ORGANIC LETTERS

2011
Vol. 13, No. 15
3767–3769

Intramolecular Diels–Alder Cycloaddition/Rearrangement Cascade of an Amidofuran Derivative for the Synthesis of (±)-Minfiensine

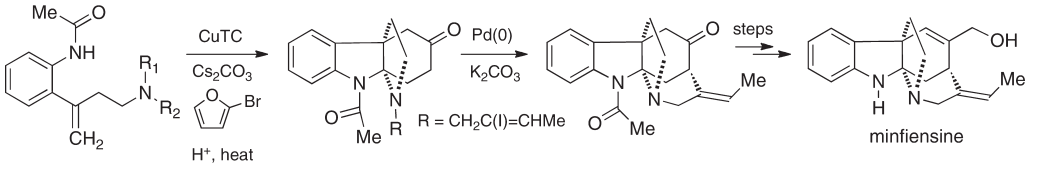
Gang Li and Albert Padwa*

Department of Chemistry, Emory University, Atlanta, Georgia 30322, United States

chemap@emory.edu

Received May 16, 2011

ABSTRACT



An efficient synthesis of (±)-minfiensine has been accomplished employing an intramolecular Diels–Alder cycloaddition/rearrangement cascade of an amidofuran derivative. Thermal reorganization of the initially formed [4 + 2]-cycloadduct affords the critical tetrahydroiminoethanocarbazole skeleton of the alkaloid in high yield.

In 1989, the indole alkaloid minfiensine (**1**) containing the 1,2,3,4-tetrahydro-9*a*,4*a*-iminoethanocarbazole core (**2**) was isolated from the African plant *Strychnos minfiensis* by Massiot and co-workers (Figure 1).[1] Since Overman's inaugural synthesis of minfiensine,[2] this structure and related akuammiline indole alkaloids have continued to attract synthetic interest due to their unusual polycyclic architecture and diverse biological activity.[3−6] In 2008, Qin and co-workers also accomplished the total synthesis of (±)-minfiensine (**1**) in 18 steps proceeding in a 0.4% overall yield by making use of an α-diazoketone cyclopropanation, ring-opening, and ring-closure reaction starting from a *N*-tosyl tetrahydrocarboline ester.[7] Later, the MacMillan group reported a more efficient synthetic route to this alkaloid using a cascade organocatalysis sequence to build the central tetracyclic pyrroloindoline framework and obtaining (+)-minfiensine in 9 steps and 21% overall yield from commercial materials.[8]

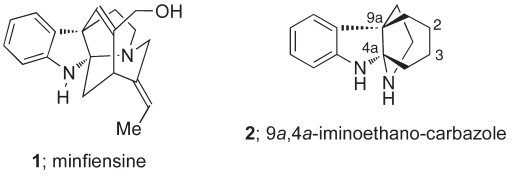


Figure 1. Core skeleton of akuammiline alkaloids.

Our retrosynthetic analysis of minfiensine (**1**) is outlined in Scheme 1. The synthetic plan that we initially had in mind involved generation of the E-ring of minfiensine by a palladium catalyzed intramolecular enolate coupling[9] of

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

(2) (a) Dounay, A. B.; Overman, L. E.; Wrobleski, A. D. *J. Am. Chem. Soc.* **2005**, *127*, 10186. (b) Dounay, A. B.; Humphreys, P. G.; Overman, L. E.; Wrobleski, A. D. *J. Am. Chem. Soc.* **2008**, *130*, 5368.

(3) Ramirez, A.; García-Rubio, S. *Curr. Med. Chem.* **2003**, *10*, 1891.

(4) (a) Manohar, H.; Ramaseshan, S. *Tetrahedron Lett.* **1961**, *22*, 814. (b) Goodson, J. A. *J. Chem. Soc.* **1932**, *134*, 2626. (c) Goodson, J. A.; Henry, T. A. *J. Chem. Soc.* **1925**, *127*, 1640.

(5) (a) Morfaux, A. M.; Mouton, P.; Massiot, G.; LeMen-Oliver, L. *Phytochemistry* **1992**, *31*, 1079. (b) Mokry, J.; Dubravkova, L.; Sefcovic, P. *Experientia* **1962**, *18*, 564.

(6) Proksa, B.; Uhrin, D.; Grossmann, E.; Voticky, Z. *Planta Med.* **1987**, *53*, 120.

