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Diastereo-, enantio-, and chemoselective sequential allylations of *N,N′*-alloc 3,3′-dimeric 2-oxindoles: formal total synthesis of (−)-idiospermuline†‡

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Calycanthaceae alkaloids feature two neighboring carbon atoms that are central to their structure (quaternary stereocenters) and a long, flexible bond between them [elongated labile C3a–C3a′s bond] with impressive biological activities. Herein, we envisioned an expeditious approach to dimeric hexahydropyrrolo[2,3*b*]-indoline *via* an unprecedented catalytic asymmetric sequential allylation of *N,N′*-alloc 3,3′-dimeric 2-oxindoles with eventual total syntheses of naturally occurring (−)-calycanthidine and a formal total synthesis of (−)-idiospermuline.

In nature, numerous organisms produce extensive arrays of natural product metabolites with similar molecular structures.[1,2] This strategy enhances functional diversity and provides an evolutionary edge against competing systems within their environment. Alkaloids comprising of multiple cyclotryptamine units adjoined at different junctures constitute a large family of structurally fascinating natural products, which display a wide range of biological activities[3] and possess retrosynthetically challenging and sterically crowded quaternary linkages. Moreover, in certain cases, the synthetic challenge is exacerbated by the heterodimeric C3a–C3a′ connectivity (Fig. 1). Significant advances have been made in the assembly of Csp^2–Csp^3 and Csp^3–Csp^3 linkages in cyclotryptamine-based alkaloids. The dimeric, heterodimeric, and oligomeric cyclotryptamine alkaloids exhibit a wide array of remarkable biological activities ranging from analgesic, antiviral, antifungal, and antibacterial properties to cytotoxic effects against human cancer cell lines.[3] (−)-Calycanthidine (**1f**), a heterodimeric cyclotryptamine alkaloid bearing an unsymmetrical dimeric hexahydropyrrolo[2,3*b*]-indole scaffold was originally isolated in 1938 from *Calycanthus floridus*,[4] but its structure was elucidated in 1962,[2a,b] followed by the assignment of its absolute stereochemistry by Overman and co-workers.[5] The higher-order members of this group, such as (−)-hodgkinsine B (**1g**) and (−)-idiospermuline (**1h**), contain an additional hexahydropyrrolo[2,3-*b*]indoline unit attached at its benzylic quaternary stereocenter to *peri* positions of the aromatic ring of other hexahydropyrrolo[2,3*b*]-indoline fragments.[5]

Stimulated by these intriguing structures along with their biological activities, several strategies have been developed.[6a–e] Recently, a few heterodimerization strategies addressing unsymmetrical dimeric hexahydropyrrolo[2,3*b*]-indole scaffolds have been developed *via* a key diastereoselective pathway.[6f–i] In this regard, dynamic kinetic asymmetric transformations (DYKAT) using carbon nucleophiles on racemic substrates stand out as versatile methods for synthesizing complex natural products.[6j]

Over the past few decades, significant research efforts have been directed towards developing methods for constructing all-carbon quaternary stereocenters asymmetrically. In 2013, Trost *et al.* have shown an elegant approach towards symmetrical hexahydropyrrolo[2,3*b*]-indole scaffolds *via* stepwise consecutive

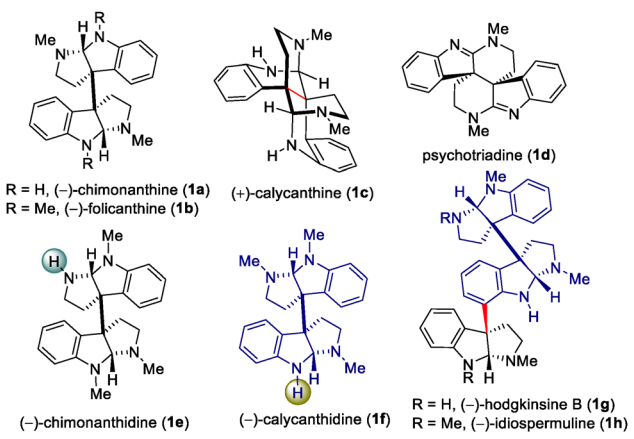

Fig. 1 Representative cyclotryptamine-based natural products.

