C1′-Cycloalkyl Side Chain Pharmacophore in Tetrahydrocannabinols

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In earlier work we have provided evidence for the presence of a subsite within the CB1 and CB2 cannabinoid receptor binding domains of classical cannabinoids. This putative subsite corresponds to substituents on the C1′-position of the C3-alkyl side chain, a key pharmacophoric feature in this class of compounds. We have now refined this work through the synthesis of additional C1′-cycloalkyl compounds using newly developed approaches. Our findings indicate that the C1′-cyclopropyl and C1′-cyclopentyl groups are optimal pharmacophores for both receptors while the C1′-cyclobutyl group interacts optimally with CB1 but not with CB2. The C1′-cyclohexyl analogs have reduced affinities for both CB1 and CB2. However, these affinities are significantly improved with the introduction of a C2′−C3′ cis double bond that modifies the available conformational space within the side chain and allows for a better accommodation of a six-membered ring within the side chain subsite. Our SAR results are highlighted by molecular modeling of key analogs.

Introduction

CB1[a] and CB2, currently the two well-characterized cannabinoid receptors,[1−3] are relatively new members in the G-protein-coupled receptor (GPCR) superfamily. CB1 is very densely distributed throughout the central nervous system and in various tissues in the periphery, whereas CB2 is present in immune cells[2] and very recently has also been identified in the brain.[4,5] Their discovery[6,7] and cloning,[7−10] along with the isolation and characterization of two families of endogenous cannabinergic ligands, represented by arachidonoyl ethanolamine[11] (anandamide) and 2-arachidonoyl glycerol[12,13] (2AG), have opened new and exciting chapters in biochemistry and pharmacology. Although the primary sequences for both CB1 and CB2 are known, their three-dimensional structure and the amino acid residues involved in ligand recognition, binding, and activation have not been well-characterized. In the absence of any X-ray crystallographic and nuclear magnetic resonance (NMR) data, information about the structural requirements for ligand−receptor interactions is obtained with the help of suitably designed molecules that serve as probes in structure−activity relationship (SAR) studies. Reviews of the existing SAR[14−23] recognized four pharmacophores associated with cannabinergic activity within the tricyclic cannabinoid structure. These include a phenolic hydroxyl, a lipophilic alkyl side chain, as well as a northern aliphatic and a southern aliphatic hydroxyl groups. The first two are encompassed in the plant-derived classical cannabinoids, while all four pharmacophores are represented in some of the synthetic nonclassical cannabinoids developed by Pfizer and exemplified by the well-known ligand 5-(1,1-dimethylheptyl)-2-[(1*R*,2*R*,5*R*)-5-hydroxy-2-(3-hydroxypropyl)-cyclohexyl]phenol (CP-55,940).[24] Our continued efforts in cannabinoid medicinal chemistry have sought to characterize and optimize all four pharmacophores.[14,16−23] It is now well-established that, among these, the side chain is a key pharmacophore in determining a ligand's affinity and pharmacological potency for both CB1 and CB2. Previous SAR studies[25−29] seeking to probe chain length and substitution pattern requirements have suggested that optimal activity is obtained with a seven or eight carbon chain substituted with 1′,1′-dimethyl (**1c**, Table 1) or 1′,2′-dimethyl groups. It has also been reported that oxygen atoms and unsaturation within the chain or substitution of the terminal carbon with carboxamido, cyano, azido, and halogen groups are well-tolerated.[16,27,30−36] Furthermore, studies in which the side chain carries aryl, cycloalkyl, and the bulky adamantyl groups,[37−41] along with the synthesis and biological testing of conformationally restricted side chain analogs,[42] have added to our understanding of the pharmacophoric features of this side chain. Earlier work from our laboratories[30,40,43−46] has suggested the existence of district subsites within the CB1 and CB2 cannabinoid receptor binding domains occupied by ring substituents at the C1′-position of the (−)-Δ^8-tetrahydrocannabinol structure [(−)-Δ^8-THCs, Table 1]. The stereochemical features of this putative subsite also have been probed through the synthesis of (−)-Δ^8-THC analogs bearing variously sized sulfur- and oxygen-containing heterocyclic rings at C1′-position.[30,44,46] These earlier results have motivated us to extend this work and further refine our understanding of the side chain pharmacophoric requirements, with special attention to the C1′-subsite. Toward this end, we have now expanded the group of cyclic C1′-substituents to include the previously unexplored respective cyclobutyl and cyclohexyl analogs. Additionally, we have explored the pharmacophoric limits of side chain length and the effects of conformational restriction at the C2′−C3′ bond by synthesizing the C1′-cycloalkyl series of *n*-octyl analogs, as well as those incorporating the respective C2′−C3′-*cis*-heptenyl chains.

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[a] Abbreviations: SAR, structure−activity relationship; CB1, cannabinoid receptor 1; CB2, cannabinoid receptor 2; GPCR, G-protein-coupled receptor; 2AG, 2-arachidonoyl glycerol; NMR, nuclear magnetic resonance; (−)-Δ^8-THC, (−)-Δ^8-tetrahydrocannabinol; DIBAL-H, diisobutylaluminum hydride; *B*-I-9-BBN, *B*-I-9-borabicyclo[3.3.1]nonane; *p*-TSA, *p*-toluenesulfonic acid.

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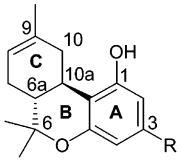
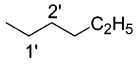
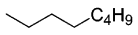
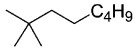
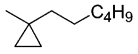
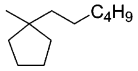
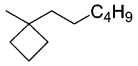
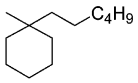
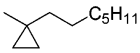
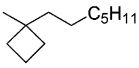
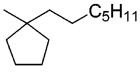
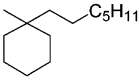
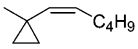
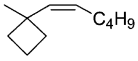
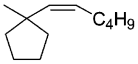
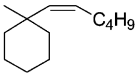
Table 1. Affinities (K_i) of Δ^8-THC Analogs for CB1 and CB2 Cannabinoid Receptors (95% Confidence Limits)



compd	R	CB1 (Ki, nM)[a]	CB2 (Ki, nM)[a]
1a		47.6[b]	39.3[b]
1b		8.8±1.5	20.8±4.5
1c		0.9[c]	1.4[c]
1d		0.44 ± 0.07[d]	0.86 ± 0.16[d]
1e		0.45 ± 0.07[e]	1.92 ± 0.4[e]
9b		1.5±0.2	11.5±3.4
9d		18.4±2.1	23.5±4.1
9e		0.48±0.09	4.2±0.8
9f		2.7±0.3	52.3±10.1
9g		9.9±1.2	45.5±8.3
9h		13.6±2.4	143.3±31.5
12a		1.5±0.2	1.7±0.3
12b		0.93±0.1	1.2±0.2
12c		0.72±0.1	1.8±0.3
12d		3.9±0.5	4.9±0.7

[a] Affinities for CB1 and CB2 were determined using rat brain (CB1) or mouse spleen (CB2) membranes and [^{3}H]CP-55,940 as the radioligand following previously described procedures.[47] K_i values were obtained from three independent experiments run in duplicate and are expressed as the mean of the three values. [b] Reported previously.[27] [c] Reported previously.[19] [d] Reported previously.[43] [e] Reported previously.[46]

As with earlier work, we used (−)-Δ^8-THC (**1a**) as our prototype, favoring it over the less stable and almost equipotent isomer (−)-Δ^9-THC. All analogs were tested for their respective affinities for CB1 and CB2.

The results were used to explore the binding domain for the cannabinoid side chain and to outline steric differences that define receptor subtype recognition using computational molecular graphics. (−)-Δ^8-THC analogs carrying a seven-carbon long side chain substituted with cyclopropyl, cyclobutyl, and cyclopentyl groups at the C1′-position exhibited remarkably high affinities for CB1 and CB2. Interestingly, within this series the cyclobutylhexyl (**9b**) and the cyclobutylheptyl (**9f**) analogs (Table 1) were found to have high affinities and significant selectivities (8-fold and 20-fold, respectively) for CB1.

Chemistry

Cyclo-bis-alkylation[40,43,45,46,48] of (3,5-dimethoxyphenyl)acetonitrile[46] (**2**) using the appropriate α,ω-dibromoalkane, after sequential deprotonation with potassium bis(trimethylsilylamide), afforded the corresponding (3,5-dimethoxyphenyl)-cycloalkane carbonitriles **3a**, **3b**, **3c**, and **3d** (62−93% yield), bearing cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl rings, respectively (Scheme 1). Reduction of the cyano group with diisobutylaluminum hydride[46,49] at −78 °C led to aldehydes **4a**−**4d** (87−98% yield), which were further olefinated with (butylmethylene)triphenylphosphorane or (pentylmethylene)-triphenylphosphorane, affording intermediates **5a**−**5d** (89−98% yield) and **5e**−**5h** (78−82% yield), bearing seven and eight carbon atom side chains, respectively. This Wittig reaction afforded exclusively the *cis*-alkene intermediates under the experimental conditions used. Catalytic hydrogenation of **5b**, **5d**, **5f**, **5g**, and **5h** led to the respective resorcinol dimethyl ethers **6b**, **6d**, **6f**, **6g**, and **6h** in 93−99% yields. These were converted to the corresponding resorcinols **7b**, **7d**, **7f**, **7g**, and **7h** in 75−97% yields, by demethylation using boron tribromide.[46,50] Because of the sensitive nature of the cyclopropane ring, milder reaction conditions were used in both the hydrogenation and demethylation steps in order to obtain resorcinol **7e**. Thus, double bond reduction[43,51] of the unsaturated precursor **5e** in the presence of *p*-toluenesulfonyl hydrazide and sodium acetate in water/DME afforded the saturated analog **6e** (76% yield), which was then demethylated[43,52] using *B*-I-9-borabicyclo[3.3.1]-nonane (*B*-I-9-BBN) to give compound **7e** in 95% yield. Friedel−Crafts allylation[30,43,46,53] of resorcinol derivatives **7b**, **7d**−**7h** with (+)-*cis/trans*-*p*-mentha-2,8-dien-1-ol[54] produced cannabidiols **8b**, **8d**−**8h**, respectively, in 46−92% yields. Treating the latter with catalytic amounts of boron trifluoride etherate resulted in a clean cyclization reaction, to produce the respective tricyclic tetrahydrocannabinols **9b**, **9d**−**9h** (46−67% yield). These were obtained as the desirable thermodynamically more stable (−)-Δ^8-THC analogs, rather than their respective (−)-Δ^9-isomers that can be isolated under controlled conditions.[34,55−57]

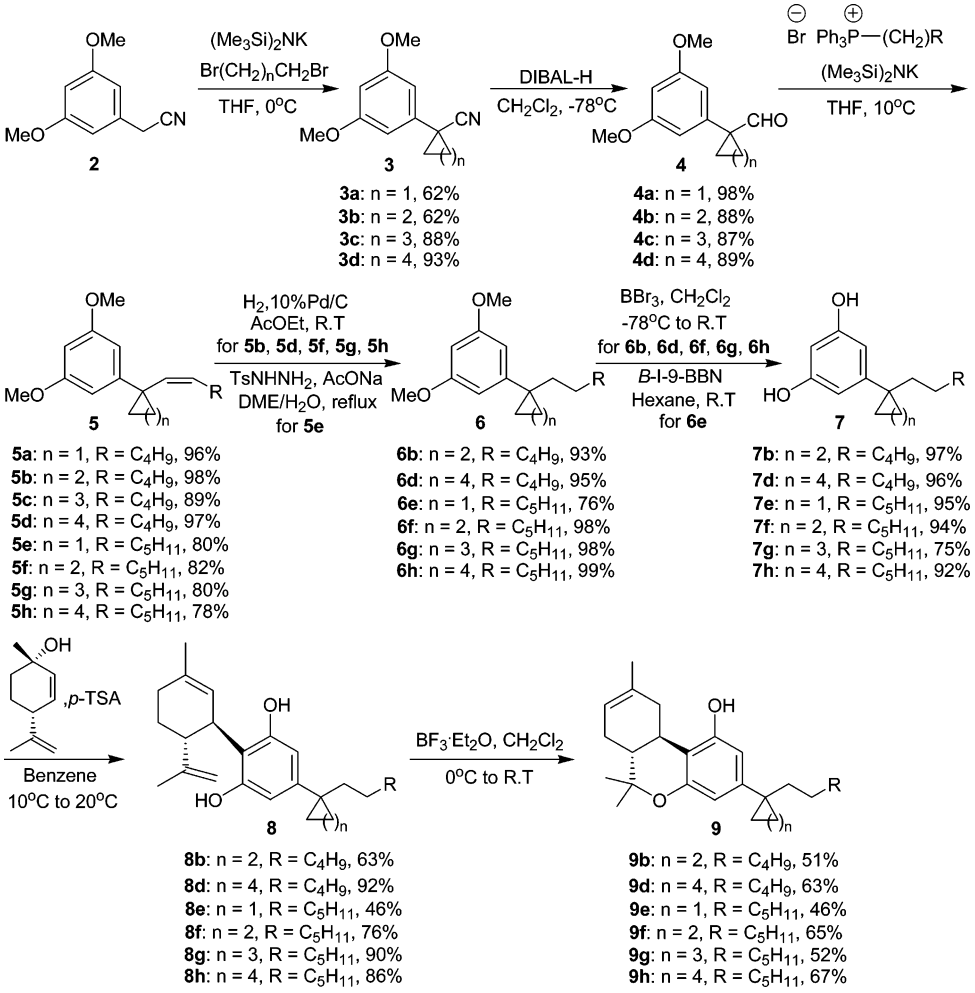
The side chain unsaturated C1′-cylopropyl, C1′-cyclobutyl, C1′-cyclopentyl, and C1′-cyclohexyl analogs **12a**−**12d** were synthesized from the respective unsaturated precursors **5a**−**5d**, as shown in Scheme 2. The phenolic hydroxyl groups in **5a**−**5d** were deprotected using the bulky *B*-I-9-BBN reagent (75−94% yield) in order to avoid double bond bromination. Subsequently, efficient coupling of the resulting resorcinols **10a**−**10d** with (+)-*cis/trans*-*p*-mentha-2,8-dien-1-ol, catalyzed by *p*-toluenesulfonic acid, produced the C1′-cyclopropyl-, C1′-cyclobutyl-, C1′-cyclopentyl-, and C1′-cyclohexylcannabidiols **11a**−**11d**, respectively, in 50−80% yields. Cyclization in the presence of boron trifluoride etherate gave the corresponding unsaturated cannabinoid analogs **12a**−**12d** in 67−91% yields.

n-Heptyl-(−)-Δ^8-THC (**1b**, Table 1) represents a starting point in our studies. Although its chemical synthesis and affinity constant (K_i, value) for the CB1 receptor have been reported,[26] the affinity of this compound for the CB2 receptor has not yet been disclosed. We have now resynthesized **1b** through a modified procedure, shown in Scheme 2. We obtained **1b** following the methodology developed in our laboratory that involved Wittig olefination of 3,5-dimethoxybenzaldehyde **13** and stepwise Friedel−Crafts allylation/dibenzopyran ring closure under mild conditions.

