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Enantioselective synthesis of 1-methoxy- and 1-deoxy-2′-methyl-Δ^8-tetrahydrocannabinols: New selective ligands for the CB_2 receptor

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Abstract—Two new series of cannabinoids were prepared and their affinities for the CB_1 and CB_2 receptors were determined. These series are the (2′*R*)- and (2′*S*)-1-methoxy- and 1-deoxy-3-(2′-methylalkyl)-Δ^8-tetrahydrocannabinols, with alkyl side chains of three to seven carbon atoms. These compounds were prepared by a route that employed the enantioselective synthesis of the resorcinol precursors to the cannabinoid ring system. All of these compounds have greater affinity for the CB_2 receptor than the CB_1 receptor and four of them, (2′*R*)-1-methoxy-3-(2′-methylbutyl)-Δ^8-THC (JWH-359), (2′*S*)-1-deoxy-3-(2′-methylbutyl)-Δ^8-THC (JWH-352), (2′*S*)-1-deoxy-3-(2′-methylpentyl)-Δ^8-THC (JWH-255), and (2′*R*)-1-deoxy-3-(2′-methylpentyl)-Δ^8-THC (JWH-255), have good affinity (K_i = 13–47 nM) for the CB_2 receptor and little affinity (K_i = 1493 to >10,000 nM) for the CB_1 receptor. In the 1-deoxy-3-(2′-methylalkyl)-Δ^8-THC series, the 2′*S*-methyl compounds in general have greater affinity for the CB_2 receptor than the corresponding 2′*R* isomers.

1. Introduction

Cannabinoids exhibit a complex array of pharmacological effects that are generally considered to be mediated through at least two G-protein coupled receptors. One of these receptors, designated CB_1, is found principally in the central nervous system while the other, designated CB_2, is expressed primarily in the periphery.[1–5] Recently, evidence has been presented that indicates the existence of an additional cannabinoid receptor or receptors.[6–9] It is generally accepted that the CB_1 receptor is responsible for most of the overt pharmacological effects of cannabinoids and there is good correlation between CB_1 receptor affinity and the in vivo activity of cannabinoids.[10,11] These effects are blocked by the cannabinoid antagonist SR141716A and are absent in CB_1 receptor knockout mice.[12,13]

Until recently, the role of the CB_2 receptor was not well defined. It is known that cannabinoids are involved in immunomodulation and since the CB_2 receptor is expressed primarily in the immune system it has been suggested that this receptor is responsible for the immunomodulatory effects of cannabinoids,[14] a conclusion that is supported by the fact that these immunomodulatory effects are absent in CB_2 receptor knockout mice.[15] There is also evidence that the CB_2 receptor is involved in inflammatory pain[16–23] and it has been implicated in cardioprotection.[24] Both CB_1 and CB_2 receptors are expressed in various cancer cells, and cannabinoid receptor agonists have been found to inhibit tumor growth.[25,26] In particular, CB_2 receptors are expressed in C6 glioma cells,[27] and both CB_1 and CB_2 receptors are expressed in nonmelanoma skin cancer cells.[28] A highly selective CB_2 receptor ligand, 3-(1′,1′-dimethylbutyl)-Δ^8-tetrahydrocannabinol (3-(1′,1′-dimethylbutyl)-Δ^8-THC, JWH-133, **1**), causes the regression of both glioma tumors and nonmelanoma skin tumors.[27,28] The CB_2 receptor has recently been found to be associated with osteoporosis.[29,30] Although a number of highly selective CB_2 receptor agonists of several structural

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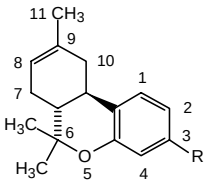
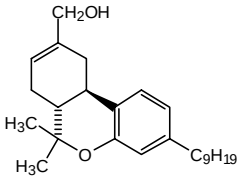
types have been described, the structure–activity relationships (SAR) at the CB_2 receptor are not as well defined as those at the CB_1 receptor.[31,32]

Based upon the observation that 3-(1′, 1′-dimethylheptyl)-1-deoxy-11-hydroxy-Δ^8-THC (**2**, JWH-051) and 3-(1′,1′-dimethylheptyl)-1-deoxy-Δ^8-THC (**3**, JWH-057) show 37-fold and nearly 8-fold selectivity, respectively, for the CB_2 receptor,[33] we synthesized a number of 1-deoxy- and 1-methoxy-Δ^8-THC analogs.[34,35] Several of these compounds show very high selectivity for the CB_2 receptor with little affinity for the CB_1 receptor. Among the most selective compounds are JWH-133 (**1**) which has $K_i = 677 \pm 132$ nM at the CB_1 receptor with $K_i = 3.4 \pm 1.0$ nM at CB_2[34] and JWH-229 (**4**, 1-methoxy-3-(1′, 1′-dimethylhexyl)-Δ^8-THC) with $K_i = 3134 \pm 110$ nM at CB_1 and $K_i = 18 \pm 2$ nM at CB_2.[35]



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



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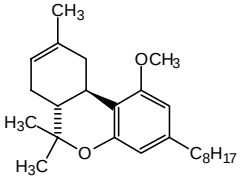

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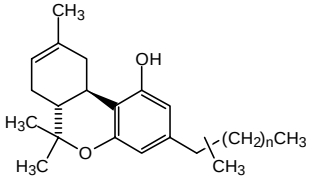


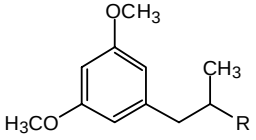
5 n = 3
6 n = 5

From earlier work in these series of 1-deoxy- and 1-methoxy-Δ^8-THC analogs and the corresponding 11-hydroxy-Δ^8-THCs, it has been possible to develop some tentative SAR at the CB_2 receptor for these traditional cannabinoids. In general, in both the 1-deoxy- and 1-methoxy-Δ^8-THC series an 11-hydroxyl substituent enhances affinity for both receptors. 1′,1′-Dimethyl substitution on the C-3 alkyl side chain leads to enhanced affinity for the CB_2 receptor, and 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). The length of the side chain plays a critical role in determining affinity at both receptors, although the effect is significantly less upon CB_2 affinity than upon CB_1 receptor affinity. For significant CB_1 affinity, a chain length of at least five carbon atoms is essential.

Several years ago, we reported the synthesis and pharmacology of all the isomeric 3-methylpentyl-Δ^8-THCs (**5**)[36] and 3-methylheptyl-Δ^8-THCs (**6**).[37] In these two series of compounds, it was found that a methyl substituent at the 1′-position increased the affinity for the CB_1 receptor from 2- to 40-fold relative to the analogs with an unsubstituted side chain. Substitution at the 2′-position increased CB_1 receptor affinity from 2- to 15-fold. It is well known that a geminal dimethyl substituent at C-1′ increases CB_1 receptor affinity in the Δ^8-THC series as it does at the CB_2 receptor in the corresponding 1-methoxy and 1-deoxy analogs.[34,35,38] To further explore the structure–activity relationships at the cannabinoid CB_2 receptor and to develop additional high affinity ligands for that receptor with little affinity for the CB_1 receptor, the enantioselective synthesis of the 3-(2′-methylalkyl)-1-deoxy- and 1-methoxy-Δ^8-THCs has been carried out, and their CB_1 and CB_2 receptor affinities have been determined.

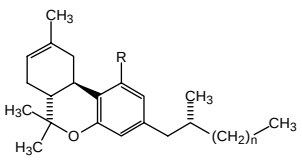
2. Results

In the synthesis of the (2′*R*)- and (2′*S*)-methyl isomers in the THC and 3-heptyl-THC series, the key intermediate, 3-(3,5-dimethoxyphenyl)-2-methylpropanoic acid (**7**), was resolved via tedious chromatographic separation of the corresponding phenethylamides.[36] Hydrolysis of the amides to the individual enantiomers of acid **7**, reduction of these acids to the corresponding alcohols (**8**), conversion to the *p*-toluenesulfonate esters, and reaction with either ethylmagnesium bromide or *n*-butylmagnesium chloride in the presence of Li_2CuCl_4 gave resorcinol ethers **9** and **10**.[36,37] Cleavage of the methyl ethers, followed by condensation with menthadienol, provided the THC analogs.

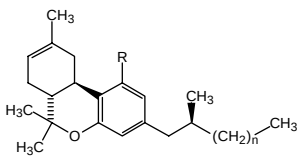


7 R = CO_2H
8 R = CH_2OH
9 R = C_3H_7
10 R = C_5H_{11}
25 R = CH_3

For the synthesis of the (2′*R*)-1-deoxy-2′-methylalkyl-(**11**, *n* = 1–4) and (2′*R*)-1-methoxy-3-(2′-methylalkyl)-Δ^8-THCs (**12**, *n* = 1–4), the corresponding (2′*R*)-3-(2′-methylalkyl)-Δ^8-THCs (**13**, *n* = 1–4) were required. For the corresponding (2′*S*)-methyl series of analogs (**14** and **15**, *n* = 1 to 4), (2′*S*)-3-(2′-methylalkyl)-THCs **16** (*n* = 1 to 4) were needed. Conversion of THCs **13** and **16** to the 1-deoxy (**11** and **14**) and 1-methoxy (**12** and **15**) analogs would be carried out by procedures used previously in our laboratory for the preparation of 1-deoxy- and 1-methoxy-cannabinoids.[34,35]

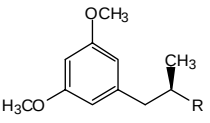


11 R = H
12 R = OCH_3
13 R = OH

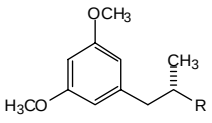


14 R = H
15 R = OCH_3
16 R = OH

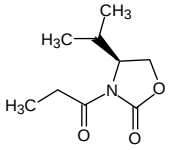
The immediate precursors to cannabinoids **16** and **13** are (*S*) and (*R*) resorcinol methyl ethers (**17** and **18**, respectively, $n = 1$–4), which are available from the (*R*) (**19**) and (*S*) (**20**) enantiomers of 2-methyl-3-(3,5-dimethoxyphenyl)-1-propanol. Although it would have been possible to obtain alcohols **19** and **20** by the classical resolution procedure employed in our earlier work, this would have required very careful and tedious chromatography on a large scale. A far more efficient approach is their preparation by asymmetric synthesis. For the preparation of the (*R*)-enantiomer of 2-methyl-3-(3,5-dimethoxyphenyl)-1-propanol (**19**), alkylation of propionyl imide **21** obtained from Evans' L-valine derived chiral auxiliary with 3,5-dimethoxybenzyl bromide to give **22** would provide an approach to the (*S*) series of resorcinol methyl ethers.[39] For the synthesis of the (*R*)-resorcinol methyl ethers, a possible approach would use imide **23** derived from the reaction of 3-(3,5-dimethoxyphenyl)propanoic acid with the Evans' chiral auxiliary. Alkylation with methyl iodide would afford (*S*)-methyl imide **24**. Although alkylation of imides similar to **21** and **23** proceeds with greater stereoselectivity using larger alkyl halides, based upon literature precedent it was anticipated that it would be possible to obtain reasonable yields of pure imide **24**.[39b] Alternatively, it would be possible to employ the enantiomer of **21** derived from the unnatural amino acid, D-valine. However D-valine is relatively costly and a second alternative approach to (*S*)-enantiomer **20** that was considered was the use of a different chiral auxiliary.



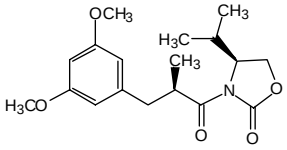
17 R = $(CH_2)_nCH_3$
19 R = CH_2OH



18 R = $(CH_2)_nCH_3$
20 R = CH_2OH



21



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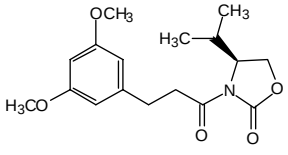

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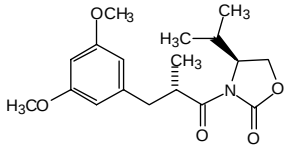


24

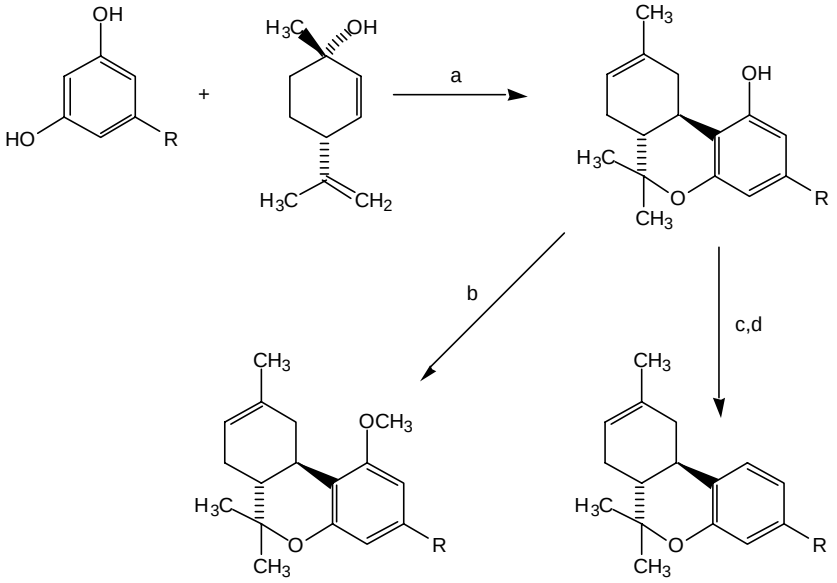
The parent members of the series of 2′-methyl-1-deoxy- and 1-methoxy-Δ^8-THCs, the 3-(2-methylpropyl) analogs **11** and **12** ($n = 0$) require achiral resorcinol dimethyl ether **25** as a precursor. This compound was prepared by the copper catalyzed reaction of isopropylmagnesium chloride with 3,5-dimethoxybenzyl bromide.[40] Reaction of **25** with boron tribromide gave the corresponding resorcinol, which was converted to Δ^8-THC analog **13** ($n = 0$) by acid catalyzed condensation with *p*-mentha-dienol as shown in Scheme 1.[34,41] Conversion to 1-deoxy cannabinoid **11** ($n = 0$) was effected by conversion to the phosphate ester followed by dissolving metal reduction.[34,35] The 1-methoxy analog (**12**, $n = 0$) was prepared by reaction with potassium hydroxide and methyl iodide.[35]

Alkylation of oxazolidinone **21**,[39] prepared by the method of Kelly et al.[42] was effected using LDA in THF at −78 °C under carefully controlled conditions. It was found necessary to treat **21** with LDA for no more than 1 min to prevent decomposition, apparently to the parent oxazolidinone and the ketene derived from propionic acid. Alkylation with 3,5-dimethoxybenzyl bromide afforded the oxazolidinone of (*R*)-3,5-dimethoxyphenyl-2-methylpropionic acid (**22**) in 94% yield as a single diastereomer. Reduction of **22** with lithium aluminum hydride gave (*R*)-3-(3,5-dimethoxyphenyl)-2-methyl-1-propanol (**19**) the spectroscopic properties of which were identical to those reported previously.[36] The optical purity of alcohol **19** was confirmed by conversion to the Mosher ester derived from (*R*)-(−)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride [(*R*)-(−)-MTPA-Cl].[43] The 500 MHz ^{1}H NMR spectrum of this Mosher ester was clearly different from that derived from (*S*)-enantiomer **20**. This spectrum was completely devoid of the signals due to the Mosher ester of **20** and indicated that alcohol **19** was optically pure within the limitations of the NMR method that was used.

