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Supporting Information

Converting unprotected monosaccharides into functionalised lactols in aqueous media: metal-mediated allylation combined with tandem hydroformylation-cyclisation

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SUPPORTING INFORMATION

EXPERIMENTAL SECTION

General remarks: All air- or sensitive operations were performed using standard Schlenk-techniques under a purified argon atmosphere. The deionised water was deoxygenated prior to use. Toluene was purified over alumina column and degassed. 9,9-Dimethyl-2,7-bissulfonato-4,5-bis(diphenylphosphino)xanthene sodium salt was prepared according to a literature procedure.[1] All other reagents were purchased and used as received. The synthesis gas [CO (99.999%)/H_2 (99.999%), 1:1] was purchased from Linde AG. NMR spectra were recorded at room temperature in MeOD using Bruker Avance 600 NMR and referenced against tetramethylsilane. ^{1}H NMR spectra of compounds **3t**, **4**, **5** and **6** were analysed by PERCH software with spin simulation/iteration techniques.[2] HRMS were recorded using Bruker Micro Q-TOF with ESI (electro spray ionisation) operated in positive mode. The ICP-OES measurements were performed with a SPECTRO CIROS^{CCD} spectrometer equipped with a free running 27.12 MHz generator at a power of 1400 W. The sample introduction was performed by a cross-flow nebulizer with a double pass Scott type spray chamber and a sample uptake rate of 2 mL/min. The outer gas flow was 12 L/min, the intermediate gas flow was 1 L/min and the nebulizer gas flow was 1.00 mL/min.

Allylation of unprotected monosaccharides – gram-scale synthesis (details given apply for the allylation of D-mannose): 5 g (27.8 mmol) of D-mannose was dissolved in 600 mL of EtOH:H_2O (10:1) at room temperature. 6.7 g (55.5 mmol, 2 eq.) of tin powder and 7.2 mL (83.4 mmol, 3 eq.) of allyl bromide were added. The reaction mixture was stirred under Ar atmosphere at room temperature for 20 min after which the temperature was gradually raised to 60 ºC. A greyish suspension was obtained after stirring for ~2 h. The colour of the reaction mixture turned gradually to yellow as the stirring was continued for 24 h. The conversion of the starting material was followed by TLC (MeOH/acetone, 1:1). After cooling to room temperature, the reaction mixture was neutralized by adding 18 mL of 5 M NaOH. 300 mL of dichloromethane and 300 mL of water were added, and the phases were separated. The aqueous phase was washed with dichloromethane (2 x 150 mL). The combined organic layers were washed with water (2 x 200 mL). The combined aqueous layers were filtered through

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[1] W. P. Mul, K. Ramkisoensing, P. C. J. Kamer, J. N. H. Reek, A. J. van der Linden, A . Marson, P. W. N. M. van Leeuwen, *Adv. Synth. Catal.* **2002,** *344*, 293-298.

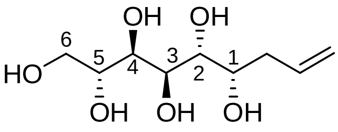
[2] R. Laatikainen, M. Niemitz, U. Weber, J. Sundelin, T. Hassinen, J. Vepsäläinen, *J. Magn. Reson. Ser. A* **1996,** *120*, 1-10.

celite. The colourless filtrate was concentrated under reduced pressure to obtain the crude product as a white solid.

^{1}H NMR analysis of the crude product: conversion 100 %, diastereomeric ratio 3:1 (threo:erythro).

The crude product was dissolved in 350 mL of EtOH (60 ºC). Upon cooling, the major diastereomer **3t** precipitated as a white crystalline solid. Typically, 2.8 g (45 %) of pure diastereomer was obtained.

Analytical data (the atoms are numbered as in the original carbohydrate structure)



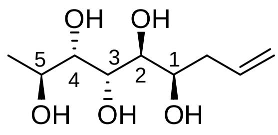
3t

Compound 3t: White solid. Mp 186-188 ºC, R_f = 0.62 (MeOH/acetone = 1:1), [a]$^{20}_{D}$ +22.8 (c 1.0, H_2O) ^{1}H NMR (600 MHz, MeOD, 25 ºC): d 5.90 (dddd, 1 H, $J_{CH,CH2b}$ = 6.5 Hz, $J_{CH,CH2a}$ = 7.5 Hz, $J_{CH,CH2-cis}$ = 10.2 Hz, $J_{CH,CH2-trans}$ = 17.2 Hz, olefinic CH), 5.14 (dddd, 1 H, $J_{CH-trans,CH2b}$ = -1.4 Hz, $J_{CH-trans,CH2a}$ = -1.5 Hz, $J_{CH-trans,CH-cis}$ = -2.2 Hz, $J_{CH-trans,CH}$ = 17.2 Hz, olefinic $CH_{2-trans}$), 5.07 (dddd, 1 H, $J_{CH-cis,CH2b}$ = -0.9 Hz, $J_{CH-cis,CH2a}$ = -0.9 Hz, $J_{CH-trans,CH-cis}$ = -2.2 Hz, $J_{CH-cis,CH}$ = 10.2 Hz, olefinic CH_{2-cis}), 3.95 (ddd, 1 H, $J_{1,2}$ = 1.6 Hz, $J_{1,CH2a}$ = 6.2 Hz, $J_{1,CH2b}$ = 7.8 Hz, H-1), 3.91 (dd, 1 H, $J_{3,4}$ = 1.1 Hz, $J_{2,3}$ = 9.2 Hz, H-3), 3.84 (dd, 1 H, $J_{5,6a}$ = 3.5 Hz, $J_{6a,6b}$ = -11.5 Hz, H-6a), 3.81 (dd, 1 H, $J_{3,4}$ = 1.1 Hz, $J_{4,5}$ = 8.5 Hz, H-4), 3.73 (ddd, 1 H, $J_{5,6a}$ = 3.5 Hz, $J_{5,6b}$ = 6.1 Hz, $J_{6a,6b}$ = -11.5 Hz, H-5), 3.66 (dd, 1 H, $J_{5,6a}$ = 6.1 Hz, $J_{6a,6b}$ = -11.5 Hz, H-6b), 3.56 (dd, 1 H, $J_{1,2}$ = 1.6 Hz, $J_{2,3}$ = 9.2 Hz, H-2), 2.39 (dddd, 1 H, $J_{CH2a, CH-cis}$ = -0.9 Hz, $J_{CH2a, CH-trans}$ = -1.5 Hz, $J_{CH2a,CH}$ = 7.5 Hz, $J_{CH2a,CH2b}$ = -14.1 Hz, CH_{2a}), 2.35 (dddd, 1 H, $J_{CH2b, CH-cis}$ = -0.9 Hz, $J_{CH2b, CH-trans}$ = -1.4 Hz, $J_{CH2b,CH}$ = 6.5 Hz, $J_{CH2a,CH2b}$ = -14.1 Hz, CH_{2b}).

