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Stereoselective Synthesis of the Epimeric Δ^7-Tetrahydrocannabinols

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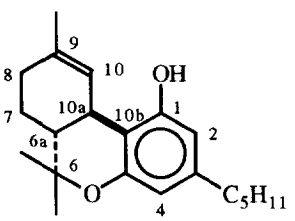
Abstract: Both C9 epimers of Δ^7-THC (**3** and **4**) have been synthesized from Δ^8-THC methyl ether (**12**). Hydroboration of **12** gave a mixture of stereoisomeric 8-hydroxyhexahydrocannabinols. The 8α-ol was converted into the 9β-methyl epimer (**4**) of Δ^7-THC, while the 8β-ol was converted into **3**. Molecular modeling indicated that **4** should have significant cannabinoid activity, while **3** was predicted to be weakly active. These predictions were borne out by both *in vitro* and *in vivo* pharmacology.

INTRODUCTION

In the 30 years since Gaoni and Mechoulam identified (-)-*trans*-Δ^9-tetrahydrocannabinol (**1**, Δ^9-THC) as the psychoactive constituent of *Cannabis sativa*,[1] a body of data has been amassed which has led to the development of empirical structure activity relationships for compounds related to **1**.[2] Although the double bond isomer of **1**, Δ^8-THC (**2**) also possesses the psychoactive effects characteristic of cannabis (marijuana), the isomer of Δ^7-THC in which the C9 methyl group is *trans* to the aromatic ring (**3**) has been reported to be inactive.[2a,3]



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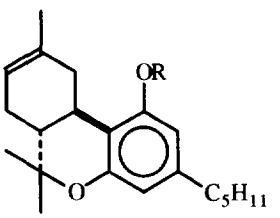
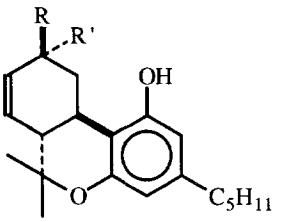


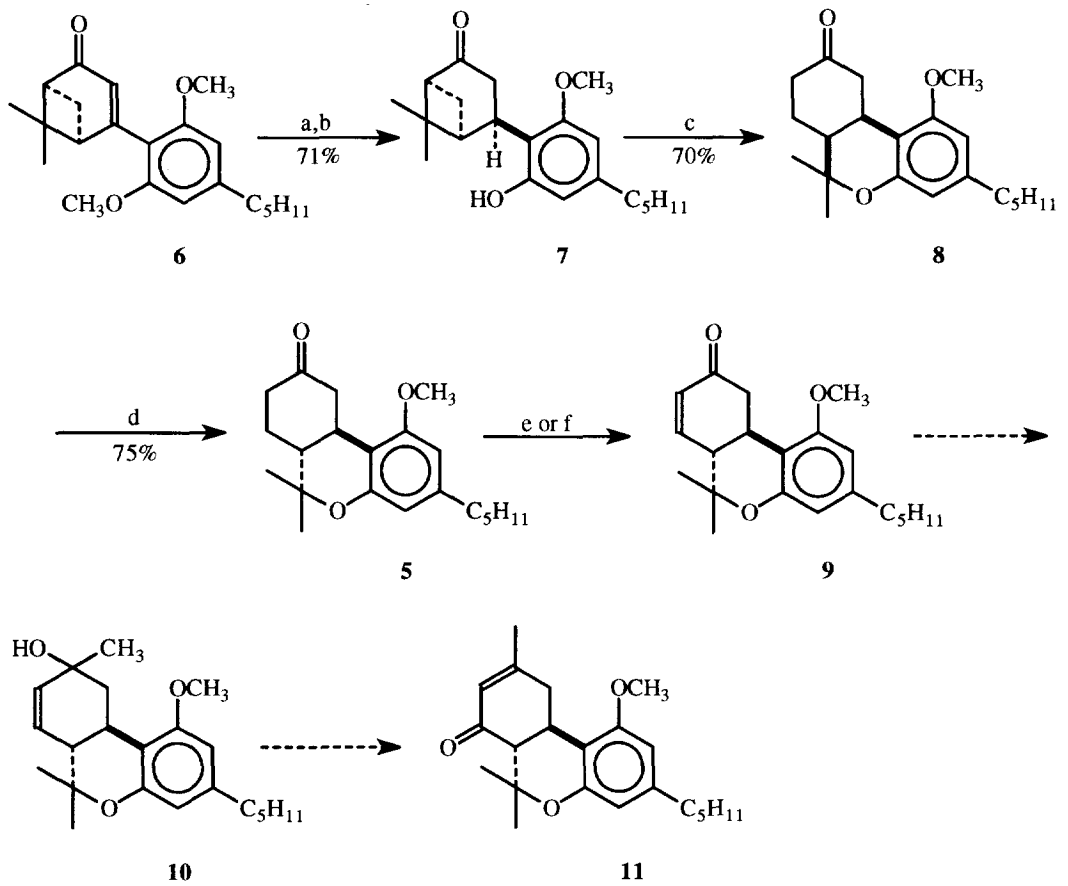
2 R=H
12 R=CH_3



3 R=H, R'=CH_3
4 R=CH_3, R'=H

Several years ago, Reggio *et al.* carried out a computational study of cannabinoids which differed from **1** only in the position or absence of unsaturation in the carbocyclic ring.[4] It was found that there was a correlation between cannabinoid activity and the orientation of a C9 substituent on the carbocyclic ring. Specifically, it was found that if a C9 substituent points into the bottom or α-face of the molecule, cannabinoid activity was abolished or significantly diminished, and the global minimum energy conformation of Δ^7-THC (**3**) was employed as one of the models for an inactive cannabinoid.[4] However, since the epimer of **3** in which the C9 methyl group is β (**4**) was apparently unknown, it was impossible to ascertain if the lack of activity of **3** was due entirely to the steric orientation of the methyl group or if Δ^7-THC is inherently less active than the Δ^8- and Δ^9-isomers.

Scheme I



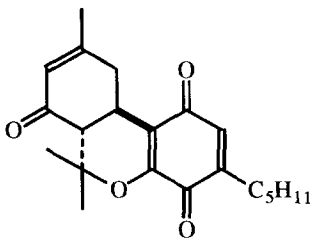
a) Li/NH_3, THF, -60°C; b) NaSPr/DMF, 120°C; c) $SnCl_4/CHCl_3$, 25°C; d) $AlCl_3/CH_2Cl_2$, 25°C; e) *t*-BDMSOTf/Et_3N, CH_2Cl_2, 25°C then $Pd(OAc)_2/CH_2Cl_2$, 40°C; f) PhSeCl/EtOAc, 25°C then H_2O_2/0°C

We now describe the synthesis of the C-9 epimer of **3** (**4**), a slightly modified preparation of **3**, refined molecular modeling studies of both **3** and **4**, and the details of the pharmacology of both epimers of Δ^7-THC.

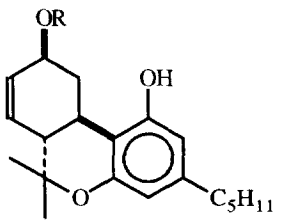
RESULTS AND DISCUSSION

The known inactive epimer of Δ^7-THC (**3**) was prepared by Mechoulam *et al.* in four steps from Δ^8-THC, however the synthetic procedure was not adapted to the synthesis of olefin **4**.[3a] Our initial synthetic approach to **4** was designed to employ ketone **5**, which is readily available from known enone **6**[5] utilizing methodology developed for the enantiodivergent synthesis of nabilone (Scheme I).[6] Reduction of **6** with Li/NH_3 proceeded stereoselectively, and thiopropoxide ether cleavage provided phenol **7**. Rearrangement of **7** using $SnCl_4$ gave *cis* ketone **8** which upon isomerization with $AlCl_3$ provided **5**. Although the optical purity of **5** was not determined, the starting material for its synthesis was commercial (-)-β-pinene of 92% optical purity. Based on comparisons with reported specific rotations for the enantiomeric nabilones, it was concluded that this synthetic route provides ketones similar to **5** in which the optical purity is defined by the starting monoterpene.[6] The projected synthesis entailed the conversion of **5** into enone **9**, which was to be reacted with methyl Grignard or methyllithium to provide tertiary allylic alcohol **10**. Oxidative rearrangement of **10** would then provide enone **11**.[5,7] Dissolving metal reduction of **11**, trapping of the derived enolate with diethyl chlorophosphate and a second dissolving metal reduction would provide the methyl ether of **4**.[8] Cleavage of the ether would provide **4**. This epimer of Δ^7-THC has a quasi-equatorial methyl group, and it was anticipated that the reduction of enone **9** would proceed stereoselectively.

