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Concise Synthesis of (–)-Hodgkinsine, (–)-Calycosidine, (–)-Hodgkinsine B, (–)-Quadrigemine C, and (–)-Psycholeine via Convergent and Directed Modular Assembly of Cyclotryptamines.

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Concise Synthesis of (-)-Hodgkinsine, (-)-Calycosidine, (-)-Hodgkinsine B, (-)-Quadrigemine C, and (-)-Psycholeine via Convergent and Directed Modular Assembly of Cyclotryptamines.

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ABSTRACT: The enantioselective total synthesis of (-)hodgkinsine, (-)-calvcosidine, (-)-hodgkinsine B, (-)quadrigemine C, and (-)-psycholeine through a diazene-directed assembly of cyclotryptamine fragments is described. Our synthetic strategy enables multiple and directed assembly of intact cyclotryptamine subunits for convergent synthesis of highly complex bis- and tris-diazene intermediates. Photoextrusion of dinitrogen from these intermediates enables completely stereoselective formation of all C3a-C3a' and C3a-C7' carbon-carbon bonds and all the associated quaternary stereogenic centers. In a representative example, photoextrusion of three dinitrogen molecules from an advanced intermediate in a single-step led to completely controlled introduction of four quaternary stereogenic centers and guided the assembly of four cyclotryptamine monomers en route to (-)-quadrigemine C. The synthesis of these complex diazenes was made possible through a new methodology for synthesis of aryl-alkyl diazenes using electronically attenuated hydrazine-nucleophiles for a silverpromoted addition to C3a-bromocyclotryptamines. The application of Rh- and Ir-catalyzed C-H amination reactions in complex settings were used to gain rapid access to C3a- and C7functionalized cyclotryptamine monomers, respectively, used for diazene synthesis. This convergent and modular assembly of intact cyclotryptamines offers the first solution to access these alkaloids through completely stereoselective union of monomers at challenging linkages and the associated quaternary stereocenters as illustated in our synthesis of five members of the oligocyclotryptamine family of alkaloids.

■ INTRODUCTION

Hexahydropyrroloindole alkaloids constitute a structurally and biologically fascinating class of natural products.¹ A subset of these natural products, alkaloids comprised of multiple cyclotryptamine units, presents a considerable synthetic challenge due to the presence of multiple quaternary stereocenters as well as numerous basic nitrogen atoms (Figure 1). While there have been significant advances in catalyst- and substrate-controlled formation of $C_{sp2}-C_{sp3}^{-2.3}$ and $C_{sp3}-C_{sp3}^{-4.5,6.7}$ quaternary stereocenters in the context of cyclotryptamine alkaloids,⁸ the synthesis of oligocyclotryptamines remains a challenge due to the paucity of methods allowing for precise introduction of all quaternary stereocenters. To date, *no method exists for the multiple and directed assembly of whole cyclotryptamine fragments with complete absolute and relative stereochemical control*. Our total syntheses of related dimeric alkaloids^{6b,c} were enabled through convergent *N*,*N*-dialkyl sulfamide synthesis followed by diazene-directed formation of C_{sp3} - C_{sp3} quaternary vicinal stereocenters.⁶ Encouraged by these results, we sought to develop a new and efficient strategy for the synthesis of aryl-alkyl diazenes as prelude for formation of the C_{sp2} - C_{sp3} bonds in complex polycyclotryptamine alkaloids. Herein, we report the implementation of this new diazene synthesis in the convergent and enantioselective total syntheses of (–)-hodgkinsine B (**3**), (–)-hodgkinsine (**4**), (–)-calycosidine (**5**), (–)-quadrigemine C (**7**), and (–)-psycholeine (**8**) via completely stereocontrolled assembly of intact cyclotryptamine subunits (Figure 1).



Figure 1. Structure of representative cyclotryptamine alkaloids.

