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Enantioselective Total Syntheses of (+)-Fendleridine and (+)-Acetylaspidobaldine

Arun K. Ghosh*, Joshua R. Born, and Luke Kassekert

Department of Chemistry and Department of Medicinal Chemistry, Purdue University, 560 Oval Drive, West Lafayette, Indiana 47907

Abstract

Enantioselective syntheses of hexacyclic aspidobaldine alkaloids (+)-fendleridine (**2**) and (+)-acetylaspidobaldine (**3**) are described. These syntheses feature an asymmetric decarboxylative allylation and photocyclization of a highly substituted enaminone. Also, the synthesis highlights the formation of the C19 hemiaminal ether via a reduction/condensation/intramolecular cyclization cascade with the C21-alcohol. The present synthesis provides convenient access to the aspidobaldine hexacyclic alkaloid family in an efficient manner.

Graphical abstract

Introduction

The indoline alkaloids constitute a large family of monoterpene natural products that display immense structural diversity.^{1,2} The structural core of these natural products is comprised of polycyclic fused ring systems with contiguous chiral centers as represented in aspidospermidine (**1**, Figure 1), one of the parent members.^{3,4} Several *Aspidosperma* alkaloids exhibit a broad range of intriguing pharmacological activity, including anticancer and antibacterial among many others.^{5,6,7} Over the years, many strategies have been developed for their syntheses, both racemic and enantioselective manner.^{1,2,8–10} However, general strategies for the synthesis of the subset aspidobaldine family of alkaloids received relatively less attention due to further structural complexity. As shown, (+)-fendleridine (**2**), also known as aspidobaldine, and (+)-1-acetylaspidobaldine (**3**), contain a unique C19 hemiaminal ether functionality in place of the C19 C-N linkage typical of aspidosperma

*Corresponding Author: akghosh@purdue.edu.

Conflicts of interest

There are no conflicts to declare.

ASSOCIATED CONTENT

Supporting Information

Full spectroscopic data for all compounds are available free of charge via the Internet at <http://pubs.acs.org>

alkaloids.^{11,12} Other representative oxidized forms of these natural products include (+)-haplocine (**4**), (+)-haplocidine (**5**), (+)-cimicine (**6**), and (–)-aspidophytine (**7**).^{13,14}

Fendleridine (**2**) was isolated from the Venezuelan tree *Aspidosperma fendleri* Woodson in 1964.¹⁵ Later, it was also isolated from the Venezuelan tree species, *Aspidosperma rhombeosignatum* Markgraph in 1979.¹⁶ The corresponding 1-acetyl derivative, 1-acetylaspidobaldine was first isolated from the Peruvian plant, *Vallesia dichotoma* Ruitz at Pav in 1963.¹⁷ Fendleridine can be viewed as a biosynthetic product of the cyclization of *N*-protected derivative of (+)-limaspermidine (**8**). A few syntheses of 1-acetylaspidobaldine were carried out by the oxidation and cyclization of **8**.^{18–20} The first total synthesis of fendleridine (**2**) and 1-acetylaspidobaldine (**3**) was reported by Ban and co-workers in 1975 and 1976.^{19,21} Overman and co-workers in 1991 also reported a formal synthesis of 1-acetylaspidobaldine (**3**) in racemic form, using the aza-Cope-Mannich reaction as the key strategy.²² Subsequently, syntheses of (–)-aspidophytine (**7**) and haplophytine, related members of aspidobaldine family were reported.^{23,24} Boger and co-workers first reported total synthesis of (+)-fendleridine (**2**) and (+)-1-acetylaspidobaldine (**3**) and unambiguously established absolute configuration of these parent members.²⁵ They utilized a (4+2)/(3+2) cycloaddition cascade reaction that constructed the pentacyclic framework.²⁶ Movassaghi and co-workers recently reported syntheses of these alkaloids via oxidation of the C19-iminium ion to install the C19-hemiaminal functionality.²⁷ These two syntheses employed the use of chiral HPLC and enzymatic resolution, respectively, to separate out the sought after intermediates. In this paper, we report enantioselective synthesis of (+)-fendleridine (**2**) and (+)-acetylaspidobaldine (**3**) in 10- and 11-steps respectively, starting from readily accessible starting materials.

Our retrosynthetic analysis of (+)-fendleridine and (+)-1-acetylaspidobaldine is shown in Scheme 1. As depicted, an *N*-protected fendleridine would be obtained from the iminium ion **9**. We planned to construct the C19-hemiaminal ether functionality with defined stereochemistry through the formation of a C19 imine from the C19 ketone and C10 amine followed by intramolecular alkylation at C8 forming the iminium ion structure **9**. Removal of the protecting group on the C21 alcohol would construct the C19-hemiaminal ether functionality. The stereochemistry of the C19 stereocenter will be defined based upon the stereochemistry of the C12-ethylamine and the C5 alkoxyethyl group on structure **10**. The elaboration of the C12 aminoethyl functionality can be achieved by alkylation of the hexahydrocarbazol-4-one **11**. The alkylation reaction with appropriate electrophile will presumably ensure the desired *cis*-stereochemistry depicted on the substituted cyclohexanone derivative **10**. We plan to construct the hexahydrocarbazolone **11** by a photocyclization of an optically active enaminone **12** (R = Bn). Such photocyclization would provide a mixture of diastereomers at the C2 and C12 carbons. Our plan for photocyclization is motivated by previous work by Gramain and co-workers who have demonstrated photocyclization of related aryl enaminone to form hexahydrocarbazolones with *trans*-ring junction stereochemistry.²⁸ The synthesis of enaminone **12** in optically active form can be achieved conveniently by using an enantioselective Stoltz decarboxylative allylation reaction.²⁹ Enaminone **13** (R = Bn) can be prepared on a multigram scale from readily available starting materials, *N*-benzylaniline and 1,3-cyclohexanedione.

As shown in Scheme 2, our synthesis commenced with the formation of multigram quantity of enaminone **13** by condensation of *N*-benzylaniline and 1,3-cyclohexanedione in toluene in the presence of *p*-TSA•H₂O at reflux for 40 h. Subsequently, enaminone **13** was alkylated with LDA and allylchloroformate at –78 °C to 23 °C for 18 h to afford β-keto ester **14** in 62% yield. Alkylation of the β-keto ester **14** with *tert*-butyl (2-iodoethoxy)dimethylsilane was carried out in DMF in the presence of Cs₂CO₃ at 100 °C for 32 h to furnish racemic keto ester **15** in 70% yield.³⁰ For catalytic asymmetric allylation, we planned to utilize Pd₂(dba)₃ in combination with (*S*)-*t*-Bu-Phox ligand since the prior work by Stoltz and coworkers already established that (*S*)-*t*-Bu-Phox provides the best enantioselectivity for allylation of enaminones.³¹ Therefore, we investigated enantioselective allylation in a number of solvents by exposure of enaminone **15** to Pd₂(dba)₃ (5 mol%) and (*S*)-*t*-Bu-Phox ligand (12.5 mol%) at 23 °C followed by heating the reaction mixture to a specified temperature. As shown in Table 1, initial attempts to use toluene without deoxygenation resulted in only a trace amount of desired allylated product, with largely recovered starting material and dealkylated byproduct.³² Subsequently, we deoxygenated all solvents by bubbling with Argon for at least an hour prior to use. The reaction in methyl *tert*-butyl ether was carried out at lower temperature due to the volatility of the solvent. This condition resulted in a trace amount of allylated product **17**. The reactions in THF and benzene at 70°C however resulted in excellent yields of allylated product **17**. To determine enantiomeric purity, compound **17** was converted to the benzoate derivative **18**. HPLC analysis of **18** using a CHIRALCEL OD-H column showed that enantioselectivity of **17** was 77% and 81% *ee*, respectively (please see supporting information for further details). Freshly deoxygenated toluene was tested last and was found to furnish the optically active enaminone **17** in 88% yield and 82% *ee*. We utilized this condition to prepare optically active **17** on a multigram scale.

