Natural Products

International Edition: DOI: 10.1002/anie.201604770
German Edition: DOI: 10.1002/ange.201604770

Total Synthesis of Calophyline A

*Guang Li[+], Xiaoni Xie[+], and Liansuo Zu**

Abstract: *Reported herein is the total synthesis of calophyline A, an indoline natural product possessing distinct ring connectivity which has not been synthesized previously. The synthetic route features several key transformations, including an aza-pinacol rearrangement to construct the nitrogen-containing bridged [3.2.2] bicycle, a Heck cyclization to assemble the fused 6/5/6/5 ring system, and a challenging late-stage aldol reaction to generate both a neopentyl quaternary stereogenic center and an oxygen-containing bridged [3.2.1] bicycle.*

The akuammiline alkaloids are a class of structurally intricate natural products which have attracted significant attention from synthetic chemists in recent years (Figure 1).[1] While many members of this alkaloid family were isolated more than 50 years ago, their chemical syntheses had not been achieved until recently. The synthetic efforts from the research groups of Qin, Garg, Ma, Smith, MacMillan, Snyder, Zhu, and Yang have led to the inventive total syntheses of vincorine,[2] aspidophylline A,[3] scholarisine A,[4] picrinine,[5] 2-(*S*)-cathafoline, and strictamine.[6] Most recently, the group of Li reported the elegant total syntheses of aspidodasycarpine and its congeners.[7] These synthetic endeavors have tremendously simplified the chemical syntheses of akuammiline alkaloids and provided valuable insights for the assembly of the polycyclic architectures.

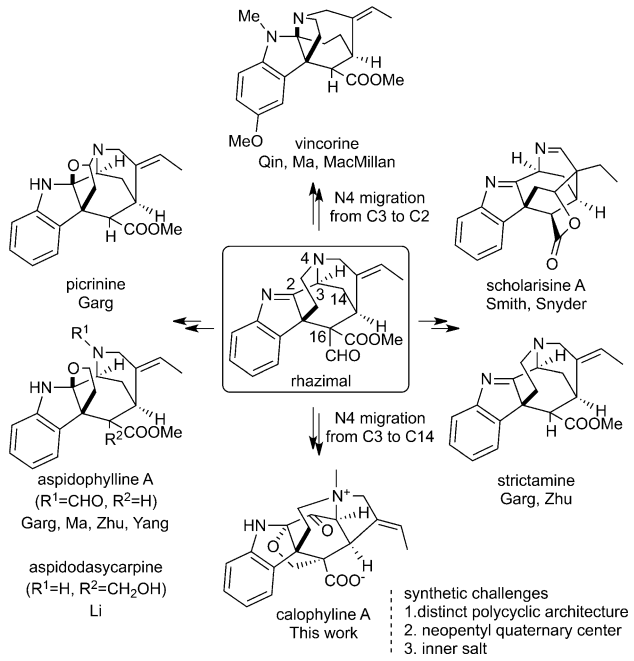


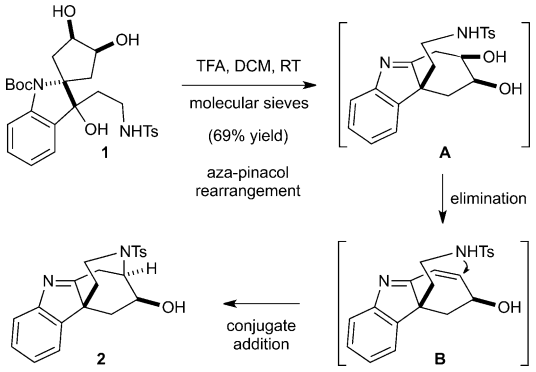
Figure 1. Representative natural products biogenetically derived from rhazimal.

