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Synthesis of a Tetracyclic, Conformationally Constrained Analogue of Δ^8-THC

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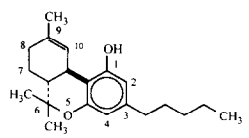
Abstract—A tetracyclic, conformationally constrained analogue of Δ^8-THC (**2**) has been synthesized in which a two carbon bridge exists between C2 and C2′. Two conceptually related syntheses of **2** are described, both of which employ 5,7-dimethoxy-4-oxo-1,2,3,4-tetrahydronaphthoic acid (**11**) as starting material. This substrate was converted to 5,7-dimethoxy-2-propyl-1,2,3,4-tetrahydronaphthalene (**7**) and its 4-keto derivative (**18**). Demethylation of **11** and **18** provided the corresponding resorcinols, which were condensed with *trans-p*-menthadienol to afford cannabinoid **2**, and a keto derivative (**20**). $LiAlH_4/AlCl_3$ reduction of **20** provided **2**. Cannabinoid **2** has relatively low affinity for the cannabinoid brain receptor ($K_i = 703 \pm 98$ nM).

Introduction

Following the elucidation of the structure of the principal psychoactive constituent of *Cannabis sativa* (marijuana), Δ^9-tetrahydrocannabinol (Δ^9-THC, **1**, numbering as indicated on the structure; the alkyl side chain is numbered beginning with the benzylic carbon as C1′) by Gaoni and Mechoulam,[1] a considerable body of data has been amassed concerning structure–activity relationships (SAR) of cannabinoids.[2] In the course of developing these SAR, it was noted that one of the most important variables in determining the potency of a given cannabinoid was the length and/or substitution pattern of the alkyl side chain at C3. In particular, if the five carbon chain was replaced by a 1,1- or 1,2-dimethylheptyl group, potency was increased, but little was known about the effect on cannabinoid activity of simple alkyl substituents on the side chain, or the stereochemistry of those substituents.[2]

In recent work from these laboratories, the synthesis and pharmacology of the seven isomeric side chain methyl analogues of Δ^8-THC was described.[3] It was found that 1′- and 2′-methyl-Δ^8-THC isomers have somewhat greater affinity for the cannabinoid brain (CB_1) receptor than Δ^8-THC, that the 3′-methyl isomers have approximately the same affinity for the receptor as Δ^8-THC, while 4′-methyl-Δ^8-THC has lower affinity. The in vivo pharmacology was consistent with the receptor affinity of these compounds.[3] There was relatively little effect upon the receptor affinity as a function of the stereochemistry of the methyl group in the 1′-, 2′- and 3′-methyl analogues. In all these compounds, the aliphatic side chain is conformationally mobile; however, it is probable that there are steric constraints associated with the lipophilic region of the cannabinoid brain receptor. In order to investigate the effect of side chain conformation upon receptor affinity, a conformationally constrained analogue of Δ^8-THC (**2**) was designed.



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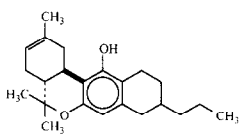

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Several years ago, Razdan and Dalzell reported the synthesis of a conformationally constrained analogue of $\Delta^{6a,10a}$-THC (**3**), which was essentially inactive in the mouse.[4] However, this compound is not a Δ^8- or Δ^9-THC, and the geometry of the appended cyclopentane ring is dissimilar to that of the acyclic alkyl groups present in natural cannabinoids, and their monomethyl

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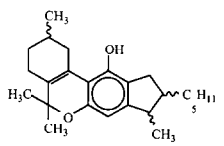
derivatives. Cannabinoid **2** is a hybrid of 2-methyl or ethyl-Δ^8-THC, and the 2′-methyl-Δ^8-THC isomers. Some years ago, it was reported that introduction of a methyl or ethyl group at C2 of Δ^8- or Δ^9-THC gave compounds which although somewhat less potent than the parent cannabinoids, were still quite active. An alkyl group at C4, however, provided compounds which were essentially inactive.[5] Both isomers of 2′-methyl-Δ^8-THC have greater affinity for the CB_1 receptor, and are somewhat more potent in vivo than Δ^8-THC.[3] Consequently, it seemed plausible that **2** should have moderate to high affinity for the CB_1 receptor, assuming the absence of conformational variations which would affect its interaction with the lipophilic portion of the receptor.

The usual method of preparation of Δ^8-THC, and its analogues is the Petrzilka synthesis, the acid catalyzed reaction of a substituted resorcinol with a monoterpene derivative, frequently *trans-p*-menthadienol.[6] In most instances, the resorcinol is a symmetrical 5-alkyl-1,3-dihydroxybenzene derivative, however for the synthesis of **2** by this method an unsymmetrical tetralin (**4**) would be required. The reaction with a symmetrical resorcinol in principle, and in practice, usually provides two products, one resulting from electrophilic alkylation between the hydroxyl groups to provide the cannabinoid; the other from alkylation between the alkyl group and a hydroxyl giving an isocannabinoid. These isomers are usually not difficult to separate due to differences in polarity of the regioisomers. However, the reaction of **4** with *trans-p*-menthadienol could conceivably provide three different products (**2**, **5** and **6**). Two are the desired product **2** and the isocannabinoid **5**, while the third results from alkylation between the hydroxyls, followed by formation of the alternative benzopyran to give **6**.