^{13}C NMR (150 MHz, MeOD, 25 ºC): d 136.6 (olefinic CH), 117.5 (olefinic CH_2), 72.9 (C-5), 72.5 (C-2), 71.1 (C-4), 71.0 (C-1), 70.2 (C-3), 65.0 (C-6), 39.3 (CH_2).

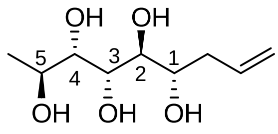
HRMS: *m/z*: calcd. for $C_9H_{18}O_6Na$ $[M+Na]^+$: 245.0996; found: 245.0984.

Compound 4: White solid. R_f = 0.74 (MeOH/acetone = 1:1). HRMS: *m/z*: calcd. for $C_9H_{18}O_5Na$ $[M+Na]^+$: 229.1046; found: 229.1051.



4t

4t: ^{1}H NMR (600 MHz, MeOD, 25 ºC): d 5.90 (dddd, 1 H, $J_{CH,CH2b}$ = 6.5 Hz, $J_{CH,CH2a}$ = 7.5 Hz, $J_{CH,CH2\text{-}cis}$ = 10.2 Hz, $J_{CH,CH2\text{-}trans}$ = 17.2 Hz, olefinic CH), 5.11 (dddd, 1 H, $J_{CH\text{-}trans,CH2b}$ = -1.5 Hz, $J_{CH\text{-}trans,CH2a}$ = -1.5 Hz, $J_{CH\text{-}trans,CH\text{-}cis}$ = -2.2 Hz, $J_{CH\text{-}trans,CH}$ = 17.2 Hz, olefinic $CH_{2\text{-}trans}$), 5.04 (dddd, 1 H, $J_{CH\text{-}cis,CH2b}$ = -1.0 Hz, $J_{CH\text{-}cis,CH2a}$ = -1.1 Hz, $J_{CH\text{-}trans,CH\text{-}cis}$ = -2.2 Hz, $J_{CH\text{-}cis,CH}$ = 10.2 Hz, olefinic $CH_{2\text{-}cis}$), 3.92 (ddd, 1 H, $J_{1,2}$ = 1.6 Hz, $J_{1,CH2a}$ = 6.3 Hz, $J_{1,CH2b}$ = 7.7 Hz, H-1), 3.91 (dd, 1 H, $J_{3,4}$ = 1.3 Hz, $J_{2,3}$ = 8.9 Hz, H-3), 3.81 (dq, 1 H, $J_{5,CH3}$ = 6.3 Hz, $J_{4,5}$ = 7.7 Hz, H-5), 3.54 (dd, 1 H, $J_{3,4}$ = 1.3 Hz, $J_{4,5}$ = 7.7 Hz, H-4), 3.52 (dd, 1 H, $J_{1,2}$ = 1.6 Hz, $J_{2,3}$ = 8.9 Hz, H-2), 2.37 (dddd, 1 H, $J_{CH2a,\ CH\text{-}cis}$ = -1.1 Hz, $J_{CH2a,\ CH\text{-}trans}$ = -1.5 Hz, $J_{CH2a,CH}$ = 7.5 Hz, $J_{CH2a,CH2b}$ = -14.0 Hz, CH_{2a}), 2.34 (dddd, 1 H, $J_{CH2b,\ CH\text{-}cis}$ = -1.0 Hz, $J_{CH2b,\ CH\text{-}trans}$ = -1.5 Hz, $J_{CH2b,CH}$ = 6.5 Hz, $J_{CH2a,CH2b}$ = -14.0 Hz, CH_{2b}), 1.27 (d, 3 H, $J_{5,CH3}$ = 6.3 Hz, CH_3).
^{13}C NMR (150 MHz, MeOD, 25 ºC): d 137.0 (olefinic *C*H), 117.1 (olefinic *C*H_2), 75.1 (C-4), 73.0 (C-2), 71.2 (C-1), 70.5 (C-3), 69.2 (C-5), 39.6 (*C*H_2), 20.6 (*C*H_3).

