A Study of the Epoxidation of Cycloolefins by the *t*-BuOH Copper-Permanganate System

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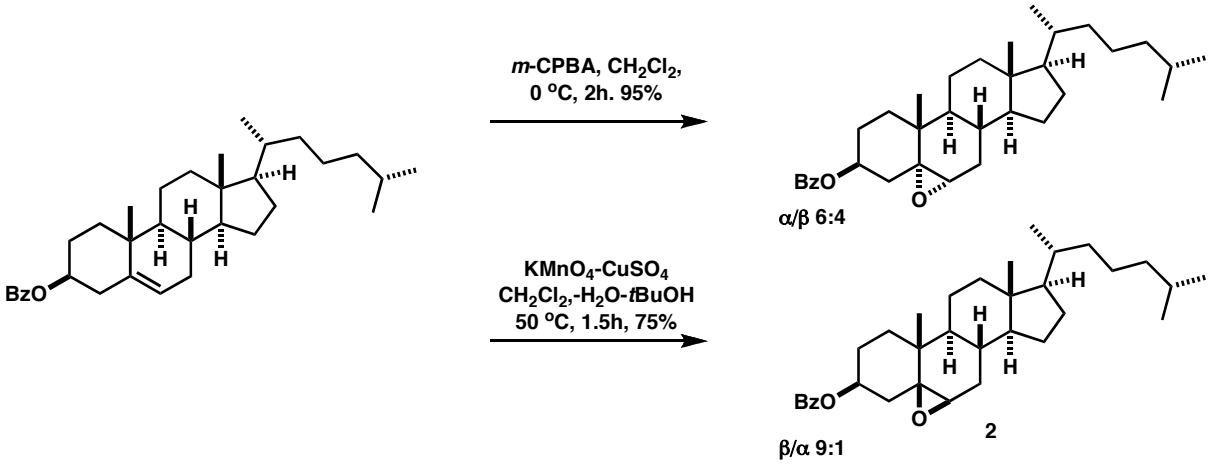
Table of content:

1. Materials and Methods. Unless stated otherwise, reactions were performed in flame dried glassware under a slight positive pressure of nitrogen using freshly distilled, dry solvent. Commercial grade reagents and solvents were used without further purification except as indicated below. Methanol (MeOH) was distilled over $CaSO_4$. Dichloromethane (CH_2Cl_2), benzene, and triethylamine (Et_3N) were distilled over calcium hydride (CaH_2). Ether (Et_2O) and tetrahydrofuran (THF) were purified by Seco Solvent Systems. Thin layer chromatography (TLC) was performed using E. Merck silica gel 60 F_{254} precoated plates (0.25 mm). Flash chromatography was performed using Baker silica gel (40 μm particle size). ^{1}H NMR spectra were recorded on Varian Mercury 400 (400 MHz) or Unity/INOVA 500 (500 MHz) spectrometers and chemical shifts are reported in ppm downfield from tetramethylsilane with the solvent resonance as internal standard (δ 7.26 ppm for CDCl3). ^{13}C NMR spectra were recorded on Varian Mercury 400 (100 MHz) or Unity/INOVA 500 (125 MHz) spectrometers with proton decoupling. Chemical shifts are reported in ppm downfield from tetramethylsilane with the solvent as internal (δ 77.16 ppm for CDCl3). IR spectra were recorded on Avatar 360 FT-IR spectrometer. Low-resolution and high-resolution mass spectral analyses were performed at the Harvard University Mass Spectrometry Center. Optical rotations were measured with a Perkin-Elmer 241 polarimeter at the indicated temperature with a sodium lamp (D line, 589 nm). Melting points (m.p.) are uncorrected and were recorded on a Thomas-Hoover Unimelt capillary melting point apparatus.

2. Experimental procedures

2.1 Studies on Δ^5 model.

Epoxidation of cholesteryl benzoate:



Epoxidation with *m*-CPBA:

To a stirred solution of cholesteryl benzoate (100 mg, 0.20 mmol) in CH_2Cl_2 (2 mL) was added *m*-CPBA (52.7 mg, 0.31 mmol) at 0 °C the reaction was completed after 2 h stirring at 0 °C. The reaction was quenched by addition of saturated solution of K_2CO_3 (aq.) (2 mL) and the aqueous phase was extracted with CH_2Cl_2 (3 x 10 mL). The organic phase was dried over Na_2SO_4 and concentrated to dryness to afford a 6:4 mixture of cholestan-5α,6α-epoxy-3β-ol benzoate and cholestan-5β,6β-epoxy-3β-ol benzoate (98 mg, 95%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.02 (d, 2H, *J* = 7.5 Hz), 7.53 (dd, 1H, *J* = 7.1 Hz, *J* = 6.9 Hz), 7.42 (m, 2H), 5.21 (1H, m, 3C*H*, α-epoxide), 5.05 (1H, m, 3C*H*, β-epoxide), 3.12 (1H, br, 6C*H*, β-epoxide)*, 2.93 (1H, d, *J* = 4.4 Hz, 6C*H*, α-epoxide)*, 2.25 (m, 1H), 2.08 (m, 1H), 1.95-1.11 (m, 16H), 1.05 (s, 3H, CH_3), 0.98 (m, 2H), 0.87 (m, 6H, 2-CH_3), 0.62 (s, 3H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.2, 165.9, 133.1, 133.0, 131.0, 130.7, 129.79, 129.76, 128.54, 128.48, 72.2, 72.1, 65.4, 63.8, 62.8, 59.4, 57.0, 56.4, 56.1, 51.2, 42.7, 42.6, 42.5, 40.0, 39.7, 38.3, 36.9, 36.5, 36.4, 36.01, 35.97, 35.33, 35.29, 32.7, 32.4, 30.13, 29.99, 29.0, 28.4, 28.3, 28.3, 27.6, 24.4, 24.3, 24.1, 24.0, 23.1, 22.8, 22.2, 20.9, 18.92, 18.88, 17.3, 16.2, 12.1, 12.0; IR (cm^{-1}): 2932, 2867, 1712, 1466, 1450, 1275, 1117, 1026, 709.

