Classical/Nonclassical Hybrid Cannabinoids: Southern Aliphatic Chain-Functionalized C-6β Methyl, Ethyl, and Propyl Analogues

David J. Drake,[†] Rader S. Jensen,[†] Jakob Busch-Petersen,[†] Joel K. Kawakami,[†] M. Concepcion Fernandez-Garcia,[†] Pusheng Fan,[‡] Alexandros Makriyannis,*[,‡] and Marcus A. Tius*[,†]

Department of Chemistry, University of Hawaii, 2545 The Mall, Honolulu, Hawaii 96822, and Department of Medicinal Chemistry, School of Pharmacy, University of Connecticut, 372 Fairfield Road, Storrs, Connecticut 06269

Received September 27, 1996

The stereoelectronic requirements for interaction of the southern aliphatic hydroxyl of cannabimimetic pharmacophores with the CB1 and CB2 receptors are explored. The stereoselective syntheses of three series of classical/nonclassical hybrid cannabinoids are described. These compounds were designed to investigate the importance of the southern aliphatic hydroxyl (SAH) pharmacophore for cannabimimetic activity. Variation in the chain length of the SAH moiety in these 6β-(hydroxyalkyl)dihydrobenzopyran analogues, from 6β-hydroxymethyl to 6β-(ω-hydroxyethyl) and 6β-(ω-hydroxypropyl), and the effects of replacing the hydroxyl functionality by hydride and iodide are reported. Our results indicate that the SAH pharmacophore has less pronounced effects than the C-3 aliphatic chain on cannabinoid activity. Furthermore, it appears that this southern molecular component is capable of interacting with two different subsites on the receptor and that the nature of this interaction is determined by the terminal substituent on the C-6β alkyl group. One of the subsites can accommodate the relatively polar SAH pharmacophore, while the second subsite interacts with more hydrophobic C-6β substituents and can accommodate large spherical pharmacophores separated by three methylene carbons from the tricyclic cannabinoid template.

Introduction

The broad spectrum of pharmacological properties exhibited by cannabis is well-known, and a great deal of effort has gone into the search for therapeutically useful agents based on the parent structure of Δ^9-THC (Chart 1).[1] A large number of analogues have been synthesized and tested for biological activity and pharmacological selectivity.[2] The recognition of two distinct cannabinoid receptors (CB1 and CB2), one first identified in the central nervous system[3] (CB1) and the other exclusively found in the periphery (CB2),[4,5] and the discovery of an endogenous ligand,[6] arachidonyl ethanolamide (anandamide), has led to efforts to define the structural requirements for receptor specificity.[2]

Four principal pharmacophores within the cannabinoid structure have been associated with cannabimimetic activity.[2,7] These include a phenolic hydroxyl at C-1 and an aliphatic side chain attached to the phenolic ring at C-3, both of which are present in the natural tetrahydrocannabinol constituents found in cannabis. Addition of a 'northern' aliphatic hydroxyl (NAH) at the C-9 or C-11 position leads to increased activity, providing the hydroxyl or hydroxymethyl at C-9 has a β-equatorial configuration, such as in 9-nor-9β-hydroxyhexahydrocannabinol (HHC, **1**).[8] The fourth pharmacophore was identified from work with nonclassical cannabinoids, the best known representative of which is CP-55,940 (**2**).[7b] The analogues in this class of cannabimimetic agents do not contain the pyran ring of the classical cannabinoids but possess a second aliphatic hydroxyl group in the 'southern' portion of the molecule. This southern aliphatic hydroxyl (SAH)[2] has been shown to produce a significant increase in activity. This important region of the molecule is the subject of the current study.

Analogue Design Strategy

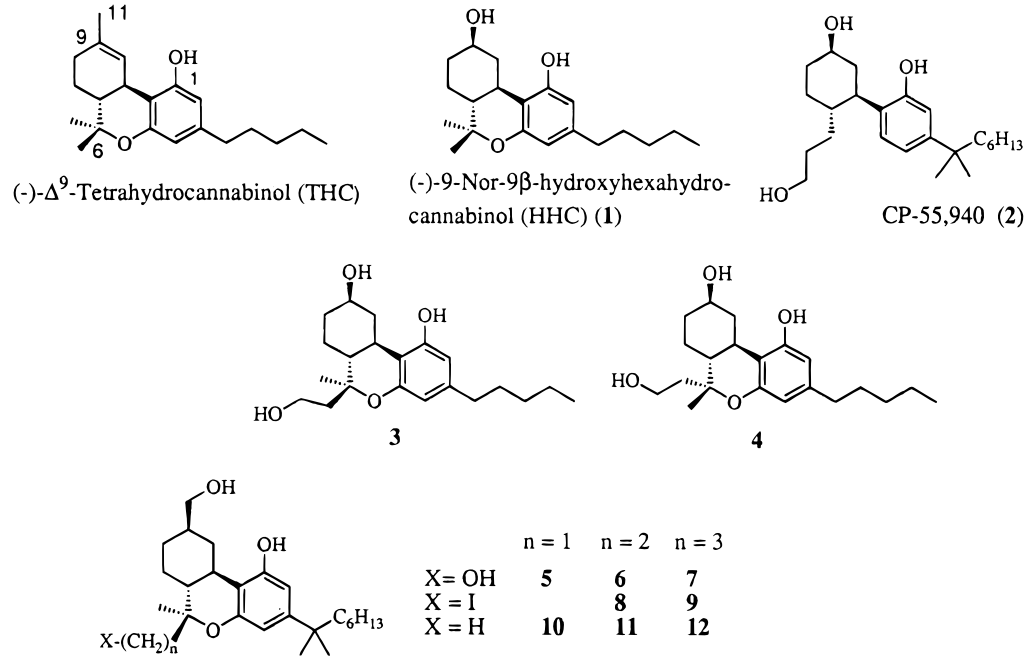
Earlier work from our group had examined the stereochemical preference of the SAH pharmacophore by restricting its spatial orientation through reintroduction of the pyran B-ring into the nonclassical cannabinoid skeleton.[9] These compounds combined the dihydrobenzopyran structure of **1** with the hydroxyalkyl chain found in **2**, and the resulting classical/nonclassical hybrid cannabinoids **3** and **4** were tested for their affinities for the CB1 receptor. Competitive binding assays, using receptor membrane isolated from rat forebrain, showed a dose-dependent displacement of the radioligand [^{3}H]CP-55,940. The β-hydroxyethyl analogue **3** showed an affinity constant (K_i) of 70.5 nM, compared to a K_i of 1353 nM for the α-epimer **4**. This receptor preference for a β-hydroxyalkyl substituent at C-6 provided key information for further study of the SAH pharmacophore.

We chose to investigate the effect of modifying the functionality of the C-6 alkyl chain with regard to affinity for the CB1 and CB2 receptors by synthesizing three series of analogues in which the 6β-alkyl chain was increased from one to three carbon atoms. In addition to the parent hydroxymethyl (n = 1) **5**, hydroxyethyl (n = 2) **6**, and hydroxypropyl (n = 3) **7** compounds, we synthesized iodides **8** (n = 2) and **9** (n = 3) and hydrocarbons **11** (n = 2) and **12** (n = 3). Iodine was chosen to examine how the size of the southern aliphatic side chain affected receptor binding. Hydride

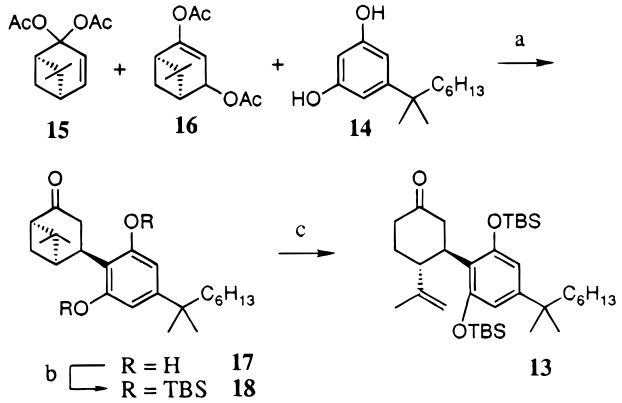
[†] University of Hawaii.
[‡] University of Connecticut.

S0022-2623(96)00677-2 CCC: $15.00
Published on Web 08/22/1998

Chart 1



Scheme 1. Synthesis of Intermediate **13**[a]



[a] (a) $TsOH \cdot H_2O$, $CHCl_3$, rt, 3 days, 61%; (b) TBSCl, imidazole, DMAP, DMF, rt, 36 h, 83%; (c) i. TMSI, CCl_4, cat. *t*-BuOH, 0 °C, 2 h, ii. DBU, PhH, 50 °C, 3 h, 68%.

provided a nonpolar side chain with which to test the southern pharmacophoric region. To maximize receptor affinity, pharmacophores demonstrated to be optimal at C-3 and C-9 were incorporated into our analogues.

This paper describes the synthesis of **5**−**7** and the stereoselective introduction of the SAH moiety. Iodides **8** and **9** and hydrocarbons **11** and **12** were synthesized from the corresponding alcohols.

Chemistry

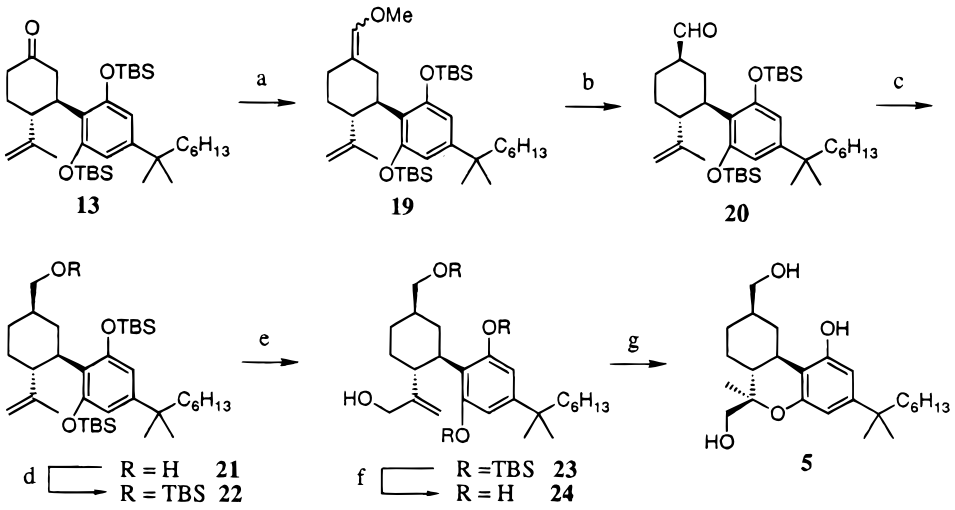
The $n = 1$ and $n = 2$ analogues were prepared from a common advanced intermediate (**13**)[10] and will be discussed first (Scheme 1). Resorcinol **14** was coupled with diacetates **15** and **16**[10] to produce **17** in 61% yield. The original procedure by Archer et al.,[10] which described the preparation of 5-(1′,1′-dimethylheptyl)resorcinol (**14**), as well as the coupling reaction, suffered from low yields (39−41%). Two factors are key to realizing a high yield of **17**. First, the enol acetate derived from (−)-*β*-pinene (98% ee; Aldrich) was treated with lead tetraacetate under *gentle* reflux for 2 h, and second, the crude product of this oxidation was used in the condensation. All attempts to purify the mixture of diacetates **15** and **16** by vacuum distillation resulted in a sharply diminished yield of **17**. The yield of **17** after recrystallizing to constant optical rotation was 61%.[11]

Both phenolic hydroxyl groups in **17** were protected as *tert*-butyldimethylsilyl (TBS) ethers, and the cyclobutane ring was cleaved using trimethylsilyl iodide. The unstable tertiary iodide intermediate was treated with DBU in benzene to generate the required isopropenyl group in **13**.[12] This reaction sequence required considerable optimization. Under rigorously anhydrous conditions the cyclobutane ring opening failed to take place, suggesting that the process was catalyzed by hydroiodic acid. The finding that 2 mol % *tert*-butyl alcohol catalyzed the reaction supports this hypothesis. Higher concentrations of HI resulted first in loss of the TBS protecting groups and then decomposition of the resorcinol through a number of reaction pathways. Decomposition of the tertiary iodide also took place on standing, presumably as a result of the spontaneous elimination of HI. Heating the tertiary iodide in the presence of the base led to **13** in good yield. Contamination of **13** even by small amounts of the tertiary iodide resulted in fairly rapid decomposition of the sample; therefore it was essential that the conversion to **13** be complete.

Introduction of the C-9 hydroxymethyl group for the $n = 1$ and $n = 2$ series was accomplished by treating **13** with (methoxymethylene)triphenylphosphorane (Scheme 2). Methyl vinyl ether **19** was hydrolyzed with wet trichloroacetic acid, and the diastereomeric mixture of C-9 aldehydes was epimerized to produce the *β*-equatorial isomer **20**.[13] Reduction with sodium borohydride followed by protection of the C-11 hydroxyl as the TBS ether led to **22**.

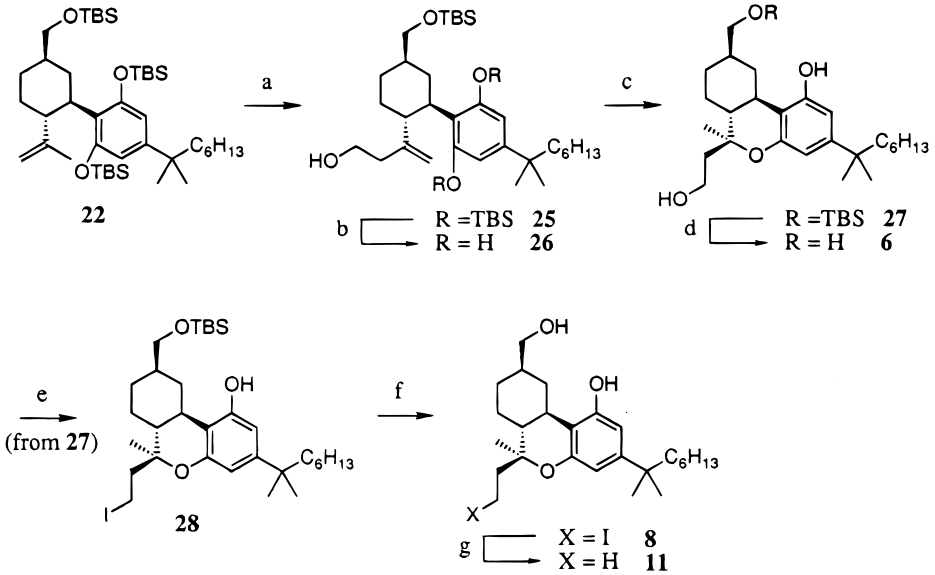
The SAH group of the $n = 1$ series was introduced by means of an allylic oxidation[14] of **22**. Removal of all silyl protecting groups from **23** by treatment with HF in acetonitrile[15] produced tetrol **24** in only modest yield.

Scheme 2. Synthesis of $n = 1$ Alcohol **5**[a]



[a] (a) $Ph_3PCH_2OMe^+Cl^-$, Na *tert*-amylate, PhH, 70 °C, 3 h, 73%; (b) i. Cl_3CCO_2H, H_2O, CH_2Cl_2, rt, 10 min, ii. K_2CO_3, EtOH, rt, 24 h, 73%; (c) $NaBH_4$, EtOH, 0 °C, 2 h, 72%; (d) TBSCl, imidazole, DMF, rt, 17 h, 99%; (e) i. SeO_2, salicylic acid, *t*-BuOOH, CH_2Cl_2, rt, 2 h, ii. $NaBH_4$, MeOH, 0 °C, 30 min, 83%; (f) i. $Et_3N{\cdot}HF$, MeCN, cat. HF, 0 °C, 4 h, ii. TBAF, THF, 0 °C, 10 min, 80%; (g) $Hg(OAc)_2$, THF, rt, 20 h, then $NaBH_4$, 1 M NaOMe in MeOH, −78 °C, 15 min, 62%.

