Total Syntheses of Calyciphylline A-type Alkaloids (−)-10-deoxydaphnipaxianine A, (+)-daphlongamine E, and (+)-calyciphylline R *via* late-stage diallylic alcohol rearrangements

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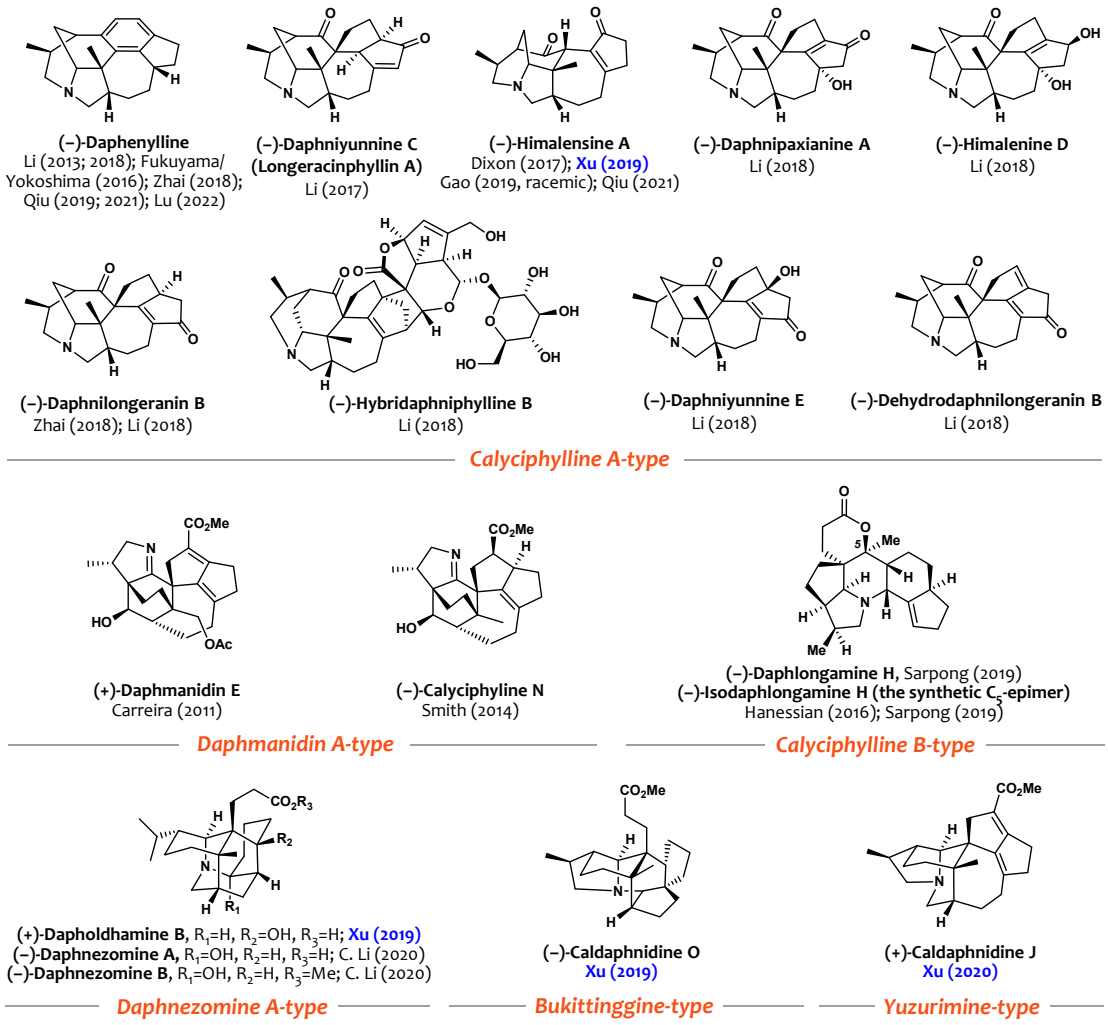
In Memory of Professor Robert H. Grubbs

