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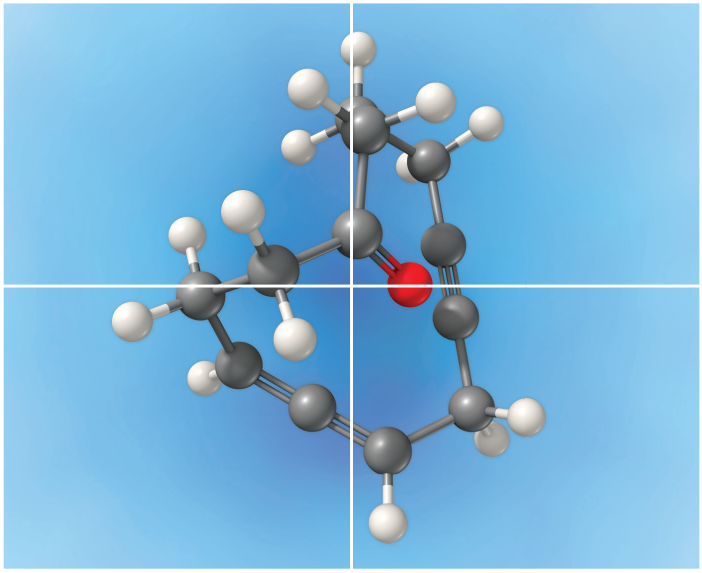

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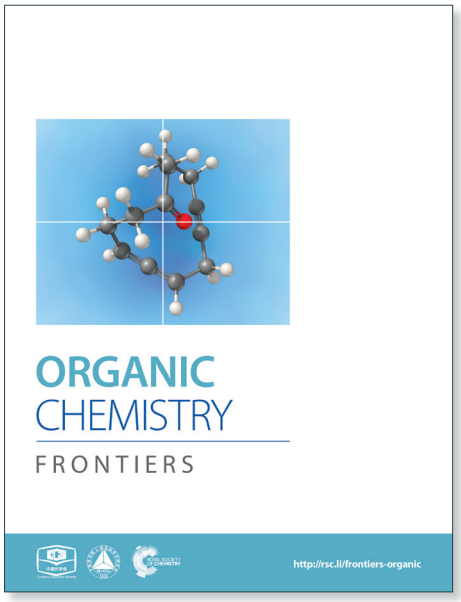

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Highly Efficient and Stereocontrolled Oxidative Coupling of Tetrahydropyrroloindoles: Synthesis of Chimonanthines, (+)-WIN 64821 and (+)-WIN 64745†

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ABSTRACT: The highly efficient and stereocontrolled dimerization of 1,2,3,8-tetrahydropyrrolo[2,3-*b*]indoles was successfully developed with I_2 as the oxidant, which allowed the rapid synthesis of *meso*- and *rac*-chimonanthines, (+)-WIN 64821 and (+)-WIN 64745 in the highest overall yields to date via oxidation–oxidation–reduction sequence.

Dimeric hexahydropyrrolo[2,3-*b*]indole alkaloids are a unique class of natural bisindole alkaloids exhibiting a diverse range of biological activities.[1] In particular, the dimeric pyrroloindole alkaloids with the C(3a)–C(3a') linkage possess the fascinating architecture of vicinal quaternary stereocenters adjacent to two aminals. Typical examples are *meso*-chimonanthine (**1**) and *rac*-chimonanthine (**2**), as well as the dimeric diketopiperazine alkaloids (+)-WIN 64821 (**3**) and (+)-WIN 64745 (**4**),[2] as shown in Figure 1. These complex structural features have attracted a considerable attention and their construction in a stereocontrolled manner continues to be actively pursued.[3–12]

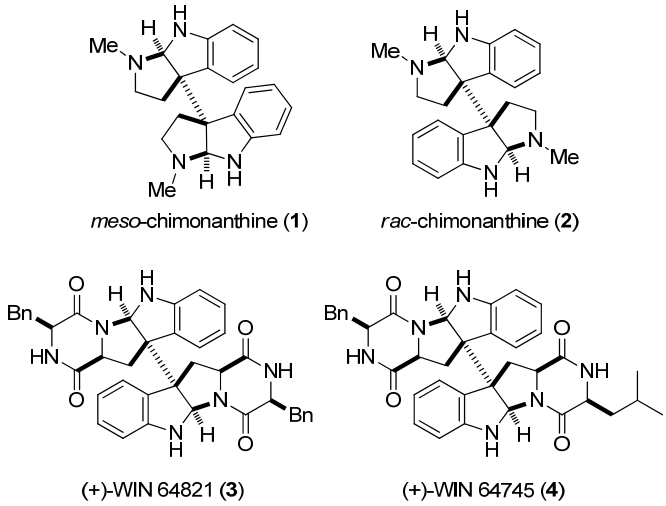

Figure 1. Representative examples of dimeric hexahydropyrroloindole alkaloids.