The conversion of ketone **5** into enone **9** was initially effected in 20% yield by the method of Trost *via* reaction of the Li enolate of **5** with diphenyl disulfide, followed by peracid oxidation to the sulfoxide and elimination to **9**.[9] A considerably better yield (51%) was obtained by a variation of the Saegusa oxidation in which the *tert*-butyldimethylsilyl enol ether of **5** was oxidized with $Pd(OAc)_2$ in acetonitrile.[10] Some difficulty was experienced in obtaining consistently good yields in the Saegusa oxidation, and the most efficient preparation of **9** followed a one pot procedure developed by Sharpless in which ketone **5** was treated with phenylselenyl chloride, and the derived α-phenylseleno ketone was oxidized *in situ* with hydrogen peroxide.[11] The yield by this procedure is slightly inferior to that obtained in the Saegusa oxidation (44%), however, the yields are reproducible and the preparation can be carried out in a single operation.



13



14 R=H
15 R=OAc

Although a satisfactory preparation of enone **9** had been developed, repeated attempts to add methyl Grignard, methyllithium or an organocerium reagent resulted in either starting material being recovered or formation of complex mixtures of products. In no case could alcohol **10** be detected in the product mixture. This behavior is similar to that of the phenol corresponding to ketone **5** which did not afford the expected addition product with a large excess of methylmagnesium iodide.[12] It is possible that **9** fails to provide adducts with organometallic reagents due to complexation of the ether oxygen with the reagent, followed by enolization. The product, a tertiary allylic alcohol, may undergo decomposition under more vigorous conditions. A final attempt to prepare enone **11** was by allylic oxidation of Δ^8-THC methyl ether using the CrO_3-3,5-dimethylpyrazole complex.[13] However, the only identifiable product from oxidation under a variety of conditions was identified as quinone **13** on the basis of IR, NMR and HRMS data (See Experimental). The Δ^8-THC used in this work was prepared from olivetol and (-)-*trans*-menthadienol by the classical Petrzilka synthesis.[14] Conversion into the methyl ether was effected by the method of Wildes *et al.*[15] In yet another approach to **4**, it was envisioned that reduction of enone **9** would afford a mixture of epimeric allylic alcohols which could be separated, converted into their respective acetates, and treated with a methyl cuprate to provide stereoselectively the Δ^7-THC methyl ethers. It is known that in cyclic systems the reaction of allylic acetates with organocopper reagents proceeds in an *anti* sense,[16] and it was expected that the steric bulk of the gem-dimethyl groups at C6 should lead predominantly to 1,2-addition.

Reduction of enone **9** with $NaBH_4$-$CeCl_3$[17] unexpectedly provided a single alcohol in 98% yield, which was converted, without purification, into the corresponding acetate (Ac_2O-DMAP). It was not possible to determine the stereochemistry of the reduction product on the basis of the ^1H NMR spectrum of the acetate since the C9 proton at δ 5.69 overlapped one of the vinyl protons. However, the alcohol, although not purified, was homogeneous to both TLC and ^{13}C NMR, and provided a well resolved ^1H NMR spectrum. The carbinol proton appeared as a seven line pattern at δ 4.59 for which it was not possible to extract coupling constants by first order analysis. On the basis of 2D COSY and HETCOR experiments, it was found that the carbinol proton is coupled to the C10 equatorial proton at δ 2.39 (J=3.6 Hz) and the C10 axial proton which is buried in the δ 1.23-1.34 multiplet (J=10.2 Hz). The carbinol proton is also coupled to the allylic C6a proton at δ 3.62 (J=6.4 Hz). Coincidentally, the vinyl protons have the same chemical shift (δ 5.89) and COSY shows only weak coupling to C6a. Given the large coupling constant of the C9 carbinol proton with the axial C10 proton it is apparent that the hydroxyl group is quasi-equatorial; the alcohol is therefore 9β-hydroxy-11-nor-Δ^7-THC (**14**) and the acetate is **15**.

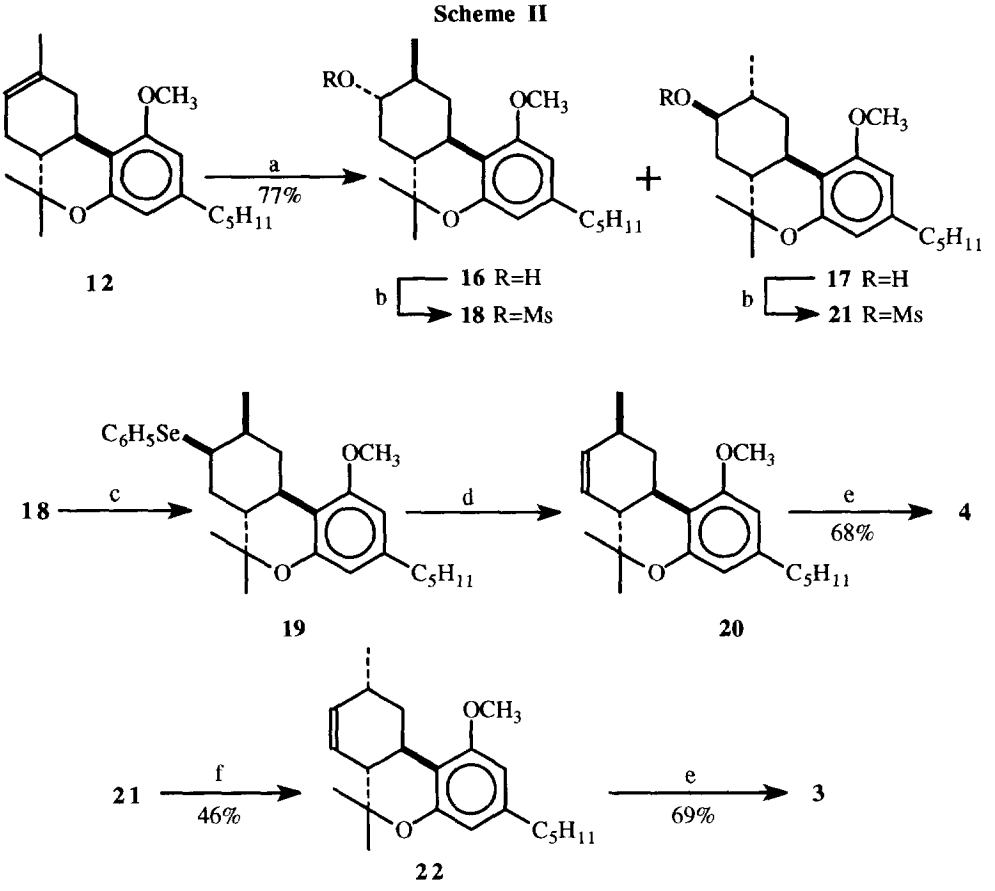
Since the reaction of allylic acetates with cuprates proceeds with net inversion, it is apparent that acetate **15** would provide the undesired inactive epimer of Δ^7-THC (**3**). Attempted Mitsunobu inversion of alcohol **14** using the conditions described recently by Chida *et al.* for a similar allylic alcohol was unsuccessful.[18] To explore the feasibility of the reaction of an allylic acetate in this series with cuprates, acetate **15** was treated with a number of different methyl copper reagents, but in all cases the starting material was recovered unchanged. Given the problems associated with the attempted inversion of alcohol **14** and the failure of acetate **15** to react with methyl cuprates, the synthesis of **4** was approached *via* a variation of the procedure employed by Mechoulam for the preparation of **3** (Scheme II).[3a]

Hydroboration of Δ^8-THC methyl ether (**12**) provided a separable mixture of 8α-ol **16** and 8β-ol **17** in 77% yield. Using a procedure described recently by the Fuchs group,[19] alcohol **16** was converted into

mesylate **18**, which without purification, was reacted with phenyl selenide to afford, with inversion, selenide **19**. This selenide was oxidized *in situ* with alkaline peroxide to afford Δ^7-THC methyl ether **20** in 60% yield from alcohol **16** *via* syn elimination. Cleavage of the methyl ether with thiopropoxide[5,6] gave **4** in 68% yield.

