Unsaturated Side Chain β-11-Hydroxyhexahydrocannabinol Analogs

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The cannabinoid side chain is a key pharmacophore in the interaction of cannabinoids with their receptors (CB1 and CB2). To study the stereochemical requirements of the side chain, we synthesized a series of cannabinoids in which rotation around the C1′−C2′ bond is blocked. The key steps in the synthesis were the cuprate addition of a substituted resorcinol to (+)-apoverbenone, the TMSOTf-mediated formation of the dihydropyran ring, and the stereospecific introduction of the β-11-hydroxymethyl group. All the analogs tested showed nanomolar affinity for the receptors, the *cis*-hept-1-ene side chain having the highest affinity for CB1 (K_i = 0.89 nM) and showing the widest separation between CB1 and CB2 affinities. The parent *n*-heptyl-β-11-hydroxyhexahydrocannabinol was the least potent binding to CB1 (K_i = 8.9 nM) and had the lowest selectivity between CB1 and CB2.

Introduction

The search for cannabinoids possessing a high degree of pharmacological potency and selectivity has led to the synthesis and testing of a large number of novel analogs from which structure−activity relationships (SAR) could be established.[1] A review of the existing literature recognized four pharmacophores on the cannabinoid structure which can be associated with cannabimimetic activity.[2] These include a phenolic hydroxyl and an aliphatic side chain attached to the phenolic ring, both of which are present in the natural tetrahydrocannabinol constituents found in Cannabis. Additionally, structural modification of the basic cannabinoid prototypes identified two further pharmacophores: a northern aliphatic hydroxyl at the 9- or 11-position of the classical and nonclassical cannabinoids and a southern aliphatic hydroxyl found in the nonclassical cannabinoids as exemplified by CP-55,940.

The importance of the aliphatic side chain was first demonstrated by Adams,[3] who showed that by substituting the *n*-pentyl chain of Δ^9-THC with a 1′,1′-dimethylheptyl chain led to a 100-fold increase in potency. While the structure−activity of various substitutions of the aliphatic alkyl chain have revealed something with regard to the nature of the pharmacophoric requirements in this region, the alkyl chain is flexible and therefore could achieve any one of a number of conformations. We therefore decided to constrain the alkyl side chain by introducing unsaturation at the 1′-position.[4] We also limited the length of the alkyl chain to seven carbons to optimize the structure−activity information that could be gleaned from imposing rotational constraints on the first three carbon atoms attached to the 3-position of 11-hydroxyhexahydrocannabinol.

Synthesis

The synthetic plan called for the preparation of the four compounds shown in Figure 1. The acetylenic compound **1** could be partially hydrogenated to provide **2**; double bond isomerization would then provide **3**; full reduction of **1** would provide **4**.

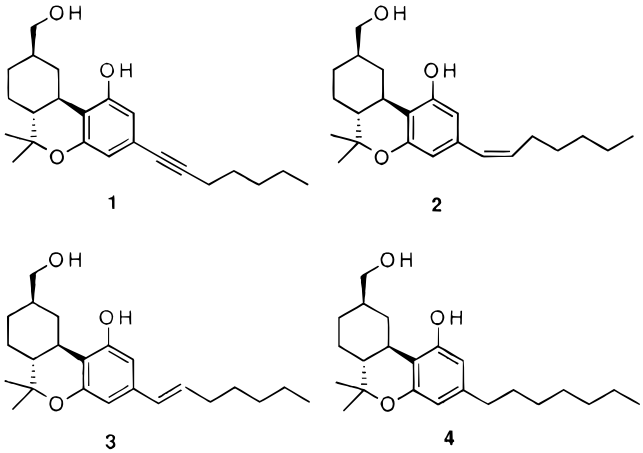

Figure 1. Target compounds used to examine the effects of sterically constraining the side chain of classical cannabinoids.

In the absence of a bulky group at the benzylic position of the side chain, Archer's procedure[5] for coupling of resorcinol and terpenic fragments cannot be used; nonregiospecific coupling takes place, and yields are <50%. Consequently, the cuprate approach making use of apoverbenone which has been developed in our group was brought to bear on the problem.[6]

Commercially available 3,5-dimethoxybenzoic acid (**5**) was converted to methyl ketone **6** by treatment with methyllithium (Scheme 1).[7] Alkyne **7** was obtained via the enol phosphate.[8] Deprotonation of **7** with methyllithium, followed by addition on *n*-amyl bromide in dimethyl sulfoxide (DMSO), led to **8**.[9] Methyl ether cleavage with BBr_3 was successful; however, rapid quenching of the reaction with aqueous $NaHCO_3$ and ice was necessary in order to suppress the formation of byproducts. The air-sensitive resorcinol product was immediately protected as bis(ethoxyethyl) species **9** (EE = 2-ethoxyethyl). The overall yield of **9** from **8** was 84%.

Lithiation of **9** at C2 and formation of the higher-order cuprate, followed by addition of the $BF_3{\cdot}Et_2O$ complex of (+)-apoverbenone, gave **10**. The reaction did not

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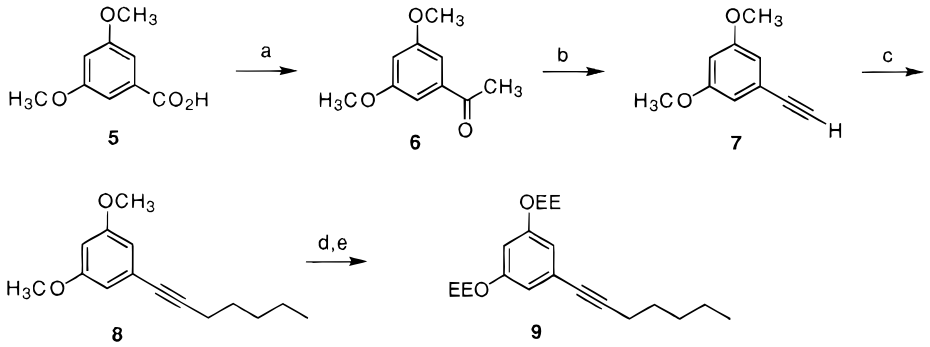
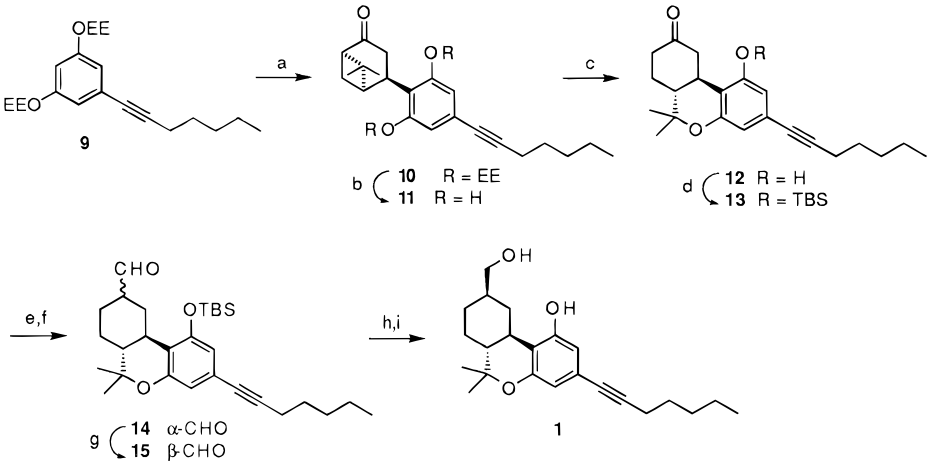
Scheme 1. Synthesis of the Acetylenic Protected Resorcinol **9** Used as the Starting Resorcinol for Coupling to (+)-Apoverbenone[a]



