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The Role of Halogen Substitution in Classical Cannabinoids: A CB1 Pharmacophore Model

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ABSTRACT

The presence of halogens within the classical cannabinoid structure leads to large variations in the compounds' potencies and affinities for the CB1 receptors. To explore the structure activity relationships within this class of analogs we have used a series of halogen-substituted (-)-Δ^8-tetrahydrocannabinol analogs and compared their affinities for the CB1 cannabinoid receptor. Our results indicate that halogen substitution at the end-carbon of the side chain leads to an enhancement in affinity with the bulkier halogens (Br, I) producing the largest effects. Conversely, 2-iodo substitution on the phenolic ring leads to a 2-fold reduction in affinity while iodo-substitution in the C1'-position of the side chain lowers the compound's affinity for CB1 by more than 8-fold. The pharmacophoric requirements resulting from halogen-substitution are explored using computer modeling methods.

KEYWORDS: tetrahydrocannabinol, halogen substitution, CB1 cannabinoid receptors.

INTRODUCTION

Cannabis and its principal bioactive constituent (-)-Δ^9-tetrahydrocannabinol ((-)-Δ^9-THC) as well as its isoactive and more stable isomer (-)-Δ^8-tetrahydrocannabinol ((-)-Δ^8-THC) are currently receiving attention as potential therapeutic agents. During the past 5 decades, many classical cannabinoids[1-4] including natural cannabis constituents, their metabolites, and other synthetic analogs have been synthesized and evaluated for their biological activities. A review[1,2,4,5] of the existing literature recognized 4 pharmacophores on the tricyclic terpenoid structure (Table 1) associated with cannabinergic activity: a phenolic hydroxyl at C1, a 5- to 8-atom-long side-chain at C3, a northern aliphatic hydroxyl at C9 or C11, and a southern aliphatic hydroxyl. The first 2 are encompassed in the plant-derived cannabinoids, while all 4 pharmacophores are represented in some of the synthetic nonclassical cannabinoids developed by Pfizer (New York, NY) and exemplified by CP-55,940.[6] Despite the wide variety of substituents in different pharmacophores on the classical THC structure, halogen substitution has received little attention. A small number of halogenated cannabinoids have been synthesized including 10-bromo-cannabidiol diacetate,[7] 3-bromo-tetrahydrocannabiorcol,[8] 11-bromo-Δ^8-THC acetate,[9] and a few fluoro-, bromo-, and iodo-substituted cannabinoids.[10-15] With the exception of iodinated derivatives, which were developed for radioimmunological assays, these halogenated analogs were obtained as synthetic intermediates and did not undergo biological testing. Furthermore, some Δ^9-tetrahydrocannabinols bearing halogens in the aromatic ring have also been reported.[16] Over the years we have synthesized several halogenated analogs as probes for cannabinergic sites of action. For example, (-)-5'-I-Δ^8-THC (Table 1) was used to study the topography of cannabinoids in membranes using small angle x-ray diffraction,[17] while (-)-5'-[^{18}F]-Δ^8-THC was synthesized as a positron emission tomography (PET) imaging probe[18] for experiments aimed at studying the localization of cannabinoid receptors in the brains of primates. Upon testing some of the halogenated analogs in both a displacement assay and in animal models, we found them to possess interesting structure activity relationship (SAR) profiles. These data provided the incentive for a more systematic SAR study of the effect of halogen substitution on the basic tetrahydrocannabinol structure. A description of the in vivo pharmacology of several analogs described here (Table 1) has already been reported in our preliminary communications.[19,20] In this work we include the synthetic procedures for the analogs described here and extend our SAR studies to include new derivatives. Evaluation of the affinities of these halogenated cannabinoids allowed us to develop a suitable pharmacophore model for the CB1 receptor.

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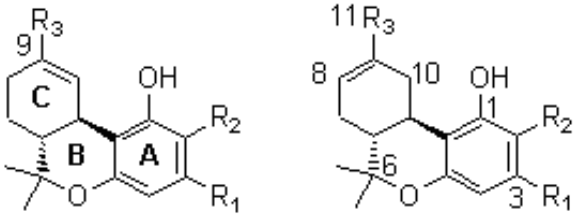
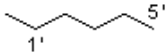
Table 1. Affinities (K_i) of Tetrahydrocannabinol Analogs for CB1 Cannabinoid Receptors (95% Confidence Limits)



Analog	Structure	R_1	R_2	R_3	CB1 (K_i, nM)*
THC[18]	(-)-Δ^9		H	CH_3	41 ± 2
THC[18]	(-)-Δ^8	$(CH_2)_4CH_3$	H	CH_3	44 ± 12
9	(-)-Δ^9	$(CH_2)_4Br$	H	CH_3	24 ± 4
15	(-)-Δ^8	$(CH_2)_4CF_3$	H	CH_3	25 ± 6
17a	(-)-Δ^8	$(CH_2)_4CH_2Br$	H	CH_3	7.6 ± 1.4
17b	(-)-Δ^8	$(CH_2)_4CH_2I$	H	CH_3	7.8 ± 2.4
20	(-)-Δ^8	$(CH_2)_4CH_2F$	H	CH_3	57 ± 2
23	(-)-Δ^8	$(CH_2)_4CH_3$	H	CH_2F	103 ± 20
31	(-)-Δ^8	$C(CH_3)_2(CH_2)_4Br$	H	CH_3	0.43 ± 0.09
32	(-)-Δ^8	$C(CH_3)_2(CH_2)_6Br$	H	CH_3	1.27 ± 0.13
34	(-)-Δ^8	$(CH_2)_4CH_3$	I	CH_3	89 ± 15
36	(-)-Δ^8	$CH(I)(CH_2)_5CH_3$	H	CH_3	328 ± 55

*Affinities for CB1 were determined using rat brain (CB1) membranes and [^{3}H]CP-55,940 as the radioligand following previously described procedures.[35] K_i values were obtained from 3 independent experiments run in duplicate and are expressed as the mean of the 3 values.

