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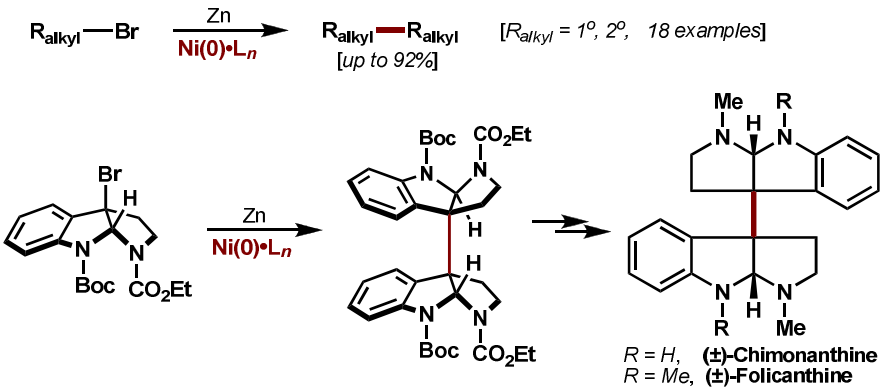
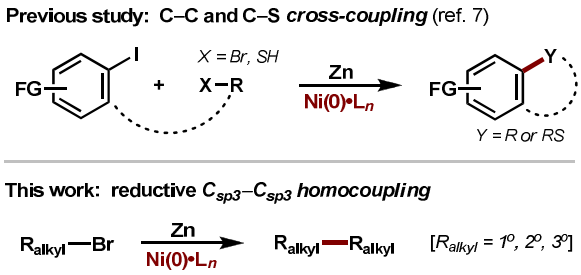


Abstract: A room temperature Ni-catalyzed reductive approach to homocoupling of unactivated primary, secondary and tertiary alkyl bromides is described. The catalytic system can be easily generated from air-stable and cheap materials and demonstrates broad functional group tolerance, thus allowing facile access to useful dimeric triterpene and lignan-like molecules. Moreover, dimerization of tertiary bromide **6** efficiently establishes sterically hindered vicinal quaternary carbons (C3a and C3a′), that 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 highly stereoselective synthesis of bisperhydrofuro[2,3-*b*]furan (**5a**) and dimeric spiroketal (**5b**), signifying the involvement of possible radical species.

Introduction

Scheme 1. Cross-Coupling *versus* Homocoupling



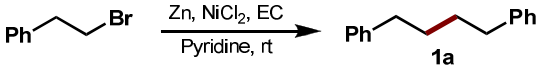
Dimeric molecules could be found in a wide array of natural occurring products and pharmaceuticals.[1] They have attracted increasing attentions due to unique biological functions compared to the respective monomers. Thus, a number of efficient methodologies for stereoseletive dimerization of two monomers have appeared, among which 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 the Csp^2–Csp^2 bond construction,[3] as 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 dimeriation[4] of alkyl halides largely limited its synthetic value. Hence, development of mild catalytic Csp^3–Csp^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[5e] and Weix's[5f] Ni/terpy-catalyzed homocoupling, and Gong's related cross-coupling[6] conditions. However, none of these studies demonstrated its use in the synthesis of complex molecules. In line with our recent work on the inter- and intramolecular C–C/C–S bond forming reactions (Scheme 1),[7] herein, we report analogous Ni/Ec and Ni/Bipy-catalyzed reductive homocoupling of (1º, 2º, 3º) alkyl bromides, with emphasis on their applications in the expeditious synthesis of dimeric sesquiterpene, lignan and pyrrolo[2,3-*b*]indoline alkaloids, respectively.

Results and Discussion

We first carried out the model study with 2-phenylethyl bromide as a 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)/pyridine,[7] where EC acts as a π-ligand to Ni. With substoichiometric amount of this catalyst, the desired reductive homocoupling indeed proceeded in DMF at room temperature, and the dimeric

product **1a** formed in 35% yield (entry 1) along with 40% recovery of starting material (SM). A good result was obtained with 30 mol% Ni complex albeit at a slower reaction rate (entry 2). Considering both the yield and reaction time (entries 3–6), CH_3CN was identified as the best solvent. This Ni catalyst can be lowered down to 15 mol%, and the triggered homocoupling reaction was completed within 4 h with 95% isolated yield of **1a** due to further suppression of competitive reduction of the bromide (entry 7).

