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Total Synthesis of (+)-Chimonanthine, (+)-Folicanthine, and (−)-Calycanthine

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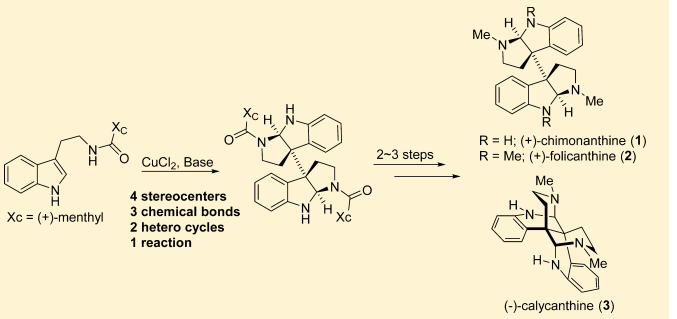
Supporting Information

ABSTRACT: Facile, straightforward, and asymmetric total syntheses of (+)-chimonanthine (**1**), (+)-folicanthine (**2**), and (−)-calycanthine (**3**) were accomplished in four to five steps from commercially available tryptamine. The synthesis features copper-mediated asymmetric cyclodimerization of chiral tryptamine derivative, which established a new entry into constructing the sterically hindered vicinal quaternary stereogenic carbon centers of dimeric hexahydropyrroloindole alkaloids in one procedure. An unprecedented base-induced isomerization from the chimonanthine skeleton to the calycanthine skeleton was observed and facilitated the synthesis of (−)-calycanthine (**3**).



INTRODUCTION

In nature, hexahydropyrroloindole skeletons are very important moieties that are widespread in a large family of natural products with wide range of attractive bioactivities.[1] Dimeric or oligomeric hexahydropyrroloindole derivatives, bearing vicinal quaternary stereogenic carbon centers at C3a and C3a′, have attracted significant interest for both synthetic and biological studies. As the representative models of these alkaloids, (+)-chimonanthine (**1**), (+)-folicanthine (**2**), and (−)-calycanthine (**3**) (shown in Figure 1) have continuously received considerable synthetic efforts from the community of synthetic chemists, especially in the past few years.[2]

With respect to the instability of the C3a−C3a′ bond, as well as the difficulties in construction of the sterically hindered vicinal stereogenic quaternary centers, efficient methods toward the enantioselective synthesis of dimeric hexahydropyrroloindole alkaloids were still challenging.[3] In 1999, Overman uncovered the first stereocontrolled total synthesis of (−)-chimonanthine (**1**) and (+)-calycanthine (**3**) (Scheme 1). In this method, the contiguous quaternary carbon centers, induced from the tartrate-derived diiodide compound, were established efficiently via double-intramolecular Heck cyclization.[3a] Movassaghi and co-workers developed an efficient Co(I)-mediated reductive homodimerization of chiral 3-bromohexahydropyrroloindole in 2007 and completed the concise enantioselective total synthesis of (+)-chimonanthine (**1**), (+)-folicanthine (**2**), and (−)-calycanthine (**3**).[3b] In 2013, Ma and co-workers developed a chiral anionic phase-transfer catalytic enantioselective bromocyclization of tryptamine. By

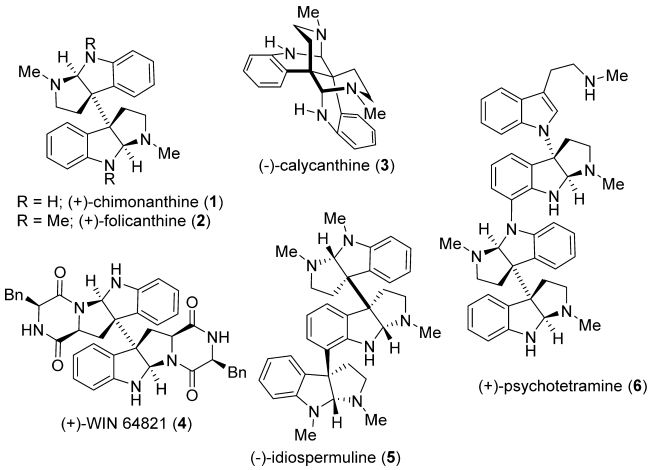


Figure 1. Representative hexahydropyrroloindole-derived family of alkaloids with C_{3a}−$C_{3a'}$ bond.

employing Movassghi's dimerization conditions, the enantioselective total synthesis of (−)-chimonanthine(**1**) was achieved from 3-bromohexahydropyrrolo[2,3,-*b*]indole.[3e] Movassaghi's coupling methodology was also frequently utilized by several other research groups toward the total synthesis of other dimeric hexahydropyrroloindole alkaloids.[3e,4] A novel enantio-

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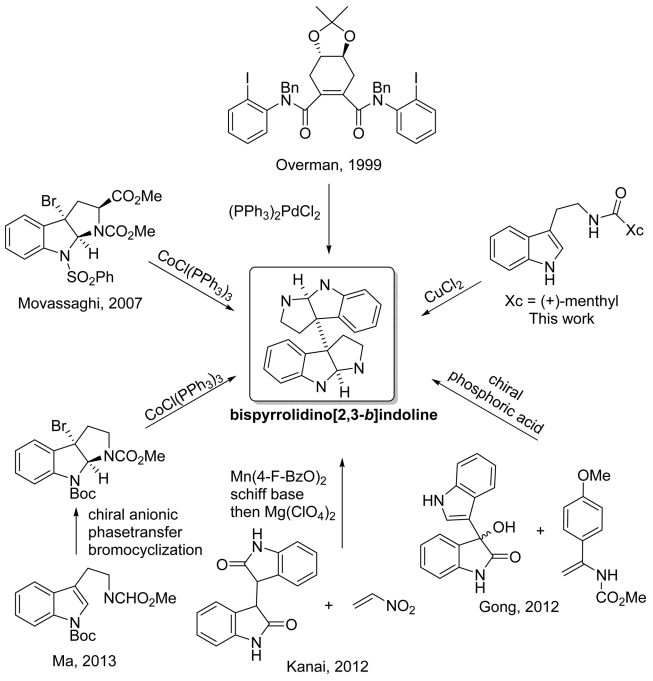
Scheme 1. Summary of the Previous Reports on Total Synthesis of Chiral Dimeric Hexahydropyrroloindole Natural Products