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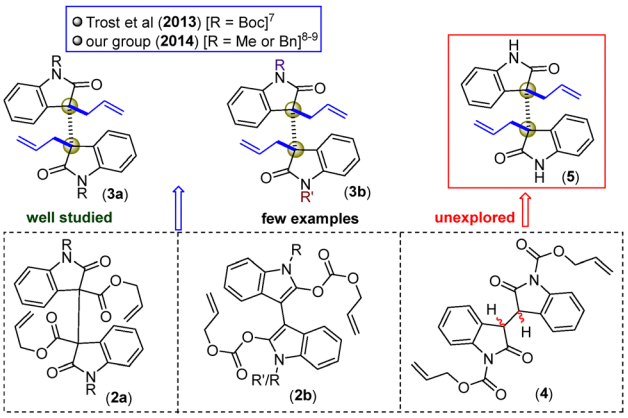
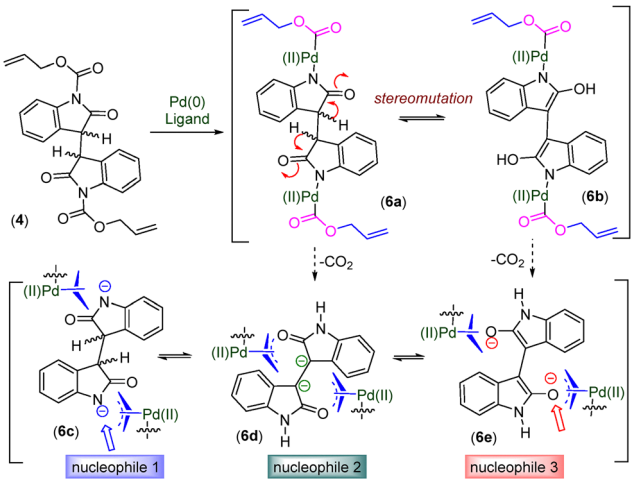


Scheme 1 Prior work on the 3,3′-bis-allyl-2-oxindole skeleton.

Pd-catalyzed two-fold decarboxylative allylations of *N*-Boc protected bis-carbonates **2b** with 92% ee (dr 3.2 : 1).[7] Our group has also demonstrated enantioselective construction of vicinal all-carbon quaternary centers with excellent diastereocontrol *via* catalytic double asymmetric decarboxylative allylation towards the total synthesis of symmetrical *N*-alkylated dimeric hexahydropyrrolo[2,3*b*]-indole alkaloids in an efficient manner (Scheme 1) in the presence of (*S*,*S*)-**L7**-Pd(0).[8,9] Although the catalytic asymmetric allylation of homo- and hetero-dimeric 2-oxindoles (**3a–b**) has been well documented (Scheme 1), no asymmetric method has been reported so far that avoids nitrogen protection (**5**). It was envisioned that a DYKAT following a Pd(0)-catalyzed highly chemo-, enantio- and diastereoselective sequential stereoablative alkylation of dimeric 2-oxindoles having two allylcarbamoyl functionalities, such as **4** (essentially bis-Alloc **4**), could be an attractive platform to synthesize N-unprotected C2-symmetric dimeric 2-oxindoles, (*R*,*R*)-**5** and its antipode (*S*,*S*)-**5** (Scheme 1).

