Pergamon

Bioorganic & Medicinal Chemistry 6 (1998) 2383–2396

BIOORGANIC & MEDICINAL CHEMISTRY

Synthesis and Pharmacology of the Isomeric Methylheptyl-Δ^8-tetrahydrocannabinols

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Received 22 May 1998; accepted 12 August 1998

Abstract—The synthesis of the 3-heptyl, and the eleven isomeric 3-methylheptyl-Δ^8-tetrahydrocannabinols (**3–7**, *R* and *S* methyl epimers, and **8**) has been carried out. The synthetic approach entailed the synthesis of substituted resorcinols, which were subjected to acid catalyzed condensation with *trans-para*-menthadienol to provide the Δ^8-THC analogue. The 1′-, 2′- and 3′-methylheptyl analogues (**3–5**) are considerably more potent than Δ^8-THC. The 4′-, 5′- and 6′-methylheptyl isomers (**6–8**) are approximately equal in potency to Δ^8-THC.

Introduction

A comprehensive set of empirical structure–activity relationships (SAR) for classical cannabinoids has been developed based on the effect of structural variations in analogues of Δ^9-tetrahydrocannabinol (THC, **1**, the benzopyran numbering system is indicated on the structure; the C-3 side chain is numbered beginning with the benzylic carbon as C-1′), the principal psychoactive component of marijuana.[1,2] It is well established that the length and substitution pattern of the alkyl side chain has a considerable effect on the biological activity of the cannabinoid analogue. In particular, with less than a five carbon chain at C-3, activity is diminished, however if the five carbon unit is replaced by either a 1,1-dimethylheptyl or 1,2-dimethylheptyl, group activity is considerably enhanced.[1]

In recent work, the effect of the substitution of a single methyl group on the cannabinoid side chain upon cannabinoid pharmacology was described.[3] In this publication, all seven possible monomethyl analogues were synthesized, and their pharmacology in vitro and in vivo was described. It was found that the affinity for the cannabinoid brain receptor was somewhat greater than that of Δ^8-THC for the 1′- and 2′-methyl analogues, similar to Δ^8-THC for the 3′-methyl isomers, and considerably less for the 4′-methyl compound.[3] The in vivo data were in general consistent with the receptor affinities, with the exception of the 3′-methyl analogues. Both 3′-diastereomers have nearly the same receptor affinities, but the 3′*R*-methyl isomer is somewhat less potent in vivo.[3] Unfortunately, with the exception of 4′-methyl-Δ^8-THC, there was relatively little difference in the receptor affinities of the other eight isomers ($K_i = 7.6–53$ nM), all of which were not that dissimilar to Δ^8-THC (**1**, $K_i = 44 \pm 12$ nM). The 4′-methyl analogue has considerably lower affinity for the cannabinoid brain receptor ($K_i = 141 \pm 52$ nM). There were also insufficient differences in the in vivo data to make any significant conclusions regarding the effect of a single branching methyl group on the Δ^8-THC side chain.[3]

Evidence for a cannabinoid brain receptor was presented a decade ago, and a three point model for the interaction of the drug with this receptor was suggested.[4] Subsequently the location of the receptor in the brain of several mammalian species was described;[5] the receptor was cloned and the primary structure

Key words: cannabinoid; THC; cannabinoid receptor; Petrzilka synthesis; structure activity relationships.
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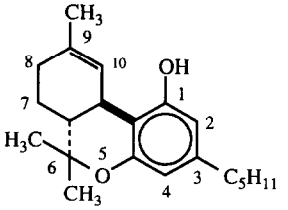
0968-0896/98/$ - see front matter
PII: S0968-0896(98)00190-4



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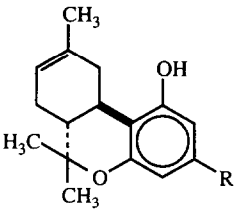


2 R = *n*-C_5H_{11}
3 R = $CH(CH_3)(CH_2)_5CH_3$
4 R = $CH_2CH(CH_3)(CH_2)_4CH_3$
5 R = $CH_2CH_2CH(CH_3)(CH_2)_3CH_3$
6 R = $(CH_2)_3CH(CH_3)CH_2CH_2CH_3$
7 R = $(CH_2)_4CH(CH_3)CH_2CH_3$
8 R = $(CH_2)_5CH(CH_3)CH_3$
9 R = *n*-C_7H_{15}

determined.[6] Docking studies employing a computer model of the cannabinoid receptor indicate that the C-3 alkyl side chain interacts with a hydrophobic pocket in the receptor, but little is known concerning the details of this interaction.[7] The methyl-Δ^8-THC isomers were investigated in order to probe this lipophilic interaction, but there were insufficient variations in pharmacology for any definitive conclusions.[3]

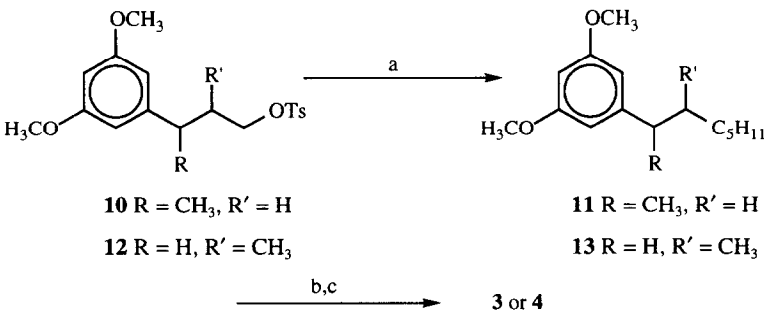
In an effort to obtain additional insight into the nature of the lipophilic portion of the receptor, and obtain more conclusive data concerning the effect of side chain branching upon the SAR of cannabinoids, the synthesis of all the possible analogues of Δ^8-THC (**2**) which contain a branching methyl group attached to a heptyl side chain (**3–8**) has been carried out. It is well known that cannabinoids with a 1′,1′-dimethylheptyl side chain are considerably more potent than those with the natural five carbon alkyl side chain.[1] Consequently, it was hypothesized that cannabinoids with a monomethyl heptyl side chain should show enhanced potency, and would be sensitive to the position and stereochemistry of the branching methyl group. Δ^8-THC derivatives were chosen rather than those of Δ^9-THC on the basis of their ease of synthesis, and because the activity of both isomers is nearly identical.[1] Derivatives of Δ^8-THC are easily prepared in a single step by the acid catalyzed reaction of an appropriately substituted resorcinol with *trans-para*-menthadienol, although the yields are frequently modest.[8] Thus the overall synthetic challenge is the synthesis of appropriate resorcinol derivatives which are condensed with the terpene to provide the Δ^8-THC derivative in a single step.[3]

Five of the six positional isomers (**3–7**, no stereochemistry indicated in the structures) have a chiral center at the point of attachment of the methyl group and for these compounds both diastereomers have been synthesized. For the 6′-methyl isomer (**8**), there is only one isomer, and as a reference compound, the unsubstitued *n*-heptyl-Δ^8-THC (**9**) was also prepared.

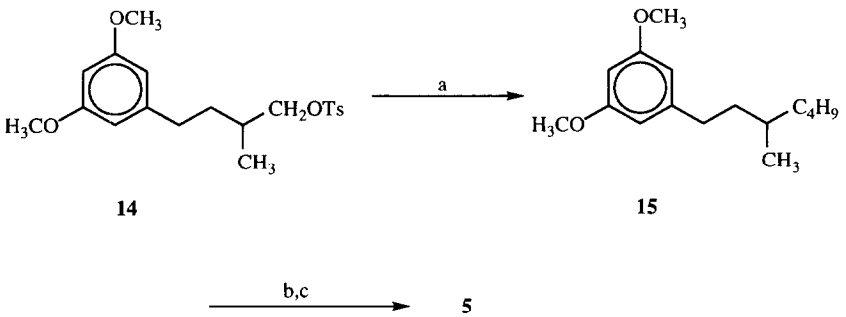
Results

The syntheses of the 1′-methyl (**3**) and 2′-methylheptyl-Δ^8-THC (**4**) analogues were based on the synthesis of the corresponding pentyl compounds described previously (Scheme 1).[3] For the synthesis of the isomers of **3**, the tosylates of (*R*)- and (*S*)-3-(3,5-dimethoxyphenyl)-1-butanol (**10**) were coupled with *n*-butylmagnesium chloride using a modification of the procedure developed by Kochi.[3,9] The enantiomeric resorcinol dimethyl ethers (**11**) that resulted were subjected to ether cleavage using BBr_3, and the resorcinols were condensed with *trans para*-menthadienol to afford (1′*R*)- and (1′*S*)-1(-methylheptyl-Δ^8-THC (**3**). The (2′*R*)- and (2′*S*)-2′-methylheptyl-Δ^8-THC isomers were prepared in an analogous manner, but employing the tosylates of (*S*)- and (*R*)-3-(3,5-dimethoxyphenyl)-2-methyl-1-propanol (**12**), respectively.[3] Conversion to the (*R*)- and (*S*)-resorcinol dimethyl ethers (**13**), was followed by conversion to cannabinoids **4** by ether cleavage, followed by condensation with menthadienol.

(3′*R*)-3′-Methylheptyl-Δ^8-THC (**5***R*) was prepared from the *S*-enantiomer of tosylate **14** (Scheme 2) employed in the synthesis of (3′*R*)-Δ^8-THC.[3] Copper catalyzed coupling with *n*-propylmagnesium bromide provided (*R*)-1-(3,5-dimethoxyphenyl)-3-methylheptane (**15***R*), which was converted to cannabinoid **5** as described above for the synthesis of **3** and **4**. The primary alcohol precursor to tosylate **14***S* was prepared as described previously from (*R*)-3-benzyloxy-1-bromo-2-methylpropane and 3,5-dimethoxybenzaldehyde.[3] The starting material, (*R*)-3-benzyloxy-1-bromo-2-methylpropane was prepared



Scheme 1. (a) Li_2CuCl_4/BuMgCl/THF, −78° to 25 °C; (b) BBr_3/CH_2Cl_2, 0° to 25 °C; (c) menthadienol/HOTs/C_6H_6, 80 °C.



