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Supporting Information

Piers-Rubinsztajn reaction to unlock an 8-step synthesis of 7-hydroxy cannabidiol

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1. General information

1.1 Instrumentations

Nuclear magnetic resonance analyses (^{1}H-NMR, ^{13}C-NMR, COSY, HSQC, HMBC and TOCSY spectra) were acquired using a Bruker Advance III 400 MHz spectrophotometer (400 MHz for ^{1}H and 101 MHz for ^{13}C) or Bruker ava600 (600 MHz for ^{1}H and 151 MHz for ^{13}C). Chemical shifts (δ) are reported in ppm relative to residual solvent signals for ^{1}H NMR (^{1}H-NMR: 7.26 ppm for $CDCl_3$) and ^{13}C NMR (^{13}C-NMR: 77.0 ppm for $CDCl_3$). Coupling constants are given in Hz. The following abbreviations are used to indicate the multiplicity: s, singlet; d, doublet; t, triplet; q, quartet; quint, quintet; sept, septet; m, multiplet; br s, broad signal. Chromatographic purifications of compound were performed using automated Biotage® Isolera LS Systems. For extremely sensitive reactions, an IT inert atmosphere glovebox was used.

Exact masses were measured on hybrid quadrupole-TOF high resolution (HRMS) mass spectrometer (Xevo G2 QTOF, Waters, Manchester, UK) using a Z-spray-ESI interface operating in positive ionization mode with resolution of the TOF mass spectrometer about 20,000 at full width half maximum (FWHM). High resolution mass spectra were recorded on a VG autospec, or Thermo/Finnigan MAT 900, mass spectrometer. Electrospray Ionization (ESI^{+}) spectra were performed using a time-of-flight (TOF) mass analyser. Data are reported in the form of m/z (intensity relative to the base peak = 100).

1.2 General Procedures

All reactions requiring inert atmosphere were set up under a nitrogen atmosphere in oven-dried glassware using standard Schlenk techniques, unless otherwise stated. Synthesis grade solvents were used as purchased. Anhydrous solvents were purchased from Merck, VWR or taken from a commercial SPS solvent dispenser. Chromatographic purification of products was accomplished using flash column chromatography (FC) on silica gel (35-70 mesh). Thin layer chromatography (TLC) analysis was performed using company precoated TLC plates (insert model), UV light as the visualizing method and either cerium ammonium molybdate (Hanessian stain) or basic aqueous potassium permanganate ($KMnO_4$), and heat as developing agents. Organic solutions were concentrated under reduced pressure on a rotary evaporator (in vacuo at 40 ºC, ~5 mbar).

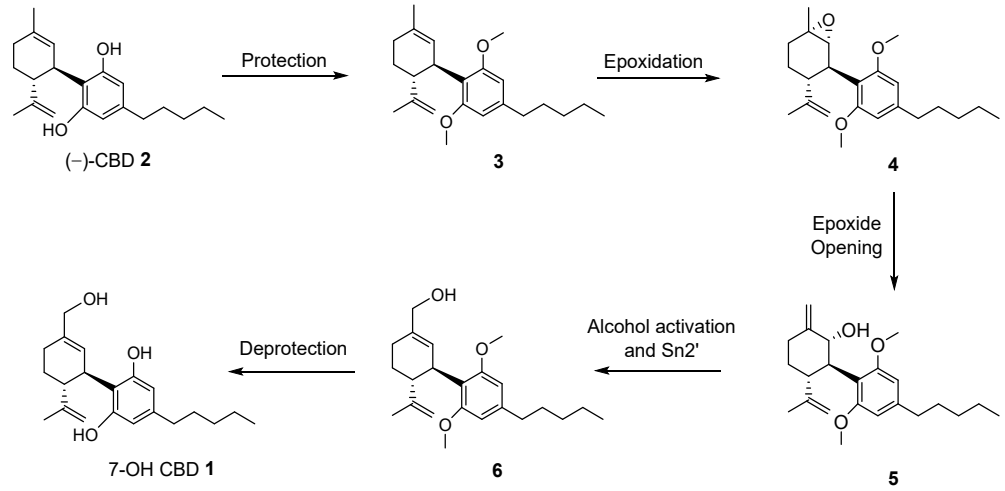
1.3 Materials

All the starting materials were commercially available. Commercial grade reagents and solvents were purchased at the highest commercial quality from Merck, TCI, Fluorochem and Carlo Erba and used as received, unless otherwise stated. Cannabidiol was provided pure by Indena S.p.A. and used as received.

2. Experimental procedures

2.1 Synthetic approach overview

The designed approach is represented in the following scheme:



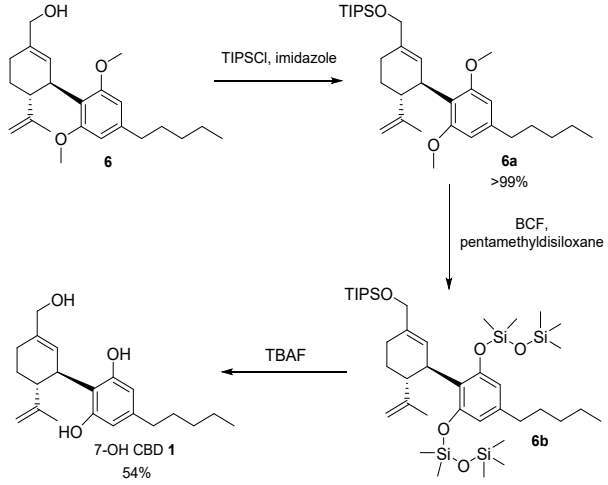
Scheme S1: Our designed approach toward 7-OH CBD (1)

The synthesis started from pure (–) - CBD **2** with a protection-epoxidation-epoxide opening sequence to afford compound **5** smoothly, given that each of these steps gave high yields: quantitative yield for the protection with methyl toluensulfonate and K_2CO_3 in dry acetone (see **2.4.1**), 82% yield for the epoxidation of **3** with *m*CPBA in CH_2Cl_2 (see **2.4.2**) and quantitative yield for the epoxide opening on **4** using LDA in dry diethyl ether (see **2.4.3**).

The secondary alcohol **5** was then activated using mesyl chloride and triethylamine in dry DCM, to afford a nucleophilic conjugated substitution reaction (S_N2') simply adding a basic solution of sodium bicarbonate in water after solvent swap from CH_2Cl_2 to DMF and gently heating (see **2.4.4**), modifying a previously reported procedure.[1] The change of solvent proved to be critical, because the reaction did not work just adding the aqueous bicarbonate to CH_2Cl_2, proving that the system needs to have a different combination of solvents. We also observed that, increasing the scale, this step shows a loss in efficiency, decreasing the yield from 70% for a 0.11 mmol scale to 50% for a multigram scale, a trend that is observed in the original procedure too, probably related to the competition between the S_N2' and the S_N2 reactions on the activated alcohol, a theory supported by the fact that the only

byproduct recovered from this step is alcohol **5**. Further engineering optimisation of vessel and mixing parameters need to be carried out when translating this on bigger scale.

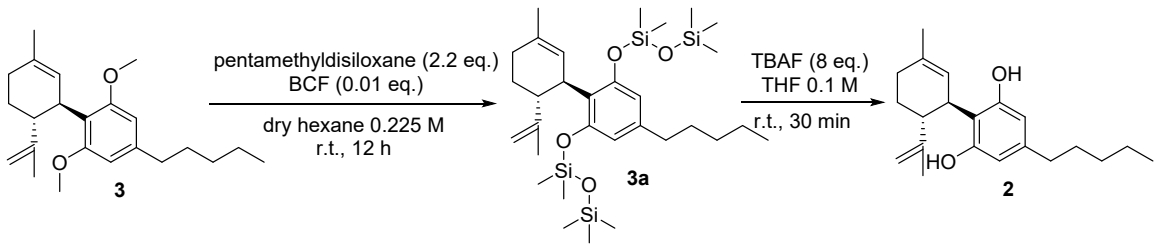
The last step proved to be the most challenging one. Indeed, due to the nature of CBD moieties, the use of strong Lewis acids to cleave the methyl aryl ethers had to be avoided, otherwise a conversion to THC moiety occurred. On the other hand, the use of Lewis bases such as NaSEt and $HPPh_2$/KO*t*Bu proved to be unsuccessful (see section **2.3**), affording only mono-deprotection.



Scheme S2: The 7-OH CBD (1) deprotection step in detail.

These facts led to the use of a modification of the BCF/pentamethyl disiloxane system[2] operating a conversion of the methyl aryl ethers to siloxane aryl ethers: these last ones were easily cleaved using TBAF (see **2.4.5**). However, the reaction showed a challenge: the elimination of primary and allylic alcohols in presence of silanes and BCF, obtaining (–) - CBD **2**. To avoid this, the allylic alcohol of compound **6** was protected, affording 7-hydroxy cannabidiol **1** in 54% yield over three steps.

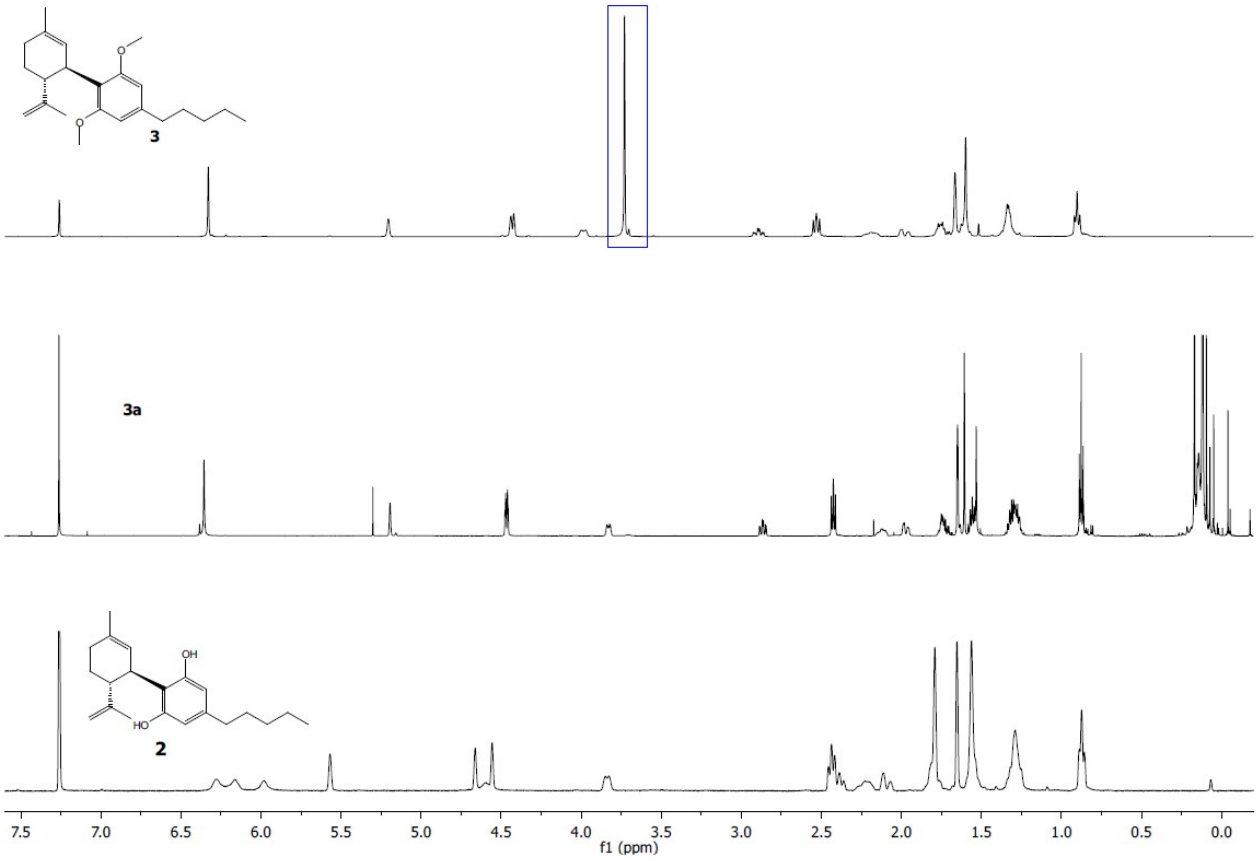
2.2 Piers-Rubinsztajin test on compound 3



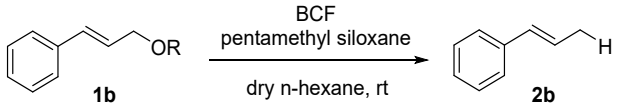
In a glovebox under Argon atmosphere, a reaction tube with a magnetic stirring bar was charged with compound **3** (200 mg, 0.58 mmol), pentamethyldisiloxane (191 mg, 1.3 mmol) and 2.5 mL of dry hexane and the solution was stirred for 1 minute. Then, BCF (0.01 eq., 3 mg) was added and the solution was left to stir in the glovebox at r.t. overnight.

Then the reaction was quenched with water, extracted with diethyl ether and washed with a saturated solution of ammonium chloride, dried over magnesium sulfate, filtered and concentrated in vacuo. The

crude ^{1}H NMR showed the disappearance of the methoxy groups (δ= 3.71 ppm). Purification via flash chromatography over silica gel (20% ethyl acetate in petroleum ether) afforded a colourless oil (**3a**). The product was then placed under nitrogen in a 50mL round bottom flask, and 4.5 mL of a solution 1M of TBAF in dry THF were added dropwise. The reaction was stirred for 20 min., then diluted with water, washed with a saturated solution of ammonium chloride , dried over magnesium sulfate, filtered and concentrated in vacuo. The crude was then purified via flash chromatography over silica gel (20% ethyl acetate in petroleum ether) affording CBD-**2**.



2.3 Protecting the allylic alcohol: testing the protecting groups



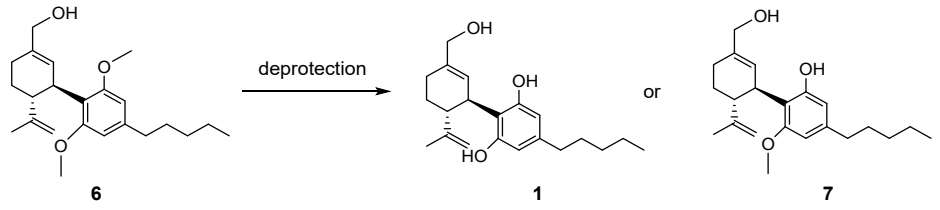
Entry	R	1b recovered (%)
1	TIPS	75[a]
2	TBDPS	80[a]

3	acetyl	0[a]
4	pivaloyl	0[a]

[a] Determined by ^{1}H-NMR.

