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Rapid Report

Novel Δ^8-Tetrahydrocannabinol Vaporizers Contain Unlabeled Adulterants, Unintended Byproducts of Chemical Synthesis, and Heavy Metals

Jiries Meehan-Atrash and Irfan Rahman*

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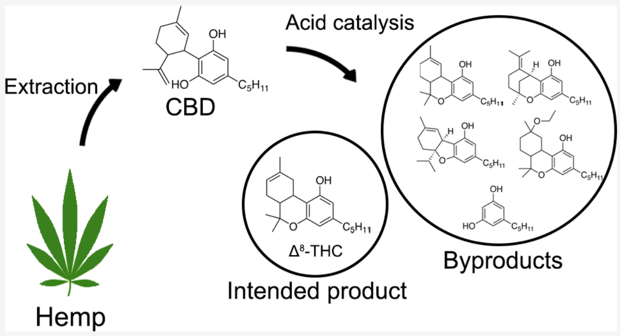
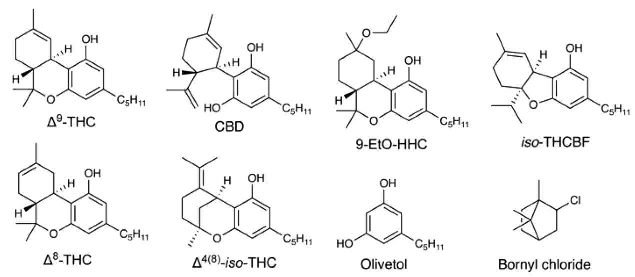
ABSTRACT: Cannabis e-cigarettes containing Δ^8-tetrahydrocannabinol (Δ^8-THC) produced synthetically from hemp-derived cannabidiol (CBD) have recently risen in popularity as a legal means of cannabis consumption, but questions surrounding purity and unlabeled additives have created doubts of their safety. Herein, NMR, GC-MS, and ICP-MS were used to analyze major components of 27 products from 10 brands, and it was determined none of these had accurate Δ^8-THC labeling, 11 had unlabeled cutting agents, and all contained reaction side-products including olivetol, Δ$^{4(8)}$-*iso*-tetrahydrocannabinol, 9-ethoxyhexahydrocannabinol, Δ^9-tetrahydrocannabinol (Δ^9-THC), heavy metals, and a novel previously undescribed cannabinoid, *iso*-tetrahydrocannabifuran.



Cannabis e-cigarettes (CECs) are a noncombustion inhalation delivery method, which uses technology adapted from electronic nicotine delivery systems. CECs vaporize an oil rich in Δ^9-THC, the psychoactive principle component of *Cannabis sativa*, and release hundreds of chemical breakdown products including carcinogenic and irritating gases such as isoprene, benzene, methacrolein, and methyl vinyl ketone.[1,2] CECs are popular with teens and young adults in the United States, with 23.7% of 12th graders having reported lifetime cannabis vaping in 2019.[3] CEC use was recently shown to be independently associated with higher odds of respiratory symptoms such as wheezing.[4] The 2019 outbreak of e-cigarette or vaping product use associated lung injury (EVALI) was centered around CECs, and though vitamin E acetate was identified as a potential causative agent, other ingredients or aerosol components were not ruled out.[5] Some CECs linked to EVALI were later found to contain unnatural cannabinoid distributions suggesting that these were of synthetic origin.[6,7] Niche online communities that recount intoxication experiences by minor or synthetic cannabinoids have existed likely for decades,[8] but it is only recently that cannabinoids other than those naturally occurring have reached broad commercial availability.[9] At the forefront of this trend is Δ^8-THC (Chart 1).

Δ^8-THC is an isomer of Δ^9-THC not produced biosynthetically[10] but present at low levels in most cannabis products as a result of spontaneous isomerization given its higher thermodynamic stability and resistance to oxidative degradation than Δ^9-THC.[10] Recent federal regulations that are permissive of hemp-derived products[11] have resulted in a rapid growth in usage of Δ^8-THC CECs that are abundantly available to consumers through brick-and-mortar and online sources. Extensive hospitalizations involving suspected Δ^8-THC consumption have been recently documented.[12] Δ^8-THC is synthesized via acid-catalyzed cyclization of CBD.[13,14] Though Δ^9-THC is the direct product of CBD cyclization (Scheme 1), Δ^8-THC is favored as a major product at longer reaction times.[15,16]

Chart 1. Relevant Structures



Hydrochloric acid (HCl), sulfuric acid, *p*-toluenesulfonic acid, boron trifluoride, and camphorsulfonic acid, among others, are viable catalysts, but the acids, solvents, and

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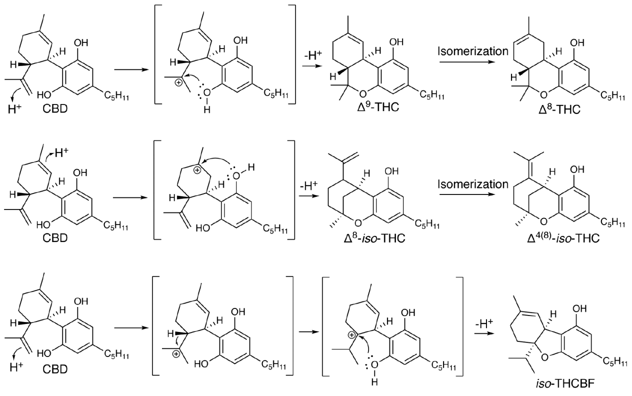
Scheme 1. Routes of Formation of Δ^8-THC (top), Δ$^{4(8)}$-*iso*-THC (middle), and *iso*-THCBF (bottom) from CBD via Acid Catalysis



purification steps used by manufacturers are not known.[15,16] In order to address this emerging class of products, available flavor formulations from different Δ^8-THC brands were obtained. Proton nuclear magnetic resonance spectroscopy (^{1}H NMR) was chosen as the primary analytical tool given this instrument's ability to characterize analytically challenging vaporizer adulterants[17] without the need for derivatization or developing dedicated chromatographic methods, which may be necessary for complex samples. Quantitative ^{1}H NMR (QNMR) was used to report component levels in these products, a facile and direct quantitative method whose limitations include the fact that some components cannot be identified or quantified due to spectral overlap of their resonances and its inherently low sensitivity precludes identification of ultratrace impurities.

Medium chain triglyceride oil was identified in B5 (3.71 ± 0.06%, $\bar{x}$ ± SEM), B6 (3.48 ± 0.06%), B8 (2.94 ± 0.05%), and B9 (5.6 ± 0.1%). Triethyl citrate (TEC) was identified in F20 (6.3 ± 0.06%), F21 (6.27 ± 0.03%), F22 (6.5 ± 0.1%), G23 (7.28 ± 0.05%), G24 (6.2 ± 0.1%), I26 (11.1 ± 0.1%), and J27 (5.34 ± 0.06%). Δ$^{4(8)}$-*iso*-Tetrahydrocannabinol (Δ$^{4(8)}$-*iso*-THC) is a previously described byproduct of acid-catalyzed CBD cyclization (Scheme 1)[18] and was detected in all 27 samples ranging from 2.36 ± 0.05% to 12.79 ± 0.06% with $\bar{x}$ ± SD of 5.4 ± 3.5% in $n = 16$ where quantification was possible (see SI). Olivetol (5-pentyl-1,3-benzenediol, Chart 1) was identified in 22/27 products, but its quantification was not possible (see SI). Olivetol has been previously shown in EVALI-associated CECs that also contain unnatural cannabinoid distributions[7] and is likely a byproduct of chemical synthesis. Olivetol is a synthetic precursor to tetrahydrocannabinols,[19,20] and its presence could indicate the use of these pathways for production. 9-Ethoxyhexahydrocannabinol (9-EtO-HHC) is a known byproduct of CBD cyclization in ethanol[21] and was detected in D13 and D14. 9-EtO-HHC presence is correlated with lower levels of Δ^8-THC ($p < 0.01$) and higher levels of Δ$^{4(8)}$-iso-THC ($p < 0.01$) than in D15 and D16, suggesting that ethanol may favor Δ$^{4(8)}$-*iso*-THC formation. Bornyl chloride (Chart 1), a known reaction product of HCl and *β*-pinene,[22] was tentatively identified by

Table 1. Major Components of 27 Products (P) from 10 Brands (B)[a]

B	P	Δ^8-THC reported	Δ^8-THC measured	Δ$^{4(8)}$-*iso*-THC	*iso*-THCBF
A	1	83.2	76 ± 1	4.24 ± 0.07	1.22 ± 0.02
	2	83.2	79.5 ± 0.1	3.45 ± 0.03	1.25 ± 0.05
	3	86.15	81.2 ± 0.6	3.48 ± 0.03	1.31 ± 0.04
	4	84.66	79.5 ± 0.8	3.9 ± 0.1	*d*
B	5	93.0821	75 ± 2	*c*	0.88 ± 0.05
	6	93.0821	77 ± 1	*c*	*e*
	7	93.0821	62.7 ± 0.7	7.96 ± 0.09	*d*
	8	93.0821	77 ± 1	*c*	*e*
	9	93.0821	78 ± 2	*c*	0.63 ± 0.03
C	10	90	74.8 ± 0.2	4.79 ± 0.03	0.957 ± 0.004
	11	90	77.4 ± 0.4	4.23 ± 0.04	0.9 ± 0.02
	12	90	79.4 ± 0.4	3.74 ± 0.05	0.9 ± 0.02
D	13	90	54.8 ± 0.2	12.79 ± 0.06	1.67 ± 0.02
	14	90	53.6 ± 0.5	12.51 ± 0.05	1.65 ± 0.04
	15	90	78.0 ± 0.7	4.13 ± 0.04	1.6 ± 0.02
	16	90	79.9 ± 0.7	2.36 ± 0.05	0.73 ± 0.02
E	17	77.71	78.8 ± 0.4	3.01 ± 0.03	0.61 ± 0.02
	18	77.71	80.3 ± 0.7	2.851 ± 0.005	0.415 ± 0.008
	19	77.71	79.7 ± 0.2	2.75 ± 0.05	0.472 ± 0.005
F	20	80.85	76.8 ± 0.3	*c*	*c*
	21	84.02	77.1 ± 0.7	*c*	*c*
	22	81.87	77 ± 1	*c*	*c*
G	23	85.000	70.9 ± 0.7	*c*	*c*
	24	81.240	78.9 ± 0.9	*c*	*c*
H	25	78.43	61.6 ± 0.3	10.79 ± 0.05	1.54 ± 0.01
I	26	*b*	72.2 ± 0.3	*c*	*c*
J	27	*b*	73.4 ± 0.2	*c*	*c*

[a]Levels are mass % ± standard error of the mean (SEM). [b]No available data. [c]NQ: identified but not quantifiable. [d]Less than limit of detection (signal-to-noise ≤3). [e]Less than limit of quantification (signal-to-noise ≤ 12).

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GC-MS (Figure S23) in A2 and A3 and is indicative of HCl as a cyclization catalyst. However, its absence in other products does not rule out the use of HCl, as its presence in A2 and A3 may simply be evidence of starting material contaminated with β-pinene. The potential for bornyl chloride to generate HCl gas when pyrolyzed[23] could present a significant inhalation hazard.

In addition to the above, a molecule which, to the best of the authors' knowledge, has never been previously described was also identified. The cannabinoid (5a*R*,9a*S*)-5a-isopropyl-8-methyl-3-pentyl-5a,6,7,9a-tetrahydrodibenzo[*b*,*d*]furan-1-ol or *iso*-tetrahydrocannabifuran (*iso*-THCBF, Chart 1) is likely the result of a hydride shift in the carbocation intermediate (Scheme 1). *iso*-THCBF was isolated from Δ^8-THC CEC products and characterized by mass spectrometry and 1D and 2D NMR (see SI). *iso*-THCBF was present in nearly all products tested but was not quantifiable in products containing TEC due to spectral overlap.

CEC screening by inductively coupled plasma-mass spectrometry (ICP-MS) shows the existence of metals such as magnesium (599 ± 391 ppb, $\bar{x}$ ± SD, $n = 10$), chromium (446 ± 758 ppb), nickel (380 ± 364 ppb), copper (509 ± 1143 ppb), zinc (1.8 ± 2.1 ppm), mercury (160 ± 162 ppb), lead (42 ± 28 ppb), and others (see SI). These metals are likely leachates from vaporizer components or production materials, and their inhalation could cause deleterious effects on the respiratory tract that stem from the generation of reactive oxygen species.[24,25] ICP-MS identified elevated levels of silicon (205 ± 108 ppm), a finding that has been previously shown for EVALI-associated CECs.[26] Silica gel may be used as a purification medium or decolorizing agent, and its potential delivery to the respiratory tract from these products is a subject of further investigation.

QNMR indicates that Δ^8-THC levels can vary as much 40% from the labeled value (Table 1), suggestive of poor testing capabilities and falsified results. For brand A, the average of the sums of Δ^8-THC and $\Delta^{4(8)}$-iso-THC for each product is not significantly different from the average reported Δ^8-THC content ($p < 0.01$), suggesting that the analysis method (HPLC-UV as stated in the certificate of analysis) cannot discriminate the two. Brands B−E appear to use one lab result for all their products when these not only have variable levels of Δ^8-THC but also contain distinct levels of byproducts indicating different manufacturing methods in products that otherwise appear identical except for flavor formulation. Significant levels of understudied ($\Delta^{4(8)}$-*iso*-THC, 9-EtO-HHC) and novel (*iso*-THCBF) cannabinoids present a danger to users as these compounds are not well characterized pharmacologically and could cause unexpected levels of intoxication. High levels of unlabeled cutting agents present a further complication given the little safety information available. Further chemical, pharmacological, and toxicological testing of these and similar products is necessary.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.chemrestox.1c00388.

Analytical methodology, structural identifications, relevant spectra, and full ICP-MS data (PDF)

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Author Contributions

The manuscript was written through contributions of all authors.

Notes

The authors declare no competing financial interest.

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■ ABBREVIATIONS

CEC, cannabis e-cigarette; EVALI, e-cigarette or vaping product use associated lung injury; CBD, cannabidiol

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Supporting Information:

Novel Δ^8-tetrahydrocannabinol vaporizers contain unlabeled adulterants, unintended byproducts of chemical synthesis, and heavy metals

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NMR methodology

^{1}H NMR was chosen as a primary method for assessing chemical composition of the Δ^8-THC CECs given this method's previously demonstrated ability to characterize molecules used as vaporizer adulterants that are difficult to characterize by GC-MS or LC-MS,[1] and for the possibility of identifying and quantifying compounds for which reference standards do not exist. In addition, NMR offers the possibility of identifying molecules without the need for developing a dedicated GC-MS or LC-MS chromatographic method, which may be necessary for samples that contain complex mixtures of isomeric cannabinoids that tend to co-elute and have similar mass spectral features. Rapid analysis of these samples was deemed necessary given the timely nature of this topic.

Triplicate quantitative ^{1}H NMR samples were prepared by massing 20-30 mg Δ^8-THC CEC oils in 1.4 mL plastic centrifuge tubes, adding 500 µL DMSO-d_6 and 10 µL of 392 mM benzoic acid in DMSO-d_6 internal standard, sonicating for ~5 min., vortexing, then transferring to Wilmad 5 mm precision 500 MHz NMR tubes (Vineland, NJ). ^{1}H NMR spectra were acquired on a Bruker 500 MHz with 32 scans, 14.5 s repetition rate (12.8 s relaxation delay was chosen as 4x the T_1 of the longest relaxing proton, the internal standard benzoic acid, 3.2 s), 90° flip angle, with 64k data points. Spectra were processed using Mestrenova with a 0.2 Hz line broadening factor, to a final data size of 64k real data points, manually phase corrected, and baseline corrected with the Mestrenova Bernstein polynomial fit. All other, non-quantitative NMR spectra were recorded with a number of scans and relaxation delay sufficient to provide adequate signal-to-noise for the purposes of the experiment, and processed in a similar manner as above. Reported Δ^8-THC data (Table 1) were obtained from product packaging or from certificates of analysis available online accessible by following QR code links on the packaging.

