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Novel 1′,1′-Chain Substituted Hexahydrocannabinols: 9β-Hydroxy-3-(1-hexyl-cyclobut-1-yl)-hexahydrocannabinol (AM2389) a Highly Potent Cannabinoid Receptor 1 (CB1) Agonist

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In pursuit of a more detailed understanding of the structural requirements for the key side chain cannabinoid pharmacophore, we have extended our SAR to cover a variety of conformationally modified side chains within the 9-keto and 9-hydroxyl tricyclic structures. Of the compounds described here, those with a seven-atom long side chain substituted with a cyclopentyl ring at C1′ position have very high affinities for both CB1 and CB2 (0.97 nM < K_i < 5.25 nM), with no preference for either of the two receptors. However, presence of the smaller cyclobutyl group at the C1′ position leads to an optimal affinity and selectivity interaction with CB1. Thus, two of the C1′-cyclobutyl analogues, namely, (6a*R*,10a*R*)-3-(1-hexyl-cyclobut-1-yl)-6,6a,7,8,10,10a-hexahydro-1-hydroxy-6,6-dimethyl-9*H*-dibenzo-[*b*,*d*]pyran-9-one and (6a*R*,9*R*,10a*R*)-3-(1-hexyl-cyclobut-1-yl)-6a,7,8,9,10,10a-hexahydro-6,6-dimethyl-6*H*-dibenzo[*b*,*d*]pyran-1,9 diol (**7e-β**, AM2389), exhibited remarkably high affinities (0.84 and 0.16 nM, respectively) and significant selectivities (16- and 26-fold, respectively) for CB1. Compound **7e-β** was found to exhibit exceptionally high in vitro and in vivo potency with a relatively long duration of action.

Introduction

The recognition of two distinct $G_{i/o}$-protein-coupled cannabinoid receptors (CB1[a] and CB2)[1−11] and the discovery of two endogenous ligands, arachidonoylethanolamine (anandamide)[12] and 2-arachidonoylglycerol,[13,14] has led to efforts to define the structural requirements for receptor specificity. A review of structure−activity relationship (SAR) studies[15−19] recognizes two pharmacophores within the classical (−)-Δ^8-tetrahydrocannabinol ((−)-Δ^8-THC, **1a**, Figure 1) template: a phenolic hydroxyl (PH), and a lipophilic side chain (SC). Of these, the aliphatic side chain was shown to play a pivotal role in determining cannabinergic potency. Optimal activity is obtained with a seven carbon length substituted with 1′,1′-dimethyl groups (**1b**) as was first demonstrated by Adams.[20] It has also been shown that in hexahydrocannabinols (HHC, Figure 1) where the C-ring is fully saturated, presence of a keto[21] or a hydroxyl[22] group at the C9 position (e.g., nabilone, **1d**) can have significant effects on the compound's ability to interact with CB receptors.[15−17] On the basis of the relative configuration at the C9 position of the 9-hydroxyhexahydrocannabinols (**1e**, **1f**), we can obtain 9β- or 9α-OH isomers. Interestingly, a study involving the axial (9α) and the equatorial (9β) alcohols **1f** and **1e**, respectively, indicates that only the 9β-hydroxyl isomer (**1e**) was an analgesic in mice.[22]

In earlier work, we have focused on novel (−)-Δ^8-tetrahydrocannabinol analogues (**1c**) that bear cyclic moieties at the C1′-position of the side chain.[23−28] This careful SAR led to (−)-Δ^8-THC analogues with high affinities for both CB1 and CB2 cannabinoid receptors and provided a good starting point for the development of more subtype selective second generation ligands.

In the current study, we chose to investigate the effect of modifying the C3 side chain in HHC's with regard to affinity and selectivity for the CB1 and CB2 cannabinoid receptors. Toward this end, a number of novel side chain hexahydrocannabinol analogues represented by the general structure **1g** were synthesized. Our design retains the keto or hydroxyl groups at C9 and replaces the 1′,1′-*gem*-dimethyl group with the larger and sterically more confined cyclobutyl and cyclopentyl groups as well as with the less hydrophobic dithiolane five-membered ring. As with earlier work on the THC template, the design of our HHC analogues has included a seven-atom-long side chain and methyl-, bromo-, or cyano-substitution at the terminal carbon (analogues **6b**, **6c**, **6e**, **15b**, **16**, **22**, **7c-β**, **7e-β**, **23**, and **24**, Table 1). 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′-cyclopentyl analogues with six- and eight-atom-long side chains (compounds **15a** and **15c**, Table 1), as well as those incorporating the respective C2′-C3′-*Z*-heptenyl chains (compounds **6a** and **6d**, Table 1).

All synthesized analogues were tested for their respective affinities for CB1 and CB2. Hexahydrocannabinols carrying

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[a] Abbreviations: CB1, cannabinoid receptor 1; CB2, cannabinoid receptor 2; SAR, structure−activity relationship; (−)-Δ^8-THC, (−)-Δ^8-tetrahydrocannabinol; PH, phenolic hydroxyl; SC, side chain; HHC, hexahydrocannabinol; *p*-TSA, *p*-toluenesulfonic acid; K-selectride, potassium tri-*sec*-butyl borohydride; TMSOTf, trimethylsilyl triflate; DMSO, dimethylsulfoxide; HEK, human embryonic kidney; NMR, nuclear magnetic resonance; DEPT, distortionless enhancement by polarization transfer; COSY, correlation spectroscopy; HSQC, heteronuclear single quantum correlation; HMBC, heteronuclear multiple bond correlation; NOESY, nuclear Overhauser effect spectroscopy.

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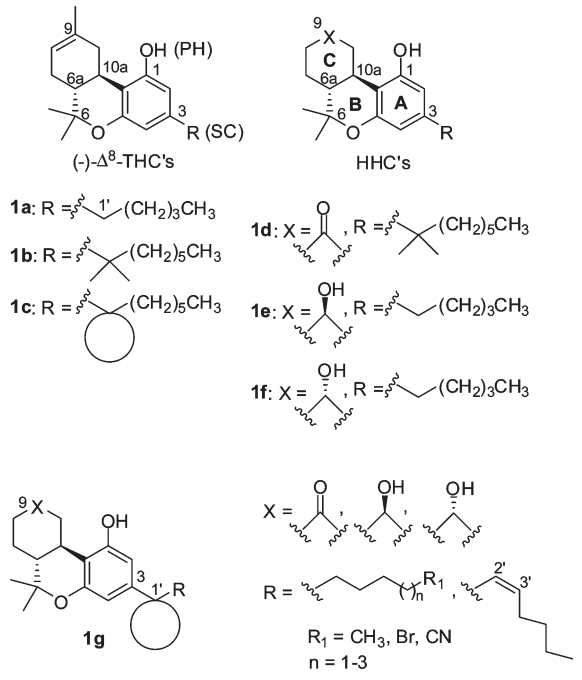


Figure 1

seven-atom-long side chains substituted with cyclobutyl and cyclopentyl groups at the C1′-position exhibited the highest affinities for CB1 and CB2. More interestingly, within this series the cyclobutylhexenyl (**6d**) and the cyclobutylhexyl (**6e** and **7e-*β***) analogues (Table 1) were found to have remarkably high affinities and significant selectivities (11- to 26-fold) for CB1. The analogue with the highest CB1 binding affinity and selectivity (**7e-*β***, AM2389[29]) was tested in rats for its ability to induce hypothermia and analgesia. The compound was found to exhibit exceptionally high in vivo potency with a relatively long duration of action. In addition, functional characterization found **7e-*β*** to be a potent CB1 agonist with an $EC_{50} = 1.5 \pm 0.3$ nM.

Chemistry

Resorcinols **4a**−**4e**, (Scheme 1) bearing C1′-cyclopentyl, C1′-dithiolanyl, and C1′-cyclobutyl-ring substituents were synthesized in four to eight steps from 3,5-dimethoxybenzaldehyde (**2**) by following our previously reported procedures.[23−27,30] We have recently described the efficient synthesis of the mixture of chiral terpene acetates **3**, which was used in the synthesis of (−)-Δ^9-tetrahydrocannabinol and (−)-Δ^9-tetrahydrocannabivarin metabolites in their native 6a*R*,10a*R* absolute configuration.[31] This mixture served as the starting point for the synthesis of the bicyclic intermediates **5a**−**5e**. Thus, coupling of resorcinol derivatives **4a**−**4e** with **3** in the presence of *p*-toluenesulfonic acid (*p*-TSA), under our optimized reaction conditions,[31] led to norpinanones **5a**−**5e** (24−58%). The structure of **5b** was established using 1D NMR spectra as well as ^{13}C DEPT spectrum, COSY, HSQC, HMBC, and NOESY correlations (available under Supporting Information). Dibenzo[*b*,*d*]pyran ring closure proceeded smoothly with catalytic trimethylsilyl triflate[31] to give ketones **6a**−**6e** in 51−67% yield. Sodium borohydride reduction of ketones **6c** and **6e** at −40 °C gave the corresponding equatorial hydroxyl compounds **7c-*β*** and **7e-*β*** along with traces (3−4% by ^{1}H NMR) of the respective axial isomers **7c-α** and **7e-α**. This was followed by flash column chromatography purification to give pure equatorial hydroxyl analogues **7c-*β*** and **7e-*β*** in 85−95% yield. The stereochemistry of the hydroxyl groups of **7c-*β***/**7c-α** and **7e-*β***/**7e-α** isomeric pairs was assigned on the basis of ^{1}H NMR (500 MHz) spectral data. Thus, in compounds **7c-*β*** and **7e-*β***, the peak half-width for the C9 protons was found to be 21−22 Hz while in compounds **7c-α** and **7e-α** was 10.5 Hz (see Experimental Section). This correlates well with an axial C9 proton in the former two compounds and an equatorial C9 proton in the latter two.

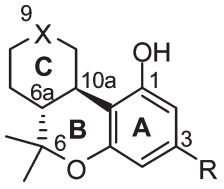
Synthesis of the C1′-cyclopentyl analogues **15a**−**15c** and **16** was accomplished by a reaction sequence shown in Scheme 2. Commercially available phenoxyalkyl bromides **8a**, **8b**, and **8c** were reacted with triphenylphosphine in refluxing benzene[32] to give the respective (phenoxyalkyl)triphenylphosphonium bromides **9a**, **9b**, and **9c** in very good yields (80−85%). Treatment of **9a**−**9c** with potassium bis(trimethylsilyl)amide and coupling of the generated phosphoranes with 1-(3,5-dimethoxyphenyl)cyclopentanecarboxaldehyde[24,25,27,30] (**10**) at 0 °C produced intermediate alkenes **11a**−**11c** (91−95%), bearing five, six, and seven carbon atom side chains, respectively. On the basis of ^{1}H NMR analysis, these Wittig olefination reactions afforded exclusively the *Z* olefins with $J_{2'H\text{-}3'H} = 11.3$ Hz. Catalytic hydrogenation of **11a**−**11c** led to the respective resorcinol dimethyl ethers **12a**−**12c** in 94−96% yields. Exposure of **12a**−**12c** to boron tribromide in methylene chloride cleaved all three ether groups and introduced the C5′, C6′, and C7′ bromo groups for **13a**, **13b**, and **13c**, respectively.[32] Coupling with terpene acetates **3** in the presence of *p*-TSA (50−54% yield), and exposure of the resulting norpinanones **14a**−**14c** to trimethylsilyl triflate gave 9-keto-hexahydrocannabinols **15a**−**15c** (73−75% yield). Treatment of bromide **15a** with sodium cyanide in dimethyl sulfoxide produced the respective side chain cyano-substituted analogue **16** in 64% yield.

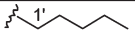
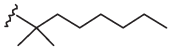
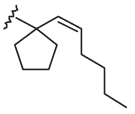
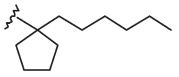
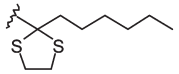
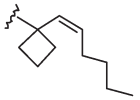
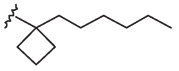
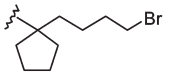
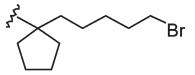
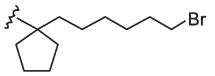
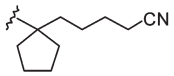
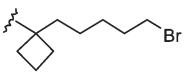
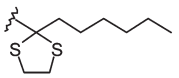
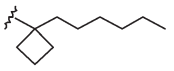
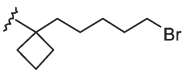
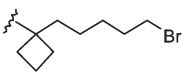
The C1′-cyclobutyl analogues **22**, **23**, and **24** were synthesized in a similar fashion from 1-(3,5-dimethoxyphenyl)cyclobutanecarboxaldehyde (**17**, Scheme 3), which was in turn obtained from commercially available **2** in five steps by a methodology developed in our laboratories.[24,25,27,30] Thus, combination of **17** and the ylide derived from (4-phenoxybutyl)-triphenylphosphonium bromide (**9b**) and potassium bis-(trimethylsilyl)amide, resulted in the exclusive formation of the *Z* isomer **18** in 91% yield ($J_{2'H\text{-}3'H} = 11.1$ Hz). Catalytic hydrogenation of **18** led to resorcinol dimethyl ether **19**, which was treated with boron tribromide to give the corresponding resorcinol **20** in quantitative yield. Condensation of **20** with terpene acetates **3** afforded norpinanone **21** (46% yield) which upon treatment with catalytic trimethylsilyl triflate gave the hexahydrocannabinol **22** in 70% isolated yield. Sodium borohydride reduction of ketone **22** in methanol (−40 °C) gave a mixture of isomeric alcohols **23** and **24** in a 97:3 ratio, respectively (by ^{1}H NMR). Pure equatorial alcohol **23** was obtained by chromatographic purification in 85% yield. Reduction of **22** with potassium tri-*sec*-butyl borohydride[33] (K-selectride) at −78 °C was very selective and gave the axial alcohol **24** exclusively (70% yield). The *n*-pentyl-HHC **1h**[31] (Table 1), which carry the side chain of the natural cannabinoid (−)-Δ^9-THC, was synthesized similarly by coupling commercially available olivetol with diacetates **3**.

Results and Discussion

Receptor Binding Studies. The abilities of **1h**, **6a**−**6e**, **15a**−**15c**, **16**, **22**, **7c-*β***, **7e-*β***, **23**, and **24** to displace radiolabeled CP-55,940 from purified rat forebrain synaptosomes

Table 1. Affinities (K_i) of Hexahydrocannabinol Analogues for rCB1 and mCB2 Cannabinoid Receptors (95% Confidence Limits)

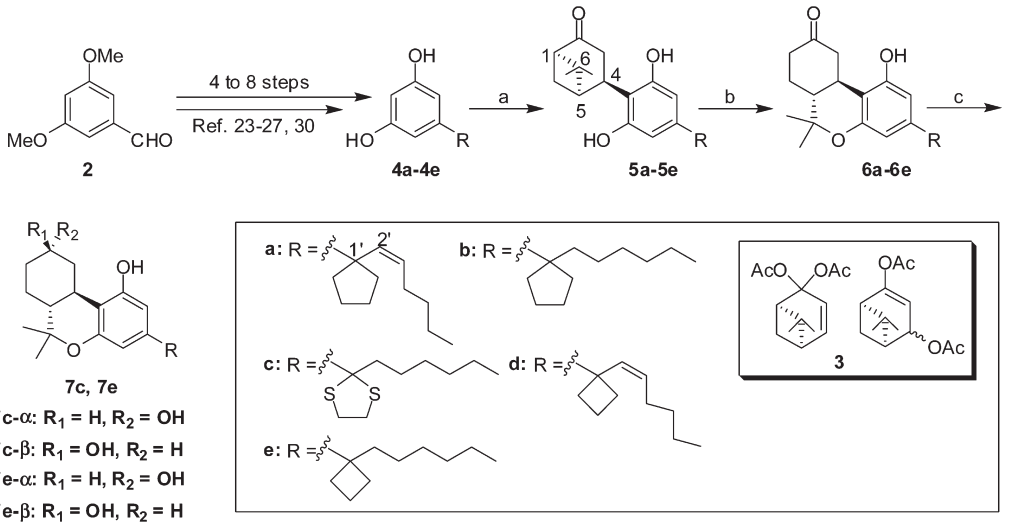


compd	X	R	rCB1 (Ki, nM)[a]	mCB2 (Ki, nM)[a]	mCB2/rCB1
1h			333	265	0.8
1b			2.2[b]	1.8[b]	0.8
6a			1.23 ± 0.22	5.25 ± 1.02	4.3
6b			1.76 ± 0.41	0.97 ± 0.29	0.6
6c			6.57 ± 1.55	42.3 ± 11.0	6.4
6d			1.13 ± 0.28	12.0 ± 3.5	10.6
6e			0.84 ± 0.18	13.7 ± 3.2	16.3
15a			13.1 ± 3.5	13.9 ± 3.8	1.1
15b			1.03 ± 0.21	2.59 ± 0.85	2.5
15c			4.96 ± 1.24	1.60 ± 0.38	0.3
16			3.14 ± 0.51	2.78 ± 0.67	0.9
22			2.33 ± 0.55	7.56 ± 1.79	3.2
7c-β			4.51 ± 0.72	13.9 ± 3.4	3.1
7e-β			0.16 ± 0.05	4.21 ± 0.93	26.3
23			1.37 ± 0.35	2.76 ± 0.63	2
24			1.50 ± 0.33	1.67 ± 0.43	1.1