All the entry were done in glovebox using 0.01 eq. of BCF and 2.2 eq. of pentamethyldisiloxane.

2.4 Unsuccessful deprotection conditions



6 **1** **7**

desired product *mono-deprotection product*

Entry	Deprotecting agent	Conversion %	7 (NMR yield %)	1 (NMR yield %)
1[a]	$AlCl_3/Et_3N$	0	-	-
2[b]	AcCl/NaI	0	-	-
3[c]	$FeCl_3$	> 95	-	-
4[d]	$AlCl_3$	>95	-	-
5[e]	$HPPh_2$	87	85	-
6[f]	EtSNa	75	70	traces on MS
7[g]	EtSNa	>95	30[j]	5[j]
8[h]	EtSNa	90	90	-
9[i]	EtSNa	85	80	-

[j] Isolated yield

Reaction conditions: a) on 0.1 mmol scale, $AlCl_3/Et_3N$ 1:2.85 eq., CH_2Cl_2, 0 °C to reflux, 3 h; b) on 0.1 mmol scale, AcCl/NaI 5:6 eq., acetonitrile/THF 1:1, 0 °C to rt, 21 h, complex mixture; c) on 0.1 mmol scale, $FeCl_3$ 1 eq., Ac_2O, 80 °C, 24 h, complex mixture; d) on 0.1 mmol scale, $AlCl_3$ 3.5 eq., CH_2Cl_2, rt, 3 h, complex mixture; e) on 0.5 mmol scale, $HPPh_2$ 4 eq., ^{t}BuOK 4 eq., dry DMF, 80 °C, 15 h; f) on 0.2 mmol scale, NaSEt 6 eq., dry DMF, 150 °C, 24 h; g) on 0.2 mmol scale, NaSEt 20 eq., dry DMF 140 °C, 24 h, then NaSEt 30 eq., dry DMF, 145 °C, 20 h; h) on 2 mmol scale, NaSEt 20 eq., dry DMF, 140 °C, 24 h, then Ac_2O, TEA, DMAP, dry DCM, rt, 12 h, then NaSEt 30 eq., dry DMF, 145 °C, 20 h; i) on 0.1 mmol scale, NaSEt 20 eq., dry DMF, 140 °C, 24 h, then MeCOOH 10.5 eq., 24 h, then NaSEt 30 eq., dry DMF, 145 °C, 20 h.

2.5 NMR analysis to confirm compound 1

The protection of **6** with TIPSCl in presence of imidazole in dry CH_2Cl_2 proved to be quantitative and it was carried over to the next step without further purifications. The transprotection operated by the BCF/siloxane system towards the intermediate **6b** (observed in the crude) proved to be quantitative, with the complete disappearance of the methoxy peak at 3.71 ppm. Once the methoxy peak fully disappeared, crude **6b** was dissolved in dry THF under nitrogen, and the silyl moieties cleaved using an excess of TBAF, affording **1** in a 54% yield over three steps.

The analysis of the NMR spectra showed the complete removal of both the TIPS and the siloxane protecting groups. The peak observed are in accordance with the desired 7OH-CBD **1**.

See below for the NMR comparison.

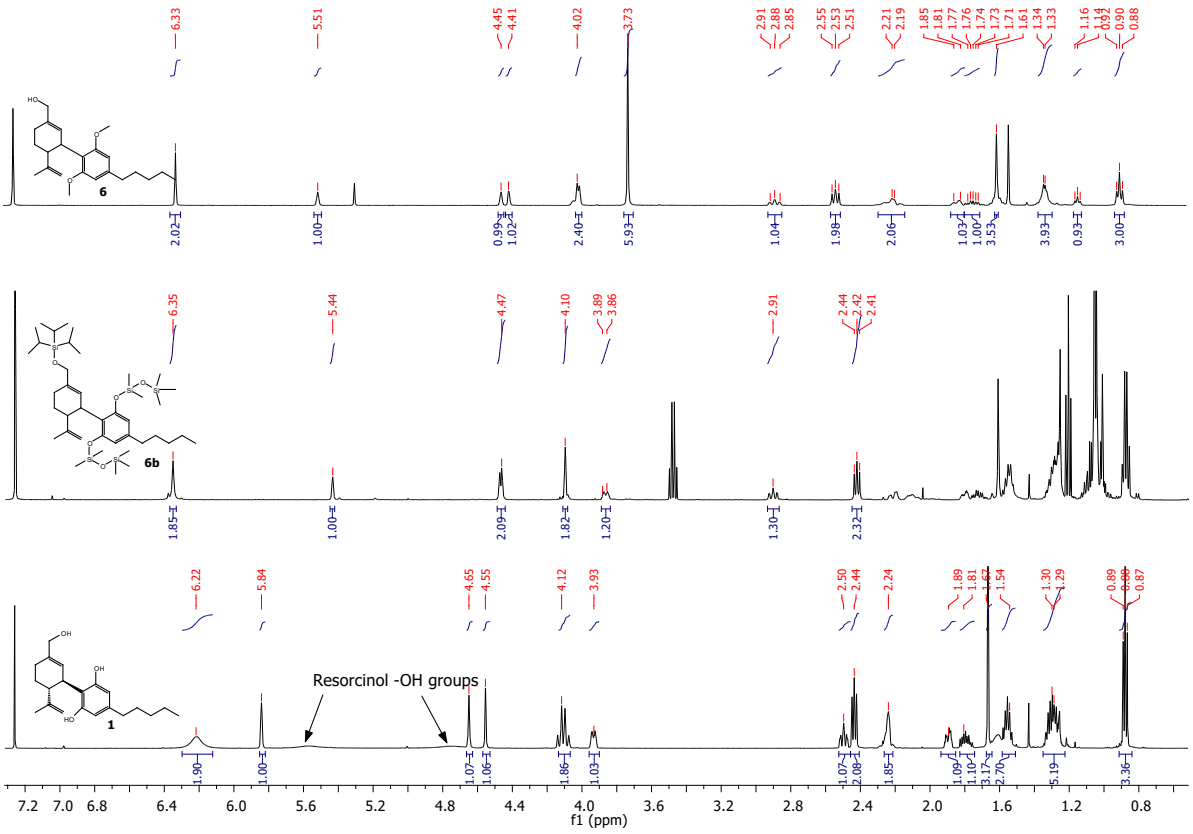
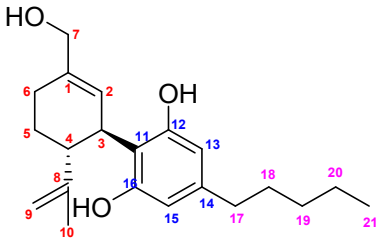


Figure S1: Comparison between the ^{1}H NMR spectra of compound 6 (upper spectrum), supposed compound 6b (mid spectrum) and the supposed compound 1 (lower spectrum).

All the peaks of the isolated product **1** (third spectrum) are in accordance with the expected ones. Moreover, the peak at 2.24 ppm present in our spectrum of **1** can be found in the spectra of **6** (2.20 ppm) and **6a** (2.19 ppm) and in all the three cases it shows the same integral (two protons).
Both proton and carbon NMR spectra and MS spectra showed interesting results that are in accordance with the desired molecule **1**.

The analysis of the 2D spectra is reported below.



1

Analysis of the COSY (the different colours are related to the entity of the crosspeak, red for J2, blue for J3, green for J4 and yellow for J5):

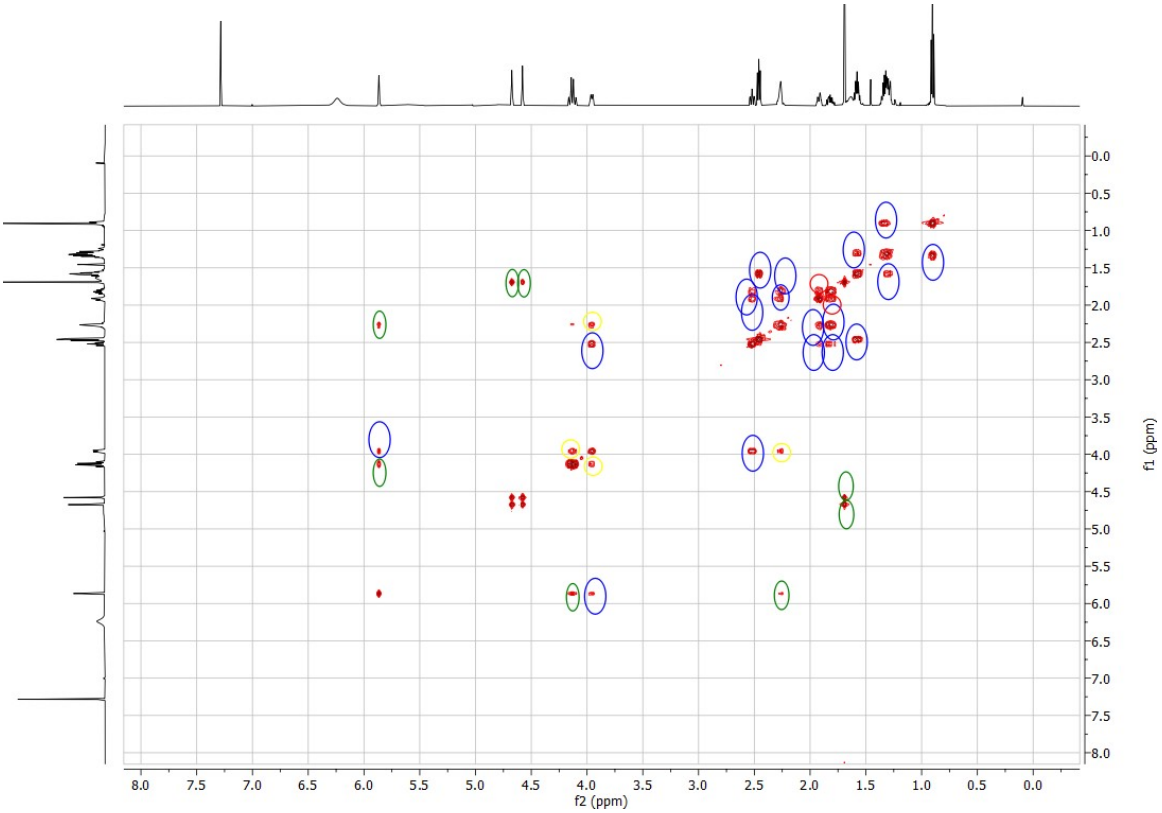


Figure S2: COSY spectrum of 7-hydroxy cannabidiol (1)

Note: due to the broadness of the peak itself, no crosspeaks can be seen for the aromatic protons at 6.21 ppm.

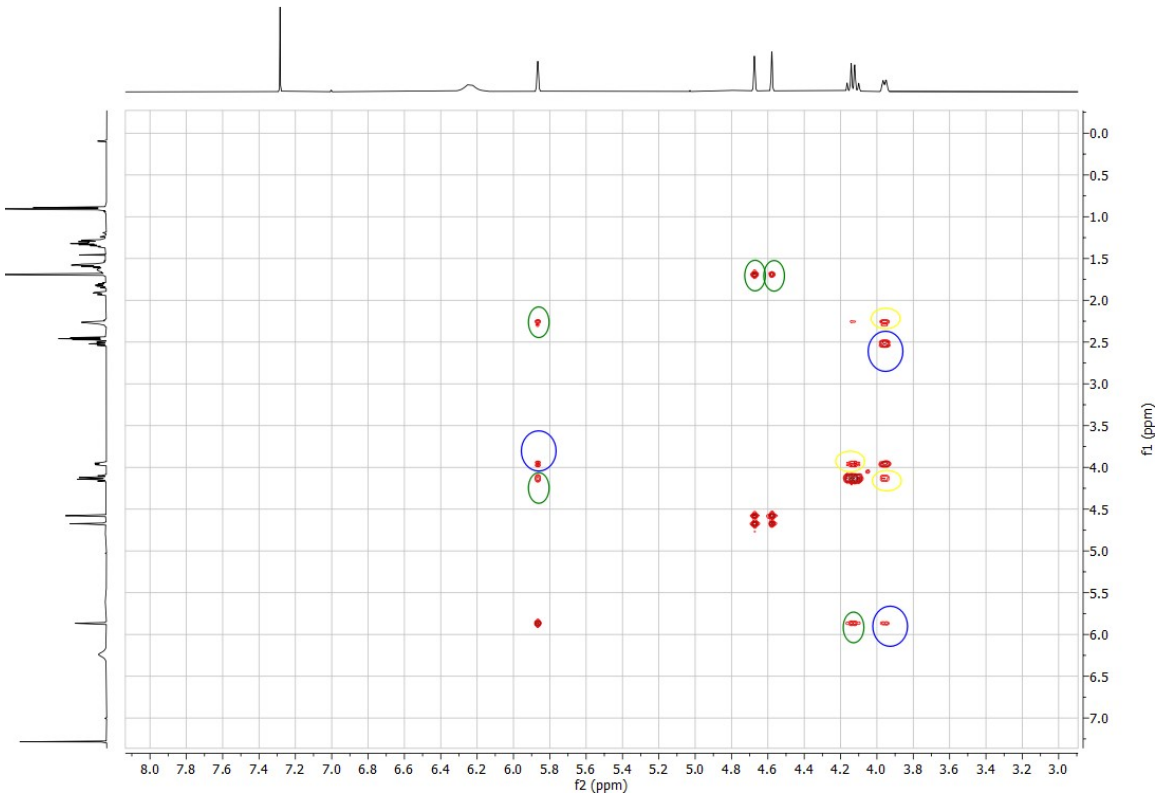


Figure S3: COSY spectrum of compound 1 (from 8.00 ppm to 3.00 ppm range)

The singlet at 5.84 ppm (1H on the C2) couples with three different sets: the quartet at 4.11 (2H on the C7) and the multiplet at 2.29-2.21 (2H on the C6) with a J4 and the doublet at 3.93 ppm (1H, probably the benzylic proton on the C3) with a J3. The presence of the J4 is explained by the fact that it is an allylic system, and it is confirmed by the respective specular crosspeaks.

The two singlets at 4.65 and 4.55 ppm belonging to the alkenyl CH2 on C9 both couple with the methyl group in C10 with a J4 being this an allylic system too. A J5 coupling can be observed between the quartet at 4.11 ppm (protons on the C7) and the doublet at 3.93 ppm, confirming this last one as the proton on C3 (the J5 coupling can be explained by the presence of the unsaturation between the C1 and C2).