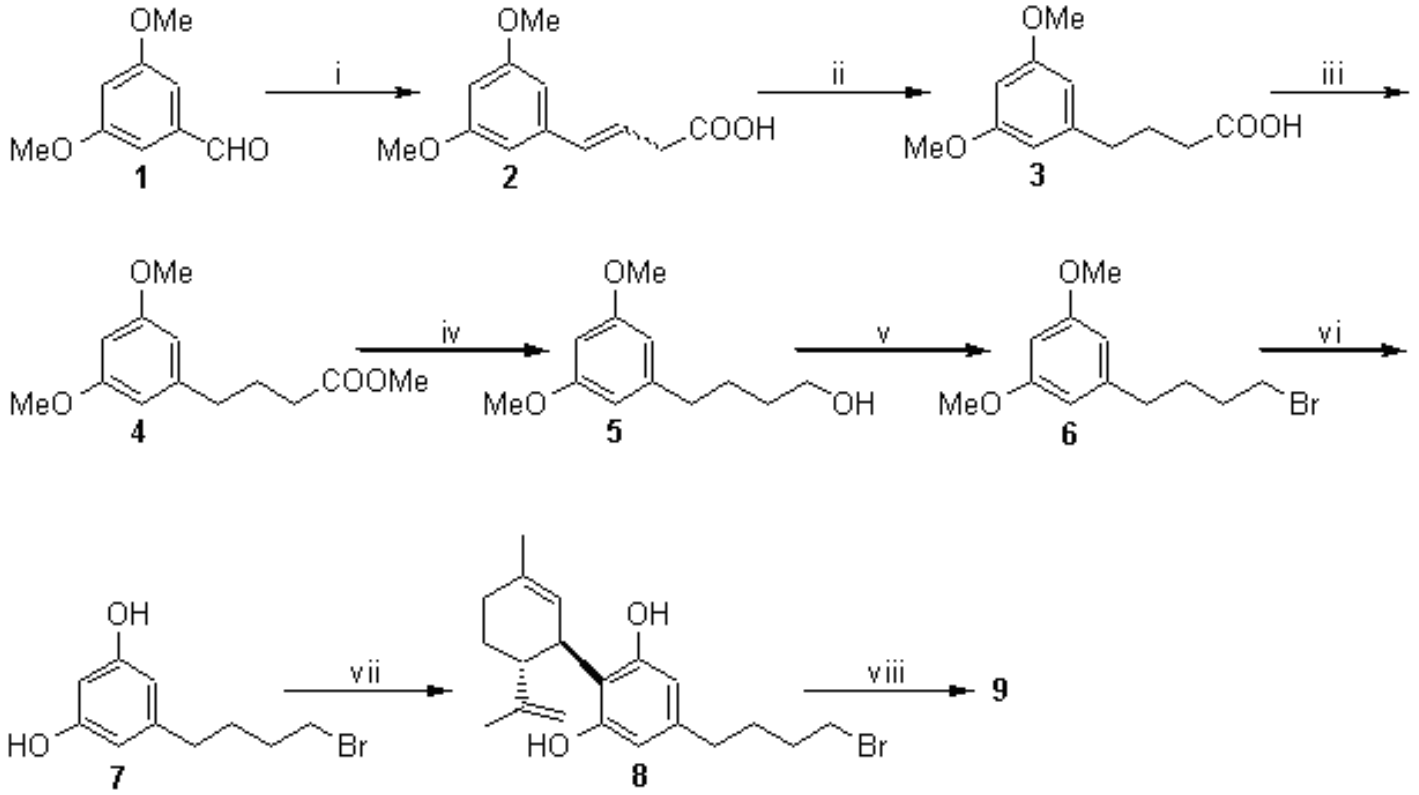
Materials and Methods

Synthesis

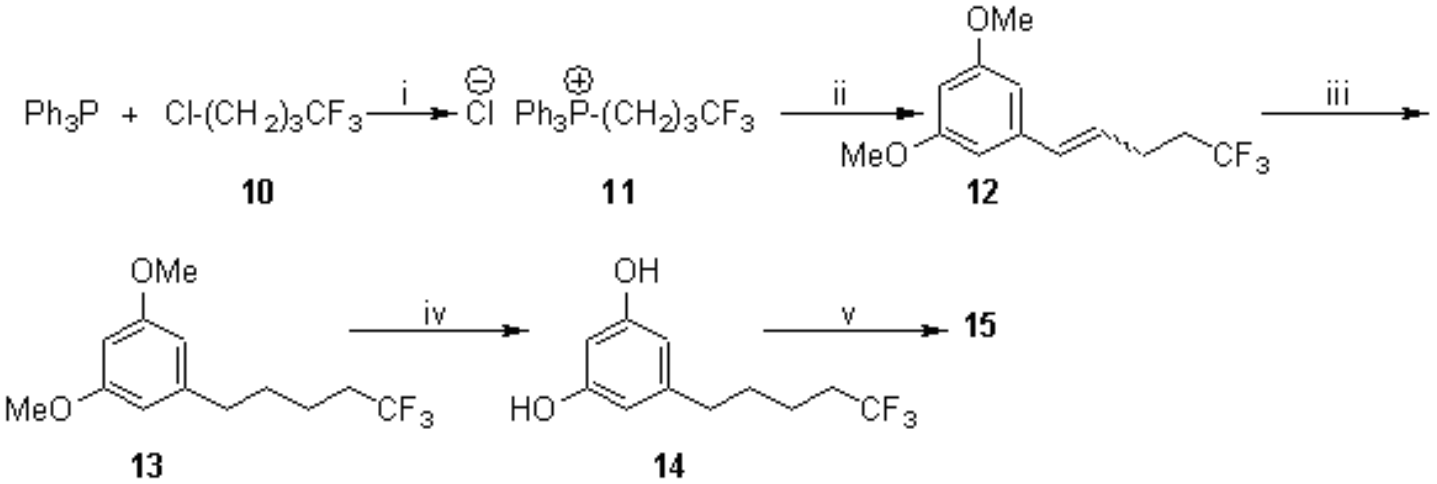
Commercially available 3,5-dimethoxybenzaldehyde **1** has served as the starting point for the synthesis of (6aR-*trans*)-3-(4-bromo-butyl)-6a,7,8,10a-tetrahydro-6,6,9-trimethyl-6*H*-dibenzo[*b*,*d*]pyran-1-ol ((-)-4'-bromo-Δ^9-tetrahydrocannabinol) **9** by a reaction sequence depicted in Scheme 1. Thus, readily available (2-carboxyethyl)triphenylphosphonium bromide[21] was treated with potassium *bis*(trimethylsilyl)amide and the generated phosphorane was coupled with **1** to furnish an isomeric mixture of 4-(3,5-dimethoxyphenyl)-3-butenoic acid **2** favoring the *trans* isomer (*trans*:*cis* = 97:3 by nuclear magnetic resonance [^{1}H NMR] spectroscopy) in 85% yield. Catalytic hydrogenation of the intermediate alkene **2** led to 4-(3,5-dimethoxyphenyl)butanoic acid **3** in 93% yield, which was methylated to the respective methyl ester **4** using diazomethane[22] in quantitative yield. Lithium aluminum hydride reduction of the ester **4** afforded 4-(3,5-dimethoxyphenyl)-1-butanol **5** (98% yield), which was converted to the respective bromide **6** by treatment with triphenylphosphine and carbon tetrabromide in 86% yield after purification. Cleavage of the 2 phenolic methyl ether groups was accomplished by exposure to boron tribromide in methylene chloride affording 5-(4-bromo-butyl)resorcinol **7** in 97% yield. This was followed by Friedel-Crafts allylation with (+)-*cis*/*trans*-*p*-mentha-2,8-dien-1-ol in the presence of catalytic amounts of *p*-toluenesulfonic acid to give the cannabidiol derivative **8** in 31% yield. Treatment of **8** with boron trifluoride etherate at 0°C resulted in a clean cyclization reaction to produce the Δ^9-tetrahydrocannabinol analog **9** in 73% isolated yield.

The synthesis of (6aR-*trans*)-3-(5,5,5-trifluoro-pentyl)-6a,7,10,10a-tetrahydro-6,6,9-trimethyl-6*H*-dibenzo[*b*,*d*]pyran-1-ol ((-)-5',5',5'-trifluoro-Δ^8-tetrahydrocannabinol) **15** was accomplished by a reaction sequence shown in Scheme 2. 4-Chlorobutanoic acid was treated with sulfur tetrafluoride under pressure[23] and the resulting 1-chloro-4,4,4-trifluoro-butane **10** was coupled with triphenylphosphine to give 1-triphenylphosphonium-4,4,4-trifluorobutyl chloride **11** in 87% yield. Reaction of **11** with 3,5-dimethoxybenzaldehyde **1** in the presence of *n*-butyllithium produced a 1:2 *cis*/*trans*-mixture of the Wittig adduct **12** in 68% yield. Catalytic hydrogenation of **12** led to the resorcinol dimethyl ether **13** (92% yield), which was converted to the corresponding resorcinol **14** in 99% yield by demethylation employing boron tribromide. Condensation of **14** with (+)-*cis*/*trans*-*p*-mentha-2,8-dien-1-ol catalyzed by *p*-toluenesulfonic acid afforded Δ^8-tetrahydrocannabinol analog **15** in 68% yield.

(-)-5'-Fluoro-Δ^8-tetrahydrocannabinol **20** was synthesized from the respective hydroxyl-precursor[10] **18** (Scheme 3), which was in turn obtained from 4-phenoxybutyl bromide **16** in 7 steps via **17a** by a procedure previously described.[10,12,24]



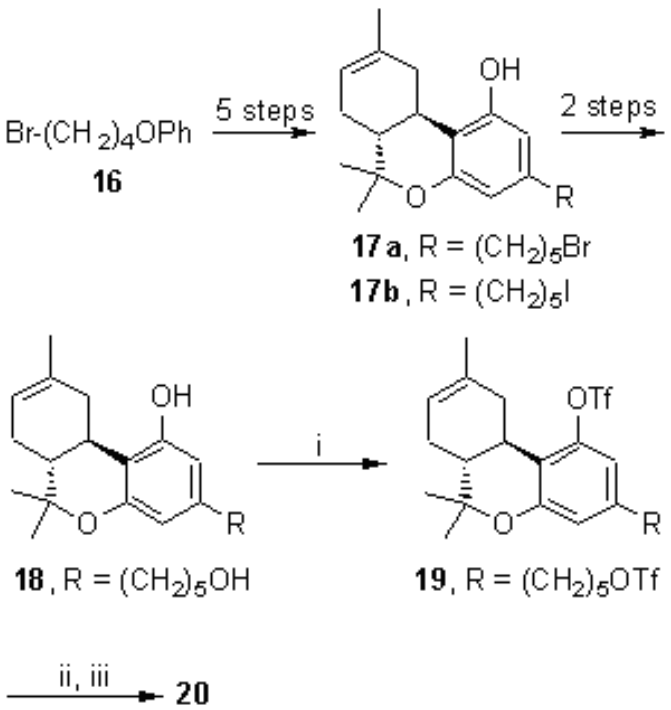
Scheme 1. Reagents and conditions: (i) Br^- Ph_3P^+-$(CH_2)_2COOH$, $(Me_3Si)_2N^-K^+$, THF, 0°C to r t, 2 hours, 85%; (ii) H_2, 10% Pd/C, AcOEt, overnight, 93%; (iii) CH_2N_2, Et_2O, r t, quantitative; (iv) $LiAlH_4$, THF, 0°C to r t, 2.5 hours, 98%; (v) Ph_3P, CBr_4, CH_2Cl_2, -5°C, 15 minutes, 86%; (vi) BBr_3, CH_2Cl_2, -10°C to r t, 6 hours, 97%; (vii) (+)-*cis*/*trans*-*p*-mentha-2,8-dien-1-ol, *p*-TSA, CH_2Cl_2, 0°C, 1.5 hours, 31%; (viii) $BF_3 \cdot Et_2O$, CH_2Cl_2, 0°C, 40 minutes, 73%.



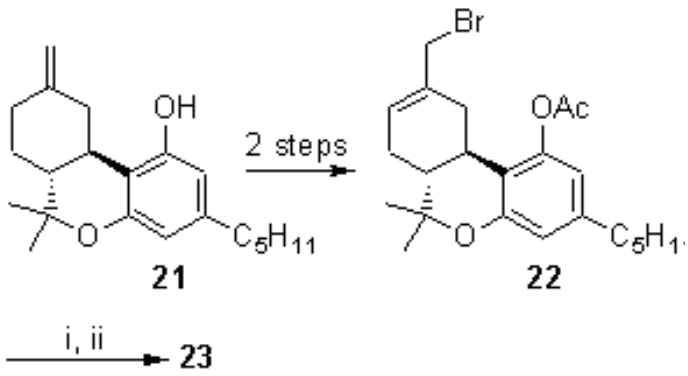
Scheme 2. Reagents and conditions: (i) benzene, 110°C, 40 hours, 87%; (ii) *n*-BuLi, **1**, Et_2O, reflux, 3 hours, 68%; (iii) H_2, Pd/C (pressure), EtOH, 8 hours, 92%; (iv) BBr_3, benzene, r t, 72 hours, 99%; (v) (+)-*cis*/*trans*-*p*-mentha-2,8-dien-1-ol, *p*-TSA, benzene, reflux, 4 hours, 67%.