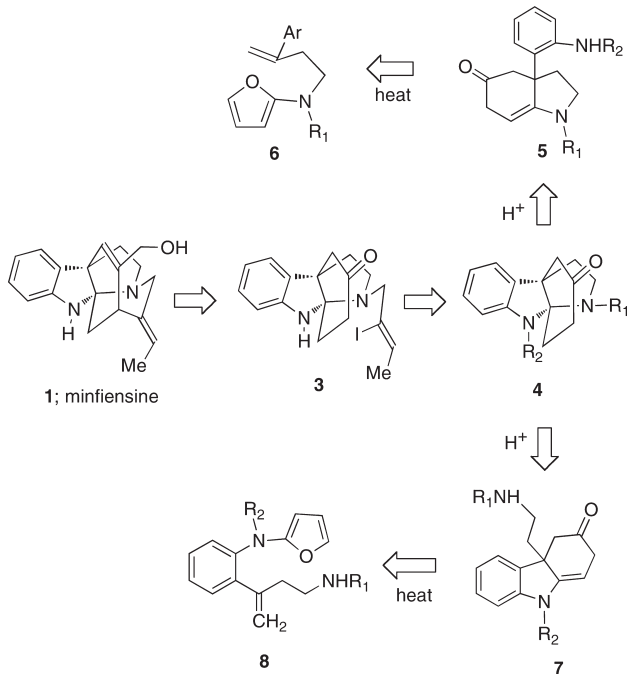
(7) Shen, L.; Zhang, M.; Wu, Y.; Qin, Y. *Angew. Chem., Int. Ed.* **2008**, *47*, 3618.

(8) Jones, S. B.; Simmons, B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2009**, *131*, 13606.

(9) (a) Solé, D.; Peidró, E.; Bonjoch, J. *Org. Lett.* **2000**, *2*, 2225. (b) Solé, D.; Diaba, J.; Bonjoch, J. *J. Org. Chem.* **2003**, *68*, 5746. (c) Bonjoch, J.; Diaba, F.; Puigbó, G.; Peidró, E.; Solé, D. *Tetrahedron Lett.* **2003**, *44*, 8387. (d) Solé, D.; Urbaneja, X.; Bonjoch, J. *Org. Lett.* **2005**, *7*, 5461.

10.1021/ol201320v
Published on Web 06/22/2011

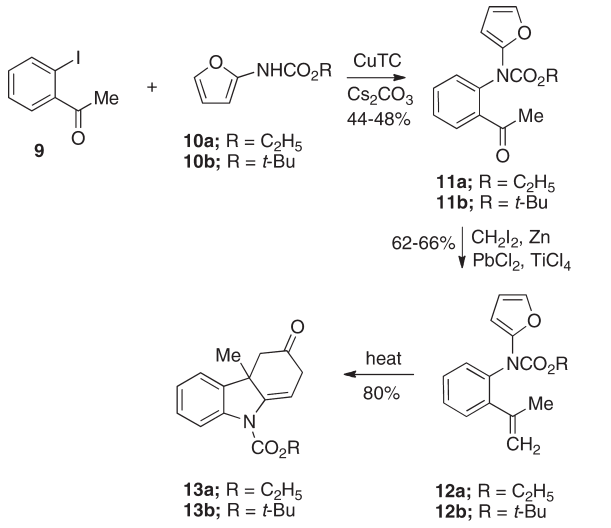
Scheme 1



the tethered vinyl iodide **3** as was recently carried out in our synthesis of strychnine.[10] Our first attempt to synthesize the required tetracyclic precursor **4** was based on the assumption that **4** would be formed by protonation of the 3*a*-aryl-2,3,3*a*,4-tetrahydro-1*H*-indol-5(6*H*)-one **5**. This compound would, in turn, be generated by an IMDAF cycloaddition reaction of amidofuran **6** followed by a subsequent rearrangement of the initially formed [4 + 2]-oxabicyclic adduct.[11] However, all of our efforts to form **5** from the thermolysis of furan **6** only resulted in recovered starting material. Apparently, the presence of a substituent group in the ortho position of the aromatic ring causes an unfavorable steric interaction with the furan ring in the reactive "*Diels–Alder conformation*"[12] thereby diminishing the overall rate of the IMDAF cycloaddition of **6**.

Having been thwarted in attempts to use amidofuran **6** as a precursor to tetracycle **4**, we decided that the simplest adjustment to our IMDAF approach would be to investigate the thermolysis of the related aminofuran **8**. As we were unsure as to whether the critical cycloaddition/rearrangement cascade would occur with **8**, we felt it prudent to first explore a model system to test the validity of this approach. With this in mind, furanyl carbamate **12** was prepared by application of a Buchwald–Hartwig copper catalyzed amidation reaction.[13] The keto group present in the resulting cross coupled product **11** derived from **9** and **10** was converted into the corresponding carbamate **12** using standard methodology.[14]

Scheme 2



We were pleased to find that heating a sample of furanyl carbamate **12a** (or **12b**) gave rise to the dihydro-2*H*-carbazolone **13a** (or **13b**) in *ca.* 80% yield (Scheme 2) thereby providing a promising prognosis for the success of our IMDAF cycloaddition approach toward minfiensine.

