

# Rapid Total Synthesis of (±)Trigonoliimine A via a Strecker/ Houben–Hoesch Sequence

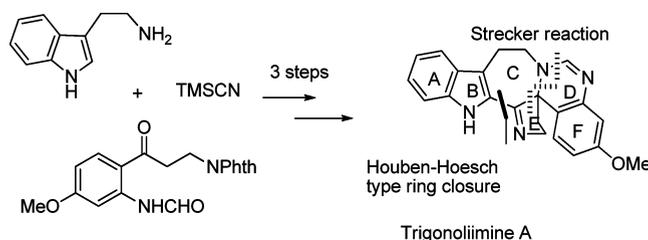
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## ABSTRACT



A novel synthetic route to the hexacyclic system of trigonoliimine A was accomplished in four steps from *N*-phthaloyl 6-OMe-tryptamine. Key reactions include a three-component Strecker-type reaction to fashion the two C–N bonds in the D ring and a subsequent Houben–Hoesch type cyclization to deliver the characteristic seven-membered C ring.

In 2010, our group reported the isolation and structural elucidation of trigonoliimines A–C (**1–3**, Figure 1) from the extract of the leaves of *Trigonostemon. lii* Y. T. Chang collected in the Yunnan Province of China.<sup>1</sup> Notably, among these three indole alkaloids, trigonoliimine A showed modest anti-HIV-1 activity ( $EC_{50} = 0.95 \mu\text{g/mL}$ ,  $TI = 7.9$ ).

Their unusual structures, in particular the unprecedented polycyclic systems, and interesting bioactive properties, attracted the attention of several synthetic research groups.<sup>2,3</sup> Methodologies for construction of the skeletons of trigonoliimines alkaloids were first inspired by the hypothesis of the oxidative rearrangement biosynthesis of some natural bisindoles.<sup>4</sup> With a near-biosynthetic view

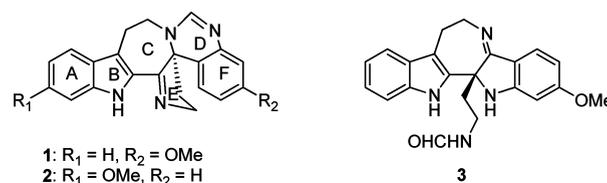


Figure 1. Trigonoliimines A–C (**1–3**).

in mind, Movassaghi et al.,<sup>2a</sup> Tambar et al.,<sup>2b</sup> and our group<sup>2c</sup> published respective synthetic studies of these molecules in 2011.

While the elegance and power of a biomimetic synthesis strategy had been fully demonstrated, a synthesis strategy was further developed by careful retrosynthetic analysis<sup>3</sup> which might suggest an alternative for library synthesis of trigonoliimines alkaloids and their analogues: Shi and co-workers<sup>3a</sup> detailed their synthetic approach to demethoxytrigonoliimine A/B (**4**) which represents the common framework in both trigonoliimines A and B. And, Zhu's group reported a concise synthesis of trigonoliimine B which was highlighted by using the Bischler–Napieralski

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(1) Tan, C. J.; Di, Y. T.; Wang, Y. H.; Zhang, Y.; Si, Y. K.; Zhang, Q.; Gao, S.; Hu, X. J.; Fang, X.; Li, S. F.; Hao, X. J. *Org. Lett.* **2010**, *12*, 2370.

