Supporting Information

Structural Revision of a Wnt/β-catenin Modulator and Confirmation of Cannabielsoin Constitution and Configuration

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1. General Experimental Details.

Liquid chromatography was performed using a CombiFlash™ NextGen 300+ instrument for forced flow (flash chromatography) on silica gel cartridges (RediSep™ Rf) purchased from Teledyne Isco. Thin layer chromatography (TLC) was performed on EMD Chemicals 0.25 mm silica gel 60 plates. Visualization was achieved using UV light (254 nm) or basic potassium permanganate in water followed by heating. All reactions were conducted in oven or flame-dried glassware under an inert atmosphere of argon. Solvents were used as fresh ACS grade or Acros anhydrous over 4Å molecular sieves. Cannabidiol (~85% CBD) was donated by PureElix, Inc. and purified to >95% purity via silica gel chromatography.

2. Experimental for synthesis of CBE (**7**) using Oxone™ conditions described in reference 1 and alternate synthesis of CBE (**7**) from CBD diacetate (**10**).

CBE (**7**) from Oxone™.

A dry 2-dram vial was charged with 62.9 mg (0.2 mmol) of cannabidiol (**2**, >95% CBD) and a Teflon stir bar. Acetone (0.6 mL) was added, followed by 184 mg (0.6 mmol) of Oxone™. The reaction was stirred for 48 hours under argon. TLC indicated that some CBD remained even after this time frame. The suspension was filtered with additional acetone wash, and the resulting solution was concentrated to dryness. The mixture was purified by silica gel chromatography ramping from 0-40% ethyl acetate in hexanes over 10 minutes to give 16.0 mg (24% yield) of cannabielsoin (**7**, CBE) as a yellow film. HRMS–ESI (m/z): [M]+ calculated for $C_{21}H_{31}O_2$, 331.2273; found, 331.2265 (-2.4 ppm).

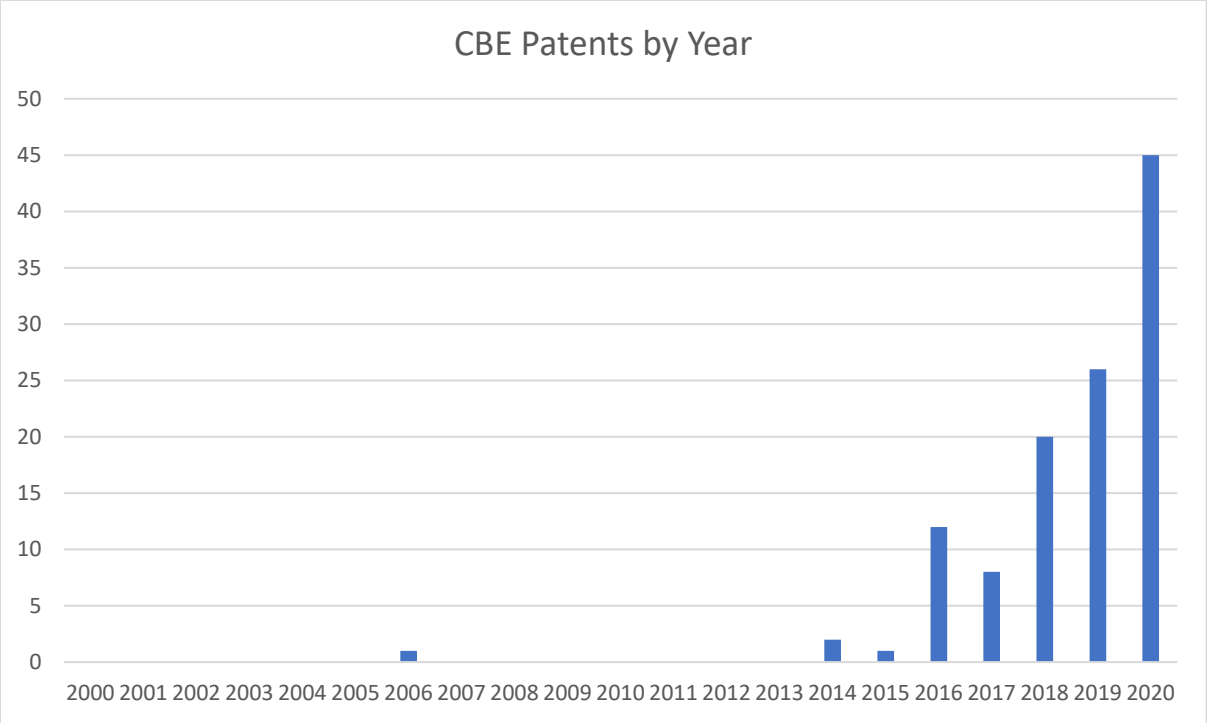
CBD diacetate (**10**).

A flame-dried 50 mL round bottom equipped with a Teflon stir bar was charged with 1.57 g of cannabidiol (**2**, ~85% CBD). Pyridine (5 mL) and acetic anhydride (5 mL) were added, and the solution was stirred under argon at room temperature for 48 hours. (Note: the product and starting material coelute on TLC in hexanes/ethyl acetate but separate in hexanes/acetone). The reaction mixture was transferred to a separatory funnel with 100 mL of MTBE. The solution was sequentially washed 2 x 50 mL of 1 M HCl, 25 mL of sat. $NaHCO_3$, and 25 mL of brine. After drying over $MgSO_4$, the suspension was filtered and concentrated. The crude oil was purified by silica gel chromatography ramping from 0-10% acetone in hexanes over 10 minutes to give 1.21 g (66% yield) of CBD diacetate (**10**) as a clear oil. NMR spectral data was consistent with a published report.[2]

CBE (**7**) from CBD diacetate (**10**).

A dry 2-dram vial was charged with 39.8 mg (0.1 mmol) of CBD diacetate (**10**) and a Teflon stir bar. Potassium bicarbonate (30.0 mg, 0.3 mmol) was added, followed by 0.4 mL of ethanol to form a suspension under argon. Benzonitrile (31 μL, 0.3 mmol) and 30% hydrogen peroxide (30 μL, 0.3 mmol) were added sequentially by syringe. The reaction was stirred for 40 hours under argon. After this time, multiple spots were observed by TLC, including CBE. An aqueous solution of 1M NaOH 0.5 mL was added and stirring was continued for 1 hour. The suspension had turned a deep purple color that dissipated upon quenching with 1 mL of 2M HCl. The aqueous mixture was extracted with 2 x 2 mL of ethyl acetate. The combined organic layer was washed with 2 mL saturated $NaHCO_3$, dried over $MgSO_4$, filtered, and concentrated. The mixture was purified by silica gel chromatography ramping from 0-25% ethyl acetate in hexanes over 10 minutes to give 19.4 mg (59% yield) of CBE (**7**) as a clear film.

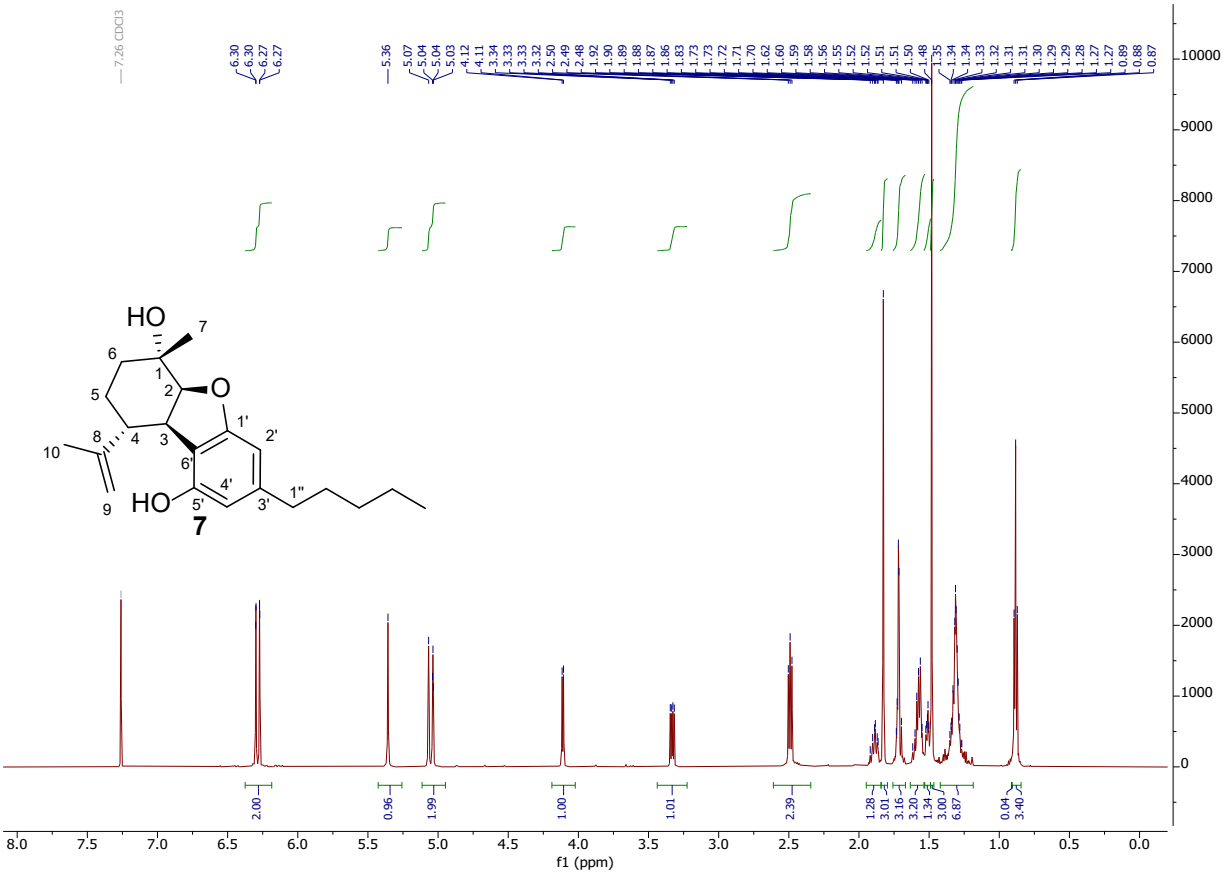
3. Graph of US Patents related to CBE by year.



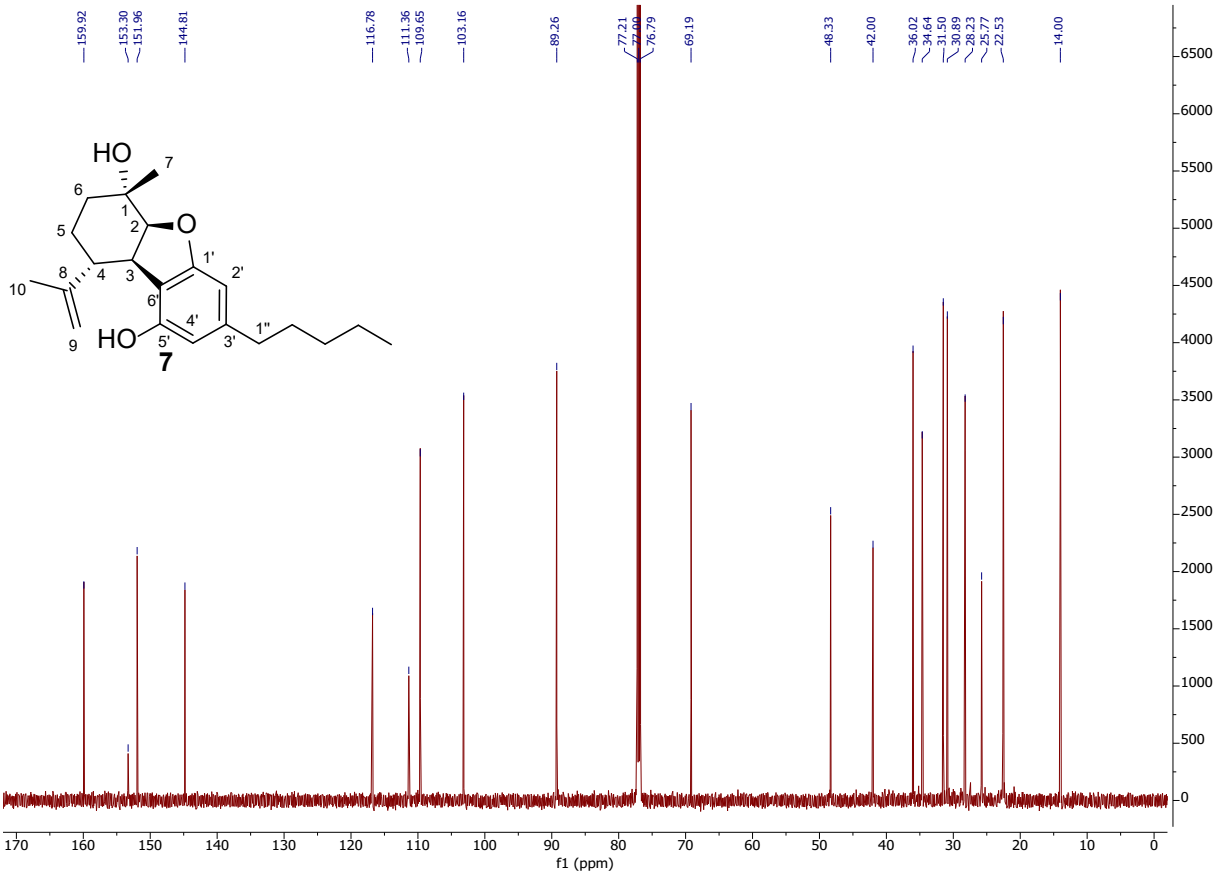
4. General Experimental Details for NMR spectroscopy acquired in this work**.**

NMR data were acquired on a 600 MHz Bruker AVANCE III spectrometer with a 5 mm BBFO probe. NMR chemical shifts were reported in ppm and referenced to residual solvent peaks (^{1}H and ^{13}C NMR in $CDCl_3$ were referenced to 7.26 ppm and 77.0 ppm, respectively).

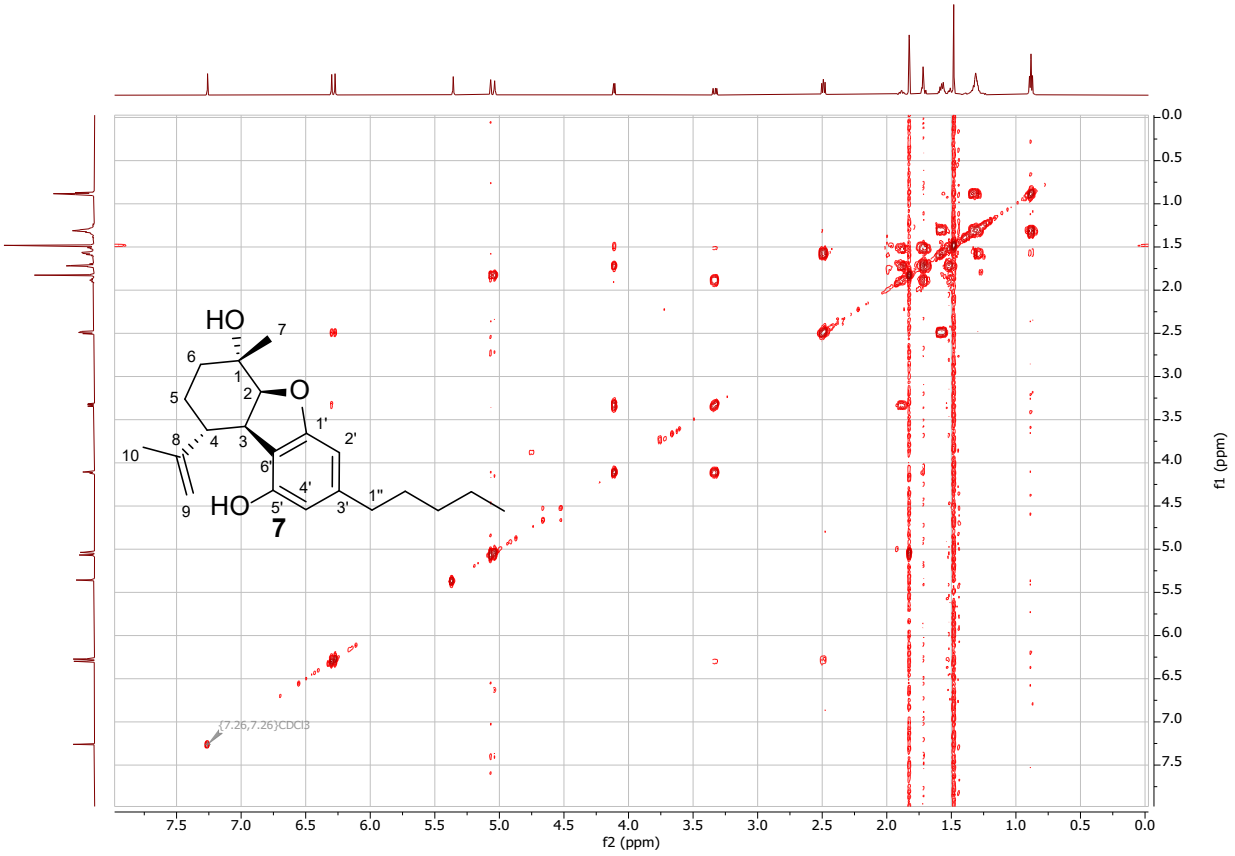
5. 1D ^{1}H NMR data (600.1 MHz) for CBE (**7**) in $CDCl_3$



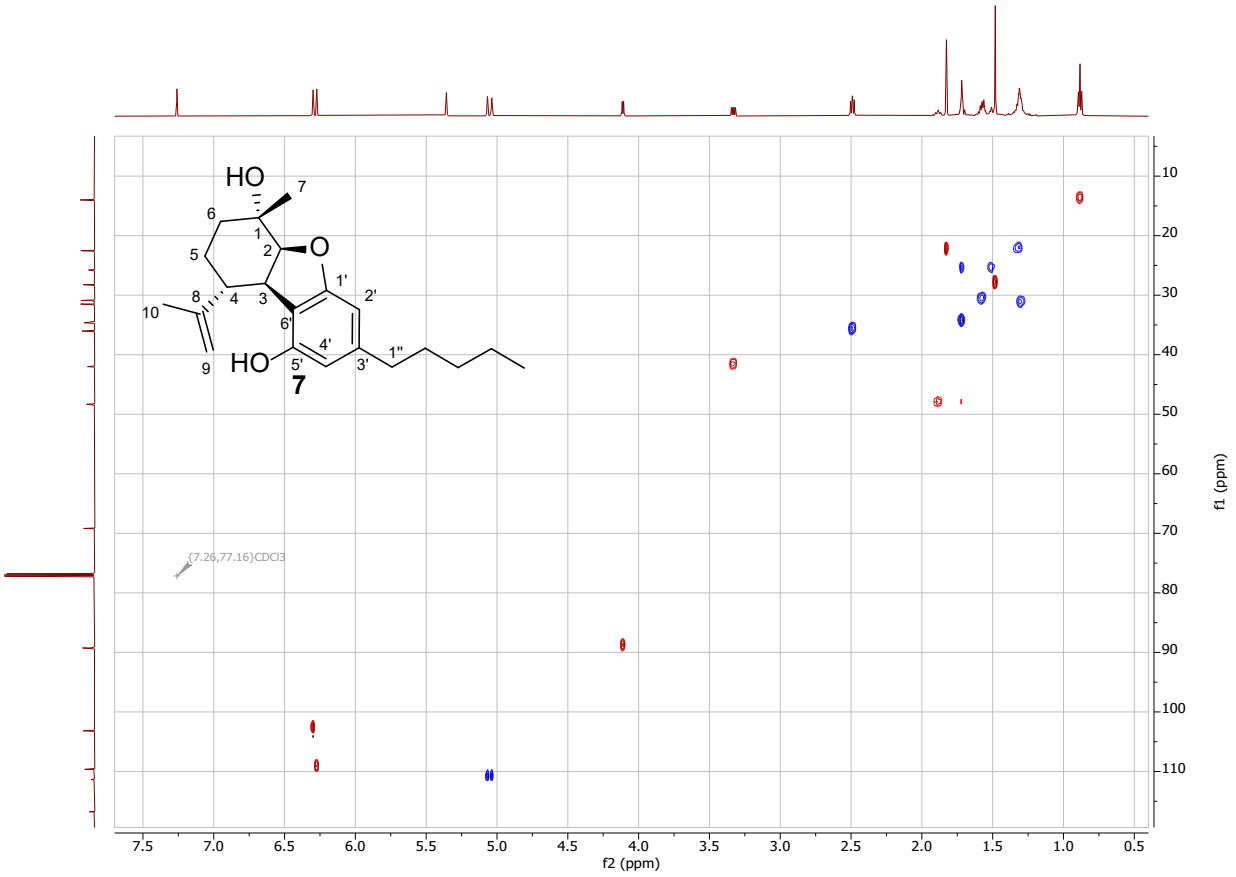
6. 1D ^{13}C NMR data (150.9 MHz) for CBE (**7**) in $CDCl_3$.



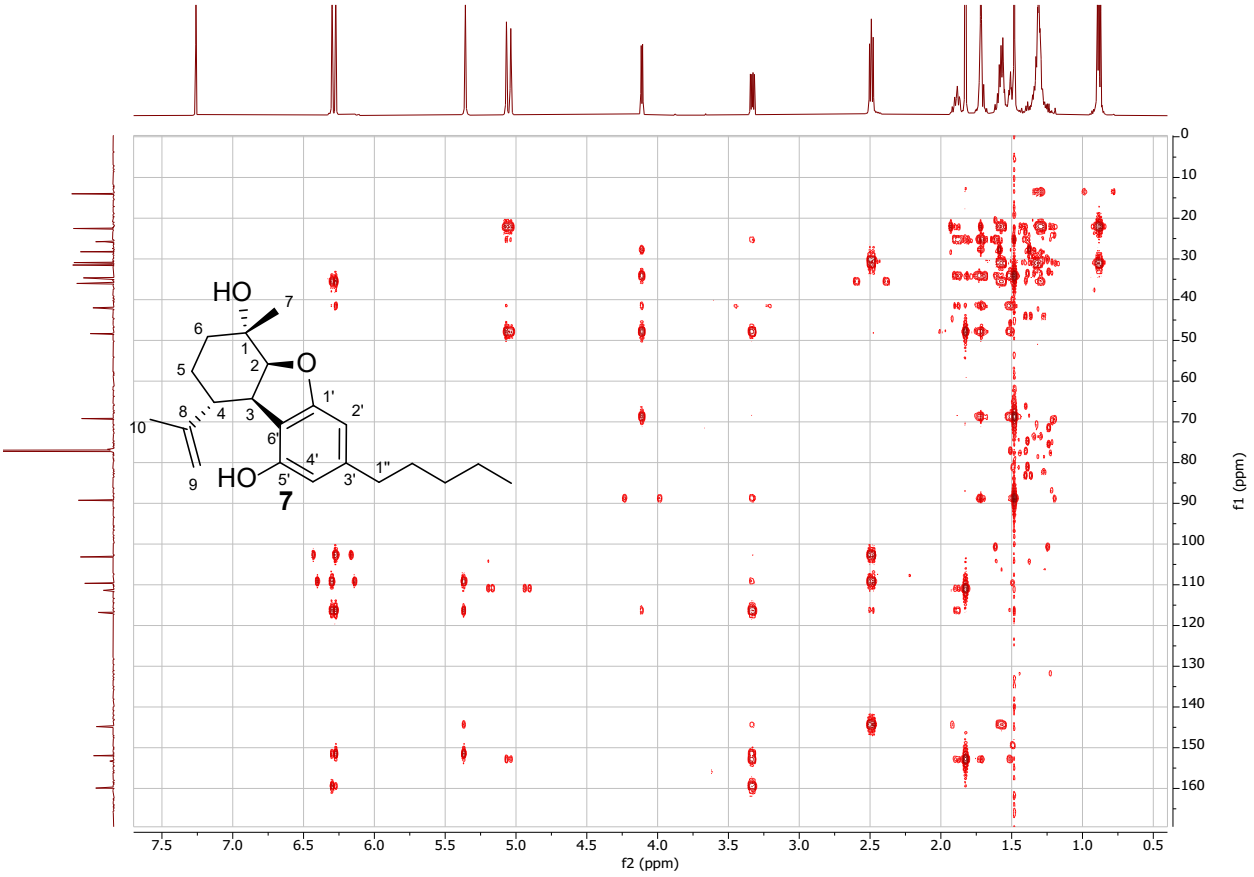
7. ^{1}H-^{1}H COSY data (600.1 MHz) for CBE (**7**).