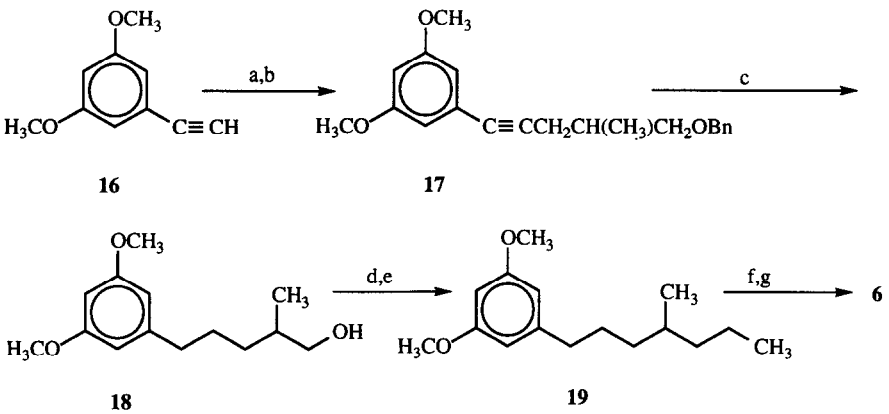
Scheme 2. (a) Li_2CuCl_4/PrMgBr/THF, −78° to 25 °C; (b) BBr_3/CH_2Cl_2, 0° to 25 °C; (c) menthadienol/HOTs/C_6H_6, 80 °C.

from methyl (*S*)-(+)-3-hydroxy-2-methylpropionate by a modification of previously published procedures.[3,10]

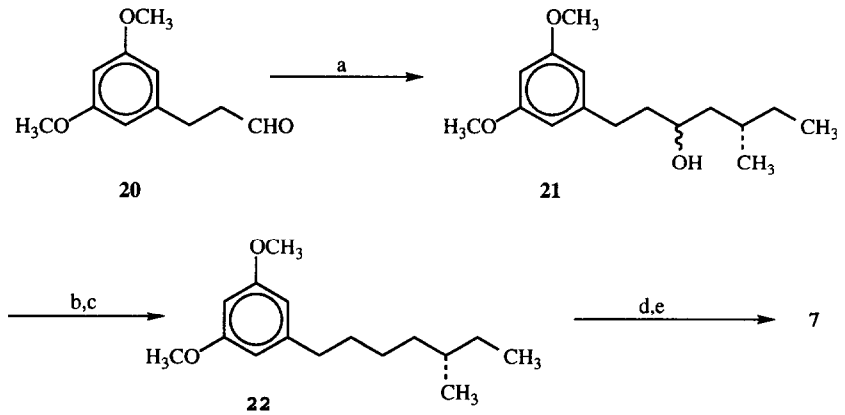
The synthesis of the 3′*S*-isomer of **5** required (*S*)-3-benzyloxy-1-bromo-2-methylpropane. This halide had been prepared previously from methyl (*R*)-(+)-3-hydroxy-2-methylpropionate as a starting material, however at the time this synthesis was initiated this compound was not available commercially.[3] (*S*)-3-Benzyloxy-1-bromo-2-methylpropane was instead prepared from methyl (*S*)-(+)-3-hydroxy-2-methylpropionate by modification of literature procedures (see Experimental).[10b,11] The first step in this synthesis was formation of the benzyl ether, which was of greater than 99% optical purity (see Experimental). Subsequent steps are such that the optical integrity of the final products is not affected. This route is actually shorter (three steps, rather than five) than that from the *R*-ester. The conversion of this halide to the *S*-enantiomer of tosylate **14** was carried out by the procedure employed for the synthesis of the *R*-tosylate.[3] The preparation of (3′*S*)-3′-methylheptyl-Δ^8-THC (**5***S*) employed the methodology used for the 3′*R* isomer (Scheme 2).

The synthesis of the 4′-methylheptyl-Δ^8-THC isomers was also designed to utilize the enantiomeric 1-bromo-3-benzyloxy-2-methylpropanes as a source for the chiral methine, but an aryl moiety with a two carbon alkyl chain was necessary. The successful synthetic approach employed 3,5-dimethoxyphenylacetylene (**16**, Scheme 3) as starting material.[12] Acetylene **16** was converted to the corresponding organolithium, reaction of which with (*R*)-3-benzyloxy-1-bromo-2-methylpropane provided substituted acetylene **17** in moderate (52%) yield. The yield was diminished by a competing E2 reaction of the alkyl halide. Hydrogenation of **17** resulted not only in reduction of the alkyne, but hydrogenolysis of the benzyl ether to provide (*S*)-5-(3,5-dimethoxyphenyl)-2-methylpentanol (**18***S*). Conversion of alcohol **18***S* to the tosylate, followed by copper catalyzed coupling with ethyl Grignard provided (*R*)-1-(3,5-dimethoxyphenyl)-4-methylheptane (**19***R*). Ether cleavage, followed by acid catalyzed condensation with menthadienol gave (4′*R*)-4′-methylheptyl-Δ^8-THC (6R). The 4′*S*-isomer (**6***S*) was prepared in the same manner, however, (*S*)-3-benzyloxy-1-bromo-2-methylpropane was employed as starting material.

The synthesis of (5′*S*)-5′-methylheptyl-Δ^8-THC (**7***S*) was effected in a straightforward manner by the reaction of the Grignard reagent derived from commercially available (*S*)-1-bromo-2-methylbutane with 3-(3,5-dimethoxyphenyl)propanal (**20**) to provide a diastereomeric mixture of alcohols **21** (Scheme 4). Aldehyde **20** was prepared by oxidation of 3-(3,5-dimethoxyphenyl)-1-propanol (see Experimental). Alcohols **21** were converted



Scheme 3. (a) BuLi/THF, 0 °C; (b) 3-benzyloxy-1-bromo-2-methylpropane/THF/DMSO, 0 °C then 25 °C; (c) H_2(g)/10% Pd(C)/EtOH/45 psi; (d) $TsCl/C_5H_5N/CHCl_3$, 0 °C; (e) Li_2CuCl_4/EtMgBr/THF, −78° to 20 °C; (f) BBr_3/CH_2Cl_2, 0° to 25 °C; (g) *p*-methadienol/HOTs/C_6H_6, 80 °C.



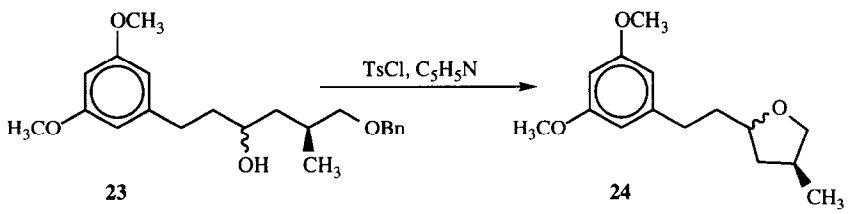
Scheme 4. (a) (*S*)-$CH_3CH_2CH(CH_3)CH_2MgBr$, 25 °C then 35 °C; (b) $TsCl/C_5H_5N/CHCl_3$, 0 °C; (c) $LiAlH_4$/ether, 35 °C; (d) BBr_3/CH_2Cl_2 0° to 25 °C; (e) *p*-menthadienol/HOTs/C_6H_6, 80 °C.

to the corresponding *p*-toluenesulfonates, reduction of which provided (*S*)-1-(3,5-dimethoxyphenyl)heptane (**22**). Ether cleavage, followed by acid catalyzed condensation with menthadienol gave (5′*S*)-5′-methylheptyl-Δ^8-THC (7*S*).

The initial approach to (5′*R*)-5′-methylheptyl-Δ^8-THC (7*R*) employed the reaction of aldehyde **20** with the Grignard reagent derived from (*R*)-3-benzyloxy-1-bromo-2-methylbutane. Although a diastereomeric mixture of alcohols **23** was produced, attempted formation of the *p*-toluenesulfonate ester provided only a mixture of stereoisomeric tetrahydrofurans **24**, presumably by a route analogous to the lactonization via a phenonium ion described recently by Nagumo et al.[13]

(5′*R*)-5′-Methyl-Δ^8-THC (7*R*) was successfully prepared from (*S*)-1-benzyloxy-2-methyl-4-pentyne (**25**, Scheme 5), which is derived from the reaction of lithium acetylide and (*R*)-1-benzyloxy-3-bromo-2-methylpropane.[10c] Conversion of **25** to the alkynyllithium and condensation with 3,5-dimethoxybenzyl bromide in the presence of lithium iodide, gave hexyne **26**. Catalytic hydrogenation proceeded with reduction of the alkyne, and hydrogenolysis of the benzyl ether to give (*S*)-6-(3,5-dimethoxyphenyl)-2-methyl-1-hexanol (**27**). Conversion to the *p*-toluenesulfonate, followed by copper catalyzed coupling with methylmagnesium bromide gave (*R*)-1-(3,5-dimethoxyphenyl)-5-methylheptane (**28**), which was converted to (5′*R*)-5′-methylheptyl-Δ^8-THC (7*R*) via condensation of the resorcinol with *p*-menthadienol.

The resorcinol precursors of 6′-methylheptyl-Δ^8-THC (**8**) and heptyl-Δ^8-THC (**9**) were both synthesized from 3,5-dimethoxybenzaldehyde by straightforward reaction sequences. 1-(3,5-Dimethoxyphenyl)-6-methylheptane, the precursor of 6′-methylheptyl-Δ^8-THC (**8**), was synthesized from 1-bromo-5-methylhexane,[14] which was prepared

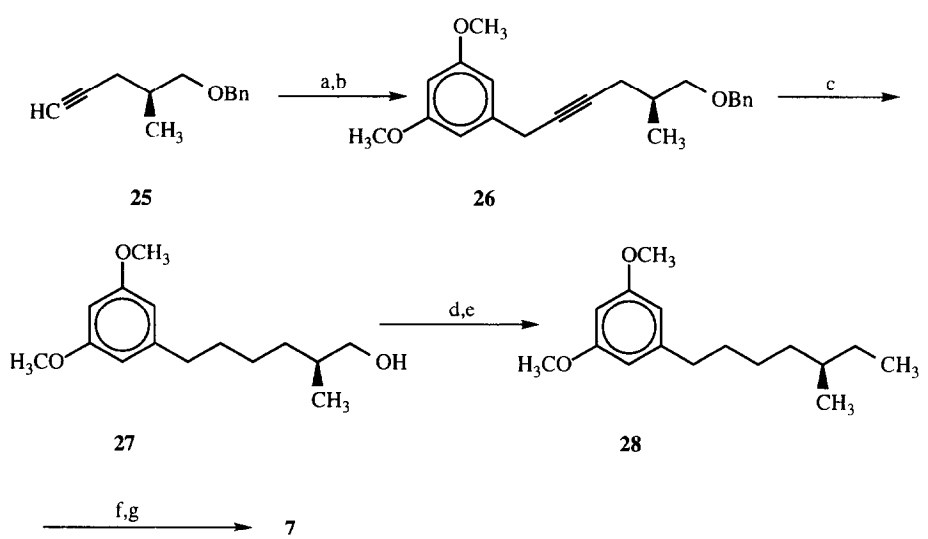


from diethyl malonate and isovaleraldehyde as described in the Experimental. Conversion to the triphenylphosphonium salt, followed by Wittig reaction with 3,5-dimethoxybenzaldehyde, and reduction provided 1-(3,5-dimethoxyphenyl)-6-methylheptane. Cannabinoid **9** was prepared from 1-(3,5-dimethoxyphenyl)heptane, which was obtained in two steps from 3,5-dimethoxybenzaldehyde; reaction of the Grignard reagent derived from 1-bromohexane with 3,5-dimethoxybenzaldehyde, followed by hydrogenolysis. The conversion of each resorcinol dimethyl ether to the corresponding cannabinoid was carried out as described above for the synthesis of Δ^8-THC analogues **3** to **7**.