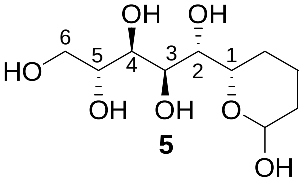


4e

4e: ^{1}H NMR (600 MHz, MeOD, 25 ºC): d 5.95 (dddd, 1 H, $J_{CH,CH2a}$ = 6.9 Hz, $J_{CH,CH2b}$ = 7.2 Hz, $J_{CH,CH2\text{-}cis}$ = 10.3 Hz, $J_{CH,CH2\text{-}trans}$ = 17.1 Hz, olefinic C*H*), 5.11 (dddd, 1 H, $J_{CH\text{-}trans,CH2a}$ = -1.3 Hz, $J_{CH\text{-}trans,CH2b}$ = -1.3 Hz, $J_{CH\text{-}trans,CH\text{-}cis}$ = -2.3 Hz, $J_{CH\text{-}trans,CH}$ = 17.1 Hz, olefinic $CH_{2\text{-}trans}$), 5.05 (dddd, 1 H, $J_{CH\text{-}cis,CH2b}$ = -1.2 Hz, $J_{CH\text{-}cis,CH2a}$ = -1.9 Hz, $J_{CH\text{-}trans,CH\text{-}cis}$ = -2.3 Hz, $J_{CH\text{-}cis,CH}$ = 10.3 Hz, olefinic $CH_{2\text{-}cis}$), 3.90 (dd, 1 H, $J_{3,4}$ = 1.3 Hz, $J_{2,3}$ = 7.7 Hz, H-3), 3.81 (dq, 1 H, $J_{5,CH3}$ = 6.2 Hz, $J_{4,5}$ = 7.7 Hz, H-5), 3.78 (ddd, 1 H, $J_{1,CH2a}$ = 3.3 Hz, $J_{1,CH2b}$ = 6.2 Hz, $J_{1,2}$ = 6.2 Hz, H-1), 3.61 (dd, 1 H, $J_{1,2}$ = 6.2 Hz, $J_{2,3}$ = 7.7 Hz, H-2), 3.54 (dd, 1 H, $J_{3,4}$ = 1.3 Hz, $J_{4,5}$ = 7.7 Hz, H-4), 2.48 (dddd, 1 H, $J_{CH2a,\ CH\text{-}trans}$ = -1.3 Hz, $J_{CH2a,\ CH\text{-}cis}$ = -1.9 Hz, $J_{CH2a,CH}$ = 6.9

Hz, $J_{CH2a,CH2b}$ = -15.2 Hz, CH_{2a}), 2.25 (dddd, 1 H, $J_{CH2b, CH-cis}$ = -1.2 Hz, $J_{CH2b, CH-trans}$ = -1.3 Hz, $J_{CH2b,CH}$ = 7.2 Hz, $J_{CH2a,CH2b}$ = -15.2 Hz, CH_{2b}), 1.26 (d, 3 H, $J_{5,CH3}$ = 6.2 Hz, CH_3).

^{13}C NMR (150 MHz, MeOD, 25 ºC): d 137.0 (olefinic *C*H), 117.1 (olefinic *C*H_2), 75.1 (C-4), 75.0 (C-2), 74.1 (C-1), 72.2 (C-3), 68.8 (C-5), 37.9 (*C*H_2), 20.6 (*C*H_3).

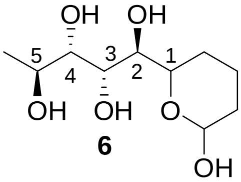


5

Compound 5: White solid, R_f = 0.22 (EtOAc/MeOH= 9:1). ^{1}H NMR (600 MHz, MeOD, 25 ºC): d 5.43 (br s, 1 H, anom. H), 4.45 (br s, 1 H, H-1), 4.10 (dd (appears as d), 1 H, $J_{2,3}$ = 9.4 Hz, H-2), 3.81 (dd, 1 H, $J_{6a,5}$ = 3.7 Hz, $J_{6a,6b}$ = -11.3 Hz, H-6a), 3.73 (dd, 1 H, $J_{3,4}$ = 1.1 Hz, $J_{4,5}$ = 8.6 Hz, H-4), 3.67 (ddd, 1 H, $J_{6a,5}$ = 3.7 Hz, $J_{6b,5}$ = 6.2 Hz, $J_{4,5}$ = 8.6 Hz, H-5), 3.62 (dd, 1 H, $J_{6b,5}$ = 6.2 Hz, $J_{6a,6b}$ = -11.3 Hz, H-6b), 3.56 (dd, 1 H, $J_{3,4}$ = 1.1 Hz, $J_{2,3}$ = 9.4 Hz, H-3), 1.95-1.87 (m, 2 H, ring-H), 1.66-1.54 (m, 4 H, ring H).

^{13}C NMR (150 MHz, MeOD, 25 ºC): d 103.9 (C-anom.), 79.0 (C-2) 76.9 (C-1), 72.8 (C-5), 71.2 (C-3), 70.9 (C-4), 65.3 (C-6), 32.2 (C-ring), 29.6 (C-ring), 17.1 (C-ring).

HRMS: *m/z*: calcd. for $C_{10}H_{20}O_7Na$ [M+Na]: 275.1101; found: 275.1096.

