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Side Chain Methyl Analogues of Δ^8-THC

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Abstract: The synthesis of both side chain epimers of 1'- (**4**), 2'- (**5**), 3'-methyl- (**6**) and 4'-methyl-Δ^8-tetrahydrocannabinol (**7**) has been carried out. The synthetic approach entailed the acid catalyzed condensation of the appropriate substituted resorcinol with menthadienol to provide the Δ^8-THC analogue. Both isomers of 1'- (**4**) and 2'-Δ^8-THC (**5**) were more potent than Δ^8-THC, both *in vitro* and *in vivo*. The 3'-methyl isomers (**6**) were approximately equal in potency to Δ^8-THC, and 4'-methyl-Δ^8-THC was less potent. There was relatively little difference in potency between the epimers of **4**, **5**, and **6**.

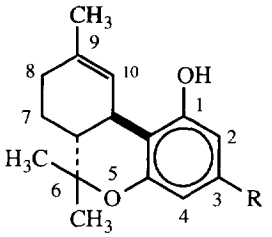
INTRODUCTION

A considerable body of data exists which has led to the development of a comprehensive interpretation of the structural and stereochemical requirements for cannabinoid activity.[1] These structure activity relationships (SAR) for classical cannabinoids have been 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.[2] In the course of developing these SAR it has been observed that the length 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. If the five carbon unit is replaced by either a 1,1-dimethylheptyl or 1,2-dimethylheptyl group activity is considerably enhanced.[1]

Although a great deal of work has been carried out on SAR in cannabinoids, little is known concerning the effect of branching on the activity in THC analogues with the natural five carbon side chain. A number of years ago Edery *et al.* reported that if a methyl group was added at C-1' in Δ^9-THC, activity was diminished, while there was little effect on the activity in the Δ^8 analogue.[3] There appear to be no other reports of the effect of the substitution of a single methyl group on the cannabinoid side chain.

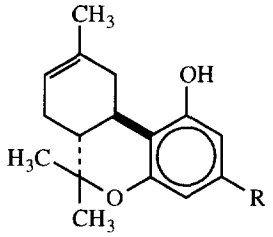
Convincing evidence for the cannabinoid brain receptor was presented several years ago, and a three point model for the interaction of the drug with the receptor was suggested.[4] Subsequently the location of the receptor in the brain of several mammalian species was described,[5] the receptor has been cloned and the primary structure 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]



1 R = n-C_5H_{11}

2 R = $CH(CH_3)CH_2CH_2CH_2CH_3$



3 R = n-C_5H_{11}

4 R = $CH(CH_3)CH_2CH_2CH_2CH_3$

5 R = $CH_2CH(CH_3)CH_2CH_2CH_3$

6 R = $CH_2CH_2CH(CH_3)CH_2CH_3$

7 R = $CH_2CH_2CH_2CH(CH_3)_2$

In order to obtain additional data concerning the nature of the lipophilic portion of the receptor, and obtain additional data concerning SAR of cannabinoids, the synthesis of all the possible analogues of Δ^8-THC (**3**) which contain a branching methyl group attached to a pentyl chain (**4-7**) has been carried out. Analogues of Δ^8-THC rather than Δ^9-THC were chosen on the basis of their ease of synthesis, considerably enhanced stability, and most importantly because the activity of both isomers is nearly identical.[1] Δ^8-THC derivatives can be 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] The overall synthetic challenge thus becomes the synthesis of the appropriate resorcinol derivatives which are condensed with the terpene to provide the Δ^8-THC derivative in a single step.

Three of the four positional isomers (**4-6**) have a chiral center at the point of attachment of the methyl group and for these compounds both diastereomers have been synthesized. With the exception of the observation by Martin *et al.* that the 3'*S* epimer of 3'-hydroxy Δ^8-THC was significantly more potent than the 3'*R* isomer,[9] little appears to be known concerning the effect of the stereochemistry of side chain substituents on cannabinoid activity. A requirement of the synthetic approaches to the resorcinol precursors of the current THC analogues was that the method employed should permit the preparation of both epimers of the side chain methyl derivatives. In the case of the resorcinol precursors which contain a single chiral center, this entails the preparation of each enantiomer of known optical purity. The synthetic routes to **4-6** were developed using racemic resorcinol derivatives[10] and the methodology was then extended to nonracemic materials.

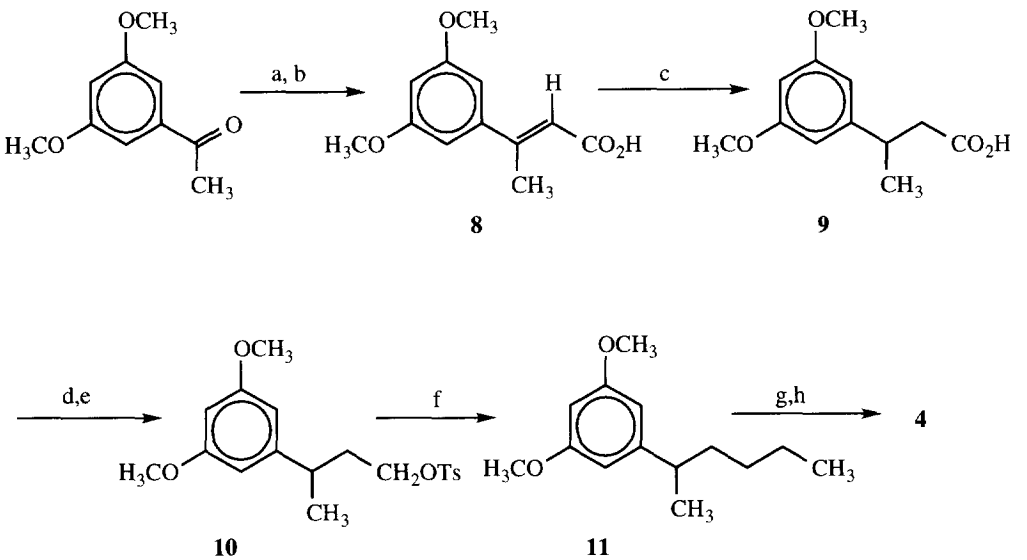
RESULTS

The synthetic approach to 1'-methyl (**4**) and 2'-methyl-Δ^8-THC (**5**) both proceeded by way of the appropriately substituted β-3,5-dimethoxyphenylpropionic acid. This method provided intermediates which could be elaborated into Δ^8-THC precursors, and which also contained the requisite functionality to allow

resolution of the racemic acids. Although enantioselective approaches to the resorcinol derivatives could be envisioned, since both enantiomers were required a resolution procedure was deemed to be more efficient.

The synthesis of 1'-methyl-Δ^8-THC (**4**, Scheme I) employed 3,5-dimethoxyacetophenone as starting material which was subjected to a Horner-Emmons reaction with triethyl phosphonoacetate to provide the cinnamate ester, hydrolysis of which provided acid **8**. Catalytic hydrogenation to **9**, was followed by reduction to the corresponding primary alcohol and conversion into tosylate **10**.[11] Conversion into racemic resorcinol dimethyl ether **11** was effected by copper catalyzed reaction with ethylmagnesium bromide using a modification of the procedure developed by Kochi.[12] Ether cleavage with boron tribromide, followed by acid catalyzed condensation with menthadienol gave 1'-methyl-Δ^8-THC (**4**) as a mixture of epimers at C-1'.

Scheme I

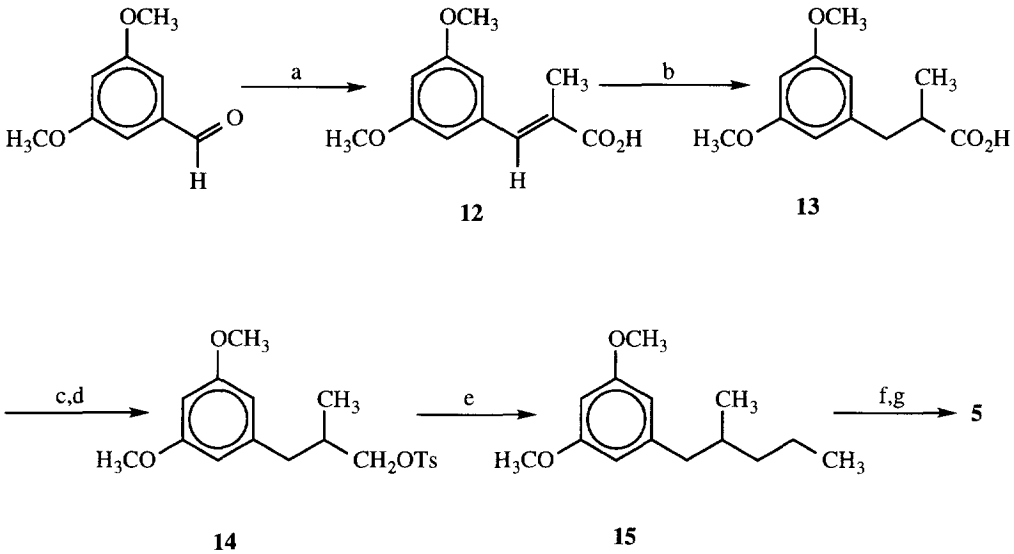


a) $(EtO)_2P(O)CH_2CO_2Et$/NaOEt/EtOH, reflux; b) KOH/MeOH, 65 °C; c) H_2(g)/10% Pd(C)/ EtOH/45 psi; d) $LiAlH_4$/THF, 25 °C; e) TsCl/C_5H_5N/$CHCl_3$, 0 °C; f) Li_2CuCl_4 /EtMgBr/THF, -78° to 25 °C; g) BBr_3/CH_2Cl_2 0° to 25 °C; h) *p*-menthadienol /HOTs/C_6H_6, 80 °C.

Acid **9** was resolved by conversion into the corresponding mixture of diastereomeric amides using (*S*)-(-)-α-phenethylamine in the presence of dicyclohexylcarbodiimide (DCC), which were separated by column chromatography. ^1H and ^{13}C NMR indicated that the amides were stereochemically homogeneous, within the limits of detection. The absolute configuration of the phenethylamide of the *R* acid was established by X-ray crystallography.[13] Although Li/NH_3 reduction to the primary amide[14] proceeded smoothly, considerable difficulty was encountered in effecting hydrolysis to *R*- and *S*-**9** under mild conditions. Olah's procedure using nitrosonium tetrafluoroborate[15] led to a complex mixture of dark colored products. Apparently the highly activated dimethoxyphenyl ring undergoes nitrosation under these conditions.[16] With one equivalent of

aqueous Na_2O_2 under the published conditions,[17] the starting amide was recovered unchanged. However, with excess (10 equivalents) of Na_2O_2, the *R* and *S* acids were obtained in acceptable yields. The chiral center in acid **9** is beta to the acyl group, thus the stereochemical integrity of the chiral center is retained during hydrolysis of the amide. The individual enantiomers of **9** were converted into the *R* and *S* isomers of **4** by the route outlined in Scheme I. The (*S*)-(-)-α-phenethylamine (Aldrich) employed for the resolution of acid **9** has 99% ee, and consequently the *R* and *S* isomers of **4** were of comparable optical purity.

