Total Synthesis

Deutsche Ausgabe: DOI: 10.1002/ange.201510861
Internationale Ausgabe: DOI: 10.1002/anie.201510861

# Total Synthesis of Isodaphlongamine H: A Possible Biogenetic Conundrum

*Amit Kumar Chattopadhyay, Vu Linh Ly, Shashidhar Jakkepally, Gilles Berger, and Stephen Hanessian**

***Abstract:*** *Herein we describe the first synthetic efforts toward the total synthesis of isodaphlongamine H, a calyciphylline B-type alkaloid. The strategy employs a chemoenzymatic process for the preparation of a functionalized cyclopentanol with a quaternary center. This molecule is elaborated to form an enantiopure 1-aza-perhydrocyclopentalene core, representing rings A and E of all calyciphylline B-type alkaloids. Further transformations involve the formation of a cyclic enaminone, 1,4-conjugate addition with a cyclopentenyl subunit, and intramolecular aldol cyclization to achieve a pentacyclic intermediate, ultimately forming isodaphlongamine H in a total of 24 steps from the commercially available compound 2-carbethoxycyclopentanone. Isodaphlongamine H exhibits promising inhibitory activity against a panel of human cancer cell lines.*

The *Daphniphyllum* alkaloids are among the structurally most diverse group of polyazacyclic natural products belonging to a single genus of the family *Daphniphyllaceae*.[1] To date, over 300 different structurally distinct alkaloids have been isolated and characterized, representing complex polyazacyclic cage-like architectures. Besides their biological activities,[1] their biosynthesis, starting with mevalonic acid and proceeding via squalene dialdehyde to progressively complex intermediates, is a fascinating example of the ingenuity of nature. Following pioneering efforts by Suzuki, Yamamura, and co-workers,[2] a unifying biosynthetic pathway to prepare the *Daphniphyllum* alkaloids was proposed by Heathcock and Ruggeri.[3] This seminal contribution paved the way to the elegant total syntheses of several members of this family by the Heathcock group.[4] Inspired by these landmark feats in the total synthesis of complex *Daphniphyllum* alkaloids, a number of groups have reported creative approaches toward the synthesis of a variety of core structures.[5] However, efforts toward the total synthesis of other complex *Daphniphyllum* alkaloids have been sparse. Only relatively recently have the total syntheses of daphmanidin E, daphenylline, and calyciphylline N been reported by the groups of Carreira,[6] Li,[7] and Smith,[8] respectively.

In 2003, Kobayashi and Morita isolated calyciphylline B (**1**) from the leaves of *D. calycinum* and the tentative structure was assigned by NMR spectroscopic analysis (Figure 1).[9] In the same year, deoxycalyciphylline B (**2**) and deoxyisocalyciphylline B (**3**) were isolated from the stem of *D. subverticillatum* by Yue and Yang.[10] In 2009, Hao and co-workers reported the isolation of daphlongamine H (**4**), a new calyciphylline B-type alkaloid with an unprecedented C6/C7 *cis*-ring junction, from the leaf extracts of the evergreen tree *D. longeracemosum* Rosenth.[11] The structure and stereochemistry of daphlongamine H was proposed based on NMR spectroscopy and its biogenetic relationship with deoxycalyciphylline B, whose structure had been confirmed by X-ray crystallography.[10] We now report the total synthesis of isodaphlongamine H, the biogenetically related 5-*epi* isomer of daphlongamine H (Figure 1).

