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Synthesis of the Tetracyclic ABCD Ring Domain of Calyciphylline A-Type Alkaloids via Reductive Radical Cyclizations

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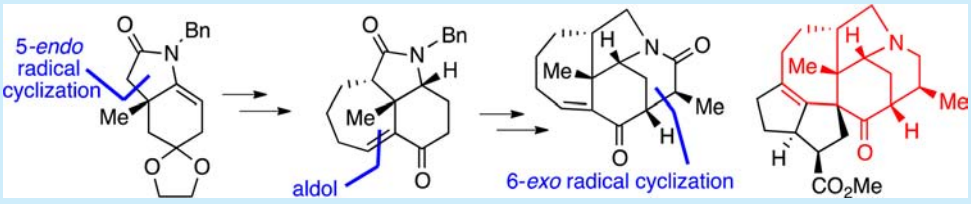
Supporting Information



ABSTRACT: A tetracyclic compound with the ABCD ring framework of calyciphylline A-type alkaloids was synthesized from a *cis*-3a-methyloctahydroindole triggered by a 5-*endo* radical cyclization. The synthesis required two additional ring-forming steps: the construction of a seven-membered ring by aldol cyclization and the azabicyclic fragment by a radical ring closure of a trichloroacetamide-tethered enol acetate followed by a diastereoselective α-methylation of the lactam group.

The calyciphylline A-type alkaloids,[1] which now number more than 30, constitute a group of architecturally complex *Daphniphyllum* alkaloids.[2] The majority of calyciphylline A-type alkaloids are structurally characterized by a hexacyclic framework [6−6−5−7−5−5]. Some are F-seco derivatives (e.g., himalensine A[3]) and bear up to nine stereogenic centers, including two vicinal all-carbon quaternary centers (Figure 1, top).

After the classic foundational biomimetic methyl homoseco-daphniphyllate synthesis by Heathcock,[4] the synthetic efforts toward *Daphniphyllum* alkaloids in the past decade have culminated in the total synthesis of daphmanidin E by Carreira,[5] calyciphylline N by Smith,[6] and daphenylline, a 22-nor-calyciphylline A-type alkaloid, by Li[7] and Fukuyama[8] (Figure 1, bottom). The calyciphylline A-type alkaloids have been the subject of intensive synthetic investigation since the isolation of the first congener in 2003.[9] However, no calyciphylline A-type natural product has been synthesized so far, despite several reports of tri-[10] and tetracyclic[11,12] fragments of these alkaloids. Here we describe a synthesis of the [6−6−5−7] tetracyclic system embedded in the structure of himalensine A and daphiyunnine A.[13] The essential features of the previous syntheses of this azatetracyclic ring are outlined in Figure 2. In

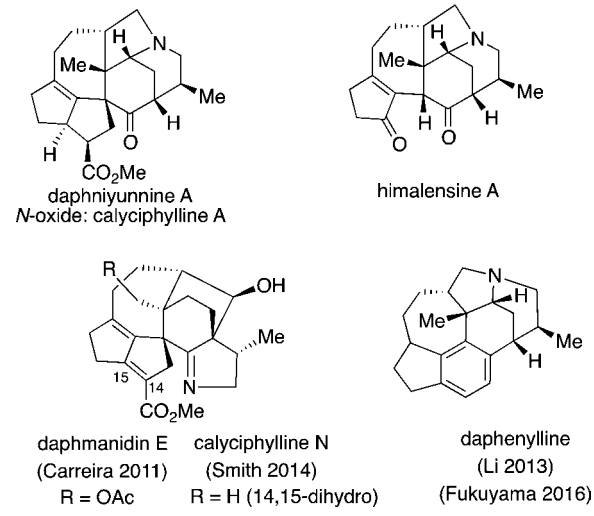


Figure 1. Calyciphylline A-type alkaloids and synthesized structurally related *Daphniphyllum* alkaloids.

