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Synthesis and pharmacology of 11-nor-1-methoxy-9-hydroxyhexahydrocannabinols and 11-nor-1-deoxy-9-hydroxyhexahydrocannabinols: New selective ligands for the cannabinoid CB_2 receptor

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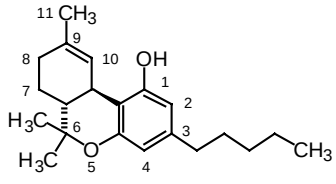
Abstract—Fourteen novel CB_2 receptor selective cannabinoids were synthesized via initial Lewis acid catalyzed rearrangement of resorcinol precursors to obtain the cannabinoid moiety. These are the 1-methoxy-9-hydroxyhexahydrocannabinols and the 1-deoxy-9-hydroxyhexahydrocannabinols, with 1′,1′-dimethylalkyl side chains of four to seven carbon atoms at C-3 of the cannabinoid nucleus. The cannabinols synthesized and described in this paper all exhibit greater affinity for the CB_2 receptor than for the CB_1 receptor. Exceptionally high CB_2 affinity was observed for 1-deoxy-9β-hydroxy-dimethylhexylhexahydrocannabinol (JWH-361, **9**, $n = 3$) $K_i = 2.7$ nM and 1-deoxy-9β-hydroxydimethylpentylhexahydrocannabinol (JWH-300, **9**, $n = 2$) $K_i = 5.3$ nM. In general, the stereochemistry of the 9-hydroxy group is important and the β-orientation enhances both CB_2 receptor affinity and selectivity.

1. Introduction

The active components of *Cannabis sativa* (marijuana) and their derivatives are classified as cannabinoids. The most potent and abundant cannabinoid found in the marijuana plant is Δ^9-tetrahydrocannabinol (THC, **1**), the structure of which was elucidated in 1964 by Gaoni and Mechoulam.[1] The medicinal value of marijuana has been known for centuries and its use almost certainly predates documented history. THC exhibits a diverse array of biological properties, including analgesic, anti-inflammatory, anti-emetic, anti-convulsive, and anti-cancer effects. The behavioral effects of cannabinoids in humans and animals are complex, and the mechanism(s) which elicits these effects has been the subject of investigation for many years.[2,3]

Following the discovery of the CB_1 and CB_2 receptors,[4,5] there has been a resurgence of interest in the medicinal chemistry and pharmacology of cannabinoids, which has resulted in significant advances in



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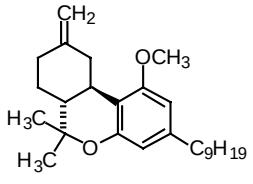

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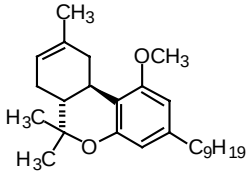

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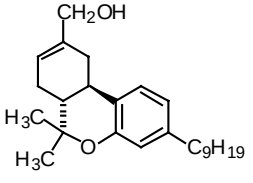

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Keywords: Cannabinoids; Structure–activity relationships; CB_2 cannabinoid receptors; Deoxycannabinoids.
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understanding the manner in which cannabinoids interact with biological systems. The CB_1 receptor is found primarily in the central nervous system and its activation is responsible for the psychotropic effects of marijuana, whereas the CB_2 receptor is almost exclusively located in tissues of the immune system such as the spleen, tonsil, and lymph nodes.[6–8] The CB_2 receptor is known to participate in regulating immune responses and/or inflammatory processes.[9–15] However, at the molecular level there remain many unanswered questions concerning the manner in which cannabinoid receptor ligands interact with these receptors.

Previous work reported by Felder et al. and Showalter et al. determined that traditional cannabinoids such as Δ^9-THC (**1**) have comparable CB_1 and CB_2 receptor affinities;[16,17] however, 1-methoxy $\Delta^{9(11)}$-THC-DMH (JWH-142, L759656, **2**) and 1-methoxy-Δ^8-THC-DMH (JWH-143, L759633, **3**) have high affinity for the CB_2 receptor, but little affinity for the CB_1 receptor (Table 1).[18,19] In 1996, it was observed that some cannabinoids lacking the characteristic hydroxyl group at C-1 have high affinity for the CB_2 receptor.[18] 1-Deoxy-11-hydroxy-Δ^8-THC-DMH (deoxy-HU-210, JWH-051, **4**) was found to have very high affinity for the CB_1 receptor ($K_i = 1.2 \pm 0.1$ nM) and exceptionally high affinity for the CB_2 receptor ($K_i = 0.032 \pm 0.019$ nM, Table 1). However, removal of the 11-hydroxy resulted in 3-(1′,1′-dimethylheptyl)-1-deoxy-Δ^8-THC (JWH-057, **5**) that was almost 10-fold selective for the CB_2 receptor (Table 1).[18] Subsequently, several 1-deoxy-Δ^8-THC analogs were prepared and a number of them were found to have significantly high selectivity for the CB_2 receptor.[20] The two most CB_2 selective ligands in this group are 3-(1′,1′-dimethylbutyl)-1-deoxy-Δ^8-THC (JWH-133, **6**) and 3-(1′,1′-dimethylpropyl)-1-deoxy-Δ^8-THC (JWH-139, **7**) with almost 200-fold and over 150-fold selectivity for the CB_2 receptor, respectively (Table 1).

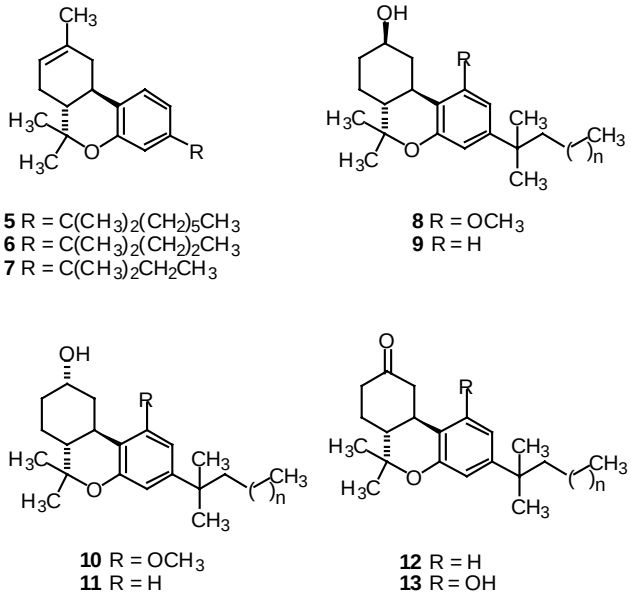


Table 1. Receptor affinities (means ± SEM) of 11-nor-9-hydroxyhexahydrocannabinols and related compounds

Compound	K_i (nM)		
	CB_1	CB_2	CB_1/CB_2
Δ^9-THC (**1**)	41 ± 2[a]	36 ± 10[b]	1.1
1-Methoxy-3-(1′,1′-dimethylheptyl)-$\Delta^{9(11)}$-THC (JWH-142, **2**)	529 ± 49[c]	35 ± 14[c]	15
1-Methoxy-3-(1′,1′-dimethylheptyl)Δ^8-THC (JWH-143, **3**)	924 ± 104[c]	65 ± 8[c]	14
1-Deoxy-11-hydroxy-3-(1′,1′-dimethylheptyl)-Δ^8-THC (JWH-051, **4**)	1.2 ± 0.1[d]	0.032 ± 0.02[d]	38
3-(1′,1′-Dimethylheptyl)-1-deoxy-Δ^8-THC (JWH-057, **5**)	23 ± 7[d]	2.9 ± 1.6[d]	8
3-(1′,1′-Dimethylbutyl)-1-deoxy-Δ^8-THC (JWH-133, **6**)	677 ± 132[c]	3.4 ± 1.0[c]	199
3-(1′,1′-Dimethylpropyl)-1-deoxy-Δ^8-THC (JWH-139, **7**)	2290 ± 505[c]	14 ± 10[c]	164
1-Deoxy-11-nor-9β-hydroxy-3-(1′,1′-dimethylheptyl)-HHC (JWH-102, **9**, $n = 4$)	7.9 ± 0.9[c]	5.2 ± 2.0[c]	1.5
1-Deoxy-11-nor-9α-hydroxy-3-(1′,1′-dimethylheptyl)-HHC (JWH-103, **11**, $n = 4$)	28 ± 3[c]	23 ± 7[c]	1.2
1-Methoxy-11-nor-9β-hydroxy-3-(1′,1′-dimethylbutyl)-HHC (JWH-298, **8**, $n = 1$)	812 ± 67	198 ± 23	4.1
1-Methoxy-11-nor-9α-hydroxy-3-(1′,1′-dimethylbutyl)-HHC (JWH-277, **10**, $n = 1$)	3905 ± 91	589 ± 65	6.6
1-Methoxy-11-nor-9β-hydroxy-3-(1′,1′-dimethylpentyl)-HHC (JWH-299, **8**, $n = 2$)	415 ± 50	30 ± 2	14
1-Methoxy-11-nor-9α-hydroxy-3-(1′,1′-dimethylpentyl)-HHC (JWH-278, **10**, $n = 2$)	906 ± 80	69 ± 6	13
1-Methoxy-11-nor-9β-hydroxy-3-(1′,1′-dimethylhexyl)-HHC (JWH-350, **8**, $n = 3$)	395 ± 20	12 ± 1	33
1-Methoxy-11-nor-9α-hydroxy-3-(1′,1′-dimethylhexyl)-HHC (JWH-349, **10**, $n = 3$)	376 ± 1	38 ± 4	10
1-Methoxy-11-nor-9β-hydroxy-3-(1′,1′-dimethylheptyl)-HHC (JWH-341, **8**, $n = 4$)	100 ± 8	10 ± 0.1	10
1-Methoxy-11-nor-9α-hydroxy-3-(1′,1′-dimethylheptyl)-HHC (JWH-340, **10**, $n = 4$)	135 ± 6	30 ± 1	4.5
1-Deoxy-11-nor-9β-hydroxy-3-(1′,1′-dimethylbutyl)-HHC (JWH-310, **9**, $n = 1$)	1059 ± 51	36 ± 3	29
1-Deoxy-11-nor-9α-hydroxy-3-(1′,1′-dimethylbutyl)-HHC (JWH-336, **11**, $n = 1$)	4589 ± 367	153 ± 15	30
1-Deoxy-11-nor-9β-hydroxy-3-(1′,1′-dimethylpentyl)-HHC (JWH-300, **9**, $n = 2$)	118 ± 16	5.3 ± 0.1	22
1-Deoxy-11-nor-9α-hydroxy-3-(1′,1′-dimethylpentyl)-HHC (JWH-301, **11**, $n = 2$)	295 ± 64	48 ± 4	6
1-Deoxy-11-nor-9β-hydroxy-3-(1′,1′-dimethylhexyl)-HHC (JWH-361, **9**, $n = 3$)	63 ± 3	2.7 ± 0.1	23
1-Deoxy-11-nor-9α-hydroxy-3-(1′,1′-dimethylhexyl)-HHC (JWH-362, **11**, $n = 3$)	127 ± 8	34 ± 5	3.8

[a] Ref. 27.
[b] Ref. 17.
[c] Ref. 20.
[d] Ref. 18.