[a] (a) 4 equiv of CH_3Li, 20 equiv of $(H_3C)_3SiCl$, H_3O^+, 79%; (b) LDA, $(EtO)_2P(O)Cl$, LDA, 91%; (c) CH_3Li, *n*-$C_5H_{11}Br$, DMSO, 72%; (d) BBr_3, CH_2Cl_2, 91%; (e) $H_2CCHOCH_2CH_3$, *p*-TSA, 92%.

Scheme 2. Synthesis of 3-Hept-1-ynyl-11-hydroxyhexahydrocannabinol[a]



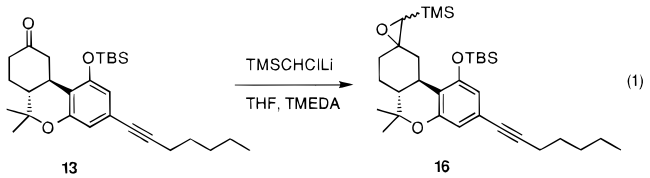
[a] (a) *n*-BuLi, THF, 0 °C, LiCuCN(imidazolide), −78 °C, (+)-apoverbenone, $BF_3{\cdot}Et_2O$; (b) *p*-TsOH, CH_3OH, 25 °C, 55% (two steps); (c) TMSOTf, CH_3NO_2, 5 °C, 89%; (d) *t*-$Bu(CH_3)_2SiCl$, imidazole, DMF, 25 °C, 92%; (e) $H_3COCHPPh_3$, PhH, 70 °C, 1.5 h; (f) Cl_3CCO_2H, $CH_2Cl_2(H_2O)$, 25 °C; (g) K_2CO_3, EtOH, 25 °C, 85% (three steps); (h) $NaBH_4$, EtOH, 0 °C; (i) *n*-Bu_4NF, THF, 0 °C, 95% (two steps).

proceed to completion. Nevertheless, hydrolytic cleavage of the phenolic protecting groups produced **11**, which was highly crystalline and could be isolated in 50−60% overall yield from **9**. In an attempt to improve the efficiency of this transformation, Lipshutz' newer technique was tried, in which imidazole is used in place of thiophene.[10] The yield of **11** was 40−55%, and unreacted **9** was easily recovered and recycled. Based on recovered starting material, the yield of **11** was 67%.

Exposure of **11** to catalytic amounts of trifluoromethanesulfonic (triflic) acid in dry nitromethane resulted in a clean and fast (4−6 h) reaction leading to **12**. This reaction was difficult to reproduce on larger scale. A clean, rapid, and reproducible process resulted when trimethylsilyl triflate was used in place of triflic acid, indicating that the reaction is inhibited by traces of water. Whether triflic acid or trimethylsilyl triflate is the catalytically active species is not clear.

The free phenolic hydroxyl in **12** was protected as the *tert*-butyldimethylsilyl (TBS) ether. Treatment of **13** with (methoxymethylene)triphenylphosphorane in benzene[11] produced a mixture of methyl enol ethers which were hydrolyzed to aldehyde diastereoisomers **14** and **15**.[12] Epimerization gave equatorial aldehyde **15** in 85% overall yield from **13**. Carbonyl reduction and desilylation led to **1** in 95% yield. HMQC, HMBC, and NOE correlations established the powerful anisotropic effects affecting the protons at C10. In the ^{1}H-NMR spectrum the strongly shielded axial proton is the furthest upfield signal at 0.75 ppm, while the equatorial proton appears at 3.25 ppm. The hydroxymethylene protons on C11 showed an interesting concentration dependency. In dilute solution they appear as a simple doublet in the ^{1}H-NMR spectrum, but at higher concentration the signal changed into a doublet of doublets. This is probably due to decreased rotation around the C9−C11 bond which may result from stacking of the molecules.

An alternative approach for the introduction of C11 was also examined (eq 1).[13] Exposure of **13** to the lithio anion of chloromethyltrimethylsilane led to diastereomeric epoxides **16**, along with unreacted **13**. The use of



(1)

excess reagent, or the addition of an aliquot during the reaction, had no effect upon the yield, which indicated that competing enolization was taking place. Exposure of **16** to catalytic $BF_3{\cdot}Et_2O$ led to a ca. 9/1 mixture of aldehydes **14** and **15**.[14] Epimerization as described above led to **15** in 79% overall yield. Although the Wittig process was more useful for accessing **15**, this

approach makes it possible to selectively prepare the thermodynamically less stable α-hydroxymethyl series.

Partial hydrogenation of **1** using Lindlar's catalyst in the presence of quinoline[15] was a slow process which produced (*Z*)-alkene **2** in 72% isolated yield, along with approximately 13% of unreacted **1**, an equal amount of the fully saturated compound, and traces of (*E*)-alkene **3**. A pure sample of **2** was isolated by HPLC. The isomerization of **2** to **3** was accomplished with thiophenol and catalytic 1,1′-azobis(cyclohexanecarbonitrile) (ACN) in refluxing benzene.[16]

The difficulties which were encountered during the partial hydrogenation of **1** were surprising since the process had been carried out successfully with **8** as a model. In striking contrast to **1**, partial hydrogenation of **8** proceeded in a highly selective manner, leading to the (*Z*)-alkene in 93% yield. The difference in reactivity between **1** and **8** may be due in part to differences in molecular shape which in the case of **1** preclude certain geometries for approach to the catalyst surface. Finally, the catalytic hydrogenation of **1** over 5% Pd/C led to the respective *n*-heptyl analog **4**.

Several features of this work are worthy of note. (1) The improved conditions for the cyclization of **11** to **12** have been applied successfully to the olivetol series and promise to be general. (2) Cuprates derived from resorcinol ethers are typically not very reactive and require specialized conditions, viz., activation of apoverbenone with a Lewis acid and use of the higher-order cuprate. The difficulty of separating the product of the cuprate reaction from the auxiliary ligand on copper is largely overcome by substituting imidazole for thiophene in the cuprate. (3) The selective synthesis of either **14** or **15** is possible by choice of reaction conditions for the homologation of **13**.

