Reprogramming of the biosynthetic network of *Daphniphyllum* alkaloids into a chemically synthetic network through generalized biomimetic strategies

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ABSTRACT: Biomimetic synthesis is a fundamental approach to the chemical synthesis of natural products, which, due to the intrinsic correlation between the biogenesis and the structure of natural products, offers many advantages. Conventional biomimetic strategies have evolved on a principle featuring "(essentially) the same substrates, similar reactions, and similar pathways", which defines the pattern of biomimetic synthesis from the structural, mechanistic, and sequential perspectives. In practice, such highly imitative approaches have proved considerably feasible and efficient. However, applicability of this type of approach is also limited by the principle. To enhance the power of biomimetic synthesis, we envision generalized biomimetic strategies focusing on the key bond formation/cleavage sites implied by the biogenesis of natural products, which allow us to take full advantage of altered substrates, reactions, and pathways while retaining the inherent advantages of biomimetic synthesis. In this study, we showcased the utility of generalized biomimetic strategies in the synthesis of fourteen *Daphniphyllum* alkaloids from the macrodaphniphyllamine, calyciphylline A,

daphnilongeranin A, and daphnicyclidin D subfamilies. The biosynthetic network of these alkaloids was reprogrammed into a powerful chemically synthetic network through substrate-, reaction-, and pathway-altering biomimetic strategies.

INTRODUCTION

Biomimetic synthesis is an approach to chemical synthesis that mimics the established or postulated biogenesis[1–3]. The structure of natural products embodies the logic of their biosynthesis. Therefore, biomimetic synthesis offers many advantages in the practice of natural product synthesis, especially in tackling the problems of ring system construction and stereochemical control. A century ago, Robinson achieved the biomimetic synthesis of tropinone through a double Mannich cascade inspired by a hypothesis about the biogenesis of this intriguing alkaloid[4]. Since then, biomimetic synthesis has evolved into a fundamental approach to natural product synthesis, which not only forged an essential part of the logic of complex molecule synthesis but also stimulated the development of useful reactions. The common pattern of natural product biomimetic synthesis is that a substrate identical (or highly similar) to its counterpart in the biosynthesis undergoes chemical reactions mechanistically similar to the corresponding enzymatic (or sometimes non-enzymatic) reactions in the biosynthesis, in the order defined by the biosynthetic pathway, to give the target molecule. Some advanced patterns have also emerged in the evolution, for instance, a) biomimetic assembly of a complex natural product with multiple natural products as building blocks (A + B + … → Z)[5–7] and b) biomimetic construction of a natural product network (B ← A → C → … → Z)[8–10], which significantly enhance the structural complexity and diversity generated by biomimetic synthesis.

The core principle of conventional biomimetic synthesis of natural products can be summarized as "(essentially) the same substrates, similar reactions, and similar pathways", which defines various biomimetic strategies from the structural, mechanistic, and sequential perspectives. It seems to be generally accepted that a high degree of imitation correlates to high feasibility and efficiency of the synthesis. However, chemists' attempts to mimic nature are often hampered by the lack of tools comparable to enzymes in terms of reactivity and selectivity. Furthermore, due to our limited

understanding of the details of natural product biosynthesis, the feasibility of biomimetic approaches is, in many cases, heavily affected by the plausibility of the biosynthetic hypotheses. Therefore, the applicability of biomimetic synthesis in the chemical synthesis of natural products is rather limited, despite its theoretical advantages. In the past decade, biomimetic syntheses accounted for approximately 10% of the cases of natural product syntheses reported in selected journals (see the Supplementary Information).

To enhance the power of biomimetic synthesis toward natural products, we envision generalized biomimetic strategies beyond the restriction of the "highly imitative" principle. These strategies focus on the key bond formation/cleavage sites implied by the biosynthesis and are reinforced by altering the biosynthetic substrates, reactions, and pathways. Of note, the conception of generalized biomimetic strategies is inspired by the accumulating examples of natural product synthesis that embody similar thoughts, including those contributed by our group (Figures S1–S3). For instance, we took advantage of an altered substrate to rescue the biomimetic synthesis of sespenine. The initial attempts to mimic the biosynthetic process were hampered by the lability of the biogenetic 3-hydroxyindolenine intermediate. A C2 substituent significantly enhanced the stability of the indolenine intermediate, thus enabling a scalable biomimetic cascade reaction directed toward the synthesis of this unusual indole sesquiterpenoid (Figure S1)[11]. Our synthesis of arcutine, a complex diterpenoid alkaloid, showcased the utility of an altered reaction in biomimetic synthesis. Imitating the biosynthetic position-selective C−H oxidation to generate a tertiary carbocation species would be a formidable challenge to chemists. Instead, we exploited Prins cyclization as a controllable means for carbocation formation, which secured the biomimetic rearrangement leading to the arcutine core (Figure S2)[12]. Our success with the "biomimetic" synthesis of 14-hydroxyaflavinine, a sterically congested indole diterpenoid, benefited from an altered pathway. In this case, the oxidative etherification in the biosynthesis of epoxyeujindole A (a congener of 14-hydroxyaflavinine) inspired a reductive ether cleavage strategy (Figure S3)[13].

On the basis of the above thoughts and experience, we initiated a research program to examine and improve the applicability of generalized biomimetic strategies to the synthesis of multiple natural product families known for greater challenges. *Daphniphyllum* alkaloids are a large class of

nortriterpenoid alkaloids with diverse and intricate structures[14,15]. They have been attractive targets for chemical synthesis for decades[16,17]; however, due to the formidable synthetic difficulty, only two dozen out of more than 300 members have been conquered so far (Figure S4). This alkaloid family has held a special position in the history of biomimetic synthesis. Guided by their insight into the biosynthesis of the daphniphylline subfamily, Heathcock and co-workers developed an elegant polycyclization cascade to convert a simple squalene derivative into *proto*-daphniphylline, the putative biogenetic ancestor of the entire family[18]. This work was not only a breakthrough in the campaign of *Daphniphyllum* alkaloid synthesis but also a landmark in the evolution of the biomimetic synthesis of natural products. However, due to the structural diversity of this large family comprising dozens of subfamilies, it is impractical to reach most other subfamilies simply by upgrading Heathcock's initial biomimetic route[19–24]. Recently, we also accomplished the syntheses of hybridaphniphylline B[25] and daphenylline[26] through bioinspired cycloaddition and rearrangement strategies, respectively, as a result of our continuous effort toward the synthesis of the calyciphylline A subfamily members[27–29]. Following our experience with the *Daphniphyllum* alkaloids, we recognized the key structural linkages and, more importantly, the underlying biosynthetic network of the macrodaphniphyllamine, calyciphylline A, daphnilongeranin A, and daphnicyclidin D subfamilies[14]. Herein, we report our endeavor to reprogram this biosynthetic network into a chemically synthetic network through substrate-, reaction-, and pathway-altering biomimetic strategies, which leads to the first synthesis of fourteen *Daphniphyllum* alkaloids from the four subfamilies.