Although structure–activity relationships (SAR) at the CB_1 receptor are reasonably well defined, those at the CB_2 receptor are not nearly as well understood.[19,21] It is known, however, that in both the 1-methoxy- and 1-deoxy-Δ^8-THC series that a C-11 hydroxyl group enhances affinity at both the CB_1 and CB_2 receptors.[22] It is also known that in the 1-methoxy-Δ^8-THC series 1′,1′-dimethylalkyl side chains of five to seven carbon atoms provide good affinity for the CB_2 receptor.[20] In the 1-deoxy-Δ^8-THC series compounds with a 1′,1′-dimethylalkyl C-3 side chain of two to seven carbon atoms all have high affinity for the CB_2 receptor. Also, 1-deoxy-2′-methyl-Δ^8-THCs with C-3 alkyl chains of three to seven carbon atoms have CB_2 receptor affinities of less than 195 nM.[23]

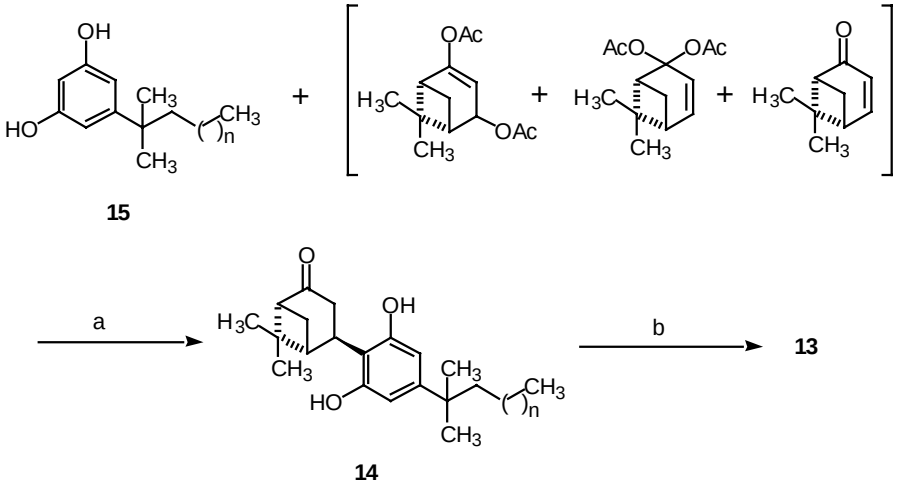
In order to further develop SAR at the CB_2 receptor and to develop additional selective ligands for the CB_2 receptor, we have carried out the synthesis of 11-nor-1-methoxy- and 11-nor-1-deoxy-9β-hydroxyhexahydrocannabinols (HHCs) with 1′,1′-dimethylbutyl to 1′,1′-dimethylheptyl C-3 side chains (**8** and **9**, $n = 1$–4). The 9α-epimers (**10** and **11**, $n = 1$–4) were also prepared to investigate the effect of stereochemistry at this center upon both CB_1 and CB_2 receptor affinities. We had previously reported the synthesis, CB_1 and CB_2 receptor affinities for two of the 1-deoxy-9-hydroxy-11-norhexahydrocannabinols (**9** and **11**, $n = 4$) and found that both these dimethylheptyl analogs have high and approximately equal affinity for both receptors. The 9β-hydroxy isomer has approximately 4-fold greater receptor affinity than the α-epimer at both receptors (Table 1).[20]

2. Results

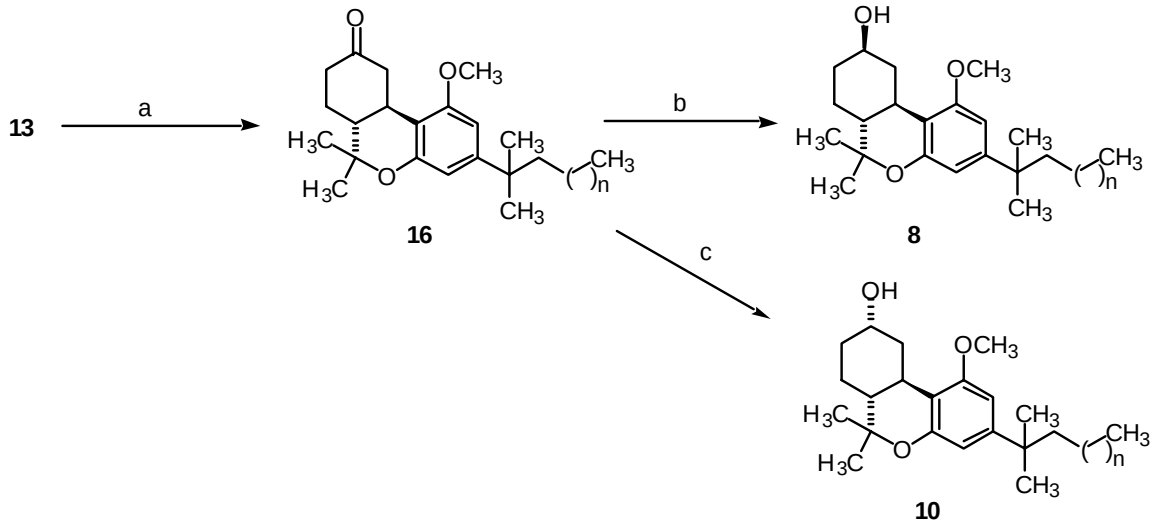
In our previous work, epimeric alcohols **9** and **11**, $n = 4$, were prepared by reduction of the corresponding ketone (deoxynabilone, **12**, $n = 4$), which was in turn prepared by the reaction of the aryllithium derived from 2-bromo-5-(1,1-dimethylheptyl)methoxybenzene with apoverbenone.[18,20] Although a similar procedure could have been employed in the synthesis of alcohols **9** and **11**, a more efficient approach employs cannabinoids **13**, $n = 1$–4. These common intermediates were then converted to the 1-methoxy (**8** and **10**) and 1-deoxy-HHCs (**9** and **11**). We had previously synthesized ketones similar to **11** using the reaction of aryllithium reagents derived from 1,3-dimethoxybenzene derivatives with apoverbenone.[24,25] An alternative approach that is more amenable to the synthesis of gram quantities of cannabinoids **13** ($n = 1$–4) is that of Tius et al.[26] In this approach, 4-(2,6-dihydroxy-4-[1′,1′-dimethylalkyl]phenyl)-6,6-dimethylbicyclo[3.1.1]heptan-2-ones (**14**, $n = 1$–4, Scheme 1) were prepared by the *p*-toluenesulfonic acid catalyzed reaction of an appropriately substituted resorcinol (**15**, $n = 1$–4) with the mixture of acetates and apoverbenone obtained by oxidation of nopinone with lead tetraacetate.[26] Tetrahydrocannabinols **13**, $n = 1$–4, were obtained by stannic chloride mediated rearrangement of **14**.

Cannabinoids **13** were converted to methoxy HHCs (**8** and **10**, $n = 1$–4) as shown in Scheme 2. Initial treatment with methyl iodide and base gave methyl ethers **16**, which upon reduction with lithium aluminum hydride gave the equatorial β-alcohols (**8**, $n = 1$–4). Stereoselective reduction with K-Selectride (potassium tri-*sec*-butylborohydride) afforded the axial α-alcohols (**10**, $n = 1$–4).

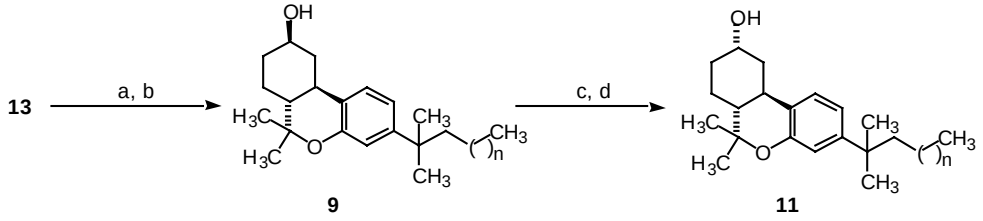
1-Deoxy-HHCs (**9** and **11**, $n = 1$–4) were prepared by the method employed previously for the synthesis of 1-deoxycannabinoids (Scheme 3).[20,22] Reaction of ketones **13**, $n = 1$–3, with sodium hydride and diethyl chlorophosphate gave the corresponding phosphate esters. Reduction with lithium in liquid ammonia removed the phosphate ester and reduced the carbonyl group to give the 9β-hydroxy-1-deoxycannabinoids (**9**, $n = 1$–3). For the preparation of the 9α-hydroxy-1-deoxycannabinoids (**11**, $n = 1$–3), alcohols **9** were oxidized to the corresponding ketones. Stereoselective reduction with K-Selectride gave the 1-deoxy-9α-hydroxy-HHCs.



Scheme 1. Reagents and conditions: (a) HOTs, $CHCl_3$, 25 °C; (b) $SnCl_4$, $CHCl_3$, 25 °C.



Scheme 2. Reagents and conditions: (a) CH_3I, K_2CO_3, acetone, reflux; (b) $LiAlH_4$, THF, −78 °C; (c) K-Selectride, THF, −78 to −25 °C, then NaOH, H_2O_2, EtOH.