[a] Affinities for rCB1 and mCB2 were determined using rat brain (CB1) or mouse spleen (CB2) membranes and [^{3}H]CP-55,940 as the radioligand following previously described procedures.[25,27,37] Data were analyzed using nonlinear regression analysis. 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.[15]

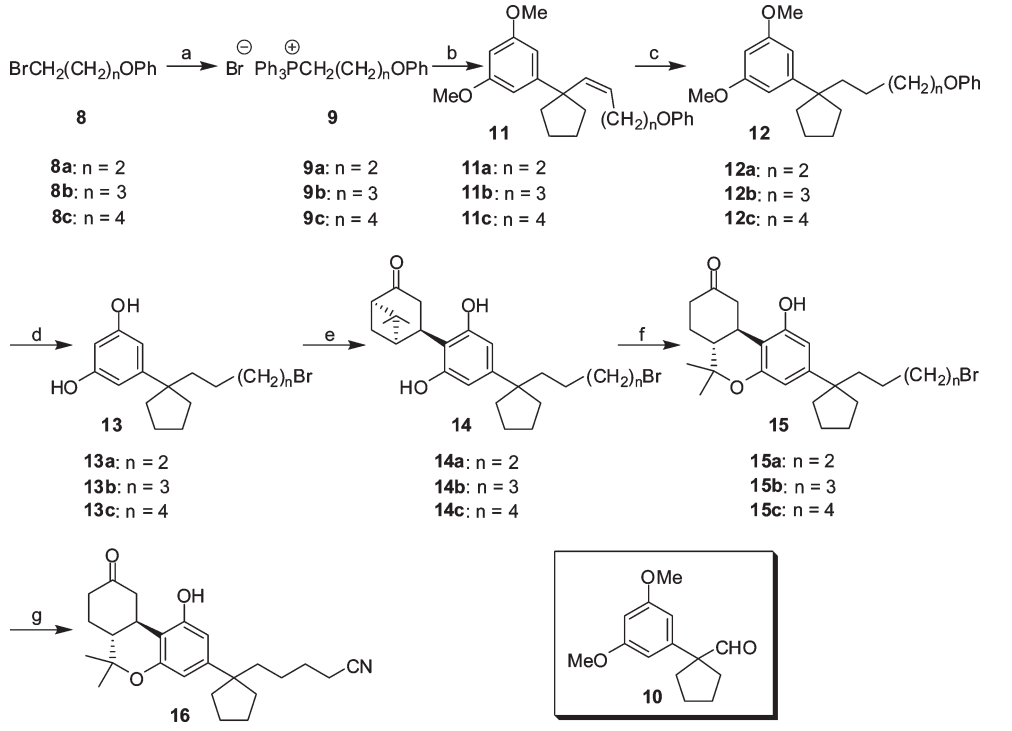
and mouse spleen synaptosomes were determined, as described in the Experimental Section. K_i values calculated from the respective displacement curves are listed in Table 1 and reflect the affinities of these hexahydrocannabinol analogues for the rat CB1 (rCB1) and mouse CB2 (mCB2) receptors.

Scheme 1[a]



[a] Reagents and conditions: (a) **3**, *p*-TSA, $CHCl_3$, 0 °C to room temperature, 3 days, 24−58%; (b) TMSOTf, CH_2Cl_2/CH_3NO_2 (3:1), 0 °C to room temperature, 3 h, 51−67%; (c) $NaBH_4$, MeOH, −40 °C, 1.5 h, 85−95%.

Scheme 2[a]

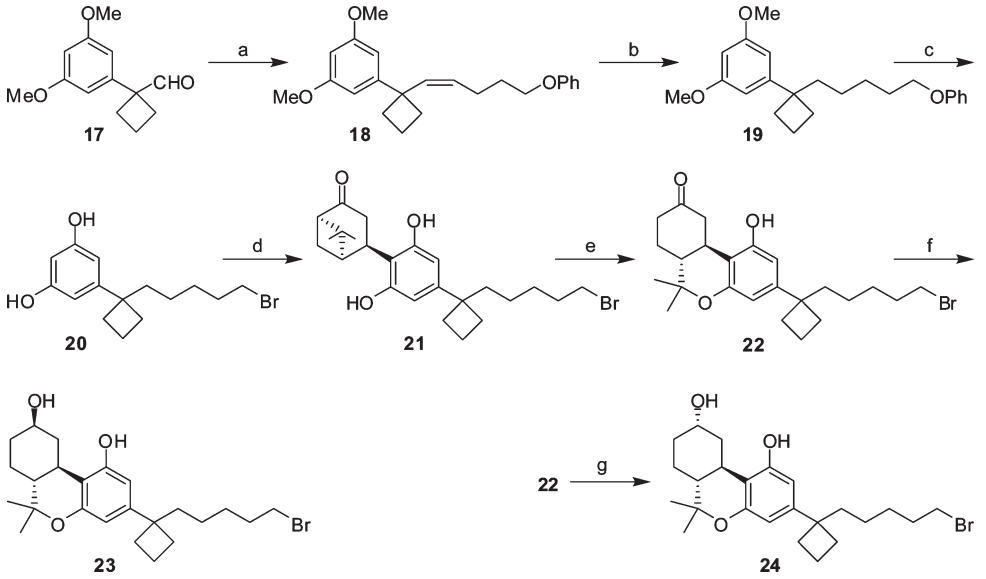


[a] Reagents and conditions: (a) Ph_3P, C_6H_6, reflux, 2 days, 80−85%; (b) $(Me_3Si)_2N^-K^+$, THF, 0 °C, 10 min, then 1-(3,5-dimethoxyphenyl)cyclopentanecarboxaldehyde (**10**), 20 min, 91−95%; (c) H_2, Pd/C, AcOEt, room temperature, overnight, 94−96%; (d) BBr_3, CH_2Cl_2, −78 °C to room temperature, 12 h, 89−93%; (e) **3**, *p*-TSA, $CHCl_3$, 0 °C to room temperature, 3 days, 50−54%; (f) TMSOTf, CH_2Cl_2/CH_3NO_2 (3:1), 0 °C to room temperature, 3 h, 73−75%; (g) NaCN, DMSO, room temperature, 20 h, 64%.

The compounds included in this study are 9-keto- and 9-hydroxyl-HHC analogues in which the six- to eight-atom long side chain pharmacophore incorporates cyclic substituents at the C1′ position. As can be observed in Table 1, the range of K_i values of the C1′-ring substituted analogues, included in this study, spans over 2 orders of magnitude. This indicates that the size and the nature of the C1′-ring substituent along with the length of the side chain can have a profound effect on the affinities of HHC analogues for both the CB1 and CB2 receptors.

A comparison of the binding data of *n*-pentyl HHC **1h** and its C1′-dimethylheptyl analogue **1b** suggests that presence of the two C1′-methyl groups enhances the ligand's affinity for both the CB1 and CB2 receptors. This interaction is optimized when the geminal dimethyl substitution is modified into a larger and sterically more confined five-membered carbocyclic ring as seen in the cyclopentane analogue **6b**. However, the affinity is reduced when the C1′-cyclopentyl group in **6b** is substituted with the bulkier dithiolane ring in analogue **6c**. This analogue now has a 4-fold lower affinity

Scheme 3[a]



[a] Reagents and conditions: (a) $PhO(CH_2)_4P^+PPh_3\ Br^-$, $(Me_3Si)_2N^-K^+$, THF, 0 °C, 10 min, then addition of **17**, 20 min, 91%; (b) H_2, Pd/C, EtOH, room temperature, 50 psi, 10 h, quantitative; (c) BBr_3, CH_2Cl_2, −78 °C to room temperature, 12 h, quantitative; (d) **3**, *p*-TSA, $CHCl_3$, 0 °C to room temperature, 3 days, 46%; (e) TMSOTf, CH_2Cl_2/CH_3NO_2 (3:1), 0 °C to room temperature, 3 h, 70%; (f) $NaBH_4$, MeOH, −40 °C, 1.5 h, 85%; (g) K-Selectride, THF, −78 °C, 2 h, 70%.

for CB1 and an even lower affinity (44-fold) for CB2. Interestingly, this reduction in affinity is more accentuated in CB2. Examination of the K_i values of the C1′-cyclopentyl analogues **6b** and **6a** indicates that while introduction of a C2′-C3′ *Z*-double bond can be tolerated at the CB1 receptor, it seems to somewhat reduce the side chain's optimal interaction with CB2. Thus, analogue **6a** has a 5-fold lower affinity for CB2 when compared to **6b**.

As seen in analogue **16**, replacement of the two terminal carbon atoms of the heptyl side chain (**6b**) with a cyano group is well tolerated in both the CB1 and CB2 receptors. Also, substitution of the terminal side chain methyl group in **6b** with a bromine atom (analogue **15b**) maintains affinity for both receptors. For ω-bromo side chains (analogues **15a**, **15b**, **15c**), extension of the seven-atom chain length to eight (**15c**) retains practically all affinity for CB1 and CB2. However, the shorter, six-atom long side chain leads to an analogue (**15a**) with a significant reduction in affinity for both the CB1 and CB2 (13-fold and 5-fold, respectively).

In summary, within the 9-keto HHC's the C1′-cyclopentyl substituted analogues appear to exhibit no significant preference for either of the two receptors. Conversely, reduction of the size of the C1′-ring substituent to a four-membered cyclobutane ring is accompanied by a preference for CB1. This is seen in analogue **22** in which the end carbon of the side chain carries a bromine atom, and more so in **6d**, where a C2′-C3′ *Z*-double bond is added. Significantly, the 11-fold CB1 selectivity for the heptenyl side chain analogue **6d** is further enhanced in its heptyl counterpart **6e** where the CB1 selectivity is now 16-fold.

A comparison of the binding affinities of the C9 equatorial hydroxyl analogues **7c-*β***, **7e-*β***, and **23** with their 9-keto counterparts **6c**, **6e**, and **22**, respectively, indicates that conversion of the 9-keto group to 9β-hydroxyl group enhances the ligand's affinity for both the CB1 and CB2 receptors. The most successful analogue from this modification is the C1′-cyclobutyl derivative **7e-*β*** with a K_i of 0.16 nM for CB1. Importantly, **7e-*β*** exhibits a 26-fold selectivity for CB1 over CB2. Finally, a comparison of the equatorial and the axial alcohols **23** and **24**, respectively, shows that the relative stereochemistry of the hydroxyl group at C9 does not affect the ligand's affinity and selectivity for CB1 and CB2. This is an apparent incongruence in previously reported in vivo data where the 9α-OH hexahydrocannabinol exhibitted reduced potency compared to its 9β-OH isomer.[22]

In conclusion, 9-keto-hexahydrocannabinol analogues bearing seven-atom long side chains substituted with a cyclopentyl ring at C1′ position have very high affinities for both CB1 and CB2 (0.97 nM < K_i < 5.25 nM), with no preference for either of the two receptors. However, presence of the smaller cyclobutyl group at C1′ position of HHC's leads to an optimal affinity and selectivity interaction with CB1. The above conclusion is strongly reinforced by our results with the C1′-cyclobutyl analogues **6e** and **7e-*β***. These compounds with K_i values of 0.84 and 0.16 nM for CB1, respectively, are cannabinergic probes with one of the highest CB1 binding affinities reported to date. In addition, compounds **6e** and **7e-*β*** shown a 16- and a 26-fold respectively selectivity for CB1 over CB2.

It is especially worthy of note that the side chain SAR trends observed in this study parallel those of (−)-Δ^8-THC analogues,[25,27] suggesting that THC's and HHC's share key binding motifs and support the hypothesis for a subsite[23−27] within CB1 and CB2 binding domain at the level of the benzylic side chain carbon in the tetrahydrocannabinol and hexahydrocannabinol series.

The rat,[3] mouse,[5,9] and human CB1 (hCB1) receptors[4] have 97−99% sequence identity across species and are not expected to exhibit variations in their K_i values. However, mouse CB2[10,11] (mCB2) exhibits only 82% sequence identity with the human clone[2] (hCB2). This divergent nature of mCB2 and hCB2 receptors could possibly result in species-based differences in affinity.[34,35] For this reason, representative HHC analogues were assayed using membranes from HEK293 cells expressing hCB2, and the results are listed in Table 2. We observe that the tested compounds exhibit

Table 2. Affinities (K_i) of Hexahydrocannabinol Analogues for hCB2 Cannabinoid Receptors (95% Confidence Limits)

compd	hCB2 (K_i, nM)[a]
6a	7.02 ± 1.62
6b	3.34 ± 1.31
6c	32.6 ± 7.1
6d	15.1 ± 4.3
6e	11.9 ± 2.4
15b	1.32 ± 0.27
15c	3.02 ± 0.73
22	5.88 ± 1.73
7e-β	5.13 ± 1.27
23	1.62 ± 0.45
24	1.63 ± 0.37

[a] Affinities for hCB2 were determined using membranes from HEK293 cells expressing human CB2 and [^{3}H]CP-55,940 as the radioligand following previously described procedures.[33] Data were analyzed using nonlinear regression analysis. K_i values were obtained from three independent experiments run in duplicate and are expressed as the mean of the three values.

similar binding affinities for both the mouse and the human CB2.

Molecular Modeling of 7e-β. A conformational search of **7e-β** in implicit water was carried out as described in the Experimental section and found the global energy minimum to be as shown in Figure 2. While the global minimum conformer is not necessarily identical to that found in the receptor binding site, it is likely that the hexyl moiety is approximately perpendicular to the tricyclic ring system. In this conformation the cyclobutane ring can engage in optimal interactions at the putative receptor-binding subsite.

Functional Characterization of 7e-β. The functional potency of **7e-β** for the CB1 receptor was obtained by measuring the decrease in foskolin-stimulated cAMP, as described in the Experimental Section, and shown to be a full agonist with EC_{50} = 1.5 ± 0.3 nM.

In Vivo Behavioral Characterization of 7e-β. We have explored the in vivo potency of our more CB1 selective high affinity analogue **7e-β** in the hypothermia and analgesia tests (detailed procedures are given under the Experimental Section).

Body temperature was measured in isolated rats over a 6 h period following drug injection. **7e-β** decreased core body temperature in a dose-dependent manner, with a dose of 0.1 mg/kg reducing body temperature up to 4.2 ± 0.5 °C from an average baseline of 38.48 ± 0.06 °C. At this dose, the onset of drug effect occurred within 60−90 min after injection, although peak effects were not obtained until 300 min after injection. Antinociception was measured using a tail-flick procedure over a 6 h period following drug injection. Prior to drug administration, the average baseline tail-flick latency was 2.1 ± 0.1 s. Compound **7e-β** increased tail-flick latency over the same dose range as in the hypothermia measurements and with a similar time course (Figure 3). Doses of 0.01−0.3 mg/kg **7e-β** had significant antinociceptive effects, with a mean (±95%CL) ED_{50} value of 0.026 mg/kg (0.020, 0.034). The onset of the antinociceptive effects occurred between 60 and 120 min after injection and these effects generally increased over the 6 h test period (Figure 4). In comparison, the mean (±95%CL) ED_{50} value of morphine was 2.8 mg/kg (2.0, 3.8) with peak effects occurring at 30−120 min after injection and decreasing by 3 h after injection.