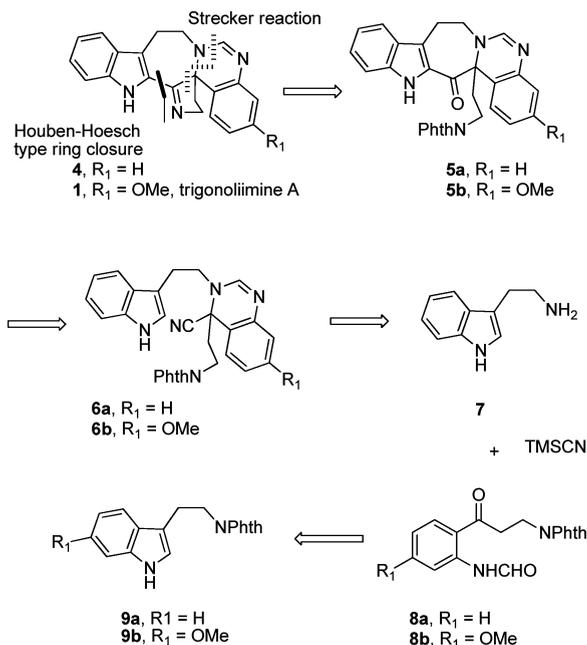
(2) (a) Han, S.; Movassaghi, M. *J. Am. Chem. Soc.* **2011**, *133*, 10768. (b) Qi, X.; Bao, H.; Tambar, U. K. *J. Am. Chem. Soc.* **2011**, *133*, 10050. (c) Liu, S.; Hao, X. J. *Tetrahedron Lett.* **2011**, *52*, 5640.

(3) (a) Feng, P.; Fan, Y.; Xue, F.; Liu, W.; Li, S.; Shi, Y. *Org. Lett.* **2011**, *13*, 5827–5829. (b) Buyck, T.; Wang, Q.; Zhu, J. P. *Org. Lett.* **2012**, *14*, 1338–1341. (c) Qiu, J.; Zhang, J. X.; Liu, S.; Hao, X. J. *Tetrahedron Lett.* **2013**, *54*, 300.

(4) Schmidt, M. A.; Movassaghi, M. *Synlett* **2008**, 313.

reaction to access the seven-membered C ring.<sup>3b</sup> Very recently, we also reported a modified approach to skeleton **4** and succeeded in shortening the synthesis to six steps, however, with a relatively low yield at the final stage.<sup>3c</sup>

**Scheme 1.** Retrosynthetic Analysis of Trigonoliimine A (**1**) and Demethoxytrigonoliimine A/B (**4**)

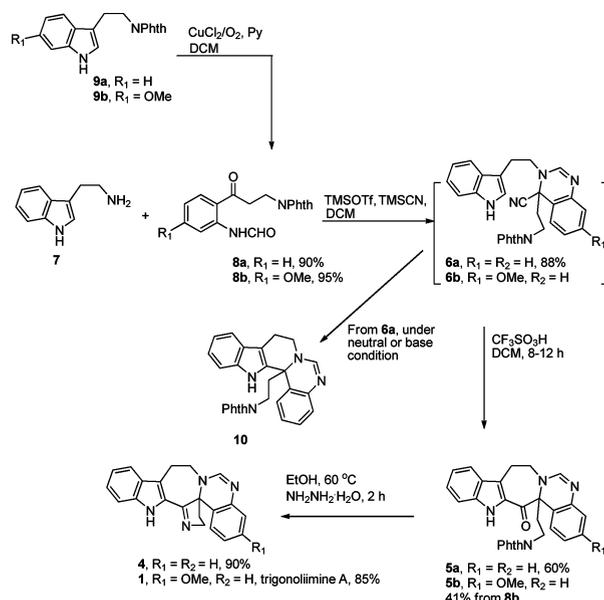


In this paper, we would like to describe a short, practical, and efficient synthesis route to both trigonoliimine A (**1**) and demethoxytrigonoliimine A/B (**4**). Scheme 1 depicts our retrosynthetic strategy. In a straightforward manner, we planned to select the Houben–Hoesch cyclization reaction to close the unusual seven-membered ring in the hexacyclic system because their precursor **6a–b** might be rapidly assembled by a Strecker-type reaction using tryptamine **7** or ketone **8a** or **8b** which could be easily produced through the oxidation of the corresponding *N*-phthaloyl protected tryptamine **9a** or **9b** and TMSCN. The most significant and challenging step in our plan was considered to be the three-component Strecker-type reaction, since most one-pot multicomponent variations of the Strecker reaction involve aldehydes, and the Strecker synthesis applied to ketones and aliphatic amines remains a more difficult reaction. Quite often, with these substrates, the reaction is carried out stepwise using pre-made imines<sup>5</sup> or under high pressure conditions.<sup>6</sup> Although risky, if realized, it would allow us to discover the shortest route to trigonoliimines alkaloids and their analogues.