Epoxidation with $KMnO_4$-$CuSO_4$:

A mixture of $KMnO_4$ (600 mg) and $CuSO_4{\cdot}5H_2O$ (300 mg) was ground to a fine powder and transferred to a reaction flask. Water (0.03 mL) was added, and mixed very well. To a stirred suspension of this mixture in CH_2Cl_2 (2 mL) was added cholesteryl benzoate (100 mg, 0.20 mmol) and *t*-BuOH (0.15 mL). The mixture was then refluxed for 1.25 h. After cooling the

mixture was filtered through a pad of Celite® and washed with CH_2Cl_2 (3x10 mL) to give, after concentration, cholestan-5β,6β-epoxy-3β-ol benzoate **2** (77 mg, 75%) as a white solid. $[\alpha]_D$ = +10 ($CHCl_3$, *c* = 0.5); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.02 (d, 2H, *J* = 7.3 Hz), 7.53 (m, 1H), 7.42 (m, 2H), 5.05 (1H, m, 3C*H*), 3.11 (1H, br, 6C*H*, β-epoxide, $\omega^{1/2}$ = 2.1 Hz) *, 2.27 (dd, 1H, *J* = 12.7 Hz, *J* = 12.2 Hz), 2.09 (d, 1H, *J* = 14.6 Hz), 1.98 (m, 2H), 1.82 (m, 1H), 1.64-1.04 (m, 14H), 1.03 (s, 3H, CH_3), 0.84 (m, 6H, $2CH_3$), 0.64 (s, 3H, CH_3). ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.2, 133.1, 130.7, 129.8, 128.54, 128.48, 72.1, 63.8, 62.8, 56.4, 51.2, 42.5, 40.0, 39.7, 38.3, 36.9, 36.4, 36.0, 35.3, 32.7, 30.0, 28.4, 28.2, 27.6, 24.4, 24.1, 23.1, 22.8, 22.2, 18.9, 17.3, 12.0; m.p. 168-170 °C, (lit. m.p. 172-174 °C)[1]; MS (ES +) *m/z* (%): 507.4 ($M + H^+$, 100).

* The equatorial hydrogen (6C*H*) in the β-epoxide isomer is easly distinguishable than the axial hydrogen (6C*H*) in the α-epoxide; 6C*H* in β-epoxide is downfield (3.11 ppm) and broad ($\omega^{1/2}$ = 2.1 Hz), whilst 6C*H* in α-epoxide is upfield (2.93 ppm) and a clear doublet (*J* = 4.3 Hz).[2]

Preparation of $Cu(MnO_4)_2$

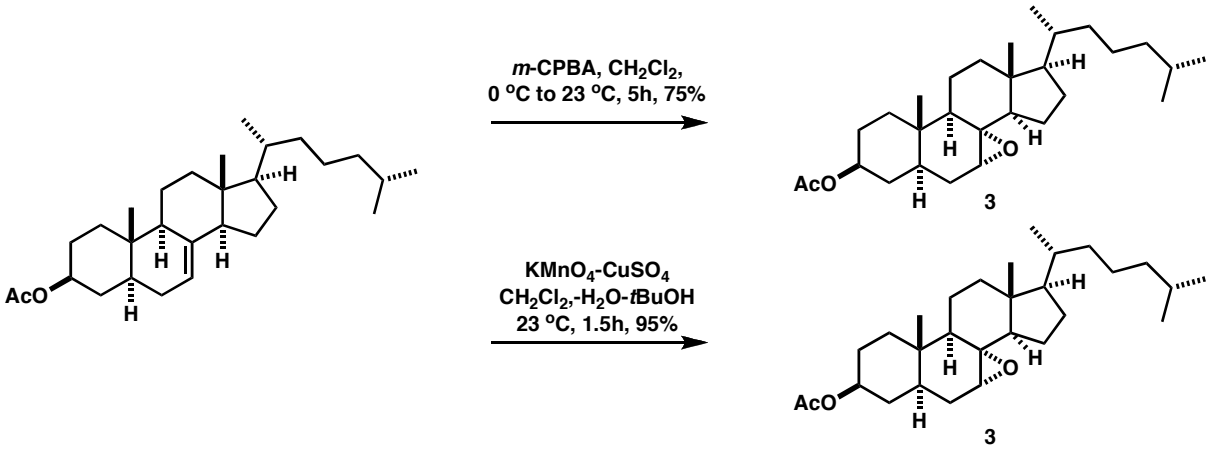
To a stirred solution of $KMnO_4$ (13.3 g, 84.3 mmol) in H_2O (200 mL) was added $Cu(BF_4)_2$ (10.0 g, 42.1 mmol) in H_2O (10 mL) at 0 °C. The resulting mixture was stirred at 0 °C for 10 minutes and then filtered to remove the precipitate of KBF_4. Evaporation of H_2O gave $Cu(MnO_4)_2$ (10g, 79%) as a grey-brown powder. $Cu(MnO_4)_2$ was also synthesized using a literature method,[6] but we found this to be much less convenient.

Epoxidation with $Cu(MnO_4)_2$:

Cholesteryl benzoate (50 mg, 0.102 mmol) was dissolved in CH_2Cl_2 (0.5 mL) and *t*-BuOH (1.5 mL). To this stirred solution, $Cu(MnO_4)_2$ (46 mg, 0.153 mmol) was added at room temperature. Stirring was continued at room temperature for 1 h. The resulting solution was passed through a short pad of silica gel which was eluted wih CH_2Cl_2 and ether. Evaporation in vacuo gave cholestan-5β,6β-epoxy-3β-ol benzoate **2** and cholestan-5α,6α-epoxy-3β-ol benzoate in a 6:1 ratio as a white solid (55 mg, quant) with physical data identical as above.

2.2 Studies on Δ^7 model.

Epoxidation of Δ^7 acetate:



Epoxidation with *m*-CPBA:

To a stirred solution of Δ^7 acetate (100 mg, 0.23 mmol) in CH_2Cl_2 (2 mL) was added *m*-CPBA (60 mg, 0.35 mmol) at 0 °C. After 2 h of stirring at 0 °C, the mixture was treated with saturated aq. solution of K_2CO_3 (2 mL) and the aqueous phase was extracted with CH_2Cl_2 (3x10 mL). The organic phase was dried over Na_2SO_4 and concentrated to dryness to afford cholestan-7α,8α-epoxy-3β-ol acetate **3** as a white solid (98 mg, 95%).

