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Diastereoselective construction of continuous all-carbon quaternary centers via intramolecular oxidative coupling reaction

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ABSTRACT

Construction of continuous all-carbon quaternary centers via intramolecular oxidative coupling was described. Intramolecular oxidative coupling of bisoxindole linked by diol derived from D-tartaric acid diastereoselectively produced C_1 or C_2 isomers of the annulation product. The selectivity was realized by judiciously choosing base and solvent employed in the reaction. As key intermediates for the synthesis of cyclotryptamine alkaloids, the resulting bisoxindole should be applicable to the total syntheses of complex indole alkaloids with continuous all-carbon quaternary centers.

Although elegant synthetic methodologies have been developed for constructing quaternary carbon center, new strategy is still continuously being invented to provide a convenient, efficient, and general way for assembling asymmetric quaternary carbon center.[1] Since asymmetric all-carbon quaternary center is commonly found in natural products and pharmaceutical molecules, designing methodologies for stereocontrolled construction of all-carbon quaternary center remains to be attractive but a significant challenge for synthetic chemists.[2] Especially when culminating complex natural products with continuous all-carbon quaternary centers (such as Communesin and Perophoramidine),[2] one faces much more challenges in stereocontrolled construction of continuous all-carbon quaternary centers because of the increasing steric repulsion and the intrinsic difficulty in controlling diastereoselectivity and enantioselectivity.

Cyclotrytamine alkaloids are a large family of indole alkaloids with complex structure and potent biological activities, which could be biosynthetically considered as oligomers of tryptamines.[3] Hexahydropyrrolo[2,3-*b*]indole is the structural unit of cyclotryptamine alkaloids, which are mainly connected by forming C3–C3′ bond or C3–C7′ bond between the two units. The vicinal and biaryl all-carbon quaternary centers and polycyclic structure of tryptamine alkaloids pose formidable challenges for synthetic chemists.[4] Extensive synthetic studies of cyclotryptamine alkaloids have been reported and elegant strategies have been developed to enantioselectively construct the vicinal all-carbon quaternary centers.[4] Although biomimetic synthesis of (±) and *meso*-Chimonanthine, dimer of tryptamine, has been achieved by oxidative coupling of tryptamine or oxindole,[5a–c] the first enantioselective synthesis of Chimonanthine was reported by Overman until 1999, who established the quaternary carbon centers by domino Heck reaction or later by dialkylation of isoindigo.[5d,5e] In 2007, Movassaghi et al. developed the reductive coupling of 3-bromopyrrolo[2,3-*b*]indole mediated by $Co(PPh_3)_2Cl$ to dimerize pyrroloindoline units, which enabled an efficient synthesis of Chimmonanthine.[5f] Recently the catalytic construction of one of the quaternary carbon centers of Folicanthine was reported by Gong,[5g] which relied on the substitution of hydroxyoxindole with enamide catalyzed by chiral phosphoric acid. Kanai and coworkers made use of asymmetric Michael reaction of isoindigo with vinylnitrate catalyzed by chiral bimetallic catalyst to establish one of the all-carbon quaternary centers of Chimonanthine.[5h] However both strategies needed additional transformations to install the other quaternary carbon center, which made the synthetic routine much longer and less efficient compared with Overman's and Movassaghi's method.

Recently we developed intramolecular oxidative coupling reactions of indole incorporated substrates to build up complex indole scaffolds including the frameworks of Communesin A, F, and