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The oligomeric cyclotryptamine alkaloids have been found to possess a variety of biological activities ranging from analgesic, antibacterial, antifungal, and anticandidal properties, to cytotoxicity against human cancer cell lines.9 However, a dearth of synthetic solutions to these alkaloids has hampered further evaluation of their properties. Amongst the existing solutions, Overman's synthesis of oligocyclotryptamine alkaloids including (-)-hodgkinsine B (3), (-)-hodgkinsine (4) and (-)quadrigemine C (7), elegantly establishes the key C3a-C7' stereocenter via a catalyst-controlled asymmetric intramolecular Heck cyclization to give α -aryl oxindoles.^{2a-f,m} Alternatively, Willis' synthesis of (-)-hodgkinsine B (3) sets the same key stereocenter via a diastereoselective substrate-controlled aarylation of an oxindole.²ⁱ Indeed, significant mismatch between catalyst and substrate control is possible, leading to substantial reduction in the level of diastereocontrol.^{2g} Recently, in Mac-Millan's synthesis of oligocyclotryptamines, the C3a-C7' linkages are introduced via a catalyst-controlled asymmetric arylation of tryptamides with excellent stereocontrol.²ⁿ However, a similar catalyst controlled approach was not applicable to the C3a-C3a' linkage, and an alternative strategy was used that provided a mixture of diastereomers.²ⁿ The existing synthetic solutions share in common the need for introduction of stereogenic centers that are at times subject to substrate control, giving rise to undesired stereochemical outcomes when substrate bias is not sought. As an alternative approach, we aimed to develop a unified synthetic strategy that would allow for the *completely* stereocontrolled union of cyclotryptamine monomers resulting in the stereospecific formation of all the stereocenters at C3a-C7' and C3a-C3a' linkages.

Our program's long-standing interest in the cyclotryptamine alkaloids has resulted in development of synthetic strategies for completely stereoselective late-stage union of whole cyclotryptamine substructures.^{3,5,6} The reductive cobalt-promoted dimerization of C3a-bromocyclotryptamines simultaneously secures two vicinal quaternary C_{sp3}-C_{sp3} stereocenters of homodimeric cyclotryptamine and cyclotryptophan alkaloids.⁵ More recently, we reported a general strategy for the diazene-directed late-stage C-C bond formation at the C3a quaternary stereocenters of two dissimilar cyclotryptamine subunits.⁶ Additionally, a convergent late-stage Friedel-Crafts directed union of two complex diketopiperazines has allowed for the regioselective formation of the key C_{sp2}-C_{sp3} linkage in the total synthesis of a number of dimeric diketopiperazines and related epipolythiodiketopiperazines.³ We now report the development of a new methodology for synthesis of aryl-alkyl diazenes and its application in the modular and completely controlled assembly of *multiple* and distinct cyclotryptamine fragments. The use of our diazenedirected stereoselective fragment assembly in the formation of both C3a-C7' and C3a-C3a' linkages, independent of stereochemical substrate bias, provides a strategy for complete relative and absolute stereochemical control in securing the required quaternary stereogenic centers.

Scheme 1. Retrosynthetic analysis of (–)-quadrigemine C (7)



RESULTS AND DISCUSSION

Our retrosynthetic analysis of the tetrameric alkaloid (-)quadrigemine C (7) is illustrative of this new approach for accessing polycyclotryptamines (Scheme 1). The principal objective of our synthetic approach to alkaloid (-)-7 was to establish a general strategy for the union of stereochemically defined cyclotryptamine units via a diazene-directed fragment assembly, thus completely controlling the absolute and relative stereochemistry within each subunit. We envisioned securing all four quaternary stereocenters via completely stereoselective C-C bond formations following dinitrogen extrusion from the trisdiazene tetramer 10. While the vicinal C_{sp3} - C_{sp3} quaternary stereocenters could be secured via oxidation of a mixed sulfa-mide intermediate,^{6,10} the introduction of the remaining C_{sp2} -C_{sp3} linked stereocenters using an analogous C3a-C7' diazene was expected to be less efficient due to competitive arenehalogenation, consistent with our previous observations.^{6c} The requirement for obviating multiple oxidative N-N bond formations in complex setting as well as our desire to develop a more direct synthesis of diazenes prompted us to investigate a new aryl-alkyl diazene synthesis using hydrazines. To date, the use of hydrazines as precursors for diazene synthesis has been largely limited to alkylation of the corresponding hydrazones^{11a} and cross-coupling of aryl hydrazides with aryl halides followed by oxidation.^{11b} We envision that the development of the required mild diazene synthesis methodology and its application to the total synthesis of tetramer (-)-7 (Scheme 1) as well as trimers (-)-3 and (-)-4 (Figure 1) could serve as a foundation for broader utility of this chemistry.

