5656 J. Med. Chem. 2010, 53, 5656–5666
DOI: 10.1021/jm100390h

Journal of Medicinal Chemistry Article

Heteroadamantyl Cannabinoids

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Received March 30, 2010

The aliphatic side chain plays a pivotal role in determining the cannabinergic potency of tricyclic classical cannabinoids. We have synthesized a series of analogues in which the C3 position is substituted either directly or through a one-carbon atom linker with an adamantylamine or with an oxa- or an oxazaadamantane. The oxaadamantane pharmacophore in analogue **16** showed the best binding profile for both receptors.

Introduction

The discovery of the two cannabinoid receptors, CB1[1,2] and CB2,[3] ushered in a new era in research into the chemistry and pharmacology of this class of compounds. Both receptors are membrane-bound and belong to the family of G-protein-coupled receptors (GPCRs). The structural analysis of CB1[a] and CB2 as well as the study of their interactions with their ligands are hampered by the lack of a crystal structure. Consequently, there is little direct evidence for the mode(s) of interaction between ligand and receptor.[4] The recognition of CB1 as an important therapeutic target for, inter alia, glaucoma,[5] pain,[6] and appetite modulation,[7] indicates a need for a better understanding of the specific interactions between the cannabinoid pharmacophore and the key amino acids associated with the CB1 binding site.

It has long been known that the aliphatic side chain is important for determining the cannabinergic potency of classical cannabinoids and also that the presence of a *tert*-alkyl appendage at C1′ potentiates receptor binding affinity.[8] Nevertheless, it was surprising that cannabinoids bearing a pendant adamantyl group at C3 in place of the *n*-pentyl group that is found in naturally occurring materials, such as (−)-3-(1-adamantyl)-Δ^8-tetrahydrocannabinol (**1**, AM411), were tolerated in both CB1 and CB2 binding sites.[9] Furthermore, considerable receptor subtype selectivity was observed depending on the relative orientation of the adamantyl group with respect to the tricyclic nucleus. The ability of the receptor to accommodate the steric bulk of the 1-adamantyl group revealed an unanticipated flexibility and furthermore suggested that introducing heteroatomic functionality on the adamantane structure could be used to interrogate the receptor. Changes in binding affinities of cannabinoids bearing heteroatom-substituted adamantyl residues might indicate the close proximity of polar amino acid residues within the binding pocket. We have reported the synthesis of cannabinoids **2** and **3**[10] from known oxazaadamantane **I**.[11−13] Oxaza-adamantyl cannabinoids **4**, **5**, **6**, and **7**, azaadamantyl cannabinoids **8**−**15**, and oxacannabinoids **16** and **17** were designed and prepared as ligands with which to interrogate the CB1 and CB2 receptors (Figure 1). The northern aliphatic hydroxyl group is known to be an important cannabimimetic pharmacophore and was introduced at C9 as an α or β hydroxyl group.

Chemistry. To prepare a diverse set of cannabinoid ligands without preparing each individual alkyl resorcinol, we designed an advanced common intermediate from which all analogues could be derived. Following an approach that had been developed in our group,[10,13] we prepared bicyclic intermediate **18a** via acid catalyzed condensation between phloroglucinol **19a** and a mixture of diacetates **20** and **21** (Scheme 1). This key step had been developed by a team at the Eli Lilly company for the synthesis of nabilone.[14] Although the condensation works beautifully in chloroform, the solvent that had been used in the nabilone synthesis, phloroglucinol is very sparingly soluble in chloroform. To overcome this problem, we had used dichloromethane/acetone for our earlier synthesis of **18a** but were able to isolate only moderate (40%) yields of the product.[10] Part of the difficulty is associated with the high reactivity of **19a** that leads to condensation with a second molecule of **20** or **21**. It also became apparent that the choice of solvent had a large effect on the yield. We had explored a variety of solvents, acids, and conditions in order to overcome this difficulty to no avail. It is a testament to the skilled efforts of the Lilly team who carefully optimized this process that chloroform appears to be uniquely suited for the reaction. Fortunately, we were able to devise a simple modification of the procedure to overcome the problems associated with the low solubility of phloroglucinol in chloroform. Exposure of phloroglucinol

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[a]Abbreviations: CB1, cannabinoid 1 receptor; CB2, cannabinoid 2 receptor; DCM, dichloromethane; DIBAL, diisobutylaluminum hydride; DIPEA, *N*,*N*-diisopropylethylamine; HEK, human embryonic kidney; L-Selectride, lithium tri-*sec*-butylborohydride; MOMCl, methyl chloromethyl ether; OPLS, optimized potentials for liquid simulations; $PdCl_2$(dppf), 1,1′-bis(diphenylphosphino)ferrocene palladium(II) dichloride; $Pd_2(dba)_3$, tris(dibenzylideneacetone)dipalladium(0); PinB-BPin, bis-pinacolato diborane; rmsd, root-mean-square deviation; SAR, structure−activity relationship; TBAF, tetrabutylammonium fluoride; TEA, triethylamine; TESCl, triethylsilyl chloride; TMSBr, trimethylsilyl bromide; TMSCl, trimethylsilyl chloride; TMSOTf, trimethylsilyl trifluoromethanesulfonate.

 Published on Web 07/01/2010

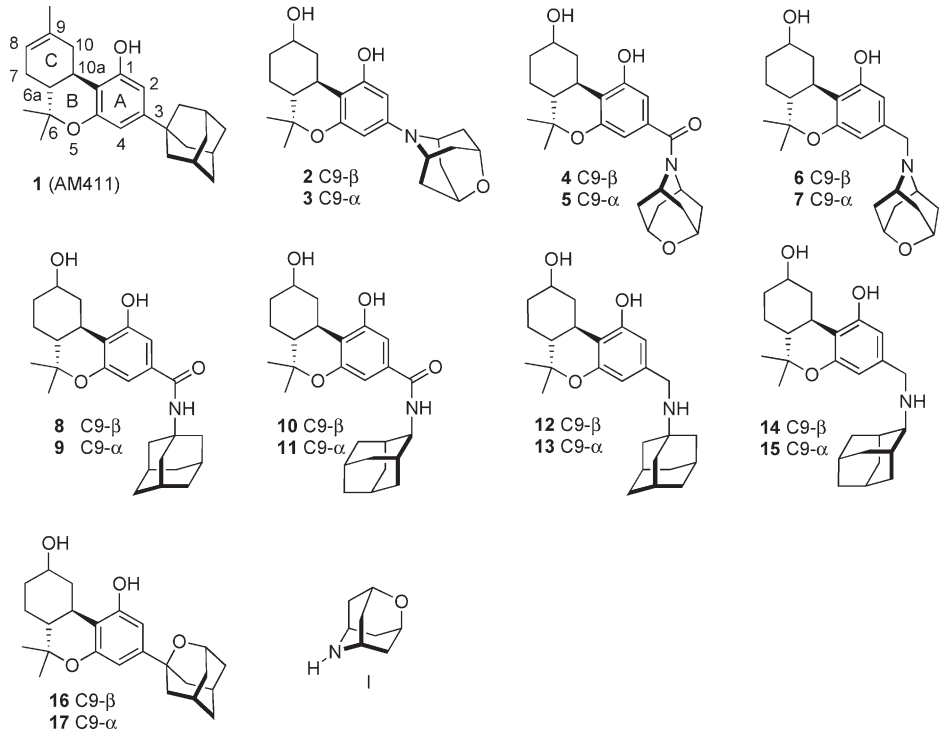


Figure 1. Adamantyl and heteroadamantyl cannabinoids.

to trimethylsilyl chloride (TMSCl) and triethylamine (TEA) in dichloromethane (DCM) led to the persilylated derivative **22** (Scheme 1). This hydrolytically sensitive material was not purified but was used in the condensation with **20** and **21** in place of phloroglucinol. Masking the phenolic hydroxyl groups as trimethylsilyl ethers led to a large increase in solubility in chloroform. This allowed us to perform the reaction in a mixture of chloroform and acetone (4/1) with *p*-toluenesulfonic acid in slight excess. This led to a much cleaner reaction and more than doubling of the yield of **18a** to approximately 70%. The phenolic trimethylsilyl groups were hydrolyzed during workup. The separation of **18a** from unreacted phloroglucinol was difficult. Although the separation can be accomplished by means of careful flash column chromatography on silica gel, we found that it was more practical to peracetylate the mixture of **18a** and **19a** following workup. The chromatographic separation of acetates **18b** and **19b** was straightforward and pure **18a** was recovered in 68% overall yield following hydrolytic cleavage of the acetoxy groups by KOH in methanol. The large improvement in the yield in the first step of the synthesis greatly increased the pace of progress.

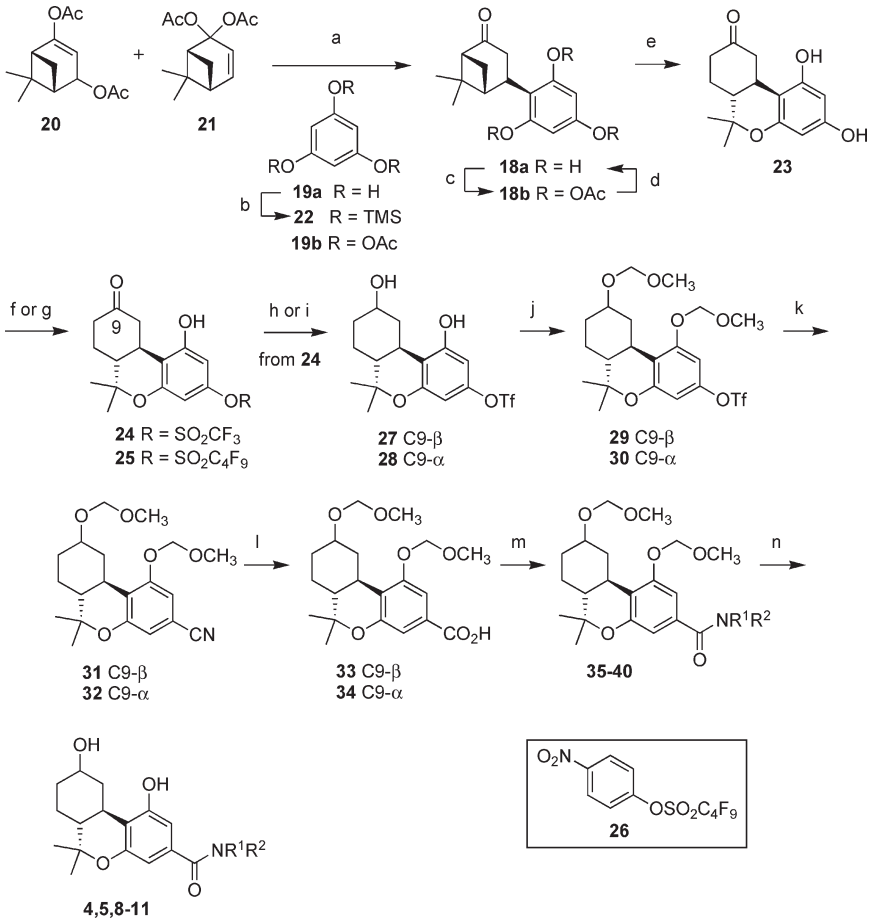
An improvement was made in the yield for the cyclocondensation step that converts **18a** to tricyclic intermediate **23** as well. In our earlier synthesis of **23**, we had used $SnCl_4$ as the Lewis acid. While on a small scale this procedure was practical, upon scale-up, the formation of emulsions during workup led to irreproducible yields of product. Trimethylsilyl triflate (TMSOTf) proved to be a much better choice of Lewis acid both in terms of the ease of workup as well as the yield (>95% vs 84%). Treatment of **23** with *N*-phenyltriflimide[15] in dichloromethane led to **24** regioselectively and in 68% yield (57% overall from **18a**). Intermediate **23** was also converted to nonaflate **25** in 57% yield through treatment with reagent **26** in the presence of CsF in *N*,*N*-dimethylformamide (DMF).

