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Tin-Free Access to the ABC Core of the Calyciphylline A Alkaloids and Unexpected Formation of a D-Ring-Contracted Tetracyclic Core

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Abstract

A tin-free strategy for the successful cyclization of a variety of internal alkyne-containing *N*-chloroamine precursors to the ABC core via cyclization of a neutral aminyl radical is established. Deuterium labeling experiments confirm that the solvent is the primary source of the final H atom in the cyclization cascade. These conditions enabled a streamlined route to a β -ketoester intermediate poised for intramolecular Knoevenagel condensation to construct the seven-membered D-ring of calyciphylline A alkaloids. However, exposure to CsF in *t*-BuOH at elevated temperatures led to an unexpected decarboxylation to form a D-ring-contracted tetracyclic core.

Graphical abstract

The *Daphniphyllum* alkaloids are a structurally complex family of polycyclic natural products isolated from deciduous shrubs and trees in Japan and Southeast Asia.¹ Relative to the large number of isolates in this family, very few of these alkaloids have been investigated for biological activity. Of those that have reported activity, compelling functions, such as

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Supporting Information

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Notes

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neurotrophic, antibacterial, and antitumor activities, have been reported.^{1,2} This combination of bioactivity and structural complexity has piqued the interest of the synthetic community, with dozens of reports of interesting strategies for the assembly of core motifs³ and several completed syntheses.⁴ Our efforts in this area were initially focused on the assembly of the ABC core of the calyciphylline A subfamily via tandem cyclization of an aminyl radical cascade mediated by a tributylstannyl radical.⁵ Here, we report the development of tin-free conditions for the construction of the ABC core that harness the H atom donating potential of THF in combination with a weak terminal H atom donor. Additionally, we describe efforts to assemble the D-ring of daphniyunnine C⁶ via a Knoevenagel condensation.

At the outset of our work, we envisioned disconnection of daphniyunnine C (**1**, also called longeracinphyllin A) to enedione **2** (Scheme 1). We hypothesized that the E- and F-rings could be assembled in one reaction vessel via phosphine-mediated [3 + 2]-cycloaddition with allene **3**,⁷ followed by addition of a catalytic acid to induce an in situ aldol condensation. Subsequent hydrogenation of the electron-rich olefin would then complete the synthesis. We envisioned that this cycloaddition approach would facilitate construction of the challenging vicinal all-carbon quaternary centers because the D-ring olefin in **2** is conjugated to the A-ring carbonyl. Thus, the first bond to be constructed would be remote from the quaternary center, rendering the construction of the new quaternary center an intramolecular event. This rationale was recently validated by Li and co-workers,⁸ who employed 1,1'-bis(diphenyl-phosphino)ferrocene and either an allenolate ester or allene **3** in cycloadditions toward daphniyunnine C^{4d} and daphenylline, respectively.^{4b} We envisioned assembly of the seven-membered ring from a ketone or β -ketoester (**4**) via aldol or Knoevenagel condensation⁹ of the corresponding enolates. The tricyclic core would be assembled via tandem cyclization of a neutral dialkyl aminyl radical derived from *N*-chloroamine **5**. Internal alkyne **5** would be assembled from lactol **6**⁵ and alkynyl azide **7**. Several possible R' groups were envisioned, including masked ketone derivatives **7a–b** and protected alcohol **7c**.

We previously reported the synthesis of the tricyclic core derived from the methallyl derivative **7a**,^{5b} but we were unable to advance the cyclization product (see **16**, Scheme 5A). Thus, we focused on assembly of the cyclization precursor derived from alkyne **7b** as described in Scheme 2.^{10,11} Generation of the lithium acetylide of alkyne **8** was followed by addition of paraformaldehyde to afford primary alcohol **8** in 67% yield. Due to challenges encountered with traditional reductive amination conditions, we imagined an alternative approach wherein an aza-Wittig reaction would be followed by reduction to the secondary amine. Thus, propargyl alcohol derivative **9** was mesylated, and then sodium azide was added to the reaction mixture to afford propargylic azide **7b**. This single-flask reaction was more efficient than a two-step process involving mesylation in dichloromethane followed by NaN₃ displacement in DMF. A mixture of crude azide **7b** and lactol *ent*-**6** was treated with triphenylphosphine, and then an in situ reduction with lithium aluminum hydride provided the targeted amine (**10**) in 85% yield. This amine could be chlorinated and the allylic alcohol oxidized in another single-flask procedure to afford the cyclization precursor *ent*-**5b** in 90% yield. By careful control of the reaction conditions, conversion of alcohol **9** to *ent*-**5b**, which

would traditionally require six steps, was completed in three steps with an overall yield of 60%.