The antinociceptive effects of **7e-β** were subsequently redetermined in a different group of animals; in these animals

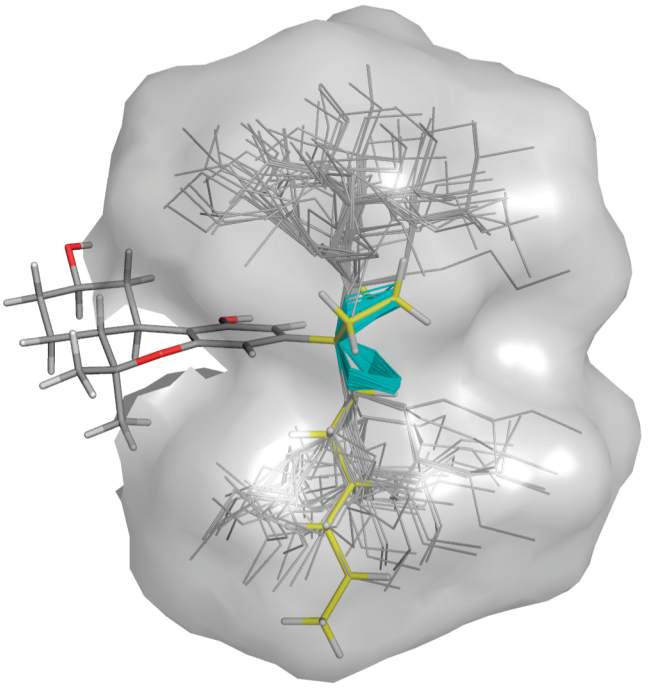


Figure 2. Accessible conformational space for the C1′-cyclobutylheptyl substituent of **7e-β** using an energy window of 5 kcal mol^{-1}. Heavy atoms are shown in line representation with the cyclobutane ring highlighted in cyan. The minimum energy conformer of **7e-β** is shown in stick representation with the cyclobutylheptyl moiety highlighted in yellow.

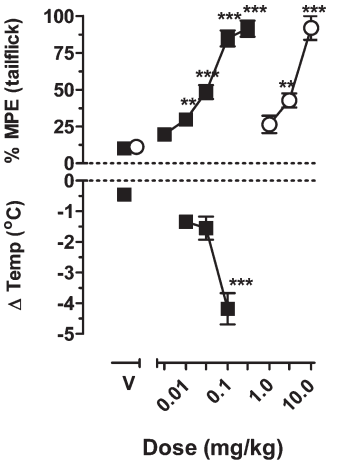


Figure 3. Effects of **7e-β** (■) and morphine (○) on antinociception (top graph) and effects of **7e-β** on body temperature (bottom graph). Symbols represent the group mean ± sem (n = 5−6 rats). Abscissa, dose in mg/kg; top ordinate, percentage of the maximum possible antinociceptive effect; bottom ordinate, change in body temperature. Asterisks indicate effects that are significantly different from vehicle, $^{**}p < 0.01$, $^{***}p < 0.001$.

0.1 mg/kg **7e-β** alone produced 100% of the maximum possible effect, and this was reduced to 85.4 ± 5.8% or 48.0 ± 10.9% by a 30 min pretreatment with 1.0 or 3.0 mg/kg rimonabant (SR141716A), respectively.

Our in vivo experiments show that **7e-β** has a slow onset and long duration of action and has potent activity in assays of hypothermia and antinociception. This compound produced full antinociceptive responses in a tail-flick assay. These effects were suppressed by the CB1-selective antagonist rimonabant, thus supporting a CB1-based mechanism

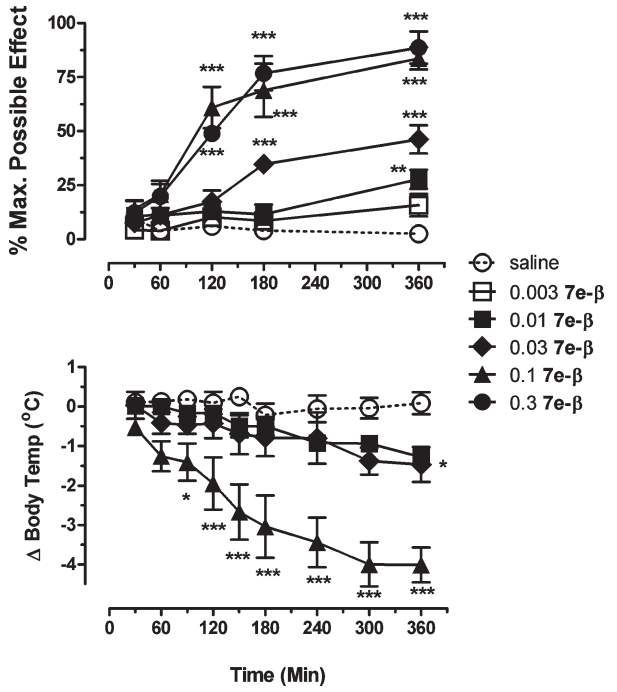


Figure 4. Effects of **7e-*β*** at different times after injection on antinociception (top graph) and body temperature (bottom graph). Abscissa, time (in minutes) after injection; top ordinate, percentage of the maximum possible antinociceptive effect; bottom ordinate, change in body temperature. Asterisks indicate effects that are significantly different from vehicle, $*p < 0.05$, $**p < 0.01$, $***p < 0.001$.

for the analgesic action of **7e-*β***. Although similar antinociceptive effects were obtained with morphine, these were approximately 100-fold lower than **7e-*β***. Furthermore, the antinociceptive effects of **7e-*β*** were longer lasting than were effective doses of morphine. The hypothermic effects of **7e-*β*** were also profound, and peak hypothermic and antinociceptive effects of **7e-*β*** occurred over the same range of doses and over similar time courses. However, small yet significant antinociceptive effects of **7e-*β*** occurred at low doses that did not significantly lower body temperature.

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 micromelting point apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer Spectrum One FT-IR spectrometer. NMR spectra were recorded in $CDCl_3$, unless otherwise stated, on a Varian Mercury-300 (^{1}H at 300 MHz, ^{13}C at 75 MHz) or on a Bruker Ultra Shield 400 WB plus (^{1}H at 400 MHz, ^{13}C at 100 MHz) or on a Bruker DMX-500 (^{1}H at 500 MHz, ^{13}C at 125 MHz) or on a Bruker Ultra Shield 700 WB plus (^{1}H at 700 MHz, ^{13}C at 175 MHz) spectrometers, 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), m (multiplet), and coupling constants (J) are reported in hertz (Hz). Low and high-resolution mass spectra were performed in School of Chemical Sciences, University of Illinois at Urbana—Champaign. Mass spectral data are reported in the form of m/z (intensity relative to base = 100). Elemental analyses were obtained in Baron Consulting Co, Milford, CT, and were within ±0.4% of the theoretical values (see Supporting Information). Purities of the tested compounds were determined by elemental analysis and were >95%.

(4*R*)-4-{4-[1-(1,2-*cis*-Hexen-1-yl)-cyclopentyl]-2,6-dihydroxy-phenyl}-6,6-dimethyl-2-norpinanone (5a). To a degassed solution of **4a**[27] (1.25 g, 4.81 mmol) and diacetates **3**[31] (2.14 g, ca. 75% pure by ^{1}H NMR, 8.99 mmol) in $CHCl_3$ (48 mL) at 0 °C, under an argon atmosphere, was added *p*-toluenesulfonic acid monohydrate (1.28 g, 6.73 mmol). The mixture was warmed to room temperature and stirred for 3 days to ensure complete formation of the product. The reaction mixture was diluted with diethyl ether and washed sequentially with water, saturated aqueous $NaHCO_3$, and brine. The organic phase was dried over $MgSO_4$, and the solvent removed under reduced pressure. The residue was chromatographed on silica gel (43% diethyl ether in hexane), and fractions containing almost pure product (TLC) were combined and evaporated. Further purification by recrystallization from $CHCl_3$ and hexane gave **5a** as a white crystalline solid (1.01 g, 53% yield); mp 171−173 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.31 (s, 2H, ArH), 5.63 (dt, J = 11.3 Hz, J = 1.5 Hz, 1H, 2′-H), 5.27 (dt, J = 11.3 Hz, J = 7.5 Hz, 1H, 3′-H), 4.92 (br s, 2H, OH), 3.94 (t, J = 8.2 Hz, 1H, 4-H), 3.49 (dd, J = 18.8 Hz, J = 7.8 Hz, 1H, 3α-H), 2.60 (dd, J = 18.9 Hz, J = 8.7 Hz, 1H, 3β-H), 2.58 (t, J = 5.1 Hz, 1H, 1-H), 2.49 (m, 1H, 7α-H), 2.46 (d, J = 10.5 Hz, 1H, 7β-H), 2.28 (t, J = 5.2 Hz, 1H, 5-H), 1.95−1.85 (m, 4H of the cyclopentane ring), 1.76−1.65 (m, 6H, 4H of the cyclopentane ring, 4′-H), 1.36 (s, 3H, 6-Me), 1.11−1.07 (m, 4H, 5′-H, 6′-H), 0.99 (s, 3H, 6-Me), 0.75 (t, J = 6.7 Hz, 3H, 7′-H). ^{13}C NMR ($CDCl_3$) δ 216.0 (C-2), 153.5 (ArC-2, ArC-6), 148.1 (ArC-4), 137.2 (>C=C<), 131.0 (>C=C<), 112.3 (ArC-1), 106.4 (ArC-3, ArC-5), 56.8, 50.5, 45.8, 41.1, 39.7, 36.8, 30.3, 28.4, 27.2, 25.1, 23.3, 22.5, 21.2, 21.0, 12.8; mass spectrum m/z (relative intensity) 396 (M^+, 73), 381 (10), 379 (14), 353 (29), 313 (100), 273 (21), 229 (20), 203 (27), 175 (24), 109 (16), 83 (34). Exact mass calculated for $C_{26}H_{36}O_3$, 396.2664; found, 396.2667. Anal. ($C_{26}H_{36}O_3$) C, H.

(4*R*)-4-[4-(1-Hexyl-cyclopentyl)-2,6-dihydroxy-phenyl]-6,6-dimethyl-2-norpinanone (5b). The synthesis was carried out as described for **5a** starting from **4b**[25] (1.9 g, 7.25 mmol), diacetates **3**[31] (4.31 g, ca. 75% pure by ^{1}H NMR, 13.57 mmol), and *p*-toluenesulfonic acid monohydrate (1.93 g, 10.15 mmol) in $CHCl_3$ (73 mL) and gave 1.68 g (58% yield) of **5b** as a white crystalline solid; mp 187−188 °C (from $CHCl_3$-hexane). IR (neat) 3330, 3089, 2958, 2924, 2873, 1676 (s, >C=O), 1616, 1583, 1417, 1372, 1343, 1262, 1189, 1051, 1019, 971, 841 cm^{-1}. ^{1}H NMR (700 MHz, $CDCl_3$) δ 6.22 (s, 2H, ArH), 4.97 (br s, 2H, OH), 3.94 (t, J = 8.1 Hz, 1H, 4-H), 3.50 (dd, J = 18.8 Hz, J = 7.8 Hz, 1H, 3α-H), 2.62 (dd, J = 18.8 Hz, J = 8.6 Hz, 1H, 3β-H), 2.59 (t, J = 5.0 Hz, 1H, 1-H), 2.51 (m, 1H, 7α-H), 2.47 (d, J = 10.6 Hz, 1H, 7β-H), 2.31 (t, J = 5.3 Hz, 1H, 5-H), 1.84−1.75 (m, 2H of the cyclopentane ring), 1.73−1.57 (m, 6H of the cyclopentane ring), 1.50−1.46 (m, 2H, 2′-H), 1.36 (s, 3H, 6-Me), 1.26−1.11 (m, 6H, 4′-H, 5′-H, 6′-H), 1.02−0.95 (m, 5H, 3′-H, 6-Me, especially 0.99, s, 3H, 6-Me), 0.83 (t, J = 6.9 Hz, 3H, 7′-H). ^{13}C NMR ($CDCl_3$) δ 217.22 (C-2), 154.55 (ArC-2, ArC-6), 149.22 (ArC-4), 113.39 (ArC-1), 107.60 (ArC-3, ArC-5), 57.96 (C-1), 50.56 (C-1′), 46.80 (C-5), 42.19 (C-6), 41.83 (C-2′), 37.97 (C-3), 37.58 (C-8′, C-11′), 31.82 (C-5′), 30.00 (C-4′), 29.52 (C-4), 26.20 (6-*C*H$_3$), 25.23 (C-3′), 24.47 (C-7), 23.32 (C-9′, C-10′), 22.72 (C-6′), 22.18 (6-*C*H$_3$), 14.09 (C-7′). Mass spectrum m/z (relative intensity) 398 (M^+, 33), 383 (7), 381 (8), 355 (13), 315 (43), 275 (17), 203 (19), 149 (28), 111 (38), 83 (66), 57 (100). Exact mass calculated for $C_{26}H_{38}O_3$, 398.2821; found, 398.2822. Anal. ($C_{26}H_{38}O_3$) C, H.

(4*R*)-4-[4-(2-Hexyl-1,3-dithiolan-2-yl)-2,6-dihydroxy-phenyl]-6,6-dimethyl-2-norpinanone (5c). The synthesis was carried out as described for **5a** starting from **4c**[23] (879 mg, 2.95 mmol),

diacetates **3**[31] (1.54 g, ca. 80% pure by ^{1}H NMR, 5.16 mmol), and *p*-toluenesulfonic acid monohydrate (785 mg, 4.13 mmol) in $CHCl_3$ (30 mL) and gave 451 mg (35% yield) of **5c** as a white solid; mp 160−161 °C (from $CHCl_3$-hexane). IR (neat) 3329, 2926, 2856, 1683 (s, >C=O), 1616, 1585, 1417, 1371, 1303, 1266, 1207, 1051, 1022, 919, 843, 793 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.68 (s, 2H, ArH), 5.02 (br s, 2H, OH), 3.95 (t, J = 8.2 Hz, 1H, 4-H), 3.44 (dd, J = 19.5 Hz, J = 7.8 Hz, 1H, 3α-H), 3.37−3.30 (m, 2H, −S(CH$_2$)$_2$S−), 3.25−3.18 (m, 2H, −S-(CH$_2$)$_2$S−), 2.60 (dd, J = 19.5 Hz, J = 8.5 Hz, 1H, 3β-H), 2.58 (t, J = 4.7 Hz, 1H, 1-H), 2.53−2.49 (m, 1H, 7α-H), 2.44 (d, J = 10.8 Hz, 1H, 7β-H), 2.30 (t, J = 5.2 Hz, 1H, 5-H), 2.26−2.22 (m, 2H, 2′-H), 1.36 (s, 3H, 6-Me), 1.27−1.19 (m, 8H, 3′-H, 4′-H, 5′-H, 6′-H), 0.99 (s, 3H, 6-Me), 0.85 (t, J = 6.5 Hz, 3H, 7′-H). Mass spectrum m/z (relative intensity) 434 (M$^+$, 18), 391 (2), 349 (100), 239 (9). Exact mass calculated for $C_{24}H_{34}O_3S_2$, 434.1949; found, 434.1948. Anal. ($C_{24}H_{34}O_3S_2$) C, H.

(4*R*)-4-{4-[1-(1,2-*cis*-Hexen-1-yl)cyclobutyl]-2,6-dihydroxyphenyl}-6,6-dimethyl-2-norpinanone (5d). The synthesis was carried out as described for **5a** starting from **4d**[27] (710 mg, 2.89 mmol), diacetates **3**[31] (1.5 g, ca. 80% pure by ^{1}H NMR, 5.06 mmol), and *p*-toluenesulfonic acid monohydrate (770 mg, 4.05 mmol) in $CHCl_3$ (29 mL) and gave 264 mg (24% yield) of **5d** as a white crystalline solid; mp 174−175 °C (from $CHCl_3$-hexane). IR (neat) 3280, 2955, 2926, 2870, 1674 (s, >C=O), 1615, 1581, 1417, 1374, 1348, 1301, 1263, 1192, 1053, 1016, 969, 920, 834, 754, 704 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.31 (s, 2H, ArH), 5.73 (d, J = 11.0 Hz, 1H, 2′-H), 5.30 (dt, J = 11.0 Hz, J = 7.5 Hz, 1H, 3′-H), 4.85 (br s, 2H, OH), 3.95 (t, J = 8.1 Hz, 1H, 4-H), 3.49 (dd, J = 18.7 Hz, J = 7.8 Hz, 1H, 3α-H), 2.60 (dd, J = 18.7 Hz, J = 8.5 Hz, 1H, 3β-H), 2.58 (t, J = 5.1 Hz, 1H, 1-H), 2.50 (m, 1H, 7α-H), 2.46 (d, J = 10.6 Hz, 1H, 7β-H), 2.43−2.38 (m, 2H of the cyclobutane ring), 2.35−2.30 (m, 2H of the cyclobutane ring), 2.29 (t, J = 5.3 Hz, 1H, 5-H), 1.99−1.92 (m, 1H of the cyclobutane ring), 1.90−1.85 (m, 1H of the cyclobutane ring), 1.84−1.78 (m, 2H, 4′-H), 1.36 (s, 3H, 6-Me), 1.22−1.16 (m, 4H, 5′-H, 6′-H), 1.00 (s, 3H, 6-Me), 0.81 (t, J = 6.7 Hz, 3H, 7′-H). Mass spectrum m/z (relative intensity) 382 (M$^+$, 100), 367 (16), 354 (18), 339 (29), 299 (27), 271 (43), 188 (41), 83 (44). Exact mass calculated for $C_{25}H_{34}O_3$, 382.2508; found, 382.2507. Anal. ($C_{25}H_{34}O_3$) C, H.

