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Synthesis of Chiral 3-Substituted Hexahydropyrroloindoline via Intermolecular Cyclopropanation

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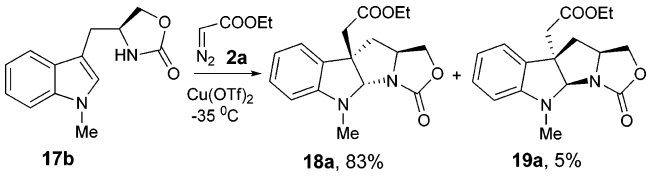
ABSTRACT



A new and efficient synthetic route to chiral 3-substituted hexahydropyrroloindoline 18 possessing absolute configurations in accordance with indole alkaloids has been developed from readily available L-tryptophan. The key step relies on the one-pot cascade reaction of oxazolidinone 17 with diazoester, which proceeds through intermolecular cyclopropanation, ring opening, and cyclization.

The structural moiety of chiral 3-substituted hexahydropyrroloindoline is widely represented in a number of bioactive indole alkaloids such as physostigmine, pseudophrynaminol, bromoflustramide, bromoflustramine, mollenine, requefortine, ardeemin, amauromine, and aszonalenin.[1] As an important precusor for the syntheses of these indole alkaloids, 3-substituted hexahydropyrroloindoline has attracted the intensive interest of synthetic chemists. A variety of methods have been reported for preparing racemic 3-substituted hexahydropyrroloindoline[2] and chiral 3-substituted hexahydropyrroloindolines, including using the catalytic asymmetric Heck reaction,[3] catalytic asymmetric alkylation and allylation,[4] chiral auxiliary induced asymmetric alkylation and rearrangment,[5] asymmetric addition−cyclization,[6,7] desulfurization−cyclization,[8] asymmetric 3,3-rearrangement,[9] and chiral resolution[10] as key steps.

We recently reported a synthesis of a pentacyclic substructure of the indole alkaloids communesin and perophora-

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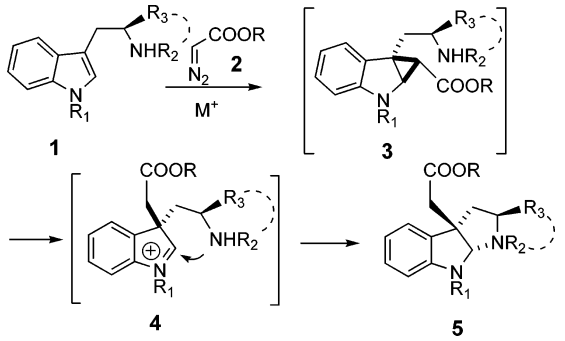
midine that proceeded through an intramolecular cyclopropanation of tryptamine derivatives, and a ring opening of the resulting cyclopropane with an in situ generated aniline.[11] In continuation of our methodology development for the syntheses of other indole alkaloids, we now describe, in this paper, a new and efficient approach to chiral 3-substituted hexahydropyrroloindolines through the one-pot cascade reactions of intermolecular cyclopropanation, ring opening, and cyclization as shown in Scheme 1.

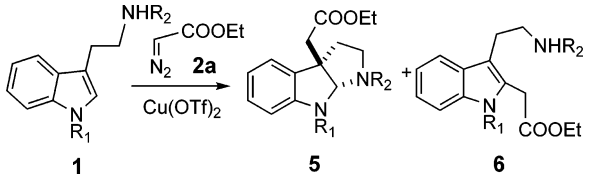
Scheme 1



Besides generating a desirable cyclopropane ring on the 2,3-double bond of **1**,[12] there are several possible reaction pathways such as direct N−H, C−H, and C−C insertion when **1** is treated with a diazoester **2**. The feasibility of effecting the desired cascade reaction to afford the 3-substituted hexahydropyrroloindoline **5** was judged to be dependent mainly on the nature of R_1 and R_2 substituents in **1**. The formation of a cyclopropane intermediate **3** and the consecutive nucleophilic attack of the amine group on the C=N double bond of the resulting indolenium **4** after collapse of cyclopropane ring would rely on the electronic density of the 2,3-double bond and the nucleophilic addition capability of the amine group. Keeping this in mind, we first explored the effects that different R_1 and R_2 substituents would have on the reaction using *N*,*N*′-disubstituted tryptamine **1**.

