Electronic Supplementary Information

Homogeneous Gold-Catalyzed Glycosylations in Continuous Flow

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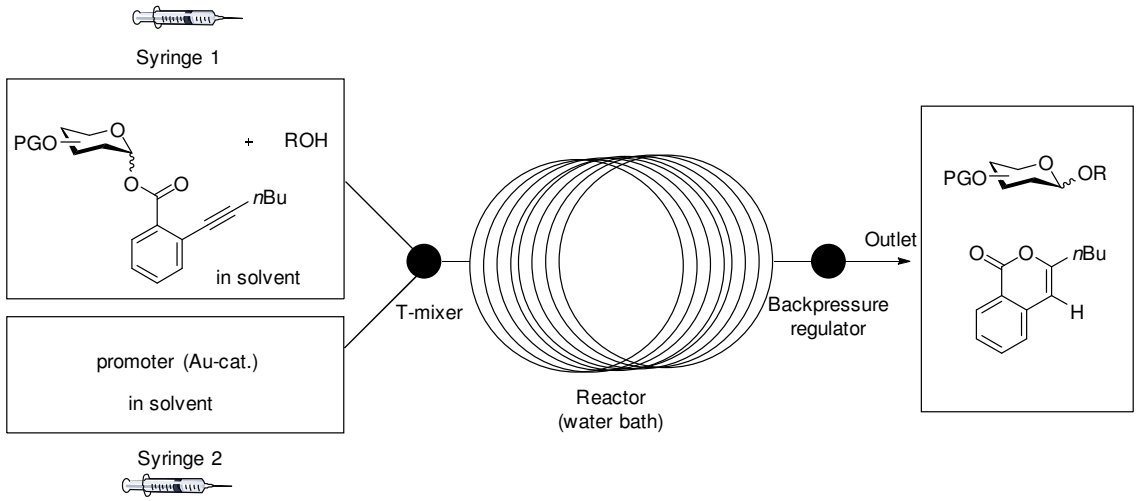
General Methods

All reagents were obtained from commercial suppliers and were used as supplied without further purification. All batch reactions were performed under an atmosphere of dried argon using standard Schlenk techniques. Anhydrous solvents were obtained from a SciMatCo Dry Solvent System. Solvents for chromatography were of technical grade and distilled under reduced pressure prior to use. Analytical thin-layer chromatography was performed on *Macherey-Nagel* silica gel SIL G-25 UV_{254} plates (0.25 mm). Compounds were visualized by UV-light at 254 nm and by dipping the plates in a cerium sulfate ammonium molybdate (CAM) solution followed by heating. Liquid chromatography was performed using forced flow of the indicated solvent on *Fluka* silica gel 60 (230-400 mesh). The compounds purified by flash chromatography were further concentrated by the removal of residual solvent under high vacuum. ^{1}H NMR spectra were obtained on a *Varian* MR-400 (400 MHz) and are reported in parts per million (δ) relative to the resonance of the solvent. Coupling constants (*J*) are reported in Hertz (Hz) and are not corrected. ^{13}C NMR spectra were obtained on a *Varian* MR-400 (100 MHz) and are reported in δ relative to the resonance of the solvent. IR Spectra were measured neat on a *Perkin-Elmer*-100 FT-IR spectrometer. Specific α_D values were measured with a Schmidt & Haensch UniPol L 1000 at a concentration (c) expressed in g/100 mL. High-resolution mass spectra (HRMS) were recorded with an Agilent 6210 ESI-TOF mass spectrometer at the Freie Universität Berlin, Mass Spectrometry Core Facility and are given in *m/z*.

General Setup for in-flow Glycosylations

Image 1: Setup of gold(I)-catalyzed glycosylations in flow.



Scheme 1: Scheme for experimental setup of gold-catalyzed glycosylations in flow.

A Harvard Apparatus syringe pump (70-4501) was used to deliver reagents using syringes to the reactor. The reactor (Vapourtec E-Series, PFA(Perfluoroalkoxy) 1.6mm (1/16") O.D., 1mm I.D. coil reactor) had a volume of 5 mL. The building blocks were dried using high vacuum prior to use. Prior to delivery of the reagents, the flow system was flushed with anhydrous CH_2Cl_2. Syringe 1 was filled with a solution of glycosyl donor and acceptor in the appropriate solvent and syringe 2 with a solution of the gold

catalyst in the same solvent. The syringes were connected to a T-mixer (IDEX Health and Science, Tee Assembly High Pressure PEEK .020 thru hole) to ensure mixing of the substrate solution with the gold catalyst solution, which, in turn, is connected to the reactor coil. The reactions were carried out at the reaction temperature and given residence time (mainly at 40°C (water bath) and a residence time of 20 minutes). At the end of the reactor tubing, a 5 bar back pressure regulator (BPR Cartridge 75 psi Gold Coating in a BPR Holder Assembly – Bio, both IDEX Health and Science) ensured volatile solvents (e.g. CH_2Cl_2) to resist elevated temperatures during the reaction time in the reactor. The tubing and the connectors (1.6mm (1/16") O.D.) were purchased from IDEX Health and Science.

General Procedure for the Gold(I)-catalyzed In-flow Glycosylations

A mixture of glycosyl acceptor (0.064 mmol) and glycosyl donor (1.3 eq, 0.084 mmol) was dissolved in CH_2Cl_2 (847 µL), loaded in a syringe and fitted to the micro reactor (**Scheme 1, Image 1**). A suspension of (chlorotriphenylphosphoranyl)gold (13 mol%, 4.1 mg, 8.37 µmol) and silvertrifluoromethanesulfonate (13 mol%, 2.2 mg, 8.37 µmol) in CH_2Cl_2 (847 µL) was sonicated for 1 min, filtered using a syringe tip filter (PTFE membrane, pore size 0.2 µm), loaded in a syringe and also attached to the syringe pump. The reagents were injected through the reactor with a total flow rate of 250 µL/min while the micro reactor coil was set at the respective temperature using a water bath. After the injection of the reaction mixtures, solvent is injected using the syringe pump to push the reaction mixture through the reactor coil. The combined crude product was filtered over silica plug. Evaporation of the solvent and purification using silica gel chromatography provided the glycosylation product.

All compounds were synthesized according to the representative synthetic procedure in a typical scale between 0.04-0.07 mmol (with respect to the glycosyl acceptor, see above). The products were obtained after column chromatographic purification in a yield given in the manuscript. The isolated amount is given below.

Data for Known Compounds

Characterization of all compounds previously reported (**5-12**, **15-22** and **24-28**) was in good agreement with the literature.

Building Block Synthesis:

The reactions were performed according to the literature protocols.

Compound	Reference
5-6, 17, 22, 25, 26	• Y. Li, Y. Yang, B. Yu, *Tetrahedron Lett.* **2008**, *49*, 3604-3608. • Y. Li, X. Yang, Y. Liu, C. Zhu, Y. Yang, B. Yu, *Chem. Eur. J.* **2010**, *16*, 1871-1882
7	A. Roën, J. I. Padrón, J. T. Vázquez, *J. Org. Chem.* **2003**, *68*, 4615-4630
8	J. Chan, A. Lu, A. J. Bennet, *J. Am. Chem. Soc.* **2011**, *133*, 2989-2997
9	A. Meijer, U. Ellervik, *J. Org. Chem.* **2004**, *69*, 6249-6256

In-flow Glycosylations:

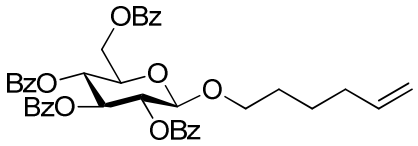
The reactions were performed according to the general procedure.

Compound	Reference	Amount of product	
10	T. Murakami, Y. Sato, M. Shibakami, *Carbohydr. Res.* **2008**, *343*, 1297-1308	28 mg	Colorless oil
11	M. Trujillo, E. Q. Morales, J. T. Vazquez, *J. Org. Chem.* **1994**, *59*, 6637-6642	44 mg	White solid
12	T. Ziegler, E. Eckhardt, V. Birault, *J. Org. Chem.* **1993**, *58*, 1090-1099	50 mg	Colorless oil
15	J. Yang, C. Cooper-Vanosdell, E. A. Mensah, H. M. Nguyen, *J. Org. Chem.* **2008**, *73*, 794-800	n.d.	Colorless oil

Compound	Reference	Amount of product	
18	• J. S. Yadav, N. N. Yadav, M. K. Gupta, N. Srivastava, B. V. Subba Reddy, *Monatsh. Chem.* **2014**, *145*, 517-520 • R. Rodebaugh, B. Fraser-Reid, *Tetrahedron* **1996**, *52*, 7663-7678	27 mg	Colorless oil
19	H. Vankayalapati, G. Singh, I. Tranoy, *Tetrahedron: Asymmetr.* **2001**, *12*, 1373-1381	53 mg	Colorless oil
20	J. Yang, C. Cooper-Vanosdell, E. A. Mensah, H. M. Nguyen, *J. Org. Chem.* **2008**, *73*, 794-800	16 mg	Colorless oil
21	M. Tsuzuki, T. Tsuchiya, *Carbohydr. Res.* **1998**, *311*, 11-24	10 mg	Colorless oil
24	C. Unverzagt, H. Kunz, *J. Prakt. Chem.* **1992**, *334*, 570-578	43 mg	White foam
27	• J. Jünnemann, I. Lundt, J. Thiem, *Liebigs Ann. Chem.* **1991**, *1991*, 759-764 • H. Wang, J. Tao, X. Cai, W. Chen, Y. Zhao, Y. Xu, W. Yao, J. Zeng, Q. Wan, *Chem. Eur. J.* **2014**, *20*, 17319-17323 • S. Adhikari, K. N. Baryal, D. Zhu, X. Li, J. Zhu, *ACS Catalysis* **2013**, *3*, 57-60	23 mg	Colorless oil
28	J. Park, S. Kawatkar, J.-H. Kim, G.-J. Boons, *Org. Lett.* **2007**, *9*, 1959-1962	41 mg	Colorless oil