Abstract: Consisting of more than 350 isolated members, the *Daphniphyllum* alkaloids possess complicated, polycyclic, and often caged skeletons along with diverse, interesting biological profiles. Among this natural product family, the representative calyciphylline A-type subfamily has triggered particular interest from the organic synthesis community. In this paper, we wish to report divergent total syntheses of three calyciphylline A-type alkaloids, namely (−)-10-deoxydaphnipaxianine A, (+)-daphlongamine E, and (+)-calyciphylline R. Our work highlights an efficient, divergent strategy *via* late-stage diallylic alcohol rearrangements, including an unprecedented oxidative Nazarov electrocyclization using an unfunctionalized diallylic alcohol and, an unusual, transannular allylic alcohol rearrangement. Other key transformations in our approach including an nitrile hydration using a highly efficient "donor-acceptor" platinum catalyst, an intramolecular Heck coupling and an intramolecular, regioselective pinacol coupling. Moreover, the power of selective amide reductions has also been showcased by novel and classic tactics. The strategies and methods used in our approach might provide further inspiration for natural product synthesis. Particularly, the novel oxidative Nazarov electrocyclization should be valuable in the chemical synthesis of other cyclopentenone-containing small molecules.

Isolated from the genus *Daphniphyllum*, calyciphylline A-type alkaloids (Figure 1 and Scheme 1) belong to a famous family of bioactive natural products, known as the *Daphniphyllum* alkaloids.[1] Biological investigations of this large family indicate a wide range of bioactivities including anti-tubulin polymerization, anti-HIV, anticarcinogenic, vasorelaxant, cytotoxic, and neurotrophic activities.[2] Equally interesting attributes of *Daphniphyllum* alkaloids are their synthetically challenging architectures, which possess sophisticated, polycyclic and caged backbones. Based on their diverse skeletons, the structures of these intriguing alkaloids can be categorized into 13−35 subfamilies,[1,3] while the title of the largest subfamilies currently shared by the calyciphylline A-type and the yuzurimine-type alkaloids, which both contain approximately 50 members.

Figure 1. Recent Total Syntheses of Calyciphylline A-type and Other Types of *Daphniphyllum* Alkaloids.



