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Calyciphylline B-Type Alkaloids: Total Syntheses of (−)-Daphlongamine H and (−)-Isodaphlongamine H

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Supporting Information

ABSTRACT: The first total synthesis of the complex hexacylic *Daphniphyllum* alkaloid (−)-daphlongamine H has been accomplished. Key to the success of the strategy are a complexity-building Mannich reaction, efficient cyclizations, and a highly diastereoselective hydrogenation to assemble multigram quantities of the tricyclic core bearing four contiguous stereocenters. Following construction of the hydro-indene substructure by means of a Pauson−Khand reaction, endgame redox manipulations delivered the natural product. Importantly, the synthetic studies have also given access to (−)-isodaphlongamine H and led to a revision of the reported structure of deoxyisocalyciphylline B.

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Daphniphyllum alkaloids are a large family of structurally distinct natural products with a wide breadth of pharmacological potential.[1] Following the pioneering synthetic studies by Heathcock and co-workers on a subset of these alkaloids,[2] the sheer complexity and varied biological activities of these natural products have continued to entice synthetic chemists to build other congeners.[1e] Specifically, calyciphylline A-type and daphmanidin A-type alkaloids have received the most attention from synthetic chemists in the past decade (Figure 1a), with the groups of Carreira,[3] Li,[4] Smith,[5] Fukuyama,[6] Zhai,[7] and Dixon[8] having elegantly solved the formidable synthetic challenges associated with preparing these dauntingly complex molecules.

The calyciphylline B-type alkaloids are a structurally distinct subfamily among the *Daphniphyllum* alkaloids, featuring a unique hexacyclic framework (rings A−F) with a central piperidine moiety decorated with seven contiguous stereocenters (Figure 1b). Following the isolation of calyciphylline B (**1**),[9] the related congeners deoxycalyciphylline B (**2**), deoxyisocalyciphylline B (**3**),[10] and daphlongamine H (**4**)[11] have been discovered in recent years.[12] The corresponding methanolysis products derived from **2** and **3** have also been reported,[13] suggesting a likely labile *δ*-lactone moiety that may open during isolation or structural elucidation. In addition, the basic tertiary amine resident in all calyciphylline B-type compounds adds to the challenge of their handling and purification.[14] Notably, of all calyciphylline B-type alkaloids isolated from nature to date, only the structure of deoxycalyciphylline B (**2**) has been unambiguously confirmed by X-ray crystallographic analysis.[10]

The closely related structures of **2**−**4**, differing only in their C5/C6 configurations, suggests a common biosynthetic

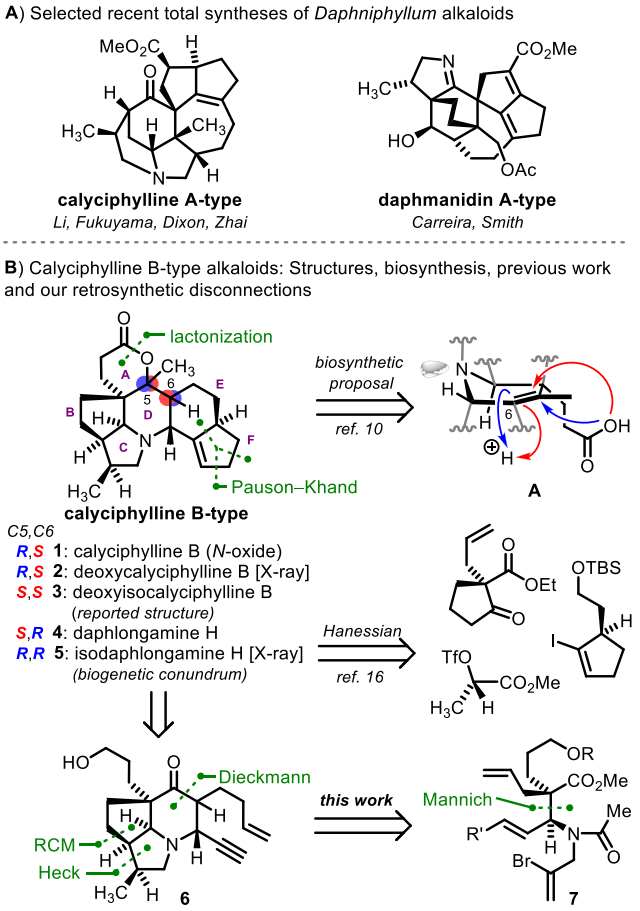

Figure 1. (A) *Daphniphyllum* alkaloids; (B) our retrosynthetic analysis of the calyciphylline B-type subfamily.