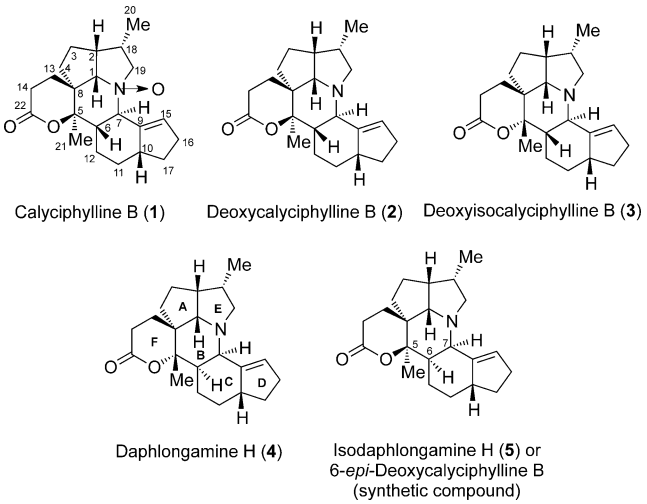



***Figure 1.*** Representative calyciphylline B-type alkaloids and their synthetic analogues.

The biosynthetic pathway proposed by Yue and Yang[10] for deoxycalyciphylline B and deoxyisocalyciphylline B, which differ only in the spatial disposition of the C5 methyl group, presents a possible conundrum (Figure 2). Thus, it is proposed that biosynthetic carbocation intermediate **A**, harboring *cis*-oriented hydrogens at the C6 and C7 positions, loses a hydrogen atom to give the neutral tetrasubstituted olefin intermediate **B**, which would capture a proton in an undefined process to give carbocation **C**, containing *trans*-oriented hydrogens at the C6 and C7 positions. Lactone formation with the appended propionic acid chain would deliver deoxycalyciphylline B (**2**) and deoxyisocalyciphylline B (**3**).

[*] Dr. A. K. Chattopadhyay, V. L. Ly, Dr. S. Jakkepally, Dr. G. Berger, Prof. Dr. S. Hanessian
Department of Chemistry, Université de Montréal
Station Centre Ville, C.P. 6128, Montréal, Qc, H3C 3J7 (Canada)
E-mail: stephen.hanessian@umontreal.ca

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201510861.

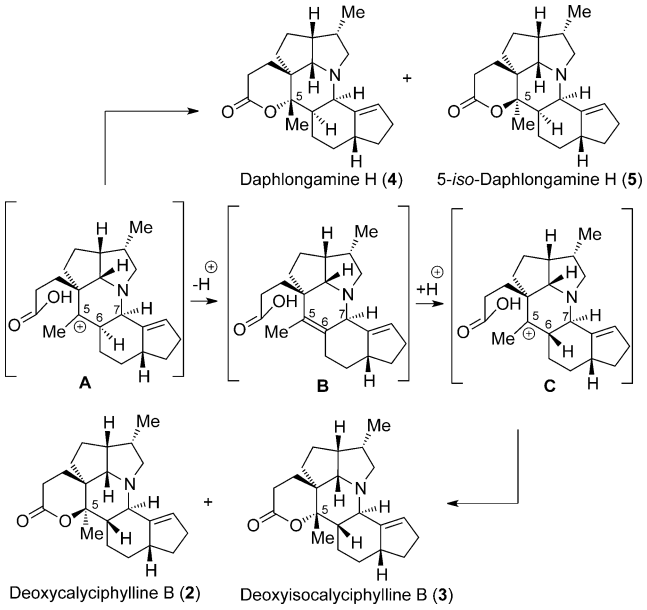



***Figure 2.*** Proposed biosynthetic pathway to deoxycalyciphylline B and deoxyisocalyciphylline B[10] and the anticipated pathway to form daphlongamine H (natural) and isodaphlongamine H (synthetic). The structures of intermediates **A**–**C** were redrawn in the perspectives shown to correspond to the drawing of the natural products. For the original drawings, see Ref. [10].

We propose that daphlongamine H can result from the direct C5 capture of the carbocation **A** with the propionic acid chain. Although not isolated from the extracts of the same plant source as yet, one would also expect lactonization of carbocation **A** to provide the 5-*epi* isomer, that is, isodaphlongamine H (**5**), in analogy with the isolation of deoxycalyciphylline B (**2**) and its 5-*iso* epimer (**3**). In this respect our synthetic isodaphlongamine H could be the "missing" fourth component in the biosynthetically related calyciphylline B-type quartet of *Daphniphyllum* alkaloids.

The unique hexacyclic framework harboring an unprecedented C6/C7 *cis*-fused stereochemistry in the deoxycalyciphylline B family, as well as the intriguing biosynthetic intermediates, encouraged us to undertake the total synthesis of daphlongamine H (**4**) and its 5-*epi* isomer (**5**). We were also cognizant that a strategy which would produce a common advanced intermediate could also be applicable toward the total synthesis of the biogenetically related deoxycalyciphylline B (**2**) and deoxyisocalyciphylline B (**3**) (Figure 2). The hexacyclic framework of daphlongamine H contains eight stereogenic carbon atoms of which one is quaternary at the C8 position. A schematic representation of the key bond-forming reactions is shown in Figure 3. We assumed that an enolate alkylation and an intramolecular cyclization would be used to access rings A and E. The central ring B could be generated from a cyclic enaminone which would undergo 1,4-conjugate addition with a cyclopentenyl organometallic subunit. Subsequent intramolecular aldol cyclization of a keto aldehyde would generate the pentacyclic framework harboring rings A–E. Finally, a late-stage lactonization would provide daphlongamine H and/or isodaphlongamine H.