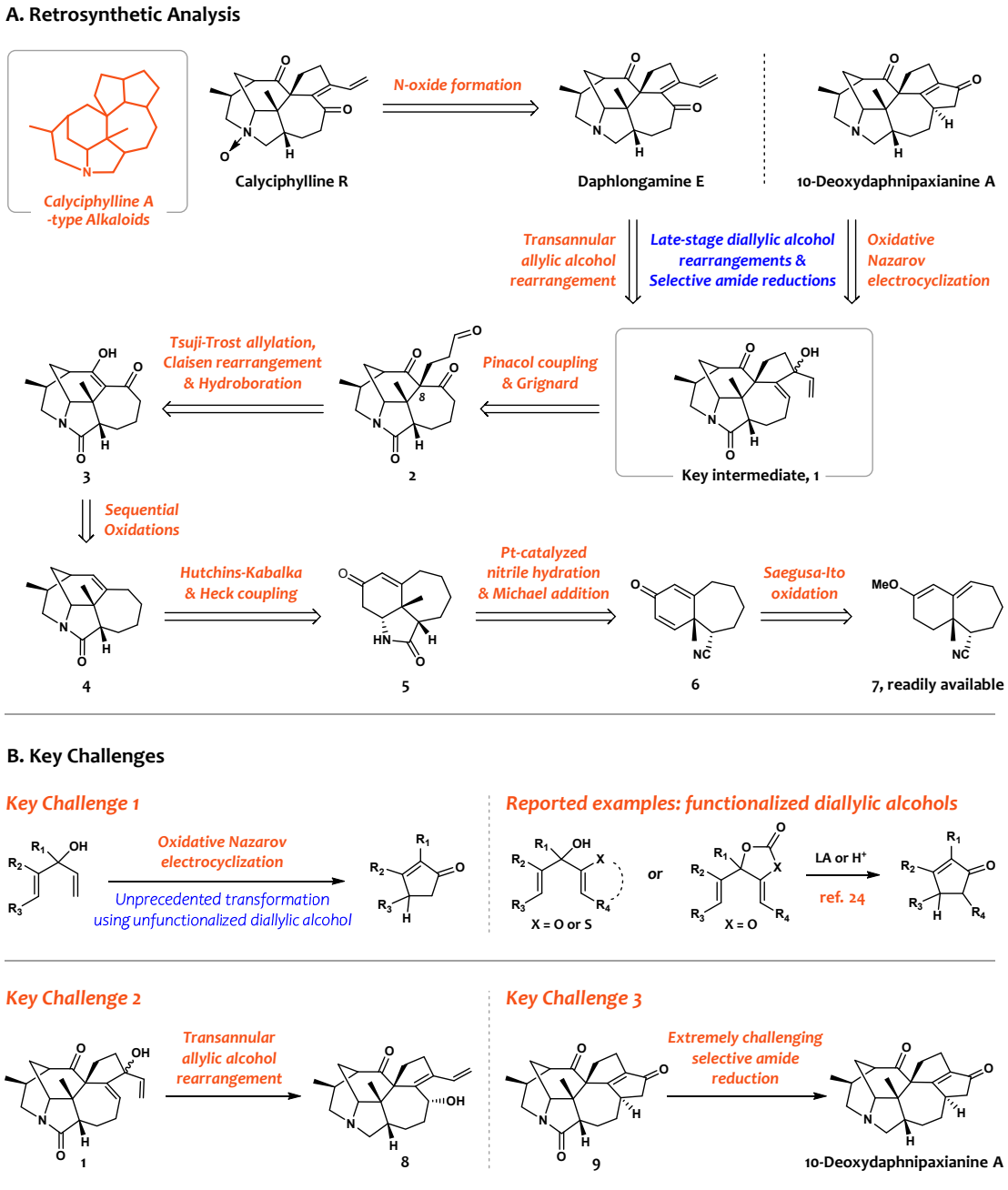
Owing to the structural and biological significance of the *Daphniphyllum* alkaloids, extensive synthetic studies have been initiated by the organic synthesis community over the last four decades.[3,4] After Heathcock's seminal work,[5] many impressive total syntheses have been achieved by the groups of Carreira,[6] Li,[7] Smith,[8] Fukuyama/Yokoshima,[9] Dixon,[10] Zhai,[11] Qiu,[12] Gao,[13] Sarpong,[14], C. Li[15] and Lu[16] (Figure 1).[17] Meanwhile, our group has achieved asymmetric total syntheses of four members from four distinct subfamilies, namely calyciphylline A-type alkaloid himalensine A, daphnezomine A-type alkaloid dapholdhamine B, bukittinggine-type alkaloid caldaphnidine O, and yuzurimine-type alkaloid caldaphnidine J (Figure 1).[4b, 18] Particularly, the calyciphylline A-type subfamily has triggered enormous synthetic activities.[4a, 19] From 2013 to 2018, the Li group accomplished remarkable total syntheses of eight calyciphylline A-type alkaloids, including daphenylline, daphniyunnine C (longeracinphyllin A), daphnipaxianine A, himalenine D, daphnilongeranin B, hybridaphniphylline B, daphniyunnine E, and dehydrodaphnilongeranin B.[7] In 2016, the Fukuyama/Yokoshima group reported their elegant total synthesis of daphenylline.[9] Continuing exploration in this subfamily also resulted in several impressive total syntheses of himalensine A (Dixon, 2017;[10] ourselves, 2019;[18a] Gao, 2019;[13] Qiu, 2021[12b]), that of daphenylline and daphnilongeranin B by Zhai in 2018[11] and that of daphenylline by Qiu in 2019[12a] and 2021[12b] and by Lu in 2022.[16]

The advances achieved in the total syntheses of those nine calyciphylline A-type alkaloids have showcased many elegant strategies and novel methods. Nevertheless, more than forty unsynthesized members within this subfamily leave much space for further innovations. Here, we wish to report divergent total syntheses of three members of calyciphylline A-type alkaloids, (−)-10-deoxydaphnipaxianine A, (+)-daphlongamine E, and (+)-calyciphylline R. Our approach highlights a divergent strategy using two different late-stage diallylic alcohol rearrangements, namely an unprecedented oxidative Nazarov electrocyclization using an unfunctionalized diallylic alcohol and, an unusual, transannular allylic alcohol rearrangement.

