ORGANIC LETTERS

2013
Vol. 15, No. 11
2601–2603

An Approach to the Skeleton of Aspidophylline A

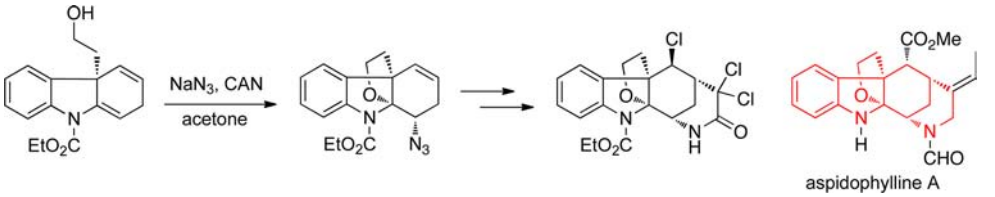
Qi Li,[†] Guang Li,[†] Shaobo Ma,[†] Pengju Feng,[†] and Yian Shi*[,†,‡]

Beijing National Laboratory of Molecular Sciences, CAS Key Laboratory of Molecular Recognition and Function, Institute of Chemistry, Chinese Academy of Sciences, Beijing 100190, China, and Department of Chemistry, Colorado State University, Fort Collins, Colorado 80523, United States

yian@lamar.colostate.edu

Received March 21, 2013

ABSTRACT



An approach to the pentacyclic core of aspidophylline A is described. The strategy features CAN-mediated intramolecular azidoalkoxylation of enecarbamate and ruthenium-catalyzed atom transfer cyclization.

Aspidophylline A (**1**), a monoterpene indole alkaloid isolated by Kam and co-workers from *K. singapurensis* in 2007, has displayed the ability to reverse drug resistance in drug-resistant KB cells (Figure 1).[1] Aspidophylline A contains an indoline fused with a tetrahydrofuran ring and five contiguous chiral centers within a cyclohexane ring. The unique structure and its interesting biological activity make aspidophylline A an attractive synthetic target. During our studies toward this compound, a total synthesis of (±)-aspidophylline A was recently reported by Garg and his colleagues, involving an elegant interrupted Fischer indole cyclization.[2] Herein, we wish to report our own efforts to assemble the skeleton of aspidophylline A.

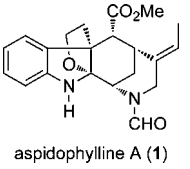
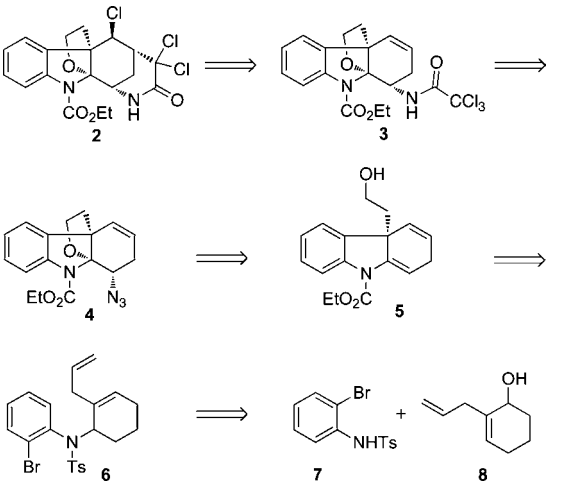


Figure 1. Structure of aspidophylline A.

Scheme 1. Retrosynthetic Analysis of Aspidophylline A Skeleton



The retrosynthetic analysis of aspidophylline A skeleton (**2**) is outlined in Scheme 1. The aza-bicycle [3,3,1] moiety of compound **2** could be constructed by ruthenium-catalyzed atom transfer cyclization from trichloroacetamide **3**, which was envisioned to be derived from azide **4**.

[†] Chinese Academy of Sciences.
[‡] Colorado State Untiversity.