Receptor Binding Studies

The abilities of **1b**, **9b**, **9d**-**9h** and **12a**-**12d** to displace radiolabeled CP-55,940 from purified rat forebrain synaptosomes

Scheme 1



and mouse spleen synaptosomes were determined, as described in the Experimental Section. K_i values calculated from the respective displacement curves are listed in Table 1 and reflect the affinities of these tetrahydrocannabinol analogs for the CB1 and CB2 receptors.

Results and Discussion

The series of (−)-Δ^8-tetrahydrocannabinol analogs reported here allows us to further refine the stereochemical features of the C3-alkyl side chain, the most critical pharmacophore in the tricyclic cannabinoid structure. As an aid in the interpretation of the data, we carried out molecular dynamics simulations to fully explore the available conformational space of the key analogs while focusing on the C3 side chain with its C1′-cyclic substituents. To access all possible low-energy conformers, we first performed high-temperature dynamics simulations followed by simulated annealing. Such a process allows us to sample the entire conformational space of the side chain beyond any local minimum. These models represent families of the most probable conformers for each analog and thus define the pharmacophoric space available for interactions with the CB1 and CB2 binding sites. The models also emphasize steric differences between ligand requirements for interaction with CB1 and CB2. Our findings can be summarized as follows:

(1) As elaborated in earlier publications, extension of the *n*-pentyl group side chain of the natural cannabinoids from five to seven carbons leads to substantial enhancement of both CB1 and CB2 affinities. However, further extension of the side chain length from seven to eight carbons generally leads to substantial reduction in CB2 affinities, with only small or no effect on CB1 affinities. Thus, the C-8 side chain analogs (**9e**−**9h**) generally exhibit enhanced CB1 selectivity.

(2) It was previously reported that the introduction of C1′-alkyl substituents, as exemplified by the C1′-dimethyl analog, leads to substantial enhancement in affinity for both CB1 and CB2 (**1c**), when compared to the unsubstituted *n*-heptyl analog (**1b**). We now show that transformation of the *gem*-dimethyl substitution into the more compact cyclopropyl ring generally leads to further enhancement in the ligand's affinities for CB1 and CB2. Thus, in the substituted heptyl analogs the C1′-cyclopropyl group distinguishes itself as an optimal pharmacophore for the C1′-subsite. Similarly, the conformationally more expanded C1′-cyclopentyl analog (**1e**) maintains favorable affinities for both receptors. This trend for enhancement in affinity due to C1′-ring substituents is reversed in the respective bulkier C1′-cyclohexyl analog (**9d**), an observation that clearly defines the limits of steric tolerance of this C1′-subsite.

(3) Unlike the C-3, C-5, and C-6 cyclic congeners, where there is no distinct preference between CB1 and CB2, introducing a C1′-cyclobutyl ring clearly produces analogs with CB1 selectivity. Such selectivity can be accounted for, almost exclusively, by reduced affinities for the CB2 receptor. This CB1 selectivity holds true for the heptyl side chain analog (**9b**) and is further enhanced in its octyl counterpart (**9f**). However, the CB1 selectivity disappears in the respective C2′−C3′-*cis*-heptene analog (**12b**), where the ligand's affinities are now

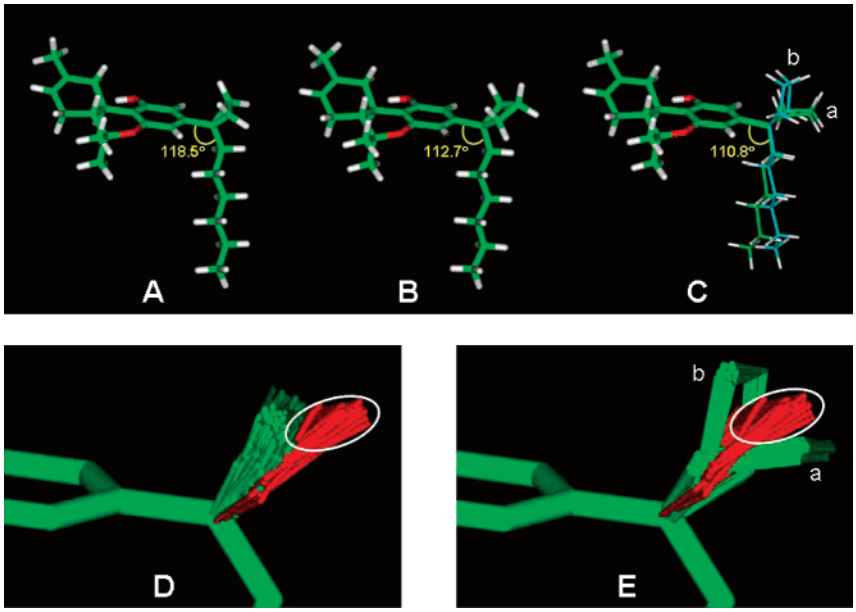
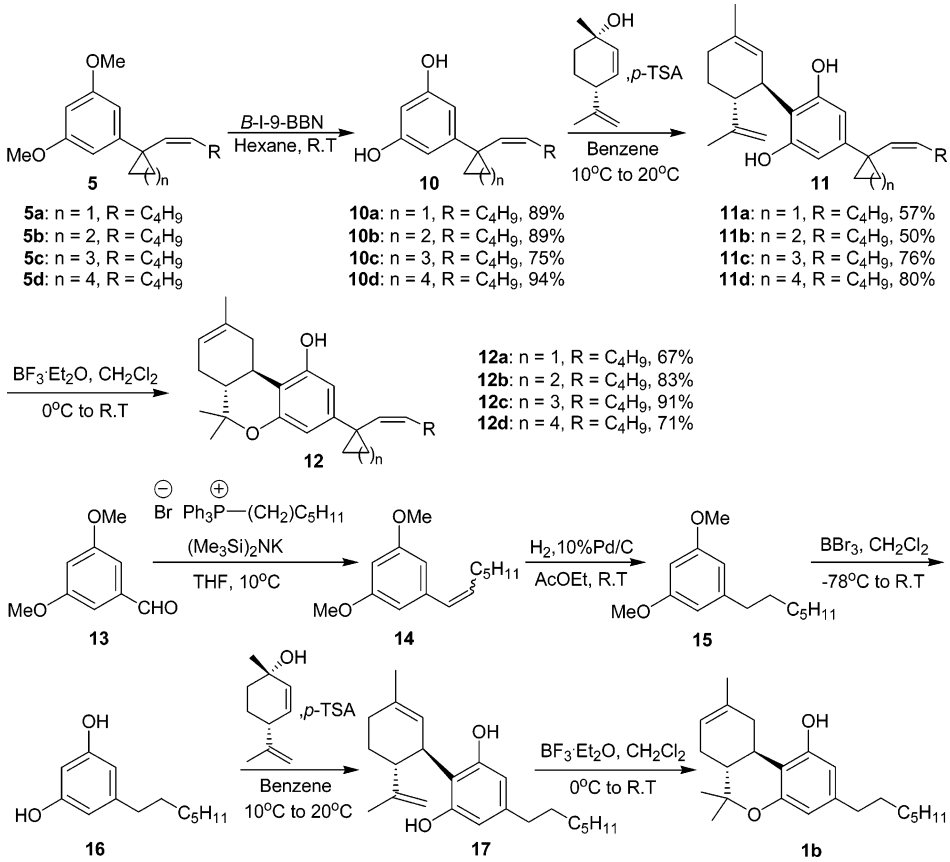


Figure 1. (Top row) Representative low-energy conformers for compounds **1d** (A), **9b** (B), and **1e** (C) as determined using molecular mechanics/molecular dynamics calculations. The two families of conformers in which the tricyclic ring system occupies the equatorial or the axial positions of the cyclopentane ring in **1e** (C) are represented by conformers **a** (green) and **b** (cyan), respectively. The models also identify differences between the three analogs related to the orientation of their respective C3 side chains. (Bottom row) Superimposition results for compounds **1d**, **9b**, and **1e** using the carbon atoms of their aromatic rings as the superimposition points. All low-energy conformers for the cyclobutane ring of **9b** (red) where superimposed with those for the cyclopropane (D) and cyclopentane (E) rings of compounds **1d** and **1e**, respectively (green). Only carbon atoms of the carbocyclic rings are shown here. The white highlighted area represents the different space required to accommodate the C1′ cyclobutyl ring substituent of the **9b**.

Scheme 2



equally high for both receptors. While seeking to interpret this interesting observation, we have determined the preferred conformations for the C1′-cyclopropyl- (**1d**), C1′-cyclopentyl- (**1e**), and C1′-cyclobutylheptyl (**9b**) analogs (Figure 1). Earlier conformational analysis of different C1′-dimethyl analogs in classical and nonclassical cannabinoids consistently showed that the C3 side chain adopts an orientation almost perpendicular to the aromatic ring.[34,58−62] Similar results were also obtained with

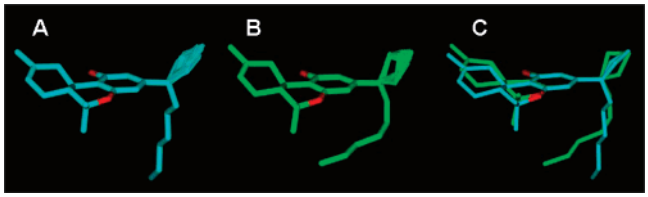


Figure 2. (A and B) Modeling of **9b** (cyan) and **12b** (green) showing representative low-energy conformers. The models also incorporate a family of 100 low-energy conformations for the C1′-cyclobutyl ring for each analog. (C) Superimposition results of **9b** and **12b** using the carbon atoms of their aromatic rings as the superimposition points.

the side chains of the C1′-cyclopentyl and C1′-dithiolane analogs.[44,46] To identify any stereochemical differences, the CB1-selective **9b** was superimposed with **1d** and **1e**. A cursory examination of the models reveals that the cyclobutyl group in **9b** occupies a distinct stereochemical space that is not shared by the other two. This is clearly seen when comparing each analog's preferred conformers. The cyclopropyl ring preferred conformers are grouped in a space left of the cyclobutyl ring. On the other hand, the cyclopentyl ring preferred conformers fall into two families flanking the cyclobutyl ring's conformational space. Our modeling exercise allows us to postulate a subsite at the CB1 receptor in which the three-, four-, and five-membered carbocyclic ring substituents can be accommodated equally well. This results in enhanced CB1 affinities, as compared to the respective unsubstituted analogs. The same subsite can be invoked with the CB2 receptor. In this case, however, the stereochemical requirements for optimal ligand−receptor interaction are more stringent. While the three- and five-membered ring analogs can interact optimally with the subsite, the four-membered ring encounters some negative pharmacophoric space that can be defined within our superimposition models (see Figure 1). An additional factor that may explain these observed differences in selectivity is the relative orientation of the C1′−C2′ bond. Indeed, as can be observed in Figure 1, the presence of the C1′-cyclobutyl ring with the fully saturated side chain (**9b**) orients the side chain somewhat differently than its respective three- and five-membered ring congeners. While such variations in chain alignment can be tolerated at the CB1 receptor, the chain orientation of the C1′-cyclobutyl analog **9b** may impede its optimal interaction with CB2. Such a postulate can explain the approximately 8-fold CB1/CB2 selectivity in **9b** that is further enhanced in the respective C-8 analog **9f**, where CB1 selectivity is now nearly 20-fold.

Interestingly, the CB1 selectivity of the cyclobutyl analog **9b** is lost in its C2′−C3′-*cis*-heptenyl analog **12b**, which exhibits equally high affinities for both the CB1 and CB2 receptors. This observation can be explained by the superimposition of the preferred conformers for **9b** and **12b** so that their respective aromatic rings overlap (Figure 2). We observed that the conformational space of the four-membered ring in **9b** is distinct from that of **12b**. Additionally, the alignment of the C3 side chain in **12b** is distinctly different than that of **9b** (Figure 2). It can thus be argued that the C1′ substituent in **12b** occupies a more favorable CB2 pharmacophoric space and aligns its side chain in a more favorable conformation compared to its congener with the fully saturated side chain (**9b**).