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



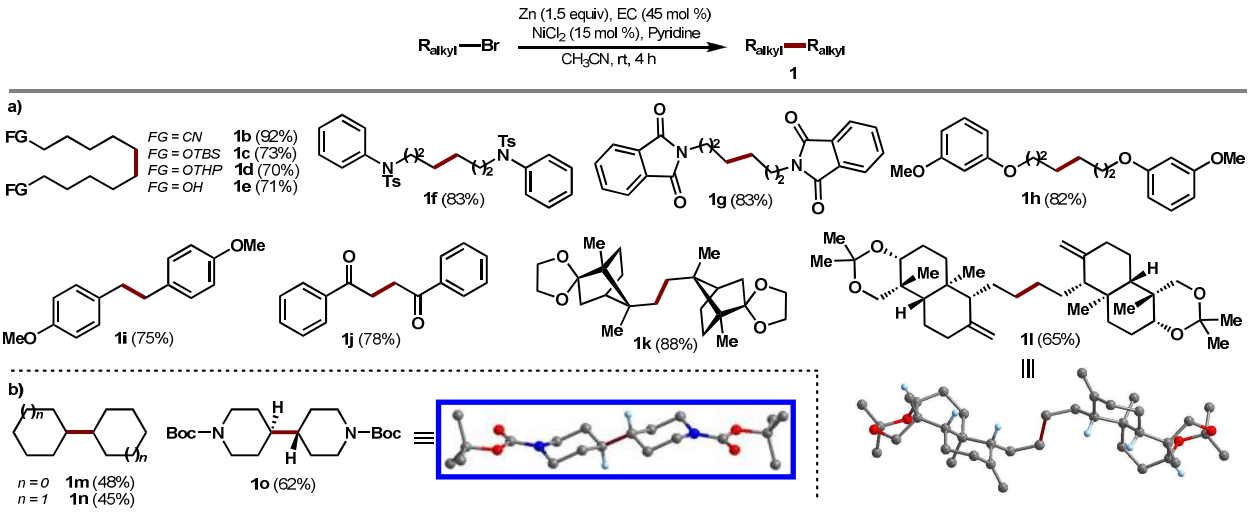
entry	$NiCl_2$ (equiv)	Zn (equiv)	solvent	time (h)	yield[b] (%) (**2a** : **SM**)
1	0.5	5	DMF	4	35 : 40
2	0.3	3	DMF	12	46 : 33
3	0.3	3	dioxane	8	44 : 40
4	0.3	3	dioxane	24	56 : 38
5	0.3	3	MeOH	5	78 : 0
6	0.3	3	CH_3CN	1	78 : 0
7	0.15	1.5	CH_3CN	4	96[c] : 0

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

With the above optimized conditions in hand, reductive homocouplings of various functionalized bromides were then investigated (Scheme 2). To our delight, the primary bromides bearing electrophilic cyano group and hydroxyl protecting-groups (OTBS and OTHP) reacted smoothly, affording the corresponding dimeric products (**1b**–**1d**) in good yields. In particular, the substrate with a free hydroxyl group also proceeded smoothly in the present conditions, and 1,10-decanediol (**1e**) was isolated in 71% yield, demonstrating the mild nature of this homocoupling reactions because its acidic proton of hydroxyl group cannot be compatible with sodium metal imparted from 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 ring was also suitable, providing *meta*-methoxyphenol-derived dimer (**1h**) in 82% yield. Activated alkyl halides such as *para*-methoxybenzyl bromide[8] and α-bromo acetophenone were next tried, and the corresponding dibenzyl **1i** and 1,4-diketone **1j** were produced in 75% and 78% yields, respectively. Unprecedented

homocoupling of the neopentyl bromide such as ethylene ketal-protected (+)-9-bromo camphor could be realized albeit 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 natural diterpene andrographolide,[7a] was exposed to this homocoupling condition as well, and the expected hexacycle (–)-**1l** was isolated in 65% yield. All of chiral centers in the starting bromide were reserved, which could be confirmed through X-ray crystal structure of **1l** (inset, Scheme 2a: selected H atoms have been omitted for clarity).[9] This case provided an alternative access to analogs of onocerane-type triterpenes, which were previously synthesized by Cp_2TiCl-catalyzed regioselective homocoupling of activated allylic bromides instead.[10] In addition, the secondary bromides can also participate the above homocoupling (Scheme 2b). The cyclopentyl and cyclohexyl bromide gave moderate yields of homodimers **1m** and **1n** due to 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) was also tolerated. The most stable conformation of **1o** was unambiguously established by its single-crystal analysis:[9] the newly formed Csp^3–Csp^3 bond occupies equatorial position in the respective chair conformation of two piperidine rings whereas two tertiary hydrogen atoms adopt 1,2-*anti* axial orientation (inset, Scheme 2b: selected H atoms have been omitted for clarity).

