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Total Synthesis of (±)-Trigonoliimine C via Oxidative Rearrangement of an Unsymmetrical Bis-Tryptamine

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S Supporting Information

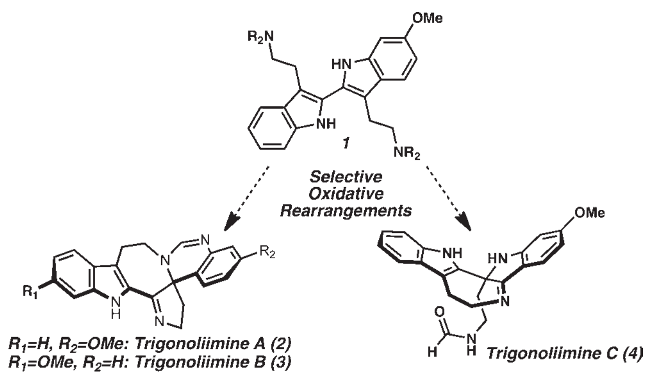
ABSTRACT: We report the first total synthesis of (±)-trigonoliimine C, a member of a family of structurally complex alkaloids, in 10 steps from tryptamine and 6-methoxytryptamine. Our convergent synthetic strategy relies on a selective oxidative rearrangement of an unsymmetrical 2,2′-bis-tryptamine.

Alkaloids with oxidatively rearranged indole substructures are abundant in nature.[1] These unique molecular architectures present synthetic challenges for chemists and inspire the development of new methods.[2] The trigonoliimines are a family of alkaloids isolated in 2010 that exemplify the structural intrigue presented by oxidatively rearranged indole systems.[3] These natural products possess unprecedented polycyclic structures that appear to arise from the union of two heteroaromatic subunits. In addition to reporting the anti-HIV-1 activity of the trigonoliimines in the original isolation paper, Hao and co-workers proposed a biosynthesis that commenced with the coupling of tryptamine and kynuramine.[4] We envisioned an alternative biogenetic origin that exploits the latent symmetry of these alkaloids and may be relevant to the biosynthesis of many other indole natural products (Scheme 1). This hypothesis involves an oxidative aryl−aryl coupling of two tryptamine derivatives to generate unsymmetrical 2,2′-binary tryptamine **1**, which is converted to trigonoliimine scaffolds **2**−**4** through a series of selective oxidative rearrangements.[5]

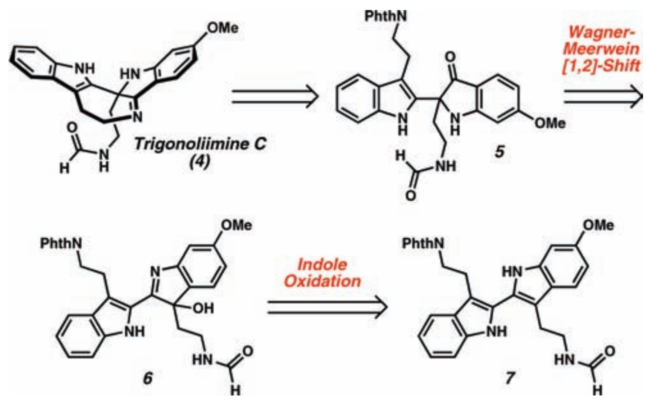
In this communication, we describe a concise and convergent total synthesis of (±)-trigonoliimine C (**4**) that is guided by our new biosynthetic hypothesis for this family of natural products. We have developed unprecedented selective methods to oxidatively functionalize either indole ring system in unsymmetrical conjugated bis-indoles. Given the prevalence of alkaloids that can conceptually arise from the selective mono-oxidation and rearrangement of unsymmetrical conjugated binary indole systems,[1,2] our strategy may provide a general route to complex natural product architectures that possess this element of structural symmetry.