RESULTS AND DISCUSSION

An envisioned chemically synthetic network of selected *Daphniphyllum* alkaloids

We undertook a systematic analysis of the biogenesis of selected *Daphniphyllum* alkaloids (**1**–**14**, Figures 1A–1D) from the macrodaphniphyllamine, calyciphylline A, daphnilongeranin A, and daphnicyclidin D subfamilies[30–40], on the basis of their structural relationships and biosynthetic hypotheses. The biosynthetic network of these alkaloids is outlined in Figure 1E. Macrodaphniphyllamine[30] (**1**) is considered to be the entry point of this network, connecting to a variety

of *Daphniphyllum* alkaloids through two routes (Figure 1E, highlighted in blue and red)[34,35,37,39,41]. On the basis of this network, we conceived a chemically synthetic network (Figure 1F). Calyciphylline A[34] (**6**), in place of **1**, is set as the entry point of the latter network, which would offer two advantages to our synthesis of these alkaloids. First, **6** is arguably the most flexible intermediate from a divergent perspective; manipulation of C4−N and C1−C8 bonds of **6** or its analogue (**6′**) may provide expeditious access to the macrodaphniphyllamine and daphnicyclidin D subfamilies. Second, our experience with the calyciphylline A-type alkaloids[25–29] could render various intermediates available for substrate-altering biomimetic synthesis. Having defined the role of **6** in the synthetic network, we further devised three routes starting from **6** (or **6′**) (Figure 1F, highlighted in blue, green, and red) for the synthesis of the macrodaphniphyllamine-type, the daphnilongeranin A-type, and the daphnicyclidin D-type alkaloids, respectively, taking advantage of a series of substrate-, reaction-, and pathway-altering biomimetic strategies (*vide infra*).

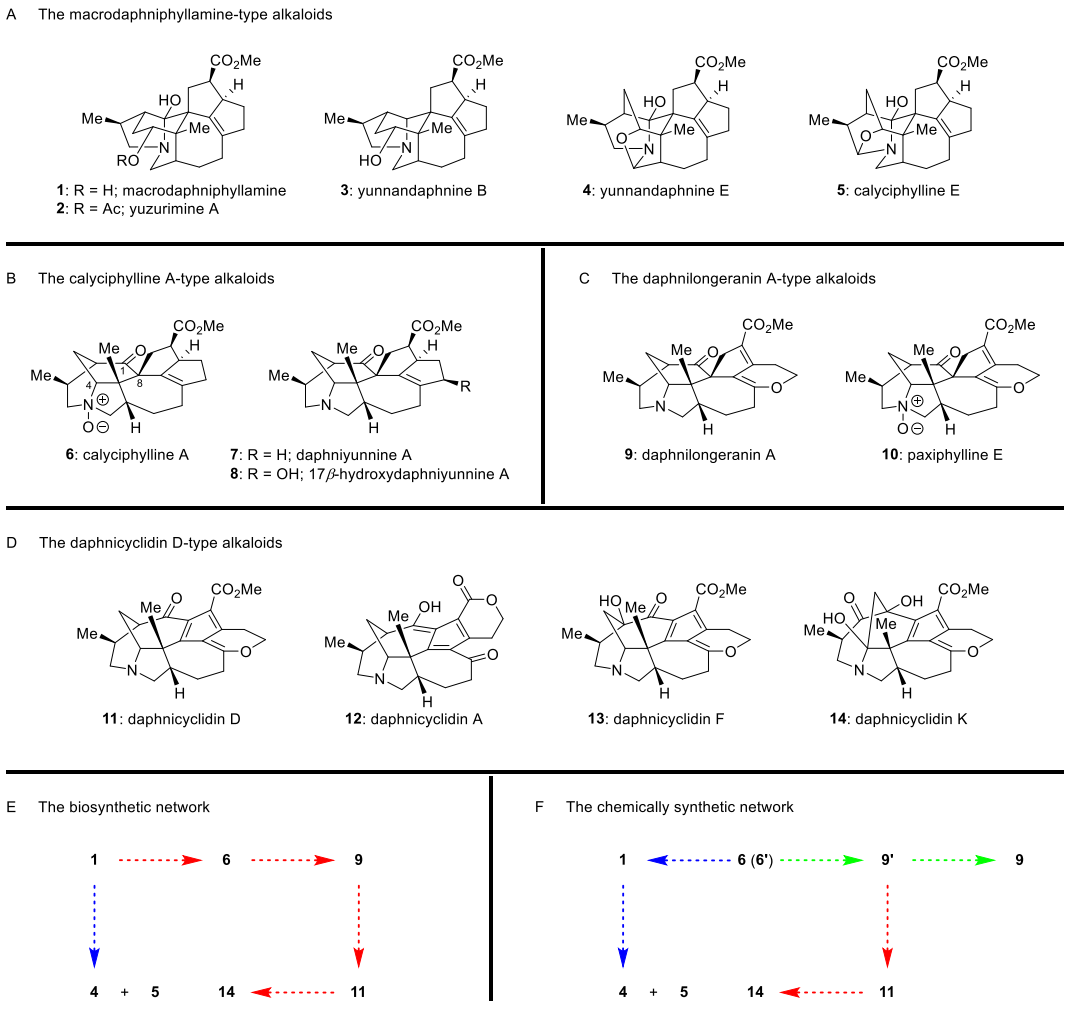

Figure 1. The networks of selected *Daphniphyllum* alkaloids from four subfamilies. (A) Representative members of the macrodaphniphyllamine subfamily. (B) Representative members of the calyciphylline A subfamily. (C) Representative members of the daphnilongeranin A subfamily. (D) Representative members of the daphnicyclidin D subfamily. (E) The postulated biosynthetic network of selected alkaloids from the four subfamilies. (F) The envisioned chemically synthetic network of selected alkaloids from the four subfamilies.

