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# The structural and synthetic implications of the biosynthesis of the calycanthaceous alkaloids, the communesins, and nomofungin

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**Abstract**—A comparison is made between the calycanthaceous alkaloids, nomofungin, and the communesins using structural and biosynthetic information from studies of the former to shed light on the structural ambiguity of the two latter species. Also, a novel biosynthetic approach for the communesins is presented that involves coupling of tryptamine with the ergot alkaloid aurantioclavine that is suitable for synthetic emulation. Preliminary synthetic studies and intermediates are reported.
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## 1. Introduction

Natural product isolation, biosynthetic studies, and natural product synthesis are often used synergistically to illuminate molecular structure and to broaden understanding of small molecule/biological interactions. Chemical transformations, purifications, conformational analysis, and structural characterization are all shared aspects of these approaches to describe natural products. Often, knowledge of the biosynthesis and the natural function of isolated compounds can suggest approaches to their synthesis and application to novel targets. Synthetic efforts can resolve ambiguities in structural assignment as well as provide material for in depth analysis. Because of this interconnectedness, comprehensive background knowledge of structural classes of compounds is essential for the practicing chemist.

Thus, organic chemists have become well acquainted with the calycanthaceous alkaloids, which were first isolated from the plant genus *Calycanthus*.[1] Early isolations of individual members showed a closely related skeleton that differed only in the aminal connectivity for the various natural products. In fact, five structural isomers are possible through aminal construction from the hypothetical intermediate **1** (see Fig. 1), though only four of these arrangements (**3**, **4**, **5**, and **6**) are currently represented by natural products. The subtle differences in possible structures mandated substantial effort to establish the relative and absolute stereochemistry of these compounds; chemical degradation studies, nuclear magnetic resonance (NMR) techniques, X-ray diffraction analysis, and total synthesis techniques were required to elucidate unambiguously the structures of these alkaloids.

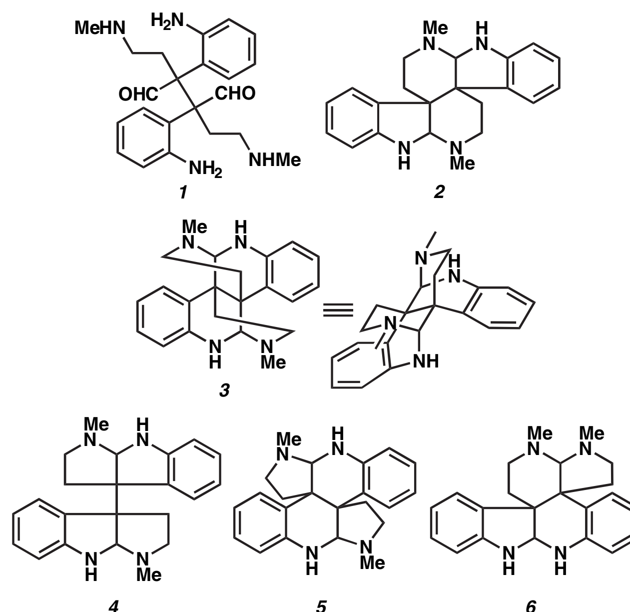


**Figure 1.** Possible topologies for the calycanthaceous alkaloids.

The first calycanthoid to be characterized was (+)-calycanthine (**3**, Fig. 2). The structure was established chemically by Robinson[2] and Woodward[3] and crystallographically by

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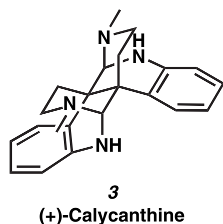



**Figure 2.** Calycanthine.

Hamor and Robertson using the dihydrobromide dihydrate salt.[4] Two appended bridged bicycles comprise this $C_2$-symmetric structure, the most intricate of the five regioisomers. The absolute stereochemistry of calycanthine was determined using circular dichroism analysis by Mason soon after the publication of the crystal structure.[5]

The structure of (−)-chimonanthine (**7**, Fig. 3), isolated from *Chimonanthus fragrans* (Hodson et al.[6]), was subsequently elucidated by Hamor and Robertson through X-ray analysis of the dihydrobromide salt.[7] Chimonanthine contains two indoline units, each with an annulated pyrrolidine, that are 3,3′-connected. Interestingly, both the $C_2$-symmetric and *meso* isomers have been identified. The absolute stereochemistry of the vicinal quaternary carbon centers of (−)-chimonanthine is identical to that of calycanthine, and the two equilibrate under acidic conditions. Two other ambiguous structures, those of calycanthidine[8] (**8**) and folicanthine[9] (**9**), were also confirmed by the chimonanthine crystal structure, as these compounds had been shown to be the successive methylation products of chimonanthine.[10]

Later, in 1992, (−)-calycanthine, *meso*-chimonanthine, and the novel *iso*-calycanthine (**11**, Fig. 4) were isolated from *Psychotria forsteriana*.[11] The first two compounds were identified by comparison to previously isolated compounds. The structure of *iso*-calycanthine was assigned based on available spectroscopic data and contrast to known isomers. Compound **11**, a *meso*-compound, bears the same diastereomeric relationship about its quaternary carbon centers as *meso*-chimonanthine. An oxidized version of skeleton **2** was later observed in extracts of *Psychotria colorata* in addition to the compounds isolated from *P. forsteriana*.[12] (8-8a),(8′-8′a)-Tetradehydroisocalycanthine (**12**) was characterized spectroscopically and via a crystal structure using the dihydrobromide salt. If performed, oxidation of **11** to **12** or reduction of **12** to **11** would further confirm the structure of **11**.

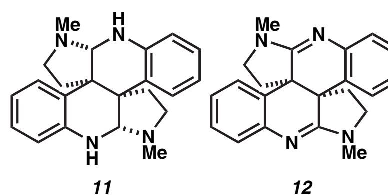



**Figure 4.** Representatives of framework **5**.

Many closely related compounds have been isolated from sources other than plants. In fact, the antipodes for the *Calycanthus*-derived structures, (−)-calycanthine and (+)-chimonanthine, were isolated from the Colombian poison-dart frog, *Phyllobates terribilis*.[13]

Similarly, skeleton **6** (Fig. 1) appears in the communesins[14] and nomofungin.[15] Communesins A and B (**14** and **15**, Fig. 5) were isolated from a strain of *Penicillum sp*. marine fungus in 1993. Communesin B had cytotoxic effects on P-388 lymphocytic leukemia cells with an effective dose of 0.45 μg mL$^{-1}$, while communesin A had an effective dose of 3.5 μg mL$^{-1}$. Later, isolations of communesins C–H showed varied substitution on the nitrogens and pendant isobutene.[16] Communesins C–F also showed antiproliferative and insecticidal activity, but G and H did not.[16c] Nomofungin (**13**) was found to disrupt microtubule formation in cultured mammalian cells. It is somewhat cytotoxic and demonstrates minimum inhibitory concentrations of 2 and 4.5 μg mL$^{-1}$ with LoVo and KB cells, respectively.