Receptor Binding Studies

The abilities of **1**−**4** to displace radiolabeled CP-55,-940 from purified rat forebrain synaptosomes and mouse spleen synaptosomes were determined as described in the methods. Figure 2 shows the displacement curves for these four novel cannabinoids, and their calculated K_i's are shown in Table 1.

Experimental Section

^{1}H- and ^{13}C-NMR spectra were recorded at 300 MHz, ^{1}H (75 MHz, ^{13}C), or 500 MHz, ^{1}H (125 MHz, ^{13}C), in either deuteriochloroform ($CDCl_3$) with chloroform (7.26 ppm, ^{1}H; 77.00 ppm, ^{13}C) or benzene-d_6 with benzene (7.15 ppm, ^{1}H; 128.0 ppm, ^{13}C) as an internal reference. Chemical shifts are given in δ; multiplicities are indicated as br (broadened), s (singlet), t (triplet), q (quartet), m (multiplet); coupling constants (J) are reported in hertz (Hz). Infrared spectra were recorded on a Perkin-Elmer IR 1430 spectrometer. Electron impact mass spectra were performed on a VG-70SE mass spectrometer. Mass spectral data are reported in the form of m/z (intensity relative to base = 100). Thin-layer chromatography (TLC) was performed on EM Reagents precoated silica gel 60 F-254 analytical plates (0.25 mm). Flash column chromatography was performed on Brinkmann silica gel (0.040−0.063 mm). Tetrahydrofuran (THF) and diethyl ether were distilled from sodium−benzophenone ketyl, *N*,*N*-dimethylformamide (DMF) and triethylamine (Et_3N) from calcium hydride, benzene from sodium, and dichloromethane (CH_2Cl_2) from phosphorus pentoxide. Other reagents were obtained commercially and used as received unless otherwise specified. All reactions were performed under a static nitrogen or argon atmosphere in flame-dried glassware. The purity and homogeneity of the products on which the high-resolution mass spectral data are reported were determined on the basis of a combination of chiral HPLC (Chiracel-OD, 2-propanol/hexane), 300 MHz ^{1}H-NMR (94%), and multiple elution TLC analysis.

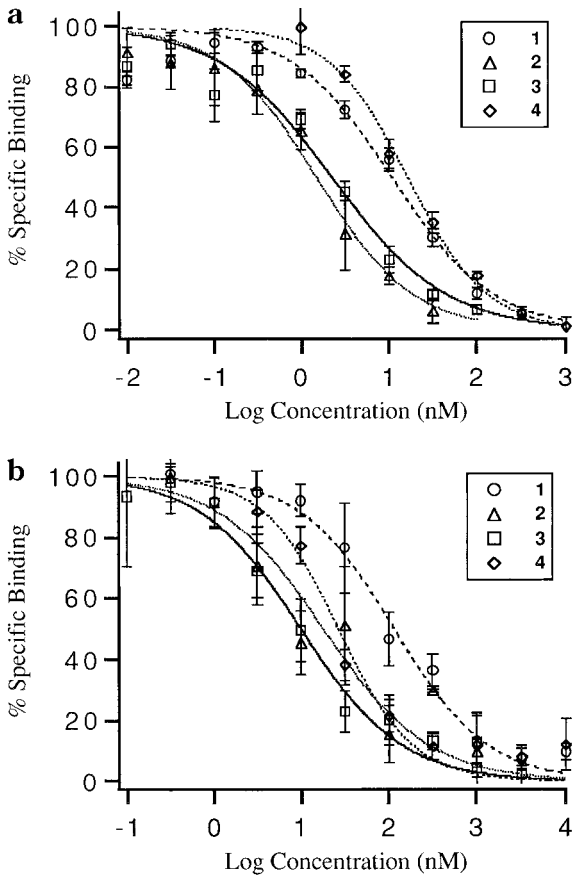


Figure 2. Concentration diplacement curves for compounds **1**−**4**: (a) displacement of specifically bound [^{3}H]CP-55,940 from a CB1-enriched rat brain microsome preparation and (b) displacement of specifically bound [^{3}H]CP-55,940 from a CB2-enriched mouse spleen preparation.

Table 1. K_i Values for Compounds **1**−**4**

	K_i (nM) (95% confidence limits)	
compd	brain	spleen
1	5.8 (5.3, 6.4)	61.6 (44.4, 85.5)
2	0.8 (0.6, 1.0)	9.5 (6.4, 14.2)
3	1.2 (1.0, 1.4)	5.3 (3.9, 7.3)
4	8.7 (7.8, 9.7)	14.3 (11.9, 17.1)
(−)-Δ^8-THC	47.6	39.3

3,5-Dimethoxyacetophenone (6). 3,5-Dimethoxybenzoic acid (**5**) (3.0 g, 16.5 mmol) was dissolved in 100 mL of THF in a 500 mL Morton flask and cooled to 0 °C. Methyllithium in ether (50.7 mL, 66 mmol) was added in a fast stream with vigorous stirring, and the solution was stirred at 0 °C for 2.5 h. Trimethylchlorosilane (43 mL, 344 mmol) was added rapidly from an addition funnel with vigorous stirring. The reaction mixture was allowed to warm to 25 °C during 40 min, after which time dilute HCl (0.5 N, 140 mL) was added. The reaction mixture was stirred for an additional 30 min. Ether was added, and the organic phase was washed with saturated $NaHCO_3$ and brine. The aqueous phase was extracted twice with ether, and the combined organic phase was dried over $MgSO_4$. Solvent evaporation followed by purification of the residue by flash chromatography on silica gel eluting with 15−18% ethyl acetate gradient in hexane gave 2.34 g (79% yield) of methyl ketone **6**: oil; IR (neat) 3090, 2970, 2840, 1680, 1600,

1360, 1260 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.04 (d, J = 2.0 Hz, 2H), 6.61 (t, J = 2.0 Hz, 1H), 3.79 (s, 6H), 2.53 (s, 3H).

(3,5-Dimethoxyphenyl)acetylene (7). A solution of *n*-butyllithium in hexane (12.6 mL, 29.1 mmol) was added to a solution of diisopropylamine (4.25 mL, 30.5 mmol) in 50 mL of THF at 0 °C. The reaction mixture was stirred at 0 °C for 2 min and at −78 °C for 10 min. Ketone **5** (5.0 mL, 27.7 mmol) was dissolved in 5 mL of THF and transferred to the reaction mixture via cannula. Stirring was continued at −78 °C for 2.5 h, after which time diethyl chlorophosphate (4.40 mL, 30.5 mmol) was added dropwise. The reaction mixture was stirred at −78 °C for 1 h and then slowly warmed to 25 °C during 1.5 h. A hexane solution of *n*-butyllithium (26.4 mL, 60.9 mmol) was added to a solution of diisopropylamine (8.70 mL, 62.3 mmol) in 100 mL of THF at −78 °C. The enol phosphate solution was cooled to −78 °C and added slowly to the solution of base via cannula. The ensuing mixture was allowed to warm to 25 °C during 5 h. The reaction was quenched with water, and the reaction mixture was diluted with ether/hexane (1:1). The organic phase was washed with 1 N HCl, the aqueous phase was extracted twice with ether/hexane, and the combined organic phases were washed with brine and dried over $MgSO_4$. Solvent evaporation followed by purification of the residue by flash chromatography on silica gel, eluting with 10% ethyl acetate in hexane, gave 4.08 g (91% yield) of acetylene **7**: oil; IR (neat) 3290, 3090, 2105, 1590, 1450, 1420, 1305, 1255 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 6.65 (d, J = 2.4 Hz, 2H), 6.47 (t, J = 2.4 Hz, 1H), 3.78 (s, 6H), 3.04 (s, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 160.4, 123.3, 110.2, 102.2, 83.6, 76.7, 55.3.