Thus, (-)-5'-hydroxyl-Δ^8-tetrahydrocannabinol **18** was converted to the triflic diester **19** (58% yield) through reaction with triflic anhydride in the presence of 2,6-lutidine. Because of its tendency to decompose, **19** was purified by flash column chromatography and was immediately used in the next step. Sequential nucleophilic substitution of the 5'-triflate with fluoride ion in the presence of kryptofix and reduction of the phenolic triflic ester using lithium aluminum hydride afforded **20** in 67% isolated yield. (-)-5'-Bromo-Δ^8-tetrahydrocannabinol **17a** served also as a starting point for the synthesis of (-)-5'-iodo-Δ^8-tetrahydrocannabinol **17b** by following a reported procedure[11] and its modification.[19]

The (-)-11-bromo-Δ^8-tetrahydrocannabinol acetate **22** was the key intermediate in the synthesis of (-)-11-fluoro-Δ^8-



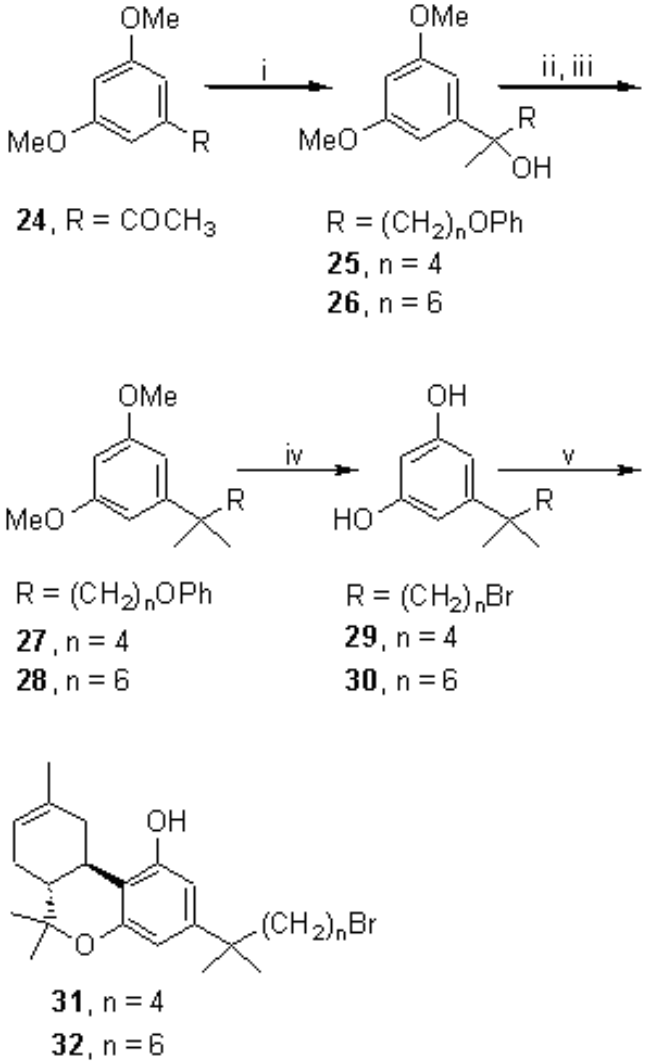
Scheme 3. Reagents and conditions: (i) Tf_2O, 2,6-lutidine, CH_2Cl_2, 0°C, 45 minutes, 58%; (ii) KF, kryptofix, CH_3CN, 80°C, 40 minutes; (iii) $LiAlH_4$, Et_2O, r t, 15 minutes, 67% from **19**.



Scheme 4. Reagents and conditions: (i) *n*-Bu_4N^+ F^-, THF, 60°C, 1 hour; (ii) 1N HCl, 30% from **22**.

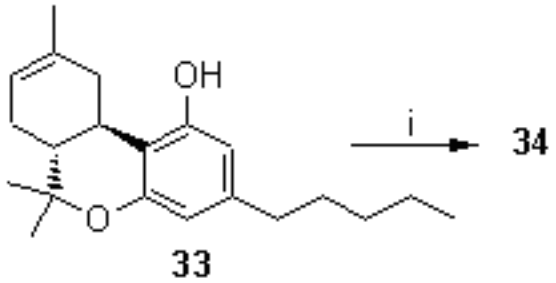
tetrahydrocannabinol **23** (Scheme 4). Compound **22** was prepared in 2 steps starting from (-)-$\Delta^{9(11)}$-tetrahydrocannabinol **21** following a previously reported procedure.[9] Nucleophilic substitution of the bromide **22** using *n*-tetrabutylammonium fluoride followed by acid-catalyzed hydrolysis of the phenolic acetate provided **23** in 30% isolated yield.

Synthesis of (-)-5'-bromo-1',1'-dimethyl-Δ^8-tetrahydrocannabinol[13,20] **31** and (-)-7'-bromo-1',1'-dimethylheptyl-Δ^8-tetrahydrocannabinol **32** is shown in Scheme 5. The first step involves a Grignard reaction of 3,5-dimethoxyacetophenone **24** with 4-phenoxybutylmagnesium bromide or 6-phenoxyhexylmagnesium bromide to give the hitherto unknown carbinols **25** and **26** in 88% and 90% yields, respectively.

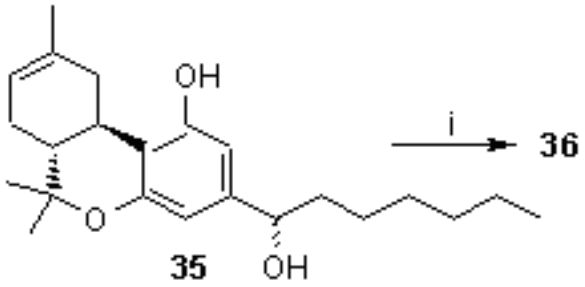


Scheme 5. Reagents and conditions: (i) $PhO(CH_2)_nMgBr$, Et_2O, reflux, 1.5 hours, 88% for n = 4, 90% for n = 6; (ii) c. HCl, hexane, 40°C, 5 hours; (iii) $Al(CH_3)_3$, 100°C, 96 hours, 51% from **25** (n = 4), 40% from **26** (n = 6); (iv) BBr_3, benzene, r t, 72 hours, 92% for n = 4, 90% for n = 6; (v) (+)-*cis*/*trans*-*p*-mentha-2,8-dien-1-ol, *p*-TSA, benzene, reflux, 4 hours, 57% for n = 4, 65% for n = 6.

Exposure of **25** and **26** to concentrated hydrochloric acid followed by treatment with trimethylaluminum afforded the corresponding resorcinol dimethyl ethers **27** (51% yield) and **28** (40% yield). It should be pointed out that this conversion is accompanied by formation of some alkene, elimination byproduct, in 17% to 25% yield. Subsequent exposure of **27** and **28** to boron tribromide in methylene chloride cleaved all 3 ether groups and introduced the C5' and C7' bromo group for **29** and **30** (90%-92% yield). Finally, condensation of resorcinols **29** and **30** with (+)-*cis*/*trans*-*p*-mentha-2,8-dien-1-ol in the presence of *p*-toluenesulfonic acid afforded (-)-Δ^8-tetrahydrocannabinol analogs **31** and **32** in 57% and 65%, yields, respectively. After our preliminary communication,[20] the analog **31** was obtained following a different synthetic approach.[13]



Scheme 6. Reagents and conditions: (i) NaI, mCPBA, 18-crown-6, CH_2Cl_2, r t, 30 minutes, 54%.



Scheme 7. Reagents and conditions: (i) PPh_3, I_2, imidazole, toluene, r t, 3 hours, 64%.

A method previously described[25] for obtaining halogenated resorcinols was followed for the synthesis of (-)-2-iodo-Δ^8-tetrahydrocannabinol **34**. This method involves treatment of (-)-Δ^8-tetrahydrocannabinol **33** with sodium iodide and m-chloroperbenzoic acid in the presence of 18-crown-6 at room temperature for 30 minutes (Scheme 6). We found that these conditions were optimal for obtaining the monoiodinated product **34** in 54% yield. Some of the 2,4-diiodinated cannabinoid was also produced in 7% yield, and this percentage could be increased if the reaction was allowed to proceed for a longer period of time.

We have recently described[26] the efficient synthesis of an equally populated diastereomeric mixture of (-)-1'-hydroxyheptyl-Δ^8-tetrahydrocannabinol **35**. This compound has served as the starting material for the synthesis of corresponding (-)-1'-iodo-heptyl-Δ^8-tetrahydrocannabinol **36**, using the triphenylphosphine, iodine, imidazole method (Scheme 7).

Experimental Procedures

All reagents and solvents were purchased from Aldrich Chemical Co (Milwaukee, WI) with the exception of (+)-*cis*/*trans*-*p*-mentha-2,8-dien-1-ol, which was supplied by Firmenich Inc, Princeton, NJ. All anhydrous reactions were performed under a static argon or nitrogen atmosphere in flame-dried glassware using scrupulously dry solvents. Organic phases were dried over $MgSO_4$ and evaporated under reduced pressure. Flash column chromatography employed silica gel 60 (230-400 mesh). All compounds were demonstrated to be homogeneous by analytical thin layer chromatography (TLC) on precoated silica gel TLC plates (60 F_{245} on glass, layer thickness 250 µm, Merck, Whitehouse Station, NJ), and chromatograms were visualized by phosphomolybdic acid staining. Melting points were determined on a micromelting point apparatus and are reported in this paper without corrections. ^{1}H NMR spectra were recorded on a Bruker DMX-500 or a Bruker AC-300 (Bruker BioSpin GmbH, Rheinstetten, Germany), or on an IBM WP-200SY (IBM Corp, White Plains, NY) spectrometer operating at 500, 300, and 200 MHz, respectively. All NMR spectra were recorded in $CDCl_3$ unless otherwise stated, and chemical shifts are reported in this paper in units of δ relative to internal tetramethylsilane (TMS). Multiplicities are indicated as br (broadened), s (singlet), d (doublet), t (triplet), q (quartet), and m (multiplet), and coupling constants (*J*) are reported in hertz (Hz). Mass spectra were obtained at Crompton Corp (Middlebury, CT) using a Kratos MS 890 hybrid tandem mass spectrometer (Kratos Analytical Inc., Chestnut Ridge, NY). High resolution mass spectra were performed in the School of Chemical Sciences, University of Illinois at Urbana-Champaign. Elemental analyses were obtained using a Perkin Elmer Elemental 2400 (Perkin Elmer, Wellesley, MA).

4-(3,5-Dimethoxyphenyl)-3-butenoic acid (2). (2-Carboxyethyl)triphenylphosphonium bromide was prepared according to a reported procedure[21] starting from 3-bromopropanoic acid. To a suspension of (2-carboxyethyl)triphenylphosphonium bromide (40.3 g, 97.1 mmol) in anhydrous tetrahydrofuran (THF) (240 mL) at 0°C, under an argon atmosphere, was added potassium *bis*(trimethylsilyl)amide (32.1 g, 161.3 mmol). The mixture was stirred for 45 minutes, and a solution of 3,5-dimethoxybenzaldehyde **1** (5.37 g, 32.3 mmol) in THF (100 mL) was added over a period of 20 minutes. Following the addition, the reaction was stirred for an additional 55 minutes and then quenched by the addition of 5% aqueous HCl. The mixture was diluted with AcOEt; the organic layer was separated; and the aqueous phase was extracted with AcOEt. The combined organic layer was washed with brine and dried over $MgSO_4$; then the solvent was evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel using 0.2% methanol in ethyl acetate to give an isomeric mixture (*trans*:*cis* = 97:3 by ^{1}H NMR) of the title compound **2** as a pale yellow solid in 85% yield (6.1 g). mp 50°C-53°C (lit.[21] mp 56°C-64°C). ^{1}H NMR ($CDCl_3$) *trans*-isomer, δ 6.53 (d, *J* = 2.2 Hz, 2H, ArH), 6.45 (d, *J* = 15.8 Hz, 1H, 4-H), 6.37 (t, *J* = 2.2 Hz, 1H, ArH), 6.27 (dt, *J* = 15.8 Hz, *J* = 7.2 Hz, 1H, 3-H), 3.79 (s, 6H, OMe), 3.29 (dd, *J* = 7.2 Hz, *J* = 1.1 Hz, 2H, 2-H); *cis*-isomer, δ 5.86 (dt, *J* = 11.3 Hz, *J* = 7.4 Hz, 1H, 3-H).