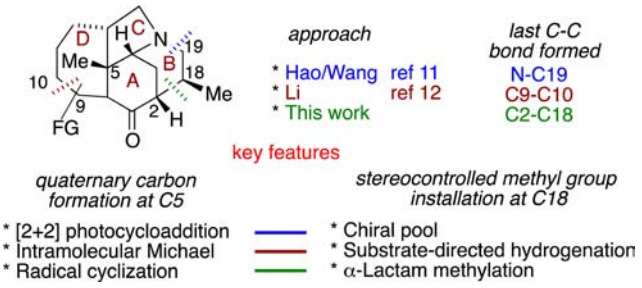


Figure 2. Previous synthetic approaches and the current strategy to the ABCD ring system of calyciphylline A-type alkaloids.

Hao−Wang's approach,[11] a [2 + 2] photocyclization was used to generate the quaternary stereocenter at C5 from an elaborated chiral pool derivative that established the configuration at C18. In Li's strategy,[12] the AC ring was constructed by an intramolecular Michael reaction, which also resulted in the formation of the quaternary C5, while the stereochemistry at C18 was controlled by a substrate-directed hydrogenation from an exocyclic double bond.

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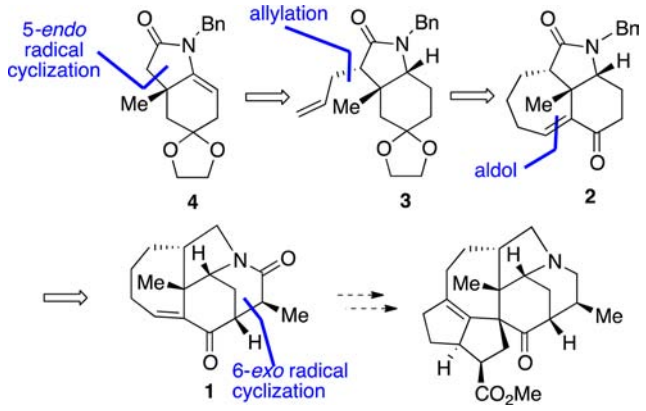
The observation in our previous work[10a] that the stereochemical course of the hydrogenation of an exocyclic methylene at C18 is sensitive to subtle changes in substrate structure prompted us to propose a synthetic plan in which the methyl group is installed by an α-lactam alkylation. The synthetic approach to the ABCD ring system of calyciphylline A-type alkaloids (Scheme 1) involves a series of stepwise annelations