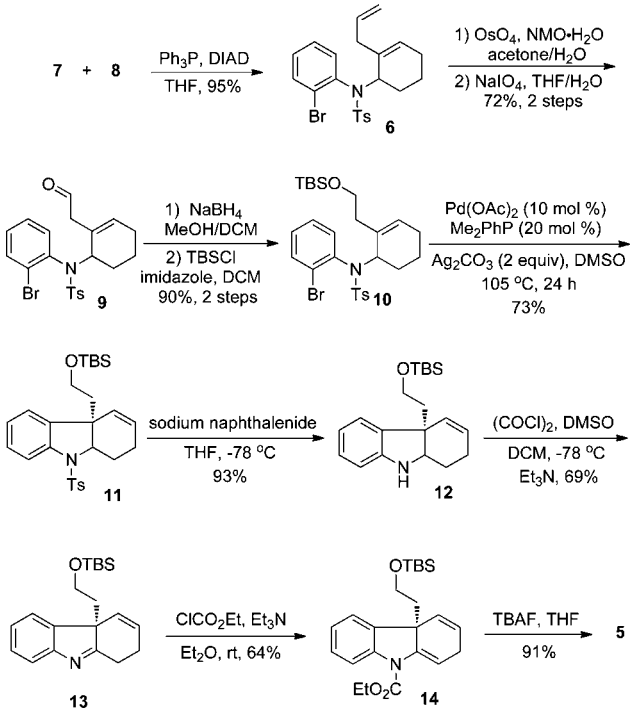
(1) Subramaniam, G.; Hiraku, O.; Hayashi, M.; Koyano, T.; Komiyama, K.; Kam, T. S. *J. Nat. Prod.* **2007**, *70*, 1783.

(2) Zu, L.; Boal, B. W.; Garg, N. K. *J. Am. Chem. Soc.* **2011**, *133*, 8877.

10.1021/ol4007713
Published on Web 05/22/2013

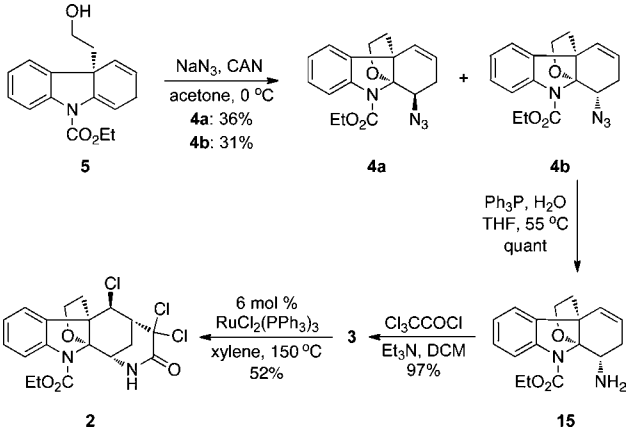
Compound **4** was conceived to be obtained by cerium ammonium nitrate (CAN) mediated azidoalkoxylation of enecarbamate **5**, which could be prepared from **6** through Heck cyclization and functional manipulations. Compound **6** could be synthesized from two known compounds *N*-tosyl-2-bromoaniline (**7**) and 2-allyl-2-cyclohexenol (**8**).

Scheme 2. Synthesis of Compound **5**



The synthesis of enecarbamate **5** is outlined in Scheme 2. Readily available compounds **7**[3] and **8**[4] were coupled via a Mitsunobu reaction to give compound **6** in 95% yield.[5] The terminal alkene of **6** was selectively dihydroxylated with OsO_4/NMO and oxidatively cleaved by $NaIO_4$ to afford aldehyde **9** in 72% yield over two steps.[5] Upon reduction by $NaBH_4$ and silylation with TBSCl, aldehyde **9** was converted to compound **10**, which was subjected to Mori's conditions [10 mol % $Pd(OAc)_2$, 20 mol % Me_2PhP, and 2 equiv of Ag_2CO_3 in DMSO at 105 °C] for the Heck cyclization to afford indoline **11** in 73% yield.[6] The choice of Me_2PhP is crucial to the suppression of the olefin isomerization during the Heck reaction. Indoline **11** was converted to enecarbamate **5** via the removal of the Ts group by sodium naphthalenide (93% yield),[6c,7] Swern oxidation (69% yield),[8] the formation of enecarbamate with $ClCO_2Et$ and Et_3N (64% yield),[9] and subsequent desilylation by TBAF (91% yield).

