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Letter

Enantioselective [4 + 2] Cycloaddition/Cyclization Cascade Reaction and Total Synthesis of *cis*-Bis(cyclotryptamine) Alkaloids

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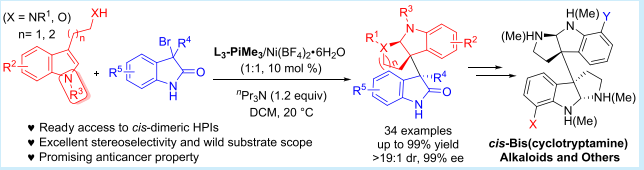
ABSTRACT: The asymmetric catalytic synthesis of 3-cyclotryptamine substituted oxindoles through formal [4 + 2] cycloaddition/cyclization cascade is described. A wide range of cyclotryptamine derivatives were obtained in enantioenriched form under mild reaction conditions and were found to have potential anticancer activity. The strategy enables ready assembly of cyclotryptamine subunits at the C_{3a}–$C_{3a'}$ positions with two quaternary stereogenic centers in *cis*-selectivity, leading to the concise synthesis of optically active *cis*-bis(hexahydropyrroloindole) and others of the cyclotryptamine alkaloid family.



Cyclotryptamine alkaloids which comprise two or more hexahydropyrroloindole (HPI) units or others represent a set of structurally and biologically interesting natural products.[1,2] The simplest member of this family, for example, chimonanthine, consists of two same cyclotryptamine subunits fused at the C_{3a} and $C_{3a'}$ positions, forming chiral or *meso*-isomers (Figure 1a). This core structure could be extended into optically active hodgkinsine B, quadrigemine C, and others upon appending an additional HPI subunit at the C7′-position. Asymmetric assembly of such molecules featured with vicinal quaternary all-carbon centers drew much attention over the past decades. Many elegant routes have been discovered, starting from the enantioselective construction of the key precursors, such as homo- or heterobisoxindoles,[3] hexahydropyrroloindole derivatives,[4] and indole-substituted oxindoles[5] (Figure 1b). Thus, these strategies have enabled concise access to the total synthesis of optically active alkaloid natural products, including chimonanthine, calycanthidine, hodgkinsine, etc.[6]

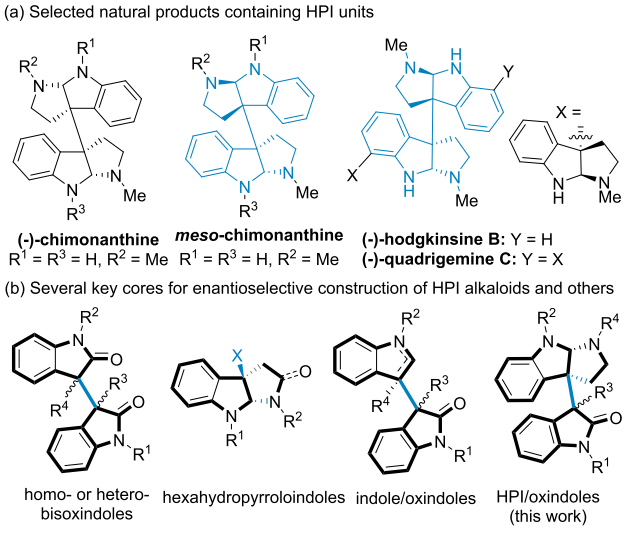


Figure 1. Representative asymmetric catalytic strategies for the construction of hexahydropyrroloindole alkaloid natural products.

In fact, most reported approaches have paid much attention to the optically active *trans*-isomers where homotype alkaloids are involved. Actually, several pyrroloindoline alkaloids, including desmethyl *meso*-chimonanthine and others, bearing a pseudo C_2-symmetric backbone have also been isolated.[1,2] Enantioselective construction of nonsymmetrical *meso*-analogues is elusive and interesting.[4g,i,7] Starting with *meso*-chimonanthine, asymmetric Heck cyclization to desymmetrization allows the total synthesis of a variety of cyclotryptamine alkaloid oligomers by Overman[8] and Wills.[9] Dalko and coworkers had realized the synthesis of desymmetrized dimeric *meso*-pyrrolidinoindoline alkaloids[10] by using s tandem [4 + 2] cycloaddition route, which was inspired by Funk for the total synthesis of perophoramidine,[5c,11] and communesin F as well.[12]