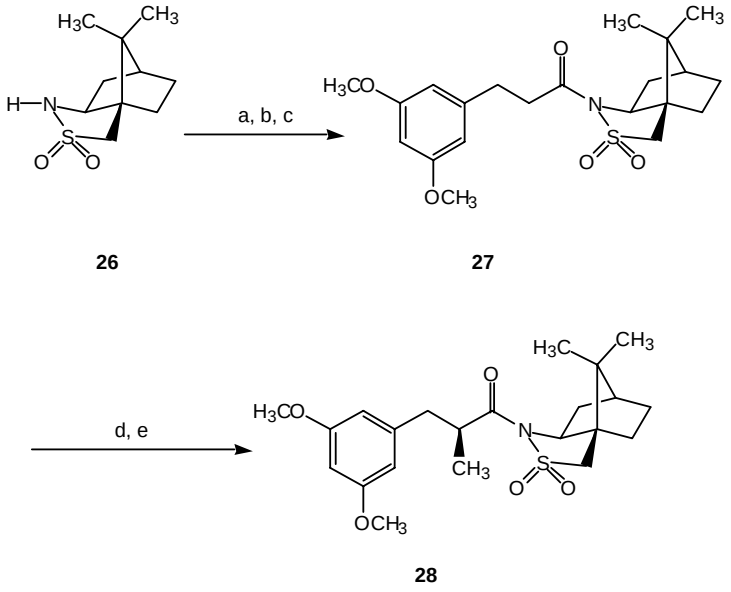
Using a modification of the procedure we reported previously, conversion of alcohol **19** to the methanesulfonate ester, followed by copper catalyzed coupling reactions using ethyl through butylmagnesium halides, provided (*S*)-resorcinol dimethyl ethers **17** ($n = 2$–4).[36,37] Reaction of the methanesulfonate ester of **19** with methylmagnesium bromide did not proceed in adequate yield; however, reaction of the trifluoromethanesulfonate ester under the same conditions gave (*S*)-1-(3,5-dimethoxyphenyl)-2-methylbutane (**17**, $n = 1$) in acceptable (70%) yield. Conversion of resorcinol methyl ethers **17** ($n = 1$–4) to (2′*S*)-3-(2′-methyl)-Δ^8-THC analogs **16** and then to 1-deoxy and 1-methoxy cannabinoids **14** and **15** ($n = 1$–4) was carried out by the procedures shown in Scheme 1.

Attempts to prepare (*S*)-alcohol **20** via methylation of chiral oxazolidinone **23** were not encouraging. Methylation of **23** under conditions similar to those employed for the alkylation of **21** provided a 3:1 mixture of the desired (*S*)-oxazolidinone (**24**) and the (*R*)-isomer (**22**). These diasteroisomeric oxazolidinones have very similar R_f values and while it was possible to separate them by very careful and rather tedious chromatography, this procedure was not practical for the preparation of quantities of (*S*)-alcohol **20** and an alternative approach to the (2*R*)-methyl series of cannabinoids was investigated.[44]

Both enantiomers of Oppolzer's camphor derived auxiliary (**26**), 1*R*,2*S*-enantiomer shown, (Scheme 2) are readily available in a few steps from the inexpensive, commercially available, enantiomeric camphor-10-sulfonic acids.[45] Reaction of **26** with sodium hydride, fol-

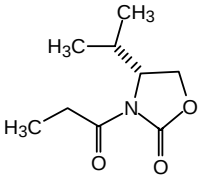


Scheme 1. Reagents and conditions: (a) HOTs/C_6H_6, 80 °C; (b) CH_3I/KOH/DMF, 25 °C; (c) NaH/THF, 0 °C then $(C_2H_5O)_2P(O)Cl$; (d) Li/NH_3, THF, −78 °C.



Scheme 2. Reagents and conditions: (a) NaH, toluene, 0 °C; (b) 3,5-dimethoxycinnamoyl chloride, 25 °C; (c) H_2, Pd/C, EtOAc; (d) $NaN(SiMe_3)_2$, THF, −78 °C; (e) MeI, HMPA, −78 to 25 °C.

lowed by treatment with 3,5-dimethoxycinnamoyl chloride and hydrogenation, gave imide **27** in 80% yield. Base catalyzed alkylation of **27** with methyl iodide provided a 92:8 mixture of the desired (2*S*)-isomer (**28**) and the (2*R*)-epimer. Although this reaction proceeded in good (78%) yield to give the mixture of stereoisomers, they could not be separated by chromatography. Repeated recrystallization gave pure **28**, but in only 30% yield. Attempts to improve the yield were unsuccessful and this approach was not pursued further.[46]



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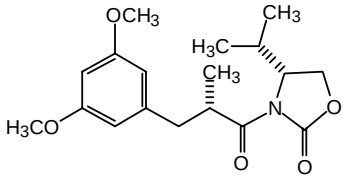

30

Since alternative approaches to (*S*)-alcohol **20**, the precursor to the (2′*R*)-methyl series of cannabinoids, were not satisfactory, these compounds were prepared from the D-valine derived enantiomer of **21** (**29**) by the procedure that was employed successfully for the synthesis of the (2′*S*) series of 1-deoxy-(**14**) and 1-methoxy-Δ^8-THC (**15**) analogs. As expected, alkylation of **29** with 3,5-dimethoxybenzyl bromide proceeded smoothly to provide **30**, which was identical to **22**, except for the sign of rotation. Lithium aluminum hydride reduction of **30** provided (*S*)-2-methyl-3-(3,5-dimethyoxyphenyl)-1-propanol (**20**). Alcohol **20** was identical to that prepared previously.[36] The 500 MHz ^{1}H NMR spectrum of the Mosher ester derived from **20** with (*R*)-(−)-MTPA-Cl is clearly different from that of its enantiomer (**19**) and showed that **20** is optically pure within the limits of the experimental method. The balance of the synthesis of the (2′*R*)-1-deoxy-(**11**) and (2′*R*)-1-methoxy-2′-methyl-Δ^8-THC (**12**) analogs was carried out as described above for the (2′*S*)-methyl series.

The affinities of the 1-methoxy- and 1-deoxy-Δ^8-THC analogs 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.[11] 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.[47] The results of these determinations are summarized in Table 1. Also included in Table 1 are the receptor affinities for JWH-133 (**1**), 1-deoxy-Δ^8-THC-DMH (**3**), Δ^8-THC-DMH, and Δ^8- and Δ^9-THC.

None of the 1-methoxy-Δ^8-THC analogs (**12** and **15**, $n = 0$–4) have appreciable affinity for the CB_1 receptor, with $K_i = 427 \pm 31$ nM (JWH-247) to >10,000 nM (JWH-339 and JWH-351). In contrast to their lack of affinity for the CB_1 receptor, several of these compounds have appreciable affinities for the CB_2 receptor. In particular, JWH-359 (**12**, $n = 1$) has very high affinity for the CB_2 receptor ($K_i = 13 \pm 0.2$ nM). This high affinity for the CB_2 receptor combined with very little affinity for the CB_1 receptor ($K_i = 2918 \pm 450$ nM) indicates that JWH-359 is more than 200-fold selective for the CB_2 receptor. JWH-358 (**12**, $n = 4$) also has relatively high affinity for the CB_2 receptor with $K_i = 52 \pm 3$ nM. JWH-256 (**15**, $n = 3$, $K_i = 97 \pm 18$ nM) and JWH-247 (**15**, $n = 4$, CB_2, $K_i = 99 \pm 4$ nM) both have appreciable affinity for the CB_2 receptor. Although these three compounds show selectivity for the CB_2 receptor, the most selective, JWH-256, is significantly less selective than JWH-359.

In the 1-deoxy series (**11** and **14**, $n = 0$–4) one compound, JWH-257 (**14**, $n = 3$) has high affinity for the CB_1 receptor with $K_i = 25 \pm 2$ nM. All of the other 1-deoxy-2′-methyl-Δ^8-THC analogs have very little affinity for the CB_1 receptor with $K_i = 332$ to >10,000 nM. These 1-deoxy-Δ^8-THC analogs all have from good to modest affinities for the CB_2 receptor with $K_i = 1$–

Table 1. Receptor affinities (means ± SEM) of 1-methoxy-2′-methylcannabinoids, 1-Deoxy-2′-methylcannabinoids and related compounds

Compound	K_i (nM)		
	CB_1	CB	CB_1/CB_2
Δ^9-THC	41 ± 2[a]	36 ± 10[b]	1.1
Δ^8-THC	44 ± 12[c]	44 ± 17[c]	1.0
1-Deoxy-Δ^8-THC-DMH (**3**)	22.8 ± 7.3[d]	2.9 ± 1.6[d]	7.9
3-(1′,1′-Dimethylbutyl)-1-deoxy-Δ^8-THC (JWH-133, **1**)	677 ± 132[c]	3.4 ± 1.0[c]	199
1-Methoxy-Δ^8-THC-DMH	924 ± 104[c]	57 ± 12[c]	16
1-Methoxy-3-(2′-methylpropyl)-Δ^8-THC (JWH-339, **12**, $n = 0$)	>10,000	2317 ± 93	>4.3
(2′*S*)-1-Methoxy-3-(2′-methylbutyl)-Δ^8-THC (JWH-351, **15**, $n = 1$)	>10,000	295 ± 3	>34
(2′*R*)-1-Methoxy-3-(2′-methylbutyl)-Δ^8-THC (JWH-359, **12**, $n = 1$)	2918 ± 450	13 ± 0.2	224
(2′*S*)-1-Methoxy-3-(2′-methylpentyl)-Δ^8-THC (JWH-254, **15**, $n = 2$)	4724 ± 509	319 ± 16	15
(2′*R*)-1-Methoxy-3-(2′-methylpentyl)-Δ^8-THC (JWH-354, **12**, $n = 2$)	1961 ± 21	241 ± 14	8.1
(2′*S*)-1-Methoxy-3-(2′-methylhexyl)-Δ^8-THC (JWH-256, **15**, $n = 3$)	4300 ± 888	97 ± 18	44
(2′*R*)-1-Methoxy-3-(2′-methylhexyl)-Δ^8-THC (JWH-356, **12**, $n = 3$)	5837 ± 701	108 ± 17	54
(2′*S*)-1-Methoxy-3-(2′-methylheptyl)-Δ^8-THC (JWH-247, **15**, $n = 4$)	427 ± 31	99 ± 4	4.3
(2′*R*)-1-Methoxy-3-(2′-methylheptyl)-Δ^8-THC (JWH-358, **12**, $n = 4$)	1243 ± 266	52 ± 3	24
1-Deoxy-3-(2′-methylpropyl)-Δ^8-THC (JWH-338, **11**, $n = 0$)	>10,000	111 ± 16	90
(2′*S*)-1-Deoxy-3-(2′-methylbutyl)-Δ^8-THC (JWH-352, **14**, $n = 1$)	>10,000	47 ± 2	212
(2′*R*)-1-Deoxy-3-(2′-methylbutyl)-Δ^8-THC (JWH-360, **11**, $n = 1$)	2449 ± 606	160 ± 8	15
(2′*S*)-1-Deoxy-3-(2′-methylpentyl)-Δ^8-THC (JWH-255, **14**, $n = 2$)	4307 ± 649	24 ± 9	179
(2′*R*)-1-Deoxy-3-(2′-methylpentyl)-Δ^8-THC (JWH-353, **11**, $n = 2$)	1493 ± 10	31 ± 1	48
(2′*S*)-1-Deoxy-3-(2′-methylhexyl)-Δ^8-THC (JWH-257, **14**, $n = 3$)	25 ± 2	1.0 ± 0.3	25
(2′*R*)-1-Deoxy-3-(2′-methylhexyl)-Δ^8-THC (JWH-355, **11**, $n = 3$)	2162 ± 220	108 ± 17	20
(2′*S*)-1-Deoxy-3-(2′-methylheptyl)-Δ^8-THC (JWH-264, **14**, $n = 4$)	332 ± 43	146 ± 28	2.3
(2′*R*)-1-Deoxy-3-(2′-methylheptyl)-Δ^8-THC (JWH-357, **11**, $n = 4$)	647 ± 78	185 ± 4	3.5

[a] Ref. 8.
[b] Ref. 47.
[c] Ref. 33.
[d] Ref. 34.

