



Communication

Asymmetric synthesis of ABC tricyclic systems in *Daphniphyllum* alkaloidHuijing Wang^{a,c}, Qiuyan Dong^b, