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C1′-Azacycloalkyl Hexahydrocannabinols

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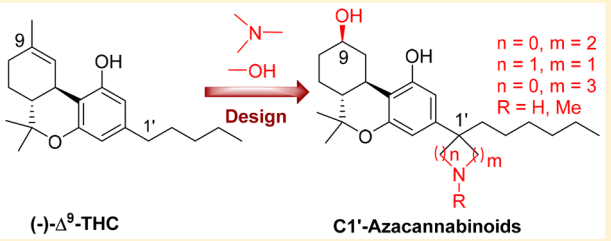
Supporting Information

ABSTRACT: We report the design, synthesis, and biological evaluation of a novel class of cannabinergic ligands, namely C1′-azacycloalkyl hexahydrocannabinols. Our synthetic approaches utilize an advanced common chiral intermediate triflate from which all analogues could be derived. Key synthetic steps involve microwave-assisted Liebeskind−Srogl C−C cross-coupling and palladium-catalyzed decarboxylative coupling reactions. The C1′-*N*-methylazetidinyl and C1′-*N*-methylpyrrolidinyl analogues were found to be high affinity ligands for the CB1 and CB2 cannabinoid receptors.



1. INTRODUCTION

Classical cannabinoids are a class of naturally occurring and synthetic compounds that have been developed following the discovery of (−)-Δ^9-tetrahydrocannabinol [(−)-Δ^9-THC, **1a**, Figure 1], the primary psychoactive ingredient of marijuana.[1] The therapeutic effects of these analogues rely on their ability to bind to and modulate the two $G_{i/o}$-protein-coupled cannabinoid receptors CB1[2] and CB2[3] that are remarkably abundant in the human body.[1,4] Within the classical cannabinoid scaffold, the C3 side chain (SC) has been recognized as the most critical pharmacophoric group.[1] On this front, earlier SAR work in our laboratories has led to a variety of successful cannabinoid side chains including for example, the sterically demanding adamantyl[5] and heteroadamantyl[6,7] groups as well as novel chains with conformational restrictions imposed by cyclic moieties at the C1′-position[8,9] (e.g., **1b**, Figure 1). Notably, among them the C1′-cyclobutyl- and C1′-cyclopentyl-substituted chains confer to the molecules exceptionally high in vitro and in vivo potency and efficacy.[8−10]

Also, a major problem for developing THC-based pharmacological tools and potential drug candidates is the high lipophilicity of these molecules which, at least in part, is due to the C3 aliphatic chain.[10,11] Thus, THC analogues exhibit a number of undesirable biopharmaceutical properties including extended residency in fatty tissue, high plasma protein binding, and extremely low water solubility that requires solubilization of these molecules with either a surfactant agent or adherence to a water-miscible substance (e.g., albumin, emulphor, or Tween).[12,13] Earlier efforts seeking to circumvent the lipophilicity issue without compromising the CNS activity of the cannabinoids have incorporated moderately basic nitrogen atoms at the B- and C-rings of the classical cannabinoid prototype.[1]

Taking all the above into consideration, we have now designed C1′-azacycloalkyl hexahydrocannabinols where a nitrogen atom was introduced at the C1′-cycloalkyl substituent of our earlier generation THC analogues. To further enhance the polar characteristics of our molecules, we also introduced a hydrophilic equatorial hydroxyl group at the C9 of the tricyclic cannabinoid structure (Figure 1). The choice of the relative stereochemistry at C9 was based on our earlier lead optimization and pharmacophore refinement work on the classical cannabinoid prototype.[5,6,8,11] The synthetic effort has resolved many challenges imposed by the presence of a benzylic nitrogen atom that renders the synthetic intermediates unstable during the chemical manipulations. Biological testing results show that the novel C1′-*N*-methylazetidinyl and C1′-*N*-methylpyrrolidinyl analogues have high binding affinities for both the CB1 and the CB2 receptors. The salts of the C1′-azetidinyl and pyrrolidinyl analogues with succinic, L-(+)-tartaric, and hydrochloric acid are also described.

2. RESULTS AND DISCUSSION

2.1. Synthesis. All materials were prepared starting from triflate **2**, which is readily accessed from (−)-*β*-pinene and persilylated phloroglucinol as we have described previously.[6] Palladium-catalyzed coupling of **2** with bis(pinacolato)diboron led to boronic ester **3** in 84% yield (Scheme 1).

The critical factor for the success of the Miyaura borylation is the base.[14] The hydrolysis of boronate ester **3** to the boronic acid was unexpectedly challenging. Conventional methods using strong acid[15] were avoided because the methoxymethyl ethers and the dihydrobenzopyran ring in **3** are susceptible to acid-

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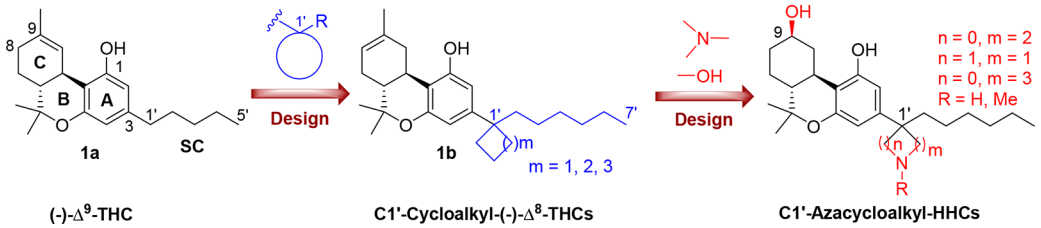
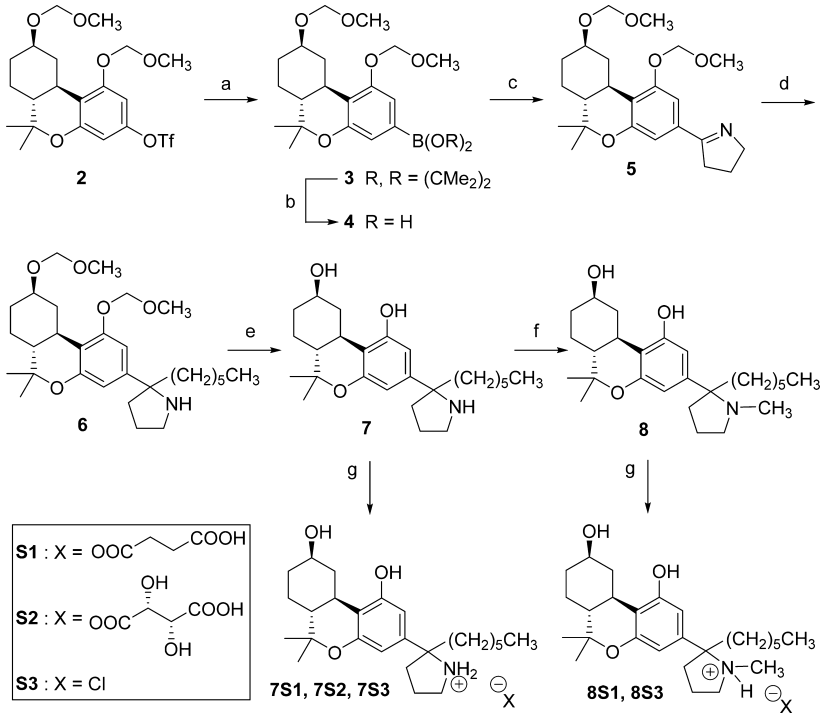


Figure 1. Design of the *C*1′-azacycloalkyl-hexahydrocannabinols and structures of the prototype (−)-Δ^9-THC and the first generation *C*1′-cycloalkyl-(−)-Δ^8-THCs.

Scheme 1. Synthesis of 2,2-Disubstituted Pyrrolidine Cannabinoids[a]



[a]Reagents and conditions: (a) AcOK, B_2pin_2, $PdCl_2(dppf)$, DMF, 90 °C, 3.5 h, 84%; (b) $NaIO_4$, NH_4OAc, $(CH_3)_2CO/H_2O$, rt, 20 h; (c) Cu(I)thiophene carboxylate, pyrrolidine-2-thione, $Pd_2(dba)_3{\cdot}CHCl_3$, PPh_3, THF, microwaves, 100 °C, 2 h, 62% from **3**; (d) i. LiCl, THF, rt, 30 min, ii. *n*-$C_6H_{13}Li$, −10 °C to rt, 2 h, 92%; (e) $Sc(OTf)_3$, 1,3-propanediol, CH_3CN, reflux, 48 h, 91%; (f) i. $(HCHO)_n$, $Ti(OiPr)_4$, diglyme, 60 °C, 30 min, rt, 30 min, ii. $NaBH_4$, rt, 3 h, 60 °C, 3 h, 80%; (g) i. succinic acid, CH_3OH, rt, 12 h for **S1**, quant. or ii. L-(+)-tartaric acid, CH_3OH, rt, 12 h for **S2**, quant. or iii. HCl, $(CH_3)_2CO$, rt, 12 h for **S3**, quant.

catalyzed cleavage. Although conversion to the potassium trifluoroborate salt by exposure to KHF_2 in aqueous methanol was successful, we were unable to isolate the product sufficiently pure for the next step. Hydrolysis of the trifluoroborate with bases, such as K_2CO_3 and LiOH,[16] or with water−silica gel[17] also provided a boronic acid sample that was unstable and underwent decomposition during hydrolysis. Hydrolysis of pinacolboronate **3** was complicated by the instability of the product as well as the propensity of the liberated diol to regenerate the pinacolboronate ester.[18] Exposure of **3** to sodium periodate in aqueous ammonium acetate and acetone led to a clean sample of the boronic acid **4** through an oxidative cleavage process. The sensitive boronic acid was used in the following step without purification.

Palladium(0)-catalyzed, copper(I)-mediated desulfitative C−C cross coupling of **4** with pyrrolidine-2-thione in a microwave reactor at 100 °C for 2 h led to cyclic imine **5** in 62% yield from **3**.[19] It is noteworthy that this Liebeskind−Srogl reaction proceeded very slowly (ca. 3 days) even with 10 mol % catalyst loading under conventional conditions of heating in refluxing THF or dioxane and led to imine **5** in only 35−46% yield, whereas only 4 mol % $Pd_2(dba)_3{\cdot}CHCl_3$ was used in the microwave reaction.