Scheme 3. Synthesis of Compound **2**



With enecarbamate **5** in hand, azidoalkoxylation was subsequently investigated. While the intermolecular azidoalkoxylation has been reported,[10−13] the intramolecular

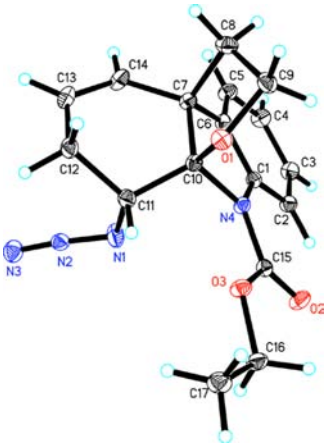


Figure 2. X-ray structure of compound **4a**.

(3) Krolski, M. E.; Renaldo, A. F.; Rudisill, D. E.; Stille, J. K. *J. Org. Chem.* **1988**, *53*, 1170.
(4) (a) Taber, D. F. *J. Org. Chem.* **1976**, *41*, 2649. (b) Taber, D. F.; Gunn, B. P.; Chiu, I. C. *Org. Synth.* 1990, *Coll. Vol. VII*, 249.
(5) (a) Kizil, M.; Murphy, J. A. *J. Chem. Soc., Chem. Commun.* **1995**, 1409. (b) Fletcher, R.; Kizil, M.; Lampard, C.; Murphy, J. A.; Roome, S. J. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2341. (c) Kizil, M.; Patro, B.; Callaghan, O.; Murphy, J. A.; Hursthouse, M. B.; Hibbs, D. *J. Org. Chem.* **1999**, *64*, 7856.
(6) (a) Oestreich, M. *The Mizoroki–Heck Reaction*; John Wiley & Sons: Chichester, U.K., 2009. (b) Heck, R. F.; Nolley, J. P., Jr. *J. Org. Chem.* **1972**, *37*, 2320. (c) Mori, M.; Nakanishi, M.; Kajishima, D.; Sato, Y. *J. Am. Chem. Soc.* **2003**, *125*, 9801.
(7) McIntosh, J. M.; Matassa, L. C. *J. Org. Chem.* **1988**, *53*, 4452.
(8) Keirs, D.; Overton, K. *J. Chem. Soc., Chem. Commun.* **1987**, 1660.
(9) Kuznetsov, V. V.; Naumov, Y. I.; Minaev, L. I.; Andreeva, E. N.; Prostakov, N. S. *Pharm. Chem. J.* **1991**, *25*, 377.
(10) For leading books or reviews on organic azides, see: (a) Bräse, S.; Banert, K. *Organic Azides: Syntheses and Applications*; John Wiley & Sons: Chichester, U.K., 2010; pp 239−267. (b) Bräse, S.; Gil, C.; Knepper, K.; Zimmermann, V. *Angew. Chem., Int. Ed.* **2005**, *44*, 5188. (c) Minozzi, M.; Nanni, D.; Spagnolo, P. *Chem.—Eur. J.* **2009**, *15*, 7830.
(11) Fujimoto, K.; Tokuda, Y.; Matsubara, Y.; Maekawa, H.; Mizuno, T.; Nishiguchi, I. *Tetrahedron Lett.* **1995**, *36*, 7483.
(12) Chavan, S. P.; Subbarao, Y. T. *Tetrahedron Lett.* **1999**, *40*, 5073.
(13) (a) Norton Matos, M. R. P.; Afonso, C. A. M.; Batey, R. A. *Tetrahedron Lett.* **2001**, *42*, 7007. (b) Le Corre, L.; Dhimane, H. *Tetrahedron Lett.* **2005**, *46*, 7495. (c) Le Corre, L.; Kizirian, J. C.; Levraud, C.; Boucher, J. L.; Bonnet, V.; Dhimane, H. *Org. Biomol. Chem.* **2008**, *6*, 3388.

