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Concise total syntheses of bis(cyclotryptamine) alkaloids *via* thio-urea catalyzed one-pot sequential Michael addition†

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Naturally occurring bis(cyclotryptamine) alkaloids feature vicinal all-carbon quaternary stereocenters with an elongated labile C-3a–C-3a′ Sigma bond with impressive biological activities. In this report, we have developed a thio-urea catalyzed one-pot sequential Michael addition of bis-oxindole onto selenone to access enantioenriched dimeric 2-oxindoles with vicinal quaternary stereogenic centers at the pseudobenzylic position (up to 96% ee and >20:1 dr). This strategy has been successfully applied for the total syntheses of either enantiomers of chimonanthine, folicanthine, and calycanthine.

Bis(cyclotryptamine) alkaloids comprise a large family of secondary metabolites that are biosynthetically derived from the oxidative cyclization of L-tryptophan.[1] The complex bridged bicyclic structure of this family, *i.e.* (+)-calycanthine **1** (Fig. 1), was the first isolated *Calycanthaceae* alkaloid way back in 1888.[2] However, after more than seven decades the correct structure of **1** was established by Woodward[3a] and Hamor,[3b] independently. In 1954, based on a hypothetical bio-synthon, dialdehyde **6**, Robinson and Teuber proposed five plausible structural isomers **1–5** (Fig. 1).[4–6] Structurally, bis(cyclotryptamine) alkaloids are characterized by the presence of vicinal quaternary all-carbon stereocenters[7] at C-3a and C-3a′ (sp^3–sp^3) with six interlocked rings (Fig. 1). Because of their intriguing architecture along with important biological activities, these alkaloids drew the attention of scientists worldwide. Towards this, most of the literature reports feature the synthesis of pyrroloindoline ring systems.

The initial contributions in this area have established a biosynthetically inspired oxidative dimerization of tryptamine and oxindole derivatives in a stereo-random manner.[8] Overman and co-workers have reported elegant approaches *via* double Heck cyclization[9a] or dialkylation[9b] to address the formation of congested all-carbon quaternary stereocenters. Subsequent pioneering Co(I)-mediated reductive dimerization was developed by Movassaghi[10a,b] and others.[10c,11] Later a number of oxidative dimerizations of 2-oxindoles were established by Liang,[12a] Ishikawa,[12b] Li,[12c] Xia,[12d] Zhang[12e] and our group.[13] Very recently, Jiang *et al.*[14] reported an Fe-catalyzed stereoselective oxidative dimerization approach to access isocalycanthine structural motifs. Furthermore, a number of impressive catalytic enantioselective approaches have been reported by various research groups.[15] These include Gong's enecarbamate addition onto 3-hydroxy 2-oxindole,[15a] Kanai and Matsunaga's Michael addition onto nitroethylene,[15b] Zhang's indole addition onto α,β-unsaturated aldehyde,[15c] asymmetric allylations independently by Trost[15d] and our group,[16a,b] dialkylations by Tu and co-workers,[15e] and malonate addition by our group.[16c,d] Despite multifarious ventures,[9] efforts towards a catalytic asymmetric one-pot sequential construction of a congested vicinal all-carbon quaternary stereocenter still hold a substantial challenge. We argued that a C_2-symmetric enantioenriched dimeric 2-oxindole **8** could be a common intermediate for asymmetric

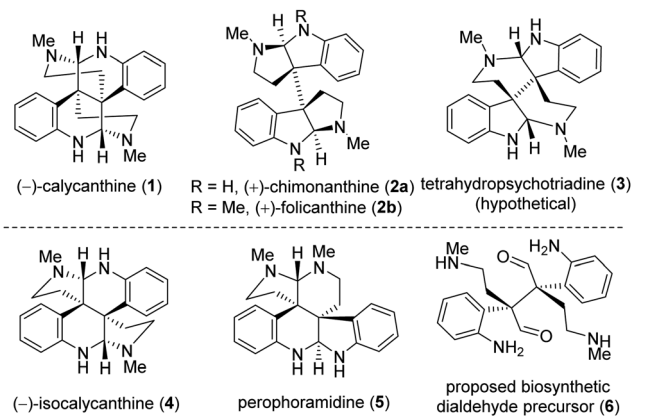

Fig. 1 Naturally occurring bis(cyclotryptamine) alkaloids (**1–5**) and hypothetical biosynthetic dialdehyde precursor **6**.