185 nM and all are selective for the CB_2 receptor. Two compounds in this series, JWH-352 (**14**, $n = 1$) and JWH-255 (**14**, $n = 2$), show >212- and 179-fold selectivity, respectively, for the CB_2 receptor. The more selective of this pair of compounds, JWH-352, has moderately high affinity for the CB_2 receptor ($K_i = 47 \pm 2$ nM) with $K_i > 10{,}000$ nM at CB_1. JWH-255 has slightly greater affinity for the CB_2 receptor ($K_i = 24 \pm 9$ nM), but also has somewhat greater affinity for the CB_1 receptor with $K_i = 4307 \pm 649$ nM. A third moderately selective ligand for the CB_2 receptor, JWH-353 (**11**, $n = 2$), has high affinity ($K_i = 31 \pm 1$ nM) for the CB_2 receptor and $K_i = 1493 \pm 10$ nM at the CB_1 receptor. JWH-257 (**14**, $n = 3$) the 1-deoxy-Δ^8-THC analog with the highest affinity at the CB_2 receptor ($K_i = 1.0 \pm 0.3$ nM) also has high affinity for the CB_1 receptor with $K_i = 25 \pm 2$ nM. Although all of the other 1-deoxy-Δ^8-THC analogs show from 2.3- to 90-fold selectivity for the CB_2 receptor, none has $K_i < 108$ nM at the CB_2 receptor.

3. Discussion

In the 2′-methyl series, none of the 1-methoxy-Δ^8-THC analogs have significant affinity for the CB_1 receptor with $K_i = 427$ to >10,000 nM. This parallels the results in the 1-methoxy-3-(1′,1′-dimethylalkyl)-Δ^8-THC series in which the CB_1 receptor affinities ranged from 677 to >10,000 nM.[35] The CB_2 receptor affinities of 1-methoxy-Δ^8-THC analogs **12** and **15** are considerably higher than their affinities for the CB_1 receptor ($K_i = 13$–2317 nM). The compound with the least affinity for the CB_2 receptor is 1-methoxy-3-(2′-methylpropyl)-Δ^8-THC (JWH-339, **12**, $n = 0$) and the compound with the greatest affinity ($K_i = 13 \pm 0.2$ nM) is the next highest homologs, (2′*R*)-2′-methylbutyl analog (JWH-359, **12**, $n = 1$). JWH-339 is a very highly selective (224-fold) ligand for the CB_2 receptor with little affinity for the CB_1 receptor. Interestingly, the epimeric (2′*S*)-2′-methylbutyl analog (JWH-351, **15**, $n = 1$) has little affinity for the CB_2 receptor with $K_i = 295 \pm 3$ nM. The other 1-methoxy-3-(2′-methyl)-Δ^8-THC analog with better than modest affinity for the CB_2 receptor is the (2′*R*)-2′-methylheptyl analog (JWH-358, **12**, $n = 4$) with $K_i = 52 \pm 3$ nM. This compound has little affinity ($K_i = 1243 \pm 266$ nM) at CB_1 and is 24-fold selective for the CB_2 receptor. Although all of these 1-methoxy-3-(2′-methylalkyl)-Δ^8-THC analogs are selective for the CB_2 receptor, only JWH-359 (**12**, $n = 1$) and JWH-358 (**12**, $n = 4$) have the combination of significant affinity for the CB_2 receptor combined with little affinity for the CB_1 receptor. In this series of 1-methoxy-Δ^8-THC analogs in general the (2′*R*)-methyl compounds have greater affinity for the CB_2 receptor than the (2′*S*)-isomers.

In the 1-deoxy-3-(2′-methyl)-Δ^8-THC series, with the exception of (2′*S*)-1-deoxy-3-(2′-methylhexyl)-Δ^8-THC (JWH-257, **14**, $n = 3$), none of the compounds have significant affinity for the CB_1 receptor. JWH-257 has very high affinity for the CB_1 receptor ($K_i = 25 \pm 2$ nM) while none of the other 1-deoxy-3-(2′-methyl)-Δ^8-THC analogs has $K_i < 647$ nM. The (2′*R*)-epimer of JWH-257 (2′*R*)-1-deoxy-3-(2′-methylhexyl)-Δ^8-THC (JWH-355, **11**, $n = 3$) has nearly 100-fold less affinity than JWH-257 for the CB_1 receptor with $K_i = 2162 \pm 220$ nM. This large difference in CB_1 receptor affinity as a function of stereochemistry at the 2′-position of the THC side chain is in contrast to the relative CB_1 receptor affinities of the 2′-methyl isomers in the Δ^8-THCs and 3-heptyl-Δ^8-THCs in which there is little difference in the affinities as a function of stereochemistry at C-2′.[36,37] At the present time, there is no obvious explanation for the large difference in the CB_1 receptor affinities of JWH-257 and JWH-355.

The 1-deoxy-3-(2′-methylalkyl)-Δ^8-THCs have affinities for the CB_2 receptor that range from 1.0 to 185 nM and all are selective for the CB_2 receptor. Three of these compounds have the desirable property of good to excellent affinity for the CB_2 receptor and little affinity for the CB_1 receptor. The most selective (>212-fold) of these 3-(2′-methyl)-1-deoxy-Δ^8-THCs is (2′*S*)-1-deoxy-3-(2′-methylbutyl)-Δ^8-THC (JWH-352, **14**, $n = 1$) with $K_i = 47 \pm 2$ nM at CB_2 and $K_i = >10{,}000$ nM at the CB_1 receptor. (2′*S*)-1-Deoxy-3-(2′-methylpentyl)-Δ^8-THC (JWH-255, **14**, $n = 2$) shows 179-fold selectivity for the CB_2 receptor with $K_i = 24 \pm 9$ nM at CB_2 and $K_i = 4307 \pm 649$ nM at CB_1. The least selective (48-fold) of these three compounds is (2′*R*)-1-deoxy-3-(2′-methylpentyl)-Δ^8-THC (JWH-353, **11**, $n = 2$) with $K_i = 31 \pm 1$ nM at CB_2 and $K_i = 1493 \pm 10$ nM at the CB_1 receptor. In contrast to the 1-methoxy series, the (2′*S*)-methyl deoxy cannabinoids have either similar or greater affinity than the (2′*R*)-epimers at the CB_2 receptor. In the (2′*S*)-methyl series, the butyl (JWH-352), pentyl (JWH-255), and hexyl (JWH-257) compounds (**14**, $n = 1$–3) all have good affinity for the CB_2 receptor with $K_i = 1.0$–47 nM. The only (2′*R*) compound with significant CB_2 receptor affinity ($K_i = 31 \pm 1$ nM) is (2′*R*)-1-deoxy-3-(2′-methylpentyl)-Δ^8-THC (JWH-353, **11**, $n = 2$).

With the exception of (2′*S*)-1-deoxy-3-(2′-methylhexyl)-Δ^8-THC (JWH-257, **14**, $n = 3$) none of these compounds in either the 1-methoxy or 1-deoxy series has significant affinity for the CB_1 receptor. JWH-257 has $K_i = 25 \pm 2$ nM at the CB_1 receptor and no other compound in either series has $K_i = <332$ nM. This is in contrast to the 1-deoxy-3-(1′,1′-dimethylalkyl)-Δ^8-THC series in which the dimethylheptyl and dimethyloctyl compounds both have good affinity for the CB_1 receptor ($K_i = 23 \pm 7$ and 51 ± 11 nM, respectively).[34] None of the 1-methoxy-Δ^8-THC analogs has significant affinity for the CB_1 receptor and this is in agreement with previous work in which it was found that in the absence of an 11-hydroxyl substituent 1-methoxy-Δ^8-THC analogs have little or no affinity for the CB_1 receptor.[35]

The SAR at the CB_2 receptor in the 1-methoxy-3-(2′-methylalky)-Δ^8-THC series (**12** and **15**, $n = 0$–4) are very different from those for the corresponding 1′,1′-dimethylalkyl-Δ^8-THCs.[35] In the 1′,1′-dimethylalkyl-Δ^8-THC series, the 1′,1′-dimethylpentyl through the 1′,1′-dimethylheptyl analogs have $K_i = 18$–57 nM,

increasing from pentyl to heptyl. In the 2′-methyl series, however, only the (2′*R*)-3-(2′-methylbutyl), JWH-359 (**12**, $n = 1$), and (2′*R*)-3-(2′-methylheptyl), JWH-358 (**12**, $n = 4$), compounds have high affinity for the CB_2 receptor ($K_i = 13 \pm 0.2$ nM and 52 ± 3 nM, respectively.). The (2′*S*) isomers have equal or less affinity for the CB_2 receptor than the (2′*R*) isomers. In the (2′*R*) series, CB_2 receptor affinity increases with chain length from three to four carbons then decreases with a five or six carbon alkyl chain. CB_2 receptor affinity then increases at seven carbons. In the (2′*S*) methyl 1-methoxy-Δ^8-THC series, none of the compounds have significant affinity for the CB_2 receptor.

In the 1-deoxy-3-(2′-methylalkyl)-Δ^8-THCs, the (2′*S*)-methyl compounds (**11**, $n = 0$, **14**, $n = 1$–4) have higher affinity for the CB_2 receptor than the corresponding (2′*R*) isomers (**11**, $n = 0$–4). Affinity increases with chain length from three to six carbon atoms and is maximum for the 2′*S*-methylhexyl compound (JWH-257, **14**, $n = 3$, $K_i = 1.0 \pm 0.3$ nM). CB_2 receptor affinity then decreases for the (2′*S*)-methylheptyl analog (JWH-357, **14**, $n = 4$) with $K_i = 185 \pm 4$ nM. In the (2′*R*)-methyl alkyl series (**11**, $n = 0$–4), only (2′*R*)-1-deoxy-3-(2′-methylpentyl)-Δ^8-THC (JWH-353, **11**, $n = 2$) has significant affinity for the CB_2 receptor with $K_i = 31 \pm 1$ nM. The trend in CB_2 receptor affinities in the (2′*S*)-methyl series is somewhat similar to that in the 1-deoxy-3-(1′,1′-dimethylalky)-Δ^8-THCs in which CB_2 receptor affinity increases from $K_i = 58$ nM for the dimethylethyl compound to $K_i = 76$ nM for the dimethyloctyl analog.[34] Those compounds in this series with three to seven carbon atoms all have $K_i < 20$ nM. Although the CB_2 receptor affinities of the 1-deoxy-(2′*S*)-methyl-Δ^8-THCs are not as great as those of the 1-deoxy-dimethylalkyl compounds, the general trends are similar. It is apparent that a (2′*R*)-methyl substituent has an adverse effect upon CB_2 receptor affinity.

4. Conclusions

Four of these 1-methoxy- and 1-deoxy-3-(2′-methylalkyl)-Δ^8-THCs, methoxy cannabinoid, JWH-359 (**12**, $n = 1$), and 1-deoxy cannabinoids, JWH-352 (**14**, $n = 1$), JWH-255 (**14**, $n = 2$), and JWH-353 (**11**, $n = 2$) are highly selective ligands for the cannabinoid CB_2 receptor, with little affinity for the CB_1 receptor. All of these 2′-methyl THC analogs were prepared by an enantioselective synthetic route using chiral auxiliaries derived from L- and D-valine. In the 1-methoxy-3-(2′-methylalkyl)-Δ^8-THC series, it was not possible to develop any systematic SAR at either the CB_1 or CB_2 receptor. In the 1-deoxy-3-(2′-methylalkyl)-Δ^8-THC series, the (2′*S*)-methyl compounds in general have greater affinity for the CB_2 receptor than the corresponding (2′*R*) isomers. In these 1-deoxy-2′*S*-methyl cannabinoids, an alkyl side chain of four to six carbon atoms provides maximum CB_2 receptor affinity. With one exception, (2′*S*)-1-deoxy-3-(2′-methylhexyl)-Δ^8-THC none of these compounds have significant affinity for the CB_1 receptor.

5. Experimental

5.1. General

^1H and ^{13}C NMR spectra were recorded on a Bruker 300AC or a JEOL 500 MHz 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 μ) 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.

5.2. 1-(3,5-Dimethoxyphenyl)-2-methylpropane (25)

To a stirred solution of 1.16 g (5.0 mmol) of 3,5-dimethoxybenzyl bromide[40] in 30 mL of dry THF was added 0.050 g (0.50 mmol) of CuCl. The reaction mixture was cooled to −78 °C and 10 mL (16 mmol) of 1.6 molar isopropylmagnesium chloride in ether was added. The reaction mixture was stirred at −78 °C for 2 h, allowed to warm to ambient temperature, and stirred for 18 h. After cooling to 0 °C, the reaction was quenched by the cautious addition of 10 mL of 1 M aqueous HCl. The resulting black slurry was filtered through a pad of Celite and extracted with three portions of ether. The combined ethereal extracts were washed with successive portions of water and brine. After drying ($MgSO_4$), the solvent was removed at reduced pressure and the residue was purified by flash chromatography (petroleum ether/dichloromethane, 20:80) to give 0.470 (56%) of 1-(3,5-dimethoxyphenyl)-2-methylpropane as a colorless oil; ^1H NMR (300 MHz, $CDCl_3$) δ 0.93 (d, $J = 6.5$ Hz, 6H), 1.85–1.95 (m, 1H), 2.43 (d, $J = 7.2$ Hz, 2H), 3.80 (s, 6H), 6.34 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 22.6, 30.3, 46.0, 55.4, 97.8, 107.4, 144.3, 160.7; MS (EI) *m*/*z* 194 (23), 152 (100).

5.3. 3-(2-Methylpropyl)-Δ^8-THC (13, $n = 0$)

Cannabinoid **13** ($n = 0$) was prepared from 1-(3,5-dimethoxyphenyl)-2-methylpropane (**25**) by the procedure described below for the preparation of **16** ($n = 1$). From 0.632 g (3.81 mmol) of 1-(3,5-dimethoxyphenyl)-2-methylpropane was obtained 0.344 g (30%) of 3-(2-methylpropyl)-Δ^8-THC (**13**, $n = 0$) following chromatography (petroleum ether/ethyl acetate, 97.5:2.5); ^1H NMR (300 MHz, $CDCl_3$) δ 0.89 (d, $J = 6.7$ Hz, 6H), 1.12 (s, 3H), 1.24–1.30 (m, 1H), 1.40 (s, 3H), 1.71 (s,

3H), 1.75–1.91 (m, 3H), 2.07–2.14 (m, 1H), 2.29–2.32, (m, 2H), 2.72 (td, $J = 4.6$, 10.8 Hz, 1H), 3.21 (dd, $J = 4.1$, 16.3 Hz, 1H), 4.91 (s, 1H), 5.44 (br d, $J = 4.0$ Hz, 1H), 6.08 (d, $J = 1.4$ Hz, 1H), 6.25 (d, $J = 1.4$ Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 18.7, 22.7, 23.7, 27.8, 28.1, 30.0, 31.8, 36.3, 45.1, 45.3, 76.6, 108.6, 110.0, 111.1, 119.5, 135.0, 141.7, 154.9; MS (EI) *m/z* 300 (48), 257 (35), 217 (100); $[\alpha]_D^{20}$ −245 (*c* 0.5, CH_2Cl_2).

