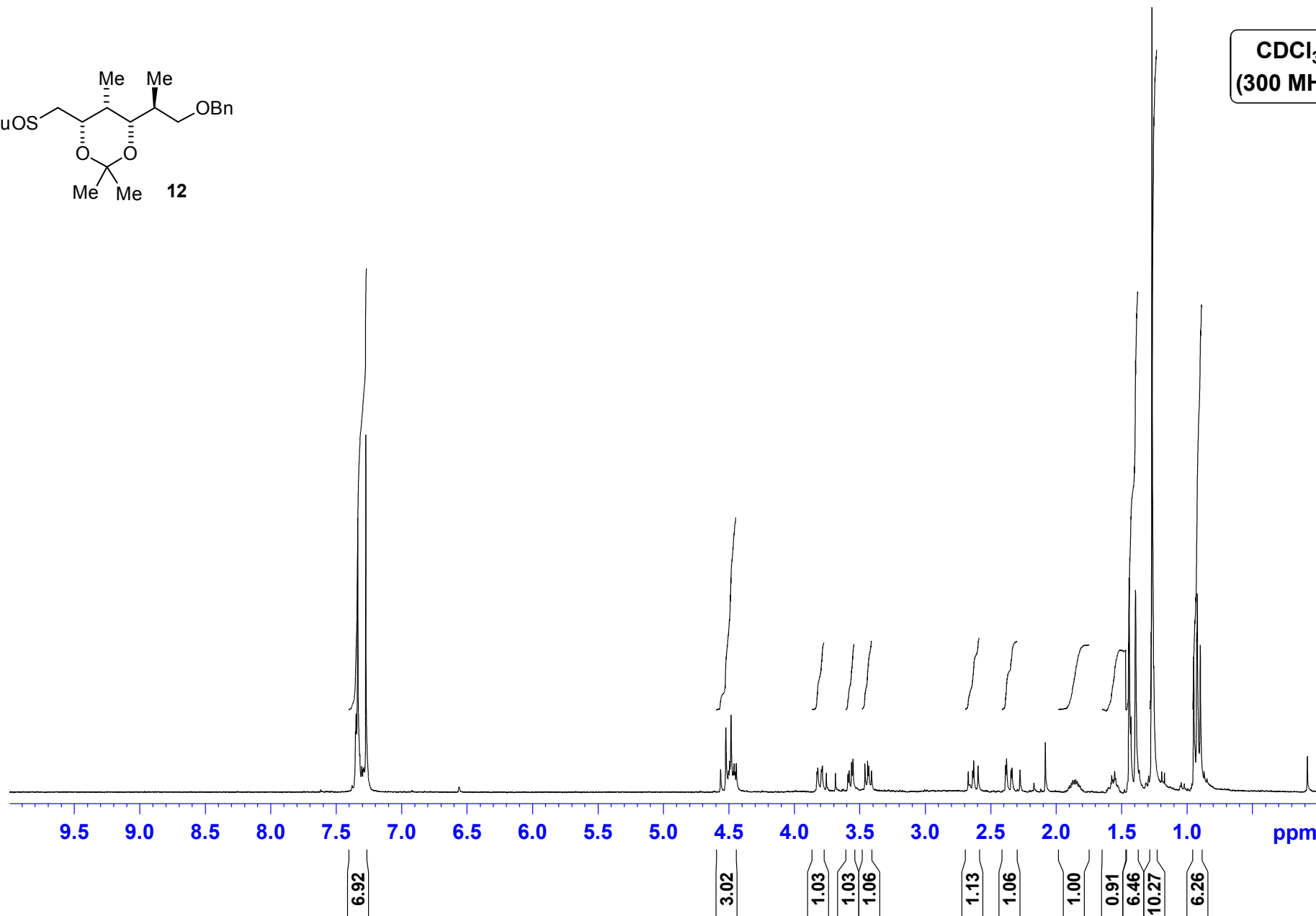
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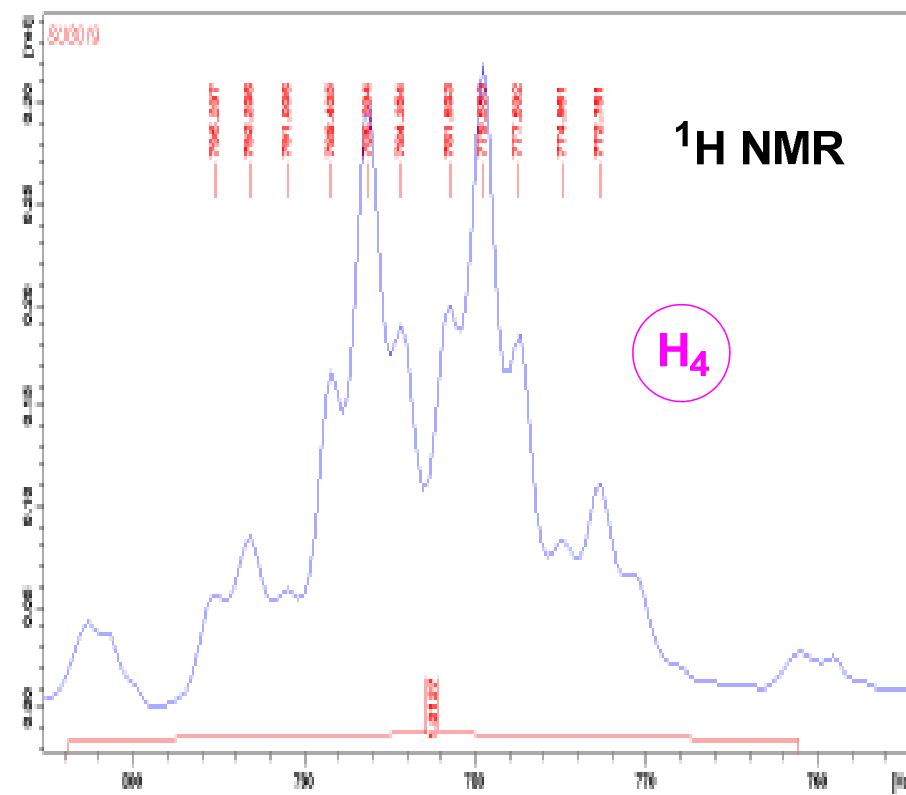
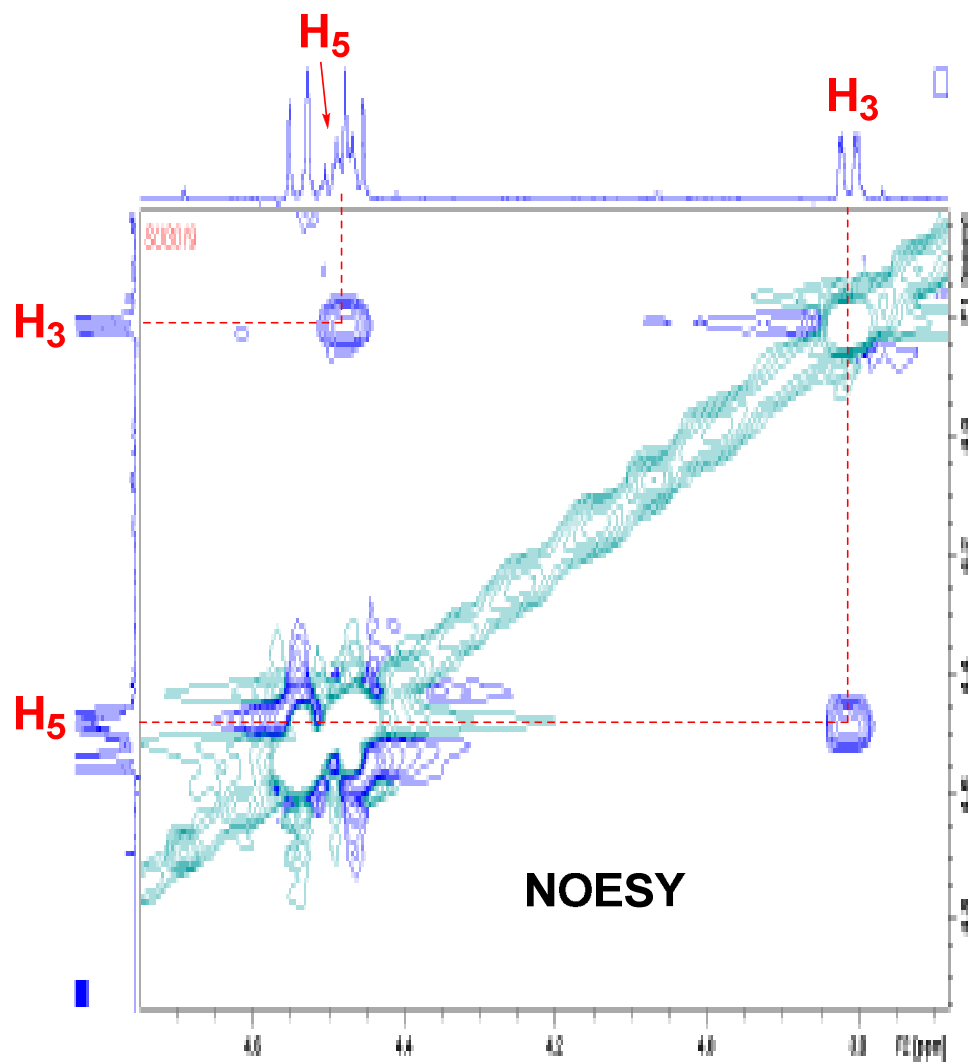
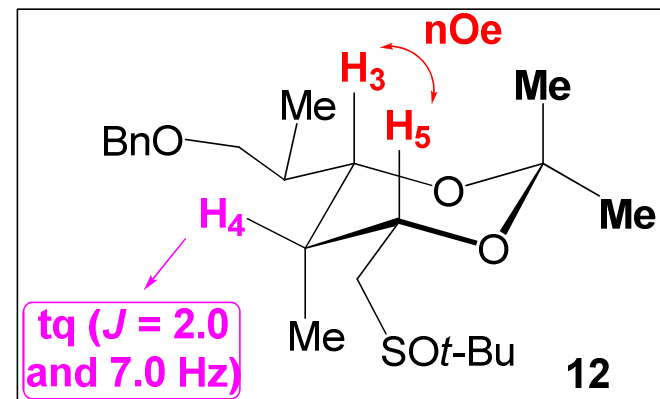
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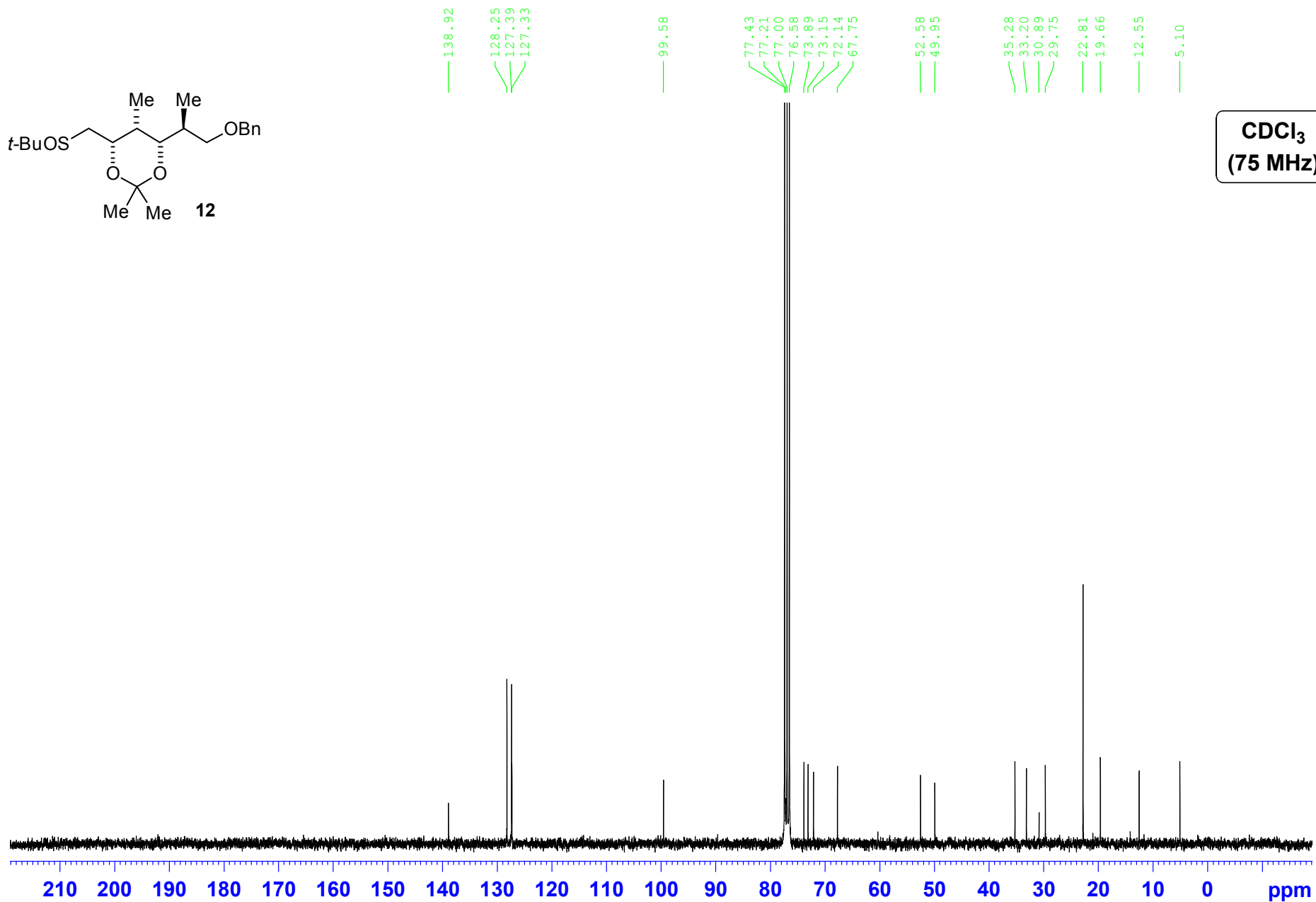
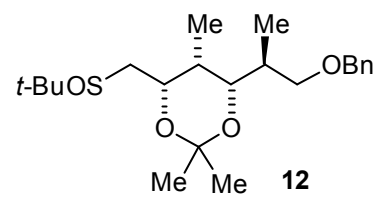
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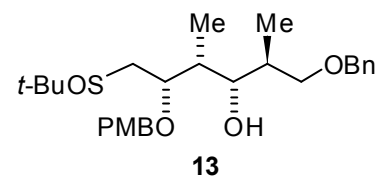