The next step was addition of *n*-hexyllithium to the imine function in **5**. Exposure of **5** to 4.0 equiv of anhydrous LiCl in THF, followed by *n*-hexyllithium, generated from 1-iodohexane through lithium−iodine exchange with *tert*-butyllithium at −10 °C to room temperature led to **6** in 92% yield. The role of the LiCl may be to deaggregate oligomeric forms of *n*-hexyllithium, thereby rendering them more highly nucleophilic.[20]

The hydrolytic cleavage of the methoxymethyl groups in **6** was predictably challenging because of the presence of the benzylic nitrogen atom which exerts a buffering effect on the acid and which can lead to decomposition through competitive generation of a benzylic carbocation in the presence of acid. We eventually determined that exposure of **6** to stoichiometric scandium(III) triflate in the presence of excess 1,3-propanediol in acetonitrile at reflux led to a clean reaction, providing **7** in 91% yield. The use of catalytic scandium triflate as described in an earlier report[21] failed to drive the reaction to completion and did

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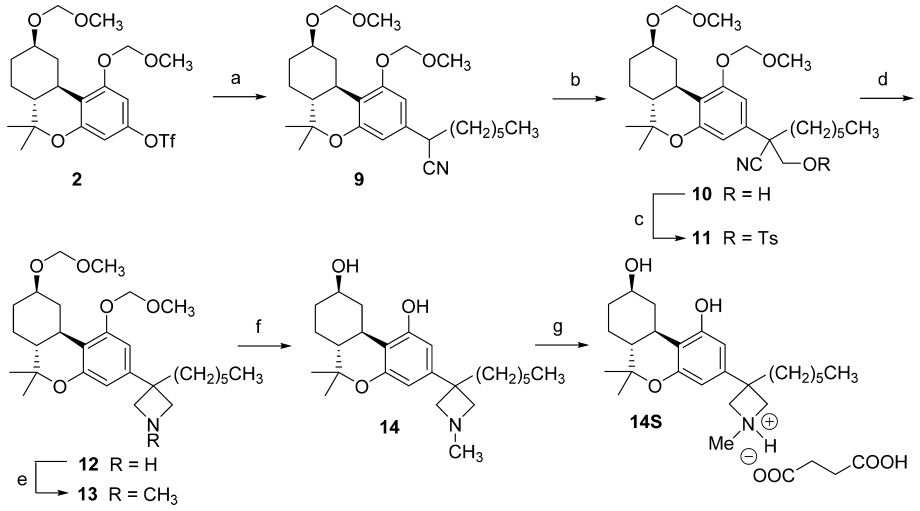
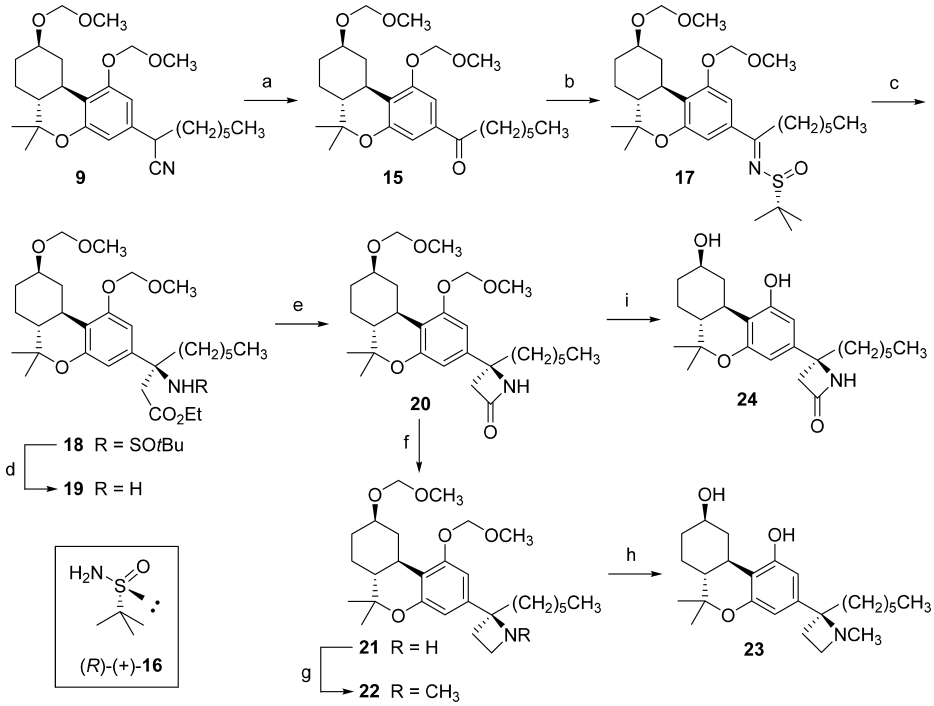
Scheme 2. Synthesis of 3,3-Disubstituted Azetidine Cannabinoids[a]



[a]Reagents and conditions: (a) $[PdCl(C_3H_5)]_2$, potassium 2-cyanooctanoate, Xantphos, xylene, 130 °C, 16 h, 82%; (b) $(HCHO)_n$, 40% Triton B/CH_3OH, toluene, 60 °C, 26 h, 95%; (c) *p*-TsCl, Et_3N, DMAP, CH_2Cl_2, rt, 4 h, 94%; (d) $LiAlH_4$, THF, rt, 3 h; (e) i. 37% HCHO (aq), CH_3OH, rt, 2 h, ii. $NaBH_4$, rt, 2 h, 62% from **11**; (f) $Sc(OTf)_3$, C_2H_5OH, CH_3CN, reflux, 12 h, 89%; (g) succinic acid, CH_3OH, rt, 12 h, quant.

Scheme 3. Diastereoselective Synthesis of 2,2-Disubstituted Azetidine Cannabinoids[a]



[a]Reagents and conditions: (a) i. NaHMDS, THF, rt, 30 min, ii. O_2 (gas), −78 °C, 30 min, iii. Na_2SO_3 (aq), 0 °C, 30 min, 74%; (b) (*R*)-(+)-**16**, $Ti(OEt)_4$, THF, reflux, 19 h, 92%; (c) $CH_3COOC_2H_5$, LDA, $TiCl(Oi\text{-}Pr)_3$, THF, −78 °C, 1 h, 81%; (d) HCl/1,4-dioxane, CH_3OH, 10 °C, 2 h, 85%; (e) CH_3MgBr, Et_2O, rt, 1.5 h, 78%;(f) $LiAlH_4$, THF, 65 °C, 24 h; (g) i. 37% HCHO (aq), CH_3OH, rt, 3 h, ii. $NaBH_4$, rt, 2 h, 70% from **20**; (h) Dowex 50W-X8, CH_3OH, rt, 30 h, 77%; (i) $LiBF_4$, CH_3CN, H_2O, 72 °C, 18 h, 87%.

not lead to the selective removal of the methoxymethyl groups. Excess scandium(III) (5 equiv) led to complicated product mixtures, from which the byproducts were not isolated. Substituting ytterbium(III) triflate for scandium triflate did not lead to a satisfactory result.

Conventional Eschweiler−Clarke conditions for N-methylation of **7** (formalin, formic acid at reflux)[22] or formaldehyde and sodium cyanoborohydride in acid[23] could not be used. The reductive N-methylation was accomplished in 80% yield by exposing **7** to paraformaldehyde and titanium isopropoxide in diglyme, followed by sodium borohydride.[24] The salts of **7** and **8** with succinic, L-(+)-tartaric or hydrochloric acid were prepared by exposure to equimolar amounts of the respective acids.

The synthesis of 3,3-disubstituted azetidine cannabinoid **14** is summarized in Scheme 2. Coupling triflate **2** to the enolate derived from ethyl 2-cyanooctanoate according to the Buchwald−Hartwig α-arylation conditions did not lead to the desired product. Most examples of this reaction have been

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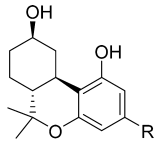
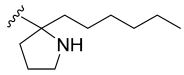
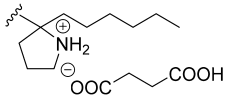
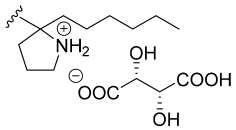
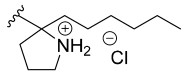
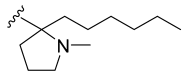
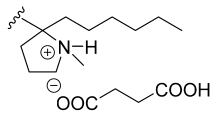
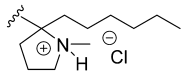
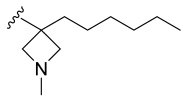
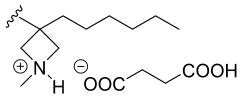
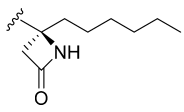
Table 1. CB1/CB2 Affinities (K_i) of C1′-Azacycloalkyl Hexahydrocannabinols and Their Quaternary Ammonium Salts (95% confidence limits)



compd	R	(K_i, nM)[a]		
		rCB1	mCB2	hCB2
(-)-Δ^9-THC		39.5[b]	40[b]	36.4[b]
7		~ 900	~ 650	~ 560
7S1		>1,000	>1,000	>1,000
7S2		~ 890	~ 780	~ 750
7S3		~ 740	~ 710	~ 730
8		36.2 ± 5.8	17.3 ± 4.1	70.7 ± 6.8
8S1		16.3 ± 1.8	12.3 ± 1.4	26.2 ± 1.1
8S3		33.9 ± 5.1	14.5 ± 3.2	50.4 ± 6.2
14		22.4 ± 3.3	33.6 ± 5.2	89.1 ± 8.3
14S		19.2 ± 2.2	21.3 ± 4.3	100 ± 8
24		216 ± 23	N D	221 ± 20

[a]Affinities for CB1 and CB2 receptors were determined using rat brain (CB1) preparations or membranes from HEK293 cells expressing mouse or human CB2 receptors and [^{3}H]CP-55,940 as the radioligand following previously described procedures.[8,10] Data were analyzed using nonlinear regression analysis. In a preliminary evaluation three-point data for all test compounds were obtained from one experiment (three points) run in triplicate (approximate K_i values). Subsequently, the most promising compounds (approximate K_i < 300 nM) were further tested using eight point curves, and K_i values were obtained from three independent experiments (eight points) run in duplicate and are expressed as the mean of the three values. [b]Reported previously.[41] ND: Not determined.

described for aryl bromides rather than aryl triflates.[25] An alternative, mechanistically intriguing procedure developed by Liu and co-workers was employed successfully.[26]

Palladium-catalyzed decarboxylative coupling of potassium 2-cyanooctanoate with **2** provided a diastereomeric mixture of nitriles **9** in 82% yield. Condensation of **9** with excess paraformaldehyde in the presence of Triton B in toluene at 60 °C in a resealable sealed tube led to diastereomeric alcohols **10** in 95% yield. Formation of tosylates **11**[27] (94% yield) was followed by reductive cyclization to **12** with $LiAlH_4$ in THF at room

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temperature.[28] Reductive methylation of crude **12** led to *N*-methylazetidine **13** in 62% overall yield for the two steps from **11**.[29] Cleavage of the methoxymethyl protecting groups with stoichiometric scandium(III) triflate in the presence of excess ethanol led to **14** in 89% yield. Using ethanol in place of 1,3-propanediol, as had been used in the case of **6**, greatly simplified the workup. *N*-Methylazetidine **14** was converted to the hemisuccinate salt.

Azacannabinoid **8** was prepared as a mixture of C1′ diastereomers. Development of a diastereoselective synthesis would be justified if strong activity had been observed. The C1′ position in **14** is not stereogenic, but in **23** it is (Scheme 3). We carried out the diastereoselective synthesis that is summarized in Scheme 3, starting from C1′ nitrile **9**. Oxidative cleavage of the cyano group from **9** led to phenone **15** in 74% yield.[30] This was followed by titanium(IV) ethoxide-mediated condensation with the Ellman reagent (*R*)-(+)-*tert*-butylsulfinamide **16** which led to *N*-sulfinylimine **17** in 92% yield.[31] Approximately 2.0−3.0 equiv of titanium ethoxide and a small excess (1.1−1.3 equiv) of the sulfinamide led to an excellent yield of **17**, whereas the reaction was slow and did not proceed to completion with stoichiometric titanium ethoxide. Sulfinylimine **17** was isolated as a single *E* geometric isomer.[32] Nucleophilic addition of the titanium enolate of ethyl acetate, generated from transmetalation of the lithium enolate, to **17** furnished ester **18** in 81% yield (dr 9:1).[33,34] Cleavage of the *tert*-butylsulfinyl group in **18** took place upon treatment in methanolic solution with 4 M HCl in dioxane at 10 °C, leading to amino ester **19** in 85% yield. Temperature and reaction time had to be controlled carefully in order to avoid methanolysis of the methoxymethyl groups. We followed the strategy originally proposed by Testa for the construction of the azetidinone ring.[35] Exposure of **19** to ca. 3 equiv of methylmagnesium bromide in ether at room temperature led to **20** in 78% yield.

