Supporting Information

Concise Synthesis of the Chemopreventitive Agent (±)-Deguelin via a Key 6-endo Hydroarylation

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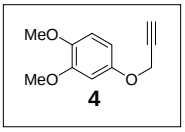
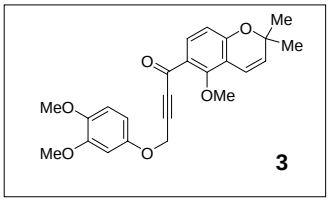
Nuclear Magnetic Resonance spectra were recorded on Bruker 300 or 400 Fourier transform NMR spectrometers. Spectra were recorded in $CDCl_3$ solutions referenced to TMS or the solvent residual peak. IR spectra were taken as neat for liquids on NaCl plates, and as KBR pellet for solids using a Perkin-Elmer 1600 FTIR spectrometer. High Resolution Mass Spectra were obtained on a JOEL JMS-HX110 HF mass spectrometer. Flash chromatography was performed on SILICYCLE silica gel (230-400 mesh). $PtCl_4$ and $PtCl_2$ were purchased from Strem and used as received. All reactions were monitored by TLC.



4

To 3,4-dimethoxy phenol **10** in DMF (0.2M) was added propargyl bromide (1.2 equiv.) and potassium carbonate (1.2 equiv.). The reaction was stirred vigorously at room temperature. After 12 hours, saturated NH_4Cl and ether was added. The organic layer was washed with water (x2), brine, and dried over $MgSO_4$. Removal of volatiles and purification of the crude residue by filtration through a pad of silica (hexanes/CH_2Cl_2 = 1:1) gave **4** as a pale yellow oil in quantitative yield. ^{1}H NMR δ 2.52 (t, J = 2.4, 1H), 3.84 (s, 3H), 3.86 (s, 3H), 4.65 (d, J = 2.4 Hz, 2H), 6.49 (dd, J = 8.7, 2.8 Hz, 1H), 6.60 (d, J = 2.8 Hz, 1H), 6.79 (d, J = 8.7 Hz, 1H).

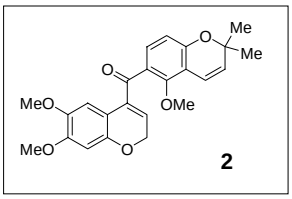


3

To a solution of **4** (1.66g, 8.66 mmol, 1.05 equiv.) in 75ml of THF was added *n*-butyl lithium (5.54 ml, 8.86 mmol, 1.075 equiv.) at –78 ^{o}C under argon. After thirty minutes, **5**[1] (1.80g, 8.25 mmol, 1 equiv.) in 50 ml of THF was added via cannula. The reaction was

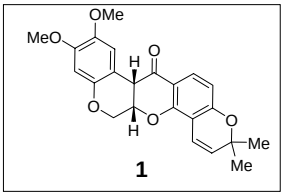
[1] Geneive, H.E.; Jacobs, H. *Tetrahedron* **2001,** *57*, 5235-5338.

stirred for 60 min and then quenched with 30 ml of saturated NH_4Cl and extracted with EtOAc (x 3). The combined organic layer was washed with brine and dried over $MgSO_4$, and the volatiles removed under reduced pressure. The crude oil was then dissolved in dichloromethane (20 ml), and MnO_2 (5.3g, 60.96 mmol, 7.0 equiv.) was added. After the reaction was stirred overnight at room temperature, ether was added and the suspension was filtered through a pad of celite and silica gel. Removal of volatiles revealed a yellow solid that was washed with hexanes and cold ether to afford **3** as a white solid (2.93 g, 87 %): IR 1638, 1582, 1510, 1264 cm^{-1}; ^1H NMR δ 1.45 (s, 6H), 3.78 (s, 3H), 3.85 (s, 3H), 3.86 (s, 3H), 4.90 (s, 2H), 5.67 (d, *J* = 10.1 Hz), 6.52-6.64 (m, 4H), 6.80 (d, *J* = 8.7 Hz, 1H), 7.79 (d, *J* = 8.7 Hz, 1H); ^{13}C NMR δ 28.2, 55.9, 56.4, 56.9, 62.9, 86.4, 86.6, 101.6, 105.0, 111.6, 112.5, 115.2, 116.2, 122.9, 130.5, 134.1, 144.4, 149.9, 152.0, 157.8, 159.6, 174.2; HRFABMS *m/z* 408.1587$(M)^+$, calcd for $C_{24}H_{24}O_6$ 408.1573.



