Dimerization of a 3-Substituted Oxindole at C-3 and Its Application to the Synthesis of (±)-Folicanthine

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Abstract: The dimerization of an oxindole in good yield at C-3 to form a benzylic quaternary carbon–carbon bond is described. A radical anion chain mechanism is proposed for the reaction. The dimeric product is transformed into (±)-folicanthine by a series of reductions. A crystalline bis-borane complex of (±)-folicanthine was obtained, and its molecular structure was determined by X-ray crystallography.

The dimeric indole alkaloids of the botanical order *Calycanthaceae* have posed a considerable structural and synthetic challenge to organic chemists. The early structural work on the pyrroloindole dimers folicanthine (**1**) and chimonanthine (**2**) and the intriguing doubly bridged alkaloid calycanthine (**3**) occupied the attention of many researchers in the 1950s and 1960s.[1-3] More recently the optical antipodes of the plant alkaloids, (+)-**2** and (–)-**3**, have been isolated from the skin of the Colombian poison dart frog *Phyllobates terribilis* and detected in a related species *P. bicolor*.[4] Synthetic efforts in this area have concentrated mainly in the 3,3-dimerization of indole[5,6] and oxindole[7] precursors. Yields in the dimerization at C-3 have been uniformly poor, reflecting the difficulty of forming a bond that connects two benzylic, quaternary carbons. Thus the oxidative dimerization of the Grignard reagent of N_b-methyltryptamine gave a complex mixture[6] from which (±)- and *meso*-chimonanthine were isolated in yields of 19% and 7%, respectively. A similar yield of mixed dimers **4** (16–27%) was obtained by photosensitized oxidation[5] of N_b-methoxycarbonyltryptamine in formic acid. The oxidative dimerization of the oxindole urethane **5** by treatment with sodium hydride and iodine produced a complex mixture. The diastereomeric dimers were separated from this mixture in yields of 13% (±) and 8% (*meso*).[7] Subsequent reduction of the (±)-dimer again yielded a mixture of products from which (±)-chimonathine could be isolated in only 3% yield and (±)-calycanthine in 0.2% yield. Chimonanthine was equilibrated in acid to produce calycanthine. The reduction of the pyrroloindole dimer **4** with lithium aluminum hydride in refluxing ether produced[5] (±)-folicanthine (**1**) in only 29% yield, again reflecting the sensitivity of the dimeric pyrroloindole system to chemical manipulation.

Our interest in the synthesis of folicanthine and N_6,N_{12}-dimethylcalycanthine was provoked by the considerable room for improvement in yield still available after the pioneering efforts of these three groups of earlier investigators, by the ready accessibility of the oxindole **6** (66% in three steps from *o*-iodoaniline), and by our experience with the chemical behavior of the pyrroloindole system gathered in recent syntheses[8] of the Calabar bean alkaloids.

Initial attempts at dimerization of **6** were centered on the preparation of **7** (by NBS bromination) and **8** (by base catalyzed elimination of HBr from **7**) for various coupling processes. Thus treatment of a 1:1 mixture of these compounds with tri-*n*-butyltin hydride to effect radical coupling only produced debrominated **7** (i.e., the oxindole **6**). Various reductive coupling methods with low valent vanadium,[9] titanium,[10] and chromium[11] species also resulted in reductive debromination of **7**. Single electron coupling of **8** with sodium in refluxing ether was not successful; the starting material was recovered. A Michael addition of the oxindole enolate generated from **6** with sodium hydride, to the unsaturated ester only gave **9**, the dimer formed by addition of the enolate oxygen to the double bond of **8**.

Returning to the dimerization of the enolate of **6** with iodine, we confirmed the earlier result that a low yield (18%, in our hands) of the (±)-dimer could be obtained in THF at –60 °C. A simple nucleophilic displacement is not the likely mechanism of this dimerization, because an attempt to react the enolate of **6** with the bromide **7** gave a complex mixture of products from which no dimer could be isolated. A search for other reagents to effect such a coupling revealed that the enolate of ethyl α,α-diphenylacetate was converted to the tetraphenyl succinate in 54% yield by 2,3-dibromo-2,3-dimethylbutane.[12] Subsequently carbon tetrachloride and tetrabromide were used[13] to efficiently halogenate enolates of esters in the α-position *via* a radical–radical anion pair intermediate. It was proposed that bromine was transferred from the tetrabromomethane radical anion to generate the products, the α-bromo ester and bromoform. More recently, tetraiodomethane was employed[14] to dimerize the dianion of β-phenylpropionic acid (at the α position) in high yield. Mindful of such precedents, we investigated the use of tetraiodomethane with the enolate of oxindole **6**. Treating the oxindole **6** in THF with a 1.05 molar proportion of sodium hydride followed by 0.48 mol of carbon tetraiodide in THF at –65 °C provided a mixture from which the (±)-dimer **10** was isolated in an average yield of 53%. This was easily the best yield ever recorded for such a dimerization and moreover the relative configuration of this product (mp 193–4 °C) determined by X-ray crystallography indicated that it was in fact the desired racemate (Figure 1).

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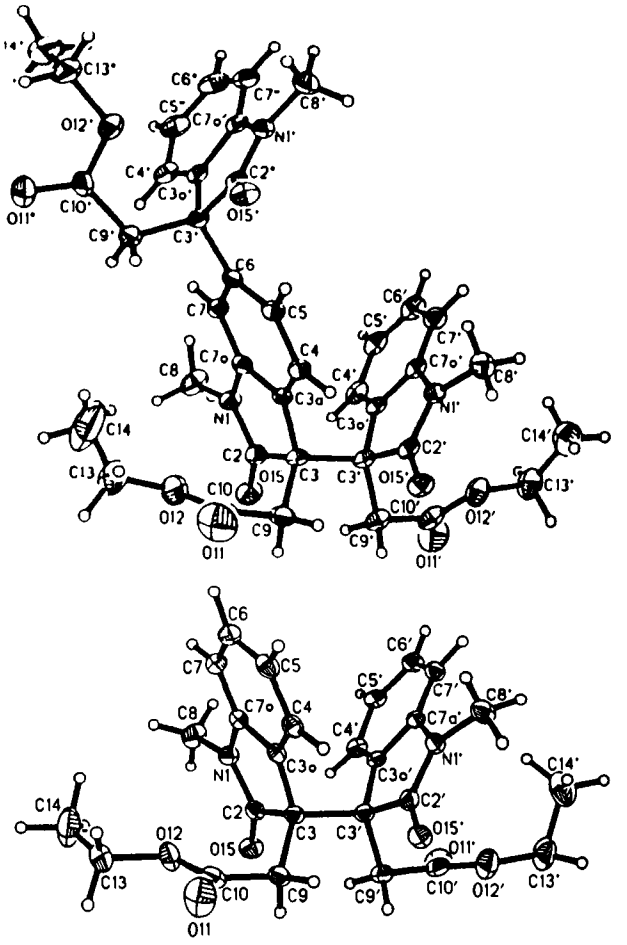

Figure 1. X-ray structures of **12** (top) and **10** (bottom).

Further examination of the other products of this reaction revealed the presence of the *meso*-dimer (*RS*)-**11** (8%), a trimer **12** (4%) whose structure and configuration was also established by X-ray crystallography (Figure 1), another dimer **13** (2%), and oxindoles **8** (4%), **14** (1%), and most significantly the C-3 diiodomethyl oxindole **15** (6%). Much of the iodine, was returned as iodoform (55%) which was isolated and characterized. In our view, a positive role must be assigned to the carbon tetraiodide to account for the *ca.* threefold increase in yield over the iodine dimerization. The reagent cannot simply be regarded as an iodinating agent. Furthermore, the plethora of products and the formation of the diiodomethyl oxindole **15** seems to imply that a radical or radical anion mechanism involving the active participation of a C-3 triiodomethyl oxindole **16** was likely. Radical anion substitution reactions had been intensively investigated by several workers, and a study of substitution at the benzylic quaternary carbon of *p*-nitrocumene by the anion from 2-nitropropane to form a bond between two quaternary carbon atoms[15] is particularly relevant to our proposal for the mechanism of the oxindole dimerization. In this proposal, outlined in Scheme 1, a radical anion chain process is initiated with the 3-(triiodomethyl)oxindole **16** which reacts with the oxindole enolate (R^-) in eq 1. The chain propagating steps 2, 3, and 4 then follow with the overall results expressed in eq 5. The (triiodomethyl)oxindole **16** is the key to the proposition made earlier that CI_4 plays an active part in the dimerization, a role that cannot be fulfilled by iodine. Use of the latter might be expected[16] to generate a 3-iodooxindole, but iodine is much too good a leaving group to permit the radical anion process to operate efficiently. The triiodomethyl anion however is a poorer leaving group, and step 2 might be regarded as a radical anion equivalent of the iodoform reaction. The isolation of the (diiodomethyl)oxindole byproduct **15** is thus easily accounted for by the loss of iodide from the radical anion (eq 6). The formation of **16** probably involves the intermediacy of a radical-anion radical pair like that suggested[13] for the reaction of tetrabromomethane with ester enolate. Tetrabromomethane also reacts with the silyl enolate of methyl octanoate

