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Asymmetric Synthesis of the Tricyclic Core of *Calyciphylline* A-Type Alkaloids via Intramolecular [3 + 2] Cycloaddition

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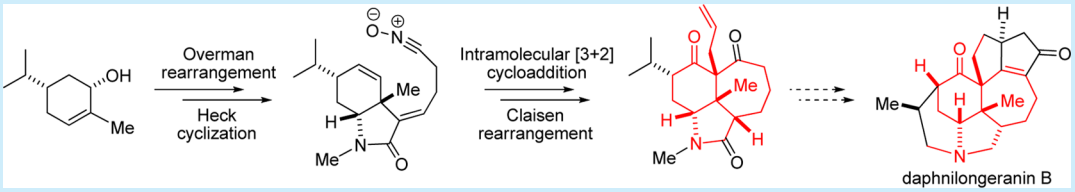
Supporting Information



ABSTRACT: Asymmetric synthesis of the [5−6−7] tricyclic system common to the *Calyciphylline* A-type alkaloids is reported, featuring Overman rearrangement, Heck cyclization, intramolecular [3 + 2] cycloaddition, diastereoselective hydrogenation, and Claisen rearrangement as strategic events. The approach is capable of installing the crucial carbonyl functionality as well as multiple stereogenic centers within a congested polycyclic ring skeleton.

Structurally complex natural products continuously serve as a powerful vehicle for the invention of novel synthetic strategies, and in such activities the desired stereochemical controls are frequently achieved through substrate-directed strategies enabled by structural characteristics of a synthetic target of interest. Among the numerous natural products uncovered in recent years, the *Daphniphyllum* alkaloids constitute a fascinating family due to their unusual polycyclic ring skeletons, stereochemical complexities,[1] and demonstrated bioactivities.[2]

Intrigued by their unprecedented structures as well as their scarce natural supply, we are particularly interested in chemical syntheses of the *Calyciphylline* A-type alkaloids within this family.[3] As highlighted in Figure 1, structural hallmarks of these substances are the shared [5−6−7] tricyclic framework possessing a carbonyl group as well as four contiguous stereogenic centers (two of which being quaternary) embedded in a highly congested ring system (in red). In our previous reports, we had described our developed strategies toward the tri- and tetracyclic skeletons of daphnilongeranin B (**1**), featuring sequentially Mannich condensation, [2 + 2] photochemical cycloaddition, and Grob fragmentation for the construction of A−C−D and A−B−C−D ring systems.[3f,k]

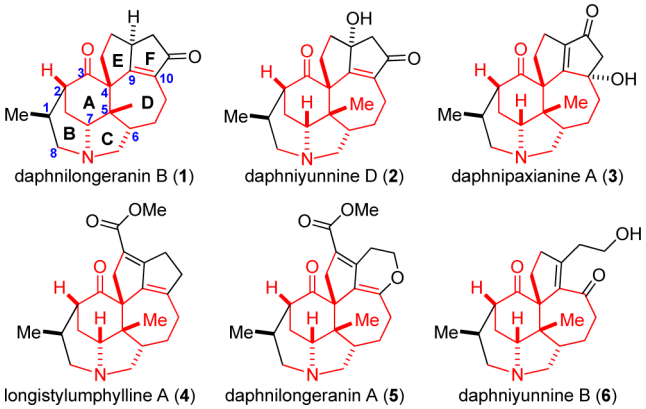


Figure 1. *Calyciphylline* A-class alkaloids featuring a common [5−6−7] tricyclic core and embedded carbonyl functionality.

The previous lesson subsequently teaches a revised retrosynthetic analysis outlined herein. With daphnilongeranin B as the exemplary target, as illustrated in Scheme 1A, a sequence involving Pauson−Khand annulation followed by base-mediated enone isomerization[3j,s] and intramolecular S_N2 displacement[3k] would efficiently degrade the target into the tricyclic intermediate **9**, to which we have already established a facile access.[3f,k] Thus, our attention was next focused on installing the requisite carbonyl group on ring A and introducing the all-carbon quaternary functionalities at C_4.

It is notable that while our synthetic explorations are in progress,[3s] Dixon and co-workers described their syntheses of A−C−D and D−E−F tricyclic cores of *Calyciphylline* A-type alkaloids.[3i,j] As shown in Scheme 1B, the Claisen rearrangement[3i] as well as Michael addition[3j] used for installation of the critical functionalities at C_4 position are particularly inspiring for our investigation. Their work demonstrated that the carbonyl groups on ring A and ring D played important roles in construction of the E−F ring system through the intended Pauson−Khand event.