In view of the structural and stereoversatility of such architecture and the challenge of catalytic asymmetric construction of the sterically congested vicinal all-carbon quaternary stereocenters in these structures, herein we performed an asymmetric catalytic [4 + 2] cycloaddition/cyclization cascade reaction between tryptamine derivatives

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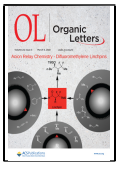

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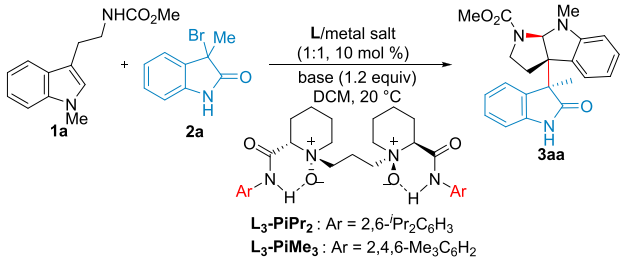
and indol-2-ones in situ generated from 3-bromooxindoles. Then, a number of enantiomerically enriched cyclotryptamine-substituted oxindole derivatives were prepared (82−99% yield, >19:1 dr, 88−99% ee). As a continuation of our research on the enantioselective synthesis of HPI alkaloids,[3f] the employment of a similar nickel complex of chiral *N*,*N*′-dioxides as the catalyst in the synthesis of *trans*-bisoxindoles from 3-bromooxindoles, stereoselective reversal synthesis of *cis*-chimonanthine analogues, and the related derivatives were established in this case. This kind of [4 + 2] cycloaddition and sequential reactions could be extended to the construction of piperidinoindoline scaffolds. Biological activity evaluation indicates that some new cyclotryptamine-substituted oxindole derivatives have promising anticancer property.

At the outset of this study, we chose tryptamine derivative **1a** and 3-methyl-3-bromooxindole **2a** as model substrates to optimize the reaction conditions (Table 1). Cs_2CO_3 was

Table 1. Optimization of the Reaction Conditions[a]



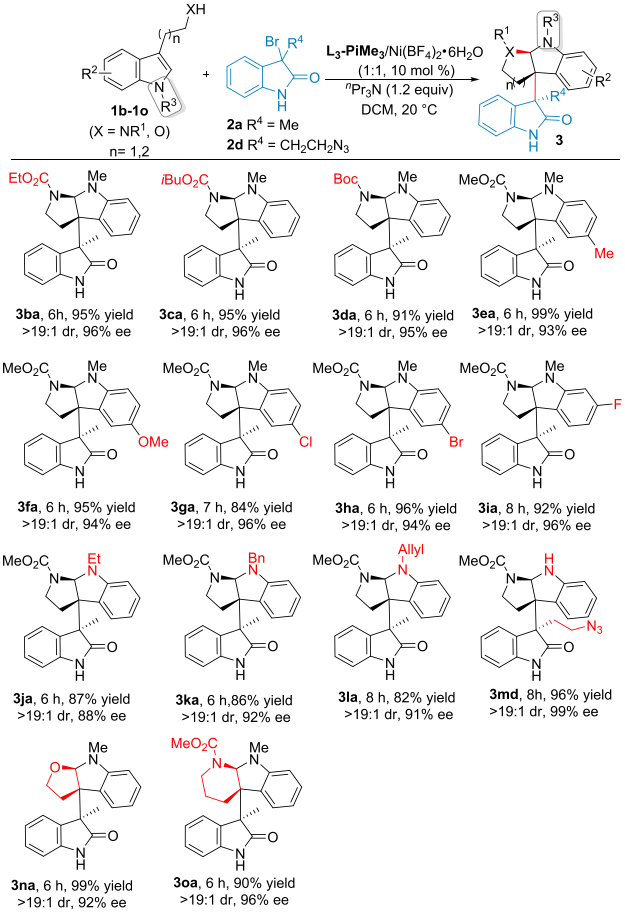
entry	metal salt	base	yield (%)[b]	dr[c]	ee (%)[c]
1	$Mg(OTf)_2$	Cs_2CO_3	82	>19:1	5
2	$Zn(OTf)_2$	Cs_2CO_3	46	90:10	3/47
3	$Cu(OTf)_2$	Cs_2CO_3	50	>19:1	25
4	$Fe(OTf)_3$	Cs_2CO_3	34	>19:1	0
5	$Ni(BF_4)_2{\cdot}6H_2O$	Cs_2CO_3	82	>19:1	84
6	$Ni(BF_4)_2{\cdot}6H_2O$	Et_3N	84	>19:1	94
7	$Ni(BF_4)_2{\cdot}6H_2O$	DIPEA	84	>19:1	95
8	$Ni(BF_4)_2{\cdot}6H_2O$	$^nPr_3N$	89	>19:1	96
9[d]	$Ni(BF_4)_2{\cdot}6H_2O$	$^nPr_3N$	89	>19:1	96

