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Formal Synthesis of (+)-Kopsihainanine A and Synthetic Study toward (+)-Limaspermidine

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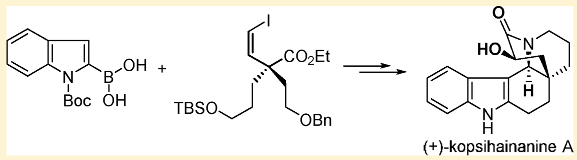
S Supporting Information

ABSTRACT: The formal synthesis of (+)-kopsihainanine A has been achieved via stereoselective reduction of tetracyclic iminium ion intermediates (**24**). However, attempts to synthesize (+)-limaspermidine by reduction of the same tetracyclic iminium ion intermediates have failed. The synthesis features a Suzuki cross-coupling reaction, a cyclization reaction mediated by trifluoromethanesulfonic anhydride, and stereoselective reduction of an iminium ion.



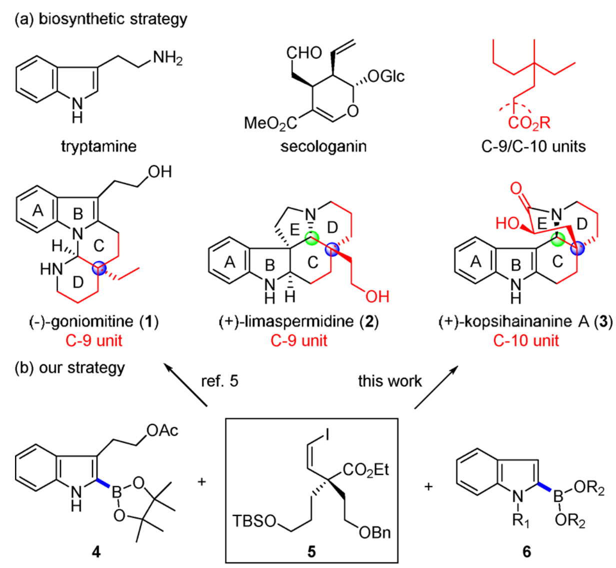
INTRODUCTION

The *Aspidosperma* family of alkaloids is the largest family of monoterpenoid indole alkaloids now known, consisting of over 250 members.[1] The unique structure of these natural products along with their potential biological activity have attracted considerable attention from synthetic chemists for many years.[2] Indeed, the *Aspidosperma* family of alkaloids has provided a fertile ground for innovation and to date remains an active and exciting area of synthetic chemistry.[3]

The biosynthetic pathway of the *Aspidosperma* family of monoterpenoid indole alkaloids involves the combination of tryptamine with the nontryptophan C-9/C-10 units containing a quaternary carbon center, which was derived from secologanin (Scheme 1a).[4] Inspired by the *Aspidosperma* biosynthesis pathway, we envisioned that coupling a tryptamine (indole) with a common C-9/C-10 intermediate might be an efficient and general strategy for the total synthesis of the skeletally diverse *Aspidosperma* alkaloids. In this context, we have recently developed an efficient method for the synthesis of the chiral C-9 unit (**5**) by diastereoselective dialkylation of diethyl L-malate, and completed the total synthesis of (−)-goniomitine (**1**) via the Suzuki−Miyaura cross-coupling of indole 2-boronic acid pinacol ester (**4**) and **5** (Scheme 1b).[5] To further evolve our synthetic strategy, we chose (+)-limaspermidine (**2**) and (+)-kopsihainanine A (**3**) as our new synthetic targets (Scheme 1b).

(+)-Limaspermidine was isolated from the trunk bark of the small tree *A. rhombeosignatum* MARKGRAF by Di Genova and co-workers in 1979,[6] and it possesses the complex and characteristic [6.5.6.6.5]-pentacyclic ABCDE framework of the *Aspidosperma* alkaloids with four contiguous stereocenters, including two all-carbon quaternary stereogenic centers.[7] (+)-Kopsihainanine A was isolated from the leaves and stems of the Chinese medicinal plant *Kopsia hainanensis* by Gao and co-workers in 2011.[8] Kopsihainanine A has an unprecedented strained [6.5.6.6.6]-pentacyclic skeleton. This natural product quickly attracted the attention of synthetic chemists, and four total synthesis and one formal synthesis have been reported to date.[9] Structurally, (+)-limaspermidine and (+)-kopsihainanine A contain a common ABCD tetracyclic framework with the same configuration of quaternary carbon center, whereas the *trans*-fused C/D ring is found in kopsihainanine A and the *cis*-fused C/D ring is found in limaspermidine. We sought to achieve the synthesis of (+)-limaspermidine and (+)-kopsihai-

Scheme 1. Selected *Aspidosperma* Alkaloids and Our Synthetic Strategy



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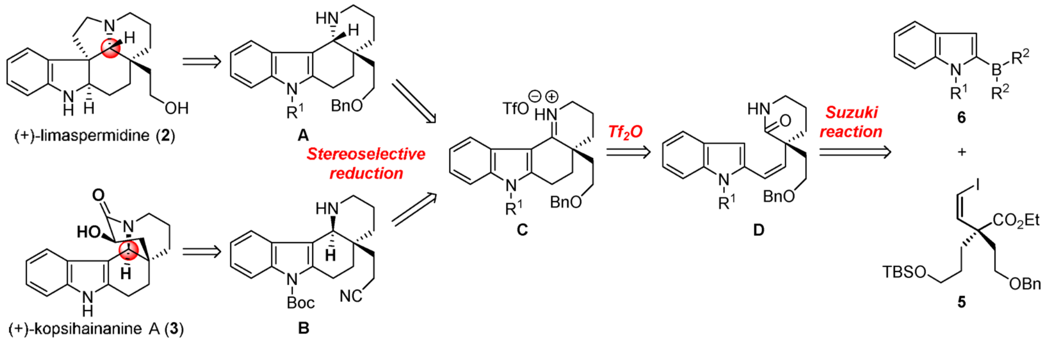
Scheme 2. Retrosynthetic Analysis of (+)-Limaspermidine and (+)-Kopsihainanine A



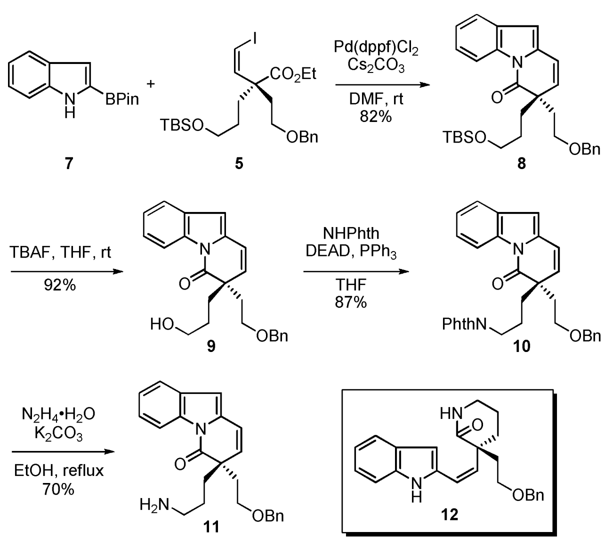
nanine A by the application of our convergent strategy in a divergent manner. Herein, we report our synthetic efforts.

