ORGANIC LETTERS

2011
Vol. 13, No. 24
6426–6428

A Concise Total Synthesis of (±)-Minfiensine

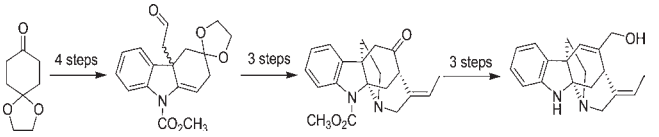
Peijun Liu, Juan Wang, Jiancun Zhang,* and Fayang G. Qiu*

Laboratory of Molecular Engineering, and Laboratory of Natural Products Synthesis, Guangzhou Institutes of Biomedicine and Health, Chinese Academy of Sciences, 190 Kaiyuan Avenue, Guangzhou 510530, China

qiu_fayang@gibh.ac.cn; zhang_jiancun@gibh.ac.cn

Received October 11, 2011

ABSTRACT



A concise total synthesis of (±)-minfiensine using all conventional methods and starting from commercial materials has been completed. The synthesis features a Fischer indole synthesis, a Heck alkylation of an intermediate ketone enolate, conversion of a ketone carbonyl into an epoxide, and transformation of the latter into an allylic alcohol.

Minfiensine (**1**), an indole alkaloid isolated from the African plant *Strychnos minfiensis* by a group led by Massiot in 1989,[1] exhibited significant biological activities including anticancer activities.[2] The molecule features a 1,2,3,4-tetrahydro-9*a*,4*a*-(iminoethano)-9*H*-carbazole tetracyclic substructure (**2**) (Figure 1), which makes it synthetically challenging. Therefore, this alkaloid and the related akuammiline indole alkaloids have attracted considerable synthetic interests. Since Overman's first synthesis, a few other total syntheses have been documented (Figure 2).[3] Especially impressive is MacMillan's synthesis which utilized only nine reaction steps from readily accessible starting materials in an enantioselective manner.[3d]

Our continued interest in the efficient total synthesis of natural products has led us to tackle this molecule from a practical point of view. Being practical refers to the requirement that the starting materials be inexpensive and commercially available and that the conditions to be used to carry out the reactions be practically convenient.

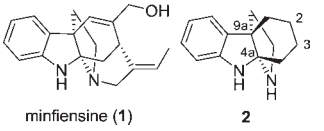


Figure 1. Structure of minfiensine and the core structure of the akuammilines.

According to our proposition described in a previous paper,[4] the molecular complexity index for minfiensine (**1**) is 13 and thus an efficient synthesis for minfiensine is limited to 12 reaction steps. Herein, we would like to describe a concise total synthesis of minfiensine (**1**) starting from inexpensive and commercially available phenylhydrazine and 1,4-cyclohexanedione monoethyleneacetal. The retrosynthetic analysis of minfiensine (**1**) is outlined in Scheme 1.

Minfiensine (**1**) may be prepared from intermediate **3**, which may be obtained from intermediate **4** through an enolate S_N2' displacement of the propargyl halide or sulfonate, after a few transformations including partial hydrogenation of the allene functionality, conversion of the ketone carbonyl into the allylic alcohol, and deprotection of the indole nitrogen. Intermediate **5**, which may be

(1) Massiot, G.; Thépenier, P.; Jacquier, M.-J.; Men-Oliver, L.; Delaude, C. *Heterocycles* **1989**, *29*, 1435–1438.

(2) Ramírez, A.; García-Rubio, S. *Curr. Med. Chem.* **2003**, *10*, 1891–1915.

(3) (a) Dounay, A. B.; Overman, L. E.; Wrobleski, A. D. *J. Am. Chem. Soc.* **2005**, *127*, 10186–10187. (b) Dounay, A. B.; Humphreys, P. G.; Overman, L. E.; Wrobleski, A. D. *J. Am. Chem. Soc.* **2008**, *130*, 5368–5377. (c) Shen, L.; Zhang, M.; Wu, Y.; Qin, Y. *Angew. Chem., Int. Ed.* **2008**, *47*, 3618–3621. (d) Jones, S. B.; Simmons, B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2009**, *133*, 13606–13607. (e) Li, G.; Padwa, A. *Org. Lett.* **2011**, *13*, 3767–3769.

(4) Qiu, F. *Can. J. Chem.* **2008**, *86*, 903.