Scheme 1

$$RCI_3 + R^- \rightarrow (R\text{–}CI_3)^{\bullet-} + R^\bullet \quad (1)$$

$$(RCI_3)^{\bullet-} \rightarrow R^\bullet + CI_3^- \quad (2)$$

$$R^\bullet + R^- \rightarrow (R\text{–}R)^{\bullet-} \quad (3)$$

$$(R\text{–}R)^{\bullet-} + RCI_3 \rightarrow R\text{–}R + (RCI_3)^{\bullet-} \quad (4)$$

$$R^- + RCI_3 \rightarrow R\text{–}R + {}^-CI_3 \quad (5)$$

$$(RCI_3)^{\bullet-} \rightarrow (RCI_2)^\bullet + I^- \rightarrow RCHI_2 \quad (6)$$

$$R^- + CI_4 \rightarrow [R^\bullet(CI_4^{\bullet-})] \rightarrow RCI_3 + I^- \quad (7)$$

under radical conditions to produce the α-tribromomethyl methyl ester in 90% yield.[17] Since the bond dissociation energy of the C–I bond in CI_4 is much less[18] than that of the C–Br bond in CBr_4, the proposal made in eq 7 for the formation of **16** seems reasonable.

The byproducts of the dimerization can also be accounted for by the radical anion mechanism of Scheme 1, oxindole **8** (4%) by elimination of CHI_3 from **16**, and **14** (1%) by oxidation of the anion or radical intermediate. In fact, **14** can be obtained in very high yield when the enolate is allowed to react with air. The preponderance of the (±)-dimer (55%) over the *meso*-dimer (8%) is understandable. The transition state of eq 3 will be more stable for dimerization in the (±) sense. The trimer **12** (3%) and the yellow dimer **13** (2%) are alike in the bond formed between the aromatic carbon and C-3 of the oxindole. It should be noted that this bond, *meta* to the nitrogen atom and *para* to C-3, is similar in situation to that found in the product of the dimerization of triphenylmethyl radicals. The stereochemistry of the double bond in the yellow dimer **13** is assigned by comparison with **8**. In both compounds the aromatic proton at C-4 is significantly deshielded (8.42 ppm in **13**, 8.55 ppm in **8**), and this is attributed to the anisotropic effect of the ester carbonyl group.

A common test[15] for a radical anion mechanism is based on the ability of an electron acceptor molecule to interrupt the chain; *p*-dinitrobenzene has been used as such an electron acceptor, and in our case the addition of 30 mol percent *p*-dinitrobenzene to the reaction inhibited the dimerization and resulted in the recovery of oxindole **6**.

The racemic dimer **10** has the correct relative configuration at C_3–$C_{3'}$ for the synthesis of (±)-folicanthine (**1**) and (±)-N_6,N_{12}-dimethylcalycanthine (**17**). Many attempts were made, to no avail, to convert **10** into (±)-folicanthine by methods similar to those previously employed[8] in our successful synthesis of physostigmine. The ester groups could be amidated[19] by reaction with trimethylaluminum and methylamine in yields that averaged 62%. The dimeric oxindole amide **18** that resulted was very sparingly soluble and not easily reduced. Treatment with various reducing agents (lithium aluminum hydride, lithium triethyl

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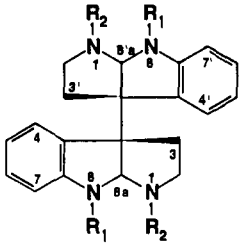
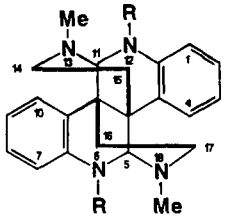
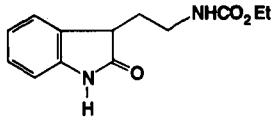
Chart I



1 (R_1=R_2=Me)
2 (R_1=H, R_2=Me)
4 (R_1=CHO, R_2=CO_2Me)



3 (R=H)
17 (R=Me)



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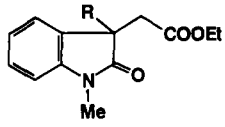
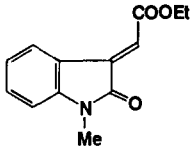


6 (R=H)
7 (R=Br)
14 (R=OH)
15 (R=CHI_2)
16 (R=Cl_3)



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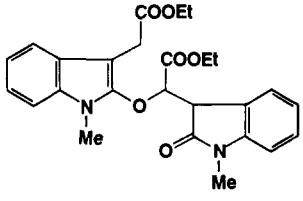

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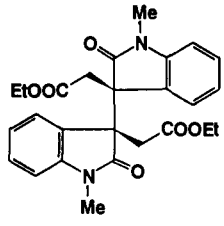

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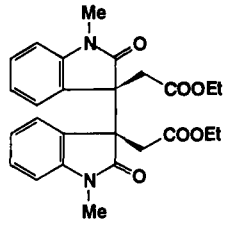

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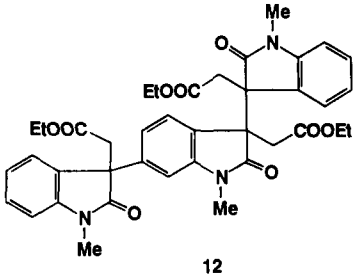

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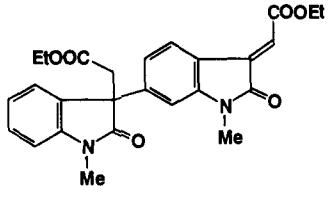

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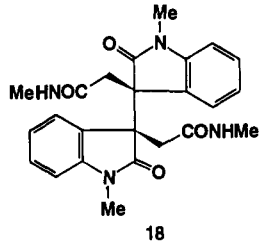

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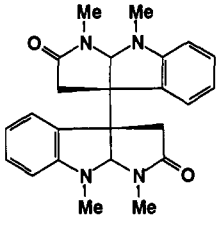

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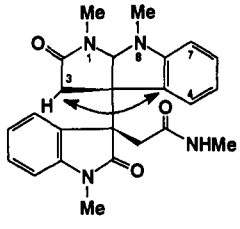

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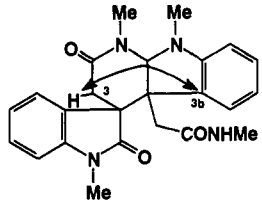

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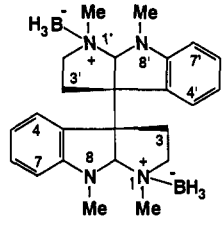

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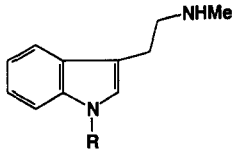

24 (R=Me)
25 (R=H)

borohydride, various borane derivatives, sodium borohydride with methanesulfonic acid in DMSO[20]) under many conditions in different solvents resulted in complex mixtures of products or no reaction at all; borane reduction of **18** produced a low yield of N_1,N-dimethyltryptamine **24** resulting from cleavage of the long (1.58 Å in **10**) C_3–$C_{3'}$ bond of **18**. An attempt to differentiate the secondary and tertiary amide functions by treatment with triethyloxonium fluoroborate before reduction of the resulting imino ether with sodium borohydride[21] also failed; the starting material was recovered. It should be remembered that earlier attempts at reduction of oxindole[7] and pyrroloindole[5] dimers had also given poor yields of the desired products most probably due to the intervention of similar cleavage and ring expansion processes. The best procedure for the reduction of **18** was eventually found to require the initial formation of the lithium salt of the secondary amide groups by treatment with lithium diisopropylamide in THF to protect against reduction of these carbonyl groups, followed by reaction with excess DIBAL-H and subsequent treatment with camphorsulfonic acid in methylene chloride. Under these conditions two products, **19** and **20**, could be isolated. The first **19**, isolated in yields of 25–35%, was

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(21) Monteiro, H. J. *Synthesis* **1974**, 137.