GC-MS methodology

GC-MS data was obtained using a Shimadzu GC-2010 wherein 1 μL of sample was injected at 250 °C with a 20x split ratio and separated on a 30 m Zebron ZB-XLB 0.25 mm i.d., 0.25 μm film thickness GC column with a constant flow of 0.95 mL/min. He at an initial oven temperature of 100 °C that was held for 3 min., then ramped to 280 °C at a rate of 24 °C/min. and held for 5 min. for a total run time of 15.5 min. The GC was interfaced with a Shimadzu GCMS-QP2010 with electron impact ionization operating with an ion source temperature of 225 °C, an interface temperature of 250 °C, and a detector voltage of 1.5 kV scanning between 50-500 amu. Mass spectral data were compared to a NIST spectral library database.

ICP-MS methodology

For this analysis, one product chosen arbitrarily from each brand of Δ^8-THC CEC was used. Each 50-90 mg sample was digested in concentrated nitric acid (ultra trace grade) on a hot block at 95°C for one hour. The red/orange colored digest was transferred to a 15 mL polypropylene tube and ultrapure water was added to a total volume of 10 mL. After addition of water a yellowish precipitate was formed and the samples were centrifuged to sediment the precipitate and leave a clear solution for analysis. For Total Quant, S, and Si analyses, kinetic energy discrimination mode was used at 4.6 mL/min He flow. Total Quant external calibration standard was a 1 ppm solution of all analyzable elements in 2% nitric acid. S and Si were calibrated at 0, 1, and 2 ppb standards of each element. The plasma RF power was 1600 W and the Ar flow was 17 L/min. Data obtained from these experiments is presented in Tables S1 and S2.

Identification of components in Δ^8-THC CECs

The presence of Δ^8-THC was confirmed by comparison of a ^{1}H NMR sample of Δ^8-THC made from evaporating two 1 mg/mL samples in methanol (Sigma Aldrich, St. Louis, MO) and working up in DMSO-d_6 (Figure S1), and assignments were aided by 2D ^{1}H correlation spectroscopy (COSY) and by comparison with previously published ^{1}H NMR data.[2] In addition, GC-MS analysis of samples in Table 1 indicated to presence of Δ^8-THC with match qualities >90% with respect to the NIST spectral database. The alkenyl proton on Δ^8-THC (δ 5.39 ppm, *m*, 1H) which shows little overlap with other resonances was chosen for quantification of Δ^8-THC. However, any potential overlap of other resonances is a potential source of systematic error. Resonances corresponding to Δ^8-THC and the adulterants were the dominant features of the ^{1}H NMR spectra (Figure S2), but upon closer inspection (Figure S3) minor resonances corresponding to terpenes, adulterants, and unidentified components are visible. The resonance corresponding to the Δ^9-tetrahydrocannabinol (Δ^9-THC) alkenyl proton is visible in all spectra but overlaps with a terpene resonance (likely β-myrcene) and Δ^9-THC was not quantifiable in any of the Δ^8-THC CECs. Medium chain triglyceride (MCT) oil was identified by spiking (Figure S4) with a sample of commercially available MCT oil (Greenive, Eden, ID) and quantified by integrating the 4.26 ppm resonance. Triethyl citrate (TEC) was identified by spiking (Figure S5) with a pure standard (Sigma Aldrich, St. Louis, MO) and quantified by integrating the 2.86 ppm resonance.

All Δ^8-THC CECs were assayed by GC-MS which identified α-pinene in 2/27 samples (avg. match quality: 93%, retention time [RT]: 2.3 min.), β-pinene in 4/27 samples (avg. match quality: 87%, RT: 2.7 min.), limonene in 3/27 samples (avg. match quality: 85%, RT: 3.6 min.), β-caryophyllene in 10/27 samples (avg. match quality: 84%, RT: 6.95 min.), α-humulene in 4/27 samples (avg. match quality: 92%, RT: 7.2 min.), ethyl citrate in 7/27 samples (avg. match quality: 87%, RT: 8.4 min.), and Δ^8-THC in 27/27 samples (avg. match quality: 92%, RT: 12.6 min.). Two or three minor and overlapping peaks eluted immediately before Δ^8-THC in all samples, but did not show matches to the NIST spectral database. These likely corresponded to minor cannabinoids with ions *m/z* = 314, 299, 271, and 231 amu as major features.

Olivetol has been speculated as a byproduct of cannabidiol (CBD) conversion to Δ^8-THC,[3] and the presence of this compound was confirmed by spiking with a pure standard (Sigma Aldrich, St. Louis, MO) which showed an increase in intensity of the phenol protons resonance (Figure S6). Given that this resonance showed overlap with another phenol resonance corresponding to a minor cannabinoid (*vide infra*) and that olivetol's other resonances were not visible due to overlap with Δ^8-THC, the presence of olivetol was further confirmed by enriching the olivetol content of a sample via acid/base extraction. ~650 mg of Δ^8-THC CEC oil was dissolved in 10 mL dichloromethane (DCM), extracted thrice in 15 mL 5% NaOH, the combined aqueous layers acidified to pH < 1, added with brine, extracted thrice in 15 mL DCM, dried over Na_2SO_4, filtered by gravity filtration, then evaporated under a gently stream of N_2. 11 mg were isolated. ^{1}H NMR determined that this extract was 1:1.9 Δ^8-THC:olivetol. The presence of olivetol was confirmed by spiking (Figure S7), and by examination of the GC-MS chromatogram of this sample as compared with a sample of pure olivetol, allowing for full confirmation of the presence on olivetol (Figure S8). Quantification of olivetol by ^{1}H NMR was not possible due to spectral overlap.

In order to ascertain the identify of minor cannabinoids that are isomeric with major cannabinoids present in all Δ^8-THC CECs, column chromatography was used to enrich minor cannabinoids visible by thin layer chromatography (TLC) in 8:2 hexanes:diethyl ether (H:E). ~650 mg of Δ^8-THC CEC oil was separated over 100 mL silica gel using a gradient elution of 400 mL 9:1 H:E, 200 mL 8:2 H:E, 200 mL 4:2 H:E, then 100 mL 3:2 H:E. Notable fractions corresponding to TLC spots of $R_f = 0.65$ (292 mg), $R_f = 0.35$ (10.4 mg), and $R_f = 0.3$ (6.2 mg) were isolated and NMR spectra were acquired in $CDCl_3$ and DMSO-d_6. Other fractions contained putative flavorants and other cannabinoids and were not investigated and discarded. The major fraction of $R_f = 0.65$ was determined to contain Δ^8-THC, Δ$^{4(8)}$-*iso*-tetrahydrocannabinol (Δ$^{4(8)}$-*iso*-THC), and an unidentified cannabinoid in a ~1:0.4:0.15 ratio, respectively (Figure S9). Δ$^{4(8)}$-*iso*-THC was predicted by Marzullo *et al.* (2020) to be present in samples similar these as an artefact of the acid-catalyzed cyclization of CBD to tetrahydrocannabinols that results from phenol lone pairs forming a bond with a carbocation on C1 instead of C9, resulting in the iso-tetrahydrocannabinol Δ^8-*iso*-THC that isomerizes to the more thermodynamically stable $\Delta^{4(8)}$-*iso*-THC.[4] While Marzullo *et al.* (2020) reported ^{1}H NMR chemical shifts for this molecule in acetone-d_6, Gaoni and Mechoulam (1966)[5] reported shifts in $CDCl_3$ which match closely to those observed herein (Figure S10). In particular, the chemical shift corresponding to H_3 (4.17 ppm in $CDCl_3$ and 4.13 in DMSO-d_6, see Figure S10) is very unique for a tetrahydrocannabinol benzyl proton due to it being nearly in the plane of the aromatic ring whose ring current deshields it.[5] A COSY experiment shows this proton couples only to a resonance at ~1.83 ppm, and though it suffers from overlap, this serves as further confirmation this proton is not a shielded alkene or phenol proton (Figure S11). Given the unique chemical shift of H_3 it was possible to quantify $\Delta^{4(8)}$-*iso*-THC in samples not containing MCT oil, given that the glyceryl methylene protons overlap with H_3. However, in samples with MCT oil, it is still possible to confirm the presence of $\Delta^{4(8)}$-*iso*-THC by examination of its phenol and aromatic protons resonances (Figure S12).

^{1}H NMR analysis of the fraction corresponding to $R_f = 0.35$ showed a pair of resonances indicative of an electron-rich aromatic ring typical for cannabinoids, suggesting this molecule is a cannabinoid or cannabinoid-derivative, in addition to the presence of 21 unique resonances in the ^{13}C NMR spectrum. However, other resonances showed chemical shifts that were unfamiliar to the authors upon review of available literature. Integration of all the ^{1}H resonances indicated the sample was reasonably pure (~90 %), and GC-MS analysis also displayed a single chromatographic peak. The mass spectrum showed prominent ions of m/z = 314 and 271 amu, indicating this molecule readily loses a propyl or isopropyl group (Figure S13) and is isomeric with the major tetrahydrocannabinols. The ^{1}H NMR spectrum showed prominent peaks indicative of an isopropyl group adjacent to a quaternary carbon, a heptet (δ 1.95 ppm, J = 6.9 Hz, 1H) and a pair of doublets (δ 0.98 ppm, J = 6.9 Hz, 3H; δ 0.94 ppm, J = 6.9 Hz, 3H). Benzoxocin and benzoxonin are cannabinoid-derived molecules with isopropyl groups (adjacent to tertiary carbons) have been previously reported,[6] but do not share similar spectral features to the compound herein. A structure for *iso*-tetrahydrocannabifuran (Chart 1) was suggested on the basis of the ^{1}H NMR and mass spectral data, and the structure was confirmed by correlating data from ^{13}C NMR, DEPT-135 ^{13}C NMR, COSY, HSQC, HMBC, and NOESY experiments, results of which are displayed in Figures S14-19 and ^{1}H and ^{13}C chemical shifts are reported therein. Connectivity in the *p*-menthyl ring is confirmed by the appearance of a coupling system of 4 unique protons on positions 6 and 7 which show coupling to each other but to no other protons, as shown in the COSY. An HMBC correlation between a H_6 with C_{5a} which, in turn, also shows an HMBC correlation with the heptet H_{11}, which in turn shows COSY crosspeaks with the two methyl doublets confirms the position of the isopropyl group. The HMBC correlation between H_{9a} and C_{5a} are further proof for this connectivity. A strong NOE correlation between H_{9a} and the isopropyl methyl groups H_{13} and H_{12} (and a correspondingly weaker one between H_{9a} and H_{11}) suggest the *cis* configuration of the two groups, which is the only possible conformation for a dibenzofuran-based structure as such. The strong COSY crosspeak between H_{9a} and H_9 are further evidence for the position of the double bond in the *p*-menthyl ring, which is also confirmed by the weak, but existent, HMBC correlation between H_9 and C_8. Though the (5a*R*,9a*S*) configuration is the configuration expected if the stereochemistry of CBD C3 position is maintained during its proposed mechanism of formation (Scheme 1), the present spectral data is not conclusive as to whether the molecule isolated is this, its (5a*S*,9a*R*) enantiomer, or a mixture of the two at some level of enantiomeric excess. Molecules with identical C-C bond connectivity but with a fully saturated cyclohexane ring were described by Arnone *et al.* (1975),[7] but these were not named or described in detail.

^{1}H NMR and GC-MS analysis of the fraction corresponding to $R_f = 0.3$ showed evidence of 9-ethoxy-hexahydrocannabinol (9-EtO-HHC). The GC-MS chromatogram of this fraction showed only one peak, the mass spectrum for which is displayed in Figure S20. The appearance of a molecular ion $m/z = 360$ amu, and fragment ion $m/z = 314$ amu is suggestive of loss of a neutral ethanol to form a Δ^9-THC molecular ion fragment. The ^{1}H NMR spectrum (Figure S21), shows a set of resonances consistent with an ethoxy group with diastereotopic methylene protons (as would be expected for the 9-EtO-HHC structure): two doublets of quartets (δ 3.58 ppm, $J = 8.8$, 7.0 Hz, 1H and δ 3.43 ppm, $J = 8.8$, 7.0 Hz, 1H) and a triplet (δ 1.21 ppm, $J = 7.0$ Hz, 3H), the connectivity of which is confirmed with the COSY (Figure S22).