(4) Introducing a C2′−C3′ cis-double bond in the chain of the cyclopropyl and cyclopentyl congeners (**12a**, **12c**) produces analogs with equal affinities for the CB1 and CB2 receptors and quite comparable to those of their congeners carrying a fully saturated side chain. However, a different trend is observed in the C1′-cyclohexyl analogs. Here, introducing a C2′−C3′ cis-double bond leads to an analog (**12d**) with enhanced affinities for both CB1 and CB2, when compared to its fully saturated counterpart (**9d**). This suggests that introducing a cis-double bond at the C2′−C3′ chain segments leads to improved interactions with both receptors. We have now shown through computer modeling that in both **9d** and **12d** the cyclohexyl ring assumes two distinct conformations in which the C1′−C7′ chain is in either the equatorial or axial position. Representative low-energy conformers for each of these are shown in Figure 3 (the full cluster simulation is available under Supporting Information). According to our models, the C1′−C7′ side chain carbons for the respective C3-heptyl (**9d**) and C3-*cis*-hept-2-enyl (**12d**) analogs assume different preferred orientations, with **12d** having the most favorable pharmacophoric conformation. We postulate that these differences in preferred side chain conformational space may reflect differences in their affinities for CB1 and CB2.

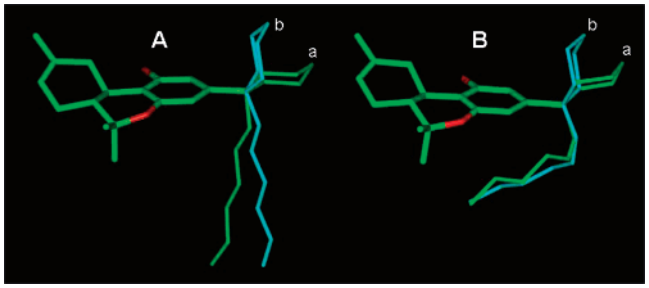


Figure 3. Representative low-energy conformers for compounds **9d** (A) and **12d** (B) as determined using molecular mechanics/molecular dynamics calculations. The two families of conformers in which the tricyclic ring system occupies the equatorial or the axial position of the cyclohexane ring are represented by conformers **a** (green) and **b** (cyan), respectively.

Conclusion

This study has helped to define the pharmacophoric elements of the C3 classical cannabinoid side chain. It also provides information needed for designing later generation analogs possessing higher potencies and selectivities for each of the two known cannabinoid receptors. This careful SAR study has revealed the pharmacophoric restrictions of the C1′-subsite for the CB2 receptor. The corresponding subsite in CB1 appears to be more sterically tolerant. Our data also argue that the putative groove with which the cannabinoid side chain interacts is somewhat more confined in the CB2 receptor, in which the C-8 side chain analogs are subjected to unfavorable steric constrains. Future work will seek to further define the pharmacophoric constraints of the distal region of the classical cannabinoid side chain.

Experimental Section

Chemistry. All reagents and solvents were purchased from Aldrich Chemical Co., unless otherwise specified, and used without further purification. All anhydrous reactions were performed under a static argon or nitrogen atmosphere in flame-dried glassware using scrupulously dry solvents. Flash column chromatography employed silica gel 60 (230−400 mesh). All compounds were demonstrated to be homogeneous by analytical TLC on precoated silica gel TLC plates (Merck, 60 F_{245} on glass, layer thickness 250 μm), and chromatograms were visualized by phosphomolybdic acid staining. Melting points were determined on a micro-melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Bruker DMX-500 or on a Bruker AC 300 spectrometer operating at 500 and 300 MHz, respectively. All NMR spectra were recorded in

$CDCl_3$, unless otherwise stated, and chemical shifts are reported in units of δ relative to internal TMS. Multiplicities are indicated as br (broadened), s (singlet), d (doublet), t (triplet), q (quartet), and m (multiplet), and coupling constants (*J*) are reported in hertz (Hz). Low- and high-resolution mass spectra were performed at the School of Chemical Sciences, University of Illinois at Urbana−Champaign, or were recorded on Varian Star 3400CX (GC) and Saturn 2000 (MS) instruments. Elemental analyses were obtained by Baron Consulting Co., Milford, CT, or carried out by the Microanalytical Section of the Institute of Organic and Pharmaceutical Chemistry, National Hellenic Research Foundation.

1-(3,5-Dimethoxyphenyl)cyclopropanecarbonitrile[45] (3a). The synthesis was carried out as with **3b** (see text below) by using **2** (500 mg, 2.82 mmol), potassium bis(trimethylsilyl)amide (3.38 g, 16.92 mmol), and 1,2-dibromoethane (1.59 g, 8.46 mmol) in dry THF (28.2 mL). The reaction was completed in 3 h at 0 °C: yield 62% (355 mg); viscous oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.44 (d, $J = 2.4$ Hz, 2H), 6.38 (t, $J = 2.4$ Hz, 1H), 3.80 (s, 6H), 1.71−1.68 (dd, $J = 7.4$ Hz, $J = 5.2$ Hz, 2H), 1.41−1.38 (dd, $J = 7.4$ Hz, $J = 5.2$ Hz, 2H); mass spectrum *m*/*z* (relative intensity) 203 (M^+, 100), 188 (22), 172 (37). Anal. ($C_{12}H_{13}NO_2$) C, H.

1-(3,5-Dimethoxyphenyl)cyclobutanecarbonitrile[45] (3b). To a solution of **2** (500 mg, 2.82 mmol) in dry THF (20 mL) at −16 °C, under an argon atmosphere, was added potassium bis-(trimethylsilyl)amide (1.69 g, 8.46 mmol). The mixture was stirred at the same temperature for 3 min, and then a solution of 1,3-dibromopropane (626 mg, 3.10 mmol) in dry THF (8.2 mL) was added dropwise. Following the addition, the reaction was stirred for 2 h at −16 °C and then quenched by the addition of saturated aqueous NH_4Cl. The mixture was diluted with Et_2O, the organic layer was separated, and the aqueous phase was extracted with Et_2O. The combined organic layer was washed with brine and dried over Na_2SO_4 and the solvent evaporated under reduced pressure to give an oily residue. Purification by flash column chromatography (25% diethyl ether−petroleum ether) afforded 379 mg (62% yield) of the compound **3b** as a viscous oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.53 (d, $J = 2.2$ Hz, 2H), 6.40 (t, $J = 2.2$ Hz, 1H), 3.80 (s, 6H), 2.82−2.76 (m, 2H of the cyclobutane ring), 2.64−2.56 (m, 2H of the cyclobutane ring), 2.46−2.35 (m, 1H of the cyclobutane ring), 2.10−201 (m, 1H of the cyclobutane ring); mass spectrum *m*/*z* (relative intensity) 217 (M^+, 100), 189 (69), 160 (13), 133 (11); exact mass calcd for $C_{13}H_{16}NO_2$ ($M^+ + 1$, FAB), 218.1181, found 218.1173. Anal. ($C_{13}H_{15}NO_2$) C, H, N.

1-(3,5-Dimethoxyphenyl)cyclopentanecarbonitrile[40,45,46] (3c). The synthetic procedure was reported previously, along with physical and spectral data.[46]

1-(3,5-Dimethoxyphenyl)cyclohexanecarbonitrile[40,45] (3d). The synthesis was carried out as described for **3b** by using **2** (500 mg, 2.82 mmol), potassium bis(trimethylsilyl)amide (1.69 g, 8.46 mmol), and 1,5-dibromopentane (713 mg, 3.10 mmol) in dry THF (28.2 mL). The reaction was completed in 2 h at 0 °C: yield 93% (643 mg); viscous oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.62 (d, $J = 1.8$ Hz, 2H), 6.38 (t, $J = 1.8$ Hz, 1H), 3.79 (s, 6H), 2.11 (m, 2H of the cyclohexane ring), 1.85−1.67 (m, 8H of the cyclohexane ring); mass spectrum *m*/*z* (relative intensity) 245 (M^+, 100), 190 (93), 165 (31), 152 (29). Anal. ($C_{15}H_{19}NO_2$) C, H.

1-(3,5-Dimethoxyphenyl)cyclopropanecarboxaldehyde[43,45] (4a). The synthesis was carried out as with **4b** (see text below) by using **3a** (355 mg, 1.75 mmol) and diisobutylaluminum hydride (4.4 mL, 1 M solution in CH_2Cl_2) in dry CH_2Cl_2 (17.5 mL). The reaction was completed in 45 min at −78 °C: yield 98% (352 mg); viscous oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.32 (s, 1H), 6.46 (d, $J = 2.4$ Hz, 2H), 6.40 (t, $J = 2.4$ Hz, 1H), 3.78 (s, 6H), 1.53 (half of AA′BB′ system, 2H of the cyclopropane ring), 1.37 (half of AA′BB′ system, 2H of the cyclopropane ring); mass spectrum *m*/*z* (relative intensity) 206 (M^+, 44), 178 (100), 163 (38), 147 (27). Anal. ($C_{12}H_{14}O_3$), C, H.

1-(3,5-Dimethoxyphenyl)cyclobutanecarboxaldehyde[45] (4b). To a solution of **3b** (379 mg, 1.75 mmol) in dry CH_2Cl_2 (17.5 mL) at −78 °C under an argon atmosphere was added diisobutylaluminum hydride (4.4 mL, 1 M solution in CH_2Cl_2). The reaction mixture was stirred at the same temperature for 1 h and then quenched by dropwise addition of potassium sodium tartrate (10% solution in water). The resulting mixture was warmed to room temperature, stirred vigorously for 40 min, and then diluted with EtOAc. The organic phase was separated and the aqueous phase extracted with EtOAc. The combined organic layer was washed with brine and dried over Na_2SO_4, and the solvent was evaporated under reduced pressure. The crude product was purified by flash column chromatography on silica gel using 15% diethyl ether−petroleum ether as eluent to give compound **4b** as a viscous oil in 88% yield (339 mg): ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.50 (s, 1H), 6.37 (t, $J = 2.3$ Hz, 1H), 6.28 (d, $J = 2.3$ Hz, 2H), 3.80 (s, 6H), 2.72−2.65 (m, 2H of the cyclobutane ring), 2.43−2.35 (m, 2H of the cyclobutane ring), 2.03−1.93 (m, 1H of the cyclobutane ring), 1.93−1.86 (m, 1H of the cyclobutane ring); mass spectrum *m*/*z* (relative intensity) 220 (M^+, 84), 192 (100), 177 (30), 164 (64); exact mass calcd for $C_{13}H_{17}O_3$ ($M^+ + 1$, FAB), 221.1178, found 221.1171. Anal. ($C_{13}H_{16}O_3$) C, H.

1-(3,5-Dimethoxyphenyl)cyclopentanecarboxaldehyde[45,46] (4c). The synthetic procedure was reported previously, along with physical and spectral data.[46]

1-(3,5-Dimethoxyphenyl)cyclohexanecarboxaldehyde[45] (4d). The synthesis was carried out as described for **4b** by using **3d** (643 mg, 2.62 mmol) and diisobutylaluminum hydride (6.6 mL, 1 M solution in CH_2Cl_2) in dry CH_2Cl_2 (26.2 mL). The reaction was completed in 45 min at −78 °C: yield 89% (578 mg); colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.31 (s, 1H), 6.44 (d, $J = 1.8$ Hz, 2H), 6.35 (t, $J = 1.8$ Hz, 1H), 3.75 (s, 6H), 2.23 (m, 2H of the cyclohexane ring), 1.80 (m, 2H of the cyclohexane ring), 1.61 (m, 3H of the cyclohexane ring), 1.45 (m, 2H of the cyclohexane ring), 1.25 (m, 1H of the cyclohexane ring); mass spectrum *m*/*z* (relative intensity) 248 (M^+, 7), 220 (100), 151 (37), 81 (13). Anal. ($C_{15}H_{20}O_3$) C, H.

3,5-Dimethoxy-1-[1-[(1*Z*)-1-hexenyl]cyclopropyl]benzene[43] (5a). The synthesis was carried out as with **5b** (see text below) by using pentyltriphenylphosphonium bromide (3.53 g, 8.55 mmol) in dry THF (48 mL), potassium bis(trimethylsilyl)amide (1.67 g, 8.38 mmol), and a solution of **4a** (352 mg, 1.71 mmol) in dry THF (5 mL). The reaction was completed in 45 min at 10 °C: yield 96% (426 mg); colorless liquid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.40 (d, $J = 2.4$ Hz, 2H), 6.26 (t, $J = 2.4$ Hz, 1H), 5.65 (d, $J = 10.4$ Hz, 1H, 2′-H), 5.51 (dt, $J = 10.4$ Hz, $J = 7.0$ Hz, 1H, 3′-H), 3.75 (s, 6H), 2.07 (m, 2H, 4′-CH_2), 1.28 (m, 4H, 5′-CH_2, 6′-CH_2), 1.08 (half of AA′BB′ system, 2H of the cyclopropane ring), 0.97 (half of AA′BB′ system, 2H, of the cyclopropane ring), 0.85 (t, $J = 7.0$ Hz, 3H); mass spectrum *m*/*z* (relative intensity) 260 (M^+, 45), 217 (100), 203 (31), 189 (33). Anal. ($C_{17}H_{24}O_2$) C, H.