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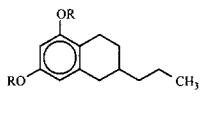
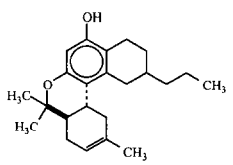


4 R = H

7 R = CH_3



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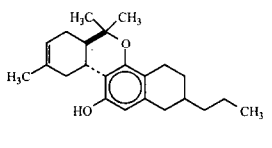
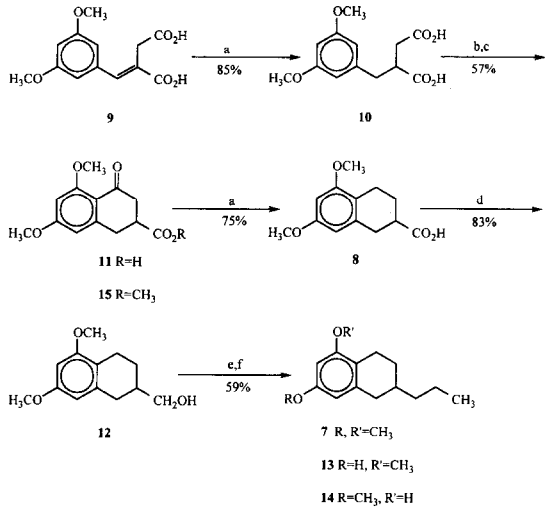


6

An alternative synthesis of cannabinoids was developed for the synthesis of 11-nor-Δ^9-THC-9-carboxylic acid, nabilone and 1-deoxy-11-hydroxy-Δ^8-THC.[7] However, this synthesis is longer than the Petrzilka synthesis, and is also based on a symmetrical resorcinol precursor to the cannabinoid. The synthetic approach chosen for conformationally constrained cannabinoid **2** was to synthesize resorcinol dimethyl ether **7**, and then to attempt to differentiate between the two methoxyls to provide an appropriate substrate for either the Petrzilka synthesis,[6] or that developed in these laboratories.[7] Although it appeared conceivable that direct condensation of resorcinol **4** with *trans-p*-menthadienol could afford cannabinoid **2**, it was also apparent that it would be very difficult to differentiate between structures **2** and **6** employing standard NMR techniques.



9 **10**

11 R=H

15 R=CH_3 **8**

12

7 R, R′=CH_3

13 R=H, R′=CH_3

14 R=CH_3, R′=H

Scheme 1. (a) H_2(g)/10% Pd(C)/EtOH/48 psi; (b) Ac_2O/reflux; (c) PPA/100 °C; (d) $LiAlH_4$/THF/25 °C; (e) TsCl/C_5H_5N/$CHCl_3$/0 °C; (f) EtMgBr/Li_2CuCl_4/THF/25 °C.

Results

A most promising synthetic approach to dimethyl ether **7** employed the known tetralin carboxylic acid (**8**, Scheme 1) as starting material.[8] This acid also provided a method for the synthesis of both 2′-epimers of **2** via resolution of **8**, should the pharmacology of the mixture of diastereomers appear sufficiently interesting.[3] Acid **8** was originally prepared from 3,5-dimethoxybenzyl bromide, and a malonic ester derivative;[8] however, a more efficient approach appeared to be the tetralone carboxylic acid synthesis based on the Stobbe condensation.[9]

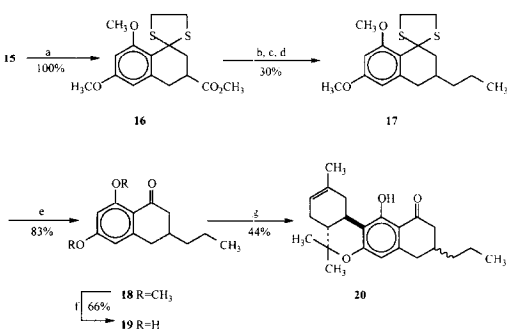
Reaction of 3,5-dimethoxybenzaldehyde with diethyl succinate in *tert*-butyl alcohol, catalyzed by potassium *tert*-butoxide provided the Stobbe product which on hydrolysis gave diacid **9** in a disappointing 40% yield after purification. Catalytic hydrogenation proceeded in 85% yield to provide the known benzylsuccinic acid **10**.[10] It was subsequently found that hydrogenation of

crude **9**, followed by purification, afforded acid **10** in 64% yield from 3,5-dimethoxybenzaldehyde. Conversion of **10** to tetralone carboxylic acid **11** and reduction to **8** was carried out using modifications of the published procedures (see Experimental section).[8,10] Lithium aluminum hydride reduction of **8** provided alcohol **12**, conversion of which to the *p*-toluenesulfonate ester and modified Kochi coupling[3] with ethylmagnesium bromide provided **7**.