■ RESULTS AND DISCUSSION

Our diversity-oriented retrosynthetic analysis is outlined in Scheme 2. We envisioned that (+)-limaspermidine could be derived from *cis*-fused C/D ring **A**[10] and that (+)-kopsihainanine A could be established from *trans*-fused C/D ring **B**. Compounds **A** and **B** could be obtained via the stereoselective reduction of the common chiral tetracyclic iminium ion intermediate **C**, which could be accessed from amide **D** via a Tf_2O-mediated cyclization reaction.[11] In turn, compound **D** could be generated via Suzuki coupling of 2-borylindole (**6**) and **5**.

As shown in Scheme 3, our synthesis commenced with the Suzuki coupling of **5** with the known indole 2-boronate **7**,

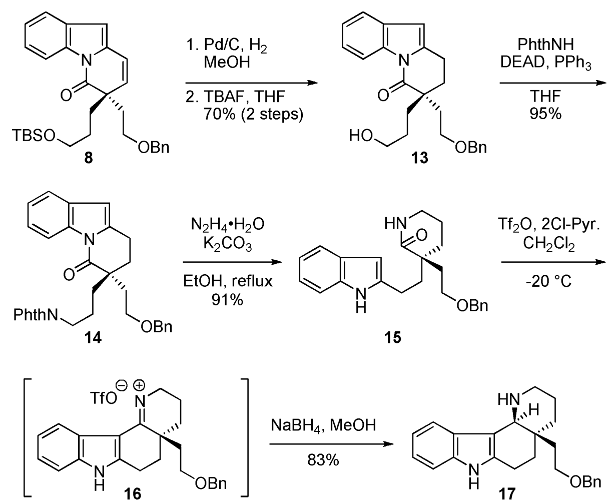
Scheme 3. Attempted Synthesis of δ-Lactam 12



which was prepared by the Ir-catalyzed C−H borylation of indole.[12] Consistent with our previous observation,[5] the Suzuki coupling afforded lactam **8** in 82% yield as the sole product. To avoid the cyclization reaction, we examined several other bases, such as NEt_3, and K_3PO_4, but unfortunately no desired products were isolated. Considering that lactam **8** could be transformed to desired product **12** via an amide exchange reaction, further conversion of compound **8** was carried out. Removal of the TBS group with TBAF gave alcohol **9** in 92% yield. Mitsunobu reaction of **9** with phthalimide (PhthNH) afforded compound **10** in 87% yield. Removal of the phthalyl group with $N_2H_4 \cdot H_2O$ in the presence of K_2CO_3 only gave amine **11**, and no amide **12** was obtained. Attempts to convert **11** to **12** were investigated using other bases or acids. However, only starting material **11** was recovered. These results indicated that the intramolecular amide exchange reaction was hard to get to take place. We hypothesized that the *cis*-double bond in **11** might prevent the intramolecular amide exchange reaction. Thus, first reducing the *cis*-double bond and subsequently performing the amide exchange reaction was pursued.

The modified synthetic route is shown in Scheme 4. Selective reduction of the *cis*-double bond of **8** followed by deprotection

Scheme 4. Synthesis of Amine 17



of TBS with TBAF provided alcohol **13** in 70% yield over two steps. A Mitsunobu reaction of **13** with PhthNH afforded compound **14** in 95% yield. Gratifyingly, agreeing with our hypothesis, treatment of **14** with $N_2H_4 \cdot H_2O$ in the presence of K_2CO_3 indeed led to removal of the phthalyl group accompanied by an intramolecular ester−amide exchange reaction, which successfully afforded desired δ-lactam **15** in 91% yield. Activation of lactam **15** with Tf_2O at −20 °C followed by reduction of the corresponding iminium ion **16** with $NaBH_4$ provided *trans*-fused C/D **17** in 83% yield as the sole product.

Because reduction of **16** only provided the *trans*-fused C/D ring **17**, synthesis of the *cis*-fused C/D ring system was further pursued. In Nicolaou's work on the synthesis of aspidophytine, reduction of iminium ion **18** afforded the *cis*-fused C/D ring **19** (Scheme 5).[10a] We speculated that the double bond in β-position of indole might influence the stereoselectivity. Thus,

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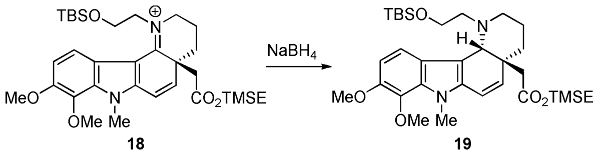
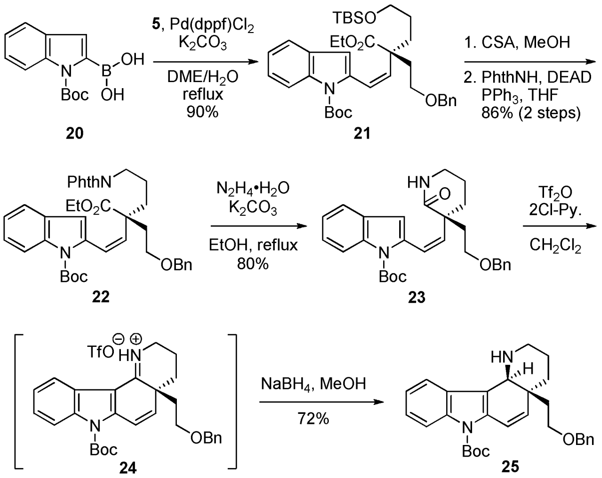
Scheme 5. Reduction of Iminium Ion 18



synthesis of the tetracyclic iminium ion intermediate bearing the double bond in the β-position of indole was performed.