Inspired by the successful nucleophilic addition of 2,6difluorophenylsulfamate at the C3a position of cyclotryptamines,^{6c} we envisioned a more direct diazene synthesis, obviating the need for formation of transient aryl-alkyl mixed sulfamides and their oxidation to the corresponding aryl-alkyl diazene (Scheme 2). A major challenge in such an approach is the incompatibility of aryl hydrazines with silver(I) promoters. We predicted the use of electronically deactivated hydrazine derivatives **15** would provide sufficient stability toward the silver promoter of choice for electrophilic activation of C3abromocyclotryptamine **17**, enabling their use as potential nucleophiles to directly access the desired aryl-alkyl diazenes.

Scheme 2. New synthesis of aryl-alkyl diazenes



Gratifyingly, electrophilic activation of cyclotryptamine bromide **21** (Scheme 3) using silver trifluoromethanesulfonate in the presence of hydrazide **19** led to the formation of the desired C3a adduct **23** in 72% yield. For comparison, the use of hydrazine **18** under identical conditions led to the recovery of cyclotryptamine bromide **21** in 56% yield with no detectable formation of the desired C3a adduct.¹²

Scheme 3. Synthesis of aryl-alkyl diazenes via nucleophilic addition of electronically deactivated hydrazines^{*a*}



^aReagents and conditions: R=COCF₃: (a) AgOTf, DTBMP, CH₂Cl₂, 22 ^oC, 1 h, 72% yield of **23**. (b) H₂NNH₂, THF, 23 ^oC, 19 h; PhI(OAc)₂, THF, 23 ^oC, 3h, 87% yield of (±)-**25**; R=SO₂Me: AgOTf, DTBMP, CH₂Cl₂, 22 ^oC, 40 min, 73% yield of (±)-**25**.

Hydrazinolysis of the trifluoroacetamide group of intermediate 23 followed by mild oxidation yielded the desired C3a diazene (\pm)-25 in 87% yield. While this approach fulfills our criteria for a more efficient and mild diazene synthesis, we sought a more direct alternative. Our design was to generate an electronically deactivated hydrazine that would spontaneously convert to the corresponding diazene upon intercepting the electrophile. We posited that the methanesulfonyl hydrazine adduct 24 could undergo spontaneous loss of methanesulfinic acid due to greater steric crowding and the accompanying elongation of the N–S bond post capture of the electrophile.¹³ Indeed, electrophilic activation of cyclotryptamine bromide 21 in the presence of methanesulfonyl hydrazide 20 directly yielded the desired aryl-alkyl diazene (\pm)-25 in a single-step and in 73% yield.