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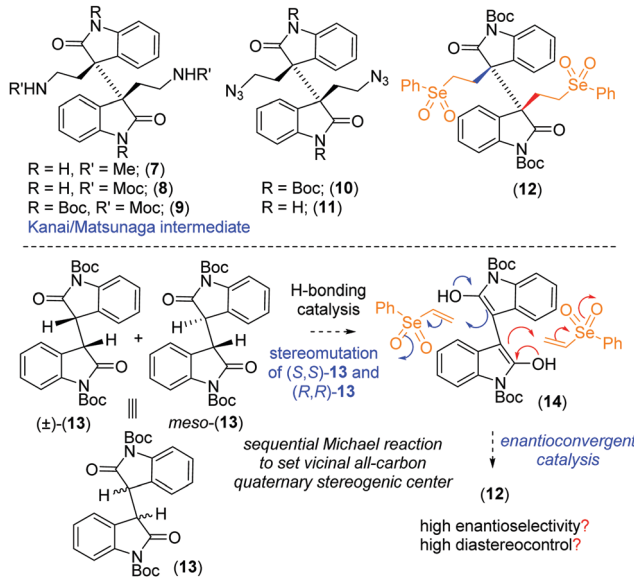


Scheme 1 Retrosynthetic analysis.

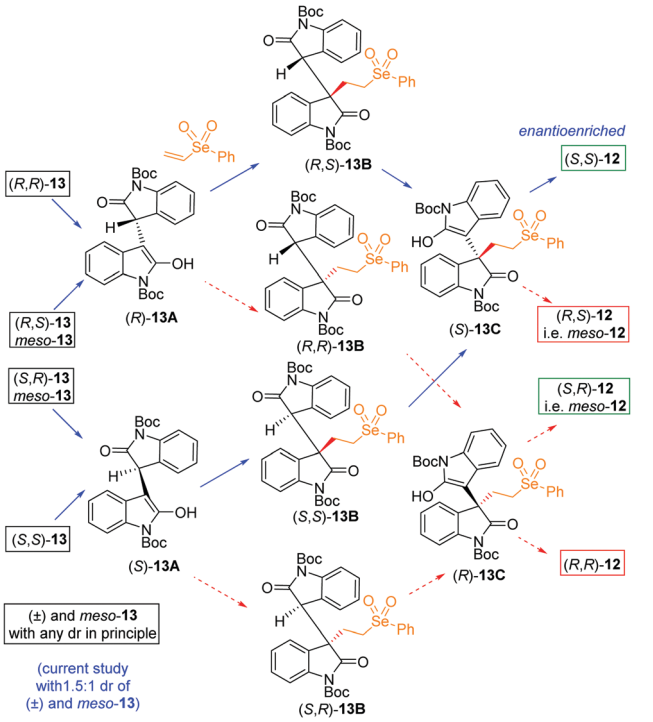


Fig. 2 Rationale of stereomutative enantioconvergent catalysis.

total syntheses of bis(cyclotryptamine) alkaloids having pyrrolidinoindolines **2a–b.**