10.1021/ol2027224
Published on Web 11/11/2011

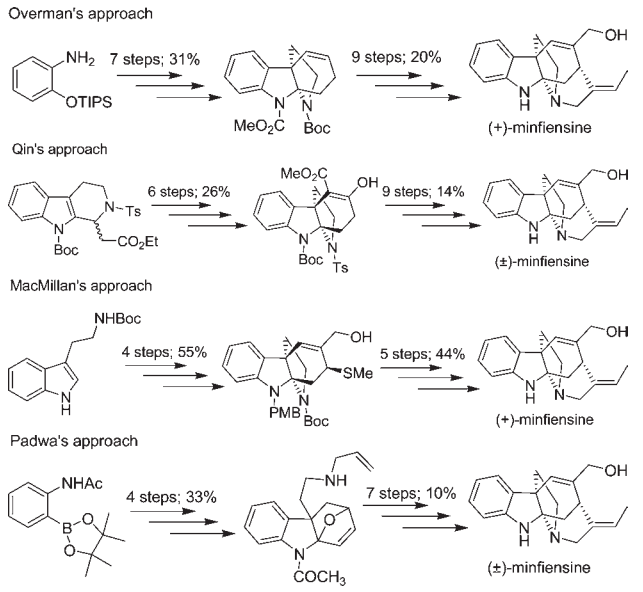
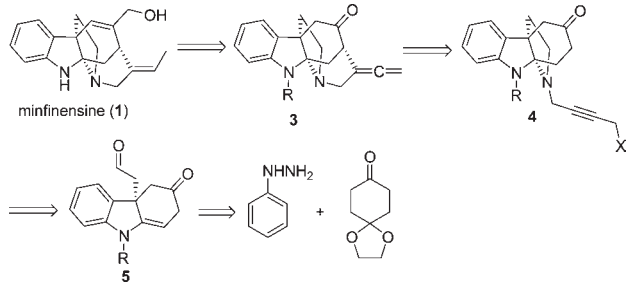


Figure 2. A brief outline of the previous syntheses of minfiensine.

Scheme 1

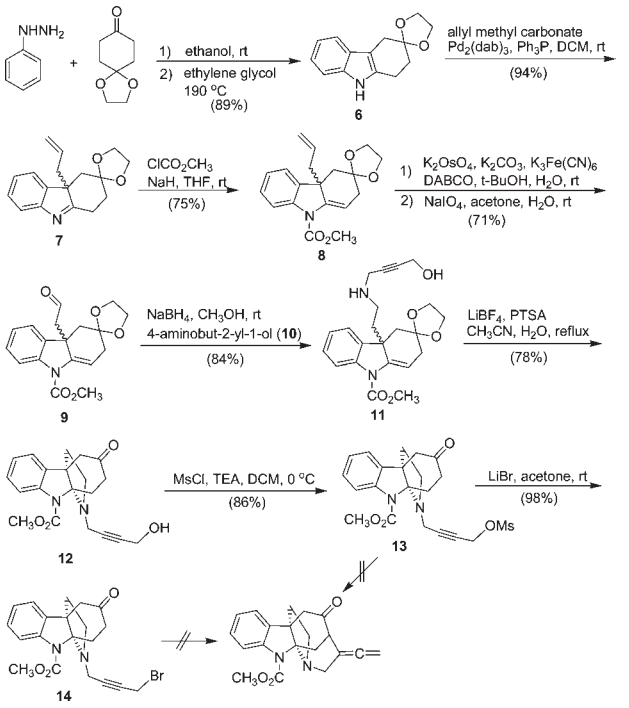


synthesized from the condensation of phenylhydrazine and 1,4-cyclohexanedione monoethyleneacetal followed by alkylation at position 3 of the indole, protection of the indole nitrogen, and oxidation of the terminal carbon−carbon double bond, may be transformed into **4** *via* a reductive amination process followed by cyclization to form the new pyrrolidine moiety.

Based on the above analysis, the synthetic design is outlined in Scheme 2. The assembly of minfiensine (**1**) began with the Fischer indole synthesis. Thus, condensation of phenylhydrazine and 1,4-cyclohexanedione monoethyleneacetal at room temperature followed by heating at 190 °C for 4.5 h furnished the desired indole product **6** in 89% yield.[5] After removal of the acidic proton with *n*-BuLi, the resulting indole anion was allylated at position 3 in 79% yield with allyl bromide at −78 °C. Alternatively, the allylation was achieved under the catalysis of $Pd_2(dba)_3$

(5) Urrutia, A.; Rodríguez, J. G. *Tetrahedron* **1999**, *55*, 11095–11108.
(6) Kagawa, N.; Malerich, J. P.; Rawal, V. H. *Org. Lett.* **2008**, *10*, 2381–2384.