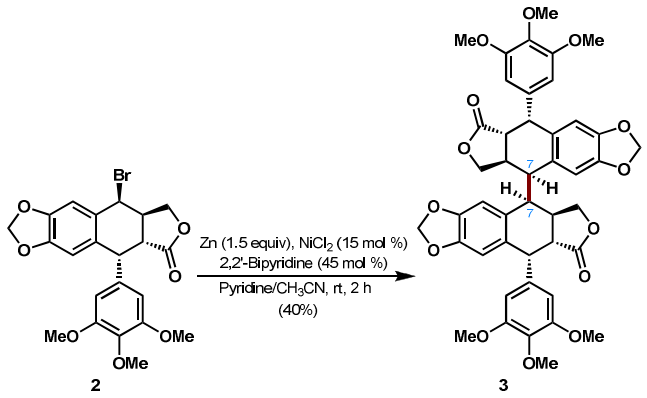
Scheme 2. Homocouplings of Primary and Secondary Bromides



Due to 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 towards 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 at providing a potential drug lead, we synthesized a new C7−C7 dimeric deoxypodophyllotoxin **3** from the easily available bromide **2** in 40% isolated yield along with 30% of (epi)podophyllotoxin being recovered. In this Ni catalytic dimerization, the ligand EC was replaced by 2,2′-bipyridine[14] that proved to be best. It is noteworthy that only dimer **3** ($[\alpha]_D^{27} = -175$) as the sole diastereomer could be detected from the reaction mixture, indicating that excellent stereoselectivity has been achieved during this Ni-catalyzed assembly.

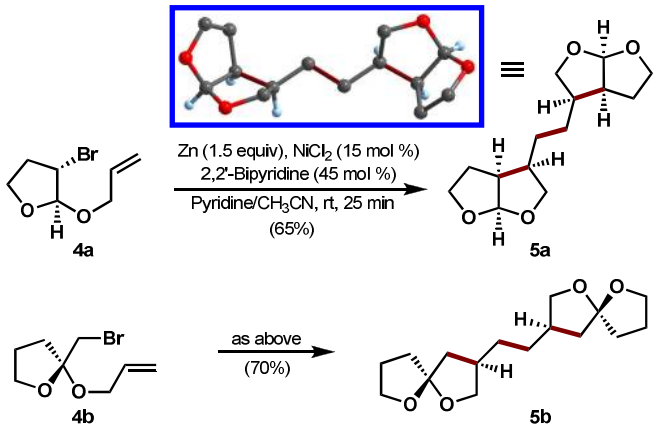
Scheme 3. Stereoselective Dimerization of Podophyllotoxin-derived Bromide



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 since the tandem reactions demonstrated in Schemes 4 could be rationalized accordingly. Upon the subjection of *β*-bromo acetal **4a** into the Ni catalytic system generated in situ from 2,2′-bipyridine, the unprecedented cyclization−homocoupling cascade indeed works, affording ethylene-bridged bisperhydrofuro[2,3-*b*]furan **5a** as the only diastereomeric isomer in 65% yield. Its *cis*/*syn*-fused relationship was unambiguously established by the single-crystal analysis (inset, Scheme 4: selected H atoms have been omitted for clarity).[9] Notably, three C–C bonds and four stereogenic centers were simultaneously formed in such a single operation. A similar stereoselective tandem reaction also occurred with *β*-bromo ketal **4b**, and the unique bisspiroketal **5b** was obtained in 70% yield under the

same condition.