A number of methods have been developed for the synthesis of these complex molecules, which generally fall into three major categories as depicted in Figure 2. In the first category, dihydroisoindigo (**A**) derivatives were used as the starting materials or served as synthetic intermediates.[4, 5] This was exemplified by Overman's first enantioselective total synthesis of chimonanthine.[4b] The second category, pioneered by Movassaghi et al.,[6] involved the Co(I)-mediated reductive dimerization of 8-protected 3a-bromohexahydropyrroloindoles such as compound **B**.[6–8] This was showcased by the concise synthesis of **3**, **4** and the more complexed ones such as (+)-11,11'-dideoxyverticillin A.[6c] Nevertheless, an excess amount of Co(I) complex was required and the yields of dimerization were not high (~ 60%). The dimerization could also be mediated by Zn/Ni or Mn/Ni, but in low efficiency and poor stereoselectivity.[9] The third approach was biomimetic oxidative coupling of tryptamine derivatives (**C**), providing a rapid access to the target molecules.[10, 11] However, it was disappointing to see that in all cases the yields were low and/or the stereoselectivity was poor. The development of more efficient and general methods is certainly highly desirable. Herein we report the facile synthesis of **1–4** via I_2-mediated, highly efficient and stereocontrolled oxidative dimerization of tetrahydropyrroloindoles (**D**).

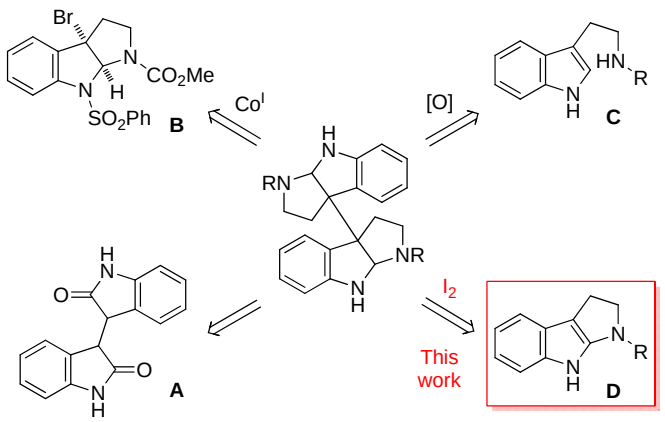

Figure 2. Representative synthetic approaches towards chimonanthines.

Our idea originated from the biosynthetic hypotheses of chimonanthine. It has long been postulated by Robinson and Teuber[13] that the biosynthesis of chimonanthine compounds involves the oxidative dimerization of two tryptamine units (**E**) via the benzyl radical intermediates **F** (Figure 3). However, an alternative pathway has recently been proposed by Movassaghi et al.,[3b] which involves the repeated oxidation and rearrangement of bisindole **G** to produce bisamidine **H** followed by subsequent reduction. Encouraged by Movassaghi's perception, we suggest

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‡ These authors contributed equally.

herein the third route as the hybrid of the above two hypotheses: tryptamine **E** rather than bisindole **G** might undergo the oxidation–oxidation–reduction sequence to produce chimonanthine via Movassaghi's intermediate bisamidine **H** (Figure 3).