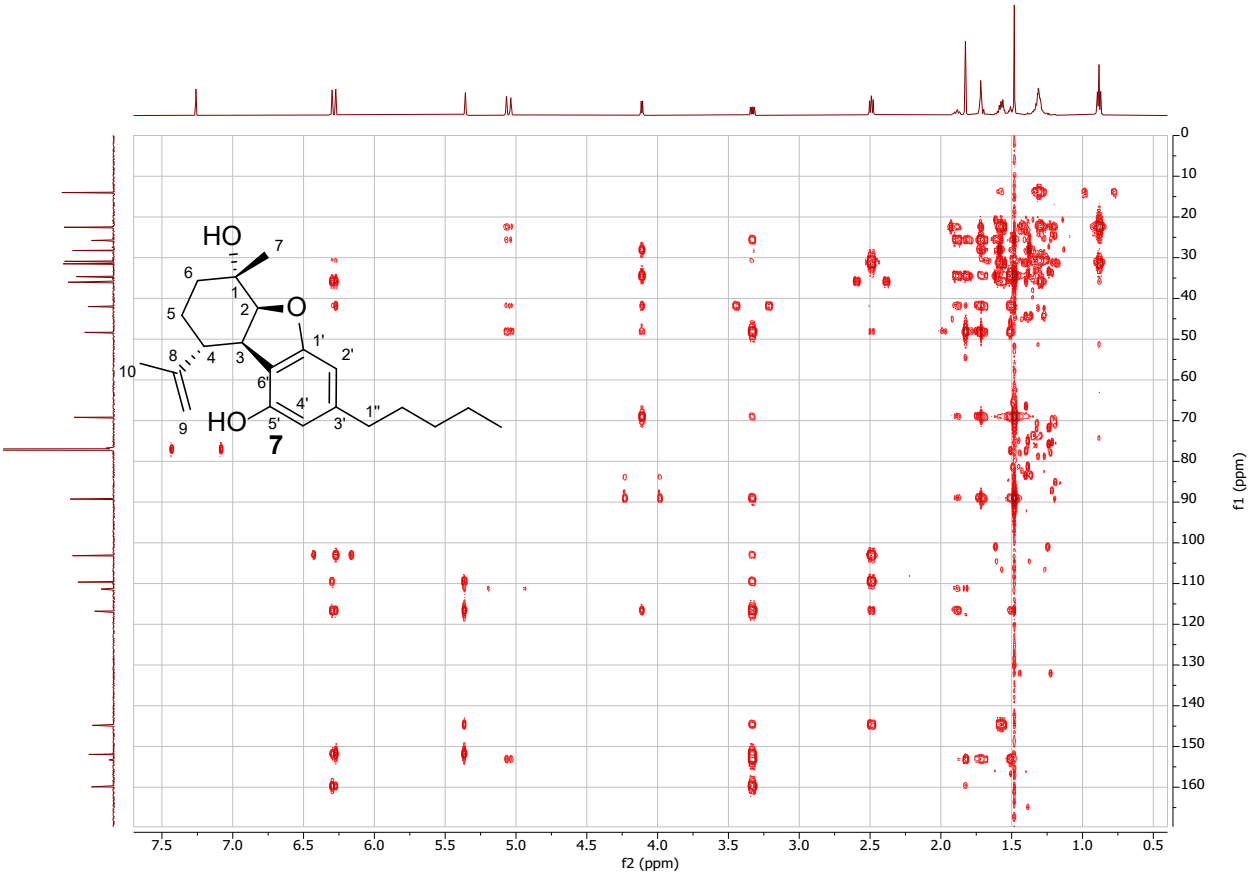
8. ^{1}H-^{13}C Multiplicity-edited HSQC (600.1 MHz) data for CBE (**7**).



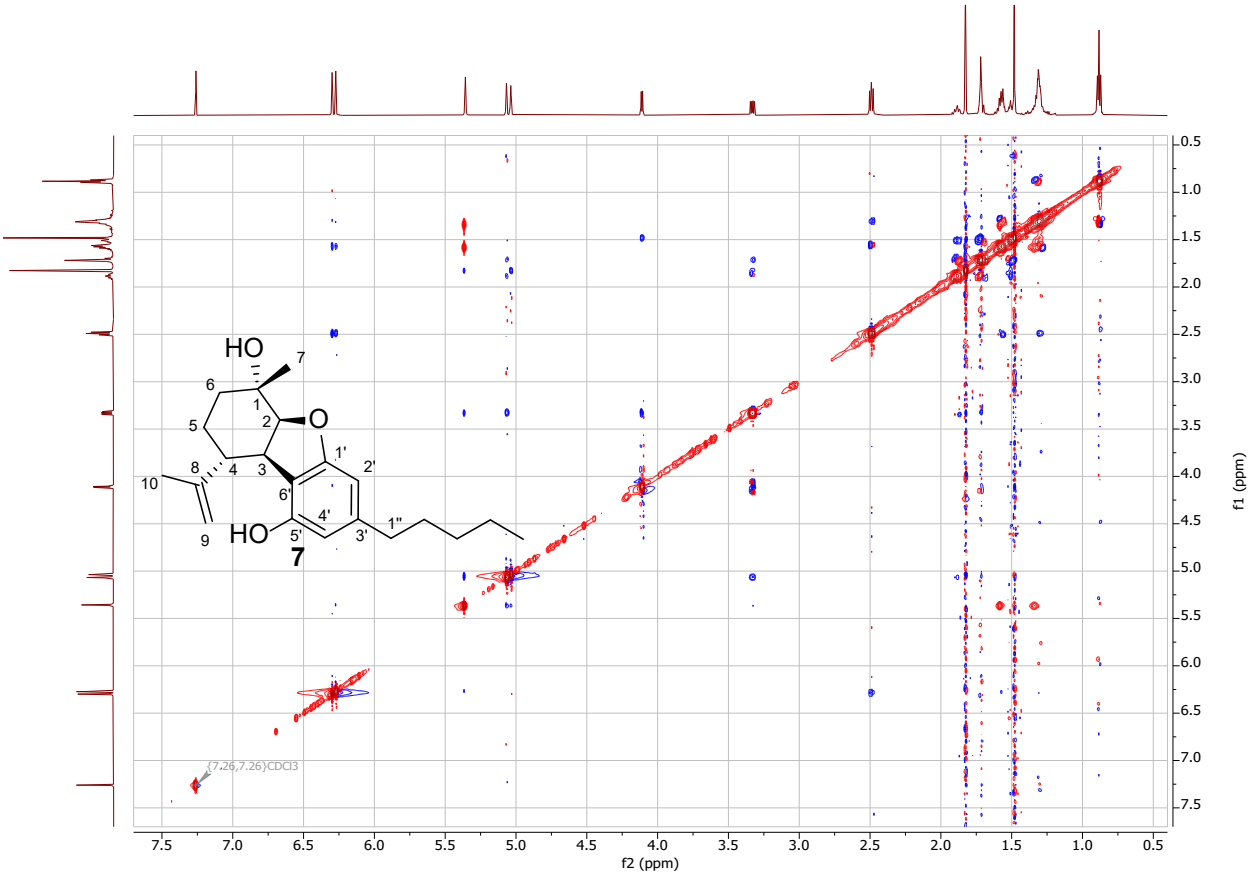
9. 8 Hz Optimized ^{1}H-^{13}C HMBC data (600.1 MHz) for CBE (**7**).



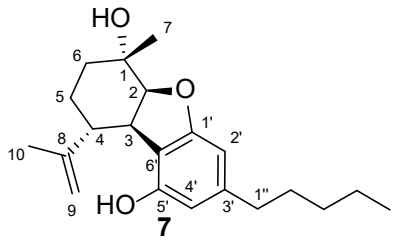
10. 3 Hz Optimized ^{1}H-^{13}C HMBC data (600.1 MHz) for CBE (**7**).



11. ^{1}H-^{1}H ROESY data (600.1 MHz, 300 ms) for CBE (**7**).



12. Table of NMR assignments for CBE (**7**).

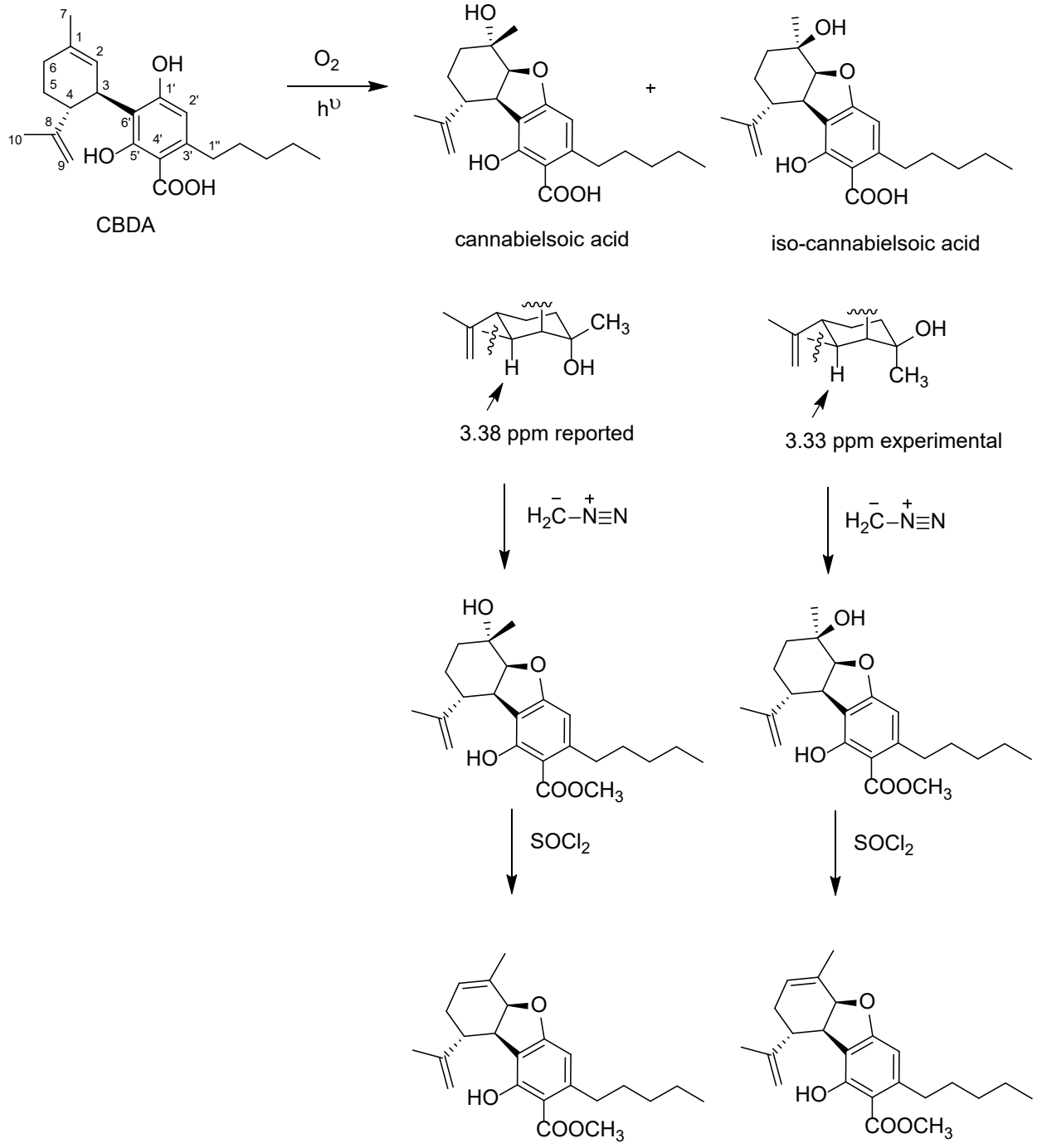


7

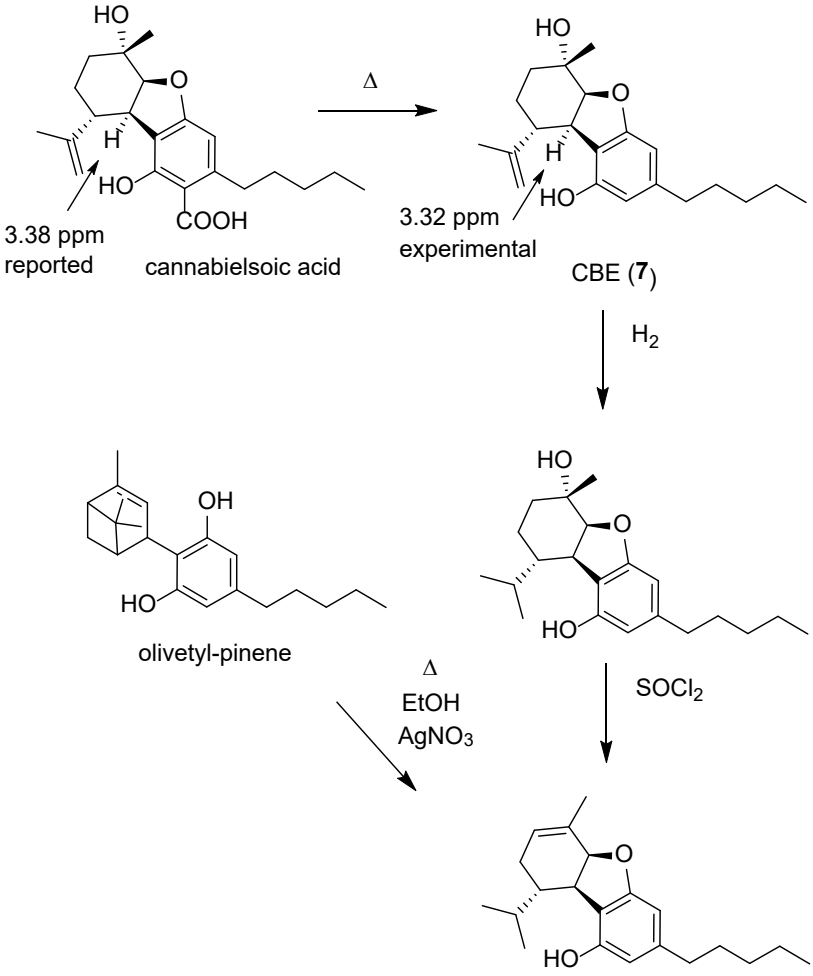
Carbon #	^{1}H δ, ppm, multiplicity (Hz)	^{13}C δ, multiplicity	HMBC Correlations
1		69.3 C	
2	4.11 d (5.9)	89.3 CH	C1, C3, C4, C6, C7, C1', (C1 in 3 Hz HMBC)
3	3.33, dd (11.1, 5.9)	42.1 CH	C2, C5, C6, C8, C1', C2', C3', C5', C6', (C2" in 3 Hz HMBC)
4	1.92-1.86 m[c]	48.2	C3, C5, C6, C8, C9, C10, C6'
5	1.76-1.66 m[c]	25.8 CH_2	C3, C4, C6
	1.54-1.48 m		
6	1.76-1.66 m[c]	34.6 CH_2	C2, C3, C5, C6
7	1.48 s	28.2 CH_3	C6, C8, C9
8		153.0 C	
9	5.07, s 5.04, t 1.6	111.4 CH_2	C6, C8, C10
10	1.83 s	22.5 CH_3	C6, C8, C9
1'		160.1	
2'	6.30 s	103.2 CH	C1', C2', C5', C1" (C1, C6' in 3 Hz HMBC)
3'		144.8 C	
4'	6.27 s	109.7 CH	C1, C1', C2', C6', C1", (C2' in 3Hz HMBC)
5'		152.0 C	
6'		116.8 C	
1"	2.49 t (8.0)	36.0 CH_2	C3', C5', C2", C3"
2"	1.61-1.55 m	30.9 CH_2	C3', C3", C4", C1"
3"	1.35-1.26 m[d]	31.5 CH_2	C1", C2", C4", C5"
4"	1.35-1.26 m[d]	22.6 CH_2	C1", C2", C4", C5"
5"	0.88 t (6.8)	14.0 CH_3	C3", C4"
OH	5.40 bs		C1', C6', C5'

13. Summary of stereochemical assignment reported in reference 3.

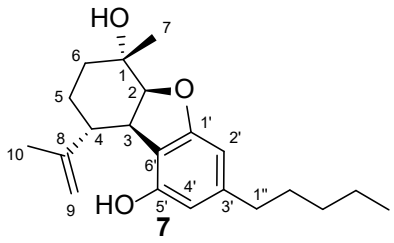
a.



b.


HO
O
H
HO
COOH
3.38 ppm
reported
cannabielsoic acid
Δ
HO
O
H
HO
3.32 ppm
experimental
CBE (7)
H2
OH
HO
olivetyl-pinene
HO
O
HO
Δ
EtOH
AgNO3
SOCl2
O
HO

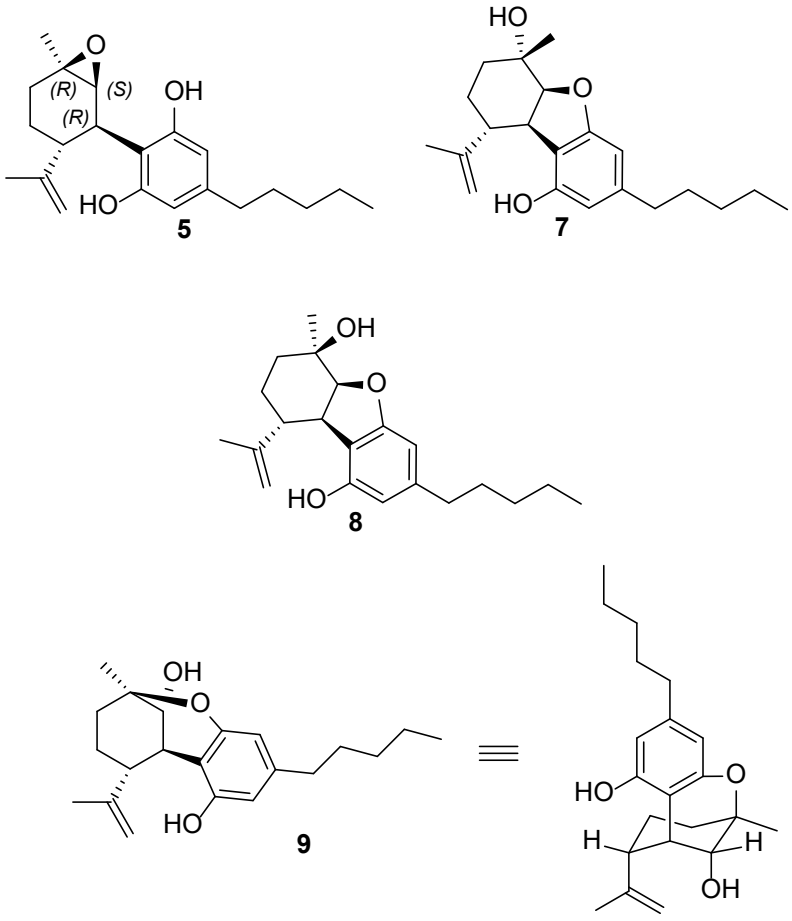
14. Comparison of actual CBE (**7**) NMR chemical shifts to those reported for the Oxone™ oxidation in reference 1.



7

Position	CBE (7) δ_H multiplicity (*J*)	Reference 1	CBE (7) δ_C multiplicity	Reference 1
1			69.3 C	69.3 C
2	4.11 d (5.9)	4.10 d (5.9)	89.3 CH	89.4 CH
3	3.33, dd (11.1, 5.9)	3.32 dd (10.9, 5.9)	42.1 CH	42.1 CH
4	1.92-1.86 m	1.92 – 1.84 m	48.2 CH_2	48.5 CH_2
5	1.76-1.66 m	1.76-1.66 m	25.8 CH_2	25.9 CH_2
	1.54-1.48 m	1.54-1.48 m		
6	1.76-1.66 m	1.76-1.66 m	34.6 CH_2	34.7 CH_2
7	1.48 s	1.48 s	28.2 CH_3	28.3 CH_3
8			153.0 C	153.2 C
9	5.07, s 5.04, t 1.6	5.03 d (11.1)	111.4 CH_2	111.4 CH_2
10	1.83 s	1.82 s	22.5 CH_3	22.5 CH_3
1'			160.1	160.1
2'	6.30 s	6.29 s	103.2 CH	103.3 CH
3'			144.8 C	144.9 C
4'	6.27 s	6.26 s	109.7 CH	109.7 CH
5'			152.0 C	152.1 C
6'			116.8 C	116.9 C
1"	2.49 t (8.0)	2.48 t (8.0)	36.0 CH_2	36.1 CH_2
2"	1.61-1.55 m	1.61-1.55 m	30.9 CH_2	30.9 CH_2
3"	1.35-1.26 m	1.35-1.26 m	31.5 CH_2	31.6 CH_2
4"	1.35-1.26 m	1.35-1.26 m	22.6 CH_2	22.6 CH_2
5"	0.88 t (6.8)	0.88 t (6.8)	14.0 CH_3	14.1 CH_3
OH	5.40 bs	5.40 bs		

15. Structures of 1*R*,2*S*-CBD epoxide (**5**), CBE (**7**), CBE with an alternate configuration at C1 (**8**) and the 6-membered cyclic ether analog (**9**).



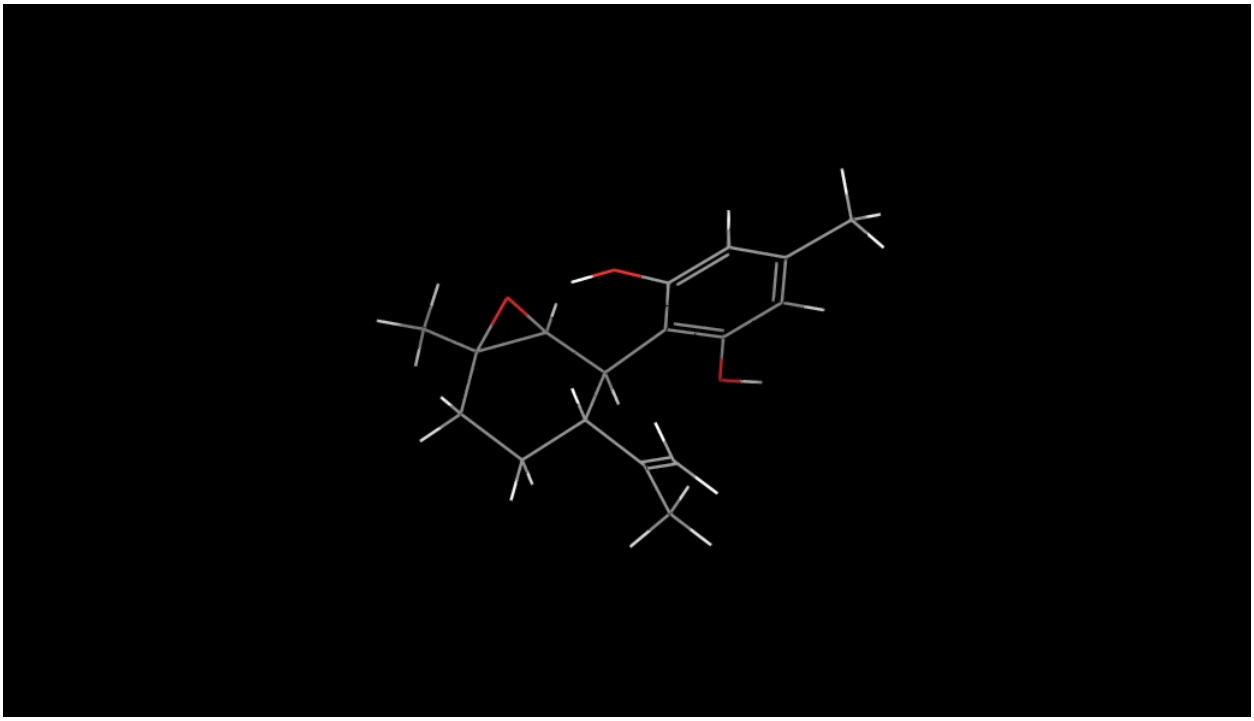
16. Experimental for (**5**), (**7**), (**8**), and (**9**) conformer search and DFT calculation of NMR parameters.