The known *N*-Boc indole 2-boronic acid **20** was chosen as the Suzuki reaction partner to avoid the formation of δ-lactam **8** (Scheme 6).[13] The Suzuki coupling of **20** with **5** provided **21** in

Scheme 6. Synthesis of Amine 25

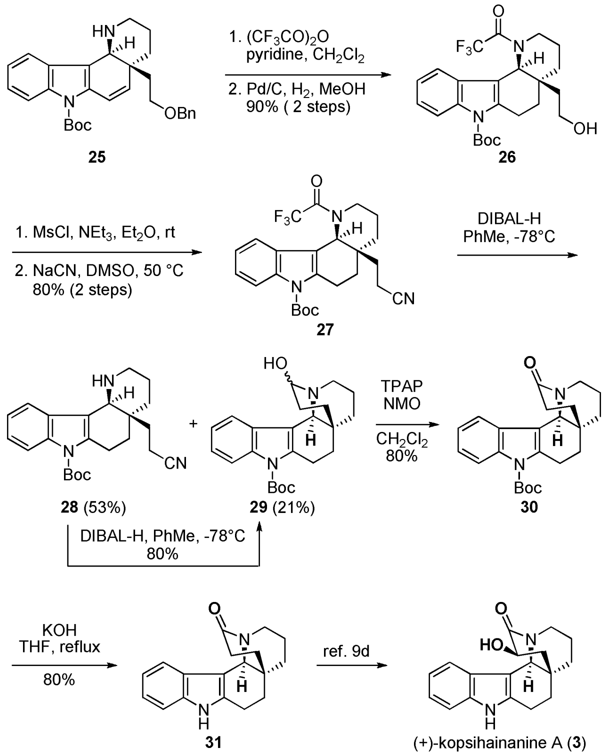


90% yield. Deprotection of TBS with D-camphor-10-sulfonic acid (CSA) followed by Mitsunobu reaction gave **22** in 86% overall yield. Treatment of **22** with $N_2H_4{\cdot}H_2O$ in the presence of K_2CO_3 afforded desired δ-lactam **23**. Compound **23** was smoothly transformed to iminium ion intermediate **24** with Tf_2O and 2-Cl-pyridine. Unfortunately, reduction of **24** with $NaBH_4$ in MeOH gave single *trans*-fused C/D ring **25**. Other reduction conditions have also been screened, such as $NaBH(OAc)_3$/HOAc,[14] Pd/C/H_2, and asymmetric reduction condition chiral *N*-sulfonated diamine Ru complexes,[15] but no desired *cis*-fused C/D ring product was isolated.

Because reduction of the tetracyclic iminium ion intermediates **16** and **24** provided only the *trans*-fused C/D ring **17** and **25**, respectively, the observed high stereoselectivity can be explained by steric hindrance between the ethyoxyl and reducing agent. Thus, other strategies had to be pursued to obtain the desired *cis*-fused C/D ring.

With compound **25** in hand, the formal synthesis of (+)-kopsihainanine A was completed (Scheme 7). Protection of amine **25** with TFAA followed by reduction of the double bond and removal of the benzyl group with Pd/C and H_2 afforded alcohol **26** in 90% overall yield. Mesylation of alcohol **26** with MsCl, followed by treatment with NaCN in DMSO, smoothly provided nitrile **27** in 80% yield. Because the trifluoroacetyl group could be removed and nitrile could be converted to aldehyde by reduction with DIBAL-H, attempts to reduce nitrile **27** directly to aza-hemiacetal **29** with DIBAL-H were performed.[16] However, we found that it yielded the desired aza-hemiacetal **29** in only 21% yield along with the TFA-deprotected product **28** in 53% yield. An assortment of

Scheme 7. Formal Synthesis of (+)-Kopsihainanine A



conditions with increasing reaction temperature, extending reaction time, increasing amounts of DIBAL-H, and changing solvents were then screened, but they gave almost the same result. Pleasantly, reduction of **28** with DIBAL-H could provide aza-hemiacetal **29** in 80% yield. Thus, no further optimization of conditions were carried out. Finally, oxidation of aza-hemiacetal **29** with Ley's TPAP/NMO system followed by deprotection of Boc with KOH/THF[9c] gave known compound **31**.[9d] Because **31** has been transformed to kopsihainanine A via a one-step oxidation reaction, this constitutes a formal synthesis of (+)-kopsihainanine A.

■ CONCLUSIONS

In summary, to further evolve our convergent synthetic strategy for the synthesis of monoterpenoid indole alkaloids (+)-limaspermidine (**2**) and (+)-kopsihainanine A (**3**), two tetracyclic iminium ion intermediates (**16** and **24**) were prepared by Suzuki cross-coupling of 2-borylindole and our chiral vinyl iodide **5**. The stereoselectivity in the reduction of these two tetracyclic iminium ion intermediates were investigated in detail, and our results indicated that they could provide only the *trans*-fused C/D ring system. The *trans*-fused C/D ring **25** was used for the formal synthesis of (+)-kopsihainanine A.

■ EXPERIMENTAL SECTION

General Methods. Unless otherwise noted, all experiments were carried out under an Ar atmosphere. Dichloromethane was distilled over CaH_2. Toluene and THF were distilled over sodium, and tetrahydrofuran was distilled over a Na−K alloy. The other reagents and solvents were directly used from the supplier without further purification unless noted. Reactions at −78 °C employed a dry ice-acetone bath. Chemical shifts were reported in δ (ppm) relative to TMS in $CDCl_3$ as internal standard (^{1}H NMR) or the residual $CHCl_3$ signal (^{13}C NMR). ^{1}H NMR spectra were tabulated as follows: chemical shift, multiplicity (br s = broad singlet, s = singlet, d =

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doublet, dd = doublet of doublets, t = triplet, q = quartet, m = multiplet), number of protons, and coupling constant (Hz). Infrared spectra were recorded with a thin layer of the product on a KBr disk and reported in frequency of absorption (cm^{-1}). High resolution mass spectra (HRMS) were acquired on an FT-MS (7.0 T) equipped with an ESI source in positive mode. The abbreviations used in this section can be found in the JOC's standard abbreviations list.

(S)-7-(2-(Benzyloxy)ethyl)-7-(3-((tert-butyldimethylsilyl)oxy)-propyl)pyrido[1,2-a]indol-6(7H)-one (8). To a 50 mL flask were added compound **7** (155 mg, 0.64 mmol, 1.3 equiv), compound **5** (146 mg, 0.5 mmol, 1.0 equiv), and Cs_2CO_3 (487 mg, 1.50 mmol, 3.0 equiv), and then DMF (16 mL) was added. The solution was saturated with an atmosphere of argon for 15 min before Pd(dppf)Cl_2 (37 mg, 0.05 mmol, 0.10 equiv) was added and then stirred at room temperature for 2 h. After the reaction was completed, water (20 mL) was added, and the resulting solution was extracted with EtOAc (3 × 20 mL). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, and concentrated. Purification of the residue by FCC (PE:EtOAc = 15:1) provided compound **8** as a colorless oil (201 mg, 82%). $[\alpha]_D^{25}$ +15.6, (*c* 0.5, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 8.48 (d, *J* = 8.0 Hz, 1H), 7.51 (d, *J* = 7.2 Hz, 1H), 7.34−7.27 (m, 2H), 7.09 (t, *J* = 7.2 Hz, 1H), 7.03 (t, *J* = 7.2 Hz, 2H), 6.92 (d, *J* = 7.2 Hz, 1H), 6.72 (d, *J* = 10.0 Hz, 1H), 6.43 (s, 1H), 5.78 (d, *J* = 9.6 Hz, 1H), 4.24 (d, *J* = 12.0 Hz, 1H), 4.17 (d, *J* = 12.0 Hz, 1H), 3.55−3.47 (m, 2H), 3.45−3.41 (m, 2H), 2.70 (m, 1H), 2.13 (m, 1H), 1.82 (m, 1H), 1.68 (m, 1H), 1.42 (m, 1H), 1.26 (m, 1H), 0.85 (s, 9H), − 0.02 (d, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.0, 137.8, 135.8, 134.7, 133.0, 130.4, 127.9, 127.3, 127.1, 125.2, 124.1, 120.3, 118.0, 116.6, 105.7, 73.0, 67.1, 62.8, 49.6, 40.0, 37.6, 27.8, 25.9, 18.3, −5.4; IR (KBr) ν_{max} 3351, 2929, 2116, 1759, 1373, 1244, 1098, 1051 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{30}H_{40}NO_3Si$ $(M + H)^+$ 490.2772, found 490.2764.