(3,5-Dimethoxyphenyl)-*n*-pentylacetylene (8). Acetylene **7** (4.08 g, 25.2 mmol) was dissolved in 11 mL of THF and cooled to 0 °C. A solution of methyllithium in ether (23.7 mL, 32.8 mmol) was added dropwise, and stirring was continued for 15 min at 0 °C. To the solution was added *n*-pentyl bromide (6.2 mL, 50.8 mmol) followed by 50 mL of DMSO. Stirring at 25 °C was continued overnight. The reaction was quenched with water and the mixture diluted with ether. The organic phase was washed with 4 × 25 mL of half-saturated brine and dried over $MgSO_4$. Solvent evaporation followed by purification of the residue by flash chromatography on silica gel, eluting with a gradient of 8−10% ethyl acetate in hexane, gave 4.13 g (72% yield) of alkyne **8**: oil; IR (neat) 3080, 2920, 2225, 1590, 1420, 1250 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 6.56 (d, J = 2.4 Hz, 2H), 6.40 (t, J = 2.4 Hz, 1H), 3.78 (s, 6H), 2.39 (t, J = 7.2 Hz, 2H), 1.63−1.57 (m, 2H), 1.45−1.34 (m, 4H), 0.92 (t, J = 7.2 Hz, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 160.5, 125.4, 109.3, 100.9, 90.1, 80.6, 55.2, 31.2, 28.4, 22.3, 19.4, 14.0; MS m/z 232 (M^+, 100), 203 (80), 189 (69), 177 (85), 151 (27). Exact mass calculated for $C_{15}H_{20}O_2$, 232.1463; found, 232.1448.

[3,5-Bis(2-ethoxyethoxy)phenyl]-*n*-pentylacetylene (9). Alkyne **8** (4.13 g, 17.8 mmol) was dissolved in 40 mL of CH_2Cl_2. 1-Methyl-1-cyclohexene (4.0 mL, 33.8 mmol) was added, and the solution was cooled to −78 °C. Boron tribromide (1.0 M in CH_2Cl_2, 53.0 mL, 53.0 mmol) was diluted with 20 mL of CH_2Cl_2, shaken with anhydrous K_2CO_3, cooled to −78 °C, and added dropwise to the reaction mixture via cannula. The temperature was slowly allowed to rise to 25 °C during 7 h. The reaction mixture was poured into vigorously stirring saturated aqueous $NaHCO_3$ at 0 °C. Stirring was continued overnight. The aqueous phase was extracted with 2 × 50 mL of ether, and the combined organic phases were washed with brine and dried over $MgSO_4$. Solvent evaporation was followed by filtration through silica gel eluting with 40% ethyl acetate in hexane to give 3.31 g (91% yield) of the resorcinol: air-sensitive oil; IR (neat) 3350 (br), 2930, 2860, 2240, 1590, 1450, 1255 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 6.65 (br s, 2H), 6.50 (d, J = 2.1 Hz, 2H), 6.32 (J = 2.1 Hz, 1H), 2.37 (t, J = 6.9 Hz, 2H), 1.59 (p, J = 7.2 Hz, 2H), 1.41−1.35 (m, 4H), 0.93 (t, J = 6.9 Hz, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 156.2, 125.8, 111.3, 103.0, 90.7, 80.1, 31.1, 28.4, 22.2, 19.3, 14.0; MS m/z 204 (M^+, 9), 147 (91), 86 (64), 84 (100). Exact mass calculated for $C_{13}H_{16}O_2$, 204.1150; found, 204.1154.

The material from the preceding step was quickly protected as the bis(ethoxyethyl) ether. The resorcinol (2.50 g, 12.2 mmol) was dissolved in 40 mL of ether and transferred via cannula to a reaction flask containing predried *p*-toluenesulfonic acid (50 mg, 2 mol %), and the solution was cooled to 0 °C. Ethyl vinyl ether (3.7 mL, 67.1 mmol) was diluted with 3.7 mL of ether at 0 °C. The vinyl ether solution was dried over molecular sieves (4 Å) for 15 min and then tranferred to the resorcinol solution via cannula. The reaction mixture was stirred at 0 °C for 5 h and then poured into vigorously stirring saturated aqueous $NaHCO_3$ at 0 °C. The aqueous phase was extracted with 2 × 40 mL of ether. The combined organic phase was washed with brine and dried over $MgSO_4$. Solvent evaporation followed by purification by flash column chromatography, eluting with 7% ethyl acetate and 1% triethylamine in hexane, gave 3.92 g (92% yield) of **9** as a mixture of diastereoisomers (due to the stereogenic carbon of each of the ethoxyethyl groups): IR (neat) 3080, 2930, 2230, 1585, 1380, 1250, 1210, 1175 cm^{-1}; ^{1}H-NMR (300 MHz, C_6D_6) δ 7.12 (s, 2H), 6.93 (s, 1H), 5.14 (q, J = 5.4 Hz, 2H), 3.58−3.53 (m, 2H), 3.27−3.22 (m, 2H), 2.21 (t, J = 7.2 Hz, 2H), 1.44 (p, J = 7.5 Hz, 2H), 1.28 (d, J = 5.4 Hz, 6H), 1.23−1.14 (m, 4H), 1.00 (t, J = 7.2 Hz, 6H), 0.80 (t, J = 7.2 Hz, 3H); MS m/z 348 (M^+, 0.2), 218 (67), 204 (72), 189 (42), 175 (59), 147 (45), 73 (100). Exact mass calculated for $C_{21}H_{32}O_4$, 348.2300; found, 348.2279.

