Synthetic Study of Calyciphylline A-type *Daphniphyllum* Alkaloids

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1. Introduction

Since the discovery of the first *Daphniphyllum* alkaloid by the Yagi group in 1909,[1] more than 330 *Daphniphyllum* alkaloids have been isolated from the genus *daphniphyllum*, which exhibit broad biological activities, such as anticancer, HIV inhibition, and vasorelaxant activities.[2] *Daphniphyllum* alkaloids are classified into over 20 sub-groups according to their skeletal features (Figure 1). The Heathcock group has proposed a reasonable biosynthetic route for these alkaloids and achieved several total syntheses of the *Daphniphyllum* alkaloids based on their hypothesis.[3]

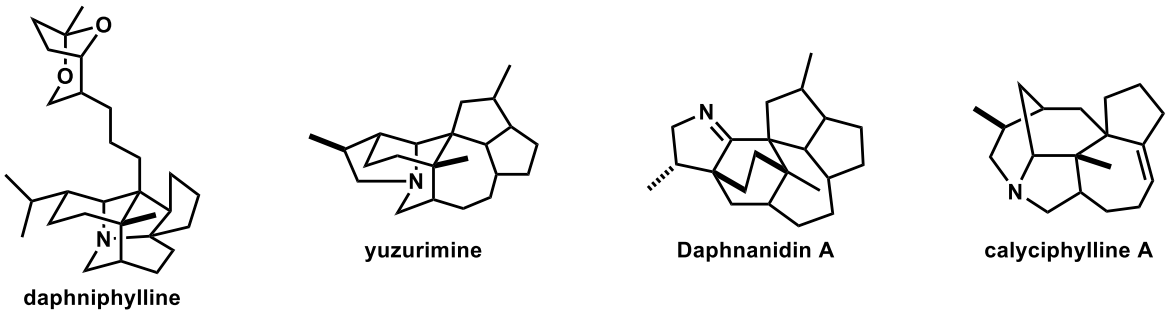
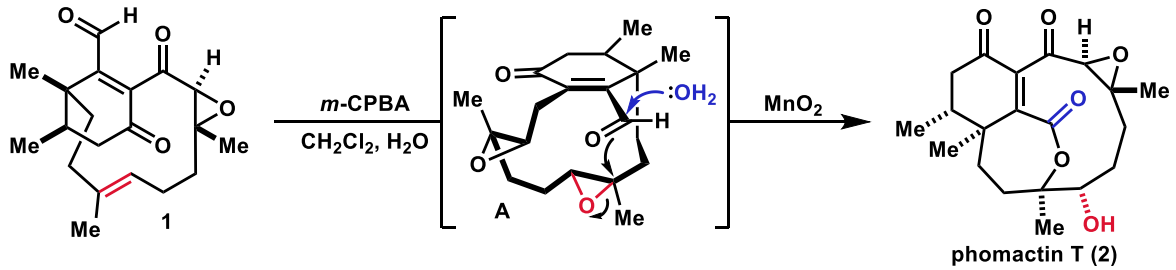


Figure 1. Representative core scaffolds of *Daphniphyllum* alkaloids.

In the past two decades, a new sub-group of *Daphniphyllum* alkaloids, the calyciphylline A-type, has been investigated, and several members in the group have been elucidated.[2] Structurally, calyciphylline A-type alkaloids possess a unique [6-6-5-7-5] *aza*-fused ring system with additional multiple stereocenters including a quaternary carbon. The complex scaffold has made calyciphylline A-type alkaloids attractive targets for chemical synthesis. Their biological properties have not been explored as much because of the limited access to sufficient quantities from natural sources. Enormous effort has been dedicated to developing effective synthetic strategies to access the calyciphylline A-type alkaloids, and several elegant total syntheses have already been achieved.[4] However, more efficient and generally applicable synthetic methodologies to access a broad range of these alkaloids are still in great demand.