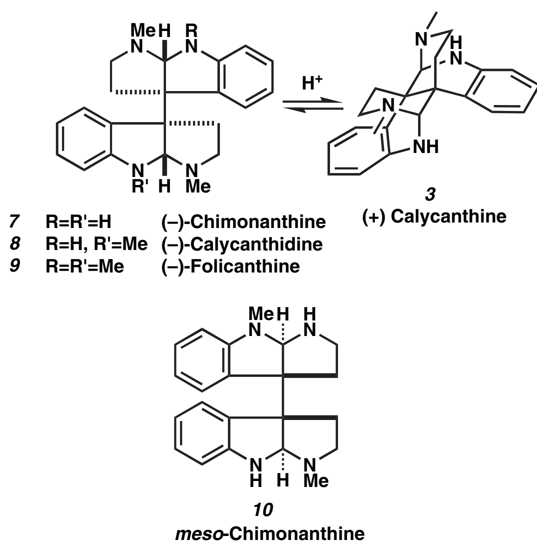
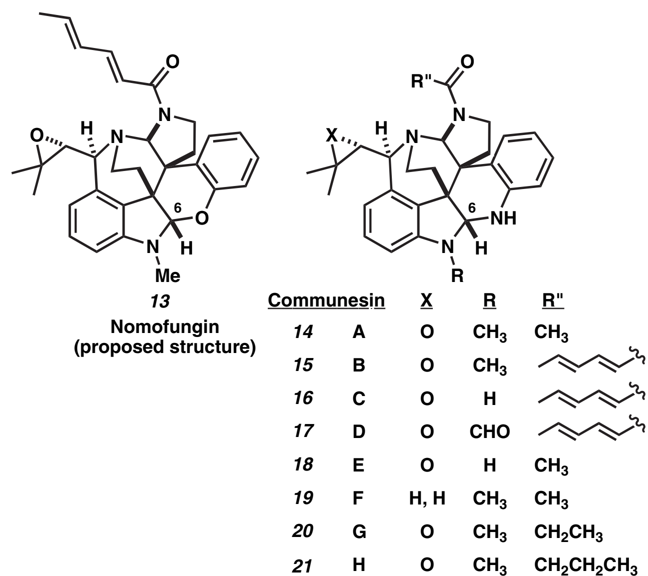



**Figure 3.** Compounds representative of scaffold **4**.




| | Communesin | X | R | R" |
|---|---|---|---|---|
| 14 | A | O | $CH_3$ | $CH_3$ |
| 15 | B | O | $CH_3$ | |
| 16 | C | O | H | |
| 17 | D | O | CHO | |
| 18 | E | O | H | $CH_3$ |
| 19 | F | H, H | $CH_3$ | $CH_3$ |
| 20 | G | O | $CH_3$ | $CH_2CH_3$ |
| 21 | H | O | $CH_3$ | $CH_2CH_2CH_3$ |

**Figure 5.** The communesins and nomofungin.

An additional recent isolate from fungal cultures (*Perophora namei* ascidia), reminiscent of the calycanthaceous alkaloids and similar in connectivity to the communesins, is perophoramidine (**22**, Fig. 6).[17] This compound demonstrated cytotoxicity with the HCT116 colon carcinoma cell line with an $IC_{50}$ of 60 μM and induced apoptosis via PARP cleavage within 24 h. Note that the arrangement of the vicinal quaternary carbon centers in perophoramidine is diastereomeric with respect to the orientation found in the communesins. Perophoramidine mimics the relative stereochemistry found in *meso*-chimonanthine, while communesin mirrors that of (±)-chimonanthine at those centers.

The apparently convergent development of the calycanthaceous alkaloids by such disparate species indicates they are a readily accessed family of compounds for many organisms and thus are likely to be important as research targets. The similarities between nomofungin and communesin B are especially striking, prompting an examination of the reported spectral data for the two compounds. Interestingly, the chemical shifts and coupling constants are essentially identical in all respects.[14,15] In particular, the chemical shift of the C(6) proton is reported to be 4.70 ppm for communesin B and 4.69 ppm for nomofungin. Analogously, the $^{13}C$ NMR chemical shift for C(6) is 82.4 ppm for both compounds. From these data, and the similarity of the full NMR data set, we concluded that communesin B and nomofungin must be the same molecule.[18]

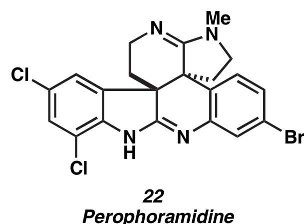



**Figure 6.** Perophoramidine.

Fortunately, structural similarity to the calycanthaceous alkaloids can potentially shed light on a potential biosynthesis of this compound and can thus help to determine which proposed structure, if any, correctly describes communesin B and nomofungin. Such a comparison of structures obviously favors the communesin structural assignment. Even so, comparison to known chemical shift values for aminal and hemiaminal functionalities confirms the tendency for the $^{1}H$ NMR chemical shifts of the former to reside upfield relative to the latter. For example, the aminal protons in isochimonanthine (**23**) and calycanthine (**3**) are 4.32 and 4.42 ppm, respectively, whereas the shifts for hemi-aminals **24**, **25**, and **27** are 5.0, 5.4, and 6.3 ppm (Fig. 7).[19] The nomofungin and communesin B value of 4.7 ppm resides closer to that for an aminal. Similarly, $^{13}C$ NMR chemical shifts for aminal carbons are typically in the range of 71.0 to 84.0 ppm, while those for hemi-aminal carbons are shifted downfield to between 97.0 and 106.0 ppm.[20] The case of the proposed and actual structures for diazonamide A, **26** and **27**, respectively, shows a general trend that additional oxygenation shifts the signals further downfield. The nomofungin and communesin shift, 82 ppm, is clearly in the range for aminal carbons. Given the $^{1}H$ and $^{13}C$ NMR chemical shift data, we have assumed that the assignment for communesin B best represents the true structure.