3,5-Dimethoxy-1-[1-[(1*Z*)-1-hexenyl]cyclobutyl]benzene (5b). To a suspension of pentyltriphenylphosphonium bromide (3.18 g, 7.7 mmol) in dry THF (42.7 mL) at 0 °C, under an argon atmosphere, was added potassium bis(trimethylsilyl)amide (1.5 g, 7.55 mmol). The mixture was warmed to 10 °C and stirred for an additional 30 min to ensure complete formation of the orange (butylmethylene)triphenylphosphorane. A solution of **4b** (339 mg, 1.54 mmol) in dry THF (4 mL) was added dropwise to the resulting slurry, at the same temperature. The reaction was stirred for 45 min and upon completion was quenched by the addition of saturated aqueous NH_4Cl. The organic layer was separated and the aqueous phase was extracted with diethyl ether. The combined organic layer was washed with brine and dried over Na_2SO_4, and the solvent was evaporated under reduced pressure. The residue was purified through a short column of silica gel using 5% diethyl ether−petroleum ether as eluent to afford the compound **5b** as a colorless liquid in 98% yield (414 mg): ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.50 (d, $J = 2.1$ Hz, 2H), 6.28 (t, $J = 2.1$ Hz, 1H), 5.78 (d, $J = 11.1$ Hz, 1H, 2′-H), 5.28 (dt, $J = 11.1$ Hz, $J = 7.5$ Hz, 1H, 3′-H), 3.77 (s, 6H), 2.51−2.45 (m, 2H of the cyclobutane ring), 2.39−2.33 (m, 2H of the cyclobutane ring), 2.02−1.95 (m, 1H of the cyclobutane ring), 1.92−1.81 (m, 3H, cyclobutane ring, 4′-CH_2), 1.24−1.15 (m, 4H, 5′-CH_2, 6′-CH_2), 0.80 (t, $J = 7.0$ Hz, 3H, 7′-CH_3); ^{13}C NMR ($CDCl_3$) δ 160.6, 151.9, 138.6, 130.8, 104.5, 96.9,

55.2, 47.9, 36.3, 31.5, 27.9, 22.4, 16.7, 13.9; mass spectrum *m*/*z* (relative intensity) 274 (M^+, 68), 231 (54), 217 (48), 203 (100), 189 (50); exact mass calcd for $C_{18}H_{27}O_2$ ($M^+ + 1$, FAB), 275.2011, found 275.2011. Anal. ($C_{18}H_{26}O_2$) C, H.

3,5-Dimethoxy-1-[1-[(1*Z*)-1-hexenyl]cyclopentyl]benzene[46] (5c). The synthetic procedure was reported previously, along with physical, spectral, and analytical data.[46]

3,5-Dimethoxy-1-[1-[(1*Z*)-1-hexenyl]cyclohexyl]benzene (5d). The synthesis was carried out as described for **5b** by using pentyltriphenylphosphonium bromide (4.82 g, 11.65 mmol) in dry THF (64.7 mL), potassium bis(trimethylsilyl)amide (2.28 g, 11.42 mmol), and a solution of **4d** (578 mg, 2.33 mmol) in dry THF (6 mL). The reaction was completed in 45 min at 10 °C: yield 97% (683 mg); colorless liquid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.58 (d, J = 2.5 Hz, 2H), 6.28 (bs, 1H), 5.66 (d, J = 11.6 Hz, 1H, 2′-H), 5.35 (dt, J = 11.6 Hz, J = 7.3 Hz, 1H, 3′-H), 3.77 (s, 6H), 1.94 (m, 2H of the cyclohexane ring), 1.70−1.57 (m, 9H, 4′-CH_2, 7H of the cyclohexane ring), 1.25 (m, 1H of the cyclohexane ring), 1.10 (m, 4H, 5′-CH_2, 6′-CH_2), 0.74 (t, J = 6.7 Hz, 3H, 7′-CH_3); ^{13}C NMR ($CDCl_3$) δ 160.3, 153.6, 136.3, 132.1, 105.2, 96.8, 55.2, 43.7, 38.9, 31.3, 28.2, 26.1, 22.8, 22.3, 13.9; mass spectrum *m*/*z* (relative intensity) 302 (M^+, 38), 259 (27), 245 (49), 219 (100), 194 (78), 177 (35), 151 (57); Anal.($C_{20}H_{30}O_2$) C, H.

3,5-Dimethoxy-1-[1-[(1*Z*)-1-heptenyl]cyclopropyl]benzene (5e). The synthesis was carried out as described for **5b** by using hexyltriphenylphosphonium bromide (3.65 g, 8.55 mmol) in dry THF (47.5 mL), potassium bis(trimethylsilyl)amide (1.67 g, 8.38 mmol), and a solution of **4a** (352 mg, 1.71 mmol) in dry THF (5 mL). The reaction was completed in 45 min at 10 °C: yield 80% (375 mg); colorless liquid (spectroscopic and elemental analysis data are available under Supporting Information).

3,5-Dimethoxy-1-[1-[(1*Z*)-1-heptenyl]cyclobutyl]benzene (5f). The synthesis was carried out as described for **5b** by using hexyltriphenylphosphonium bromide (3.29 g, 7.7 mmol) in dry THF (42.8 mL), potassium bis(trimethylsilyl)amide (1.51 g, 7.55 mmol), and a solution of **4b** (339 mg, 1.54 mmol) in dry THF (4 mL). The reaction was completed in 1 h at 10 °C: yield 82% (364 mg); colorless liquid (spectroscopic and elemental analysis data are available under Supporting Information).

3,5-Dimethoxy-1-[1-[(1*Z*)-1-heptenyl]cyclopentyl]benzene (5g). The synthesis was carried out as described for **5b** by using hexyltriphenylphosphonium bromide (4.57 g, 10.7 mmol) in dry THF (59.4 mL), potassium bis(trimethylsilyl)amide (2.09 g, 10.49 mmol), and a solution of **4c** (500 mg, 2.14 mmol) in dry THF (7 mL). The reaction was completed in 45 min at 10 °C: yield 80% (517 mg); colorless liquid (spectroscopic and elemental analysis data are available under Supporting Information).

3,5-Dimethoxy-1-[1-[(1*Z*)-1-heptenyl]cyclohexyl]benzene (5h). The synthesis was carried out as described for **5b** by using hexyltriphenylphosphonium bromide (4.98 g, 11.65 mmol) in dry THF (64.7 mL), potassium bis(trimethylsilyl)amide (2.28 g, 11.42 mmol), and a solution of **4d** (578 mg, 2.33 mmol) in dry THF (7 mL). The reaction was completed in 45 min at 10 °C: yield 78% (575 mg); colorless liquid (spectroscopic and elemental analysis data are available under Supporting Information).

3,5-Dimethoxy-1-(1-hexylcyclobutyl)benzene (6b). To a solution of **5b** (414 mg, 1.51 mmol) in EtOAc (13.7 mL) was added 10% Pd/C (75 mg), and the resulting suspension was stirred vigorously under hydrogen atmosphere overnight at room temperature. The catalyst was removed by filtration through Celite and the filtrate was evaporated under reduced pressure to afford the crude product. Purification through a short column of silica gel using 5% diethyl ether−petroleum ether yielded compound **6b** as a colorless liquid (388 mg, 93% yield): ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.27 (t, J = 2.0 Hz, 1H), 6.25 (d, J = 2.0 Hz, 2H), 3.79 (s, 6H), 2.34−2.26 (m, 2H of the cyclobutane ring), 2.09−1.97 (m, 3H of the cyclobutane ring), 1.83−1.76 (m, 1H of the cyclobutane ring), 1.74−1.69 (m, 2H, 2′-CH_2), 1.26−1.15 (m, 6H, 4′-CH_2, 5′-CH_2, 6′-CH_2), 1.05−0.97 (m, 2H, 3′-CH_2), 0.84 (t, J = 7.1 Hz, 3H, 7′-CH_3); ^{13}C NMR ($CDCl_3$) δ 160.3, 153.4, 104.2, 96.6, 55.2, 46.8, 42.5, 32.8, 31.8, 29.8, 24.6, 22.7, 15.8, 14.1; mass spectrum *m*/*z* (relative intensity) 276 (M^+, 84), 248 (34), 205 (100), 192 (46), 178 (81), 165 (21), 152 (15); exact mass calcd for $C_{18}H_{28}O_2$, 276.2089, found 276.2093. Anal. ($C_{18}H_{28}O_2$) C, H.

3,5-Dimethoxy-1-(1-hexylcyclohexyl)benzene (6d). The synthesis was carried out as described for **6b** by using **5d** (683 mg, 2.26 mmol) and 10% Pd/C (123 mg) in EtOAc (20.6 mL). The reaction was completed in 4 h at room temperature: yield 95% (653 mg); colorless liquid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.50 (d, J = 1.9 Hz, 2H), 6.31 (t, J = 1.9 Hz, 1H), 3.80 (s, 6H), 2.02 (m, 2H of the cyclohexane ring), 1.55−1.40 (m, 10H, 2′-CH_2, 8H of the cyclohexane ring), 1.22−1.13 (m, 6H, 4′-CH_2, 5′-CH_2, 6′-CH_2), 0.96 (m, 2H, 3′-CH_2), 0.83 (t, J = 6.7 Hz, 3H, 7′-CH_3); ^{13}C NMR ($CDCl_3$) δ 160.5, 150.2, 105.7, 96.3, 55.1, 43.8, 41.5, 36.4, 31.7, 30.0, 26.6, 23.4, 22.7, 22.5, 14.1; mass spectrum *m*/*z* (relative intensity) 304 (M^+, 30), 220 (100), 208 (28), 165 (25), 151 (42). Anal. ($C_{20}H_{32}O_2$) C, H.

3,5-Dimethoxy-1-(1-heptylcyclopropyl)benzene (6e). To a solution of **5e** (375 mg, 1.37 mmol) in 1,2-dimethoxyethane (38.1 mL) was added *p*-toluenesulfonhydrazide (3.06 g, 16.44 mmol). The resulting mixture was refluxed and a solution of sodium acetate (2.92 g, 35.62 mmol) in water (37 mL) was added over a period of 4 h. Stirring and reflux continued for another 8 h and the mixture was then allowed to cool at room temperature. Water was added, followed by dilution with diethyl ether. The organic layer was separated and the aqueous phase was extracted with diethyl ether. The combined organic layer was washed with brine and dried over Na_2SO_4, and the solvent was evaporated under reduced pressure. Purification through a column of silica gel using 2% diethyl ether−petroleum ether yielded compound **6e** as a colorless liquid (287 mg, 76% yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.46 (d, J = 2.4 Hz, 2H), 6.29 (t, J = 2.4 Hz, 1H), 3.78 (s, 6H), 1.54 (m, 2H, 2′-CH_2), 1.30−1.15 (m, 10H, 3′-CH_2, 4′-CH_2, 5′-CH_2, 6′-CH_2, 7′-CH_2), 0.85 (t, J = 7.1 Hz, 3H, 8′-CH_3), 0.76 (half of AA′BB′ system, 2H of the cyclopropane ring), 0.62 (half of AA′BB′ system, 2H of the cyclopropane ring); ^{13}C NMR ($CDCl_3$) δ 160.3, 148.1, 107.1, 97.6, 55.2, 40.3, 31.9, 29.7, 29.3, 27.2, 26.0, 22.6, 14.1, 13.2. Anal. ($C_{18}H_{28}O_2$) C, H.

3,5-Dimethoxy-1-(1-heptylcyclobutyl)benzene (6f). The synthesis was carried out as described for **6b** by using **5f** (364 mg, 1.26 mmol) and 10% Pd/C (66 mg) in EtOAc (11.2 mL). The reaction was completed in 6 h at room temperature: yield 98% (358 mg); colorless liquid (spectroscopic and elemental analysis data are available under Supporting Information).

3,5-Dimethoxy-1-(1-heptylcyclopentyl)benzene (6g). The synthesis was carried out as described for **6b** by using **5g** (517 mg, 1.71 mmol) and 10% Pd/C (93 mg) in EtOAc (15.5 mL). The reaction was completed in 6 h at room temperature: yield 98% (511 mg); colorless liquid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.43 (d, J = 1.8 Hz, 2H), 6.29 (t, J = 1.8 Hz, 1H), 3.79 (s, 6H), 2.05−1.50 (m, 10H, 2′-CH_2, 8H of the cyclopentane ring), 1.25−1.10 (m, 8H, 4′-CH_2, 5′-CH_2, 6′-CH_2, 7′-CH_2), 0.99 (m, 2H, 3′-CH_2), 0.84 (t, J = 7.1 Hz, 3H, 8′-CH_3); ^{13}C NMR ($CDCl_3$) δ 160.2, 151.8, 105.6, 96.5, 55.2, 51.3, 41.9, 37.7, 31.9, 30.3, 29.2, 25.2, 23.2, 22.6, 14.1. Anal. ($C_{20}H_{32}O_2$) C, H.

3,5-Dimethoxy-1-(1-heptylcyclohexyl)benzene (6h). The synthesis was carried out as described for **6b** by using **5h** (575 mg, 1.82 mmol) and 10% Pd/C (104 mg) in EtOAc (16.5 mL). The reaction was completed in 7 h at room temperature: yield 99% (572 mg); colorless liquid (spectroscopic and elemental analysis data are available under Supporting Information).