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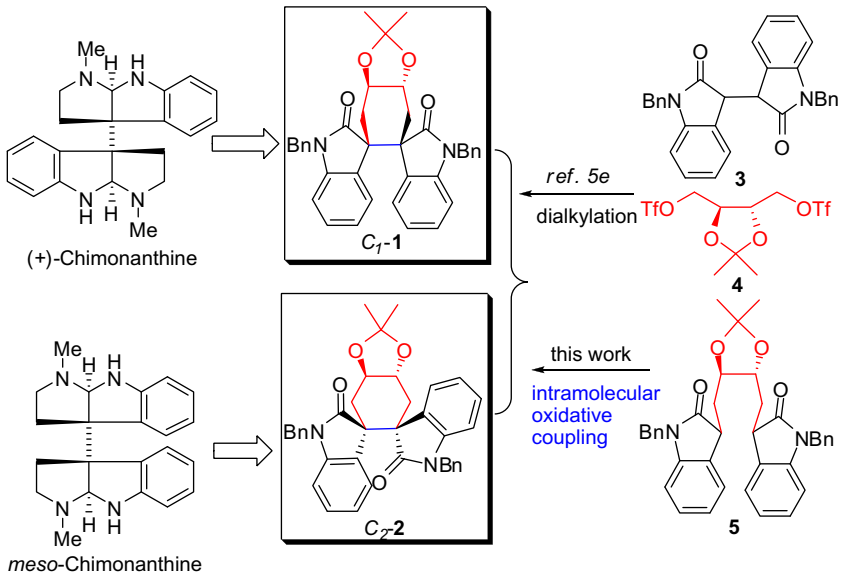
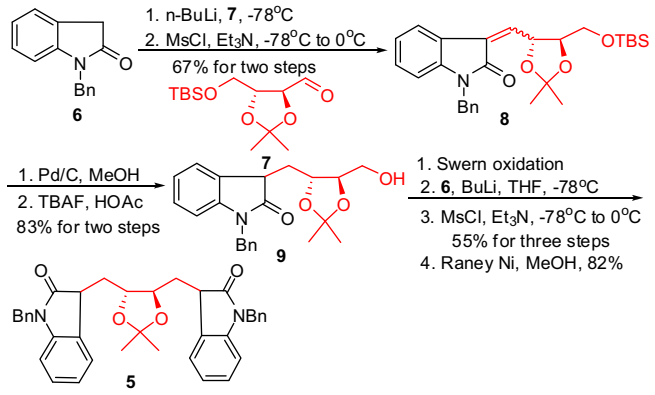


Figure 1. Strategies for synthesis of Chimonanthine alkaloids.

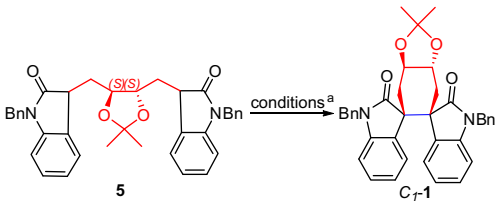


Scheme 1. Synthesis of bisoxindole **5**.

(−)-Vincorine,[2c,d,6] which demonstrated the powerful potential of intramolecular oxidative coupling on the synthesis of complex indole alkaloid motifs. Despite of the recent advances of intramolecular oxidative coupling,[7] diastereoselective formation of continuous all-carbon quaternary centers via intramolecular oxidative coupling is still less explored. Herein we would like to report on diatereoselectively constructing continuous all-carbon quaternary centers of cyclotryptamine alkaloids via intramolecular oxidative coupling.

During the course of the synthesis of cyclotryptamine alkaloids, we encountered the problem of establishing both stereoisomers of the continuous all-carbon quaternary centers. To this end, Oveman's dialkylation strategy seemed more appealing, since both bisoxindole C_1-**1** and C_2-**2**, which were the key intermediate to cyclotryptamine alkaloids (Fig. 1),[4b] were accessible by dialkylation of isdingo **3** with ditriflate **4** under different reaction conditions.[4b,5d,9]

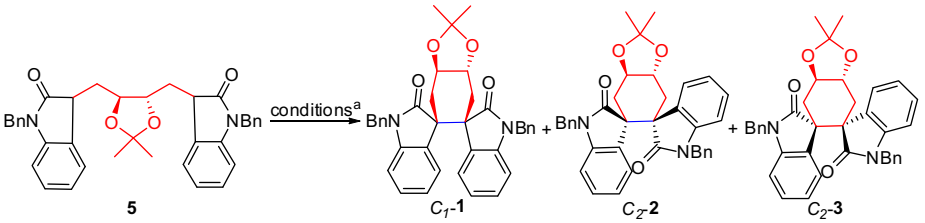
Table 1
Optimization of intramolecular oxidative coupling condition for bisoxindole C_1-**1**



