Title: Unified, Biosynthesis-Inspired, Completely Stereocontrolled Total Synthesis of All Highest-Order [n+1] Oligocyclotryptamine Alkaloids

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Abstract: We describe the unified enantioselective total synthesis of the polycyclotryptamine natural products (+)-quadrigemine H, (+)-isopsychotridine C, (+)-oleoidine, and (+)-caledonine. Inspired by our hypothesis for the biogenesis of these alkaloids via an iterative concatenative addition of homochiral cyclotryptamines to a *meso*-chimonanthine headcap, we leverage the modular, diazene-directed assembly of stereodefined cyclotryptamines to introduce successive C3a–C7' quaternary stereocenters on a heterodimeric *meso*-chimonanthine surrogate with full stereochemical control at each quaternary linkage. We developed a new strategy for iterative aryl-alkyl diazene synthesis using increasingly complex oligomeric hydrazide nucleophiles and a bifunctional cyclotryptamine bearing a C3a leaving group and a pendant C7 pronucleophile. The utility of this strategy is demonstrated by the first total synthesis of heptamer (+)-caledonine and hexamer (+)-oleoidine. Enabled by our completely stereoselective total syntheses and expanded characterization data sets, we provide the first complete stereochemical assignment of pentamer (+)-isopsychotridine C, provide evidence that it is identical to the alkaloid known as (+)-isopsychotridine B, and report that tetramer (+)-quadrigemine H is identical to the alkaloid called (+)-quadrigemine I, resolving longstanding questions about the structures of the highest-order [n+1] oligocyclotryotamine alkaloids.

The oligomeric cyclotryptamine alkaloids are a subset of pyrroloindoline natural products comprised of C–C linked cyclotryptamine units.[1] Isolated primarily from plants in the *Psychotria* genus, these alkaloids display a range of biological activities, including antibiotic, analgesic, and antifungal properties, as well as cytotoxicity again human cancer cell lines.[2] The oligocyclotryptamines present a longstanding challenge for chemical synthesis due to their multiple C3a quaternary stereocenters, two of which are vicinal, in addition to a labile C3a–C3a linkage, multiple basic nitrogen centers, and severe steric crowding.[1f] While innovative synthetic approaches to secure the C3a–C7′ linkages have been developed,[3] including asymmetric palladium- and copper- catalyzed methods, many higher-order oligomers remain inaccessible to total synthesis and lack robust stereochemical assignment. Cognizant of substructural patterns preserved in members of this alkaloid family, we sought to explore a unified synthetic strategy inspired by a new hypothesis for their biosynthesis,[4] involving the iterative formation of C3a"–C7' linkages on a dimeric headcap.[2a] Herein, we report the successful application of this biosynthesis-inspired concatenative synthetic strategy as a unified solution for the highest-order [n+1] oligocyclotryptamine alkaloids, including the first total synthesis of hexamer (+)-oleoidine (**2**), and heptamer (+)-caledonine (**1**, Scheme 1A). Additionally, for the first time we provide evidence that tetramer (+)-quadrigemine H is the

same as the alkaloid called (+)-quadrigemine I, and pentamer (+)-isopsychotridine C is the same as the alkaloid known as (+)-isopsychotridine B.

In addition to the synthetic challenge posed by their complex molecular structures, the oligomeric cyclotryptamine alkaloids present significant obstacles in terms of structural and stereochemical characterization. While the position of the labile C3a–C3a' linkages of the oligocyclotryptamines can be deduced from mass spectrometry fragmentation data,[1f] NMR analysis is complicated by significant atropisomerism and signal broadening, making stereochemical assignment particularly challenging.[2a] As a result, the isolation literature for these alkaloids contains reports of purportedly distinct alkaloids without complete stereochemical assignment, hampered by insufficient characterization data.[2] Along with these reports, the presumption that the oligocyclotryptamines arise from a stereorandom biogenesis persists,[3c,3h] despite increasing evidence that some of these alkaloids previously assumed to be distinct compounds may be the same.[3g]

Stereocontrolled total chemical synthesis of these complex alkaloids offers an important opportunity for structural validation and assignment. For example, the Overman group demonstrated that other than (–)-quadrigemine C (**7**), no other synthetic [2+2] tetramer was consistent with literature reports, leading to the conclusion that alkaloids known as quadrigemines A and E are likely identical to (–)-quadrigemine C (**7**).[3g] The persistence of similar long-unresolved ambiguities about the identity and structure of the higher-order oligocyclotryptamines, and the absence of any total synthesis or confirmed stereochemical assignment of a hexameric or heptameric oligocyclotryptmine natural alkaloids, prompted this study.