A low mode/torsional conformer search for each structure was performed using the Schrodinger Macromodel software package. A 1,000-step search using the OPLS3e forcefield identified all unique conformers within 5.0 kcal of the global energy minimum. These structures were first subjected to geometry optimization and energy calculations using the Schrodinger Jaguar package at the M06-2X-D3/6-31G(d,p) levels in parallel. Next, the M06-2X-D3/6-31G(d,p) geometry-optimized structure was subjected to GIAO NMR chemical shift calculations at the mPW1PW91/6-311+G(2d,p) level. NMR chemical shifts for the latter calculations were referenced and scaled according to the following reference: Pierens, G. K. *J. Comput. Chem*. **2014**, **35**, 1388-1394.

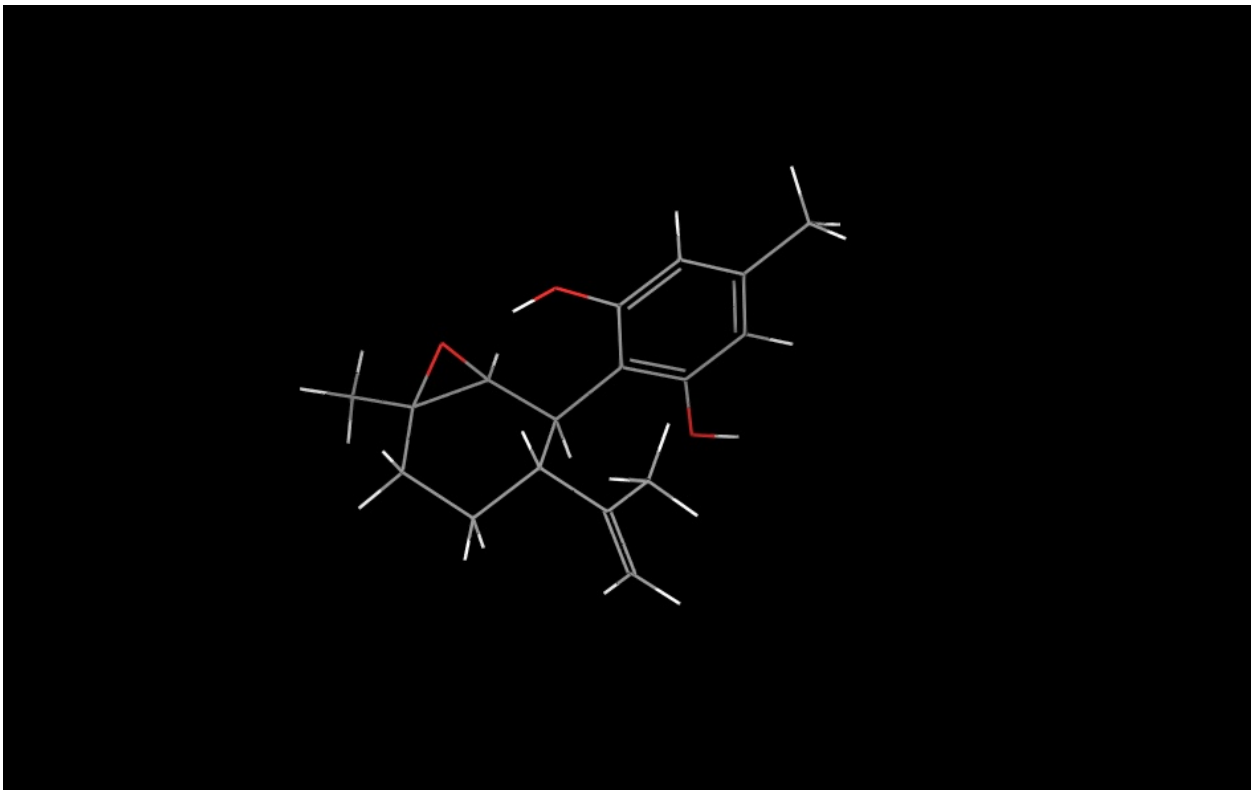
See excerpts from Jaguar and Gaussian output files for additional details in SI-2.

