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Synthesis of Covalent Probes for the Radiolabeling of the Cannabinoid Receptor

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The main psychoactive constituent of marijuana, (−)-Δ^9-tetrahydrocannabinol, produces most of its physiological effects by interacting with the CB1 cannabinoid receptor, a membrane protein belonging to the large superfamily of G-protein coupled receptors. The 3-D structure of the receptor binding site is of value in the design of novel medications for a variety of therapeutic indications. To obtain information on the amino acid residues associated with this binding site, we have designed and synthesized a cannabinergic CB1 ligand prototype carrying an electrophilic isothiocyanato group capable of reacting covalently with amino acid residues bearing thiol or unprotonated amino groups. The ligand also incorporates an iodide atom, which can serve as a high-activity radiolabel. The key step in our synthesis involves a rapid intramolecular Diels−Alder reaction of a transiently formed *o*-quinone methide, which proceeds stereospecifically with the formation of the tricyclic cannabinoid template. Introduction of the iodo group is the last step in the sequence and is compatible with the use of ^{125}I-radiolabel.

Introduction

The main psychoactive constituent of marijuana, (−)-Δ^9-tetrahydrocannabinol, was shown to bind specifically to the two known cannabinoid receptors, CB1 and CB2. Both of these are membrane-bound proteins and belong to the large superfamily of G-protein-coupled receptors (GPCRs) characterized by seven transmembrane-spanning helical domains connected by intervening intracellular and extracellular loops. CB1 has been recognized as an important therapeutic target for pain, appetite modulation, glaucoma, neurodegeneration, and several other indications and is currently receiving increasing attention by the pharmaceutical industry and other drug discovery laboratories.[1−4] Thus, understanding the structural and functional properties of this receptor is of great value in the design of novel, more selective and more potent drug candidates. Unfortunately, the structural analysis of GPCRs is severely limited by the difficulties associated with their purification and crystallization. A major development in this field has been the recent publication of the three-dimensional crystallographic structure of bovine rhodopsin,[5] a GPCR associated with visual signal transduction. The 2.8 Å resolution crystal structure has provided a much-awaited basis for the development of realistic computational models of other GPCRs including CB1.[6] However, there are very few direct data regarding the CB1 active site. A method currently pursued in our laboratories for obtaining such information is based on the identification of key amino acid residues associated with the receptor's binding domain. This experimental approach involves the development of high-affinity selective ligands capable of forming a covalent bond with an amino acid residue within the receptor binding site or immediately adjacent to it. The identity of the labeled amino acid residue is then revealed through purification of the ligand−receptor complex followed by digestion of the entire protein and analysis of the individual peptide fragments using sequencing or mass spectral analysis. Overall, this is a laborious process, which can be greatly enhanced by the availability of an ^{125}I-iodine radiolabeled covalent probe with high specific radioactivity (over 2000 Ci/mmol) and capable of serving as a highly sensitive marker.

Receptor covalent probes can be designed by incorporating potentially reactive groups into a high-affinity reversible prototypic ligand followed by suitable structural modifications, if necessary, to ensure that the novel

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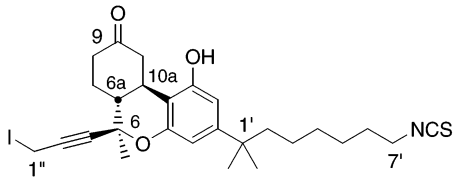


FIGURE 1. Bifunctional nonclassical cannabinoid.

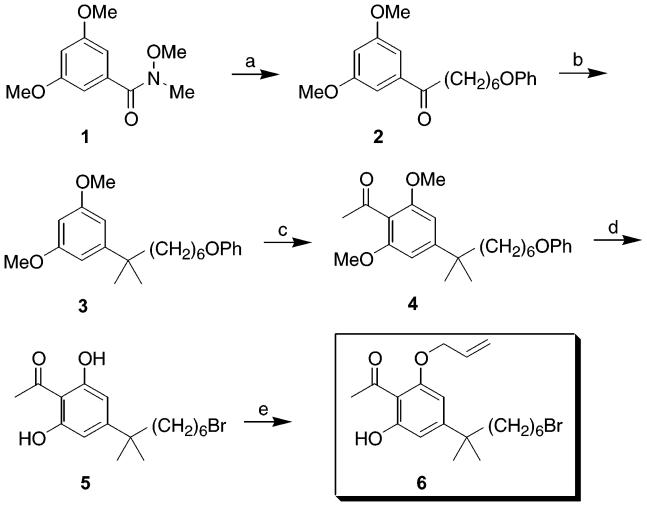
ligand maintains its high affinity for the binding site. Over the past decade our laboratory has been successful in designing a number of CB1 receptor ligands incorporating an isothiocyanato group in a strategic position within the ligand.[7,8] This moderately reactive electrophile is capable of reacting with amino acid residues bearing either sulfhydryl or unprotonated amino side chains. The isothiocyanate-bearing covalent probes, which have been utilized in other receptor systems, offer the advantage of high selectivity. Thus, they react very slowly with water and other hydroxyl groups and form covalent bonds only with more reactive nucleophiles that are suitably positioned for a nucleophilic addition reaction within the ligand binding site.

In earlier work, our laboratory had demonstrated the usefulness of introducing either a photoactivatable group[9] or an isothiocyanato at the end of the side chain at the C-3 position of the aliphatic side chain. The design was optimized with the development of 7′-isothiocyanato-11-hydroxy-1′,1′-dimethylheptyl tetrahydrocannabinol[7] with a pseudo Ki value of 3.2 nm, which was shown to attach covalently to a CB1 receptor preparation. Our present task involved the introduction of an ^{125}I-radiolabel while maintaining at least part of the ligand's reactivity at the binding site. To optimize our radiochemical procedures, the radiolabel should also be preferably introduced as the last reaction step. This proved to be a difficult task because earlier work on the tetrahydrocannabinols had revealed that the introduction of bulky groups within the tricyclic terpenoid structure of cannabinoids significantly reduced their affinities for the receptor.

We addressed this problem by designing a bifunctional probe capable of bearing both an isothiocyanato group and an iodo substituent using as a prototype a group of classical/nonclassical hybrid cannabinoid ligands earlier developed by our laboratories.[10] This earlier work had revealed a strong correlation between the stereochemistry at C-6 and chain length of the attached substituent with the ligand's affinity for the CB1 receptor. A particularly surprising result was the finding of a strong increase in affinity for CB1 for the hybrid cannabinoid bearing a β 1-iodopropyl group at C-6. Rather than excluding the cannabinoid ligand from the binding site for steric reasons, the large iodo substituent potentiated its affinity for the receptor.[10] To explore the above findings, we decided to explore the possibility of preparing bifunctional cannabinoids bearing reactive groups at C-7′ and C-1″. Our first successful foray into this area is described in what follows.

