Synthetic Methods

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# Core-Structure-Oriented Asymmetric Organocatalytic Substitution of 3-Hydroxyoxindoles: Application in the Enantioselective Total Synthesis of (+)-Folicanthine**

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Cyclotryptamine alkaloids constitute a large family of natural products (Figure 1) which show fascinating biological activities.[1] For example, (+)-chaetocin not only shows antibacterial and cytostatic activity, but is also a potent inhibitor of a lysine-specific histone methyltransferase.[2] The compound WIN 64821, first isolated from *Aspergillus* sp.,[3] is a potent competitive substance P antagonist with respect to human neurokinin-1 and the cholecystokinin B receptor.[4] Moreover, other members of the cyclotryptamine alkaloid family have also been found to exhibit important biological and pharmaceutical activities.[5]

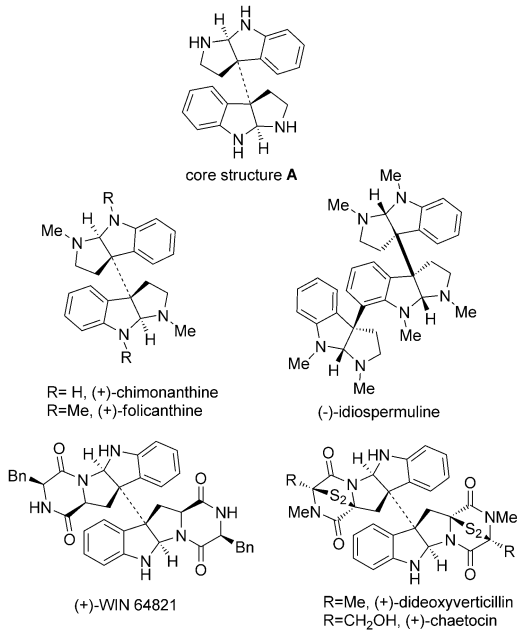


***Figure 1.*** Representative cyclotryptamine alkaloids. Bn = benzyl.

In addition to their wide range of bioactivities, the cyclotryptamine alkaloids contain an octahydro-3a,3′a-bispyrrolo[2,3-*b*]indole subunit (core structure **A**, Figure 1), which is characterized by vicinal all-carbon quaternary stereogenic centers. These compounds have been a long-standing challenge in organic synthesis.[6] The unique structural arrays and interesting biological activities displayed by these alkaloids have led to a demand for efficient asymmetric synthetic methods. Much effort has been directed toward the development of new synthetic methods for the construction of hexahydropyrroloindole skeletons from research groups around the world.[7] Overman and co-workers reported the enantioselective total synthesis of optically pure chimonanthines, wherein intramolecular double Heck and dialkylation reactions were exploited to construct the cyclotryptamine core, and the stereochemical control came from a tartrate derivative.[8] Movassaghi and co-workers have established a reductive homodimerization of 3-bromo-hexahydropyrroloindole, readily derived from L-tryptophan, which provided facile construction of the vicinal quaternary stereogenic centers that led to the enantioselective total synthesis of several optically pure cyclotryptamine alkaloids.[9] Very recently, Sodeoka and co-workers applied a related strategy to the total synthesis of (+)-chaetocin.[10] In addition, Overman and co-workers have described the catalyst-controlled enantioselective total syntheses of cyclotryptamine alkaloids from meso derivates of the core structure **A**.[7,11] In spite of these elegant achievements, the development of an enantioselective catalytic method to access cyclotryptamine structures of type **A** still holds great importance in the total synthesis of the hexahydropyrroloindole alkaloid family.