Element	Brand 1	2	3	4	5	6	7	8	9	10
S	1.1E+05	2.9E+04	3.1E+04	2.7E+04	4.5E+04	1.9E+04	1.4E+05	9.5E+04	1.3E+05	7.4E+04
Li	1.6E+02	4.9E+01	5.3E+01	3.0E+01	2.1E+01	9.1E+00	1.7E+02	2.0E+02	1.5E+02	1.4E+02
Be	0.0E+00	8.3E+00	3.4E-01	4.2E+00	0.0E+00	1.3E+00	3.7E-01	0.0E+00	0.0E+00	1.0E+01
Mg	5.1E+02	1.4E+03	1.5E+02	4.2E+02	4.6E+02	1.5E+02	8.6E+02	6.6E+02	1.0E+03	3.8E+02
Si	7.1E+04	1.3E+05	1.8E+05	1.6E+05	2.3E+05	1.6E+05	7.0E+04	3.6E+04	1.2E+05	6.6E+04
P	0.0E+00	3.0E+01	4.6E+01	9.3E+01	9.6E+01	4.0E+01	4.9E+01	0.0E+00	0.0E+00	0.0E+00
K	3.9E+03	2.7E+03	2.7E+03	7.2E+03	7.8E+03	2.3E+03	6.4E+03	3.5E+03	1.4E+04	2.3E+03
Ca	7.7E+02	1.2E+04	3.2E+02	6.1E+02	4.7E+02	1.9E+02	8.7E+02	1.4E+03	8.2E+02	0.0E+00
Ti	1.8E+02	5.1E+01	8.7E+00	2.0E+02	1.8E+01	7.8E+00	1.8E+02	1.7E+02	3.6E+02	1.4E+02
V	3.6E+00	7.4E+00	1.0E+00	3.8E+00	2.9E-01	1.6E+00	3.3E+00	5.5E+00	1.1E+01	8.5E+00
Cr	5.2E+02	3.8E+01	4.1E+01	5.6E+01	2.4E+01	2.3E+01	4.0E+02	5.3E+02	2.5E+03	3.1E+02
Mn	8.0E+01	1.8E+01	8.7E+00	1.8E+01	4.4E+01	4.7E+00	2.2E+01	4.9E+01	1.2E+02	3.2E+01
Fe	9.3E+03	5.2E+02	5.2E+02	5.6E+02	4.1E+02	2.6E+02	1.8E+03	4.0E+03	1.1E+04	4.5E+03
Co	3.2E+01	7.0E+00	1.4E+00	5.8E+01	2.5E+00	4.9E+00	1.3E+01	2.3E+00	1.8E+01	6.1E+00
Ni	3.5E+02	3.5E+02	6.5E+01	1.0E+03	5.5E+01	1.1E+02	2.2E+02	1.0E+03	5.6E+02	9.4E+01
Cu	3.7E+03	4.1E+01	5.1E+01	6.2E+01	5.6E+01	1.3E+02	2.3E+02	4.4E+02	2.7E+02	5.9E+01
Zn	3.9E+03	6.0E+02	2.5E+02	4.4E+02	6.7E+02	4.6E+02	2.3E+03	1.7E+03	6.8E+03	1.5E+03
Ga	5.8E+00	9.3E+00	1.2E+00	4.8E+00	2.0E+00	0.0E+00	3.9E+00	3.4E+00	7.0E+00	8.1E+00
Ge	0.0E+00	9.3E+00	0.0E+00	0.0E+00	0.0E+00	0.0E+00	0.0E+00	9.3E-01	0.0E+00	3.4E+00
As	1.5E+01	1.1E+01	0.0E+00	7.8E+00	0.0E+00	0.0E+00	1.2E+01	1.5E+01	1.4E+01	2.0E+01
Se	0.0E+00	3.2E+01	1.3E+01	0.0E+00	6.8E+01	0.0E+00	0.0E+00	2.7E+01	5.6E+01	9.9E+01
Rb	3.3E+00	1.0E+01	3.6E+00	1.1E+01	1.4E+01	3.1E+00	9.6E+00	6.7E+00	1.4E+01	9.0E+00
Sr	2.6E+01	2.8E+01	0.0E+00	9.1E+00	0.0E+00	0.0E+00	3.0E+01	3.7E+01	3.2E+01	2.5E+01
Zr	1.9E+02	9.5E+01	1.4E+01	2.9E+01	1.2E+01	9.8E+00	2.7E+02	2.2E+02	2.4E+02	2.0E+02
Nb	3.0E+00	2.3E+02	4.6E+01	8.1E+01	2.8E+01	3.1E+01	2.9E+00	4.0E+00	3.1E+00	2.1E+01
Mo	3.2E+01	4.7E+01	4.9E+00	1.7E+01	0.0E+00	0.0E+00	3.8E+01	3.4E+01	8.9E+01	4.0E+01
Ru	0.0E+00	5.4E+00	2.7E-01	3.0E+00	0.0E+00	3.3E-01	1.6E-01	0.0E+00	0.0E+00	4.9E+00
Rh	5.2E-01	8.2E+00	2.8E+00	1.0E+01	6.7E-01	1.3E+00	6.9E-01	5.2E-01	3.8E-01	5.1E+00
Pd	1.1E+01	2.7E+02	7.1E+01	1.4E+02	5.5E+01	5.4E+01	1.0E+01	1.0E+01	1.3E+01	2.8E+01
Ag	4.9E+00	4.6E+03	5.7E+02	1.8E+03	1.1E+02	2.0E+02	4.4E+00	1.2E+01	5.4E+00	3.5E+01
Cd	0.0E+00	7.1E+00	1.1E+00	8.3E-01	0.0E+00	0.0E+00	3.3E+01	0.0E+00	2.1E+01	0.0E+00
In	1.5E+00	8.3E+00	0.0E+00	4.0E+00	0.0E+00	0.0E+00	1.6E+00	2.3E+00	1.6E+00	6.6E+00
Sn	2.3E+02	1.3E+02	1.4E+02	1.2E+02	1.4E+02	1.1E+02	1.3E+02	1.3E+02	2.7E+02	1.6E+02
Sb	1.7E-01	6.3E+00	0.0E+00	3.1E+00	0.0E+00	0.0E+00	2.9E+00	6.8E+00	2.9E+00	1.3E+01
Te	0.0E+00	6.8E+00	0.0E+00	0.0E+00	0.0E+00	0.0E+00	4.6E+00	6.3E+00	0.0E+00	1.1E+01
Cs	2.4E+01	1.2E+01	4.0E+00	9.0E+00	0.0E+00	1.6E+00	2.6E+01	3.1E+01	2.8E+01	2.9E+01
Ba	2.9E+01	8.0E+01	8.3E+00	2.4E+02	1.1E+02	5.8E+00	2.7E+01	1.0E+02	6.9E+01	2.4E+01
Hf	5.7E+00	4.1E+02	7.1E+01	1.2E+02	3.9E+01	4.7E+01	7.9E+00	7.6E+00	7.2E+00	2.3E+01
Ta	1.9E+01	9.0E+02	3.0E+02	4.3E+02	1.9E+02	2.2E+02	1.7E+01	2.7E+01	1.9E+01	5.2E+01
W	6.2E+00	2.6E+02	4.4E+01	1.2E+02	5.0E+00	1.8E+01	4.5E+00	7.8E+00	9.5E+00	2.2E+01
Re	2.9E-02	9.1E+00	4.5E-01	4.6E+00	0.0E+00	8.6E-02	6.3E-02	1.2E-01	5.9E-02	6.5E+00
Ir	3.1E+01	8.5E+01	5.3E+01	1.1E+02	3.8E+01	3.2E+01	6.2E+01	1.8E+01	3.1E+01	2.9E+01
Pt	2.3E+00	1.8E+01	6.9E-01	6.2E+00	0.0E+00	0.0E+00	2.7E+00	2.9E+00	3.0E+00	1.2E+01
Au	2.0E+01	2.0E+02	7.2E+01	1.3E+02	2.7E+01	3.7E+01	1.3E+01	3.0E+01	1.7E+01	5.6E+01
Hg	1.4E+02	2.7E+02	4.2E+01	1.3E+02	2.9E+01	7.1E+00	8.7E+01	2.1E+02	1.3E+02	5.6E+02
Tl	1.6E+00	1.4E+02	2.3E+01	5.7E+01	7.9E+00	1.1E+01	1.2E+00	2.9E+00	1.3E+00	1.5E+01
Pb	9.6E+01	2.6E+01	1.4E+01	7.5E+01	5.0E+01	1.6E+01	2.1E+01	6.4E+01	3.4E+01	2.3E+01
Bi	6.3E+00	4.4E+01	8.5E-01	1.1E+01	1.2E+02	1.9E+01	3.2E+00	7.8E+01	2.0E+02	1.6E+01
U	7.4E+00	4.3E+01	1.7E+01	7.5E+01	0.0E+00	2.3E+00	8.3E+00	8.4E+00	9.1E+00	5.3E+01

Table S1. ICP-MS Total Quant analysis data in ppb. Experimental error of the reported values is approximately ±50%.

Brand	Si	S
1	1.1E+05	1.4E+05
2	2.1E+05	5.0E+04
3	3.0E+05	6.1E+04
4	2.7E+05	8.9E+04
5	4.0E+05	8.2E+04
6	2.8E+05	8.0E+04
7	1.1E+05	2.0E+05
8	6.1E+04	6.6E+04
9	1.9E+05	1.5E+05
10	1.0E+05	1.4E+04

Table S2. ICP-MS data obtained from Si and S calibrations in ppb. Experimental error for reported values is ± 5%.

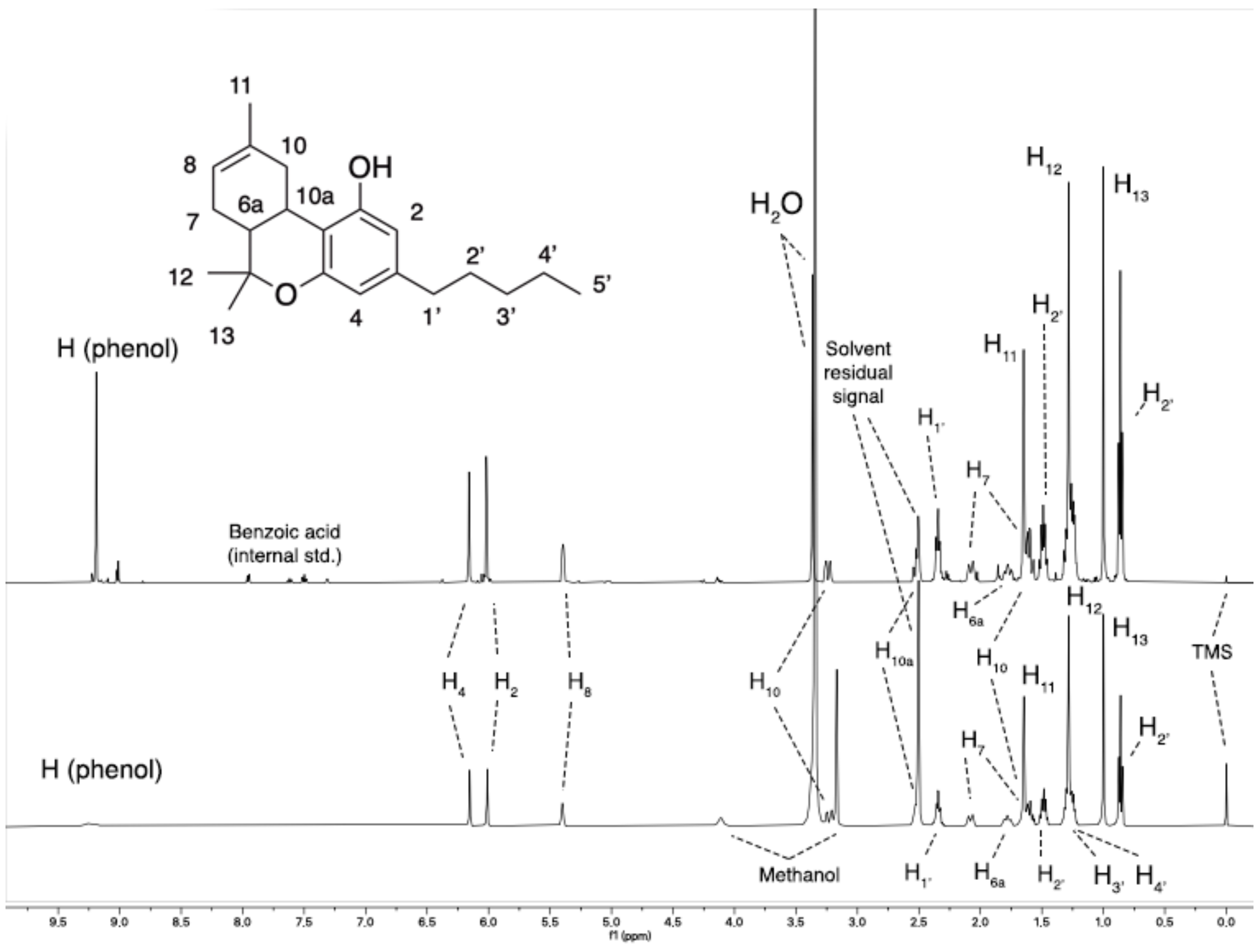


Figure S1. Overlay of a Δ^8-THC CEC (upper) and a pure standard of Δ^8-THC (lower) in DMSO-d_6. The phenol proton suffers from considerable broadening in the lower spectrum due to elevated levels of residual water that was absorbed during evaporation of the methanol solution.

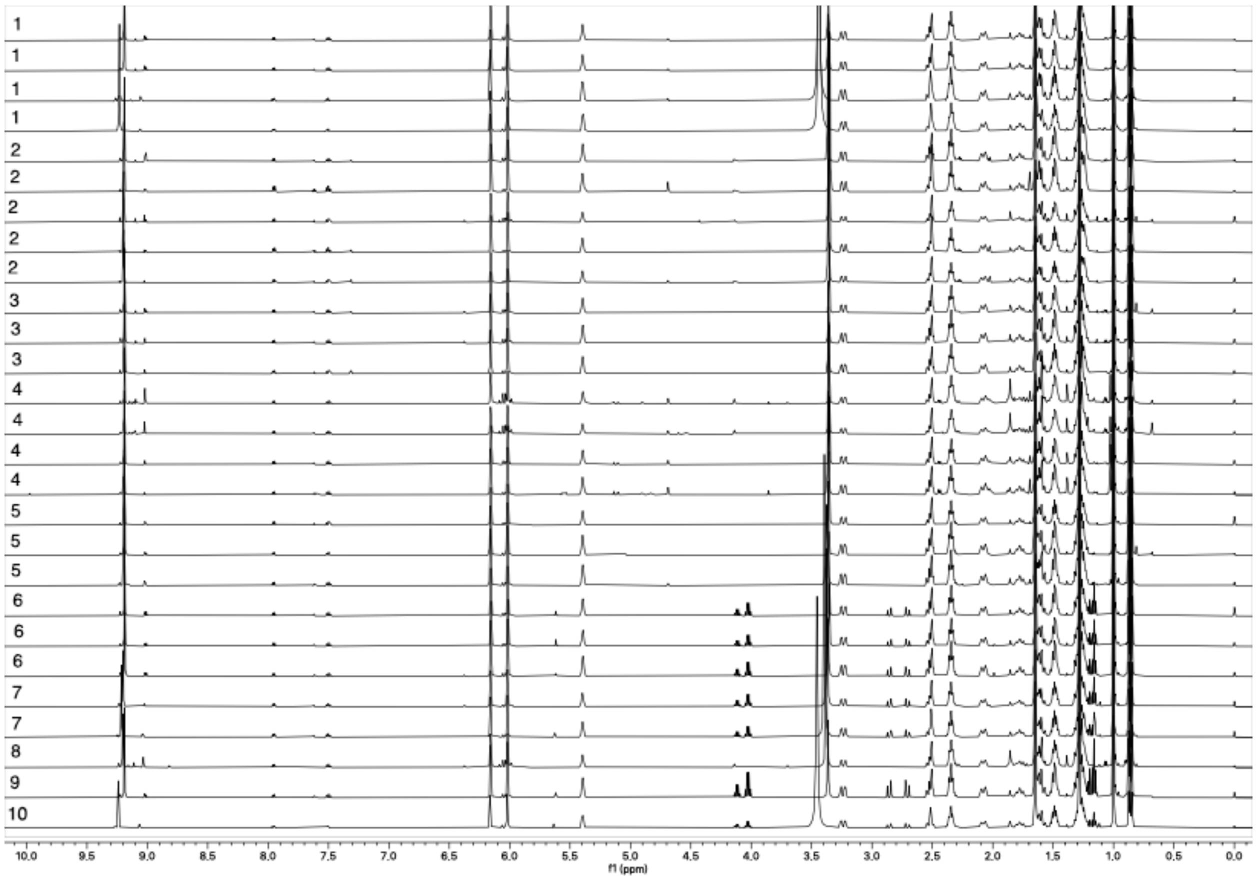


Figure S2. Overlaid ^{1}H NMR spectra in DMSO-d_6 of all Δ^8-THC CECs tested. Major resonances visible correspond to Δ^8-THC. Other resonances correspond to cutting agents such as MCT oil and TEC, the internal standard used for quantification, benzoic acid, and water.

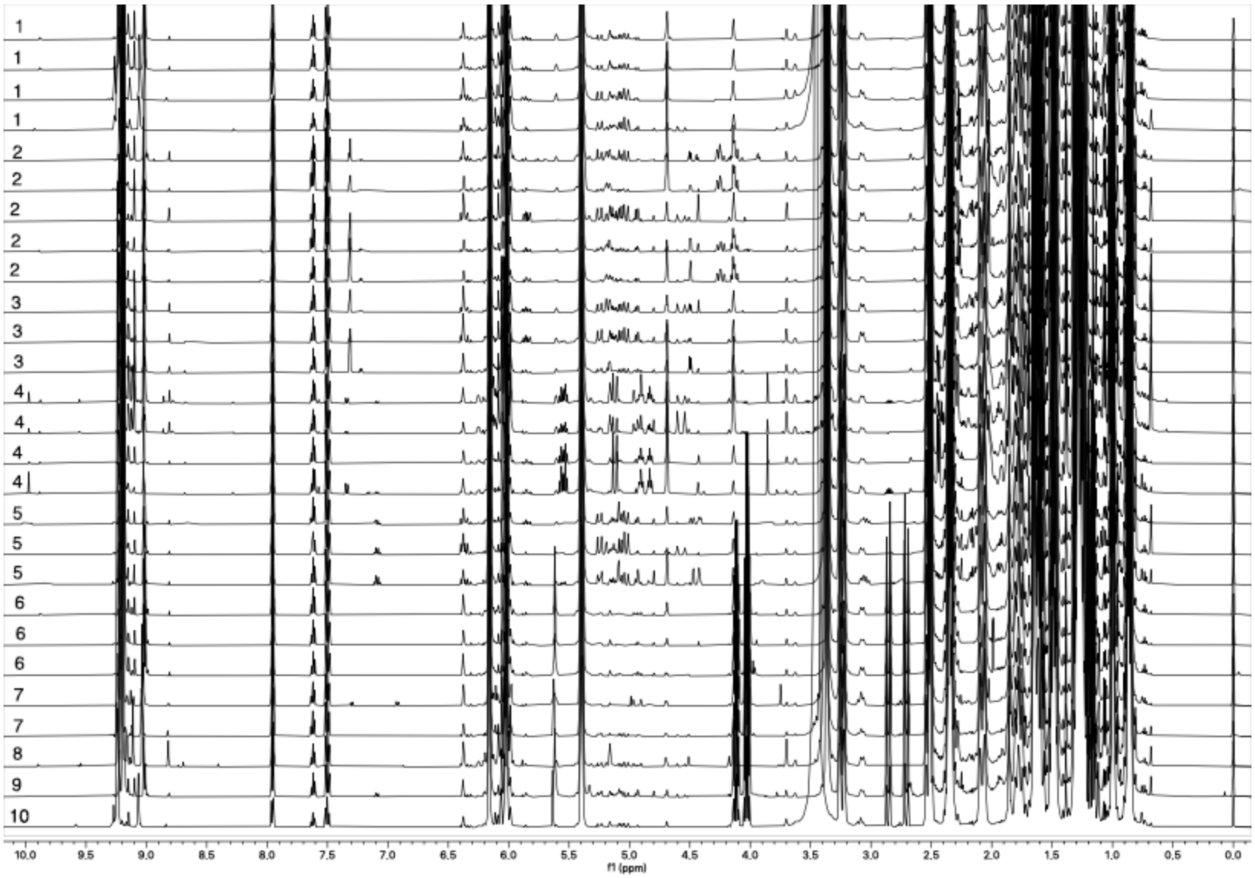


Figure S3. An amplified image of the overlaid spectra in Figure S2 to highlight the abundance of minor components including flavorants, cutting agents, and reaction byproducts.

