Electrochemical Oxidation of Δ^9-Tetrahydrocannabinol: A Simple Strategy for Marijuana Detection

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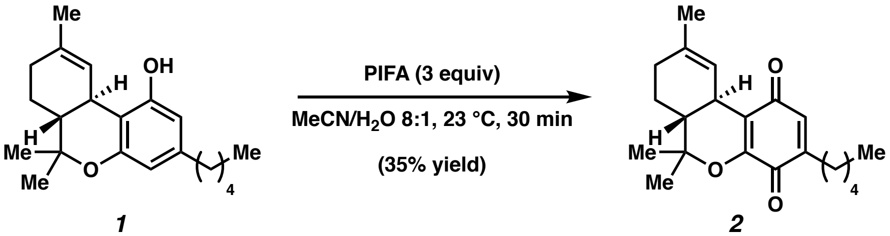
Supporting Information – Table of Contents

Part I. Experimental Section.

Materials and Methods. Unless stated otherwise, reactions were conducted in flame-dried glassware under an atmosphere of nitrogen using anhydrous solvents (freshly distilled or passed through activated alumina columns). All commercially obtained reagents were used as received unless otherwise specified. Δ^9-THC (**1**) was purchased from Sigma–Aldrich (www.sigmaaldrich.com; product number T2386) under DEA approval. Tetrabutylammonium tetrafluoroborate was purchased from Combi Blocks (98% purity; product number SRT-7754) and was recrystallize three times from EtOH/H_2O 3:1 then dried under reduced pressure (0.34 torr) at 100 °C for 24 h prior to use. MeCN was purchased from VWR (99.5% purity; product number BDH1103-4LG). The solvent was dried for 14 h with 10% wt/wt 4Å molecular sieves and was distilled from CaH prior to use. Thin layer chromatography (TLC) was conducted with EMD gel 60 F254 pre-coated plates (0.25 mm) and visualized using a combination of UV light, anisaldehyde, and potassium permanganate staining. Silicycle Siliaflash P60 (particle size 0.040–0.063 mm) was used for flash column chromatography. ^{1}H-NMR spectra were recorded on a Bruker spectrometer (at 500 MHz) and are reported relative to the residual solvent signal. Data for ^{1}H-NMR spectra are reported as follows: chemical shift (δ ppm), multiplicity, coupling constant (Hz) and integration. ^{13}C-NMR spectra were recorded on a Bruker spectrometer (at 125 MHz) and are reported relative to the residual solvent signal. Data for ^{13}C-NMR spectra are reported in terms of chemical shift and, when necessary, multiplicity, and coupling constant (Hz). IR spectra were obtained on a Perkin-Elmer UATR Two FT-IR spectrometer and are reported in terms of frequency of absorption (cm^{-1}). DART-MS spectra were collected on a Thermo Exactive Plus MSD (Thermo Scientific) equipped with an ID-CUBE ion source and a Vapur Interface (IonSense Inc.). Both the source and MSD were controlled by Excalibur software v. 3.0. The analyte was spotted onto OpenSpot sampling cards (IonSense Inc.) using $CDCl_3$ as the solvent. Ionization was accomplished using UHP He (Airgas Inc.) plasma with no additional ionization agents. The mass calibration was carried out using Pierce LTQ Velos ESI (+) and (–) Ion calibration solutions (Thermo Fisher Scientific). UV-Vis spectra were recorded using a JASCO C-770 UV-Visible/NIR spectrophotometer. The UV-Vis spectra were recorded using a 1-cm quartz cuvette, with freshly distilled tetrahydrofuran (THF). Cyclic voltammetry spectra were measured using a C-H Instruments CHI620E potentiostat. The analyte (5.00 mM) was dissolved in dry and degassed 0.1 M NBu_4BF_4 in MeCN. Spectra were collected at a sweep rate of 100 mV/s at 23 °C. Ferrocene (Strem 99% purity; product number 26-1700) was added to each sample after each scan for reference. All spectra were collected using a glassy carbon working electrode (CH-Instruments product number CHI104), a platinum counter electrode (CH-Instruments product number CHI112), and a Ag/Ag$^+$ reference electrode (CH-Instruments product number CHI112). The reference electrode was prepared with a 10 mM solution of $AgNO_3$ (Strem 99.9% purity; product number 47-1325) in MeCN. The platinum wire was heated with a Bunsen burner till it glowed prior to each measurement. The glassy working electrode was polished to a mirror using 0.05 micron MicroPolish powder (CH-Instrumnets; product number CHI120) prior to each measurement. The Electrochemical reactions were performed using an IKA Electrasyn 2.0. Platinum (IKA; product number 0040002852), glassy carbon (IKA; product number 0040002842), and graphite (IKA; product number 0040002858) electrodes were purchased from IKA and were used as received.

Experimental Procedures.

A. Chemical Oxidation of Δ^9-THC (1) to Δ^9-THCQ (2).



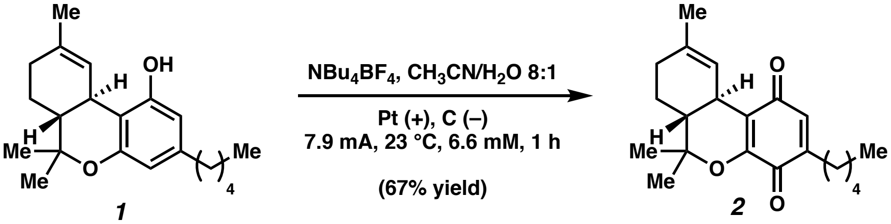
1 *2*

Δ^9-THCQ 2. A 5 mL round bottom flask equipped with a stir bar was flame dried under reduced pressure and cooled to 23° C under nitrogen. A THC solution (1.00 mL of 25 mg/mL solution in ethanol; 25.0 mg, 79.5 µmol, 1.00 equiv) was added to this flask and was concentrated under reduced pressure to give a clear oil. Next, MeCN (2.50 mL) and water (0.500 mL) were sequentially added to this vial to dissolve **1**. A second 5 mL round bottom flask was flame dried under reduced pressure and was cooled to 23° C under nitrogen. To this flask was added PIFA (103 mg, 238 µmol, 3.00 equiv), which was subsequently dissolved in MeCN (2.50 mL). The PIFA solution was then added to the THC solution dropwise over 2 minutes resulting in a yellow solution. This reaction was stirred for an additional 30 min, at which point it was quenched with saturated $NaHCO_3$ (1.00 mL). The reaction was diluted with water (2.00 mL) and was extracted with EtOAc (3 x 1.00 mL). The organic layers were combined, washed with water (3 x 1.00 mL), washed with brine (1.00 mL), and then dried over anhydrous sodium sulfate. The solution was filtered over cotton and was then concentrated under reduced pressure to give a yellow oil. This crude material was dissolved in CH_2Cl_2 (0.400 mL) and loaded onto a preparative TLC plate. This was developed with 100% benzene to give the desired product (9.00 mg, 35% yield) as an orange oil. THCQ (**2**): R_f 0.49 (Benzene); $[\alpha]^{22.7}_D$ –60.0° (*c* 1.00, CH_2Cl_2); ^{1}H-NMR (500 MHz, $CDCl_3$): δ 6.28 (s, 1H, H2), 6.00 (s, 1H, H10), 3.08–3.04 (m, 2H, H10a), 2.43–2.29 (m, 2H, H1'), 2.21–2.06 (m, 2H, H8), 1.91–1.83 (m, 1H, 7β), 1.66 (s, 3H, H11), 1.58 (dd, *J* = 10.7, 1.8 Hz, 1H, H6a)) , 1.52 (s, 3H, H12), 1.51–1.44 (m, 2H, H2'), 1.46–1.37 (m, 1H, 7α), 1.35–1.32 (m, 2H, H3'), 1.31–1.29 (m, 2H, H4'), 1.34 (s, 3H, H13), 0.88 (t, J = 7.1 Hz, 3H, H5'). ^{13}C-NMR (125 MHz, $CDCl_3$): δ 187.4 (C4), 182.6 (C1), 152.8 (C5), 146.5 (C3), 135.0 (C9), 133.4 (C2), 122.0 (C10), 119.3 (C5a), 81.9 (C6), 45.0 (C6a), 32.7 (10a), 31.5 (C4'), 31.4 (C8), 28.6 (C1'), 27.5 (C2'), 27.1 (C12), 24.7 (C7), 23.4 (C11), 22.5 (C3'), 20.1 (C13), 14.1 (C5'); IR (film): 2928,

1673, 1649, 1630, 1593, 1459 cm^{-1}; HRMS–APCI (*m/z*) $[M + H]^+$ calcd for $C_{21}H_{29}O_3^+$, 329.2112; found, 329.2105.

B. Electrochemical Oxidation of Δ^9-THC (1) to Δ^9-THCQ (2).

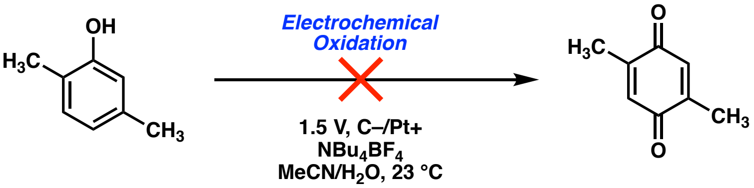
General Procedure for Electrochemical Oxidation.