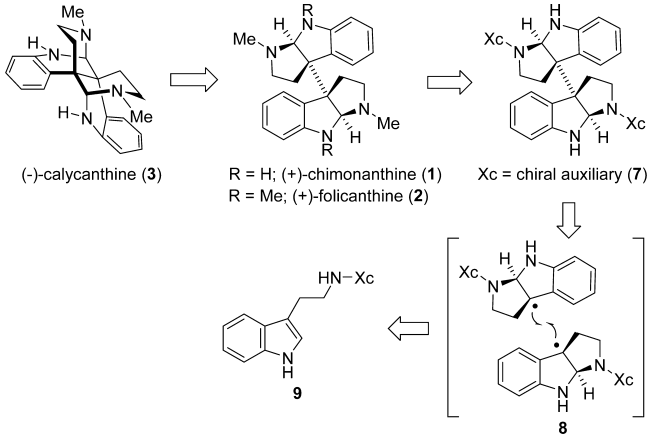


selective nucleophilic substitution reaction of 3-hydroxyoxindoles with enecarbamates for C3a and C3a′ coupling for the synthesis of disubstituted oxindoles was developed by Gong and co-workers in 2012.[3d] This methodology was strategically utilized for the total synthesis of (+)-folicanthine (**2**) with several additional steps. Soon afterward, a catalytic asymmetric double-Michael addition of bisoxindole was developed by Kanai's research group, which provided alternative choice for the synthesis of (+)-chimonanthine (**1**), (+)-folicanthine (**2**), and (−)-calycanthine (**3**).[3c] Very recently, a copper catalyzed sequential arylation−oxidative dimerization reaction as the key step for the synthesis of (+)-chimonanthine (**1**), (+)-folicanthine (**2**) and (−)-calycanthine (**3**) was developed with sulfonamide as chiral auxiliary.[5] Herein, we disclosed a concise, straightforward, and asymmetric total synthesis of (+)-chimonanthine (**1**), (+)-folicanthine (**2**), and (−)-calycanthine (**3**) via an oxidative cyclodimerization method.

RESULTS AND DISCUSSION

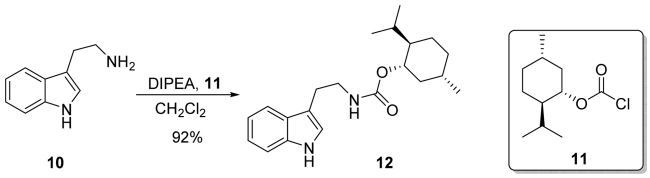
To start with the synthesis of the target compounds, a general and convergent retrosynthetic approach for (+)-chimonanthine (**1**), (+)-folicanthine (**2**), and (−)-calycanthine (**3**) was designed. As outlined in Scheme 2, (+)-chimonanthine (**1**) was envisioned as the common intermediate for both (+)-folicanthine (**2**) and (−)-calycanthine (**3**) by a later stage of N1-methylation or isomerization. We inferred that (+)-chimonanthine (**1**) could be prepared from dimer **7** with all the stereogenic centers located close together. A powerful homodimeric coupling reaction would be strategically involved in the construction of the 3a,3a′-bispyrrolidino[2,3-*b*]indoline framework via intermediate **8**, establishing the vicinal quaternary stereogenic carbon centers at the C3a and C3a′ positions from readily available chiral monomer **9** or its analogues.

Scheme 2. Retrosynthetic Analysis of (+)-Chimonanthine (1), (+)-Folicanthine (2), and (−)-Calycanthine (3)



The (+)-menthyl group was utilized as a chiral source to induce the global chirality (Scheme 3). The chiral carbamate **12**

Scheme 3. Synthesis of Chiral Carbamate 17



was easily synthesized on a multigram scale by treating commercially available tryptamine **10** with (+)-menthyl chloroformate **11** in the presence of excessive DIPEA. The enantiomerically pure carbamate **12** was obtained in 92% yield by crystallization from the crude residue in a mixture of petroleum ether and CH_2Cl_2 at low temperature.

Having a sufficient amount of dimeric precursor **12** in hand, we then focused on the study of the crucial homodimeric coupling step. During the application of the previously reported cyclodimerization conditions ($CuCl_2$ (1.1 equiv) and DBU (2.5 equiv) in CH_3CN under anaerobic conditions),[6] we encountered difficulties with low conversion rate (<10% yield). We then turned our attention to diverse metal oxidants to improve the efficiency of the cyclodimerization reaction. A wide range of metal salts (1.1 equiv), such as $CoCl_2$, $FeCl_3$, $MgCl_2$, $Mn(OAc)_3$, $ZnCl_2$, $CeCl_3$, $ZrCl_4$, and $NiCl_2$, were screened in the presence of DBU (2.5 equiv), but none of them were found to proceed effectively. Furthermore, other copper sources, such as $Cu(OAc)_2$, $Cu(acac)_2$, $Cu(OTf)_2$, $CuSO_4$, $Cu(NO_3)_2$, and Cu(2-ethylhexanoate)$_2$, were also tested but failed. It was noticed that this cyclodimerization reaction could be initiated by none of them except $CuCl_2$, which revealed the importance of the counterpart anion in copper salt. We reasoned that $CuCl_2$ was superior for the oxidation of N1-anion comparing to other copper salts, while without a strong coordination effect. In this case, we thus returned to the $CuCl_2$/base protocol. As illustrated in Table 1, no significant improvements were achieved after intensive survey of various reaction temperatures, concentrations, times, bases, and the amounts of base. To our delight, the reaction was effectively promoted as the amount of $CuCl_2$ was increased to 1.5 equiv in association with *t*-BuOK, which was far beyond our knowledge. According to our previous results, the dimeric hexahydropyrroloindole analogues

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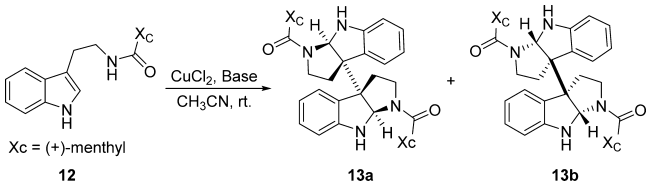
Table 1. Studies on the Cyclodimerization Reaction



entry	$CuCl_2$ (equiv)	base (equiv)	conc (M)	yield[a] (%)	brsm[c] (%)	13a:13b
1	1.1	DBU (2.5)	0.1	<10[b]		
2	1.1	NaH (2.5)	0.1	*b*		
3	1.1	*t*-BuOK (2.5)	0.1	*b*		
4	1.5	*t*-BuOK (2.5)	0.1	39	60	3:2
5	1.5	*t*-BuOK (2.5)	0.05	40	59	3:2
6	2.0	*t*-BuOK (2.5)	0.05	25	33	3:2
7	1.5	*t*-BuOK (1.1)	0.05	45	59	3:2
8	1.5	*t*-BuOK (1.1)	0.05	42[d]	56	3:2

