Pergamon

Bioorganic & Medicinal Chemistry 10 (2002) 4119–4129

BIOORGANIC & MEDICINAL CHEMISTRY

1-Methoxy-, 1-Deoxy-11-hydroxy- and 11-Hydroxy-1-methoxy-Δ^8-tetrahydrocannabinols: New Selective Ligands for the CB_2 Receptor

John W. Huffman,[a,*] Simon M. Bushell,[a] John R. A. Miller,[a] Jenny L. Wiley[b] and Billy R. Martin[b]

[a]*Howard L. Hunter Laboratory, Clemson University, Clemson, SC 29634-1905, USA*
[b]*Department of Pharmacology and Toxicology, Medical College of Virginia Campus, Virginia Commonwealth University, Richmond, VA 23298-0613, USA*

Received 8 March 2002; accepted 11 June 2002

Abstract—Three series of new cannabinoids were prepared and their affinities for the CB_1 and CB_2 cannabinoid recptors were determined. These are the 1-methoxy-3-(1′,1′-dimethylalkyl)-, 1-deoxy-11-hydroxy-3-(1′,1′-dimethylalkyl)- and 11-hydroxy-1-methoxy-3-(1′,1′-dimethylalkyl)-Δ^8-tetrahydrocannabinols, which contain alkyl chains from dimethylethyl to dimethylheptyl appended to C-3 of the cannabinoid. All of these compounds have greater affinity for the CB_2 receptor than for the CB_1 receptor, however only 1-methoxy-3-(1′,1′-dimethylhexyl)-Δ^8-THC (JWH-229, **6e**) has effectively no affinity for the CB_1 receptor ($K_i = 3134 \pm 110$ nM) and high affinity for CB_2 ($K_i = 18 \pm 2$ nM).
© 2002 Elsevier Science Ltd. All rights reserved.

Introduction

The complex pharmacological effects of cannabinoids are considered to be mediated through at least two G-protein-coupled, transmembrane receptors. One of these, designated as CB_1, is found predominantly in the central nervous system and is responsible for most of the overt pharmacological effects of cannabinoids.[1–4] A second receptor, designated CB_2, was originally identified from macrophages present in the spleen, and is expressed primarily in the periphery.[5] Very recently evidence has been presented for the existence of a third cannabinoid receptor, which has been detected in mouse brain.[6]

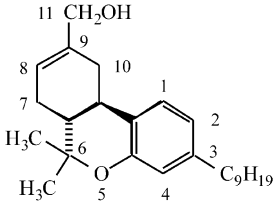
It is generally accepted that the CB_1 receptor is implicated in eliciting the in vivo effects of cannabinoids; a good correlation has been found between the CB_1 receptor affinities of a series of cannabinoids and their in vivo effects.[7,8] These in vivo effects are blocked by SR141716A, an inverse agonist for the CB_1 receptor, and are absent in CB_1 receptor knockout mice.[9,10] Although it has been known for some time that cannabinoids are involved in immunomodulation,[11] the discovery that the CB_2 receptor is expressed primarily in cells of the immune system led to the suggestion that the CB_2 receptor was responsible for the immunomodulatroy effects of cannabinoids.[5] This suggestion has been confirmed recently by the observation that these immunomodulatory effects are absent in CB_2 receptor knockout mice.[12] Although there is evidence that the CB_2 receptor is not expressed in the central nervous system,[13] it has recently been found that this receptor is expressed in adult rat retina.[14]

Although it has been known for several years that the CB_2 receptor is expressed in cells in the immune system, it has only been within the past few years that specific effects mediated by this receptor have been recognized. These effects included the discovery that a CB_2 selective receptor ligand, JWH-133, is effective in reducing spasticity in the mouse model of multiple sclerosis,[15] and the same CB_2 selective ligand also inhibits the in vivo growth of glioma tumors.[16] Other effects modulated by the CB_2 receptor include peripheral antinociception,[17] and at least in part, the antitumor properties of ajulemic acid.[18]

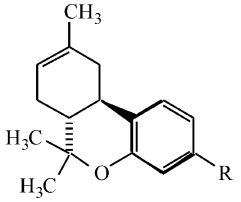
*Corresponding author. Tel.: +1-864-656-3133; fax: +1-864-656-6613; e-mail: huffman@clemson.edu

0968-0896/02/$ - see front matter © 2002 Elsevier Science Ltd. All rights reserved.
PII: S0968-0896(02)00331-0

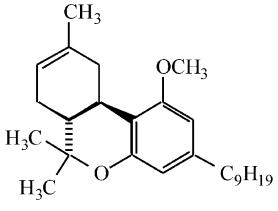
Several years ago we reported that 3-(1′,1′-dimethylheptyl)-1-deoxy-11-hydroxy-Δ^8-tetrahydrocannabinol (1-deoxy-11-hydroxy-Δ^8-THC-DMH, deoxy-HU-210, JWH-051, **1**), a traditional cannabinoid lacking a 1-hydroxyl group, has very high affinity for the CB_1 receptor ($K_i = 1.2 \pm 0.1$ nM), and exhibits characteristic cannabinoid in vivo pharmacology. Cannabinoid **1** also has exceptionally high affinity for the CB_2 receptor ($K_i = 0.032 \pm 0.019$ nM).[19] A second 1-deoxycannabinoid, 3-(1′,1′-dimethylheptyl)-1-deoxy-Δ^8-THC (1-deoxy-Δ^8-THC-DMH, JWH-057, **2**), is also potent in vivo, has significant affinity for the CB_1 receptor ($K_i = 23 \pm 7$ nM), and nearly ten times greater affinity for the CB_2 receptor ($K_i = 2.9 \pm 1.6$ nM).[19] Based on these observations, we synthesized a number of 1-deoxy-Δ^8-THC analogues.[20] Several of these compounds have high affinity for the CB_2 receptor, with low affinity for the CB_1 receptor, and one of them, 3-(1′,1′-dimethylbutyl)-1-deoxy-Δ^8-THC (JWH-133, **3**) with $K_i = 3.4 \pm 1.0$ nM at CB_2 and 677 ± 132 nM at CB_1 is highly selective. In the same publication, we developed some preliminary structure–activity relationships (SAR) for the CB_2 receptor. These preliminary SAR demonstrated that a 1′,1′-dimethyl group leads to enhanced affinity for the CB_2 receptor, and that in the 1′,1′-dimethyl-1-deoxy-Δ^8-THC series, compounds with a three to seven carbon side chain all have high affinity for the CB_2 receptor ($K_i = < 20$ nM). Also, affinity for both receptors is enhanced by the presence of an 11-hydroxyl group.



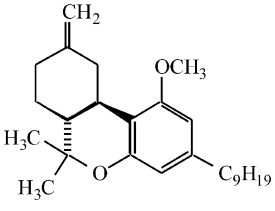
1



2 R = C_9H_{19}
3 R = $C(CH_3)_2(CH_2)_2CH_3$



4



5

A group at Merck Frosst described two 1-methoxy cannabinoids, 1-methoxy-Δ^8-THC-DMH (**4**), and 1-methoxy-$\Delta^{9(11)}$-THC-DMH (**5**) which were reported to have affinities for the CB_2 receptor in the 20 nM range, and virtually no affinity for the CB_1 receptor.[21] An additional CB_2 selective agonist, HU-308 was reported by Hanus et al.; this compound has no affinity for the CB_1 receptor ($K_i > 10{,}000$ nM), and good affinity for the CB_2 receptor ($K_i = 22.7 \pm 3.9$ nM).[22] HU-308 is inactive in the mouse behavioral tetrad, reduces blood pressure and shows peripheral analgesic activity. These hypotensive and analgesic effects are blocked by SR-144528, a CB_2 antagonist.

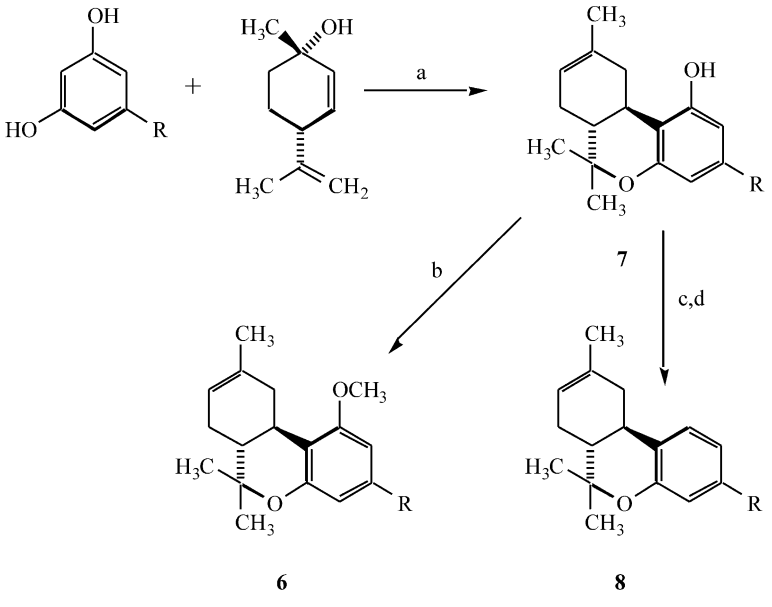
In view of the continuing recognition of the importance of the CB_2 receptor, we have taken advantage of the currently available knowledge of the SAR of 1-methoxy- and 1-deoxy-Δ^8-THC analogues to design three series of CB_2 selective cannabinoid receptor ligands. Based on the knowledge that the side chain in the 1-deoxy-Δ^8-THC series can be shortened significantly without seriously attenuating CB_2 receptor affinity, and that an 11-hydroxyl enhances both CB_1 and CB_2 receptor affinities,[20] the initial synthetic targets included a series of 1-deoxy-3-(1′,1′-dimethylalkyl)-11-hydroxy-Δ^8-THC analogues. Since 1-methoxy-Δ^8-THC-DMH (**4**) is also a CB_2 selective cannabinoid ligand,[20,21,23] a series of 3-(1′,1′-dimethylalkyl)-1-methoxy-Δ^8-THCs was also prepared. The third series of CB_2 selective compounds consisted of 11-hydroxy-3-(1′,1′-dimethylalkyl)-1-methoxy-Δ^8-THC analogues which combined the structural features of the other two series.