Δ^9-THCQ 2. A 5 mL ElectraSyn 2.0 vial equipped with a stir bar was flame dried under reduced pressure and was cooled to 23 °C under nitrogen. Next, the Δ^9-THC (**1**) solution (0.280 mL of 25 mg/mL solution in ethanol; 7.00 mg, 22.3 µmol, 1.00 equiv) was added to this vial, which was then concentrated under reduced pressure to afford a clear oil. Electrolyte (3.00 mL, NBu_4BF_4 0.100 M in MeCN, 6.60 mM) was then added to the vial, followed by water (0.400 mL). The solution was stirred open to air for 60 seconds to ensure full dissolution of the substrate. Next, the vial was equipped with a platinum anode and a graphite cathode. This vial was then connected to the ElectraSyn 2.0 instrument, which was set to run for 60 minutes under a constant current of 7.9 mA and at a stir rate of 400 rpm. The polarity was set to alternate every 60 seconds to reduce build up at each electrode over the course of the reaction. Once the reaction was complete, the reaction was diluted with saturated sodium bicarbonate (1.00 mL) and was extracted with diethyl ether (3 x 2.00 mL). The organic layers were pooled and were subsequently washed with water (3 x 2.00 mL) and brine (2.00 mL). Finally, the organic solution was dried over sodium sulfate (0.500 g) and then filtered over cotton. This crude reaction solution was concentrated under reduced pressure to give an orange oil. This orange oil was dissolved in CH_2Cl_2 (0.300 mL) and was loaded onto a preparative TLC plate. This was then developed with 100% benzene. The product was collected as an orange oil (4.90 mg, 67% yield). THCQ **2**: R_f 0.49 (Benzene); $[\alpha]^{22.7}_D$ –60.0° (*c* 1.00, CH_2Cl_2); ^{1}H-NMR (500 MHz, $CDCl_3$): δ 6.28 (s, 1H, H2), 6.00 (s, 1H, H10), 3.08–3.04 (m, 2H, H10a), 2.43–2.29 (m, 2H, H1'), 2.21–2.06 (m, 2H, H8), 1.91–1.83 (m, 1H, 7β), 1.66 (s, 3H, H11), 1.58 (dd, J = 10.7, 1.8 Hz, 1H, H6a)) , 1.52 (s, 3H, H12), 1.51–1.44 (m, 2H, H2'), 1.46–1.37 (m, 1H, 7α), 1.35–1.32 (m, 2H, H3'), 1.31–1.29 (m, 2H, H4'), 1.34 (s, 3H, H13), 0.88 (t, J = 7.1 Hz, 3H, H5'). ^{13}C-NMR (125 MHz, $CDCl_3$): δ 187.4 (C4), 182.6 (C1), 152.8 (C5), 146.5 (C3), 135.0 (C9), 133.4 (C2), 122.0 (C10), 119.3 (C5a), 81.9 (C6), 45.0 (C6a), 32.7 (10a), 31.5 (C4'), 31.4 (C8), 28.6 (C1'), 27.5 (C2'), 27.1 (C12), 24.7 (C7), 23.4 (C11), 22.5 (C3'), 20.1 (C13), 14.1 (C5'); IR (film): 2928, 1673, 1649, 1630, 1593, 1459 cm^{-1}; HRMS–APCI (*m/z*) $[M + H]^+$ calcd for $C_{21}H_{29}O_3^+$, 329.2112; found, 329.2106.

C. Model System for Electrochemical Phenol Oxidation.

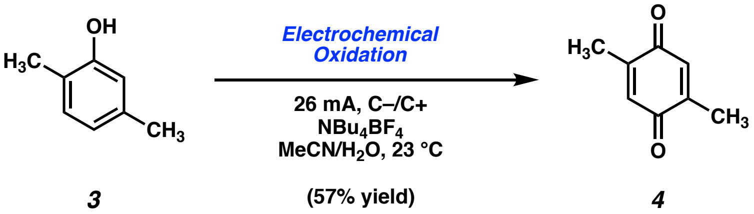
Literature Conditions for Simple Phenol Electrochemical Oxidation.



3 *4*

2,5-dimethylcyclohexa-2,5-diene-1,4-dione 4. A 5 mL ElectraSyn 2.0 vial equipped with a stir bar was flame dried under reduced pressure and was cooled to 23 °C under nitrogen. Next, 2,5-dimethylphenol (**3**) (30.0 mg, 246 µmol, 1.00 equiv). Electrolyte (3.00 mL, $LiClO_4$ 0.100 M in MeCN, 6.60 mM) was then added to the vial, followed by water (0.400 mL). The solution was stirred open to air for 60 seconds to ensure full dissolution of the substrate. Next, the vial was equipped with a platinum anode and a graphite cathode. This vial was then connected to the ElectraSyn 2.0 instrument, which was set to run for 120 minutes under a constant voltage of 1.5 V and at a stir rate of 400 rpm. Once the reaction was complete, the reaction was diluted with saturated sodium bicarbonate (1.00 mL) and was extracted with diethyl ether (3 x 2.00 mL). The organic layers were pooled and were subsequently washed with water (3 x 2.00 mL) and brine (2.00 mL). Finally, the organic solution was dried over sodium sulfate (0.500 g) and then filtered over cotton. This crude reaction solution was concentrated under reduced pressure to give an insoluble brown solid that showed no signs of starting material or product.

Optimized Procedure for Model System Electrochemical Oxidation.



2,5-dimethylcyclohexa-2,5-diene-1,4-dione 4. A 5 mL ElectraSyn 2.0 vial equipped with a stir bar was flame dried under reduced pressure and was cooled to 23 °C under nitrogen. Next, 2,5-dimethylphenol (**3**) (30.0 mg, 246 µmol, 1.00 equiv). Electrolyte (3.00 mL, NBu_4BF_4 0.100 M in MeCN, 6.60 mM) was then added to the vial, followed by water (0.400 mL). The solution was stirred open to air for 60 seconds to ensure full dissolution of the substrate. Next, the vial was equipped with a graphite anode and a graphite cathode. This vial was then connected to the ElectraSyn 2.0 instrument, which was set to run for 60 minutes under a constant current of 26 mA and at a stir rate of 400 rpm. Once the reaction was complete, the reaction was diluted with saturated sodium bicarbonate (1.00 mL) and was extracted with diethyl ether (3 x 2.00 mL). The organic layers were pooled and were subsequently washed with water (3 x 2.00 mL) and brine (2.00 mL). Finally, the organic solution was dried over sodium sulfate (0.500 g) and then filtered over cotton. This crude reaction solution was concentrated under reduced pressure to give an orange oil. This orange oil was dissolved in CH_2Cl_2 (0.300 mL) and was loaded onto a preparative TLC plate. This was then developed with 1:4 Et_2O/Pentane. The product was collected as an orange solid (3.20 mg, 57% yield). 2,5-dimethylbenzoquinone **4**: R_f 0.50 (1:4 Et_2O/Pentane). Spectral data matched those previously reported.[1]

D. Select Results from Electrochemical Conditions Screening.

Table S1: Effect of electrodes. Conditions identical to section B except the electrode configuration below was used.

Entry	Cathode/Anode	%Yield
1	C–/C+	0
2	Pt–/Pt+	30
3	Glassy C–/Pt+	27
4	C–/Pt+	68

Table S2: Effect of concentration. Conditions identical to section B where the total volume was held constant and the amount of starting material was changed. (Entry 1: 3.50 mg, 11.1 mmol; Entry 2: 7.00 mg, 22.3 µmol; Entry 3: 14.0 mg, 44.6 µmol).

Entry	Concentration	%Yield (brsm)
1	3.9 mM	10 (20)
2	6.6 mM	68 (68)
3	13 mM	17 (21)

Table S3: Effect of water ratio. Conditions identical to section B except the volume of electrolyte and water listed below are adjusted to account for a total volume of 3.40 mL.

Entry	Electrolyte:Water	%Yield (brsm)
1	100:1	0 (0)
2	80:1	5 (17)
3	8:1	68 (68)
4	1:1	11 (15)

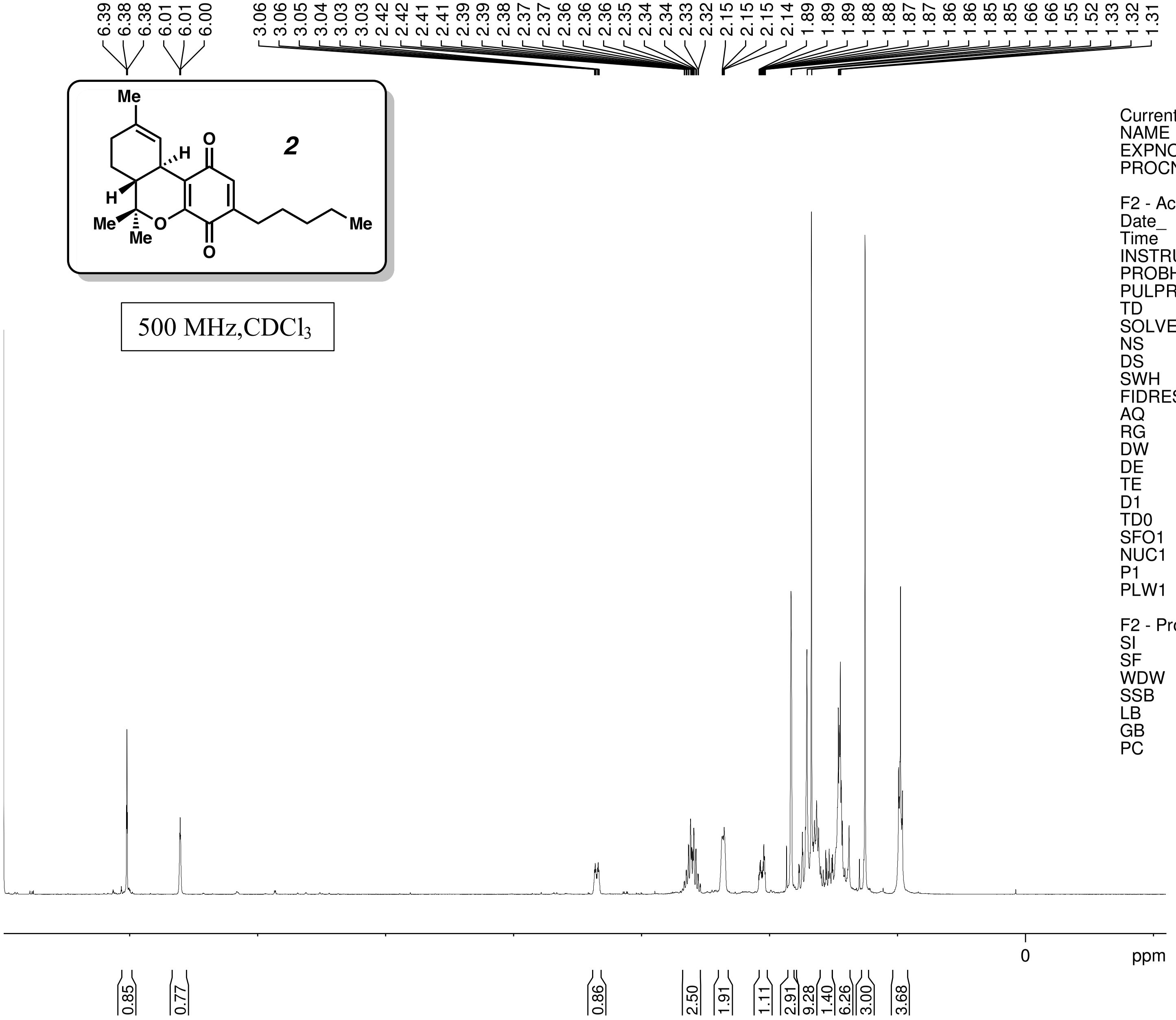
Table S4: Effect of current. Conditions identical to section B except with the constant current set to the value listed below.

