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Ni-Catalyzed Reductive Homocoupling of Unactivated Alkyl Bromides at Room Temperature and Its Synthetic Application

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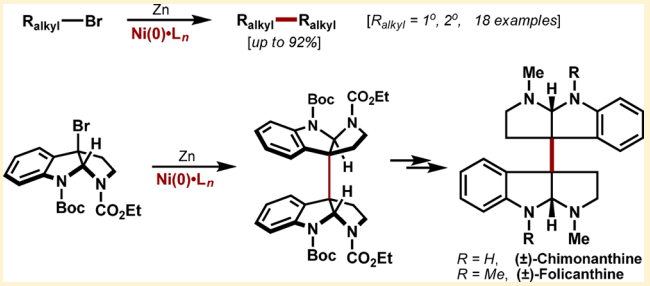
Supporting Information

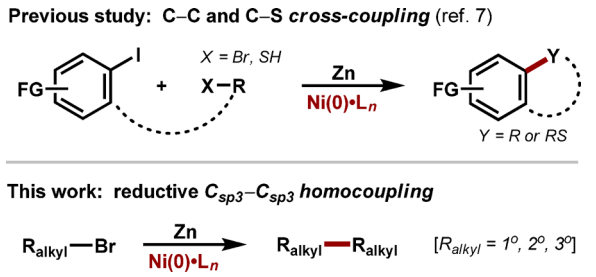
ABSTRACT: A room-temperature Ni-catalyzed reductive approach to homocoupling of unactivated primary, secondary, and tertiary alkyl bromides is described. The catalytic system can be easily generated from air-stable and cheap materials and demonstrates broad functional group tolerance, thus allowing facile access to useful dimeric triterpene and lignan-like molecules. Moreover, the dimerization of tertiary bromide **6** efficiently establishes sterically hindered vicinal quaternary carbons (C3a and C3a′), which is a key linkage of intriguing bispyrrolo[2,3-*b*]indoline alkaloids, thereby enabling us to complete the total syntheses of racemic chimonanthine (**9**) and folicanthine (**10**). In addition, this dimerization method can be expanded to the highly stereoselective synthesis of bisperhydrofuro[2,3-*b*]furan (**5a**) and the dimeric spiroketal **5b**, signifying the involvement of possible radical species.



INTRODUCTION

Dimeric molecules can be found in a wide array of naturally occurring products and pharmaceuticals.[1] They have attracted increasing attention because of their unique biological functions compared with the respective monomers. Thus, a number of efficient methodologies for stereoseletive dimerization of two monomers have appeared, among which the biomimetic Diels–Alder cycloaddition reaction[2] has demonstrated its powerful capacity. Alternatively, transition-metal-catalyzed reductive homocoupling of organohalides is a valuable transformation, but the current advances are mainly directed toward C(sp^2)–C(sp^2) bond construction,[3] as is evident for the synthesis of biaryl or 1,3-diene motifs in the target molecules. Moreover, the harsh conditions (large excess of Na) associated with the classic Wurtz dimerization[4] of alkyl halides largely limit its synthetic value. Hence, the development of a mild catalytic C(sp^3)–C(sp^3) reductive homocoupling of unactivated alkyl halides is of high importance,[5] especially considering its potential application in the total synthesis of complex dimeric molecules. Indeed, such protocols have been nicely documented in Leigh's Ni/Pybox-catalyzed[5e] and Weix's Ni/terpy-catalyzed[5f] homocouplings and Gong's related cross-coupling[6] conditions. However, none of these studies has been used in the synthesis of complex molecules. In line with our recent work on inter- and intramolecular C–C/C–S bond-forming reactions (Scheme 1),[7] herein we report analogous Ni/Ec- and Ni/Bipy-catalyzed reductive homocouplings of 1°, 2°, and 3° alkyl bromides, with emphasis on their applications in the expeditious syntheses of dimeric sesquiterpene, lignan, and pyrrolo[2,3-*b*]indoline alkaloids, respectively.

Scheme 1. Cross-Coupling versus Homocoupling



RESULTS AND DISCUSSION

We first carried out a model study with 2-phenylethyl bromide as the substrate (Table 1). The Ni(0)·2EC·Py catalyst can be easily prepared in situ from a mixture of Zn, $NiCl_2$, ethyl crotonate (EC), and pyridine,[7] where EC acts as a π-ligand to Ni. With a substoichiometric amount of this catalyst, the desired reductive homocoupling indeed proceeded in DMF at room temperature, and the dimeric product **1a** was formed in 35% yield (entry 1) along with 40% recovery of the starting material (SM). A good result was obtained with 30 mol % Ni complex, albeit at a lower reaction rate (entry 2). Considering both the yield and reaction time (entries 3–6), CH_3CN was identified as the best solvent. When the Ni catalyst loading was lowered to 15 mol %, the triggered homocoupling reaction was

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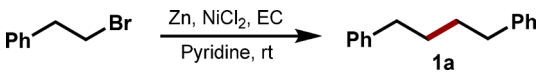
Table 1. Optimization of Conditions for Reductive Homocoupling[a]



entry	equiv of $NiCl_2$	equiv of Zn	solvent	time (h)	yield (%)[b] (2a:SM)
1	0.5	5	DMF	4	35:40
2	0.3	3	DMF	12	46:33
3	0.3	3	dioxane	8	44:40
4	0.3	3	dioxane	24	56:38
5	0.3	3	MeOH	5	78:0
6	0.3	3	CH_3CN	1	78:0
7	0.15	1.5	CH_3CN	4	96[c]:0

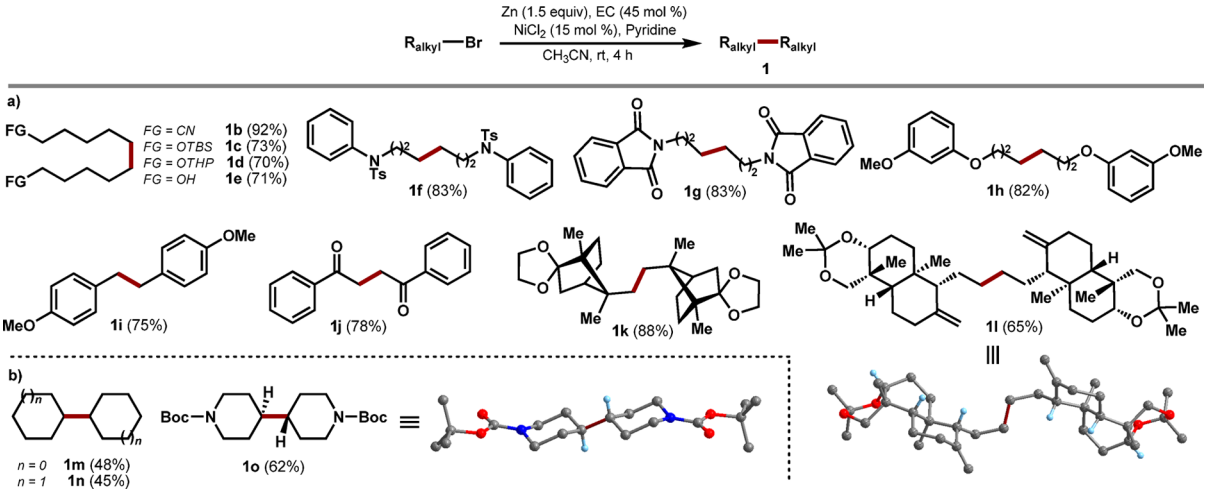
[a]The reaction was run on a 1 mmol scale. A mixture of Zn (indicated by table), $NiCl_2$ (indicated by table), EC (3 equiv relative to Ni), and pyridine (0.5 mL) was employed for the generation of Ni(0)·2EC·Py at 55 °C, and then a solution of 2-phenylethyl bromide in CH_3CN (2 mL) was added to the above Ni(0) complex dropwise over a 10 s period at RT. [b]The yields were estimated by ^1H NMR spectroscopic analysis with diethyl phthalate as an internal standard. [c]The isolated yield was 95%.

completed within 4 h with a 95% isolated yield of **1a** as a result of further suppression of competitive reduction of the bromide (entry 7).