Because it was our goal to produce both diastereomers of the C9 alcohol, ketone **24** was reduced with $NaBH_4$ in 97% yield to give a ca. 95/5 mixture of C9-β (equatorial) alcohol **27** and C9-α (axial) diastereomer **28**. Alcohol **28** was the exclusive product of the reduction of ketone **24** with L-Selectride at −78 °C.

The phenolic and aliphatic hydroxyl groups in **27** and **28** were simultaneously protected as the methoxymethyl ether, leading to **29** and **30** in 93% and 94% yield, respectively, setting the stage for palladium catalyzed cyanation. Exposure of the aryl triflates to catalytic $Pd(PPh_3)_4$ and $Zn(CN)_2$ in DMF led to nitriles **31** and **32**, however, the reaction was not always reproducible. Addition of 10 wt % polymethylhydrosiloxane (PMHS)[16] to the reaction mixture as an oxygen scavenger resulted in a consistent and reproducible yield of greater than 95% for each of the diastereomers **31** and **32**. Nitriles **31** and **32** were hydrolyzed in the next step with LiOH in aqueous methanol, yielding carboxylic acids **33** (91% yield) and **34** (91% yield), respectively. Condensation of **33** with **I**, 1-adamantylamine, or 2-adamantylamine using 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDCI) and 4-dimethylaminopyridine (DMAP) led to amides **35** (91% yield), **37** (90% yield), and **39** (90% yield), respectively. Condensation of **34** with **I**, 1-adamantylamine, or 2-adamantylamine under the same conditions led to amides **36** (88% yield), **38** (91% yield), and **40** (91% yield), respectively. Cleavage of the methoxymethyl ether protecting groups with *n*-BuSH/$ZnBr_2$[17] led to amides **4**, **5**, and **8**−**11** in yields ranging from 77% to 92%.

The next task was to prepare compounds **6** and **7** that incorporate a methylene spacer group between amine **I** and the tricyclic cannabinoid nucleus. The synthesis from carboxylates **33** and **34** is summarized in Scheme 2. Reduction of acids **33** and **34** with borane−tetrahydrofuran (THF) complex led to benzylic alcohols **41** and **42**, each in 88% yield. Mesylation followed by immediate displacement of the

Scheme 1. Synthesis of Amides **4**,**5** and **8**−**11**[a]



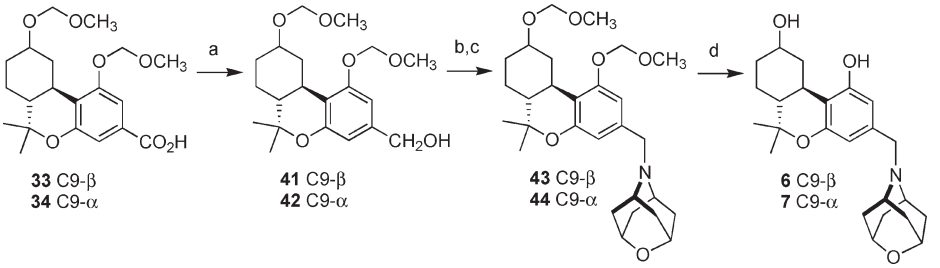
[a] Reagents and conditions: (a) *p*-TsOH, $CHCl_3$/acetone (4/1), 0 °C, 1 h; rt, 1 h; ca. 70%; (b) Me_3SiCl, Et_3N, CH_2Cl_2, 0 °C to rt; (c) CH_2Cl_2, DMAP (cat.), pyr, Ac_2O, 0 °C to rt, 12 h; (d) KOH, MeOH, 0 °C, 2 h; 68% overall from **20** and **21**; (e) Me_3SiOTf, $MeNO_2$, 0 °C, 2.5 h, >95%; (f) $PhNTf_2$, Et_3N, CH_2Cl_2, 0 °C to rt; 57% from **18a**; (g) CsF, **26**, DMF, rt, 12 h; 57%; (h) $NaBH_4$, MeOH, 0 °C, 1 h; 97% **27** + **28**, ca. 95/5; (i) L-Selectride, THF, −78 °C, 2 h; rt, 1 h; 90%; (j) $MeOCH_2Cl$, $(i\text{-}Pr)_2NEt$, CH_2Cl_2, 0 °C to rt, 2.5 h; **29**, 93%; **30**, 94%; (k) $Zn(CN)_2$, $Pd(PPh_3)_4$ (cat.), 10 wt % PMHS, DMF, 60 °C, 8 h; **31**, 96%; **32**, 97%; (l) LiOH, MeOH/H_2O (4/1), 70 °C, 3 d; **33**, 91%; **34**, 91%; (m) **I**, 1-adamantylamine or 2-adamantylamine, EDCI, DMAP, CH_2Cl_2, rt, 2 h; from **33**: **35**, 91%; **37**, 90%; **39**, 90%; from **34**: **36**, 88%; **38**, 91%; **40**, 91%; (k) *n*-BuSH, $ZnBr_2$, CH_2Cl_2, 45 °C; **4**, 77%; **5**, 89%; **8**, 89%; **9**, 92%; **10**, 91%; **11**, 90%.

mesylate by bromide gave the diastereomeric benzylic bromides. These were allowed to react in DMF with a slight excess of amine **I** at ambient temperature to give oxaza-adamantylamines **43** and **44** in 75% and 72% yield, respectively. Protecting group removal was carried out as in Scheme 1 by exposure to *n*-BuSH/$ZnBr_2$[17] in dichloromethane at 45 °C, leading to oxaza adamantylcannabinoids **6** and **7** in 81% and 73% yield, respectively. It should be noted that all attempts to remove the ether protecting groups from **43** and **44** by means of trimethylsilyl bromide (TMSBr) conditions that we found to be satisfactory in molecules bearing an aromatic nitrogen atom[10] led to inferior yields of **6** and **7**. This is quite likely due of the buffering effect of the more basic benzylic nitrogen atom in **6** and **7**. In contrast, the conditions for methoxymethyl ether group cleavage developed by Rawal and co-workers were optimal in our system and should be given consideration for similar applications in synthesis.

We followed a slightly different strategy for the synthesis of compounds **12**−**15**, all of which were prepared by means of reductive amination reactions (Scheme 3). Nitriles **31** and **32** were deprotected by treatment with $ZnBr_2$ and *n*-BuSH. Temporary masking of the hydroxyl groups as triethylsilyl (TES) ethers was followed by reduction of the nitrile to the aldehyde and fluorodesilylation to produce **47** and **48**, both in 61% overall yield for the three steps. Removal of the methoxymethyl groups in the presence of the aldehyde took place in poor yield, making the protecting group exchange necessary. Imine formation with 1- or 2-adamantylamine was followed by catalytic hydrogenation with 10% Pd/C in methanol under an atmosphere of hydrogen, resulting in the clean formation of compounds **12**−**15**.

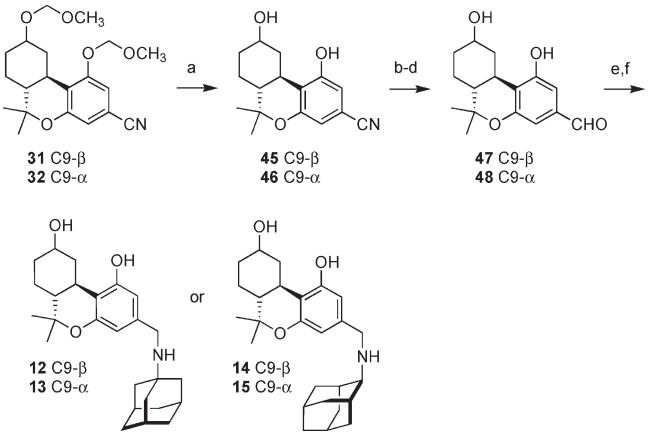
The synthesis of oxaadamantyl cannabinoids **16** and **17** proved to be a difficult challenge. Our first approach was an attempt to trap a cannabinoid-derived benzyne with an appropriate carbon nucleophile, a strategy that had served us well in the past.[10] Ultimately we were unable to define effective reaction conditions and were forced to abandon this approach in favor of a cross coupling process. The synthesis of the required vinyl boronate is summarized in Scheme 4. Treatment of commercially available 1,3-adamantanediol with benzenesulfonyl chloride[18] in a mixture of pyridine and benzene at 70 °C led to the Grob fragmentation product **49**. Ozonolysis in the next step gave diketone **50** in 66% yield over the two steps. Selective protection of one of the two ketone carbonyl groups as the ethylene ketal formed **51** in

Scheme 2. Synthesis of Benzylamines **6** and **7**[a]



[a] Reagents and conditions: (a) $BH_3 \cdot THF$, THF, 0 °C; 0 °C to rt; **41**, 88%; **42**, 88%; (b) MsCl, Et_3N, THF, 0 °C to rt; LiBr, THF, rt; (c) **I**, DMF, K_2CO_3, rt; **43**, 75%; **44**, 72%; (d) *n*-BuSH, $ZnBr_2$, CH_2Cl_2, 45 °C; **6**, 81%; **7**, 73%.