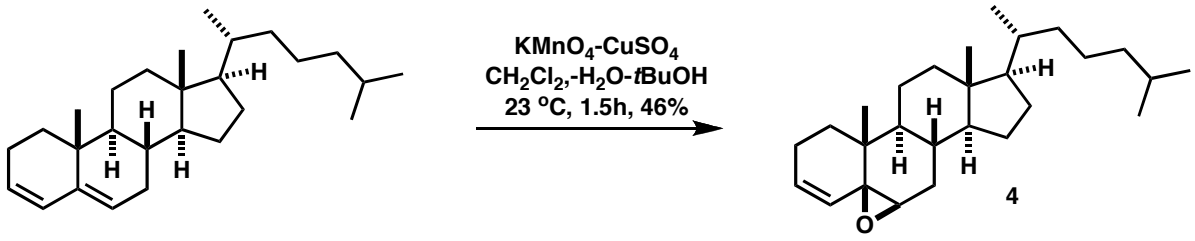
Epoxidation with $KMnO_4$-$CuSO_4$:

A mixture of $KMnO_4$ (420 mg) and $CuSO_4 \cdot 5H_2O$ (210 mg) was ground to a fine powder and transferred to a reaction flask. H_2O (0.025 mL) was added, and mixed very well. To a stirred suspension of this mixture in CH_2Cl_2 (1.5 mL) at 23 °C was added Δ^7 acetate (100 mg, 0.23 mmol) and *t*-BuOH (0.10 mL). The mixture was refluxed for 1.25 h, cooled and treated with saturated $Na_2S_2O_4$ (aq), filtered through a pad of Celite® and washed with CH_2Cl_2 (3x10 mL). The organic phase was separated and the aqueous phase was extracted with CH_2Cl_2 (3x10 mL). The combined organic phase was dried over Na_2SO_4 and evaporated to give cholestan-7α,8α-epoxy-3β-ol acetate **3** (99 mg, 95%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.61 (br, 1H, 3C*H*), 3.26 (1H, br, 7C*H*, α-epoxide)*, 1.98 (s, 3H, CH_3), 1.73-1.19 (m, 26H), 1.09 (s, 3H, CH_3), 0.84 (m, 9H, $3CH_3$), 0.68 (s, 3H, CH_3). ^{13}C NMR (125 MHz, $CDCl_3$) δ170.7, 73.4, 62.5, 59.2, 56.2, 54.6, 46.2, 42.8, 39.7, 38.6, 37.5, 36.3, 36.2, 34.4, 33.9, 33.4, 30.0, 28.2, 27.6, 27.5, 24.1, 23.0, 22.8, 22.4, 21.6, 19.1, 15.1, 12.7; IR (cm^{-1}): 2948, 2867, 1731, 1467, 1364, 1240, 1029, 736; m.p. 207-210 °C (lit. m.p. 95-97 °C).[3]; MS (ES +) *m/z* (%): 445.4 ($M + H^+$, 10), 427.3 ($M - H_2O + H^+$, 100).

* The axial hydrogen (7C*H*) in the α-epoxide isomer is easly distinguishable than the equatorial hydrogen (7C*H*) in the β-epoxide; 7C*H* in α-epoxide is down field (3.26 ppm) and broad ($\omega^{1/2}$ = 2.1 Hz), whilst 7C*H* in β-epoxide is upfield (2.80 ppm) and doublet (*J* = 5.3 Hz).[3]

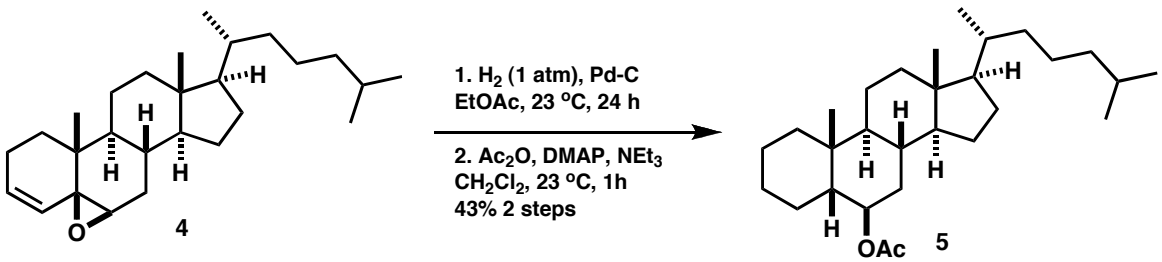
2.5 Studies on $\Delta^{3,5}$ model.

Epoxidation of 3,5-Cholestadiene ($\Delta^{3,5}$ model):



A mixture of $KMnO_4$ (1.4 g) and $CuSO_4 \cdot 5H_2O$ (0.7 g) was ground to a fine powder and transferred to a reaction flask. H_2O (0.04 mL) was added, and mixed very well. To a stirred suspension of this mixture in CH_2Cl_2 (10 mL) was added 3,5-cholestadiene[8] (369 mg, 1 mmol) at r.t., followed by the addition of *tert*-butanol (0.4 mL). The solution was stirred at r.t. for 3h by which time TLC indicated that the epoxidation was completed. The reaction was quenched with isopropyl alcohol, filtered through a pad of Celite® and washed with EtOAc (7x10 mL). Evaporation gave a crude mixture of **4** (174 mg, 46%), which used in the next step. Analysis of the crude: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.02 (m, 1H), 4.95 (m, 1H), 3.12 (br, 1H, 6C*H,* β-epoxide), 2.20-1.78 (m, 6H), 1.60-0.98 (m, 18H), 0.97 (s, 3H, CH_3), 0.88 (m, 6H, $2CH_3$), 0.66 (s, 3H, CH_3). ^{13}C NMR (125 MHz, $CDCl_3$) δ 132.9, 130.8, 62.1, 56.51, 56.47, 50.2, 42.6, 40.0, 39.7, 36.5, 36.4, 36.01, 35.97, 34.1, 32.5, 29.9, 28.4, 28.2, 24.5, 24.0, 23.0, 22.8, 22.3, 21.6, 18.9, 16.5, 12.0; IR (cm^{-1}): 2933, 2867, 1707, 1466, 1351, 1025, 737, 703.

