ORGANIC LETTERS

2012
Vol. 14, No. 5
1338–1341

A Concise Total Synthesis of (±)-Trigonoliimine B

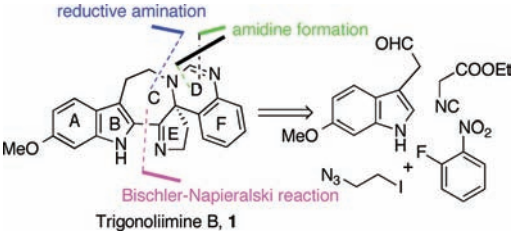
Thomas Buyck, Qian Wang, and Jieping Zhu*

Institut of Chemical Sciences and Engineering, École Polytechnique Fédérale de Lausanne, EPFL-SB-ISIC-LSPN, CH-1015 Lausanne, Switzerland

jieping.zhu@epfl.ch

Received January 31, 2012

ABSTRACT



Trigonoliimine B, a hexacyclic alkaloid, is synthesized in seven steps from simple starting materials. The synthesis features the use of an α-isocyanoacetate as a glycine template for the preparation of an α,α-disubstituted α-amino ester that is appropriately functionalized for the construction of C, D, and E rings. Sulfolane was found to be the solvent of choice for the unprecedented Bischler−Napieralski reaction implemented for the construction of a seven-membered ring with concurrent formation of an *exo*-imine function.

Trigonoliimine B (**1**) belongs to a family of oxidatively rearranged bisindole alkaloids.[1] It was isolated, along with trigonoliimines A (**2**) and C (**3**), by Hao and co-workers in 2010 from the leaves of *Trigonostemon lii* Y. T. Chang collected in the Yunnan Province of China (Figure 1).[2] Trigonoliimine A was found to exhibit modest anti-HIV activity (EC_{50} = 0.95 μg/mL, TI = 7.9).[2] Structurally, trigonoliimines A and B contain a quaternary carbon whose four substituents are cross-linked to form five-, six-, and seven-membered tricyclic cores of the hexacyclic structure. The fascinating molecular architecture of trigonoliimines has attracted attention of synthetic chemists. While pursuing our synthetic endeavor, one enantioselective synthesis of trigonoliimines A, B, and C, one synthesis of (±)-trigonoliimine C, and two syntheses of model trigonoliimines B and C were reported. On the basis of their earlier hypotheses on the biosynthesis of dimeric hexahydropyrroloindole alkaloids,[3] Movassaghi and Han developed a unified strategy allowing them to access all three natural products via the same enantioenriched hydroxyindolenines, which were in turn prepared by enantioselective oxidation of bistryptamine.[4] These syntheses also allowed them to revise the stereochemistry of these alkaloids. Simultaneously, Tambar et al. published a total synthesis of (±)-trigonoliimine C based on the same insightful biogenetic hypothesis.[5] Shortly after, Hao's group described a similar biomimetic synthesis of the trigonoliimine C skeleton,[6] and very recently, Shi and co-workers detailed their synthetic approach to the hexacyclic skeleton of trigonoliimines A and B.[7] We report herein our own efforts