Scheme 3. Synthesis of Benzylamines **12**−**15**[a]



[a] Reagents and conditions: (a) *n*-BuSH, $ZnBr_2$, CH_2Cl_2, rt; **45**, 90%, **46**, 76%; (b) Et_3SiCl, (*i*-Pr)$_2$NEt, CH_2Cl_2, 0 °C to rt; (c) DIBAL, CH_2Cl_2, PhMe, −78 °C; (d) TBAF, THF, rt; **47**, 61% from **45**; **48**, 61% from **46**; (e) PhH, 1- or 2-adamantylamine, 4 Å MS, reflux, Dean−Stark; (f) Pd/C, H_2, MeOH, rt; **12**, 81% from **47**; **13**, 78% from **48**; **14**, 60% from **47**; **15**, 84% from **48**.

94% yield. Sequential treatment of **51** with lithium diisopropylamide (LDA) and *N*-phenyltriflimide followed by acid catalyzed exchange of the ketal led to vinyl triflate **52** in 82% yield over the two steps from **51**. Suzuki coupling of **52** with *bis*-pinacolato diborane (PinB-BPin) led to keto boronate **53** in good yield.[19,20]

Vinyl boronate **53** was coupled with aryl triflates **29** and **30** (Scheme 5). Treatment of **29** or **30** with 1,1′-bis(diphenylphosphino)ferrocene palladium(II) dichloride ($PdCl_2$(dppf)), K_2CO_3, and a slight excess of **53** in a mixture of DMF/EtOH (4:1) at 70 °C led to products **54** and **55** in 87% and 67% yield, respectively. Because **53** is racemic whereas **29** and **30** are homochiral, products **54** and **55** are formed as diastereomeric mixtures. For the sake of simplicity, only one diastereomeric structure is shown in Scheme 5. Exposure of **54** and **55** to sodium borohydride unsurprisingly led exclusively to the *endo* alcohols **56** and **57** in 90% and 82% yield, respectively. Removal of the methoxymethyl protecting groups from **56** and **57** with $ZnBr_2$ and *n*-BuSH induced cyclization of the *seco*-oxaadamantanes forming **16** and **17** in 95% and 79% yield, respectively.

Results and Discussion

Structure−Activity Relationships. Earlier work from our laboratory[9] has shown that tetrahydrocannabinol analogues substituted at the 3-position of the phenolic ring exhibit moderate to high affinities for the CB1 and CB2 receptors where the 1-adamantyl analogue **1** exhibited preferential affinity for CB1 while its 2-adamantyl regioisomer (−)-3-(2-adamantyl)-Δ^8-tetrahydrocannabinol (AM744) had higher affinity for CB2. Our effort to introduce heteroatoms within the novel adamantyl cannabinoid structures involved the use of 9β- and 9α-hydroxy hexahydrocannabinols as prototypes for the novel ligands. This was motivated by earlier work in which we have demonstrated that the tricyclic component in this series of analogues is a very successful pharmacophore for the two known cannabinoid receptors.[21]

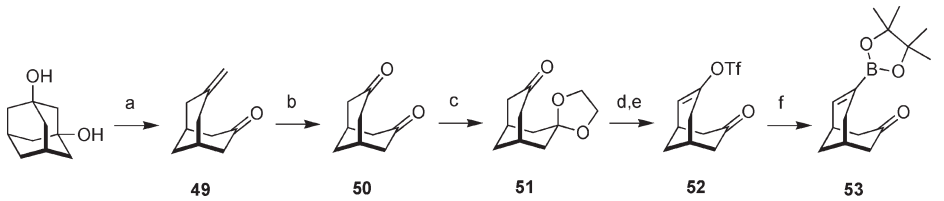
To probe the stereoelectronic requirements of the adamantyl group and also explore potential opportunities for improving the polar properties of the adamantyl cannabinergic ligands, we synthesized three groups of heteroadamantyl cannabinoids. The first includes analogues in which heteroatoms are incorporated into the adamantyl group either as a 2,6-oxazaadamantyl ring in which the ring nitrogen is directly attached to the 3-position of the tricyclic ring (**2**, **3**) or alternatively as a 2-oxaadamantyl substituent (**16**, **17**) (see **1** in Figure 1). In the second group, the heteroatom(s) are incorporated into the carbocyclic 1- or 2-adamantyl residue appended at C3 through carboxamido (**8**−**11**) or methylamino (**12**−**15**) groups. In the third group, the 2, 6-oxazaadamantyl ring is attached to the 3-position either through carbonyl (**4**, **5**) or methylene groups (**6**, **7**).

The SAR of all novel adamantyl analogues was examined by measuring their respective affinities for the CB1 and CB2 receptors (Table 1). All novel oxazacannabinoids exhibited reduced affinities for both receptors when compared with the earlier reported carbocyclic cannabinoids.[9] The 9β-OH analogues exhibited more favorable affinities for both receptors when compared to their 9α-OH isomers. Compounds belonging to the second group (**8**−**15**) generally had low affinities for both receptors, although all analogues had significant CB2 selectivities over CB1. This is congruent with the earlier data suggesting that the CB2 receptors, either human or mouse, are capable of accommodating larger side chain substituents when compared to CB1. The data also suggest that mCB2 is capable of accommodating larger groups compared to hCB2.

Analogues from the third group (**4**−**7**) carrying an appended oxazaadamantyl ring exhibited a similar affinity trend as group I. Again, all analogues showed substantial CB2 vs CB1 selectivities where the mCB2 had somewhat more favorable affinities than hCB2. Also, at the CB2 receptors, 9β-OH analogues (**12**, **14**) had slightly more favorable affinities compared to their 9α-OH analogues.

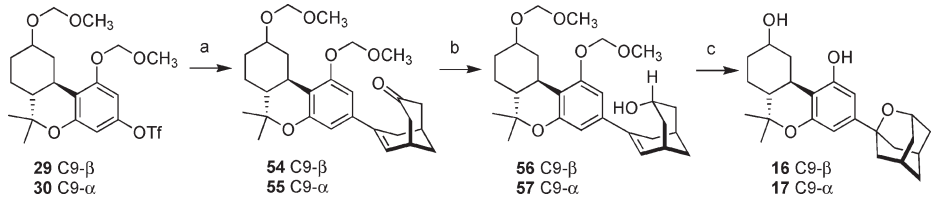
The first group of heterocannabinoids carries the structurally most compact 3-substituents. Their synthesis was

Scheme 4. Synthesis of Ketone **53**[a]



[a] Reagents and conditions: (a) $PhSO_2Cl$, PhH, pyr, 70 °C; (b) O_3, CH_2Cl_2, −78 °C; Me_2S; 66% for two steps; (c) $HO(CH_2)_2OH$, PhH, TsOH (cat.), reflux, Dean−Stark; 94%; (d) LDA, THF, −78 °C; $PhNTf_2$, THF, warm to 0 °C; (e) acetone, TsOH (cat.), rt; 82% from **51**; (f) $PdCl_2(PPh_3)_2$, PPh_3, K_2CO_3, 1,4-dioxane, PinB-BPin, 70 °C; 73%.

Scheme 5. Synthesis of Oxaadamantane Cannabinoids **16** and **17**[a]



[a] Reagents and conditions: (a) **53**, $PdCl_2(dppf)$, K_2CO_3, DMF/EtOH (4/1), 70 °C; **54**, 87%; **55**, 67%; (b) $NaBH_4$, MeOH, 0 °C; **56**, 90%; **57**, 82%; (c) *n*-BuSH, $ZnBr_2$, CH_2Cl_2, rt; **16**, 95%; **17**, 79%.

Table 1. Affinities (K_i) for CB1 and CB2 Cannabinoid Receptors[a]

	K_i (μM)[a]		
compd	rCB1	mCB2	hCB2
1[9a]	0.0068	0.052	NA
2	1.8	1.2	1.8
3	22.4	17	14.9
4	no binding	2.5	20
5	no binding	8.6	25
6	10	8.7	15
7	125	7.5	5
8	80	0.5	8.7
9	375	7.5	35
10	15	1.2	2.7
11	100	3.7	15
12	150	0.5	10
13	100	5	25
14	150	6.2	20
15	no binding	7.5	25
16	0.023	0.018	0.019
17	0.55	0.54	1.3

[a]Affinities for CB1 and CB2 were determined using rat brain (CB1) or membranes from HEK293 cells expressing mouse or human CB2 and [^{3}H]CP-55,940 as the radioligand following previously described procedures. [26] K_i values for compounds **2**, **3**, **16**, and **17** were obtained from one experiment (8 point) run in triplicate. K_i values for compounds **4**−**15**, which were all in the micromolar range, were derived from a single experiment (2 points) run in triplicate.

motivated by work with analogues carrying a carbocyclic adamantyl group which exhibited interesting pharmacological profiles.

In earlier work, we synthesized a pair of 2,5-oxazacannabinoids (**2**, **3**) in which the ring nitrogen is directly attached to the 3-phenolic position. Both of these analogues had low affinities for both CB1 and CB2.[10] To further explore the basis for this somewhat surprising finding, we have now synthesized the respective 2-oxaadamantyl analogues in which the 1-adamantyl carbon is directly attached to the tricyclic cannabinoid 3-position. We were pleased to observe that both 9β-OH (**16**) and 9α-OH (**17**) isomers exhibited favorable affinities for both receptors. Expectedly the 9β-isomer had the higher affinity. This interesting new compound had a somewhat different pharmacological profile than its reported carbocyclic isomer **1**. Unlike **1**, which exhibited selectivity for CB1, **16** had only modest selectivity (2-fold) for CB2. The new oxaadamantyl analogues have more polar properties (clogP) than **1** and may serve as the basis for the design of novel heteroadamantyl analogues with improved physicochemical and pharmacological properties.