Synthesis of the macrodaphniphyllamine-type alkaloids through a pathway-altering biomimetic strategy.

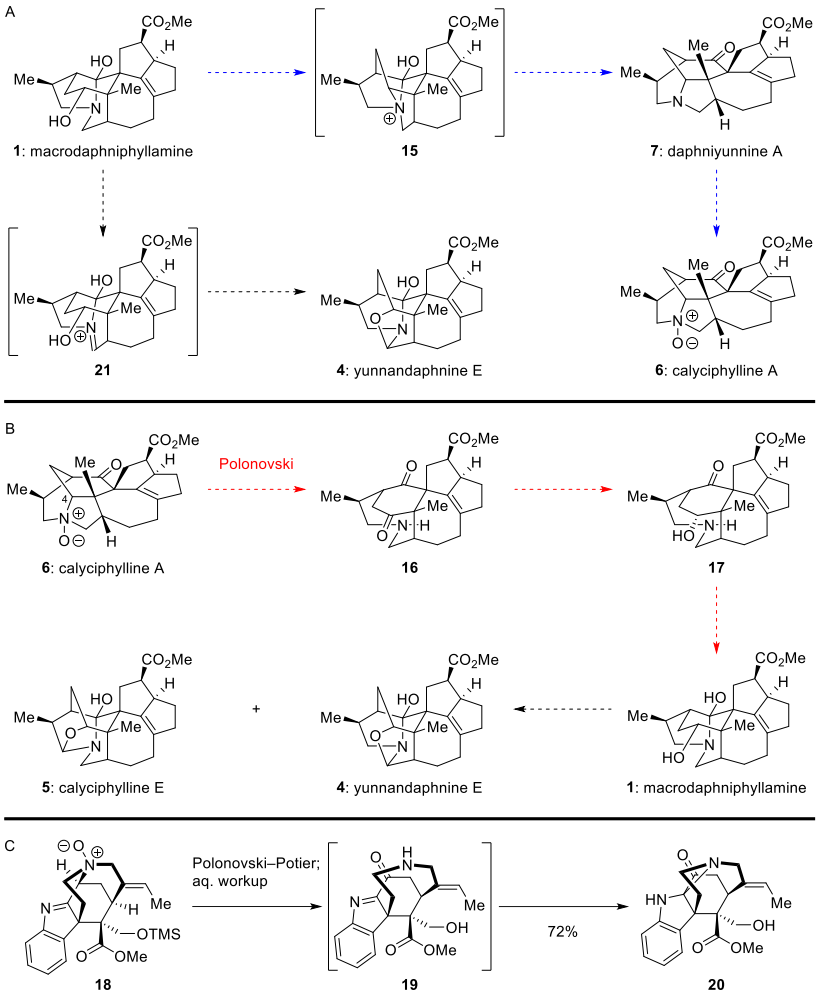

Figure 2. A pathway-altering biomimetic strategy toward the synthesis of macrodaphniphyllamine-type alkaloids. (A) The biosynthetic relationship between the macrodaphniphyllamine subfamily and the calyciphylline A subfamily. (B) An envisioned pathway-altering biomimetic approach to the synthesis of macrodaphniphyllamine-type alkaloids. (C) An inspiring example of C–N bond cleavage in our synthesis of indole alkaloid echitamine.

The strategic consideration for chemical synthesis of the macrodaphniphyllamine-type alkaloids is illustrated in Figure 2. A pathway-altering biomimetic strategy (or more specifically, a reverse biomimetic strategy), was expected to play a central role in the synthesis. In contrast to the hypothetical

biosynthetic pathway from **1** to **6** (**1** → **15** → **7** → **6**, Figure 2A) featuring intramolecular amination[34,35,41], a reverse sequence (**6** → **16** → **17** → **1**, Figure 2B) was designed for the chemical synthesis, which involves cleavage of the C4−N bond of **6** followed by chemoselective ketone reduction and hemiaminal formation. The key C4−N bond cleavage could be achieved through a Polonovski reaction[42] inspired by the initial step of a cascade sequence (**18** → **19** → **20**, Figure 2C) in our synthesis of indole alkaloid echitamine[43]. In view of the biosynthetic pathway from **1** to yunnandaphnine E (**4**) via an iminium ion species (**21**, Figure 2A), we anticipated that a second Polonovski reaction would convert **1** into **4** and calyciphylline E (**5**) (Figure 2B).