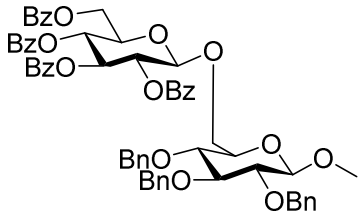
Experimental Data for New Compounds

5-Hexen-1-yl 2,3,4,5,6-tetra-*O*-benzoyl-β-D-glucopyranoside (13)



Colorless oil; yield n.d.; R_f = 0.38 (20%EtOAc/hexanes); $[\alpha]_D^{20}$ = +20 (*c* = 0.85, CH_2Cl_2); IR (film) ν_{max} 3068, 2927, 2858, 1723, 1642, 1603, 1586, 1493, 1452, 1373, 1316, 1260, 1178, 1091, 1068, 1027, 1002, 937, 912, 854, 803, 738, 706, 686 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 8.02 (d, *J* = 7.6 Hz, 2H), 7.96 (d, *J* = 7.6 Hz, 2H), 7.90 (d, *J* = 7.6 Hz, 2H), 7.84 (d, *J* = 7.6 Hz, 2H), 7.59 – 7.46 (m, 3H), 7.44 – 7.27 (m, 9H), 5.90 (t, *J* = 9.7 Hz, 1H), 5.67 (t, *J* = 9.7 Hz, 1H), 5.63 – 5.48 (m, 2H), 4.88 – 4.78 (m, 3H), 4.64 (dd, *J* = 12.0, 2.9 Hz, 1H), 4.50 (dd, *J* = 12.0, 5.2 Hz, 1H), 4.18 – 4.12 (m, 1H), 3.92 (dt, *J* = 9.6, 6.2 Hz, 1H), 3.55 (dt, *J* = 9.4, 6.6 Hz, 1H), 1.89 (dd, *J* = 14.1, 7.0 Hz, 2H), 1.62 – 1.47 (m, 2H), 1.37 – 1.26 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 166.2, 165.8, 165.2, 165.1, 138.4, 133.4, 133.2, 133.2, 133.1, 129.8, 129.8, 129.7, 129.6, 129.3, 128.8, 128.8, 128.4, 128.3, 128.3, 114.4, 101.3, 72.9, 72.1, 71.9, 70.1, 69.8, 63.2, 33.2, 28.8, 25.0; HR ESI MS Calcd for $C_{40}H_{38}O_{10}$ [M+Na^+]: 701.2357 found: 701.2339.

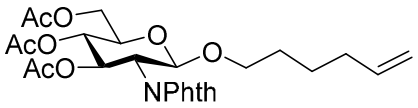
Methyl 2,3,4-tri-*O*-benzyl-6-*O*-(2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl)-β-D-gluco-pyranoside (14)



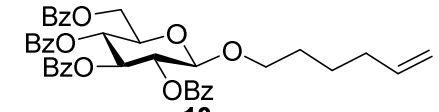
Colorless oil; 40 mg isolated; R_f = 0.47 (30%EtOAc/hexanes); $[\alpha]_D^{20}$ = +5 (*c* = 1.0, $CHCl_3$); IR (film) ν_{max} 3066, 3035, 2879, 1731, 1603, 1586, 1497, 1453, 1361, 1316, 1265, 1178, 1093, 1069, 1028, 854, 802, 738, 709 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 8.00 (d, *J* = 7.4 Hz, 2H), 7.89 (d, *J* = 7.7 Hz, 4H), 7.81 (d, *J* = 7.5 Hz, 2H), 7.55 – 7.10 (m, 27H), 5.87 (t, *J* = 9.6 Hz, 1H), 5.68 (t, *J* = 9.7 Hz, 1H), 5.57 (dd, *J* = 9.5, 8.1 Hz, 1H),

4.93 (d, *J* = 7.8 Hz, 1H), 4.84 (d, *J* = 11.0 Hz, 2H), 4.68 (d, *J* = 10.9 Hz, 1H), 4.65 – 4.59 (m, 3H), 4.50 (dd, *J* = 12.1, 4.9 Hz, 1H), 4.40 (d, *J* = 11.0 Hz, 1H), 4.20 – 4.06 (m, 3H), 3.69 (dd, *J* = 11.1, 6.4 Hz, 1H), 3.54 (t, *J* = 9.0 Hz, 1H), 3.48 – 3.42 (m, 1H), 3.32 (s, 3H), 3.36 – 3.25 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 166.09, 165.82, 165.11, 164.94, 138.45, 138.41, 137.81, 133.40, 133.22, 133.14, 133.08, 129.79, 129.71, 129.51, 129.17, 128.75, 128.71, 128.37, 128.30, 128.01, 127.79, 127.76, 127.59, 127.54, 104.37, 101.31, 84.42, 82.07, 77.77, 75.55, 74.82, 74.64, 74.47, 72.86, 72.13, 71.78, 69.62, 68.52, 63.08, 56.80; HR ESI MS Calcd for $C_{62}H_{58}O_{15}$ [M+Na^+]: 1065.3668 found: 1065.3722.

5-Hexen-1-yl 3,4,6-tri-*O*-acetyl-2-deoxy-2-phthalimido-β-D-glucopyranoside (23)