Scheme 3. Synthesis of $n = 2$ Analogues[a]



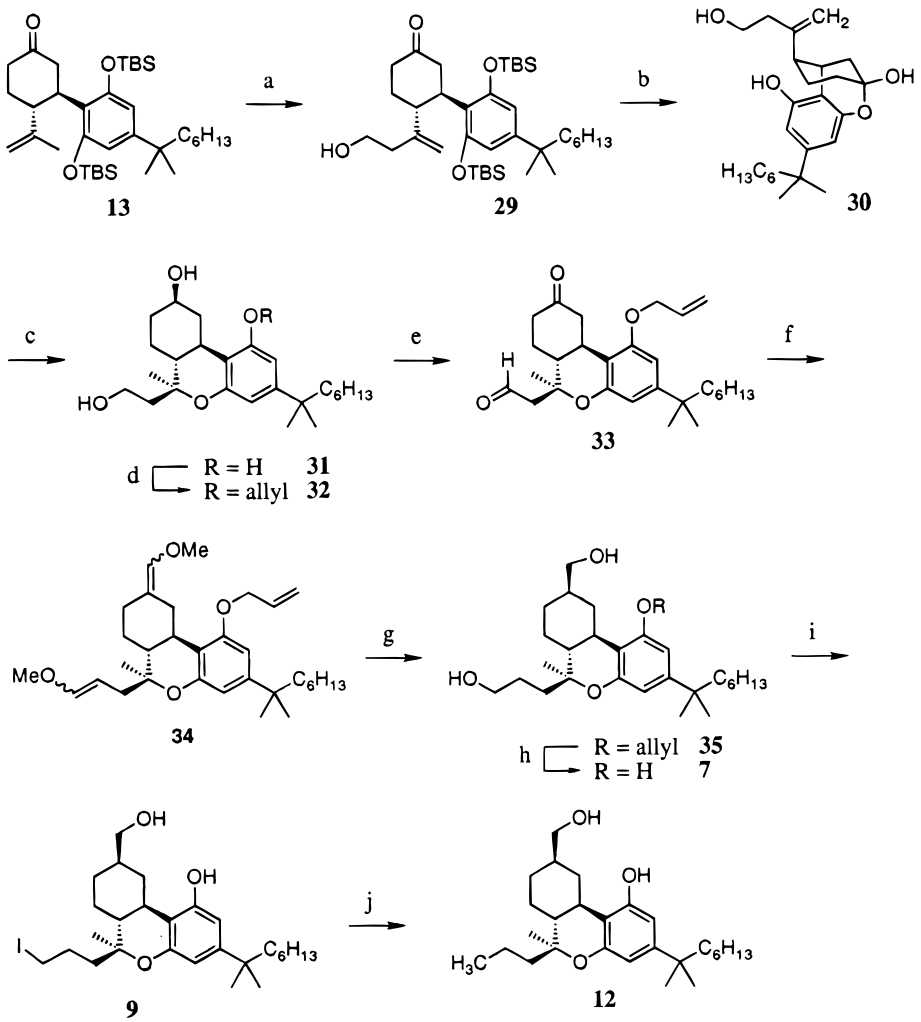
[a] (a) Me_3Al, 2,6-diphenylphenol, *sym*-trioxane, CH_2Cl_2, 0 °C, 1 h, 82%; (b) TBAF, THF, −78 °C, 2 h, 95%; (c) i. $Hg(OAc)_2$, THF, rt, 24 h, ii. 2.5 N NaOH, *n*-Bu_4NOH, $NaBH_4$, CH_2Cl_2, 0 °C, 10 min, 43%; (d) $Et_3N{\cdot}HF$, MeCN, cat. HF, 0 °C, 1.5 h, 76%; (e) I_2, Ph_3P, imidazole, PhH, 45 °C, 45 min, 82%; (f) $Et_3N{\cdot}HF$, MeCN, cat. HF, 0 °C, 1.5 h, 73%; (g) $LiAlH_4$, THF, rt, 3 h, 71%.

This compound was particularly sensitive to acid; therefore the protecting groups were removed in two steps. Exposure of **23** to triethylamine hydrofluoride and catalytic HF selectively deprotected the TBS group on the C-11 hydroxyl.[16] Subsequent treatment with tetra-*n*-butylammonium fluoride[17] gave **24** in 80% overall yield for the two steps. Cyclization of **24** to the tricyclic cannabinoid skeleton was accomplished by means of the intramolecular oxymercuration−demercuration reaction which we developed.[9,18] The origins of the stereoselectivity have been discussed elsewhere.[19] Compound **5** was obtained in 62% yield as the major diastereomer following purification by HPLC.

The additional carbon atom present in the $n = 2$ series was introduced by means of a Lewis acid-catalyzed ene reaction (Scheme 3). Intermediate **22** was treated with Yamamoto's methylaluminum bis(2,6-diphenylphenoxide) formaldehyde reagent[20] to produce **25** in 82% yield. The phenolic hydroxyls were selectively desilylated by exposure to tetra-*n*-butylammonium fluoride to give **26**, which was cyclized in the same way as **24**.[9] Deprotection of **27** with triethylamine hydrofluoride gave **6**. Iodide **8** and hydrocarbon **11** were prepared from **27**. Treatment of **27** with triphenylphosphine, iodine, and imidazole led to iodide **28**,[21] which was deprotected under acidic conditions in order to avoid dehydroiodination. Iodide **8** was converted to **11** by reduction with an excess of lithium aluminum hydride.

A concise synthesis of the $n = 3$ series of analogues was implemented by operating simultaneously on the northern and southern regions of the molecule. Treatment of **13** with Yamamoto's reagent[20] produced the hydroxybutyl compound **29** in excellent yield (Scheme 4). Deprotection of the phenolic hydroxyl groups led to

Scheme 4. Synthesis of $n = 3$ Analogues[a]



[a] (a) Me_3Al, 2,6-diphenylphenol, *sym*-trioxane, CH_2Cl_2, 0 °C, 1.5 h, 80%; (b) TBAF, THF, 0 °C, 20 min, 86%; (c) $Hg(OAc)_2$, THF, rt, 24 h, then $NaBH_4$, 1 M NaOMe in MeOH, −78 °C, 66%; (d) allyl bromide, *n*-Bu_4NOH, CH_2Cl_2/H_2O, rt, 3 h, 80%; (e) Dess−Martin periodinane, CH_2Cl_2, rt, 2 h, 90%; (f) $Ph_3PCH_2OCH_3^+Cl^-$, Na *tert*-amylate, PhH, 70 °C, 3 h, 84%; (g) i. Cl_3CCO_2H, H_2O, CH_2Cl_2, rt, 10 min, ii. K_2CO_3, EtOH, rt, 17 h, then $NaBH_4$, 0 °C, 1 h, 61%; (h) $(Ph_3P)_4Pd$, $NaBH_4$, THF, rt, 6 h, 92%; (i) I_2, Ph_3P, imidazole, PhH, 50 °C, 25 min, 80%; (j) $LiAlH_4$, THF, rt, 3 h, 80%.

the formation of hemiketal **30**, by nucleophilic attack of one of the phenolic hydroxyls on the ketone carbonyl group. The oxymercuration−demercuration procedure[9] produced the desired tricyclic β-hydroxyethyl derivative **31** in 66% yield. The success of this reaction suggests that **30** is in equilibrium with the corresponding ketone. The greater acidity of the phenol relative to the two aliphatic hydroxyl groups in **31** was exploited in a phase-transfer-catalyzed allylation which produced **32**. Simultaneous oxidation of the two alcohols with freshly prepared Dess−Martin periodinane[22] gave keto aldehyde **33** in 90% yield. Homologation with (methoxymethylene)triphenylphosphorane produced bis-enol ether **34** as a mixture of geometrical isomers. Hydrolysis of **34** with wet trichloroacetic acid, epimerization of the C-9 aldehyde to the more stable β-equatorial configuration, and reduction in situ with sodium borohydride produced diol **35** in 61% overall yield for the three steps.

The next task required the selective functionalization of the primary alcohol on the C-6 side chain in the presence of another primary alcohol at C-11. Removal of the phenolic allyl protecting group under reductive conditions in the presence of a primary iodo group represented a potentially serious obstacle. Although the removal of the protecting group before the functionalization step might introduce a different set of problems, this approach was followed. In the event, palladium-catalyzed reductive cleavage of the allyl[23] took place in 92% yield. By exploiting the subtle difference in susceptibility toward nucleophilic displacement at the terminal carbon of the C-6 side chain, it was possible to convert **7** to monoiodide **9** in 80% yield. A modest amount of the diiodide (ca. 20%) was also obtained, but none of the C-11 monoiodide was isolated. The difference in reactivity between the two primary alcohols can be attributed to the β-branching at C-9 which hinders nucleophilic attack at C-11. Reductive cleavage of the iodo group with lithium aluminum hydride furnished **12**.

Cannabinoid Receptor Binding Assays. Analogues **5**−**12** were tested for their ability to displace radiolabeled CP-55,940 from purified rat forebrain synaptosomes (CB1) and mouse spleen synaptosomes (CB2) as previously described.[13,24] The calculated K_i's are shown in Table 1.

Table 1. K_i Values (nM) for Functionalized Cannabinoid Analogues **5**−**12′** Competing with [^{3}H]CP-55,940 for CB1 (Brain) and CB2 (Spleen) Receptors[a]

	$n = 1$		$n = 2$		$n = 3$	
X	brain	spleen	brain	spleen	brain	spleen
	5		**6**		**7**	
OH	1.9 (1.7, 2.0)	1.4 (1.2, 1.7)	2.8 (2.2, 3.6)	2.3 (1.8, 2.9)	2.2 (2.0, 2.4)	3.4 (3.1, 3.8)
			8		**9**	
I			40.7 (36.5, 45.4)	9.7 (8.4, 11.1)	2.2 (2.0, 2.7)	4.3 (3.5, 6.3)
	10		**11**		**12**	
H	2.3 (2.0, 2.7)	2.3 (2.0, 2.7)	11.1 (10.0, 12.2)	21.5 (17.7, 26.1)	14.4 (13.2, 15.7)	38.9 (29.9, 50.6)

[a] The reported values are averages of at least three experiments; numbers in parentheses represent extreme values.

Results and Discussion

Three series of functionalized cannabinoids have been synthesized to investigate the importance of the southern pharmacophoric region of the hybrid classical/nonclassical cannabinoid molecule with regard to its affinity for the cannabinoid receptors. To maximize the affinity of our analogues for the receptor, we optimized each of the other cannabinoid pharmacophores and chose the β-11-hydroxyhexahydrocannabinol as the tricyclic component with a 1′,1′-dimethylheptyl group in the side chain. This choice was based on earlier work from our laboratory involving the design and synthesis of a corresponding highly potent cannabinoid analogue.[25,26] The C-6β alkyl side chain was substituted with hydroxy and iodo functionalities, and the unsubstituted alkyl chain was also synthesized in each case. The series differed in the length of the alkyl side chain, having one, two, or three carbons in the C-6 side chain.

The synthesis of the materials is notable for several reasons. Advanced intermediate **13** was prepared in multigram quantities following improvements in the protocol of Archer *et al.*[10] The highly stereoselective cyclization of the pyran ring through an intramolecular oxymercuration−demercuration has been extended to several new systems with this work and appears to be completely general. This method promises to be broadly applicable in synthesis and not limited to the cannabinoid series. Furthermore, the highly chemoselective transformation of **7** to **9** demonstrates that it is possible to perform selective functionalizations in this series without recourse to tedious protecting group manipulations.

Our data on the respective affinities of our analogues for CB1 and CB2 indicate that the SAH pharmacophore plays a significant role in determining cannabimimetic activity, although this role is less prominent than that of the C-3 side chain. Below we have interpreted these data in terms of pharmacophoric requirements for the two cannabinoid receptor subtypes, CB1 and CB2.

6β-(ω-Hydroxyalkyl) Analogues. In this series we observe relatively insignificant variations in affinity between the $n = 1$, $n = 2$, and $n = 3$ analogues. There was also no difference in affinities between CB1 and CB2. It thus appears that the southern aliphatic hydroxyl pharmacophore does not discriminate between the CB1 and CB2 receptors. Furthermore, the alkyl C-6β chain is flexible enough to apparently allow equally optimal interactions between the southern hydroxyl and a corresponding receptor subsite located no further than 2 Å from the subsite with which the tricyclic cannabinoid component interacts. A more refined topological examination of this interaction will require the development of novel analogues in which the southern aliphatic chain is further confined.

6β-Alkyl Analogues. The prototype in this series (**10**) was synthesized earlier in our laboratory,[25] as well as by Mechoulam and co-workers,[26] using different synthetic approaches. Both of these groups showed that, in vivo, this compound is a very potent classical cannabinoid with potency approximately 100-fold higher than that of (−)-Δ^9-THC. Mechoulam's group also reported that this molecule had a very high affinity for the CB1 receptor with a $K_i = 45$ pM. This result differs from our current data where we show a $K_i = 2.3$ nM. The discrepancy may be due to the use of different radioligands and different binding assays by the two groups. Irrespective of this discrepancy, the compound remains as one of the most potent CB1 ligands available to date. In this series the increase in chain length from $n = 1$ to $n = 3$ results in progressively lower affinities toward both CB1 and CB2. This observation serves to define the limits of steric tolerance for hydrophobic groups at that subsite in both receptors. It thus appears that the 6β-alkyl pharmacophore within the otherwise optimized cannabinoid structure exhibits different structure−activity relationship (SAR) characteristics than the previously discussed corresponding 6β-hydroxyalkyl group. This observation implies that the two southern pharmacophores, namely, the 6-alkyl and 6-hydroxyalkyl groups, either interact differently within the same CB1 and CB2 southern subsite or alternatively interact with different southern subsites within the CB1 and CB2 active sites.

6β-(ω-Iodoalkyl) Analogues. Because of the hydrophobic character of this southern pharmacophore, the analogues in this group were expected to exhibit analogous SAR profiles to those characteristic of the corresponding 6β-alkyl analogues. This indeed is the case with the iodoethyl analogue in the series, where the introduction of the bulky iodo substituent results in a decreased affinity for both CB1 and CB2. However, the most interesting SAR effect in this group of analogues was observed with the iodopropyl compound (**9**) which exhibits increased affinities for both receptors when compared with its lower homologues. The effect is most dramatic with the CB1 receptor for which the bulky iodopropyl analogue exhibits 20-fold higher affinity than its iodoethyl homologue. Although the same effect is observed with the CB2 receptor, the effect is much less stark. Based on the above data, it is tempting to

speculate on the existence of a special hydrophobic cavity at the southern hydrophobic subsite at the receptor resembling perhaps a "baseball glove" with which the "baseball"-like iodo group interacts and significantly enhances the affinity of this analogue for the receptor. To reach this subsite the iodo group must be separated by at least three methylene carbons from the C-6 carbon of the cannabinoid tricyclic system.

Conclusions

In this work we have sought to study the SAR of the southern cannabinoid pharmacophores and to extend earlier work[7b] in which the effects of chain length variation at the SAH group in nonclassical cannabinoids were described, as well as work from our own laboratory which showed that the 6β-substitution in tricyclic cannabinoids is preferred over the corresponding 6α-compounds. The present work serves to explore in greater detail the pharmacophoric requirements of the southern aliphatic cannabinoid pharmacophores with respect to the CB1 and CB2 active sites. It should also serve as a basis for refining existing cannabinoid receptor models, a task which we are currently pursuing.

It is clear from our results that the effects of varying the southern aliphatic chain in the classical and nonclassical cannabinoid ring system on biological activity are not as stark as those observed with the 3-alkyl side chain where we observe changes in biological activity and receptor affinity of up to 3 orders of magnitude. Within a more modest range, the SAR of the southern pharmacophore is also distinct and will allow us to pursue the design of more selective CB1 and CB2 receptor probes.