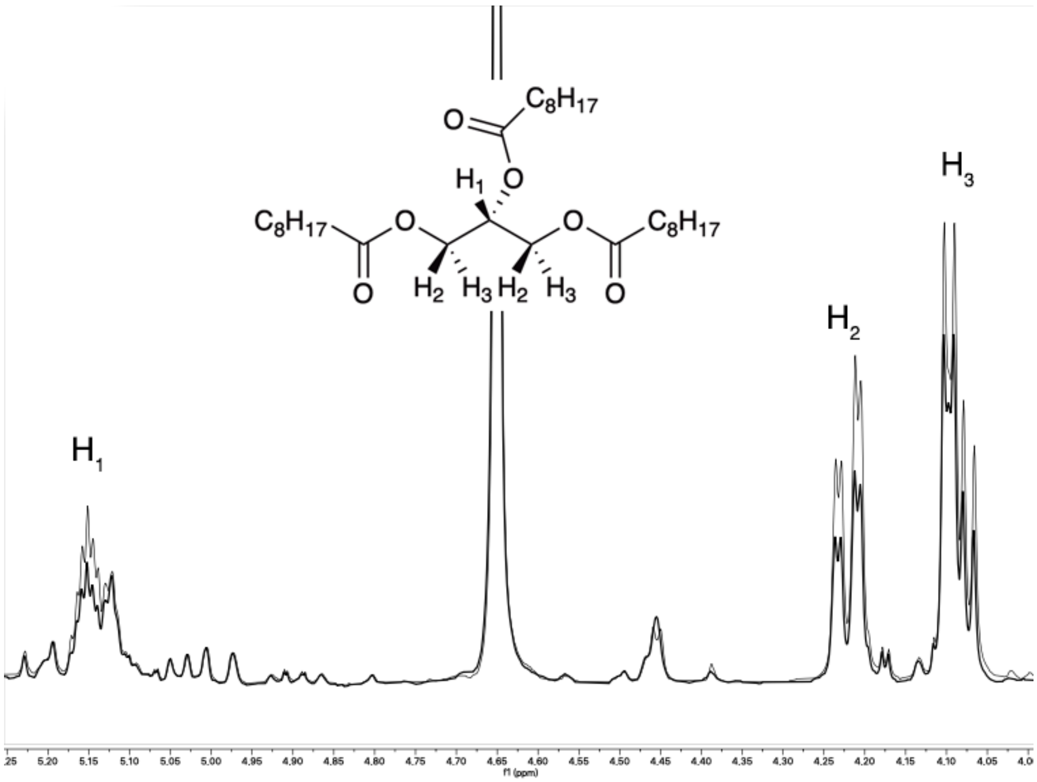


Figure S4. [1]H NMR spectrum of an MCT oil-containing Δ^8-THC CEC containing 14.3 mg of the same in 500 μL DMSO-d_6 (bold) overlaid with a spectrum of the same sample spiked with 0.4 μL of a commercially available MCT oil which is quoted for use as a "carrier oil." [1]H NMR analysis of this MCT oil using peak integrations of glyceryl and alkyl resonances indicates a molecular formula of $C_{30}H_{56}O_6$ and a molar mass of 512 g/mol, indicating the fatty acid content is approximately 1:1 capric and caprylic acids, based on an average chain length of 9 carbons. Spiking shows an increase in intensity of the following resonances from the MCT oil: H_1, the proton α to the central glycerol ester which is split by the adjacent protons into a triplet of triplets (δ 5.19 ppm, J = 6.7, 3.6 Hz); H_2, the two chemically-equivalent protons β and cis to H_1 (δ 4.26 ppm, dd, J = 12, 3.6 Hz); and H_3, the two chemically equivalent protons β and trans to H_1 (δ 4.12 ppm, dd, J = 12, 6.7 Hz). The other resonances are not visible due to overlap with Δ^8-THC.

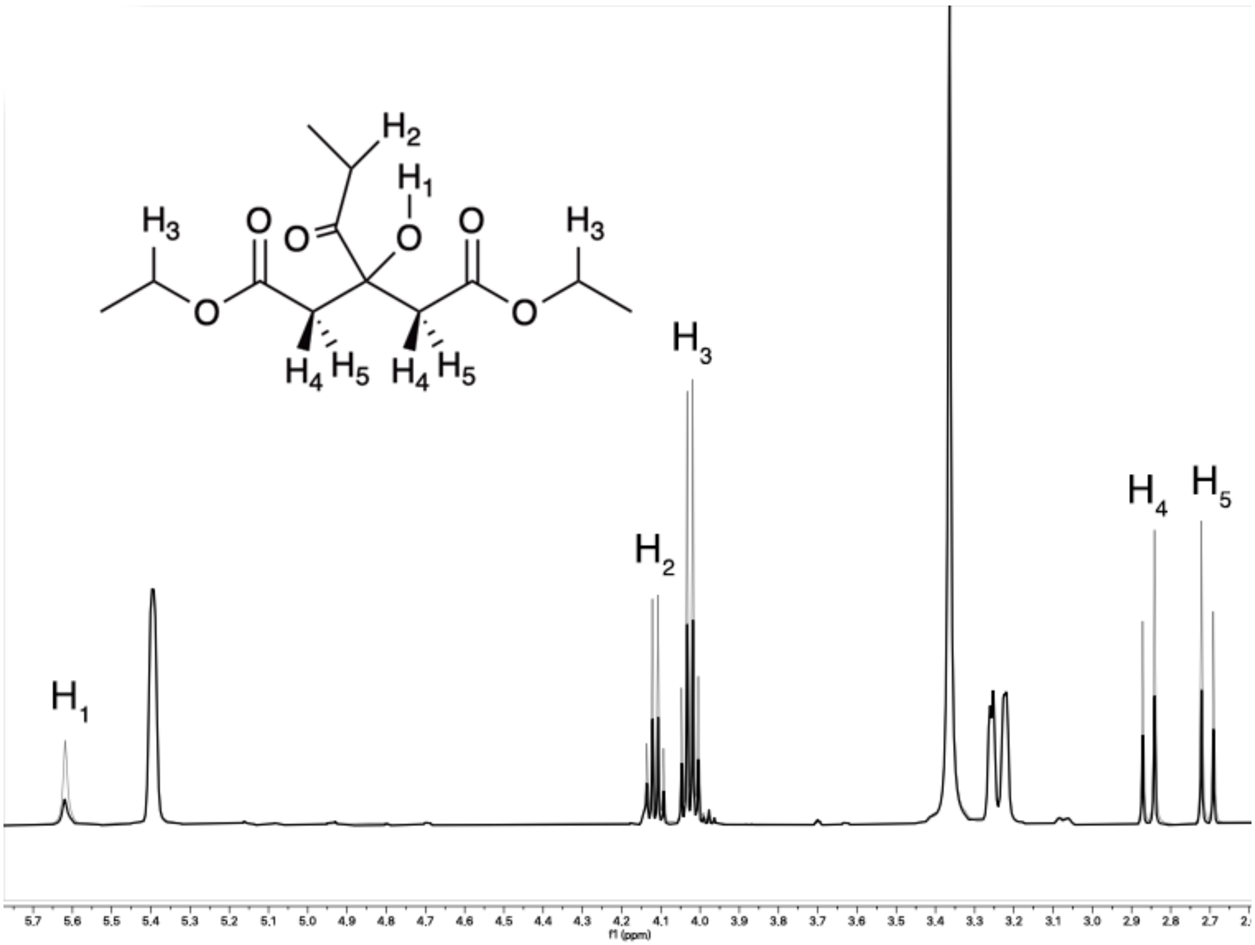


Figure S5. ^{1}H NMR spectrum of a TEC-containing Δ^{8}-THC CEC containing 23.71 mg of the same in 500 µL DMSO-d_6 (bold) overlaid with a spectrum of the same sample spiked with 2.5 µL of TEC. This shows an increase in intensity of the following resonances from TEC: H_1, the hydroxyl proton (δ 5.62 ppm, s, 1H); H_2, the methylene protons from the central ethyl ester (δ 4.11 ppm, q, J = 7.1 Hz, 2H); H_3, the methylene protons from the two terminal ethyl esters (δ 4.03 ppm, q, J = 7.1 Hz, 4H); H_4, the two chemically equivalent methylene protons β to the alcohol (δ 2.86 ppm, d, J = 15.1 Hz, 2H); and H_5, the two other chemically equivalent methylene protons β to the alcohol (δ 2.71 ppm, d, J = 15.1 Hz, 2H). The other resonances are not visible due to overlap with Δ^{8}-THC.

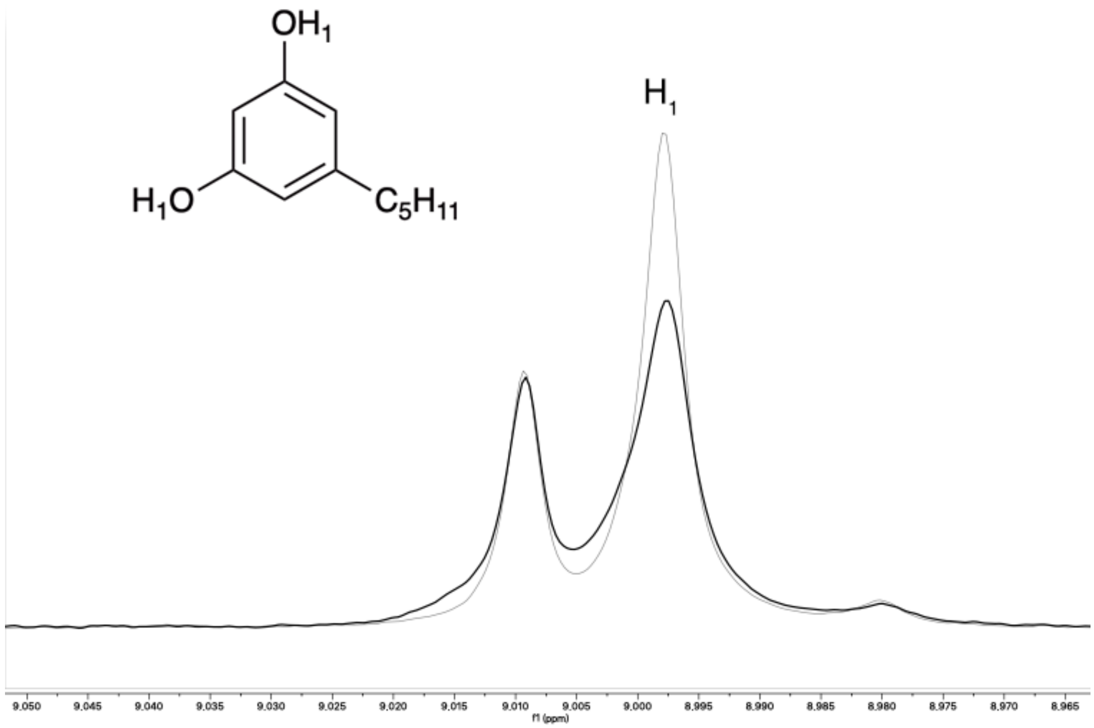


Figure S6. ^{1}H NMR spectrum of ~20 mg Δ^8-THC CEC in 500 µL DMSO-*d*6 (bold) overlaid with a spectrum of the same sample spiked with 2 µL of a 48.98 mg/mL solution of olivetol in DMSO-*d*6. This shows an increase in intensity of the resonance corresponding to the two chemically-equivalent phenol protons (δ 9.0 ppm, s, 2H). The other resonances are not visible due to overlap with Δ^8-THC.

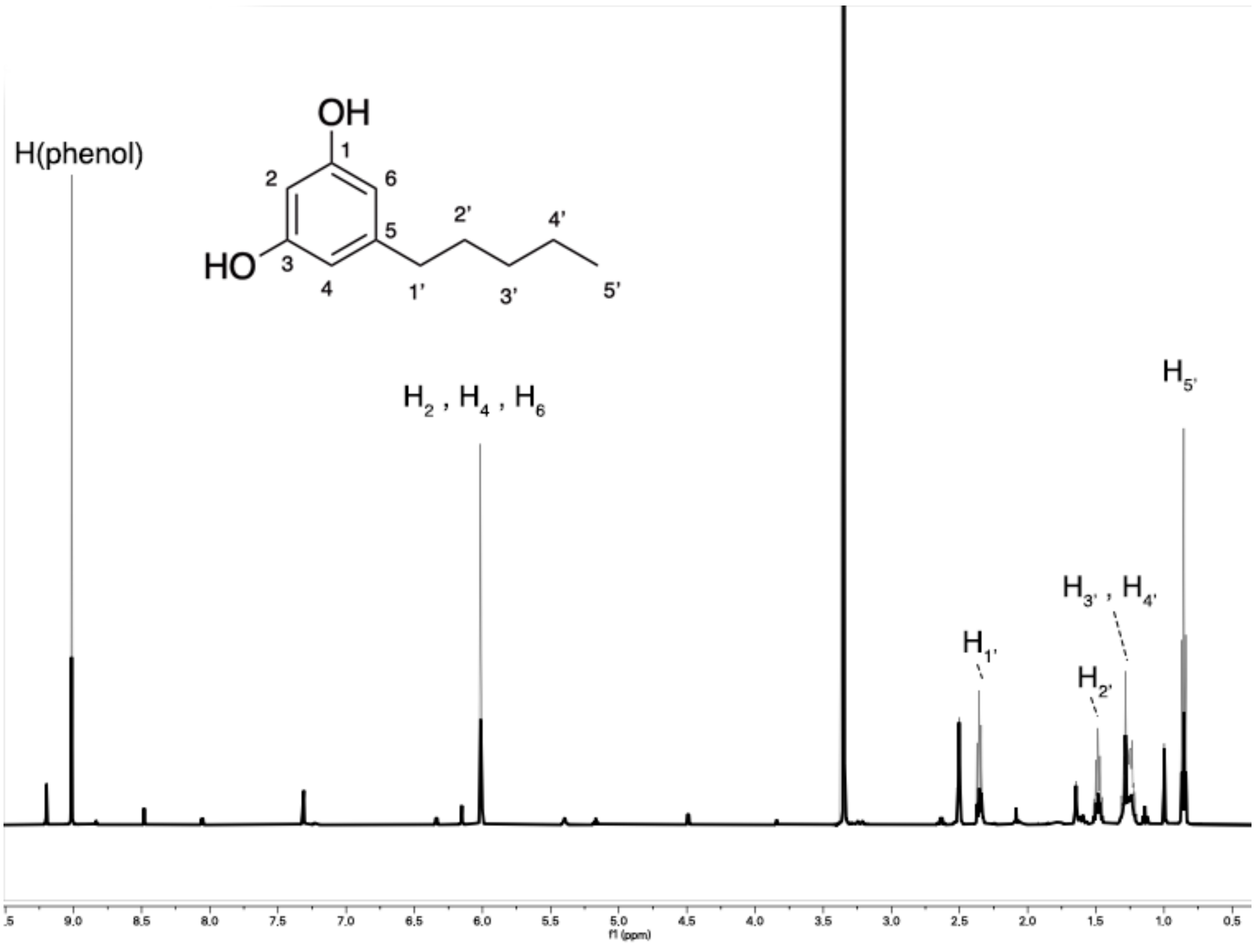


Figure S7. ^{1}H NMR spectrum of ~10 mg Δ^{8}-THC CEC acid/based extract in 500 μL DMSO-d_6 (bold) overlaid with a spectrum of the same sample spiked with ~4 mg olivetol. This shows an increase in intensity of all the olivetol resonances.