Entry	Solvent	Base	Oxidant	Temperature (°C)	Concentration (M)	Yield[b] (%)
1	THF	LDA	$Fe(acac)_3$ (2.2 equiv)	−78 to rt	0.05	ND[c]
2	THF	LDA	$Cu(2\text{-ethylhexanate})_2$ (2.2 equiv)	−78 to rt	0.05	ND[c]
3	THF	LDA	I_2 (2.2 equiv)	−78 to rt	0.05	47
4	THF	LDA	I_2 (1.1 equiv)	−78	0.05	54
5	THF	LDA	NBS (1.1 equiv)	−78	0.05	37
6	THF	LDA	NIS (1.1 equiv)	−78	0.05	53
7	THF	LiHMDS	I_2 (1.1 equiv)	−78	0.05	30
8	THF	NaHMDS	I_2 (1.1 equiv)	−78	0.05	63
9	THF	KHMDS	I_2 (1.1 equiv)	−78	0.05	ND[c]
10	Toluene	NaHMDS	I_2 (1.1 equiv)	−78 to rt	0.05	47
11	Et_2O	NaH MDS	I_2 (1.1 equiv)	−78 to rt	0.05	43
12	THF	NaHMDS	I_2 (1.1 equiv)	−78	0.005	77
13	THF	NaHMDS	I_2 (1.1 equiv)	−78 to rt	0.005	84

[a] **5** (1.0 equiv), Base (2.2 equiv), THF, −78 °C, 30 min, then addition of oxidant, −78 °C 2 h or −78 °C to rt 30 min.
[b] Isolated yield.
[c] Complex mixture, no desired product was isolated.

Table 2
Screening of intramolecular oxidative coupling condition for bisoxindole C_2-**2**



Entry	Solvent	Base	Oxidant	Temperature (°C)	Concentration (M)	Ratio (**1**:**2** + **3**)	Ratio **2**:**3**	Yield (**2** + **3**)[c] (%)
1	THF/HMPA 9:1	LDA	I_2 (2.2 equiv)	−78	0.05	1:2	5.8:1	37
2	THF/HMPA 9:1	LDA	I_2 (1.1 equiv)	−78	0.05	1:2	4.0:1	68
3	THF/HMPA 9:1	LDA	NBS (1.1 equiv)	−78	0.05	1:6	3.4:1	60
4	THF/HMPA 9:1	LiHMDS	I_2 (1.1 equiv)	−78	0.05	1:5	3.7:1	60
5	THF/HMPA 9:1	NaHMDS	I_2 (1.1 equiv)	−78	0.05	1.4:1	1.8:1	27
6	THF/HMPA 9:1	KHMDS	I_2 (1.1 equiv)	−78	0.05	—[b]	NA	ND[d]
9	THF/HMPA 9:1	LDA	I_2 (1.1 equiv)	−78	0.005	—[b]	9:1	80
8	THF/HMPA 9:1	LDA	I_2 (1.1 equiv)	−78 to rt	0.005	—[b]	7:1	73
9	THF/HMPA 8:2	LDA	I_2 (1.1 equiv)	−55	0.005	—[b]	5.:1	70
10	THF/HMPA 7:3	LDA	I_2 (1.1 equiv)	−50	0.005	—[b]	4.4:1	63

[a] **4** (1.0 equiv), Base (2.2 equiv), THF/HMPA, −78 °C, 30 min, then addition of oxidant, −78 °C 2 h or −78 °C to rt 30 min.
[b] No C_1-**1** was detected.
[c] Isolated yield.
[d] Complex mixture, no desired product was isolated.

In their procedure, bisoxindole C_1-**1** could be obtained in 90% yield using NaHMDS as base, while bisoxindole C_2-**2** was only achieved in moderate yield (58%) under the optimal condition (LiHMDS as base). To develop an alternative route to bisoxindole C_1-**1** and C_2-**2**, we envisaged that they could be constructed by intramolecular oxidative coupling of bisoxindole **5**. By employing D-tartaric acid derived diol as linker, a tighter transient state could be produced in the oxidative coupling reaction, which would result in good diastereoselectivity.