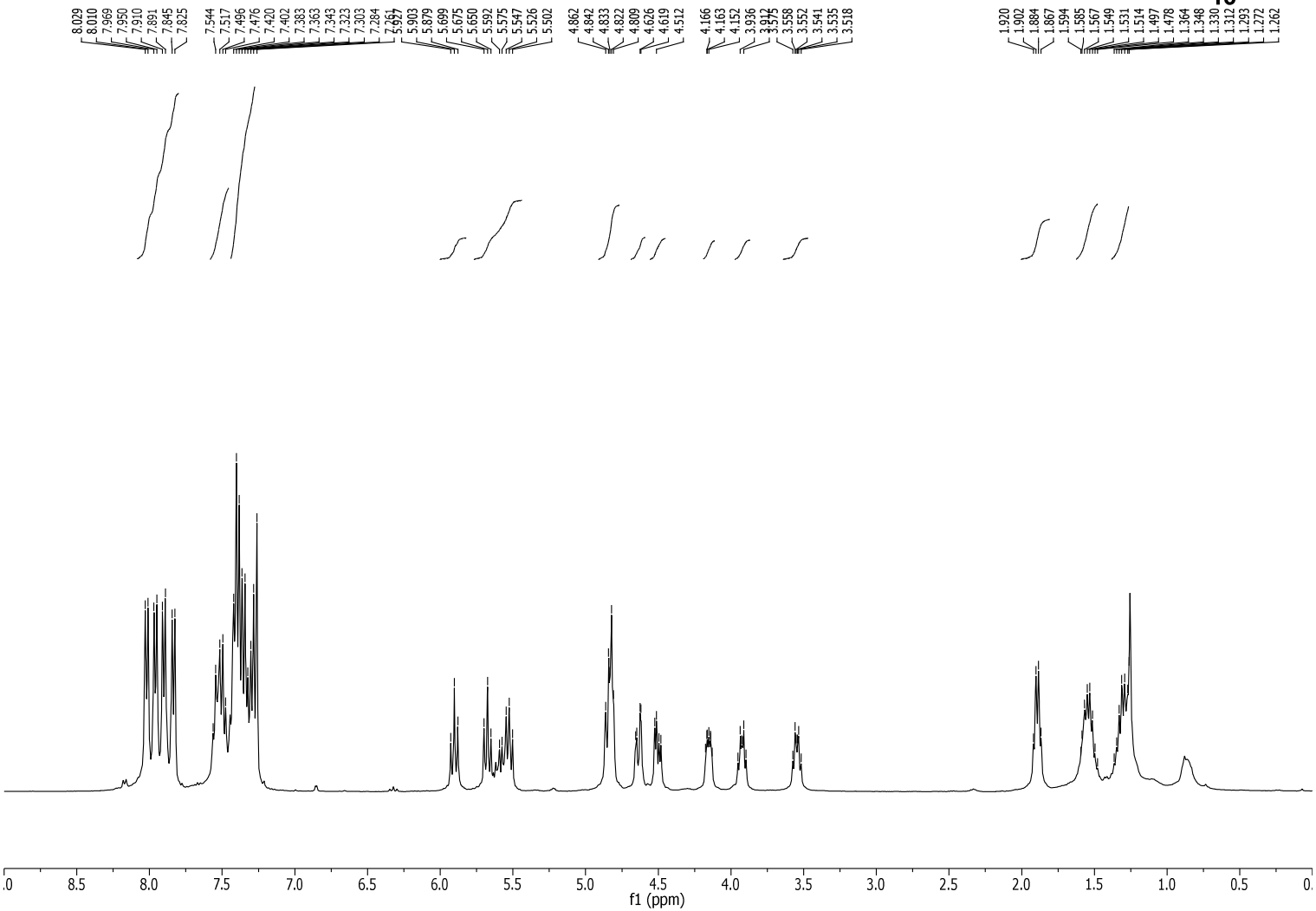


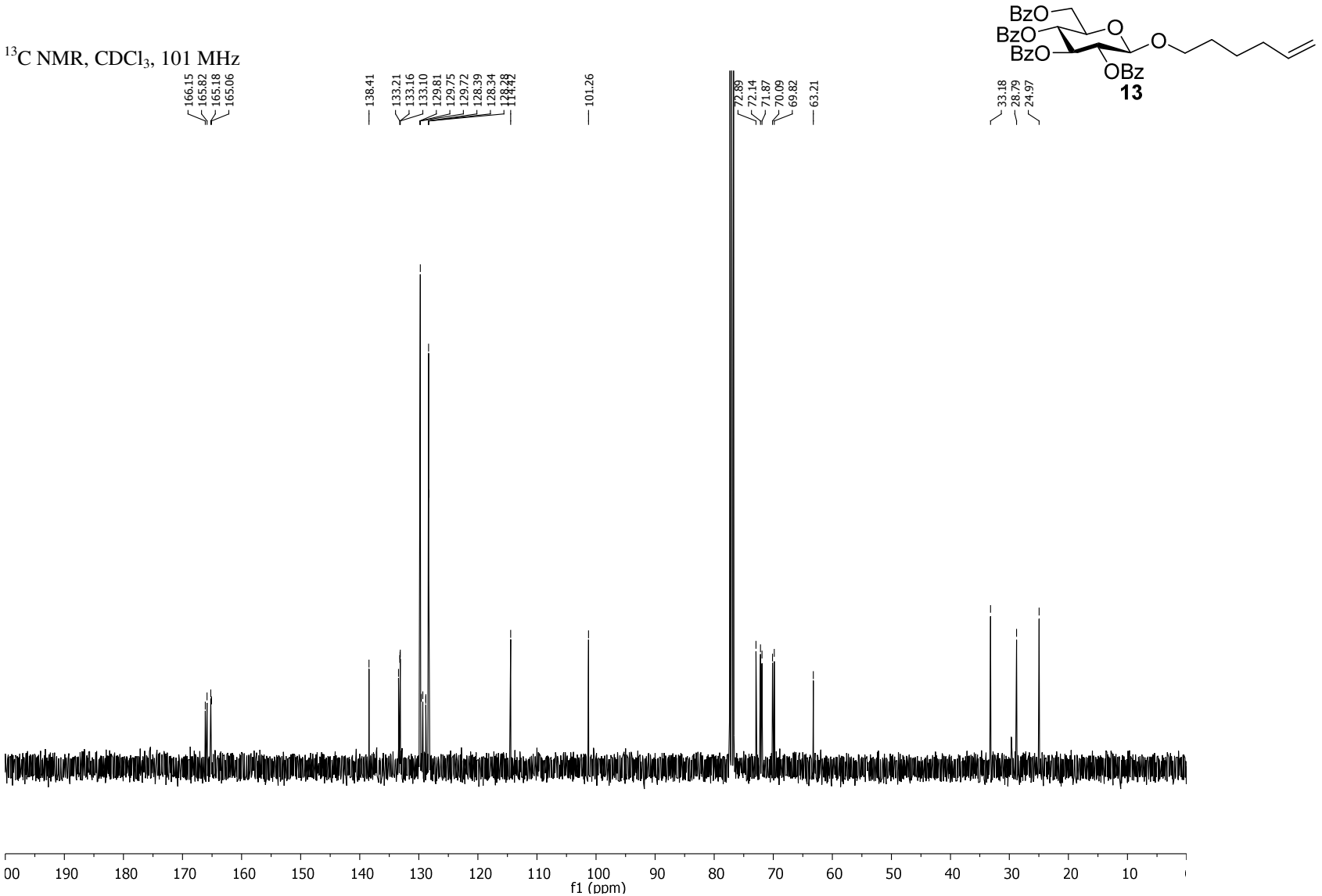
White foam; 27 mg isolated; R_f = 0.09 (20%EtOAc/hexanes); $[\alpha]_D^{20}$ = +23 (*c* = 1.0, $CHCl_3$); IR (film) ν_{max} 2935, 2861, 1779, 1747, 1717, 1642, 1614, 1524, 1470, 1432, 1387, 1367, 1223, 1172, 1105, 1075, 1034, 974, 902, 873, 796, 743, 723 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.87 – 7.82 (m, 2H), 7.76 – 7.71 (m, 2H), 5.78 (dd, *J* = 10.7, 9.1 Hz, 1H), 5.55 – 5.43 (m, 1H), 5.35 (d, J = 8.5 Hz, 1H), 5.17 (t, *J* = 9.6 Hz, 1H), 4.78 – 4.75 (m, 1H), 4.73 (t, *J* = 1.4 Hz, 1H), 4.35 – 4.27 (m, 2H), 4.16 (dd, *J* = 12.2, 2.2 Hz, 1H), 3.88 – 3.79 (m, 2H), 3.43 (dt, *J* = 9.7, 6.6 Hz, 1H), 2.10 (s, 3H), 2.02 (s, 3H), 1.86 (s, 3H), 1.84 – 1.77 (m, 2H), 1.50 – 1.35 (m, 2H), 1.21 – 1.11 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 171.0, 170.5, 169.8, 138.5, 134.6, 131.6, 123.9, 114.6, 98.4, 72.1, 71.0, 70.2, 69.3, 62.3, 54.9, 33.3, 28.9, 25.2, 21.1, 20.9, 20.8; HR ESI MS Calcd for $C_{26}H_{31}NO_{10}$ [M+Na^+]: 540.1840 found: 540.1952.



13

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




^{13}C NMR, $CDCl_3$, 101 MHz
166.15
165.82
165.18
165.06
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133.21
133.16
133.10
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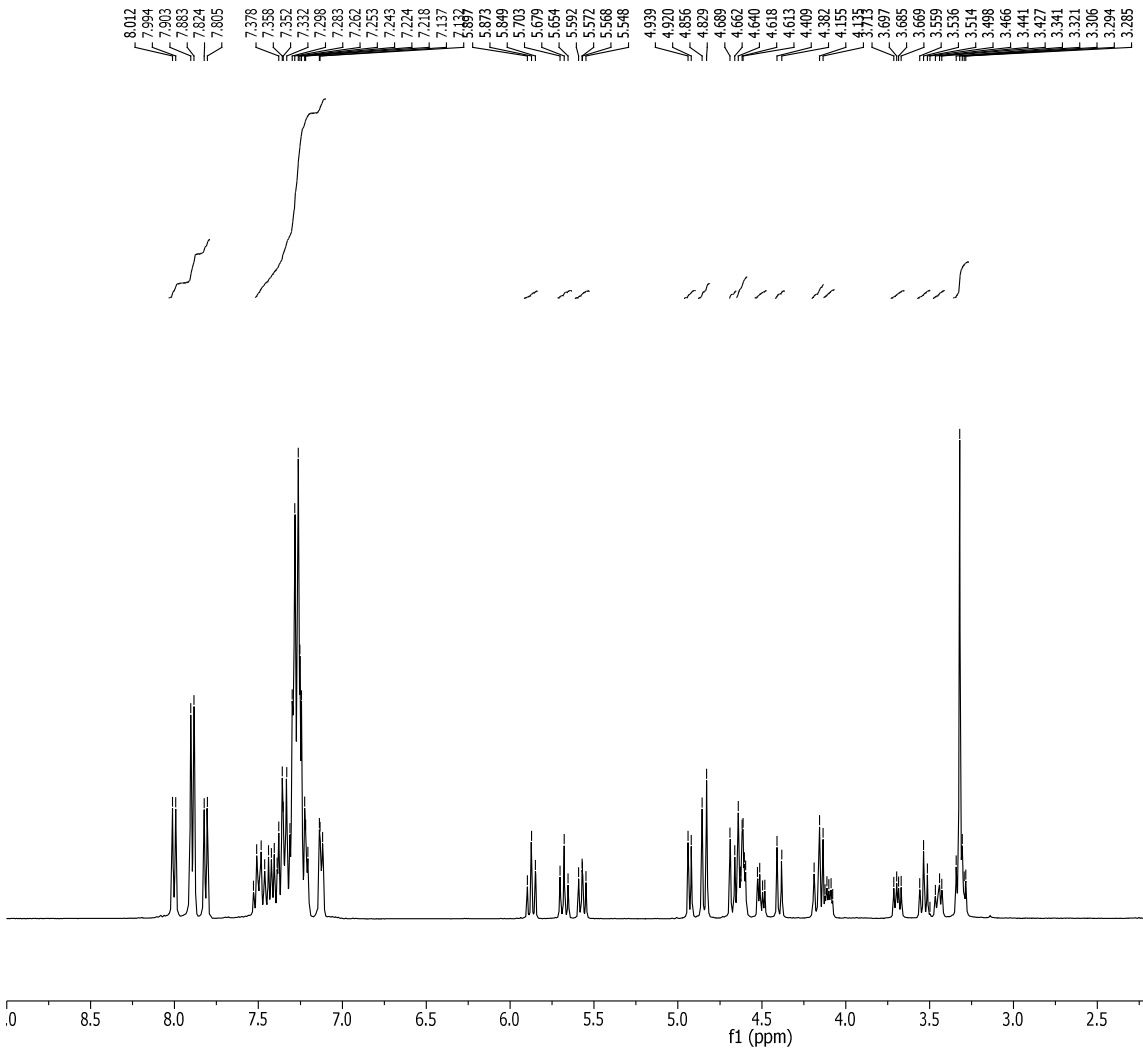
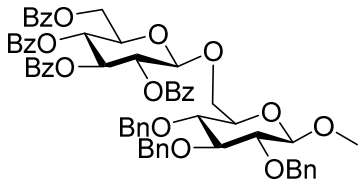
129.75
129.72
128.39
128.34
101.26
72.89
72.14
71.87
70.09
69.82
63.21
33.18
28.79
24.97
BzO
BzO
BzO
OBz
O
O
13
f1 (ppm)