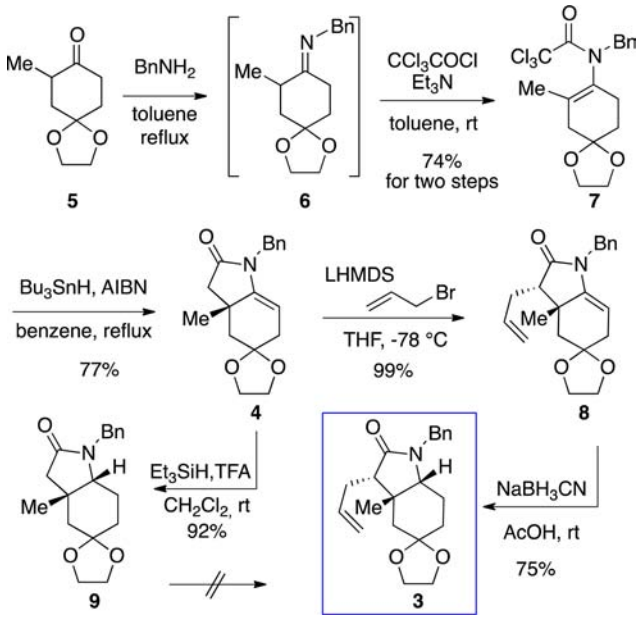
Scheme 1. Synthetic Approach



from 2-methyl-1,4-cyclohexanedione monoethylene acetal, which preforms the carbocyclic A ring of the target. The crucial steps of the synthesis are as follows: (i) closure of the pyrrolidine C ring by a 5-*endo-trig* radical cyclization and generation of the quaternary center at C5, (ii) closure of the D ring using an aldol condensation, and (iii) elaboration of the B ring using a synthetic methodology developed in our group for the synthesis of morphan compounds[14] based on the radical cyclization of trichloroacetamides.[15] The functionalization of the cyclized tetracyclic compound allowed a stereocontrolled introduction of the methyl group to achieve the targeted compound **1**.

At the outset of this synthetic endeavor, it was perceived that radical cyclization could serve as an effective means for the construction of the C ring and generation of the all-carbon quaternary center (Scheme 2). Treatment of ketone **5** with benzylamine under Dean−Stark conditions afforded imine **6**, which was trapped with trichloroacetyl chloride to give enamide **7**. The trichloroacetamide was treated with Bu_3SnH/AIBN (syringe pump addition) in refluxing benzene to give the 5-*endo-trig* cyclization product, hydroindole **4**,[16] containing the all-carbon quaternary center, in 77% yield (10 g scale).[17,18] The success of this cyclization from a trichloroacetamide is due to the electrophilicity of the carbamoyldichloromethyl radical and a relatively low energy barrier for the rotation around both the NCO amide[19] and *N*-alkenyl[20] bonds. Enamide **4** was allylated using LHMDS and allyl bromide at −78 °C to diastereoselectively afford **8** in near-quantitative yield. The selectivity of the allylation was controlled by the steric hindrance generated by the neighboring methyl group. Reduction of the acyliminium generated from **8** using cyanoborohydride in acidic medium[21] selectively afforded *cis*-octahydroindole **3**.[22] The structure of **3** was unequivocally confirmed by X-ray analysis (Figure 3).[23] Notably, when enamide **4** was reduced before the allylation step, giving octahydroindole **9**, the installation of the allyl group was unsuccessful under the reaction conditions used for the transformation of **4** → **8**, and the starting lactam **9** was recovered. The withdrawing nature of the olefin in **4** may render α-lactam hydrogen more acidic than in lactam **9**.

Scheme 2. Synthesis of the AC Octahydroindole Subunit



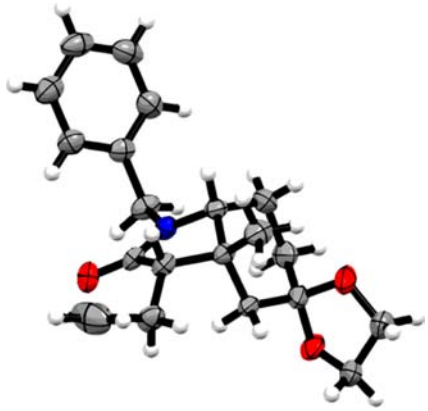


Figure 3. X-ray structure of **3**.

Starting from alkene **3**, a low-catalyst-loading cross-metathesis reaction with a Grubbs second-generation catalyst and CuI as an additive[24] afforded α,β-unsaturated aldehyde **10**. The latter was carefully hydrogenated to afford the corresponding aldehyde (not shown), in which the acetal group was removed using an aqueous solution of HCl in THF to afford keto aldehyde **11**. Aldol cyclization leading to the seven-membered ring was carried out using *p*-toluenesulfonic acid in benzene at reflux. Thus, the D ring was closed, enone **2** formed, and the ACD tricyclic ring achieved. The ketone carbonyl group was protected using ethylene glycol in acetic medium, and as expected,[25] a migration of the double bond occurred, acetal **12** being isolated exclusively (Scheme 3). Its stereochemistry was disclosed by NOE experiments in which a strong interaction between the axially located protons at H-8 (δ 2.96) and H-2 (δ 1.25) was observed.

