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Copper-Mediated Dimerization to Access 3a,3a′-Bispyrrolidinoindoline: Diastereoselective Synthesis of (+)-WIN 64821 and (−)-Ditryptophenaline

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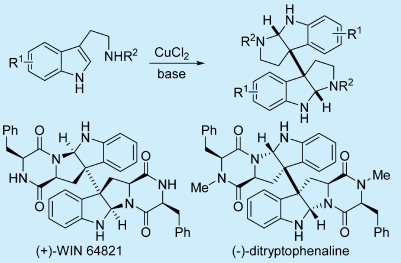
Supporting Information

ABSTRACT: A copper-mediated cyclization and dimerization of tryptamine or tryptophan was developed to generate a C_2-symmetry $C_3(sp^3)-C_3(sp^3)$ bridge with two contiguous stereogenic quaternary carbons in one step. Impressively, the ratio between exo and endo cyclization products varies when different protecting groups of Nb are utilized. This dimerization reaction could be conducted in gram scale. With this dimerization method, both endocyclotryptophan (+)-WIN 64821 and exocyclotryptophan (−)-ditryptophenaline were synthesized in 5 steps.



The 3a,3a′-bispyrrolidino[2,3-*b*]indoline structure is embedded as a core unit in larger members of the dimeric and oligomeric cyclotryptamine and cyclotryptophan alkaloid family (Figure 1). In this core, two contiguous stereogenic quaternary

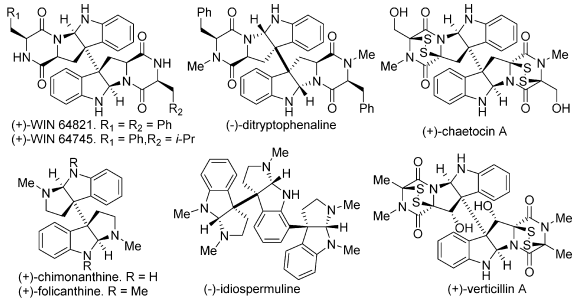


Figure 1. Structures of related 3a,3a′-bispyrrolidinoindoline natural products.

carbons are joined through either a *meso* or a C_2-symmetry $C_3(sp^3)-C_3(sp^3)$ bridge. The structural diversification of these compounds arises primarily from different configurations of the 3a,3a′-bispyrrolidinoindoline cores, the condensation of different amino acids with tryptophan, modification of the amide nitrogen, the construction of disulfide bridges, and the hydroxylation of the carbon framework. In addition to their diverse molecular architectures, these compounds exhibit various interesting biological activities. For instance, (+)-WIN 64821 and (−)-ditryptophenaline, two diketopiperazine dimers produced by an *Aspergillus* sp., are competitive antagonists to substance P at the human NK1 receptor.[1] In addition, (+)-11,11′-dideoxyverticillin A, isolated from a marine *Penicillium* sp., exhibits potent in vitro cytotoxicity against HCT-116 human colon carcinoma (IC_{50} = 30 ng/mL).[2] Furthermore, (+)-chaetocin, produced by *Chaetronium minutum*, is known to be a potent inhibitor of lysine-specific histone methyltransferases with antibacterial and cytostatic activities.[3] Finally, verticillin A, obtained from *Verticillium* sp., exhibits antimicrobial activity against Gram-positive bacteria and potent antitumor activity in HeLa cell lines.[4]

As a basic framework for these natural alkaloids, research on the synthesis of the 3a,3a′-bispyrrolidinoindoline core has received considerable attention. The most challenging aspect of the synthesis is the stereoselective construction of vicinal quaternary carbons.[5] Overman et al. have enantioselectively established the quaternary stereocenters using two intramolecular double Heck or dialkylation reactions.[6] Many similar protocols were also developed for the construction of vicinal all-carbon quaternary centers from the oxindole intermediate.[7] Movassaghi et al. developed a cobalt-mediated reductive homodimerization of 3a-bromopyrroloindolines that has been utilized by several groups to synthesize related 3a,3a′-bispyrrolidinoindoline alkaloids.[8] A similar transversion can also be mediated by Zn/Ni or Mn/Ni.[9] Movassaghi et al. also reported a different strategy for linked heterodimeric hexahydropyrroloindoles by diazene fragmentation.[10] Very recently, Kawasaki et al. described a thionium-based one-pot synthesis of homo-/heterodimeric pyrroloindoline from the protected tryptamine.[11] Methods that provided the target molecules by intramolecular carbamoylketene-alkene [2 + 2] cycloaddition,[12]