With an efficient synthesis of chloroamine **ent-5b** in hand, we turned our attention to the key tandem cyclization to form the ABC core. Application of our previously optimized conditions⁵ led to highly variable results, with yields of **11** ranging from 0% to 48% yield, with the latter only achieved in one reaction (Scheme 3). Previous deuterium labeling studies established that H atom donation by the solvent was critical to achieving good cyclization yields.^{5b} Thus, we screened other solvents capable of donating H atoms, including solvents with weaker and stronger C–H bonds. In all cases, some of the desired product was observed, but the reaction performed in a sealed vessel at 100 °C in THF formed the fewest side products.¹²

We next turned our attention to the H atom donor. Tributyltin hydride has been a privileged participant in reductive radical chain processes because of its relatively weak Sn–H bond (78 kcal/mol) coupled with the higher strength of the Sn–Cl bond (97 kcal/mol).^{13,14} Indeed, to the best of our knowledge, all previously reported thermal cyclizations of dialkyl aminyl radicals ($R_2N\cdot$) initiated at N–Cl bonds have employed Bu_3SnH .^{15,16} In our reactions, the most frequently isolated byproduct is the uncyclized reduction product (R_2NH). Thus, we envisioned that we could simultaneously avoid use of the toxic Bu_3SnH and minimize N–H bond formation (88 kcal/mol, H atom abstraction by **12**) by employing a weaker H atom donor (Scheme 4). Meanwhile, the H atom donor would need to form the final vinylic C–H bond (105 kcal/mol, trapping of **14**) with relative ease. Thus, we envisioned that an H atom donor with an X–H bond between 88 and ~100 kcal/mol would provide optimal reactivity. Notably, the BDE for THF falls into this range. Inspection of the reported bond dissociation energies (BDEs)¹⁴ for several H atom donors revealed that trialkylsilanes possessed bonds to hydrogen in this range (Me_3Si-H = 95 kcal/mol, Et_3SiH = 96 kcal/mol, $(t-Bu)_3SiH$ = 86.6 kcal/mol). Finally, a silane donor would also form a strong Si–Cl bond (113 kcal/mol for $TMSCl$), minimizing the formation of Cl atom transfer products.

A brief optimization was conducted, leading to the optimal conditions: 2 equiv of TIPS-H, 0.2 equiv of AIBN, and 0.009 M THF added all at once, followed by heating to 100 °C in a sealed tube. Importantly, these weak H atom donor conditions obviated the need for a slow addition of AIBN and the donor. At 66 °C in THF or at 100 °C in benzene, no cyclization product was observed, but reduction products were detected. Use of TIPS-H in toluene at 100 °C led to low conversions (<15%). These studies were complicated by the tendency of the product tricycle to react with CH_2Cl_2 during flash chromatography.^{17,18} Use of EtOAc/hexanes on alumina led to a 68% yield of tricycle **11** on 49-mg scale. Unfortunately, on larger scale, the yield dropped, and it proved difficult to advance significant amounts of material.¹⁹ We hypothesize that 1,5-H atom transfer (HAT)²⁰ from a ketal C–H to the vinylic radical²¹ may be followed by nonspecific decomposition in this substrate.

Previously, we achieved consistent cyclization (58% yield) with methallyl substrate **ent-5a** using AIBN, Bu_3SnH in toluene at reflux.^{5b} For comparison, we treated **ent-5a** with various silanes in THF at 100 °C to good effect (Scheme 5A). Given the similar yields observed for these silanes, whose BDEs range from ~86 to ~95 kcal/mol,¹⁴ we hypothesized that the

solvent serves as the primary, if not exclusive, H atom donor to form the vinylic C–H bond in these reactions and that the silane is a secondary donor of either a H atom or hydride. This hypothesis is further supported by >99% incorporation of D during the cyclization of terminal alkyne substrate **17**⁵ in the presence of d₈-THF (Scheme 5B).

At this point, we directed our attention to the synthesis of cyclization precursor **4b**, derived from known alkynyl azide **7c**²² bearing a TBS ether, which was expected to improve the solubility of our highly polar intermediates (Scheme 6). Assembly of *N*-chloroamine **4b** began with an aza-Wittig reaction of lactol **ent-6** with azide **7c**, followed by in situ reduction of the resulting imine with lithium aluminum hydride to form amine **19** in 84% yield. Chlorination with NCS at –78 °C, followed by warming to 0 °C and addition of Dess-Martin periodinane under buffered conditions, afforded *N*-chloro enone **ent-5c**. Cyclization of *N*-chloroamine **ent-5c** under the optimized conditions led to the desired tricycle as well as some chlorine atom transfer product.¹¹ Hydrogenation of both cyclization products with Adams' catalyst (20 mol %) afforded tricycle **20** in 73% combined isolated yield over two steps.