Biogenetically, all the akuammiline alkaloids could be derived from the natural product rhazimal through enzymatic redox transformations or skeletal rearrangements (Figure 1).[1e] While the central N4–C3 bond is maintained for the biosynthetic generation of most akuammiline alkaloids, the structure of vincorine is a result of an N4 migration from C3 to C2 in rhazimal. By contrast, calophyline A, isolated from *Winchia calophylla* by Li, Zou, and co-workers in 2012,[8] biogenetically stems from rhazimal by an unprecedented N4 migration from C3 to C14.[9] To our knowledge, this is the only natural product that possesses the N4–C14 connectivity, which results in a distinct polycyclic architecture associated with this member of the class. The structural uniqueness of calophyline A includes the fused 6/5/6/5 ring system, a nitrogen-containing bridged [3.2.2] bicycle, an oxygen-containing bridged [3.2.1] bicycle, and the form of an inner salt. These structural features present significant synthetic challenges, and by far no synthetic studies toward the chemical synthesis of this natural product have been documented. Herein, we report the first total synthesis of calophyline A based on our previously developed aza-pinacol rearrangement.[10] Moreover, the introduction of the neopentyl quaternary stereogenic center (C16) has been difficult in this area. The group of Li creatively addressed this problem at the relative early state of their syntheses.[7] We, in contrast, relied on a late-stage aldol reaction on an extremely congested bridged polycycle.

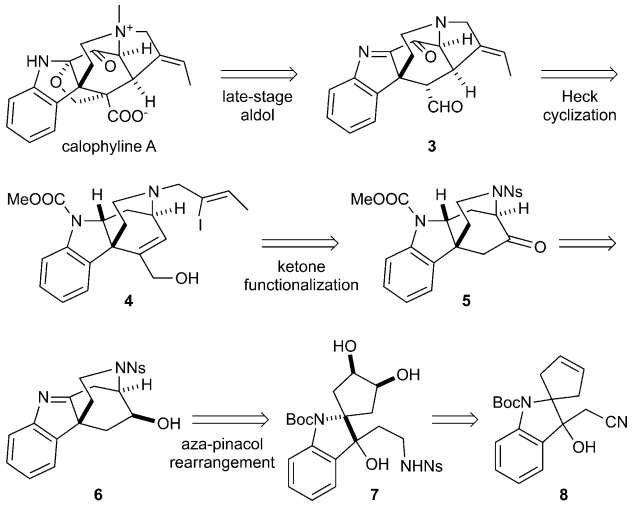
Inspired by the intricate polycyclic structures of akuammiline alkaloids, we have recently developed a conceptually distinct strategy for the synthesis of the hydrocarbazole framework from an unprecedented aza-pinacol rearrangement.[10a] Specifically, the compound **2**, which represents the core structure of calophyline A, was obtained from the triol **1** with good yield and excellent diastereoselectivity (Scheme 1). This remarkable single-step transformation highlights a highly efficient cascade reaction sequence involving the removal of a Boc protecting group, aza-pinacol rearrangement (**A**), regioselective elimination of water (**B**), and aza-conjugate addition to furnish the bridged [3.2.2] bicycle. The overall conversion of **1** into **2** represents one of the most complex examples of aza-pinacol rearrangements, which have not been extensively studied in natural product synthesis.[10b]

[*] Dr. G. Li,[+] X. Xie,[+] Prof. Dr. L. Zu
School of Pharmaceutical Sciences, Tsinghua University
Beijing 100084 (China)
E-mail: zuliansuo@biomed.tsinghua.edu.cn
Prof. Dr. L. Zu
Collaborative Innovation Center for Biotherapy, State Key Laboratory of Biotherapy and Cancer Center, West China Hospital, West China Medical School, Sichuan University, Chengdu, 610041 (China)
[+] These authors contributed equally to this work.

Supporting information for this article can be found under: http://dx.doi.org/10.1002/anie.201604770.



Scheme 1. Aza-pinacol rearrangement based strategy. DCM = dichloromethane, TFA = trifluoroacetic acid, Boc = *tert*-butoxycarbonyl, Ts = 4-toluenesulfonyl.