Complexation of the nonbonding electron pair of the basic nitrogen atom in **19** with the Lewis acidic magnesium atom of the Grignard reagent may lead to kinetic N−H deprotonation. The nucleophilic amide thus formed would undergo rapid cyclization, leading to azetidinone **20**. Once formed, **20** is converted to the bromomagnesium salt through rapid deprotonation by the Grignard reagent that is present in excess and is thus protected against nucleophilic attack. Alternatively, the azetidinone ring may be formed through an indirect process that involves the initial formation of the ester enolate. Because the amine is much less acidic than the ester (the difference in pK_a values is approximately 10)[36,37] in any thermodynamically controlled process the amide anion would be present as a minor component in equilibrium with the ester enolate. Even so, the small amount of deprotonated amine could attack the adjacent ester carbonyl group to form lactam **20**.

Reduction of lactam **20** with $LiAlH_4$ in THF at 65 °C gave azetidine **21** in a clean reaction. Reductive methylation of crude **21** with aqueous formaldehyde in methanol and sodium borohydride led to *N*-methylazetidine **22** in 70% yield for the two steps from **20**. In contrast to **6** and **13**, attempted cleavage of the methoxymethyl protecting groups of **20** with scandium triflate led to complicated mixtures; however, clean removal of both protecting groups was accomplished by exposure to $LiBF_4$ in aqueous acetonitrile in 87% yield.[38] Cleavage of the methoxymethyl ether groups from **22** was accomplished by exposure to Dowex 50W-X8 resin (H^+ form) in methanol at room temperature, leading to **23** in 77% yield.[39] Tertiary amine **23** was labile and quickly formed what appeared by ^{1}H NMR and ESI-MS to be the *N*-oxide. Because of this unexpected reactivity, the cannabinoid activity of tertiary amine **23** was not determined. Instead, lactam **24** was prepared and its activity was evaluated.

2.2. Biological Evaluations. The abilities of C1′-aza-hexahydrocannabinoids **7**, **8**, **14**, **24**, and their salts **7S1**, **7S2**, **7S3**, **8S1**, **8S3**, and **14S** to displace the radiolabeled CB1/CB2 agonist CP-55,940 from membranes prepared from rat brain (source of CB1) and HEK 293 cells expressing either mouse CB2 or human CB2 were determined as described previously,[8,10] and inhibition constant values (K_i) from the respective competition binding experiments are listed in Table 1 in which the prototype (−)-Δ^9-THC is also included for comparison. Because of its low chemical stability the 2,2-disubstituted *N*-methylazetidine analogue **23** was not evaluated for binding affinities. Also, in our receptor binding assays we have used two CB2 receptor preparations in order to address species differences that we observed previously.[40]

The compounds included in this study are C9-hydroxy-substituted hexahydrocannabinol analogues in which a seven atom long side chain carries a four- or five-membered nitrogen-containing ring at the C1′-position. The binding data depicted in Table 1 show that the introduction of different ring substituents at the benzylic carbon atom of the side chain can lead to a wide range of affinities for the CB1 and CB2 receptors (∼11−1000 nM), indicating a very stringent SAR for this class of analogues. Thus, the 2,2-disubstituted *N*-methylpyrrolidine analogue **8** exhibits similar binding affinities to that of the cannabinoid prototype (−)-Δ^9-THC. A comparison of the binding data of the two 2,2-disubstituted pyrrolidine analogues **7** and **8** demonstrates the remarkable effects of a tertiary versus a secondary nitrogen in the five-membered ring. Thus, the *N*-methylpyrrolidine analogue **8** exhibits 25-, 37-, and 8-fold higher binding affinities for the rCB1, mCB2, and hCB2 receptors, respectively, when compared to the pyrrolidine analogue **7**. We also observe that the corresponding succinic, hydrochloric, and L-(+)-tartaric salts of these C1′-pyrrolidinyl analogues match the binding affinity trends of their parent amines.

A cursory examination of the binding affinities of the two *N*-methyl cyclic amine analogues **8** and **14** as well as their respective succinic salts **8S1** and **14S** reveals that contraction of the five-membered *N*-methyl pyrrolidine ring to the four-membered azetidine maintains the affinity of the ligand for both the CB1 and CB2 receptors. However, conversion of the C1′-*N*-methylazetidinyl and C1′-*N*-methylpyrrolidinyl substituents seen in **8** and **14** to a four-membered lactam (compound **24**) results in a reduction of the ligands' affinity which is more accentuated in CB1 (∼6- to 10-fold). A comparison of the CB2 binding affinity data of the most successful C1′-*N*-methylazetidinyl and C1′-*N*-methylpyrrolidinyl analogues as well as their quaternary ammonium salts show that these C1′-azacannabinoids exhibit a slight preference for the mouse versus the human CB2 receptors (approximately 2- to 4-fold).

3. CONCLUSION

We report the design, synthesis, and biological evaluation of a novel class of cannabinergic ligands namely C1′-azacycloalkyl hexahydrocannabinols. Our synthetic approaches utilize an advanced common chiral intermediate triflate from which all analogues could be derived. Key synthetic steps involve microwave-assisted Liebeskind−Srogl C−C cross-coupling and palladium-catalyzed decarboxylative coupling reactions. We conclude that this study adds to earlier work in which we focused on the cannabinoid chain's benzylic position and the

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related subsite within the receptor's binding domain.[8,9] The current SAR extends the mapping of the C1′ pharmacophoric space to include druggable bioisosteric groups such as four- and five-membered nitrogen-containing heterocyclic rings. The most successful *C*1′-*N*-methylazetidinyl and *C*1′-*N*-methylpyrrolidinyl analogues were converted to their quaternary ammonium salts. Further in vitro and in vivo pharmacological evaluation of the key *C*1′-aza-hexahydrocannabinoids reported here is underway.

4. EXPERIMENTAL SECTION

General. ^{1}H NMR and ^{13}C NMR spectra were recorded 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. Microwave irradiation experiments: Microwave reactions were carried out using a CEM Discovery SP Microwave System with an Explorer 12 hybrid autosampler attachment, including Synergy software. Experiments were carried out in sealed microwave process vials utilizing the standard absorbance level (300 W maximum power). The reaction vials (35 mL) were placed in the microwave reactor where the temperature was raised to 100 °C in 10 min and held at that temperature for 2 h. The temperature was measured with an IR sensor on the outside of the reaction vessel.

*2-((6aR,9R,10aR)-1,9-Bis(methoxymethoxy)-6,6-dimethyl-6a,7,8,9,10,10a-hexahydro-6H-benzo[c]chromen-3-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**3**).* To a mixture of triflate **2** (485 mg, 1.0 mmol), diboron pinacol ester (305 mg, 1.20 mmol), KOAc (295 mg, 3.0 mmol), and $PdCl_2$(dppf) (30 mg, 0.04 mmol) under an argon atmosphere at room temperature was added DMF (10 mL), and the reaction mixture was stirred at 90 °C for 3.5 h. After the mixture was cooled to room temperature, water was added, and the organic material was extracted with benzene/Et_2O (1/1). The combined organic layer was washed with water, brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash silica gel column chromatography with EtOAc/hexane (1/4) as eluent to afford pinacol boronic ester **3** (387 mg, 84% yield) as a light yellow amorphous solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.97 (d, J = 1.0 Hz, 1H), 6.95 (d, J = 1.0 Hz, 1H), 5.28−5.17 (m, 2H), 4.77−4.69 (m, 2H), 3.75 (tt, J = 11.1, 4.5 Hz, 1H), 3.51 (s, 3H), 3.46−3.40 (m, 1H), 3.38 (s, 3H), 2.49 (td, J = 11.3, 2.6 Hz, 1H), 2.23−2.14 (m, 1H), 1.93−1.86 (m, 1H), 1.57−1.49 (m, 1H), 1.49−1.39 (m, 1H), 1.37 (s, 3H), 1.30 (s, 6H), 1.29 (s, 6H), 1.18−1.04 (m, 2H), 1.02 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.0, 154.4, 128.3, 118.0, 117.3, 110.5, 94.6, 94.4, 83.6, 76.5, 75.6, 56.4, 55.1, 48.6, 36.4, 34.2, 33.1, 27.7, 26.1, 24.8, 24.7, 18.7. ^{11}B NMR (160 MHz, $CDCl_3$) δ 31.6 (external reference BF_3·Et_2O). IR (thin film, cm^{-1}): 3048, 2940, 2878, 1558, 1365, 1141, 1042, 979, 856, 740. HRMS ((+)-ESI-TOF) m/z calcd for $C_{25}H_{40}BO_7$ $[M + H]^+$, 463.2862; found 463.2888. $[\alpha]^{23}_D$ −46.8° (c 3.0, CH_3OH).

*5-((6aR,9R,10aR)-1,9-Bis(methoxymethoxy)-6,6-dimethyl-6a,7,8,9,10,10a-hexahydro-6H-benzo[c]chromen-3-yl)-3,4-dihydro-2H-pyrrole (**5**).* To a solution of pinacol boronic ester **3** (231 mg, 0.50 mmol) in acetone/water (10 mL, 1/1) were subsequently added $NaIO_4$ (320 mg, 1.50 mmol) and NH_4OAc (135 mg, 1.75 mmol). After being flushed with nitrogen, the thick suspension was stirred at room temperature until most of **3** was consumed as judged by TLC (ca. 20 h). Solvent was partially removed under reduced pressure at 23 °C, and the organic material was extracted with EtOAc. The combined organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure at 23 °C. Toluene was added in aliquots during concentration to avoid the decomposition of boronic acid **4**. The crude concentrated toluene solution (ca. 1 mL) of **4** was immediately diluted with THF (10 mL), and the solution was added to a microwave process vial containing pyrrolidine-2-thione (51 mg, 0.50 mmol), CuTC (285 mg, 1.50 mmol), Pd_2dba_3·$CHCl_3$ (21 mg, 0.02 mmol), and PPh_3 (21 mg, 0.08 mmol) under an argon atmosphere. The mixture was heated in a microwave reactor at 100 °C for 2 h. After cooling to room temperature, the mixture was concentrated under reduced pressure. $CHCl_3$ (120 mL) was added, and the organic layer was washed with 25% aqueous ammonia (40 mL × 3). The aqueous layer was back extracted with $CHCl_3$ (40 mL × 3). The combined organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography with EtOAc/hexane (2/3) as eluent to afford imine **5** (126 mg, 62% yield from **3**) as a light yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29 (d, J = 1.6 Hz, 1H), 6.81 (d, J = 1.6 Hz, 1H), 5.32−5.20 (m, 2H), 4.76−4.68 (m, 2H), 4.07−3.96 (m, 2H), 3.80−3.68 (m, 1H), 3.49 (s, 3H), 3.44−3.35 (m, 4H), 2.98−2.83 (m, 2H), 2.49 (td, J = 11.3, 2.6 Hz, 1H), 2.23−2.14 (m, 1H), 2.06−1.96 (m, 2H), 1.93−1.84 (m, 1H), 1.57−1.50 (m, 1H), 1.48−1.34 (m, 4H), 1.18−1.01 (m, 5H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.9, 156.4, 154.6, 133.1, 117.0, 112.0, 103.9, 94.7, 94.5, 77.1, 75.5, 60.6, 56.5, 55.1, 48.4, 36.3, 34.8, 34.1, 33.0, 27.6, 26.0, 22.3, 18.7. IR (neat, cm^{-1}): 3055, 2940, 2878, 1612, 1566, 1427, 1350, 1265, 1150, 1041, 987, 918, 740. HRMS ((+)-ESI-TOF) m/z calcd for $C_{23}H_{33}NNaO_5$ $[M + Na]^+$, 426.2251; found 426.2230. $[\alpha]^{23}_D$ −42.3° (c 2.0, CH_3OH).