A number of attempts were made to effect the selective removal of the apparently less hindered methyl ether to obtain phenol **13**. It was considered that condensation of **13** with menthadienol would provide the methyl ether of **2**. A variety of procedures, including sodium thiopropoxide,[7] K-Selectride[11] and trimethylsilyl iodide[12] all provided mixtures of the desired monoether **13**, and an isomer **14** resulting from cleavage of the other ether, in which the undesired isomer **14** was invariably the major product.[13]

It was ultimately found that the ketonic carbonyl of acid **11** could be employed to obtain the desired regioselectivity through stabilization of the adjacent hydroxyl group by intramolecular hydrogen bonding. Several unsuccessful approaches using acid **11**, or its methyl ester **15** were explored before it was found that ester **15** could be smoothly converted to the corresponding thioketal **16** (Scheme 2) which was carried through the synthetic protocol employed for the synthesis of tetralin **7**.[14] Accordingly, $LiAlH_4$ reduction of **16** provided the primary alcohol, the *p*-toluenesulfonate ester of which underwent modified Kochi coupling with ethyl Grignard to provide tetralin derivative **17**. Treatment of the thioketal with aqueous-methanolic methyl iodide provided ketone **18**.[15]

Although several potentially regioselective transformations of ether **18** were considered, it seemed probable that



Scheme 2. (a) $HSCH_2CH_2SH/BF_3{\cdot}Et_2O/CH_2Cl_2/25\,^{\circ}C$; (b) $LiAlH_4/THF/25\,^{\circ}C$; (c) $TsCl/C_5H_5N/CHCl_3/0\,^{\circ}C$; (d) $EtMgBr/Li_2CuCl_4/THF/25\,^{\circ}C$; (e) $CH_3I/CH_3OH/H_2O$/reflux; (f) $BBr_3/CH_2Cl_2/25\,^{\circ}C$; (g) *trans*-*p*-menthadienol/HOTs/C_6H_5F/reflux.

resorcinol **19** should show selectivity between the two hydroxyls due to stabilization of the hydroxyl proximate to the carbonyl as noted above. Ether cleavage was smoothly effected with BBr_3, and an attempt was made to carry out the Petrzilka condensation with *p*-menthadienol. The rationale for this transformation was based on the assumption that if the initial Friedel–Crafts alkylation took place only two products were probable. One is the desired cannabinoid **20**, and the other was analogous to isocannabinoid **5**. Cyclization to the hydrogen bonded hydroxyl of the precursor to **20** seemed unlikely. Although Friedel–Crafts alkylation of aromatic substrates containing strongly electron withdrawing groups is normally unfavorable, the presence of the two strongly activating hydroxyl groups should facilitate alkylation. Some precedent for the reaction existed in that Petrzilka had described the successful alkylation of methyl 2,4-dihydroxy-5-pentylbenzoate with menthadienol.[6]

Reaction of resorcinol **19** with *p*-menthadienol in benzene in the presence of *p*-toluenesulfonic acid, the usual conditions for this reaction, provided a mixture of products. On the basis of the NMR spectrum of the crude reaction mixture it was apparent that benzene was competing with the resorcinol in the alkylation step. Fluorobenzene was investigated as an alternative solvent, and it was ultimately found that reaction of **19** with five equivalents of *p*-menthadienol and one equivalent of toluenesulfonic acid in refluxing fluorobenzene provided in 44% yield an inseparable mixture of two compounds which had virtually identical ^{13}C NMR spectra. The ^{1}H NMR spectrum showed a one proton signal at δ 13.2, characteristic of a strongly intramolecularly hydrogen bonded proton. On the basis of the near identity of the ^{13}C spectra, this mixture was assigned either structure **20**, both isomers at C-2′, or the isocannabinoid structure analogous to **5**. Reduction of the ketonic carbonyl group using $LiAlH_4$–$AlCl_3$[16] gave a material which although homogeneous to TLC, was again a mixture of very similar compounds.

On the basis of these data, it was apparent that the reduction product was either a mixture of C-2′-isomers of the desired cannabinoid **2** or isocannabinoid **5**. The structure was assigned on the basis of an NOE experiment, in which irradiation of the aromatic proton at δ 6.20 in this reduction product resulted in a 4% enhancement of a proton at δ 2.85. This NOE enhancement is only consistent with cannabinoid structure **2**, in which the quasi-equatorial benzylic proton is within 3 Å of the aromatic proton. In isocannabinoid **5** there is no proton sufficiently close to the aromatic proton to provide the observed NOE enhancement.[17] Ultimately, it was found that reaction of resorcinol **4**, obtained by reaction of dimethyl ether **7** with boron tribromide, gave cannabinoid **2** as the only isolable product in 45% yield.

The affinity of tetracyclic cannabinoid **2** for the cannabinoid brain (CB_1) receptor was determined by measuring the ability of the compound to displace the very potent cannabinoid, [^{3}H] CP 55,940, from its binding site in a membrane preparation.[18] For **2**, $K_i = 703 \pm 98$ nM, considerably less than that of Δ^8-THC ($K_i = 44 \pm 12$).[19] In view of the low affinity for the receptor, the synthesis of the individual isomers of **2** was not carried out.