As speculated, initial experiments revealed that the substituents R_1 and R_2 had substantial effects on the reactivity of **1** under standard diazo decomposition conditions (4 equiv of **2a**, 5 mol % of $Cu(OTf)_2$, CH_2Cl_2, room temperature). When R_1 was an electron-donating group (R_1 = Me, Bn), the reactions of **1d** and **1e** (R_2 = Ac) with ethyl diazoacetate **2a** gave compounds **5d** and **5e** in 16% and 22% yields, respectively, as well as the C−H insertion product **6e** in less than 3% yield (Table 1, entry 5). Further screening the effect of the R_2 group in **1** showed that an electron-withdrawing

Table 1. Condition Optimization of of *N*,*N*′-Disubstituted Tryptamine

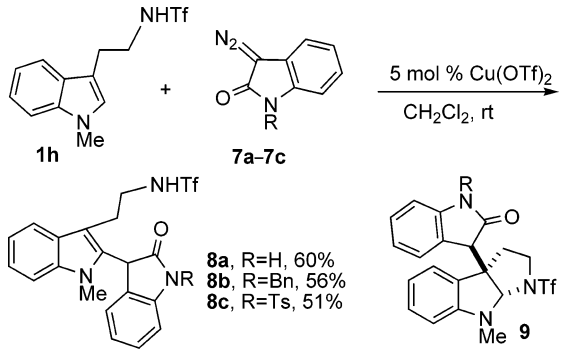


entry	**1**	R^1	R^2	**5** (%)	**6** (%)
1	**1a**	H	Ac	**5a** (0)	**6a** (0)
2	**1b**	Ts	Ac	**5b** (0)	**6b** (0)
3	**1c**	Boc	Ac	**5c** (0)	**6c** (0)
4	**1d**	Bn	Ac	**5d** (16)	**6d** (0)
5	**1e**	Me	Ac	**5e** (22)	**6e** (3)
6	**1f**	Me	Bn	**5f** (0)	**6f** (0)
7	**1g**	Me	Boc	**5g** (27)	**6g** (0)
8	**1h**	Me	Tf	**5h** (33)	**6h** (0)
9	**1i**	Me	Ns	**5i** (36)	**6i** (o)

group for R_2 was required for a successful cascade reaction (Table 1, entries 6−9). With the strongest electron-withdrawing groups Tf and Ns (Table 1, entries 8 and 9), **5h** and **5i** were isolated in 33% and 36% yields. Compound **6** was generated either through the collapse of the cyclopropane intermediate **3** or through the direct C−H insertion of carbene at position 2 of the indole core. Besides $Cu(OTf)_2$, CuOTf also catalyzed the reaction to give a similar result. However, $Cu(CH_3CN)_4PF_6$, $Rh_2(OAc)_2$, and $(Ph_3P)_3RhCl$ were inactive for the reaction. Replacement of methylene chloride with other solvents such as 1,2-dichloroethane, chloroform, nitroethane, and toluene did not significantly improve the yield of desired compound **5**.

Encouraged by the above successful one-pot cascade reaction, our efforts were next directed toward the synthesis of compound **9** possessing oxoindole substituent at position 3. The latter might serve as an important intermediate in the synthesis of calycanthaceous alkaloids (Scheme 2).[13] Un-

Scheme 2



fortunately, when **1h** reacted with diazo compounds **7a**−**c**, derived from isatin, in the presence of 5 mol % of $Cu(OTf)_2$ in methylene chloride at room temperature, the reactions provided exclusively the C−H insertion products **8** in

(11) Yang, J.; Song, H.; Xiao, X.; Wang, J.; Qin, Y. *Org. Lett.* **2006**, *8*, 2187.

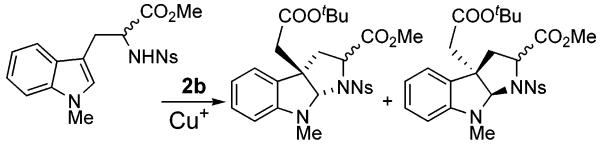
(12) There were only two reports found in the literature which described the formation of a cyclopropane ring on the 2,3-double bond of simple *N*-substituted indoles by the metal catalyzed diazo decomposition reaction, see: (a) Gnad, F.; Poleschak, M.; Reiser, O. *Tetrahedron Lett.* **2004**, *45*, 4277. (b) Welstead, W. J.; Stauffer, H. F.; Sancilio, L. F. *J. Med. Chem.* **1974**, *17*, 544.

moderate yield, instead of affording the anticipated products **9**. This was probably due to steric effects in **7**, which precluded formation of the cyclopropane ring on the 2,3-double bond of tryptamine **1h**.