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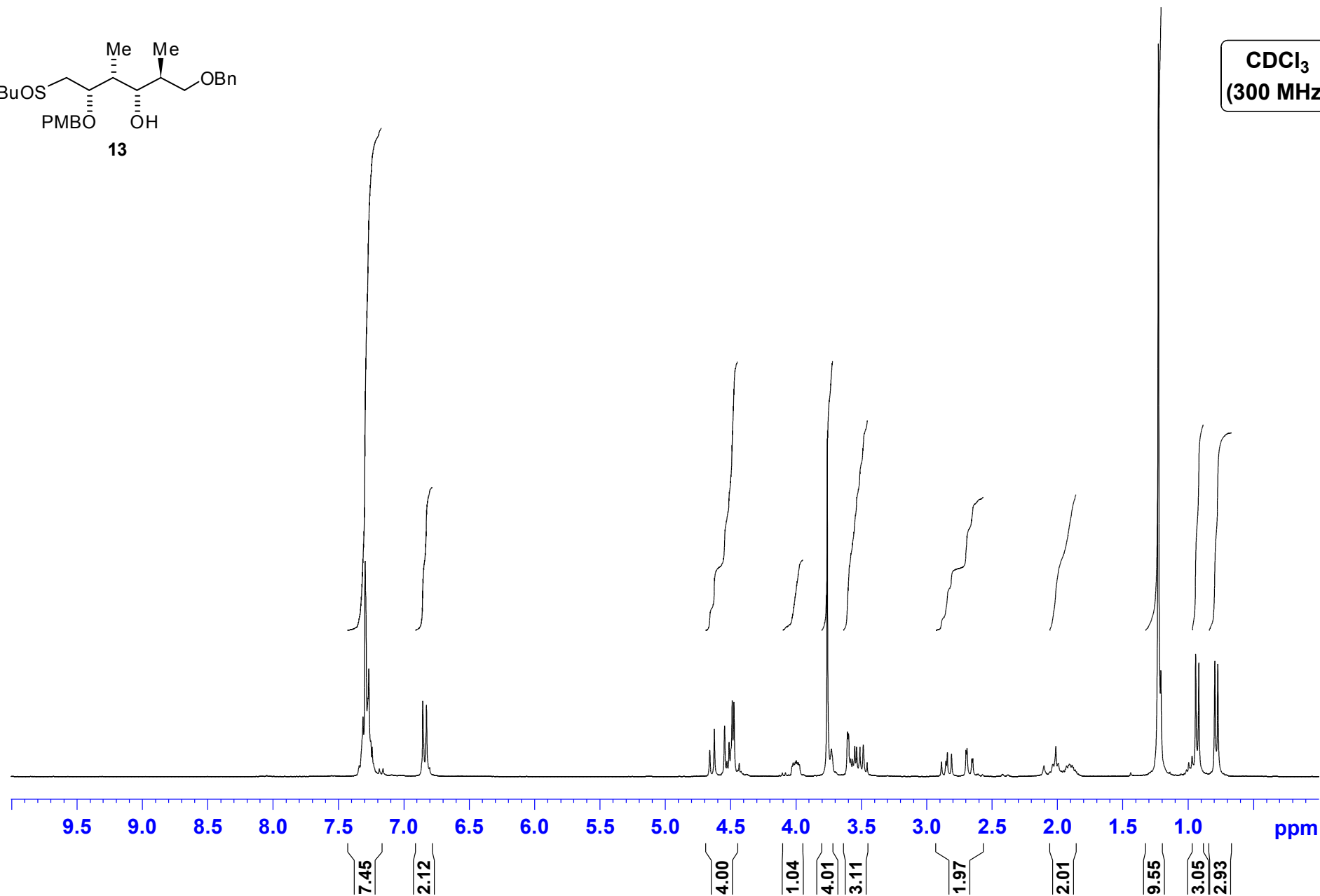
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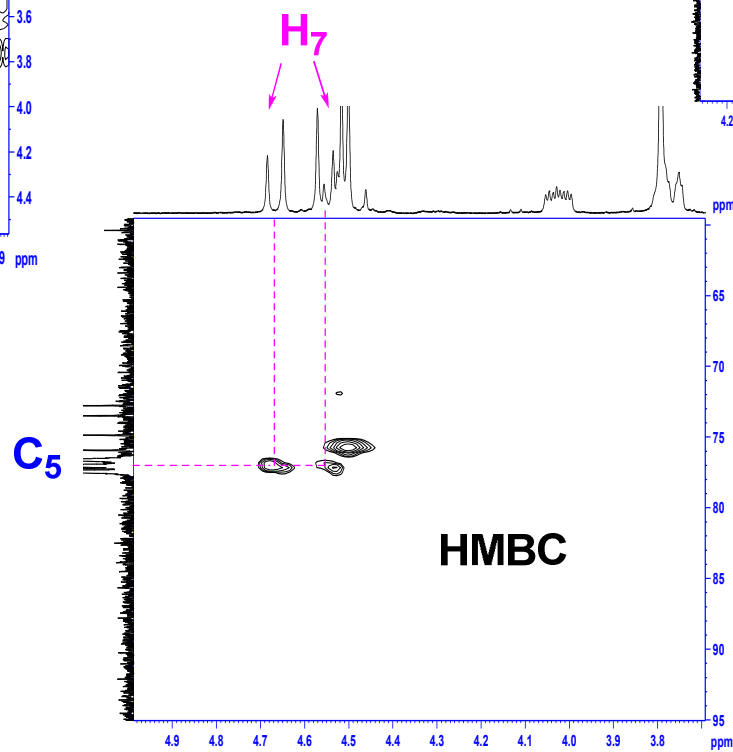
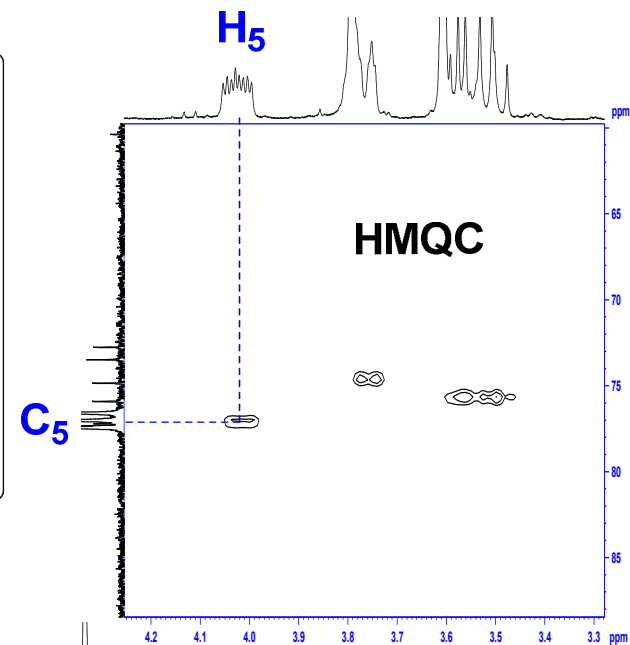
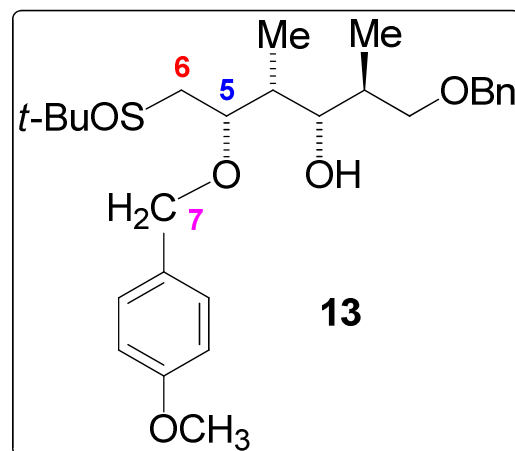
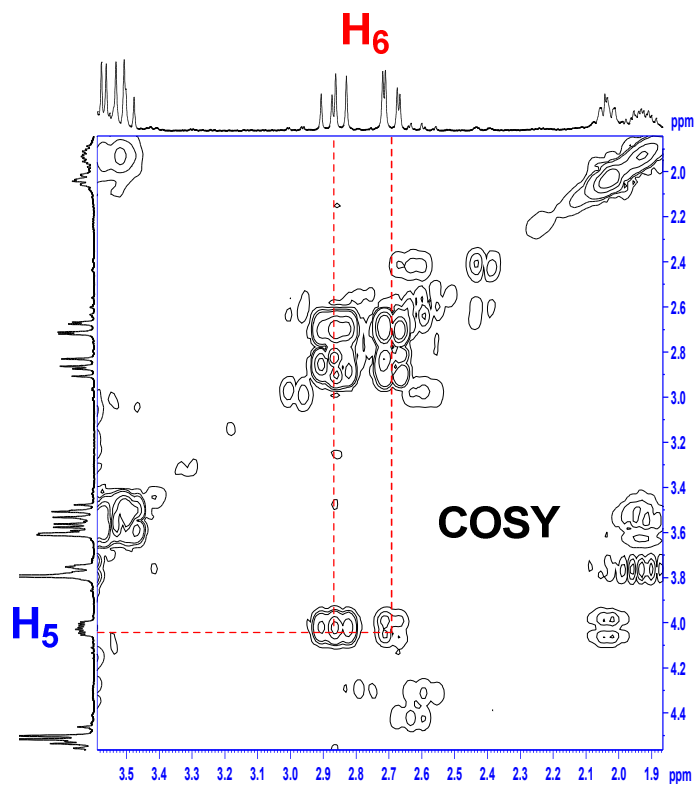
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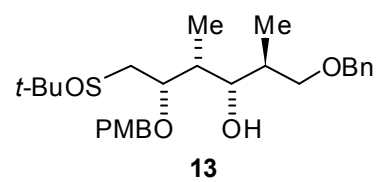
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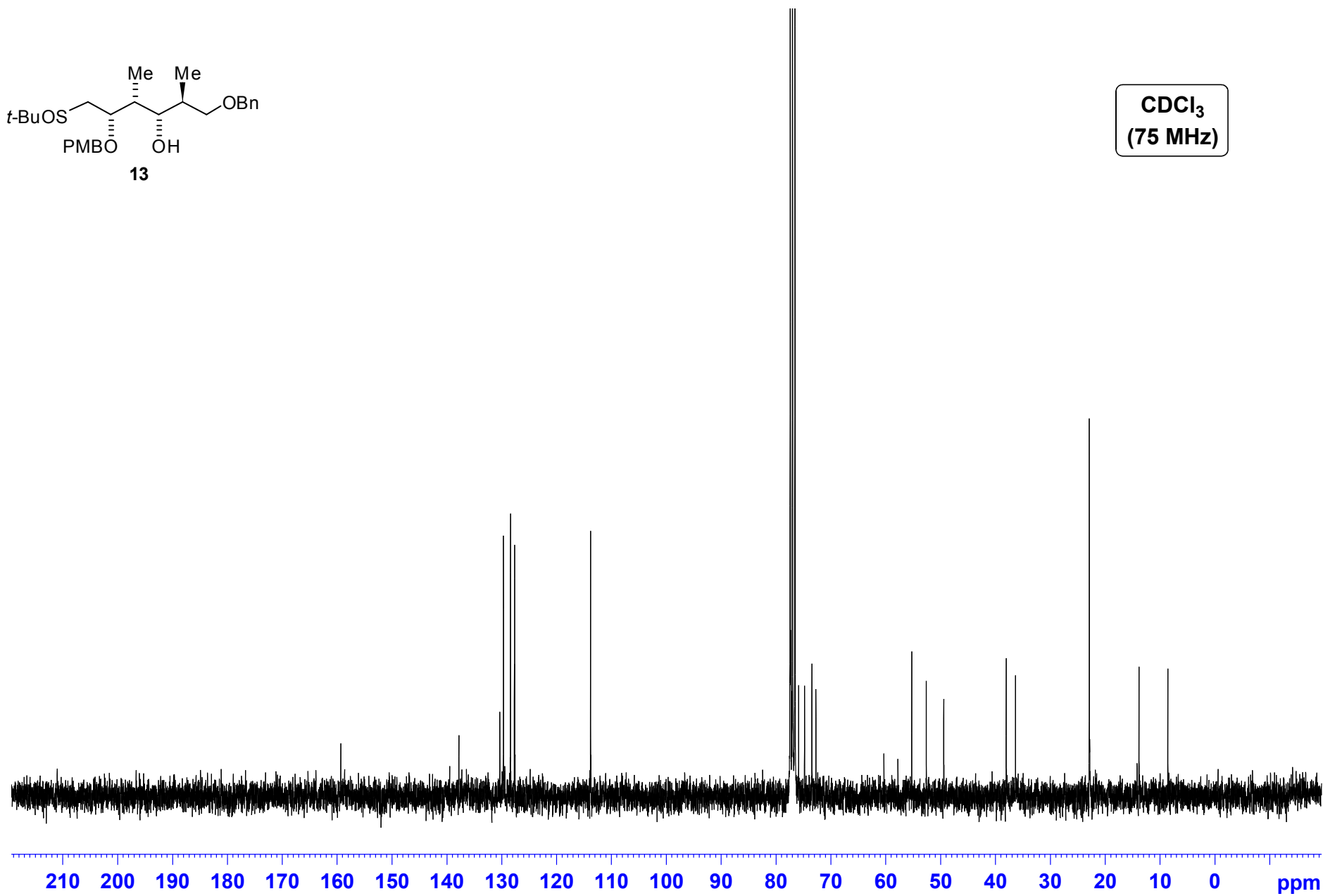