pathway. As has been proposed,[10] precursor **A** (Figure 1b) containing a tetrasubstituted olefin (ΔC5−C6) and appended propionic acid side chain was hypothesized to undergo nonselective hydroacyloxylation to give diastereomeric lactone products. In this respect, synthetic and computational studies by Hanessian and co-workers have provided valuable insight.[15] Their efforts culminated in an elegant total synthesis of isodaphlongamine H (**5**)[16] starting from three chiral building blocks. Importantly, Hanessian's studies introduced isodaphlongamine H (**5**) as possibly being the "missing"

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diastereomeric congener of the calyciphylline B-type alkaloid quartet that has yet to be isolated from natural sources.

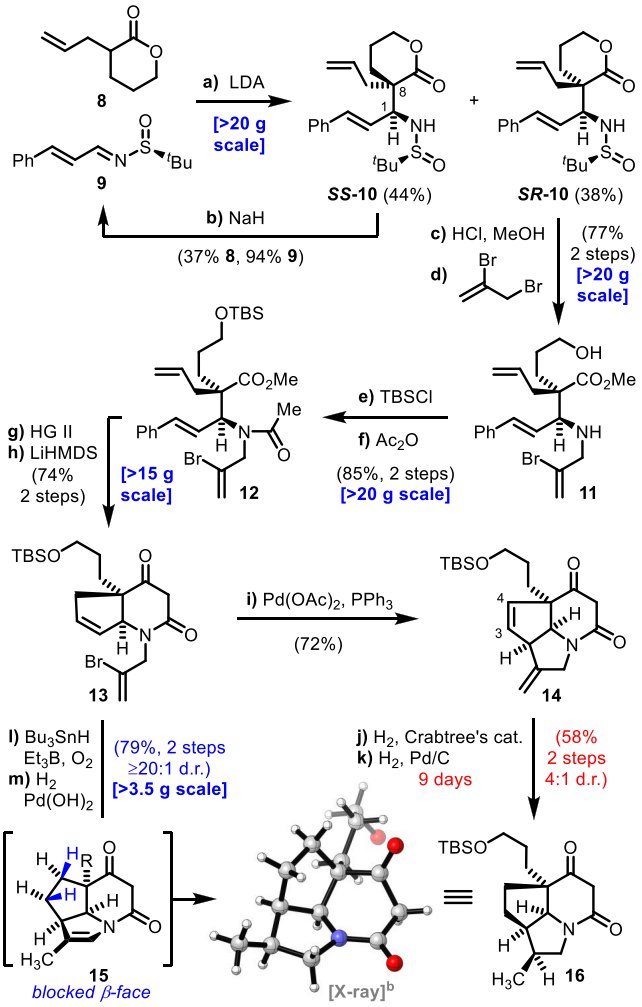
Given the limited synthetic studies focusing on the calyciphylline B-type subfamily,[17] and their fascinating architectures, we embarked on a synthesis of these compounds. Herein, we detail studies which have culminated in total syntheses of (−)-daphlongamine H (**4**) and (−)-isodaphlongamine H (**5**).

A pivotal feature of our retrosynthesis was a recognition that all six rings in **1**−**5** could arise from an acyclic precursor.[18] Careful orchestration of subsequent cyclizations would forge the highly fused framework in a diastereoselective manner from a precursor bearing a single chiral center. Thus, the calyciphylline B-type framework was traced back to enyne **6** as a substrate for a late-stage Pauson−Khand reaction (Figure 1b). In turn, the tricyclic substructure of **6** would be forged from acyclic precursor **7** that contains the retron for a simplifying Mannich reaction.