Cuprate Addition to Apoverbenone. Preparation of 10. Protected resorcinol **9** (1.05 g, 3.05 mmol) was dissolved in 55 mL of THF and cooled to 0 °C. A solution of *n*-butyllithium in hexane (2.4 mL, 3.66 mmol) was added very slowly (over ca. 10 min), and the reaction mixture was stirred at 0 °C for 1 h and at 25 °C for 1.5 h and subsequently cooled to −78 °C. Imidazole (207 mg, 3.05 mmol) was dissolved in 28 mL of THF and cooled to −78 °C. A solution of *n*-butyllithium in hexane (2.20 mL, 3.36 mmol) was added, and stirring was continued at −78 °C for 1 h. The solution was removed from the dry ice/acetone bath and allowed to warm to 25 °C. Cuprous cyanide (327 mg, 3.65 mmol) was added in small portions via an internal glass connection while the reaction mixture was stirred vigorously at 25 °C. Stirring at 25 °C was continued for 5 min, after which time the reaction mixture was cooled to −78 °C (green solution). The lithiated resorcinol was added slowly to this solution via cannula. As soon as the addition was complete, the reaction mixture was cooled in an ice bath for 20 min (yellow solution) and then cooled once again to −78 °C. Apoverbenone (331 mg, 2.44 mmol) was dissolved in 3 mL of THF. This solution was dried over molecular sieves (4 Å) for 15 min and then cooled to −78 °C. Boron trifluoride etherate (0.30 mL, 2.44 mmol) was added, the solution of Lewis acid−enone complex was transferred to the cuprate mixture via cannula, and stirring at −78 °C was continued for 2 h. The reaction was quenched with concentrated NH_4OH/saturated NH_4Cl (1:9), and 50 mL of ether was added. The aqueous phase was extracted with 2 × 40 mL of ether. The combined organic phase was washed with brine and dried over $MgSO_4$. Solvent evaporation followed by purification by flash column chromatography, eluting with a gradient of 7−10% ethyl acetate in hexane, gave 728 mg of crude cuprate adduct which was contaminated with ca. 20 mol % of unreacted apoverbenone (pure product ca. 646 mg).

This mixture was dissolved in 10 mL of methanol, and *p*-toluenesulfonic acid (32 mg, 4 mol %) was added. The reaction mixture was stirred at 25 °C overnight. Most of the methanol was removed in vacuo, and the concentrated solution was diluted with ether and washed with saturated $NaHCO_3$/brine (1:1). The aqueous phase was extracted with 2 × 40 mL of ether. The combined organic phase was washed with brine and dried over $MgSO_4$. Solvent evaporation followed by purification by flash column chromatography, eluting with 20% ethyl acetate in hexane, gave 461 mg of diol **11** (55% yield, 67% based on recovered **9**): mp 167 °C; $[\alpha]_D$ +54.7° (c = 0.66, $CHCl_3$, 25 °C); IR (neat) 3350 (br), 2930, 2860, 2240, 1695, 1610, 1590, 1450, 1255 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 6.39 (s, 2H), 5.84 (br s, 2H), 3.96 (t, J = 8.1 Hz, 1H), 3.45 (dd, J = 18.9, 7.6 Hz, 1H), 2.68−2.40 (m, 2H) 2.37−2.28 (m, 1H), 2.35 (t, J = 7.2 Hz, 2H), 1.56 (p, J = 7.2 Hz, 2H), 1.42−1.25 (m, 6H), 1.35 (s, 3H), 0.99 (s, 3H), 0.90 (t, J = 7.1 Hz, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 219.2, 155.3 (2C), 122.6 (2C), 116.8, 111.6, 90.1, 79.9, 58.0, 46.7, 42.3, 37.6, 31.1, 29.6, 28.4, 26.1, 24.5, 22.2 (2C), 19.3, 14.0; MS m/z 340 (M^+, 84), 338

(58), 297 (59), 257 (100), 241 (66), 217 (88). Exact mass calculated for $C_{22}H_{28}O_3$, 340.2065; found, 340.2038.

Cyclization of the Dihydrobenzopyran Ring. Synthesis of 12. Resorcinol **11** (164 mg, 0.48 mmol) was dissolved in 27 mL of dry nitromethane, and the solution was cooled to 5 °C. Trimethylsilyl triflate (0.29 M in nitromethane, 0.60 mL, 34 mol %) was added dropwise. Stirring was continued for 1.5 h while the temperature was allowed to rise to 25 °C. The reaction was quenched with saturated aqueous $NaHCO_3$/brine (1:1), and 60 mL of ether was added. The aqueous phase was extracted with 2 × 40 mL of ether, and the combined organic phase was washed with brine and dried over $MgSO_4$. Solvent evaporation followed by filtration through silica gel, eluting with 25% ethyl acetate in hexane, gave 146 mg (89% yield) of **12**: oil; $[\alpha]_D$ −54.4° (c = 0.16, $CHCl_3$, 25 °C); IR (neat) 3230 (br), 2930, 2860, 2230, 1695, 16.15, 1570, 1415, 1360, 1100 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.29 (br s, 1H), 6.46 (s, 1H), 6.44 (s, 1H), 4.03 (dt, J = 14.7, 1.8 Hz, 1H), 2.87 (td, J = 11.1, 3.6 Hz, 1H), 2.62 (br d, J = 15.6 Hz, 1H), 2.54−2.42 (m, 2H), 2.35 (t, J = 6.9 Hz, 2H), 2.18−2.12 (m, 1H), 2.10 (q, J = 14.7 Hz, 1H), 1.94 (td, J = 11.7, 2.7 Hz, 1H), 1.60−1.25 (m, 6H), 1.46 (s, 3H), 1.09 (s, 3H), 0.91 (t, J = 6.9 Hz, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 215.6, 155.5, 154.7, 123.5, 112.8, 111.0, 110.3, 89.9, 80.1, 76.8, 47.7, 44.2, 40.6, 34.9, 31.1, 28.4, 27.6, 26.9, 22.2, 19.3, 18.7, 14.0; MS m/z 340 (M^+, 100), 325 (36), 297 (24), 257 (88), 217 (23), 175 (20). Exact mass calculated for $C_{22}H_{28}O_3$, 340.2065; found, 340.2041.