Biosynthetic comparison to the calycanthaceous alkaloids can also provide insight to the atomic makeup of

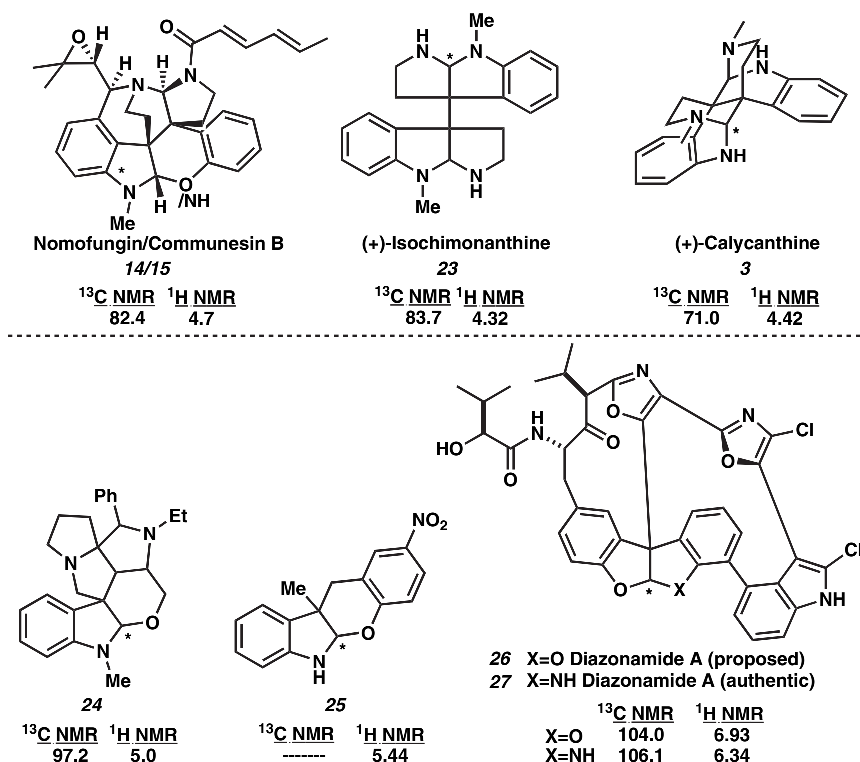
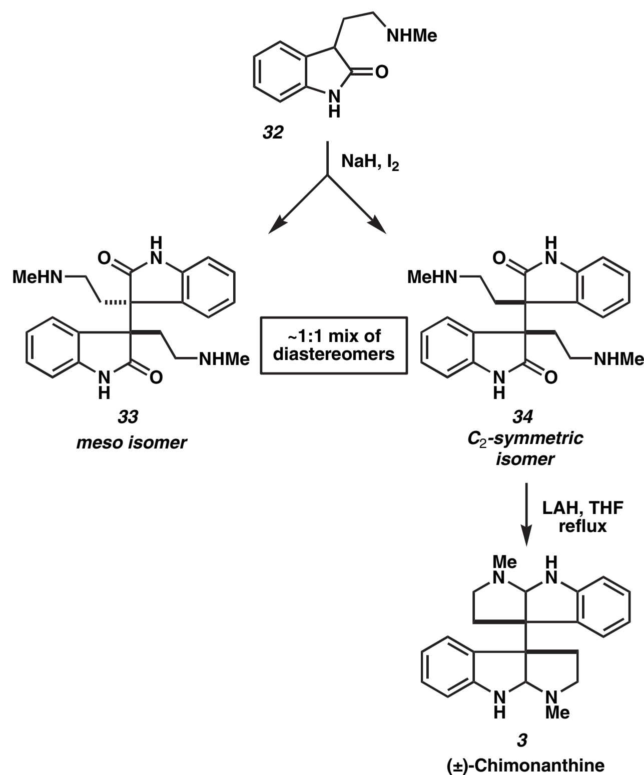



**Figure 7.** Peak frequencies of known compounds.[19,20]

communesin and nomofungin. Both biosynthetic labeling and biomimetic syntheses of the calycanthoids have established structural assignments and an accepted biosynthesis, which is predicated on an oxidative dimerization of *N*-methyl tryptamine (**28**, Scheme 1). The newly formed bis-indolenine can undergo hydrolysis to access hypothetical intermediate **1**, or it can easily form the chimonanthine scaffold **2** or scaffold **4** by attack of the free amines on the indolenine imines. As scaffold **2** remains unrepresented by isolated natural products, the chimonanthine scaffold **4** is likely the favored product of aminal closure. This scaffold can then be modified to provide the various chimonanthine derivatives. The other scaffolds (i.e., **3** and **5**) are accessible from intermediate **1**.

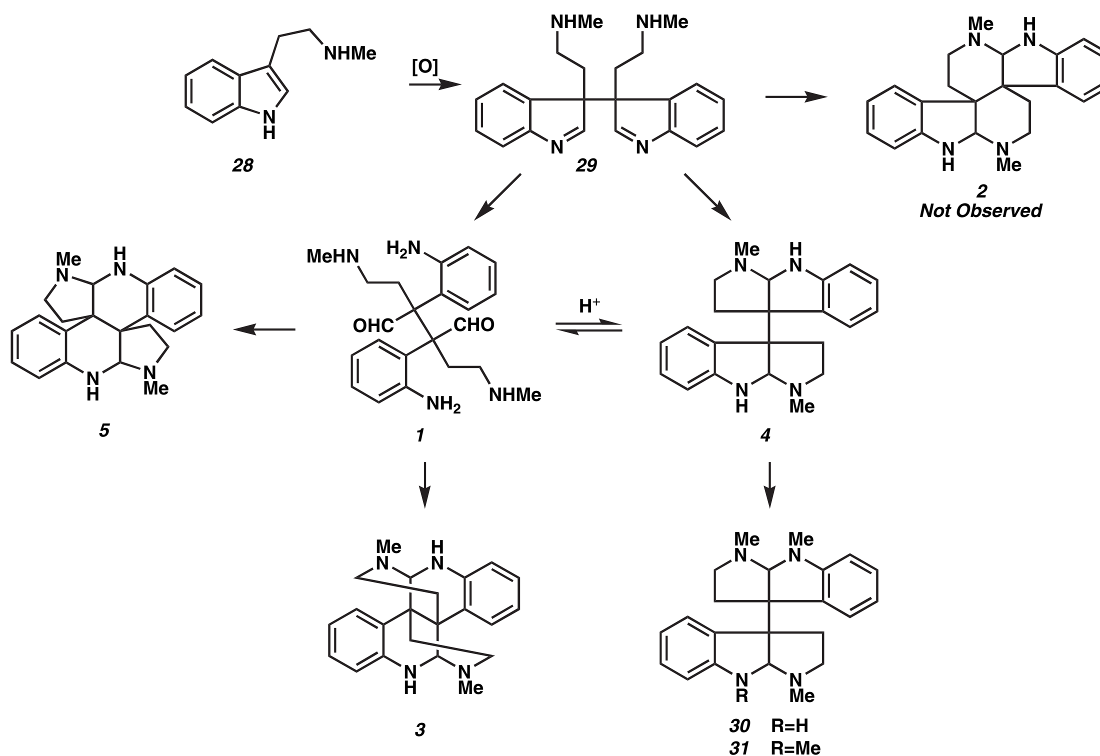
The oxidative coupling of tryptamine equivalents has been replicated in the laboratory using several oxidants. In an early study, Hendrickson et al. performed the coupling using sodium hydride and iodine to afford the bis-oxindoles **33** and **34** as a 1:1 mixture of diastereomers ($C_2$-symmetric and *meso*, Scheme 2). The $C_2$-symmetric isomer can be reductively cyclized with LAH in refluxing THF to form (±)-chimonanthine.[1]