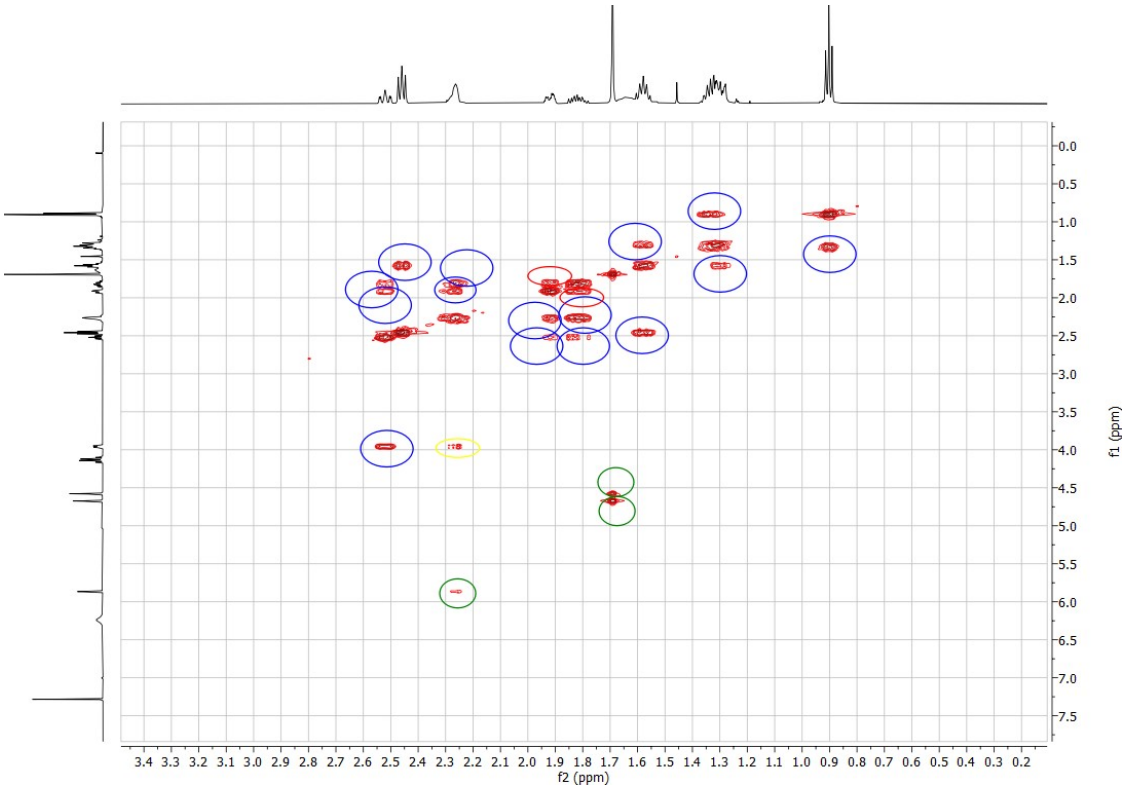


Figure S4: COSY spectrum of compound 1 (from 3.00 ppm to 0.00 ppm range)

The multiplet at 2.52 – 2.48 ppm (1H) shows three J3 crosspeaks that let us suppose it is the proton on the C4: indeed, it couples with the proton on the C3 and with the two multiplets at 1.91 – 1.88 ppm and 1.83 – 1.76 (both integrating for 1H and that can be identified with the two protons on the C5). Meanwhile, the triplet at 2.44 ppm (integrating for 2H) can be identified as the two benzylic protons on the C17, showing a crosspeak (J3) with the dt at 1.55 ppm (2H) only. Then, the dt at 1.55 ppm refers to the two protons on the C18 due to its two J3 coupling with both the benzylic protons on C17 and the multiplet at 1.35 – 1.26 ppm that can be identified with the four aliphatic protons on C19 and C20. As expected, the triplet at 0.88 ppm (integrating for 3H) can be confirmed as the methyl group C21 due to it J3 coupling with the four protons on C19 and C20 only.

Analysis of the TOCSY (the different colours refer to the different moieties coupling; green for aromatics, red for the cyclic terpene, yellow for the isopropylene and violet for the n-pentyl moiety):

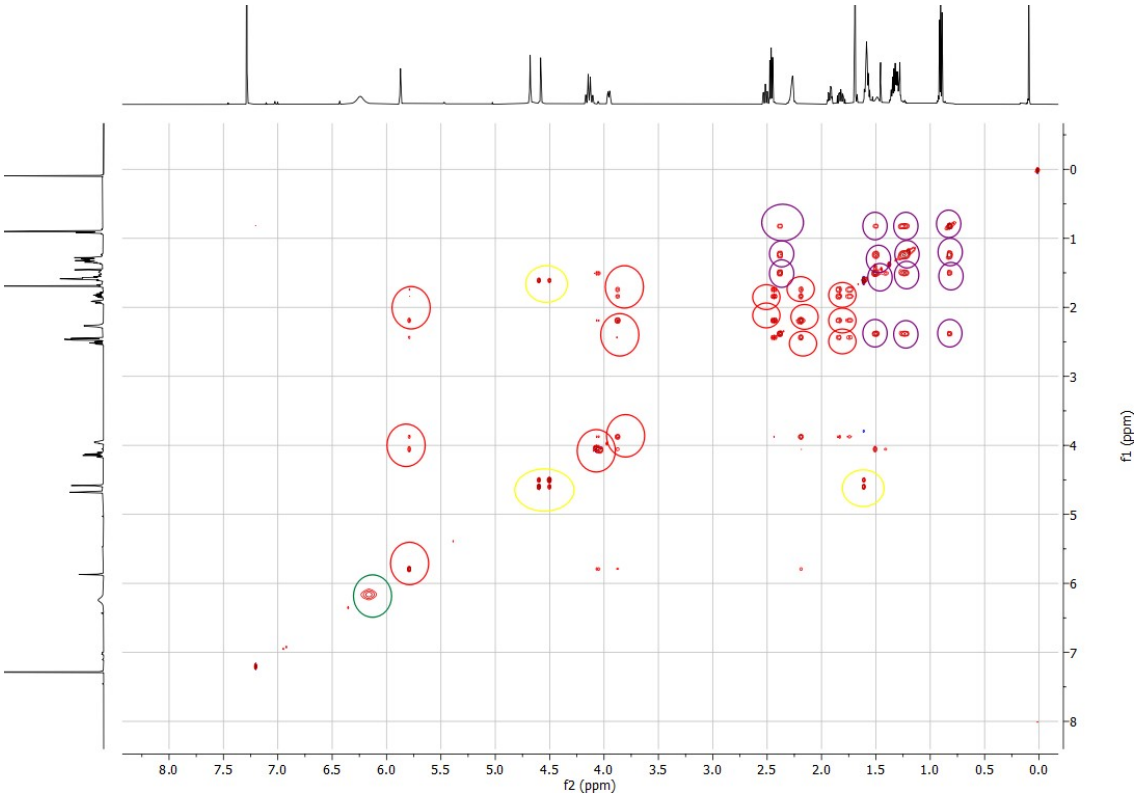
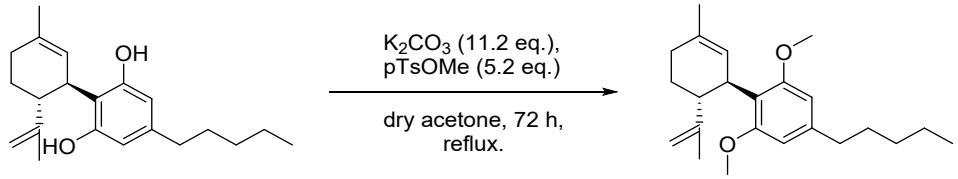


Figure S5: TOCSY spectrum of compound 1

The TOCSY spectrum confirms the assignation obtained from the COSY. Indeed, all the protons belonging to a specific region of the molecule couple each other with clear crosspeaks.

2.5.1 Synthesis of compound 3



2 (CBD) **3**

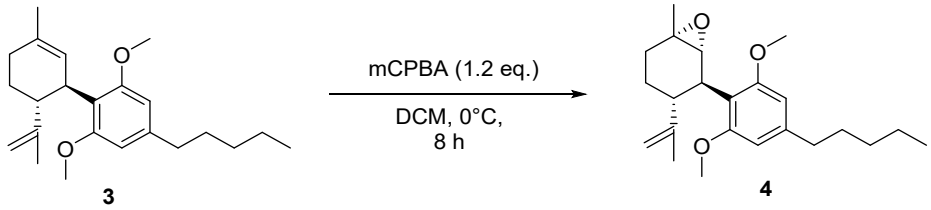
In a flame dried two-necked flask equipped with a condenser, to a solution of (–) - CBD **2** (3 g, 9.54 mmol) in dry acetone (48 mL), potassium carbonate (11.2 eq., 14.8 g, 107 mmol) was added under a nitrogen atmosphere. After 30 minutes, methyl *p*-toluensulfonate (5.2 eq., 9.24 g, 49.6 mmol) was added and the system was let to reflux under nitrogen atmosphere for 72 hours. Upon completion of the reaction, as indicated by TLC analysis, the reaction was quenched with a saturated aqueous solution of sodium bicarbonate and the two layers were separated. The aqueous layer was extracted with diethyl ether (20 mL x 3 times), then the organic layers were combined, washed with brine, dried over magnesium sulfate, filtered and concentrated in vacuo. Flash chromatography over silica gel (10% of diethyl ether in petroleum ether) afforded compound **3** as a yellow oil in quantitative yield (3.3 g).

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.33 (s, 2H), 5.20 (s, 1H), 4.43 (d, J = 6.7 Hz, 2H), 3.99 (d, J = 10.7 Hz, 1H), 3.73 (s, 6H), 2.89 (td, J = 10.8, 4.1 Hz, 1H), 2.53 (t, J = 7.8 Hz, 2H), 2.23 – 2.17 (m, 1H), 2.0 – 1.96 (m, 1H), 1.77 – 1.74 (m, 2H), 1.66 (s, 3H), 1.60 (s, 5H), 1.34 – 1.33 (m, 5H), 0.90 (t, J = 6.6 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 149.7, 142.0, 131.3, 126.1, 119.2, 109.7, 105.2, 56.1, 45.4, 36.6, 36.2, 31.9, 31.1, 30.9, 29.9, 23.6, 22.7, 19.2, 14.2.

Analytical data are in agreement with those reported in literature.[3]

2.5.2 Synthesis of compound 4



3 **4**

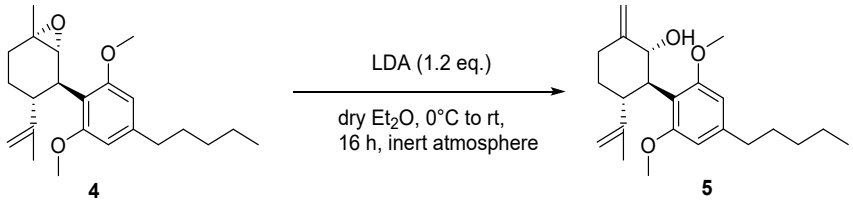
Following a literature reported procedure:[4] 3-chloro-perbenzoic acid (1.2 eq., 0.92 g, 5.31 mmol) was dissolved in 45 mL of CH_2Cl_2 and then cooled to 0 °C. A solution of compound **3** (1.49 g, 4.35 mmol) in 15 mL of CH_2Cl_2 was added dropwise to the system. The starting material disappeared after 8 h, as indicated by TLC analysis. The reaction was quenched with a saturated solution of sodium bicarbonate, then the two layers were separated, and the aqueous layer was extracted with diethyl ether (15 mL x 3 times). The combined organic layers were washed with brine, dried over magnesium sulfate, filtered and concentrated in vacuo. Flash chromatography over silica gel (7% of diethyl ether in petroleum ether) afforded compound **4** as a colorless oil in 82% yield (1.3 g).

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.34 (d, J = 11.1 Hz, 2H), 4.38 (s, 1H), 4.18 (s, 1H), 3.80 (s, 3H), 3.72 (s, 3H), 3.59 (d, J = 10.8 Hz, 1H), 2.91 (s, 1H), 2.55 (t, J = 8 Hz, 2H), 2.29 – 2.23 (m, 1H), 2.06 – 2.03 (m, 1H), 1.87 – 1.79 (m, 1H), 1.70 – 161 (m, 6H), 1.36 – 1.26 (m, 8H), 0.90 (t, J = 6.6 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 158.2, 148.6, 142.7, 117.5, 110.3, 104.4, 65.6, 58.7, 55.9, 55.6, 53.5, 46.4, 36.6, 34.8, 31.8, 31.2, 30.7, 24.9, 23.4, 22.7, 18.5, 15.4, 14.2.

Analytical data are in agreement with those reported in literature.[3]

2.5.3 Synthesis of compound 5



4 5

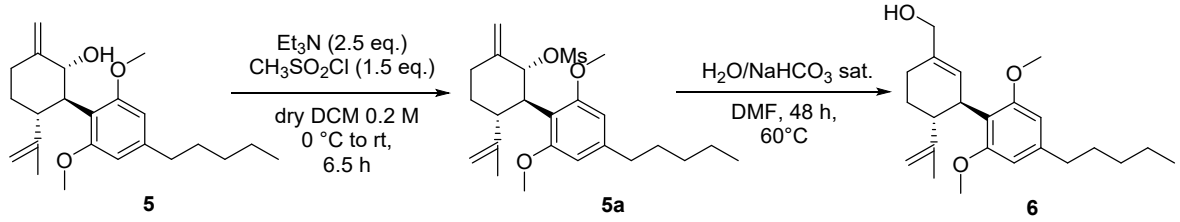
The procedure for the preparation of **5** was a slight modification from a literature procedure:[4] To a flame dried two-necked flask with 8 mL of dry diethyl ether, 1.06 mL (1.2 eq., 2.64 mmol) of *n*BuLi 2.5 M in hexane were added and the system was cooled to 0 °C. At this point, freshly distilled diisopropyl amine (1.2 eq., 2.64 mmol, 0.371 mL) was added under nitrogen atmosphere and the system was stirred for 1 hour at room temperature. Afterwards, the solution was cooled to 0 °C and compound **4** (2.2 mmol, 790 mg) was added to the reaction mixture; the system was stirred at room temperature for 12 h. Upon the completion of the reaction, as indicated by TLC analysis, the system was cooled to 0 °C and the reaction was quenched with water. The organic and aqueous layers were then separated, the aqueous layer was extracted with diethyl ether (15 mL x 2), the combined organic layers were washed with HCl 2 M (10 mL) and brine, dried over magnesium sulfate, filtered and concentrated in vacuo.