As depicted in Scheme 1, the synthesis of bisoxindole **5** commenced with aldol condensation of oxindole **6** with aldehyde **7**[8] derived from D-tartaric acid followed by dehydration with MsCl/Et_3N to afford alkylidene oxindole **8** in 67% yield. Hydrogenation catalyzed by Pd/C and desilylation by TBAF which was neutralized with HOAc smoothly gave primary alcohol **9**. The addition of HOAc proved critical since hydroxyl indole was isolated as the main product owing to the oxidation of oxindole by air. Swern oxidation of the primary alcohol and the second aldol condensation with oxindole **6** furnished bisoxindole which was dehydrated and hydrogenated by Raney Nickel to provide bisonindole **5** in acceptable yield.

With bisoxindole **5** in hand, various reactions conditions were screened to deliver the oxidative coupling product (Table 1). We first followed Baran's condition by using Fe(III) or Cu(II) salts as oxidant (entries 1 and 2).[9] To our disappointment, no product could be isolated and only decomposition of starting material was detected due to the sensitivity of substrate to Lewis acids. After series of trials, halogen reagents were found to be effective for the oxidative coupling (entries 3–6). Iodine gave slightly better yield (54%) than NBS (37%) and NIS (43%). To our delight, only one isomer was isolated and determined to be C_1 symmetric isomer C_1-**1**[11] by comparison of NMR spectra with those of reported compound.[5d,10] The yield of the reaction were also depended on the base used in the reaction (entries 6–9). NaHMDS afforded the best results (entry 8) and too strong base KHMDS led to decomposition of starting material. Other solvents such as toluene, ether was less efficient than THF as shown in entries 10 and 11. Fortunately, the yield was improved to 77% by diluting the reaction to 0.005 M (entry 12) and eventually 84% yield could be achieved by immediate removal the reaction flask from cold bath after addition of oxidant.

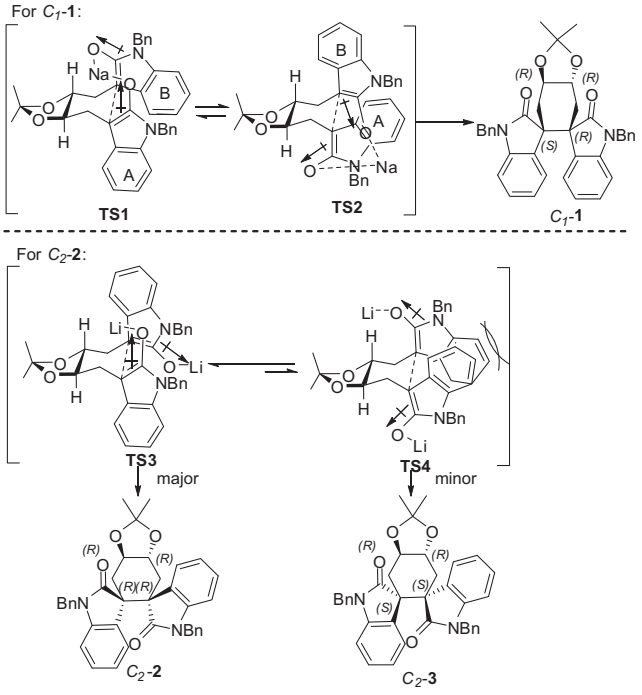
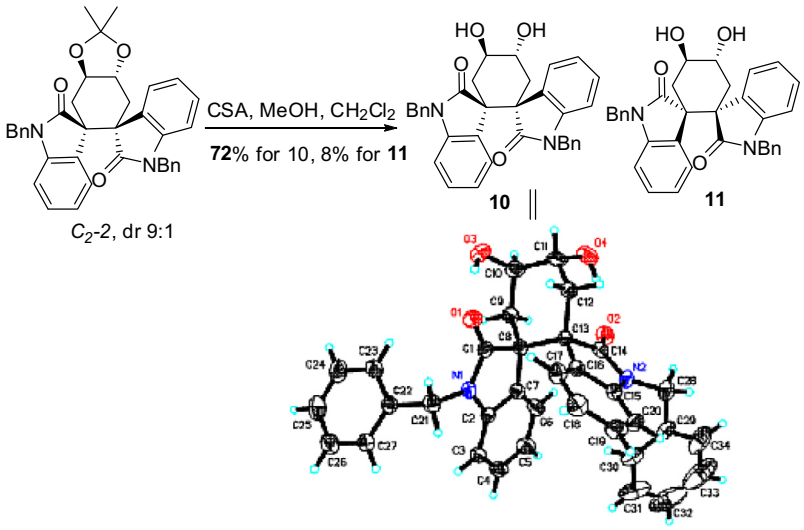