In a later study, Scott et al. prepared the magnesium salt of methyl tryptamine and oxidatively dimerized it using iron (III) chloride to produce the indolenine dimer **29** (Scheme 3).[21] Subsequent aminal formation by the tryptamine side chains under the reaction conditions afforded *meso*- and (±)-chimonanthine in one step. Moreover, (±)-calycanthine is accessible by treating (±)-chimonanthine with aqueous acid, demonstrating that scaffold **3** is thermodynamically preferred to scaffold **4**.[1,21]

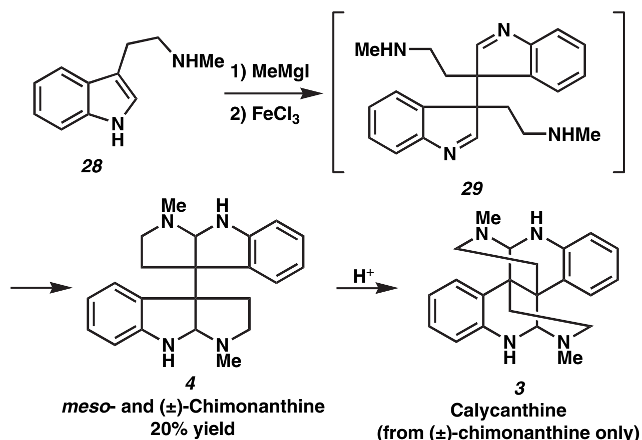



**Scheme 2.** Biomimetic synthesis studies by Hendrickson.

Both of these sequences, though characterized by low yields of the desired product,[22] demonstrate the feasibility of the proposed biosynthesis.[23,24] The model by Scott et al., however, better approximates the actual biosynthetic pathway,




**Scheme 1.** Biosynthetic pathway to the calycanthaceous alkaloids.




**Scheme 3.** Scott's direct biomimetic synthesis.

as Kirby has shown that 2-tritio-tryptophan and 2-tritio-tryptamine (**35**) retain their label when processed by *Calycanthus floridus* into chimonanthine (Fig. 8).[25] The retention of the 2-tritio label excludes the possibility of oxindole intermediates.

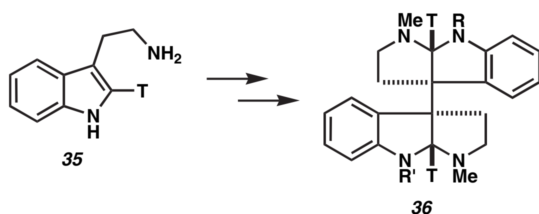
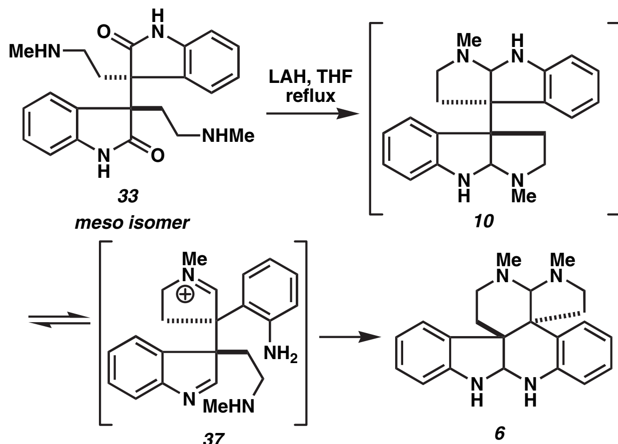



**Figure 8.** Label studies with chimonanthine.

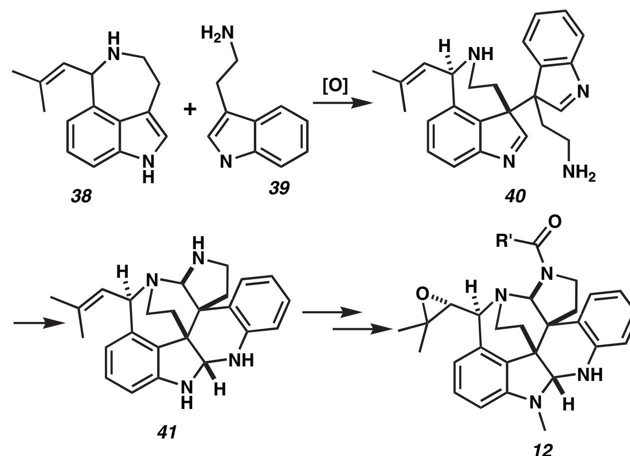
An interesting side-note emerges from the oxidative indole coupling reported by Hendrickson, in which the $C_2$-symmetric oxindole dimer **34** produces (±)-chimonanthine when reduced. Unusually, the *meso*-dimer **33** does not produce *meso*-chimonanthine upon treatment with LAH, but affords the isomeric hexacycle **6** (Scheme 4) under LAH treatment. Presumably, reduction occurs similarly to the $C_2$-symmetric adduct, but the Lewis acidic nature of LAH promotes an aminal rearrangement to a preferred geometry. This study suggests that a biosynthetic pathway optimized to produce a *meso*-tryptamine or tryptophan adduct could produce indole alkaloids with framework **6**.