Entry	Current (mA)	%Yield (brsm)
1	3.90	34 (56)
2	7.90	68 (68)
3	16.0	0 (0)

Table S5: Effect of additives. Conditions identical to section B except with addition of 1 equiv of additive added to the reaction vial prior to electrode insertion.

Entry	Additive (1 equiv)	%Yield (brsm)
1	H_2O_2	45 (73)
2	*t*BuOOH	0 (0)
3	NBu_4OH	0 (0)
4	(tBuO)$_2$OPONBu$_4$	12 (12)
6	Cl_4NHPI	32 (32)

^{1}H-NMR Spectra:



2

500 MHz,CDCl$_3$

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PROCNO 1

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SOLVENT CDCl3
NS 8
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SWH 10000.000 Hz
FIDRES 0.305176 Hz
AQ 3.2767999 sec
RG 7.35
DW 50.000 usec
DE 10.00 usec
TE 298.0 K
D1 2.00000000 sec
TD0 1
SFO1 500.1330008 MHz
NUC1 1H
P1 10.00 usec
PLW1 13.50000000 W

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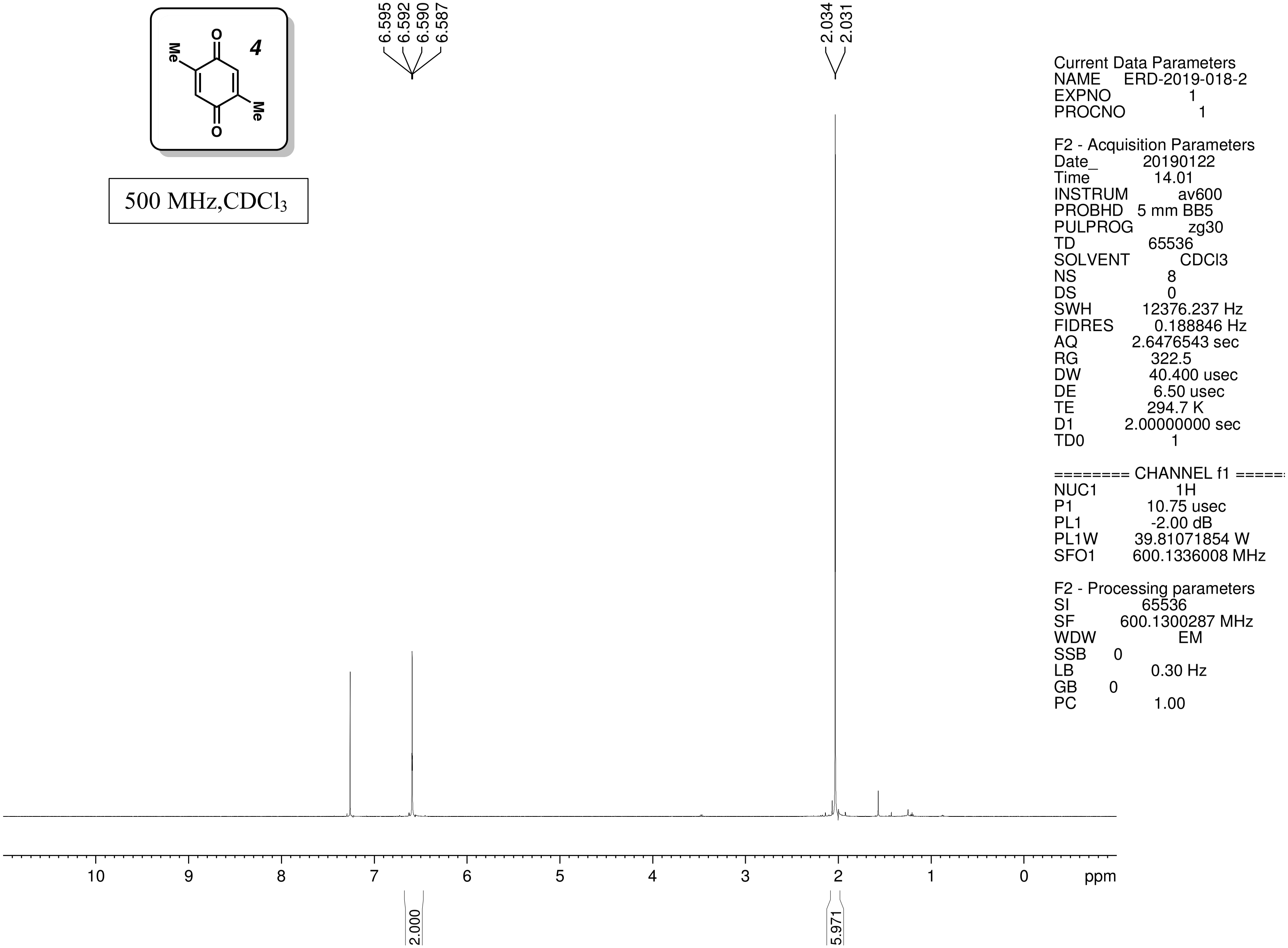
SSB 0
LB 0.30 Hz
GB 0
PC 1.00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4
Me
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500 MHz,CDCl$_3$
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6.590
6.587
2.034
2.031
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SWH 12376.237 Hz
FIDRES 0.188846 Hz
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RG 322.5
DW 40.400 usec
DE 6.50 usec
TE 294.7 K
D1 2.00000000 sec
TD0 1
======== CHANNEL f1 ======
NUC1 1H
P1 10.75 usec
PL1 -2.00 dB
PL1W 39.81071854 W
SFO1 600.1336008 MHz
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SF 600.1300287 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
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9
8
7
6
5
4
3
2
1
0
ppm
2.000
5.971

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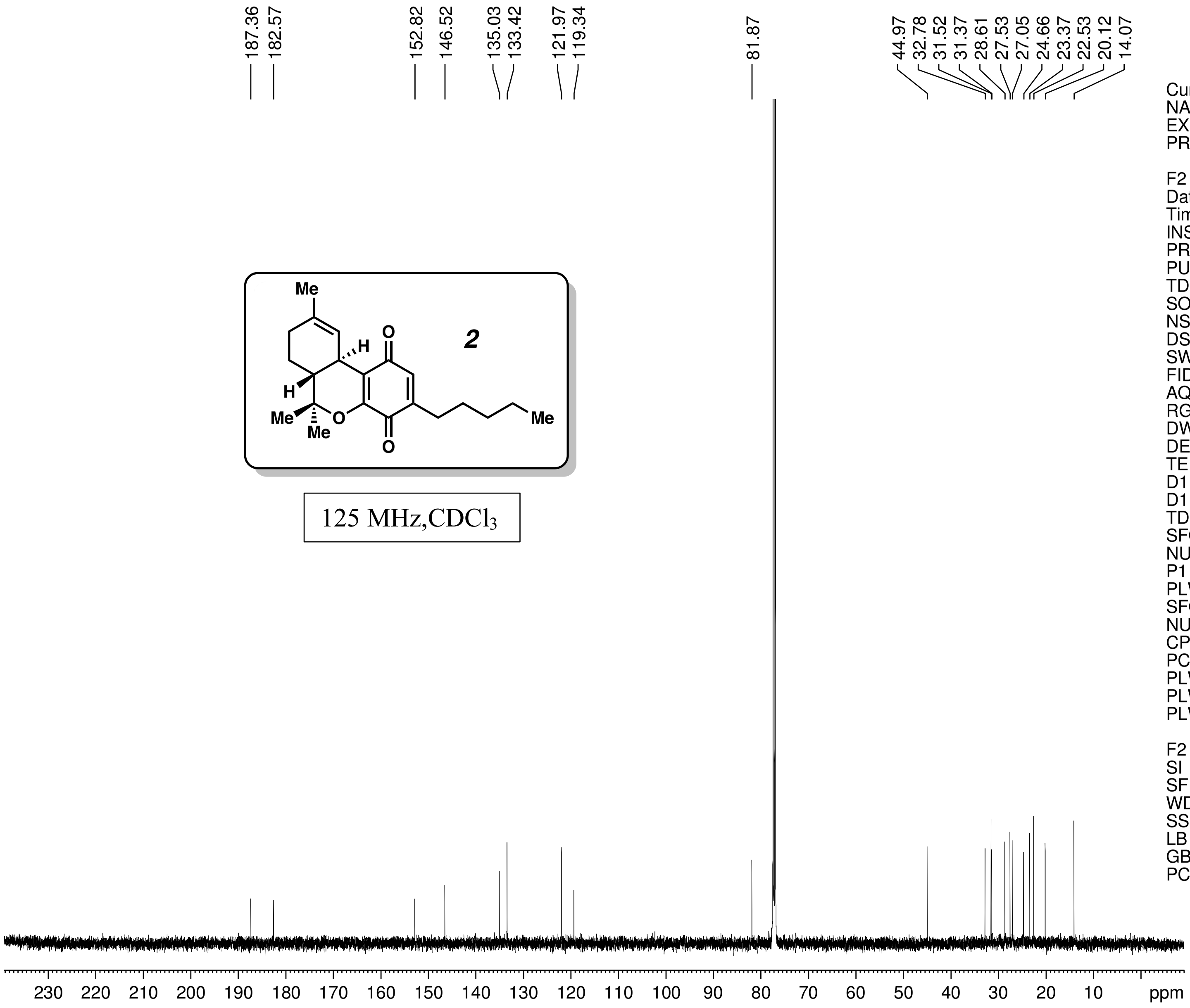