The calyciphylline A-type alkaloid 10-deoxydaphnipaxianine A was isolated from the Nepalese plant *Daphniphyllum himalense* by Yue *et al*. in 2016. [20] Its natural analog (+)-daphlongamine E was isolated from *Daphniphyllum longeracemosum* by the Hao group in 2009,[21] while the *N*-oxide form of daphlongamine E, namely calyciphylline R, was isolated from *Daphniphyllum macropodum* by the Tang lab in 2014.[22] Their complicated structures features a pentacyclic or a hexacyclic caged-like skeleton that

contain multiple contiguous stereogenic centers and two vicinal all-carbon quaternary centers. Although little is known about their biological potency, their highly synthetically challenging architectures provide intriguing opportunities for strategical and tactical innovations.

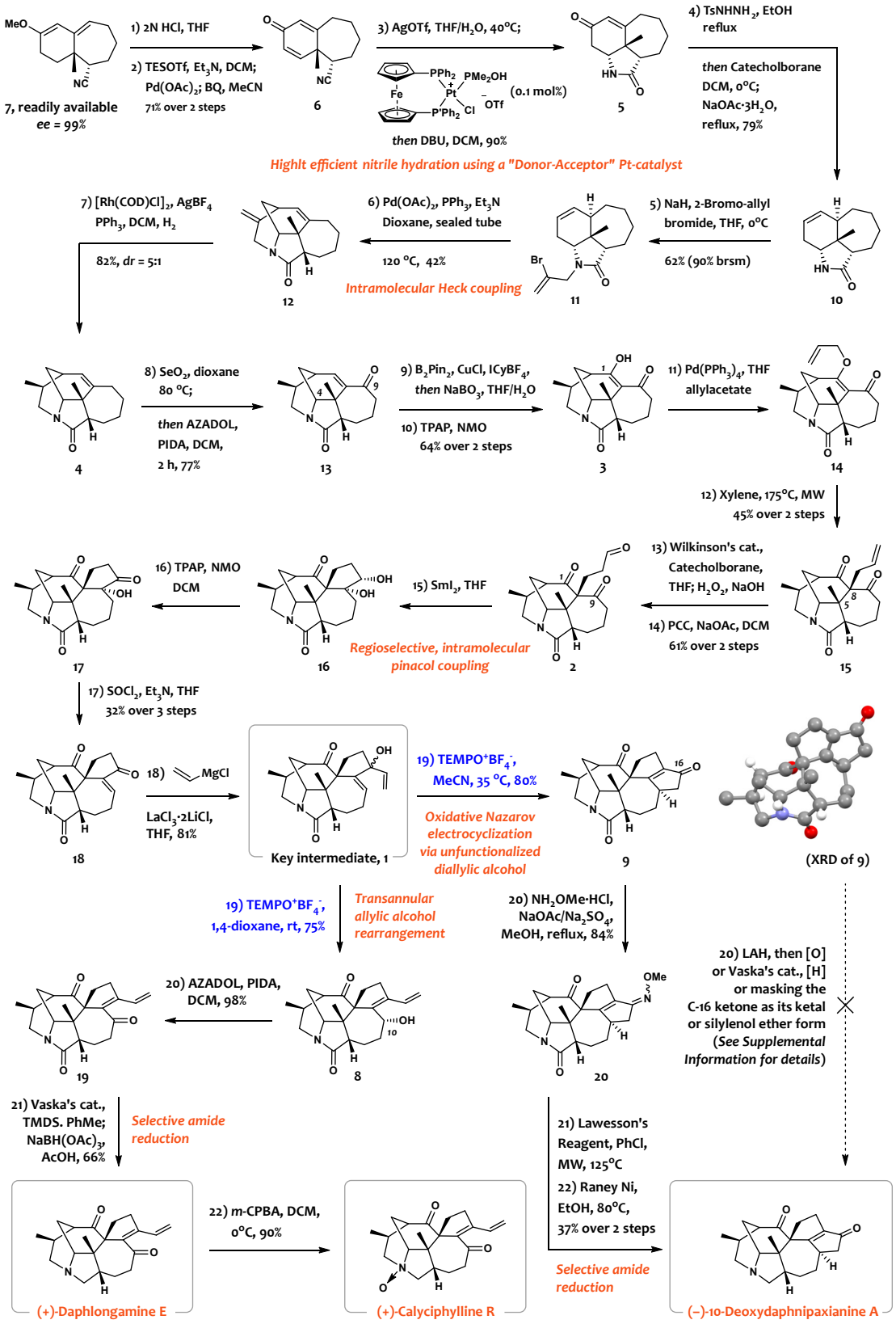
Scheme 1. (A) Retrosynthetic Analysis of Calyciphylline A-type Alkaloids (B) Key Challenges Encountered in Our Approach.