Results

The 1-methoxy-Δ^8-THC analogues (**6a**–**6e**) were prepared by direct methylation of the corresponding Δ^8-THC (**7a**–**7e**) using methyl iodide/KOH in DMF in unoptimized yields of 43–97% (Scheme 1). The cannabinoid substrates are all known compounds which were prepared by the acid catalyzed condensation of the corresponding alkyl resorcinol with *trans-p*-menthadienol.[20,24,25]

The 1-deoxy-11-hydroxy-Δ^8-THCs (**9a**–**9e**, Scheme 2) were prepared from the corresponding 1-deoxy-Δ^8-THC (**8a**–**8e**, Scheme 1) by initial selenium dioxide oxidation to the 11-oxo compounds (**10a**–**10e**), followed by reduction of the aldehyde. The requisite 1-deoxy-Δ^8-THCs (**8a**–**8e**) were prepared from the corresponding Δ^8-THC by conversion to the phosphate ester, followed by dissolving metal reduction using procedures we have described previously (Scheme 1).[20] Selenium dioxide oxidation of cannabinoids **8a**–**8e** using a procedure developed by Razdan's group provided aldehydes **10a**–**10e**,[26] which were reduced to the 11-hydroxy analogues without extensive purification. Lithium aluminum hydride reduction of aldehydes **10a**–**10e** provided alcohols **9a**–**9e** in modest yields for the two steps. Improved yields of alcohols **9** were obtained by the method of Luche (sodium borohydride-cerium (III) chloride).[27]

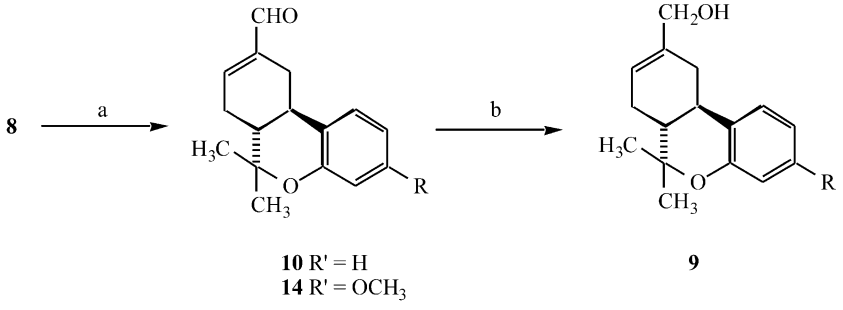
In the 11-hydroxy-3-(1′,1′-dimethylalkyl)-1-methoxy-Δ^8-THC series, in addition to the dimethylethyl through dimethylhexyl analogues (**11a**–**11e**), 11-hydroxy-3-(1′,1′-dimethylheptyl)-1-methoxy-Δ^8-THC was prepared. The dimethylheptyl analogues in the methyl ether series (**4**) and 1-deoxy-11-hydroxy (**1**) series had been prepared previously.[19–21] The initial synthetic approach to this series of compounds was based upon a procedure developed by Mechoulam for the synthesis of 11-hydroxy-Δ^8-THC-DMH (HU-210), and which we had used previously in the synthesis of 11-hydroxy-(1′*S*,2′*R*)-dimethylheptyl-Δ^8-THC.[28,29] In a modification of this protocol, the appropriate resorcinol is condensed with 4-hydroxymyrtenyl pivalate (**12**, Scheme 3) to provide the 11-pivaloyloxy-Δ^8-THC (**13a** and **13b**). Conversion



a, R = $C(CH_3)_3$; **b**, R = $C(CH_3)_2CH_2CH_3$; **c**, R = $C(CH_3)_2(CH_2)_2CH_3$

d, R = $C(CH_3)_2(CH_2)_3CH_3$; **e**, R = $C(CH_3)_2(CH_2)_4CH_3$

Scheme 1. (a) $HOTs/C_6H_6$, 80 °C; (b) CH_3I/KOH/DMF, 25 °C; (c) NaH/THF, 0 °C then $(C_2H_5O)_2P(O)Cl$; (d) Li/NH_3, THF, −78 °C.



a, R = $C(CH_3)_3$; **b**, R = $C(CH_3)_2CH_2CH_3$; **c**, R = $C(CH_3)_2(CH_2)_2CH_3$

d, R = $C(CH_3)_2(CH_2)_3CH_3$; **e**, R = $C(CH_3)_2(CH_2)_4CH_3$;

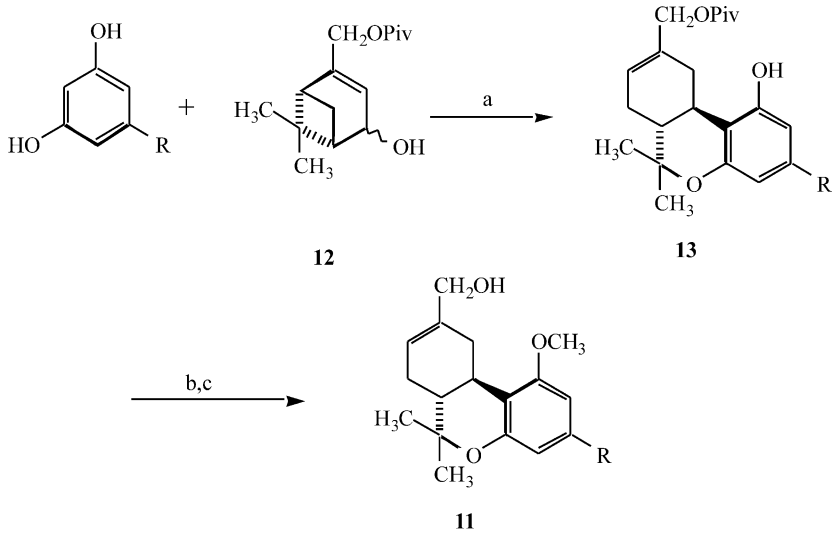
f, R = $C(CH_3)_2(CH_2)_5CH_3$

Scheme 2. (a) SeO_2/EtOH, 80 °C; (b) $LiAlH_4$/THF, 25 °C or $NaBH_4/CeCl_3{\cdot}7H_2O$/MeOH.

to the methyl ether, followed by reduction with lithium aluminum hydride provides the corresponding 11-hydroxy-3-(1′,1′-dimethylalkyl)-1-methoxy-Δ^8-THC. This procedure was employed to prepare the first two members of the homologeous series (**11a** and **11b**), however the overall yields were quite low. The other three members of this series (**11c**–**11e**) were prepared from the corresponding 1-methyl ether (**6c**–**6e**) by selenium dioxide oxidation followed by reduction of the corresponding aldehyde in a procedure analogous to that employed for the synthesis of the 1-deoxy-11-hydroxy compounds (Scheme 2). Reduction of the 11-oxo compounds using Luche conditions[27] gave excellent yields of the corresponding 11-hydroxy cannabinoids (**11c**–**11e**).

The affinities of 1-methoxy-, 11-hydroxy- and 11-hydroxy-1-methoxy-Δ^8-THC analogues **6**, **9** and **11** for the CB_1 receptor were determined by measuring their ability to displace the potent cannabinoid [^{3}H] CP 55,940 from its binding site in a membrane preparation from rat brain as described by Compton et al.[8] Affinities for the CB_2 receptor were determined by measuring the ability of the compounds to displace [^{3}H] CP 55,940 from a cloned human receptor preparation using the procedure described by Showalter et al.[30] The results of these determinations are summarized in Table 1. Also included in Table 1 are the receptor affinities for cannabinoids **1**–**4**, Δ^8- and Δ^9-THC.

In the 1-methoxy-Δ^8-THC series (**6a**–**6e**) none of these compounds have appreciable affinity for the CB_1 receptor, with K_i values of 3134 ± 110 nM for the dimethylhexyl analogue (**6e**) to $K_i > 10{,}000$ nM for the dimethylethyl through dimethylbutyl compounds (**6a**–**6c**). This series



a, R = $C(CH_3)_3$; **b**, R = $C(CH_3)_2CH_2CH_3$; **c**, R = $C(CH_3)_2(CH_2)_2CH_3$

d, R = $C(CH_3)_2(CH_2)_3CH_3$; **e**, R = $C(CH_3)_2(CH_2)_4CH_3$;

f, R = $C(CH_3)_2(CH_2)_5CH_3$

Scheme 3. (a) $BF_3{\cdot}Et_2O/CH_2Cl_2$, −20 °C; (b) CH_3I/KOH/DMF, 25 °C; (c) $LiAlH_4$/THF, 25 °C or $NaBH_4/CeCl_3{\cdot}7H_2O$/MeOH.

Table 1. Receptor affinities (mean ± SEM) of 1-deoxycannabinoids and related compounds