4-(3,5-Dimethoxyphenyl)-butanoic acid (3). To a solution of **2** (5.58 g, 25.1 mmol) in AcOEt (230 mL) was added 10% Pd/C (0.95 g), and the resulting suspension was stirred vig-

orously under hydrogen atmosphere and left overnight at room temperature. The catalyst filtered off through celite and the filtrate was evaporated under reduced pressure to afford the title compound **3** as a white solid in 93% yield (5.24 g). mp 63°C-65°C. (lit.[27] mp 64°C-65°C); ^{1}H NMR ($CDCl_3$) δ 6.34 (d, *J* = 1.7 Hz, 2H, ArH), 6.31 (t, *J* = 1.7 Hz, 1H, ArH), 3.78 (s, 6H, OMe), 2.62 (t, *J* = 7.5 Hz, 2H, 2-H), 2.38 (t, *J* = 7.4 Hz, 2H, 4-H), 1.95 (qt, *J* = 7.5 Hz, 2H, 3-H).

Methyl 4-(3,5-dimethoxyphenyl)butyrate (4). Diazomethane solution in diethyl ether (~2.8 g in 100 mL) was prepared according to a reported procedure.[22] To a solution of **3** (4.47 g, 20 mmol) in Et_2O (70 mL) was added an ethereal solution of diazomethane (40 mL) at room temperature. Evaporation of the ether left the title compound **4**[27] as pale yellow oil in quantitative yield (4.74 g). ^{1}H NMR ($CDCl_3$) δ 6.34 (d, *J* = 1.8 Hz, 2H, ArH), 6.31 (t, *J* = 1.8 Hz, 1H, ArH), 3.78 (s, 6H, OMe), 3.67 (s, 3H, COOMe), 2.59 (t, *J* = 7.5 Hz, 2H), 2.33 (t, *J* = 7.4 Hz, 2H), 1.94 (qt, *J* = 7.5 Hz, 2H).

4-(3,5-Dimethoxyphenyl)-1-butanol (5). To a stirred suspension of lithium aluminum hydride (LAH) (2.1 g, 55.3 mmol) in anhydrous THF (150 mL) at 0°C under an argon atmosphere was added a solution of **4** (4.4 g, 18.5 mmol) in anhydrous THF (35 mL) over a period of 10 minutes. The reaction mixture was stirred vigorously for 2.5 hours at the same temperature and then quenched by adding NaF (2.33 g, 55.5 mmol) followed by dropwise addition of 10% aqueous NaOH. The mixture was warmed to room temperature, diluted with ethyl acetate and water, and filtered through celite. The organic layer was separated and the aqueous phase was extracted twice with ethyl acetate. The combined organic layer was washed with brine and dried over $MgSO_4$; the solvent was evaporated under reduced pressure. Purification by flash column chromatography on silica gel (50% ethyl acetate in hexane) afforded the title compound **5**[28] as colorless oil in 98% yield (3.8 g). ^{1}H NMR ($CDCl_3$) δ 6.35 (d, *J* = 2.1 Hz, 2H, ArH), 6.30 (t, *J* = 2.1 Hz, 1H, ArH), 3.78 (s, 6H, OMe), 3.65 (t, *J* = 6.1 Hz, 2H, 1-H), 2.59 (t, *J* = 7.2 Hz, 2H, 4-H), 1.79-1.54 (m, 4H, 2-H, 3-H).

4-(3,5-Dimethoxyphenyl)-1-bromo-butane (6). To a stirred solution of **5** (3.07 g, 14.6 mmol) and carbon tetrabromide (7.27 g, 21.9 mmol) in anhydrous CH_2Cl_2 (73 mL) at -5°C under an argon atmosphere was added triphenylphosphine (6.5 g, 24.8 mmol) portionwise. After addition was complete, the mixture was stirred for an additional 15 minutes, whereupon the solvent was removed in vacuo. The residue was purified by flash column chromatography on silica gel using 15% diethyl ether in hexane as eluent to give the title compound **6**[28] as pale yellow oil (3.44 g, 86% yield). ^{1}H NMR ($CDCl_3$) δ 6.34 (d, *J* = 2.0 Hz, 2H, ArH), 6.30 (t, *J* = 2.0 Hz, 1H, ArH), 3.78 (s, 6H, OMe), 3.42 (t, *J* = 6.4 Hz, 2H, 1-H), 2.59 (t, *J* = 7.3 Hz, 2H, 4-H), 1.95-1.69 (m, 4H, 2-H, 3-H).

5-(4'-bromo-butyl)resorcinol (7). To a solution of **6** (3.16 g, 11.6 mmol) in dry CH_2Cl_2 (90 mL) at -5°C under an argon atmosphere was added boron tribromide (25.5 mL, 1 M solution in CH_2Cl_2). Following the addition, the reaction temperature was gradually raised to room temperature and stirring was continued until completion of the reaction (6 hours). Unreacted boron tribromide was destroyed by addition of methanol and ice at 0°C. The resulting mixture was warmed at room temperature and stirred for 40 minutes; the volatiles were removed in vacuo. The residual was diluted with EtOAc and washed with saturated $NaHCO_3$ solution, water, and brine. The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by flash column chromatography (40% EtOAc in hexane) afforded 2.75 g (97% yield) of the compound **7** as a white solid. mp 40°C-42°C; ^{1}H NMR ($CDCl_3$) δ 6.25 (d, *J* = 2.1 Hz, 2H, 4-H, 6-H), 6.19 (t, *J* = 2.1 Hz, 1H, 2-H), 4.89 (br s, 2H, OH), 3.41 (t, *J* = 6.7 Hz, 2H, 4'-H), 2.53 (t, *J* = 7.6 Hz, 2H, 1'-H), 1.90-1.84 (m, 2H), 1.76-1.70 (m, 2H); mass spectrum *m/z* (relative intensity) 247 (M^++2, 17), 245 (M^+, 18), 195(32), 135(46), 119(100). Exact mass (FAB) calculated for $C_{10}H_{14}BrO_2$ (MH^+), 245.0177; found, 245.0177.

(-)-2-[3-3,4-*trans*-*p*-Menthadien-(1,8)-yl]-5-(4'-bromobutyl)resorcinol (8). To a solution of **7** (1.38 g, 5.63 mmol) in CH_2Cl_2 (50 mL) at 0°C under an argon atmosphere was added *p*-toluenesulfonic acid (96 mg, 0.56 mmol), followed by the addition of a solution of (+)-*cis*/*trans*-*p*-mentha-2,8-dien-1-ol (1.03 g, 6.76 mmol) in CH_2Cl_2 (6 mL). The reaction mixture was stirred at 0°C for 1.5 hours, at which time TLC indicated the complete consumption of starting material. The reaction mixture was diluted with diethyl ether, and the ethereal solution was washed with saturated $NaHCO_3$ solution, water, and brine. The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by flash column chromatography (17% diethyl ether in hexane) afforded 660 mg (31% yield) of the title compound **8** as pale yellow viscous oil. ^{1}H NMR ($CDCl_3$) δ 6.27 (br s, 1H, ArH), 6.16 (br s, 1H, ArH), 6.00 (br s, 1H, OH), 5.56 (s, 1H, 2-H), 4.68 (br s, 1H, OH), 4.66 (s, 1H, 9-H), 4.55 (s, 1H, 9-H), 3.84 (m as br d, *J* = 8.7 Hz, 1H, 3-H), 3.40 (t, *J* = 6.7 Hz, 2H, 4'-H), 2.48 (t, *J* = 7.5 Hz, 2H, 1'-H), 2.39 (td, *J* = 11.0 Hz, *J* = 3.1 Hz, 1H, 4-H), 2.27-2.20 (m, 1H), 2.13-2.07 (m, 1H), 1.88-1.76 (m, 7H, especially 1.80, s, 7-$CH_3$3), 1.75-1.69 (m, 2H), 1.66 (s, 3H, 10-CH_3); mass spectrum *m/z* (relative intensity) 380 (M^++2, 15), 378 (M^+, 15), 312(33), 310(34), 299(100), 297(100), 215(31), 121(27). Exact mass calculated for $C_{20}H_{27}BrO_2$, 378.1194; found, 378.1192. Analysis calculated: C, 63.33; H, 7.17. Found: C, 63.15; H, 6.88.

(-)-4'-bromo-Δ^9-tetrahydrocannabinol (9). To a stirred solution of **8** (290 mg, 0.77 mmol) in anhydrous CH_2Cl_2 (15 mL) at 0°C under an argon atmosphere was added boron trifluoride etherate (0.24 mL 1.92 mmol). Stirring was contin-

ued for 40 minutes, and the reaction was quenched by the addition of saturated $NaHCO_3$ solution. The organic layer was separated, and the aqueous phase was extracted with CH_2Cl_2. The combined organic layer was washed with brine and dried over $MgSO_4$; the solvent evaporated under reduced pressure. Purification by flash column chromatography on silica gel (25% diethyl ether in hexane) afforded 213 mg (73% yield) of the title compound **9** as gum. ^{1}H NMR ($CDCl_3$) δ 6.29 (br s, 1H, 10-H), 6.26 (s, 1H, 4-H), 6.14 (s, 1H, 2-H), 4.86 (br s, 1H, OH), 3.40 (t, J = 6.4 Hz, 2H, 4'-H), 3.20 (m as br d, J = 11.0 Hz, 1H, 10a-H), 2.48 (t, J = 7.1 Hz, 2H, 1'-H), 2.24-2.10 (m, 2H), 2.01-1.60 (m, 9H, especially 1.68, s, C_9-CH_3), 1.53-1.25 (m, 4H, especially 1.41, s, 6ß-CH_3), 1.09 (s, 3H, 6α-CH_3); mass spectrum *m/z* (relative intensity) 380 (M^++2, 68), 378 (M^+, 69), 365(50), 363(51), 339(27), 337(27), 299(69), 297(100), 295(96), 215(33). Exact mass calculated for $C_{20}H_{27}BrO_2$, 378.1194; found, 378.1199. Analysis calculated: C, 63.33; H, 7.17. Found: C, 62.94; H, 7.26.