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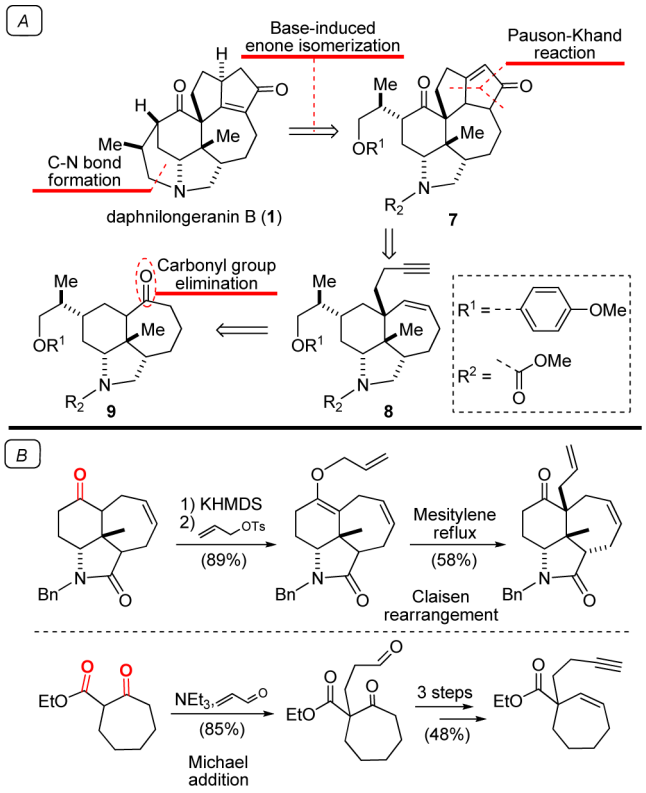
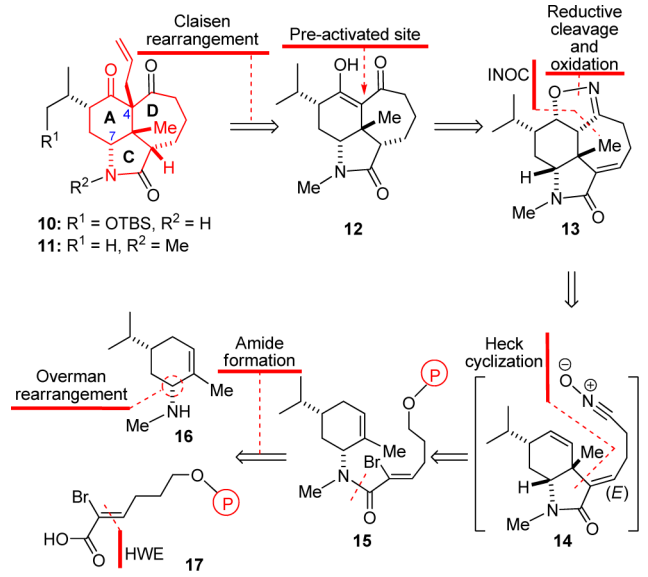
Scheme 1



Scheme 2. Retrosynthetic Analysis of the New Strategy



After numerous unsuccessful attempts to construct the C_4 quaternary center as well as exploring carbonyl-directed C−H oxidations at C_3,[4] we elected to proceed through a revised new scenario for *simultaneous entries to both of the ring skeleton and the embedded carbonyl functionality*. For this purpose, a tricyclic diketone **10** and its simplified analogue **11** thus constituted an ideal platform for examining the feasibility of the proposed strategies. We envisioned that the terminal alkene could be transformed into the requisite alkyne[5,3j,p] and the carbonyl group on ring D could be selectively converted to an olefin,[6] which would set the stage for Pauson−Khand annulation to furnish the E−F ring system (Scheme 1A).

As shown in Scheme 2, we envisioned that the stereogenicity at C_4 could be installed via a substrate-directed Claisen rearrangement.[5,3i] The seven-membered ring D and both of the carbonyl groups in **11** could be accessed with an intramolecular nitrile oxide cycloaddition (INOC)[7] followed by reductive cleavage of the N−O bond and oxidation of the resulting secondary alcohol. With C_7 chirality as a critical stereochemical control element, the five-membered C ring as well as the C_5 all-carbon quaternary center could be established by a stereoselective Heck reaction of bromide **15**, from which the released double bond moiety would provide the needed alkenyl partner to engage on the subsequent INOC process. The precursor **15** would next be assembled by an amide formation event between enantiopure allylic amine **16** and unsaturated carboxylic acid **17**. Finally, the key C_7-chirality in **16** could be introduced by an Overman rearrangement established in our previous synthetic routes and, through a series of substrate-directed stereochemical controls, it would serve as the foundation for securing all of the rest stereogenicities present in the target compound **1**.[3f,k] Notably, within this scenario, a (*Z*)-conjugated carboxylic acid **17** must be employed for the delivery of (*E*)-*exo*-trisubstituted double bond in **14** that should facilitate the intended INOC event.[8]