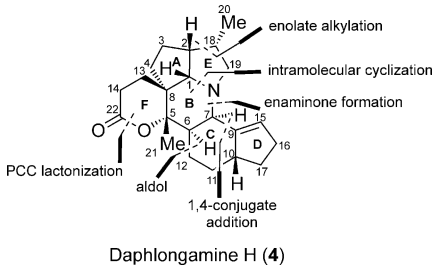
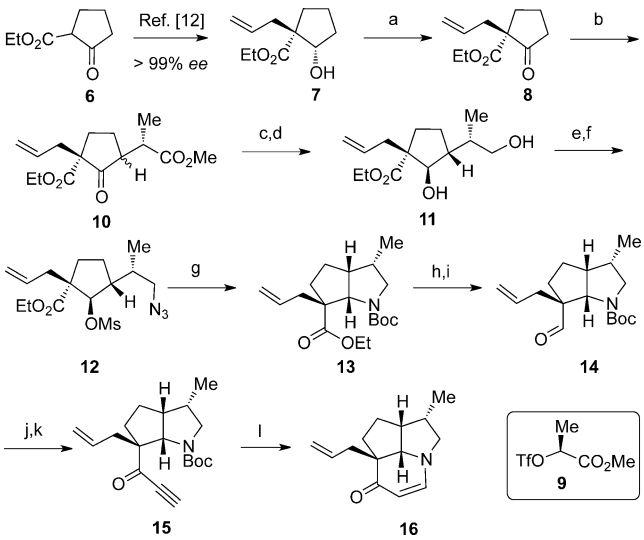



***Figure 3.*** Key synthetic steps toward daphlongamine H (**4**).

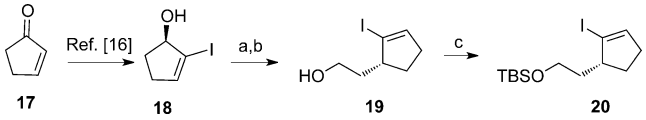
We commenced our synthetic efforts with 2-carbethoxycyclopentanone (**6**) which was transformed to enantiopure cyclopentanol **7** in two consecutive steps using a known chemoenzymatic process[12] (Scheme 1). Swern oxidation of **7** provided β-ketoester **8** in 96% yield. A diastereoselective alkylation of the corresponding Na enolate with triflate **9** prepared from D-lactic acid afforded a 1:1 inseparable mixture of **10** in 41% yield.[13,14] Reduction of **10** was best achieved under Luche conditions to give the corresponding cyclopentanol as a single isomer after chromatographic separation, which was then converted into diol **11** by reduction of the ester with DIBAL-H. Bis-mesylation, followed by selective monoazidation using $Bu_4NN_3$ in toluene afforded **12** in 76% yield over two steps. Treatment of **12**




***Scheme 1.*** Synthesis of tricyclic enaminone **16**. Reagents and conditions: a) $(COCl)_2$, $(Me)_2SO$, $CH_2Cl_2$, $Et_3N$, −78 to 0°C, 96%; b) NaHMDS, toluene, −78 to −40 to −78°C, then **9**, −78 to −40°C, 41% yield (75% brsm), 1:1 mixture of diastereomers; c) $NaBH_4$, $CeCl_3{\cdot}7H_2O$, MeOH, 0°C, 43%; d) DIBAL-H, $CH_2Cl_2$, −78°C, 69%; e) MsCl, pyridine, DMAP, $CH_2Cl_2$, RT, 92%; f) $Bu_4NN_3$, toluene, RT, 83%; g) $PPh_3$, THF, 1 N aqueous NaOH, RT, then $(Boc)_2O$, 91%; h) DIBAL-H, $CH_2Cl_2$, −78 to −40°C, 75%; i) Dess–Martin periodinane, $CH_2Cl_2$, RT, 91%; j) Ethynyl MgBr, THF, 0°C to RT; k) Dess–Martin periodinane, $CH_2Cl_2$, RT, 85% (two steps); l) formic acid, NaI, RT, then evaporated to dryness, then $K_2CO_3$, MeOH, RT, 80%. HMDS = 1,1,1,3,3,3-hexamethyldisilazane, THF = tetrahydrofuran, DIBAL-H = diisobutylaluminum hydride, Ms = methane sulfonyl, DMAP = 4-dimethylaminopyridine, Boc = *tert*-butyl carbonyl; brsm = based on recovered starting material.