Since the modeling studies described below indicated that the previously described epimer of Δ^7-THC (**3**) had an accessible conformation which should show cannabinoid activity, and since **3** had not been evaluated using contemporary methods of pharmacology, **3** was synthesized from alcohol **17** using a modification of Mechoulam's procedure.[3a] Alcohol **17** was converted into mesylate **21**, which was treated with potassium *tert*-amylate to give Δ^7-THC methyl ether **22** in 46% yield. Ether cleavage was effected with thiopropoxide to give **3** in 69% yield. The spectroscopic properties of **3** were in accord with those reported by Mechoulam.[3a]

Scheme II



a) BH_3/THF, 0°C; H_2O_2/NaOH, 25°C; b) MsCl/Et_3N, CH_2Cl_2, -40° to -5°C; c) Ph_2Se_2, $NaBH_4$/EtOH, 25°C, then 78°C; d) H_2O_2/$NaHCO_3$, THF, 60% for two steps; e) NaSPr/DMF, 120°C; f) KO*t*-Am/*t*-AmOH, 102°C.

MODELING STUDIES

In initial modeling studies Reggio *et al.* chose the global minimum energy conformer of Δ^7-THC (**3**) as one of several inactive cannabinoids and hypothesized that the reason for the inactivity of these compounds is that the molecule is shaped improperly.[4] Specifically, it was observed that the upper portion of the carbocyclic ring in active cannabinoids protrudes into the top face of the molecule. This was quantitated by measuring the non-bonded torsional angle (τ_1 = C11-C9-C1-O) in the optimized structures of a series of cannabinoids. The angle τ_1 measures the orientation of the top part of the carbocyclic ring with respect to the phenolic hydroxyl oxygen and these results imply that only compounds for which $\tau < 0$ are shaped properly to fit at the cannabinoid CB1 receptor.[4] Those compounds such as **3**, in which the carbocyclic ring of the global minimum conformer protrudes into the bottom face of the molecule ($\tau > 0$) may protrude into a region occupied by atoms of the receptor itself (i.e. into a region of steric interference). This region of steric interference is termed a receptor essential volume (REV) in the Active Analogue Approach,[20] and an REV for the CB1 receptor has been characterized in three dimensions recently by Reggio *et al.* using this approach.[21] In this study it was shown that this REV can be used to account for the activity/inactivity of many cannabinoid ligands, all of which possess the other necessary pharmacophoric elements for activity.[2]

In the present work the structures of the previously described Δ^7-THC (**3**)[3], and its epimer (**4**) have been studied in relation to the previously calculated cannabinoid REV, employing an expanded conformational study of each compound.[21] The crystal structure of Δ^9-THC acid B was used as the starting geometry for each cannabinoid.[22] The MODIFY facility within the Chem-X molecular modeling system was used to delete unnecessary atoms and to add necessary ones at standard bond lengths and bond angles.[23] Initially, the characterization of each cannabinoid involved the elucidation of the conformations which each compound may assume and the relative probability of each conformation. The structure of each cannabinoid was optimized using MMP2(85).[24] In the MM2 force field special parameters must be included to account for the lone pairs of electrons on oxygen in ethers and alcohols. Therefore, lone pairs (type=20) were explicitly included in each optimization for all ether and phenolic hydroxyl oxygens in this work.

Earlier calculations on **3** focused on the global minimum conformer only. To find alternative minimum energy conformers of **3** and **4** after initial optimization, MMP2 dihedral or torsional angle driver studies were performed.[25] It has been shown that the tricyclic ring system of cannabinoids can assume more than one conformation and that in certain cases it is a higher energy conformer which is probably the bioactive form.[21] Therefore calculations of alternate conformations are fundamental to the studies described here. The selection of torsional angles to be driven to accomplish conformational interconversion depended upon the molecule to be studied. In torsional angle driver studies of flexible rings, two torsional angles in the same ring are usually driven in order to explore the entire conformational space of the molecule. However, the fused ring structure of cannabinoids results in a molecule of limited flexibility and the carbocyclic and dihydropyran rings each have at most one other possible minimum energy conformer. Driving one torsional angle in each ring locates the only other minimum energy conformer associated with each ring. In the work reported here, one torsional angle (in each ring) was driven to accomplish conformational conversions.

To study possible alternate conformations of the dihydropyran ring, the C10b-C4a-O5-C6 (in **3**) and the C10a-C6a-C6-O5 torsional angle (in **4**) was driven. For 3 and **4**, the C6a-C10a-C10-C9 torsional angle was

driven to explore possible alternate conformations of the carbocyclic ring. In each case, if a different fused ring conformation for a molecule was identified by the driver studies, the geometry of this new conformer was again optimized using MMP2(85). After all the fused ring conformations for each cannabinoid were identified, conformers within 6.00 kcal/mol above the lowest minimum energy conformer (global minimum) were identified as accessible conformers.[26]

Conformational analyses revealed that in the global minimum conformers of **3** and **4**, both the cyclohexene ring and dihydropyran ring exist in half-chair conformations. The global minimum of **3** was found to be 0.65 kcal/mol higher in steric energy than that of **4**. Two other minimum energy fused ring conformations were identified for **3**. In one, the carbocyclic ring assumes a near boat conformation while the dihydropyran ring remains in the half-chair conformation mentioned above. This conformer was found to be 2.27 kcal/mol above the global minimum conformer. In the other higher energy conformer of **3**, the carbocyclic ring is in a slightly distorted half-chair conformation, while the dihydropyran ring assumes a boat conformation such that the C6 methyl group nearly eclipses H6a along the C6 - C6a bond. The half-chair, boat conformer of **3** was found to be 2.56 kcal/mol above the global minimum. Since both higher minimum energy conformers of **3** were less than 6.00 kcal/mol above the global minimum, each was considered accessible. Using the Boltzmann relationship at 298K and assuming no significant entropic differences between the conformers of **3**, the relative amounts of half-chair, half-chair conformer, boat, half-chair conformer, and half-chair, boat conformer of **3** were calculated to be 96.6%, 2.1% and 1.3% respectively. Figure 1 depicts these accessible conformers of **3** (In Figures 1-3 the C3 side chain has been removed. The perspective of the carbocyclic ring is viewed in the direction parallel to a vector from C2 to C10b.).

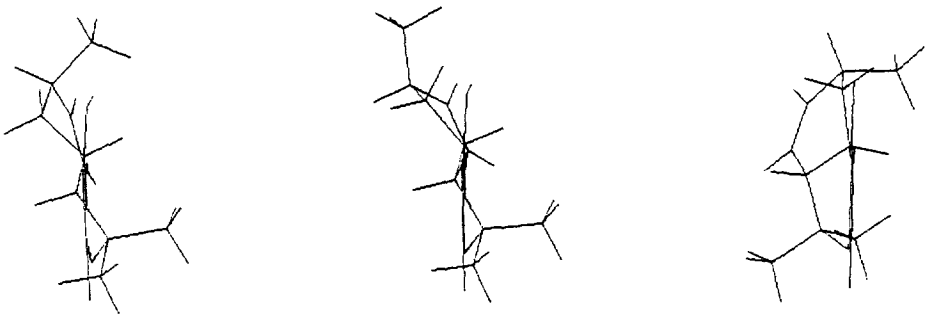


Figure 1. Accessible fused ring conformations of 9α-methyl-Δ^7-THC (**3**) as determined by MMP2(85): (a) the half-chair, half-chair conformer ; (b) the boat, half-chair conformer; (c) the half-chair, boat conformer.

One other minimum energy fused-ring conformer of **4** was identified which was 2.58 kcal/mol higher in steric energy than the global minimum energy conformer. In this second conformer, the carbocyclic ring is in a slightly distorted half-chair, while the dihydropyran ring assumes a boat conformation as described above for **3**.

This second conformer was well within the 6.00 kcal/mol cut-off for accessibility. Boltzmann calculations, as described above for **3**, indicated that the relative amounts of half-chair, half-chair and half-chair, boat conformers of **4** at 298K were 98.7% and 1.3% respectively. Figure 2 depicts these accessible conformers of **4**.