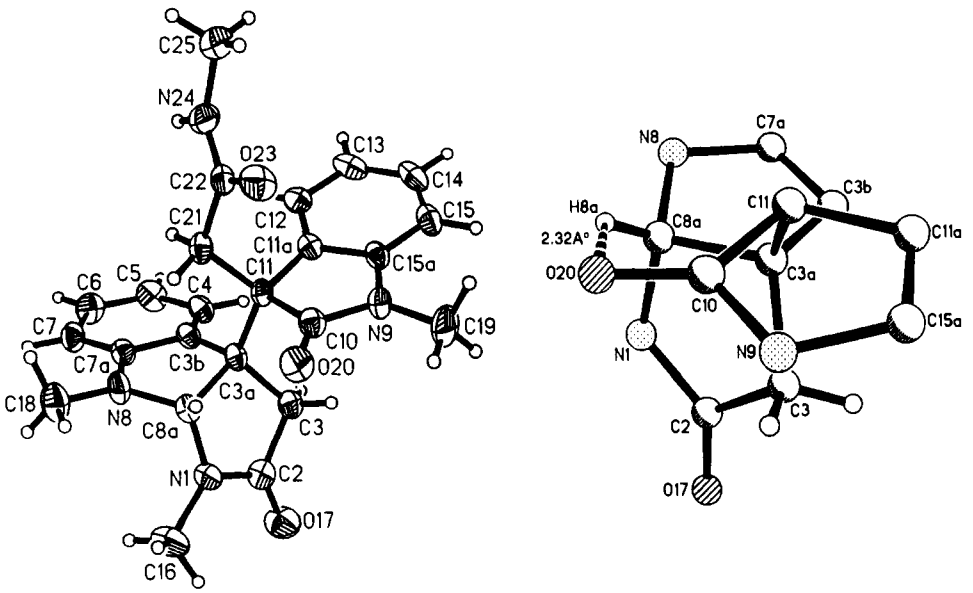
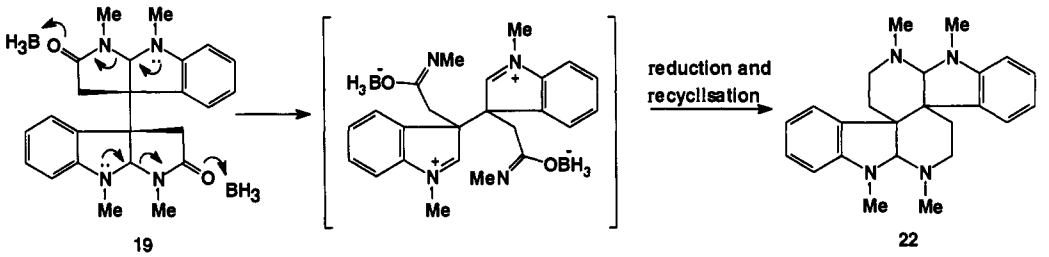


Figure 2. X-ray structure of **20** showing the spatial relationship of H-8a to the C_{10}–O_{20} carbonyl group.

Scheme 2



identified by spectroscopic means. The IR, mass, and ^{1}H NMR data supported the assigned structure, and the symmetry of the molecule was particularly evident in its ^{1}H NMR spectrum. The second compound **20** (30–42% yield) was clearly not symmetrical, and its ^{1}H NMR spectrum had features found in both **18** and **19**, but the aminal proton was located at surprisingly low field (5.93 ppm) in **20** in comparison with 4.39 ppm in **19**, the usual region for this absorption in similar systems. The 5/5, 6/5 ring structure **21** was discounted by ^{1}H–^{13}C one bond and three bond correlations; in particular the existence of a three bond correlation H-3 to C-3b as indicated, mitigated against the alternative structure **21**. The structure of **20** was confirmed by X-ray crystallography (Figure 2) and by conversion to **19** upon reduction with lithium aluminum hydride. In this manner, an average yield of 52% was obtainable in the conversion of **18** to **19**. This was a satisfactory, if experimentally inconvenient, result, but in addition to ensuring chemoselectivity in the reduction of two of the four amide carbonyl groups, a major source of the difficulties encountered in these reductions, C_3–C_{3a} cleavage, ring expansion, and isomerization of the 5/5 system, appears to have been minimized. It is still mystifying, however, why the reduction of two "identical" oxindole carbonyl groups should terminate after one had been reduced. Strong coordination of the aluminum to the nitrogen and/or oxygen atoms of **20** in some way is responsible, perhaps, for preventing reduction of the second oxindole carbonyl group. The conformation about the C_{3a}–C_{11} bond adopted in the crystal (Figure 2) places H-8a only 2.32 Å away from O-20 and 1.03 Å above the plane of the oxindole carbonyl group (C_{10}–O_{20}). This orientation is probably responsible for the large downfield shift ($\Delta\delta$ 1.54 ppm) observed in the H-8a aminal proton of **20** in comparison with H-8a, H-8a′ of **19**. Subsequently, the existence of some **20** was recognized in the complex mixture obtained from the lithium aluminum hydride reduction of **18**.

The synthesis of (±)-folicanthine (**1**) from **19** merely requires the reduction of the lactam carbonyl groups of the latter. Lithium aluminum hydride was not satisfactory for this conversion; only a small amount of the desired product could be isolated from the complex mixture. Reduction with an excess of the borane–THF reagent gave a single crystalline product (mp 184–5 °C), not (±)-folicanthine, in 71% yield. The 500 MHz ^{1}H NMR spectrum showed two doublets (6.97 and 6.25 ppm) and two triplets (7.07 and 6.67 ppm) for the aromatic protons, a singlet at 5.02 ppm and two singlets at 3.09 and 2.34 ppm representing the aminal proton and the *N*-methyl groups, respectively, and four separated complex absorptions at 3.06–3.11, 2.84, 2.55, and 2.09 ppm each integrating for one proton. Difference NOE spectra showed strong correlations between the singlet at 5.02 ppm and the doublet at 6.97 ppm and singlet at 3.09 ppm. Similarly the doublet at 6.97 ppm correlated with the singlet at 5.02 ppm, the triplet at 6.67 ppm, and an aliphatic proton signal at 2.09 ppm. Weaker correlation with the *N*-methyl signals were also observed. The upfield aromatic doublet at 6.25 ppm showed strong correlations to the downfield triplet at 7.07 ppm and the *N*-methyl signal at 3.09 ppm but to no other signals. A reasonable structure **22** containing a C_2 axis could be assigned, and its formation from **19** rationalized as shown in Scheme 2. This ring system was one structural proposal[22] seriously considered,[1-3] for calycanthine during the early structural investigations. The mass spectrum of the crystalline material, however, showed an ion of low abundance corresponding to $C_{24}H_{30}N_4$ at m/z 374 (<2%) but in addition a more abundant ion at m/z 388 (16%) and a very weak ion at m/z 402 (<1%). The IR spectrum of the crystalline material (KBr) displayed no sign at all of any carbonyl groups but a moderate absorption at 2363 cm^{-1} was clearly evident. The isotopic peaks for the ions at m/z 388 and 402 were consistent with the presence of one boron and two boron atoms, respectively, and the possibility that the molecule contained two borane (B–H str[23] at 2363 cm^{-1}) groups so placed as to not destroy its C_2 symmetry was considered.

(22) Robinson, R.; Teuber, H. J. *Chem. Ind.* **1954**, 783.
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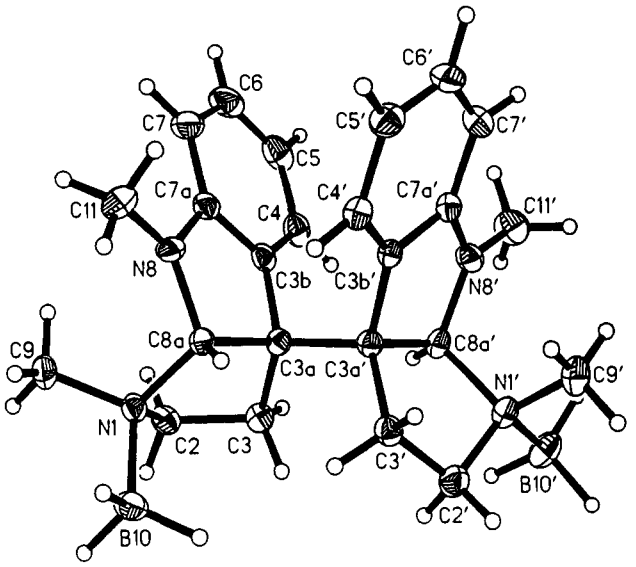

Figure 3. X-ray structure of (±)-folicanthine bis-borane **23**.