Scheme II



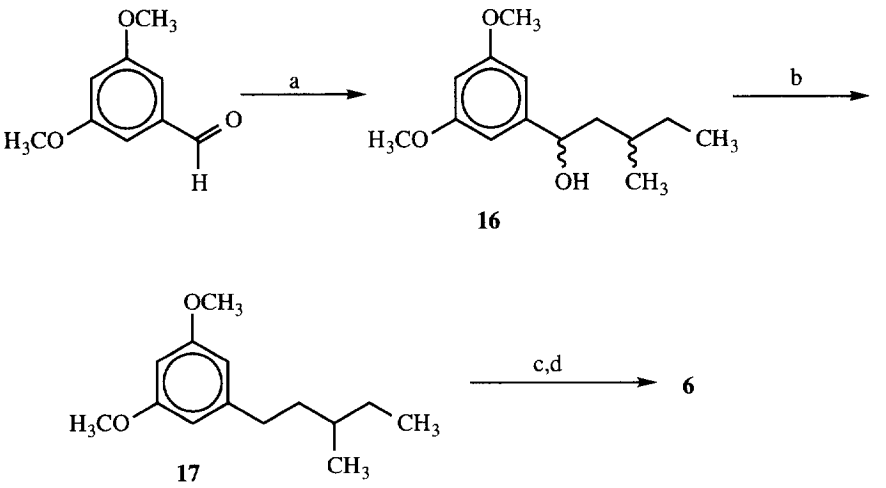
a) $(EtO)_2P(O)CH(CH_3)CO_2Et$/NaOEt/EtOH, reflux; b) H_2(g)/10% Pd(C)/EtOH/48 psi; c) $LiAlH_4$/THF, 25 °C; d) TsCl/C_5H_5N/$CHCl_3$, 0 °C; e)Li_2CuCl_4/EtMgBr/THF, -78° to 25 °C; f) BBr_3/CH_2Cl_2 0° to 25 °C; g) *p*-menthadienol/HOTs/ C_6H_6, 80 °C.

The synthesis of 2'-methyl-Δ^8-THC (**5**, Scheme II) was similar to that employed for **4**, with the exception that 3,5-dimethoxybenzaldehyde was subjected to a Horner-Emmons reaction with triethyl phosphonopropionate as the first step. The cinnamate ester underwent essentially complete hydrolysis during work up and was not isolated. Acid **12** was hydrogenated to **13**, reduced to the corresponding alcohol and converted into tosylate **14** as described as above. Reaction with ethylmagnesium bromide as described above provided **15** which was subjected to ether cleavage and reaction with menthadienol to give **5**, again as a mixture of epimers at C-2'.[10]

Resolution of acid **13** was carried out using (*S*)-(-)-α-phenethylamine as described for the resolution of **9**. In **13** the chiral center is adjacent to the carbonyl of the acyl group, and although the phenethylamides were stereochemically homogeneous to NMR, even very careful hydrolysis of the derived primary amides at temperatures at or below 50 °C occasionally resulted in partial racemization. Although the temperature of these

hydrolysis reactions was monitored carefully, the results were not completely reproducible from run to run. In addition to the unsuccessful methods described above for the hydrolysis of the amide of acid **9**, an attempt was made to employ lithium hydroperoxide,[18] however the starting material was recovered unchanged. The optical purity of the resolved acids was determined by converting a portion of the resolved material into the (*S*)-phenethylamide under conditions known to proceed without racemization (DCC/hydroxybenztriazole [HOBT][19]). The optical purity of the amide was determined by ^{1}H NMR (See Experimental Section). The *R* acid contained 7.5% of the *S* enantiomer (85% ee), while the *S* acid was obtained optically pure within the limits of the NMR method used for analysis. The configuration of the *R* acid was determined by X-ray crystallography of the phenethylamide.[13]

Scheme III



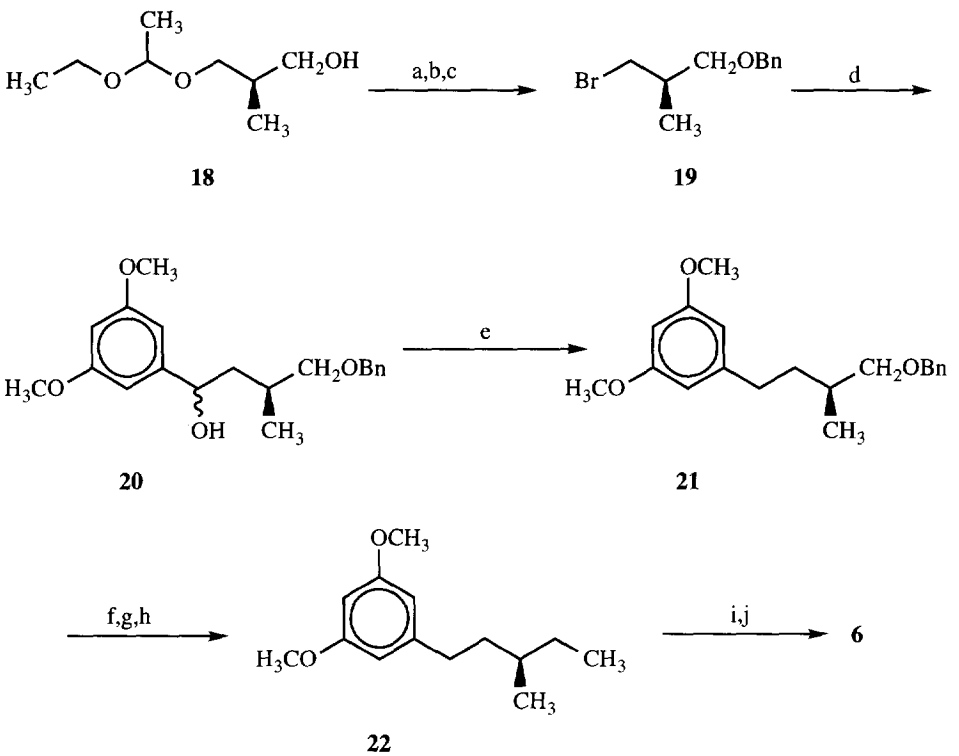
a) $CH_3CH_2CH(CH_3)CH_2MgBr$, 25 °C then 35 °C; b) H_2(g)/10% Pd(C)/EtOH/CF_3CO_2H/45 psi; c) BBr_3/CH_2Cl_2 0° to 25 °C; d) *p*-menthadienol/HOTs/C_6H_6, 80 °C.

The 3'-methyl analogue (**6**, Scheme III) was initially prepared as a mixture of 3'*RS* isomers from 3,5-dimethoxybenzaldehyde by reaction with the Grignard reagent derived from racemic 1-bromo-2-methylbutane[20] which provided alcohols **16** as a diastereomeric mixture. This mixture was not separated inasmuch as the chirality due to the benzyl hydroxyl was destroyed by reduction to provide racemic **17**. Ether cleavage to the resorcinol and condensation with menthadienol provided **6**. The 3'*S*-isomer of **6** was prepared by the same route, but employed commercial (Aldrich) (*S*)-(+)-1-bromo-2-methylbutane at the first step.[10]

Initially it was intended to effect the synthesis of the 3'*R*-isomer by the route employed for the *S*- and *RS*-isomers. This proposed route required (*R*)-1-bromo-2-methylbutane, which was to be prepared from *R*-(-)-2-methyl-1-butanol. Resolution of racemic 2-methylbutanoic acid *via* the (*S*)-phenethylamine salt[21] afforded the *R*-acid of 88% ee, as determined by analysis of the ^{1}H NMR spectrum of a mixture of the diastereomeric

phenethylamides. The acid was converted into *R*-(-)-2-methyl-1-butanol by $LiAlH_4$ reduction, however reaction with PBr_3 did not proceed smoothly, and purification of the very volatile (*R*)-1-bromo-2-methylbutane on a small scale proved to be exceedingly inefficient. The synthesis of (*R*)-1-bromo-2-methylbutane from methyl (*S*)-(+)-3-hydroxy-2-methylpropionate by the method of Tius *et al.* could not be repeated as described, due to the lability of ethoxyethyl protected intermediates to chromatography on silica gel.[22]

Scheme IV



a) $KH/C_6H_5CH_2Br/DMF$, 25 °C; b) PPTS/10% HCl/THF, reflux; c) $Ph_3P/NBS/CH_2Cl_2$, 25 °C; d) $Mg/BrCH_2CH_2Br/HOTs/Et_2O$, then 3,5-dimethoxybenzaldehyde, reflux; e) $AlCl_3/LiAlH_4/Et_2O$, 25 °C; f) $Li/NH_3/Et_2O$, -78 °C; g) $TsCl/C_5H_5N/CHCl_3$, 0 °C; h) $Li_2CuCl_4/MeMgBr/THF$, -78° to 25 °C; i) BBr_3/CH_2Cl_2, 0° to 25 °C; j) *p*-menthadienol/HOTs/ C_6H_6, 80 °C.

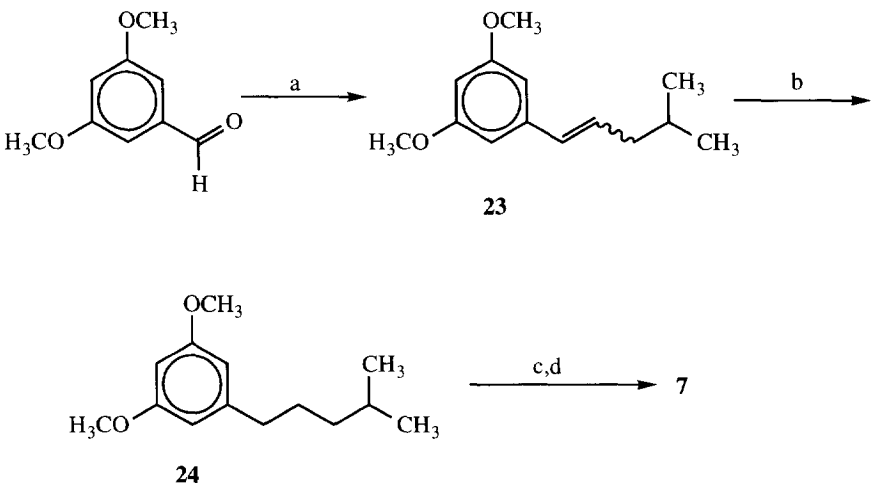
An alternative and ultimately successful approach employed (*R*)-3-(1-ethoxyethyl)-2-methylpropanol (**18**, Scheme IV)[22] as starting material, which was converted into (*S*)-3-benzyloxy-1-bromo-2-methylpropane (**19**) by a modification of the published procedures.[23] Bromide **19** was converted into the corresponding alkylmagnesium bromide employing an entrainment procedure in the presence of 1,2-dibromoethane, with the addition of a trace of *p*-toluenesulfonic acid under rigorously controlled conditions (see experimental section).