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





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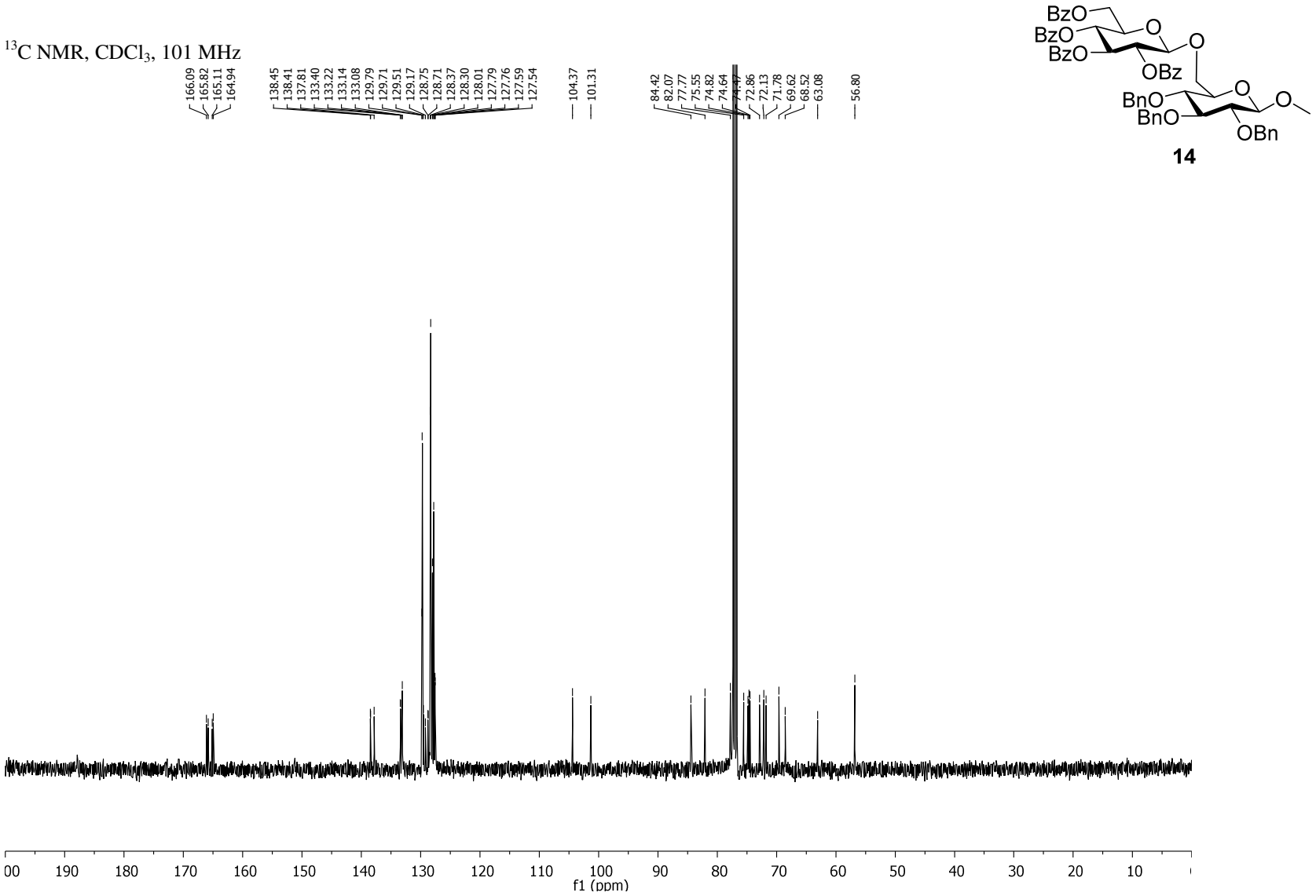
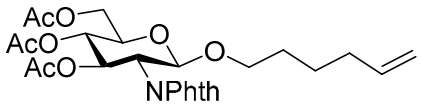

^{13}C NMR, CDCl$_3$, 101 MHz
166.09
165.82
165.11
164.94
138.45
138.41
137.81
133.40
133.22
133.14
133.08
129.79
129.71
129.51
129.17
128.75
128.71
128.37
128.30
128.01
127.79
127.76
127.59
127.54
104.37
101.31
84.42
82.07
77.77
75.55
74.82
74.64
72.86
72.13
71.78
69.62
68.52
63.08
56.80
f1 (ppm)