(1) For selected recent examples, see: (a) May, J. A.; Zeidan, R. K.; Stoltz, B. M. *Tetrahedron Lett.* **2003**, *44*, 1203–1205. (b) Fuchs, J. R.; Funk, R. L. *J. Am. Chem. Soc.* **2004**, *126*, 5068–5069. (c) May, J. A.; Stoltz, B. M. *Tetrahedron* **2006**, *62*, 5262–5271. (d) Sabahi, A.; Novikov, A.; Rainier, J. D. *Angew. Chem., Int. Ed.* **2006**, *45*, 4317–4320. (e) Movassaghi, M.; Schmidt, M. A. *Angew. Chem., Int. Ed.* **2007**, *46*, 3725–3728. (f) Steven, A.; Overman, L. E. *Angew. Chem., Int. Ed.* **2007**, *46*, 5488–5508. (g) Yang, J.; Wu, H.; Shen, L.; Qin, Y. *J. Am. Chem. Soc.* **2007**, *129*, 13794–13795. (h) Kim, J.; Ashenhurst, J. A.; Movassaghi, M. *Science* **2009**, *324*, 238–241. (i) Newhouse, T.; Lewis, C. A.; Eastman, K. J.; Baran, P. S. *J. Am. Chem. Soc.* **2010**, *132*, 7119–7137. (j) Zhou, Z.; Xie, W.; Ma, D. *J. Am. Chem. Soc.* **2010**, *132*, 13226–13228. (k) Liu, P.; Seo, J.-H.; Weinreb, S. M. *Angew. Chem., Int. Ed.* **2010**, *49*, 2000–2003. (l) Furst, L.; Narayanam, J. M. R.; Stephenson, C. R. J. *Angew. Chem., Int. Ed.* **2011**, *50*, 9655–9659. (m) For a short review on the chemistry of communesin, see: Siengalewicz, P.; Gaich, T.; Mulzer, J. *Angew. Chem., Int. Ed.* **2008**, *47*, 8170–8176.

(2) 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*, 2370–2373.

(3) Schmidt, M. A.; Movassaghi, M. *Synlett* **2008**, 313–324.

(4) Han, S.; Movassaghi, M. *J. Am. Chem. Soc.* **2011**, *133*, 10768–10771.

(5) Qi, X.; Bao, H.; Tambar, U. K. *J. Am. Chem. Soc.* **2011**, *133*, 10050–10053.

(6) Liu, S.; Hao, X.-J. *Tetrahedron Lett.* **2011**, *52*, 5640–5642.

(7) Feng, P.; Fan, Y.; Xue, F.; Liu, W.; Li, S.; Shi, Y. *Org. Lett.* **2011**, *13*, 5827–5829.

10.1021/ol300249y
Published on Web 02/22/2012

that culminated in a concise total synthesis of (±)-trigonoliimine B.

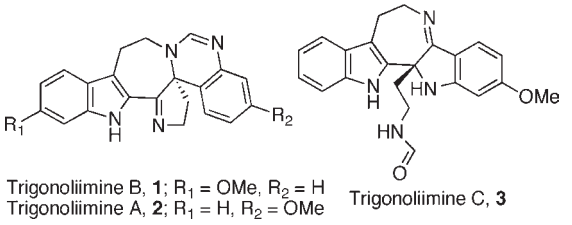
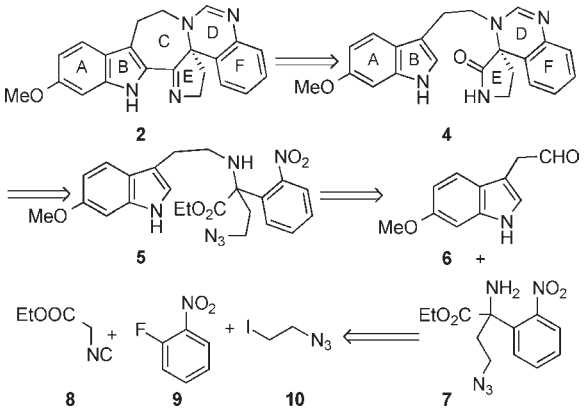


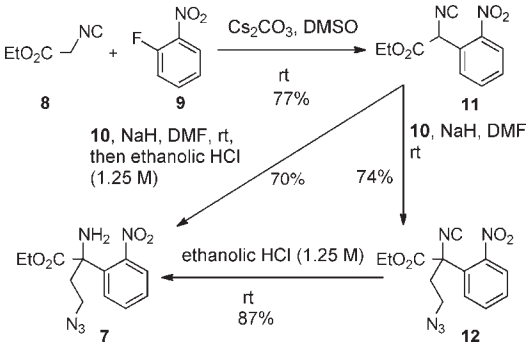
Figure 1. Structures of trigonoliimines A, B, and C.