Several existing synthetic solutions to polycyclotryptamines employ innovative transition metal-catalyzed stereoselective construction of the C3a–C7' linkages. Notably, Overman's Pd-catalyzed asymmetric Heck cyclization[3a-3d,3f] and MacMillan's Cu-catalyzed asymmetric tryptamide arylation[3g] establish key C3a stereocenters in complex settings with excellent levels of enantio- and diastereoselectivity. Given our longstanding interest in the stereocontrolled total synthesis of cyclotryptamine alkaloids,[5] we developed diazene-directed fragment assembly for the generation of C3a–C3a' and C3a–C7' quaternary linkages present in these alkaloids. Notably, when applied to stereochemically defined cyclotryptamines, this strategy ensures complete stereochemical control at both types of linkages irrespective of any potential substrate bias. Previously, we reported the total synthesis of alkaloids **5**-**8** via the modular, diazene-directed assembly of cyclotryptamines,[5c] and used a related strategy to complete the first total synthesis of the [3+2]-pentamer (–)-psychotridine (**8**), allowing its full stereochemical assignment nearly five decades after its isolation.[5e] Building on the success of our diazene chemistry, we sought to develop a general strategy for the synthesis of unaddressed highest-order polycyclotryptamines to enable complete structure assignment or validation as prelude to further chemical and biological studies. We targeted the largest [n+1] oligocyclotryptamine isolated to date, heptamer (+)-caledonine (**1**). The isolation report for (+)-caledonine (**1**) provided a preliminary stereochemical assignment that contains substructures matching the proposed structures of simpler [n+1]-oligocyclotryptamines **2**-**5**. This structural homology suggests that an iterative approach to heptamer (+)-**1** would give access to alkaloids (+)-**2**-**4**, and we hypothesized that this approach may be relevant to nature's synthesis of these alkaloids.

It has long been hypothesized that *meso*-chimonanthine is formed via the oxidative dimerization of *N*-methyl tryptamine.[6] While far less is known about the biogenesis of the C3a–C7 linkages of the oligocyclotryptamines,[2f,7] given the conserved relative stereochemistry of the C3a–C3a' linkage, variation in oligomer chain length, and the absence of any natural alkaloids lacking a C3a–C3a' linkage, we postulated that C3a–C3a' bond formation precedes successive C3a–C7' bond formation. Thus, trimeric alkaloids (–)-hodgkinsine (**5**) and (–)-hodgkinsine B (**6**) can be traced back to C3a–C3a' dimer *meso*-chimonanthine. We posit that after the initial C3a–C7' bond forming event, all known higher-order oligomers arise from successive stereospecific top-down chain elongation of trimer **5** (to alkaloids **1**-**4**, the [n+1] series) and the isomeric trimer **6** (to alkaloids **7** and **8**, the [n+2] series) as illustrated in Scheme 1B.[4] This biosynthetic model is a departure from earlier depictions of a biogenesis involving a stereorandom oligomerization that generates multiple sets of diastereomeric alkaloids,[3c,3h] and is

consistent with more recent evidence[2a,3g] for only one naturally occurring stereoisomeric oligomer within each series.

Guided by this biosynthetic hypothesis, we aimed to employ diazene-directed fragment assembly to stereoselectively generate successive C3a–C7' linkages on a C3a–C3a' linked "headcap" cyclotryptamine dimer. We demonstrate the application of our bioinspired iterative synthetic approach via the unified, completely stereocontrolled total synthesis and structural validation of oligocyclotryptamine alkaloids (+)-**1-4**.

Our retrosynthetic analysis for (+)-caledonine (**1**), a heptameric cyclotryptamine alkaloid, illustrates our new biosynthesis-inspired approach to the oligocyclotryptamine natural products (Scheme 1C). We aimed to secure all seven quaternary stereocenters present in **1** through the diazene-directed assembly of whole cyclotryptamines. We planned to establish the terminal Csp3-Csp2 bond of alkaloid **1** through photoextrusion of dinitrogen from heptacyclotryptamine diazene **9**. We sought the synthesis of diazene **9** from the union of hexacyclotryptamine hydrazide **10** and a terminal cyclotryptamine unit, leading to the desired endcap.[5c] We envisioned preparing **10** from a functionalized *meso*-chimonanthine derivative through four cycles of an iterative process involving hydrazide synthesis, diazene-directed C–C bond formation, and diazene synthesis. Informed by early observations regarding the feasibility and practicality of photolyzing consecutive aryl-alkyl diazenes,[4] we opted to forge the C–C bond in each iteration. This process constitutes the chain elongation domain of the synthesis via concatenation of whole cyclotryptamine units, tracing **10** to a functionalized *meso*-chimonanthine surrogate **11** or **12**. We anticipated flexibility in the timing of C3a–C3a' bond formation given our prior experience with concurrent photolysis of Csp3-Csp3 and Csp2-Csp3 diazenes.[5c,5e] Importantly, this iterative strategy would also allow us to prepare [5+1] hexamer (+)-oleoidine (**2**) and [4+1] pentamer (+)-isopsychotridine C (**3**) by performing the iteration twice or once, as well the [3+1] tetramer (+)-quadrigemine H (**4**) by installing the endcap with no further iteration, tracing all four natural alkaloids **1-4** to enantioenriched cyclotryptamines **13** and **14**, for convergent heterodimer synthesis, and binfunctional cyclotryptamine **15**, for iterative chain elongation.

Our total synthesis of alkaloids **1-4** commenced with the preparation of heterodimeric diazene (+)-**12** (Scheme 1D). Silver(I)-promoted ionization of readily available bromocyclotryptamine (–)-**16**[5c,8] (96% ee) in the presence of 2,6-difluorophenyl sulfamate followed by sulfamate hydrolysis furnished amine (–)-**13** in 86% overall yield. The other headcap building block, C7-azido bromocyclotryptamine (+)-**17** (95% ee), was prepared from tryptamine methyl carbamate in 5 steps using our Ir-catalyzed C7–H borylation methodology.[4,9] Attempted ionization of bromide (+)-**16** under the mild activation conditions used for C7 unsubstituted bromide (–)-**16** led to recovery of the starting material, indicating that accessing C3a carbocations with an inductively withdrawing C7 substituent is more challenging. Under the optimal ionization conditions (2,6-difluorophenyl sulfamate, AgOTf, 2,6-di-*tert*-butyl-4-methylpyridine, 1,2-dichloroethane, 70 ºC) bromide (+)-**17** was converted to sulfamate ester (+)-**14** in 80% yield. Importantly, the N8 (trimethylsilyl)ethyl (SES) sulfonamide[5d,10] was completely stable to the more forcing conditions required for C3a activation of C7 aminated cyclotryptamines, whereas the trimethylsilyl)ethyl carbamate (Teoc) derivatives we previously used[5c,5e] did not survive.