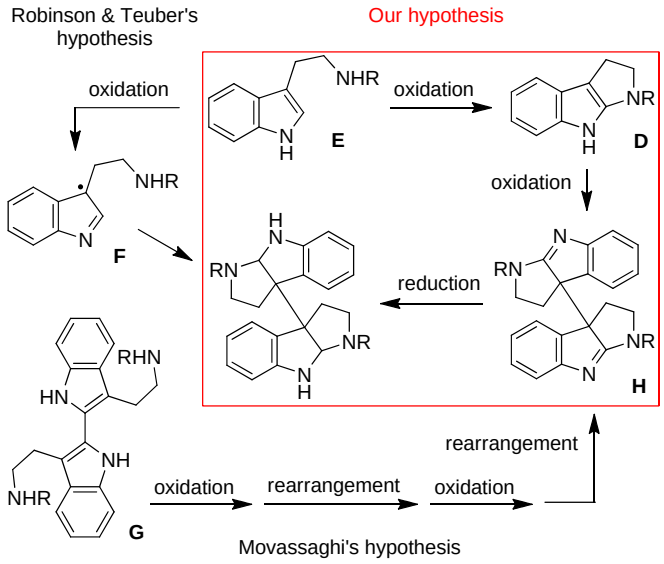
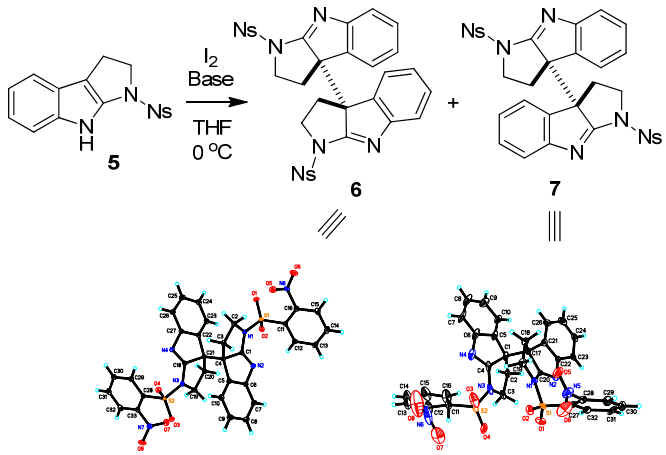


Figure 3. Hypotheses of the biosynthesis of chimonanthine.

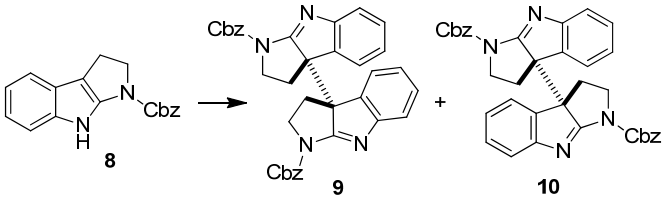
Thus, 1-nosyltetrahydropyrroloindole (**5**) was initially used to test our hypothesis. Substrate **5** was readily prepared in 78% yield from *N*-nosyl tryptamine by reaction with ^{t}BuOCl/Et$_3$N according to the literature methods.[14] The treatment of **5** with lithium bis(trimethylsilyl)amide (LiHMDS) and iodine[15] in THF at 0 °C afforded the coupling products in 53% yield as the mixture of **6** and **7** in a 3:1 ratio, whose structures were unambiguously established by their X-ray diffraction experiments (Scheme 1).[16] Interestingly, when NaH was used as the base, the reaction of **5** with I_2 gave the mixture of **6** and **7** in a 1:10 ratio in a combined yield of 67%.

Scheme 1. Oxidative coupling of **5**.



Intrigued by the above results, we decided to study the oxidative coupling in detail. 1-(Benzoxycarbonyl)-tetrahydropyrroloindole (**8**) rather than **5** was then chosen as the model in consideration of simplifying the total synthesis of **1** and **2** (vide infra). The results are summarized in Table 1. With NaH as the base and THF as the solvent, the oxidation of **8** by I_2 at 0 °C for 10 min gave the coupling products **9** (17%) and **10** (72%). The efficiency and stereoselectivity were both increased when KH was used as the base (entries 1 and 2). Lowering the temperature increased the yield of **9** while the stereoselectivity was dramatically reversed when the solvent was switched to DMF (entries 3 and 4). On the other hand, the formation of **9** was partially inhibited when the reaction concentration was diluted from 0.1 M to 0.02 M (entries 2 and 5). KHMDS and NaHMDS showed similar effects as KH and NaH in terms of stereoselectivity (entries 6 and 7). However, with LiHMDS as the base, a high selectivity in favor of **9** was now observed. When the temperature was lowered to -40 °C, compound **9** was obtained in 95% yield almost exclusively (entries 8 and 9). Note that in all cases the oxidative dimerization of **8** showed an excellent efficiency, in sharp contrast to the direct oxidative coupling of its tryptamine precursors. The dramatically different effects of alkali metal ions on the stereoselectivity of dimerization were also remarkable.

Table 1. Iodine-mediated oxidative coupling of **8**.