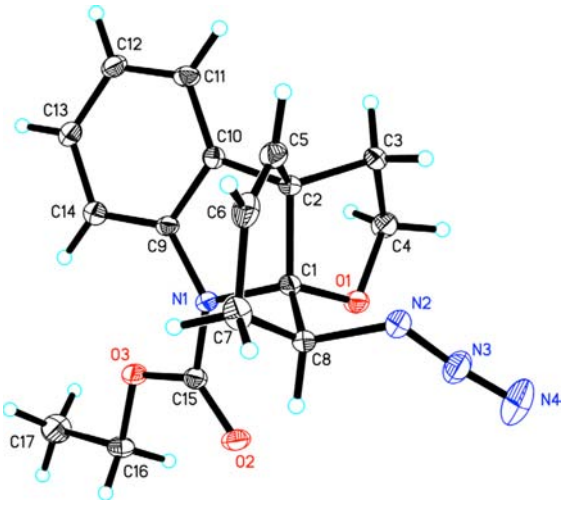


Figure 3. X-ray structure of compound **4b**.

process is less explored. Treating **5** with NaN_3 and CAN in acetone at 0 °C gave azides **4a** and **4b** in 36% and 31% yield, respectively (Scheme 3). The X-ray structures of **4a** and **4b** are shown in Figures 2 and 3. Compound **4b** was readily reduced to amine **15** with Ph_3P in quantitative yield.[14] Acylation of **15** with trichloroacetyl chloride and Et_3N gave trichloroacetamide **3** in 97% yield. Treatment of **3** with 6 mol % $RuCl_2(PPh_3)_3$ in xylene at 150 °C yielded the skeleton of aspidophylline A (**2**) in 52% yield (for the X-ray structure see: Figure 4).[15,16]

In summary, we have developed a rapid synthetic route to the pentacyclic core of aspidophylline A. The key steps involve CAN-mediated intramolecular azidoalkoxylation of an enecarbamate to construct the fused tetrahydrofuran ring and ruthenium-catalyzed intramolecular atom transfer cyclization to form the aza-bicycle [3,3,1] fragment. The synthesis of aspidophylline A and its analogues using this strategy will be pursued.

(14) (a) Staudinger, H.; Meyer, J. *Helv. Chim. Acta* **1919**, *2*, 635. (b) Yokokawa, F.; Asano, T.; Shioiri, T. *Org. Lett.* **2000**, *2*, 4169.

(15) For leading reviews on ruthenium- or copper-catalyzed atom transfer cyclization, see: (a) Iqbal, J.; Bhatia, B.; Nayyar, N. K. *Chem. Rev.* **1994**, *94*, 519. (b) Trost, B. M.; Toste, F. D.; Pinkerton, A. B. *Chem. Rev.* **2001**, *101*, 2067. (c) Matyjaszewski, K.; Xia, J. *Chem. Rev.* **2001**, *101*, 2921. (d) Clark, A. J. *Chem. Soc. Rev.* **2002**, *31*, 1.

(16) (a) Nagashima, H.; Seki, K.; Ozaki, N.; Wakamatsu, H.; Itoh, K.; Tomo, Y.; Tsuji, J. *J. Org. Chem.* **1990**, *55*, 985. (b) Nagashima, H.; Wakamatsu, H.; Ozaki, N.; Ishii, T.; Watanabe, M.; Tajima, T.; Itoh, K. *J. Org. Chem.* **1992**, *57*, 1682.

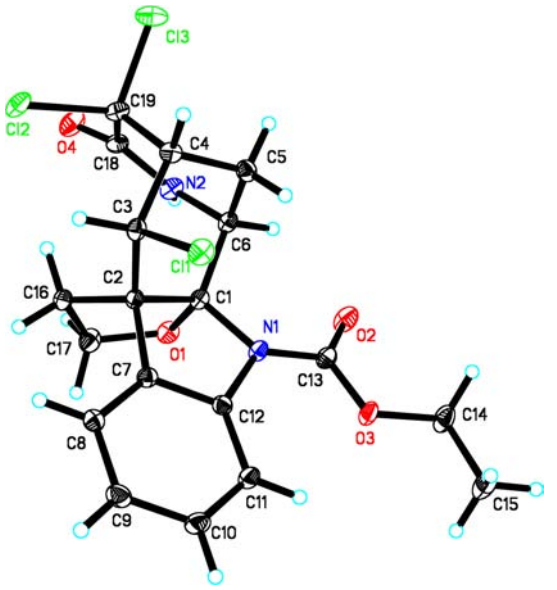


Figure 4. X-ray structure of compound **2**.

Acknowledgment. We gratefully acknowledge the National Basic Research Program of China (973 program, 2011CB808600) and the Chinese Academy of Sciences for the financial support.

Supporting Information Available. Experimental procedures, characterization data, and X-ray data of **4a**, **4b**, and **2** along with NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.