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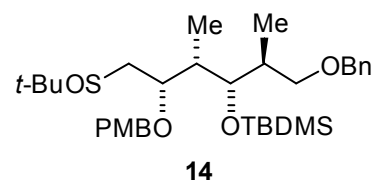
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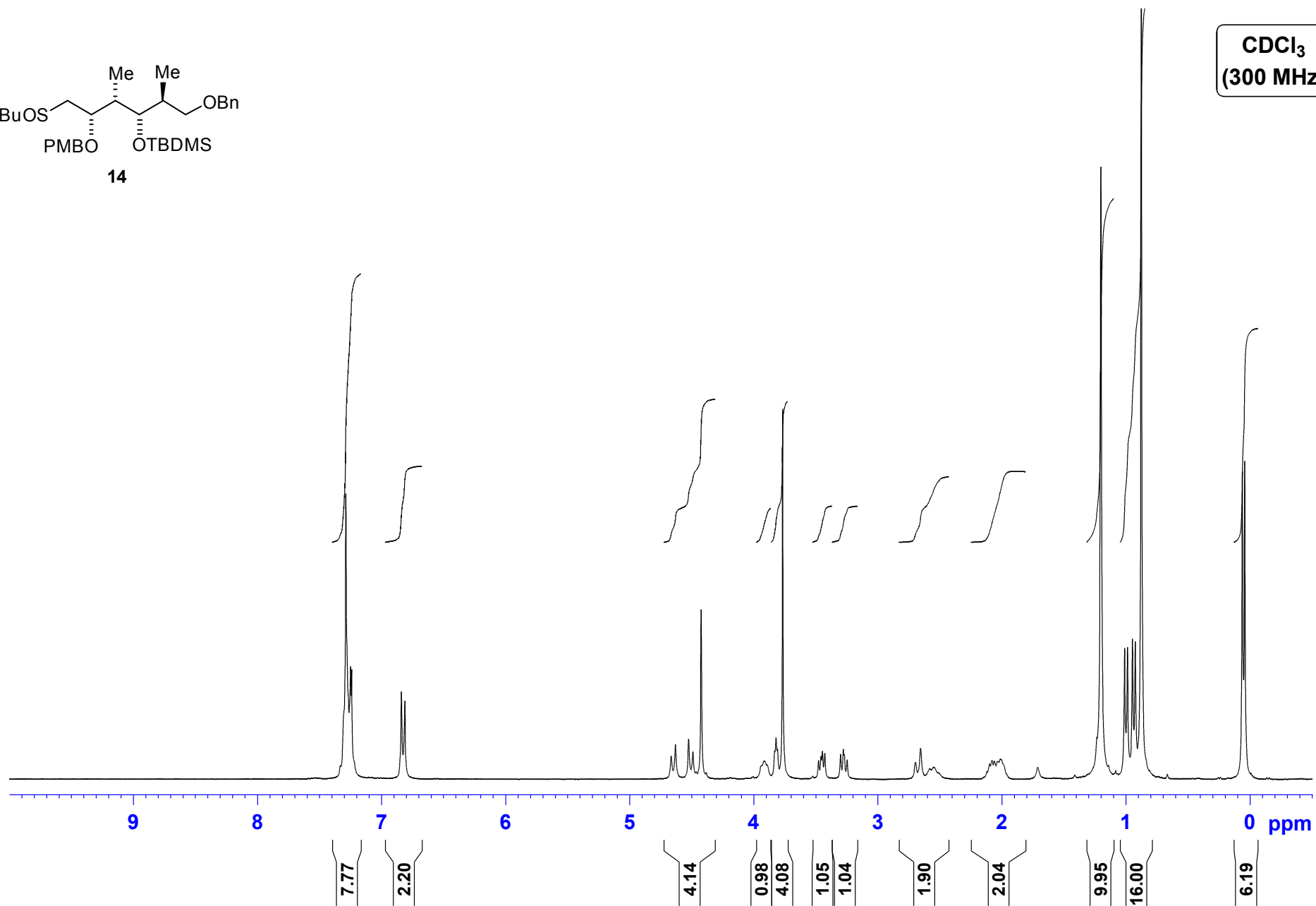
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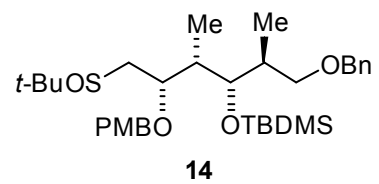
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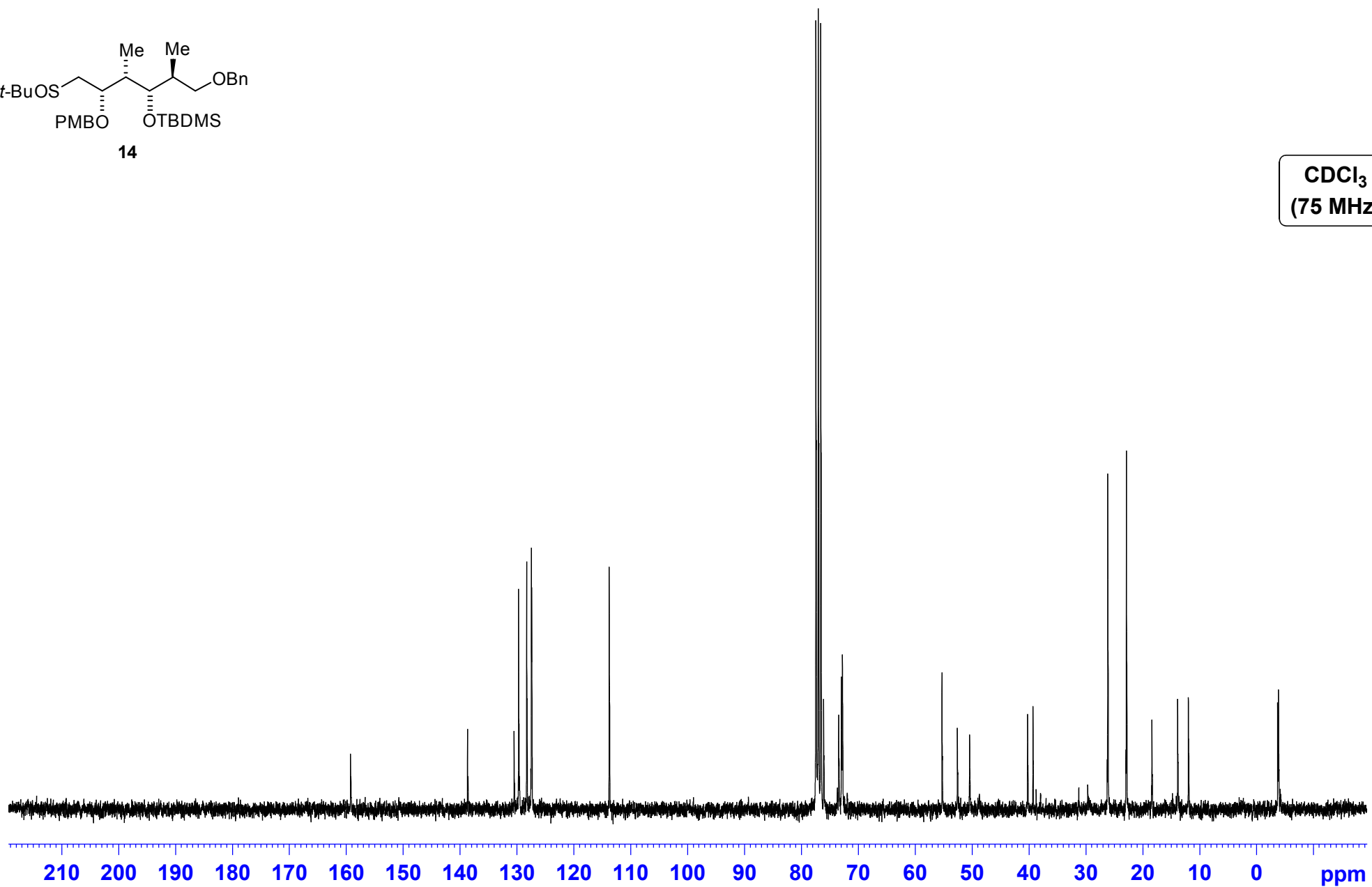
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S-20

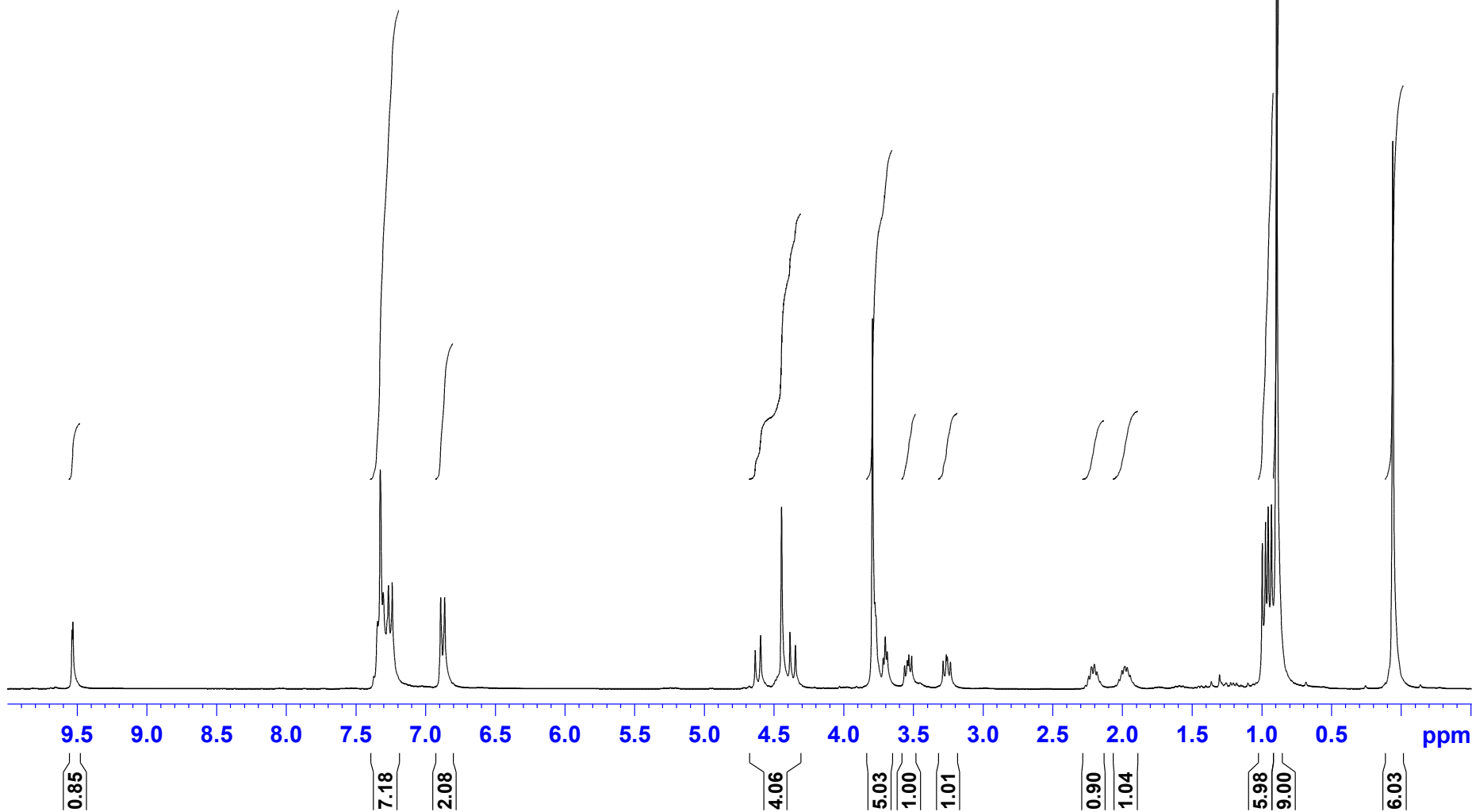
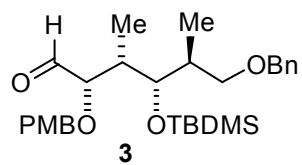