*2-((6aR,9R,10aR)-1,9-Bis(methoxymethoxy)-6,6-dimethyl-6a,7,8,9,10,10a-hexahydro-6H-benzo[c]chromen-3-yl)-2-hexylpyrrolidine (**6**).* To a solution of 1-iodohexane (318 mg, 1.50 mmol) in Et_2O (3.0 mL) under an argon atmosphere at −78 °C was added a 0.9 M solution of *t*-BuLi in pentane (3.0 mL, 2.70 mmol) dropwise. The reaction mixture was stirred at −78 °C for an additional 30 min, warmed to room temperature over 20 min, and stirred at room temperature for an additional 1 h, at which time the mixture became a cloudy suspension. In another flask, a mixture of imine **5** (202 mg, 0.50 mmol), freshly azeotroped with benzene, and anhydrous LiCl (84 mg, 2.0 mmol) in THF (20 mL) under an argon atmosphere was stirred at room temperature for 30 min. The homogeneous solution was then cooled to −10 °C, followed by dropwise addition of *n*-hexyllithium via cannula. The reaction mixture was slowly warmed up from −10 °C to room temperature over 2 h. A solution of pH 7 phosphate buffer (3 mL) was added via syringe, and the organic material was extracted with Et_2O. The combined organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography with $NH_4OH_{(aq)}$/CH_3OH/CH_2Cl_2 (1/5/94) as eluent to afford amine **6** (225 mg, 92% yield) as a mixture of diastereoisomers at C1′ (brown oil). Interpretation of the ^{1}H and ^{13}C NMR spectra was rendered difficult by the presence of the two diastereomers that led to overlapping signals. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.78−6.74 (m, 1H), 6.48−6.43 (m, 1H), 5.34−5.18 (m, 2H), 4.77−4.68 (m, 2H), 3.73 (tt, J = 11.1, 4.5 Hz, 1H), 3.49 (s, 3H), 3.45−3.27 (m, 5H), 3.16−3.03 (m, 1H), 2.48−2.40 (m, 1H), 2.35−2.24 (m, 1H), 2.23−2.13 (m, 1H), 2.02−1.78 (m, 6H), 1.60−1.40 (m, 2H), 1.38 (s, 3H), 1.35−1.04 (m, 9H), 1.04 (s, 3H), 0.92−0.82 (m, 1H), 0.80 (t, J = 6.8 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.55, 154.61, 140.82, 113.00, 108.92, 103.78, 94.84, 94.65, 75.56, 71.16, 63.02, 56.49, 55.13, 53.39, 48.46, 44.02, 40.31, 36.31, 33.77, 33.13, 32.74, 31.48, 29.31, 27.72, 26.09, 24.77, 22.49, 18.84, 13.99. IR (neat, cm^{-1}): 3471, 3055, 2940, 2878, 1612, 1574, 1419, 1265, 1157, 1042, 918, 740. HRMS ((+)-ESI-TOF) m/z calcd for $C_{29}H_{48}NO_5$ $[M + H]^+$, 490.3527; found 490.3548.

*(6aR,9R,10aR)-3-(2-Hexylpyrrolidin-2-yl)-6,6-dimethyl-6a,7,8,9,10,10a-hexahydro-6H-benzo[c]chromene-1,9-diol (**7**).* To a mixture of amine **6** (49 mg, 0.10 mmol) and 1,3-propanediol (38 mg, 0.50 mmol) in CH_3CN (10 mL) at room temperature was added $Sc(OTf)_3$ (49 mg, 0.10 mmol). After being flushed with nitrogen, the reaction mixture was refluxed for 48 h. CH_3CN was removed under reduced pressure, and a minimum amount of pH 7 phosphate buffer (0.5 mL) was added and the reaction mixture was stirred for 10 min. The organic material was extracted with Et_2O, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography with $NH_4OH_{(aq)}$/CH_3OH/CH_2Cl_2

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(1/5/94 → 1/9/90) as eluent to afford amine **7** (36 mg, 91% yield) as a mixture of diastereoisomers at C1′ (brown amorphous solid). Interpretation of the ^{1}H and ^{13}C NMR spectra was rendered difficult by the presence of the two diastereomers that led to overlapping signals. ^{1}H NMR (500 MHz, CD_3OD): δ 6.31−6.26 (m, 2H), 3.74 (tt, J = 11.0, 4.5 Hz, 1H), 3.53−3.46 (m, 1H), 3.45−3.38 (m, 1H), 3.29−3.24 (m, 1H), 2.47 (td, J = 11.3, 5.7 Hz, 1H), 2.39−2.05 (m, 5H), 1.99−1.83 (m, 3H), 1.49−1.15 (m, 11H), 1.12−0.80 (m, 10H). ^{13}C NMR (126 MHz, CD_3OD): δ 158.6, 156.9, 139.4, 114.0, 107.3, 105.8, 78.4, 73.8, 71.2, 50.0, 44.6, 39.6, 38.9, 36.6, 34.9, 32.5, 30.2, 29.4, 28.1, 27.1, 25.3, 23.5, 22.9, 19.2, 14.3. IR (thin film, cm^{-1}): 3184−3584 (br), 3055, 2936, 2870, 1620, 1582, 1421, 1265, 1174, 1029, 741, 704, 638. HRMS ((+)-ESI-TOF) m/z calcd for $C_{25}H_{40}NO_3$ $[M + H]^+$, 402.3003; found 402.2991.

*(6aR,9R,10aR)-3-(2-Hexyl-1-methylpyrrolidin-2-yl)-6,6-dimethyl-6a,7,8,9,10,10a-hexahydro-6H-benzo[c]chromene-1,9-diol (**8**).* To a mixture of secondary amine **7** (ca. 10 mg, 0.025 mmol) and paraformaldehyde (ca. 3 mg) under an argon atmosphere at room temperature was added a 0.05 M solution of Ti(O*i*-Pr)$_4$ in freshly distilled diglyme (1 mL, 0.05 mmol). The reaction mixture was stirred at 60 °C for 30 min and then at room temperature for an additional 30 min. $NaBH_4$ (ca. 20 mg, 0.53 mmol) was added, and the resulting mixture was stirred at room temperature for 3 h and then at 60 °C for an additional 3 h. After the mixture was cooled to 0 °C, a 2 M aqueous solution of ammonia (1.5 mL) was added slowly during 15 min, and the organic material was extracted with Et_2O. The combined organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure at 60 °C (to remove diglyme). The residue was purified by silica gel column chromatography with $NH_4OH_{(aq)}/CH_3OH/CH_2Cl_2$ (1/5/94) as eluent to afford tertiary amine **8** (ca. 8 mg) as a mixture of diastereoisomers at C1′ (light pink oil). Interpretation of the ^{1}H and ^{13}C NMR spectra was rendered difficult by the presence of the two diastereomers that led to overlapping signals. ^{1}H NMR (500 MHz, CD_3OD): δ 6.32−6.26 (m, 1H), 6.24−6.19 (m, 1H), 3.73 (tt, J = 11.0, 4.4 Hz, 1H), 3.57−3.45 (m, 1H), 3.08−2.94 (m, 1H), 2.64−2.51 (m, 1H), 2.47 (td, J = 11.3, 2.6 Hz, 1H), 2.43−2.37 (m, 1H), 2.29−2.07 (m, 5H, NMe and 2CH), 2.04−1.85 (m, 4H), 1.54−1.13 (m, 12H), 1.14−0.83 (m, 10H). ^{13}C NMR (126 MHz, CD_3OD): δ 157.6, 156.0, 137.9, 112.8, 109.7, 108.1, 78.0, 71.7, 71.3, 54.4, 50.1, 39.7, 36.6, 35.9, 34.9, 32.8, 32.7, 31.0, 29.7, 28.2, 27.2, 26.4, 23.7, 22.1, 19.2, 14.4. IR (neat, cm^{-1}): 3192−3584 (br), 3051, 2933, 2868, 1618, 1573, 1413, 1364, 1265, 1139, 1053, 897, 733, 703, 677. HRMS ((+)-ESI-TOF) m/z calcd for $C_{26}H_{42}NO_3$ $[M + H]^+$, 416.3159; found 416.3165.

*2-((6aR,9R,10aR)-1,9-Bis(methoxymethoxy)-6,6-dimethyl-6a,7,8,9,10,10a-hexahydro-6H-benzo[c]chromen-3-yl)octanenitrile (**9**).* To a mixture $Pd_2(allyl)_2Cl_2$ (18 mg, 0.05 mmol), Xantphos (116 mg, 0.20 mmol), and potassium 2-cyanooctanoate (311 mg, 1.50 mmol) under an argon atmosphere was added a solution of triflate **2** (484 mg, 1.0 mmol) in dry (4 Å molecular sieves), deoxygenated (argon bubbling) xylene (20 mL). The reaction mixture was stirred at room temperature for 15 min and then moved to a preheated oil bath at 130 °C. Upon completion of the reaction (ca. 16 h), the mixture was cooled to room temperature, Celite was added, and xylene was removed under reduced pressure at 50 °C. The residue was purified by silica gel column chromatography with EtOAc/hexane (1/4) as eluent to afford nitrile **9** (377 mg, 82% yield) as a mixture of diastereoisomers at C1′ (light yellow oil). Interpretation of the ^{1}H and ^{13}C NMR spectra was rendered difficult by the presence of the two diastereomers that led to overlapping signals. ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.60−6.41 (m, 2H), 5.24−5.11 (m, 2H), 4.77−4.68 (m, 2H), 3.73 (tt, J = 11.1, 4.5 Hz, 1H), 3.65−3.56 (m, 1H), 3.49 (s, 3H), 3.42−3.34 (m, 4H), 2.45 (td, J = 11.3, 2.6 Hz, 1H), 2.24−2.14 (m, 1H), 1.94−1.76 (m, 3H), 1.54−1.39 (m, 3H), 1.38 (s, 3H), 1.34−1.21 (m, 7H), 1.18−1.05 (m, 2H), 1.04 (s, 3H), 0.87 (t, J = 6.8 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 156.9, 155.1, 135.7, 120.9, 113.7, 110.4, 105, 94.8, 94.6, 77.1, 75.6, 56.3, 56.1, 48.4, 37.2, 36.3, 35.4, 33.8, 33.1, 31.4, 28.6, 27.7, 27.1, 26.0, 22.5, 18.8, 14.0. IR (neat, cm^{-1}): 2930, 2872, 2239 (CN), 1614, 1574, 1558, 1431, 1404, 1369, 1337, 1153, 1103, 1057, 922, 737, 625. HRMS ((+)-ESI-TOF) m/z calcd for $C_{27}H_{41}NNaO_5$ $[M + Na]^+$, 482.2877; found 482.2869.