The hybrid tricyclic cannabinoids represent a much greater challenge to the synthetic chemist than the relative simplicity of their structures suggests. Few of the compounds or of the intermediates are crystalline, and the electron-rich phenolic portion of these molecules is prone to oxidation by air. This process is especially rapid in basic media. Unlike the natural tricyclic cannabinoids, C-6 is stereogenic in this series. This fact increases the complexity of the problem, especially since one is limited to kinetically controlled processes for the control of C-6 stereochemistry, since there is an insignificant energy difference between the two C-6 diastereoisomers. This fact precludes one from making use of the methodologies that have been developed for the preparation of Δ^8- and Δ^9-THC. The task that we set before ourselves in this work has an added complication, namely, the need to introduce multiple reactive groups within the molecule.[10]

SCHEME 1[a]



[a] (a) 6-phenoxyhexyl bromide, Mg(0), THF, 0 °C, 6 h; 75%; (b) $TiCl_4$, $Zn(CH_3)_2$, CH_2Cl_2, −30 °C to rt, 6 h; 84%; (c) Ac_2O, $Yb(OTf)_3$, CH_3NO_2, rt, 14 h; 76%; (d) BBr_3, CH_2Cl_2, −78 °C to rt, 36 h; 100%; (e) allyl bromide, *n*-Bu_4NOH, CH_2Cl_2, H_2O, rt, 24 h; 77%.

Discussion

The preparation of the aromatic portion of the molecule is summarized in Scheme 1 and is a modified version of a procedure we reported earlier.[12] Weinreb amide **1** was derived from commercially available 3,5-dimethoxybenzoic acid and was treated in THF with 6-phenoxyhexylmagnesium bromide to produce phenone **2** in 75% yield. The conversion of the phenone carbonyl group to the geminal dimethyl function took place in high yield in the presence of $TiCl_4$ and dimethyl zinc.[13] Friedel−Crafts acylation of **3** with acetic anhydride was catalyzed by $Yb(OTf)_3$.[14] It is noteworthy that the acylation is completely regioselective, leading exclusively to **4**. The presence of the *tert*-alkyl group in **3** completely suppressed competi-

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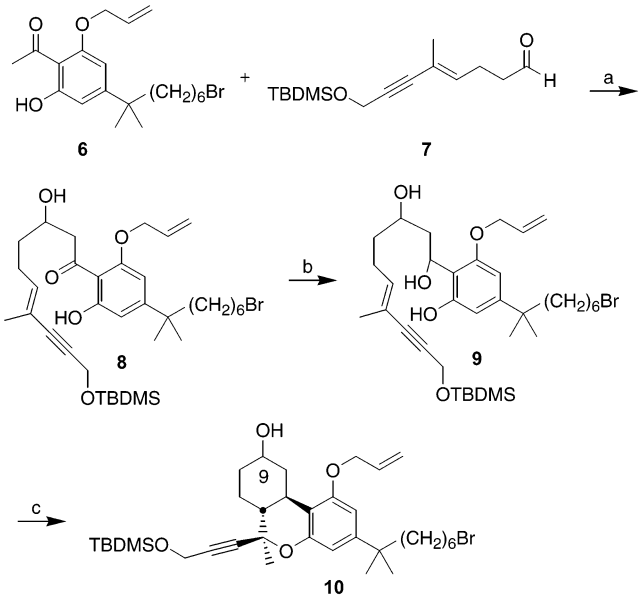
SCHEME 2[a]



[a] (a) LDA, THF, −78 °C, 30 min; 77%; (b) $NaBH_4$, MeOH, rt, 5 min; 98%; (c) TFA, $CHCl_3$, 0 °C, 3 h; 88%.

tive acylation at C-4 and C-6. Exposure of **4** to an excess of BBr_3 led to cleavage of both methoxy groups as well as the C-7′ phenoxy group, leading to **5** in quantitative yield. Introduction of the reactive primary alkyl bromide function at C-7′ at such an early stage carried the risk of frustrating our plans by limiting our options. While the presence of the bromide had to be taken into consideration at each step, we were able to design combinations of reagent, solvent, and reaction conditions to suppress or limit any interference from this functional group. This is reflected in the uniformly high yields for each of the subsequent steps in the synthesis. Selective protection of one of the phenolic hydroxyl groups in **5** under phase transfer conditions led to mono-allyl ether **6** in 77% yield.

The keto group in **6** provides the functionality to join the two large fragments of the target (Scheme 2). The synthesis of aldehyde **7** has been described. We had predicted that the primary bromide function in **6** would not interfere with the very fast aldol coupling reaction with **7**. This proved to be the case, since aldol adduct **8** was formed in 77% yield. It was, however, necessary to quench the aldol reaction with aqueous acetic acid prior to workup so as to suppress the base-catalyzed retro-aldol fragmentation of **8** back to **6** and **7**. Reduction of **8** with sodium borohydride in methanol led to diol **9** as a mixture of two diastereomers. No attempt was made to separate these isomers. Rather, the mixture was treated at 0 °C with trifluoroacetic acid in chloroform to produce a 1:1 mixture of C-9 diastereoisomers **10** in 88% yield. That the products of the cyclization reaction differed only at C-9 was demonstrated by oxidizing the C-9 equatorial isomer of **10** to the C-9 ketone with the Dess−Martin periodinane[15] (81% yield), then reducing the ketone with L-Selectride to the C-9 axial isomer of **10** (89% yield).[16]

The mechanism of the cyclization reaction leading to **10** can be thought of either as an intramolecular Diels−Alder reaction of a transiently formed *o*-quinone methide or as a cation-olefin cyclization process. The stereospecificity of the process in which the stereochemistry at C-6, C-6a, and C-10a are formed in a controlled fashion, suggests a fast, possibly synchronous, process and does not support the intermediacy of long-lived cationic intermediates. The cyclization reaction assembles the tricyclic cannabinoid skeleton with control of the ring junction stereochemistry and also the critical stereochemistry at C-6. What remained to be accomplished was the delicate task of introducing the sensitive functionality at C-7′ and C-1″. After several unsuccessful forays, we settled on the approach that is summarized in Scheme 3.

Oxidation of the C-9 diastereomer of **10** with the Dess−Martin reagent led to ketone **11** in 81% yield. It was now necessary to remove the allyl protecting group. The reductive protocol that makes use of borohydride and Pd(0) had served us well in the past, but the C-9 keto group interfered by undergoing reduction back to the alcohol.[17] Moreover, once the phenolic hydroxyl group is unmasked, it is not possible to reoxidize C-9 for the reason indicated in the Introduction. Consequently, C-9 was first protected as dimethyl ketal **12**, then the allyl protecting group was removed to give **13**. Although nonreductive methods are known for removing the allyl protecting group, these typically require activation of the ether through complexation with a Lewis acid, followed by nucleophilic cleavage of the allyl group.[18] These conditions are incompatible with the sensitive tertiary propargyl ether function that is present in **11**. The sequence in which the subsequent reactions were carried out was critical. Displacement of the bromide in **13** by tetramethylguanidinium azide led to C-7′ azide **14** in quantitative yield.[19] Exposure of this material first to triphenyl phosphine, then to carbon disulfide converted azide to isothiocyanate, leading to **15** in 93% yield.[20]

Our next task was to remove both the ketal and silyl ether protecting groups. We had surmised that once the propargyl iodide was present, our options would be limited by the lability of this group. Hydrolytic removal of the dimethyl ketal would have to be carried out before introduction of the iodide. Luckily, simultaneous removal of both protecting groups could be accomplished in good yield (76%) by exposure of **15** to oxalic acid in aqueous THF at room temperature for 18 h. The two free hydroxyl functions in ketodiol **16** presented us with a potential problem, as the next step required us to selectively functionalize the propargyl alcohol. We had hoped to convert alcohol to iodide by exposure of **16** to the combination of iodine, triphenylphosphine, and imidazole.[21] After many failures to do so, we settled on a two-step sequence, whereby the alcohol was first converted to mesylate **17**, and the mesylate displaced by iodide. This led in excellent overall yield to our target cannabinoid.

