Electronic Supplementary Material (ESI) for RSC Advances.

Supplementary Information

Concise and Stereoselective Synthesis of (±)-Hagen's Gland Lactone

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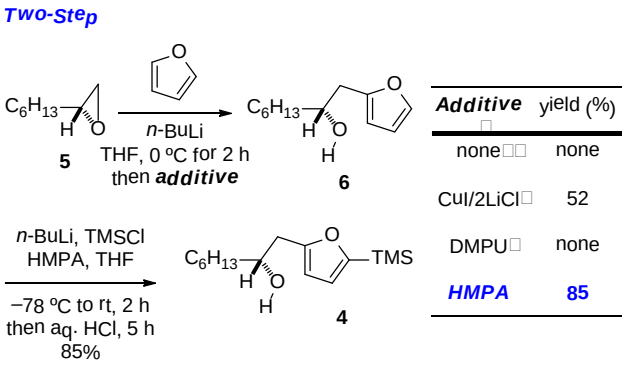
General Procedure

Proton (^{1}H) and carbon (^{13}C) NMR spectra were obtained on a Varian Mercury 400 (400/100 MHz) spectrometer. Chemical shifts are reported in ppm units with Me_4Si or $CHCl_3$ as the internal standard. All reactions were routinely carried out under an inert atmosphere of dry nitrogen. Reactions were checked by thin layer chromatography (Kieselgel 60 F254, Merck). Spots were detected by viewing under a UV light, and by colorizing with charring after dipping in anisaldehyde solution in a mixture of acetic acid, sulfuric acid, and methanol. In aqueous work-up, all organic solutions were dried over anhydrous sodium sulfate and filtered prior to rotary evaporation. The crude compounds were purified by column chromatography on a silica gel (Kieselgel 60, 70-230 mesh, Merck). Unless otherwise noted, materials and all solvents were obtained from commercial suppliers and were used without purification. THF was freshly distilled from sodium and benzophenone.

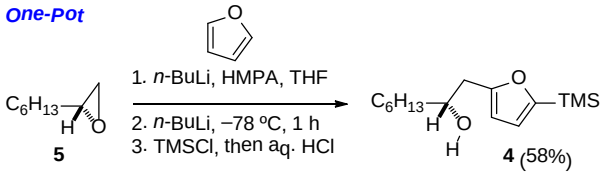
Two-Step Synthesis of Hydroxy TMS-Furan 4



Hydroxyfuran 6. To a cooled (–78 ºC) solution of furan (1.90 mL = 1.782 g, 26.2 mmol) in THF (50 mL) was added dropwise *n*-BuLi (11.0 mL, 2.5 M in hexane, 27.5 mmol). The resulting mixture was stirred for 1 h at 0 ºC before (±)-1,2-epoxyoctane (2 mL = 1.678 g, 13.1 mmol) and HMPA (5 mL, 28.7 mmol) were added. After stirred for 24 h at room temperature, the reaction mixture was quenched with saturated aqueous NH_4Cl and diluted with Et_2O. The layers were separated, and the aqueous layer was extracted

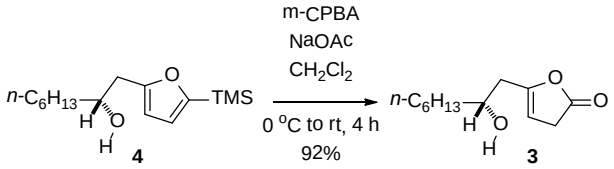
with Et_2O. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, hexanes/EtOAc, 5/1) to afford hydroxy furan **6** (2.174 g, 85%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (d, *J* = 2.0 Hz, 1H), 6.31 (dd, *J* = 3.2, 2.0 Hz, 1H), 6.10 (d, *J* = 2.8 Hz, 1H), 3.88 (brs, 1H), 2.85 (dd, *J* = 15.2, 4.0 Hz, 1H), 2.71 (dd, *J* = 14.8, 8.0 Hz, 1H), 1.76 (d, *J* = 3.6 Hz, 1H), 1.26–1.53 (m, 10H), 0.88 (dd, *J* = 7.2, 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.9, 141.4, 110.3, 106.9, 70.5, 36.9, 36.3, 32.0, 29.5, 25.8, 22.8, 14.3; IR (neat) 3296, 2936, 2907, 1039 cm^{-1}; HRMS (ESI-TOF) m/z: $[M]^+$ Calcd for $C_{12}H_{20}O_2$ 196.1463; Found 196.1444. **Hydroxy TMS-Furan 4.** To a cooled (–78 ºC) solution of hydroxy furan **6** (2.174 g, 11.08 mmol) in HMPA/THF (9:1, total 50 mL) was added dropwise *n*-BuLi (9.0 mL, 2.5 M in hextane, 22.5 mmol). The resulting mixture was stirred for 2 h at the same temperature before TMSCl (5.7 mL, 44.9 mmol) was added dropwise. After stirred for 2 h at –30 ºC, the reaction mixture was quenched with saturated aqueous NH_4Cl and acidified with 1 N HCl. The resulting mixture was stirred for 5 h at room temperature and diluted with Et_2O. The layers were separated, and the aqueous layer was extracted with Et_2O. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, hexanes/EtOAc, 5/1) to afford hydroxy TMS-furan **4** (2.536 g, 85%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.54 (d, *J* = 2.8 Hz, 1H), 6.09 (d, *J* = 2.8 Hz, 1H), 3.85–3.96 (m, 1H), 2.88 (dd, *J* = 15.2, 4.0 Hz, 1H), 2.75 (dd, *J* = 14.8, 7.6 Hz, 1H), 1.82 (d, *J* = 4.4 Hz, 1H), 1.47–1.51 (m, 4H), 1.29–1.34 (m, 6H), 0.89 (dd, *J* = 7.2, 7.2 Hz, 3H), 0.25 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.2, 157.1, 120.5, 107.0, 70.6, 37.0, 36.6, 32.0, 29.5, 25.8, 22.8, 14.3, −1.3; IR (neat) 3311, 2938, 2828, 1025 cm^{-1}; HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{15}H_{28}O_2SiNa$ 291.1756; Found 291.1744.

One-Pot Preparation of Hydroxy TMS-Furan 4.



To a cooled (–78 ºC) solution of furan (1.90 mL = 1.782 g, 26.2 mmol) in THF (50 mL) was added dropwise *n*-BuLi (11 mL, 2.5 M in hexane, 27.5 mmol), and the resulting mixture was stirred for 1 h at 0 ºC before (±)-1,2-epoxyoctane (2 mL = 1.678 g, 13.1 mmol) and HMPA (5 mL, 28.7 mmol) were added. After stirred for 24 h at room temperature, the reaction mixture was cooled to –78 ºC, and *n*-BuLi (6.0 mL, 2.5 M in hexane, 15.0 mmol) was added dropwise. The resulting mixture was stirred for 2 h at the same temperature before TMSCl (5.7 mL, 44.9 mmol) was added dropwise. After stirred for 2 h at –30 ºC, the reaction mixture was quenched with saturated aqueous NH_4Cl and acidified with 1 N HCl. The resulting mixture was stirred for 5 h at room temperature and diluted with Et_2O. The layers were separated, and the aqueous layer was extracted with Et_2O. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, hexanes/EtOAc, 5/1) to afford hydroxy TMS-furan **4** (2.047 g, 58%) along with hydroxyl furan **6** (0.284 g, 11%).

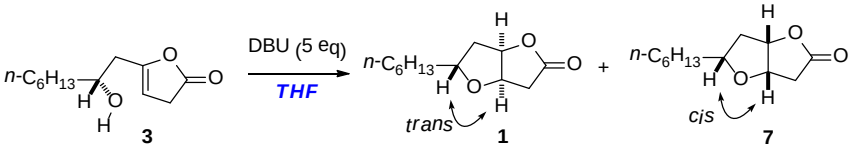
Preparation of Hydroxybutenolide 3.



To a cool (0 ºC) solution of hydroxy butenolide **4** (843.5 mg, 3.142 mmol) in CH_2Cl_2 (50 mL) were added NaOAc (1.031 g, 12.57 mmol) and *m*-CPBA (704 mg, ~77%, 3.142 mmol). The reaction mixture was stirred at the same temperature for 1 h. And an addition of *m*-CPBA (704 mg, ~77%, 3.142 mmol)

