

Total Synthesis of (–)-Calyciphylline N

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S Supporting Information

ABSTRACT: The total synthesis of the architecturally complex *Daphniphyllum* alkaloid (–)-calyciphylline N has been achieved. Highlights of the synthesis include a Et_2AlCl -promoted, highly stereoselective, substrate-controlled intramolecular Diels–Alder reaction, a transannular enolate alkylation, an effective Stille carbonylation/Nazarov cyclization sequence, and a high-risk diastereoselective hydrogenation of a fully substituted conjugated diene ester.

The *Daphniphyllum* alkaloids comprise a large family of complex natural products including more than 180 known members,¹ many with diverse biological activities, that have proven challenging as targets for total synthesis.² We in particular became interested in the calyciphylline alkaloids, largely due to their unique frameworks and at the time, limited synthetic studies.^{3,4} Calyciphylline N [(–)-1, Figure 1], isolated in 2008 by Kobayashi and co-workers,⁵ was chosen as our initial target.

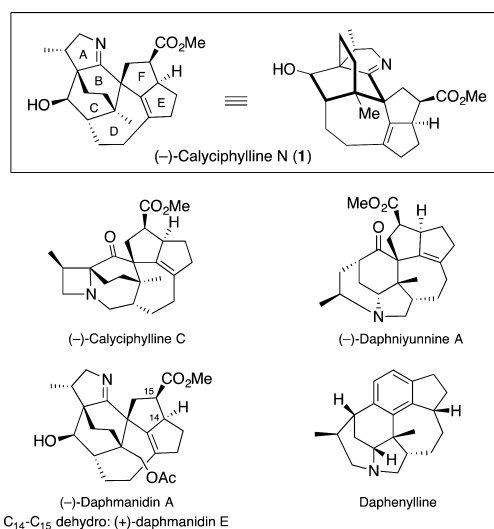


Figure 1. (–)-Calyciphylline N and related congeners.⁶

While the biological activity of (–)-calyciphylline N (1) has not been investigated, we reasoned that a synthetic effort toward this alkaloid would not only unveil a wealth of interesting reactivity but also permit access to other congeners of the family. Notable structural features of 1 include six contiguous stereogenic centers, three of which are quaternary

bridgehead, a fused A ring dihydropyrrole, and a DEF decahydrocyclopentazulene ring system surrounding a central bicyclo[2.2.2]octane BC core.

Retrosynthetically (Figure 2), we envisioned that the dihydropyrrole A ring could arise via condensation of a primary

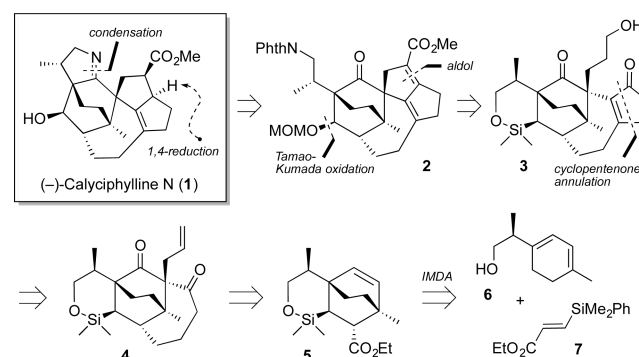


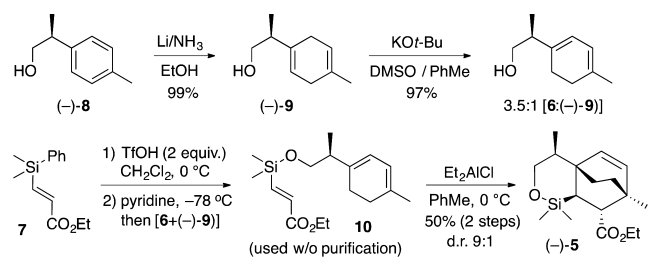
Figure 2. Retrosynthetic analysis.