Our synthesis of the alkaloid minfiensine began with commercially available boronate **14** which was smoothly transformed through a Suzuki–Miyaura cross-coupling reaction with vinyl iodide **15** into the *o*-styryl substituted amide **16** in 63% yield (Scheme 3). Conversion of the alcohol into the corresponding mesylate **17** followed by reaction with allyl amine provided the expected secondary amine **18** (R = H) which was easily converted to the corresponding *t*-Boc carbamate **19** (72%). After a thorough screening of various catalytic systems (including several Pd(0) catalysts and *bis*-phosphine ligand combinations), we found that Buchwald's CuI catalytic system gave the most consistent and promising results.[15] Thus, heating a mixture of **19** together with catalytic copper(I)-thiophene-2-carboxylate (CuTC) and Cs_2CO_3 in toluene at 90 °C produced the Diels–Alder cycloadduct **21** derived from a subsequent [4 + 2]-cycloaddition of the expected cross-coupled product (i.e., **8**). Further heating of **21** at 120 °C afforded **23** (81%) obtained from the sequential ring-opening–deprotonation cascade.[12] A related sequence of reactions occurred when the simpler NH-amine **18** was

(10) (a) Zhang, H.; Boonsombat, J.; Padwa, A. *Org. Lett.* **2007**, *9*, 279. (b) Boonsombat, J.; Zhang, H.; Chughtai, M. J.; Hartung, J; Padwa, A. *J. Org. Chem.* **2008**, *73*, 3539.

(11) Bobeck, D. R.; France, S.; Leverett, C. A.; Sanchez-Cantalejo, F.; Padwa, A. *Tetrahedron Lett.* **2009**, *50*, 3145.

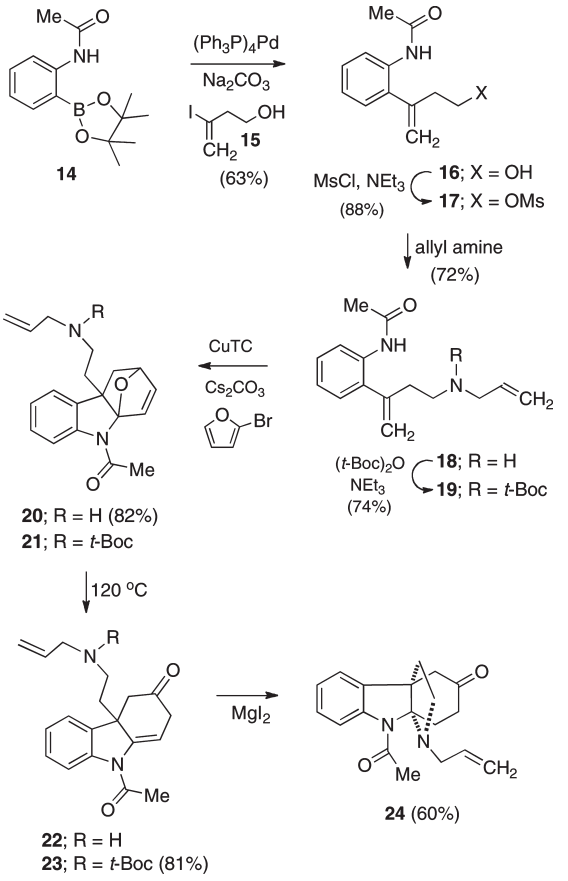
(12) (a) Padwa, A.; Dimitroff, M.; Waterson, A. G.; Wu, T. *J. Org. Chem.* **1997**, *62*, 4088. (b) Padwa, A.; Brodney, M. A.; Dimitroff, M. *J. Org. Chem.* **1998**, *63*, 5304. (c) Padwa, A.; Brodney, M. A.; Satake, K.; Straub, C. S. *J. Org. Chem.* **1999**, *64*, 4617.

(13) (a) Wolfe, J. P.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 1144. (b) Hartwig, J. F. *Angew. Chem., Int. Ed.* **1998**, *37*, 2047. (c) For several methods to synthesize 2-amido substituted furans, see: Padwa, A.; Crawford, K. R.; Rashatasakhan, P.; Rose, M. *J. Org. Chem.* **2003**, *68*, 2609.