With the above optimized conditions in hand, we then investigated the reductive homocouplings of various functionalized bromides (Scheme 2). To our delight, the primary bromides bearing the electrophilic cyano group and hydroxyl protecting groups (OTBS and OTHP) reacted smoothly, affording the corresponding dimeric products **1b–d** in good yields. In particular, the substrate with a free hydroxyl group also reacted smoothly under the present conditions, and 1,10-decanediol (**1e**) was isolated in 71% yield, demonstrating the mild nature of this homocoupling reaction, as the acidic proton of the hydroxyl group cannot be compatible with sodium metal imparted from the Wurtz coupling conditions. The desired dimers with differently protected amino groups such as NTs (**1f**) and NPhth (**1g**) were obtained in high yields. Other bromide-containing benzene rings were also suitable, providing *m*-methoxyphenol-derived dimer **1h** in 82% yield. Activated alkyl halides such as *p*-methoxybenzyl bromide[8] and α-bromoacetophenone were next tried, and the corresponding dibenzyl (**1i**) and 1,4-diketone (**1j**) were produced in 75% and 78% yield, respectively. Unprecedented homocoupling of a neopentyl bromide such as ethylene ketal-protected (+)-9-bromocamphor could be realized despite its notorious steric hindrance, leading to the chiral dimer **1k** in 88% yield. The sophisticated primary bromide with a labile acetonide, which is degraded from the natural diterpene andrographolide,[7a] was exposed to these homocoupling conditions as well, and the expected hexacycle (−)-**1l** was isolated in 65% yield. All of the chiral centers in the starting bromide were preserved, as confirmed by the X-ray crystal structure of **1l** (Scheme 2a inset; selected H atoms have been omitted for clarity).[9] This case provided an alternative access to analogues of onocerane-type triterpenes, which were previously synthesized by Cp_2TiCl-catalyzed regioselective homocoupling of activated allylic bromides instead.[10] In addition, secondary bromides can also participate the above homocoupling (Scheme 2b). Cyclopentyl and cyclohexyl bromide gave moderate yields of the corresponding homodimers **1m** and **1n** because of their volatile nature. Moreover, reductive homocoupling of Boc-protected 4-bromopiperidine afforded the desired 4,4′-bipiperidine **1o** in 62% yield, suggesting that this common amino protecting group (Boc) is also tolerated. The most stable conformation of **1o** was unambiguously established by single-crystal X-ray analysis:[9] the newly formed $C(sp^3)–C(sp^3)$ bond occupies equatorial positions in the respective chair conformations of the two piperidine rings, whereas two tertiary hydrogen atoms adopt a 1,2-*anti* axial orientation (Scheme 2b inset; selected H atoms have been omitted for clarity).

Because of our ongoing interest in the total synthesis of bioactive lignans,[11] we next utilized the above-developed methodology for the synthesis of their dimers (Scheme 3). We chose natural (−)-podophyllotoxin as a monomer precursor because extensive studies of pharmaceutical chemistry toward this natural product[12] and its monomer derivatives have led to the invention of several anticancer drugs such as etoposide and etopophos. However, the development of its dimeric derivatives is relatively rare,[13] therefore hampering further investigation of their structure–activity relationship. Aiming to provide a potential drug lead, we synthesized a new C7–C7 dimeric deoxypodophyllotoxin, **3**, from the readily available bromide **2** in 40% isolated yield along with 30%

Scheme 2. Homocouplings of Primary and Secondary Bromides



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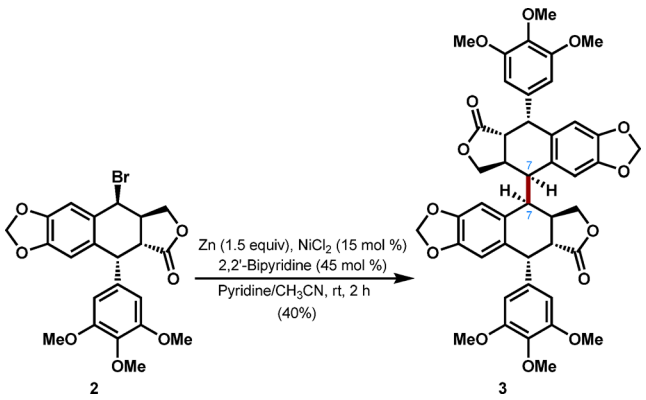
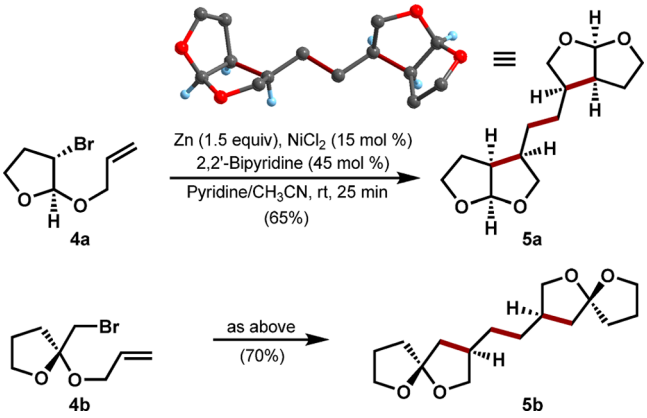
Scheme 3. Stereoselective Dimerization of Podophyllotoxin-Derived Bromide



recovery of (epi)podophyllotoxin. In this Ni-catalyzed dimerization, the EC ligand was replaced by 2,2′-bipyridine,[14] which proved to be best. It is noteworthy that only dimer **3** ($[\alpha]_D^{27}$ = −175) as the sole diastereomer could be detected in the reaction mixture, indicating that excellent stereoselectivity was achieved during this Ni-catalyzed assembly.

On the basis of our previous mechanistic hypotheses about the reductive cross-coupling of alkyl halides,[7a] a similar catalytic cycle with Ni^{I}–Ni^{III} species[15] probably occurs for the present homocoupling. However, the involvement of radical species[16] is also possible, as the tandem reactions demonstrated in Scheme 4 could be rationalized accordingly. When β-bromoacetal **4a**

Scheme 4. Stereoselective Cyclization–Homocoupling Cascade



was subjected to the Ni catalytic system generated in situ from 2,2′-bipyridine, the unprecedented cyclization–homocoupling cascade indeed took place, affording ethylene-bridged bisperhydrofuro[2,3-*b*]furan **5a** as the only diastereomer in 65% yield. Its *cis*/*syn*-fused relationship was unambiguously established by single-crystal X-ray analysis (Scheme 4 inset; selected H atoms have been omitted for clarity).[9] Notably, three C–C bonds and four stereogenic centers were simultaneously formed in a single operation. A similar stereoselective tandem reaction also occurred with β-bromoketal **4b**, and the unique bisspiroketal **5b** was obtained in 70% yield under the same conditions.