We have used molecular modeling to explain the observed high differences in affinities among the heteroadamantyl cannabinoids described here. Since among the series of analogues reported the only pharmacophoric variable is the 3-substituent, we focused our attention on the conformational and stereoelectronic properties of this moiety and examined the conformational space available for the C3 substituents in each of the analogues. To explore the energetically favorable conformations in each analogue, we used force field methods and retained all conformers within 6 kcal/mol from the global minimum. Representative examples for each of the three groups of analogues are shown in Figure 2. It is clear that the conformational space for the 3-substituents in the second and third groups covers a significantly larger volume than that of the first group. It can thus be argued that the low affinity of these hexahydrocannabinol analogues is attributable to steric factors as well as large desolvation penalties due to their polar linkers. Accordingly, these bulky substituents are unable to engage in an optimal interaction at the adamantyl side chain with its respective pharmacophoric site within the cannabinoid receptors. This is more accentuated in their interaction with CB1 compared to CB2. It should be pointed out that three of the ligands from the second family (**8**, **10**, **12**) exhibited the most favorable K_i values for mCB2 with **8** and **12** having the highest affinity (K_i = 0.5 μM). Conversely, all three analogues had 10−50-fold lower affinities for CB1. This observed preference of ligands carrying 3-substituents capable of assuming larger conformational space for the CB2 vs CB1 receptor is congruent with our earlier work with carbocyclic adamantyl analogues. In this work, we have argued that the CB2 selectivity of 2-adamantyl analogues exhibited a larger

conformational space for this pharmacophore with the mCB2 being more accommodating than hCB2.

Our arguments for the low affinities of analogues for groups 2 and 3 cannot be easily applied to the compounds belonging to the first group. A comparison of the pharmacophoric space for compounds **2** and **16** does not reveal striking differences in the accessible conformational volumes of the two analogues. To further explore potential differences in the manner in which the low affinity oxaza analogue (**2**) and the high-affinity oxa analogues (**16**, **17**) interact with the two cannabinoid receptors, we calculated the energy barriers for rotation of these compounds around the Ph−N (**2**) or Ph−C (**16**, **17**) respectively (Figure 3). Our calculations show that while the oxa analogues have a rotational barrier of ~6.3 kcal/mol, the oxaza analogue has a significantly higher barrier of ~12.3 kcal/mol. We would thus argue that while both analogues in question occupy similar conformational spaces, entropic advantages associated with a more facile rotation for the oxaadamantyl analogues may improve ligand binding affinity. Alternatively, it can be argued that in the 3-oxaza compounds (**2** and **3**) both N and O heteroatoms undergo unfavorable interactions within its allowable pharmacophoric space.

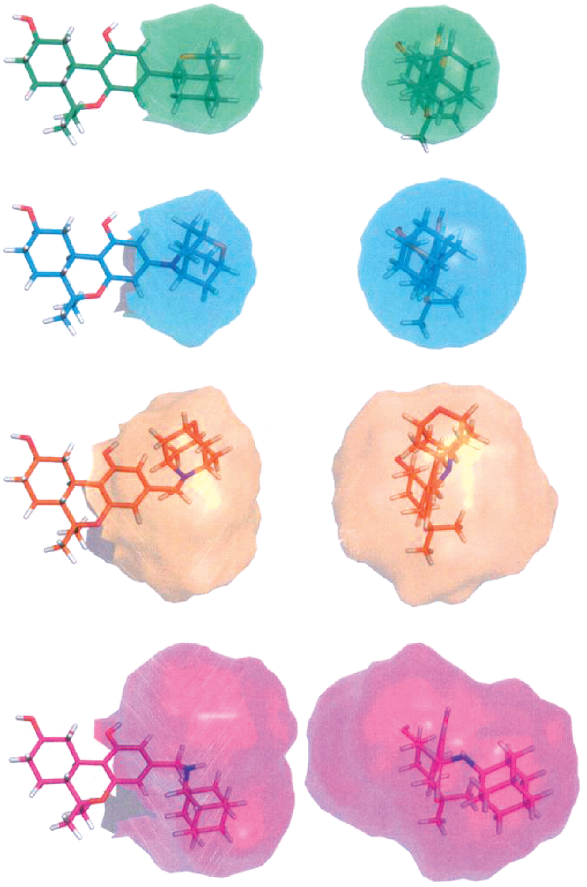


Figure 2. Accessible conformers with 6 kcal/mol of the global energy minimum for **16** (green), **2** (cyan), **7** (orange), and **14** (magenta). Analogues are shown superimposed at their aromatic rings.

Methods. Along with entropic factors, the conformational space available to the analogues may offer insight into the steric factors required for CB1 and CB2 selectivity. To explore the permissible rotations of the bulky substituent, a conformational search was performed using optimized potentials for liquid simulations (OPLS) force field.[23,24] The cannabinoid tricyclic moiety was held fixed and minimization on the remaining geometric parameters was performed.[23] Conformers with greater than 0.5 Å root-mean-square deviation (rmsd) with 6 kcal mol^{-1} of the global minimum were retained. All calculations were performed in Macromodel.[25] The entropic factors involved for a ligand are also important, and compounds **2** and **16** were of particular interest and higher level calculations were performed at the B3LYP/6-31G** level. In these computationally more demanding calculations, a conformational scan was performed using dihedral drive around the C3−C1′ bond. The dihedral angle was restrained at a value between 0 and 360° in 10° steps, and minimization on the remaining geometric parameters was performed.

Summary

The 3-phenyl substituents of cannabinoid ligands are an essential pharmacophore capable of significantly modulating their affinities for the CB1 and CB2 cannabinoid receptors. In earlier work, we have shown that the 3-alkyl groups of

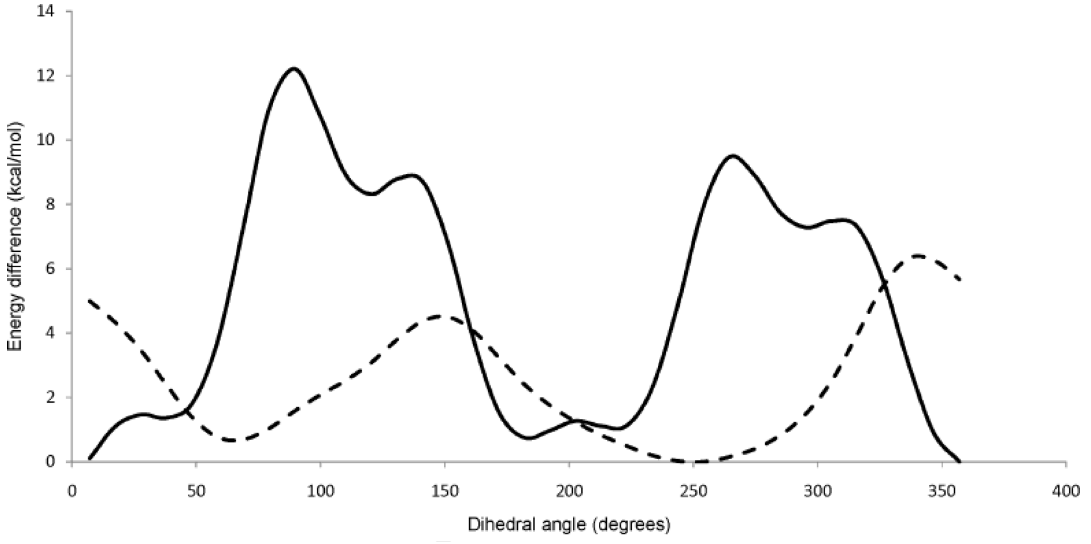


Figure 3. Plot of the QM energy relative to the lowest energy structure calculated at the B3LYP/6-31G** level for **16** (dashed) and **2** (solid) during a coordinate scan around the C3−C1′ bond.

classical cannabinoids can be successfully substituted with an adamantyl ring. The present work is aimed at further exploring this interesting pharmacophore. In addition to exploring the steric requirements of the adamantyl ring, we have sought to introduce heteroatoms within the ring or within the pendant fragment connecting the ring to the tricyclic component in order to modulate the hydrophobic physical properties of the ligands.

Our results indicate that optimal affinities are obtained with compounds in which the adamantyl pharmacophore is directly attached to the 3-position of the phenolic ring. The ligands' affinities for both receptors are severely diminished if the adamantyl unit is attached through a linker, an observation attributable to the larger pharmacophoric space required by these compounds. The most successful ligands were the 2-oxaadamantyl analogues, suggesting that the oxygen atom in the adamantyl ring could be accommodated within the binding domain of the CB1 and CB2 receptors. However, the oxaza analogues in which the nitrogen atom is directly attached to the ring exhibited reduced affinities for both receptors. This is attributed to entropic factors because of restricted rotation around the N−Ph bond. The overall SAR of the new compounds follows trends congruent with earlier work in the classical cannabinoid field. This includes the observation that 9β-OH analogues have higher affinities compared to their 9α-stereoisomers. The work also confirmed earlier observations suggesting that the space for the adamantyl pharmacophore is most restricted at the CB1 receptor. Additionally, there appears to be a species difference with the mCB2 receptor being more accommodating than hCB2.

Experimental Section

Chemistry. ^{1}H NMR and ^{13}C NMR spectra were recorded either at 300 MHz (^{1}H) and 75 MHz (^{13}C) or at 500 MHz (^{1}H) and 126 MHz (^{13}C). Chemical shifts are reported in parts per million (δ) and are referenced to the solvent, i.e. 7.26/77.0 for $CDCl_3$. Multiplicities are indicated as br (broadened), s (singlet), d (doublet), t (triplet), q (quartet), quint (quintet), sept (septet), or m (multiplet). Coupling constants (J) are reported in Hertz (Hz). Thin layer chromatography (TLC) was performed on glass plates 250 μm, particle size 5−17 μm, pore size 60 Å. Flash column chromatography was performed on silica gel, 200−400 mesh, or premium silica gel, 60 Å, 40−75 μm. All moisture sensitive reactions were performed under a static atmosphere of nitrogen or argon in oven-dried or flame-dried glassware. Purity and homogeneity of all materials was determined to be at least 95% from TLC, ^{1}H NMR, ^{13}C NMR, and HPLC. All optical rotations were measured on a JASCO digital polarimeter in a 0.1 dL cell.