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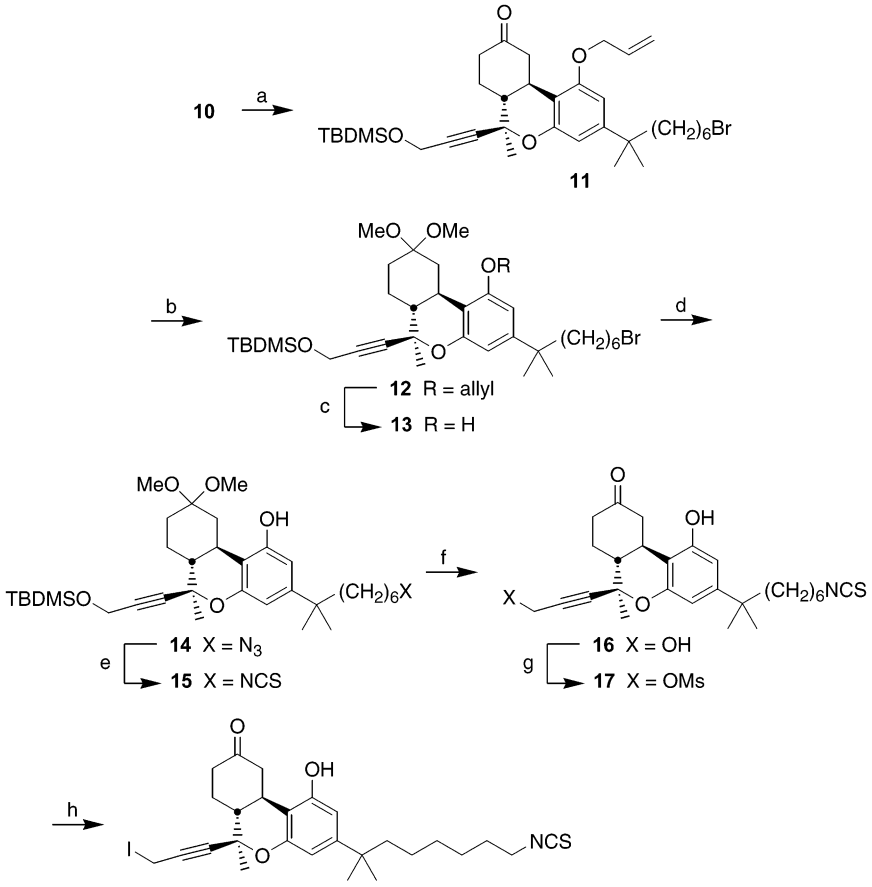
SCHEME 3[a]



[a] (a) Dess−Martin periodinane, CH_2Cl_2, 0 °C to rt, 3 h; 81%; (b) $HC(OMe)_3$, $Yb(OTf)_3$, MeOH, rt, 12 h; 73%; (c) $Pd(PPh)_4$, $NaBH_4$, THF, rt, 14 h; 85%; (d) $TMGN_3$, $MeNO_2$, 50 °C, 3 h; 100%; (e) PPh_3, PhH, 50 °C, 1 h; CS_2, 50 °C, 2 h; 93%; (f) $(COOH)_2$, THF, H_2O, rt, 18 h; 76%; (g) MsCl, 2,6-lutidine, CH_2Cl_2, 0 °C to rt, 14 h; 93%; (h) NaI, acetone, reflux, 12 h; 79%.

Earlier experiments have shown that our target compound is indeed a successful covalent CB1 receptor probe. When tested on a membrane receptor preparation obtained from rat brains, our nonradiolabeled iodinated bifunctional ligand at a concentration of 25 nM was capable of irreversibly occupying approximately 50% of the CB1 binding sites. Details of this work will be reported elsewhere. We have also shown that the S_N2 reaction of iodide with the mesylate precursor proceeds at a satisfactory rate, thus ensuring that development of the ^{125}I-radiolabeled ligand is within reach.

Conclusions

The availability of a bifunctional high-affinity covalent probe for the CB1 receptor opens the door for a series of radiolabeling experiments that can greatly assist in identifying the binding site of cannabinoid ligands within this receptor. This task is currently being pursued using CB1 receptor preparations expressed in mammalian cell cultures. Furthermore, the chemistry discussed here demonstrates the versatility of the cyclization strategy that we have developed for accessing the multifunctional cannabinoid analogues. It is especially worthy of note that multiple sites of high reactivity can be built into the tricyclic cannabinoid scaffold.

Experimental Section

Proton and ^{13}C NMR spectra were recorded on a GE QE-300 spectrometer operating at 300 MHz (^{1}H) or 75 MHz (^{13}C), unless noted otherwise. Chemical shifts are reported in δ units and are referenced to solvent (7.26/77.0 for $CDCl_3$). Infrared spectra were recorded on a Perkin-Elmer IR 1430 spectrometer. EI mass spectra were obtained from a VG-70SE mass spectrometer. Purity and homogeneity of all materials was determined from TLC, ^{1}H NMR, ^{13}C NMR, and HPLC.

1-(3,5-Dimethoxyphenyl)-7-phenoxyheptan-1-one, 2. To a suspension of 885 mg (36.4 mmol) of magnesium turnings in 22.5 mL of THF at room temperature was added dropwise over 1 h a solution of 7.040 g (27.3 mmol) of 6-phenoxyhexyl bromide in 18 mL of THF. The mixture was stirred for 30 min, during which time heat was evolved and a gray suspension was formed. The solution was cooled to 0 °C, and to the cooled suspension was added neat Weinreb amide **1** (4.100 g, 18.2 mmol). The reaction mixture was stirred for 6 h at room temperature and then quenched by addition of 1 M HCl. The aqueous phase was separated and extracted with ether (3 × 100 mL) followed by brine (3 × 100 mL), then dried over $MgSO_4$, filtered, and concentrated to give a pale yellow solid (7.423 g). Flash column chromatography on silica gel afforded pure phenone **2** (4.642 g, 75% yield) as a white solid: mp 51−52 °C; R_f = 0.32 (15% EtOAc in hexanes); ^{1}H NMR ($CDCl_3$) δ 7.27 (t, J = 8.0 Hz, 1H), 7.10 (d, J = 2.4 Hz, 2H), 6.94−6.88 (m, 4H), 6.65 (t, J = 2.4 Hz, 1H), 3.96 (t, J = 7.0 Hz, 2H), 3.84 (s, 6H), 2.94 (t, J = 7.0 Hz, 2H), 1.78 (quint, J = 7.0 Hz, 4H), 1.56−1.45 (m, 4H), 1.18−1.12 (m, 2H); ^{13}C NMR ($CDCl_3$) δ

200.0, 160.8, 159.1, 139.0, 129.4, 120.5, 114.5, 105.9, 105.1, 67.7, 55.6 (2× OCH_3), 38.6, 29.1, 29.0, 25.9, 24.3; IR (neat) 3932, 2857, 1734, 1684, 1600, 1464, 1420, 1307, 1249, 1152, 1065 cm^{-1}; mass spectrum (EI) *m/z* 342 (M^+, 14), 249 (M^+ − OPh, 11), 180 (47), 165 (100), 152 (23), 137 (33), 122 (24), 94 (34), 77 (24); exact mass calcd for $C_{21}H_{26}O_4$ 342.1831, found 342.1840.