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PROCNO               1

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SOLVENT           CDCl3
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DS                  2
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RG             204.54
DW              16.000 usec
DE              28.00 usec
TE              298.0 K
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D11        0.03000000 sec
TD0                 1
SFO1      125.7722511 MHz
NUC1              13C
P1              10.50 usec
PLW1      23.00000000 W
SFO2      500.1330008 MHz
NUC2               1H
CPDPRG[2        waltz16
PCPD2           80.00 usec
PLW2      13.50000000 W
PLW12      0.21094000 W
PLW13      0.10610000 W

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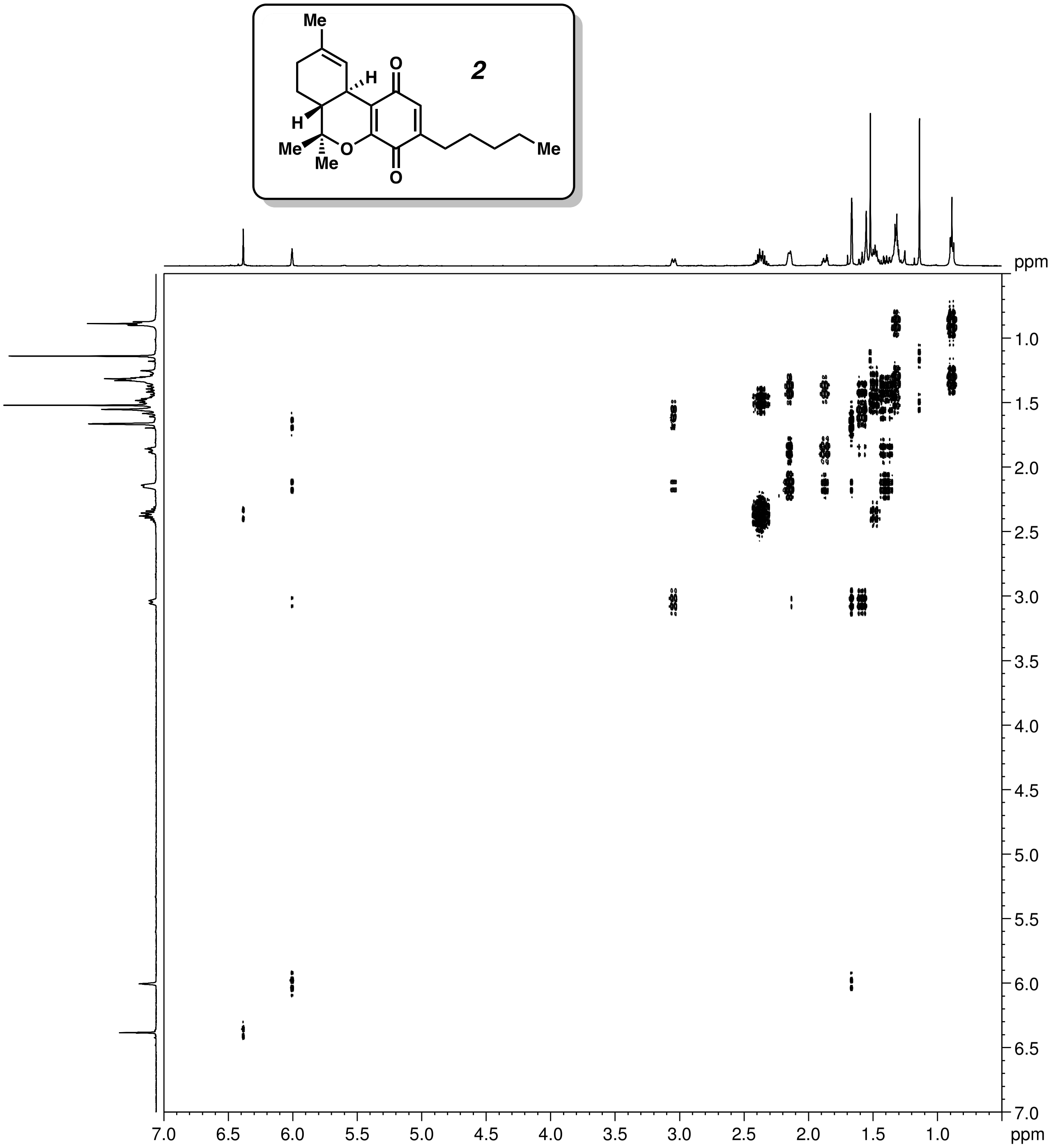
2D-NMR Spectra:

COSY



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DW            100.000 usec
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D1         2.00000000 sec
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IN0        0.00020000 sec
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NUC1              1H
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P2             20.00 usec
PLW1       13.50000000 W
GPNAM[1]     SMSQ10.100
GPZ1           10.00 %
GPNAM[2]     SMSQ10.100
GPZ2           20.00 %
P16          1000.00 usec

F1 - Acquisition parameters
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FIDRES      39.062500 Hz
SW             9.997 ppm
FnMODE      States-TPPI

F2 - Processing parameters
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SF         500.1300125 MHz
WDW              SINE
SSB               1
LB      0 Hz
GB      0
PC             1.40

F1 - Processing parameters
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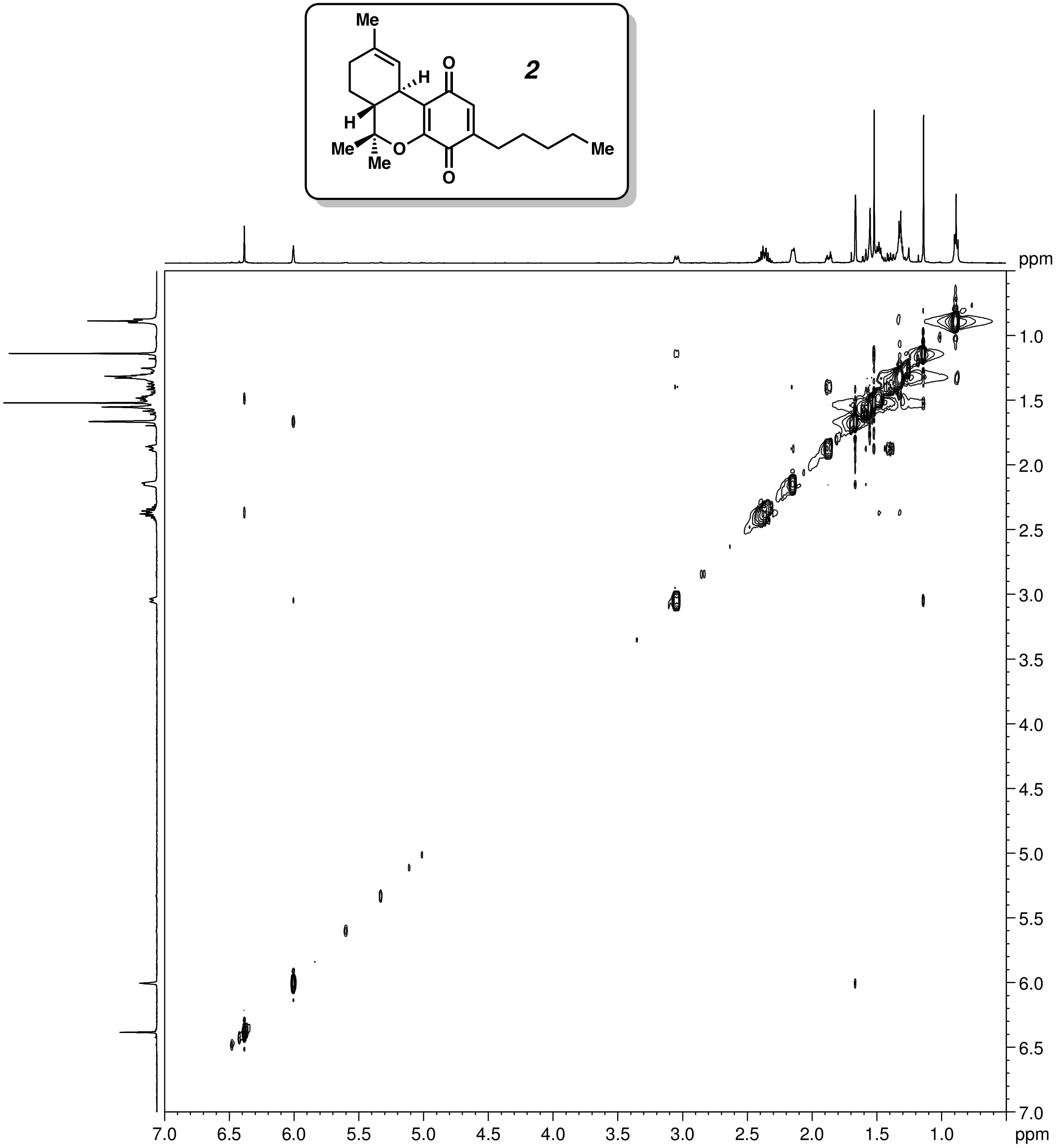
NOESY



Current Data Parameters

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PROCNO	1

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TE	298.0 K
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D8	0.75000000 sec
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PLW1	13.50000000 W
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GPZ1	40.00 %
P16	1000.00 usec

F1 - Acquisition parameters

TD	256
SFO1	500.1325 MHz
FIDRES	39.062500 Hz
SW	9.997 ppm
FnMODE	States-TPPI

F2 - Processing parameters

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SF	500.1300126 MHz
WDW	QSINE
SSB	2
LB	0 Hz
GB	0
PC	1.40