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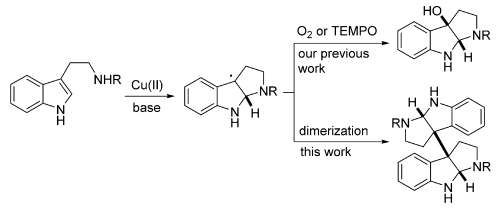
nucleophilic dimerization of 1-hydroxymelatonin,[13] photolysis of 3a-phenylselenylpyrroloindoline,[14] and the biomimetic oxidative coupling of submitted tryptamine/tryptophan derivatives have also been reported.[15] Despite these elegant achievements, the development of new methods for the efficient construction of vicinal quaternary carbon stereocenters still holds great importance in the total synthesis of the 3a,3a′-bispyrrolidinoindoline alkaloids.

In our previous studies, we developed a Cu-catalyzed intramolecular radical cyclization reaction to access 3-hydroxypyrroloindoline skeletons (Scheme 1).[16] The 3-hydroxyl group

Scheme 1. Copper-Mediated Radical Dimerization of Tryptamine Derivatives

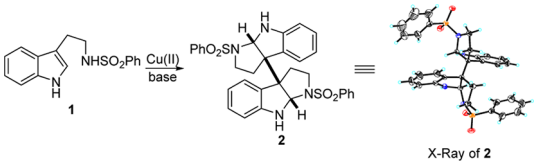


was introduced by trapping the C3 radical intermediate by O_2 or TEMPO, and the different configurations of the 3-hydroxypyrroloindoline skeletons were furnished by changing the Nb (the nitrogen of branched chain) protecting groups. As an extension of this work, we envisioned that the C3 radical intermediate might directly dimerize when these radical trapping reagents were absent (Scheme 1). Herein, we report this Cu-mediated radical dimerization to synthesize 3a,3a′-bispyrrolidinoindoline directly from tryptamine/tryptophan derivatives and demonstrate the efficiency of this method through the diastereoselective synthesis of (+)-WIN 64821 and (−)-ditryptophenaline.

In view of the previous report, we first treated tryptamine derivative **1** with 1.5 equiv of copper(II) chloride in the presence of 3 equiv of DBU under argon in CH_3CN (0.2 M) for 36 h. The racemic bispyrrolidinoindoline **2** was isolated in 16% yield (Table 1, entry 1). The relative configuration of isolated **2**, which has a C_2-symmetry $C_3(sp^3)$−$C_3(sp^3)$ bridge, was confirmed by X-ray crystallography. While optimizing the reaction conditions, we observed that dimer **2** could be isolated in 41% yield when the reaction was quenched after 2 h (Table 1, entry 2). We proposed that the product may be degraded under the conditions in our reaction system. To verify this hypothesis, we treated isolated **2** with $CuCl_2$ and DBU in CH_3CN under the same conditions used for the dimerization reaction. We observed that bispyrrolidinoindoline **2** decomposed slowly. To circumvent this problem, we surveyed the influence of the reaction temperature, concentration, time, and the amounts of oxidant and base. After various attempts, **2** was isolated in 70% yield under the optimized conditions (Table 1, entry 3). In an attempt to seek better reaction conditions, different oxidants (Table 1, entries 4−6) and bases (Table 1, entries 7−12) were examined, yet no further improvements were achieved.

With the optimized conditions established, the scope of this novel dimerization process was then explored by varying the substituents on the aromatic nucleus. When the substrate was substituted with a methyl group, the corresponding dimerization product **3** was isolated in fairly good yield (Scheme 2). In contrast, halogenated substrates gave smaller amounts of the desired products (Scheme 2, **4** and **5**). We reasoned that the

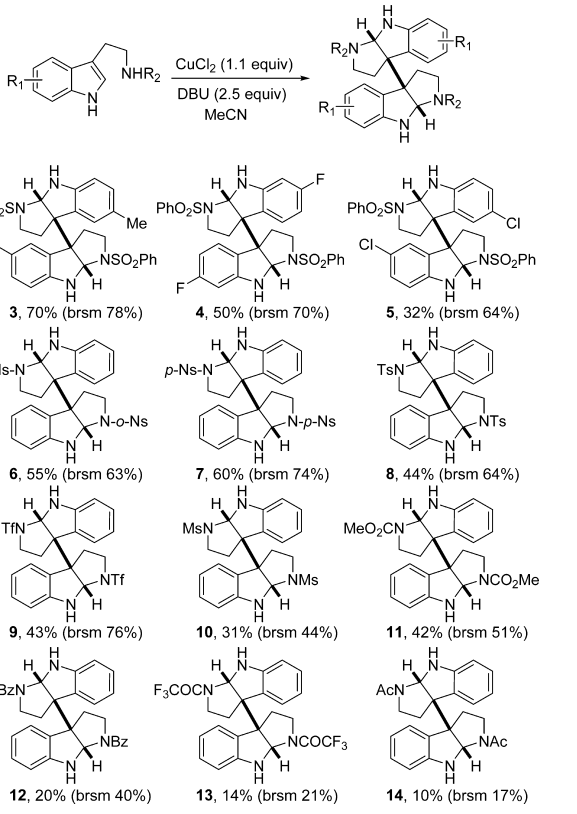
Table 1. Optimization Studies for Copper-Mediated Radical Dimerization to Synthesize 3a,3a′-Bispyrrolidinoindoline