Reaction with 3,5-dimethoxybenzaldehyde provided a mixture of diastereomeric alcohols **20**, and the corresponding ketone in a ratio of approximately two to one. Attempted catalytic hydrogenolysis of either the mixture of diastereomeric alcohols or the ketone, as employed for the conversion of **16** into **17**, resulted in debenzylation, but no reduction of the benzylic oxygen. Similar results were obtained upon reduction with Li/NH_3.

The desired conversion was ultimately effected in two steps; reduction with $LiAlH_4/AlCl_3$ to provide benzyl ether **21**[24] followed by dissolving metal (Li/NH_3) reduction to the primary alcohol. Although the inseparable mixture of diastereomeric alcohols **20** and the ketone could be characterized, in practice this two step sequence was carried out on the crude reaction mixture. The primary alcohol was converted into the corresponding tosylate, and subjected to modified Kochi coupling with methyl Grignard to provide (*R*)-1-(3,5-dimethoxyphenyl)-3-methylpentane (**22**). Conversion of **22** into the 3'*R*-isomer of **6** was carried out using the method employed for the synthesis of the *S*-isomer. Alcohol **18** was prepared from methyl (*S*)-3-hydroxy-2-methylpropionate of 99% optical purity, and the final product, 3'*R*-**6** was of comparable optical purity.

The synthesis of the 4'-methyl analogue (**7**, Scheme V) employed as the first step the Wittig reaction of the ylide derived from isoamyltriphenylphosphonium bromide and 3,5-dimethoxybenzaldehyde to give olefins **23** as a mixture of *cis* and *trans* isomers. The mixture was reduced to resorcinol dimethyl ether **24**. Ether cleavage, followed by condensation with menthadienol provided **7**.

Scheme V



a) $(CH_3)_2CHCH_2CH_2P^+(C_6H_5)_3\ Br^-$/BuLi/Ether, 25 °C; b) H_2(g)/10% Pd(C)/EtOH/ CF_3CO_2H/45 psi; c) BBr_3/CH_2Cl_2, 25 °C; d) *p*-menthadienol/HOTs/C_6H_6, 80 °C.

The pharmacology of all compounds, both *in vitro* and *in vivo*, was evaluated using standard cannabinoid assays. The *in vitro* pharmacology was evaluated by measuring the ability of the compound to displace the very potent cannabinoid, [^{3}H] CP 55,940, from its binding site in a membrane preparation.[25] The

in vivo pharmacology was evaluated in the mouse model of cannabimimetic activity which measures spontaneous activity (SA), antinociception (as tail flick, TF) and rectal temperature (RT).[26] The pharmacology of the side chain mixtures of *RS*-cannabinoids **5**, **6**, *S*-**6**, and **7** has been reported previously.[10]

Edery *et al.* reported that the (1'*RS*)-1'-methyl cannabinoid (**4**) is approximately equal in potency to Δ^8-THC (**3**);[3] however, we find that it has greater affinity (K_i=7.1±0.2 nM) for the receptor than Δ^8-THC (K_i=44±12 nM). The *in vivo* data also indicate that (1'*RS*)-**4** is more potent than Δ^8-THC. These data, plus the *in vitro* and *in vivo* pharmacology of the individual side chain epimers of **4**-**6**, and 4'-methyl-Δ^8-THC (**7**) are presented in Table 1. The previously reported data for the side chain mixtures of *RS*-cannabinoids **5**, **6** are also included in Table 1.

The data summarized in Table 1 indicate that the 1'-methyl- (**4**), and 2'-methyl-Δ^8-THC (**5**) isomers all have greater affinity for the receptor than Δ^8-THC. Both isomers of 3'-methyl-Δ^8-THC (**6**) have similar affinities for the cannabinoid receptor, and K_i for each is the same as Δ^8-THC (**3**), within experimental error. Finally, the 4'-methyl isomer (**7**) has approximately one-third the affinity of Δ^8-THC (**3**) for the cannabinoid brain receptor. The *in vivo* pharmacology data for the 1'-methyl- (**4**), 2'-methyl- (**5**), and 4'-methyl-Δ^8-THC (**7**) analogues are in general consistent with the receptor affinity of these Δ^8-THC analogues. Although the 3'*S*-isomer has nearly the same activity *in vivo* as Δ^8-THC, the 3'*R* isomer is less potent. The difference in the *in vivo* potency between the 3'*R* and 3'*S*-methyl isomers is much less than that reported for the epimers of 3'-hydroxy-Δ^8-THC, however the trend is in the same direction.[9] It is possible that the difference in potency for the epimers of 3'-hydroxy-Δ^8-THC may be attributed to stereoselective hydrogen bonding, an interaction which is not possible for the methyl THC isomers.

Table 1. *In vitro* and *in vivo* pharmacology of Δ^8-THC (**3**), 1'-methyl- (**4**), 2'-methyl- (**5**), 3'-methyl- (**6**), and 4'-methyl–Δ^8-THC (**7**).

Compound	K_i(nM)	ED_{50} (μmol/kg)		
		SA	TF	RT
3	44±12	2.9	4.8	4.5
4*RS*	7.1±0.2	4.9	1.2	0.9
4*R*	7.6±0.6	6.1	1.5	2.4
4*S*	20±4	0.3	4.8	4.8
5*RS*	10.1±2	4.7	0.24	2.1
5*R*	19±5	0.6	2.1	2.1
5*S*	11±1	0.6	6.1	1.5
6*RS*	54±18	3	1	30
6*R*	38±3	10.4	5.2	12.2
6*S*	53±1	3	1.2	4.8
7	141±52	3	1	30

It is well known that not only does the structure of the cannabinoid side chain have a profound effect upon the potency of a given cannabinoid, but that many variations in side chain structure are possible without loss of potency.[1] The data summarized in Table 1 for the side chain methyl analogues of Δ^8-THC underscore this observation, in that all of these compounds retain cannabinoid activity. The detailed implications of the variations in potency of these compounds must await a detailed description of the structure of that portion of the CB1 receptor which interacts with the lipophilic side chain.

EXPERIMENTAL

General. IR spectra were obtained using Nicolet 5DX or Magna spectrometers; ^{1}H 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 University of Alabama or 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 (32-63μ) using the indicated solvents as eluents. All new compounds were homogeneous to TLC and ^{13}C NMR.

***E*-3-(3,5-Dimethoxyphenyl)-2-butenoic acid (8).** To a solution of sodium ethoxide, prepared from 2.55 g (1.18 equiv) of Na in 200 ml of dry ethanol, was added 18.7 ml (94.3 mmol) of triethylphosphonoacetate. The solution was stirred for 2.5 h at 25 °C and 10.0 g (55.5 mmol) of 3,5-dimethoxyacetophenone in 20 ml of ethanol were added. The reaction mixture was stirred for 72 h at ambient temperature, quenched with water and the alcohol was removed *in vacuo*. The aqueous residue was extracted with ether, and the combined ether extracts were washed with water and brine. The ether was removed *in vacuo* to give 12.23 g (88 %) of ester as a pale yellow oil which was chromatographed (petroleum ether/ether 4:1): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.32 (t, J=7.1 Hz, 3H), 2.54 (d, J=1.3 Hz, 3H), 3.80 (s, 6H), 4.21 (dd, J=7.1 Hz, 2H), 6.11 (t, J=1.3 Hz, 1H), 6.46 (t, J=2.2 Hz, 1H), 6.60 (d, J=2.2 Hz, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.3, 18.1, 55.3, 59.8, 100.8, 104.6, 117.3, 144.4, 155.4, 160.7, 166.7; IR (neat) 1716, 1629, 1589 cm^{-1}. The ester was hydrolyzed without further purification.

To a solution of 3.56 g (63.4 mmol) of KOH in 40 ml of methanol was added 1.01 g (4.04 mmol) of the ester in 2 ml of methanol. The reaction mixture was heated at reflux for 6 h, cooled to room temperature, and 20 ml of water was added. The methanol was removed *in vacuo*, and the aqueous layer was extracted with ether to remove any unreacted ester. The aqueous layer was acidified with 3 M HCl and extracted with three portions of ether. The ethereal extracts were washed with water and brine, dried ($MgSO_4$) and the solvent was removed *in vacuo* to give 0.84 g (93%) of acid as a white crystalline solid which was recrystallized from ether: m.p. 123-125 °C (lit.[27] m.p. 123.5-124.5 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.57 (d, J=1.0 Hz, 3H), 3.82 (s, 6H), 6.16 (t, J=1.3 Hz, 1H), 6.48 (t, J=2.1 Hz, 1H), 6.61 (d, J=2.4 Hz, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 18.5, 55.4, 101.1, 104.7, 116.7, 144.2, 158.5, 160.7, 172.2; IR (Nujol) 1696, 1616, 1596 cm^{-1}; Anal. Calcd for $C_{12}H_{14}O_4$: C, 64.85; H, 6.35; Found: C, 64.93; H, 6.38.

3-(3,5-Dimethoxyphenyl)butanoic acid (9). To a solution of 1.17 g (5.29 mmol) of 3-(3,5-dimethoxyphenyl)butenoic acid (**8**) in 150 ml of ethanol was added 0.28 g of 10% Pd on carbon and the mixture was shaken under an atmosphere of H_2 (45 psi) for 20 h. The reaction mixture was filtered through celite and the ethanol was removed *in vacuo* to give 1.18 g (99%) of **9** as a pale yellow oil which was used without further purification This acid has been described previously as a liquid:[27] ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.29 (d, J=6.9 Hz, 3H), 2.54 (dd, J=8.3, 15.5 Hz, 1H), 2.66 (dd, J=6.6, 15.5 Hz, 1H), 3.16-3.24 (m, 1H), 3.77 (s, 6H), 6.32 (t, J=2.2 Hz, 1H), 6.38 (d, J=2.1 Hz, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 21.6, 36.4, 42.4, 55.2, 98.2, 104.9, 148.0, 160.8, 178.5; IR (neat) 3450-2400, 1709, 1596 cm^{-1}; HRMS Calcd for $C_{12}H_{16}O_4$: 224.1049, Found 224.1051.