Scheme 3. Reagents and conditions: (a) NaH/THF, 0 °C then $(C_2H_5O)_2P(O)Cl$; (b) Li/NH_3, THF, −78 °C; (c) CrO_3, acetone, 0 °C; (d) K-Selectride, THF, −78 to −25 °C, then NaOH, H_2O_2, EtOH.

The affinities of the 11-nor-1-methoxy- and 11-nor-1-deoxyhexahydrocannabinols 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.[27] 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.[17] The results of these determinations are summarized in Table 1. Also included in Table 1 are the receptor affinities for Δ^9-THC (**1**), JWH-142 (**2**), JWH-143 (**3**), JWH-051 (**4**), JWH-057 (**5**), JWH-133 (**6**), and JWH-139 (**7**) that were reported previously.

With the exception of the dimethylheptyl analogs (JWH-341, **8** and JWH-340 **10**, $n = 4$), none of the 1-methoxy-9-hydroxy-HHCs (**8** and **10**, $n = 1$–3) has appreciable affinity for the CB_1 receptor, with $K_i > 375$ nM. The dimethylheptyl compounds, JWH-341 and JWH-340, have modest affinity for the CB_1 receptor with $K_i = 100 \pm 8$ nM for the 9β-isomer (JWH-341, **8**, $n = 4$) and $K_i = 135 \pm 6$ nM for the α-epimer (JWH-340, **10**, $n = 4$). All of these 1-methoxy-9-hydroxy-HHCs have 4- to 33-fold greater affinity for the CB_2 receptor than for the CB_1 receptor. With the exception of the dimethylbutyl analogs (JWH-298, **8** and, JWH-277, **10**, $n = 1$), all of the 1-methoxy HHCs have significant affinity for the CB_2 receptor with $K_i < 70$ nM. One of these compounds, the 9β-hydroxy-3-(1′,1′-dimethylhexyl)-HHC (JWH-350, **8**, $n = 3$), shows excellent, 33-fold, selectivity for the CB_2 receptor with $K_i = 12 \pm 1$ nM at the CB_2 receptor and $K_i = 395 \pm 20$ nM at the CB_1 receptor. The 9β-hydroxydimethylpentyl analog (JWH-299, **8**, $n = 2$) also has useful CB_2 selectivity with $K_i = 30 \pm 2$ nM at CB_2 and $K_i = 415 \pm 50$ at the CB_1 receptor.

With the exception of the 11-nor-1-deoxy-9-hydroxy-3-(1′,1′-dimethylbutyl)-HHCs (JWH-310, **9** and JWH-336, **11**, $n = 1$), the 1-deoxy compounds have a significantly higher affinity for the CB_1 receptor than the corresponding 1-methoxy analogs. The 1′,1′-dimethylheptyl analogs (JWH-102, **9** and JWH-103, **11**, $n = 4$), which we reported previously, both have very high affinity for the CB_1 receptor.[20] The dimethylpentyl- and dimethylhexyl-HHCs have modest CB_1 receptor affinities ranging from $K_i = 63 \pm 3$ nM for the 9β-hydroxydimethylhexyl analog (JWH-361, **9**, $n = 3$) to $K_i = 295 \pm 64$ nM for the 9α-hydroxydimethylpentyl compound (JWH-301, **11**, $n = 2$). These 11-nor-1-deoxy-HHCs all have from high to modest affinity for the CB_2 receptor. The 9α-hydroxydimethylbutyl analog (JWH-336, **11**, $n = 1$) has the least affinity for the CB_2 receptor with $K_i = 153 \pm 15$ nM. The other 1-deoxy analogs all have $K_i < 50$ nM at the CB_2 receptor. One of

these compounds, the 9β-hydroxydimethylbutyl analog (JWH-310, **9**, $n = 1$), has 29-fold selectivity for the CB_2 receptor with the desirable combination of high affinity for the CB_2 receptor, $K_i = 36 \pm 3$ nM, and little affinity for the CB_1 receptor, $K_i = 1059 \pm 51$ nM.

3. Discussion

In common with other 1-methoxy-Δ^8-THCs lacking a 11-hydroxyl substituent, hexahydrocannabinols **8** and **10** ($n = 1$–3) have little affinity for the CB_1 receptor with $K_i = 376$–3905 nM (Table 1).[19,21–23] The dimethylheptyl analogs (**8** and **10**, $n = 4$) have considerably higher, but still modest, affinity for this receptor. The equatorial β-isomer (JWH-341, **8**, $n = 4$) with $K_i = 100 \pm 8$ nM has a slightly higher affinity for the CB_1 receptor than the axial α-epimer (JWH-340, **10**, $n = 4$) with $K_i = 135 \pm 6$ nM. These CB_1 receptor affinities are intermediate between those of the corresponding 1-methoxy- and 11-hydroxy-1-methoxy-3-(1′,1′-dimethylalkyl)-Δ^8-THCs.[21,22] It has been suggested that in a 1-deoxy-Δ^8-THC a cannabinoid 11-hydroxyl group may serve as a surrogate for the phenolic 1-hydroxyl group in a hydrogen bonding interaction with Lys 192 of the CB_1 receptor.[18] This effect is also seen in a series of 11-hydroxy-1-methoxy-Δ^8-THCs.[22] In the 1-methoxy-11-nor-9-hydroxy-HHCs, this effect would appear to be operative, but to a considerably lesser extent.

With the exception of the 1′,1′-dimethylbutyl analogs (**8** and **10**, $n = 1$) these 1-methoxy-HHCs all have from moderate to high affinity for the CB_2 receptor. The dimethylhexyl and dimethylheptyl compounds (**8** and **10**, $n = 3$ and 4) have similar high affinity for the CB_2 receptor. The 9β-(equatorial alcohols), JWH-350 (**8**, $n = 3$), $K_i = 12 \pm 1$ nM, and JWH-341 (**8**, $n = 4$) with $K_i = 10 \pm 0.1$ nM have somewhat greater affinity for the CB_2 receptor than the corresponding axial epimers. For the 9α-(axial) isomers, the dimethylhexyl compound (JWH-349, **10**, $n = 3$) has $K_i = 38 \pm 4$ nM and the dimethylheptyl analog (JWH-340, **10**, $n = 4$) has $K_i = 30 \pm 1$ nM. Three of these methoxy HHCs exhibit good selectivity for the CB_2 receptor with the combination of high affinity for the CB_2 receptor and very weak affinity for the CB_1 receptor. One of these is JWH-350 (**8**, $n = 3$) with 33-fold affinity for the CB_2 receptor. For this compound $K_i = 395 \pm 20$ nM at CB_1 and $K_i = 12 \pm 1$ nM at the CB_2 receptor. The other two compounds, JWH-299 (**8**, $n = 2$) and JWH-349 (**10**, $n = 3$), with 14- and 10-fold selectivity for the CB_2 receptor are considerably less selective than JWH-350. For JWH-299 at the CB_2 receptor $K_i = 30 \pm 2$ nM and at the CB_1 receptor $K_i = 415 \pm 50$ nM. At the CB_2 receptor JWH-349 has $K_i = 38 \pm 4$ nM and at CB_1 $K_i = 376 \pm 1$ nM.

In the 1-deoxy series (**9** and **11**, $n = 1$–4), all these compounds exhibit selectivity for the CB_2 receptor, however the previously reported 1′,1′-dimethylheptyl compounds (JWH-102, **9** and JWH-103, **11**, $n = 4$) have quite high affinity for the CB_1 receptor.[20] The 9β-alcohol (JWH-102) has very high CB_1 receptor affinity with $K_i = 7.9 \pm 0.9$ nM, while the 9α-epimer has only slightly less affinity with $K_i = 28 \pm 3$ nM. For both these compounds the CB_2 receptor affinities are only slightly higher than those at the CB_1 receptor. For the 1-deoxy-1′,1′-dimethylhexyl analogs, the 9β-isomer (JWH-361, **9**, $n = 3$) has moderate affinity for the CB_1 receptor with $K_i = 63 \pm 3$ nM and the 9α-alcohol (JWH-362, **11**, $n = 3$) has modest affinity, $K_i = 127 \pm 8$ nM. The 1-deoxy-9β-hydroxy-3-(1′,1′-dimethylpentyl)-HHC (JWH-300, **9**, $n = 2$) also has some affinity for the CB_1 receptor with $K_i = 118 \pm 16$ nM. However, the 9α-hydroxy-3-(1′,1′-dimethylpentyl)-isomer (JWH-301, **11**, $n = 2$) and the 1′,1′-dimethylbutyl-HHCs (JWH-310, **9** and JWH-336, **11**, $n = 1$) have from slight to effectively no affinity for the CB_1 receptor with $K_i = 295 \pm 64$ nM for JWH-301 to $K_i = 4589 \pm 367$ nM (JWH-336).

With the exception of 11-nor-9α-hydroxy-3-(1′,1′-dimethylbutyl)-HHC (JWH-336, **11**, $n = 1$) with $K_i = 153 \pm 15$ nM all the 1-deoxy compounds have from good to very high affinity for the CB_2 receptor. The highest CB_2 receptor affinity in this series is for the 9β-hydroxy dimethylhexyl analog (JWH-361, **9**, $n = 3$) with $K_i = 2.7 \pm 0.1$ nM. The CB_2 receptor affinities for the other 1-deoxy-11-nor-9-hydroxy-3-(1′,1′-dimethylalkyl)-HHCs range from $K_i = 5.2 \pm 2$ nM (JWH-102, **9**, $n = 4$) to $K_i = 48 \pm 4$ nM for the 9α-hydroxydimethylpentyl analog (JWH-301, **11**, $n = 2$). Although all of these 1-deoxy-HHCs have from 1.2- to 30-fold selectivity for the CB_2 receptor, the only one with the desirable properties of high affinity for the CB_2 receptor and little affinity for the CB_1 receptor is the 9β-hydroxy-3-(1′,1′-dimethylbutyl) analog (JWH-310, **9**, $n = 1$) with $K_i = 1059 \pm 51$ nM at the CB_1 receptor and $K_i = 36 \pm 3$ nM at the CB_2 receptor. 1-Deoxy-11-nor-9β-hydroxy-3-(1′,1′-dimethylpentyl)-HHC (JWH-300, **9**, $n = 2$) has modest affinity, $K_i = 118 \pm 16$ nM, for the CB_1 receptor and very high affinity for the CB_2 receptor with $K_i = 5.3 \pm 0.1$ nM.