Compound	K_i (nM)		
	CB_1	CB_2	Ratio CB_2/CB_1
Δ^9-THC	41 ± 2[a]	36 ± 10[b]	1.1
Δ^8-THC	44 ± 12[c]	44 ± 17[c]	1.0
1-Deoxy-11-hydroxy-3-(1′,1′-dimethylheptyl)-Δ^8-THC (**1**)	1.2 ± 0.1[d]	0.03 ± 0.02[d]	40
1-Deoxy-3-(1′,1′-dimethylheptyl)-Δ^8-THC (**2**)	22.8 ± 7.3[d]	2.9 ± 1.6[d]	7.9
3-(1′,1′-Dimethylheptyl)-1-methoxy-Δ^8-THC (**4**)	713 ± 68	57 ± 12	12
3-(1′,1′-Dimethylheptyl)-1-methoxy-Δ^8-THC (**4**)	924 ± 104[c]	65 ± 8.2[c]	14
3-(1′,1′-Dimethylbutyl)-1-deoxy-Δ^8-THC (**3**)	677 ± 132[c]	3.4 ± 1.0[c]	199
3-(1′,1′-Dimethylethyl)-1-methoxy-Δ^8-THC (**6a**)	> 10,000	1867 ± 867	5.4
3-(1′,1′-Dimethylpropyl)-1-methoxy-Δ^8-THC (**6b**)	> 10,000	1404 ± 66	7.1
3-(1′,1′-Dimethylbutyl)-1-methoxy-Δ^8-THC (**6c**)	> 10,000	325 ± 70	31
3-(1′,1′-Dimethylpentyl)-1-methoxy-Δ^8-THC (**6d**)	4001 ± 282	43 ± 3	93
3-(1′,1′-Dimethylhexyl)-1-methoxy-Δ^8-THC (**6e**)	3134 ± 110	18 ± 2	174
1-Deoxy-11-hydroxy-3-(1′,1′-dimethylethyl)-Δ^8-THC (**9a**)	270 ± 58	18 ± 2	15
1-Deoxy-11-hydroxy-3-(1′,1′-dimethylpropyl)-Δ^8-THC (**9b**)	187 ± 23	5.6 ± 1.7	33
1-Deoxy-11-hydroxy-3-(1′,1′-dimethylbutyl)-Δ^8-THC (**9c**)	84 ± 16	3.4 ± 0.5	25
1-Deoxy-11-hydroxy-3-(1′,1′-dimethylpentyl)-Δ^8-THC (**9d**)	8.8 ± 1.4	1.6 ± 0.03	5.5
1-Deoxy-11-hydroxy-3-(1′,1′-dimethylhexyl)-Δ^8-THC (**9e**)	1.8 ± 0.3	0.52 ± 0.03	3.5
11-Hydroxy-3-(1′,1′-dimethylethyl)-1-methoxy-Δ^8-THC (**11a**)	1856 ± 148	333 ± 104	5.6
11-Hydroxy-3-(1′,1′-dimethylpropyl)-1-methoxy-Δ^8-THC (**11b**)	1008 ± 117	85 ± 21	12
11-Hydroxy-3-(1′,1′-dimethylbutyl)-1-methoxy-Δ^8-THC (**11c**)	347 ± 34	28 ± 1	12
11-Hydroxy-3-(1′,1′-dimethylpentyl)-1-methoxy-Δ^8-THC (**11d**)	40 ± 6	4.4 ± 0.3	9.1
11-Hydroxy-3-(1′,1′-dimethylhexyl)-1-methoxy-Δ^8-THC (**11e**)	15 ± 3	1.4 ± 0.1	11
11-Hydroxy-3-(1′,1′-dimethylheptyl)-1-methoxy-Δ^8-THC (**11f**)	14 ± 3	1.0 ± 0.3	14

[a]ref 8.
[b]ref 30.
[c]ref 20.
[d]ref 19.

of compounds does, however, show considerable selectivity for the CB_2 receptor. There is an incremental increase in CB_2 receptor affinity with $K_i = 1867 \pm 867$ for the dimethylbutyl compound (**6c**), increasing to $K_i = 18 \pm 2$ nM for 3-(1′,1′-dimethylhexyl)-1-methoxy-Δ^8-THC (**6e**). 3-(1′,1′-Dimethylhexyl)-1-methoxy-Δ^8-THC (**6e**) shows nearly 175 fold selectivity for the CB_2 receptor. For 3-(1′,1′-dimethylheptyl)-1-methoxy-Δ^8-THC (**4**) we reported $K_i = 924 \pm 104$ nM at CB_1 and 65 ± 8 nM at CB_2.[20] However, for the same compound, Gareau et al. found $K_i = 15{,}850 \pm 2960$ nM at CB_1 and 20 ± 12 nM at CB_2.[21] Ross et al. found somewhat different values, $K_i = 1043 \pm 296$ nM at CB_1 and 6.4 ± 2.2 nM at CB_2.[23] In view of these variations in the reported data for 1-methoxy-Δ^8-THC-DMH (**4**), the preparation of this compound was repeated, and new binding data for

both receptors were obtained. The new data, $K_i = 713 \pm 68$ nM at CB_1 and $K_i = 57 \pm 12$ nM at CB_2 are essentially the same as those we reported previously.[20]

The differences in receptor affinity between those we have determined and those determined by other groups may be due to a number of factors, including somewhat different cell lines and slightly different laboratory procedures employed in carrying out the determinations. As mentioned above, our CB_1 receptor affinities were determined using a rat brain membrane preparation while Gareau et al. employed a human CB_1 receptor preparation which was not described in detail.[21] The binding assays described by Ross et al. were carried out using CHO (Chinese hamster ovary) cells transfected with human CB_1 and CB_2 receptors.[23] Our CB_2 data were obtained as described in the Experimental using HEK (human embronyic kidney) cells transfected with human CB_2 receptors.

The 1-deoxy-11-hydroxy-Δ^8-THC analogues (**9a**–**9e**) have from modest to very high affinity for the CB_1 receptor, and show moderate selectivity for the CB_2 receptor. The first member of the homologeous series, 1-deoxy-3-(1′,1′-dimethylethyl)-11-hydroxy-Δ^8-THC (**9a**) has $K_i = 270 \pm 58$ nM at the CB_1 receptor, with $K_i = 18 \pm 2$ nM at CB_2. Receptor affinity at CB_1 improves to $K_i = 1.8 \pm 0.3$ nM and CB_2 affinity increases to $K_i = 0.52 \pm 0.03$ nM for the dimethylhexyl analogue (**9e**). The most selective compound in this series is the dimethylpropyl analogue (**9b**) which has 25 fold greater affinity for the CB_2 receptor ($K_i = 187 \pm 23$ nM at CB_1 and $K_i = 5.6 \pm 1.7$ nM at CB_2).

The compounds in the 11-hydroxy-3-(1′,1′-dimethylalkyl)-1-methoxy-Δ^8-THC series (**11a**–**11f**) also show moderate selectivity for the CB_2 receptor, but the CB_1 receptor affinities increase significantly in the higher members of this homologous series. For 11-Hydroxy-3-(1′,1′-dimethylethyl)-1-methoxy-Δ^8-THC (**11a**), $K_i = 1856 \pm 148$ nM at CB_1 and $K_i = 333 \pm 104$ at CB_2. Affinity for both receptors improves to $K_i = 15 \pm 3$ nM at CB_1 for 11-hydroxy-3-(1′,1′-dimethylhexyl)-1-methoxy-Δ^8-THC (**11e**) with $K_i = 1.4 \pm 0.3$ nM at CB_2. The receptor affinities for 11-hydroxy-3-(1′,1′-dimethylheptyl)-1-methoxy-Δ^8-THC (**11f**) are essentially identical to those for the dimethylhexyl analogue, with $K_i = 14 \pm 3$ nM at CB_1 and 1.0 ± 0.3 at CB_2.

The data summarized in Table 1, are in general agreement with the preliminary SAR for the CB_2 receptor which we developed based upon our study of 1-deoxy-Δ^8-THC analogues.[20] In the 1′,1′-dimethyl-1-deoxy-Δ^8-THC series described previously, those compounds with a three to seven carbon side chain (**2** and **8b**–**8e**) all have high affinity for the CB_2 receptor ($K_i = < 20$ nM). Of the three new series of CB_2 selective cannabinoid receptor ligands, only the 1-deoxy-11-hydroxy-Δ^8-THC analogues (**1** and **9a**–**9e**) show uniformly high affinity for the CB_2 receptor, with $K_i = 0.032 \pm 0.019$ nM for the dimethylheptyl analogue (**1**)[19] to $K_i = 18.1 \pm 1.8$ nM for the lowest member of the homologous series (**9a**). As would be expected there is a progressive improvement in CB_2 receptor affinity as the length of the side chain increases from two to seven carbon atoms. These compounds also show from modest to high affinity for the CB_1 receptor, increasing from $K_i = 270 \pm 58$ nM for the dimethylethyl analogue (**9a**) to $K_i = 1.2 \pm 0.1$ nM for the dimethylheptyl compound (**1**) reported previously.[19] The relatively high CB_1 receptor affinities for the compounds in this series may be attributed to the 11-hydroxyl group serving as a surrogate for the phenolic hydroxyl in more traditional cannabinoids as suggested by molecular modeling studies carried out on **1**, combined with a 3-(1′,1′-dimethylalkyl) substituent of sufficient length to interact with the lipophilic portion of the receptor.[19]

The compounds in the 1-methoxy series (**4** and **6a** to **6e**) all have little affinity for the CB_1 receptor, with CB_2 affinities ranging from very slight for the dimethylethyl analogue (**6a**, $K_i = 1867 \pm 867$ nM) to quite high for the dimethylhexyl compound (**6e**, $K_i = 18 \pm 2$ nM). As reported previously, the dimethylheptyl analogue (**4**) has little affinity for the CB_1 receptor and moderate affinity for the CB_2 receptor. The dimethylhexyl methyl ether (**6e**) is a highly selective CB_2 receptor ligand with good affinity for the CB_2 receptor and very little affinity for the CB_1 receptor.

The compounds of the 11-hydroxy-1-methoxy series (**11a**–**11f**) are intermediate between those of the other two series of ligands in their affinities for both receptors. The lower members of this series (**11a**–**11c**) have little affinity for the CB_1 receptor with $K_i = 1856 \pm 148$ nM for the dimethylethyl analogue (**11a**) and $K_i = 347 \pm 34$ nM for the dimethylbutyl compound (**11c**). The higher members of this series have from moderate affinity (**11d**, $K_i = 40 \pm 6$ nM) for the CB_2 receptor to high affinity for the dimethylhexyl (**11e**) and dimethylheptyl (**11f**) analogues. The affinities of **11e** and **11f** are identical within experimental error for each receptor, with $K_i = 14$ nM at CB_1 and 1.2 nM at CB_2.

In terms of the SAR for 1-methoxy-, 1-deoxy-11-hydroxy and 11-hydroxy-1-methoxy-Δ^8-THC analogues, it is apparent that an 11-hydroxyl substituent enhances affinity for both the CB_1 and CB_2 receptors. Also, in the 3-(1,1-dimethylalkyl) series the length of the side chain plays a critical role in determining affinity for both receptors. It is somewhat important for CB_2 affinity, particularly in the methyl ether series (**6**), but for significant CB_1 affinity a chain length of at least five carbon atoms is essential.

In summary, although several of these compounds show selectivity for the CB_2 receptor, only five of them, 1-methoxy cannabinoids **6d** and **6e**, 1-deoxy-11-hydroxy compounds **9a** and **9b**, and 11-hydroxy-3-(1′,1′-dimethylbutyl)-1-methoxy-Δ^8-THC (**11c**) have a combination of high affinity for the CB_2 receptor and little affinity for the CB_1 receptor. Only 3-(1′,1′-dimethylhexyl)-1-methoxy-Δ^8-THC (**6e**, JWH-229) with $K_i = 3134 \pm 110$ nM at CB_1 and $K_i = 18 \pm 2$ nM at CB_2 is comparable in selectivity to 1-deoxy-3-(1′,1′-dimethylhexyl)-Δ^8-THC (**3**, JWH-133) with $K_i = 677 \pm 132$ nM at CB_1 and $K_i = 3.4 \pm 1.0$ nM at CB_2.[20] Although JWH-229

(**6e**) has slightly less affinity for the CB_2 receptor than JWH-133 (**3**), it has significantly lower affinity for CB_1, and is thus a potentially useful CB_2 selective cannabinoid ligand with very little affinity for CB_1.