3-(3,5-Dimethoxyphenyl)-1-butanol. A solution of 0.69 g (3.07 mmol) of **9** in 5 ml of dry THF was added dropwise to a suspension of 0.23 g (6.14 mmol) of $LiAlH_4$ in 75 ml of THF at 0 °C in a N_2 atmosphere. The reaction mixture was stirred for 16 h while the temperature was allowed to slowly warm to room temperature. The reaction was quenched by the cautious addition of water and the THF was removed *in vacuo*. The aqueous layer was acidified with 10% aqueous HCl and extracted with ether. The ethereal extracts were washed with water and brine, dried ($MgSO_4$) and the ether was removed *in vacuo* to give the crude alcohol as a pale yellow oil which was chromatographed (petroleum ether/ether 4:1) to afford 0.62 g (95%) of pure material: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.21 (m, 1H), 1.25 (d, J=6.8 Hz, 3H), 1.54 (br s, 1H), 1.82 (dd, J=7.2, 6.7 Hz, 2H), 2.78-2.85 (m, 1H), 3.47-3.62 (m, 2H), 3.78 (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 22.2, 36.8, 40.7, 55.2, 61.1, 97.7, 105.1, 149.4, 160.8; IR (neat) 3369, 1602 cm^{-1}; HRMS Calcd for $C_{12}H_{18}O_3$: 210.1256, Found 210.1280.

2-(3,5-Dimethoxyphenyl)hexane (11). To a solution of 0.51 g (2.42 mmol) of 3-(3,5-dimethoxyphenyl)butanol in 5 ml of dry $CHC1_3$ at 0 °C was added 0.29 ml of dry pyridine. The reaction was stirred for 10 min and 0.46 g (2.42 mmol) of *p*-toluenesulfonyl chloride was added and stirring was continued for 3 h at 0 °C. The reaction mixture was diluted with water and extracted with ether. The ethereal extracts were washed successively with 10% aqueous HCl, saturated aqueous $NaHCO_3$, water and brine, dried ($MgSO_4$) and the solvent removed *in vacuo* to give crude tosylate **10** as a yellow oil which was chromatographed (petroleum ether/ether 4:1) to provide 0.54 g (62%) of pure material: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.18 (d, J=6.9 Hz, 3H), 1.80-1.92 (m, 2H), 2.42 (s, 3H), 2.72-2.80 (m, 1H), 3.75 (s, 6H), 3.77-4.00 (m, 2H), 6.25 (d, J=2.2 Hz, 2H), 6.28 (t, J=2.2 Hz, 1H), 7.30 (d, J=8.3 Hz, 2H), 7.73 (d, J=8.2 Hz, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 21.4, 21.7, 36.0, 36.7, 55.0, 68.7, 97.8, 104.8, 127.6, 129.6, 132.7, 144.5, 147.7, 160.7; IR (neat) 1608, 1597 cm^{-1}. The tosylate was used in the subsequent step without additional purification.

A solution of 0.0031 g (0.073 mmol) of LiCl and 0.0049 g (0.0363 mmol) of $CuC1_2$ in 9 ml of dry THF was stirred under N_2 to produce the Li_2CuC1_4 complex. This solution was added dropwise to a solution of 0.22 g (0.605 mmol) of **10** and 3.43 ml of ethylmagnesium bromide (3.0 M in ether) in 6 ml of dry THF at -78 °C to give a brown precipitate. The reaction mixture was stirred for 16 h while it warmed slowly to ambient temperature. The reaction was monitored by TLC and upon completion it was quenched with 10 ml of saturated aqueous NH_4Cl and the THF was removed *in vacuo*. The aqueous residue was extracted with ether and the ether extracts were filtered to remove the precipitated copper salts. After washing with successive portions of 10% aqueous HCl, water and brine, drying ($MgSO_4$), the solvent was removed *in vacuo* to give 0.12 g (89%) of **11** as a pale yellow oil which was purified by distillation: b.p. 140 °C/0.25 mm Hg; ^{1}H NMR (300 MHz,

$CDCl_3$) δ 0.85 (t, J=6.9 Hz, 3H), 1.13-1.32 (m, 7H), 1.46-1.62 (m, 2H), 2.60 (q, J=7.0, 7.1 Hz, 1H), 3.78 (s, 6H), 6.29 (t, J=2.2 Hz, 1H), 6.35 (d, J=2.1 Hz, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.0, 22.2, 22.8, 29.7, 38.0, 40.3, 55.2, 97.4, 105.2, 150.6, 160.6; IR (neat) 1604 cm^{-1}; HRMS Calcd for $C_{14}H_{22}O_2$: 222.1619, Found 222.1616.

(1'*RS*)-1'-Methyl-Δ^8-tetrahydrocannabinol (4). At 0 °C, 0.83 g (3.73 mmol) of **11** was stirred with 4.47 ml of BBr_3 (1.0 M in CH_2Cl_2). The reaction mixture was allowed to warm slowly to room temperature, stirred for 16 h, carefully quenched with water and extracted with ether. The ethereal extracts were washed with brine, dried ($MgSO_4$) and the solvent removed *in vacuo* to give 0.72 g (99%) of the substituted resorcinol as a brown resinous oil which was used in the next step without purification: ^1H NMR (300 MHz, $CDCl_3$) δ 0.83 (t, J=6.7 Hz, 3H), 1.11-1.32 (m, 7H), 1.44-1.52 (m, 2H), 2.45-2.55 (m, 1H), 5.85 (br s, 2H), 6.19 (t, J=2.2 Hz, 1H), 6.25 (d, J=2.2 Hz, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.0, 22.1, 22.7, 29.8, 37.9, 39.9, 100.4, 106.5, 151.3, 156.7; IR (neat) 3401, 1604 cm^{-1}.

To a solution of 0.27 g (1.36 mmol) of the resorcinol in 12 ml of dry benzene was added 0.21 g (1.50 mmol) of *trans-p*-menthadienol followed by 0.026 g of *p*-toluenesulfonic acid monohydrate. The reaction mixture was heated at reflux for 2.5 h, cooled and the benzene solution was washed with water and brine. After drying ($MgSO_4$), the solvent was removed *in vacuo* and the product was purified by chromatography (petroleum ether/ethyl acetate 9:1) to give 0.24 g (55%) of **4** as a yellow gum: ^1H NMR (300 MHz, $CDCl_3$) δ 0.84 (t, J=6.7 Hz, 3H), 1.10 (s, 3H), 1.13 (d, J=7.0 Hz, 3H), 1.15-1.31 (m, 4H), 1.38 (s, 3H), 1.41-1.52 (m, 2H), 1.68 (s, 3H), 1.74-1.92 (m, 3H), 2.06-2.14 (m, 1H), 2.46 (q, J=6.8, 13.7 Hz, 1H), 2.70 (dt, J=4.5, 4.5, 10.8 Hz, 1H), 3.22 (dd, J=4.2, 16.5 Hz, 1H), 5.18 (s, 1H), 5.42 (br d, J=3.9 Hz, 1H), 6.09 (d, J=1.1 Hz, 1H), 6.30 (d, J=1.1 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.0 18.5, 21.8, 22.0, 22.7, 23.4, 27.5, 27.8, 29.9, 31.6, 35.9, 37.8, 37.9, 39.4, 44.9, 76.7, 106.4, 108.4, 108.6, 110.6, 119.2, 134.7, 147.9, 154.6, 154.7; IR (neat) 3.88, 1635, 1585 cm^{-1}; HRMS Calcd for $C_{22}H_{32}O_2$: 328.2402, Found 328.2407.

N-[(1*S*)-1-Phenylethyl]-(3*R,S*)-3-(3,5-dimethoxyphenyl)butanamides. To a solution of 3.08 g of racemic **9** in 150 ml of dry CH_2Cl_2 at room temperature was added sequentially 2.04 ml (15.8 mmol) of (*S*)-(-)-α-phenethylamine (Aldrich, 99% ee) and 3.53 g (17.1 mmol) of DCC. The reaction mixture was stirred for 12 h, the bulk of the dicyclohexylurea was filtered off (Celite) and the solvent removed *in vacuo*. The mixture of diastereomeric amides was separated by flash chromatography (petroleum ether/ethyl acetate 9:2) to give 0.98 g (44%) of the amide derived from the *R* enantiomer of **9**, m.p. 87-88 °C after recrystallization from petroleum ether: ^1H NMR (300 MHz, $CDCl_3$) δ 1.28 (t, J=7.0 Hz, 6H), 2.39 (dd, J=2.7, 6.4 Hz, 2H), 3.21 (q, J=7.2, 9.4 Hz, 1H), 3.76 (s, 6H), 5.00-5.07 (m, 1H) 5.50 (br d, J=7.7 Hz, 1H), 6.32 (t, J=2.2 Hz, 1H), 6.39 (d, J=2.2 Hz, 2H), 7.17-7.32 (m, 5H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 21.4, 21.7, 37.6, 45.9, 48.6, 55.3, 98.2, 105.0, 126.1, 127.3, 128.6, 143.0, 148.4, 161.0, 170.6; IR (Nujol) 3259, 1635 cm^{-1}; $[\alpha]_D^{20}$ -49.7° (c=0.762, $CHCl_3$); Anal. Calcd for $C_{20}H_{25}NO_3$: C, 73.37; H, 7.70; N, 4.28; Found: C, 73.24; H, 7.75; N, 4.26.

Further elution with the same solvent mixture gave 0.58 g (26%) of the amide derived from the *S* enantiomer of **9**, m.p. 101-102 °C after recrystallization from petroleum ether : ^1H NMR (300 MHz, $CDCl_3$) δ 1.28 (d, J=7.0 Hz, 3H), 1.39 (d, J=6.9 Hz, 3H), 2.40 (d, J=7.5 Hz, 2H), 3.18-3.25 (m, 1H), 3.72 (s, 6H), 4.99-5.08 (m, 1H), 5.60 (br d 7.9, 1H), 6.30 (t, J=2.2 Hz, 1H), 6.35 (d, J=2.2 Hz, 2H), 7.01-7.04 (m, 2H), 7.17-7.27 (m, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 21.7, 37.4, 45.8, 48.4, 55.2, 98.2, 104.9, 125.9, 127.0, 128.4, 142.9,

148.3, 160.9, 170.5; IR (Nujol) 3314, 1635 cm^{-1}; $[\alpha]_D^{20}$ -23.3° (c=0.838, $CHCl_3$). HRMS Calcd for $C_{20}H_{25}NO_3$: 327.1834; Found: 327.1812.