Over the past several years, numerous endeavors have been directed toward the enantioselective synthesis of all-carbon quaternary 3,3′-disubstituted oxindoles,[12] but these protocols have not provided a chiral intermediate for the synthesis of the 3a,3a′-bispyrrolidino[2,3-*b*]indoline skeleton. The unmet challenge of this catalytic enantioselective synthesis prompted us to consider a new approach. Our strategy to synthesize the core structure **A**, as indicated by the retrosynthetic analysis in Scheme 1, involves accessing structures of type **A** from diamide **1** by the Rodrigo protocol.[13] The diamide **1** would be prepared from **2** through oxidation/alkylation reactions. A Beckmann rearrangement reaction would give **2** from **3**, which is considered to be the key intermediate for the synthesis of the core structure **A**, and could be obtained from an enantioselective substitution

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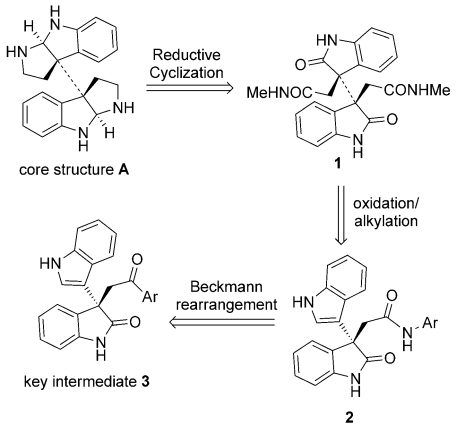
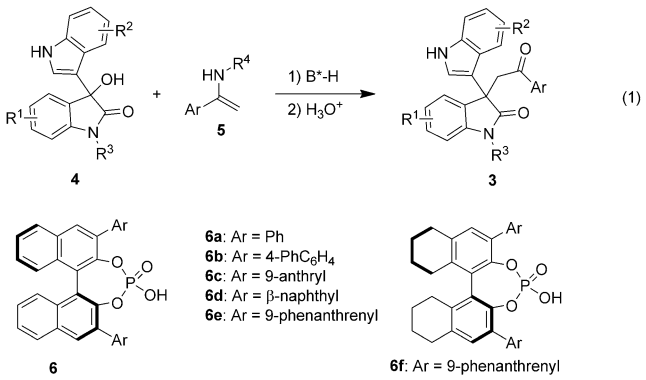



***Scheme 1.*** Retrosynthetic analysis of the core structure **A**.

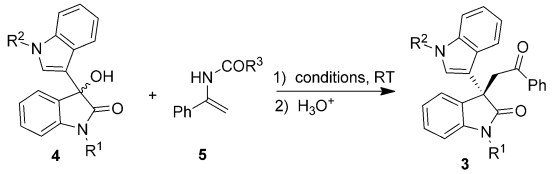
reaction of 3-hydroxyoxindoles [Eq. (1)]. Herein, we report the development of a highly enantioselective organocatalytic substitution reaction of 3-hydroxyoxindoles [Eq. (1)] and its application to the first catalytic enantioselective total synthesis of (+)-folicanthine.[14]




(1)

Our preliminary studies were focused on evaluating a substitution reaction[15] of the 3-hydroxy-3,3′-bisindolin-2-one **4a**[16] with methyl 1-phenylvinylcarbamate **5a** catalyzed by a chiral phosphoric acid **6a**[17] (see Eq. (1) for catalyst structure) in dichloromethane at room temperature (Table 1, entry 1). To our delight, the reaction proceeded smoothly to afford the desired product **3a** in 63% yield and 77% enantiomeric excess (*ee*). Encouraged by these preliminary results, a variety of chiral phosphoric acids derived from binol were evaluated (Table 1, entries 2–6). We determined that the 3,3′-di(β-naphthyl) phosphoric acid **6d** was the optimal catalyst, thus providing a fairly good yield and excellent enantioselectivity (Table 1, entry 4). Trials using other solvents led to no improvement in the reaction performance (Table 1, entries 7–10). The N substituents in the oxindole moiety were tolerated (Table 1, entries 11–12), whereas the introduction of an N substituent to the indole subunit led to less satisfactory results (Table 1, entry 13). The variation of the N substituent of the enamides exerted considerable influence on the enantioselectivity (Table 1, entries 14–16). As compared to other analogues of **5**, the benzyl 1-phenylvinylcarbamate **5c** gave higher enantioselectivity (Table 1, entries 4 and 14–16). Additional optimization of the reaction conditions revealed that lowering the concentration resulted in a slightly enhanced enantioselectivity of 94% *ee* (Table 1, entry 17). Interestingly, the highest product yield at which the *ee* value was maintained was obtained when the reaction was conducted in the presence of anhydrous sodium sulfate (Table 1, entry 18). The anhydrous sodium sulfate presumably serves as a scavenger of water generated from the dehydration reaction and thereby inhibits the decomposition of the enamide.