[7-(3,5-Dimethoxyphenyl)-7-methyloctyloxy]benzene, 3. To a solution of 0.66 mL (6.0 mmol) of $TiCl_4$ in 12 mL of CH_2Cl_2 at −30 °C was added dropwise 3.0 mL of a 2.0 M solution of dimethylzinc in toluene. The solution was stirred at −30 °C for 30 min, and to this mixture was added a cooled (−30 °C) solution of phenone **2** (1.027 g, 3.0 mmol) in 12 mL of CH_2Cl_2. The reaction mixture was warmed to room temperature, stirred for 6 h, and quenched by slowly pouring into ice/saturated aqueous $NaHCO_3$ solution. Acidification with 1 M HCl solution was followed by extraction of the aqueous phase with ether (3 × 50 mL). The combined organic extracts were washed with brine (3 × 50 mL), dried ($MgSO_4$), filtered, and evaporated to produce 1.183 g of crude product. Purification by flash column chromatography on silica gel afforded pure product **3** as a pale yellow oil (902 mg, 84% yield): R_f = 0.54 (15% EtOAc in hexanes); ^{1}H NMR ($CDCl_3$) δ 7.30 (t, J = 8.0 Hz, 1H), 6.97−6.90 (m, 4H), 6.53 (d, J = 2.2 Hz, 2H), 6.34 (t, J = 2.2 Hz, 1H), 3.94 (t, J = 7.0 Hz, 2H), 3.82 (s, 6H), 1.75 (quint, J = 7.0 Hz, 2H), 1.64−1.59 (m, 2H), 1.43 (quint, J = 7.0 Hz, 2H), 1.34−1.26 (m, 2H), 1.30 (s, 6H), 1.18−1.12 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 160.4, 159.1, 152.4, 129.3, 120.4, 114.4, 104.6, 96.6, 67.7, 55.1, 44.4, 37.9, 30.0, 29.2, 28.9, 25.9, 24.6; IR (neat) 2932, 2857, 1599, 1496, 1456, 1421, 1244, 1204, 1155, 1054 cm^{-1}; mass spectrum (EI) *m/z* 356 (M^+, 14), 263 (M^+ − OPh, 23), 180 (100), 165 (17), 151 (22), 139 (20), 94 (20), 75 (24); exact mass calcd for $C_{23}H_{32}O_3$ 356.2351, found 356.2354.

1-[4-(1,1-Dimethyl-7-phenoxyheptyl)-2,6-dimethoxyphenyl]ethan-1-one, 4. To a solution of 1.780 g (5.0 mmol) of dimethoxy aromatic compound **3** in 50 mL of nitromethane at room temperature was added 620 mg (1.0 mmol) of ytterbium triflate in a single portion. To the resulting suspension was added dropwise 2.36 mL (25.0 mmol) of acetic anhydride, and the reaction mixture was stirred at room temperature for 14 h. The reaction was quenched by addition of saturated aqueous $NaHCO_3$ solution. The aqueous phase was extracted with ether (3 × 100 mL), the combined organic extracts were washed first with saturated aqueous $NaHCO_3$ solution (3 × 50 mL), followed by brine (3 × 50 mL), and then dried ($MgSO_4$), filtered, and concentrated to give the crude product as a dark brown oil (2.166 g). Purification by flash column chromatography on silica gel afforded pure **4** as a yellow oil (1.509 g, 76% yield): R_f = 0.30 (10% EtOAc in hexanes); ^{1}H NMR ($CDCl_3$) δ 7.29−7.25 (m, 2H), 6.92 (t, J = 7.6 Hz, 1H), 6.88 (t, J = 7.6 Hz, 2H), 6.50 (s, 2H), 3.92 (t, J = 7.0 Hz, 2H), 3.80 (s, 6H), 2.48 (s, 3H), 1.73 (quint, J = 7.0 Hz, 2H), 1.61−1.57 (m, 2H), 1.40 (quint, J = 7.0 Hz, 2H), 1.31−1.24 (m, 2H), 1.28 (s, 6H), 1.13−1.05 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 202.96, 159.0, 156.5, 153.4, 129.4, 120.4, 118.0, 114.4, 101.9, 67.7, 55.8 (2x OCH_3), 44.4, 38.4, 32.4, 30.0, 29.2, 28.9, 25.9, 24.6; IR (neat) 2934, 2859, 1701, 1604, 1576, 1497, 1459, 1406, 1242, 1127, 1032 cm^{-1}; mass spectrum (EI) *m/z* 398 (M^+, 16), 383 (M^+ − CH_3, 46), 305 (M^+ − OPh, 16), 222 (100), 207 (18), 179 (14), 94 (27), 91 (11); exact mass calcd for $C_{25}H_{34}O_4$ 398.2457, found 398.2467.

1-[4-(7-Bromo-1,1-dimethylheptyl)-2,6-dihydroxyphenyl]ethan-1-one, 5. To a solution of 996 mg (2.5 mmol) of phenone **4** in 5 mL of CH_2Cl_2 at −78 °C was added 12.5 mL of a 1 M solution of BBr_3 in CH_2Cl_2. The reaction mixture was slowly warmed to room temperature and stirred for 26 h. Quenching by careful addition of saturated aqueous $NaHCO_3$ solution at 0 °C was followed by extraction of the aqueous phase with ether (3 × 30 mL). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ solution (3 × 30 mL), followed by brine (3 × 30 mL), then dried ($MgSO_4$), filtered, and concentrated to give the crude product as a deep orange oil (1.073 g). Distillation of the volatiles (Kugelrohr apparatus) yielded a residue of the product **5** (893 mg, 100% yield). No further purification was performed, and the product was carried to the next step. Phenone **5**: R_f = 0.13 (10% EtOAc in hexanes); ^{1}H NMR ($CDCl_3$) δ 9.5−9.1 (br s, 2H), 6.35 (s, 2H), 3.37 (t, J = 7.2 Hz, 2H), 2.71 (s, 3H), 1.79 (quint, J = 7.2 Hz, 2H), 1.56−1.51 (m, 2H), 1.36 (quint, J = 7.2 Hz, 2H), 1.27−1.19 (m, 2H), 1.22 (s, 6H), 1.10−1.02 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 204.3, 160.9, 159.5, 108.1, 106.3, 43.8, 38.2, 34.0, 33.1, 32.7, 29.3, 28.4, 24.4; IR (neat) 3310, 2932, 2860, 1636, 1588, 1421, 1375, 1264, 1069 cm^{-1}; mass spectrum (EI) *m/z* 358, 356 (M^+, 3), 277 (M^+ − Br, 7), 228 (5), 194 (93), 179 (25), 109 (6), 84 (100); exact mass calcd for $C_{17}H_{25}BrO_3$ 356.0987, found 356.0984.