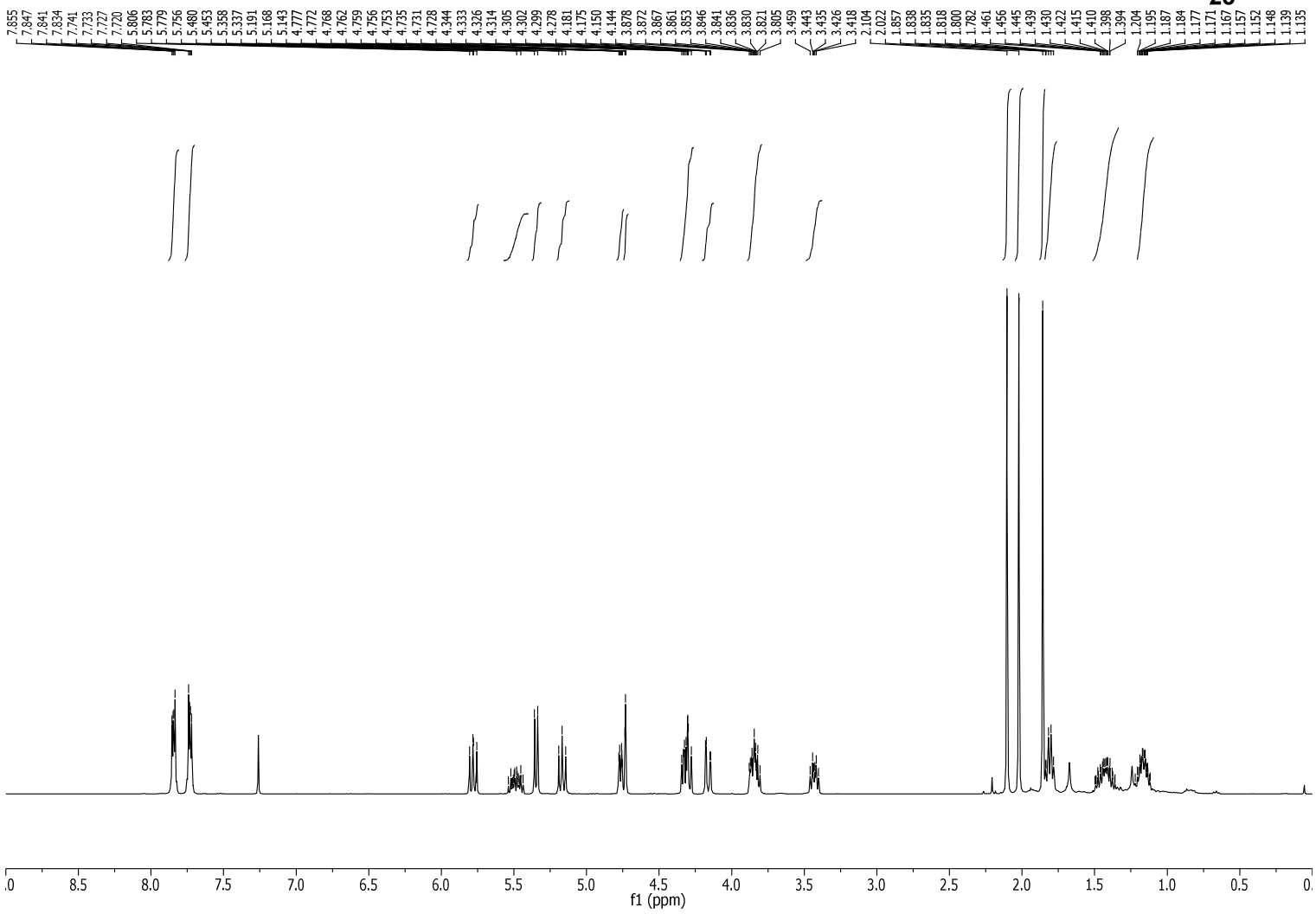
BzO
BzO
BzO
O
O
OBz
BnO
BnO
O
O
OBn

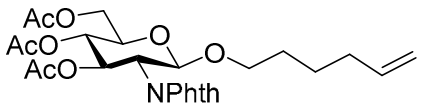
14



23

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





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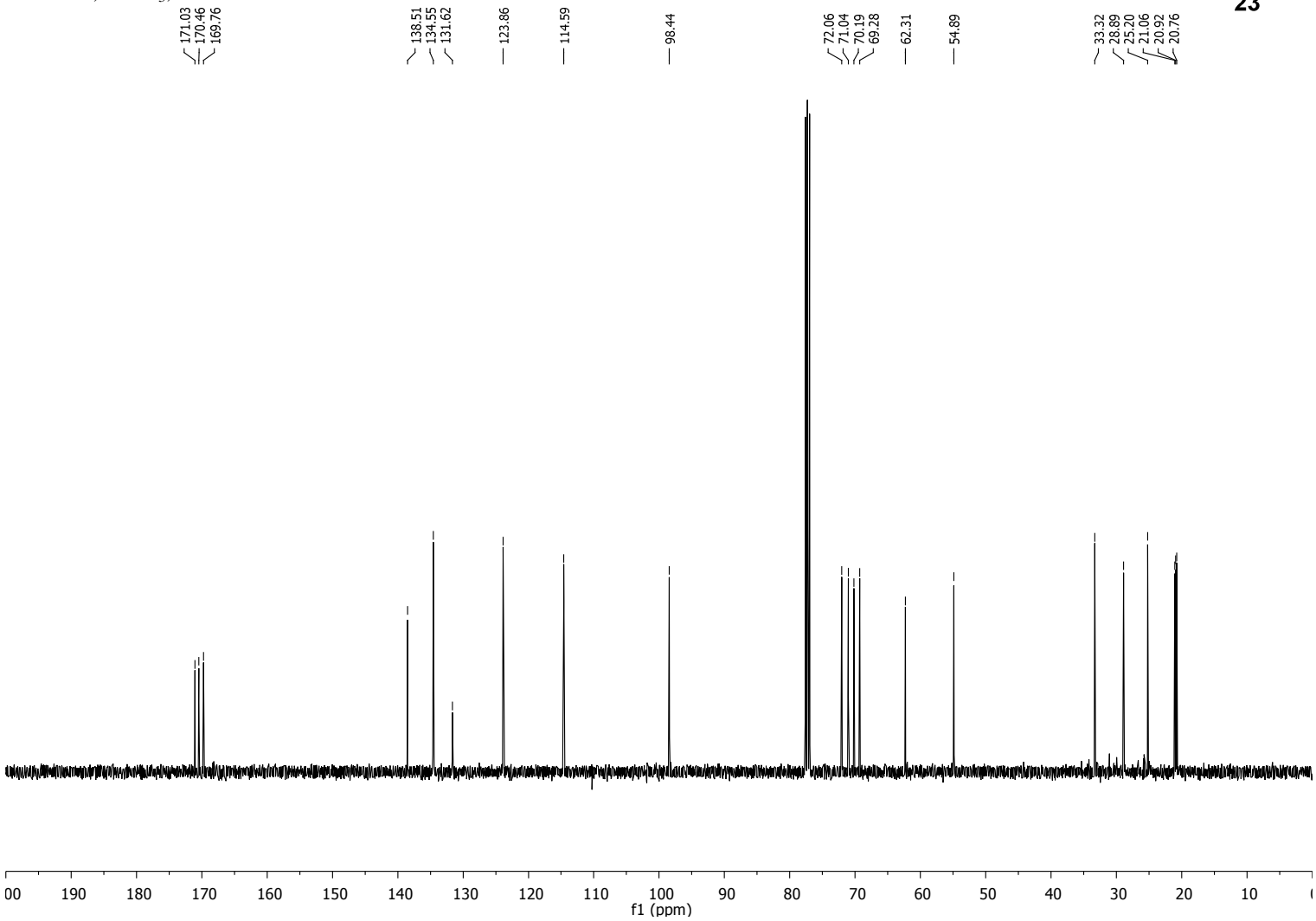
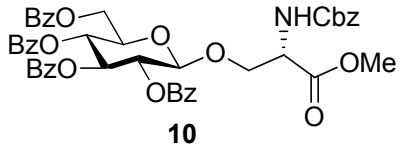
^{13}C NMR, $CDCl_3$, 101 MHz





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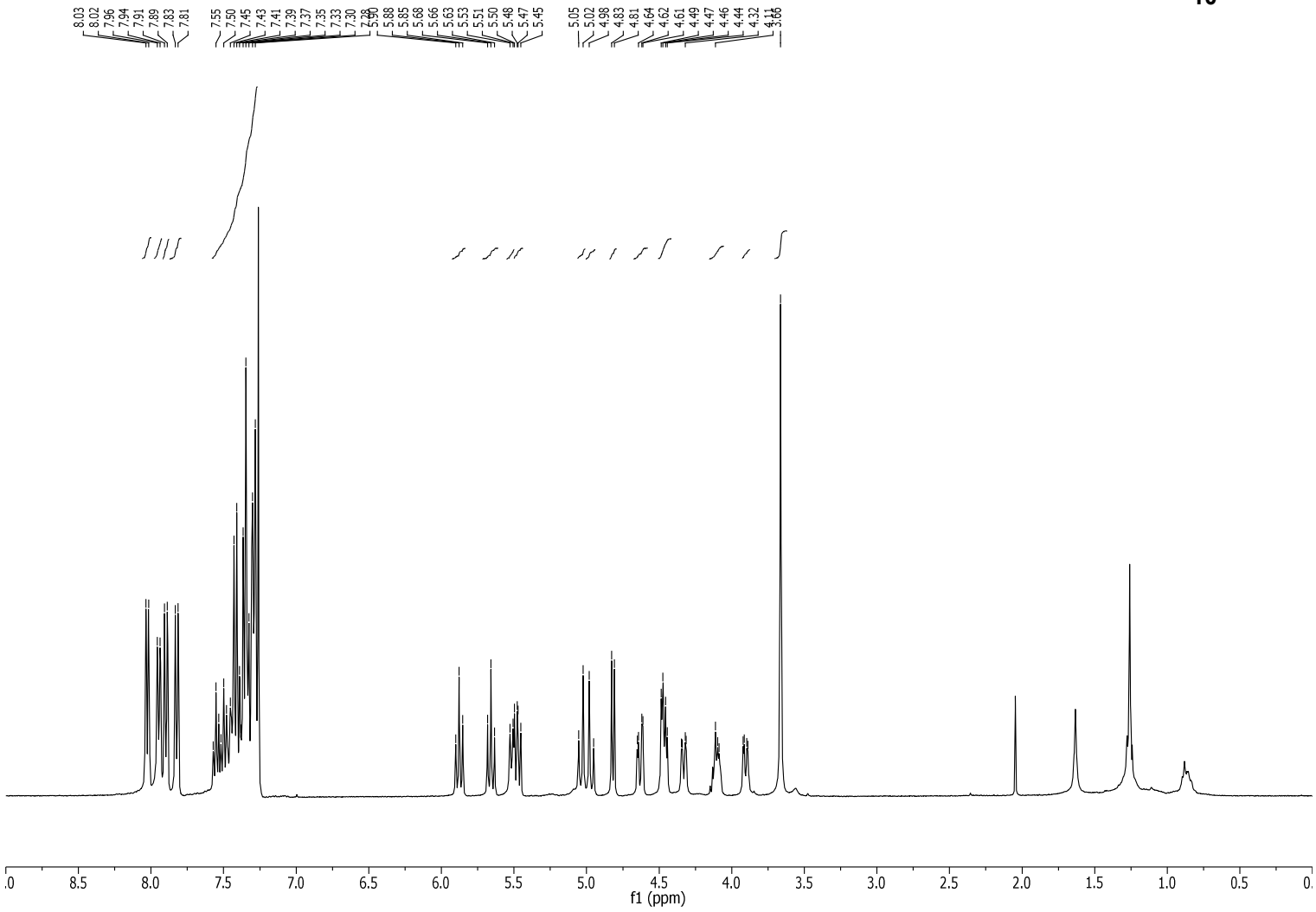
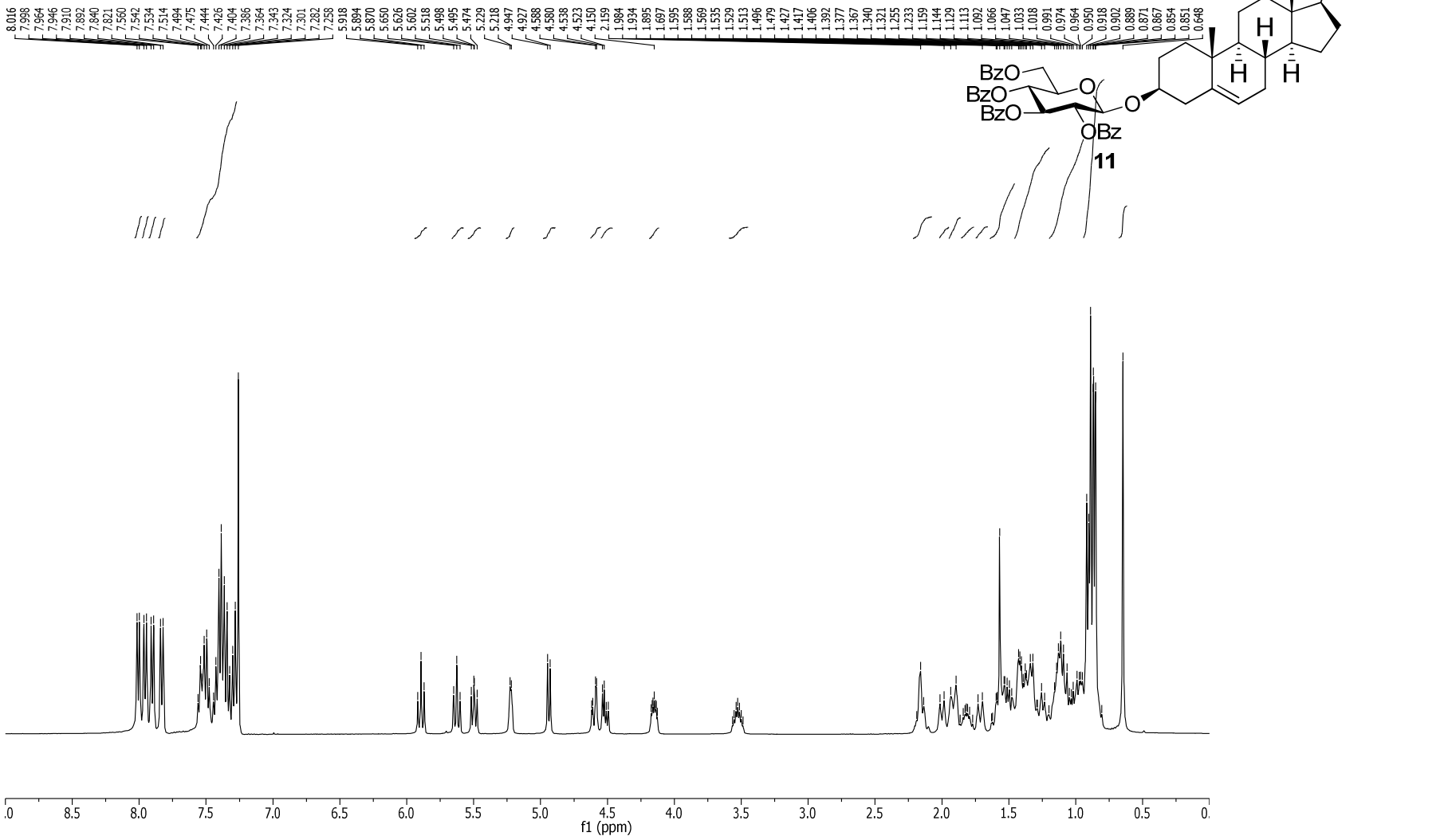
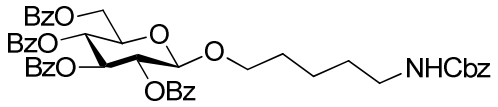
^{1}H NMR, $CDCl_3$, 400 MHz