The synthesis of hexahydrocarbazolone ring system is shown in Scheme 3. Our initial attempt to photocyclize **17** in benzene with a mercury lamp (450 W) provided inseparable mixture (1:1) of *trans*-diastereomeric indoline derivatives **19** and **20** along with the corresponding oxidized indole byproduct **21**. Gramin and co-workers reported such a photocyclization on unsubstituted enaminone to provide hexahydrocarbazolone and the corresponding oxidized indole product.²⁸ We attempted optimization of the photocyclization to inhibit the formation of indole byproduct **21**. It turns out that careful degassing of the apparatus with benzene as the solvent and shorter reaction times afforded the indolines **19** and **20** as the major products and only a trace amount of indole byproduct **21**. It is important to note that photochemical *trans*-indoline products are quite prone to oxidation to the indole byproduct **21**. Mechanistic insights into this photocyclization reaction were recently reported by Bach and coworkers.³³ For our synthesis, we utilized the crude mixture of diastereomers for the next alkylation reaction immediately. The crude photocyclization product mixture was treated with KHMDS in THF at 23 °C and then cooled to 0 °C and stirred at that temperature for 10 min. Bromoacetonitrile was added and reaction was stirred for 40 min at 0 °C. This provided inseparable *cis*-diastereomeric products **22** and **23** in 63% yield over two steps.^{28b}

Hydroboration of the mixture of nitrile derivatives with *in situ* formed Cy_2BH in freshly distilled THF at 0 °C to 23 °C for 2.5 h followed by oxidation with $\text{NaBO}_3 \cdot 4\text{H}_2\text{O}$ afforded 1:1 mixture of alcohols in 98% combined yield.³⁴ The mixture was separated by silica gel chromatography to provide the alcohols **24** and **25** as pure separable compounds. The stereochemical identity of **24** and **25** was primarily determined using extensive ^1H -NMR NOESY experiments (See SI for details).

To further ascertain stereochemical identity of alcohols **24** and **25**, our plan was to convert to the respective spiroketal derivative, thus creating a more rigid conformation for 2D NMR analysis. As shown in Scheme 4, the alcohols **24** and **25** were converted to the corresponding tosylate derivatives **26** and **27** in 79% and 85% yields, respectively. The TBS group of tosylate **26** was then removed by exposure to TBAF in THF at 23 °C for 7.5 h. This resulted in the formation of spiroketal derivative **28** in near quantitative yield. Similarly, we have converted **27** to spiroketal derivative **29** in excellent yield. The stereochemical assignment of the diastereomeric spiroketals **28** and **29** was carried out by extensive 2D NMR studies. The results are summarized in Figure 2. The observed specific NOESY interactions between H_a - H_b and H_a - H_c for spiroketal **28** is consistent with the depicted chemistry. Similarly, the observed NOESY between H_a - H_d and H_a - H_e support the assigned stereochemistry of spiroketal **29** (please see supporting information for more details). Based upon these stereochemical assignments of spiroketal structures **28** and **29**, we then speculated that if the assigned stereochemistry of tosylate **27** is correct, our planned formation of iminium ion **9** ($\text{R}=\text{Bn}$, $\text{PG}=\text{TBS}$) may not be feasible upon reduction of nitrile to amine from **27**. Reduction of nitrile **27** was carried out by exposure to Ra-Ni 2800 in methanol under 60 psi hydrogen in a parr apparatus at 23 °C for 21 h. These conditions resulted in the formation of the corresponding ethyl amine which concomitantly cyclized to imine **30**. This further corroborated our assignment of stereochemical identity.

Tosyl derivative **26** was readily converted to (+)-fendleridine **2** as shown in Scheme 5. Tosylate **26** was subjected to Ra-Ni 2800 under hydrogen at 60 psi to afford highly polar iminium salt **31**. Treatment of the crude salt **31** with TBAF at 0 °C to 23 °C for 13.5 h removed the silyl group and concomitantly formed the C19-hemiaminal ether. Purification over basic alumina provided benzyl derivative **32** in 62% yield over two steps. The *N*-benzyl group was successfully deprotected using lithium in liquid NH_3 at -78 °C for 1.5 h to furnish synthetic (+)-fendleridine **2** in 70% yield after purification by alumina using 5% ethyl acetate in hexanes as the eluent. The ^1H -NMR and ^{13}C -NMR spectra of synthetic (+)-fendleridine **2** $\{[\alpha]_{\text{D}}^{20} +53.7$ (c , 0.2, CHCl_3) $\}$ are in complete agreement with reported^{25,27} spectra for synthetic and natural (+)-fendleridine. We have also converted (+)-fendleridine **2** to its acetyl derivative by acetylation with acetic anhydride and pyridine in CH_2Cl_2 at 23 °C for 1 h to provide synthetic (+)-1-acetyl-aspidobidine **3** $\{[\alpha]_{\text{D}}^{20} +30.2$ (c , 0.15, CHCl_3) $\}$ in quantitative yield after purification over alumina column. The ^1H -NMR and ^{13}C -NMR spectra of synthetic (+)-1-acetyl-aspidobidine **3** are in complete agreement with reported^{25,27} spectra with rotational isomers.

In summary, we have developed a short and enantioselective total syntheses of (+)-fendleridine and (+)-1-acetylaspidoalbidine. The syntheses of (+)-fendleridine and (+)-1-

acetylaspidoalbidine were achieved in 10-and 11-steps, respectively, from readily available starting materials. The synthesis highlights the construction of the highly substituted hexahydrocarbazolone ring system by a photochemical reaction. The synthesis also utilizes the enantioselective formation of an enaminone containing a quaternary carbon center by Stoltz decarboxylative allylation processes. The chirality on the enaminone ensures the formation of the unique C19-hemiaminal ether functionality inherent to aspidoalbine family of alkaloids. The Ra-Ni catalyzed reduction of nitrile and subsequent cascade cyclization to iminium salt leads to the C19-hemiaminal ether very efficiently. Further application of photocyclization and synthesis of pharmacologically important indoline alkaloids are underway.

Experimental Section

General Procedural/Analytical Methods.

All reactions were done in oven-dried round-bottom flasks followed by flame-drying in the case of moisture sensitive reactions. The flasks were fitted with rubber septa and kept under a positive pressure of Argon. Cannula were used in the transfer of moisture sensitive liquids. Heated reactions were ran using an oil bath on a hot plate equipped with a temperature probe. Hydrogenations were carried out using a ParrTM shaking apparatus inside a thick-walled non-reactant borosilicate glass vessel. Photochemical transformations were done using a Hanovia 450 W Hg Lamp. TLC analysis was conducted using glass-backed thin-layer silica gel chromatography plates (60 Å, 250 µm thickness, F-254 indicator), or with glass-backed thin-layer Alumina N chromatography plates (250 µm thickness, UV 254). Flash chromatography was done using 230–400 mesh, 60 Å pore diameter silica gel, or with 80–200 mesh Alumina. Organic solutions were concentrated at 30–35 °C on rotary evaporators capable of achieving a minimum pressure of ~30 torr, and further concentrated on a Hi-vacuum pump capable of achieving a minimum pressure of ~4 torr. ¹H NMR spectra were recorded on 400, 500 and 800 MHz spectrometers. ¹³CNMR spectra were recorded at 100, 125, and 200 MHz on the respective NMRs. Chemical shifts are reported in parts per million and are referenced to the deuterated residual solvent peak (CDCl₃, 7.26 ppm for ¹H and 77.16 ppm for ¹³C). NMR data is reported as δ value (chemical shift, J-value (Hz), integration, where s = singlet, bs = broad singlet, d = doublet, t = triplet, q = quartet, p = quintet, m = multiplet, dd = doublet doublets, and so on. Optical rotations were recorded on a digital polarimeter. LRMS spectra was obtained using a quadrupole LCMS under ESI+. HRMS spectra were recorded at the Purdue University Department of Chemistry Mass Spectrometry Center. These experiments were performed under ESI+ and APCI+ conditions using an Orbitrap XL Instrument.