Hydrogenation and Acetylation of Cholest-5β,6β-epoxy-3-ene:



To a stirred solution of cholest-5β,6β-epoxy-3-ene **4** (170 mg, 0.44 mmol) in EtOAc (5 mL) was added Pd/C (28 mg, 10 wt. %). The reaction mixture was placed under an atmosphere of H_2 (1 atm) and the mixture was stirred for 24 h. After filtration through a pad of Celite®,

washing with EtOAc (3x5 mL) and concentration, the residue was purified by flash chromatography (hexanes/EtOAc; 10:0 → 8:2) to afford coprostan-6β-ol (76 mg, 45%) as a thick syrup. To a stirred solution of coprostan-6β-ol (75 mg, 0.19 mmol) in CH_2Cl_2 (4 mL) was added DMAP (3 mg, 0.02 mmol) and Et_3N (0.01 mL, 0.57 mmol) at r.t. To this mixture acetic anhydride (0.05 mL, 0.29 mmol) was added. The reaction mixture was stirred for 1h and then treated with saturated NH_4Cl (5 mL). The aqueous phase was extracted with CH_2Cl_2 (3x5 mL) and the organic phase was dried with Na_2SO_4. Evaporation gave a crude mixture (88 mg), which purified by flash chromatography (100:0 to 90:10 hexanes/EtOAc) to afford coprostan-6β-ol acetate **5** (80 mg, 96%) as a white solid. $[\alpha]_D$ = +16 ($CHCl_3$, *c* = 0.55), lit. $[\alpha]_D$ = +22 (*c* = 0.55).[4]; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.70 (d, 1H, 6C*H*, *J* = 1.8 Hz), 2.03 (s, 3H, CH_3), 1.99 (m, 1H), 1.82 (m, 1H), 1.70 (m, 3H), 1.56 (m, 4H), 1.42-1.03 (m, 10H), 0.99 (s, 3H, CH_3), 0.88 (m, 6H, $2CH_3$), 0.68 (s, 3H, CH_3). ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.8, 76.0, 56.6, 65.5, 46.8, 43.0, 40.7, 40.4, 39.8, 37.8, 36.4, 36.0, 35.2, 32.0, 31.7, 28.5, 28.2, 26.8, 26.7, 26.1, 24.5, 24.1, 23.0, 22.8, 22.0, 21.0, 20.8, 18.9, 12.4; IR (cm^{-1}): 2929, 2849, 1739, 1462, 1369, 1244, 1016, 737; m.p. 104-106 °C (lit. m.p. 109-111 °C).[4] MS (ES +) *m/z* (%): 372.4 ($[M - OAc]^+$, 30), 371.4 ($M - OAc - H]^+$, 100).

Epoxidation of Stigmasteryl Acetate with $Cu(MnO_4)_2$.

Stigmasteryl acetate (50 mg, 0.11 mmol) was dissolved in 0.5 mL of CH_2Cl_2, and treated with 1.5 mL of *t*-BuOH. To this stirred solution, $Cu(MnO_4)_2$ (50 mg, 0.165 mmol) was added at room temperature. Stirring was continued at room temperature for 1 h. The resulting solution was passed through a short pad of silica gel which was eluted wih CH_2Cl_2 and ether. Evaporation of the solvent *in vacuo* gave 5β,6β-epoxy-derivative **6** and 5α,6α-epoxy-derivative in a 6:1 ratio as a white solid (51 mg, 99%) with physical data identical to the literature.[5]

3. References :

(1) Marchon, J.-C.; Ramasseul, R. *Synthesis* **1989**, 389-391.

(2) Yamada, T.; Imagawa, K.; Mukaiyama, T. *Chem. Lett*. **1992**, 2109-2112.

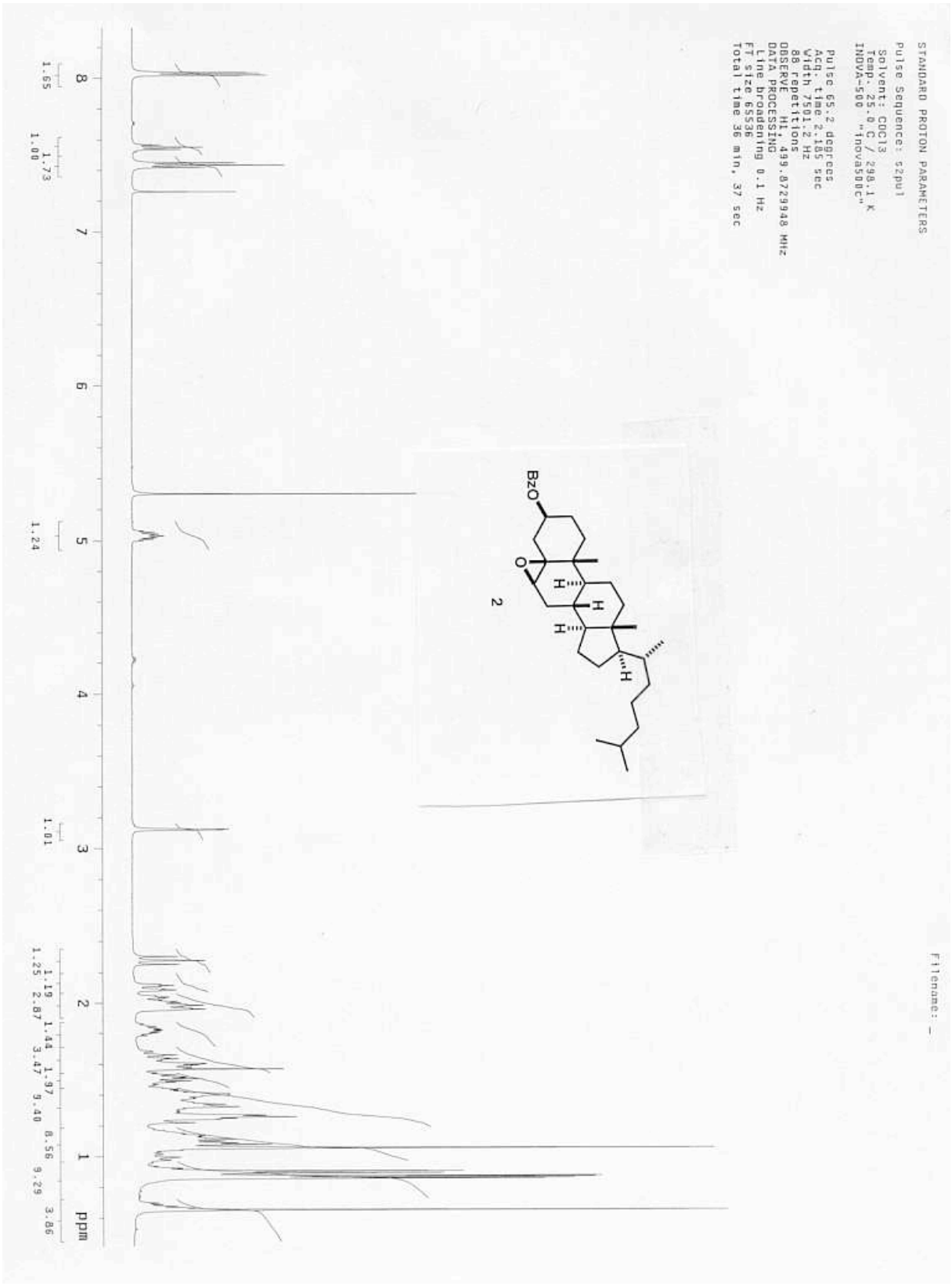
(3) Eguchi, S.; Yamaguchi, S.; Furuya, M.; Morisaki, M. *Chem. Pharm. Bull*. **1988**, *36*, 2813-2818.