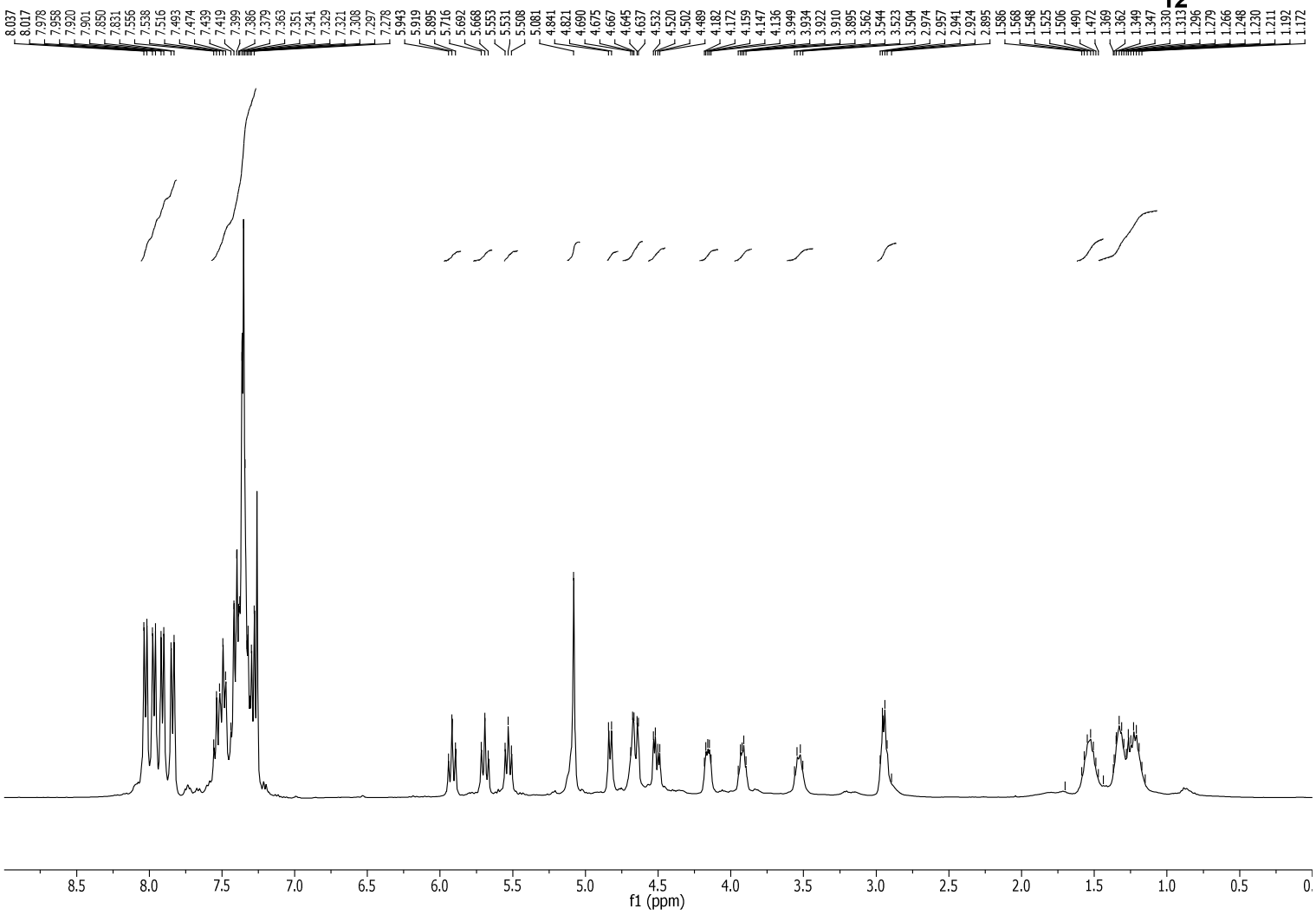
^{1}H NMR, $CDCl_3$, 400 MHz

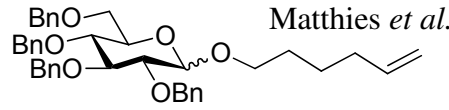




12

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





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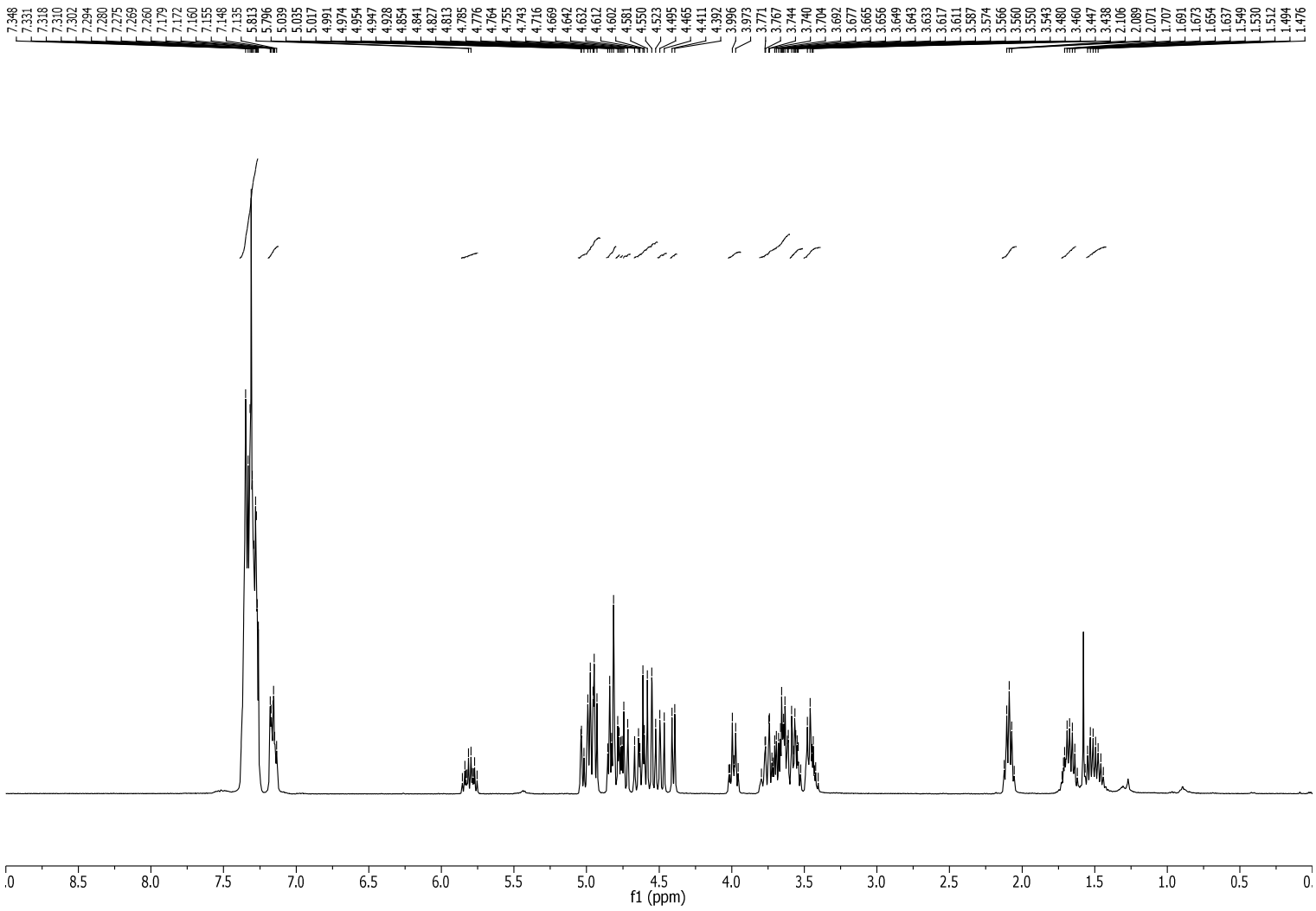
^{1}H NMR, $CDCl_3$, 400 MHz