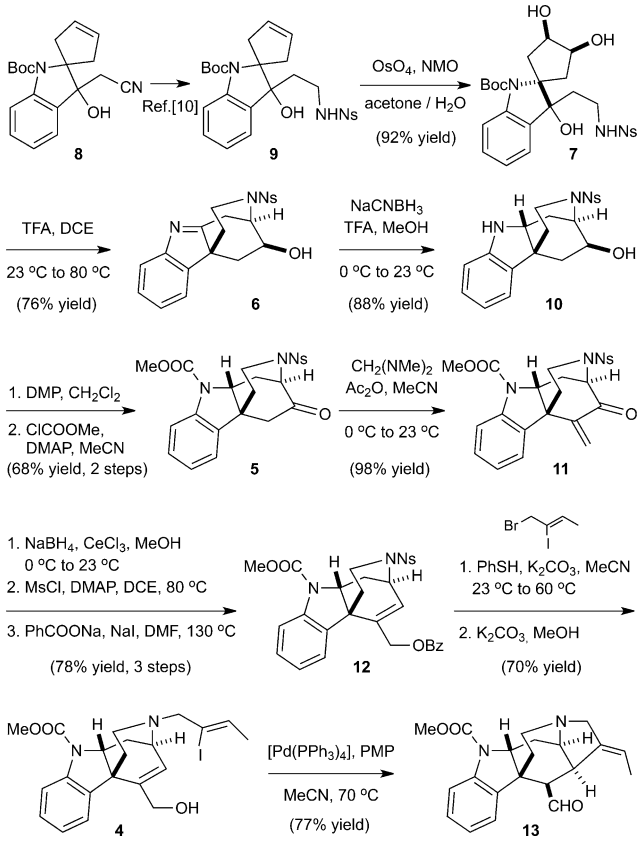


Scheme 2. Retrosynthetic analysis of calophyline A. Ns = *o*-nitrobenzenesulfonyl.

Based on this strategy, the retrosynthetic analysis of calophyline A is depicted in Scheme 2.

We envisioned access to calophyline A from the aldehyde **3** by a late-stage aldol reaction with formaldehyde (Scheme 2). The nitrogen-containing fused five-membered ring in **3** could be constructed by a palladium-catalyzed Heck cyclization of **4**, which in turn could be assembled by the functionalization of the ketone **5**. The compound **5** could be traced back to **6**, the product of the aza-pinacol rearrangement of **7**. The synthesis of **7** could be achieved by the synthetic manipulations of **8**, an intermediate which was previously utilized for the divergent synthesis of a variety of polycyclic structures and the formal total synthesis of natural product minfiensine.[10a]

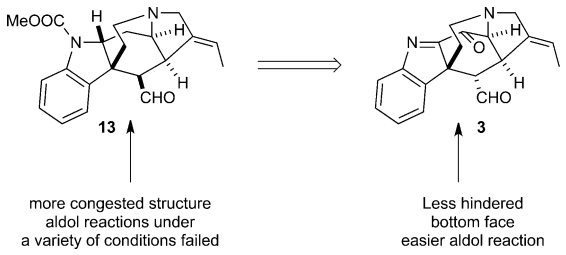
The synthesis of calophyline A commenced with the preparation of **7**, the precursor for the aza-pinacol rearrangement (Scheme 3). Diastereoselective dihydroxylation of **9**, which was previously prepared from **8** in a one-pot reduction/protection procedure,[10] delivered **7** in 92% yield. The aza-pinacol rearrangement initiated cascade reaction of **7** proceeded with high efficiency and excellent diastereoselectivity,



Scheme 3. Synthesis of **13** by Heck cyclization. Unless stated otherwise, reactions were performed at room temperature (RT, approximately 23 °C). DCE = 1,2-dichloroethane, DMAP = 4-dimethylaminopyridine, DMF = dimethylformamide, DMP = Dess–Martin periodinane, MsCl = methanesulfonyl chloride, NMO = 4-methylmorpholine *N*-oxide, PMP = 1,2,2,6,6-pentamethylpiperidine.