Our studies commenced with the synthesis of α-quaternary β-amino ester **7** using the key complexity-building Mannich reaction. While Ellman's pioneering studies have revealed that adding ester enolates to *N-tert*-butanesulfinyl imines result in good diastereoselectivities at the β-amino stereocenter,[19] the selectivity outcome at the α-center remains difficult to predict when fully substituted, unsymmetrical enolates are employed. Following an initial survey of imines and enolates,[20] allylated valerolactone **8**[21] and sulfinyl imine **9**[22] were identified as suitable precursors (Scheme 1). Thus, reaction of **9** with the lithium enolate derived from **8** led to an intriguing Mannich−retro-Mannich equilibration of the β-amino lactones (*SS*-**10** and *SR*-**10**), and optimization studies eventually yielded an ∼1:1 mixture of C8 epimers in 82% combined yield on multigram scale.[20] Following chromatographic separation, undesired β-amino lactone *SS*-**10** was recycled to furnish **8** and **9**.[23] Treatment of *SR*-**10** with HCl in methanol effected cleavage of the sulfinyl group with concomitant methanolysis of the lactone. The intermediate ammonium salt was *N*-alkylated to furnish vinyl bromide **11** which, after silylation of the hydroxy group and acetylation of the secondary amine, gave amide **12**.

This acyclic precursor was then subjected to a stepwise tricyclization sequence that commenced with a ring-closing methathesis. Treatment of the resulting intermediate with LiHMDS smoothly induced a Dieckmann condensation and gave bromo bicycle **13**. For the synthesis of the tricyclic substructure, we initially conducted an intramolecular Heck coupling to furnish diene **14**. Although this cyclization proved efficient, the subsequent hydrogenation to access tricycle **16** was unexpectedly troublesome. Ultimately, a two-step protocol was identified using Crabtree's catalyst (50 atm of H_2), followed by a hetereogeneous hydrogenation that gave **16** (4:1 d.r.).[24] This sequence proved impractical on larger scales because of extended reaction times and difficult separation of the diastereomers. To circumvent challenges associated with the hydrogenation of **14**, we sought to prepare a related tricycle, saturated at C3−C4, that would present a sterically more biased concave face. To this end, we discovered that **13** underwent efficient organoborane-initiated,[25] reductive radical ring closure to give a tricyclic core (91% yield) containing an exocyclic olefin that could be reduced with excellent diastereoselectivity (≥20:1 d.r.). Notably, under the optimized hydrogenation conditions, rapid initial isomerization of the *exo*-olefin to enamide **15** took place.[20] This improved sequence

Scheme 1. Gram Scale Synthesis of Tricyclic Core 16[a]



[a]Reagents and conditions: (a) LDA, **8**, THF, −78 °C, then **9** (44%, 53% brsm **SS-10**; 38%, 45% brsm **RS-10**); (b) NaH, THF, −78 to 23 °C (37% **8**; 94% **9**); (c) 4 M HCl in 1,4-dioxane, MeOH, 50 °C; (d) 2,3-dibromopropene, ^{i}Pr$_2$NEt, CH_3CN, 80 °C, (77%, 2 steps, + 11% from second cycle); (e) TBSCl, imidazole, CH_2Cl_2, 0 to 23 °C (89%); (f) Ac_2O, PhH, 90 °C (96%); (g) Hoveyda−Grubbs II catalyst, CH_2Cl_2, 40 °C (82%); (h) LiHMDS, THF, −78 °C (90%); (i) $Pd(OAc)_2$, PPh_3, NEt_3, MeCN, 50 °C (72%); (j) 50 atm H_2, $[Ir(cod)(PCy_3)(py)]PF_6$, CH_2Cl_2, 23 °C; (k) 1 atm H_2, Pd/C, $NaHCO_3$, MeOH, 23 °C (58%, 2 steps, 4:1 d.r.); (l) Bu_3SnH, Et_3B, O_2, PhH, 23 °C (91%); (m) 1 atm H_2/Ar (1:1), $Pd(OH)_2$, CH_2Cl_2, 23 °C (87%, ≥ 20:1 d.r.). [b]TBS omitted for clarity.

gave access to multigram quantities of tricycle **16** whose structure was confirmed by single crystal X-ray analysis.