X-ray crystallography established the structure **23** (Figure 3) and indicated that the compound was in fact a bis-borane adduct of folicanthine. This molecule has two chiral nitrogen atoms, the termini of an array of six contiguous chiral atoms (N_1–C_{8a}–C_{3a}–$C_{3a'}$–$C_{8a'}$–$N_{1'}$) arranged in three pairs (all S or all R) with the whole molecule preserving the C_2 axis of **1**. The conformation adopted in the crystal, which places H-8a close to H-4′ (2.37 Å) and H-8a′ to H-4, is evidently similar to that in $CDCl_3$ solution, thus accounting for the NOE results; the obligatory *cis* fusion of the 5/5 segment of each pyrroloindole moiety brings H-3β close to H-4 and H-3′β to H-4′ (2.57 and 2.83 Å in the crystal). Thus the aliphatic proton signal at 2.09 ppm can be assigned to H-3β (and H-3′β). The reduction of amides with borane has been known[24] to produce amine boranes. The reduction of **19** with Red-Al produced (±)-folicanthine directly in 53% yield and **1** was also obtained from **23** by exposing it to ammonia in refluxing methanol. Both samples had spectroscopic and other physical properties consistent with their structures and identical with published data.[5]

Acid hydrolysis of chimonanthine (**2**) has been reported[6,7] to cause equilibration of the 5/5 system to the 6/6 of calycanthine. Using the same conditions (aqueous acetic acid[6]), the hydrolysis of our synthetic (±)-folicanthine as well as N_6,N_{12}-dimethylcalycanthine prepared from natural (+)-calycanthine[25] gave the identical major product N_1,N-dimethyltryptamine **24** identified by high field ^1H and ^{13}C NMR comparisons with commercial N-methyltryptamine. Two other attempts at acid degradation of calycanthine and folicanthine have been reported, with N-methyltryptamine **25**[26] and the dimethyl compound **24**,[27] respectively, being the major products isolated.

Experimental Section

Melting points are uncorrected. Column chromatography was performed on silica gel 60 (70–230 mesh) and thin-layer chromatography on the silica G/UV_{254} plates in the specified solvent system. IR spectra were obtained on a Bomem FT spectrophotometer. ^1H NMR and ^{13}C NMR spectra were recorded on Bruker AC-200, AM-250, and AMX-500 spectrometers in $CDCl_3$ unless otherwise specified. Low- and high-resolution mass spectra were obtained at the South-Western Ontario Regional Mass Spectrometry Center at McMaster University, Hamilton, Ontario, in the DEI or DCI mode. Elemental analyses were performed by M-H-W Laboratories, Phoenix, AZ, USA. All solvents were dried and freshly distilled before use, and reactions were conducted under an inert atmosphere (N_2 or Ar). In all instances where no elemental analysis was obtained, chromatographic separation, NMR (^1H and ^{13}C), and high-resolution mass spectrometry were used to ensure the purity (>95%) and identity of the material.

3-Bromo-3-((ethoxycarbonyl)methyl)-1-methylindol-2-one (7). A mixture of the oxindole **6** (1.07 g, 4.6 mmol), NBS (0.9 g, 5.05 mmol), and AIBN (96 mg, 0.58 mmol) in CCl_4 (20 mL) was heated at reflux for 7 h and then cooled to 0 °C. The solid succinimide was filtered, and the filtrate was evaporated under reduced pressure. The residue was chromatographed (20% ethyl acetate in hexane) and recrystallized to afford **7** (1.29 g, 90%): mp 90–92 °C (Et_2O–hexane); IR (KBr) 1740, 1716, 1610, 1474, 1375, 1210, 752, 660 cm^{-1}; ^1H NMR (200 MHz) δ 1.01 (t, J 7.1, 3H, $COOCH_2CH_3$), 3.28 (s, 3H, NCH_3), 3.50, 3.65 (d each, J 16.7, 2H, CH_2COOEt), 3.91 (AB of ABX_3, 2H, $COOCH_2CH_3$), 6.5 (d, J 7.8, 1H, H-7), 7.07 (t, J 7.6, 1H, H-5), 7.36 (m, 2H, H-4 and H-6); MS (EI) m/z 311 (M^+, 1), 313 ($M^+ + 2$, 1), 233 (32), 232 (27), 231 (60), 186 (29), 160 (58), 159 (100), 130 (16). Anal. Calcd for $C_{13}H_{14}BrNO_3$: C, 50.02; H, 4.52. Found: C, 50.01; H, 4.60.

3-((Ethoxycarbonyl)methenyl)-1-methylindol-2-one (8). A mixture of the bromide **7** (1.29 g, 4.16 mmol) and Et_3N (0.87 mL, 6.25 mmol) in ether (40 mL) was refluxed for 9 h and then cooled to room temperature. The amine salt was filtered, and the filtrate was concentrated to give the yellow unsaturated oxindole **8** (0.8 g, 84%): mp 74–76 °C (Et_2O–hexane); IR (KBr) 1710, 1660, 1606, 1490, 1470, 1370, 1186, 1024 cm^{-1}; ^1H NMR (250 MHz) δ 1.37 (t, J 7.1, 3H, $COOCH_2CH_3$), 3.23 (s, 3H, N-Me), 4.33 (q, J 7.1, 2H, $COOCH_2CH_3$), 6.79 (d, J 7.8, 1H, H-7), 6.90 (s, 1H, C=CHCOOEt), 7.06 (dt, J 7.7, 0.9, 1H, H-5), 7.36 (dt, J 7.7, 1.1, 1H, H-6), 8.55 (d, J 7.7, 1H, H-4); MS (EI) m/z 231 (M^+, 100), 186 (46), 160 (9), 159 (48), 130 (18). Anal. Calcd for $C_{13}H_{13}NO_3$: C, 67.51; H, 5.67. Found: C, 67.58; H, 5.81.

Preparation of Oxygen Linked Dimer (9). To a suspension of NaH (92 mg, 2.3 mmol, 60% wt dispersion in mineral oil, washed with dry hexane (2 × 3 mL)) in THF (8 mL) was added a solution of the oxindole **6** (0.49 g, 2.1 mmol) in THF (10 mL) at 0 °C. After 30 min, the resulting mixture was cooled to −65 °C, and a solution of **8** (0.5 g, 2.16 mmol) in THF (10 mL) was added. The mixture was stirred for 3 days at room temperature. Usual workup and chromatography (15% EtOAc in hexane) gave the main product **9** (270 mg, 33%): mp 122–123 °C (ether); IR (KBr) 1736, 1719, 1610, 1493, 1187, 750 cm^{-1}; ^1H NMR (250 MHz) δ 0.96, 1.40 (t each, J 7.1, 6H, 2 × $COOCH_2CH_3$), 2.75, 2.77 (s each, 6H, N-1-Me and N-1′-Me), 3.22, 3.32 (d each, J 16.1, 2H, CH_2COOEt), 3.78 (d, J 2.0, 1H, H-3′), 3.83 (q, J 7.1, 2H, $COOCH_2CH_3$), 4.31(d, J 1.7, 1H, O-CHCOOEt), 4.39, (AB of ABX_3, 2H, $COOCH_2CH_3$), 6.21 (d, J 7.6, 1H, H-7 or H-7′), 6.32 (d, J 7.7, 1H, H-7 or H-7′), 6.87–7.07 (m, 4H, aromatic H), 7.28 (d, J 7.5, 1H, H-4 or H-4′), 7.48 (d, J 7.3, 1H, H-4 or H-4′); MS (DCI) m/z 465 ($M^+ + 1$, 100), 234 (45), 232 (36); HRMS (DCI) m/z 465.2024, $M^+ + 1$, 465.2026 calcd for $C_{26}H_{29}N_2O_6$.