Recently, Zultanski and Fu[17] reported the first Ni-catalyzed Suzuki arylations of tertiary alkyl halides; however, reductive homocouplings of this kind of challenging substrate with the aid of Ni catalysts have not been found to date, to the best of our knowledge. Thus, we expanded the substrate scope of the above homocoupling reactions to tertiary bromide **6** (Scheme 5) in order to realize the total synthesis of chimonanthine (**9**) and folicanthine (**10**).[18,19] These two natural products were isolated from dendrobatid frog and various plants,[20] and they are the simplest and typical members of the C3a–C3a′-bispyrrolo[2,3-*b*]indoline alkaloid family.[21] Their challenging structure and biological activities have attracted significant attention from the synthetic community, and especially they can serve as a versatile platform for the development of novel synthetic methods such as the relevant Co^{I}-mediated dimerization by Movassaghi.[19d] As shown in Scheme 5, our strategy involves Ni-catalyzed reductive homocoupling of tertiary bromide (±)-**6** to establish two vicinal quaternary carbons (C3a and C3a′) with steric congestion. To this end, treatment of tryptamine with ethyl chloroformate followed by protection of N_a with di-*tert*-butyl dicarbonate provided N_a-Boc-N_b-ethoxycarbonyltryptamine in 80% yield over two steps. Following the protocol by de Lera and co-workers,[22] the desired racemic precursor **6** can be prepared in 92% yield and sufficient amount, which set the stage for the key reductive homocoupling. When this tricyclic bromide was subjected to the optimized Ni catalytic system, the C_2-symmetric bispyrrolo-[2,3-*b*]indoline **7** with the connection of vicinal quaternary stereocenters was obtained in 21% yield. The *meso* isomer **7′** resulting from the dimerization of **6** and *ent*-**6** was also isolated in 22% yield. Its structure was unambiguously assigned by single-crystal X-ray analysis (Scheme 5 inset; selected H atoms have been omitted for clarity).[9] Starting from **7**, successive steps to the ultimate targets (**9** and **10**) were straightforward. Cleavage of the two Boc protecting groups in **7** using iodotrimethylsilane gave rise to bisester **8** in 87% yield. Reduction of the N_b-ethoxycarbonyl groups in **8** with bis(2-methoxyethoxy)aluminum hydride (Red-Al) afforded (±)-chimonanthine (**9**) in 82% yield. Eventually, methylation of N_a in **9** completed the synthesis of (±)-folicanthine (**10**) in 87% yield. The spectroscopic data for the synthetic samples were consistent with those published in the previous syntheses.[18a,c,19a–d]

CONCLUSION

We have developed a versatile method for $C(sp^3)$–$C(sp^3)$ bond construction based on reductive homocoupling reactions of various alkyl halides catalyzed by a Ni complex generated in situ from air-stable and cheap materials. Exceptionally mild conditions and broad functional groups tolerance make this method especially valuable for accessing structurally complex dimeric natural-product-like molecules such as **11** and **3**. Moreover, the successful syntheses of racemic chimonanthine (**9**) and folicanthine (**10**) using this protocol as a key step further demonstrates its remarkable power for the establishment of sterically hindered vicinal all-carbon quaternary stereocenters. We believe that this method holds great promise in the expeditious synthesis of many other dimeric natural products and pharmaceutical molecules.

EXPERIMENTAL SECTION

General. For product purification by flash column chromatography, silica gel (200–300 mesh) and petroleum ether (bp 60–90 °C) were used. All solvents were purified and dried by standard techniques and distilled prior to use. Organic extracts were dried over Na_2SO_4 or $MgSO_4$, unless otherwise noted. Experiments were conducted under

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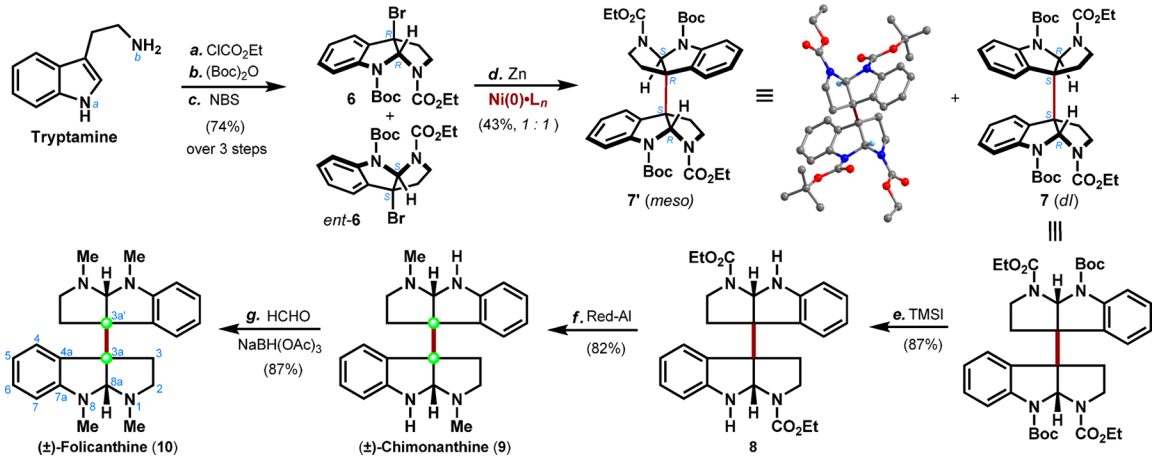
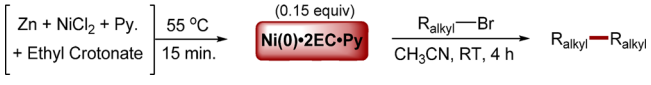
Scheme 5. Total Syntheses of (±)-Chimonanthine and (±)-Folicanthine[a]



[a]Reagents and conditions: (a) $ClCO_2Et$ (1.0 equiv), $CHCl_3$/aq. NaOH, 0 °C, 10 min, then rt, 1.5 h, 91%; (b) $(n\text{-}Bu)_4NHSO_4$ (0.1 equiv), NaOH (5.0 equiv), CH_2Cl_2, rt, 30 min, then $(Boc)_2O$ (1.1 equiv), 0 °C to rt, 2 h, 88%; (c) NBS (1.0 equiv), PPTs (1.0 equiv), CH_2Cl_2, rt, 10 min, 92%; (d) Zn (1.5 equiv), $NiCl_2$ (15 mol %), 2,2′-bipyridine (45 mol %), pyridine/CH_3CN, 25 °C, 30 min, 43%; (e) TMSI (3.0 equiv), CH_3CN, 0 °C to rt, 4 h, 87%; (f) Red-Al (10.0 equiv), toluene, rt to 90 °C, 1.5 h, 82%; (g) aq. HCHO (10.0 equiv), $NaBH(OAc)_3$ (10.0 equiv), rt, CH_3CN, 1.5 h, 87%.

an argon or nitrogen atmosphere in oven-dried or flame-dried glassware with magnetic stirring, unless otherwise specified. NMR spectra were measured on 300, 400, and 600 MHz instruments at room temperature. High-resolution mass spectral data were measured with electrospray ionization (ESI). Infrared spectra were recorded on an FT-IR spectrophotometer. The following chemicals were purchased and used as received: Zn (99.9%, powder), $NiCl_2$ (99%), pyridine (99.5%, SuperDry, with molecular sieves), DMF (99.8%, SuperDry, with molecular sieves), CH_3CN (99.9%, SuperDry, with molecular sieves).