With the exception of the 1-methoxy-11-nor-9-hydroxy-3-(1′,1′-dimethylhexyl)-HHCs (JWH-350, **8** and JWH-349, **10**, $n = 3$) the CB_1 receptor affinities of the equatorial 9β-alcohols are from somewhat to significantly higher than those of the axial 9α-alcohols. For the epimeric 1-methoxy-3-(1′,1′-dimethylhexyl) analogs (JWH-350 and JWH-349) the CB_1 receptor affinities are identical. The CB_2 receptor affinities of the 9β-alcohols in both the 1-methoxy and the 1-deoxy series are from slightly more than 2-fold to more than 12-fold greater than those of the axial 9α-alcohols.

A number of years ago, Reggio et al. carried out a computational study that indicated a correlation between the stereochemical orientation of substituents at C-9 of the classical cannabinoid skeleton and the cannabinoid activity of a compound.[28] The results of this study indicated that classical cannabinoid receptor ligands similar to Δ^9-THC (**1**) in which the substituent at C-9 was oriented toward the bottom (α) face of the molecule had little or no cannabinoid activity. The cannabinoid activities cited by Reggio were based upon drug discrimination studies in rhesus monkeys and were carried out prior to the recognition of the existence of cannabinoid

receptor subtypes. Since the overt behavioral effects of cannabinoids are considered to be mediated through the CB_1 receptor, it was probable that the conclusions reached by Reggio et al. apply to that receptor. This was verified subsequently by the synthesis and modeling studies of the C-9 epimers of Δ^7-THC. The 9β-methyl isomer, in which the methyl group is directed above the plane of the molecule, has K_i = 71.5 nM at the CB_1 receptor and was somewhat less potent in vivo than Δ^9-THC[29] (**1**). The 9α-epimer, in which the methyl group is oriented behind the plane of the ring system, has K_i = 304 nM and is much less potent in vivo. The CB_1 receptor affinities of the 1-methoxy- and 1-deoxy-11-nor-9-hydroxy-HHCs in general follow the same trend. Although the original observations regarding the stereochemical orientation of the C-9 substituent pertained to the CB_1 receptor, the same trends are observed at the CB_2 receptor in the 11-nor-9-hydroxy-HHC series.

4. Conclusions

Three of these 1-methoxy- and 1-deoxy-11-nor-9-hydroxy-3-(1′,1′-dimethlyalkyl)-hexahydrocannabinols have moderate 22- to 33-fold selectivity for the cannabinoid CB_2 receptor with the desirable combination of good affinity for the CB_2 receptor and little affinity for the CB_1 receptor. Two of these selective ligands are 1-deoxy analogs, JWH-300 (**9**, n = 2) and JWH-310 (**9**, n = 1), and one, JWH-350 (**8**, n = 3), is a 1-methoxy-HHC. Although these compounds are selective for the CB_2 receptor, they are not nearly as selective as JWH-133 (**6**), JWH-139 (**7**) or several 2′-methyl-Δ^8-THC analogs.[23] Two additional 1-methoxy analogs, JWH-299 (**8**, n = 2) and JWH-349 (**10**, n = 3), have some, 14- and 10-fold, selectivity, respectively, for the CB_2 receptor. These compounds were all synthesized from the corresponding 11-nor-9-keto-3-(1′,1′-dimethylalkyl)-Δ^8-hexahydrocannabinols (**14**, n = 1–4). Hexahydrocannabinols **14** were synthesized by a variation of a procedure developed by Tius et al.[26] In common with other cannabinoids, CB_1 receptor affinity increased as the length of the C-3 alkyl side chain increased from four to seven carbon atoms, and in general the 9β-hydroxy analogs had somewhat greater affinity for both the CB_1 and CB_2 receptors than the 9α-epimers. This steric effect was greater at the CB_2 receptor than at the CB_1 receptor.

5. Experimental

5.1. General

^{1}H 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 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.

5.2. 11-Nor-3-(1′,1′-dimethylbutyl)-9-keto-hexahydrocannabinol (13, n = 1)

To a solution of 1.39 g (7.14 mmol) of dimethylbutyl resorcinol (**15**, n = 1) and 1.33 g (7.0 mmol) of p-TsOH in 75 mL of $CHCl_3$ was added with stirring 1.52 g of the mixture of acetates derived from the $Pb(OAc)_4$ oxidation of nopinone.[26] The reaction mixture was stirred at ambient temperature for 48 h, ether was added, and the resultant solution was washed with 10% $NaHCO_3$, water, dried ($MgSO_4$), and concentrated in vacuo to give 1.99 g (95%) of **14**, n = 1, as a brown paste. The unstable crude product was used immediately without purification.

To a solution of 1.01 g (3.05 mmol) of 4-(2,6-dihydroxy-4-[1′,1′-dimethylbutyl]-phenyl)-6,6-dimethylbicyclo[3.1.1]-heptan-2-one (**14**, n = 1) in 70 mL $CHCl_3$ was added 11 mL (11 mmol) of 1 M $SnCl_4$ in $CHCl_3$ with stirring under an argon atmosphere. The reaction mixture was stirred at room temperature for 21 h, poured onto crushed ice, and extracted with ether. The organic extract was washed with 1 M aqueous HCl, water, 5% aqueous $NaHCO_3$, dried ($MgSO_4$), and concentrated in vacuo. The residue was chromatographed (hexanes/ethyl acetate, 3:1) to give 0.475 g (47%) of **13**, n = 1 as a brown paste: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.78–0.82 (m, 4H), 1.02–1.28 (m, 2H), 1.12 (s, 3H), 1.20 (s, 6H), 1.50 (s, 3H), 1.50–1.60 (m, 2H), 1.90–2.01 (m, 1H), 2.15–2.19 (m, 2H), 2.47–2.54 (m, 1H), 2.61–2.67 (m, 1H), 2.86–2.94 (m, 1H), 4.14–4.17 (m, 1H), 6.35 (d, J = 1.6 Hz, 1H), 6.39 (d, J = 1.6 Hz, 1H), 7.92 (1H, br s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.0, 17.9, 18.8, 26.8, 27.8, 28.6, 28.7, 34.7, 37.4, 40.8, 44.9, 46.8, 47.3, 76.6, 105.5, 106.9, 107.7, 150.7, 154.1, 155.0, 214.1.

5.3. 1-Methoxy-11-nor-3-(1′,1′-dimethylbutyl)-9-keto-hexahydrocannabinol (16, n = 1)

To a solution of 0.079 g (0.239 mmol) of **13**, n = 1 in 2.5 mL of dry acetone was added with stirring 0.265 g K_2CO_3. The reaction mixture was stirred at ambient temperature for 15 min and 0.1 mL (1.60 mmol) of iodomethane was added. The reaction mixture was stirred at reflux under nitrogen for 6 h. The hot reaction mixture was filtered, the residue was washed with hot acetone, and the filtrate was dried ($MgSO_4$) and concentrated in vacuo to give 0.083 g (100%) of **16**, n = 1, as a transparent paste: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.76–0.81 (m, 4H), 0.98–1.22 (m, 2H), 1.13 (s, 3H), 1.21 (s, 6H), 1.43 (s, 3H), 1.43–1.51 (m, 2H), 1.86–1.95 (m, 1H), 2.00–2.13 (m, 2H), 2.37–2.41 (m, 1H) 2.50–2.59 (m, 1H), 2.74–2.79 (m, 1H), 3.68–3.80 (m, 1H), 3.79 (s, 3H), 6.32–6.33 (d, J = 1.7 Hz, 1H), 6.39–6.40 (d, J = 1.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.7, 18.7, 26.5, 27.7, 28.7, 31.0, 34.5, 37.7, 40.7, 45.7, 46.9, 47.4, 54.9, 76.6, 100.6, 108.0, 109.3, 150.4, 153.8, 158.1, 211.2.

5.4. 1-Methoxy-11-nor-3-(1′,1′-dimethylbutyl)-9β-hydroxy-hexahydrocannabinol (JWH-298, 8, *n* = 1)

To a solution of 0.097 g, (0.28 mmol) of 1-methoxy-11-nor-3-(1′,1′-dimethylbutyl)-9-keto-hexahydrocannabinol (**16**, *n* = 1) in 2 mL of dry THF was added with stirring at −78 °C 0.029 g, (0.69 mmol) of 95% $LiAlH_4$. The reaction mixture was stirred overnight, quenched with water, and extracted with ether. The organic extract was washed with brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was chromatographed (hexanes/ethyl acetate, 3:1) to give 0.081 g (84%) of JWH-298 as a light brown paste: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.79–0.84 (t, J = 7.2 Hz, 3H), 1.03–1.40 (m, 6H), 1.15 (s, 3H), 1.24 (s, 6H), 1.41 (s, 3H), 1.49–1.54 (m, 2H), 1.85–1.90 (m, 2H), 2.14–2.17 (br s, 1H), 2.39–2.47 (td, J = 2.4, 11.2 Hz, 1H), 3.33–3.37 (m, 1H), 3.78 (s, 3H), 3.78–3.86 (m, 1H), 6.35–6.36 (d, J = 1.4 Hz, 1H), 6.40–6.41 (d, J = 1.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.7, 17.9, 18.8, 26.0, 27.8, 28.6, 28.8, 33.5, 35.7, 37.7, 39.3, 46.9, 48.5, 54.9, 70.7, 76.6, 100.5, 108.1, 110.1, 149.7, 154.0, 158.3; MS(EI) *m*/*z*: 346 (32), 304 (100), 286 (24), 221 (15), 192 (28); HRMS: Calcd for $C_{22}H_{34}O_3$ 346.2508. Found: 346.2508.