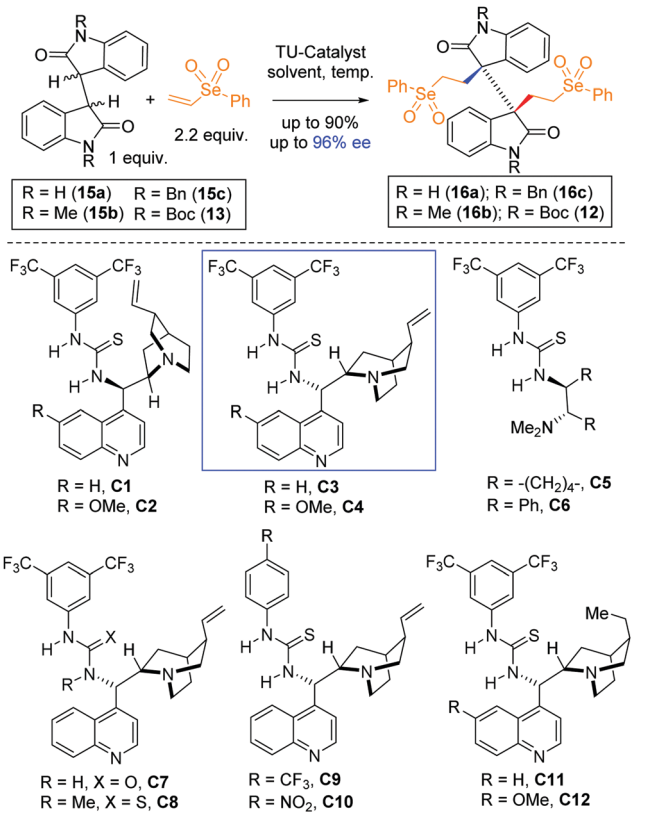
Retrosynthetically, we imagined that a unified approach to (+)-chimonanthine (**2a**) and (−)-calycanthine (**1**) [*via* **2a**] could be possible from Kanai/Matsunaga's intermediate[15b] **9** *via* a reductive cyclization (Scheme 1), which in turn could be accessed from bis-selenone **12** following azide displacement and synthetic manipulations (see compounds **9–11**).

Towards this, we thought of exploring a thio-urea catalyzed[17,18] stereo-mutative[19] asymmetric sequential Michael addition of dimeric 2-oxindole such as **13** onto vinyl selenone[20] for the installation of a vicinal all-carbon quaternary stereogenic center in a highly enantioselective manner with excellent diastereocontrol.[21] In this regard, Liu and Chen's TU-catalyzed Michael addition of 2-oxindole onto vinyl selenone at room temperature ionic liquids (RTILs) afforded the product in up to 95% ee.[20a] We hypothesized that compound **13** having a mixture of active [(±)-**13**] and *meso*-isomer (**13**), of any ratio, could be efficiently transformed onto dienol (**14**) in the presence of a quinuclidine moiety of thio-urea, thereby affecting the stereomutation required for an enantioconvergent catalysis. However, the major difficulties with such a transformation include the presence of pre-existing stereocentres in **13**, that would be responsible for developing mismatched catalyst–substrate interactions, and thus, negatively impact the chemical yield (Fig. 2).[15b] Therefore, catalytic asymmetric transformation of such a complex mixture of **13** would be challenging and needs special attention.

The rationale of our stereomutative enantioconvergent catalysis is depicted in Fig. 2. Under the optimized conditions, the mixture of diastereomers of **13** must undergo stereomutative[19] enolization to produce racemic enols **13A**, which upon subsequent Michael addition on vinyl selenone may form intermediate **13B** (Fig. 2). If the enantiopure TU-catalyst controls the formation of the new stereocentre, a pair of diastereomers **13B** *i.e.*, (*R*,*S*)-**13B** and (*S*,*S*)-**13B** will predominantly form over the other pair, *i.e.*, (*R*,*R*)-**13B** and (*S*,*R*)-**13B.** The influence of the remaining substrate stereocentre may either reinforce or conflict with catalyst control during this process. A second stereomutative enolization from diastereomeric pairs (*R*,*S*)-**13B** and (*S*,*S*)-**13B** would then generate a mixture of enols (*S*)-**13C** and (*R*)-**13C.** Finally, a second facially selective Michael addition onto vinyl selenone would afford the bis-Michael product as a diastereomeric mixture of enantioenriched (*S*,*S*)-**12** and optically inactive *meso*-**12** (Fig. 2). We also thought that if the enantiopure thio-urea catalyst imposes a high degree of facial selectivity at both steps of C–C bond formation, the simultaneous Michael addition of the complex mixture of **13** may be smoothly converged into a single product with excellent levels of diastereo and enantioselectivity.[22,23]