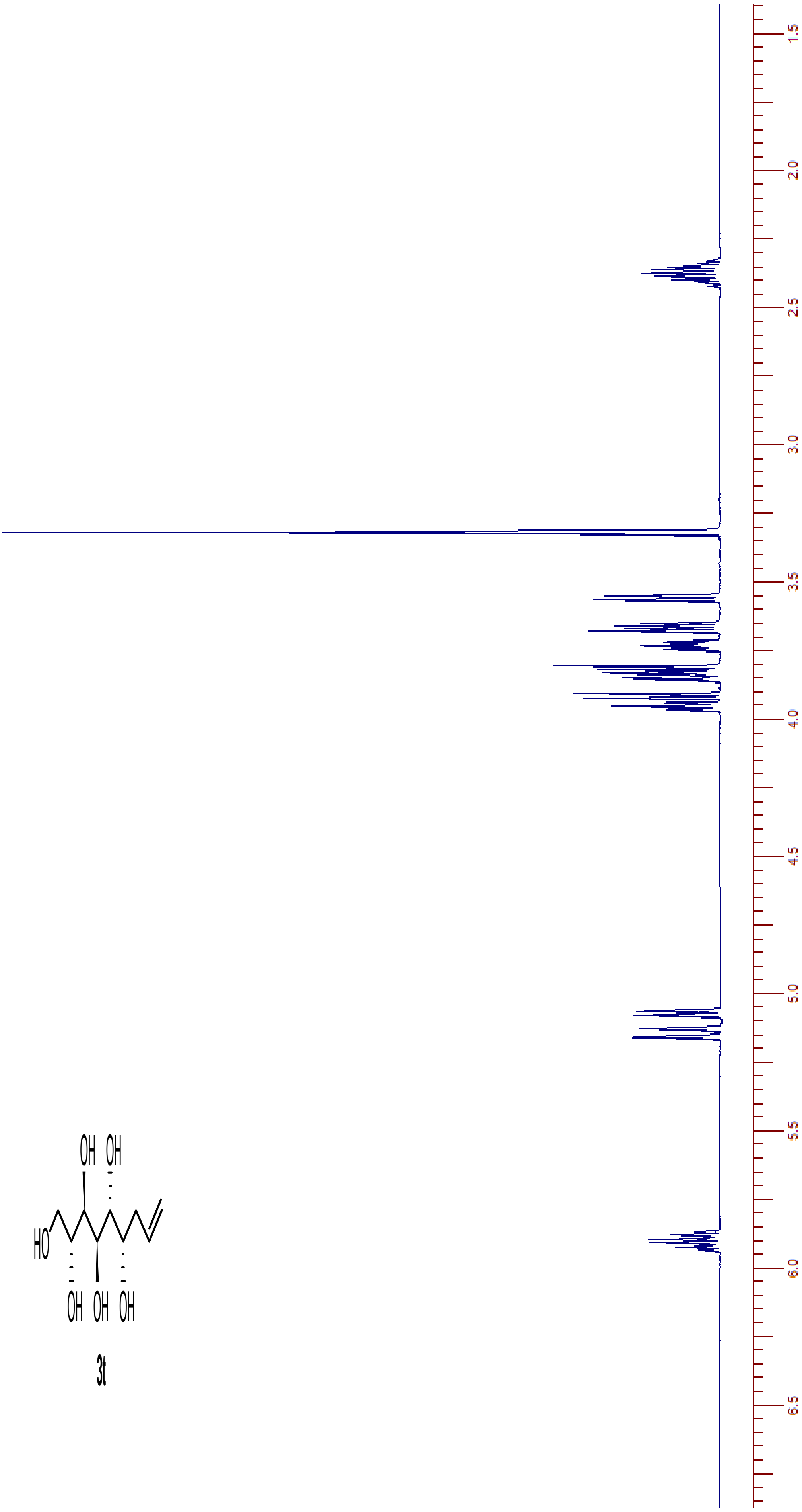


6

Compound 6: White solid, R_f = 0.54 (EtOAc/MeOH= 9:1). ^{1}H NMR (600 MHz, MeOD, 25 ºC): d 5.43 (br s, 1 H, anom. H), 4.45 (br s, 1 H, H-1), 4.08 (dd (appears as d), 1 H, $J_{2,3}$ = 9.4 Hz, H-2), 3.77 (dq, 1 H, $J_{5,CH3}$ = 6.3 Hz, $J_{4,5}$ = 8.1 Hz, H-5), 3.58 (dd, 1 H, $J_{3,4}$ = 1.2 Hz, $J_{2,3}$ = 9.4 Hz, H-3), 3.47 (dd, 1 H, $J_{3,4}$ = 1.2 Hz, $J_{4,5}$ = 8.1 Hz, H-4), 1.95-1.87 (m, 2 H, ring H), 1.66-1.53 (m, 4 H, ring H), 1.26 (d, 3 H, $J_{5,CH3}$ = 6.3 Hz, CH_3).

^{13}C NMR (150 MHz, MeOD, 25 ºC): d 103.8 (C-anom), 79.2 (C-2), 76.8 (C-1), 74.6 (C-4), 70.9 (C-3), 68.2 (C-5), 32.1 (C-ring) 29.6 (C-ring), 20.6 (CH_3), 17.0 (C-ring).

HRMS: *m/z*: calcd. for $C_{10}H_{20}O_6Na$ $[M+Na]^+$: 259.1152; found: 259.1139.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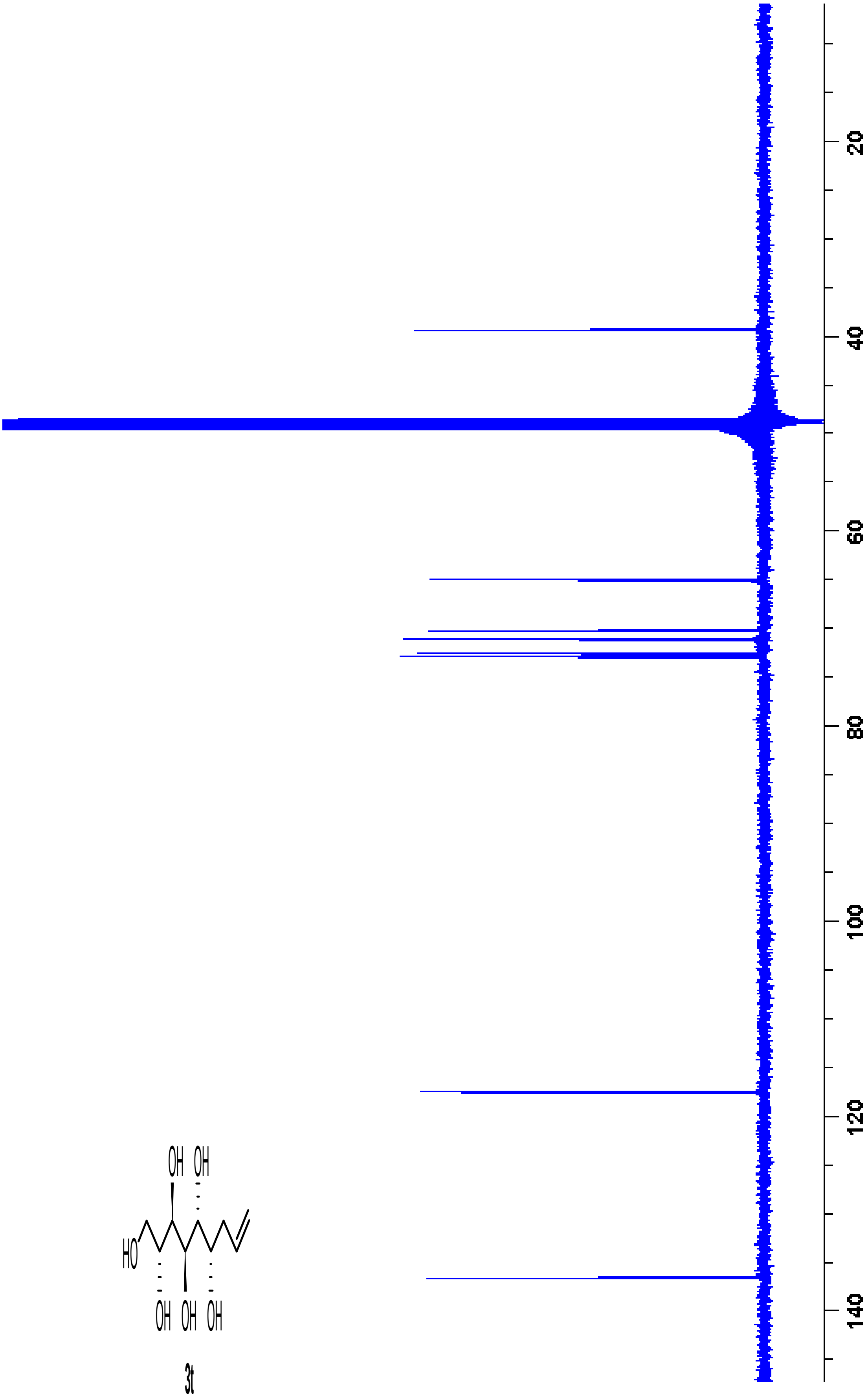