amine with the carbonyl group in ring B, while the stereochemistry of the EF ring system could be installed by a challenging/critical late-stage α,β -reduction of an exceptionally hindered diene ester (2). The secondary hydroxyl in ring C could in turn be generated via a Tamao–Kumada⁷ oxidation of the siloxane ring, while construction of ring F would entail an aldol condensation, simplifying the structure to 3, the latter accessible from 4 via a cyclopentenone annulation involving a Stille carbonylation⁸/Nazarov cyclization⁹ sequence. Continuing with this analysis, tetracycle 4 could be accessed through elaboration of bicyclic ester 5, anticipated to be the product of an intramolecular Diels–Alder (IMDA) reaction.¹⁰ The requisite IMDA triene, in turn, would arise via union of enantiomerically pure homoallylic alcohol 6 and known silyl acrylate 7.¹¹

The synthesis of (–)-calyciphylline N (1) began with alcohol (–)-8 (Scheme 1), prepared in three steps from commercially available *p*-tolylacetic acid.¹² Birch reduction¹³ readily furnished the desired cyclohexadiene; olefin isomerization with KO^tBu in DMSO ¹⁴ then provided an inseparable mixture (3.5:1) of the 1,3- and 1,4-dienes 6 and (–)-9, respectively, in excellent yield. Silyl acrylate 7, obtained via oxidative hydrosilylation of ethyl acrylate with phenyldimethylsilane,¹¹ was subsequently appended, employing a method introduced by Sieburth.¹⁵ To this end, treatment of 7 with TfOH at 0 °C, followed by sequential

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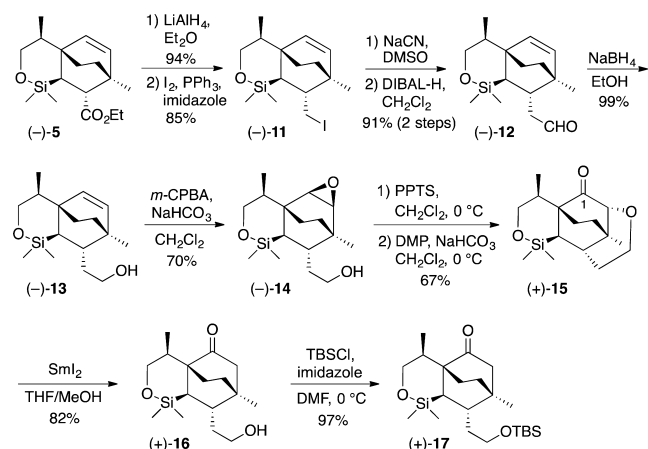
Scheme 1



addition of pyridine and the mixture of the alcohols **6** and **(-)-9** at $-78\text{ }^{\circ}\text{C}$, led to the requisite triene **10** for the IMDA reaction. However, due to the instability of **10** toward silica gel chromatography, the mixture was carried forward without purification. Interestingly, while the thermal Diels–Alder reaction led to a mixture of all possible diastereomers (as determined by ^1H NMR), we were pleased to discover that the Et_2AlCl -promoted cyclization provided a 9:1 mixture of diastereomers in favor of the desired cycloadduct **(-)-5**.

One-carbon homologation of **(-)-5** to alcohol **(-)-13** (Scheme 2) was next achieved by LiAlH_4 reduction and