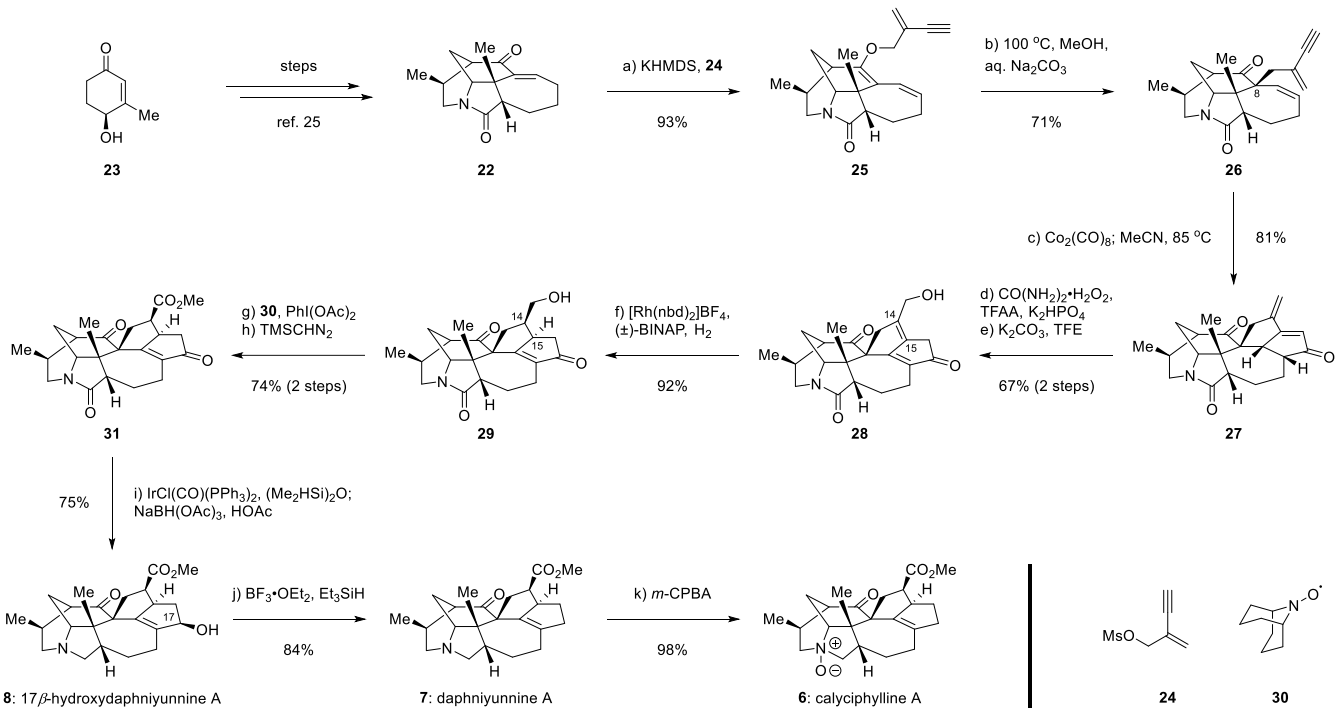

Figure 3. Synthesis of the calyciphylline A-type alkaloids.

Following the above consideration, we prepared **6** as the starting point of the route to the macrodaphniphyllamine subfamily (Figure 3). The hexacyclic skeleton of **6** was constructed through a Claisen/Pauson−Khand approach. Tetracyclic compound **22** arising from readily available *α*,*β*-unsaturated enone **23** is a signature intermediate used in our previous syntheses of *Daphniphyllum* alkaloids[25]. Deprotonation of **22** with KHMDS and *O*-allylation of the resultant enolate with mesylate **24** afforded dienol ether **25** in 93% yield, which served as a substrate for the Claisen rearrangement. Taking advantage of a protocol (aq. Na_2CO_3/MeOH, 100 °C) modified from that developed for our

synthesis of hybridaphniphylline B[25], we obtained ketone **26** as a single C8 diastereoisomer in 71% yield; undesired Cope rearrangement of **26** was largely suppressed under these conditions. This functionalized 1,6-enyne underwent an intramolecular Pauson−Khand reaction [$Co_2(CO)_8$; MeCN, 85 °C] to form conjugated dienone **27** as the predominant stereoisomer in 81% yield. Having assembled its hexacyclic framework, we continued to elaborate the bicyclo[3.3.0]octenone motif of **6**. Epoxidation of the exocyclic C═C bond of **27** with TFPAA generated in situ[44] followed by a base-promoted double bond migration−*δ*-alkoxy elimination cascade delivered hydroxy dienone **28** in 67% overall yield. A position- and face-selective hydrogenation reaction was required to establish the vicinal C14 and C15 tertiary centers from the fully substituted diene substrate. A survey of catalysts revealed that the combination of $[Rh(nbd)_2]BF_4$ and (±)-BINAP was optimal for this demanding transformation, giving compound **29** in 92% yield as a single detectable stereoisomer. Oxidation of this primary alcohol with ABNO (**30**) and $PhI(OAc)_2$ provided the corresponding carboxylic acid[45], methylation of which with $TMSCHN_2$ in MeOH furnished ester **31** in 74% overall yield. Under the modified Nagashima conditions [$IrCl(CO)(PPh_3)_2$, $(Me_2SiH)_2O$][26,46], the lactam within **31** was converted into the corresponding enamine, and the cyclopentenone underwent 1,2-reduction from the convex face. Enamine reduction with $NaBH(OAc)_3$ in the presence of HOAc[26] afforded 17*β*-hydroxydaphniyunnine[36] (**8**) smoothly. Deoxygenation of this allylic alcohol (Et_3SiH, $BF_3{\cdot}OEt_2$) gave daphniyunnine A[35] (**7**) in 84% yield, oxidation of which with *m*-CPBA rendered **6**[34] in 98% yield. The structures of **26**–**29**, **31**, the 4-bromobenzoate derivative of **8**, and **7** were all confirmed by X-ray crystallographic analysis (Figure S5).

With **6** in hand, we developed a reverse biomimetic route to **1** (Figure 4). Selective cleavage of the C4−N bond of **6** is a key issue for this route. Under the Polonovski conditions [Ac_2O, 2,6-di-*tert*-butylpyridine (**32**)][42,43], an inseparable mixture of hemiaminals **33** and **34** (ca. 1.5:1) was obtained in 63% yield; the latter presumably arose from the former via diketone intermediate **16**. Of note, undesired 6,7-dehydrodaphniyunnine was isolated as a minor product, which is fortunately amenable to recycling through enamine reduction (*vide supra*) and *N*-oxidation. The next challenge is to drive the equilibrium between **33** and **34** in the direction of the latter, which contains the characteristic hexacyclic scaffold of the macrodaphniphyllamine subfamily. Chemoselective reduction of the C4 carbonyl of **34** in the

presence of the hemiaminal and ketone within **33** was expected to fulfill this requirement. A survey of reductants revealed that the SmI_2−water reagent system[47,48] was optimal; the mixture was converted into **1**[30,32] in 86% yield. This alkaloid then served as a common intermediate for collective synthesis of other members in the same subfamily. Selective acetylation of its C4 hydroxyl (Ac_2O, Et_3N, 4-DMAP) afforded yuzurimine A[31] (**2**) in 96% yield. Reduction of the hemiaminal within **1** ($NaBH_3CN$, HOAc) provided yunnandaphnine B[32] (**3**) in 97% yield. Furthermore, we exploited a dehydrogenation reaction mechanistically similar to the Polonovski reaction to prepare **4** and **5** from **1** in one pot. Treatment of **1** with I_2 and K_2CO_3 presumably generated quaternary ammonium intermediate **35**, which underwent divergent HI elimination−hydroxyl attack sequences to give **4**[32] in 72% yield and **5**[33] in 19% yield, via iminium ion species **21** and **36**, respectively[49]. The structures of **1**–**5** were confirmed by X-ray crystallographic analysis (Figure S5).