With this aryl-alkyl diazene synthesis method in hand, we next aimed to develop an efficient synthesis of enantiomerically enriched cyclotryptamine monomers with appropriate functional groups at the C3a and C7 positions (Scheme 4). Enantioselective bromocyclization^{7e} of N1-Teoc-tryptamine methyl carbamate catalyzed by (S)-3,3'-bis(2,4,6-triisopropylphenyl)-1,1'binaphthyl-2,2'-diyl hydrogenphosphonate (TRIP)¹⁴ afforded C3a-bromocyclotryptamine (+)-26 in 99% yield and 94% enantiomeric excess on multi-gram scale.¹⁵ Electrophilic activation³ of bromocyclotryptamine (+)-26 using silver trifluoromethanesulfonate in the presence of 2,6difluorophenylsulfamate led to the desired sulfamate ester (+)-27 in 83% yield. Alternatively, sulfamate ester (+)-27 could be obtained starting from the reduced C3a-H intermediate (+)-29 via Du Bois' Rh-catalyzed amination,¹⁶ a method that proved advantageous in later stages of our synthesis. Exposure of sulfamate ester (+)-27 to pyridine in an acetonitrile-water mixture at 70 °C afforded the amine (+)-28 in 81% yield. With a highly expedient synthesis of the C3a-amine (+)-28 secured, we turned our attention to the C7-aminocyclotryptamines. While our early approach to synthesis of C7-substituted cyclotryptamines relied on the synthesis of C7-substituted tryptamine derivatives, we sought a more direct approach inspired by the latest advances in C-H amination chemistry.^{17,18} Mild reduction of bromocyclotryptamine (+)-26 using tris(trimethylsilyl)silane and triethylborane furnished cyclotryptamine (+)-29 in 85% yield. Under optimal conditions, this compound was an outstanding substrate for a (trimethylsilyl)ethyl carbamate-directed iridiumcatalyzed C7-amination using methanesulfonyl azide.¹⁵ Notably, this reaction proceeded in 97% yield to afford the sulfonamide (+)-30 as a single regioisomer. Electrophilic amination of sulfonamide (+)-30 using sodium hydride and O-(diphenylphosphinyl) hydroxylamine afforded hydrazide (+)-31 in 84% yield. The application of selective C-H amination allows for exceptionally efficient generation of fully functional C-7 cyclotryptamine hydrazide (+)-31 in only three steps from bromocyclotryptamine (+)-26.

Scheme 4. Synthesis of C3a-amine (+)-28 and C7-cyclotryptamine hydrazide (+)- 31^{a}



^aReagents and conditions: (a) 2,6-difluorophenyl sulfamate, AgOTf, DTBMP, CH₂Cl₂, 22 °C, 1 h, 83%. (b) pyridine, MeCN-H₂O, 70 °C, 23 h, 81%. (c) (Me₃Si)₃SiH, Et₃B, THF, air, 22 °C, 3 h, 85%. (d) MeSO₂N₃, [Cp*IrCl₂]₂, AgNTf₂, AgOAc, CICH₂CH₂Cl, 22 °C, 20 h, 97%. (e) NaH, THF, 0 °C, 30 min; Ph₂P(O)ONH₂, 22 °C, 1 h, 84%. Ar = 2,6-difluorobenzene.

The same strategy was used to access the corresponding enantiomeric C3a- and C7-functionalized cyclotryptamines.¹⁵ Aminocyclotryptamine (–)-**28** was prepared from bromocyclotryptamine (–)-**26** (96% ee) in two steps and 74% overall yield via hydrolysis of the corresponding sulfamate ester (–)-**27**. Similarly, hydrazide (–)-**31** was prepared in three steps using a mild reduction of tertiary bromide followed by a C7-selective

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59 60 iridium-catalyzed amination and an electrophilic amination in 59% overall yield from bromocyclotryptamine (-)-**26**.

With both enantiomers of hydrazide 31 in hand, we endeavored to utilize these functional monomers (Scheme 4) in the aryl-alkyl diazene methodology described above (Scheme 3). We were delighted to find that the electrophilic activation of bromocyclotryptamine (+)-26 using silver trifluoromethanesulfonate in the presence of hydrazide (-)-31 directly afforded the first aryl-alkyl dimeric diazene (+)-32 in 60% yield (Scheme 5). Similarly, the use of enantiomeric hydrazide (+)-31 as nucleophile under identical conditions led to the formation of diastereomeric diazene dimer (-)-33 in 59% yield. Importantly, the formation of either dimeric diazene diastereomer proceeds with equal efficiency, offering complete control of the relative and absolute stereochemistry within each subunit. We focused specifically on the synthesis of diastereomers (+)-32 and (-)-33 due to the presence of such dimeric substructures in a number of cyclotryptamine alkaloids (Figure 1) and their close resemblance to the dimeric fragments present in (-)-hodgkinsine B (3), (-)-hodgkinsine (4) and (-)-quadrigemine C (7).