Discussion

The weak affinity of tetracyclic cannabinoid **2** for the CB_1 receptor is somewhat surprising due to the observation that 2-methyl and 2-ethyl-Δ^8-THC retain cannabinoid activity,[5] and that 2′*R* and 2′*S*-methyl-Δ^8-THC have good affinity for the receptor with $K_i = 19 \pm 5$ and 11 ± 1 nM, respectively.[3] However, in the 2-alkyl, and 2′-methyl analogues the lipophilic side chain is free to rotate and thus may adopt any one of many more conformations than are possible for **2**. In particular, rotation about the C3–C1′ and C1′–C2′ bonds in tetracyclic cannabinoid **2** is not possible. Following the completion of this work, the Makriyannis group reported the synthesis of an analogue of **2** in which the cannabinoid side chain was seven rather than five carbon atoms. This compound was also reported as a mixture of C2′ epimers, and has relatively little affinity for the cannabinoid brain receptor ($K_i = 402$ nM).[20] In contrast, the epimeric 2′*R* and 2′*S*-methylheptyl-Δ^8-THCs both have very high affinity for the CB_1 receptor ($K_i = 1.4 \pm 0.2$ nM and 2.0 ± 0.8 nM, respectively).[21]

In view of the fact that THC, and its 2′-methyl analogues in which the side chain is not constrained in its rotation about the C3–C1′ and C1′–C2′ bonds have high affinity for the CB_1 receptor, it is apparent that the geometry in this region of **2** interferes with the interaction of the cannabinoid with the lipophilic region of the receptor. Cannabinoid **2** was prepared as a mixture of epimers at C2′, however molecular modeling studies using PCModel indicates that the minimized structures of the half-chair conformers of each epimer with an equatorial propyl group, are effectively superimposable.[22] These epimers are also superimposable on a low energy conformer of THC, however there are many other accessible side chain conformations for THC and its side chain analogues which would appear to be responsible for the high receptor affinity of these compounds.

Experimental

General

IR spectra were obtained using Nicolet 5DX or Magna spectrometers; ^{1}H and ^{13}C NMR spectra were recorded on a Bruker 300AC spectrometer. Mass spectral analyses were performed on a Hewlett–Packard 5890A gas chromatograph with a mass sensitive detector, and HRMS data were provided by the Mass Spectrometry Laboratory, School of Chemical Sciences, University of Illinois. Ether and THF were distilled from Na-benzophenone ketyl immediately before use, and other solvents were purified using standard procedures. Column chromatography was carried out on Universal silica gel (32–63 μ) using the indicated solvents as eluents. All new compounds were homogeneous to TLC and ^{13}C NMR, unless otherwise noted.

3,5-Dimethoxybenzylidenesuccinic acid (9). To a solution of potassium *tert*-butoxide, from 6.50 g (166 mg atom) of potassium, in 96 mL of *tert*-butyl alcohol at reflux was added 22.0 mL (132 mmol) of freshly distilled diethyl succinate in 13.0 mL of *tert*-butyl alcohol. A solution of 19.6 g (118 mmol) of 3,5-dimethoxybenzaldehyde in 13.0 mL of *tert*-butyl alcohol was immediately added dropwise and the resulting heterogeneous mixture was stirred and heated at reflux for 2 h. After cooling, 175 mL of water was added and the *tert*-butyl alcohol was removed by distillation. To this mixture was added a solution of 15.0 g of KOH in 50 mL of water and the solution was heated at reflux for 4 h. The cooled mixture was washed with ether, and concd HCl was added to pH 1. After chilling (ice bath) for 3 h, the precipitate was filtered off, washed with water, air dried, and finally dried in vacuo to give 29.8 g of crude product. The crude product was recrystallized from cyclohexane/ethyl acetate, to give 12.8 g (40%) of pale yellow solid: mp 172–174 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.36 (s, 2H), 3.75 (s, 6H), 6.53 (t, $J = 2.1$ Hz, 1H), 6.56 (d, $J = 2.1$ Hz, 2H), 7.67 (s, 1H), 11.4 (br s, 2H); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 33.7, 55.2, 100.8, 106.9, 127.7, 136.8, 140.0, 160.5, 168.4, 172.2. Anal. calcd for $C_{13}H_{14}O_6$: C, 58.65; H, 5.30. Found: C, 58.54; H, 5.39.[23]

3,5-Dimethoxybenzylsuccinic acid (10). A. To a solution of 12.8 g (48 mmol) of 3,5-dimethoxybenzylidenesuccinic acid (**9**) in 300 mL of absolute ethanol was added 1.28 g of 10% Pd/C and the mixture was shaken under H_2 (48 psi) for 48 h. The catalyst was filtered off through Celite, and the solvent was removed in vacuo. The gummy residue crystallized when treated with benzene, and gave, after recrystallization from benzene, 10.9 g (85%) of acid **10**, mp 131–133 °C (lit.[10] mp 128 °C): ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.41–2.53 (m, 1H), 2.58–2.74 (m, 2H), 3.04–3.20 (m, 2H), 3.76 (s, 6H), 6.33 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 34.4, 37.5, 42.7, 55.3, 98.8, 107.0, 139.9, 161.0, 178.4, 180.6.