The installation of a vicinal all-carbon quaternary stereogenic center in a highly enantioselective manner with excellent diastereocontrol remains a significant synthetic challenge. We hypothesized that a mixture containing all four stereoisomers of **4** could be efficiently converted to the corresponding enantioenriched diallyl **5** in the presence of a chiral Pd(0) complex, following a stereomutation process required for enantioconvergent catalysis (Scheme 2). However, the major challenge with such a transformation is the potential mismatch between the catalyst and the substrate, ultimately leading to low yields (Scheme 2).[6] Initially, Pd(0)-catalyzed decarboxylative deallylation would proceed through intermediates **6a and b**, which would immediately furnish the Pd(II)-π-allyl dimeric 2-oxindole intermediates **6c–e**. Possible reactive intermediates in this reaction from intermediates **6a and b** are shown in Scheme 2. Besides this, compound **4** would react with Pd to form different π-allyl complexes (Scheme 2).

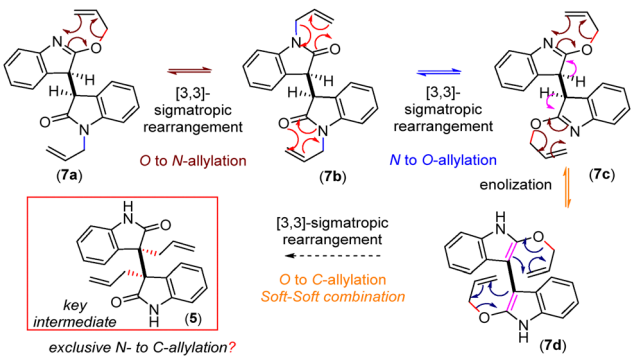
Here, we thought three types of nucleophilic centers would be generated, namely, *N*-center (**6c**), C-center (**6d**) and O-center (**6e**). According to soft–hard principles, the C-center (**6d**) nucleophilic π-allyl complex might be more stable because of soft–soft interactions (Scheme 2). Therefore, catalytic asymmetric transformation of such a complex mixture of **5** would be challenging and needs special attention.



Scheme 2 Plausible nucleophilic center of bis-*N*-alloc-2-oxindoles (**4**).

Based on the well-documented studies by Trost,[7] Kozlowski[10a] and Wills[10b] research groups, we hypothesized that bis-*N*-alloc compounds could directly provide access to bis-allyl intermediates (Scheme 3) that can be extended to the total synthesis of alkaloids sharing a dimeric hexahydropyrrolo-[2,3-*b*]indole framework. So, based on our hypothesis, we assumed that bis-*N*-alloc oxindole (**4**) could provide compound **7a** *via* a series of [3,3]-sigmatropic rearrangements through various *N*-allyl and *O*-allyl intermediates. **7a** converted to **7b** *via* a [3,3]-sigmatropic rearrangement to form bis-*N*-allyl oxindole. **7a** converted to **7b** followed by [3,3]-sigmatropic rearrangement to provide compound **7c**. Similarly, **7b**, **7c**, and **7d** would be possible intermediates that are capable of undergoing [3,3]-sigmatropic rearrangements, ultimately converted to a common product. Therefore, we thought that *O*-allyl as well as *N*-allyl substrates would be converted to a more stable C-allyl oxindole (because of a soft–soft combination) under our reaction conditions *via* [3,3]-sigmatropic rearrangement.[10a]

Primarily, we planned to explore the Pd(0)-catalyzed Tsuji–Trost reaction. Towards this direction, for Pd-catalyzed enantioselective processes, we select 2-phosphino-oxazoline (PHOX) ligands (*S*)-**L1–L4**,[11] 2-phosphino-carboxamide ligands (*S*,*S*)-**L5–L7**[12a,b] and binap base ligands (*S*)-**L8–L10**[12c,d] for our double allylation reaction. First, we carried out an optimization of Pd-catalyzed sequential



Scheme 3 A dynamic equilibrium through the establishment of [3,3]-sigmatropic rearrangement.