***Table 1:*** Catalyst screening and optimization of the reaction conditions.[a]




**4a**: $R^1$ = $R^2$ = H
**4b**: $R^1$ = Bn, $R^2$ = H
**4c**: $R^1$ = Boc, $R^2$ = H
**4d**: $R^3$ = H, $R^2$ = Me

**5a**: $R^3$ = OMe
**5b**: $R^3$ = OEt
**5c**: $R^3$ = OBn
**5d**: $R^3$ = Ph

**3a**: $R^1$ = $R^2$ = H
**3b**: $R^1$ = Bn, $R^2$ = H
**3c**: $R^1$ = Boc, $R^2$ = H
**3d**: $R^3$ = H, $R^2$ = Me

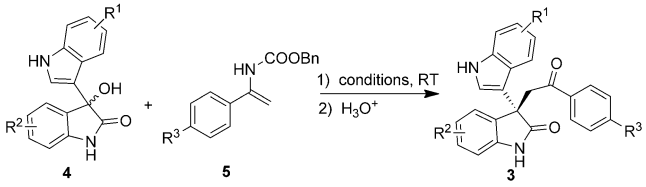
| Entry | 6 | 4 | 5 | 3 | Solvent | Yield [%][b] | *ee* [%][c] |
|---|---|---|---|---|---|---|---|
| 1 | **6a** | **4a** | **5a** | **3a** | $CH_2Cl_2$ | 63 | 77 |
| 2 | **6b** | **4a** | **5a** | **3a** | $CH_2Cl_2$ | 71 | 86 |
| 3 | **6c** | **4a** | **5a** | **3a** | $CH_2Cl_2$ | 57 | 65 |
| 4 | **6d** | **4a** | **5a** | **3a** | $CH_2Cl_2$ | 71 | 90 |
| 5 | **6e** | **4a** | **5a** | **3a** | $CH_2Cl_2$ | 62 | 85 |
| 6 | **6f** | **4a** | **5a** | **3a** | $CH_2Cl_2$ | 60 | 85 |
| 7 | **6d** | **4a** | **5a** | **3a** | $CHCl_3$ | 37 | 73 |
| 8 | **6d** | **4a** | **5a** | **3a** | 1,2-DCE | 43 | 88 |
| 9 | **6d** | **4a** | **5a** | **3a** | toluene | 51 | 85 |
| 10 | **6d** | **4a** | **5a** | **3a** | $Et_2O$ | 75 | 89 |
| 11 | **6d** | **4b** | **5a** | **3b** | $CH_2Cl_2$ | 76 | 89 |
| 12 | **6d** | **4c** | **5a** | **3c** | $CH_2Cl_2$ | 70 | 90 |
| 13 | **6d** | **4d** | **5a** | **3d** | $CH_2Cl_2$ | 53 | 60 |
| 14 | **6d** | **4a** | **5b** | **3a** | $CH_2Cl_2$ | 50 | 87 |
| 15 | **6d** | **4a** | **5c** | **3a** | $CH_2Cl_2$ | 73 | 93 |
| 16 | **6d** | **4a** | **5d** | **3a** | $CH_2Cl_2$ | 40 | 60 |
| 17 | **6d** | **4a** | **5c** | **3a** | $CH_2Cl_2$ | 75 | 94[d] |
| 18 | **6d** | **4a** | **5c** | **3a** | $CH_2Cl_2$ | 92 | 94[d,e] |

[a] Reaction conditions: **4** (1.0 equiv), **5** (1.5 equiv), 10 mol% catalyst, with solvent indicated 0.1 M. [b] Yield of the isolated product. [c] The *ee* value was determined by HPLC analysis using a chiral stationary phase. [d] The reaction was performed at 0.05 M. [e] In the presence of $Na_2SO_4$ (100 mg). Boc = *tert*-butoxycarbonyl, 1,2-DCE = 1,2-dichloroethane.