*2-((6aR,9R,10aR)-1,9-Bis(methoxymethoxy)-6,6-dimethyl-6a,7,8,9,10,10a-hexahydro-6H-benzo[c]chromen-3-yl)-2-(hydroxymethyl)octanenitrile (**10**).* To a suspension of nitrile **9** (322 mg, 0.70 mmol) and paraformaldehyde (315 mg) in toluene (70 mL) in a resealable sealed tube was added Triton B/CH_3OH 40% (1.0 mL) dropwise. The resealable tube was sealed, and the reaction mixture was stirred at ambient temperature for 3 min and then at 60 °C for 26 h. After the reaction mixture was cooled to room temperature, saturated aqueous $NaHCO_3$ (25 mL) was added, and the organic material was extracted with EtOAc. The combined organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography with EtOAc/hexane (2/3) as eluent to afford alcohol **10** (325 mg, 95% yield) as a mixture of diastereoisomers at C1′ (light yellow foam). Interpretation of the ^{1}H and ^{13}C NMR spectra was rendered difficult by the presence of the two diastereomers that led to overlapping signals. ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.66−6.64 (m, 1H), 6.55−6.53 (m, 1H), 5.22−5.13 (m, 2H), 4.76−4.69 (m, 2H), 3.85−3.79 (m, 2H), 3.72 (tt, J = 11.0, 4.4 Hz, 1H), 3.48 (s, 3H), 3.41−3.37 (m, 4H), 2.45 (td, J = 11.4, 2.6 Hz, 1H), 2.22−2.16 (m, 1H), 2.16 (br s, OH), 2.06−1.94 (m, 1H), 1.93−1.85 (m, 1H), 1.85−1.75 (m, 1H), 1.54−1.39 (m, 3H), 1.38 (s, 3H), 1.32−1.19 (m, 7H), 1.18−1.06 (m, 2H), 1.04 (s, 3H), 0.84 (t, J = 6.6 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 157.0, 155.1, 135.7, 121.5, 114.0, 109.5, 104.1, 94.7, 94.7, 77.2, 75.6, 69.2, 56.3, 56.1, 50.9, 48.3, 36.2, 35.3, 33.7, 33.0, 31.4, 29.1, 27.6, 26.0, 24.8, 22.5, 18.9, 14.0. IR (neat, cm^{-1}): 3447 (br), 2930, 2872, 2237 (CN), 1614, 1574, 1558, 1465, 1423, 1402, 1385, 1370, 1334, 1265, 1153, 1157, 921, 736, 660. HRMS ((+)-ESI-TOF) m/z calcd for $C_{28}H_{43}NNaO_6$ $[M + Na]^+$, 512.2983; found 512.3001.

*2-((6aR,9R,10aR)-1,9-Bis(methoxymethoxy)-6,6-dimethyl-6a,7,8,9,10,10a-hexahydro-6H-benzo[c]chromen-3-yl)-2-cyanooctyl 4-Methylbenzenesulfonate (**11**).* To a solution of alcohol **10** (295 mg, 0.60 mmol) in CH_2Cl_2 (60 mL) were added *p*-TsCl (345 mg, 1.80 mmol), Et_3N (1.0 mL, 7.17 mmol), and DMAP (88 mg, 0.72 mmol), and the reaction mixture was stirred at room temperature for 4 h. Saturated aqueous $NaHCO_3$ (10 mL) was added, and the organic material was extracted with EtOAc. The combined organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography with EtOAc/hexane (3/7) as eluent to afford tosylate **11** (362 mg, 94%) as a mixture of diastereoisomers at C1′ (light yellow foam). Interpretation of the ^{1}H and ^{13}C NMR spectra was rendered difficult by the presence of the two diastereomers that led to overlapping signals. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.74 (dd, J = 8.3, 4.2 Hz, 2H), 7.32 (dd, J = 8.3, 2.0 Hz, 2H), 6.61−6.54 (m, 1H), 6.48−6.42 (m, 1H), 5.18−5.08 (m, 2H), 4.76−4.68 (m, 2H), 4.17−4.04 (m, 2H), 3.72 (tt, J = 11.2, 4.5 Hz, 1H), 3.47 (s, 3H), 3.41−3.44 (m, 4H), 2.49−2.38 (m, 4H), 2.23−2.15 (m, 1H), 2.08−1.98 (m, 1H), 1.94−1.86 (m, 1H), 1.83−1.74 (m, 1H), 1.54−1.31 (m, 6H), 1.31−1.05 (m, 9H), 1.03 (s, 3H), 0.86−0.81 (m, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 157.0, 155.1, 145.2, 133.8, 132.1, 129.9, 128.0, 119.5, 114.5, 109.7, 104.0, 94.7, 94.7, 77.3, 75.5, 72.8, 56.3, 56.1, 48.3, 47.7, 36.2, 35.5, 33.7, 33.0, 31.3, 28.9, 27.6, 26.0, 24.5, 22.4, 21.6, 18.9, 13.9. IR (neat, cm^{-1}): 2930, 2872, 2243 (CN), 1610, 1573, 1558, 1454, 1423, 1402, 1362, 1179, 1057, 1042, 841, 814, 737, 663. HRMS ((+)-ESI-TOF) m/z calcd for $C_{35}H_{50}NO_8S$ $[M + H]^+$, 644.3252; found 644.3236.

*3-((6aR,9R,10aR)-1,9-Bis(methoxymethoxy)-6,6-dimethyl-6a,7,8,9,10,10a-hexahydro-6H-benzo[c]chromen-3-yl)-3-hexyl-1-methylazetidine (**13**).* To a stirred suspension of $LiAlH_4$ (65 mg, 1.74 mmol) in THF (5.0 mL) under a nitrogen atmosphere at 0 °C was added a solution of cyanotosylate **11** (110 mg, 0.17 mmol) in THF (12 mL) slowly, and the reaction mixture was stirred at room temperature for 3 h. (*Note: more $LiAlH_4$ was used on smaller scale to reduce most of starting material within 3−4 h).* The reaction mixture was quenched with a minimum amount of Na_2SO_4 paste (ca. 100 μL), which was prepared by cooling hot saturated aqueous Na_2SO_4, diluted with Et_2O, and stirred at room temperature for 30 min. The organic material was taken up with Et_2O, dried over solid K_2CO_3, filtered, and concentrated under reduced pressure to give crude azetidine **12** as a colorless oil. To a solution of amine **12** in CH_3OH (17 mL) was slowly added a 37% formaldehyde in aqueous solution (1.0 mL), and the reaction mixture was stirred at room

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temperature for 2 h. $NaBH_4$ (40 mg, 1.06 mmol) was added in many portions at 0 °C, and the reaction mixture was stirred at 0 °C for 5 min and then at ambient temperature for 2 h. Solvents were carefully removed under reduced pressure to give a white solid, followed by addition of a small amount of aqueous 10 M NaOH (ca. 100 μL), diluted with CH_2Cl_2, and stirred for 5 min. The organic material was extracted with CH_2Cl_2, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography with CH_3OH/CH_2Cl_2 (5/95) as eluent to afford *N*-methylazetidine **13** (52 mg, 62% yield from **11**) as a colorless foam. ^1H NMR (500 MHz, $CDCl_3$): δ 6.23 (s, 1H), 6.13 (s, 1H), 5.18−5.08 (m, 2H), 4.76−4.68 (m, 2H), 3.91 (d, *J* = 8.1 Hz, 2H), 3.72 (tt, *J* = 11.1, 4.4 Hz, 1H), 3.61 (d, *J* = 8.1 Hz, 2H), 3.47 (s, 3H), 3.40−3.35 (m, 4H), 2.57 (s, 3H, NMe), 2.43 (td, *J* = 11.3, 2.6 Hz, 1H), 2.22−2.14 (m, 1H), 2.04−1.92 (m, 2H), 1.92−1.84 (m, 1H), 1.53−1.38 (m, 3H), 1.37 (s, 3H), 1.26−0.99 (m, 12H), 0.80 (t, *J* = 6.7 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 156.7, 154.6, 144.9, 112.2, 108.6, 103.1, 94.7, 94.6, 77.1, 75.6, 65.5, 56.2, 55.1, 48.4, 44.2, 42.2, 40.6, 36.4, 33.7, 33.1, 31.6, 29.2, 27.7, 26.0, 24.4, 22.5, 18.9, 14.0. IR (neat, cm^{-1}): 2930, 2857, 1614, 1568, 1557, 1447, 1402, 1366, 1361, 1153, 1103, 1057, 922, 737, 702, 660. HRMS ((+)-ESI-TOF) *m*/*z* calcd for $C_{29}H_{48}NO_5$ $[M + H]^+$, 490.3527; found 490.3540. $[\alpha]^{23}_D$−39.0° (*c* 0.5, CH_3OH).

*(6aR,9R,10aR)-3-(3-Hexyl-1-methylazetidin-3-yl)-6,6-dimethyl-6a,7,8,9,10,10a-hexahydro-6H-benzo[c]chromene-1,9-diol (**14**).* To a mixture of amine **13** (30 mg, 0.06 mmol) and ethanol (220 mg, 4.78 mmol) in CH_3CN (6.0 mL) at room temperature was added $Sc(OTf)_3$ (30 mg, 0.06 mmol). After being flushed with nitrogen, the reaction mixture was refluxed for 12 h. CH_3CN was removed under reduced pressure, and a minimum amount of pH 7 phosphate buffer (300 μL) was added and stirred for 10 min. The organic material was extracted with Et_2O, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography with $NH_4OH_{(aq)}/CH_3OH/CH_2Cl_2$ (2/5/93) as eluent to afford amine **14** (22 mg, 89%) as a colorless amorphous solid. ^1H NMR (500 MHz, CD_3OD): δ 6.04 (d, *J* = 1.7 Hz, 1H), 5.99 (d, *J* = 1.7 Hz, 1H), 3.72 (tt, *J* = 11.0, 5.5 Hz, 1H), 3.54−3.48 (m, 1H), 3.48−3.41 (m, 4H), 2.44 (td, *J* = 11.3, 2.6 Hz, 1H), 2.34 (s, 3H), 2.16−2.06 (m, 1H), 1.98−1.80 (m, 3H), 1.47−1.35 (m, 2H), 1.34 (s, 3H), 1.29−1.13 (m, 8H), 1.08−0.99 (m, 4H), 0.99−0.88 (m, 1H), 0.84 (t, *J* = 6.9 Hz, 3H). ^{13}C NMR (126 MHz, CD_3OD): δ 157.7, 156.1, 147.0, 111.2, 107.4, 105.9, 77.8, 71.3, 67.4, 50.3, 45.8, 43.1, 42.5, 39.9, 36.7, 34.9, 32.9, 30.6, 28.1, 27.2, 25.7, 23.6, 19.2, 14.4. IR (thin film, cm^{-1}): 3092−3582 (br), 2930, 2857, 1614, 1418, 1362, 1184, 1138, 1057, 840, 737, 691, 660. HRMS ((+)-ESI-TOF) *m*/*z* calcd for $C_{25}H_{40}NO_3$ $[M + H]^+$, 402.3003; found 402.3012. $[\alpha]^{23}_D$ −30.0° (*c* 0.3, CH_3OH).