(S)-7-(2-(Benzyloxy)ethyl)-7-(3-hydroxypropyl)pyrido[1,2-a]indol-6(7H)-one (9). To a solution of compound **8** (150 mg, 0.3 mmol, 1.0 equiv) in THF (15 mL) was added anhydrous TBAF (1 M in THF, 0.9 mL, 0.9 mmol, 3.0 equiv). The reaction solution was stirred at room temperature for 6 h before the solvent was concentrated. Purification of the residue by FCC (PE:EtOAc = 2:1) provided compound **9** as a colorless oil (108 mg, 92%). $[\alpha]_D^{25}$ +32.3, (*c* 0.3, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 8.47 (d, *J* = 8.0 Hz, 1H), 7.50 (d, *J* = 7.2 Hz, 1H), 7.32 (m, 1H), 7.28 (m, 1H), 7.08 (m, 1H), 7.02 (t, *J* = 7.2 Hz, 2H), 6.91 (d, *J* = 7.2 Hz, 2H), 6.72 (d, *J* = 10.0 Hz, 1H), 6.43 (s, 1H), 5.77 (d, *J* = 9.6 Hz, 1H), 4.23 (d, *J* = 11.6, 1H), 4.15 (d, *J* = 11.6 Hz 1H), 3.54−3.44 (m, 2H), 3.43−3.41 (m, 2H), 2.69 (m, 1H), 2.20 (m, 1H), 1.80 (m, 1H), 1.65 (m, 1H), 1.46 (m, 1H), 1.38 (s, 1H), 1.30 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.0, 137.7, 135.7, 134.6, 132.7, 130.4, 127.9, 127.3, 127.2, 125.3, 124.2, 120.4, 118.2, 116.5, 105.9, 73.0, 67.0, 62.4, 49.5, 40.0, 37.3, 27.7; IR (KBr) ν_{max} 3708, 2922, 2109, 1732,1699, 1454, 1389, 1107, 744 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{24}H_{26}NO_3$ $(M + H)^+$ 376.1907, found 376.1916.

(S)-2-(3-(7-(2-(Benzyloxy)ethyl)-6-oxo-6,7-dihydropyrido[1,2-a]-indol-7-yl)propyl)isoindoline-1,3-dione (10). Compound **9** (188 mg, 0.5 mmol, 1.0 equiv) was dissolved in dry THF (15 mL), and PPh_3 (184 mg, 0.7 mmol, 1.4 equiv), PhthNH (103 mg, 0.7 mmol, 1.4 equiv), and DEAD (0.36 mL, 0.8 mmol, 1.6 equiv) were added in order at room temperature. The reaction solution was stirred at room temperature for 2 h before the solvent was concentrated. Purification of the residue by FCC (PE:EtOAc = 3:1) provided compound **10** as a colorless oil (220 mg, 87%). $[\alpha]_D^{25}$ −25.2 (*c* 0.5, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 8.44 (d, *J* = 7.6 Hz, 1H), 7.79 (m, 2H), 7.68 (m, 2H), 7.48 (d, *J* = 6.8 Hz, 1H), 7.30 (t, *J* = 7.2 Hz, 1H), 7.27 (t, *J* = 7.2 Hz, 1H), 7.07 (m, 1H), 7.00 (t, *J* = 7.2 Hz, 2H), 6.88 (d, *J* = 7.2 Hz, 2H), 6.71 (d, *J* = 10.0 Hz, 1H), 6.41 (s, 1H), 5.74 (d, *J* = 10.0 Hz, 1H), 4.21 (d, *J* = 11.6, 1H), 4.14 (d, *J* = 11.6 Hz, 1H), 3.64−3.57 (m, 2H), 3.42−3.39 (m, 2H), 2.68 (m, 1H), 2.20 (m, 1H), 1.79 (m, 1H), 1.59 (m, 1H), 1.43 (m, 1H), 1.25 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.5, 168.3, 137.7, 135.6, 134.7, 133.9, 132.3, 130.4, 127.9, 127.3, 127.2, 125.3, 124.1, 123.6, 123.2, 120.4, 118.5, 116.7, 106.1, 73.0, 66.9, 49.5, 40.0, 38.3, 37.8, 23.9; IR (KBr) ν_{max} 2927, 2110, 1732, 1440, 1388, 1244, 1155, 1112, 762 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{32}H_{29}N_2O_4$ $(M + H)^+$ 505.2127, found 505.2129.

(S)-7-(2-(Benzyloxy)ethyl)-7-(3-hydroxypropyl)-8,9-dihydropyrido[1,2-a]indol-6(7H)-one (13). To a solution of compound **8** (150 mg, 0.3 mmol, 1.0 equiv) in MeOH (15 mL) was added Pd/C (31.8 mg, 0.03 mmol Pd, 0.1 equiv) before the flask was equipped with a H_2 balloon. The reaction was stirred at room temperature for 30 min. Then catalyst was removed by filtering through a Celite pad and washing the pad with EtOAc. The solvent was removed by rotary evaporation. The crude product was dissolved in dry THF (15 mL), and anhydrous TBAF (0.9 mL, 0.9 mmol, 3.0 equiv) was added. The reaction solution was stirred at room temperature for 6 h before the solvent was concentrated. Purification of the residue by FCC (PE:EtOAc = 2:1) provided compound **13** as a colorless oil (78 mg, 70%). $[\alpha]_D^{25}$ +21.7, (*c* 0.3, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 8.46 (m, 1H), 7.46 (m, 1H), 7.26−7.23 (m, 7H), 6.29 (s, 1H), 4.45 (m, 2H), 3.72−3.59 (m, 4H), 3.06 (m, 2H), 2.25 (m, 1H), 2.10−1.92 (m, 4H), 1.82−1.74 (m, 1H), 1.68−1.61 (m, 2H), 1.55 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.7, 138.1, 137.5, 135.2, 130.1, 128.4, 128.3, 127.5, 123.9, 123.8, 119.6, 116.6, 104.6, 73.1, 66.5, 62.8, 45.2, 35.2, 32.2, 29.7, 27.2, 19.7; IR (KBr) ν_{max} 3468, 2923, 1705, 1597, 1453, 1363, 748, 522, 477 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{24}H_{28}NO_3$ $(M + H)^+$ 378.2064, found 378.2055.