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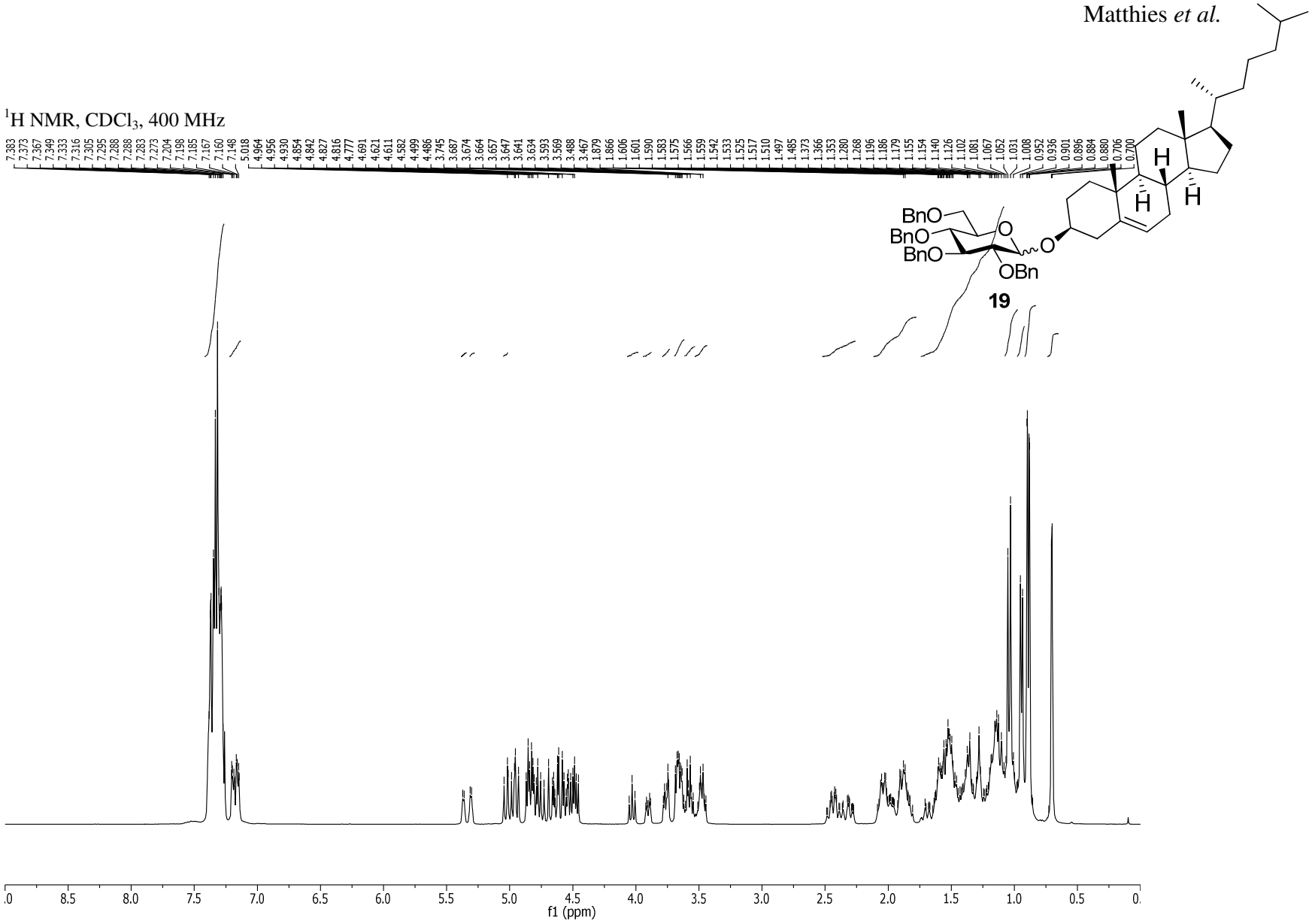

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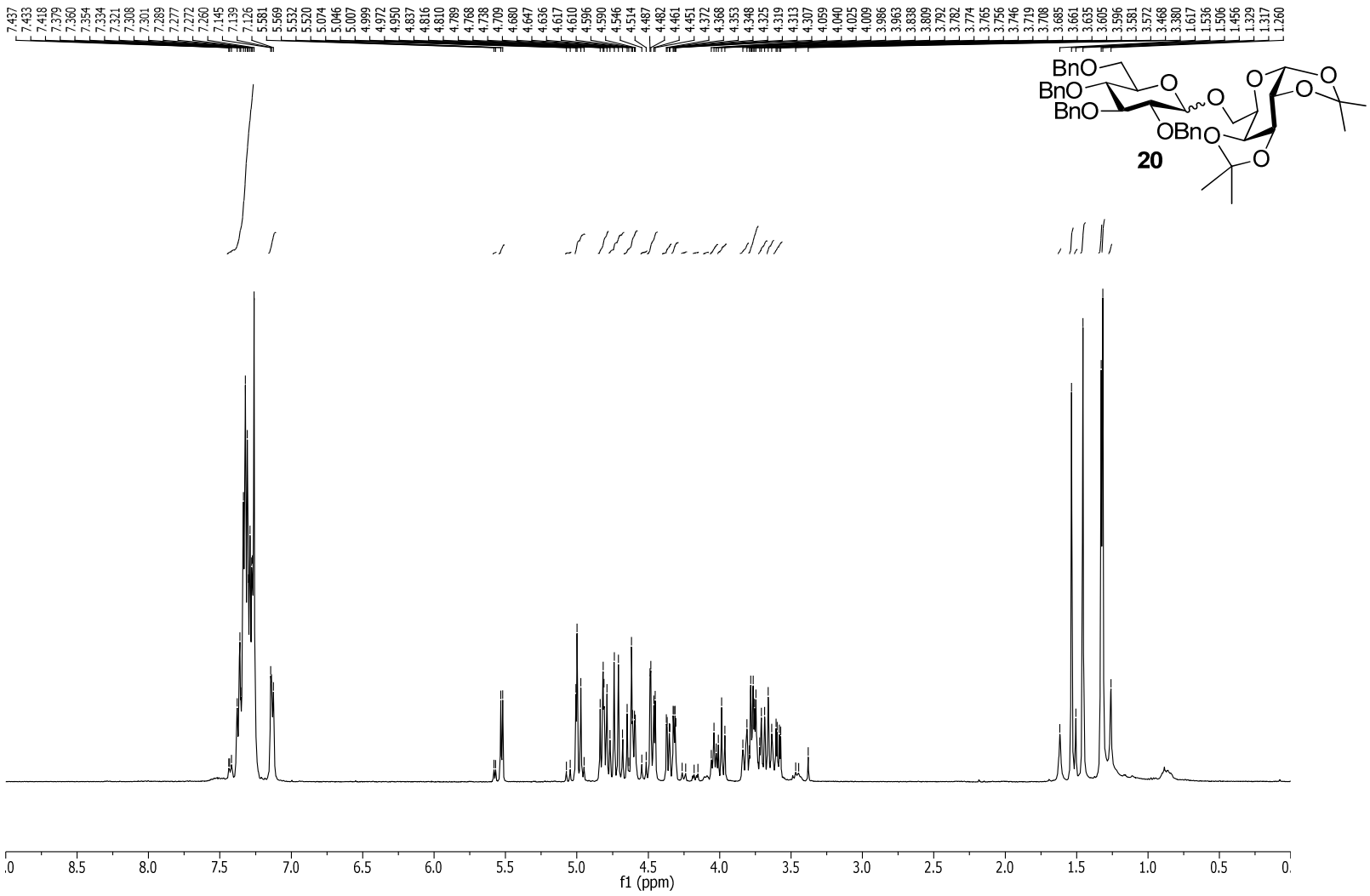

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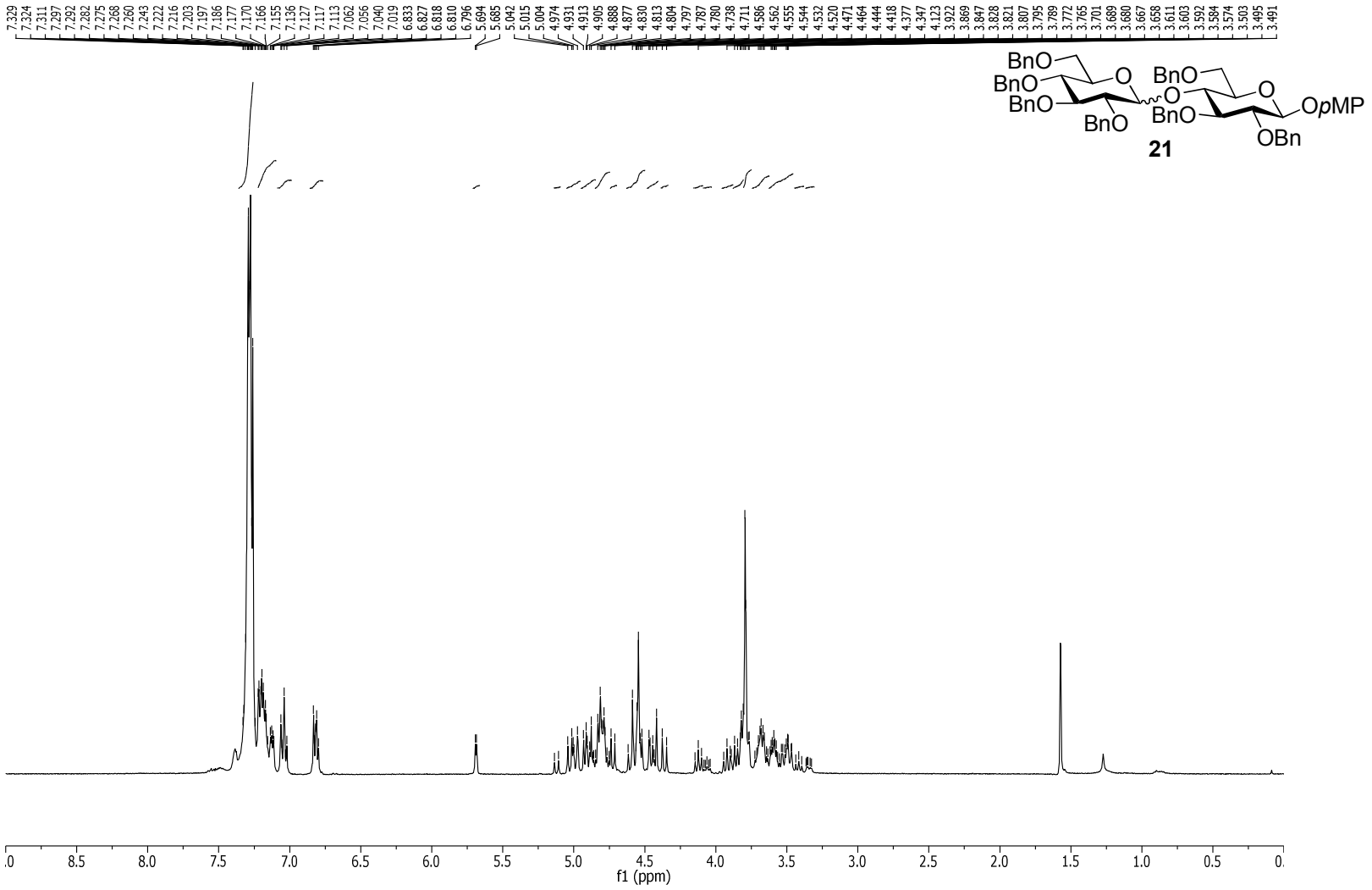