[a]0.3 mmol of substrate was used unless otherwise mentioned. [b]A low conversion rate was observed by TLC analysis. [c]Based on recovered starting material. [d]Gram scale.

were liable to decompose rapidly with excess $CuCl_2$ (1.5 equiv).[6] With further optimization, we disclosed that the amounts of both $CuCl_2$ and *t*-BuOK were very critical for this cyclodimerization reaction. Two diastereomers, **13a** and **13b**, were identified as homodimeric coupling products in 45% yield (59% brsm). At this stage, we were unable to confirm the relative configurations at all newly formed stereocenters of these two diastereomers. However, the diastereomeric ratio of them was measured to be 3:2 after isolation by reversed-phase preparative HPLC. The relative configurations of these two isomers **13a** and **13b** were confirmed at the end of the synthesis. We found that the spectroscopic data (^{1}H NMR, ^{13}C NMR, and specific rotation) of **13a**-derived synthetic material matched those of the isolated natural products (+)-chimonanthine (**1**), and the **13b**-derived synthetic material had the same ^{1}H NMR and ^{13}C NMR, while with the opposite specific rotation. Most importantly, the C_2-symmetry was predominant in this reaction, and no meso-isomers or any other regioisomers were detected.[2f,7] It should also be noted that the process of this tandem sequence was highly efficient (four stereogenic centers, three chemical bonds, and two heterocycles were simultaneously constructed in a single step). In particular, even when the reaction was scaled up to 1 g, the combined yield was still well maintained. This was highly helpful from a practical point of view, in particular for large-scale preparation of each diastereomer.

To investigate the copper-mediated oxidization process, a nitrogen-masking experiment was designed and explored. The reaction was completely suppressed by a large excess of Et_3B, which usually served as a deactivator of indole N1 to inhibit its functionality.[8] We also discovered that no reactions occurred when N1 was protected with a methyl or sulfonyl group.[9] These experiments demonstrated that the radical species oxidized by $CuCl_2$ was originated from indole N1.

On the basis of the experimental results above, a plausible mechanism is proposed in Scheme 4. The indole N1 was deprotonated, followed by a single-electron oxidation process, to generate the corresponding indole N1 free radical species, which then delocalized to indole C3. Then two indole C3 radicals dimerized first, and the 5-*exo*-*trig* annulation occurred afterward. In this manner, the C3 free-radical species, consisting of the auxiliary located remotely, underwent the frequent conformational inversion process (TS-**1** and TS-**2**), leading to poor final diastereoselectivity. In addition, the meso dimerization process (TS-**3** and TS-**4**) was unfavorable owing to the steric interaction between the two side chains. .

With this key intermediate **13a** in hand, we then focused on accomplishing the total synthesis of this family of natural products, which seems easily obtained. Thus, several promising reagents for the reduction of (+)-menthyl group in **13a**, such as lithium aluminum hydride ($LiAlH_4$),[10] diisobutyl aluminum hydride (DIBAL-H),[11] or bis(2-methoxyethoxy)aluminum hydride (Red-Al), were explored under various conditions with different temperatures or solvents. However, the straightforward transformation of compound **13a** to (+)-chimonanthine (**1**) turned out to be highly challenging under reductive conditions. Notably, after compound **13a** was treated with $LiAlH_4$ either in THF or Et_2O, the corresponding monomer or its derivatives were isolated. This experimental evidence indicated that an unexpected anionic fragmentation process of the C3a−C3a′ bond predominated.[3b] Moreover, if Red-Al was utilized as reducing reagent, a major product was obtained and further identified as compound **14** wherein a pyrrole ring-opening process occurred. As depicted in Scheme 5, we proposed that the Al(III)-mediated ring opening occurred, followed by reduction of the imine intermediate, affording mono-ring-opening product **14**.

To verify the proposed decomposition mechanism, the N1 was protected with methyl groups by reductive methylation to give compound **15**. Thus, compound **15** would not form the nitrogen anion intermediate under reductive conditions, consequently preventing the ring-opening reaction. As expected, after compound **15** was treated with Red-Al, (+)-folicanthine (**2**) was achieved in high yield without the detection of ring-opening byproducts (Scheme 6). These experimental results confirmed our proposed mechanism as depicted in Scheme 5.

For the preparation of another two natural products, (+)-chimonanthine (**1**) and (−)-calycanthine (**3**), which have no methyl groups at the N1 position, the bulky menthyl groups in **13a** were globally removed by KOH in heated EtOH (Scheme 7). The reaction mixture was then treated with $ClCO_2Me$ to successfully deliver the desired carbamate **16** along with isomerized product **17**. Pleasingly, the C3a−C3a′ bond fragmentation occurred even at temperatures up to 155 °C under basic conditions. The specific rotation [$[\alpha]_D^{23}$ = +414.1 (*c* 0.41, CH_3Cl); lit. $[\alpha]_D^{22.3}$ = +437.0 (*c* 1.47, CH_3Cl) by Kanai's group[3c] and $[\alpha]_D^{22}$ = +474.0 (*c* 1.00, CH_2Cl_2) by Movassaghi's group[3b]] of carbamate **16** was in agreement with the values published for the title compound. Notably, rather than employing acidic conditions like many research groups to date,[2b,c,i,3a−c,12] it was first time that this kind of skeleton isomerization process was achieved under basic conditions. The ratio between desired product **16** and isomerized product **17** depended on the duration of the deprotecting step, and it was convenient to control the ratio between the two intermediates by verifying the reaction duration. The ratio between product **17** and **16** could reach up to 8.3:1 in 70% overall yield with a deprotection duration of 80 h. Then, reducing the two