Our next task was to construct the bridged piperidine ring for the targeted polycyclic system.[26,27] Initially, lactam **12** was debenzylated using sodium in liquid ammonia at −78 °C, followed by reduction of secondary lactam **13** using $LiAlH_4$ to afford secondary amine **14** in excellent overall yield (Scheme 4). After exploring several approaches to achieve the final ring closure,[28] a radical cyclization proved fruitful. The trichloroacetylation of **14** afforded **15**, which was treated in acid medium

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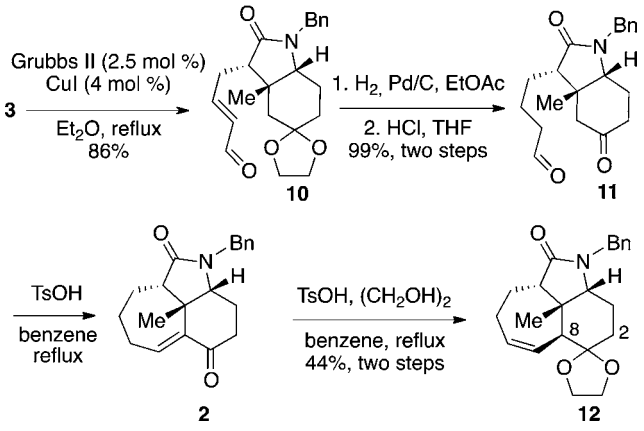
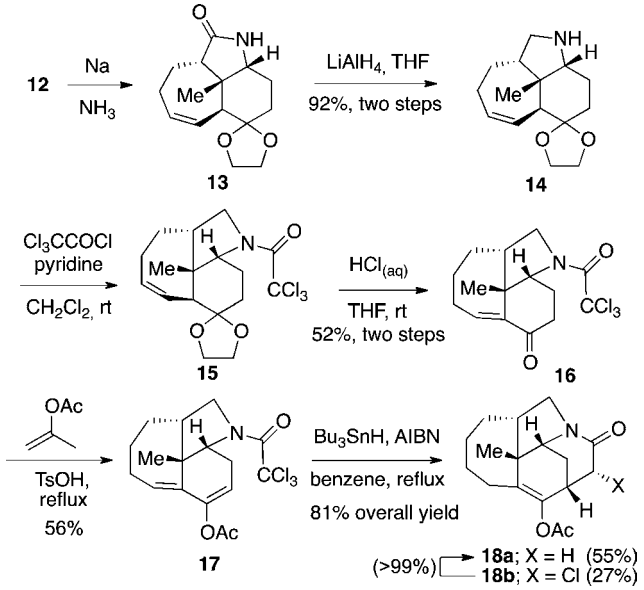
Scheme 3. Synthesis of the ACD Ring System



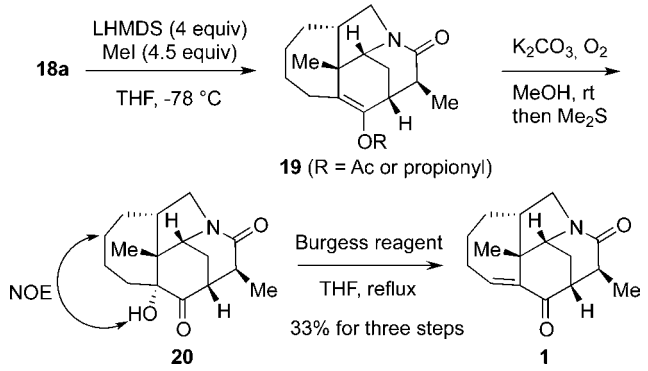
Scheme 4. Synthesis of the ABCD Ring System



to regenerate the α,β-unsaturated ketone moiety (i.e., enone **16**). The required radical acceptor, enol acetate **17**, was obtained by treatment of **16** with *p*-toluenesulfonic acid and isopropenyl acetate. Reaction of enol acetate **17** with Bu_3SnH (3.2 equiv) and AIBN under reaction conditions similar to those used for the synthesis of **4** (see above) provided the morphan ring system in **18** in 82% overall yield (cyclization and reduction steps).[29] During the course of the reaction, translocation of the radical occurred at C10 to afford the more stable alkene.