In summary, the present work indicates that the SAH pharmacophore may interact with a polar subsite at the receptor situated very near the cannabinoid tricyclic component ($\approx$2 Å). All three homologues interact equally with this subsite and show differences between CB1 and CB2. Transformation of the polar southern hydroxyalkyl pharmacophore into hydrophobic alkyl or haloalkyl groups reveals the presence of an additional binding subsite. Within this subsite a large cavity can accommodate hydrophobic groups at least as large as an iodine atom at a distance of at least 4.0 Å from the cannabinoid template. Currently, we are further refining the pharmacophoric requirements of the southern subsites through the design and synthesis of conformationally more defined analogues.

Experimental Section

^{1}H NMR and ^{13}C NMR spectra were recorded on a General Electric QE 300 spectrometer at 300 MHz ^{1}H (75 MHz ^{13}C) or a GE Omega 500 at 500 spectrometer MHz ^{1}H (125 MHz ^{13}C) in deuteriochloroform ($CDCl_3$) with chloroform (7.26 ppm ^{1}H, 77.00 ppm ^{13}C) as internal reference. Chemical shifts are given in ppm (δ); multiplicities are indicated as br (broadened), s (singlet), d (doublet), 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 Sigma precoated silica gel 60 F-254 glass plates (0.25 mm). Flash column chromatography was performed using ICN Biomedicals silica gel (32−63 μm). Tetrahydrofuran (THF) and diethyl ether were distilled from sodium-benzophenone ketyl; *N*,*N*-dimethylformamide (DMF), triethylamine, and 1,8-diazabicyclo[5.4.0]-undec-7-ene (DBU) from calcium hydride; carbon tetrachloride (CCl_4) and dichloromethane (CH_2Cl_2) from phosphorus pentoxide; benzene from sodium metal; and methanol from magnesium/iodine. Other reagents were obtained commercially and used as received, unless otherwise stated. All anhydrous reactions were performed under a static nitrogen or argon atmosphere in flame-dried glassware. The purity and the homogeneity of the products on which high-resolution mass spectral data are reported were determined on the basis of a combination of chiral HPLC (Chiracel-OD, Bakerbond OD, or Chiralpak OD), 300 MHz ^{1}H NMR, and multiple elution TLC analysis. The materials which were used for the binding affinity assays were purified by chiral HPLC (multiple injections and peak-shaving to get the center cut).

(4*R*)-4-[4-(1′,1′-Dimethylheptyl)-2,6-dihydroxyphenyl]-6,6-dimethyl-2-norpinanone, 17. To a solution of 8.8 g of resorcinol **14** (37.0 mmol) and 10.5 g of diacetates **15** and **16** (44.0 mmol, ca. 85% pure by ^{1}H NMR) in 320 mL of $CHCl_3$ was added *p*-toluenesulfonic acid monohydrate (8.37 g, 44.0 mmol), and the solution stirred at room temperature for 3 days. The reaction was diluted with ether and washed sequentially with water, saturated aqueous $NaHCO_3$, and brine. The organic phase was dried ($MgSO_4$) and solvent removed in vacuo to give a brown oil. Recrystallization from CH_2Cl_2 and hexane gave **17** as a white crystalline solid (8.4 g, 61% yield): mp 174−176 °C [lit.[10] mp 171−174 °C]; $[\alpha]^{20}_D$ +57.2° (*c* 1.0, $CHCl_3$) [lit.[10] $[\alpha]^{20}_D$ +55.8° (*c* 1.0, $CHCl_3$)]; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.27 (s, 2H), 4.87 (s, 2H), 3.94 (t, J = 8.1 Hz, 1H), 3.49 (dd, J = 18.6, 7.8 Hz, 1H), 2.66−2.44 (m, 4H), 2.30 (t, J = 5.1 Hz, 1H), 1.52−1.47 (m, 2H), 1.36 (s, 3H), 1.28−1.18 (m, 6H), 1.20 (s, 6H), 1.07 (br s, 2H), 1.00 (s, 3H), 0.85 (t, J = 6.6 Hz, 3H);^{13}C NMR (75 MHz, $CDCl_3$) δ 216.9, 154.7, 150.0, 113.5, 106.6, 57.9, 46.8, 44.4, 42.2, 37.9, 37.2, 31.8, 30.0, 29.5, 28.7, 26.2, 24.6, 24.4, 22.7, 22.2, 14.1; IR (neat) 3300, 2920, 1680, 1580, 1420, 1370, 1330, 1265 cm^{-1}; mass spectrum *m/z* (relative intensity) 372 (M^+, 44), 355 (13), 329 (19), 289 (100), 269 (11), 249 (38), 217 (23), 178 (54), 149 (22), 109 (15), 83 (75). Exact mass calculated for $C_{24}H_{36}O_3$, 372.2655; found, 372.2648. Anal. Calcd: C, 77.34; H, 9.74. Found: C, 77.19; H, 9.53.

(4*R*)-4-[4-(1′,1′-Dimethylheptyl)-2,6-bis(*tert*-butyldimethylsilyloxy)phenyl]-6,6-dimethyl-2-norpinanone, 18. To a solution of 5.8 g of imidazole (85.0 mmol, dried at 40 °C/0.1 mmHg for 2 h) and DMAP (275 mg, 2.0 mmol, resublimed) in 25 mL of DMF was added a solution of 8.1 g of **17** (22.0 mmol) in 20 mL of DMF. To this mixture was added a solution of *tert*-butyldimethylsilyl chloride (10.3 g, 68.0 mmol) in 23 mL of DMF, and the reaction was allowed to stir at room temperature for 36 h. The reaction was quenched by addition of saturated aqueous $NaHCO_3$ and extracted with 3 × 200 mL of ether. The combined ethereal extracts were washed with 2 × 200 mL of water and brine and dried ($MgSO_4$). Solvent evaporation gave a pale yellow oil which was purified by flash chromatography (5% ether in hexane) to produce **18** as a colorless oil (10.9 g, 83% yield): $[\alpha]^{20}_D$ +51.6° (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.40 (s, 2H), 3.99 (br t, J = 8.1 Hz, 1H), 3.79 (dd, J = 19.0, 7.0 Hz, 1H), 2.56−2.37 (m, 4H), 2.30 (t, J = 5.1 Hz, 1H), 1.52−1.46 (m, 2H), 1.32 (s, 3H), 1.27−1.15 (m, 6H), 1.19 (s, 6H), 1.07 (br s, 2H), 0.99 (s, 18H), 0.97 (s, 3H), 0.84 (t, J = 6.9 Hz, 3H), 0.27 (s, 12H);^{13}C NMR (75 MHz, $CDCl_3$) δ 215.4, 154.7, 148.2, 119.6, 110.0, 57.9, 47.4, 44.6, 41.9, 37.3, 31.8, 30.2, 30.0, 28.9, 26.7, 26.0, 25.7, 24.7, 24.2, 22.7, 22.2, 18.8, 14.1, −3.0, −3.5, −3.6; IR (neat) 2955, 2930, 2860, 1715, 1605, 1560, 1470, 1465, 1415, 1260, 1095, 1070, 830, 785, 670 cm^{-1}; mass spectrum *m/z* (relative intensity) 600 (M^+, 7), 543 (100), 503 (7), 435 (51), 119 (5). Exact mass calculated for $C_{36}H_{64}O_3Si_2$, 600.4377; found, 600.4400.

(3*R*,4*R*)-3-[4-(1′,1′-Dimethylheptyl)-2,6-bis(*tert*-butyldimethylsilyloxy)phenyl]-4-isopropenylcyclohexan-1-one, 13. To a solution of 2.1 g of iodine (8.2 mmol) in 61 mL of CCl_4 at 0 °C in the dark was added allyltrimethylsilane (1.3 mL, 8.2 mmol), and the reaction was allowed to stir for 2 h at 0 °C.

Ketone **18** (3.65 g, 6.1 mmol) was dissolved in a 3 mM solution of *tert*-butyl alcohol in CCl_4 (41 mL) and added slowly to the TMSI solution. Stirring was continued for 1.5 h at 0 °C. The reaction was diluted with 200 mL of ether and washed with saturated aqueous sodium thiosulfate and saturated aqueous $NaHCO_3$. The organic phase was dried ($MgSO_4$) and evaporated to give a yellow oil. To a solution of this oil in 36 mL of benzene was added DBU (2.7 mL, 18.1 mmol), and the reaction was allowed to stir at 50 °C in the dark for 3 h. An aliquot was withdrawn and examined by ^{1}H NMR to ensure that no tertiary iodide remained. The reaction was diluted with 100 mL of ether, washed with water, and dried ($MgSO_4$) and the solvent evaporated to give 3.5 g of a brown oil. Purification by flash chromatography (5% ether in hexane) gave **13** as a pale yellow oil (2.49 g, 68% yield): R_f = 0.40 (5% ether in hexane); $[\alpha]^{20}_D$ −18.7° (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.33 (s, 2H), 4.63 (s, 1H), 4.49 (s, 1H), 3.63 (dt, *J* = 12.3, 4.2 Hz, 1H), 3.39 (dt, *J* = 11.6, 3.0 Hz, 1H), 3.19 (t, *J* = 14.1 Hz, 1H), 2.46 (dd, *J* = 9.6, 4.7 Hz, 2H), 2.31 (dd, *J* = 14.1, 4.2 Hz, 1H), 2.04−1.98 (m, 1H), 1.84−1.69 (m, 1H), 1.55 (s, 3H), 1.48−1.43 (m, 2H), 1.31−1.25 (m, 2H), 1.25−1.14 (m, 4H), 1.19 (s, 6H), 1.05 (br s, 9H), 1.03−0.95 (m, 2H), 0.99 (br s, 9H), 0.84 (t, *J* = 6.9 Hz, 3H), 0.32 (br s, 6H), 0.23 (s, 3H), 0.15 (s, 3H);^{13}C NMR (75 MHz, $CDCl_3$) δ 211.4, 148.3, 147.4, 119.2, 110.7, 109.8, 109.5, 45.8, 45.1, 44.7, 41.6, 38.7, 37.3, 31.9, 31.8, 29.9, 28.6, 26.4, 25.9, 24.5, 22.5, 19.2, 14.0, −3.8, −4.2; IR (neat) 3065, 2850, 1710, 1640, 1560, 1410, 1250, 1185, 1090, 1045, 830, 775, 665 cm^{-1}; mass spectrum *m*/*z* (relative intensity) 600 (M^+, 12), 585 (4), 543 (100), 517 (6), 487 (15), 433 (40). Exact mass calculated for $C_{36}H_{64}O_3Si_2$, 600.4377; found, 600.4395.

(3*R*,4*R*)-3-[4-(1′,1′-Dimethylheptyl)-2,6-bis(*tert*-butyldimethylsilyloxy)phenyl]-4-isopropenyl-1-(methoxymethylene)cyclohexane, 19. To a suspension of (methoxymethyl)-triphenylphosphonium chloride (1.5 g, 4.3 mmol, dried at 60 °C/0.1 mmHg for 1 h) in 25 mL of benzene was added sodium *tert*-amylate (5.0 mL, 4.3 mmol; 0.85 M solution in benzene), and the mixture stirred at room temperature for 15 min until a clear, deep red solution was obtained. A solution of 900 mg of ketone **13** (1.5 mmol) in 15 mL of benzene was added dropwise to the ylide, and the reaction stirred at 70 °C for 3 h. The reaction was quenched by dropwise addition of saturated aqueous NH_4Cl and diluted with 40 mL of ether and the organic phase separated. The aqueous phase was extracted with 3 × 10 mL of ether, the combined ethereal extracts were dried ($MgSO_4$), and the solvent was evaporated to give an orange oil. Purification by flash chromatography (30% benzene in hexane) gave **19** as a colorless oil (684 mg, 73% yield, mixture of geometric isomers): R_f = 0.22 and 0.25 (30% benzene in hexane); IR (neat) 3065, 2950, 2920, 2850, 1680, 1640, 1600, 1560, 1460, 1410, 1250, 1205, 1125, 1090, 830, 775, 675 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) higher R_f isomer δ 6.30 (s, 1H), 6.29 (s, 1H), 5.77 (s, 1H), 4.57 (d, *J* = 2.4 Hz, 1H), 4.39 (s, 1H), 3.48 (s, 3H), 3.17−3.14 (m, 2H), 2.67 (dd, *J* = 13.5, 2.1 Hz, 1H), 2.37 (t, *J* = 12.0 Hz, 1H), 2.10−1.90 (m, 2H), 1.74 (br d, *J* = 13.5 Hz, 1H), 1.53 (s, 3H), 1.48−1.42 (m, 2H), 1.38−1.27 (m, 1H), 1.25−1.10 (m, 4H), 1.18 (s, 6H), 1.05 (br s, 9H), 1.01 (br s, 9H), 0.98−0.91 (m, 4H), 0.84 (t, *J* = 6.7 Hz, 3H), 0.30 (s, 3H), 0.29 (s, 3H), 0.23 (s, 3H), 0.17 (s, 3H); lower R_f isomer δ 6.31 (s, 1H), 6.29 (s, 1H), 5.72 (s, 1H), 4.55 (s, 1H), 4.39 (s, 1H), 3.53 (s, 3H), 3.20−3.11 (m, 2H), 2.84 (br d, *J* = 14.0 Hz, 1H), 2.67 (t, *J* = 12.0 Hz, 1H), 1.91 (d, *J* = 13.5 Hz, 1H), 1.81−1.74 (m, 2H), 1.51 (s, 3H), 1.48−1.43 (m, 2H), 1.39−1.34 (m, 1H), 1.25−1.12 (m, 4H), 1.18 (s, 6H), 1.05 (br s, 9H), 1.01 (br s, 9H), 1.00−0.94 (m, 4H), 0.84 (t, *J* = 6.7 Hz, 3H), 0.31 (s, 3H), 0.30 (s, 3H), 0.24 (s, 3H), 0.17 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) higher R_f isomer δ 155.0, 153.5, 149.6, 147.2, 138.9, 121.7, 118.0, 109.9, 109.4, 109.2, 59.0, 47.1, 44.9, 38.8, 37.2, 34.6, 31.8, 30.2, 30.0, 28.9, 28.8, 28.7, 26.5, 25.9, 24.6, 22.6, 19.3, 18.8, 18.3, 14.1, −3.6, −3.7, −3.8, −4.8; lower R_f isomer δ 155.0, 153.5, 149.4, 147.4, 139.0, 121.5, 118.5, 109.9, 109.3, 109.2, 59.3, 47.1, 44.8, 40.1, 37.2, 33.9, 33.3, 31.8, 29.9, 28.9, 28.6, 26.5, 26.0, 25.2, 24.6, 22.5, 19.3, 18.8, 18.3, 14.0, −3.6, −3.7, −3.8, −4.5; mass spectrum *m*/*z* (relative intensity) 628 (M^+, 35), 570 (21), 543 (16), 477 (41), 433 (10), 208 (10), 151 (100). Exact mass calculated for $C_{38}H_{68}O_3Si_2$, 628.4689; found, 628.4683.