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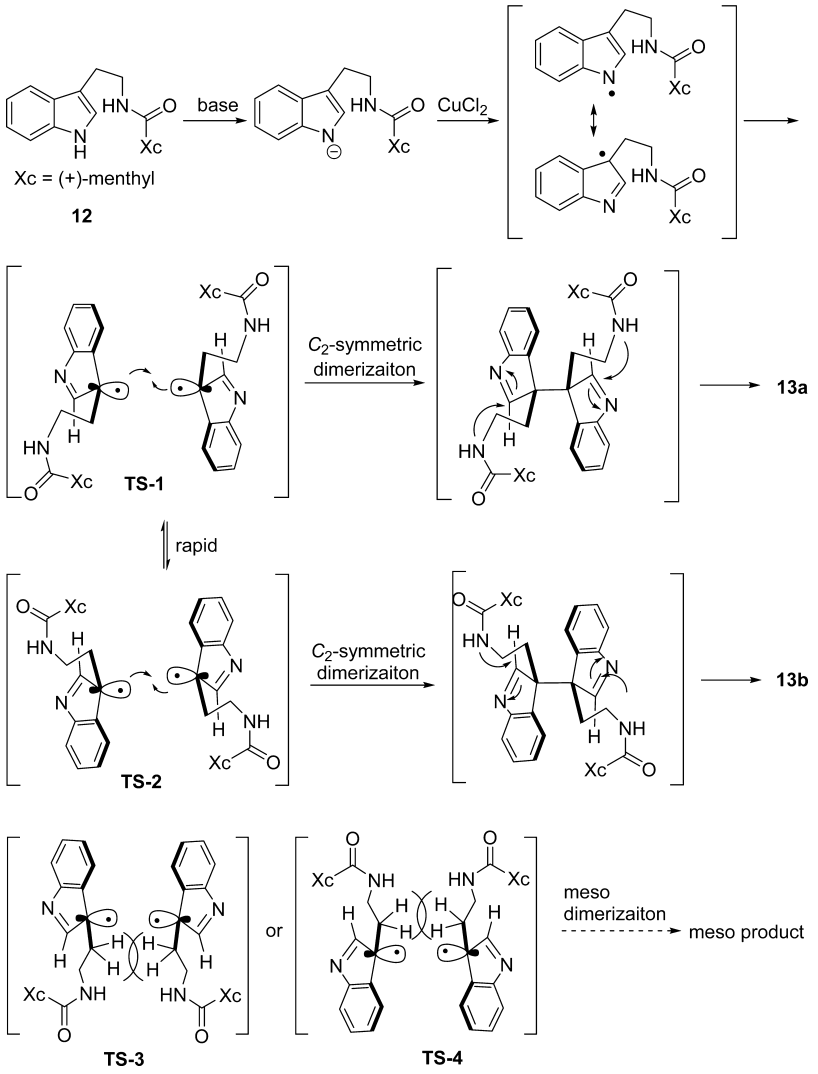
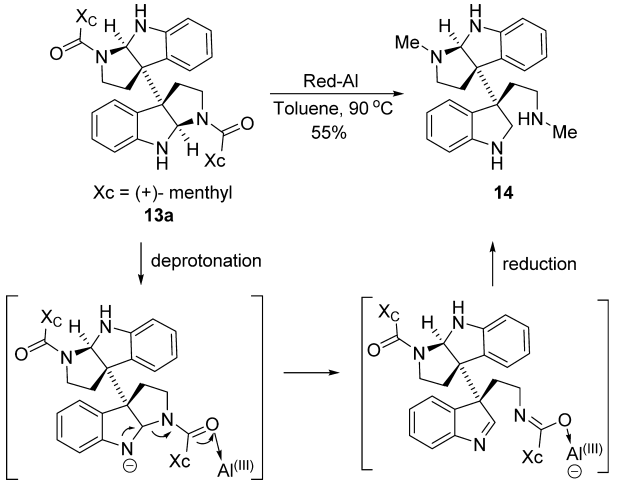
Scheme 4. Plausible Mechanism for the Cyclodimerization Reaction



Scheme 5. Attempts at Reducing the (+)-Menthyl Auxiliary of Dimer 13a



methoxycarbonyl groups of **17** with a large excess of Red-Al smoothly gave (−)-calycanthine (**3**) in 84% yield. Competitive with this three-step sequence, direct *N*-methylation of the crude mixture of intermediate **16a** and **17a** was chemoselectively achieved in the presence of excessive K_2CO_3 and MeI, affording (−)-calycanthine (**3**) in 54% yield over two steps. More interestingly, (+)-chimonanthine (**1**) and other overmethylation products were not observed. Finally, carbamate **16** was transformed to (+)-chimonanthine (**1**) also via a large excess of Red-Al and gave (+)-chimonanthine (**1**) in 83% yield. All of the spectroscopic data of (+)-chimonanthine (**1**), (+)-folicanthine (**2**), and (−)-calycanthine (**3**) for the synthetic samples were identical to those reported in the literature.

CONCLUSIONS

In summary, we have developed a facile asymmetric synthetic route to the total synthesis of three representative C_2-symmetric bispyrrolidinoindoline-derived natural products, (+)-chimonanthine (**1**), (+)-folicanthine (**2**), and (−)-calycanthine (**3**), with the shortest steps so far. The key steps of this synthesis featured a novel and efficient copper-mediated asymmetric homodimeric coupling reaction from readily available chiral tryptamine derivative. Additionally, other new discoveries in this synthesis included an unprecedented base-induced skeleton isomerization and a direct chemoselective methylation. This straightforward strategy could be applied to synthesize other high-order hexahydropyrroloindole alkaloids and derivatives, which also holds great potential for the

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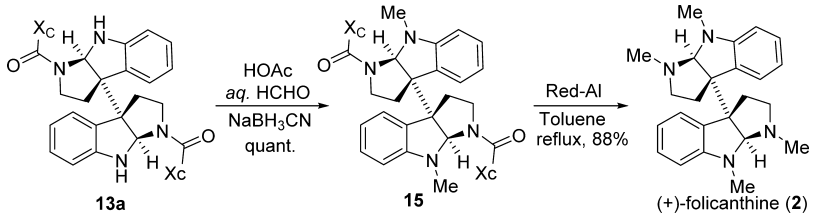
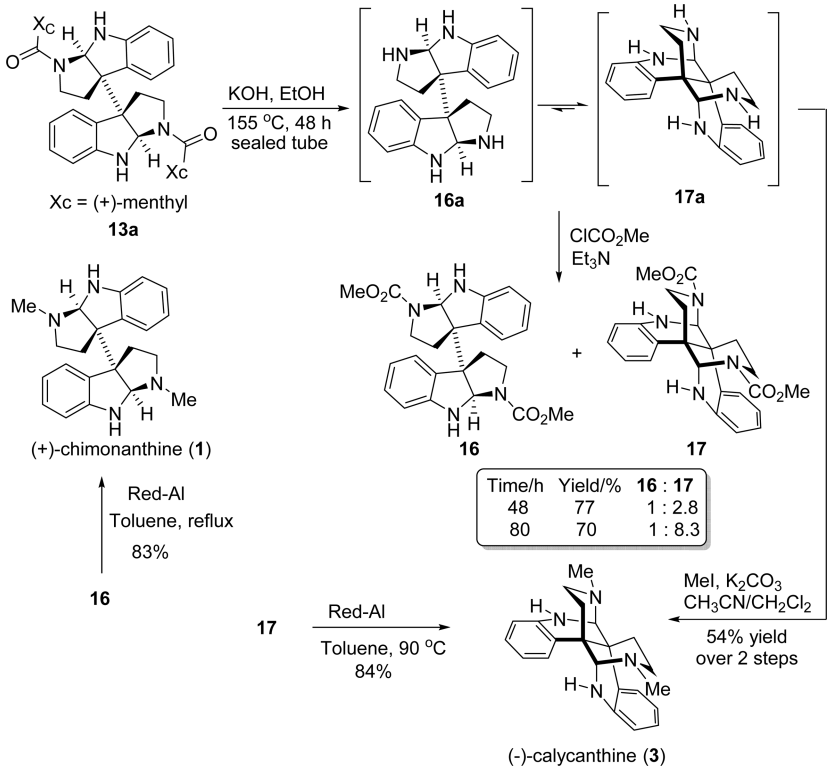
Scheme 6. Total Synthesis of (+)-Folicanthine (2)