Figure 2. Rationale for the observed diastereoselectivity.

Interestingly, when adding HMPA as co-solvent, C_2 symmetric isomer C_2-2[12] was generated as the major product albeit in low yield and diastereoselectivity (Table 2, entry 1). This result was quite encouraging since like Overman's procedure we could obtain both stereoisomers from the same starting material just by changing reaction conditions. I_2 was also proved to be the best oxidant (entries 2 and 3). On the contrast, LDA was found to be the optimal base as other base gave deleterious results (entries 4–6). The diastereoselectivity was greatly enhanced (only C_2 isomer, C_2-2/C_2-3 9:1) when lowing the concentration of the reaction mixture to 0.005 M (entry 9). It was also found that higher temperature have



Scheme 2. Deprotection of C_2-**2** and ORTEP drawing of diol **10**.

negative influence on the diastereoselectivity as well as yield (entry 8). Increasing the ratio of HMPA led to decreased diastereoselectivity as the reaction had to be run at higher temperature because of solidification of reaction mixture at −78 °C. To establish the absolute configuration of C_2-2 and C_2-3, removal of acedonide of oxidative coupling product with CAS in MeOH and CH_2Cl_2 afforded two separable isomers, diol 10 together with the minor isomer 11 (Scheme 2). X-ray crystallography of diol 10[13] showed that the absolute configuration of the newly formed stereocenters of C_2-2 were *R*,*R*, while C_2-3 had *S*,*S* configuration as determined by diol 11, which was a known compound.[5e,10]

To explain the observed diastereoselectivity, we proposed the transition state of the reaction as shown in Figure 2. In the course of forming C_1-**1**, both enolates coordinated to sodium cation despite the electronic repulsion between the two enolates in the presence of NaHMDS, which was similar to Overman's proposal.[5d,10] Additionally the backbone of the transition species adopted a six-membered chair conformation which was fixed by the acetonide protected diol. Although two enolates could point up or down to the six-membered ring, the two transition states **TS1** and **TS2** were equal to each other. After oxidative coupling, both transition states led to C_1 symmetric isomer C_1-**1**. On the contrary, when LDA was used as base and THF/HMPA as solvent, two enolates of oxindole had to be pointed against each other for electronic repulsion between the two enolates and two unequal transition states **TS3** and **TS4** thus were formed. As the two aromatic rings of oxindoles in **TS4** suffered more seriously steric repulsion than those in **TS3**, **TS4** had a greater energy barrier and the reaction preferred to proceed along with **TS3** pathway. After oxidative coupling, **TS3** went to the major product C_2-**2** isomer while **TS4** led to the minor product C_2-**3** isomer.

In conclusion, a highly diastereoselective synthesis of continuous all-carbon quaternary centers was realized by intramolecular oxidative coupling of bisoxindole linked by diol derived from D-tartaric acid. From the same cyclization precursor, both stereoisomers could be obtained under different reaction conditions in excellent yield and diastereoselectivity. This reaction represents one of the few examples of diastereoselective construction of continuous all-carbon quaternary centers in one step. As the cyclized bisoxindoles were the key intermediates for asymmetric syntheses of Chimonanthine and related alkaloids, this reaction provided an alternative route to those alkaloids. The further application of this methodology on the syntheses of complex indole alkaloids is actively being pursued in our lab.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.05.146.