entry[a]	oxidant (equiv)	base (equiv)	conv (%)	yield[e] (%)
1[b,c]	$CuCl_2$ (1.5)	DBU (3.0)	100	16
2[b,d]	$CuCl_2$ (1.5)	DBU (3.0)	67	41
3	$CuCl_2$ (1.1)	DBU (2.5)	86	70
4	$CuBr_2$ (1.1)	DBU (2.5)	78	25
5	$Cu(OAc)_2$ (1.1)	DBU (2.5)	52	11
6	$Cu(OTf)_2$ (1.1)	DBU (2.5)	78	16
7	$CuCl_2$ (1.1)	TMG (2.5)	35	21
8	$CuCl_2$ (1.1)	Et_3N (2.5)	–	trace
9	$CuCl_2$ (1.1)	NaH (2.5)	67	14
10	$CuCl_2$ (1.1)	*t*-BuOK (2.5)	74	45
11	$CuCl_2$ (1.1)	NaOH (2.5)	25	13
12	$CuCl_2$ (1.1)	Cs_2CO_3 (2.5)	–	trace

[a]General reaction conditions: **1** (0.30 mmol) reacted with the copper(II) and the base in CH_3CN (0.1 M) for 10 h at 0 °C. [b]The substrate concentration was 0.2 M, and the reaction temperature was 25 °C. [c]The reaction time was 36 h. [d]The reaction time was 2 h. [e]Isolated yield by column chromatography.

Scheme 2. Scope of Copper-Mediated Radical Dimerization



electron-withdrawing substituents of the aromatic moiety might affect the generation of the radical intermediate or decrease the lifetime of the radical, thus leading to low efficiency. Next, different protecting groups of tryptamine were examined. A large number of protecting groups were observed to initiate the

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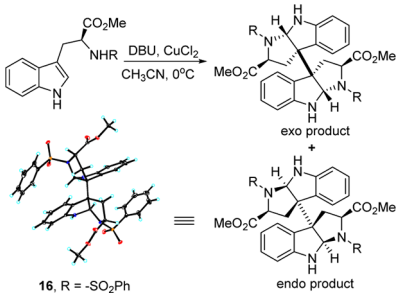
dimerization reaction under the standard conditions (Scheme 2, **6**–**14**), and the substrates with strong electron-withdrawing protecting groups proceeded better than those with weak electron-withdrawing groups. These results are attributable to the N-atom protected by a strong electron-withdrawing protecting group exhibiting a lower pK_a value and easier formation of the anion, which favor the formation of the cyclization 3-C radical immediate.

Inspired by the successful dimerization of various tryptamine derivatives, we used a variety of tryptophan derivatives with different protecting groups to investigate the diastereoselectivity of the this cyclization/dimerization sequence (Table 2). When

Table 2. Diastereoselective Dimerization of Different Nb-Protected Tryptophan Derivatives

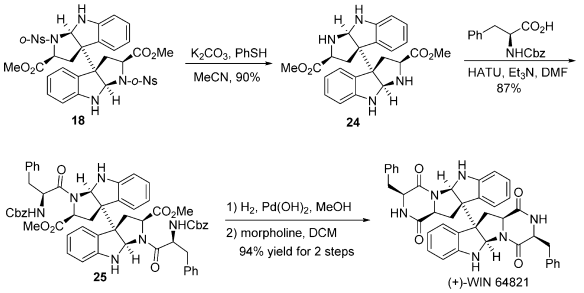


entry	R	ratio (exo/endo)	yield (%)	brsm (%)
1	SO_2Ph	**15**/**16** (1:2)	42	56
2	*o*-Ns	**17**/**18** (1:3)	37	55
3	Ts	**19**/**20** (1:1.3)	41	59
4	*p*-Ns	**21**/**22** (3:1)	47	63