General Procedure for the Homocoupling Reaction Catalyzed by the Ni(0)·2EC·Py Complex. To a stirred slurry of Zn (195 mg, 1.5 mmol) in pyridine (0.5 mL) was added ethyl crotonate (0.06 mL, 0.45 mmol) at room temperature. Under vigorous stirring, $NiCl_2$ (19 mg, 0.15 mmol) was added to the above mixture. The temperature then rose to 55 °C, and stirring was continued for 15 min. The resulting red-brown Ni(0)·2EC·Py complex was cooled to room temperature, and a solution of the alkyl bromide (1.0 mmol) in CH_3CN (2 mL) was added dropwise over a 10 s period. After 4 h, the mixture was filtered with a short plug (elution with 30 mL of Et_2O), washed with water and brine, dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by flash chromatography on silica gel to afford desired dimeric product.



1a[5f] was prepared as a colorless solid (95% yield) according to the general procedure. R_f = 0.20 (petroleum ether); mp 54−55 °C. IR (film): ν_{max} = 3057, 2931, 2854, 1600, 1493, 1459, 1341, 1063, 1028, 907, 750, 700 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.27 (t, J = 8.0 Hz, 4H), 7.20−7.16 (m, 2H), 7.17 (d, J = 8.0 Hz, 4H), 2.63 (t, J = 6.8 Hz, 4H), 1.67 (quint, J = 4.0 Hz, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 142.5 (2C), 128.4 (4C), 128.2 (4C), 125.6 (2C), 35.8 (2C), 31.1 (2C). EI-MS (70 eV): m/z 210 $[M]^+$.

1b[23] was prepared as a colorless oil (92% yield) according to the general procedure. R_f = 0.40 (petroleum ether/EtOAc = 4:1). IR (film): ν_{max} = 2930, 2857, 2245, 1607, 1464, 1426, 1354, 1328, 1242, 1217, 1135, 1071, 845, 724 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 2.34 (t, J = 7.2 Hz, 4H), 1.66 (quint, J = 7.2 Hz, 4H), 1.45 (quint, J = 7.2 Hz, 4H), 1.31 (brs, 8H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 119.8 (2C), 29.1 (2C), 28.63 (2C), 28.56 (2C), 25.3 (2C), 17.1 (2C). ESI-MS: m/z 193.3 $[M + H]^+$.

1c[24] was prepared as a colorless oil (73% yield) according to the general procedure. R_f = 0.20 (petroleum ether/EtOAc = 4:1). IR (film): ν_{max} = 2930, 2899, 2857, 1467, 1387, 1361, 1253, 1101, 1006, 837, 775, 661 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 3.60 (t, J = 6.8 Hz, 4H), 1.51 (quint, J = 6.8 Hz, 4H), 1.28 (brs, 12H), 0.90 (s, 18H), 0.05 (s, 12H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 63.3 (2C), 32.9 (2C), 29.6 (2C), 29.4 (2C), 26.0 (6C), 25.8 (2C), 18.4 (2C), −5.3 (4C). ESI-MS: m/z 403.4 $[M + H]^+$.

1d[25] was prepared as a colorless oil (70% yield) according to the general procedure. R_f = 0.22 (petroleum ether/EtOAc = 4:1). IR (film): ν_{max} = 2931, 2856, 1457, 1351, 1261, 1200, 1124, 1075, 1031, 986, 906, 870, 814 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 4.57 (t, J = 4.4 Hz, 2H), 3.91−3.85 (m, 2H), 3.73 (dt, J = 6.8, 9.2 Hz, 2H), 3.49 (dd, J = 4.8, 10.4 Hz, 2H), 3.38 (dt, J = 6.8, 9.6 Hz, 2H), 1.87−1.79 (m, 2H), 1.76−1.68 (m, 2H), 1.62−1.51 (m, 12H), 1.40−1.25 (m, 12H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 98.8 (2C), 67.7 (2C), 62.3 (2C), 30.7 (2C), 29.7 (2C), 29.5 (2C), 29.4 (2C), 26.2 (2C), 25.5 (2C), 19.7 (2C). ESI-MS: m/z 360.4 $[M + NH_4]^+$.

1e[26] was prepared as a colorless solid (71% yield) according to the general procedure. R_f = 0.23 (petroleum ether/EtOAc = 4:1); mp 63−65 °C. IR (film): ν_{max} = 3405, 3338, 2924, 2849, 1460, 1361, 1057, 1018, 969, 727, 616 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 3.64 (t, J = 6.8 Hz, 4H), 1.56 (quint, J = 6.8 Hz, 4H), 1.47 (s, 2H, −O*H*), 1.37−1.27 (m, 12H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 63.0 (2C), 32.7 (2C), 29.5 (2C), 29.4 (2C), 25.7 (2C). ESI-MS: m/z 175.3 $[M + H]^+$.

1f[27] was prepared as a colorless solid (83% yield) according to the general procedure. R_f = 0.20 (petroleum ether/EtOAc = 4:1); mp 156−157 °C. IR (film): ν_{max} = 3059, 2930, 2859, 1596, 1491, 1454, 1347, 1214, 1158, 1075, 908, 816, 771, 698, 657, 576, 549 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.44 (d, J = 8.4 Hz, 4H), 7.30−7.26 (m, 6H), 7.22 (d, J = 8.0 Hz, 4H), 7.02−6.98 (m, 4H), 3.47 (t, J = 6.8 Hz, 4H), 2.40 (s, 6H), 1.33 (t, J = 5.6 Hz, 4H), 1.26 (d, J = 6.0 Hz, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.2 (2C), 138.9 (2C), 135.0 (2C), 129.2 (4C), 128.8 (4C), 128.6 (4C), 127.7 (2C), 127.5 (4C), 50.1 (2C), 27.8 (2C), 25.7 (2C), 21.4 (2C). ESI-MS: m/z 577.3 $[M + H]^+$.

1g[28] was prepared as a colorless solid (83% yield) according to the general procedure. R_f = 0.20 (petroleum ether/EtOAc = 4:1); mp 180−181 °C. IR (film): ν_{max} = 2929, 2858, 1765, 1610, 1466, 1436, 1398, 1371, 1063, 970, 717, 625, 529 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.83 (dd, J = 3.2, 5.6 Hz, 4H), 7.70 (dd, J = 3.2, 5.6 Hz, 4H), 3.67 (t, J = 7.2 Hz, 4H), 1.67 (quint, J = 6.8 Hz, 4H), 1.39 (quint, J = 3.6 Hz, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.3 (4C), 133.7 (4C), 132.0 (4C), 123.0 (4C), 37.8 (2C), 28.3 (2C), 26.3 (2C). ESI-MS: m/z 377.3 $[M + H]^+$.