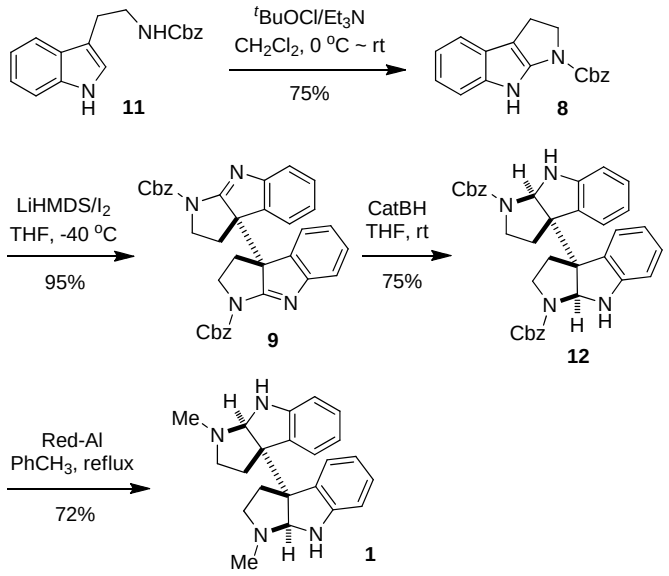


Entry[a]	Base	Solvent	Temp (°C)	Yield (%)[b] 9	10
1	NaH	THF	0	17	72
2	KH	THF	0	14	85
3	KH	DMF	0	66	33
4	KH	THF	-40	21	69
5[c]	KH	THF	0	7	87
6	KHMDS	THF	0	14	76
7	NaHMDS	THF	0	22	62
8	LiHMDS	THF	0	80	10
9	LiHMDS	THF	-40	95	trace

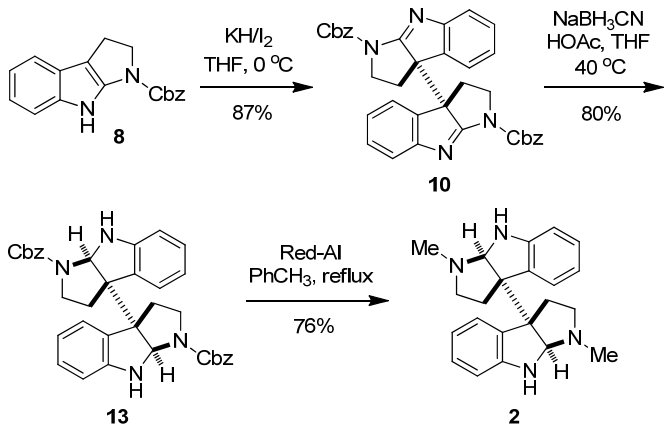
[a] Reaction conditions: **8** (0.20 mmol), I_2 (0.15 mmol), base (0.22 mmol), solvent (2 mL), 10 min. [b] Isolated yield based on **8**. [c] THF (10 mL) was used.

The synthesis of *meso*- and *rac*-chimonanthine thus becomes simple based on the above results. The four-step stereocontrolled synthesis of **1** starting from the readily available tryptamine **11** is summarized in Scheme 2. Compound **9** was reduced to **12** by catecholborane (CatBH) at RT. The subsequent conversion of the cbz groups to methyl ones by Red-Al furnished *meso*-chimonanthine **1** in an overall 38% yield. In a similar fashion (Scheme 3), the reduction of **10** by $NaBH_3CN$ gave compound **13**, which was readily transformed to **2** by Red-Al in an overall 40% yield (based on **11**). The spectra of **1** and **2** thus synthesized were identical with those reported in the literature.[4a, 12a]

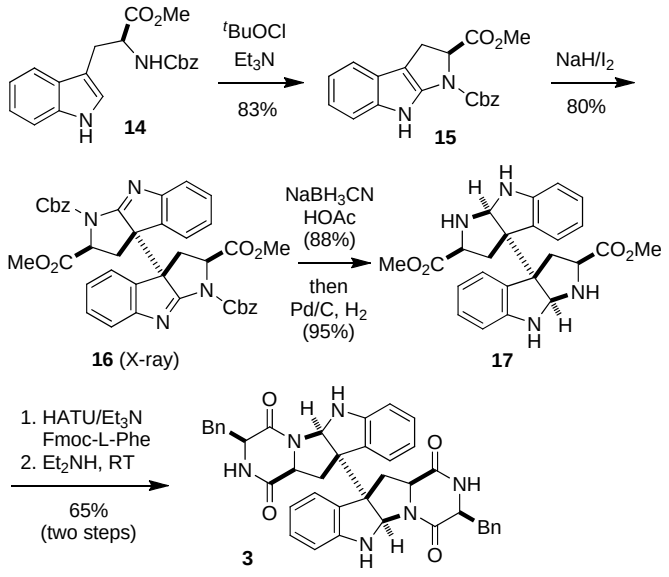
Scheme 2. Synthesis of *meso*-chimonanthine.