(R)-2-(3-(7-(2-(Benzyloxy)ethyl)-6-oxo-6,7,8,9-tetrahydropyrido-[1,2-a]indol-7-yl)propyl)isoindoline-1,3-dione (14). Compound **14** (colorless oil) was prepared from compound **13** following the same procedure as that of compound **10** in 95% yield. $[\alpha]_D^{25}$ +12.6 (*c* 0.3, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 8.41 (dd, *J* = 2.4 Hz, 6 Hz, 1H), 7.82 (dd, *J* = 2.8 Hz, 5.6 Hz, 2H), 7.70 (dd, *J* = 2.8 Hz, 5.6 Hz, 2H), 7.45−7.42 (m, 1H), 7.25−7.19 (m, 7H), 6.26 (s, 1H), 4.41 (m, 2H), 3.70−3.58 (m, 4H), 3.02 (m, 2H), 2.08−2.02 (m, 1H), 2.01−1.90 (m, 4H), 1.87−1.77 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.2, 168.3, 138.2, 137.4, 135.2, 133.9, 132.1, 130.1, 128.2, 127.5, 127.4, 123.9, 123.8, 123.2, 119.6, 116.6, 104.6, 73.0, 66.5, 45.3, 38.2, 35.2, 33.3, 29.6, 23.3, 19.7; IR (KBr) ν_{max} 3736, 2925, 1766, 1711, 1454, 1372, 1242, 1051, 720 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{32}H_{30}N_2O_4Na$ $(M + Na)^+$ 529.2098, found 529.2076.

(R)-3-(2-(1H-Indol-2-yl)ethyl)-3-(2-(benzyloxy)ethyl)piperidin-2-one (15). To a solution of compound **14** (260 mg, 0.5 mmol, 1 equiv) in dry EtOH (15 mL) was added to K_2CO_3 (340 mg, 2.5 mmol, 5.0 equiv) and $N_2H_4{\cdot}H_2O$ (0.3 mL, 6.0 mmol, 12.0 equiv). The solution was heated to reflux for 4 h before being cooled to room temperature. Water (20 mL) was added, and the mixture was extracted with EtOAc (30 mL × 3). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, and concentrated. Purification of the residue by FCC (CH_2Cl_2:MeOH = 30:1) provided compound **15** as a white foamy solid (170 mg, 91%). $[\alpha]_D^{25}$ −18.3 (*c* 0.3, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 8.26 (br s, 1H), 7.49 (d, *J* = 7.6 Hz, 1H), 7.33−7.24 (m, 6H), 7.09 (m, 1H), 7.04 (m, 1H), 6.19 (s, 1H), 5.72 (s, 1H), 4.49 (s, 2H), 3.64 (m, 2H), 3.29 (m, 2H), 2.86 (m, 1H), 2.71 (m, 1H), 2.19−2.06 (m, 2H), 2.01−1.80 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.3, 139.6, 138.4, 136.1, 129.6, 128.7, 128.4, 127.6, 120.9, 119.7, 119.4, 110.5, 99.3, 73.1, 67.0, 44.0, 42.8, 38.0, 37.6, 30.6, 23.6, 19.5; IR (KBr) ν_{max} 2993, 2116, 1759, 1380, 1244, 1056, 832 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{24}H_{29}N_2O_2$ $(M + H)^+$ 377.2224, found 377.2225.

(4aR,11cS)-4a-(2-(Benzyloxy)ethyl)-2,3,4,4a,5,6,7,11c-octahydro-1H-pyrido[3,2-c]carbazole (17). To a stirred solution of compound **15** (38 mg, 0.1 mmol, 1.0 equiv) and 2-Cl-pyridine (11 μL, 0.12 mmol, 1.2 equiv) in dry CH_2Cl_2 (5 mL) at −20 °C was added Tf_2O (16 μL, 0.11 mmol, 1.1 equiv). The reaction mixture was stirred for 10 min at −20 °C and 15 min at room temperature by which time a deep pink color had formed. The mixture was cooled to −20 °C again, and the solution of $NaBH_4$ (7.6 mg, 0.2 mmol, 2 equiv) in MeOH (2 mL) was then added dropwise over 5 min. The color rapidly disappeared, and after being stirred for a further 1 h, the reaction mixture was quenched with saturated Na_2CO_3 solution (5 mL) and diluted with CH_2Cl_2 (10 mL). The organic phase was separated, and the aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo. Purification of the

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residue by FCC (PE:EtOAc = 3:1 + NEt_3) provided compound **17** as a yellow oil (30 mg, 83%). $[\alpha]_D^{25}$ +28.3 (*c* 0.3, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.89 (d, *J* = 7.6 Hz, 1H), 7.73 (br s, 1H), 7.35−7.24 (m, 6H), 7.07 (t, *J* = 6.8 Hz, 1H), 7.01 (t, *J* = 7.6 Hz, 1H), 4.49 (s, 2H), 3.91 (s, 1H), 3.59 (m, 2H), 3.29 (m, 1H), 2.92−2.87 (m, 2H), 2.67−2.62 (m, 1H), 2.01 (m, 1H), 1.89−1.80 (m, 2H), 1.79−1.71 (m, 1H), 1.64−1.52 (m, 2H), 1.47−1.40 (m, 1H), 1.34−1.23 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.7, 136.0, 133.1, 128.3, 127.4 (2C), 127.2, 120.7, 120.4, 119.1, 111.0, 110.2, 72.9, 67.3, 64.5, 47.1, 35.3, 34.3, 32.8, 24.5, 22.7, 20.5; IR (KBr) ν_{max} 2928, 2100, 1759, 1376, 1244, 1056 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{24}H_{28}N_2O$ (M + H)$^+$ 361.2274, found 361.2276.

tert-Butyl-(S,Z)-2-(3-(2-(benzyloxy)ethyl)-6-((tert-butyldimethylsilyl)oxy)-3-(ethoxycarbonyl)hex-1-en-1-yl)-1H-indole-1-carboxylate (21). To a 100 mL flask were added compound **20** (1.18 g, 4.56 mmol, 2.0 equiv), compound **5** (1.24 g, 2.28 mmol, 1.0 equiv), Na_2CO_3 (0.73 g, 6.84 mmol, 3.0 equiv), and Pd(dppf)Cl_2 (0.15 g, 0.23 mmol, 0.10 equiv), and then 30 mL of DME and 6 mL of H_2O were added. The solution was saturated with an atmosphere of argon for 15 min and then refluxed for 2 h. After the reaction was completed, water (30 mL) was added to quench the reaction. The organic phase was separated, and the aqueous phase was extracted with EtOAc (3 × 30 mL). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, and concentrated. Purification of the residue by FCC (PE:EtOAc = 20:1) provided compound **21** as a yellow oil (1.12 g, 90%). $[\alpha]_D^{25}$ +3.2 (*c* 0.5, MeOH); ^1H NMR (400 MHz, $CDCl_3$) δ 8.11 (d, *J* = 8.4 Hz, 1H), 7.47 (d, *J* = 7.6 Hz, 1H), 7.33−7.24 (m, 6H), 7.19 (m, 1H), 6.62 (d, *J* = 12.4 Hz, 1H), 6.37 (s, 1H), 5.77 (d, *J* = 12.4 Hz, 1H), 4.43 (s, 2H), 3.65−3.50 (m, 6H), 2.16 (t, *J* = 6.8 Hz, 2H), 1.86−1.81 (m, 2H), 1.66 (s, 9H), 1.55−1.45 (m, 2H), 0.99 (t, *J* = 7.2 Hz, 3H), 0.87 (s, 9H), −0.01 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.8, 150.2, 138.4, 136.1, 135.0, 133.8, 129.0, 128.3, 127.6, 127.5, 124.2, 123.0, 122.8, 120.4, 115.4, 109.9, 84.0, 73.0, 66.9, 63.2, 60.5, 49.4, 36.8, 34.5, 28.2, 27.8, 25.9, 18.3, 13.7, −5.4; IR (KBr) ν_{max} 3449, 2926, 2855, 2108, 1729, 1656, 1455, 1367, 1112, 836, 746, 473 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{37}H_{53}NO_6SiNa$ (M + Na)$^+$ 658.3540, found 658.3543.