**Scheme 4.** Formation of the framework **6**.

The defining feature of construct **6** is the unique presence of non-equivalent *N*-methyl groups, a trait easily recognized by proton NMR. This skeletal arrangement was unknown for naturally occurring alkaloids until the isolation of the communesins, nomofungin, and perophoramidine. These structures represent appended or oxidized versions of **6**. Hendrickson's findings suggest these compounds could arise from dimerization of tryptamine derivatives in a similar fashion to the calycanthus alkaloids.[1,26,27]

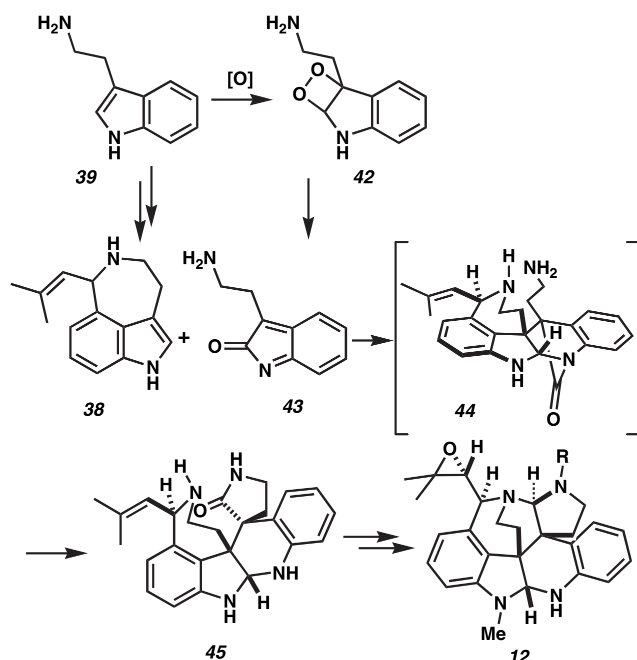
Specifically, the product of combination of the aminal formation from a dimer of the *Penicillum* fungal alkaloid aurantioclavine[28] and tryptamine would then be the communesin core **41**, and functionalization of the appropriate nitrogens and oxidation of the butenyl group to generate the epoxide yields communesin B (Scheme 5). However, a concern with the formation of **41** exists. Unlike perophoramidine, the vicinal quaternary carbon centers of the communesins possess a diastereomeric relationship akin to that of (±)-chimonanthine, which preferentially forms the connectivity found in calycanthine, not **6**. However, the additional carbocycle of intermediate **40** might bias the system toward formation of the less symmetrical framework **41**. Importantly, nomofungin cannot be formed through this biosynthetic pathway from known biogenic compounds. The precedent of *Calycanthus* biosynthesis and synthetic efforts with model systems[18] indicate that **15** likely represents the correct structure for both communesin B and nomofungin.




**Scheme 5.** Communesin biosynthesis.

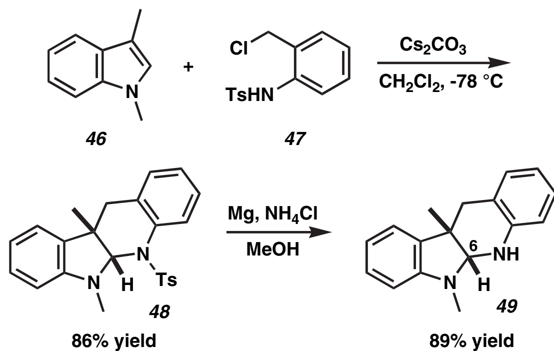
Unfortunately, directly adapting the theoretical biosynthesis outlined above to a synthetic approach to the communesins is unlikely because of the need for a selective dimerization event. However, an alternate biosynthetic pathway was proposed for the communesin family in 2003, where tryptophan or tryptamine is transformed into the quinone methide imine **43** (Scheme 6).[18] This electron deficient diene can then react with aurantioclavine (**38**) through an *exo* inverse-demand Diels–Alder reaction to generate the bridged lactam **44**. This intermediate, possessing a highly twisted lactam (analogous to the strained quinuclidone ring system) should readily undergo transamidation with the residual primary amine to produce the spiro lactam **45**. Biosynthetic reduction of the lactam, aminal closure, epoxidation, and acylation affords the communesins.[29] Again, a reasonable, equivalent biosynthetic pathway that would lead to the proposed structure for

nomofungin cannot be formulated. Furthermore, this hypothetical biosynthesis allowed for a plausible synthetic approach to communesin B.[30,31]



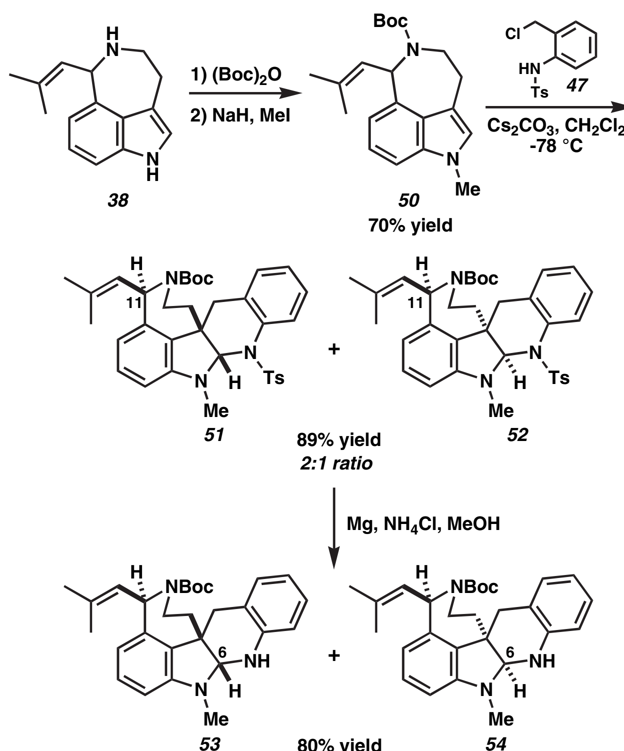

**Scheme 6.** An alternate communesin biosynthesis.

As a model system for the proposed Diels–Alder type cycloaddition of **38** and **43**, we investigated the cyclization of 1,3-dimethylindole (**46**) and chloroaniline **47** (Scheme 7) using conditions previously developed by Corey for the cycloaddition of **47** with electron-rich olefins.[32] To our delight, upon slow addition of chloride **47** to a mixture of indole **46** and $Cs_2CO_3$ in $CH_2Cl_2$ at −78 °C, a reaction immediately occurred to provide a single diastereomer of adduct **48** in 86% yield. Cleavage of the sulfonamide group by exposure of tetracycle **48** to Mg, MeOH, and $NH_4Cl$ produced aminal **49**. Interestingly, the $^1$H NMR chemical shift of the proton at C(6) is at 4.14 ppm, and the $^{13}$C resonance is at 83.9 ppm. These shifts are in good accord with the values of 4.69–4.70 ppm ($^1$H) and 82.4 ppm ($^{13}$C) reported for both communesin B and nomofungin, strongly suggesting that the communesin structure is the appropriate representation for the natural product.[33,34]