Most of the current approaches for the complex azapolycycles of calyciphylline A-type alkaloids rely on stepwise ring formation, which is one of the most reliable strategies to access complex fused-ring systems with high stereoselectivity, although it demands steps to prepare appropriate precursors for each cyclization event. In the Sarpong group, a transannular approach was demonstrated in accessing the phomactin terpenoids (Scheme 1).[5] A transannular reaction concomitantly assembled the fused ring system of phomactin T (**2**) from macrocycle precursor **1** through epoxide intermediate **A** with the creation of two new stereogenic centers. The remarkable efficiency in this process is derived from the restricted macrocycle conformation which sets up the reactive centers in an ideal position for reaction. Inspired by this precedent, we envisioned the novel synthesis of himalensine A (**3**), isolated by the Yao group in 2016,[6] based on a transannular strategy. Himalensine A (**3**) is one of the simplest calyciphylline A type



Scheme 1. Transannular reaction of macrocycle **1** toward phomactin T (**2**).

alkaloids. We also anticipated that a synthesis of **3** could provide an opportunity to develop divergent access to the other calyciphylline congeners. In this report, we describe our research progress featuring a transannular approach towards calyciphylline A-type alkaloids himalensine A (**3**), himalenine C (**4**),[7] himalenine D (**5**),[7] and longistylunphylline A (**6**) (Figure 2).[8]

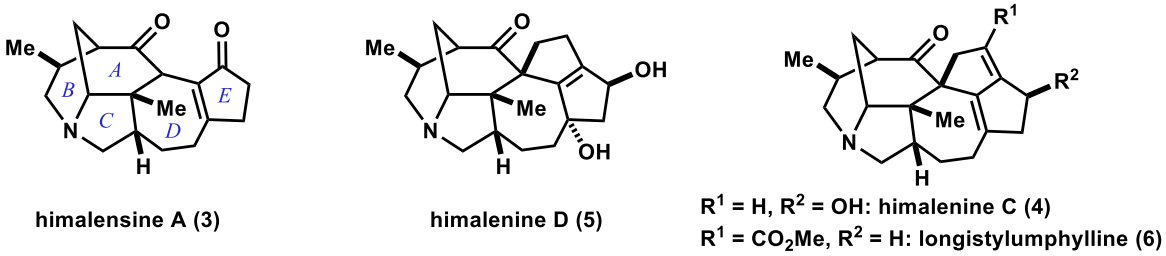


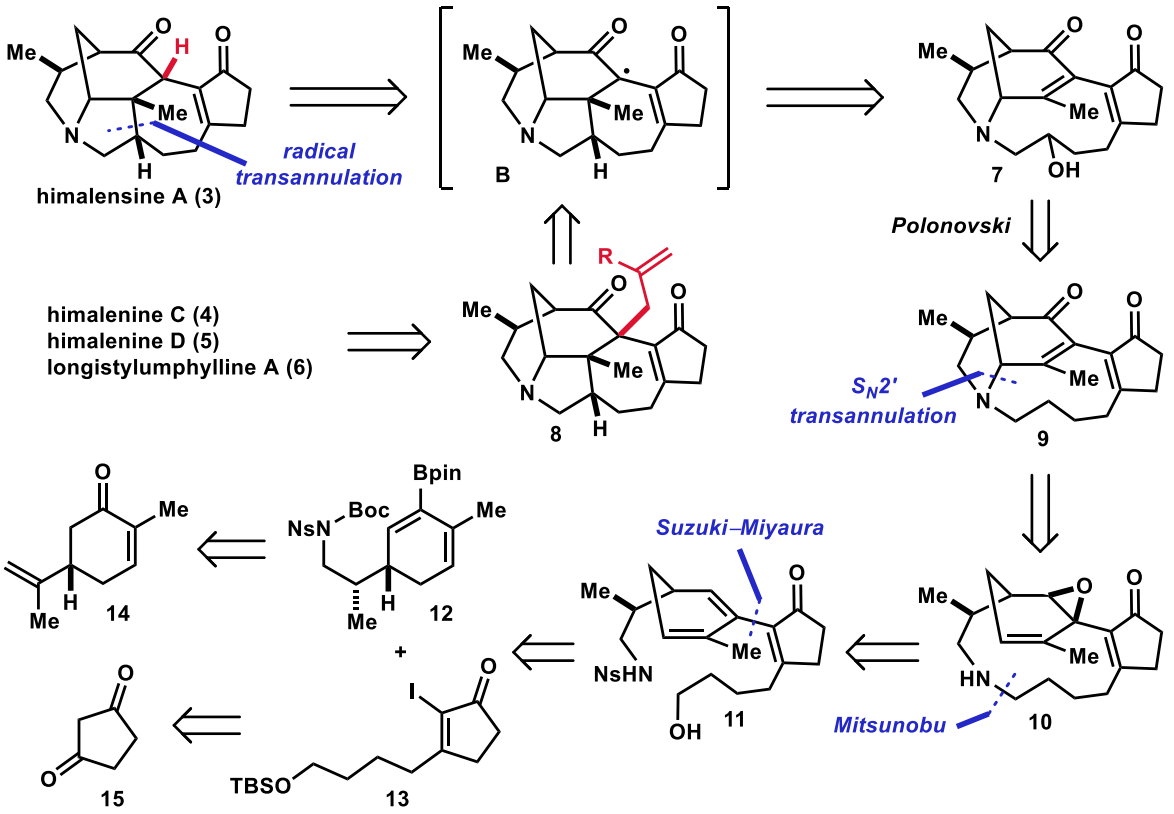
Figure 2. Synthetic targets of Calyciphylline A-type alkaloids.