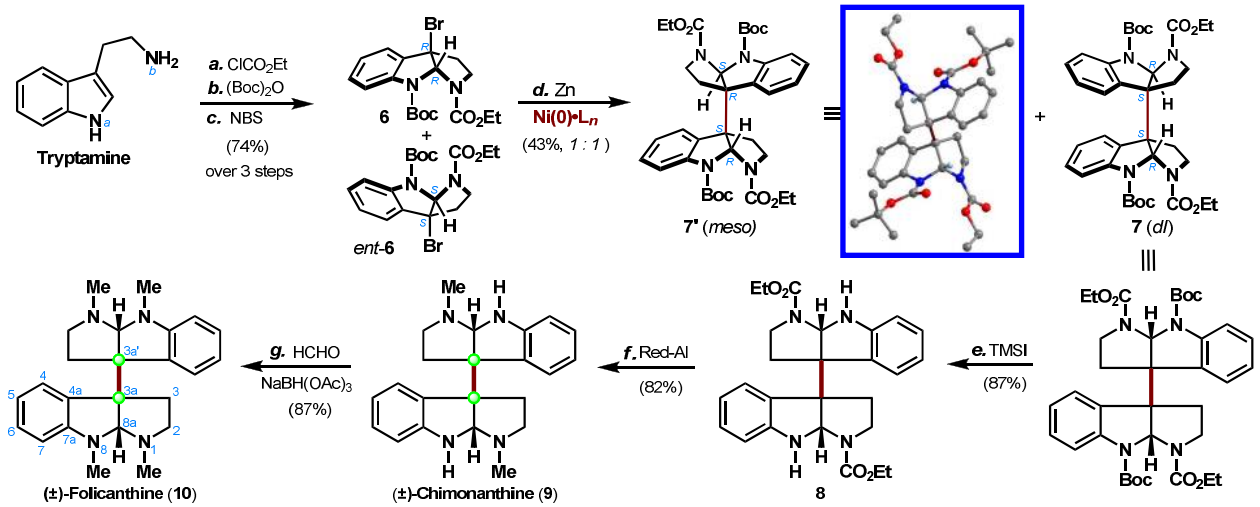
Scheme 4. Stereoselective Cyclization–Homocoupling Cascade



Recently, Fu and co-worker reported the first Nickel-catalyzed Suzuki arylations of tertiary alkyl halides;[17] however, the reductive homocouplings of this kind of challenging substrates with the aid of Ni catalyst have not been found yet, 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 in C3a–C3a′-bispyrrolo[2,3-*b*]indoline alkaloids family.[21] Their challenging structure and biological activities have attracted significant attention from the synthetic community, and especially they can be served 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 is Ni-catalyzed reductive homocoupling of tertiary bromide (±)-**6** for the establishment of two vicinal quaternary carbons (C3a and C3a′) with steric congestion. To this end, treatment of tryptamine with ethyl chloroformate followed by N_a-protection 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 key reductive homocoupling. Subjection of this tricyclic bromide into 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. *Meso*-isomer **7′** resulting from the dimerization of **6** and *ent*-**6**, was also isolated in 22% yield. Its structure was unambiguously assigned

by the single-crystal analysis (inset, Scheme 5: 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 two Boc protecting-groups in **7** by iodotrimethylsilane gave rise to bisester **8** in 87% yield. Reduction of N_b-ethoxycarbonyl groups in **8** with bis(2-methoxyethoxy)aluminum hydride (Red-Al) afforded (±)-Chimonanthine (**9**) in 82% yield. Eventually, N_a-methylation of **9** completed the synthesis of (±)-Folicanthine (**10**) in 87% yield. Spectroscopic data of synthetic samples are consistent with those published in the previous syntheses.[18a,18c,19a–d]

Scheme 5. Total Synthesis of (±)-Chimonanthine and (±)-Folicanthine



Reagents and conditions: (a) $ClCO_2Et$ (1.0 equiv), $CHCl_3$/aq. NaOH, 0 ºC, 10 min then rt, 1.5 h, 91%; (b) nBu_4NHSO_4 (0.1 equiv), NaOH (5.0 equiv), CH_2Cl_2, rt, 30 min; then $(Boc)_2O$ (1.1 equiv), 0 ºC 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%), and pyridine/CH_3CN, 25 ºC, 30 min, 43%; (e) TMSI (3.0 equiv), CH_3CN, 0 ºC to rt, 4 h, 87%; (f) Red-Al (10.0 equiv), toluene, rt to 90 ºC, 1.5 h, 82%; (g) aq. HCHO (10.0 equiv), $NaBH(OAc)_3$ (10.0 equiv), rt, CH_3CN, 1.5 h, 87%.