Although the yield was not that high, the one-pot cascade reaction of **1** with **2** was practical for setting up the cis-stereochemical centers at positions 2 and 3 of the indole core at the same time.

We next explored the application of our process to (*S*)-*N*-methyl-*N*′-Ns-tryptophan methyl ester **10a** derived from L-tryptophan (Scheme 3). When **10a** was treated with *tert*-butyl diazoacetate **2b** under the same condition, two diastereoisomers **11a** and **12a** preferably with *endo*-selectivity[4b] were isolated in 10% and 32% yields, respectively. The stereochemistry of **11a** and **12a** was determined by NOE experiments. The reaction of (*R*)-**10b** derived from D-tryptophan with **2b** gave **11b** and **12b** in 45% combined yield and a 3:1 ratio.

Scheme 3

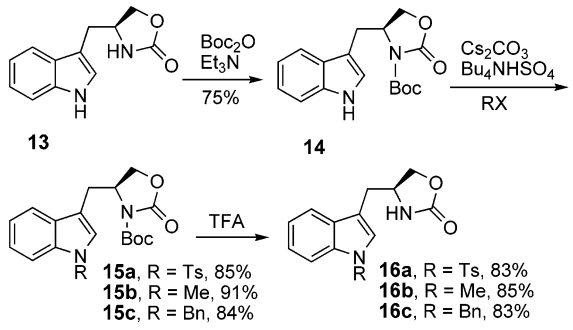


(*S*)-**10a** **11a** 1 : 3 **12a**

(*R*)-**10b** **11b** 3 : 1 **12b**

The low diastereoselectivity (1:3) induced by **10** was most likely attributable to the flexiblity of the side chain. To improve the diastereoselectivity as well as the yield, the side chain of tryptophan was fixed as an oxazolidinone substructure. In this approach, the carbamate functional group also served as an electron-withdawing group to enhance the nucleophilic capability of the amine group. Oxazolidinone **16** was readily prepared through a three-step route from commercially available (*S*)-**13** as shown in Scheme 4.

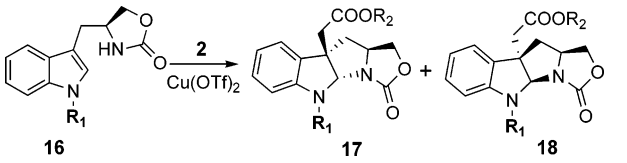
Scheme 4



Protection of the amide group in **13** with Boc led to the formation of compound **14**. Alkylation or tosylation of **14** under phase-transfer conditions provided compounds **15a**−**c** in 84−91% yield. Treatment of **15** with 20% TFA in CH_2Cl_2 afforded oxazolidinone **16** in high yield.

With indole oxazolidinone **16** in hand, we were able to test whether a side chain with a rigid carbamate functional group would improve the yield and diastereoselectivity (Table 2). It was not surprising that only the N−H insertion product and oxygen adduct were produced when **16a**, with an electron-withdrawing group on the indole nitrogen, reacted with **2b** at room temperature (Table 2, entry 1). To our delight, the *exo*-diastereoselectivity[6a] was greatly enhanced to a 17:1 ratio when oxazolidinone **16b** (R = Me) reacted with **2a** at −35 °C, and the major isomer **17a** and minor isomer **18a** were isolated in 83% and 5% yields, respectively (Table 2, entry 5). Similarly, reaction of **16b** with **2b** at 0 °C provided **17b** in 76% yield at an 8:1 ratio (Table 2, entry 8). Unlike the reaction of **16b** with **2** that gave a high yield and a high diastereoselectivity, the reaction of **16c** (R = Bn) with **2b** afforded the desirable compound **17c** in 18% low yield. The N−H insertion product (30% yield) was the major product (Table 2, entry 10).

Table 2.[a]



entry	**16**	R^1	R^2	temp, °C	tim,e h	**17** (%)	**18** (%)
1	**16a**	Ts	^{t}Bu	25	4		—[b]
2	**16b**	Me	Et	25	3	**17a** (50)	**18a** (35)
3	**16b**	Me	Et	0	5	**17a** (55)	**18a** (25)
4	**16b**	Me	Et	−25	7	**17a** (71)	**18a** (10)
5	**16b**	Me	Et	−35	30	**17a** (83)	**18a** (5)
6	**16b**	Me	Et	−45	30	**17a** (0)	**18a** (0)
7	**16b**	Me	^{t}Bu	25	4	**17b** (62)	**18b** (9)
8	**16b**	Me	^{t}Bu	0	6	**17b** (76)	**18b** (10)[c]
9	**16b**	Me	^{t}Bu	−5	12	**17b** (52)	**18b** (5)[d]
10	**16c**	Bn	^{t}Bu	0	30	**17c** (18)	**18c** (0)[e]
11	**16c**	Bn	^{t}Bu	−25	30	**17c** (0)	**18c** (0)[f]