Standard cannabinoid protocols were employed to evaluate the pharmacology of all compounds, both in vitro and in vivo. The in vitro affinity for the cannabinoid brain (CB_1) receptor was determined by measuring the ability of the ligand to displace the very potent cannabinoid, [^{3}H] CP 55,940, from its binding site in a membrane preparation.[15] The pharmacology was evaluated in vivo using the mouse model of cannabimimetic activity which measures spontaneous activity (SA), antinociception (as tail flick, TF) and rectal temperature (RT).[16]

The data, summarized in Table 1, indicate that 3-heptyl-Δ^8-THC (**9**) has greater affinity for the CB_1 receptor than Δ^8-THC, and is significantly more potent in vivo. The 1′-methylheptyl- (**3**), and 2′-methylheptyl-Δ^8-THC (**4**) isomers all have very high affinity for the receptor, at least an order of magnitude greater than Δ^8-THC or cannabinoid **9**. All four compounds are very potent in vivo, although the 1′*S*-analogue shows only 72% efficacy at 84 μmol/kg. Although the 3′*R*-methylheptyl analogue has slightly less affinity for the CB_1 receptor than the 3′*S*-isomer, both compounds are very potent in vivo. The 4′-methyl, and 5′-methylheptyl isomers all have affinities for the receptor comparable to those of Δ^8-THC (**3**) and its heptyl analogue (**9**). The potency of these four isomers in the mouse is also similar to that of cannabinoids **3** and **9**. The 6′-methylheptyl analogue (**8**) has receptor affinity comparable to that of the straight chain compound (**9**), and is slightly less potent in vivo.

It is clear that Δ^8-THC analogues, in which the five carbon alkyl side chain is replaced with a monomethylheptyl group are very potent cannabinoids. In particular, the 1′*R*-isomer (**3**) has high affinity for the brain receptor ($K_i = 0.51 \pm 0.02$ nM), and while only



Scheme 5. (a) BuLi/THF, 0 to 25 °C; (b) 3,5-dimethoxybenzyl bromide/THF, then LiI, reflux; (c) H_2(g)10% Pd(C)/EtOH/45 psi; (d) $TsCl/C_5H_5N/CHCl_3$, 0 °C; (e) Li_2CuCl_4/MeMgBr/THF, −78° to 25 °C; (f) BBr_3/CH_2Cl_2, 25 °C; (g) *p*-menthadienol/HOTs/C_6H_6, 80 °C.

Table 1. In vitro and in vivo pharmacology of Δ^8-THC (**2**), heptyl-Δ^8-THC (**9**), and methylheptyl-Δ^8-THC isomers **3** through **8**

Compound	K_i (nM)	ED_{50} (95% CL)		
		SA (μmol/kg)	TF (μmol/kg)	RT (μmol/kg)
2	44 ± 12a	2.9[a]	4.8[a]	4.5[a]
9	22 ± 4	0.4 (b–28.9)	1.7 (0.9–3.3)	0.4 (b–12.9)
3*R*	0.51 ± 0.02	1.4 (0.7–2.7)	0.1 (b–0.8)	0.12 (b–0.4)
3*S*	2.0 ± 0.3	c	0.4 (b–7.6)	0.4 (b–5.1)
4*R*	1.4 ± 0.2	0.2 (0.1–0.3)	0.4 (0.3–0.6)	0.2 (0.1–0.2)
4*S*	2.0 ± 0.8	0.4 (0.1–1.1)	0.3 (0.2–0.5)	0.2 (0.2–0.3)
5*R*	9.5 ± 2.9	0.2[d] (b–b)	0.8 (b–13.8)	0.8 (b–11.2)
5*S*	1.3 ± 0.2	0.3 (0.1–0.9)	0.2 (0.1–0.3)	0.2 (0.1–0.4)
6*R*	18 ± 2	4.6 (2.0–10.5)	2.0 (1.0–3.7)	2.4 (1.3–4.7)
6*S*	32 ± 5	5.1[e] (1.3–19.8)	1.9 (1.0–3.8)	4.8 (2.7–8.4)
7*R*	75 ± 9	3.8 (3.0–4.8)	2.4 (1.6–3.6)	4.8 (2.3–10.0)
7*S*	38 ± 5	0.8[f] (0.3–1.9)	2.6 (1.8–3.7)	2.7 (1.7–4.1)
8	19 ± 1	1.2 (0.4–3.1)	2.3 (1.4–3.6)	2.3 (1.1–4.7)

[a]Martin, B. R.; Compton, D. R.; Semus, S. F.; Lin, S.; Marciniak, G.; Grzybowska, J.; Charalambous, A.; Makriyannis, A. *Pharmacol. Biochem. Behav.* **1193**, *46*, 205.
[b]Out of range tested.
[c]72% at 84 μmol/kg.
[d]Variable.
[e]Maximum 67%.
[f]Maximum 74%.

slightly more effective than Δ^8-THC in the spontaneous activity assay, it is nearly 50 times more potent in the tail flick measure of antinociception, and in causing hypothermia. This isomer of **3** is comparable in receptor affinity, and in vivo potency to 1′,1′-dimethylheptyl-Δ^8-THC, one of the most potent traditional cannabinoids known.[17] It is, however, significantly less potent than (1′*S*,2′*R*)-1′,2′-dimethylheptyl-Δ^8-THC.[18] All of the other 1′-, 2′-, and 3′-methylheptyl isomers also have high affinity for the receptor, and are significantly more potent in vivo than Δ^8-THC. The 4′-, 5′- and 6-methylheptyl-Δ^8-THC isomers are comparable in potency and receptor affinity to the parent cannabinoid. There are no significant differences in either potency or receptor affinity as a function of stereochemistry between pairs of diastereomers.

These data are in contrast to the trends in the monomethyl analogues reported previously, in which the 1′- and 2′-methyl isomers have slightly greater affinity for the receptor than Δ^8-THC, and were of comparable potency in vivo.[3] In this series the 3′*R*-methyl isomer was somewhat less potent in vivo than the 3′*S* analogue, which was in turn comparable to Δ^8-THC. The 4′-methyl cannabinoid has significantly less affinity for the receptor than Δ^8-THC, and is much less effective in causing hypothermia.[3]

The structure of the cannabinoid side chain is known to have a profound effect upon the potency of a given cannabinoid; variations in side chain structure are possible without loss of potency, and some variations in side chain substitution are known to cause a great increase in potency.[1] The data reported previously for the side chain methyl analogues of Δ^8-THC,[3] and those summarized in Table 1 for the isomeric methylheptyl-Δ^8-THC isomers are consistent with this observation. All of these compounds retain cannabinoid activity, and many of them are considerably more potent than the side chain methyl analogues of Δ^8-THC. It is also apparent that there is relatively little effect upon potency or receptor affinity as a function of stereochemistry at the chiral centers on the side chain in cannabinoids **3** to **7**. Methylheptyl-Δ^8-THC analogues **3** through **8**, and the unsubstituted heptyl-Δ^8-THC (**9**) are also equal to, or more potent than THC, and cannabinoids with a 1′,1′- or 1′,2′-dimethylheptyl side chain are considerably more potent than THC.[1,17,18] The origins of these effects are unclear, but may be the result of the increased lipophilicity of a substituted heptyl side chain, or they may be a result of the geometry of the portion of the receptor which interacts with the cannabinoid side chain. The detailed explanations of the variations in potency of cannabinoids as a function of side chain structure must await a detailed description of the structure of the appropriate portion of the CB_1 receptor.

Experimental

General. IR spectra were obtained using Nicolet 5DX or Magna spectrometers; ^1H and ^{13}C NMR spectra were recorded on a Bruker 300AC spectrometer. Mass spectral analyses were performed on a Hewlett–Packard

5890A gas chromatograph with a mass sensitive detector, and HRMS data were provided by the Mass Spectrometry Laboratory, School of Chemical Sciences, University of Illinois. Ether and THF were distilled from Na-benzophenone ketyl immediately before use, and other solvents were purified using standard procedures. Column chromatography was carried out on Universal silica gel (32–63 μ) using the indicated solvents as eluents. All new compounds were homogeneous to TLC and ^{13}C NMR.

(*R*)-2-(3,5-Dimethoxyphenyl)octane (11*R*). To a stirred solution of 1.17 g (3.2 mmol) of the tosylate of (*R*)-3-(3,5-dimethoxyphenyl)-1-butanol (**10***R*)[3] in 5 mL of dry THF at −78 °C under an atmosphere of dry N_2 was added 32.0 mL (0.3 mmol) of a freshly prepared 0.01 M solution of Li_2CuCl_4 in THF, followed by 24.0 mL (48.0 mmol) of *n*-butylmagnesium chloride (2.0 M in ethyl ether). The mixture was warmed to ambient temperature, stirred for 48 h and quenched with saturated aqueous NH_4Cl. After the addition of ether, the reaction was washed with successive portions of saturated aqueous $NaHCO_3$ and brine, dried ($MgSO_4$) and the solvent removed in vacuo. The crude product was purified by Kugelrohr distillation (130 °C/0.1 mm Hg) to yield 0.60 g (75%) of **11***R* as a colorless oil: ^1H NMR (300 MHz, $CDCl_3$) δ 0.86 (t, J = 6.9 Hz, 3H), 1.19–1.27 (m, 11H), 1.53 (m, 2H), 2.58 (hextet, J = 7.1 Hz, 1H), 3.79 (s, 6H), 6.30 (t, J = 2.2 Hz, 1H), 6.35 (d, J = 2.2 Hz, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.1, 22.2, 22.7, 27.7, 29.4, 31.8, 38.3, 40.3, 55.2, 97.4, 105.2, 150.7, 160.7; IR (neat) 2935, 1610 cm^{-1}; $[\alpha]_D^{20}$ −21.3° (*c* 3.7, $CHCl_3$); HRMS calcd for $C_{16}H_{26}O_2$: 250.1932, Found: 250.1935.