Synthesis of 18b. To a suspension of phloroglucinol **19a** (5.50 g, 43.7 mmol) in 300 mL of DCM at 0 °C was added TEA (24.3 mL, 174.6 mmol) followed by TMSCl (22.3 mL, 174.6 mmol). After 20 min, the cooling bath was removed and the mixture was allowed to stir at room temperature for an additional 2 h. The salts were removed via filtration and the filtrate was washed with ice cold water (3×), dried over Na_2SO_4, and concentrated affording persilylated phloroglucinol **22**. Crude **22** was then dissolved in 440 mL of a 4:1 mixture of $CHCl_3$:acetone and cooled to 0 °C. In a separate flask, diacetates **20** and **21** (4.42 g, 18.6 mmol; 5.2 g of 85% pure diacetates **20** and **21** were used) were dissolved in 150 mL of 4:1 $CHCl_3$:acetone along with $TsOH\cdot H_2O$ (4.57 g, 24.0 mmol). The $TsOH\cdot H_2O$ and diacetates mixture was then added dropwise to persilylated phloroglucinol **22** at a rate of approximately 1 drop/s via an addition funnel. The reaction mixture was then slowly warmed to room temperature. Once the diacetates were shown to be consumed by TLC, the reaction was quenched with saturated $NaHCO_3$ and stirred for 45 min. The organic layer was separated and dried over $MgSO_4$ while the aqueous layer was back-extracted with EtOAc (6×) and dried over $MgSO_4$. To the crude condensation product **18a** and DMAP (100 mg, 0.82 mmol) in 200 mL of DCM at 0 °C was added pyridine (13.0 mL, 160.0 mmol) followed by Ac_2O (15.1 mL, 160.0 mmol) and stirred for 12 h. The mixture was quenched with ice cold water, washed with 1 M HCl and brine, and dried over $MgSO_4$. The crude product was then purified via flash column chromatography on silica gel eluting with 30% EtOAc/hexanes affording **18b** (4.90 g, 68% yield over 2 steps) as a white solid.

^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.83 (s, 2H), 3.63 (t, J = 8.4 Hz, 1H), 2.84−2.75 (m, 1H), 2.66−2.57 (m, 3H), 2.29−2.25 (m, 10H), 2.15−2.11 (m, 1H), 1.37 (s, 3H), 0.95 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 212.4, 168.5, 168.4, 149.5, 148.5, 125.0, 114.6, 57.1, 45.3, 42.0, 38.7, 30.6, 26.0, 24.5, 21.8, 20.9; mp: 138−140 °C. IR (neat, cm^{-1}): 2947, 1769, 1709, 1608, 1427, 1371, 1185, 1122, 1031, 903. Mass spec calcd for $C_{21}H_{24}O_7$, 388.1522; found, 388.1532. EI+(amu): 388 (M+, 10), 346 (62), 304 (33), 303 (25), 262 (30), 262 (51), 244 (27), 219 (53), 207 (20), 194 (32), 177 (34), 152 (50), 83 (100); $[\alpha]^{23}_D$ −8.0° (c 0.010, EtOAc).

Synthesis of 18a. To a solution of the triacetate **18b** (4.90 g, 12.6 mmol) in 50 mL of MeOH at 0 °C was added KOH (2.48 g, 44.2 mmol) under N_2. The reaction mixture was stirred at this temperature for an additional 2 h and then quenched with 1 N HCl. MeOH was removed under reduced pressure, and the residue was diluted with EtOAc, washed with brine, and dried over $MgSO_4$. The crude product was carried on without further purification. An analytical sample could be purified via flash column chromatography on silica gel eluting with 50% EtOAc/hexanes, affording **18a** (3.30 g, 100% yield) as an off-white foam that typically entrains 10−15% ethyl acetate.

^{1}H NMR (MeOH-d_4, 300 MHz) δ 5.85 (s, 2H), 3.95 (t, J = 8.1 Hz, 1H), 3.67 (dd, J = 18.6 Hz, 7.5 Hz, 1H), 2.62−2.57 (m, 1H), 2.48−2.35 (m, 3H), 2.14 (t, J = 6.0 Hz, 1H), 1.35 (s, 3H), 0.94 (s, 3H). ^{13}C NMR (MeOH-d_4, 75 MHz) δ 220.2, 158.5, 157.3, 108.9, 95.9, 59.3, 48.8, 43.2, 38.8, 30.0, 26.6, 24.9, 22.4.

Synthesis of 23. To a solution of **18a** (1.02 g, 3.89 mmol; the mass of pure ketone **18a** was 1.20 g; ethyl acetate was present as an impurity) in 300 mL of $MeNO_2$ at 0 °C was added TMSOTf (1.76 mL, 9.73 mmol) dropwise. The resulting mixture was stirred for 2.5 h at 0 °C and then quenched with solid K_2CO_3 and stirred for 45 min at rt. The solids were filtered off and the solvent removed under reduced pressure. Crude **23** was used without further purification in the next step.

^{1}H NMR (MeOH-d_4, 300 MHz) δ 5.85 (d, J = 2.4 Hz, 1H), 5.76 (d, J = 2.4 Hz, 1H), 3.81 (dd, J = 15.0 Hz, 3.0 Hz, 1H), 2.79−2.70 (m, 1H), 2.47−2.25 (m, 2H), 2.18−2.02 (m, 2H), 1.92 (td, J = 12.3 Hz, 2.4 Hz, 1H), 1.57−1.45 (m, 1H), 1.42 (s, 3H), 1.08 (s, 3H). ^{13}C NMR (MeOH-d_4, 75 MHz) δ 214.6, 158.3, 156.6, 111.2, 104.3, 96.7, 96.6, 77.8, 46.8, 41.5, 36.0, 28.1, 27.9, 19.0.

Synthesis of 24. To crude ketone **23** (1.02 g, 3.89 mmol) in 40 mL of DCM at 0 °C was added TEA (1.62 mL, 11.7 mmol) followed by dropwise addition of *N*-phenyltrifluoromethanesulfonimide (1.60 g, 4.47 mmol) in 40 mL of DCM via cannula. The reaction mixture was allowed to warm to room temperature over 12 h, was quenched with 1 N HCl, and washed with water. The aqueous layer was back extracted with DCM, washed with brine, and dried over $MgSO_4$. The crude product was purified via flash column chromatography on silica gel eluting with 20, 30, and 40% EtOAc/hexanes affording **24** (874 mg, 57% yield over 2 steps) as a white semisolid.

^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.39 (d, J = 2.4 Hz, 1H), 6.33 (d, J= 2.4 Hz, 1H), 4.13 (d, J=15.0 Hz, 1H), 2.94−2.84 (m, 1H), 2.73−2.66 (m, 1H), 2.59−2.47 (m, 1H), 2.25−1.95 (m, 3H), 1.62−1.49 (m, 4H), 1.29−1.12 (m, 4H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 215.9, 156.6, 155.6, 148.8, 110.7, 102.3, 100.9, 77.8, 46.9, 44.2, 40.7, 34.7, 27.6, 26.8, 18.8. IR (neat, cm^{-1}): 3415(br),

1617, 1423, 1246, 1211, 1141, 1099. Mass spec calcd for $C_{16}H_{17}F_3O_6S$, 394.0698; found, 394.0681. EI+(amu): 394 (M+, 13), 279 (28), 270 (72), 243 (69), 225 (80), 207 (100), 195 (70); $[\alpha]^{23}_D$ −45.0° (*c* 0.006, CH_2Cl_2).

(6a*S*,9*R*,10a*R*)-6a,7,8,9,10,10a-Hexahydro-1,9-dihydroxy-6,6-dimethyl-6*H*-benzo[*c*]chromen-3-yl trifluoromethanesulfonate 27. To ketone **24** (583 mg, 1.48 mmol) in 15 mL of MeOH at 0 °C was added $NaBH_4$ (280 mg, 7.40 mmol) in 3 portions over 5 min. The reaction mixture was then stirred for 1 h, quenched with dropwise addition of 1 N HCl, and diluted with EtOAc. The organic layer was washed with brine and dried over $MgSO_4$. The crude product was then purified via flash column chromatography on silica gel eluting with 30% then 40% EtOAc/hexanes, affording alcohol **27** and minor alcohol **28** (570 mg, 97% combined yield; the minor diastereomer is easily removed during column chromatography after the subsequent protection) as a white foam.

^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.19 (br s, 1H), 6.27 (s, 1H), 6.18 (s, 1H), 4.00−3.89 (m, 1H), 3.68−3.60 (m, 1H), 2.50−2.42 (m, 2H), 2.20−2.15 (m, 1H), 1.93−1.88 (m, 1H), 1.51−1.42 (m, 2H), 1.37 (s, 3H), 1.20−1.11 (m, 1H), 1.06−0.99 (m, 4H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 156.5, 155.9, 148.3, 119.9, 102.3, 100.6, 77.8, 71.5, 47.7, 37.1, 35.7, 33.3, 27.6, 25.8, 18.9. IR (neat, cm^{-1}): 3245(br), 2937, 2873, 1597, 1420, 1245, 1213, 1141, 989, 857. Mass spec calcd for $C_{16}H_{19}F_3O_6S$, 396.0855; found, 396.0863. EI+(amu): 396 (M+, 79), 378 (45), 336 (57), 335 (100), 186 (29), 69 (71); $[\alpha]^{23}_D$ −63.9° (*c* 0.015, CH_2Cl_2).

(6a*S*,9*S*,10a*R*)-6a,7,8,9,10,10a-Hexahydro-1,9-dihydroxy-6,6-dimethyl-6*H*-benzo[*c*]chromen-3-yl trifluoromethanesulfonate 28. To ketone **24** (299 mg, 0.76 mmol) in 8 mL of THF at −78 °C was added a 1 M solution of L-Selectride in THF (3.00 mL, 3.00 mmol). The reaction was maintained at −78 °C for 2 h and then stirred at room temperature for 1 h. The flask was cooled to −78 °C and solid $NaHCO_3$ (930 mg, 11.1 mmol) was added followed by dropwise addition of a 30% aqueous solution of H_2O_2 (1.60 mL). After the addition of 30% H_2O_2 was complete, the cooling bath was removed and the reaction mixture was stirred for 1 h at rt. A saturated solution of sodium thiosulfate (5 mL) was added and the reaction mixture was stirred for an additional 30 min. Ether was added and the organic layer was separated, then washed with brine and dried over $MgSO_4$. The crude product was purified via flash column chromatography on silica gel eluting with 40% EtOAc/hexanes, affording alcohol **28** (269 mg, 90% yield) as a white solid. Alcohol **27** was not observed in the ^{1}H NMR at 300 MHz.

^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.66 (br s, 1H), 6.30 (d, *J* = 2.5 Hz, 1H), 6.26 (d, *J* = 2.5 Hz, 1H), 4.35 (s, 1H), 3.24 (d, *J* = 14.1 Hz, 1H), 2.93−2.86 (m, 1H), 2.54 (br s, 1H), 1.99−1.94 (m, 1H), 1.77−1.68 (m, 2H), 1.56−1.46 (m, 2H), 1.37−1.26 (m, 4H), 0.99 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 156.1, 148.3, 112.8, 102.9, 101.3, 77.7, 67.5, 48.8, 35.3, 33.5, 28.9, 27.2, 22.5, 18.8; mp: 188.5−192.5 °C. IR (neat, cm^{-1}): 3210 (br), 2938, 1597, 1506, 1419, 1245, 1212, 1140, 1102, 987, 879, 839, 735. Mass spec calcd for $C_{16}H_{19}F_3O_6S-H_2O$, 378.0749; found, 378.0743. EI+(amu): 396 (M+, 8), 378 (64), 335 (56), 309 (31), 202 (14), 151 (42), 101 (39), 92 (19), 69 (100); $[\alpha]^{23}_D$ −57.7° (*c* 0.014, CH_2Cl_2).