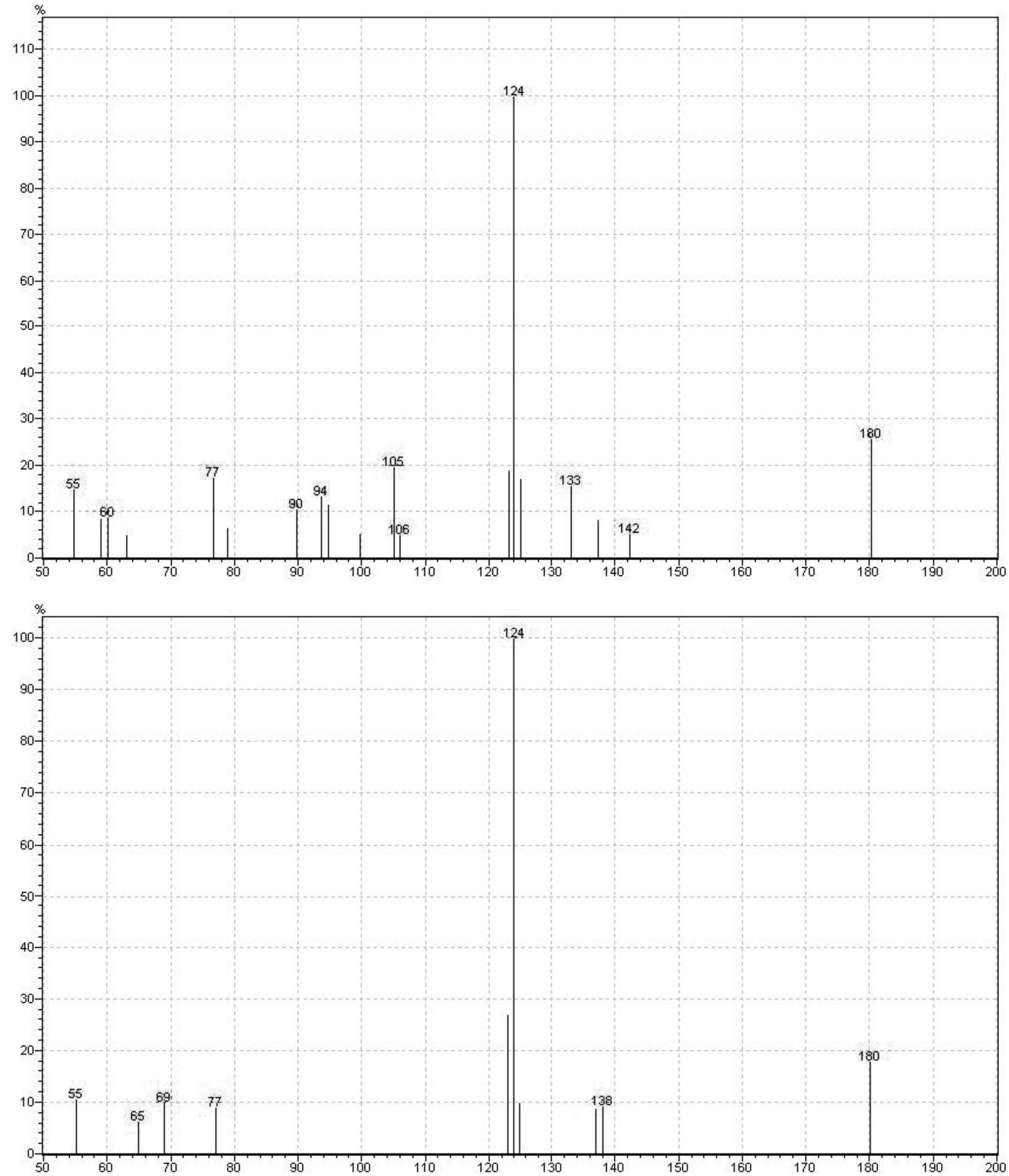


Figure S8. Comparison of the mass spectrum of the peak eluting at RT = 9.967 min. from an injection of ~1000 ng/uL acid/base extract sample (upper) with the mass spectrum of a peak eluting at RT = 9.5 min. from an injection of ~1000 ng/uL pure olivetol. The appearance of *m/z* = 180 amu corresponding to $[C_{11}H_{16}O_2]^+$ molecular ion and *m/z* = 124 amu corresponding to $[C_7H_8O_2]^+$ in both spectra confirm the presence of olivetol.

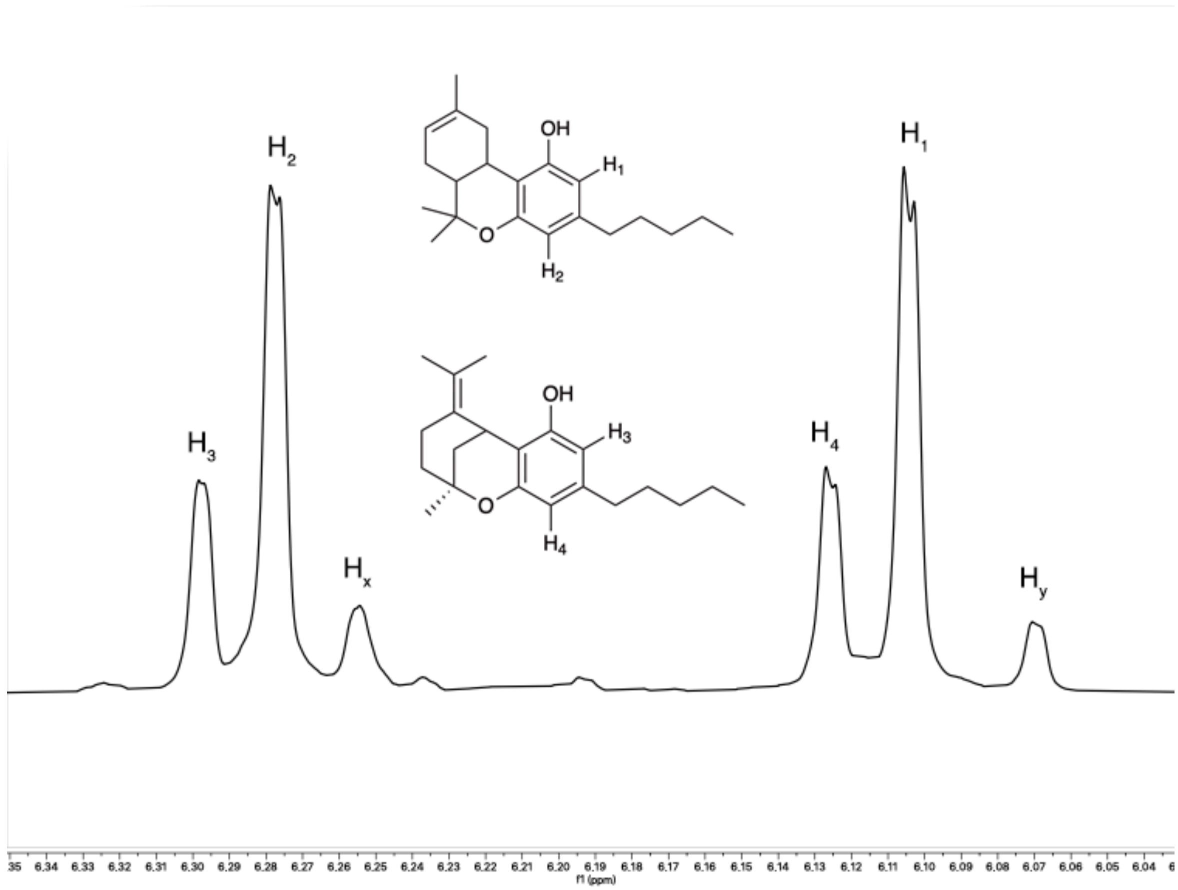


Figure S9. ^1H NMR spectrum in $CDCl_3$ of the aromatic region of the column fraction corresponding to R_f = 0.65. The largest resonances correspond to the aromatic protons on Δ^8-THC, H_2 and H_1, the chemical shifts of which, 6.27 and 6.10 ppm. The second largest pair of resonances correspond to the aromatic protons on $\Delta^{4(8)}$-*iso*-THC, H_3 and H_4. The smallest pair of highlighted resonances likely correspond to a minor, unidentified cannabinoid.

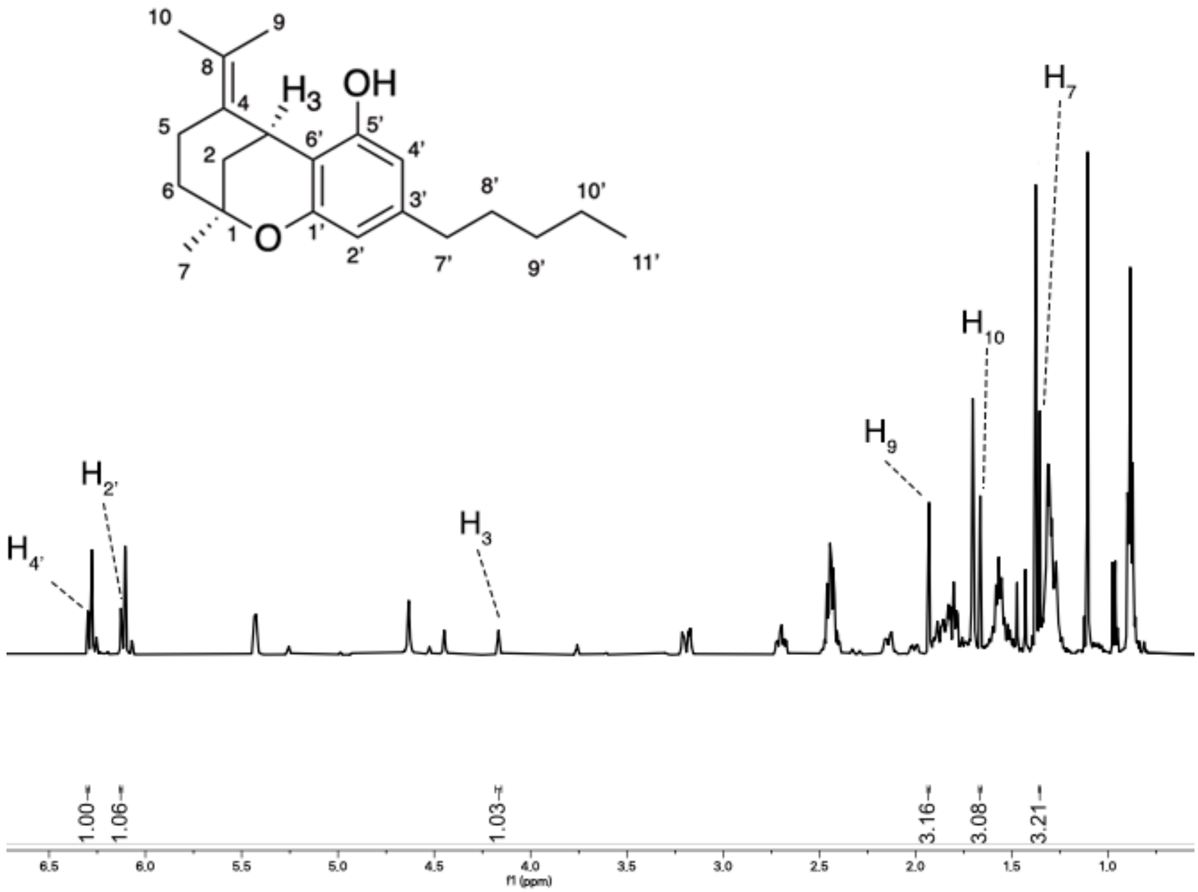


Figure S10. Full ^{1}H NMR spectrum of the column fraction corresponding to $R_f = 0.65$. While the major resonances present correspond to Δ^8-THC, certain resonances corresponding to $\Delta^{4(8)}$-*iso*-THC are visible, specifically: the two aromatic protons $H_{4'}$ (δ 6.29 ppm, m, 1H) and $H_{2'}$ (δ 6.13 ppm, m, 1H), the benzyl proton H_3 (δ 4.17 ppm, m, 1H), the two olefinic protons H_9 (δ 1.93 ppm, s, 3H) and H_{10} (δ 1.66 ppm, s, 3H), and the protons α to the ether linkage H_7 (δ 1.35 ppm, s, 3H). The chemical shifts reported by Gaoni and Mechoulam (1966)[5] for $\Delta^{4(8)}$-*iso*-THC match well with the above: H_3 (4.19 ppm), H_9 (δ 1.94 ppm), H_{10} (1.69 ppm), (δ 1.36 ppm). The aromatic protons' chemical shifts, reported Taylor *et al.* (1966)[8] as δ 6.31 ppm and δ 6.13 ppm, also match well with those shown above, despite the fact that this publication had erroneously assigned them to Δ^8-*cis*-THC, as shown by Gaoni and Mechoulam (1966).[5]

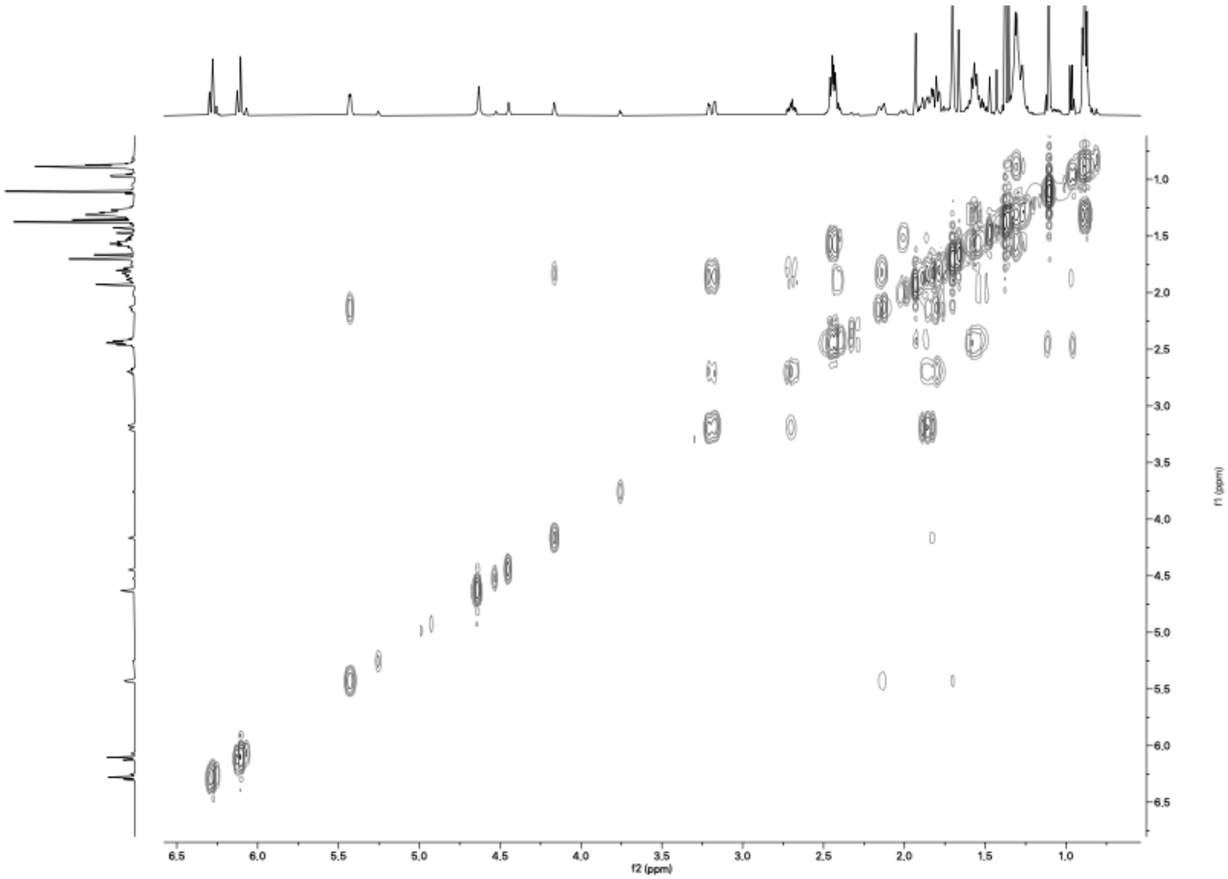


Figure S11. COSY spectrum of the column fraction corresponding to R_f = 0.65. The crosspeak appearing 4.17 x 1.83 ppm is similar to that reported by Marzullo *et al.*[4] despite differences in chemical shift due to it being reported in acetone-d_6 therein, and $CDCl_3$ herein.