(1′*R*)-1′-Methylheptyl-Δ^8-tetrahydrocannabinol (3*R*). At 0 °C, 0.59 g (2.4 mmol) of dimethyl ether **11***R* was stirred with 2.61 mL of BBr_3 (1.0 M in CH_2Cl_2). The reaction mixture was allowed to warm to room temperature, stirred for 12 h, carefully quenched with water and extracted with ether. The ethereal extracts were washed with brine, dried ($MgSO_4$) and concentrated to yield 0.53 g (100%) of the substituted resorcinol as a brown oil, which was used in the next step without purification: ^1H NMR (300 MHz, $CDCl_3$) δ 0.86 (t, J = 6.9 Hz, 3H), 1.19–1.27 (m, 11H), 1.53 (m, 2H), 2.58 (m, 1H), 6.30 (t, J = 2.2 Hz, 1H), 6.35 (d, J = 2.2 Hz, 2H). To a solution of 0.53 g (2.4 mmol) of resorcinol in 13 mL of dry benzene was added 0.40 g (2.6 mmol) of *trans-p*-menthadienol followed by 0.04 g of *p*-toluenesulfonic acid monohydrate. The reaction mixture was heated at reflux for 3 h, cooled and the benzene solution washed with water and brine. After drying ($MgSO_4$), the solvent was removed in vacuo and the product was purified by flash chromatography (petroleum ether/ether, 4/1) to give 0.60 g (72%) of cannabinoid **3***R* as a viscous oil: ^1H NMR (300 MHz, $CDCl_3$) δ 0.80–0.90 (m, 4H), 1.11–1.26 (m, 11H), 1.38 (s, 3H), 1.42–1.52 (m, 3H), 1.69 (s, 3H), 1.74–1.93 (m, 4H), 2.11–2.14 (m, 1H), 2.46 (m, 1H), 2.67–2.75 (m, 1H), 3.22 (dd, J = 16.5, 4.1 Hz, 1H), 5.13 (s, 1H), 5.42 (d, J = 3.8 Hz, 1H), 6.09 (s, 1H), 6.28 (s, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.1, 18.5, 22.0, 22.6, 23.4, 27.5, 27.7, 27.9, 29.4, 31.6, 31.8, 36.0, 38.2, 39.5, 44.9, 76.7, 106.4, 108.5, 110.6, 119.3, 134.7, 147.9, 154.7, 154.7; IR (neat) 3405, 2930, 1630, 1588 cm^{-1}; $[\alpha]_D^{20}$ −206.9° (*c* 13.5, $CHCl_3$); HRMS calcd for $C_{24}H_{36}O_2$: 356.2715, Found: 356.2717.

(1′*S*)-1′-Methylheptyl-Δ^8-tetrahydrocannabinol (3*S*). The 1′*S*-isomer was prepared by the same route as the 1′*R*-isomer starting from the tosylate of (*S*)-3-(3,5-dimethoxyphenyl)-1-butanol (**10***S*).[3] The *S*-resorcinol dimethyl ether, $[\alpha]_D^{20}$ +18.5° (*c* 4.8, $CHCl_3$) has spectroscopic data identical to those of the enantiomer. (*S*)-Cannabinoid **3***S* was prepared as described above: ^1H NMR (300 MHz, $CDCl_3$) δ 0.81–0.90 (m, 4H), 1.11–1.25 (m, 11H), 1.38 (s, 3H), 1.42–1.54 (m, 3H), 1.69 (s, 3H), 1.78–1.93 (m, 4H), 2.11–2.16 (m, 1H), 2.47 (m, 1H), 2.66–2.74 (m, 1H), 3.21 (dd, J = 16.2, 4.4 Hz, 1H), 4.98 (s, 1H), 5.42 (d, J = 4.3 Hz, 1H), 6.09 (d, J = 1.1 Hz, 1H), 6.27 (d, J = 1.0 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.1, 18.5, 21.8, 22.7, 23.5, 27.6, 27.6, 27.9, 29.4, 31.6, 31.8, 36.0, 38.3, 39.5, 44.9, 76.7, 106.2, 108.7, 110.6, 119.3, 134.8, 147.9, 154.7, 154.7; IR (neat) 3405, 2930, 1630, 1580 cm^{-1}; $[\alpha]_D^{20}$ −191.1° (*c* 12.9, $CHCl_3$); HRMS calcd for $C_{24}H_{36}O_2$: 356.2715, Found: 356.2710.

(*R*)-1-(3,5-Dimethoxyphenyl)-2-methylheptane (13*R*). Heptane **13***R* was prepared from the tosylate of (*S*)-3-(3,5-dimethoxyphenyl)-2-methyl-1-propanol (**12***S*)[3] by the method described above. The tosylate was coupled with *n*-butylmagnesium chloride using the procedure described above for the preparation of **11***R*. From 0.83 g (2.38 mmol) of tosylate there was obtained 0.23 g (40%) of dimethyl ether **13***R*: ^1H NMR (300 MHz, $CDCl_3$) δ 0.76–0.83 (m, 6H), 1.19–1.28 (m, 8H), 1.65–1.70 (m, 1H), 2.17–2.45 (m, 1H), 2.48–2.54 (m, 1H), 3.71 (s, 6H), 6.24 (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, 107.3, 144.2, 160.5; IR (neat) 2936, 1600 cm^{-1}; $[\alpha]_D^{20}$ +4.76° (*c* 14.2, $CHCl_3$); HRMS calcd for $C_{16}H_{26}O_2$: 250.1932, Found: 250.1933.

(2′*R*)-2′-Methylheptyl-Δ^8-tetrahydrocannabinol (4*R*). Cannabinoid **4***R* was prepared from (*R*)-dimethyl ether **13***R* by the procedure described above for the preparation of **3***R*. From 0.19 g (0.8 mmol) of (*R*)-1-(3,5-dimethoxyphenyl)-2-methylheptane (**13***R*) there was obtained 0.15 g (89%) of the substituted resorcinol: ^1H NMR (300 MHz, $CDCl_3$) δ 0.76–0.83 (m, 6H), 1.19–1.28 (m, 8H), 1.65–1.70 (m, 1H), 2.17–2.45 (m, 1H), 2.48–2.54 (m, 1H), 3.71 (s, 6H), 6.24 (s, 3H).

From 0.15 g of the resorcinol there was obtained 0.12 g (52%) of cannabinoid **4***R* as a viscous, amber oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.81–0.90 (m, 6H), 1.10 (s, 3H), 1.20–1.24 (m, 8H), 1.38 (s, 3H), 1.64–1.70 (m, 4H), 1.78–1.93 (m, 3H), 2.10–2.17 (m, 2H), 2.46–2.53 (m, 1H), 2.67–2.71 (m, 1H), 3.15–3.24 (m, 1H), 4.74 (s, 1H), 5.43 (br s, 1H), 6.07 (s, 1H), 6.24 (s, 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, 36.1, 36.8, 43.3, 44.9, 76.8, 108.4, 110.5, 110.8, 119.3, 134.4, 141.6, 154.4; IR (neat) 3405, 2931 cm^{-1}; $[\alpha]_D^{20}$ −69.7° (*c* 6.8, $CHCl_3$); HRMS calcd for $C_{24}H_{36}O_2$: 356.2715, Found: 356.2710.

(2′*S*)-2′-Methylheptyl-Δ^8-tetrahydrocannabinol (4*S*). The 2′*S*-isomer was prepared by the same route as the 2′*R*-isomer starting from the tosylate of (*R*)-3-(3,5-dimethoxyphenyl)-2-methyl-1-propanol (12*R*).[3] The resorcinol dimethyl ether, $[\alpha]_D^{20}$ −4.96° (*c* 7.95, $CHCl_3$) has spectroscopic data identical to those of the enantiomer (**13***S*). Cannabinoid **4***S* was prepared as described above: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.81–0.89 (m, 6H), 1.10 (s, 3H), 1.20–1.25 (m, 8H), 1.38 (s, 3H), 1.66–1.70 (m, 4H), 1.78–1.86 (m, 3H), 2.12–2.20 (m, 2H), 2.43–2.49 (m, 1H), 2.68–2.72 (m, 1H), 3.16–3.21 (m, 1H), 4.88 (s, 1H), 5.43 (br s, 1H), 6.06 (s, 1H), 6.24 (s, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.1, 18.5, 19.6, 22.7, 23.5, 26.8, 27.6, 27.9, 31.6, 32.1, 34.6, 36.1, 36.8, 43.4, 44.9, 76.8, 108.3, 110.9, 111.0, 119.3, 134.7, 141.5, 154.6; IR (neat) 3400, 2930cm^{-1}; $[\alpha]_D^{20}$ −177.0° (*c* 12.1, $CHCl_3$); HRMS calcd for $C_{24}H_{36}O_2$: 356.2715, Found: 356.2713.

(*R*)-1-(3,5-Dimethoxyphenyl)-3-methylheptane (15*R*). Heptane **15***R* was prepared from the tosylate of (*S*)-4-(3,5-dimethoxyphenyl)-2-methyl-1-butanol (14*S*).[3] The crude tosylate was coupled with propylmagnesium bromide using the procedure described above for the preparation of **11***R*. From 0.32 g (0.9 mmol) of tosylate **14***S* there was obtained 0.56 g (91%) of dimethyl ether **15***R*: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.80–0.98 (m, 6H), 1.09–1.51 (m, 8H), 1.54–1.74 (m, 1H), 2.42–2.67 (m, 2H), 3.74 (s, 6H), 6.28 (t, *J* = 2.2 Hz, 1H), 6.34 (d, *J* = 2.1 Hz, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.1, 19.5, 23.0, 29.2, 32.4, 33.8, 36.5, 38.6, 55.0, 97.4, 106.3, 145.5, 160.6; $[\alpha]_D^{20}$ −7.4° (*c* 0.53, $CHCl_3$); HRMS calcd for $C_{16}H_{26}O_2$: 250.1933, Found: 250.1931.