Silyl Ether 13. Ketophenol **12** (146 mg, 0.43 mmol) was dissolved in DMF containing *tert*-butyldimethylsilyl chloride (1.05 mL of a 1.11 M in DMF, 0.96 mmol) at 25 °C. Imidazole (100 mg, 1.45 mmol) was added to the solution after the starting material had dissolved. The reaction mixture was stirred at 25 °C overnight, and the reaction was subsequently quenched with water. Addition of 40 mL of ether/hexane (1:1) was followed by extraction of the aqueous phase with 2 × 25 mL of hexane. The combined organic phase was washed with brine and dried over $MgSO_4$. Solvent evaporation was followed by purification by filtration through silica gel, eluting with 10% ethyl acetate in hexane, to produce 180 mg (92% yield) of the silyl ether **13**: oil; $[\alpha]_D$ −45.7° (c = 1.68, EtOH, 25 °C); IR (neat) 2970, 2920, 2850, 2220, 1705, 1600, 1545, 1460, 1400, 1355, 1250, 830 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 6.53 (d, J = 1.2 Hz, 1H), 6.38 (d, J = 1.2 Hz, 1H), 3.72 (dt, J = 14.7, 1.8 Hz, 1H), 2.71 (td, J = 11.8, 3.3 Hz, 1H), 2.55 (br d, J = 15.6 Hz, 1H), 2.45−2.35 (m, 2H), 2.35 (t, J = 6.9 Hz, 2H), 2.16−2.09 (m, 1H), 2.06 (q, J = 14.7 Hz, 1H), 1.93 (td, J = 11.7, 2.7 Hz, 1H), 1.60−1.25 (m, 6H) 1.45 (s, 3H), 1.06 (s, 3H), 1.00 (s, 9H), 0.91 (t, J = 6.9 Hz, 3H), 0.26 (s, 3H), 0.17 (s, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 209.9, 154.5, 154,4, 123.3, 115,4, 114.4, 114.2, 90.0, 80.1, 76.7, 47.8, 45.5, 40.7, 35.2, 31.1, 28.4, 27.6, 26.7, 25.9 (3C), 22.2, 19.3, 18.5, 18.2, 14.0, −3.3, −3.7; MS m/z 454 (M^+, 36), 397 (100), 341 (10), 315 (8), 287 (7). Exact mass calculated for $C_{28}H_{42}O_3Si$, 454.2871; found, 454.2905.

Aldehyde 15. (Methoxymethyl)triphenylphosphonium chloride (247 mg, 0.72 mmol) was suspended in 6 mL of dry benzene. Sodium *tert*-amylate (1.24 M in benzene, 0.58 mL, 0.72 mmol), from NaH and *tert*-amyl alcohol, was added, and the reaction mixture was stirred for 5 min at 25 °C. Protected ketone **12** (107 mg, 0.24 mmol) was dissolved in the minimum amount of benzene and transferred to the solution of the ylide via cannula. The reaction mixture was stirred at 70 °C for 1.5 h. Quenching with saturated aqueous NH_4Cl, dilution with ether, and extraction (3 × 10 mL) with ether produced an organic phase which was washed with brine, dried ($MgSO_4$), and evaporated. The residue was dissolved in 16 mL of dichloromethane, 155 mg (ca. 0.9 mmol) of wet trichloroacetic acid was added, and the mixture was stirred at 25 °C for 30 min. The reaction was quenched with saturated aqueous $NaHCO_3$/brine (1:1), and the mixture was diluted with dichloromethane. The aqueous phase was extracted with 3 × 20 mL of dichloromethane, and the combined organic extract was washed with brine, dried ($MgSO_4$), and evaporated. The residue which consisted of a mixture of aldehydes **14** and **15** was dissolved in 10 mL of ethanol and added to 71 mg (0.54 mmol) of powdered potassium carbonate suspended in 10 mL of ethanol. The heterogeneous mixture was stirred at 25 °C for 4 h; then the reaction was quenched with saturated aqueous NaH_2PO_4 and the mixture diluted with ether. The aqueous phase was extracted with 4 × 20 mL of ether; the combined organic extracts were dried ($MgSO_4$), evaporated, and purified by flash column chromatography, eluting with 5% ethyl acetate in hexane, to produce 94 mg (85% overall yield) of **15**: oil; $[\alpha]_D$ −82.2° (c = 0.59, EtOH, 25 °C); IR (neat) 3060, 2920, 2850, 2710, 2230, 1725, 1600, 1550, 1460, 1405, 1355, 1350, 1250, 1135, 1060, 835 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.62 (s, 1H), 6.50 (d, J = 1.2 Hz, 1H), 6.38 (d, J = 1.2 Hz, 1H), 3.42 (br d, J = 12.3 Hz, 1H), 2.44−2.33 (m, 1H), 2.40 (td, J = 10.8, 2.4 Hz, 1H), 2.35 (t, J = 6.9 Hz, 2H), 2.10 (br d, J = 12.9 Hz, 1H), 1.98 (br d, J = 12.9 Hz, 1H), 1.63−1.11 (m, 9H), 1.36 (s, 3H), 1.03 (s, 3H), 0.99 (s, 9H), 0.91 (t, J = 6.9 Hz, 3H), 0.90 (m, 1H), 0.28 (s, 3H), 0.16 (s, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 203.3, 154.7 (2C), 154.7, 122.9, 116.1, 114.3, 114.2, 89.7, 80.3, 76.6, 50.5, 49.0, 35.6, 31.1, 30.2, 28.4, 27.4, 26.9, 25.9, 25.8 (3C), 22.2, 19.3, 18.6, 18.2, 14.0, −3.7, −4.3; MS m/z 468 (M^+, 38), 411 (48), 167 (36), 149 (100), 73 (31). Exact mass calculated for $C_{29}H_{44}O_3Si$, 468.3059; found, 468.3071.

Diol 1. Aldehyde **15** (45 mg, 0.124 mmol) was dissolved in 1.5 mL of EtOH and cooled to 0 °C. A solution of 11 mg (0.289 mmol) of $NaBH_4$ dissolved in 0.5 mL of EtOH was added via cannula. The reaction mixture was stirred at 0 °C for 30 min, the reaction quenched with water, and the mixture diluted with ether. The aqueous phase was extracted twice with ether, and the combined organic extract was washed with brine and dried ($MgSO_4$). The solvent was evaporated, and the crude product was dissolved in 3 mL of THF and cooled to 0 °C. Tetrabutylammonium fluoride (48 mg, 0.188 mmol) in 0.7 mL of THF was added, the mixture was stirred at 0 °C for 45 min, and then the reaction was quenched with water. Ether was added (5 mL), and the aqueous phase was extracted with 2 × 10 mL of ether. The combined organic extract was washed with brine, dried ($MgSO_4$), evaporated, and purified by flash chromatography (35% ethyl acetate in hexane) to produce 34 mg of **1** (95% overall yield): oil; $[\alpha]_D$ −110.9° (c = 1.02, EtOH, 25 °C); IR (neat) 3320 (br), 2920, 2850, 2230, 1610, 1455, 1410, 1260, 1035 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 6.45 (d, J = 1.4 Hz, 1H), 6.30 (d, J = 1.4 Hz, 1H), 6.00 (br s, 1H), 3.55 (dd, J = 10.6, 5.9 Hz, 1H), 3.48 (dd, J = 10.6, 5.9 Hz, 1H), 3.25 (br d, J = 12.5 Hz, 1H), 2.45 (td, J = 11.3, 2.6 Hz, 1H), 2.34 (t, J = 6.9 Hz, 2H), 1.91−1.88 (m, 2H), 1.79−1.75 (m, 1H), 1.56 (p, J = 7.0 Hz, 2H), 1.46 (td, J = 11.8, 1.7 Hz, 1H), 1.43−1.29 (m, 4H), 1.35 (s, 3H), 1.11 (m, 2H), 1.03 (s, 3H), 0.91 (t, J = 7.2 Hz, 3H), 0.75 (q, J = 11.8 Hz, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 154.9, 154.9, 122.7, 113.5, 113.2, 110.3, 89.7, 80.2, 77.1, 68.5, 49.3, 40.4, 35.1, 33.0, 31.0, 29.6, 28.4, 27.6, 27.4, 22.2, 19.3, 18.9, 14.0; MS m/z 356 (M^+, 100), 313 (46), 217 (95), 149 (33), 121 (23), 95 (34). Exact mass calculated for $C_{23}H_{32}O_3$, 356.2351; found, 356.2337.