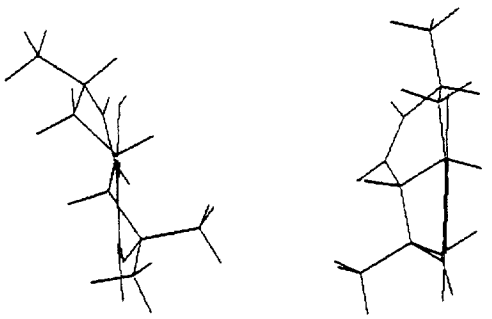


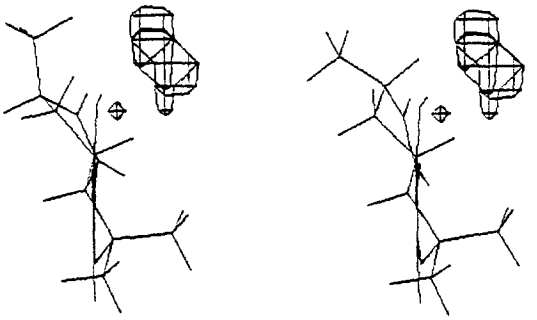
Figure 2. Accessible fused ring conformations of 9β-methyl-Δ^7-THC (**4**) as determined by MMP2(85): (a) the half-chair, half-chair conformer ; (b) the half-chair, boat conformer.

Each accessible conformer of **3** and **4** was screened for its ability to clear the cannabinoid REV map.[21] The conformers were first superimposed on the REV template molecules by fitting the molecules together at C1, C2, C10b and the phenolic oxygen. Each accessible conformer of **3** and **4** was then contoured at its van der Waals' radii and the structure assessed for protrusion into the previously calculated REV region.[21] For **3** only the boat, half-chair conformer (2.1% abundance at 298K, Figure 1b) was able to clear the REV. When the two accessible conformers of **4** (half-chair, half-chair and half-chair, boat) were contoured at their van der Waals' radii in relation to the REV, only the global minimum half-chair, half-chair conformer of **4** (98.7% abundance at 298K) was able to clear the REV. Figure 3 depicts the accessible conformers of **3** and **4** which clear the REV in relation to this REV region.

Because the half-chair, half-chair conformer of **4** is shaped properly to fit at the CB1 receptor and is the predominant conformer (98.7% abundance at 298K, Figure 2a), this epimer of Δ^7-THC should be an active cannabinoid. Since calculations indicate that the only conformer of **3** which is able to clear the REV (boat, half-chair, Figure 1b.) is in very low abundance at 298K (2.1%), **3** should show diminished cannabinoid activity relative to its C10 epimer (**4**). This finding is interesting since an early pharmacological screen of **3** found this molecule to be inactive.[3]

Finally, it is important to note that the pharmacological activity of a compound is dependent upon many parameters including its solubility, pharmacokinetics, receptor affinity and metabolism. The modeling studies reported here probe only one aspect of affinity, i.e. receptor recognition. Thus, while it might be expected that **3** and **4** would exhibit similar solubility, pharmacokinetics and metabolism, the actual percentage of the conformers of **3** able to clear the REV versus that of **4** cannot be directly interpreted as the relative activities of the two

compounds. However, the modeling results can be interpreted to predict that **4** will exhibit higher activity relative to **3**, and that **3** should exhibit some activity.



a b

Figure 3. The accessible conformers of **3** and **4** which clear the REV are shown in relation to the REV map: (a) the boat, half-chair conformer of **3** and (b) the half-chair, half-chair conformer of **4**. The cage represents a region in space termed the receptor essential volume (REV) which is sterically forbidden for cannabinoid ligands. See ref. 21 for details of the REV calculation.

PHARMACOLOGY

Both epimers of Δ^7-THC were evaluated *in vitro* by measuring their ability to displace the very active cannabinoid [^{3}H] CP-55,940 from its binding site in a membrane preparation as described previously.[27] As predicted by the modeling studies described above, the epimer of Δ^7-THC with a quasi-equatorial methyl group (**4**) showed binding to the cannabinoid receptor in the same range as Δ^9-THC (**1**, K_I= 41 nM[27]) with K_I=71.5 nM. Although the quasi-axial isomer of Δ^7-THC (**3**) has been reported to be devoid of cannabinoid activity, the modeling studies indicated that a minor conformer should be active. In accord with this prediction, **3** showed weak affinity for the cannabinoid receptor (K_I=304 nM). Both **3** and **4** were also evaluated *in vivo* using the mouse tetrad model.[27] Cannabinoids are known to produce sedation, hypothermia, antinociception and catalepsy; this composite model has been shown to be a quantitative measure of cannabinoid activity, and the average of the ED_{50} values for these behavioral procedures correlate well with K_I.[27] For the less active quasi-axial epimer (**3**), this average ED_{50}=52.5 μM, while for **4**, ED_{50}=16.3 μM. For Δ^9-THC (**1**), ED_{50}=4.70 μM,[27] and as indicated by the binding data, **3** is a weakly active cannabinoid when compared to Δ^9-THC, while **4** is only slightly less active than the natural cannabinoid.

CONCLUSIONS

Both C9 epimers of Δ^7-THC have been synthesized, detailed molecular modeling studies of each have been carried out, which indicated that the principal conformer of **4** would clear the receptor essential volume of the

cannabinoid receptor, while the major conformer of **3** would interfere with the receptor. A minor conformer of **3** was, however, predicted to have cannabinoid activity. These predictions were borne out by the pharmacological evaluation of **3** and **4**, in which **3** was found to be weakly active, while **4** was only slightly less active than Δ^9-THC (**1**), the active principle of marijuana. These results are in excellent agreement with modeling studies which indicate a correlation between the geometry of cannabinoids in the region of C9 and their biological activity.[4,21]

EXPERIMENTAL

General. IR spectra were obtained using a Nicolet 5DX spectrometer; ^{1}H and ^{13}C NMR spectra were recorded on a Bruker 300AC spectrometer. Mass spectral analyses were performed on a GC/MS and HRMS data were provided by the University of Alabama. 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 (32-63μ) using hexanes-ethyl acetate mixtures as eluents. All new compounds were homogeneous to TLC and ^{13}C NMR.

4-(2,6-Dimethoxy-4-pentylphenyl)-6,6-dimethylbicyclo[3.1.1]heptan-2-one. To a solution of 0.015 g (2.1 mg/atoms) of Li in 15 ml of liquid NH_3 at -60° C was added dropwise a solution of 0.240 g (0.70 mmol) of enone **6**[6] in 1 ml of dry THF. After stirring for 1 h. at -33° C, the reaction was quenched with solid NH_4Cl. The NH_3 was evaporated and the solid residue was taken up in water and extracted with ether. The ethereal layers were washed with 10% aqueous HCl, water, and dried ($MgSO_4$). Removal of the solvent afforded an oil which was chromatographed by MPLC to give 0.206 g (86%) of saturated ketone: m.p. 91-92° C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.91 (t, J=6.8 Hz, 3H), 0.93 (s, 3H), 1.32-1.36 (m, 4H), 1.38 (s, 3H), 1.48 (d, J=10.5 Hz, 1H), 1.57-1.67 (m, 2H), 2.52-2.59 (m, 4H), 2.62-2.72 (m, 1H), 3.04-3.09 (m, 1H), 3.28-3.39 (m, 1H), 3.68-3.74 (m, 1H), 3.77 (s, 6H), 6.35 (s, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.0, 22.5, 23.5, 26.5, 29.0, 31.0, 31.6, 35.3, 36.2, 40.1, 42.0, 46.1, 55.0, 58.1, 104.0, 117.1, 142.3, 158.1, 215.6; IR (neat) 2930, 1708 cm^{-1}; MS (EI) *m/z* 344 (31), 316 (10), 302 (19), 273 (52), 247 (25), 234 (90), 221 (37); $[\alpha]_D^{20}$ -23.3° (c=0.094, $CHCl_3$); Anal. Calcd for $C_{22}H_{32}O_3$: C, 76.70; H, 9.36; Found: C, 76.87; H, 9.29.