(3′*R*)-3′-Methylheptyl-Δ^8-tetrahydrocannabinol (5*R*). Cannabinoid **5***R* was prepared from dimethyl ether **15***R* by the procedure described above for the preparation of **3***R*. From 0.18 g (0.7 mmol) of (*R*)-1-(3,5-dimethoxyphenyl)-3-methylheptane (**15***R*) there was obtained 0.16 g (100%) of substituted resorcinol: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.77–0.99 (m, 6H), 1.04–1.46 (m, 8H), 1.46–1.65 (m, 1H), 2.29–2.56 (m, 2H), 6.21 (s, 1H), 6.26 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 14.0, 19.4, 22.9, 29.1, 29.6, 32.4, 33.3, 36.5, 38.4, 100.3, 107.9, 146.2, 156.5. From 0.16 g of the resorcinol there was obtained 0.15 g (42%) of cannabinoid **5***R* as a viscous oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.76–0.97 (m, 6H), 1.10 (s, 3H), 1.37 (s, 3H), 1.69 (s, 3H), 1.17–1.49 (m, 8H), 1.49–1.63 (m, 1H), 1.73–1.96 (m, 3H), 2.03–2.22 (m, 1H), 2.28–2.55 (m, 2H), 2.61–2.88 (m, 1H), 3.10–3.27 (m, 1H), 5.02 (s, 1H), 5.42 (d, *J* = 4.1 Hz, 1H), 6.09 (s, 1H), 6.27 (s, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.1, 18.5, 19.6, 23.0, 23.5, 27.5, 27.9, 29.2, 31.5, 32.5, 32.9, 36.0, 36.6, 38.3, 44.9, 76.7, 107.6, 109.9, 110.5, 119.2, 134.7, 142.9, 154.8; $[\alpha]_D^{20}$ −185° (*c* 2.4, $CHCl_3$); HRMS calcd for $C_{24}H_{36}O_2$: 356.2715, Found: 356.2717.

Methyl (*S*)-(+)-3-benzyloxy-2-methylpropionate. To a stirred solution of 3.30 mL (30.0 mmol) of methyl (*S*)-3-hydroxy-2-methylpropionate and 9.85 g (39.0 mmol) of benzyl 2,2,2-trichloroacetimidate in 40 mL of cyclohexane and 20 mL of CH_2Cl_2 under N_2 was added slowly 0.50 mL of trifluoromethanesulfonic acid. The mixture was stirred at ambient temperature for 2 h, and poured into a mixture of water and ethyl acetate. The organic phase was separated and washed with saturated aqueous $NaHCO_3$ and brine. After drying ($MgSO_4$) the solvent was removed to give an oil which was chromatographed (petroleum ether/ether, 9/1) to afford 4.26 g (68%) of pure product as a colorless oil: $[\alpha]_D^{20}$ 11.3° (*c* 0.67, $CHCl_3$, lit. $[\alpha]_D^{20}$ −11.6° for the enantiomer[11]). The spectroscopic properties are identical to those reported.[11] The optical purity was determined by chiral HPLC employing a Diacel chiralcel analytical column with hexanes/isopropyl alcohol 95/5 as solvent at a flow rate of 1.0 mL/min. An ISCO 2350 isocratic pump coupled to an ISCO V^4 UV detector set at 214 nm with a Hewlett Packard 3396 series II integrator was used for the determinations. A small sample of the enantiomer was prepared for reference, and base line separation of enantiomers was observed. The optical purity of methyl (*S*)-(+)-3-benzyloxy-2-methylpropionate was greater than 99%.

(*R*)-3-Benzyloxy-2-methyl-1-propanol. To a stirred suspension of 1.70 g (44.7 mmol) of $LiAlH_4$ in 40 mL of dry ether was added dropwise a solution of 4.26 g (20.5 mmol) of methyl (*S*)-(+)-3-benzyloxy-2-methylpropionate in 10 mL of dry ether at 0 °C. The resulting mixture was allowed to warm to ambient temperature and stirred for 18 h. The mixture was again cooled to 0 °C, and 5 mL of water was added carefully to quench the reaction, followed by the sequential addition of 5 mL of 15% NaOH and 15 mL of water with constant agitation. The suspension was filtered, the white solid was thoroughly washed with ether, and the combined ethereal layers were washed with brine and dried ($MgSO_4$). Concentration afforded 3.40 g (92%) of alcohol as a colorless oil. The spectroscopic data are in

agreement with those reported for the enantiomer.[10b] The alcohol was converted into (*S*)-3-benzyloxy-1-bromo-2-methylpropane by the literature procedure.[10b,10c]

(3′*S*)-3′-Methylheptyl-Δ^8-tetrahydrocannabinol (5*S*). The 3′*S*-isomer was prepared by a route similar to that employed for the *R*-isomer, but using (*S*)-3-Benzyloxy-1-bromo-2-methylpropane as starting material. (*R*)-4-(3,5-dimethoxyphenyl)-2-methyl-1-butanol was converted into the *S*-dimethyl ether (**15***S*), $[\alpha]_D^{20}$ +6.7° (*c* 1.2, $CHCl_3$), the spectroscopic properties of which were identical to those of the *R*-enantiomer described above. (3′*S*)-3′-Methylheptyl-Δ^8-THC (5*S*) was prepared from the dimethyl ether by the method described above: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.77–0.97 (m, 6H), 1.09 (s, 3H), 1.37 (s, 3H), 1.05–1.63 (m, 9H), 1.68 (s, 3H), 1.74–1.96 (m, 3H), 2.00–2.23 (m, 1H), 2.29–2.55 (m, 2H), 2.61–2.78 (m, 1H), 3.14–3.30 (m, 1H), 5.28 (s, 1H), 5.41 (d, *J* = 3.8 Hz, 1H), 6.08 (d, *J* = 1.0 Hz, 1H), 6.28 (d, *J* = 1.0 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.1, 18.4, 19.6, 23.0, 23.4, 27.5, 27.8, 29.1, 31.5, 32.4, 32.9, 35.9, 36.5, 38.2, 44.9, 76.7, 107.7, 109.9, 110.5, 119.2, 134.7, 142.9, 154.6, 154.8; $[\alpha]_D^{20}$ −140.3° (*c* 0.53, $CHCl_3$); HRMS calcd for $C_{24}H_{36}O_2$: 356.2715, Found: 356.2714.

(*S*)-1-Benzyloxy-5-(3,5-dimethoxyphenyl)-2-methylpent-4-yne (17*S*). To a solution of 0.65 g (4.0 mmol) of (3,5-dimethoxyphenyl)acetylene (**16**)[12] in 2 mL of dry THF at 0 °C in a N_2 atmosphere was added 1.6 mL (4.0 mmol) of *n*-butyllithium (2.5 M in hexanes). The pale-yellow solution was stirred at 0 °C for 15 min, and a solution of 0.97 g (4.0 mmol) of (*R*)-3-benzyloxy-1-bromo-2-methylpropane in 2 mL of dry THF was added followed by 10 mL of dry DMSO. The reaction mixture was stirred for 3 h and was allowed to slowly warm to room temperature, quenched with 5 mL of saturated aqueous NH_4Cl and extracted with ether. The combined extracts were washed with water, brine and dried ($MgSO_4$). The solvent was evaporated in vacuo to give the crude benzyl ether as a yellow oil which was chromatographed (petroleum ether/ethyl acetate, 19/1) to afford 0.68 g (52%) of pure material as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.06 (d, *J* = 6.7 Hz, 3H), 2.02–2.12 (m, 1H), 2.39 (dd, *J* = 6.8, 16.8 Hz, 1H), 2.53 (dd, *J* = 5.6, 16.8 Hz, 1H), 3.35–3.45 (m, 2H), 3.69 (s, 6H), 4.45 (s, 2H), 6.38 (t. *J* = 2.2 Hz, 1H), 6.54 (d, *J* = 2.2 Hz, 2H), 7.20–7.32 (m, 5H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 16.5, 23.2, 33.1, 55.0, 72.8, 74.1, 81.6, 88.0, 100.8, 109.2, 125.2, 127.3, 128.1, 138.5, 160.3; IR (neat) 1590, 1450, 1150 cm^{-1}; $[\alpha]_D^{20}$ −12.1° (*c* 0.92, $CHCl_3$); HRMS calcd for $C_{21}H_{24}O_3$: 324.1725, Found: 324.1725.

(*S*)-5-(3,5-Dimethoxyphenyl)-2-methyl-1-pentanol (18*S*). To a solution of 0.55 g (1.7 mmol) of (*S*)-1-benzyloxy-5-(3,5-dimethoxyphenyl)-2-methylpent-4-yne (17*S*) in 50 mL of ethanol was added 0.10 g of 10% Pd on carbon and the mixture was shaken under an atmosphere of H_2 (45 psi) for 16 h. The reaction mixture was filtered through Celite and the ethanol was removed in vacuo to give 0.37 g (92%) of (**18***S*) as a yellow oil, which was used without further purification: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.82 (d, *J* = 6.7 Hz, 3H), 1.01–1.62 (m, 5H), 2.28 (br s, 1H), 2.39–2.50 (m, 2H), 3.29 (dd, *J* = 6.5, 10.5 Hz, 1H), 3.37 (dd, *J* = 5.8, 10.5 Hz, 1H), 3.67 (s, 6H), 6.20 (t, *J* = 2.1 Hz, 1H), 6.25 (d, *J* = 2.1 Hz, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 16.4, 28.5, 32.6, 35.5, 36.3, 55.0, 67.9, 97.4, 106.3, 144.9, 160.5; IR (neat) 3370, 1600 cm^{-1}; $[\alpha]_D^{20}$ −12.4° (*c* 1.00, $CHCl_3$); HRMS calcd for $C_{14}H_{22}O_3$: 238.1569, Found: 238.1568.

(*R*)-1-(3,5-Dimethoxyphenyl)-4-methylheptane (19*R*). To a solution of 0.30 g (1.3 mmol) of (*S*)-5-(3,5-dimethoxyphenyl)-2-methyl-1-pentanol (**18***S*) and 0.20 mL (2.5 mmol) of pyridine in 2 mL of dry chloroform at 0 °C was added 0.36 g (1.9 mmol) of *p*-toluenesulfonyl chloride. The reaction mixture was stirred at ambient temperature for 3 h, diluted with ether, and washed with successive portions of 10% aqueous HCl, saturated aqueous $NaHCO_3$ and brine. After drying ($MgSO_4$), the solvent was removed at reduced pressure to give a yellow oil, which after chromatography (petroleum ether/ethyl acetate, 4/1) gave 0.38 g (77%) of tosylate, which was used in the next step without further purification: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.89 (d, *J* = 6.7 Hz, 3H), 1.12–1.82 (m, 5H), 2.42 (s, 3H), 2.47 (t, *J* = 7.5 Hz, 2H), 3.76 (s, 6H), 3.80 (dd, *J* = 6.3, 9.4 Hz, 1H), 3.86 (dd, *J* = 5.8, 9.4 Hz, 1H), 6.29 (s, 3H), 7.32 (d, *J* = 8.1 Hz, 2H), 7.77 (d, *J* = 8.1 Hz, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 16.2, 21.4, 28.0, 32.1, 32.5, 36.0, 55.0, 74.8, 97.4, 106.2, 127.6, 129.7, 132.9, 144.4, 144.5, 160.5; IR (neat) 1590 cm^{-1}.