double decarboxylative allylations of bis-*N*-alloc-2-oxindoles (**4**) in the presence of 2.5 mol% $Pd_2(dba)_3$ in combination with 7.5 mol% ligands **L1–L10**[2d] in diethyl ether toluene and THF at room temperature and the results are presented in Table 1. After screening of various ligands, it was observed that ligand **L7** afforded the product (*S*,*S*)-**5** in 90% yield with 79% ee and dr up to 5 : 1 at room temperature (entry 7) (Table 1). We further focused on optimization by testing different solvents and reducing the temperature. Finally, we observed highly enantioselective (*S*,*S*)-**5** (up to 96% ee) with high diastereoselectivity (up to 14 : 1) and yield (up to 92%) (entry **19**) (Table 1).

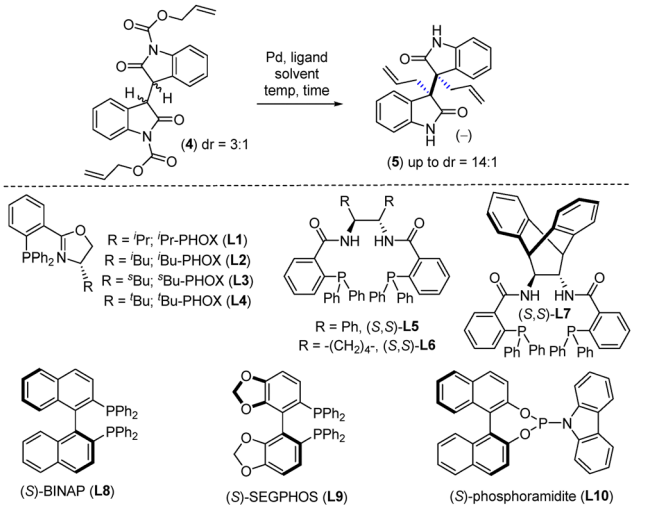
After successful stereoconvergent development of vicinal stereogenic all-carbon quaternary centers of enantioenriched (*S*,*S*)-**5**, we thereafter focused our efforts on the elaboration of this compound for the total synthesis of the homo- and heterodimeric cyclotryptamine alkaloids. To achieve this, (*S*,*S*)-**5** was reacted with methyl iodide in the presence of NaH to the corresponding N-methyl oxindole (*S*,*S*)-**8a** (Scheme 4).

Next, (*S*,*S*)-**8a** was treated with OsO_4 to achieve dihydroxylation of allyl groups such as (+)-**9a**, which, without further purification, underwent periodate cleavage to furnish bis-aldehyde (−)-**10a** in 86% yield over 2 steps. Next, bis-aldehyde (−)-**10a** was dissolved in a MeOH solution of $MeNH_2$, followed by $NaBH_4$ reduction in one pot to form a dimeric bis-amine intermediate (**11a**); subsequent reduction with Red-Al in toluene at 110 °C completed the total synthesis of (+)-folicanthine (**1b**) with approximately 40% overall yield in the LLS (Scheme 4). We also completed the total synthesis of (−)-chimonanthine (**1a**) following a similar synthetic strategy as shown in Scheme 4. Here, (*S*,*S*)-**5** was reacted with benzyl bromide in the presence of NaH to the corresponding *N*-benzyl oxindole (*S*,*S*)-**8b** (Scheme 4). Then (*S*,*S*)-**8b** was treated with OsO_4 and underwent periodate cleavage to afford bis-aldehyde (−)-**10b** in 82% yield over 2 steps.

Next, bis-aldehyde (−)-**10b** was dissolved in a MeOH solution of $MeNH_2$, followed by $NaBH_4$ reduction in one pot to form a dimeric bis-amine intermediate (**11b**), which underwent subsequent reduction with Red-Al to form the bis-tricyclic core (−)-**12a**. Finally, debenzylation of (−)-**12a** using Pd/C with 5 bar H_2 pressure completed the total synthesis of (−)-chimonanthine (**1a**) (Scheme 4). We next turned our attention to the utilization of (−)-chimonanthine (**1a**) for the total synthesis of (+)-calycanthine (**1c**) as planned. Thus, a biomimetic route to (+)-calycanthine (**1c**) from (−)-chimonanthine (**1a**) was realized using a refluxing AcOH/H_2O mixture (59% yield).