4-(2-Methoxy-4-pentyl-6-hydroxyphenyl)-6,6-dimethylbicyclo[3.1.1]heptan-3-one (7). To a stirred suspension of 0.140 g (5.80 mmol) of NaH (from 0.233 g of 60% NaH in mineral oil) in 35 ml of DMF at ambient temperature was added dropwise 0.54 ml of 1-propanethiol and the mixture was stirred until it became clear. A solution of 0.200 g (0.58 mmol) of the saturated ketone described above in 2 ml of DMF was added and the mixture was stirred at 120° C for 3 h. After cooling, the reaction mixture was poured into 10% aqueous HCl and extracted with ether. The extracts were washed with brine, dried ($MgSO_4$) and the solvent was removed at reduced pressure to give a pale brown oil. The crude product was purified by MPLC on silica gel to give 0.158 g (83%) of phenol **7**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.88 (t, J=6.7 Hz, 3H), 0.95 (s, 3H), 1.22-1.35 (m, 4H), 1.37 (s, 3H), 1.47-1.58 (m, 3H), 2.45 (t, J=7.6 Hz, 2H), 2.60-2.84 (m, 3H), 3.10-3.15 (m, 1H), 3.42-3.52 (m, 1H), 3.72 (s, 3H), 3.74-3.76 (m, 1H), 6.24 (s, 1H), 6.26 (s, 1H), 7.50. br s (1); ^{13}C

NMR (75.5 MHz, $CDCl_3$) δ 14.0, 22.5, 23.5, 26.5, 28.9, 29.7, 30.9, 31.6, 35.3, 40.4, 41.7, 45.9, 55.0, 58.1, 103.4, 109.0, 115.4, 142.4, 155.0, 158.4, 218.5; IR (neat) 3330, 1687 cm^{-1}; MS (EI) *m/z* 330.

(6a*S*,10a*R*(-)-1-Methoxy-3-pentyl-6,6a,7,8,10,10a-hexahydro-6,6-dimethyl-9*H*-dibenzo-[*b,d*]pyran-9-one (8). To a solution of 0.098 g (0.29 mmol) of phenol **7** in 1 ml of $CHCl_3$ was added 0.076 g (0.29 mmol) of $SnCl_4$. The resulting mixture was stirred at room temperature for 18 h, poured onto ice and extracted with ether. The organic extracts were combined, washed with 10% aqueous HCl, saturated sodium bicarbonate, water and brine. After drying ($MgSO_4$), evaporation of the solvent yielded an oil which was chromatographed by MPLC to afford 0.068 g (70%) of ketone **8**: ^1H NMR (300 MHz, $CDCl_3$) δ 0.89 (t, J=6.7 Hz, 3H), 1.30 (s, 3H), 1.30-1.34 (m, 4H), 1.38 (s, 3H), 1.54-1.64 (m, 2H), 1.72-1.80 (m, 1H), 2.09-2.19 (m, 2H), 2.37-2.44 (m, 2H), 2.50 (t, J=7.6 Hz, 2H), 2.86 (q, J=16.2, 9.3 Hz, 1H), 3.00 (q, J=16.2, 5.4 Hz, 1H), 3.42-3.45 (m, 1H), 3.79 (s, 3H), 6.26 (d, J=1.4 Hz, 1H), 6.31 (d, J=1.4 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.0, 22.2, 22.5, 23.9, 26.7, 30.3, 30.7, 31.6, 36.0, 38.5, 39.9, 41.8, 55.2, 76.1, 103.2, 108.9, 110.0, 143.2, 153.7, 158.6, 213.2; IR (neat) 2930, 1708, 1616 cm^{-1}; HRMS Calcd for $C_{21}H_{30}O_3$: 330.2195, found 330.2205.

(6a*R*,10a*R*)-(-)-1-Methoxy-3-pentyl-6,6a,7,8,10,10a-hexahydro-6,6-dimethyl-9*H*-dibenzo-[*b.d*] pyran-9-one (5). To a solution of 0.060 g (0.18 mmol) of *cis* ketone **8** in 2 ml of CH_2Cl_2 was added 0.073 g (0.60 mmol) of $AlCl_3$ at ambient temperature. The mixture was stirred for 12 h at room temperature, poured onto ice and extracted with ether. The ether extracts were washed with 10% aqueous HCl, saturated aqueous $NaHCO_3$, water and dried ($MgSO_4$). Concentration at reduced pressure gave an oil which was chromatographed on silica gel using MPLC to give 0.045 g (75%) of ketone **5** as an oil: ^1H NMR (300 MHz, $CDCl_3$) δ 0.89 (t, J=6.8 Hz, 3H), 1.10 (s, 3H), 1.29-1.34 (m, 4H), 1.46 (s, 3H), 1.55-1.62 (m, 3H), 1.93 (dt, J=12.1, 2.1 Hz, 1H), 2.03-2.16 (m, 2H), 2.41-2.57 (m, 4H), 2.83 (dt, J=2.3, 11.2 Hz, 1H), 3.72-3.73 (m, 1H), 3.78 (s, 3H), 6.24 (d, J=1.4 Hz, 1H), 6.32 (d, J=1.4 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.0, 18.6, 22.5, 26.5, 27.7, 30.7, 31.5, 34.5, 35.9, 40.7, 45.5, 47.4, 55.0, 76.5, 103.0, 109.5, 110.1, 143.2, 154.1, 158.3, 211.1; IR (neat) 2931, 1707 cm^{-1}; MS (EI) *m/z* 330 (71), 315 (27), 290 (29), 288 (36), 274 (74), 247 (67), 220 (44), 164 (96); $[\alpha]_D^{23}$ -76.4° (c=0.0108, $CHCl_3$). The spectroscopic data are in agreement with those reported.[15]

(6a*R*,10a*R*)-(-)-1-Methoxy-3-pentyl-6,6a,10,10a-tetrahydro-6,6-dimethyl-9*H*-dibenzo-[*b,d*]-pyran-9-one (9). A. To a stirred solution of 0.010 g (0.03 mmol) of ketone **5** and 0.006 ml (0.045 mmol) of dry triethylamine in 5 ml of dry CH_2Cl_2 at 25°C was added 0.014 ml (0.06 mmol) of *tert*-butyl-dimethylsilyl triflate. The mixture was stirred for 1 h under N_2, diluted with water and extracted with ether. The ether extracts were washed with water and brine, dried (Na_2SO_4), and the solvent evaporated to provide the silyl enol ether. The crude silyl enol ether was dissolved in 5 ml of dry CH_2Cl_2 and added to a stirred solution of 0.076 g (0.036 mmol) of $Pd(OAc)_2$ in 3 ml of dry acetonitrile. The mixture was heated at reflux under N_2 for 2 h, cooled and filtered through a pad of glass wool. The filtrate was diluted with ether and water, the ether layer was separated, washed with water and brine, dried (Na_2SO_4), and the solvent removed at reduced pressure. The crude product was chromatographed on silica gel to give 0.005 g (51%) of enone **9** as a white solid, which

was recrystallized from hexane: m.p. 156-158°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.90 (t, J=6.6 Hz, 3H), 1.14 (s, 3H), 1.30-1.35 (m, 5H), 1.48-1.65 (m, 3H), 1.56 (s, 3H), 2.19 (dd, J=10.9, 13.1 Hz, 1H), 2.51 (t, J=7.9 Hz, 2H), 2.60 (dt, J=11.1, 2.4 Hz, 1H), 3.13 (td, J=11.4, 3.3 Hz, 1H), 3.79 (s, 3H), 3.97 (ddd, J=17.2, 3.2, 1.0 Hz, 1H), 6.13 (ddd, J=10.3, 2.93, 1.0 Hz, 1H), 6.26 (d, J=1.4 Hz, 1H), 6.35 (d, J=1.4 Hz, 1H), 7.02 (dd, J=10.0, 2.1 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.0, 20.2, 22.5, 27.3, 30.7, 31.6, 34.2, 36.0, 43.6, 48.1, 55.0, 75.4, 103.1, 108.2, 110.1, 130.9, 143.6, 149.6, 153.8, 158.7, 200.2; IR (neat) 1686, 1623 cm^{-1}; $[\alpha]_D^{23}$ -283° (c=0.00143, $CHCl_3$); HRMS Calcd for $C_{21}H_{28}O_3$: 328.2038, found 328.2039.