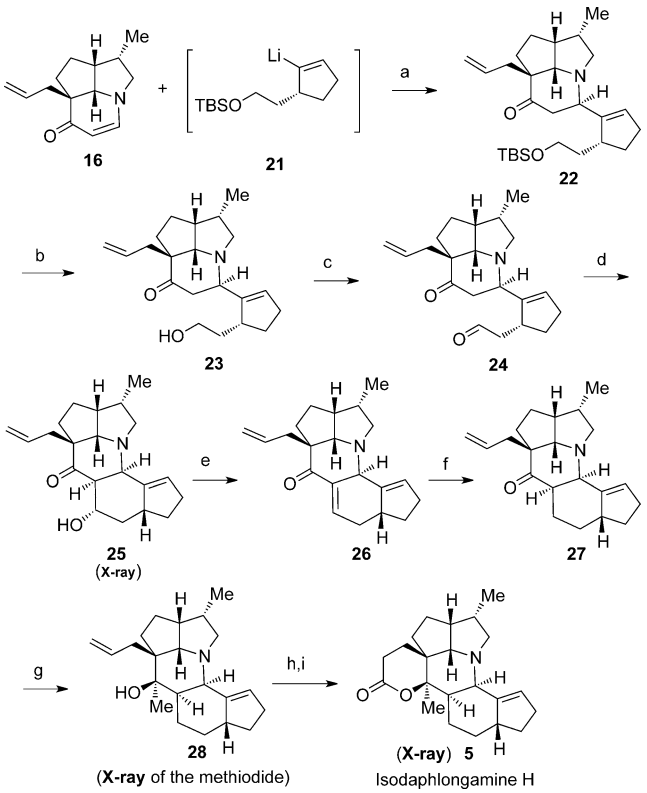
under Staudinger conditions led to the primary amine, which underwent in situ intramolecular cyclization to give the azaoctahydropentalene core unit **13** as the N-Boc derivative in 91% yield. DIBAL-H reduction of the ethyl ester, followed by Dess–Martin oxidation of the corresponding alcohol, afforded aldehyde **14** which was treated with ethynylmagnesium bromide, and the resulting alcohol was oxidized to ynone **15**. Cyclization in the presence of formic acid, NaI and $K_2CO_3$ according to the procedure of Georg et al.[15] afforded the cyclic enaminone **16** with an overall yield of 68% for the three steps.

The synthesis of the cyclopentene subunit corresponding to ring D started with the known enantiopure alcohol **18** (Scheme 2).[16] A Johnson–Claisen rearrangement in the presence of catalytic propionic acid at 145°C led to the homoallylic ester which was reduced with DIBAL-H, and the resulting alcohol **19** was protected as the TBS ether **20** in a maximum of 37% overall yield.




***Scheme 2.*** Synthesis of the cyclopentene subunit. Reagents and conditions: a) $CH_3C(OCH_3)_3$, propionic acid, 145°C; b) DIBAL-H, $CH_2Cl_2$, −78 to −40°C, 25–40% (two steps); c) TBSCl, $Et_3N$, $CH_2Cl_2$, RT, 93%. TBS = *tert*-butyl dimethyl silyl.

With the tricyclic enaminone **16** and cyclopentenyl iodide **20** in hand, we proceeded with the intended 1,4-conjugate addition. Thus, treatment of the iodide **20** with *n*BuLi generated the vinyllithium reagent **21**, which was added to the enaminone **16** in the presence of $BF_3{\cdot}Et_2O$ and $CuBr{\cdot}Me_2S$, based on related precedents by Comins and coworkers,[17] to give adduct **22** in 92% yield and 90% d.e. (Scheme 3). Silyl deprotection to the alcohol **23** gave a single diastereomer which was oxidized with PCC to the ketoaldehyde intermediate **24** in 59% yield over two steps. Following several trials with various bases, we found that TBD (1,5,7-triazabicyclo[4.4.0]dec-5-ene) led to intramolecular aldol cyclization to give **25** in 90% yield.[18] A single crystal X-ray structure analysis confirmed the stereochemistry of the cyclization product including the *cis*-orientation at the B/C ring junction.[14,19] Treatment of **25** with *p*-TSA in 1,1,2-trichloroethane at 65°C resulted in smooth elimination to give the enone **26** which was subjected to conjugate reduction with L-Selectride to afford the pentacyclic intermediate **27** in 42% yield for two steps. Addition of MeLi afforded exclusively the tertiary alcohol **28** whose structure and stereochemistry were determined by X-ray crystallography of the corresponding methiodide salt.[14,19] Considering the *cis*-junction of rings B and C in **27**, it is not surprising that the trajectory of approach of the MeLi reagent toward the carbonyl group favored the less hindered α-face. In view of this result, we chose to complete the synthesis of isodaphlongamine H (**5**). Thus, the allylic double bond in **28** was hydroborated to the primary alcohol and the latter was oxidized with PCC to the lactol which was further trans-