17. Conformations of 1R, 2S-epoxy CBD (**5**) used for calculation of NMR parameters.

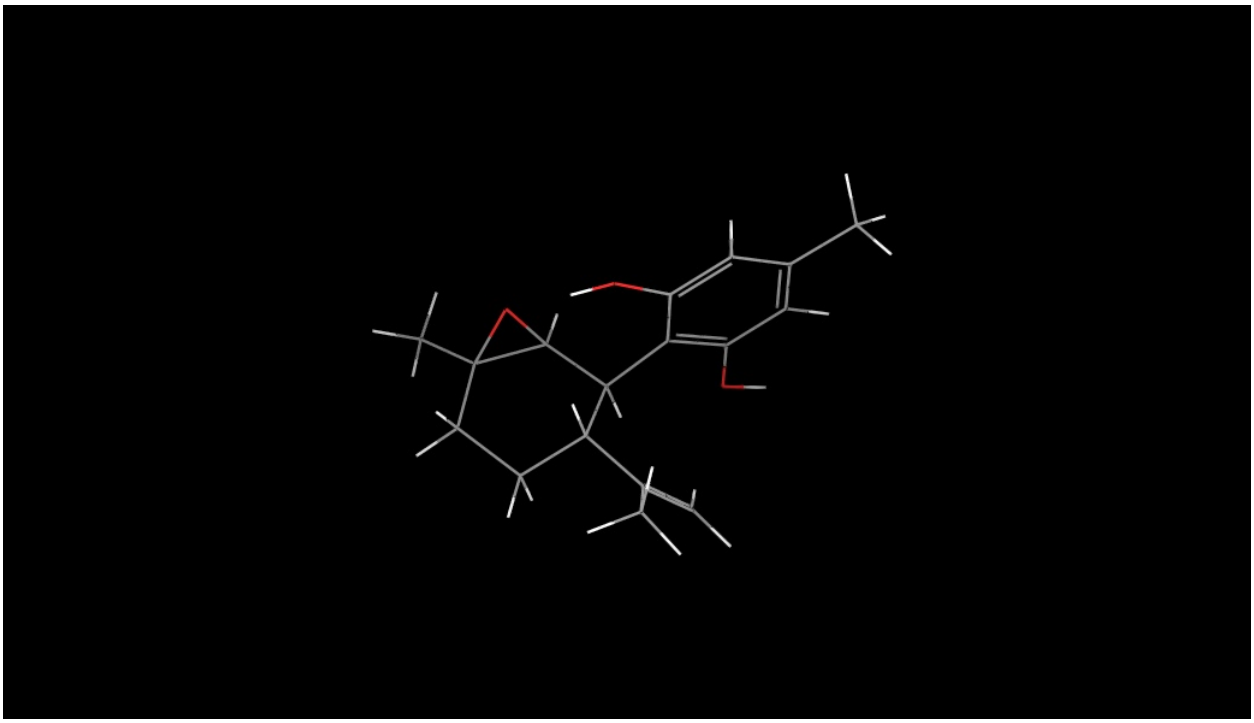
Conformation 1



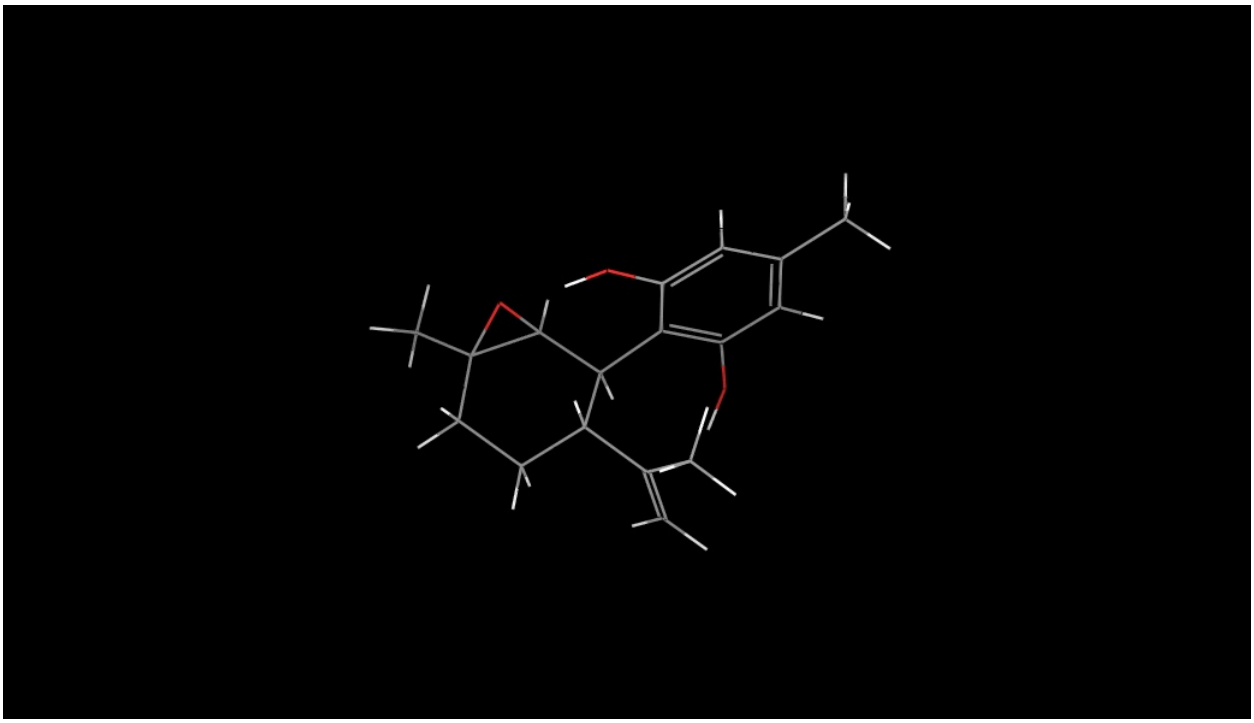
Conformation 2



Conformation 3



Conformation 4

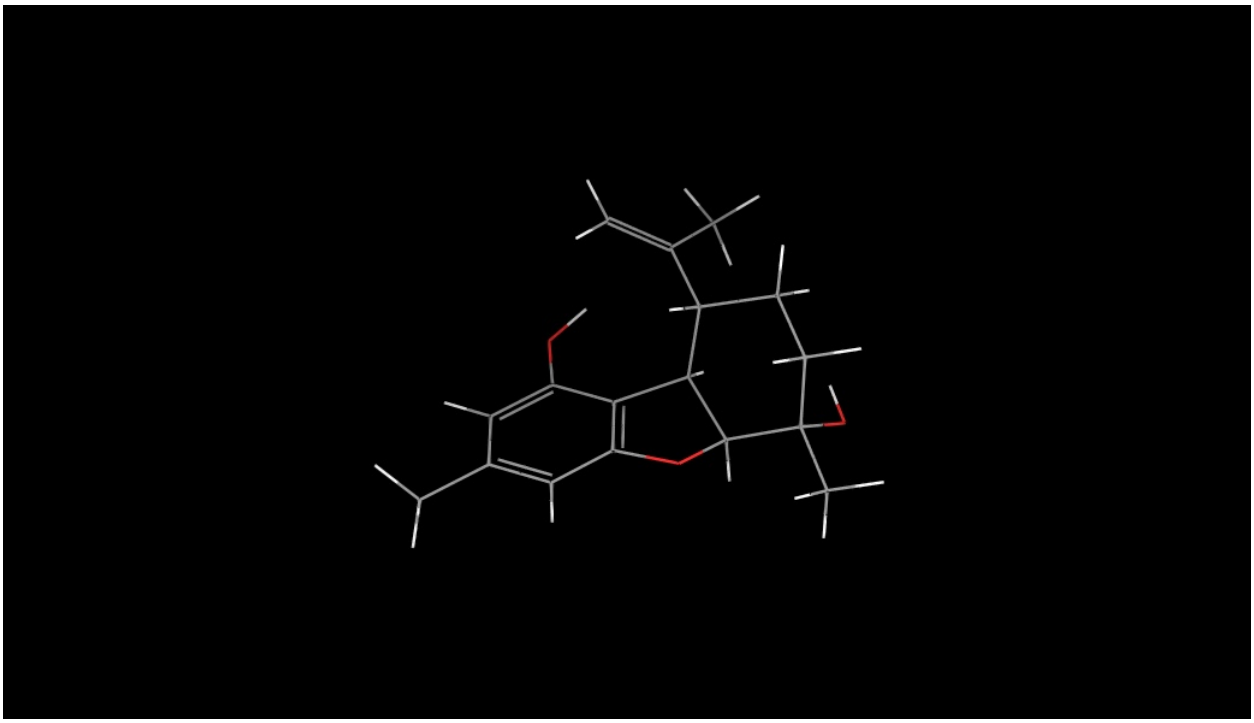


18. Conformations of CBE (**7**) used for calculation of NMR parameters.

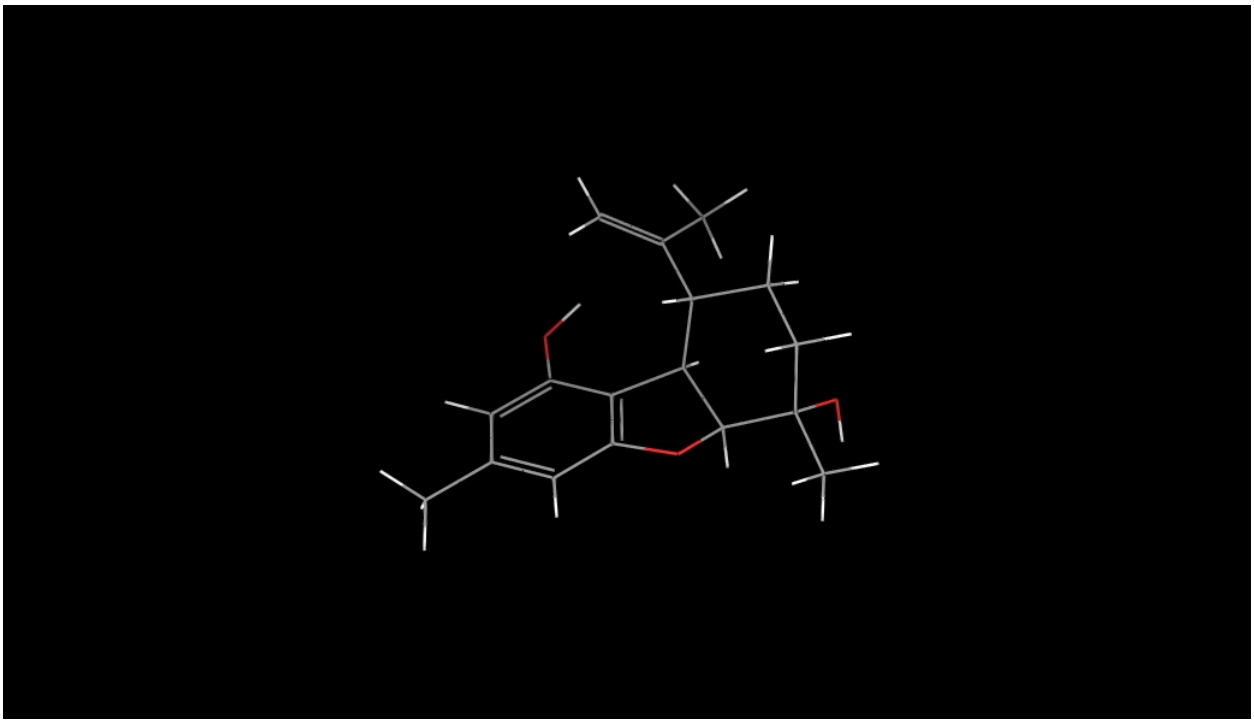
Conformation 1

Conformation 2

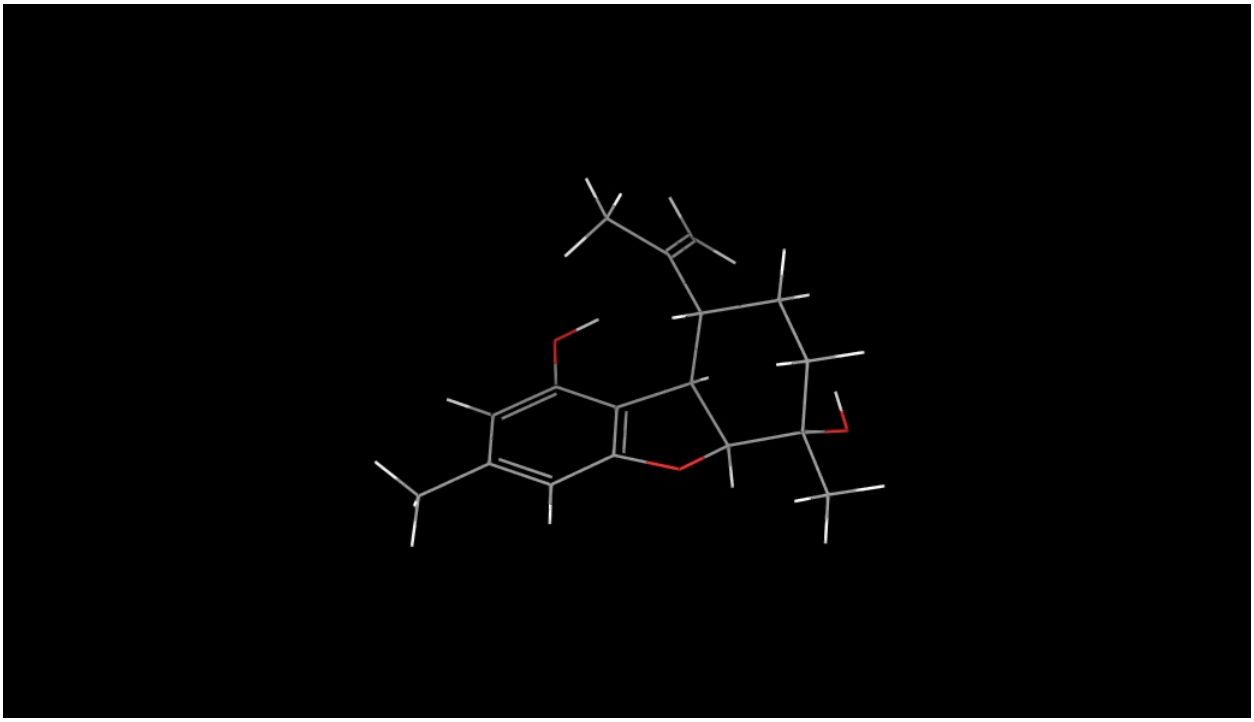
Conformation 3



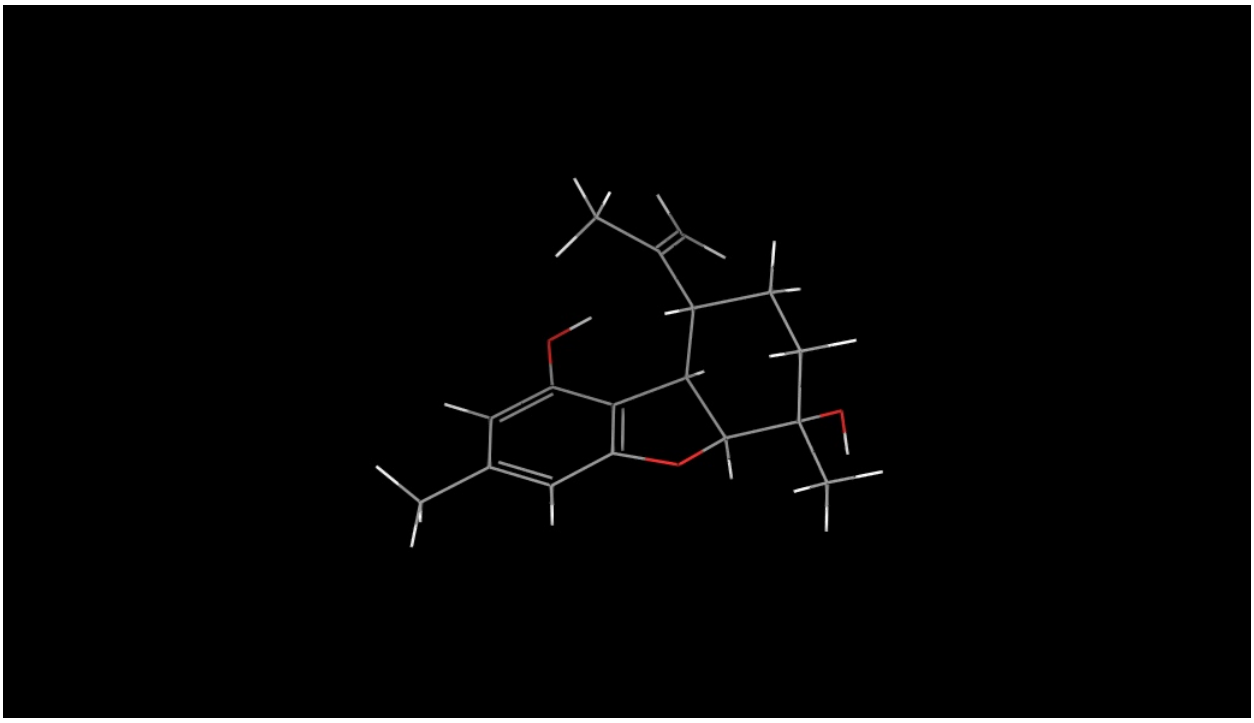
Conformation 4



Conformation 5



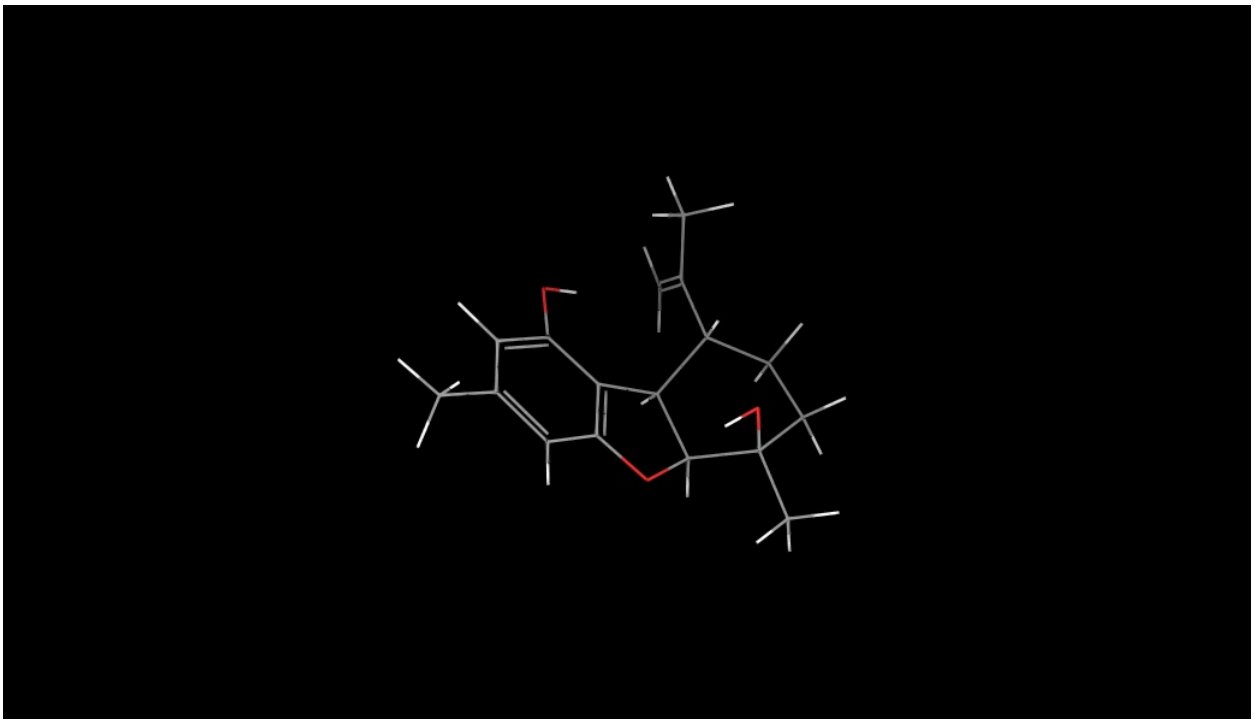
Conformation 6



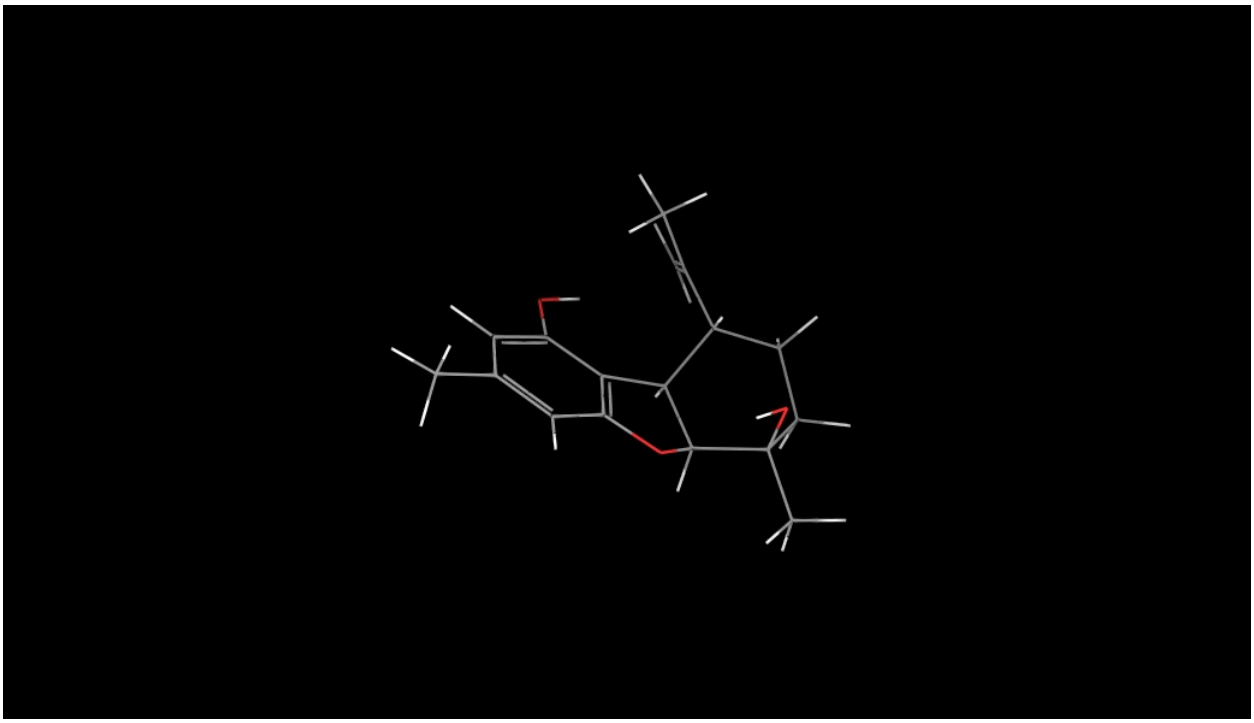
19. Conformations of CBE with alternate configuration at C1 (**8**) used for calculation of NMR parameters.

Conformation 1

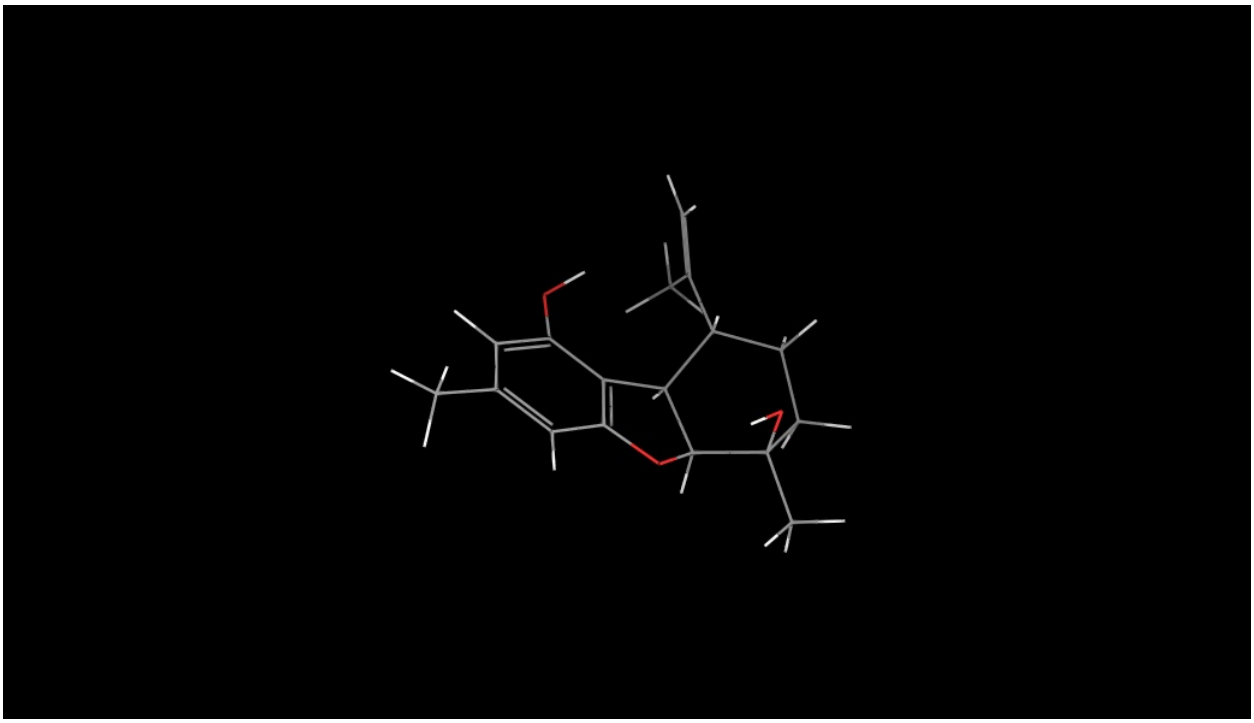
Conformation 2



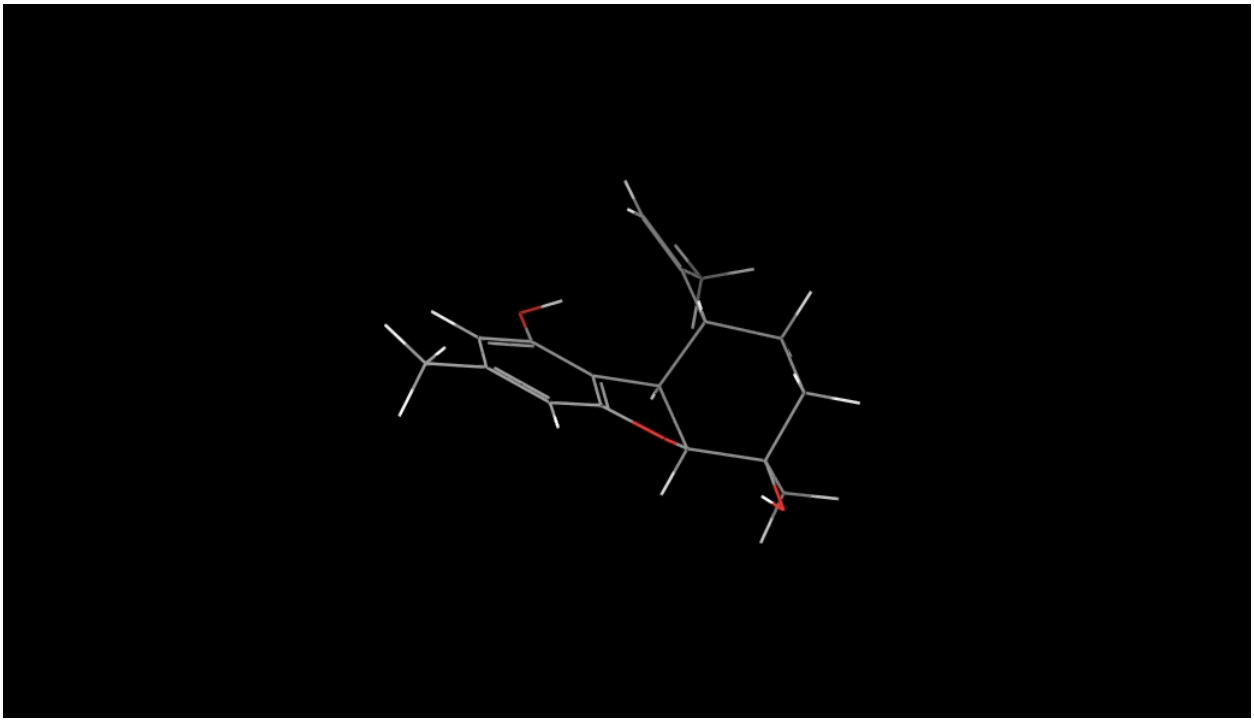
Conformation 3



Conformation 4



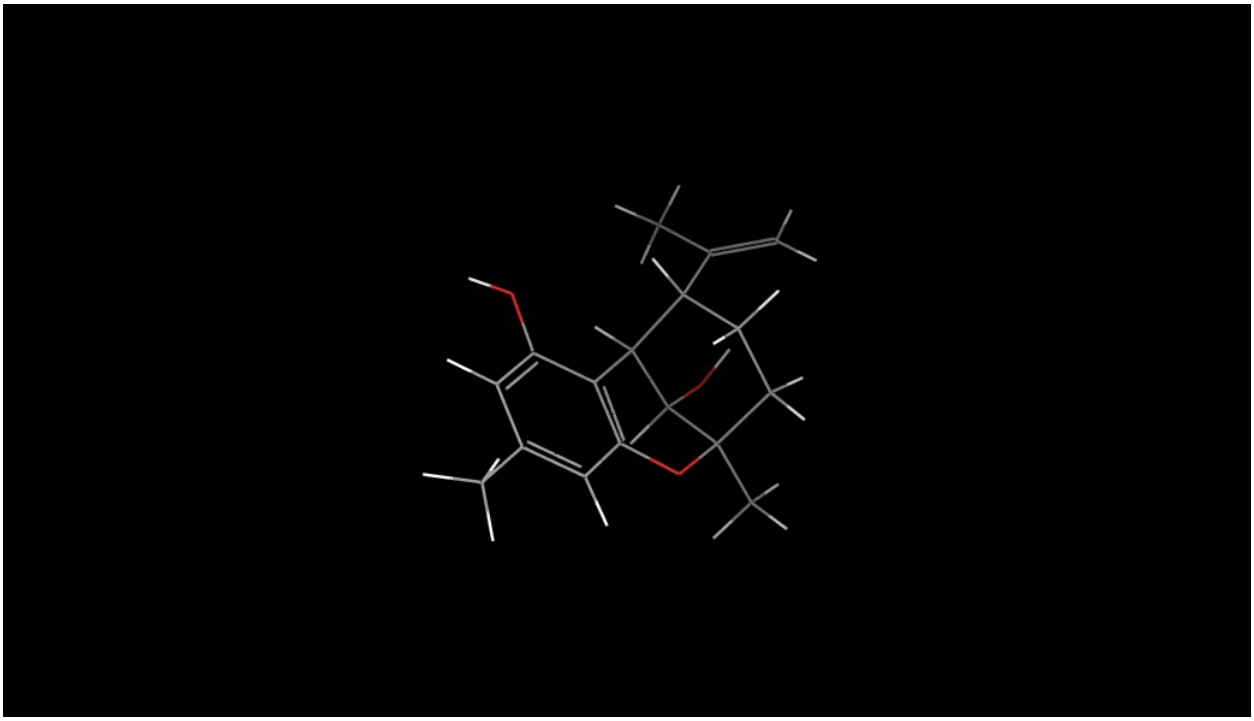
Conformation 5



Conformation 6

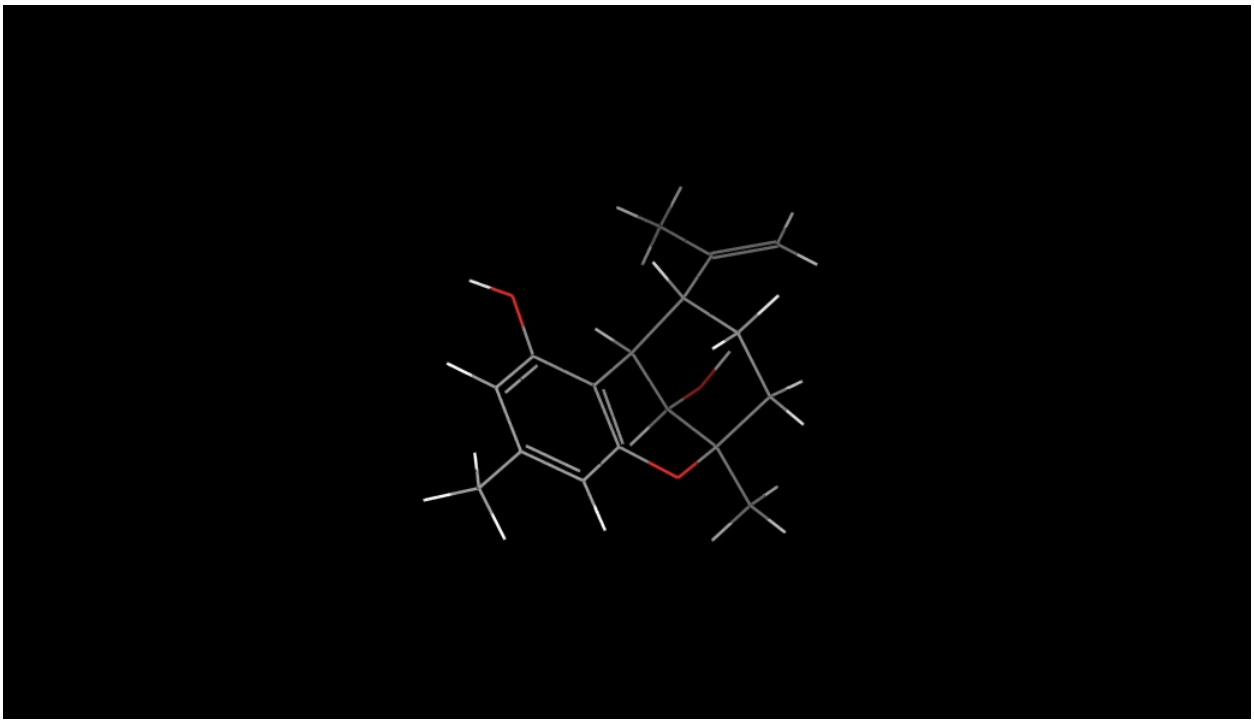
20. Conformations of 6-membered cyclic ether (**9**) used for calculation of NMR parameters.

Conformation 1

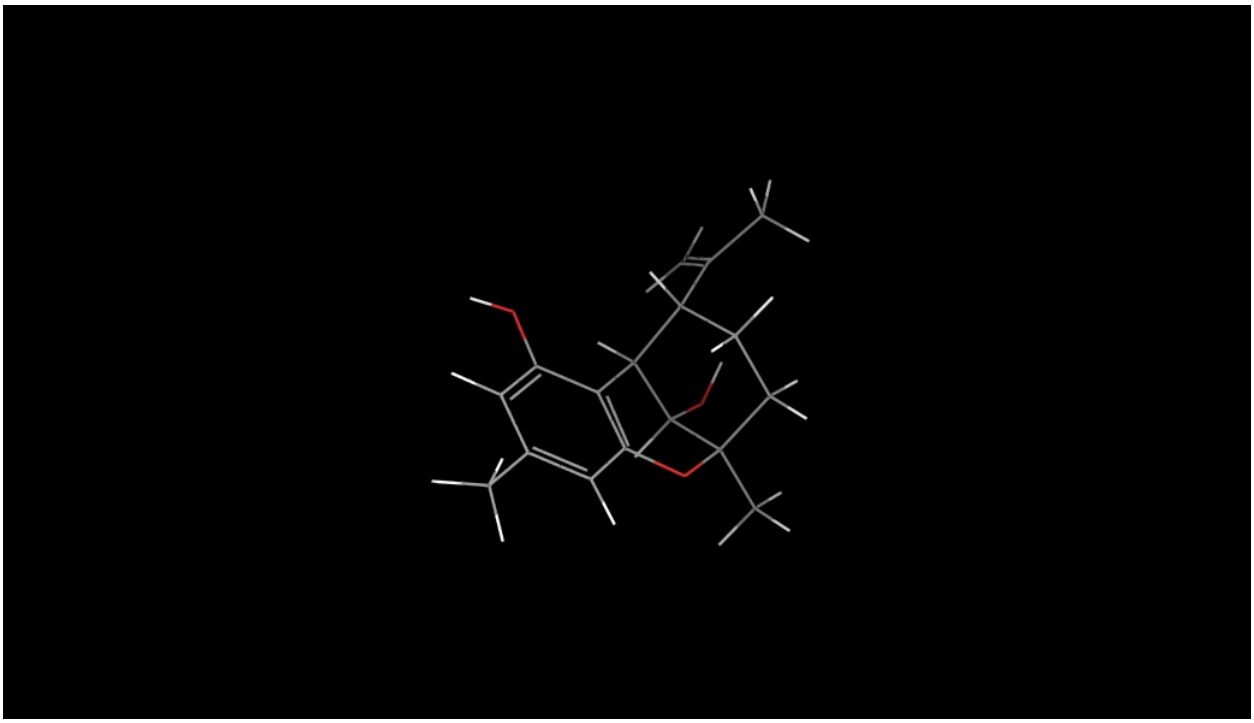


Conformation 2

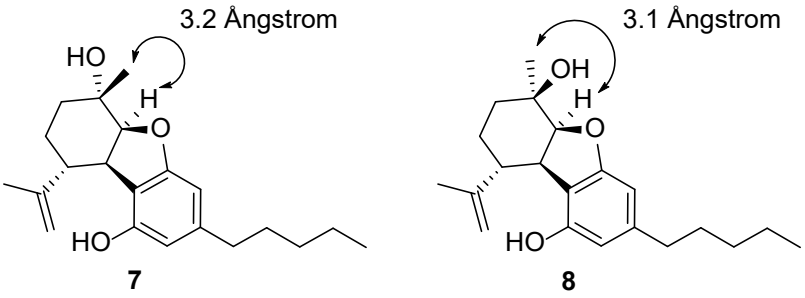
Conformation 3



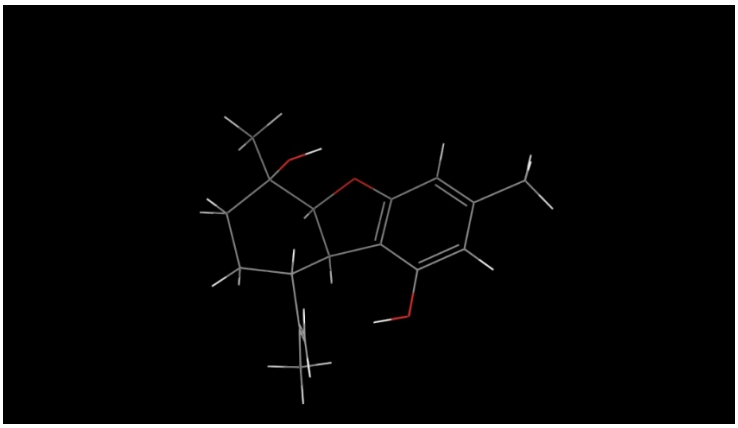
Conformation 4



21. Comparison of ROESY analysis for (**7**) and (**8**).

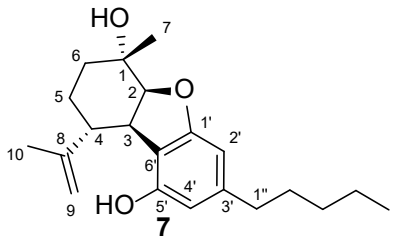


7

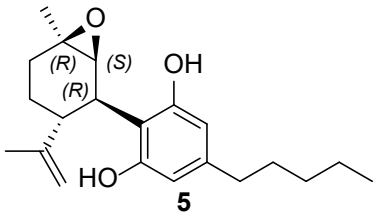


8

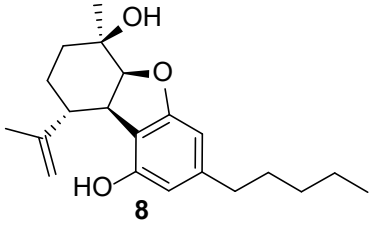
22. Table of calculated ^{13}C chemical shifts for (**5**), (**7**), (**8**), and (**9**) from calculations performed at the mPW1PW91/6-311+G(2d,p)//M06-2X-D3/6-31G(d,p) level.



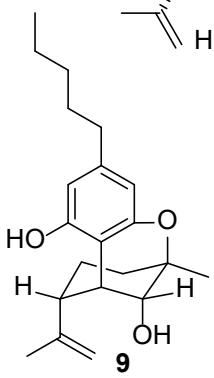
7



5



8

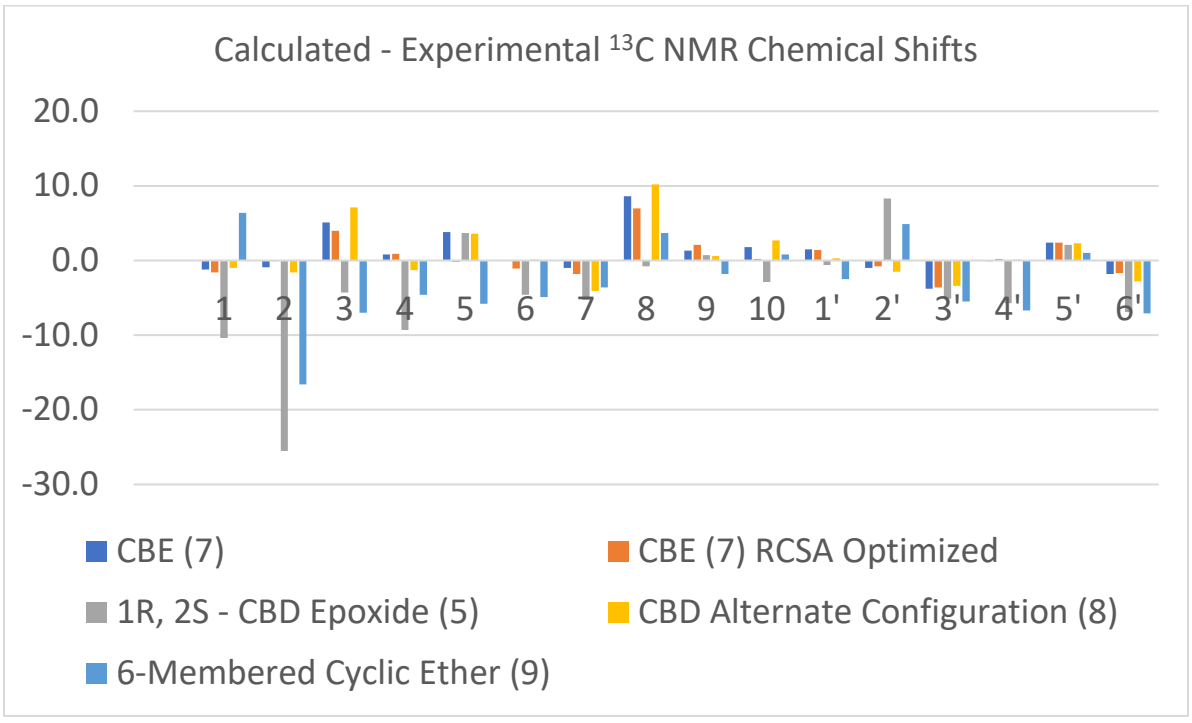


9

Atom #	CBE (7)	CBE RCSA Optimized (7)	1*R*, 2*S*-CBD Epoxide (5)	CBD Alternate Configuration at C1 (8)	6-Memered Cyclic Ether (9)
1	68.1	67.7	58.9	68.3	75.7
2	88.5	89.3	63.9	87.8	72.8
3	47.2	46.1	37.8	49.2	35.1
4	49.3	49.4	39.2	47.2	43.9
5	29.7	25.7	29.6	29.5	20.1
6	34.7	33.6	30.1	34.8	29.8
7	27.3	26.5	23	24.2	24.7
8	161.8	160.2	152.4	163.4	156.9
9	112.7	113.5	112.1	112	109.6
10	24.3	22.7	19.6	25.2	23.3
1'	154.5	161.5	154.2	154.4	153.1
2'	115.1	102.5	110	114.1	109.8
3'	161.6	141.3	159.5	160.4	157.6
4'	102.3	109.9	111.6	101.8	108.2
5'	141.1	154.5	139.8	141.5	139.4
6'	109.6	115.2	104	109.8	103
MAE	**2.2**	**1.8**	**6**	**2.7**	**5.2**

23. Graphical comparison of calculated experimental ^{13}C chemical shifts (ppm) for (**7**), (**5**), (**8**) and (**9**) from calculations performed at the mPW1PW91/6-311+G(2d,p)//M06-2X-D3/6-31G(d,p) level.