B. To a solution of 0.21 g (0.64 mmol) of ketone **5** in 6 ml of dry ethyl acetate under N_2 was added 0.15 g (0.77 mmol) of phenylselenyl chloride. After 10-20 min the solution turned pale yellow, 1.2 ml of H_2O were added and the mixture was stirred for 5 min. After separation of the water, the solution was cooled to 0°C and 2.7 ml of THF and 0.19 ml of 30% H_2O_2 were added. The reaction mixture was stirred for 2 h at 0°C, diluted with 20 ml of ethyl acetate and the organic layer was washed with water and 10 % aqueous Na_2CO_3. The organic phase was dried ($MgSO_4$) and the solvent was removed *in vacuo* to yield a yellow oil which was purified by chromatography on silica gel to give 0.081 g (44 %) of **9** and 0.010 g (5 %) of recovered **5**. This material was identical in all respects to that described in part A above.

Chromic Acid Oxidation of Δ^8-THC Methyl Ether. To a vigorously stirred suspension of 1.83 g (18.3 mmol) of dry CrO_3 in 25 ml of dry CH_2Cl_2 at -25°C was added rapidly 2.01 g (18.3 mmol) of 3,5-dimethylpyrazole. After 35 min a solution of 0.3 g (0.91 mmol) of Δ^8-THC methyl ether (**12**)[15] in 2 ml of dry CH_2Cl_2 was added dropwise. The reaction mixture was stirred at or below 20°C for 5 h, and 5 ml of 5 M aqueous NaOH was added and stirring was continued for 1 h. The layers were separated, the aqueous phase was washed with two portions of CH_2Cl_2 and the combined organic extracts were washed successively with three portions of 3M HCl, saturated aqueous $NaHCO_3$, and brine. After drying (Na_2SO_4), the solvent was removed to give a dark yellow oil which after chromatography gave 0.10 g (32%) of quinone **13** as a yellow oil: IR(neat) 1679, 1649, 1627, 1601cm^{-1};^{1}H NMR (300 MHz, $CDCl_3$) δ 0.90 (t, J=6.8 Hz, 3H,), 1.20 (s, 3H), 1.32-2.46 (m, 9H), 1.57 (s, 3H), 1.78 (s, 3H), 2.90 (t, J=6.9 Hz, 2H), 3.48 (dd, J=3.3, 18.2 Hz, 1H), 5.86 (s, 1H), 6.40 (s, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 13.8, 19.7, 22.3, 23.8, 27.3, 27.8, 28.5, 31.3, 31.7, 37.0, 41.6, 54.0, 61.4, 80.0, 118.7, 126.5, 133.1, 148.7, 160.7, 187.6, 195.4; HRMS Calcd for $C_{21}H_{26}O_4$: 342.1831, found 342.1816.

11-Nor-9β-acetoxy-Δ^7-THC methyl ether (15). A solution of 0.31 g (0.94 mmol) of enone **9** and 0.53 g (1.41 mmol) of $CeCl_3$ in 5 ml of dry methanol under N_2 was cooled to 0°C, stirred for 5 min., and 0.042 g (1.12 mmol) of $NaBH_4$ was added. The reaction mixture was stirred at 0°C for 45 min. and 0.064 ml of glacial acetic acid was added. The methanol was removed *in vacuo*, the residue was dissolved in ethyl acetate and washed successively with saturated aqueous $NaHCO_3$, water and brine. The organic extracts were dried ($MgSO_4$) and the solvent was removed *in vacuo* to afford 0.31 g (98 %) of crude alcohol **14** which was converted to acetate **15** without purification : ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.89 (t, J=6.8 Hz, 3H), 1.05 (s, 3H), 1.23-1.34 (m, 6H), 1.45 (s, 3H), 1.53-1.61 (m, 2H), 2.39 (dd, J=3.5, 10.9 Hz, 1H), 2.49 (t, J=7.6 Hz, 2H), 2.71 (t, J=10.6 Hz, 1H), 3.62 (dd, J=6.5, 11.4 Hz 1H), 3.80 (s, 3H), 4.59 (ddd, J=3.8, 6.5, 10.1 Hz,

1H), 5.79 (s, 2H), 6.25 (d, J=1.4 Hz, 1H), 6.30 (d, J=1.4 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.00, 19.9, 22.6, 27.4, 30.8, 31.6, 32.5, 36.0, 37.1, 48.2, 55.1, 69.2, 76.2, 103.0, 109.2, 110.1, 129.3, 132.6, 143.0, 154.4, 158.8.

A solution of 0.31 g (0.92 mmol) of crude **14** described above in 5 ml of dry CH_2Cl_2 under N_2 was added to a solution of 0.011 g (0.092 mmol) of 4,4-dimethylaminopyridine in 0.22 ml of dry pyridine. To this stirred solution was added 0.13 ml (1.39 mmol) of acetic anhydride. The reaction was stirred for 1 h at ambient temperature, then diluted with 5 ml of CH_2Cl_2. The organic layer was washed with saturated aqueous $NaHCO_3$, water and brine, dried ($MgSO_4$) and the solvent removed *in vacuo*. The crude acetate was purified by chromatography on silica gel to give 0.30 g (88 %) of **15** as a pale yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.89 (t, J=6.7 Hz, 3H), 1.05 (s, 3H), 1.25-1.41 (m, 5H), 1.45 (s, 3H), 1.54-1.62 (m, 2H), 2.07 (s, 3H), 2.41-2.52 (m, 3H), 2.76 (t, J=10.6 Hz, 1H), 3.55-3.61 (m, 1H), 3.79 (s, 3H), 5.67-5.74 (m, 2H), 5.90 (d, J=6.7 Hz, 1H), 6.24 (d, 1H), 6.30 (d, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.0, 19.9, 21.3, 22.5, 27.3, 30.7, 31.6, 32.4, 32.7, 35.9, 47.9, 55.1, 71.5, 76.0, 102.9, 108.8, 110.1, 128.5, 131.3, 143.1, 154.4, 158.8, 170.8; $[\alpha]_D^{23}$ -60.1° (c=0.0144, $CHCl_3$); HRMS Calcd for $C_{23}H_{32}O_4$: 372.2301, found 372.2290.

Hydroboration of Δ^8-THC Methyl Ether. To a solution of 1.00 g (3.07 mmol) of Δ^8-THC methyl ether (**12**)[15] in 25 ml of dry THF at 0°C, was added dropwise 3.10 ml of 1 M BH_3 in THF, and the reaction mixture was stirred for 1 h at 0°C under N_2. The reaction mixture was allowed to warm to room temperature and was stirred for an additional hour. To the stirred reaction mixture, 7.5 ml of water, 3.5 ml of 3 M NaOH and 3.5 m of 30 % H_2O_2 were added in that order and the reaction mixture was stirred for 0.5 h, extracted with ether and dried ($MgSO_4$). The ether was removed *in vacuo* and the resulting oil was chromatographed on silica gel using MPLC with a gradient solvent system starting with 10:1 hexanes/ethyl acetate and ending with a 6:1 mixture to yield 0.38 g (35 %) of 8β-ol **17** as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.88 (t, J=6.8 Hz, 3H), 1.06 (s, 3H), 1.12 (d, J=7.4 Hz, 3H), 1.25-1.36 (m, 5H), 1.35 (s, 3H), 1.45-1.77 (m, 5H), 1.92-2.01 (m, 2H), 2.49 (t, J=8.2 Hz, 2H), 2.62 (td, J=2.7, 11.5 Hz, 1H), 2.72 (dd, J=2.2, 13.1 Hz, 1H), 3.77 (s, 3H), 3.87 (d, J=2.4 Hz, 1H), 6.22 (d, J=1.4 Hz, 1H), 6.28 (d, J=1.4 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.0, 17.6, 18.9, 22.5, 27.4, 29.3, 30.8, 31.6, 35.7, 42.5, 55.1, 71.5, 76.4, 103.0, 110.2, 111.2, 142.4, 154.6, 158.7; IR (neat) 3415, 1609 cm^{-1}; $[\alpha]_D^{23}$ -123° (c=0.0108, $CHCl_3$); HRMS Calcd for $C_{22}H_{34}O_3$: 346.2508, found 346.2509.