5-(3,5-Dimethoxyphenyl)-1,1,1-trifluoro-pentane (13). 1-Chloro-4,4,4-trifluoro-butane **10** was prepared from the corresponding chlorobutanoic acid and sulfur tetrafluoride under pressure at 60°C, according to a reported procedure.[23] A solution of triphenylphosphine (32 g, 122.9 mmol) and **10** (12 g, 81.9 mmol) in benzene (20 mL) was placed in a pressured bottle and heated at 110°C for 40 hours. The mixture was then cooled to room temperature, and the solvent was evaporated to yield 29 g (87%) of **11** as a white solid (mp 168°C-170°C), which was used into the next step without further purification. To a suspension of **11** (23 g, 56.4 mmol) in anhydrous Et_2O (60 ml) at 0°C, under an argon atmosphere, was added dropwise *n*-butyllithium (24.8 mL, 62 mmol, 2.5 M solution in hexane). The red-colored mixture was stirred for 30 minutes, and a solution of 3,5-dimethoxybenzaldehyde **1** (14.1 g, 84.9 mmol) in Et_2O (75 mL) was added over a period of 10 minutes. Following the addition, the reaction mixture was refluxed for 2 hours, the solvent was evaporated, and the residue obtained was extracted with refluxing benzene. The concentrate was purified by column chromatography using 10% chloroform in hexane as an eluent to give 10 g (68% yield) of **12** as a 1:2 *cis*/*trans*-mixture. ^{1}H NMR ($CDCl_3$) δ 6.45 (d, J = 12.0 Hz, 1H, 5-H), 6.38 (br s, 3H, ArH), 5.62-5.56 (m, 1H, 4-H), 3.78 (s, 6H, OMe), 2.65-2.54 (m, 2H, 2-H), 2.27-2.14 (m, 2H, 3-H). A solution of **12** (9.3 g, 35.7 mmol) in absolute EtOH (10 mL) and 10% Pd/C (30 mg) was placed in a Parr apparatus (Parr Instrument Co, Moline, IL) and treated overnight with hydrogen at 60 psi. The catalyst was filtered off through celite, and the filtrate was evaporated under reduced pressure to leave the title compound **13** as a light yellow oil in 92% yield (8.6 g). ^{1}H NMR ($CDCl_3$) δ 6.31 (br s, 3H, ArH), 3.77 (s, 6H, OMe), 2.57 (t, J = 7.0 Hz, 2H, 5-H), 2.14-2.01 (m, 2H, 2-H), 1.96-1.53 (m, 4H, 3-H, 4-H). Analysis calculated: C, 59.53; H, 6.53. Found: C, 59.79; H, 6.82.

5-(5',5',5'-trifluoro-pentyl)resorcinol (14). A solution of boron tribromide (3.93 mL, 41.6 mmol) in benzene (20 mL) was added dropwise to a solution of **13** (8.4 g, 32 mmol) in benzene (80 mL) previously cooled to 0°C. The reaction mixture was stirred at room temperature for 72 hours. The reaction was quenched by careful addition of ice water, and the organic fraction was washed with a 5% solution of sodium sulfite, brine, and water. After drying, the solvent was removed, and the residue obtained was purified by column chromatography using 1% methanol in chloroform as an eluent to yield 7.4 g (99% yield) of **14** as a light brown viscous oil. ^{1}H NMR ($CDCl_3$) δ 6.24 (br s, 2H, 4-H, 6-H), 6.20 (br s, 1H, 2-H), 2.40 (t, J = 6.8 Hz, 2H, 1'-H), 2.10-1.92 (m, 2H, 4'-H), 1.52-1.50 (m, 4H, 2'-H, 3'-H). Analysis calculated: C, 56.41; H, 5.59. Found: C, 56.74; H, 5.88.

(-)-5',5',5'-Trifluoro-Δ^8-tetrahydrocannabinol (15). A solution of **14** (4.06 g, 17.3 mmol), (+)-*cis*/*trans*-*p*-mentha-2,8-dien-1-ol (3.3 g, 21.7 mmol) and *p*-toluenesulfonic acid (0.4 g, 2.32 mmol) in benzene (100 mL) was refluxed for 4 hours. The reaction was quenched with a 5% solution of sodium bicarbonate, and the organic fraction was washed with water. After drying, the solvent was removed in vacuo, and the residue obtained was purified by column chromatography using 10% diethyl ether in hexane as an eluent to give 4.3 g (67% yield) of **15** as a yellow gum. ^{1}H NMR ($CDCl_3$) δ 6.26 (s, 1H, 4-H), 6.10 (s, 1H, 2-H), 5.42 (br s, 1H, 8-H), 3.18 (dd, J = 16.0 Hz, J = 3.5 Hz, 1H, 10α-H), 2.70 (td, J = 10.3 Hz, J = 4.5 Hz, 1H, 10a-H), 2.47 (t, J = 7.0 Hz, 2H, 1'-H), 1.70 (s, 3H, C_9-CH_3), 1.38 (s, 3H, 6ß-CH_3), 1.10 (s, 3H, 6α-CH_3); mass spectrum *m/z* 368 (M^+). Analysis calculated: C, 68.46; H, 7.39. Found: C, 68.21; H, 7.58.

(-)-5'-Fluoro-Δ^8-tetrahydrocannabinol (20). To a solution of **18**[10,12,24] (303 mg, 0.92 mmol) and 2,6-lutidine (0.53 mL, 4.58 mmol) in methylene chloride (6 mL) cooled to 0°C was added triflic anhydride (0.68 mL, 4.06 mmol), and the mixture was stirred for 45 minutes. The solvent was then removed using a stream of nitrogen, and the residue obtained was purified by flash column chromatography on florisil using 5% diethyl ether in hexane to yield 319 mg (58%) of fairly pure (-)-5'-trifluoromethylsulfonyloxy-Δ^8- tetrahydrocannabinol triflate **19**. ^{1}H NMR ($CDCl_3$) δ 6.66 (s, 1H, 4-H), 6.60 (s, 1H, 2-H), 5.44 (br s, 1H, 8-H), 4.53 (t, J = 6.5 Hz, 2H, 5'-H), 2.88 (m, 2H, 10α-H, 10a-H), 2.56 (t, J = 7.0 Hz, 2H, 1'-H), 1.70 (s, 3H, C_9-CH_3), 1.39 (s, 3H, 6ß-CH_3), 1.11 (s, 3H, 6α-CH_3). A mixture of **19** (319 mg, 0.54 mmol), kryptofix (203 mg, 0.54 mmol) and potassium fluoride (44 mg, 0.76 mmol) in acetonitrile (5 mL) was stirred at 80°C for 40 minutes. While the reaction mixture was still warm, the solvent was removed using a stream of nitrogen. The residue obtained was dissolved in diethyl ether (5 mL), the solution was cooled to 0°C, and lithium aluminum hydride (2 mL, 1 M solution in Et_2O) was added dropwise. The mixture was allowed to reach room temperature and was stirred for 30 minute. It was then cooled

to 0°C, quenched by addition of ethyl acetate, and neutralized with 1N HCl. After extraction with Et_2O, the organic fraction was dried, the solvent was removed under reduced pressure, and the product was purified by column chromatography (15% diethyl ether in hexane) to yield 120 mg (67% yield) of **20** as gum. ^{1}H NMR ($CDCl_3$) δ 6.27 (s, 1H, 4-H), 6.10 (s, 1H, 2-H), 5.42 (br s, 1H, 8-H), 4.43 (dt, $J_{H\text{-}F}$ = 47.3 Hz, 2H, 5'-H), 3.16 (dd, *J* = 16.1 Hz, *J* = 3.4 Hz, 1H, 10α-H), 2.70 (td, *J* = 10.3 Hz, *J* = 4.5 Hz, 1H, 10a-H), 2.46 (t, *J* = 7.0 Hz, 2H, 1'-H), 1.69 (s, 3H, C_9-CH_3), 1.37 (s, 3H, 6ß-CH_3), 1.10 (s, 3H, 6α-CH_3). Analysis calculated: C, 75.87; H, 8.79. Found: C, 75.64; H, 9.05.

(-)-11-Fluoro-Δ^8-tetrahydrocannabinol (23). *n*-Tetrabutylammonium fluoride in THF (1 M, 12 mL, 12 mmol) was mixed with (-)-11-bromo-Δ^8-tetrahydrocannabinol acetate **22**[9] (536 mg, 1.23 mmol), and the resulting solution was heated to 60°C for 45 minutes. After cooling, the mixture was poured in a 1N HCl solution (30 mL) and extracted with diethyl ether. The organic fraction was dried, the solvent was removed under reduced pressure, and the residue obtained was purified by column chromatography using chloroform as an eluent to give 122 mg (30% yield) of the title compound as a gum. ^{1}H NMR ($CDCl_3$) δ 6.28 (s, 1H, 4-H), 6.11 (s, 1H, 2-H), 5.85 (s, 1H, 8-H), 4.75 (d, $J_{H\text{-}F}$ = 48.0 Hz, 2H, 11-H), 3.46 (dd, *J* = 16.0 Hz, *J* = 3.5 Hz, 1H, 10α-H), 2.73 (td, *J* = 10.3 Hz, *J* = 4.5 Hz, 1H, 10a-H), 2.45 (t, *J* = 7.1 Hz, 2H, 1'-H), 1.40 (s, 3H, 6ß-CH_3), 1.12 (s, 3H, 6α-CH_3), 0.85 (t, *J* = 7.0 Hz, 3H, 5'-H); mass spectrum *m/z* 332 (M^+). Analysis calculated: C, 75.87; H, 8.79. Found: C, 76.20; H, 8.97.