1-[2-Allyloxy-4-(7-bromo-1,1-dimethylheptyl)-6-hydroxyphenyl]ethanone, 6. To a solution of the resorcinol **5** from the preceding reaction in 10 mL of CH_2Cl_2/water (10:7, v/v) was added a large excess of allyl bromide at room temperature. To this mixture was added 1.64 mL of a 40 wt % solution of nBu$_4$NOH in water, and the reaction mixture was stirred vigorously for 24 h. Quenching with 1 M HCl was followed by extraction of the aqueous phase with ether (3 × 25 mL). The combined organic extracts were washed with brine (3 × 25 mL), dried ($MgSO_4$), filtered, and concentrated to give the crude product as a dark brown oil (961 mg). Purification by flash column chromatography afforded pure **6** as a pale yellow oil (761 mg, 77% yield): R_f = 0.52 (10% EtOAc in hexanes); ^{1}H NMR ($CDCl_3$) δ 6.53 (d, J = 1.5 Hz, 1H), 6.33 (d, J = 1.5 Hz, 1H), 6.09 (ddt, J = 17.4, 10.5, 5.4 Hz, 1H), 5.43 (dd, J = 17.4, 1.2 Hz, 1H), 5.34 (dd, J = 10.5, 1.2 Hz, 1H), 4.63 (d, J = 5.4 Hz, 2H), 3.37 (t, J = 7.1 Hz, 2H), 2.68 (s, 3H), 1.79 (quint, J = 7.1 Hz, 2H), 1.60−1.54 (m, 2H), 1.36 (quint, J = 7.1 Hz, 2H), 1.26−1.19 (m, 2H), 1.20 (s, 6H), 1.10−1.04 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 204.4, 164.4, 160.1, 159.2, 132.7, 118.6, 109.4, 108.6, 100.5, 69.7, 43.9, 38.6, 33.9, 33.6, 32.7, 29.4, 28.4, 24.5; IR (neat) 3214, 2933, 2860, 1634, 1564, 1463, 1417, 1372, 1307, 1222, 1102 cm^{-1}; mass spectrum (EI) *m/z* 398, 396 (M^+, 7), 317 (M^+ − Br, 16), 275 (6), 234 (100), 219 (13), 193 (47), 165 (39), 149 (14), 121 (8), 82 (29); exact mass calcd for $C_{20}H_{29}BrO_3$ 396.1300, found 396.1281.

Phenone 8. A solution of LDA was prepared from 320 μL of diisopropylamine (2.42 mmol) and 990 μL of a 2.38 M solution of *n*-BuLi in 4.5 mL of THF at −78 °C. To the LDA solution was added dropwise a solution of 480 mg (1.21 mmol) of phenone **6** in 1.5 mL of THF, and the mixture was allowed to react for 30 min. To the reaction mixture was added dropwise a solution of 293 mg (1.10 mmol) of aldehyde **7** in 1.5 mL of THF. Stirring for another 30 min was followed by warming of the mixture to 5 °C and quenching by addition of 280 μL of acetic acid. The reaction mixture was partitioned between ether and water, and the aqueous layer was extracted with ether (3 × 15 mL). The combined ether extracts were washed with brine (3 × 15 mL), dried ($MgSO_4$), filtered, and concentrated to produce the crude product (895 mg). Purification by flash column chromatography on silica gel led to 562 mg of aldol product **8** (77% yield) as a pale yellow oil: R_f = 0.24 (10% EtOAc in hexanes); ^{1}H NMR ($CDCl_3$) δ 6.54 (d, J = 1.5 Hz, 1H), 6.32 (d, J = 1.5 Hz, 1H), 6.08 (ddt, J = 17.2, 10.5, 5.5 Hz, 1H), 5.84 (t, J = 7.5 Hz, 1H), 5.44 (dd, J = 17.2, 1.2 Hz, 1H), 5.37 (dd, J = 10.5, 1.2 Hz, 1H), 4.62 (d, J = 5.5 Hz, 2H), 4.42 (s, 2H), 4.19−4.13 (m, 1H), 3.37 (t, J = 6.7 Hz, 2H), 3.30 (dd, J = 18.5, 2.3 Hz, 1H), 3.13 (dd, J = 18.5, 9.3 Hz, 1H), 2.26−2.21(m, 2H), 1.83−1.52 (m, 6H), 1.80 (s, 3H), 1.36−0.97 (m, 6H), 1.24 (s, 6H), 0.91 (s, 9H), 0.13 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 206.3, 164.7, 160.2, 159.9, 137.4, 132.5, 119.1, 118.1, 109.0, 100.8, 88.0, 84.6, 69.9, 67.4, 52.4, 51.8, 44.0, 43.8, 38.8, 35.9, 33.9, 32.9, 29.5, 28.6, 28.2, 26.1, 24.74, 24.69, 18.5, 17.2, −4.8; IR (neat) 3422, 2929, 2857, 2248, 1626, 1600, 1563, 1462, 1412, 1371, 1256, 1222, 1096 cm^{-1}; mass spectrum (EI) *m/z* 646, 644 (M^+ − H_2O, 1), 589, 587 (M^+ − H_2O, *t*Bu, 11, 10),

396 (34), 341 (17), 317 (100), 275 (40); exact mass calcd for $C_{31}H_{44}BrO_4Si$ ($M^+ - H_2O$, *t*Bu) 587.2193, found 587.2206.

Triol 9. To a solution of 550 mg (0.83 mmol) of aldol product **8** in 11 mL of methanol was added 47 mg (1.24 mmol) of $NaBH_4$ in a single portion at room temperature. The reaction mixture was stirred for 5 min at room temperature and then quenched by the addition of 360 μL of acetic acid. The reaction mixture was stirred at room temperature for 30 min, then partitioned between ether and water. The aqueous layer was extracted with ether (3 × 15 mL), and the combined organic layers were washed with brine (3 × 20 mL), dried ($MgSO_4$), filtered, and concentrated to give the crude product (606 mg). Purification by simple filtration through a short plug of silica gel gave pure product **9** as a ca. 1:1 mixture of diastereoisomers (540 mg, 98% yield, colorless oil). Diasteroisomeric mixture **9**: R_f = 0.46 and 0.39 (20% EtOAc in hexanes); ^{1}H NMR ($CDCl_3$) δ 6.48 (d, J = 1.2 Hz, 2H), 6.33 (d, J = 1.4 Hz, 2H), 6.08−5.94 (m, 2H), 5.81 (dd, J = 17.2, 8.4 Hz, 2H), 5.71 (dd, J = 10.0, 2.0 Hz, 1H), 5.56 (dd, J = 9.0, 3.6 Hz, 1H), 5.41−4.34 (m, 2H), 5.29−5.25 (m, 2H), 4.51 (d, J = 5.0 Hz, 4H), 4.42 (s, 2H), 4.41 (s, 2H), 4.08−3.90 (m, 4H), 3.36 (t, J = 6.8 Hz, 4H), 2.20−2.12 (m, 4H), 1.83−1.48 (m, 12H), 1.78 (s, 3H), 1.77 (s, 3H), 1.40−1.16 (m, 8H), 1.22 (s, 12H), 1.14−0.99 (m, 4H), 0.91 (s, 12H), 0.13 (s, 6H), 0.12 (s, 6H); IR (neat) 3397, 2929, 2857, 2109, 1626, 1579, 1419, 1365, 1253, 1221, 1082 cm^{-1}; mass spectrum (EI) *m*/*z* 648, 646 ($M^+ - H_2O$, 1), 407 (18), 405 (17), 217 (23), 192 (25), 165 (14), 91 (26), 75 (100); exact mass calcd for $C_{35}H_{55}BrO_4Si$ ($M^+ - H_2O$) 646.3055, found 646.3050.