5.5. 1-Methoxy-11-nor-3-(1′,1′-dimethylbutyl)-9α-hydroxyhexahydrocannabinol (JWH-277, 10, *n* = 1)

To a solution of 0.083 g (0.24 mmol) of 1-methoxy-11-nor-3-(1′,1′-dimethylbutyl)-9-keto-hexahydrocannabinol (**16**, *n* = 1) in 2 mL of dry THF was added with stirring at −78 °C 1 mL (1.0 mmol) of K-Selectride (1.0 M in THF). The reaction mixture was allowed to warm to room temperature and stirred overnight. After quenching with 3 mL of water, 10 mL of ethanol, 4 mL of 1 M aqueous NaOH, and 4 mL of 30% H_2O_2 were added. After stirring for 20 min ,the mixture was extracted with ether and the organic extract was washed with brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was chromatographed (hexane/ethyl acetate, 3:1) to give 0.049 g (60%) of JWH-277 as a white solid, mp 76–78 °C: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.79–0.84 (t, J = 7.1 Hz, 3H), 1.10 (s, 3H), 1.06–1.30 (m, 3H), 1.24 (s, 6H), 1.38 (s, 3H), 1.46–1.56 (m, 4H), 1.56–1.66 (m, 2H), 1.82 (br s, 1H), 1.93–1.98 (m, 1H), 2.87–2.91 (m, 1H), 3.16–3.21 (m, 1H), 3.79 (s, 3H), 4.23 (br s, 1H), 6.35 (d, J = 1.5 Hz, 1H), 6.40 (d, J = 1.6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.7, 17.9, 19.0, 22.6, 27.6, 28.7, 28.8, 29.0, 33.2, 37.2, 37.7, 46.9, 49.3, 55.1, 66.8, 76.6, 100.7, 108.2, 110.8, 149.5, 154.3, 158.4; MS(EI) *m*/*z*: 346 (31), 304 (100), 285 (43), 207 (24), 192 (26), 178 (16); HRMS: Calcd for $C_{22}H_{34}O_3$ 346.2508. Found: 346.2504.

5.6. 1-Deoxy-11-nor-3-(1′,1′-dimethylbutyl)-9β-hydroxy-hexahydrocannabinol (JWH-310, 9, *n* = 1)

To a solution of 0.49 (1.49 mmol) of **13**, *n* = 1, in 5 mL of dry THF under a nitrogen atmosphere at 0 °C was added with stirring 0.080 g (2.0 mmol) of NaH (60% dispersion in oil). The reaction mixture was stirred at 0 °C for 15 min and 0.43 mL (2.97 mmol) of diethyl chlorophosphate was added dropwise. The reaction mixture was allowed to warm to room temperature and stirred for 3 h. After dilution with ether, the resulting solution was washed with 10% aqueous NaOH, and brine. After drying ($MgSO_4$), the solution was concentrated in vacuo and the crude product was chromatographed (hexanes/ethyl acetate, 3:1) to give 0.54 g (79%) of the phosphate ester as a yellow oil that was used in the next step without further purification: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.80–0.85 (m, 4H), 1.02–1.11 (m, 2H), 1.14 (s, 3H), 1.27 (s, 6H), 1.29–1.40 (m, 6H), 1.49 (s, 3H), 1.51–1.56 (m, 2H), 1.94–2.10 (m, 1H), 2.15–2.24 (m, 2H), 2.42–2.57 (m, 1H), 2.58–2.60 (m, 1H), 2.98–3.02 (m, 1H), 3.54–3.61 (m, 1H), 4.17–4.27 (m, 4H), 6.65 (s, 1H), 6.84 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.4, 15.8, 15.9, 17.6, 26.3, 27.4, 28.2, 28.4, 34.2, 37.3, 40.3, 45.4, 46.4, 47.2, 64.3, 64.4, 76.6, 110.1, 111.8, 112.5, 112.6, 148.9, 150.4, 153.9, 209.3.

To a solution of 0.51 g lithium in 5 mL of liquid NH_3 at −78 °C was added 0.134 g (0.29 mmol) of the above phosphate ester in 3 mL of dry THF and the reaction mixture was stirred for 2 h. Excess lithium was quenched with NH_4Cl and the ammonia was allowed to evaporate. The mixture was diluted with water, extracted with ether, the organic extract was dried ($MgSO_4$) and concentrated in vacuo. The residue was chromatographed (hexanes/ethyl acetate, 4:1) to give 0.044 g (48%) of JWH-310 as a white solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.79–0.83 (t, J = 7.1 Hz, 3H), 1.0–1.40 (m, 6H), 1.16 (s, 3H), 1.24 (s, 6H), 1.41 (s, 3H), 1.49–1.55 (m, 2H), 1.82 (m, 2H), 2.11–2.15 (m, 1H), 2.14–2.49 (m, 1H), 2.69–2.73 (m, 1H), 3.77–3.84 (m, 1H), 6.74 (d, J = 1.9 Hz, 1H), 6.81–6.85 (dd, J = 1.9, 8.1 Hz, 1H), 7.09–7.12 (d, J = 8.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.7, 17.9, 25.8, 28.1, 28.7, 28.8, 33.7, 35.3, 37.4, 39.7, 46.2, 46.9, 70.5, 76.6, 114.6, 117.5, 121.0, 125.1, 149.7, 152.7; MS(EI) *m*/*z*: 316 (33), 274 (32), 273 (100), 255 (8); HRMS: Calcd for $C_{25}H_{40}O_3$ 316.2402. Found: 316.2406.

5.7. 1-Deoxy-11-nor-3-(1′,1′-dimethylbutyl)-9-keto-hexahydrocannabinoid (12, *n* = 1)

A solution of 0.100 g (0.316 mmol) of 1-deoxy-11-nor-3-(1′,1′-dimethylbutyl)-9β-hydroxy-hexahydrocannabinol (**9**, *n* = 1) in the minimum volume of acetone was stirred with cooling (ice bath) and Jones' reagent was added dropwise until the reaction mixture maintained a dark orange color. The reaction mixture was stirred for 4 h, quenched with ethanol, and the resulting solution was decanted. The green residue was washed twice with acetone and the organic phases were combined. To this mixture saturated aqueous $NaHCO_3$ was added dropwise until the pH was neutral. Saturated brine was added and the reaction mixture was extracted with ether. The extracts were dried ($MgSO_4$) and concentrated in vacuo. The crude product was purified by chromatography (hexane/ethyl acetate, 3:1) to give 0.033 g (33%) of **12**, *n* = 1, as a white solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.79–0.85 (t, J = 7 Hz, 3H), 1.01–1.23 (m, 3H), 1.17 (s, 3H), 1.25 (s, 6H), 1.48 (s, 3H), 1.49–1.58 (m, 2H), 1.88–1.95 (m, 1H), 2.15–2.18 (m, 1H), 2.27–2.54 (m, 3H), 2.86–2.88 (m, 1H,), 3.05–3.12 (m, 1H,), 6.79–6.81 (d,

J = 1.7 Hz, 1H), 6.84–6.88 (dd, J = 8.0, 1.8 Hz, 1H), 6.98–7.01 (d, J = 8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.8, 19.7, 26.6, 27.0, 28.5, 28.8, 35.4, 36.4, 40.3, 44.5, 45.8, 47.4, 77.1, 114.9, 118.0, 125.2, 150.1, 153.0, 213.0.

5.8. 1-Deoxy-11-nor-3-(1′,1′-dimethylbutyl)-9α-hydroxyhexahydrocannabinol (JWH-336, 11, *n* = 1)

Deoxycannabinol **11**, n = 1, was prepared from 1-deoxy-11-nor-3-(1′,1′-dimethylbutyl)-9-keto-hexahydrocannabinoid (**12**, n = 1) by the procedure used to prepare methoxy hexahydrocannabinol **10**, n = 1. From 0.091 g (0.29 mmol) of ketone **16**, n = 1, there was obtained after chromatography (hexanes/ethyl acetate, 3:1) 0.067 g (73%) of JWH-336 as a pale brown paste: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.78–0.83 (t, J = 7.1 Hz, 3H), 1.02–1.13 (m, 3H), 1.20 (s, 3H), 1.24 (s, 6H), 1.40 (s, 3H), 1.44–1.57 (m, 4H), 1.61–1.64 (m, 2H), 1.83 (br s, 1H), 1.91–1.96 (m, 1H), 2.50–2.55 (m, 1H), 2.80–2.89 (m, 1H), 4.26–4.27 (m, 1H), 6.74 (d, J = 1.8 Hz, 1H), 6.79–6.83 (dd, J = 1.8, 8.1 Hz, 1H), 7.06–7.08 (d, J = 8.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.7, 17.9, 20.2, 21.5, 27.8, 28.7, 28.8, 28.9, 32.7, 37.3, 37.3, 37.6, 47.0, 66.1, 76.6, 114.5, 117.3, 121.8, 125.1, 149.4, 152.9; MS(EI) *m*/*z*: 316 (43), 274 (40), 273 (100), 255 (51), 190 (13), 147 (13); HRMS: Calcd for $C_{21}H_{32}O_2$ 316.2402. Found: 316.2398.

5.9. 11-Nor-3-(1′,1′-dimethylpentyl)-9-keto-hexahydrocannabinol (13, *n* = 2)

Resorcinol **14**, n = 2, was prepared by the method described above for the preparation of **14**, n = 1. From 1.38 g (6.63 mmol) of dimethylpentyl resorcinol (**15**, n = 2) there was obtained 2.15 g (96%) of **14**, n = 2, as an unstable brown solid that was used without purification.

Cannabinoid **13**, n = 2, was prepared by the procedure described above for the preparation of **13**, n = 1. From 1.708 g (4.97 mmol) of 4-(2,6-dihydroxy-4-[1′,1′-dimethylpentyl]-phenyl)-6,6-dimethylbicyclo[3.1.1]heptan-2-one (**14**, n = 2) there was obtained 0.654 g (38%) of **13**, n = 2, as a light brown transparent paste: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.79–0.85 (m, 4H), 1.05–1.21 (m, 4H), 1.14 (s, 3H), 1.21 (s, 6H), 1.48 (s, 3H), 1.50–1.62 (m, 2H), 1.90–2.02 (m, 1H), 2.05–2.20 (m, 2H), 2.43–2.54 (m, 1H), 2.63–2.66 (m, 1H), 2.86–3.04 (m, 1H), 4.12–4.17 (m, 1H), 6.36 (s, 2H), 7.41 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.0, 18.9, 23.4, 26.9, 27.9, 28.7, 34.7, 37.3, 40.8, 44.1, 44.9, 47.4, 76.6, 105.5, 107.0, 150.8, 154.9, 213.5.