(*Z*)-Alkene 2. Acetylenic diol **1** (111 mg, 0.312 mmol) was dissolved in 3.5 mL of benzene. Lindlar catalyst (2.5% on $CaCO_3$, 53 mg, 4 mol %) was suspended in 1.45 mL of a 0.03 M solution of quinoline in benzene under ca. 1 atm of hydrogen. The solution of **1** was added via cannula, and the reaction mixture was stirred for 2.5 h. The catalyst was removed by filtration through Celite and washed with ether, and the solvent was evaporated to give the crude product. Purification was effected by HPLC (Whatman Partisil 10 M9/50, normal phase, 35% ethyl acetate in hexane) to produce alkene **2** in 65% yield: oil; $[\alpha]_D$ −84.6° (c = 0.74, EtOH, 25 °C); IR (neat) 3350 (br), 2920, 2850, 1615, 1565, 1425, 1400, 1260, 1130, 1040, 850 cm^{-1}; ^{1}H-NMR (500 MHz, C_6D_6) δ 6.85 (s, 1H), 6.39 (d, J = 11.8 Hz, 1H), 6.08 (s, 1H), 5.59 (dt, J = 11.8, 7.1 Hz, 1H), 5.34 (br s, 1H), 3.48 (br d, J = 12.8 Hz, 1H), 3.25 (dd, J =10.4, 5.6 Hz, 1H), 3.23 (dd, J = 10.4, 6.5 Hz, 1H), 2.53 (td, J = 10.9, 2.4 Hz, 1H), 2.38 (qd, J = 7.5, 1.4 Hz, 2H), 1.65−1.63 (m, 1H), 1.58−1.54 (m, 2H), 1.42 (td, J = 10.8, 1.9 Hz, 1H), 1.33 (p, J = 7.5 Hz, 2H), 1.28 (s, 3H), 1.20−1.14 (m, 4H), 0.98 (s, 3H), 0.84−0.78 (m, 2H), 0.83 (t, J = 7.1 Hz, 3H), 0.71 (q, J = 11.8 Hz, 1H); ^{13}C-NMR (125 MHz, C_6D_6) δ 156.0, 155.7, 137.7, 133.1, 129.1, 112.2, 111.0, 108.9, 76.8, 68.6, 49.7, 40.7, 35.6, 33.7, 31.8, 30.1, 29.7, 29.3, 27.8, 27.7, 22.9, 19.1, 14.2;

MS *m/z* 358 (M^+, 100), 315 (45), 297 (17), 219 (64), 175 (16). Exact mass calculated for $C_{23}H_{34}O_3$, 358.2508; found, 358.2500.

***(E)*-Alkene 3.** Crude (*Z*)-alkene **2** from the semihydrogenation of **1** (86 mg, 0.168 mmol, ca. 70% *Z*) was dissolved in 4.3 mL of benzene containing thiophenol (0.02 M) and ACN (0.006 M). The reaction mixture was heated to reflux for 4 h. After cooling to 25 °C, the reaction mixture was diluted with ether and washed twice with brine. The aqueous phase was extracted with 3 × 10 mL of ether; the combined organic extracts were dried ($MgSO_4$) and evaporated. Filtration of the residue through silica gel (50% ethyl acetate in hexane) followed by purification by HPLC (Whatman Partisil 10 M9/50 normal phase, 35% ethyl acetate in hexane) produced 44 mg (74% yield) of **3**: oil; $[\alpha]_D$ −54.4° (*c* = 0.24, EtOH, 25 °C); IR (neat) 3350 (br), 2920, 2850, 1660, 1630, 1600, 1460, 1410, 1380, 1260, 1090, 1000, 820 cm^{-1}; ^{1}H-NMR (500 MHz, C_6D_6) δ 6.84 (s, 1H), 6.29 (d, *J* = 15.6 Hz, 1H), 6.13 (dt, *J* = 15.6, 7.1 Hz, 1H), 5.88 (s, 1H), 4.22 (br s, 1H), 3.34 (br d, *J* = 12.8 Hz, 1H), 3.27 (dd, *J* = 10.4, 6.1 Hz, 1H), 3.23 (dd, *J* = 10.4, 6.6 Hz, 1H), 2.53 (td, *J* = 10.9, 2.4 Hz, 1H), 2.38 (q, *J* = 6.6 Hz, 2H), 1.73−1.70 (m, 1H), 1.57−1.52 (m, 2H), 1.42 (td, *J* = 10.3, 2.4 Hz, 1H), 1.37−1.24 (m, 6H), 1.28 (s, 3H), 0.97 (s, 3H), 0.90−0.77 (m, 2H), 0.87 (t, *J* = 7.1 Hz, 3H), 0.70 (q, *J* = 11.8 Hz, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 156.0, 155.7, 137.9, 130.6, 130.2, 112.0, 108.6, 105.3, 76.7, 68.4, 49.6, 40.8, 35.7, 33.6, 31.7, 30.2, 29.9, 29.5, 27.8, 27.6, 22.9, 19.1, 14.2; MS *m/z* 358 (M^+, 100), 315 (28), 297 (12), 271 (20), 219 (71). Exact mass calculated for $C_{23}H_{34}O_3$, 358.2508; found, 358.2503.

Alkane 4. A mixture of acetylenic diol **1** (7.8 mg, 0.022 mmol) and 10% palladium on carbon in 0.4 mL of absolute ethanol was stirred at room temperature under 1 atm of hydrogen for 5 h. The catalyst was removed by filtration through Celite using diethyl ether as solvent. The solvents were then removed, and the residue was chromatographed on silica gel using 30% diethyl ether−petroleum ether as eluent to afford 6.5 mg (82%) of **4**: oil; IR (neat) 3350 (br), 2920, 2850, 1620, 1575, 1450, 1135, 1040 cm^{-1}; ^{1}H-NMR (300 MHz, C_6D_6) δ 6.64 (d, *J* = 0.9 Hz, 1H), 5.79 (d, *J* = 0.9 Hz, 1H), 4.90 (br s, 1H), 3.45 (br d, *J* = 12.0 Hz, 1H), 3.25 (d, *J* = 6.0 Hz, 2H), 2.51 (td, *J* = 11.1, 2.4 Hz, 1H), 2.45 (t, *J* = 7.8 Hz, 2H), 1.69−1.63 (m, 1H), 1.59−1.52 (m, 2H), 1.42 (td, *J* = 10.3, 2.4 Hz, 1H), 1.37−1.22 (m, 10H), 1.28 (s, 3H), 0.99 (s, 3H), 0.90−0.77 (m, 2H), 0.87 (t, *J* = 7.1 Hz, 3H), 0.71 (q, *J* = 12.0 Hz, 1H); MS *m/z* 360 (M^+, 100), 358 (35), 317 (63), 276 (90), 221 (82). Exact mass calculated for $C_{23}H_{36}O_3$, 360.2664; found, 360.2635.