5-(1-Hexylcyclobutyl)resorcinol (7b). To a solution of **6b** (388 mg, 1.41 mmol) in dry CH_2Cl_2 (47 mL) at −78 °C under an argon atmosphere was added boron tribromide (3.4 mL, 1 M solution in CH_2Cl_2). Following this addition, the reaction temperature was gradually raised over a period of 3 h to 0 °C, and the stirring continued at that temperature until the reaction was completed (28 h). Unreacted boron tribromide was destroyed by adding methanol at −78 °C. The resulting mixture was warmed at room temperature and stirred for 40 min, and the volatiles were removed in vacuo. The residue was diluted with EtOAc and washed with saturated $NaHCO_3$ solution, water, and brine. The organic layer was dried

over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by flash column chromatography (45% diethyl ether−petroleum ether) afforded 340 mg (97% yield) of the compound **7b** as a slightly brown viscous oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.17−6.13 (m, 3H, ArH), 5.84 (br s, 2H, OH), 2.30−2.21 (m, 2H of the cyclobutane ring), 2.06−1.98 (m, 3H, of the cyclobutane ring), 1.82−1.77 (m, 1H of the cyclobutane ring), 1.71−1.67 (m, 2H, 2′-CH_2), 1.25−1.15 (m, 6H, 4′-CH_2, 5′-CH_2, 6′-CH_2), 1.02−0.97 (m, 2H, 3′-CH_2), 0.84 (t, J = 6.9 Hz, 3H, 7′-CH_3); ^{13}C NMR ($CDCl_3$) δ 156.2, 154.3, 105.7, 99.7, 46.6, 42.5, 32.7, 31.8, 29.8, 24.6, 22.7, 15.8, 14.1; mass spectrum *m*/*z* (relative intensity) 248 (M^+, 86), 220 (13), 177 (35), 163 (14), 150 (100), 91 (7), 77 (8); exact mass calcd for $C_{16}H_{24}O_2$ 248.1776, found 248.1779. Anal. ($C_{16}H_{24}O_2$) C, H.

5-(1-Hexylcyclohexyl)resorcinol (7d). The synthesis was carried out as described for **7b** by using **6d** (653 mg, 2.15 mmol) and boron tribromide (5.2 mL, 1 M solution in CH_2Cl_2), in anhydrous CH_2Cl_2 (71.6 mL). The reaction was completed in 72 h at −78 °C to room temperature: yield 96% (569 mg); slightly brown viscous oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.39 (d, J = 1.9 Hz, 2H), 6.18 (t, J = 1.9 Hz, 1H), 5.14 (br s, 2H, OH), 1.93 (m, 2H of the cyclohexane ring), 1.49−1.36 (m, 10H, 2′-CH_2, 8H of the cyclohexane ring), 1.25−1.10 (m, 6H, 4′-CH_2, 5′-CH_2, 6′-CH_2), 0.92 (m, 2H, 3′-CH_2), 0.82 (t, J = 6.7 Hz, 3H, 7′-CH_3); ^{13}C NMR ($CDCl_3$) δ 156.2, 151.4, 106.9, 100.0, 43.6, 41.2, 36.2, 31.7, 30.0, 26.5, 23.4, 22.7, 22.4, 14.1. Anal. ($C_{18}H_{28}O_2$) C, H.

5-(1-Heptylcyclopropyl)resorcinol (7e). To a solution of **6e** (287 mg, 1.04 mmol) in anhydrous hexane (20 mL) under an argon atmosphere was added *B*-I-9-borabicyclo[3.3.1]nonane (3.3 mL, 1 M solution in hexanes) at room temperature. The resulting mixture was stirred for 2 h until the reaction was completed. The reaction mixture was then concentrated and the residual was diluted with anhydrous Et_2O (3 mL). A solution of ethanolamine (209 mg, 3.43 mmol) in anhydrous THF (1.56 mL) was added, causing spontaneous precipitation of a white solid. The resulting suspension was stirred for 1 h, the white solid was filtered off, and the filtrate was evaporated. Purification by flash column chromatography (2% methanol, 18% ethyl acetate−petroleum ether) afforded 246 mg (95% yield) of the compound **7e** as a viscous oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.35 (br s, 2H), 6.17 (br s, 1H), 5.24 (br s, 2H, OH), 1.47 (m, 2H, 2′-CH_2), 1.25−1.20 (m, 10H, 3′-CH_2, −4′-CH_2, 5′-CH_2, 6′-CH_2, 7′-CH_2), 0.86 (t, J = 6.7 Hz, 3H, 8′-CH_3), 0.72 (half of AA′BB′ system, 2H of the cyclopropane ring), 0.59 (half of AA′BB′ system, 2H of the cyclopropane ring); ^{13}C NMR ($CDCl_3$) δ 156.3, 148.9, 108.4, 100.4, 40.1, 31.9, 29.7, 29.3, 27.2, 25.6, 22.6, 14.1, 13.2.

5-(1-Heptylcyclobutyl)resorcinol (7f). The synthesis was carried out as described for **7b** by using **6f** (358 mg, 1.23 mmol) and boron tribromide (3 mL, 1 M solution in CH_2Cl_2), in anhydrous CH_2Cl_2 (41 mL). The reaction was completed in 72 h at −78 °C to room temperature: yield 94% (303 mg); slightly brown viscous oil (spectroscopic and elemental analysis data are available under Supporting Information).

5-(1-Heptylcyclopentyl)resorcinol (7g). The synthesis was carried out as described for **7b** by using **6g** (511 mg, 1.68 mmol) and boron tribromide (4.0 mL, 1 M solution in CH_2Cl_2), in anhydrous CH_2Cl_2 (56 mL). The reaction was completed in 72 h at −78 °C to room temperature: yield 75% (348 mg); slightly brown viscous oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.36 (d, J = 1.8 Hz 2H), 6.19 (bs, 1H), 5.89 (bs, 2H, OH), 1.78−1.43 (m, 10H, 2′-CH_2, 8H of the cyclopentane ring), 1.14 (m, 8H, −4′-CH_2, 5′-CH_2, 6′-CH_2, 7′-CH_2), 0.91 (m, 2H, 3′-CH_2), 0.83 (t, J = 6.7 Hz, 3H, 8′-CH_3); ^{13}C NMR ($CDCl_3$) δ 156.1, 152.7, 106.8, 99.8, 51.1, 41.8, 37.6, 31.9, 30.3, 29.2, 25.2, 23.2, 22.6, 14.1.

5-(1-Heptylcyclohexyl)resorcinol (7h). The synthesis was carried out as described for **7b** by using **6h** (572 mg, 1.80 mmol) and boron tribromide (4.3 mL, 1 M solution in CH_2Cl_2), in anhydrous CH_2Cl_2 (60 mL). The reaction was completed in 72 h at −78 °C to room temperature: yield 92% (482 mg); slightly brown viscous oil (spectroscopic and elemental analysis data are available under Supporting Information).

(−)-2-[3−3,4-*trans*-*p*-Menthadien-(1,8)-yl]-5-(1-hexylcyclobutyl)resorcinol (8b). To a solution of **7b** (340 mg, 1.37 mmol) in dry benzene (13.7 mL) at 10 °C under an argon atmosphere was added *p*-toluenesulfonic acid (49 mg, 0.26 mmol), followed by the addition of a solution of (+)-*cis/trans*-*p*-mentha-2,8-dien-1-ol (292 mg, 1.92 mmol) in dry benzene (4 mL). The reaction mixture was stirred at 10−20 °C for 1 h, and at which time TLC indicated the complete consumption of starting material. The reaction mixture was diluted with ethyl acetate and washed with saturated $NaHCO_3$ solution, water, and brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by flash column chromatography (7% diethyl ether−petroleum ether) afforded 329 mg (63% yield) of the title compound **8b** as colorless viscous oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.11 (br s, 2H, ArH), 5.95 (br s, 1H, OH), 5.58 (s, 1H, 2-H), 4.73 (br s, 1H, OH), 4.65 (s, 1H, >C=CH_2), 4.54 (s, 1H, >C=CH_2), 3.83 (m, 1H, 3-H), 2.38 (dt, J = 10.5 Hz, J = 4.1 Hz, 1H, 4-H), 2.32−1.60 (m, 18H, 2′-CH_2, cyclobutane ring, 5-CH_2, 6-CH_2, and especially 1.79, s, 3H, 7-CH_3 and 1.63, s, 3H, 10-CH_3), 1.25−1.10 (m, 6H, 4′-CH_2, 5′-CH_2, 6′-CH_2), 0.94 (m, 2H, 3′-CH_2), 0.82 (t, J = 6.8 Hz, 3H, 7′-CH_3); mass spectrum *m*/*z* (relative intensity) 382 (M^+, 97), 355 (28), 339 (25), 325 (17), 311 (72), 299 (83), 271 (100), 261 (43), 243 (35), 229 (22), 201 (40), 119 (35), 91 (45); exact mass calcd for $C_{26}H_{38}O_2$ 382.2872, found 382.2862. Anal. ($C_{26}H_{38}O_2$) C, H.

(−)-2-[3−3,4-*trans*-*p*-Menthadien-(1,8)-yl]-5-(1-hexylcyclohexyl)resorcinol (8d). The synthesis was carried out as described for **8b** by using **7d** (569 mg, 2.06 mmol), (+)-*cis/trans*-*p*-mentha-2,8-dien-1-ol (438 mg, 2.88 mmol), and *p*-toluenesulfonic acid (74 mg, 0.39 mmol) in anhydrous benzene (20.6 mL): yield 92% (777 mg); colorless viscous oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.33 (br s, 2H, ArH), 5.91 (br s, 1H, OH), 5.61 (s, 1H, 2-H), 4.65 (br s, 2H, >C=CH_2, OH), 4.53 (s, 1H, >C=CH_2), 3.81 (d, J = 8.8 Hz, 1H, 3-H), 2.37 (dt, J = 10.5 Hz, J = 4.3 Hz, 1H, 4-H), 2.28−2.07 (m, 2H), 2.01−1.75 (m, 7H, especially 1.80, s, 3H, 7-CH_3), 1.65−1.10 (m, 19H, 2′-CH_2, 4′-CH_2, 5′-CH_2, 6′-CH_2, 8H of the cyclohexane ring and especially 1.62, s, 3H, 10-CH_3), 0.88 (m, 2H, 3′-CH_2), 0.81 (t, J = 6.9 Hz, 3H, 7′-CH_3); mass spectrum *m*/*z* (relative intensity) 410 (M^+, 33), 395 (11), 368 (5), 327 (100), 289 (9), 257 (7); exact mass calcd for $C_{28}H_{42}O_2$ 410.3185, found 410.3185. Anal. ($C_{28}H_{42}O_2$) C, H.

(−)-2-[3−3,4-*trans*-*p*-Menthadien-(1,8)-yl]-5-(1-heptylcyclopropyl)resorcinol (8e). The synthesis was carried out as described for **8b** by using **7e** (246 mg, 0.99 mmol), (+)-*cis/trans*-*p*-mentha-2,8-dien-1-ol (211 mg, 1.39 mmol), and *p*-toluenesulfonic acid (36 mg, 0.19 mmol) in anhydrous benzene (9.9 mL): yield 46% (174 mg); colorless viscous oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.34 (br s, 2H, ArH), 5.99 (br s, 1H, OH), 5.57 (s, 1H, 2-H), 4.66 (br s, 2H, >C=CH_2, OH), 4.54 (s, 1H, >C=CH_2), 3.82 (d, J = 8.7 Hz, 1H, 3-H), 2.37 (dt, J = 10.4 Hz, J = 3.7 Hz, 1H, 4-H), 2.26−2.02 (m, 2H), 1.88−1.74 (m, 5H, especially 1.79, s, 3H, 7-CH_3), 1.64 (s, 3H, 10-CH_3), 1.45 (m, 2H, 2′-CH_2), 1.30−1.18 (m, 10H 3′-CH_2, 4′-CH_2, 5′-CH_2, 6′-CH_2, 7′-CH_2), 0.85 (t, J = 6.7 Hz, 3H, 8′-CH_3), 0.71 (half of AA′BB′ system, 2H of the cyclopropane ring), 0.57 (half of AA′BB′ system, 2H of the cyclopropane ring); ^{13}C NMR ($CDCl_3$) δ 149.4, 145.7, 140.2, 124.0, 113.9, 110.8, 46.0, 40.0, 37.4, 31.8, 30.4, 29.7, 29.3, 28.3, 27.2, 25.1, 23.7, 22.7, 20.7, 14.1, 13.3, 13.2; mass spectrum (FAB) *m*/*z* (relative intensity) 383 ($M^+ + 1$, 98), 261 (100), 135 (93); exact mass calcd for $C_{26}H_{39}O_2$ ($M^+ + 1$, FAB) 383.2950, found 383.2950. Anal. ($C_{26}H_{38}O_2$) C, H.

(−)-2-[3−3,4-*trans*-*p*-Menthadien-(1,8)-yl]-5-(1-heptylcyclobutyl)resorcinol (8f). The synthesis was carried out as described for **8b** by using **7f** (303 mg, 1.16 mmol), (+)-*cis/trans*-*p*-mentha-2,8-dien-1-ol (247 mg, 1.62 mmol), and *p*-toluenesulfonic acid (42 mg, 0.22 mmol) in anhydrous benzene (11.6 mL): yield 76% (349 mg); colorless viscous oil (spectroscopic and elemental analysis data are available under Supporting Information).