5.10. 1-Methoxy-11-nor-3-(1′,1′-dimethylpentyl)-9-keto-hexahydrocannabinol (16, *n* = 2)

Methoxycannabinoid **16**, n = 2, was prepared by the procedure described above for the preparation of **16**, n = 1. From 0.150 g (0.436 mmol) of **13**, n = 1, there was obtained 0.149 g (95%) of **16**, n = 2, as a pale yellow transparent paste: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.72–0.77 (m, 4H), 0.92–1.00 (m, 4H), 1.08 (s, 3H), 1.16 (s, 6H), 1.39 (s, 3H), 1.43–1.52 (m, 2H), 1.82–1.90 (m, 1H), 2.01–2.09 (m, 2H), 2.33–2.39 (m, 1H), 2.46–2.55 (m, 1H), 2.70–2.78 (m, 1H), 3.56–3.73 (m, 1H), 3.73 (s, 3H), 6.29 (s, 1H), 6.34–6.35 (d,J = 1.3 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.9, 18.6, 23.2, 26.5, 26.7, 27.7, 28.6, 28.7, 34.4, 37.5, 40.6, 44.0, 45.6, 47.3, 54.8, 76.4, 100.4, 108.0, 109.2, 150.3, 153.7, 158.0, 210.9.

5.11. 1-Methoxy-11-nor-3-(1′,1′-dimethylpentyl)-9β-hydroxyhexahydrocannabinol (JWH-299, 8, *n* = 2)

Methoxycannabinol **8**, n = 2, was prepared by the method described above for the preparation of **8**, n = 1. From 0.067 g (0.19 mmol) of 1-methoxy-11-nor-3-(1′,1′-dimethylpentyl)-9-keto-hexahydrocannabinol (**8**, n = 2) there was obtained after chromatography (hexanes/ethyl acetate, 3:1) 0.068 g (71%) of JWH-299 as a colorless gum: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.81–0.85 (t, J = 7.1 Hz, 3H), 1.03–1.40 (m, 8H), 1.12 (s, 3H), 1.21 (s, 6H), 1.38 (s, 3H), 1.50–1.56 (m, 2H), 1.82–1.87 (m, 2H), 2.13 (br s, 1H), 2.43–2.44 (m, 1H), 3.34–3.37 (m, 1H), 3.72–3.82 (m, 1H), 3.74 (s, 3H), 6.35–6.36 (d, J = 1.5 Hz, 1H), 6.40–6.41 (d, J = 1.7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.9, 18.8, 23.3, 25.5, 26.0, 26.8, 27.8, 28.7, 33.5, 35.7, 37.5, 39.3, 44.1, 48.5, 54.9, 70.6, 76.6, 100.5, 108.1, 110.1, 149.7, 154.0, 158.3; MS(EI) *m*/*z*: 360 (38), 304 (100), 290 (33), 235 (16), 192 (19), 178 (15); HRMS: Calcd for $C_{23}H_{36}O_3$ 360.2664. Found: 360.2673.

5.12. 1-Methoxy-11-nor-3-(1′,1′-dimethylpentyl)-9α-hydroxyhexahydrocannabinol (JWH-278, 10, *n* = 2)

Methoxy hexahydrocannabinol **10**, n = 2, was prepared by the method described above for the preparation of **10**, n = 1. From 0.149 g (0.42 mmol) of 1-methoxy-11-nor-3-(1′,1′-dimethylpentyl)-9-keto-hexahydrocannabinol (**16**, n = 2) there was obtained after chromatography (hexanes/ethyl acetate, 3:1) 0.097 g (65%) of JWH-278 as a pale brown gum: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.81–0.86 (t, J = 7.1 Hz, 3H), 1.09 (s, 3H), 1.05–1.56 (m, 9H), 1.23 (s, 6H), 1.38 (s, 3H), 1.65–1.67 (m, 2H), 1.96–2.00 (m, 1H), 2.52 (br s, 1H), 2.87–2.93 (t, J = 9.2 Hz, 1H), 3.17–3.23 (m, 1H), 3.78 (s, 3H), 4.38 (m, 1H), 6.35–6.42 (dd, J = 1.5, 17.8 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.0, 18.9, 20.6, 22.5, 23.3, 26.8, 27.5, 28.7, 29.0, 32.9, 37.0, 37.5, 44.2, 49.1, 55.0, 67.1, 76.6, 100.7, 108.2, 110.7, 149.6, 154.3, 158.3; MS(EI) *m*/*z*: 360 (27), 304 (100), 285 (25), 207 (18), 192 (23), 178 (22), 57 (39); HRMS: Calcd for $C_{23}H_{36}O_3$ 360.2664. Found: 360.2662.

5.13. 1-Deoxy-11-nor-3-(1′,1′-dimethylpentyl)-9β-hydroxyhexahydrocannabinol (JWH-300, 9, *n* = 2)

Cannabinoid **13**, n = 2, was converted to the phosphate ester as described above for the preparation of the phosphate ester of **13**, n = 1. From 0.100 g (0.291 mmol) **13**, n = 2 there was obtained 0.139 g (99%) of the phosphate ester as a yellow oil following chromatography (hexanes/ethyl acetate, 3:1) that was used in the next step without further purification: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.80–0.85 (m, 4H), 1.03–1.13 (m, 4H), 1.18

(s, 3H), 1.26 (s, 6H), 1.30–1.39 (m, 6H), 1.49 (s, 3H), 1.50–1.55 (m, 2H), 1.96–2.10 (m, 1H), 2.15–2.24 (m, 2H), 2.44–2.56 (m, 1H), 2.56–2.60 (m, 1H), 2.98–3.04 (m, 1H), 3.54–3.60 (m, 1H), 4.18–4.26 (m, 4H), 6.64 (s, 1H), 6.84 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.9, 16.0, 16.1, 23.2, 26.5, 26.8, 27.6, 28.5, 34.4, 37.5, 40.5, 43.9, 45.7, 47.4, 64.5, 76.9, 110.4, 112.1, 113.0, 148.7, 150.8, 154.1, 209.6.

JWH-300 (**9**, $n = 2$) was prepared by reduction of the phosphate ester as described above for the preparation of 1-deoxy-11-nor-3-(1′,1′-dimethylbutyl)-9β-hydroxy-hexahydrocannabinol (**9**, $n = 1$). From 0.150 g (0.45 mmol) phosphate ester there was obtained after chromatography (hexanes/ethyl acetate, 4:1) 0.042 g (42%) of JWH-300 as an off-white solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.79–0.85 (t, $J = 7$ Hz, 3H), 1.0–1.40 (m, 8H), 1.16 (s, 3H), 1.24 (s, 6H), 1.39 (s, 3H), 1.51–1.57 (m, 2H), 1.86–1.91 (m, 2H), 2.11–2.17 (m, 1H), 2.41–2.51 (td, $J = 3.2$, 11.6 Hz, 1H), 2.69–2.74 (m, 1H), 3.77–3.84 (m, 1H), 6.74–6.75 (d, $J = 1.8$ Hz, 1H), 6.82–6.85 (dd, $J = 1.8$, 8.1 Hz, 1H), 7.09–7.11 (d, $J = 8.1$ Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.0, 20.2, 23.3, 25.8, 26.9, 28.1, 28.8, 33.7, 35.3, 37.3, 39.7, 44.2, 46.2, 70.5, 77.0, 114.6, 117.5, 121.0, 125.1, 149.8, 152.7; MS(EI) *m*/*z*: 330 (43), 274 (33), 273 (100), 207 (15), 147 (17), 69 (26), 57 (36), 55 (30); HRMS: Calcd for $C_{22}H_{34}O_3$ 330.2559. Found: 330.2564.

5.14. 1-Deoxy-11-nor-3-(1′,1′-dimethylpentyl)-9-keto-hexahydrocannabinol (12, $n = 2$)

Ketone **12**, $n = 2$, was prepared by the procedure described above for the preparation of **12**, $n = 1$. Oxidation of 0.100 g (0.303 mmol) of **9**, $n = 2$, gave 0.035 g (35%) of **12**, $n = 2$ as a white solid following chromatography (hexanes/ethyl acetate, 3:1): ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.80–0.85 (t, $J = 7.1$ Hz, 3H), 1.02–1.25 (m, 5H), 1.18 (s, 3H), 1.24 (s, 6H), 1.47 (s, 3H), 1.47–1.57 (m, 2H), 1.87–1.96 (m, 1H), 2.15–2.17 (m, 1H), 2.28–2.54 (m, 3H), 2.84–2.86 (m, 1H), 3.07–3.13 (m, 1H), 6.78–6.79 (d, $J = 1.8$ Hz, 1H), 6.84–6.87 (dd, $J = 8.1$, 1.8 Hz, 1H), 6.99–7.01 (d, $J = 8.1$ Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.0, 19.9, 23.4, 26.9, 27.2, 28.2, 28.8, 35.8, 37.4, 40.8, 44.2, 45.8, 77.0, 114.8, 117.9, 125.1, 150.0, 153.0, 212.1.

5.15. 1-Deoxy-11-nor-3-(1′,1′-dimethylpentyl)-9α-hydroxyhexahydrocannabinol (11, $n = 2$)

JWH 301 (**11**, $n = 2$) was prepared from 1-deoxy-11-nor-3-(1′,1′-dimethylpentyl)-9-keto-hexahydrocannabinoid (**12**, $n = 2$) by the procedure employed for the preparation of **11**, $n = 1$ described above. From 0.057 g (0.18 mmol) of **12**, $n = 2$, there was obtained after chromatography (hexanes/ethyl acetate, 3:1) 0.047 g (82%) of JWH-301 as a colorless paste: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.79–0.84 (t, $J = 7.3$ Hz, 3H), 0.99–1.13 (m, 3H), 1.18 (s, 3H), 1.24 (s, 6H), 1.41 (s, 3H), 1.45–1.56 (m, 6H), 1.61–1.64 (m, 2H), 1.74 (br s, 1H), 1.92–1.96 (m, 1H), 2.50–2.54 (m, 1H), 2.84–2.92 (m, 1H), 4.27 (m, 1H), 6.73–6.74 (d, $J = 1.9$ Hz, 1H), 6.80–6.83 (dd, $J = 1.7$, 8.1 Hz, 1H), 7.07–7.09 (d, $J = 8.0$ Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.0, 20.2, 21.5, 23.3, 26.9, 27.8, 28.8, 28.9, 32.7, 37.2, 37.6, 44.2, 47.0, 66.1, 76.9, 114.5, 117.4, 121.8, 125.1, 149.5, 152.9; MS(EI) *m*/*z*: 330 (50), 274 (40), 273 (100), 255 (34), 213 (11), 147 (18), 57 (44), 55 (26); HRMS: Calcd for $C_{22}H_{34}O_2$ 330.2559. Found: 330.2560.

