Communication

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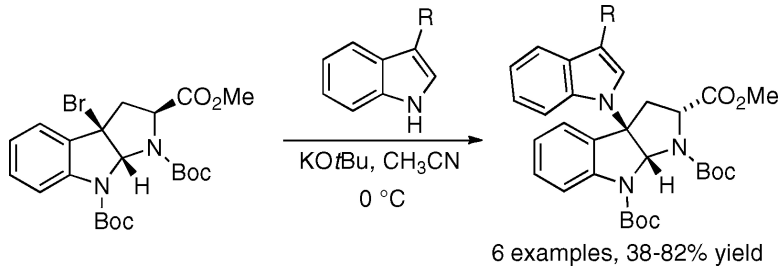

6 examples, 38-82% yield

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An Expeditious Synthesis of C(3)−N(1′) Heterodimeric Indolines

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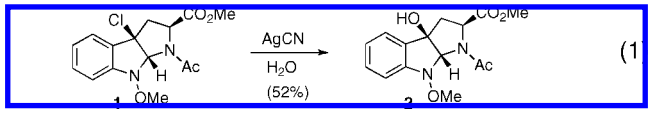
Although the synthesis of C(3)−C(3′) tryptophan dimers has received a substantial amount of attention from the synthetic community, much less attention has focused on related C(3)−N(1′) dimers.[1−3] This lack of attention comes in spite of the fact that C(3)−N(1′) dimers are present in a number of structurally and biologically interesting natural products including the antiangiogenesis agent chaetomin[4] and the cytotoxic cyclic peptides of the kapakahine family (Figure 1).[5] From an interest in finding a concise route to these natural products, we disclose here that readily available bromopyrroloindolines undergo anionic coupling reactions with indole nucleophiles to give the corresponding heterodimers.

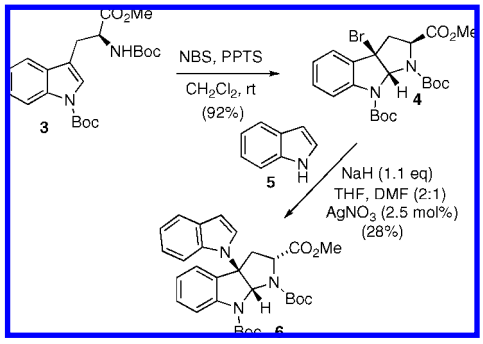
Our plan to use 3-bromopyrroloindolines as precursors to C(3)−N(1′) heterodimers was inspired by reports from a number of other laboratories describing the use of bromo-, chloro-, and selenopyrroloindolines as precursors to the formation of C−C and C−O bonds.[6] We were particularly drawn to work from Somei's laboratory that outlined the generation of 3-hydroxy pyrroloindoline **2** from the coupling of chloropyrroloindoline **1** with water in the presence of AgCN (eq 1).[7]



We chose to initially examine reaction conditions related to those outlined above and synthesized bis-Boc-protected bromopyrroloindoline **4** from bis-Boc-tryptophan **3** as shown.[8] In our initial experiment, we were pleased to isolate heterodimer **6** in 28% yield as a single diastereomer from the reaction of **4** with the sodium salt of indole in the presence of a catalytic amount of $AgNO_3$ (Scheme 1). Interestingly, in addition to the construction of the desired C(3)−N(1′) bond, the methyl ester had epimerized from the exo-position in **4** to the thermodynamically more favorable endo-position in **6**.[9] The relative connectivity and stereochemistry of **6** was characterized spectroscopically using extensive 1D and 2D NMR experiments.[10]

While the generation of **6** from **4** was encouraging, we recognized that the 28% yield needed to be improved in order for the reaction to

Scheme 1. C(3)−N(1′) Heterodimeric Indoline Formation



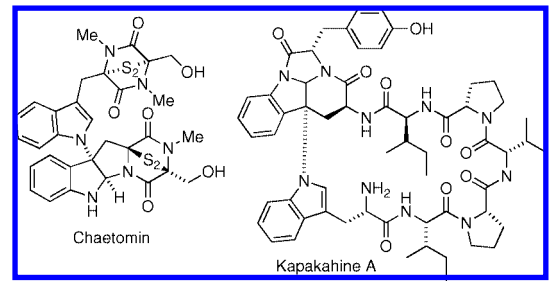
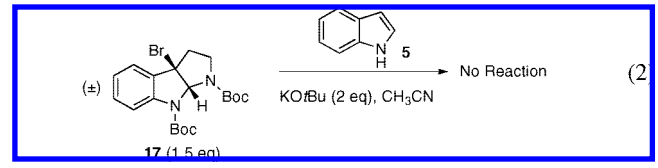