The reaction was repeated on a 1.64 g scale and **5** was used without further purifications.

In order to remove impurities for the sole purpose of NMR characterisation, flash chromatography over silica gel (25% of diethyl ether in petroleum ether) was carried out on the smaller scale reaction, to afford compound **5** as pale-yellow oil in quantitative yield (0.788 g).

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.34 (s, 2H), 5.09 (s, 1H), 4.82 (s, 1H), 4.62 (d, J = 14.6 Hz, 1H), 4.49 (s, 1H), 4.39 (s, 1H), 3.80 (s, 3H), 3.75 (s, 3H), 3.34 – 3.27 (m, 1H), 3.20 (td, J = 11.7, 3.3 Hz, 1H), 2.56 – 2.53 (m, 2H), 2.53 – 2.50 (m, 1H), 2.46 (td, J = 13.4, 4.1 Hz, 1H), 1.6274 (ddd, J = 12.5, 7.4, 3.2 Hz, 1H), 1.66 – 1.57 (m, 2H), 1.49 (s, 3H), 1.38 – 1.28 (qd, J = 6.3, 3.3 Hz, 4H), 0.91 (t, 3H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 159.2, 159.0, 150.9, 148.0, 143.0, 113.3, 110.0, 104.5, 104.2, 72.8, 55.9, 55.0, 47.4, 47.1, 36.5, 34.1, 33.5, 31.7, 30.8, 22.5, 18.6, 14.0.
Analytical data are in agreement with those reported in literature.[3]

2.5.4 Synthesis of compound 6



Synthesis of 5a: The procedure for the preparation of **5a** was a slight modification from a literature procedure:[1] In a flame dried two-neck flask, **5** (5.86 mmol, 2.1 g) was dissolved in 20 mL of dry CH_2Cl_2 and the solution was cooled to 0 °C. At this point dry triethylamine (2.5 eq., 14.6 mmol, 2.04 mL) was added, and methanesulfonyl chloride (1.5 eq., 8.79 mmol, 0.682 mL) was added after 30 minutes. The system was stirred for 6 h at room temperature until complete disappearance of the starting material, as indicated by TLC analysis. The reaction was then cooled to 0 °C and quenched with water. The layers were then separated, and the aqueous phase extracted with CH_2Cl_2 (20 mL x 3 times), the organic layers were combined, washed with a saturated solution of ammonium chloride and brine, dried over magnesium sulfate, filtered and concentrated in vacuo. The product was used without purification in the next step. (The formation of **5a** was confirmed by crude ^{1}H NMR, see section **4. NMR spectra**). **^{1}H NMR (400 MHz, $CDCl_3$)** δ 6.32 (s, 2H), 4.42 (d, J = 26.6 Hz, 2H), 4.04 (s, 2H), 3.72 (s, 6H), 2.82 (t, J = 11.2 Hz, 1H), 2.55 – 2.51 (m, 2H), 2.35 – 2.19 (m, 2H), 1.86 – 1.72 (m, 2H), 1.61 (s, 3H),1.54 (s, 2H), 1.33 – 1.25 (m, 5H), 0.98 – 0.81 (m, 3H).

Synthesis of compound 6: The procedure for the preparation of **6** was a slight modification from a literature procedure:[1] Crude compound **5a** (50 mg, 0.115 mmol) was dissolved in 0.5 mL of DMF, then 0.15 mL of water and 0.15 mL of a sat. solution of $NaHCO_3$ were added. The reaction was heated to 60 °C and stirred for 48 h. Upon disappearance of the starting material, as indicated by TLC analysis, the reaction was diluted with water and extracted with diethyl ether (2 mL x 3 times), then the organic layers were combined, washed with water and brine, dried over magnesium sulfate, filtered and concentrated in vacuo. Flash chromatography over silica gel eluting in petroleum ether/diethyl ether 8:2 afforded compound **6** as a colorless sticky oil in 70% yield over two steps (30 mg).

Preparation on 2.5g scale: Crude compound **5a** (2.5 g, 5.73 mmol) was dissolved in 25 mL of DMF, then 7.5 mL of water and 7.5 mL of sat. $NaHCO_3$ were added. At this point the temperature is set to 60 °C and the reaction is let to stir for 48 h. When the starting material disappeared on TLC, the reaction was diluted with water and extracted with diethyl ether (10 mL x 3 times), then the organic layer was washed with water, brine, dried over magnesium sulfate, filtered and concentrated in vacuo. Flash chromatography over silica gel (20% of diethyl ether in petroleum ether) afforded 1.04 g of product **6** as a colorless sticky oil. Yield = 50% (over two steps).

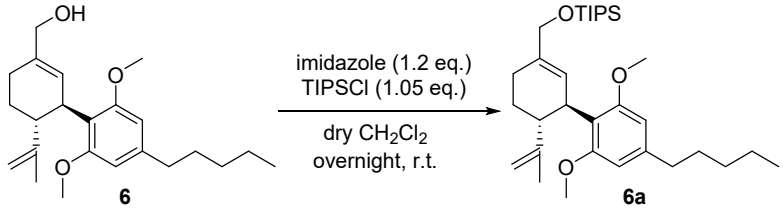
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.33 (s, 2H), 5.51 (s, 1H), 4.44 (d, J = 17.0 Hz, 2H), 4.04 – 4.01 (m, 3H), 3.73 (s, 6H), 2.92 – 2.85 (m, 1H), 2.54 (t, J= 8 Hz, 2H), 2.27 – 2.15 (m, 2H), 1.86 – 1.82 (m, 1H), 1.79 – 1.71 (m, 1H), 1.64 – 1.57 (m, 5H), 1.39 – 1.23 (m, 5H), 0.90 (t, J = 6.8 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 149.0, 142.2, 135.0, 128.6, 118.0, 109.9, 104.8, 67.7, 55.8, 45.5, 36.4, 35.9, 31.7, 31.0, 29.3, 26.4, 22.5, 19.0, 14.0.

MS-ESI: 359.2581 (calculated mass of C23 H35 O3, [M+H$^+$]), found: 359.2574; 381.2400 (calculated mass of C23 H34 O3 Na 1, [M+Na$^+$]), found: 381.2397.

Analytical data are in agreement with those reported in literature.[3]

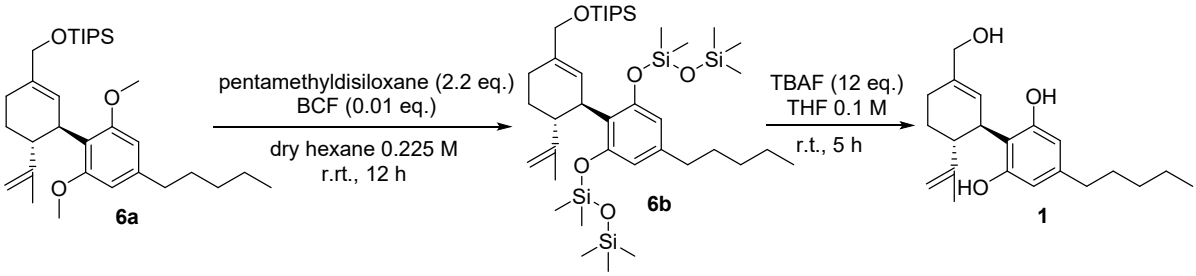
2.5.5 Synthesis of compound 1 (7-OH CBD)



Synthesis of 6a: The procedure for the preparation of **6a** was a slight modification from a literature procedure:[4] a Schlenk flask containing 0.5 mL of dry CH_2Cl_2, 24 mg of imidazole (0.34 mmol, 1.2 eq.) and 100 mg of **6** (0.28 mmol) was cooled to 0 °C. 62.2 µl of triisopropylsilyl chloride (0.30 mmol, 1.05 eq.) was added dropwise and the reaction mixture stirred at room temperature overnight. Upon the completion of the reaction as indicated by ^{1}H NMR analysis, water was added, the organic layer separated, and the aqueous layer extracted with diethyl ether (3 mL x 3 times). The combined organic layers were dried over $MgSO_4$, filtered and the solvent removed in vacuo. Without any purification, the crude (171.4 mg, quantitative yield) was used for the next step.

^{1}H NMR (601 MHz, $CDCl_3$) δ: 6.31 (s, 2H), 5.45 (s, 1H), 4.44 (s, 1H), 4.40 (s, 1H), 4.11 (s, 2H), 4.03 – 4.01 (d, J = 4.9 Hz, 1H), 3.71 (s, 6H), 2.91 – 2.85 (m, 1H), 2.55 – 2.50 (m, 2H), 2.19 (d, J = 2.6 Hz, 2H), 1.83 – 1.78 (m, 1H), 1.73 (ddd, J = 16.0, 11.3, 6.0 Hz, 1H), 1.61 – 1.60 (m, 4H), 1.33 (dd, J = 14.5, 7.6 Hz, 4H), 1.09 – 1.03 (m, 21H), 0.90 (t, J = 7.0 Hz, 3H).

MS-ESI: 515.3915 (calculated mass of C32 H55 O3 Si1, [M+H$^+$]), found: 515.3919; 537.3733 (calculated mass of C32 H54 O3 Si1 Na 1, [M+Na$^+$]), found: 537.3718.



Synthesis of compound 6b:[2] in glovebox under Argon atmosphere, the aryl ether substrate **6a** (50 mg, 0.097 mmol) dissolved in 0.44 mL of dry n-hexane (0.225 M) was added in a reaction tube equipped with a magnetic stirring bar. Pentamethyldisiloxane (1.10 eq. per aryl ether functionality, 41.8 µl, 0.22 mmol) was added and the solution stirred for 1 minute. $B(C_6F_5)_3$ (0.01 eq., 0.5 mg, 0.001 mmol) was added and the reaction was stirred in the glovebox at room temperature for 12 h. Afterwards the reaction was carried out of the glovebox, quenched with water (1 mL), extracted with diethyl ether (2 mL x 3 times), dried over magnesium sulfate, filtered and concentrated in vacuo. ^{1}H NMR analysis on the crude mixture showed a clean deprotection of the methoxy groups on the aromatic ring (the peak at 3.71 ppm disappeared completely, see crude spectrum **6b** below in the Spectra Section, the

presence of the desired intermediate was confirmed by ESI analysis) and used for the next step without any further purification.

MS-ESI: 779.4768 (calculated mass of C40 H79 O5 Si5, [M+H$^+$]), found: 779.4766; 801.4588 (calculated mass of C40 H78 O5 Si5 Na1, [M+Na$^+$]), found: 801.4565.

Synthesis of 7-OH CBD 1: In a two necked flame dried flask crude **6b** was diluted in 1 mL of dry THF, under nitrogen atmosphere, and 1.2 mL of TBAF 1M in THF (12.0 eq.) was added dropwise at 0 °C. The reaction was then allowed to warm to room temperature and stirred for 5 hours. The reaction was then quenched with a saturated aqueous solution of ammonium chloride, extracted with diethyl ether (2 mL x 3 times), dried over magnesium sulfate, filtered and concentrated in vacuo. Flash chromatography over silica gel eluting with petroleum ether ethyl acetate solvent mixture from 100% petroleum ether to 100% ethyl acetate afforded product **1** as a yellow sticky oil in 54% yield over three steps (18 mg).

^{1}H NMR (601 MHz, $CDCl_3$) δ: 6.22 (s, 2H), 5.84 (s, 1H), 4.65 (s, 1H), 4.55 (s, 1H), 4.11 (q, J = 13.3 Hz, 2H), 3.95 – 3.92 (m, 1H), 2.52 – 2.47 (m, 1H), 2.44 (t, J = 7.6 Hz, 2H), 2.27 – 2.24 (m, 2H), 1.91 – 1.88 (m, 1H), 1.83 – 1.76 (m, 1H), 1.67 (s, 3H), 1.55 (dt, J = 15.0, 7.6 Hz, 2H), 1.34 – 1.25 (m, 4H), 0.88 (t, J = 7.1 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ: 148.8, 143.2, 142.0, 125.3, 113.4, 111.0, 66.5, 46.4, 36.7, 35.5, 31.5, 30.6,, 28.2, 26.0, 22.5, 20.2, 14.0.

MS-ESI: 331.2268 (calculated mass of C21H31O3, [M+H$^+$]), found: 331.2265; 353.2087 (calculated mass of C21H30O3Na, [M+Na$^+$]), found: 352.2085.

$[\alpha]_D^{25}$ = – 115.5 (c =8.26·10^{-3} g/mL, $CHCl_3$).