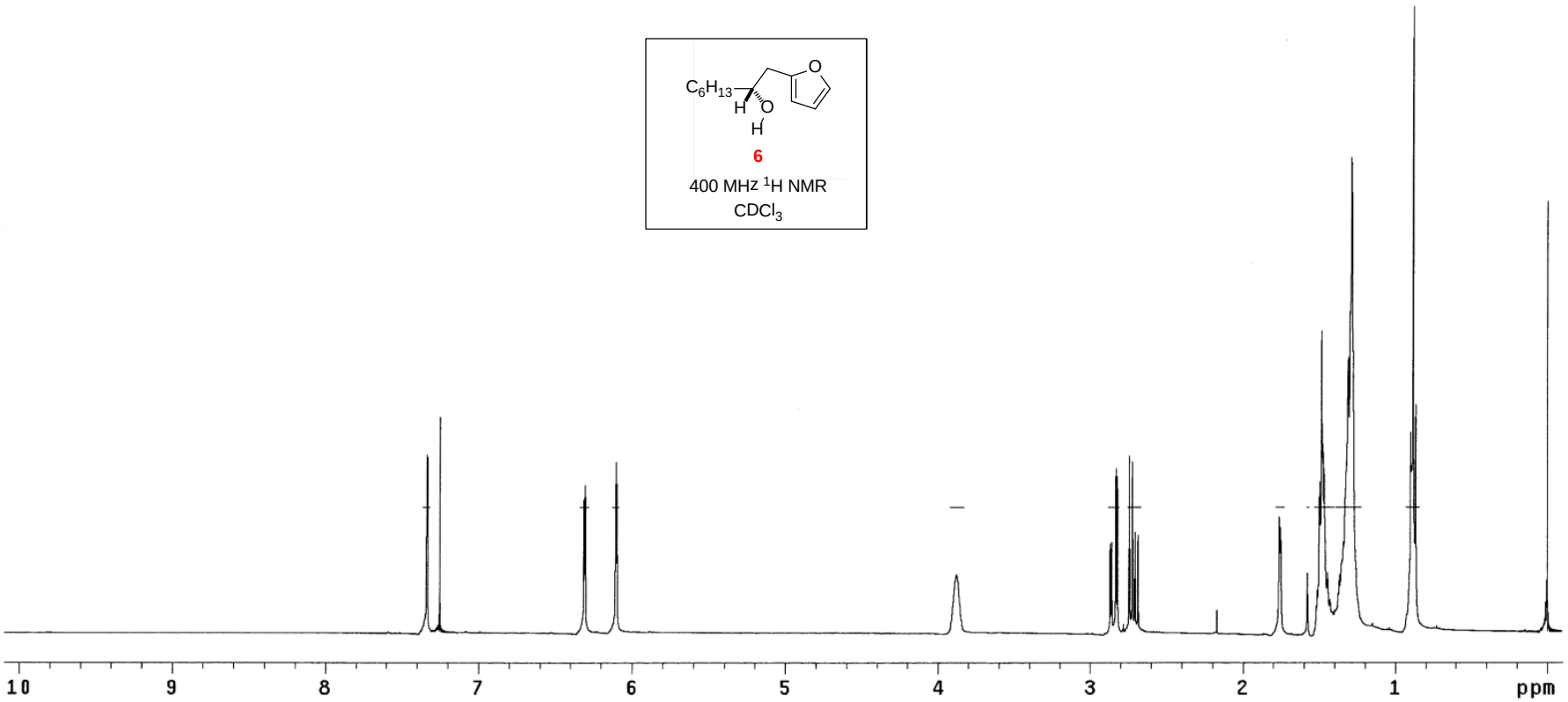
was repeated three time every 1 h. The reaction was quenched with saturated aqueous Na_2SO_3. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, *n*-hexane/ethyl acetate, 4/1 to 2/1) to afford hydroxybutenolide **3** (615.3 mg, 926%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.27 (apparently s, 1H), 3.90 (br s, 1H), 3.21 (ddd, *J* = 2.4, 2.4, 2.4 Hz, 1H), 2.51 (dd, *J* = 14.8, 7.6 Hz, 1H), 2.41 (dd, *J* = 14.8, 7.6 Hz, 1H), 1.79 (br s, 1H), 1.20–1.54 (m, 10H), 0.89 (dd, *J* = 6.8, 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 192.0, 176.6, 154.1, 101.0, 68.7, 37.3, 36.7, 34.1, 32.0, 29.4, 25.7, 22.8, 14.3; IR (neat) 3311, 1791, 1037 cm^{-1}; HRMS (ESI-TOF) m/z: $[M]^+$ Calcd for $C_{12}H_{20}O_3$ 212.1412; Found 212.1435.

Preparation of (±)-Hagen's Gland Lactone (1).



To a solution solution of hydroxybutenolide **4** (615.3 mg, 2.898 mmol) in THF (290 mL, 0.01 M) was added dropwise DBU (2.2 mL,14.5 mmol) at room temperature. The reaction mixture was stirred for 10 h at the same temperature, quenched with saturated aqueous NH_4Cl, diluted with Et_2O. The layers were separated, and the aqueous layer was extracted with Et_2O. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, *n*-hexane/ethyl acetate, 10/1 to 5/1) to afford Hagen's gland lactone (**1)** (487.3 mg, 79%) and its isomer **7** (68.1 mg, 11%) along with the mixture of **1** and **7** (36.6 mg, 6%) as colorless oils: **[For 1]** ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.12 (ddd, *J* = 7.2, 4.4, 2.4 Hz, 1H), 4.51 (ddd, *J* = 4.0, 4.0, 4.0 Hz, 1H), 3.94 (ddd, *J* = 14.0, 7.2, 7.2 Hz, 1H), 2.73 (s, 1H), 2.72 (s, 1H), 2.43 (ddd, *J* = 14.0, 6.8, 6.8