Scheme 5. Synthesis of C3a–C7' aryl-alkyl diazenes (+)-**32** and (–)-**33** through directed dimerization of cyclotryptamines^{*a*}



^aReagents and conditions: (a) AgOTf, DTBMP, CH₂Cl₂, 22 °C, 1 h, (60% for (+)-**32** and 59% for (–)-**33**).

After accessing the requisite monomeric and dimeric cyclotryptamine substructures, we turned our attention to their directed and convergent assembly towards the synthesis of (–)hodgkinsine B (**3**) which bears three cyclotryptamine monomers connected via a head-to-head C3a'–C3a" linkage as well as a head-to-tail C3a–C7' linkage (Figure 1). Alkaloid (–)-**3** was first synthesized in 2003 via an asymmetric intramolecular Heck cyclization providing the C3a–C7' linkage.^{2c,i} The observed level of catalyst stereocontrol resulted in the synthetic alkaloid (–)-**3** being prepared in 83% enantiomeric excess.^{2c} Most recently, alkaloid (–)-**3** was prepared efficiently along with alkaloid (–)-**4** following a diastereoselective (1.4:1 dr) step providing the C3a'–C3a" bond of these alkaloids.²ⁿ

In our approach, we envisioned the formation of trimeric cyclotryptamine (-)-3 via sequential coupling of three cyclotryptamine components. Having secured the C3a–C7' dimeric diazene (+)-32 through the union of two cyclotryptamine monomers (+)-26 and (-)-31, we envisaged the synthesis of a C3a'_{sp3}-C3a"_{sp3} diazene linker arising from the coupling of a dimeric sulfamate ester and the monomeric amine (+)-28 (Scheme 6). Synthesis of the sulfamate ester (+)-34 was accomplished using Du Bois' Rh-catalyzed intermolecular C_{3a}–H amination¹⁶ starting from dimeric (+)-32 in 58% yield (Scheme 6). We were pleased to find that exposure of sulfamate ester (+)-34 to amine (+)-28 in the presence of 4-(*N*,*N*-dimethylamino)pyridine (DMAP) in tetrahydrofuran yielded the desired mixed sulfamide (+)-**35** in 94% yield. Notably, this reaction proceeded in high yield, using only a slight excess (1.1 equiv) of amine (+)-**28**, despite the greatly crowded C3a-steric environment. Next, oxidation of mixed sulfamide (+)-**35** using 1,3-dichloro-5,5-dimethylhydantoin (DCDMH) in the presence of 1,8-diazabicyclo[5.4.0]undec-7ene (DBU) provided the trimeric bisdiazene (+)-**36** in 91% isolated yield (Scheme 6).

Scheme 6. Total synthesis of (-)-hodgkinsine B $(3)^{a}$



^a Reagents and conditions: (a) 2,6-difluorophenyl sulfamate, Rh₂(esp)₂, Ph(Me)₂CCO₂H, PhI(OAc)₂, MgO, 5Å MS, *i*-PrOAc, 22 °C, 22 h, 58%. (b) DMAP, THF, 22 °C, 24 h, 94%. (c) 1,3-dichloro-5,5'dimethylhydantoin, 1,8-diazabicyclo[5.4.0]undec-7-ene, MeCN, 22 °C, 1 h, 91%. (d) *hv* (380 nm), 25 °C, 15 h, 73%. (e) *hv* (300 nm), 25 °C, 30 h, 51%. (f) TBAF, THF, 22 °C, 1 h, 98%. (g) Red-Al, PhMe, 70 °C, 1 h, 68%. Ar = 2,6-difluorobenzene