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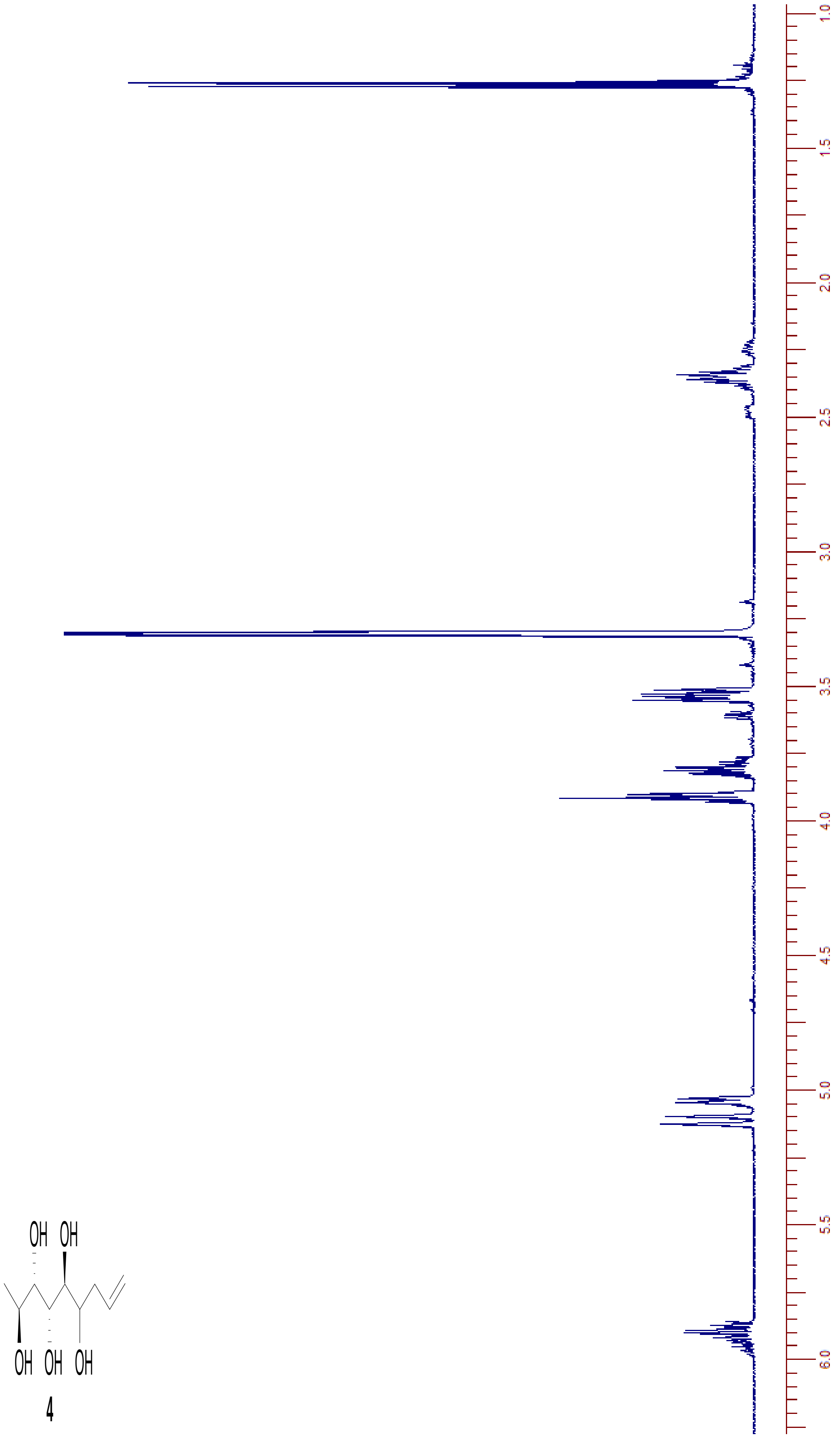