Based on our hypothesis, initially we choose dimeric 2-oxindoles **15a–c** and reacted them with 2.2 equivalents of phenylvinylselenone in the presence of 10 mol% of thio-urea (TU) **C1.** However, to our displeasure, there were no reactions observed and **15a–c** were isolated almost quantitatively (entries 1–3). This probably indicates that the choice of an electron-withdrawing group such as Boc-group on the nitrogen might be necessary in order to tune the electronics. This could essentially decrease the pK_a of hydrogen situated at the pseudobenzylic position.[17] To our delight, bis-Boc protected dimeric 2-oxindole **13** afforded bis-Michael addition product (*S*,*S*)-**12** in 84% ee (79% yield) in the presence of 10 mol% **C1.** Gratifyingly, this reaction afforded **12** in >20 : 1 dr (entry 4). With this encouraging result, we then checked the efficiencies of other TU-based catalysts (Table 1). A quick

Table 1 Sequential Michael addition of dimeric 2-oxindoles onto phenylvinylselenone



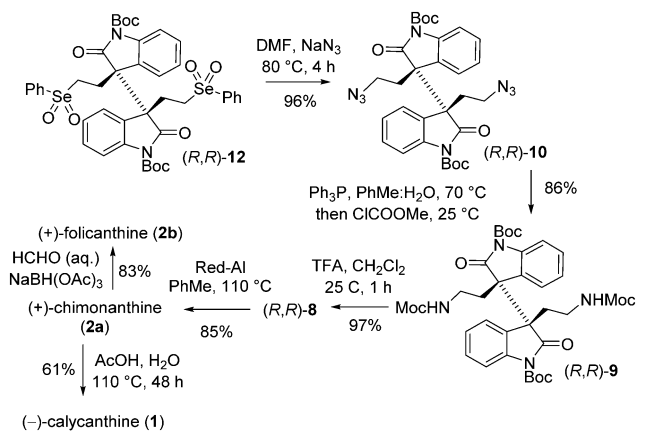
S. n.	Substrate/ Cat.[a]	solvent	Temp. (°C)	dr[b]	Time/ product	Yield (%)	ee[c] (%)
1	**15a/C1**	CH_2Cl_2	25 °C	—	5d/**16a**	—	—
2	**15b/C1**	CH_2Cl_2	25 °C	—	5d/**16b**	—	—
3	**15c/C1**	CH_2Cl_2	25 °C	—	5d/**16c**	—	—
4	**13/C1**	CH_2Cl_2	25 °C	~20 : 1	72 h/**12**	79	−84
5	**13/C1**	PhMe	25 °C	~12 : 1	72 h/**12**	62	−87
6	**13/C1**	MeCN	25 °C	~20 : 1	72 h/**12**	88	−89
7	**13/C2**	MeCN	25 °C	~20:1	72 h/**12**	86	−93
8	**13/C2**	MeCN	0 °C	~20 : 1	96 h/**12**	64	−90
9	**13/C3**	MeCN	25 °C	~20 : 1	72 h/**12**	90	96
10	**13/C3**	MeCN	0 °C	~20 : 1	96 h/**12**	72	93
11	**13/C3**	$CHCl_3$	0 °C	~20 : 1	96 h/**12**	72	91
12	**13/C4**	MeCN	25 °C	~20 : 1	72 h/**12**	84	87
13	**13/C5**	MeCN	25 °C	~9 : 1	96 h/**12**	72	70
14	**13/C6**	MeCN	25 °C	~12 : 1	96 h/**12**	81	67
15	**13/C7**	MeCN	25 °C	~20 : 1	96 h/**12**	80	78
16	**13/C8**	MeCN	25 °C	~9 : 1	96 h/**12**	41	ND
17	**13/C9**	MeCN	25 °C	~20 : 1	72 h/**12**	82	76
18	**13/C10**	MeCN	25 °C	~20 : 1	72 h/**12**	76	72
19	**13/C11**	MeCN	25 °C	~20 : 1	72 h/**12**	82	91
20	**13/C12**	MeCN	25 °C	~20 : 1	72 h/**12**	79	83