Our initial reservations regarding the stability of a bisdiazene notwithstanding, this intermediate proved to be an isolable compound. Applying previously developed conditions,⁶ a thin film of bis-diazene trimer (+)-36 was photolyzed using 380 nm light, selectively activating the more labile C3a'-C3a" diazene, and affording cleanly the desired mono-diazene trimer (+)-37. Notably, according to our design, the more robust C3a-C7' diazene linker remained intact during this process. Photolysis of the diazene trimer (+)-37 as a thin film was achieved using higher energy 300 nm light to give trimer (+)-38 in 51% yield. Importantly, the application of our diazene-based fragment assembly strategy allowed the synthesis of a *complex*, functionalized cyclotryptamine trimer with complete control over the absolute as well as relative stereochemistry within all subunits, including three quaternary stereocenters. Treatment of trimer (+)-38 with tetra-n-butylammonium fluoride (TBAF) resulted in global removal of (trimethylsilyl)ethyl carbamates in high yield. The choice of this N1-protective group was important as the steric constraints of the C3a-C7' linkage rendered other groups difficult to remove. We postulated that the removal of the (trimethylsilyl)ethyl carbamate may be facilitated by nucleophilic attack at the more accessible trimethylsilyl group. Exhaustive reduction of the methyl carbamates with Red-Al afforded (-)-hodgkinsine B (3) in 68% yield. Significantly, alkaloid (-)-3 was prepared in seven steps from readily available precursors (+)-**28** and (+)-**32**, which in turn are accessible from the two enantiomers of cyclotryptamine **26** in four steps or less. All ¹H and ¹³C NMR data, as well as optical rotation (observed $[\alpha]_D^{24} = -88 \ (c = 0.21, \text{ CHCl}_3)$; lit.: $[\alpha]_D^{27} = -77.0 \ (c = 1, \text{ CHCl}_3), ^{2c_i} [\alpha]_D^{27} = -55.0 \ (c = 0.8, \text{ CHCl}_3, 83\% \text{ ee})^{2c}$ and $[\alpha]_D^{25} = -69.5 \ (c = 1, \text{ CHCl}_3)^{2i}$) for synthetic (-)-**3** were consistent with literature data.

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With rapid access to both enantiomers of amine **28**, bromide **26** and hydrazide **31**, we sought to apply our synthetic strategy for union of three distinct monomeric cyclotryptamines to access (–)-calycosidine (**5**) after an acid-catalyzed rearrangement of (–)-hodgkinsine (**4**). Originally isolated in 1961 from *Hodg-kinsonia frutescens*, ¹⁹ alkaloid (–)-**4** was found to show a strong dose-dependent analgesic activity against capsaicin-induced pain^{9f} as well as cytotoxicity against human cancer cell lines HCT-116, SF-295 and OVACR-8.^{9g}

Scheme 7. Total synthesis of (–)-hodgkinsine (4) and (–)-calycosidine $(5)^a$



^aReagents and conditions: (a) 2,6-difluorophenyl sulfamate, Rh₂(esp)₂, Ph(Me)₂CCO₂H, PhI(OAc)₂, MgO, 5Å MS, *i*-PrOAc, 22 °C, 14 h, 60%. (b) DMAP, THF, (-)-**28**, 22 °C, 24 h, 98%; (c) 1,3-dichloro-5,5'dimethylhydantoin, 1,8-diazabicyclo[5.4.0]undec-7-ene, MeCN, 22 °C, 1 h, 88%; (d) *hv* (380 nm), 25 °C, 15 h, 73%. (e) *hv* (300 nm), 25 °C, 15 h, 62%. (f) TBAF, THF, 22 °C, 1 h, 96%. (g) Red-Al, PhMe, 70 °C, 1 h, 73%. (h) H₂O, CH₃COOH, 95 °C, 36 h, 42%. Ar = 2,6-difluorobenzene.