(5) (a) Warmuth, R.; Munsch, T. E.; Stalker, R. A.; Li, B.; Beatty, A. *Tetrahedron* **2001**, *57*, 6383. (b) Surendra, K.; Krishnaveni, N. S.; Mahesh, A.; Rao, K. R. *J. Org. Chem.* **2006**, *71*, 2532.

(6) (a) Jenner, G.; Salem, R. B.; Kim, J. C.; Matsumoto, K. *Tetrahedron Lett.* **2003**, *44*, 447. (b) Matsumoto, K.; Kim, J. C.; Iida, H.; Hamana, H.; Kumamoto, K.; Kotsuki, H.; Jenner, G. *Helv. Chim. Acta* **2005**, *88*, 1734. (c) Kumamoto, K.; Iida, H.; Hamana, H.; Kotsuki, H.; Matsumoto, K. *Heterocycles* **2005**, *66*, 675.

**Scheme 2.** Synthesis of Trigonoliimine A (**1**) and Demethoxytrigonoliimine A/B (**4**)



The synthetic work commenced with the copper(I) chloride catalyzed oxidation<sup>7</sup> of the tryptamine derivatives **9a–b** (Scheme 2). The reaction proceeded smoothly at ambient temperature with absorption of oxygen during a course of 4–8 h and afforded the desired ketones **8a** and **8b** in good yields. Optimization of the next Strecker reaction conditions started with using ketone **8a** to react with tryptamine **7** and TMSCN as the model substrate, after a series of both Lewis (LiClO<sub>4</sub>,<sup>8a,d</sup> Sc(OTf)<sub>3</sub>,<sup>8b</sup> InCl<sub>3</sub>,<sup>8c</sup> BF<sub>3</sub>·OEt<sub>2</sub>,<sup>8d</sup> ZnI<sub>2</sub>,<sup>8e</sup> and TMSOTf<sup>8f</sup>) and Brønsted acids (TfOH and CF<sub>3</sub>CH<sub>2</sub>OH<sup>8g</sup>) were examined. Fortunately, we found that a catalytic amount of TMSOTf could uniquely promote the demanding transformation, and the desired compound **6a** was produced with good efficiency, yet the rest of the acids resulted in no requisite product being detected. Particularly noteworthy is the fact that although nitrile **6a** was cleanly produced under these conditions, it was partly decomposed to **10** when the reaction was quenched by adding 5% NaHCO<sub>3</sub> solution. A detailed investigation indicated that nitrile compound **6a** was unstable in either a base or neutral environment; however, it can be purified by silica gel using acidic eluents and it was even rather stable in CDCl<sub>3</sub> for the weakly acidic environment.

With this critical nitrile **6a** in hand, the stage was now set for the seven-membered Houben–Hoesch-type cyclization.<sup>9</sup>

(7) Tsuji, J.; Kezuka, H.; Takayanagi, H.; Yamamoto, K. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 2369.

(8) For Strecker reaction conditions: (a) Heydari, A.; Fatemi, P.; Alizadeh, A. A. *Tetrahedron Lett.* **1998**, *39*, 3049. (b) Kobayashi, S.; Busujima, T.; Nagayama, S. *Chem. Commun.* **1998**, *9*, 981. (c) Ranu, B. C.; Dey, S. S.; Hajra, A. *Tetrahedron* **2002**, *58*, 2529. (d) Prasad, B. A. B.; Bisai, A.; Singh, V. K. *Tetrahedron Lett.* **2004**, *45*, 9565. (e) Kazemeini, A.; Azizi, N.; Saidi, M. R. *Russ. J. Org. Chem.* **2006**, *42*, 48. (f) Prakash, G. K. S.; Panja, C.; Do, C.; Mathew, T.; Olah, G. A. *Synlett* **2007**, 2395. (g) Heydari, A.; Khaksar, S.; Tajbakhsh, M. *Tetrahedron Lett.* **2009**, *50*, 77.