3-(benzyl(phenyl)amino)cyclohex-2-en-1-one (13).^{28c,35}

To a 500 mL one-neck round bottom flask equipped with a stir bar and 1,3-dicyclohexadiene (15 g, 133.8 mmol, 1.0 equiv), *N*-benzylaniline (26.97 g, 147.2 mmol, 1.1 equiv), and *p*-toluenesulfonic acid monohydrate (4.07 g, 21.4 mmol, 0.16 equiv) were added sequentially. A Dean-Stark apparatus with a reflux condenser was then attached and the entire vessel evacuated and flushed with Argon several times. Toluene (267 mL) was added and the reaction heated at 160 °C for 40 h. After this period, the reaction was cooled, diluted with

EtOAc, washed with 1 M NaOH, brine, dried over Na₂SO₄, and concentrated. The crude mixture was purified via column chromatography over silica gel using 100% EtOAc as the eluent. Enaminone **13** was obtained as brown oil (34.57 g, 93%) TLC: Silica Gel (100% EtOAc), R_f = 0.31. ¹H NMR (400 MHz, CDCl₃) δ 7.36 – 7.15 (m, 8H), 7.11 (d, *J* = 7.1 Hz, 2H), 5.36 (s, 1H), 4.80 (s, 2H), 2.28 (dd, *J* = 14.2, 6.4 Hz, 4H), 1.88 (p, *J* = 6.4 Hz, 2H); ¹³C{¹H} NMR (101 MHz, CDCl₃) δ 197.6, 164.9, 144.4, 136.3, 129.6, 128.6, 127.7, 127.5, 127.4, 126.8, 101.6, 56.6, 36.1, 28.6, 22.5; LRMS-ESI (+) *m/z* 278.1 [M + H]⁺.

Allyl 4-(benzyl(phenyl)amino)-2-oxocyclohex-3-ene-1-carboxylate ((±)-14).

To a flame-dried 1L round bottom flask under Argon, diisopropylamine (34.1 mL, 243 mmol, 2.5 equiv) in freshly distilled THF (144 mL) was added. To this solution at 0 °C, *n*-BuLi (1.6 M in hexanes, 152 mL, 243 mmol, 2.5 equiv) was added and the reaction was stirred for 50 min. In a separate flame-dried 1 L flask enaminone **13** (27 g, 97.2 mmol, 1 equiv) was dissolved in THF (125 mL) and the solution was cannulated to the yellow solution of above LDA at –78 °C. The resulting mixture was stirred at –78 °C for 1 h then allyl chloroformate (13.4 mL, 126.4 mmol, 1.3 equiv) was added dropwise. The resulting reaction was allowed to warm slowly to 23 °C for 12 h. The reaction was quenched with saturated NH₄Cl (250 mL), extracted with EtOAc (3x), washed with brine, dried over Na₂SO₄, and concentrated. The crude mixture was purified via column chromatography over silica gel to provide product as a viscous dark red oil (21.8 g, 62% yield), and unreacted starting material (4.9 g) was recovered (76% yield, brsm). TLC: Silica Gel (50% EtOAc:Hexanes), R_f = 0.34. ¹H NMR (400 MHz, CDCl₃) δ 7.37 – 7.20 (m, 6H), 7.17 (d, *J* = 7.0 Hz, 2H), 7.11 (d, *J* = 7.0 Hz, 2H), 5.90 (ddt, *J* = 17.2, 10.5, 5.6 Hz, 1H), 5.39 (s, 1H), 5.31 (dq, *J* = 17.2, 1.5 Hz, 1H), 5.19 (dq, *J* = 10.4, 1.2 Hz, 1H), 4.82 (s, 2H), 4.69 – 4.58 (m, 2H), 3.32 (dd, *J* = 8.7, 5.0 Hz, 1H), 2.57 – 2.46 (m, 1H), 2.36 – 2.23 (m, 2H), 2.17 – 2.06 (m, 1H); ¹³C{¹H} NMR (101 MHz, CDCl₃) δ 191.0, 170.7, 164.6, 144.0, 136.0, 132.0, 129.7, 128.7, 127.8, 127.7, 127.5, 126.9, 118.1, 100.5, 65.5, 56.7, 51.5, 26.6, 25.2; HRMS-ESI (+) *m/z* calcd for C₂₃H₂₃NO₃ [M + H]⁺: 362.1751, found 362.1755.

Allyl 4-(benzyl(phenyl)amino)-1-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-2-oxocyclohex-3-ene-1-carboxylate ((±)-15).

To a flame-dried 1L round bottom flask under Argon equipped with a stir bar and reflux condenser, racemic **14** (21.8 g, 60.2 mmol, 1 equiv) in DMF (500 mL) was added. To this solution, *tert*-butyl(2-iodoethoxy)dimethylsilane (33.4 mL, 150.4 mmol, 2.5 equiv) followed by Cs₂CO₃ (39.2 g, 120.4 mmol, 2.0 equiv) was added. The resulting reaction was heated in an oil bath to 100 °C for 32 h. After this period, the reaction was quenched with H₂O and brine (100 mL each). The resulting mixture was extracted with CH₂Cl₂, washed with 5% aqueous LiCl solution. The crude mixture was concentrated and purified via column chromatography over silica gel using 25 – 55% EtOAc/Hexanes as the eluent to yield allyl carbonate **15**, (21.9 g, 70.1% yield) as an orange amorphous solid. Unreacted starting material was recovered (3.2 g, 82 % yield, brsm). TLC: Silica Gel (25% EtOAc:Hexanes), R_f = 0.2. ¹H NMR (400 MHz, CDCl₃) δ 7.38 – 7.27 (m, 5H), 7.25 (d, *J* = 7.0 Hz, 1H), 7.18 (d, *J* = 6.7 Hz, 2H), 7.10 (d, *J* = 6.8 Hz, 2H), 5.89 (ddt, *J* = 17.2, 10.7, 5.5 Hz, 1H), 5.36 (s, 1H), 5.29 (dq, *J* = 16.8, 1.4 Hz, 1H), 5.19 (dq, *J* = 10.5, 1.4 Hz, 1H), 4.81 (s, 2H), 4.61 (dtdd, *J* = 14.9, 13.4, 5.0, 1.5 Hz, 2H), 3.72 (t, *J* = 6.6 Hz, 2H), 2.60 – 2.26 (m, 4H), 1.98

(dq, J = 14.0, 7.4, 6.6 Hz, 2H), 0.85 (s, 9H), 0.02 (d, J = 2.7 Hz, 6H); $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) δ 193.5, 172.2, 163.9, 144.2, 136.3, 132.2, 129.8, 128.8, 127.9, 127.8, 127.6, 127.0, 118.0, 100.3, 65.5, 60.2, 56.7, 54.4, 36.5, 29.6, 26.0, 25.9, 18.3, -5.3; HRMS-ESI (+) m/z calcd for $\text{C}_{31}\text{H}_{42}\text{NO}_4\text{Si}$ $[\text{M} + \text{H}]^+$: 520.2878, found 520.2874.

(S)-6-allyl-3-(benzyl(phenyl)amino)-6-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)cyclohex-2-en-1-one (17).