Treatment of sulfamate ester (+)-**14** with a slight excess (1.20 equiv) of amine (–)-**13** in the presence of 4-dimethylaminopyridine (DMAP) furnished mixed sulfamide (–)-**18** in 84% yield. Sulfamide oxidation with 1,3-dichloro-5-5-dimethylhydantoin (DCDMH) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) provided diazene dimer (–)-**19** in 95% yield.. Mild azide reduction with dithiothreitol and triethylamine followed by aniline sulfonylation delivered diazene dimer sulfonamide (+)-**20** in 93% yield over two steps. Single crystal X-ray diffraction of dimer (+)-**20** unambiguously confirmed its stereochemistry, including the *trans* configuration of the dialkyl diazene. Next, electrophilic amination of the sulfonamide with sodium hydride and *O*-diphenylphosphinyl hydroxylamine (DPPH) generated diazene dimer hydrazide (+)-**12** in 88% yield. We found that diazene dimer hydrazide (+)-**12** displayed enhanced nucleophilicity relative to its C–C linked variant,[4] thus, C3a–C3a' bond formation was strategically delayed until after the first concatenation.

With a scalable route to heterodimeric headcap nucleophile (+)-**12**, we turned our attention to designing a bifunctional cyclotryptamine for iterative chain elongation. We envisioned employing C3a electrophiles with a latent C7 pronucleophile, obviating the need to iteratively perform directed C–H functionalization on substrates with increasing sites of Lewis basic functional groups, a significant challenge we observed in our synthesis of pentamer (–)-**8**.[5e] Our first generation bifunctional monomer, bromide (+)-**15** (Scheme 2), prepared from (+)-**17** in 91% overall yield over two steps, contains a C3a bromide for Ag(I)-promoted carbocation formation and a pendant C7 sulfonamide for one-step conversion to a nucleophilic sulfonyl hydrazide.

With a bifunctional monomer in hand, we proceeded to examine its utility as an electrophile for aryl-alkyl diazene synthesis. In our initial approach to the coupling, treatment of hydrazide (+)-**12** with an excess of (3.50 equiv) bifunctional monomer (+)-**15** in the presence of super-stoichiometric AgOTf and 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP) in 1,2-dichloroethane (1,2-DCE) at 60 ºC led to low yields (30–35%) of the desired bis-diazene trimer (+)-**22**. Notably, despite full consumption of the electrophile to undesired oligomeric side products, we observed significant amounts (40-50%) of unreacted hydrazide (+)-**12**. We hypothesized that the hydrazide may be sequestered by excess Lewis acid activator, hampering its ability to trap the transient C3a carbocation. This hypothesis was supported by the observation that lowering the effective concentration of AgOTf through portionwise addition increased the efficiency of the transformation, affording (+)-**22** in 54% yield.

While these results were encouraging, we sought to develop a more optimal coupling. Our group has explored a variety of leaving groups at the C3a position as carbocation precursors, including halides, sulfonates, and imidates. In previous studies, the bromide derivatives were optimal in terms of access, stability, and reactivity. In this case, however, we sought an electrophile that could be selectively ionized with sub-stoichiometric activator. Moreover, we recognized that the increased stability of our N8–SES coupling partners to heat and acid could accommodate more forcing conditions for the key diazene synthesis reaction. With these considerations and inspired by the precedent for the catalytic activation of trichloroacetimidates in the Overman rearrangement,[11] the Schmidt glycosylation,[12] and C3a-derivatization of cyclotryptamines using trichloroacetimidates,[13] we were prompted to re-investigate the use of C3a–imidates for our diazene synthesis methodology. Accordingly, we prepared our second-generation bifunctional monomer (+)-**21** from (+)-**15** in 86% yield over two steps. After significant experimentation,[4] we found that treatment of hydrazide (+)-**12** and trichloroacetimidate (+)-**21** (3.50 equiv) with sub-stoichiometric trifluoromethanesulfonic acid (15.0 mol% relative to the hydrazide) in dichloroethane at 60 ºC afforded bis-diazene trimer (+)-**22** in 77% yield on 3 gram scale (Scheme 2).

Having established a robust method for coupling complex sulfonyl hydrazides with C7-aminated bifunctional cyclotryptamines, we completed our first iterative cycle. Exposure of (+)-**22** to 300 nm light led to concomitant Csp2-Csp3 and Csp3-Csp3 diazene photolysis, providing C–C linked trimer (+)-**23** in 45% yield as a single diastereomer. Subsequent electrophilic amination with sodium hydride and *O*-(diphenylphosphinyl)hydroxylamine delivered trimer hydrazide (+)-**24** in 90% yield, generating the requisite trimeric C7" nucleophile for the next concatenation.