As summarized in Scheme 3, (*S*)-carvone was converted into carbamate **19** with a series of known procedures involving an Overman rearrangement,[3f] thus establishing the original chirality in the target, in a combined yield of 68% over the four-step sequence. $LiAlH_4$ reduction of **19** then gave allylic amine **16** in nearly quantitative yield. Condensation of amine **16** with unsaturated acid **17** afforded amide **20**, the precursor for the key Heck cyclization, in 84% isolated yield. The initial reaction condition screenings involving the use of 10 mol % of $Pd(OAc)_2$ as precatalyst, 20 mol % of BINAP as ligand, and 5 equiv of Et_3N as base and revealed a significant solvent effect: while the use of MeOH, EtOH, toluene, or THF led to low product yields (0−37%), the use of CH_3CN and DMF promoted a remarkable improvement (78% and 83% yield, respectively). The use of simpler PPh_3 in place of bidentate BINAP enhanced further the yield of **21** to 91% when the Heck cyclization was performed at 100 °C in DMF. The C_5-**Me** and C_7-**H** were confirmed to adopt spatially a *syn*-orientation (NOESY). Compound **21** was next transformed into oxime **22** in very high yield by sequential oxidative removal of the PMB group, oxidation of the alcohol, and condensation with hydroxylamine. Delightfully, upon exposure to the oxidant NaOCl, **22** underwent smoothly intramolecular 1,3-dipolar cycloaddition via the nitrile oxide intermediate **14** to afford the tetracyclic isoxazoline **13** as a single diastereomer[12] and in excellent isolated yield (90%). The facile formation of **13** laid the foundation for not only constructing the seven-membered D ring but also site-specific functionalization on the C_3-carbon in the six-membered A ring. With **13** in hand, an appropriate reaction condition for effecting the N−O bond cleavage was then investigated. The use of activated zinc,[7a] molybdenum hexacarbonyl,[9a] Fe/NH_4Cl,[9b] and samarium diiodide[9c] all failed to produce the desired product. A notable improvement while using Raney nickel/H_3BO_3[10] in place of Pd/C[9d] was next observed, leading to the hydroxy ketone **23** in 92% yield upon hydrogenolysis at 45 °C for 8 h in an optimal solvent mixture of MeOH and H_2O (in 5:1 volume ratio). Compound **23** was readily oxidized by Dess−Martin periodinane via a 1,3-diketone intermediate **24** to exclusively generate enol **25**, whose

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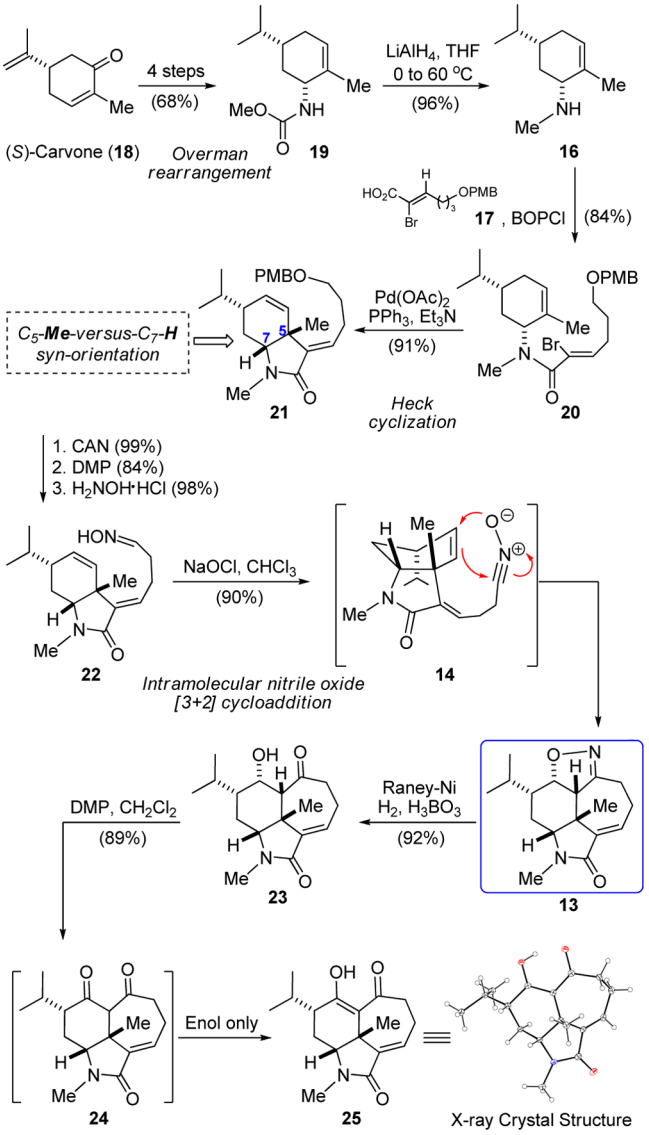
Scheme 3. Synthesis of the [5−6−7] Tricyclic Skeleton 25