Scheme 3. Synthesis of *rac*-chimonanthine.

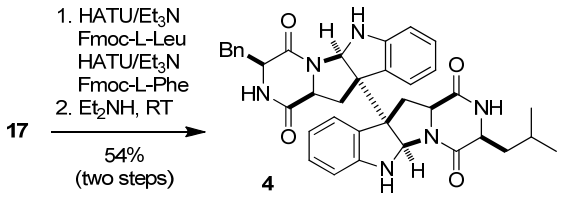


Scheme 4. Synthesis of (+)-WIN 64821.



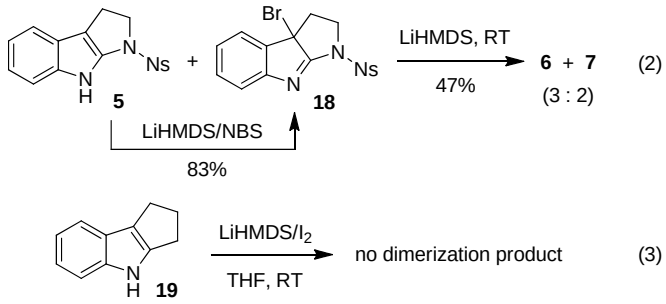
The above results also prompted us to extend the oxidation–oxidation–reduction sequence to tryptophan derivatives. Thus the oxidation of *N*-Cbz-L-tryptophan methyl ester (**14**) with ^{t}BuOCl/Et_3N gave tetrahydropyrroloindole **15** (83% yield). Further oxidative dimerization of **15** with NaH/I_2 in THF at 0 °C produced bisamidine **16** in 80% yield as a single diastereoisomer, whose structure was firmly established by its X-ray diffraction experiments[17] (see the Supporting Information).[18] The $NaBH_3CN$ reduction of **16** (88% yield) followed by deprotection with Pd/C–H_2 (95% yield) led to compound **17**. The *O*-(7-azabenzotriazol-1-yl)-*N*,*N*,*N*',*N*'-tetramethyluronium hexafluorophosphate (HATU)[19]/Et_3N-promoted condensation of **17** with Fmoc-L-phenylalanine followed by the removal of the Fmoc group by Et_2NH at RT furnished **3** in 65% yield (Scheme 4).[20] Thus (+)-WIN 64821 was synthesized in six steps starting from **14** in an overall 36% yield.

The intermediate **17** could also be utilized for the synthesis of (+)-WIN 64745. As shown in Equation 1, the successive condensation of **17** with Fmoc-L-leucine and Fmoc-L-phenylalanine followed by deprotection with Et_2NH gave rise to the target molecule **4** in 54% yield. This constitutes the six-step synthesis of (+)-WIN 64745 starting from tryptophan **14** with an overall 30% yield. The spectra of **3** and **4** thus synthesized were identical with those reported in the literature.[7a] Furthermore, it is conceivable that optically active (+)-chimonanthine (+)-**2** can also be synthesized from **17** via N-methylation and decarboxylation.[21]



(1)

To gain more insight into the highly efficient and stereoselective dimerization of tetrahydropyrroloindoles, we designed the following experiments. In the presence of 10 equivalents of 2,2,6,6-tetramethylpiperidin-1-oxy radical (TEMPO), the treatment of **8** with LiHMDS/I_2 at -40 °C gave the products **9** (93% yield) and **10** (5% yield), indicating that TEMPO had no effect on the dimerization. TEMPO showed no influence at all on the reaction of **8** with KH/I_2 either. These two experiments indicate that the dimerization of **8** is unlikely a free radical process. Next, *N*-bromosuccinimide (NBS) was used as the substitute for iodine. The reaction of **5** with LiHMDS/NBS at -78 °C led to the formation of bromide **18** in 83% yield. Treatment of **5** with equimolar amount of LiHMDS followed by the addition of bromide **18** at RT furnished the mixture of **6** and **7** in 47% yield (Eq 2). Finally, 1,2,3,4-tetrahydrocyclopenta[*b*]indole (**19**) was prepared as the substitute for tetrahydropyrroloindoles **5** and **8**. However, the reaction of **19** with LiHMDS/I_2 or KH/I_2 gave no expected dimerization product at all and most of the starting material **19** was recovered after the usual workup (Eq 3).