[a] Reactions were carried out with 4 equiv of **2** and 5 mol % of $Cu(OTf)_2$. [b] 66% yield of N−H insertion product and 30% yield of *O*-adduct were isolated. [c] 6% yield of N−H insertion product was isolated. [d] 7% of N−H insertion product was isolated. [e] 48% yield of N−H insertion product was isolated. [f] 30% yield of N−H insertion product was isolated, see the Supporting Information.

The stereochemistry of major and minor isomers was confirmed by NOE experiments (Figure 1). We were happy to find that the absolute configurations (*5S, 6aR, 11aS*) of the major isomer were in agreement with that found in aforesaid alkaloids. In the NOE experiments, the correlation between the α-proton of ester (H_{13}) and the aminal proton (H_{11a}) in **17b** was observed. Besides the correlation between the α-proton of ester (H_{13}) and the aminal proton (H_{11a}), the correlation between the aminal proton (H_{11a}) and the proton-H_5 of the oxazolidinone ring in **18b** was also observed.

(13) May, J. A.; Stoltz, B. *Tetrahedron* **2006**, *62*, 5262.

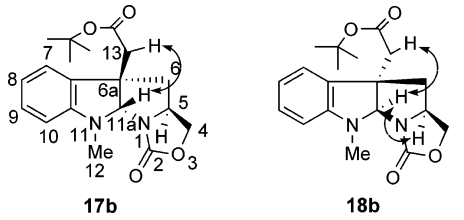


Figure 1. NOE experiments.

The effect of reaction temperature on the yield and diasteroselectivity was carefully studied to gain insight into the detailed mechanism of diastereoselectivity (Table 2). Both reactions of oxazolidinone **16b** with individual diazoesters **2a** and **2b** showed a narrow window of suitable temperature. For the reaction of **16b** with **2a**, the diastereoselectivity was greatly enhanced from a 1.4:1 ratio to a 17:1 ratio by lowering the temperature from 25 to −35 °C (Table 2, entries 2−5). For the reaction of **16b** with more bulky diazoester **2b**, the diastereoselectivity was slightly improved from a 7:1 to a 10:1 ratio by lowering the temperature from 25 to −5 °C (Table 2, entries 7−9). The temperature effect indicated that the cascade reaction proceeded under kinetic control. A tentative mechanism is suggested in Figure 2. Since the intermediates **19** and **20** were not detected during the reaction by TLC, it is reasonable to believe that the first step of cyclopropanation to form **19** and **20** should be the rate-controlling step in the cascade reaction, and that it proceeds much slower than the consecutive two steps of ring opening and cyclization. Because of the steric interaction between the oxazolidinone moiety and the indoline moiety in **20**, the formation of kinetically favorable transition state **19** should be easier than the transition state **20** that would lead to compound **18**. Presumably these effects are magnified at lower temperature.

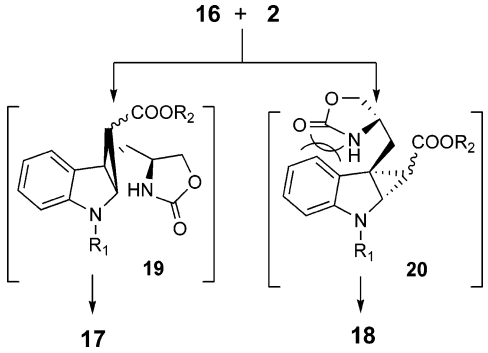


Figure 2. Proposed mechanism.

In summary, we have described a new and efficient synthetic method of chiral 3-substituted hexahydropyrroloindoline **17** in high yield by a one-pot cascade reaction from readily available L-tryptophan derivatives. Importantly, the synthesized framework **17** possesses the same absolute configurations as that appearing in natural products and necessary functional groups. Current methodology development has provided us an opportunity of synthetic approach to a variety of indole alkaloids such as physostigmine, bromoflustramide, mollenine, requefortine, ardeemin, amauromine, and aszonalenin.

Acknowledgment. The financial support of this work from NSFC (No. 20372048), Ministry of Education (NCET and RFDP), and Sichuan Province Governoment (No. 04ZQ026−011) is gratefully acknowledged.

Supporting Information Available: Experimental procedure and spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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