Conclusion

In summary, we have developed a versatile method for Csp^3–Csp^3 bond construction based on reductive homocoupling reactions of various alkyl halides catalyzed by the Ni complex generated in situ from air-stable and cheap materials. Exceptionally mild conditions and broad functional groups tolerance make this method especially valuable to access structurally complex dimeric natural product-like molecules such as **1l** and **3**. Moreover, the successful synthesis 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

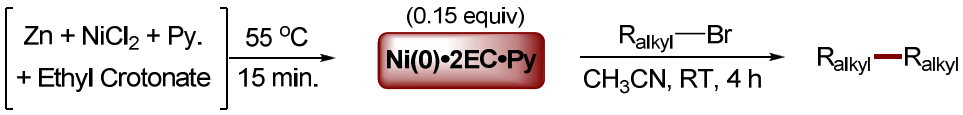
and pharmaceutical molecules.

Experimental Section

General. For product purification by flash column chromatography, silica gel (200~300 mesh) and petroleum ether (bp. 60~90 °C) are used. All solvents were purified and dried by standard techniques, and distilled prior to use. All organic extracts were dried over Na_2SO_4 or $MgSO_4$, unless otherwise noted. All experiments were conducted under 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 spectra data were measured with electrospray ionization mode (ESI). Infrared spectra were recorded on 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).

Typical procedure for homocoupling reaction catalyzed by Ni(0)•2EC•Py complex.

(General Procedure)



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 stirring vigorously, $NiCl_2$ (19 mg, 0.15 mmol) was added to the above mixture. Then the temperature 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, to which the solution of alkyl bromide (1.0 mmol) in CH_3CN (2 mL) was added dropwise over a 10 second period. After 4 h, the mixture was filtered with a short plug (elution with 30 mL Et_2O) and 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 products.

1a[5f] was prepared as a colorless solid (95% yield) according to 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) ppm; ^{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) ppm; EI–MS (70 eV): m/z 210 $[M]^+$.

1b[23] was prepared as a colorless oil (92% yield) according to 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}; ^{1}H 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) ppm; ^{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) ppm; ESI–MS: m/z 193.3 $[M+H]^+$.

1c[24] was prepared as a colorless oil (73% yield) according to 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}; ^{1}H 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) ppm; ^{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) ppm; ESI–MS: m/z: 403.4 $[M+H]^+$.

1d[25] was prepared as a colorless oil (70% yield) according to 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}; ^{1}H 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) ppm; ^{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) ppm; ESI–MS: m/z 360.4 $[M+NH_4]^+$.

1e[26] was prepared as a colorless solid (71% yield) according to 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}; ^{1}H 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) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 63.0 (2C), 32.7 (2C), 29.5 (2C), 29.4 (2C), 25.7 (2C) ppm; ESI–MS: m/z 175.3 $[M+H]^+$.

1f[27] was prepared as a colorless solid (83% yield) according to 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}; ^{1}H 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) ppm; ^{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) ppm; ESI–MS: m/z 577.3 $[M+H]^+$.

1g[28] was prepared as a colorless solid (83% yield) according to 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}; ^{1}H 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) ppm; ^{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) ppm; ESI–MS: m/z 377.3 $[M+H]^+$.

1h was prepared as a colorless solid (82% yield) according to 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, 1394, 1337, 1288, 1262, 1201, 1154, 1089, 1047, 1025, 922, 839, 813, 762, 687 cm^{-1}; ^{1}H 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) ppm; ^{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) ppm; ESI–MS: m/z 331.3 $[M+H]^+$; HRMS (ESI): 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 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}; ^{1}H 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) ppm; ^{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) ppm; EI–MS (70 eV): m/z 242 $[M]^+$.

1j[30] was prepared as a colorless solid (78% yield) according to 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}; ^{1}H 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) ppm; ^{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) ppm; ESI–MS: m/z 239.2 $[M+H]^+$.

1k was prepared as a colorless solid (88% yield) according to 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) ppm; ^{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) ppm; ESI–MS: m/z 391.3 $[M+H]^+$; HRMS (ESI): 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 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, 29876, 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) ppm; ^{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) ppm; HRMS (ESI): 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 two days, colorless single crystals were obtained by slow evaporation of solvent at room temperature.

1m[5f] was prepared as a colorless oil (48% yield) according to 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) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 46.4 (2C), 31.8 (4C), 25.4 (4C) ppm; EI–MS (70 eV): m/z 138 $[M]^+$

1n[5e,31] was prepared as a colorless oil (45% yield) according to 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) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 43.5 (2C), 30.2 (4C), 26.9 (6C) ppm; EI–MS (70 eV): m/z 166 $[M]^+$.