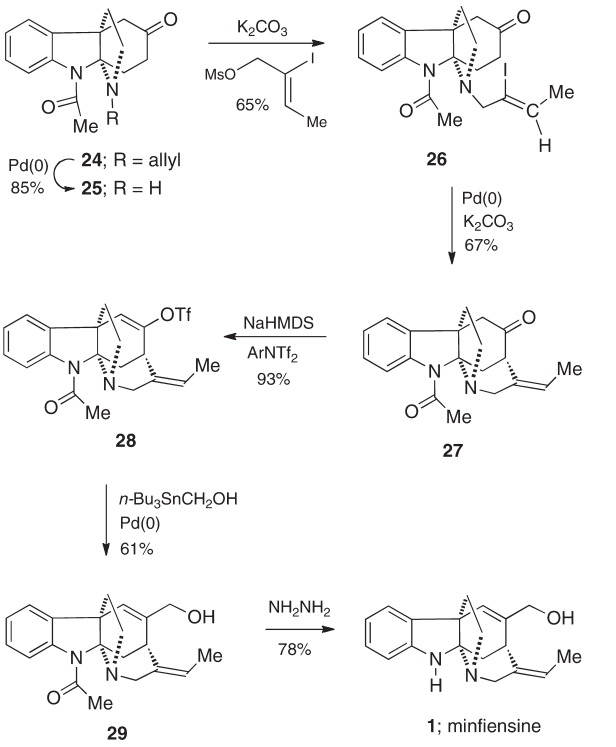
(14) Pine, S. *Org. React.* **1993**, *43*, 2.

(15) Klapars, A.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 7421.

Scheme 3



Scheme 4



cross-coupled with 2-bromofuran using CuTC as the catalyst. In this case, cycloadduct **20** was obtained in 82% yield. When **20** was heated in toluene at 120 °C in the presence of catalytic MgI_2, the only product isolated in 60% yield corresponded to tetracycle **24** presumably derived from an acid catalyzed cyclization of **22**. Removal of the *N*-allyl group from **24** was easily realized with $Pd(PPh_3)_4$ and *N*,*N*-dimethylbarbituric acid using a procedure developed by Guibé and co-workers in 85% yield.[16] The required vinyl iodide cyclization precursor **26** was then secured in 67% yield by reaction of secondary amine **25** with *Z*-2-iodo-2-butenyl mesylate[17] employing K_2CO_3 as the base in acetonitrile at 70 °C. With tetracyclic iodoketone **26** in hand, we turned toward the formation of minfiensine by a palladium-catalyzed intramolecular enolate/vinyl iodide coupling (Scheme 4).[9,18] The reaction was carried out in methanol using 10 mol % of $PdCl_2$-(dppf) and 4 equiv of K_2CO_3 at 70 °C which afforded the expected pentacyclic ketone **27** in 67% yield. Straightforward conversion of **27** to the corresponding enol triflate **28** using Comins' reagent followed by a Stille cross-coupling reaction with tri-*n*-butylstannylmethanol[19] furnished pentacycle **29**. Finally, removal of the acetyl group with hydrazine led to the isolation of (±)-minfiensine in 78% yield.

In summary, an efficient synthesis of (±)-minfiensine has been achieved. A distinctive feature of the synthesis is the use of an intramolecular Diels–Alder cycloaddition/rearrangement cascade of an amidofuran derivative. The synthetic sequence starts with an easily prepared *o*-styryl substituted amide by a Suzuki–Miyaura cross-coupling reaction. A subsequent Buchwald–Hartwig amidation leads to a transient furanyl amide which undergoes ready [4 + 2]-cycloaddition across the tethered p-bond. Thermal reorganization of the resulting cycloadduct affords the critical tetrahydroiminoethanocarbazole skeleton of the alkaloid in high yield. The functionality present in the pentacyclic skeleton allowed for the final elaboration to (±)-minfiensine.

Acknowledgment. We appreciate the financial support provided by the National Science Foundation (CHE-1057350).

Supporting Information Available. Spectroscopic data and experimental details for the preparation of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

(16) Garro-Helion, F.; Merzouk, A.; Guibé, F. *J. Org. Chem.* **1993**, *58*, 6109.

(17) Wanner, M. J.; Boots, R. N. A.; Eradus, B.; de Gelder, R.; Van Maarseveen, J. H.; Hiemstra, H. *Org. Lett.* **2009**, *11*, 2579.

(18) Zhang, H.; Boonsombat, J.; Padwa, A. *Org. Lett.* **2007**, *9*, 279.

(19) Danheiser, R. L.; Romines, K. R.; Koyama, H.; Gee, S. K.; Johnson, C. R; Medich, J. R. *Org. Synth.* **1993**, *71*, 133.