2

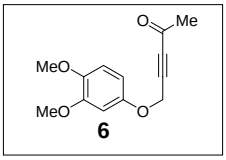
In a flame dried 10 ml round bottom flask was added **3** (55 mg, 0.135 mmol) and $PtCl_2$ (1.8 mg, 5 mol %). The flask was evacuated and flushed with argon three times, followed by the addition of toluene (1.8ml, 0.1 M). The reaction was allowed to stir at 55 ^oC for 10h and the volatiles were removed. Purification of the crude residue by flash chromatography on silica gel (hexanes/EtOAc, 7:2) afforded **2** as a yellow oil which solidifies with time (50 mg, 91 %): IR 1652, 1590, 1509, 1466, 1371, 1273, 1220, 1194, 1154, 1114 cm^{-1}; ^1H NMR δ 1.44 (s, 6H), 3.73 (s, 3H) 3.78 (s, 3H), 3.83 (s, 3H), 4.78 (d, *J* = 4.1 Hz, 2H), 5.66 (d, *J* = 10.1 Hz, 1H), 6.13 (t, *J* = 4.1 Hz, 1H), 6.48 (s, 1H), 6.56-6.61 (m, 2H), 7.34-7.35 (m, 2H); ^{13}C NMR δ 28.0, 55.9, 56.3, 63.1, 64.7, 76.8, 100.5, 109.0, 111.8, 112.0, 114.8, 116.5, 124.6,128.1, 130.5, 131.6, 135.6, 143.5, 148.8, 150.1,157.4, 193.9**;** HRFABMS *m/z* 408.1587 $(M)^+$, calcd for $C_{24}H_{24}O_6$ 408.1573.



1

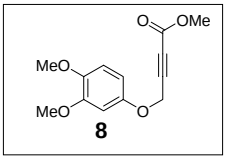
To a flame dried 10 ml round bottom flask was added **2** (45 mg, 0.111 mmol) and dichloromethane (2 ml). The solution was cooled to – 78 ^oC and boron trichloride (133 μl, 1 M solution in CH_2Cl_2, 0.133 mmol, 1.2 equiv.) was added. After stirring for 1 h the reaction was quenched with saturated NH_4Cl, extracted with EtOAc (x3), dried over $MgSO_4$, and concentrated under reduce pressure. The crude residue was dissolved in ethanol, saturated with potassium acetate and refluxed for 1 h. To the cooled reaction was added EtOAc and water. The layers were separated and the aqueous washed with EtOAc (x2) the combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The crude residue was filtered through silica gel (hexanes/EtOAc, 3:1) to yield (±)-Deguelin **1** as a white solid (37 mg, 86%). The ^1H

NMR and ^{13}C NMR spectra are identical to those of the natural compound[2]: ^{1}H NMR δ 1.38 (s, 3H), 1.45 (s, 3H), 3.77 (s, 3H), 3.80 (s, 3H), 3.84 (d, *J* = 4.1 Hz, 1H), 4.19 (d, *J* = 12.0 Hz, 1H), 4.63 (dd, *J* = 12.0, 3.1 Hz, 1H), 4.92 (t, *J* = 3.1 Hz, 1H), 5.55 (d, *J* = 10.1 Hz, 1H), 6.45 (t, J_{av} = 4.4 Hz, 2H), 6.64 (d, *J* =10.1 Hz, 1H), 6.79 (s, 1H), 7.74 (d, *J* = 8.7 Hz, 1H); ^{13}C NMR δ 28.1, 28.5, 44.4, 55.8, 56.3, 66.3, 72.4, 77.7, 100.9, 104.8, 109.1, 110.5, 111.5, 112.8, 115.7, 128.5, 128.7, 143.9, 147.4, 149.5, 156.9, 160.1, 189.2; HRFABMS *m/z* 394.1419 $(M)^{+}$, calcd for $C_{23}H_{22}O_6$ 394.1416.