3. References

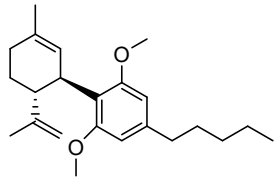
1: McAulay, K.; Clark, J. S. Total Synthesis of 7-Epi-Pukalide and 7-Acetylsinumaximol B. *Chemistry - A European Journal* **2017**, *23* (41), 9761–9765. https://doi.org/10.1002/chem.201702591

2: Torrens, A. A.; Ly, A. L.; Fong, D.; Adronov, A. Rapid and Mild Cleavage of Aryl-Alkyl Ethers to Liberate Phenols. *European J Org Chem* **2022**, *2022* (27). https://doi.org/10.1002/ejoc.202200570

3: S. Tchilibon, R. Mechoulam Synthesis of a Primary Metabolite of Cannabidiol *Org. Lett.* **2000**, *2* (21), 3301-3303. https://doi.org/10.1021/ol006369a

4: Arms, M. R.; Wilcox, C. S. Intramolecularly Sensitized Precipitons: A Model System for Application to Metal Sequestration *J. Am. Chem. Soc.* **2006**, *128*, 250-256. https://doi.org/10.1021/ja0561340

4. NMR Spectra



3

Figure S6: ***Compound 3*** **^{1}H NMR**

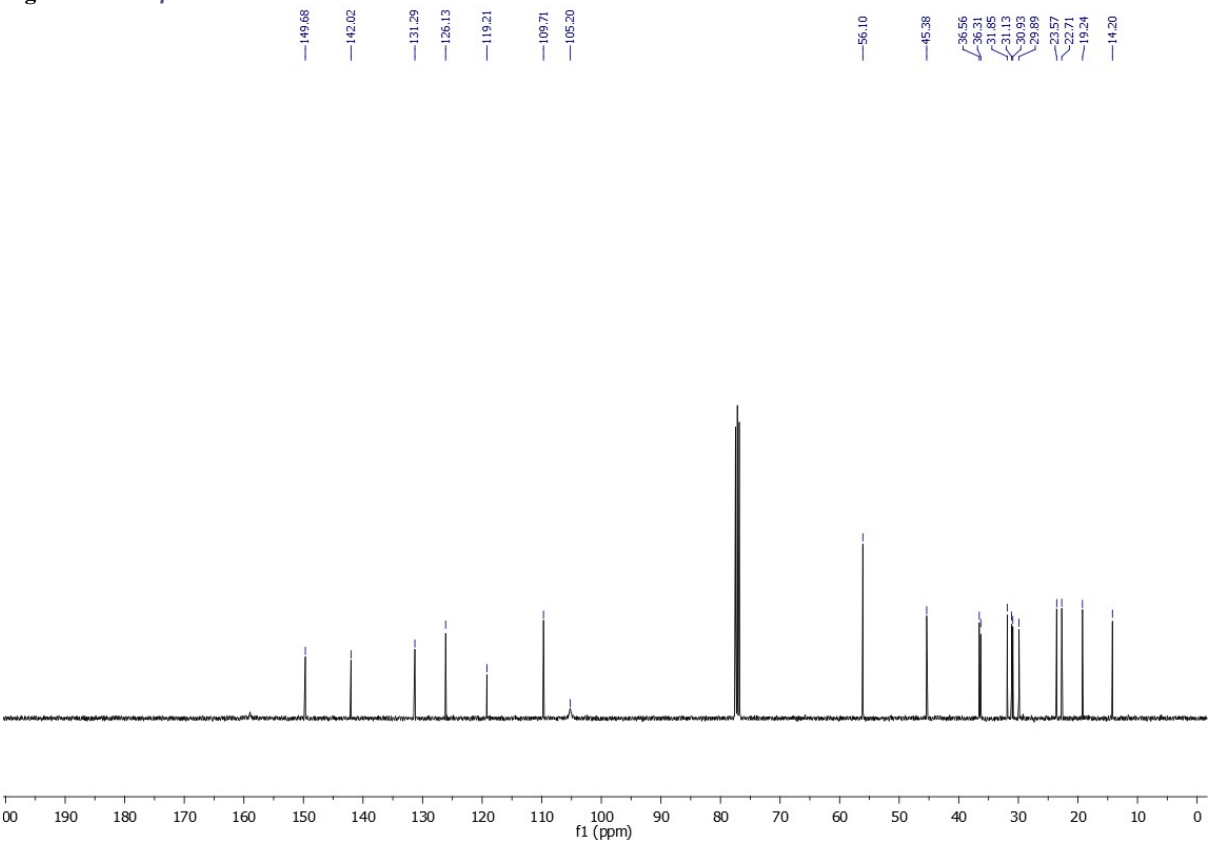


Figure S7: ***Compound 3*** **^{13}C NMR**

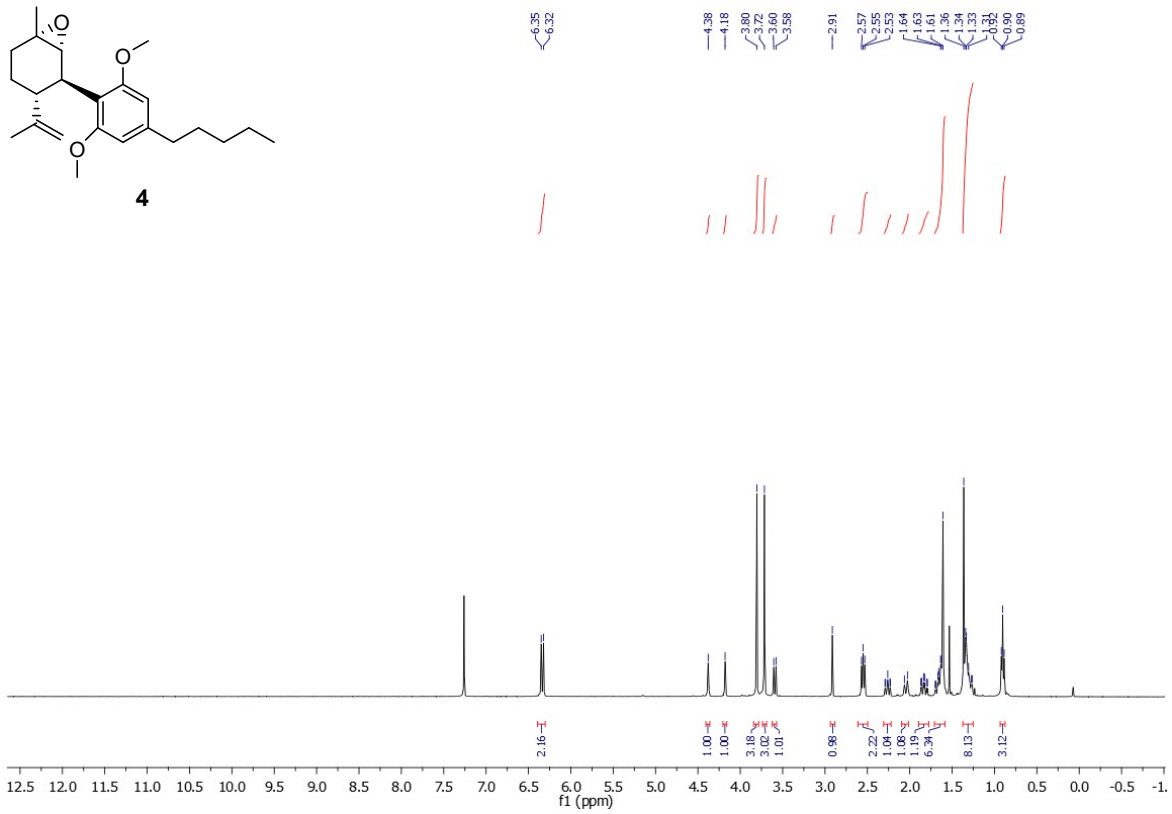


Figure S8: ***Compound 4*** **^{1}H NMR**

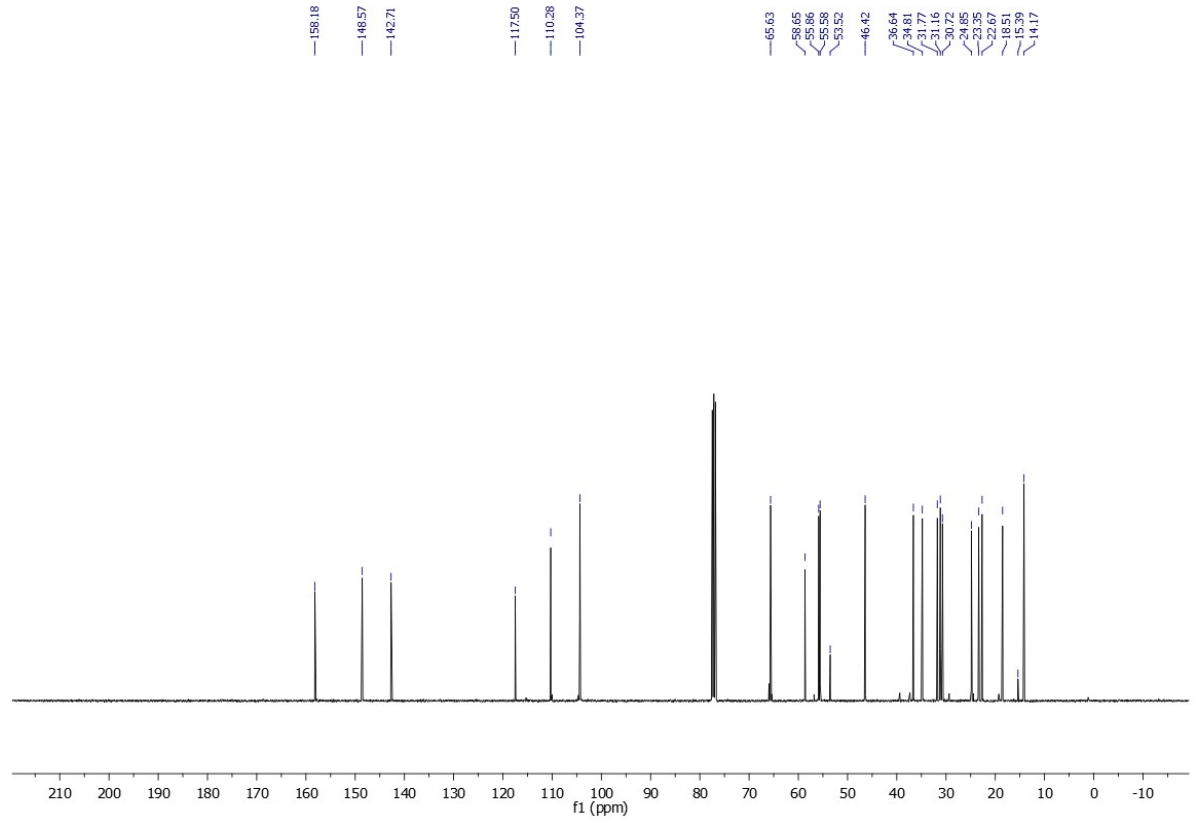


Figure S9: ***Compound 4*** **^{13}C NMR**

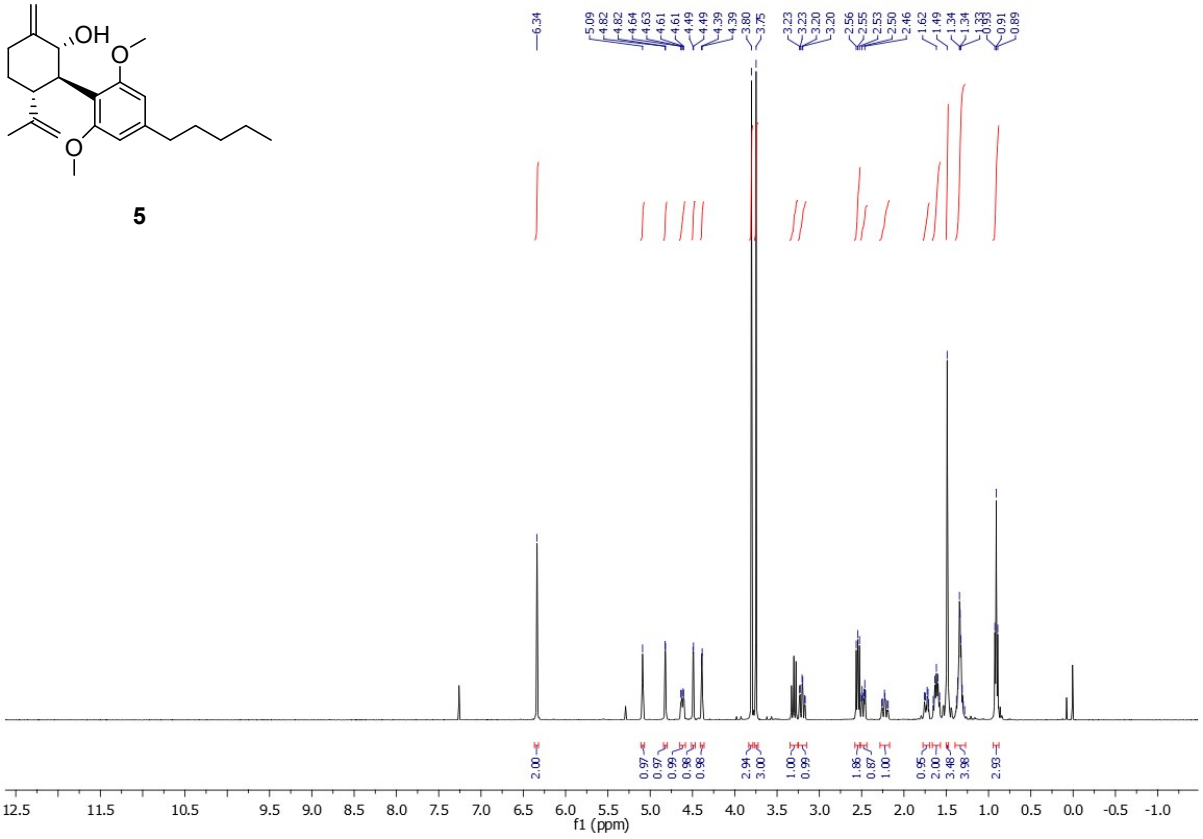


Figure S10: ***Compound 5*** **^{1}H NMR**

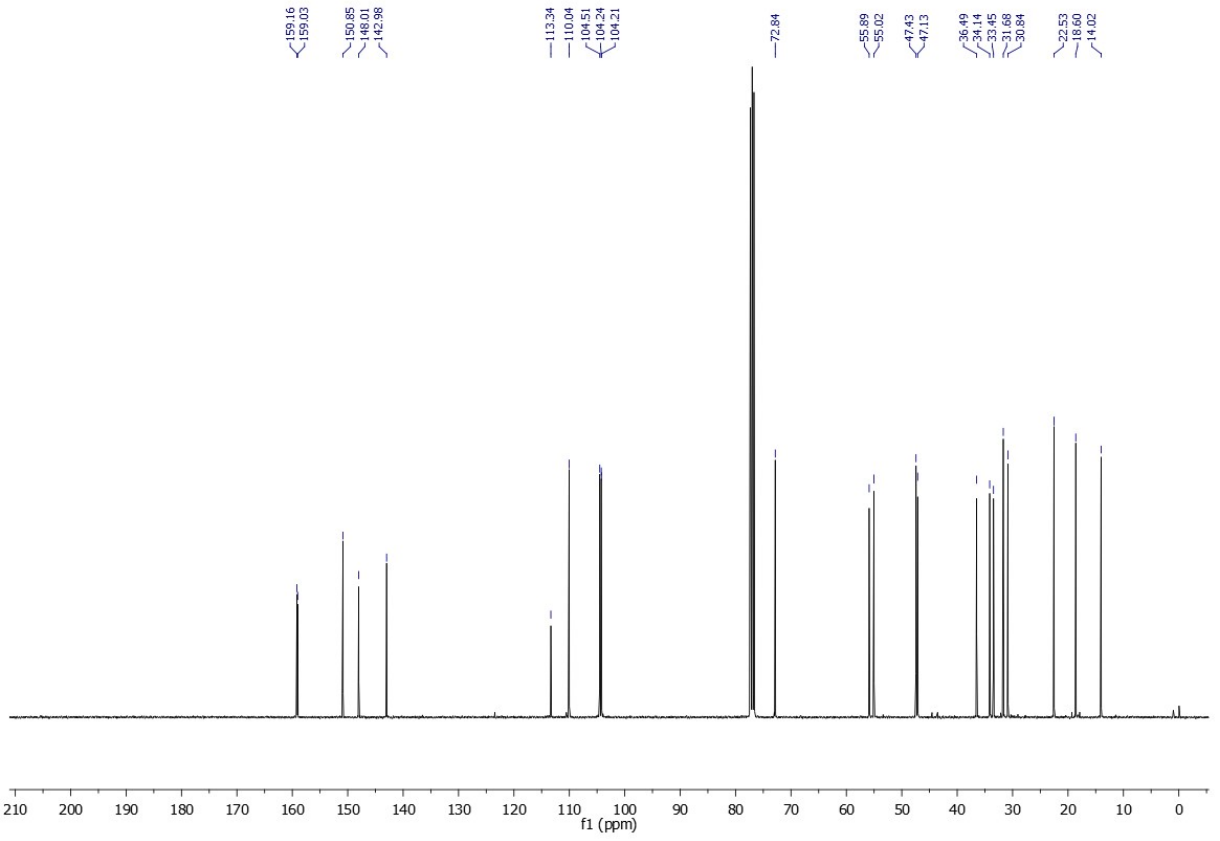
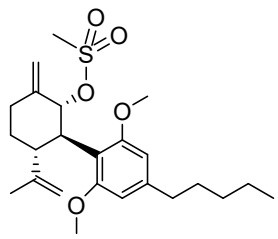