2-(3,5-Dimethoxyphenyl)-6-phenoxyhexan-2-ol (25). A few drops of a solution of 4-phenoxybutyl bromide (7.63 g, 33.3 mmol) in diethyl ether (70 mL) were added to a slurry of diethyl ether (10 mL) cooled to 0°C containing magnesium turnings (0.94 g, 39 mmol) and a crystal of iodine. The reaction was initiated with gentle refluxing, and the remaining bromide was added dropwise over a period of 3 hours. When most of the magnesium was consumed, the reaction mixture was cooled to 0°C and a solution of 3,5-dimethoxyacetophenone (5 g, 27.7 mmol) in diethyl ether (50mL) was added dropwise. The mixture was refluxed for 1.5 hours and then stirred at room temperature overnight. After cooling to 0°C, the reaction was quenched with 50% ammonium chloride solution. The mixture was then extracted with diethyl ether, and the organic fraction was washed with water and brine. After drying, the solvent was evaporated, and the residue obtained was purified by column chromatography using 20% diethyl ether in hexane as an eluent to give 8.1 g (88% yield) of **25** as oil. ^{1}H NMR ($CDCl_3$) δ 7.30-6.91 (m, 5H, OPh), 6.59 (s, 2H, ArH), 6.35 (s, 1H, ArH), 3.93 (t, *J* = 6.2 Hz, 2H, 6-H), 3.79 (s, 6H, OMe), 1.54 (s, 3H, 1-H), 1.89-1.17 (m, 6H, 3-H, 4-H, 5-H). Analysis calculated: C, 72.70; H, 7.93. Found: C, 73.05; H, 8.14.

2-(3,5-Dimethoxyphenyl)-8-phenoxyoctan-2-ol (26). A mixture of 6-phenoxyhexyl bromide[29] (6.17 g, 24 mmol) and magnesium turnings (0.68 g, 28 mmol) in diethyl ether (70 mL) were converted to 6-phenoxyhexylmagnesium bromide, which was subsequently treated with a solution of 3,5-dimethoxyacetophenone (3.71 g, 10.6 mmol) in diethyl ether (40 mL) according to the procedure described for compound **25**. Purification by column chromatography (20% diethyl ether in hexane) afforded 6.63 g (90% yield) of **26** as oil. ^{1}H NMR ($CDCl_3$) δ 7.78-6.85 (m, 5H, OPh), 6.47 (s, 2H, ArH), 6.34 (s, 1H, ArH), 3.90 (t, *J* = 6.3 Hz, 2H, 8-H), 3.80 (s, 6H, OMe), 1.53 (s, 3H, 1-H), 1.86-1.17 (m, 10H, 3-H, 4-H, 5-H, 6-H, 7-H); mass spectrum *m/z* 358 (M^+). Analysis calculated: C, 73.71; H, 8.44. Found: C, 73.99; H, 8.62.

2-(3,5-Dimethoxyphenyl)-2-methyl-6-phenoxyhexane (27). A mixture of a solution of **25** (3.05 g, 9.2 mmol) in hexane (12 mL, also containing a few drops of diethyl ether to increase the substrate's solubility) and concentrated HCl (10 mL) was stirred vigorously at 40°C for 5 hours. The 2 layers were separated, and the organic fraction was washed with water, saturated sodium bicarbonate solution, and brine. The organic fraction was then dried and the solvent was removed under reduced pressure to give 2-chloro-2-(3,5-dimethoxyphenyl)-6-phenoxyhexane (3.09 g), which was used without further purification. To a solution of the above chloride (3.09 g) in toluene (10 mL) cooled to 0°C was added a solution of trimethylaluminum in toluene (2N, 18 mL, 35.8 mmol). The resulting mixture was refluxed for 6 days, cooled to 0°C, and neutralized by slow addition of concentrated HCl. The organic fraction was washed with water, saturated sodium bicarbonate solution, and brine. After drying, the solvent was removed under reduced pressure and the residue obtained was purified by column chromatography (5% diethyl ether in hexane) to give 1.553 g (51.4% yield) of **27**[13,20] as oil. ^{1}H NMR ($CDCl_3$) δ 7.30-6.80 (m, 5H, OPh), 6.48 (s, 2H, ArH), 6.30 (s, 1H, ArH), 3.87 (t, *J* = 6.3 Hz, 2H, 6-H), 3.78 (s, 6H, OMe), 1.76-1.57 (m, 6H, 3-H, 4-H, 5-H), 1.27 (s, 6H, gem-CH_3). Analysis calculated: C, 76.79; H, 8.59. Found: C, 76.44; H, 8.72.

2-(3,5-Dimethoxyphenyl)-2-methyl-8-phenoxyoctane (28). A mixture of **26** (7.0 g, 19.5 mmol) and concentrated HCl (20 mL) was stirred vigorously for 7 hours at 50°C. After extraction with hexane and washing with water, saturated sodium bicarbonate, and brine, 2-chloro-2-(3,5-dimethoxyphenyl)-8-phenoxyoctane (6.06 g) was obtained and used without further purification. Methylation was achieved following the procedure described for **27** by dissolving the chloride in toluene (18 mL) and using trimethylaluminum (2N solution in toluene, 33 mL, 65 mmol). The resulting solution was heated to 100°C and stirred for 5 days. After workup, the residue obtained was purified by column chromatography (5% diethyl ether in hexane) to give 2.75 g (40% yield) of **28** as oil. ^{1}H NMR ($CDCl_3$) δ 7.30-6.85 (m,

5H, OPh), 6.47 (s, 2H, ArH), 6.28 (s, 1H, ArH), 3.90 (t, J = 6.3 Hz, 2H, 8-H), 3.79 (s, 6H, OMe), 1.26 (s, 6H, gem-CH_3), 1.75-1.07 (m, 10H). Analysis calculated: C, 77.49; H, 9.05. Found: C, 77.27; H, 8.74.

5-(5'-Bromo-1',1'-dimethylpentyl)resorcinol (29). To a solution of **27** (2.14 g, 6.52 mmol) in benzene (100 mL) cooled to 0°C was slowly added boron tribromide (1.5 mL, 15.8 mmol). The mixture was stirred at room temperature. At 24-hour and 48-hour intervals more boron tribromide was added (1 mL, 10.6 mmol and 0.5 mL, 5.3 mmol, respectively). The reaction was allowed to proceed for a total of 80 hours. The reaction mixture was then quenched with ice water, and the organic phase was washed with a 5% solution of sodium sulfite and brine. After drying, the solvent was removed, and the residue obtained was purified by column chromatography (20% ethyl acetate in hexane) to give 1.73 g (92.5% yield) of **29**[13,20] as viscous oil. ^{1}H NMR ($CDCl_3$) δ 6.38 (d, J = 1.9 Hz, 2H, 4-H, 6-H), 6.25 (t, J = 1.9 Hz 1H, 2-H), 3.33 (t, J = 6.6 Hz, 2H, 5'-H), 1.82-1.50 (m, 6H), 1.23 (s, 6H, gem-CH_3). Analysis calculated: C, 54.37; H, 6.67. Found: C, 54.14; H, 7.01.

5-(7'-Bromo-1',1'-dimethylheptyl)resorcinol (30). A solution of **28** (2.75 g, 7.72 mmol) in benzene (30 mL) was treated with boron tribromide (1.5 mL, 15.8 mmol) as described for compound **29**. More boron tribromide was added 24 hours and 48 hours later (1 mL, 10.6 mmol and 0.5 mL, 5.3 mmol, respectively). The mixture was stirred at room temperature for a total of 72 hours. The residue obtained after workup was purified by column chromatography (25% ethyl acetate in hexane) to give 2.2 g (90% yield) of **30** as viscous oil. ^{1}H NMR ($CDCl_3$) δ 6.38 (d, J = 1.9 Hz, 2H, 4-H, 6-H), 6.17 (t, J = 1.9 Hz, 1H, 2-H), 3.38 (t, J = 6.7 Hz, 2H, 7'-H), 1.25 (s, 6H, gem-CH_3), 1.79-1.06 (m, 10H); mass spectrum *m/z* 314 (M^+). Analysis calculated: C, 57.15; H, 7.35. Found: C, 57.27; H, 7.64.

(-)-5'-Bromo-1',1'-dimethyl-Δ^8-tetrahydrocannabinol (31). A solution of **29** (3.28 g, 11.43 mmol), (+)-*cis*/*trans*-*p*-mentha-2,8-dien-1-ol (2.19 g, 14.4 mmol) and *p*-toluenesulfonic acid (0.41 g, 2.4 mmol) in benzene (90 mL) was refluxed for 4 hours. Following the procedure described for analog **15**, the residue obtained was purified by column chromatography (25% diethyl ether in hexane) to give 2.74 g (57% yield) of **31**[13,20] as gum. ^{1}H NMR ($CDCl_3$) δ 6.37 (s, 1H, 4-H), 6.22 (s, 1H, 2-H), 5.43 (br s, 1H, 8-H), 3.33 (t, J = 6.6 Hz, 2H, 5'-H), 3.22 (dd, J = 16.1 Hz, J = 3.4 Hz, 1H, 10α-H), 2.69 (td, J = 10.3 Hz, J = 4.5 Hz, 1H, 10a-H), 1.70 (s, 3H, C_9-CH_3), 1.39 (s, 3H, 6ß-CH_3), 1.22 (s, 6H, gem-CH_3), 1.11 (s, 3H, 6α-CH_3); mass spectrum *m/z* 420 (M^+). Analysis calculated: C, 65.55; H, 7.89. Found: C, 65.37; H, 7.61.

(-)-7'-Bromo -1',1'-dimethylheptyl -Δ^8-tetrahydrocannabinol (32). Following the procedure described for compound **31**, a solution of **30** (2.5 g, 7.94 mmol), (+)-*cis*/*trans*-*p*-mentha-2,8-dien-1-ol (1.52 g, 9.93 mmol) and *p*-toluenesulfonic acid (0.283 g, 1.647 mmol) were refluxed in benzene (100 mL) for 4 hours. The residue obtained after workup was purified by column chromatography (10% diethyl ether in hexane) to give 2.32 g (65% yield) of **32** as gum. ^{1}H NMR ($CDCl_3$) δ 6.37 (s, 1H, 4-H), 6.21 (s, 1H, 2-H), 5.42 (br s, 1H, 8-H), 3.35 (t, J = 6.7 Hz, 2H, 7'-H), 3.19 (dd, J = 16.0 Hz, J = 3.4 Hz, 1H, 10α-H), 2.69 (td, J = 10.3 Hz, J = 4.4 Hz, 1H, 10a-H), 1.69 (s, 3H, C_9-CH_3), 1.38 (s, 3H, 6ß-CH_3), 1.20 (s, 6H, gem-CH_3), 1.11 (s, 3H, 6α-CH_3); mass spectrum *m/z* 448 (M^+). Analysis calculated: C, 66.81; H, 8.30. Found: C, 66.56; H, 8.40.