With access to our common intermediate, we proceeded to examine our strategy for installation of the endcap through preparation of [3+1] alkaloid (+)-quadrigemine H (**4**). Tetramer (+)-**4** was first reported in 1986 and has demonstrated antifungal and anticandidal activity.[14,15] Its absolute structure was confirmed by x-ray crystallographic analysis of a tetramethiodide derivative in its isolation and MacMillan's recent total synthesis.[3h,14] We planned to secure the tetrameric skeleton of (+)-**4** by performing diazene synthesis with trimer (+)-**24** and a C7 unsubstituted cyclotryptamine.

Accordingly, treatment of trimer hydrazide (+)-**24** and trichloroacetimidate (+)-**33** (prepared from bromide (+)-**15** in 97% yield over two steps) with catalytic trifluoromethanesulfonic acid delivered diazene tetramer (+)-**34** in 79% yield.[16] Under the optimal conditions, irradiation of a thin film of diazene (+)-**34** with 300 nm light at 5 ºC afforded C–C linked tetramer (+)-**35** in 59% yield.[17] Treatment of tetramer (+)-**35** with excess tris(dimethylamino)sulfonium difluorotimethylsilicate (TASF) resulted in global removal of the (trimethylsilyl)ethyl sulfonamides in 97% yield. Finally, exhaustive methyl carbamate

reduction with alane dimethylethyl amine complex and quinuclidine gave (+)-quadrigemine H (**4**) in 78% yield. Importantly, addition of quinuclidine to the final reduction eliminated persistent byproducts resulting from partial reduction, presumably via formation of an alane-quinuclidine complex.[4,18] ^{1}H and ^{13}C NMR data collected at 500 MHz for alkaloid (+)-**4** in $CDCl_3$ at 25 ºC and optical rotation measurements (EtOH) were consistent with literature values for (+)-quadrigemine H (observed $[\alpha]_D^{23}$ = +193 (c = 0.35, EtOH); lit. $[\alpha]_D$ = +209 (c = 0.25, EtOH)).[3g]

With high-quality data for (+)-quadrigemine H (**4**), we sought to clarify whether it was also consistent with data for the alkaloid called (+)-quadrigemine I, which is depicted in the literature with the same molecular structure as alkaloid (+)-**4**. While it is not clear why (+)-quadrigemine I was deemed a novel alkaloid, it was characterized under different conditions, preventing a direct comparison: ^{1}H and ^{13}C NMR spectra were collected at a different temperature (–13 ºC), and its optical rotation was measured in a different solvent ($CHCl_3$). We found that, consistent with (+)-quadrigemine I, our synthetic (+)-quadrigemine H (**4**) exists as two conformers in a 1.5:1 ratio in $CDCl_3$ at –13 ºC. ^{1}H NMR data for both conformers are consistent with the reported data for (+)-quadrigemine I. While the reported ^{13}C data is incomplete (21 resonances), our expanded data set (43 resonances) is in agreement with reported values. Moreover, optical rotation data in chloroform and ethanol (observed $[\alpha]_D^{23}$ = +18 (c = 0.28, $CHCl_3$), $[\alpha]_D^{23}$ = +193 (c = 0.35, EtOH); lit: $[\alpha]_D$ = +16 (c = 0.34, $CHCl_3$), lit. $[\alpha]_D$ = +199 (c = 0.34, EtOH)) were consistent with literature values for (+)-quadrigemine I. Based on the complete consistency of our synthetic (+)-**4** with literature data for both (+)-quadrigemine H and (+)-quadrigemine I, we conclude that these alkaloids are the same.

Having developed optimal conditions for endcap synthesis, we proceeded to target the [4+1] pentamer (+)-isopsychotridine C (**3**). First isolated from *Psychotria forsteriana* in 1985 with no stereochemical assignment, alkaloid (+)-**3** demonstrates inhibition of isolated human platelet aggregation as well potent cytotoxicity against HTC cancer cells.[19,20] MacMillan's recent synthesis of (+)-**3** resulted in a mixture of diastereomers (1.5:1 d.r.) at the C3a−C3a' bond that were unassignable by NMR. While one of their synthetic isopsychotridine diastereomers was in good agreement with literature data for (+)-**3**, they were unable to fully assign its stereochemistry.[3g] In line with our proposed biosynthesis, we hypothesized that natural (+)-isopsychotridine C (**3**) is the stereoisomer shown in Scheme 1A. We aimed to confirm this hypothesis and offer the first complete stereochemical assignment of this alkaloid.

Consistent with our iterative retrosynthesis, alkaloid (+)-**3** required one round of iteration with bifunctional monomer (+)-**21** before endcap installation. Thus, ionization of imidate (+)-**21** (5.0 equiv) with trifluoromethanesulfonic acid in the presence of trimer hydrazide (+)-**24** provided diazene tetramer sulfonamide (+)-**25** in 59% yield. We found that optimal coupling of the increasingly hindered C–C linked oligomeric hydrazides with bifunctional electrophiles occurred at higher temperature (75 ºC) compared to the diazene dimer nucleophile. Subsequently, irradiation of a thin film of diazene (+)-**25** with 300 nm light for 6 h afforded C–C linked tetramer sulfonamide (+)-**26** in 55% yield along with 15% recovered starting material (65% yield based on recovered starting material). We observed a pronounced sensitivity of higher order C–C linked cyclotryptamines to 300 nm light, and as a result optimal mass balance was achieved by stopping the reaction before full conversion. Subsequent electrophilic amination afforded tetramer hydrazide (+)-**27** in 86% yield.