A plausible mechanism is therefore proposed based on the above mechanistic studies (Figure 4). The deprotonation of **8** by a strong base generates the anion **H** or its tautomer **I**, which affords the iodide **J** on reaction with iodine. The intermediate **J** then loses an iodide ion to give the carbocation **L** presumably driven by the nucleophilicity of the amide nitrogen. The coupling between **K** and **I** lead to the dimerization products **9** and/or **10**. Note that only a half equivalent of I_2 is required according to this mechanism, consistent with our experimental results in Table 1. The failure of **19** in dimerization can thus be attributed to the lack of driving force in the iodide elimination step (from **J** to **L**). Furthermore, the stereoselectivity of dimerization shown in Table 1 might be rationalized by **M1** or **M2** intermediacy shown in Figure 4. In the case of LiHMDS as the base, the lithium ion chelates to the carbonyl oxygen and the nitrogen atom. The coupling between **K** and **I** then adopts the conformations of least steric hindrance such as **M1** to give bisamidine **9**. On the other hand, in the case of KH as the base, the potassium ion coordinates to two carbonyl oxygen atoms in **K** and **I**, and thus the coupling proceeds via **M2**-like intermediacy to give **10**. The use of DMF as solvent destabilizes **M2** and therefore lowers the stereoselectivity, in excellent agreement with the experimental observation (entry 3, Table 1). The above mechanistic discussion might also shed light on the mechanisms of other I_2-mediated oxidative coupling reactions.[15]

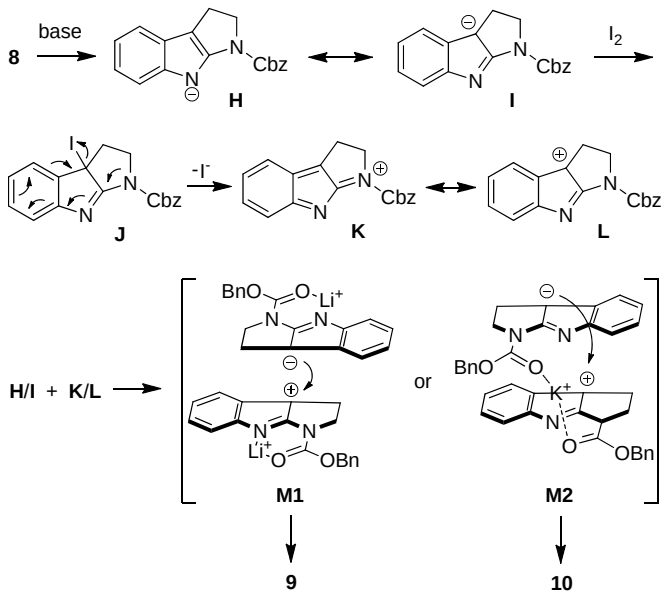


Figure 5. Proposed Mechanism for the dimerization of **8**.

In conclusion, we have successfully developed a new strategy, the oxidation–oxidation–reduction sequence, for the construction of 3a,3a'-bis(hexahydropyrrolo[2,3-*b*]indole) skeleton based on our hypothesis of the biosynthesis of chimonanthine. Our approach features the I_2-mediated, highly efficient oxidative dimerization of 1,2,3,8-tetrahydropyrrolo[2,3-*b*]indoles in a stereocontrolled manner, thus enabling the convenient synthesis of *meso*- and *rac*-chimonanthine, (+)-WIN 64821 and (+)-WIN 64745 in the highest overall yields to date. The key role of 1,2,3,8-tetraydropyrrolo-indoles demonstrated above also sheds light on the more challenging synthesis[22] of higher-order hexahydropyrroloindole alkaloids (such as hodgkinsine and quadrigemine C)[3] having the 3a,7'-connection, which is actively pursued in our laboratory.

Acknowledgements

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[16] CCDC references numbers 1012369 (**6**) and 1012368 (**7**).

[17] CCDC reference number 1012367.

[18] The reaction of **15** with LiHMDS/I_2 in THF at -40 ^{o}C also afforded **16**, but in a low yield (~ 40%). Apparently the effect of C2-ester moiety in **15** prevailed in controlling the stereoselectivity of dimerization.

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[20] Lera et al. synthesized **3** from **17** in 3 steps and the last step had to be performed at 180 ^{o}C (ref. 7a). Ishikawa et al. reported the one-step synthesis of **3** from the ethyl ester analog of **17** (ref. 11a). However, it was run at 230 ^{o}C under vacuum. Compared to their methods, our conditions are much milder (RT for both steps).

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