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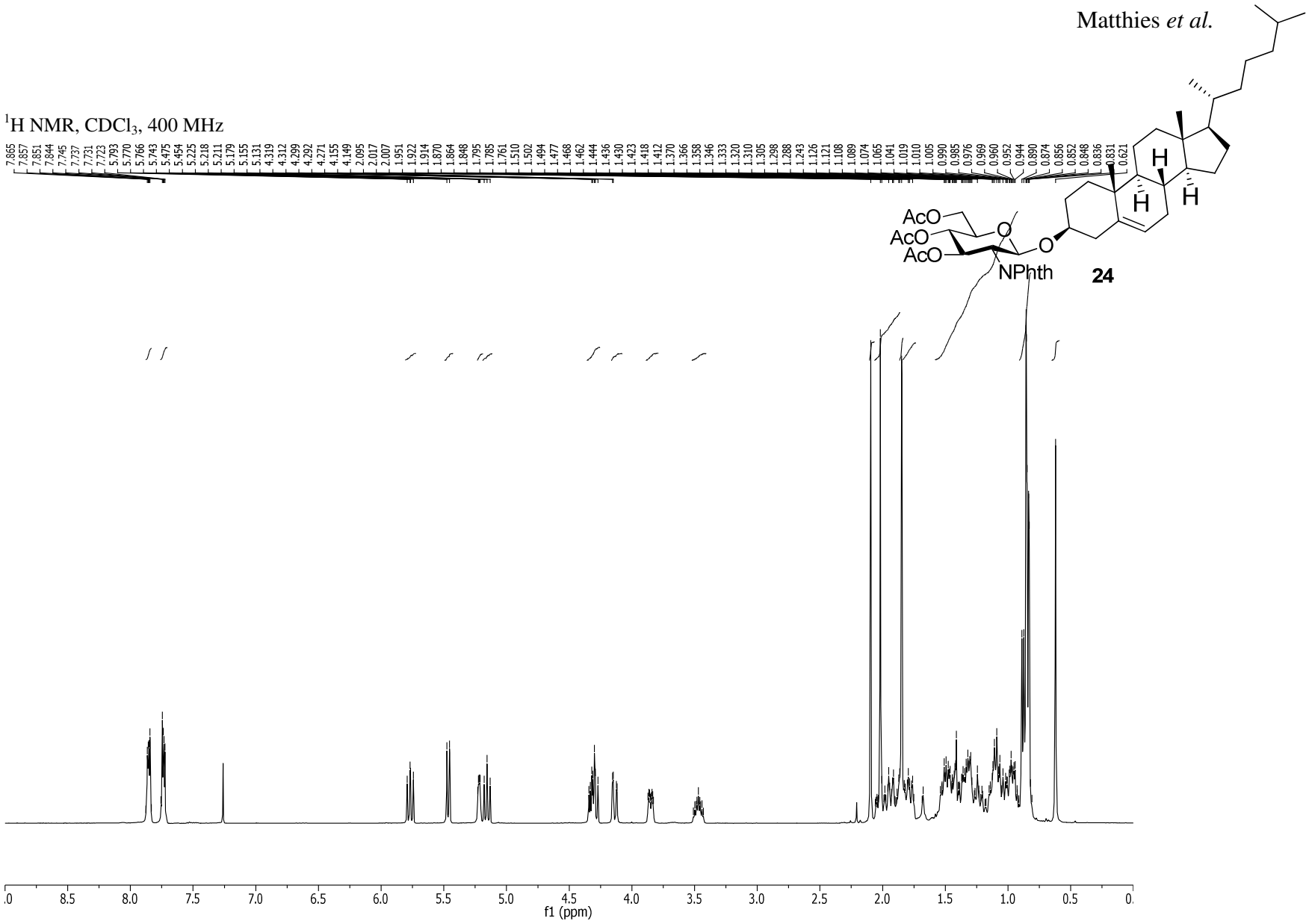
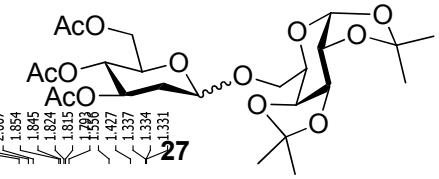


^{1}H NMR, $CDCl_3$, 400 MHz



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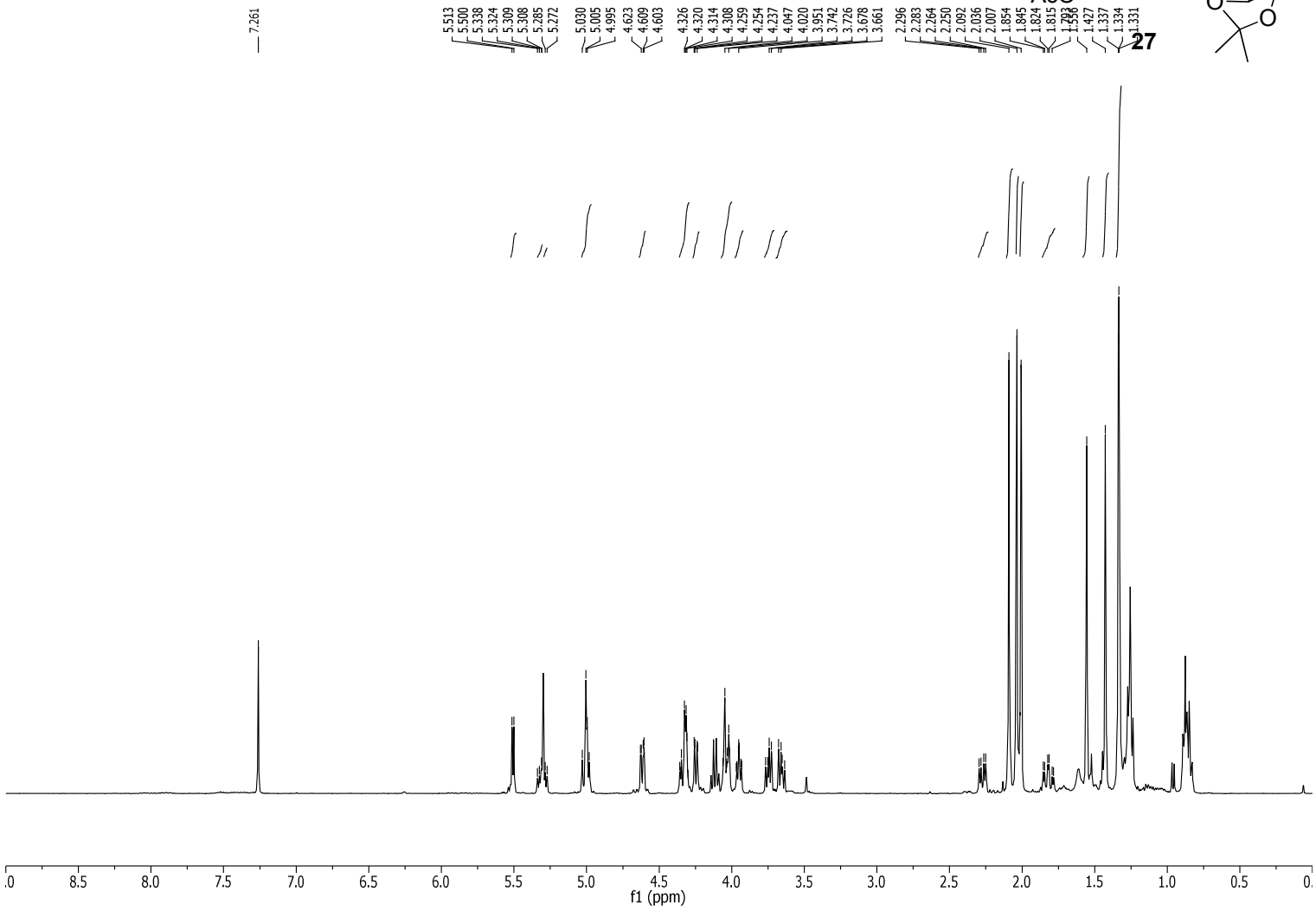

^{1}H NMR, $CDCl_3$, 400 MHz