Experimental

General

IR spectra were obtained using Nicolet 5DX or Magna spectrometers; ^1H and ^{13}C NMR spectra were recorded on a Bruker 300AC spectrometer. Mass spectral analyses were performed on a Hewlett-Packard 5890A capillary gas chromatograph equipped with a mass sensitive detector. HRMS data were obtained in 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 Sorbent Technologies silica gel (32–63 μm) using the indicated solvents as eluents. All new compounds were homogeneous to TLC and ^{13}C NMR. All target compounds were homogeneous to GLC or TLC in two different solvent systems. TLC was carried out using 200 μm silica gel plates using the indicated solvents. GLC analyses were performed on the Hewlett-Packard 5890A GC/MS using a 60 m carbowax column and helium gas as a carrier. An initial column temperature of 60 °C was employed and the temperature was increased at a rate of 1.5 °C/min to a maximum temperature of 300 °C with a total run time of 20 min. Elemental analyses were performed by Atlantic Microlab, Norcross, GA.

1-Methoxy-3-(1′,1′-dimethylpropyl)-Δ^8 -THC (6b). To a solution of 0.569 g (1.8 mmol) of 3-(1′,1′-dimethylpropyl)-Δ^8-THC (**7b**)[20] in 14 mL of dry DMF under N_2 was added 0.151 g (2.7 mmol) of KOH and 0.33 mL (5.4 mmol) of methyl iodide. The reaction mixture was stirred for 48 h at ambient temperature before being quenched by the addition of 2 mL of aqueous NH_4Cl and removal of the DMF in vacuo. The residue was extracted with three portions of ether and the combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo. The crude product was initially purified by dry flash chromatography (petroleum ether:ether, 97:3) followed by gradient elution chromatography (petroleum ether:dichloromethane, 9:1 to 8:1) to afford 0.309 g (52%) of **6b** as a colorless oil. Further chromatography (petroleum ether:dichloromethane, 85:15) of 0.104 g of this material gave 0.100 g of pure **6b**, R_f 0.46 (petroleum ether: dichloromethane, 85:15); ^1H NMR (500 MHz, $CDCl_3$) δ 0.79 (t, J = 7.1 Hz, 3H), 1.09 (s, 3H), 1.24 (s, 6H), 1.38 (s, 3H), 1.54–1.60 (m, 2H), 1.70 (s, 3H), 1.74–1.81 (m, 3H), 2.12–2.14 (m, 1H), 2.67 (td, J = 4.7, 11.1 Hz, 1H), 3.15 (dd, J = 4.7, 17.1 Hz, 1H), 3.81 (s, 3H), 5.42 (br. s, 1H), 6.38 (d, J = 1.6 Hz, 1H), 6.42 (d, J = 1.6 Hz, 1H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 14.1, 18.4, 23.4, 27.8, 27.9, 28.7, 31.7, 36.3, 37.6, 44.3, 45.0, 55.1, 76.4, 100.7, 108.3, 111.2, 119.2, 135.0, 149.8, 153.9, 158.6; MS (EI) m/z 328 (65), 299 (45), 245 (100); $[\alpha]_D^{20}$ −210° (c = 0.29, CH_2Cl_2) HRMS calcd for $C_{22}H_{32}O_2$: 328.2404, found 328.2402.

1-Methoxy-3-(1′,1′-dimethylethyl)-Δ^8-THC (6a). Methoxy cannabinoid **6a** was prepared by the procedure described above for the preparation of **6b**. Methylation of 0.384 g (1.28 mmol) of **7a**[20] gave 0.173 g (43%) of **6a** as a colorless oil: ^1H NMR (300 MHz, $CDCl_3$) δ 1.10 (s, 3H), 1.29 (s, 9H), 1.38 (s, 3H), 1.74 (s, 3H), 1.76–1.82 (m, 3H), 2.11–2.14 (m, 1H), 2.65 (td, J = 4.5, 10.9 Hz, 1H), 3.15 (dd, J = 3.8, 17.3 Hz, 1H), 3.81 (s, 3H), 5.41 (d, J = 4.6 Hz, 1H), 6.44 (d, J = 1.6 Hz, 1H), 6.48 (d, J = 1.6 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 18.5, 23 (5), 27.6, 28.0, 31.2, 31.7, 34.7, 36.1, 45.0, 55.1, 76.5, 100.2, 107.6, 111.7, 119.2, 135.0, 150.9, 154.0, 158.7; MS (EI) m/z 314 (52), 299 (8), 246 (13), 231 (100); $[\alpha]_D^{20}$ −206° (c = 2.65, CH_2Cl_2); HRMS calcd for $C_{21}H_{30}O_2$: 314.2245, found 314.2246.

1-Methoxy-3-(1′,1′-dimethylbutyl)-Δ^8-THC (6c). Methoxy cannabinoid **6c** was prepared by the procedure described above for the preparation of **6b**. Methylation of 0.782 g (2.38 mmol) of **7c**[20] gave 0.461 g (43%) of **6c** as a colorless oil: ^1H NMR (500 MHz, $CDCl_3$) δ 0.82 (t, J = 7.4 Hz, 3H), 1.09 (s, 3H), 1.05–1.15 (m, 2H), 1.25 (s, 6H), 1.38 (s, 3H), 1.49–1.55 (m, 2H), 1.70 (s, 3H), 1.74–1.85 (m, 3H), 2.09–2.16 (m, 1H), 2.66 (td, J = 4.6, 11.0 Hz, 1H), 3.16 (dd, J = 3.2, 16.5 Hz, 1H), 3.78 (s, 3H), 5.42 (d, 4.1H), 6.38 (d, J = 0.9 Hz, 1H), 6.43 (d, J = 0.9 Hz, 1H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 14.9, 18.1, 18.5, 23.7, 27.7, 28.1, 28.9, 29.0, 31.8, 36.3, 37.8, 45.2, 47.2, 55.2, 76.9, 100.9, 108.3, 111.7, 119.4, 135.1, 149.7, 154.1, 158.8; MS (EI) m/z 342 (37), 300 (100), 286 (20), 259 (38); $[\alpha]_D^{20}$ −258° (c = 0.79, $CHCl_3$); HRMS calcd for $C_{23}H_{34}O_2$: 342.2564, found 342.2559.

1-Methoxy-3-(1′,1′-dimethylpentyl)-Δ^8-THC (6d). Methoxy cannabinoid **6d** was prepared by the procedure described above for the preparation of **6b**. Methylation of 2.80 g (8.17 mmol) of **7d**[20] gave 2.83 g (97%) of **6d** as a colorless oil: ^1H NMR (300 MHz, $CDCl_3$) δ 0.83 (t, J = 7.1 Hz, 3H), 1.03–1.11 (m, 2H), 1.10 (s, 3H), 1.16–1.29 (m, 2H), 1.25 (s, 6H), 1.38 (s, 3H), 1.51–1.60 (m, 2H), 1.70 (s, 3H), 1.73–1.90 (m, 3H), 2.05–2.12 (m, 1H), 2.66 (td, J = 4.7, 10.8 Hz, 1H), 3.06 (dd, J = 4.0 Hz, 1H), 3.81 (s, 3H), 5.41 (d, J = 4.8 Hz, 1H), 6.38 (d, J = 1.6 Hz, 1H), 6.43 (d, J = 1.6 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.1, 18.4, 23.4, 23.5, 26.9, 27.6, 27.9, 28.8, 31.7, 36.2, 37.6, 44.3, 45.0, 55.1, 76.5, 100.7, 108.2, 111.6, 119.2, 135.0, 149.7, 153.9, 158.7; MS (EI) m/z 356 (45), 300 (100), 286 (25), 273 (30); HRMS calcd for $C_{24}H_{36}O_2$: 356.2716, found 356.2715; $[\alpha]_D^{20}$ −234° (c = 0.24, $CHCl_3$).

1-Methoxy-3-(1′,1′-dimethylhexyl)-Δ^8-THC (6e). Methoxy cannabinoid **6e** was prepared by the procedure described above for the preparation of **6b**. Methylation of 2.59 g (7.26 mmol) of **7e**[20] gave 2.54 g (94%) of **6e** as a colorless oil: ^1H NMR (300 MHz, $CDCl_3$) δ 0.83 (t, J = 7.1 Hz, 3H), 1.01–1.30 (m, 6H), 1.10 (s, 3H), 1.24 (s, 6H), 1.38 (s, 3H), 1.48–1.56 (m, 2H), 1.65–1.90 (m, 3H), 1.70 (s, 3H), 2.11–2.18 (m, 1H), 2.67 (td, J = 4.7, 10.9 Hz, 1H), 3.15 (dd, J = 4.1, 17.0 Hz, 1H), 3.81 (s,

3H), 5.41 (s, 1H), 6.38 (d, $J=1.6$ Hz, 1H), 6.42 (d, $J=1.6$ Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.1, 18.4, 22.5, 23.5, 24.3, 27.6, 27.7, 28.0, 28.8, 31.7, 32.6, 36.2, 37.7, 44.5, 45.1, 55.1, 76.4, 100.7, 108.3, 111.6, 119.2, 135.1, 149.7, 153.9, 158.7; MS (EI) *m/z* 370 (40), 300 (100), 287 (35); $[\alpha]_D^{20}$ −219° ($c=0.21$, $CHCl_3$); HRMS calcd for $C_{25}H_{38}O_2$: 370.2871, found 370.2872.

1-Deoxy-3-(1′,1′-dimethylpropyl)-11-hydroxy-Δ^8-THC (9b). To a stirred suspension of 1.07 g (3.58 mmol) of 1-deoxycannabinoid **8b**[20] in 16 mL of ethanol at ambient temperature was added dropwise over 30 min a solution of 0.96 g of SeO_2 (8.73 mmol) in 17.6 mL of ethanol/water (10:1). The reaction mixture was heated at reflux for 18 h, filtered through a pad of Celite, which was subsequently washed with three portions of methanol, and the combined organic extracts were concentrated in vacuo. The residue was extracted with three portions of ether and the resulting ethereal solution was washed successively with water then saturated $NaHCO_3$. The organic phase was dried ($MgSO_4$) and concentrated in vacuo to afford crude aldehyde **10b** which was purified by dry flash chromatography (ethyl acetate: petroleum ether, 9:1) to afford 0.96 g of **10b** as a light brown oil which was used without further purification.