5.4. 1-Methoxy-3-(2-methylpropyl)-Δ^8-THC (JWH-339, 12, *n* = 0)

Methyl ether **12** ($n = 0$) was prepared from cannabinoid **13** ($n = 0$) by the procedure employed for the preparation of **15** ($n = 1$) described below. From 0.065 g (0.216 mmol) of **13** ($n = 0$) was obtained 0.058 g (85%) of JWH-339 following chromatography (petroleum ether/ethyl acetate, 99:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.93 (d, $J = 6.6$ Hz, 6H), 1.11 (s, 3H), 1.44 (s, 3H), 1.80 (s, 3H), 1.50–1.93 (m, 4H), 2.00–2.30 (m, 1H), 2.40 (d, $J = 7.2$ Hz, 2H), 2.66–2.71 (m, 1H), 3.17 (dd 3.5, $J = 13.6$ Hz, 1H), 3.82 (s, 3H), 5.46 (br s, 1H), 6.24 (s, 1H), 6.30 (d, $J = 1.1$ Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 18.6, 22.8, 23.8, 27.8, 28.2, 30.2, 32.1, 36.5, 45.3, 45.8, 55.3, 76.6, 103.9, 111.3, 112.2, 119.5, 135.2, 141.4, 154.4, 159.0; MS (EI) *m/z* 314 (85), 271 (33), 231 (100); $[\alpha]_D^{20}$ −227 (*c* 0.5, CH_2Cl_2); HRMS Calcd for $C_{21}H_{30}O_2$, 314.2246; found: 314.2248.

5.5. 1-Deoxy-3-(2-methylpropyl)-Δ^8-THC (JWH-338, 11, *n* = 0)

Deoxyannabinoid **11** ($n = 0$) was prepared from cannabinoid **13** ($n = 0$) by the procedure employed for the preparation of **14** ($n = 1$). From 0.160 g (0.53 mmol) of **13** ($n = 0$) was obtained 0.067 g (44% for two steps) of JWH-338 following chromatography (petroleum ether/ether, 98:2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.93 (d, $J = 6.6$ Hz, 3H), 0.94 (d, $J = 6.6$ Hz, 3H), 1.19 (s, 3H), 1.43 (s, 3H), 1.65–2.05 (m, 4H), 1.77 (s, 3H), 2.10–2.25 (m, 1H), 2.37–2.45 (m, 2H), 2.60–2.80 (m, 2H), 5.49 (br s, 1H), 6.63 (d, $J = 1.4$ Hz, 1H), 6.70 (dd, $J = 1.5$, 7.8 Hz, 1H), 7.13 (d, $J = 7.7$ Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 19.4, 22.7, 22.8, 23.7, 27.7, 27.9, 30.2, 32.4, 36.8, 43.1, 45.3, 76.9, 117.8, 120.2, 121.1, 123.2, 126.5, 133.7, 141.3, 152.9; MS (EI) *m/z*; 284 (100), 241 (35), 201 (100); $[\alpha]_D^{20}$ −190 (*c* 0.5, CH_2Cl_2); HRMS Calcd for $C_{20}H_{28}O$, 284.2140; found: 284.2147.

5.6. Oxazolidinone of (*R*)-2-methyl-3,5-dimethoxyphelyl-propanoic acid (22)

To a solution of 1.51 g (15 mmol) of diisopropylamine in 15 mL of dry THF at 0 °C under argon was added 7.46 mL of 2 M *n*-butyllithium in hexanes (15 mmol) and the mixture was stirred at 0 °C for 10 min. After cooling to −78 °C, a solution of 2.76 g (15 mmol) of the L-valine derived oxazolidinone of propionic acid (**21**)[39,40] in 45 mL of dry THF was added and the deep yellow solution was stirred for no more than 1 min. A solution of 3.46 g (15 mmol) of 3,5-dimethoxybenzyl bromide and 2.85 mL (16.4 mmol) HMPA in 20 mL of dry THF was added. It is important that the addition of the benzyl bromide takes place as soon as possible following deprotonation of the acyl oxazolidinone to avoid decomposition of the anion via a ketene acetal. The reaction mixture was stirred at −78 °C for an additional 4 h and quenched with pH 7 buffer. After warming to ambient temperature, the THF was removed in vacuo and the residue was taken up in ether. The ethereal solution was washed with water and dried ($MgSO_4$). The solvent was removed in vacuo to afford 4.72 g (94%) of **22**, mp 93–95 °C, as a single diastereomer. GLC indicated that less than 1% of the other diastereomer was present. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.84 (d, $J = 7.0$ Hz, 3H), 0.88 (d, $J = 7.0$ Hz, 3H), 1.13 (d, $J = 6.6$ Hz, 3H), 2.29–2.34 (m, 1H), 2.57 (dd, $J = 7.3$, 13.4 Hz, 1H), 2.93 (dd, $J = 7.7$, 13.4 Hz, 1H), 3.77 (s, 6H), 4.08–4.23 (m, 3H), 4.41–4.43 (m, 1H), 6.41 (t, $J = 1.8$ Hz, 1H), 6.43 (d, $J = 1.8$ Hz, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.7, 17.6, 17.9, 28.4, 39.2, 39.9, 55.2, 58.6, 63.3, 98.5, 106.9, 141.6, 153.6, 160.5, 176.5; MS (EI) *m/z* 335 (45), 179 (100). The oxazolidinine (**30**), mp 93–95 °C, derived from D-valine via **29** has identical spectroscopic properties.

5.7. (*R*)-2-Methyl-3-(3,5-dimethoxyphenyl)-1-propanol (19)

To a stirred solution of 0.870 g (2.6 mmol) of acyl oxazolidinone **22** in 20 mL of dry THF was added 0.300 g (7.9 mmol) of lithium aluminum hydride. The reaction mixture was stirred at ambient temperature for 1 h and then quenched by the cautious addition of aqueous HCl (1 M). The THF was removed in vacuo and the resulting paste was taken up in ether and washed well with KOH (1 M) and water. After drying ($MgSO_4$), the solvent was removed at reduced pressure to give 0.546 g (99%) of alcohol as a colorless oil after chromatography (petroleum ether/ethyl acetate, 4:1). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.92 (d, $J = 6.7$ Hz, 3H), 1.57 (br s, 1H), 1.89–2.00 (m, 1H), 2.35 (dd, $J = 8.1$, 13.3 Hz, 1H), 2.70 (dd, $J = 6.4$, 13.3 Hz, 1H), 3.44–3.55 (m, 2H), 3.78 (s, 6H), 6.31 (t, $J = 2.1$ Hz, 1H), 6.34 (d, $J = 2.1$ Hz, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 16.5, 37.6, 40.0, 55.2, 67.6, 97.7, 107.1, 143.1, 160.6; MS (EI) *m/z* 210 (50), 152 (100); $[\alpha]_D^{20}$ +29.3 (*c* 0.41, CH_2Cl_2). (*S*)-2-Methyl-3-(3,5-dimethoxyphenyl)-1-propanol (**20**) was prepared from oxazolidinone **30** by the same procedure and had identical spectroscopic properties. Alcohols **19** and **20** are identical to the alcohols prepared previously through resolution of 3-(3,5-dimethoxyphenyl)propanoic acid (**7**).[36]

5.8. Mosher ester of (*R*)-3-(3,5-dimethoxyphenyl)-2-methyl-1-propanol

To a stirred solution of 0.0088 g (0.042 mmol) of (*R*)-3,5-dimethoxyphenyl-2-methyl-1-propanol (**19**) and 0.0104 g (0.082 mmol) DMAP in 2 mL of dichloromethane at ambient temperature was added 0.015 g (0.060 mmol) (*R*)-(−)-MTPA-Cl.[43] The reaction mixture was stirred for 24 h, quenched with saturated aqueous NH_4Cl, and the mixture was extracted with three portions of dichloromethane. The combined extracts were washed successively with 1 M aqueous HCl, water, and brine. After drying ($MgSO_4$), the solvent was removed

in vacuo and the residue was chromatographed (petroleum ether/ether, 9:1) to give 0.011 g of the Mosher ester as a pale yellow gum; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.94 (d, J = 6.9 Hz, 3H), 2.39 (dd, J = 7.8, 13, 8 Hz, 1H), 2.60 (dd, J = 6.8, 13.3 Hz, 1H), 3.56 (s, 3H), 3.76 (s, 6H), 4.14 (dd, J = 5.5, 10.6 Hz, 1H), 4.20 (dd, J = 6.0, 11.0 Hz, 1H), 6.26 (d, J = 2.3 Hz, 2H), 6.31 (t, J = 2.3 Hz, 1H), 7.39–7.43 (m, 3H), 7.50–7.55 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 16.8, 34.5, 39.8, 55.3, 55.5, 70.3, 98.1, 107.2, 127.5, 128.6, 129.8, 132.4, 142.0, 160.8, 166.7; MS (EI) m/z 426 (52), 152 (100); $[\alpha]_D^{20}$ −40.8 (c 0.6, CH_2Cl_2).

5.9. Mosher ester of (*S*)-3-(3,5-dimethoxyphenyl)-2-methyl-1-propanol

The (*R*)-(−)-MTPA-Cl derived Mosher ester of (*S*)-(3,5-dimethoxyphenyl)-2-methyl-1-propanol was prepared by the procedure used for the (*R*)-enantiomer. From 0.0055 g (0.026 mmol) of alcohol was obtained 0.0093 g (84%) of the ester as a pale yellow gum. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.93 (d, J = 6.9 Hz, 3H), 2.12–2.22 (m, 1H), 2.41 (dd, J = 7.3, 13.8 Hz, 1H), 2.61 (dd, J = 6.8, 13.3 Hz, 1H), 3.56 (s, 3H), 3.76 (s, 6H), 4.09 (dd, J = 6.0, 10.5 Hz, 1H), 4.27 (dd, J = 5.5, 11.0 Hz, 1H), 6.27 (d, J = 2.3 Hz, 2H), 6.32 (t, J = 2.3 Hz, 1H), 7.40–7.42 (m, 3H), 7.50–7.60 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 16.8, 34.4, 39.8, 55.3, 55.5, 70.3, 98.1, 107.2, 127.5, 128.6, 129.7, 132.0, 141.9, 160.8, 167.0; MS (EI) m/z 426 (44), 152 (100); $[\alpha]_D^{20}$ −13.0 (c 0.37, CH_2Cl_2).

5.10. Trifluoromethanesulfonate of (*R*)-2-methyl-3-(3,5-dimethoxyphenyl)-1-propanol

To a stirred solution of 0.349 g (1.66 mmol) of alcohol **19** and 0.17 mL (1.99 mmol) of dry pyridine in 10 mL of dichloromethane at −78 °C was added 0.33 mL of trifluoromethanesulfonic anhydride. The reaction was stirred for 3 h at −78 °C and then quenched with water. The phases were separated and the aqueous phase was extracted with three portions of dichloromethane. The combined organic extracts were washed with successive portions of water and saturated brine, dried ($MgSO_4$), and the solvent was removed in vacuo. The trifluoromethanesulfonate was obtained as a pale brown liquid that was used in subsequent reactions without further purification. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.04 (d, J = 6.9 Hz, 3H), 2.20–2.30 (m, 1H), 2.51 (dd, J = 7.4, 13.3 Hz, 1H), 2.67 (dd, J = 6.9 Hz, 1H), 3.77 (s, 6H), 4.35 (dd, J = 5.5, 9.2 Hz, 1H), 4.38 (dd, J = 5.0, 9.2 Hz, 1H), 6.28–6.32 (m, 2H), 6.34 (t, J = 2.3 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 16.2, 35.2, 39.1, 55.3, 81.0, 98.5, 107.1, 140.9, 161.0. The trifluoromethanesulfonate of (*S*)-2-methyl-3-(3,5-dimethoxyphenyl)-1-propanol (**20**) was prepared by the same procedure and had identical spectroscopic properties.

5.11. (*S*)-1-(3,5-Dimethoxyphenyl)-2-methylbutane (17, *n* = 1)

To a stirred solution of 0.568 g (1.66 mmol) of the triflate of alcohol **19** in 12 mL of THF was added 2 mL Li_2CuCl_4 prepared from 0.0142 g (0.34 mmol) LiCl and 0.023 g (0.17 mmol) $CuCl_2$. To this solution was added at −78° C 4.17 mL of ethereal methylmagnesium bromide (3.17 M) over 2 min; the solution was allowed to warm to ambient temperature and stirred for 24 h. The reaction was cooled to 0 °C and quenched by the cautious addition of water. The resulting slurry was passed through a short pad of Celite and concentrated in vacuo. The concentrated solution was taken up in ether, washed with successive portions of 1 N HCl, water, and brine. After drying ($MgSO_4$), the solvent was removed in vacuo and the residue was chromatographed (petroleum ether/ether, 9:1) to give 0.274 g (70%) of **17** (n = 1) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.85 (d, J = 6.6 Hz, 3H), 0.90 (t, J = 7.4 Hz, 3H), 1.09–1.26 (m, 1H), 1.33–1.44 (m, 1H), 1.58–1.67 (m, 1H), 2.29 (dd, J = 8.1, 13.3 Hz, 1H), 2.57 (dd, J = 6.3, 13.3 Hz, 1H), 3.78 (s, 6H), 6.31 (6, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 11.5, 18.9, 29.2, 36.5, 43.7, 55.2, 97.5, 107.2, 144.2, 160.5; MS (EI) m/z 208 (50), 152 (100); $[\alpha]_D^{20}$ −18.2 (c 0.75, CH_2Cl_2).