5.16. 11-Nor-3-(1′,1′-dimethylhexyl)-9-keto-hexahydrocannabinol (13, $n = 3$)

Resorcinol **14**, $n = 3$, was prepared by the method described above for the preparation of **14**, $n = 1$. From 1.0 g (4.50 mmol) of dimethylpentyl resorcinol (**15**, $n = 3$) there was obtained 1.53 g (95%) of **14**, $n = 3$, as an unstable brown solid that was used without purification.

Cannabinoid **13**, $n = 3$, was prepared by the procedure described above for the preparation of **13**, $n = 1$. From 2.13 g (5.95 mmol) of 4-(2,6-dihydroxy-4-[1′,1′-dimethylhexyl]-phenyl)-6,6-dimethylbicyclo[3.1.1]heptan-2-one (**14**, $n = 3$) there was obtained 0.86 g (41%) of **13**, $n = 3$ as a brown paste: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.80–0.85 (m, 4H), 1.04–1.20 (m, 6H), 1.16 (s, 3H), 1.20 (s, 6H), 1.50 (s, 3H), 1.52–1.63 (m, 2H), 1.90–2.00 (m, 1H), 2.04–2.22 (m, 2H), 2.45–2.54 (m, 1H), 2.64–2.67 (m, 1H), 2.86–3.05 (m, 1H), 4.13–4.17 (m, 1H), 6.38 (s, 2H), 7.45 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.9, 18.9, 22.3, 23.4, 26.9, 27.9, 28.7, 34.7, 37.3, 40.6, 44.1, 44.8, 47.4, 76.8, 106.0, 107.0, 151.0, 155.0, 214.0.

5.17. 1-Methoxy-11-nor-3-(1′,1′-dimethylhexyl)-9-keto-hexahydrocannabinol (16, $n = 3$)

Methoxy hexahydrocannabinol **16**, $n = 3$, was prepared by the procedure described above for the preparation of **16**, $n = 1$. From 0.346 g (0.966 mmol) of **13**, $n = 3$, there was obtained 0.257 g (72%) of **16**, $n = 3$, as a transparent paste: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.75–0.85 (t, $J = 7$ Hz, 3H,), 1.0–1.45 (m, 7H), 1.15 (s, 3H), 1.24 (s, 6H) 1.5 (s, 3H), 1.52–1.60 (m, 3H), 1.86–2.20 (m, 3H), 2.35–2.70 (m, 2H), 2.75 (td, $J = 3.6$, 11.4 Hz, 1H) 3.80 (s, 3H), 6.37 (d, $J = 1.8$ Hz, 1H), 6.44 (d, $J = 1.8$ Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.9, 18.6, 22.3, 24.0, 26.8, 28.7, 29.1, 32.5, 34.6, 37.7, 40.8, 45.8, 47.5, 55.0, 76.6, 100.6, 108.2, 109.4, 150.5, 153.9, 158.2, 211.1.

5.18. 1-Methoxy-11-nor-3-(1′,1′-dimethylhexyl)-9β-hydroxyhexahydrocannabinol (JWH-350, 8, $n = 3$)

JWH-350 (**8**, $n = 3$) was prepared from 1-methoxy-11-nor-3-(1′,1′-dimethylhexyl)-9-keto-hexahydrocannabinol (**16**, $n = 3$) by the procedure described above for the preparation of **8**, $n = 1$. From 0.131 g (0.35 mmol) of ketone **16**, $n = 3$, there was obtained after chromatography (hexanes/ethyl acetate, 3:1) 0.098 g (75%) of JWH-350 as a colorless gum: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.80–0.95 (t, $J = 7$ Hz, 3H), 1.05–1.38 (m, 10H), 1.13 (s, 3H), 1.25 (s, 6H), 1.40 (s, 3H), 1.50 (m, 2H), 1.73 (br s, 1H), 1.85–1.95 (m, 1H), 2.15–2.25 (m, 1H), 2.40–2.51 (td, $J = 2.1$, 11.1 Hz, 1H), 3.30–3.41 (m, 1H),

3.75–3.90 (m, 1H), 3.85 (s, 3H), 6.36–6.43 (d, $J = 14.1$ Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1, 18.9, 22.5, 24.3, 26.1, 27.9, 28.8, 32.6, 33.6, 35.8, 37.7, 39.4, 44.4, 48.5, 55.0, 70.8, 77.0, 100.6, 108.2, 110.2, 149.9, 154.1, 158.4; MS(EI) *m/z*: 375 (37), 318 (15), 305 (20), 303 (22), 286 (10), 249 (10), 192 (12); HRMS: Calcd for $C_{24}H_{38}O_3$ 374.2821. Found: 374.2821.

5.19. 1-Methoxy-11-nor-3-(1′,1′-dimethylhexyl)-9α-hydroxyhexahydrocannabinol (JWH-349, 10, *n* = 3)

Alcohol **10**, $n = 3$, JWH 349, was prepared from 1-methoxy-11-nor-3-(1′,1′-dimethylpentyl)-9-keto-hexahydrocannabinol (**16**, $n = 3$) by the procedure used for the preparation of **10**, $n = 1$. From 0.135 g (0.36 mmol) of **16**, $n = 3$, there was obtained after chromatography (hexanes/ethyl acetate, 3:1) to give 0.096 g (71%) of JWH-349: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.81–0.90 (t, $J = 7.1$ Hz, 3H), 1.05–1.38 (m, 6H), 1.12 (s, 3H), 1.25 (s, 6H), 1.40 (s, 3H), 1.48–1.73 (m, 7H), 1.92–2.04 (m, 1H), 2.88–3.00 (m, 1H), 3.15–3.27 (m, 1H), 3.81 (s, 3H), 4.24 (br s, 1H), 6.36–6.43 (dd, $J = 1.8$, 16.2 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1, 19.1, 22.5, 22.6, 24.3, 27.6, 28.8, 29.1, 36.6, 33.2, 37.3, 37.6, 44.4, 49.3, 55.1, 66.9, 76.6, 100.7, 108.3, 110.8, 149.7, 154.4, 158.4; MS(EI) *m/z*: 374 (32), 356 (12), 319 (14), 314 (16), 305 (22), 304 (100), 286 (30), 285 (24), 249 (16), 192 (19); HRMS: Calcd for $C_{24}H_{38}O_3$ 374.2821. Found: 374.2827.

5.20. 1-Deoxy-11-nor-3-(1′,1′-dimethylhexyl)-9β-hydroxyhexahydrocannabinol (JWH-361, 9, *n* = 3)

Cannabinoid **13**, $n = 3$, was converted to the phosphate ester by the procedure described above for the preparation of **9**, $n = 1$. From 0.195 g (0.545 mmol) **13**, $n = 3$, there was obtained 0.186 g (69%) of phosphate ester as a yellow oil following chromatography (hexanes/ethyl acetate, 3:2): ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.81–0.85 (m, 4H), 1.00–1.14 (m, 6H), 1.19 (s, 3H), 1.25 (s, 6H), 1.27–1.39 (m, 6H), 1.48 (s, 3H), 1.50–1.54 (m, 2H), 1.97–2.10 (m, 1H), 2.16–2.25 (m, 2H), 2.45–2.55 (m, 1H), 2.56–2.61 (m, 1H), 2.98–3.03 (m, 1H), 3.54–3.61 (m, 1H), 4.17–4.26 (m, 4H), 6.65 (s, 1H), 6.83 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.9, 16.1, 16.3, 22.2, 24.6, 25.9, 26.8, 27.9, 28.5, 34.5, 37.3, 40.9, 43.8, 45.5, 47.2, 64.2, 76.9, 110.2, 112.1, 113.1, 147.7, 151.0, 154.4, 209.7.

The phosphate ester was reduced to JWH-361 by the procedure employed for the synthesis of **9**, $n = 1$. From 0.186 g (0.38 mmol) of phosphate ester there was obtained after chromatography (hexanes/ethyl acetate, 3:2) 0.068 g (53%) of JWH-361 as a white solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.80–0.90 (t, $J = 7.1$ Hz, 3H), 1.0–1.39 (m, 10H), 1.16 (s, 3H), 1.26 (s, 6H), 1.43 (s, 3H), 1.49–1.60 (m, 2H), 1.76 (br s, 1H), 1.86–1.94 (m, 1H), 2.14–2.19 (m, 1H), 2.45–2.55 (m, 1H), 2.70–2.79 (m, 1H), 3.76–3.89 (m, 1H), 6.77 (s, 1H), 6.82–6.90 (d, $J = 8.1$ Hz, 1H), 7.10–7.17 (d, $J = 7.8$ Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1, 20.2, 22.6, 24.4, 25.8, 28.2, 28.8, 28.9, 32.6, 33.8, 35.4, 37.4, 39.8, 44.5, 46.2, 70.6, 77.0, 114.6, 117.5, 121.1, 125.1, 149.8, 152.7; MS(EI) *m/z*: 344 (35), 274 (34), 273 (100), 271 (16); HRMS: Calcd for $C_{23}H_{36}O_2$ 344.2715. Found: 344.2710.

5.21. 1-Deoxy-11-nor-3-(1′,1′-dimethylhexyl)-9-keto-hexahydrocannabinol (12, *n* = 3)

Ketone **12**, $n = 3$, was prepared by the procedure described above for the preparation of **12**, $n = 1$. From 0.060 g (0.174 mmol) of **9**, $n = 3$, there was obtained 0.035 g (59%) of **12**, $n = 3$, as a white solid following chromatography (hexanes/ethyl acetate, 3:1): ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.81–0.85 (t, $J = 7.1$ Hz, 3H), 1.01–1.26 (m, 5H), 1.20 (s, 3H), 1.25 (s, 6H), 1.46 (s, 3H), 1.47–1.59 (m, 2H), 1.90–1.96 (m, 1H), 2.17–2.19 (m, 1H), 2.26–2.55 (m, 3H), 2.83–2.86 (m, 1H), 3.10–3.15 (m, 1H), 6.75–6.78 (d, $J = 1.8$ Hz, 1H), 6.86–6.89 (dd, $J = 8.1$, 1.8 Hz, 1H), 7.00–7.02 (d, $J = 8.1$ Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.9, 20.0, 22.3, 23.6, 26.6, 27.1, 28.3, 28.7, 35.6, 37.3, 40.8, 44.1, 46.4, 77.0, 115.1, 118.0, 125.2, 150.7, 153.0, 211.2.