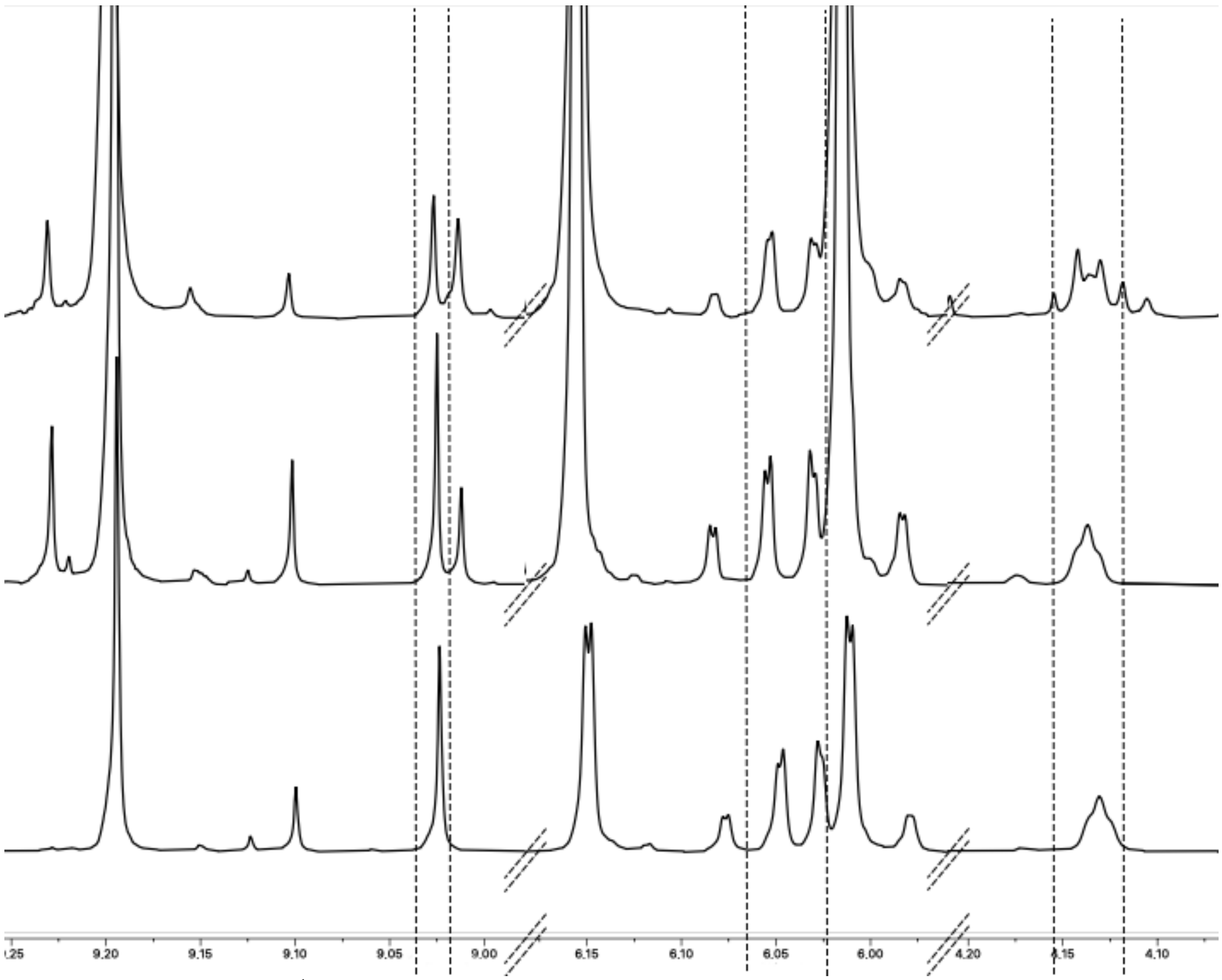


Figure S12. Overlay of ^{1}H NMR spectra in DMSO-d_6 of the column fraction corresponding to R_f = 0.65 that contains $\Delta^{4(8)}$-*iso*-THC (bottom), a Δ^8-THC CEC that does not contain MCT oil (middle), and one that does contain MCT oil (top). In the top spectrum, the $\Delta^{4(8)}$-*iso*-THC benzyl proton (4.13 ppm) is obscured by the MCT oil glyceryl methylene protons, but its phenol protons resonance (9.02 ppm) is still plainly visible despite partial overlap with the olivetol phenol proton resonance (see Figure S4), as are its aromatic protons resonances despite partial overlap with those from Δ^8-THC.

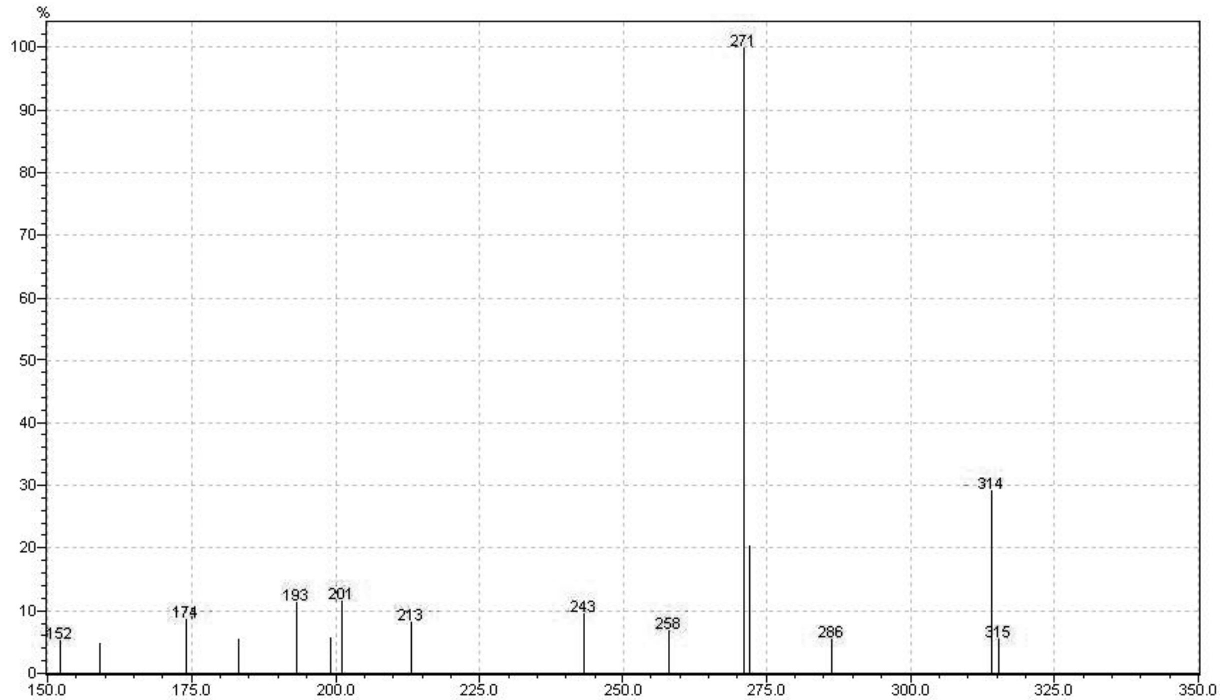


Figure S13. Mass spectrum of *iso*-THCBF.

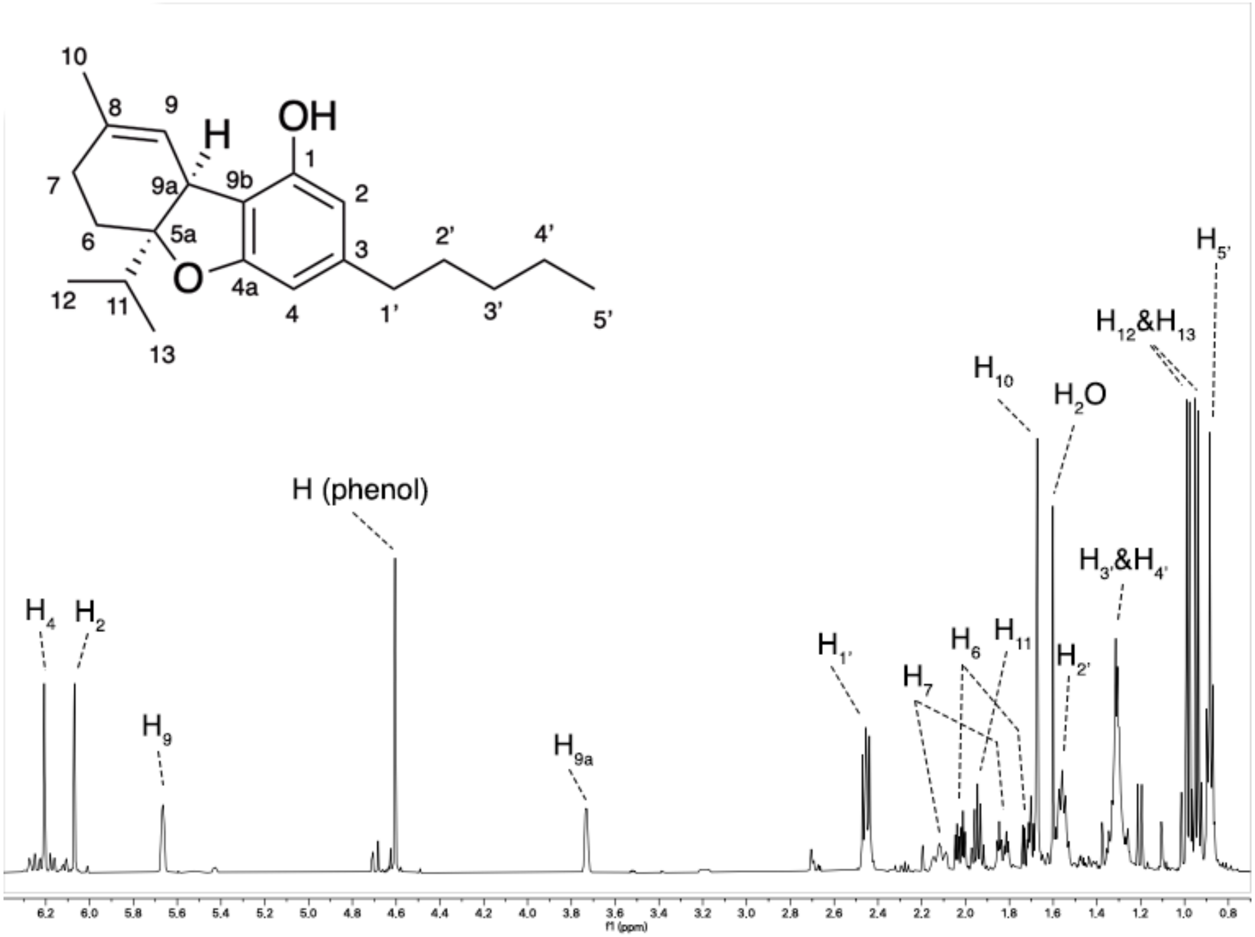


Figure S14. ^{1}H NMR of *iso*-THCBF in $CDCl_3$. H_4, 6.21 ppm (d, J = 1.2 Hz, 1H); H_2, 6.07 ppm (d, J = 1.2 Hz); H_9, 5.67 ppm (br, 1H); H(phenol), 4.61 (s, 1H); H_{9a}, 3.73 ppm (d, J = 3.2 Hz, 1H); $H_{1'}$, 2.47-2.43 ppm (m, 2H); H_7, 2.16-2.08 (m, 1H) & 1.83 ppm (dt, J = 16.6, 4.4 Hz, 1H); H_6, 2.03 ppm (ddd, J = 13.8, 4.6, 3.7 Hz, 1H) & 1.72 ppm (m, 1H); H_{11}, 1.95 ppm (h, 6.9 Hz, 1H); H_{10}, 1.68-1.67 ppm (br, 3H); $H_{2'}$, 1.56 ppm (m, 2H); $H_{3'}$ & $H_{4'}$, 1.33-1.28 ppm (m, 6H); H_{12} & H_{13}, 0.98 ppm (d, J = 6.9 Hz, 3H) & 0.94 ppm (d, J = 6.9 Hz, 3H); $H_{5'}$, 0.9-0.87 ppm (m, 3H). Minor impurities present appear to be cannabinoids or other similar molecules and are responsible for resonances that overlap with *iso*-THCBF.