6

To a solution of **4** (715 mg, 3.71 mmol) in 30ml of THF was added *n*-butyl lithium at –78 ^{o}C. After 30 minutes acetaldeyde (1 ml, 17.8 mmol, 4.8 equiv.) was added. After allowing the reaction to warm to ambient temperature, saturated NH_4Cl was added and the majority of the solvent was removed. The reaction was diluted with EtOAc and the organic layer washed with water. The aqueous layer was extracted with EtOAc and the combined organic layers were washed with brine, and dried with $MgSO_4$. Volatiles were removed and the crude residue was dissolved in CH_2Cl_2 (30ml). PCC (1.75g, 8.16 mmol, 2.2 equiv) was added and the reaction was stirred overnight. The reaction was diluted with ether and filtered through celite. Volatiles were removed and purification of the crude residue by flash chromatography on silica gel (hexanes/EtOAc, 5:1 to 3:1) afforded **6** (417mg, 48 %) as a pale yellow oil. IR 2216, 1679, 1599, 1512, 1453, 1361, 1229,1196, 1160, 1026 cm $^{-1}$; ^{1}H NMR δ 2.33 (s, 3H), 3.83 (s, 3H), 3.85 (s, 3H), 4.78 (s, 3H), 6.45 (dd, *J* =8.7, 2.8 Hz, 1H), 6.56 (d, *J* = 2.8 Hz, 1H), 6.78 (s, *J* = 8.7 Hz, 1H); ^{13}C NMR δ 32.5, 55.8, 56.2, 56.3, 85.8, 85.9, 101.2, 104.2, 111.2, 144.1, 149.5, 151.4, 183.2; APCI *m/z* 235.0847 $(M+H)^{+}$, calcd for $C_{13}H_{15}O_4$ 235.0970.



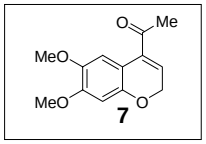
8

To a solution of **4** (630 mg, 3.28 mmol) in 30ml of THF was added *n*-butyl lithium at –78 ^{o}C. After 30 minutes $ClCO_2Me$ (315 μl, 4.92 mmol, 1.5 equiv.) was added. The reaction was allowed to warm to ambient temperature. Volatiles were removed and purification of the residue by flash chromatography on silica gel (hexanes/EtOAc, 5:1) afforded **8** (750mg, 91 %) as a pale yellow oil. IR 2242, 1717, 1600, 1511, 1438, 1261, 1026 cm $^{-1}$; ^{1}H NMR δ 3.76 (s, 3H), 3.84 (s, 3H), 3.86 (s, 3H), 4.75 (s, 3H), 6.45 (dd, *J* = 8.7, 2.8 Hz, 1H), 6.56 (d, *J* = 2.8 Hz, 1H), 6.77 (d, *J* = 8.7 Hz, 1H); ^{13}C NMR δ 52.9, 55.9, 56.3, 78.2, 82.3, 101.4, 104.4, 111.3, 144.2, 149.5, 151.5, 153.0; APCI *m/z* 251.0714 $(M+H)^{+}$, calcd for $C_{13}H_{15}O_5$ 251.0920.

[2] Luyengi, L.; Lee, I. S.; Mar, W.; Fong, H. H. S.; Pezzuto, J. M.; Kinghorn, A. D. *Phytochemistry*; **1994,** *36*, 1523-1526.

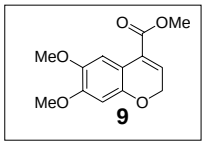
General procedure for the preparation of 7 and 9:

A solution of **7** or **9** in dioxane (0.1M) and $PtCl_4$ (5 mol %) or toluene (0.1M) and $PtCl_2$ (5 mol %) were stirred under argon at 60 ^oC. The solvent was evaporated and the products purified by flash chromatography (hexanes/EtOAc, 5:1). For yields see Scheme 2.