To a flame-dried round bottom flask under Argon equipped with a stir bar and reflux condenser, (*S*)-*t*Bu-Phox (429.6 mg, 1.11 mmol, 12.5 mol%) and $\text{Pd}_2(\text{dba})_3$ (406 mg, 0.44 mmol, 5 mol %) were added. Deoxygenated toluene (61 mL) was added and the resulting mixture was stirred at 23 °C for 30 min. A solution of allyl carbonate **15** (4.61 g, 8.87 mmol, 1 equiv) in toluene (61 mL) was then slowly cannulated to the orange solution containing the catalyst at 23 °C. The resulting reaction mixture was heated to 70 °C for 35 min. After this period, the orange reaction mixture was cooled and then filtered over Celite®. The filter cake was washed with CH_2Cl_2 . The solvent was concentrated and the residue was purified via column chromatography over silica gel using 15 – 20% EtOAc:Hexanes as the eluent to provide product allylated product **17** (3.69 g, 88% yield) as viscous brown oil. TLC: Silica Gel (15% EtOAc:Hexanes), R_f = 0.16. $[\alpha]_D^{20}$ -2.9 (c 0.068, CHCl_3); ^1H NMR (500 MHz, CDCl_3) δ 7.37 – 7.27 (m, 5H), 7.24 (m, 1H), 7.19 (d, J = 7.2 Hz, 2H), 7.12 (d, J = 7.1 Hz, 2H), 5.82 – 5.70 (m, 1H), 5.29 (s, 1H), 5.04 (s, 1H), 5.02 (d, J = 4.3 Hz, 1H), 4.82 (s, 2H), 3.72 (ddd, J = 10.1, 8.5, 6.2 Hz, 1H), 3.63 (ddd, J = 10.3, 8.7, 5.7 Hz, 1H), 2.42 (m, 2H), 2.30 (dt, J = 17.5, 5.7 Hz, 1H), 2.21 (dd, J = 13.9, 8.0 Hz, 1H), 1.87 – 1.78 (m, 3H), 1.75 – 1.69 (m, 1H), 0.87 (s, 9H), 0.03 (s, 6H); $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 200.5, 163.2, 144.5, 136.7, 135.2, 129.8, 128.8, 128.0, 127.59, 127.55, 127.1, 117.6, 100.9, 59.9, 56.7, 44.5, 40.3, 37.9, 31.0, 26.1, 25.5, 18.4, -5.1, -5.2; HRMS-ESI (+) m/z calcd for $\text{C}_{30}\text{H}_{42}\text{NO}_2\text{Si}$ $[\text{M} + \text{H}]^+$: 476.2979, found 476.2969.

(S)-2-(1-allyl-4-(benzyl(phenyl)amino)-2-oxocyclohex-3-en-1-yl)ethyl benzoate (18).

To a flame-dried round bottom flask under argon equipped with a stir bar allyl derivative **17** (21 mg, 0.04 mmol, 1.0 equiv) in freshly distilled THF (0.5 mL, 0.1 M) was added. To this solution, TBAF (1.0 M in THF, 46 μL , 0.05 mmol, 1.05 equiv) was added dropwise at 0 °C and the resulting mixture was stirred at 0 °C to 23 °C for 12 h. Reaction was then quenched with H_2O and brine (~0.5 mL each), extracted with EtOAc (3x), washed brine, dried Na_2SO_4 , and concentrated. The crude mixture was purified via silica gel column chromatography, using 65% EtOAc:Hexanes as the eluent to provide the corresponding alcohol as an amorphous solid (16 mg, 100% yield). TLC: Silica (65% EtOAc:Hexanes), R_f = 0.50 (UV and PMA). ^1H NMR (400 MHz, CDCl_3) δ 7.40 – 7.19 (m, 6H), 7.19 (m, 2H), 7.13 (m, 2H), 5.72 (m, 1H), 5.34 (s, 1H), 5.09 (m, 1H), 5.06 (m, 1H), 4.84 (s, 2H), 3.86 (bs, 1H), 3.81 (ddd, J = 12.1, 8.2, 4.4 Hz, 1H), 3.64 (dt, J = 10.7, 4.9 Hz, 1H), 2.46 – 2.29 (m, 4H), 1.84 – 1.67 (m, 4H). $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) δ 202.6, 164.4, 144.2, 136.3, 134.2, 129.9, 128.9, 127.9 (2C), 127.7, 127.1, 118.4, 100.5, 58.9, 56.9, 45.0, 38.9, 37.9, 32.0, 25.4. LRMS-ESI (+) m/z 362.1 $[\text{M} + \text{H}]^+$.

To a flame-dried round bottom flask under Argon, equipped with a stir bar, above alcohol (15 mg, 41 μmol , 1.0 equiv) in CH_2Cl_2 (0.5 mL) was added. To this solution at 0 °C, DMAP

(1.0 mg, 8 μ mol, 0.2 equiv), triethylamine (8.4 mg, 12 μ L, 0.08 mmol, 2.0 equiv), and benzoyl chloride (7 mg, 6 μ L, 0.05 mmol, 1.2 equiv) were added. The resulting reaction mixture was stirred at 0 °C to 23 °C for 2.5 h. Reaction was then quenched with H₂O and brine (~0.5 mL each), extracted with CH₂Cl₂ (3x), washed brine, dried Na₂SO₄, and concentrated. The crude mixture was purified via column chromatography over silica gel to provide benzoate **18** (18.5 mg, 96% yield) as an oil. TLC: Silica (30% EtOAc:Hexanes), R_f = 0.32 (UV and PMA) ¹H NMR (400 MHz, CDCl₃) δ 8.01 (d, *J* = 7.1 Hz, 2H), 7.54 (t, *J* = 7.4 Hz, 1H), 7.41 (t, *J* = 7.7 Hz, 2H), 7.35 (t, *J* = 7.5 Hz, 2H), 7.31 – 7.22 (m, 4H), 7.18 (d, *J* = 6.8 Hz, 2H), 7.12 (d, *J* = 7.6 Hz, 2H), 5.85 – 5.75 (m, 1H), 5.34 (s, 1H), 5.09 (s, 1H), 5.06 (d, *J* = 4.4 Hz, 1H), 4.81 (s, 2H), 4.44 – 4.34 (m, 2H), 2.48 – 2.28 (m, 4H), 2.23 – 2.16 (m, 1H), 1.93 – 1.85 (m, 3H). ¹³C{¹H} NMR (101 MHz, CDCl₃) δ 199.78, 166.71, 163.20, 144.34, 136.49, 134.45, 132.92, 130.51, 129.82, 129.69, 128.86, 128.44, 127.97, 127.70, 127.60, 127.02, 118.25, 100.73, 62.13, 56.71, 44.42, 40.41, 33.79, 30.44, 25.32. LRMS-ESI (+) *m/z* 466.2 [M + H]⁺.

2-((3S)-3-allyl-9-benzyl-3-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-4-oxo-1,2,3,4,9,9a-hexahydro-4aH-carbazol-4a-yl)acetonitrile (22** and **23**).**

To a flame-dried round bottom flask under Argon fitted with a reflux condenser and stir bar, allylated **17** (1.55 g, 3.26 mmol, 1.0 equiv) was added. Deoxygenated Benzene (163 mL) was added and the resulting mixture was flushed under Argon multiple times. Photocyclization reaction then was carried out with a 450 W Hg lamp for 1.5 h. After this period, the reaction was concentrated under reduced pressure in the dark. The resulting crude product was immediately subjected to next step.

