Total Synthesis of Cryptopleurine and its Analogues

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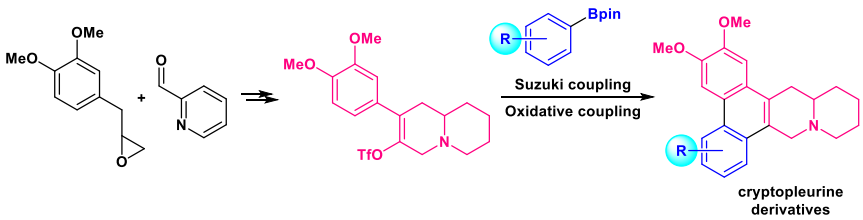

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Abstract Total synthesis of phenanthroquinolizidine alkaloid cryptopleurine was achieved in 8 steps from commercially available 2-pyridinecarboxaldehyde and epoxide derived from methyl eugenol. The key intermediate **5** enables the divergent synthesis of cryptopleurine derivatives by late-stage installation of various substituents on the C-ring.

Key words heterocycles, phenanthroquinolizidines, cryptopleurine, natural product synthesis, cyclization, anticancer agents

Phenanthroquinolizidine and phenanthroindolizine alkaloids, represented by cryptopleurine (**1**) and antofine (**2**), have received attention recent years because of their attractive biological activities (Figure 1).[1] They exhibit low nano-molar levels of *in vitro* activity against a variety of tumor cell lines. The specific target of these alkaloids is still unknown, however, several studies have indicated that these might show their several unique modes of action, different from currently available drugs.[2] Tylocrebrine, a phenanthroindolizine alkaloid, was advanced to clinical trials in the early 1960's but failed due to central nervous system toxicity.[3] Suffness proposed that more polar analogs would prevent side effects due to the passage of the blood brain barrier.

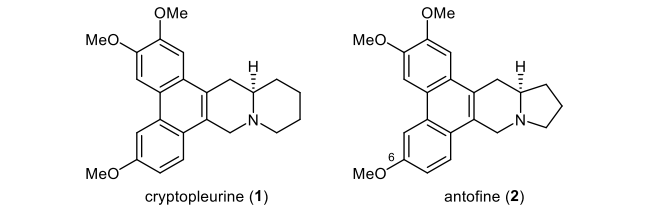
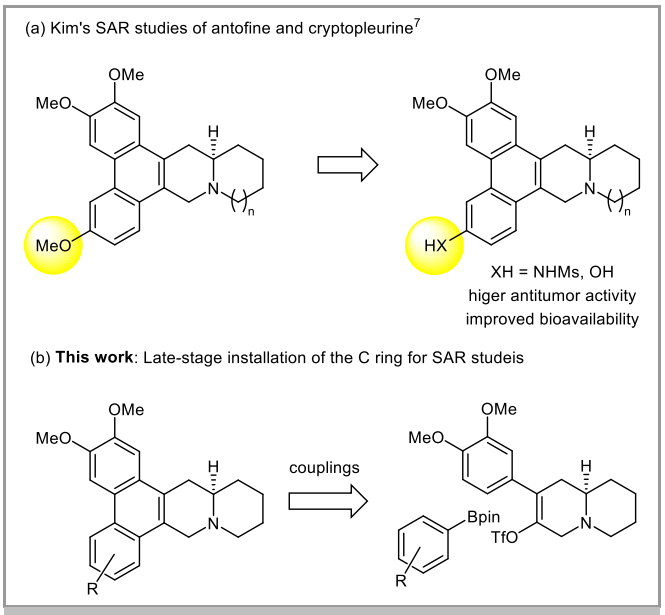


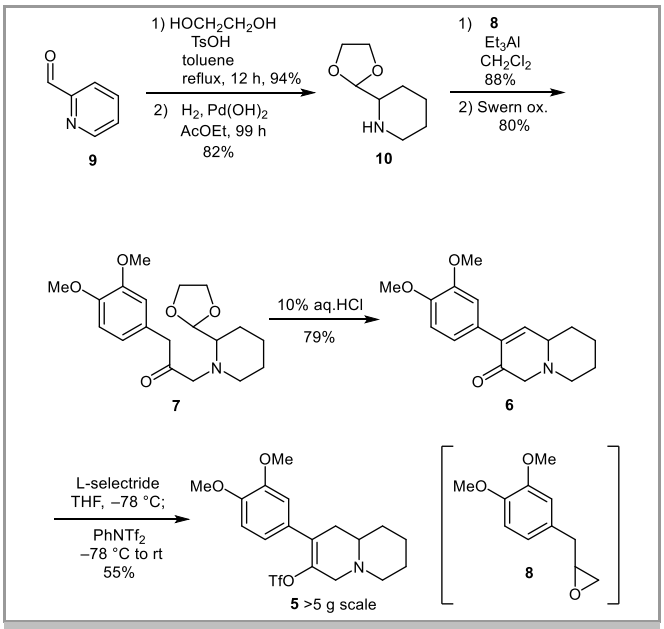
Figure 1 Structures of cryptopleurine (**1**) and antofine (**2**)

Thus, structure-activity relationship (SAR) studies of penanthroquinolizidine and phenanthroindolizine alkaloids are well investigated.[4-7] These results indicate that phenanthrene skeleton[4] and basic nitrogen[5] are important for a cytotoxic activity. Furthermore, Lack of indolizidine and quinolizidine core of these natural products also decrease their activity in cancer cell growth assays.[6] Recently, SAR studies on the phenanthrene ring of antofine and cryptopleurine were reported by Kim group[7] revealed that modification of the C-6 methoxy group on the C-ring is allowed to improve their bioactivity. In addition, they have also found that the cytotoxicity is further enhanced by introducing substituents that are hydrogen donors at C-6 position (Scheme 1a). Thus, the efficient synthesis of cryptopleurine analogue bearing several substitutions on the C ring is highly required for exploring further anticancer activity (Scheme 1b). Although many reports of total synthesis of cryptopleurine have been reported by other groups [1, 8] and us[9], most of them involve the introduction of the C-ring of these natural products in the early stage of the synthesis. Therefore, the development of a simple, direct approach for the synthesis of cryptopleurine in which the C ring is introduced at the end of the synthesis is highly desirable.[10]

Herein we report the total synthesis of cryptopleurine and its derivatives via the late-installation of various C-rings. We proposed retrosynthetic analysis of cryptopleurine as shown in Scheme 2. The phenanthrene skeleton of cryptopleurine could be constructed by Suzuki-Miyaura cross coupling followed by oxidative coupling of vinyl triflate **5** as a key intermediate with several aryl boronates. This strategy allows for the efficient installation of a variety of C-rings. Vinyl triflate **5** could be synthesized from 1,4-reduction of enone **6** and triflation of the generated enolate. Enone **6** could be prepared from the known epoxide **8**[11] and commercially available 2-pyridinecarboxaldehyde (**9**).

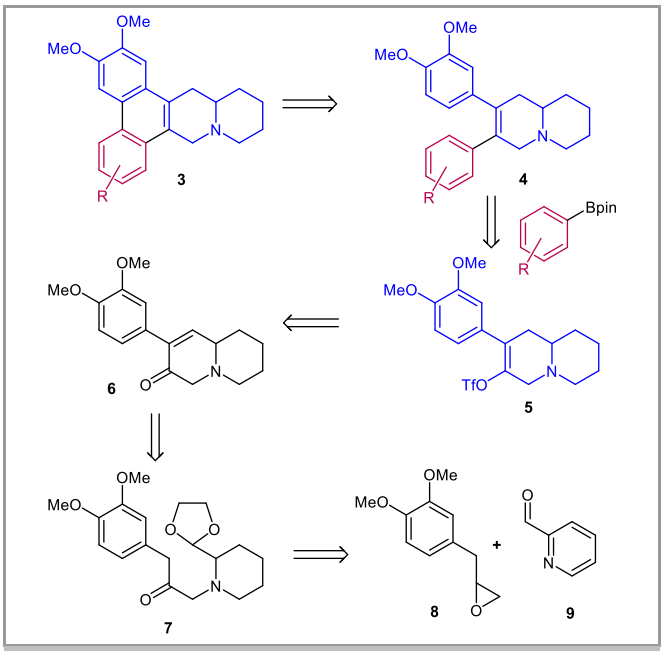


Scheme 1 SAR studies of Phenanthroquinolizidine and phenanthroindolizine alkaloids for improving the antitumor activity. And our aim.