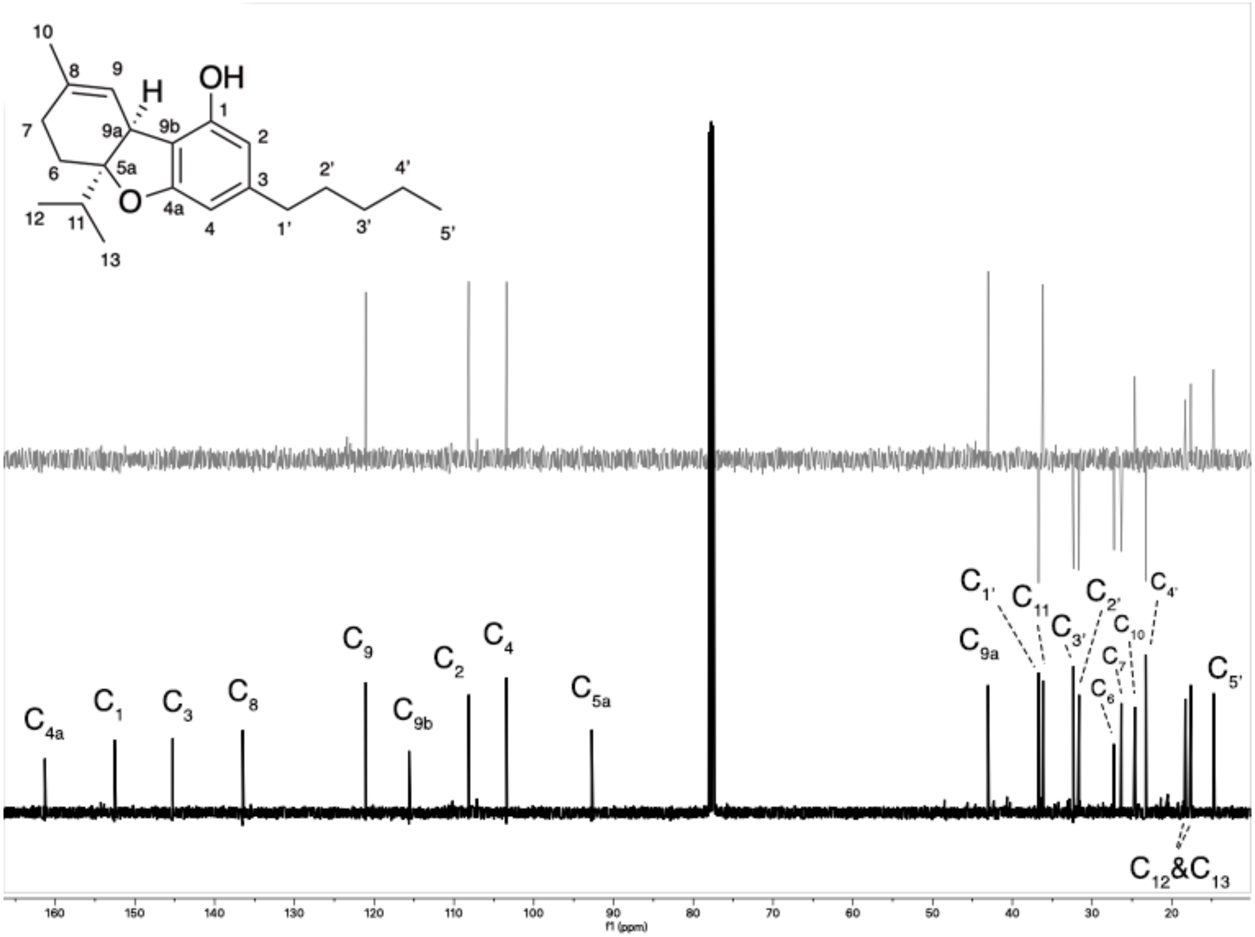


Figure S15. [13]C NMR (lower) and DEPT-135 (upper) of *iso*-THCBF in $CDCl_3$. C_{4a}, 160.70 ppm; C_1, 151.96 ppm; C_3, 144.67 ppm; C_8, 135.89 ppm; C_9, 120.47 ppm; C_{9b}, 115.05 ppm; C_2, 107.56 ppm; C_4, 102.83 ppm; C_{5a}, 92.15 ppm; C_9, 42.46 ppm; $C_{1'}$, 36.13 ppm; C_{11}, 35.57 ppm; $C_{3'}$, 31.76 ppm; $C_{2'}$, 31.04 ppm; C_6, 26.69 ppm; C_7, 25.74 ppm; C_{10}, 24.05 ppm; $C_{4'}$, 22.69 ppm; C_{12} & C_{13}, 17.73 & 17.04 ppm; $C_{5'}$, 14.17 ppm.

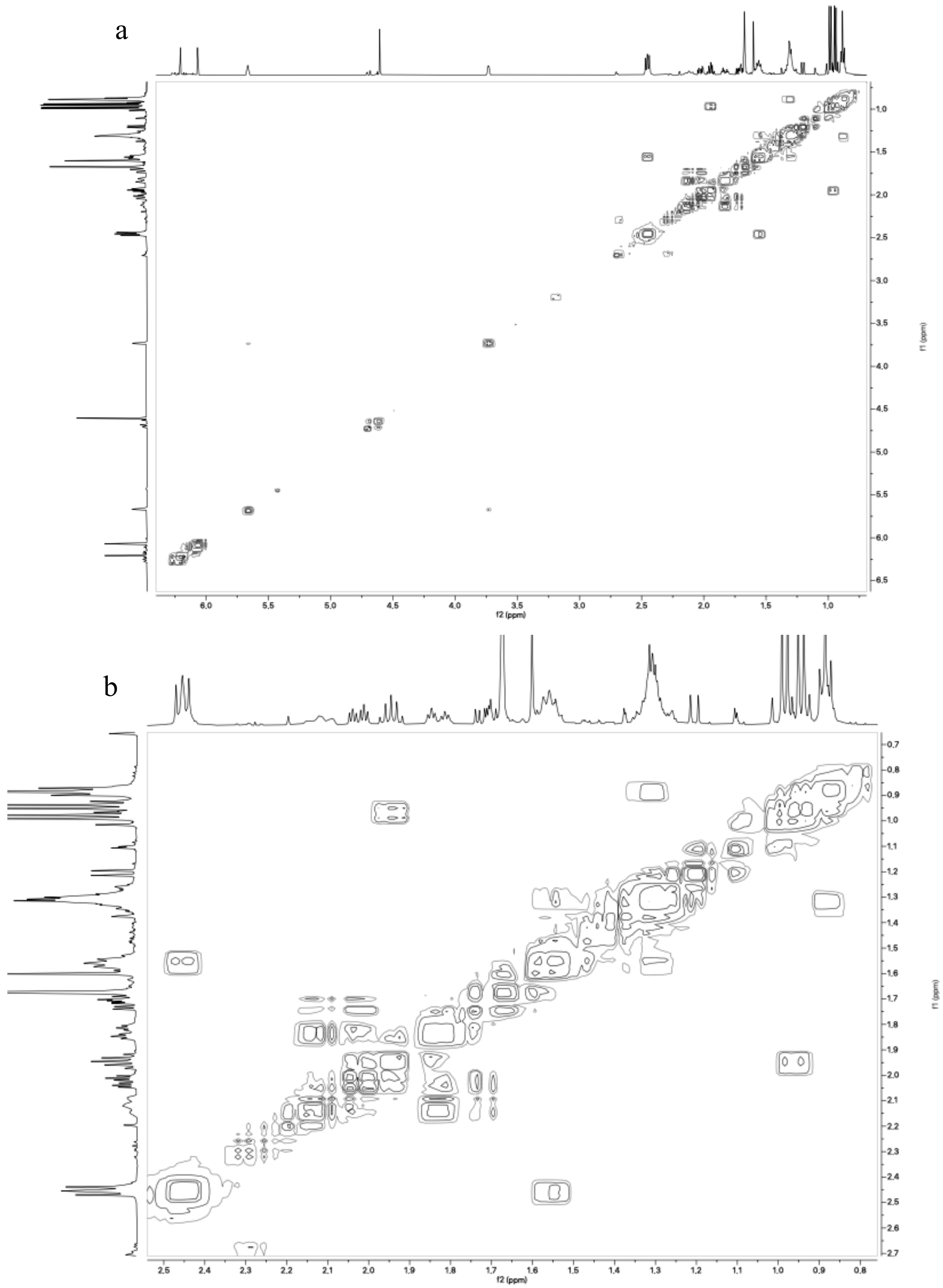
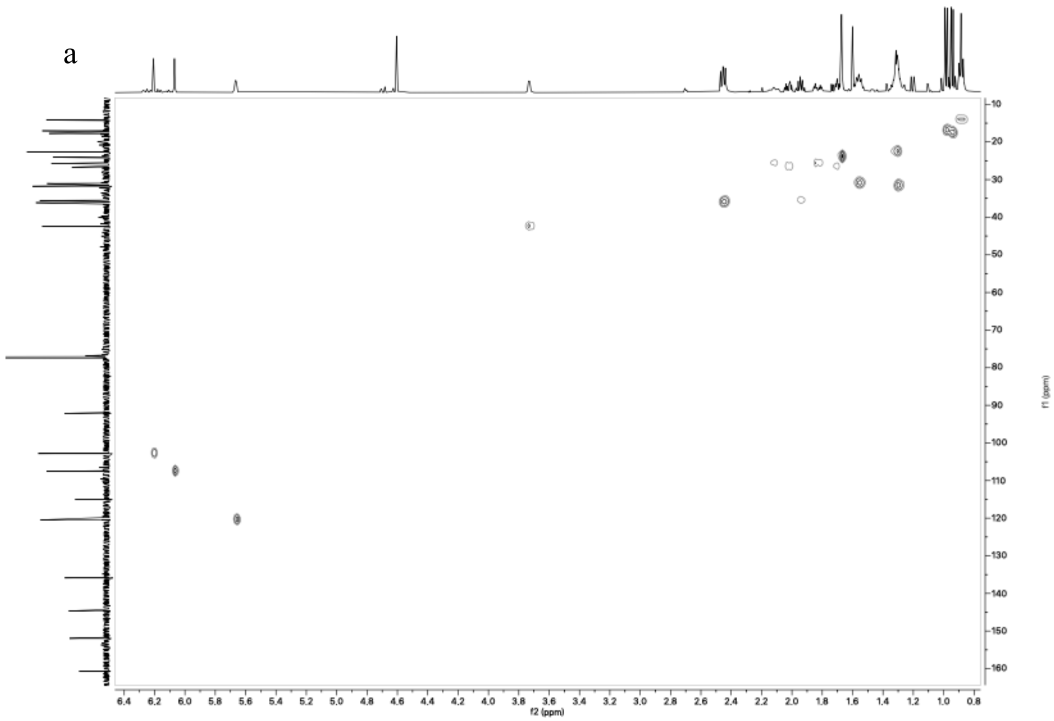


Figure S16. *iso*-THCBF COSY spectrum full (a) and of alkyl region (b) in $CDCl_3$.

a



b

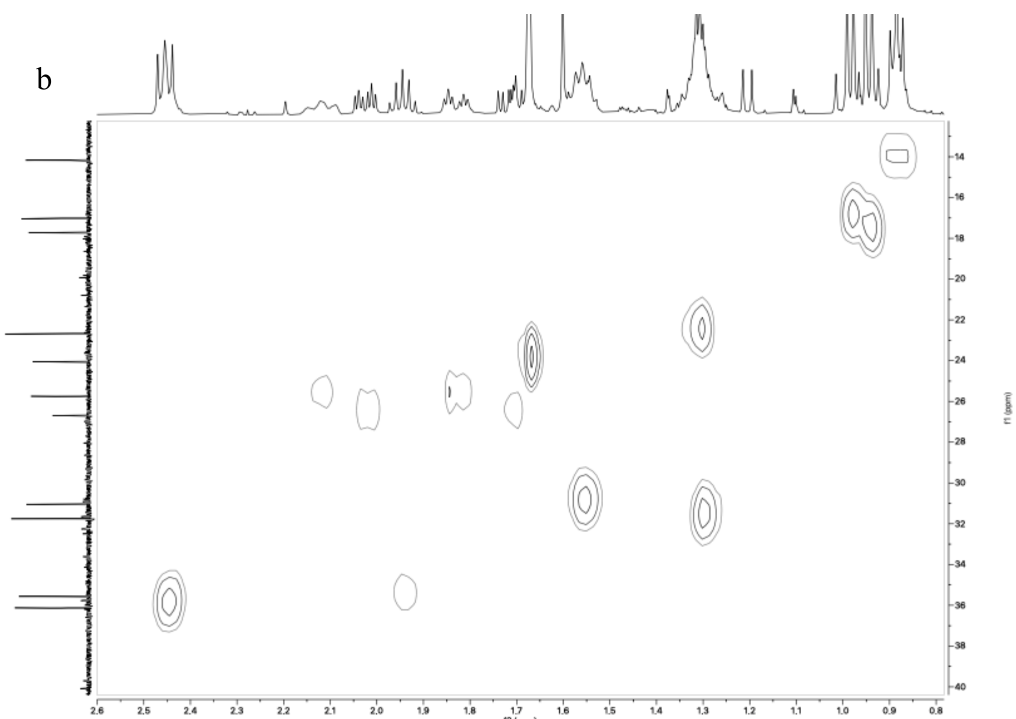


Figure S17. *iso*-THCBF HSQC spectrum full (a) and of alkyl region (b) in $CDCl_3$.

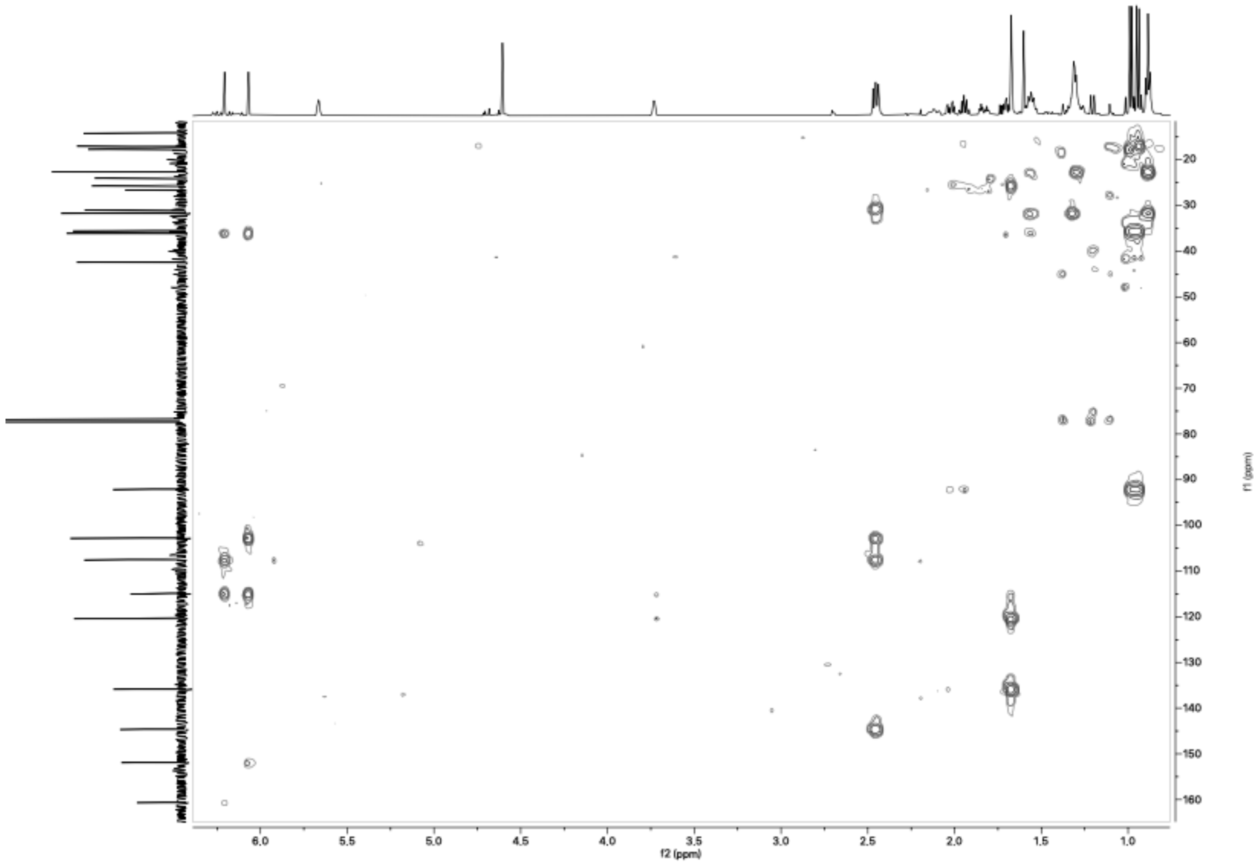


Figure S18. HMBC spectrum of *iso*-THCBF in $CDCl_3$.