*1-((6aR,9R,10aR)-1,9-Bis(methoxymethoxy)-6,6-dimethyl-6a,7,8,9,10,10a-hexahydro-6H-benzo[c]chromen-3-yl)heptan-1-one (**15**).* To a solution of nitrile **9** (230 mg, 0.50 mmol) in THF (10 mL) under a nitrogen atmosphere at room temperature was added a 2.0 M solution of NaHMDS in THF (1 mL, 2.0 mmol) dropwise over 10 min, and the reaction mixture was stirred at room temperature for an additional 20 min. A stream of dry oxygen gas (from tank) was bubbled through the mixture over 30 min at −78 °C. A 1.0 M aqueous solution of sodium sulfite (5.0 mL) was added, and the mixture was stirred at 0 °C for 30 min. The organic material was extracted with Et_2O, and the combined organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography with EtOAc/hexane (1/4) as eluent to afford ketone **15** (166 mg, 74% yield) as a light yellow oil. ^1H NMR (500 MHz, $CDCl_3$) δ 7.19 (d, *J* = 1.6 Hz, 1H), 7.07 (d, *J* = 1.6 Hz, 1H), 5.29−5.17 (m, 2H), 4.78−4.67 (m, 2H), 3.75 (tt, *J* = 11.0, 4.5 Hz, 1H), 3.50 (s, 3H), 3.44−3.39 (m, 1H) 3.38 (s, 3H), 2.86 (t, *J* = 7.4 Hz, 2H), 2.50 (td, *J* = 11.3, 2.6 Hz, 1H), 2.24−2.16 (m, 1H), 1.95−1.89 (m, 1H), 1.72−1.65 (m, 2H), 1.62−1.23 (m, 11H), 1.19−1.07 (m, 2H), 1.04 (s, 3H), 0.87 (t, *J* = 6.9 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 199.9, 156.6, 154.7, 136.7, 119.2, 111.9, 104.2, 94.7, 94.4, 77.3, 75.5, 56.4, 55.2, 48.4, 38.5, 36.2, 34.2, 33.1, 31.6, 29.0, 27.6, 26.0, 24.4, 22.5, 18.8, 14.0. IR (neat, cm^{-1}): 3055, 2932, 2870, 1682 (C═O), 1574, 1466, 1366, 1157, 1042, 918, 740. HRMS ((+)-ESI-TOF) *m*/*z* calcd for $C_{26}H_{41}O_6$ $[M + H]^+$, 449.2898; found 449.2898. $[\alpha]^{23}_D$ −61.0° (*c* 1.0, CH_3OH).

*(R,E)-N-(1-((6aR,9R,10aR)-1,9-Bis(methoxymethoxy)-6,6-dimethyl-6a,7,8,9,10,10a-hexahydro-6H-benzo[c]chromen-3-yl)-heptylidene)-2-methylpropane-2-sulfinamide (**17**).* To a solution of ketone **15** (318 mg, 0.71 mmol) and (*R*)-2-methylpropane-2-sulfinamide (95 mg, 0.78 mmol) in THF (3.0 mL) was added $Ti(OEt)_4$ (ca. 0.45 mL, 2.13 mmol), and the mixture was refluxed under nitrogen atmosphere for 19 h. After cooling to 0 °C, the reaction mixture was quenched with saturated aqueous NaCl, diluted with CH_2Cl_2, and stirred at 0 °C for 15 min. The mixture was filtered, and the filter cake was washed with CH_2Cl_2. The combined organic layer was separated, washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography with EtOAc/hexane (1/4) as eluent to afford ketimine **17** (359 mg, 92% yield) as a light yellow oil. ^1H NMR (500 MHz, $CDCl_3$) δ 7.19 (s, 1H), 6.90 (s, 1H), 5.21−5.12 (m, 2H), 4.75−4.63 (m, 2H), 3.71 (tt, *J* = 11.0, 4.5 Hz, 1H), 3.46 (s, 3H), 3.41−3.33 (m, 4H), 3.17−2.97 (m, 2H), 2.47 (td, *J* = 11.3, 2.5 Hz, 1H), 2.22−2.13 (m, 1H), 1.92−1.83 (m, 1H), 1.66−1.57 (m, 2H), 1.55−1.47 (m, 1H), 1.46−1.34 (m, 6H), 1.31−1.25 (m, 13H), 1.17−1.04 (m, 2H), 1.02 (s, 3H), 0.85−0.82 (m, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 179.5, 156.5, 154.6, 137.3, 117.7, 110.8, 104.7, 94.7, 94.5, 77.2, 75.5, 57.3, 56.1, 55.0, 48.3, 36.1, 34.0, 33.0, 32.4, 31.3, 29.5, 28.8, 27.5, 25.9, 22.5, 22.4, 18.7, 13.9. IR (neat, cm^{-1}): 3055, 2932, 2870, 1728, 1612, 1558, 1458, 1334, 1157, 1042, 918, 732. HRMS ((+)-ESI-TOF) *m*/*z* calcd for $C_{30}H_{49}NNaO_6S$ $[M + Na]^+$, 574.3173; found 574.3158. $[\alpha]^{23}_D$ −49.0° (*c* 0.5, CH_3OH).

*(3S)-Ethyl 3-((6aR,9R,10aR)-1,9-Bis(methoxymethoxy)-6,6-dimethyl-6a,7,8,9,10,10a-hexahydro-6H-benzo[c]chromen-3-yl)-3-(1,1-dimethylethylsulfinamido)nonanoate (**18**).* To a solution of diisopropylamine (1.20 mmol) in THF (5 mL) under an argon atmosphere at −10 °C (ice−salt bath) was added over 10 min a 2.0 M solution of *n*-BuLi in hexane (0.6 mL, 1.20 mmol), and the solution was stirred at −10 °C for an additional 10 min. The solution was then cooled to −78 °C, a solution of EtOAc (1.20 mmol) in THF (1 mL) was added slowly over 5 min, and the reaction mixture was stirred at −78 °C for 30 min. To this solution was added a solution of $TiCl(Oi\text{-}Pr)_3$ (2.50 mmol) in THF/toluene (2 mL, 1/1) dropwise, and the yellow solution was stirred for 20 min at −78 °C. *(Note: the solution of $TiCl(Oi\text{-}Pr)_3$ was prepared from 1.0 equiv of $TiCl_4$ and 3.0 equiv of $Ti(Oi\text{-}Pr)_4$ in toluene at −10 °C and diluted with THF).* After that time, a solution of *N*-sulfinyl imine **17** (330 mg, 0.60 mmol) in THF (2 mL) was added slowly, and the reaction mixture was stirred at −78 °C for 1 h. Saturated aqueous NH_4Cl (4 mL) was added, the mixture was warmed to 0 °C and stirred for 15 min, and the organic material was extracted with Et_2O. The combined organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography with EtOAc/hexane (3/7 → 2/3) as eluent to afford ester **18** (310 mg, 81% yield) as a colorless oil. ^1H NMR (500 MHz, $CDCl_3$) δ 6.66 (d, *J* = 1.8 Hz, 1H), 6.37 (d, *J* = 1.9 Hz, 1H), 5.49 (s, NH), 5.15−5.07 (m, 2H), 4.75−4.70 (m, 2H), 3.98 (q, *J* = 7.1 Hz, 2H), 3.72 (tt, *J* = 11.1, 4.5 Hz, 1H), 3.45 (s, 3H), 3.40−3.37 (m, 4H), 3.21 (d, *J* = 16.7 Hz, 1H), 3.02 (d, *J* = 16.7 Hz, 1H), 2.42 (td, *J* = 11.3, 2.6 Hz, 1H), 2.22−2.09 (m, 2H), 1.93−1.84 (m, 1H), 1.83−1.73 (m, 1H), 1.53−1.41 (m, 2H), 1.41−1.35 (m, 4H), 1.32 (s, 9H), 1.27−1.03 (m, 12H), 1.02 (s, 3H), 0.81 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.0, 156.4, 154.4, 144.2, 112.5, 108.6, 104.2, 94.8, 94.7, 77.2, 76.9, 75.7, 61.4, 60.3, 56.2, 56.0, 55.1, 48.5, 45.4, 39.9, 36.4, 33.8, 33.1, 31.4, 29.1, 27.7, 26.1, 23.0, 22.4, 18.8, 14.0, 13.9. IR (neat, cm^{-1}): 3279, 3055, 2940, 2870, 1721 (C═O), 1612, 1574, 1458, 1334, 1265, 1157, 1042, 740. HRMS ((+)-ESI-TOF) *m*/*z* calcd for $C_{34}H_{57}NNaO_8S$ $[M + Na]^+$, 662.3697; found 662.3706. $[\alpha]^{23}_D$ −48.0° (*c* 1.0, CH_3OH).

*(S)-Ethyl 3-Amino-3-((6aR,9R,10aR)-1,9-bis(methoxymethoxy)-6,6-dimethyl-6a,7,8,9,10,10a-hexahydro-6H-benzo[c]chromen-3-yl)nonanoate (**19**).* To a solution of *N*-*tert*-butanesulfinyl β-amino ester **18** (200 mg, 0.31 mmol) in CH_3OH (10 mL) at 0 °C was added a 4.0 M solution of HCl in 1,4-dioxane (1 mL, 4.0 mmol) dropwise. The resulting mixture was stirred at ca.10 °C until most of the starting material was consumed as judged by TLC (ca. 2 h). The mixture was cooled to 0 °C and then quenched with cold saturated aqueous $NaHCO_3$. The organic material was extracted with Et_2O, and the

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combined organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography with CH_3OH/CH_2Cl_2 (3/97) as eluent to afford β-amino ester **19** (141 mg, 85% yield) as a colorless oil. ^{1}H NMR (500 MHz, CD_3OD) δ 6.62 (d, *J* = 2.0 Hz, 1H), 6.46 (d, *J* = 2.0 Hz, 1H), 5.25−5.17 (m, 2H), 4.71 (s, 2H), 4.04 (qd, *J* = 7.1, 1.4 Hz, 2H), 3.72 (tt, *J* = 11.3, 4.6 Hz, 1H), 3.50−3.43 (m, 4H), 3.36 (d, *J* = 2.0 Hz, 3H), 3.01 (d, *J* = 15.9 Hz, 1H), 2.79 (d, *J* = 16.0 Hz, 1H), 2.48 (td, *J* = 11.3, 2.7 Hz, 1H), 2.22−2.15 (m, 1H), 1.98−1.77 (m, 2H), 1.52−1.29 (m, 6H), 1.27−1.07 (m, 12H), 1.04−0.96 (m, 4H), 0.89−0.82 (m, 3H). ^{13}C NMR (126 MHz, CD_3OD) δ 172.4, 158.1, 156.2, 143.2, 114.8, 109.6, 104.4, 96.0, 95.9, 78.2, 77.3, 61.8, 59.7, 56.8, 55.5, 50.1, 45.0, 42.6, 38.0, 35.0, 34.3, 32.8, 32.6, 30.4, 28.1, 27.1, 24.2, 23.5, 19.1, 14.4. IR (neat, cm $^{-1}$): 3302, 3156, 3055, 2932, 2870, 1728 (C═O), 1612, 1574, 1465, 1334, 1265, 1157, 1041, 918, 740. HRMS ((+)-ESI-TOF) *m*/*z* calcd for $C_{30}H_{50}NO_7$ $[M + H]^+$, 536.3582; found 536.3601. $[\alpha]^{23}_D$ −76.0° (*c* 1.5, CH_3OH).