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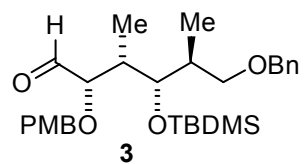


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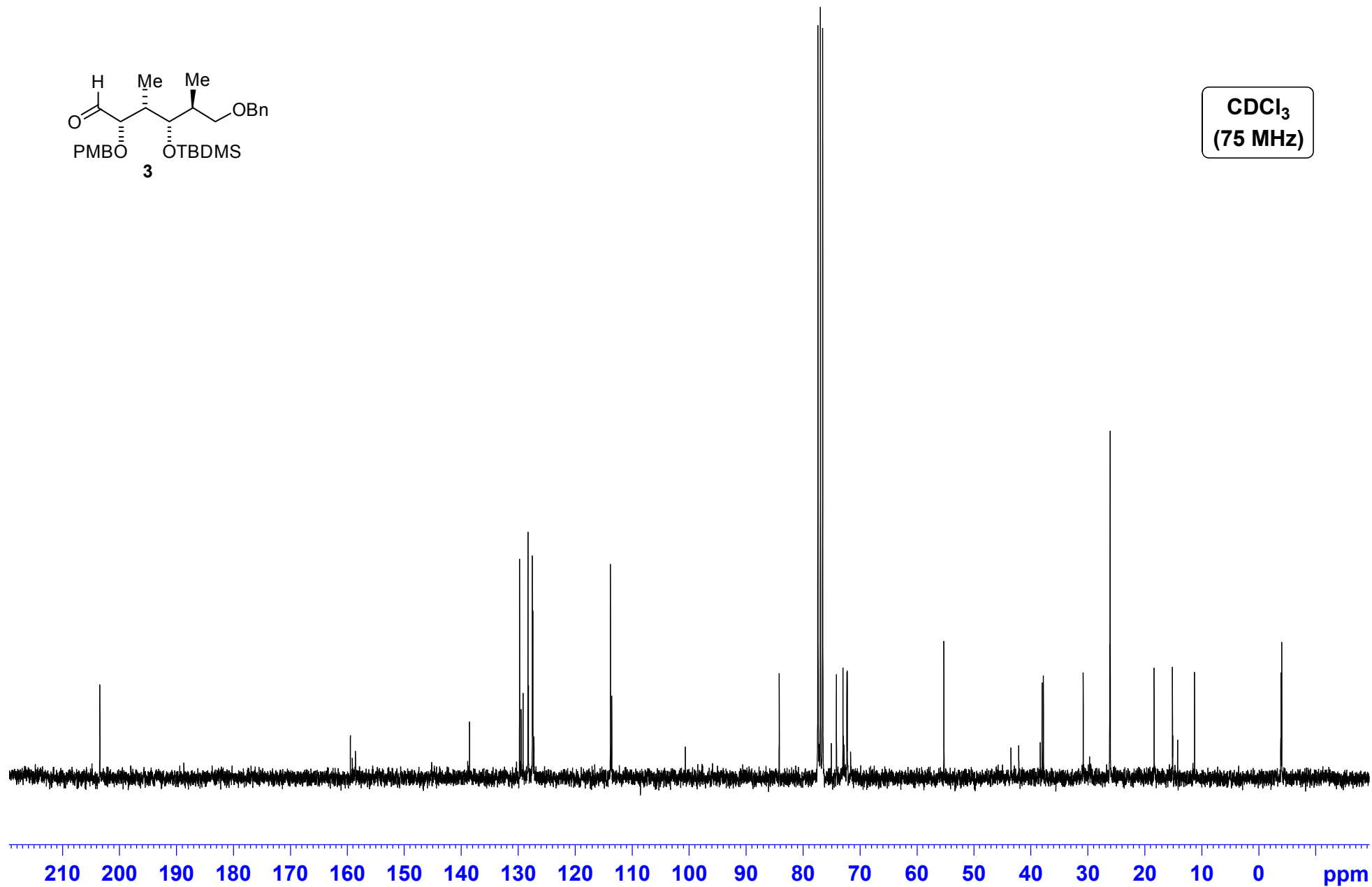
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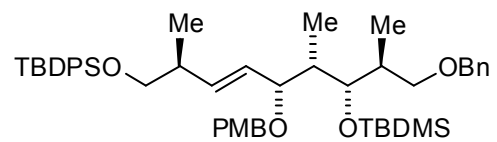
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CDCl₃
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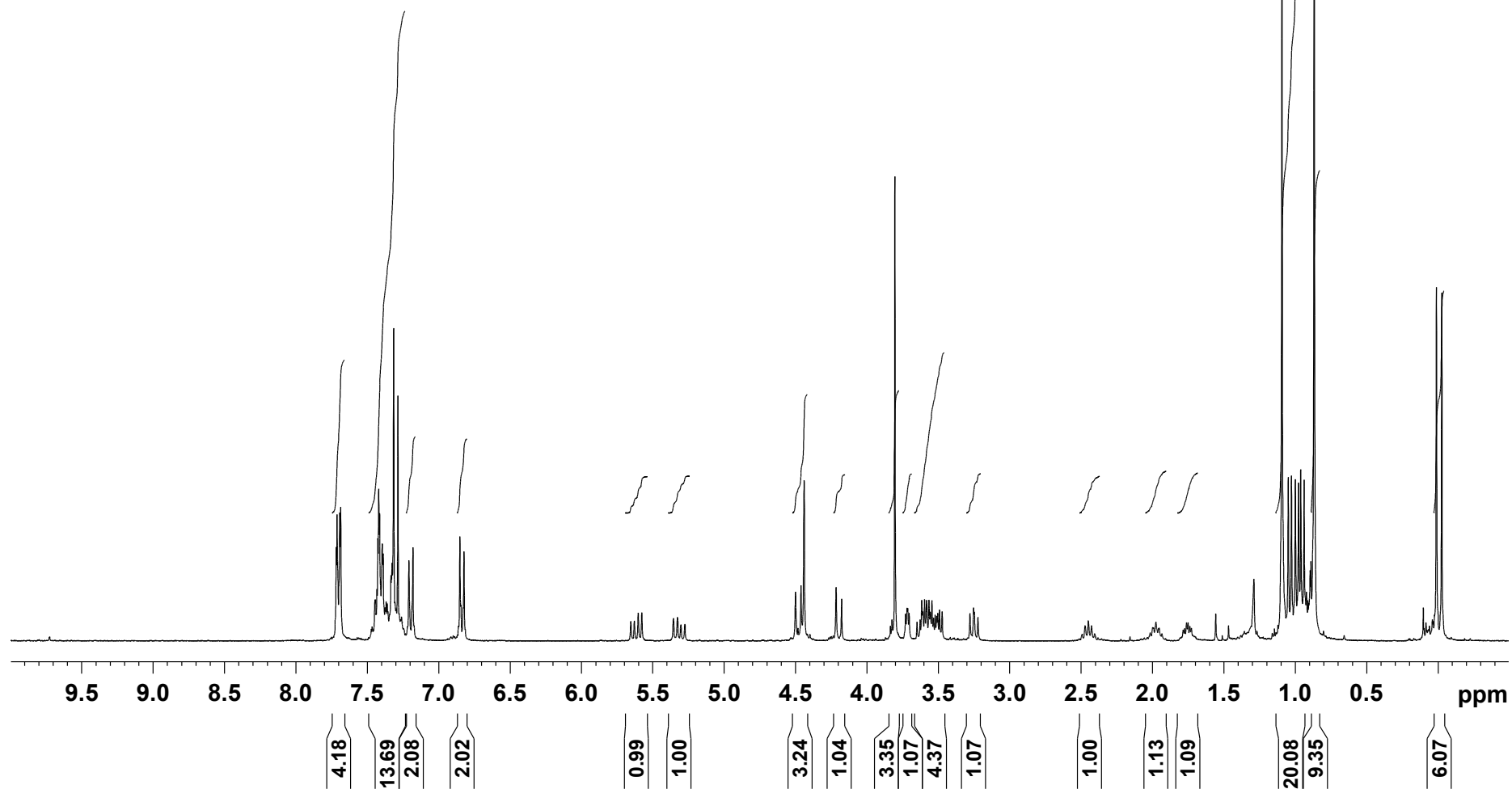