As depicted in Scheme 1A, the retrosynthetic analysis of our target molecules indicated that they could be derived from common key intermediate **1** through late-stage diallylic alcohol rearrangements followed by selective amide reductions. Specifically, the enone moieties in daphlongamine E and its *N*-oxide analog, calyciphylline R, should both be accessible from **1** using a transannular allylic alcohol rearrangement. Instead, the pivotal cyclopentenone in 10-deoxydaphnipaxianine A can be traced back to the unfunctionalized diallylic alcohol motif through a Nazarov-type cyclization. Next, we envisioned that compound **1** can be easily produced from aldehyde **2** *via* an intramolecular, regioselective pinacol coupling followed by a Grignard 1,2-addition. The aldehyde appendix along with the critical C-8 all-carbon quaternary center in compound **2** could be derived from 1,3-diketone **3** using a three-step transformation including a Tsuji-Trost allylation, a Claisen rearrangement and a hydroboration-oxidation reaction. We further envisaged that intermediate **3** could be obtained *via* oxidation state manipulations from tetracyclic alkene **4**, which can be further traced back to tricycle **5** through a Hutchins-Kabalka reductive rearrangement and an intramolecular Heck coupling reaction. The γ-lactam moiety in compound **5** could be derived from dienone **6** using a Pt-catalyzed nitrile hydration followed by an *aza*-Michael addition. Finally, dienone **6** could be readily prepared from known chiral nitrile compound **7**.[18a]

Despite the seemingly straightforward synthetic design, several key challenges embedded in our approach are particularly worth mentioning (Scheme 1B). First, Nazarov-type cyclizations using unfunctionalized diallylic alcohols usually favor the Dauben-Michno rearrangement pathway.[23] Only a few reported examples[24] involving heteroatom-functionalized diallylic alcohols underwent Nazarov-type or decarboxylative Nazarov-type cyclizations (Scheme 1B),[25] thereby signifying the remarkable challenges presented in our desired transformation. The second critical problem arises from the production of alcohol **8** or its ketone form by a transannular allylic alcohol rearrangement, which has only been demonstrated a limited number of times.[26] Last, although the methods for selective amide reduction in presence of ketones have appeared as critical tools especially in the synthesis of *Daphniphyllum* alkaloids, significant challenges have been encountered in the transformation from compound **9** to (−)-10-deoxydaphnipaxianine A. Therefore, in the following sections, we would like to introduce our efforts on unraveling these fascinating puzzles that eventually resulted in total syntheses of three complex calyciphylline A-type alkaloids.

Scheme 2. Total Syntheses of (−)-10-Deoxydaphnipaxianine A, (+)-Daphlongamine E and (+)-Calyciphylline R