*(S)-4-((6aR,9R,10aR)-1,9-Bis(methoxymethoxy)-6,6-dimethyl-6a,7,8,9,10,10a-hexahydro-6H-benzo[c]chromen-3-yl)-4-hexylazetidin-2-one (**20**).* To a solution of β-amino ester **19** (107 mg, 0.20 mmol) in Et_2O (20 mL) under a nitrogen atmosphere at room temperature was added a 1.0 M solution of CH_3MgBr in THF/toluene (0.6 mL, 0.60 mmol) dropwise, and the mixture was stirred at room temperature for 1.5 h. The reaction mixture was quenched with saturated aqueous NH_4Cl and stirred until the two layers became clear. The organic material was extracted with Et_2O. The combined organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography with EtOAc/hexane (3/2) as eluent to afford azetidinone **20** (76 mg, 78% yield) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.47 (br s, NH), δ 6.47 (d, *J* = 1.6 Hz, 1H), 6.37 (d, *J* = 1.6 Hz, 1H), 5.19−5.13 (m, 2H), 4.76−4.70 (m, 2H), 3.73 (tt, *J* = 10.6, 4.5 Hz, 1H), 3.48 (s, 3H), 3.43−3.35 (m, 4H), 3.07−2.93 (m, 2H), 2.45 (td, *J* = 11.3, 2.6 Hz, 1H), 2.23−2.15 (m, 1H), 2.07−1.99 (m, 1H), 1.93−1.79 (m, 3H), 1.56−1.35 (m, 5H), 1.28−1.07 (m, 9H), 1.05 (s, 3H), 0.84 (t, *J* = 6.8 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.5, 156.7, 154.5, 142.9, 112.7, 108.4, 103.0, 94.7, 94.6, 77.1, 75.6, 59.7, 56.2, 55.1, 50.8, 48.5, 40.7, 36.4, 33.8, 33.1, 31.5, 29.2, 27.7, 26.1, 24.7, 22.5, 18.9, 14.0. IR (neat, cm^{-1}): 3433, 3055, 2932, 2870, 1751 (C═O), 1612, 1574, 1420, 1265, 1157, 1041, 918, 741. HRMS ((+)-ESI-TOF) *m*/*z* calcd for $C_{28}H_{43}NNaO_6$ $[M + Na]^+$, 512.2983; found 512.2980. $[\alpha]^{23}_D$ −48.0° (*c* 0.5, CH_3OH).

*(S)-2-((6aR,9R,10aR)-1,9-Bis(methoxymethoxy)-6,6-dimethyl-6a,7,8,9,10,10a-hexahydro-6H-benzo[c]chromen-3-yl)-2-hexyl-1-methylazetidine (**22**).* To a stirred suspension of $LiAlH_4$ (ca. 50 mg, 1.31 mmol) in THF (1.5 mL) under a nitrogen atmosphere at 0 °C was added a solution of azetidinone **20** (10 mg, 0.02 mmol) in THF (1.5 mL) dropwise. The reaction mixture was heated at 65 °C (oil bath) for 24 h. After cooling to 0 °C, the reaction mixture was quenched with a minimum amount of Na_2SO_4 paste, diluted with Et_2O, and stirred at room temperature for 30 min. The organic material was taken up with Et_2O, dried over solid K_2CO_3, filtered, and concentrated under reduced pressure to give crude azetidine **21** as a colorless oil (ca. 10 mg). To a solution of amine **21** in CH_3OH (2 mL) was slowly added a 37% formaldehyde in aqueous solution (ca. 80 μL), and the reaction mixture was stirred at room temperature for 3 h. $NaBH_4$ (ca. 50 mg, 1.31 mmol) was added in many portions at 0 °C, and the reaction mixture was stirred at 0 °C for 5 min and then at ambient temperature for 2 h. Solvents were carefully removed under reduced pressure to give a white solid, followed by addition of a minimum amount of aqueous 10 M NaOH, diluted with CH_2Cl_2, and stirred for 5 min. The organic material was extracted with CH_2Cl_2, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography with CH_3OH/CH_2Cl_2 (6/94) as eluent to afford *N*-methylazetidine **22** (ca. 7 mg) as a colorless oil. ^{1}H NMR (500 MHz, CD_3OD) δ 6.57 (d, *J* = 1.8 Hz, 1H), 6.43 (d, *J* = 1.8 Hz, 1H), 5.32−5.19 (m, 2H), 4.71 (s, 2H), 3.84−3.78 (m, 1H), 3.73 (tt, *J* = 10.7, 4.5 Hz, 1H), 3.67−3.58 (m, 1H), 3.50−3.42 (m, 4H), 3.36 (s, 3H), 2.96−2.84 (m, 1H), 2.62 (s, 3H), 2.52 (td, *J* = 11.3, 2.5 Hz, 1H), 2.42−2.33 (m, 1H), 2.31−2.16 (m, 2H), 2.14−2.04 (m, 1H), 1.97−1.85 (m, 2H), 1.66−1.55 (m, 1H), 1.54−1.46 (m, 1H), 1.41−1.20 (m, 11H), 1.08−0.93 (m, 4H), 0.86 (t, *J* = 6.6 Hz, 3H). ^{13}C NMR (126 MHz, CD_3OD) δ 158.2, 156.5, 141.1, 115.7, 109.8, 104.1, 96.0, 95.6, 78.4, 77.5, 77.2, 56.7, 55.5, 51.5, 50.0, 37.9, 36.7, 35.9, 35.1, 34.3, 32.7, 30.4, 28.1, 27.8, 27.0, 24.5, 23.7, 19.1, 14.5. HRMS ((+)-ESI-TOF) *m*/*z* calcd for $C_{29}H_{48}NO_5$ $[M + H]^+$, 490.3527; found 490.3519. IR (neat, cm^{-1}): 2931, 2858, 1612, 1567, 1440, 1261, 1155, 920, 736. $[\alpha]^{23}_D$ −52.0° (*c* 0.5, CH_3OH).

*(6aR,9R,10aR)-3-((S)-2-Hexyl-1-methylazetidin-2-yl)-6,6-dimethyl-6a,7,8,9,10,10a-hexahydro-6H-benzo[c]chromene-1,9-diol (**23**).* To a solution of amine **22** (ca. 4 mg, mmol) in CH_3OH (0.5 mL) at room temperature was added Dowex 50W-X8 (H^+ form) (ca. 250 mg, excess). *(Note: Dowex 50W-8X had been previously washed with distilled water, 1 M aqueous NaOH, distilled water, 1 M aqueous HCl, and distilled water before it was used).* After being flushed with nitrogen, the reaction mixture was stirred vigorously at room temperature for 30 h. *(Note: the reaction was not clean without flushing with nitrogen).* The reaction was quenched with a minimum amount of saturated aqueous $NaHCO_3$ (until pH ∼ 8). The organic material was extracted with Et_2O, dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography with CH_3OH/CH_2Cl_2 (1/4) as eluent to afford amine **23** (ca. 2.5 mg) as a colorless amorphous solid. ^{1}H NMR (500 MHz, CD_3OD) δ 6.23 (d, *J* = 1.9 Hz, 1H), 6.20 (d, *J* = 1.9 Hz, 1H), 3.73 (tt, *J* = 10.8, 5.2 Hz, 1H), 3.54−3.39 (m, 3H), 2.77−2.64 (m, 1H), 2.50−2.41 (m, 4H), 2.26−2.18 (m, 1H), 2.16−2.04 (m, 2H), 2.01−1.84 (m, 3H), 1.47−1.41 (m, 1H), 1.41−1.34 (m, 4H), 1.34−1.10 (m, 8H), 1.02 (s, 3H), 0.99−0.89 (m, 1H), 0.85 (t, *J* = 6.7 Hz, 3H). HRMS ((+)-ESI-TOF) *m*/*z* calcd for $C_{25}H_{40}NO_3$ $[M + H]^+$, 402.3003; found 402.2987.

*(S)-4-((6aR,9R,10aR)-1,9-Dihydroxy-6,6-dimethyl-6a,7,8,9,10,10a-hexahydro-6H-benzo[c]chromen-3-yl)-4-hexylazetidin-2-one (**24**).* To a solution of azetidinone **20** (ca. 7 mg, 0.014 mmol) in CH_3CN (2.0 mL) and water (0.2 mL) at room temperature was added $LiBF_4$ (40 mg, 0.43 mmol). After being flushed with nitrogen, the reaction mixture was heated at 72 °C for 18 h. CH_3CN was removed under reduced pressure, pH 7 phosphate buffer (2 mL) was added, and the organic material was extracted with EtOAc. The combined organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography with EtOAc/hexane (4/1) as eluent to afford azetidinone **24** (ca. 5 mg) as a light yellow amorphous solid. ^{1}H NMR (500 MHz, CD_3OD) δ 6.21 (d, *J* = 1.9 Hz, 1H), 6.18 (d, *J* = 1.9 Hz, 1H), 3.73 (tt, *J* = 11.0, 4.4 Hz, 1H), 3.55−3.48 (m, 1H), 2.98 (d, *J* = 14.6 Hz, 1H), 2.83 (d, *J* = 14.6 Hz, 1H), 2.45 (td, *J* = 11.3, 2.6 Hz, 1H), 2.16−2.06 (m, 1H), 2.06−1.96 (m, 1H), 1.93−1.85 (m, 1H), 1.84−1.73 (m, 1H), 1.49−1.40 (m, 1H), 1.40−1.32 (m, 4H), 1.30−1.09 (m, 9H), 1.03 (s, 3H), 1.00−0.91 (m, 1H), 0.89−0.82 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, CD_3OD) δ 170.7, 158.0, 156.1, 143.9, 112.1, 106.9, 105.4, 78.0, 71.3, 60.5, 51.1, 50.2, 42.0, 39.8, 36.6, 34.9, 32.8, 30.4, 28.2, 27.2, 25.8, 23.6, 19.1, 14.4. HRMS ((−)-ESI-TOF) *m*/*z* calcd for $C_{24}H_{34}NO_4$ $[M-H]^-$, 400.2488; found 400.2474. IR(thin film, cm^{-1}): 3369, 2930, 2859, 1723 (C═O), 1622, 1580, 1421, 1274, 1142, 1056, 738. $[\alpha]^{23}_D$ −67.0° (*c* 1.0, CH_3OH).