(−)-2-[3−3,4-*trans*-*p*-Menthadien-(1,8)-yl]-5-(1-heptylcyclopentyl)resorcinol (8g). The synthesis was carried out as described for **8b** by using **7g** (348 mg, 1.26 mmol), (+)-*cis/trans*-*p*-mentha-2,8-dien-1-ol (268 mg, 1.76 mmol), and *p*-toluenesulfonic acid (46

mg, 0.24 mmol) in anhydrous benzene (12.6 mL): yield 90% (463 mg); colorless viscous oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.29 (br s, 2H, ArH), 5.95 (br s, 1H, OH), 5.59 (s, 1H, 2-H), 4.65 (br s, 2H, >C=CH_2, OH), 4.54 (s, 1H, >C=CH_2), 3.81 (d, J = 8.5 Hz, 1H, 3-H), 2.37 (dt, J = 10.4 Hz, J = 4.3 Hz, 1H, 4-H), 2.32−2.05 (m, 2H), 1.88−1.77 (m, 7H, especially 1.79, s, 3H, 7-CH_3), 1.73−1.57 (m, 9H, especially 1.62, s, 3H, 10-CH_3), 1.46 (m, 2H, 2′-CH_2), 1.25−1.06 (m, 8H, 4′-CH_2, 5′-CH_2, 6′-CH_2, 7′-CH_2), 0.93 (m, 2H, 3′-CH_2), 0.83 (t, J = 6.7 Hz, 3H, 8′-CH_3); mass spectrum (FAB) m/z (relative intensity) 411 (M^+ + 1, 84), 410 (M^+, 68), 342 (58), 327 (100), 289 (67); exact mass calcd for $C_{28}H_{43}O_2$ (M^+ + 1, FAB) 411.3263, found 411.3263. Anal. ($C_{28}H_{42}O_2$) C, H.

(−)-2-[3−3,4-*trans*-*p*-Menthadien-(1,8)-yl]-5-(1-heptylcyclohexyl)resorcinol (8h). The synthesis was carried out as described for **8b** by using **7h** (482 mg, 1.67 mmol), (+)-*cis*/*trans*-*p*-mentha-2,8-dien-1-ol (356 mg, 2.34mmol), and *p*-toluenesulfonic acid (61 mg, 0.32 mmol) in anhydrous benzene (16.7 mL): yield 86% (611 mg); colorless viscous oil (spectroscopic and elemental analysis data are available under Supporting Information).

(6a*R*-*trans*)-3-(1-Hexylcyclobutyl)-6a,7,10,10a-tetrahydro-6,6,9-trimethyl-6*H*-dibenzo[*b*,*d*]pyran-1-ol (9b). To a solution of **8b** (329 mg, 0.86 mmol) in anhydrous CH_2Cl_2 (24.6 mL) at 0 °C under an argon atmosphere was added boron trifluoride etherate (0.75 mL, 6.02 mmol). Following the addition the mixture was stirred at 0 °C for 1 h and then at room temperature for 7 h. The reaction was quenched by the addition of saturated $NaHCO_3$ solution, and the volatiles were removed under reduced pressure. The crude residual was diluted with EtOAc and the organic layer was washed with water and brine and dried over Na_2SO_4. Solvent evaporation and purification by flash column chromatography on silica gel (5% diethyl ether−petroleum ether) afforded 168 mg (51% yield) of the title compound **9b** as viscous oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.18 (d, J = 1.9 Hz, 1H, 4-H), 6.01 (d, J = 1.9 Hz, 1H, 2-H), 5.43 (br s, 1H, 8-H), 4.69 (s, 1H, OH), 3.20 (dd, J = 16.2 Hz, J = 4.0 Hz, 1H, 10α-H), 2.68 (m, 1H, 10a-H), 2.32−2.13 (m, 3H, 7α-H, 2H of the cyclobutane ring), 2.02−1.59 (m, 12H, 2′-CH_2, 4H of the cyclobutane ring, 10β-H, 7β-H, 6a-H, especially 1.70, s, 9-CH_3), 1.38 (s, 3H, 6β-CH_3), 1.32−1.13 (m, 6H, 4′-CH_2, 5′-CH_2, 6′-CH_2), 1.11 (s, 3H, 6α-CH_3), 1.01 (m, 2H, 3′-CH_2), 0.84 (t, J = 6.7 Hz, 3H, 7′-CH_3); mass spectrum m/z (relative intensity) 382 (M^+, 100), 354 (22), 311 (51), 298 (25), 271 (14), 200 (6); exact mass calcd for $C_{26}H_{38}O_2$ 382.2872, found 382.2865. Anal. ($C_{26}H_{38}O_2$) C, H.

(6a*R*-*trans*)-3-(1-Hexylcyclohexyl)-6a,7,10,10a-tetrahydro-6,6,9-trimethyl-6*H*-dibenzo[*b*,*d*]pyran-1-ol (9d). The synthesis was carried out as described for **9b** by using **8d** (777 mg, 1.90 mmol) and boron trifluoride etherate (1.19 mL, 9.5 mmol), in anhydrous CH_2Cl_2 (54.3 mL): yield 63% (492 mg); colorless viscous oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.37 (d, J = 1.7 Hz, 1H, 4-H), 6.20 (d, J = 1.7 Hz, 1H, 2-H), 5.42 (d, J = 4.5 Hz, 1H, 8-H), 4.70 (s, 1H, OH), 3.19 (dd, J = 16.3 Hz, J = 4.1 Hz, 1H, 10α-H), 2.69 (m, 1H, 10a-H), 2.13 (m, 1H, 7α-H), 1.93−1.72 (m, 5H, 2H of the cyclohexane ring, 10β-H, 7β-H, 6a-H), 1.70 (s, 3H, 9-CH_3), 1.48−1.30 (m, 13H, 8H of the cyclohexane ring, 2′-CH_2, especially 1.38 s, 3H, 6β-CH_3), 1.20−1.00 (m, 9H, 4′-CH_2, 5′-CH_2, 6′-CH_2, especially 1.11 s, 3H, 6α-CH_3), 0.93 (m, 2H, 3′-CH_2), 0.81 (t, J = 6.7 Hz, 3H, 7′-CH_3); mass spectrum m/z (relative intensity) 410 (M^+, 46), 368 (5), 326 (100), 314 (17), 271 (9); exact mass calcd for $C_{28}H_{42}O_2$ 410.3185, found 410.3182. Anal. ($C_{28}H_{42}O_2$) C, H.

(6a*R*-*trans*)-3-(1-Heptylcyclopropyl)-6a,7,10,10a-tetrahydro-6,6,9-trimethyl-6*H*-dibenzo[*b*,*d*]pyran-1-ol (9e). The synthesis was carried out as described for **9b** by using **8e** (174 mg, 0.46 mmol) and boron trifluoride etherate (0.29 mL, 2.3 mmol) in anhydrous CH_2Cl_2 (13.1 mL): yield 46% (81 mg); viscous oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.34 (br s, 1H, 4-H), 6.19 (br s, 1H, 2-H), 5.41 (d, J = 3.9 Hz, 1H, 8-H), 4.66 (s, 1H, OH), 3.18 (dd, J = 15.6 Hz, J = 4.0 Hz, 1H, 10α-H), 2.68 (ddd as dt, J = 10.8 Hz, J = 4.9 Hz, 1H, 10a-H), 2.12 (m, 1H, 7α-H), 1.90−1.73 (m, 3H, 10β-H, 7β-H, 6a-H), 1.69 (s, 3H, 9-CH_3), 1.45 (m, 2H, 2′-CH_2), 1.37 (s, 3H, 6β-CH_3), 1.28−1.14 (m, 10H, 3′-CH_2, 4′-CH_2, 5′-CH_2, 6′-CH_2, 7′-CH_2), 1.10 (s, 3H, 6α-CH_3), 0.85 (t, J = 6.7 Hz, 3H, 8′-CH_3), 0.72 (half of AA′BB′ system, 2H of the cyclopropane ring), 0.56 (half of AA′BB′ system, 2H of the cyclopropane ring); ^{13}C NMR ($CDCl_3$) δ 154.5, 154.4, 145.4, 134.7, 119.3, 110.6, 110.3, 107.7, 44.8, 39.9, 35.9, 31.9, 31.5, 29.8, 29.3, 27.9, 27.6, 27.2, 25.0, 23.5, 22.7, 18.5, 14.1, 13.5, 13.2; mass spectrum (FAB) m/z (relative intensity) 383 (M^+ + 1, 100), 261 (17); exact mass calcd for $C_{26}H_{39}O_2$ (M^+ + 1, FAB) 383.2950, found 383.2950. Anal. ($C_{26}H_{38}O_2$) C, H.

(6a*R*-*trans*)-3-(1-Heptylcyclobutyl)-6a,7,10,10a-tetrahydro-6,6,9-trimethyl-6*H*-dibenzo[*b*,*d*]pyran-1-ol (9f). The synthesis was carried out as described for **9b** by using **8f** (349 mg, 0.88 mmol) and boron trifluoride etherate (0.55 mL, 4.4 mmol) in anhydrous CH_2Cl_2 (25.1 mL): yield 65% (227 mg); colorless viscous oil (spectroscopic and elemental analysis data are available under Supporting Information).

(6a*R*-*trans*)-3-(1-Heptylcyclopentyl)-6a,7,10,10a-tetrahydro-6,6,9-trimethyl-6*H*-dibenzo[*b*,*d*]pyran-1-ol (9g). The synthesis was carried out as described for **9b** by using **8g** (463 mg, 1.13 mmol) and boron trifluoride etherate (0.71 mL, 5.65 mmol) in anhydrous CH_2Cl_2 (32.3 mL): yield 52% (241 mg); colorless viscous oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.33 (d, J = 1.8 Hz, 1H, 4-H), 6.16 (d, J = 1.8 Hz, 1H, 2-H), 5.42 (d, J = 4.3 Hz, 1H, 8-H), 4.62 (s, 1H, OH), 3.18 (dd, J = 16.2 Hz, J = 3.4 Hz, 1H, 10α-H), 2.69 (ddd as dt, J = 10.4 Hz, J = 4.9 Hz, 1H, 10a-H), 2.14 (m, 1H, 7α-H), 1.93−1.58 (m, 14H, 8H of the cyclopentane ring, 10β-H, 7β-H, 6a-H, especially 1.70, s, 9-CH_3), 1.48 (m, 2H, 2′-CH_2), 1.38 (s, 3H, 6β-CH_3), 1.25−1.11 (m, 8H, 4′-CH_2, 5′-CH_2, 6′-CH_2, 7′-CH_2), 1.10 (s, 3H, 6α-CH_3), 0.97 (m, 2H, 3′-CH_2), 0.83 (t, J = 6.7 Hz, 3H, 8′-CH_3); mass spectrum (FAB) m/z (relative intensity) 411 (M^+ + 1, 100) 312 (47); exact mass calcd for $C_{28}H_{43}O_2$ (M^+ + 1, FAB), 411.3263, found 411.3263. Anal. ($C_{28}H_{42}O_2$) C, H.

(6a*R*-*trans*)-3-(1-Heptylcyclohexyl)-6a,7,10,10a-tetrahydro-6,6,9-trimethyl-6*H*-dibenzo[*b*,*d*]pyran-1-ol (9h). The synthesis was carried out as described for **9b** by using **8h** (611 mg, 1.44 mmol) and boron trifluoride etherate (0.90 mL, 7.2 mmol) in anhydrous CH_2Cl_2 (41.1 mL): yield 67% (409 mg); colorless viscous oil (spectroscopic and elemental analysis data are available under Supporting Information).

5-[1-[(1*Z*)-1-Hexenyl]cyclopropyl]resorcinol (10a). The synthesis was carried out as described for **7e** by using **5a** (426 mg, 1.64 mmol) and *B*-I-9-borabicyclo[3.3.1]nonane (5.25 mL, 1 M solution in hexanes) in anhydrous hexane (32.8 mL). The reaction was completed in 2 h at room temperature: yield 89% (339 mg); slightly brown viscous oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.27 (d, J = 2.4 Hz, 2H), 6.13 (t, J = 2.4 Hz, 1H), 5.63−5.48 (m, 2H, 2′-H, 3′-H), 4.42 (br s, 2H, OH), 2.04 (m, 2H, 4′-CH_2), 1.26 (m, 4H, 5′-CH_2, 6′-CH_2), 1.03 (half of AA′BB′ system, 2H of the cyclopropane ring), 0.95 (half of AA′BB′ system, 2H of the cyclopropane ring), 0.84 (t, J = 6.7 Hz, 3H, 7′-CH_3); ^{13}C NMR ($CDCl_3$) δ 156.5, 149.1, 135.0, 131.9, 105.9, 99.9, 31.4, 28.2, 22.8, 22.5, 17.9, 13.9.

5-[1-[(1*Z*)-1-Hexenyl]cyclobutyl]resorcinol (10b). The synthesis was carried out as described for **7e** by using **5b** (414 mg, 1.51 mmol) and *B*-I-9-borabicyclo[3.3.1]nonane (4.8 mL, 1 M solution in hexanes) in anhydrous hexane (30.2 mL). The reaction was completed in 2 h at room temperature: yield 89% (331 mg); slightly brown viscous oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.40 (d, J = 2.1 Hz, 2H), 6.16 (t, J = 2.1 Hz, 1H), 5.76 (d, J = 11.0 Hz, 1H, 2′-H), 5.29 (dt, J = 11.0 Hz, J = 7.5 Hz, 1H, 3′-H), 4.84 (br s, 2H, OH), 2.47−2.41 (m, 2H of the cyclobutane ring), 2.36−2.30 (m, 2H of the cyclobutane ring), 2.01−1.93 (m, 1H of the cyclobutane ring), 1.90−1.79 (m, 3H, 1H of the cyclobutane ring, 4′-CH_2), 1.21−1.15 (m, 4H, 5′-CH_2, 6′-CH_2), 0.81 (t, J = 7.0 Hz, 3H, 7′-CH_3); ^{13}C NMR ($CDCl_3$) δ 156.3, 148.7, 135.0, 131.9, 105.8, 99.5, 34.5, 34.2, 31.4, 28.2, 22.8, 22.5, 18.2; mass spectrum m/z (relative intensity) 246 (M^+, 57), 218 (17), 203 (19), 189 (56), 175 (100), 161 (43), 110 (33), 91 (13); exact mass calcd for $C_{16}H_{22}O_2$ 246.1620, found 246.1620.