Under the optimized reaction conditions, we investigated the generalities for both reaction components (Table 2). The introduction of either electron-withdrawing or electron-donating substituents on the indole moiety was tolerated and provided products with 90–95% *ee* (Table 2, entries 1–6). Moreover, the substitution pattern on the oxindole subunit exerted little effect. Thus, excellent *ee* values were obtained for the reaction involving substrates **4k** and **4l**, which possess a fluoro and a methyl substituent, respectively, at the 5-position (Table 2, entries 7 and 8). The presence of substituents on both the indole and oxindole moieties were also amenable to the reaction, thus affording high levels of stereochemical control (Table 2, entries 9–11). The generality

***Table 2:*** Asymmetric alkylation of 3-hydroxyoxindoles with enecarbamates catalyzed by **6d**.[a]




| Entry | **4** ($R^1$, $R^2$) | **5** ($R^3$) | **3** | Yield [%][b] | *ee* [%][c] |
|---|---|---|---|---|---|
| 1 | **4e** (5′-Br, H) | **5c** (H) | **3e** | 72 | 90 |
| 2 | **4f** (5′-MeO, H) | **5c** (H) | **3f** | 76 | 91 |
| 3 | **4g** (5′-Cl, H) | **5c** (H) | **3g** | 78 | 92 |
| 4 | **4h** (6′-Me, H) | **5c** (H) | **3h** | 85 | 95 |
| 5 | **4i** (5′-F, H) | **5c** (H) | **3i** | 78 | 93 |
| 6 | **4j** (6′-F, H) | **5c** (H) | **3j** | 92 | 94 |
| 7 | **4k** (H, 5-F) | **5c** (H) | **3k** | 79 | 92 |
| 8 | **4l** (H, 5-Me) | **5c** (H) | **3l** | 84 | 92 |
| 9 | **4m** (6′-Me, 5-Me) | **5c** (H) | **3m** | 75 | 94 |
| 10 | **4n** (6′-Me, 5-F) | **5c** (H) | **3n** | 88 | 94 |
| 11 | **4o** (5′-F, 5-F) | **5c** (H) | **3o** | 70 | 92 |
| 12 | **4a** (H, H) | **5e** (Me) | **3p** | 87 | 91 |
| 13 | **4a** (H, H) | **5f** (Cl) | **3q** | 92 | 96 |

[a] Reaction conditions: **4** (1.0 equiv), **5** (1.5 equiv), 10 mol% **6d** in $CH_2Cl_2$ (2 mL), were performed on a 1 mmol scale with 100 mg $Na_2SO_4$. [b] Yield of the isolated product. [c] The *ee* value was determined by HPLC analysis using a chiral stationary phase.

of the protocol for the enecarbamate nucleophiles was also examined. Variation of the *para* substituent on the phenyl group led to smooth reactions with high levels of enantioselectivity. Notably, the benzyl 1-(4-chlorophenyl)vinylcarbamate **5f** offered the highest enantioselectivity (Table 2, entry 13).