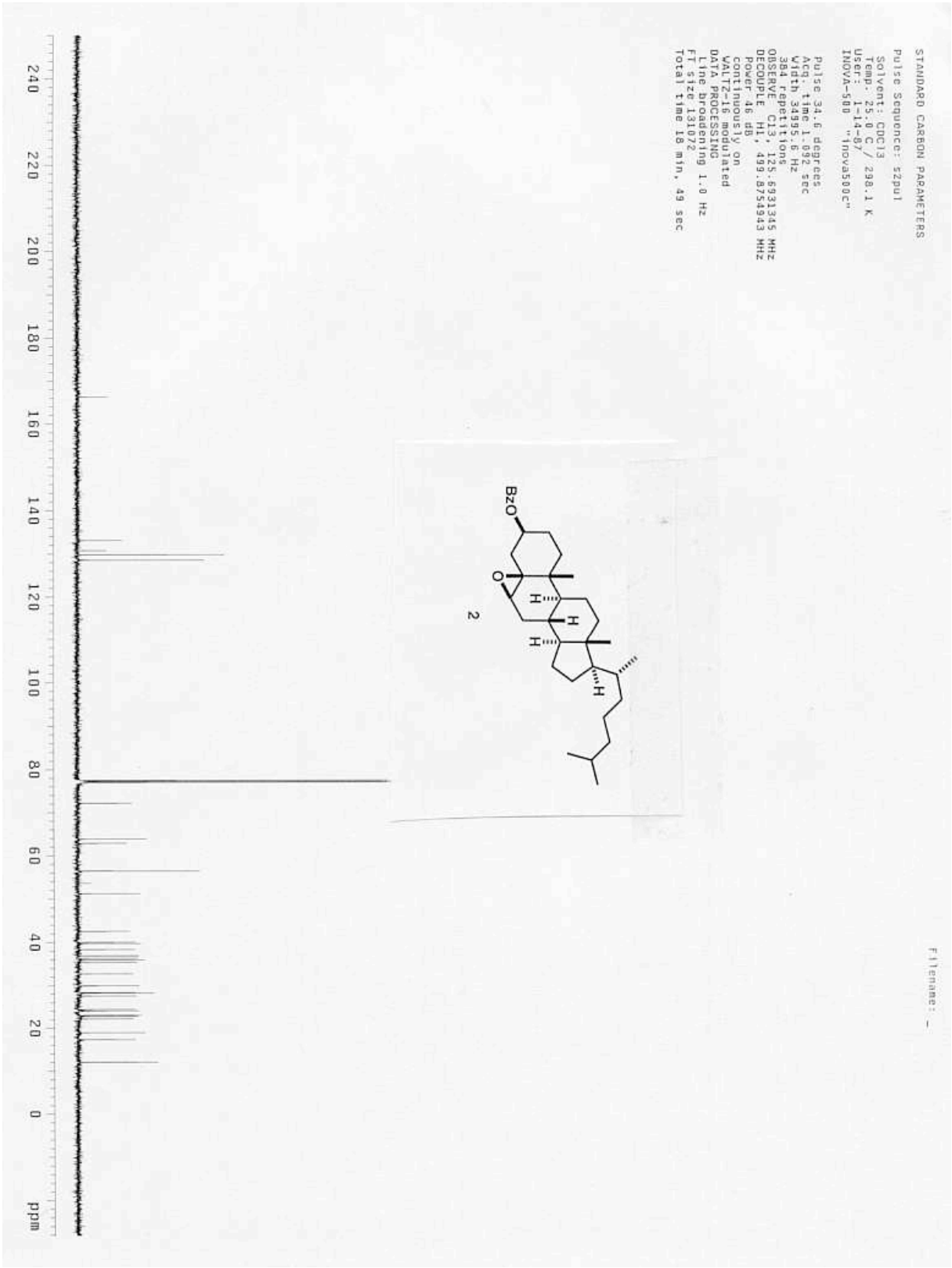
(4) Jones, D.N.; Shoppee, C.W.; Summers, G.H.R.; *J. Chem. Soc.* **1955**, 2876-2887.

(5) Syamala, M. S.; Das, J.; Baskaran, S.; Chandrasekaran, S. *J. Org. Chem*. **1992**, *57*, 1928-1930.

(6) Kotai, Lé; Sajo, I. E.; Gacs, I.; Sharma, P. K.; Banerji, K. K. Z. *Anorg. Allg. Chem*. **2007**, *633*, 1257.