To a solution of 0.96 g (3.10 mmol) of the crude aldehyde in 35 mL of dry THF at 0 °C under N_2 was added 0.12 g (3.07 mmol) of $LiAlH_4$. The reaction mixture was allowed to warm to room temperature, stirred for 2 h and then quenched with aqueous NH_4Cl. After filtering through a pad of Celite, which was subsequently washed with diethyl ether, the combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo to afford the crude product. Initial chromatography (gradient elution with 17% diethyl ether to 35% diethyl ether in petroleum ether) gave a pale yellow resin which was further purified by chromatography (gradient elution with 5% acetone to 7% acetone in petroleum ether) to afford 0.31 g (32% for two steps) of **9b** as a white foam: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.69 (t, $J=7.8$ Hz, 3H), 1.17 (s, 3H), 1.24 (s, 6H), 1.40 (s, 3H), 1.60 (q, $J=7.4$ Hz, 1H), 1.72–2.02 (m, 5H), 2.20–2.28 (m, 1H), 2.69 (td, $J=5.5$, 11.0 Hz, 1H), 2.80 (dd, $J=4.2$, 16.5 Hz, 1H), 4.05 (d, $J=12.8$ Hz, 1H), 4.08 (d, $J=12.8$ Hz, 1H), 5.76 (br. s, 1H), 6.76 (d, $J=1.8$ Hz, 1H), 6.85 (dd, $J=1.8$, 7.8 Hz, 1H), 7.14 (dd, $J=0.9$, 8.2 Hz, 1H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 9.34, 19.2, 27.3, 27.8, 28.5, 31.9, 32.1, 36.9, 37.7, 43.2, 67.0, 76.9, 114.9, 118.0, 121.7, 122.2, 126.2, 137.1, 149.4, 152.6; MS (EI) *m/z* 314 (59), 312 (20), 299 (13), 285 (100), 207 (100); $[\alpha]_D^{20}$ −126° ($c=9.0$, $CHCl_3$); HRMS calcd for $C_{21}H_{30}O_2$: 314.2251, found 314.2246.

1-Deoxy-3-(1′,1′-dimethylethyl)-11-hydroxy-Δ^8-THC (9a). 11-Hydroxycannabinoid **9a** was prepared by the procedure described above for the preparation of **9b**. Stepwise oxidation and reduction of 1.27 g (4.46 mmol) of **8a**[20] gave 0.35 g (26% for two steps) of hydroxy cannabinoid **9a** as a white foam: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.17 (s, 3H), 1.29 (s, 9H), 1.41 (s, 3H), 1.76 (dt, $J=5.8$, 13.0 Hz, 1H), 1.80–1.90 (m, 1H), 1.94 (br. t, $J=13.0$ Hz, 1H), 2.08–2.28 (m, 2H), 2.69 (dt, $J=5.8$, 13.1 Hz, 1H), 2.80 (dd, $J=5.3$, 17.5 Hz, 1H), 4.04 (d, $J=17.0$ Hz, 1H), 4.08 (d, $J=17.0$ Hz, 1H), 5.77 (br. s, 1H), 6.84 (d, $J=1.4$ Hz, 1H), 6.92 (dd, $J=1.8$, 8.2 Hz, 1H), 7.17 (d, $J=8.2$ Hz, 1H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 19.3, 27.3, 27.8, 31.4, 31.9, 32.1, 34.4, 43.2, 66.9, 77.0, 114.2, 117.4, 121.7, 126.4, 122.4, 137.1, 150.9, 152.6; MS (EI) *m/z* 300 (100), 298 (42), 285 (36), 207 (51); $[\alpha]_D^{20}$ −103° ($c=10.4$, $CHCl_3$); HRMS calcd for $C_{20}H_{28}O_2$: 300.2090, found 300.2089.

1-Deoxy-3-(1′,1′-dimethylbutyl)-11-hydroxy-Δ^8-THC (9c). 11-Hydroxycannabinoid **9c** was prepared by the procedure described above for the preparation of **9b**. Stepwise oxidation and reduction of 1.20 g (4.09 mmol) of **8c**[20] gave 0.33 g (25% for two steps) of hydroxy cannabinoid **9c** as a white foam: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.81 (t, $J=7.4$ Hz, 3H), 1.03–1.14 (m, 2H), 1.16 (s, 3H), 1.25 (s, 6H), 1.40 (s, 3H), 1.49–1.56 (m, 2H), 1.74 (td, $J=5.0$, 11.9 Hz, 1H), 1.82–1.90 (m, 1H), 1.91–2.02 (m, 2H), 2.23 (br. d, $J=17.8$ Hz, 1H), 2.68 (td, $J=5.5$, 11.0 Hz, 1H), 2.80 (dd, $J=5.0$, 17.0 Hz, 1H), 4.04 (d, $J=12.8$ Hz, 1H), 4.08 (d, $J=12.8$ Hz, 1H), 5.75 (br. s, 1H), 6.76 (d, $J=1.8$ Hz, 1H), 6.84 (dd, $J=1.8$, 8.2 Hz, 1H), 7.13 (d, $J=7.8$ Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.7, 17.9, 19.1, 27.1, 27.6, 28.7, 28.8, 31.8, 32.0, 37.4, 43.0, 46.9, 66.8, 76.6, 114.6, 117.7, 121.5, 122.0, 126.0, 136.9, 149.5, 152.4; MS (EI) *m/z* 328 (46), 285 (100), 207 (60); $[\alpha]_D^{20}$ −153° ($c=10.3$, $CHCl_3$); HRMS calcd for $C_{22}H_{32}O_2$: 328.2402, found 328.2402.

1-Deoxy-3-(1′,1′-dimethylpentyl)-11-hydroxy-Δ^8-THC (9d). Hydroxycannabinoid **9d** was prepared by the procedure described above for the preparation of **9b**. Stepwise oxidation and reduction of 1.60 g (4.90 mmol) of **8d**[20] gave 0.48 g (28% for two steps) of hydroxy cannabinoid **9d** as a white foam: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.81 (t, $J=7.3$ Hz, 3H), 1.01–1.09 (m, 2H), 1.17 (s, 3H), 1.17–1.23 (m, 2H), 1.24 (s, 6H), 1.41 (s, 3H), 1.51–1.57 (m, 2H), 1.76 (td, $J=4.6$, 11.4 Hz, 1H), 1.82–1.91 (m, 1H), 1.95–2.03 (m, 2H), 2.25 (dt, $J=8$, 17.9 Hz, 1H), 2.69 (dt, $J=5.5$, 11.4 Hz, 1H), 2.80 (dd, $J=4.6$, 16.5 Hz, 1H), 4.06 (d, $J=12.8$ Hz, 1H), 4.09 (d, $J=12.8$ Hz, 1H), 5.76 (br. s, 1H), 6.76 (d, $J=1.8$ Hz, 1H), 6.84 (dd, $J=1.8$, 7.8 Hz, 1H), 7.14 (d, $J=8.2$ Hz, 1H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 14.2, 19.2, 23.5, 27.0, 27.3, 27.8, 29.0, 31.9, 32.1, 37.4, 43.1, 44.4, 67.1, 76.9, 114.8, 117.9, 121.8, 122.2, 126.2, 137.1, 149.8, 152.6; MS (EI) *m/z* 342 (33), 285 (100,), 269 (29), 255 (19); $[\alpha]_D^{20}$ +63° ($c=14.3$, $CHCl_3$); HRMS calcd for $C_{23}H_{34}O_2$: 342.2562, found 342.2559;.

1-Deoxy-3-(1′,1′-dimethylhexyl)-11-hydroxy-Δ^8-THC (9e). 11-Hydroxycannabinoid **9e** was prepared by the procedure described above for the preparation of **9b**. Stepwise oxidation and reduction of 1.72 g (5.05 mmol) of **8e**[20] gave 0.231 g (13% for two steps) of hydroxy cannabinoid **9e** as a white foam: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.82 (t, $J=6.8$ Hz, 3H), 1.03–1.12 (m, 2H), 1.15–1.24 (m, 4H), 1.16 (s, 3H), 1.24 (s, 6H), 1.40 (s, 3H), 1.51–1.57 (m, 2H), 1.76 (td, $J=4.6$, 11.9 Hz, 1H), 1.81–2.03 (m, 3H), 2.23 (dt, $J=8.0$, 16.5 Hz, 1H), 2.69 (td, $J=5.5$, 11.0 Hz, 1H), 2.79 (dd, $J=5.0$, 17.0 Hz, 1H), 4.04 (d, $J=12.8$ Hz, 1H), 4.08 (d, $J=12.8$ Hz, 1H), 5.75

(br. s, 1H), 6.76 (d, $J=2.3$ Hz, 1H), 6.84 (dd, $J=1.8$, 8.2 Hz, 1H), 7.13 (d, $J=8.2$ Hz, 1H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 14.2, 19.2, 22.7, 24.5, 27.3, 27.8, 28.9, 29.0, 31.9, 32.1, 32.7, 37.5, 43.2, 44.6, 67.0, 77.2, 114.8, 117.9, 121.7, 122.2, 126.2, 137.1, 149.8, 152.6; MS (EI) m/z 356 (32), 285 (100), 269 (18); $[\alpha]_D^{20}$ −144° ($c=6.5$, $CHCl_3$); HRMS calcd for $C_{24}H_{36}O_2$: 356.2715, found 356.2715.