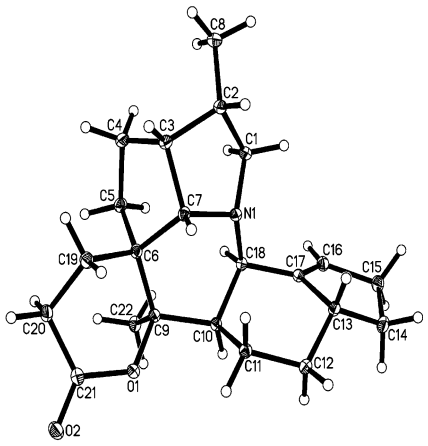



***Scheme 3.*** Synthesis of isodaphlongamine H. Reagents and conditions: a) **20**, *n*BuLi, $Et_2O$, −78°C; then $CuBr{\cdot}Me_2S$, $BF_3{\cdot}Et_2O$, THF, −78°C, then **16**, −78°C to RT, 92%; b) (±)-CSA, $CH_2Cl_2$, MeOH, RT, 91%; c) PCC, $CH_2Cl_2$, RT, 65%; d) TBD, THF, RT, 90%; e) *p*-TSA, 1,1,2-trichloroethane, 65°C, 70%; f) L-Selectride, $Et_2O$, −78 to −20°C, 60%; g) MeLi, THF, −78 to +10°C, 85%; h) 9-BBN, THF, RT; then 2 N NaOH, $H_2O_2$, RT; i) PCC, $CH_2Cl_2$, RT, 65% (two steps). CSA = camphorsulfonic acid, PCC = pyridinium chlorochromate, TBD = 1,5,7-triazabicyclo[4.4.0]dec-5-ene, *p*-TSA = *p*-toluenesulfonic acid, 9-BBN = 9-borabicyclo[3.3.1]nonane; L-Selectride = lithium tri-*sec*-butylborohydride.

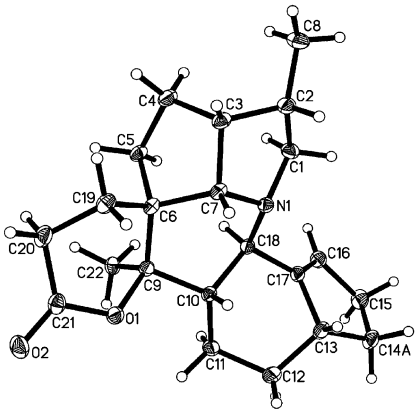
formed in situ to lactone **5**. An X-ray crystal structure analysis of **5** confirmed the absolute stereochemistry.[14,19] It is interesting to note that in the crystal structure of deoxycalyciphylline B, ring C adopts a boat conformation,[14] whereas the crystal structure of our synthetic isodaphlongamine H (or 6-*epi*-deoxycalyciphylline B) shows a chair conformation (Figure 4).[14] DFT calculations also suggest that isodaphlongamine H is 3.3 kcal mol$^{-1}$ more stable than deoxycalyciphylline B.[14]

Considering the proposed biosynthetic pathway, it is intriguing that intermediate **A** would preferentially give the tetrasubstituted intermediate olefin **B**, which would be subject to severe $A^{1,3}$-strain only to reprotonate to **C**, then to cyclize to deoxycalyciphylline B (**2**) and deoxyisocalyciphylline B (**3**). In an attempt to reproduce the synthetic equivalent of the proposed tetrasubstituted intermediate **B** in the biosynthetic pathway[10] (Figure 2), we investigated the tertiary alcohol **28** under a variety of elimination reaction conditions. These led exclusively to the exocyclic methylene product **29** (Scheme 4). All attempts to isomerize it to the endocyclic pentacycle **30** corresponding to the intermediate **B** in the biosynthesis

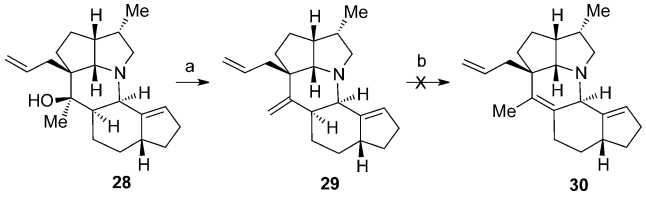



**Isodaphlongamine H**




**Deoxycalyciphylline B**

***Figure 4.*** ORTEP diagrams of isodaphlongamine H and deoxycalyciphylline B.[19]




***Scheme 4.*** Attempted synthesis of the tetrasubstituted intermediate **B** reported by Yue and Yang (Ref. [10]). Reagents and conditions: a) $BF_3{\cdot}Et_2O$, $CH_2Cl_2$, 80%; or $SOCl_2$, pyridine, THF, −50 to +10°C, 85%; b) oxalic acid, toluene, 115°C; or *p*-TSA, 1,1,2-trichloroethane, 115°C.