Our retrosynthetic analysis for trigonoliimine C was based on the assumption that bis-indole **7** could be converted selectively to mono-oxidized hydroxyindolenine **6**, followed by a Wagner−Meerwein [1,2]-shift[6] to generate indoxyl **5** (Scheme 2). While the tandem indole oxidation/Wagner−Meerwein [1,2]-shift is a well-established method in alkaloid synthesis for constructing oxindoles,[7] the selective generation of indoxyl products is less developed.[8] Moreover, we were interested in employing this

Scheme 1. Alternative Biosynthetic Hypothesis for the Trigonoliimines



Scheme 2. Symmetry-Guided Retrosynthetic Analysis of Trigonoliimine C (4)



strategy for the conversion of a 2,2′-binary indole such as **7** into sterically congested, indole-substituted indoxyl **5**. This rearrangement process would address the major synthetic challenges of this alkaloid, which include the dense polycyclic scaffold and the fully substituted tertiary carbinamine stereocenter.

To test the feasibility of our synthetic strategy for trigonoliimine C, we explored the oxidative rearrangement of model 2,2′-indole dimer **9** (Scheme 3). Phthalimide protected tryptamine **8** was subjected to a two-step metal-free oxidative coupling protocol to

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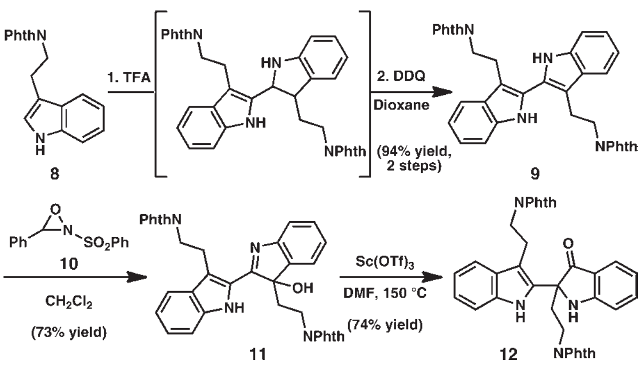
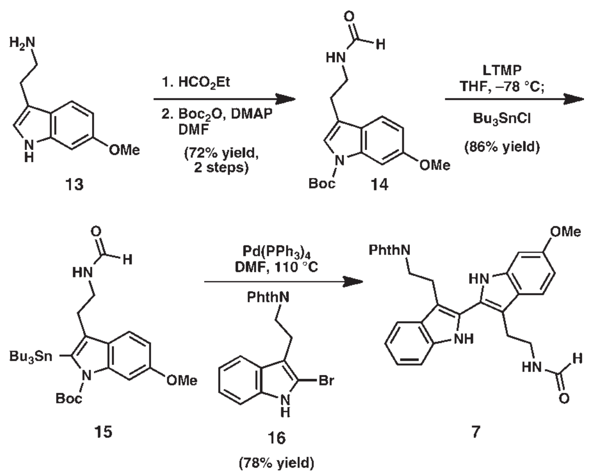
generate dimer **9**,[9] which was treated with oxaziridine **10**[10] to yield mono-oxidized hydroxyindolenine **11**. In the presence of $Sc(OTf)_3$ and dimethylformamide as solvent, hydroxyindolenine **11** was converted selectively to indoxyl **12**.[11] The efficient synthesis of indoxyl **12** bode well for our retrosynthetic strategy of trigonoliimine C, given its similarity to the proposed indoxyl intermediate **5**.

Motivated by the success of our model studies in the generation of indoxyl **12**, we commenced our synthesis of trigonoliimine C

Scheme 3. Synthesis of Model Indoxyl 12



Scheme 4. Assembly of Unsymmetrical Binary Tryptamine 7

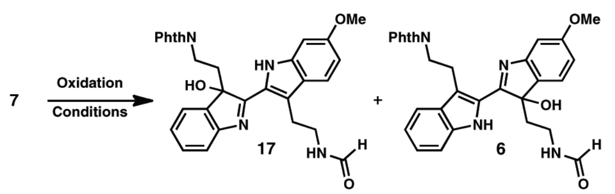


with the convergent assembly of unsymmetrical bis-indole **7** (Scheme 4). Boc-protected tryptamine **14** was constructed in a short series of steps from 6-methoxytryptamine **13**. This intermediate was then subjected to a Boc-directed lithiation/stannylation sequence, which resulted in the formation of stannylindole **15**. Bis-indole **7** was synthesized in good yield under Stille cross-coupling conditions between stannylindole **15** and bromoindole **16**, which was assembled from tryptamine in two steps. Interestingly, formation of the C2-bis-indole linkage was accompanied by concomitant cleavage of the Boc directing group to unveil the deprotected binary tryptamine **7**.

Once we had access to bis-indole **7**, we attempted several mono-oxidation reactions with the expectation that the electron-rich 6-methoxyindole system would be oxidized preferentially over the indole system (**6** vs **17**, Table 1). To our surprise, exposure of unsymmetrical bis-indole **7** to a diverse set of oxidants led to the formation of the undesired mono-oxidation product **17** as the major product (e.g., entries 1–3).[12] For example, in the presence of oxaziridine **10**, which was utilized in our model studies, the undesired hydroxyindolenine **17** was generated in a ratio of 6:1 (entry 2). We also observed that certain oxidation protocols formed both hydroxyindolenines **6** and **17** in approximately equimolar amounts (entries 4–7). We were particularly intrigued by the facile mono-oxidation of **7** under an atmosphere of O_2 (entry 6) and even ambient air (entry 7). Gratifyingly, after considerable experimentation we discovered that iodine(III) reagents such as $PhI(OAc)_2$ and $PhI(TFA)_2$ preferentially produced the desired hydroxyindolenine **6** (entries 8 and 9). The favorable oxidation of the methoxy-substituted indole system was attributed to the formation of covalent adduct **18**, which would be susceptible to intermolecular nucleophilic attack by a molecule of water.[13] While several attempts were made to realize an enantioselective mono-oxidation of unsymmetrical bis-tryptamine **7** with chiral iodine(III) reagents, the addition of water at C3 of the methoxyindole system, which is remote to the chiral framework of the oxidant, resulted in little to no enantioselectivity.[14,15] Nevertheless, we now had methods to selectively mono-oxidize either the electron-poor (entry 2) or electron-rich (entry 9) aromatic system of an unsymmetrical conjugated binary indole.

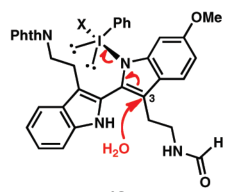
With a selective synthesis of hydroxyindolenine **6** in hand, we explored its rearrangement under the conditions developed for

Table 1. Selective Oxidation of Unsymmetrical Binary Tryptamine 7



(structures were confirmed by X-ray)

Entry	Conditions[a]	Yield (%)	17 : 6[b]
1	Oxone, H_2O, Acetone	57	7 : 1
2	10, CH_2Cl_2, 0 °C	89	6 : 1
3	*m*-CPBA, CH_2Cl_2	48	2.2 : 1
4	OsO_4, NMO, THF	71	1.2 : 1
5	TPAP, NMO, THF	54	1 : 1.4
6	O_2, CH_2Cl_2, 12 h	65	1 : 1.1
7	Air, CH_2Cl_2, 30 h	41	1.6 : 1
8	$PhI(OAc)_2$, MeCN, H_2O, 0 °C	57	1 : 3
9	$PhI(TFA)_2$, MeCN, H_2O, 0 °C	67	1 : 13



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[a] Unless stated otherwise, reaction times were 30 min.
[b] Ratio of products were determined by NMR and HPLC.