Scheme 1. Retrosynthetic Analysis of Trigonoliimine B



While the elegance and power of a biomimetic synthesis strategy[8] is fully demonstrated in these reported syntheses, the regioselectivity in the oxidation of dissymmetric bistryptamine remained an issue. Indeed, two regioisomeric 3-hydroxyindolenines were formed in both reported syntheses.[4,5] Our retrosynthetic analysis of trigonoliimine B revealed an alternative, nonbiomimetic approach to this natural product that hinged on the much simpler prospective of sequential construction of the C–D–E ring system from simple α,α-disubstituted α-amino ester **5** (Scheme 1). Specifically, we planned to conclude the synthesis by closing the C ring from the lactam **4**, and the Bischler–Napieralski reaction[9] was selected, although risky, for this demanding transformation. If realized, it would allow us not only to close the seven-membered C ring but also to install at the same time the potentially labile imine function (*exo* to C ring) in E ring. The spirolactam **4** could in turn be prepared from **5** through sequential lactamization and amidine formation. Compound **5** was expected to be obtained by reductive amination of 2-(6-methoxy-1*H*-indol-3-yl)acetaldehyde with α,α-disubstituted α-amino ester **7**. The latter could be obtained by functionalization of α-isocyanoacetate **8** via an arylation–alkylation sequence using 2-fluoronitrobenzene **9** and 2-azidoiodoethane **10**, respectively, as electrophiles.

Scheme 2. Synthesis of α,α-Disubstituted α-Amino Ester



Our synthesis started with the functionalization of the commercially available α-isocyanoacetate (Scheme 2). An S_NAr reaction between ethyl α-isocyanoacetate (**8**)[10] and 2-fluoronitrobenzene (**9**) in the presence of cesium carbonate in DMSO afforded α-aryl-α-isocyanoacetate **11** in 77% yield.[11] Due to the presence of the three electron-withdrawing groups around the α-carbon of **11**, the corresponding enolate was expected to be highly stabilized, hence less reactive as a nucleophile. After some experimentation, it was found that alkylation of **11** with 2-azidoiodoethane (**10**)[12] proceeded smoothly to afford the desired α,α-disubstituted α-isocyanoacetate **12** in 74% yield.[13] Hydrolysis of the isocyanide group to amine was realized with ethanolic HCl (1.25 M) to furnish the amino ester **7** in 87% yield. Subsequent optimization allowed us to combine these two steps into a one-pot process without isolating the alkylation product **12**. Thus, after completion of the alkylation, careful addition of ethanolic HCl (1.25 M) to the reaction mixture afforded **7** directly in 70% overall yield. We therefore accessed, in only two steps, the highly functionalized key building block **7** whose four functional groups, an ester and three orthogonally differentiated amino functions, were strategically positioned for the construction of the central C, D, and E rings of the natural product. The use of ethyl α-isocyanoacetate **8** as a glycine template was essential in this case. Our initial effort using malonate as a latent amino ester function met only

(8) Bulger, P. G.; Bagal, S. K.; Marquez, R. *Nat. Prod. Rep.* **2008**, *25*, 254–297. (b) Kim, J.; Movassaghi, M. *Chem. Soc. Rev.* **2009**, *38*, 3035–3050.

(9) Whaley, W. M.; Govindachari, T. R. *Org. React.* **1951**, *6*, 74–150.

(10) (a) Zhu, J. *Eur. J. Org. Chem.* **2003**, 1133–1144. (b) Gulevich, A. V.; Zhdanko, A. G.; Orru, R. V.; Nenajdenko, V. G. *Chem. Rev.* **2010**, *110*, 5235–5331.