**Scheme 7.** The inverse-demand Diels–Alder reaction with indole.

Furthermore, we have prepared (±)-aurantioclavine (**38**) by known methods[35] and utilized the *N*-Boc-1-methyl derivative **50** in the cycloaddition reaction with **47** (Scheme 8). Cycloaddition again proceeded smoothly upon treatment with $Cs_2CO_3$ to produce the adducts **51** and **52**. Unfortunately, the putative cycloadduct was produced as a 2:1 mixture of diastereomers with respect to the methylpropenyl side chain at C(11). Following cleavage of the sulfonyl group with Mg and $NH_4Cl$ in MeOH, separation of the diastereomers was possible by preparative thin-layer silica gel chromatography. Importantly, the $^{13}$C NMR residues for C(6) of diastereomers **53** and **54** were at 84.8 and 83.9 ppm, again in full accord with the data for the communesins and nomofungin.




**Scheme 8.** The Diels–Alder reaction with aurantioclavine.

Fortunately, the minor diastereomer, **54**, could be recrystallized by slow cooling from refluxing heptane and subsequent slow evaporation of the solvent to provide crystals suitable for single-crystal X-ray diffraction studies. The structure thus obtained is shown in Figure 9.[36] Here, the isobutenyl group is on the same face as electrophile addition. Thus, the major isomer was generated by addition of the electrophile to the aurantioclavine face opposite the pendant olefin, indicating a small capacity for the olefin to direct the reaction. One possible reason for the modest selectivity is also seen in the crystal structure; the Boc group resides on the face opposite the pendant olefin and thus competes for directional control. A smaller protecting group is likely to improve the selectivity of the reaction.

In conclusion, we have proposed that the natural products nomofungin and communesin B are, in fact, identical molecules and that the structure of communesin B more correctly represents the actual structure. We initially came to this

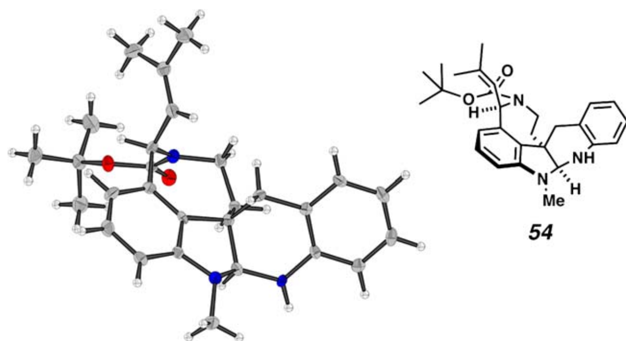



**Figure 9.** Structure confirmation by single-crystal X-ray diffraction.

conclusion based on comparison to the calycanthaceous alkaloids and biosynthetic hypotheses. Moreover, comparison of the reported data for the compounds to similar species and to the $^{1}$H NMR chemical shift data of synthetic analogs have bolstered this argument. Finally, a potential intermediate (**51**) in our synthesis of communesin B has been prepared by a [4+2] cycloaddition route (Scheme 8) that is similar to the biosynthetic proposal outlined in Scheme 6. Efforts to complete the total synthesis of communesin B (also known as nomofungin) by such biomimetic routes are ongoing.

## 2. Experimental

### 2.1. General

Reactions were performed in flame-dried glassware under a nitrogen atmosphere using freshly purified solvents. Solvents were purified by passing through an activated alumina column. All other reagents were used as received from commercial sources. Reaction temperatures were controlled by an IKAmag temperature modulator. Thin-layer chromatography (TLC) was performed using E. Merck silica gel 60 F254 precoated plates (0.25 mm) and visualized by UV, *p*-anisaldehyde staining, or ceric ammonium molybdate staining (CAM). ICN silica gel (particle size 0.032–0.063 mm) was used for flash chromatography. $^{1}$H and $^{13}$C NMR spectra were recorded on a Varian Mercury 300 spectrometer (at 300 MHz and 75 MHz, respectively) in $CDCl_3$ and are internally referenced to the residual chloroform peak (7.27 ppm and 77.23 ppm, respectively) relative to $Me_4Si$. Data for $^{1}$H NMR spectra are reported as follows: chemical shift ($\delta$ ppm), multiplicity, coupling constant (Hz), and integration. Data for $^{13}$C NMR spectra are reported in terms of chemical shift. IR spectra were recorded on a Perkin Elmer Paragon 1000 spectrometer and are reported in frequency of absorption ($cm^{-1}$). High resolution mass spectra were obtained from the California Institute of Technology Mass Spectrometry Facility.

**2.1.1. Indoline 48.** To a cooled solution of 1,3-dimethylindole (**46**, 23 mg, 0.16 mmol) and $Cs_2CO_3$ (168 mg, 0.360 mmol) in 0.2 mL anhydrous $CH_2Cl_2$ at −78 °C was added chloroaniline **47** (53 mg, 0.179 mmol) in anhydrous $CH_2Cl_2$ (0.8 mL) via syringe pump over 4 h. The solution was then warmed to 23 °C for 30 min, immediately filtered over a Celite plug, rinsing with $CH_2Cl_2$ (3×10 mL), concentrated under reduced pressure, and subjected to flash column chromatography (6:1 hexane/ethyl acetate eluent) to provide the Diels–Alder adduct **48** (54.7 mg, 86% yield) as a white solid. $^{1}$H NMR (300 MHz, $CDCl_3$) 7.55 (dd, $J$=7.9, 1.2 Hz, 1H), 7.48 (d, $J$=8.5 Hz, 2H), 7.22 (d, $J$=8.2 Hz, 2H), 7.11 (t, $J$=7.6 Hz, 1H), 6.98 (td, $J$=7.6, 4.4 Hz, 1H), 6.88 (dd, $J$=7.6, 7.6 Hz, 1H), 6.76 (dd, $J$=7.6, 7.6 Hz, 2H), 6.45 (dd, $J$=7.3, 7.3 Hz, 1H), 6.14 (d, $J$=7.9 Hz, 1H), 5.66 (s, 1H), 2.99 (s, 3H), 2.52 (d, $J$=14.1 Hz, 1H), 2.42 (s, 3H), 1.62 (s, $J$=14.1 Hz, 1H), 1.34 (s, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) 150.0, 143.8, 137.9, 135.3, 135.1, 132.8, 129.8, 128.4, 128.2, 128.0, 127.3, 127.2, 126.8, 121.6, 117.0, 104.5, 86.5, 51.0, 38.1, 29.9, 29.2, 21.8; IR (neat) 3052, 3028, 2951, 2920, 1608, 1494 $cm^{-1}$; MS $m/z$ calcd for $[C_{24}H_{24}N_2O_2S+H]^+$: 405.1637, found 405.1634.