Hz, 1H), 1.88 (ddd, *J* = 14.0, 7.6, 2.0 Hz, 1H), 1.60–1.68 (m, 1H), 1.51–1.57 (m, 1H), 1.25–1.41 (m, 8H), 0.88 (dd, *J* = 7.6, 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.3, 84.6, 80.3, 78.2, 38.4, 36.4, 35.6, 31.8, 29.3, 26.1, 22.7, 14.2; IR (neat) 2938, 2865, 2844, 1765, 1051, 1033, 1024 cm^{-1}; HRMS (ESI-TOF) m/z: $[M]^+$ Calcd for $C_{12}H_{20}O_3$ 212.1412; Found 212.1436. **[For 7]** ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.12 (dd, *J* = 4.8, 4.8 Hz, 1H), 4.81 (dd, *J* = 5.2, 5.2 Hz, 1H), 4.06 (dddd, *J* = 10.8, 6.0, 6.0, 6.0 Hz, 1H), 2.77 (dd, *J* = 19.2, 6.4 Hz, 1H), 2.63 (d, *J* = 18.8 Hz, 1H), 2.37 (dd, *J* = 14.0, 4.8 Hz, 1H), 1.67 (ddd, *J* = 14.0, 10.8, 5.2 Hz, 1H), 1.77–1.65 (m, 1H), 1.46–1.55 (m, 1H), 1.25–1.41 (m, 7H), 0.88 (dd, *J* = 6.8, 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.1, 85.2, 78.5, 77.6, 39.1, 37.0, 35.0, 32.1, 29.6, 26.4, 22.9, 14.4; IR (neat) 2981, 1756, 1055, 1033, 1010 cm^{-1}; HRMS (ESI-TOF) m/z: $[M]^+$ Calcd for $C_{12}H_{20}O_3$ 212.1412; Found 212.1418.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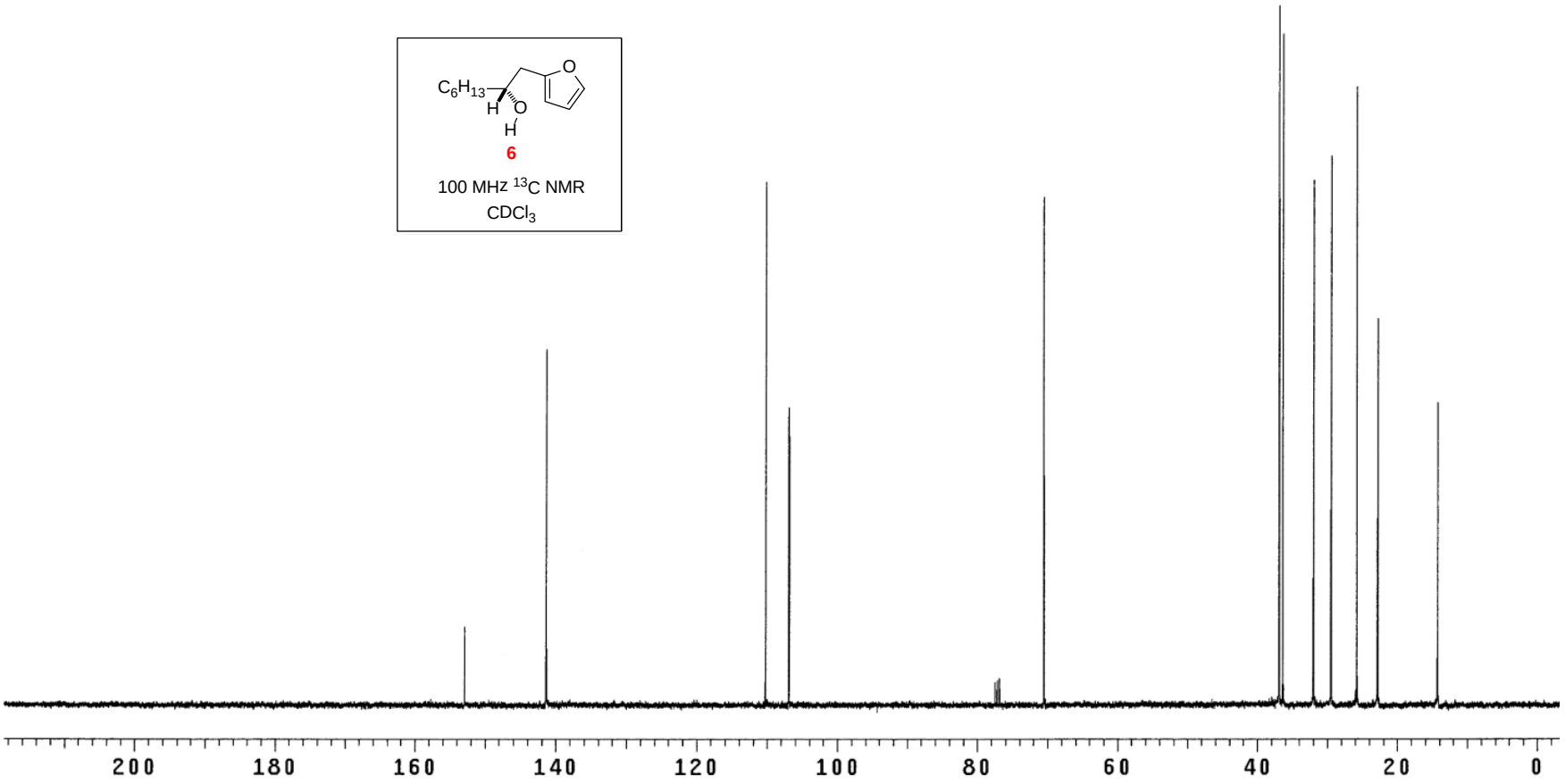