Synthetic efforts then continued toward construction of the E and F rings by alkylation of **16** to furnish alkene **17** (Scheme 2). Next, reduction of the δ-lactam carbonyl group to give enaminone **18** following elimination was investigated. A survey of various reduction methods revealed Dixon's combination of Vaska's complex and TMDS[8,26] to be uniquely effective. While careful control of the reaction conditions and workup procedure was required, the successful reduction of the lactam amide as a part of a 1,3-dicarbonyl system in the presence of a very sensitive terminal olefin group highlights the remarkable chemoselectivity of these conditions. Interestingly, attempts to carry out the analogous reduction of tricycle **16** (prior to alkylation) were unsuccessful. Activation of enaminone **18** with

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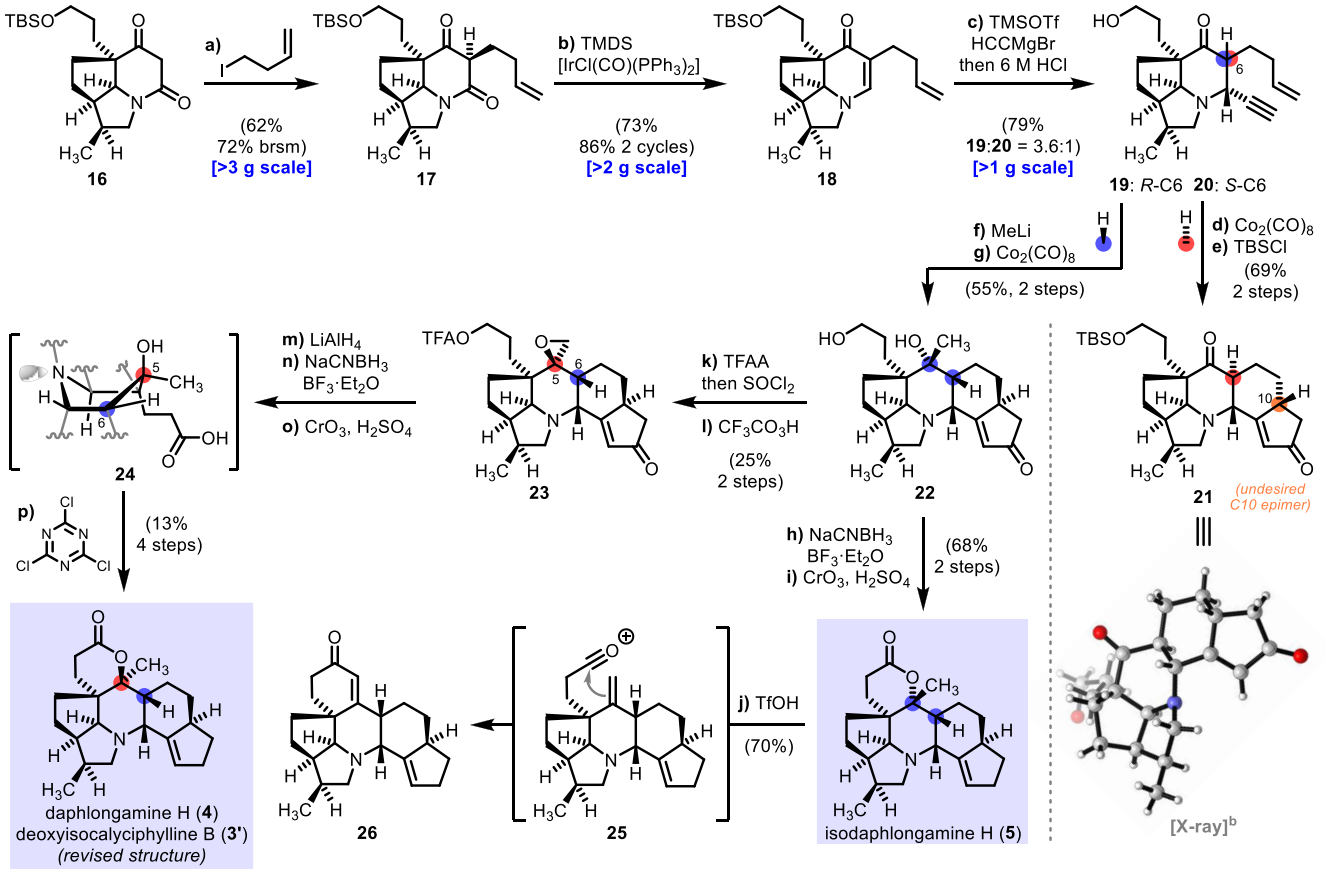
Scheme 2. Synthesis of Daphlongamine H (4) and Isodaphlongamine H (5)[a]