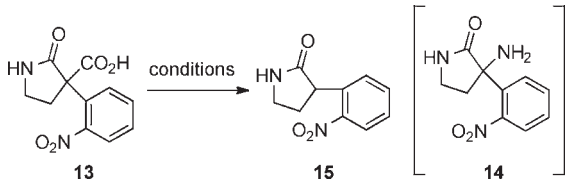
(11) Lalli, C.; Bouma, M. J.; Bonne, D.; Masson, G.; Zhu, J. *Chem.—Eur. J.* **2011**, *17*, 880–889.

(12) Nulwala, H.; Burke, D. J.; Khan, A.; Serrano, A.; Hawker, C. J. *Macromolecules* **2010**, *43*, 5474–5477. (b) Macleod, F.; Lang, S.; Murphy, J. A. *Synlett* **2010**, *4*, 529–534.

(13) The order of the arylation/alkylation is important since alkylation of α-isocyanoacetate provided the α,α-dialkylated product as a major product even with substoichiometric amount of electrophiles. See: (a) Hoppe, D. *Angew. Chem., Int. Ed. Engl.* **1974**, *13*, 789–804. (b) Schöllkopf, U. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 339–348. (c) Housseman, C.; Zhu, J. *Synlett* **2006**, 1777–1779.

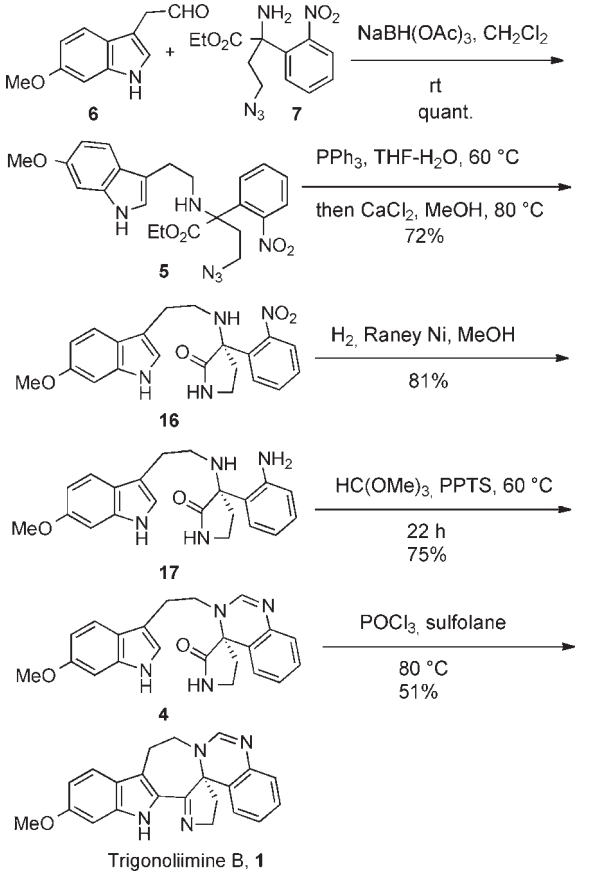
with failure. For example, all attempts to convert the acid **13** to the corresponding amino derivative **14** failed. Under a range of reaction conditions varying the solvents, and the coupling reagents and the azide sources to promote the desired Curtius rearrangement, only the decarboxylated product **15** was isolated (Scheme 3). The facile decarboxylation of **13** is due presumably to the high stability of the resulting enolate intermediate.