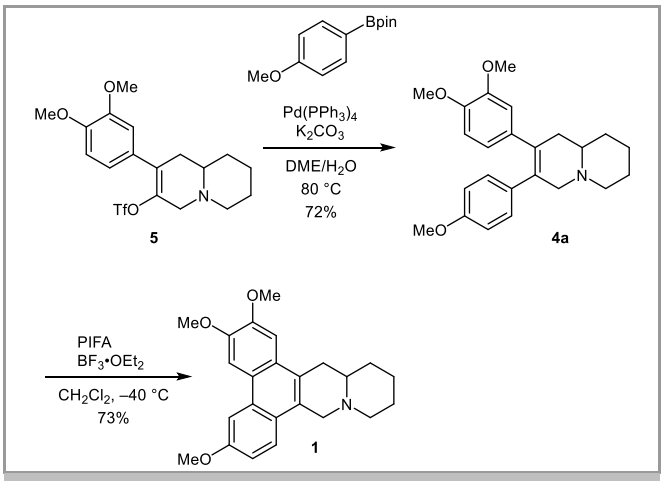
Scheme 3 The synthesis of vinyl triflate **5** as the key intermediate

We began the synthesis of the key intermediate **5** from 2-pyridinecarboxaldehyde (**9**) (Scheme 3). Acetalization of formyl group of **9** under acidic conditions, followed by hydrogenation of pyridine moiety catalyzed by palladium hydroxide under hydrogen atmosphere afforded the desired product **10**. Nucleophilic ring-opening of the epoxide **8**[11] with piperidine **10** in the presence of Et_3Al[12] afforded the mixture of diastereomeric alcohols in high yield. The resulting secondary alcohols were converted into ketone **7** by Swern Oxidation. Treatment of compound **7** with 10% aqueous HCl provided enone **6** via a deacetalization–aldol condensation cascade reaction.[13] Enone **6** was subjected to a tandem 1,4-reduction/enolate trapping to achieve the synthesis of the key vinyl triflate **5** on a >5 g scale without any problems.



Scheme 2 Retrosynthetic analysis of cryptopleurine derivatives

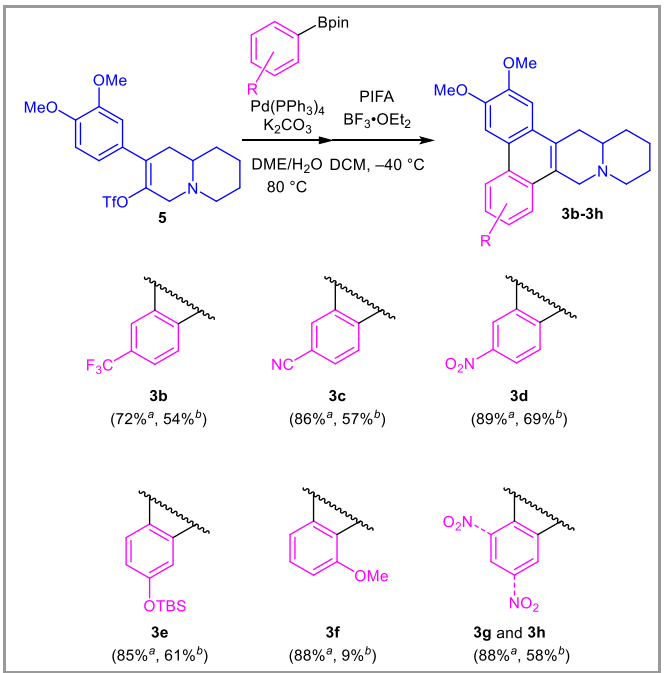
To accomplish the total synthesis of cryptopleurine, two coupling reactions with triflate **5** were conducted (Scheme 4). Suzuki-Miyaura coupling of vinyl triflate **5** with 4-methoxyphenyl boronic acid pinacol ester as the C-ring of the natural product gave the desired compound **4a** in high yield. Finally, oxidative biaryl coupling[7b] of **4a** in the presence of [Bis(trifluoroacetoxy)iodo]benzene (PIFA)/$BF_3{\cdot}OEt_2$ afforded cryptopleurine (**1**) in 73% yield. We accomplished the total synthesis of cryptopleurine via the late-installation of the C-ring in total 8 steps (Scheme 4).



Scheme 4 Endgame of total synthesis of cryptopleurine (**1**)

Finally, to demonstrate our proof of concept, we synthesized cryptopleurine derivatives with various substituents on the C-ring (Scheme 5). Other functional group, such as trifluoromethyl (**3b**), cyano (**3c**), and nitro (**3d**) groups also could be introduced at the C-6 position using the corresponding *para*-substituted aryl boronic acid pinacol esters as coupling partners. When 3-*tert*-butyldimethylsilyloxyphenylboronic acid pinacol ester was used, the compound **3e** with siloxy group at the 7-position could be

selectively obtained.[14] The use of 2-methoxyphenylboronic acid pinacol ester as a coupling partner afforded the compound **3f** with methoxy group at the C-8 position albeit in low yield due to the steric hindrance. The use of 3-nitrophenylboronic acid pinacol ester as a coupling partner afforded inseparable regioisomers **3g/3h** with nitro group at the C-5 and C-7 position, respectively. For separation of regioisomers, further derivatization was conducted. Hydrogenation of a mixture of **3g** and **3h** afforded the corresponding amines **S1a** and **S1b**, which could be separated by silica gel column chromatography.



Scheme 5 The synthesis of cryptopleurine derivatives: [a]Isolated yields of Suzuki coupling, [b]Isolated yields of oxidative coupling.

In conclusion, we have achieved the total synthesis of cryptopleurine (**1**) in 8 steps from commercially available materials. The key features of our synthesis are: (i) multi-gram synthesis of vinyl triflate **5** as the key intermediate, and (ii) consecutive cross-coupling and oxidative coupling to construct the phenanthrene ring. This strategy enables the efficient synthesis of cryptopleurine derivatives bearing several substituents on the C-ring. The syntheses and biological evaluation of these analogues of cryptopleurine are currently underway.

Dehydrated solvents for the reactions were purchased and used without further desiccation. For reactions that require heating, oil bath was used as a heat source. Reactions were monitored by thin-layer chromatography (TLC) carried out on Wako TLC silica gel 70 F_{254}. Column chromatography was performed using silica gel 60N (Spherical, neutral, 63–210 μm) from Kanto Chemical with visualization by ultraviolet (UV) irradiation at 254 nm. Nuclear magnetic resonance (NMR) spectra were recorded on a JEOL JNM-LA (500 MHz for ^{1}H and 125 MHz for ^{13}C) or a JEOL JNM ECZ600R (600 MHz for ^{1}H and 150 MHz for ^{13}C). Chemical shifts are presented in ppm relative to tetramethylsilane (^{1}H, 0.00) or solvents as follows: $CDCl_3$ (^{13}C, 77.0). The following abbreviations were used to explain NMR peak multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. High-resolution mass spectra (HRMS) were recorded on a SHIMADZU LCMS-IT-TOF fitted with an ESI. IR experiments were recorded on a SHIMADZU IRAffinity-1 spectrometer. The wave numbers of maximum absorption peaks of IR spectroscopy are presented in cm^{-1}.