(4*R*)-4-[4-(1-Hexyl-cyclobutyl)-2,6-dihydroxy-phenyl]-6,6-dimethyl-2-norpinanone (5e). The synthesis was carried out as with **5a** by using **4e**[27] (514 mg, 2.07 mmol), diacetates **3**[31] (1.077 g, ca. 80% pure by ^{1}H NMR, 3.62 mmol), and *p*-toluenesulfonic acid monohydrate (551 mg, 2.9 mmol) in $CHCl_3$ (21 mL). Yield 49% (390 mg); white crystalline solid; mp 194−196 °C (from $CHCl_3$-hexane). IR (neat) 3315, 3080, 2944, 2930, 2855, 1675 (s, >C=O), 1615, 1582, 1417, 1373, 1345, 1262, 1190, 1053, 1039, 1018, 968, 837, 761 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.06 (s, 2H, ArH), 4.85 (br s, 2H, OH), 3.95 (t, J = 8.1 Hz, 1H, 4-H), 3.49 (dd, J = 18.7 Hz, J = 7.8 Hz, 1H, 3α-H), 2.61 (dd, J = 18.7 Hz, J = 8.6 Hz, 1H, 3β-H), 2.58 (t, J = 5.0 Hz, 1H, 1-H), 2.51 (m, 1H, 7α-H), 2.47 (d, J = 10.6 Hz, 1H, 7β-H), 2.30 (t, J = 5.4 Hz, 1H, 5-H), 2.26−2.20 (m, 2H of the cyclobutane ring), 2.04−1.92 (m, 3H of the cyclobutane ring), 1.81−1.75 (m, 1H of the cyclobutane ring), 1.69−1.66 (m, 2H, 2′-H), 1.36 (s, 3H, 6-Me), 1.27−1.16 (m, 6H, 4′-H, 5′-H, 6′-H), 1.03−0.96 (m, 5H, 3′-H, 6-Me, especially 0.99, s, 3H, 6-Me), 0.85 (t, J = 6.9 Hz, 3H, 7′-H). Mass spectrum m/z (relative intensity) 384 (M$^+$, 100), 367 (9), 341 (31), 313 (48), 301 (27), 273 (47), 176 (39), 83 (46). Exact mass calculated for $C_{25}H_{36}O_3$, 384.2664; found, 384.2662. Anal. ($C_{25}H_{36}O_3$) C, H.

(6a*R*,10a*R*)-3-[1-(1,2-*cis*-Hexen-1-yl)-cyclopent-1-yl]-6,6a,7,8,10,10a-hexahydro-1-hydroxy-6,6-dimethyl-9*H*-dibenzo[*b*,*d*]pyran-9-one (6a). The synthesis was carried out analogous to the preparation of **6b** (see text below) using **5a** (467 mg, 1.18 mmol) and trimethylsilyl trifluoromethanesulfonate (1.2 mL, 0.3 M solution in CH_3NO_2, 0.36 mmol) in anhydrous CH_2Cl_2/CH_3NO_2 (3:1 mixture, 24 mL); yield 61% (284 mg); white foam. IR (neat) 3266 (br, OH), 2953, 2871, 1694 (s, >C=O), 1619, 1574, 1415, 1336, 1258, 1203, 1183, 1135, 1093, 1041, 966, 835 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.42 (d, J = 1.5 Hz, 1H, Ar-H), 6.31 (d, J = 1.5 Hz, 1H, Ar-H), 5.95 (br s, 1H, OH), 5.63 (d, J = 11.2 Hz, 1H, 2′-H), 5.25 (dt, J = 11.2 Hz, J = 7.5 Hz, 1H, 3′-H), 3.97 (ddd, J = 15.0 Hz, J = 3.5 Hz, J = 2.0 Hz, 1H, 10eq-H), 2.87 (m as td, J = 12.0 Hz, J = 3.4 Hz, 1H, 10a-H), 2.63−2.59 (m, 1H, 8eq-H), 2.48−2.40 (m, 1H, 8ax-H), 2.18−2.12 (m, 2H, 10ax-H, 7eq-H), 1.99−1.92 (m, 3H, cyclopentane ring, 6a-H), 1.91−1.83 (m, 2H, cyclopentane ring), 1.77−1.65 (m, 6H, 4′-H, cyclopentane ring), 1.57−1.45 (m, 4H, 7ax-H, 6-Me, especially 1.47, s, 6-Me), 1.12−1.04 (m, 7H, 5′-H, 6′-H, 6-Me, especially 1.11, s, 6-Me), 0.73 (t, J = 6.8 Hz, 3H, 7′-H). Mass spectrum m/z (relative intensity) 396 (M$^+$, 39), 381 (3), 379 (4), 353 (16), 339 (13), 313 (44), 302 (22), 220 (16), 205 (56), 83 (100). Exact mass calculated for $C_{26}H_{36}O_3$, 396.2664; found, 396.2669. Anal. ($C_{26}H_{36}O_3$) C, H.

(6a*R*,10a*R*)-3-(1-Hexyl-cyclopent-1-yl)-6,6a,7,8,10,10a-hexahydro-1-hydroxy-6,6-dimethyl-9*H*-dibenzo[*b*,*d*]pyran-9-one (6b). To a stirred solution of **5b** (550 mg, 1.38 mmol) in anhydrous CH_2Cl_2/CH_3NO_2 (3:1 mixture, 28 mL) at 0 °C under an argon atmosphere was added trimethylsilyl trifluoromethanesulfonate (1.4 mL, 0.3 M solution in CH_3NO_2, 0.42 mmol). Stirring was continued for 3 h while the temperature was allowed to rise to 25 °C. The reaction was quenched with saturated aqueous $NaHCO_3$/brine (1:1), and diethyl ether was added. The organic phase was separated, the aqueous phase was extracted with diethyl ether, and the combined organic phase was washed with brine and dried over $MgSO_4$. Solvent evaporation and purification by flash column chromatography on silica gel (47% diethyl ether-hexane) afforded 359 mg (65% yield) of the title compound **6b** as white foam. IR (neat) 3292 (br, OH), 2953, 2927, 2870, 1695 (s, >C=O), 1620, 1574, 1414, 1344, 1259, 1202, 1184, 1137, 1093, 1038, 838 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.33 (d, J = 1.5 Hz, 1H, ArH), 6.19 (d, J = 1.5 Hz, 1H, ArH), 5.50 (br s, 1H, OH), 3.93 (ddd, J = 15.0 Hz, J = 3.5 Hz, J = 2.0 Hz, 1H, 10eq-H), 2.88 (m as td, J = 12.0 Hz, J = 3.5 Hz, 1H, 10a-H), 2.62−2.58 (m, 1H, 8eq-H), 2.48−2.41 (m, 1H, 8ax-H), 2.19−2.13 (m, 2H, 10ax-H, 7eq-H), 1.97 (m as td, J = 12.1 Hz, J = 2.7 Hz, 1H, 6a-H), 1.84−1.79 (m, 2H, cyclopentane ring), 1.74−1.45 (m, 12H, cyclopentane ring, 7ax-H, 2′-H, 6-Me, especially 1.47, s, 6-Me), 1.22−1.10 (m, 9H, 4′-H, 5′-H, 6′-H, 6-Me, especially 1.13, s, 6-Me), 1.01−0.91 (m, 2H, 3′-H), 0.82 (t, J = 6.8 Hz, 3H, 7′-H). Mass spectrum m/z (relative intensity) 398 (M$^+$, 57), 383 (4), 381 (3), 356 (8), 314 (100), 302 (22), 220 (5), 204 (22), 83 (39). Exact mass calculated for $C_{26}H_{38}O_3$, 398.2821; found, 398.2822. Anal. ($C_{26}H_{38}O_3$) C, H.

(6a*R*,10a*R*)-3-(2-Hexyl-1,3-dithiolan-2-yl)-6,6a,7,8,10,10a-hexahydro-1-hydroxy-6,6-dimethyl-9*H*-dibenzo[*b*,*d*]pyran-9-one (6c). The synthesis was carried out analogous to the preparation of **6b** using **5c** (180 mg, 0.41 mmol) and trimethylsilyl trifluoromethanesulfonate (0.4 mL, 0.3 M solution in CH_3NO_2, 0.12 mmol) in anhydrous CH_2Cl_2/CH_3NO_2 (3:1 mixture, 8.2 mL); yield 67% (121 mg); white foam. IR (neat) 3252 (br, OH), 2925, 2854, 1693 (s, >C=O), 1616, 1574, 1411, 1332, 1259, 1203, 1182, 1136, 1093, 1044, 968 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.76 (d, J = 1.8 Hz, 1H, ArH), 6.64 (d, J = 1.8 Hz, 1H, ArH), 5.85 (br s, 1H, OH), 3.94 (m as d, J = 14.6 Hz, 1H, 10eq-H), 3.36−3.30 (m, 2H, −S(CH$_2$)$_2$S−), 3.28−3.21 (m, 2H, −S(CH$_2$)$_2$S−), 2.87 (m as td, J = 11.9 Hz, J = 3.3 Hz, 1H, 10a-H), 2.63−2.59 (m, 1H, 8eq-H), 2.48−2.40 (m, 1H, 8ax-H), 2.27 (m, 2H, 2′-H), 2.18−2.14 (m, 2H, 10ax-H, 7eq-H), 1.96 (m as td, J = 11.7 Hz, J = 2.0 Hz, 1H, 6a-H), 1.56−1.45 (m, 4H, 7ax-H, 6-Me, especially 1.48, s, 6-Me), 1.26−1.19 (m, 8H, 3′-H, 4′-H, 5′-H, 6′-H), 1.12 (s, 3H, 6-Me), 0.84 (t, J = 7.0 Hz, 3H, 7′-H). Mass spectrum m/z (relative intensity) 434 (M$^+$, 6), 398 (2), 349 (43), 264 (20), 222 (29), 194 (13), 152 (100), 137 (67), 83 (8). Exact mass calculated for $C_{24}H_{34}O_3S_2$, 434.1949; found, 434.1949. Anal. ($C_{24}H_{34}O_3S_2$) C, H.

(6a*R*,10a*R*)-3-[1-(1,2-*cis*-Hexen-1-yl)-cyclobut-1-yl]-6,6a,7,8,10,10a-hexahydro-1-hydroxy-6,6-dimethyl-9*H*-dibenzo[*b*,*d*]pyran-9-one (6d). The synthesis was carried out analogous to the preparation of **6b** using **5d** (140 mg, 0.37 mmol) and trimethylsilyl

trifluoromethanesulfonate (0.37 mL, 0.3 M solution in CH_3NO_2, 0.11 mmol) in anhydrous CH_2Cl_2/CH_3NO_2 (3:1 mixture, 7.5 mL); yield 51% (72 mg); white foam. IR (neat) 3254 (br, OH), 2954, 2931, 2870, 1694 (s, >C=O), 1617, 1574, 1414, 1337, 1259, 1202, 1183, 1135, 1093, 1039, 962, 835 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 6.45 (d, J = 1.5 Hz, 1H, ArH), 6.23 (d, J = 1.5 Hz, 1H, ArH), 5.74 (d, J = 11.1 Hz, 1H, 2′-H), 5.34 (br s, 1H, OH), 5.27 (dt, J = 11.1 Hz, J = 7.5 Hz, 1H, 3′-H), 3.90 (ddd, J = 15.0 Hz, J = 3.5 Hz, J = 2.0 Hz, 1H, 10eq-H), 2.87 (m as td, J = 12.5 Hz, J = 3.6 Hz, 1H, 10a-H), 2.62−2.56 (m, 1H, 8eq-H), 2.48−2.38 (m, 3H, 8ax-H, cyclobutane ring), 2.34−2.28 (m, 2H, cyclobutane ring), 2.18−2.12 (m, 2H, 10ax-H, 7eq-H), 1.98−1.90 (m, 2H, 6a-H, cyclobutane ring), 1.89−1.80 (m, 3H, 4′-H, cyclobutane ring), 1.54−1.49 (m, 1H, 7ax-H), 1.47 (s, 3H, 6-Me), 1.20−1.15 (m, 4H, 5′-H, 6′-H), 1.11 (s, 3H, 6-Me), 0.79 (t, J = 6.7 Hz, 3H, 7′-H). Mass spectrum m/z (relative intensity) 382 (M^+, 100), 354 (31), 339 (14), 311 (17), 272 (26), 201 (19). Exact mass calculated for $C_{25}H_{34}O_3$, 382.2508; found, 382.2511. Anal. ($C_{25}H_{34}O_3$) C, H.

(6a*R*,10a*R*)-3-(1-Hexyl-cyclobut-1-yl)-6,6a,7,8,10,10a-hexahydro-1-hydroxy-6,6-dimethyl-9*H*-dibenzo[*b*,*d*]pyran-9-one (6e). The synthesis was carried out analogous to the preparation of **6b** using **5e** (218 mg, 0.57 mmol) and trimethylsilyl trifluoromethanesulfonate (0.57 mL, 0.3 M solution in CH_3NO_2, 0.17 mmol) in anhydrous CH_2Cl_2/CH_3NO_2 (3:1 mixture, 12 mL); yield 64% (140 mg); white foam. IR (neat) 3247 (br, OH), 2925, 2856, 1694 (s, >C=O), 1619, 1575, 1415, 1358, 1259, 1203, 1183, 1138, 1093, 1053, 970, 839 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 6.19 (d, J = 1.4 Hz, 1H, ArH), 6.02 (d, J = 1.4 Hz, 1H, ArH), 5.34 (br s, 1H, OH), 3.90 (ddd, J = 15.0 Hz, J = 3.5 Hz, J = 2.0 Hz, 1H, 10eq-H), 2.87 (m as td, J = 12.4 Hz, J = 3.4 Hz, 1H, 10a-H), 2.62−2.57 (m, 1H, 8eq-H), 2.48−2.40 (m, 1H, 8ax-H), 2.29−2.21 (m, 2H, cyclobutane ring), 2.19−2.13 (m, 2H, 10ax-H, 7eq-H), 2.10−1.97 (m, 4H, 6a-H, cyclobutane ring), 1.82−1.73 (m, 1H, cyclobutane ring), 1.69−1.64 (m, 2H, 2′-H), 1.57−1.46 (m, 4H, 7ax-H, 6-Me, especially 1.47, s, 6-Me), 1.27−1.15 (m, 6H, 4′-H, 5′-H, 6′-H), 1.13, s, 6-Me), 1.05−0.96 (m, 2H, 3′-H), 0.84 (t, J = 6.8 Hz, 3H, 7′-H). Mass spectrum m/z (relative intensity) 384 (M^+, 100), 356 (38), 341 (9), 313 (27), 274 (30), 203 (18). Exact mass calculated for $C_{25}H_{36}O_3$, 384.2664; found, 384.2655. Anal. ($C_{25}H_{36}O_3$) C, H.