3-(1′,1′-Dimethylpropyl)-11-pivaloyloxy-Δ^8-THC (13b). To a solution of 0.507 g (2.81 mmol) of crude 2-methyl-2-(3,5-dihydroxyphenyl)propane and 0.709 g (2.81 mmol) of 4-hydroxymyrtenyl pivalate (**12**) in 188 mL of dry dichloromethane at −20 °C was added dropwise with stirring 1.94 mL (14.1 mmol) of boron trifluoride etherate. The mixture was allowed to warm to 0 °C and stirred for 2 h, poured onto ice and neutralized with saturated aqueous $NaHCO_3$. After extraction with ether, the combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo to afford the crude product as a dark brown foam. Chromatography (petroleum ether:-ethyl acetate, 95:5) and subsequent recrystallization (heptane:ethyl acetate, 95:5) afforded 0.233 g (20%) of pure **13b** as white crystals, mp 214–215 °C: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.67 (t, $J=7.4$ Hz, 3H), 1.10 (s, 3H), 1.18 (s, 6H), 1.20 (s, 9H), 1.38 (s, 3H), 1.56 (q, $J=7.3$ Hz, 2H), 1.80–1.91 (m, 3H), 2.21–2.29 (m, 1H), 2.71 (td, $J=4.6$, 11.1 Hz, 1H), 3.36 (dd, $J=3.9$, 16.8 Hz, 1H), 4.48 (s, 2H), 5.20 (br. s, 1H), 5.73 (d, $J=4.9$ Hz, 1H), 6.21 (d, $J=1.8$ Hz, 1H), 6.37 (d, $J=1.7$ Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 9.2, 18.4, 27.2, 28.2, 31.2, 31.6, 36.8, 38.9, 44.8, 68.1, 76.5, 105.6, 107.8, 109.7, 123.2, 133.9, 149.7, 154.3, 154.7, 178.8; anal. calcd for $C_{26}H_{38}O_4$: C, 75.33; H, 9.24; found: C, 75.15; H, 9.34.

1-Methoxy-3-(1′,1′-dimethylpropyl)-11-pivaloyloxy-Δ^8-THC. Methylation of 0.556 g (1.34 mmol) of **13b** by the procedure used for the preparation of **6b** gave 0.454 g (79%) of the corresponding methyl ether as a colorless oil following chromatography (petroleum ether:ether, 97.5:2.5 to 95:5): ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.70 (t, $J=7.4$ Hz, 3H), 1.10 (s, 3H), 1.24 (s, 15H), 1.39 (s, 3H), 1.57 (q, $J=7.7$ Hz, 2H), 1.70–1.92 (m, 3H), 2.21–2.29 (m, 1H), 2.67 (td, $J=4.6$, 11.1 Hz, 1H), 3.30 (dd, $J=3.9$, 16.8 Hz, 1H), 3.79 (s, 3H), 4.49 (s, 2H), 5.76 (br. s, 1H), 6.38 (d, $J=1.5$ Hz, 1H), 6.43 (d, $J=1.6$ Hz, 1H).

1-Methoxy-3-(1′,1′-dimethylpropyl)-11-hydroxy-Δ^8-THC (11b). To a solution of 0.454 g (1.06 mmol) of pivalate ester in 33 mL of dry THF under N_2 at 0 °C was added 0.051 g (1.34 mmol) of $LiAlH_4$. The mixture was allowed to warm to room temperature, stirred for 1 h and quenched with 15 mL of aqueous NH_4Cl. The solids were filtered off through a pad of Celite, which was subsequently washed with ether. The combined organic fractions were dried ($MgSO_4$) and concentrated in vacuo to afford the crude product. Chromatography (gradient elution, petroleum ether:acetone, 95:5 to 93:7) gave 0.233 g (68%) of pure **11b** as a colorless resin: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.69 (t, $J=7.3$ Hz, 3H), 1.11 (s, 3H), 1.25 (s, 6H), 1.39 (s, 3H), 1.59 (q, $J=7.4$ Hz, 2H), 1.78–1.91 (m, 3H), 2.18–2.26 (m, 1H), 2.67 (td, $J=4.6$, 11.0 Hz, 1H), 3.31 (dd, $J=4.6$, 16.5 Hz, 1H), 3.80 (s, 3H), 4.03 (d, $J=13.3$ Hz, 1H), 4.06 (d, $J=13.3$ Hz, 1H), 5.73 (d, $J=4.6$ Hz, 1H), 6.38 (d, $J=1.6$ Hz, 1H), 6.43 (d, $J=1.6$ Hz, 1H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 9.3, 18.5, 27.6, 27.7, 28.4, 31.6, 31.9, 36.9, 38.0, 45.3, 55.2, 67.2, 76.6, 100.8, 108.4, 111.3, 120.8, 138.6, 149.5, 154.0, 158.7, 158.7; MS (EI) m/z 344 (29), 315 (24), 281 (28), 245 (64), 207 (100); $[\alpha]_D^{20}$ −209° ($c=0.46$, CH_2Cl_2); HRMS calcd for $C_{22}H_{32}O_3$: 344.2351, found 344.2351.

3-(1′,1′-Dimethylethyl)-11-pivaloyloxy-Δ^8-THC (13a). 11-Pivaloyloxycannabinoid **13a** was prepared by the procedure described above for the preparation of **13b**. From 1.62 g (9.76 mmol) of resorcinol 0.892 g (23%) of **13a** was obtained as a colorless oil following chromatography (petroleum ether/ether, 97.5:2.5 to 95:5): ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.05 (s, 3H), 1.15 (s, 9H), 1.16 (s, 9H), 1.32 (s, 3H), 1.73–1.82 (m, 3H), 2.14–2.20 (m, 1H), 2.63 (td, $J=4.6$, 11.0 Hz, 1H), 3.30 (dd, $J=4.2$, 11.9 Hz, 1H), 4.43 (br. s, 2H), 5.35 (br. s, 1H), 5.68 (d, $J=4.6$ Hz, 1H), 6.24 (d, $J=1.8$ Hz, 1H), 6.36 (d, $J=1.8$ Hz, 1H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 18.6, 27.3, 27.6, 27.7, 31.3, 31.4, 34.4, 39.0, 44.8, 68.3, 76.9, 105.1, 107.2, 109.9, 123.3, 133.9, 151.4, 154.5, 154.9, 178.9, 154.9.

1-Methoxy-3-(1′,1′-dimethylethyl)-11-pivaloyloxy-Δ^8-THC. Methylation of 0.523 g (1.31 mmol) of **13a** by the procedure used for the preparation of **6b** gave 0.447 g (82%) of the corresponding methyl ether as a colorless oil following chromatography (petroleum ether/ether, 97.5:2.5 to 95:5): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.11 (s, 3H), 1.23 (s, 9H), 1.29 (s, 9H), 1.39 (s, 3H), 1.74–1.87 (m, 3H), 2.19–2.30 (m, 1H), 2.67 (td, $J=4.5$, 10.9 Hz, 1H), 3.31 (dd, $J=3$, 9, 16.9 Hz, 1H), 3.80 (s, 3H), 4.49 (br s, 2H), 5.75 (d, $J=4.4$ Hz, 1H), 6.44 (d, $J=1.6$ Hz, 1H), 6.49 (d, $J=1.6$ Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) d 18.4, 27.2, 27.5, 27.7, 31.2, 31.4, 31.8, 39.0, 44.9, 55.0, 68.1, 76.3, 100.2, 107.6, 111.2, 123.4, 134.1, 149.9, 154.0, 158.7, 178.4.

1-Methoxy-3-(1′,1′-dimethylethyl)-11-hydroxy-Δ^8-THC (11a). Reduction of 0.447 g (1.08 mmol) of the pivalate ester by the procedure used for the preparation of **11b** gave 0.176 g (49%) of hydroxy cannabinoid **11a** as a colorless resin: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.10 (s, 3H), 1.27 (s, 9H), 1.38 (s, 3H), 1.76–1.90 (m, 3H), 2.17–2.24 (m, 1H), 2.65 (td, $J=4.6$, 11.0 Hz, 1H), 3.30 (dd, $J=4.6$, 16.5 Hz, 1H), 3.80 (s, 3H), 4.02 (d, $J=13.3$ Hz, 1H), 4.05 (d, $J=13.3$ Hz, 1H), 5.72 (d, $J=5.0$ Hz, 1H), 6.43 (d, $J=1.9$ Hz, 1H), 6.48 (d, $J=1.8$ Hz, 1H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 18.5, 27.7, 31.3, 31.5, 31.8, 34.8, 45.2, 55.2, 67.2, 76.6, 100.2, 107.6, 111.4, 120.8, 138.6, 151.1, 154.0, 158.8; MS (EI) m/z 330 (34), 299 (14), 231 (100), 207 (92); $[\alpha]_D^{20}$ −225° ($c=1.08$, CH_2Cl_2); HRMS calcd for $C_{21}H_{30}O_3$: 330.2194, found 330.2195.

3-(1′,1′-Dimethylbutyl)-1-methoxy-11-oxo-Δ^8-THC (14c). Selenium dioxide oxidation of 0.290 g (0.847 mmol) of **6c**, using the procedure described above for the preparation of **10b**, gave, after chromatography (petroleum ether/ethyl acetate, 9:1), 0.196 g (65%) of aldehyde as a

yellow solid: mp 109–110 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.82 (t, J = 7.2 Hz, 3H), 1.03–1.13 (m, 2H), 1.10 (s, 3H), 1.25 (s, 6H), 1.43 (s, 3H), 1.50–1.55 (m, 2H), 1.79–1.93 (m. 2), 2.04–2.15 (m, 1H), 2.51–2.56 (m, 1H), 2.61 (td, J = 4.5, 11.2 Hz, 1H), 3.73 (dd, J = 2.1, 17.9 Hz, 1H), 3 .82, (s, 3H), 6.39 (d, J = 1.6 Hz, 1H), 6.42 (d, J = 1.6 Hz, 1H), 6.83 (s, 1H), 9.50 (s, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.8, 17.9, 18.2, 27.5, 28.7, 29.2, 30.8, 37.6, 44.9, 47.0, 55.1, 75.8, 100.7, 108.2, 110.2, 142.2, 148.9, 150.1, 153.7, 158.6, 193.7; MS (EI) m/z 356 (55), 306 (100).