Procedures

2-(1,3-Dioxolan-2-yl)piperidine (10)

To a solution of 2-(1,3-dioxolan-2-yl)pyridine[15](20 g, 132 mmol) in AcOEt (150 mL) was added $Pd(OH)_2$ (5.0 g, 5% on Carbon, 1.8 mmol). After flushing with H_2, the solution was stirred for 99 h at 23 °C. After completion of the reaction, the reaction mixture was filtered over Celite. The filtrate was concentrated under reduced pressure and purified by column chromatography on silica gel ($CHCl_3$/MeOH) to afford **10** (17 g, 82%) as a white waxy solid.

IR (neat): 3387, 3321, 3252, 2936, 2889, 2859, 2828, 1647, 1605, 1443, 1408, 1312, 1211 cm^{-1}.

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 4.68 (d, *J* = 4.9 Hz, 1H), 4.03–3.92 (m, 2H), 3.91–3.84 (m, 2H), 3.09 (dddd, *J* = 11.6, 4.0, 2.0, 2.0 Hz, 1H), 2.67–2.58 (m, 2H), 1.87–1.77 (m, 2H), 1.74–1.68 (m, 1H), 1.63–1.56 (m, 1H), 1.44 (ddddd, *J* = 12.5, 12.5, 3.9, 3.9, 3.9 Hz, 1H), 1.38–1.23 (m, 2H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ = 105.6, 64.7, 64.5, 58.5, 46.0, 26.9, 25.7, 23.7.

HRMS (ESI): *m/z* [M+H]$^+$ calcd for $C_8H_{16}NO_2$: 158.1176; found: 158.1183.

1-[2-(1,3-Dioxolan-2-yl)piperidin-1-yl]-3-(3,4-dimethoxyphenyl)propan-2-one (7)

To a solution of **10** (10.3 g, 65.5 mmol) in CH_2Cl_2 (150 mL) was added a 1.1 M toluene solution of $AlEt_3$ (77.4 mL, 85.1 mmol) dropwise at 0 °C under argon atmosphere. After stirring for 30 min, a solution of 2-(3,4-dimethoxybenzyl)oxirane (**8**)[10] (14.0 g, 72.0 mmol) in CH_2Cl_2 (150 mL) was added dropwise to the mixture. After stirring for 1.5 h at 23 °C, the reaction mixture was quenched by 10% aqueous NaOH (150 mL). After stirring for 5 min, the reaction mixture was extracted with $CHCl_3$ (150 mL × 3) and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel ($CHCl_3$/MeOH = 10/1) to afford 1-[2-(1,3-dioxolan-2-yl)piperidin-1-yl]-3-(3,4-dimethoxyphenyl)propan-2-ol (20.0 g, 88%, dr = 63:37 based on the crude ^{1}H NMR) as colorless oil.

IR (neat): 3418, 2936, 1721, 1589, 1512, 1462, 1420, 1261, 1234 cm^{-1}.

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 6.85–6.74 (m, 3H), 5.05–4.90 (m, 1H), 3.99–3.76 (m, 12H), 3.99–3.76 (m, 7H), 1.78–1.27 (m, 6H) as a mixture of diastereomers.

^{13}C NMR ($CDCl_3$, 125 MHz): δ = 148.52, 148.50, 147.24, 147.22, 131.31, 131.25, 121.09, 121.02, 112.41, 112.39, 110.98, 110.92, 104.20, 103.24, 68.26, 68.21, 64.75, 64.67, 64.63, 64.47, 62.07, 61.56, 59.35, 59.01, 55.75, 55.65, 52.00, 49.61, 40.83, 40.55, 25.33, 24.44, 24.01, 23.59, 22.68, 21.59 (one peak is missing due to incidental equivalence) as a mixture of diastereomers.

HRMS (ESI): *m/z* [M+H]$^+$ calcd for $C_{19}H_{30}NO_5$ 352.2118; found 352.2106.

To a solution of $(COCl)_2$ (22 mL, 256 mmol) in CH_2Cl_2 (140 mL) at –78 °C was added DMSO (36 mL, 511 mmol) dropwise under argon atmosphere. The mixture was stirred for 15 min. Then, a solution of 1-[2-(1,3-dioxolan-2-yl)piperidin-1-yl]-3-(3,4-dimethoxyphenyl)propan-2-ol (20 g, 56.8 mmol) in CH_2Cl_2 (50 mL) was added dropwise to the mixture. After stirring for 1 h, Et_3N (79 mL, 568 mmol) was added, and the reaction mixture was stirred for 30 min with warming up to 23 °C. The reaction mixture was washed with water (150 mL × 3) and the organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane/AcOEt) to afford **7** (15.9 g, 80%) as yellow oil.

IR (neat): 2936, 1717, 1589, 1516, 1450, 1420, 1261, 1238 cm^{-1}.

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 6.82 (d, *J* = 8.3 Hz, 1H), 6.79–6.75 (m, 2H), 4.74 (d, *J* = 4.8 Hz, 1H), 3.90–3.83 (m, 2H), 3.87 (s, 3H), 3.85 (s, 3H), 3.80–3.73 (m, 2H), 3.68 (d, *J* = 14.5 Hz, 1H), 3.64 (d, *J* = 14.5 Hz, 1H), 3.63 (d, *J* = 17.9 Hz, 1H), 3.53 (d, *J* = 17.9 Hz, 1H), 2.76–2.67 (m, 2H), 2.63–2.56 (m, 1H), 1.81–1.75 (m, 1H), 1.75–1.69 (m, 1H), 1.58–1.51 (m, 2H), 1.49–1.40 (m, 1H), 1.37–1.28 (m, 1H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ = 208.4, 148.8, 147.8, 126.9, 121.6, 112.5, 111.1, 105.0, 64.7, 64.2, 63.7, 61.7, 55.84, 55.79, 53.9, 46.8, 26.5, 25.4, 22.9.

HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{19}H_{28}NO_5$ 350.1962; found 350.1956.

8-(3,4-Dimethoxyphenyl)-1,3,4,9a-tetrahydro-2*H*-quinolizin-7(6*H*)-one (6)

10% Aqueous HCl (377 mL) added to **7** and the aqueous solution was refluxed at 120 °C for 2 h. The solution was cooled to 23 °C and quenched with saturated aqueous $NaHCO_3$ (2 L). The reaction mixture was extracted with $CHCl_3$ (500 mL × 3), and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel by column chromatography on silica gel (hexane/AcOEt = 1/1) to afford **6** (8.56 g, 79%) as yellow oil.

IR (neat): 2997, 2936, 2835, 2793, 2739, 1682, 1605, 1516, 1462,1362, 1250, 1231 cm^{-1}.

^1H NMR ($CDCl_3$, 500 MHz): δ = 6.95–6.91 (m, 2H), 6.85 (d, *J* = 8.6 Hz, 1H), 6.74 (d, *J* = 1.7 Hz, 1H), 3.88 (s, 6H), 3.51 (d, *J* = 16.0 Hz, 1H), 3.10 (dd, *J* = 15.9, 2.7 Hz, 1H), 2.99–2.93 (m, 1H), 2.93–2.88 (m, 1H), 2.27 (ddd, *J* = 11.5, 11.5, 3.3 Hz, 1H), 1.95–1.88 (m, 2H), 1.76–1.60 (m, 2H), 1.59–1.41 (m, 2H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ = 194.5, 149.2, 148.8, 148.3, 137.4, 127.4, 120.8, 111.8, 110.7, 63.7, 61.2, 55.78, 55.76 54.6, 31.2, 24.8, 24.5.

HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{17}H_{22}NO_3$ 288.1594; found 288.1594.

8-(3,4-Dimethoxyphenyl)-1,3,4,6,9,9a-hexahydro-2*H*-quinolizin-7-yl trifluoromethanesulfonate (5)

To a solution of **6** (8.56 g, 29.8 mmol) in THF (100 mL) was added a 1.0 M THF solution of L-Selectride® (31.3 mL, 31.3 mmol) dropwise at –78 °C under argon atmosphere. After stirring at same temperature for 1 h, to the reaction mixture was added a solution of $PhNTf_2$ (12.8 g, 35.8 mmol) in THF (50 mL). The reaction mixture was stirred for 15 h with gradually warming up to 23 °C. The reaction was quenched with saturated aqueous $NaHCO_3$ (300 mL) and extracted with AcOEt (300 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (Hexane/AcOEt) to afford **5** (6.93 g, 55%) as yellow oil.

IR (neat): 2396, 1520, 1450, 1416, 1246, 1211 cm^{-1}.

^1H NMR ($CDCl_3$, 500 MHz): δ = 6.87–6.83 (m, 3H), 3.89 (s, 3H), 3.87 (s, 3H), 3.48 (d, *J* = 16.0 Hz, 1H), 3.15–3.03 (m, 2H), 2.53 (d, *J* = 17.2 Hz, 1H), 2.43–2.26 (m, 2H), 2.15 (dd, *J* = 11.5, 11.5 Hz, 1H), 1.87–1.77 (m, 2H), 1.76–1.70 (m, 1H), 1.69–1.53 (m, 1H), 1.40–1.23 (m, 2H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ = 148.8, 148.5, 138.4, 128.2, 127.5, 118.0 (q, J_{C-F} = 318 Hz), 120.3, 111.2, 110.8, 57.0, 55.71, 55.67, 55.3, 55.1, 38.5, 32.4, 25.3, 23.8.

HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{18}H_{23}F_3NO_5S$ 422.1244; found 422.1235.

8-(3,4-dimethoxyphenyl)-7-(4-methoxyphenyl)-1,3,4,6,9,9a-hexahydro-2*H*-quinolizine (4a)

To a mixture of **5** (104 mg, 0.247 mmol), 4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)anisole (69.3 mg, 0.296 mmol), $Pd(PPh_3)_4$ (8.6 mg, 7.4 μmol) and K_2CO_3 (102 mg, 0.740 mmol) was added a solution of DME/H_2O (2.4 mL, v/v = 2/1) under Argon atmosphere. After stirring at 80 °C for 2 h, the mixture was cooled to 23 °C and diluted with water (25 mL). The mixture was extracted with $CHCl_3$ (25 mL × 3), and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (AcOEt /MeOH). The residue was diluted with AcOEt (15 mL) and extracted with 10% aqueous HCl (15 mL × 3). The resulting aqueous layers were basified with 10% aqueous NaOH (70 mL) and then extracted with $CHCl_3$ (50 mL × 3). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure to afford **4a** (67.4 mg, 72%) as white solids. Spectroscopic properties were consistent with those reported in the literature.[8c]

cryptopleurine (1)

To a solution of 8-(3,4-dimethoxyphenyl)-7-(4-methoxyphenyl)-1,3,4,6,9,9a-hexahydro-2*H*-quinolizine (**4**) (22.8 mg, 60.1 μmol) and PIFA (28.5 mg, 66.1 μmol) in CH_2Cl_2 (0.30 mL) was added $BF_3 \cdot OEt_2$ (22.9 μL, 0.180 mmol) at –40 °C. After stirring at same temperature for 24 h, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ (2 mL) and diluted with water (20 mL). the mixture was extracted with $CHCl_3$ (25 mL × 3) and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (AcOEt/MeOH) to afford cryptopleurine (**1**) (17.2 mg, 73%) as white solids. Spectroscopic properties were consistent with those reported in the literature.[9a]

2,3-Dimethoxy-6-(trifluoromethyl)-11,12,13,14,14a,15-hexahydro-9*H*-dibenzo[*f,h*]pyrido[1,2-*b*]isoquinoline (3b)

To a mixture of **5** (100 mg, 0.238 mmol), 4,4,5,5-tetramethyl-2-[4-(trifluoromethyl)phenyl]-1,3,2-dioxaborolane (97.1 mg, 0.357 mmol), $Pd(PPh_3)_4$ (27.7 mg, 23.8 μmol) and K_2CO_3 (98.5 mg, 0.713 mmol) was added a solution of DME/H_2O (2.4 mL, v/v = 1/1) under argon atmosphere. After stirring at 80 °C for 2 h, the mixture was cooled to 23 °C and diluted with water (25 mL). The solution was extracted with AcOEt (25 mL × 5), and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (AcOEt /MeOH = 20/1). The residue was diluted with AcOEt (10 mL) and extracted with 10% aqueous HCl (10 mL × 3). The resulting aqueous layer was basified with 10% aqueous NaOH (70 mL) and then extracted with $CHCl_3$ (50 mL × 3). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure to afford 8-(3,4-dimethoxyphenyl)-7-[4-(trifluoromethyl)phenyl]-1,3,4,6,9,9a-hexahydro-2*H*-quinolizine (71.3 mg, 72%) as yellow solids.

IR (neat): 2936, 1605, 1512, 1462, 1323, 1254 cm^{-1}.

^1H NMR ($CDCl_3$, 500 MHz): δ = 7.41 (d, *J* = 8.0 Hz, 2H), 7.17 (d, *J* = 8.0 Hz, 2H), 6.68 (d, *J* = 8.0 Hz, 1H), 6.64 (dd, *J* = 8.5, 2.0 Hz, 1H), 6.40 (d, *J* = 2.0 Hz, 1H), 3.81 (s, 3H), 3.60 (d, *J* = 17.0 Hz, 1H), 3.51 (s, 3H), 3.12–3.08 (m, 2H), 2.57–2.52 (m, 1H) 2.47–2.40 (m, 1H), 2.35–2.31 (m, 1H), 2.13 (td, *J* = 11.0, 4.0 Hz, 1H), 1.88–1.81 (m, 2H), 1.75–1.70 (m, 2H), 1.40–1.34 (m, 2H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ = 147.9, 147.5, 144.7, 133.5, 133.4, 130.9, 129.3, 128.2 (q, J_{C-F} = 32 Hz), 124.0 (q, J_{C-F} = 270 Hz), 124.7 (q, J_{C-F} = 4.0 Hz), 120.5, 112.6, 110.5, 59.7, 57.7, 55.6, 55.4, 55.3, 39.4, 33.2, 25.8, 24.2.

HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{24}H_{27}F_3NO_2$ 418.1988; found 418.1992.

To a solution of 8-(3,4-dimethoxyphenyl)-7-{4-(trifluoromethyl)phenyl}-1,3,4,6,9,9a-hexahydro-2*H*-quinolizine (139 mg, 0.333 mmol) and PIFA (158 mg, 0.366 mmol) in CH_2Cl_2 (1.7 mL) was added $BF_3 \cdot OEt_2$ (127 μL, 0.999 mmol) at –40 °C. After stirring at same temperature for 24 h the reaction mixture was quenched with saturated aqueous $NaHCO_3$ (5 mL) and extracted with $CHCl_3$ (15 mL × 3). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (AcOEt/MeOH) to afford **3b** (74.3 mg, 54%) as yellow solids.

IR (neat): 2932, 2855, 2253, 1620, 1516, 1470, 1420, 1331, 1296, 1258 cm^{-1}.