The crude tosylate was coupled with ethylmagnesium bromide using the procedure described above for the preparation of **11***R*. From 0.30 g of tosylate there was obtained 0.15 g (78%) of **19***R*: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.84–0.89 (m, 6H), 1.08–1.63 (m, 9H), 2.52 (t, *J* = 7.5 Hz, 2H), 3.77 (s, 6H), 6.29 (t, *J* = 2.2 Hz, 1H), 6.35 (d, *J* = 2.2 Hz, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.4, 19.6, 20.1, 28.8, 32.4, 36.6, 36.7, 39.3, 55.2, 97.5, 106.4, 145.4, 160.7; IR (neat) 1600 cm^{-1}; $[\alpha]_D^{20}$ −3.2° (*c* 0.80, $CHCl_3$); HRMS calcd for $C_{16}H_{26}O_2$: 250.1933, Found: 250.1933.

(4′*R*)-4′-Methyl-Δ^8-tetrahydrocannabinol (6*R*). Cannabinoid **6***R* was prepared from dimethyl ether **19***R* by the procedure described above for the preparation of **3**. From 0.11 g (0.4 mmol) of (*R*)-1-(3,5-dimethoxyphenyl)-4-methylheptane (**19***R*) there was obtained 0.09 g (92%) of substituted resorcinol: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.81–0.87 (m, 6H), 1.02–1.53 (m, 9H), 2.38 (t, *J* = 6.8 Hz,

2H), 6.17–6.32 (m, 5H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.3, 19.5, 20.1, 28.5, 32.3, 36.1, 36.8, 39.3, 100.3, 108.3, 146.4, 156.1; IR (neat) 3330 cm^{-1}.

From 0.09 g of the resorcinol there was obtained 0.07 g (45%) of cannabinoid **6*R*** as a viscous, amber oil after chromatography (petroleum ether/ethyl acetate, 19/1): ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.82–0.88 (m, 6H), 1.10 (s, 3H), 1.37 (s, 3H), 1.69 (s, 3H), 1.04–1.37 (m, 6H), 1.51–1.58 (m, 2H), 1.72–1.92 (m, 4H), 2.02–2.20 (m, 1H), 2.36–2.44 (m, 2H), 2.67 (dt, J=4.3, 10.7 Hz, 1H), 3.20 (dd, J=4.2, 16.3 Hz, 1H), 4.88 (s, 1H), 5.42 (d, J=4.2 Hz, 1H), 6.10 (s, 1H), 6.27 (s, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.4, 18.5, 19.6, 20.1, 23.5, 27.6, 28.0, 28.5, 31.6, 32.4, 35.8, 36.0, 36.8, 39.3, 44.9, 76.7, 107.6, 110.0, 110.5, 119.3, 134.7, 142.7, 154.8; IR (neat) 3400, 2970, 2930, 1620, 1570, 1420 cm^{-1}; $[\alpha]_D^{20}$ −163.1° (*c* 3.0, $CHCl_3$); HRMS calcd for $C_{24}H_{36}O_2$: 356.2715, Found: 356.2714.

(4′*S*)-4′-Methyl-Δ^8-tetrahydrocannabinol (6*S*). Cannabinoid **6*S*** was prepared from (*S*)-3-benzyloxy-1-bromo-2-methylpropane by the route described above for the preparation of the (4′*R*)-4′-methyl-isomer (**6*R***). The benzyl ether (**17*R***) $[\alpha]_D^{20}$ +15.2° (*c* 2.0, $CHCl_3$) was hydrogenated to give the primary alcohol $[\alpha]_D^{20}$ +10.9° (*c* 1.1, $CHCl_3$) which was converted into dimethyl ether **19*S***, $[\alpha]_D^{20}$ +4.9° (*c* 2.0, $CHCl_3$). From 0.12 g of the resorcinol there was obtained 0.08 g (42%) of 4′*S*-cannabinoid **6*S*** as a viscous oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.82–0.89 (m, 6H), 1.13 (s, 3H), 1.41 (s, 3H), 1.51–1.58 (m, 2H), 1.69 (s, 3H), 1.04–1.37 (m, 6H), 1.72–1.92 (m, 4H), 2.02–2.20 (m, 1H), 2.40 (t, J=7.8 Hz, 2H), 2.70 (dt, J=4.3, 10.6 Hz, 1H), 3.20 (dd, J=4.2, 16.4 Hz, 1H), 4.99 (s, 1H), 5.42 (d, J=4.0 Hz, 1H), 6.10 (s, 1H), 6.27 (s, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.4, 18.5, 19.6, 20.1, 23.5, 27.5, 27.9, 28.4, 31.6, 32.4, 35.9, 36.0, 36.8, 39.3, 44.9, 76.7, 107.7, 110.0, 110.6, 119.3, 134.7, 142.7, 154.8; IR (neat) 3400, 2970, 2930, 1620, 1570, 1420 cm^{-1}; $[\alpha]_D^{20}$ −161.4° (*c* 3.0, $CHCl_3$); HRMS calcd for $C_{24}H_{36}O_2$: 356.2715, Found: 356.2714.

3-(3,5-Dimethoxyphenyl)propanal (20). To a solution of 2.3 mL (26.4 mmol) of oxalyl chloride in 50 mL of dry CH_2Cl_2 under a dry N_2 atmosphere at −60 °C was added, dropwise over 5 min, a solution of 4.1 mL (57.9 mmol) of DMSO in 20 mL of dry CH_2Cl_2. The solution was stirred for 10 min at −60 °C and a solution of 4.70 g (24.0 mmol) of 3-(3,5-dimethoxyphenyl)-1-propanol[19] in 20 mL of dry CH_2Cl_2 was added over 5 min. The reaction mixture was stirred for 15 min, 17.0 mL (122.2 mmol) of triethylamine was added and the reaction allowed to warm to room temperature over 2 h, quenched by the addition of water and extracted with CH_2Cl_2. The combined extracts were washed with successive portions of 10% aqueous HCl, saturated aqueous $NaHCO_3$ and brine. After drying ($MgSO_4$), the solvent was removed at reduced pressure to give 4.45 g (96%) of aldehyde **20** as a pale-yellow oil which was used in the next step without further purification: ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.77 (t, J=6.8 Hz, 2H), 2.90 (t, J=6.8 Hz, 2H), 3.78 (s, 6H), 6.31 (s, 1H), 6.35 (s, 2H), 9.82 (s, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 28.2, 44.9, 55.1, 98.0, 106.2, 142.6, 160.8, 201.4; MS (EI) *m/z* 197 (10), 196 (50), 152 (100).

(*S*)-1-(3,5-Dimethoxyphenyl)-5-methylheptane (22). To a stirred mixture of 0.48 g (20.0 mmol) of Mg turnings and two small crystals of *p*-toluenesulfonic acid monohydrate in an atmosphere of dry N_2 was added a solution of 1.5 g (9.9 mmol) of (*S*)-1-bromo-2-methylbutane in 25 mL of dry ether. The mixture was heated to reflux, and 0.87 mL (10.1 mmol) of 1,2-dibromoethane was added in small portions over 0.5 h. The mixture was heated at reflux for 2 h, and a solution of 1.5 g (7.7 mmol) of aldehyde **20** in 10 mL of dry ether was added dropwise over 15 min. The reaction mixture was heated at reflux for 2 h, cooled to ambient temperature, quenched with water, acidified to pH 3, and extracted with ether. The combined ethereal extracts were washed with saturated aqueous $NaHCO_3$ and brine, dried ($MgSO_4$) and the solvent was removed in vacuo to give the crude product mixture. Chromatography (petroleum ether/ethyl acetate, 7/1) gave 1.15 g (56%) of alcohols **21** as a mixture of diastereomers, which was used in the next step without separation: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.84–0.90 (m, 6H), 1.14–1.78 (m, 7H), 2.59–2.77 (m, 2H), 3.68–3.73 (m, 1H), 3.76 (s, 6H), 6.30 (t, J=2.2 Hz, 1H), 6.37 (d, J=2.2 Hz, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 11.1, 11.3, 18.8, 19.7, 29.0, 30.3, 30.7, 31.0, 32.3, 32.4, 39.1, 39.7, 44.6, 44.8, 55.1, 69.0, 69.4, 97.7, 106.4, 144.6, 160.7; IR (neat) 3400, 1600 cm^{-1}.

The conversion of alcohols **21** into the corresponding tosylates was carried out using the procedure described above for the preparation of **19*R***. From 0.70 g of alcohols there was obtained 0.69 g (79%) of a diastereomeric mixture of tosylates after purification by chromatography (petroleum ether/ethyl acetate, 4/1) which was used in the subsequent step without further purification: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.71–0.80 (m, 6H), 0.94–1.67 (m, 5H), 1.86 (q, J=7.7 Hz, 2H), 2.39 (s, 3H), 2.45–2.57 (m, 2H), 3.73 (s, 6H), 4.62–4.67 (m, 1H), 6.22 (d, J=2.1, 2H), 6.28 (t, J=2.1, 3H), 7.29 (d, J=8.2 Hz, 2H), 7.75 (d, J=8.2 Hz, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 10.7, 18.5, 18.9, 21.2, 28.8, 29.4, 30.2, 30.3, 30.9, 31.0, 35.6, 36.1, 40.9, 54.9, 81.8, 81.9, 97.7, 106.1, 127.4, 129.5, 134.3, 143.1, 143.2, 144.3, 160.6; IR (neat) 1600, 1470 cm^{-1}.

