Total Synthesis

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Total Synthesis of Isodaphlongamine H: A Possible Biogenetic Conundrum

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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).

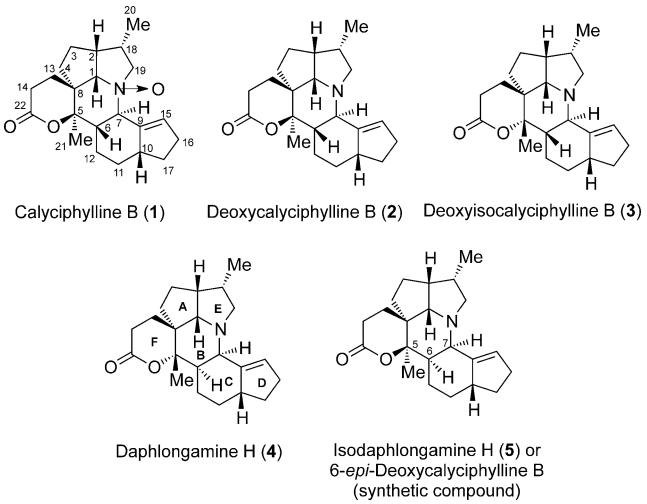

Figure 1. Representative calyciphylline B-type alkaloids and their synthetic analogues.

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**).

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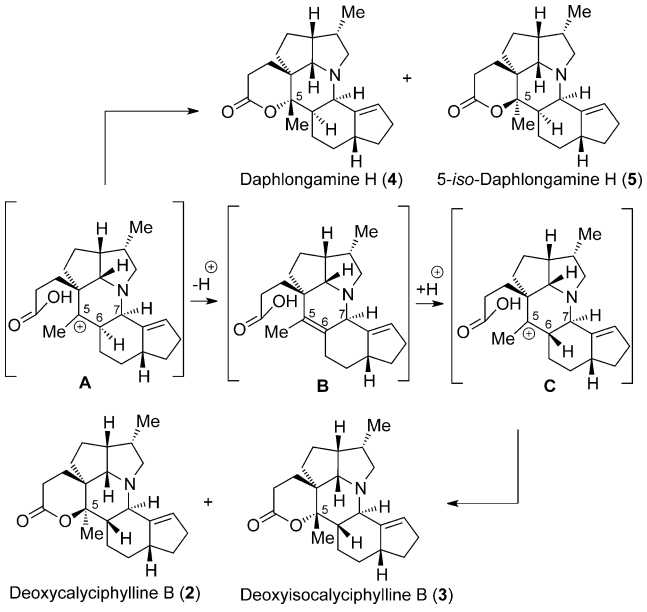


Figure 2. Proposed biosynthetic pathway to deoxycalyciphylline B and deoxyisocalyciphylline B[10] and the anticipated pathway to form daphlongamine H (natural) and isodaphlongamine H (synthetic). The structures of intermediates **A**–**C** were redrawn in the perspectives shown to correspond to the drawing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

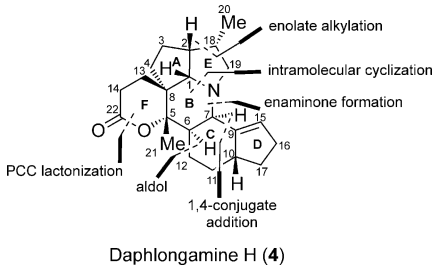
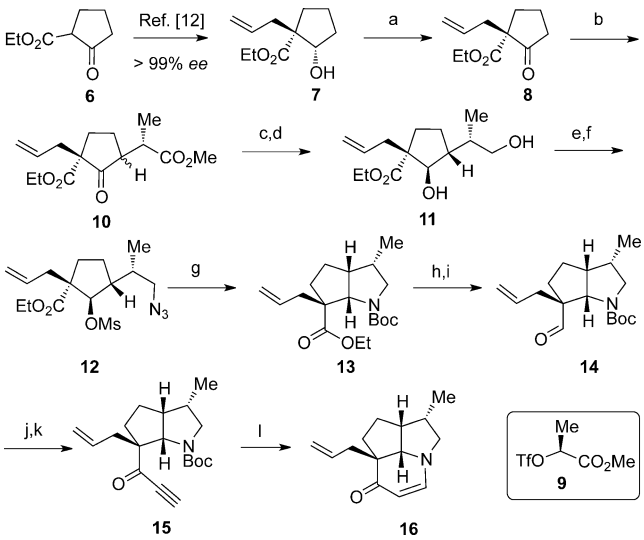


Figure 3. Key synthetic steps toward daphlongamine H (**4**).

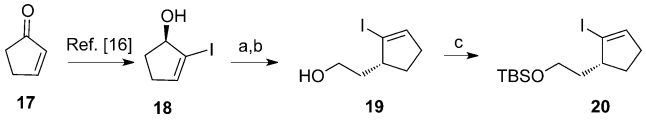
We commenced our synthetic efforts with 2-carbethoxycyclopentanone (**6**) which was transformed to enantiopure cyclopentanol **7** in two consecutive steps using a known chemoenzymatic process[12] (Scheme 1). Swern oxidation of **7** provided β-ketoester **8** in 96% yield. A diastereoselective alkylation 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.