Figure 1. C(3)−N(1′) heterodimeric tryptophan natural products.

be of use to us synthetically. Thus, as outlined in Table 1, we examined the effect of base, nucleophile, and solvent on the reaction. Surprisingly, the reaction did not require the use of $AgNO_3$ (entries 2−7), implying that it does not proceed through the expected benzylic cation intermediate. In addition, the temperature and the solvent had an impact on the yield and the endo:exo ratio. As far as solvent was concerned, the yield increased when HMPA or a mixture of HMPA and DMF was used (entries 2 and 5). Unfortunately, these improvements were accompanied by the generation of a mixture of endo and exo esters. It turns out that the reaction does not require either NaH or HMPA; lower yields with respect to the HMPA, and DMF reactions but higher diastereoselectivities were observed with KO*t*Bu and CH_3CN (entries 3, 4, 6, and 7). For the temperature, the diastereoselectivity was enhanced but at the expense of yield when the temperature was kept at 0 °C (entries 3, 6, and 7). Finally, the reaction was not restricted to unsubstituted indole: skatole **7** and *N*-Boc-tryptamine derivative **8** gave heterodimers **9** and **10**, respectively (entries 5−7).

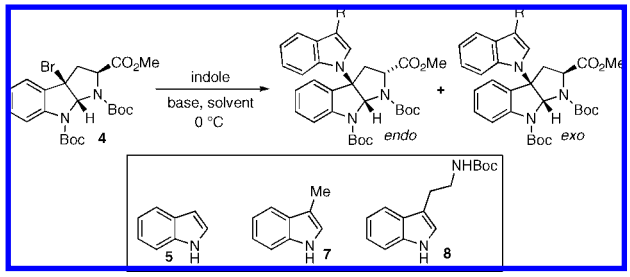
Concerned about the possible decomposition of **4** under the reaction conditions,[11] we examined the effect of excess **4** on the yield of the reaction and found the effect to be significant. In our best conditions to date, we utilized 1.5 equiv of **4** and 2 equiv of KO*t*Bu to give the corresponding heterodimers in yields that ranged from 38 to 82% (Table 2). Included among the substrates employed in these studies were tryptophan and tryptamine derivatives **8**, **11**, and **13** to give heterodimers **10**, **14**, and **16**, respectively (entries 5, 6, and 8). Of particular note was the generation of heterodimer **15** in 76% yield when diketopiperazine **12** was coupled with **4** (entry 7). That chaetomin's skeleton is closely related to **15** speaks to the potential utility of this reaction.

Interestingly, when tryptamine-derived bromopyrroloindoline **17** was exposed to the conditions that were successful for tryptophan derivative **4**, no heterodimer was observed, illustrating the importance of the methyl ester (eq 2).



10.1021/ja8061908 CCC: $40.75

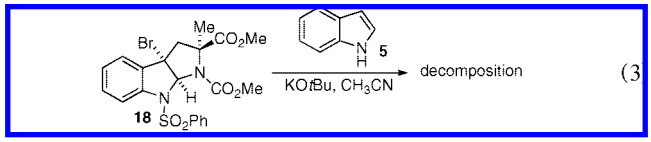
Table 1. Synthesis of C(3)−N(1′) Dimers



entry	indole (equiv)	base (equiv)	solvent	dimer	yield (%)	*endo*:*exo*
1	**5**(1.2)	NaH (1.1)[a]	THF:DMF (2:1)	**6**	28	>95:5
2	**5**(2.0)	NaH (1.75)	HMPA[b]	**6**	63	3:1
3	**5**(1.5)	KO*t*Bu (1.2)	CH_3CN	**6**	43	13:1
4	**5**(1.5)	KO*t*Bu (1.2)	CH_3CN[b]	**6**	47	5:1
5	**7**(1.5)	NaH (1.4)	DMF:HMPA (5:1)[b]	**9**	59	4:1
6	**7**(1.5)	KO*t*Bu (1.2)	CH_3CN	**9**	43	11:1
7	**8**(1.3)	KO*t*Bu (2.0)	CH_3CN	**10**	26	>95:5