In a crucial step to achieve valuable intermediates toward calyciphylline A-type alkaloids, alkylation of lactam **18** diastereoselectively installed the methyl substituent, giving the same configuration as the targeted natural products.[30] The unpurified enol acetate **19**[31] was deprotected using K_2CO_3 in MeOH. Unexpectedly, α-hydroxylated ketone **20** was isolated instead of a ketone, and the configuration at the new stereogenic quaternary center was unequivocally established from a NOESY experiment, which revealed a correlation between OH and the axially positioned proton at C-11. In order to improve the conversion yield, the reaction was carried out under an oxygen atmosphere and using dimethyl sulfide as a reductor of the presumed hydroperoxide intermediate.[32] Finally, the tertiary alcohol in **20** was dehydrated using Burgess' reagent to afford **1** in 33% yield over three steps (70% yield for each of the three separate chemical events from **18**) (Scheme 5).

Scheme 5. Completion of the Synthesis of the [6−6−5−7] Tetracyclic Core of Calyciphylline A-Type Alkaloids



In summary, we have developed a synthetic route to the tetracyclic core of calyciphylline A-type alkaloids (Figure 4). The

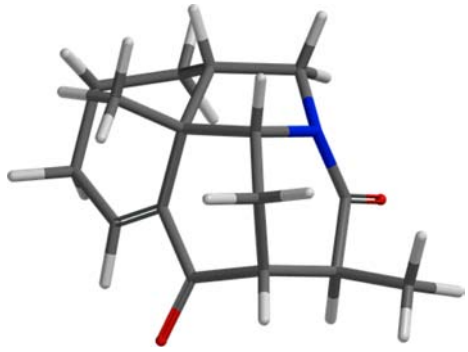


Figure 4. Stereoview of the ABCD ring system of calyciphylline A-type alkaloids.

key steps involve a Bu_3SnH-mediated intramolecular 5-*endo-trig* and 6-*exo-trig* radical cyclization of trichloroacetamides to construct the C and B rings and a ring-closing aldol condensation in acidic conditions to build the D ring. The synthesis of himalensine A and related calyciphylline A-type alkaloids using this strategy will be pursued.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b00035.

Experimental procedures, spectroscopic and analytical data, NMR spectra of new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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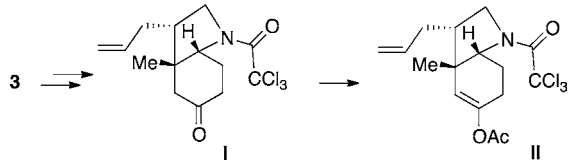
(26) It is worth noting that an alternative sequence based on a previous formation of the piperidine ring from octahydroindole **3** through trichloroacetamide radical cyclization proved to be unfeasible. This is because ketone **I** gave rise to the enol acetate **II**, which precluded the building of the ABC ring before the D ring.



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(29) The overall yield refers to the direct yield (55%) of isolated **18a** plus the additional quantities (27%) obtained after quantitative reduction of its monochloro derivative **18b**.
(30) The ^{13}C NMR chemical shift at methylene C3 allows the diagnosis of the stereochemistry at C18. In natural products, the crowding of a C−H bond at C3 with the axially located methyl group induces a shift at C3, which resonates at δ 18−21. In contrast, in the epimers at C18 in synthetic compounds, the chemical shift at C3 is in the range of δ ∼26.
(31) In addition to compound **19**, the reaction mixture contains an amount of a product methylated at the acetate group. However, this is synthetically irrelevant since the enol was removed in the next step.
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