1h was prepared as a colorless solid (82% yield) according to the general procedure. R_f = 0.25 (petroleum ether/EtOAc = 2:1); mp 142−143 °C. IR (film): ν_{max} = 2939, 2866, 2837, 1598, 1494, 1454,

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1394, 1337, 1288, 1262, 1201, 1154, 1089, 1047, 1025, 922, 839, 813, 762, 687 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.17 (t, J = 8.0 Hz, 2H), 6.50 (d, J = 8.0 Hz, 2H), 6.49 (d, J = 8.4 Hz, 2H), 6.47 (d, J = 2.0 Hz, 2H), 3.95 (t, J = 6.4 Hz, 4H), 3.79 (s, 6H), 1.81 (quint, J = 6.4 Hz, 4H), 1.53 (quint, J = 3.6 Hz, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.8 (2C), 160.4 (2C), 129.8 (2C), 106.7 (2C), 106.2 (2C), 101.0 (2C), 67.8 (2C), 55.2 (2C), 29.2 (2C), 25.9 (2C). ESI-MS: m/z 331.3 $[M + H]^+$. HRMS (ESI) m/z: calcd for $C_{20}H_{27}O_4^+$ $[M + H]^+$ 331.1904, found 331.1905.

1i[29] was prepared as a colorless solid (75% yield) according to the general procedure. R_f = 0.30 (petroleum ether/EtOAc = 2:1); mp 126−127 °C. IR (film): ν_{max} = 2916, 2850, 1606, 1580, 1508, 1457, 1298, 1243, 1175, 1028, 828, 540 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.13 (d, J = 8.8 Hz, 4H), 6.87 (d, J = 8.8 Hz, 4H), 3.83 (s, 6H), 2.88 (s, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.7 (2C), 133.9 (2C), 129.3 (4C), 113.6 (4C), 55.2 (2C), 37.2 (2C). EI-MS (70 eV): m/z 242 $[M]^+$.

1j[30] was prepared as a colorless solid (78% yield) according to the general procedure. R_f = 0.30 (petroleum ether/EtOAc = 2:1); mp 142−143 °C. IR (film): ν_{max} = 2906, 1679, 1592, 1444, 1397, 1373, 1354, 1257, 1223, 1179, 1066, 991, 774, 737, 693 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 8.05 (d, J = 7.2 Hz, 4H), 7.61−7.56 (m, 2H), 7.49 (t, J = 7.2 Hz, 4H), 3.48 (s, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 198.7 (2C), 136.7 (2C), 133.2 (2C), 128.6 (4C), 128.1 (4C), 32.6 (2C). ESI-MS: m/z 239.2 $[M + H]^+$.

1k was prepared as a colorless solid (88% yield) according to the general procedure. R_f = 0.55 (petroleum ether/EtOAc = 10:1); $[\alpha]_D^{24}$ = +42 (c = 0.5, $CHCl_3$); mp 215−216 °C. IR (film): ν_{max} = 2965, 2875, 1607, 1509, 1476, 1452, 1381, 1304, 1262, 1245, 1182, 1114, 1044, 966, 895, 841, 740 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 3.97−3.91 (m, 2H), 3.89−3.79 (m, 4H), 3.77−3.71 (m, 2H), 2.00−1.91 (m, 4H), 1.84 (t, J = 4.4 Hz, 2H), 1.65−1.56 (m, 2H), 1.46 (dd, J = 4.0, 12.0 Hz, 2H), 1.40 (d, J = 13.2 Hz, 2H), 1.31−1.18 (m, 2H), 1.25 (d, J = 12.0 Hz, 2H), 1.07 (d, J = 12.0 Hz, 2H), 1.01 (s, 6H), 0.81 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 117.5 (2C), 65.0 (2C), 63.6 (2C), 53.3 (2C), 50.9 (2C), 44.5 (2C), 41.9 (2C), 29.6 (2C), 27.0 (2C), 26.8 (2C), 16.7 (2C), 9.9 (2C). ESI-MS: m/z 391.3 $[M + H]^+$. HRMS (ESI) m/z: calcd for $C_{24}H_{39}O_4^+$ $[M + H]^+$ 391.2842, found 391.2842.

1l was prepared as a colorless solid (65% yield) according to the general procedure. R_f = 0.30 (petroleum ether/EtOAc = 3:1); $[\alpha]_D^{24}$ = −38 (c = 0.5, $CHCl_3$); mp 126−127 °C. IR (film): ν_{max} = 3088, 2987, 2937, 2870, 2852, 1642, 1513, 1464, 1377, 1225, 1149, 1094, 1070, 1028, 998, 886, 864 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 4.84 (s, 2H), 4.53 (s, 2H), 3.98 (d, J = 11.6 Hz, 2H), 3.48 (dd, J = 3.6, 8.8 Hz, 2H), 3.16 (d, J = 11.6 Hz, 2H), 2.39 (dd, J = 3.6, 10.8 Hz, 2H), 2.03−1.91 (m, 4H), 1.80−1.68 (m, 6H), 1.59−1.51 (m, 2H), 1.42 (s, 6H), 1.38 (brs, 6H), 1.36 (s, 6H), 1.29−1.23 (m, 6H), 1.20 (s, 6H), 1.10 (brs, 2H), 0.87 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.2 (2C), 107.1 (2C), 99.0 (2C), 63.9 (2C), 56.6 (2C), 52.5 (2C), 38.5 (2C), 38.2 (2C), 37.9 (2C), 34.5 (2C), 29.4 (2C), 27.4 (2C), 26.1 (2C), 25.3 (4C), 25.2 (2C), 24.2 (2C), 23.5 (2C), 16.2 (2C). HRMS (ESI) m/z: calcd for $C_{38}H_{62}O_4Na^+$ $[M + Na]^+$ 605.4540, found 605.4542. This dimeric product was dissolved in hexane/EtOAc (5:1). After 2 days, colorless single crystals were obtained by slow evaporation of the solvent at room temperature.

1m[5f] was prepared as a colorless oil (48% yield) according to the general procedure. R_f = 0.80 (petroleum ether). IR (film): ν_{max} = 2949, 2865, 1450, 1362, 1327, 1247, 927, 894 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.76−1.69 (m, 4H), 1.63−1.55 (m, 6H), 1.54−1.46 (m, 4H), 1.18−1.07 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 46.4 (2C), 31.8 (4C), 25.4 (4C). EI-MS (70 eV): m/z 138 $[M]^+$.

1n[5e,31] was prepared as a colorless oil (45% yield) according to the general procedure. R_f = 0.80 (petroleum ether). IR (film): ν_{max} = 2923, 2851, 2667, 1448, 1350, 1263, 996, 889, 847 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.75−1.61 (m, 10H), 1.26−1.13 (m, 6H), 1.12−0.90 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 43.5 (2C), 30.2 (4C), 26.9 (6C). EI-MS (70 eV): m/z 166 $[M]^+$.

1o was prepared as a colorless solid (62% yield) according to the general procedure. R_f = 0.40 (petroleum ether/EtOAc = 4:1); mp 151−152 °C. IR (film): ν_{max} = 2975, 2931, 2855, 1694, 1513, 1421, 1365, 1274, 1239, 1168, 1023, 867, 769 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 4.12 (d, J = 12.8 Hz, 4H), 2.63 (t, J = 12.0 Hz, 4H), 1.65 (d, J = 12.0 Hz, 4H), 1.45 (s, 18H), 1.30−1.10 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.8 (2C), 79.2 (2C), 44.2 (br, 2C), 41.0 (4C), 29.2 (4C), 28.5 (6C). HRMS (ESI) m/z: calcd for $C_{20}H_{37}N_2O_4^+$ $[M + H]^+$ 369.2748, found 369.2744. This dimeric product was dissolved in hexane/EtOAc (1:1). After 1 day, colorless single crystals were obtained by slow evaporation of the solvent at room temperature.