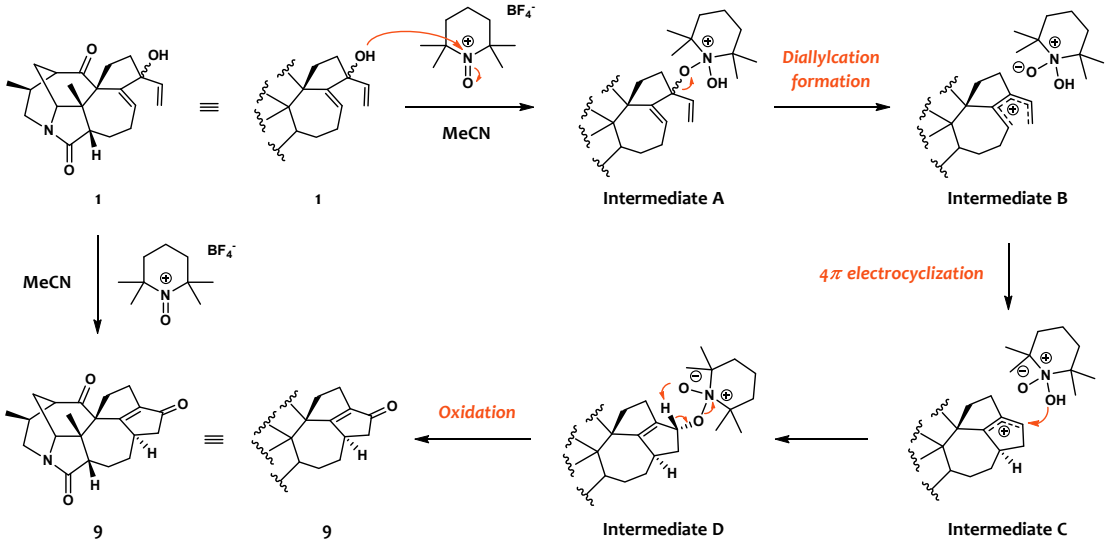


We began our approach from chiral nitrile **7**[18a] by hydrolyzing its enol methylether moiety followed by a Saegusa-Ito oxidation to yield dienone **6** (Scheme 2). Next, a novel "donor-acceptor" Pt-catalyst, which was developed by Grubbs *et al.*,[27] has shown remarkable efficiency (0.1 mol%) that facilely hydrated the nitrile motif in compound **6** into the corresponding primary amide motif. The following *aza*-Michael addition was triggered by adding DBU into aforementioned reaction mixture to give γ-lactam **5** (90% from **6**). Subsequently, a Hutchins-Kabalka reductive rearrangement[28] furnished alkene **10** from compound **5**. The critical 2-azabicyclo[3.3.1]nonane moiety in tetracycle **12** was then fabricated by *N*-alkylation followed by an intramolecular Heck reaction ($Pd(OAc)_2$, PPh_3, Et_3N, dioxane, 120 °C, 42%). The 1,1-disubstituted alkene in compound **12** was regioselectively and diastereoselectively hydrogenated (dr = 5:1) under Li's conditions (H_2, $[Rh(COD)Cl)]_2$)[7b–7d] to give intermediate **4**. At this juncture, a carbonyl group was required at C-9 position. Screening of various allylic oxidation conditions indicated that classic Riley oxidation was able to give the best yield (SeO_2, 1,4-dioxane, 80 °C, ca. 85% yield), while other conditions gave only poor yields or the C-4 *N,O*-hemiacetal derivatives as interesting side products (See SI for details). To our knowledge, this is the first example of a transannular allylic oxidation on a [6,7]-fused bicycle system. Without isolation, a one-pot oxidation (PIDA, AZADOL) successfully furnished enone **13** in a 77% combined yield. A conjugate boron-addition[29] to the α,β-unsaturated enone motif in compound **13** followed by sequential oxidations furnished the 1,3-diketone functionality in compound **3** (64%, 2 steps). Other attempts at this transformation, such as hydroboration/oxidation or epoxidation/epoxide opening/oxidation process, either suffered low yields or decomposition of starting materials. In turn, a palladium-catalyzed Tsuji-Trost allylation reaction introduced the allyl group, yielding the *O*-alkylated product **14** instead of the *C*-alkylated product **15**. Hence, a Claisen rearrangement[6,7d,19g] was employed to convert enol ether **14** into compound **15**, which bears the pivotal C-8 quaternary center that is vicinal to the C-5 quaternary center. This critical Claisen rearrangement occurred on the convex face and, the stereochemistry of substrate **15** was later assigned by the single-crystal X-ray diffraction of its descendant, compound **9**. We next required an efficient tactic to fabricate the cyclopentane motif. While routine hydroboration conditions (BH_3 or 9-BBN) failed to convert the terminal alkene motif in compound **15** into the corresponding primary alcohol, other conditions such as anti-Markovnikov Wacker oxidation[30] or olefin cross-metathesis[31] were also fruitless. Alternatively, a two-step functionalization of this terminal alkene, using a Rhodium-