Scheme 2

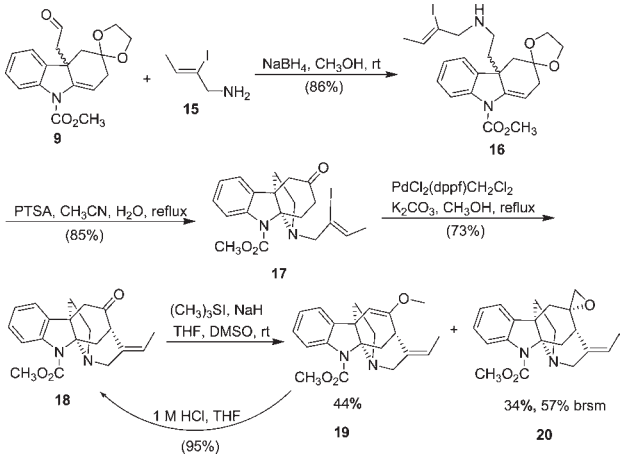


at room temperature in 94% yield.[6] Formation of the methyl carboxamide was accomplished when the allylated intermediate was treated sequentially with sodium hydride and methyl chloroformate at room temperature. With this diene in hand, the next step was to selectively convert the terminal carbon−carbon double bond into an aldehyde functionality. However, poor yields (20−41%) were obtained when the alkene was treated with OsO_4 and NMO under a variety of conditions. After many attempts, we were able to realize the requisite cleavage of the double bond using a combination of the Sharpless dihydroxylation method[7] and sodium periodinate. Reductive amination of the resulting aldehyde with butynylamine **10**,[8] prepared from the reaction of the monomesylate of 2-butyne-1,4-diol and *o*-phthalimide, afforded the desired product **11** in 84% yield. Treatment of the latter with PTSA afforded the cyclization product **12** in 78% yield. However, the subsequent conversion was problematic. When the propargyl alcohol was converted into mesylate **13** or bromide **14**, the following S_N2' alkylation did not proceed

(7) Eames, J.; Mitchell, H. J.; Nelson, A.; O'Brien, P.; Warren, S.; Wyatt, P. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1095–1103.
(8) Lukinavičius, G.; Lapienė, V.; Staševskij, Z.; Dalhoff, C.; Weinhold, E.; Klimašauskas, S. *J. Am. Chem. Soc.* **2007**, *129*, 2758–2759.
(9) (a) Solé, D.; Peidró, E.; Bonjoch, J. *Org. Lett.* **2000**, *2*, 2225–2228. (b) Solé, D.; Diaba, F.; Bonjoch, J. *J. Org. Chem.* **2003**, *68*, 5746–5749. (c) Bonjoch, J.; Diaba, F.; Puigbó, G.; Peidró, E.; Solé, D. *Tetrahedron Lett.* **2003**, *44*, 8387–8390. (d) Solé, D.; Urbaneja, X.; Bonjoch, J. *Org. Lett.* **2005**, *7*, 5461–5464.
(10) Kraff, M. E.; Cran, J. W. *Synlett* **2005**, 1263–1266.
(11) Corey, E. J.; Chaykovsky, M. *J. Am. Chem. Soc.* **1965**, *87*, 1353–1364.
(12) Murara, S.; Suzuki, M.; Noyori, R. *J. Am. Chem. Soc.* **1979**, *101*, 2738–2739.

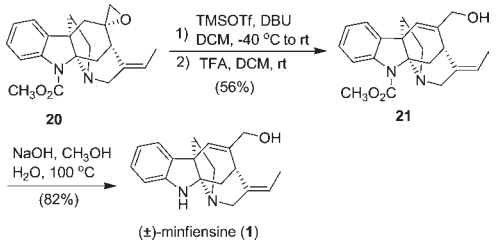
as we desired. The anion of the base such as methoxide or diisopropylamide functioned as a nucleophile instead. At this point, we turned our attention to a Heck type of alkylation,[9] and the synthetic design was modified as is shown in Scheme 3.

Scheme 3



Thus, reductive amination of aldehyde **9** with sodium borohydride and 2-iodocrotylamine **15**, prepared from (*Z*)-2-iodobut-2-en-1-ol,[10] was achieved in 86% yield in methanol at room temperature. Intramolecular addition of the amine functionality to the protected enamine in refluxing acetonitrile afforded the desired cyclization product **17** (85%), and the subsequent Heck type of alkylation was realized in 73% yield. The next step was to convert the ketone carbonyl into an olefin functionality. To our surprise, this material was resistant to olefination when either the Wittig reagent, the HEW method, or the Tebbe condition was used. After a few unsuccessful attempts, we decided to convert the ketone carbonyl group into the epoxide directly. Initial attempts concluded that the reaction did not occur as monitored by TLC analysis. Thus, trimethylsulfonium iodide and sodium hydride in DMSO was then tried.[11] Delightfully, the desired product **20** was obtained in 34% yield, though accompanied by the formation of **19**, the methyl enol ether of the starting material (44%), which was then hydrolyzed back to intermediate **18** in 95% yield. The reaction yield of the desired product was promoted to 57% based on recovered starting material. Conversion of epoxide **20** into the corresponding allyl alcohol **21** was achieved (Scheme 4) using trimethylsilyl triflate and DBU (56%).[12] After hydrolysis of the carbamide functionality in **21** with sodium hydroxide, the final product, obtained in 82% yield, exhibited identical characteristic patterns in the proton and carbon-13 NMR spectra to those of the natural material reported.

Scheme 4



In conclusion, a concise total synthesis of (±)-minfiensine has been achieved in 10 reaction steps starting from inexpensive commercial materials.

Acknowledgment. The authors are grateful to the National Natural Science Foundation of China (via Grant No. 21072191) and Guangzhou Institutes of Biomedicine and Health (with a start-up fund) for financial support of this work.

Supporting Information Available. Full experimental procedures and characterization for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.