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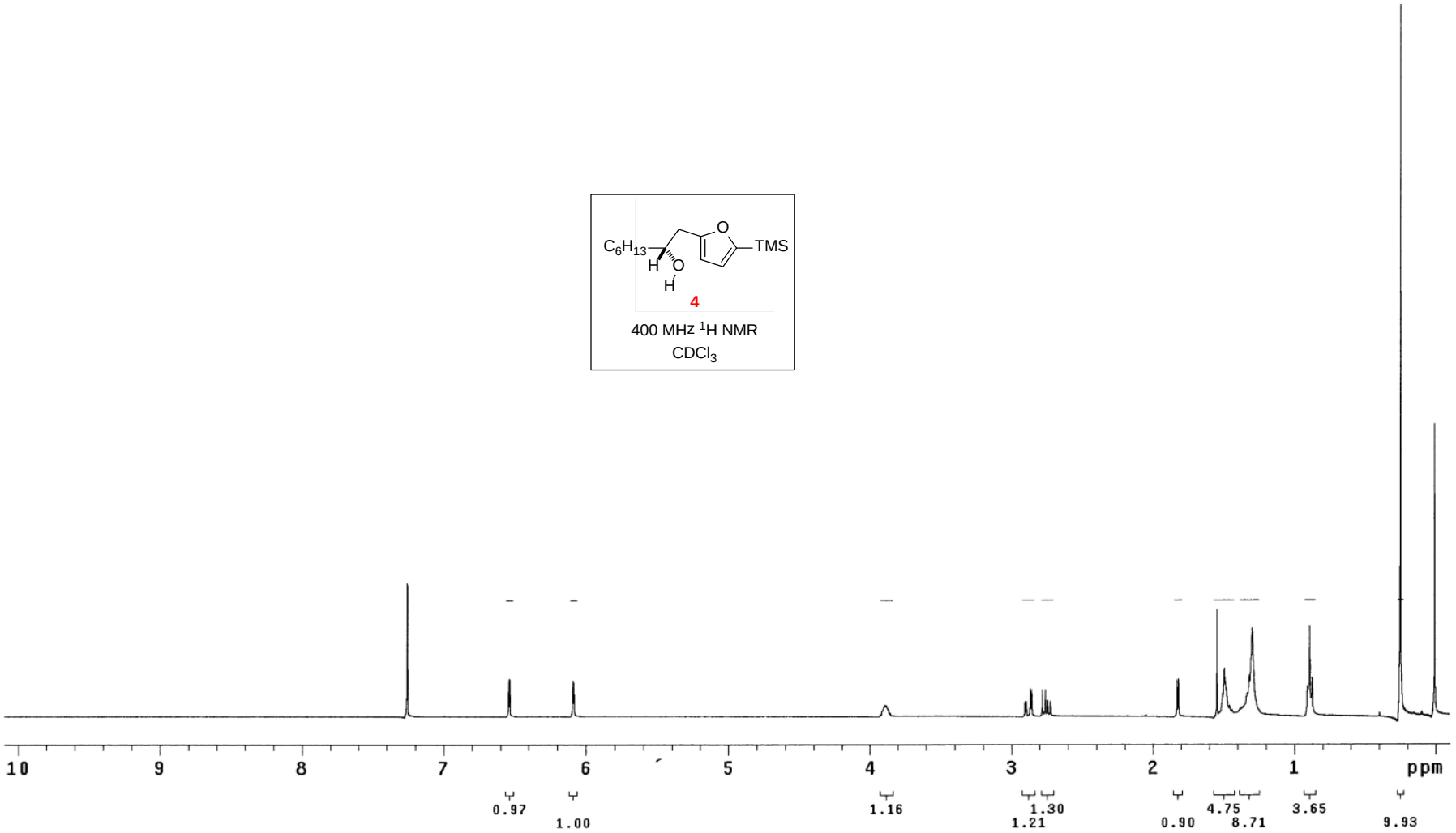
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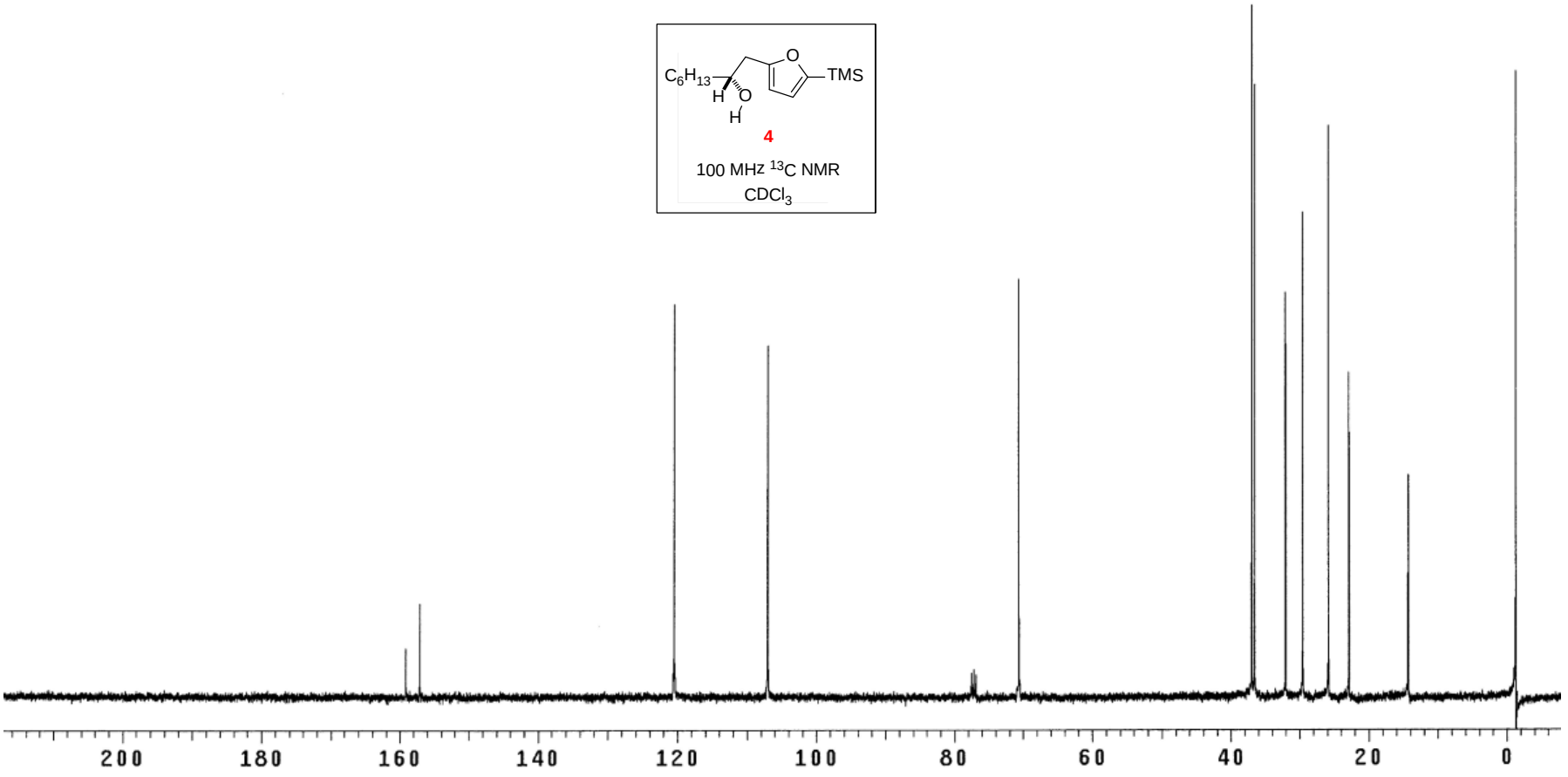
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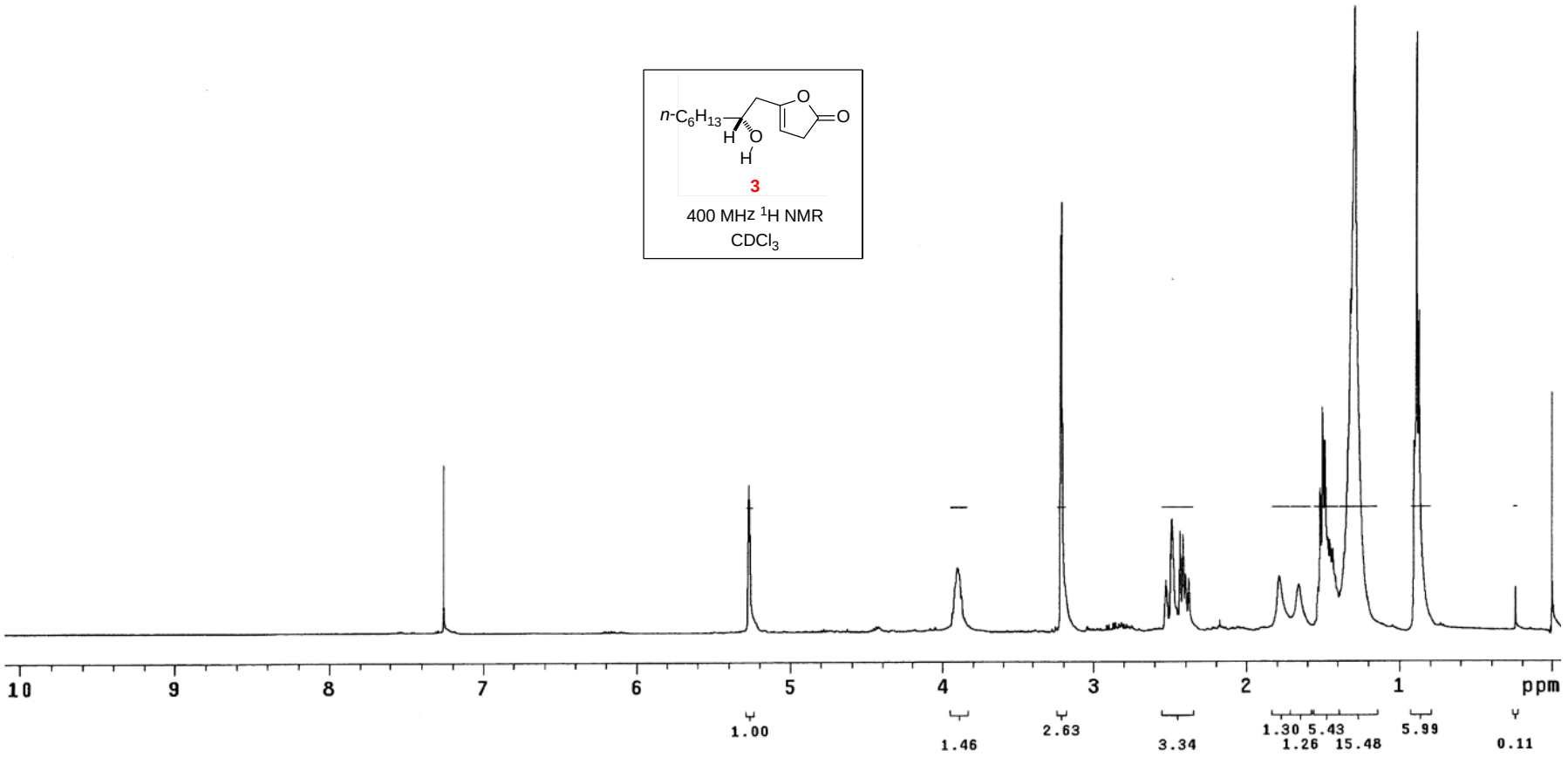
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H
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CDCl3
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8
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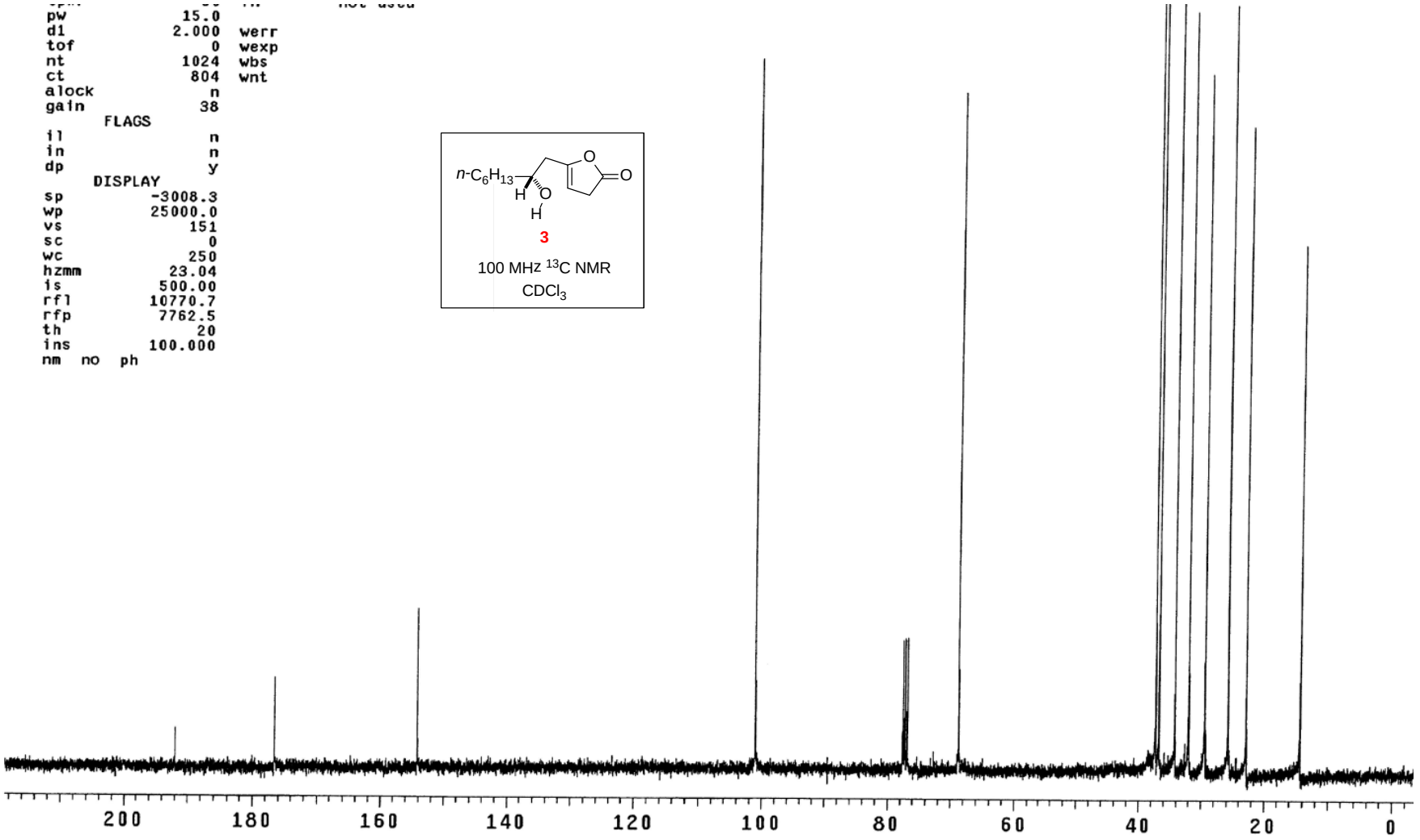
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rfp 7762.5
th 20
ins 100.000
nm no ph
werr
wexp
wbs
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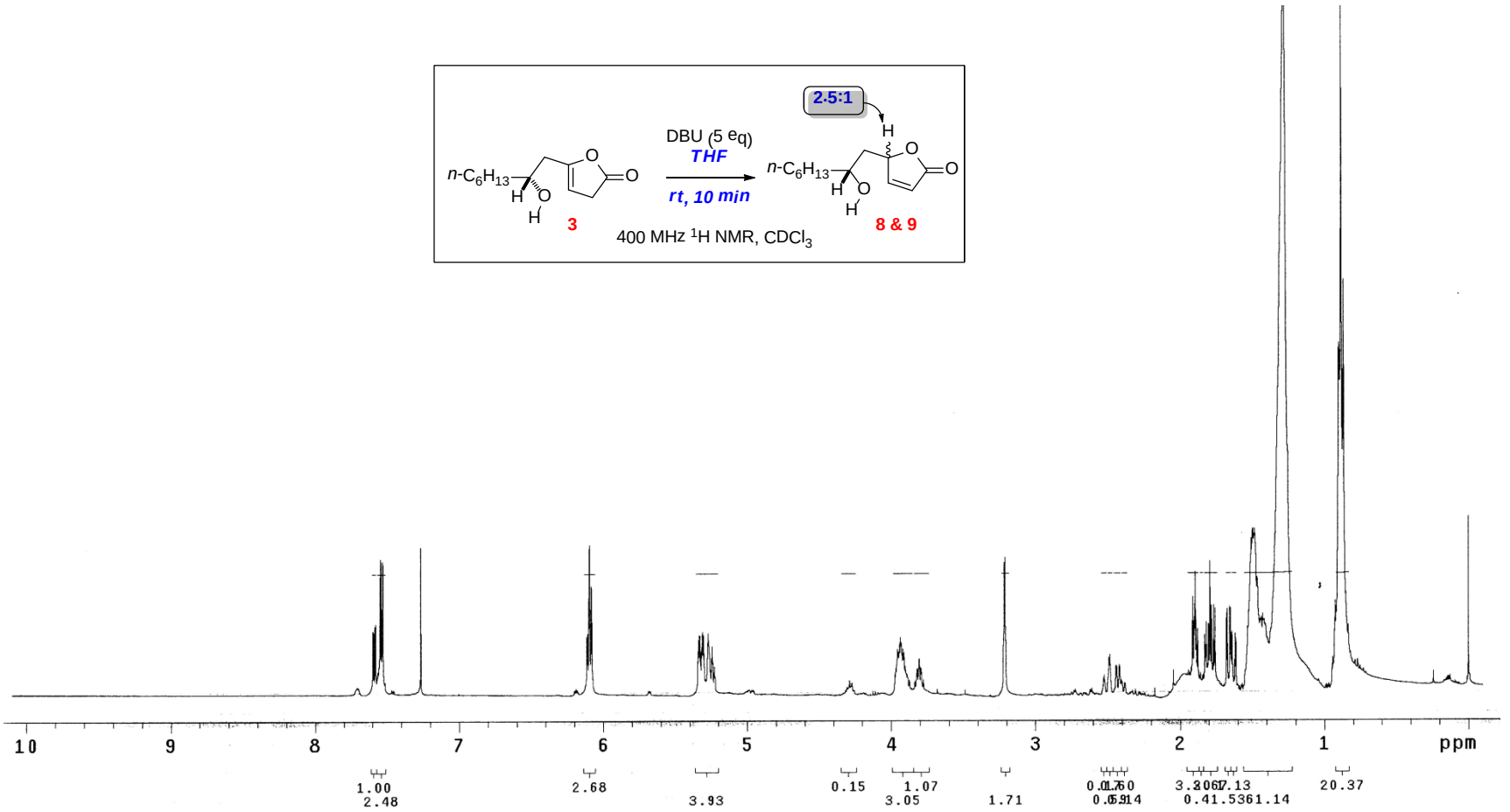
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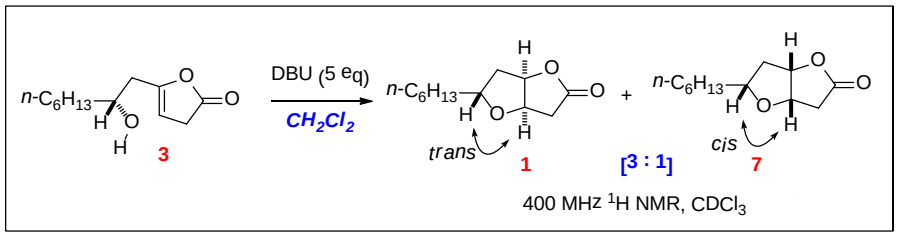
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+
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H
H
cis
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400 MHz 1H NMR, CDCl3