1-Methoxy-3-(1′,1′-dimethylbutyl)-11-hydroxy-Δ^8-THC (11c). To a suspension of 0.196 g (0.551 mmol) of aldehyde **14c** in 3.5 mL of dry methanol was added sequentially 0.205 g (0.551 mmol) of $CeCl_3 \cdot 7H_2O$ and 0.021 g (0.551 mmol) of $NaBH_4$. The reaction mixture was stirred at ambient temperature for 2 h, the pH was adjusted to 7.0 by the addition of 1M aqueous HCl. After pouring into water the mixture was extracted with three portions of CH_2Cl_2, dried ($MgSO_4$) and the solvent was removed in vacuo. The residue was purified by chromatography (petroleum ether:ethyl acetate, 4:1) to give 0.185 g (94%) of cannabinoid **11c** as a pale yellow gum: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.82 (t, J = 7.1 Hz, 3H), 1.05–1.14 (m, 2H), 1.11 (s, 3H), 1.25 (s, 6H), 1.39 (s, 3H), 1.50–1.54 (m, 2H), 1.79–1.92 (m, 3H), 2.17–2.24 (m, 1H), 2.67 (td, J = 4.6, 11.0 Hz, 1H), 3.31 (dd, J = 4.6, 16.5 Hz, 1H), 3.80 (s, 3H), 4.05 (s, 2H), 5.73 (s, 1H), 6.38 (d, 1.6. 1H), 6.43 (d, J = 1.6 Hz, 1H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 14.7, 17.9, 18.3, 27.5, 27.6, 28.7, 28.8, 31.4, 31.8, 37.6, 45.1, 46.9, 55.0, 66.8, 76.2, 100.5, 108.1, 111.1, 120.4, 138.4, 149.6, 153.8, 158.5; $[a]_D^{20}$ −238° (c = 0.50, $CHCl_3$); HRMS calcd for $C_{23}H_{34}O_3$: 358.2508, found 358.2509.

1-Methoxy-3-(1′,1′-dimethylpentyl)-11-oxo-Δ^8-THC (14d). Selenium dioxide oxidation of 2.00 g (5.17 mmol) of **6d**, using the procedure described above for the preparation of **10b**, gave, after chromatography (petroleum ether/ethyl acetate, 87.5:12.5), 1.17 g (50%) of aldehyde **14d** as a pale orange solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.83 (t, J = 7.4 Hz, 3H), 1.02–1.09 (m, 2H), 1.14 (s, 3H), 1.18–1.28 (m, 2H), 1.25 (s, 6H), 1.43 (s, 3H), 1.52–1.60 (m, 2H), 1.76–1.94 (m, 2H), 2.05–2.19 (m, 1H), 2.53–2.58 (m, 1H), 2.61 (td, J = 4.5, 11.2 Hz, 1H), 3.74 (dd, J = 3.6, 16.1 Hz, 1H), 3.83 (s, 3H), 6.39 (d, J = 1.6 Hz, 1H), 6.43 (d, J = 1.6 Hz, 1H), 6.83–6.84 (m, 1H), 9.50 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1, 18.2, 23.4, 26.9, 27.6, 28.7, 28.8, 29.2, 30.8, 37.9, 44.2, 45.0, 47.3, 55.1, 75.8, 100.7, 108.1, 110.2, 142.5, 148.9, 150.2, 153.7, 158.6, 193.8; MS (EI) m/z 370 (35), 314 (100), 300 (25).

1-Methoxy-3-(1′,1′-dimethylpentyl)-11-hydroxy-Δ^8-THC (11d). Luche reduction of 0.500 g (1.35 mmol) of aldehyde **14d** by the procedure described above for the reduction of **14c** gave after chromatography (petroleum ether/ethyl acetate, 4:1) 0.350 g (70%) of 11-hydroxy cannabinoid **11d** as a pale yellow gum: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.83 (t, J = 7.3 Hz, 3H), 1.00–1.10 (m, 2H), 1.11 (s, 3H), 1.16–1.28 (m, 2H), 1.24 (s, 6H), 1.39 (s, 3H), 1.49–1.57 (m, 2H), 1.77–1.91 (m, 3H), 2.20–2.25 (m, 1H), 2.66 (td, J = 4.6, 10.9 Hz, 1H), 3.31 (dd, J = 3.6, 17.1 Hz, 1H), 3.80 (s, 3H), 4.05 (s, 2H), 5.73 (d, J = 4.2 Hz, 1H), 6.37 (d, J = 1.6 Hz, 1H), 6.42 (d, J = 1.6 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.1, 18.4, 23.4, 26.9, 27.6, 27.7, 28.8, 31.5, 31.8, 37.6, 44.2, 45.2, 67.1, 76.3, 100.6, 108.2, 111.1, 120.7, 138.5, 149.8, 153.8, 158.6; $[\alpha]_D^{20}$ −284° (c = 0.25, $CHCl_3$); HRMS calcd for $C_{24}H_{36}O_3$: 372.2664, found 372.2663.

1-Methoxy-3-(1′,1′-dimethylhexyl)-11-oxo-Δ^8-THC (14e). Selenium dioxide oxidation of 2.25 g (6.07 mmol) of **6e**, using the procedure described above for the preparation of **10b** gave 1.40 g (60%) of aldehyde **14e** as an orange solid, mp 117–119 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.83 (t, J = 7.1 Hz, 3H), 1.02–1.30 (m, 6H), 1.10 (s, 3H), 1.25 (s, 6H), 1.43 (s, 3H), 1.51–1.56 (m, 2H), 1.80–1.93 (m, 2H), 2.05–2.18 (m, 1H), 2.49–2.56 (m, 1H), 2.62 (td, J = 4.5, 11.2 Hz, 1H), 3.73 (dd, J = 4.1, 15.7 Hz, 1H), 3.82 (s, 3H), 6.39 (d, J = 1.6 Hz, 1H), 6.42 (d, J = 1.6 Hz, 1H), 6.84 (br. s, 1H), 9.50 (s, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.1, 18.2, 22.5, 24.3, 27.5, 28.7, 28.8, 29.3, 30.9, 32.5, 37.7, 44.5, 44.9, 55.2, 75.8, 100.7, 108.1, 110.3, 142.5, 148.9, 150.2, 153.7, 158.7, 193.8; MS (EI) m/z 384 (20), 314 (100).

1-Methoxy-3-(1′,1′-dimethylhexyl)-11-hydroxy-Δ^8-THC (11e). Luche reduction of 0.404 g (1.05 mmol) of aldehyde **14e** by the procedure described above for the reduction of **14c** gave after chromatography (petroleum ether/ethyl acetate, 4:1) 0.354 g (87%) of 11-hydroxy cannabinoid **11e** as a pale yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.83 (t, J = 7.3 Hz, 3H), 1.07–1.34 (m, 6H), 1.11 (s, 3H), 1.25 (s, 6H), 1.40 (s, 3H), 1.51–1.58 (m, 2H), 1.78–1.88 (m, 3H), 2.21–2.25 (m, 1H), 2.67 (td, J = 4.6, 10.9 Hz, 1H), 3.31 (dd, J = 3.5, 17.2 Hz, 1H), 3.81 (s, 3H), 4.06 (s, 2H), 5.73 (d, J = 4.4 Hz, 1H), 6.38 (d, J = 1.6 Hz, 1H), 6.43 (d, J = 1.6 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.1, 18.4, 22.6, 24.3, 27.6, 27.7, 28.8, 28.9, 31.5, 31.9, 32.6, 44.4, 45.2, 55.2, 67.2, 76.3, 100.7, 108.3, 111.2, 120.8, 138.6, 149.9, 154.0, 158.7; HRMS calcd for $C_{25}H_{38}O_3$: 386.2821, found 386.2818.

3-(1′,1′-Dimethylheptyl)-1-methoxy-11-oxo-Δ^8-THC (14f). Selenium dioxide oxidation of 1.64 g (4.27 mmol) of **4**, using the procedure described above for the preparation of **10b** gave 1.12 g (66%) of aldehyde **14f** as an orange solid: mp 118–119 °C; R_f 0.31 (petroleum ether/ethyl acetate, 94:6); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.84 (t, J = 6.9 Hz, 3H), 1.06–1.27 (m, 8H), 1.14 (s, 3H), 1.24 (s, 6H), 1.43 (s, 3H), 1.51–1.57 (m, 2H), 1.66–1.68 (m, 1H), 1.88 (td, J = 4.1, 11.6 Hz, 1H), 2.07–2.18 (m, 1H), 2.51–2.57 (m, 1H), 2.61 (td, J = 4.1, 11.2 Hz, 1H), 3.73 (dd, J = 4.5, 17.1 Hz, 1H), 3.81 (s, 3H), 6.39 (d, J = 1.6 Hz, 1H), 6.42 (d, J = 1.6 Hz, 1H), 6.83 (s, 1H), 9.50 (s, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.1, 18.2, 22.6, 24.6, 27.5, 28.7, 28.9, 29.2, 30.0, 30.8, 31.7, 37.7, 44.5, 45.0, 55.1, 75.8, 100.7, 108.1, 110.2, 142.5, 148.9, 150.2, 153.7, 158.6, 193.8; MS (EI) m/z 398 (25), 314 (50), 281 (66), 207 (100).

11-Hydroxy-3-(1′,1′-dimethylheptyl)-1-methoxy-Δ^8-THC (11f). Luche reduction of 0.314 g (0.789 mmol) of aldehyde **14f** by the procedure described above for the

preparation of **14c** gave after chromatography (petroleum ether/ethyl acetate, 85:15) 0.270 g (93%) of 11-hydroxy cannabinoid **11f** as a pale yellow oil: R_f 0.30 (petroleum ether/ethyl acetate, 85:15); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.84 (t, J = 6.9 Hz, 3H), 0.95–1.26 (m, 8H), 1.10 (s, 3H), 1.24 (s, 6H), 1.39 (s, 3H), 1.51–1.56 (m, 2H), 1.78–1.90 (m, 4H), 2.19–2.26 (m, 1H), 2.66 (td, J = 4.1, 10.8 Hz, 1H), 3.30 (dd, J = 3.3, 16.6 Hz, 1H), 3.79 (s, 3H), 4.03 (br s, 2H), 5.71 (s, 1H), 6.37 (d, J = 1.6 Hz, 1H), 6.42 (d, J = 1.6 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.0, 18.3, 22.6, 24.5, 27.5, 27.6, 28.7, 28.8, 29.6, 29.9, 31.4, 31.7, 37.6, 44.4, 45.1, 55.0, 66.9, 76.3, 100.6, 108.2, 111.1, 120.5, 138.5, 149.7, 153.8, 158.6; $[\alpha]_D^{20}$ −175° (c = 0.3, CH_2Cl_2); HRMS calcd for $C_{26}H_{40}O_3$: 400.2977, found 400.2979.