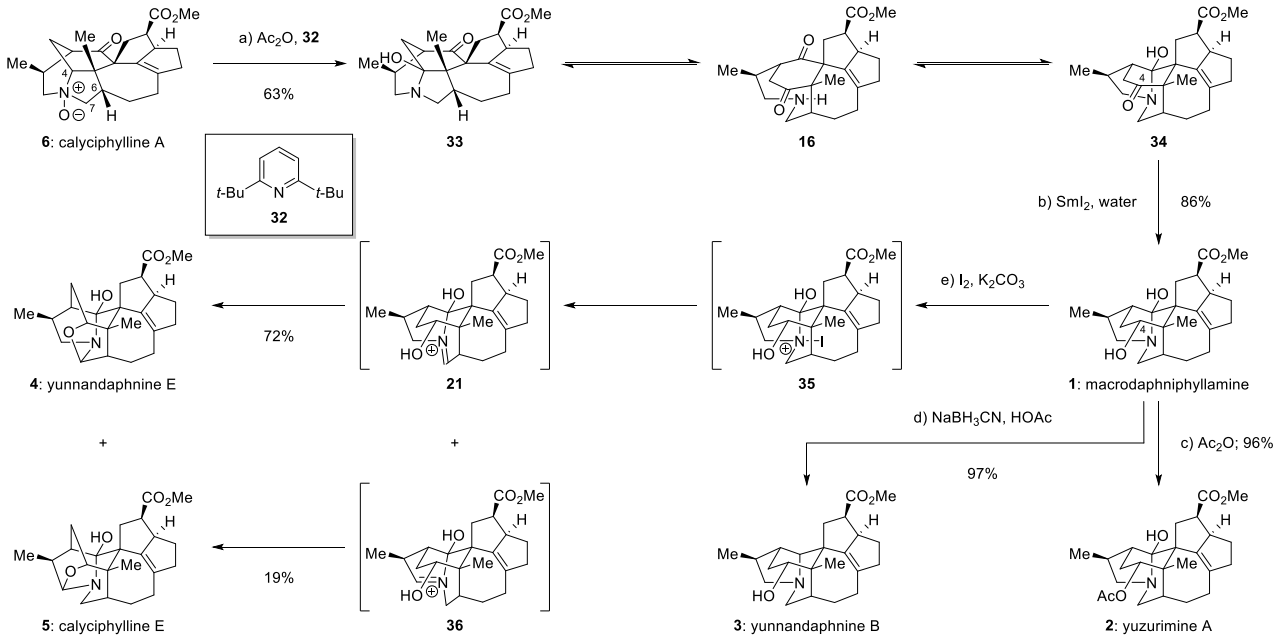

Figure 4. Synthesis of the macrodaphniphyllamine-type alkaloids.

Synthesis of the daphnilongeranin A-type and daphnicyclidin D-type alkaloids through substrate- and reaction-altering biomimetic strategies.

The road map for chemical synthesis of the daphnilongeranin A-type and daphnicyclidin D-type alkaloids is elaborated in Figure 5. The envisioned routes take full advantage of a substrate-altering biomimetic strategy. Daphnilongeranin A (**9**) holds a key position in the biosynthetic pathway

connecting the calyciphylline A and daphnicyclidin D subfamilies (Figure 5A); however, this molecule itself is not an ideal intermediate from a synthetic perspective. On one hand, the biogenesis of **9** from daphniyunnine A (**7**) (**7** → **9**, Figure 5A) involves mechanistically puzzling oxygen atom insertion into the C10−C17 bond[37], which is difficult for us to imitate. On the other hand, the biosynthetic pathway from **9** to daphnicyclidin D (**11**) (**9** → **11**, Figure 5A) features an intriguing process of C1−C8 bond cleavage and C1−C13 bond formation, presumably with the intermediacy of a cyclopropanol species (such as **37**), which originates in an insightful cyclization−fragmentation hypothesis proposed by Yue and co-workers[41]. However, a suitable reaction mode based on this hypothesis has yet to be established in practice. Therefore, we elaborately designed compound **9′** (Figure 5B), which is structurally altered from **9**, as a common intermediate for construction of the daphnilongeranin A-type and daphnicyclidin D-type alkaloids. This intermediate may arise from **6′**, a pentacyclic analogue of **6**, which could be prepared by using a [3 + 2] cycloaddition approach based on our experience with the calyciphylline A-type alkaloids[26,29]. The synthetic versatility of **9′** would ensure the feasibility of the routes to the two subfamilies (Figure 5B, highlighted in blue and red). On one hand, reductive methoxycarbonylation of **9′** followed by elimination of MeOH should deliver **9** expeditiously. On the other hand, under suitable conditions, **9′** could undergo an aldol cyclization/retro-aldol fragmentation cascade to form compound **38** possessing the characteristic hexacyclic core of the daphnicyclidin D-type alkaloids, via intermediates **39** and **40**. A sequence of MeOH elimination and enolization would lead to compound **41** and thus pave the way for preparation of **11** and daphnicyclidin F (**13**). In view of the corresponding biosynthetic pathway (Figure 5A)[40], we anticipated further converting **13** into daphnicyclidin K (**14**) through α-ketol rearrangement[50] followed by C4 hydroxylation (Figure 5B).

The particular transformation of the 5,6-spirocyclic ring system of **9** into the 5,7-fused bicyclic ring system of **11** is based on the reaction-altering biomimetic strategy depicted in Figure 5B. This strategy is inspired by the clues to the cleavage and formation of key C−C bonds implied by the biogenesis[41] (Figure 5A) coupled with our experience with the daphenylline synthesis[26] (Figure 5C). The cyclopropanation proposal (**9′** → **39**, Figure 5B) is supported by a similar vinylogous aldol reaction (**42** → **43**, Figure 5C) in a cascade sequence leading to daphenylline precursor **44**[26]. From a chemical point

of view, this reaction is considerably more feasible than its biosynthetic counterpart. Of note, the driving force for the cleavage of the C1−C8 bond of **39** may arise from the relief of the cyclopropane ring strain and the stabilization of the resultant negative charge by the *α*,*β*-unsaturated enone (Figure 5B); the latter offers a significant advantage lacking in the biosynthetic reaction.