tert-Butyl-(S,Z)-2-(3-(2-(benzyloxy)ethyl)-6-(1,3-dioxoisoindolin-2-yl)-3-(ethoxycarbonyl)hex-1-en-1-yl)-1H-indole-1-carboxylate (22). Compound **21** (1.07 g, 1.96 mmol) was dissolved in the solution of D-camphor-10-sulfonic acid (CSA) in methanol (0.016 M). The solution was stirred at room temperature for 30 min before the solvent was concentrated with a vacuum pump. Purification of the residue by FCC (PE:EtOAc = 3:1) provided the alcohol as a colorless oil (95%, 0.97 g). To a solution of the alcohol (0.97 g, 1.86 mmol, 1.0 equive) in dry THF (30 mL) was added PPh_3 (0.73 g, 2.79 mmol, 1.5 equiv) and PhthNH (0.41 g, 2.79 mmol, 1.5 equiv). The solution was cooled to 0 °C, and DEAD (1.3 mL, 2.79 mmol, 1.5 equiv) was added dropwise via a syringe. The solution was warmed to room temperature and stirred for 30 min before 30 mL of water was added to quench the reaction. The organic phase was separated, and the aqueous phase was extracted with EtOAc (30 mL × 3). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, and concentrated. Purification of the residue by FCC (PE:EtOAc = 8:1) provided compound **22** as a colorless oil (1.09 g, 90%). $[\alpha]_D^{25}$ +6.4 (*c* 0.5, MeOH); ^1H NMR (400 MHz, $CDCl_3$) δ 8.07 (d, *J* = 8.4 Hz, 1H), 7.80−7.76 (m, 2H), 7.70−7.66 (m, 2H), 7.41 (d, *J* = 7.6 Hz, 1H), 7.32−7.22 (m, 6H), 7.15 (t, *J* = 7.4 Hz, 1H), 6.59 (d, *J* = 12.0 Hz, 1H), 6.31 (s, 1H), 5.71 (d, *J* = 12.0 Hz, 1H), 4.40 (s, 2H), 3.64−3.47 (m, 6H), 2.12 (t, *J* = 7.4 Hz, 2H), 1.88 (t, *J* = 8 Hz, 2H), 1.78−1.65(m, 2H), 1.63 (s, 9H), 0.93 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.5, 168.2, 150.1, 138.4, 136.1, 134.7, 133.8, 133.1, 132.0, 128.9, 128.3, 127.6, 127.5, 124.2, 123.2, 123.1, 122.7, 120.5, 115.4, 110.0, 84.0, 73.0, 66.8, 60.6, 49.5, 38.1, 36.8, 35.1, 28.2, 23.8, 13.7; IR (KBr) ν_{max} 3466, 2928, 2858, 1773, 1452, 1397, 1209, 1088, 1162, 744, 470 cm^{-1}; HRMS (ESI) *m/z* calcd for (M + Na)$^+$ $C_{39}H_{42}N_2O_7Na$ 673.2890, found 673.2892.

tert-Butyl-(S,Z)-2-(2-(3-(2-(benzyloxy)ethyl)-2-oxopiperidin-3-yl)-vinyl)-1H-indole-1-carboxylate (23). Compound **22** (1.09 g, 1.67 mmol, 1 equiv) was dissolved in dry EtOH and K_2CO_3 (0.23 g, 8.35 mmol, 5.0 equiv), and then $N_2H_4 \cdot H_20$ (0.98 mL, 20.0 mmol, 12.0 equiv) was added. The solution was heated to reflux for 2 h before being cooled to room temperature. Water (20 mL) was added, and the mixture was extracted with EtOAc (30 mL × 3). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, and concentrated. Purification of the residue by FCC (PE:EtOAc = 4:1) provided compound **23** as a white foamy solid (0.63 g, 80%). $[\alpha]_D^{25}$ −10.8 (*c* 0.5, MeOH); ^1H NMR (400 MHz, $CDCl_3$) δ 8.14 (d, *J* = 8.0 Hz, 1H), 7.48 (d, *J* = 7.6 Hz, 1H), 7.31−7.28 (m, 6H), 7.20 (t, *J* = 7.4 Hz, 1H), 6.61 (d, *J* = 12.0 Hz, 1H), 6.55 (s, 1H), 5.90 (d, *J* = 12.4 Hz, 1H), 5.74 (br s, 1H), 4.48 (s, 2H), 3.73−3.67 (m, 2H), 3.12−3.03 (m, 2H), 2.19 (t, *J* = 6.8 Hz, 2H), 1.94−1.88 (m, 1H), 1.82−1.76 (m, 1H), 1.70−1.67 (m, 2H), 1.64 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.5, 150.1, 138.5, 136.0, 135.8, 135.2, 129.1, 128.3, 127.6, 127.5, 124.1, 123.8, 122.8, 120.4, 115.5, 110.6, 84.0, 73.0, 67.4, 46.7, 42.4, 39.3, 31.3, 28.2, 19.0; IR (KBr) ν_{max} 3446, 2930, 2862, 1730, 1660, 1483, 1333, 1162, 1028, 745, 471 cm^{-1}; HRMS (ESI) *m/z* calcd for (M + H)$^+$ $C_{29}H_{35}N_2O_4$ 475.2587, found 475.2596.