To the above mixture, freshly-distilled THF (21.7 mL), and KHMDS (0.7 M in toluene, 5.12 mL, 3.58 mmol, 1.1 equiv) were added sequentially at 23 °C (solution went from orange gold to dark brown). The reaction cooled to 0 °C and after 10 min, BrCH₂CN (238 μ L, 3.42 mmol, 1.05 equiv) was added dropwise. The resulting mixture was stirred for 40 min at 0 °C. After this period, the reaction was quenched with saturated NH₄Cl (15 mL). Reaction extracted with EtOAc (3x), the combined extracts were washed brine, dried with Na₂SO₄, and concentrated. The crude mixture was purified via column chromatography over silica gel using 5% EtOAc:Hexanes as the eluent to provide: **22** and **23** as an inseparable mixture as an oil (1.05 g, 63% over two steps). TLC: Silica Gel (15% EtOAc:Hexanes), R_f = 0.44. ¹H NMR (500 MHz, CDCl₃) δ 7.40 – 7.28 (m, 5H), 7.13 (t, *J* = 7.0 Hz, 1H), 6.93 (d, *J* = 7.6 Hz, 1H), 6.66 (t, *J* = 8.7 Hz, 1H), 6.49 (d, *J* = 7.9 Hz, 1H), 5.76 (m, 0.5H), 5.54 (m, 0.5H), 5.08 (m, 1H), 5.00 (d, *J* = 10.1 Hz, 0.5H), 4.87 (d, *J* = 17.0 Hz, 0.5H), 4.53 (d, *J* = 12.4 Hz, 1H), 4.32 (d, *J* = 12.4 Hz, 1H), 3.95 (m, 1H), 3.68 (t, *J* = 7.1 Hz, 1H), 3.50 – 3.45 (m, 0.5H), 3.42 – 3.38 (m, 0.5H) 3.07 (d, *J* = 10.4 Hz, 1H), 2.59 – 2.52 (m, 1.5H), 2.28 (dd, *J* = 11.1, 6.38, Hz, 0.5H), 2.09 – 2.05 (m, 0.5H), 2.02 – 1.96 (m, 1H), 1.91 – 1.45 (m, 5.5H), 0.89 (s, 5H), 0.83 (s, 4H), 0.06 (d, *J* = 4.1 Hz, 3H), –0.04 (d, *J* = 9.4 Hz, 3H). ¹³C{¹H} NMR (126 MHz, CDCl₃) δ 210.9, 210.5, 150.1, 149.9, 137.7, 137.7, 133.9, 132.6, 130.5, 130.4, 128.9, 127.7, 127.5, 127.03, 126.97, 124.0, 123.8, 118.9, 118.8, 118.5, 118.3, 117.69, 117.67, 107.7, 68.99, 68.97, 59.6, 59.0, 58.2, 57.9, 49.7, 49.6, 49.5, 43.2, 41.0, 40.3, 39.3, 31.7, 27.2, 26.7, 26.6, 26.1, 26.0, 25.4, 22.8, 22.3, 22.2, 18.4, 18.3, 14.2, –5.2, –5.3; HRMS-ESI (+) *m/z* calcd for C₃₂H₄₃N₂O₂Si [M + H]⁺: 515.3088, found 515.3095.

2-((3S)-9-benzyl-3-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-3-(3-hydroxypropyl)-4-oxo-1,2,3,4,9,9a-hexahydro-4aH-carbazol-4a-yl)acetonitrile (24 and 25).

To a flame-dried round bottom flask under Argon equipped with a stir bar cyclohexene (1.4 mL, 13.9 mmol, 6.5 equiv) was added to freshly distilled THF (6 mL) was added at 0 °C. To this solution at 0 °C, borane dimethyl sulfide complex (neat, 607 μ L, 6.4 mmol, 3.0 equiv) added dropwise. A thick white slurry started to form after 1 min. Additional amounts of THF (1 mL) was added and the reaction was continued to stir at 0 °C for 1 h. After this period, a solution of **22** and **23** (1.10 g, 2.1 mmol, 1.0 equiv), in THF (5 mL) was cannulated in at 0 °C and the resulting reaction was warmed slowly to 23 °C for 2.5 h. The reaction was quenched with slow addition of NaBO₃•4H₂O (3.3 g, 21.3 mmol, 10 equiv) and H₂O (7 mL, 0.3M), and the resulting reaction mixture was continued to stir for 12 h. The reaction was diluted in brine, extracted with EtOAc (3x), dried with Na₂SO₄, and concentrated. The crude mixture was purified via column chromatography over silica gel using 40% EtOAc:Hexanes as the eluent to provide alcohol diastereomers **24** and **25** (1.12 g, 98% combined yield) which were separated. TLC: Silica Gel (40% EtOAc:Hexanes), R_f = 0.52 and 0.38 (lower spot desired diastereomer).

2-((3S,4aS,9aS)-9-benzyl-3-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-3-(3-hydroxypropyl)-4-oxo-1,2,3,4,9,9a-hexahydro-4aH-carbazol-4a-yl)acetonitrile (25).

¹H NMR (500 MHz, CDCl₃) δ 7.39 – 7.28 (m, 5H), 7.12 (td, *J* = 7.7, 1.3 Hz, 1H), 6.90 (dd, *J* = 7.5, 1.2 Hz, 1H), 6.64 (td, *J* = 7.5, 1.0 Hz, 1H), 6.49 (d, *J* = 7.8 Hz, 1H), 4.53 (d, *J* = 15.5 Hz, 1H), 4.31 (d, *J* = 15.5 Hz, 1H), 3.95 (dd, *J* = 7.1, 4.3 Hz, 1H), 3.65 (m, 2H), 3.35 (m, 2H), 3.04 (d, *J* = 16.4 Hz, 1H), 2.56 (d, *J* = 16.4 Hz, 1H), 2.04 (m, 1H), 1.88 – 1.65 (m, 5H), 1.44 – 1.35 (m, 1H), 1.34 – 1.29 (m, 2H), 1.25 (m, 1H), 0.88 (s, 9H), 0.05 (d, *J* = 3.9 Hz, 6H); ¹³C{¹H} NMR (126 MHz, CDCl₃) δ 210.6, 150.0, 137.6, 130.6, 129.0, 127.8, 127.6, 127.1, 123.6, 118.1, 117.8, 107.9, 69.1, 62.9, 59.6, 58.0, 49.6, 49.4, 38.7, 35.0, 28.4, 26.9, 26.7, 26.1, 22.5, 18.4, –5.2; LRMS-ESI (+) *m/z* 533.3 [M + H]⁺.

2-((3S,4aR,9aR)-9-benzyl-3-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-3-(3-hydroxypropyl)-4-oxo-1,2,3,4,9,9a-hexahydro-4aH-carbazol-4a-yl)acetonitrile (24).

[α]_D²⁰ –144 (*c* 0.08, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ 7.39 – 7.28 (m, 5H), 7.12 (td, *J* = 7.7, 1.3 Hz, 1H), 6.91 (dd, *J* = 7.5, 1.2 Hz, 1H), 6.66 (td, *J* = 7.5, 0.9 Hz, 1H), 6.48 (d, *J* = 7.9 Hz, 1H), 4.52 (d, *J* = 15.4 Hz, 1H), 4.30 (d, *J* = 15.4 Hz, 1H), 3.93 (m, 1H), 3.62 (m, 2H), 3.47 (m, 1H), 3.39 (m, 1H), 3.08 (d, *J* = 16.3 Hz, 1H), 2.52 (d, *J* = 16.3 Hz, 1H), 1.87 – 1.76 (m, 4H), 1.69 – 1.59 (m, 3H), 1.55 (m, 1H), 1.51 – 1.40 (m, 2H), 0.81 (s, 9H), –0.06 (d, *J* = 9.4 Hz, 6H); ¹³C{¹H} NMR (126 MHz, CDCl₃) δ 211.4, 149.8, 137.7, 130.4, 129.0, 127.8, 127.5, 127.3, 123.8, 118.6, 117.9, 107.9, 69.0, 63.3, 59.0, 58.1, 49.6, 49.4, 40.3, 32.5, 27.6, 27.3, 26.6, 26.0, 22.1, 18.3, –5.3; HRMS-ESI (+) *m/z* calcd for C₃₂H₄₄N₂O₃SiNa [M + Na]⁺: 555.3013, found 555.3009.

3-((3S,4aR,9aR)-9-benzyl-3-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-4a-(cyanomethyl)-4-oxo-2,3,4,4a,9,9a-hexahydro-1H-carbazol-3-yl)propyl 4-methylbenzenesulfonate (26).