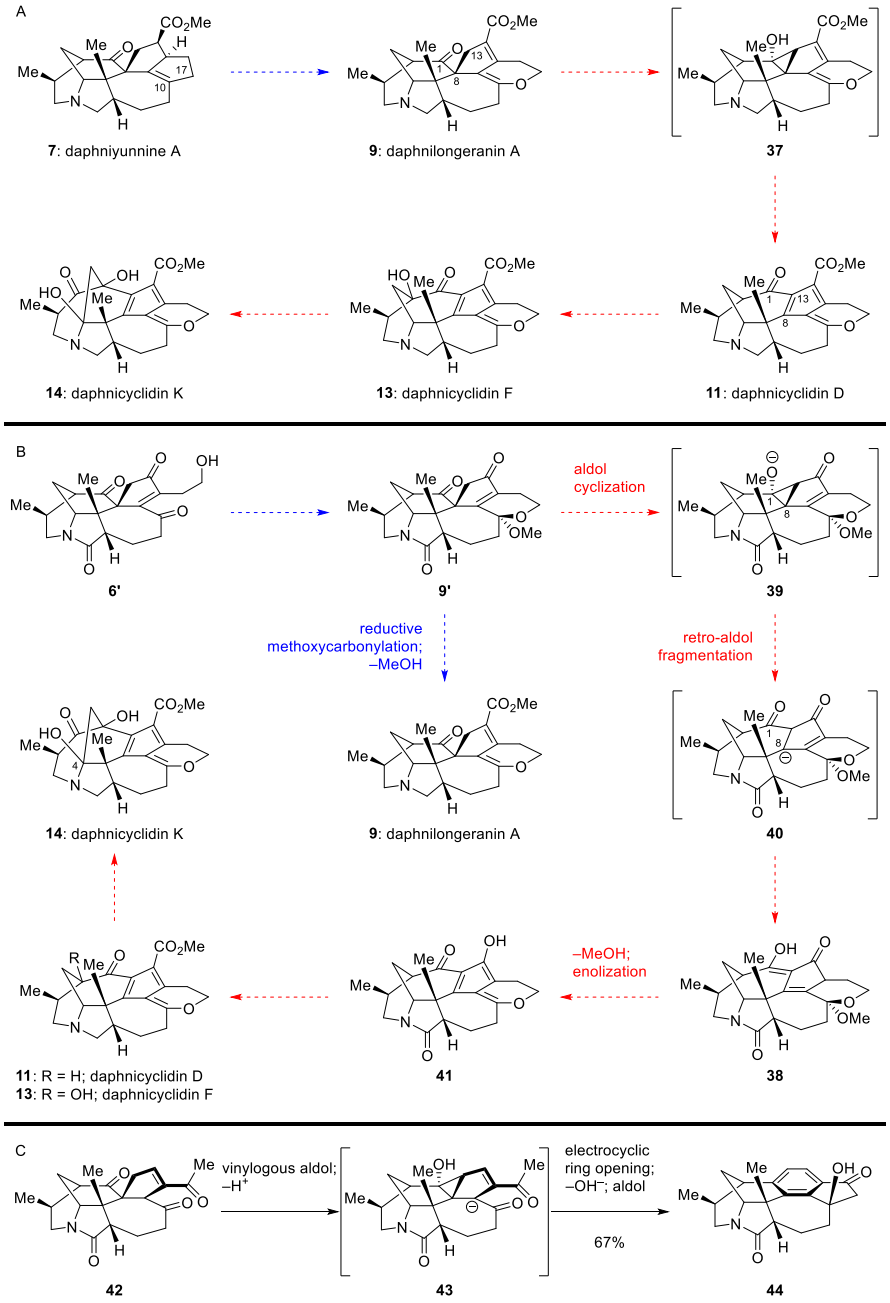

Figure 5. Substrate- and reaction-altering biomimetic strategies toward the synthesis of the daphnilongeranin A-type and daphnicyclidin D-type alkaloids. (A) The biosynthetic relationships among the calyciphylline A subfamily, the daphnilongeranin A subfamily, and the daphnicyclidin D subfamily. (B) Envisioned substrate- and reaction-altering biomimetic approaches to the synthesis of daphnilongeranin A-type and daphnicyclidin D-type alkaloids. (C) An inspiring example of cyclopropanation−fragmentation in our synthesis of *Daphniphyllum* alkaloid daphenylline.