catalyzed hydroboration[32] followed by a PCC oxidation produced aldehyde **2** (61%, 2 steps). In turn, the crucial cyclopentane motif was assembled by a SmI_2-mediated, regioselective, intramolecular pinacol coupling that successfully differentiated the C-1 ketone and the C-9 ketone, most likely due to the different steric hindrances between two ketone groups. Next, a Ley oxidation of the secondary hydroxyl group in diol **16** furnished α-hydroxyl ketone **17**, in which the α-hydroxyl group was eliminated under $SOCl_2$/pyridine conditions to give α,β-unsaturated enone **18**. Furthermore, nucleophilic 1,2-addition to the enone motif in compound **2**, using vinyl Grignard reagent with $LaCl_3$•2LiCl as an additive, produced key intermediate **1** (dr ≈ ca. 2:1).

With a sufficient amount of key intermediate **1** in hand, our original plan was to employ a Dauben-Michno rearrangement[23] to fabricate the enone moiety in compound **19**, which would allow us to access (+)-daphlongamine E and (+)-calyciphylline R. To our great surprise, under Iwabuchi's conditions ($TEMPO^+BF_4^-$, MeCN),[23b] diallylic alcohol **1** underwent an unprecedented oxidative Nazarov cyclization to afford pentacycle **9** in 80% yield. The structure of compound **9** have been unambiguously confirmed *via* a single-crystal X-ray diffraction.[33] As previously mentioned, only a few reported examples[24,25] of heteroatom-functionalized diallylic alcohols have undergone Nazarov-type or decarboxylative Nazarov-type cyclizations (Scheme 1B). Therefore, using an unfunctionalized diallylic alcohol, this novel oxidative Nazarov electrocyclization provided an important and facile method for the synthesis of cyclopentenone-containing molecules. A plausible mechanism for this unique transformation is depicted in Scheme 3. We envisioned that adduct **A** is formed by the addition of the tertiary hydroxyl group to the oxoammonium ion. Next, the diallylcation formation converts intermediate **A** to intermediate **B**, which further undergo a 4π-electrocyclization to give intermediate **C** as an allylcation. *N*-hydroxyl trapping of this allylcation produces intermediate **D**, which is subsequently oxidized into compound **9**. The success of this novel transformation might be attributed to the formation of the counteranion-stabilized diallyl cation, intermediate **B**. Moreover, the fact that either diastereomeric isomers of intermediate **1** (ca. 2:1) can be converted into compound **9** also suggests the diallyl cation/4π-electrocyclization pathway. The full scope of this novel oxidative Nazarov cyclization has been studied in parallel and will be reported separately.

Scheme 3. Proposed Mechanism of the Oxidative Nazarov Electrocyclization



Our next mission was to convert compound **9** into one of our target molecules, (−)-10-deoxydaphnipaxianine A, through a selective amide reduction in presence of the enone motif and C-1 ketone moiety. Unexpectedly, despite several similar reported examples,[7b-7d, 12b, 13, 18a] this seemingly simple reduction proved extremely difficult. Attempts using Vaska's conditions resulted in only a trace amount of desired product, while global reductions of all three carbonyl groups using $LiAlH_4$ followed by various oxidation conditions were also fruitless. Instead, treating compound **9** with Lawesson's reagent or P_2S_5 at room temperature or 40 °C converted only the C-16 carbonyl into its sulfur carbonyl derivative, leaving the amide carbonyl group untouched. Other trials using Lawesson's reagent or P_2S_5 under elevated temperature resulted in unidentifiable mixtures. Detailed conditions of these unsuccessful attempts are listed in the Supporting Information. These failed attempts forced us to consider masking the C-16 carbonyl group in compound **9**. Initial attempts to convert it into its ketal form failed to give any desired product, while its silyl ether derivatives are regrettably unstable. Gratifyingly, mixing compound **9** with methoxyamine produced *O*-methyloxime **20**, which was poised for assembly of our final target, (−)-10-deoxydaphnipaxianine A. It is worth mentioning that, although *O*-alkyloximes[34] have rarely been used as protecting groups for ketones, their unique stability and reactivity were unexpectedly suitable for the final transformation in our approach. Finally, microwaving oxime **20** with Lawesson's reagent in chlorobenzene at 125 °C followed by treatment with Raney nickel smoothly reduced the amide functionality to its amine form, while the *O*-methyloxime group was concurrently removed, thus afforded our target molecule, (−)-10-deoxydaphnipaxianine A. This synthetic compound gave spectral characteristics (^1H and ^{13}C NMR