Consistent with our approach to (-)-hodgkinsine B (3), our synthetic plan for accessing (-)-hodgkinsine (4) relied on the sequential coupling of the appropriate cyclotryptamine subunits, including bromocyclotryptamine (+)-26, hydrazide (+)-31, and amine (-)-28, via the formation of the C3a'-C3a" and C3a-C7' diazenes. Starting with dimeric diazene (-)-33, the Rh-catalyzed C-H amination afforded the sulfamate ester (-)-39 in 60% yield (Scheme 7). Notably, this challenging transformation proceeds with equal efficiency on both diazene diastereomers (+)-32 and (-)-33. Treatment of sulfamate ester (-)-39 with DMAP in the presence of amine (-)-28, followed by a mild oxidation of the mixed sulfamide (-)-40 to the corresponding diazene afforded the bis-diazene trimer (-)-41 in 86% yield over two steps. Stepwise photolysis of the two diazenes yielded the trimer (-)-42 in 45% yield over two steps. Importantly, exposure of bis-diazene (-)-41 to photolysis at 300 nm light for 19 h affords trimer (-)-

42 in 41% yield in a single-step. A global removal of (trimethylsilyl)ethyl carbamates followed by an exhaustive reduction using Red-Al led to formation of (-)-hodgkinsine (**4**) in 70% yield over two steps. Notably, alkaloid (-)-**4** was obtained in seven steps from readily available precursors (-)-**28** and (-)-**33**, which in turn are accessible from cyclotryptamine **26** in four steps or less.¹⁵ All spectroscopic data as well as the optical rotation for alkaloid (-)-**4** (observed $[\alpha]_D^{24} = -39$ (c = 0.38, CHCl₃); lit.: $[\alpha]_D^{24} = -33.6$ (c = 1, CHCl₃)²⁰) were consistent with previously reported values. Finally, exposure of alkaloid (-)-**4** to aqueous acetic acid^{2a,5a} at 95 °C led to the formation of isomeric (-)-calycosidine (**5**) whose spectroscopic data as well as optical rotation (observed $[\alpha]_D^{24} = -7$ (c = 0.11, CHCl₃); lit.: $[\alpha]_D = -18$ (c = 1, CHCl₃)²¹) were consistent with literature data.

In order to further demonstrate the versatility of our functional cyclotryptamine monomers in a highly convergent diazene-directed fragment assembly approach, we envisioned the synthesis of a complex tetrameric alkaloid (–)-psycholeine (8) via the acid-catalyzed rearrangement of isomeric (–)quadrigemine C (7). First isolated in 1987 from an extract of *Psychotria oleoides*,^{21a} (–)-quadrigemine C (7) is reported to be an antagonist of the somatostatin receptor (SRIF),^{9d} an inhibitor of human platelet aggregation^{9a} and has displayed cytotoxicity against two invasive cancer cell lines DU145 and A2058.^{2m} Overman's synthesis of (–)-quadrigemine C (7) stands as a superb demonstration of a challenging double enantioselective Heck cyclization (diastereoselection 9.3:2.0:1.0, 90% ee for major isomer) in a complex setting.^{2a,m}