(1*R*,3*R*,4*R*)-3-[4-(1′,1′-Dimethylheptyl)-2,6-bis(*tert*-butyldimethylsilyloxy)phenyl]-4-isopropenyl-1-formylcyclohexane, 20. To a solution of 360 mg of methyl enol ether **19** (0.57 mmol) in 34 mL of CH_2Cl_2 was added aqueous trichloroacetic acid (320 mg, 1.96 mmol, 3.4 equiv), and the solution stirred for 10 min at room temperature. The reaction was quenched by addition of saturated aqueous $NaHCO_3$, washed with brine, and dried (K_2CO_3) and the solvent evaporated. Aldehyde resonances at δ 9.83 (br s) and 9.60 (d, *J* = 1.5 Hz) in the ^{1}H NMR spectrum of the crude product indicated that the reaction had taken place. The crude product was dissolved in 20 mL of absolute ethanol and stirred with 158 mg of anhydrous K_2CO_3 (1.14 mmol, 2.0 equiv) for 24 h at room temperature. Examination of an aliquot by ^{1}H NMR showed that epimerization was complete. Purification by flash chromatography (5% EtOAc in hexane) gave **20** as a colorless oil (258 mg, 73% yield over 2 steps): R_f = 0.20 (10% EtOAc in hexane); $[\alpha]^{20}_D$ −18.8° (*c* 1.0, $CHCl_3$); IR (neat) 2840, 1725, 1640, 1600, 1230, 1120, 1000 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.60 (d, *J* = 1.5 Hz, 1H), 6.31 (s, 1H), 6.30 (s, 1H), 4.57 (br s, 1H), 4.43 (br s, 1H), 3.28 (td, *J* = 11.7, 3.3 Hz, 1H), 3.00 (td, *J* = 11.4, 3.0 Hz, 1H), 2.40−2.18 (m, 1H), 2.12 (dd, *J* = 12.6, 3.3 Hz, 1H), 2.05−2.00 (m, 1H), 1.88−1.80 (m, 2H), 1.54 (s, 3H), 1.50−1.40 (m, 4H), 1.18 (s, 6H), 1.27−1.13 (m, 8H), 1.04 (s, 9H), 1.02 (s, 9H), 0.83 (t, *J* = 7.2 Hz, 3H), 0.30 (s, 6H), 0.24 (s, 3H), 0.15 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 204.3, 155.0, 153.4, 148.9, 147.7, 120.9, 109.9, 109.8, 109.3, 51.1, 46.2, 44.8, 37.5, 37.2, 31.81, 31.8, 29.9, 29.5, 28.9, 28.6, 26.4, 25.9, 24.6, 22.5, 19.4, 18.8, 18.3, 14.0, −3.6, −3.8, −4.5; mass spectrum *m*/*z* (relative intensity) 614 (M^+, 2), 585 (7), 557 (7), 477 (24), 107 (14), 73 (100). Exact mass calculated for $C_{37}H_{66}O_3Si_2$, 614.4533; found, 614.4553.

(1*R*,3*R*,4*R*)-3-[4-(1′,1′-Dimethylheptyl)-2,6-bis(*tert*-butyldimethylsilyloxy)phenyl]-4-isopropenyl-1-(hydroxymethyl)cyclohexane, 21. To a solution of 258 mg of aldehyde **20** (0.42 mmol) in 42 mL of absolute ethanol at 0 °C was added 63 mg of $NaBH_4$ (1.68 mmol, 4 equiv). The mixture was warmed to room temperature, stirred for 2 h, and then quenched by dropwise addition of saturated aqueous NH_4Cl and the solvent evaporated. The residual white solid was dissolved in water and extracted with EtOAc. The combined organic extracts were washed with brine and dried ($MgSO_4$), and the solvent was evaporated. Purification by flash chromatography (5% EtOAc in hexane) gave **21** as a colorless oil (186 mg, 72% yield): R_f = 0.10 (5% EtOAc in hexane); $[\alpha]^{20}_D$ −15.9° (*c* 1.0, $CHCl_3$); IR (neat) 3320, 2920, 1565, 1470, 1410, 775, 665 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.31 (d, *J* = 1.7 Hz, 1H), 6.30 (d, *J* = 1.7 Hz, 1H), 4.57 (d, *J* = 1.9 Hz, 1H), 4.41 (d, *J* = 1.0 Hz, 1H), 3.47 (br heptet, *J* = 5.9 Hz, 2H), 3.26 (td, *J* = 11.9, 3.1 Hz, 1H), 3.01 (td, *J* = 11.7, 2.9 Hz, 1H), 1.92−1.86 (m, 1H), 1.84−1.76 (m, 1H), 1.68−1.58 (m, 1H), 1.55−1.42 (m, 5H), 1.44−1.38 (m, 1H), 1.25−1.00 (m, 12H), 1.19 (br s, 6H), 1.06 (s, 9H), 1.03 (s, 9H), 0.84 (br t, *J* = 6.9 Hz, 3H), 0.31 (s, 6H), 0.24 (s, 3H), 0.16 (s, 3H) [positive NOE from H-1 (δ 1.68−1.58) to H-3 (δ 3.26)]; ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.9, 153.4, 149.7, 147.3, 121.8, 109.9, 109.3, 109.2, 68.8, 46.7, 44.8, 41.1, 37.8, 37.2, 33.0, 32.4, 31.8, 29.9, 29.3, 28.9, 28.6, 26.4, 25.9, 24.6, 22.6, 19.4, 18.8, 18.3, 14.0, −3.5, −3.7, −3.8, −4.4; mass spectrum *m*/*z* (relative intensity) 616 (M^+, 21), 598 (3), 585 (7), 557 (7), 477 (24), 437 (13), 73 (100). Exact mass calculated for $C_{37}H_{68}O_3Si_2$, 616.4689; found, 616.4725.

(1*R*,3*R*,4*R*)-3-[4-(1′,1′-Dimethylheptyl)-2,6-bis(*tert*-butyldimethylsilyloxy)phenyl]-4-isopropenyl-1-[(*tert*-butyldimethylsilyloxy)methyl]cyclohexane, 22. To a solution of 233 mg of imidazole (3.43 mmol) in 1 mL of DMF was added 1.09 g of **21** (1.77 mmol) in 2 mL of DMF followed by 410 mg of *tert*-butyldimethylsilyl chloride (2.72 mmol) in 2.2 mL of DMF. The reaction was allowed to stir at room temperature for 17 h, quenched by addition of saturated aqueous $NaHCO_3$, and extracted with 3 × 20 mL of ether. The combined ethereal extracts were washed with 2 × 20 mL of

water and brine and dried ($MgSO_4$), and the solvent was evaporated to give a pale yellow oil. Purification by flash chromatography (hexane) gave **22** as a colorless oil (1.29 g, 100% yield): $R_f = 0.80$ (hexane); $[\alpha]^{20}_D$ −80.9° (*c* 1.0, $CHCl_3$); IR (neat) 2945, 2920, 2845, 1600, 1560, 1190, 1120, 1000, 880 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.30 (s, 1H), 6.29 (s, 1H), 4.55 (d, $J = 1.5$ Hz, 1H), 4.39 (d, $J = 0.9$ Hz, 1H), 3.40 (br dd, $J = 6.3$, 1.5 Hz, 2H), 3.12 (td, $J = 11.4$, 3.9 Hz, 1H), 2.99 (td, $J = 11.4$, 2.7 Hz, 1H), 1.95−1.80 (m, 1H), 1.80−1.60 (m, 1H), 1.60−1.45 (m, 3H), 1.53 (s, 3H), 1.45−1.40 (m, 1H), 1.26−1.18 (m, 3H), 1.18 (br s, 6H), 1.05 (s, 9H), 1.01 (s, 9H), 1.00−0.80 (m, 11H), 0.87 (s, 9H), 0.29 (s, 6H), 0.22 (s, 3H), 0.13 (s, 3H), 0.02 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.9, 153.5, 149.9, 147.1, 122.2, 109.9, 109.4, 109.1, 69.0, 46.9, 44.9, 41.2, 37.9, 37.2, 33.3, 32.6, 31.8, 29.9, 29.5, 28.9, 28.6, 26.5, 26.0, 25.9, 24.6, 22.5, 19.4, 18.8, 18.4, 18.3, 14.0, −3.6, −3.8, −4.5, −5.3, −5.4; mass spectrum *m*/*z* (relative intensity) 731 (M^+, 6), 585 (12), 477 (18), 281 (9), 189 (20), 147 (82), 73 (100). Exact mass calculated for $C_{43}H_{82}O_3Si_3$, 730.5550; found, 730.5561. Anal. Calcd: C, 70.69; H, 11.31. Found: C, 69.53; H, 11.11.

(1*R*,3*R*,4*R*)-1-[(*tert*-Butyldimethylsilyloxy)methyl]-3-[4-(1′,1′-dimethylheptyl)-2,6-bis(*tert*-butyldimethylsilyloxy)-phenyl]-4-[2′-(3′-hydroxyprop1′-enyl)]cyclohexane, 23. To a stirred mixture of selenium dioxide (1 mg, 0.009 mmol) and salicylic acid (3 mg, 0.002 mmol) in 1 mL of CH_2Cl_2 was added *tert*-butyl hydroperoxide (60 mL, 0.41 mmol) at room temperature. After 5 min, 85 mg of **22** (0.11 mmol) in 2 mL of CH_2Cl_2 was added dropwise and the solution allowed to stir at room temperature for 2 h. Benzene (1 mL) was added to the reaction and the solvent removed in vacuo. The residue was dissolved in ether, washed with 1 N aqueous NaOH and brine, and dried ($MgSO_4$), and the solvent was evaporated. This material was dissolved in 1 mL of methanol, and 5 mg of $NaBH_4$ (0.13 mmol) was added at 0 °C. The reaction was stirred at room temperature for 30 min and then quenched with saturated aqueous NH_4Cl. The methanol was evaporated and the residual aqueous phase extracted three times with ether. The combined ethereal extracts were washed with brine, dried ($MgSO_4$), and evaporated to give a colorless oil. Purification by flash chromatography (1% EtOAc in hexane) gave **23** as a colorless oil (68 mg, 83% yield): $R_f = 0.50$ (5% EtOAc in hexane); $[\alpha]^{20}_D$ −17.2° (*c* 1.0, $CHCl_3$); IR (neat) 3460 br, 2950, 2920, 2850, 1600, 1560, 1460, 1410, 1250, 1120, 1095, 1055, 825, 770, 660 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.33 (s, 1H), 6.30 (s, 1H), 4.80 (s, 1H), 4.77 (s, 1H), 3.96 (dd, $J =$ 14.0, 6.5 Hz, 1H, part of ABq), 3.85 (dd, $J = 14.0$, 6.3 Hz, 1H, part of ABq), 3.42 (d, $J = 6.3$ Hz, 2H), 3.27 (td, $J = 11.5$, 3.6 Hz, 1H), 2.95 (td, $J = 11.5$, 2.4 Hz, 1H), 1.86 (br d, $J = 11.5$ Hz, 2H), 1.74 (t, $J = 12.5$ Hz, 1H), 1.68−1.59 (m, 2H), 1.48−1.43 (m, 2H), 1.35 (t, $J = 6.3$ Hz, 1H), 1.25−1.13 (m, 7H), 1.18 (s, 6H), 1.05 (s, 9H), 1.03 (s, 9H), 1.05−0.95 (m, 2H), 0.90−0.85 (m, 1H), 0.88 (s, 9H), 0.84 (t, $J = 6.7$ Hz, 3H), 0.30 (s, 6H), 0.22 (s, 3H), 0.15 (s, 3H), 0.02 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.8, 153.5, 153.1, 147.6, 122.1, 110.3, 109.8, 109.2, 68.8, 65.0, 44.8, 43.6, 41.1, 38.8, 37.2, 33.4, 33.2, 30.0, 29.6, 28.9, 28.6, 26.5, 26.0, 25.9, 24.6, 22.6, 18.8, 18.4, 18.3, 14.0, −3.6, −3.8, −4.5, −5.3, −5.4; mass spectrum *m*/*z* (relative intensity) 746 (M^+, 11), 731 (6), 689 (63), 601 (52), 557 (47), 477 (100), 435 (95), 73 (95). Exact mass calculated for $C_{43}H_{82}Si_3O_4$, 746.5499; found, 746.5526.

(1*R*,3*R*,4*R*)-1-(Hydroxymethyl)-4-[2′-(3′-hydroxyprop-1′-enyl)]-3-[4-(1′,1′-dimethylheptyl)-2,6-dihydroxyphenyl]cyclohexane, 24. To a solution of 68 mg of **23** (0.09 mmol) in 3.5 mL of acetonitrile at 0 °C was added 70 mg of triethylamine hydrogen fluoride (0.58 mmol) followed by 6 drops of a 20% solution of hydrofluoric acid (49% aqueous) in acetonitrile. The reaction was stirred at 0 °C for 4 h, quenched with saturated aqueous $NaHCO_3$, and extracted with EtOAc. The combined organic extracts were dried ($MgSO_4$), and the solvent was evaporated to give a colorless oil (54 mg) which was used without further purification: $R_f = 0.50$ (20% EtOAc in hexane); ^1H NMR (300 MHz, $CDCl_3$) δ 6.33 (s, 1H), 6.30 (s, 1H), 4.80 (s, 1H), 4.77 (s, 1H), 3.96 (dd, $J = 14.0$, 6.5 Hz, 1H, part of ABq), 3.85 (dd, $J = 14.0$, 6.3 Hz, 1H, part of ABq), 3.45 (br s, 2H), 3.27 (td, $J = 11.5$, 3.6 Hz, 1H), 2.95 (td, $J = 11.5$, 2.4 Hz, 1H), 1.86 (br d, $J = 11.5$ Hz, 2H), 1.74 (t, $J = 12.5$ Hz, 1H), 1.68−1.59 (m, 2H), 1.48−1.43 (m, 2H), 1.35 (t, $J = 6.3$ Hz, 1H), 1.25−1.13 (m, 7H), 1.18 (s, 6H), 1.05 (s, 9H), 1.03 (s, 9H), 1.05−0.95 (m, 2H), 0.90−0.85 (m, 1H), 0.84 (t, $J = 6.7$ Hz, 3H), 0.30 (s, 6H), 0.22 (s, 3H), 0.15 (s, 3H).

The material was dissolved in 2 mL of THF at 0 °C and treated dropwise with 93 mg of tetra-*n*-butylammonium fluoride hydrate (0.34 mmol) in 1 mL of THF. The reaction was stirred for 10 min at 0 °C, then 1 M aqueous $NaHCO_3$ was added, and the mixture was extracted with EtOAc. The organic phase was washed with water, dried (Na_2SO_4), and evaporated to give a colorless oil. Purification by flash chromatography (60% EtOAc in hexane + 1% Et_3N) gave **24** as a white foam (29 mg, 80% yield over 2 steps): $R_f = 0.65$ (80% EtOAc in hexane + 1% NEt_3); $[\alpha]^{20}_D$ −17.0° (*c* 1.0, MeOH); IR (neat) 3300 br, 2920, 2850, 1640, 1580, 1450, 1415, 1010 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.31 (d, $J = 1.7$ Hz, 1H), 6.19 (d, $J = 1.7$ Hz, 1H), 4.81 (s, 1H), 4.80 (s, 1H), 4.12 (d, $J = 12.6$ Hz, 1H, part of ABq), 3.96 (d, $J = 12.6$ Hz, 1H, part of ABq), 3.50 (d, $J = 6.2$ Hz, 2H), 3.18 (td, $J = 11.6$, 3.6 Hz, 1H), 2.95 (td, $J = 11.6$, 2.8 Hz, 1H), 1.94−1.86 (m, 3H), 1.76 (br d, $J = 13.0$ Hz, 1H), 1.73−1.60 (m, 3H), 1.55 (qd, $J =$ 13.0, 2.8 Hz, 1H), 1.47−1.43 (m, 2H), 1.26−1.12 (m, 7H), 1.17 (s, 6H), 1.02−0.94 (m, 2H), 0.89−0.85 (m, 1H), 0.84 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.8, 153.6, 151.3, 149.4, 115.4, 112.1, 107.2, 106.9, 68.5, 65.7, 44.5, 44.4, 40.9, 39.3, 37.2, 33.4, 32.3, 31.8, 30.0, 29.4, 28.7, 28.6, 24.6, 22.6, 14.1; mass spectrum *m*/*z* (relative intensity) 404 (M^+, 24), 371 (25), 320 (29), 287 (16), 249 (100), 229 (8), 163 (38). Exact mass calculated for $C_{25}H_{40}O_4$, 404.2916; found, 404.2922.