Figure S11: ***Compound 5*** **^{13}C NMR**



5a

Figure S12: *Crude compound 5a* ^{1}H NMR

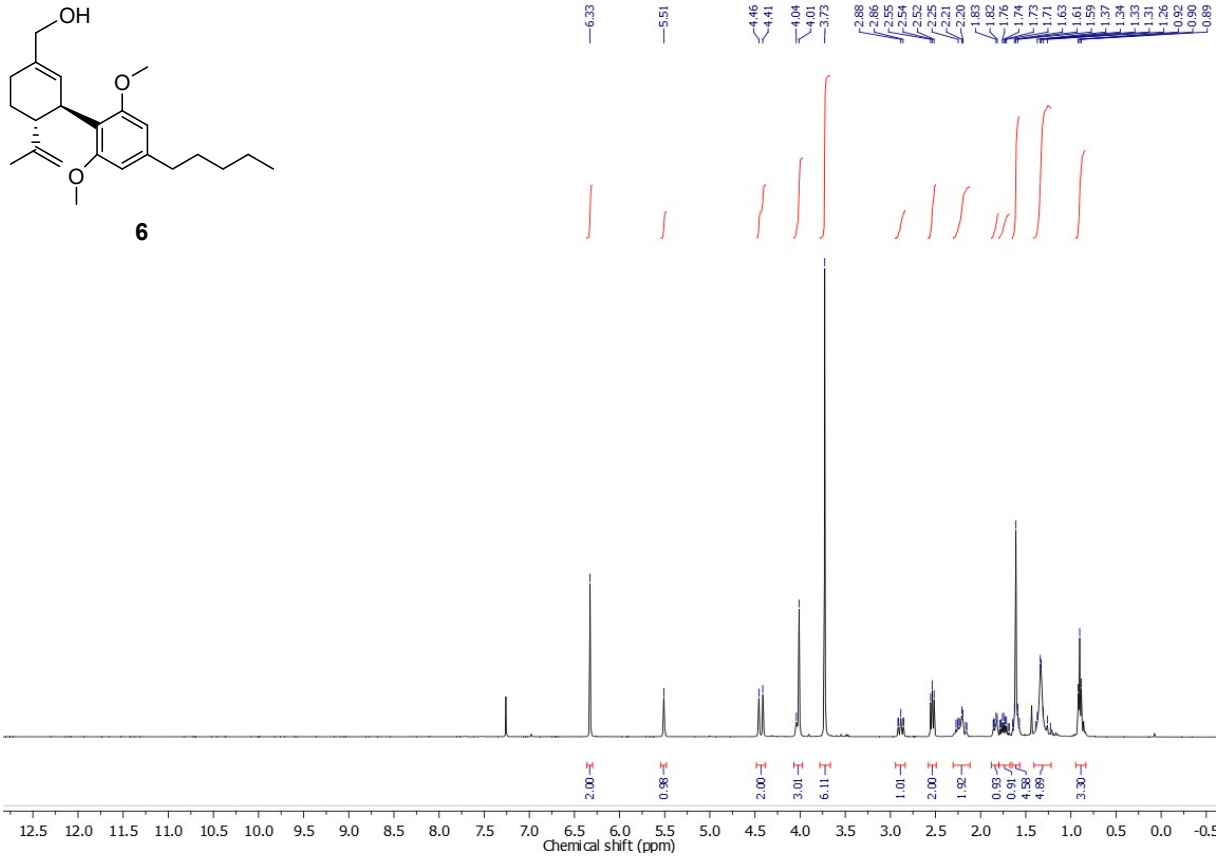


Figure S13: *Compound 6* ^{1}H NMR

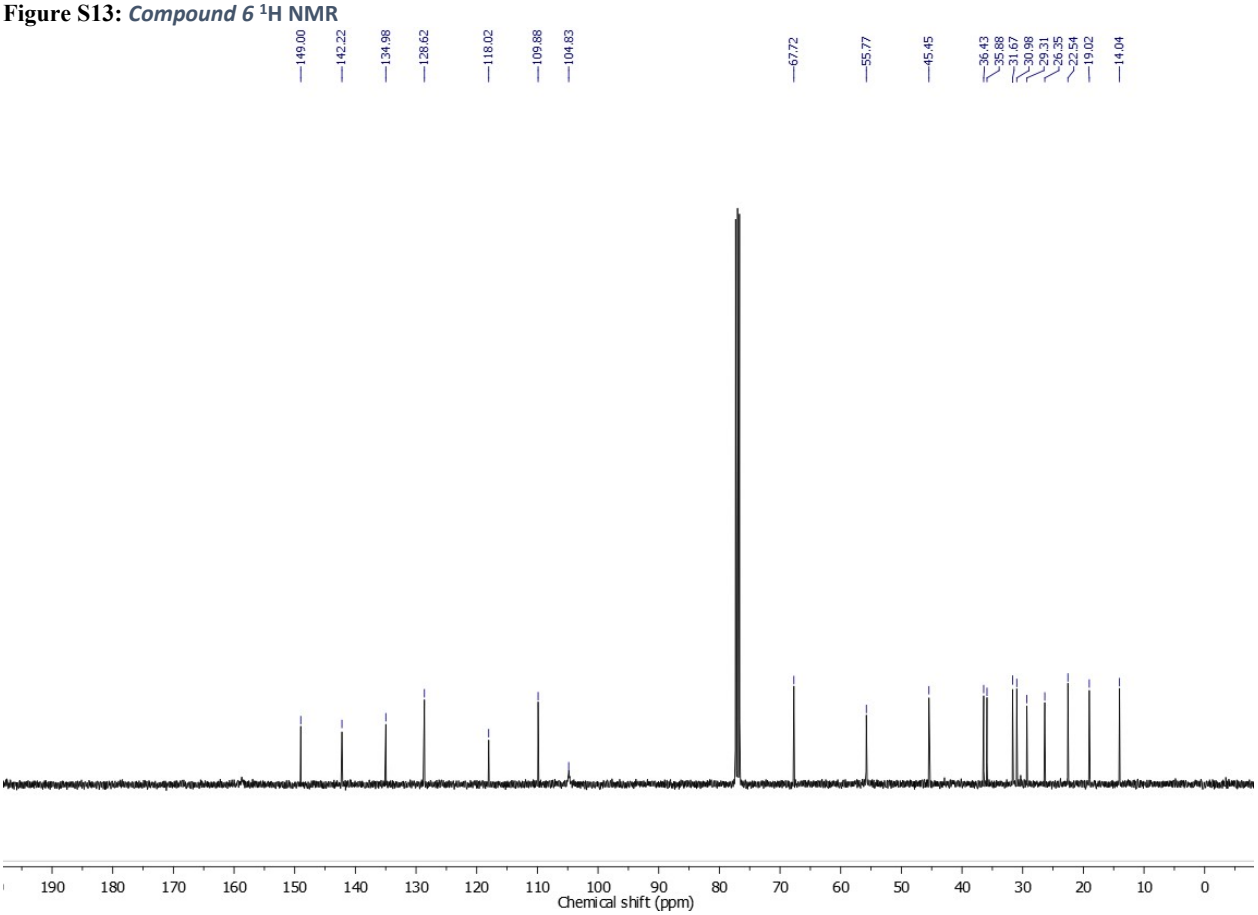


Figure S14: *Compound 6* ^{13}C NMR

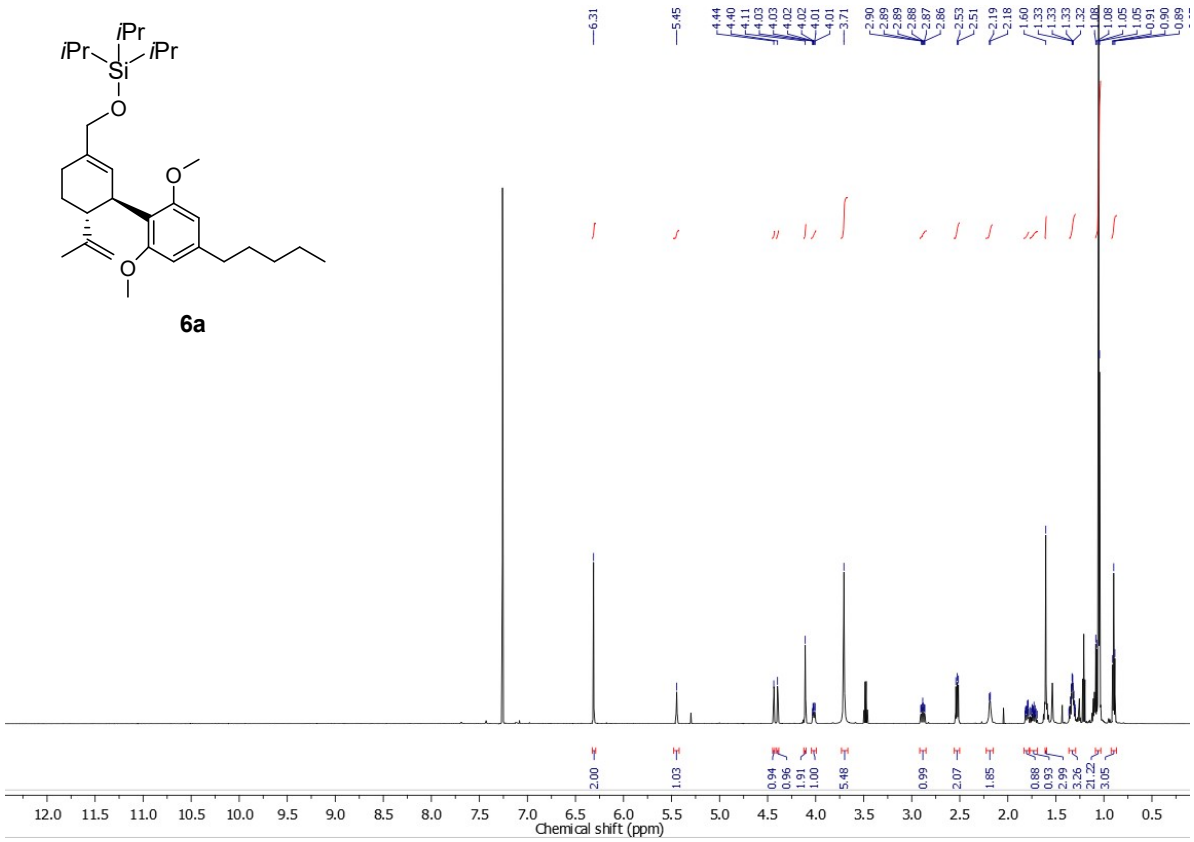


Figure S15: *Crude compound 6a* ^{1}H NMR

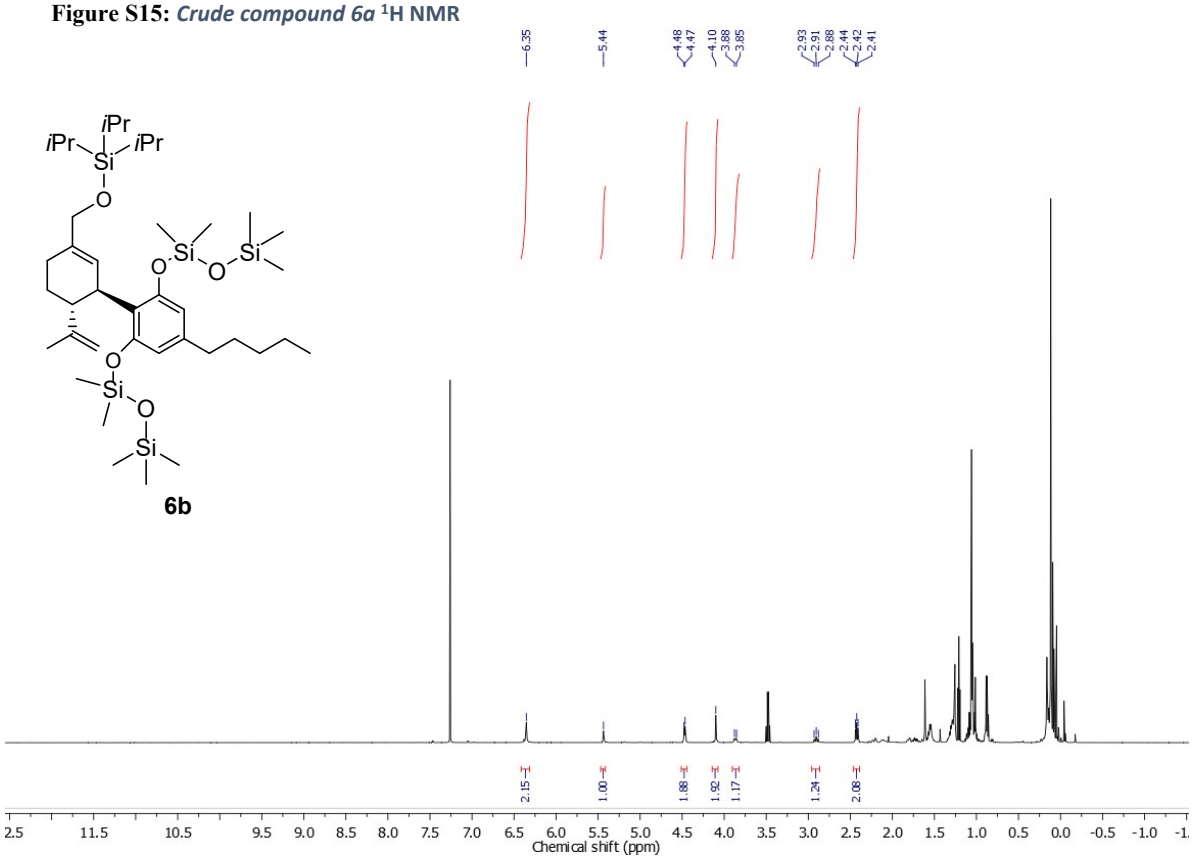