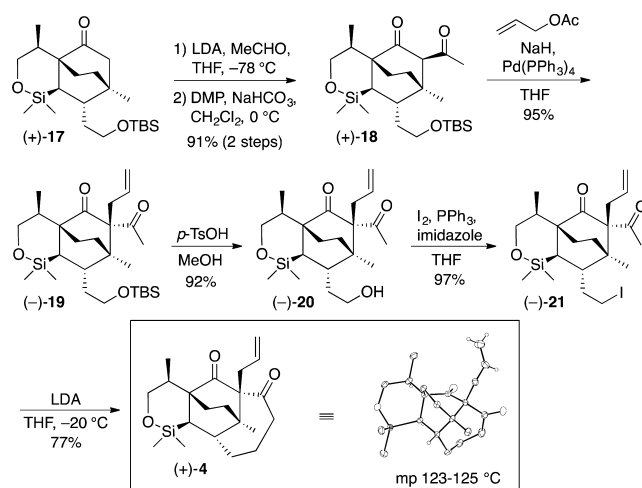
Scheme 2



conversion to the corresponding iodide **(-)-11**, followed by cyanide displacement and a two-step reduction of the resulting nitrile. The overall yield for the five steps was 65%. Epoxidation of the olefin in **(-)-13** with *m*-CPBA then led to **(-)-14** as a single diastereomer in 70% yield. Installation of the C_1 ketone was next achieved in two steps and 67% yield via an acid-promoted epoxide opening and oxidation of the resulting secondary alcohol, employing Dess–Martin periodinane (DMP),¹⁶ to deliver **(+)-15**. Reductive cleavage of the tetrahydropyran ring with SmI_2 in a mixture of THF/MeOH then led to hydroxy ketone **(+)-16** in 82% yield,¹⁷ the primary alcohol of which was protected as the TBS ether (TBSCl/imidazole in DMF) to provide **(+)-17**.

Elaboration of the requisite side chain for eventual construction of ring D called for introduction of disubstitution α to the carbonyl in ketone **(+)-17** (Scheme 3). Initially, **(+)-17** proved unreactive toward standard acylating agents (EtOAc , Ac_2O , 1-acetyl-imidazole, etc.) employing the lithium, potassium, or sodium enolates, with the exception of AcCl , which led to complex mixtures of *C*- and *O*-acylated products. However, an LDA-mediated aldol reaction with acetaldehyde, followed without purification by DMP oxidation of the β -

Scheme 3

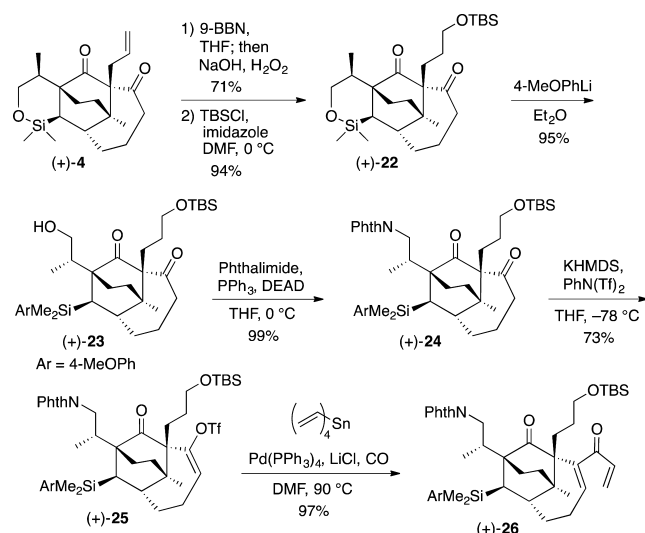


hydroxy ketone, provided diketone **(+)-18** in 91% yield for the two steps.¹⁸ Introduction of the allyl group via the Tsuji–Trost allylation¹⁹ then furnished **(-)-19** as a single diastereomer (95%), which upon exposure to catalytic *p*-TsOH in MeOH cleanly led to the corresponding alcohol **(-)-20**; the latter converted to primary iodide **(-)-21** in 97% yield. Pleasingly, transannular cyclization utilizing LDA delivered tetracycle **(+)-4** as a crystalline solid (mp 123–125 $^{\circ}\text{C}$), completing the construction of ring D. Interestingly, use of NaHMDS led only to elimination of the iodide. Single-crystal X-ray analysis of **(+)-4** confirmed the structure, as well as the relative and absolute configurations.