[a]Reagents and conditions: (a) NaH, 4-iodo-butene, DMF, 0 °C (62%, 72% brsm); (b) TMDS, $[IrCl(CO)(PPh_3)_2]$, PhMe, 23 °C (73%, + 13% from second cycle); (c) TMSOTf, CH_2Cl_2, −78 °C, then HCCMgBr, THF, −78 to 0 °C, then aq. 6 M HCl, 0 to 23 °C (62% **19**; 17% **20**); (d) $Co_2(CO)_8$, CH_2Cl_2, 23 °C, then TMANO·$2H_2O$, 0 to 23 °C; (e) TBSCl, imidazole, CH_2Cl_2, 23 °C (69%, 2 steps); (f) $LaCl_3$·2LiCl, THF, 23 °C, then MeLi, −25 °C (94%, ≥ 20:1 d.r.); (g) $Co_2(CO)_8$, CH_2Cl_2, 23 °C, then MeCN, TMANO·$2H_2O$, −78 to 23 °C (59%); (h) $NaCNBH_3$, BF_3·Et_2O, THF, 23 to 66 °C; (i) CrO_3, H_2SO_4, H_2O, acetone, 0 °C (68%, 2 steps); (j) TfOH, $MeNO_2$, 23 °C (70%); (k) TFAA, CH_2Cl_2, −78 °C, then $SOCl_2$, −78 to 0 °C (71%); (l) aq. H_2O_2, TFAA, CH_2Cl_2, 0 to 23 °C (35%); (m) $LiAlH_4$, THF, −78 to 66 °C; (n) $NaCNBH_3$, BF_3·Et_2O, THF, 23 to 66 °C; (o) CrO_3, H_2SO_4, H_2O, acetone, 0 °C; (p) cyanuric chloride, NEt_3, MeCN, 23 °C (13%, 4 steps). [b]TBS omitted for clarity.

TMSOTf, followed by addition of ethynylmagnesium bromide, gave a silyl enol ether (≥20:1 d.r.) that was hydrolyzed upon workup to furnish C6-epimeric enynes **19** and **20** (3.6:1 ratio) in 79% combined yield.[27] With an eye toward the synthesis of deoxycalyciphylline B (**2**) and the reported structure of deoxyisocalyciphylline B (**3**), which feature the *S*-C6 configuration, enyne **20** was subjected to a Pauson−Khand reaction, followed by silylation of the primary hydroxy group to give enone **21**. Single-crystal X-ray analysis of **21** confirmed the *trans*-disposed enyne moiety in **20** being unsuitable for the syntheses of **2** and **3**, since **21** was generated with undesired C10 stereochemistry. Attempts to epimerize 10-Hβ in enone **21** (and derivatives thereof) were unsuccessful, leading us to conclude that the calyciphylline B-type alkaloids with *S*-C6 configuration were not easily accessible from enyne **20**.