^1H NMR ($CDCl_3$, 600 MHz): δ = 8.73 (s, 1H), 7.95 (s, 1H), 7.93 (d, *J* = 8.3 Hz, 1H),7.72 (d, *J* = 8.4 Hz, 1H), 7.25 (s, 1H), 4.44 (d, *J* = 16.0 Hz, 1H), 4.14 (s, 3H), 4.07 (s, 3H), 3.65–3.61 (m, 1H), 3.29 (d, *J* = 11.0 Hz, 1H) 3.10 (dd, *J* = 16.0, 3.0 Hz, 1H), 2.93–2.88 (m, 1H), 2.40–2.36 (m, 1H), 2.31 (td, *J* = 12.0, 3.0 Hz, 1H), 2.04 (d, *J* = 13.0 Hz, 1H), 1.90 (d, *J* = 12.0 Hz, 1H), 1.84–1.74 (m, 2H), 1.57–1.41 (m, 2H).

^{13}C NMR ($CDCl_3$, 150 MHz): δ = 149.8, 149.0, 130.6, 129.4, 128.0, 124.7 (q, J_{C-F} = 270 Hz), 126.8 (q, J_{C-F} = 31.5 Hz), 126.2, 125.2, 123.7, 123.3, 121.4 (q, J_{C-F} = 2.8 Hz), 119.8 (q, J_{C-F} = 2.7 Hz), 103.7, 103.4, 57.3, 56.2, 56.1, 56.0, 55.9 34.9, 33.7, 25.8, 24.2.

HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{24}H_{25}F_3NO_2$ 416.1832; found 416.1827.

2,3-Dimethoxy-11,12,13,14,14a,15-hexahydro-9*H*-dibenzo[*f,h*]pyrido[1,2-*b*]isoquinoline-6-carbonitrile (3c)

To a mixture of **5** (294 mg, 0.696 mmol), 2-(4-cyanophenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (192 mg, 0.836 mmol), $Pd(PPh_3)_4$ (24.1 mg, 20.9 μmol) and K_2CO_3 (289 mg, 2.09 mmol) was added a solution of DME/H_2O (7.0 mL, v/v = 2/1) under argon atmosphere. After stirring at 80 °C for 2.5 h, the mixture was cooled to 23 °C and diluted with water (25 mL). The solution was extracted with AcOEt (25 mL × 5), and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (AcOEt/MeOH). The residue was diluted with AcOEt (10 mL) and extracted with 10% aqueous HCl (10 mL × 3). The resulting aqueous layer was basified with 10% aqueous NaOH (70 mL) and then extracted with $CHCl_3$ (50 mL × 3). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure to afford 4-[8-(3,4-dimethoxyphenyl)-1,3,4,6,9,9a-hexahydro-2*H*-quinolizin-7-yl]benzonitrile (225 mg, 86%) as white solids.

IR (neat): 2932, 2226, 1605, 1512, 1462, 1258 cm^{-1}.

^1H NMR ($CDCl_3$, 500 MHz): δ = 7.43 (d, *J* = 8.0 Hz, 2H), 7.15 (d, *J* = 8.5 Hz, 2H), 6.66 (d, *J* = 8.5 Hz, 1H), 6.57 (dd, *J* = 8.5, 2.0 Hz, 1H), 6.42 (d, *J* = 2.0 Hz, 1H), 3.81 (s, 3H), 3.60–3.58 (m, 4H), 3.11–3.07 (m, 2H), 2.56–2.52 (m, 1H), 2.47–2.40 (m, 1H), 2.36–2.30 (m, 1H), 2.13 (td, *J* = 12.0, 4.0 Hz, 1H), 1.88–1.82 (m, 2H), 1.78–1.68 (m, 2H), 1.43–1.33 (m, 2H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ = 148.2, 147.8, 145.9, 134.6, 133.2, 131.7, 130.3, 129.8, 120.8, 118.8, 112.3, 110.7, 109.8, 59.4, 57.7, 55.7, 55.51, 55.47, 39.6, 33.1, 25.8, 24.6.

HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{24}H_{27}N_2O_2$ 375.2067; found 375.2065.

To a solution of 4-[8-(3,4-dimethoxyphenyl)-1,3,4,6,9,9a-hexahydro-2*H*-quinolizin-7-yl]benzonitrile (225 mg, 0.602 mmol) and PIFA (285 mg, 0.662 mmol) in CH_2Cl_2 (3.0 mL) was added $BF_3 \cdot OEt_2$ (229 μL, 1.81 mmol) at –40 °C. After stirring at same temperature for 24 h, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ (9 mL) and extracted with $CHCl_3$ (15 mL × 3). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (AcOEt/MeOH) to afford **3c** (127 mg, 57%) as yellow solids.

IR (neat): 2924, 2851, 2226, 1612, 1520, 1466, 1420, 1258 cm^{-1}.

^1H NMR ($CDCl_3$, 600 MHz): δ = 8.81 (s, 1H), 7.90–7.86 (m, 2H), 7.69 (d, *J* = 8.4 Hz, 1H), 7.25 (s, 1H), 4.41 (d, *J* = 15.0 Hz, 1H), 4.14 (s, 3H), 4.08 (s, 3H), 3.61 (d, *J* = 16.0 Hz, 1H), 3.29 (d, *J* = 11.0 Hz, 1H) 3.15–3.10 (m, 1H), 2.94–2.89 (m, 1H), 2.44–2.38 (m, 1H), 2.32 (td, *J* = 13.0, 3.6 Hz, 1H), 2.07–2.05 (m, 1H), 1.92–1.90 (m, 1H), 1.85–1.74 (m, 2H), 1.58–1.42 (m, 2H).

^{13}C NMR ($CDCl_3$, 150 MHz): δ = 150.0, 149.3, 130.9, 130.8, 128.2, 128.0, 126.9, 126.3, 125.1, 123.5, 123.0, 119.8, 108.3, 103.7, 103.2, 57.2, 56.12, 56.06, 56.0, 55.6, 35.0, 33.6, 25.8, 24.2.

HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{24}H_{25}N_2O_2$ 373.1911; found 373.1909.

2,3-Dimethoxy-6-nitro-11,12,13,14,14a,15-hexahydro-9*H*-dibenzo[*f,h*]pyrido[1,2-*b*]isoquinoline (3d)

To a mixture of **5** (150 mg, 0.357 mmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)nitrobenzene (133 mg, 0.535 mmol), $Pd(PPh_3)_4$ (41.2 mg, 35.7 μmol) and K_2CO_3 (148 mg, 1.07 mmol) was added a solution of DME/H_2O (3.6 mL, v/v = 1/1) under argon atmosphere. After stirring at 80 °C for 2.5 h, the mixture was cooled to 23 °C and diluted with water (25 mL). The solution was extracted with $CHCl_3$ (25 mL × 3), and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (AcOEt/MeOH). The residue was diluted with AcOEt (15 mL) and extracted with 10% aqueous HCl (15 mL × 3). The resulting aqueous layer was basified with 10% aqueous NaOH (70 mL) and then extracted with $CHCl_3$ (50 mL × 3). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure to afford 8-(3,4-dimethoxyphenyl)-7-(4-nitrophenyl)-1,3,4,6,9,9a-hexahydro-2*H*-quinolizine (125 mg, 89%) as yellow solids.

IR (neat): 2936, 1593, 1516, 1462, 1342, 1254 cm^{-1}.