(-)-2-Iodo-Δ^8-tetrahydrocannabinol (34). (-)-Δ^8-tetrahydrocannabinol **33** (500 mg, 1.59 mmol) in methylene chloride (2 mL), sodium iodide (1.2 g, 8.0 mmol) and 18-crown-6 (42 mg, 0.16 mmol) were added to a solution of m-chloroperbenzoic acid (410 mg, 2.38 mmol) in methylene chloride (10 mL). The mixture was stirred at room temperature for 30 minutes, diluted with diethyl ether, and washed with a 10% sodium metabisulfite solution. The organic fraction was further washed with water and dried. The solvent was evaporated and the residue obtained was purified by column chromatography using cyclohexane as an eluent to give 380 mg (54% yield) of **34** as brown gum. ^{1}H NMR ($CDCl_3$) δ 6.39 (s, 1H, 4-H), 5.42 (br s, 1H, 8-H), 3.24 (dd, J = 16.0 Hz, J = 3.3 Hz, 1H, 10α-H), 2.74 (td, J = 10.4 Hz, J = 4.3 Hz, 1H, 10a-H), 2.59 (t, J = 7.0 Hz, 2H, 1'-H), 1.70 (s, 3H, C_9-CH_3), 1.38 (s, 3H, 6ß-CH_3), 1.09 (s, 3H, 6α-CH_3), 0.86 (t, J = 6.9 Hz, 3H, 5'-H); mass spectrum *m/z* 440 (M^+). Analysis calculated: C, 57.28; H, 6.64. Found: C, 57.59; H, 6.82.

(-)-1'-Iodo-heptyl-Δ^8-tetrahydrocannabinol (36). An oven-dried, 5-mL, round-bottomed flask was equipped with a magnetic stirring bar, and an argon atmosphere was secured. The flask was charged with alcohol **35** (30 mg, 0.09 mmol), dry toluene (0.2 mL), triphenylphosphine (44 mg, 0.17 mmol), imidazole (17 mg, 0.26 mmol), and iodine (43 mg, 0.17 mmol). The resulting mixture was stirred vigorously at room temperature for 3 hours. Upon completion, solvent evaporation and purification by flash column chromatography on silica gel (5% diethyl ether-petroleum ether) afforded 25 mg (64% yield) of the title compound **36** as viscous oil. ^{1}H NMR ($CDCl_3$) δ 6.46, 6.44, 6.31, 6.29 (s, 0.5H each, mixture of diastereomers, ArH), 5.43 (d, J = 3.9 Hz, 1H, 8-H), 4.95-4.93 (m, 1H, mixture of diastereomers, 1´-CH-), 4.76 (s, 1H, OH), 3.18 (dd, J = 16.9 Hz, J = 4.0 Hz, 1H, 10α-H), 2.67 (ddd as td, J = 10.6 Hz, J = 4.6 Hz, 1H, 10a-H), 2.26-2.16 (m, 3H, 7α-H, 10ß-H, 7ß-H), 2.03-1.66 (m, 6H, 6a-H, 2'-CH_2-, especially 1.66, s, 9-CH_3), 1.42-1.24 (m, 11H, 3'-CH_2-, 4'-CH_2-, 5'-CH_2-, 6'-CH_2-, 6ß-CH_3), 1.09 (s, 3H, 6α-CH_3), 0.85, 0.83, (t, J = 7.1 Hz, 3H, mixture of diastereomers, 7'-CH_3).

Radioligand Binding Assay

Forebrain synaptosomal membranes were prepared from frozen rat brains by the method of Dodd et al[30] and were used to assess the affinities of the cannabinoid analogs for the CB1 binding sites. The displacement of specifically tritiated CP-55,940 from these membranes was used to determine the IC_{50} values for the test compounds. The assay was conducted in a 96-well microfilter plate. The samples were filtered using a Packard Filtermate Harvester (Packard Instrument Co, Meriden, CT) and Whatman GF/B unifilter-96 plates (Whatman, Kent, UK), and 0.5% bovine serum albumin (BSA) was incorporated into the wash buffer. Radioactivity was detected using MicroScint 20 scintillation cocktail (Packard Instruments) added to the dried filter plates and was counted using a Packard Instruments Top Count. Data were collected from 3 independent experiments between 100% and 0% specific binding for [^{3}H]CP-55,940, determined using 0 and 100 nM CP-55,940. The normalized data from 3 independent experiments were combined and analyzed using a 4-parameter logistic equation to yield IC_{50} values, which were converted to K_i values using the assumptions of Cheng and Prussoff.[31]

Molecular Modeling

Computational studies were performed using the Insight II/Discover software program[32] on a SGI Fuel workstation (SGI, Mountain View, CA). Each analog was first constructed with bond angles and bond distances supplied by the molecule Builder feature and given the CFF91 force field. Molecular mechanics and dynamics[33] were then used to study the low energy conformers with each iteration assigned an interval of 1 femtosecond. First, each structure was minimized using the steepest descent method for 100 iterations until the maximum derivative was less than 0.1 kcal/mol. Next, molecular dynamics was initialized for 1000 iterations at 1000 K in order to equilibrate each analog. Following equilibration, the dynamics procedure was continued for 300 000 iterations at the same temperature in order to thoroughly sample each analog's available conformational space. At 1000 iteration intervals, atomic coordinates were recorded into an archive file for a total of 300 conformations per analog. Following the dynamics run, the conformers in each archive file were subjected to minimization using the steepest descent method for 100 iterations followed by the conjugate gradient method for 5000 iterations until the maximum derivation was less than 0.001 kcal/mol. Dihedral angle (C2-C3-C1'-C2' and C3-C1'-C2'-C3') values were obtained from each conformer for analysis. In addition, volume contours of each analog's side chain were calculated with the TRIPOS SYBYL[34] multiple-contour module in order to observe the space occupied by each side chain.

Results and Discussion

The abilities of the synthesized analogs to displace radiolabeled CP-55,940 from purified rat forebrain synaptosomes were determined as described in the Materials and Methods section. K_i values calculated from the respective displacement curves are listed in Table 1 and serve as indicators for the affinities of these analogs for the CB1 receptors.

A cursory examination of the affinities reveals some interesting structure function correlations that can be summarized as follows:

- Halogen substitution at the terminal carbon of the side chain leads to enhancement in the ligand's affinity for CB1 with the large halogens having the higher affinities. Thus, for the C1'-unsubstituted series, where the side chain can be represented by $(CH_2)_4R$, the order of affinities for the different R substituents is as follows: $CH_2I = CH_2Br > Br > CF_3 > CH_3 > CH_2F$. This order correlates well with the size of the terminal carbon segment of the chain, suggesting a hydrophobic interaction with a respective site on the CB1 receptor. Our results show that the 5'-iodopentyl (**17b**) and 5'-bromopentyl (**17a**) analogs have the highest affinities, while compounds with the methyl ((-)-Δ^8-THC) and fluoromethyl (**20**) groups have the lowest. Also, the 4'-bromo-analog (**9**) interacts more effectively than the parent (-)-Δ^9-THC reflecting the larger volume of a bromo group compared with a methyl group.
- The introduction of a 1',1'-dimethyl substituent enhances the interactions of the halogenated side chain with CB1 as is observed in the 1',1'-dimethyl-5'-bromopentyl (**31**) and 1',1'-dimethyl-7'-bromoheptyl (**32**) analogs. The pentyl analog has a somewhat higher affinity than the corresponding heptyl analog, suggesting that the optimal chain length for an ω-bromo side chain is within a 5 and 7 carbon chain length. The presence of 1',1'-dimethyl substitution in the chain leads up to more than a 15-fold increase in affinity. This observation is congruent with the presence of a hydrophobic subsite at CB1 as has been discussed in our earlier publications.[26,36,37] However, the situation is very different in the 1'-iodo-analog (**36**), where the presence of one iodo group results in a severe reduction in affinity for the CB1 receptor. This finding reflects either the inability of the CB1 subsite to accommodate a large group such as an iodo substituent or the effect that the halogen may have on the preferred conformation of the side chain.
- Introduction of a fluoro group at the 11-position (**23**) leads to a 2-fold decrease in binding affinity.
- Introduction of 2-iodo substitution (**34**) leads to a 2-fold reduction in affinity. This result may be attrib-