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11. C_1-**1**: $[a]_D^{23.7}$ −264.0 (*c* 0.95, $CHCl_3$), (lit. $[a]_D^{23.7}$ +290 (*c* 0. 5, $CHCl_3$),[10] for the enantiomer of C_1-**1**; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.88 (d, *J* = 7.2 Hz, 1H), 7.32–7.30 (m, 2H), 7.25–7.15 (m, 5), 7.07 (t, *J* = 7.8 Hz, 2H), 6.96 (t, *J* = 7.2 Hz, 2H), 6.57–6.48 (m, 4H), 6.31 (d, *J* = 7.5 Hz, 2H), 6.05 (d, *J* = 7.5 Hz, 1H), 5.30–5.28 (m, 1H), 5.17 (d, *J* = 15.9 Hz, 1H), 5.01 (d, *J* = 15.7 Hz, 1H), 4.89 (d, *J* = 15.6 Hz, 1H), 4.52–4.43 (m, 1H), 4.30 (d, *J* = 16.2 Hz, 1H), 3.28 (t, *J* = 12.0 Hz, 1H), 2.36 (t, *J* = 12.9 Hz, 1H), 2.30 (dd, *J* = 13.2, 4.8 Hz, 1H), 2.04 (dd, *J* = 13.2, 4.5 Hz, 1H), 1.59 (s, 6H); ESIMS *m*/*z* 593.1 $(M+Na)^+$; HRMS calcd for $C_{37}H_{34}N_2O_4$ Na $(M+Na)^+$ requires 593.2421, found: 593.2422.
12. C_2-**2** (Mixture of two inseparable isomers), major isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (m, 8H), 7.09 (m, 4H), 6.98 (t, *J* = 8.0 Hz, 2H), 6.77 (t, *J* = 7.6 Hz, 2H), 6.41 (d, *J* = 7.6 Hz, 2H), 5.10 (m, H), 4.96 (d, *J* = 15.6 Hz, 2H), 4.47 (d, *J* = 15.6 Hz, 2H), 2.55 (dd, d, *J* = 13.4, 6.8 Hz, 2H), 2.28 (dd, *J* = 13.2, 9.6 Hz, 2H), 1.55 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.2, 142.0, 135.3, 130.3, 128.7, 128.5, 127.6, 127.4, 127.3, 125.1, 122.6, 110.5, 108.6, 74.7, 53.1, 43.8, 34.3, 27.5; ESIMS *m*/*z* 593.1 $(M+Na)^+$; HRMS calcd for $C_{37}H_{34}N_2O_4$ Na $(M+Na)^+$ requires 593.2421, found: 593.2422.
13. $[a]_D^{23.7}$ 172.7 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (m, 7H), 7.11 (m, 3H), 7.05 (t, *J* = 7.6 Hz, 2H), 6.82 (t, *J* = 7.6 Hz, 2H), 6.48 (d, *J* = 7.6 Hz, 2H), 6.14 6.48 (d, *J* = 11.6 Hz, 2H), 4.96 (d, *J* = 15.6 Hz, 2H), 4.63 (d, *J* = 16.0 Hz, 2H), 4.23 (d, *J* = 11.2 Hz, 2H). 3.25 (dd, d, *J* = 15.6, 3.2 Hz, 2H), 2.43 (br s, 2H), 1.93 (d, *J* = 15.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.4, 142.0, 134.8, 129.4, 129.1, 128.1, 127.1, 127.6, 124.8, 123.8, 109.7, 71.4, 51.8, 44.2, 30.1; IR (film) 3368, 1678, 1610, 1384, 1083, 763 cm^{-1}; ESIMS *m*/*z* 531.1 $(M+H)^+$, 553.1 $(M+Na)^+$; HRMS calcd for $C_{34}H_{31}N_2O_4$ $(M+H)^+$ requires 531.2778, found: 531.2268.