tert-Butyl-(4aS,11cS)-4a-(2-(benzyloxy)ethyl)-1,2,3,4,4a,11c-hexahydro-7H-pyrido[3,2-c]carbazole-7-carboxylate (25). To a stirred solution of compound **23** (300 mg, 0.63 mmol, 1.0 equiv) and 2-Cl-pyridine (89 μL, 0.95 mmol, 1.5 equiv) in dry CH_2Cl_2 (12 mL) at −20 °C was added Tf_2O (0.14 mL, 1.01 mmol, 1.6 equiv). The reaction mixture was stirred for 15 min at −20 °C and 15 min at room temperature by which time a deep brown color had formed. The mixture was cooled to 0 °C; the solution of $NaBH_4$ (48 mg, 1.26 mmol, 2 equiv) in MeOH (2 mL) was then added dropwise over 5 min. The color rapidly disappeared, and after being stirred for a further 10 min, the reaction mixture was quenched with saturated Na_2CO_3 (15 mL) and diluted with CH_2Cl_2 (10 mL). The organic phase was separated, and the aqueous phase was extracted with CH_2Cl_2 (2 × 20 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo. Purification of the residue by FCC (PE:EtOAc = 4:1) provided compound **25** as a white foamy solid (208 mg, 72%). $[\alpha]_D^{25}$ +7.3 (*c* 0.5, MeOH); ^1H NMR (400 MHz, $CDCl_3$) δ 8.10 (d, *J* = 8.4 Hz, 1H), 7.95 (d, *J* = 8.0 Hz, 1H), 7.33−7.19 (m, 6H), 7.15 (t, *J* = 7.2 Hz, 1H), 7.08 (d, *J* = 10.4 Hz, 1H), 5.80 (d, *J* = 10.4 Hz, 1H), 4.40 (s, 2H), 4.14 (s, 1H), 3.57−3.51 (m, 1 H), 3.47−3.41 (m, 1H), 3.30 (dd, *J* = 4.0 Hz, 16.0 Hz, 1H), 2.83 (dt, *J* = 4.0 Hz, 12.0 Hz, 1H), 2.05−1.85 (m, 5H), 1.83−1.74 (m, 1H), 1.69 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.5, 138.9, 138.5, 136.3, 133.1, 128.3 (2C), 127.5, 127.4, 123.6, 122.7, 120.4, 119.4, 117.3, 115.6, 83.9, 72.8, 67.7, 64.5, 47.0, 37.2, 32.5, 28.3, 26.5, 22.6; IR (KBr) ν_{max} 3449, 2925, 2854, 1730, 1639, 1452, 1367, 1152, 1117, 745, 472 cm^{-1}; HRMS (ESI) *m/z* calcd for (M + H)$^+$ $C_{29}H_{35}N_2O_3$ 459.2648, found 459.2637.

tert-Butyl-(4aR,11cS)-4a-(2-hydroxyethyl)-1-(2,2,2-trifluoroacetyl)-1,2,3,4,4a,5,6,11c-octahydro-7H-pyrido[3,2-c]carbazole-7-carboxylate (26). To a stirred solution of compound **25** (206 mg, 0.45 mmol, 1.0 equiv) and Et_3N (0.076 mL, 0.54 mmol, 1.2 equiv) in CH_2Cl_2 (9 mL) at 0 °C was added under vigorous stirring trifluoroacetic anhydride (0.066 mL, 0.47 mmol, 1.05 equiv). The mixture was stirred for 1 h, and then saturated 10 mL of Na_2CO_3 solution was added. The organic phase was separated, and the aqueous phase was extracted with CH_2Cl_2 (10 mL × 3). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, and concentrated. The residue was dissolved in MeOH (8 mL) and transferred to a hydrogen tank. Palladium on carbon (87 mg of 10% Pd, 0.082 mmol Pd, 0.20 equiv) was added to the tank, and the suspension was stirred under an atmosphere of hydrogen (4 atm) for 3 h. Then, catalyst was removed by filtering through a Celite pad and washing the pad with EtOAc. The solvent was removed by rotary evaporation. Purification of the residue by FCC (PE:EtOAc = 4:1) provided compound **26** as a white foamy solid (172 mg, 90%). $[\alpha]_D^{25}$ +88.0 (*c* 0.5, MeOH); ^1H NMR (400 MHz, $CDCl_3$) δ 8.06 (d, *J* = 8.4 Hz, 1H), 7.21−7.18 (m, 2H), 7.13−7.11 (m, 1H), 4.30−4.25 (m, 2H), 3.86−3.74 (m, 2H), 3.41 (dt, *J* = 2.8 Hz, 13.6 Hz, 1H), 3.07−3.05 (m, 2H), 2.24−2.17 (m, 1H), 2.14−1.99 (m, 3H), 1.83−1.76 (m, 2H), 1.67 (s, 9H), 1.53−1.45 (m, 1H), 1.42−1.34 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.3 (q, *J* = 35 Hz), 150.4, 135.6, 133.4, 129.0, 123.4,

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122.7, 118.1, 116.2 (q, J = 288 Hz), 115.5, 113.8, 83.6, 67.1, 58.9, 49.7, 38.2, 34.7, 33.2, 28.7, 28.2, 23.5, 22.5; IR (KBr) ν_{max} 3442, 2926, 2855, 1698, 1651, 1456, 1400, 1149, 748, 513 cm^{-1}; HRMS (ESI) m/z calcd for (M + H)$^+$ $C_{24}H_{30}F_3N_2O_4$ 467.2158, found 467.2153.

*tert-Butyl-(4aR,11cS)-4a-(2-cyanoethyl)-1-(2,2,2-trifluoroacetyl)-1,2,3,4,4a,5,6,11c-octahydro-7H-pyrido[3,2-c]carbazole-7-carboxylate (**27**).* To a solution of compound **26** (172 mg, 0.37 mmol, 1.0 equiv) and triethylamine (0.078 mL, 0.56 mmol, 1.5 equiv) in CH_2Cl_2 (10 mL) was added methanesulfonyl chloride (0.034 mL, 0.44 mmol, 1.2 equiv), and the resulting reaction mixture was stirred at room temperature for 1 h. The crude mixture was partitioned between methylene chloride and a solution of sodium hydrogen carbonate (4%). The organic layer was washed with water and brine, and the solvent was removed under reduced pressure to give the crude product, which was used in the next step without further purification. To a solution of the crude product in dimethyl sulfoxide (8 mL) was slowly added sodium cyanide (54 mg, 1.11 mmol, 3.0 equiv). The reaction mixture was stirred at 50 °C overnight. The crude was partitioned between ether and water, and the organic layer was washed with water. The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, and concentrated. Purification of the residue by FCC (PE:EtOAc = 8:1) provided compound **27** as a white foamy solid (141 mg, 80%). $[\alpha]_D^{25}$ +65.5 (c 0.5, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (d, J = 8.4 Hz, 1H), 7.23−7.12 (m, 3H), 4.33 (s, 1H), 4.25 (d, 13.6 Hz, 1H), 3.40 (t, J = 12.0 Hz, 1H), 3.10 (dd, J = 4.0 Hz, 18.0 Hz, 1H), 3.01−2.93 (m, 1H), 2.43−2.26 (m, 3H), 2.07−1.93 (m, 3H), 1.89−1.80 (m, 2H), 1.68 (s, 9H), 1.59−1.50 (m, 1H), 1.45−1.39 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.5 (q, J = 35 Hz), 150.3, 135.7, 132.8, 128.6, 123.7, 122.9, 119.8, 118.1, 115.6, 115.5 (q, J = 288 Hz), 113.3, 83.9, 66.5, 49.7, 38.6, 33.6, 32.3, 28.2, 23.4, 22.2, 22.0, 11.6; IR (KBr) ν_{max} 3450, 2928, 2856, 1699, 1640, 1456, 1369, 1149, 1057, 748, 654 cm^{-1}; HRMS (ESI) m/z calcd for (M + Na)$^+$ $C_{25}H_{28}F_3N_3O_3Na$ 498.1960, found 498.1964.