Scheme 7. Total Synthesis of (+)-Chimonanthine (1) and (−)-Calycanthine (3)



discovery of leading drug candidates containing the poly hexahydropyrroloindole substructure.

EXPERIMENTAL SECTION

General Methods. All reactions were performed under argon atmosphere using oven-dried glassware unless otherwise noted. CH_3CN, CH_2Cl_2, and DMSO were distilled over CaH_2. THF and toluene were distilled over Na/benzophenone. All other reagents were commercially available and used without further purification unless indicated otherwise. Thin-layer chromatography (TLC) was carried out on GF254 plates (0.25 mm layer thickness). Flash chromatography was performed with 300−400 mesh silica gels. Visualization of the developed chromatogram was performed by fluorescence quenching, ceric ammonium molybdate, or $KMnO_4$ stain. Yields reported were for isolated, spectroscopically pure compounds. ^1H NMR and ^{13}C NMR experiments were recorded on a 400 MHz instrument at ambient temperature unless otherwise noted. The residual solvent protons (^1H) or the solvent carbons (^{13}C) were used as internal standards. ^1H NMR data are presented as follows: chemical shift in ppm downfield from tetramethylsilane (multiplicity, coupling constant, integration). The following abbreviations are used in reporting NMR data: s, singlet; br s, broad singlet; d, doublet; dd, doublet of doublets; t, triplet; q, quartet; m, multiplet. Optical rotations were measured with a polarimeter at ambient temperature using a 1 mL capacity cell with 1 dm path length. Infrared (IR) spectra were recorded using a thin film supported on KBr disks or dispersed in a KBr pellet. High-resolution ESI mass spectra were recorded on a triple-quadrupole mass spectrometer operating in positive-ion mode.

(1*S*,2*R*,5*S*)-2-Isopropyl-5-methylcyclohexyl (2-(1*H*-Indol-3-yl)ethyl) Carbamate (12). To a stirred solution of tryptamine **10** (5.00 g, 31.3 mmol) and DIPEA (10.9 mL, 62.7 mmol) in 150 mL of CH_2Cl_2 was added (+)-menthyl chloroformate **11** (7.3 mL, 34.4 mmol) dropwise at 0 °C. Then the reaction mixture was warmed to room temperature and stirred for 2 h before it was quenched with saturated aqueous NH_4Cl (120 mL). The resulting mixture was extracted with CH_2Cl_2 (2 × 100 mL), and the organic phase was washed with brine (1 × 100 mL), dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude product was crystallized three times in a mixture of CH_2Cl_2 and petroleum ether at 4 °C to afford 9.8 g (92%) of **12** as an amorphous solid: R_f = 0.4 (EtOAc/petroleum ether, 1/4); ^1H NMR (400 MHz, $CDCl_3$) δ 8.22 (s, 1H), 7.62 (d, J = 7.8 Hz, 1H), 7.37 (d, J = 8.1 Hz, 1H), 7.21 (t, J = 7.4 Hz, 1H), 7.13 (t, J = 7.4 Hz, 1H), 7.00 (s, 1H), 4.72 (s, 1H), 4.58 (dd, J = 10.1, 6.8 Hz, 1H), 3.52 (d, J = 6.0 Hz, 2H), 2.98 (t, J = 6.4 Hz, 2H), 2.06 (d, J = 11.7 Hz, 1H), 1.92 (s, 1H), 1.67 (d, J = 4.3 Hz, 2H), 1.56−1.42 (m, 1H), 1.28 (t, J = 10.6 Hz, 1H), 1.13−1.00 (m, 1H), 0.98−0.85 (m, 8H), 0.81 (d, J = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.5, 136.4, 127.3, 122.1, 119.3, 118.8, 113.0, 111.2, 74.4, 47.3, 41.5, 41.2, 34.3, 31.3, 26.2, 25.8, 23.5, 22.0, 20.8, 16.4; IR (KBr) ν 3413, 2915, 2869, 1690, 1531, 1454, 1263, 1142, 1017, 740 cm^{-1}; $[\alpha]_D^{23}$ = +43.9 (c 1.10, CH_3Cl); HRMS (ESI) m/z calcd for $C_{21}H_{30}N_2O_2Na$ $[M + Na]^+$ 365.2199, found 365.2198.