spectroscopy and HRMS data) consistent with those of the naturally occurring (−)-10-deoxydaphnipaxianine A, while the optical rotation also matched with that of the natural product (synthetic: $[\alpha]_D^{18}$= −94.0 (c = 0.2 in MeOH); natural: $[\alpha]_D^{25}$ = −111.0 (c = 0.2 in MeOH).[20]

Finally, we investigated the syntheses of (+)-daphlongamine E and (+)-calyciphylline R (Scheme 2). The key to success relied on a Dauben-Michno rearrangement[23] or a transannular allylic alcohol rearrangement of diallylic alcohol **1**. Despite the fact that these types of rearrangements have been widely used in the synthesis of β-disubstituted enones, its transannular version was unexpectedly difficult and rare.[26] Surprisingly, our variation ($TEMPO^+BF_4^-$, 1,4-dioxane) on Iwabuchi's conditions[23b] converted diallylic tertiary alcohol **1** to secondary alcohol **8** in 75% yield. It was observed that the $TEMPO^+BF_4^-$ moderately dissolves in dioxane, while it is fully soluble in acetonitrile. Thus, it is presumed that the solubility of $TEMPO^+BF_4^-$ was key to the selectivity between the two drastically different rearrangements. It is also notable that the highly sterically hindered C-10 hydroxyl group in compound **8** could not be further oxidized under our conditions, until more powerful oxidation conditions were employed (AZADOL, PIDA, 98%) to furnish enone **19**. Interestingly, under selective amide reduction conditions using Vaska's catalyst followed by a hydride reduction,[7b-7d, 12b, 13, 18a] compound **19** behaved dramatically different than its analog **9** and, smoothly yielded (+)-daphlongamine E in 66% yield. Furthermore, subjecting (+)-daphlongamine E to *m*-CPBA afforded its *N*-oxide derivative, (+)-calyciphylline R. The synthetic products, thus obtained, possessed identical spectroscopic and analytical properties to those reported for the natural products, while the optical rotations were also in good agreement with that of the natural products (see SI for details).[21,22]

In conclusion, we have accomplished the first total syntheses of three complicated calyciphylline A-type alkaloids, namely (−)-10-deoxydaphnipaxianine A, (+)-daphlongamine E and (+)-calyciphylline R, in 21-22 linear steps from chiral nitrile **7** with minimal use of protecting groups[35]. Our synthetic strategy is highly flexible since intermediate **15** allows general and diversifiable accesses to various calyciphylline A-type alkaloids. Importantly, embedding with different enone motifs, our target molecules can be easily accessed *via* late-stage diallylic alcohol rearrangements from key intermediate **1**. A rare, transannular allylic alcohol rearrangement was key to the success of the syntheses of (+)-daphlongamine E and (+)-calyciphylline R. Even more noteworthy is the unprecedented, oxidative Nazarov electrocyclization using an unfunctionalized diallylic alcohol. Followed by a novel amide reduction *via* an *O*-

alkyloxime masked enone, these novel transformations eventually paved the way to the total synthesis of (−)-10-deoxydaphnipaxianine A. Our efficient, diversifiable strategy and novel findings in synthetic methods may be inspiring in the chemical synthesis of many other natural products.

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Notes

The authors declare no competing financial interest.

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