*tert-Butyl-(4aR,11cS)-4a-(2-cyanoethyl)-1,2,3,4,4a,5,6,11c-octahydro-7H-pyrido[3,2-c]carbazole-7-carboxylate (**28**).* To a solution of compound **27** (100 mg, 0.21 mmol, 1.0 equiv) in toluene (11 mL) was added diisobutylaluminum hydride (1.0 M in cyclohexane, 0.84 mL, 0.84 mmol, 4.0 equiv) dropwise at −78 °C. The reaction mixture was stirred at the same temperature for 1 h. The reaction mixture was quenched with saturated $NaHCO_3$ solution (10 mL) and stirred for 15 min. The organic phase was separated, and the aqueous phase was extracted with EtOAc (3 × 10 mL). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, and concentrated. Purification of the residue by FCC (PE:EtOAc = 4:1) provided compound **28** as a white foamy solid (42 mg, 53%) and compound **29** as a colorless oil (17 mg, 21%). Compound **28** was transformed to **29** by the same procedure as above in 80% yield. Compound **28**: $[\alpha]_D^{25}$ +21.7 (c 0.5, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (d, J = 8.0 Hz, 1H), 8.00 (d, J = 7.6 Hz, 1H), 7.21 (t, J = 7.6 Hz, 1H), 7.15 (t, J = 8.0 Hz, 1H), 3.91 (s, 1H), 3.32 (dd, J = 4.0 Hz, 13.6 Hz, 1H), 3.13 (dd, J = 6.0 Hz, 18.8 Hz, 1H), 2.90 (dt, J = 3.6 Hz, 12.8 Hz, 2H), 2.33−2.28 (m, 2H), 2.10−2.02 (m, 2H), 1.82−1.71 (m, 1H), 1.68 (s, 9H), 1.59−1.53 (m, 2 H), 1.35 (dt, J = 3.6 Hz, 13.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.6, 136.0, 134.3, 128.7, 123.3, 122.3, 120.8, 120.3, 116.0, 115.3, 83.8, 63.5, 46.9, 34.5, 33.1, 31.8, 28.3, 23.0, 22.2, 21.4, 11.8; IR (KBr) ν_{max} 3452, 2923, 2852, 1638, 1457, 1400, 1255, 1150, 1111, 747 cm^{-1}; HRMS (ESI) m/z calcd for (M + H)$^+$ $C_{23}H_{30}N_3O_2$ 380.2338, found 380.2331.

*tert-Butyl-(1R,4aR)-2-oxo-3,4,6,11c-tetrahydro-2H-1,4a-propanopyrido[3,2-c]carbazole-7(5H)-carboxylate (**30**).* To a solution of compound **29** (50 mg, 0.13 mmol, 1.0 equiv) in CH_2Cl_2 (5 mL), containing some MS 4 Å, were added NMO (15 mg, 0.26 mmol, 2.0 equiv) and TPAP (9 mg, 0.026 mmol, 0.2 equiv); then, the resulting mixture was stirred at rt for 2 h. After solvent was removed, chromatography (PE: EtOAc = 6:1) afforded product **30** as a white foamy solid (40 mg, 80%). $[\alpha]_D^{25}$ −50.5, (c 0.5, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (d, J = 8.4 Hz, 1H), 7.72 (d, 7.6 Hz, 1H), 7.23 (t, J = 7.6 Hz, 1H), 7.15 (t, J = 8.0 Hz, 1H), 4.41 (dd, J = 5.0 Hz, 13.2 Hz, 1 H), 4.22 (s, 1H), 3.24−3.11 (m, 3H), 2.11−1.89 (m, 6H), 1.81−1.73 (m, 2H), 1.69 (s, 9H), 1.55−1.49 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 185.7, 150.6, 136.1, 135.0, 126.6, 123.9, 122.7, 120.4, 116.7, 115.3, 83.9, 63.9, 53.7, 39.7, 36.0, 34.8, 28.3, 27.4, 22.4, 22.3; IR (KBr) ν_{max} 3461, 2926, 2853, 2570, 1729, 1647, 1514, 1399, 1155, 842, 424 cm^{-1}; HRMS (ESI) m/z calcd for (M + H)$^+$ $C_{23}H_{29}N_2O_3$ 381.2178, found 381.2169.

*(1R,4aR)-3,4,5,6,7,11c-Hexahydro-2H-1,4a-propanopyrido[3,2-c]-carbazol-2-one (**31**).* To a solution of compound **30** (20 mg, 0.053 mmol, 1.0 equiv) in THF (3 mL) was added KOH (8.9 mg, 0.16 mmol, 3.0 equiv). The mixture was heated to reflux for 3 h and cooled to room temperature. Water (10 mL) was added, and the mixture was extracted with EtOAc (4 × 10 mL). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, and concentrated. Purification of the residue by FCC (PE:EtOAc = 3:1) provided product **31** as a white foamy solid (12 mg, 80%).[9d] $[\alpha]_D^{25}$ −17.5, (c 0.5, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (br s, 1H), 7.69 (d, J = 7.6 Hz, 1H), 7.27−7.26 (m, 1H), 7.12 (t, J = 8.0 Hz, 1H), 7.02 (t, J = 7.4 Hz, 1H), 4.41 (dd, J = 5.4 Hz, 12.8 Hz, 1H), 4.34 (s, 1H), 3.15 (dt J = 2.8 Hz, 12.8 Hz, 1H), 3.07−2.98 (m, 1H), 2.76 (dd, J = 5.6 Hz, 16.4 Hz, 1H), 2.07 (t, J = 4.6 Hz, 2H), 2.02−1.82 (m, 4H), 1.72−1.68 (m, 2H), 1.58−1.48 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 185.9, 136.2, 133.1, 125.0, 121.8, 120.2, 119.6, 111.1, 110.3, 64.3, 53.6, 39.8, 36.9, 34.8, 34.5, 27.6, 22.4, 19.7. IR (KBr) ν_{max} 3452, 2923, 2851, 2066, 1640, 1463, 1408, 1124, 688 cm^{-1}; HRMS (ESI) m/z calcd for (M + H)$^+$ $C_{18}H_{21}N_2O$ 281.1654, found 281.1656.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b02402.

^{1}H and ^{13}C NMR spectra for compounds **8−10**, **13−15**, **17**, **21−23**, **25−28**, and **30−31** (PDF)

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Notes

The authors declare no competing financial interest.

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