(6a*R*,9*R*,10a*R*)-3-(2-Hexyl-1,3-dithiolan-2-yl)-6a,7,8,9,10,10a-hexahydro-6,6-dimethyl-6*H*-dibenzo[*b*,*d*]pyran-1,9 diol (7c-*β*). To a solution of **6c** (26 mg, 0.06 mmol) in anhydrous methanol (1.2 mL) at −40 °C under an argon atmosphere was added $NaBH_4$ (8 mg, 0.21 mmol). The reaction mixture was stirred for 1.5 h at −40 °C and then quenched by the addition of saturated NaCl solution. The mixture was warmed to room temperature, diluted with H_2O, and extracted with ethyl acetate. The organic layer was washed with brine, dried ($MgSO_4$) and evaporated to a semisolid material **7c**. On the basis of ^1H NMR analysis, **7c** is a mixture of two isomeric alcohols **7c-α** (R_f = 0.27, 45% AcOEt in hexane) and **7c-*β*** (R_f = 0.25, 45% AcOEt in hexane) in a ratio 4:96, respectively. Purification of this material by flash column chromatography on silica gel (50% AcOEt in hexane) gave, in order of elution, 3 mg of a mixture of **7c-α** and **7c-*β*** (1:2 ratio by ^1H NMR) and 20 mg of pure **7c-*β*** as a glassy substance (mp = 91−93 °C). Overall yield for **7c-*β***: 85% (22 mg). Compound **7c-*β***: IR (neat) 3246 (br, OH), 2927, 2857, 1615, 1573, 1411, 1364, 1332, 1274, 1140, 1044, 820 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 6.70 (d, J = 1.5 Hz, 1H, ArH), 6.59 (d, J = 1.5 Hz, 1H, ArH), 5.98 (br s, 1H, OH), 3.87 (dddd, J = 15.5 Hz, J = 15.0 Hz, J = 4.5 Hz, J = 4.5 Hz, 1H, 9ax-H, peak half-width = 21 Hz), 3.50 (m as br d, J = 11.0 Hz, 1H, 10eq-H), 3.37−3.29 (m, 2H, $-S(CH_2)_2S-$), 3.27−3.18 (m, 2H, $-S(CH_2)_2S-$), 2.47 (ddd, J = 12.0 Hz, J = 11.5 Hz, J = 2.5 Hz, 1H, 10a-H), 2.27−2.23 (m, 2H, 2′-H), 2.17 (m as br d, J = 10.6 Hz, 1H, 8eq-H), 1.91−1.85 (m as br d, J = 14.0 Hz, 1H, 7eq-H), 1.49 (ddd, J = 12.0 Hz, J = 11.5 Hz, J = 2.5 Hz, 1H, 6a-H), 1.45−1.37 (m and s overlapping, 4H, 8ax-H, 6-Me, especially 1.38, s, 6β-Me), 1.30−1.09 (m, 10H, 3′-H, 4′-H, 5′-H, 6′-H, 7ax-H, 10ax-H), 1.06 (s, 3H, 6-Me), 0.84 (t, J = 6.8 Hz, 3H, 7′-H). Mass spectrum m/z (relative intensity) 436 (M^+, 17), 351 (100), 205 (5). Exact mass calculated for $C_{24}H_{36}O_3S_2$, 436.2106; found, 436.2107. Anal. ($C_{24}H_{36}O_3S_2$) C, H. Compound **7c-α**: 4.32 (m, 1H, 9eq-H, peak half-width = 10.5 Hz).

(6a*R*,9*R*,10a*R*)-3-(1-Hexyl-cyclobut-1-yl)-6a,7,8,9,10,10a-hexahydro-6,6-dimethyl-6*H*-dibenzo[*b*,*d*]pyran-1,9 Diol (7e-*β*). The synthesis was carried out analogous to the preparation of **7c-*β*** using **6e** (300 mg, 0.78 mmol) and $NaBH_4$ (104 mg, 2.74 mmol) in anhydrous methanol (15.6 mL). On the basis of ^1H NMR analysis, the crude material (**7e**) obtained after workup, is a mixture of two isomeric alcohols **7e-α** (R_f = 0.28, 40% AcOEt in hexane) and **7e-*β*** (R_f = 0.25, 40% AcOEt in hexane) in a ratio 3:97, respectively. Purification by flash column chromatography on silica gel (45% AcOEt in hexane) gave, in order of elution, 36 mg of a mixture of **7e-α** and **7e-*β*** (1:3 ratio by ^1H NMR) and 260 mg of pure **7e-*β*** as a glassy substance (mp = 79−81 °C). Overall yield for **7e-*β***: 95% (287 mg). Compound **7e-*β***: IR (neat) 3277 (br, OH), 2924, 2855, 1620, 1572, 1454, 1414, 1360, 1271, 1185, 1140, 1052, 972, 836 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 6.15 (d, J = 1.5 Hz, 1H, ArH), 5.97 (d, J = 1.5 Hz, 1H, ArH), 5.24 (br s, 1H, OH), 3.86 (dddd, J = 15.5 Hz, J = 15.0 Hz, J = 4.5 Hz, J = 4.5 Hz, 1H, 9ax-H, peak half-width = 22 Hz), 3.48 (m as br d, J = 7.0 Hz, 1H, 10eq-H), 2.48 (ddd, J = 12.0 Hz, J = 11.5 Hz, J = 2.5 Hz, 1H, 10a-H), 2.30−2.21 (m, 2H, cyclobutane ring), 2.17 (m as br d, J = 10.5 Hz, 1H, 8eq-H), 2.03−1.93 (m, 3H, cyclobutane ring), 1.92−1.86 (m as br d, J = 14.0 Hz, 1H, 7eq-H), 1.82−1.72 (m, 1H, cyclobutane ring), 1.70−1.64 (m, 2H, 2′-H), 1.51 (ddd, J = 12.0 Hz, J = 11.5 Hz, J = 2.0 Hz, 1H, 6a-H), 1.46−1.36 (m and s overlapping, 4H, 8ax-H, 6-Me, especially 1.39, s, 6-Me), 1.29−1.09 (m, 8H, 4′-H, 5′-H, 6′-H, 7ax-H, 10ax-H), 1.08 (s, 3H, 6-Me), 1.04−0.96 (m, 2H, 3′-H), 0.84 (t, J = 7.0 Hz, 3H, 7′-H). Mass spectrum m/z (relative intensity) 386 (M^+, 100), 358 (42), 315 (22), 297 (19), 274 (15), 203 (11), 83 (16). Exact mass calculated for $C_{25}H_{38}O_3$, 386.2821; found, 386.2823. Anal. ($C_{25}H_{38}O_3$) C, H. Compound **7e-α**: 4.25 (m, 1H, 9eq-H, peak half-width = 10.5 Hz).

(3-Phenoxypropyl)triphenylphosphonium Bromide (9a). A mixture of 3-phenoxypropyl bromide (**8a**) (12 g, 55.8 mmol) and triphenylphosphine (15.35 g, 58.6 mmol) in anhydrous benzene (100 mL) was refluxed with vigorous stirring for two days under argon. The reaction mixture was cooled to room temperature, and the precipitating product (**9a**) was isolated by filtration under reduced pressure as a white microcrystalline solid (mp 154−156 °C) in 80% yield (21.3 g). ^1H NMR (500 MHz, $CDCl_3$) δ 7.87 (dd, J = 12.1 Hz, J = 8.0 Hz, 6H, $-PPh_3$), 7.79 (td, J = 8.0 Hz, J = 1.4 Hz, 3H, $-PPh_3$), 7.69 (td, J = 8.0 Hz, J = 3.5 Hz, 6H, $-PPh_3$), 7.24 (t, J = 8.1 Hz, 2H, 3-H, 5-H, −OPh), 6.92 (t, J = 8.1 Hz, 1H, 4-H, −OPh), 6.85 (d, J = 8.1 Hz, 2H, 2-H, 6-H, −OPh), 4.33 (t, J = 5.4 Hz, 2H, $-CH_2OPh$), 4.10 (dt, J = 12.4 Hz, J = 8.0 Hz, 2H, $-CH_2PPh_3$), 2.27−2.19 (m, 2H).

(4-Phenoxybutyl)triphenylphosphonium Bromide (9b). The synthesis was carried out analogous to the preparation of 9a using 4-phenoxybutyl bromide (8b) (22.0 g, 96 mmol) and triphenylphosphine (26.2 g, 100 mmol) in anhydrous benzene (100 mL); yield 85% (40.0 g); white solid, m p 185−186 °C. ^1H NMR (500 MHz, $CDCl_3$) δ 7.96 (dd, J = 12.0 Hz, J = 8.0 Hz, 6H, $-PPh_3$), 7.88 (td, J = 8.0 Hz, J = 1.5 Hz, 3H, $-PPh_3$), 7.80 (td, J = 8.0 Hz, J = 3.5 Hz, 6H, $-PPh_3$), 7.25 (t, J = 7.9 Hz, 2H, 3-H, 5-H, −OPh), 6.92 (t, J = 7.9 Hz, 1H, 4-H, −OPh), 6.82 (d, J = 7.9 Hz, 2H, 2-H, 6-H, −OPh), 4.09 (t, J = 5.5 Hz, 2H, $-CH_2OPh$), 4.01 (dt, J = 12.6 Hz, J = 8.1 Hz, 2H, $-CH_2PPh_3$), 2.25 (qt, J = 6.4 Hz, 2H), 1.93−1.85 (m, 2H).

(5-Phenoxypentyl)triphenylphosphonium Bromide (9c). The synthesis was carried out analogous to the preparation of **9a** using 5-phenoxypentyl bromide (**8c**) (6.96 g, 28.63 mmol) and triphenylphosphine (8.25 g, 31.5 mmol) in anhydrous benzene (70 mL); yield 83% (12 g); white solid, mp 174−176 °C. ^1H NMR (500 MHz, $CDCl_3$) δ 7.86 (dd, J = 12.1 Hz, J = 8.0 Hz,

6H, $-PPh_3$), 7.78 (td, J = 8.0 Hz, J = 1.5 Hz, 3H, $-PPh_3$), 7.68 (td, J = 8.0 Hz, J = 3.5 Hz, 6H, $-PPh_3$), 7.24 (t, J = 7.9 Hz, 2H, 3-H, 5-H, −OPh), 6.91 (t, J = 7.9 Hz, 1H, 4-H, −OPh), 6.78 (d, J = 7.9 Hz, 2H, 2-H, 6-H, −OPh), 3.92 (t, J = 5.6 Hz, 2H, $-CH_2OPh$), 3.85 (dt, J = 12.5 Hz, J = 8.0 Hz, 2H, $-CH_2PPh_3$), 1.90−1.79 (m, 4H), 1.77−1.69 (m, 2H).

3,5-Dimethoxy-1-[1-(1,2-*cis*-4-phenoxybuten-1-yl)cyclopentyl]-benzene (11a). To a stirred suspension of (3-phenoxypropyl)triphenylphosphonium bromide (**9a**) (17.2 g, 36 mmol) in dry THF (180 mL) at 0 °C, under an argon atmosphere, was added potassium bis(trimethylsilyl)amide (7.16 g, 36 mmol). The mixture was stirred for 10 min, and a solution of aldehyde **10**[25,27] (1.68 g, 7.2 mmol) in anhydrous THF (10 mL) was added dropwise. The reaction was stirred for an additional 20 min and upon completion (TLC) was quenched by the addition of saturated aqueous NH_4Cl (40 mL). The reaction mixture was warmed to room temperature, 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 $MgSO_4$, and the solvent evaporated under reduced pressure. The residue was chromatographed through a short column of silica gel (10% diethyl ether in hexane) to give compound **11a** as a colorless liquid in 91% yield (2.3 g). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.24 (t, J = 7.9 Hz, 2H, OPh), 6.91 (t, J = 7.9 Hz, 1H, OPh), 6.77 (d, J = 7.9 Hz, 2H, OPh), 6.54 (d, J = 2.4 Hz, 2H, ArH), 6.28 (t, J = 2.4 Hz, 1H, ArH), 5.86 (d, J = 11.3 Hz, 1H, 2′-H), 5.45 (dt, J = 11.3 Hz, J = 7.3 Hz, 1H, 3′-H), 3.76 (s, 6H, OMe), 3.70 (t, J = 6.8 Hz, 2H, 5′-H), 2.23 (q, J = 6.8, 2H, 4′-H), 2.10−1.89 (m, 4H of the cyclopentane ring), 1.79−1.65 (m, 4H of the cyclopentane ring). Mass spectrum m/z (relative intensity) 352 (M^+, 35), 258 (15), 231 (29), 205 (100), 152 (29), 77 (31). Exact mass calculated for $C_{23}H_{28}O_3$, 352.2038; found, 352.2038.

3,5-Dimethoxy-1-[1-(1,2-*cis*-5-phenoxypenten-1-yl)cyclopentyl]-benzene (11b). The synthesis was carried out as described for **11a** using (4-phenoxybutyl)triphenylphosphonium bromide (**9b**) (21 g, 42.8 mmol) in anhydrous THF (100 mL), potassium bis(trimethylsilyl)amide (8.52 g, 42.8 mmol), and a solution of **10**[25,27] (2 g, 8.7 mmol) in anhydrous THF (10 mL). The crude product obtained after work up was purified by flash column chromatography on silica gel (10% diethyl ether in hexane) to give compound **11b** as a colorless liquid in 94% yield (2.99 g). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25 (t, J = 8.2 Hz, 2H, OPh), 6.90 (t, J = 8.2 Hz, 1H, OPh), 6.80 (d, J = 8.2 Hz, 2H, OPh), 6.53 (d, J = 2.2 Hz, 2H, ArH) 6.27 (t, J = 2.2 Hz, 1H, ArH), 5.77 (d, J = 11.3 Hz, 1H, 2′-H), 5.31 (dt, J = 11.3 Hz, J = 7.5 Hz, 1H, 3′-H), 3.76 (s, 6H, OMe), 3.65 (t, J = 6.8 Hz, 2H, 6′-H), 2.03−1.97 (m, 2H of the cyclopentane ring), 1.96−1.89 (m, 4H, 4′-H and cyclopentane ring, overlapping), 1.76−1.65 (m, 4H of the cyclopentane ring), 1.64−1.55 (m, 2H). Mass spectrum m/z (relative intensity) 366 (M^+, 57), 272 (23), 246 (36), 231 (67), 205 (100), 189 (17), 177 (23), 151 (43), 77 (33). Exact mass calculated for $C_{24}H_{30}O_3$, 366.2195; found, 366.2193.

3,5-Dimethoxy-1-[1-(1,2-*cis*-6-phenoxyhexen-1-yl)cyclopentyl]-benzene (11c). The synthesis was carried out as described for **11a** using (5-phenoxypentyl)triphenylphosphonium bromide (**9c**) (11.60 g, 22.95 mmol) in anhydrous THF (50 mL), potassium bis(trimethylsilyl) amide (4.56 g, 22.95 mmol), and a solution of **10**[25,27] (1.07 g, 4.59 mmol) in anhydrous THF (10 mL). The crude product obtained after work up was purified by flash column chromatography on silica gel (10% diethyl ether in hexane) to give compound **11c** as a colorless liquid in 95% yield (1.66 g). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26 (t, J = 8.0 Hz, 2H, OPh), 6.91 (t, J = 8.0 Hz, 1H, OPh), 6.83 (d, J = 8.0 Hz, 2H, OPh), 6.52 (d, J = 2.1 Hz, 2H, ArH), 6.26 (t, J = 2.1 Hz, 1H, ArH), 5.74 (d, J = 11.3 Hz, 1H, 2′-H), 5.29 (dt, J = 11.3 Hz, J = 7.5 Hz, 1H, 3′-H), 3.77−3.73 (t and s overlapping, 8H, OMe and 7′-H), 2.04−1.97 (m, 2H of the cyclopentane ring), 1.94−1.88 (m, 2H of the cyclopentane ring), 1.80 (q, J = 7.0 Hz, 2H, 4′-H), 1.75−1.65 (m, 4H of the cyclopentane ring), 1.58−1.52, (m, 2H), 1.29 (qt, J = 7.5 Hz, 2H). Mass spectrum m/z (relative intensity) 380 (M^+, 29), 287 (14), 262 (7), 246 (24), 231 (26), 205 (100), 191 (22), 177 (15), 152 (27), 77 (34). Exact mass calculated for $C_{25}H_{32}O_3$, 380.2351; found, 380.2353.

3,5-Dimethoxy-1-[1-(4-phenoxybutyl)cyclopentyl]benzene (12a). To a solution of **11a** (704 mg, 2 mmol) in EtOAc (20 mL) was added 10% Pd/C (106 mg), and the suspension 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 give the product **12a** as a colorless liquid, in 96% yield (680 mg), which was used in the next step without further purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25 (t, J = 8.1 Hz, 2H, 3-H, 5-H, OPh), 6.91 (t, J = 8.1 Hz, 1H, 4-H, OPh), 6.83 (d, J = 8.1 Hz, 2H, 2-H, 6-H, OPh), 6.43 (d, J = 3.0 Hz, 2H, 2-H, 6-H, ArH) 6.29 (t, J = 3.0 Hz, 1H, 4-H, ArH), 3.83 (t, J = 7.2 Hz, 2H, 5′-H), 3.78 (s, 6H, OMe), 1.95−1.51 (m, 12H, 8H of the cyclopentane ring and 4H of the 4-phenoxybutyl group), 1.21−1.11 (m, 2H of the 4-phenoxybutyl group). Mass spectrum m/z (relative intensity) 354 (M^+, 32), 270 (13), 261 (22), 206 (100), 177 (9), 165 (20), 151 (30), 107 (16), 77 (20). Exact mass calculated for $C_{23}H_{30}O_3$, 354.2195; found, 354.2198.