Before turning to elaboration of the eastern hemisphere, we investigated the proposed Tamao–Kumada⁷ oxidation of the siloxane ring in **(+)-4**. Unfortunately, the siloxane was found to be completely inert to the oxidation. Standard conditions (various fluoride sources, H_2O_2 , and bicarbonate salts)^{7,20} led only to the recovery of starting material, while strongly basic conditions²¹ resulted in decomposition. Curiously, the use of TBAF (with or without oxidant) resulted in desilylation rather than oxidation.²² Attempts to transform the siloxane to a more reactive silane (e.g., silyl halide or hydride)²³ prior to oxidation also proved unrewarding. Earlier studies, however, had demonstrated that a similar siloxane was a substrate for nucleophilic ring-opening at the Si–O bond upon treatment with aryllithium reagents. Such reactivity was recently employed for the development of siloxanes as recoverable transfer agents in Pd-catalyzed cross-coupling reactions.²⁴ We surmised that an arylsilane could be converted to the corresponding alcohol via the Fleming modification²⁶ of the Tamao–Kumada oxidation.

With these earlier observations in mind, attempted siloxane opening in **(+)-4** resulted in partial isomerization of the terminal alkene (not shown). We therefore functionalized the allyl group before moving forward (Scheme 4). Brown hydroboration (9-BBN) and oxidation (NaOH and H_2O_2)²⁵ delivered the expected primary alcohol in 71% yield. Protection of the alcohol with TBSCl then furnished **(+)-22** in 94% yield. Pleasingly, the siloxane could now be converted to arylsilane **(+)-23** in excellent yield by treatment with 4-methoxyphenyllithium at room temperature. Selection of the methoxyphenyl substituent was in anticipation of greater reactivity toward the protodesilylation step of the Fleming–Tamao oxidation.²⁶ Notably, both hindered carbonyls in **(+)-22** remained

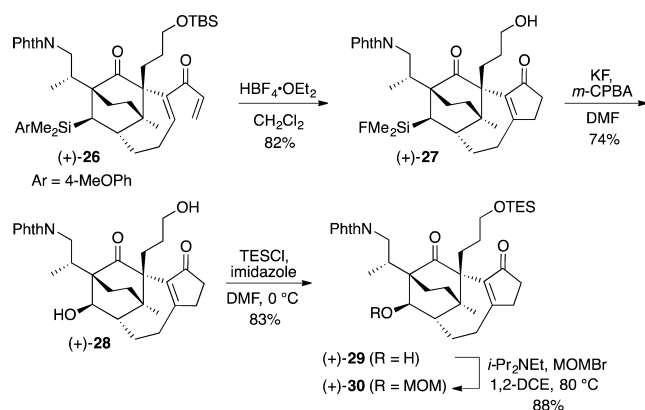
Scheme 4



completely inert to nucleophilic addition. Moving forward, rather than protect the newly generated primary alcohol, we introduced the requisite nitrogen with protection via treatment of (+)-23 with phthalimide under Mitsunobu conditions²⁷ to provide (+)-24 in 99% yield.

Turning to construction of ring E via the proposed Stille carbonylation⁸/Nazarov⁹ cyclization sequence, exposure of (+)-24 to KHMDS in the presence of PhN(Tf)₂ at -78 °C furnished vinyl triflate (+)-25, which underwent a highly efficient Stille carbonylation in DMF at 90 °C, employing only 1 atm. of CO, to provide dienone (+)-26 in 97% yield. Given that both Nazarov cyclizations and protodesilylations can be achieved with protic acid,^{9,26} we reasoned that both transformations could be accomplished in the same flask. Indeed, treatment of (+)-26 with HBF₄·OEt₂ at ambient temperature directly furnished silyl fluoride (+)-27 in 82% overall yield (Scheme 5). Under these conditions, the primary TBS group

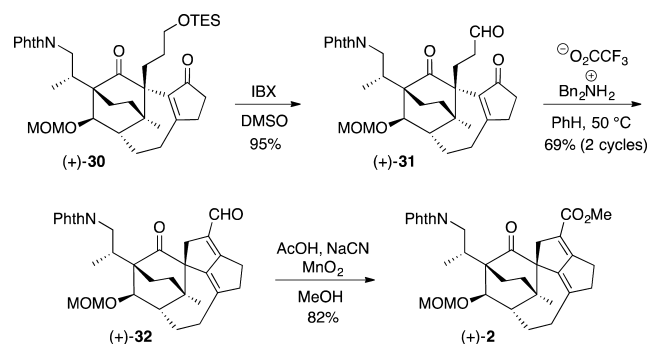
Scheme 5



was also removed. We were also pleased to discover that treatment of (+)-27 with KF and *m*-CPBA in DMF resulted in the successful Fleming–Tamao oxidation to diol (+)-28 in 74% yield. Differentiation of the alcohols was then realized via chemoselective protection of the primary alcohol as the TES ether, followed by MOM protection of the secondary alcohol to afford protected diol (+)-30.