B. The crude 3,5-dimethoxybenzylidenesuccinic acid from 22.8 g of 3,5-dimethoxybenzaldehyde was hydrogenated as described above without purification, and provided after recrystallization from benzene 23.5 g

(64% from 3,5-dimethoxybenzaldehyde) of pure **10**. The properties of this compound were identical to those of material prepared by method **A**.

5,7-Dimethoxy-4-oxo-1,2,3,4-tetrahydro-2-naphthoic acid (11). Keto acid **11** was prepared from **10** as described by Horii et al.[10] From 10.8 g (40.3 mmol) of acid **10** there was obtained 7.2 g of crude product which after recrystallization from acetone provided 5.78 g (57%) of yellowish solid, mp 207–208 °C (lit.[8] 201–203 °C): ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.53–2.66 (m, 2H), 2.92–3.18 (m, 3H), 3.74 (s, 3H), 3.81 (s, 3H), 6.44 (d, J=2.2 Hz, 1H), 6.49 (d, J=2.1 Hz, 1H); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 32.9, 39 (buried in DMSO peaks), 42.0, 55.5, 55.6, 97.4, 105.3, 115.1, 146.5, 162.0, 163.7, 174.6, 192.2.

The methyl ester **15** was prepared by stirring a mixture of 1.00 g (4.00 mmol) of acid **11**, 2.60 g (7.98 mmol) of Cs_2CO_3 and 1.20 mL (19.3 mmol) of methyl iodide in 40 mL of freshly distilled DMF at room temperature for 6 h. Water was added to quench the reaction, and the aqueous phase was extracted with ethyl acetate. The combined organic layers were washed with water and dried ($MgSO_4$). Concentration afforded an oil which was chromatographed (ethyl acetate) to give 0.99 g (94%) of ester **15**: ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 33.2, 39.2, 41.9, 51.8, 55.1, 55.6, 97.2, 104.7, 115.2, 146.1, 162.3, 164.0, 173.2, 192.9. The ^{1}H NMR data are consistent with those reported by Glatz et al.[14]

5,7-Dimethoxy-1,2,3,4-tetrahydro-2-naphthoic acid (8). A mixture of 5.78 g of acid **11** and 0.58 g of 10% Pd/C in 200 mL of ethanol was shaken under H_2 (48 psi) for 30 h. The catalyst was removed by filtering the mixture through Celite, the solvent was removed in vacuo, and the crude product was recrystallized from ethyl acetate to give 4.08 g (75%) of **8**, mp 163–165 °C (lit.[8] mp 165.5–167 °C): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.70–1.93 (m, 1H), 2.19–2.34 (m, 1H), 2.42–2.60 (m, 1H), 2.65–2.90 (m, 2H), 2.92–3.05 (m, 2H), 3.78 (s, 3H), 3.79 (s, 3H), 6.25 (d, J=2.3 Hz, 1H), 6.29 (d, J=2.2 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 21.9, 25.5, 31.8, 39.6, 55.25, 55.31, 96.2, 104.2, 117.0, 136.3, 158.1, 158.5, 181.6.

5,7-Dimethoxy-2-hydroxymethyl-1,2,3,4-tetrahydronaphthalene (12). To a solution of 4.08 g (17.3 mmol) of acid **11** in 30 mL THF was added 2.0 g of $LiAlH_4$ at 0 °C, and the mixture was stirred at ambient temperature for 18 h. The reaction was quenched with water, acidified, and extracted into ether. The combined ethereal layers were washed with $NaHCO_3$, brine and dried ($MgSO_4$). Concentration afforded an oil which was chromatographed using ether to give 3.20 g (83%) of pure **12** as a pale yellow solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.16–1.48 (m, 1H), 1.82–2.08 (m, 2H), 2.20 (br s, 1H), 2.36–2.56 (m, 2H), 2.72–2.91 (m, 2H), 3.59 (d, J=6.4 Hz, 2H), 3.76 (s, 3H), 3.77 (s, 3H), 6.23 (d, J=2.3 Hz, 1H), 6.27 (d, J=2.3 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 22.0, 25.5, 32.9, 36.6, 55.1, 55.2, 67.4, 95.7, 104.3, 117.9, 137.6, 158.0 (two peaks); HRMS calcd for $C_{13}H_{18}O_3$: 222.1256. Found 222.1247.

5,7-Dimethoxy-2-propyl-1,2,3,4-tetrahydronaphthalene (7). To a solution of 1.45 g (6.51 mmol) of alcohol **12** and 1.04 mL (12.9 mmol) of pyridine in 20 mL of dry $CHCl_3$ at 0 °C was added 1.86 g (9.76 mmol) of *p*-toluenesulfonyl chloride. The reaction mixture was stirred at ambient temperature for 18 h, diluted with ether, and washed with successive portions of 10% aqueous HCl, saturated aqueous $NaHCO_3$ and brine. After drying ($MgSO_4$) the solvent was removed at reduced pressure to give a yellow oil which was chromatographed using petroleum ether:ether (1:1) to give 2.03 g (83%) of tosylate as a colorless oil which was used in the subsequent step without further purification: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.16–1.38 (m, 1H), 1.75–1.92 (m, 1H), 1.92–2.10 (m, 1H), 2.39 (s, 3H), 2.24–2.46 (m, 2H), 2.59–2.78 (m, 2H), 3.70 (s, 6H), 3.94 (dd, J=6.6, 1.7 Hz, 2H), 6.13 (d, J=2.2 Hz, 1H), 6.23 (d, J=2.3 Hz, 1 H), 7.29 (d, J=8.1 Hz, 2H), 7.77 (d, J=8.3 Hz, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 21.1, 21.2, 24.7, 32.0, 33.3, 54.7, 73.8, 95.5, 104.0, 116.7, 127.4, 129.5, 132.6, 136.0, 144.4, 157.7, 158.0.