4. Copies of selected ^{1}H and ^{13}C NMR spectras:

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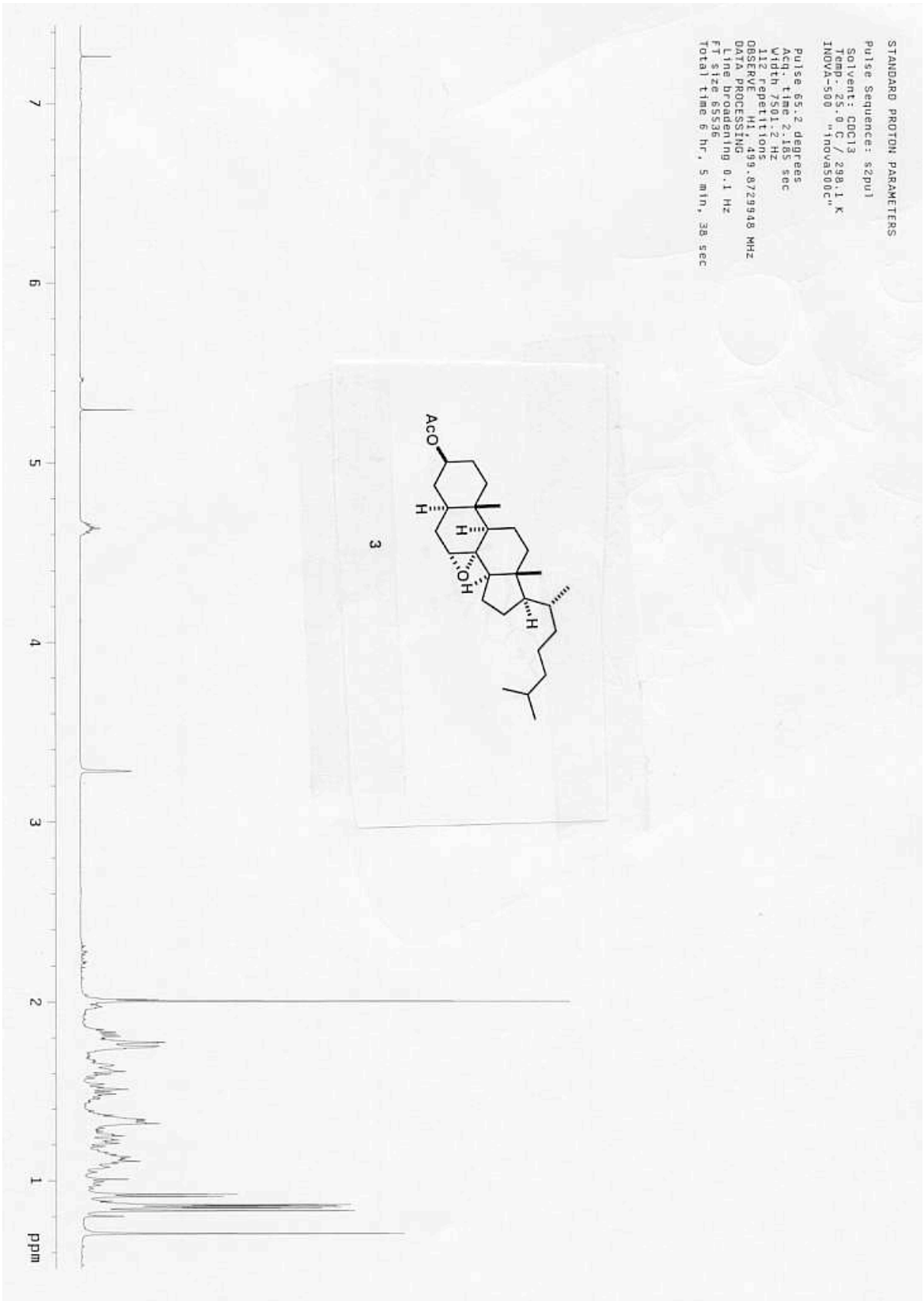
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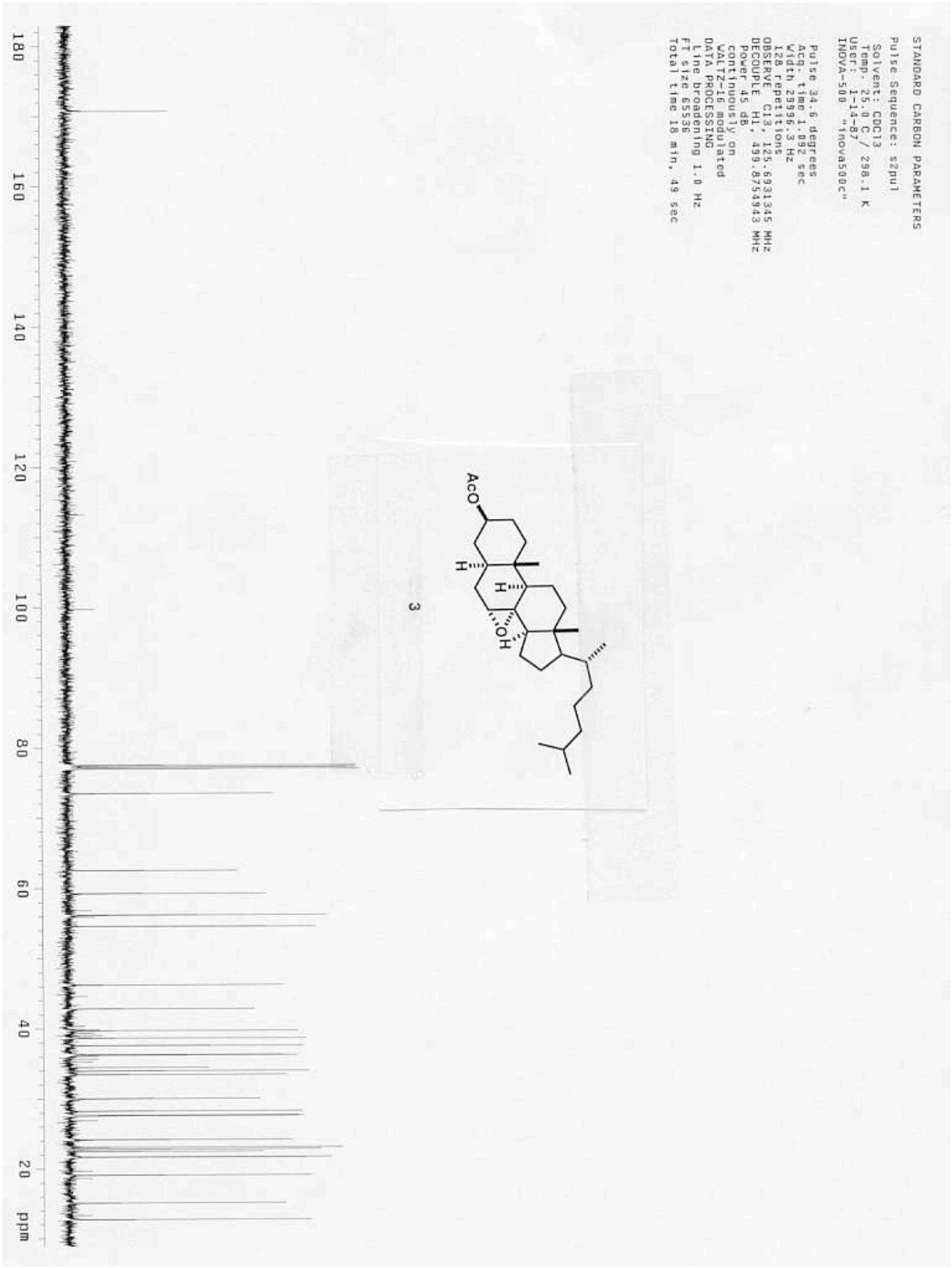
ppm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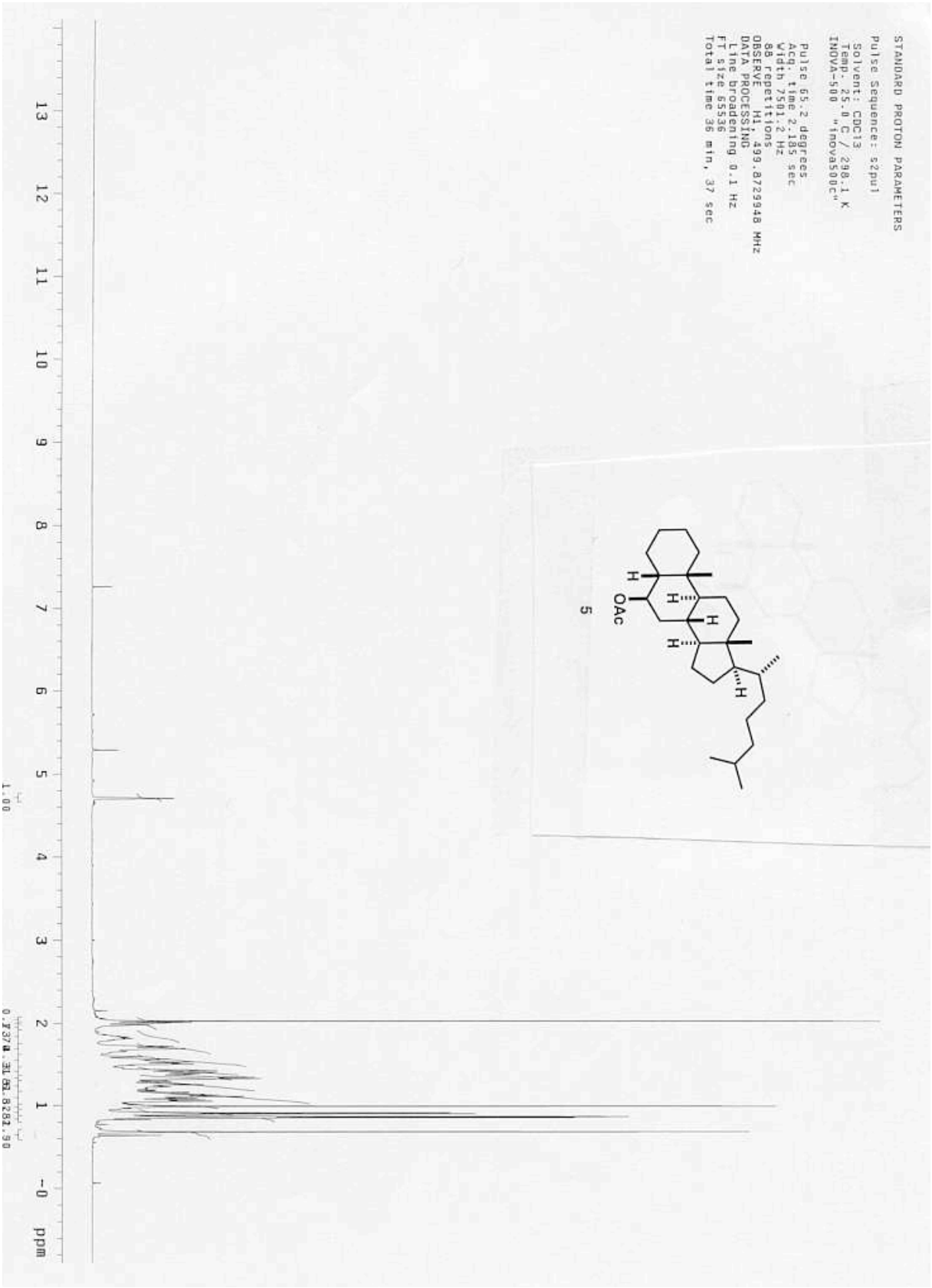
ppm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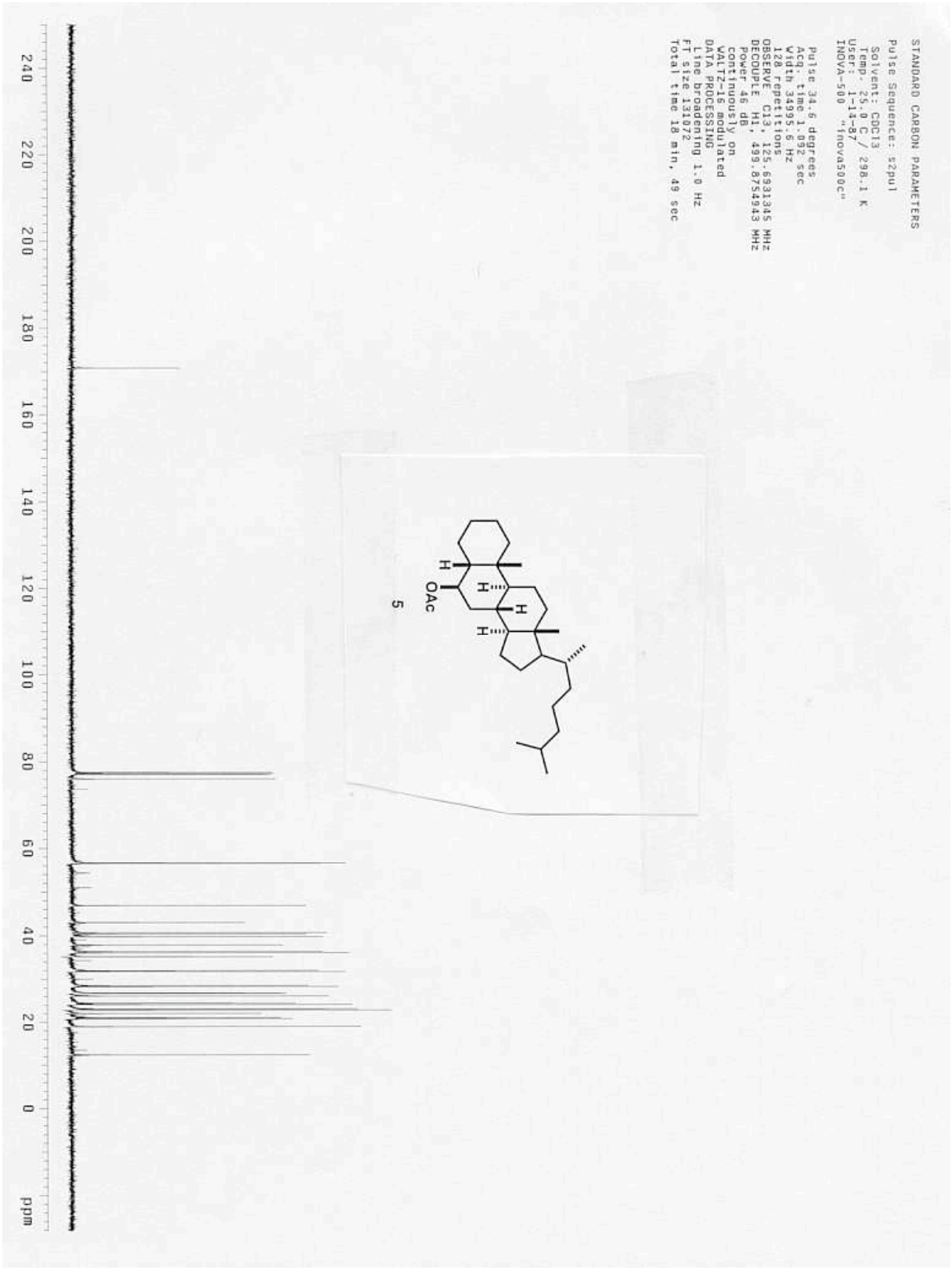
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128 repetitions
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DECOUPLE H1, 499.8754943 MHz
Power 46 dB
continuously on