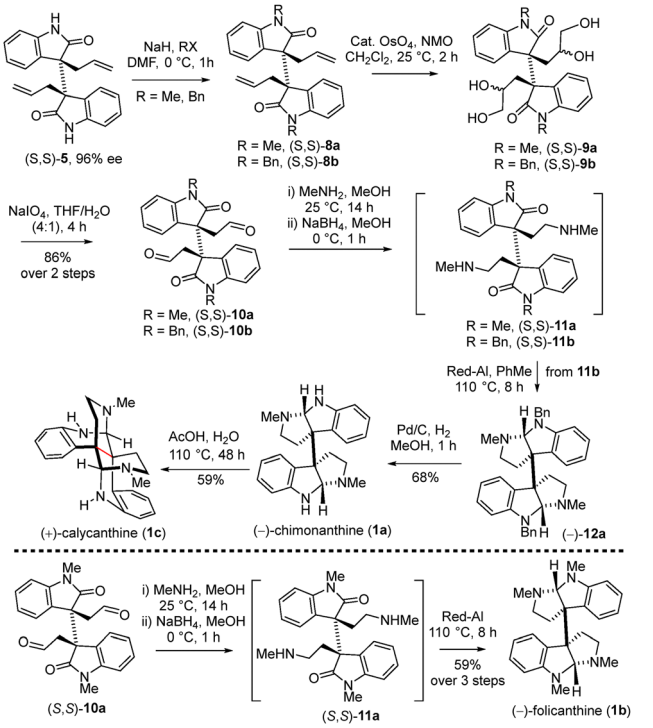
Furthermore, we have synthesized unsymmetrical dimeric 2-oxindole from (*S*,*S*)-**5** (Scheme 5). Accordingly, desymmetrization of (*S*,*S*)-**5** was carried out through a reaction with one equivalent of MeI

Table 1 Enantioselective double decarboxylative allylation of bis-*N*-alloc-oxindoles