failed, most likely because of severe $A^{1,3}$-strain. DFT calculations concur with these results, showing that structure **30** is 2.5 kcal mol$^{-1}$ higher in energy compared to **29**.[14] The value for the corresponding propionic acid (represented by intermediate **B** in Figure 2) is 3.7 kcal mol$^{-1}$ higher compared to that of an exocyclic methylene isomer.[14]

Clearly, the biosynthetic steps involving the transformation of C6/C7 *cis*-pentacyclic intermediate **A** to the *trans* isomer **C** as found in deoxycalyciphylline B and its 5-*iso* congener (Figure 2) remain unresolved[9] and warrant further study. Based on the carbocation intermediate **A** proposed by Yue, it seems highly probable that daphlongamine H and isodaphlongamine H can be formed by direct lactonization.

The only biological activity in this unique family of hexacyclic alkaloids has been reported for calyciphylline B ($IC_{50}$ = 12 μM against L1210 cells).[9] With the new synthetic alkaloid isodaphlongamine H (**5**; 6-*epi*-deoxycalyciphylline B) in hand, we have obtained in vitro data on a panel of NCI human cancer cell lines. Preliminary studies showed that isodaphlongamine H exhibited good cytotoxicity against HOP-92 (lung), SNB-75 (central nervous system), MDA_MB-435 (melanoma), and UO-31 (renal) cell lines with $GI_{50}$ (50% growth inhibition) values of 38, 35, 48, and 43 μM respectively.[14] The natural product deoxycalyciphylline B, tested for the first time, was found to be only two times more active than isodaphlongamine H.

In conclusion, we have reported a highly convergent total synthesis of isodaphlongamine H accomplished in 24 linear steps from the commercially available 2-carbethoxycyclopentanone **6**. Isodaphlongamine H, the 5-*epi* isomer of daphlongamine H (the only *cis*-fused naturally occurring *Daphniphyllum* alkaloid isolated to date among the calyciphylline B family), is believed to be the missing component in this quartet of structurally unique hexacyclic alkaloids. Their hitherto unreported antitumor activities against a variety of cancer cell lines warrants further effort toward the total synthesis of related congeners.

## Acknowledgements

We thank Steven Cummings (McGill University) and Gabriel Meilleur (Université de Montréal) as undergraduate research participants for Baker's yeast resolution experiments. We are thankful to Dr. Michel Simard for X-ray crystallography and to Dr. Cédric Malveau for high-resolution NMR studies. We are also very grateful to Professor Yue for an X-ray quality sample of deoxycalyciphylline B as a reference compound. Anticancer activity was determined at the National Cancer Institute (Washington, D.C.) for which we are highly appreciative.

**Keywords:** alkaloids · deoxycalyciphylline B · enaminones · natural products · total synthesis

**How to cite:** *Angew. Chem. Int. Ed.* **2016**, *55*, 2577–2581
*Angew. Chem.* **2016**, *128*, 2623–2627

[1] a) B. Kang, P. Jakubec, D. J. Dixon, *Nat. Prod. Rep.* **2014**, *31*, 550–562; b) H. Wu, X. Zhang, L. Ding, S. Chen, J. Yang, X. Xu, *Planta Med.* **2013**, *79*, 1589–1598; c) J. Kobayashi, T. Kubota, *Nat. Prod. Rep.* **2009**, *26*, 936–962; d) C. H. Heathcock, *Angew. Chem. Int. Ed. Engl.* **1992**, *31*, 665–681; *Angew. Chem.* **1992**, *104*, 675–691.

[2] a) K. T. Suzuki, S. Okuda, H. Niwa, M. Toda, Y. Hirata, S. Yamamura, *Tetrahedron Lett.* **1973**, *14*, 799–802; b) H. Niwa, Y. Hirata, K. T. Suzuki, S. Yamamura, *Tetrahedron Lett.* **1973**, *14*, 2129–2132.

[3] R. B. Ruggeri, C. H. Heathcock, *Pure Appl. Chem.* **1989**, *61*, 289–292.