[a]Unless otherwise noted, all reactions were carried out with **1a** (0.10 mmol), **2a** (0.12 mmol), **L$_3$-PiPr$_2$**/metal salt (1:1, 10 mol %), base (0.12 mmol) in DCM (1.0 mL) at 20 °C for 8−10 h. [b]Yield of isolated product. [c]Determined by chiral HPLC. [d]Ligand was replaced by **L$_3$-PiMe$_3$**.

initially selected as the base to generate indol-2-one intermediate from **2a**. First, a variety of metal salts combined with chiral ligand *N*,*N*′-dioxide **L$_3$-PiPr$_2$** were tested in DCM at 20 °C (entries 1−5). It was found although the desired hexahydropyrroloindole derivative **3aa** could be isolated in moderate to good yield, the enantioselectivity was poor by the use of many typical Lewis acids, such as $Mg(OTf)_2$, $Zn(OTf)_2$, $Cu(OTf)_2$, or $Fe(OTf)_3$. In comparison, $Ni(BF_4)_2{\cdot}6H_2O$ provided promising results as 82% yield with >19:1 dr and 84% ee (entry 5). Then, different bases were explored to minimize base-accelerated racemic reaction.[10] An obviously increased enantioselectivity was observed when organic bases were used (entries 6−8), and sterically hindered $^nPr_3N$ could give the best results in 89% yield with >19:1 dr and 96% ee (entry 8). Moreover, when the ligand was changed to **L$_3$-PiMe$_3$**, which is much easier to be prepared, the excellent outcomes could be retained (entry 9).

With the optimal conditions in hand (Table 1, entry 9), the scope of tryptamine derivatives was explored in the cascade reaction with **2a** (Scheme 1). It was found that the reaction

Scheme 1. Substrate Scope of Tryptamine Derivatives[a]



[a]Unless otherwise noted, all reactions were carried out with **1** (0.10 mmol), **2** (1.2 equiv), **L$_3$-PiMe$_3$**/$Ni(BF_4)_2{\cdot}6H_2O$ (1:1, 10 mol %), $^nPr_3N$ (1.2 equiv) in DCM (1.0 mL) at 20 °C for 6−8 h. Yield of isolated product, dr values were determined by ^1H NMR, and ee values were determined by HPLC analysis.

tolerated tryptamines with various carbamate functions at the side chain nitrogen, affording the related products **3ba**−**3da** in eminent results (91−95% yield, 95−96% ee). Either electron-donating groups or electron-withdrawing groups at the 5- or 6-position of the indole ring of tryptamines had no significant impact on the outcomes, providing the corresponding pyrroloindolines **3ea**−**3ia** in outstanding results (84−99% yield, 93−96% ee). Examination of the possible substitution on the indolic nitrogen demonstrated that a range of alkyl protecting groups are compatible; for example, *N*-methyl, *N*-benzyl, and *N*-allyl-substituted tryptamines underwent cyclization in good yield and enantiocontrol (**3ja**−**3la**; 82−87% yield, 88−92% ee). Moreover, *N*-H based tryptamine derivative **1m** could react with indol-2-one of **2d** to afford the related product **3md** in 96% yield with 99% ee. Next, we considered utilizing this methodology for the construction of a variant of the cyclic core structure. It seemed likely that the formation of tetrahydrofuran (**3na**; 99% yield, 92% ee) and piperidinyl indoline (**3oa**; 90% yield, 96% ee) was readily available with