(3*R*)-3-(3,5-Dimethoxyphenyl)butanoic acid (9). To a solution of 0.33 g (47.9 mmol) of Li dissolved in 120 ml of liquid NH_3 at -60 °C was added a solution of 0.63 g (1.91 mmol) of the phenethylamide of the *R* enantiomer of **9** in 30 ml of wet THF. The reaction was stirred at reflux (-33 °C) for 0.5 h and quenched with solid NH_4Cl. The NH_3 was evaporated, the residue was taken up in water and extracted with ethyl acetate. The extracts were washed with water and brine, dried ($MgSO_4$) and the solvent removed *in vacuo*. The residue was chromatographed (ethyl acetate) to give 0.33 g (78%) of amide as a white solid which was recrystallized from ethyl acetate: m.p. 80-82 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 1.30 (d, J=6.9 Hz, 3H), 2.45 (dd, J=14.3, 21.2 Hz, 2H), 3.17-3.24 (m, 1H), 3.78 (s, 6H), 5.37 (br s, 1H), 5.61 (br s, 1H), 6.31 (t, J=2.1 Hz, 1H), 6.40 (d, J=2.2 Hz, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 21.7, 30.1, 44.6, 55.2, 98.1, 104.9, 148.3, 160.9, 174.0. To a suspension of 0.30 g (1.34 mmol) of amide in 10 ml of water was added 1.04 g (13.4 mmol) of Na_2O_2 and the reaction was heated at 50 °C for 12 h. After cooling the mixture was acidified with 10% aqueous HCl and extracted with ethyl acetate. The extracts were washed with water and brine, dried ($MgSO_4$) and the solvent removed *in vacuo* to give 0.29 g (99%) of **9** as a yellow oil: $[\alpha]_D^{20}$ -34.0° (c=0.862, $CHCl_3$). The spectroscopic properties were identical to those of the racemic acid.

(3*S*)-3-(3,5-Dimethoxyphenyl)butanoic acid (9). The phenethylamide of the *S* acid was reduced to the primary amide as described above for the *R* acid. From 0.25 g of phenethylamide there was obtained 0.14 g (89%) of primary amide, the spectroscopic properties of which were identical to those of the *R* amide. Hydrolysis of 0.18 g as described above gave 0.16 g (89%) of *S* acid: $[\alpha]_D^{20}$ +31.9° (c=0.952, $CHCl_3$). The spectroscopic properties were identical to those of the racemic acid.

(1'*R*)-1'-Methyl-Δ^8-tetrahydrocannabinol (4). Reduction of the *R* enantiomer of **9** as described above in the racemic series gave the primary alcohol $[\alpha]_D^{20}$ -23.6° (c=1.20, $CHCl_3$). Conversion into dimethyl ether **11**, $[\alpha]_D^{20}$ -16.6° (c=1.16, $CHCl_3$), and then to cannabinoid **4**, $[\alpha]_D^{20}$ -227.2° (c=1.18, $CHCl_3$), was carried out as described above.

(1'*S*)-1'-Methyl-Δ^8-tetrahydrocannabinol (4). The 1'*S*-isomer of **4** was prepared by the same route as the *R*-isomer. The *S* primary alcohol, $[\alpha]_D^{20}$ +22.7° (c=1.13, $CHCl_3$), was converted into *S* dimethyl ether **11**, $[\alpha]_D^{20}$ +22.6° (c=1.10, $CHCl_3$). Cannabinoid **4** was prepared as described above: $[\alpha]_D^{20}$ -208.6° (c=1.83, $CHCl_3$).

***E*-3-(3,5-Dimethoxyphenyl)-2-methylpropenoic acid (12).** To a solution of sodium ethoxide, prepared from 5.50 g (7.94 equiv) of Na in 300 ml of dry ethanol, was added 5.00 g (30.1 mmol) of triethyl-2-phosphonopropionate. The solution was stirred for 10 min at 25 °C and 7.86 g (47.5 mmol) of 3,5-dimethoxybenzaldehyde were added. The solution was heated at reflux for 19.5 h, quenched with water and the solvent removed at reduced pressure which resulted in saponification of the crude ester. The reaction mixture was extracted with ether, and the aqueous layer was cooled and acidified with conc. HCl. The product was isolated by filtration and recrystallized from ether/ethanol to yield 6.25 g (93%) of **12**: m.p. 151-153 °C (lit.[28] m.p. 152-153 °C). The spectroscopic data agree with those reported previously.[28]

3-(3,5-Dimethoxyphenyl)-2-methylpropanoic acid (13). The hydrogenation of **12** was carried out as described for the conversion of **8** into **9**. From 6.36 g of **12** there was obtained 6.38 g (99%) of **13**: b.p. 240 °C/3 mm Hg. The spectroscopic data agree with those reported previously.[28,29]

3-(3,5-Dimethoxyphenyl)-2-methyl-1-propanol. The reduction of acid **13** was carried out by the method employed for the reduction of **9**. From 3.00 g of **13** there was obtained 2.54 g (90%) of alcohol: b.p. 180 °C/2.5 mm Hg; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.92 (d, J=6.8 Hz, 3H), 1.92-1.99 (m, J=6.6, 1H), 2.31-2.43 (m, 1H), 2.67-3.2.74 (m, 1H), 3.46-3.57 (m, 2H), 3.79 (s, 6H), 6.33-6.35 (m, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 15.6, 37.6, 40.1, 55.2, 67.7, 97.8, 107.2, 143.1, 160.6; IR (neat) 3363 cm^{-1}; Anal. Calcd for $C_{12}H_{18}O_4$: C, 68.54; H, 8.62; Found: C, 68.48; H, 8.68.

1-(3,5-Dimethoxyphenyl)-2-methylpentane (15). The conversion of 3-(3,5-dimethoxyphenyl)-2-methyl-1-propanol into the corresponding tosylate was carried out using the procedure described above for the preparation of **10**. From 1.00 g of alcohol there was obtained 1.22 g (78%) of tosylate **14** after purification by chromatography (petroleum ether/ethyl acetate 4:1): ^{1}H NMR (300 MHz $CDCl_3$) δ 0.90 (d, J=6.8 Hz, 3H), 2.17 (m, 1H), 2.35 (q, J=14.6, 7.9 Hz, 1H), 2.46 (s, 3H), 2.67 (q, J=14.4, 6.7 Hz, 1H), 3.77 (s, 6H), 3.87 (d, J=5.7 Hz, 2H), 6.25 (d, J=2.3 Hz, 2H), 6.31 (t, J=2.3 Hz, 1H), 7.35 (d, J=8.0 Hz, 2H) 7.89 (d, J=8.3 Hz, 2H); The crude tosylate was coupled with ethylmagnesium bromide using the procedure described above for the preparation of **11**. From 0.57 g of **14** there was obtained 0.28 g (80%) of **15**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.89 (m, 6H), 1.23-1.46 (m, 1H), 1.72-1.85 (m, 1H), 2.30 (q, J=13.3, 8.2 Hz, 1H), 2.59 (q, J=13.3, 6.1 Hz, 1H), 3.79 (s, 6H), 6.32 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.3, 19.4, 20.2, 34.5, 39.0, 44.0, 55.2, 97.5, 107.2, 144.2, 160.5; IR (neat) 2980 cm^{-1}. HRMS Calcd for $C_{14}H_{22}O_2$: 222.1620; Found: 222.1610.

2'-Methyl-Δ^8-tetrahydrocannabinol (5). Ether **15** was demethylated as described above for the preparation of **4**. From 0.15 g of **15** there was obtained 0.12 g (94%) of the substituted resorcinol, which was used in the subsequent step without purification: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.86 (m, 6H), 1.27 (m, 4H), 1.68 (m, 1H), 2.23 (q, J=13.2, 8.0 Hz, 1H), 2.52 (q, J=13.3, 6.1 Hz, 1H), 4.85 (s, 2H), 6.18 (t, J=2.2 Hz, 1H), 6.21 (d, J=2.2 Hz, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.3, 19.4, 20.2, 34.4, 39.0, 43.6, 100.2, 108.8, 146.4, 156.4.

Condensation of the resorcinol with *p*-menthadienol was carried out as described above for the preparation of **4**. From 0.12 g of the phenol and 0.10 g of menthadienol there was obtained 0.09 g (45%) of **5**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.85 (m, 6H), 1.16 (s, 3H), 1.25-1.42 (m, 7H), 1.71 (s, 3H), 1.80-1.90 (m, 3H), 2.10-2.22 (m, 2H), 2.44-2.61 (m, 1H), 2.72-2.82 (m, 1H), 3.22 (dd, J=16.3, 4.4 Hz, 1H), 4.98 (s, 1H), 5.44 (d, J=4.0 Hz, 1H), 6.09 (d, J=1.4 Hz, 1H), 6.26 (d, J=1.4 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.3, 15.2, 18.5, 19.5, 20.2, 23.5, 27.5, 27.9, 31.6, 34.3, 36.0, 39.1, 43.3, 44.9, 108.4, 110.6, 110.8, 119.3, 134.7, 141.5, 154.6. HRMS Calcd for $C_{22}H_{32}O_2$: 328.2402; Found: 328.2388.

N-[(1*S*)-1-Phenylethyl]-(2*R*,*S*)-3-(3,5-dimethoxyphenyl)-2-methylpropanamides. Racemic **13** was converted into the mixture of diastereomeric amides as described above for acid **9.** The mixture of amides was separated by chromatography (petroleum ether/ethyl acetate 7:3). From 3.00 g of racemic **13** there was obtained 0.80 g (37%) of the amide of *R* **13**, m.p. 97-99 °C after recrystallization from ethyl acetate/cyclohexane: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.18 (d, J=6.8 Hz, 3H), 1.28 (d, J=6.8 Hz, 3H), 2.64 (q, J=6.0, 13.3 Hz, 1H), 2.88 (q, J=9.0, 13.3 Hz, 1H), 3.76 (s, 6H), 5.02 (m, 1H), 5.39 (d 7.5 Hz, 1H), 6.33 (t, J=2.3 Hz, 1H), 7.25 (m, 5H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 17.7, 21.4, 40.9, 43.7, 55.2, 98.3, 107.0, 126.0, 127.2, 128.6, 142.3, 143.2, 160.8, 174.4; IR (Nujol) 1655, 1603 cm^{-1}; $[\alpha]_D^{20}$ -45.7° (c=0.058, $CHCl_3$); Anal. Calcd for $C_{20}H_{25}NO_3$: C, 73.37; H, 7.70; N, 4.28; Found: C, 73.23; H, 7.69; N, 4.31.

Further elution with the same solvent mixture gave 0.99 g (45%) of the amide derived from the *S* enantiomer of **13**, m.p. 98-100 °C after recrystallization from ethyl acetate/cyclohexane: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.24 (d, J=6.7 Hz, 3H), 1.41 (d, J=6.8 Hz, 3H), 2.42 (m, 1H), 2.65 (q, J=6.0, 13.3 Hz, 1H), 2.89 (q, J=9.0, 13.3 Hz, 1H), 3.78 (s, 6H), 5.50 (d, J=2.3 Hz, 1H), 6.35 (t, J=2.2 Hz, 3H), 7.02 (m, 2H), 7.27 (m, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 18.0, 21.8, 40.8, 43.9, 48.3, 55.2, 98.4, 106.9, 125.9, 127.0, 128.5, 143.6, 144.4, 160.7, 174.3; IR (Nujol) 1655, 1603 cm^{-1}; $[\alpha]_D^{20}$ +8.35° (c=1.04, $CHCl_3$); Anal. Calcd for $C_{20}H_{25}NO_3$: C, 73.37; H, 7.70; N, 4.28; Found: C, 73.32; H, 7.72; N, 4.29.