While the Houben–Hoesch reaction has been extensively used for the synthesis of five- and six-membered aryl ketones (xanthenes, 4-hydroxyquinolin-2(1*H*)-ones, etc.),<sup>9,10</sup> using this reaction to construct a cycloheptanoid skeleton was rare. To our delight, the desired cyclization occurred uneventfully catalyzed by TfOH (trifluoromethanesulfonic acid)<sup>9d,f,10a</sup> in DCM at room temperature, and the resulting imine mixture was subsequently neutralized and hydrolyzed by adding saturated aqueous NaHCO<sub>3</sub> solution, thus producing the seven-membered ketone **5a** in 60% yield. Further, unveiling the amino group of **5a** by hydrazine in EtOH with concurrent five-membered cyclization furnished the final product **4**.

It seemed logical to us that continuing the synthesis following the established procedure for compound **4** with fragment **8b** would deliver trigonoliimine A (**1**); even the corresponding Strecker adduct **6b** also could be produced following the above procedure. However, our attempts in the purification of this unstable intermediate were unsuccessful, since decomposition was concomitant during workup. We were able to circumvent this problem by a modified one-pot procedure: when the unstable intermediate

**6b** had been generated *in situ*, then TfOH was directly added to the Strecker reaction mixture. By this optimized operation, **5b** could be obtained with a combined yield of 41% through two steps from **8b**. Under the previous deprotection step, trigonoliimine A (**1**) was provided in 85% yield. The spectroscopic data of the synthetic trigonoliimines A (**1**) and skeleton **4** matched those provided in the literature,<sup>1,2a,3</sup> confirming the molecular structure of these compounds.

In summary, to provide a starting point for syntheses and biological evaluation of trigonoliimines alkaloids and their analogues, we have developed a concise approach to the hexacyclic ring system of trigonoliimines alkaloids. Trigonoliimine A (**1**), together with demethoxytrigonoliimine A/B (**4**), was delivered in four steps with extreme atom economy (only one protective group, ‘Phth’, was adopted). The convergent character and operational simplicity make this chemistry remarkable. Efforts are currently underway to explore applications of this novel Strecker/Houben–Hoesch approach to construct a trigonoliimine A-like library which will be biologically evaluated and reported in due course.

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

(9) For Houben-Hoesch type cyclization, see: (a) Cameron, D. W.; Deutscher, K. R.; Feutrill, G. I.; Hunt, D. E. *Aust. J. Chem.* **1982**, *35*, 1451–1468. (b) Amer, M. I.; Booth, B. L.; Noori, G. F. M.; Proenca, M. F. J. R. P. *J. Chem. Soc., Perkin Trans. 1* **1983**, 1075–1081. (c) Sato, Y.; Yato, M.; Ohwada, T.; Saito, S.; Shudo, K. *J. Am. Chem. Soc.* **1995**, *117*, 3037–3043. (d) Colquhoun, H. M.; Lewis, D. F.; Williams, D. J. *Org. Lett.* **2001**, *3*, 2337. (e) Tran, Y. S.; Kwon, O. *J. Am. Chem. Soc.* **2007**, *129*, 12632. (f) Nakamura, S.; Sugimoto, H.; Ohwada, T. *J. Org. Chem.* **2008**, *73*, 4219. (g) Kobayashi, Y.; Katagiri, K.; Azumaya, I.; Harayama, T. *J. Org. Chem.* **2010**, *75*, 2741 and references cited therein.

(10) For recent applications of the Houben–Hoesch reaction in total synthesis, see: (a) Deguchi, J.; Hirahara, T.; Oshimi, S.; Hirasawa, Y.; Ekasari, W.; Shiota, O.; Honda, T.; Morita, H. *Org. Lett.* **2011**, *13*, 4344. (b) Kim, J.; Schneekloth, J. S., Jr; Sorensen, E. J. *Chem. Sci.* **2012**, *3*, 2849.

The authors declare no competing financial interest.