12*β*-Hydroxy-9-nor-9*β*-(hydroxymethyl)hexahydrocannabinol DMH, 5. To a solution of 25 mg of **24** (0.06 mmol) in THF was added 38 mg of mercuric acetate (0.12 mmol), and the solution was stirred for 20 h at room temperature. The reaction was cooled to −78 °C, and 36 mg of $NaBH_4$ (0.94 mmol) in 1 M sodium methoxide/methanol (3 mL) was added in a single portion. The mixture was stirred at −78 °C for 15 min, quenched with degassed saturated aqueous NH_4Cl, and allowed to warm to room temperature. The reaction was diluted with ether and washed with brine and the aqueous phase extracted with ether. The combined ethereal phases were dried ($MgSO_4$), and the solvent was evaporated to give a yellow oily solid. Elution through a short column of silica (50% EtOAc in hexane) followed by purification by HPLC (10-mm × 250-mm Phenomenex silica column, 50% EtOAc in hexane, 1.5 mL/min, RI detection) gave **5** as a white foam (15 mg, 62% yield) with a retention time of 12 min. Chiral HPLC (1-cm × 25-cm Chiracel OD column, 10% 2-propanol in hexane, 2.5 mL/min, UV detection at 254 nm) showed **5** (16.30-min retention time, 92.66%) and the enantiomer of **5** (22.71-min retention time, 4.12%), 92% ee: $R_f = 0.20$ (50% EtOAc in hexane); $[\alpha]^{20}_D$ −37.5° (*c* 1.0, $CHCl_3$); IR (neat) 3340 br, 2920, 2850, 1625, 1575, 1420, 1330, 1050, 1035, 965, 840 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.34 (d, $J = 1.8$ Hz, 1H, H-2), 6.25 (d, $J = 1.8$ Hz, 1H, H-4), 6.19 (br s, 1H, O*H*), 3.67 (s, 2H, H-12*β*), 3.55−3.47 (m, 2H, H-11), 3.31 (br d, $J = 12.7$ Hz, 1H, H-10), 2.52 (td, $J = 11.0$, 2.5 Hz, 1H, H-10a), 2.27 (br s, 2H, O*H*), 1.91−1.76 (m, 4H, H-6a, H-7, H-8, H-9), 1.50−1.46 (m, 2H, H-2′), 1.27−1.15 (m, 7H, H-8, H-4′, H-5′, H-6′), 1.18 (s, 6H, H-8′, H-9′), 1.12 (br d, $J = 9.2$ Hz, 1H, H-7), 1.10−1.02 (m, 2H, H-3′), 0.92 (s, 3H, H-12α), 0.84 (t, $J = 6.9$ Hz, 3H, H-7′), 0.83−0.78 (m, 1H, H-10); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.8 (C-5), 154.1 (C-1), 150.1 (C-3), 109.6 (C-10b), 107.7 (C-2), 105.9 (C-4), 79.0 (C-6), 68.5 (C-11), 67.9 (C-12*β*), 44.4 (C-2′), 43.2 (C-6a), 40.4 (C-9), 37.3 (C-1′), 34.4 (C-10a), 33.2 (C-10), 31.8 (C-6′), 30.0 (C-4′), 29.4 (C-8), 28.7 and 28.6 (C-8′, C-9′), 26.8 (C-7), 24.6 (C-3′), 22.7 (C-5′), 14.9 (C-12α), 14.1 (C-7′); mass spectrum *m*/*z* (relative intensity) 404 (M^+, 42), 373 (45), 320 (100), 249 (27), 163 (20). Exact mass calculated for $C_{25}H_{40}O_4$, 404.2916; found, 404.2918.

(1*R*,3*R*,4*R*)-1-[(*tert*-Butyldimethylsilyloxy)methyl]-3-[4-(1′,1′-dimethylheptyl)-2,6-bis(*tert*-butyldimethylsilyl-

oxy)phenyl]-4-[2′-(4′-hydroxybut-1′-enyl)]cyclohexane, 25. To a solution of 2.1 g of 2,6-diphenylphenol (8.4 mmol) in 28 mL of CH_2Cl_2 was added $Al(CH_3)_3$ (4.2 mmol; 1.7 mL of a 2.5 M solution in hexane) at room temperature, and the solution was stirred for 1 h. The reaction was cooled to 0 °C, 140 mg of trioxane (1.6 mmol) in 5 mL of CH_2Cl_2 added, and stirring continued at 0 °C for 1 h. A solution of 940 mg of **22** (1.4 mmol) in 28 mL of CH_2Cl_2 was added to the reaction, and stirring at 0 °C was continued for 2 h. The reaction was quenched with saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The aqueous layer was stirred with potassium sodium tartrate for 30 min and extracted with CH_2Cl_2. The combined organic phases were dried ($MgSO_4$), and the solvent was evaporated to give a yellow solid. Purification by flash chromatography (50% benzene in hexane) gave **25** as a colorless oil (872 mg, 82% yield): $R_f = 0.13$ (50% benzene in hexane); $[\alpha]^{20}_D$ −10.5° (*c* 1.0, $CHCl_3$); IR (neat) 3490 br, 3070, 2950, 2920, 2850, 1600, 1560, 1460, 1410, 1250, 1120, 1095, 1055, 825, 770, 665 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.33 (s, 1H), 6.30 (s, 1H), 4.92 (s, 1H), 4.59 (s, 1H), 3.50 (q, $J = 6.0$ Hz, 2H), 3.42 (d, $J = 6.3$ Hz, 2H), 3.27 (td, $J = 11.4$, 3.6 Hz, 1H), 2.87 (br t, $J = 11.4$ Hz, 1H), 2.18−2.03 (m, 2H), 1.86 (br d, $J = 10.5$ Hz, 2H), 1.76 (t, $J = 12.0$ Hz, 1H), 1.68−1.59 (m, 2H), 1.48−1.43 (m, 2H), 1.35−1.12 (m, 7H), 1.17 (s, 6H), 1.08−0.97 (m, 2H), 1.05 (s, 9H), 1.03 (s, 9H), 0.88 (s, 9H), 0.86−0.78 (m, 1H), 0.83 (t, $J = 6.9$ Hz, 3H), 0.31 (s, 3H), 0.30 (s, 3H), 0.23 (s, 3H), 0.14 (s, 3H), 0.02 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.7, 153.5, 149.7, 147.6, 122.1, 110.6, 110.1, 109.6, 68.8, 60.0, 45.5, 44.7, 41.2, 38.2, 38.0, 37.2, 33.9, 31.8, 33.1, 30.0, 29.6, 28.9, 28.7, 26.5, 26.0, 25.9, 24.6, 22.6, 18.8, 18.4, 18.3, 14.1, −3.5, −3.6, −3.8, −4.5, −5.3, −5.4; mass spectrum *m*/*z* (relative intensity) 760 (M^+, 21), 730 (66), 673 (52), 585 (91), 477 (100), 433 (46), 294 (23), 147 (37), 121 (57), 73 (81). Exact mass calculated for $C_{44}H_{84}O_4Si_3$, 760.5655; found, 760.5672.

(1*R*,3*R*,4*R*)-1-[(*tert*-Butyldimethylsilyloxy)methyl]-3-[4-(1′,1′-dimethylheptyl)-2,6-dihydroxyphenyl]-4-[2′-(4′-hydroxybut-1′-enyl)]cyclohexane, 26. To a solution of 860 mg of **25** (1.13 mmol) in 10 mL of THF at −78 °C was added dropwise 1.0 g of tetra-*n*-butylammonium fluoride hydrate (3.8 mmol) in 10 mL of THF. After 2 h the solution was allowed to slowly warm to 0 °C, then diluted with EtOAc, washed with water and brine, dried ($MgSO_4$), and evaporated. Purification by flash chromatography (10% EtOAc in hexane) gave **26** as a white solid (570 mg, 95% yield): $R_f = 0.25$ (10% EtOAc in hexane); mp 138−139 °C; $[\alpha]^{20}_D$ −9.7° (*c* 1.0, $CHCl_3$); IR (neat) 3330 br, 2920, 2860, 1620, 1590, 1470, 1420 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.26 (s, 1H), 6.20 (s, 1H), 5.36 (br s, 2H), 4.93 (s, 1H), 4.64 (s, 1H), 3.66−3.57 (m, 2H), 3.50−3.39 (m, 2H), 3.24−3.15 (m, 1H), 2.85 (br t, $J = 11.4$ Hz, 1H), 2.24−2.16 (m, 2H), 1.90 (br d, $J = 10.8$ Hz, 2H), 1.81−1.74 (m, 2H), 1.69 (br s, 1H), 1.48−1.43 (m, 2H), 1.35−1.09 (m, 8H), 1.17 (s, 6H), 1.05−0.96 (m, 2H), 0.89 (s, 9H), 0.86−0.78 (m, 1H), 0.83 (t, $J = 6.9$ Hz, 3H), 0.03 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.1, 153.9, 149.4, 149.2, 115.4, 111.0, 106.7, 105.9, 68.8, 60.4, 45.9, 44.7, 41.0, 38.0, 37.8, 37.2, 33.6, 33.3, 31.8, 30.0, 28.7, 26.0, 24.6, 22.6, 18.5, 14.1, −5.2; mass spectrum *m*/*z* (relative intensity) 532 (M^+, 17), 514 (6), 502 (51), 445 (33), 418 (81), 355 (19), 323 (100), 249 (99), 135 (32), 109 (72), 73 (89). Exact mass calculated for $C_{32}H_{56}O_4Si$, 532.3933; found, 532.3967.

12*β*-(Hydroxymethyl)-9-nor-9*β*-[(*tert*-butyldimethylsilyloxy)methyl]hexahydrocannabinol DMH, 27. To a flask containing 21 mg of mercuric acetate (0.067 mmol) was added 30 mg of **26** (0.056 mmol) in 3.6 mL of THF, and the solution was stirred at room temperature for 24 h. The solvent was evaporated under a stream of nitrogen and the residue dissolved in 2 mL of CH_2Cl_2. The solution was cooled to 0 °C, and to it were added 0.5 mL of 2.5 N degassed aqueous NaOH and 2 drops of tetra-*n*-butylammonium hydroxide (40% aqueous solution). After stirring for 5 min, 0.5 mL of 2.5 N degassed aqueous NaOH and 10 mg of $NaBH_4$ (0.265 mmol) were added dropwise. After 5 min, the mixture was diluted with 5 mL of CH_2Cl_2 and neutralized with degassed 1 N aqueous H_2SO_4. The mixture was extracted with CH_2Cl_2, and the combined organic phases were washed with brine, dried ($MgSO_4$), and evaporated. Purification by flash chromatography (10% EtOAc in hexane) gave **27** (13 mg, 43% yield): $R_f = 0.45$ (15% EtOAc in hexane); $[\alpha]^{20}_D$ −34.0° (*c* 1.0, $CHCl_3$); IR (neat) 3250, 2920, 2850, 1620, 1565, 1410, 1260, 1040, 830, 735 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.31 (d, $J = 1.8$ Hz, 1H), 6.22 (d, $J = 1.8$ Hz, 1H), 4.72 (s, 1H), 3.94−3.91 (m, 2H), 3.52−3.41 (m, 2H), 3.15 (br d, $J = 13.2$ Hz, 1H), 2.84−2.82 (m, 1H), 2.50 (td, $J = 11.1$, 2.4 Hz, 1H), 1.98−1.95 (m, 2H), 1.83 (br d, $J = 8.4$ Hz, 1H), 1.76−1.57 (m, 2H), 1.51−1.45 (m, 2H), 1.25−1.10 (m, 9H), 1.19 (s, 6H), 1.12 (s, 3H), 1.07−1.03 (m, 2H), 0.93−0.80 (m, 4H), 0.90 (s, 9H), 0.04 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.9, 153.5, 150.1, 109.7, 107.8, 106.0, 80.1, 68.5, 59.1, 47.3, 44.4, 41.0, 40.6, 37.3, 34.8, 33.3, 31.8, 31.6, 30.1, 30.0, 29.8, 28.7, 27.3, 26.0, 24.6, 22.7, 18.0, 14.1, −5.3; mass spectrum *m*/*z* (relative intensity) 532 (M^+, 100), 448 (91), 323 (84), 249 (88), 164 (32). Exact mass calculated for $C_{32}H_{56}O_4Si$, 532.3933; found, 532.3974.

12*β*-(Hydroxymethyl)-9-nor-9*β*-(hydroxymethyl)hexahydrocannabinol DMH, 6. To 10 mg of silyl ether **27** (0.019 mmol) in 0.5 mL of acetonitrile at 0 °C was added triethylamine hydrogen fluoride (12 mg, 0.1 mmol) followed by 2 drops of a 20% solution of HF (49% aqueous) in acetonitrile. The reaction was stirred at 0 °C for 1.5 h, diluted with Et_2O, washed with saturated aqueous $NaHCO_3$ and brine, and dried ($MgSO_4$), and the solvent was evaporated. Purification by flash chromatography (25% EtOAc in hexane) gave **6** as a white foam (6 mg, 76% yield). Chiral HPLC (1-cm × 25-cm Chiracel OD column, 10% 2-propanol in hexane, 2.5 mL/min, UV detection at 254 nm) showed **6** (22.17-min retention time, 92.09%) and the enantiomer of **6** (36.45-min retention time, 5.35%), 90% ee: $[\alpha]^{20}_D$ −51.2° (*c* 0.04, $CHCl_3$); IR (neat) 3550 br, 2960, 2920, 2850, 1620, 1570, 1420, 1260, 1080, 1040, 790 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.32 (d, $J = 1.7$ Hz, 1H, H-2), 6.22 (d, $J = 1.7$ Hz, 1H, H-4), 4.88 (br s, 1H, O*H*), 3.97−3.89 (br m, 2H, H-13), 3.56−3.49 (m, 2H, H-11), 3.22 (d, $J = 12.2$ Hz, 1H, H-10), 2.78 (br s, 1H, O*H*), 2.53 (td, $J = 11.1$, 2.7 Hz, 1H, H-10a), 1.98−1.96 (m, 3H, H-12*β*, H-8), 1.86 (dt, $J = 8.3$, 2.7 Hz, 1H, H-7), 1.80−1.76 (m, 1H, H-9), 1.67 (td, $J = 11.1$, 2.0 Hz, 1H, H-6a), 1.48 (ddd, $J = 10.8$, 5.9, 1.9 Hz, 2H, H-2′), 1.25−1.10 (m, 8H, H-7, H-8, H-4′, H-5′, H-6′), 1.19 (s, 6H, H-8′, H-9′), 1.13 (s, 3H, H-12α), 1.07−1.02 (m, 2H, H-3′), 0.85 (q, $J = 12.2$ Hz, 1H, H-10), 0.85 (t, $J = 7.3$ Hz, 3H, H-7′); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.4 (C-5), 153.6 (C-1), 150.2 (C-3), 109.5 (C-10b), 108.0 (C-2), 106.0 (C-4), 80.0 (C-6), 68.5 (C-11), 59.0 (C-13), 47.3 (C-6a), 44.4 (C-2′), 41.0 (C-12*β*), 40.5 (C-9), 37.3 (C-1′), 34.7 (C-10a), 33.2 (C-10), 31.8 (C-6′), 30.0 (C-4′), 29.6 (C-8), 28.7 and 28.6 (C-8′, C-9′), 27.2 (C-7), 24.6 (C-3′), 22.6 (C-5′), 18.0 (C-12α), 14.1 (C-7′); mass spectrum *m*/*z* (relative intensity) 418 (M^+, 45), 334 (100), 277 (42), 249 (31), 164 (30). Exact mass calculated for $C_{26}H_{42}O_4$, 418.3072; found, 418.3100.