Figure S16: *Crude compound 6b* ^{1}H NMR

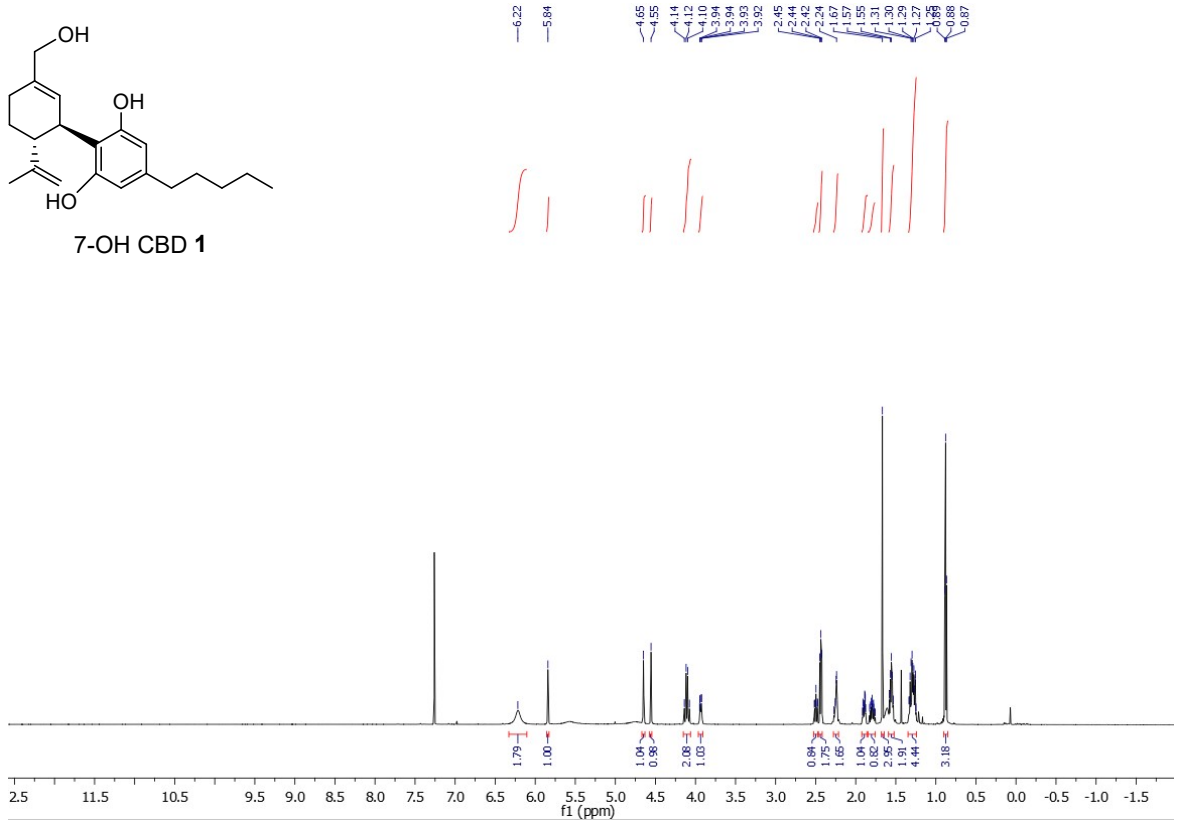


Figure S17: ***Compound 1*** **^{1}H NMR**

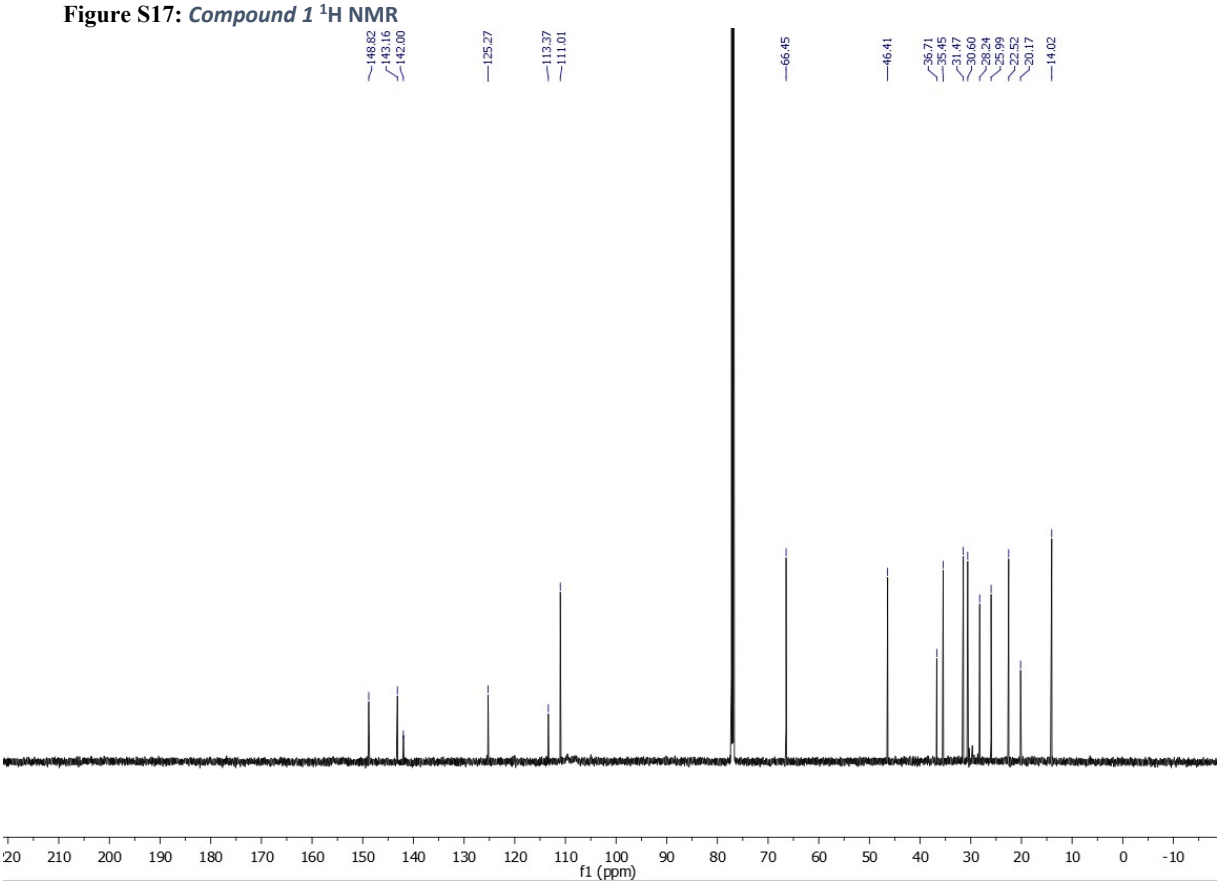


Figure S18: ***Compound 1*** **^{13}C NMR**

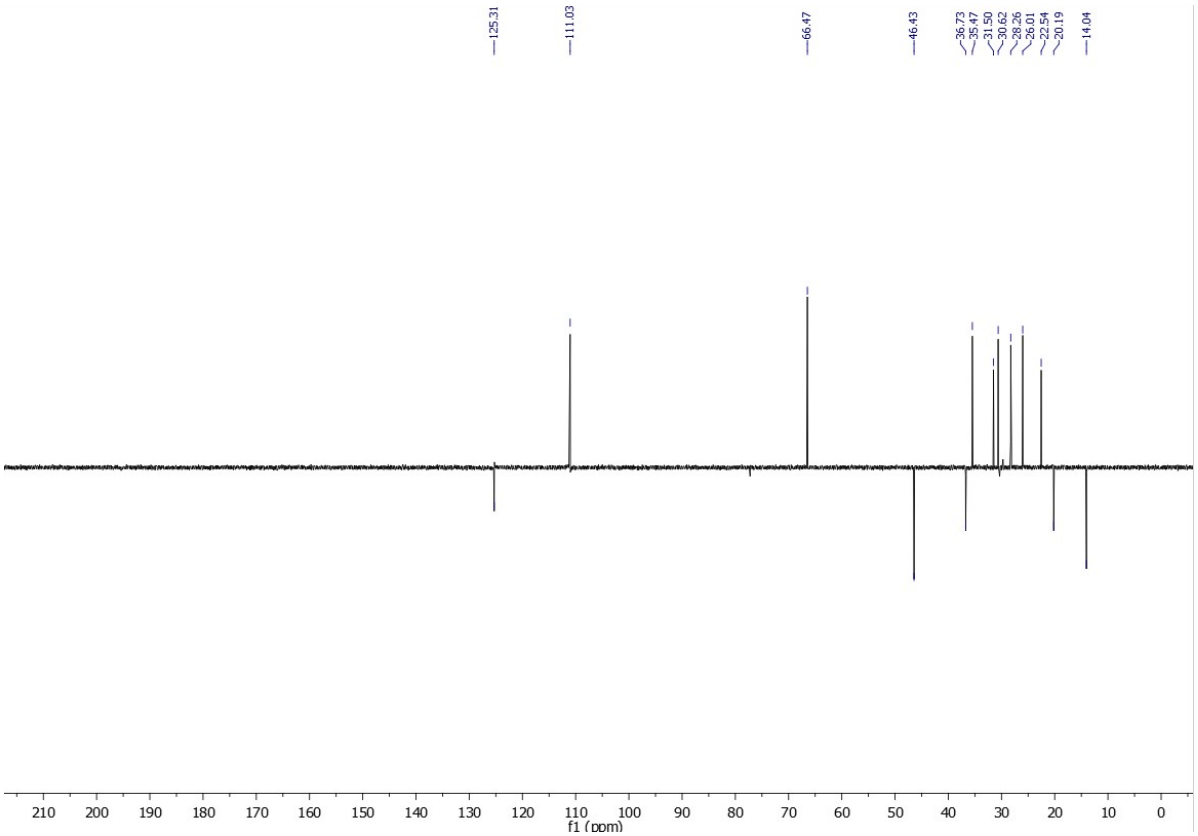


Figure S19: ***Compound 1*** **^{13}C NMR DEPT-135**

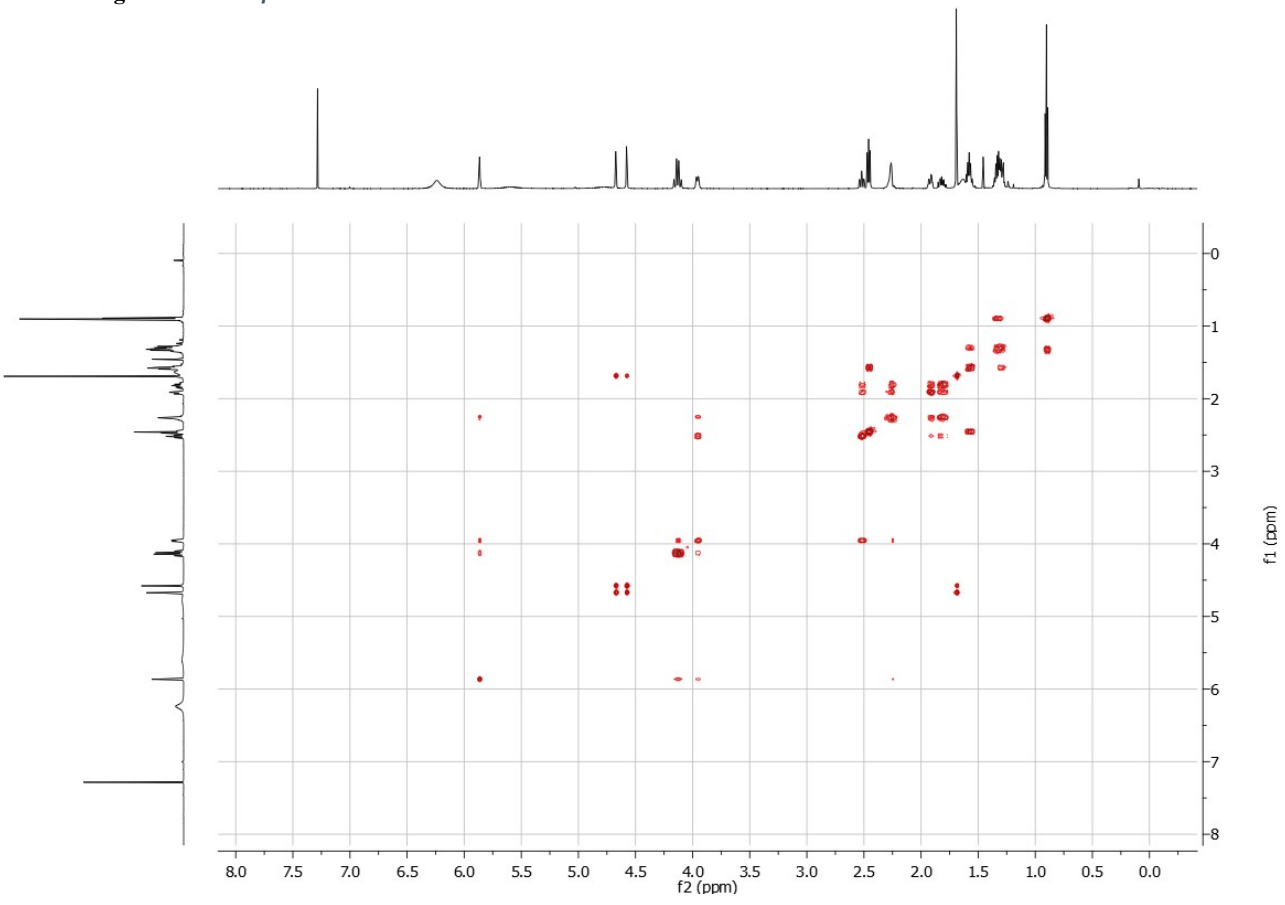


Figure S20: ***Compound 1*** **^{1}H-^{1}H correlation COSY**