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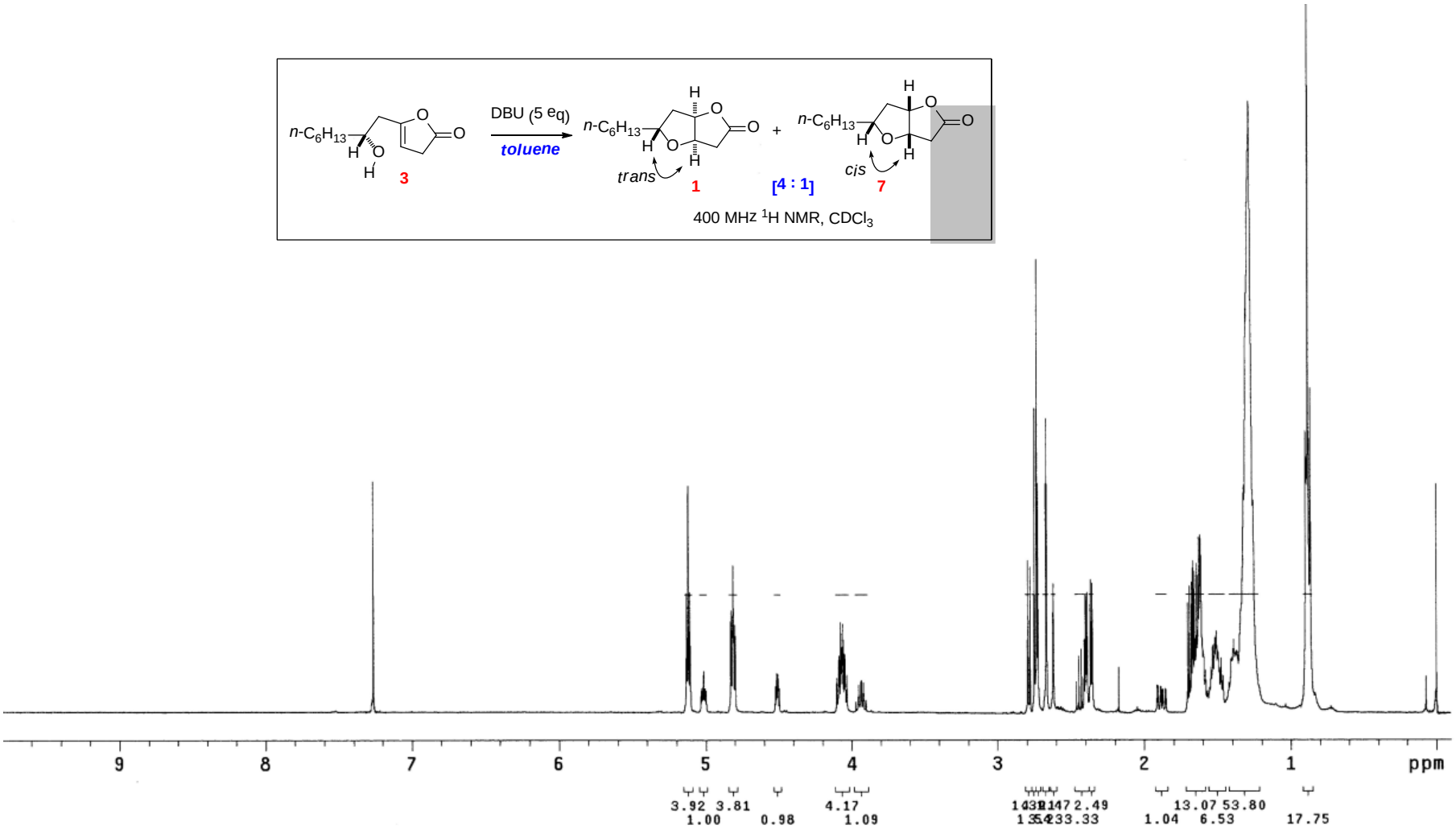
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+
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O
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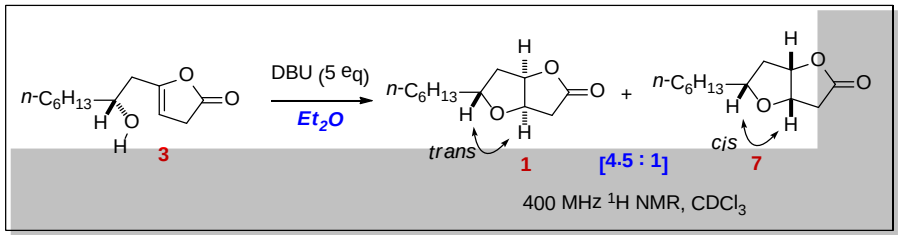
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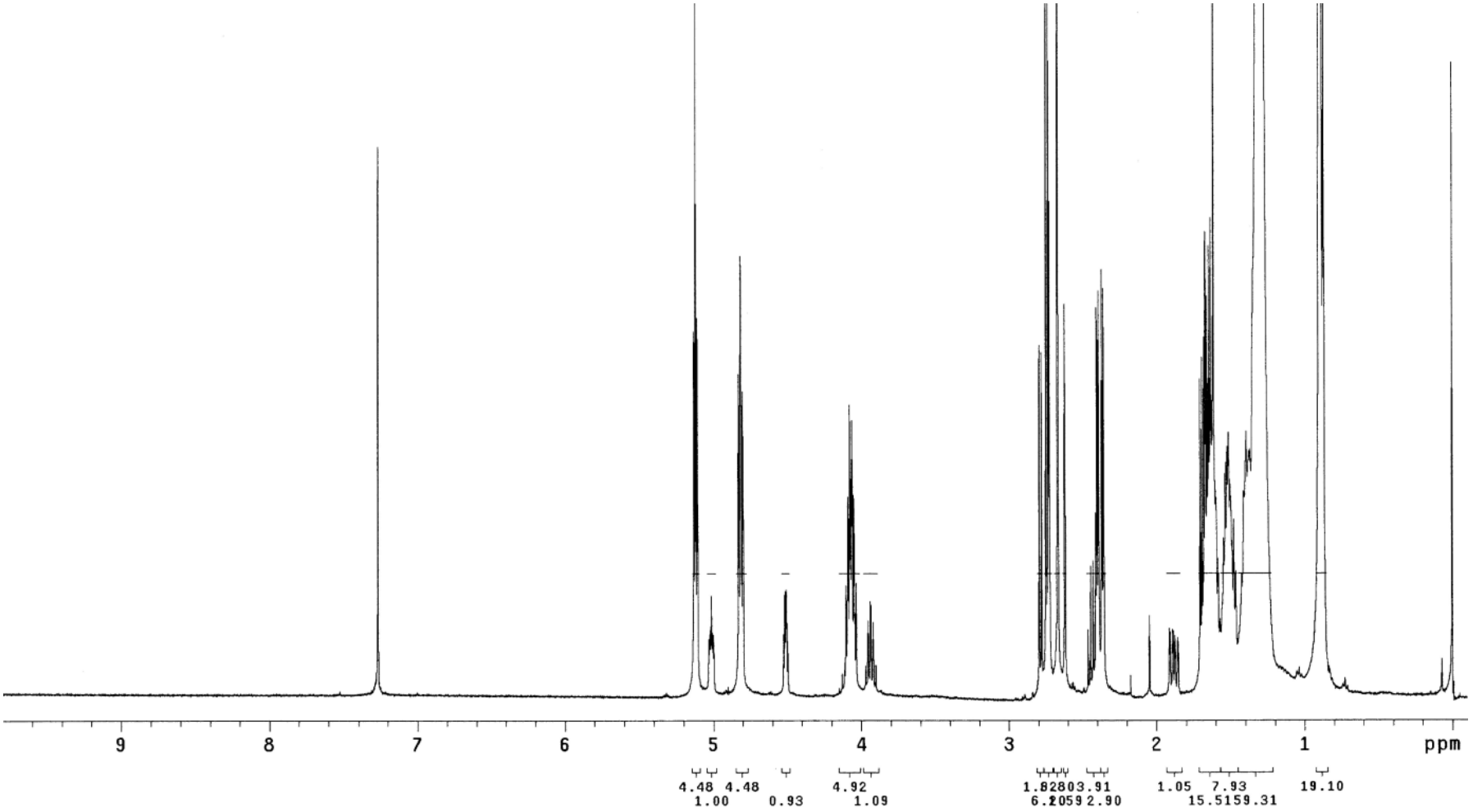
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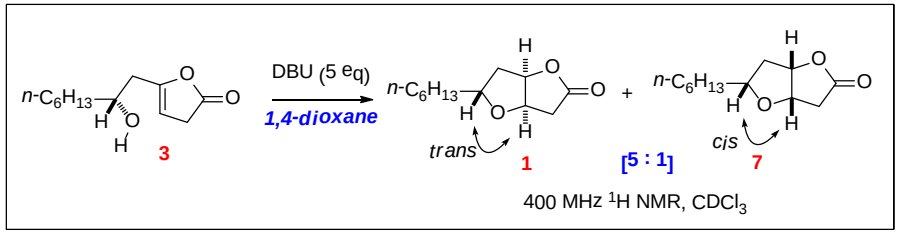
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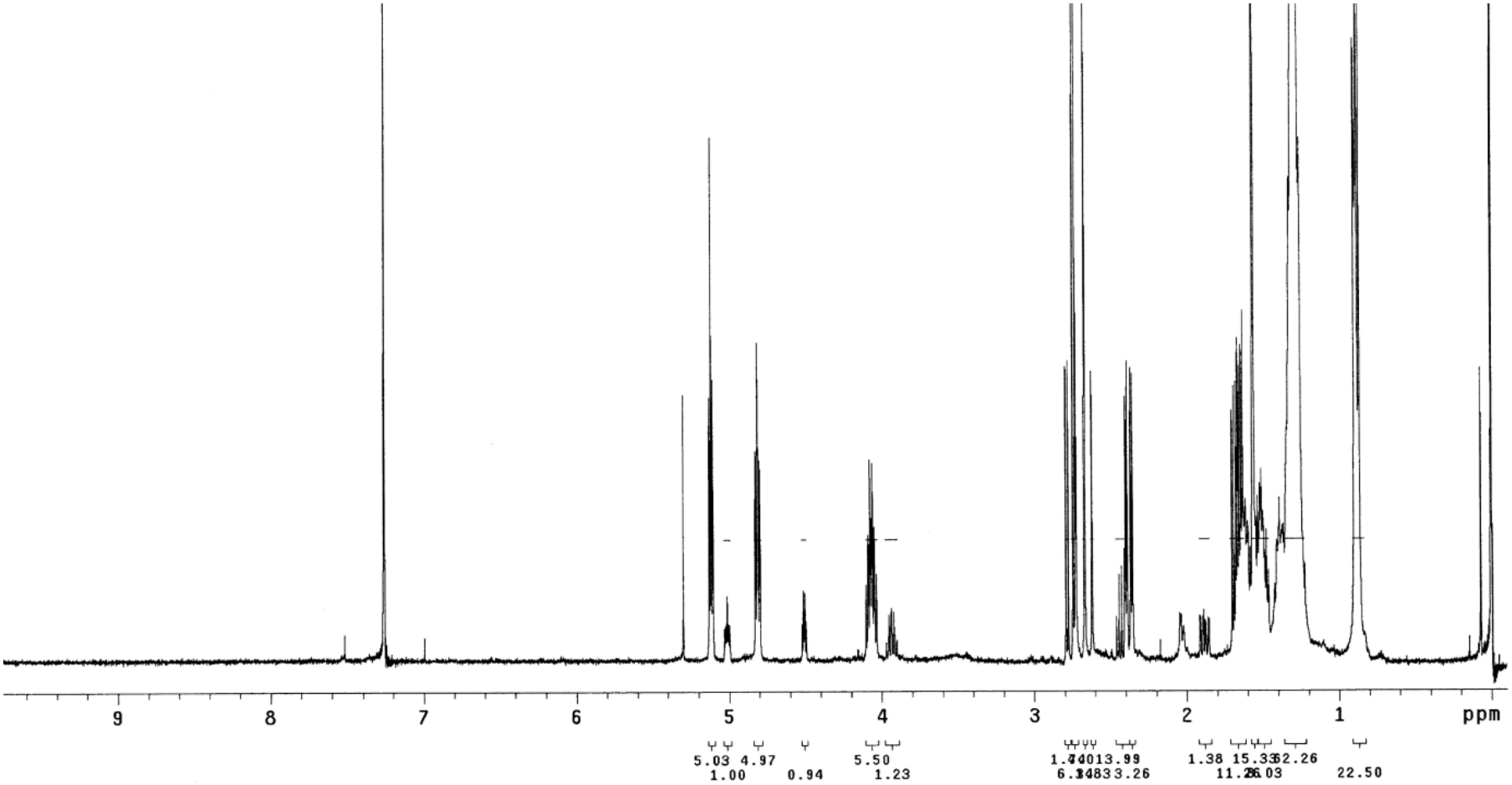
400 MHz 1H NMR, CDCl3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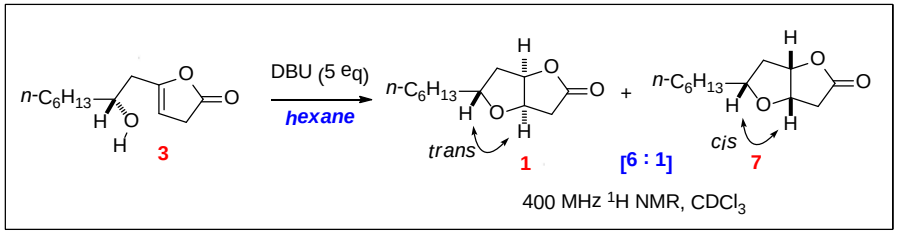
22.50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+
[6 : 1]
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O
O
H
H
cis
7
400 MHz 1H NMR, CDCl3