There was also obtained 0.46 g (42 %) of 8α-ol **16**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.88 (t, J=6.8 Hz, 3H), 1.06 (d, J=7.0 Hz, 3H), 1.07 (s, 3H), 1.28-1.35 (m, 5H), 1.37 (s, 3H), 1.50-1.61 (m, 5H), 1.80 (br s, 1H), 2.09 (dt, J=2.4, 11.7 Hz, 1H), 2.43-2.51 (m, 3H), 3.02 (dt, J=3.6, 12.7 Hz, 1H), 3.30 (dt, J=4.5, 10.3 Hz, 1H), 3.78 (s, 3H), 6.23 (d, J=1.4, 1H), 6.28 (d, 1.4 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.0, 18.5, 18.9, 22.5, 27.7, 30.7, 31.6, 35.2, 35.9, 36.9, 37.0, 40.3, 47.6, 55.0, 76.3, 76.7, 103.0, 110.1, 110.6, 142.6, 154.3, 158.8; IR (neat) 3389, 1616 cm^{-1}; $[\alpha]_D^{23}$ -97.9° (c=0.0129, $CHCl_3$); HRMS Calcd for $C_{22}H_{34}O_3$: 346.2508, found 346.2507.

9β-Methyl-Δ^7-Tetrahydrocannabinol Methyl Ether (20). To a stirred solution of 0.28 g (0.80 mmol) of 8α-ol **16** and 0.21 ml (1.52 mmol) of triethylamine in dry CH_2Cl_2 under N_2 and cooled to -40°C was added dropwise 0.086 ml (1.11 mmol) of methanesulfonyl chloride. The reaction was stirred for 50 min. while it

slowly warmed to -5°C. The reaction mixture was poured into chilled 10% aqueous $NaHCO_3$, extracted with ether and the extracts were washed with successive portions of water and brine, dried ($MgSO_4$) and the ether was removed *in vacuo* to give 0.32 g (95 %) of mesylate **18** which was used in the next step without further purification: ^1H NMR (300 MHz, $CDCl_3$) δ 0.89 (t, J=6.9 Hz, 3H), 1.07 (s, 3H), 1.09 (d, J=7.7 Hz, 3H), 1.25-1.35 (m, 6H), 1.37 (s, 3H), 1.53-1.63 (m, 4H), 1.82-1.89 (m, 1H), 2.35-2.42 (m, 1H), 2.48 (t, J=7.0 Hz, 2H), 3.04 (s, 3H), 3.14 (dt, J=3.9, 12.6 Hz, 1H), 3.79 (s, 3H), 4.36 (dt, J=4.9, 10.4 Hz, 1H), 6.23 (d, J=1.4 Hz, 1H), 6.29 (d, J=1.4 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.0, 18.6, 22.5, 27.5, 30.7, 31.5, 34.7, 35.0, 35.9, 36.6, 37.6, 38.5, 47.3, 55.0, 76.0, 87.2, 109.6, 110.1, 142.8, 154.0, 158.6.

A suspension of 0.24 g (0.79 mmol) of diphenyl diselenide in 2 ml of dry ethanol was cooled to 0°C and 0.06 g of $NaBH_4$ was added over 1 h. The resulting pale yellow solution was stirred at ambient temperature for 1.5 h and a solution of 0.32 g (0.76 mmol) of 8α-mesylate in 1.5 ml of ethanol was added. The mixture was heated at reflux for 6.5 h cooled to 0°C, and 1 ml of THF, 0.15 g of solid $NaHCO_3$, and 1.07 ml of 30% H_2O_2 were added in that order. The reaction was allowed to gradually warm to room temperature and stirred for 36 h. After the removal of most of the ethanol under vacuum, the residue was diluted with ether, washed with water and brine, and dried ($MgSO_4$). The solvent was removed *in vacuo* to yield a pale yellow oil which was chromatographed on silica gel to provide 0.16 g (63 %) of **20**: ^1H NMR (300 MHz, $CDCl_3$) δ 0.89 (t, J=6.8 Hz, 3H), 1.03 (d, J=7.0 Hz, 3H), 1.06 (s, 3H), 1.25-1.36 (m, 5H), 1.44 (s, 3H), 1.55-1.65 (m, 3H), 2.30 (dd, J=3.5, 11.0 Hz, 1H), 2.50 (t, J=8.0 Hz, 2H), 2.67 (dt, J=1.7, 9.5 Hz, 1H), 3.20-3.27 (m, 1H), 3.80 (s, 3H), 5.61 (s, 2H), 6.24 (d, J=1.4 Hz, 1H), 6.31 (d, J=1.4 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.0, 19.7, 21.6, 22.6, 27.4, 30.8, 31.6, 32.9, 33.3, 36.0, 36.1, 47.9, 55.1, 76.5, 103.0, 110.1, 110.7, 125.6, 135.7, 142.6, 154.5, 159.1; IR (neat) 1616 cm^{-1}; HRMS Calcd for $C_{22}H_{32}O_2$: 328.2402, found 328.2404.

9β-Methyl-Δ^7-Tetrahydrocannabinol (4). To a suspension of 0.25 g of NaH (8.35 mmol) in 10 ml of dry DMF under N_2 was added dropwise with vigorous stirring 0.84 ml (9.28 mmol) of 1-propanethiol. To this solution of sodium thiopropoxide was added dropwise a solution of 0.152 g (0.46 mmol) of **20** in 2 ml of dry DMF. The reaction mixture was heated with stirring at 120°C for 3 h. After cooling, 12 ml of 3 M HCl was added and the reaction mixture was extracted with ether The ethereal extracts were washed with water and brine, dried ($MgSO_4$) and the ether was removed *in vacuo*. The resulting yellow oil was purified by preparative TLC using petroleum ether/ethyl acetate (9:1) to give 0.10 g (68 %) of **4** as a pale yellow oil: ^1H NMR (300 MHz, $CDCl_3$) δ 0.87 (t, J=6.8 Hz, 3H), 1.03 (d, J=7.0 Hz, 3H), 1.07 (s, 3H), 1.25-1.34 (m, 5H), 1.45 (s, 3H), 1.48-1.58 (m, 2H), 2.30 (dd, J=3.3, 11.1 Hz, 1H), 2.40 (t, J=8.3 Hz, 2H), 2.45-2.55 (m, 1H), 2.72 (dt, J=1.4, 9.8 Hz, 1H), 3.30 (dd, J=6.3, 11.8 Hz, 1H), 5.10 (s, 1H), 5.57 (s, 2H), 6.07 (d, J=1.4 Hz, 1H), 6.27 (d, J=1.4 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.0, 19.9, 21.6, 22.5, 27.4, 30.6, 31.6, 32.8, 33.0, 35.4, 35.9, 47.8, 76.7, 107.7, 109.5, 109.9, 125.4, 135.7, 142.8, 154.8, 154.9; $[\alpha]_D^{21}$ -146.2° (c=0.00833, $CHCl_3$); HRMS Calcd for $C_{21}H_{30}O_2$: 314.2244, found 314.2239.

9α-Methyl-Δ^7-Tetrahydrocannabinol Methyl Ether (22). Reaction of 0.29 g (0.83 mmol) of 8β-ol **17** with 0.86 ml (1.11 mmol) of methanesulfonyl chloride under the conditions used to prepare the 8α-epimer provided 0.31 g (84%) of mesylate **21** which was used without purification in the next step: ^1H NMR (300 MHz, $CDCl_3$) δ 0.89 (t, J=6.8 Hz, 3H), 1.07 (s, 3H), 1.19 (d, J=11.7 Hz, 3H), 1.36 (s, 3H), 1.29-1.38 (m,

5H), 1.52-1.64 (m, 5H), 1.97 (t, J=12.7 Hz, 1H), 2.06 (d, J=14.0 Hz, 1H), 2.29 (br s, 1H), 2.49 (t, J=7.3 Hz, 2H), 2.66 (dt, J=2.7, 11.6 Hz, 1H), 2.82 (d, J=13.3 Hz, 1H), 3.00 (s, 3H), 3.77 (s, 3H), 4.88 (d, J=2.3 Hz, 1H), 6.22 (d, J=1.4 Hz, 1H), 6.29 (d, J=1.4 Hz, 1H).