5.12. (2′*S*)-3-(2′-Methylbutyl)-Δ^8-tetrahydrocannabinol (16, *n* = 1)

To 0.060 g (0.29 mmol) of dimethyl ether **17** (n = 1) at 0 °C was added 0.6 mL of 1 M boron tribromide in CH_2Cl_2. The solution was stirred at 0 °C for 1 h, warmed to ambient temperature, and stirred for 18 h. After cooling to 0 °C, water was added to quench the reaction. After dilution with CH_2Cl_2, the aqueous phase was drawn off and the CH_2Cl_2 was washed with brine and dried ($MgSO_4$). The solvent was removed in vacuo to give 0.051 g (99%) of resorcinol as a brown oil which was used in the next step without purification. ^{1}H NMR (300 MHz, $CHCl_3$) δ 0.82 (d, J = 6.6 Hz, 3H), 0.87 (t, J = 7.3 Hz, 3H), 1.08–1.18 (m, 1H), 1.25–1.40 (m, 1H), 1.54–1.59 (m, 1H), 2.21 (dd, J = 8.1, 13.3 Hz, 1H), 2.49 (dd, J = 6.3, 13.3 Hz, 1H), 4.94 (br s, 2H), 6.32 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 11.4, 18.9, 29.1, 36.3, 43.2, 100.2, 108.9, 145.0, 156.3.

To a stirred solution of 0.050 g (0.28 mmol) of the resorcinol derived from ether **17** (n = 1) and 0.042 g (0.28 mmol) of *p*-menthadienol in 3 mL of dry benzene at room temperature was added 0.005 g *p*-toluenesulfonic acid and the solution was heated at reflux for 2 h. After cooling to ambient temperature, the brown solution was poured into water and extracted with two portions of ethyl acetate, dried ($MgSO_4$), and the solvent was removed in vacuo. The residue was chromatographed (petroleum ether/dichloromethane, 3:2) to give 0.086 g (91%) of (2′*S*)-3-(2′-methylbutyl)-Δ^8-tetrahydrocannabinol (**16**, n = 1) as a yellow gum; ^{1}H NMR (300 MHz, $CHCl_3$) δ 0.83–0.91 (m, 6H), 1.11–1.47 (m, 2H), 1.12 (s, 3H), 1.38 (s, 3H), 1.55–1.62 (m, 1H), 1.70 (s, 3H), 1.78–1.90 (m, 3H), 2.13–2.23 (m, 2H), 2.45 (dd, J = 6.2, 13.3 Hz, 1H), 2.70 (td, J = 4.0, 10.8 Hz, 1H), 3.20 (dd, J = 4.0, 16.3 Hz, 1H), 4.79 (br s, 1H), 5.42 (br s, 1H), 6.07 (d, J = 1.2 Hz, 1H), 6.24 (d, J = 1.2 Hz, 1H); ^{13}C NMR (75.5 MHz, $CHCl_3$) δ 11.5, 18.5, 19.1, 23.5, 27.5, 29.2, 31.5, 36.0, 36.3, 42.9, 44.9, 76.6, 108.4, 110.5, 110.9, 119.3, 134.7, 141.5, 154.6;

MS (EI) *m/z* 314 (50), 258 (100); $[\alpha]_D^{20}$ −213 (*c* 0.5, CH_2Cl_2).

5.13. (2′*S*)-1-Methoxy-3-(2′-methylbutyl)-Δ^8-tetrahydrocannabinol (JWH-351, 15, *n* = 1)

To a solution of 0.045 g (0.143 mmol) of cannabinoid **16** (*n* = 1) in 1 mL DMF was added 0.010 g KOH. The solution was stirred at ambient temperature for 10 min and 0.050 g (0.348 mmol) of methyl iodide was added. The reaction mixture was stirred at ambient temperature for 18 h, poured into water, and extracted with three portions of ether. The combined extracts were washed with water, dried ($MgSO_4$), and the solvent was removed in vacuo to give, after chromatography (petroleum ether/ether, 3:2), 0.039 g (83%) of methoxy cannabinoid **16** (*n* = 1) as a colorless oil. ^{1}H NMR (500 MHz, $CHCl_3$) δ 0.85 (d, *J* = 6.9 Hz, 3H), 0.90 (t, *J* = 7.8 Hz, 3H), 1.08 (s, 3H), 1.10–1.20 (m, 1H), 1.33–1.45 (m, 1H), 1.40 (s, 3H), 1.56–1.66 (m, 1H), 1.70 (s, 3H), 1.71–1.85 (m, 3H), 2.10–2.18 (m, 1H), 2.26 (dd, *J* = 8.3, 13.3 Hz, 1H), 2.52 (dd, *J* = 6.0, 13.3 Hz, 1H), 2.66 (dt, *J* = 5.0, 11.0 Hz, 1H), 3.15 (dd, *J* = 4.6, 16.5 Hz, 1H), 3.79 (s, 3H), 5.41 (br d, *J* = 4.2 Hz, 1H), 6.21 (d, *J* = 1.4 Hz, 1H), 6.27 (d, *J* = 1.4 Hz, 1H); ^{13}C NMR (125 MHz, $CHCl_3$) δ 11.6, 18.5, 19.2, 23.7, 27.7, 28.1, 29.4, 31.9, 36.4, 36.5, 43.6, 45.2, 55.2, 76.9, 103.8, 111.2, 112.0, 119.4, 135.1, 141.3, 154.2, 158.9; MS (EI) *m/z* 328 (98), 272 (95), 245 (100); $[\alpha]_D^{20}$ −275 (*c* 0.48, CH_2Cl_2); Calcd for $C_{22}H_{32}O_2$, 328.2402; found: 328.2402.

5.14. (2′*S*)-1-Deoxy-3-(2′-methylbutyl)-Δ^8-tetrahydrocannabinol (JWH-352, 14, *n* = 1)

To a stirred solution of 0.090 g (0.29 mmol) of cannabinoid **16** (*n* = 1) in 1 mL of dry THF at ambient temperature was added 0.011 g (0.27 mmol) of sodium hydride (60% in mineral oil). The resulting slurry was stirred until the evolution of hydrogen ceased, then cooled to 0 °C, and 0.063 g (0.58 mmol) of diethyl chlorophosphate was added. The reaction mixture was allowed to warm to ambient temperature, stirred for 3 h, poured into water, and extracted with three portions of ether. The combined ethereal extracts were washed with water and 1 M aqueous KOH, dried ($MgSO_4$), and the solvent was removed in vacuo. Chromatography (petroleum ether/ethyl acetate, 4:1) gave 0.090 g (70%) of phosphate ester as a yellow oil which was used in the next step without further purification; ^{1}H NMR (500 MHz, $CHCl_3$) δ 0.84 (d, *J* = 6.9 Hz, 3H), 0.88 (t, *J* = 7.8 Hz, 3H), 1.09 (s, 3H), 1.30 (t, *J* = 6.8 Hz, 3H), 1.34–1.44 (m, 1H), 1.35 (t, *J* = 6.4 Hz, 3H), 1.56–1.67 (m, 1H), 1.69 (s, 3H), 1.74–1.94 (m, 3H), 2.08–2.20 (m, 1H), 2.25 (dd, *J* = 8.3, 13.3 Hz, 1H), 2.51 (dd, *J* = 6.4, 13.3 Hz, 1H), 2.78 (dt, *J* = 4.6, 10.5 Hz, 1H), 3.05 (dd, *J* = 4.1, 17 Hz, 1H), 4.10–4.30 (m, 4H), 5.42 (br d, *J* = 4.6 Hz, 1H), 6.46 (s, 1H), 6.69 (s, 1H); ^{13}C NMR (125 MHz, $CHCl_3$) δ 11.6, 16.2 (m), 18.5, 19.0, 23.5, 27.5, 27.9, 29.3, 31.8, 36.2, 36.4, 43.0, 64.5 (d, *J* = 5.7 Hz), 76.9, 112.7, 115.1 (d, *J* = 6.7 Hz), 115.1, 119.5, 134.5, 141.7, 149.8 (d, *J* = 6.7 Hz), 154.5; MS (EI) *m/z* 450 (28), 367 (100), 296 (34); $[\alpha]_D^{20}$ −150 (*c* 0.5, CH_2Cl_2).

To approximately 25 mL of liquid NH_3 at −78 °C was added, with stirring, 0.016 g of Li metal. The deep blue solution was stirred at −78 °C for 10 min and a solution of 0.080 g (0.18 mmol) of phosphate ester in 2 mL of dry THF was added via cannula. The solution was stirred at −78 °C for 2 h and then quenched with solid NH_4Cl. The resulting suspension was warmed to ambient temperature and following evaporation of the NH_3 the residue was taken up in a mixture of ether and water. The organic phase was separated and the aqueous phase was extracted with three portions of ether. The combined organic extracts were washed with water, dried ($MgSO_4$), and the solvent was removed at reduced pressure. The residue was chromatographed (petroleum ether/ethyl acetate, 99.5:0.5) to give 0.043 g (81%) of deoxycannabinoid as a colorless oil. ^{1}H NMR (500 MHz, $CHCl_3$) δ 0.84 (d, *J* = 6.5 Hz, 3H), 0.89 (t, *J* = 7.4 Hz, 3H), 1.09–1.20 (m, 1H), 1.15 (s, 3H), 1.34–1.45 (m, 1H), 1.38 (s, 3H), 1.58–1.75 (m, 2H), 1.73, (s, 3H), 1.77–1.87 (m, 1H), 1.91–2.00 (m, 1H), 2.10–2.20 (m, 1H), 2.27 (dd, *J* = 8.3, 13.8 Hz, 1H), 2.52 (dd, *J* = 6.4, 13.3 Hz, 1H), 2.60 (dd, *J* = 5.5, 16.5 Hz, 1H), 2.64–2.72 (m, 1H), 5.44 (br d, *J* = 2.8 Hz, 1H), 6.59 (d, *J* = 1.8 Hz, 1H), 6.66 (dd, *J* = 1.4, 7.8 Hz, 1H), 7.09 (d, *J* = 7.8 Hz, 1H); ^{13}C NMR (125 MHz, $CHCl_3$) δ 11.6, 19.2, 19.3, 23.6, 27.6, 27.8, 29.3, 32.3, 36.6, 36.7, 43.0, 43.1, 76.9, 117.8, 120.1, 121.1, 123.0, 126.4, 133.6, 141.2, 152.8; MS (EI) *m/z* 298 (100), 215 (72); $[\alpha]_D^{20}$ −220 (*c* 0.5, CH_2Cl_2); Calcd for $C_{21}H_{30}O$, 298.2297; found: 298.2292.

5.15. (2′*R*)-3-(2′-Methylbutyl)-Δ^8-tetrahydrocannabinol (13, *n* = 1)

Cannabinoid **13** (*n* = 1) was prepared from 2*R*-methyl-1-(3,5-dimethoxyphenyl)butane (**18**, *n* = 1) by the procedure used for the synthesis of **16** (*n* = 1). From 0.165 g (0.79 mmol) of 2*R*-methyl-1-(3,5-dimethoxyphenyl)butane was obtained 0.100 g (40% for two steps) (2′*R*)-3-(2′-methylbutyl)-Δ^8-tetrahydrocannabinol (**13**, *n* = 1) as a pale yellow gum following chromatography (petroleum ether/ether, 92:8). ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.82 (d, *J* = 6.9 Hz, 3H), 0.88 (t, *J* = 7.3 Hz, 3H), 1.10 (s, 3H), 1.09–1.19 (m, 1H), 1.31–1.43 (m, 1H), 1.37 (s, 3H), 1.53–1.63 (m, 1H), 1.69 (s, 3H), 1.67–1.73 (m, 1H), 1.73–1.90 (m, 3H), 2.08–2.20 (m, 2H), 2.47 (dd, *J* = 6.0, 13.3 Hz, 1H), 2.68 (dt, *J* = 4.6, 10.6 Hz, 1H), 3.2 (dd, *J* = 4.6, 16.5 Hz, 1H), 5.41 (br d, *J* = 4.2 Hz, 1H), 6.07 (d, *J* = 1.4 Hz, 1H), 6.23 (d, *J* = 1.4 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 11.5, 18.6, 19.2, 23.6, 27.7, 28.0, 29.3, 31.7, 36.1, 36.4, 43.0, 45.0, 76.9, 108.5, 110.6, 110.9, 119.4, 134.9, 141.6, 154.7, 154.8; MS (EI) *m/z* 314 (61), 258 (93), 231 (100); $[\alpha]_D^{20}$ −215 (*c* 0.5, CH_2Cl_2).

5.16. (2′*R*)-1-Methoxy-3-(2′-methylbutyl)-Δ^8-tetrahydrocannabinol (JWH-359, 12, *n* = 1)

Methoxycannabinoid **12** (*n* = 1) was prepared as described above for the synthesis of **15** (*n* = 1). From 0.055 g (0.175 mmol) of cannabinoid **13** (*n* = 1) was obtained 0.047 g (82%) of JWH-359. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.85 (d, *J* = 6.4 Hz, 3H), 0.90 (t, *J* = 7.3 Hz,

3H), 1.09 (s, 3H), 1.10–1.22 (m, 1H), 1.33–1.45 (m, 1H), 1.37 (s, 3H), 1.58–1.68 (m, 1H), 1.70 (s, 3H), 1.73–1.85 (m, 3H), 2.08–2.20 (m, 1H), 2.23 (dd, $J = 8.3$, 13.3 Hz, 1H), 2.54 (dd, $J = 6.5$, 13.3 Hz, 1H), 2.65 (dt, $J = 4.6$, 11.0 Hz, 1H), 3.15 (dd, $J = 5.5$, 17.0 Hz, 1H), 3.79 (s, 3H), 5.41 (br d, $J = 4.2$ Hz, 1H), 6.21 (d, $J = 1.4$ Hz, 1H), 6.27 (d, $J = 1.4$ Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 11.6, 18.5, 19.2, 23.7, 27.7, 28.1, 29.4, 31.9, 36.4, 36.5, 43.6, 45.2, 55.2, 76.9, 103.9, 111.2, 112.0, 119.4, 135.1, 141.4, 154.3, 158.9; MS (EI) *m/z* 328 (67), 272 (69), 245 (100); $[\alpha]_D^{20}$ −269 (*c* 0.5, CH_2Cl_2); HRMS Calcd for $C_{22}H_{32}O_2$, 328.2402; found: 328.2405.