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Bis((1*S*,2*R*,5*S*)-2-isopropyl-5-methylcyclohexyl) (3a*R*,3′a*R*,8a*R*,8′a*R*)-2,2′,3,3′,8,8a,8′,8′a-Octahydro-1*H*,1′*H*-[3a,3′a-bipyrrolo[2,3-*b*]indole]-1,1′-dicarboxylate (13a) and bis((1*S*,2*R*,5*S*)-2-isopropyl-5-methylcyclohexyl) (3a*S*,3′a*S*,8a*S*,8′a*S*)-2,2′,3,3′,8,8a,8′,8′a-octahydro-1*H*,1′*H*-[3a,3′a-bipyrrolo[2,3-*b*]indole]-1,1′-dicarboxylate (13b). To a stirred solution of **12** (103 mg, 0.30 mmol) in 6 mL of degassed CH_3CN was added *t*-BuOK (37 mg, 0.33 mmol) in one portion at room temperature. The reaction mixture was stirred at the same temperature for 1 h. Then $CuCl_2$ (61 mg, 0.45 mmol) was added at the same temperature in one portion successively and the mixture stirred for 10 h. The reaction mixture was quenched with aqueous HCl (1M, 10 mL), extracted with EtOAc (3 × 20 mL), washed with brine (1 × 20 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue was subjected to flash column chromatography to afford a mixture of **13a** and **13b** and combined with 22 mg of **12**. The mixture of **13a** and **13b** was further purified by reversed-phase preparative HPLC (Agilent Zorbax SB-C18 column, MeOH/H_2O = 95/5) to afford 28 mg (27%) of **13a** as an amorphous solid and 19 mg (19%) of **13b** as an amorphous solid with a ratio of 3:2. On a larger scale, reaction of **12** (1.00 g, 2.90 mmol) provided 251 mg of **13a**, 170 mg of **13b**, and 249 mg of recovered **12**. Dimeric product **13a**: R_f = 0.5 (EtOAc/petroleum ether, 1/4); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22 (d, J = 9.1 Hz, 1.5H), 7.13 (br s, 2.5H), 6.77 (d, J = 7.2 Hz, 2H), 6.63 (d, J = 6.7 Hz, 2H), 5.22 (br s, 1H), 4.85 (d, J = 6.3 Hz, 1H), 4.61 (br s, 2H), 4.47 (d, J = 9.9 Hz, 2H), 3.71 (d, J = 7.6 Hz, 1H), 3.55 (br s, 1H), 2.86 (br s, 2H), 2.70−2.48 (m, 2H), 2.28−1.85 (m, 4H), 1.78−1.34 (m, 9H), 0.97−0.45 (m, 24 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.7, 154.6, 153.6, 150.7, 150.6, 150.3, 150.1, 129.3, 129.2, 129.1, 129.0, 128.6, 128.4, 128.3, 125.5, 124.9, 124.8, 124.4, 119.2, 118.9, 118.5, 118.1, 109.7, 109.6, 109.5, 79.3, 78.8, 78.1, 77.9, 75.3, 75.2, 75.1, 61.84, 61.77, 61.1, 60.8, 47.34, 47.26, 47.2, 45.2, 41.7, 41.6, 34.3, 31.8, 31.7, 31.4, 26.3, 26.2, 23.6, 22.0, 20.8, 20.72, 20.69, 16.5, 16.4; IR (KBr) ν3415, 2955, 2927, 1691, 1608, 1469, 1412, 1202, 1109, 741 cm^{-1}; $[\alpha]_D^{23}$ = +420.0 (c 1.05, $CHCl_3$); HRMS (ESI) m/z calcd for $C_{42}H_{59}N_4O_4$ $[M + H]^+$ 683.4531, found 683.4534. Dimeric product **13b**: R_f = 0.5 (EtOAc/petroleum ether, 1/4); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22−7.07 (m, 4H), 6.85−6.72 (m, 2H), 6.62 (m, 2H), 5.26 (s, 1.2H), 5.26−5.10 (br s, 0.8H), 5.09−4.81 (m, 1.5H), 4.67−4.46 (m, 2.5H), 3.76−3.61 (m, 0.8H), 3.53 (t, J = 9.2 Hz, 1.2H), 2.94−2.80 (m, 2H), 2.50−2.70 (m, 2H), 2.18−1.99 (m, 1H), 1.99−1.80 (m, 5H), 1.74−1.52 (m, 4H), 1.44 (br s, 3.5H), 1.35−1.21 (m, 1.5H), 1.12−0.73 (m, 24H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.7, 154.6, 153.9, 153.8, 150.6, 150.5, 150.2, 150.1, 129.3, 129.1, 129.0 128.6, 128.5, 128.4, 125.7, 125.3, 125.1, 119.1, 118.8, 118.4, 118.1, 109.7, 109.6, 79.4, 79.0, 78.5, 78.4, 75.1, 74.9, 62.0, 61.1, 60.8, 47.4, 47.3, 47.2, 45.5, 45.3, 45.2, 41.6, 41.5, 41.4, 34.2, 31.9, 31.6, 31.39, 31.35, 29.6, 29.3, 26.72, 26.65, 26.2, 26.1, 23.3, 23.2, 22.7, 22.0, 21.0, 20.9, 16.4, 16.2, 14.1; $[\alpha]_D^{23}$ = +291.8 (c 0.60, CH_3Cl); HRMS (ESI) m/z calcd for $C_{42}H_{59}N_4O_4$ $[M + H]^+$ 683.4531, found 683.4530.

***N*-Methyl-2-((*R*)-3-((3a*S*,8a*R*)1-methyl-2,3,8,8a-tetrahydropyrrolo[2,3-*b*]indol-3a(1*H*)-yl)indolin-3-yl)ethan-1-amine (14).** To a stirred solution of **13a** (73 mg, 0.11 mmol) in 11 mL of toluene was added Red-Al (65% in toluene, 0.33 mL, 1.06 mmol) dropwise at room temperature. The reaction mixture was heated at 90 °C, stirred for 1 h, cooled to room temperature, and quenched by the slow addition of MeOH/CH_2Cl_2 (1/19) saturated with ammonia. The resulting mixture was concentrated under reduced pressure, and the residue was purified by flash column chromatography (MeOH/CH_2Cl_2 saturated with ammonia, 1/19) to afford 20 mg (55%) of **14** as a colorless oil: R_f = 0.3 (MeOH/CH_2Cl_2, 1/9); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25−7.17 (t, J = 8.5, 2H), 7.06 (dd, J = 17.6, 7.8 Hz, 2H), 6.72 (q, J = 7.3 Hz, 2H), 6.60 (t, J = 7.6 Hz, 2H), 4.28 (s, 1H), 4.15 (s, 1H), 3.39 (d, J = 10.1 Hz, 1H), 3.26 (d, J = 10.1 Hz, 1H), 2.70−2.59 (m, 1H), 2.52−2.45 (m, 1H), 2.45−2.36 (m, 2H), 2.36−2.26 (m, 5H), 2.26−2.13 (m, 5H), 2.07−1.96 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.6, 151.1, 132.7, 130.4, 128.2, 125.7, 125.6, 118.5, 118.2, 109.7, 109.2, 85.4, 65.8, 53.8, 53.5, 53.1, 48.5, 37.6, 36.5, 35.4, 34.6; IR (KBr) ν 3419, 2925, 1631, 1604, 1484, 1463, 1249, 1154, 1102, 742 cm^{-1}; $[\alpha]_D^{23}$ = +190.3 (c 0.60, CH_3Cl); HRMS (ESI) m/z calcd for $C_{22}H_{29}N_4$ $[M + H]^+$ 349.2387, found 349.2382.