Atom #	**CBE (7)**	**CBE (7) RCSA Optimized**	**1*R*, 2*S*-CBD Epoxide (5)**	**CBD Alternate Configuration (8)**	**6-Membered Cyclic Ether (9)**
1	-1.2	-1.6	-10.4	-1.0	6.4
2	-0.9	-0.1	-25.5	-1.6	-16.6
3	5.1	4.0	-4.3	7.1	-7.0
4	0.8	0.9	-9.3	-1.3	-4.6
5	3.8	-0.2	3.7	3.6	-5.8
6	0.0	-1.1	-4.6	0.1	-4.9
7	-1.0	-1.8	-5.3	-4.1	-3.6
8	8.6	7.0	-0.8	10.2	3.7
9	1.3	2.1	0.7	0.6	-1.8
10	1.8	0.2	-2.9	2.7	0.8
1'	1.5	1.4	-0.6	0.3	-2.5
2'	-1.0	-0.8	8.3	-1.5	4.9
3'	-3.8	-3.6	-5.1	-3.4	-5.5
4'	-0.1	0.2	-5.7	0.1	-6.7
5'	2.4	2.4	2.1	2.3	1.0
6'	-1.8	-1.7	-6.9	-2.8	-7.1
MAE	**2.2**	**1.8**	**6.0**	**2.7**	**5.2**



24. Experimental for RCSA sample preparation and analysis for CBE (**7**).

A total of 66.1 mg of poly-γ-benzyl-L-glutamate (PBLG, Sigma-Aldrich Cat# P5136, Lot# SLBP1675V, MW by viscosity 249,000) – 150 – 350 KDa molecular weight range – was iteratively added to the 600 µL $CDCl_3$ solution (11.0% w/v) of 4.0 mg of CBE (**7**) contained in a 5 mm NMR tube. Multiple tube inversion and spin down cycles in a centrifuge allowed the PBLG to fully dissolve, providing a homogenous viscous liquid. A ^{2}H NMR spectrum (92.1 MHz, 4201.7 Hz spectral width, 32,768 points and 4 scans) was acquired with the Bruker pulse sequence "zg2h" to confirm that the solution was biphasic. 1D ^{13}C NMR data (150.9 MHz, 36,231 Hz spectral width, 65,536 points and 20480 scans) were then acquired using the Bruker pulse sequence "zgdc30" utilizing GARP decoupling (60 µsec 90^{o} pulse at 17.942 watts).

25. Certificate of analysis for PBLG used in this study.

SIGMA-ALDRICH®

sigma-aldrich.com

3050 Spruce Street, Saint Louis, MO 63103, USA
Website: www.sigmaaldrich.com
Email USA: techserv@sial.com
Outside USA: eurtechserv@sial.com

Certificate of Analysis

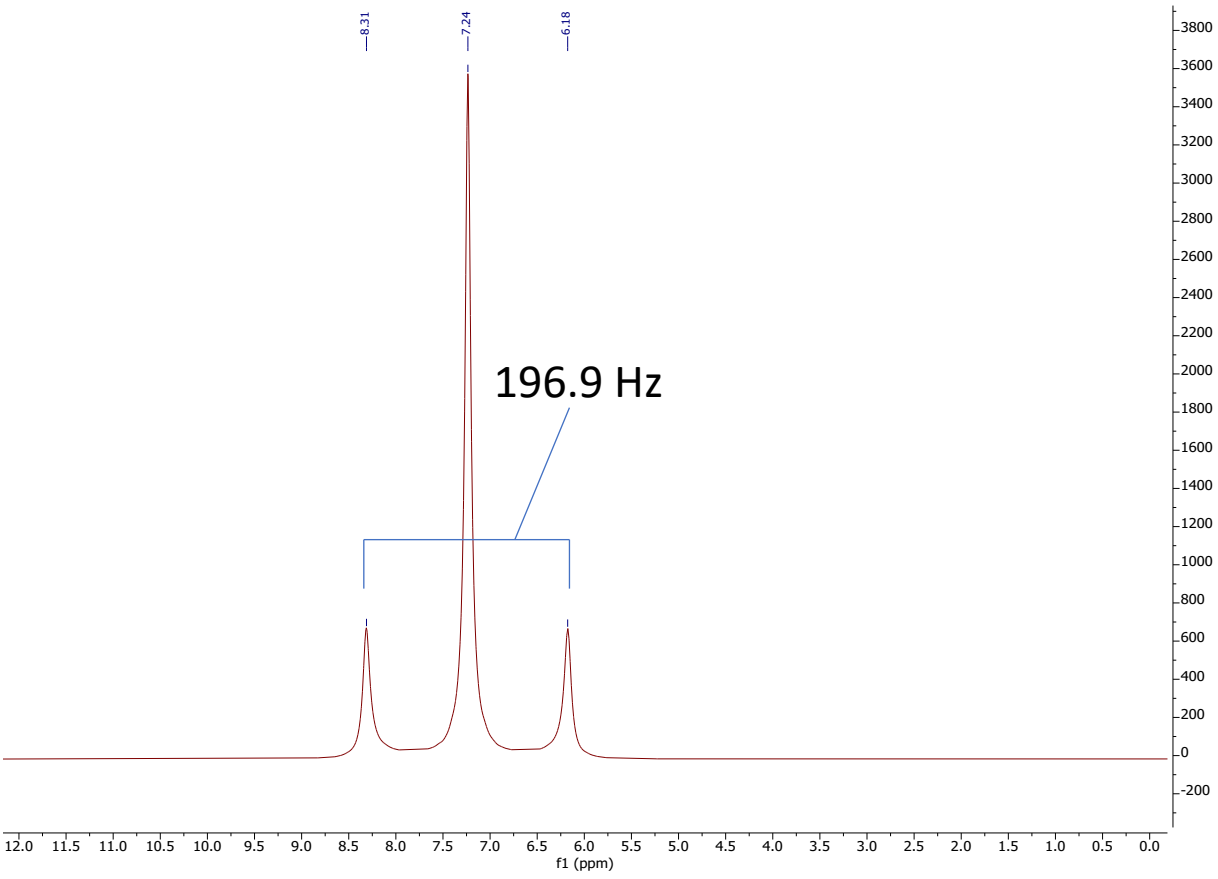
Product Name:
Poly-γ-benzyl-L-glutamate - mol wt 150,000-350,000

Product Number:	**P5136**
Batch Number:	**SLBP1675V**
Brand:	SIGMA
CAS Number:	25014-27-1
MDL Number:	MFCD00166357
Storage Temperature:	Store at -20 °C
Quality Release Date:	12 OCT 2015

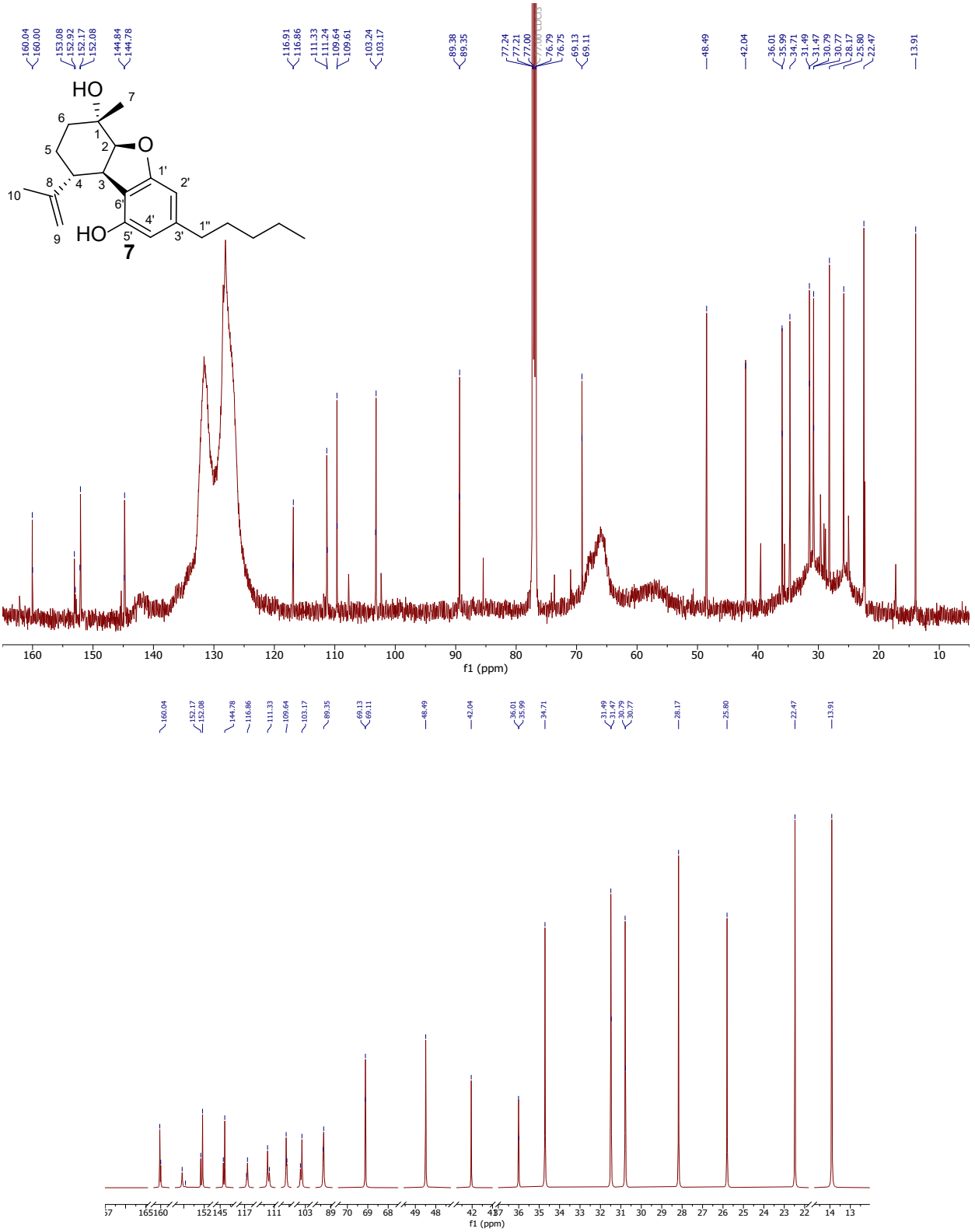
Test	Specification	Result
Appearance (Color)	White to Light Yellow	White
Appearance (Form)	Powder	Powder
Solubility (Color)	Colorless to Light Yellow	Colorless
Solubility (Turbidity) 50 mg/mL, CHCl3	Clear to Slightly Hazy	Very Slightly Hazy
Water (by Karl Fischer)	≤ 10 %	0 %
Degree of Polymerization by viscosity	685 - 1598	1137
Molecular Weight by Viscosity	150000 - 350000	249000

Rodney Burbach, Manager
Analytical Services
St. Louis, Missouri US

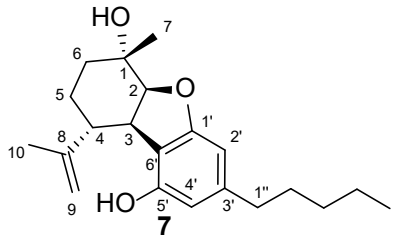
26. 1D ^{2}H NMR (92.1 MHz) of biphasic isotropic/anisotropic CBE (**7**) and PBLG in $CDCl_3$. The ^{2}H quadrupolar splitting was 196.9 Hz.



27. 1D ^{13}C NMR data (150.9 MHz) for biphasic isotropic/anisotropic CBE (**7**) in PBLG/ $CDCl_3$. Top spectrum: Normal processing parameters. Bottom spectrum: Processed with Global Spectral deconvolution.



28. Numbering key for DFT and SVD calculations.



7

	CBE (7) & Alternate CBE configuration at C1 (8)	**1*R*,2*S*-CBD epoxide (5)**	**6-membered cyclic ether (9)**
Literature Numbering	**DFT numbering**	**DFT numbering**	**DFT numbering**
1	6	6	6
2	5	5	5
3	4	4	4
4	3	3	3
5	2	2	2
6	1	1	1
7	7	7	7
8	8	14	8
9	20	15	18
10	19	16	19
1'	11	13	12
2'	9	8	9
3'	10	9	10
4'	14	10	15
5'	13	11	14
6'	12	12	13

29. MSPIN input files for (**5**) (all carbons). Values recorded as zero arise from unresolved isotropic/anisotropic NMR resonance pairs that preclude the accurate measurement of these small differences in NMR chemical shift.

rcsa_data {

carbon number then dmax-dmin in ppm!!!!

9 -0.04565

14 -0.16207

11 0.08614

13 0.06831

8 0.04512

15 -0.08978

12 -0.03923

10 0.07401

5 0.02869

6 0.00987

#3 0.00000

4 -0.01557

1 0.00901

#7 0.00000

#2 0.00000

16 0.03207

}

30. MSPIN input files for (**7**) (all carbons). Values recorded as zero arise from unresolved isotropic/anisotropic NMR resonance pairs that preclude the accurate measurement of these small differences in NMR chemical shift.

rcsa_data {

carbon number then dmax-dmin in ppm!!!!

10 -0.04565

8 -0.16207

11 0.08614

13 0.06831

9 0.04512

20 -0.08978

12 -0.03923

14 0.07401

5 0.02869

6 0.00987

#3 0.00000

4 -0.01557

1 0.00901

#7 0.00000

#2 0.00000

19 0.03207

}

31. MSPIN input files for (**8**) (all carbons). Values recorded as zero arise from unresolved isotropic/anisotropic NMR resonance pairs that preclude the accurate measurement of these small differences in NMR chemical shift.

rcsa_data {

carbon number then dmax-dmin in ppm!!!!

10 -0.04565

8 -0.16207

11 0.08614

13 0.06831

9 0.04512

20 -0.08978

12 -0.03923

14 0.07401

5 0.02869

6 0.00987

#3 0.00000

4 -0.01557

1 0.00901

#7 0.00000

#2 0.00000

19 0.03207

}

32. MSPIN input files for (**9**) (all carbons). Values recorded as zero arise from unresolved isotropic/anisotropic NMR resonance pairs that preclude the accurate measurement of these small differences in NMR chemical shift.

rcsa_data {

carbon number then dmax-dmin in ppm!!!!

10 -0.04565

8 -0.16207

12 0.08614

14 0.06831

9 0.04512

#18 -0.08978

13 -0.03923

15 0.07401

5 0.02869

6 0.00987

#3 0.00000

4 -0.01557

1 0.00901

#7 0.00000

#2 0.00000

19 0.03207

}

33. MSPIN output files for (**5**) using all carbons in the SVD analysis.

!* MSpin-RDC Plugin *!

****

!* Computation flags *!

Method: SVD

Scaling mode: Hz

Field (T): 14.092

1H Larmor Frequency: 600

Scale QCSA with axial component: False

Include CSA gel shift (isotropic) correction:False

Optimize CSA gel shift (isotropic) correction scale:False

Estimate CSA gel shift (isotropic) correction scale:False

Gel Shift Correction Scale: 0.15

Single Tensor: True

Optimize populations: True

Grid search points: 16

Superimpose: False

Average methyl groups: True

Average methylene groups: False

Average phenyl groups: False

Bootstrapping: False

RDC Std. Error [ppm]: 1

CSA Std. Error [ppm]: 0.01

PCS Std. Error [ppm]: 0.01

DQ Std. Error [Hz]: 1

****

!* Permutations *!

There are no permutations on the original data set

****

Data set: #1

Computed data for frame #1

CSA Data:

I	Exp. [ppm]	Comp. [ppm]
C9	-0.0457	-0.0285
C14	-0.1621	0.0588
C11	0.0861	0.0822
C13	0.0683	0.0729
C8	0.0451	0.0508
C15	-0.0898	0.1053
C12	-0.0392	-0.0571
C10	0.0740	0.0575
C5	0.0287	0.0217
C6	0.0099	-0.0038
C4	-0.0156	-0.0080
C1	0.0090	-0.0085
C16	0.0321	-0.0243

Cornilescu Quality factor (*Q*): 1.23716

Computed data for frame #2

CSA Data:

I	Exp. [ppm]	Comp. [ppm]
C9	-0.0457	-0.0198
C14	-0.1621	-0.1424
C11	0.0861	0.0843
C13	0.0683	0.0823
C8	0.0451	0.0597
C15	-0.0898	-0.1240

C12	-0.0392	-0.0486
C10	0.0740	0.0609
C5	0.0287	0.0188
C6	0.0099	-0.0061
C4	-0.0156	-0.0059
C1	0.0090	-0.0076
C16	0.0321	0.0448

Cornilescu Quality factor (*Q*): 0.251422

Computed data for frame #3

CSA Data:

I	Exp. [ppm]	Comp. [ppm]
C9	-0.0457	-0.0426
C14	-0.1621	-0.3379
C11	0.0861	0.0629
C13	0.0683	0.0359
C8	0.0451	0.0390
C15	-0.0898	-0.2223
C12	-0.0392	-0.0746
C10	0.0740	0.0364
C5	0.0287	0.0210
C6	0.0099	-0.0052
C4	-0.0156	-0.0139
C1	0.0090	-0.0088
C16	0.0321	0.0711

Cornilescu Quality factor (*Q*): 0.957979

Computed data for frame #4

CSA Data:

I	Exp. [ppm]	Comp. [ppm]
C9	-0.0457	0.0023
C14	-0.1621	-0.0787
C11	0.0861	0.1344
C13	0.0683	0.1769
C8	0.0451	0.0877
C15	-0.0898	-0.0853
C12	-0.0392	0.0368
C10	0.0740	0.1050
C5	0.0287	0.0174
C6	0.0099	-0.0058
C4	-0.0156	-0.0063
C1	0.0090	-0.0117
C16	0.0321	0.0387

Cornilescu Quality factor (*Q*): 0.74154

Computed data for frame #5

CSA Data:

I	Exp. [ppm]	Comp. [ppm]
C9	-0.0457	0.0177
C14	-0.1621	0.2931
C11	0.0861	0.1751
C13	0.0683	0.2144
C8	0.0451	0.1184
C15	-0.0898	0.2300
C12	-0.0392	0.0553
C10	0.0740	0.1324
C5	0.0287	0.0227
C6	0.0099	-0.0039

C4 -0.0156 0.0015

C1 0.0090 -0.0010

C16 0.0321 -0.0454

Cornilescu Quality factor (*Q*): 2.47715

Computed data for frame #6

CSA Data:

I Exp. [ppm] Comp. [ppm]

C9 -0.0457 0.0415

C14 -0.1621 0.2137

C11 0.0861 0.1824

C13 0.0683 0.1746

C8 0.0451 0.1169

C15 -0.0898 0.1913

C12 -0.0392 -0.0038

C10 0.0740 0.1426

C5 0.0287 0.0439

C6 0.0099 0.0177

C4 -0.0156 0.0163

C1 0.0090 -0.0124

C16 0.0321 -0.0354

Cornilescu Quality factor (*Q*): 2.1078

!Conformationally averaged data

!Populations

Frame #1: 15.4%

Frame #2: 0.0%

Frame #3: 66.4%

Frame #4: 0.0%

Frame #5: 18.2%

Frame #6: 0.0%

CSA Data:

I	Exp. [ppm]	Comp. [ppm]
C9	-0.0457	-0.0294
C14	-0.1621	-0.1617
C11	0.0861	0.0863
C13	0.0683	0.0741
C8	0.0451	0.0553
C15	-0.0898	-0.0894
C12	-0.0392	-0.0482
C10	0.0740	0.0571
C5	0.0287	0.0214
C6	0.0099	-0.0047
C4	-0.0156	-0.0102
C1	0.0090	-0.0073
C16	0.0321	0.0351

Cornilescu Quality factor (*Q*): 0.149457

Alignment tensor information:

A'x=-2.485e-04

A'y=-1.959e-03

A'z= 2.208e-03

Saupe tensor

S'x=-3.727e-04

S'y=-2.939e-03

S'z= 3.312e-03

Alignment tensor eigenvectors

e[x]=(0.902, 0.398, 0.168)

e[y]=(0.031, 0.328,-0.944)

e[z]=(-0.431, 0.857, 0.283)

Alignment tensor in laboratory coordinates:

[2.059e-04,-9.239e-04,-2.504e-04]

[-9.239e-04,1.371e-03,1.126e-03]

[-2.504e-04,1.126e-03,-1.576e-03]

SVD condition number is 2.761e+01

Axial component Aa = 3.312e-03

Rhombic component Ar = 1.711e-03

Field=14.09 Teslas[3.02]

rhombicity R = 0.517

Asimmetry parameter etha =7.749e-01

GDO = 4.361e-03

ZY'Z'' Euler Angles (degrees)

Set 1

(116.7,73.5,-100.1)

Set 2

(-63.3,-73.5,79.9)

****

MSpin-RDC pluginMon Feb 8 13:48:25 2021

34. MSPIN output files for (**7**) using all carbons in the SVD analysis.

!* MSpin-RDC Plugin *!

****

!* Computation flags *!

Method: SVD

Scaling mode: Hz

Field (T): 14.092

1H Larmor Frequency: 600

Scale QCSA with axial component: False

Include CSA gel shift (isotropic) correction:False

Optimize CSA gel shift (isotropic) correction scale:False

Estimate CSA gel shift (isotropic) correction scale:False

Gel Shift Correction Scale: 0.15

Single Tensor: True

Optimize populations: True

Grid search points: 16

Superimpose: False

Average methyl groups: True

Average methylene groups: False

Average phenyl groups: False

Bootstrapping: False

RDC Std. Error [ppm]: 1

CSA Std. Error [ppm]: 0.01

PCS Std. Error [ppm]: 0.01

DQ Std. Error [Hz]: 1

****

!* Permutations *!