At this juncture, we returned to enyne **19** and focused on the final synthetic stages toward daphlongamines **4** and **5**. Treatment of **19** with excess methyllithium furnished the corresponding tertiary alcohol in 94% yield (≥20:1 d.r.).[28] In line with Hanessian and co-workers' studies,[15,16] we were unsuccessful in altering this stereochemical outcome using other methyl nucleophiles. The enyne diol generated in this manner then underwent Pauson−Khand reaction[29] to give pentacyclic enone **22** bearing the desired 10-Hα orientation.[30]

With all eight stereogenic centers in place, the final redox adjustments were pursued. Pleasingly, treatment of **22** with excess $NaCNBH_3$ in the presence of a Lewis acid[31] resulted in an efficient one-step deoxygenation of the enone moiety to furnish the corresponding cyclopentene. Finally, Jones oxidation forged the *cis*-lactone and thus completed the synthesis of isodaphlongamine H (**5**). The spectroscopic data for **5** were in full agreement with those reported by Hanessian and co-workers.[16]

Given the proposed biosynthetic pathway to the calyciphylline B-type alkaloids,[10,16] we envisioned that subjecting isodaphlongamine H (**5**) to acidic conditions might induce a sequence involving elimination−hydroacyloxylation (cf. **A**, Figure 1b) to deliver a mixture of **2**−**5**. In practice, treatment of **5** with various acids (AcOH, TFA, $HClO_4$, *p*TsOH, H_2SO_4, 23 to 80 °C) returned either unreacted starting material or led to nonspecific decomposition. The only productive conversion, upon treating **5** with excess TfOH in nitromethane, was the formation of enone **26**. Mechanistically, we hypothesize that this formal dehydration results from a Prins-like cyclization of acylium intermediate **25**.

Finally, for the synthesis of daphlongamine H (**4**), the formal stereochemical inversion of the tertiary alcohol in pentacyclic enone **22** was pursued. Subjecting **22** to TFAA and

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then $SOCl_2$ smoothly protected the primary and eliminated the tertiary hydroxy groups, respectively. The resulting exocyclic alkene was treated with trifluoroperacetic acid[32] to afford epoxide **23**.[33] Opening of the epoxide at the terminal position was carried out with $LiAlH_4$, and the resulting triol was subjected to the established deoxygenation conditions. After Jones oxidation of the thus obtained amino diol, the resulting, highly polar *trans*-seco acid **24** did not undergo facile lactonization, unlike in the case of isodaphlongamine (**5**), which possesses the *cis*-lactone. Eventually we identified cyanuric chloride as a viable reagent[34] for the final bond formation and were able to isolate daphlongamine H (**4**) possessing the highly strained and sensitive *trans*-lactone.[35]

Interestingly, initial NMR spectra for our synthetic daphlongamine H (**4**) did not match the reported spectroscopic data of **4**,[11] but surprisingly were in good agreement with those reported for deoxyisocalyciphylline B (**3**).[10] Eventually, it was discovered that, by recording NMR spectra of our synthetic daphlongamine H (**4**) using *old* $CDCl_3$ (putatively containing residual acid), we were able to obtain spectroscopic data that was in better agreement with the reported values for **4**. Furthermore, interpretation of both our and the reported 2D NMR data of deoxyisocalyciphylline B (**3**) revealed that the *S*-C6 configuration in **3** had been misassigned.[20] We therefore conclude that isolated deoxyisocalyciphylline B (revised structure: **3′**) and daphlongamine H (**4**) are effectively the *same* natural product. It appears that the structure of the former had been misassigned, while the reported spectroscopic data of the latter correspond to its putative ammonium salt. The structural revision of **3** as **4** via total synthesis warrants further study of the proposed biosynthetic pathway for all members of the calyciphylline B-type alkaloids.[10,15,16,20]

In conclusion, we have developed the first total synthesis of the complex *Daphniphyllum* alkaloid (−)-daphlongamine H (**4**). Furthermore, our synthetic approach has provided access to (−)-isodaphlongamine H (**5**) and led to revision of the reported structure of deoxyisocalyciphylline B (**3**). Key features of the synthesis include a Mannich reaction using an Ellman sulfinimine derivative, rapidly building target-relevant complexity in the opening step. Finally, a series of efficient ring-forming events using an acyclic precursor forged the complex, hexacyclic framework of the calyciphylline B-type alkaloids.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.9b03576.

Experimental procedures, analytical data (^1H and ^{13}C NMR, HRMS, IR, $[\alpha]_D$), and optimization tables (PDF)

Crystallographic data for **16** (CIF)

Crystallographic data for **21** (CIF)

Crystallographic data for **S27** (CIF)

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Notes

The authors declare no competing financial interest.

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