F1 - Processing parameters

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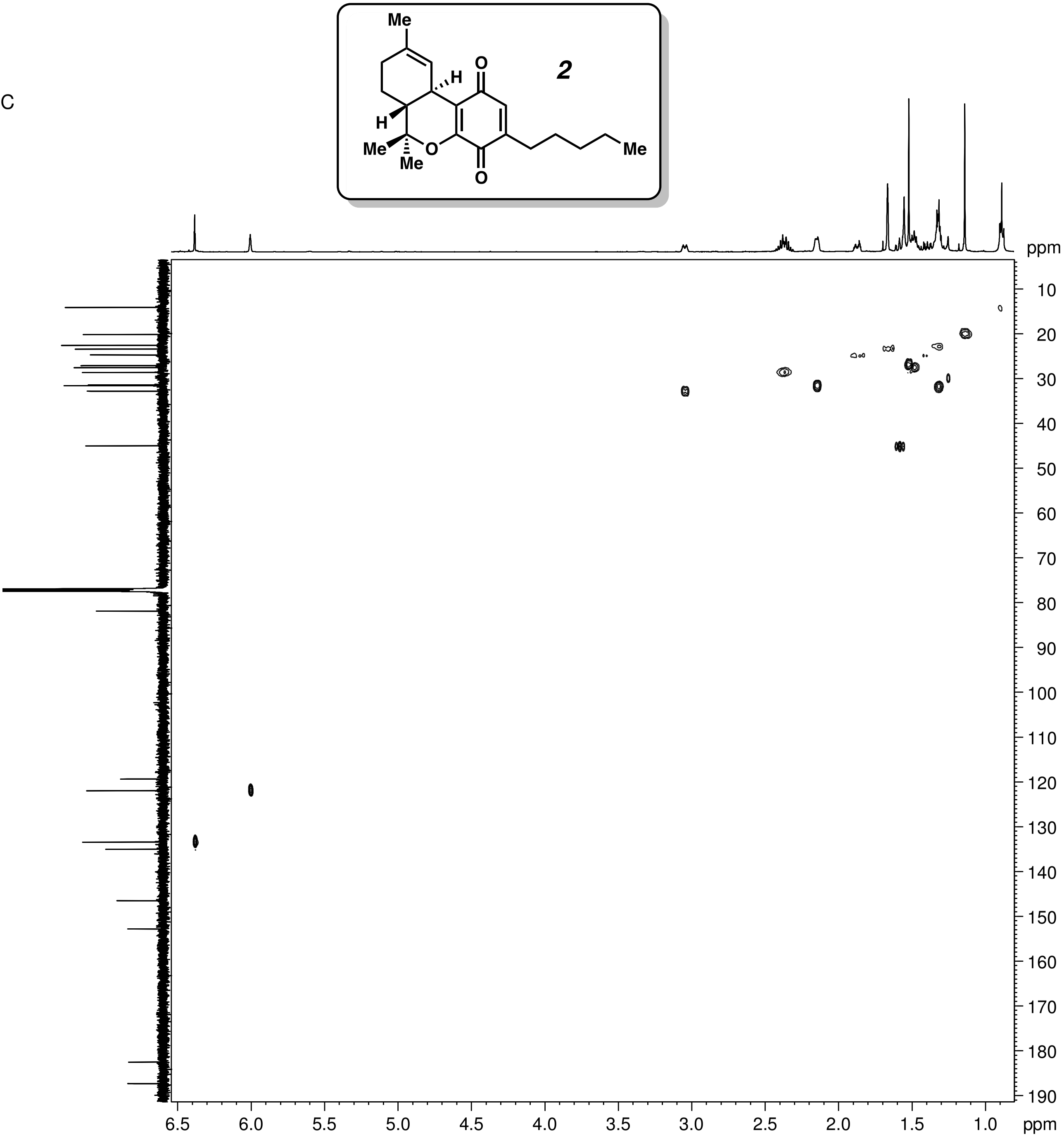
HSQC



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D4       0.00172414 sec
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D13      0.00000400 sec
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D21      0.00345000 sec
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NUC1              1H
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P2             20.00 usec
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PLW1     13.50000000 W
SFO2     125.7703648 MHz
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CPDPRG[2        garp
P3             10.50 usec
P4             21.00 usec
PCPD2          70.00 usec
PLW2     23.01399994 W
PLW12     0.51780999 W
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GPZ1           80.00 %
GPNAM[2]   SMSQ10.100
GPZ2           20.10 %
P16          1000.00 usec

F1 - Acquisition parameters
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SFO1        125.7704 MHz
FIDRES    196.293976 Hz
SW           199.774 ppm
FnMODE  Echo-Antiecho

F2 - Processing parameters
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SF       500.1300146 MHz
WDW            QSINE
SSB                2
LB      0 Hz
GB      0
PC              1.40

F1 - Processing parameters
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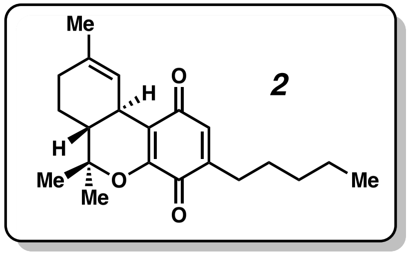
HMBC



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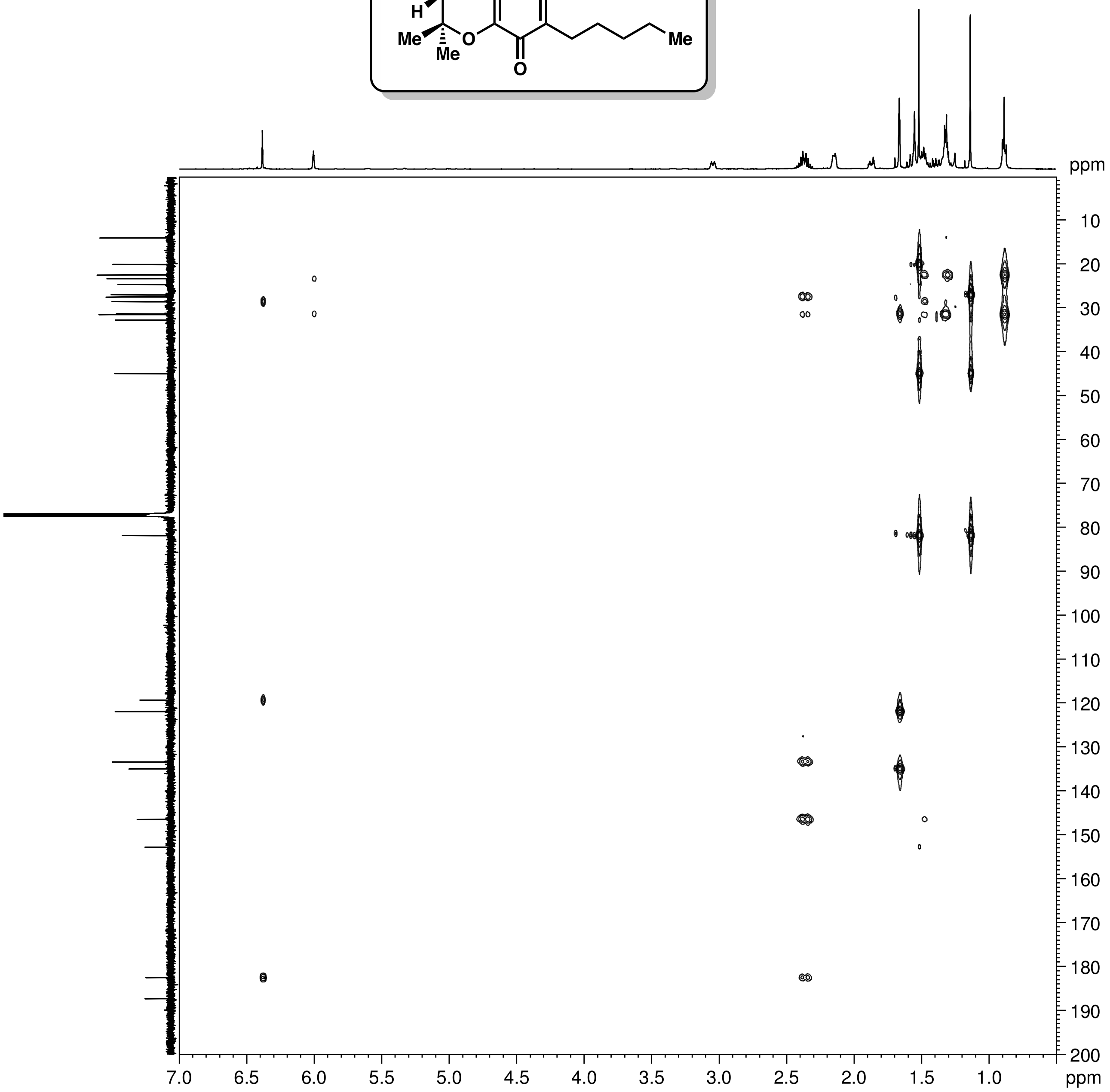

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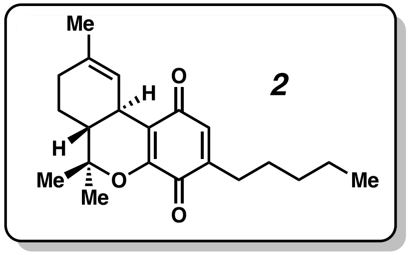
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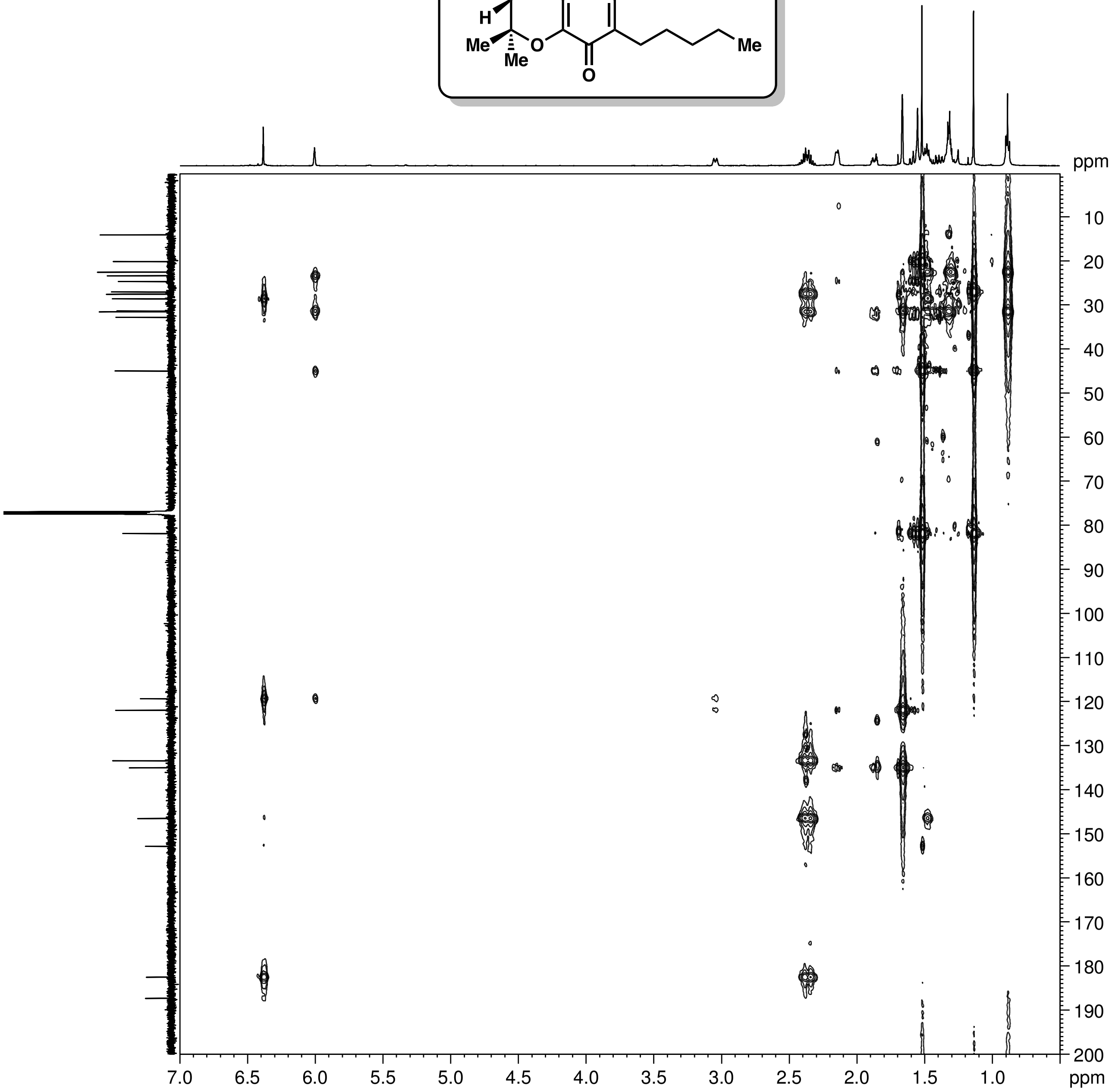