There are no permutations on the original data set

****

Data set: #1

Computed data for frame #1

CSA Data:

I	Exp. [ppm]	Comp. [ppm]
C10	-0.0457	-0.0453
C8	-0.1621	0.0080
C11	0.0861	0.0956
C13	0.0683	0.0810
C9	0.0451	0.0408
C20	-0.0898	0.0729
C12	-0.0392	-0.0397
C14	0.0740	0.0777
C5	0.0287	0.0093
C6	0.0099	0.0082
C4	-0.0156	-0.0001
C1	0.0090	0.0146
C19	0.0321	-0.0135

Cornilescu Quality factor (*Q*): 0.988024

Computed data for frame #2

CSA Data:

I	Exp. [ppm]	Comp. [ppm]
C10	-0.0457	-0.0459
C8	-0.1621	-0.3120
C11	0.0861	0.0776
C13	0.0683	0.0512
C9	0.0451	0.0360
C20	-0.0898	-0.2259
C12	-0.0392	-0.0497

C14 0.0740 0.0686

C5 0.0287 0.0096

C6 0.0099 0.0158

C4 -0.0156 -0.0248

C1 0.0090 0.0137

C19 0.0321 0.0667

Cornilescu Quality factor (*Q*): 0.850903

Computed data for frame #3

CSA Data:

I Exp. [ppm] Comp. [ppm]

C10 -0.0457 -0.0429

C8 -0.1621 0.0114

C11 0.0861 0.0955

C13 0.0683 0.0844

C9 0.0451 0.0372

C20 -0.0898 0.0702

C12 -0.0392 -0.0320

C14 0.0740 0.0814

C5 0.0287 0.0152

C6 0.0099 0.0080

C4 -0.0156 -0.0027

C1 0.0090 0.0125

C19 0.0321 -0.0138

Cornilescu Quality factor (*Q*): 0.990363

Computed data for frame #4

CSA Data:

I Exp. [ppm] Comp. [ppm]

C10	-0.0457	-0.0472
C8	-0.1621	0.0029
C11	0.0861	0.0953
C13	0.0683	0.0824
C9	0.0451	0.0382
C20	-0.0898	0.0713
C12	-0.0392	-0.0369
C14	0.0740	0.0807
C5	0.0287	0.0174
C6	0.0099	0.0116
C4	-0.0156	-0.0006
C1	0.0090	0.0101
C19	0.0321	-0.0131

Cornilescu Quality factor (*Q*): 0.967213

Computed data for frame #5

CSA Data:

I	Exp. [ppm]	Comp. [ppm]
C10	-0.0457	-0.0434
C8	-0.1621	-0.3144
C11	0.0861	0.0782
C13	0.0683	0.0579
C9	0.0451	0.0337
C20	-0.0898	-0.2311
C12	-0.0392	-0.0421
C14	0.0740	0.0738
C5	0.0287	0.0161
C6	0.0099	0.0165
C4	-0.0156	-0.0277

C1 0.0090 0.0107

C19 0.0321 0.0671

Cornilescu Quality factor (*Q*): 0.86818

Computed data for frame #6

CSA Data:

I	Exp. [ppm]	Comp. [ppm]
C10	-0.0457	-0.0470
C8	-0.1621	-0.3142
C11	0.0861	0.0773
C13	0.0683	0.0557
C9	0.0451	0.0312
C20	-0.0898	-0.2279
C12	-0.0392	-0.0420
C14	0.0740	0.0734
C5	0.0287	0.0189
C6	0.0099	0.0193
C4	-0.0156	-0.0258
C1	0.0090	0.0089
C19	0.0321	0.0669

Cornilescu Quality factor (*Q*): 0.859246

!Conformationally averaged data

!Populations

Frame #1: 0.1%

Frame #2: 0.0%

Frame #3: 0.4%

Frame #4: 46.8%

Frame #5: 52.6%

Frame #6: 0.1%

CSA Data:

I	Exp. [ppm]	Comp. [ppm]
C10	-0.0457	-0.0452
C8	-0.1621	-0.1643
C11	0.0861	0.0863
C13	0.0683	0.0695
C9	0.0451	0.0358
C20	-0.0898	-0.0881
C12	-0.0392	-0.0396
C14	0.0740	0.0771
C5	0.0287	0.0167
C6	0.0099	0.0141
C4	-0.0156	-0.0149
C1	0.0090	0.0105
C19	0.0321	0.0292

Cornilescu Quality factor (*Q*): 0.0682985

Alignment tensor information:

A'x= 2.806e-04

A'y= 1.360e-03

A'z=-1.641e-03

Saupe tensor

S'x= 4.209e-04

S'y= 2.041e-03

S'z=-2.461e-03

Alignment tensor eigenvectors

e[x]=(-0.333, 0.448,-0.829)

e[y]=(0.678, 0.725, 0.120)

e[z]=(0.655,-0.523,-0.546)

Alignment tensor in laboratory coordinates:

[-4.727e-05,1.189e-03,7.745e-04]

[1.189e-03,3.234e-04,-4.543e-04]

[7.745e-04,-4.543e-04,-2.761e-04]

SVD condition number is 1.055e+01

Axial component Aa = -2.461e-03

Rhombic component Ar = -1.080e-03

Field=14.09 Teslas[3.02]

rhombicity R = 0.439

Asimmetry parameter etha =6.580e-01

GDO = 3.135e-03

ZY'Z'' Euler Angles (degrees)

Set 1

(-38.6,123.1,8.2)

Set 2

(141.4,-123.1,-171.8)

****

MSpin-RDC pluginWed Feb 3 15:26:06 2021

35. MSPIN output files for (**8**) using all carbons in the SVD analysis.

!* MSpin-RDC Plugin *!

****

!* Computation flags *!

Method: SVD

Scaling mode: Hz

Field (T): 14.092

1H Larmor Frequency: 600

Scale QCSA with axial component: False

Include CSA gel shift (isotropic) correction:False

Optimize CSA gel shift (isotropic) correction scale:False

Estimate CSA gel shift (isotropic) correction scale:False

Gel Shift Correction Scale: 0.15

Single Tensor: True

Optimize populations: True

Grid search points: 16

Superimpose: False

Average methyl groups: True

Average methylene groups: False

Average phenyl groups: False

Bootstrapping: False

RDC Std. Error [ppm]: 1

CSA Std. Error [ppm]: 0.01

PCS Std. Error [ppm]: 0.01

DQ Std. Error [Hz]: 1

****

!* Permutations *!

There are no permutations on the original data set

****

Data set: #1

Computed data for frame #1

CSA Data:

I	Exp. [ppm]	Comp. [ppm]
C10	-0.0457	-0.1451
C8	-0.1621	-0.0557
C11	0.0861	0.0345
C13	0.0683	0.0456
C9	0.0451	0.0109
C20	-0.0898	0.0082
C12	-0.0392	-0.1284
C14	0.0740	0.0164
C5	0.0287	-0.0811
C6	0.0099	0.0522
C4	-0.0156	-0.0050
C1	0.0090	-0.0330
C19	0.0321	-0.0102

Cornilescu Quality factor (*Q*): 1.03373

Computed data for frame #2

CSA Data:

I	Exp. [ppm]	Comp. [ppm]
C10	-0.0457	-0.1343
C8	-0.1621	-0.2834
C11	0.0861	0.0329
C13	0.0683	0.0418
C9	0.0451	0.0151
C20	-0.0898	-0.2070
C12	-0.0392	-0.1124

C14	0.0740	0.0254
C5	0.0287	-0.0749
C6	0.0099	0.0503
C4	-0.0156	-0.0197
C1	0.0090	-0.0313
C19	0.0321	0.0538

Cornilescu Quality factor (*Q*): 1.02577

Computed data for frame #3

CSA Data:

I	Exp. [ppm]	Comp. [ppm]
C10	-0.0457	-0.0825
C8	-0.1621	-0.3733
C11	0.0861	0.0741
C13	0.0683	0.0781
C9	0.0451	0.0391
C20	-0.0898	-0.2813
C12	-0.0392	-0.0670
C14	0.0740	0.0565
C5	0.0287	-0.0317
C6	0.0099	0.0376
C4	-0.0156	-0.0107
C1	0.0090	-0.0128
C19	0.0321	0.0722

Cornilescu Quality factor (*Q*): 1.23005

Computed data for frame #4

CSA Data:

I	Exp. [ppm]	Comp. [ppm]

C10	-0.0457	-0.0999
C8	-0.1621	-0.0755
C11	0.0861	0.0758
C13	0.0683	0.0807
C9	0.0451	0.0360
C20	-0.0898	0.0126
C12	-0.0392	-0.0915
C14	0.0740	0.0494
C5	0.0287	-0.0410
C6	0.0099	0.0423
C4	-0.0156	0.0066
C1	0.0090	-0.0117
C19	0.0321	-0.0086

Cornilescu Quality factor (*Q*): 0.743882

Computed data for frame #5

CSA Data:

I	Exp. [ppm]	Comp. [ppm]
C10	-0.0457	-0.0414
C8	-0.1621	-0.0200
C11	0.0861	0.0889
C13	0.0683	0.0720
C9	0.0451	0.0337
C20	-0.0898	0.0561
C12	-0.0392	-0.0356
C14	0.0740	0.0724
C5	0.0287	0.0240
C6	0.0099	-0.0143
C4	-0.0156	-0.0034

C1 0.0090 0.0101

C19 0.0321 -0.0090

Cornilescu Quality factor (*Q*): 0.858804

Computed data for frame #6

CSA Data:

I Exp. [ppm] Comp. [ppm]

C10 -0.0457 -0.0300

C8 -0.1621 -0.3391

C11 0.0861 0.0831

C13 0.0683 0.0672

C9 0.0451 0.0409

C20 -0.0898 -0.2335

C12 -0.0392 -0.0303

C14 0.0740 0.0763

C5 0.0287 0.0189

C6 0.0099 -0.0135

C4 -0.0156 -0.0259

C1 0.0090 0.0106

C19 0.0321 0.0705

Cornilescu Quality factor (*Q*): 0.954991

!Conformationally averaged data

!Populations

Frame #1: 0.0%

Frame #2: 0.0%

Frame #3: 15.3%

Frame #4: 0.0%

Frame #5: 54.6%

Frame #6: 30.1%

CSA Data:

I	Exp. [ppm]	Comp. [ppm]
C10	-0.0457	-0.0443
C8	-0.1621	-0.1701
C11	0.0861	0.0849
C13	0.0683	0.0715
C9	0.0451	0.0367
C20	-0.0898	-0.0826
C12	-0.0392	-0.0388
C14	0.0740	0.0711
C5	0.0287	0.0139
C6	0.0099	-0.0061
C4	-0.0156	-0.0113
C1	0.0090	0.0068
C19	0.0321	0.0273

Cornilescu Quality factor (*Q*): 0.110241

Alignment tensor information:

A'x= 2.608e-04

A'y= 1.469e-03

A'z=-1.729e-03

Saupe tensor

S'x= 3.912e-04

S'y= 2.203e-03

S'z=-2.594e-03

Alignment tensor eigenvectors

e[x]=(0.168,-0.563, 0.809)

e[y]=(0.860, 0.485, 0.159)

e[z]=(-0.482, 0.669, 0.566)

Alignment tensor in laboratory coordinates:

[6.921e-04,1.145e-03,7.072e-04]

[1.145e-03,-3.462e-04,-6.606e-04]

[7.072e-04,-6.606e-04,-3.459e-04]

SVD condition number is 1.143e+01

Axial component Aa = -2.594e-03

Rhombic component Ar = -1.208e-03

Field=14.09 Teslas[3.02]

rhombicity R = 0.466

Asimmetry parameter etha =6.984e-01

GDO = 3.341e-03

ZY'Z'' Euler Angles (degrees)

Set 1

(125.8,55.5,168.9)

Set 2

(-54.2,-55.5,-11.1)

****

MSpin-RDC pluginWed Feb 3 15:29:12 2021

36. MSPIN output files for (**9**) using all carbons in the SVD analysis.

!* MSpin-RDC Plugin *!

****

!* Computation flags *!

Method: SVD

Scaling mode: Hz

Field (T): 14.092

1H Larmor Frequency: 600

Scale QCSA with axial component: False

Include CSA gel shift (isotropic) correction:False

Optimize CSA gel shift (isotropic) correction scale:False

Estimate CSA gel shift (isotropic) correction scale:False

Gel Shift Correction Scale: 0.15

Single Tensor: True

Optimize populations: True

Grid search points: 16

Superimpose: False

Average methyl groups: True

Average methylene groups: False

Average phenyl groups: False

Bootstrapping: False

RDC Std. Error [ppm]: 1

CSA Std. Error [ppm]: 0.01

PCS Std. Error [ppm]: 0.01

DQ Std. Error [Hz]: 1

****

!* Permutations *!

There are no permutations on the original data set

****

Data set: #1

Computed data for frame #1

CSA Data:

I	Exp. [ppm]	Comp. [ppm]
C10	-0.0457	-0.0423
C8	-0.1621	-0.1607
C12	0.0861	0.0921
C14	0.0683	0.0499
C9	0.0451	0.0292
C13	-0.0392	-0.0208
C15	0.0740	0.0981
C5	0.0287	0.0123
C6	0.0099	-0.0303
C4	-0.0156	-0.0088
C1	0.0090	-0.0032
C19	0.0321	0.0127

Cornilescu Quality factor(*Q*): 0.278406

Computed data for frame #2

CSA Data:

I	Exp. [ppm]	Comp. [ppm]
C10	-0.0457	-0.0425
C8	-0.1621	-0.1490
C12	0.0861	0.0973
C14	0.0683	0.0416
C9	0.0451	0.0352
C13	-0.0392	-0.0281
C15	0.0740	0.0625

C5 0.0287 0.0089

C6 0.0099 -0.0314

C4 -0.0156 -0.0061

C1 0.0090 -0.0050

C19 0.0321 0.0107

Cornilescu Quality factor (*Q*): 0.28509

Computed data for frame #3

CSA Data:

I Exp. [ppm] Comp. [ppm]

C10 -0.0457 -0.0416

C8 -0.1621 -0.1605

C12 0.0861 0.0933

C14 0.0683 0.0488

C9 0.0451 0.0312

C13 -0.0392 -0.0264

C15 0.0740 0.0825

C5 0.0287 0.0117

C6 0.0099 -0.0307

C4 -0.0156 -0.0088

C1 0.0090 -0.0033

C19 0.0321 0.0128

Cornilescu Quality factor (*Q*): 0.255772

Computed data for frame #4

CSA Data:

I Exp. [ppm] Comp. [ppm]

C10 -0.0457 -0.0740

C8 -0.1621 -0.2018

C12 0.0861 0.0677

C14 0.0683 0.0247

C9 0.0451 0.0019

C13 -0.0392 -0.0486

C15 0.0740 0.0767

C5 0.0287 0.0054

C6 0.0099 -0.0458

C4 -0.0156 -0.0115

C1 0.0090 -0.0039

C19 0.0321 0.0298

Cornilescu Quality factor (*Q*): 0.448838

!Conformationally averaged data

!Populations

Frame #1: 0.0%

Frame #2: 0.0%

Frame #3: 100.0%

Frame #4: 0.0%

CSA Data:

I Exp. [ppm] Comp. [ppm]

C10 -0.0457 -0.0416

C8 -0.1621 -0.1605

C12 0.0861 0.0933

C14 0.0683 0.0488

C9 0.0451 0.0312

C13 -0.0392 -0.0264

C15 0.0740 0.0825

C5 0.0287 0.0117

C6 0.0099 -0.0307

C4 -0.0156 -0.0088

C1 0.0090 -0.0033

C19 0.0321 0.0128

Cornilescu Quality factor (*Q*): 0.255772

Alignment tensor information:

A'x= 8.934e-04

A'y= 1.910e-03

A'z=-2.803e-03

Saupe tensor

S'x= 1.340e-03

S'y= 2.865e-03

S'z=-4.205e-03

Alignment tensor eigenvectors

e[x]=(0.683, 0.660, 0.314)

e[y]=(0.299,-0.645, 0.703)

e[z]=(0.667,-0.386,-0.638)

Alignment tensor in laboratory coordinates:

[-6.582e-04,7.547e-04,1.786e-03]

[7.547e-04,7.655e-04,-1.371e-03]

[1.786e-03,-1.371e-03,-1.073e-04]

SVD condition number is 1.480e+01

Axial component Aa = -4.205e-03

Rhombic component Ar = -1.017e-03

Field=14.09 Teslas[3.02]

rhombicity R = 0.242

Asimmetry parameter etha =3.626e-01

GDO = 5.013e-03

ZY'Z'' Euler Angles (degrees)

Set 1

(-30.1,129.6,114.1)

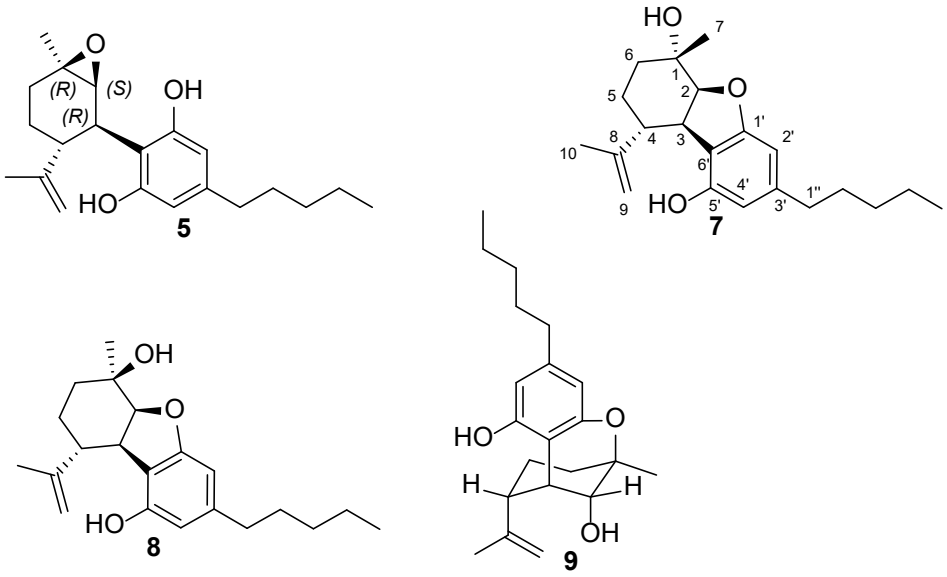
Set 2

(149.9,-129.6,-65.9)

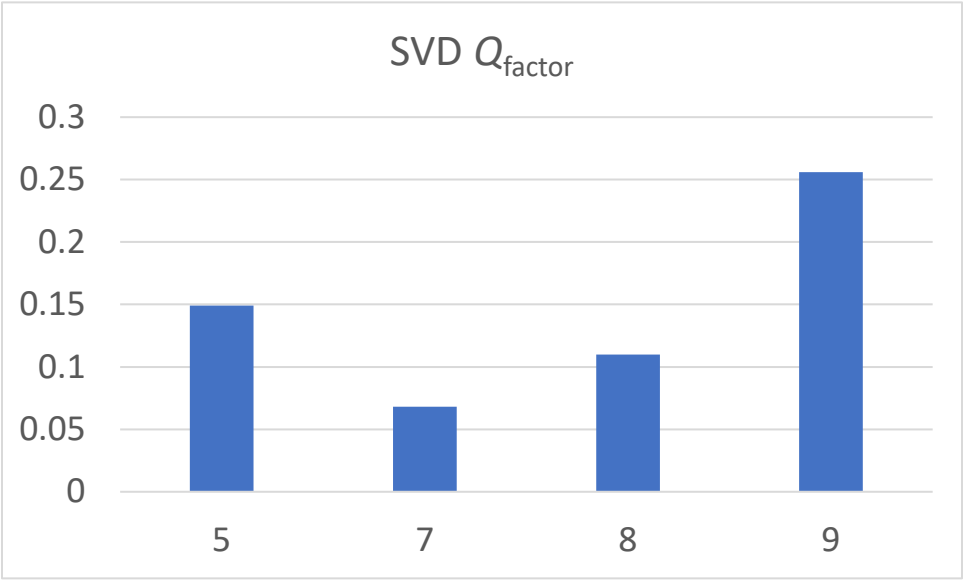
****

MSpin-RDC pluginWed Feb 3 15:32:47 2021

37. Table and bar graph of *Q*-factor determined from SVD for structures (**5**), (**7**), (**8**), and (**9**).



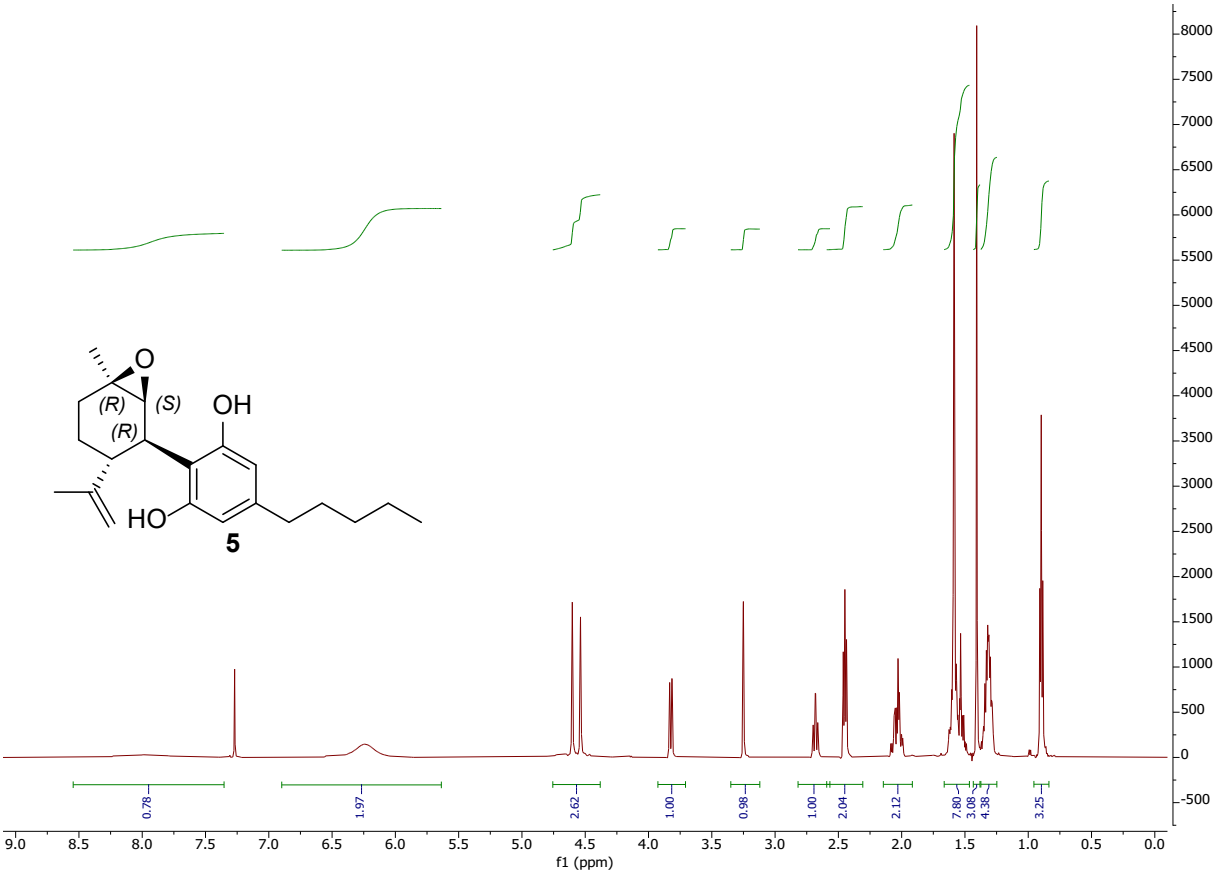
Structure	**5**	**7**	**8**	**9**
SVD Q_{factor}	0.149	0.068	0.110	0.256



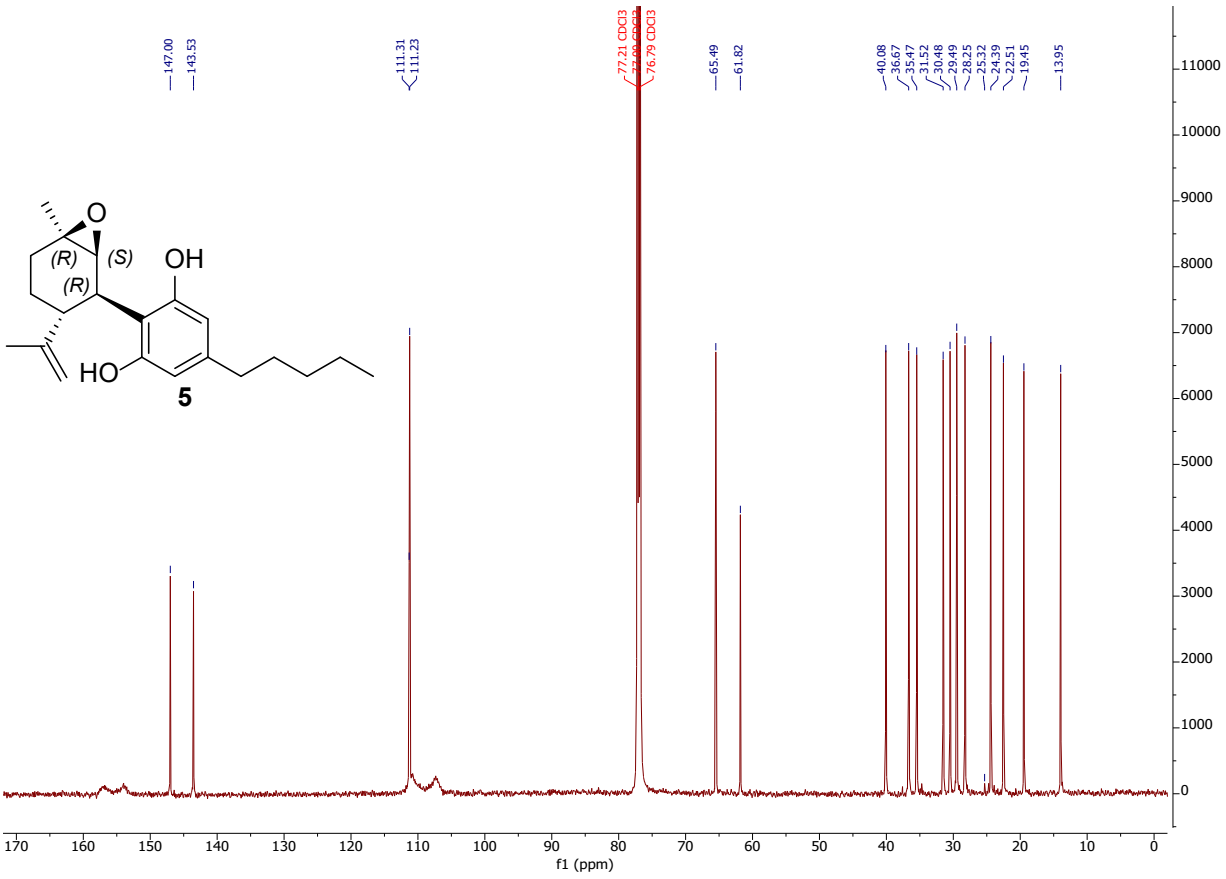
38. Experimental for synthesis of 1*R*,2*S*-CBD epoxide (**5**).