Scheme 3. Decarboxylation of **13** Leading to **15** under Curtius Rearrangement Conditions



The 2-(6-methoxy-1*H*-indol-3-yl)acetaldehyde **6** was synthesized by a palladium-catalyzed heteroannulation between 2-iodo-5-methoxy aniline and 4-acetoxy butanal (cf. Supporting Information).[14−16] Reductive amination of aldehyde **6** with amine **7** under standard conditions [$NaBH(OAc)_3$, CH_2Cl_2, room temperature] afforded the secondary amine **5** in essentially quantitative yield. Compound **5** is appropriately functionalized for the construction of the tricyclic core of trigonoliimine B, and different order of ring construction is, in principle, possible. In this preliminary study, the sequence involving the construction of the E ring followed by the D ring and finally the C ring was adopted. Toward this end, Staudinger reduction of **5** (PPh_3, THF/H_2O) was carried out. While the reduction took place smoothly to afford the corresponding primary amine, the expected ring closure leading to γ-lactam did not occur under these conditions. We reasoned that the neopentyl nature of the ester carbonyl carbon might render the nucleophilic addition of amine difficult. Fortunately, cycloamidation proceeded smoothly in the presence of $CaCl_2$ (MeOH, 80 °C),[17] and we were pleased to find that the reduction/cyclization can be performed in a one-pot fashion (PPh_3, THF/H_2O then $CaCl_2$, MeOH) to provide the desired γ-lactam **16** in 72% isolated yield. Reduction of the nitro group in **16** was best realized by hydrogenation in the presence of Raney nickel catalyst (H_2, MeOH) to provide aniline **17** in 81% yield. Treatment of the diamine **17** with trimethyl orthoformate (PPTs, 60 °C) yielded the spirocycle **4** without event (Scheme 4).[4]

Scheme 4. Completion of the Synthesis of Trigonoliimine B



To complete the synthesis, the Bischler−Napieralski (BN) reaction was envisioned to close the remaining seven-membered ring.[9] While the BN reaction has been extensively used for the synthesis of tetrahydrocarbolines, to the best of our knowledge, there is no example in the literature dealing with the formation of a hexahydroazepino[4,5-*b*]indole skeleton with the concurrent formation of an *exo*-imine function. Initially, we examined the classical conditions including $POCl_3$/toluene/reflux and $POCl_3/P_2O_5$/toluene/reflux; none of them afforded the desired compound, and the starting material was partially recovered even with an excess of activating agent. Performing the BN reaction in DMPU according to Nicolaou and Chen[18] provided trigonoliimine B (**1**) in about 10% yield. This encouraging result prompted us to examine other polar solvents (e.g., HMPA,[19] sulfolane,[20] and neat $POCl_3$) in the presence or absence of base (pyridine) for this reaction.

(14) Chen, C.-Y.; Lieberman, D. R.; Larsen, R. D.; Verhoeven, T. R.; Reider, P. J. *J. Org. Chem.* **1997**, *62*, 2676–2677.

(15) (a) Baran, P. S.; Guerrero, C. A.; Ambhaikar, N. B.; Hafensteiner, B. D. *Angew. Chem., Int. Ed.* **2005**, *44*, 606–609. (b) Baran, P. S.; Hafensteiner, B. D.; Ambhaikar, N. B.; Guerrero, C. A.; Gallagher, J. D. *J. Am. Chem. Soc.* **2006**, *128*, 8678–8693.

(16) (a) Jia, Y. X.; Zhu, J. *Synlett* **2005**, 2469–2472. (b) Jia, Y. X.; Zhu, J. *J. Org. Chem.* **2006**, *71*, 7826–7834. For applications of this reaction in natural product synthesis, see: (c) Jia, Y. X.; Bois-Choussy, M.; Zhu, J. *Org. Lett.* **2007**, *9*, 2401–2404. (d) Velthuisen, E. J.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2007**, *129*, 10640–10641. (e) Jia, Y. X.; Bois-Choussy, M.; Zhu, J. *Angew. Chem., Int. Ed.* **2008**, *47*, 4167–4172. (f) Michaux, J.; Retailleau, P.; Campagne, J. M. *Synlett* **2008**, 1532–1536. (g) Xu, Z.; Li, Q.; Zhang, L.; Jia, Y.-X. *J. Org. Chem.* **2009**, *74*, 6859–6862. (h) Wang, Z. H.; Bois-Choussy, M.; Jia, Y. X.; Zhu, J. *Angew. Chem., Int. Ed.* **2010**, *49*, 2018–2022.