Dimerization of the Oxindole 6. To a suspension of NaH (920 mg, 23.0 mmol, 60% wt dispersion in mineral oil, washed with dry hexane (2 × 10 mL)) in THF (80 mL) was added a solution of the oxindole **6** (5.1 g, 21.9 mmol) in THF (70 mL) at 0 °C. After being stirred for 30 min, the reaction mixture was cooled to −65 °C, and then a solution of CI_4 (5.46 g, 10.5 mmol) in THF (70 mL) was slowly added over 4 h. After addition was complete, the reaction mixture was allowed to reach room temperature and stirred for 70 h. $Na_2S_2O_3$ solution (5 mL, 10%) and brine (20 mL) were added, and the THF was evaporated at reduced pressure. The residue was extracted with EtOAc (3 × 80 mL), washed (brine), and dried (Na_2SO_4). After evaporation of solvent, careful flash chromatography (10–15% ethyl acetate in hexane) and recrystallization afforded (±)-**dimer 10** (R_f 0.43, 49–57%), ***meso*-dimer 11** (R_f 0.19, 8 %), **trimer 12** (R_f 0.11, 3–4%), **yellow dimer 13** (R_f 0.33, 2%), **3-hydroxyoxindole 14** (R_f 0.27, 1%), **3-diiodomethyloxindole 15** (R_f 0.63, 8%), **oxindole 8** (R_f 0.70, 4%), and CHI_3 (R_f 0.89, 55%). The R_f values stated above are for thin-layer chromatograms on silica G/UV_{254} in ethyl acetate–hexane (1:1). (±)-**Dimer (10)**: mp 193–194 °C (EtOAc/hexane); IR (KBr) 1740, 1710, 1610, 1488, 1191, 762 cm^{-1}; ^1H NMR (250 MHz) δ 0.90 (t, J 7.2, 6H, 2 × $COOCH_2CH_3$), 3.09 (s, 6H, N-1-Me and N-1′-Me), 3.19, 4.03 (d each, J 15.8, 4H, 2 × CH_2COOEt), 3.77 (AB of ABX_3, 4H, 2 × $COOCH_2CH_3$), 6.38 (d, J 7.7, 2H, H-7 and H-7′), 6.80 (t, J 7.3, 2H, H-5 and H-5′), 7.01 (m, 4H, H-4, H-4′, H-6 and H-6′); ^{13}C NMR (62.86 MHz) δ 13.77 (2 × $COOCH_2CH_3$), 25.79 (2 × CH_2COOEt), 34.07 (N-1-*Me* and N-1′-*Me*), 52.54 (C-3 and C-3′), 60.34 (2 × $COOCH_2CH_3$), 107.30 (C-7 and C-7′), 122.41 (C-5 and C-5′), 122.93

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(C-4 and C-4′ or C-6 and C-6′), 126.98 (C-4 and C-4′ or C-6 and C-6′), 128.81 (C-3a and C-3a′), 143.98 (C-7a and C-7a′), 169.71 (C-2 and C-2′), 176.62 (2×*C*OOEt); MS (EI) *m/z* 464 (M^+, 17), 419 (8), 233 (91), 232 (82), 186 (38), 160 (100), 77 (12). Anal. Calcd for $C_{26}H_{28}N_2O_6$: C, 67.21; H, 6.08. Found: C, 67.14; H, 6.17.

***meso*-Dimer (11)**: mp 155–156 °C (EtOAc/hexane); IR (KBr) 1740, 1715, 1610, 1495, 1189, 754 cm^{-1}; ^1H NMR (250 MHz) δ 0.92 (t, *J* 7.2, 6H, 2 × $COOCH_2CH_3$), 2.96 (s, 6H, N-1-CH_3 and N-1′-CH_3), 3.13, 3.72 (d each, *J* 16.0, 4H, 2 × CH_2COOEt), 3.78 (AB of ABX_3, 4H, 2 × $COOCH_2CH_3$), 6.52 (d, *J* 7.0, 2H, H-7 and H-7′), 6.69 (d, *J* 7.8, 2H, H-4 and H-4′), 6.84 (t, *J* 7.3, 2H, H-5 and H-5′), 7.25 (dt, *J* 7.7, 1.0, 2H, H-6 and H-6′); ^{13}C NMR (62.86 MHz) δ 13.71 (2 × $COOCH_2CH_3$), 25.97 (2 × CH_2COOEt), 35.65 (N-1-Me and N-1′-Me), 53.19 (C-3 and C-3′), 60.43 (2 × $COOCH_2CH_3$), 107.85 (C-7 and C-7′), 121.32, (C-5 and C-5′), 123.50 (C-4 and C-4′ or C-6 and C-6′), 127.18 (C-4 and C-4′ or C-6 and C-6′), 129.12 (C-3a and C3a′), 145.16 (C-7a and C-7a′), 169.25 (C-2 and C-2′), 175.47 (2 × *C*OOEt); MS (EI) *m/z* 464 (M^+, 2), 419 (2), 233 (6), 232 (11), 186 (9), 160 (100), 77 (10). Anal. Calcd for $C_{26}H_{28}N_2O_6$: C, 67.21; H, 6.08. Found: C, 66.98; H, 6.15.

Trimer (12): mp 207–208 °C (methanol); IR (KBr) 1740, 1720, 1613, 1467, 1367, 1185, 754 cm^{-1}; ^1H NMR (500 MHz) δ 0.89, 0.91, 0.95 (t each, *J* 7.1, 9H, 3 × $COOCH_2CH_3$), 2.96, 3.03, 3.19, (s each, 9H, 3 × N-CH_3), 2.96, 3.36 (d each, *J* 16.1, 2H, CH_2COOEt), 3.15, 3.96 (d each, *J* 16.2, 2H, CH_2COOEt), 3.16, 3.97 (d each, *J* 15.9, 2H, CH_2COOEt), 3.71, 3.88 (m, 6H, 3 × $COOCH_2CH_3$), 6.26 (t, *J* 1.1, 1H, H-7), 6.34 (d, *J* 7.7, 2H, H-7′ or H-7″), 6.79 (dt, *J* 7.6, 1.1, 1H, H-5′ or H-5″), 6.86 (d, *J* 7.7, 1H, H-7″), 6.92 (d, *J* 1.1, 2H, H-4 and H-5), 6.96 (dd, *J* 7.6, 0.8, 1H, H-4′ or H-4″), 7.01 (dt, *J* 7.7, 1.2, 1H, H-6′ or H-6″), 7.05 (dt, *J* 7.4, 1.0, 1H, H-5′ or H-5″), 7.09 (dd, *J* 7.4, 1.0, 1H, H-4′ or H-4″), 7.32 (dt, *J* 7.7, 1.5, 1H, H-6′ or H-6″); ^{13}C NMR (62.86 MHz) δ 13.37 (3 × $COOCH_2CH_3$), 25.70, 25.78, 26.60 (3 × CH_2COOEt), 33.82, 33.94, 42.71 (3 × N-CH_3), 52.38, 52.47, 53.02 (C-3, C-3′ and C-3″), 60.32, 60.41, 60.50 (3 × $COOCH_2CH_3$), 105.68, 106.96, 108.33 (C-7, C7′ and C-7″), 122.73 (C-4 and C-5), 119.63, 121.45, 122.19, 129.36, 122.82, 124.31, 126.70, 128.74, 130.42, 140.19, 143.77, 144.19, 144.47 (aromatic-C), 169.09, 169.63, 169.73 (C-2, C-2′ and C-2″), 176.42, 176.61, 177.36 (3 × *C*OOet); MS (EI) *m/z* 695 (M^+, 5), 463 (100), 391 (28), 303 (30), 186 (4), 160 (16), 77 (8). Anal. Calcd for $C_{39}H_{41}N_3O_9$: C, 67.31; H, 5.94. Found: C, 67.16; H, 5.98.

Yellow dimer (13): mp 149–151 °C (ether–hexane); IR (KBr) 1722, 1652, 1614, 1373, 1192 cm^{-1}; ^1H NMR (500 MHz) δ 1.00 (t, *J* 7.0, 3H, $CH_2COOCH_2CH_3$), 1.34 (t, *J* 7.1, 3H, C=CHCOOCH$_2$*CH*$_3$), 3.19, 3.25 (s each, 6H, N-1-Me and N-1′-Me), 3.25, 3.52 (d each, *J* 16.1, 2H, CH_2COOEt), 3.85–3.95 (AB of ABX_3, 2H, $CH_2COOCH_2CH_3$), 4.29 (q, *J* 7.1, 2H, C=CHCOO*CH*$_2$CH$_3$), 6.86 (s, 1H, C=*CH*COOCH$_2$-CH$_3$), 6.88 (d, *J* 1.5, 1H, H-7), 6.93 (d, *J* 8.0, 2H, H-5 and H-7′), 7.14 (dt, *J* 7.6, 1.0, 1H, H-5′ or H-6′), 7.32 (dd, *J* 7.4, 1.3, 1H, H-4′), 7.38 (dt, *J* 7.8, 1.0, 1H, H-5′ or H-6′), 8.42 (d, *J* 8.2, 1H, H-4); MS (EI) *m/z* 462 (M^+, 100), 417 (19), 375 (75), 303 (30), 233 (14), 160 (28); HRMS (EI) *m/z* 462.1791, M^+, 462.1790 calcd for $C_{26}H_{26}N_2O_6$.