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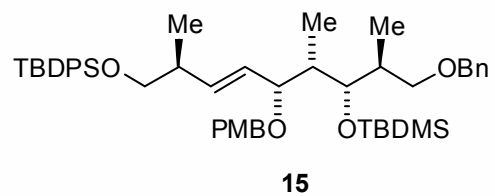


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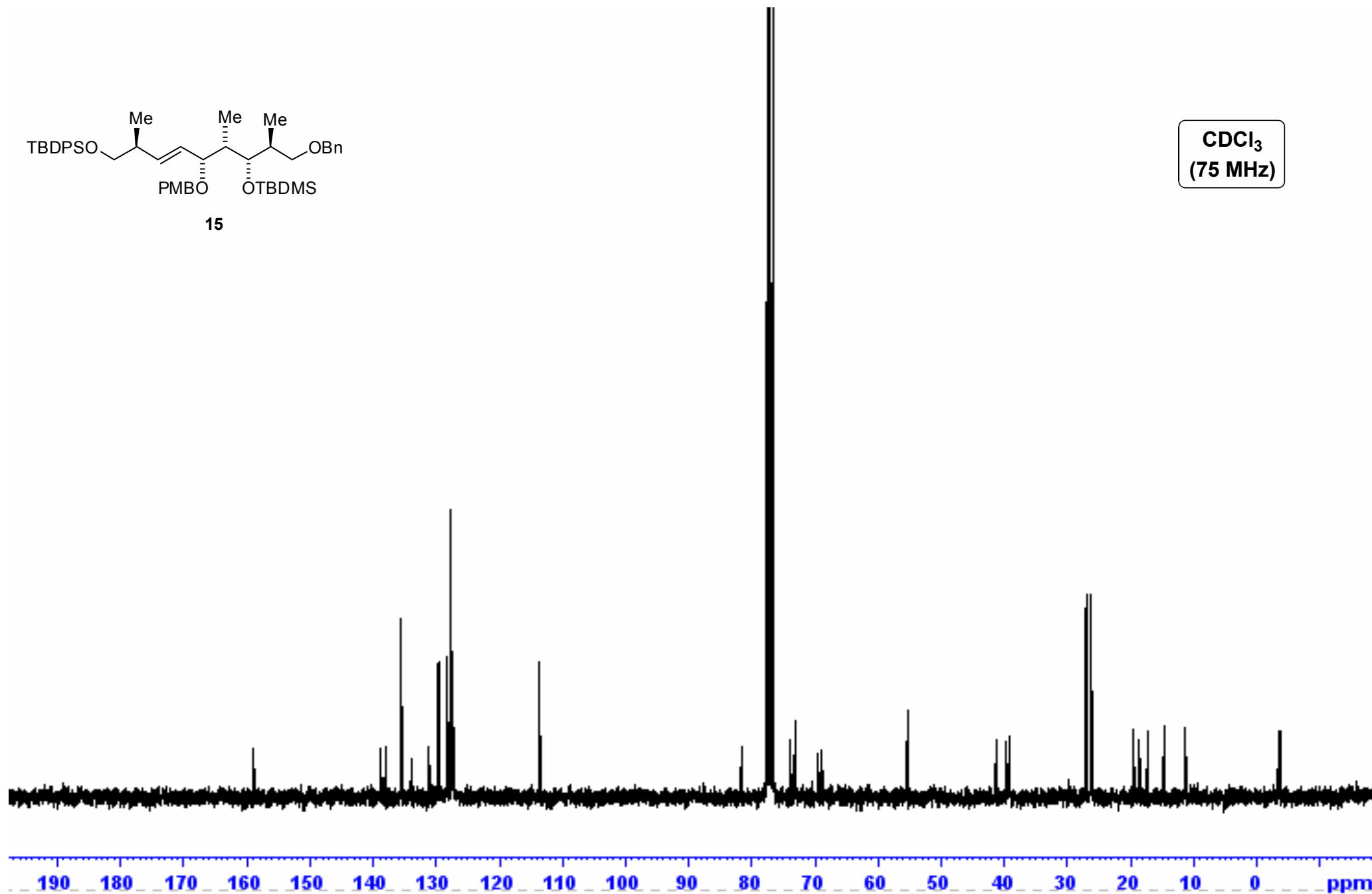
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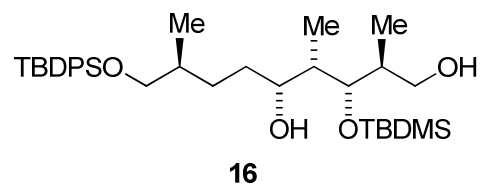
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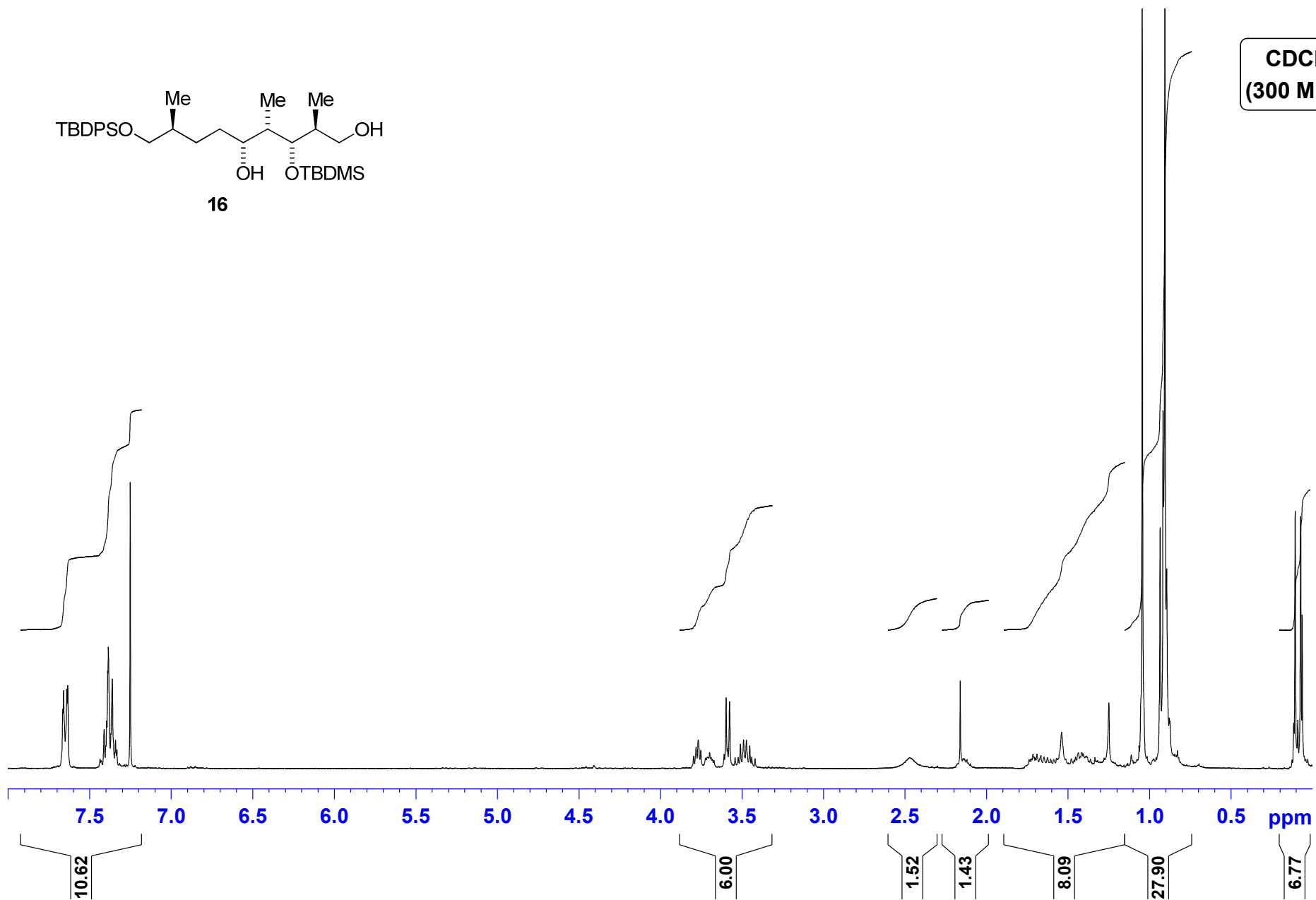
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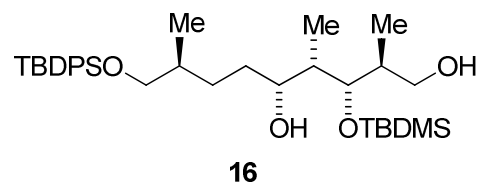