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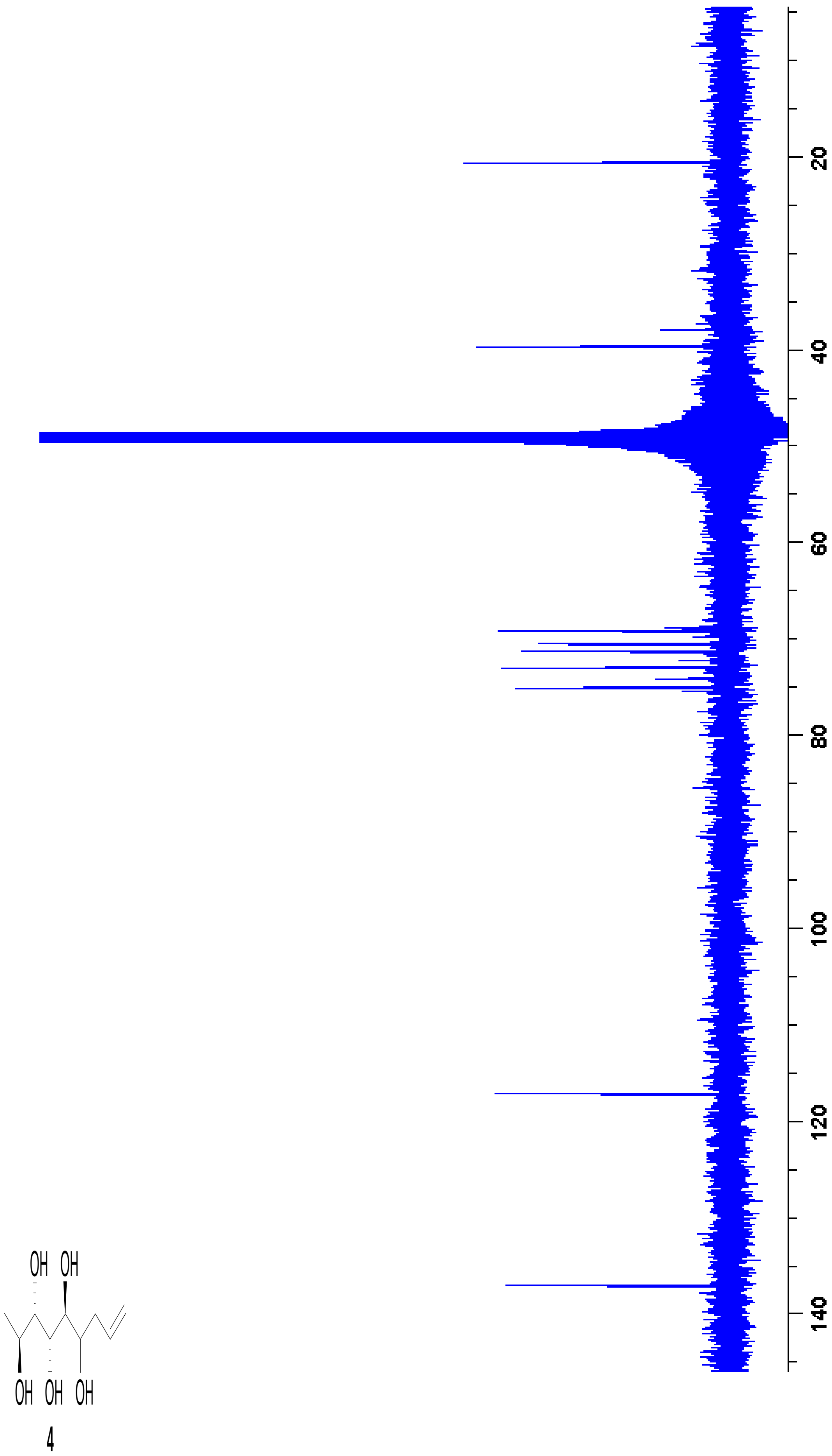
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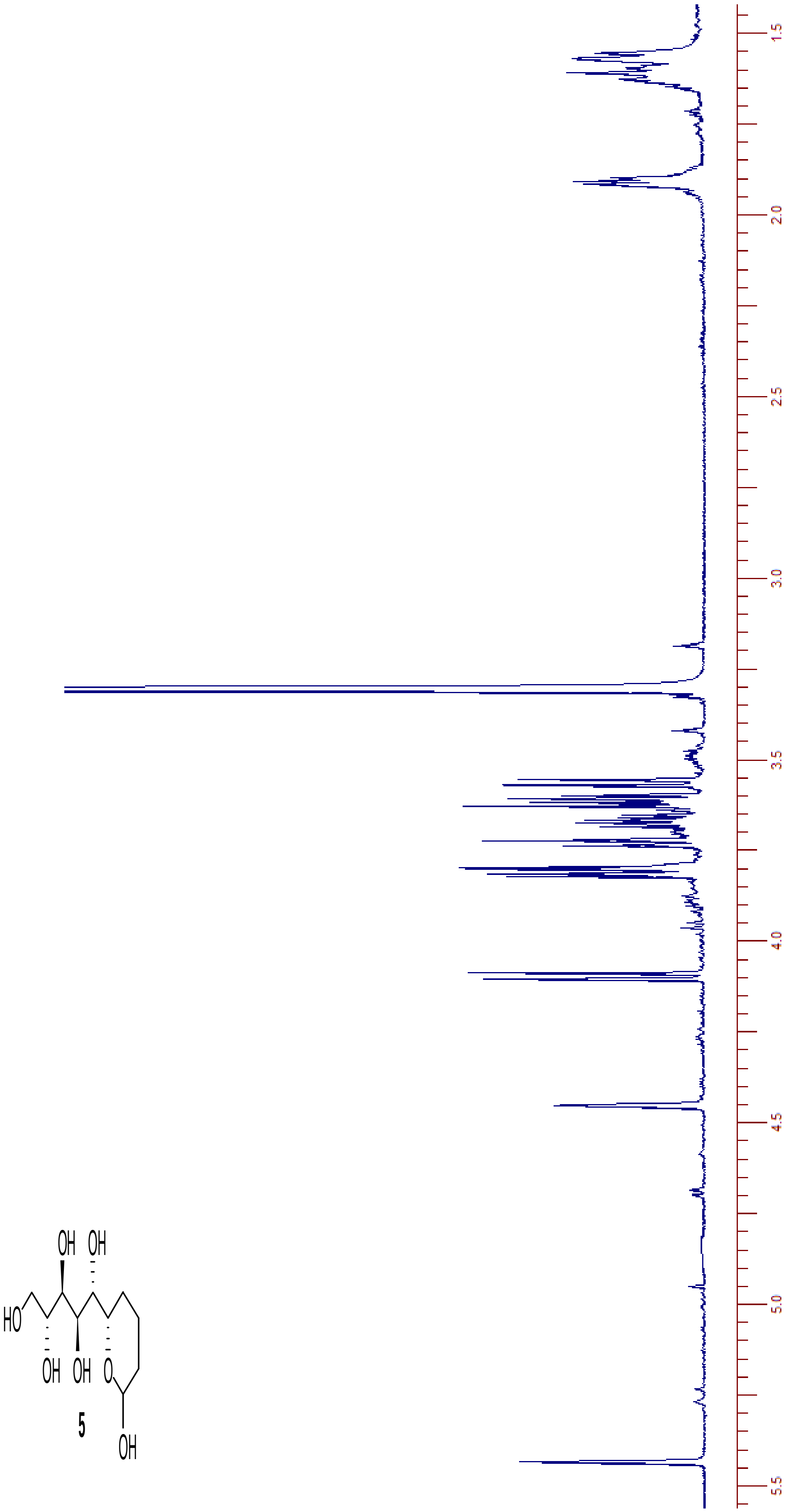