A dry 2-dram vial was charged with 62.9 mg (0.2 mmol) of cannabidiol (**2**, >95% CBD) and a Teflon stir bar. Potassium bicarbonate (20.0 mg, 0.2 mmol) was added, followed by 1.0 mL of methanol to form a suspension under argon. Benzonitrile (31 μL, 0.3 mmol) and 30% hydrogen peroxide (30 μL, 0.3 mmol) were added sequentially by syringe. The reaction was stirred for 40 hours under argon. After this time, the suspension was filtered with additional methanol wash. The resulting filtrate was concentrated to dryness. The mixture was purified by silica gel chromatography ramping from 0-20% ethyl acetate in hexanes over 10 minutes to give 28.5 mg (43% yield) of 1*R*,2*S*-CBD epoxide (**5**) as a clear film. HRMS–ESI (m/z): [M]+ calculated for $C_{21}H_{31}O_2$, 331.2273; found, 331.2270 (-0.9 ppm).

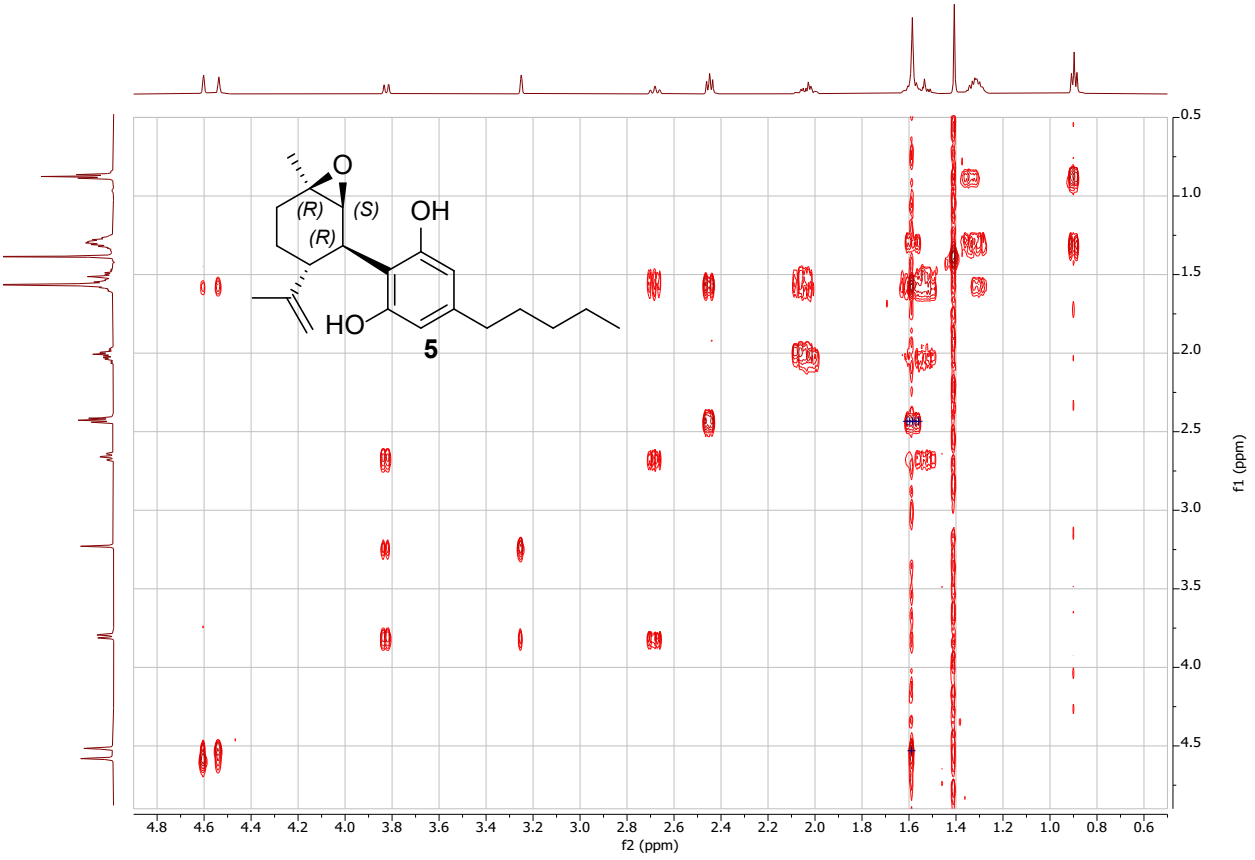
39. 1D ^{1}H NMR data (600.1 MHz) for 1*R*,2*S*-CBD epoxide (**5**) in $CDCl_3$.



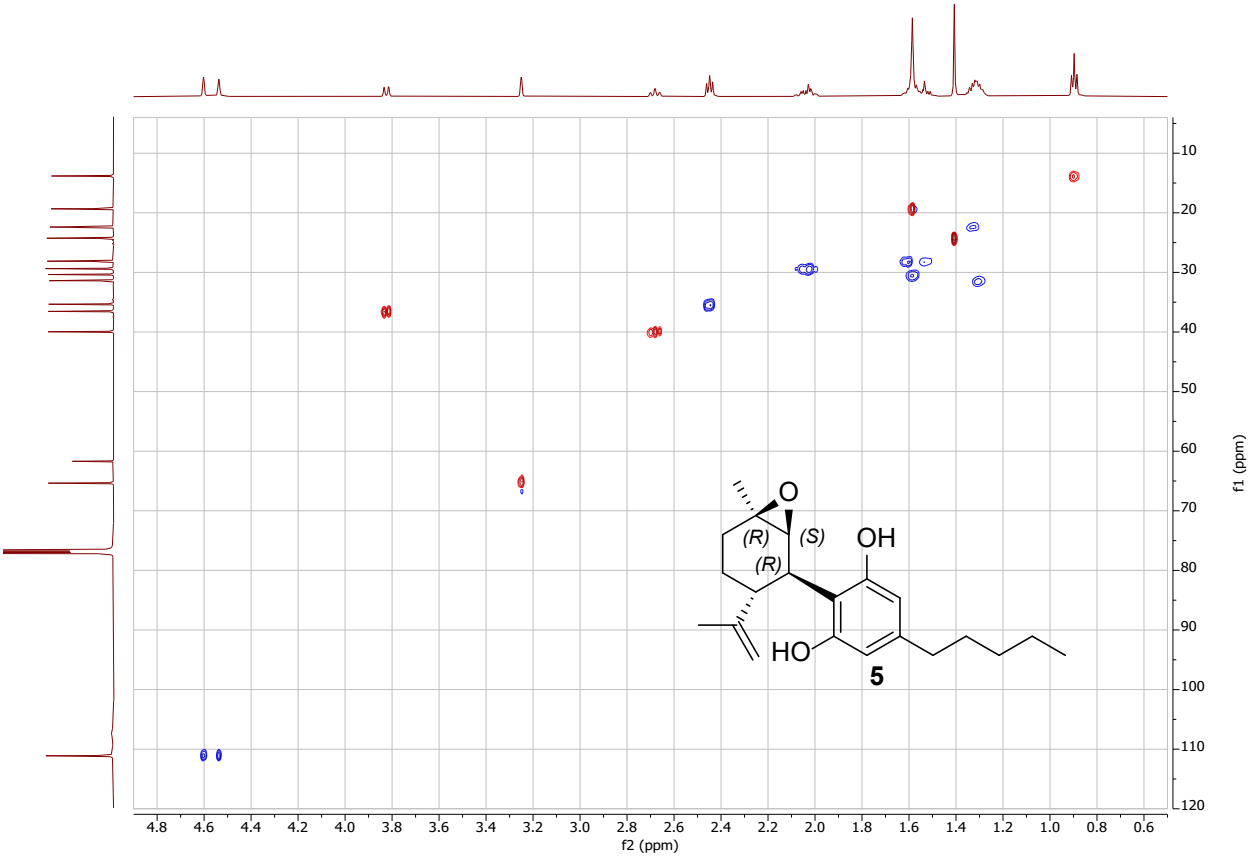
40. 1D ^{13}C NMR data (150.9 MHz) for 1*R*,2*S*-CBD epoxide (**5**) in $CDCl_3$.



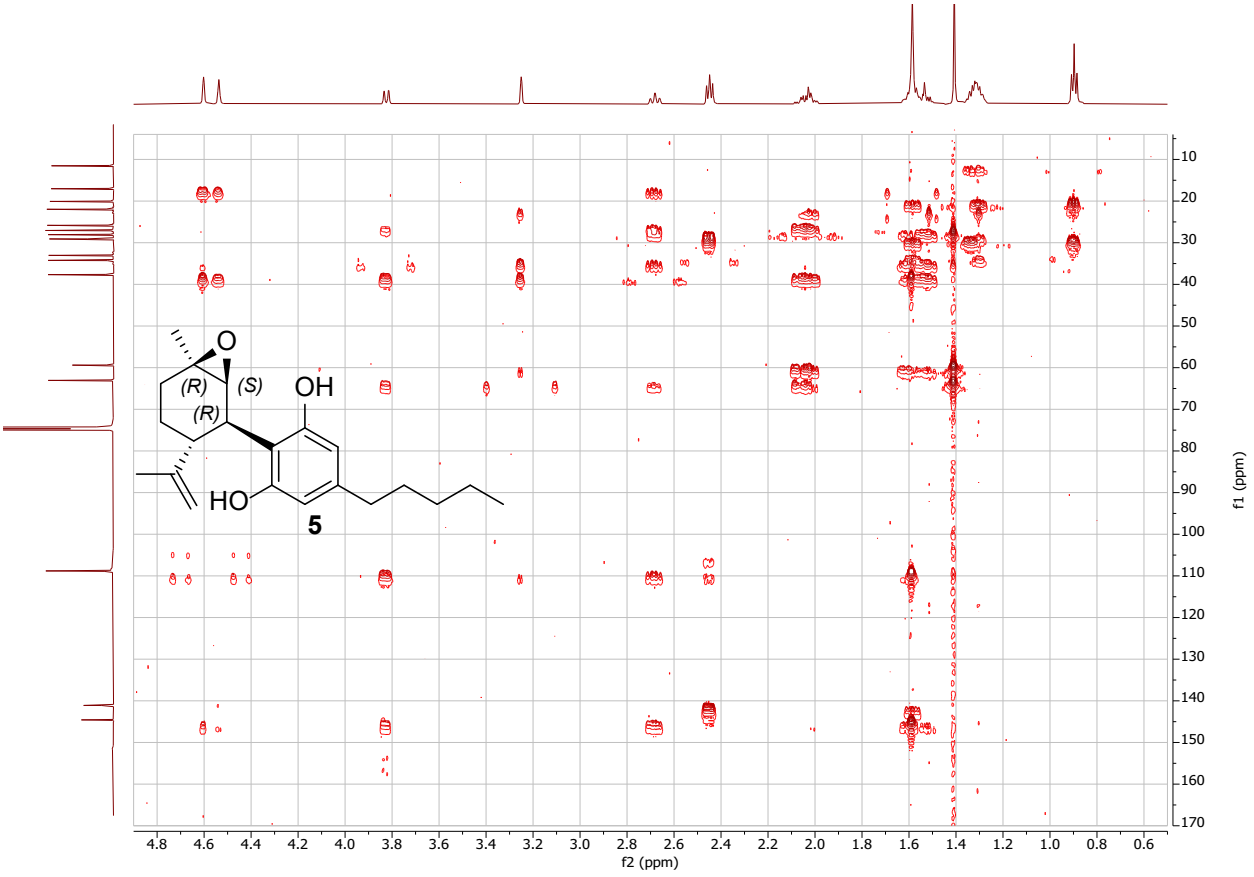
41. ^{1}H-^{1}H COSY data (600.1 MHz) for 1*R*,2*S*-CBD epoxide (**5**).



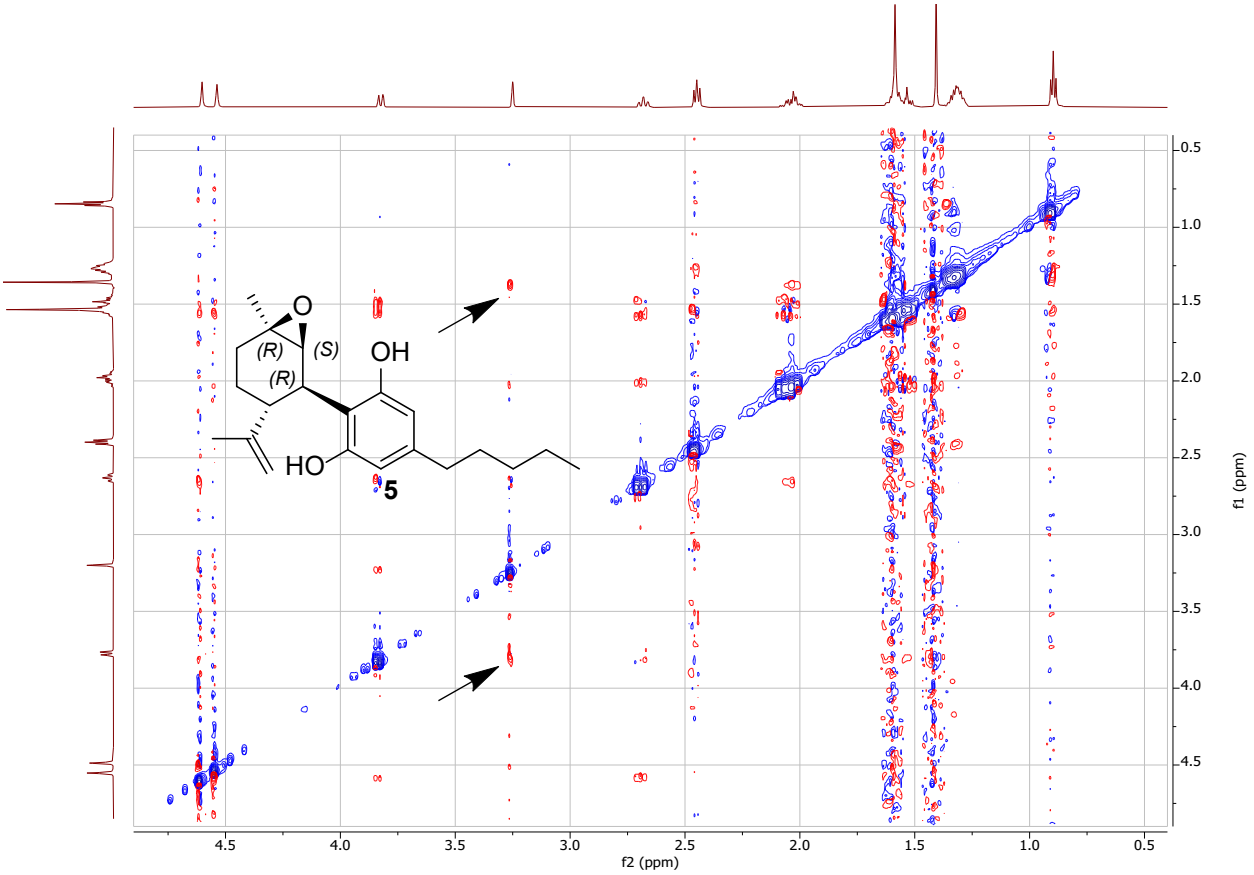
42. ^{1}H-^{13}C Multiplicity-edited HSQC data (600.1 MHz) for 1*R*,2*S*-CBD epoxide (**5**).

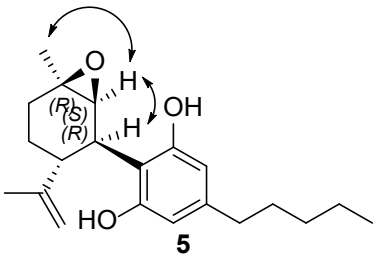


43. 8 Hz Optimized ^{1}H-^{13}C HMBC data (600.1 MHz) for 1*R*,2*S*-CBD epoxide (**5**).

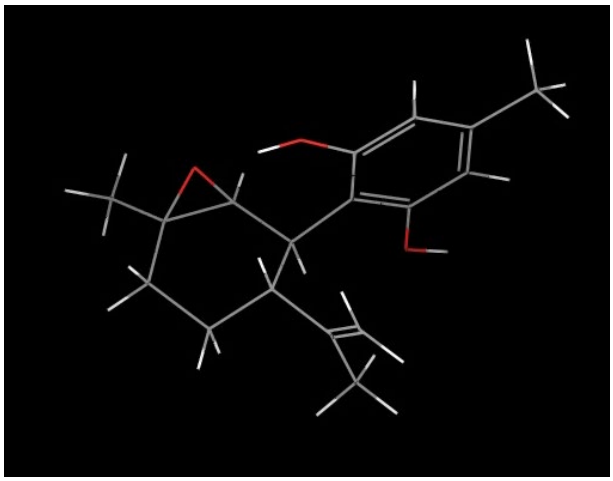


44. ^{1}H-^{1}H ROESY data (600.1 MHz, 300 ms) for 1*R*,2*S*-CBD epoxide (**5**).





ROESY Correlations Define Relative Configuration



1*R*,2*S*-CBD epoxide (**5**) Conformation 1

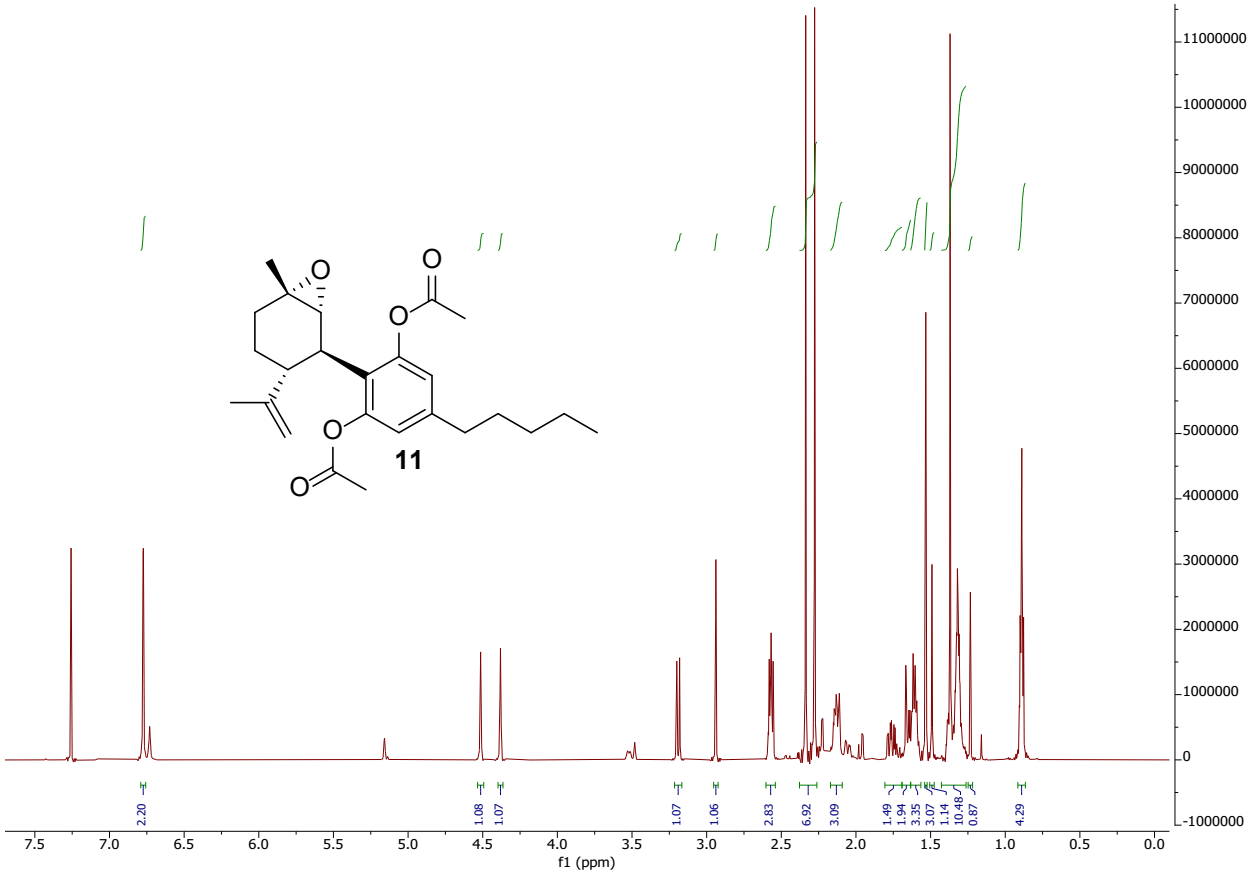
45. Table of NMR assignments for 1*R*,2*S*-CBD epoxide (**5**).