Preparation of Amine Salts (Compounds 7S1, 7S2, 7S3, 8S1, 8S3, and 14S). *General Procedure.* To amine **7**, **8**, or **14** (0.02 mmol) under a nitrogen atmosphere was added a 0.02 M solution of acid HX in solvent (CH_3OH or CH_3COCH_3) (1 mL, 0.02 mmol, 1.0 equiv), and the mixture was stirred at room temperature for 12 h. Solvent was removed under reduced pressure to give the corresponding amine salts.

*2-((6aR,9R,10aR)-1,9-Dihydroxy-6,6-dimethyl-6a,7,8,9,10,10a-hexahydro-6H-benzo[c]chromen-3-yl)-2-hexylpyrrolidin-1-ium 3-Carboxypropanoate (**7S1**).* Hemisuccinate salt **7S1** (mixture of diastereomers at C1′) was prepared by treatment of amine **7** (mixture of diastereomers at C1′) with succinic acid in CH_3OH. ^{1}H NMR (500 MHz, CD_3OD): δ 6.34−6.24 (m, 2H), 3.74 (tt, *J* = 11.1, 4.4 Hz, 1H), 3.53−3.46 (m, 1H), 3.46−3.37 (m, 1H), 3.29−3.23 (m, 1H), 2.55 (s, 4H, succinate), 2.47 (td, *J* = 11.2, 2.4 Hz, 1H), 2.39−2.05 (m, 5H), 1.97−1.84 (m, 3H), 1.48−1.15 (m, 11H), 1.11−0.76 (m, 10H). ^{13}C NMR (126 MHz, CD_3OD): δ 176.2, 158.5, 156.9, 139.4, 113.9, 107.3, 105.8, 78.4, 73.8, 71.2, 50.0, 44.6, 39.6, 38.9, 36.6, 34.9, 32.5, 30.2, 29.9, 29.4, 28.1, 27.1, 25.3, 23.5, 22.9, 19.2, 14.3. IR (neat, cm^{-1}): 3165−3584 (br), 3053, 2936, 2870, 1714, 1620, 1581, 1421, 1265, 1174, 1030, 739,

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704, 638. HRMS ((+)-ESI-TOF) m/z calcd for $C_{25}H_{40}NO_3$ $[M + H]^+$, 402.3003; found 402.2995.

*2-((6aR,9R,10aR)-1,9-Dihydroxy-6,6-dimethyl-6a,7,8,9,10,10a-hexahydro-6H-benzo[c]chromen-3-yl)-2-hexylpyrrolidin-1-ium (2R,3S)-3-Carboxy-2,3-dihydroxypropanoate (**7S2**).* Hemitartrate salt **7S2** (mixture of diastereomers at C1′) was prepared by treatment of amine **7** (mixture of diastereomers at C1′) with L-(2*R*,3*R*)-(+)-tartaric acid in CH_3OH. ^1H NMR (500 MHz, CD_3OD): δ 6.34−6.26 (m, 2H), 4.54 (s, 2H, tartrate), 3.74 (tt, J = 11.1, 4.7 Hz, 1H), 3.53−3.47 (m, 1H), 3.47−3.39 (m, 1H), 3.30−3.24 (m, 1H), 2.47 (td, J = 11.3, 2.4 Hz, 1H), 2.39−2.03 (m, 5H), 1.98−1.84 (m, 3H), 1.51−1.12 (m, 11H), 1.11−0.81 (m, 10H). ^{13}C NMR (126 MHz, CD_3OD): δ 174.9, 158.5, 156.9, 139.4, 113.9, 107.3, 105.8, 78.4, 73.8, 73.4, 71.2, 50.0, 44.6, 39.6, 38.9, 36.6, 34.9, 32.5, 30.2, 29.4, 28.1, 27.1, 25.3, 23.5, 22.9, 19.2, 14.3. IR (neat, cm^{-1}): 3167−3584 (br), 3062, 2936, 2870, 1732, 1620, 1581, 1423, 1273, 1170, 1029, 739, 638. HRMS ((+)-ESI-TOF) m/z calcd for $C_{25}H_{40}NO_3$ $[M + H]^+$, 402.3003; found 402.3015.

*2-((6aR,9R,10aR)-1,9-Dihydroxy-6,6-dimethyl-6a,7,8,9,10,10a-hexahydro-6H-benzo[c]chromen-3-yl)-2-hexylpyrrolidin-1-ium Chloride (**7S3**).* Chloride salt **7S3** (mixture of diastereomers at C1′) was prepared by treatment of amine **7** (mixture of diastereomers at C1′) with hydrochloric acid in acetone.

^1H NMR (500 MHz, CD_3OD): δ 6.33−6.25 (m, 2H), 3.74 (tt, J = 11.0, 4.4 Hz, 1H), 3.53−3.47 (m, 1H), 3.46−3.38 (m, 1H), 3.29−3.25 (m, 1H), 2.47 (td, J = 11.3, 5.8 Hz, 1H), 2.36−2.06 (m, 5H), 1.97−1.83 (m, 3H), 1.49−1.15 (m, 11H), 1.11−0.78 (m, 10H). ^{13}C NMR (126 MHz, CD_3OD): δ 158.5, 156.9, 139.4, 113.9, 107.3, 105.8, 78.4, 73.8, 71.2, 50.0, 44.6, 39.6, 38.9, 36.6, 34.9, 32.5, 30.2, 29.5, 28.1, 27.1, 25.3, 23.5, 22.9, 19.2, 14.3. IR (neat, cm^{-1}): 3165−3584 (br), 3055, 2953, 2870, 1614, 1582, 1423, 1360, 1246, 1172, 1030, 843, 737, 702, 638. HRMS ((+)-ESI-TOF) m/z calcd for $C_{25}H_{40}NO_3$ $[M + H]^+$, 402.3003; found 402.2992.

*2-((6aR,9R,10aR)-1,9-Dihydroxy-6,6-dimethyl-6a,7,8,9,10,10a-hexahydro-6H-benzo[c]chromen-3-yl)-2-hexyl-1-methylpyrrolidin-1-ium 3-Carboxypropanoate (**8S1**).* Hemisuccinate salt **8S1** (mixture of diastereomers at C1′) was prepared by treatment of amine **8** (mixture of diastereomers at C1′) with succinic acid in CH_3OH. ^1H NMR (500 MHz, CD_3OD): δ 6.47−6.35 (m, 2H), 3.74 (tt, J = 11.1, 4.4 Hz, 1H), 3.64−3.54 (m, 1H), 3.24−3.09 (m, 1H), 2.69−2.59 (m, 1H), 2.57−2.53 (m, 3H, NMe), 2.53−2.46 (m, 5H, succinate and 1CH), 2.32−2.16 (m, 4H), 2.14−2.09 (m, 1H), 1.93−1.87 (m, 1H), 1.85−1.73 (m, 1H), 1.51−1.42 (m, 1H), 1.42−1.14 (m, 11H), 1.13−0.83 (m, 10H). ^{13}C NMR (126 MHz, CD_3OD): δ 178.5, 158.7, 156.9, 134.8, 114.8, 109.6, 107.6, 78.4, 77.4, 71.2, 54.8, 49.9, 39.5, 36.6, 36.0, 34.9, 32.6, 32.5, 32.0, 30.5, 29.6, 28.1, 27.1, 25.9, 23.6, 21.3, 19.2, 14.3. IR (neat, cm^{-1}): 3176−3584 (br), 3503, 2934, 2870, 1714, 1576, 1418, 1265, 1057, 737, 704. HRMS ((+)-ESI-TOF) m/z calcd for $C_{26}H_{42}NO_3$ $[M + H]^+$, 416.3159; found 416.3153.

*2-((6aR,9R,10aR)-1,9-Dihydroxy-6,6-dimethyl-6a,7,8,9,10,10a-hexahydro-6H-benzo[c]chromen-3-yl)-2-hexyl-1-methylpyrrolidin-1-ium Chloride (**8S3**).* Chloride salt **8S3** (mixture of diastereomers at C1′) was prepared by treatment of amine **8** (mixture of diastereomers at C1′) with hydrochloric acid in acetone. ^1H NMR (500 MHz, CD_3OD): δ 6.41−6.27 (m, 2H), 3.73 (tt, J = 11.1, 4.4 Hz, 1H), 3.59−3.50 (m, 1H), 3.14−3.03 (m, 1H), 2.75−2.58 (m, 1H), 2.53−2.47 (m, 3H, NMe), 2.38−2.04 (m, 6H), 1.93−1.88 (m, 1H), 1.88−1.79 (m, 1H), 1.49−1.42 (m, 1H), 1.40−1.22 (m, 11H), 1.09−0.79 (m, 10H). ^{13}C NMR (126 MHz, CD_3OD): δ 158.6, 157.0, 133.7, 115.3, 110.1, 107.9, 78.5, 77.0, 71.2, 54.5, 49.9, 39.5, 37.3, 36.6, 34.9, 32.5, 32.2, 30.4, 29.5, 28.1, 27.1, 26.0, 23.5, 20.9, 19.2, 14.3. IR (neat, cm^{-1}): 3194−3584 (br), 3053, 2931, 2870, 1620, 1579, 1418, 1360, 1265, 1144, 1057733, 704. HRMS ((+)-ESI-TOF) m/z calcd for $C_{26}H_{42}NO_3$ $[M + H]^+$, 416.3159; found 416.3156.

*3-((6aR,9R,10aR)-1,9-Dihydroxy-6,6-dimethyl-6a,7,8,9,10,10a-hexahydro-6H-benzo[c]chromen-3-yl)-3-hexyl-1-methylazetidin-1-ium 3-Carboxypropanoate (**14S**).* Hemisuccinate salt **14S** was prepared by treatment of amine **14** with succinic acid in CH_3OH. ^1H NMR (500 MHz, CD_3OD): δ 6.06 (s, 1H), 6.06 (s, 1H), 4.15 (s, 4H), 3.73 (tt, J = 10.9, 4.3 Hz, 1H), 3.54−3.46 (m, 1H), 2.80 (s, 3H, NMe), 2.50 (s, 4H, succinate), 2.45 (td, J = 11.3, 2.2 Hz, 1H), 2.15−2.07 (m, 1H), 1.98−1.85 (m, 3H), 1.47−1.40 (m, 1H), 1.40−1.31 (m, 4H), 1.28−1.13 (m, 8H), 1.09−0.99 (m, 4H), 0.98−0.87 (m, 1H), 0.84 (t, J = 6.8 Hz, 3H). ^{13}C NMR (126 MHz, CD_3OD): δ 179.5, 158.3, 156.5, 143.8, 112.2, 107.2, 105.5, 78.0, 71.2, 66.4, 50.2, 43.2, 42.7, 41.7, 39.8, 36.6, 34.9, 32.9, 32.7, 30.3, 28.2, 27.2, 25.3, 23.6, 19.2, 14.4. IR (neat, cm^{-1}): 3208−3610 (br), 2926, 2855, 1712, 1645, 1556, 1418, 1277, 1184, 1076, 922, 840, 737. HRMS ((+)-ESI-TOF) m/z calcd for $C_{25}H_{40}NO_3$ $[M + H]^+$, 402.3003; found 402.3014. $[\alpha]^{23}_D$ −56.0° (c 1.0, CH_3OH).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.7b00988.

^1H NMR and ^{13}C NMR spectra for compounds (PDF)

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Notes

The authors declare no competing financial interest.

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