14: mp 90–92 °C (EtOAc/hexane); IR (KBr) 3248, 1740, 1710, 1617, 1500, 1249, 625 cm^{-1}; ^1H NMR (200 MHz) δ 1.20 (t, *J* 7.1, 3H, $COOCH_2CH_3$), 2.93 (s, 2H, CH_2COOEt), 3.21 (s, 3H, NCH_3), 4.13 (q, *J* 7.1, 2H, $COOCH_2CH_3$), 4.46 (br, 1H, OH), 6.83 (d, *J* 7.8, 1H, H-7), 7.09 (dt, *J* 7.8, 0.7, 1H, H-5), 7.26–7.42 (m, 2H, H-4 and H-6); MS (EI) *m/z* 249 (M^+, 29), 175 (20), 162 (100), 134 (20), 132 (13), 104 (13), 77 (25), 45 (68). Anal. Calcd for $C_{13}H_{15}NO_4$: C, 62.63; H, 6.07. Found: C, 62.78; H, 6.15.

15: mp 123–124 °C (EtOAc/hexane); IR (KBr) 1740, 1720, 1610, 1493, 1468, 1357 1196, 755 cm^{-1}; ^1H NMR (250 MHz) δ 0.97 (t, *J* 7.1, 3H, $COOCH_2CH_3$), 3.06, 3.15 (d each, *J* 15.8, 2H, CH_2COOEt), 3.24 (s, 3H, N-CH_3), 5.11 (s, 1H, CHI_2), 7.06 (d, *J* 7.8, 1H, H-7), 7.12 (dt, *J* 7.8, 0.9, 1H, H-5), 7.42 (dt, *J* 7.8, 1.3, 1H, H-6), 7.67 (d, *J* 7.6, 1H, H-4); ^{13}C NMR (62.86 MHz) δ −21.31 (CHI_2), 14.06 ($COOCH_2CH_3$), 26.49 (CH_2COOEt), 42.59 (N-Me), 54.41 (C-3), 60.06 ($COOCH_2CH_3$), 109.12 (C-7), 122.63, 123.96 (C-4 and C-5), 128.94 (C-6), 130.45 (C-3a), 145.97 (C-7a), 168.28 (C-2), 174.30 (*C*OOEt); MS (EI) *m/z* 499 (M^+, 28), 245 (100), 172 (22), 160 (19), 77 (8); HRMS (EI) *m/z* 498.9160, M^+, 498.9141 calcd for $C_{14}H_{15}NO_3I_2$.

(±)-Diamide 18: To a solution of Me_3Al (7.1 mL, 2.0 M in hexane, 14.3 mmol) in CH_2Cl_2 (15 mL) was added dropwise a solution of methylamine (427 mg, 13.5 mmol, cooled to −78 °C) in CH_2Cl_2 (5 mL) at −10 °C. After addition was complete, the mixture was stirred for 30 min, the cooling bath was removed, and the solution was warmed to room temperature. A solution of (±)-dimer **10** (696 mg, 1.5 mmol) in CH_2Cl_2 (8 mL) was added. The resulting solution was refluxed for 40–72 h (monitored by TLC), then cooled to 0 °C, and 3% HCl (20 mL) was added dropwise to avoid excessive foaming at the beginning of the hydrolysis. After addition of 1 mL of the HCl, the solution was diluted with chloroform (80 mL), and the rest of HCl was added slowly. The organic layer was separated, and the aqueous phase was extracted with chloroform (2 × 50 mL). The combined extracts were washed with brine, dried ($MgSO_4$), and evaporated. The crude residue was dissolved in chloroform (3 mL), and acetone (6 mL) was added. The white powder **(±)-diamide 18** (62%) was obtained by filtration. It can be used for the next step without recrystallization: mp 284–285 °C (methanol); IR (KBr) 3320, 1679, 1610, 1544, 1349, 744 cm^{-1}; ^1H NMR (200 MHz, DMSO-d_6) δ 2.17 (d, *J* 4.5, 6H, 2 × NHCH_3), 2.79, 3.63 (d each, *J* 15.2, 4H, 2 × CH_2CONHMe), 2.88 (s, 6H, N-1-CH_3 and N-1′-CH_3), 6.40 (d, *J* 7.7, 2H, H-7 and H-7′), 6.75 (m, *J* 7.3, 4H, H-4, H-4′, H-5 and H-5′), 6.89 (m, 2H, H-6 and H-6′); ^{13}C NMR (62.86 MHz, DMSO-d_6) δ 25.12 (2 × CONH-*Me*), 25.42 (N-1-*Me* and N-1′-*M*), 34.58 (2 × CH_2-CONHMe), 52.15 (C-3 and C-3′), 107.04 (C-7 and C-7′), 120.32 (C-5 and C-5′), 122.02 (C-4 and C-4′), 127.44 (C-6 and C-6′), 127.84 (C-3a and C-3a′), 143.91 (C-7a and C-7a′), 168.55 (2 × *C*ONHMe), 176.50 (C-2 and C-2′); MS (EI) *m/z* 434 (M^+, 4), 218 (29), 160 (100), 159 (25), 130 (13). Anal. Calcd for $C_{24}H_{26}N_4O_4$: C, 66.33; H, 6.03. Found: C, 66.13; H, 6.26.

DIBAL-H Reduction of 18. To a suspension of diamide **18** (217 mg, 0.5 mmol) in THF (150 mL) was added a solution of lithium diisopropylamide (1.25 mmol, made freshly from diisopropylamine and *n*-BuLi) at −10 °C, and then stirring was continued until the mixture became soluble over 30–60 min. The reaction mixture was cooled to −30 °C and diisobutylaminium hydride (5 mL, 1.0 M in hexane, 5 mmol) was added with a syringe and then stirred 12–24 h until the starting material disappeared (monitored by TLC) at room temperature. Saturated potassium sodium tartrate (40 mL) was added, and the mixture was stirred vigorously for 3 h. The organic phase was separated, and the aqueous layer was extracted with ether (2 × 50 mL). The combined extracts were washed with brine (20 mL) once, dried (Na_2SO_4), and concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 (50 mL), treated with 10-camphorsulfonic acid (25 mg), and stirred overnight at room temperature. The solution was washed with 5% aqueous $NaHCO_3$ and dried (Na_2SO_4). Concentration and flash chromatography (3% methanol in ethyl acetate) afforded **dimeric lactam 19** (25–35%) and **lactam amide 20** (30–42%). **19**: mp 261–263 °C (MeOH/EtOAc); IR (KBr) 1692, 1606, 1494, 1426, 1234, 752 cm^{-1}; ^1H NMR (250 MHz) δ 2.72 (s, 6H, N-1-CH_3 and N-1′-CH_3), 2.82, 3.04 (d each, *J* 17.0, 4H, H-3 and H-3′), 3.05 (s, 6H, N-8-CH_3 and N-8′-CH_3), 4.39 (s, 2H, H-8a and H-8a′), 6.46 (d, *J* 7.8, 2H, H-7 and H-7′), 6.76 (t, *J* 7.5, 2H, H-5 and H-5′), 7.13 (d, *J* 7.4, 2H, H-4 and H-4′), 7.20 (dt, *J* 7.7, 0.9, 2H, H-6 and H-6′); ^{13}C NMR (62.86 MHz) δ 27.79 (N-1-Me and N-1′-Me), 34.58 (N-8-Me and N-8′-Me), 38.93 (C-3 and C-3′), 53.58 (C-3a and C-3a′), 86.89 (C-8a and C-8a′), 106.94 (C-7 and C-7′), 118.35 (C-5 and C-5′), 123.87 (C-4 and C-4′), 129.49, (C-6 and C-6′), 129.90 (C-3b and C-3b′), 149.14 (C-7a and C-7a′), 171.19 (C-2 and C-2′); MS (EI) *m/z* 402 (M^+, 4), 201 (8), 186 (6), 144 6), 88 (13), 43 (100); HRMS (EI) *m/z* 402.2057, M^+, 402.2056 calcd for $C_{24}H_{26}N_4O_2$.