The β -ketoester for the Knoevenagel strategy was prepared from tricycle **20** via a three-step procedure that is completed without purification of the intermediates (Scheme 7).²³ Desilylation was executed by treatment with concentrated aqueous HCl in diethyl ether. The resulting primary alcohol was treated with 1 equiv of TFA to protonate the tertiary amine in situ, and then the alcohol was oxidized with DMP. Roskamp coupling²⁴ was effected upon treatment with tin(II) chloride and ethyl diazoacetate, affording **ent-4b** in 54% yield over the three steps.

At this point, we were poised for cyclization of the D-ring via a Knoevenagel cyclization approach. Several bases were evaluated. Amine bases, including DBU, TEA, pyrrolidine, and piperidine, led to no reaction or trace conversion to enamines. Fluoride bases have proven to be effective mediators of Knoevenagel condensation in a variety of reports.²⁵ We selected CsF for its favorable solubility. Because of the neopentyl nature of the A-ring ketone, we chose an alcohol with a higher boiling point as solvent. Thus, β -ketoester **ent-23**, in the presence of CsF in *t*-BuOH, was heated to 100 °C for 17 h (Scheme 8).¹² No desired products were isolated, despite the complete consumption of the starting material (**ent-20**). Rather, D-ring-contracted methyl ketone **30** and pendant methyl ketone **31** were the only isolable products (11% yield each). We hypothesize that either ester hydrolysis in the presence of adventitious water and CsF leads to decarboxylation or transesterification of **ent-20** by *t*-BuOH²⁶ is followed by deprotonation to release isobutylene and CO₂ and form ketone **31**. Subsequent 5-*exo* cyclization then affords D-ring-contracted tetracycle **30**. We were intrigued to find that the [6–6–5–5] framework of tetracycle **30** has never been reported. In a control experiment omitting the CsF, we isolated only the noncyclized methyl ketone (**31**).

Based on the failure of a thermodynamically favored anion to add to the A-ring ketone, it is clear that formation of a tetrahedral intermediate directly adjacent to the existing all-carbon quaternary center must be coupled to a kinetically favored process, such as the observed 5-*exo* cyclization, or to a stronger thermodynamic driving force than enone formation. A

similar challenge was encountered by Li and co-workers during an attempt to form the D-ring via aldol condensation.^{3e} Currently, efforts to rapidly assemble the seven-membered D-ring are focused on installation of the C–C bond adjacent to this quaternary center prior to the tandem cyclization event. Subsequent ring closure at a remote position is envisioned via several potential annulation strategies.

In summary, we strategically employed solvents bearing homolytically labile H atoms and a weak stoichiometric H atom donor to develop tin-free conditions for the tandem cyclization of neutral aminyl radicals. Deuterium labeling experiments were consistent with the solvent as the exclusive H atom donor to the substrate. Several silanes with BDEs between 86 and 95 proved viable for internal alkyne substrates. We expect these conditions to facilitate cyclization in related systems to access a variety of nitrogen-containing polycyclic scaffolds. Attempted Knoevenagel condensation of an ABC core bearing a pendant β -ketoester led to isolation of a novel D-ring-contracted [6–6–5–5] tetracyclic core. Efforts to access a seven-membered D-ring via several alternative strategies are ongoing and will be reported in due course.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Scheme 1.
Retrosynthetic Analysis of Daphniyunnine C

Scheme 2.

Synthesis of Ketal-Appended Cyclization Substrate via aza-Wittig/in situ LAH Reduction

Scheme 3.
Inconsistent Tandem Cyclization with Bu₃SnH/PhMe

Scheme 4.
Mechanism and Approximate Relevant BDEs for the Tandem Cyclization

Scheme 5.

(A) Efficient Cyclization of Methallyl Substrate in the Presence of Various Silanes and (B) Incorporation of D Using *d*₈-THF

Scheme 6.
Synthesis of ABC Core for Knoevenagel Approach

Scheme 7.
Roskamp Coupling Affords Knoevenagel Precursor

Scheme 8.

Attempted Knoevenagel Cyclization Yields Undesired Ring-Contracted Product