Cyclization to Form 10. To a solution of 197 mg (0.30 mmol) of the diastereomers of **9** in 15 mL of chloroform at 0 °C was added 37 mg (0.33 mmol) of trifluoroacetic acid dropwise. The reaction mixture was stirred at 0 °C for 3 h. Quenching with saturated aqueous $NaHCO_3$ solution was followed by extraction of the aqueous phase with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ solution (1 × 20 mL) and brine (3 × 20 mL), then dried ($MgSO_4$) and evaporated to give 183 mg of crude product. Purification by flash column chromatography on silica gel gave 86 mg of the α-C-9 diastereomer and 83 mg of the β-C-9 diastereomer, both as pale yellow oils (89% combined yield. α-C-9 diastereomer: R_f = 0.49 (20% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.48 (d, J = 1.3 Hz, 1H), 6.36 (d, J = 1.3 Hz, 1H), 6.07 (ddt, J = 17.2, 11.5, 5.1 Hz, 1H), 5.45 (dd, J = 17.2, 1.5 Hz, 1H), 5.28 (dd, J = 11.5, 1.5 Hz, 1H), 4.52 (d, J = 5.1 Hz, 2H), 4.42 (s, 2H), 4.23 (s, 1H), 3.36 (t, J = 6.9 Hz, 2H), 3.25 (d, J = 13.9 Hz, 1H), 2.99 (dt, J = 11.5, 7.8 Hz, 1H), 1.99 (t, J = 14.7 Hz, 2H), 1.87−1.48 (m, 10 H), 1.39 (s, 3H), 1.37−1.31 (m, 2H), 1.21 (s, 6H), 1.10−1.04 (m, 2H), 0.92 (s, 9H), 0.13 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 215.8, 157.4, 153.3, 149.7, 133.8, 117.2, 114.4, 108.9, 102.8, 86.3, 83.8, 74.8, 69.1, 67.1, 52.0, 48.5, 44.5, 27.9, 37.6, 34.2, 33.4, 29.6, 29.0, 28.8, 28.3, 26.1, 26.0, 24.7, 23.6, 19.8, −4.8; IR (neat) 3433, 2930, 2857, 2109, 1654, 1568, 1462, 1412, 1365, 1328, 1259, 1120, 1089 cm^{-1}. β-C-9 diastereomer: R_f = 0.39 (20% EtOAc in hexanes); ^{1}H NMR ($CDCl_3$) δ 6.48 (d, J = 1.5 Hz, 1H), 6.37 (d, J = 1.5 Hz, 1H), 6.07 (ddt, J = 16.9, 10.8, 5.3 Hz, 1H), 5.40 (dd, J = 16.9, 1.5 Hz, 1H), 5.28 (dd, J = 10.8, 1.5 Hz, 1H), 4.48 (d, J = 5.3 Hz, 2H), 4.41 (s, 2H), 4.12−4.04 (m, 1H), 3.43−3.37 (m, 1H), 3.33 (t, J = 7.0 Hz, 2H), 2.51 (dt, J = 11.2, 2.4 Hz, 1H), 2.21−2.16 (m, 2H), 1.84−1.47 (m, 10H), 1.34 (s, 3H), 1.40−1.04 (m, 4H), 1.21 (s, 6H), 0.91 (s, 9H), 0.13 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 223.2, 157.5, 153.4, 150.0, 133.8, 117.3, 108.8, 102.7, 86.4, 83.9, 74.7, 71.0, 69.1, 52.0, 47.7, 44.5, 39.6, 37.9, 35.9, 34.2, 33.1, 33.0, 29.6, 29.0, 28.3, 28.1, 27.1, 26.0, 24.7, 19.7, −4.8; IR (neat) 3433, 2930, 2857, 2109, 1654, 1568, 1462, 1412, 1365, 1328, 1259, 1120, 1089 cm^{-1}; mass spectrum (EI) *m*/*z* 648, 646 (M^+, 1), 630, 628 ($M^+ - H_2O$, 1), 548 (1), 484 (2), 445 (5), 407 (17), 405 (17), 217 (23), 192 (25), 75 (100); exact mass calcd for $C_{35}H_{55}BrO_4Si$ 646.3053, found 646.3050.

C-9 Ketone 11. To a solution of 60 mg (0.09 mmol) of the α-C-9 diastereoisomer of 10 at 0 °C in 3.6 mL of CH_2Cl_2 was added 79 mg (0.19 mmol) of the Dess−Martin periodinane in a single portion. The reaction mixture turned orange, and a white precipitate was formed. The reaction mixture was allowed to slowly warm to room temperature, and stirring was continued at room temperature for 3 h. The reaction was quenched by the addition of saturated aqueous $NaHCO_3$ solution and 90 mg of solid $Na_2S_2O_3$. After 5 min the two-phase mixture was diluted with CH_2Cl_2 and water. The aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL), and the combined organic extracts were washed with brine (3 × 15 mL), dried ($MgSO_4$), and concentrated to give 61 mg of crude product. Purification by flash column chromatography on silica gel gave 49 mg (81% yield) of pure **11** as a pale yellow oil: R_f = 0.25 (10% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.51 (s, 1H), 6.38 (s, 1H), 6.06 (ddt, J = 17.4, 10.5, 5.4 Hz, 1H), 5.39 (dd, J = 17.4, 1.0 Hz, 1H), 5.29 (dd, J = 10.5, 1.0 Hz, 1H), 4.53 (d, J = 5.4 Hz, 2H), 4.43 (s, 2H), 3.82 (d, J = 14.0 Hz, 1H), 3.36 (t, J = 6.8 Hz, 2H), 2.88 (dt, J = 12.0, 3.2 Hz, 1H), 2.62−2.40 (m, 2H), 2.28 (t, J = 11.0 Hz, 1H), 2.13 (t, J = 14.0 Hz, 1H), 1.79 (quint, J = 7.2 Hz, 2H), 1.60−1.49 (m, 2H), 1.40 (s, 3H), 1.38−1.32 (m, 2H), 1.30−1.17 (m, 2H), 1.22 (s, 6H), 1.10−1.04 (m, 2H), 0.92 (s, 9H), 0.90−0.86 (m, 2H), −0.14 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 210.5, 157.0, 152.6, 150.5, 133.2, 117.6, 109.0, 108.6, 102.5, 85.5, 84.0, 74.3, 68.9, 51.7, 46.5, 45.6, 44.2, 40.8, 37.8, 33.9, 33.8, 32.8, 29.4, 28.8, 28.7, 28.0, 27.4, 25.8, 24.4, 19.3, 18.2, −5.1; IR (neat) 2932, 2857, 2109, 1715, 1649, 1614, 1571, 1461, 1414, 1361, 1252, 1096, 1059 cm^{-1}; mass spectrum (EI) *m*/*z* 646, 644 (M^+, 11), 587 (3), 565 (3), 482 (11), 105 (16), 83 (16), 75 (100); exact mass calcd for $C_{35}H_{53}BrO_4Si$ 644.2896, found 644.2896.