2. Retrosynthetic Analysis

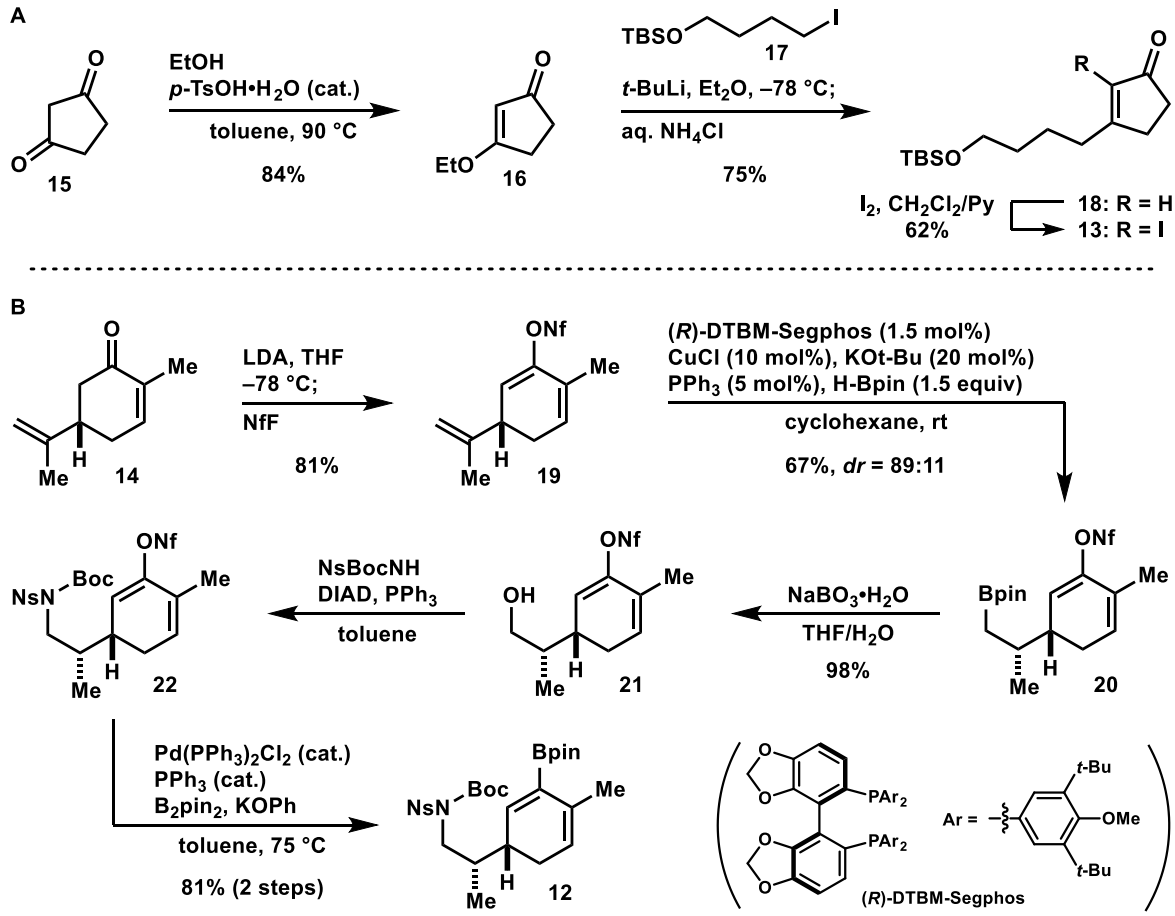
Our retrosynthesis is presented in Scheme 2. We envisioned both the C and D rings of himalensine A (**3**) arising from radical transannular reaction from 10-membered cyclic amine **7** in the final stage of the synthesis. We anticipated that radical intermediate **B** could be trapped by an allyl species, and the resulting alkyl adduct (**8**) would be converted into himalenine C (**4**), himalenine D (**5**), and longistylunphylline A (**6**). The hydroxy group of **7** could be installed through a Polonovski reaction from tertiary amine **9**. The [3.3.1]bicyclononane structure would be derived from vinyl epoxide **10** via S_N2' transannular reaction. The *aza*-macrocycle in **10** would be synthesized through a Mitsunobu reaction. The requisite conjugate enone **11** was traced back to chiral boronate ester **12** and iodocyclopentenone **13** via a Suzuki—Miyaura cross coupling. The six-membered ring fragment (**12**) was to be derived from commercially available (*S*)-carvone (**14**) through a stereoselective hydroboration, while cyclopentenone fragment **13** could be prepared from commercially available 1,3-cyclopentanedione (**15**).