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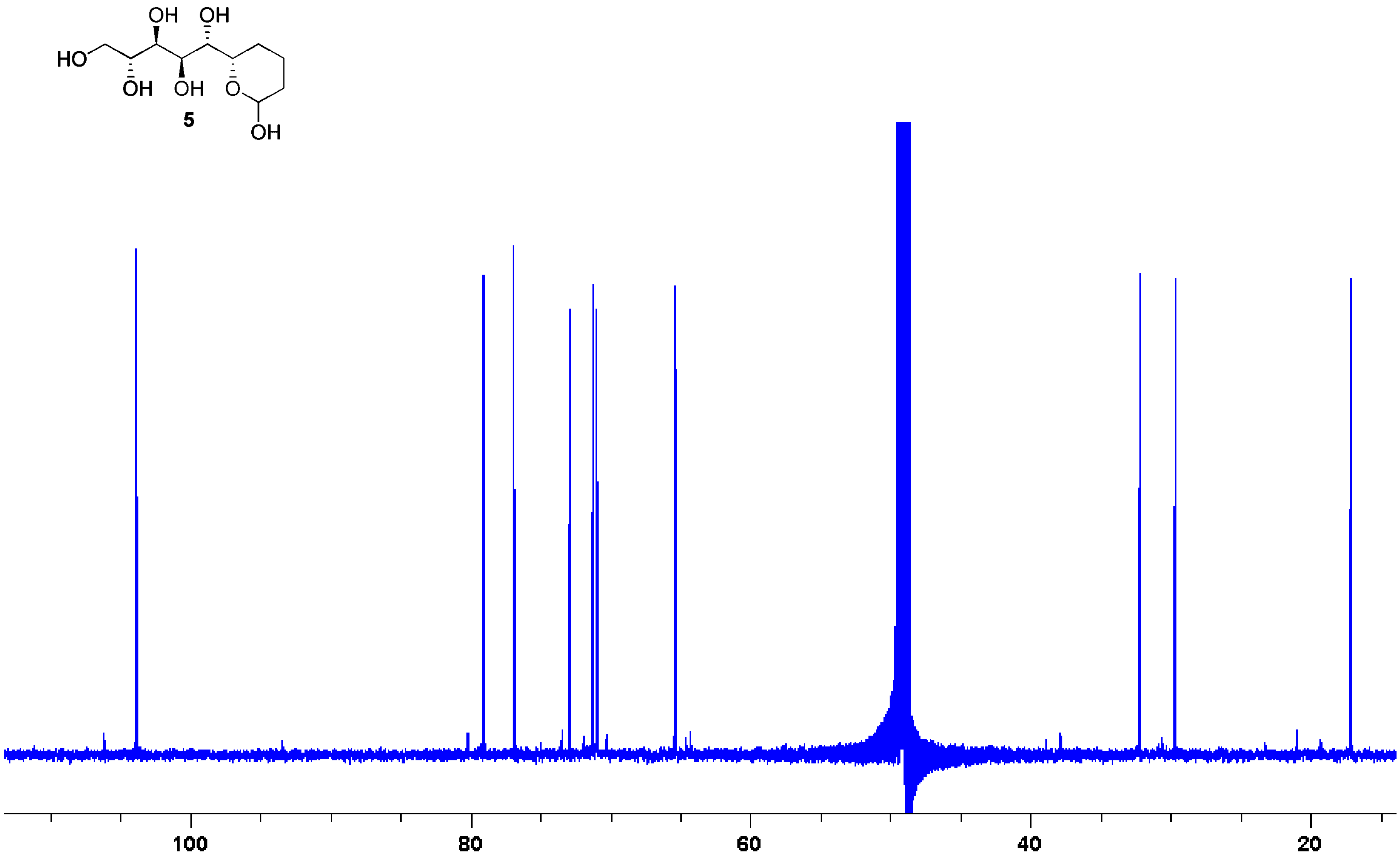