(6a*S*,9*R*,10a*R*)-6a,7,8,9,10,10a-Hexahydro-1,9-bis(methoxymethoxy)-6,6-dimethyl-6*H*-benzo[*c*]chromen-3-yl trifluoromethanesulfonate 29. Alcohol **27** (430 mg, 1.08 mmol) was dissolved in 10 mL of DCM, was cooled to 0 °C, and was treated with DIPEA (1.13 mL, 6.48 mmol) and dropwise addition of MOMCl (492 μL, 6.48 mmol). After 45 min, the cooling bath was removed and the reaction mixture was stirred at room temperature for another 1 h 45 min. Saturated $NaHCO_3$ was added to quench the reaction, and the resulting mixture was diluted with Et_2O. The organic layers were washed with $CuSO_4$ and brine and then dried over $MgSO_4$. The crude product was purified via flash column chromatography on silica gel eluting with 20% EtOAc/hexanes, affording **29** (487 mg, 93% yield) as a clear, colorless oil.

^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.56 (d, *J* = 2.5 Hz, 1H), 6.40 (d, *J* = 2.5 Hz, 1H), 5.19−5.12 (m, 2H), 4.74−4.69 (m, 2H), 3.75−3.67 (m, 1H), 3.47 (s, 3H), 3.69 (s, 3H), 3.35−3.30 (m, 1H), 2.44 (td, *J* = 11.3 Hz, 2.4 Hz, 1H), 2.21−2.16 (m, 1H), 1.92−1.86 (m, 1H), 1.55−1.37 (m, 5H), 1.19−1.03 (m, 5H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 157.1, 155.4, 148.5, 114.2, 104.3, 99.5, 94.8, 94.6, 77.8, 75.5, 56.3, 55.1, 48.1, 36.1, 33.7, 33.0, 27.4, 25.9, 18.8. IR (neat, cm^{-1}): 3197, 3105, 2940, 2789, 1603. Mass spec calcd for $C_{20}H_{27}F_3O_8S$, 484.1379; found, 484.1403. EI+-(amu): 484 (M+, 7), 379 (33), 378 (100), 335 (25), 245 (19); $[\alpha]^{23}_D$ −67.6° (*c* 0.017, CH_2Cl_2).

(6a*S*,9*R*,10a*R*)-6a,7,8,9,10,10a-Hexahydro-1,9-bis(methoxymethoxy)-6,6-dimethyl-6*H*-benzo[*c*]chromene-3-carbonitrile 31. To triflate **29** (435 mg, 0.90 mmol) was added $Zn(CN)_2$ (84 mg, 0.72 mmol), $Pd_2(dba)_3$ (82 mg, 0.090 mmol), and PPh_3 (188 mg, 0.718 mmol) followed by PMHS (44 mg, 10 wt %) and 27 mL of DMF under an atmosphere of argon. The reaction mixture was further degassed by bubbling argon through the mixture for 15 min. The reaction mixture was heated to 60 °C and stirred for 8 h. The solvent was removed under reduced pressure, and the residue was adsorbed onto celite. The crude product was subjected to flash column chromatography on silica gel eluting with 10%, 20%, and 30% EtOAc/hexanes, affording **31** as a clear, colorless viscous oil (313 mg, 96% yield).

^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.90 (d, *J* = 1.6 Hz, 1H), 6.77 (d, *J* = 1.6 Hz, 1H), 5.21 (d, *J* = 6.8 Hz, 1H), 5.16 (d, *J* = 6.8 Hz, 1H), 4.73 (dd, *J* = 8.0 Hz, 7.1 Hz, 2H), 3.79−3.68 (m, 1H), 3.49 (s, 3H), 3.40−3.30 (m, 4H), 2.49 (td, *J* = 11.4 Hz, 2.4 Hz, 1H), 2.23−2.18 (m, 1H), 1.94−1.89 (m, 1H), 1.57−1.39 (m, 5H), 1.20−1.03 (m, 5H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 156.7, 155.2, 119.8, 118.8, 115.6, 110.9, 108.7, 94.9, 94.5, 77.8, 75.5, 56.4, 55.2, 48.2, 36.1, 34.1, 33.0, 27.5, 25.9, 18.7. IR (neat, cm^{-1}): 2939, 2880, 2228, 1565, 1423, 1369, 1336, 1207, 1155, 1103, 1058. Mass spec Calcd for $C_{20}H_{27}NO_5$, 361.1889; found, 361.1880. EI+(amu): 361 (M+, 11), 285 (19), 255 (100), 240 (25), 212 (75), 69 (10); $[\alpha]^{23}_D$ −77.9° (*c* 0.007, CH_2Cl_2).

(6a*S*,9*R*,10a*R*)-6a,7,8,9,10,10a-Hexahydro-1,9-bis(methoxymethoxy)-6,6-dimethyl-6*H*-benzo[c]chromene-3-carboxylic Acid 33. To nitrile **31** (52 mg, 0.15 mmol) in a screw cap vial was added MeOH:H_2O (4:1, 1 mL) and LiOH (61 mg, 1.45 mmol) and the mixture was heated to 70 °C in an oil bath for 3 days. Conc HCl was added to the reaction mixture, and the resultant milky solution was extracted with $CHCl_3$, washed with saturated brine, and dried over Na_2SO_4. Acid **33** was obtained as a clear, colorless oil (50 mg, 91% yield). No purification was necessary.

^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.29 (s, 1H), 7.24 (s, 1H), 5.26 (d, *J* = 6.6 Hz, 1H), 5.20 (d, *J* = 6.6 Hz, 1H), 4.74 (dd, *J* = 9.3 Hz, 6.9 Hz, 2H), 3.81−3.70 (m, 1H), 3.51 (s, 3H), 3.47−3.40 (m, 4H), 2.51 (td, *J* = 11.1 Hz, 1.8 Hz, 1H), 2.25−2.18 (m, 1H), 1.92−1.87 (m, 1H), 1.60−1.40 (m, 5H), 1.25−1.04 (m, 5H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 171.2, 156.3, 154.8, 128.7, 120.1, 113.7, 106.5, 94.8, 94.5, 77.4, 75.7, 56.4, 55.2, 48.4, 36.2, 34.3, 33.1, 27.6, 26.1, 18.7. IR (neat, cm^{-1}): 2939, 1719, 1690, 1574, 1424, 1375, 1211, 1149, 1100, 1051. Mass spec calcd for $C_{20}H_{28}O_7$, 380.1835; found, 380.1827. EI+(amu): 380 (M+, 3), 293 (11), 149 (100), 71 (26); $[\alpha]^{23}_D$ −86.0° (*c* 0.014, CH_2Cl_2).

***β*-C9 Oxaza Amide 35 (Procedure for Amidation Reaction).** To a solution of **33** (30 mg, 0.079 mmol) in 2 mL of DCM was added amine **I** (30 mg, 0.12 mmol) followed by DMAP (39 mg, 0.32 mmol) and EDCI (30 mg, 0.16 mmol). The flask was sealed with a Teflon cap and stirred overnight at rt. The mixture was diluted with EtOAc, washed with 1 N HCl and brine and dried over $MgSO_4$. The crude product was directly adsorbed onto celite and purified via flash column chromatography eluting with 80% EtOAc/hexanes, affording amide **35** as a clear, colorless oil (36 mg, 91% yield).

^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.66 (s, 1H), 6.49 (s, 1H), 5.21 (d, *J* = 6.6 Hz, 1H), 5.12 (d, *J* = 6.6 Hz, 1H), 5.05 (br s, 1H), 4.72 (dd, *J* = 9.6 Hz, 6.9 Hz, 2H), 4.24−4.18 (m, 3H), 3.78−3.68 (m, 1H), 3.47 (s, 3H), 3.43−3.34 (m, 4H), 2.47 (td, *J* = 11.2 Hz, 2.0 Hz, 1H), 2.21−1.75 (m, 10H), 1.57−1.37 (m, 5H), 1.21−1.02 (m, 5H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 169.1, 156.6, 154.8, 135.4,

115.5, 109.4, 103.9, 94.7, 94.5, 77.2, 75.6, 66.7, 56.2, 55.1, 49.0, 48.4, 42.9, 36.3, 35.1, 34.3, 33.9, 33.1, 27.6, 26.0, 18.8. IR (neat, cm^{-1}): 2937, 1626, 1566, 1424, 1370, 1148, 1101, 1048. Mass spec calcd for $C_{28}H_{39}NO_7$, 501.2727; found, 501.2702. EI+(amu): 501 (M+, 28), 457 (23), 395 (100), 380 (13), 352 (20), 257 (30), 167 (17), 149 (44), 95 (21), 71 (24), 69 (30); $[\alpha]^{23}_D$ −33.3° (*c* 0.011, CH_2Cl_2).

Procedure for Deprotection of MOM Ethers (4−11). β-C9 Oxaza Amide 4. To a solution of amide **35** (36 mg, 0.072 mmol) and *n*-BuSH (180 μL, 1.68 mmol) in 2 mL of DCM was added $ZnBr_2$ (81 mg, 0.36 mmol) all in one portion. The reaction flask was placed in an oil bath and heated at 45 °C for 8 h. The flask was then cooled to room temperature, diluted with EtOAc, and quenched with saturated $NaHCO_3$. The organic layer was washed with brine and dried over Na_2SO_4. The crude product was adsorbed onto Celite and subjected to column chromatography on silica gel using a gradient elution of 2.5, 5, 10% MeOH/DCM. Amide **4** is a white glass obtained in 77% yield (23 mg). Chiral HPLC (0.46 cm ×25 cm Chiralcel AD-H, 50% 2-propanol in hexanes, 1 mL/min, UV detection at 280 nm) 7.50 min and 98.6% pure.