Terminal diazene synthesis with hydrazide (+)-**27** and endcap cyclotryptamine (+)-**33** efficiently formed diazene pentamer (+)-**36** in 87% yield. Photolysis of the diazene gave pentacyclotryptamine (+)-**37** in 61% yield. Finally, sulfonamide removal and global methyl carbamate reduction afforded (+)-isopsychotridine C (**3**) in 65% over two steps. While the original isolation report for (+)-isopsychotridine C (**3**) does not contain ^{1}H NMR data, the ^{13}C data in $CDCl_3$ provided closely matches our data for synthetic (+)-**3**. Additionally, the optical rotation (EtOH) was consistent with literature values (observed $[\alpha]_D^{23}$ = +175 (c = 0.42, EtOH); lit. $[\alpha]_D$ = +183 (c = 0.05, EtOH)).[19] Moreover, all ^{1}H and ^{13}C NMR data collected in $CDCl_3$ as well as optical rotation for our synthetic (+)-**3** in ethanol are in excellent agreement with data from MacMillan's total synthesis.[3g] Thus, our fully stereocontrolled synthesis of **3** allows us to provide

the first complete stereochemical assignment of (+)-isopsychotridine C (**3**) as the [4+1] stereoisomer with headcap stereochemistry fully consistent with related alkaloids **1**-**8**.

Prompted by our findings about quadrigemines H and I (**4**) being identical, and similar ambiguities in the isolation literature for the [4+1] isopsychotridines, we decided to compare data for our synthetic (+)-isopsychotridine C (**3**) with data for the alkaloid called (+)-isopsychotridine B. (+)-Isopsychotridine B was first isolated from *Psychotria oleoides* in 1987.[21] A subsequent report re-isolated (+)-isopsychotridine B alongside alkaloids (+)-**1**, (+)-**2,** (+)-**4**, (–)-**5**, (–)-**7**, and (–)-**8**. The report did not provide new NMR data, but offered a tentative stereochemical assignment as the [4+1] pentamer with the *same stereochemistry* as our synthetic (+)-isopsychotridine C (**3**) based on CD analysis, degradation studies, and biogenetic hypothesis.[2a] On the other hand, MacMillan's report claims that the headcap stereochemistry of (+)-isopsychotridine B corresponds to the minor diastereomer produced in their C3a−C3a' bond formation towards pentameric oligocylotryptamines, without assigning its headcap stereochemistry.[3g] We undertook careful comparison of data collected for our (+)-isopsychotridine C (3) with data for (+)-isopsychotridine B, including ^{1}H and ^{13}C NMR, optical rotation in chloroform and ethanol, and CD.[4] The totality of our expanded set of characterization data suggests that the presumed structure of (+)-isopsychotridine B as a diastereomer of (+)-isopsychotridine C (**3**) as described in MacMillan's report[3g] is incorrect, and that isopsychotridines B and C are the same alkaloid.[4]

To further demonstrate the utility of our iterative approach, we aimed to achieve the first total synthesis of hexameric alkaloid (+)-oleoidine (**2**). First isolated from *Psychotria oleoides* in 1999, this compound has been shown to stimulate the release of growth hormone in rats.[2a,22] Consistent with our synthetic plan, the hexameric skeleton of (+)-**2** required an additional cycle of chain iteration before endcap installation. Accordingly, subjecting tetramer hydrazide (+)-**27** to bifunctional cyclotryptamine (+)-**21** (6.00 equiv) under trifluoromethanesulfonic acid activation delivered diazene pentamer sulfonamide (+)-**28** in 62% yield. Irradiation of a thin film of sensitive pentameric diazene for 5 h delivered C–C linked pentamer sulfonamide (+)-**29** in 47% yield and 26% recovered starting material (+)-**28** (64% yield based on recovered starting material-BRSM). Electrophilic amination (89%) followed by chain termination of pentamer hydrazide (+)-**30** with endcap monomer (+)-**33** gave diazene hexamer (+)-**38** in 75% yield. As before, diazene photolysis (51% yield), sulfonamide removal and methyl carbamate reduction (49% over two steps) completed the first total synthesis of (+)-oleoidine (**2**). Importantly, though this was far less pronounced for the tetramer or pentamer, we found that the addition of quinuclidine was critical for preventing complete decomposition of alkaloid (+)-**2** under the reaction conditions.[4] We posited that quinuclidine could inhibit coordination of aluminum reducing agent to a tertiary amine in the fully reduced product, preventing aminal activation and subsequent decomposition. ^{1}H and ^{13}C NMR data for alkaloid (+)-**2** in $CDCl_3$ at 500 MHz and optical rotation were consistent with literature values (observed $[\alpha]_D^{23}$ = +334 (c = 0.17, EtOH); lit. $[\alpha]_D$ = +371 (c = 0.2, EtOH); observed $[\alpha]_D^{23}$ = +81 (c = 0.17, $CHCl_3$), lit. $[\alpha]_D$ = +89 (c = 0.4, $CHCl_3$)).[2a]