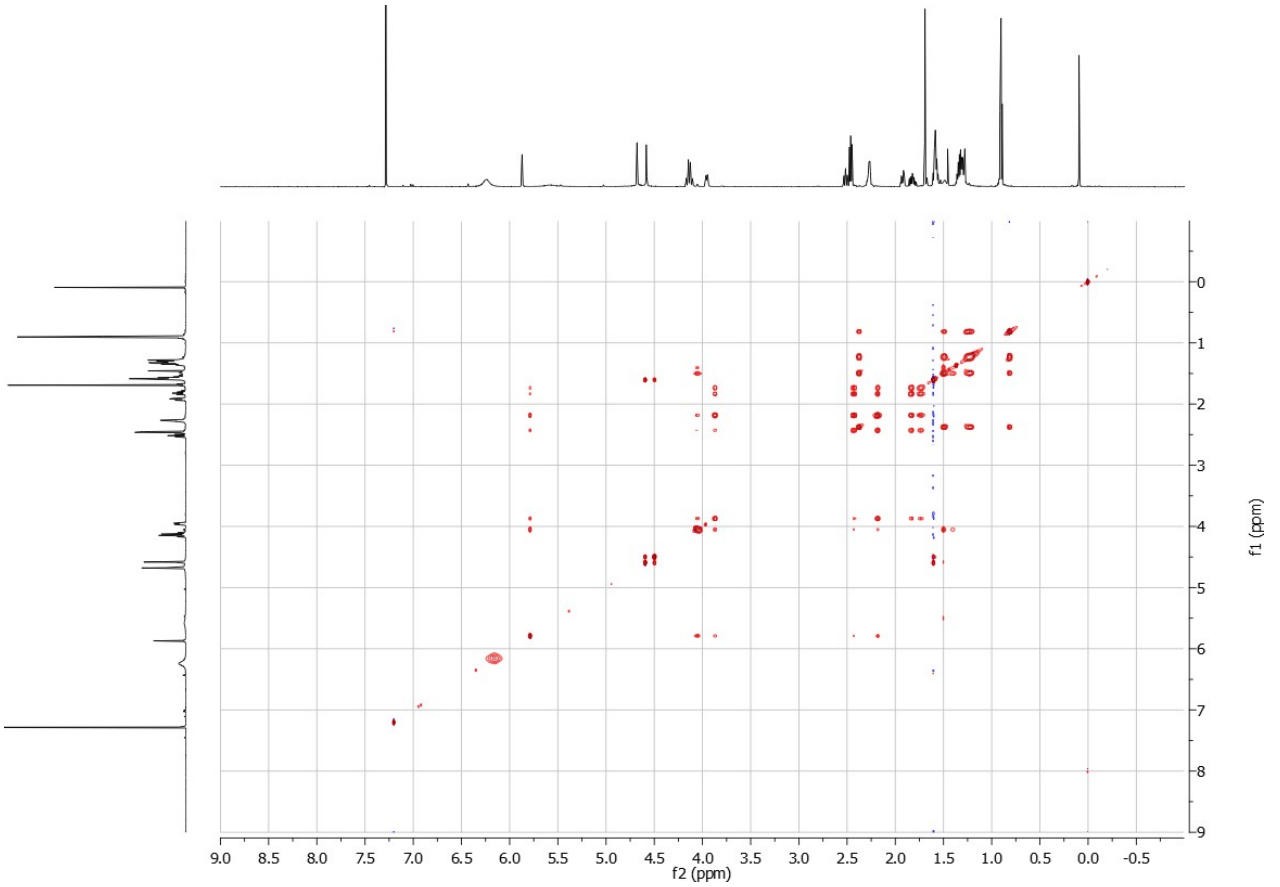


Figure S21: *Compound 1 ^{1}H-^{1}H correlation* TOCSY

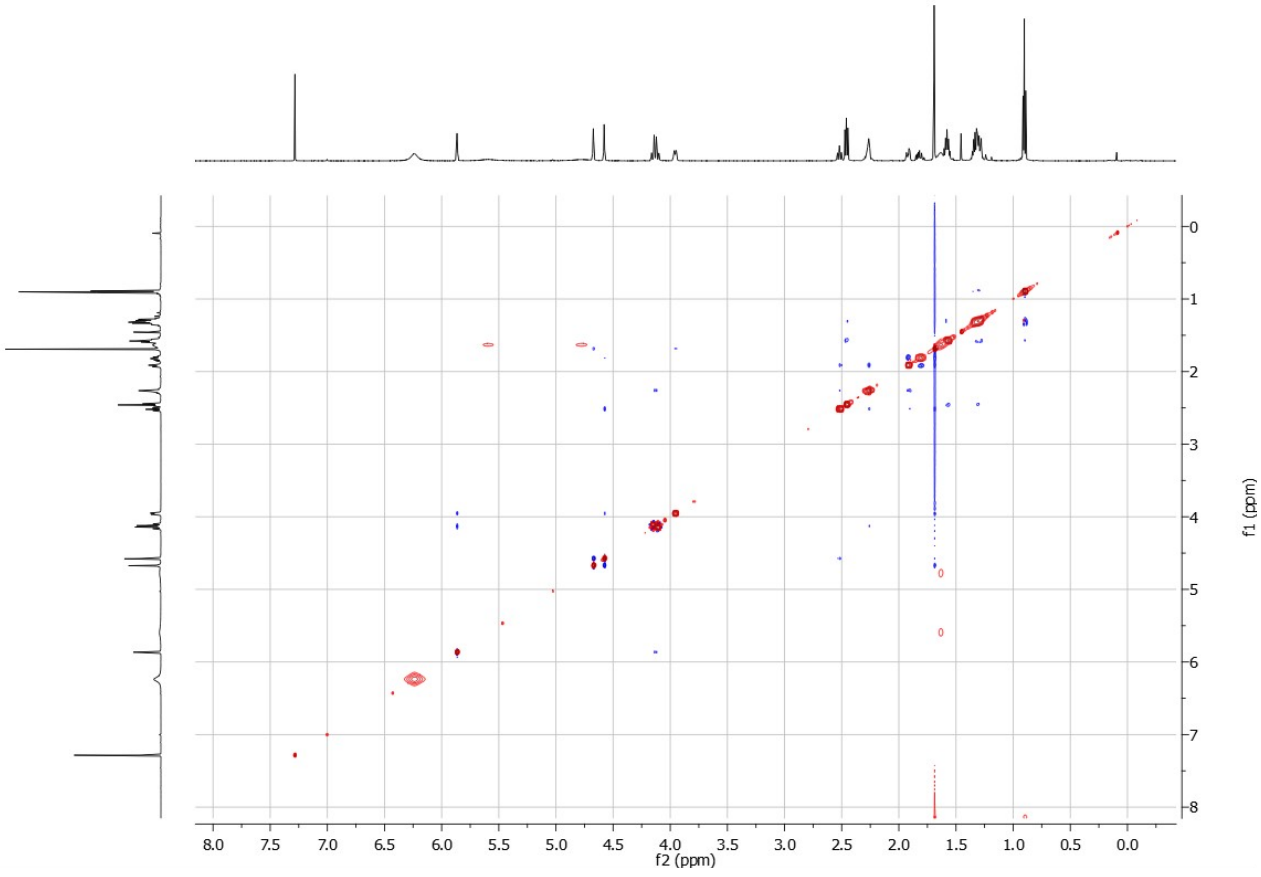


Figure S22: *Compound 1 ^{1}H-^{1}H correlation* NOESY

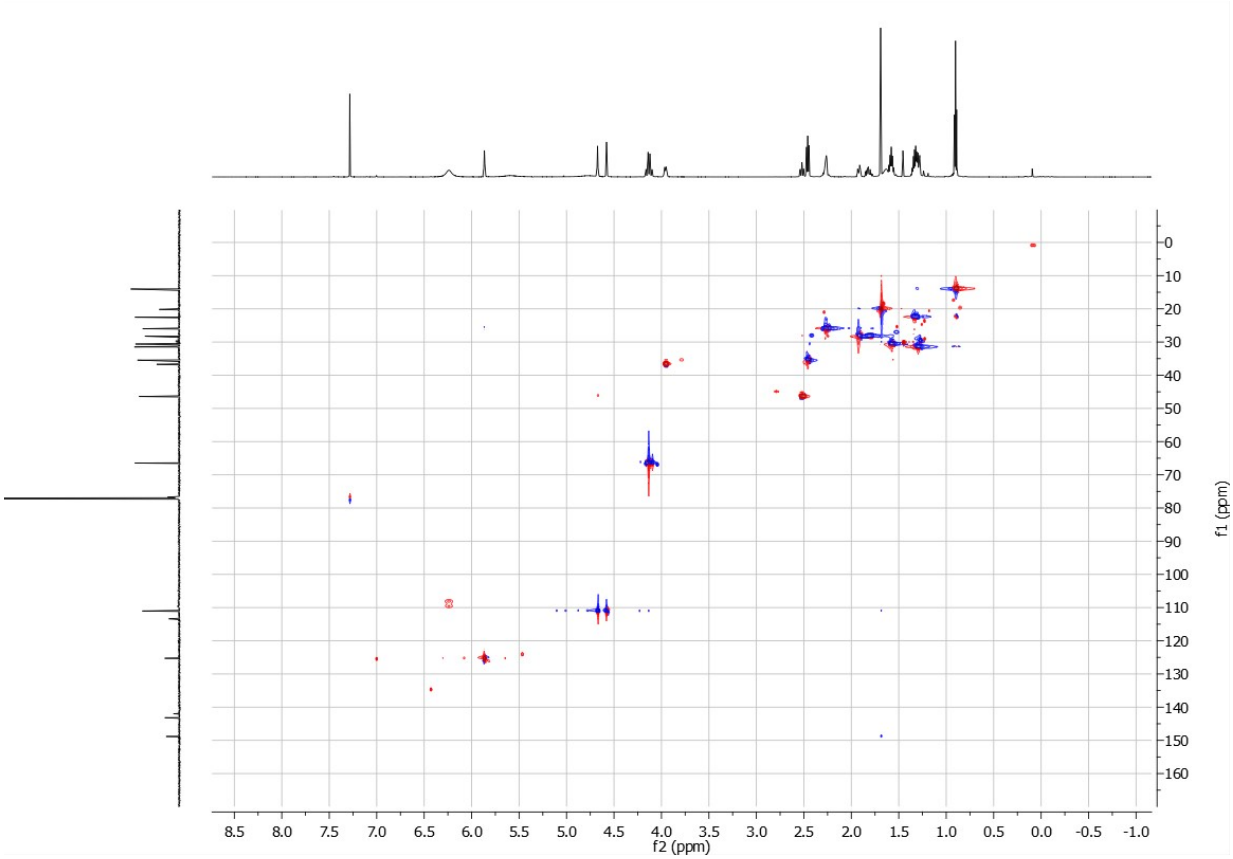


Figure S23: *Compound 1 ^{1}H-^{13}C correlation* HSQC

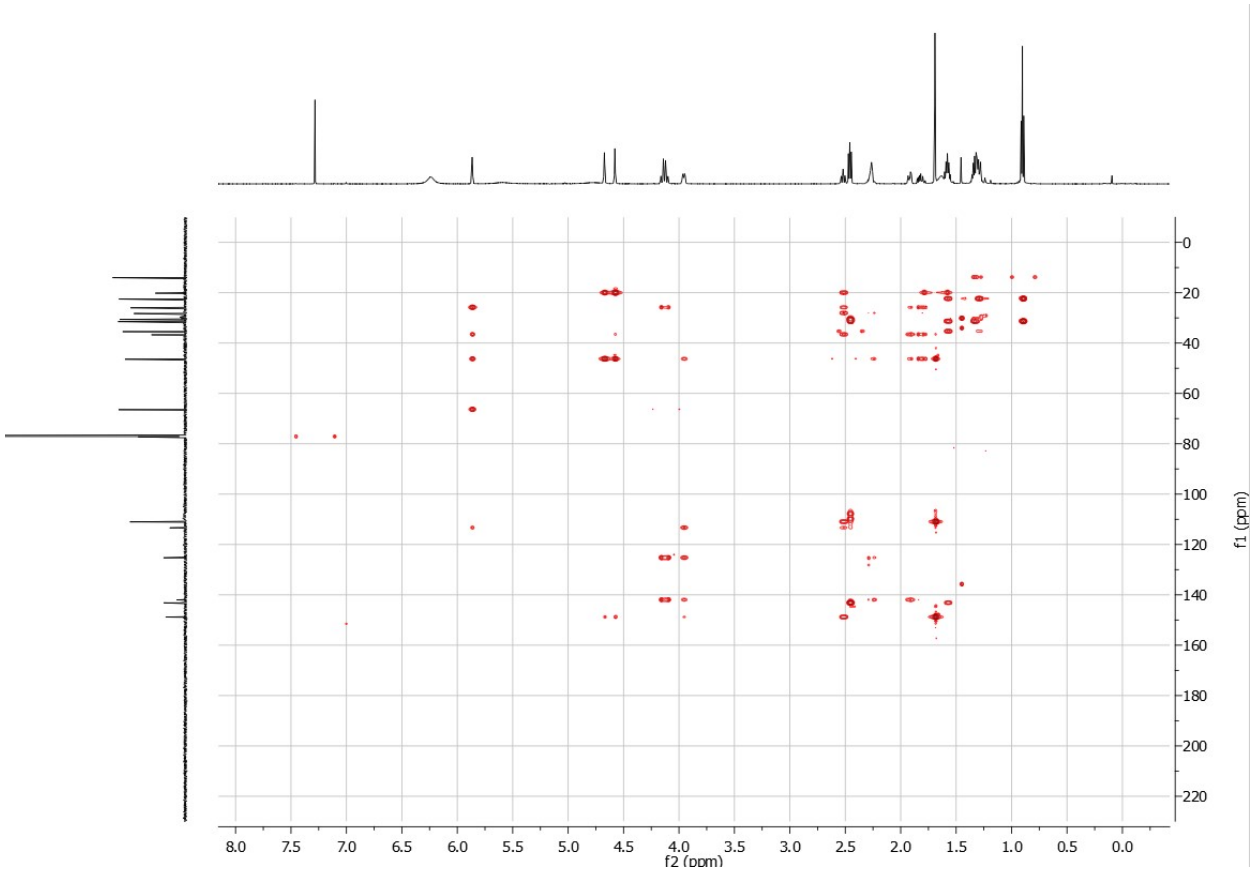


Figure S24: *Compound 1 ^{1}H-^{13}C correlation* HMBC