To a stirred slurry of 0.050 g (1.3 mmol) of $LiAlH_4$ in 1 mL of dry ether in an atmosphere of dry N_2 was added

a solution of 0.25 g (0.60 mmol) of the tosylates in 1 mL of dry ether. The reaction mixture was heated at reflux for 1 h, cooled to ambient temperature, quenched with water and extracted with ether. The combined ether extracts were washed well with saturated aqueous $NaHCO_3$ and brine, dried ($MgSO_4$) and the solvent removed in vacuo to afford 0.12 g (81%) of dimethyl ether **22** as a pale-yellow oil. This material was used in the next step without further purification: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.80–0.87 (m, 6H), 1.07–1.34 (m, 7H), 1.53–1.63 (m, 2H), 2.54 (t, J=7.8 Hz, 2H), 3.76 (s, 6H), 6.29 (t, J=2.1 Hz, 1H), 6.34 (d, J=2.1 Hz, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 11.4, 19.2, 26.8, 29.4, 31.6, 34.3, 36.3, 36.4, 55.1, 97.5, 106.4, 145.3, 160.6; IR (neat) 1600 cm^{-1}; $[\alpha]_D^{20}$ −7.5° (*c* 1.5, $CHCl_3$); HRMS calcd for $C_{16}H_{26}O_2$: 250.1933, Found: 250.1933.

(5′*S*)-5′-Methyl-Δ^8-tetrahydrocannabinol (7*S*). Cannabinoid **7*S*** was prepared from **22** by the procedure described above for the preparation of **3*R***. From 0.11 g of (*S*)-1-(3,5-dimethoxyphenyl)-5-methylheptane (**22**) there was obtained 0.01 g (100%) of the substituted resorcinol: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.80–0.85 (m, 6H), 1.06–1.46 (m, 9H), 2.39 (t, J=7.8 Hz, 2H), 6.17 (s, 1H), 6.26 (s, 2H), 6.30 (br s, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 11.3, 19.1, 26.8, 29.6, 31.3, 34.3, 35.8, 36.4, 100.3, 108.3, 146.4, 156.0.

From 0.10 g of the resorcinol there was obtained 0.08 g (53%) of cannabinoid **7*S*** as a viscous oil after chromatography (petroleum ether/ethyl acetate, 19/1): ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.82–0.87 (m, 6H), 1.10–1.93 (m, 12H), 1.10 (s, 3H), 1.38 (s, 3H), 1.70 (s, 3H), 2.08–2.13 (m, 1H), 2.43 (t, J=7.7 Hz, 2H), 2.69 (dt, J=4.5, 10.7 Hz, 1H), 3.18 (dd, J=4.2, 16.1 Hz, 1H), 4.75 (s, 1H), 5.43 (d, J=4.0 Hz, 1H), 6.11 (s, 1H), 6.28 (s, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 11.4, 18.5, 19.2, 23.5, 26.9, 27.6, 27.9, 29.5, 31.2, 31.6, 34.3, 35.5, 36.0, 36.4, 44.9, 76.7, 107.6, 110.1, 110.5, 119.3, 134.7, 142.7, 154.7, 154.8; IR (neat) 3400, 1630, 1580 cm^{-1}; $[\alpha]_D^{20}$ −127.8° (*c* 0.70, $CHCl_3$); HRMS calcd for $C_{24}H_{36}O_2$: 356.2715, Found: 356.2714.

(*S*)-1-Benzyloxy-6-(3,5-dimethoxyphenyl)-2-methylhex-4-yne (26). To a solution of 0.45 g (2.4 mmol) of (*S*)-1-benzyloxy-2-methylpent-4-yne (**25**)[10c] in 3 mL of dry THF at 0 °C in a dry N_2 atmosphere was added 1.0 mL (2.5 mmol) of *n*-butyllithium (2.5 M in hexanes). The solution was allowed to warm slowly to room temperature, stirred for 1.5 h, and a solution of 0.56 g (2.4 mmol) of 3,5-dimethoxybenzyl bromide in 1 mL of dry THF was added followed by 0.32 g (2.4 mmol) of lithium iodide. The resulting solution was heated at reflux for 2 h, cooled to ambient temperature, carefully quenched with saturated aqueous NH_4Cl and extracted with ether. The combined ethereal extracts were dried ($MgSO_4$) and the ether evaporated in vacuo to give the crude product which was chromatographed (petroleum ether/ethyl acetate, 24/1) to provide 0.58 g (72%) of **26** as a yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.04 (d, J=6.8 Hz, 3H), 1.97–2.06 (m, 1H), 2.18–2.40 (m, 2H), 3.36 (dd, J=5.9, 9.2 Hz, 1H), 3.41 (dd, J=7.2, 9.2 Hz, 1H), 3.51 (s, 2H), 3.75 (s, 6H), 4.49 (s, 2H), 6.32 (t, J=2.1 Hz, 1H), 6.51 (d, J=2.1 Hz, 2H), 7.21–7.33 (m, 5H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 16.5, 22.9, 25.3, 33.2, 55.2, 72.9, 74.3, 78.4, 80.7, 98.4, 105.8, 127.3, 127.4, 128.2, 138.6, 139.9, 160.9; IR (neat) 1585 cm^{-1}; $[\alpha]_D^{20}$ +11.6° (*c* 3.0, $CHCl_3$); HRMS calcd for $C_{22}H_{26}O_3$: 338.1882, Found: 338.1882.

(*S*)-6-(3,5-Dimethoxyphenyl)-2-methyl-1-hexanol (27). To a solution of 0.50 g (1.5 mmol) of **26** in 50 mL of ethanol was added 0.10 g of 10% Pd on carbon and the mixture was shaken under an atmosphere of H_2 (45 psi) for 16 h. The reaction mixture was filtered through Celite and the ethanol was removed in vacuo to give 0.35 g (94%) of **27** as a yellow oil, which was used without further purification: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.86 (d, J=7.8 Hz, 3H), 1.06–1.48 (m, 5H), 1.48–1.61 (m, 2H), 2.53 (t, J=7.6 Hz, 2H), 2.88 (br s, 1H), 3.35 (dd, J=6.4, 10.3 Hz, 1H), 3.45 (dd, J=5.9, 10.3 Hz, 1H), 3.73 (s, 6H), 6.28 (t, J=1.8 Hz, 1H), 6.33 (d, J=1.8 Hz, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 16.3, 26.4, 31.2, 32.7, 35.4, 35.9, 54.8, 67.7, 97.3, 106.1, 144.8, 160.3; IR (neat) 3380, 1580 cm^{-1}; $[\alpha]_D^{20}$ +31.0° (*c* 1.0, $CHCl_3$); HRMS calcd for $C_{15}H_{24}O_3$: 252.1725, Found: 252.1725.

(*R*)-1-(3,5-Dimethoxyphenyl)-5-methylheptane (28). The conversion of alcohol **27** into the corresponding tosylate was carried out using the procedure described above for the preparation of **19*R***. From 0.28 g of alcohol there was obtained 0.35 g (78%) of tosylate after purification by chromatography (petroleum ether/ethyl acetate, 4/1): ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.85 (d, J=6.3 Hz, 3H), 1.07–1.33 (m, 4H), 1.51 (p, J=7.2 Hz, 2H), 1.72 (m, 1H), 2.39 (s, 3H), 2.47 (t, 7.2 Hz, 2H), 3.73 (s, 6H), 3.78–3.87 (m, 2H), 6.28 (s, 1H), 6.30 (s, 2H), 7.30 (d, J=7.7 Hz, 2H), 7.75 (d, J=7.7 Hz, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 16.1, 21.3, 26.0, 31.0, 32.2, 32.5, 35.8, 54.9, 74.8, 97.4, 106.1, 127.6, 129.6, 132.9, 144.4, 144.6, 160.5; IR (neat) 1590 cm^{-1}.

The crude tosylate was coupled with methylmagnesium bromide using the procedure described above for the preparation of **11*R***. From 0.30 g of tosylate there was obtained 0.16 g (87%) of **28**. The spectroscopic properties of this compound were identical to those of the (5*S*)-isomer. $[\alpha]_D^{20}$ +5.9° (*c* 1.5, $CHCl_3$).

(5*R*)-5-Methyl-Δ^8-tetrahydrocannabinol (7*R*). Cannabinoid **7*R*** was prepared from **28** by the procedure descri-

bed above for the preparation of **3***R*. From 0.13 g of (5*R*)-1-(3,5-dimethoxyphenyl)-5-methylheptane there was obtained 0.11 g (95%) of the substituted resorcinol, the spectroscopic properties of which were identical to those of the enantiomer described above. This material was used in the next step without purification.

From 0.10 g of the resorcinol there was obtained 0.07 g (41%) of (5′*R*)-5′-methylheptyl-Δ^8-tetrahydrocannabinol (**7***R*) as a viscous, amber oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.73–0.87 (m, 6H), 1.05–1.40 (m, 6H), 1.10 (s, 3H), 1.37 (s, 3H), 1.53 (p, J = 6.8 Hz, 2H), 1.66–1.93 (m, 4H), 1.70 (s, 3H), 2.07–2.13 (m, 1H), 2.40–2.46 (m, 2H), 2.70 (dt, J = 4.5, 10.8 Hz, 1H), 3.20 (dd, J = 4.3, 16.3 Hz, 1H), 4.86 (s, 1H), 5.42 (d, J = 3.9 Hz, 1H), 6.10 (s, 1H), 6.28 (s, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 11.4, 18.5, 19.2, 23.5, 26.9, 27.5, 27.9, 29.5, 31.2, 31.6, 34.3, 35.5, 36.0, 36.4, 44.9, 76.7, 107.6, 110.1, 110.5, 119.3, 134.7, 142.7, 154.8; IR (neat) 3400, 1630, 1580 cm^{-1}; $[\alpha]_D^{20}$ −108.0° (*c* 2.0, $CHCl_3$); HRMS calcd for $C_{24}H_{36}O_2$: 356.2715, Found: 356.2715.

1-Bromo-5-methylhexane. Ethyl 2-carboethoxy-5-methylethyl-2-hexenoate was prepared from diethyl malonate and isovaleraldehyde,[20] followed by catalytic hydrogenation to the saturated diester, which was decarboxylated by the method of Krapcho.[21] This ester was reduced with $LiAlH_4$ under standard conditions to give 5-methyl-1-hexanol which was converted to the bromide using the conditions of Quirico and Fischli[22] in 63% yield. The spectral data are consistent with previously reported data:[14] ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.88 (d, J = 6.5 Hz, 6H), 1.18–1.25 (m, 2H), 1.30–1.61 (m, 3H), 1.84 (m, 2H), 3.42 (t, J = 6.8 Hz, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 22.5, 26.0, 27.8, 33.1, 34.0, 38.0; IR (neat) 3270, 1465 cm^{-1}.