Carbon #	^{1}H δ, ppm, multiplicity (*J* Hz)	^{13}C δ, multiplicity	HMBC Correlations
1		61.8 C	
2	3.25 d (2.0)	65.5 CH	C1, C3, C4, C7, C6'
3	3.82 dd (11.5, 2.1)	36.7 CH	C1, C2, C4, C5, C8, C1', C5', C6'
4	2.68 td (11.9, 2.7)	40.1 CH	C2, C3, C5, C6, C8, C9, C10, C6'
5	1.61 m, 1.54 m	28.3 CH_2	C1, C3, C4, C6, C8
6	2.05 m, 2.01 m	29.5 CH_2	C1, C2, C3, C4, C5, C7
7	1.41 s	24 .4 CH_3	C1, C2, C6
8		147.0 C	
9	4.54 s, 4.60 s	111.0 CH_2	C4, C8, C10
10	1.61 s	19.5 CH_3	C4, C8, C9
1’		156.7 C	
2’	6.24 broad s	107.3 CH	None Observed
3’		143.5 C	
4’	6.24 broad s	107.3 CH	None Observed
5’		154.0 C	
6’		110.8 C	
1’’	2.45 t (7.8)	35.5 CH_2	C2’. C3’, C4’, C2’’, C3’’
2’’	1.58 m	30.5 CH_2	C3’, C1’’, C3’’, C4’’
3’’	1.31 m	31.6 CH_2	C1’’, C2’’, C4”, C5”
4’’	1.33 m	22.5 CH_2	C2’’, C3’’, C5’’
5’’	0.90 t (6.9)	14.3 CH_3	C3’’, 4’’
OH	7.94 bs		None Observed

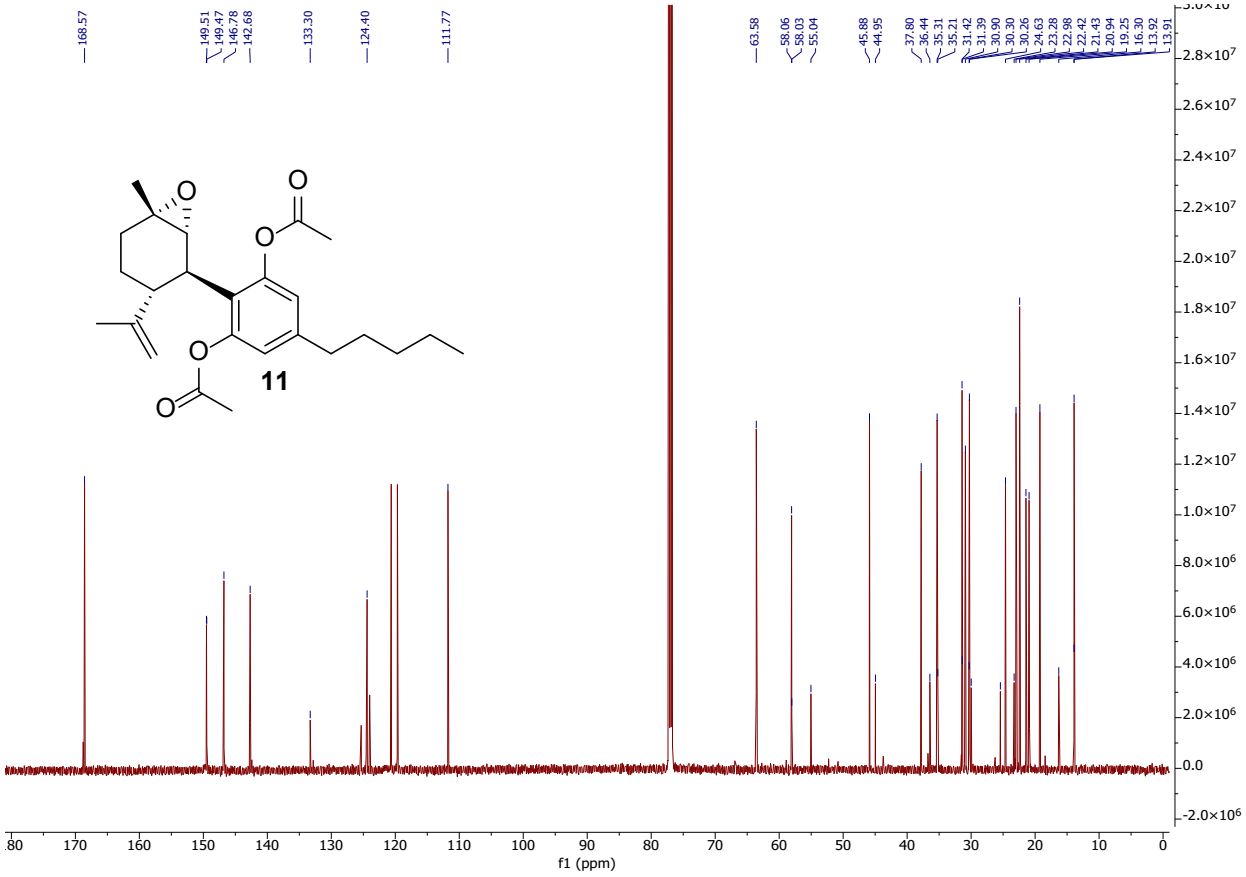
46. Experimental for synthesis of 1*S*,2*R*-CBD epoxide diacetate (**11**).

A dry 2-dram vial was charged with 39.8 mg (0.1 mmol) of CBD diacetate (**10**) and a Teflon stir bar. Sodium bicarbonate (25.2 mg, 0.3 mmol) was added, followed by 1.0 mL dichloromethane to form a suspension under argon. After cooling the reaction mixture to 0 °C, 25.3 mg of *m*-chloroperbenzoic acid (75% purity, 0.11 mmol) was added all at once. The reaction was stirred for 1 hour at 0 °C under argon. After this time, 1.0 mL of 10% aqueous $Na_2S_2O_3$ was added, and the suspension was warmed to room temperature. The mixture was extracted with 2 x 2 mL of dichloromethane. The combined organic layer was dried over $MgSO_4$, filtered, and concentrated. The mixture was purified by silica gel chromatography ramping from 0-20% ethyl acetate in hexanes over 10 minutes to give 17.5 mg (42% yield) of 1*S*,2*R*-CBD epoxide diacetate (**11**) as a clear film. HRMS–ESI (m/z): [M]+ calculated for $C_{25}H_{34}O_5Na$, 437.2304; found, 437.2300 (-0.9 ppm).

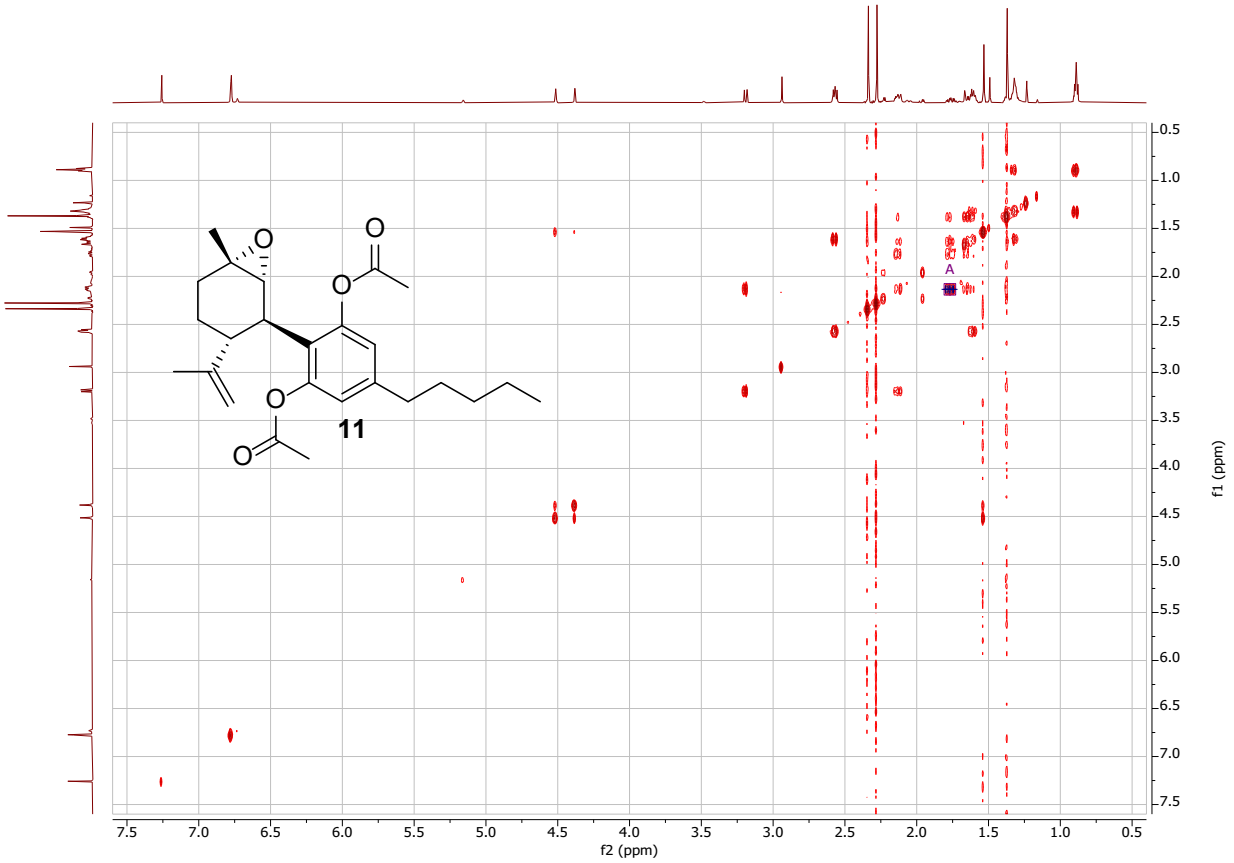
47. 1D ^{1}H NMR data (600.1 MHz) for 1*S*,2*R*-CBD epoxide diacetate (**11**) in $CDCl_3$.



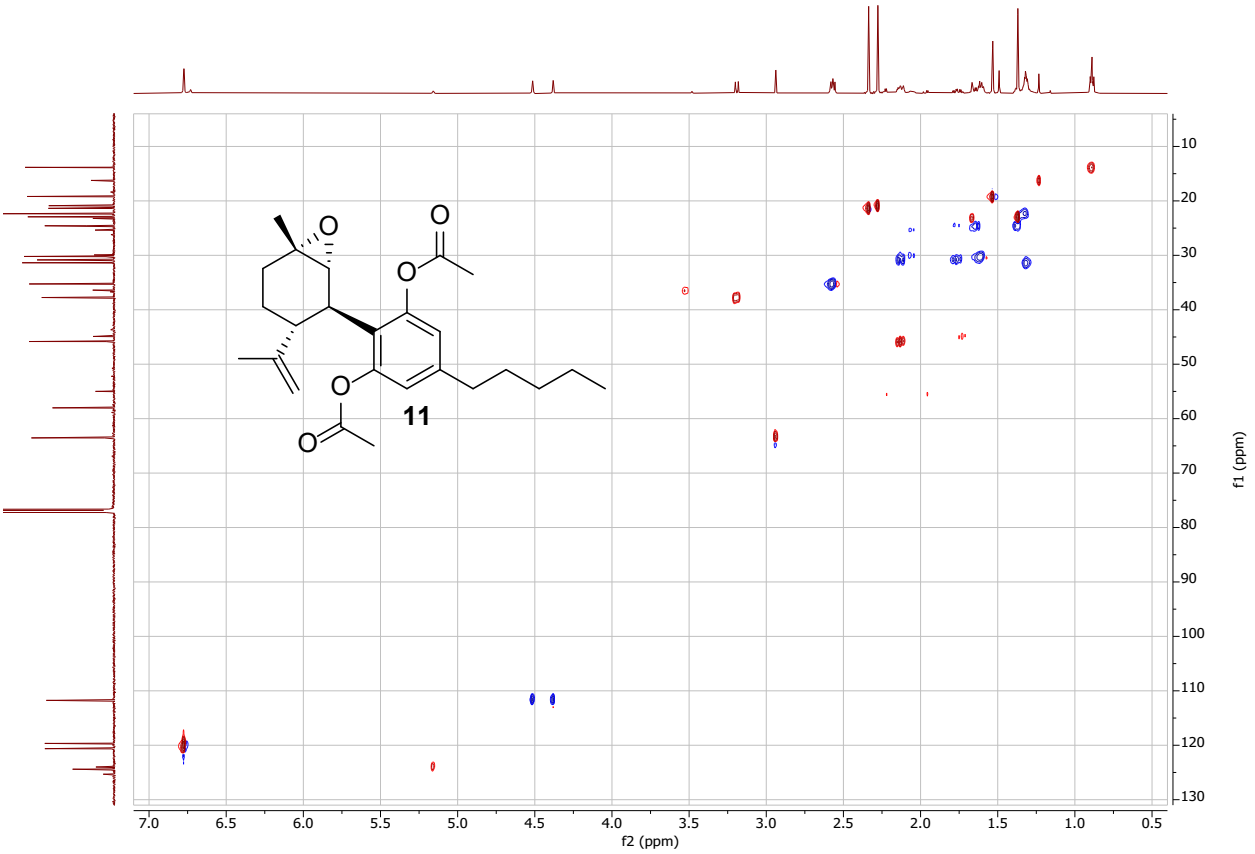
48. 1D ^{13}C NMR data (150.9 MHz) for 1*S*,2*R*-CBD epoxide diacetate (**11**) in $CDCl_3$.



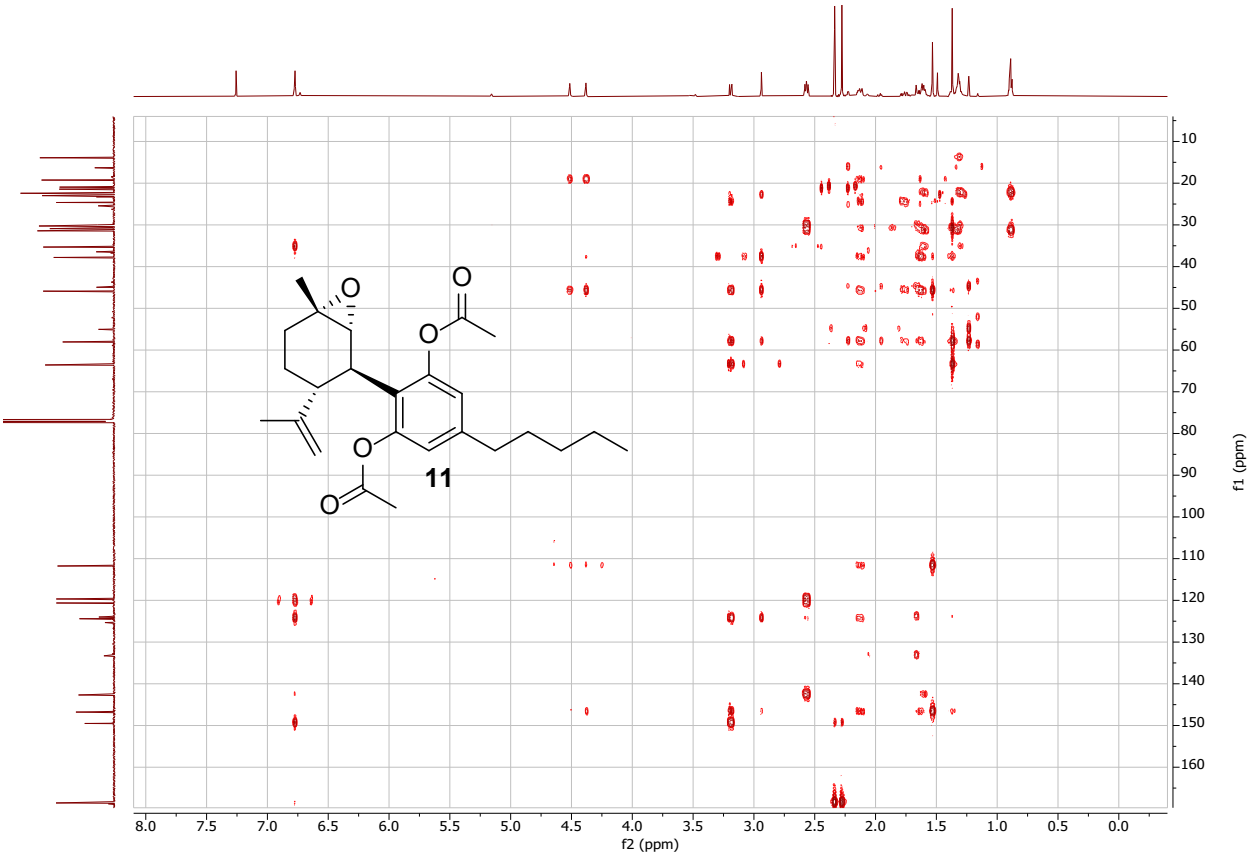
49. ^{1}H-^{1}H COSY data (600.1 MHz) for 1*S*,2*R*-CBD epoxide diacetate (**11**).



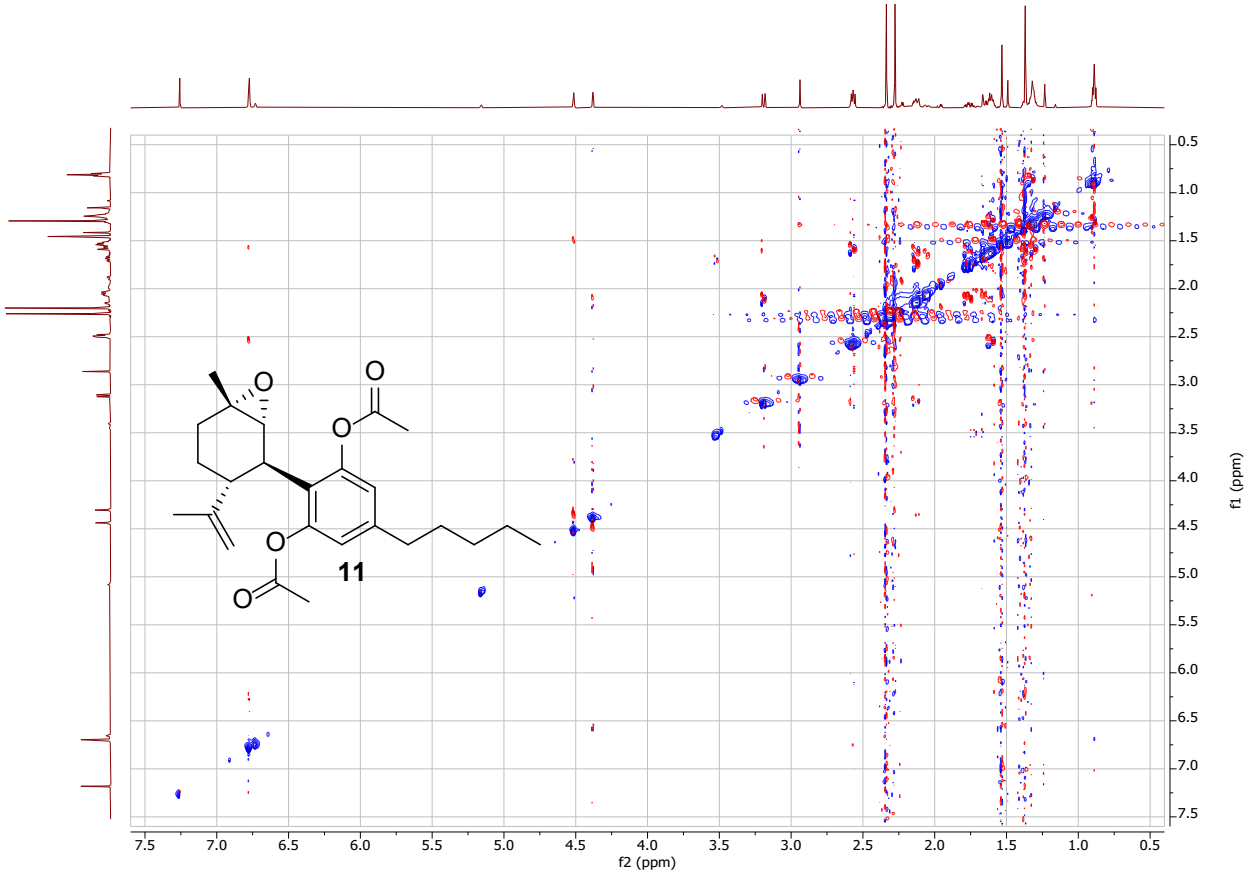
50. ^{1}H-^{13}C Multiplicity-edited HSQC data (600.1 MHz) for 1*S*,2*R*-CBD epoxide diacetate (**11**).



51. 8 Hz Optimized ^{1}H-^{13}C HMBC data (600.1 MHz) for 1*S*,2*R*-CBD epoxide diacetate (**11**).



52. ^{1}H-^{1}H ROESY data (600.1 MHz, 300 ms) for 1*S*,2*R*-CBD epoxide diacetate (**11**).



53. Table of NMR assignments for 1*S*,2*R*-CBD epoxide diacetate (**11**).

Carbon #	^{1}H δ, ppm, multiplicity (*J* Hz)	^{13}C δ, multiplicity	HMBC Correlations
1		58.0, C	
2	2.94, s	63.6, CH	C1, C3, C4, C7, C6'
3	3.19, d (11.3)	37.8, CH	C1, C2, C4, C5, C8, C1', C5', C6'
4	2.13, m	45.9, CH	C2, C3, C5, C6, C8, C9, C10, C6'
5	1.76, ddd (14.4, 12.7, 4.6)	24.6, CH_2	C1, C3, C4, C6, C8
6	1.67, s	30.3, CH_2	C1, C2, C3, C4, C5, C7
7	1.37, s	23.0, CH_3	C1, C2, C6
8		146.8, C	
9	4.51, s 4.38, s	111.8, CH_2	C4, C8, C10
10	1.53, s	19.3, CH_3	C4, C8, C9
			C1, C3, C4, C7, C6'
1'		149.51, C	
2'	6.77, s	119.7, CH	C1', C2', C4', C5', C6', C1"
3'		142.7, C	
4'	6.77, s	120.6, CH	C1', C2', C4', C5', C6', C1"
5'		149.47, C	
6'		124.4, C	
7'		168.6, C	
8'	2.28, s	20.9, CH_3	C1', C7'
9'		168.6, C	
10'	2.34, s	21.4, CH_3	C5', C9'
1"	2.57, t (7.8)	35.3, CH_2	C2'. C3', C4', C2'', C3''
2"	1.60, m	30.9, CH_2	C3', C1'', C3'', C4''
3"	1.32, m	31.4, CH_2	C1'', C2'', C4", C5"
4"	1.32, m	22.4, CH_2	C2'', C3'', C5''
5"	0.89, t (6.8)	13.9, CH_3	C3'', 4''

54. Improved synthesis of CBE (**7**) from CBD (**2**).

A dry 2-dram vial was charged with 37.0 mg (0.1 mmol) of cannabidiol (**2**, ~85% CBD) and a Teflon stir bar. N,O-Bis(trimethylsilyl)trifluoroacetamide (BSTFA, 200 μL) was added and the mixture was heated to 60 °C under argon. After 30 min, TLC indicated CBD was consumed and a new non-polar spot was formed. Volatiles were removed *in vacuo*.

The silylated CBD mixture was dissolved in 400 μL of dichloromethane. After cooling the reaction mixture to 0 °C, 30.4 mg of *m*-chloroperbenzoic acid (75% purity, 0.13 mmol) was added all at once. The reaction was stirred for 1 hour at 0 °C under argon. After this time, 1.0 mL of 1M NaOH was added, and the suspension was warmed to room temperature. The mixture was extracted with 2 x 2 mL of ethyl acetate, and the combined organic layers were concentrated.

The resulting crude mixture was dissolved in 400 μL of methanol and treated with 200 μL of 1M NaOH. The rection was stirred for 1 hour and TLC indicated no intermediate epoxide remained. The suspension had turned a deep purple color that dissipated upon quenching with 200 μL of 2M HCl. The aqueous mixture was extracted with 2 x 2 mL of ethyl acetate. The combined organic layer was washed with 2 mL brine, dried over $MgSO_4$, filtered, and concentrated. The mixture was purified by silica gel chromatography ramping from 0-35% ethyl acetate in hexanes over 10 minutes to give 23.9 mg (72% yield) of CBE (**7**) as a pale-yellow film.

55. References

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