To a flame-dried round bottom under Argon flask equipped with a stir bar, TsCl (50.1 mg, 0.26 mmol, 2.0 equiv) and DMAP (1.6 mg, 0.01 mmol, 10 mol %) in 0.3 mL CH₂Cl₂ were

added at 0°C. To this solution, alcohol **24** (70 mg, 0.13 mmol, 1.0 equiv) in CH₂Cl₂ (0.3 mL), followed by triethylamine addition (20.1 µL, 0.14 mmol, 1.1 equiv) was added. Additional amounts of TsCl and trimethylamine (0.5 and 0.4 equiv, respectively) were further added. The resulting reaction was warmed to 23 °C, quenched with saturated NaHCO₃, (5 mL) extracted with CH₂Cl₂ (3x), washed with brine, dried Na₂SO₄, and concentrated. The crude mixture was purified via column chromatography over silica gel using 10 – 15% EtOAc:Hexanes as the eluent to provide tosylate **26** as an oil (71.4 mg, 79% yield). TLC: Silica Gel (20% EtOAc:Hexanes), R_f = 0.31. [α]_D²⁰ –101.20 (c 0.171, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ 7.78 (d, *J* = 8.3 Hz, 2H), 7.39 – 7.28 (m, 7H), 7.12 (td, *J* = 7.7, 1.3 Hz, 1H), 6.87 (dd, *J* = 7.5, 1.2 Hz, 1H), 6.65 (td, *J* = 7.5, 1.0 Hz, 1H), 6.47 (d, *J* = 7.9 Hz, 1H), 4.51 (d, *J* = 15.4 Hz, 1H), 4.28 (d, *J* = 15.4 Hz, 1H), 4.00 (m, 2H), 3.89 (dd, *J* = 7.4, 4.5 Hz, 1H), 3.46 – 3.40 (m, 1H), 3.38 – 3.31 (m, 2H), 3.03 (d, *J* = 16.3 Hz, 1H), 2.48 (d, *J* = 16.3 Hz, 1H), 2.44 (s, 3H), 1.84 – 1.77 (m, 2H), 1.77 – 1.65 (m, 3H), 1.58 – 1.47 (m, 4H), 1.40 (ddd, *J* = 14.0, 8.3, 5.7 Hz, 1H), 0.80 (s, 9H), –0.07 (d, *J* = 9.0 Hz, 6H); ¹³C{¹H} NMR (126 MHz, CDCl₃) δ 210.9, 149.6, 144.9, 137.6, 133.1, 130.5, 130.0, 129.0, 128.1, 127.8, 127.5, 127.2, 123.7, 118.6, 117.8, 107.9, 71.0, 68.9, 58.8, 58.1, 49.5, 49.3, 40.0, 32.3, 27.3, 26.4, 26.0, 24.0, 22.0, 21.8, 18.3, –5.3; HRMS-ESI (+) *m/z* calcd for C₃₉H₅₁N₂O₅SSi [M + H]⁺: 687.3283, found 687.3276.

3-((3*S*,4*aS*,9*aS*)-9-benzyl-3-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-4*a*-(cyanomethyl)-4-oxo-2,3,4,4*a*,9,9*a*-hexahydro-1*H*-carbazol-3-yl)propyl 4-methylbenzenesulfonate (27**).**

Same experimental as in the transformation of **24** to **26**. The crude mixture was isolated via column chromatography over silica gel using 15–20% EtOAc:Hexanes as the eluent to provide tosylate **27** as yellow oil (463.2 mg, 85% yield). TLC: Silica (20% EtOAc:Hexanes), R_f = 0.29. ¹H NMR (400 MHz, CDCl₃) δ 7.68 (d, *J* = 8.3 Hz, 2H), 7.40 – 7.28 (m, 7H), 7.11 (td, *J* = 7.7, 1.3 Hz, 1H), 6.80 (dd, *J* = 7.6, 1.3 Hz, 1H), 6.58 (td, *J* = 7.4, 0.9 Hz, 1H), 6.49 (d, *J* = 7.9 Hz, 1H), 4.52 (d, *J* = 15.5 Hz, 1H), 4.30 (d, *J* = 15.5 Hz, 1H), 3.97 – 3.87 (m, 1H), 3.76 (m, 1H), 3.67 (m, 1H), 3.59 (td, *J* = 6.8, 1.5 Hz, 2H), 3.00 (d, *J* = 16.3 Hz, 1H), 2.53 (d, *J* = 16.4 Hz, 1H), 2.45 (s, 3H), 1.95 (m, 1H), 1.84 – 1.65 (m, 4H), 1.61 (m, 1H), 1.54 – 1.44 (m, 1H), 1.44 – 1.32 (m, 1H), 1.27 (td, *J* = 12.7, 4.5 Hz, 2H), 1.09 (td, *J* = 13.1, 3.4 Hz, 1H), 0.86 (s, 9H), 0.02 (d, *J* = 2.6 Hz, 6H); ¹³C{¹H} NMR (101 MHz, CDCl₃) δ 210.4, 150.1, 144.8, 137.6, 133.1, 130.7, 129.9, 129.0, 128.0, 127.8, 127.6, 126.8, 123.4, 118.3, 117.7, 107.9, 70.4, 69.0, 59.5, 58.0, 49.7, 49.1, 38.4, 34.7, 28.3, 26.7, 26.1, 23.4, 22.5, 21.8, 18.4, –5.2; LRMS-ESI (+) *m/z* 687.3 [M + H]⁺.

2-((4*aS*,6*aR*,11*bR*,11*cS*)-7-benzyl-3,4,5,6,6*a*,7-hexahydro-2*H*,11*bH*-11*c*,4*a*-(epoxyethano)pyrano[3,2-*c*]carbazol-11*b*-yl)acetonitrile (28**).**

To a flame-dried round bottom flask under Argon equipped with a stir bar, tosylate **26** (27 mg, 39 µmol, 1.0 equiv) was dissolved in freshly distilled THF (0.4 mL, 0.1 M). To this solution at 23 °C, TBAF (1.0 M in THF, 47 µL, 47 µmol, 1.2 equiv) was added dropwise and the reaction mixture was stirred for 12 h. Reaction was then quenched with H₂O and brine (~0.5 mL each), extracted with EtOAc (3x), washed brine, dried Na₂SO₄, and concentrated. The crude mixture was purified via column chromatography over silica gel using 15% EtOAc:Hexanes as the eluent to provide tosylate **28** (15.7 mg, 99% yield) as a white amorphous solid. TLC: Silica (20% EtOAc:Hexanes), R_f = 0.34. [α]_D²⁰ +45.13 (c 0.203,

CHCl₃); ¹H NMR (400 MHz, Chloroform-*d*) δ 7.34 – 7.24 (m, 6H), 7.07 (td, *J* = 7.7, 1.3 Hz, 1H), 6.62 (td, *J* = 7.4, 1.0 Hz, 1H), 6.34 (d, *J* = 8.3 Hz, 1H), 4.45 (d, *J* = 16.0 Hz, 1H), 4.35 (d, *J* = 16.0 Hz, 1H), 4.09 (ddd, *J* = 10.8, 8.4, 6.2 Hz, 1H), 3.91 (td, *J* = 8.6, 1.1 Hz, 1H), 3.77 (m, 2H), 3.68 (m, 1H), 2.95 (d, *J* = 16.6 Hz, 1H), 2.80 (d, *J* = 16.6 Hz, 1H), 2.02 (tt, *J* = 13.6, 3.5 Hz, 1H), 1.81 – 1.58 (m, 6H), 1.54 – 1.36 (m, 3H); ¹³C{¹H} NMR (101 MHz, Chloroform-*d*) δ 152.1, 138.9, 129.9, 129.5, 128.7, 127.4, 127.2, 125.9, 119.3, 117.2, 108.8, 105.9, 68.3, 67.3, 61.3, 54.9, 50.9, 41.4, 38.6, 36.5, 31.3, 28.0, 24.9, 21.3; HRMS-APCI (+) *m/z* calcd for C₂₆H₂₉N₂O₂ [M + H]⁺: 401.2223, found 401.2220.

2-((4a*S*,6a*S*,11*bS*,11*cS*)-7-benzyl-3,4,5,6,6a,7-hexahydro-2*H*,11*bH*-11*c*,4a-(epoxyethano)pyrano[3,2-*c*]carbazol-11*b*-yl)acetonitrile (29).