Pharmacological Methods. Rat forebrain synaptosomal membranes were prepared by the method of Dodd et al.[17] and were used to assess the affinity of **1**−**4** for the CB1 binding sites. Mouse spleen membranes were used as the source material for CB2 receptors. The displacement of specifically bound tritiated CP-55,940 from these membranes using a standard filtration assay was used to determine the IC_{50} for the test compounds. Briefly, 40 μg of protein was incubated for 1 h at 30 °C in the presence of 0.76 nM [^{3}H]CP-55,940 and various concentrations of test compound, final volume 200 μL. Nonspecific binding was defined by 100 nM cold CP-55,940. The incubation was terminated by rapid filtration and washing, and the amount of specifically bound [^{3}H]CP-55,940 was determined. Data normalized between 0 and 100% specific binding were plotted against log concentration of test compound, and IC_{50} values were determined from the average of at least three experiments run in duplicate, by fitting to a four-variable nonparametric equation, holding the maximum to 100 and the minimum to 0. IC_{50} values were converted to K_i values according to the method of Cheng and Prusoff.[18]

Molecular Modeling. Molecular modeling was carried out with the Tripos SYBYL molecular modeling package on an Indigo2 SGI workstation. A molecular model of Δ^9-THC was initially generated from the X-ray crystallographic data of Δ^9-tetrahydrocannabinolic acid[19] and energy-minimized using the Tripos program. The minimum energy conformation of Δ^9-THC was then used as a starting template, and the structures of **1**−**4** were generated by deletion and/or addition of atoms at standard bond lengths and bond angles. Dihedral drives were used to probe the rotational space of the side chain and calculate rotational energy barriers. Intervals of 5° were used for single-bond rotations and 10° for two-bond rotations. Each sampled conformer was minimized with a two-step minimization: steepest descent method for the first 100 iterations and then conjugate gradient method until the maximum derivative was less than 0.001 kcal mol^{-1} $Å^{-1}$.

Discussion

A review of the existing literature reveals that the cannabinoid side chain plays a major role in determining the drug's potency, indicative of a hydrophobic pocket in the receptor. Although a considerable number of structure−activity correlations have dealt with the cannabinoid side chain, most of these have focused on chain length, its branching, or the introduction of heteroatoms,[1,2,20] and little attention has been given to stereochemical considerations. This present contribution has sought to restrict rotation around the C1′−C2′ bond through the introduction of double or triple bonds to obtain two 1′-alkenes (cis and trans) and the corresponding 1′-alkyne side chain analogs. The flexible *n*-heptyl analog was synthesized and used as the prototype in our comparisons. Our design has also incorporated in the above group of analogs pharmacophoric features that are expected to lead to optimal interaction with the cannabinoid receptor (CB1). These include a seven-carbon side chain and a 9β-hydroxymethyl group as the northern aliphatic hydroxyl pharmacaphore.

Our study was also extended to include the newly discovered cannabinoid receptor subtype CB2. The affinity of all four analogs for the two receptors was obtained by a displacement binding assay using the standard cannabinoid radioligand [^{3}H]CP-55,940 and suitable membrane preparations known to contain CB1 and CB2 receptors. While the rat brain has been shown to be a reliable source for CB1, there is still no standard CB2 preparation. Recent work has utilized membranes from cell lines transfected with the CB2 receptors.[21] In our laboratory we have found the mouse spleen to be an excellent source of CB2,[22] a finding congruent with an earlier report by Kaminski et al.[23]

Our results indicate that all the side chain analogs reported here have relatively high affinities for both CB1 and CB2, thus supporting earlier SAR[1,2] according to which seven carbon chains in cannabinoids are associated with high potencies and affinities. Although this observation appears to be true for both CB1 and CB2, the affinities for the CB2 were invariably somewhat lower. This observation may suggest different side chain SAR criteria for CB2, especially with regard to side chain length and branching.

The data clearly indicate that the *cis*-alkene analog **2** had the highest affinity for CB1 followed by the *trans*-alkene **3**. The parent *n*-heptyl had the lowest affinity, while the l′-alkyne analog was intermediate.

Our results also suggest differences between CB1 and CB2 with regard to classical cannabinoid side chain SAR. Of all the analogs, **2** showed the widest separation in affinities for CB1 and CB2, while the more flexible *n*-heptyl analog **4** showed the smallest separation. It is difficult at this time to fully explain these results in terms of ligand−receptor interactions. This task is rendered difficult by the fact that all analogs discussed here still possess a large degree of flexibility. Nevertheless, the stereochemical differences between analogs with respect to their abilities for optimal interactions

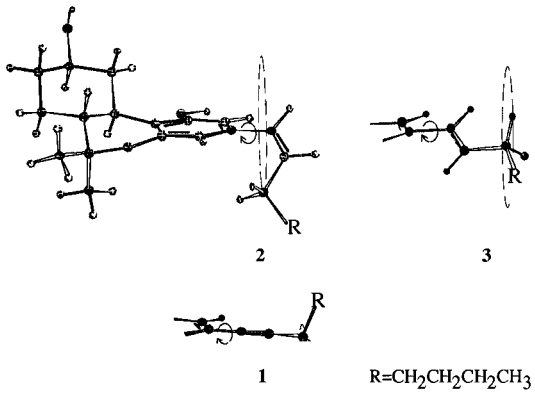


Figure 3. Rotation around the C1′−C2′ bond restricted in the three cannabinoids (**1**−**3**). As a result these analogs experience different conformational spaces upon rotation around the Ar−C1′ bond.

with the CB receptor sites of action are more visible if we explore the differences in available conformational space for the analogs in question. An exploration of the conformational space is shown in Figure 3.

It is interesting to note that the side chain in **2** is expected to orient in a manner similar with the dimethylheptyl analogs[24] running perpendicular to the long axis of the tricyclic system and being in closest proximity with the phenolic ring when compared with the other analogs. Conversely the alkyne analog would orient furthest from the phenolic ring. There is also an interesting similarity between the pharmacophorically optimal *cis*-hept-l′-ene chain and that of the last seven carbons of the arachidonic acid portion of the putative native ligand anandamide.

The results presented here are encouraging and lead us to the prediction that stereochemically defined side chain analogs of classical cannabinoids can define the requirements for interaction with CB receptor sites and open the door for compounds which are selective between CB1 and CB2. These goals are currently being pursued through design and synthesis of other more conformationally restricted side chain cannabinoids.

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