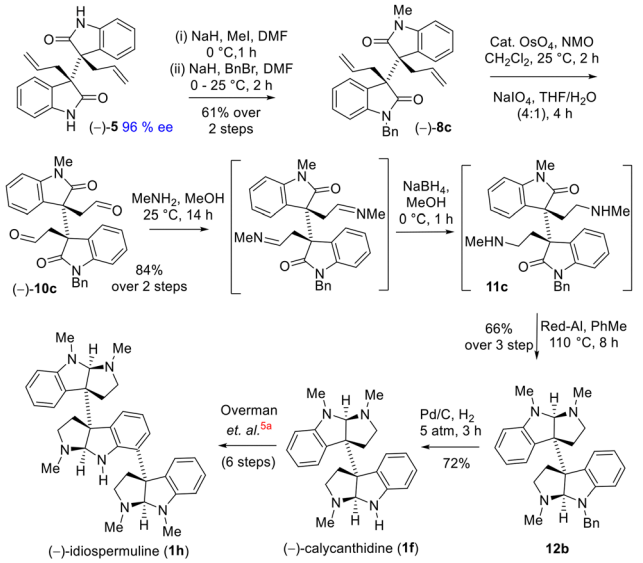


S. no.[a]	Solvent	Ligand	Temp. (°C)	dr[b]	Time/product (h)	Yield (%)	ee[c] (%)
1	Et_2O	**L1**	25	3 : 1	10	58	18
2	Et_2O	**L2**	25	4 : 1	10	62	15
3	Et_2O	**L3**	25	5 : 1	10	73	17
4	Et_2O	**L4**	25	2 : 1	10	74	23
5	Et_2O	**L5**	25	3 : 1	10	79	52
6	Et_2O	**L6**	25	7 : 1	10	79	56
7	Et_2O	**L7**	25	5 : 1	10	90	79
8	Et_2O	**L8**	25	3 : 1	10	82	35
9	Et_2O	**L9**	25	5 : 1	8	78	66
10	Et_2O	**L10**	25	6 : 1	9	80	64
11	PhMe	**L7**	25	4 : 1	9	78	69
12	THF	**L7**	0	8 : 1	12	88	73
13	PhMe	**L7**	0	7 : 1	10	91	71
14	Et_2O	**L7**	0	8 : 1	10	86	83
15	Et_2O	**L7**	0	6 : 1	10	91	90
16	MTBE	**L7**	0	6 : 1	10	86	69
17	THF	**L7**	−10	9 : 1	12	90	74
18	Et_2O	**L7**	−10	9 : 1	12	86	85
19	Et_2O	**L7**	−25	14 : 1	16	92	96
20	Et_2O	**L7**	−40	10 : 1	24	89	88

[a] Reactions were carried out on 0.037 mmol of the substrate in 3 mL of the solvent in a sealed tube. [b] dr values were calculated from ^{1}H-NMR spectra of the crude reaction mixture. [c] ee values were determined using a Chiralpak OJ-3 column.



Scheme 4 Total synthesis of (−)-chimonanthine (**1a**), (−)-folicanthine (**1b**), and (+)-calycanthine (**1c**).



Scheme 5 Total synthesis of (−)-calycanthidine (**1f**) and formal synthesis of (−)-idiospermuline (**1h**).

[mono-alkylation of one of the N–H groups of C_2-symmetric (−)-**5**] in the presence of NaH to obtain the corresponding unsymmetrical *N*-methyl 2-oxindole (*S*,*S*)-**8a** (see the ESI‡ for details). Compound (*S*,*S*)-**8a** upon *N*-benzylation furnished heterodimeric oxindole (*S*,*S*)-**10c** (Scheme 5). In an alternative approach, mono-benzylation of one of the N–H groups of C_2-symmetric (−)-**5** afforded *N*-benzyl oxindole (*S*,*S*)-**8b** (see the ESI‡ for details). Next, *N*-methylation of (*S*,*S*)-**8b** furnished heterodimeric oxindole (*S*,*S*)-**8c** in a synthetically useful yield (Scheme 5). With (*S*,*S*)-**8c** in hand, we have disclosed the total synthesis of (−)-calycanthidine (**1f**) (Scheme 5). In this regard, following a similar sequence of reactions as shown in Scheme 4, we have synthesized the unsymmetrical dimeric hexahydropyrrolo-[2,3-*b*]indole core (−)-**12b** (Scheme 5). Thus, a total synthesis of (−)-calycanthidine (**1f**) has been accomplished by debenzylation of (−)-**12b** under 5 atm pressure. Since the total synthesis of (−)-idiospermuline (**1h**) from (−)-calycanthidine (**1f**) is known, our effort culminated in the formal total syntheses of this alkaloid.

In conclusion, we have successfully developed a two-fold Pd-catalyzed decarboxylative asymmetric allylation of dimeric oxindoles to construct vicinal quaternary carbon stereocenters in an efficient manner. This strategy not only offers a general approach to the synthesis of cyclotryptamine alkaloids, but also clearly demonstrates the potential of double enantioselective transformation in the construction of molecules with a high level of stereochemical complexity. Thus, the total syntheses of naturally occurring (−)-folicanthine (**1b**), (−)-chimonanthine (**1a**), (+)-calycanthine (**1c**), and (−)-calycanthidine (**1f**) and the formal total synthesis of (−)-idiospermuline (**1h**) have been accomplished using this unprecedented sequential allylation.

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Conflicts of interest

There are no conflicts to declare.

Data availability

The data supporting this article have been included in the ESI.‡

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