^1H NMR ($CDCl_3$, 500 MHz): δ = 8.00 (d, *J* = 8.6 Hz, 2H), 7.20 (d, *J* = 3.3 Hz, 2H), 6.66 (d, *J* = 8.0 Hz, 1H), 6.57 (dd, *J* = 8.0, 1.7 Hz, 1H), 6.45 (d, *J* = 2.3 Hz, 1H), 3.81 (s, 3H), 3.59 (s, 3H), 3.63–3.57 (m, 1H), 3.15–3.07 (m, 2H), 2.55 (ddd, *J* = 17.8, 3.4, 3.4 Hz, 1H), 2.45 (dddd, *J* = 17.8, 10.3, 2.3, 1.7 Hz, 1H), 2.37–2.30 (m, 1H), 2.14 (ddd, *J* = 11.7, 11.7, 3.4 Hz, 1H), 1.90–1.80 (m, 2H), 1.79–1.65 (m, 2H), 1.44–1.30 (m, 2H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ = 148.2, 148.1, 147.9, 146.0, 135.2, 133.2, 130.1, 129.8, 123.2, 120.9, 112.2, 110.7, 59.4, 57.7, 55.7, 55.6, 55.5, 39.8, 33.2, 25.8, 24.2.

HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{23}H_{27}N_2O_4$ 395.1965; found 395.1973.

To a solution of 8-(3,4-dimethoxyphenyl)-7-(4-nitrophenyl)-1,3,4,6,9,9a-hexahydro-2*H*-quinolizine (310 mg, 0.786 mmol) and PIFA (372 mg, 0.865 mmol) in CH_2Cl_2 (4.0 mL) was added $BF_3 \cdot OEt_2$ (150 μL, 1.18 mmol) at –40 °C. After stirring at same temperature for 24 h, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ (5 mL) and extracted with $CHCl_3$ (15 mL × 3). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (AcOEt/MeOH) to afford **3d** (212 mg, 69%) as yellow solids.

IR (neat): 2932, 1616, 1516, 1470, 1416, 1339, 1300, 1258, 1207 cm^{-1}.

^1H NMR ($CDCl_3$, 500 MHz): δ = 9.42 (d, *J* = 2.3 Hz, 1H), 8.32 (dd, *J* = 9.2, 2.3 Hz, 1H), 8.01 (s, 1H), 7.97 (d, *J* = 9.2 Hz, 1H), 7.31 (s, 1H), 4.46 (d, *J* = 15.5 Hz, 1H), 4.17 (s, 3H), 4.09 (s, 3H), 3.68 (d, *J* = 15.5 Hz, 1H), 3.30 (d, *J* = 10.9 Hz, 1H), 3.19 (dd, *J* = 17.0, 3.3 Hz, 1H), 2.95 (dd, *J* = 16.5, 10.2 Hz, 1H), 2.48–2.40 (m, 1H), 2.35 (ddd, *J* = 11.7, 11.7, 3.0 Hz, 1H), 2.11–2.05 (m, 1H), 1.95–1.88 (m, 1H), 1.88–1.73 (m, 2H), 1.56–1.42 (m, 2H).

^{13}C NMR ($CDCl_3$, 150 MHz): δ = 150.2, 149.5, 144.8, 132.4, 131.8, 128.2, 126.5, 125.4, 124.1, 123.7, 119.3, 118.8, 103.8, 103.5, 57.2, 56.2, 56.0, 55.9, 35.2, 33.8, 25.9, 24.3 (one peak is missing due to incidental equivalence).

HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{23}H_{25}N_2O_4$ 393.1809; found 393.1818.

7-[(*tert*-Butyldimethylsilyl)oxy]-2,3-dimethoxy-11,12,13,14,14a,15-hexahydro-9*H*-dibenzo[*f,h*]pyrido[1,2-*b*]isoquinoline (3e)

To a mixture of **5** (309 mg, 0.734 mmol), *tert*-butyldimethyl[3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy]silane (244 mg, 0.729 mmol), $Pd(PPh_3)_4$ (25.4 mg, 22.0 μmol) and K_2CO_3 (304 mg, 2.20 mmol) was added a solution of DME/H_2O (7.4 mL, v/v = 2/1) under argon atmosphere. After stirring at 80 °C for 1.5 h, the solution was cooled to 23 °C and diluted with water (25 mL). The solution was extracted with AcOEt (25 mL × 5), and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (AcOEt/MeOH). The residue was diluted with AcOEt (10 mL) and extracted with 10% aqueous HCl (10 mL × 3). The resulting aqueous layer was basified with 10% aqueous NaOH (70 mL) and then extracted with $CHCl_3$ (50 mL × 3). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure to afford 7-{3-[(*tert*-butyldimethylsilyl)oxy]phenyl}-8-(3,4-dimethoxyphenyl)-1,3,4,6,9,9a-hexahydro-2*H*-quinolizine (300 mg, 85%) as yellow oil.

IR (neat): 2930, 2857, 2835, 2733, 1597, 1576, 1512, 1481, 1464, 1441, 1425, 1416, 1395, 1360, 1321, 1306, 1281, 1261, 1248, 1217 cm^{-1}.

^1H NMR ($CDCl_3$, 600 MHz): δ = 7.03 (t, *J* = 7.9 Hz, 1H), 6.74–6.71 (m, 1H), 6.66 (s, 2H), 6.61–6.57 (m, 1H), 6.52–6.49 (m, 1H), 6.48 (s, 1H), 3.79 (s, 3H), 3.60 (d, *J* = 16.5 Hz, 1H), 3.54 (s, 3H), 3.12–3.01 (m, 2H), 2.56–2.49 (m, 1H), 2.43–2.35 (m, 1H), 2.34–2.26 (m, 1H), 2.11 (td, *J* = 11.0, 4.1 Hz, 1H), 1.90–1.79 (m, 2H), 1.77–1.68 (m, 2H), 1.42–1.32 (m, 2H), 0.887 (s, 9H), –0.01 (s, 3H), –0.02 (s, 3H).

^{13}C NMR ($CDCl_3$, 150 MHz): δ = 155.2, 147.9, 147.3, 142.3, 134.2, 131.8, 131.6, 128.8, 122.0, 121.1, 120.4, 118.3, 112.7, 110.4, 60.2, 57.8, 55.6, 55.5, 55.4, 39.4, 33.3, 25.8, 25.6, 24.3, 18.1, –4.75, –4.77.

HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{29}H_{42}NO_3Si$ 480.2928; found 480.2927.

To a solution of 7-{3-[(*tert*-butyldimethylsilyl)oxy]phenyl}-8-(3,4-dimethoxyphenyl)-1,3,4,6,9,9a-hexahydro-2*H*-quinolizine (152 mg, 0.317 mmol) and PIFA (150 mg, 0.349 mmol) in CH_2Cl_2 (1.6 mL) was added $BF_3 \cdot OEt_2$ (118 μL, 0.951 mmol) at –40 °C. After stirring at same temperature for 24 h, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ (5 mL) and extracted with $CHCl_3$ (15 mL × 3). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (EtOAc/MeOH) to afford **3e** (92.5 mg, 61%) as brown oil.

IR (neat): 2928, 2859, 1616, 1504, 1466, 1427, 1234, 1215 cm^{-1}.

^1H NMR ($CDCl_3$, 600 MHz): δ = 8.40 (d, *J* = 9.0 Hz, 1H), 7.92 (s, 1H), 7.25 (s, 1H), 7.23 (d, *J* = 2.8 Hz, 1H), 7.13 (dd, *J* = 9.0, 2.8 Hz, 1H), 4.35 (d, *J* = 15.8 Hz, 1H), 4.09 (s, 3H), 4.05 (s, 3H), 3.57 (d, *J* = 15.2 Hz, 1H), 3.30 (d, *J* = 11.0 Hz, 1H), 3.11 (dd, *J* = 16.5, 3.4 Hz, 1H), 2.90 (dd, *J* = 15.8, 10.3 Hz, 1H), 2.44–2.36 (m, 1H), 2.32 (td, *J* = 11.7, 2.8 Hz, 1H), 2.04 (d, *J* = 12.4 Hz, 1H), 1.89 (d, *J* = 12.4 Hz, 1H), 1.85–1.73 (m, 2H), 1.59–1.49 (m, 1H), 1.49–1.40 (m, 1H), 1.03 (s, 9H), 0.264 (s, 6H).