[4] a) C. H. Heathcock, J. A. Stafford, D. L. Clark, *J. Org. Chem.* **1992**, *57*, 2575 – 2585; b) C. H. Heathcock, S. K. Davidsen, S. Mills, M. A. Sanner, *J. Am. Chem. Soc.* **1986**, *108*, 5650 – 5651; c) C. H. Heathcock, R. B. Ruggeri, K. F. McClure, *J. Org. Chem.* **1992**, *57*, 2585 – 2594; d) C. H. Heathcock, J. A. Stafford, D. L. Clark, *J. Org. Chem.* **1992**, *57*, 2566 – 2574; e) C. H. Heathcock, J. C. Kath, R. B. Ruggeri, *J. Org. Chem.* **1995**, *60*, 1120 – 1130.

[5] For recent examples of *Daphniphyllum* alkaloids core structure syntheses, see: a) F. Diaba, A. Martínez-Laporta, G. Coussanes, I. Fernandez, J. Bonjoch, *Tetrahedron* **2015**, *71*, 3642 – 3651; b) J. L. Stockdill, A. M. Lopez, A. A. Ibrahim, *Tetrahedron Lett.* **2015**, *56*, 3503 – 3506; c) D. Ma, H. Cheng, C. Huang, L. Xu, *Tetrahedron Lett.* **2015**, *56*, 2492 – 2495; d) W. Wang, G.-P. li, S.-F. Wang, Z.-F. Shi, X.-P. Cao, *Chem. Asian J.* **2015**, *10*, 377 – 382; e) I. Hayakawa, K. Niida, H. Kigoshi, *Chem. Commun.* **2015**, *51*, 11568 – 11571; f) J.-J. Guo, Y. Li, B. Cheng, T. Xu, C. Tao, X. Yang, D. Zhang, G. Yan, H. Zhai, *Chem. Asian J.* **2015**, *10*, 865 – 868; g) L. Wang, C. Xu, L. Chen, X. Hao, D. Z. Wang, *Org. Lett.* **2014**, *16*, 1076 – 1079; h) X. Xiong, Y. Li, Z. Lu, M. Wan, J. Deng, S. Wu, H. Shao, A. Li, *Chem. Commun.* **2014**, *50*, 5294 – 5297; i) A. A. Ibrahim, A. N. Golonka, A. M. Lopez, J. L. Stockdill, *Org. Lett.* **2014**, *16*, 1072 – 1075; j) H. Li, Y. Qiu, C. Zhao, Z. Yuan, X. Xie, X. She, *Chem. Asian J.* **2014**, *9*, 1274 – 1277; k) D. R. Williams, P. K. Mondal, S. A. Bawel, P. P. Nag, *Org. Lett.* **2014**, *16*, 1956 – 1959; l) S. Dorich, J. R. Del Valle, S. Hanessian, *Synlett* **2014**, 799 – 804; m) S. Hanessian, S. Dorich, H. Menz, *Org. Lett.* **2013**, *15*, 4134 – 4137; n) B. Fang, H. Zheng, C. Zhao, P. Jing, H. Li, X. Xie, X. She, *J. Org. Chem.* **2012**, *77*, 8367 – 8373; o) H. Li, J. Zheng, S. Xu, D. Ma, C. Zhao, B. Feng, X. Xie, X. She, *Chem. Asian J.* **2012**, *7*, 2519 – 2522; p) C. Xu, L. Wang, X. Hao, D. Z. Wang, *J. Org. Chem.* **2012**, *77*, 6307 – 6313; q) M. Yang, l. Wang, S.-H. Wang, S.-Y. Zhang, Y.-Q. Tu, F.-M. Zhang, *Org. Lett.* **2012**, *14*, 5114 – 5117; r) Y. Yao, G. Liang, *Org. Lett.* **2012**, *14*, 5499 – 5501; s) B. Darses, I. N. Michaelides, F. Sladojevich, J. W. Ward, P. R. Rzepa, D. Dixon, *Org. Lett.* **2012**, *14*, 1684 – 1687; t) G. Bélanger, J. Boudreault, F. Lévesque, *Org. Lett.* **2011**, *13*, 6204 – 6207; u) I. Coldham, L. Watson, H. Adams, N. G. Martin, *J. Org. Chem.* **2011**, *76*, 2360 – 2366; v) I. Coldham, A. J. M. Burrell, H. D. S. Guerrand, N. Oram, *Org. Lett.* **2011**, *13*, 1267 – 1269; w) F. Sladojevich, I. N. Michaelides, B. Darses, J. W. Ward, D. J. Dixon, *Org. Lett.* **2011**, *13*, 5132 – 5135; x) C. Xu, Z. Liu, H. Wang, B. Zhang, Z. Xiang, X. Hao, D. Z. Wang, *Org. Lett.* **2011**, *13*, 1812 – 1815; y) S. Ikeda, M. Shibuya, N. Kanoh, Y. Iwabuchi, *Org. Lett.* **2009**, *11*, 1833 – 1836; z) T. B. Dunn, J. M. Ellis, C. C. Kofink, J. R. Manning, L. E. Overman, *Org. Lett.* **2009**, *11*, 5658 – 5661; aa) S. E. Denmark, R. Y. Baiazitov, S. T. Nguyen, *Tetrahedron* **2009**, *65*, 6535 – 6548; ab) S. E. Denmark, S. T. Nguyen, R. Y. Baiazitov, *Heterocycles* **2008**, *76*, 143 – 154; ac) M. Ueda, M. A. A. Walczak, P. Wipf, *Tetrahedron Lett.* **2008**, *49*, 5986 – 5989; ad) A. Cordero-Vargas, X. Urbaneja, J. Bonjoch, *Synlett* **2007**, 2379 – 2382; ae) S. E. Denmark, R. Y. Baiazitov, *J. Org. Chem.* **2006**, *71*, 593 – 605; af) D. Solé, X. Urbaneja, J. Bonjoch, *Org. Lett.* **2005**, *7*, 5461 – 5464.