Next, oxidative removal of the TES ether with IBX (Scheme 6) directly provided aldehyde (+)-31 in excellent yield.²⁸ The

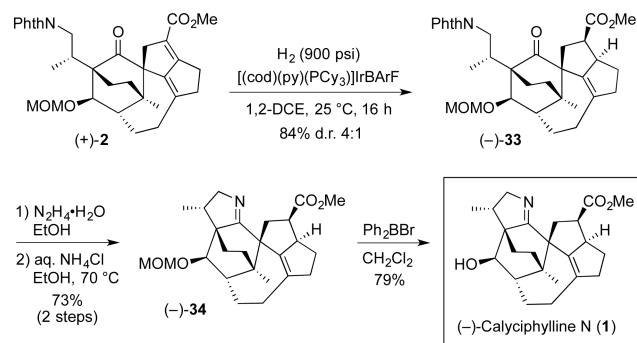
Scheme 6



requisite aldol condensation to prepare (+)-32 was then achieved employing the conditions reported by Weiss and Carreira (Bn₂NH₂O₂CCF₃, PhH, 50 °C) in their synthesis of (+)-daphmanidin E.³

Turning to the critical 1,4-reduction of the conjugated diene in (+)-32, extensive experimentation on a less advanced aldehyde revealed a set of conditions involving the combination of ZnCl₂, Ph₂SiH₂, and catalytic Pd(PPh₃)₄ as uniquely effective (see Supporting Information). Unfortunately, when applied to (+)-32, this reduction protocol resulted only in decomposition. Undeterred, aldehyde (+)-32 was oxidized to methyl ester (+)-2 (AcOH, NaCN, MeOH, then MnO₂) via the method of Corey.³⁰ A screen of cationic hydrogenation catalysts was next explored with the intent of directing the hydrogenation to the α,β-olefinic bond. Pleasingly, the BARF analogue of the Crabtree catalyst,³¹ developed by Wuestenberg and Pfaltz,³² employing 900 psi of H₂ pressure, proved effective in reducing (+)-2 to furnish a mixture (4:1) of diastereomers in 84% yield (Scheme 7). Detailed 2D NMR analysis revealed the

Scheme 7



major diastereomer to be (-)-33. This transformation, possibly directed by the C₁ carbonyl in (+)-2, should prove useful in accessing natural congeners bearing the same monounsaturated DEF ring system (Figure 1).

Exposure of (-)-33 to hydrazine in EtOH led cleanly to removal of the phthalimide. Ring A construction involving imine formation was then readily achieved by heating the resulting amine with aqueous NH₄Cl (sat.) in EtOH at 70 °C.³ Completion of the total synthesis of (-)-calyciphylline N entailed treatment of (-)-34 with Ph₂BBr³³ to remove the MOM acetal. Totally synthetic (-)-calyciphylline N displayed

spectral properties in excellent agreement with those derived from the natural product [i.e., ^1H and ^{13}C NMR (500 and 125 MHz, respectively), HRMS parent ion identification, and chiroptic properties].

In summary, the first total synthesis of a member of the calyciphylline alkaloids, (–)-calyciphylline N (**1**), has been achieved with a longest linear sequence of 37 steps from known alcohol (–)-**8**. Application of the strategies presented herein for the synthesis of other members of the *Daphniphyllum* alkaloids continues in our laboratory.

■ ASSOCIATED CONTENT

● Supporting Information

Experimental details, spectra, and X-ray crystallographic data (CIF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interest.

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