To gain insight into the origin of the enantioselectivity observed in the substitution reaction, we performed theoretical calculations on the transition state of the **6d**-catalyzed substitution of 3-hydroxyoxindole **4a** with enecarbamate **5a** by the density-functional theory (DFT) method.[18] The fully optimized structures of the vinylogous iminium intermediate generated from the dehydration[15,19] suggested that the *cis* isomer was more stable than the *trans* isomer by approximately 1 kcal mol$^{-1}$.[20] Consequently, enecarbamate **5a** and the *cis*-vinylogous iminium species were employed in the next set of calculations. As a result, two transition structures, **TS-1** and **TS-2**, were identified (Figure 2), thus illustrating that the

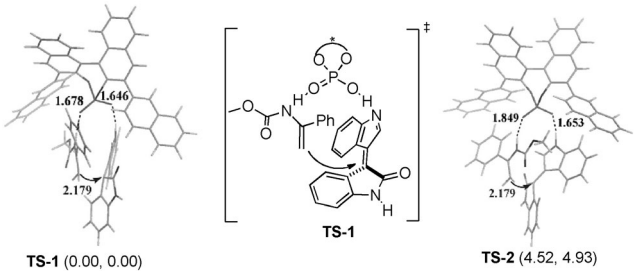


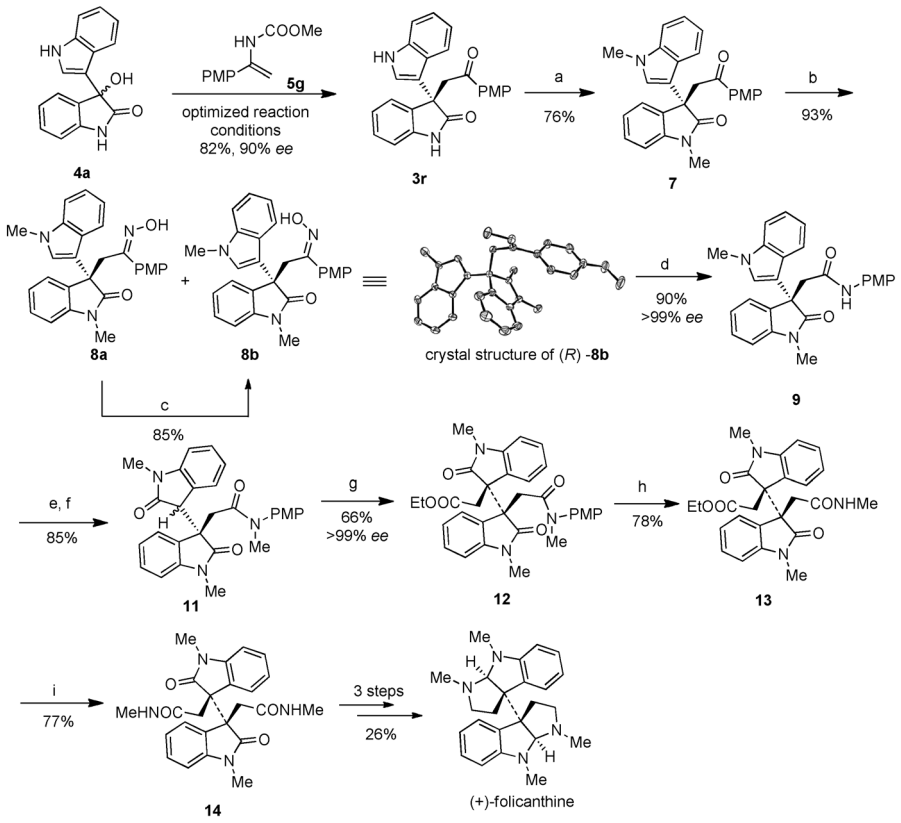

***Figure 2.*** Located transition-state structures with distance parameters in angstroms and relative energies in enthalpy and free energy, respectively in kcal mol$^{-1}$.

phosphoric acid **6d** acts as a bifunctional catalyst to simultaneously activate the enecarbamate and the vinylogous iminium compound through hydrogen-bonding interactions, and thereby facilitates the enantioselective conjugate addition.[21] **TS-1** was predicted to be more stable than **TS-2** by 4.52 kcal mol$^{-1}$ because of the steric repulsion between the phenyl ring of enecarbamate **5a** and the β-naphthyl ring of the catalyst **6d**. As such, the *R*-configured product that is observed experimentally was favorably formed (see Scheme 2).