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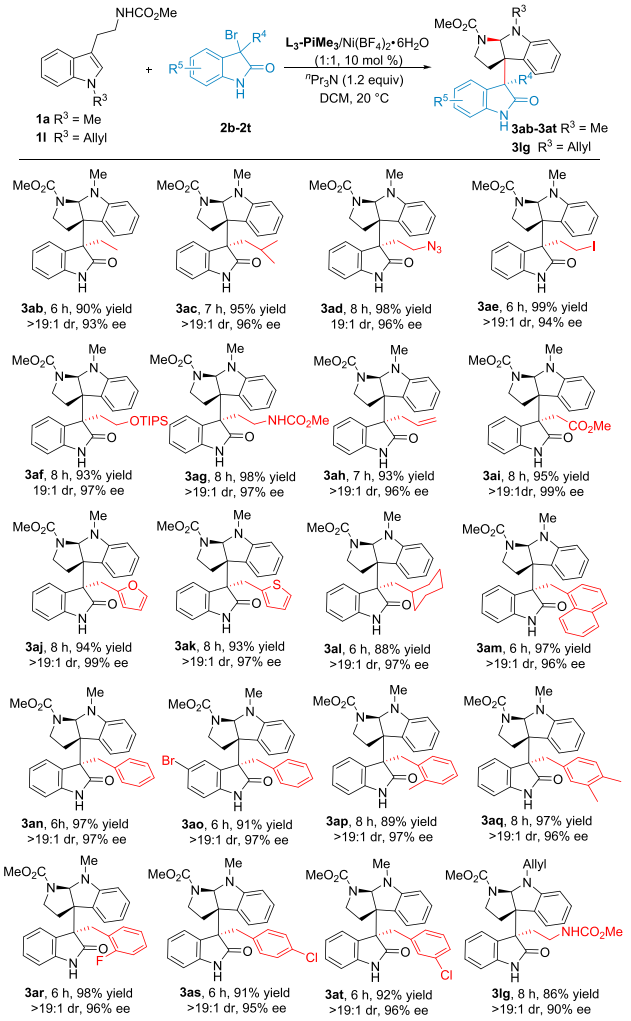
great enantiocontrol upon using tryptophol or indole propionamide substrate.

We next turned to the intramolecular variant of this cascade reaction to 3-alkyl-3-bromoindolin-2-ones (Scheme 2). For

Scheme 2. Substrate Scope of 3-Substituted-3-Bromooxindoles[a]

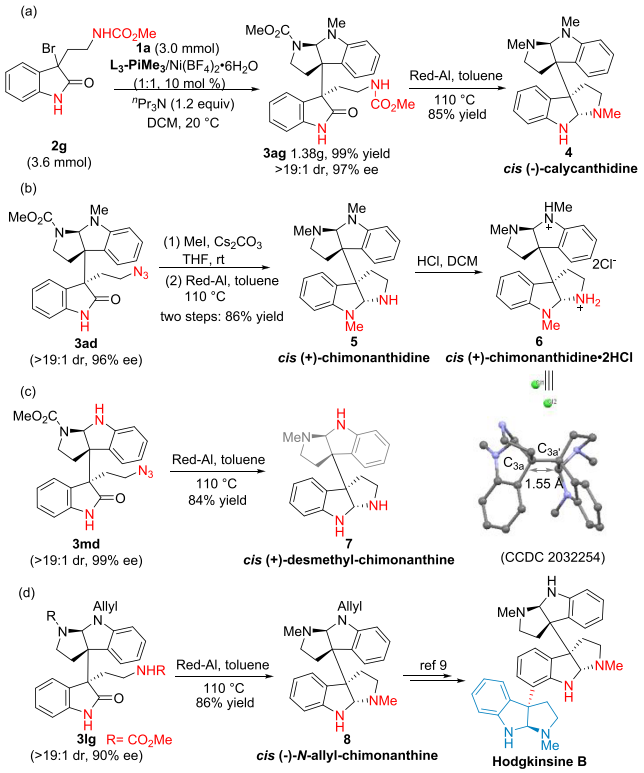


[a]Standard conditions.