**2.1.2. Indoline 49.** A vial (20 mL) equipped with a Teflon stirbar was charged with tosylamine **48** (28 mg, 0.069 mmol), which was subsequently dissolved in MeOH (2.7 mL). To this solution was added solid $NH_4Cl$ (131 mg, 2.45 mmol) and Mg (131 mg, 5.39 mmol). Equal masses of $NH_4Cl$ and Mg were added every few hours (usually to hundreds of equivalents) until all the starting material was converted to product as visualized by TLC. The solution was then filtered over a Celite plug, rinsing with $CH_2Cl_2$ (3×10 mL), and concentrated under reduced pressure. Purification was performed via flash column chromatography (9:1 hexanes/ethyl acetate eluent) to afford **49** (21.2 mg, 0.0847 mmol, 89% yield) as a white solid. $R_f$ 0.44 (3:1 hexane/ethyl acetate eluent); $^{1}$H NMR (300 MHz, $CDCl_3$) 7.17–7.12 (comp. m, 2H), 7.06 (dd, $J$=7.3, 7.9 Hz, 1H), 7.00 (d, $J$=7.3 Hz, 1H), 6.79 (dd, $J$=7.0, 7.6 Hz, 1H), 6.69 (dd, $J$=7.3, 7.3 Hz, 1H), 6.64 (d, $J$=7.9 Hz, 1H), 6.54 (d, $J$=7.6 Hz, 1H), 4.65 (br s, 1H), 4.14 (s, 1H), 2.81 (d, $J$=15.2 Hz, 1H), 2.78 (s, 3H), 2.51 (d, $J$=15.2 Hz, 1H), 1.24 (s, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) 149.2, 141.1, 137.2, 129.2, 127.9, 127.1, 121.5, 121.4, 118.8, 118.0, 113.5, 108.1, 83.9, 39.1, 37.7, 32.5, 21.7; IR (neat) 3404, 2956, 2851, 1609 $cm^{-1}$; MS $m/z$ calcd for $[C_{17}H_{18}N_2+H]^+$: 250.1470, found 250.1461.

**2.1.3. Aurantioclavine 38.** A flame-dried flask (50 mL) equipped with a Teflon stirbar was charged with 2-terbutyldimethylsilyl-4-(3-methyl-3-hydroxy)but-1-enylgramine[35] (20.4 g, 49.19 mmol), which was subsequently dissolved in benzene (100 mL). To the resulting solution was added methyl iodide (12.4 mL, 199 mmol). The mixture was stirred for 12 h. The reaction was then concentrated under reduced pressure. The resulting salt was redissolved in THF (100 mL) and dry nitromethane (30 mL). A solution of TBAF (1 M in THF, 74 mL, 74 mmol) was added slowly after the reaction had been cooled to 0 °C. After allowing the reaction to come to room temperature and stir for 15 min, the reaction was quenched with water and extracted three times with ether. The organic layers were combined, the solution was dried over magnesium sulfate, and the solvent was then removed under reduced pressure. Purification was performed via flash column chromatography (5:1 to 0:1 gradient of hexanes/ethyl acetate) and washing the resulting solid with dichloromethane to afford (*E*)-2-methyl-4-(3-(2-nitroethyl)-1*H*-indol-4-yl)but-3-en-2-ol[35] (3.25 g, 11.85 mmol, 24% yield) as a yellow solid.

A flame-dried flask (250 mL) equipped with a Teflon stirbar was charged with (*E*)-2-methyl-4-(3-(2-nitroethyl)-1*H*-indol-4-yl)but-3-en-2-ol[35] (400.1 mg, 1.458 mmol), which

was subsequently dissolved in MeOH (104 mL) and 2 N HCl (36 mL). To this solution was added amalgamated zinc, which had been formed from zinc dust (5.33 g, 62.42 mmol) and mercuric chloride (793 mg, 2.92 mmol) in 2 N HCl (36 mL) and subsequently rinsed with MeOH. The mixture was stirred at reflux for 3 h. The reaction was then decanted from the remaining amalgam and basified to pH>10. The solid was removed by filtration, and the resulting solution was extracted five times with dichloromethane. The organic layers were combined, the solution was dried over magnesium sulfate, and the solvent was then removed under reduced pressure. Purification was performed via flash column chromatography (18:1 dichloromethane/methanol with 0.5% $NH_4OH$) to afford aurantioclavine **38** (204.7 mg, 0.904 mmol, 62% yield) as a yellow foam that had spectral characteristics identical to those previously reported.[35]

**2.1.4. *N*-Boc-1-methylaurantioclavine (50).** A flame-dried flask (10 mL) equipped with a Teflon stirbar was charged with aurantioclavine (**38**, 100 mg, 0.442 mmol). Dioxane (4.5 mL) was then added, and the solution was cooled to 10 °C. $(Boc)_2O$ (164.2 mg, 0.752 mmol) was then added, and the solution was warmed to room temperature. After 30 min, water (100 μL) was added to quench any excess reagent, then brine was added. The mixture was extracted three times with ethyl acetate, the combined organic layers were dried over $Na_2SO_4$, and the solution was filtered and concentrated under vacuum. Purification by flash column chromatography (3:1 hexanes/ethyl acetate eluent) yielded *N*-Boc-aurantioclavine (127.4 mg, 0.390 mmol, 88% yield) as a light yellow oil; $R_f$ 0.23 (3:1 hexanes/ethyl acetate eluent). A flame-dried flask (25 mL), equipped with a Teflon stirbar, was charged with NaH (35.7 mg, 0.893 mmol) and THF (1 mL), and the mixture was cooled to 0 °C. Boc-aurantioclavine (125.2 mg, 0.384 mmol) was then added in a solution of THF (2 mL) dropwise. MeI (119 μL, 1.90 mmol) was added and the solution was warmed to room temperature. After 30 min, water (100 μL) was added to quench any excess reagent, then brine was added. The mixture was extracted three times with ethyl acetate, the combined organic layers were dried over $Na_2SO_4$, and the solution was filtered and concentrated under vacuum. Purification by flash column chromatography (9:1 hexanes/ethyl acetate eluent) yielded **50** (102.9 mg, 0.302 mmol, 79% yield) as a yellow oil; $R_f$ 0.40 (3:1 hexanes/ethyl acetate eluent).