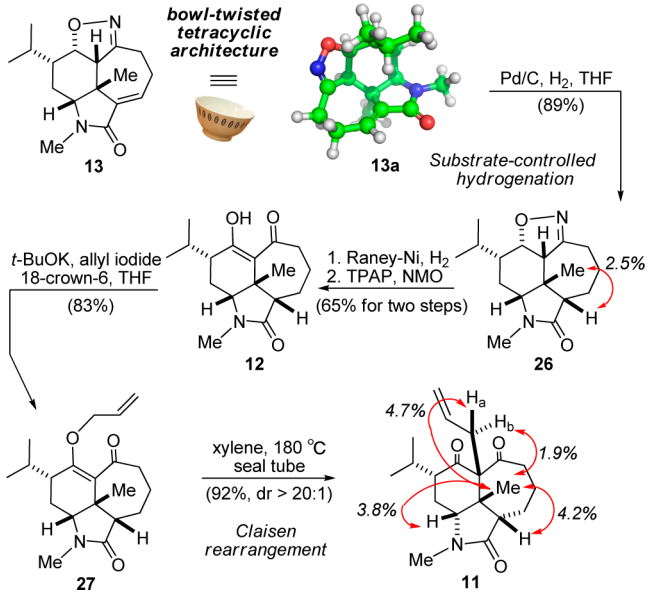


structure and stereochemistry were established by X-ray crystallographic analysis.[11]

The above success prompted us to progress further to the synthesis of the tricyclic system **11** (Scheme 4).

Considering both reactivity and stereoselectivity in the bowl-shaped architecture disclosed in our previous work,[3k] we believed that the tetracyclic core **13** (see the 3D structure of **13a** in Scheme 4) was the appropriate substrate for installing the correct chiral center at C_6. To our delight, upon exposure to simple Pd/C hydrogenation conditions, **26** was obtained in 89% yield as a single isomer.[12] Treatment of **26** with Raney nickel protocol followed by oxidation with TPAP exclusively afforded enol **12**. The enolic double bond was determined to reside within the six-membered ring A on the basis of 2D NMR spectroscopic analysis, which was consistent with the structure of **25**.[12] The resulting enol **12** was subjected to allylation with *t*-BuOK, [18]crown-6,[13] and allyl iodide to give the corresponding allyl enol ether **27** (83%), which in turn underwent Claisen rearrangement at 180 °C in xylene to afford ketone **11** in excellent selectivity and yield (dr >20:1, 92%). The stereochemistry of compound **11** was clearly manifested via 2D-NMR

Scheme 4. Synthesis of the Tricyclic Skeleton 11



study and their nuclear Overhauser effect (NOE) correlations.[12]

In summary, a concise and fully stereochemically controlled synthetic route to the [5−6−7] tricyclic framework of the *Daphniphyllum* subclass *Calyciphylline* A-type alkaloids has been demonstrated. Success hinged on such key events as Heck cyclization to install a congested quaternary stereogenic center, an intramolecular nitrile oxide [3 + 2] cycloaddition to deliver both seven-membered ring and the crucial carbonyl functionalities, diastereoselective hydrogenation to furnish a *cis*-[5−7] ring junction, and a late-stage Claisen rearrangement to yield allyl-substituted 1,3-diketone amendable for further structural editing toward Pauson−Khand annulation. Further studies directed toward enantioselective total synthesis of certain members of these alkaloids are currently underway in our laboratories.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, X-ray crystallographic analysis, and ^{1}H and ^{13}C NMR spectra for new compounds. 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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(11) The crystal structure of **25** was deposited at the Cambridge Crystallographic Data Centre (tracking no. 951031).
(12) For detailed NMR spectroscopic analysis, see the Supporting Information.
(13) 18-Crown-6 was obtained from Adamas-beta Chemical Company (Switzerland).