Bis((1*S*,2*R*,5*S*)-2-isopropyl-5-methylcyclohexyl) (3a*R*,3′a*R*,8a*R*,8′a*R*)-8,8′-Dimethyl-2,2′,3,3′,8,8a,8′,8′a-octahydro-1*H*,1′*H*-[3a,3′a-bipyrrolo[2,3-*b*]indole]-1,1′-dicarboxylate (15). To a stirred solution of **13a** (36 mg, 0.05 mmol) in 3 mL of CH_3CN were added formalin (37%, 52 μL, 0.64 mmol), HOAc (15 μL, 0.26 mmol), and $NaBH_3CN$ (17 mg, 0.27 mmol) successively at room temperature. The reaction mixture was stirred at the same temperature for 1 h before it was quenched with saturated aqueous $NaHCO_3$ (10 mL) and extracted with EtOAc (3 × 10 mL), and the organic phase was washed with brine (1 × 10 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The obtained residue was subjected to flash column chromatography on silica gel (EtOAc/petroleum ether, 1/12) to afford 37 mg (100%) of **15** as a colorless oil: R_f = 0.3 (EtOAc/petroleum ether, 1/9); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22−6.96 (m, 4H), 6.74−6.51 (m, 2H), 6.35 (d, J = 7.8 Hz, 2H), 5.53−4.62 (m, 2H), 4.58−4.25 (m, 2H), 3.96−3.63 (m, 2H), 3.03−2.68 (m, 8H), 2.56−2.28 (m, 2H), 2.21−1.88 (m, 4H), 1.85−1.20 (m, 6H), 1.53−1.14 (m, 6H), 1.11−0.37 (m, 26H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.1, 151.6, 129.4, 129.2, 128.6, 124.2, 123.9, 117.3, 116.8, 106.0, 105.7, 83.7, 82.9, 75.1, 61.6, 61.1, 60.4, 47.4, 45.2, 44.9, 41.6, 41.1, 34.3, 33.0, 32.8, 32.5, 32.2, 31.9, 31.2, 29.7, 26.4, 25.9, 25.5, 23.7, 23.2, 22.7, 22.0, 21.2, 20.6, 16.6, 15.9; IR (KBr) ν 2954, 2870, 1702, 1605, 1493, 1406, 1227, 1099, 994, 890, 744 cm^{-1}; $[\alpha]_D^{23}$ = +390.5 (c 0.82, CH_3Cl); HRMS (ESI) m/z calcd for $C_{44}H_{63}N_4O_4$ $[M + H]^+$ 711.4844, found 711.4850.

(+)-Folicanthine (2). To a stirred solution of product **15** (13 mg, 0.02 mmol) in 2 mL of toluene was added Red-Al (65% in toluene, 57 uL, 0.18 mmol) dropwise at room temperature. Then the reaction mixture was heated at reflux and stirred for 1 h. After being allowed to cool to room temperature, the reaction mixture was quenched by the slow addition of MeOH/CH_2Cl_2 (1/20) saturated with ammonia. The resulting mixture was concentrated under reduced pressure, and the residue was subjected to flash column chromatography on silica gel (MeOH/CH_2Cl_2 saturated with ammonia, 1/60) to afford 6 mg (88%) of (+)-folicanthine (**2**) as a colorless solid: R_f = 0.3 (MeOH/CH_2Cl_2, 1/9); ^{1}H NMR (400 MHz, $CDCl_3$, 50 °C) δ 6.97 (t, J = 7.8 Hz, 2H), 6.93 (d, J = 7.3 Hz, 2H), 6.50 (t, J = 7.4 Hz, 2H), 6.26 (d, J = 7.8 Hz, 2H), 4.35 (s, 2H), 2.99 (s, 6H), 2.63−2.61 (m, 2H), 2.50−2.33 (m, 10H), 2.02−1.90 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, 50 °C) δ 153.0, 132.9, 128.1, 123.7, 116.7, 105.8, 92.1, 62.8, 52.7, 38.0, 35.29, 35.26; IR (KBr) ν 3045, 2926, 1602, 1491, 1346, 1257, 1158, 1019, 919, 739 cm^{-1}; $[\alpha]_D^{23}$ = +213.1 (c 0.15, MeOH); HRMS (ESI) m/z calcd for $C_{24}H_{31}N_4$ $[M + H]^+$ 375.2543, found 375.2539.

Dimethyl (3a*R*,3′a*R*,8a*R*,8′a*R*)-2,2′,3,3′,8,8a,8′,8′a-Octahydro-1*H*,1′*H*-[3a,3′a-bipyrrolo[2,3-*b*]indole]1,1′-dicarboxylate (16) and Dimethyl (4b*R*,5*R*,10b*R*,11*S*)5,6,11,12-tetrahydro-5,10b:11,4b-bis(epiminoethano)dibenzo[*c*,*h*][2,6]-naphthyridine-13,18-dicarboxylate (17). To a stirred solution of **13a** (100 mg, 0.15 mmol) in 4 mL of EtOH was added KOH (2 M in EtOH, 5.9 mL, 11.8 mmol) dropwise at room temperature. Then the reaction mixture was heated to 155 °C in a sealed tube and stirred for 48 h. After being allowed to cool to room temperature, the reaction mixture was quenched with saturated NH_4Cl and extracted with $CHCl_3$ (5 × 10 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude product was directly used in the next step without further purification.

To a stirred solution of the above crude product in 8 mL of CH_2Cl_2 were added Et_3N (62 μL, 0.45 mmol) and $ClCO_2Me$ (25 μL, 0.33 mmol) dropwise at 0 °C successively. After being stirred at the same temperature for 5 min before it was quenched with saturated aqueous NH_4Cl (10 mL) and extracted with CH_2Cl_2 (3 × 10 mL), the organic phase was washed with brine (1 × 10 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The obtained residue was subjected to flash column chromatography on silica gel (acetone/CH_2Cl_2, 1/60) to afford 37 mg (58%, over two steps) of **17** as colorless oil and 12 mg (19% over two steps) of **16** as a colorless oil. Carbamate **17**: R_f = 0.4 (EtOAc/petroleum ether, 2/3); ^{1}H NMR (400