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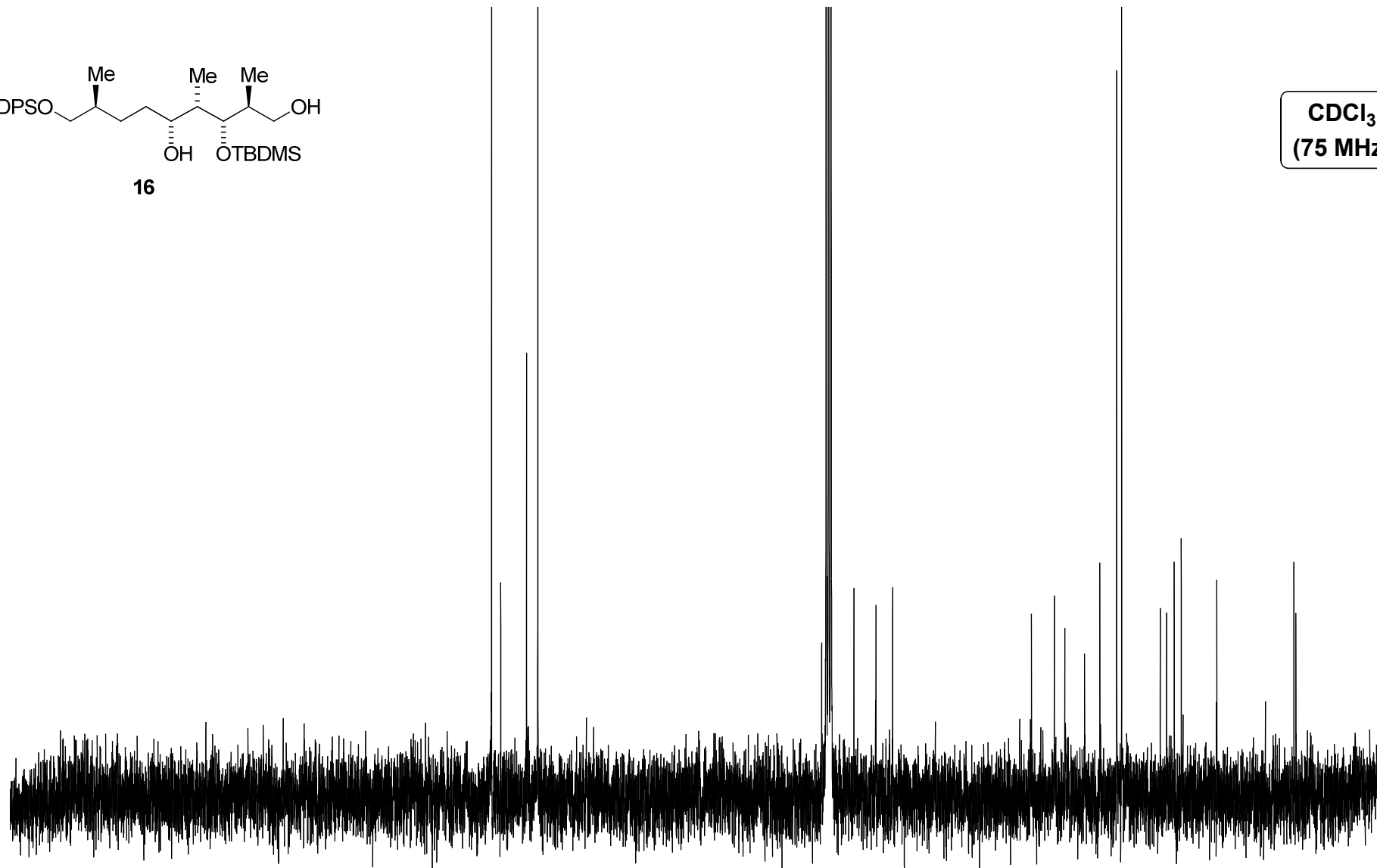
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S-26

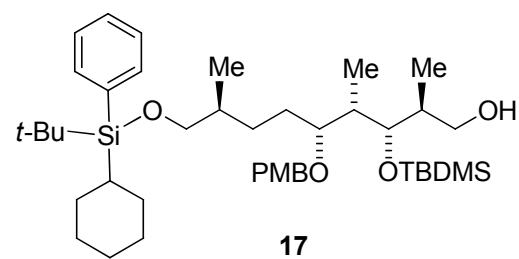


CDCl₃
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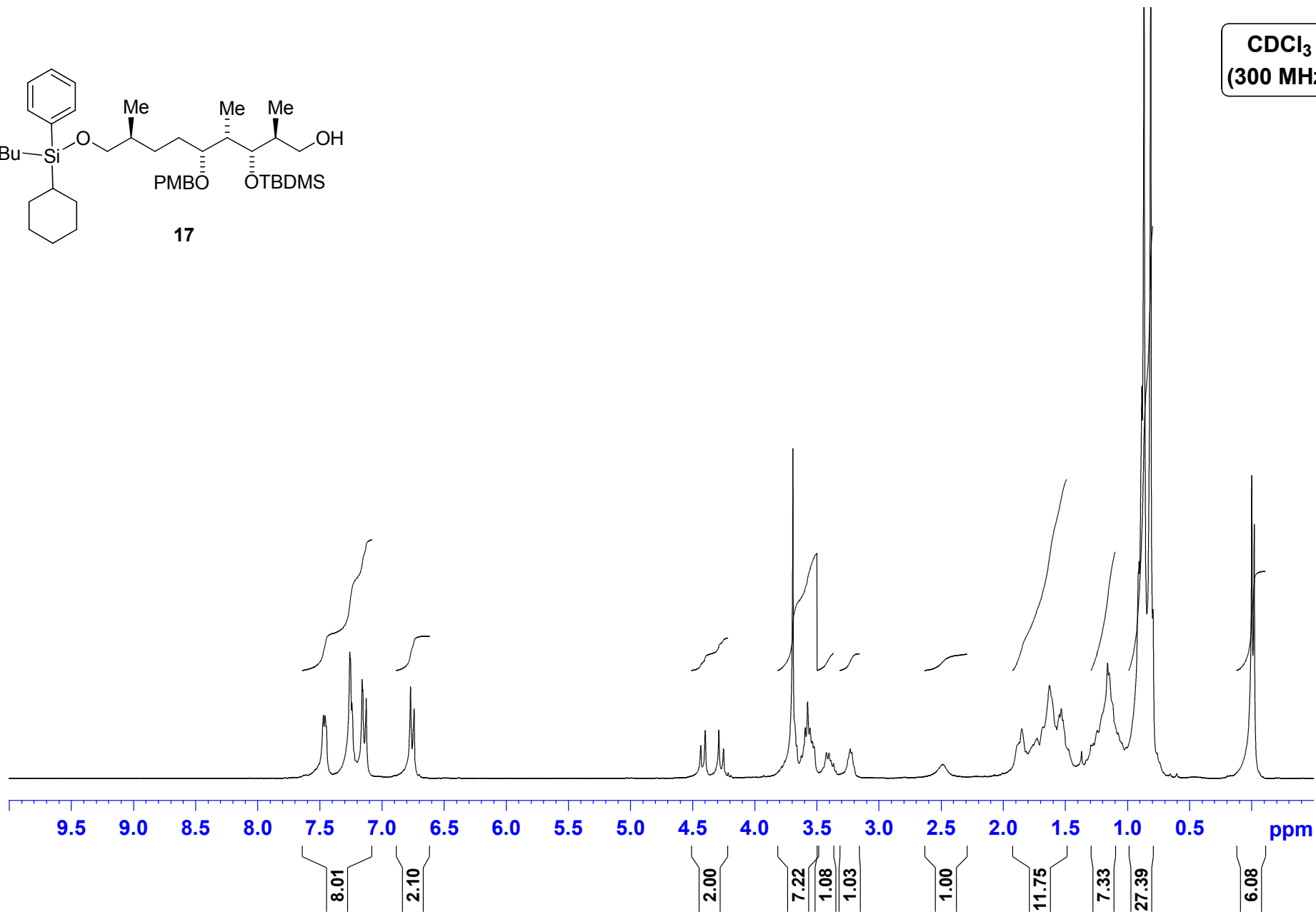
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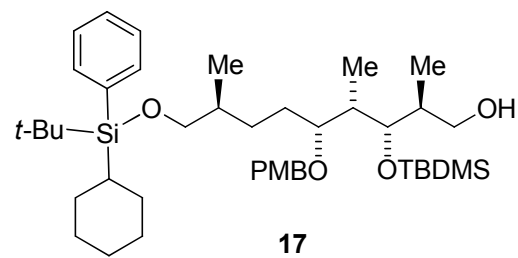


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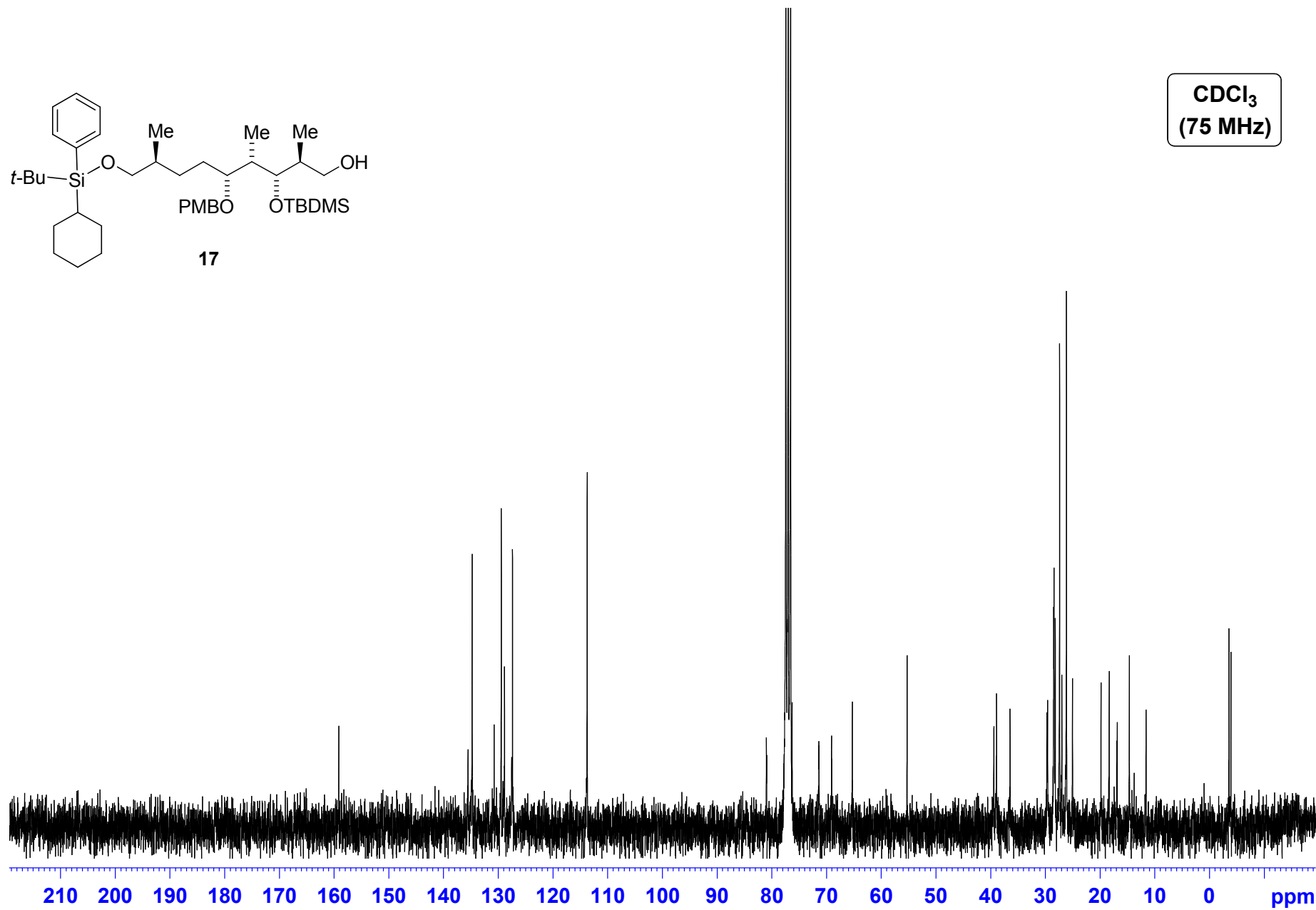