5.17. (2′*R*)-1-Deoxy-3-(2′-methylbutyl)-Δ^8-tetrahydrocannabinol (JWH-360, 11, *n* = 1)

Deoxycannabinoid **11** ($n = 1$) was prepared from (2′*R*)-3-(2′-methylbutyl)-Δ^8-tetrahydrocannabinol (**13**, $n = 1$) by the procedure used for the preparation of **14** ($n = 1$). From 0.099 g (0.31 mmol) of (2′*R*)-3-(2′-methyl butyl)-Δ^8-tetrahydrocannabinol was obtained 0.060 g (62% for two steps) of deoxycannabinoid JWH-360 as a colorless oil after chromatography (petroleum ether/ether, 98:2). ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.84 (d, $J = 6.9$ Hz, 3H), 0.89 (t, $J = 7.8$ Hz, 3H), 1.10–1.21 (m, 1H), 1.15 (s, 3H), 1.34–1.44 (m, 1H), 1.38 (s, 3H), 1.57–1.76 (m, 2H), 1.73 (s, 3H), 1.77–1.86 (m, 1H), 1.91–2.00 (m, 1H), 2.11–2.20 (m, 1H), 2.25 (td, $J = 8.3$, 13.3 Hz, 1H), 2.50–2.72 (m, 3H), 5.45 (br d, $J = 2.8$ Hz, 1H), 6.60 (d, $J = 1.9$ Hz, 1H), 6.66 (dd, $J = 1.4$, 7.8 Hz, 1H), 7.09 (d, $J = 7.8$ Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 11.7, 19.2, 19.3, 23.6, 27.6, 27.8, 29.4, 32.3, 36.6, 36.7, 43.0, 43.1, 76.9, 117.8, 120.1, 121.2, 123.0, 126.4, 133.6, 141.2, 152.8; MS (EI) *m/z* 298 (100), 215 (85); $[\alpha]_D^{20}$ −157 (*c* 1.0, CH_2Cl_2); HRMS Calcd for $C_{21}H_{30}O$, 298.2297; found: 298.2298.

5.18. Methanesulfonate of *R*-2-Methyl-3-(3,5-dimethoxyphenyl)-1-propanol

To a stirred solution of 0.750 g (3.57 mmol) of alcohol **19** in 6 mL of dry $CHCl_3$ were added sequentially 0.5 mL (3.57 mmol) of triethylamine, 0.409 g (3.57 mmol) of methanesulfonyl chloride, and 0.043 g (0.357 mmol) of 4-DMAP. The reaction mixture was stirred at ambient temperature for 1 h, poured into water, and washed with 1 M aqueous KOH, and water. After drying ($MgSO_4$), the solvent was removed in vacuo and the residue was chromatographed (petroleum ether/ethyl acetate, 4:1) to give 0.966 g (94%) of mesylate as a yellow oil that was used in subsequent reactions without further purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.01 (d, $J = 6.7$ Hz, 3H), 2.14–2.25 (m, 1H), 2.47 (dd, $J = 7.6$, 13.5 Hz, 1H), 2.70 (dd, $J = 6.9$, 13.5 Hz, 1H), 3.00 (s, 3H), 3.78 (s, 6H), 4.01–4.13 (m, 2H), 6.32 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 16.5, 34.8, 37.2, 39.4, 55.3, 73.6, 98.2, 107.2, 141.5, 160.8; MS (EI) *m/z* 288 (50), 151 (100); $[\alpha]_D^{20}$ +25.4 (*c* 0.21, CH_2Cl_2).

5.19. (*S*)-1-(3,5-Dimethoxyphenyl)-2-methylpentane (17, *n* = 2)

To a stirred solution of 0.373 g (1.30 mmol) of the mesylate of alcohol **19** in 7 mL of dry THF at −78 °C were added sequentially 0.013 g (0.13 mmol) of CuCl and 1.17 mL (3.90 mmol) of 3 M ethylmagnesium bromide in ether. The yellow-green solution was stirred at −78 °C for 6 h, warmed to ambient temperature, and stirred for 18 h. The black slurry was filtered through Celite and the residue was washed well with ether. The ethereal solution was dried ($MgSO_4$), and the solvent was removed at reduced pressure. Chromatography (petroleum ether/ethyl acetate, 95:5) gave 0.199 g (87%) of *S*-1-(3,5-dimethoxyphenyl)-2-methylpentane (**17**, $n = 2$) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.85–0.91 (m, 6H), 1.10–1.39 (m, 4H), 1.69–1.73 (m, 1H), 2.28 (dd, $J = 8.2$, 13.3 Hz, 1H), 2.57 (dd, $J = 6.1$, 13.3 Hz, 1H), 3.78 (s, 6H), 6.31 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.3, 19.4, 20.2, 34.5, 39.0, 44.1, 55.2, 97.5, 107.2, 144.2, 160.5; MS (EI) *m/z* 222 (50), 152 (100); $[\alpha]_D^{20}$ −14.6 (*c* 0.50, CH_2Cl_2). (*R*)-1-(3,5-Dimethoxyphenyl)-2-methylpentane (**18**, $n = 2$) was prepared from alcohol **20** in 76% yield by the same procedure. The spectroscopic properties are identical to those of the *S*-enantiomer and are identical to those reported previously for these compounds.[36]

5.20. (2′*S*)-3-(2′-Methylpentyl)-Δ^8-tetrahydrocannabinol (16, *n* = 2)

Cannabinoid **16** ($n = 2$) was prepared from dimethyl ether **17** ($n = 2$) by the procedure employed for the preparation of **16** ($n = 1$). From 0.250 g (1.13 mmol) of **17** ($n = 2$) 0.101 g (29% for two steps) of (2′*S*)-3-(2′-methylpentyl)-Δ^8-tetrahydrocannabinol (**16**, $n = 2$) was obtained as a yellow gum following chromatography (petroleum ether/dichloromethane, 3:2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.82 (d, $J = 6.5$ Hz, 3H), 0.86 (t, $J = 6.8$ Hz, 3H), 1.05–1.41 (m, 4H), 1.10 (s, 3H), 1.37 (s, 3H), 1.66–1.72 (m, 1H), 1.69 (s, 3H), 1.78–1.89 (m, 3H), 2.12–2.19 (m, 2H), 2.45 (dd, $J = 5.9$, 13.3 Hz, 1H), 2.69 (td, $J = 4.2$, 10.8 Hz, 1H), 3.21 (dd, $J = 4.2$, 16.2 Hz, 1H), 5.05 (br s, 1H), 5.42 (br s, 1H), 6.06 (d, $J = 1.2$ Hz, 1H), 6.24 (d, $J = 1.2$ Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.2, 18.4, 19.5, 20.2, 23.4, 27.5, 27.8, 31.6, 34.3, 36.0, 39.1, 43.3, 44.9, 76.6, 108.4, 110.6, 110.8, 119.3, 134.7, 141.4, 154.7; MS (EI) *m/z* 328 (50), 258 (100); $[\alpha]_D^{20}$ −219 (*c* 0.5, CH_2Cl_2). The spectroscopic properties are identical to those reported previously.[36]

5.21. (2′*S*)-1-Methoxy-3-(2′-methyl pentyl)-Δ^8-tetrahydrocannabinol (JWH-254, 15, *n* = 2)

Methyl ether **15** ($n = 2$) was prepared from cannabinoid **16** ($n = 2$) by the procedure employed for the preparation of **15** ($n = 1$). From 0.038 g (0.116 mmol) of **16** ($n = 2$) was obtained 0.039 g (99%) of JWH-254 as a yellow oil following chromatography (petroleum ether/dichloromethane, 3:2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.83–0.90 (m, 6H), 1.08–1.43 (m, 4H), 1.12 (s, 3H), 1.37 (s, 3H), 1.66–1.72 (m, 1H), 1.70 (s, 3H), 1.77–1.82 (m, 3H), 2.12–2.13 (m, 1H), 2.24 (dd, $J = 8.2$, 13.3 Hz, 1H), 2.53 (dd, $J = 6.0$, 13.3 Hz, 1H), 2.65 (td, $J = 6.0$, 10.8 Hz, 1H), 3.15 (dd, $J = 6.0$, 17.0 Hz, 1H), 3.79 (s, 3H), 5.42 (d, $J = 4.1$ Hz, 1H), 6.21 (d, $J = 1.2$ Hz, 1H), 6.27 (d, $J = 1.1$ Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$)

δ 14.3, 18.4, 19.5, 20.2, 23.5, 27.6, 28.0, 31.8, 34.4, 36.3, 39.2, 43.9, 45.1, 55.1, 76.4, 103.7, 111.1, 119.3, 135.0, 141.2, 154.1, 158.8; MS (EI) *m/z* 342 (50), 272 (100); $[\alpha]_D^{20}$ −131 (*c* 0.3, CH_2Cl_2); HRMS Calcd for $C_{23}H_{32}O_2$, 342.2554; found: 342.2558.

5.22. (2′*S*)-1-Deoxy-3-(2′-methyl pentyl)-Δ^8-tetrahydrocannabinol (JWH-255, 14, *n* = 2)

Deoxyannabinoid **14** (*n* = 2) was prepared from cannabinoid **16** (*n* = 2) by the procedure employed for the preparation of **14** (*n* = 1). From 0.060 g (0.183 mmol) of **16** (*n* = 2) was obtained 0.060 g (70% for two steps) of JWH-255 as a yellow gum following chromatography (petroleum ether/ethyl acetate, 4:1). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.82–0.90 (m, 6H), 1.09–1.43 (m, 4H), 1.15 (s, 3H), 1.38 (s, 3H), 1.66–1.73 (m, 2H), 1.70 (s, 3H), 1.81–1.99 (m, 2H), 2.12–2.19 (m, 1H), 2.25 (dd, *J* = 8.2, 13.3 Hz, 1H), 2.52–2.70 (m, 2H), 2.55 (dd, *J* = 5.8, 13.3 Hz, 1H), 5.42 (d, *J* = 4.0 Hz, 1H), 6.59 (d, *J* = 1.5 Hz, 1H), 6.66 (dd, *J* = 1.5, 7.8 Hz, 1H), 7.10 (d, *J* = 7.8 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.3, 19.2, 19.5, 20.2, 23.5, 27.5, 27.7, 32.2, 34.5, 36.6, 39.1, 42.9, 43.4, 76.8, 117.7, 119.9, 120.9, 122.9, 126.2, 133.5, 141.1, 152.7; MS (EI) *m/z* 312 (60), 229 (100); $[\alpha]_D^{20}$ −119 (*c* 0.5, CH_2Cl_2); HRMS Calcd for $C_{22}H_{32}O$, 312.2457; found: 312.2453.

5.23. (2′*R*)-3-(2′-methylpentyl)-Δ^8-tetrahydrocannabinol (13, *n* = 2)

Cannabinoid **13** (*n* = 2) was prepared from (*R*)-2-methyl-1-(3,5-dimethoxyphenyl)pentane (**18**, *n* = 2) by the procedure used for the synthesis of **16** (*n* = 1). From 0.389 g (1.14 mmol) of (*R*)-2-methyl-1-(3,5-dimethoxy phenyl)pentane was obtained 0.200 g (56% for two steps) of cannabinoid **13** (*n* = 2) as a pale yellow gum following chromatography (petroleum ether/ether, 9:1). ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.82 (d, *J* = 6.4 Hz, 3H), 0.86 (t, *J* = 6.9 Hz, 3H), 1.06–1.18 (m, 1H), 1.12 (s, 3H), 1.20–1.43 (m, 3H), 1.38, (s, 3H), 1.70 (s, 3H), 1.60–1.75 (m, 1H), 1.76–1.93 (m, 3H), 2.09–2.20 (m, 2H), 2.48 (dd, *J* = 6.0, 13.3 Hz, 1H), 2.69 (dt, *J* = 4.6, 11.0 Hz, 1H), 3.20 (dd, *J* = 4.2, 16.0 Hz, 1H), 4.83 (d, *J* = 1.8 Hz, 1H), 5.42 (br d, *J* = 4.6 Hz, 1H), 6.06 (d, *J* = 1.4 Hz, 1H), 6.24 (d, *J* = 1.9 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.4, 18.6, 19.6, 20.3, 23.6, 27.7, 28.0, 31.7, 34.4, 36.1, 39.2, 43.4, 45.0, 76.9, 108.6, 110.7, 111.0, 119.4, 134.9, 141.6, 154.7, 154.8; MS (EI) *m/z* 328 (80), 258 (100), 245 (79); $[\alpha]_D^{20}$ −231 (*c* 0.6, CH_2Cl_2). The spectroscopic properties of this compound are identical to those reported previously.[36]

5.24. (2′*R*)-1-Methoxy-3-(2′-methylpentyl)-Δ^8-tetrahydrocannabinol (JWH-354, 12, *n* = 2)

Methoxycannabinoid **12** (*n* = 2) was prepared as described above for the synthesis of **15** (*n* = 1). From 0.060 g (0.182 mmol) of **13** (*n* = 2) was obtained 0.045 g (72%) of JWH-354. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.84 (d, *J* = 6.9 Hz, 3H), 0.88 (t, *J* = 7.4 Hz, 3H), 1.06–1.17 (m, 1H), 1.09 (s, 3H), 1.23–1.44 (m, 3H), 1.38 (s, 3H), 1.63–1.86 (m, 4H), 1.70 (s, 3H), 2.12 (br dd, *J* = 3.7, 8.7 Hz, 1H), 2.20 (dd, *J* = 8.3, 13.3 Hz, 1H), 2.55 (dd, *J* = 6.0, 13.3 Hz, 1H), 2.65 (dt, *J* = 4.6, 11.0 Hz, 1H), 3.15 (dd, *J* = 5.0, 17.0 Hz, 1H), 3.79 (s, 3H), 5.41 (d, *J* = 3.7 Hz, 1H), 6.20 (s, 1H), 6.28 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.4, 18.5, 19.6, 20.3, 23.7, 27.7, 28.1, 31.9, 34.6, 36.4, 39.3, 44.0, 45.2, 55.2, 76.9, 103.9, 111.2, 112.0, 119.4, 135.2, 141.4, 154.3, 158.9; MS (EI) *m/z* 342 (81), 272 (95), 259 (100); $[\alpha]_D^{20}$ −244 (*c* 0.32, CH_2Cl_2); HRMS Calcd for $C_{23}H_{34}O_2$, 342.2559; found: 342.2554.