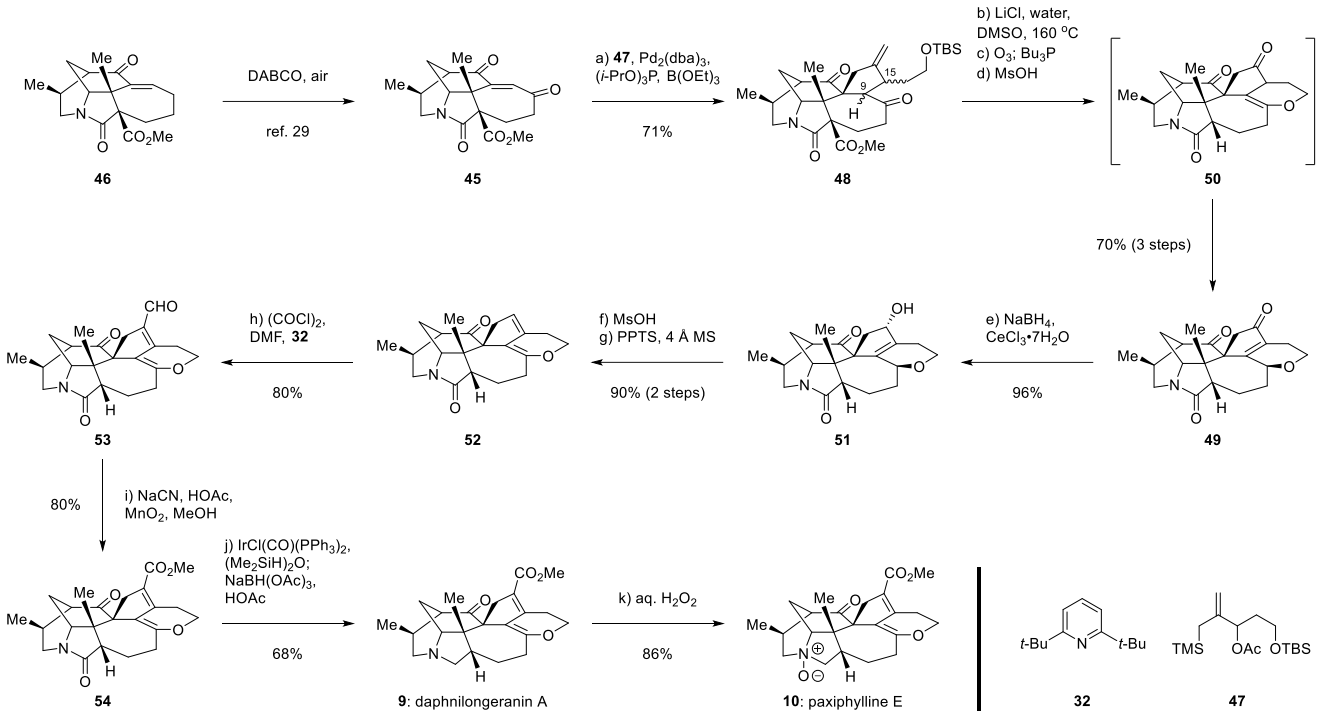

Figure 6. Synthesis of the daphnilongeranin A-type alkaloids.

With these thoughts in mind, we first prepared a **9′**-type intermediate, which enables rapid access to the daphnilongeranin A subfamily (Figure 6). Trimethylenemethane (TMM) [3 + 2] cycloaddition[51] was responsible for assembling the densely substituted five-membered carbocycle of this type of intermediate. Enedione **45** is readily available from enone **46** (an analogue of **22**) through γ-oxidation[29]. Under the modified Trost conditions[52] [$Pd_2(dba)_3$, (i-PrO)$_3$P, B(OEt)$_3$], **45** and TMM precursor **47** were converted into a mixture of C9 and C15 stereoisomers[53] (**48**) in 71% combined yield. The mixture underwent a sequence of Krapcho demethoxycarbonylation[25–29] (LiCl, water, DMSO, 160 °C), ozonolysis, and desilylative cyclization (MsOH). Interestingly, the anticipated hemiketal was not observed, whereas α,β-unsaturated enone **49** was obtained with good overall efficiency, presumably through in situ dehydration−double bond migration involving an enol ether intermediate (**50**). We recognized that **49** could replace **9′** as a suitable common intermediate for divergent synthesis of members of the two subfamilies. Accordingly, a concise approach to the synthesis of the daphnilongeranin A-type alkaloids was developed. Luche reduction of **49** afforded allylic alcohol **51** as a single diastereoisomer in 96% yield. Exposure of **51** to MsOH furnished a mixture of diene **52** and a δ-hydroxyketone resulting from the hydrolysis of **52**, treatment of which with PPTS and 4 Å molecular

sieves gave **52** alone in 90% overall yield. Under the Vilsmeier−Haack conditions[54] [DMF, $(COCl)_2$, **32**], this electron-rich diene was converted into aldehyde **53** in 80% yield, which underwent Corey oxidative esterification[55] (NaCN, HOAc, MnO_2, MeOH) to form compound **54** with good efficiency. This lactam was subjected to Nagashima amide reduction [$IrCl(CO)(PPh_3)_2$, $(Me_2SiH)_2O$] followed by enamine reduction [$NaBH(OAc)_3$, HOAc][26], and **9**[37] was obtained in 68% overall yield. Oxidation of this tertiary amine with aq. H_2O_2 provided paxiphylline E[38] (**10**) in 86% yield. The structures of the *N*-(4-bromophenyl)carbamate derivative of **51** and **54** were confirmed by X-ray crystallographic analysis (Figure S5).