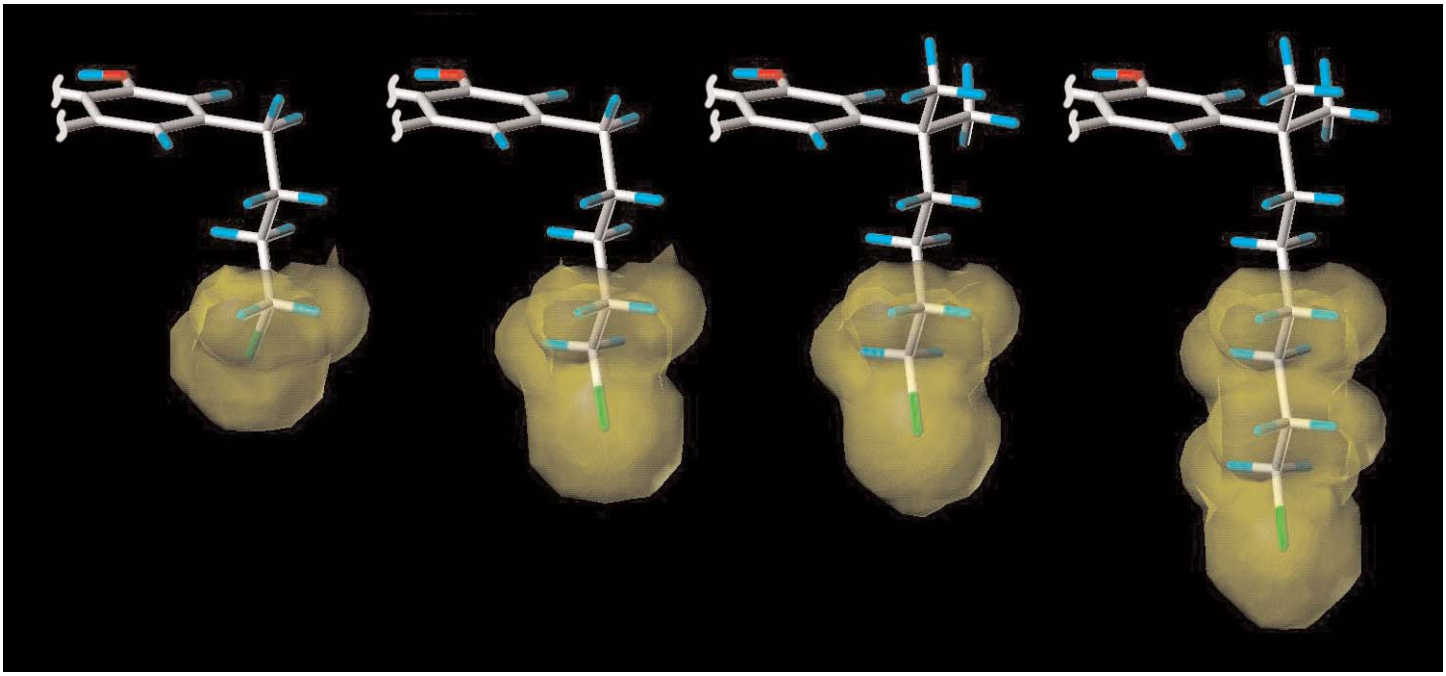


Figure 1. Side chain volume contours of analogs **9**, **17a**, **31**, and **32** (left to right). Only the phenolic A ring of the cannabinoids is depicted here. To more effectively represent the side chain terminal pharmacophoric space, dihedral angle C2-C3-C1′-C2′ was fixed at -120 degrees for the analogs displayed. This value represents the lowest energy conformers for **31** and **32**. The corresponding conformers for **9** and **17a** represent conformations only slightly higher than those of their lowest energy (ΔG = 1.13 kcal/mol). (Interactive figure available in online version.)

uted to steric effects either related to changes in the conformation of the side chain or to a relatively small unfavorable interaction of the bulky iodo group at the CB1 binding site. Another possible unfavorable contribution of the 2-iodo group is its electronic effect on the phenolic hydroxyl group of the cannabinoids.

The above data provide interesting additions to the currently available SAR for the cannabinoid side chain. To graphically depict these results we have used computational methods that allowed us to more accurately define the stereoelectronic requirements of this pharmacophore.[33] We performed molecular mechanics and dynamics calculations on the 4'-bromobutyl (**9**), 5'-bromopentyl (**17a**), 1',1'-dimethyl-5'-bromopentyl (**31**), 1',1'-dimethyl-7'-bromoheptyl (**32**), and 1'-iodoheptyl (**36**) analogs and determined their respective low energy conformers. Subsequently, we focused on the C2-C3-C1'-C2' and C3-C1'-C2'-C3' dihedral angles. Our results show that, with the exception of the 1'-iodoheptyl analog (**36**), the conformations of the side chains exhibit similar preferences that can be used as a basis for explaining the differences in binding CB1 affinities for the conformers. The increased affinity of **17a** versus **9** is probably the result of an increase in side chain length from $(CH_2)_4Br$ to $(CH_2)_4CH_2Br$. Indeed, an inspection of the side chain volumes in Figure 1 reveals the more extensive space occupied by the side chain terminus of **17a**. This space may correspond to a hydrophobic region within the CB1 binding pocket that when occupied imparts a higher affinity for the ligand. This hydrophobic region is probably optimal for terminal halogen substitution on C5 or C6 side chains. The greater terminus side chain volume of the C7 compound **32** versus **31** (Figure 1) leads to a slight decrease in CB1 binding affinity. The enhanced affinities of all C1'-dimethyl substituted analogs can be attributed to their interaction with a respective subsite within the CB1 binding site as discussed in our earlier publications.[26,36,37] An additional reason for these enhanced affinities may be related to the preferred conformations of these ligands around the C3-C1' bond. As shown in Table 2, in the absence of the two 1',1'-methyl groups in **17a**, the C2-C3-C1'-C2' dihedral angle is approximately ±90 degrees. However, in all 1',1'-dimethyl analogs, such as **31**, the value of this dihedral angle is near 60°, which may also correspond to the pharmacophoric conformation of the side chain and lead to higher CB1 affinities. Finally, a comparison of the R and S enantiomers of the 1'-iodo analog (**36**) shows that their dihedral angle values, as expected, are the same in magnitude but opposite in sign. As stated earlier, **36** has a poor binding CB1 affinity compared with the other 4 analogs. While the presence of the C1' iodine may cause some unfavorable electrostatic interactions within the CB1 binding pocket, its presence also yields a dihedral angle for C3-C1'-C2'-C3' of ±165 degrees, a value that is not present in any of the other 4 analogs' conformers (Figure 2). Arguably, this conformation may prevent the ligand from engaging in a favorable interaction with the CB1, thus leading to a relatively low affinity for this receptor.

Table 2. Conformer Dihedral Angle Values for Analogs **9**, **17a**, **31**, **32**, and **36** (R and S Enantiomers)*

Analog	Dihedral Angle (C2-C3-C1′-C2′)
9	91 ± 12 (179); -89 ± 11 (121)
17a	90 ± 11 (120); -89 ± 12 (180)
31	177 ± 5 (4); 121 ± 5 (78); 60 ± 5 (76); 3 ± 6 (8); -61 ± 4 (70); -118 ± 5 (64)
32	180 ± 5 (19); 120 ± 5 (92); 62 ± 5 (52); 3 ± 1 (8); -62 ± 5 (76); -116 ± 6 (53)
36R	125 ± 9 (81); -55 ± 7 (219)
36S	56 ± 8 (106); -125 ± 9 (194)
Analog	**Dihedral Angle (C3-C1′-C2′-C3′)**
9	180 ± 2 (136); 64 ± 2 (82); -64 ± 2 (82)
17a	180 ± 2 (138); 64 ± 4 (76); -64 ± 3 (86)
31	180 ± 3 (69); 59 ± 6 (112); -59 ± 7 (119)
32	180 ± 3 (112); 58 ± 8 (66); -57 ± 7 (122)
36R	-165 ± 5 (106); -62 ± 4 (160); 55 ± 5 (34)
36S	166 ± 4 (89); 62 ± 4 (176); -56 ± 7 (35)

*The number in parentheses represents the number of conformers of that analog having the corresponding dihedral angle value.

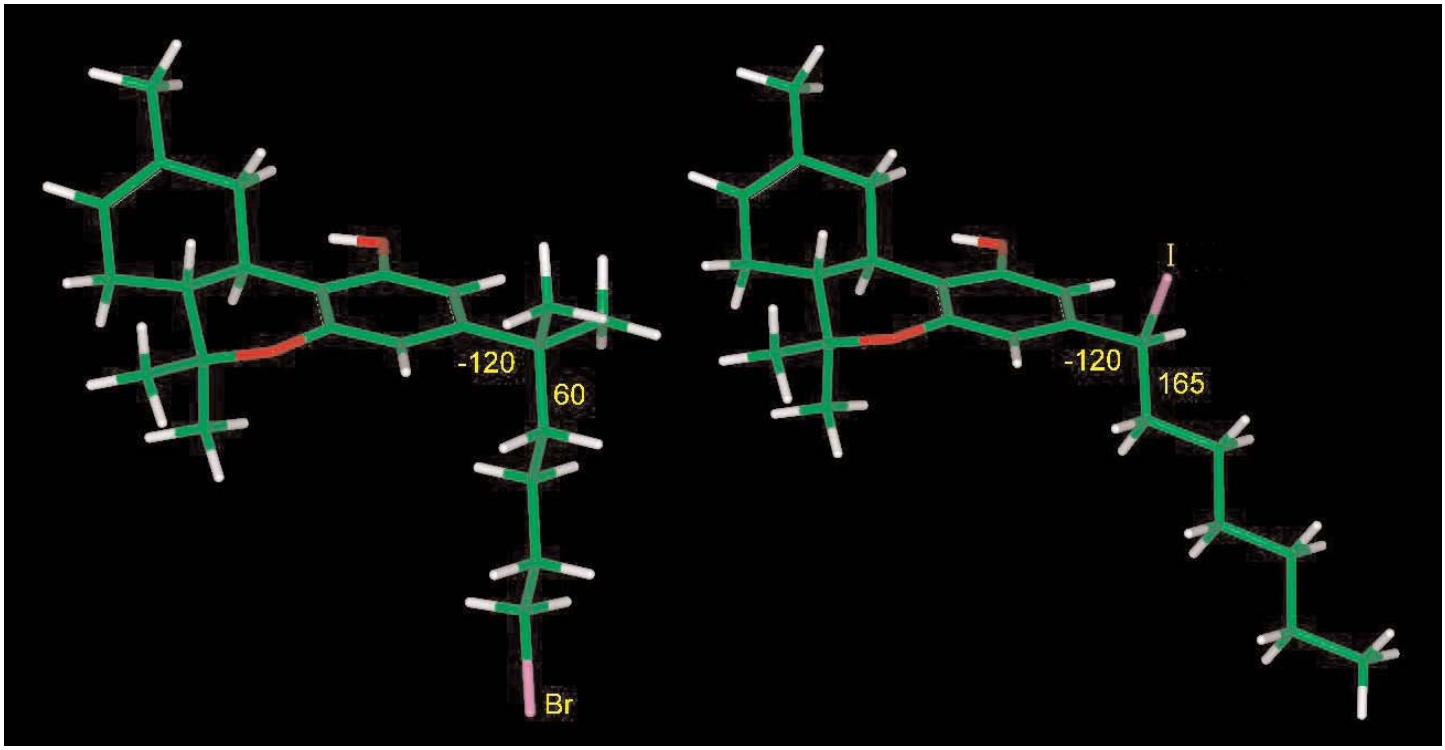


Figure 2. Low energy conformation of analog **31** (left) vs that of analog **36**'s S enantiomer. The dihedral angle values for C2-C3-C1′-C2′ and C3-C1′-C2′-C3′ are shown in yellow. (Interactive figure available in online version.)

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