Having prepared both enantiomers of all the functionalized monomers present in the tetrameric alkaloid (-)-7, bromide (+)-26 and both enantiomers of hydrazide 31, we sought to access alkaloid (-)-7 from the tetrameric tris-diazene intermediate (+)-44 via coupling of the corresponding diazene dimers (+)-34 and (-)-43 (Scheme 8). The amine (-)-43 was accessed in 84% yield via hydrolysis of the corresponding sulfamate ester (-)-39. The coupling of amine (-)-43 and sulfamate ester (+)-34 followed by oxidation of the mixed sulfamide proceeded in 70% overall yield to give tris-diazene tetramer (+)-44. The modular design of our synthetic strategy has potential for highly convergent assembly of cyclotryptamine monomers into any diastereomer of tris-diazene tetramer (+)-44 while exerting complete control over absolute and relative stereochemistry within each subunit. Selective photolysis of the C3a'-C3a" diazene led to bis-diazene tetramer (+)-45 in 72% yield. Photolysis of both C3a-C7' and C3a"-C7" diazenes on intermediate (+)-45 using 300 nm light afforded tetramer (+)-46 in 44% yield. Notably, starting with tris-diazene tetramer (+)-44, photolysis using 300 nm light afforded tetramer (+)-46 in 22% yield, offering an example where three molecules of dinitrogen are photoextruded from a single intermediate to adjoin four monomers via three carbon-carbon bonds. Significantly, this transformation secured all four quaternary stereocenters with complete stereocontrol in a singlestep. Removal of (trimethylsilyl)ethyl carbamates followed by an exhaustive reduction of methyl carbamates gave (-)quadrigemine C (7) in 54% yield over two steps, providing an expedient eight-step route from readily available dimers (+)-32 and (-)-33 (Scheme 5). All spectroscopic data as well as optical rotation for alkaloid (-)-7 (observed $[\alpha]_D^{24} = -81$ (c = 0.51, CHCl₃); lit.: $[\alpha]_D = -69$ (c = 1, CHCl₃)^{21a}) were in agreement with literature. Exposure of (-)-quadrigemine C (7) to aqueous acetic acid^{2a,5a} led to the formation of isomeric (-)-psycholeine (8) in 36% yield, whose spectroscopic data as well as optical rotation (observed $[\alpha]_D^{20} = -155$ (c = 0.14, EtOH); lit.: $[\alpha]_D^{20} = -150$ (c = 0.4, EtOH)²² and $[\alpha]_D^{28} = -150$ (c = 0.1, EtOH)^{2a}) were consistent with the previously reported values.

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59 60 Scheme 8. Convergent and completely stereoselective total synthesis of (-)-quadrigemine C (7) and (-)-psycholeine $(8)^a$



^aReagents and conditions: (a) pyridine, MeCN–H₂O, 70 °C, 24 h, 84%. (b) DMAP, THF, 22 °C, 7 h, 94%. (c) 1,3-dichloro-5,5'-dimethylhydantoin, 1,8-diazabicyclo[5.4.0]undec-7-ene, MeCN, 22 °C, 1 h, 74%. (d) *hv* (380 nm), 25 °C, 24 h, 72%. (e) *hv* (300 nm), 25 °C, 18 h, 44%. (f) *hv* (300 nm), 25 °C, 19 h, 22%. (g) TBAF, THF, 22 °C, 1 h, 87%. (h) EtN(Me)₂-AlH₃, PhMe, 60 °C, 1 h, 62%. (i) H₂O, CH₃COOH, 95 °C, 36 h, 36%. Ar = 2,6-difluorobenzene.

■ CONCLUSIONS

In summary, we have developed a versatile strategy for the modular synthesis of polycyclotryptamine alkaloids via the convergent and directed assembly of whole cyclotryptamine subunits. This approach is enabled by our new methodology for synthesis of aryl-alkyl diazenes through the coupling of electronically-deactivated aryl hydrazines with bromocyclotryptamines. Our diazene-guided stereoselective assembly of cyclotryptamine fragments at both the C3a-C3a' and C3a-C7' linkages was used to secure quaternary stereocenters with complete relative and absolute stereochemical control. The synthesis of the C3a- and C7-functionalized cyclotryptamine monomers was realized through the systematic application of Rh- and Ir-catalyzed C-H amination chemistry, respectively, in complex settings. The combination of advanced C-H amination chemistry, the new aryl-alkyl diazene synthesis methodology, and our diazenedirected fragment coupling enables highly convergent and modular assembly of cyclotryptamine monomers. Successful implementation of this chemistry is demonstrated by the total synthesis of (-)-hodgkinsine B (3), (-)-hodgkinsine (4), (-)calycosidine (5), (-)-quadrigemine C (7), and (-)-psycholeine (8) through the modular and directed assembly of intact cyclotryptamines with complete stereochemical control at all quaternary stereocenters.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures, spectroscopic data, and copies of NMR spectra. This material is available free of charge via the Internet at <u>http://pubs.acs.org</u>

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Notes

The authors declare no competing financial interests.

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