Stereoselective Dimerization of Podophyllotoxin-Derived Bromide 2. To a stirred slurry of Zn (100 mg, 1.5 mmol) and $NiCl_2$ (20 mg, 0.15 mmol) in pyridine (0.5 mL) was added 2,2′-bipyridine (70 mg, 0.45 mmol) at room temperature. The temperature then rose to 55 °C, and vigorous stirring was continued for 10 min. The resulting black Ni(0) complex was cooled to room temperature, and a solution of bromide **2**[32] (477 mg, 1 mmol) in CH_3CN (2 mL) was added dropwise. The mixture was stirred for 2 h and then filtered with a short plug of silica (elution with 80 mL of Et_2O), and the combined organic phases were washed with water (2 × 10 mL) and brine (10 mL), dried over Na_2SO_4, filtered, and concentrated. The crude product was carefully purified by flash column chromatography (petroleum ether/EtOAc = 4:1) on silica gel to afford desired bisdeoxypodophyllotoxin **3** (160 mg, 40%) as a colorless solid. R_f = 0.20 (petroleum ether/EtOAc = 4:1); $[\alpha]_D^{27}$ = −175 (c = 0.04, $CHCl_3$); mp 256−258 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 6.43 (s, 2H), 6.29 (s, 4H), 5.83 (s, 2H), 5.71 (s, 2H), 5.69 (s, 2H), 4.75 (d, J = 4.0 Hz, 2H), 4.39 (t, J = 7.2 Hz, 2H), 4.07 (t, J = 9.6 Hz, 2H), 3.81 (s, 6H), 3.75 (s, 12H), 3.51 (s, 2H), 3.26 (d, J = 3.2 Hz, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.0 (2C), 152.5 (4C), 146.8 (2C), 146.3 (2C), 137.2 (2C), 135.7 (2C), 131.1 (2C), 129.7 (2C), 109.8 (2C), 108.9 (2C), 108.4 (4C), 101.0 (2C), 68.0 (2C), 60.7 (2C), 56.2 (4C), 43.8 (2C), 42.4 (2C), 40.3 (2C), 36.4 (2C). ESI-MS: m/z 795.2 $[M + H]^+$. HRMS (ESI) m/z: calcd for $C_{44}H_{43}O_{14}^+$ $[M + H]^+$ 795.2647, found 795.2653.

Stereoselective Cyclization−Homocoupling Cascade. To a stirred slurry of Zn (100 mg, 1.5 mmol) and $NiCl_2$ (20 mg, 0.15 mmol) in pyridine (0.5 mL) was added 2,2′-bipyridine (70 mg, 0.45 mmol) at room temperature. The temperature then rose to 55 °C, and vigorous stirring was continued for 15 min. The resulting black Ni(0) complex was cooled to room temperature, and a solution of bromide **4a**[7a] (208 mg, 1.0 mmol) in CH_3CN (2 mL) was added dropwise (ca. 10 s). The mixture was stirred for 25 min and then filtered with a short plug of silica (elution with 60 mL of Et_2O), and the combined organic phases were washed with water (10 mL) and brine (10 mL), dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by flash column chromatography (petroleum ether/EtOAc = 4:1) on silica gel to afford the desired product **5a** (83 mg, 65%) as a colorless solid. R_f = 0.20 (petroleum ether/EtOAc = 1:1); mp 94−96 °C. IR (film): ν_{max} = 2942, 2867, 1489, 1453, 1371, 1257, 1206, 1109, 1082, 1018, 954, 923, 829, 733 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 5.73 (d, J = 5.2 Hz, 2H), 3.95 (q, J = 7.2 Hz, 2H), 3.88 (t, J = 7.2 Hz, 4H), 3.43 (t, J = 10.0 Hz, 2H), 2.81 (quint, J = 6.8 Hz, 2H), 2.36−2.26 (m, 2H), 1.85 (ddd, J = 2.4, 6.8, 9.2 Hz, 4H), 1.52−1.34 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 109.60, 109.58, 72.24, 72.21, 68.93, 68.89, 45.20, 45.13, 42.30, 42.19, 26.48, 26.37, 24.75, 24.67. ESI-MS: m/z 255.2 $[M + H]^+$. HRMS (ESI) m/z: calcd for $C_{14}H_{23}O_4^+$ $[M + H]^+$ 255.1591, found 255.1594. This dimeric product was dissolved in hexane/EtOAc (5:1). After 2 days, colorless single crystals were obtained by slow evaporation of the solvent at room temperature.

5b was prepared as a colorless oil (70% yield) starting from **4b** according to the above procedure for **5a**. R_f = 0.50 (petroleum ether/EtOAc = 1:1). IR (film): ν_{max} = 2971, 2935, 2878, 1456, 1440, 1343, 1283, 1174, 1153, 1114, 1019, 949, 921, 830 cm^{-1}. ^1H NMR (400 MHz, C_6D_6): δ 3.94−3.85 (m, 4H), 3.74 (q, J = 7.6 Hz, 2H), 3.55 (dt, J = 6.0, 8.0 Hz, 2H), 2.01 (dd, J = 3.6, 8.4 Hz, 2H), 1.98 (dd, J = 3.2, 8.4 Hz, 2H), 1.95−1.84 (m, 4H), 1.77 (quint, J = 5.6 Hz, 2H), 1.67−1.61 (m, 1H), 1.62 (dd, J = 7.6, 11.6 Hz, 1H), 1.59−1.50 (m, 2H), 1.35−1.15 (m, 4H). ^{13}C NMR (100 MHz, C_6D_6): δ 114.8 (2C), 72.4 (2C), 66.9 (2C), 41.4, 41.3, 39.3 (2C), 35.8 (2C), 32.8 (2C), 24.7 (2C). ESI-MS: m/z: 283.3 $[M + H]^+$. HRMS (ESI) m/z: calcd for $C_{16}H_{27}O_4^+$ $[M + H]^+$ 283.1904, found 283.1902.

Total Syntheses of (±)-Chimonanthine and (±)-Folicanthine. To a stirred solution of tryptamine (3.2 g, 20 mmol) in $CHCl_3$ (60 mL) was added a solution of NaOH (0.8 g, 20 mmol, 1.0 equiv) in H_2O (5 mL) dropwise at 0 °C. The resulting mixture was treated with $ClCO_2Et$ (1.9 mL, 20 mmol, 1.0 equiv) dropwise at 0 °C and then allowed to warm to room temperature after 10 min. The stirring was continued for 1.5 h, after which the mixture was diluted with CH_2Cl_2 (100 mL) and poured into a separatory funnel containing H_2O (10 mL). The combined organic layers were washed with water (3 × 20 mL) and brine (20 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (petroleum ether/EtOAc = 2:1) on silica gel (basicified with Et_3N) to afford the desired N_b-ethoxycarbonyltryptamine[33] (4.23 g, 91%) as a brown oil. R_f = 0.32 (petroleum ether/EtOAc = 1:1). IR (film): ν_{max} = 3409, 3327, 3057, 2980, 2932, 1697, 1620, 1523, 1457, 1338, 1259, 1141, 1094, 1037, 955, 778, 743 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 8.28 (brs, 1H, −N*H*), 7.59 (d, J = 8.0 Hz, 1H), 7.34 (d, J = 8.4 Hz, 1H), 7.19 (t, J = 8.0 Hz, 1H), 7.11 (t, J = 8.0 Hz, 1H), 6.97 (s, 1H), 4.79 (brs, 1H, −N*H*), 4.12 (q, J = 6.8 Hz, 2H), 3.50 (q, J = 6.4 Hz, 2H), 2.95 (t, J = 6.8 Hz, 2H), 1.21 (t, J = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.8, 136.4, 127.2, 122.1, 122.0, 119.3, 118.6, 112.7, 111.2, 60.7, 41.1, 25.7, 14.6. ESI-MS: m/z 233.2 $[M + H]^+$.