12*β*-(Iodomethyl)-9-nor-9*β*-[(*tert*-butyldimethylsilyl)-oxymethyl]hexahydrocannabinol DMH, 28. A screw cap vial was charged with 10 mg of **27** (0.019 mmol), 0.2 mL of benzene, 5 mg of triphenylphosphine (0.019 mmol), 4 mg of imidazole (0.059 mmol), and 5 mg of iodine (0.020 mmol). The solution was blanketed with argon and capped and the reaction stirred for 45 min at 45 °C. The mixture was cooled to room temperature, diluted with ether, washed with water, aqueous sodium thiosulfate, and brine, dried ($MgSO_4$), and evaporated. Purification by flash chromatography (2−5% ether gradient in hexane) gave **28** as a colorless oil (10 mg, 82% yield): $R_f = 0.60$ (10% EtOAc in hexane); ^1H NMR (300 MHz, $CDCl_3$) δ 6.31 (d, $J = 1.5$ Hz, 1H), 6.20 (d, $J = 1.5$ Hz, 1H), 4.66 (s, 1H), 3.52−3.40 (m, 2H), 3.38−3.32 (m, 2H), 3.16 (br d, $J = 12.6$ Hz, 1H), 2.48 (td, $J = 11.1$, 2.4 Hz, 1H), 2.36−2.28 (m, 2H), 1.95 (br d, $J = 10.0$ Hz, 1H), 1.83−1.80 (m, 1H), 1.76−1.67 (m, 1H), 1.52−1.46 (m, 2H), 1.25−1.12 (m, 7H), 1.19 (s, 6H), 1.11−1.02 (m, 4H), 1.05 (s, 3H), 0.93−0.73 (m, 1H), 0.90 (s, 9H), 0.85 (t, $J = 6.9$ Hz, 3H), 0.04 (s, 6H).

12*β*-(Iodomethyl)-9-nor-9*β*-(hydroxymethyl)hexahydrocannabinol DMH, 8. The same procedure which was used to convert **27** to **6** was followed: 10 mg of iodide **28** (0.016

mmol) gave **8** as a white foam (6 mg, 73% yield). Chiral HPLC (1-cm × 25-cm Bakerbond OD column, 10% 2-propanol in hexane, 2.5 mL/min, UV detection at 254 nm) showed **8** (9.69-min retention time, 96.84%) and the enantiomer of **8** (7.00-min retention time, 2.11%), 96% ee; $[\alpha]^{20}_D$ −26.0° (*c* 1.0, $CHCl_3$); IR (neat) 3320 br, 2950, 2920, 2850, 1620, 1570, 1410, 1165, 1030 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.33 (d, J = 2.0 Hz, 1H), 6.21 (d, J = 2.0 Hz, 1H), 5.32 (br s, 1H), 3.56−3.49 (m, 2H), 3.40−3.31 (m, 2H), 3.26 (br d, J = 12.6 Hz, 1H), 2.49 (td, J = 11.1, 2.8 Hz, 1H), 2.38−2.25 (m, 2H), 1.96−1.94 (m, 1H), 1.85−1.82 (m, 1H), 1.80−1.75 (m, 1H), 1.71−1.62 (br m, 2H), 1.57−1.45 (m, 3H), 1.26−1.10 (m, 7H), 1.19 (s, 6H), 1.09−1.03 (m, 2H), 1.04 (s, 3H), 0.85 (t, J = 7.0 Hz, 3H), 0.81 (q, J = 12.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.4, 154.2, 150.2, 109.2, 107.8, 105.6, 79.4, 68.4, 46.2, 45.1, 44.4, 40.4, 37.2, 34.6, 33.2, 31.7, 30.0, 29.9, 28.7, 28.6, 27.0, 24.6, 22.6, 17.7, 14.0, −1.0; mass spectrum *m/z* (relative intensity) 528 (M^+, 49), 444 (87), 400 (12), 316 (25), 249 (70), 164 (59), 128 (100). Exact mass calculated for $C_{26}H_{41}IO_3$, 528.2089; found, 528.2137.

12*β*-Methyl-9-nor-9*β*-(hydroxymethyl)hexahydrocannabinol DMH, 11. To 10 mg of $LiAlH_4$ (0.26 mmol) under argon was added a solution of 4 mg of iodide **8** (0.007 mmol) in 0.4 mL of THF, and the reaction was allowed to stir at room temperature for 3 h. The reaction was quenched by dropwise addition of saturated aqueous NH_4Cl and extracted with ether. The combined ethereal extracts were dried ($MgSO_4$), and the solvent was evaporated to give a colorless oil. Purification by flash chromatography (50% EtOAc in hexane) gave **11** as a white foam (2 mg, 71% yield). Chiral HPLC (1-cm × 25-cm Chiralpak OD column, 10% ethanol in hexane, 2.5 mL/min, UV detection at 254 nm) showed **11** (13.01-min retention time, 94.68%) and the enantiomer of **11** (15.98-min retention time, 0.52%), 99% ee: $[\alpha]^{20}_D$ −61.0° (*c* 1.0, $CHCl_3$); IR (neat) 3330 br, 2950, 2920, 2850, 1615, 1565, 1460, 1450, 1410, 1330, 1035, 965, 840 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.35 (d, J = 1.9 Hz, 1H), 6.21 (d, J = 1.9 Hz, 1H), 3.56−3.49 (m, 2H), 3.27 (br d, J = 12.8 Hz, 1H), 2.50 (td, J = 11.0, 2.5 Hz, 1H), 1.94−1.91 (m, 1H), 1.87−1.82 (m, 1H), 1.81−1.76 (br m, 2H), 1.75−1.64 (m, 2H), 1.59−1.54 (m, 1H), 1.51−1.47 (m, 2H), 1.26−1.15 (m, 7H), 1.19 (s, 6H), 1.13−1.03 (m, 4H), 1.02 (s, 3H), 1.00 (t, J = 7.3 Hz, 3H), 0.85 (t, J = 7.0 Hz, 3H), 0.82 (q, J = 12.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.0, 154.5, 149.9, 109.6, 107.9, 105.3, 78.0, 68.6, 45.7, 44.4, 40.5, 37.3, 34.7, 33.3, 32.3, 31.8, 30.0, 29.7, 28.7, 28.6, 27.1, 24.6, 22.7, 18.7, 14.1, 7.0; mass spectrum *m/z* (relative intensity) 402 (M^+, 32), 345 (10), 318 (100), 249 (32), 164 (57), 84 (92). Exact mass calculated for $C_{26}H_{42}O_3$, 402.3123; found, 402.3142.

(3*R*,4*R*)-3-[4-(1′,1′-Dimethylheptyl)-2,6-bis(*tert*-butyldimethylsilyloxy)phenyl]-4-[2′-(4′-hydroxybut-1′-enyl)]cyclohexan-1one, 29. To 2.0 g of 2,6-diphenylphenol (8.1 mmol) in 21 mL of CH_2Cl_2 was added trimethylaluminum (2.13 mL, 4.04 mmol; 1.9 M solution in hexane) at room temperature, and the solution was stirred for 1 h. The reaction was cooled to 0 °C, and 122 mg of trioxane (1.35 mmol) in 2.5 mL CH_2Cl_2 was added. Stirring was continued at 0 °C for 1 h. A solution of **13** (485 mg, 0.77 mmol) in 9 mL of CH_2Cl_2 was added to the reaction, and stirring at 0 °C was continued for 1.5 h. The reaction was quenched with saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The aqueous layer was stirred with potassium sodium tartrate for 30 min and further extracted with EtOAc. The combined organic phases were dried ($MgSO_4$), and the solvent was evaporated to give a yellow solid (2.1 g). Purification by flash chromatography (10−30% EtOAc gradient in hexane) gave **29** as a pale yellow oil (388 mg, 80% yield): R_f = 0.05 (5% ether in hexane); $[\alpha]^{20}_D$ −22.6° (*c* 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 6.38 (s, 1H), 6.33 (s, 1H), 4.96 (s, 1H), 4.67 (s, 1H), 3.68 (dt, J = 12.3, 4.2 Hz, 1H), 3.53 (br t, J = 5.4 Hz, 2H), 3.33−3.20 (m, 2H), 2.47−2.42 (m, 2H), 2.33 (dd, J = 14.4, 3.6 Hz, 1H), 2.20−1.99 (two m, 3H), 1.76−1.62 (m, 1H), 1.49−1.44 (m, 2H), 1.31−1.25 (m, 2H), 1.20−1.18 (m, 4H), 1.18 (s, 6H), 1.05 (s, 9H), 0.99 (s, 9H), 0.88−0.81 (m, 2H), 0.84 (t, J = 6.9 Hz, 3H), 0.35 (s, 3H), 0.32 (s 3H), 0.23 (s, 3H), 0.15 (s, 3H); IR (neat) 3500 br, 3080, 2960, 2940, 2865, 1720, 1650, 1640, 1610, 1570, 1420, 1260, 1190, 1100, 1050, 830 cm^{-1}; mass spectrum *m/z* (relative intensity) 630 (M^+, 1), 612 (2), 600 (6), 573 (11), 555 (18), 543 (100), 487 (27), 433 (96), 246 (44). Exact mass calculated for $C_{37}H_{66}O_4Si_2$, 630.4482; found, 630.4498.

(3*R*,4*R*)-3-[4-(1′,1′-Dimethylheptyl)-2,6-dihydroxyphenyl]-4-[2′-(4′-hydroxybut-1′-enyl)]cyclohexan-1-one Ketal, 30. To 3.7 g of **29** (5.8 mmol) in 40 mL of THF at 0 °C was added dropwise a solution of 6.3 g of tetra-*n*-butylammonium fluoride hydrate (24.0 mmol) in 20 mL of THF. The solution turned pale green and was allowed to stir at 0 °C for 20 min. The reaction was diluted with ether and washed with water. The organic layer was dried ($MgSO_4$), and solvent was evaporated to give a yellow oil. Purification by flash chromatography (30−50% EtOAc gradient in hexane) gave **30** as a white foam (2.0 g, 86% yield): R_f = 0.05 (20% EtOAc in hexane); $[\alpha]^{20}_D$ −28.2° (*c* 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 6.41 (s, 1H; an OH overlaps this signal), 6.34 (s, 1H), 5.08 (s, 1H), 5.04 (s, 1H), 4.06−3.99 (m, 1H), 3.81 (br t, J = 9.0 Hz, 1H), 3.60 (br s, 1H), 2.89 (s, 1H, OH), 2.76−2.67 (m, 1H), 2.58 (br s, 1H), 2.42 (ddd, J = 15.0, 6.0, 3.5 Hz, 1H), 2.20 (s, 1H, OH), 2.07−2.01 (m, 2H), 1.96−1.84 (m, 2H), 1.77−1.65 (m, 2H), 1.53−1.48 (m, 2H), 1.23−1.19 (m, 6H), 1.21 (s, 6H), 1.08−1.05 (m, 2H), 0.84 (t, J = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.9, 152.4, 150.7, 147.1, 113.1, 109.5, 105.3, 104.4, 98.3, 62.4, 44.5, 40.4, 38.3, 37.5, 34.9, 31.8, 31.0, 30.5, 30.0, 28.8, 24.6, 22.7, 21.4, 14.1; IR (neat) 3360 br, 3085, 2955, 2925, 2850, 1625, 1585, 1415, 1140, 1070, 1045, 905, 735 cm^{-1}; mass spectrum *m/z* (relative intensity) 402 (M^+, 13), 372 (9), 318 (17), 304 (13), 289 (100), 249 (26), 219 (25), 178 (46). Exact mass calculated for $C_{25}H_{38}O_4$, 402.2760; found, 402.2771.

12*β*-(Hydroxymethyl)-9-nor-9*β*-hydroxyhexahydrocannabinol DMH, 31. To 380 mg of **30** (0.95 mmol) in 55 mL of THF was added 759 mg of mercuric acetate (2.36 mmol), and the solution was allowed to stir at room temperature for 24 h. The reaction was cooled to −78 °C, and a solution of 359 mg of $NaBH_4$ (9.50 mmol) in 15 mL of 1 M sodium methoxide/methanol was added in a single portion. The mixture was stirred at −78 °C for 15 min, quenched with degassed saturated aqueous NH_4Cl, and allowed to warm to room temperature. The reaction was diluted with 100 mL of ether and washed with brine and the aqueous phase extracted with 3 × 50 mL of ether. The combined ethereal phases were dried ($MgSO_4$), and solvent was evaporated to give a gray/white oily solid. Purification by flash chromatography (60% EtOAc in hexane) gave **31** as a white solid (253 mg, 66% yield). Chiral HPLC (1-cm × 25-cm Chiracel OD column, 10% 2-propanol in hexane, 2.5 mL/min, UV detection at 254 nm) showed **31** to be 95% of a single enantiomer with retention time of 22.17 min (minor enantiomer retention time = 36.45 min): R_f = 0.30 (60% EtOAc in hexane); mp 153−154 °C; $[\alpha]^{20}_D$ −59.4° (*c* 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 6.31 (s, 1H), 6.22 (s, 1H), 5.92 (br s, 1H), 3.96−3.87 (m, 2H), 3.90−3.81 (m, 1H), 3.48 (br d, J = 10.2 Hz, 1H), 2.78 (br s, 1H), 2.53 (td, J = 10.2, 2.0 Hz, 1H), 2.16 (br d, J = 10.2 Hz, 1H), 1.97 (t, J = 5.7 Hz, 2H), 1.84 (br d, J = 10.2 Hz, 1H), 1.68 (br t, J = 11.5 Hz, 1H), 1.51−1.43 (m, 2H), 1.48−1.35 (m, 2H), 1.27−1.18 (m, 6H), 1.19 (s, 6H), 1.16−0.99 (m, 4H), 1.12 (s, 3H), 0.84 (t, J = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.8, 153.4, 150.3, 108.7, 107.5, 106.0, 79.9, 70.9, 58.9, 46.3, 44.4, 41.1, 38.7, 37.3, 35.6, 33.2, 31.8, 30.0, 28.6, 25.8, 24.6, 22.7, 17.9, 14.1; IR (neat) 3340 br, 2960, 2930, 2860, 1625, 1575, 1460, 1420, 1050, 975, 845 cm^{-1}; mass spectrum *m/z* (relative intensity) 404 (M^+, 48), 386 (10), 320 (100), 302 (22), 249 (35), 178 (49). Exact mass calculated for $C_{25}H_{40}O_4$, 404.2916; found, 404.2935.

1-(Allyloxy)-12*β*-(hydroxymethyl)-9-nor-9*β*-hydroxyhexahydrocannabinol DMH, 32. Stock solutions of allyl bromide (160 μL) in CH_2Cl_2 (2 mL) and tetra-*n*-butylammonium hydroxide (TBAH) (723 μL, 40% aqueous) in water (7.5 mL) were prepared. To a mixture of 162 mg of **31** (0.40 mmol), 5.4 mL of CH_2Cl_2, and 2.7 mL of water was added 2.7 mL of the TBAH stock solution (1 equiv) and 538 μL of the allyl bromide stock solution (1 equiv), and the reaction was stirred at room temperature. The reaction was monitored closely by

TLC, and after 1 h an additional 54 μL of the allyl bromide stock solution (0.1 equiv) was added. After another 1 h at room temperature, additional portions of TBAH stock solution (540 μL, 0.2 equiv) and allyl bromide stock solution (54 μL, 0.1 equiv) were added and the reaction stirred for 1 h, at which time negligible starting material remained as judged by TLC. The reaction was quenched with saturated aqueous NH_4Cl, extracted with 3 × 30 mL of CH_2Cl_2, and dried ($MgSO_4$), and the solvent was evaporated to give a brown oil. Purification by flash chromatography (40−60% EtOAc gradient in hexane) gave **32** as a colorless oil (142 mg, 80% yield): R_f = 0.45 (60% EtOAc in hexane); $[\alpha]^{20}_D$ −64.4° (*c* 1.0, $CHCl_3$); IR (neat) 3340 (br), 3080, 2930, 2850, 1610, 1565, 1460, 1450, 1410, 1130, 1080, 1050, 985, 925, 850, 730 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.38 (s, 1H), 6.36 (s, 1H), 6.12−6.03 (m, 1H), 5.40 (dd, *J* = 17.3, 1.2 Hz, 1H), 5.28 (dd, *J* = 10.8, 1.2 Hz, 1H), 4.54 (d, *J* = 5.1 Hz, 2H), 3.99−3.85 (m, 2H, an OH overlaps this signal), 3.87−3.78 (m, 1H), 3.42 (dt, *J* = 11.7, 1.8 Hz, 1H), 2.79 (br s, 1H), 2.53 (td, *J* = 11.1, 2.1 Hz, 1H), 2.17 (br d, *J* = 10.8 Hz, 1H), 1.97 (t, *J* = 5.7 Hz, 2H), 1.84 (br d, *J* = 12.6 Hz, 1H), 1.68 (br t, *J* = 11.4 Hz, 2H), 1.53−1.48 (m, 2H), 1.29−1.13 (m, 6H), 1.21 (s, 6H), 1.13−1.00 (m, 4H), 1.10 (s, 3H), 0.85 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.2, 153.1, 149.8, 133.6, 117.0, 110.3, 108.2, 102.5, 79.7, 70.5, 68.8, 58.8, 46.6, 44.3, 41.1, 39.5, 37.6, 35.6, 33.2, 31.7, 29.9, 28.7, 25.7, 24.5, 22.6, 17.7, 14.0; mass spectrum *m*/*z* (relative intensity) 444 (M^+, 100), 402 (7), 360 (92), 313 (16), 289 (34), 218 (28), 175 (20). Exact mass calculated for $C_{28}H_{44}O_4$, 444.3228; found, 444.3236.