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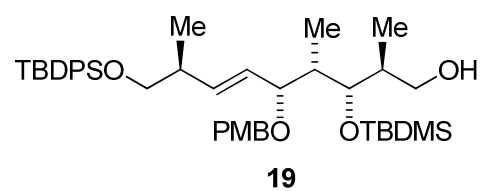
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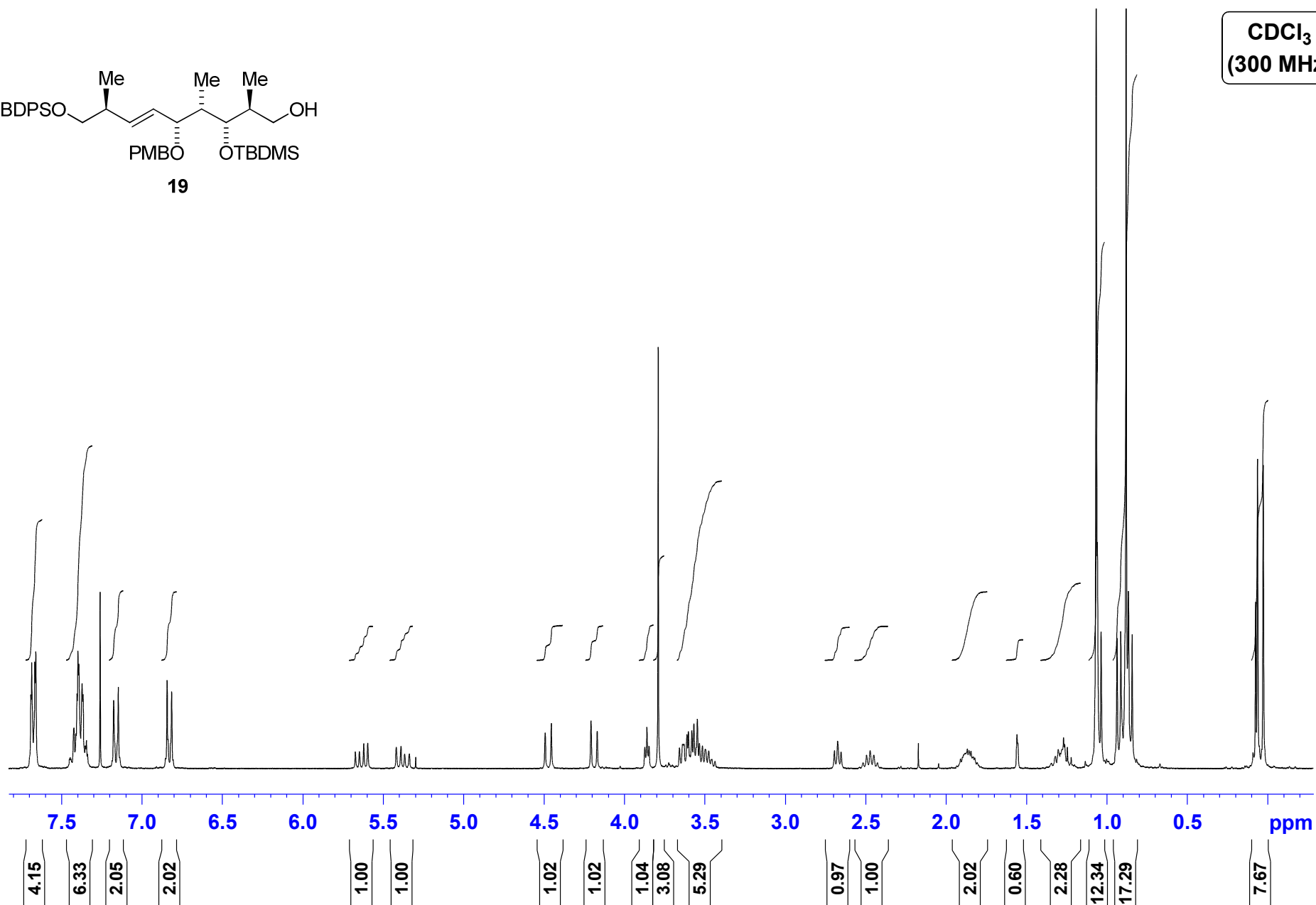
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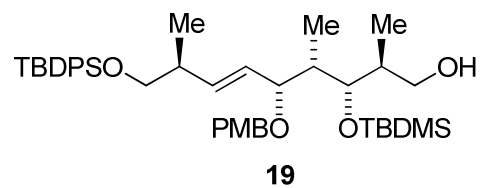
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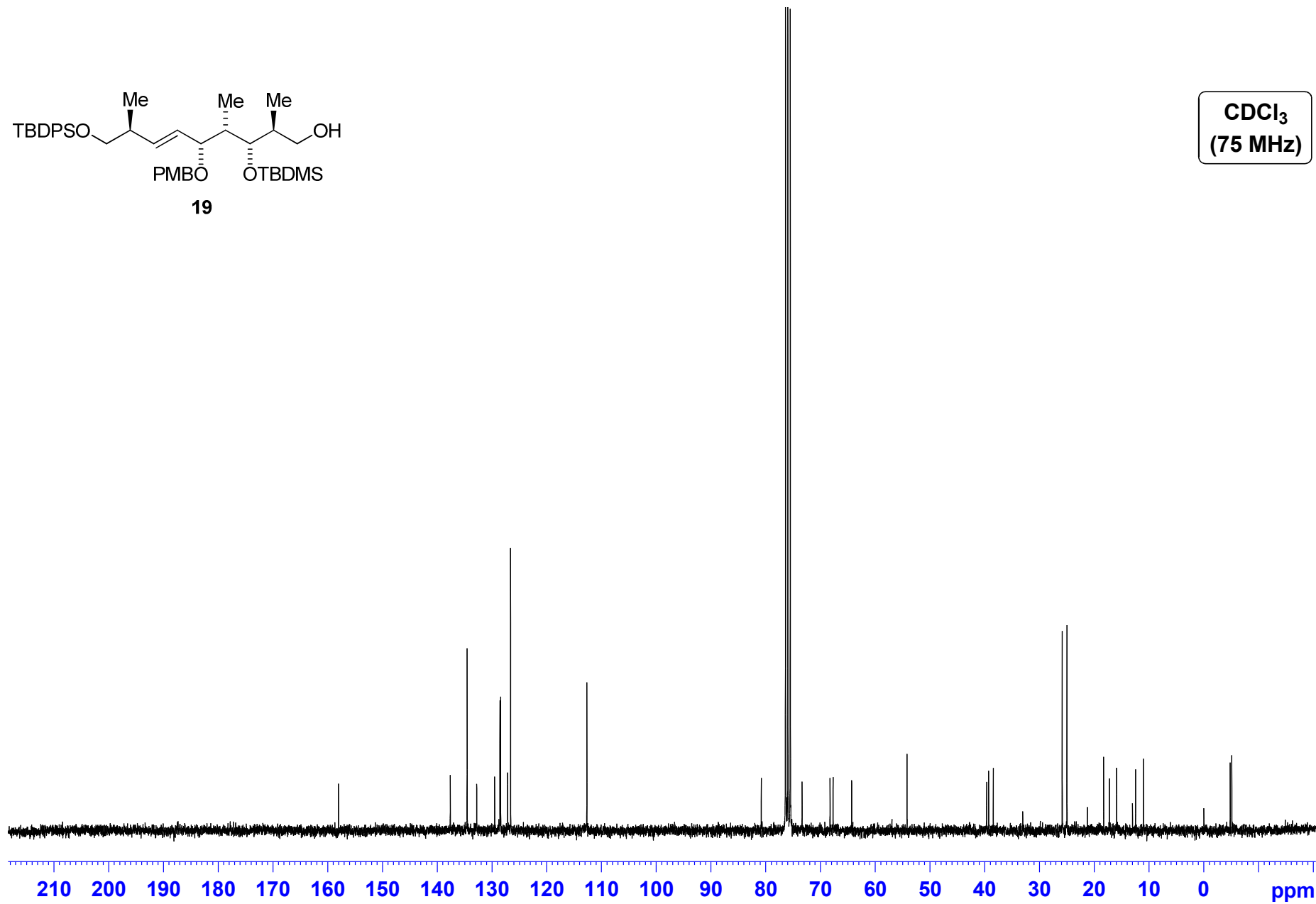
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S-30

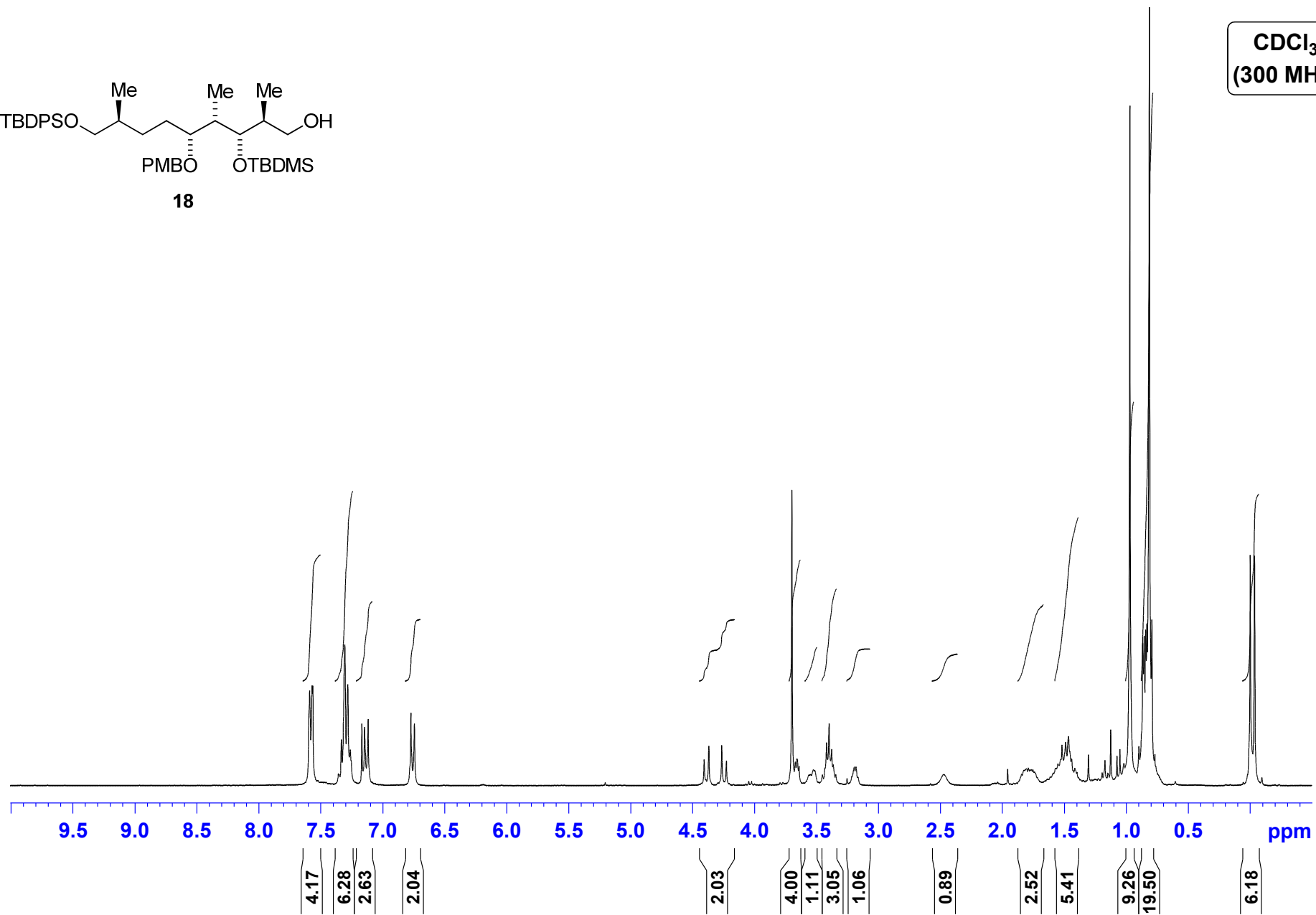
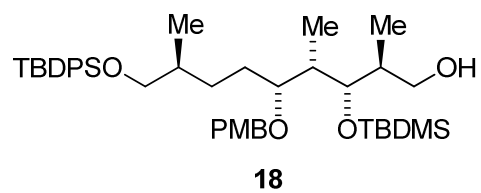