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GPNAM[5]    SMSQ10.100
GPZ5         -10.00 %
GPNAM[6]    SMSQ10.100
GPZ6          -5.00 %
P16         1000.00 usec

F1 - Acquisition parameters
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FIDRES    196.293976 Hz
SW           199.774 ppm
FnMODE            QF

F2 - Processing parameters
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GB       0
PC             1.40

F1 - Processing parameters
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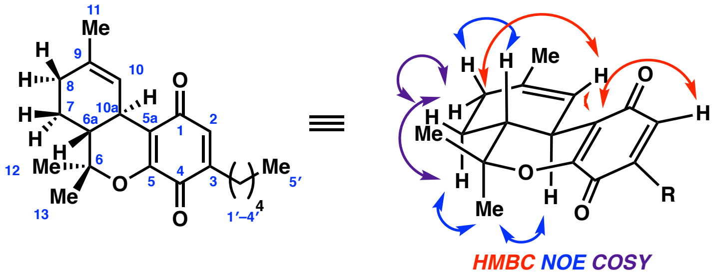
Structural Assignment of 2.

Figure S1: Δ^9-THCQ (**2**) correlations.

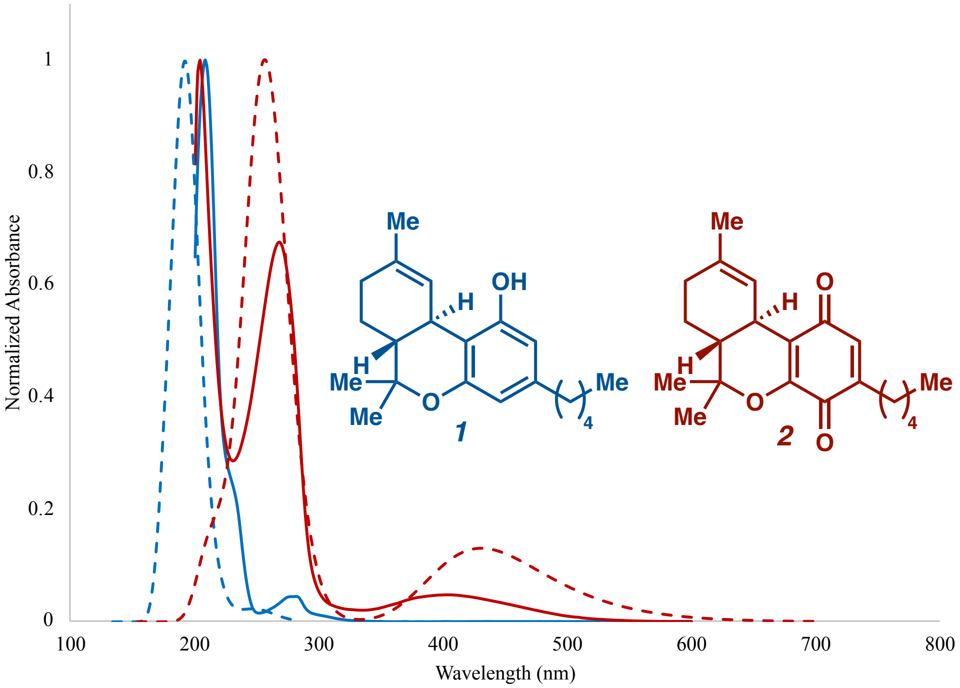


2D NMR spectroscopy was used to provide evidence of the desired *p*-quinone as opposed to the *o*-quinone and supported an assigning with the alkene in the 9-position, as opposed to the more thermodynamically favored 8-position. The structure of **2** was numbered according to modern conventions[2] and was assigned using a variety of NMR techniques. The alkene position was assigned according to COSY interaction between H10a and H10 as well as an HMBC correlation between H10 to C5a, C8, C9, and C11. Additionally, and HMBC between H10a to C6a, C10, and C5a support the assignment of the alkene. The position of the quinone carbonyl at C4 proved to be more difficult as the corresponding *o*-quinone at C2 would be expected to have similar correlations. An HMBC was used to correlate H2 to C1, C3, C5, C5a, and C1'. Although this alone cannot thoroughly rule out the *o*-quinone, an analogous assignment was made by Mechoulam in their synthesis. In their case, the carbonyls at C1 and C4 have chemical shifts of 187.6 and 182.6 ppm respectively. This is in line with the chemical shifts of C1 and C4 for **2** at 187.4 and 182.6 respectively.

Photophysical Data.

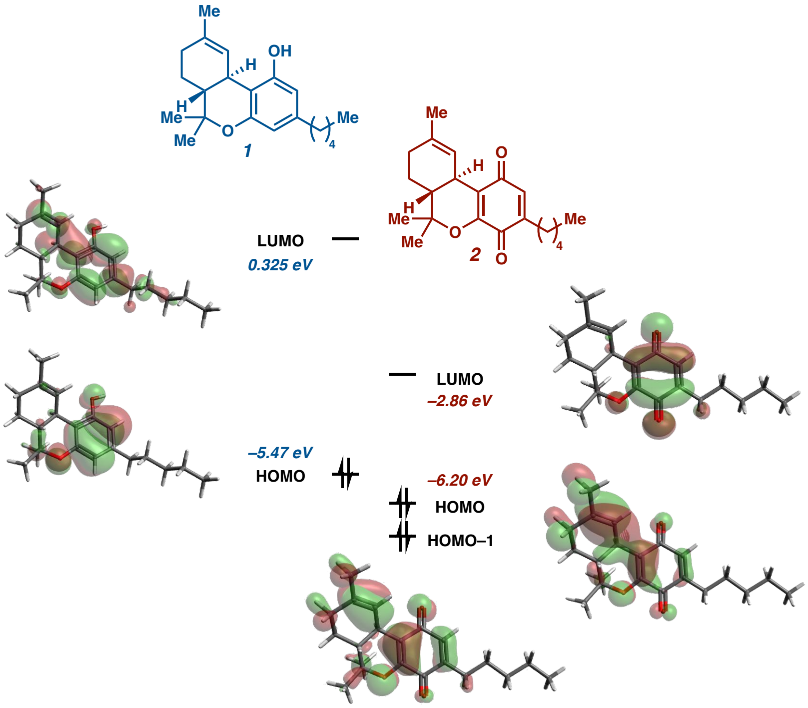
Photophysical properties were investigated using UV/Vis spectroscopy. The UV/Vis spectrum of Δ^{9}-THC (**1**) (Figure S2) showed absorbances in the UV region with major peaks at 208 nm, 232 nm, and 282 nm in accordance with previous reports.[3] The oxidized Δ^{9}-THCQ (**2**) showed strong absorbance peaks in the UV region at 204 nm and 266 nm, as well as a diagnostic peak in the visible spectrum at 402 nm. We were pleased to find strong correlation with our initial TDDFT calculations (Figure S2) for both **1** and **2** and used this computational data to gain further insight into the differences between these two spectra.

Figure S2: Experimental (solid line) UV/Vis spectra of Δ^{9}-THC (**1**), (blue) and Δ^{9}-THCQ (**2**), (red) in THF at 23 °C. The calculated TDDFT spectrum (dashed line) was calculated using B3LYP/6-31G(d) in the gas phase.



Specifically, we sought to look at the orbital contributions to the key electronic transitions as well as the orbital distributions and energies to understand the differences in the spectra for **1** and **2**. The lowest energy transition for Δ^9-THC (**1**) had an experimental peak at 282 nm and was found to be primarily comprised of the HOMO–LUMO transition with orbital densities of both located on the electron rich aromatic system (Figure S3). The red shifted visible absorbance for Δ^9-THCQ (**2**) was found to be comprised of a combination of the HOMO–LUMO and HOMO-1–LUMO transition. In this case, the HOMO and HOMO-1 are distributed over the electron rich alkene while the LUMO is localized on the electron poor quinone. This π-π* transition is reminiscent of a donor–acceptor interaction. The electronegative carbonyl groups lead to a net lowering of the LUMO energy, a narrowing of the HOMO–LUMO transition energy, and ultimately a red-shift into the visible spectrum for Δ^9-THCQ (**2**) relative to Δ^9-THC (**1**). The striking differences in photophysical properties prompted an investigation into the redox properties of (**1**) and (**2**) again, informed by the changes in orbital densities and energies predicted using computational chemistry.