^{13}C NMR ($CDCl_3$, 150 MHz): δ = 153.6, 148.54, 148.49, 130.3, 127.3, 124.9, 124.8, 124.1, 123.9, 123.6, 119.6, 111.7, 103.8, 103.2, 57.4, 56.2, 55.93, 55.89, 55.84, 34.9, 33.8, 25.9, 25.8, 24.3, 18.4, –4.27, –4.29.

HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{29}H_{39}NO_3Si$ 478.2772; found 478.2772.

2,3,8-Trimethoxy-11,12,13,14,14a,15-hexahydro-9*H*-dibenzo[*f,h*]pyrido[1,2-*b*]isoquinoline (3f)

To a mixture of **5** (279 mg, 0.661 mmol), 2-(2-Methoxyphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (186 mg, 0.794 mmol), $Pd(PPh_3)_4$ (22.9 mg, 19.8 μmol) and K_2CO_3 (274 mg, 1.98 mmol) was added a solution of DME/H_2O (6.6 mL, v/v = 2/1) under argon atmosphere. After stirring at 80 °C for 3 h, the mixture was cooled to 23 °C and diluted with water (25 mL). The solution was extracted with AcOEt (25 mL × 5), and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (AcOEt/MeOH). The residue was diluted with AcOEt (10 mL) and extracted with 10% aqueous HCl (10 mL × 3). The resulting aqueous layer was basified with 10% aqueous NaOH (70 mL) and then extracted with $CHCl_3$ (50 mL × 3). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure to afford 8-(3,4-dimethoxyphenyl)-7-(2-methoxyphenyl)-1,3,4,6,9,9a-hexahydro-2*H*-quinolizine (221 mg, 88%) as brown oil.

IR (neat): 2932, 2832, 1597, 1578, 1512, 1489, 1462, 1435, 1416, 1242 cm^{-1}.

^1H NMR ($CDCl_3$, 600 MHz): δ = 7.10 (t, *J* = 8.3 Hz, 1H), 6.87 (br s, 1H), 6.77 (d, *J* = 8.3 Hz, 1H), 6.72 (t, *J* = 7.2 Hz, 1H), 6.68 (d, *J* = 8.3 Hz, 1H), 6.64 (d, *J* = 8.3 Hz, 1H), 6.50 (s, 1H), 3.77 (s, 3H), 3.72 (s, 3H), 3.57–3.42 (m, 1H), 3.50 (s, 3H), 3.05 (d, *J* = 11.0 Hz, 2H), 2.62–2.30 (m, 3H), 2.15–2.00 (m, 1H), 1.90–1.65 (m, 4H), 1.46–1.30 (m, 2H).

^{13}C NMR ($CDCl_3$, 150 MHz): δ = 157.1, 147.4, 147.0, 134.4, 131.9, 131.1, 129.9, 127.9, 120.4, 119.5, 112.0, 110.2, 110.0, 59.3, 57.8, 55.5, 55.3, 55.2, 55.0, 38.7, 33.0, 25.6, 24.2 (one peak is missing due to incidental equivalence).

HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{24}H_{30}NO_3$ 380.2220; found 380.2214.

To a solution of 8-(3,4-dimethoxyphenyl)-7-(2-methoxyphenyl)-1,3,4,6,9,9a-hexahydro-2*H*-quinolizine (235 mg, 0.620 mmol) and PIFA (294 mg, 0.682 mmol) in CH_2Cl_2 (3.0 mL) was added $BF_3 \cdot OEt_2$ (236 μL, 1.86 mmol) at –10 °C. After stirring at same temperature for 15 h, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ (9 mL) and extracted with $CHCl_3$ (15 mL × 3). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (AcOEt/MeOH) to afford **3f** (21.7 mg, 9%) as a brown oil.

IR (neat): 2932, 2855, 2832, 1585, 1528, 1504, 1466, 1431, 1300, 1254, 1207 cm^{-1}.

^1H NMR ($CDCl_3$, 600 MHz): δ = 8.12 (d, *J* = 8.3 Hz, 1H), 7.93 (s, 1H), 7.45 (t, *J* = 8.3 Hz, 1H), 7.19 (s, 1H), 6.94 (d, *J* = 7.6 Hz, 1H), 4.75 (d, *J* = 16.5 Hz, 1H), 4.08 (s, 3H), 4.03 (s, 3H), 4.01–3.95 (m, 1H), 3.93 (s, 3H), 3.26 (d, *J* = 10.3 Hz, 1H), 3.14–3.04 (m, 1H), 3.01–2.90 (m, 1H), 2.47–2.35 (m, 1H), 2.35–2.25 (m, 1H), 2.07–1.98 (m, 1H), 1.87 (d, *J* = 12.4 Hz, 1H), 1.83–1.72 (m, 2H), 1.59–1.48 (m, 1H), 1.48–1.37 (m, 1H).

^{13}C NMR ($CDCl_3$, 150 MHz): δ = 157.8, 149.3, 148.4, 131.2, 126.1, 126.0, 125.5, 123.5, 121.1, 115.2, 107.0, 104.0, 103.3, 59.5, 56.7, 55.8, 55.8, 55.5, 35.1, 33.4, 25.5, 24.0 (two peak is missing due to incidental equivalence).

HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{24}H_{28}NO_3$ 378.2064; found 378.2066.

2,3-dimethoxy-5-nitro-11,12,13,14,14a,15-hexahydro-9*H*-dibenzo[*f,h*]pyrido[*1,2-b*]isoquinoline (3g) and 2,3-dimethoxy-7-nitro-11,12,13,14,14a,15-hexahydro-9*H*-dibenzo[*f,h*]pyrido[*1,2-b*]isoquinoline (3h)

To a mixture of **5** (116 mg, 0.275 mmol), 3-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)nitrobenzene (103 mg, 0.413 mmol), $Pd(PPh_3)_4$ (9.5 mg, 8.3 μmol) and K_2CO_3 (114 mg, 0.83 mmol) was added a solution of DME/H_2O (2.7 mL, v/v = 2/1) under argon atmosphere. After stirring at 80 °C for 2 h, the mixture was cooled to 23 °C and diluted with water (25 mL) and extracted with $CHCl_3$ (25 mL × 3). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (AcOEt/MeOH). The residue was diluted with AcOEt (15 mL) and extracted with 10% aqueous HCl (15 mL × 3). The resulting aqueous layer was basified with 10% aqueous NaOH (70 mL) and then extracted with $CHCl_3$ (100 mL × 3). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure to afford 8-(3,4-dimethoxyphenyl)-7-(3-nitrophenyl)-1,3,4,6,9,9a-hexahydro-2*H*-quinolizine (95.0 mg, 88%) as yellow amorphous.

IR (neat): 2932, 1573, 1462, 1346, 1254 cm^{-1}.

^1H NMR ($CDCl_3$, 500 MHz): δ = 7.99 (s, 1H), 7.96 (d, *J* = 8.0 Hz, 1H), 7.33 (d, *J* = 7.4 Hz, 1H), 7.30–7.25 (m, 1H), 6.66 (d, *J* = 8.3 Hz, 1H), 6.60 (dd, *J* = 8.3, 1.7 Hz, 1H), 6.45 (d, *J* = 1.4 Hz, 1H), 3.80 (s, 3H), 3.58 (s, 3H), 3.65–3.55 (m, 1H), 3.17–3.08 (m, 2H), 2.58 –2.51 (m, 1H), 2.49–2.41 (m, 1H), 2.38–2.31 (m, 1H), 2.15 (ddd, *J* = 11.5, 11.5, 3.4 Hz, 1H), 1.90–1.80 (m, 2H), 1.80–1.67 (m, 2H), 1.45–1.30 (m, 2H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ = 148.2, 147.9, 147.7, 142.5, 135.6, 134.8, 133.1, 129.7, 128.7, 123.6, 121.2, 120.9, 112.2, 110.7, 59.5, 57.7, 55.6, 55.54, 55.46, 39.7, 33.2, 25.8, 24.2.

HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{23}H_{27}N_2O_4$ 395.1965; found 395.1954.

To a solution of 8-(3,4-dimethoxyphenyl)-7-(3-nitrophenyl)-1,3,4,6,9,9a-hexahydro-2*H*-quinolizine (254 mg, 0.644 mmol) and PIFA (305 mg, 0.708 mmol) in CH_2Cl_2 (3.2 mL) was added $BF_3 \cdot OEt_2$ (245 μL, 1.93 mmol) at –40 °C. After stirring at same temperature for 24 h, the reaction was quenched with saturated aqueous $NaHCO_3$ (10 mL) and extracted with $CHCl_3$ (15 mL × 3). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (AcOEt/MeOH) to afford a mixture of 2,3-dimethoxy-5-nitro-11,12,13,14,14a,15-hexahydro-9*H*-dibenzo[*f,h*]pyrido[*1,2-b*]isoquinoline (**3g**) and 2,3-dimethoxy-7-nitro-11,12,13,14,14a,15-hexahydro-9*H*-dibenzo[*f,h*]pyrido[*1,2-b*]isoquinoline (**3h**) (148 mg, 58% regio-selectivity ratio = 45:55) as brown oil.

IR (neat): 2932, 2855, 1612, 1519, 1465, 1334, 1261 cm^{-1}.

^1H NMR ($CDCl_3$, 500 MHz): δ = 8.72 (d, *J* = 2.0 Hz, 1H, major), 8.54 (d, *J* = 9.2 Hz, 1H, major), 8.29 (d, *J* = 9.0 Hz, 1H, major), 8.02-7.94 (m, 1H, minor), 7.92 (s, 1H, major), 7.66 (d, *J* = 7.7 Hz, 1H, minor), 7.55-7.50 (m, 1H, minor), 7.38 (s, 1H, minor), 7.25 (s, 1H, major), 7.25 (s, 1H, minor), 4.48-4.36 (m, 1H, major and minor), 4.12 (s, 1H, major), 4.09 (s, 1H, major), 4.05 (s, 1H, minor), 3.95 (s, 1H, minor), 3.70-3.59 (m, 2H, major and minor), 3.35-3.21 (m, 1H, major and minor), 3.15-3.03 (m, 1H, major and minor), 2.96-2.81 (m, 1H, major and minor), 2.42-2.24 (m, 2H, major and minor), 2.09-2.00 (m, 1H, major and minor), 1.96-1.38 (m, 5H, major and minor).

^{13}C NMR ($CDCl_3$, 125 MHz): δ = 150.7, 149.8, 149.0, 148.9, 148.1, 144.8, 132.4, 130.7, 129.4, 128.1, 127.6, 127.5, 126.1, 125.6, 125.0, 124.3, 123.5, 122.7, 121.1, 119.8, 119.3, 118.7, 118.6, 106.1, 104.0, 103.6, 103.4, 57.2, 57.0, 56.1, 56.0, 55.8, 55.7, 55.6, 34.9, 34.8, 33.7, 33.6, 25.8, 24.21, 24.18.

HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{23}H_{25}N2O_4$ 393.1809; found 393.1803.

2,3-Dimethoxy-11,12,13,14,14a,15-hexahydro-9*H*-dibenzo[*f,h*]pyrido[*1,2-b*]isoquinolin-5-amine (S1a)

and

2,3-Dimethoxy-11,12,13,14,14a,15-hexahydro-9*H*-dibenzo[*f,h*]pyrido[*1,2-b*]isoquinolin-7-amine (S1b)

To a solution of the mixture of **3g** and **3h** (148 mg, 0.38 mmol) in MeOH/AcOH (5.0 mL, v/v =4/1) was added Pd/C (3.9 mg, 10% on Carbon, 3.7 μmol). After flushing with H_2, the reaction mixture was stirred for 6 h. After completion of the reaction, the reaction mixture was filtered over Celite, and the filtrate was concentrated under reduced pressure and purified by column chromatography on silica gel (AcOEt/MeOH) to afford **S1a** (32.8 mg, 14% in 2 steps) as brown oil, and **S1b** (31.4 mg, 13% in 2 steps) as yellow solids.

S1a: IR (neat): 2932, 1616,1508, 1466, 1258 cm^{-1}.

^1H NMR ($CDCl_3$, 600 MHz): δ = 8.85 (s, 1H), 7.35–7.28 (m, 2H), 7.23 (s, 1H), 6.93 (d, *J* = 6.9 Hz, 1H), 4.42 (d, *J* = 15.2 Hz, 1H), 4.31–4.26 (m, 2H), 4.04 (s, 3H), 4.01 (s, 3H), 3.62 (d, *J* = 14.5 Hz, 1H), 3.31 (d, *J* = 11.0 Hz, 1H), 3.04 (d, *J* = 16.5 Hz, 1H), 2.99–2.90 (m, 1H), 2.47–2.29 (m, 2H), 2.04 (d, *J* = 12.4 Hz, 1H), 1.90 (d, *J* = 13.1 Hz, 1H), 1.85–1.79 (m, 2H), 1.59 (ddd, *J* = 11.7, 11.0, 11.0 Hz, 1H), 1.50–1.40 (m, 1H).

^{13}C NMR ($CDCl_3$, 150 MHz): δ = 147.7, 147.1, 144.3, 130.9, 126.7, 126.4, 125.9, 124.3, 118.9, 114.6, 113.7, 107.6, 103.7, 57.3, 56.2, 56.0, 55.9, 55.8, 34.5, 33.2, 25.5, 24.0 (one peak is missing due to incidental equivalence).

HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{23}H_{27}N_2O_2$ 363.2067; found 363.2049.

S1b: IR (neat): 3368, 3314, 2932, 1767, 1620, 1508, 1466, 1246 cm^{-1}.

^1H NMR ($CDCl_3$, 500 MHz): δ = 8.33 (d, *J* = 8.9 Hz, 1H), 7.88 (s, 1H), 7.22 (s, 1H), 7.04 (d, *J* = 2.3 Hz, 1H), 6.99 (dd, *J* = 8.6, 2.3 Hz, 1H), 4.33 (d, *J* = 15.2 Hz, 1H), 4.08 (s, 3H), 4.03 (s, 3H), 4.01–3.68 (m, 2H), 3.54 (d, *J* = 15.4 Hz, 1H), 3.26 (d, *J* = 11.2 Hz, 1H), 3.09 (dd, *J* = 16.6, 2.9 Hz, 1H), 2.88 (dd, *J* = 15.9, 10.7 Hz, 1H), 2.36 (dddd, *J* = 10.3, 9.7, 3.4, 3.2 Hz, 1H), 2.29 (ddd, *J* = 11.2, 11.2, 4.0 Hz, 1H), 2.05–1.99 (m, 1H), 1.92–1.85 (m, 1H), 1.84–1.72 (m, 2H), 1.59–1.38 (m, 2H).

^{13}C NMR ($CDCl_3$, 150 MHz): δ = 148.5, 148.1, 144.2, 130.3, 127.2, 124.4, 124.2, 123.9, 121.8, 115.7, 105.8, 103.8, 102.9, 57.4, 56.2, 56.1, 55.9, 55.8, 34.9, 33.7, 25.9, 24.3 (one peak is missing due to incidental equivalence).

HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{23}H_{27}N_2O_2$ 363.2067; found 363.2056.

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Supporting Information

YES (this text will be updated with links prior to publication)

Primary Data

NO (this text will be deleted prior to publication)

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