1-(3,5-Dimethoxyphenyl)-6-methylheptane. To a solution of 1.20 g (6.7 mmol) of 1-bromo-5-methylhexane in 10 mL of toluene was added 1.75 g (6.7 mmol) of triphenylphosphine and the mixture was heated at reflux for 48 h. The mixture was cooled to 0 °C, the solid filtered, washed with ether and dried in vacuo to give 3.2 g (74%) of the phosphonium salt as a white solid which was used in the next step without further purification: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.82 (d, J = 6.6 Hz, 6H), 1.14–1.19 (m, 2H), 1.40–1.51 (m, 1H), 1.55–1.65 (m, 4H), 3.36–3.68 (m, 2H), 7.47–7.87 (m, 15H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 22.0, 22.3, 22.7, 27.1, 27.7, 27.9, 37.7, 117.1, 118.2, 130.0, 130.1, 133.0, 133.1, 134.6; MS (EI) *m*/*z* 361 (5), 262 (100).

To a stirred slurry of 0.70 g (1.6 mmol) of 5-methylhexyltriphenylphosphonium bromide in 2 mL of dry THF at 0 °C was added 0.65 mL of 2.5 M *n*-butyllithium (1.63 mmol). The mixture was stirred at ambient temperature for 2 h and a solution of 3,5-dimethoxybenzaldehyde in 2 mL of dry THF was added. The reaction mixture was stirred for an additional 2 h, poured into water and extracted with ethyl acetate. The combined extracts were washed with 10% aqueous HCl and water, dried ($MgSO_4$) and the solvent removed under reduced pressure to give the crude olefin as a mixture of *E* and *Z* isomers. The mixture was chromatographed (petroleum ether/ethyl acetate, 9/1) to give 0.31 g (80%) of the stereoisomeric olefins as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.88–0.97 (m, 6H), 1.21–1.28 (m, 2H), 1.43–1.60 (m, 3H), 1.16–2.36 (m, 2H), 3.80 (s, 6H), 5.63–5.72 (m, 1H), 6.18–6.53 (m, 4H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 22.6, 27.1, 27.7, 27.9, 29.0, 33.2, 38.5, 38.7, 55.1, 98.7, 99.0, 104.0, 106.8, 128.7, 129.7, 131.7, 133.6, 139.6, 140.0, 160.4, 160.8; MS (EI) *m*/*z* 248 (100), 152 (95).

A solution of 0.20 g (8.1 mmol) of the above olefins in 20 mL of ethanol, containing 0.02 g of 10% Pd on carbon was hydrogenated at 45 psi for 24 h. The catalyst was filtered through a pad of Celite and the solvent was removed under reduced pressure to give 0.19 g (94%) of 1-(3,5-dimethoxyphenyl)-6-methylheptane as a colorless oil. The crude product was used in the next step without further purification. For characterization, a portion of the crude material was distilled bp 130 °C (0.5 mm Hg): ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.86 (d, J = 6.6 Hz, 6H), 1.17 (m, 2H), 1.31 (m, 4H), 1.47–1.60 (m, 3H), 2.54 (t, J = 7.9 Hz, 2H), 3.78 (s, 6H), 6.29 (t, J = 2.2 Hz, 1H), 6.35 (d, J = 2.2 Hz, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 22.6, 27.2, 27.9, 29.6, 31.3, 36.3, 38.9, 55.2, 97.5, 106.4, 145.4, 160.6; IR (neat) 2931, 1604 cm^{-1}; Anal. calcd for $C_{16}H_{26}O_2$: C, 76.75; H, 10.47, Found: C, 76.60; H, 10.51.

6′-Methylheptyl-Δ^8-tetrahydrocannabinol (8). Cannabinoid **8** was prepared from the resorcinol dimethyl ether by the procedure described above for the preparation of **3**. From 0.44 g (1.8 mmol) of 1-(3,5-dimethoxyphenyl)-6-methylheptane there was obtained 0.39 g (100%) of substituted resorcinol: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.86 (d, J = 6.6 Hz, 6H), 1.17 (m, 2H), 1.31 (m, 4H), 1.47–1.60 (m, 3H), 2.54 (t, J = 7.9 Hz, 2H), 6.29 (t, J = 2.2 Hz, 1H), 6.35 (d, J = 2.2 Hz, 2H).

From 0.39 g of resorcinol there was obtained 0.21 g (28%) of 6′-methylheptyl-Δ^8-THC (**8**) as a viscous oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.84–0.90 (m, 6H), 1.10–1.15 (m, 5H), 1.28 (s, 4H), 1.37 (s, 3H), 1.48–1.53 (m, 3H), 1.69 (s, 3H), 1.78–1.81 (m, 3H), 2.12 (s, 1H), 2.41 (t, J = 7.6 Hz, 2H), 2.71 (m, 1H), 3.18–3.24 (m, 1H), 5.20 (s, 1H), 5.42 (s, 1H), 6.10 (s, 1H), 6.29 (s, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 18.5, 22.6, 23.5, 27.2, 27.5, 27.9, 27.9, 29.6, 30.9, 31.6, 35.5, 35.7, 36.0, 38.9, 44.9, 76.7, 107.7, 110.0, 110.6, 119.3, 134.7, 142.6, 154.7,

154.8; IR (neat) 3405, 2931, 1629 cm^{-1}; $[\alpha]_D^{20}$ −151.7° (*c* 4.1, $CHCl_3$); HRMS calcd for $C_{24}H_{36}O_2$: 356.2715, Found: 356.2713.

1-(3,5-Dimethoxyphenyl)-1-heptanol. To a solution of *n*-hexylmagnesium bromide prepared from 0.70 mL (5.0 mmol) of 1-bromohexane in 10 mL of dry ether was added a solution of 0.75 g (4.5 mmol) of 3,5-dimethoxybenzaldehyde in 10 mL of dry ether. The reaction mixture was heated at reflux for 2 h, cooled to ambient temperature, and the reaction was quenched with water, and acidified to pH 3 with dilute HCl. The ether solution was washed with saturated $NaHCO_3$, brine and dried ($MgSO_4$). The solvent was removed in vacuo to give an oil, which was purified by chromatography (petroleum ether/ether, 1/1) to give 0.81 g (72%) of alcohol as a colorless oil: ^1H NMR (300 MHz, $CDCl_3$) δ 0.87 (t, J = 6.9 Hz, 3H), 1.17–1.47 (m, 8H), 1.57–1.85 (m, 2H), 2.34 (s, 1H), 3.77 (s, 6H), 4.55 (t, J = 7.0 Hz, 1H), 6.34 (t, J = 2.3 Hz, 1H), 6.48 (d, J = 2.2 Hz, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.0, 22.5, 25.7, 29.1, 31.7, 38.9, 55.2, 74.6, 99.1, 103.7, 147.6, 160.6; Anal. calcd for $C_{15}H_{24}O_3$: C, 71.39; H, 9.59, Found: C, 71.48; H, 9.68.

1-(3,5-Dimethoxyphenyl)heptane. To a solution of 0.27 g (1.1 mmol) of 1-(3,5-dimethoxyphenyl)-1-heptanol in 100 mL of ethanol was added 4 mL of trifluoroacetic acid and 0.12 g of 10% Pd/C. The mixture was hydrogenated (50 psi) for seven days, the catalyst was filtered off through a pad of Celite and the solvent was removed in vacuo to give 0.18 g (73%) of pure 1-(3,5-dimethoxyphenyl)heptane as a colorless liquid, after distillation (130 °C/0.5 mm Hg): ^1H NMR (300 MHz, $CDCl_3$) δ 0.88 (t, J = 7.0 Hz, 3H), 1.19–1.41 (m, 8H), 1.53–1.68 (m, 2H), 2.52 (t, J = 8.0 Hz, 2H), 3.72 (s, 6H), 6.27 (t, J = 2.2 Hz, 1H), 6.33 (d, J = 2.2 Hz, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 13.9, 22.6, 29.1, 29.2, 31.2, 31.7, 36.2, 54.8, 97.3, 106.3, 145.1, 160.6. Anal. calcd for $C_{15}H_{24}O_2$: C, 76.23; H, 10.23, Found: C, 76.16; H, 10.28.

Heptyl-Δ^8-tetrahydrocannabinol (9). Cannabinoid **9** was prepared from the resorcinol dimethyl ether by the procedure described above for the preparation of **3*R***. From 0.24 g (1.0 mmol) of 1-(3,5-dimethoxyphenyl)heptane there was obtained 0.24 g (100%) of substituted resorcinol as a brown oil which was used in the next step without purification: ^1H NMR (300 MHz, $CDCl_3$) δ 0.86 (t, J = 7.0 Hz, 3H), 1.10–1.36 (m, 8H), 1.41–1.60 (m, 2H), 2.41 (t, J = 8.0 Hz, 2H), 5.90 (br s, 2H), 6.19 (d, J = 1.9 Hz, 1H), 6.25 (d, J = 1.9 Hz, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.0, 22.6, 29.1, 29.3, 31.0, 31.8, 35.8, 100.3, 108.0, 146.2, 156.4.

From 0.24 g of resorcinol there was obtained 0.19 g (57%) of cannabinoid **9** as a yellow gum: ^1H NMR (300 MHz, $CDCl_3$) δ 0.87 (t, J = 7.0 Hz, 3H), 1.09 (s, 3H), 1.37 (s, 3H), 1.68 (s, 3H), 1.13–1.42 (m, 8H), 1.42–1.61 (m, 2H), 1.71–1.95 (m, 3H), 2.02–2.22 (m, 1H), 2.41 (t, J = 7.8 Hz, 2H), 2.60–2.78 (m, 1H), 3.14–3.31 (m, 1H), 5.41 (s, 1H), 5.78 (s, 1H), 6.09 (d, J = 1.1 Hz, 1H), 6.26 (d, J = 1.3 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.0, 18.4, 22.6, 23.4, 27.5, 27.8, 29.1, 29.3, 30.9, 31.5, 31.7, 35.5, 35.9, 44.9, 76.6, 107.7, 109.7, 110.6, 119.2, 134.7, 142.5, 154.6, 155.0; MS (EI) *m/z*: 342 (41), 299 (24), 259 (100), 221 (19), 174 (13), 119 (10), 91 (8), 57 (15); $[\alpha]_D^{20}$ −152° (*c* 4.2, $CHCl_3$); HRMS calcd for $C_{23}H_{34}O_2$: 342.2559, Found: 342.2557.

Acknowledgements

The work at Clemson was supported by Grant DA03590 and that at Virginia Commonwealth University by Grant DA03672, both from the National Institute on Drug Abuse. We thank Dr. Percy S. Manchand of Hoffmann–La Roche for a generous gift of methyl (*S*)-3-hydroxy-2-methylpropionate.

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