Dimethyl Acetal 12. To a solution of 55 mg (85 μmol) of ketone **11** in 3.5 mL of methanol was added 350 μL of trimethyl orthoformate dropwise at room temperature. To this mixture was added 5 mg (ca. 8.5 μmol) of ytterbium triflate in a single portion, and stirring was continued at room temperature for 12 h. The reaction was quenched by addition of saturated aqueous $NaHCO_3$ solution, and the mixture was diluted with water and ether. The aqueous layer was extracted with ether (3 × 5 mL), and the combined organic phase was washed with saturated aqueous $NaHCO_3$ solution (1 × 5 mL) followed by brine (3 × 5 mL). Drying (K_2CO_3), filtration, and evaporation of the solvent gave the crude product. Purification by flash column chromatography on silica gel led to 43 mg (73% yield) of pure acetal **12** as a pale yellow oil: R_f = 0.48 (10% EtOAc in hexanes); ^{1}H NMR ($CDCl_3$) δ 6.51 (d, J = 1.6 Hz, 1H), 6.38 (d, J = 1.6 Hz, 1H), 6.09 (ddt, J = 17.0, 10.8, 5.6 Hz, 1H), 5.45 (dd, J = 17.0, 1.3 Hz, 1H), 5.28 (dd, J = 10.8, 1.3 Hz, 1H), 4.53 (d, J = 5.6 Hz, 2H), 4.44 (s, 2H), 3.54−3.47 (m, 1H), 3.39 (t, J = 6.8 Hz, 2H), 3.29 (s, 3H), 3.26 (s, 3H), 2.64 (dt, J = 11.6, 2.3 Hz, 1H), 2.25−2.10 (m, 2H), 1.92−1.78 (m, 1H), 1.69−1.64 (m, 2H), 1.58−1.21 (m, 7H), 1.39 (s, 3H), 1.24 (s, 6H), 1.16−1.05 (m, 2H), 0.95−0.88 (m, 2H), 0.94 (s, 9H), 0.09 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 157.5, 152.8, 149.8, 133.7, 118.0, 110.2, 108.9, 102.5, 100.7, 86.4, 83.8, 74.7, 69.4, 52.0, 48.2, 47.9, 44.5, 37.9, 36.5, 33.9, 33.6, 30.6, 29.9, 29.6, 29.0, 28.3, 25.5, 24.7, 19.8, 18.4, −4.8; IR (neat) 2930, 2855, 2109, 1613, 1569, 1459, 1412, 1362, 1250, 1099, 1050 cm^{-1}; mass spectrum (EI) *m*/*z* 692, 690 (M^+, 2,3), 660 (3), 619 (9), 496 (7), 262 (10), 183 (16), 149 (30), 69 (100); exact mass calcd for $C_{37}H_{59}BrO_5Si$ 690.3315, found 690.3317.

Phenol 13. To a solution of 200 mg (0.31 mmol) of dimethyl acetal **12** in 20 mL of THF at room temperature was added 36 mg (ca. 0.03 mmol) of $Pd(PPh_3)_4$ and 117 mg (3.1 mmol) of sodium borohydride. The reaction mixture was stirred at room temperature for 14 h and was then quenched by addition of saturated aqueous KH_2PO_4 solution. The mixture was neutralized with saturated aqueous $NaHCO_3$ solution, and the aqueous layer was extracted with ether (3 × 20 mL). The combined organic extracts were washed with brine (3 × 20 mL), dried (K_2CO_3), filtered, and concentrated to give the crude product. Purification by flash column chromatography on silica gel gave 158 mg (79% yield) of pure **13** as a pale yellow oil: R_f = 0.15

(10% EtOAc in hexanes); ^{1}H NMR ($CDCl_3$) δ 6.44 (d, J = 1.7 Hz, 1H), 6.20 (d, J = 1.5 Hz, 1H), 5.16 (br s, 1H), 4.41 (s, 2H), 3.54 (d, J = 13.7 Hz, 1H), 3.37 (t, J = 6.8 Hz, 2H), 3.29 (s, 3H), 3.28 (s, 3H), 2.63 (dt, J = 10.3, 3.8 Hz, 1H), 2.24−2.07 (m, 2H), 1.90−1.73 (m, 1H), 1.67−1.43 (m, 7H), 1.38 (s, 3H), 1.35−1.04 (m, 6H), 1.19 (s, 6H), 0.91 (s, 9H), 0.13 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 154.6, 153.4, 150.0, 108.2, 107.9, 105.8, 100.9, 86.1, 83.6, 74.5, 51.8, 47.7, 47.6, 44.2, 37.3, 36.3, 35.4, 34.0, 33.3, 32.8, 30.7, 29.4, 28.7, 28.6, 28.0, 25.8, 25.2, 24.4, 19.6, 18.2, −5.1; IR (neat) 3324, 2931, 2856, 1622, 1576, 1459, 1414, 1363, 1254, 1092, 1054 cm^{-1}; mass spectrum (EI) m/z 620, 618 (M^+ − MeOH, 14, 13), 563 (12), 561 (12), 479 (12), 477 (12), 456 (28), 383 (13), 381 (10), 323 (18), 159 (38), 73 (100); exact mass calcd for $C_{33}H_{51}BrO_4Si$ (M^+ − MeOH) 618.2741, found 618.2782.

Azide 14. To a solution of 152 mg (0.23 mmol) of bromide **13** in 12.5 mL of CH_2Cl_2 was added 55 mg (0.35 mmol) of tetramethylguanidinium azide in a single portion at room temperature. The reaction mixture was stirred at 50 °C for 3 h and was subsequently cooled to room temperature. The workup consisted of solvent evaporation followed by filtration of the residue through a short plug of silica gel eluting with ether. This removed the tetramethylguanidinium salt and afforded pure azide **14** (156 mg, 100% yield) as a colorless oil following solvent evaporation. Azide **14**: R_f = 0.18 (10% EtOAc in hexanes); ^{1}H NMR ($CDCl_3$) δ 6.46 (d, J = 1.7 Hz, 1H), 6.23 (d, J = 1.5 Hz, 1H), 5.29 (br s, 1H), 4.43 (s, 2H), 3.58−3.50 (m, 1H), 3.31 (s, 3H), 3.29 (s, 3H), 3.24 (t, J = 7.2 Hz, 2H), 2.65 (dt, J = 11.3, 2.1 Hz, 1H), 2.27−2.09 (m, 2H), 1.89 (dt, J = 11.7, 2.2 Hz, 1H), 1.66−1.38 (m, 7H), 1.45 (s, 3H), 1.32−1.06 (m, 6H), 1.27 (s, 6H), 0.94 (s, 9H), 0.15 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 154.6, 153.4, 150.0, 108.1, 107.9, 105.7, 101.1, 86.0, 83.5, 74.5, 51.8, 47.7, 47.5, 44.2, 37.3, 35.3, 33.3, 30.6, 29.7, 28.7, 28.6, 26.5, 25.8, 25.2, 24.4, 19.6, 18.2, −5.1; IR (neat) 3324, 2932, 2861, 2095, 1623, 1577, 1458, 1414, 1364, 1258, 1138, 1093, 1043 cm^{-1}; mass spectrum (EI) m/z 581 (M^+ − OMe, 1), 553 (2), 540 (7), 494 (8), 456 (8), 393 (11), 303 (15), 277 (15), 239 (10), 159 (30), 75 (100); exact mass calcd for $C_{33}H_{51}N_3O_4Si$ (M^+ − OMe) 581.3651, found 581.3539.