3,5-Dimethoxy-1-[1-(5-phenoxypentyl)cyclopentyl]benzene (12b). The synthesis was carried out as described for **12a** using **11b** (2.35 g, 6.42 mmol) and 10% Pd/C (360 mg) in EtOAc (60 mL) to give the product **12b** as a colorless liquid in 94% yield (2.22 g), which was used in the next step without further purification. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26 (t, J = 7.9 Hz, 2H, 3-H, 5-H, OPh), 6.91 (t, J = 7.9 Hz, 1H, 4-H, OPh), 6.84 (d, J = 7.9 Hz, 2H, 2-H, 6-H, OPh), 6.43 (d, J = 2.2 Hz, 2H, 2-H, 6-H, ArH) 6.29 (t, J = 2.2 Hz, 1H, 4-H, ArH), 3.85 (t, J = 6.5 Hz, 2H, 6′-H), 3.79 (s, 6H, OMe), 1.92−1.85 (m, 2H of the cyclopentane ring), 1.80−1.74 (m, 2H of the cyclopentane ring), 1.73−1.61 (m, 6H, 4H of the cyclopentane ring and 2H of the 5-phenoxypentyl group, overlapping), 1.60−1.54 (m, 2H, 2′-H), 1.31 (qt, J = 7.7 Hz, 2H of the 5-phenoxypentyl group), 1.10−1.02 (m, 2H of the 5-phenoxypentyl group). Mass spectrum m/z (relative intensity) 368 (M^+, 21), 275 (7), 248 (15), 206 (100), 165 (17), 151 (24), 77 (13). Exact mass calculated for $C_{24}H_{32}O_3$, 368.2351; found, 368.2350.

3,5-Dimethoxy-1-[1-(6-phenoxyhexyl)cyclopentyl]benzene (12c). The synthesis was carried out as described for **12a** using **11c** (1.08 g, 2.84 mmol) and 10% Pd/C (162 mg) in EtOAc (25 mL) to give the product **12c** as a colorless liquid in 95% yield (1.03 g), which was used in the next step without further purification. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26 (t, J = 7.8 Hz, 2H, 3-H, 5-H, OPh), 6.90 (t, J = 7.8 Hz, 1H, 4-H, OPh), 6.83 (d, J = 7.8 Hz, 2H, 2-H, 6-H, OPh), 6.43 (d, J = 1.9 Hz, 2H, 2-H, 6-H, ArH) 6.29 (t, J = 1.9 Hz, 1H, 4-H, ArH), 3.88 (t, J = 6.4 Hz, 2H, 7′-H), 3.78 (s, 6H, OMe), 1.93−1.87 (m, 2H of the cyclopentane ring), 1.80−1.73 (m, 2H of the cyclopentane ring), 1.72−1.60 (m, 6H, 4H of the cyclopentane ring and 2H of the 6-phenoxyhexyl group, overlapping), 1.59−1.53 (m, 2H, 2′-H), 1.39−1.20 (m, 4H of the 6-phenoxyhexyl group), 1.09−1.01 (m, 2H of the 6-phenoxyhexyl group). Mass spectrum m/z (relative intensity) 382 (M^+, 23), 306 (4), 289 (12), 262 (17), 220 (100), 179 (27), 165 (30), 77 (15). Exact mass calculated for $C_{25}H_{34}O_3$, 382.2508; found, 382.2505.

5-[1-(4-Bromobutyl)cyclopentyl]resorcinol (13a). To a stirred solution of **12a** (650 mg, 1.84 mmol) in dry CH_2Cl_2 (20 mL), at −78 °C, under an argon atmosphere, was added boron tribromide (6 mL, 1 M solution in CH_2Cl_2). Following the addition, the reaction mixture was gradually warmed to room temperature and the stirring was continued at that temperature until completion of the reaction (12 h). Unreacted boron tribromide was destroyed by the addition of methanol and ice at 0 °C. The mixture was warmed to room temperature, and volatiles were removed in vacuo. The residue was diluted with ethyl acetate and washed with saturated $NaHCO_3$ solution, water, and brine. The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by flash column

chromatography on silica gel (50% diethyl ether in hexane) afforded 535 mg (93% yield) of **13a** as a slightly brown viscous oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.32 (d, J = 2.3 Hz, 2H, ArH), 6.17 (t, J = 2.3 Hz, 1H, ArH), 4.72 (br s, 2H, OH), 3.30 (t, J = 6.6 Hz, 2H, 5′-H), 1.91−1.85 (m, 2H of the cyclopentane ring), 1.78−1.59 (m, 8H, 6H of the cyclopentane ring and 2H of the 4-bromobutyl group, overlapping), 1.57−1.51 (m, 2H, 2′-H), 1.17−1.09 (m, 2H, 4-bromobutyl group). Mass spectrum m/z (relative intensity) 314 ($M^+ + 2$, 5), 312 (M^+, 5), 271 (3), 233 (27), 191 (7), 177 (100), 161 (8), 149 (16), 137 (39), 123 (62), 67 (39). Exact mass calculated for $C_{15}H_{21}BrO_2$, 312.0725; found, 312.0734.

5-[1-(5-Bromopentyl)cyclopentyl]resorcinol (13b). The synthesis was carried out as described for **13a** using **12b** (2.0 g, 5.43 mmol) and boron tribromide (18 mL, 1 M solution in CH_2Cl_2) in anhydrous CH_2Cl_2 (50 mL). The crude product obtained after work up was purified by flash column chromatography on silica gel (50% diethyl ether in hexane) to give pure **13b** as a slightly brown viscous oil in 89% yield (1.58 g). ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.32 (d, J = 2.1 Hz, 2H, ArH), 6.16 (t, J = 2.1 Hz, 1H, ArH), 4.66 (br s, 2H, OH), 3.32 (t, J = 6.8 Hz, 2H, 6′-H), 1.90−1.79 (m, 2H of the cyclopentane ring), 1.78−1.59 (m, 8H, 6H of the cyclopentane ring and 2H of the 5-bromopentyl group, overlapping), 1.54−1.49 (m, 2H, 2′-H), 1.29 (qt, J = 7.5 Hz, 2H, 5-bromopentyl group), 1.05−0.96 (m, 2H, 5-bromopentyl group). Mass spectrum m/z (relative intensity) 328 ($M^+ + 2$, 8), 326 (M^+, 7), 247 (13), 232 (6), 230 (6), 217 (7), 191 (4), 177 (100), 161 (7), 149 (14), 137 (16), 123 (43), 67 (24). Exact mass calculated for $C_{16}H_{23}BrO_2$, 326.0881; found, 326.0875.

5-[1-(6-Bromohexyl)cyclopentyl]resorcinol (13c). The synthesis was carried out as described for **13a** using **12c** (1.0 g, 2.62 mmol) and boron tribromide (9 mL, 1 M solution in CH_2Cl_2) in anhydrous CH_2Cl_2 (20 mL). The crude product obtained after work up was purified by flash column chromatography on silica gel (50% diethyl ether in hexane) to give **13c** as a slightly brown viscous oil in 93% yield (830 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.32 (d, J = 1.9 Hz, 2H, ArH), 6.17 (t, J = 1.9 Hz, 1H, ArH), 4.91 (br s, 2H, OH), 3.35 (t, J = 6.8 Hz, 2H, 7′-H), 1.89−1.80 (m, 2H of the cyclopentane ring), 1.79−1.59 (m, 8H, 6H of the cyclopentane ring and 2H of the 6-bromohexyl group, overlapping), 1.54−1.48 (m, 2H, 2′-H), 1.32 (qt, J = 7.8 Hz, 2H, 6-bromohexyl group), 1.17 (qt, J = 7.7 Hz, 2H, 6-bromohexyl group), 1.04−0.95 (m, 2H, 6-bromohexyl group). Mass spectrum m/z (relative intensity) 342 ($M^+ + 2$, 6), 340 (M^+, 6), 261 (12), 246 (6), 244 (6), 219 (4), 191 (4), 177 (100), 161 (5), 149 (11), 137 (17), 123 (46), 67 (29). Exact mass calculated for $C_{17}H_{25}BrO_2$, 340.1038; found, 340.1031.

(4*R*)-4-{4-[1-(4-Bromobutyl)cyclopentyl]-2,6-dihydroxy-phenyl}-6,6-dimethyl-2-norpinanone (14a). The synthesis was carried out as described for **5a** using **13a** (450 mg, 1.44 mmol), diacetates **3**[31] (730 mg, ca. 75% pure by ^{1}H NMR, 2.3 mmol), and *p*-toluenesulfonic acid monohydrate (548 mg, 2.3 mmol) in $CHCl_3$ (15 mL); yield 54% (350 mg); white solid, mp 180−182 °C (from $CHCl_3$-hexane). IR (neat) 3348, 2938, 2869, 1676 (s, >C=O), 1618, 1582, 1417, 1372, 1265, 1188, 1051, 1016, 920, 845 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.22 (s, 2H, ArH), 4.95 (br s, 2H, OH), 3.94 (t, J = 8.2 Hz, 1H, 4-H), 3.48 (dd, J = 18.9 Hz, J = 7.6 Hz, 1H, 3α-H), 3.31 (t, J = 7.0 Hz, 2H, 5′-H), 2.61 (dd, J = 18.9 Hz, J = 8.7 Hz, 1H, 3β-H), 2.59 (t, J = 5.0 Hz, 1H, 1-H), 2.52 (m, 1H, 7α-H), 2.46 (d, J = 10.6 Hz, 1H, 7β-H), 2.31, (t, J = 5.3 Hz, 1H, 5-H), 1.87−1.79 (m, 2H of the cyclopentane ring), 1.76−1.57 (m, 8H, 6H of the cyclopentane ring and 2H of the 4-bromobutyl group, overlapping), 1.54−1.48 (m, 2H, 2′-H), 1.36 (s, 3H, 6-Me), 1.17−1.10 (m, 2H, 4-bromobutyl group), 1.00 (s, 3H, 6-Me). mass spectrum m/z (relative intensity) 450 ($M^+ + 2$, 15), 448 (M^+, 14), 433 (17), 407 (15), 405 (15), 379 (16), 365 (77), 314 (43), 285 (27), 259 (24), 243 (33), 203 (81), 189 (29), 149 (34), 123 (56), 83 (100). Exact mass calculated for $C_{24}H_{33}BrO_3$, 448.1613; found, 448.1604. Anal. ($C_{24}H_{33}BrO_3$) C, H.

(4*R*)-4-{4-[1-(5-Bromopentyl)cyclopentyl]-2,6-dihydroxy-phenyl}-6,6-dimethyl-2-norpinanone (14b). The synthesis was carried out as described for **5a** using **13b** (1 g, 3.06 mmol), diacetates **3**[31] (1.55 g, ca. 75% pure by ^{1}H NMR, 4.90 mmol), and *p*-toluenesulfonic acid monohydrate (930 mg, 4.9 mmol) in $CHCl_3$ (30 mL); yield 53% (750 mg); white solid, mp 152−154 °C (from $CHCl_3$-hexane). IR (neat) 3307, 2926, 2866, 1673 (s, >C=O), 1618, 1582, 1417, 1373, 1301, 1264, 1206, 1052, 1020, 922, 836, 728 cm^{-1}.; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.21 (s, 2H, ArH), 5.03 (br s, 2H, OH), 3.95 (t, J = 8.2 Hz, 1H, 4-H), 3.48 (dd, J = 18.8 Hz, J = 7.8 Hz, 1H, 3α-H), 3.32 (t, J = 7.2 Hz, 2H, 6′-H), 2.61 (dd, J = 18.8 Hz, J = 8.7 Hz, 1H, 3β-H), 2.58 (t, J = 5.1 Hz, 1H, 1-H), 2.52 (m, 1H, 7α-H), 2.47 (d, J = 10.6 Hz, 1H, 7β-H), 2.31, (t, J = 5.2 Hz, 1H, 5-H), 1.88−1.60 (m, 10H, 8H of the cyclopentane ring and 2H of the 5-bromopentyl group, overlapping), 1.53−1.47 (m, 2H, 2′-H), 1.36 (s, 3H, 6-Me), 1.29 (qt, J = 9.3 Hz, 2H, 5-bromopentyl group), 1.09−0.98 (m and s overlapping, 5H, especially 1.00, s, 3H, 6-Me). Mass spectrum m/z (relative intensity) 464 ($M^+ + 2$, 16), 462 (M^+, 17), 447 (15), 421 (14), 419 (13), 393 (12), 381 (55), 379 (57), 341 (23), 339 (24), 314 (100), 299 (12), 271 (13), 243 (32), 203 (67), 189 (24), 149 (34), 83 (74). Exact mass calculated for $C_{25}H_{35}BrO_3$, 462.1770; found, 462.1760. Anal. ($C_{25}H_{35}BrO_3$) C, H.

(4*R*)-4-{4-[1-(6-Bromohexyl)cyclopentyl]-2,6-dihydroxy-phenyl}-6,6-dimethyl-2-norpinanone (14c). The synthesis was carried out as described for **5a** using **13c** (800 mg, 2.35 mmol), diacetates **3**[31] (1.2 g, ca. 75% pure by ^{1}H NMR, 3.76 mmol), and *p*-toluenesulfonic acid monohydrate (887 mg, 3.76 mmol) in $CHCl_3$ (25 mL); yield 50% (560 mg); white solid, mp 156−158 °C (from $CHCl_3$-hexane). IR (neat) 3308, 3109, 2939, 2865, 1674 (s, >C=O), 1618, 1583, 1462, 1418, 1373, 1347, 1301, 1262, 1206, 1189, 1052, 1019, 921, 841, 725 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.22 (s, 2H, ArH), 5.01 (br s, 2H, OH), 3.95 (t, J = 8.2 Hz, 1H, 4-H), 3.49 (dd, J = 18.7 Hz, J = 7.5 Hz, 1H, 3α-H), 3.36 (t, J = 6.8 Hz, 2H, 7′-H), 2.61 (dd, J = 18.7 Hz, J = 8.6 Hz, 1H, 3β-H), 2.59 (t, J = 5.1 Hz, 1H, 1-H), 2.52 (m, 1H, 7α-H), 2.46 (d, J = 10.6 Hz, 1H, 7β-H), 2.31, (t, J = 5.3 Hz, 1H, 5-H), 1.85−1.74 (m, 4H, 2H of the cyclopentane ring and 2H of the 6-bromohexyl group, overlapping), 1.72−1.60 (m, 6H of the cyclopentane ring), 1.52−1.46 (m, 2H, 2′-H), 1.38−1.30 (s and m overlapping, 5H, especially 1.36, s, 3H, 6-Me), 1.17 (qt, J = 7.8 Hz, 2H, 6-bromohexyl group), 1.04−0.96 (s and m overlapping, 5H, especially 1.00, s, 3H, 6-Me). Mass spectrum m/z (relative intensity) 478 ($M^+ + 2$, 17), 476 (M^+, 17), 461 (18), 435 (16), 433 (16), 407 (16), 395 (67), 393 (69), 355 (24), 353 (25), 314 (91), 271 (16), 243 (35), 203 (84), 189 (32), 149 (34), 123 (23), 83 (100). Exact mass calculated for $C_{26}H_{37}BrO_3$, 476.1926; found, 476.1931. Anal. ($C_{26}H_{37}BrO_3$) C, H.

(6a*R*,10a*R*)-3-[1-(4-Bromobutyl)cyclopentyl]-6,6a,7,8,10,10a-hexahydro-1-hydroxy-6,6-dimethyl-9*H*-dibenzo[*b*,*d*]pyran-9-one (15a). The synthesis was carried out analogous to the preparation of **6b** using **14a** (100 mg, 0.23 mmol) and trimethylsilyl trifluoromethanesulfonate (0.23 mL, 0.3 M solution in CH_3NO_2, 0.07 mmol) in anhydrous CH_2Cl_2/CH_3NO_2 (3:1 mixture, 5 mL); yield 75% (75 mg); white foam. IR (neat) 3279 (br, OH), 2952, 2869, 1694 (s, >C=O), 1620, 1576, 1414, 1346, 1257, 1184, 1093, 1037, 838. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.33 (d, J = 1.0 Hz, 1H, ArH), 6.21 (d, J = 1.1 Hz, 1H, ArH), 5.76 (br s, 1H, OH), 3.96 (m as br d, J = 15.1 Hz, 1H, 10eq-H), 3.29 (t, J = 6.7 Hz, 2H, 5′-H), 2.88 (m as td, J = 12.5 Hz, J = 3.6 Hz, 1H, 10a-H), 2.66−2.57 (m, 1H, 8eq-H), 2.50−2.42 (m, 1H, 8ax-H), 2.20−2.13 (m, 2H, 10ax-H, 7eq-H), 1.97 (m as td, J = 12.0 Hz, J = 1.7 Hz, 1H, 6a-H), 1.91−1.83 (m, 2H of the cyclopentane ring), 1.78−1.43 (m, 14H, 6H of the cyclopentane ring, 2′-H, 4′-H, 7ax-H, 6-Me, overlapping, especially 1.48, s, 6-Me), 1.19−1.02 (m and s overlapping, 5H, 3′-H, 6-Me, especially 1.13, s, 6-Me). Mass spectrum m/z (relative intensity) 450 ($M^+ + 2$, 16), 448 (M^+, 16), 435 (4), 433 (5), 407 (5), 369 (93), 314 (100), 286 (17), 273 (20), 259 (17), 245 (19), 229 (8), 204 (52), 189 (17), 163 (14), 149 (18), 123 (22), 83 (23), 69 (47). Exact mass

calculated for $C_{24}H_{33}BrO_3$, 448.1613; found, 448.1607. Anal. ($C_{24}H_{33}BrO_3$) C, H.