Nb was protected with a benzenesulfonyl group, the reaction provided both the exo product **15** and the endo product **16** in a 1:2 ratio (Table 2, entry 1).[17] These two diastereoisomers could be easily separated by chromatography and were identified by ^{1}H NMR spectroscopy on the basis of the characteristic methyl ester resonance of both isomers.[18] The endo isomer **16** shows a remarkable upfield signal at a chemical shift of 3.1 ppm, and its absolute stereochemistry was unambiguously assigned by X-ray crystallography. In contrast, the exo isomer **15** shows a more common resonance at ∼3.6 ppm. The *o*-nitrobenzenesulfonyl and tosyl groups gave the same diastereoselectivity trend (exo/endo = 1:3 and 1:1.3, respectively) (Table 2, entries 2 and 3). To our delight, the diastereoselectivity trend of the reaction could be reversed when Nb was protected by a *p*-nitrobenzenesulfonyl group (exo/endo = 3:1) (Table 2, entry 4). We hypothesized that the dominant controlling factors for the different selectivity are steric hindrance and the stability of the radical intermediate.

Given the high efficiency and the interesting diastereoselectivity of this cyclization/dimerization sequence, we then turned to the stereoselective synthesis of endocyclotryptophan (+)-WIN 64821 and exocyclotryptophan (−)-ditryptophenaline. In the past decades, considerable efforts have been directed toward synthetic studies of these two alkaloids because of their interesting biological activities and spectacular structure.[6f,8d−f,9b,15e−g,19] Guided by our studies on the diastereoselectivity of the reaction, the synthesis of endocyclotryptophan (+)-WIN 64821 commenced with the *o*-nitrobenzenesulfonyl-protected dimer **18** (Scheme 3). The *o*-nitrobenzenesulfonyl-protected groups were then deprotected under Fukuyama's deprotection conditions, which utilized thiophenol and potassium carbonate in CH_3CN at rt, with a 90% yield.[20] Next,

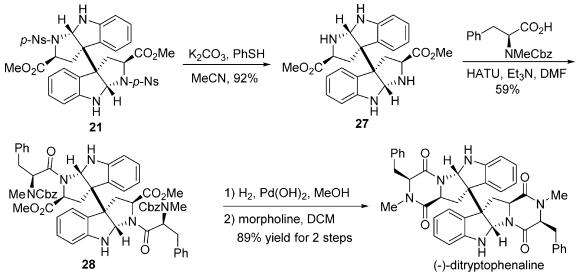
Scheme 3. Total Synthesis of (+)-WIN 64821



the deprotected intermediate **24** was condensed with *N*-Cbz-L-phenylalanine in the presence of HATU and Et_3N in DMF to give the tetrapeptide **25** in 87% yield.[8e,f,21] The *N*-Cbz protecting groups were hydrogenated by $Pd(OH)_2$ in MeOH providing the diamine. Instead of heating to 180 °C,[8e,22] the ring closure was efficiently effected by directly stirring the crude diamine in CH_2Cl_2/morpholine (10:1)[8d] at rt to afford (+)-WIN 64821 (94% in 2 steps).

The synthesis of exocyclotryptophan (−)-ditryptophenaline was performed using similar procedures (Scheme 4). The *p*-

Scheme 4. Total Synthesis of (−)-Ditryptophenaline



nitrobenzenesulfonyl groups of dimer **21** were also deprotected under Fukuyama's deprotection conditions with a 92% yield. However, the coupling of the deprotected intermediate **27** with *N*-Cbz-methyl-L-phenylalanine under the established conditions gave the desired tetrapeptide **28** only in moderate yield (59%). Then catalytic hydrogenolysis of the *N*-Cbz and subsequent ester−amine exchange delivered (−)-ditryptophenaline in good yield (89% in 2 steps).

In conclusion, we have developed a novel, efficient method of constructing 3a,3a′-bispyrrolidinoindoline through a Cu-mediated radical dimerization process from a wide range of readily available tryptamine derivatives. This method holds great potential for syntheses of natural products and drugs that incorporate the dimer 3a,3a′-bispyrrolidinoindoline. Importantly, this reaction enables the stereoselective synthesis of the endo and exo 3a,3a′-bispyrrolidinoindoline skeletons that exist in nature via simply changing the Nb protecting groups, which has not been previously accomplished. The dimerization reacion could be performed in gram scale. The efficiency and utility of the method was further demonstrated by the diastereoselective synthesis of (+)-WIN 64821 and (−)-ditryptophenaline.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and compound characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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