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8
7
6
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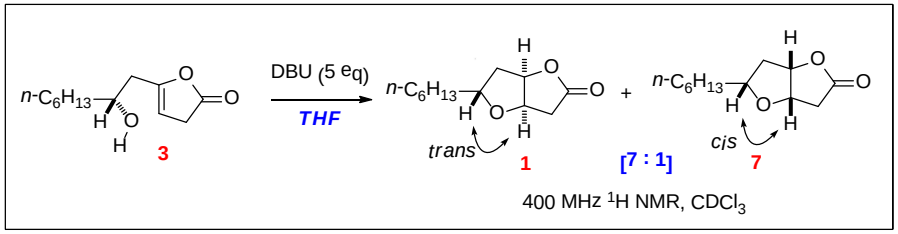
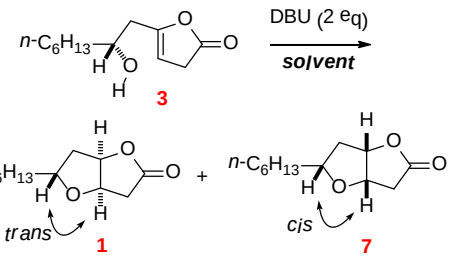
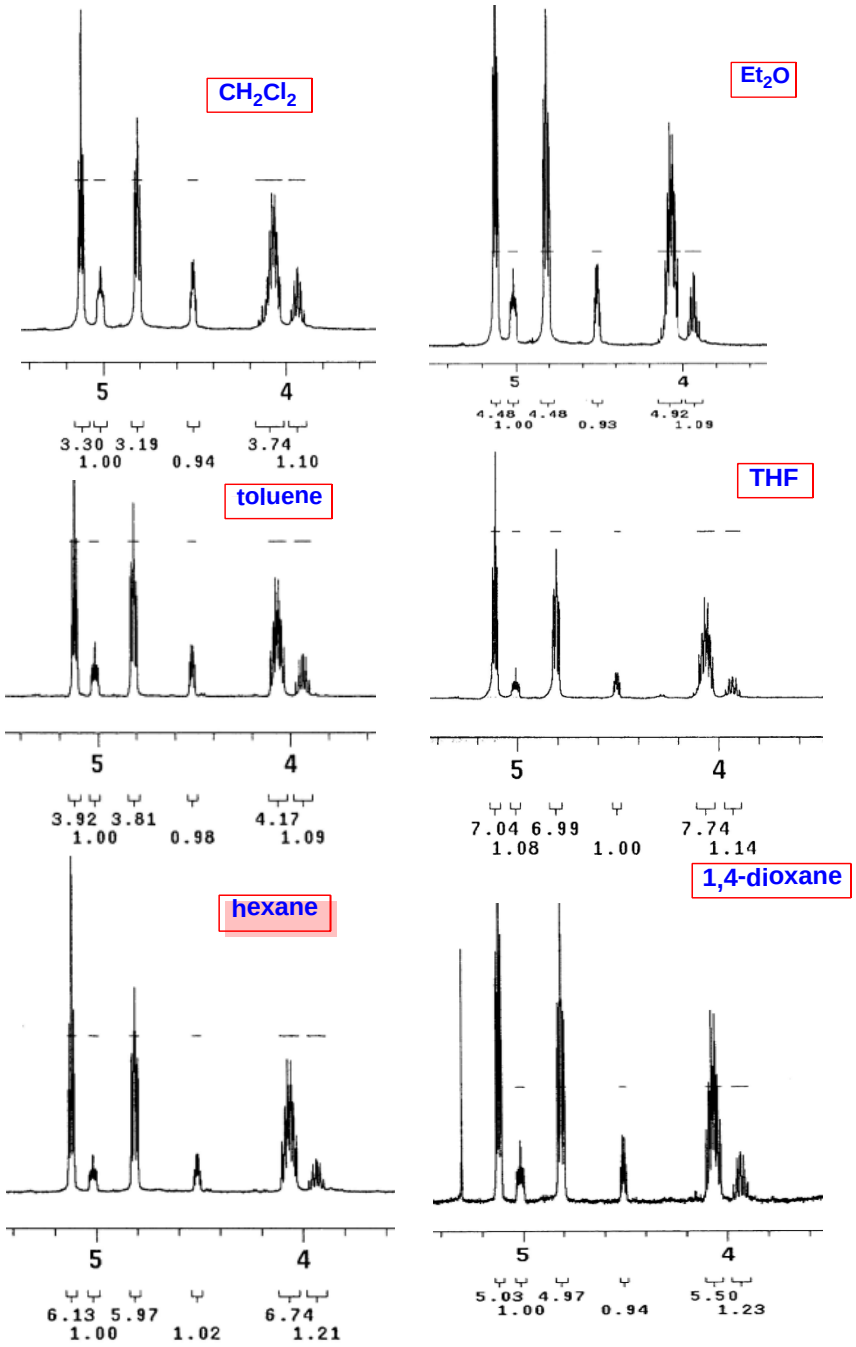