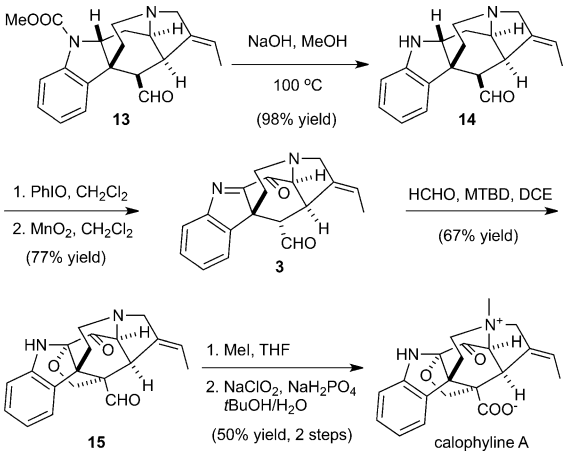
thus establishing the intricate polycycle **6** bearing three stereogenic centers. Reduction of the indolenine afforded **10**, which underwent Dess–Martin oxidation of the secondary alcohol and N-protection to provide the ketone **5**. The α-functionalization of this ketone turned out to be very challenging because of the steric hindrance imposed by the adjacent quaternary stereogenic center. For instance, attempts to directly install a methyl ester using methyl cyanoformate or dimethyl carbonate under a variety of reaction conditions by enolate chemistry proved fruitless.[11] Gratifyingly, α-methylenation using bis(dimethylamino)methane and acetic anhydride, reaction conditions recently utilized by Reisman and co-workers for the α-methylenation of a complex cyclopentanone,[12] led to the formation of the exocyclic enone **11**, which contains the suitable functionality for subsequent elaboration. The internal alkene **12** was prepared from **11** in three steps, including Luche reduction, O-mesylation, and S_N2' substitution. From **12**, a one-pot manipulation, involving denosylation, S_N2 alkylation and the removal of the Bz group, afforded **4**, the precursor for the Heck cyclization.[13,14] Upon treatment of **4** with $[Pd(PPh_3)_4]$ and pentamethylpiperidine (PMP) under reaction conditions reported by the groups of Vanderwal and Garg,[14c,3a] the fused five-membered ring in **13** was successfully constructed with the concomitant generation of an aldehyde group.

At this stage, **13** served as a potential substrate to engage in a late-stage aldol reaction required to generate the neopentyl quaternary stereogenic center of the natural product. However, the reaction of **13** with formaldehyde or its surrogates under a variety of reaction conditions failed, thus indicating that this bridged polycycle is very congested and difficult to be decorated. We envisioned that the planar geometry of a more advanced indolenine **3** might render the bottom face less hindered, and thus the late-stage aldol reaction should be easier to proceed in a facial-selective manner (Scheme 4).



Scheme 4. Analysis of the late-stage aldol reaction.

Thus, we turned our attention to the construction of **3** and the total synthesis of this structurally unique natural product (Scheme 5). From **13**, removal of the methyl carbamate protecting group delivered **14**, which was subsequently oxidized by PhIO[4c] and MnO_2 to provide the aldehyde **3**, the necessary substrate for the late-stage aldol reaction. It should be noted that an epimerization occurred during the oxidation process at the α-carbon atom of the aldehyde, presumably because of the favorable placement of this side chain at the less hindered bottom face. The epimerization was inconsequential for the subsequent transformation involving an enol intermediate, whereas strongly implied that the late-stage aldol reaction would probably be facial selective. Not surprisingly, the late-stage introduction of the neopentyl quaternary stereogenic center, namely the conversion of **3** into **15,** proved to be challenging. To our knowledge, this type of late-stage reaction of the extremely congested bridged polycycle has not been achieved in the syntheses of akuammiline alkaloids. In the presence of alkali salts, reagents utilized by Cook and co-workers for aldol reactions with bulky substrates,[15] the reactions of **3** with formaldehyde only led to the decomposition of the starting material. Moreover, the aldol product tended to release the steric repulsion by retro-aldol reaction under strongly basic conditions. After extensive optimization, we were able to identify suitable reaction conditions for this critical transformation. Using 7-methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene (MTBD)[16] as the base, the facial-selective aldol reaction occurred with the concomitant cyclization of the resulting alcohol onto the indolenine, thus generating **15** in 67% yield.[17] Finally, a one-pot N-methylation and Pinnick oxidation led to the completion of the first total synthesis of calophyline A. The NMR spectra and mass spectrometric data of the synthetic sample match those reported.[8]



Scheme 5. Total synthesis of calophyline A. Unless stated otherwise, reactions were performed at RT (approximately 23 °C). MTBD = 7-methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene, DCE = 1,2-dichloroethane, THF = tetrahydrofuran.