To a flame-dried round bottom flask under Argon equipped with a stir bar, compound **27** (30 mg, 44 μmol, 1.0 equiv) in freshly distilled THF (0.44 mL, 0.1 M) was added. To this solution at 23 °C, TBAF (1.0 M in THF, 52 μL, 52 μmol, 1.2 equiv) was added and the resulting reaction was stirred for 12 h. Reaction was then quenched with H₂O (0.5 mL), extracted with EtOAc (3x), washed brine, dried Na₂SO₄, and concentrated. The crude mixture was purified via column chromatography over silica gel using 20% EtOAc:Hexanes as the eluent to provide product **29** (17.5 mg, quantitative yield) as amorphous white solid. TLC: Silica (20% EtOAc:Hexanes), R_f = 0.30. [α]_D²⁰ –68.82 (*c* 0.364, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ 7.53 (dd, *J* = 7.5, 1.3 Hz, 1H), 7.37 – 7.30 (m, 4H), 7.26 (m, 1H), 7.05 (td, *J* = 7.7, 1.4 Hz, 1H), 6.58 (td, *J* = 7.5, 1.0 Hz, 1H), 6.30 (dd, *J* = 7.9, 0.9 Hz, 1H), 4.47 (d, *J* = 15.9 Hz, 1H), 4.39 (d, *J* = 15.9 Hz, 1H), 4.17 (ddd, *J* = 10.6, 8.7, 4.9 Hz, 1H), 3.98 (ddd, *J* = 12.0, 9.8, 1.9 Hz, 1H), 3.93 (ddd, *J* = 9.6, 8.6, 7.5 Hz, 1H), 3.75 (ddd, *J* = 12.3, 10.4, 6.9 Hz, 1H), 3.66 (d, *J* = 3.7 Hz, 1H), 2.98 (d, *J* = 16.6 Hz, 1H), 2.93 (d, *J* = 16.5 Hz, 1H), 2.51 (ddd, *J* = 13.5, 10.6, 7.5 Hz, 1H), 1.99 – 1.89 (m, 1H), 1.83 (ddd, *J* = 14.0, 9.6, 4.9 Hz, 1H), 1.73 – 1.63 (m, 2H), 1.58 – 1.45 (m, 3H), 1.38 – 1.34 (m, 1H), 1.23 – 1.15 (m, 1H); ¹³C{¹H} NMR (126 MHz, CDCl₃) δ 152.4, 138.9, 129.4, 128.7, 128.4, 127.5, 127.2, 126.5, 119.2, 116.7, 109.4, 105.2, 67.8, 67.0, 58.6, 53.1, 50.4, 43.3, 38.2, 35.1, 28.4, 27.8, 23.8, 19.0; HRMS-APCI (+) *m/z* calcd for C₂₆H₂₉N₂O₂ [M + H]⁺: 401.2223, found 401.2219.

3-((4*S*,6a*S*,11*bS*)-7-benzyl-4-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-2,4,5,6,6a,7-hexahydro-1*H*-pyrrolo[2,3-*d*]carbazol-4-yl)propyl 4-methylbenzenesulfonate (30).

To a Parr Reactor vessel under argon was added 2800 Ra-Ni (1.21 g, 300 wt %). A solution of tosylate **27** (403 mg, 0.59 mmol, 1.0 equiv) in MeOH (22 mL, 27 mM) was then cannulated in. The mixture was shaken in a ParrTM apparatus under hydrogen at 60 Psi pressure for 46 h. After this period, the resulting white solution mixture was filtered through Celite® and filter-cake was washed with MeOH and CH₂Cl₂ (15 mL each). Solvents were evaporated to yield imine **30** (359.5 mg, 90.8% yield). TLC: Silica (30% EtOAc:Hexanes), R_f = 0.46. ¹H NMR (500 MHz, CDCl₃) δ 7.68 (d, *J* = 8.3 Hz, 2H), 7.36 – 7.27 (m, 7H), 7.03 (td, *J* = 7.7, 1.3 Hz, 1H), 6.63 (dd, *J* = 7.3, 1.2 Hz, 1H), 6.48 (t, *J* = 5.9 Hz, 1H), 6.40 (d, *J* = 7.9 Hz, 1H), 4.48 (d, *J* = 15.5 Hz, 1H), 4.24 (d, *J* = 15.5 Hz, 1H), 3.91 (dd, *J* = 15.4, 8.5 Hz, 1H), 3.80 (m, 1H), 3.74 (m, 1H), 3.68 (m, 1H), 3.62 (td, *J* = 7.2, 3.0 Hz, 2H), 3.47 (t, *J* = 5.7 Hz, 1H), 2.45 (s, 3H), 2.19 (dt, *J* = 12.2, 6.6 Hz, 1H), 1.91 (m, 1H), 1.80 (dt, *J* = 13.9, 6.7 Hz, 1H), 1.69 (m, 2H), 1.57 (m, 2H), 1.46 (m, 2H), 1.16 (td, *J* = 13.0, 5.3 Hz, 1H), 1.04 (td, *J* = 13.1, 3.2 Hz, 1H), 0.85 (s, 9H), 0.01 (d, *J* = 1.9 Hz, 7H); ¹³C{¹H} NMR (126 MHz,

CDCl₃) δ 180.8, 149.2, 144.5, 138.4, 133.2, 132.4, 129.8, 128.7, 128.7, 127.9, 127.4, 127.3, 122.0, 117.4, 107.2, 71.6, 71.0, 61.0, 59.4, 56.9, 49.2, 43.5, 41.8, 38.6, 32.6, 31.4, 26.0, 23.7, 22.5, 21.7, 18.3, -5.3; LRMS-ESI (+) m/z 673.3 [M + H]⁺.

1-Benzyl Fendleridine (**32**).²⁵

To a Parr reactor vessel under Argon was added 2800 Ra-Ni (51 mg, 300 wt %). A solution of tosylate **26** (17 mg, 25 μ mol, 1.0 equiv) in MeOH (1 mL, 27 mM) was then cannulated in the flask. The mixture was shaken in a ParrTM apparatus under hydrogen at 60 Psi pressure for 21 h. After this period, the resulting white solution mixture was filtered through Celite® and filter-cake was washed with MeOH and CH₂Cl₂ (10 mL each). Solvents were evaporated and the crude material (**31**) was used directly for the next reaction. LRMS-ESI (+) m/z 501.3 [M]⁺.

To a flame-dried flask under Argon equipped with a stir bar, above crude product (**31**) was dissolved in freshly distilled THF (0.3 mL, 0.1 M) and TBAF (1 M in THF, 30 μ L, 0.03 mmol, 1.2 equiv) was added and the resulting reaction mixture was stirred for 12 h. Reaction was then quenched with H₂O (~.5 mL), extracted with EtOAc (3x), washed with brine, dried with Na₂SO₄, and concentrated. The crude mixture was purified via column chromatography over silica gel using 70% -80% EtOAc:Hexanes as the eluent to provide benzyl derivative **32** (5.9 mg, 62% yield over 2 steps) as an off-white amorphous solid. TLC: Alumina (5% EtOAc:Hexanes), R_f = 0.50. [α]_D²⁰ +3.0 (*c* 0.155, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 7.36 (dd, *J* = 7.4, 1.3 Hz, 1H), 7.29 – 7.15 (m, 5H), 6.94 (td, *J* = 7.6, 1.3 Hz, 1H), 6.59 (td, *J* = 7.4, 1.1 Hz, 1H), 6.27 (dd, *J* = 7.8, 1.0 Hz, 1H), 4.34 (d, *J* = 15.4 Hz, 1H), 4.06 (d, *J* = 15.4 Hz, 1H), 3.89 – 3.75 (m, 2H), 3.22 (dd, *J* = 7.6, 4.1 Hz, 1H), 2.91 – 2.82 (m, 2H), 2.74 – 2.64 (m, 1H), 2.59 – 2.51 (m, 1H), 2.14 (ddd, *J* = 13.2, 8.9, 6.6 Hz, 1H), 1.98 – 1.84 (m, 2H), 1.77 (dd, *J* = 21.1, 10.6 Hz, 1H), 1.64 – 1.50 (m, 3H), 1.50 – 1.38 (m, 3H), 1.29 – 1.19 (m, 2H); ¹³C{¹H} NMR (101 MHz, CDCl₃) δ 151.2, 139.0, 135.0, 128.6, 127.7, 127.5, 127.1, 125.9, 117.9, 106.5, 101.9, 71.5, 64.9, 57.9, 49.6, 49.2, 44.1, 38.6, 38.3, 36.9, 34.7, 27.4, 21.64, 21.56; HRMS-ESI (+) m/z calcd for C₂₆H₃₁N₂O [M + H]⁺: 387.2431, found 387.2429.