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MHz, $CDCl_3$) δ 7.22−7.09 (m, 2H), 6.88 (t, J = 7.5 Hz, 2H), 6.64 (t, J = 7.4 Hz, 2H), 6.29 (d, J = 7.9 Hz, 2H), 5.92 (2br s, 2H), 4.20−3.89 (m, 2H), 3.74 (s, 6H), 2.96 (d, J = 9.8 Hz, 2H), 2.48 (td, J = 13.2, 5.8 Hz, 2H), 1.42 (d, J = 9.9 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.8, 143.2, 127.4, 124.8, 122.3, 117.6, 112.6, 63.1, 52.8, 36.7, 35.9, 30.1, 29.7; IR (KBr) ν 3411, 2937, 2856, 1606, 1477, 1323, 1055, 745 cm^{-1}; $[\alpha]_D^{23}$ = −589.7 (c 0.81, CH_3Cl); HRMS (ESI) m/z calcd for $C_{24}H_{27}N_4O_4$ $[M + H]^+$ 435.2027, found 435.2030. Carbamate **16**: R_f = 0.3 (EtOAc/petroleum ether, 2/3); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23−7.08 (m, 4H), 6.86−6.74 (m, 2H), 6.67 (t, J = 8.6 Hz, 2H), 5.12−4.86 (m, 2H), 3.69−3.62 (m, 7H), 3.55 (t, J = 9.1 Hz, 1H), 2.88 (td, J = 10.7, 6.0 Hz, 2H), 2.66−2.52 (m, 2H), 2.17−1.97 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.2, 154.3, 150.6, 150.2, 129.3, 129.2, 128.3, 128.1, 125.3, 118.9, 118.8, 118.5, 109.93, 109.87, 79.2, 79.0, 78.4, 61.7, 60.8, 60.7, 52.5, 52.3, 45.5, 45.3, 31.6, 31.5, 31.3; IR (KBr) ν 3358, 2951, 1691, 1605, 1451, 1383, 1244, 1072, 901, 744 cm^{-1}; $[\alpha]_D^{23}$ = +414.1 (c 0.41, CH_3Cl); HRMS (ESI) m/z calcd for $C_{24}H_{27}N_4O_4$ $[M + H]^+$ 435.2027, found 435.2023.

(+)-Chimonanthine (1). To a stirred solution of **16** (38 mg, 0.09 mmol) in 9 mL of toluene was added Red-Al (65% in toluene, 0.27 mL, 0.88 mmol) dropwise at room temperature. Then the reaction mixture was heated at reflux and stirred for 1 h. After being allowed to cool to room temperature, the reaction mixture was quenched by the slow addition of MeOH/CH_2Cl_2 (1/20) saturated with ammonia. The resulting mixture was concentrated under reduced pressure, and the residue was subjected to flash column chromatography on silica gel (MeOH/CH_2Cl_2 saturated with ammonia, 1/20) to afford 25 mg (83%) of (+)-chimonanthine (**1**) as a colorless solid: R_f = 0.2 (MeOH/CH_2Cl_2, 1/9); ^{1}H NMR (400 MHz, $CDCl_3$, 50 °C) δ 7.18 (d, J = 7.4 Hz, 2H), 6.98 (t, J = 7.5 Hz, 2H), 6.65 (t, J = 7.4 Hz, 2H), 6.53 (d, J = 7.8 Hz, 2H), 4.41 (s, 2H), 4.24 (s, 2H), 2.61−2.51 (m, 6H), 2.32 (s, 6H), 2.05 (dd, J = 10.8, 4.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, 50 °C) δ 150.8, 133.4, 128.1, 124.4, 118.6, 109.2, 85.3, 63.6, 52.7, 37.1, 35.7; IR (KBr) ν 3424, 2930, 1605, 1484, 1465, 1354, 1317, 1251, 1158, 747 cm^{-1}; $[\alpha]_D^{23}$ = +228.1 (c 0.27, EtOH); HRMS (ESI) m/z calcd for $C_{22}H_{27}N_4$ $[M + H]^+$ 347.2230, found 347.2228.

(−)-Calycanthine (3). *Reduction of Nb-methoxycarbonyl.* To a stirred solution of **17** (24 mg, 0.06 mmol) in 6 mL of toluene was added Red-Al (65% in toluene, 0.17 mL, 0.55 mmol) dropwise at room temperature. Then the reaction mixture was heated at 90 °C and stirred for 1 h. After being allowed to cool to room temperature, the reaction mixture was quenched by the slow addition of MeOH/CH_2Cl_2 (1/20) saturated with ammonia. The resulting mixture was concentrated under reduced pressure,, and the residue was purified by flash column chromatography (MeOH/CH_2Cl_2 saturated with ammonia, 1/60) to afford 16 mg (84%) of (−)-calycanthine (**3**).

Direct N-Methylation. To a stirred solution of **13a** (100 mg, 0.15 mmol) in 4 mL of EtOH was added KOH (2 M in EtOH, 5.9 mL, 11.8 mmol) dropwise at room temperature. Then the reaction mixture was heated to 155 °C in a sealed tube and stirred for 48 h. After being allowed to cool to room temperature, the reaction mixture was quenched with saturated NH_4Cl and extracted with $CHCl_3$ (5 × 10 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude product was directly used in the next step without further purification.

To a stirred solution of above crude product in 6 mL of CH_3CN/CH_2Cl_2 (2/1) were added K_2CO_3 (81 mg, 0.59 mmol) and MeI (55 μL, 0.91 mmol) at 0 °C succcessively. After being stirred at room temperature for 4 h, the reaction mixture was quenched with saturated aqueous NH_4Cl (10 mL) and extracted with CH_2Cl_2 (5 × 10 mL), and the organic phase was dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The obtained residue was subjected to flash column chromatography on silica gel (MeOH/CH_2Cl_2 saturated with ammonia, 1/60) to afford 27 mg (54%, over two steps) of (−)-calycanthine (**3**) as a colorless solid: R_f = 0.5 (MeOH/CH_2Cl_2, 1/15); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.00 (d, J = 7.7 Hz, 2H), 6.81 (t, J = 7.5 Hz, 2H), 6.54 (t, J = 7.4 Hz, 2H), 6.27 (d, J = 7.9 Hz, 2H), 4.58 (br s, 2H), 4.32 (s, 2H), 3.13 (td, J = 13.2, 5.5 Hz, 2H), 2.63 (dd, J = 11.3, 5.0 Hz, 2H), 2.42 (s, 6H), 2.26 (td, J = 12.9, 4.0 Hz, 2H), 1.29 (dd, J = 13.4, 3.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.2, 126.5, 124.9, 124.4, 116.4, 112.0, 71.0, 46.5, 42.5, 35.9, 31.6; IR (KBr) ν 3420, 2924, 2852, 1604, 1495, 1311, 1039, 1023, 743 cm^{-1}; $[\alpha]_D^{23}$ = −599.9 (c 0.50, EtOH); HRMS (ESI) m/z calcd for $C_{22}H_{27}N_4$ $[M + H]^+$ 347.2230, found 347.2229.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b01907.

^{1}H and ^{13}C NMR spectra of all new compounds described in the Experimental Section (PDF)

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Notes

The authors declare no competing financial interest.

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