In summary, we have achieved the total synthesis of calophyline A, an indoline natural product possessing distinct ring connectivity which has not been synthesized previously. Our synthetic route to this natural product features several key transformations, including an aza-pinacol rearrangement to construct the nitrogen-containing bridged [3.2.2] bicycle, a Heck cyclization to assemble the fused 6/5/6/5 ring system, and a challenging late-stage aldol reaction to generate both a neopentyl quaternary stereogenic center and an oxygen-containing bridged [3.2.1] bicycle. The synthesis successfully demonstrated the synthetic utility of our previously developed aza-pinacol rearrangement in complex natural product synthesis and set the stage for future synthetic endeavors.

Acknowledgments

We are grateful to Tsinghua University, "1000 Talents Recruitment Program", and Collaborative Innovation Center for Biotherapy (Tsinghua University and Sichuan University) for financial support.

Keywords: aldol reactions · alkaloids · natural products · rearrangements · total synthesis

How to cite: *Angew. Chem. Int. Ed.* **2016**, *55*, 10483–10486
Angew. Chem. **2016**, *128*, 10639–10642

[1] For selected accounts, highlights, and reviews of akuammiline alkaloids, see: a) A. Ramirez, S. Garcia-Rubio, *Curr. Med. Chem.* **2003**, *10*, 1891–1915; b) D. Zhang, H. Song, Y. Qin, *Acc. Chem. Res.* **2011**, *44*, 447–457; c) R. Eckermann, T. Gaich, *Synthesis* **2013**, *45*, 2813–2823; d) E. Doris, *Angew. Chem. Int. Ed.* **2014**, *53*, 4041–4042; *Angew. Chem.* **2014**, *126*, 4121–4122; e) J. M. Smith, J. Moreno, B. W. Boal, N. K. Garg, *Angew. Chem. Int. Ed.* **2015**, *54*, 400–412; *Angew. Chem.* **2015**, *127*, 410–422; f) W. Zi, Z. Zuo, D. Ma, *Acc. Chem. Res.* **2015**, *48*, 702–711.

[2] For total synthesis of vincorine, see: a) M. Zhang, X. Huang, L. Shen, Y. Qin, *J. Am. Chem. Soc.* **2009**, *131*, 6013–6020; b) W. Zi, W. Xie, D. Ma, *J. Am. Chem. Soc.* **2012**, *134*, 9126–9129; c) B. D.