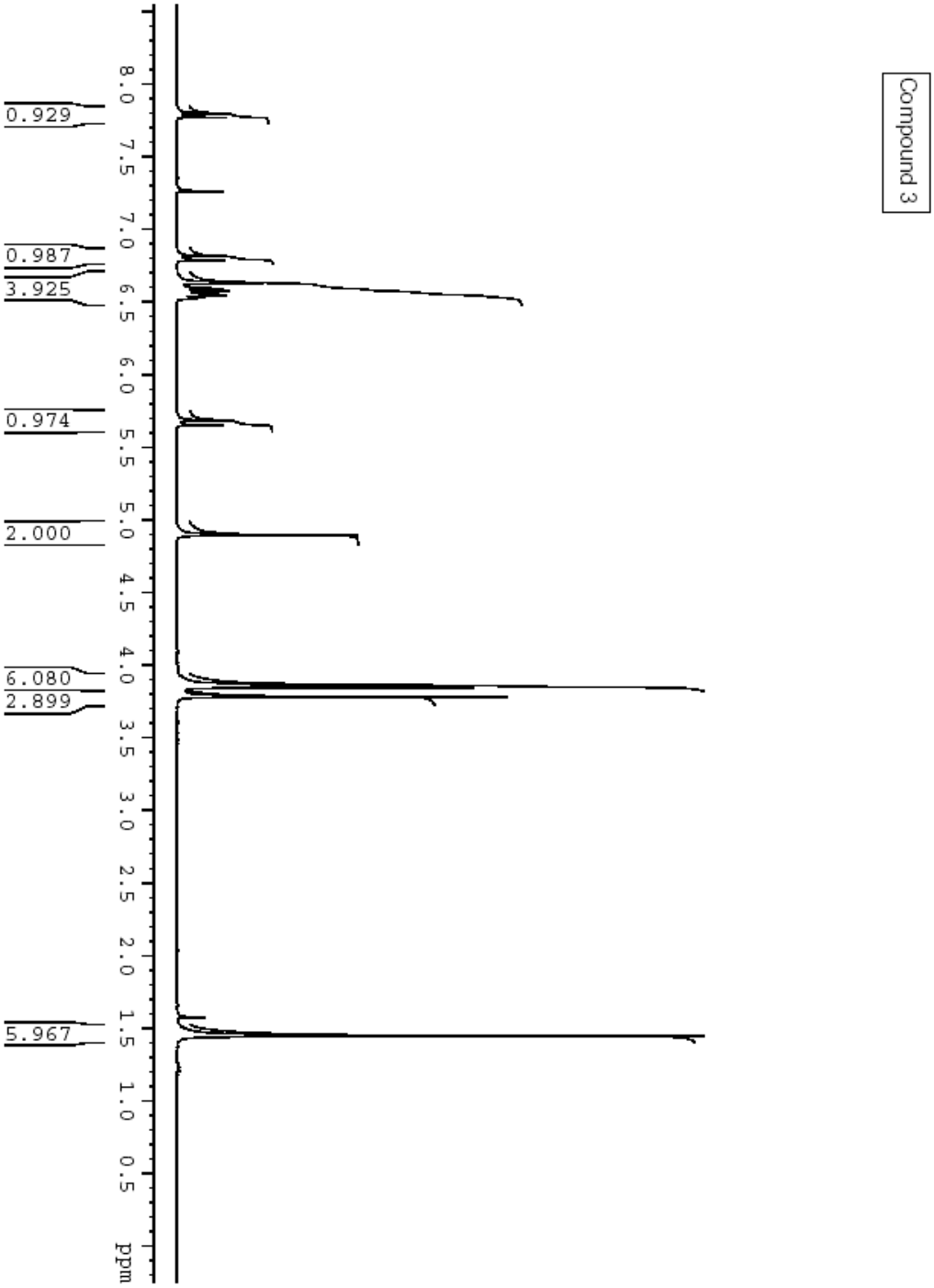
7

IR 1670, 1609, 1510, 1450, 1410, 1240, 1197, 1135cm $^{-1}$; ^1H NMR δ 2.45 (s, 3H), 3.83 (s, 3H), 3.84 (s, 3H), 4.75 (d, *J* = 4.3 Hz, 2H), 6.45 (s, 1H), 6.56 (t, *J* = 4.3 Hz, 1H), 7.58 (s, 1H); ^{13}C NMR δ 28.1, 56.5, 56.9, 65.0, 100.8, 110.3, 111.8, 129.3, 134.8, 143.8, 149.3, 150.3, 198.0; APCI *m/z* 235.0953 $(M+H)^+$, calcd for $C_{13}H_{15}O_4$ 235.0970.