To a solution of potassium *t*-amylate, prepared from 0.54 g (13.7 mmol) of potassium metal in 10 ml of *t*-amyl alcohol under N_2 was added 0.31 g (0.72 mmol) of crude mesylate **21** in 2 ml of *t*-amyl alcohol. The reaction mixture was stirred for 6 h under reflux, cooled to 5° C, water was added and the mixture was extracted with two portions of ether. The ethereal solution was washed with 5% HCl, saturated aqueous $NaHCO_3$, and brine and dried ($MgSO_4$). After removing the ether *in vacuo*, the resulting yellow oil was chromatographed on silica gel to provide 0.13 g (55%) of **22**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.89 (t, J=6.8 Hz, 3H), 1.06 (s, 3H), 1.15 (d, J=7.4 Hz, 3H), 1.25-1.37 (m, 5H), 1.44 (s, 3H), 1.51-1.70 (m, 2H), 2.24 (d, J=11.2 Hz, 1H), 2.42-2.52 (m, 3H), 2.60 (dt, J=1.9, 11.4 Hz, 1H), 2.93 (dt, J=1.1, 12.9 Hz, 1H), 3.79 (s, 3H), 5.60-5.69 (m, 2H), 6.24 (d, J=1.4 Hz, 1H), 6.31 (d, J=1.4 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.0, 19.6, 21.7, 22.6, 27.3, 28.4, 30.7, 30.8, 31.7, 33.5, 36.0, 48.3, 55.1, 77.8, 105.1, 110.1, 110.9, 126.0, 135.3, 142.5, 154.6, 159.0; IR (neat) 1616 cm^{-1}; HRMS Calcd for $C_{22}H_{32}O_2$: 328.2402, found 328.2393.

9α-Methyl-Δ^7-Tetrahydrocannabinol (3). From 0.15 g of methyl ether **22**, using the procedure described above for the cleavage of ether **20** there was obtained 0.10 g (69%) of **3**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.88 (t, J=6.8 Hz, 3H), 1.10 (s, 3H), 1.18 (d, J=10.4 Hz, 3H), 1.25-1.34 (m, 5H), 1.45 (s, 3H), 1.50-1.65 (m, 3H), 2.25 (dd, J=1.50, 11.0 Hz, 1H), 2.42 (t, J=8.2 Hz, 2H), 2.64 (dt, J=2.0, 11.5 Hz, 1H), 2.99 (dt, J=1.1, 13.0 Hz, 1H), 4.85 (s, 1H), 5.50-5.72 (m, 2H), 6.07 (d, J=1.4 Hz, 1H), 6.27 (d, J=1.4 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.0, 19.7, 21.7, 22.5, 27.3, 27.9, 30.5, 30.6, 31.6, 33.2, 35.3, 35.9, 48.1, 76.9, 107.7, 109.5, 109.9, 125.8, 135.2, 142.7, 154.7, 155.1; $[\alpha]_D^{21}$ -26.1° (c=0.0130, $CHCl_3$); lit. $[\alpha]_D$ -37° (EtOH);[3a] These ^{1}H NMR data are in accord with those reported by Mechoulam.[3a]

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REFERENCES AND NOTES

(1) Gaoni, Y.; Mechoulam, R. *J. Am. Chem. Soc.* **1964**, *86*, 1646.

(2) (a) Razdan, R. K. *Pharmacol. Rev.* **1986**, *38*, 75. (b) Mechoulam, R.; Devane, W. A.; Glaser, R. Cannabinoid Geometry and Biological Behavior. In *Marijuana/Cannabinoids: Neurobiology and Neurophysiology;* Murphy, L; Bartke, A.; CRC Press, Boca Raton 1992; pp 1-33.

(3) (a) Mechoulam, R.; Ben-Zvi, Z.; Varconi, H.; Samuelov, Y. *Tetrahedron* **1973**, *29*, 1615. (b) Mechoulam, R.; Edery, H. Structure Activity Relationships in the Cannabinoid Series. In *Marijuana Chemistry, Pharmacology, Metabolism and Clinical Effects* Mechoulam R.; Academic Press, New York,

1973, pp 101-136. (c) Binder, M.; Edery, H.; Porath, G. Delta-7-THC, a Nonpsychotropic Cannabinoid: Structure Activity Considerations in the Cannabinoid Series. In *Marihuana: Biological Effect*, Nahas, G. G.; Paton, W. D. M.; Pergamon Press, Oxford, 1979, p 71.

(4) Reggio, P. H.; Greer, K. V.; Cox, S. M. *J. Med. Chem.* **1989**, *32*, 1630

(5) Huffman, J. W.; Zhang, X,; Wu, M.-J.; Joyner, H. H.; Pennington, W. T. *J. Org. Chem.* **1991**, *56*, 1481.

(6) Huffman, J. W., Joyner, H. H., Lee, M. D., Jordan, R. D., Pennington, W. T. *J. Org. Chem.* **1991**, *56*, 2082.

(7) Dauben, W. G.; Michno, D. M. *J. Org. Chem.* **1977**, *42*, 682

(8) (a) Ireland, R. E.; Pfister, G. *Tetrahedron Lett.* **1969**, 2145. (b) Huffman, J. W.; Miller, C. A.; Pinder, A. R. *J. Org. Chem.* **1976**, *41*, 3705.

(9) (a) Trost, B. M.; Salzmann, T. N.; Hiroi, K. *J. Am. Chem. Soc.* **1976**, *98*, 4887. (b) Zoorob, G. K. M.S. Thesis, Clemson University, 1992.

(10) (a) Ito, Y.; Hirao, T.; Saegusa, T. *J. Org. Chem.* **1978**, *43*, 1011. (b) Hauser, F. M.; Caringal, Y. *J. Org. Chem.* **1990**, *55*, 555.

(11) Sharpless, K. B.; Lauer, R. F.; Teranishi, A. Y. *J. Am. Chem. Soc.* **1973**, *95*, 6137.

(12) Fahrenholtz, K. E.; Lurie, M.; Kierstead, R. W. *J. Am. Chem. Soc.* **1967**, *89*, 5934.

(13) Salmond, W. G.; Barta, M. A.; Havens, J. L. *J. Org. Chem.* **1978**, *43*, 2057.

(14) Petrzilka, T.; Sikemeier, C. *Helv. Chim. Acta* **1967**, *50*, 1416. These authors find $[\alpha]_D^{18}$ -262° (c=0.04, EtOH). We find $[\alpha]_D^{22}$ -222° (c=0.0126, EtOH).

(15) Wildes, J. W.; Martin, N. H.; Pitt, C. G.; Wall, M. E. *J. Org. Chem.*, **1971**, *36*, 721.

(16) Goering, H. L.; Tseng, C. C. *J. Org. Chem.* **1983**, *48*, 3986.

(17) (a) Gemal, A. L.; Luche, J. L. *J. Am. Chem. Soc.* **1981**, *103*, 5454. (b) Luche, J. L.; Gemal, A. L.; Crabbe, P. *J. Chem. Soc., Chem. Commun.* **1978**, 60.

(18) Chida, N.; Ohtsuka, M.; Ogawa, S. *J. Org. Chem.* **1993**, *58*, 4441.

(19) Charles, K.-F.; Chiu, S. V.; Fuchs, P. L. *J. Org. Chem.* **1994**, *59*, 311.

(20) Sufrin, J. R.; Dunn, D. A.; Marshall, G. R. *Mol. Pharmacol.* **1981**, *19*, 307.

(21) Reggio, P. H.; Panu, A. M. Miles, S. *J. Med. Chem.*, **1993**, *36*, 1761.

(22) Rosenqvist, E., Ottersen, T. *Acta. Chem. Scand.*, **1975**, *B29* 379.

(23) Chem-X, developed and distributed by Chemical Design, Ltd., Chipping Norton, UK.

(24) Allinger, N.L. MMP2(85), distributed by Molecular Design, Ltd., San Leandro, CA.

(25) Burkert, U., Allinger, N.L. *Molecular Mechanics, ACS Monograph Series 177*, American Chemical Society, Washington, 1982.

(26) Reggio, P. H.; McGaughey, G. B.; Odear, D. F.; Seltzman, H. H.; Compton, D. R.; Martin, B. R. *Pharmacol. Biochem. Behav.* **1991**, *40*, 479.

(27) Compton, D. R.; Rice, K. C.; De Costa, B. R.; Razdan, R. K.; Melvin, L. S.; Johnson, M. R.; Martin, B. R. *J. Pharmacol. Exp. Ther.* **1993**, *46*, 1781.

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