To a stirred solution of 1.08 g (2.87 mmol), of tosylate in 10 mL of dry THF at −78 °C under an atmosphere of dry N_2 was added 1.70 mL (0.170 mmol) of 0.10 M Li_2CuCl_4 in dry THF, followed by 15.0 mL (45.0 mmol) of 3.0 M ethylmagnesium bromide. The mixture was warmed to ambient temperature, stirred for five days, and quenched by the careful addition of saturated aqueous NH_4Cl. After the addition of ether, the reaction mixture was washed with successive portions of saturated aqueous $NaHCO_3$ and brine, dried ($MgSO_4$) and the solvent was removed in vacuo. After chromatography (MPLC, hexanes:ethyl acetate, 90:1) there was obtained 0.470 g (71%) of **7** as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.92 (t, J=7.3 Hz, 3H), 1.17–1.50 (m, 5H), 1.59–1.77 (m, 1H), 1.85–2.02 (m, 1H), 2.29–2.52 (m, 2H), 2.67–2.85 (m, 2H), 3.77 (s, 3H), 3.78 (s, 3H), 6.22 (d, J=2.3 Hz, 1H), 6.27 (d, J=2.3 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.3, 20.0, 22.5, 29.2, 33.6, 36.8, 38.6, 55.2, 55.3, 95.7, 104.4, 118.2, 138.7, 158.2; EIMS *m/z*: 234 (100), 191 (96), 164 (39), 152 (35), 91 (28); HRMS calcd for $C_{15}H_{22}O_2$: 234.1620. Found 234.1616.

Methyl 3′,4′-dihydro-6′,8′-dimethoxyspiro[1,3-dithiolane-2,1′(2*H*)-naphthalene-3-carboxylate] (16). A mixture of 3.36 g (12.7 mmol) of ester **15**, 1.80 mL (21.5 mmol) of 1,2-ethanedithiol, and 0.30 mL (3.5 mmol) of BF_3 ethe-

rate in 10 mL of dry CH_2Cl_2 was stirred at room temperature for 18 h. The reaction was quenched with 10 mL of 15% aqueous sodium hydroxide and extracted with ether. The ether extracts were washed with water, brine and dried ($MgSO_4$). Concentration gave the crude product which was chromatographed using petroleum ether:ether (2:3) to yield 4.31 g (100%) of **16** as a cream solid, mp 104–106 °C: ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.29–2.48 (m, 1H), 2.64–2.79 (m, 1H), 2.93–3.12 (m, 3H), 3.25–3.41 (m, 1H), 3.45–3.58 (m, 2H), 3.58–3.71 (m, 1H), 3.74 (s, 3H), 3.76 (s, 3H), 3.88 (s, 3H), 6.22 (d, J=2.4 Hz, 1H), 6.38 (d, J=2.4 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 33.0, 40.1, 41.2, 41.8, 48.7, 51.8, 55.1, 56.0, 64.7, 99.1, 104.6, 119.2, 137.5, 159.7, 159.8, 174.6; EIMS *m/z*: 340 (23), 312 (26), 280 (57), 221 (44), 188 (100), 175 (54), 115 (19); HRMS calcd for $C_{16}H_{20}O_4S_2$: 340.0803. Found 340.0802.[14]

3′,4′-Dihydro-3′-hydroxymethyl-6′,8′-dimethoxyspiro[1,3-dithiolane-2,1′(2*H*)-naphthalene]. Reduction of **16** was carried out as described above for the preparation of **12**. From 4.31 g (12.7 mmol) of **16** there was obtained after chromatography (petroleum ether:ethyl acetate, 1:1) 3.71 g (94%) of pure alcohol as a cream solid, mp 168–170 °C: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.99 (br s, 1H), 2.03–2.31 (m, 2H), 2.41–2.62 (m, 2H), 2.74–2.89 (m, 1H), 3.22–3.37 (m, 1H), 3.41–3.56 (m, 2H), 3.56–3.71 (m, 3H), 3.76 (s, 3H), 3.88 (s, 3H), 6.21 (d, J=2.5 Hz, 1H), 6.37 (d, J=2.5 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 34.0, 37.3, 41.3, 41.7, 49.8, 55.1, 56.0, 64.9, 66.6, 99.0, 104.9, 120.0, 138.8, 159.5, 159.9; EIMS *m/z*: 312 (23), 280 (34), 221 (36), 188 (100), 175 (45), 115 (28); HRMS calcd for $C_{17}H_{20}O_3S_2$: 312.0854. Found 312.0852.[14]