9

IR 1721, 1614, 1509, 1454, 1253, 1140 cm $^{-1}$; ^1H NMR δ 3.83 (s, 3H), 3.84 (s, 3H), 3.86 (s, 3H), 4.75 (d, *J* = 4.2 Hz, 2H), 6.44 (s, 1H), 6.70 (t, *J* = 4.2 Hz), 7.59 (s, 1H); ^{13}C NMR δ 51.9, 55.9, 56.4, 64.7, 100.5, 109.7, 111.5, 126.9, 129.1, 143.6, 148.9, 150.1, 165.3; APCI *m/z* 251.0936 $(M+H)^+$, calcd for $C_{13}H_{15}O_5$ 251.0920.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6.5
6.0
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4.5
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3.5
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2.0
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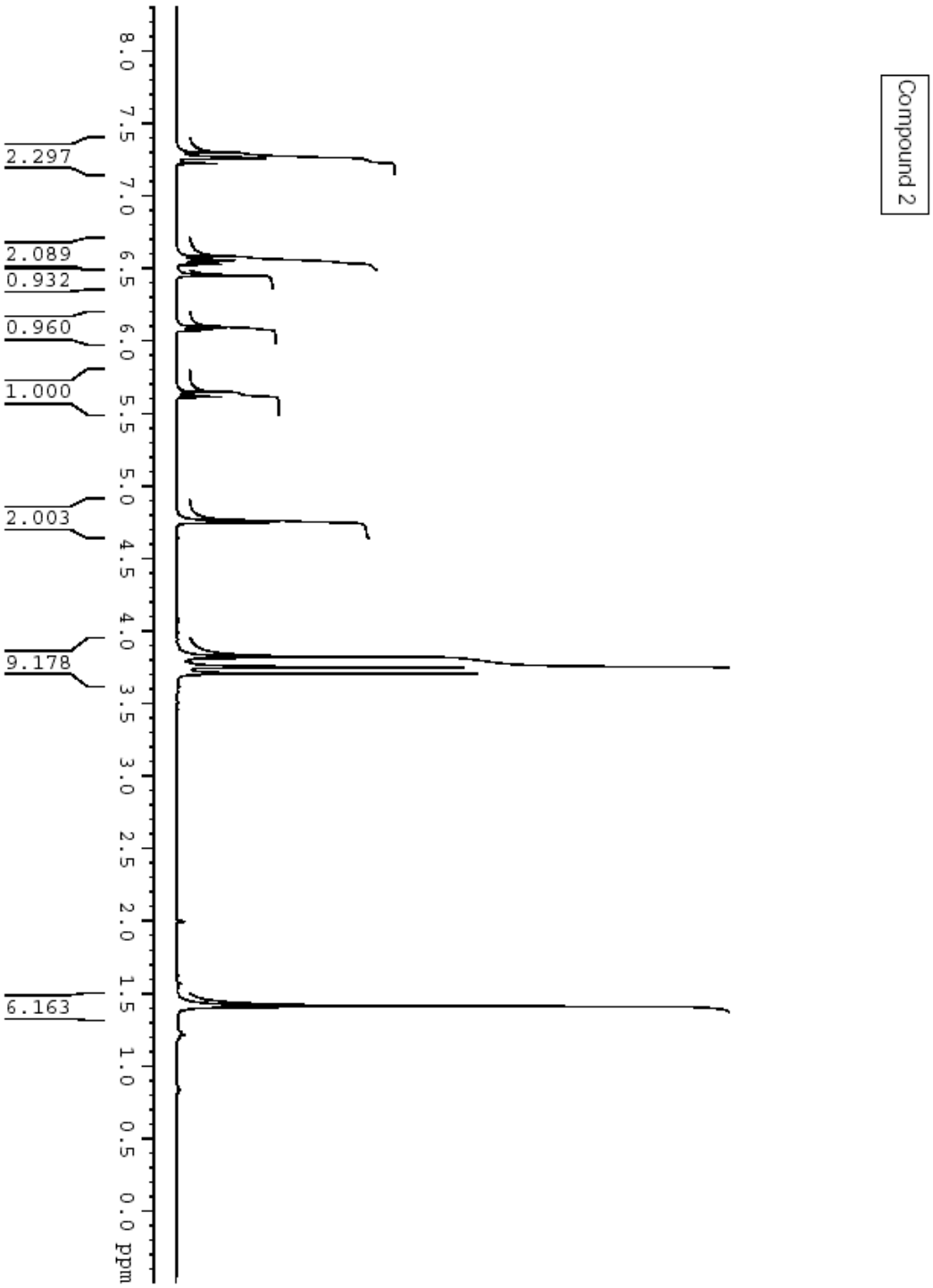
1.0
0.5
ppm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1.000
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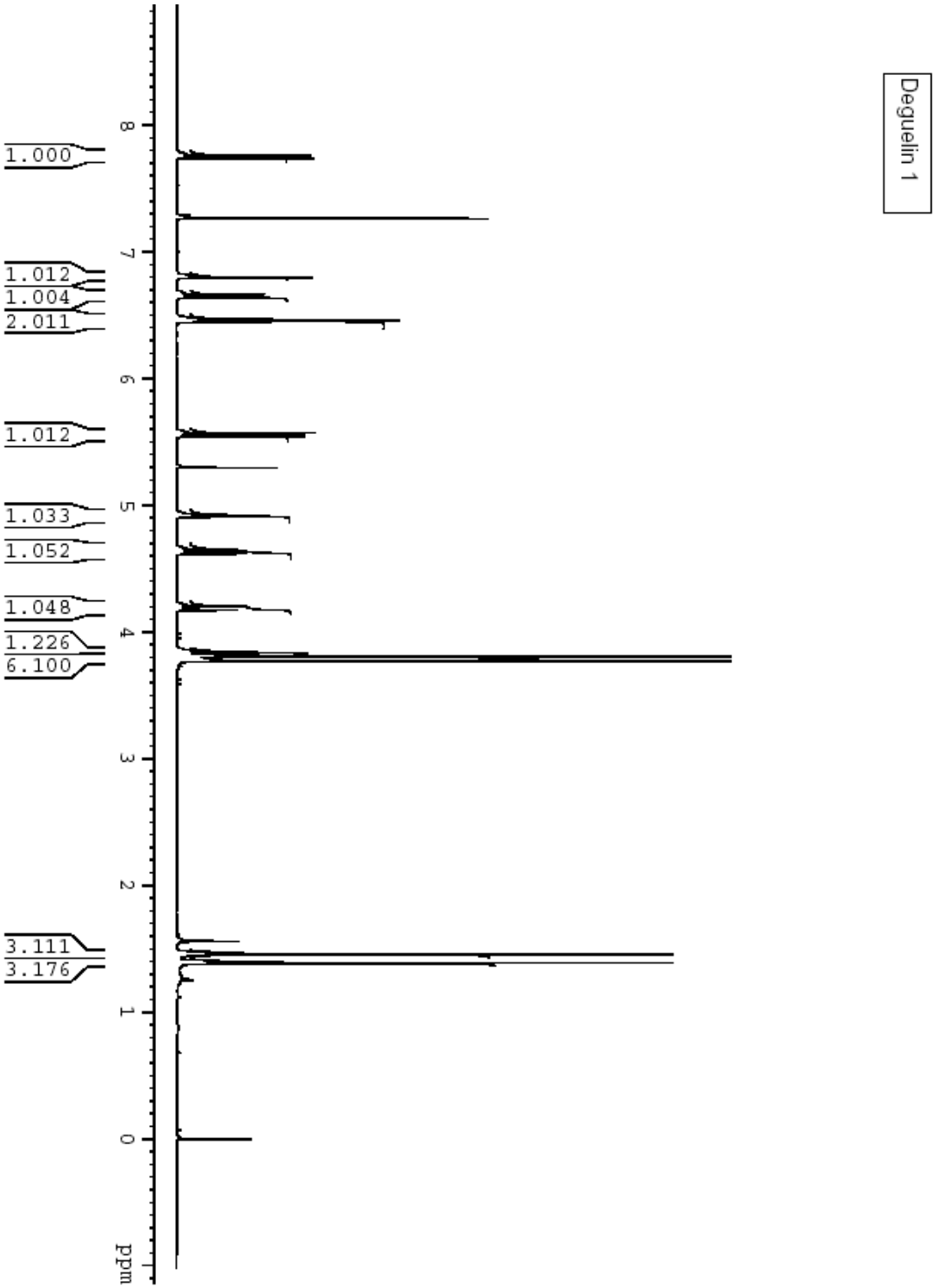
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8
7
6
5
4
3
2
1
0
ppm