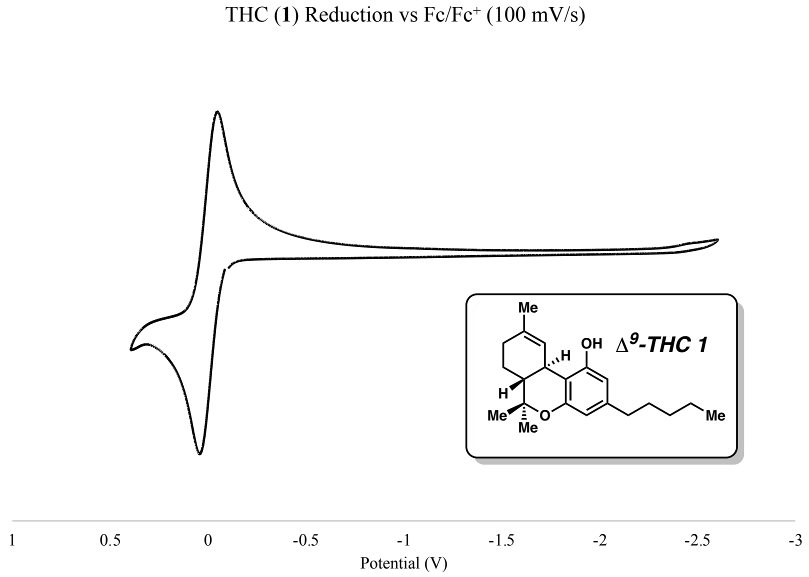
Figure S3: DFT calculated (B3LYP/6-31G(d)) HOMO and LUMO energy levels and orbital distributions for THC (1) and THCQ (2).



Electrochemical Data.

Cyclic voltammetry spectra were measured using a C-H Instruments CHI620E potentiostat. The analyte (5.00 mM) was dissolved in dry degassed 0.1 M NBu_4BF_4 in MeCN. Spectra were collected at a sweep rate of 100 mV/s at 23 °C. Ferrocene (Strem 99% purity; product number 26-1700) was added to each sample after each scan for reference. All spectra were collected using a glassy carbon working electrode (CH-Instruments product number CHI104), a platinum counter electrode (CH-Instruments product number CHI112), and a Ag/Ag$^+$ reference electrode (CH-Instruments product number CHI112). The reference electrode was prepared with a 10 mM solution of $AgNO_3$ (Strem 99.9% purity; product number 47-1325) in MeCN. The platinum wire was heated with a Bunsen burner until it glowed prior to each measurement. The glassy working electrode was polished to a mirror using 0.05 micron MicroPolish powder (CH-Instrumnets; product number CHI120) prior to each measurement.

Figure S4: Δ^9-THC (**1**) reduction vs Fc/Fc$^+$



THC (**1**) Reduction vs Fc/Fc$^+$ (100 mV/s)

Figure S5: Δ^9-THCQ (**2**) reduction vs Fc/Fc$^+$

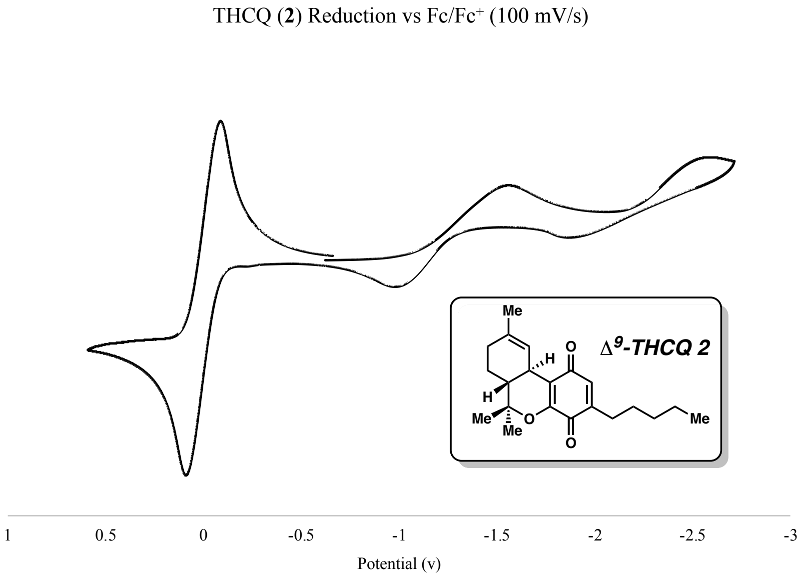


Figure S6: Δ^9-THC (**1**) oxidation vs Fc/Fc$^+$

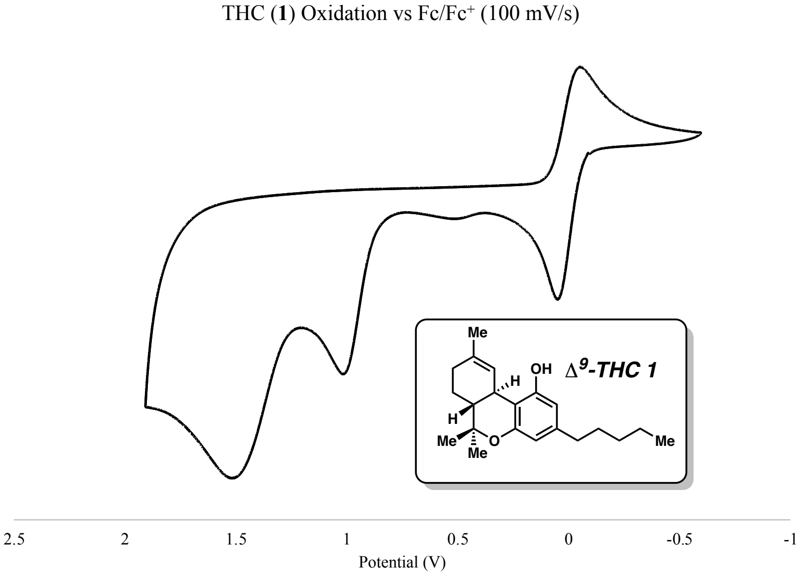
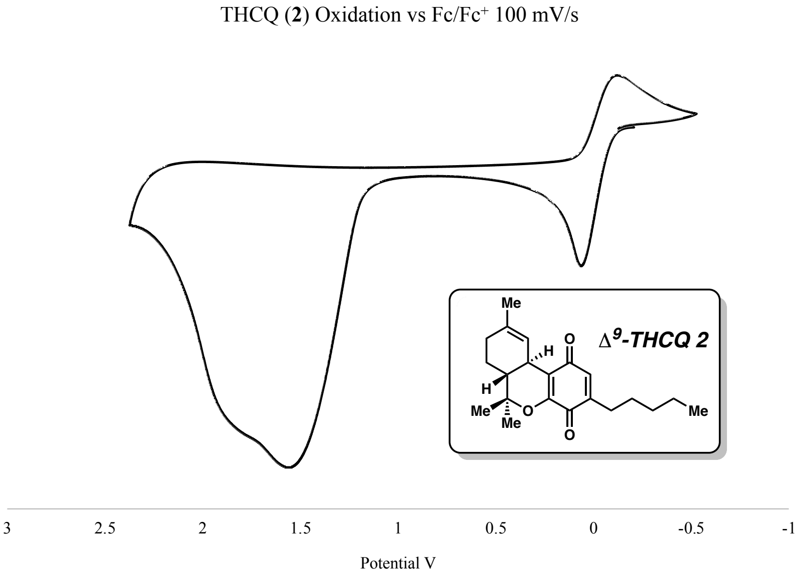


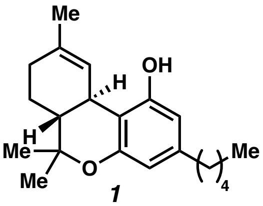
Figure S7: Δ^9-THCQ (**2**) oxidation vs Fc/Fc$^+$



Part II: Computational Section.

Computational Methods. All calculations were carried out with the Gaussian 09 package.[4] Geometry optimizations were performed with B3LYP with the 6-31G(d) basis set. Frequency analysis was conducted at the same level of theory to verify the stationary points to be minima or saddle points. Free energy corrections were calculated both with and without Truhlar's quasiharmonic oscillator approximation. A geometry minimization in the gas phase was conducted for compounds 1 and 2. All TD-DFT calculations were carried out as siblge point calculations using B3LYP/6-31G(d).

Cartesian Coordinates and Energies.



1

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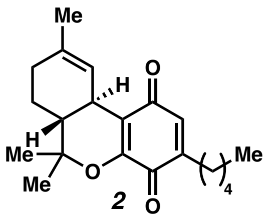
C	1.72999	0.58467	-0.40928
C	1.02903	-0.51942	0.11005
C	1.77662	-1.69177	0.33552
C	3.11709	-1.79808	-0.04077
C	3.75671	-0.70291	-0.62242
H	3.55625	1.37373	-1.20783
H	3.65504	-2.72823	0.13306
O	1.14051	-2.73671	0.96306
H	1.77124	-3.4679	1.05168
O	1.16243	1.81626	-0.5784
C	-0.44693	-0.38606	0.46814
H	-0.51198	-0.32816	1.56865
C	-1.02372	0.92112	-0.11671
H	-1.05068	0.79544	-1.20952
C	-0.0815	2.11602	0.1165
C	-1.33929	-1.53912	0.02951
C	-2.63801	-1.3951	-0.26795
H	-0.89095	-2.52557	-0.01002
C	-3.34038	-0.05411	-0.21968
H	-4.27306	-0.14589	0.35617
H	-3.65894	0.21124	-1.24093
C	-2.47305	1.07604	0.36323
H	-2.8914	2.04477	0.06823
H	-2.50393	1.03797	1.46053