5-[1-[(1*Z*)-1-Hexenyl]cyclopentyl]resorcinol (10c). The synthesis was carried out as described for **7e** by using **5c** (500 mg,

1.74 mmol) and *B*-I-9-borabicyclo[3.3.1]nonane (5.60 mL, 1 M solution in hexanes) in anhydrous hexane (34.8 mL). The reaction was completed in 2 h at room temperature: yield 75% (339 mg); colorless viscous oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.42 (d, J = 1.8 Hz, 2H), 6.16 (t, J = 1.8 Hz, 1H), 5.64 (d, J = 11.0 Hz, 1H, 2′-H), 5.52 (br s, 2H, OH), 5.25 (dt, J = 11.0 Hz, J = 7.9 Hz, 1H, 3′-H), 1.88 (m, 4H, 4′-CH_2, 2H of the cyclopentane ring), 1.67 (m, 6H of the cyclopentane ring), 1.09 (m, 4H, 5′-CH_2, 6′-CH_2), 0.75 (t, J = 6.7 Hz, 3H, 7′-CH_3); ^{13}C NMR ($CDCl_3$) δ 156.5, 147.9, 134.8, 131.9, 105.4, 100.1, 37.9, 37.9, 31.4, 28.2, 22.8, 22.5; mass spectrum *m*/*z* (relative intensity) 260 (M^+, 55), 217 (32), 203 (74), 191 (17), 177 (100), 166 (41), 149 (25), 123 (62).

5-[1-[(1*Z*)-1-Hexenyl]cyclohexyl]resorcinol (10d). The synthesis was carried out as described for **7e** by using **5d** (683 mg, 2.26 mmol) and *B*-I-9-borabicyclo[3.3.1]nonane (7.23 mL, 1 M solution in hexanes) in anhydrous hexane (45.2 mL). The reaction was completed in 2 h at room temperature: yield 94% (581 mg); colorless viscous oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.28 (d, J = 2.5 Hz, 2H), 6.16 (t, J = 2.5 Hz, 1H), 5.60 (d, J = 11.6 Hz, 1H, 2′-H), 5.35 (dt, J = 11.6 Hz, J = 7.3 Hz, 1H, 3′-H), 4.77 (br s, 1H, OH), 4.43 (br s, 1H, OH), 1.90 (m, 2H, 4′-CH_2), 1.71−1.60 (m, 9H, of the cyclohexane ring), 1.31 (m, 1H, of the cyclohexane ring), 1.07 (m, 4H, 5′-CH_2, 6′-CH_2), 0.74 (t, J = 6.7 Hz, 3H, 7′-CH_3); ^{13}C NMR ($CDCl_3$) δ 156.8, 148.1, 134.6, 132.3, 105.4, 99.7, 38.9, 38.6, 31.4, 28.1, 27.1, 23.0, 21.5.

(−)-2-[3−3,4-*trans*-*p*-Menthadien-(1,8)-yl]-5-[1-[(1*Z*)-1-hexenyl]-cyclopropyl]resorcinol (11a). The synthesis was carried out as described for **8b** by using **10a** (339 mg, 1.46 mmol), (+)-*cis*/*trans*-*p*-mentha-2,8-dien-1-ol (311 mg, 2.04 mmol), and *p*-toluenesulfonic acid (53 mg, 0.28 mmol) in anhydrous benzene (14.6 mL): yield 57% (305 mg); colorless viscous oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.24 (br s, 2H, ArH), 5.93 (br s, 1H, OH), 5.59 (d, J = 10.4 Hz, 1H, 2′-H), 5.54 (br s, 1H, 2-H), 5.48 (dt, J = 10.4 Hz, J = 6.7 Hz, 1H, 3′-H), 4.65 (s, 2H, >C=CH_2, -OH), 4.55 (s, 1H, >C=CH_2), 3.82 (d, J = 9.8 Hz, 1H, 3-H), 2.38 (dt, J = 10.4 Hz, J = 3.7 Hz, 1H, 4-H), 2.20−2.11 (m, 2H), 2.03 (m, 2H) 1.80−1.75 (m, 5H, especially 1.78, s, 3H, 7-CH_3), 1.64 (s, 3H, 10-CH_3), 1.25 (m, 4H, 5′-CH_2, 6′-CH_2), 1.03 (half of AA′BB′ system, 2H of the cyclopropane ring), 0.91 (half of AA′BB′ system, 2H of the cyclopropane ring), 0.84 (t, J = 7.0 Hz, 3H, 7′-CH_3); ^{13}C NMR ($CDCl_3$) δ 149.3, 145.8, 140.0, 134.6, 132.3, 124.1, 113.5, 110.8, 46.1, 37.2, 31.4, 30.3, 28.3, 28.1, 23.7, 22.6, 22.5, 20.5, 17.8, 17.6, 13.9; mass spectrum *m*/*z* (relative intensity) 366 (M^+, 65), 299 (50), 283 (100), 245 (32); exact mass calcd for $C_{25}H_{34}O_2$ 366.2559, found 366.2556. Anal. ($C_{25}H_{34}O_2$) C, H.

(−)-2-[3−3,4-*trans*-*p*-Menthadien-(1,8)-yl]-5-[1-[(1*Z*)-1-hexenyl]-cyclobutyl]resorcinol (11b). The synthesis was carried out as described for **8b** by using **10b** (331 mg, 1.35 mmol), (+)-*cis*/*trans*-*p*-mentha-2,8-dien-1-ol (287 mg, 1.89 mmol), and *p*-toluenesulfonic acid (49 mg, 0.26 mmol) in anhydrous benzene (13.5 mL): yield 50% (256 mg); colorless viscous oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.31 (br s, 2H, ArH), 5.97 (br s, 1H, OH), 5.78 (d, J = 11.0 Hz, 1H, 2′-H), 5.57 (br s, 1H, 2-H), 5.26 (dt, J = 11.0 Hz, J = 7.3 Hz, 1H, 3′-H), 4.68−4.57 (br s, 2H, > C=CH_2, OH), 4.55 (s, 1H, >C=CH_2), 3.83 (d, J = 9.2 Hz, 1H, 3-H), 2.42−2.23 (m, 7H, 4-H, cyclobutane ring), 2.16−2.05 (m, 2H), 1.94−1.83 (m, 7H, especially 1.79, s, 3H, 7-CH_3), 1.64 (s, 3H, 10-CH_3), 1.15 (m, 4H, 5′-CH_2, 6′-CH_2), 0.81 (t, J = 6.7 Hz, 3H, 7′-CH_3); ^{13}C NMR ($CDCl_3$) δ 149.5, 140.1, 138.9, 130.8, 124.1, 113.4, 110.8, 64.9, 47.1, 46.0, 37.4, 36.2, 36.1, 31.5, 30.4, 28.3, 27.9, 23.7, 22.4, 20.7, 16.7, 13.9; mass spectrum *m*/*z* (relative intensity) 380 (M^+, 100), 312 (35), 297 (82), 269 (85); exact mass calcd for $C_{26}H_{36}O_2$ 380.2715, found 380.2711. Anal. ($C_{26}H_{36}O_2$) C, H.

(−)-2-[3−3,4-*trans*-*p*-Menthadien-(1,8)-yl]-5-[1-[(1*Z*)-1-hexenyl]-cyclopentyl]resorcinol (11c). The synthesis was carried out as described for **8b** by using **10c** (339 mg, 1.30 mmol), (+)-*cis*/*trans*-*p*-mentha-2,8-dien-1-ol (277 mg, 1.82 mmol), and *p*-toluenesulfonic acid (47 mg, 0.25 mmol) in anhydrous benzene (13 mL): yield 76% (390 mg); colorless viscous oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.37 (br s, 2H, ArH), 5.92 (br s, 1H, OH), 5.65 (d, J = 11.0 Hz, 1H, 2′-H), 5.56 (br s, 1H, 2-H), 5.23 (dt, J = 11.0 Hz, J = 7.3 Hz, 1H, 3′-H), 4.64 (br s, 2H, >C=CH_2, OH), 4.53 (s, 1H, >C=CH_2), 3.82 (dd, J = 11.0 Hz, J = 1.8 Hz, 1H, 3-H), 2.38 (dt, J = 11.0 Hz, J = 4.3 Hz, 1H, 4-H), 2.26−2.06 (m, 2H) 1.93−160 (m, 18H, especially 1.80, s, 3H, 7-CH_3 and 1.63, s, 3H, 10-CH_3), 1.10 (m, 4H, 5′-CH_2, 6′-CH_2), 0.77 (t, J = 6.9 Hz, 3H, 7′-CH_3); ^{13}C NMR ($CDCl_3$) δ 149.6, 149.4, 139.9, 138.7, 131.9, 124.1, 113.4, 110.7, 51.7, 46.1, 40.9, 40.5, 37.4, 31.5, 30.4, 28.4, 28.2, 23.7, 23.6, 22.3, 20.6, 13.9; mass spectrum *m*/*z* (relative intensity) 394 (M^+, 35), 311 (100), 273 (26), 243 (20); exact mass calcd for $C_{27}H_{38}O_2$ 394.2872, found 394.2866. Anal. ($C_{27}H_{38}O_2$) C, H.

(−)-2-[3−3,4-*trans*-*p*-Menthadien-(1,8)-yl]-5-[1-[(1*Z*)-1-hexenyl]-cyclohexyl]resorcinol (11d). The synthesis was carried out as described for **8b** by using **10d** (581 mg, 2.12 mmol), (+)-*cis*/*trans*-*p*-mentha-2,8-dien-1-ol (451 mg, 2.97 mmol), and *p*-toluenesulfonic acid (77 mg, 0.40 mmol) in anhydrous benzene (21.2 mL): yield 80% (692 mg); colorless viscous oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.41 (br s, 2H, ArH), 5.91 (br s, 1H, OH), 5.62 (d, J = 11.6 Hz, 1H), 5.56 (br s, 1H, 2-H), 5.29 (dt, J = 11.6 Hz, J = 7.3 Hz, 1H), 4.63 (br s, 2H, >C=CH_2, OH), 4.53 (s, 1H, >C=CH_2), 3.82 (d, J = 8.5 Hz, 1H, 3-H), 2.38 (dt, J = 10.4 Hz, J = 4.3 Hz, 1H, 4-H), 2.26−2.05 (m, 2H), 1.88−1.55 (m, 20H, especially 1.78, s, 3H, 7-CH_3 and 1.63, s, 3H, 10-CH_3), 1.08 (m, 4H, 5′-CH_2, 6′-CH_2), 0.76 (t, J = 6.7 Hz, 3H, 7′-CH_3); ^{13}C NMR ($CDCl_3$) δ 151.3, 149.4, 139.9, 136.4, 131.9, 124.2, 113.2, 110.7, 65.9, 46.1, 42.9, 38.8, 38.5, 37.3, 31.4, 30.4, 28.4, 28.1, 26.0, 23.6, 22.8, 22.3, 20.6, 15.2, 13.9; mass spectrum *m*/*z* (relative intensity) 408 (M^+, 45), 340 (40), 325 (100), 287 (25); exact mass calcd for $C_{28}H_{40}O_2$ 408.3028, found 408.3032. Anal. ($C_{28}H_{40}O_2$) C, H.

(6a*R*-*trans*)-3-[1-[(1*Z*)-1-Hexenyl]cyclopropyl]-6a,7,10,10a-tetrahydro-6,6,9-trimethyl-6*H*-dibenzo[*b*,*d*]pyran-1-ol (12a). The synthesis was carried out as described for **9b** by using **11a** (305 mg, 0.83 mmol) and boron trifluoride etherate (0.5 mL, 4.15 mmol) in anhydrous CH_2Cl_2 (23.7 mL): yield 67% (204 mg); viscous oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.23 (d, J = 1.8 Hz, 1H, 4-H), 6.16 (d, J = 1.8 Hz, 1H, 2-H), 5.61 (d, J = 11.0 Hz, 1H, 2′-H), 5.49 (dt, J = 11.0 Hz, J = 6.7 Hz, 1H, 3′-H), 5.42 (br s, 1H, 8C-H), 4.59 (s, 1H, OH), 3.17 (m, 1H, 10α-H), 2.65 (m, 1H, 10a-H), 2.38 (m, 1H, 7α-H), 2.09 (m, 2H, 4′-CH_2), 1.90−1.62 (m, 6H, 10β-H, 7β-H, 6a-H, especially 1.69, s, 3H, 9-CH_3), 1.38−1.15 (m, 7H, 5′-CH_2, 6′-CH_2, especially 1.36, s, 3H, 6β-CH_3), 1.12−0.98 (m, 5H, half of AA′BB′ system, 2H of the cyclopropane ring, especially 1.08, s, 3H, 6α-CH_3), 0.92−0.78 (m, 5H, half of AA′BB′ system, 2H of the cyclopropane ring, 7′-CH_3); ^{13}C NMR ($CDCl_3$) δ 154.9, 145.5, 134.7, 132.1, 124.3, 119.3, 107.6, 105.9, 104.8, 76.5, 44.8, 35.9, 31.5, 29.7, 28.2, 27.9, 27.5, 23.5, 22.5, 18.5, 17.6, 13.9; mass spectrum *m*/*z* (relative intensity) 366 (M^+, 100), 323 (38), 283 (35), 149 (20); exact mass calcd for $C_{25}H_{34}O_2$ 366.2559, found 366.2558. Anal. ($C_{25}H_{34}O_2$) C, H.