(17) Bundesmann, M. W.; Coffey, S. B.; Wright, S. W. *Tetrahedron Lett.* **2010**, *51*, 3879–3882.

(18) Nicolaou, K. C.; Dalby, S. M.; Li, S.; Suzuki, T.; Chen, D. Y. K. *Angew. Chem., Int. Ed.* **2009**, *48*, 7616–7620.

(19) $POCl_3$ is known to react with HMPA leading to O=P(Cl)-$(NMe_2)_2$, but the resulting species is still capable of activating the alcohol toward elimination. See: Trost, B. M.; Jungheim, L. N. *J. Am. Chem. Soc.* **1980**, *102*, 7910–7925.

Gratefully, when the reaction was carried out in sulfolane at 80 °C, the cyclization took place smoothly to provide the natural product **1** in 51% yield. To our knowledge, this is the first example of a 7-*exo*-*trig* Bischler−Napieralski reaction for the construction of a seven-membered ring with an *exo*-imine function. The spectroscopic data of the synthetic trigonoliimine B (**1**) were identical to those reported for the natural product.[2]

Knowledge or simply a hypothesis of natural product biosynthesis can often provide an elegant approach to their synthesis as illustrated, in the present case, by Movassaghi and Tambar's synthesis of trigonoliimines A−C. However, careful analysis of target structures can sometimes suggest an alternative laboratory synthesis that could be competitive to the biomimetic ones. In this paper, we have accomplished an efficient non-biomimetic-inspired total synthesis of (±)-trigonoliimine B (**1**) in seven steps from commercially available ethyl α-isocyanoacetate (**8**) and 2-fluoronitrobenzene (**9**) with an overall yield of 12%. The synthesis is highly constructive with a minimum amount of redundant steps.[21]

From a synthesis design viewpoint, the use of readily accessible α,α-disubstituted α-amino ester **7** as a pivotal intermediate is key to the conciseness of the synthetic route since it allowed us to construct the central tricyclic C−D−E ring system in a straightforward manner. All of the transformations have been carried out under very simple conditions (acidic and basic media). An additional feature of this synthesis included the use of sulfolane as solvent for the Bischler−Napieralski reaction that led to the formation of a seven-membered ring with concurrent creation of an *exo*-imine group. We believed that this solvent could find application in performing a Bischler−Napieralski reaction that is difficult to realize otherwise. Studies to extend the utility of this solvent in organic transformations and application of our synthetic strategy to other trigonoliimines are ongoing.

Acknowledgment. We thank EPFL (Switzerland), Swiss National Science Foundation (SNF), and Swiss National Centres of Competence in Research (NCCR) for financial support.

Supporting Information Available. Experimental procedures, product characterization, and copies of the ^{1}H and ^{13}C NMR spectra of all synthetic compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

(20) For a general discussion on the solvent property of sulfolane, see: Meindersma, G. W.; Sanchez, L. M. G.; Hansmeier, A. R.; de Haan, A. B. *Monatsh. Chem.* **2007**, *138*, 1125–1136.

(21) For reviews dealing with the synthesis efficiency, see: (a) Trost, B. M. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 259–281. (b) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115–136. (c) Wender, P. A.; Miller, B. L. *Nature* **2009**, *160*, 197–201. (d) Touré, B. B.; Hall, D. G. *Chem. Rev.* **2009**, *109*, 4439–4486. (e) Young, I. S.; Baran, P. S. *Nat. Chem.* **2009**, *1*, 193–205. (f) Hoffmann, R. W. *Synthesis* **2006**, 3531–3541. (g) Burns, N. Z.; Baran, P. S.; Hoffmann, R. W. *Angew. Chem., Int. Ed.* **2009**, *48*, 2854–2867.