(2*R*) and (2*S*)-3-(3,5-Dimethoxyphenyl)-2-methylpropanoic acid (13). The *R* and *S* enantiomers of **13** were prepared from the phenethylamides by the procedure employed for the preparation of *R* and *S* **9**. From 0.27 g of the amide of *R* **13**, there was obtained 0.06 g (34%) of primary amide. Hydrolysis of 0.55 g of this amide provided 0.25 g (46%) of *R* **13**; $[\alpha]_D^{20}$ -9.5° (c=0.46, $CHCl_3$). From 2.82 g of the phenethylamide of *S* **13**, there was obtained 1.53 g (80%) of primary amide. Hydrolysis of 1.21 g of this amide using Na_2O_2 as described above gave 0.64 g (53%) of *S* **13**; $[\alpha]_D^{20}$ +10.2° (c=1.52, $CHCl_3$). The spectroscopic properties were identical to those of the racemic acids.

Determination of the optical purity of *R* and *S* 13. To a stirred solution of 0.02 g, (0.089 mol) of *R* or *S* acid **13** in 1 ml of CH_2Cl_2 at 0 °C was added sequentially 0.012 g (0.089 mmol) of hydroxybenztriazole, 0.013 ml (0.089 mmol) of *S*-(-)-α-phenethylamine, and 0.020 g (0.098 mmol) of dicyclohexylcarbodiimide. The reaction was allowed to warm to ambient temperature and stirred for 18 h. The dicyclohexylurea was filtered off, washed with CH_2Cl_2, the combined CH_2Cl_2 solutions were dried ($MgSO_4$) and the solvent removed *in vacuo*. The amide was purified by chromatography (petroleum ether/ethyl acetate 7:3). The optical purity of the acid was determined by integration of the ^{1}H NMR signals of the methyl groups (δ 1.18, 1.28 for the amide of *R* **13** and δ 1.24, 1.41 for the amide of *S* **13**).

(2'*S*)-2'-Methyl-Δ^8-tetrahydrocannabinol (5). Reduction of the *R* enantiomer of **13** as described above in the racemic, series gave the primary alcohol $[\alpha]_D^{20}$ +5.85° (c=0.41, $CHCl_3$). Conversion into *S*-dimethyl ether **15**, and then to the 2'*S*-isomer of cannabinoid **5**, $[\alpha]_D^{20}$ -194° (c=3.65, $CHCl_3$), was carried out as described above.

(2'*R*)-2'-Methyl-Δ^8-tetrahydrocannabinol (5). The 2'*R*-isomer of **5** was prepared by the same route as the *S*-isomer. The *S* -primary alcohol, $[\alpha]_D^{20}$ -4.5° (c=0.65, $CHCl_3$), was converted into *R*-dimethyl ether **15**, and then to *R* cannabinoid **5**, prepared as described above: $[\alpha]_D^{20}$ -220° (c=0.32, $CHCl_3$).

1-(3,5-Dimethoxyphenyl)-3-methyl-1-pentanol (16). A solution of 9.00 g (59.0 mmol) of 1-bromo-3-methylbutane[20] in 25 ml of dry ether was combined with 1.43 g (59.0 mmol) of magnesium turnings, under an atmosphere of N_2, and stirred at ambient temperature until the magnesium was consumed. A solution of 9.90 g (59.0 mmol) of 3,5-dimethoxybenzaldehyde in 30 ml of dry ether was added dropwise and the reaction mixture was stirred at ambient temperature for 2 h, then stirred at reflux for 1 h, cooled and poured into 100 ml of water. The ether layer was separated, dried ($MgSO_4$) and the solvent removed *in vacuo*. The crude product was chromatographed (petroleum ether/ethyl acetate 8:1) to give 3.25 g (24%) of **16** as a mixture of diastereomers, which was used in the next step without separation: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.83-0.95 (m, 6H), 1.14-1.28 (m, 1H), 1.33-1.46 (m, 2H), 1.62-1.78 (m, 2H), 2.04 (s, 1H), 3.79 (s, 6H), 4.65-4.70 (m, 1H), 6.35-6.36 (m, 1H), 6.50-6.51 (m, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 10.9, 11.2, 18.7, 19.5,

29.0, 30.0, 30.9, 45.9, 46.3, 55.2, 72.3, 72.9, 99.0, 99.1, 103.6, 103.8, 147.7, 148.2, 160.7; IR (neat) 3416, 2966, 2875, 2839, 1602, 1462, 1152 cm^{-1}.

1-(3,5-Dimethoxyphenyl)-3-methylpentane (17). To a solution of 1.00 g (4.20 mmol) of **16** in 25 ml of ethanol was added 0.40 g of 10% Pd/C and 5 ml of CF_3CO_2H. The mixture was shaken under H_2 at 45 psi for 7 days. The solution was filtered through a pad of Celite, and the solution was concentrated *in vacuo* to give the crude product, which was purified by chromatography (petroleum ether/ether 1:1) to give 0.70 g (75%) of **17** as a pale yellow oil: ^1H NMR (300 MHz, $CDCl_3$) δ 0.85 (t, J=7.4 Hz, 3H), 0.92 (d, J=6.2 Hz, 3H), 1.14-1.25 (m, 2H), 1.36-1.47 (m, 2H), 1.58-1.66 (m, 1H), 2.45-2.64 (m, 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 11.3, 19.1, 29.3, 33.8, 34.1, 38.2, 55.2, 97.5, 106.4, 145.6, 160.7; IR (neat) 2959, 2872, 1599, 1460, 1152 cm^{-1}; HRMS Calcd for $C_{14}H_{22}O_2$: 222.1620, Found 222.1615.

3'-Methyl-Δ^8-tetrahydrocannabinol (6). Cannabinoid **6** was prepared from **17** by the procedure described above for the preparation of **4**. From 0.89 g of **17** there was obtained 0.67 g (87%) of substituted resorcinol which was used in the next step without further purification: ^1H NMR (300 MHz, $CDCl_3$) δ 0.78-0.83 (m, 6H), 1.04-1.21 (m, 1H), 1.27-1.34 (m, 3H), 1.44-1.52 (m, 1H), 2.28-2.47 (m, 2H), 5.00 (br s, 2H), 6.18 (d, J=1.7 Hz, 1H), 6.25 (d, J=1.7 Hz, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 11.2, 19.0, 29.3, 34.3, 34.5, 37.9, 100.1, 107.9, 146.3, 156.7.

From 0.67 g of the resorcinol there was obtained 0.27 g (24%) of **6** as a viscous oil: ^1H NMR (300 MHz, $CDCl_3$) δ 0.82-0.88 (m, 6H), 1.09 (s, 3H), 1.12-1.19 (m, 1H), 1.38 (s, 3H), 1.51-1.59 (m, 1H), 1.68 (s, 3H), 1.80-1.92 (m, 4H), 2.08-2.14 (m, 1H), 2.37-2.45 (m, 2H), 2.67-2.73 (m, 1H), 3.21 (dd, J=12.7, 3.8 Hz, 1H), 5.33 (s, 1H), 5.40 (br d, J=3.7 Hz, 1H), 6.09 (s, 1H), 6.28 (s, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 11.2, 18.4, 19.0, 23.4, 22.5, 27.8, 29.3, 31.5, 32.9, 34.0, 35.9, 37.8, 44.8, 76.7, 107.7, 109.8, 110.6, 119.2, 134.7, 142.9, 154.6, 154.8; IR (neat) 3400, 2970, 2930, 1620, 1580, 1460, 1425 cm^{-1}; HRMS Calcd for $C_{22}H_{32}O_2$: 328.2402, Found 328.2399.

(3'*S*)-3'-Methyl-Δ^8-tetrahydrocannabinol (6). This compound was prepared by the method employed for the (3'*RS*)-isomers. The reaction of the Grignard reagent derived from 6.12 g (41 mmol) of commercially available (Aldrich) *S*-(+)-1-bromo-3-methylbutane with 6.73 g (41 mmol) of 3,5-dimethoxybenzaldehyde provided 4.20 g (43%) of a mixture of diastereomeric alcohols (**16**). Catalytic hydrogenation of 4.20 g (17.6 mmol) of this mixture afforded 3.16 g (81%) of (3*S*)-1-(3,5-dimethoxyphenyl)-3-methylpentane (**17**), $[\alpha]_D^{20}$ +9.74° (c=0.952, $CHCl_3$). Demethylation of 1.00 g (4.5 mmol) of *S*-**17** provided 0.80 g (92%) of the resorcinol, which was reacted with 0.68 g (4.5 mmol) of menthadienol to provide 0.17 g (13%) of **6**, $[\alpha]_D^{25}$ -151° (c=17.5, $CHCl_3$). The spectroscopic properties of these compounds were identical to those of the (3'*RS*)-isomers.

(*S*)-3-Benzyloxy-2-methyl-1-propanol. To a suspension of 8.3 g (73 mmol) of KH (35% in mineral oil) in 50 ml of dry DMF at -18 °C was added dropwise with vigorous stirring 11.0 g (67.9 mmol) of alcohol **18**, prepared as described by Tius, but used without purification.[22] The mixture was stirred for 20 min at -18 °C and 8.00 ml (67.3 mmol) of benzyl bromide were added dropwise. The mixture was allowed to warm to ambient temperature, stirred for 1 h, poured into water and extracted with five portions of ether. The combined ethereal extracts were washed with three portions of brine, dried ($MgSO_4$) and the solvent removed *in vacuo* to give 18.4 g of crude product which was used in the next step without purification: ^1H NMR (300 MHz,

$CDCl_3$) δ 0.98 (d, J=7.0 Hz, 3H), 1.19 (t, J=7.0 Hz, 3H), 1.28 (d, J=5.3 Hz, 3H), 1.90-2.14 (m, 1H), 3.26-3.72 (m, 6H), 4.49 (s, 2H), 4.64 (q, J=5.3 Hz, 1H), 7.18-7.42 (m, 5H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.5, 15.2, 19.7, 34.3, 60.7, 67.5, 72.7, 72.9, 99.8, 127.3, 127.4, 128.2, 138.6.