3′,4′-Dihydro-6′,8′-dimethoxy-3′-propylspiro[1,3-dithiolane-2,1′(2*H*)-naphthalene] (17). The alcohol described above was converted to the tosylate as described for the preparation of **7**. From 3.71 g (11.9 mmol) of alcohol there was obtained, after chromatography (petroleum ether: ethyl acetate, 3:2), 4.77 g (86%) of pure material: ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.04 (t, J=11.8 Hz, 1H), 2.23–2.62 (m, 3H), 2.45 (s, 3H), 2.70–2.85 (m, 1H), 3.15–3.32 (m, 1H), 3.39–3.53 (m, 2H), 3.53–3.68 (m, 1H), 3.75 (s, 3H), 3.86 (s, 3H), 3.90–4.18 (m, 2H), 6.15 (d, J=2.2 Hz, 1H), 6.36 (d, J=2.3 Hz, 1H), 7.36 (d, J=8.0 Hz, 2H), 7.82 (d, J=8.2 Hz, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 21.6, 33.5, 34.3, 41.2, 41.7, 49.0, 55.1, 56.0, 64.5, 73.5, 99.2, 104.7, 119.5, 127.9, 129.8, 132.9, 137.6, 144.8, 159.6, 159.9.

Reaction of the tosylate with ethylmagnesium bromide was carried out as described above in the preparation of **7**. Reaction of 1.91 g (4.09 mmol) of tosylate with 23.2 mL (69.6 mmol) of 3.0 M ethylmagnesium bromide with 4.1 mL of 0.10 M Li_2CuCl_4 in THF as catalyst, and stirring for 18 h, gave, after chromatography (petroleum ether:ethyl acetate, 5:1), 0.492 g (37%) of pure **17**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.94 (t, J=6.8 Hz, 3H), 1.25–1.51 (m, 4H), 1.89–2.09 (m, 2H), 2.32–2.49 (m, 2H), 2.68–2.85 (m, 1H), 3.21–3.35 (m, 1H), 3.40–3.55 (m, 2H), 3.55–3.68 (m, 1H), 3.74 (s, 3H), 3.86 (s, 3H), 6.18 (d, J=2.4 Hz, 1H), 6.35 (d, J=2.4 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.1, 19.5, 34.0, 37.6, 38.0, 41.1, 41.5, 53.8, 54.9, 55.9, 65.3, 98.8, 104.6, 120.2, 139.5, 159.3, 159.8; EIMS *m/z*: 324 (31), 281 (17), 264 (63), 221 (73), 188 (100), 115 (15); HRMS calcd for $C_{17}H_{24}O_2S_2$: 324.1218. Found 324.1216.

5,7-Dimethoxy-4-oxo-1,2,3,4-tetrahydro-2-propylnaphthalene (18). A mixture of 0.492 g (1.52 mmol) of thioketal **17**, 1.50 mL (83 mmol) of water, and 3.0 mL (48 mmol) of methyl iodide in 20 mL of methanol was heated at reflux for 24 h. After cooling, water was added, and the mixture was extracted with ether. The ether extracts were washed with water, brine, and dried ($MgSO_4$). Concentration gave an oil which was chromatographed (petroleum ether:ethyl acetate, 2:1) to give 0.312 g (83%) of pure **18**, mp 51–54 °C: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.91 (t, J=6.9 Hz, 3H), 1.31–1.48 (m, 4H), 2.02–2.31 (m, 2H), 2.53–2.75 (m, 2H), 2.84–2.99 (m, 1H), 3.84 (s, 3H), 3.87 (s, 3H), 6.33 (s, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.0, 19.5, 34.2, 37.5, 37.7, 46.9, 55.2, 55.7, 96.9, 104.7, 115.8, 148.5, 162.2, 163.8, 196.2; EIMS *m/z*: 248 (52), 219 (26), 178 (100), 149 (21), 91 (22), 77 (21); HRMS calcd for $C_{15}H_{20}O_3$: 248.1412. Found 248.1411.

12-Hydroxy-11-oxo-1,1a,4,4a,8,9,11-octahydro-9-propyl-2,5,5-trimethyl-5*H*-benzo[*d*]naphtho[2,3-*b*]pyran (20). To 2.5 mL (2.5 mmol) of BBr_3 (1 M) in CH_2Cl_2 at 0 °C was added 0.158 g (0.637 mmol) of ether **18**. The reaction mixture was allowed to warm to ambient temperature, and stirred for 18 h. After quenching with 10% aqueous NaOH, the mixture was stirred for 1 h, acidified with 10% aqueous HCl, and diluted with ether. The organic layer was separated, washed with brine, and dried ($MgSO_4$). The solvents were removed in vacuo to give the crude product as a brown resinous oil which was chromatographed (petroleum ether:ether, 3:1) to provide first 0.029 g (19%) of a by-product, apparently a monoether, and on further elution 0.093 g (66%) of substituted resorcinol **19**, which was used in the subsequent step without further purification: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.93 (t, J=6.1 Hz, 3H), 1.30–1.59 (m, 4H), 1.92–2.22 (m, 1H), 2.22–2.45 (m, 1H), 2.45–2.61 (m, 1H), 2.61–2.77 (m, 1H), 2.77–2.99 (m, 1H), 6.24 (s, 2H), 8.24 (s, 1H), 12.8 (s, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.0, 19.5, 34.5, 36.2, 37.6, 44.3, 101.1, 107.8, 111.1, 147.8, 163.8, 165.3, 203.7.