^{1}H NMR (MeOH-d_4, 500 MHz): δ 6.33 (d, *J* = 1.8 Hz, 1H), 6.29 (d, *J* = 1.8 Hz, 1H), 4.96 (br s, 1H), 4.20 (br s, 3H), 3.77−3.71 (m, 1H), 3.53−3.49 (m, 1H), 2.50 (td, *J* = 11.3 Hz, 2.5 Hz, 1H), 2.18−2.09 (m, 3H), 2.06−2.00 (m, 2H), 1.93−1.80 (m, 5H), 1.46 (td, *J* = 11.8 Hz, 2.3 Hz, 1H), 1.42−1.33 (m, 4H), 1.24−1.15 (m, 1H), 1.04 (s, 3H), 0.98−0.91 (m, 1H). ^{13}C NMR (MeOH-d_4, 126 MHz): δ 171.7, 158.4, 156.7, 136.0, 115.4, 107.7, 105.8, 78.4, 71.3, 68.2(2), 51.0, 50.1, 44.8, 39.6, 36.6, 36.0, 35.9, 35.2, 35.1, 28.1, 27.2, 19.1. IR (neat, cm^{-1}): 3454 (br), 2932, 1738, 1727, 1604, 1572, 1441, 1381, 1240, 1057. Mass spec calcd for $C_{24}H_{31}NO_5$, 413.2234; found, 413.2322. EI+(amu): 413 (M+, 100), 395 (26), 352 (20), 275 (30), 149 (56); $[\alpha]^{23}_D$ −92.6° (*c* 0.007, MeOH).

((6a*S*,9*R*,10a*R*)-6a,7,8,9,10,10a-Hexahydro-1,9-bis(methoxymethoxy)-6,6-dimethyl-6*H*-benzo[*c*]chromen-3-yl)methanol 41. To carboxylic acid **33** (12 mg, 0.032 mmol) in 0.1 mL of THF was added excess $BH_3 \cdot THF$ (100 μL, 1 mmol, 1 M) at 0 °C, and the mixture was allowed to warm to room temperature overnight. Six N HCl was added slowly and carefully at 0 °C, and the mixture was diluted with $CHCl_3$. The organic layers were washed with brine and dried over Na_2SO_4. The crude product was purified via flash column chromatography on silica gel using 50% EtOAc/hexanes as the eluent which resulted in alcohol **41** (10 mg, 88% yield) as a clear, colorless oil.

^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.63 (s, 1H), 6.50 (s, 1H), 5.21 (d, *J* = 6.3 Hz, 1H), 5.16 (d, *J* = 6.3 Hz, 1H), 4.72 (dd, *J* = 13.3 Hz, 6.8 Hz, 2H), 4.57 (br s, 2H), 3.77−3.71 (m, 1H), 3.50 (s, 3H), 3.44−3.39 (m, 4H), 2.47 (td, *J* = 11.3 Hz, 2.5 Hz, 1H), 2.23−2.17 (m, 1H), 1.93−1.88 (m, 1H), 1.56−1.40 (m, 2H), 1.39 (s, 3H), 1.18−1.06 (m, 2H), 1.04 (s, 3H). ^{13}C NMR ($CDCl_3$, 126 MHz): δ 156.7, 154.9, 140.8, 113.3, 109.8, 104.2, 94.8, 94.4, 76.9, 75.7, 65.2, 56.3, 55.2, 48.6, 36.5, 33.9, 33.2, 27.7, 26.1, 18.8. IR (neat, cm^{-1}): 3409 (br), 2918, 2849, 1577, 1431, 1056, 1042. Mass spec calcd for $C_{20}H_{30}O_6$, 366.2042; found, 366.2035. EI+(amu): 366 (M+, 26), 260 (100), 245 (28), 217 (34), 177 (10); $[\alpha]^{23}_D$ −65.8° (*c* 0.012, CH_2Cl_2).

β-C9 Oxaza Benzyl Amine 43. Alcohol **41** (55 mg, 0.15 mmol) was dissolved in 2 mL of THF under N_2, was cooled to −40 °C, and was treated with NEt_3 (125 μL, 0.90 mmol) and MsCl (50 μL, 0.65 mmol). The reaction mixture was allowed to stir at this temperature for 45 min and then was warmed to 0 °C and stirred for an additional 30 min. A solution of LiBr (130 mg, 1.50 mmol) in 2 mL of THF was added via cannula, and the reaction mixture was allowed to warm to room temperature and was stirred for 4 h. The reaction mixture was quenched with ice cold saturated $NaHCO_3$, extracted with Et_2O, washed with brine, and dried over Na_2SO_4. The crude bromide and amine **I** (24 mg, 0.17 mmol) were dissolved in 1 mL of DMF under N_2. K_2CO_3 (124 mg, 0.90 mmol) was added, and the mixture was stirred overnight. The solvent was removed under vacuum and then diluted with EtOAc, washed with water and brine and dried over Na_2SO_4. The crude product was subjected to column chromatography on silica gel eluting with 50% then 80% EtOAc/hexanes, affording amine **43** (55 mg, 75% yield over 2 steps) as a clear, colorless oil.

^{1}H NMR (MeOH-d_4, 300 MHz): δ 6.70 (d, *J* = 1.5 Hz, 1H), 6.47 (d, *J* = 1.5 Hz, 1H), 5.21 (d, *J* = 6.5 Hz, 1H), 5.16 (d, *J* = 6.5 Hz, 1H), 4.71 (s, 2H), 4.22−4.06 (m, 3H), 3.80 (s, 2H), 3.78−3.67 (m, 1H), 3.51−3.43 (m, 4H), 3.37 (s, 3H), 3.06−3.00 (m, 2H), 2.49 (td, *J* = 11.3 Hz, 2.4 Hz, 1H), 2.24−2.03 (m, 5H), 1.96−1.85 (m, 5H), 1.52−1.36 (m, 5H), 1.20 (td, *J* = 12.6 Hz, 3.5 Hz, 1H), 1.02 (s, 3H). ^{13}C NMR (MeOH-d_4, 126 MHz): δ 158.0, 156.0, 114.5, 112.9, 107.7, 95.9, 95.8, 77.9, 77.4, 68.9, 57.7, 56.6, 55.5, 50.9, 50.3, 38.2, 35.2, 34.4, 33.5, 32.8, 28.1, 27.1, 19.0. IR (neat, cm^{-1}): 2930, 1573, 1429, 1335, 1154, 1106, 1057. Mass spec calcd for $C_{28}H_{41}NO_6$, 487.2934; found, 487.2950. EI+(amu): 487 (M+, 61), 364 (19), 258 (100), 215 (62), 152 (35), 95 (51), 69 (73); $[\alpha]^{23}_D$ −60.3° (*c* 0.029, MeOH).

(6a*S*,9*R*,10a*R*)-6a,7,8,9,10,10a-Hexahydro-1,9-dihydroxy-6,6-dimethyl-6*H*-benzo[*c*]chromene-3-carbonitrile 45. To nitrile **31** (132 mg, 0.365 mmol) in 3.5 mL of DCM at rt was added *n*-BuSH (390 μL, 3.65 mmol) followed by $ZnBr_2$ (544 mg, 2.41 mmol) all at once. The reaction mixture was stirred for 15 min and then diluted with EtOAc, washed with saturated $NaHCO_3$ and brine, and dried over Na_2SO_4. The crude product was subjected to flash column chromatography on silica gel eluting with 50% then 80% EtOAc/hexanes, resulting in nitrile **45** (90 mg, 90% yield) as a white solid.

^{1}H NMR (MeOH-d_4, 300 MHz): δ 6.55 (s, 2H), 4.62 (br s, 1H), 3.80−3.70 (m, 1H), 3.52−3.44 (m, 1H), 2.50 (td, *J* = 11.2 Hz, 2.4 Hz, 1H), 2.17−2.08 (m, 1H), 1.94−1.86 (m, 1H), 1.52−1.31 (m, 5H), 1.22−1.16 (m, 1H), 1.03 (s, 3H), 1.00−0.89 (m, 1H). ^{13}C NMR (MeOH-d_4, 75 MHz): δ 158.7, 157.0, 119.8, 119.6, 113.6, 111.3, 110.6, 78.8, 71.1, 49.7, 39.2, 36.4, 35.2, 28.0, 27.0, 19.1; mp: 212.1 °C (dec). IR (neat, cm^{-1}): 3234 (br), 2982, 2972, 2864, 2224, 1711, 1568, 1424, 1344, 1270, 1057. HRMS calcd for $C_{16}H_{19}NO_3$, 273.1365; found, 273.11360. EI+(amu): 273 (M+, 72), 240 (53), 212 (100), 186 (18), 69 (36); $[\alpha]^{23}_D$ −152.6° (*c* 0.010, MeOH).

(6a*S*,9*R*,10a*R*)-6a,7,8,9,10,10a-Hexahydro-1,9-dihydroxy-6,6-dimethyl-6*H*-benzo[*c*]chromene-3-carbaldehyde 47. To an ice cold solution of nitrile **45** (140 mg, 0.51 mmol) in 5 mL of DCM was added DIPEA (460 μL, 2.56 mmol) followed by dropwise addition of TESCl (300 μL, 1.31 mmol). The reaction mixture was stirred for 20 min and then quenched with ice cold saturated $NaHCO_3$, diluted with Et_2O, washed with brine, and dried over Na_2SO_4. The crude nitrile was dissolved in 5 mL of DCM, cooled to −78 °C, and stirred for 10 min. DIBAL in PhMe (1.10 mL, 1.32 mmol, 1.2 M) was added dropwise, and the resulting mixture was stirred for 1 h. Excess DIBAL was quenched with acetone at −78 °C, and the reaction mixture was stirred with saturated Rochelle's salt at room temperature until the biphasic mixture was clear. EtOAc was added and the organic layer was separated, washed with brine, and dried over Na_2SO_4. The crude product was purified on a plug of silica gel eluting with 5% EtOAc/hexanes with 2% TEA present. The silylated aldehyde was dissolved in 5 mL of THF, treated with TBAF (550 mg, 1.74 mmol) at rt, and stirred until the reaction was shown to be complete by TLC analysis. Solid $CaCO_3$ was added to the flask and stirred for 15 min. EtOAc was added and the organic layer was separated, washed with brine, and dried over Na_2SO_4. The crude product was purified via flash column chromatography on silica gel eluting with 50% then 80% EtOAc/hexanes, resulting in aldehyde **47** (44 mg, 61% yield over 3 steps) as a white foam.