5.25. (2′*R*)-1-Deoxy-3-(2′-methylpentyl)-Δ^8-tetrahydrocannabinol (JWH-353, 11, *n* = 2)

Deoxycannabinoid **11** (*n* = 2) was prepared from (2′*R*)-3-(2′-methyl pentyl)-Δ^8-tetrahydrocannabinol (**13**, *n* = 2) by the procedure used for the preparation of **15** (*n* = 1). From 0.099 g (0.31 mmol) of **13** (*n* = 2) was obtained 0.060 g (62% for two steps) of JWH-353 as a colorless oil after chromatography (petroleum ether/ether, 98:2). ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.75 (d, *J* = 6.9 Hz, 3H), 0.80 (t, *J* = 6.9 Hz, 3H), 1.00–1.11 (m, 1H), 1.07 (s, 3H), 1.17–1.35 (m, 3H), 1.31 (s, 3H), 1.58–1.68 (m, 2H), 1.65 (s, 3H), 1.68–1.78 (m, 1H), 1.83–1.93 (m, 1H), 2.03–2.11 (m, 1H), 2.15 (dd, *J* = 8.3, 13.3 Hz, 1H), 2.46–2.57 (m, 2H), 2.60 (dt, *J* = 5.5, 11.5 Hz, 1H), 5.37 (br s, 1H), 6.52 (d, *J* = 1.4 Hz, 1H), 6.58 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.01 (d, *J* = 8.7 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.4, 19.3, 19.6, 20.3, 23.6, 27.6, 27.8, 32.3, 34.7, 36.7, 39.3, 43.0, 43.5, 76.9, 117.7, 120.1, 121.2, 123.0, 126.4, 133.6, 141.2, 152.8; MS (EI) *m/z* 312 (100), 229 (65); $[\alpha]_D^{20}$ −157 (*c* 0.8, CH_2Cl_2); HRMS Calcd for $C_{22}H_{32}O$, 312.2453; found: 312.2446.

5.26. (*S*)-1-(3,5-Dimethoxyphenyl)-2-methylhexane (17 *n* = 3)

Dimethyl ether **17** (*n* = 3) was prepared from the mesylate of alcohol **19** by the procedure employed for the preparation of **17** (*n* = 2), however *n*-propylmagnesium bromide was used in place of ethylmagnesium bromide. From 0.400 g (1.39 mmol) of mesylate was obtained 0.250 g (76%) of **17** (*n* = 3) as a yellow oil following chromatography (petroleum ether/ethyl acetate, 95:5). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.83–0.91 (m, 6H), 1.09–1.34 (m, 6), 1.57–1.67 (m, 1H), 2.27 (dd, *J* = 8.3, 13.3 Hz, 1H), 2.57 (dd, *J* = 6.1, 13.3 Hz, 1H), 3.78 (s, 6H), 6.31 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.1, 19.5, 22.9, 29.3, 34.8, 36.5, 44.0, 55.2, 97.5, 107.2, 144.2, 160.5; MS (EI) *m/z* 236 (50), 152 (100); $[\alpha]_D^{20}$ −9.2 (*c* 0.75, CH_2Cl_2).

5.27. (2′*S*)-3-(2′-Methylhexyl)-Δ^8-tetrahydrocannabinol (16, *n* = 3)

Cannabinoid **16** (*n* = 3) was prepared from dimethyl ether **17** (*n* = 3) by the procedure employed for the preparation of **16** (*n* = 1). From 0.250 g (1.06 mmol) of **16** (*n* = 3) was obtained 0.140 g (39% for two steps) of (2′*S*)-3-(2′-methylhexyl)-Δ^8-tetrahydrocannabinol following chromatography (petroleum ether/dichloromethane, 3:2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.81 (d,

J = 6.6 Hz, 3H), 0.87 (t, J = 6.6 Hz, 3H), 1.05–1.41 (m, 6H), 1.10 (s, 3H), 1.38 (s, 3H), 1.63–1.74 (m, 1H), 1.69 (s, 3H), 1.78–1.88 (m, 3H), 2.11–2.28 (m, 2H), 2.45 (dd, J = 5.9, 13.3 Hz, 1H), 2.70 (td, J = 4.2, 11.0 Hz, 1H), 3.21 (dd, J = 4.2, 16.2 Hz, 1H), 5.12 (br s, 1H), 5.40 (br s, 1H), 6.05 (d, J = 1.2 Hz, 1H), 6.24 (d, J = 1.2 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.1, 18.4, 19.5, 22.9, 23.5, 27.5, 27.9, 29.4, 31.6, 34.5, 36.0, 36.5, 43.3, 44.9, 76.6, 108.4, 110.5, 110.8, 119.3, 134.7, 141.5, 154.5; MS (EI) m/z 342 (50), 258 (100); $[\alpha]_D^{20}$ −207 (c 0.45, CH_2Cl_2).

5.28. (2′*S*)-1-Methoxy-3-(2′-methylhexyl)-Δ^8-tetrahydrocannabinol (JWH-256, 15, *n* = 3)

Methyl ether **15** (n = 3) was prepared from cannabinoid **16** (n = 3) by the procedure employed for the preparation of **15** (n = 1). From 0.060 g (0.175 mmol) of **16** (n = 3) was obtained 0.052 g (85%) of JWH-256 following chromatography (petroleum ether/dichloromethane, 3:2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.83–0.90 (m, 6H), 1.08–1.43 (m, 6H), 1.12 (s, 3H), 1.37 (s, 3H), 1.68–1.72 (m, 1H), 1.69 (s, 3H), 1.76–1.82 (m, 3H), 2.12–2.13 (m, 1H), 2.24 (dd, J = 8.3, 13.3 Hz, 1H), 2.53 (dd, J = 5.9, 13.3 Hz, 1H), 2.65 (td, J = 4.7, 10.8 Hz, 1H), 3.15 (dd, J = 4.7 Hz, 16.5. 1H), 3.79 (s, 3H), 5.42 (d, J = 4.0 Hz, 1H), 6.20 (d, J = 1.2 Hz, 1H), 6.27 (d, J = 1.2 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.2, 18.4, 19.6, 23.0, 23.5, 27.6, 28.0, 29.4, 31.8, 34.7, 36.3, 36.6, 43.9, 45.1, 55.1, 76.4, 103.7, 111.1, 119.3, 135.0, 141.2, 154.1, 158.8; MS (EI) m/z 356 (50), 272 (100); $[\alpha]_D^{20}$ −126 (c 0.5, CH_2Cl_2); HRMS Calcd for $C_{24}H_{36}O_2$, 356.2714; found: 356.2715.

5.29. (2′*S*)-1-Deoxy-3-(2′-methyl hexyl)-Δ^8-tetrahydrocannabinol (JWH-257, 14, *n* = 3)

Deoxyannabinoid **14** (n = 3) was prepared from cannabinoid **16** (n = 3) by the procedure employed for the preparation of **14** (n = 1). From 0.080 g (0.225 mmol) of **16** (n = 3) was obtained 0.058 g (76% for two steps) of **14** (n = 3) following chromatography (petroleum ether/ethyl acetate, 4:1). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.84–0.91 (m, 6H), 1.10–1.40 (m, 8H), 1.16 (s, 3H), 1.39 (s, 3H), 1.66–1.73 (m, 2H), 1.69 (s, 3H), 1.81–1.99 (m, 2H), 2.14–2.18 (m, 1H), 2.25 (dd, J = 8.2, 13.3 Hz, 1H), 2.52–2.70 (m, 2H), 2.55 (dd, J = 5.8, 13.3 Hz, 1H), 5.45 (d, J = 4.1 Hz, 1H), 6.60 (d, J = 1.5 Hz, 1H), 6.67 (dd, J = 1.5, 7.8 Hz, 1H), 7.11 (d, J = 7.8 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.1, 19.2, 19.6, 22.7, 23.5, 27.0, 27.5, 27.7, 29.7, 32.2, 34.8, 36.6, 36.8, 42.9, 43.4, 76.7, 117.7, 119.9, 121.0, 122.9, 126.2, 133.5, 141.5, 152.7; MS (EI) m/z 340 (100), 257 (75); $[\alpha]_D^{20}$ −104 (c 0.17, CH_2Cl_2); HRMS Calcd for $C_{23}H_{34}O$, 326.2605; found: 326.2609.

5.30. (*R*)-2-Methyl-1-(3,5-dimethoxyphenyl)hexane (18, *n* = 3)

This compound was prepared from the triflate of alcohol **20** (n = 3) by the procedure employed for the synthesis of (*S*)-2-methyl-1-(3,5-dimethoxyphenyl)butane (**17**, n = 1). From 0.567 g (1.66 mmol) of triflate was obtained 0.350 g (89%) of **18** (n = 3) as a colorless oil after chromatography (petroleum ether/ether, 96.5:3.5). The spectroscopic properties are identical to those of the *S*-enantiomer: $[\alpha]_D^{20}$ +6.75 (c 1.41, CH_2Cl_2).

5.31. (2′*R*)-3-(2′-Methylhexyl)-Δ^8-tetrahydrocannabinol (13, *n* = 3)

Cannabinoid **13** (n = 3) was prepared from (*R*)-2-methyl-1-(3,5-dimethoxyphenyl)hexane (**18**, n = 3) by the procedure used for the synthesis of **16** (n = 1). From 0.527 g (1.54 mmol) of (*R*)-2-methyl-1-(3,5-dimethoxyphenyl)hexane was obtained 0.210 g (45% for two steps) of cannabinoid **13** (n = 3) as a pale yellow gum following chromatography (petroleum ether/ether, 91:9). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.82 (d, J = 6.4 Hz, 3H), 0.87 (t, J = 6.4 Hz, 3H), 1.10 (s, 3H), 1.07–1.18 (m, 1H), 1.20–1.36 (m, 5H), 1.37 (s, 3H), 1.59–1.72 (m, 1H), 1.70 (s, 3H), 1.75–1.90 (m, 3H), 2.12 (dd, J = 8.3, 13.3 Hz, 2H), 2.48 (dd, J = 5.5, 13.3 Hz, 1H), 2.68 (dt, J = 4.6, 6.0 Hz, 1H), 3.19 (dd, J = 4.6, 16.5 Hz, 1H), 4.89 (s, 1H), 5.41 (d, J = 4.1 Hz, 1H), 6.06 (d, J = 1.4 Hz, 1H), 6.23 (d, J = 1.4 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.3, 18.6, 19.6, 23.0, 23.6, 27.7, 28.0, 29.5, 31.7, 34.7, 36.1, 36.7, 43.4, 45.0, 76.9, 108.5, 110.6, 110.9, 119.4, 134.9, 141.6, 154.7, 154.8; MS (EI) m/z 342 (54), 258 (100); $[\alpha]_D^{20}$ −211 (c 0.45, CH_2Cl_2).

5.32. (2′*R*)-1-Methoxy-3-(2′-methyl hexyl)-Δ^8-tetrahydrocannabinol (JWH-356, 12, *n* = 3)

Methoxycannabinoid **12** (n = 3) was prepared as described above for the synthesis of **15** (n = 1). From 0.060 g (0.175 mmol) of cannabinoid **13** (n = 3) was obtained 0.053 g (85%) of JWH-356. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.84 (d, J = 6.9 Hz, 3H), 0.88 (t, J = 6.9 Hz, 3H), 1.08 (s, 3H), 1.10–1.19 (m, 1H), 1.20–1.40 (m, 5H), 1.37 (s, 3H), 1.62–1.87 (m, 4H), 1.70 (s, 3H), 2.08–2.18 (m, 1H), 2.21 (dd, J = 8.3, 13.3 Hz, 1H), 2.55 (dd, J = 6.0, 13.3 Hz, 1H), 2.65 (dt, J = 5.1, 11.0 Hz, 1H), 3.15 (dd, J = 5.1, 17.0 Hz, 1H), 3.79 (s, 3H), 5.41 (d, J = 4.1 Hz, 1H), 6.20 (d, J = 1.4 Hz, 1H), 6.27 (d, J = 1.8 Hz, 1H);^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.3, 18.5, 19.7, 23.0, 23.7, 27.7, 28.1, 29.5, 31.9, 34.8, 36.4, 36.7, 43.9, 45.2, 55.2, 76.9, 103.9, 111.2, 112.0, 119.4, 135.1, 141.4, 154.3, 158.9; MS (EI) m/z 356 (79), 273 (100), 272 (72); $[\alpha]_D^{20}$ −234 (c 0.7, CH_2Cl_2); HRMS Calcd for $C_{24}H_{36}O_2$, 356.2715; found: 356.2712.

5.33. (2′*R*)-1-Deoxy-3-(2′-methyl hexyl)-Δ^8-tetrahydrocannabinol (JWH-355, 11, *n* = 3)

Deoxycannabinoid **11** (n = 3) was prepared from **13** (n = 3) by the procedure used for the preparation of **14** (n = 1). From 0.067 g (0.19 mmol) of **13** (n = 3) was obtained 0.054 g (84% for two steps) of JWH-355 as a colorless oil after chromatography (petroleum ether/ether, 97.5:2.5): ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.84 (d, J = 6.4 Hz, 3H), 0.89 (t, J = 6.9 Hz, 3H), 1.10–1.20 (m, 1H), 1.16 (s, 3H), 1.23–1.38 (m, 5H), 1.39 (s, 3H), 1.66–1.75 (m, 2H), 1.74 (s, 3H), 1.77–1.88 (m, 1H), 1.92–2.01 (m, 1H), 2.12–2.20 (m, 1H), 2.23 (dd, J = 8.7, 13.3 Hz, 1H), 2.55–2.75 (m, 3H), 5.46 (br s,

1H), 6.60 (d, J = 1.4 Hz, 1H), 6.67 (dd, J = 1.9, 7.8 Hz, 1H), 7.10 (d, J = 8.3 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.3, 19.3, 19.6, 23.0, 23.6, 27.6, 27.8, 29.5, 32.3, 34.9, 36.7, 43.0, 43.5, 76.9, 117.7, 120.1, 121.1, 123.0, 126.4, 133.6, 141.3, 152.8; MS (EI) m/z 326 (100), 243 (88); $[\alpha]_D^{20}$ −160 (c 0.55, CH_2Cl_2); HRMS Calcd for $C_{23}H_{34}O$, 326.2610; found: 326.2604.