A solution of the crude benzyl ether described above and 0.12 g of PPTS in 30 ml of THF was heated to reflux. A solution of 0.50 ml of 10% aqueous HCl in 5.0 ml of water was added in portions over 5 h at a rate to maintain homogeneity, and the solution was heated at reflux for 18 h. After cooling, the mixture was poured into saturated aqueous $NaHCO_3$, and extracted with three portions of ether. The combined ethereal extracts were washed with brine, dried ($MgSO_4$) and the solvent was removed *in vacuo*. The crude alcohol was chromatographed (petroleum ether/ethyl acetate 3:1) to give 6.0 g (49% from **18**) of pure alcohol: ^1H NMR (300 MHz, $CDCl_3$) δ 0.88 (d, J=7.1 Hz, 3H), 1.91-2.11 (m, 1H), 2.97 (br s, 1H), 3.35-3.51 (m, 2H), 3.56 (d, J=5.9 Hz, 2H), 4.49 (s, 2H), 7.19-7.40 (m, 5H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 13.4, 35.5, 66.9, 73.1, 74.7, 127.4, 127.5, 128.2, 138.0. These data are in agreement with those reported previously.[23]

This alcohol was converted into (*R*)-1-bromo-3-benzyloxy-2-methyl-1-propane (**19**) by the literature procedure.[23]

(*S*)-1-Benzyloxy-4-(3,5-dimethoxyphenyl)-2-methylbutane (21). To a stirred mixture of 0.14 g (5.83 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 0.71 g (2.92 mmol) of bromide **19** in 10 ml of dry ether. The mixture was heated to reflux, and 0.25 ml (2.9 mmol) of 1,2-dibromoethane was added in small portions over 0.5 h. The mixture was heated at reflux for 1.5 h, and a solution of 0.40 g (2.41 mmol) of 3,5-dimethoxybenzaldehyde in 10 ml of dry ether was added *via* a syringe pump over 1 h. The reaction mixture was heated at reflux for 2 h, cooled to ambient temperature, quenched with water, acidified to pH 3, and extracted with three portions of ether. The combined ether extracts were washed successively 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 2:1) gave 0.17 g of (*S*)-4-benzyloxy-1-(3,5-dimethoxyphenyl)-3-methyl-1-butanone as an oil: ^1H NMR (300 MHz, $CDCl_3$) δ 1.01 (d, J=6.7 Hz, 3H), 2.41-2.62 (m, 1H), 2.65-2.78 (m, 1H), 3.12-3.26 (m, 1H), 3.30-3.50 (m, 2H), 3.81 (s, 6H), 4.49 (s, 2H), 6.65 (s, 1H), 7.09 (s, 2H), 7.22-7.41 (m, 5H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 17.2, 30.5, 42.7, 55.5, 73.0, 75.0, 105.2, 105.9, 127.5, 128.3, 138.5, 139.3, 160.8, 199.6; MS (EI) *m/z* (rel intensity) 328 (6), 222 (98), 180 (90), 165 (84), 152 (74), 137 (45), 91 (100).

Further elution with petroleum ether/ether 2:1 gave 0.34 g of an inseparable mixture of alcohols **20**: ^1H NMR (300 MHz, $CDCl_3$) δ 0.89-1.03 (m, 3H), 1.50-2.15 (m, 3H), 3.25-3.53 (m, 3H), 3.73 (s, 6H), 4.42-4.54 (m, 2H), 4.59-4.76 (m, 1H), 6.30-6.36 (m, 1H), 6.44-6.54 (m, 2H), 7.19-7.36 (m, 5H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 17.5, 17.8, 29.9, 31.3, 43.9, 44.9, 55.0, 71.8, 72.5, 72.9, 75.6, 76.1, 98.9, 103.5, 127.4, 128.2, 138.0, 147.6, 148.1, 160.6; MS (EI) *m/z* 330 (24), 329 (100), 313 (40), 312 (30), 311 (84), 248 (33), 246 (37), 245 (26), 244 (29), 239 (25), 221 (44).

To a stirred mixture of 20.0 g (150 mmol) of $AlCl_3$ in 50 ml of dry ether was added 50 ml (50 mmol) of 1.0 M $LiAlH_4$ in ether. To this suspension was added dropwise the crude mixture of alcohols **20** and the corresponding ketone, obtained from a reaction carried out as described above, employing 3.35 g (13.8 mmol) of bromide **19** in 25 ml of dry ether. The reaction mixture was stirred at ambient temperature for 40 h, cooled to 0 °C, carefully quenched with water and acidified with 10% aqueous HCl. The organic layer was washed

with successive portions of saturated aqueous $NaHCO_3$ and brine. After drying ($MgSO_4$), the solvent was removed *in vacuo* to give an oil which was chromatographed (petroleum ether/ethyl acetate 20:1) to afford 0.89 g (21% based on **20**) of **21** which was used in the subsequent step without further purification: ^1H NMR (300 MHz, $CDCl_3$) δ 0.98 (d, J=6.6 Hz, 3H), 1.35-1.54 (m, 1H), 1.68-1.89 (m, 2H), 2.41-2.69 (m, 2H), 3.21-3.38 (m, 2H), 3.74 (s, 6H), 4.48 (s, 2H), 6.28 (t, J=2.2 Hz, 1H), 6.34 (d, J=2.2 Hz, 2H), 7.18-7.38 (m, 5H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 17.0, 33.1, 33.6, 35.2, 55.1, 72.9, 75.6, 97.6, 106.3, 127.3, 127.4, 128.2, 138.7, 145.1, 160.6.

(*S*)-4-(3,5-dimethoxyphenyl)-2-methyl-1-butanol. To a stirred solution of 0.12 g (16.7 mg atom) of Li in 100 ml of liquid NH_3 at -78 °C was added dropwise a solution of 0.89 g (2.83 mmol) of benzyl ether **21** in 10 ml of dry ether. The solution became colorless after *ca.* 5 min, and an additional 0.12 g of Li was added. After stirring for 0.5 h, the reaction was quenched by the cautious addition of solid NH_4Cl, and the NH_3 was evaporated at ambient temperature. The residue was slurried with water, and extracted with three portions of ether. The combined ether extracts were washed with successive portions of 10% aqueous HCl, saturated aqueous $NaHCO_3$, brine and dried ($MgSO_4$). The solvent was removed *in vacuo* to give an oil which after chromatography (petroleum ether/ethyl acetate 2:1) gave 0.61 g (95%) of pure alcohol: ^1H NMR (300 MHz, $CDCl_3$) δ 0.96 (d, J=6.6 Hz, 3H), 1.31-1.50 (m, 1H), 1.57-1.81 (m, 2H), 1.99 (br s, 1H), 2.45-2.71 (m, 2H), 3.37-3.55 (m, 2H), 3.76 (s, 6H), 6.29 (t, J=2.2 Hz, 1H), 6.35 (t, J=2.1 Hz, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 16.4, 33.5, 34.6, 35.2, 55.1, 67.9, 97.5, 106.3, 145.0, 160.6; MS (EI) *m/z* (rel intensity) 224 (8), 206 (8), 153 (10), 152 (100), 151 (35); $[\alpha]_D^{20}$ -21.4° (c=2.10, $CHCl_3$); HRMS Calcd for $C_{13}H_{20}O_3$: 224.1412, Found 224.1412.

(*R*)-1-(3,5-dimethoxyphenyl)-3-methylpentane (22). To a solution of 0.74 g (3.30 mmol) of (*S*)-4-(3,5-dimethoxyphenyl)-2-methyl-1-butanol and 0.53 ml (6.6 mmol) of pyridine in 10 ml of dry $CHCl_3$ at 0 °C was added 0.94 g (4.93 mmol) of *p*-toluenesulfonyl chloride. The reaction mixture was stirred at ambient temperature for 18 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 was chromatographed (petroleum ether/ethyl acetate 4:1) to give 0.971 g (78%) of tosylate, which was used in the next step without further purification: ^1H NMR (300 MHz, $CDCl_3$) δ 0.94 (d, J=6.7 Hz, 3H), 1.33-1.51 (m, 1H), 1.58-1.91 (m, 2H), 2.36-2.62 (m, 2H), 2.44 (s, 3H), 3.77 (s, 6H), 3.80-3.95 (m, 2H), 6.28 (s, 3H), 7.33 (d, J=8.2 Hz, 2H), 7.78 (d, J=8.3 Hz, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 16.3, 21.5, 32.2, 33.1, 34.1, 55.1, 74.7, 97.7, 106.3, 127.8, 129.8, 133.0, 144.1, 144.6, 160.7.

To a stirred solution of 0.27 g (0.72 mmol) of tosylate in 10 ml of dry THF at -78 °C under an atmosphere of dry N_2 was added 0.55 ml (0.073 mmol) of a freshly prepared 0.133 M solution of Li_2CuCl_4 in THF, followed by 4.10 ml (12.3 mmol) of 3.0 M methylmagnesium bromide. The mixture was warmed to ambient temperature, stirred for 48 h, and quenched by the careful addition of saturated aqueous NH_4Cl. After the addition of ether, the reaction mixture was washed with successive portions of saturated aqueous $NaHCO_3$ and brine, dried ($MgSO_4$) and the solvent was removed *in vacuo*. After chromatography (petroleum ether/ethyl acetate 20:1), there was obtained 0.15 g (96%) of ether **22** as a colorless oil: ^1H NMR (300 MHz, $CDCl_3$) δ 0.83-0.99 (m, 6H), 1.12-1.28 (m, 1H), 1.31-1.52 (m, 3H), 1.55-1.70 (m, 1H), 2.45-2.64 (m, 2H), 3.77 (s, 6H), 6.29 (t, J=2.1 Hz, 1H), 6.35 (d, J=2.1 Hz, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 11.3, 19.1, 29.3,

33.8, 34.1, 38.2, 55.2, 97.5, 106.4, 145.6, 160.7; MS (EI) *m/z* (rel intensity) 222 (10), 165 (6), 153 (11), 152 (100), 151 (13); $[\alpha]_D^{20}$ -7.72° (c=11.0, $CHCl_3$).

(3'*R*)-3'-methyl-Δ^8-tetrahydrocannabinol (6). Cannabinoid **6** was prepared from **22** by the procedure described above for the preparation of **4**. From 0.18 g of **22** there was obtained 0.16 g of substituted resorcinol, the spectroscopic properties of which were identical to those of the racemate described above. This material was used in the next step without further purification

From 0.16 g of the resorcinol there was obtained 0.132 g (51%) of (3'*R*)-3'-methyl-Δ^8-tetrahydrocannabinol (**6**) as a viscous oil: ^1H NMR (300 MHz, $CDCl_3$) δ 0.79-0.98 (m, 6H), 1.10 (s, 3H), 1.37 (s, 3H), 1.69 (s, 3H), 1.04-1.97 (m, 8H), 2.05-2.22 (m, 1H), 2.29-2.55 (m, 2H), 2.63-2.77 (m, 1H), 3.22 (dd, J=16.5, 4.1 Hz, 1H), 5.10 (s, 1H), 5.41 (s, 1H), 6.09 (s, 1H), 6.28 (s, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 11.2, 18.4, 19.0, 23.4, 27.5, 27.8, 29.3, 31.5, 32.9, 34.0, 35.9, 37.8, 44.8, 76.7, 107.6, 109.9, 110.5, 119.2, 134.7, 142.9, 154.7, 154.8; MS (EI) *m/z* 328 (24), 259 (21), 258 (100), 245 (36), 215 (16); $[\alpha]_D^{20}$ -202° (c=16.0, $CHCl_3$); HRMS Calcd for $C_{22}H_{32}O_2$: 328.2402, Found 328.2402.