(6a*R*,10a*R*)-3-[1-(5-Bromopentyl)cyclopentyl]-6,6a,7,8,10,10a-hexahydro-1-hydroxy-6,6-dimethyl-9*H*-dibenzo[*b*,*d*]pyran-9-one (15b). The synthesis was carried out analogous to the preparation of **6b** using **14b** (200 mg, 0.43 mmol) and trimethylsilyl trifluoromethanesulfonate (0.43 mL, 0.3 M solution in CH_3NO_2, 0.13 mmol) in anhydrous CH_2Cl_2/CH_3NO_2 (3:1 mixture, 10 mL); yield 73% (146 mg), white foam. IR (neat) 3282 (br, OH), 2933, 2869, 1695 (s, >C=O), 1620, 1575, 1414, 1345, 1257, 1184, 1093, 1037, 837. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.32 (d, J = 1.1 Hz, 1H, ArH), 6.21 (d, J = 1.1 Hz, 1H, ArH), 5.80 (br s, 1H, OH), 3.96 (ddd, J = 15.0 Hz, J = 3.5 Hz, J = 2.0 Hz, 1H, 10eq-H), 3.29 (t, J = 6.8 Hz, 2H, 6′-H), 2.88 (m as td, J = 12.6 Hz, J = 3.6 Hz, 1H, 10a-H), 2.65−2.57 (m, 1H, 8eq-H), 2.49−2.40 (m, 1H, 8ax-H), 2.19−2.12 (m, 2H, 10ax-H, 7eq-H), 1.97 (m as td, J = 12.0 Hz, J = 1.8 Hz, 1H, 6a-H), 1.87−1.79 (m, 2H of the cyclopentane ring), 1.77−1.58 (m, 8H, 6H of the cyclopentane ring and 2H of the 5-bromopentyl group, overlapping), 1.57−1.45 (m and s overlapping, 6H, 7ax-H, 2′-H, 6-Me, especially 1.47, s, 6-Me), 1.28 (qt, J = 7.5 Hz, 2H, 5-bromopentyl group), 1.12 (s, 3H, 6-Me), 1.07−0.98 (m, 2H, 5-bromopentyl group). Mass spectrum m/z (relative intensity) 464 (M^+ + 2, 10), 462 (M^+, 10), 449 (3), 447 (3), 383 (14) 353 (10), 314 (100), 299 (7), 273 (4), 245 (8), 204 (27), 189 (8), 175 (5), 149 (13), 83 (11), 69 (37). Exact mass calculated for $C_{25}H_{35}BrO_3$, 462.1770; found, 462.1767. Anal. ($C_{25}H_{35}BrO_3$) C, H.

(6a*R*,10a*R*)-3-[1-(6-Bromohexyl)cyclopentyl]-6,6a,7,8,10,10a-hexahydro-1-hydroxy-6,6-dimethyl-9*H*-dibenzo[*b*,*d*]pyran-9-one (15c). The synthesis was carried out analogous to the preparation of **6b** using **14c** (150 mg, 0.31 mmol) and trimethylsilyl trifluoromethanesulfonate (0.30 mL, 0.3 M solution in CH_3NO_2, 0.09 mmol) in anhydrous CH_2Cl_2/CH_3NO_2 (3:1 mixture, 7 mL); yield 74% (111 mg), white foam. IR (neat) 3292 (br, OH), 2932, 2869, 1695 (s, >C=O), 1620, 1574, 1414, 1345, 1264, 1184, 1092, 1037, 838. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.32 (d, J = 1.4 Hz, 1H, ArH), 6.23 (d, J = 1.4 Hz, 1H, ArH), 5.99 (br s, 1H, OH), 3.99 (m as br d, J = 15.1 Hz, 1H, 10eq-H), 3.33 (t, J = 6.9 Hz, 2H, 7′-H), 2.89 (m as td, J = 12.6 Hz, J = 3.5 Hz, 1H, 10a-H), 2.65−2.57 (m, 1H, 8eq-H), 2.49−2.41 (m, 1H, 8ax-H), 2.19−2.13 (m, 2H, 10ax-H, 7eq-H), 1.97 (m as td, J = 12.0 Hz, J = 1.6 Hz, 1H, 6a-H), 1.87−1.80 (m, 2H of the cyclopentane ring), 1.79−1.60 (m, 8H, 6H of the cyclopentane ring and 2H of the 6-bromohexyl group, overlapping), 1.59−1.45 (m and s overlapping, 6H, 7ax-H, 2′-H, 6-Me, especially 1.47, s, 6-Me), 1.32 (qt, J = 7.5 Hz, 2H, 6-bromohexyl group), 1.16 (qt, J = 7.6 Hz, 2H, 6-bromohexyl group), 1.12 (s, 3H, 6-Me), 1.08−0.99 (m, 2H, 6-bromohexyl group). Mass spectrum m/z (relative intensity) 478 (M^+ + 2, 5), 476 (M^+, 5), 465 (3), 463 (3), 447 (4), 397 (10), 381 (14), 379 (15), 341 (6), 339 (7), 314 (100), 299 (4), 220 (7), 205 (42), 189 (15), 149 (18), 83 (28), 69 (43). Exact mass calculated for $C_{26}H_{37}BrO_3$, 476.1926; found, 476.1918. Anal. ($C_{26}H_{37}BrO_3$) C, H.

(6a*R*,10a*R*)-3-[1-(4-Cyanobutyl)cyclopentyl]-6,6a,7,8,10,10a-hexahydro-1-hydroxy-6,6-dimethyl-9*H*-dibenzo[*b*,*d*]pyran-9-one (16). To a stirred solution of **15a** (50 mg, 0.11 mmol) in DMSO (2 mL), at room temperature, under an argon atmosphere, was added NaCN (27 mg, 0.55 mmol). After stirring at the same temperature for 20 h, the reaction mixture was cooled to 0 °C and diluted with water. The mixture was extracted with diethyl ether and the organic layer was washed with brine, dried over $MgSO_4$, and the solvent was removed in vacuo. The residue was purified by flash column chromatography on silica gel (70% EtOAc in hexane) to give **16** as a white foam in 64% yield (28 mg). IR (neat) 3376, 2946, 2869, 2243 (w, CN), 1695 (s, >C=O), 1621, 1575, 1509, 1453, 1385, 1355, 1258, 1184, 1136, 1093, 1037, 948, 839. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.32 (d, J = 1.5 Hz, 1H, ArH), 6.22 (d, J = 1.5 Hz, 1H, ArH), 5.99 (br s, 1H, OH), 3.97 (ddd, J = 15.0 Hz, J = 3.5 Hz, J = 2.0 Hz, 1H, 10eq-H), 2.88 (m as td, J = 12.7 Hz, J = 3.5 Hz, 1H, 10a-H), 2.65−2.57 (m, 1H, 8eq-H), 2.50−2.41 (m, 1H, 8ax-H), 2.23 (t, J = 7.2 Hz, 2H, 5′-H), 2.21−2.12 (m, 2H, 10ax-H, 7eq-H), 1.98 (m as td, J = 12.2 Hz, J = 1.6 Hz, 1H, 6a-H), 1.91−1.82 (m, 2H of the cyclopentane ring), 1.75−1.61 (m, 6H of the cyclopentane ring), 1.56−1.46 (m, 8H, 2′-H, 4′-H, 7ax-H, 6-Me, overlapping, especially 1.48, s, 6-Me), 1.21−1.11 (m and s overlapping, 5H, 3′-H, 6α-Me, especially 1.13, s, 6-Me). Mass spectrum m/z (relative intensity) 395 (M^+, 59), 380 (13), 368 (29), 353 (6), 327 (7), 314 (100), 285 (13), 272 (8), 245 (47), 227 (6), 215 (9), 203 (37), 177 (12), 149 (16), 115 (11), 91 (17), 69 (53). Exact mass calculated for $C_{25}H_{33}NO_3$, 395.2460; found, 395.2456. Anal. ($C_{25}H_{33}NO_3$) C, H, N.

3,5-Dimethoxy-1-[1-(1,2-*cis*-5-phenoxypenten-1-yl)cyclobutyl]-benzene (18). The synthesis was carried our as described for **11a** using (4-phenoxybutyl)triphenylphosphonium bromide (**9b**) (33.13 g, 67.42 mmol) in anhydrous THF (375 mL), potassium bis(trimethylsilylamide) (13.40 g, 67.19 mmol), and a solution of aldehyde **17**[27] (4.95 g, 22.47 mmol) in anhydrous THF (75 mL). The crude product obtained after work up was purified by flash column chromatography on silica gel (4% diethyl ether in hexanes) to give compound **18** as a colorless liquid in 91% yield (7.2 g). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25 (t, J = 8.2 Hz, 2H, 3-H, 5-H, OPh), 6.91 (t, J = 8.2 Hz, 1H, 4-H, OPh), 6.80 (d, J = 8.2 Hz, 2H, 2-H, 6-H, OPh), 6.50 (d, J = 2.2 Hz, 2H, 2-H, 6-H, ArH) 6.28 (t, J = 2.2 Hz, 1H, 4-H, ArH), 5.88 (d, J = 11.1 Hz, 1H, 2′-H), 5.31 (dt, J = 11.1 Hz, J = 7.5 Hz, 1H, 3′-H), 3.77 (s, 6H, OMe), 3.74 (t, J = 6.8 Hz, 2H, 6′-H), 2.52−2.46 (m, 2H of the cyclobutane ring), 2.39−2.33 (m, 2H of the cyclobutane ring), 2.05−2.00 (tdd, J = 7.5 Hz, J = 7.5 Hz, J = 1.5 Hz, 2H, 4′-H), 1.99−1.83 (m, 2H of the cyclobutane ring), 1.72−1.66 (quintet, J = 7.0 Hz, 2H, 5′-H). Mass spectrum m/z (relative intensity) 352 (M^+, 71), 324 (9), 259 (19), 231 (58), 217 (45), 203 (70), 189 (100), 177 (14), 151 (32), 77 (23). Exact mass calculated for $C_{23}H_{28}O_3$, 352.2038; found, 352.2031.

3,5-Dimethoxy-1-[1-(5-phenoxypentyl)cyclobutyl]benzene (19). To a solution of alkene **18** (7.9 g, 22.41 mmol) in absolute EtOH (80 mL) was added Pd (10% on activated carbon, 1.4 g), and the resulting suspension was hydrogenated under pressure (50 psi) at room temperature for 10 h. The catalyst was removed by filtration through Celite, and the filtrate was evaporated under vacuum to give 7.88 g (quantitative yield) of liquid alkane **19**, which was used in the next step without further purification. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.24 (t, J = 7.5 Hz, 2H, 3-H, 5-H, OPh), 6.90 (t, J = 7.5 Hz, 1H, 4-H, OPh), 6.84 (d, J = 7.5 Hz, 2H, 2-H, 6-H, OPh), 6.27−6.25 (m, 3H, 2-H, 4-H, 6-H, ArH), 3.86 (t, J = 7 Hz, 2H, 6′-H), 3.76 (s, 6H, OMe), 2.34−2.28 (m, 2H of the cyclobutane ring), 2.09−1.98 (m, 3H of the cyclobutane ring), 1.83−1.74 (m, 3H, 1H of the cyclobutane ring and 2′-H), 1.69 (quintet, J = 7.5 Hz, 2H, 5′-H), 1.35 (quintet, J = 7.5 Hz, 2H, 4′-H), 1.12−1.06 (m, 2H, 3′-H). Mass spectrum m/z (relative intensity) 354 (M^+, 82), 326 (14), 277 (10), 261 (12), 233 (45), 205 (100), 192 (42), 178 (53), 165 (29), 151 (39), 77 (12). Exact mass calculated for $C_{23}H_{30}O_3$, 354.2195; found, 354.2190.

5-[1-(5-Bromopentyl)cyclobutyl]resorcinol (20). The synthesis was carried our as described for **13a** using **19** (7.59 g, 21.41 mmol) and boron tribromide (94 mL, 1 M solution in CH_2Cl_2) in anhydrous CH_2Cl_2 (350 mL). The crude product obtained after work up was purified by flash column chromatography on silica gel (25% ethyl acetate in hexane) to give **20** as a slightly brown viscous oil in quantitative yield (6.7 g). ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.15 (s, 3H, ArH), 4.70 (br s, 2H, OH), 3.33 (t, J = 6.5 Hz, 2H, 6′-H), 2.30−2.24 (m, 2H of the cyclobutane ring), 2.06−2.00 (m, 3H of the cyclobutane ring), 1.84−1.76 (m, 3H, 2H of 5-bromopentyl group and 1H of cyclobutane ring), 1.75−1.71 (m, 2H, 2′-H), 1.33 (quintet, J = 7.0 Hz, 2H, 5-bromopentyl group), 1.06−0.99 (m, 2H, 5-bromopentyl group). Exact mass calculated for $C_{15}H_{21}BrO_2$, 312.0725; found, 312.0731.

(4*R*)-4-{4-[1-(5-Bromopentyl)cyclobutyl]-2,6-dihydroxy-phenyl}-6,6-dimethyl-2-norpinanone (21). The synthesis was carried out as described for **5a** using **20** (5.8 g, 18.5 mmol), diacetates **3**[31] (6.86 g,

ca. 90% pure by ^{1}H NMR, 28.8 mmol), and *p*-toluenesulfonic acid monohydrate (4.93 g, 25.9 mmol) in $CHCl_3$ (370 mL); yield 46% (3.8 g), white solid, mp 164−165 °C (dec) (from $CHCl_3$-hexane). IR (neat) 3368 (OH), 2936 (CH aromatic), 1684 (>C=O), 1620, 1585 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.06 (s, 2H, 3-H, 5-H, ArH), 5.04 (br s, 2H, OH), 3.95 (t, J = 8.1 Hz, 1H, 4-H), 3.49 (dd, J = 18.7 Hz, J = 7.8 Hz, 1H, 3α-H), 3.35 (t, J = 6.5 Hz, 2H, 6′-H), 2.61 (dd, J = 18.7 Hz, J = 8.6 Hz, 1H, 3β-H), 2.59 (t, J = 5.0 Hz, 1H, 1-H), 2.52 (m, 1H, 7α-H), 2.47 (d, J = 10.6 Hz, 1H, 7β-H), 2.31 (t, J = 5.4 Hz, 1H, 5-H), 2.28−2.20 (m, 2H of the cyclobutane ring), 2.06−1.95 (m, 3H of the cyclobutane ring), 1.84−1.74 (m, 3H, 5′-H, cyclobutane ring), 1.72−1.67 (m, 2H, 2′-H), 1.37 (s, 3H, 6-Me), 1.34 (quintet, J = 8.0 Hz, 2H, 4′-H), 1.08−1.01 (m, 2H, 3′-H), 1.00 (s, 3H, 6-Me). ^{13}C NMR (175 MHz, $CDCl_3$) δ 217.75 (>C=O), 154.95 (ArC-2, ArC-6), 150.44 (ArC-4), 113.49 (ArC-1), 106.49 (ArC-3, ArC-5), 58.11 (C-1), 46.95 (C-5), 46.17 (C-1′), 42.38 (C-6 or C-2′), 42.34 (C-2′ or C-6), 38.09 (C-3), 34.22 (C-6′), 32.93 (cyclobutane ring or C-5′), 32.85 (cyclobutane ring or C-5′), 32.81 (cyclobutane ring or C-5′), 29.67 (C-4), 28.76 (C-4′), 26.35 (6-Me), 24.62 (C-7), 24.04 (C-3′), 22.34 (6-Me), 15.95 (cyclobutane ring). Mass spectrum m/z (relative intensity) 450 ($M^+ + 2$, 55), 448 (M^+, 55), 69 (100). Exact mass calculated for $C_{24}H_{33}BrO_3$, 448.1613; found, 448.1621.