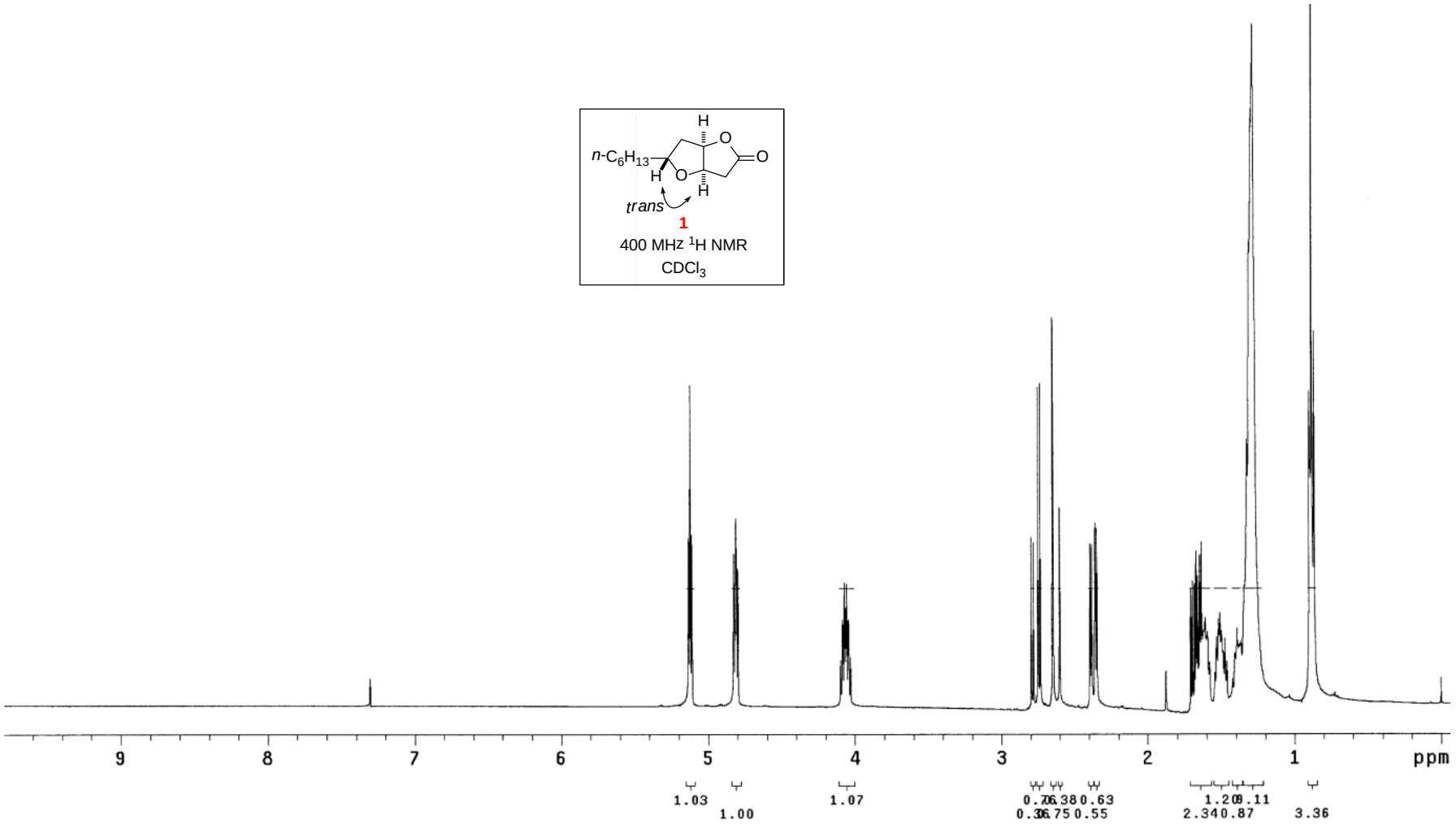
400 MHz ^{1}H NMR, $CDCl_3$

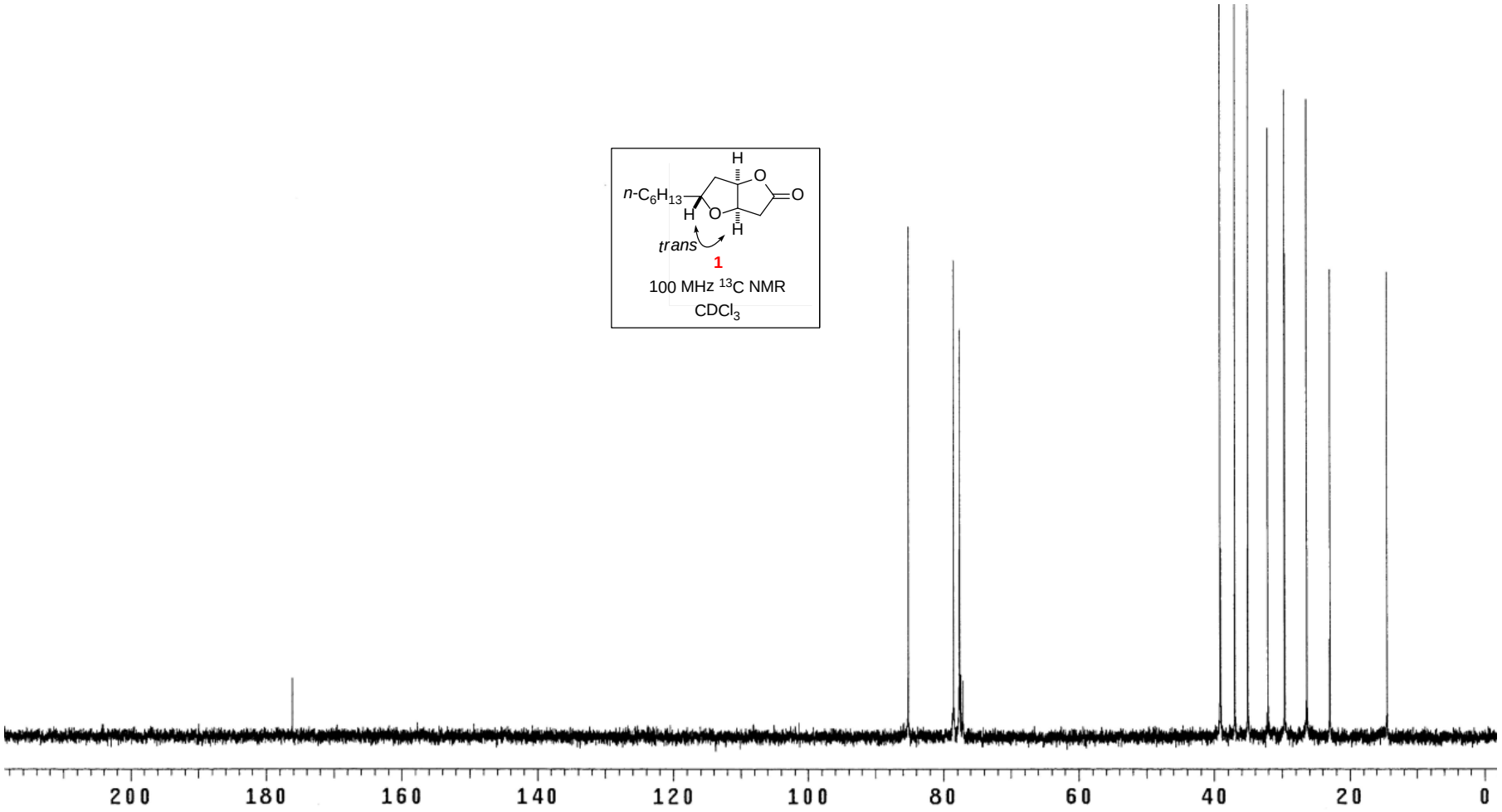


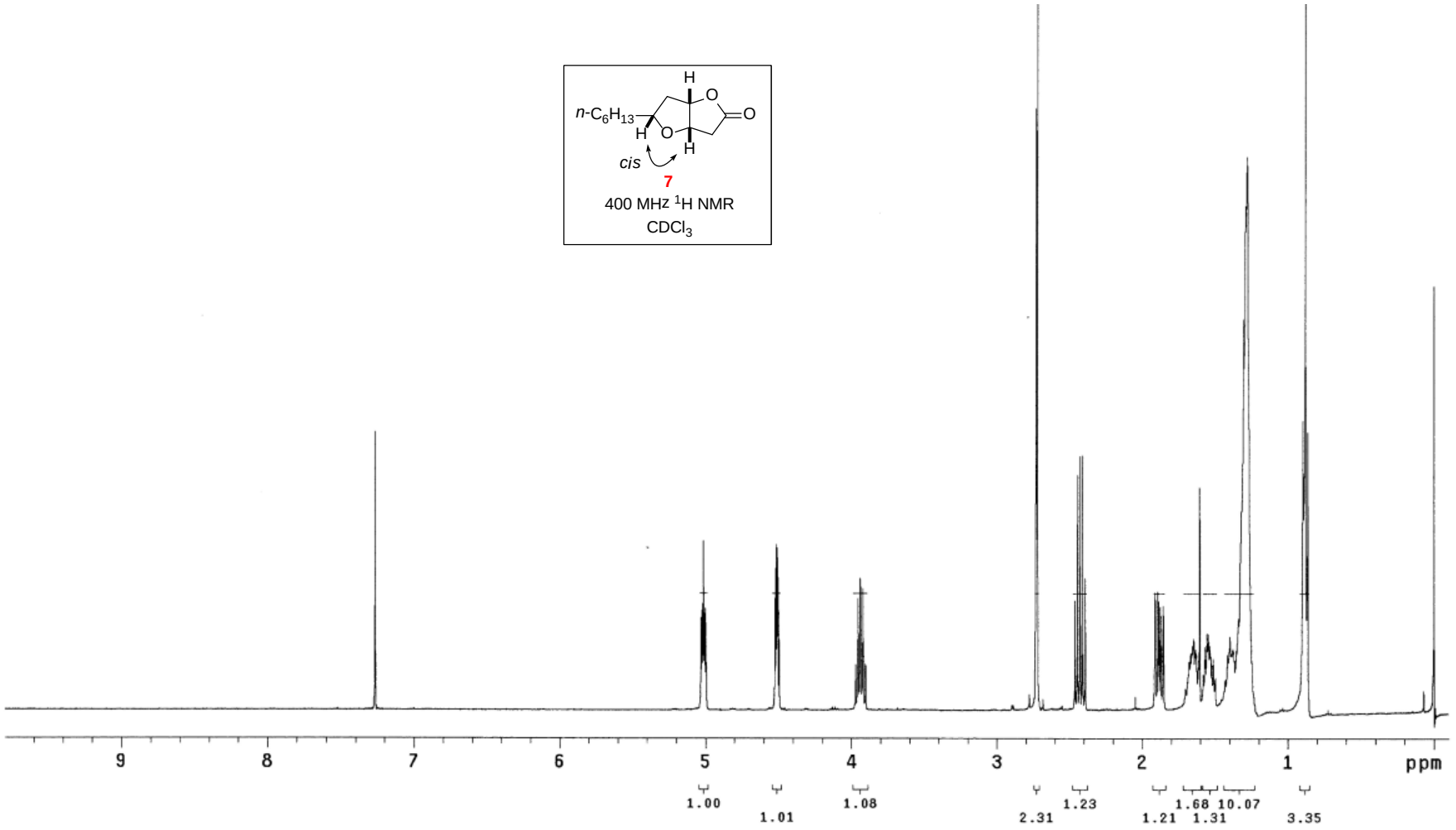
400 MHz ^{1}H NMR, $CDCl_3$

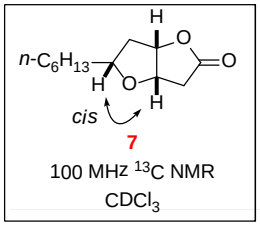
solvent	dr (1:7)	yield (%)	solvent	dr (1:7)	yield (%)
CH_2Cl_2	3:1	90	Et_2O	4.5:1	85
toluene	4:1	81	***THF***	**7:1**	**96**
hexane	6:1	79	dioxane	5:1	91




H
O
n-C6H13
O
O
H
H
trans
1
400 MHz 1H NMR
CDCl3
9
8
7
6
5
4
3
2
1
ppm
1.03
1.00
1.07
0.70
6.38
0.63
0.36
6.75
0.55
1.20
9.11
2.34
0.87