A mixture of 0.093 g (0.42 mmol) of resorcinol, 0.320 g (2.11 mmol) of *trans-p*-menthadienol, and 0.088 g

(0.46 mmol) of *p*-toluenesulfonic acid in 5 mL of fluorobenzene was heated at reflux for 1 h. After cooling, the mixture was diluted with ether, washed with brine, and dried ($MgSO_4$). The solvent was removed in vacuo to give a brown gum which was chromatographed (petroleum ether:ether, 35:1) to give 0.066 g (44%) of cannabinoid **20** as a viscous pale yellow oil: ^1H NMR (300 MHz, $CDCl_3$) δ 0.79–1.04 (m, 3H), 1.12 (s, 3H), 1.40 (s, 3H), 1.19–1.56 (m, 4H), 1.70 (s, 3H), 1.56–2.96 (m, 10H), 3.26–3.45 (m, 1H), 5.32–5.50 (m, 1H), 6.07–6.27 (m, 1H), 13.0 (2 peaks, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.0, 18.8, 19.7, 23.4, 27.3, 27.6, 31.0, 34.4, 34.7, 35.3, 35.4, 35.9, 36.2, 37.7, 37.9, 44.4, 44.5, 44.6, 44.8, 78.3, 108.7, 108.8, 109.9, 110.7, 111.0, 118.8, 134.8, 143.9, 160.6 (two peaks), 164.5 (two peaks), 203.1 (two peaks).

12-Hydroxy-1,1a,4,4a,8,9,11-octahydro-9-propyl-2,5,5-trimethyl-5*H*-benzo[*d*]naphtho[2,3-*b*]pyran (2). A. To a stirred mixture of 0.63 g of $AlCl_3$ and 0.060 g of $LiAlH_4$ in 50 mL of dry ether was added dropwise a solution of 0.066 g (0.19 mmol) of ketone **20** in 3 mL of ether. The reaction mixture was stirred at ambient temperature for 18 h, cooled to 0 °C, carefully quenched with saturated NH_4Cl and acidified with HCl. The organic layer was washed with water, dried ($MgSO_4$), and the solvent was removed in vacuo to give an oil. Chromatography (petroleum ether:ether, 10:1) gave 0.025 g (40%) of **2**: ^1H NMR (300 MHz, $CDCl_3$) δ 0.92 (t, J = 6.8 Hz, 3H), 1.13 (s, 3H), 1.39 (s, 3H), 1.70 (s, 3H), 1.24–1.49 (m, 5H), 1.58–2.80 (m, 11H), 3.14–3.30 (m, 1H), 4.93 (two peaks, 1H), 5.39–5.46 (m, 1H), 6.20 (two peaks 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.2, 18.4, 19.9, 22.0, 22.4, 23.4, 27.5, 27.9, 29.0, 29.3, 30.8, 31.8, 33.2, 33.5, 35.9, 36.0, 36.1, 36.3, 38.3, 38.6, 45.1, 76.2, 109.6, 110.4, 110.5, 113.6, 119.3, 134.7, 136.6, 152.3, 152.5, 152.6; EIMS *m/z*: 340 (2), 257 (4), 191 (4), 165 (6), 123 (10), 71 (58), 57 (100); HRMS calcd for $C_{23}H_{32}O_2$: 340.2016. Found 340.2014.

B. From 0.280 g (1.20 mmol) of 5,7-dimethoxy-2-propyl-1,2,3,4-tetrahydronaphthalene (**7**) on reaction with BBr_3 as described above there was obtained after chromatography (hexanes:ether, 1:1), 0.200 g (81%) of substituted resorcinol **4** which was used in the next step without further purification: ^1H NMR (300 MHz, $CDCl_3$) δ 0.91 (t, J = 6.8 Hz, 3H), 1.13–1.51 (m, 5H), 1.55–1.74 (m, 1H), 1.82–2.00 (m, 1H), 2.21–2.55 (m, 2H), 2.57–2.84 (m, 2H), 6.15 (s, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.3, 20.0, 22.2, 29.0, 33.4, 36.4, 38.5, 100.0, 107.8, 115.5, 139.7, 153.9, 154.2.

A mixture of 0.200 g (0.97 mmol) of the substituted resorcinol, 0.165 g (1.09 mmol) of *trans-p*-menthadienol and 0.020 g (0.11 mmol) of *p*-toluenesulfonic acid in 10 mL of benzene was heated at reflux for 3 h. After cooling, the mixture was diluted with ether, washed with brine, and dried ($MgSO_4$). The solvent was removed in vacuo to give a brown gum which was chromatographed using petroleum ether:ether (10:1) to give 0.150 g (45%) of cannabinoid **2** as a viscous pale yellow oil. The spectroscopic properties of this material were identical to those of **2** prepared in A above.

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