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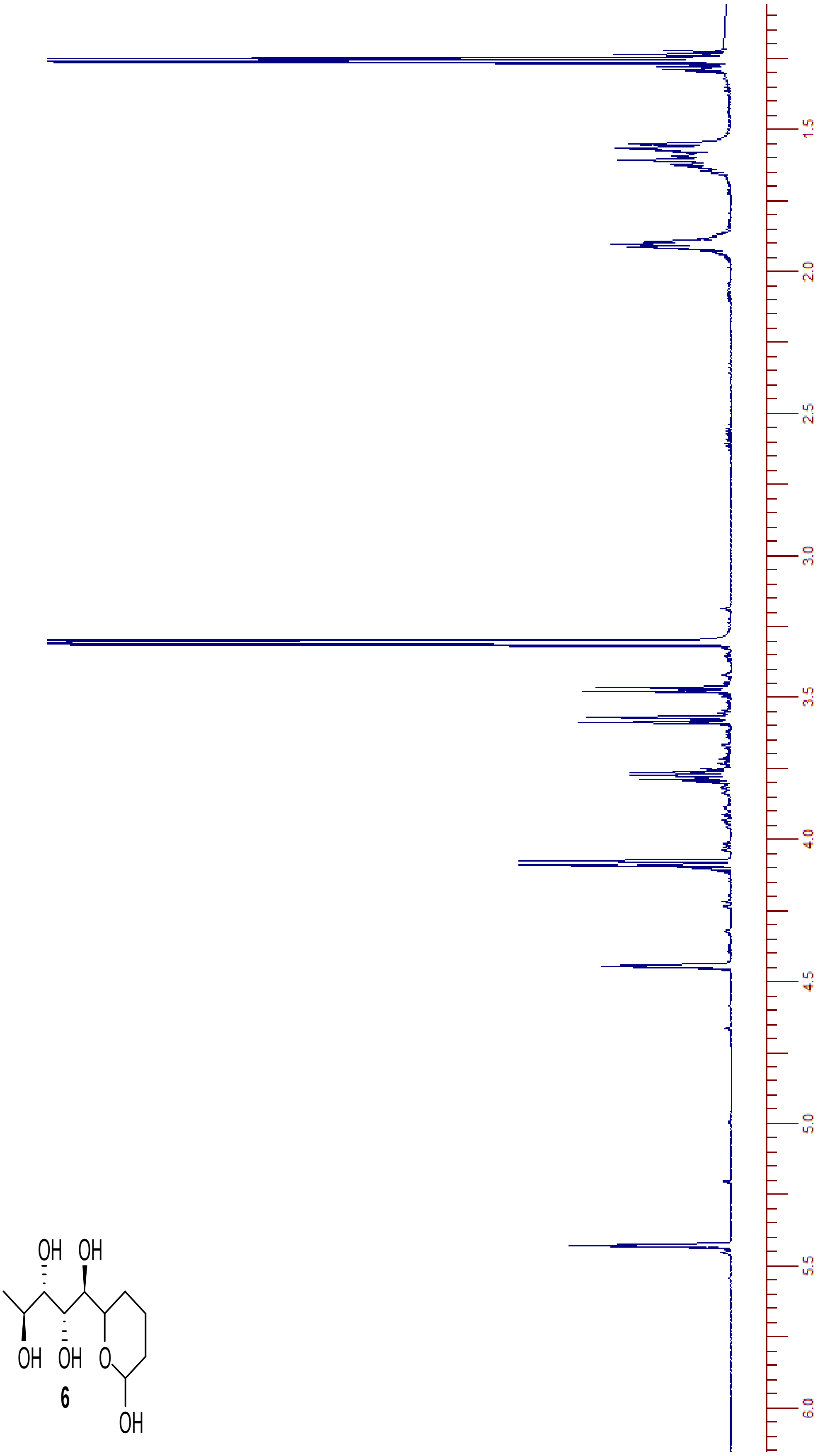

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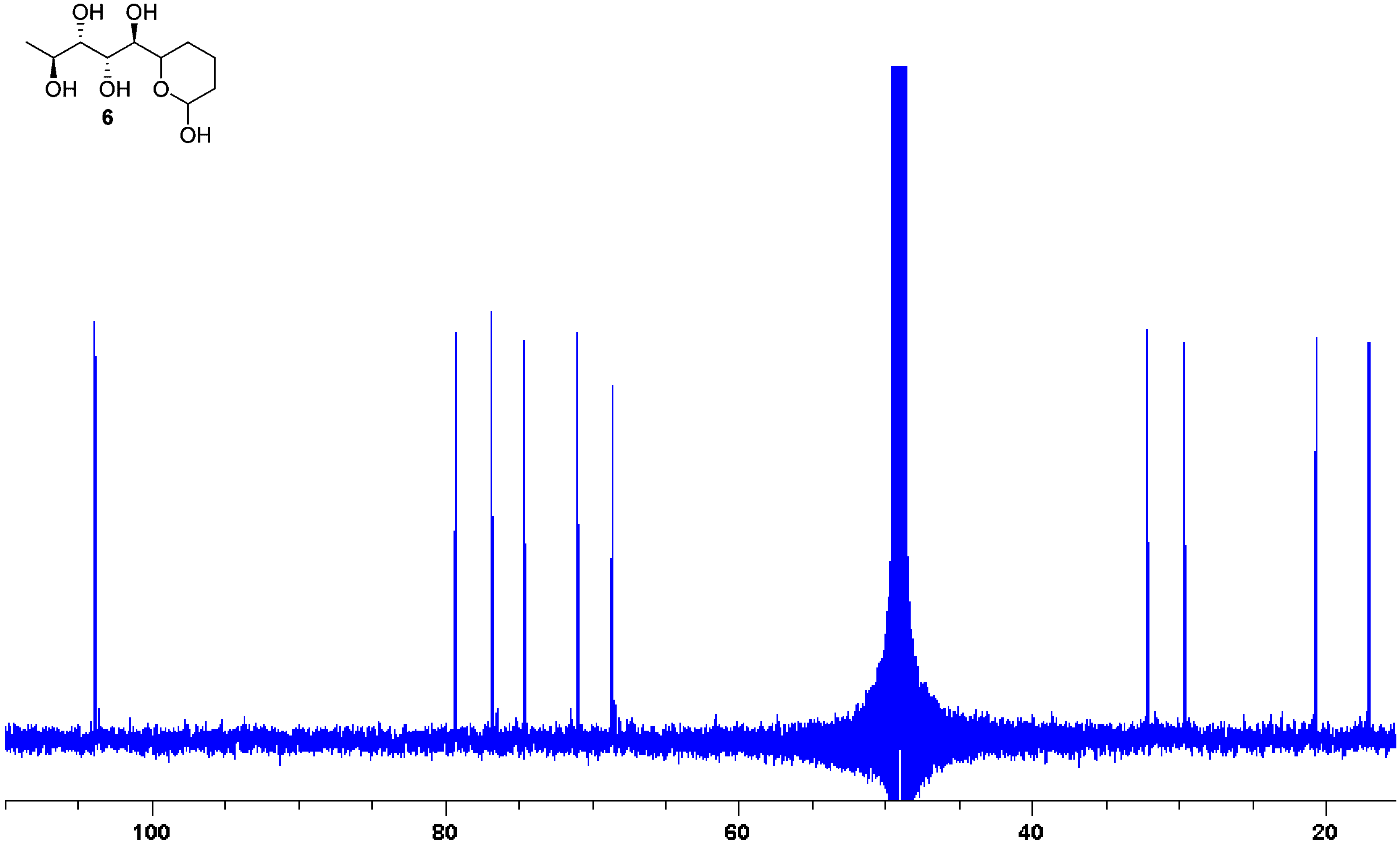

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