Finally, we demonstrate the versatility of this iterative approach through the synthesis of the largest [n+1] oligocyclotryptamine alkaloid isolated to date, heptamer (+)-caledonine (**1**). Alkaloid (+)-**1** was isolated in 1999 from *Psychotria oleoides* and has been shown to modulate growth hormone release in rats. Accordingly, taking pentamer hydrazide (+)-**30** through our three-step iteration: diazene synthesis with bifunctional monomer (+)-**21** (55% yield), diazene photolysis (48% yield, 63% yield BRSM), and electrophilic amination (83% yield) provided the necessary hexameric hydrazide (+)-**4**. Terminal coupling of hydrazide (+)-**4** with endcap cyclotryptamine (+)-**33** gave diazene heptamer (+)-**9** in 62% yield. Photoextrusion of dinitrogen from diazene (+)-**9** (56% yield) followed by global desulfonylation and exhaustive methyl carbamate reduction (51% yield over two steps) delivered (+)-caledonine (**1**). Significantly, the desired product results from the cleavage of seven N–S bonds and the delivery of 21 hydride equivalents on a highly complex heptacyclotryptamine. Unsurprisingly, heptamer (+)-**1** displays extreme atopisomerism (only 35 of the theoretical 77 ^{13}C NMR resonances were observed; the isolation report lists 26 resonances). Spectroscopic data as well as optical rotation for our synthetic (+)-**1** were

consistent with literature values (observed $[\alpha]_D^{23}$ = +487 (c = 0.03, EtOH); literature $[\alpha]_D$ = +462 (c = 0.2, EtOH); $[\alpha]_D^{23}$ = +132 (c = 0.17, $CHCl_3$), literature $[\alpha]_D$ = +125 (c = 0.4, $CHCl_3$)).[2a]

In summary, we have developed a unified synthetic strategy for the iterative total synthesis of polycyclotryptamine natural products (+)-quadrigemine H (**4**), (+)-isopsychotridine C (**3**), (+)-oleoidine (**2**), and (+)-caledonine (**1**). We proposed a common biogenesis for all known higher-order oligocyclotryptamines and emulated this bond-forming sequence by leveraging diazene-directed complex fragment assembly to iteratively introduce C3a–C7' quaternary linkages on an advanced heterodimeric intermediate to access all higher order [n+1] oligocyclotryptamine alkaloids. We developed new conditions to enable the application of our diazene-directed fragment union to the most complex substrates to date, facilitated by a novel strategy for aryl-alkyl diazene synthesis through the Brønsted acid-catalyzed coupling of bifunctional C3a-trichloroacetimidate-cyclotryptamines and oligocyclotryptamine sulfonyl hydrazides. The success of our bioinspired iterative assembly of whole cyclotryptamines is demonstrated by the first total synthesis of heptameric alkaloid (+)-caledonine (**1**) and hexameric alkaloid (+)-oleoidine (**2**). Additionally, we completed the fully stereocontrolled total synthesis of (+)-quadrigemine H and pentamer (+)-isopsychotridine C through our unified iterative strategy. We acquired the most detailed characterization data to date for these alkaloids, leading us to conclude that (+)-quadrigemine H (**4**) is identical to the alkaloid called (+)-quadrigemine I, and that alkaloid (+)-isopsychotridine C (**3**) is identical to the pentameric alkaloid called (+)-isopsychotridine B, resolving longstanding questions about the identity and structures of complex oligocyclotryptamine alkaloids. This study highlights the impact of a plausible biosynthetic hypothesis to the development of a novel chemical synthesis strategy that can provide exceptional access to complex molecules while assisting their structure assignment and enabling future investigation of these alkaloids with stereochemical clarity.

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Competing interests Authors declare that they have no competing interests.

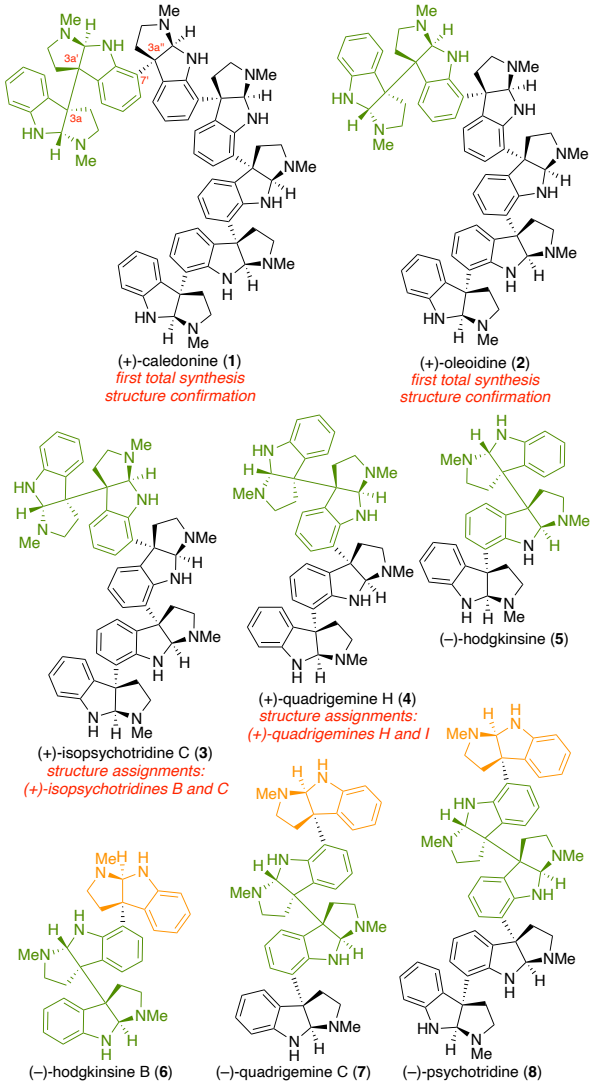
Data and materials availability: Experimental procedures, spectroscopic data, and copies of NMR spectra are available in supplementary information. Structural parameters for diazene dimer sulfonamide (+)-**20** are freely available from the Cambridge Crystallographic Data Centre under CCDC-2223453.