Isothiocyanate 15. To a solution of 147 mg (0.24 mmol) of azide **14** in 10.5 mL of benzene was added 69 mg (0.26 mmol) of PPh_3 in a single portion at room temperature. The reaction mixture was stirred at 50 °C for 1 h and was subsequently cooled to room temperature. To the mixture was added dropwise 37 mg (0.48 mmol) of carbon disulfide and the mixture stirred at 50 °C for 2 h. The solvent was evaporated and the crude product purified by flash column chromatography on silica gel to provide 140 mg (93% yield) of pure isothiocyanate **15** as a colorless oil: R_f = 0.34 (10% EtOAc in hexanes); ^{1}H NMR ($CDCl_3$) δ 6.41 (d, J = 1.7 Hz, 1H), 6.20 (d, J = 1.7 Hz, 1H), 6.00 (br s, 1H), 4.41 (s, 2H), 3.65 (d, J = 13.7 Hz, 1H), 3.45 (t, J = 6.6 Hz, 2H), 3.31 (s, 3H), 3.30 (s, 3H), 2.61 (dt, J = 11.7, 2.2 Hz, 1H), 2.25−2.09 (m, 2H), 1.85 (dt, J = 11.5, 2.0 Hz, 1H), 1.65−1.45 (m, 7H), 1.38 (s, 3H), 1.35−1.04 (m, 6H), 1.18 (s, 6H), 0.91 (s, 9H), 0.13 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 154.6, 153.4, 149.9, 129.6, 108.3, 108.0, 105.8, 100.8, 86.1, 83.7, 74.6, 51.8, 45.0, 47.74, 47.70, 47.6, 45.0, 44.2, 37.3, 35.5, 33.3, 30.7, 29.8, 29.3, 28.7, 28.6, 26.4, 25.8, 25.2, 24.3, 19.6, 18.2, −5.1; IR (neat) 3324, 2931, 2859, 2184, 2101, 1624, 1578, 1456, 1414, 1360, 1258, 1138, 1093, 1043 cm^{-1}; mass spectrum (EI) m/z 526 (M^+ − OMe, CH_2NCS, 8), 412 (3), 378 (4), 184 (20), 105 (22), 75 (100); exact mass calcd for $C_{32}H_{50}O_4Si$ (M^+ − OMe, CH_2NCS) 526.2355, found 526.2355.

Ketodiol 16. To a solution of 55 mg (87 μmol) of **15** in 10.4 mL of THF and 2.0 mL of water was added 110 mg (87 μmol) of oxalic acid in a single portion at room temperature. The reaction mixture was stirred at room temperature for 18 h and was subsequently quenched by addition of saturated aqueous $NaHCO_3$ solution. The aqueous phase was extracted with ether (3 × 10 mL), and the combined organic extracts were washed with saturated aqueous $NaHCO_3$ solution (3 × 15 mL) and brine (3 × 15 mL) and were then dried ($MgSO_4$). Filtration and solvent evaporation gave the crude product, which was purified by flash column chromatography on silica gel to give 34 mg (76% yield) of pure **16** as a colorless oil: R_f = 0.15 (30% EtOAc in hexanes); ^{1}H NMR ($CDCl_3$) δ 6.48 (d, J = 1.7 Hz, 1H), 6.39 (d, J = 1.7 Hz, 1H), 4.42 (s, 2H), 4.07 (d, J = 15.1 Hz, 1H), 3.49 (t, J = 13.2 Hz, 2H), 2.94 (dt, J = 12.0, 3.0 Hz, 1H), 2.71−2.48 (m, 2H), 2.34 (dt, J = 11.8, 1.8 Hz, 1H), 2.21 (dt, J = 13.9, 1.7 Hz, 1H), 1.76−1.50 (m, 6H), 1.45 (s, 3H), 1.39−1.02 (m, 6H), 1.23 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 212.7, 154.8, 152.8, 150.9, 129.5, 107.6, 107.2, 106.2, 86.6, 83.5, 74.3, 51.1, 46.2, 45.0, 44.8, 44.1, 40.8, 37.4, 33.8, 29.8, 29.3, 28.8, 28.6, 27.5, 26.4, 24.3, 19.6; IR (neat) 2933, 2857, 2184, 2104, 1702, 1615, 1570, 1462, 1414, 1360, 1259, 1098, 1050 cm^{-1}; mass spectrum (EI) m/z 468 (M^+ − H, 1), 412 (M^+ − SCN, 5), 328 (10), 289 (7), 178 (11), 148 (89), 69 (100); exact mass calcd for $C_{27}H_{34}NO_4S$ (M^+ − H) 468.2209, found 468.2564.

Mesylate 17. To a solution of 7.5 mg (14.5 μmol) of ketodiol **16** at 0 °C in 0.5 mL of CH_2Cl_2 was added 3.5 μL (2.1 equiv) of 2,6-lutidine followed by methanesulfonyl chloride (0.5 mL of a 0.35 μM solution in CH_2Cl_2, 1.2 equiv). The reaction mixture was stirred at 0 °C for 3 h and then at room temperature for 12 h. Solvent evaporation was followed by flash column chromatography on silica gel to give ca. 8 mg (93% yield) of pure mesylate **17** as an oil: R_f = 0.32 (20% EtOAc in hexanes); ^{1}H NMR ($CDCl_3$) δ 6.45 (d, J = 1.7 Hz, 1H), 6.38 (d, J = 1.7 Hz, 1H), 4.98 (s, 2H), 4.06 (d, J = 14.9 Hz, 1H), 3.49 (t, J = 7.0 Hz, 2H), 3.18 (s, 3H), 2.94 (dt, J = 12.1, 3.0 Hz, 1H), 2.73−2.43 (m, 2H), 2.39−2.16 (m, 2H), 1.67−1.51 (m, 6H), 1.46 (s, 3H), 1.39−1.04 (m, 6H), 1.23 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 212.1, 154.8, 152.5, 151.0, 129.5, 107.5, 107.1, 106.4, 90.5, 74.2, 65.8, 60.4, 57.2, 46.0, 45.0, 44.8, 44.1, 40.7, 37.4, 33.7, 29.8, 29.3, 28.7, 28.6, 27.4, 26.3, 19.3; IR (neat) 3279, 2933, 2857, 2184, 2102, 1700, 1684, 1653, 1623, 1576, 1506, 1457, 1414, 1369, 1256, 1174, 1095, 1033 cm^{-1}.

Bifunctional Cannabinoid. To a solution of 11 mg (ca. 19 μmol) of mesylate **17** in 0.8 mL of anhydrous acetone was added 12 mg (4 equiv) of NaI in a single portion. The reaction mixture was heated to reflux for 12 h, then the solvents were evaporated. The crude product was dissolved in CH_2Cl_2, and the inorganic precipitate was filtered off. Concentration of the filtrate followed by flash column chromatography on silica gel gave ca. 9.5 mg of the desired product as an oil (79% yield): R_f = 0.28 (10% EtOAc in hexanes); ^{1}H NMR ($CDCl_3$) δ 6.48 (d, J = 1.7 Hz, 1H), 6.38 (d, J = 1.7 Hz, 1H), 4.42 (s, 2H), 4.05 (dd, J = 13.7, 1.2 Hz, 1H), 3.49 (t, J = 6.6 Hz, 2H), 2.93 (dt, J = 11.7, 3.4 Hz, 1H), 2.71−2.47 (m, 2H), 2.37−2.16 (m, 2H), 1.76−1.49 (m, 6H), 1.45 (s, 3H), 1.30−1.03 (m, 6H), 1.23 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 212.2, 154.6, 152.8, 150.9, 129.5, 107.8, 107.3, 106.2, 86.4, 83.5, 74.3, 51.1, 46.2, 45.0, 44.9, 44.1, 40.8, 37.4, 33.8, 29.8, 29.3, 28.7, 28.6, 27.5, 26.3, 24.3, 19.5; IR (neat) 3354, 2932, 2857, 2184, 2101, 1702, 1621, 1579, 1462, 1415, 1360, 1333, 1259, 1178, 1096, 1034 cm^{-1}; mass spectrum (EI) m/z 452 (M^+ − I, 1), 412 (M^+ − I, SCN, 4), 328 (8), 289 (7), 148 (89), 69 (100).

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Supporting Information Available: Spectroscopic data (^{13}C NMR) for **2**−**6**, **8**−**11**, **13**−**17**, and the bifunctional cannabinoid. This material is available free of charge via the Internet at http://pubs.acs.org.

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