1-(3,5-Dimethoxyphenyl)-4-methyl-1-pentene (23). To a solution of 8.00 g (19.4 mmol) of isoamyltriphenylphosphonium bromide in 40 ml of ether was added 9.3 ml of 2.5 M *n*-butyllithium (23.2 mmol, 1.2 equiv). The mixture was stirred at ambient temperature for 2 h and a solution of 3.22 g (19.4 mmol) of 3,5-dimethoxybenzaldehyde in 10 ml of dry ether was added. The reaction mixture was stirred 18 h at ambient temperature, poured into 100 ml of water, and extracted with three portions of ether. The combined ether extracts were washed with 10% aqueous HCl and water, dried ($MgSO_4$) and the solvent removed at reduced pressure to give the crude olefin as a mixture of *E* and *Z* isomers which was filtered through a silica gel column (petroleum ether/ether) to give 3.52 g (83%) of **23** as a pale yellow oil: ^1H NMR (300 MHz, $CDCl_3$) δ 0.86 (d, J=7.0 Hz, 6H), 1.65-1.69 (m, 1H), 2.05-2.25 (m, 2H), 3.78 (s, 6H), 6.14-6.51 (m, 5H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 22.3, 28.5, 29.0, 37.6, 42.3, 55.2, 98.6, 99.0, 103.9, 106.8, 129.2, 130.4, 130.7, 132.4, 139.7, 139.9, 160.4, 160.8.

1-(3,5-Dimethoxyphenyl)-4-methylpentane (24). A solution of 3.50 g (15.9 mmol) of **23** in 50 ml of ethanol, containing 0.35 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 evaporated. The crude product was purified by Kugelrohr distillation (oven temperature 125 °C/0.5 mm Hg) to give 2.50 g (71%) of **24** as a colorless oil: ^1H NMR (300 MHz, $CDCl_3$) δ 0.87 (d, J=6.6 Hz, 6H), 1.17-1.25 (m, 2H), 1.49-1.65 (m, 3H), 2.52 (t, J=7.7 Hz, 2H), 3.77 (s, 6H), 6.28-6.30 (m, 1H), 6.35 (d, J=2.2 Hz, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 22.6, 27.9, 29.1, 36.5, 38.6, 55.1, 97.5, 106.4, 145.4, 160.6; HRMS Calcd for $C_{14}H_{22}O_2$: 222.1620, Found 222.1619.

4'-Methyl-Δ^8-tetrahydrocannabinol (7). Cannabinoid **7** was prepared from **24** by the procedure used for the preparation of **4**. From 2.36 g of **24** there was obtained 2.06 g (100%) of crude substituted resorcinol which was used in the next step without further purification: ^1H NMR (300 MHz, $CDCl_3$) δ 0.84 (d, J=6.6 Hz, 6H), 1.13-1.20 (m, 2H), 1.46-1.56 (m, 3H), 2.41 (t, J=7.7 Hz, 2H), 6.21 (br s, 1H), 6.26 (br s, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.9, 22.5, 27.8, 28.8, 36.1, 38.5, 100.3, 107.9, 146.0, 156.5.

From 2.00 g of resorcinol there was obtained 1.88 g (56%) of **7**: ^1H NMR (300 MHz, $CDCl_3$) δ 0.85 (d, J=6.6 Hz, 6H), 1.09 (s, 3H), 1.14-1.28 (m, 3H), 1.38 (s, 3H), 1.47-1.57 (m, 3H), 1.68 (s, 3H), 1.77-1.87 (m, 2H), 2.07-2.11 (m, 1H), 2.38 (t, J=7.5 Hz, 2H), 2.70 (m, 1H), 3.23 (dd, J=17.6, 0.7 Hz, 1H), 5.41 (d, J=0.4 Hz, 1H), 5.67 (br s, 1H), 6.09 (d, J=0.3 Hz, 1H), 6.29 (d, J=0.3 Hz, 1H); ^{13}C NMR (75.5 MHz,

$CDCl_3$) δ 18.4, 22.5, 23.4, 27.4, 27.8, 28.7, 31.5, 35.7, 35.9, 38.7, 44.9, 76.8, 107.8, 109.8, 110.6, 119.2, 134.7, 142.6, 154.5, 154.9; IR (neat) 3528, 3442, 2851, 2731, 1669, 1629, 1164, 965 cm^{-1}; HRMS Calcd for $C_{22}H_{32}O_2$: 328.2402, Found 328.2391.

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REFERENCES AND NOTES

1. (a) Razdan, R. K. *Pharmacol. Rev.* **1986**, *38*, 75. (b) Mechoulam, R.; Devane, W. A.; Glaser, R. Cannabinoid Geometry and Biological Behavior. In *Marijuana/Cannabinoids: Neurobiology and Neurophysiology;* Murphy, L.; Bartke, A.; CRC Press, Boca Raton 1992; pp 1-33.
2. Gaoni, Y.; Mechoulam, R. *J. Am. Chem. Soc.* **1964**, *86*, 1646.
3. Edery, H.; Grunfeld, Y.; Porath, G.; Ben-Zvi, Z.; Shani, A.; Mechoulam, R. *Arzneim.-Forsch.* **1972**, *22*, 1995.
4. Devane, W. A.; Dysarz, F. A., III; Johnson, M. R.; Melvin, L. S.; Howlett, A. C. *Mol. Pharmacol.* **1988**, *34*, 605.
5. Herkenham, M.; Lynn, A. B.; Little, M. D.; Johnson, M. R.; Melvin, L. S.; DeCosta, B. R.; Rice, K. C. *Proc. Natl. Acad. Sci. U.S.A.* **1990**, *87*, 1932.
6. Matsuda, L. A.; Lolait, S. J.; Brownstein, M. J.; Young, A. C.; Bonner, T. H. *Nature (London)*, **1990**, *346*, 561.
7. Huffman, J. W.; Yu, S.; Showalter, V.; Abood, M. E.; Wiley, J. L.; Compton, D. R.; Martin, B. R.; Bramblett, R. D.; Reggio, P. H. *J. Med. Chem.* In press. For construction of the model of the receptor helix bundle see: Bramblett, R. D.; Panu, A. M.; Ballesteros, J. A.; Reggio, P. H. *Life Sci.* **1995**, *56*, 1971.
8. Petrzilka, T.; Sikemeier, C. *Helv. Chim. Acta.* **1967**, *50*, 1416.
9. Martin, B. R.; Kallman, M. J.; Kaempf, G. F.; Harris, L. S.; Dewey, W. L.; Razdan, R. K. *Pharmacol. Biochem. Behav.* **1984**, *21*, 61.
10. Huffman, J. W.; Lainton, J. A. H.; Dai, D.; Jordan, R. D.; Duncan, S. G. *Life Sci.* **1995**, *56*, 2021, presents a summary of the synthesis of 2'*RS*-**5**, 3'*RS*-**6**, *S*-**6**, and **7**, plus a preliminary account of their pharmacology.
11. Kabalka, G. W.; Varna, M.; Varna, R. S.; Srivastava, P. C.; Knapp, F. F. *J. Org. Chem.* **1986**, *61*, 2386.
12. Tamura, M.; Kochi, J. *Synthesis*, **1971**, 303.
13. The authors thank W. T. Pennington for carrying out the crystallographic study which will be published elsewhere.
14. Webster, F. X.; Millar, J. G.; Silverstein, R. M. *Tetrahedron Lett.* **1986**, *27*, 4941.

15. Olah, G. A.; Olah, J. A. *J. Org. Chem.* **1965**, *30*, 2386.
16. Bosch, E.; Kochi, J. K. *J. Org. Chem.* **1994**, *59*, 5573.
17. Vaughn, H. L.; Robbins, M. D. *J .Org. Chem.* **1975**, *40*, 1187.
18. Evans, D. A.; Britton, T. C.; Ellman, J. A. *Tetrahedron Lett.* **1987**, *28*, 6141.
19. (a) König, W.; Geiger, R. *Chem. Ber.* **1970**, *103*, 788. (b) Bosshard, H. R.; Schecter, I.; Berger, A. *Helv. Chim. Acta* **1973**, *56*, 717.
20. Brauns, D. H. *J. Res. Nat. Bur. Stand.* **1937**, *18*, 315.
21. Odham, G. *Arkiv. Kemi*, **1962**, *20*, 507.
22. Tius, M. A.; Gu, X.-q; Truesdell, J. W.; Savariar, S.; Crooker, P. P. *Synthesis*, **1988**, 36. We thank Prof. Tius for helpful comments regarding the preparation and purification of **19** and related compounds.
23. (a) Branca, Q.; Fischli, A. *Helv. Chim. Acta*, **1977**, *60*, 925. (b) Kocienski, P. J.; Street, S. D. A.; Yeates, C.; Cambell, S. F. *J. Chem. Soc. Perkin Trans 1*, **1987**, 2189.
24. (a) Brown, B. R.; White, A. M. S. *J. Chem. Soc.* **1957**, 3755. (b) Brewster, J. H.; Bayer, H. O.; Osman, S. F. *J. Org. Chem.* **1964**, *29*, 110.
25. Compton, D. R.; Rice, K. C.; DeCosta, B. R.; Razdan, R. K.; Melvin, L. S.; Johnson, M. R.; Martin, B. R. *J. Pharmacol. Exp. Ther.* **1993**, *265*, 218.
26. (a) Martin, B. R.; Compton, D. R.; Little, P. J.; Martin, T. J.; Beardsley, P. M. Pharmacological Evaluation of Agonistic and Antagonistic Activity of Cannabinoids. In *Structure Activity Relationships in Cannabinoids*, Rapaka, R. S.; Makriyannis, A. NIDA Research Monograph 79, National Institute on Drug Abuse, Rockville, MD, 1987, pp 108-122. (b) Little, P. J.; Compton, D. R.; Johnson, M. R.; Melvin, L. S.; Martin, B. R. *J. Pharmacol. Exp. Ther.* **1988**, *247*, 1046.
27. Woodruff, E. H. *J. Am. Chem. Soc.* **1942**, *64*, 2859.
28. Kendall, J. K.; Fisher, T. H.; Schultz, H. P.; Schultz, T. P. *J. Org. Chem.* **1989**, *54*, 4218.
29. Carter, R. H.; Colver, R. M.; Hill, R. A.; Staunton, J. *J. Chem. Soc. Perkin Trans. 1*, **1976**, 1438.

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