example, indolinones with 3-alkyl substituent ranged from methyl to isobutyl with increased steric hindrance gave rise to the desired products in remarkable yield and enantioselectivity (**3ab**, 90% yield with 93% ee; and **3ac**, 95% yield with 96% ee). Moreover, a range of functional groups at the terminal position of the 3-alkyl chain, such as azide, iodine, ether, methyl carbamate, allyl, or ester, were introduced, and they could indeed be accomplished to deliver the products **3ad**−**3ai** with perfect enantioselectivities (94−99% ee), which will play promising roles in further transformations. Moreover, the reaction was amenable to other benzyl or heteroaromatic groups, including the furyl, thienyl or 1-naphthyl group (**3aj**, **3ak**, **3am**). We also employed 3-benzyl-3-bromooxindoles containing electron-donating or electron-withdrawing groups at different positions on the benzyl moiety, and the reaction afforded the corresponding products (**3an**-**3at**) with admirable results (89−97% yield, 95−97% ee).

Furthermore, the synthetic utility of this reaction was investigated. A gram-scale reaction between tryptamine **1a** and methyl carbamate 3-bromooxindole **2g** was performed, furnishing the product **3ag** in nearly quantitative yield, >19:1 dr, 97% ee (Scheme 3a). Reducing of **3ag** by red-Al at high

Scheme 3. Gram Scale-Up and Synthetic Utility



temperature via a reductive amination/cyclization of oxindole moiety generated the final alkaloid **4** as *cis*-(−)-calycanthidine in 85% yield. Accordingly, the asymmetric total synthesis *cis*-(+)-chimonanthidine **5** was efficiently obtained from azide-containing product **3ad** upon methylation and reducing after a one-column purification with 86% overall yield (Scheme 3b). The presence of multiple low-energy conformations around the vicinal quaternary carbon of these alkaloids leads to difficulty in crystalline samples for X-ray analysis.[6a] After acidification with hydrochloric acid, the structure of *cis*-(+)-chimonanthidine **5** was unambiguously and first assigned by X-ray crystallographic analysis (Scheme 3b).[13] The C_{3a}−$C_{3a'}$ σ-bond is 1.55 Å in the salt of the compound **5**, indicating steric congestion in this kind of diastereoisomer. Similarly, *cis*-(+)-*N*-desmethyl-chimonanthine **7** and *cis*-(+)-*N*-allyl-chimonanthine **8** could be synthesized by reductive cyclization of the product **3md** and **3lg** respectively in high yields (Scheme 3c and d).[4g] Taken together, these syntheses highlight the versatility of this method and suggest that its use in even more complex contexts might prove feasible (for example, hodgkinsine B).[8,9,14]

Considering the importance of these indole-based structures, we investigated the bioactivity of several cyclotryptamine-oxindole products **3**. The in vitro cytotoxicity against human colorectal carcinoma (HCT-116), renal carcinoma (ACHN), and hepatocellular carcinoma (HCCLM3) cells were evaluated. IC_{50} values ranged from 11.79 to 68.18 μM, which are listed in Figure 2. The effects are moderate, but two are more

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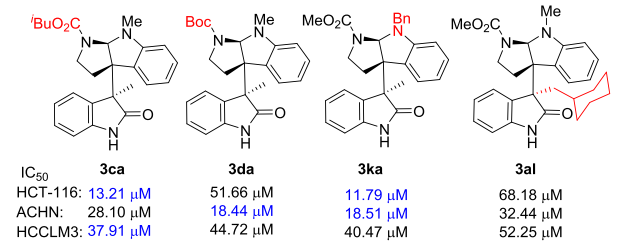
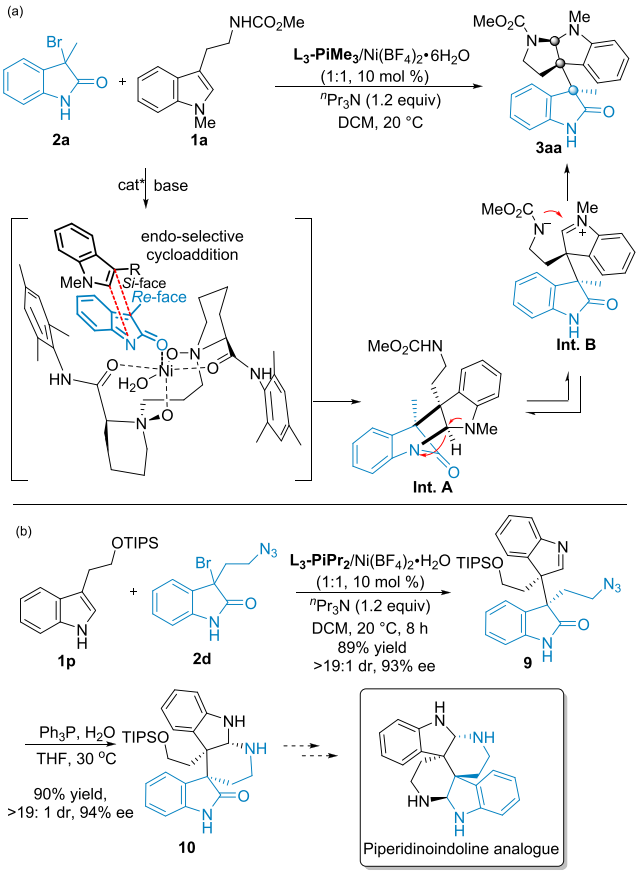