[6] M. E. Weiss, E. M. Carreira, *Angew. Chem. Int. Ed.* **2011**, *50*, 11501 – 11505; *Angew. Chem.* **2011**, *123*, 11703 – 11707.

[7] Z. Lu, Y. Li, J. Deng, A. Li, *Nat. Chem.* **2013**, *5*, 679 – 684.

[8] a) A. Shvartsbart, A. B. Smith III, *J. Am. Chem. Soc.* **2015**, *137*, 3510 – 3519; b) A. Shvartsbart, A. B. Smith III, *J. Am. Chem. Soc.* **2014**, *136*, 870 – 873.

[9] H. Morita, J. Kobayashi, *Org. Lett.* **2003**, *5*, 2895 – 2898.

[10] S.-P. Yang, J.-M. Yue, *J. Org. Chem.* **2003**, *68*, 7961 – 7966.

[11] C.-S. Li, Y.-T. Di, Q. Zhang, Y. Zhang, C.-J. Tan, X.-J. Hao, *Helv. Chim. Acta* **2009**, *92*, 653 – 659.

[12] a) Z. Hng, Z. Wang, K. Ding, *Adv. Synth. Catal.* **2011**, *353*, 1584 – 1590; b) C. A. M. Fraga, E. J. Barreiro, *Chirality* **1996**, *8*, 305 – 310.

[13] For related examples of enolate alkylation, see: a) E. Vedejs, O. Dauguils, *J. Am. Chem. Soc.* **2003**, *125*, 4166 – 4173; b) E. Vedejs, O. Dauguils, *J. Am. Chem. Soc.* **1999**, *121*, 5813 – 5814; c) C. P. Decicco, D. J. Nelson, R. L. Corbett, J. C. Dreabit, *J. Org. Chem.* **1995**, *60*, 4782 – 4785; d) R. V. Hoffman, H.-O. Kim, *J. Org. Chem.* **1995**, *60*, 5107 – 5113.

[14] Please see the Supporting Information.

[15] a) M. J. Niphakis, B. J. Turunen, G. I. Georg, *J. Org. Chem.* **2010**, *75*, 6793 – 6805; b) B. J. Turunen, G. I. Georg, *J. Am. Chem. Soc.* **2006**, *128*, 8702 – 8703; For recent reviews on cyclic enaminones, see: c) A. K. Chattopadhyay, S. Hanessian, *Chem. Commun.* **2015**, *51*, 16437 – 16449; d) A. K. Chattopadhyay, S. Hanessian, *Chem. Commun.* **2015**, *51*, 16450 – 16467.

[16] a) J. Li, P. Yang, M. Yao, J. Deng, A. Li, *J. Am. Chem. Soc.* **2014**, *136*, 16477 – 16480; b) M. Kabat, J. Kiegiel, N. Cohen, K. Toth, P. M. Wovkulich, M. R. Uskokoric, *Tetrahedron Lett.* **1991**, *32*, 2343 – 2346.

[17] J. D. Brown, M. A. Foley, D. L. Comins, *J. Am. Chem. Soc.* **1988**, *110*, 7445 – 7447.

[18] C. Ghobril, C. Sabot, C. Mioskowshi, R. Baati, *Eur. J. Org. Chem.* **2008**, 4104 – 4108.

[19] CCDC 1437874 (**25**), 1437875 (methiodide of **28**), 1437876 (**5**), and 1437873 (**2**) contain the supplementary crystallographic data for this paper. These data are provided free of charge by The Cambridge Crystallographic Data Centre.

Received: November 23, 2015
Published online: January 14, 2016