20: mp 244–246 °C (MeOH/EtOAc); IR (KBr) 3336, 1687, 1609, 1244, 751 cm^{-1}; ^1H NMR (500 MHz) δ 2.46 (d, *J* 4.5, 3H, CONHCH_3), 2.85, 3.12, 3.25 (s each, 9H, N-1-Me, N-8-Me and N-9-Me), 2.37, 3.10 (d each, *J* 14.8, 2H, CH_2CONHMe), 2.38, 2.55 (d each, *J* 17.4, 2H, H-3) 5.25 (br, 1H, NH), 5.93 (s, 1H, H-8a), 6.38 (d, *J* 7.7, 1H, aromatic-H), 6.71 (dt, *J* 7.5, 0.8, 1H, aromatic-H), 6.99 (d, *J* 7.5, 1H, aromatic-H), 7.17 (dt, *J* 7.5, 1.0, 1H, aromatic-H), 6.80 (d, *J* 7.7, 1H, aromatic-H), 7.00 (dt, *J* 7.5, 0.9, 1H, aromatic-H), 7.10 (d, *J* 7.5, 1H, aromatic-H), 7.27 (dt, *J* 7.5, 0.8, 1H, aromatic-H); ^{13}C NMR (62.86 MHz) δ 26.52 (CONH*Me*), 27.01 (N-9-Me), 28.83 (N-1-Me), 34.38 (N-8-Me), 38.03 (C-12), 38.10 (C-3), 53.19 (C-11), 54.61 (C-3a), 85.25 (C-8a), 107.64 (C-7), 108.83 (C-15), 118.25 (C-5), 121.99 (C-13), 125.18 (C-12), 125.97 (C-4), 129.47 (C-14), 130.58 (C-6), 128.55 (C-11a), 129.83 (C-3b), 144.93 (C-15a), 150.27 (C-7a), 169.38 (*C*ONHMe), 172.29 (C-2), 178.45 (C-10); MS (EI) *m/z* 418 (M^+, 5), 218 (43), 202 (15), 201 (100), 160 (22), 159 (21), 49 (15), 43 (8); HRMS (EI) *m/z* 418.1993, M^+, 418.2004 calcd for $C_{24}H_{26}N_4O_3$.

Reduction of 20: To a suspension of $LiAlH_4$ (38 mg, 1 mmol) in THF (10 mL) was added a solution of **20** (140 mg, 0.33 mmol) in THF (5 mL) at 0 °C with syringe. The resulting mixture was stirred for 5 h at room temperature and quenched with 5% HCl (1.5 mL) at 0 °C. Usual workup and flash chromatography afforded **19** (71 mg, 52%).

Red-Al Reduction of 19 (Preparation of (±)-Folicanthine 1). To a stirred solution of **19** (75 mg, 0.19 mmol) in benzene (20 mL) was added

dropwise a solution of vitride (Red-Al) (767 mg, 3.8 mmol) in benzene (10 mL) at room temperature. The reaction mixture was stirred for 5 h, the excess vitride was decomposed with acetone (2 mL), and 10% NaOH (10 mL) was added. The mixture was extracted with benzene (2 × 20 mL), and the extracts were washed (brine) and dried (Na_2SO_4). After removal of the solvent, flash chromatography (benzene:EtOAc:Et_2NH, 70:20:1) gave folicanthine **1** (37.3 mg, 53%); mp 168–169 °C (ether/hexane); IR (KBr) 1609, 1495, 745 cm^{-1}; ^1H NMR (250 MHz) δ 1.92–1.98 (m, 2H, H-2 and H-2′ or H-3 and H-3′), 2.30-2.49 (m, 4H, H-2 and H-2′ or H-3 and H-3′), 2.58–2.67 (m, 2H, H-2 and H-2′ or H-3 and H-3′), 2.40 (s, 6H, N-1-Me and N-1′-Me), 3.00 (s, 6H, N-8-Me and N-8′-Me), 4.38 (s, 2H, H-8a and H-8a′), 6.25 (d, J 7.8, 2H, H-7 and H-7′), 6.49 (t, J 7.3, 2H, H-5 and H-5′), 6.89–6.99 (m, 4H, H-4, H-4′, H-6 and H-6′); ^{13}C NMR (62.86 MHz) δ 35.28 (C-3 and C-3′), 35.38 (N-1-Me and N-1′-Me), 37.90 (N-8-Me and N-8′-Me), 52.61 (C-2 and C-2′), 62.65 (C-3a and C-3a′), 92.95 (C-8a and C-8a′), 105.78 (C-7 and C-7′), 116.60 (C-5 and C-5′), 123.60 (C-4 and C-4′), 128.02 (C-6 and C-6′), 132.78 (C-3b and C-3b′), 152.87 (C-7a and C-7a′); MS (EI) *m/z* 374 (M^+, 10), 188 (44), 187 (85), 186 (100), 185 (41), 172 (20), 145 (45), 144 (80); HRMS (EI) *m/z* 374.2462, M^+, 374.2470 calcd for $C_{24}H_{30}N_4$.

Borane Reduction of 19. To a solution of **19** (35 mg, 0.087 mmol) in THF (5 mL) was added BH_3–THF (1.4 mL, 1.0 M in THF) at room temperature, and the resulting mixture was stirred until the starting material had disappeared (monitored by TLC). The excess BH_3 was destroyed with methanol, and the solution evaporated. The residue was purified by flash chromatography (10% EtOAc in hexane) to give **bis-borane complex (23)** (23 mg, 71%): mp 184–185 °C (EtOAc/hexane); IR (KBr) 2950 (br), 2368, 1606, 1491, 1173, 743 cm^{-1}; ^1H NMR (500 MHz) δ 2.09 (ddd, *J* 10.5, 5.9, 4.6, 2H, CH_2), 2.34 (s, 6H, N-1-Me and N-1′-Me), 2.55 (ddd, *J* 15.2, 9.2, 6.0, 2H, CH_2), 2.84 (ddd, *J* 15.8, 9.5, 6.8, 2H, CH_2), 3.06–3.11 (m, 2H, CH_2), 3.09 (s, 6H, N-8-Me and N-8′-Me), 5.02 (s, 2H, H-8a and H-8a′), 6.25 (d, *J* 7.8, 2H, H-7 and H-7′), 6.67 (dt, *J* 7.5, 1.0, 2H, H-5 and H-5′), 6.97 (dd, *J* 7.5, 0.7, 2H, H-4 and H-4′), 7.07 (dt, *J* 7.7, 1.2, 2H, H-6 and H-6′); ^{13}C NMR (62.86 MHz) δ 31.46 (C-3 and C-3′), 34.13 (N-1-CH_3 and N-1′-CH_3), 45.48 (N-8-CH_3 and N-8′-CH_3), 61.32 (C-2 and C-2′), 61.74 (C-3a and C-3a′), 96.11 (C-8a and C-8a′), 105.51 (C-7 and C-7′), 117.74 (C-5 and C-5′), 123.26 (C-4 and C-4′), 129.33 (C-6 and C-6′), 129.63 (C-3b and C-3b′), 149.84 (C-7a and C-7a′); MS (EI) *m/z* 402 (M^+, 0.5), 388 ($M^+ - BH_3$, 16), 374 ($M^+ - 2BH_3$, 1.3), 187 (55), 186 (100), 201 (34), 145 (17), 144 (72); HRMS (EI) *m/z* 388.2806, $M^+ - BH_3$, 388.2798 calcd for $C_{24}H_{33}N_4B$.

Methanol/NH_3 Treatment of 23. **23** (10 mg, 0.25 mmol) was dissolved in methanol (5 mL, saturated with NH_3), and the resulting mixture was refluxed for 2 h. After being cooled to 0 °C, brine (2 mL) was added, and the methanol evaporated. The aqueous residue was extracted with ethyl acetate (3 × 10 mL), and usual workup and chromatography afforded (±)-folicanthine (7 mg, 75%).