5.34. (*S*)-1-(3,5-Dimethoxyphenyl)-2-methylheptane (17, *n* = 4)

Dimethyl ether **17** (n = 4) was prepared from the mesylate of alcohol **19** by the procedure employed for the preparation of **17** (n = 2), however, n-butylmagnesium bromide was used in place of ethylmagnesium bromide. From 0.400 g (1.39 mmol) of mesylate was obtained 0.309 g (89%) of **17** (n = 4) as a yellow oil following chromatography (petroleum ether/ethyl acetate, 95:5). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.83–0.91 (m, 6H), 1.05–1.43 (m, 8H), 1.60–1.69 (m, 1H), 2.28 (dd, J = 8.3, 13.3 Hz, 1H), 2.58 (dd, J = 6.0, 13.3 Hz, 1H), 3.78 (s, 6H), 6.30 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.1, 19.5, 22.7, 26.8, 32.1, 34.8, 36.8, 44.1, 55.2, 97.5, 107.5, 144.2, 160.5; MS (EI) m/z 250 (50), 152 (100); $[\alpha]_D^{20}$ −5.10 (c 0.65, CH_2Cl_2). The spectroscopic properties of this compound are identical to those reported previously.[37]

5.35. (2′*S*)-3-(2′-methylheptyl)-Δ^8-tetrahydrocannabinol (16, *n* = 4)

Cannabinoid **16** (n = 4) was prepared from dimethyl ether **17** (n = 4) by the procedure employed for the preparation of **16** (n = 1). From 0.470 g (1.88 mmol) of **17** (n = 4) was obtained 0.320 g (49% for two steps) of **16** (n = 4) following chromatography (petroleum ether/dichloromethane, 3:2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.82 (d, J = 6.6 Hz, 3H), 0.87 (d, J = 6.6 Hz, 3H), 1.08–1.42 (m, 8H), 1.10 (s, 3H), 1.38 (s, 3H), 1.68–1.74 (m, 1H), 1.70 (s, 3H), 1.78–1.90 (m, 3H), 2.12–2.20 (m, 2H), 2.46 (dd, J = 6.0, 13.3 Hz, 1H), 2.70 (td, J = 4.3, 10.8 Hz, 1H), 3.20 (dd, J = 4.3, 16.2 Hz, 1H), 4.76 (br s, 1H), 5.43 (d, J = 4.0 Hz, 1H), 6.07 (d, J = 1.2 Hz, 1H), 6.24 (d, J = 1.2 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.1, 18.5, 19.5, 22.7, 23.5, 26.8, 27.6, 27.9, 31.6, 32.1, 34.6, 36.0, 36.8, 43.4, 44.9, 76.6, 108.4, 110.5, 111.0, 119.3, 134.7, 141.5, 154.6; MS (EI) m/z 356 (50), 258 (100); $[\alpha]_D^{20}$ −185 (c 0.5, CH_2Cl_2). The spectroscopic properties of this compound are identical to those reported previously.[37]

5.36. (2′*S*)-1-Methoxy-3-(2′-methyl heptyl)-Δ^8-tetrahydrocannabinol (JWH-247, 15, *n* = 4)

Methyl ether **15** (n = 4) was prepared from cannabinoid **16** (n = 4) by the procedure employed for the preparation of **15** (n = 1). From 0.150 g (0.421 mmol) of **16** (n = 4) was obtained 0.152 g (98%) of JWH-247 following chromatography (petroleum ether/dichloromethane, 3:2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.83–0.90 (m, 6H), 1.08–1.37 (m, 8H), 1.08 (s, 3H), 1.37 (s, 3H), 1.70 (s, 3H), 1.70–1.73 (m, 1H), 1.76–1.81 (m, 3H), 2.12–2.20 (m, 1H), 2.25 (dd, J = 8.3, 13.3 Hz, 1H), 2.53 (dd, J = 6.0, 13.3 Hz, 1H), 2.66 (td, J = 4.3, 10.8 Hz, 1H), 3.14 (dd, J = 4.3, 16.5 Hz, 1H), 3.80 (s, 3H), 5.41 (d, J = 4.0 Hz, 1H), 6.20 (d, J = 1.2 Hz, 1H), 6.27 (d, J = 1.2 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.2, 18.3, 19.7, 23.1, 23.5, 27.6, 28.0, 29.4, 31.8, 34.7, 36.3, 36.6, 37.2, 43.9, 45.1, 55.2, 76.4, 103.7, 111 (1), 119.2, 135.1, 141.3, 154.1, 158.8; MS (EI) m/z 370 (50), 272 (100); $[\alpha]_D^{20}$ −122 (c 0.18, CH_2Cl_2); HRMS Calcd for $C_{25}H_{38}O_2$, 370.2872; found: 370.2876.

5.37. (2′*S*)-1-Deoxy-3-(2′-methyl heptyl)-Δ^8-tetrahydrocannabinol (JWH-264, 14, *n* = 4)

Deoxyannabinoid **14** (n = 4) was prepared from cannabinoid **16** (n = 4) by the procedure employed for the preparation of **14** (n = 1). From 0.080 g (0.225 mmol) of **16** (n = 4) was obtained 0.058 g (76% for two steps) of JWH-264 following chromatography (petroleum ether/ethyl acetate, 4:1): ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.84–0.91 (m, 6H), 1.10–1.40 (m, 8H), 1.16 (s, 3H), 1.39 (s, 3H), 1.66–1.73 (m, 2H), 1.69 (s, 3H), 1.81–1.99 (m, 2H), 2.14–2.18 (m, 1H), 2.25 (dd, J = 8.2, 13.3 Hz, 1H), 2.52–2.70 (m, 2H), 2.55 (dd, J = 5.8, 13.3 Hz, 1H), 5.45 (d, J = 4.1 Hz, 1H), 6.60 (d, J = 1.5 Hz, 1H), 6.67 (dd, J = 1.5, 7.8 Hz, 1H), 7.11 (d, J = 7.8 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.1, 19.2, 19.6, 22.7, 23.5, 27.0, 27.5, 27.7, 29.7, 32.2, 34.8, 36.6, 36.8, 42.9, 43.4, 76.7, 117.7, 119.9, 121.0, 122.9, 126.2, 133.5, 141.5, 152.7; MS (EI) m/z 340 (100), 257 (75); $[\alpha]_D^{20}$ −104 (c 0.17, CH_2Cl_2); HRMS Calcd for $C_{24}H_{36}O$, 340.2766; found: 340.2774.

5.38. (*R*)-2-Methyl-1-(3,5-dimethoxyphenyl)heptane (18, *n* = 4)

This compound was prepared from the triflate of (*S*)-2-methyl-3-(3,5-dimethoxyphenyl)-1-propanol by the procedure employed for the synthesis of (*S*)-2-methyl-1-(3,5-dimethoxyphenyl)butane. From 0.567 g (1.66 mmol) of triflate was obtained 0.290 g (70%) of **18** (n = 4) as a colorless oil after chromatography (petroleum ether/ether, 94:6). The spectroscopic properties are identical to those of the *S*-enantiomer and of material previously reported:[37] $[\alpha]_D^{20}$ +5.44 (c 1.34, CH_2Cl_2).

5.39. (2′*R*)-3-(2′-Methylheptyl)-Δ^8-tetrahydrocannabinol (13, *n* = 4)

Cannabinoid **13** (n = 4) was prepared from (*R*)-2-methyl-1-(3,5-dimethoxyphenyl)heptane by the procedure used for the synthesis of **16** (n = 1). From 0.256 g (1.06 mmol) of (*R*)-2-methyl-1-(3,5-dimethoxyphenyl)heptane was obtained 0.135 g (36% for two steps) of cannabinoid **13** (n = 4) as a pale yellow gum following chromatography (petroleum ether/ether, 9:1). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.82 (d, J = 6.5 Hz, 3H), 0.87 (t, J = 6.9 Hz, 3H), 1.06–1.15 (m, 1H), 1.10 (s, 3H), 1.8–1.38 (m, 7H), 1.37 (s, 3H), 1.60–1.72 (m, 1H), 1.70 (s, 3H), 1.75–1.91 (m, 3H), 2.13 (dd, J = 8.8, 13.3 Hz, 2H), 2.49 (dd, J = 5.5, 13.3 Hz, 1H), 2.68 (dt, J = 6.4, 11.0 Hz, 1H), 3.19 (dd, J = 4.6, 16.0 Hz, 1H), 4.79 (s, 1H), 5.42 (br d, J = 4.6 Hz, 1H), 6.06 (d, J = 1.4 Hz, 1H), 6.23 (d, J = 1.9 Hz, 1H); ^{13}C NMR (75.5 MHz,

$CDCl_3$) δ 14.2, 18.6, 19.6, 22.8, 23.6, 26.9, 27.7, 28.0, 31.7, 32.2, 34.7, 36.1, 36.9, 43.4, 45.0, 76.7, 108.5, 110.6, 111.0, 119.4, 134.9, 141.6, 154.7, 154.8; MS (EI) *m/z* 356 (79), 273 (100), 258 (100); $[\alpha]_D^{20}$ −216 (*c* 0.4, CH_2Cl_2). The spectroscopic properties of this compound are identical to those reported previously.[37]

5.40. (2′*R*)-1-Methoxy-3-(2′-methyl heptyl)-Δ^8-tetrahydrocannabinol (JWH-358, 12, *n* = 4)

Methoxycannabinoid **12** (*n* = 4) was prepared as described above for the synthesis of **15** (*n* = 1). From 0.045 g (0.126 mmol) of cannabinoid **13** (*n* = 4) was obtained 0.043 g (92%) of JWH-358 as a colorless oil after chromatography (petroleum ether). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.83 (d, *J* = 6.5 Hz, 3H), 0.87 (t, *J* = 6.9 Hz, 3H), 1.05–1.18 (m, 1H), 1.08 (s, 3H), 1.20–1.42 (m, 7H), 1.37 (s, 3H), 1.62–1.86 (m, 4H), 1.70 (s, 3H), 2.07–2.18 (m, 1H), 2.20 (dd, *J* = 8.3, 13.3 Hz, 1H), 2.55 (dd, *J* = 6.0, 13.3 Hz, 1H), 2.66 (dt, *J* = 5.0, 1.0 Hz, 1H), 3.15 (dd, *J* = 5.1, 17.0 Hz, 1H), 3.79 (s, 3H), 5.41 (br d, *J* = 4.1 Hz, 1H), 6.20 (d, *J* = 1.8 Hz, 1H), 6.27 (d, *J* = 1.4 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.2, 18.5, 19.7, 22.8, 23.7, 26.9, 27.7, 28.1, 31.9, 33.2, 34.8, 36.4, 37.0, 44.0, 45.2, 55.2, 76.9, 103.9, 111.2, 112.0, 119.4, 135.1, 141.4, 154.3, 158.9; MS (EI) *m/z* 370 (100), 287 (66), 272 (86); $[\alpha]_D^{20}$ −221 (*c* 0.5, CH_2Cl_2); HRMS Calcd for $C_{25}H_{38}O_2$, 370.2872; found: 370.2870.

5.41. (2′*R*)-1-Deoxy-3- (2′-methylheptyl)-Δ^8-tetrahydrocannabinol (JWH-357, 11, *n* = 4)

Deoxycannabinoid **11** (*n* = 4) was prepared from (2′*R*)-1-Methoxy-3-(2′-methyl heptyl)-Δ^8-tetrahydrocannabinol by the procedure used for the preparation of **14** (*n* = 1). From 0.069 g (0.19 mmol) of **13** (*n* = 4) was obtained 0.051 g (76% for two steps) of JWH-357 as a colorless oil after chromatography (petroleum ether/ether, 97.5:2.5). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.83 (d, *J* = 6.4 Hz, 3H), 0.88 (t, *J* = 7.4 Hz, 3H), 1.09–1.43 (m, 8H), 1.15 (s, 3H), 1.39 (s, 3H), 1.63–1.76 (m, 2H), 1.74 (s, 3H), 1.78–1.89 (m, 1H), 1.91–2.02 (m, 1H), 2.11–2.20 (m, 1H), 2.22 (dd, *J* = 8.7, 13.3 Hz, 1H), 2.50–2.73 (m, 3H), 5.46 (br s, 1H), 6.60 (d, *J* = 1.4 Hz, 1H), 6.66 (dd, *J* = 1.9, 7.8 Hz, 1H), 7.10 (d, *J* = 8.3 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.3, 19.3, 19.6, 22.8, 23.6, 26.9, 27.6, 27.8, 32.2, 32.3, 34.9, 36.7, 37.0, 43.0, 43.5, 76.9, 117.7, 120.1, 121.2, 123.0, 126.4, 133.6, 141.3, 152.8; MS (EI) *m/z* 340 (100), 257 (55); $[\alpha]_D^{20}$ −129 (*c* 0.6, CH_2Cl_2); HRMS Calcd for $C_{24}H_{36}O$, 340.2766; found: 340.2761.

5.42. Receptor binding assays

5.42.1. CB_1 assay. [^{3}H]CP-55,940 (K_D = 690 nM) binding to P_2 membranes was conducted as described elsewhere,[48] 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.

5.42.2. 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.[11,47] Cells were harvested in phosphate-buffered saline containing 1 mM EDTA and centrifuged at 500*g*. The cell pellet was homogenized in 10 mL 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 was washed three times in solution A with subsequent centrifugation. The combined supernatants were centrifuged at 1,00,000*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 no 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.[49]

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