To a stirred solution of the above N_b-ethoxycarbonyltryptamine (3.7 g, 16 mmol) in CH_2Cl_2 (50 mL) were added NaOH (3.2 g, 80 mmol, 5.0 equiv) and $(n\text{-}Bu)_4NHSO_4$ (544 mg, 1.6 mmol, 0.1 equiv) portionwise at room temperature. The reaction system was cooled to 0 °C, and $(Boc)_2O$ (3.84 g, 17.6 mmol, 1.1 equiv) was added portionwise. The resulting mixture was then allowed to warm to room temperature and stirred for 2 h. Eventually the reaction mixture was diluted with CH_2Cl_2 (90 mL) and poured into a separatory funnel containing H_2O (10 mL). The combined organic layers were washed with water (3 × 20 mL) and brine (20 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (petroleum ether/EtOAc = 2:1) on silica gel (basicified with Et_3N) to afford the desired N_a-Boc-N_b-ethoxycarbonyltryptamine (4.67 g, 88%) as a brown oil. R_f = 0.41 (petroleum ether/EtOAc = 1:1). IR (film): ν_{max} = 3341, 2980, 2934, 1730, 1610, 1527, 1477, 1454, 1382, 1331, 1309, 1255, 1226, 1160, 1092, 1060, 1035, 912, 857, 768, 747 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 8.13 (d, J = 6.8 Hz, 1H), 7.54 (d, J = 7.6 Hz, 1H), 7.42 (s, 1H), 7.32 (t, J = 8.0 Hz, 1H), 7.23 (t, J = 7.6 Hz, 1H), 4.89 (brs, 1H), 4.11 (q, J = 6.8 Hz, 2H), 3.50 (q, J = 6.8 Hz, 2H), 2.90 (t, J = 6.8 Hz, 2H), 1.66 (s, 9H), 1.23 (t, J = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.6, 149.6, 135.5, 130.3, 124.4, 123.1, 122.4, 118.8, 117.5, 115.2, 83.5, 60.6, 40.4, 28.1 (3C), 25.5, 14.6. ESI-MS: m/z 665.2 $[2M + H]^+$. HRMS (ESI) m/z: calcd for $C_{36}H_{48}N_4O_8Na^+$ $[2M + Na]^+$ 687.3364, found 687.3353.

To a stirred solution of the above N_a-Boc-N_b-ethoxycarbonyltryptamine (3.19 g, 9.6 mmol) in CH_2Cl_2 (25 mL) were added NBS (1.71 g, 9.6 mmol, 1.0 equiv) and PPTs (2.41 g, 9.6 mmol, 1.0 equiv) portionwise at room temperarure. After 10 min, the resulting mixture was diluted with CH_2Cl_2 (80 mL) and poured into a separatory funnel containing H_2O (10 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (3 × 20 mL) and brine (3 × 15 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (petroleum ether/EtOAc = 2:1) on silica gel (basicified with Et_3N) to afford the desired tertiary benzylic bromide (±)-**6** (3.63 g, 92%) as a brown oil. R_f = 0.65 (petroleum ether/EtOAc = 2:1). IR (film): ν_{max} = 2980, 2933, 2894, 1713, 1604, 1538, 1479, 1414, 1383, 1369, 1331, 1289, 1273, 1256, 1231, 1200, 1154, 1113, 1098, 1077, 1017, 904, 754, 732 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.61 (d, J = 7.6 Hz, 1H), 7.37 (d, J = 7.6 Hz, 1H), 7.30 (t, J = 7.6 Hz, 1H), 7.11 (t, J = 7.6 Hz, 1H), 6.41 (s, 1H), 4.19 (q, J = 7.2 Hz, 2H), 3.77 (dd, J = 7.6, 10.4 Hz, 1H), 2.91−2.81 (m, 2H), 2.77 (dd, J = 7.6, 12.0 Hz, 1H), 1.59 (s, 9H), 1.29 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.1, 151.9, 141.9, 132.4, 130.3, 124.0, 123.6, 117.3, 83.8, 81.9, 61.9, 61.5, 46.0, 40.8 (br), 28.1 (3C), 14.5. ESI-MS: m/z 411.1 $[M + H]^+$. HRMS (ESI) m/z: calcd for $C_{18}H_{23}{}^{79}BrN_2O_4Na^+$ $[M + Na]^+$ 433.0733, found 433.0734.

To a stirred slurry of Zn (197 mg, 3 mmol, 1.5 equiv) and $NiCl_2$ (40 mg, 0.3 mmol, 0.15 equiv) in pyridine (1.5 mL) was added 2,2′-bipyridine (141 mg, 0.9 mmol, 0.45 equiv) at room temperature. The temperature then rose to 55 °C, and vigorous stirring was continued for 10 min. The resulting black Ni(0) complex was cooled to room temperature, and a solution of bromide **6** (822 mg, 2 mmol) in CH_3CN (10 mL) was added dropwise. The mixture was stirred for 30 min and then filtered with a short plug of silica (elution with 25 mL of EtOAc), and the combined organic phases were washed with water (3 × 10 mL) and brine (3 × 10 mL), dried over Na_2SO_4, filtered, and concentrated. The crude product was carefully purified by flash column chromatography (petroleum ether/EtOAc = 6:1 → petroleum ether/acetone = 8:1) on silica gel (basicified with Et_3N) to afford 148 mg (22%) of *meso* dimer **7′** as a pale-yellow solid and 141 mg (21%) of *dl*-dimer **7** as a pale-yellow oil. Data for **7**: R_f = 0.36 (petroleum ether/acetone = 4:1). IR (film): ν_{max} = 3049, 2979, 2933, 2889, 1711, 1600, 1539, 1481, 1463, 1411, 1384, 1318, 1278, 1254, 1236, 1203, 1161, 1103, 1019, 902, 857, 753, 737 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.37 (brs, 2H), 7.09 (d, J = 7.6 Hz, 2H), 7.06 (t, J = 7.6 Hz, 2H), 6.84 (t, J = 7.6 Hz, 2H), 6.42 (brs, 2H), 4.19 (q, J = 6.8 Hz, 4H), 3.81 (dd, J = 8.0, 11.2 Hz, 2H), 2.80 (td, J = 5.6, 11.2 Hz, 2H), 2.24 (td, J = 8.0, 11.6 Hz, 2H), 2.14 (dd, J = 5.2, 12.0 Hz, 2H), 1.60 (s, 18H), 1.30 (t, J = 7.2 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.4 (2C), 152.0 (2C), 142.8 (2C), 131.4 (2C), 128.9 (2C), 123.4 (br, 2C), 122.9 (2C), 116.5 (br, 2C), 81.7 (2C), 78.7 (2C), 61.5 (2C), 60.5 (2C), 45.1 (2C), 33.0 (br, 2C), 28.4 (6C), 14.7 (2C). ESI-MS: m/z 685.5 $[M + Na]^+$. HRMS (ESI) m/z: calcd for $C_{36}H_{46}N_4O_8Na^+$ $[M + Na]^+$ 685.3208, found 685.3191. Compound **7′** was dissolved in hexane/EtOAc (1:1). After 1 day, colorless single crystals were obtained by slow evaporation of the solvent at room temperature. Data for **7′**: R_f = 0.38 (petroleum ether/acetone = 4:1); mp 198−199 °C. ^1H NMR (600 MHz, $CDCl_3$, 50 °C): δ 7.58 (brs, 2H), 7.23 (t, J = 7.8 Hz, 2H), 6.96 (brs, 2H), 6.84 (brs, 2H), 6.21 (brs, 2H), 4.14 (d, J = 7.2 Hz, 4H), 3.71 (brs, 2H), 2.82 (td, J = 5.4, 11.4 Hz, 2H), 2.11 (dd, J = 5.4, 12.0 Hz, 2H), 1.93 (brs, 2H), 1.52 (s, 18H), 1.25 (t, J = 7.2 Hz, 6H). ^{13}C NMR (150 MHz, $CDCl_3$, 50 °C): δ 154.4 (2C), 151.8 (2C), 143.8 (2C), 131.7 (2C), 129.34 (2C), 129.25 (2C), 123.5 (2C), 117.5 (br, 2C), 81.6 (2C), 78.0 (2C), 61.3 (2C), 60.1 (2C), 45.6 (2C), 33.0 (br, 2C), 28.3 (6C), 14.7 (2C). HRMS (ESI) m/z: calcd for $C_{36}H_{46}N_4O_8Na^+$ $[M + Na]^+$ 685.3208, found 685.3196.