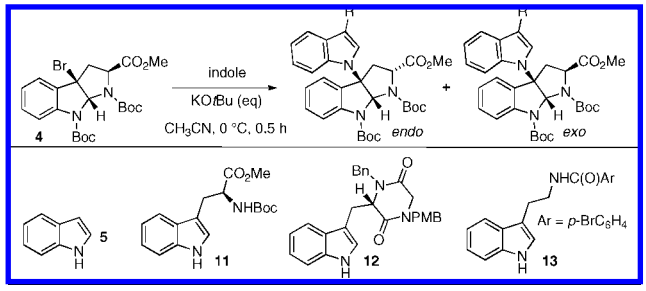
[a] $AgNO_3$ (2.5 mol %) was used as an additive. [b] Reaction mixture was allowed to warm to room temperature.

In an attempt to further define the role of the ester, we synthesized alkylated bromopyrroloindoline **18** and subjected it to indole and KO*t*Bu (eq 3).[12] Telling was that no heterodimer formed and, in addition to recovered starting material, only the decomposition of **18** was observed.



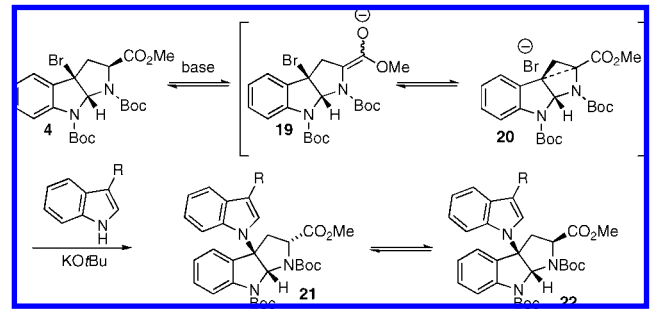
While speculative at this juncture, the mechanism outlined in Scheme 2 is consistent with the experiments that have been outlined above. It is clear that the ability to access enolate **19** from **4** is critical. That is, with substrates lacking an ester (e.g., **17**) or under conditions in which deprotonation cannot occur (eq 3), no coupling reaction was observed. We propose that the importance of the enolate is related to its ability to assist the bromide in leaving via a transiently formed

Table 2. The Synthesis of C(3)-N(1′) Dimers



entry	**4** (equiv)	indole	KO*t*Bu (equiv)	dimer	yield (%)	*endo*:*exo*
1	2	**5**	2	**6**	82	7:1
2	1.5	**5**	2	**6**	79	5:1
3	1.5	**5**	1.5	**6**	64	10:1
4	1.5	**7**	2	**9**	81	3:1
5	1.5	**11**	2	**14**	38	>95:5
6	1.5	**8**	2	**10**	48	>95:5
7	1.5	**12**	2	**15**	76	5:1
8	1.5	**13**	2	**16**	78	>95:5

Scheme 2. Mechanistic Hypothesis for Heterodimer Formation



cyclopropane (e.g., **20**).[13] Coupling of the nucleophile with **20** results in endo isomer **21** after kinetic protonation. Equilibration leads to the exo isomer **22**.

In summary, this communication has described a unique and facile entry into the C(3)−N(1′) bond of dimeric indolines. We intend to continue to optimize the reaction and to examine its scope while also targeting heterodimeric indoline natural products.

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

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(2) To the best of our knowledge, there have been two syntheses of C(3)−N(1′) heterodimers and both were focused on psychotrimine. See: (a) Matsuda, Y.; Kitajima, M.; Takayama, H. *Org. Lett.* **2008**, *10*, 125. (b) Newhouse, T.; Baran, P. S. *J. Am. Chem. Soc.* **2008**, *130*, 10886–10887.
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(10) We also attempted to chemically modify *endo*-**6**. These experiments included a failed attempt to convert **6** into the corresponding tosylated indole, the successful generation of a C(3′) thioether derivative, and the generation of a camphorsulfonamide analogue of **6**. See Supporting Information.
(11) We did not recover bromoindoline **4** from the reactions of Table 1.
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