**2.1.5. Diels–Alder adducts 51 and 52.** A flame-dried flask (5 mL) equipped with a Teflon stirbar was charged with $Cs_2CO_3$ (62.1 mg, 0.191 mmol) and *N*-Boc-*N*-methylaurantioclavine (**50**, 19.3 mg, 0.0567 mmol). Dichloromethane was then added, and the mixture was cooled to −78 °C. 2-Chloromethyltosylaniline (**47**, 24.5 mg, 0.0828 mmol) was added dropwise in a solution of dichloromethane (400 μL). The combined solution was stirred for 1 h and then allowed to warm to room temperature slowly (30 min) before quenching with water (500 μL). The mixture was extracted three times with ethyl acetate, the combined organic layers were dried over $Na_2SO_4$, and the solution was filtered and concentrated under vacuum. Purification by flash column chromatography (15:1 to 9:1 hexanes/ethyl acetate eluent) gave an inseparable mixture of **51** and **52** (30.1 mg, 0.0502 mmol, 89% yield) as a white solid.

**2.1.6. Indoline alkaloids 53 and 54.** A vial (20 mL) equipped with a Teflon stirbar was charged with the mixture of tosylamines **51** and **52** (30 mg, 0.05 mmol), which were subsequently dissolved in MeOH (5 mL). To this solution was added solid $NH_4Cl$ (137 mg, 2.56 mmol) and Mg (137 mg, 5.64 mmol). Equal masses of $NH_4Cl$ and Mg were added every few hours (usually to hundreds of equivalents) until all the starting material was converted to product as visualized by TLC with stain. Purification was performed via preparative thin-layer chromatography (4:1 hexanes/ethyl acetate eluent run four times) to afford **51** (13.4 mg, 0.0301 mmol, 60% yield) and **52** (4.8 mg, 0.0108 mmol, 22% yield) as white solids.

**2.1.7. Indoline 51.** $R_f$ 0.33 (3:1 hexane/ethyl acetate eluent); $^1H$ NMR (300 MHz, $CDCl_3$, 50 °C) 7.10–7.05 (comp. m, 3H), 6.79 (dd, *J*=7.1, 7.7 Hz, 1H), 6.63 (d, *J*=8.2 Hz, 1H), 6.54 (br s, 1H), 6.42 (d, *J*=7.7 Hz, 1H), 6.15 (br d, *J*=6.5 Hz, 1H), 5.34 (br s, 1H), 4.59 (br s, 1H), 4.01 (br s, 2H), 3.20–3.12 (m, 1H), 2.77 (app. s, 2H), 2.73 (s, 3H), 1.82 (s, 3H), 1.77 (s, 3H), 1.69–1.62 (comp. m, 3H), 1.53 (s, 9H); $^{13}C$ NMR (75 MHz, $CDCl_3$, 50 °C) 155.1, 141.2, 139.6, 132.6, 129.8, 129.4, 128.0, 127.2, 124.4, 121.0, 118.0, 113.2, 106.7, 84.8, 80.0, 57.6, 56.4, 40.0, 33.2, 32.1, 29.0, 25.9, 18.7; IR (neat) 3371, 2975, 2245, 1672, 1600 $cm^{-1}$; MS *m/z* calcd for $[C_{28}H_{35}N_3O_2-H]^+$: 444.2651, found 444.2640.

**2.1.8. Indoline 52.** Crystals suitable for X-ray diffraction studies could be grown from heptane.[36] $R_f$ 0.32 (3:1 hexane/ethyl acetate eluent); $^1H$ NMR (300 MHz, $CDCl_3$, 50 °C), 7.25 (d, *J*=4.0 Hz, 1H), 7.09–7.01 (comp. m, 2H), 6.69 (dd, *J*=6.0, 7.7 Hz, 1H), 6.63 (d, *J*=7.1 Hz, 1H), 6.52 (br s, 1H), 6.45 (d, *J*=7.7 Hz, 1H), 6.0 (d, *J*=57.7 Hz, 1H), 5.43 (br s, 1H), 4.58 (br s, 1H), 3.96 (s, 1H), 3.91–3.70 (m, 1H), 3.50–3.35 (m, 1H), 3.09–2.80 (comp. m, 2H), 2.74 (s, 3H), 1.84 (s, 3H), 1.77 (s, 3H), 1.57–1.29 (comp. m, 2H), 1.42 (s, 9H); $^{13}C$ NMR (75 MHz, $CDCl_3$, 23 °C) 154.9, 150.3, 141.4, 141.2, 140.6, 138.5, 138.3, 132.6, 132.2, 129.8, 128.1, 127.8, 127.5, 124.3, 120.1, 119.9, 118.8, 117.9, 113.6, 113.5, 107.5, 83.9, 79.9, 79.5, 59.0, 57.7, 41.7, 41.5, 38.7, 38.1, 33.2, 33.1, 32.5, 32.4, 31.2, 28.7, 26.1, 18.6, 18.5; IR (neat) 3363, 2973, 2242, 1672, 1594 $cm^{-1}$; MS *m/z* calcd for $[C_{28}H_{35}N_2O_2]^+$: 445.2729, found 445.2731.

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29. Subsequent to our initial report, the Funk lab proposed a similar biosynthesis in a report on synthetic efforts toward perophoramidine (Ref. 31), differing only in the use of 4-prenyltryptamine in place of aurantioclavine and addition of a late-stage oxidative amino cyclization with the prenyl group is proposed.
30. (a) The Weinreb lab has a synthetic strategy toward perophoramidine using an oxindole-forming carbonylative Heck reaction, building one of the quaternary carbon centers in the process (Ref. 26); (b) A successful synthesis of perophoramidine was reported by the Funk lab that utilized chemistry related to the biosynthesis proposed in Scheme 6 (Ref. 31).
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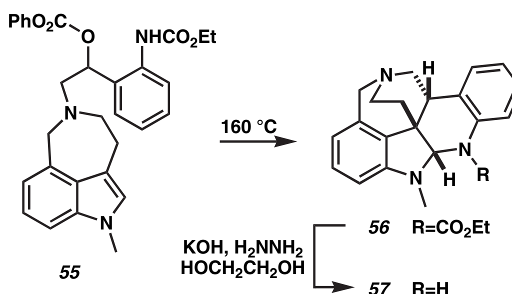
33. As additional confirmation, the Funk lab generated indole **55**, which upon heating in dichlorobenzene and subjection to hydrolysis generated a polycyclic framework **57** similar to that of the communesins. NMR data from this study further confirmed the structural assignment of communesin B (Ref. 34).

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36. Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Center as supplementary publication numbers CCDC 220259.