[a] Reactions were carried out with 0.25 mmol of **15a–c** and **13** with 0.60 mmol of phenylvinylselenone in 5 mL of solvent in the presence of 10 mol% of TU catalysts under N_2-atm. [b] dr's were calculated from crude ^{1}H-NMR. [c] ee's were determined by IA column by converting the product to bis-carbamate **8** (see, Scheme 2).

optimization showed that acetonitrile is a better choice as compared to other solvents. Following exhaustive optimization, it was observed that 10 mol% catalyst **C2** furnished (*S*,*S*)-**12** in 93% ee (86% yield) with >20 : 1 dr (entry 7). Noteworthy to observe was that 10 mol% of a pseudoenantiomeric catalyst **C3** afforded (*R*,*R*)-**12** in 96% ee (90% yield) with >20 : 1 dr (entry 9). It was observed that the ee's were compromised a bit when the reaction was carried out at 0 °C (entries 8, 10 and 11). Further optimization revealed that TU catalysts **C5–C6** and urea **C7** were inferior as compared to **C2** and **C3** (entries 13–15). In order to have an efficient reaction both NH of the TU catalyst must be free, as *N*-Me thio-urea **C8** failed to provide the product (entry 16). TU catalysts **C9** and **C10** furnished product (*R*,*R*)-**12** only in 72-76% ee, however maintaining >20 : 1 dr (entries 17–18). Furthermore, TU catalysts **C11** and **C12** afforded (*R*,*R*)-**12** in 83–91% ee with >20 : 1 dr (entries 19–20). Gratifyingly, the reaction can be scaled up to 1.5 g scale of **13**, which afforded (*R*,*R*)-**12** in 93% ee (85% yield) with >20 : 1 dr (96 h).

We next turned our attention to the utilization of (*R*,*R*)-**12** for the total syntheses of (+)-chimonanthine (**2a**) and (−)-calycanthine (**1**) as planned. Towards this end, nucleophilic displacement of selenone with sodium azide furnished (*R*,*R*)-**10** in 96% yield (Scheme 2), and subsequent Staudinger reaction followed by protection with ClCOOMe afforded (*R*,*R*)-**9** in 86% yield over 2 steps. The latter on treatment with TFA furnished our proposed intermediate (*R*,*R*)-**8** in 97% yield.

However, lithium aluminum hydride reduction of (*R*,*R*)-**8** led to a complex mixture of products, which we were unable to characterize. To our delight, reduction of (*R*,*R*)-**8** using sodium bis(2-methoxyethoxy)aluminum hydride (Red-Al) afforded (+)-chimonanthine **2a** in 85% isolated yield. Next, *N*-methylation using formaldehyde and $NaBH(OAc)_3$ completed the synthesis of (+)-folicanthine (**2b**) following Overman's[9c] and Movassaghi's protocol.[10a] Furthermore, a biomimetic route to (−)-calycanthine (**1**) from (+)-chimonanthine (**2a**) was carried out under refluxing AcOH[9c] (61% yield). Since both the antipodes of **1** and **2a–b** are naturally occurring,[7] we undertook the total synthesis of (−)-chimonanthine (*ent*-**2a**), (−)-folicanthine (*ent*-**2b**), and (+)-calycanthine (*ent*-**1**) starting from (*S*,*S*)-**12** (see SI for the details). Of note, we have carried out C2 catalyzed sequential Michael reaction of **13** at 1.5 g scale to access (*S*,*S*)-**12** in 93% ee (87% yield) with >20 : 1 dr (96 h).



Scheme 2 Total syntheses of (+)-chimonanthine (**2a**), (+)-folicanthine (**2b**) and (−)-calycanthine (**1**).

In conclusion, we developed a catalytic asymmetric approach to a general strategy to bis(cyclotryptamine) alkaloids. Our approach features a catalytic enantioselective synthesis of dimeric 2-oxindoles bearing vicinal quaternary stereocenters with an overwhelming control of the absolute and relative stereochemistry. The approach demonstrated that the designed chiral precursor **8** was an excellent complement for cyclotryptamine alkaloid synthesis. Furthermore, total syntheses of both antipodes to naturally occurring alkaloids have been shown.

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Conflicts of interest

There are no conflicts to declare.

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