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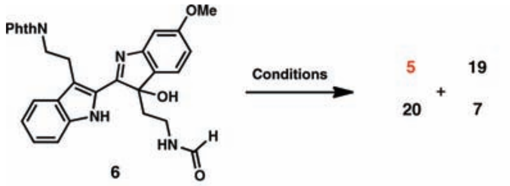
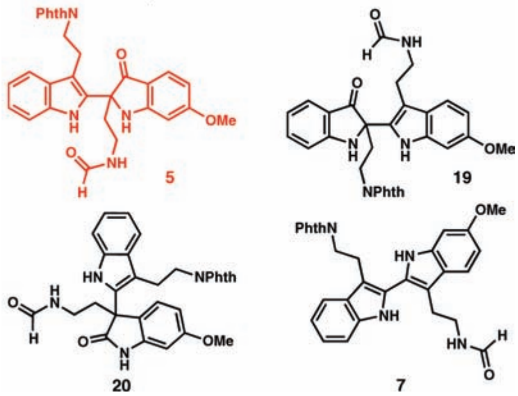
Table 2. Selective Wagner−Meerwein [1,2]-Shift To Generate Indoxyl 5



Entry	Conditions for 1,2 Shift	5:19:20:7[a,b]
1	$Sc(OTf)_3$, DMF, 150 °C, 4 h	0:100:0:0
2	HCO_2H, PhMe, 110 °C, 12 h	10:0:60:30
3	HCO_2H, DMF, 150 °C, 12 h	0:0:0:100
4	HCl (4M in Dioxane), DMF, 110 °C, 12 h	25:40:0:25
5	HCl (4M in Dioxane), DMF, 150 °C, 1 h	64:6:0:30
6	HCl (4M Dioxane), wet DMA, 150 °C, 30 min	100:0:0:0 (56% yield)[c]

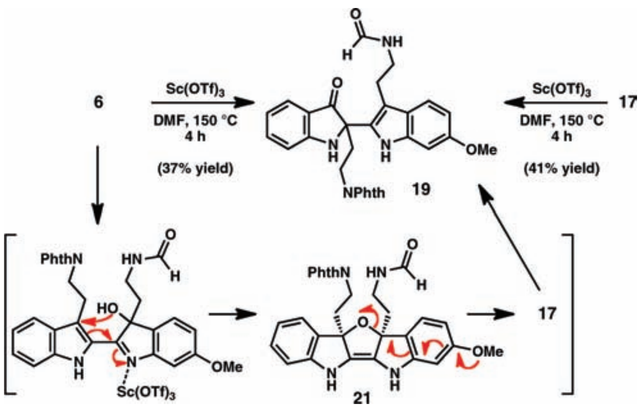
[a] All reactions proceeded to 100% conversion.
[b] Ratio of products were determined by NMR.
[c] Isolated yield.



the rearrangement of model hydroxyindolenine **11** (Table 2). Unexpectedly, exposure to $Sc(OTf)_3$ in dimethylformamide did not yield the desired indoxyl **5**. Instead, the isomeric indoxyl **19** was formed (entry 1), presumably through a transfer of the hydroxyl functionality from the 6-methoxyindole fragment to the unfuctionalized indole fragment via the putative dihydrofuran intermediate **21** (Scheme 5).[16,17] Although this hydroxyl migration may have also occurred in our model studies (Scheme 3), it was inconsequential for pseudosymmetric hydroxyindolenine **11**. Unfortunately, the formation of the undesired indoxyl **19** was deleterious for our efforts to synthesize trigonoliimine C, since we could not determine a straightforward method to convert this unexpected indoxyl into the indole natural product. In addition, subjection of hydroxyindolenine **17** to these reaction conditions resulted in the same indoxyl product **19**, without any hydroxyl migration (Scheme 5).