C	0.23526	2.39549	1.59229
H	0.90963	3.25445	1.67093
H	-0.67912	2.62541	2.15045
H	0.72236	1.54061	2.07001
C	-0.57528	3.38743	-0.57706
H	-0.84608	3.18237	-1.61817
H	-1.44505	3.80837	-0.0638
H	0.22115	4.13829	-0.57291
C	-3.49047	-2.56474	-0.69105
H	-4.32934	-2.71846	0.00271
H	-3.93502	-2.39508	-1.68237
H	-2.91185	-3.49286	-0.73407
C	5.23424	-0.81518	-1.04182
H	5.86039	-0.53587	-0.22035
H	5.42045	-0.1636	-1.86987
C	5.54258	-2.26724	-1.45176
H	5.55189	-2.8893	-0.58122
H	4.79078	-2.61375	-2.12972
C	6.91956	-2.32528	-2.1389
H	7.65958	-1.90415	-1.49088
H	6.88634	-1.76825	-3.05187
C	7.27928	-3.79111	-2.44471
H	7.30129	-4.35064	-1.53293
H	6.54543	-4.20881	-3.10188
C	8.66354	-3.85047	-3.11696
H	9.39689	-3.42987	-2.46107
H	8.91486	-4.8692	-3.32656
H	8.64064	-3.29358	-4.03033

SCF Energy: –968.759262035 Hartrees
Zero-point correction: 0.470113 Hartrees
Thermal correction to enthalpy: 0.494643 Hartrees
Thermal correction to Gibbs free energy: 0. 416797 Hartrees
Sum of electronic and zero-point energies: –968.289148 Hartrees
Sum of electronic and thermal free energies: –968.265562 Hartrees



2

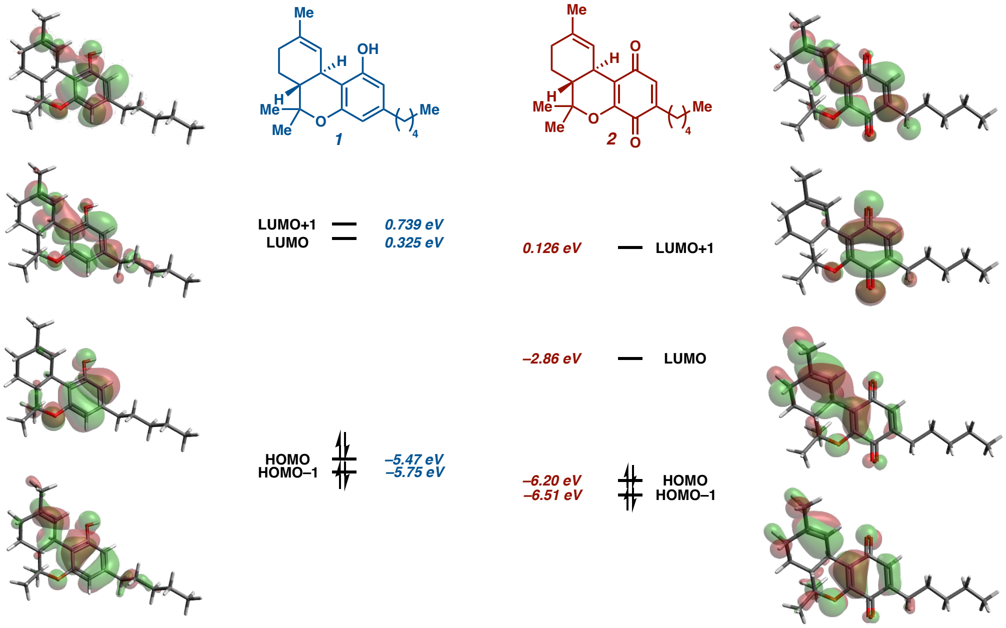
C	3.00972	0.03848	-0.56927
C	1.57238	0.29496	-0.1893
C	0.73289	-0.69926	0.21867
C	1.2968	-2.0365	0.47502
C	2.7131	-2.30447	0.08634
C	3.50893	-1.34447	-0.40266
H	3.04866	-3.32515	0.24699
O	0.65369	-2.93729	1.01457
O	1.25081	1.58896	-0.31786
C	-0.72286	-0.38622	0.52117
H	-0.81921	-0.31304	1.61817
C	-1.08851	0.97663	-0.10449
H	-1.04098	0.84413	-1.19592
C	-0.03728	2.05595	0.21584
C	-1.7254	-1.43144	0.05538
C	-2.96677	-1.13255	-0.35045
H	-1.40739	-2.46698	0.10279
C	-3.48758	0.2892	-0.39915
H	-4.47519	0.33487	0.08207
H	-3.66706	0.5648	-1.45091
C	-2.54239	1.31345	0.25247
H	-2.81348	2.32239	-0.07769
H	-2.66693	1.29073	1.34325
C	0.15933	2.32881	1.71151
H	0.93296	3.08988	1.85306
H	-0.77013	2.69588	2.15969
H	0.46659	1.4287	2.25175
C	-0.28181	3.3582	-0.54706
H	-0.4538	3.16192	-1.61036
H	-1.14756	3.89103	-0.14328
H	0.59417	4.00751	-0.45612
C	-3.93384	-2.19984	-0.79616
H	-4.83186	-2.2132	-0.16251
H	-4.28084	-2.01635	-1.82315
H	-3.48102	-3.19548	-0.76404
O	3.72412	0.93396	-0.99101
C	4.97625	-1.58246	-0.80508
H	5.10854	-1.33061	-1.83657
H	5.61489	-0.96986	-0.20361
C	5.33399	-3.0646	-0.58859

H	5.20774	-3.31483	0.44406
H	4.69117	-3.6775	-1.18526
C	6.79863	-3.30448	-0.99955
H	7.44136	-2.69066	-0.40372
H	6.9246	-3.05544	-2.03251
C	7.15691	-4.78625	-0.78137
H	6.51814	-5.39978	-1.38176
H	7.02519	-5.03685	0.2505
C	8.6241	-5.02432	-1.18421
H	8.87251	-6.05423	-1.0343
H	8.75622	-4.77203	-2.21561
H	9.26298	-4.41211	-0.5826

SCF Energy: –1042.75671785 Hartrees
Zero-point correction: 0.475526 Hartrees
Thermal correction to enthalpy: 0.476470 Hartrees
Thermal correction to Gibbs free energy: 0.397421 Hartrees
Sum of electronic and zero-point energies: –1042.305430 Hartrees
Sum of electronic and thermal free energies: –1042.281192 Hartrees

Orbital Density Maps and Energies.

Figure S8: TDDFT photophysical manifolds and orbital density maps for Δ^9-THC (**1**) and Δ^9-THCQ (**2**). B3LYP/6-31G(d).



TDDFT Transitions.

Table S6: Major electronic transitions for Δ^9-THC (**1**) (B3LYP/6-31G(d)).

Energy (cm^{-1})	Wavelength (nm)	Osc. Strength	Major Contributions
39846.2085	250.964907	0.014	H-1->L+1 (22%), HOMO->LUMO (71%)
44591.1682	224.259655	0.0278	H-1->LUMO (68%), HOMO->L+1 (23%)
46396.237	215.534721	0.0078	H-2->LUMO (71%), HOMO->L+1 (12%), HOMO->L+2 (11%)
47045.5133	212.560121	0.0609	H-2->LUMO (19%), HOMO->L+2 (64%)
48209.3713	207.42855	0.0495	H-1->L+2 (59%), HOMO->L+1 (19%)
49265.9576	202.979917	0.1031	H-2->L+1 (62%), H-1->L+1 (23%)
50602.4183	197.619014	0.6879	H-1->LUMO (13%), H-1->L+2 (29%), HOMO->L+1 (36%)
51980.0133	192.381636	0.0535	HOMO->L+3 (74%)
52259.8877	191.351349	0.2964	H-2->L+1 (23%), H-1->L+1 (31%), HOMO->LUMO (13%), HOMO->L+3 (14%)
54969.104	181.920375	0.0012	H-1->L+3 (87%), HOMO->L+3 (10%)
56203.1323	177.926026	0.2766	H-3->LUMO (11%), H-2->L+2 (73%)
57763.8151	173.118759	0.006	HOMO->L+4 (82%)

Table S7: Major electronic transitions for Δ^9-THCQ (**2**) (B3LYP/6-31G(d)).

Energy (cm^{-1})	Wavelength (nm)	Osc. Strength	Major Contributions
20966.38238	476.9540027	0.0019	H-2->LUMO (67%), HOMO->LUMO (22%)
21471.28545	465.7383006	0.0036	H-2->LUMO (27%), HOMO->LUMO (66%)
23804.64742	420.0860372	0.0088	H-3->LUMO (39%), H-1->LUMO (55%)
24085.32836	415.1905198	0.002	H-3->LUMO (49%), H-1->LUMO (38%)
36382.86374	274.8546698	0.1396	H-4->LUMO (81%)
37028.10728	270.0651136	0.0156	H-5->LUMO (93%)
40166.41056	248.964243	0.0102	H-6->LUMO (86%)
42503.8053	235.2730521	0.0083	H-7->LUMO (90%)
43123.2391	231.8935268	0.0145	H-9->LUMO (89%)

References:

[1] More, N. Y.; Jeganmohan, M. Solvent-contrilled selective synthesis of biphenols and quinones via oxidative coupling of phenols. *Chem. Commun.* **2017**, *53*, 9616–9619.

[2] Hanuš, L. O.; Meyer, S. M.; Muñoz, E.; Taglialatela-Scafati, O.; Appendino, G. Phytocannabinoids: a unified critical inventory. *Nat. Prod. Rep.* **2016**, *33*, 1357–1448.

[3] Hazekamp, A.; Peltenburg, A.; Verpoorte, R.; Giroud, C. Chromatographic and spectroscopic data of cannabinoids from *Cannabis sativa* L. *J. Liq. Chromatogr. Relat. Technol.* **2005**, *28*, 2361–2382.

[4] M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G. A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H. P. Hratchian, A. F. Izmaylov, J. Bloino, G. Zheng, J. L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, J. A. Montgomery Jr., J. E. Peralta, F. Ogliaro, M. Bearpark, J. J. Heyd, E. Brothers, K. N Kudin, V. N. Staroverov, T. Keith, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, N. Rega, J. M. Millam, M. Klene, J. E. Knox, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, R. L. Martin, K. Morokuma, V. G. Zakrzewski, G. A. Voth, P. Salvador, J. J. Dannenberg, S. Dapprich, A. D. Daniels, O. Farkas, J. B. Foresman, J. V. Ortiz, J. Cioslowski, D. J. Fox. Gaussian 09, Rev. D.01; Gaussian, Inc., Wallingford, CT (2010).