^{1}H NMR ($CDCl_3$, 300 MHz): δ 9.76 (s, 1H), 6.85 (d, *J* = 1.4 Hz, 1H), 6.79 (d, *J* = 1.4 Hz, 1H), 4.01−3.90 (m, 1H), 3.67−3.63 (m, 1H), 2.55 (td, *J* = 11.1 Hz, 2.1 Hz, 1H), 2.25−2.16 (m, 1H), 1.97−1.86 (m, 1H), 1.57−1.41 (m, 5H), 1.25−1.15 (m, 2H), 1.07 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 193.9, 158.7, 157.0, 137.4, 120.8, 112.5, 107.2, 78.4, 71.2, 49.9, 39.3, 36.5, 35.5, 28.1, 27.1, 19.1. IR (neat, cm^{-1}): 3338 (br), 2976, 2934, 2872, 1716,

1684, 1577, 1558, 1338, 1144, 1057. Mass spec calcd for $C_{16}H_{20}O_4$, 276.1362; found, 276.1375. EI+(amu): 276 (M+, 75), 258 (42), 243 (33), 215 (100), 189 (54), 142 (66); $[\alpha]^{23}_D$ −154.4° (*c* 0.007, MeOH).

Procedure for Reductive Amination (12−15). β-C9 1-Adamantyl Benzylamine 12. To a round-bottom flask equipped with a stir bar, reflux condenser, and Dean−Stark trap was added aldehyde **47** (10 mg, 0.036 mmol), 1-adamantanamine (6 mg, 0.040 mmol), and two 4 Å molecular sieve beads in benzene. The reaction mixture was heated at reflux overnight. The progress of the reaction was followed by IR, monitoring the disappearance of the carbonyl absorption. The solvent was removed under vacuum, and the crude imine was dissolved in dry MeOH and was treated with a spatula tip of 10% Pd/C. The reaction flask was purged with H_2 gas three times and the mixture was allowed to stir at room temperature overnight. The Pd/C was filtered off through a plug of celite. The crude product was purified on silica gel using 2.5, 5, 10% MeOH/DCM as the eluent resulting in amine **12** as a brown oil (12 mg, 81% yield over the 2 steps). HPLC (0.10 cm ×25 cm Luna C8(2) 5 μ, 20−60% MeCN in water (both containing 0.1% HCO_2H) over 30 min, 3 mL/min, UV detection at 280 nm) 15.87 min and 96.1% pure.

^{1}H NMR (MeOH-d_4, 500 MHz): δ 6.26 (d, *J* = 1.0 Hz, 1H), 6.24 (d, *J* = 1.0 Hz, 1H), 3.77−3.70 (m, 1H), 3.52 (br s, 3H), 2.44 (td, *J* = 11.2 Hz, 2.3 Hz, 1H), 2.14−2.06 (m, 4H), 1.92−1.88 (m, 1H), 1.81−1.63 (m, 13H), 1.47−1.29 (s, 5H), 1.19 (td, *J* = 12.8 Hz, 3.3 Hz, 1H), 1.01 (s, 3H), 0.95−0.88 (m, 1H). ^{13}C NMR (MeOH-d_4, 126 MHz): δ 158.1, 156.3, 140.8, 112.2, 109.8, 108.6, 77.7, 71.3, 52.4, 50.3, 45.3, 42.8, 40.0, 37.7, 36.7, 35.0, 31.0, 28.2, 27.2, 19.1. IR (neat, cm^{-1}): 3282 (br), 2976, 2906, 2844, 1576, 1363, 1232, 1134, 1054. Mass spec calcd for $C_{26}H_{37}NO_3$, 411.2773; found, 411.2760. EI+(amu): 411 (M+, 10), 207 (23), 151 (82), 135 (28), 94 (100), 77 (30), 67 (23); $[\alpha]^{23}_D$ −109.5° (*c* 0.008, MeOH).

Procedure for Suzuki−Miyaura Coupling. β-C9 Styrenyl ketone 54. A 4:1 solution of DMF/EtOH(abs) over 4 Å molecular sieves was degassed by bubbling Ar through the solution for 20 min. In a separate flask equipped with a stir bar was added triflate **29** (65 mg, 0.13 mmol), boronate **53** (45 mg, 0.17 mmol), K_2CO_3 (62 mg, 0.45 mmol), and $PdCl_2$(dppf)·DCM (12 mg, 0.015 mmol). The reaction flask was evacuated and purged with Ar three times, then 2 mL of the DMF/EtOH mixture was added and the reaction mixture was heated at 70 °C for 6 h. The flask was cooled to room temperature; the mixture was filtered through cCelite and concentrated directly onto celite. The crude product was purified via flash column chromatography on silica gel eluting with 10, 20, 30, and 40% EtOAc/hexanes, resulting in ketone **54** as a clear, colorless oil as a mixture of diastereomers (55 mg, 87% yield).

^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.63 (d, *J* = 6.0 Hz, 1H), 6.51−6.47 (m, 1H), 6.12 (d, *J* = 5.7 Hz, 1H), 5.22−5.12 (m, 2H), 4.73 (dd, *J* = 10.5 Hz, 6.9 Hz, 1H), 3.79−3.68 (m, 1H), 3.49 (s, 3H), 3.43−3.34 (m, 4H), 2.91−2.83 (br s, 1H), 2.80−1.84 (m, 13H), 1.55−1.25 (m, 5H), 1.20−1.03 (m, 5H). IR (neat, cm^{-1}): 2924, 2853, 1712, 1608, 1564, 1422, 1367, 1209, 1141, 1105, 1056, 1041. Mass spec calcd for $C_{28}H_{38}O_6$, 470.2668; found, 470.2667. EI+(amu): 470 (M+, 26), 85 (100), 83 (51), 69 (26), 67 (21).

Procedure for $NaBH_4$ Reduction of Styrenyl Ketones. β-C9 *endo*-Alcohol 56. Ketone **54** (55 mg, 0.117 mmol) in 2 mL of MeOH was cooled to 0 °C and $NaBH_4$ (22 mg, 0.58 mmol) was added all at once and stirred for 30 min. The reaction was quenched with brine and the crude product was extracted with EtOAc and dried over Na_2SO_4. The crude product was quickly purified via flash column chromatography eluting with 50% EtOAc/hexanes, affording a diastereomeric mixture of endoalcohol **56** as a clear, colorless oil (50 mg, 90% yield).

^{1}H NMR (C_6D_6, 300 MHz): δ 6.99−6.95 (m, 2H), 6.43 (d, *J* = 6.0 Hz, 1H), 5.03−5.00 (m, 1H), 4.92−4.90 (d, *J* = 6.6 Hz, 1H), 4.77−4.70 (dd, *J* = 14.6 Hz, 6.8 Hz, 2H), 3.93 (br s, 1H), 3.74−3.67 (m, 2H), 3.28−3.23 (m, 7H), 2.60−2.48 (m, 4H), 2.20−1.81 (m, 5H), 1.68 (dt, *J* = 14.7 Hz, *J* = 5.1 Hz, 1H), 1.57−1.22 (m, 8H), 0.96 (s, 3H), 0.82−0.69 (m, 1H). IR (neat, cm^{-1}): 3566 (br), 2974, 2923, 2825, 1610, 1561, 1153, 1106, 1055, 1042. Mass spec calcd for $C_{28}H_{40}O_6$, 472.2825; found, 472.2823. EI+(amu): 472 (M+, 100), 366 (94), 360 (14), 279 (14), 149 (44), 91 (31), 79 (30), 69 (35).

Deprotection and Cyclization Reaction. β-C9 Oxaadamantane 16. To alcohol **56** (26 mg, 0.055 mmol) in 2 mL of DCM was added *n*-BuSH (135 μL, 1.27 mmol) at rt followed by $ZnBr_2$ (62 mg, 0.28 mmol) all at once. The reaction mixture was stirred for 20 min and then diluted with EtOAc and saturated $NaHCO_3$. The organic layer was washed with brine and dried over Na_2SO_4. The crude product was purified via flash column chromatography eluting with 40% and then 50% EtOAc/hexanes, affording oxaadamantane **16** (20 mg, 95% yield) as a white glass. Chiral HPLC (0.46 cm ×25 cm Chiralcel AD-H, 50% 2-propanol in hexanes, 1 mL/min, UV detection at 280 nm) 7.50 min and 98.1% pure.

^{1}H NMR (C_6D_6, 500 MHz): δ 8.51 (br s, 1H, OH), 6.87 (s, 1H), 6.79 (s, 1H), 4.24 (br s, 1H), 4.01−3.99 (m, 1H), 3.85−3.80 (m, 1H), 2.56 (br t, *J* = 10.8 Hz, 1H), 2.15−1.87 (m, 8H), 1.63−1.15 (m, 12H), 0.97 (s, 3H), 0.81−0.74 (m, 1H). ^{13}C NMR (C_6D_6, 126 MHz): δ 156.8, 155.6, 147.6, 111.0, 105.8, 104.3, 76.6, 73.0, 71.6, 69.2, 48.5, 42.3, 41.9, 38.6, 35.8, 35.7, 35.2, 34.2, 28.0, 26.4, 19.3. IR (neat, cm^{-1}): 3336 (br), 2975, 2928, 2852, 1622, 1577, 1418, 1051. Mass spec calcd for $C_{24}H_{32}O_4 + H^+$, 385.2380; found, 385.2379. $[\alpha]^{23}_D$ −98.7° (*c* 0.008, MeOH)

Binding Assays: Rat brain CB1, mouse and human CB2 binding assays. Compounds were tested for their affinities for the CB1 and CB2 receptors using membrane preparations from rat brain or HEK293 cells expressing either mCB2 or hCB2, respectively, and [^{3}H]CP-55,940, as previously described.[22,26−29] Results from the competition assays were analyzed using nonlinear regression to determine the IC_{50} values for the ligand; K_i values were calculated from the IC_{50}[30] (Prizm by GraphPad Software, Inc.). Each experiment was performed in triplicate and K_i values determined from one experiment.

Acknowledgment. We thank The National Institute on Drug Abuse (DA07215, 2 P01 DA09158, 5 R01 DA03801) for generous support of this research. The contributions of Yan Peng, Shivangi Joshi, and Han Zhou in performing the binding assays are also acknowledged by the authors. We thank Dr. David Le Goanvic for supplying compounds **2** and **3**.

Supporting Information Available: Optimized experimental procedures for the synthesis of **1**. Preparation of vinyl boronate **53**. Spectroscopic data for **30**, **32**, **36**−**40**, **5**, **7**−**11**, **42**, **44**, **46**, **48**, **13**−**15**, **55**, **57**, **17**, **49**−**53**; reproductions of ^{1}H and ^{13}C NMR spectra of **4**−**17**, **24**, **25**, **27**−**50**, **52**, **53**. This material is available free of charge via the Internet at http://pubs.acs.org.

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