1-(Allyloxy)-12β-formyl-9-nor-9-oxohexahydrocannabinol DMH, 33. To a suspension of 859 mg of Dess−Martin periodinane (2.03 mmol) in 8 mL of CH_2Cl_2 was added 300 mg of **32** (0.68 mmol) in 8 mL of CH_2Cl_2, and the resulting mixture was stirred at room temperature for 2 h. The reaction was diluted with 20 mL of ether and stirred for 10 min with 20 mL of saturated aqueous $NaHCO_3$ containing a 7-fold excess of sodium thiosulfate (750 mg). The organic layer was separated, washed with saturated aqueous $NaHCO_3$ and water, and dried ($MgSO_4$), and the solvent was evaporated to give an orange oil. Purification by flash chromatography (25% EtOAc in hexane) gave **33** as a colorless oil (269 mg, 90% yield): R_f = 0.73 (60% EtOAc in hexane); $[\alpha]^{20}_D$ −59.1° (*c* 1.0, $CHCl_3$); IR (neat) 2950, 2920, 2850, 1720, 1710, 1610, 1565, 1415, 1115, 1095, 930, 830, 760, 700 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 10.07 (t, *J* = 2.7 Hz, 1H), 6.45 (s, 1H), 6.40 (s, 1H), 6.12−5.99 (m, 1H), 5.40 (dd, *J* = 16.8, 0.9 Hz, 1H), 5.29 (dd, *J* = 10.5, 0.9 Hz, 1H), 4.54 (d, *J* = 5.1 Hz, 2H), 3.83 (br d, *J* = 15 Hz, 1H), 2.91 (dt, *J* = 11.7, 3.6 Hz, 1H), 2.80 (dd, *J* = 14.7, 2.1 Hz, 1H), 2.70 (dd, *J* = 14.7, 3.6 Hz, 1H), 2.59 (td, *J* = 11.1, 2.1 Hz, 1H), 2.45−2.35 (m, 1H), 2.17−2.03 (m, 3H), 1.55−1.49 (m, 2H), 1.33−1.14 (m, 7H), 1.23 (s, 6H), 1.20 (s, 3H), 1.11−0.99 (m, 2H), 0.84 (t, *J* = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 210.2, 201.9, 157.0, 153.0, 150.7, 133.2, 117.5, 109.2, 108.2, 102.5, 77.8, 68.8, 52.4, 46.1, 45.6, 44.3, 40.3, 37.7, 34.1, 31.7, 29.9, 28.7, 25.9, 24.5, 22.6, 18.1, 14.0; mass spectrum *m*/*z* (relative intensity) 440 (M^+, 43), 356 (100), 315 (25), 287 (14). Exact mass calculated for $C_{28}H_{40}O_4$, 440.2916; found, 440.2945.

1-(Allyloxy)-12β-(2-methoxyethenyl)-9-nor-9-(methoxymethylene)hexahydrocannabinol DMH, 34. (Methoxymethyl)triphenylphosphonium chloride was dried overnight at 60 °C/0.1 mmHg. To a suspension of 1.19 g of this salt (3.46 mmol) in 8 mL of benzene was added sodium *tert*-amylate (4.07 mL, 3.46 mmol; 0.85 M solution in benzene), and the mixture stirred at room temperature for 15 min until a clear, deep red solution was obtained. A solution of 254 mg of keto aldehyde **33** (0.58 mmol) in 3 mL of benzene was added dropwise to the ylide and the reaction stirred at 70 °C for 3 h. The reaction was quenched by dropwise addition of saturated aqueous NH_4Cl and diluted with 25 mL of ether and the organic phase separated. The aqueous phase was extracted with 3 × 25 mL of ether, the combined ethereal extracts were dried ($MgSO_4$), and the solvent was evaporated to give an orange oil. Purification by flash chromatography (30% benzene in hexane) gave **34** as a colorless oil (240 mg, 84% yield) (mixture of geometrical isomers): R_f = 0.2 (30% benzene in hexane); IR (neat) 3050, 2920, 2850, 1680, 1665, 1650, 1610, 1565, 1450, 1410, 1375, 1330, 1200, 1130, 1095, 990, 930 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.41 (s), 6.35 (s,), 6.22−6.04 (m), 6.02 (d, *J* = 6.3 Hz), 5.84 (br s), 5.50 (td, *J* = 15.6, 1.5 Hz), 5.28 (dd, *J* = 10.5, 6.3 Hz), 4.99−4.90 (m,), 4.70−4.62 (m), 4.53 (br d, *J* = 3.0 Hz), 4.26 (dd, *J* = 13.5, 2.4 Hz), 3.60, 3.58, 3.57 & 3.56 (four s), 3.47 (dd, *J* = 13.5, 1.2 Hz), 2.89 (br d, *J* = 13.5 Hz), 2.58−2.14 (m), 2.05−1.60 (m), 1.54−1.49 (m), 1.42−1.30 (m), 1.25−1.14 (m), 1.23 (s), 1.11−1.04 (m), 1.03 (s), 1.00 (s), 0.84 (t, *J* = 6.5 Hz); mass spectrum *m*/*z* (relative intensity) 496 (M^+, 4), 425 (100), 385 (11), 339 (8), 262 (11), 183 (18), 137 (5), 84 (19). Exact mass calculated for $C_{32}H_{48}O_4$, 496.3540; found, 496.3561. Anal. Calcd: C, 77.36; H, 9.74. Found: C, 77.56; H, 9.66.

1-(Allyloxy)-12β-(2-hydroxyethyl)-9-nor-9β-(hydroxymethyl)hexahydrocannabinol DMH, 35. To a solution of 75 mg of bis-enol ether **34** (0.15 mmol) in 10 mL of CH_2Cl_2 was added aqueous trichloroacetic acid (98 mg, 0.60 mmol), and the mixture stirred at room temperature for 10 min. The reaction was quenched by addition of saturated aqueous $NaHCO_3$, washed with brine, and dried ($MgSO_4$) and the solvent evaporated to give a pale yellow oil: R_f = 0.54 and 0.59 (20% EtOAc in hexane); ^1H NMR (300 MHz, $CDCl_3$) aldehyde resonances at δ 9.87 (br s, C-13 and C-9a aldehydes), 9.63 (br s, C-9b aldehyde).

This oil was dissolved in 10 mL of absolute ethanol and stirred with 176 mg of anhydrous K_2CO_3 (1.28 mmol) at room temperature for 17 h. Examination by ^1H NMR of an aliquot taken from the reaction showed epimerization had occurred: R_f = 0.54 (20% EtOAc in hexane); ^1H NMR δ 9.87 (br s, 1H), 9.63 (br s, 1H), 6.37 (s, 1H), 6.36 (s, 1H), 6.11−6.00 (m, 1H), 5.40 (d, *J* = 16.2 Hz, 1H), 5.27 (d, *J* = 10.5 Hz, 1H), 4.54 (d, *J* = 5.1 Hz, 2H), 3.49 (br d, *J* = 13.5, 1H), 2.85−2.75 (m, 1H), 2.68 (t, *J* = 6.9 Hz, 1H), 2.60−2.45 (m, 2H), 2.13−1.91 (m, 3H), 1.70 (br s, 1H), 1.54−1.41 (m, 4H), 1.25−1.10 (m, 8H), 1.15 (s, 6H), 1.09−0.97 (m, 2H), 1.07 (s, 3H), 0.84 (m, 3H).

To the ethanolic solution of the dialdehyde was added 67 mg of $NaBH_4$ (1.76 mmol) at 0 °C. The reaction was warmed to room temperature, stirred for 1 h, and then quenched by dropwise addition of saturated aqueous NH_4Cl, and the solvent was evaporated. The residual white solid was dissolved in 10 mL of water and extracted with 3 × 30 mL of EtOAc. The combined organic phases were dried ($MgSO_4$), and the solvent was evaporated to give a yellow oil. Purification by flash chromatography (40−60% EtOAc gradient in hexane) gave diol **35** as a white foam (43 mg, 61% yield over 3 steps): R_f = 0.37 (40% EtOAc in hexane); $[\alpha]^{20}_D$ −69.7° (*c* 1.0, $CHCl_3$); IR (neat) 3350 (br), 3075, 2920, 2850, 1610, 1565, 1410, 1130, 1075, 1045 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.37 (s, 1H), 6.35 (s, 1H), 6.13−6.01 (m, 1H), 5.42 (dd, *J* = 17.1, 1.2 Hz, 1H), 5.26 (dd, *J* = 10.5, 1.2 Hz, 1H), 4.52 (d, *J* = 4.8 Hz, 2H), 3.73 (br s, 2H), 3.49 (t, *J* = 5.5 Hz, 2H), 3.22 (br d, *J* = 12.3 Hz, 1H), 2.52 (td, *J* = 10.8, 2.4 Hz, 1H), 2.00−1.92 (m, 1H), 1.92−1.82 (m, 1H), 1.83−1.70 (br m, 3H), 1.65−1.57 (m, 2H), 1.53−1.48 (m, 2H), 1.25−1.03 (br m, 12H), 1.19 (s, 6H), 1.07 (s, 3H), 0.84 (t, *J* = 6.9 Hz, 3H), 0.82−0.71 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.5, 154.0, 149.7, 133.8, 116.7, 111.2, 108.3, 102.2, 77.9, 68.9, 68.6, 63.3, 46.6, 44.5, 40.7, 37.6, 36.0, 35.0, 33.6, 31.7, 30.0, 29.8, 28.8, 28.7, 27.2, 26.0, 24.6, 22.6, 18.3, 14.1; mass spectrum *m*/*z* (relative intensity) 472 (M^+, 67), 388 (99), 347 (31), 289 (100), 249 (44), 203 (54), 163 (71). Exact mass calculated for $C_{30}H_{48}O_4$, 472.3540; found, 472.3577. Anal. Calcd: C, 76.28; H, 10.24. Found: C, 76.35; H, 10.40.

12β-(2-Hydroxyethyl)-9-nor-9β-(hydroxymethyl)hexahydrocannabinol DMH, 7. To a solution of 38 mg of allyl ether **35** (0.08 mmol) in 1.5 mL of THF was added tetrakis-(triphenylphosphine)palladium(0) (2 mg, 0.002 mmol, 0.02 equiv), and the solution stirred at room temperature for 5 min. Sodium borohydride (12 mg, 0.32 mmol) was added, and the reaction was allowed to stir for 6 h. The reaction was quenched by dropwise addition of saturated aqueous NH_4Cl, extracted with 3 × 30 mL of EtOAc, and dried ($MgSO_4$), and the solvent was evaporated to give a brown oil. Purification

by flash chromatography (30−50% EtOAc gradient in hexane) gave **7** as a white solid (32 mg, 92% yield). Chiral HPLC (1-cm × 25-cm Chiracel OD column, 10% 2-propanol in hexane, 2.5 mL/min, UV detection at 254 nm) showed **7** (22.47-min retention time, 82.97%) and the enantiomer of **7** (32.57-min retention time, 5.78%), 88% ee: R_f = 0.28 (60% EtOAc in hexane); mp 175−176 °C; $[\alpha]^{20}_D$ −44.5° (*c* 1.0, $CHCl_3$); IR (neat) 3340 br, 2920, 2850, 1620, 1570, 1410, 1040 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.33 (d, J = 1.8 Hz, 1H, H-2), 6.20 (d, J = 1.8 Hz, 1H, H-4), 5.08 (br s, 1H, OH), 3.74−3.71 (m, 2H, H-14), 3.52 (m, 2H, H-11), 3.23 (br d, J = 12.5 Hz, 1H, H-10), 2.52 (td, J = 11.0, 2.6 Hz, 1H, H-10a), 1.88−1.86 (m, 1H, H-8), 1.82−1.73 (m, 8H, H-7, H-9, H-12β, H-13, 2xOH), 1.57 (td, J = 11.1, 2.2 Hz, 1H, H-6a), 1.50−1.46 (m, 2H, H-2′), 1.25−1.13 (m, 8H, H-7, H-8, H-4′, H-5′, H-6′), 1.16 (s, 6H, H-8′, H-9′), 1.10−1.04 (m, 2H, H-3′), 1.01 (s, 3H, H-12α), 0.83 (t, J = 6.8 Hz, 3H, H-7′), 0.77 (q, J = 12.0 Hz, 1H, H-10); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.5 (C-5), 154.4 (C-1), 150.0 (C-3), 109.5 (C-10b), 107.8 (C-2), 105.5 (C-4), 78.0 (C-6), 68.5 (C-11), 63.4 (C-14), 46.3 (C-6a), 44.4 (C-2′), 40.5 (C-9), 37.3 (C-1′), 36.0 (C-12β), 34.8 (C-10a), 33.2 (C-10), 31.8 (C-6′), 30.0 (C-4′), 29.6 (C-8), 28.7 and 28.6 (C-8′, C-9′), 27.1 (C-7), 26.0 (C-13), 24.6 (C-3′), 22.7 (C-5′), 18.4 (C-12α), 14.1 (C-7′); mass spectrum *m*/*z* (relative intensity) 432 (M^+, 34), 348 (100), 249 (65), 163 (49). Exact mass calculated for $C_{27}H_{44}O_4$, 432.3228; found, 432.3226.

12β-(2-Iodoethyl)-9-nor-9β-(hydroxymethyl)hexahydrocannabinol DMH, 9. Stock solutions of iodine (123 mg in 500 μL of benzene) and triphenylphosphine (123 mg in 500 μL of benzene) were prepared. To a dry septum-capped vial containing 7 mg of imidazole (0.093 mmol) was added 10 mg of **7** (0.023 mmol) in 200 μL of benzene followed by 50 μL (0.046 mmol) of the triphenylphosphine stock solution. The iodine stock solution was added dropwise to the stirred reaction mixture until a yellow coloration persisted. The reaction was stirred at 50 °C for 25 min, at which time TLC showed the absence of starting material. After cooling to room temperature, the reaction was diluted with ether/EtOAc, washed with water, saturated aqueous sodium thiosulfate, and brine, dried ($MgSO_4$), and evaporated to give a pale yellow oil. Purification by flash chromatography (40% EtOAc in hexane) gave **9** as a white foam (10 mg, 80% yield). Chiral HPLC (1-cm × 25-cm Bakerbond OD column, 10% 2-propanol in hexane, 2.5 mL/min, UV detection at 254 nm) showed **9** (9.73-min retention time, 93.27%) and the enantiomer of **9** (7.04-min retention time, 2.14%), 96% ee: R_f = 0.56 (80% EtOAc in hexane); $[\alpha]^{20}_D$ −35.2° (*c* 1.0, $CHCl_3$); IR (neat) 3320 br, 2920, 2850, 1620, 1570, 1410, 1040 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.32 (d, J = 1.75 Hz, 1H), 6.20 (d, J = 1.75 Hz, 1H), 4.74 (br s, 1H), 3.52 (d, J = 6.5 Hz, 2H), 3.31−3.20 (m, 3H), 2.51 (td, J = 11.0, 2.6 Hz, 1H), 2.13−2.05 (m, 1H), 2.03−1.98 (m, 1H), 1.97−1.93 (m, 1H), 1.89−1.83 (m, 1H), 1.79−1.69 (m, 3H), 1.70−1.58 (br m, 2H), 1.51−1.46 (m, 2H), 1.25−1.05 (m, 10H), 1.19 (s, 6H), 1.06 (s, 3H), 0.89−0.78 (m, 1H), 0.84 (t, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.6, 154.4, 150.1, 109.3, 107.9, 105.4, 77.7, 68.5, 46.4, 44.4, 40.7, 40.5, 37.3, 34.8, 33.2, 31.8, 30.0, 29.6, 28.7, 28.6, 27.1, 27.0, 24.6, 22.7, 18.4, 14.1, 7.7; mass spectrum *m*/*z* (relative intensity) 542 (M^+, 61), 458 (100), 414 (6), 330 (25), 249 (55), 164 (54), 128 (65). Exact mass calculated for $C_{27}H_{43}IO_3$, 542.2245; found, 542.2266.