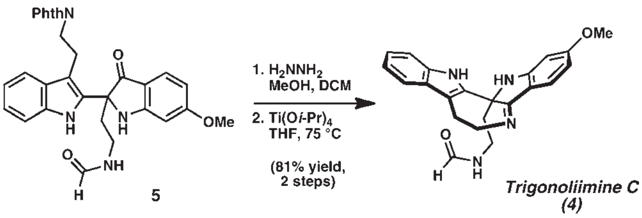
While the $Sc(OTf)_3$ mediated conditions did not generate the desired rearrangement product, Brønsted acids proved to be more promising. For example, a small amount of the desired indoxyl **5** was generated in the presence of HCO_2H and PhMe as solvent, with considerable formation of undesired and thermodynamically more stable oxindole **20** (entry 2). Unfortunately, the use of HCO_2H also yielded large amounts of reduced bis-indole **7** (entries 2−3), which most likely formed by formic acid reduction of hydroxyindolenine **6**.[18] The use of Brønsted acids that are not hydride sources, such as HCl, improved the efficiency of indoxyl formation (entries 4−5), but considerable amounts of bis-indole **7** were still generated, presumably by decomposition of dimethylformamide to HCO_2H.[19] Fortunately, by simply switching to dimethylacetamide as solvent, we eliminated the formation of HCO_2H and exclusively formed the desired indoxyl **5** (entry 6).

Scheme 5. Unexpected Hydroxyl Migration between Indole Systems



To complete the synthesis of trigonoliimine C, we examined numerous methods to assemble the strained seven-membered Schiff base of the natural product. While most conditions for intramolecular imine formation were unsuccessful, eventually we discovered that deprotection of the phtahlimide group and subsequent $Ti(Oi\text{-}Pr)_4$ mediated cyclization efficiently converted intermediate **5** into (±)-trigonoliimine C (Scheme 6). The spectroscopic data obtained for our synthetic sample of **4** were identical with the data reported by Hao in the original isolation paper.

Scheme 6. Total Synthesis of (±)-Trigonoliimine C (4)



In conclusion, we have developed the first convergent total synthesis of the alkaloid (±)-trigonoliimine C in 10 steps from tryptamine and 6-methoxytryptamine. Our strategy relies on a selective mono-oxidation of 2,2′-bis-tryptamine **7**, followed by a Wagner−Meerwein [1,2]-shift to indoxyl **5**. We have discovered methods to oxidize either the electron-poor or electron-rich indole system in an unsymmetrical conjugated binary indole, which may have a broader impact for the construction of other structurally complex indole alkaloids. The application of this strategy to the other trigonoliimines, the synthesis of unnatural analogs, and the exploration of biological activity for these alkaloids are ongoing interests in our group.

■ ASSOCIATED CONTENT

Supporting Information. Complete experimental procedures and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) The structures of isomers **6** and **17** were confirmed by X-ray crystallography. See Supporting Information.

(13) When we subjected bis-phthalyl protected unsymmetrical 6-MeO 2,2′-bis-tryptamine to the optimized oxidation conditions (Table 1, entry 9), the electron-rich indole ring was still oxidized preferentially (albeit in a diminished ratio of 4:1). This suggests that both the methoxy substituent and the formamide influence the high selectivity during mono-oxidation of **7**. See Supporting Information for details.

(14) See Supporting Information for details of our attempts to use chiral iodine(III) reagents in the enantioselective mono-oxidation of bis-tryptamine **7**. While enantioselective iodine(III) mediated additions of intramolecular nucleophiles have been reported, difficulties associated with enantioselective iodine(III)-mediated additions of intermolecular nucleophiles such as water persist: Quideau, S.; Lyvinec, G.; Marguerit, M.; Bathany, K.; Ozanne-Beaudenon, A.; Buffeteau, T.; Cavagnat, D.; Chénedé, A. *Angew. Chem., Int. Ed.* **2009**, *48*, 4605–4609.

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(16) The assigned structures of **5**, **19**, and **20** were supported by detailed NMR analysis. See Supporting Information for details.

(17) The selective conversion of dihydrofuran **21** into indoxyl **19** may be due to the resonance-stabilized electron donation of the methoxy group, which dictates the fragmentation depicted in Scheme 5.

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