1o was prepared as a colorless solid (62% yield) according to 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) ppm; ^{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) ppm; HRMS (ESI): 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 one day, colorless single crystals were obtained by slow evaporation of 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. Then the temperature rose to 55 °C and vigorous stirring was continued for 10 min. The resulting black Ni(0) complex was cooled to room temperature, to which the solution of bromide **2**[32] (477 mg, 1 mmol) in CH_3CN (2 mL) was added dropwise. After stirring for 2 h, the mixture was filtered with a short plug of silica (elution with 80 mL Et_2O), and the combined organic phase was 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 bis-deoxypodophyllotoxin **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) ppm; ^{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) ppm; ESI–MS: m/z 795.2 $[M+H]^+$; HRMS (ESI): 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. Then the temperature rose to 55 °C and

vigorous stirring was continued for 15 min. The resulting black Ni(0) complex was cooled to room temperature, to which the solution of bromide **4a**[7a] (208 mg, 1.0 mmol) in CH_3CN (2 mL) was added dropwise (ca. 10s). After stirring for 25 min, the mixture was filtered with a short plug of silica (elution with 60 mL Et_2O), and the combined organic phase was 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 desired **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) ppm; ^{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 ppm; ESI–MS: m/z 255.2 $[M+H]^+$; HRMS (ESI): 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 two days, colorless single crystals were obtained by slow evaporation of 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) ppm; ^{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) ppm; ESI–MS: m/z: 283.3 $[M+H]^+$; HRMS (ESI): calcd. for $C_{16}H_{27}O_4^+$ $[M+H]^+$: 283.1904, found: 283.1902.

Total synthesis of (±)-chimonanthine and (±)-folicanthine

To a stirred solution of tryptamine (3.2 g, 20 mmol) in $CHCl_3$ (60 mL) was added the 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 $ClCO_2Et$ (1.9 mL, 20 mmol, 1.0 equiv) dropwise at 0 °C then allowed to warm to room temperature after 10 min. The stirring was continued for 1.5 h, and the mixture was diluted with CH_2Cl_2 (100 mL) and poured into a separatory funnel that contained 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 (basified 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) ppm; ^{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 ppm; 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) was 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 temperarure. The reaction system was cooled down to 0 °C followed by the addition of $(Boc)_2O$ (3.84 g, 17.6 mmol, 1.1 equiv) portionwise. Then the resulting mixture was 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 that contained 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 (basified 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) ppm; ^{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 ppm; ESI–MS: *m*/*z* 665.2 $[2M+H]^+$; HRMS (ESI): 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) was 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 that contained 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 (basified 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) ppm; ^{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 ppm; ESI–MS: m/z 411.1 $[M+H]^+$; HRMS (ESI): 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. Then the temperature rose to 55 °C and vigorous stirring was continued for 10 min. The resulting black Ni(0) complex was cooled to room temperature, to which the solution of bromide **6** (822 mg, 2 mmol) in CH_3CN (10 mL) was added dropwise. After stirring for 30 min, the mixture was filtered with a short plug of silica (elution with 25 mL EtOAc), and the combined organic phase was 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 (basified 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. (**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) ppm; ^{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) ppm; ESI–MS: *m*/*z* 685.5 $[M+Na]^+$; HRMS (ESI): calcd. for $C_{36}H_{46}N_4O_8Na^+$ $[M+Na]^+$: 685.3208, found: 685.3191. *meso*-Dimer **7′** was dissolved in Hexane/EtOAc (1 : 1). After a day, colorless single crystals were obtained by slow evaporation of solvent at room temperature. (**7′**): R_f = 0.38 (petroleum ether/acetone = 4 : 1); Mp. 198–199 °C; ^{1}H 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) ppm; ^{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) ppm; HRMS (ESI): 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 second period. The resulting mixture was allowed to warm to room temperature, and stirred for 4 h then diluted with CH_2Cl_2 (50 mL) and poured into a separatory funnel that contained 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 **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}; ^{1}H 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) ppm; ^{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 ppm; ESI–MS: *m*/*z* 463.2 $[M+H]^+$; HRMS (ESI): 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 up to 90 °C and stirred for 1.5 h. Then the reaction system was cooled down 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 (±)-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) ppm; ^{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 ppm; ESI–MS: m/z 347.3 $[M+H]^+$; HRMS (ESI): 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) was 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, 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 (±)-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) ppm; ^{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): calcd. for $C_{24}H_{31}N_4^+$ $[M+H]^+$: 375.2543, found: 375.2540.

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Supporting Information: Copies of ^1H, ^{13}C NMR, 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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