CDCl₃
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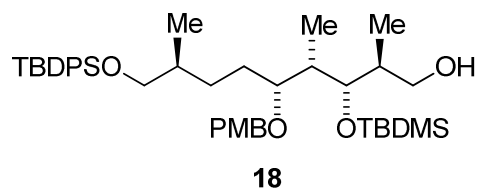


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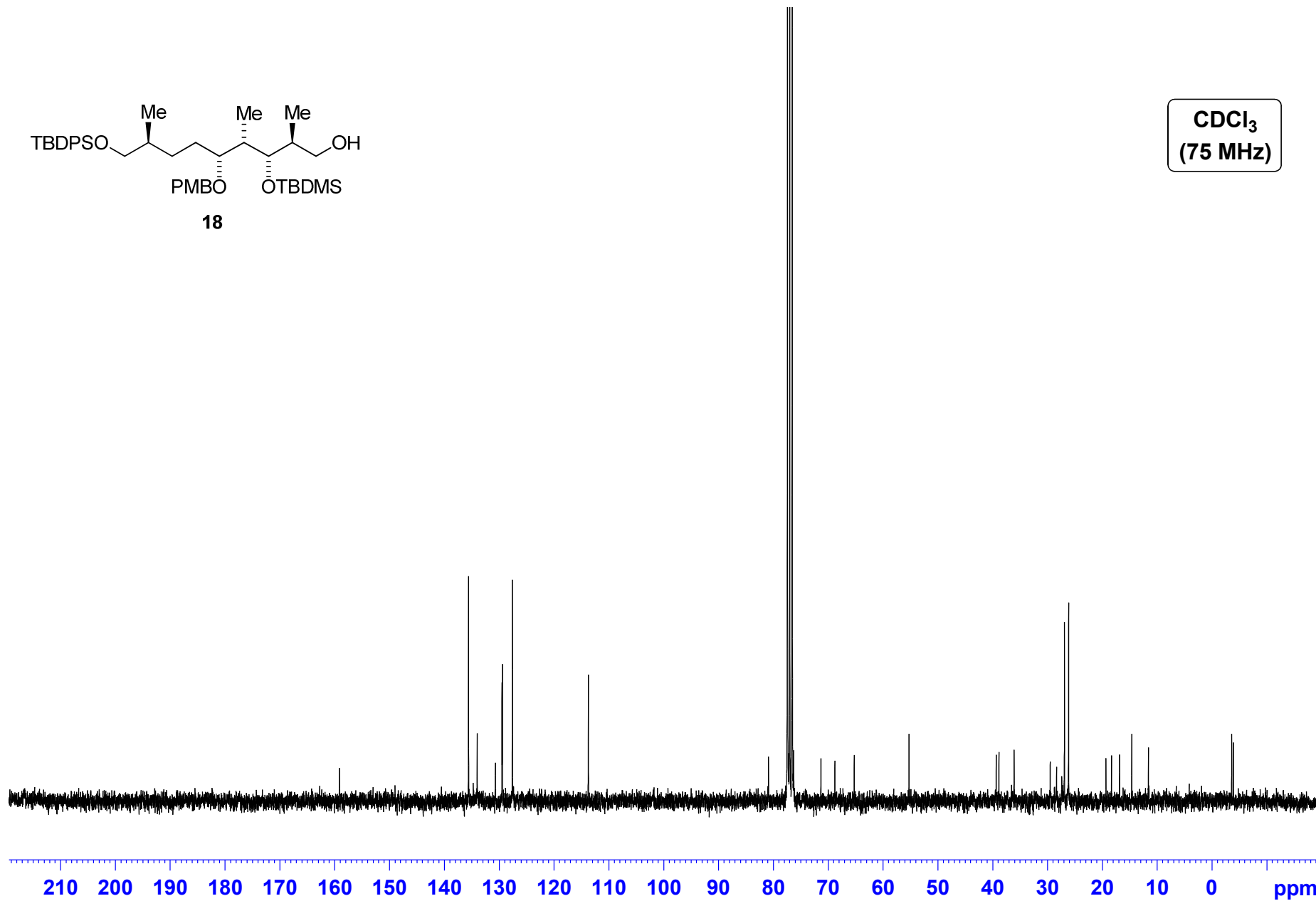
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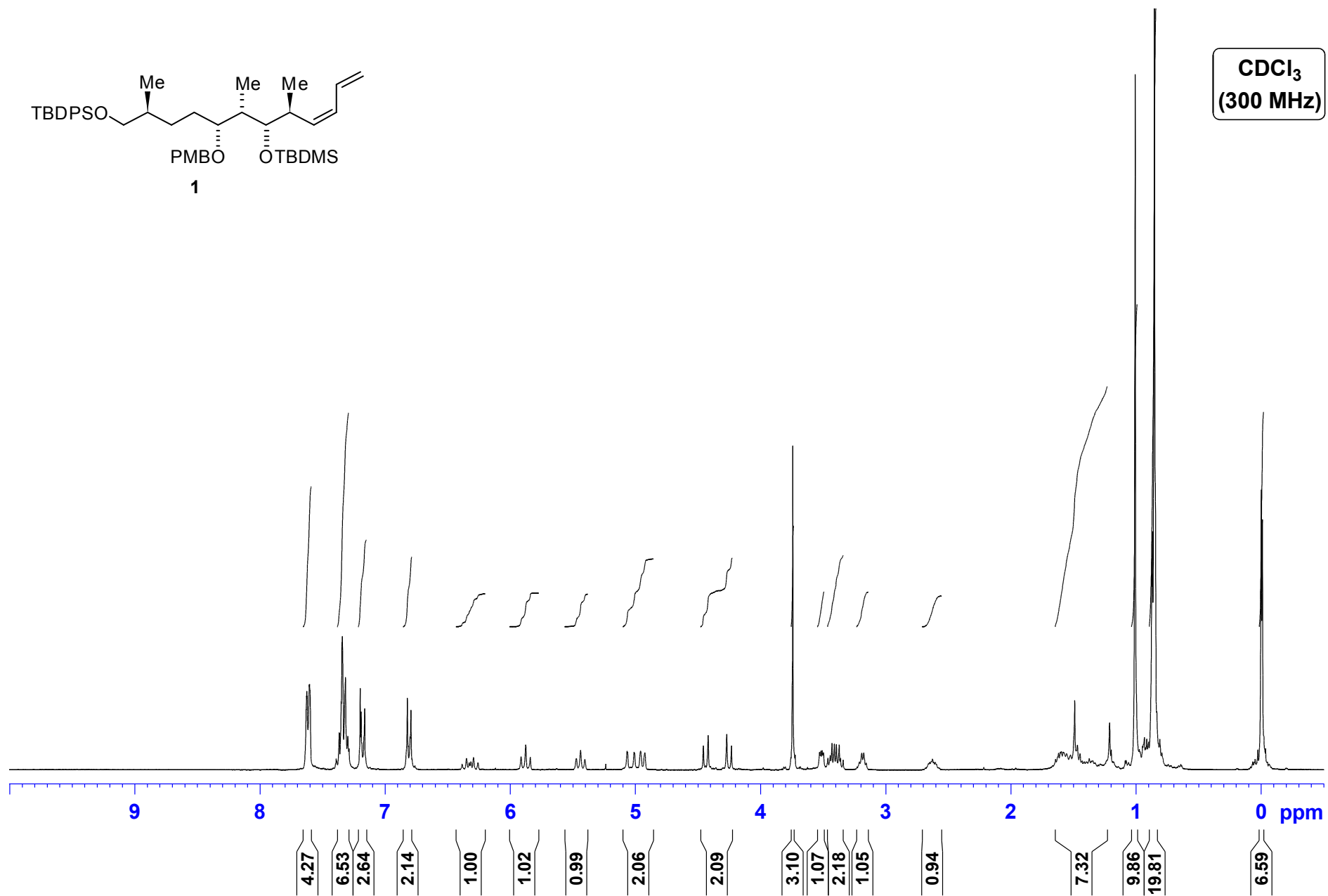
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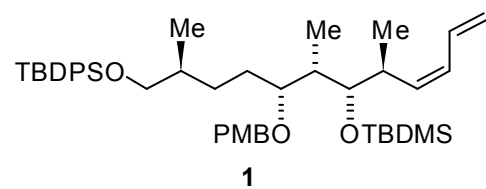
CDCl_3
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S-33



S-34



CDCl₃
(75 MHz)