5.22. 1-Deoxy-11-nor-3-(1′,1′-dimethylhexyl)-9α-hydroxyhexahydrocannabinol (JWH-362, 11, *n* = 3)

JWH-362 was prepared from 1-deoxy-11-nor-3-(1′,1′-dimethylhexyl)-9-keto-hexahydrocannabinoid (**12**, $n = 3$) by the method used for the synthesis of **11**, $n = 1$. From 0.035 g (0.10 mmol) of **12**, $n = 3$, there was obtained after chromatography (hexanes/ethyl acetate, 3:1) 0.027 g (77%) of JWH-362 as a colorless gum: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.81–0.89 (t, $J = 6$ Hz, 3H), 1.02–1.32 (m, 6H), 1.20 (s, 3H), 1.26 (s, 6H), 1.43 (s, 3H) 1.47–1.73 (m, 7H), 1.90–2.06 (m, 2H), 2.50–2.59 (m, 1H), 2.87–2.94 (m, 1H), 4.33 (s, 1H), 6.76 (d, $J = 1.8$ Hz, 1H), 6.82 (dd, $J = 1.8$, 8.1 Hz, 1H), 7.11 (d, $J = 8.1$ Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1, 20.2, 20.6, 21.6, 22.6, 24.4, 27.9, 28.8, 28.8, 29.0, 32.6, 37.3, 37.5, 44.5, 47.0, 66.5, 77.0, 114.6, 117.5, 121.8, 125.2, 149.6, 152.9; MS(EI) *m/z*: 345 (15), 344 (59), 283 (11), 274 (43), 273 (100), 255 (32); HRMS: Calcd for $C_{23}H_{36}O_2$ 344.2715. Found: 344.2716.

5.23. 11-Nor-3-(1′,1′-dimethylheptyl)-9-keto-hexahydrocannabinol (13, *n* = 4)

Resorcinol **14**, $n = 4$, was prepared by the method described above for the preparation of **14**, $n = 1$. From 4.30 g (18.2 mmol) of dimethylpentyl resorcinol (**15**, $n = 4$), there was obtained 6.26 g (92%) of **14**, $n = 4$, as an unstable brown solid that was used without purification.

Cannabinoid **13**, $n = 4$, was prepared by the procedure described above for the preparation of **13**, $n = 1$. From 3.83 g (11.32 mmol) of 4-(2,6-dihydroxy-4-[1′,1′-dimethylheptyl]-phenyl)-6,6-dimethylbicyclo[3.1.1]heptan-2-one (**14**, $n = 4$) there was obtained 1.62 g (42%) of **13**, $n = 4$, as a transparent brown paste: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.81–0.86 (m, 4H), 1.0–1.3 (m, 8H), 1.13 (s, 3H), 1.20 (s, 6H), 1.50 (s, 3H), 1.50–1.60 (m, 2H), 1.89–2.02 (m, 1H), 2.10–2.20 (m, 2H), 2.47–2.51 (m,

1H), 2.63–2.67 (m, 1H), 2.87–2.90 (m, 1H), 4.14–4.19 (m, 1H), 6.35–6.39 (d, J = 11 Hz, 2H), 7.88 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.0, 18.8, 22.6, 24.5, 26.8, 27.8, 28.6, 29.9, 31.7, 34.7, 37.2, 40.7, 44.3, 44.9, 47.3, 76.6, 105.5, 106.8, 107.6, 150.7, 154.1, 155.1, 214.7.

5.24. 1-Methoxy-11-nor-3-(1′,1′-dimethylheptyl)-9-keto-hexahydrocannabinol (16, *n* = 4)

Cannabinoid **16**, n = 4, was prepared by the procedure described above for the preparation of **16**, n = 1. From 0.129 g (0.347 mmol) of **13**, n = 4, there was obtained 0.095 g (71%) of **16**, n = 4, as a pale yellow transparent paste: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.75–0.90 (m, 4H), 1.0–1.4 (m, 8H), 1.15 (s, 3H), 1.25 (s, 6H), 1.55 (s, 3H), 1.50–1.70 (m, 2H), 1.90–2.20 (m, 3H), 2.30–2.65 (m, 2H), 2.80–2.90 (td, J = 3.6, 12 Hz, 1H), 3.80 (m, 1H), 3.85 (s, 3H), 6.38 (s, 1H), 6.44 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1, 18.8, 22.7, 24.6, 26.7, 27.9, 28.8, 30.0, 31.8, 34.6, 37.8, 40.8, 44.4, 45.8, 47.5, 55.0, 76.6, 100.6, 108.2, 109.3, 150.6, 153.9, 158.2, 211.3.

5.25. 1-Methoxy-11-nor-3-(1′,1′-dimethylheptyl)-9β-hydroxyhexahydrocannabinol (JWH-341, 8, *n* = 4)

JWH-341 was prepared from 1-methoxy-11-nor-3-(1′,1′-dimethylheptyl)-9-keto-hexahydrocannabinol (**16**, n = 4) by the procedure described above for the synthesis of **8**, n = 1. From 0.095 g (0.25 mmol) of **16**, n = 4, there was obtained after chromatography (hexanes/ethyl acetate, 3:1) 0.090 g (97%) JWH-341 as a pale brown gum: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.83–0.92 (t, J = 6 Hz, 3H), 1.0–1.42 (m, 12H), 1.10 (s, 3H), 1.25 (s, 6H), 1.41 (s, 3H), 1.55–1.60 (m, 2H), 1.66 (br s, 1H), 1.85–1.94 (m, 1H), 2.14–2.26 (m, 1H), 2.40–2.50 (td, J = 2.4, 11.1 Hz, 1H), 3.30–3.44 (m, 1H), 3.80 (m, 1H), 3.81 (s, 3H), 6.37–6.43 (dd, J = 1.8, 14 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1, 18.9, 22.7, 24.6, 26.1, 27.9, 28.8, 29.7, 30.0, 31.8, 33.6, 35.8, 37.7, 39.4, 44.5, 48.5, 55.0, 70.8, 77.0, 100.6, 108.2, 110.1, 149.9, 154.1, 158.4; MS(EI) *m*/*z*: 389 (11), 388 (41), 346 (12), 332 (17), 305 (23), 304 (100), 303 (24), 286 (12), 263 (10), 192 (12); HRMS: Calcd for $C_{25}H_{40}O_3$ 388.2977. Found: 388.2982.

5.26. 1-Methoxy-11-nor-3-(1′,1′-dimethylheptyl)-9α-hydroxyhexahydrocannabinol (JWH-340, 10, *n* = 4)

JWH-340 was prepared from 1-methoxy-11-nor-3-(1′,1′-dimethylpentyl)-9-keto-hexahydrocannabinol (**16**, n = 4) by the procedure employed for the synthesis of **10**, n = 1. From 0.071 g (0.18 mmol) of **16**, n = 4, there was obtained after chromatography (hexanes/ethyl acetate, 3:1) 0.044 g (62%) JWH-340 as a colorless gum: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.82–0.93 (t, J = 7 Hz, 3H), 1.03–1.38 (m, 12H), 1.21 (s, 3H), 1.25 (s, 6H), 1.40 (s, 3H), 1.47–1.82 (m, 4H), 1.95–1.99 (m, 1H), 2.85–2.97 (m, 1H), 3.15–3.25 (m, 1H), 3.80 (s, 3H), 4.24 (m, 1H), 6.36–6.43 (dd, J = 1.8, 16.8 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1, 19.1, 22.6, 22.7, 24.6, 27.6, 28.8, 29.1, 30.0, 31.8, 33.2, 37.3, 37.7, 44.5, 49.3, 55.1, 66.9, 77.0, 100.7, 108.3, 110.8, 149.7, 154.4, 158.4; MS(EI) *m*/*z*: 389 (12), 388 (45), 370 (12), 332 (15), 318 (15), 305 (21), 304 (100), 303 (16), 285 (19), 263 (11), 192 (11); HRMS: Calcd for $C_{25}H_{40}O_3$ 388.2977. Found: 388.2982.

5.26.1. CB_1 assay. [^{3}H]CP-55,940 (K_D = 690 nM) binding to P_2 membranes was conducted as described elsewhere,[30] except whole brain (rather than cortex only) was used. Displacement curves were generated by incubating drugs with 1 nM [^{3}H]CP-55,940. The assays were performed in triplicate, and the results represent the combined data from three individual experiments.

5.26.2. 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 CB2pcDNA3 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, and 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 and coworkers.[17,31] Cells were harvested in phosphate-buffered saline containing 1 mM EDTA and centrifuged at 500*g*. The cell pellet was homogenized in 10 mL of solution A (50 mM Tris–HCl, 320 mM sucrose, 2 mM EDTA, and 5 mM $MgCl_2$, pH 7.4). The homogenate was centrifuged at 1600*g* (10 min), the supernatant saved, and the pellet washed three times in solution A with subsequent centrifugation. The combined supernatants were centrifuged at 100,000*g* (60 min). The (P_2 membrane) pellet was resuspended in 3 mL buffer B (50 mM Tris–HCl, 1 mM EDTA, and 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 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 ice-cold buffer D, which was also filtered, and the filters were subsequently rinsed twice with 4 mL ice-cold buffer D. Before radioactivity was quantitated by

liquid scintillation spectrometry, filters were shaken for 1 h in 5 mL of scintillation fluid.

CP-55,940 and all cannabinoid analogs were prepared by suspension in assay buffer from a 1 mg/mL ethanolic stock without evaporation of the ethanol (final concentration of not more than 0.4%). Competition assays were conducted with 1 nM [^{3}H]CP-55,940 and six 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]

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