Receptor binding assays

1. CB_1 assay. [^{3}H]CP-55,940 (K_D = 690 nM) binding to P_2 membranes was conducted as described elsewhere,[31] except whole brain (rather than cortex only) was used. Displacement curves were generated by incubating drugs with 1 nM of [^{3}H]CP-55,940. The assays were performed in triplicate, and the results represent the combined data from three individual experiments.

2. CB_2 assay. Human embryonic kidney 293 cells were maintained in Dulbecco's modified Eagle's medium (DMEM) with 10% fetal clone II (HyClone, Logan UT) and 5% CO_2 at 37 °C in a Forma incubator. Cell lines were created by transfection of CB_2pcDNA3 into 293 cells by the Lipofectamine reagent (Life Technologies, Gaithersburg, MD). The human CB_2 cDNA was provided by Dr. Sean Munro (MRC, Cambridge, England). Stable transformants were selected in growth medium containing geneticin (1 mg/mL, reagent, Life Technologies, Gaithersburg, MD). Colonies of about 500 cells were picked (about 2 weeks post transfection) and allowed to expand, then tested for expression of receptor mRNA by northern blot analysis. Cell lines containing moderate to high levels of receptor mRNA were tested for receptor binding properties. Transfected cell lines were maintained in DMEM with 10% fetal clone II plus 0.3–0.5 mg/mL geneticin and 5% CO_2 at 37 °C in a Forma incubator.

The current assay is a modification of Compton et al.[8] Cells were harvested in phosphate-buffered saline containing 1 mM EDTA and centrifuged at 500g. The cell pellet was homogenized in 10 mL of solution A (50 mM Tris–HCl, 320 mM sucrose, 2 mM EDTA, 5 mM $MgCl_2$, pH 7.4). The homogenate was centrifuged at 1600g (10 min), the supernatant saved, and the pellet washed three times in solution A with subsequent centrifugation. The combined supernatants were centrifuged at 100,000g (60 min). The (P_2 membrane) pellet was resuspended in 3 mL of buffer B (50 mM Tris–HCl, 1 mM EDTA, 3 mM $MgCl_2$, pH 7.4) to yield a protein concentration of approximately 1 mg/mL. The tissue preparation was divided into equal aliquots, frozen on dry ice, and stored at −70 °C. Binding was initiated by the addition of 40–50 μg membrane protein to silanized tubes containing [^{3}H]CP-55,940 (102.9 Ci/mmol) and a sufficient volume of buffer C (50 mM Tris–HCl, 1 mM EDTA, 3 mM $MgCl_2$, and 5 mg/mL fatty acid free BSA, pH 7.4) to bring the total volume to 0.5 mL. The addition of 1 μM unlabelled CP-55,940 was used to assess nonspecific binding. Following incubation (30 °C for 1 h), binding was terminated by the addition of 2 mL of ice cold buffer D (50 mM Tris–HCl, pH 7.4, plus 1 mg/mL BSA) and rapid vacuum filtration through Whatman GF/C filters (pretreated with polyethyleneimine (0.1%) for at least 2 h). Tubes were rinsed with 2 mL of ice cold buffer D, which was also filtered, and the filters subsequently rinsed twice with 4 mL of ice cold buffer D. Before radioactivity was quantitated by liquid scintillation spectrometry, filters were shaken for 1 h in 5mL of scintillation fluid.

CP-55,940 and all cannabinoid analogues were prepared by suspension in assay buffer from a 1 mg/mL ethanolic stock without evaporation of the ethanol (final concentration of no more than 0.4%). When anandamide was used as a displacing ligand, experiments were performed in the presence of phenylmethylsulfonyl fluoride (50 μM). Competition assays were conducted with 1 nM [^{3}H]CP-55,940 or 1 nM [^{3}H]SR141716A and 6 concentrations (0.1 nM to 10 μM displacing ligands). Displacement IC_{50} values were originally determined by unweighted least-squares linear regression of log concentration-percent displacement data and then converted to K_i values using the method of Cheng and Prusoff.[32]

Acknowledgements

The work at Clemson was supported by grant DA03590, and that at Virginia Commonwealth University by grant DA03672 (Billy R. Martin), both from the National Institute on Drug Abuse.

References and Notes

1. Matsuda, L. A.; Lolait, S. J.; Brownstein, M. J.; Young, A. C.; Bonner, T. H. *Nature* **1990**, *346*, 561.
2. Herkenham, M.; Lynn, A. B.; Little, M. D.; Johnson, M. R.; Melvin, L. S.; De Costa, D. R.; Rice, K. C. *Proc. Natl. Acad. Sci. U.S.A.* **1990**, *87*, 1932.
3. Pertwee, R. G. *Curr. Med. Chem.* **1999**, *6*, 635.
4. Huffman, J. W.; Lainton, J. A. H. *Curr. Med. Chem.* **1996**, *3*, 101.
5. Munro, S.; Thomas, K. L.; Abu-Shar, M. *Nature (London)* **1993**, *365*, 61.
6. Breivogel, C. S.; Griffin, G.; Di Marzo, V.; Martin, B. R. *Mol. Pharmacol.* **2001**, 155.
7. Little, P. J.; Compton, D. R.; Johnson, M. R.; Melvin, L. S.; Martin, B. R. *J. Pharmacol. Exp. Ther.* **1988**, *247*, 1046.
8. 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**, *265*, 218.
9. Compton, D. R.; Aceto, M. D.; Lowe, J.; Martin, B. R. *J. Pharmacol. Exp. Ther.* **1996**, *277*, 586.
10. Zimmer, A.; Zimmer, A. M.; Hohmann, A. G.; Herkenham, M.; Bonner, T. L. *Proc. Natl. Acad. Sci. U.S.A.* **1999**, *96*, 5780.
11. Klein, T. W.; Friedman, H.; Specter, S. *J. Neuroimmunol.* **1998**, *83*, 102.

12. Buckley, N. E.; McCoy, K. L.; Mezey, E.; Bonner, T.; Zimmer, A.; Felder, C. C.; Glass, M.; Zimmer, A. *Eur. J. Pharmacol.* **2000**, *396*, 141.
13. Griffin, G.; Wray, E. J.; Tao, Q.; McAllister, S. D.; Rorrer, W. K.; Aung, M. M.; Martin, B. R.; Abood, M. E. *Eur. J. Pharmacol.* **1999**, *317*, 117.
14. Lu, Q.; Straiker, A.; Lu, Q.; Maguire, G. *Vis. Neurosci.* **2000**, *17*, 91.
15. Baker, D.; Pryce, G.; Croxford, J. L.; Brown, P.; Pertwee, R. G.; Huffman, J. W.; Layward, L. *Nature (London)* **2000**, *404*, 84.
16. Sanchez, C.; de Ceballos, M. L.; Gómez del Pulgar, T.; Rueda, D.; Corbacho, C.; Velasco, G.; Galve-Roperh, I.; Huffman, J. W.; Ramón y Cajal, S.; Guzmán, M. *Cancer Res.* **2001**, *61*, 5784.
17. Malan, T. P.; Ibrahim, M. M.; Deng, H.; Liu, Q.; Mata, H. P.; Vanderah, T.; Porreca, F.; Makriyannis, A. *Pain* **2001**, *93*, 239.
18. Recht, L. D.; Salmonsen, R.; Rosetti, R.; Jang, T.; Pipia, G.; Kubiatowski, T.; Karim, P.; Ross, A. H.; Zurier, R.; Litofsky, N. S.; Burstein, S. *Biochem. Pharmacol.* **2001**, *62*, 755.
19. Huffman, J. W.; Yu, S.; Showalter, V.; Abood, M. E.; Wiley, J. L.; Compton, D. R.; Martin, B. R.; Bramblett, R. D.; Reggio, P. H. *J. Med. Chem.* **1996**, *39*, 3875.
20. Huffman, J. W.; Liddle, J.; Yu, S.; Aung, M. M.; Abood, M. E.; Wiley, J. L.; Martin, B. R. *Bioorg. Med. Chem.* **1999**, *7*, 2905.
21. Gareau, Y.; Dufresne, C.; Gallant, M.; Rochette, C.; Sawyer, N.; Slipetz, D. M.; Tremblay, N.; Weech, P. K.; Metters, K. M.; Labelle, M. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 189.
22. Hanus, L. R.; Fride, E. *Proc. Natl. Acad. Sci. U.S.A.* **1999**, *96*, 14228.
23. Ross, R. A.; Brockie, H. C.; Stevenson, L. A.; Murphy, V. L.; Templeton, F.; Makriyannis, A.; Pertwee, R. G. *Br. J. Pharmacol.* **1999**, *126*, 665.
24. Dominianni, S. J.; Ryan, C. W.; De Armitt, C. W. *J. Org. Chem.* **1977**, *42*, 344.
25. Petrzilka, T.; Sikemeier, C. *Helv. Chim. Acta* **1967**, *50*, 1416.
26. (a) Ben Zvi, Z.; Mechoulam, R.; Burstein, S. H. *Tetrahedron Lett.* **1970**, 4495. (b) Inayama, S.; Sawa, A.; Hosoya, E. *Chem. Pharm. Bull.* **1974**, *22*, 1519. (c) Mahadevan, A.; Siegel, C.; Martin, B. R.; Abood, M. E.; Belatskaya, I.; Razdan, R. K. *J. Med. Chem.* **2000**, *43*, 3778.
27. Gemal, A. L.; Luche, J.-L. *J. Am. Chem. Soc.* **1981**, *103*, 5454.
28. Mechoulam, R.; Lander, N.; Breuer, A.; Zahalka, J. *Tetrahedron Asymmetry* **1990**, *1*, 315.
29. (a) Liddle, J.; Huffman, J. W.; Wiley, J. L.; Martin, B. R. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 2223. (b) Liddle, J.; Huffman, J. W. *Tetrahedron* **2001**, *57*, 7607.
30. Showalter, V. M.; Compton, D. R.; Martin, B. R.; Abood, M. E. *J. Pharmacol. Exp. Ther.* **1996**, *278*, 989.
31. Martin, B. R.; Compton, D. R.; Thomas, B. F.; Prescott, W. R.; Little, P. J.; Razdan, R. K.; Johnson, M. R.; Melvin, L. S.; Mechoulam, R.; Ward, S. J. *Pharmacol. Biochem. Behav* **1991**, *40*, 471.
32. Cheng, Y. C.; Prusoff, W. H. *Biochem. Pharmacol.* **1973**, *22*, 3099.