3.36


H
O
O
n-C6H13
H
O
H
trans
1
100 MHz 13C NMR
CDCl3
200
180
160
140
120
100
80
60
40
20
0

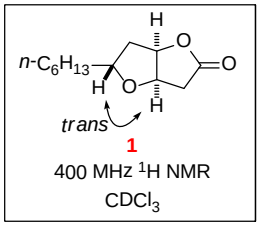

H
O
n-C6H13
O
H
O
H
cis
7
400 MHz 1H NMR
CDCl3
9
8
7
6
5
4
3
2
1
ppm
1.00
1.01
1.08
2.31
1.23
1.21
1.68
1.31
10.07
3.35



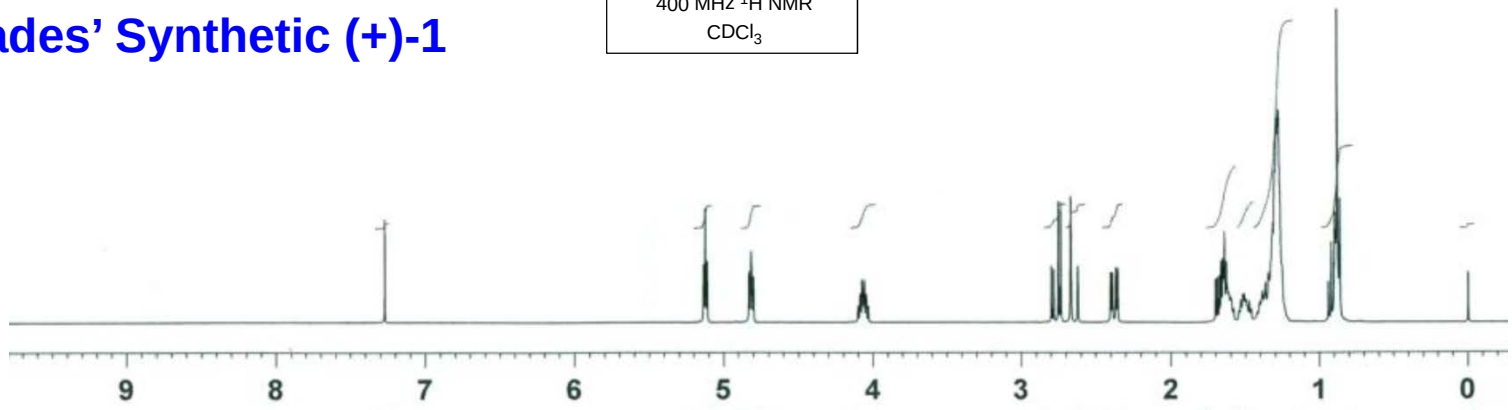
7

100 MHz ^{13}C NMR

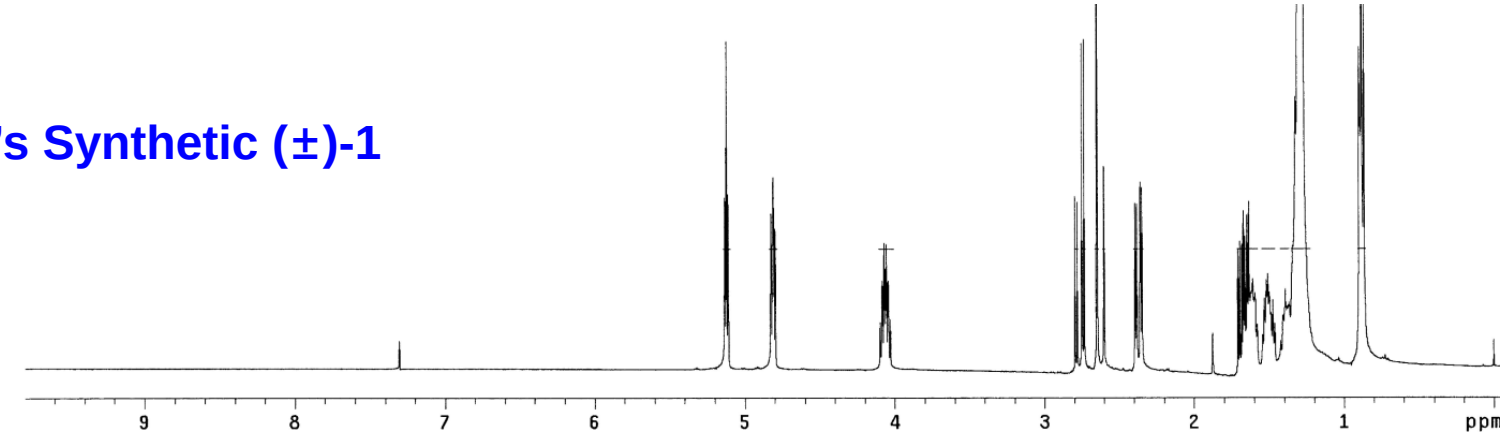
$CDCl_3$

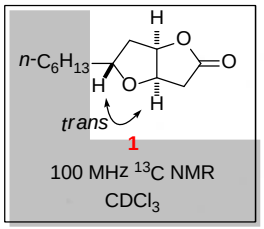


Fernades' Synthetic (+)-1



Kim's Synthetic (±)-1





Fernades' Synthetic (+)-1

Kim's Synthetic (±)-1