In addition to **9**, 12β-(2-iodoethyl)-9-nor-9β-(iodomethyl)-hexahydrocannabinol DMH (3 mg, 20%) was isolated: R_f = 0.84 (80% EtOAc in hexane); IR (neat) 3400 br, 2920, 2850, 1620, 1570, 1410, 1040 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.33 (d, J = 1.9 Hz, 1H), 6.18 (d, J = 1.9 Hz, 1H), 4.70 (br s, 1H), 3.32−3.27 (m, 2H), 3.25−3.20 (m, 2H), 3.14 (dd, J = 9.8, 6.7 Hz, 1H), 2.53 (td, J = 11.0, 2.6 Hz, 1H), 2.14−2.04 (m, 2H), 2.05−1.96 (m, 1H), 1.86−1.84 (m, 1H), 1.79−1.72 (m, 2H), 1.71−1.64 (br m, 1H), 1.51−1.47 (m, 3H), 1.27−1.12 (m, 10H), 1.19 (s, 6H), 1.06 (s, 3H), 0.92−0.84 (m, 1H), 0.85 (t, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.7, 154.3, 150.2, 108.9, 108.0, 105.4, 77.6, 46.0, 44.4, 40.8, 39.7, 37.0, 34.8, 33.4, 31.8, 30.0, 29.7, 28.7, 28.6, 27.0, 26.9, 24.6, 22.7, 18.4, 15.5, 14.1, 7.7; mass spectrum *m*/*z* (relative intensity) 652 (M^+, 27), 568 (47), 524 (21), 440 (24), 396 (8), 355 (16), 249 (41), 164 (12), 128 (100). Exact mass calculated for $C_{27}H_{42}I_2O_2$, 652.1262; found, 652.1285.

11-Hydroxy-3-(1,1′-dimethylheptyl)hexahydrocannabinol (10) was prepared according to the procedure of Yan et al.[25] Chiral HPLC (1-cm × 25-cm Chiralpak OD column, 10% ethanol in hexane, 2.5 mL/min, UV detection at 254 nm) showed **10** (13.69-min retention time, 91.73%) and the enantiomer of **10** (18.29-min retention time, 5.86%), 88% ee.

12β-Ethyl-9-nor-9β-(hydroxymethyl)hexahydrocannabinol DMH, 12. To 28 mg of $LiAlH_4$ (0.74 mmol) under argon was added 10 mg of **9** (0.018 mmol) in 1 mL of THF, and the reaction was allowed to stir at room temperature for 3 h. The reaction was quenched by dropwise addition of saturated aqueous NH_4Cl and extracted with ether. The combined ethereal extracts were dried ($MgSO_4$), and solvent was evaporated to give a colorless oil. Purification by HPLC (10-mm × 250-mm Phenomenex silica column, 30% EtOAc in hexane, 3 mL/min, UV detection at 254 nm) gave **12** as a white foam (6 mg, 80% yield, 90.3% pure) with a retention time of 25 min: R_f = 0.25 (60% EtOAc in hexane); $[\alpha]^{20}_D$ −95.5° (*c* 1.0, $CHCl_3$); IR (neat) 3320 br, 2950, 2920, 2860, 1620, 1565, 1460, 1450, 1410, 1330, 1035, 960, 840 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.34 (d, J = 2.0 Hz, 1H), 6.19 (d, J = 2.0 Hz, 1H), 4.84 (br s, 1H), 3.52 (dd, J = 6.5, 1.0 Hz, 2H), 3.23 (br d, J = 12.8 Hz, 1H), 2.50 (td, J = 11.0, 2.7 Hz, 1H), 1.95−1.91 (m, 1H), 1.86−1.83 (m, 1H), 1.80−1.72 (br m, 1H), 1.68−1.64 (m, 1H), 1.64−1.60 (m, 2H), 1.58−1.51 (m, 2H), 1.50−1.47 (m, 2H), 1.48−1.43 (m, 1H), 1.25−1.17 (m, 7H), 1.19 (s, 6H), 1.12−1.04 (m, 3H), 1.03 (s, 3H), 0.96 (t, J = 6.7 Hz, 3H), 0.88−0.78 (m, 1H), 0.84 (t, J = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.0, 154.5, 150.0, 109.5, 108.0, 105.3, 78.2, 68.6, 46.3, 44.5, 42.2, 40.6, 37.3, 34.8, 33.4, 31.8, 30.1, 29.7, 28.7, 28.6, 27.2, 24.6, 22.7, 18.5, 15.7, 14.6, 14.1; mass spectrum *m*/*z* (relative intensity) 416 (M^+, 31), 345 (17), 332 (100), 249 (57), 164 (21), 85 (38), 71 (66). Exact mass calculated for $C_{27}H_{44}O_3$, 416.3279; found, 416.3313.

Pharmacological Methods. Rat forebrain synaptosomal membranes were prepared by the method of Dodd et al.[27] and were used to assess the affinity of **5**−**12** 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.[28]

Acknowledgment. NIDA (Grants DA 09158 and DA 07215) is thanked for generous support of this work. We also thank Dr. Liu Dai for experimental assistance.

References

(1) (a) *Cannabinoids as Therapeutic Agents*; Mechoulam, R., Ed.; CRC Press: Boca Raton, FL, 1986. (b) Nye, J. S.; Snowman, A. M.; Voglmaier, S.; Snyder, S. H. High-Affinity Cannabinoid Binding Site: Regulation by Ions, Ascorbic Acid, and Nucleotides. *J. Neurochem.* **1989**, *52*, 1892−1897. (c) Little, P. J.; Compton, D. R.; Johnson, M. R.; Melvin, L. S.; Martin, B. R. Pharmacology and Stereoselectivity of Structurally Novel Cannabinoids in Mice. *J. Pharmacol. Exp. Ther.* **1988**, *247*, 1046−1051. (d) Feigenbaum, J. J.; Richmond, S. A.; Weissman, Y.; Mechoulam, R. Inhibition of Cisplatin-Induced Emesis in the Pigeon by a Non-Psychotropic Synthetic Cannabinoid. *Eur. J. Pharmacol.* **1989**, *169*, 159−165. (e) Howlett, A. C.; Johnson, M. R.; Melvin, L. S.; Milne, G. M. Nonclassical Cannabinoid Analgetics Inhibit Adenylate Cyclase: Development of a Cannabinoid Receptor Model. *Mol. Pharmacol.* **1988**, *33*, 297−302.

(2) Makriyannis, A.; Rapaka, R. S. The Molecular Basis of Cannabinoid Activity. *Life Sci.* **1990**, *47*, 2173−2184.
(3) (a) Devane, W. A.; Dysarz, F. A., III; Johnson, M. R.; Melvin, L. S.; Howlett, A. C. Determination and Characterization of a Cannabinoid Receptor in Rat Brain. *Mol. Pharmacol.* **1988**, *34*, 605−613. (b) Matsuda, L. A.; Lolait, S. J.; Brownstein, M. J.; Young, A. C.; Bonner, T. I. Structure of a Cannabinoid Receptor and Functional Expression of the Cloned cDNA. *Nature* **1990**, *346*, 561−564.
(4) Munro, S.; Thomas, K. L.; Abu-Shaar, M. Molecular Characterization of a Peripheral Receptor for Cannabinoids. *Nature* **1993**, *365*, 61−65.
(5) Kaminski, N. E.; Abood, M. E.; Kessler, F. K.; Martin, B. R.; Schatz, A. R. Identification of a Functionally Relevant Cannabinoid Receptor on Mouse Spleen Cells that is Involved in Cannabinoid-Mediated Immune Modulation. *Mol. Pharmacol.* **1992**, *42*, 736−742.
(6) Devane, W. A.; Hanus, L.; Breuer, A.; Pertwee, R. G.; Stevenson, L. A.; Griffin, G.; Gibson, D.; Mandelbaum, A.; Etinger, A.; Mechoulam, R. Isolation and Structure of a Brain Constituent that Binds to the Cannabinoid Receptor. *Science* **1992**, *258*, 1946−1949.
(7) (a) Razdan, R. K. Structure−Activity Relationships in Cannabinoids. *Pharmacol. Rev.* **1986**, *38*, 75−149. (b) Johnson, M. R.; Melvin, L. S. In *Cannabinoids as Therapeutic Agents*; Mechoulam, R., Ed.; CRC Press: Boca Raton, FL, 1986; pp 121−145.
(8) Wilson, R. S.; May, E. L. Analgesic Properties of the Tetrahydrocannabinols, Their Metabolites and Analogues. *J. Med. Chem.* **1975**, *18*, 700−703.
(9) Tius, M. A.; Makriyannis, A.; Zou, X. L.; Abadji, V. Conformationally Restricted Hybrids of CP-55,940 and HHC: Stereoselective Synthesis and Activity. *Tetrahedron* **1994**, *50*, 2671−2680.
(10) Archer, R. A.; Blanchard, W. B.; Day, W. A.; Johnson, D. W.; Lavagnino, E. R.; Ryan, C. W.; Baldwin, J. E. Cannabinoids. 3. Synthetic Approaches to 9-Ketocannabinoids. Total Synthesis of Nabilone. *J. Org. Chem.* **1977**, *42*, 2277−2284.
(11) Since the original submission of this manuscript, we have improved this process by using a mixture of dichloromethane−ethyl acetate−hexane (1:1:20) for the recrystallizaton. Under these conditions, the yield of **17** is 76%: Tius, M. A.; Kawakami, J. K.; Hill, W. A. G.; Makriyannis, A. Selectivity in Aromatic Fluorination. Introduction of Fluorine Probes into Nabilone. *J. Chem. Soc., Chem. Commun.* **1996**, 2085−2086.
(12) Kato, M.; Kamat, V. P.; Tooyama, Y.; Yoshikoshi, A. Electrophile-Initiated Cyclobutane Ring Cleavage of (+)-*cis*-3-Methylnopinone. *J. Org. Chem.* **1989**, *54*, 1536−1538.
(13) Busch-Petersen, J.; Hill, W. A. G.; Fan, P.; Khanolkar, A.; Xie, X.-Q.; Tius, M. A.; Makriyannis, A. Unsaturated Side Chain *β*-11-Hydroxyhexahydrocannabinol Analogues. *J. Med. Chem.* **1996**, *39*, 3790−3796.
(14) Umbreit, M. A.; Sharpless, K. B. Allylic Oxidation of Olefins by Catalytic and Stoichiometric Selenium Dioxide with *tert*-Butyl Hydroperoxide. *J. Am. Chem. Soc.* **1977**, *99*, 5526−5528.
(15) Newton, R. F.; Reynolds, D. P.; Finch, M. A. W.; Kelly, D. R.; Roberts, S. M. An Excellent Reagent for the Removal of the *tert*-Butyldimethylsilyl Protecting Group. *Tetrahedron Lett.* **1979**, *20*, 3981−3982.
(16) (a) Collington, E. W.; Finch, H.; Smith, I. J. Selective Deprotection of Alcoholic and Phenolic Silyl Ethers. *Tetrahedron Lett.* **1985**, *26*, 681−684. (b) Nyström, J.-E.; McCanna, T. D.; Helquist, P.; Iyer, R. S. Short Intramolecular Diels−Alder Approach to Functionalized Spiro[4.5]dienes. *Tetrahedron Lett.* **1985**, *26*, 5393−5396.
(17) Corey, E. J.; Venkateswarlu, A. Protection of Hydroxyl Groups as *tert*-Butyldimethylsilyl Derivatives. *J. Am. Chem. Soc.* **1972**, *94*, 6190−6191.
(18) Brown, H. C.; Geoghegan, P. J., Jr. Solvomercuration-Demercuration. I. The Oxymercuration-Demercuration of Representative Olefins in Aqueous System. A Convenient Mild Procedure for the Markovnikov Hydration of the Carbon−Carbon Double Bond. *J. Org. Chem.* **1970**, *35*, 1844−1850.
(19) Tius, M. A.; Busch-Petersen, J. Stereochemical Control in the Oxymercuration of 5-Alken-1-ols. *Tetrahedron Lett.* **1994**, *35*, 5181−5184.
(20) (a) Nonoshita, K.; Banno, H.; Maruoka, K.; Yamamoto, H. Organoaluminum-Promoted Claisen Rearrangement of Allyl Vinyl Ethers. *J. Am. Chem. Soc.* **1990**, *112*, 316−322. (b) Maruoka, K.; Concepcion, A. B.; Hirayama, N.; Yamamoto, H. Generation of a Stable Formaldehyde-Organoaluminum Complex and Its Synthetic Utility. *J. Am. Chem. Soc.* **1990**, *112*, 7422−7423.
(21) Nicolaou, K. C.; Daines, R. A.; Ogawa, Y.; Chakraborty, T. K. Total Synthesis of Amphotericin B. 3. The Final Steps. *J. Am. Chem. Soc.* **1988**, *110*, 4696−4705.
(22) (a) Ireland, R. E.; Lui, L. An Improved Procedure for the Preparation of the Dess−Martin Periodinane. *J. Org. Chem.* **1993**, *58*, 2899. (b) Dess, D. B.; Martin, J. C. Readily Accessible 12-I-5[1] Oxidant for the Conversion of Primary and Secondary Alcohols to Aldehydes and Ketones. *J. Org. Chem.* **1983**, *48*, 4155−4156.
(23) Beugelmans, R.; Bourdet, S.; Bigot, A.; Zhu, J. Reductive Deprotection of Aryl Allyl Ethers with $Pd(PPh_3)_4/NaBH_4$. *Tetrahedron Lett.* **1994**, *35*, 4349−4350.
(24) Abadji, V.; Lin, S.; Taha, G.; Griffin, G.; Stevenson, L. A.; Pertwee, R. G.; Makriyannis, A. (*R*)-Methanandamide: A Chiral Novel Anandamide Possessing Higher Potency and Metabolic Stability. *J. Med. Chem.* **1994**, *37*, 1889−1893.
(25) Yan, G.; Yin, D.; Khanolkar, A. D.; Compton, D. R.; Martin, B. R.; Makriyannis, A. Synthesis and Pharmacological Properties of 11-Hydroxy-3-(1′,1′-dimethylheptyl)hexahydrocannabinol: A High-Affinity Cannabinoid Agonist. *J. Med. Chem.* **1994**, *37*, 2619−2622.
(26) Devane, W. A.; Breuer, A.; Sheskin, T.; Järbe, T. U. C.; Eisen, M. S.; Mechoulam, R. A Novel Probe for the Cannabinoid Receptor. *J. Med. Chem.* **1992**, *35*, 2065−2069.
(27) Dodd, P. R.; Hardy, J. A.; Oakley, A. E.; Edwardson, J. A.; Perry, E. K.; Delaunoy, J.-P. A Rapid Method for Preparing Synaptosomes: Comparison, with Alternative Procedures. *Brain Res.* **1981**, *226*, 107−118.
(28) Cheng, Y. C.; Prusoff, W. H. Relationship Between the Inhibition Constant (K_i) and the Concentration of Inhibitor Which Causes 50% Inhibition (IC_{50}) of an Enzymatic Reaction. *Biochem. Pharmacol.* **1973**, *22*, 3099−3102.

JM960677Q