Horning, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2013**, *135*, 6442 – 6445.
[3] For total synthesis of aspidophylline A, see: a) L. Zu, B. W. Boal, N. K. Garg, *J. Am. Chem. Soc.* **2011**, *133*, 8877 – 8879; b) M. Teng, W. Zi, D. Ma, *Angew. Chem. Int. Ed.* **2014**, *53*, 1814 – 1817; *Angew. Chem.* **2014**, *126*, 1845 – 1848; c) W. Ren, Q. Wang, J. Zhu, *Angew. Chem. Int. Ed.* **2014**, *53*, 1818 – 1821; *Angew. Chem.* **2014**, *126*, 1849 – 1852; d) S. Jiang, X. Zeng, X. Liang, T. Lei, K. Wei, Y. Yang, *Angew. Chem. Int. Ed.* **2016**, *55*, 4044 – 4048; *Angew. Chem.* **2016**, *128*, 4112 – 4116.
[4] For total synthesis of scholarisine A, see: a) G. L. Adams, P. J. Carroll, A. B. Smith III, *J. Am. Chem. Soc.* **2012**, *134*, 4037 – 4040; b) G. L. Adams, P. J. Carroll, A. B. Smith III, *J. Am. Chem. Soc.* **2013**, *135*, 519 – 528; c) M. W. Smith, S. A. Snyder, *J. Am. Chem. Soc.* **2013**, *135*, 12964 – 12967.
[5] For total synthesis of picrinine, see: a) J. M. Smith, J. Moreno, B. W. Boal, N. K. Garg, *J. Am. Chem. Soc.* **2014**, *136*, 4504 – 4507; b) J. M. Smith, J. Moreno, B. W. Boal, N. K. Garg, *J. Org. Chem.* **2015**, *80*, 8954 – 8967.
[6] For total syntheses of 2-(*S*)-cathafoline and strictamine, see: a) J. Moreno, E. Picazo, L. A. Morrill, J. M. Smith, N. K. Garg, *J. Am. Chem. Soc.* **2016**, *138*, 1162 – 1165; b) W. Ren, Q. Wang, J. Zhu, *Angew. Chem. Int. Ed.* **2016**, *55*, 3500 – 3503; *Angew. Chem.* **2016**, *128*, 3561 – 3564.
[7] Y. Li, S. Zhu, A. Li, *J. Am. Chem. Soc.* **2016**, *138*, 3982 – 3985.
[8] L. Li, T. Yang, Y. Liu, J. Liu, M. Li, Y. Wang, S. Yang, Q. Zou, G. Li, *Org. Lett.* **2012**, *14*, 3450 – 3453.
[9] B. M. Hudson, J. G. Harrison, D. J. Tantillo, *Tetrahedron Lett.* **2013**, *54*, 2952 – 2955.
[10] a) Y. Yu, G. Li, L. Jiang, L. Zu, *Angew. Chem. Int. Ed.* **2015**, *54*, 12627 – 12631; *Angew. Chem.* **2015**, *127*, 12818 – 12822; b) Y. Yu, G. Li, L. Zu, *Synlett* **2016**, *27*, 1303 – 1309.
[11] For recent examples in total synthesis, see: a) A. B. Dounay, P. G. Humphreys, L. E. Overman, A. D. Wrobleski, *J. Am. Chem. Soc.* **2008**, *130*, 5368 – 5377; b) Z. Bian, C. C. Marvin, S. F. Martin, *J. Am. Chem. Soc.* **2013**, *135*, 10886 – 10889; c) I. T. Chen, I. Baitinger, L. Schreyer, D. Trauner, *Org. Lett.* **2014**, *16*, 166 – 169; d) S. He, W. Yang, L. Zhu, G. Du, C. Lee, *Org. Lett.* **2014**, *16*, 496 – 499.
[12] a) E. C. Taylor, Y. Shvo, *J. Org. Chem.* **1968**, *33*, 1719 – 1727; b) S. J. DeSolms, *J. Org. Chem.* **1976**, *41*, 2650 – 2651; c) J. T. S. Yeoman, V. W. Mak, S. E. Reisman, *J. Am. Chem. Soc.* **2013**, *135*, 11764 – 11767.
[13] For reviews of the Heck reaction, see: a) C. Amatore, A. J. Jutand, *Organomet. Chem.* **1999**, *576*, 254 – 278; b) I. P. Beletskaya, A. V. Cheprakov, *Chem. Rev.* **2000**, *100*, 3009 – 3066; c) A. B. Dounay, L. E. Overman, *Chem. Rev.* **2003**, *103*, 2945 – 2963.
[14] For the use of the Heck reaction in the synthesis of Strychnos alkaloids, see: a) V. H. Rawal, C. Michoud, R. F. Monestel, *J. Am. Chem. Soc.* **1993**, *115*, 3030 – 3031; b) V. H. Rawal, S. J. Iwasa, *Org. Chem.* **1994**, *59*, 2685 – 2686; c) D. B. C. Martin, C. D. Vanderwal, *J. Am. Chem. Soc.* **2009**, *131*, 3472 – 3473; d) S. B. Jones, B. Simmons, A. Mastracchio, D. W. C. MacMillan, *Nature* **2011**, *475*, 183 – 188.
[15] a) J. Yu, X. Z. Wearing, J. M. Cook, *J. Org. Chem.* **2005**, *70*, 3963 – 3979; b) W. Yin, J. Ma, F. M. Rivas, J. M. Cook, *Org. Lett.* **2007**, *9*, 295 – 298.
[16] R. Schwesinger, *Chimia* **1985**, *39*, 269.
[17] The NH was also reacted with formaldehyde by 1,2-addition, thus forming an unstable hemiaminal, which was converted into **15** upon silica gel chromatography. See the Supporting Information.

Received: May 16, 2016
Published online: June 13, 2016