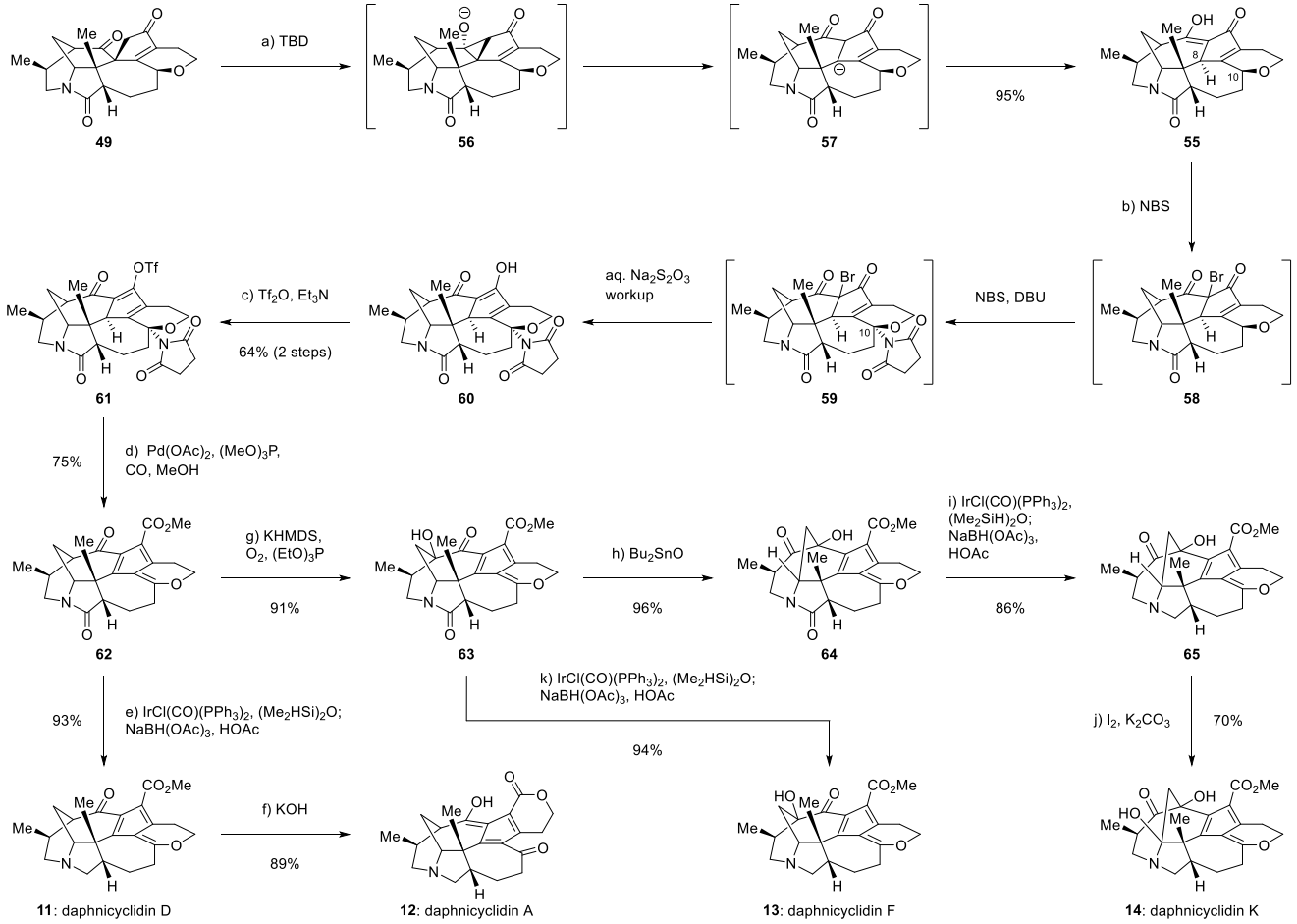

Figure 7. Synthesis of the daphnicyclidin D-type alkaloids.

Taking advantage of the synthetic versatility of **49**, we established an expeditious route to **11** (Figure 7). The devised aldol cyclization/retro-aldol fragmentation cascade calls for a suitable promoter for the first cyclopropanation step. On the basis of our experience with the tandem reaction in the daphenylline synthesis[26], TBD was found to be an effective reagent to initiate the cascade sequence

presumably by facilitating the intramolecular aldol reaction of **49**. Compound **55** bearing the desired 5,7-fused bicyclic ring system was obtained as a single C8 diastereoisomer in 95% yield, possibly via intermediates **56** and **57**. The next challenge is to forge the fulvene domain of **11**. *γ*-Bromination of the *α*,*β*-unsaturated enone within **55** followed by elimination of HBr, which is derived from our original proposal (**38** → **41**, Figure 5B), would provide a straightforward solution to this problem. However, the enol within the same compound turned out to be more reactive under the bromination conditions; exposure of **55** to NBS gave mainly bromide **58**. Interestingly, this intermediate can be efficiently converted back to its precursor by workup with aq. $Na_2S_2O_3$. This observation suggests an opportunity for formally position-selective oxidative modification at C10. Upon in situ treatment with DBU and an excess of NBS, **58** underwent a sequence of C10 bromination and imide anion-based substitution to generate intermediate **59**. As expected, aq. $Na_2S_2O_3$ workup furnished enol **60**, triflation of which afforded compound **61** in 64% overall yield from **55**. Methoxycarbonylation of **61** proceeded smoothly under the modified Shair conditions[56] [$Pd(OAc)_2$, $(MeO)_3P$, CO (1300 psi), Et_3N, MeOH/DMSO], and elimination of succinimide occurred spontaneously in the weakly basic environment, presumably due to the enhanced acidity of the cyclopentadiene moiety. Thus, methyl ester **62** was directly isolated in 75% yield. One-pot lactam reduction (*vide supra*) delivered **11**[39] in 93% yield. The polarized nature of its fulvene domain containing two electron-withdrawing groups inspired us to develop a conjugate addition−lactol ring opening−lactonization sequence mediated by KOH, which led to daphnicyclidin A[39] (**12**) in 89% yield in one pot.

Finally, we prepared daphnicyclidin K (**14**), which possesses a bridged ring system different from that of **11**, through biomimetic *α*-ketol rearrangement (Figure 7). Ketone **62**, the immediate precursor of **11**, was subjected to *α*-hydroxylation[57] [KHMDS, O_2, $(EtO)_3P$] to give compound **63** in 91% yield. A variety of acidic, basic, and thermal conditions were examined for the *α*-ketol rearrangement reaction. To our delight, treatment of **63** with a catalytic amount of Bu_2SnO[58] at 80 °C afforded the desired product (**64**) in 96% yield. Both the hydroxyl and the carbonyl groups of **63** were presumably activated through the intermediacy of a chelated Sn(IV) species. Lactam reduction furnished "*proto*-daphnicyclidin K" (**65**) smoothly, which might be a naturally occurring alkaloid yet to be discovered.

Exposure of this tertiary amine to I_2 and K_2CO_3 provided **14**[40] in 70% yield. Of note, daphnicyclidin F[39] (**13**) was also obtained efficiently from **63** through lactam reduction. The structures of **55**, **61**, **64**, **65**, **11**, and **14** were confirmed by X-ray crystallographic analysis (Figure S5).

CONCLUSION

We systematically analyzed the biosynthetic network of the macrodaphniphyllamine-type, calyciphylline A-type, daphnilongeranin A-type, and daphnicyclidin D-type *Daphniphyllum* alkaloids and extracted the key bond formation/cleavage information from the network. Substrate-, reaction-, and pathway-altering biomimetic strategies were then developed, which escaped the restriction of the conventional "highly imitative" principle and focused simply on the C4−N and C1−C8 bonds of calyciphylline A (**6**). Taking advantage of this generalized biomimetic approach, we reprogrammed the biosynthetic network into a powerful chemically synthetic network, thereby achieving the syntheses of fourteen complex *Daphniphyllum* alkaloids for the first time.

From a broad perspective, the generalized biomimetic approach is expected to improve the applicability of biomimetic synthesis and thus enhance its power toward complex natural products. Chemical synthesis networking through this approach may accelerate exploration of the chemical space occupied by natural product-like molecules. More importantly, the integration of generalized biomimetic strategies with emerging synthetic tools could build new momentum for research in natural product synthesis. On one hand, this synthetic analysis mode might facilitate the development of computer-assisted synthesis planning. Key bond formation/cleavage information could be extracted by machine learning, in a manner similar in principle to that showcased in this work. Embedding this information in the retrosynthetic logic may enable synthesis planning algorithms to effectively tackle the challenges in the synthesis of complex natural products, such as ring system construction and stereochemical control. On the other hand, transition metal-catalyzed and enzyme engineering-based reactions would empower the generalized biomimetic strategies with a comprehensive "non-natural" toolbox, and conversely, this type of strategies may further stimulate the development of useful methods,

for instance, the direct C−N bond and C−C bond activation that could streamline the syntheses described herein.

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