Supplementary Information

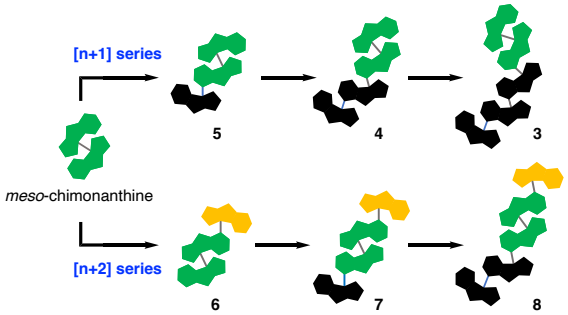
Materials and Methods; Spectral Data; Figs. S1 to S2; Schemes S1 to S5; Tables S1 to S15

Scheme 1. A) Representative oligocyclotryptamine alkaloids. B) Our hypothesis for biosynthesis of alkaloids **3–8**. C) Retrosynthetic analysis of (+)-caledonine (**1**). D) Synthesis of heterodimeric headcap (+)-**12**.

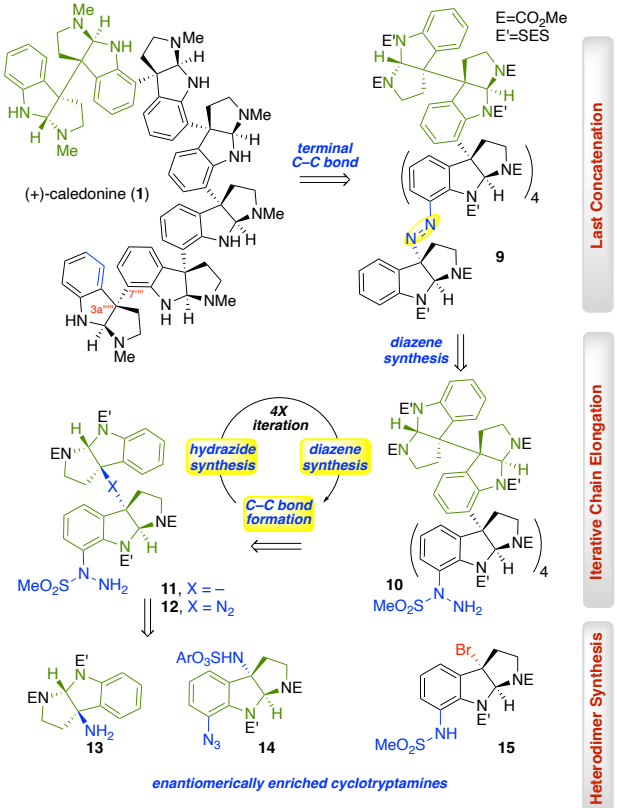
A. Representative oligocyclotryptamine alkaloids



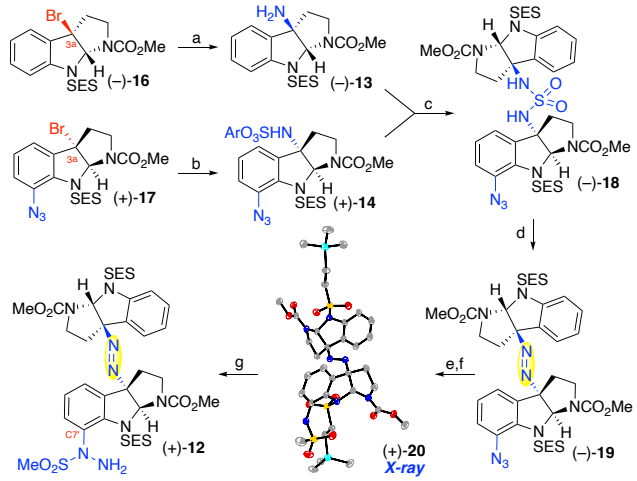
B. Our hypothesis for biosynthesis of alkaloids 3–8