(6a*R*,10a*R*)-3-[1-(5-Bromopentyl)cyclobutyl]-6,6a,7,8,10,10a-hexahydro-1-hydroxy-6,6-dimethyl-9*H*-dibenzo[*b*,*d*]pyran-9-one (22). The synthesis was carried out analogous to the preparation of **6b** using **21** (2.0 g, 4.45 mmol) and trimethylsilyl trifluoromethanesulfonate (4.45 mL, 0.3 M solution in CH_3NO_2, 1.34 mmol) in anhydrous CH_2Cl_2/CH_3NO_2 (3:1 mixture, 90 mL); yield 70% (1.4 g), white foam, mp 69−70 °C. IR (neat) 3292 (OH), 2932 (CH aromatic), 1693(>C=O), 1619, 1575 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.17 (d, J = 1.5 Hz, 1H, ArH), 6.03 (d, J = 1.5 Hz, 1H, ArH), 5.69 (br s, 1H, OH), 3.95 (ddd, J = 15.0 Hz, J = 3.5 Hz, J = 2.0 Hz, 1H, 10eq-H), 3.33 (t, J = 7.0 Hz, 2H, 6′-H), 2.88 (ddd, J = 14.0 Hz, J = 13.5 Hz, J = 3.5 Hz, 1H, 10a-H), 2.65−2.58 (m, 1H, 8eq-H), 2.45 (ddd, J = 15.5 Hz, J = 13.5 Hz, J = 7.5 Hz, 1H, 8ax-H), 2.32−2.23 (m, 2H, cyclobutane ring), 2.21−2.13 (m, 2H, 10ax-H, 7eq-H), 2.22−1.92 (m, 4H, 6a-H, cyclobutane ring), 1.82−1.74 (m, 3H, 5′-H, cyclobutane ring), 1.73−1.68 (m, 2H, 2′-H), 1.52 (dddd, J = 15.0 Hz, J = 13.5 Hz, J = 13.0 Hz, J = 5.0 Hz, 1H, 7ax-H), 1.48 (s, 3H, 6-Me), 1.32 (quintet, J = 7.5 Hz, 2H, 4′-H), 1.13 (s, 3H, 6-Me), 1.08−1.00 (m, 2H, 3′-H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 214.93 (>C=O), 155.43 (ArC), 154.53 (ArC), 151.43 (ArC), 107.96 (ArC), 107.20 (ArC-2 or ArC-4), 105.57 (ArC-4 or ArC-2), 47.76 (C-6a), 46.54 (C-1′), 45.35 (C-10), 42.48 (C-2′), 41.18 (C-8), 35.16 (C-10a), 34.38 (C-6′), 33.12 (cyclobutane ring or C-5′), 33.07 (cyclobutane ring or C-5′), 32.96 (cyclobutane ring or C-5′), 28.95 (C-4′), 28.21 (6-*C*H$_3$), 27.25 (C-7), 24.14 (C-3′), 19.23 (6-*C*H$_3$), 16.12 (cyclobutane ring). Mass spectrum m/z (relative intensity) 450 ($M^+ + 2$, 77), 448 (M^+, 77), 422 (33), 420 (33), 369 (82), 313 (78), 203 (55), 69 (100). Exact mass calculated for $C_{24}H_{33}BrO_3$, 448.1613; found, 448.1606. Anal. ($C_{24}H_{33}BrO_3$) C, H.

(6a*R*,9*R*,10a*R*)-3-[1-(5-Bromopentyl)cyclobutyl]-6a,7,8,9,10,10a-hexahydro-6,6-dimethyl-6*H*-dibenzo[*b*,*d*]pyran-1,9 diol (23). The synthesis was carried out analogous to the preparation of **7c-*β*** using **22** (200 mg, 0.445 mmol) and $NaBH_4$ (59 mg, 1.56 mmol) in anhydrous methanol (10 mL). On the basis of ^{1}H NMR analysis, the crude material obtained after the workup is a mixture of two isomeric alcohols **24** (R_f = 0.30, 40% AcOEt in hexane) and **23** (R_f = 0.27, 40% AcOEt in hexane) in a ratio 3:97, respectively. Purification by flash column chromatography on silica gel (45% AcOEt in hexane) gave, in order of elution, 24 mg of a mixture of **24** and **23** (1:3 ratio by ^{1}H NMR) and 153 mg of pure **23** as a glassy substance (mp = 59−60 °C). Overall yield for **23**: 85% (171 mg). IR (neat) 3328 (OH), 2932 (CH aromatic), 1622, 1574 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.15 (d, J = 2.0 Hz, 1H, ArH), 5.97 (d, J = 2.0 Hz, 1H, ArH), 5.09 (br s, 1H, ArOH), 3.86 (dddd, J = 15.5 Hz, J = 15.0 Hz, J = 4.5 Hz, J = 4.5 Hz, 1H, 9ax-H, peak half-width = 22 Hz), 3.47 (dddd, J = 12.0 Hz, J = 4.5 Hz, J = 2.5 Hz, J = 2.0 Hz, 1H, 10eq-H), 3.35 (t, J = 7.0 Hz, 2H, 6′-H), 2.48 (ddd, J = 12.0 Hz, J = 11.5 Hz, J = 2.5 Hz, 1H, 10a-H), 2.32−2.23 (m, 2H, cyclobutane ring), 2.17 (m as br d, J = 9.0 Hz, 1H, 8eq-H), 2.04−1.93 (m, 3H, cyclobutane ring), 1.90 (dddd, J = 13.5 Hz, J = 3.5 Hz, J = 2.5 Hz, J = 2.0 Hz, 1H, 7eq-H), 1.82−1.74 (m and quintet overlapping, 3H, 5′-H, cyclobutane ring, especially 1.78, quintet, J = 7.0 Hz, 5′-H), 1.69 (m, 2H, 2′-H), 1.51 (ddd, J = 12.0 Hz, J = 11.5 Hz, J = 2.5 Hz, 1H, 6a-H), 1.42 (dddd, J = 15.5 Hz, J = 15.0 Hz, J = 13.0 Hz, J = 3.5 Hz, 1H, 8ax-H), 1.39 (s, 3H, 6-Me), 1.32 (quintet, J = 8.0 Hz, 2H, 4′-H), 1.16 (dddd, J = 13.5 Hz, J = 13.0 Hz, J = 12.0 Hz, J = 3.5 Hz, 1H, 7ax-H), 1.12 (ddd, J = 15.5 Hz, J = 12.0 Hz, J = 12.0 Hz, 1H, 10ax-H), 1.08 (s, 3H, 6-Me), 1.07−1.00 (m, 2H, 3′-H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.92 (ArC), 154.43 (ArC), 150.86 (ArC), 109.52 (ArC), 108.05 (C-2 or C-4), 106.84 (C-4 or C-2), 71.43 (C-9), 48.47 (C-6a), 46.22 (C-6), 41.72 (C-2′), 38.61 (C-10), 35.98 (C-8), 34.26 (C-6′), 34.21 (C-1′), 33.41 (C-10a), 33.02 (C-5′), 32.65 (cyclobutane ring), 29.32 (C-4′), 27.73 (6-Me), 26.22 (C-7), 24.03 (C-3′), 19.23 (6-Me), 15.92 (cyclobutane ring). Mass spectrum m/z (relative intensity) 452 ($M^+ + 2$, 45), 450 (M^+, 45), 422 (23), 406 (119), 315 (57), 189 (38), 62 (100). Exact mass calculated for $C_{24}H_{35}BrO_3$, 450.1770; found, 450.1775. Anal. ($C_{24}H_{35}BrO_3$) C, H.

(6a*R*,9*S*,10a*R*)-3-[1-(5-Bromopentyl)cyclobutyl]-6a,7,8,9,10,10a-hexahydro-6,6-dimethyl-6*H*-dibenzo[*b*,*d*]pyran-1,9 diol (24). To a stirred solution of ketone **22** (703 mg, 1.56 mmol) in anhydrous THF (80 mL) was added K-Selectride (4.69 mL, 1 M solution in THF), under an argon atmosphere, at −78 °C. Stirring was continued at that temperature for 2 h, and then the reaction was quenched by the addition of brine. The organic phase was separated, and the pH of the aqueous phase was adjusted to 4−5 using a 5% solution of hydrochloric acid. The aqueous phase was extracted with EtOAc, and the combined organic layer was washed with brine, dried over $MgSO_4$, and evaporated to give an oily residue, which was further purified by Biotage column chromatography (30% ethyl acetate in hexanes) to afford 490 mg (70% yield) of **24** as a white solid; mp 41−43 °C. IR (neat) 3337 (OH), 2930 (CH aromatic), 1620, 1568 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.14 (br s, 1H, ArOH), 6.14 (d, J = 1.5 Hz, 1H, ArH), 6.10 (d, J = 1.5 Hz, 1H, ArH), 4.30 (m as br s, 1H, 9eq-H, peak half-width = 10.5 Hz), 3.33 (t, J = 7.0 Hz, 2H, 6′-H), 3.25 (ddd, J = 14.5 Hz, J = 3.0 Hz, J = 2.5 Hz, 1H, 10eq-H), 2.95 (ddd, J = 12.0 Hz, J = 11.0 Hz, J = 2.5 Hz, 1H, 10a-H), 2.30−2.21 (m, 2H, cyclobutane ring), 2.02−1.92 (m, 4H, 8eq-H, cyclobutane ring), 1.82−1.72 (m, 3H, 5′-H, cyclobutane ring), 1.71−1.60 (m, 4H, 2′-H, 8ax-H, 7-H), 1.57−1.49 (m, 2H, 6a-H, 7-H), 1.42−1.26 (m, s and quintet overlapping, 6H, 6-Me, 4′-H, 10ax-H, especially 1.37, s, 6-Me and 1.30, quintet, J = 7.5 Hz, 4′-H), 1.08−0.98 (m and s overlapping, 5H, 6-Me, 3′-H, especially 1.04, s, 6-Me). ^{13}C NMR (175 MHz, $CDCl_3$) δ 154.80 (ArC), 154.39 (ArC), 150.46 (ArC), 109.46 (ArC), 107.85 (C-2 or C-4), 105.96 (C-4 or C-2), 67.33 (C-9), 49.46 (C-6a), 46.29 (C-6), 42.34 (C-2′), 36.48 (C-10), 34.23 (C-6′), 33.47 (C-8), 32.93 (C-5′, C-1′), 32.68 (cyclobutane ring), 29.00 (C-10a), 28.78 (C-4′), 27.69 (6-Me), 23.95 (C-3′), 22.84 (C-7), 19.12 (6-Me), 15.93 (cyclobutane ring). Mass spectrum m/z (relative intensity) 452 ($M^+ + 2$, 53), 450 (M^+, 53), 422 (18), 406 (15), 389 (12), 371 (54), 315 (42), 189 (31), 149 (40), 62 (100). Exact mass calculated for $C_{24}H_{35}BrO_3$, 450.1770; found, 450.1770. Anal. ($C_{24}H_{35}BrO_3$) C, H.

Radioligand Binding Assays. Forebrain synaptosomal membranes were prepared from frozen rat brains by the method described by Dodd et al.[36] and were used to assess the affinities of the novel analogues 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.[37] Membrane preparations from HEK293 cells expressing human CB2 (hCB2) receptor were used to assess the affinities of representative analogues for hCB2.[33] 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.[38]

Molecular Modeling. Compound **7e-*β*** underwent torsional sampling using the MCMM (Monte Carlo multiple minimum) protocol[39,40] in MacroModel.[41]The search was conducted using the OPLS_2005 force field[42] in a GB/SA water model[43] with a constant dielectric of 1.0 and an extended cutoff. An energy window of 21.0 kJ mol^{-1} (5 kcal mol^{-1}) was employed, and redundant conformers were eliminated using a rmsd cutoff of 0.5 Å for all atoms.

cAMP Assay. HEK293 cells stably expressing rCB1 receptor were used for the studies. The cAMP assay was carried out using PerkinElmer's Lance ultra cAMP kit following the protocol of the manufacturer. Briefly, the assay was carried out in a 384-well plate using 1000 cells/well. The cells were harvested with nonenzymatic cell dissociation reagent Versene, and they were washed once with HBSS and resuspended in the stimulation buffer. The various concentrations of **7e-*β*** (5 μL) in forskolin (2 μM final concentration) containing stimulation buffer were added to the plate followed by the cell suspension (5 μL). The cells were stimulated for 30 min at room temperature. Then Eu-cAMP tracer working solution (5 μL) and Ulight-anti-cAMP working solution (5 μL) were added to the plate and incubated at room temperature for 60 min. The plate was read on a PerkinElmer Envision instrument. The EC_{50} was determined by nonlinear regression analysis using GraphPad Prism software (GraphPad Software, Inc., San Diego, CA).

Methods for In Vivo Behavioral Characterization of 7e-*β*. Subjects. Female Sprague−Dawley rats (n = 5−6/group), weighing between 200 and 350 g (Charles River, Wilmington MA), were used. Rats were tested repeatedly with at least three days intervening between drug sessions. Experiments occurred at roughly the same time (10:00 a.m.−5:00 pm) during the light portion of the daily light/dark cycle. Outside of experimental sessions, rats were group housed (2/cage) in a climate controlled vivarium, and they had unrestricted access to food and water except during the 6 h test sessions.

Procedure. Temperature was recorded using a thermistor probe (model 401, Measurement Specialties, Inc., Dayton, OH) inserted to a depth of 7.5 cm and secured to the tail with micropore tape. Rats were minimally restrained and isolated in 38 cm × 50 cm × 10 cm plastic stalls. Temperature was read to the nearest 0.01 °C using a thermometer (model 4000A, Measurement Specialties, Inc.). Two baseline temperature measures were recorded at 15 min intervals, and drugs were injected immediately after the second baseline was recorded. After injection, temperature was recorded every 30 min for 3 h and every hour thereafter for a total of 6 h. The change in temperature was determined for each rat by subtracting temperature readings from the average of the two baseline measures.

Antinociception was measured using modified version of the tail-flick procedure of D'Amour and Smith.[44] Radiant heat from a halogen lamp was focused on the tail using a commercial tail-flick apparatus (model LE7106, Harvard Apparatus, Holliston, MA); movement of the tail activated a photocell, turning off the lamp and a reaction timer. The lamp intensity was adjusted to yield baseline values of 2−3 s, and a maximum latency of 6.0 s was imposed to avoid damage to the tail. Two baseline tail-flick latencies were obtained in each rat at 10 min intervals, and drugs were injected immediately after the second baseline was recorded. Tail-flick responses were recorded at 30, 60, 120, 180, and 360 min after injection.

Drugs. Compound **7e-*β*** was initially dissolved in a solution of 20% ethanol, 20% alkamuls, and 60% saline, and was further diluted with saline. Morphine sulfate was dissolved in saline. Injections were administered sc in a volume of 1.0 mL/kg, and drug doses are expressed as the weight of the free base.

Data Analysis. For each rat, the two baseline values recorded prior to drug injection were averaged to obtain a single baseline value. Temperatures recorded after drug injection were expressed as a change from baseline, calculated for each animal by subtracting the baseline temperature from the temperatures recorded postinjection. Tail-flick responses are expressed as a percentage of the maximum possible effect (%MPE) calculated according to the equation: 100 × (test latency−baseline latency)/(6-baseline latency), where 6 represents the cutoff latency. Dose−effect functions were constructed using the maximum effect recorded in each rat at a given dose of drug. Group means and SEM were calculated and time-effect functions were analyzed using two-way repeated measures ANOVA procedures followed by Bonferroni's posthoc test; dose−effect functions were analyzed using one-way repeated measures ANOVA procedures followed by Dunnett's multiple comparison t test; p was set at < 0.05, and statistical analyses were performed using GraphPad Prism 5.03 (GraphPad Software, San Diego, CA).

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Supporting Information Available: Elemental analysis results for compounds **5a**−**5e**, **6a**−**6e**, **14a**−**14c**, **15a**−**15c**, **16**, **22**, **7c-*β***, **7e-*β***, **23**, and **24** as well as ^{1}H NMR, ^{13}C NMR, ^{13}C DEPT, COSY, HSQC, HMBC, and NOESY spectra of compound **5b** in $CDCl_3$ solutions. This material is available free of charge via the Internet at http://pubs.acs.org.

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