To a stirred solution of **7** (20 mg, 0.03 mmol) in CH_3CN (3 mL) was added TMSI (10 μL, 0.09 mmol, 3.0 equiv) at 0 °C over a 10 s period. The resulting mixture was allowed to warm to room temperature, stirred for 4 h, and then diluted with CH_2Cl_2 (50 mL) and poured into a separatory funnel containing H_2O (5 mL). The combined organic layers were washed with saturated aqueous $Na_2S_2O_3$ (20 mL), water (3 × 10 mL), and brine (20 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (CH_2Cl_2/MeOH/Et_3N = 49:1:1) on silica gel to afford the desired compound **8** (12 mg, 87%) as a colorless oil. R_f = 0.15 (petroleum ether/EtOAc/MeOH = 8:1:1). IR (film): ν_{max} = 3354, 2977, 2928, 2880, 1691, 1606, 1482, 1467, 1420, 1381, 1348, 1320, 1239, 1202, 1173, 1112, 1065, 896, 745 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ (rotamers) 7.18 (d, J = 7.5 Hz, 2H), 7.11 (d, J = 7.5 Hz, 2H), 6.78 (t, J = 6.9 Hz, 2H), 6.64 (t, J = 7.5 Hz, 2H), 5.23 (s, 0.5H), 5.18 (s, 0.5H), 5.14 (s, 1H), 5.01 (s, 0.5H), 4.97 (s, 0.5H), 4.88 (s, 0.5H), 4.73 (s, 0.5H), 4.23−4.00 (m, 4H), 3.71−3.62 (m, 1H), 3.56 (dd, J = 8.1, 10.2 Hz, 1H), 2.95−2.83 (m, 2H), 2.66−2.52 (m, 2H), 2.15−1.97 (m, 2H), 1.27 (t, J = 7.2 Hz, 3H), 1.21 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (rotamers) 154.8, 150.64, 150.57, 129.2, 129.1, 125.4, 125.2, 118.9, 118.7, 118.5, 118.4, 109.9, 109.8, 79.2, 78.4, 61.3, 61.1, 60.9, 60.8, 45.4, 45.2, 31.6, 31.5, 14.8, 14.6. ESI-MS: m/z 463.2 $[M + H]^+$. HRMS (ESI) m/z: calcd for $C_{26}H_{31}N_4O_4^+$ $[M + H]^+$ 463.2340, found 463.2340.

To a stirred solution of **8** (45 mg, 0.097 mmol) in toluene (8 mL) was added Red-Al (0.3 mL, 70% in toluene, 1.0 mmol, 10.0 equiv) dropwise at room temperature. The resulting mixture was heated to 90 °C and stirred for 1.5 h. The reaction system was then cooled to room

temperature and concentrated directly under reduced pressure. The resulting residue was purified by flash column chromatography (CH_2Cl_2/MeOH/Et_3N = 60:1:1) on silica gel to afford the desired product (±)-chimonanthine (**9**) (28 mg, 82%) as a colorless crystal. R_f = 0.15 (CH_2Cl_2/MeOH = 8:1); mp 165−167 °C. IR (film): ν_{max} = 3365, 3047, 2955, 2927, 2855, 2673, 2477, 1607, 1485, 1470, 1373, 1352, 1318, 1248, 1215, 1156, 1076, 1044, 749 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.20 (d, J = 7.5 Hz, 2H), 7.01 (t, J = 7.5 Hz, 2H), 6.68 (t, J = 7.5 Hz, 2H), 6.56 (d, J = 7.5 Hz, 2H), 4.46 (br, 4H), 2.64−2.46 (m, 6H), 2.34 (s, 6H), 2.11−2.04 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.6, 133.1, 128.2, 124.4, 118.7, 109.3, 85.3, 63.3, 52.7, 37.2, 35.5. ESI-MS: m/z 347.3 $[M + H]^+$. HRMS (ESI) m/z: calcd for $C_{22}H_{27}N_4^+$ $[M + H]^+$ 347.2230, found 347.2231.

To a stirred solution of (±)-chimonanthine (16 mg, 0.046 mmol) in CH_3CN (10 mL) were added HCHO (35 μL, 37% in water, 10.0 equiv) and $NaBH(OAc)_3$ (99 mg, 0.46 mmol, 10.0 equiv) successively at room temperature. The reaction mixture was stirred for 1.5 h and then concentrated directly under reduced pressure. The resulting residue was purified by flash column chromatography (CH_2Cl_2/MeOH = 49:1) on silica gel to afford the desired product (±)-folicanthine (**10**) (15 mg, 87%) as a colorless crystal. R_f = 0.20 (CH_2Cl_2/MeOH = 8:1); mp 175−177 °C. IR (film): ν_{max} = 3046, 2959, 2928, 2858, 2792, 1602, 1492, 1463, 1427, 1380, 1347, 1325, 1299, 1254, 1211, 1159, 1124, 1040, 1022, 1021, 965, 927, 743, 725 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 6.97 (t, J = 7.2 Hz, 2H), 6.91 (brs, 2H), 6.49 (t, J = 6.8 Hz, 2H), 6.26 (d, J = 7.6 Hz, 2H), 4.39 (brs, 2H), 2.99 (s, 6H), 2.64 (brs, 2H), 2.48−2.39 (m, 4H), 2.40 (s, 6H), 1.98−1.92 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.8 (2C), 132.7 (2C), 128.0 (2C), 123.6 (2C), 116.6 (2C), 105.8 (2C), 91.9 (2C), 62.6 (2C), 52.6 (2C), 37.8 (2C), 35.4 (2C), 35.2 (2C). ESI-MS: m/z 375.1 $[M + H]^+$. HRMS (ESI) m/z: calcd for $C_{24}H_{31}N_4^+$ $[M + H]^+$ 375.2543, found 375.2540.

■ ASSOCIATED CONTENT

Supporting Information

Copies of ^1H and ^{13}C NMR spectra and crystallographic information files (CIFs) for **1l**, **1o**, **5a**, and **7′**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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