C. Retrosynthetic analysis of (+)-caledonine (1)

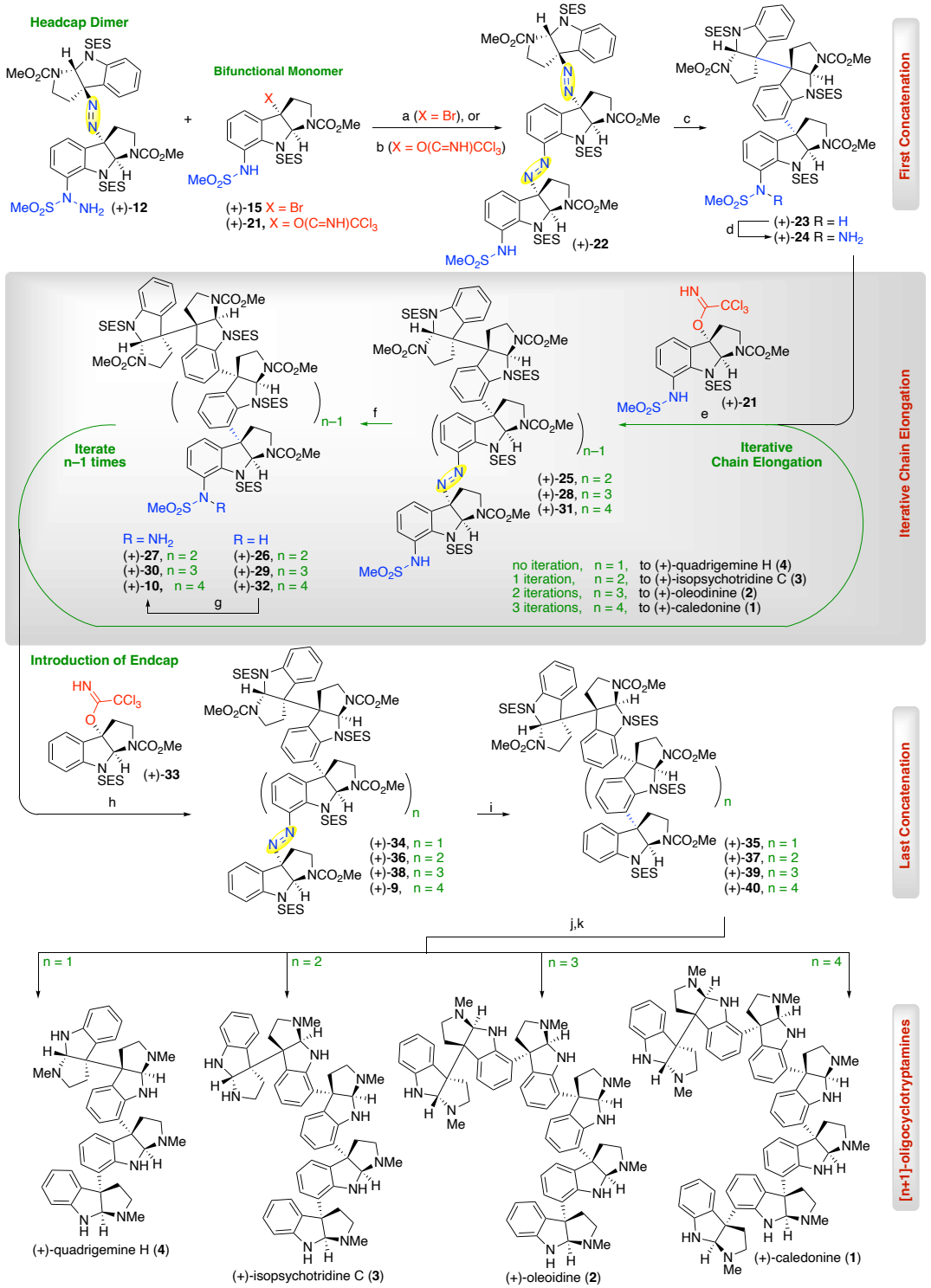


D. Synthesis of heterodimeric headcap (+)-12[a]



[a] Reagents and conditions: (a) 2,6-difluorophenyl sulfamate, AgOTf, DTBMP, CH_2Cl_2, 23 °C; pyridine, MeCN, H_2O, 70 °C, 86% over two steps; (b) 2,6-difluorophenyl sulfamate, AgOTf, DTBMP, 1,2-DCE, 70 °C, 80%; (c) DMAP, THF, 84%; (d) 1,3-dichloro-5,5-dimethylhydantoin, MeOH, DBU, 95%; (e) dithiothreitol, NEt_3, MeOH, CH_2Cl_2, 23 °C; (f) $MeSO_2Cl$, pyridine, 23 °C. 93% over 2 steps; (g) NaH, THF, 0 → 23 °C, then $Ph_2P(O)ONH_2$, 23 °C, 88%; Ar = 2,6-difluorobenzene. In the ORTEP representation of diazene dimer (+)-**20**, thermal ellipsoids are drawn at 30% probability and hydrogen atoms are omitted for clarity.

Scheme 2. Total synthesis of (+)-quadrigemine H (**4**), (+)-isopsychotridine C (**3**), (+)-oleoidine (**2**), and (+)-caledonine (**1**).[a]



[a] Reagents and conditions: (a) AgOTf, DTBMP, 1,2-DCE, 60 °C, 54% (b) CF_3SO_3H, 1,2-DCE, 60 °C, 77%; (c) hv (300 nm), thin film, 25 °C, 45%; (d) NaH, THF, 0 → 23 °C, then $Ph_2P(O)ONH_2$, 23 °C, 90%; (e) CF_3SO_3H, 1,2-DCE, 75 °C, 59% for (+)-**25**, 62% for (+)-**26**, 58% for (+)-**27**; (f) hv (300 nm), thin film, 25 °C, 55% for (+)-**28**, 48% for (+)-**29**, 47% for (+)-**30**. (g) NaH, THF, 0 → 23 °C, then $Ph_2P(O)ONH_2$, 23 °C, 86% for (+)-**31**, 89% for (+)-**32**, 83% for (+)-**4**; (h) CF_3SO_3H, CH_2Cl_2, 23 °C, 79% for (+)-**34**, 87% for (+)-**35**, 75% for (+)-**36**, 62% for (+)-**9**; (i) hv (300 nm), thin film, 5 °C, 59% for (+)-**37**, 61% for (+)-**38**, 51% for (+)-**39**, 56% for (+)-**40**; (j) TASF, DMF, 45 °C; (k) $EtNMe_2{\cdot}AlH_3$, quinuclidine, PhMe , 70 °C, 76% over two steps for (+)-**4**, 65% over two steps for (+)-**3**, 49% over two steps for (+)-**2**, 51% over two steps for (+)-**1.**

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(17) If conducted at 25 °C, the same photolysis affords tetramer (+)-**37** in 48% yield.

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