3. Results

Our synthesis commenced with the formation of five-membered ring fragment **13** (Scheme 3). Vinylogous ester **16** was synthesized from 1,3-cyclopentanedione **15** with EtOH in the presence of *p*-TsOH catalyst. The resulting ester was subjected to Stork—Danheiser reaction conditions with an alkyllithium species prepared from TBS-protected alkyl iodide **17** to furnish cyclopentenone **18** in 75% yield.[9] Treatment of enone **18** with iodine resulted in *a*-iodoenone **13**



Scheme 2. Retrosynthetic analysis of himalensine A (**3**) and calyciphylline A-type alkaloid congeners **4**, **5**, and **6**.

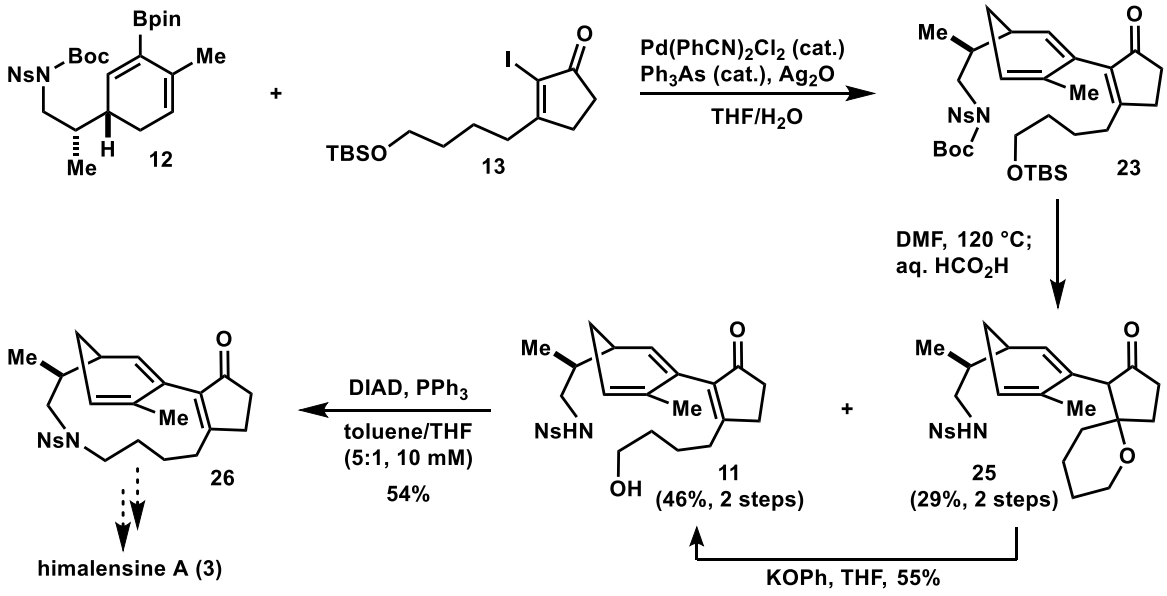


Scheme 3. Synthesis of (A) 5-membered ring fragment **13**, (B) chiral 6-membered ring fragment **12**.

in 62% yield.

For the preparation of vinyl boronate ester fragment **12**, the lithium enolate prepared from (*S*)-carvone (**14**) and LDA was trapped with NfF to afford vinyl nonaflate **19** in 81% yield (Scheme 3). We next investigated a stereoselective hydroboration according to Yun's methodology with a chiral copper catalyst.[10] After extensive study, we found that when vinyl nonaflate **19** was treated with a mixture of (*R*)-DTBM-Segphos (1.5 mol%), CuCl (10 mol%), KO*t*-Bu (20 mol%), PPh_3 (5 mol%), and H-Bpin (1.5 equiv) in cyclohexane, the reaction proceeded smoothly at room temperature to provide hydroboration product **20** in 67% yield with acceptable stereoselectivity (d.r. = 89:11). These diastereomers were inseparable at this stage.