Preparation of Dimethylcalycanthine (17). To a stirred solution of calycanthine (346 mg, 1.0 mmol) and 37% formaldehyde (2 mL) in acetonitrile (10 mL) was added in portions sodium cyanoborohydride (0.2 g, 3.2 mmol).[28] The reaction mixture was stirred for 30 min, and the glacial acetic acid (3.2 mL) was added dropwise to maintain the pH of the solution near neutrality. After addition was complete, the solvent was evaporated at reduced pressure, and 20% NaOH (15 mL) was added to the residue. The resulting mixture was extracted with EtOAc (2 × 20 mL), washed (brine), and dried (Na_2SO_4). Concentration and flash chromatography (benzene:EtOAc:diethylamine, 90:10:1) gave **17** (206 mg, 55%): mp 303–304.5 °C (EtOAc/hexane); IR (KBr) 3056, 3028, 1595, 1475, 1371, 738, 625 cm^{-1}; ^1H NMR (250 MHz) δ 1.35 (dd, *J* 13.0, 2.9, 2H, CH_2), 2.19 (dt, *J* 12.9, 4.0, 2H, CH_2), 2.45 (s, 6H, N-13-Me and N-18-Me), 2.59 (dd, *J* 11.3, 5.1, 2H, CH_2), 3.03 (s, 6H, N-6-Me and N-12-Me), 2.98–3.11 (m, 2H, CH_2), 4.31 (s, 2H, 5-H and 11-H), 6.21 (d, *J* 8.0, 2H, H-1 and H-7), 6.50 (t, *J* 7.1, 2H, H-3 and H-9), 6.85 (d, *J* 7.7, 2H, H-4 and H-10), 6.88 (t, *J* 7.9, 2H, H-2 and H-8); ^{13}C NMR (62.86 MHz) δ 32.04 (C-15 and C-16), 36.51 (C-4b and C-10b), 42.26 (N-13-Me and N-18-Me), 43.95 (N-6-Me and N-12-Me), 46.78 (C-14 and C-17), 81.35 (C-5 and C-11), 108.32 (C-1 and C-7), 114.93 (C-3 and C-9), 123.75 (C-4 and C-10), 125.37 (C-4a and C-10a), 126.65 (C-2 and C-8), 146.94 (C-6a and C-12a); MS (EI) *m/z* (M^+, 374, 100), 330 (29), 261 (18), 245 (14), 187 (17), 186 (28), 144 (35); HRMS (EI) *m/z* 374.2474, M^+, 374.2470 calcd for $C_{24}H_{30}N_4$.

Acetic Acid Hydrolysis of Folicanthine (1) and Dimethylcalycanthine (17). To a suspension of folicanthine (**1**, 32 mg, 0.09 mmol) in water (6 mL) was added acetic acid (9 drops), and the resulting mixture was heated for 24 h at 100 °C until the starting material had disappeared. The reaction mixture was neutralized with saturated $NaHCO_3$ solution, extracted with ethyl acetate, dried (Na_2SO_4), and concentrated. Flash chromatography (benzene:EtOAc:diethylamine, 90:10:1) afforded the N_1,*N*-dimethyltryptamine (**24**) (8 mg, 25%). Similarly, hydrolysis of dimethylcalycanthine (**17**) (250 mg, 6.7 mmol) in water (35 mL) with acetic acid (4 mL) afforded **24** (65 mg, 26%): IR (neat) 3407, 2900, 1709, 1613, 1469, 744 cm^{-1}; ^1H NMR (250 MHz) δ 1.66 (s, 1H, *NH*Me), 2.43 (s, 3H, NH*Me*), 2.88–2.98 (m, 4H, CH_2CH_2), 3.73 (s, 3H, N-1-Me), 6.88 (s, 1H, H-2), 7.09 (dt, *J* 6.6, 1.1, 1H, H-5), 7.17–7.29 (m, 2H, H-6 and H-7), 7.60 (d, *J* 7.8, 1H, H-4); ^{13}C NMR (62.86 MHz) δ 25.46 (CH_2NHMe), 32.56 (N-1-*Me*), 36.29 (CH_2NH*Me*), 52.55 (C3-CH_2), 109.16 (C-7), 112.49 (C-3), 118.68 (C-5), 118.98 (C-2), 121.53 (C-4), 126.73 (C-6), 127.87 (C-3a), 137.13 (C-7a); MS (EI) *m/z* 188 (M^+, 4), 157 (10), 145 (83), 144 (100), 77 (12).

***N*-Methyltryptamine (25):** ^1H NMR (250 MHz) δ 1.09 (s, 1H, *NH*Me), 2.42 (s, 3H, NH*Me*), 2.90–3.00 (m, 4H, CH_2CH_2), 6.90 (d, *J* 1.7, 1H, H-2), 7.05–7.19 (m, 2H, H-5 and 6-H), 7.27 (d, *J* 7.3, 1H, H-7), 7.61 (d, *J* 7.3, 1H, H-4), 9.18 (s, 1H, N-1-H); ^{13}C NMR (62.86 MHz) δ 25.49 (CH_2NHMe),), 36.10 (CH_2NH*Me*), 51.91 (C3-CH_2), 111.16 (C-7), 113.31 (C-3), 118.66 (C-5), 118.92 (C-2), 121.53 (C-4), 126.73 (C-6), 126.81 (C-3a), 137.13 (C-7a).

X-ray Crystal Structure Determinations of 10, 12, 20, and 23. The data were collected on a Nicolet LT2 equipped Nicolet-Siemens R3m/V diffractometer employing MoKα radiation (λ = 0.710 73 Å) and a graphite monochromator. Absorption corrections were by face-indexed analytical methods, the crystal dimensions quoted being referenced to common centers. The structures were solved by direct methods and refined by full-matrix least-squares methods using Siemens SHELXTL PLUS software. Weighting schemes employed were based on counting statistics ($w^{-1} = \sigma^2(F)$). Full details of the X-ray analyses are included in the supplementary material.

10: crystals of $C_{26}H_{28}N_2O_6$, *M* = 464.5, are triclinic, space group *P*1, *a* = 9.118(2) Å, *b* = 11.538(2) Å, *c* = 12.197(2) Å, α = 66.14(2)°, β = 89.09(2)°, γ = 88.55(2)°, *V* = 1173.2(3) Å^3, with *Z* = 2, D_c = 1.315 g cm^{-3}, *F*(000) = 492, *T* = 200 K. Crystal dimensions were 0.16{110} × 0.26{101} × 0.21{011} mm. From 3888 independent reflections measured 2θ ≤ 50°), 3128 (with $F \geq 6\sigma(F)$) were considered observed and used in the structure solution and refinement to give *R* and R_w values of 3.73 and 3.82%.

12: crystals of $C_{39}H_{41}N_3O_9$, *M* = 695.7, are triclinic, space group *P*1, *a* = 8.947(2) Å, b = 12.498(3) Å, c = 16.731(3) Å, α = 71.28(2), β = 83.36(2), γ = 85.71(2)°, *V* = 1758.5(6) Å^3, with *Z* = 2, D_c = 1.314 g cm^{-3}, *F*(000) = 736, *T* = 200 K. Crystal dimensions were 0.25{100} × 0.23{010} × 0.20{001} nm. From 5555 independent reflections measured (2θ ≤ 48°), 4227 (with $F \geq 6\sigma(F)$) were considered observed and used in the structure solution and refinement to give *R* and R_w values of 4.74 and 4.85%.

20: crystals of $C_{24}H_{26}N_4O_3$, *M* = 418.5, are triclinic, space group *P*1, *a* = 11.702(2) Å, b = 12.144(2) Å, c = 16.550(3) Å, α = 78.88(1), β = 70.00(1), γ = 75.23(1)°, *V* = 2122.6(6) Å^3, with *Z* = 4, D_c = 1.310 g cm^{-3}, *F*(000) = 888, *T* = 295 K. Crystal dimensions were 0.16{101} × 0.18{121} × 0.26{012} mm. From 5571 independent reflections measured (2θ ≤ 45°), 3705 (with $F \geq 6\sigma(F)$) were considered observed and used in the structure solution and refinement to give *R* and R_w values of 3.34 and 3.09%.

23: crystals of $C_{24}H_{36}B_2N_4$, *M* = 402.2, are monoclinic, space group $P2_1/c$, *a* = 8.418(3) Å, b = 17.815(5) Å, c = 15.377(3) Å, β = 93.46(2)°, *V* = 2301.8(11) Å^3, with *Z* = 4, D_c = 1.161 g cm^{-3}, *F*(000) = 872, *T* = 180 K. Crystal dimensions were 0.15{010} × 0.22{001} × 0.10{100} × 0.10{110} mm. From 4072 independent reflections measured (2θ ≤ 50°), 2585 (with $F \geq 6\sigma(F)$) were considered observed and used in the structure solution and refinement to give *R* and R_w values of 3.65 and 3.46%.

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Supplementary Material Available: Full details of X-ray analyses of **10**, **12**, **20**, and **23** (43 pages); tables of observed and calculated structure factors (79 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.