(+)-Fendleridine (**2**).^{25,27a}

A flame-dried round bottom flask under Argon was equipped with a stir bar and cold-finger condenser with dry ice and acetone. NH₃ was allowed to condense into the flask (1 mL) and the cold finger condenser was removed and a septum with an Argon balloon quickly replaced it. To this, small chunks of freshly cut Li (30 mg, 167 equiv) washed with hexanes were added. The solution turned dark blue. Benzyl derivative **32** (10 mg, 0.03 mmol, 1 equiv) in a mixture (10:1) of THF and *t*-BuOH (0.5 mL) was added and the reaction was allowed to stir for 2 h. Reaction was quenched with solid NH₄Cl (~100 mg, 72.3 eq) and cooling bath was removed and the reaction was warmed to 23 °C. Reaction diluted with EtOAc (1 mL), filtered through cotton plug with CH₂Cl₂ and EtOAc (5 mL each), and concentrated. The crude mixture was purified via column chromatography over alumina using 5% EtOAc:Hexanes as the eluent to provide synthetic (+)fendleridine, (+)-**2** as off-white amorphous solid (5.3 mg, 70%). TLC: Alumina (5% EtOAc:Hexanes), R_f = 0.13. [α]_D²⁰ +53.7 (*c* 0.177, CHCl₃); ¹H NMR (800 MHz, CDCl₃) δ 7.45 (d, *J* = 7.5 Hz, 1H),

7.01 (t, $J = 7.6$ Hz, 1H), 6.73 (t, $J = 7.5$ Hz, 1H), 6.60 (d, $J = 7.7$ Hz, 1H), 4.03 – 3.95 (m, 2H), 3.52 (bs, 1H), 3.40 (dd, $J = 9.5, 4.8$ Hz, 1H), 3.00 (td, $J = 8.7, 4.1$ Hz, 1H), 2.92 (dt, $J = 15.6, 8.7$ Hz, 1H), 2.79 (t, $J = 11.4$ Hz, 1H), 2.65 (d, $J = 11.1$ Hz, 1H), 2.24 (ddd, $J = 13.4, 8.7, 5.9$ Hz, 1H), 1.92 – 1.83 (m, 2H), 1.81 (td, $J = 12.9, 4.0$ Hz, 1H), 1.78 – 1.71 (m, 2H), 1.71 – 1.59 (m, 2H), 1.51 (dt, $J = 12.1, 3.2$ Hz, 1H), 1.45 (dt, $J = 13.8, 4.8$ Hz, 1H), 1.35 (d, $J = 13.0$ Hz, 1H), 1.24 (dd, $J = 11.9, 5.5$ Hz, 1H); $^{13}\text{C}\{^1\text{H}\}$ NMR (201 MHz, CDCl_3) δ 150.3, 134.4, 127.3, 126.1, 119.4, 110.0, 102.1, 66.6, 64.9, 58.9, 49.3, 44.1, 39.2, 37.0, 35.8, 34.1, 27.3, 27.0, 21.5; HRMS-ESI (+) m/z calcd for $\text{C}_{19}\text{H}_{25}\text{N}_2\text{O}$ $[\text{M} + \text{H}]^+$: 297.1961, found 297.1964.

(+) – Acetylaspidobalbidine (3).^{25,27a}

To a flame-dried round bottom flask under Argon equipped with a stir bar, synthetic fendleridine (7.9 mg, 0.027 mmol, 1.0 equiv) was dissolved in CH_2Cl_2 (1 mL), was added. Pyridine (11 μL , 0.13 mmol, 5.0 equiv) and acetic anhydride (7.5 μL , 0.08 mmol, 3.0 equiv) were added sequentially. Reaction was quenched with saturated NaHCO_3 (~ 0.1 mL), extracted 3x with CH_2Cl_2 , dried Na_2SO_4 , and concentrated. The crude mixture was purified via column chromatography using 15 – 20% EtOAc:Hexanes as the eluent to provide products (+)-**3** (rotamers) as white amorphous solid (9 mg, quantitative yield). TLC: Alumina (5% EtOAc:Hexanes), $R_f = 0.08$. $[\alpha]_D^{20} +30.2$ (c 0.145, CHCl_3); ^1H NMR (800 MHz, CDCl_3) δ 8.14 (d, $J = 8.0$ Hz, 1H), 7.67 (d, $J = 3.5$ Hz, 0.3H) 7.60 (d, $J = 7.7$ Hz, 1H, minor rotamer), 7.19 (t, $J = 7.7$ Hz, 1H), 7.05 (t, $J = 7.5$ Hz, 1H), 4.42 (dd, $J = 9.12, 4.16$ Hz, minor rotamer), 4.16 (t, $J = 8.6$ Hz, 1H), 4.09 (dt, $J = 10.5, 7.5$ Hz, 1H), 3.86 (dd, $J = 11.0, 5.2$ Hz, 1H), 3.02 (td, $J = 8.8, 4.1$ Hz, 1H), 2.93 (dd, $J = 15.7, 9.0$ Hz, 1H), 2.80 (td, $J = 11.5, 2.8$ Hz, 1H), 2.65 (d, $J = 10.7$ Hz, 1H), 2.39 (s, 0.6H, minor rotamer), 2.26 (s, 2.1H), 2.10 (ddd, $J = 14.6, 9.1, 6.1$ Hz, 1H), 2.07 – 2.00 (m, 1H), 1.93 (m, 1H), 1.86 (m, 1H), 1.83 – 1.66 (m, 4H), 1.55 (dt, $J = 12.7, 3.6$ Hz, 0.8H), 1.50 (t, $J = 13.9$ Hz, 2 H, minor rotamer), 1.43 (dt, $J = 14.0, 3.9$ Hz, 1H), 1.38 (d, $J = 12.9$ Hz, 1H), 1.27 (m, 1H); $^{13}\text{C}\{^1\text{H}\}$ NMR (201 MHz, CDCl_3 , major rotamer) δ 168.2, 141.2, 137.9, 127.5, 124.9, 124.8, 117.9, 102.2, 69.0, 65.1, 58.4, 49.1, 44.1, 39.8, 37.3, 34.9, 33.2, 26.6, 25.5, 23.5, 21.2; $^{13}\text{C}\{^1\text{H}\}$ NMR (201 MHz, CDCl_3 , minor rotamer) δ 168.0, 140.6, 140.1, 127.1, 126.1, 124.3, 115.1, 102.5, 67.1, 65.0, 57.2, 48.9, 43.9, 39.6, 37.0, 35.2, 33.5, 26.8, 24.4, 23.8, 21.2; HRMS-ESI (+) m/z calcd for $\text{C}_{21}\text{H}_{27}\text{N}_2\text{O}_2$ $[\text{M} + \text{H}]^+$: 339.2067, found 339.2064.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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(+)-Aspidospermidine (1)

(+)-Fendleridine (2, R = H)

(+)-Acetylaspidoalbidine (3, R = Ac)

(+)-Haplocine (4, R = Et)

(+)-Haplocidine (5, R = Me)

(+)-Cimicine (6)

(-)-Aspidophytine (7)

(+)-Limaspermidine (8)

Figure 1.
Structures of selected aspidosperma alkaloids

Figure 2.
Representative NOESY correlation of compounds **28** and **29**.

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Scheme 2.
Enantioselective synthesis of enaminone **17**

Scheme 3.
Synthesis of diastereomeric alcohols **24** and **25**

Scheme 4.
Stereochemical studies of ketal products **28** and **29**.

Scheme 5.

Synthesis of (+)-fendleridine and (+)-1-acetylaspidobidene

Table 1.Asymmetric allylation of enaminone **15**

Solvent	Temperature	Duration	Percent Yield of 17	% <i>ee</i> of 18
Toluene ^a	70°C	12 h	Trace	N/A
MTBE	40°C	12 h	Trace	N/A
THF	70°C	30 min	97%	77%
Benzene	70°C	30 min	98%	81%
Toluene ^b	70°C	30 min	88%	82%

^a Solvent not degassed.^b Reaction carried out on multigram scale.