[11] Addition of a substoichiometric amount of PPh_3 was crucial to keeping the unligated copper species active which contributed to the higher yield. It is noteworthy that a decline in stereoselectivity was not observed on large scale (35 g scale). The product (**20**) was subjected to mild oxidation conditions with $NaBO_3$ to furnish primary alcohol **21** in 98% yield. Mitsunobu reaction of alcohol **21** afforded protected amide **22**, and subsequent standard Miyaura—Ishiyama borylation conditions resulted in formation of desired chiral boronate ester **12** (81% yield, two steps).[12]

With fragments **12** and **13** in hand, we demonstrated their Suzuki—Miyaura cross coupling with Ag_2O as a base in the presence of Pd catalyst to successfully generate coupling product **23** in considerable yield (Scheme 4).[13] Enone **23** was then subjected to a one-pot deprotection of both the alcohol and amine under high temperature in degassed DMF followed by aqueous formic acid treatment to provide amino alcohol **11** (46% yield, two steps) and spiro ketone **25** (29% yield, two steps) respectively.[14] Upon treatment with KOPh, ring opening of **25** gave rise to alcohol **11** in 55% yield. Finally, our key macrocycle was achieved by Mitsunobu conditions in a toluene-THF cosolvent (10 mM), resulting in smooth formation of *aza*-macrocycle **26** in 54% yield.[15] Diastereomers derived from stereoselecive hydroboration were separable at this stage.



Scheme 4. Synthesis of *aza*-macrocycle **26**.

In conclusion, we have developed an efficient synthetic route toward *aza*-macrocycle **26** in 8 steps (LLS) from commercially available (*S*)-carvone (**14**). Further investigation into the planned transannular reactions toward himalensine A (**3**) is currently proceeding.

4. Acknowledgement

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