Figure 2. Bioactivities of some cyclotryptamine-oxindole products.

sensitive than the natural products against HCT-116, including (−)-chimonanthine and *meso*-chimonanthine (see the Supporting Information for details).[15] These synthesized cyclotryptamine-oxindole derivatives and the stereoisomers of the natural products might be promising compounds for discovering more applications in medicinal chemistry.

The stereocontrol of this coupling reaction was considered based on the previous study of the catalyst structure[16] and the outcome of this reaction process. The stereoarrangement at C_3 position of oxindole products in the current case is a reversal to the oxindole derivative synthesized via nucleophilic addition of 3-substituted oxindoles with 3-bromoindolin-2-ones in our previous work,[3f] even in the presence of the same chiral catalyst. We propose that this appearance is due to a different activation manner although the same electrophile is involved. A different diastereo- and enantioselective nucleophilic attack model (Scheme 4a) was suggested.[10−12] The in situ generated indol-2-one could be activated after coordinating to the *N*,*N*′-dioxide/Ni^{II} complex. The *Si*-face of the indol-2-one is shielded by the amide unit of the ligand, and the tandem [4 + 2] cyclization/addition with tryptamine **1a** occurs preferentially from the *Re*-facial of indol-2-one. There might be stabilizing $\pi-\pi$ stacking interaction between the two indoline rings of the two substrates, and the nucleophilicity of the C_3 position of the tryptamine enables the addition to the less-electron-rich C_3 carbon of indol-2-one in an *endo*-selective cycloaddition manner.[16c] The primary cycloadduct Int A was unstable, and it could spontaneously rearrange into the cyclic imine Int B, which in turn could be trapped by the nucleophilic side chain of tryptamine to give the desired pyrrolidinoindoline skeleton.

Scheme 4. (a) Proposed Mechanism and Stereoselectivity Control. (b) Enantioselective Synthesis of Piperidindoline Derivative



Based on the understanding of the reaction process, we carried out tandem reaction between 3-bromoindolin-2-one **2d** and *N*-H free indole derivative **1p** (Scheme 4b), which has been reported by Wang and co-workers for the enantioselective total synthesis of perophoramidine.[5c] The asymmetric formal [4 + 2] cycloaddition/rearrangement process occurred smoothly under the standard condition, delivering the imine product **9** in excellent diastereo- and enantioselectivity. After reduction and crossover cyclization, a piperidinolindoline scaffold **10** was constructed with high yield and stereoselectivity, which is the key subunit of the dihydropsychotriadine, the elusive scaffold of bis(cyclotryptamine) alkaloids.[17]

In summary, we have developed an efficient route to the synthesis of cyclotryptamine-oxindole architectures bearing vicinal quaternary carbon stereocenters via asymmetric catalytic [4 + 2] cycloaddition/cyclization cascade reactions. The *endo*- and enantioselective cycloaddition process following late-stage C−N bond formation enabled the formation of *cis*-bis(cyclotryptamine) units, which represent an important framework of the hexahydropyrroloindole alkaloid family. These cyclotryptamine derivatives showed promising biological activity. Additional applications of this methodology are underway.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c00260.

Experimental procedures, crystallographic data, compound characterization, NMR spectra, and HPLC spectra (PDF)

Accession Codes

CCDC 2032254 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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