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DATA PROCESSING
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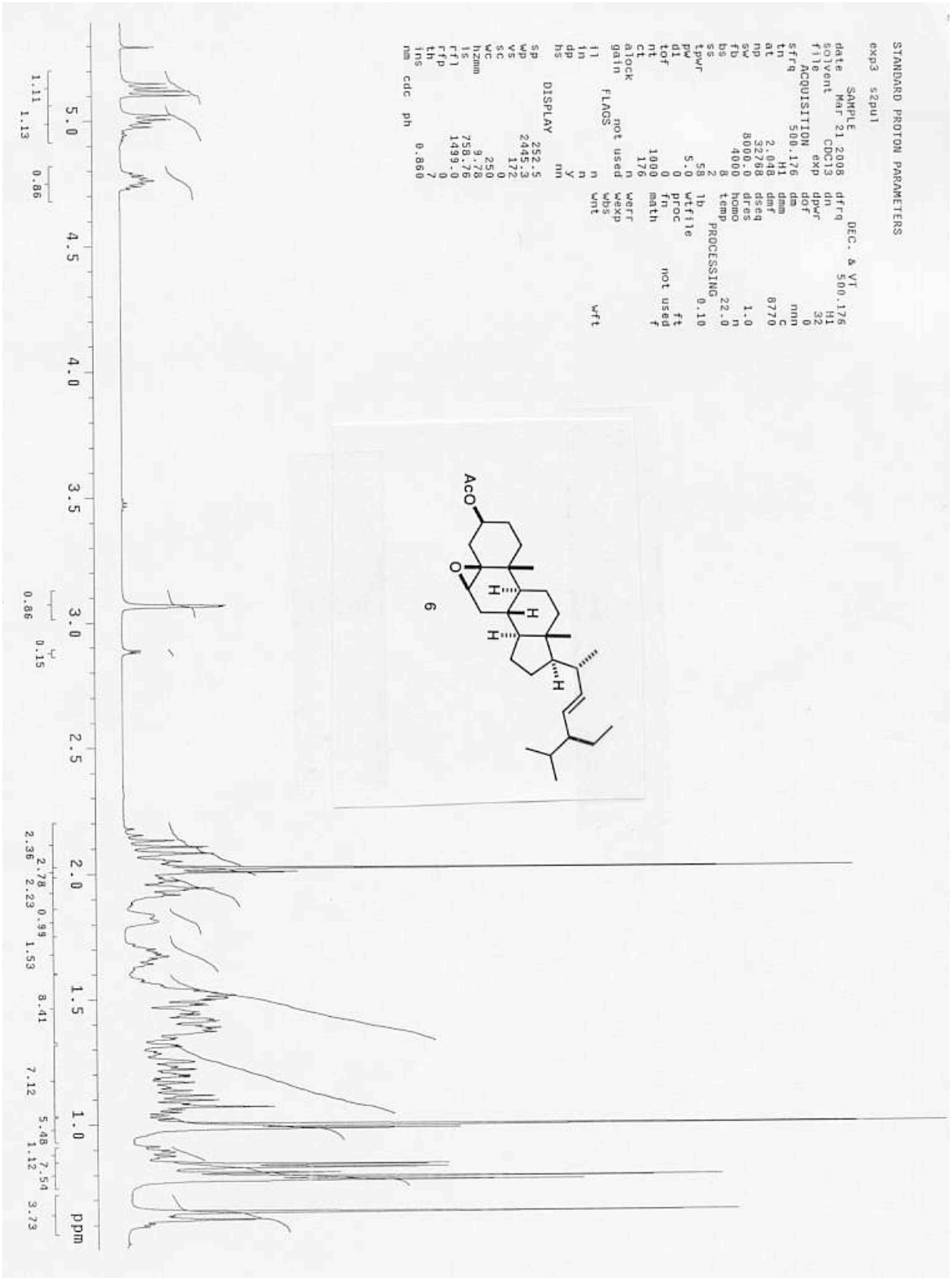
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ct 176
alock n
gain not used
FLAGS
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in n
dp y
hs nn
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dmm c
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dseq
dres 1.0
homo n
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proc ft
fn not used
math f
werr
wexp
wbs
wnt
wft
AcO
O
H
H
H
H
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5.0
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4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm
1.11
1.13
0.86
0.86
0.15
2.36
2.23
2.78
0.99
1.53
8.41
7.12
5.48
1.12
7.54
3.73

STANDARD CARBON PARAMETERS

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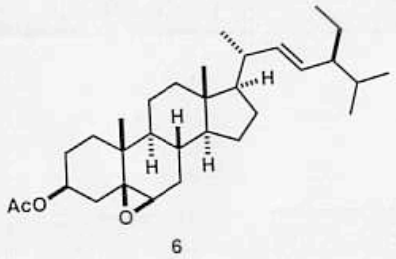
sw	34995.6	dres	1.0
fb	19000	homo	n
bs	16	temp	22.0
tpwr	57	PROCESSING	
pw	8.0	lb	1.00
d1	0.100	wtfile	
tof	0	proc	ft
nt	1000	fn	not used
ct	144	math	f
alock	n		
gain	56	werr	
FLAGS		wexp	
il	n	wbs	
in	n	wnt	
dp	y		
hs	nn		
DISPLAY			
sp	-5547.7		
wp	34995.1		
vs	56		
sc	0		
wc	250		
hzmm	139.98		
is	500.00		
rfl	5548.2		
rfp	0		
th	16		
ins	100.000		

nm cdc ph



6