We demonstrated the importance of this reaction in the construction of the 3a,3a′-bispyrrolidino[2,3-*b*]indoline core structure by applying it to the catalytic enantioselective total synthesis of (+)-folicanthine (Scheme 2). Under optimized reaction conditions, the enantioselective substitution reaction gave **3r** in 82% yield and 90% *ee*. The dimethylation of **3r** furnished **7** in 76% yield. When initial attempts to conduct the Baeyer–Villiger oxidation of **7** and its derivatives failed under various reaction conditions, we turned our attention to the Beckmann rearrangement, a reliable tool to convert ketones into amides. The treatment of compound **7** with $NH_2OH{\cdot}HCl$ in EtOH under basic conditions gave rise to the desired ketoximes **8a** and **8b** (**8a**/**8b** = 1:2) in 93% yield. Interestingly, **8a** could be completely converted into **8b** in the presence of *p*-toluenesulfonic acid (PTSA). A single recrystallization provided enantiopure **8b** in 75% overall yield from ketone **7**, and the absolute configuration of **8b** was assigned as *R* by X-ray analysis.[22] We screened numerous reaction conditions and found that mercury(II) chloride promoted **8b** to undergo a clean Beckmann rearrangement at 80°C to furnish amide **9** in 90% yield.[23] After introducing a methyl group to the amide nitrogen atom, the resulting product **10** in the crude reaction mixture was oxidized by DMSO/HCl, thus producing bis(oxindole) **11** in high yield. Compound **11** then underwent an alkylation to afford **12** in 66% yield. The removal of the *p*-methoxyphenyl (PMP) group by means of ceric ammonium nitrate (CAN) furnished the compound **13**. The amidation of **13** with methyl amine afforded the intermediate **14** in 77% yield. Following the procedure reported by Rodrigo and co-workers,[13] compound **14** was transformed into (+)-folicanthine by a three-step sequence in 26% overall yield. All of the spectroscopic and optical rotation data of the synthetic (+)-folicanthine were in agreement with those reported previously.[9a,13]

In summary, we have developed a highly enantioselective nucleophilic substitution reaction of 3-hydroxyoxindoles with enecarbamates catalyzed by chiral phosphoric acids (up to 96% *ee*), thus providing a new entry into 3,3′-disubstituted oxindoles with the creation of a quaternary all-carbon stereogenic center at C3. Theoretical studies on the transition states using DFT calculations suggested that the reaction might proceed through a sequential dehydration/Michael addition reaction with the phosphoric acid activating the unsaturated iminium species and the enecarbamate through hydrogen-bonding interactions. This method holds great potential in asymmetric total syntheses of hexahydropyrroloindole alkaloids. In this context, we used this protocol to prepare a key chiral building block, and accomplished the first catalytic enantioselective total synthesis of (+)-folicanthine:




***Scheme 2.*** Total synthesis of (+)-folicanthine. Reaction conditions: a) $n$Bu$_4$NHSO$_4$, KOH, MeI, RT (25 °C); b) NH$_2$OH·HCl, pyridine, EtOH, RT, **8a**/**8b** = 1:2.1. (90% *ee*, >99% *ee* after single recrystallization); c) PTSA, EtOH, RT; d) HgCl$_2$, MeCN, 80 °C; e) $t$BuOK, MeI, tetrahydrofuran (THF), RT; f) dimethyl sulfoxide (DMSO), HCl/HOAc, RT, d.r. = 1:1; g) BrCH$_2$COOEt, $n$Bu$_4$NHSO$_4$, aq. NaOH, toluene, RT; h) CAN, MeCN/H$_2$O; i) MeNH$_2$, EtOH, 60 °C. Thermal ellipsoids in X-ray crsytal structure shown at 40% probability.

synthesized in 12 steps from 3-hydroxyoxindole in 3.7% overall yield. Additional studies focusing on the extension of this methodology to a variety of other hexahydropyrroloindole alkaloids are in progress.

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