(6a*R*-*trans*)-3-[1-[(1*Z*)-1-Hexenyl]cyclobutyl]-6a,7,10,10a-tetrahydro-6,6,9-trimethyl-6*H*-dibenzo[*b*,*d*]pyran-1-ol (12b). The synthesis was carried out as described for **9b** by using **11b** (256 mg, 0.67 mmol) and boron trifluoride etherate (0.42 mL, 3.35 mmol) in anhydrous CH_2Cl_2 (19.1 mL): yield 83% (211 mg); viscous oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.44 (d, J = 1.2 Hz, 1H, 4-H), 6.20 (d, J = 1.2 Hz, 1H, 2-H), 5.74 (d, J = 11.0 Hz, 1H, 2′-H), 5.43 (br s, 1H, 8-H), 5.26 (dt, J = 11.0 Hz, J = 7.3 Hz, 1H, 3′-H), 4.70 (s, 1H, OH), 3.18 (m, 1H, 10α-H), 2.68 (m, 1H, 10a-H), 2.46−2.26 (m, 6H of the cyclobutane ring), 2.12 (m, 1H, 7α-H), 1.90−1.80 (m, 5H, 4′-CH_2, 10β-H, 7β-H, 6a-H), 1.69 (s, 3H, 9-CH_3), 1.38 (s, 3H, 6β-CH_3), 1.25−1.10 (m, 4H, 5′-CH_2, 6′-CH_2), 1.10 (s, 3H, 6α-CH_3), 0.80 (t, J = 6.7 Hz, 3H, 7′-CH_3); ^{13}C NMR ($CDCl_3$) δ 154.6, 138.8, 134.7, 130.6, 125.5, 119.3, 110.2, 107.9, 105.6, 64.9, 47.2, 44.9, 36.0, 31.5, 30.3, 29.7, 27.9, 27.6, 23.5, 22.4, 18.5, 16.7, 13.9; mass spectrum *m*/*z* (relative intensity) 380 (M^+, 100), 352 (25), 297 (32), 269 (20); exact mass calcd for $C_{26}H_{36}O_2$ 380.2715, found 380.2717. Anal. ($C_{26}H_{36}O_2$) C, H.

(6a*R*-*trans*)-3-[1-[(1*Z*)-1-Hexenyl]cyclopentyl]-6a,7,10,10a-tetrahydro-6,6,9-trimethyl-6*H*-dibenzo[*b*,*d*]pyran-1-ol (12c). The synthesis was carried out as described for **9b** by using **11c** (390 mg, 0.99 mmol) and boron trifluoride etherate (0.62 mL, 4.95 mmol) in anhydrous CH_2Cl_2 (28.3 mL): yield 91% (355 mg); viscous oil;

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.42 (d, J = 1.8 Hz, 1H, 4-H), 6.24 (d, J = 1.8 Hz, 1H, 2-H), 5.63 (d, J = 11.0 Hz, 1H, 2′-H), 5.42 (d, J = 3.7 Hz, 1H, 8-H), 5.23 (dt, J = 11.0 Hz, J = 7.3 Hz, 1H, 3′-H), 4.60 (s, 1H, OH), 3.17 (dd, J = 16.5 Hz, J = 4.3 Hz, 1H, 10α-H), 2.68 (dt, J = 11.0 Hz, J = 4.3 Hz, 1H, 10a-H), 2.14 (m, 1H, 7α-H), 1.94−1.66 (m, 16H, 4′-CH_2, 10β-H, 7β-H, 6a-H, 8H of the cyclopentane ring and especially 1.69, s, 3H, 9-CH_3), 1.37 (s, 3H, 6β-CH_3), 1.08 (br s, 7H, 6α-CH_3, 5′-CH_2, 6′-CH_2), 0.73 (t, J = 6.7 Hz, 3H, 7′-CH_3); ^{13}C NMR ($CDCl_3$) δ 154.3, 149.2, 138.7, 134.8, 131.8, 119.3, 110.2, 108.7, 106.6, 51.8, 44.9, 40.7, 40.6, 36.0, 31.5, 31.3, 28.1, 27.9, 23.6, 23.5, 22.3, 18.4, 13.9; mass spectrum m/z (relative intensity) 394 (M^+, 100), 351 (30), 311 (87); exact mass calcd for $C_{27}H_{38}O_2$ 394.2872, found 394.2865. Anal. ($C_{27}H_{38}O_2$) C, H.

(6a*R*-*trans*)-3-[1-[(1*Z*)-1-Hexenyl]cyclohexyl]-6a,7,10,10a-tetrahydro-6,6,9-trimethyl-6*H*-dibenzo[*b*,*d*]pyran-1-ol (12d). The synthesis was carried out as described for **9b** by using **11d** (692 mg, 1.70 mmol) and boron trifluoride etherate (1.1 mL, 8.5 mmol) in anhydrous CH_2Cl_2 (49 mL): yield 71% (492 mg); viscous oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.46 (d, J = 1.2 Hz, 1H, 4-H), 6.27 (d, J = 1.2 Hz, 1H, 2-H), 5.59 (d, J = 11.6 Hz, 1H, 2′-H), 5.41 (br s, 1H, 8-H), 5.30 (dt, J = 11.6 Hz, J = 7.3 Hz, 1H, 3′-H), 4.60 (s, 1H, OH), 3.17 (dd, J = 16.5 Hz, J = 4.9 Hz, 1H, 10α-H), 2.68 (dt, J = 11.0 Hz, J = 4.3 Hz, 1H, 10a-H), 2.12 (m, 1H, 7α-H), 1.92−1.77 (m, 5H, 4′-CH_2, 10β-H, 7β-H, 6a-H), 1.69 (s, 3H, 9-CH_3), 1.56 (m, 10H of the cyclohexane ring), 1.37 (s, 3H, 6β-CH_3), 1.08 (s, 3H, 6α-CH_3), 1.04 (m, 4H, 5′-CH_2, 6′-CH_2), 0.71 (t, J = 6.7 Hz, 3H, 7′-CH_3); ^{13}C NMR ($CDCl_3$) δ 154.3, 150.8, 136.5, 134.7, 131.9, 119.3, 110.1, 108.5, 106.3, 65.8, 44.9, 43.0, 38.8, 38.5, 36.0, 31.5, 31.2, 29.7, 28.1, 27.9, 27.6, 26.1, 23.5, 22.8, 22.3, 18.4, 13.9; mass spectrum m/z (relative intensity) 408 (M^+, 100), 365 (25), 351 (30), 325 (87), 300 (40); exact mass calcd for $C_{28}H_{40}O$, 408.3028, found 408.3032. Anal. ($C_{28}H_{40}O_2$) C, H.

3,5-Dimethoxy-1-(1-heptenyl)benzene (14, mixture of *Z* and *E* isomers in 91:9 ratio respectively, according to ^{1}H NMR data). The synthesis was carried out as described for **5b** by using hexyltriphenylphosphonium bromide (12.9 g, 30.2 mmol) in dry THF (120 mL), potassium bis(trimethylsilyl)amide (5.9 g, 29.6 mmol), and a solution of **13** (1 g, 6.02 mmol) in dry THF (30 mL): yield 92% (1.30 g); colorless liquid; ^{1}H NMR (500 MHz, $CDCl_3$, *Z*-isomer) δ 6.43 (d, J = 2.2 Hz, 2H, ArH), 6.35 (t, J = 2.2 Hz, 1H, ArH), 6.33 (d, J = 11.5 Hz, 1H, 1′-H), 5.65 (dt, J = 11.5, J = 7.0 Hz, 1H, 2′-H), 3.97 (s, 6H, OMe), 2.32 (qd, J = 7.3 Hz, J = 1.7 Hz, 2H, 3′-CH_2), 1.46 (quintet, J = 7.3 Hz, 2H, 4′-CH_2), 1.40−1.21 (m, 4H, 5′-CH_2, 6′-CH_2), 0.88 (t, J = 7.1 Hz, 3H, 7′-CH_3); ^{1}H NMR (500 MHz, $CDCl_3$, E-isomer) δ 6.50 (d, 2H, J = 2.2 Hz, ArH), 6.21 (dt, J = 15.8 Hz, J = 6.8 Hz, 1H, 2′-H), the remaining protons are overlapping with those of the Z-isomer.

3,5-Dimethoxy-1-heptylbenzene (15). The synthesis was carried out as described for **6b** by using **14** (1.25 g, 5.34 mmol) and 10% Pd/C (0.19 g) in EtOAc (50 mL): yield 95% (1.20 g); colorless liquid; spectral and analytical data were reported previously.[26]

5-Heptylresorcinol (16). The synthesis was carried out as described for **7b** by using **15** (1.18 g, 5 mmol) and boron tribromide (11 mL, 11 mmol, 1 M solution in CH_2Cl_2) in anhydrous CH_2Cl_2 (40 mL): yield 91% (0.95 g); slightly brown solid; mp 53−54 °C (lit.[63] mp 55−56 °C); spectral and analytical data were reported previously.[26]

(−)-2-[3-3,4-*trans*-*p*-Menthadien-(1,8)-yl]-5-heptylresorcinol (17). The synthesis was carried out as described for **8b** by using **16** (930 mg, 4.47 mmol), (+)-*cis/trans*-*p*-mentha-2,8-dien-1-ol (746 mg, 4.9 mmol), and *p*-toluenesulfonic acid (76 mg, 0.45 mmol) in anhydrous benzene (45 mL): yield 32% (489 mg); colorless viscous oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.26 (br s, 1H, ArH), 6.17 (br s, 1H, ArH), 5.97 (br s, 1H, OH), 5.57 (br s, 1H, 2-H), 4.66 (s, 1H, >C=CH_2), 4.63 (br s, 1H, OH), 4.56 (s, 1H, >C=CH_2), 3.84 (m as br d, J = 8.7 Hz, 1H, 3-H), 2.44 (t, J = 7.6 Hz, 2H, 1′-H), 2.39 (td, J = 10.5 Hz, J = 3.2 Hz, 1H, 4-H), 2.28−2.18 (m, 1H), 2.14−2.06 (m, 1H), 1.86−1.73 (m, 5H, especially 1.79, s, 3H, 7-CH_3), 1.65 (s, 3H, 10-CH_3), 1.58−1.51 (m, 2H, 2′-CH_C), 1.34−1.23 (m, 8H, 3′-CH_2, 4′-CH_2, 5′-CH_2, 6′-CH_2), 0.87 (t, J = 7.1 Hz, 3H, 7′-CH_3).

(6a*R*-*trans*)-3-Heptyl-6a,7,10,10a-tetrahydro-6,6,9-trimethyl-6*H*-dibenzo[*b*,*d*]pyran-1-ol (1b). The synthesis was carried out as described for **9b** by using **17** (72 mg, 0.21 mmol) and boron trifluoride etherate (0.1 mL, 0.80 mmol) in anhydrous CH_2Cl_2 (5 mL): yield 53% (38 mg); colorless viscous oil; spectral and analytical data were reported previously.[26]

Radioligand Binding Assays. Forebrain synaptosomal membranes were prepared from frozen rat brains by the method described by Dodd et al.[64] and were used to assess the affinities of the novel analogs for the CB1 binding sites, while affinities for the CB2 sites were measured using a membrane preparation from frozen mouse spleen using a similar procedure.[47] The displacement of specifically tritiated CP-55,940 from these membranes was used to determine the IC_{50} values for the test compounds. The assay was conducted in a 96-well microfilter plate. The samples were filtered using a Packard Filtermate Harvester and Whatman GF/B unifilter-96 plates, and 0.5% BSA was incorporated into the wash buffer. Radioactivity was detected using MicroScint 20 scintillation cocktail added to the dried filter plates and was counted using a Packard Instruments Top Count. Data were collected from three independent experiments between 100% and 0% specific binding for [^{3}H]CP-55,940, determined using 0 and 100 nM CP-55,940. The normalized data from three independent experiments were combined and analyzed using a four-parameter logistic equation to yield IC_{50} values that were converted to K_i values using the assumptions of Cheng and Prussoff.[65]

Molecular Modeling. Computational calculations were performed on the cannabinoid analogs using the Biosym InsightII/Discover molecular modeling software package[66] on a SGI Fuel workstation. The Biosym integrated CVFF force field was employed in the calculation. Each cannabinoid analog was first constructed with bond angles and bond distances supplied by the molecule builder module and then underwent constrained molecular dynamics performed by heating it to 1000 K (or 1500K for analogs **9d** and **12d**) and recording 100 atomic coordinate trajectories every 10 000 iterations (1 fs per iteration). A restraint file was incorporated in each dynamics run in order to prevent possible *cis*/*trans* isomerizations at the B/C ring junction and/or C2′−C3′ double bond. Next, each trajectory was subjected to simulated annealing followed by energy minimization with the steepest descent method for 100 iterations. This in turn was followed by the conjugate gradient method until the maximum derivative was less than 0.001 kcal/mol. The resulting structures were then superimposed by minimum rmsd alignment of the analogs.

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Supporting Information Available: Experimental details and spectroscopic data, elemental analysis results, and whole cluster simulations of the side chains of **9d** and **12d**. This material is available free of charge via the Internet at http://pubs.acs.org

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