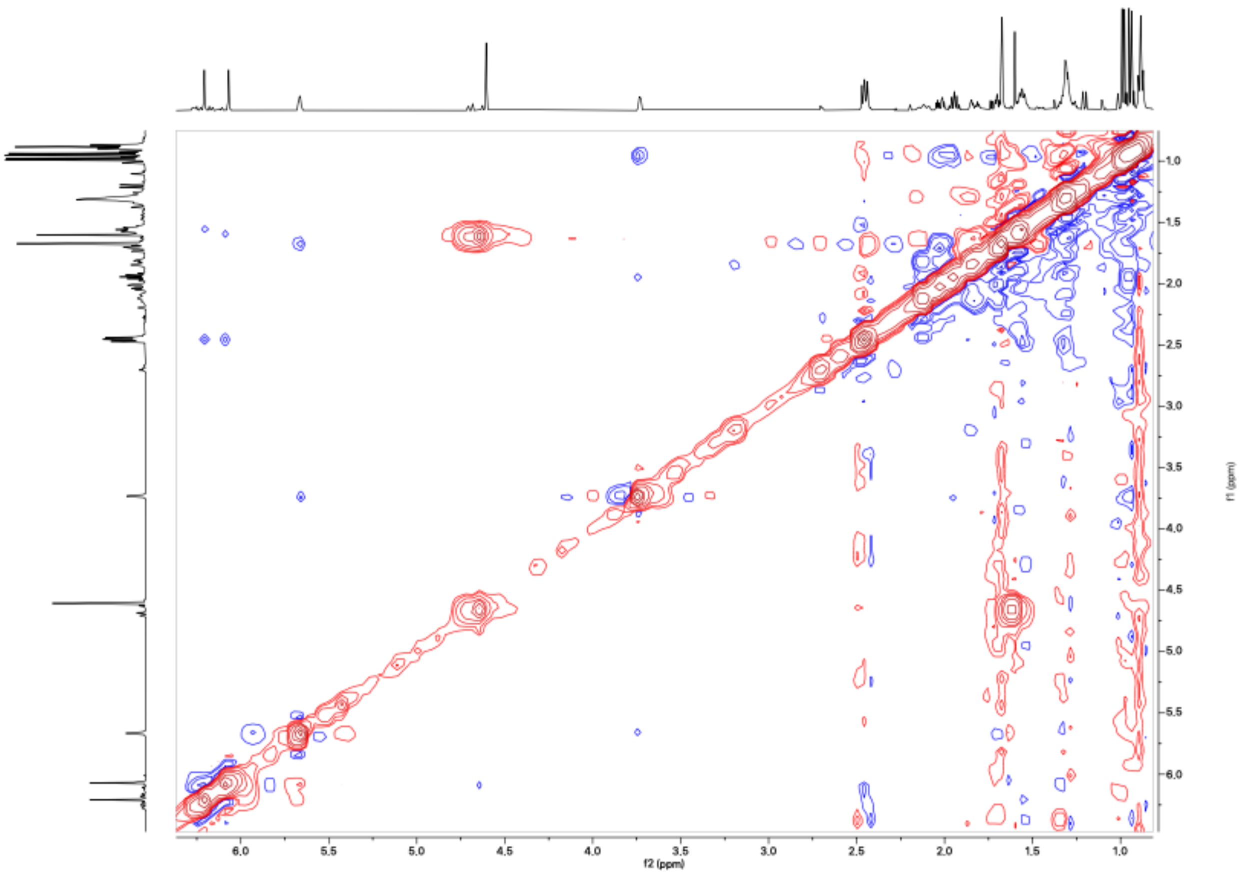


Figure S19. NOESY spectrum of *iso*-THCBF in $CDCl_3$. This spectrum must be viewed in full color in order to differentiate in-phase (blue) from out-of-phase (red) signals.

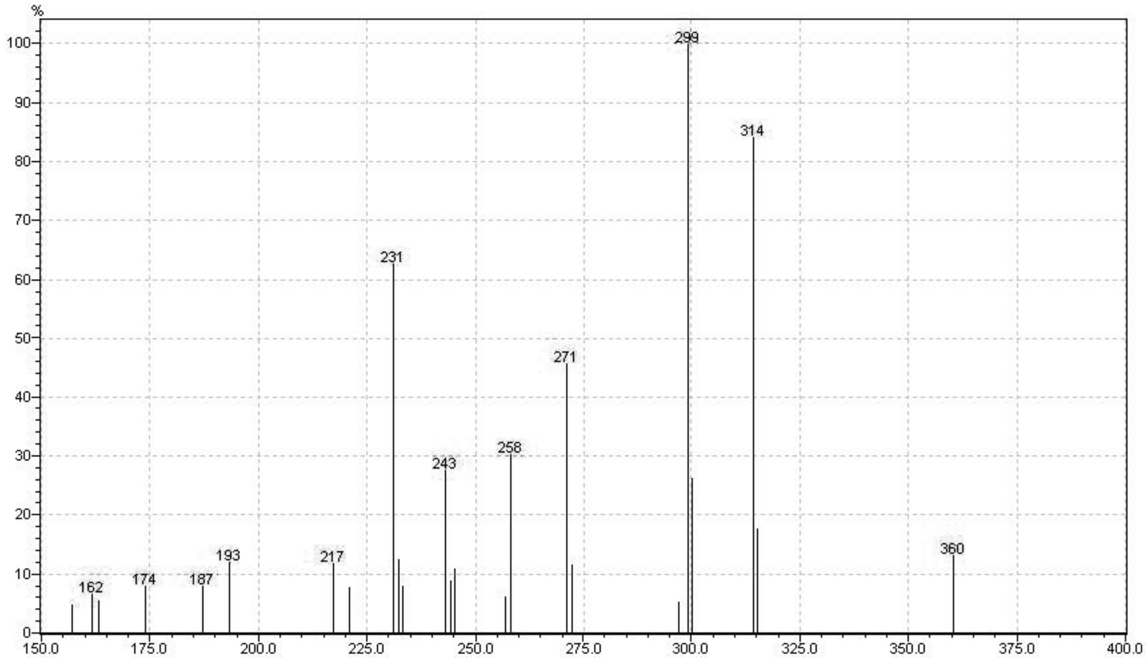


Figure S20. Mass spectrum of 9-EtO-HHC.

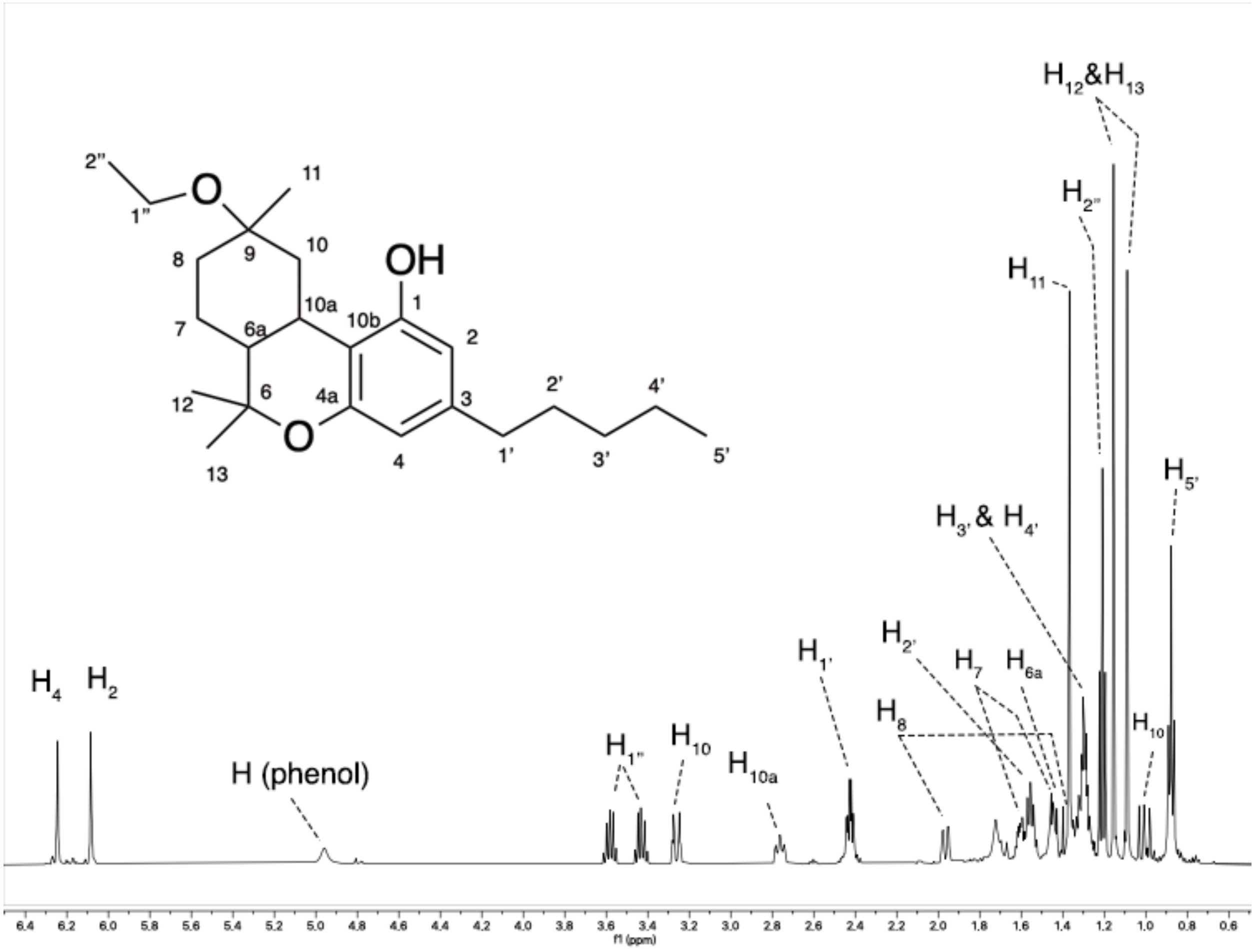


Figure S21. ^{1}H NMR spectrum of 9-EtO-HHC.

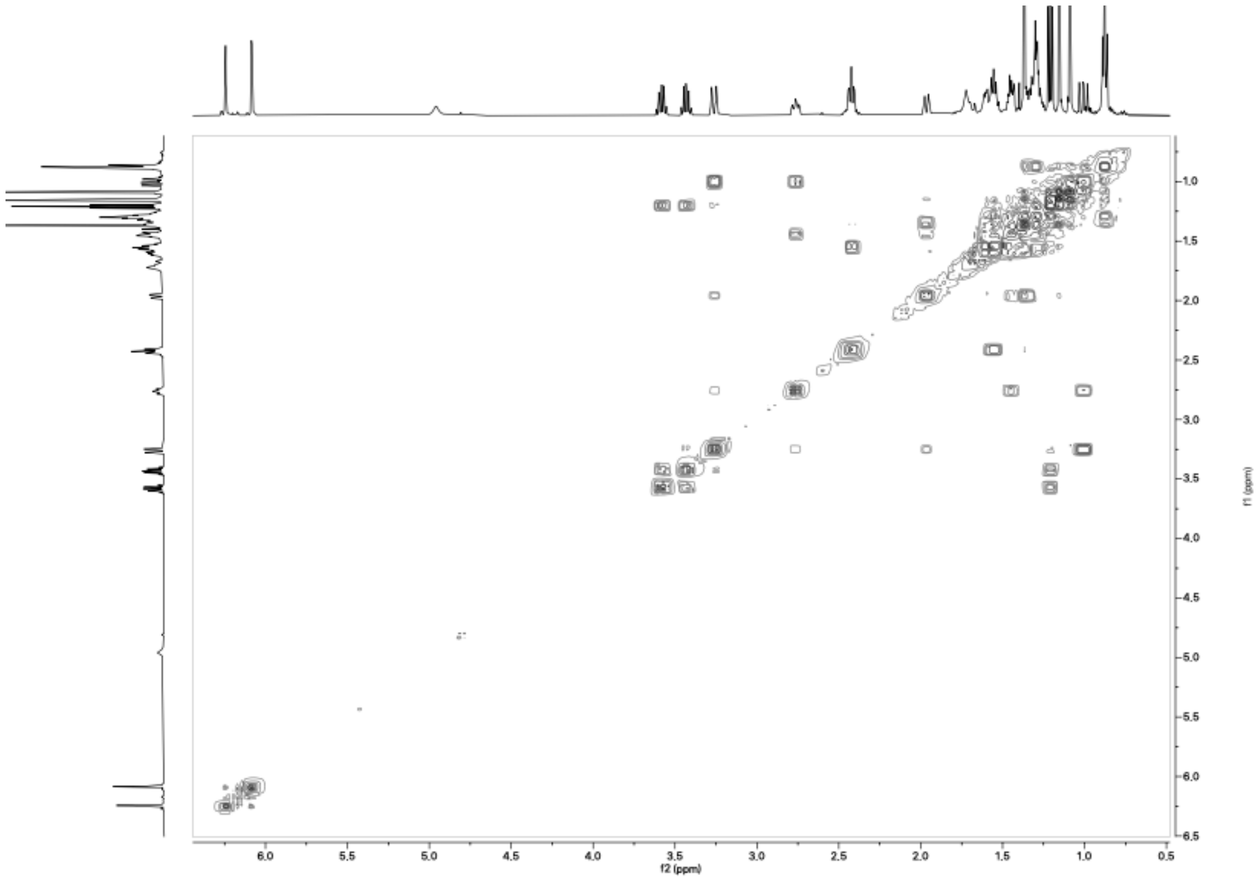


Figure S22. COSY spectrum of 9-EtO-HHC.

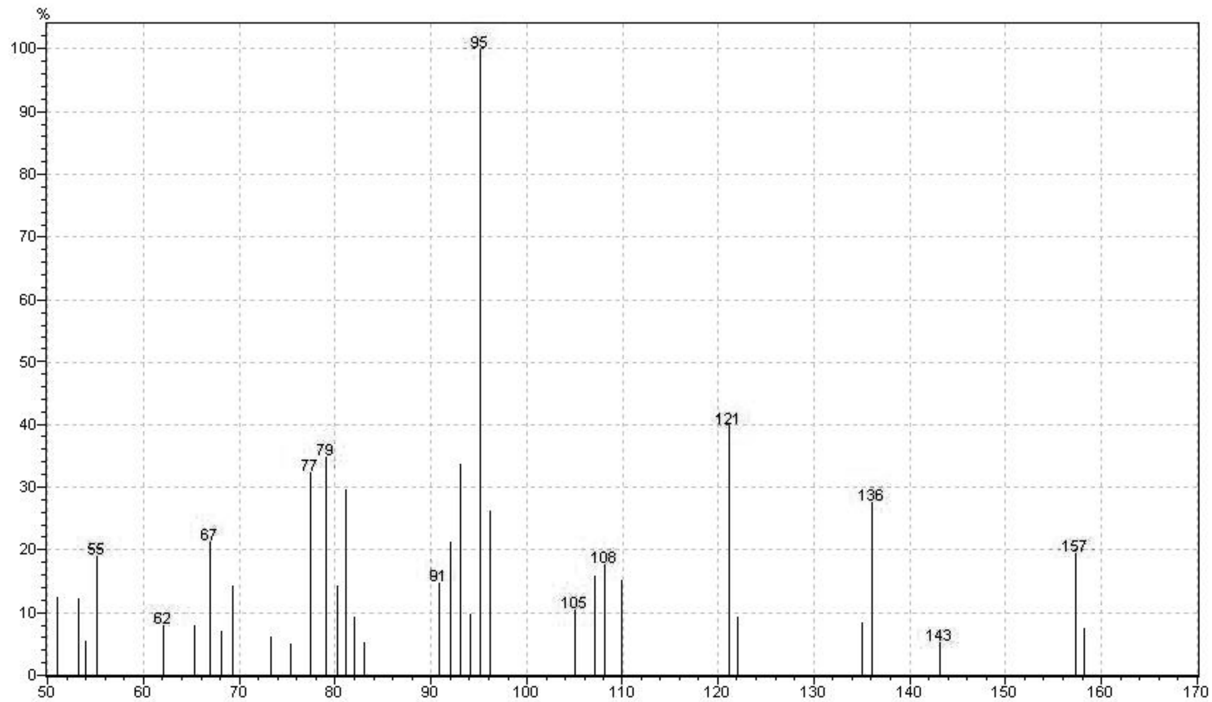


Figure S23. Mass spectrum tentatively identified as bornyl chloride in products 2 and 3 from brand 1. This eluted at 4.95 & 4.93 min., respectively, with match qualities to NIST spectral database of 80 & 81 %.

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