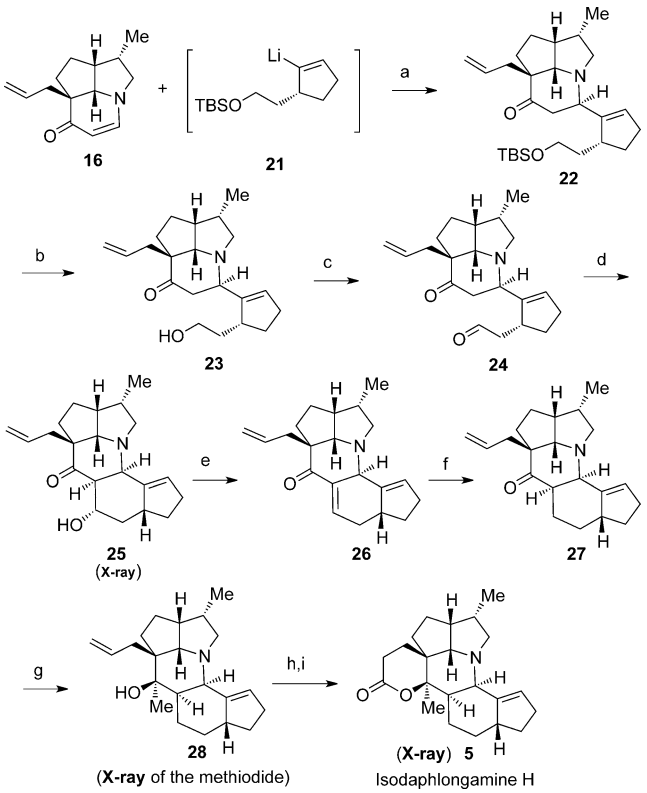
under Staudinger conditions led to the primary amine, which underwent in situ intramolecular cyclization to give the aza-octahydropentalene core unit **13** as the N-Boc derivative in 91% yield. DIBAL-H reduction of the ethyl ester, followed by Dess–Martin oxidation of the corresponding alcohol, afforded 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.

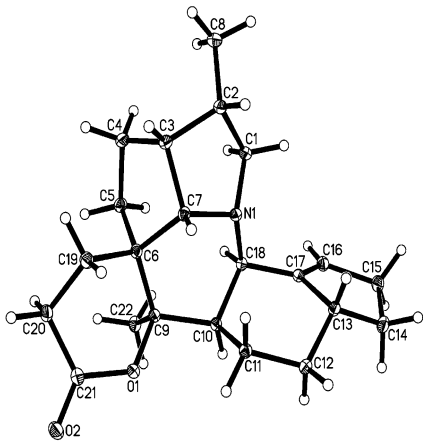
With the tricyclic enaminone **16** and cyclopentenyl iodide **20** in hand, we proceeded with the intended 1,4-conjugate addition. Thus, treatment of the iodide **20** with *n*BuLi generated the vinyllithium reagent **21**, which was added to the enaminone **16** in the presence of $BF_3{\cdot}Et_2O$ and $CuBr{\cdot}Me_2S$, based on related precedents by Comins and co-workers,[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 keto-aldehyde 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-



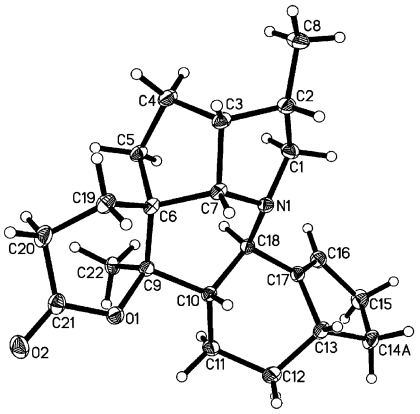
Scheme 3. Synthesis of isodaphlongamine H. Reagents and conditions: a) **20**, *n*BuLi, Et_2O, −78°C; then $CuBr{\cdot}Me_2S$, $BF_3{\cdot}Et_2O$, THF, −78°C, then **16**, −78°C to RT, 92%; b) (±)-CSA, CH_2Cl_2, MeOH, RT, 91%; c) PCC, CH_2Cl_2, RT, 65%; d) TBD, THF, RT, 90%; e) *p*-TSA, 1,1,2-trichloroethane, 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

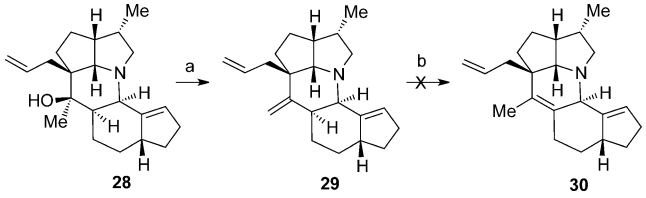


Isodaphlongamine H



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.

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

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[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.

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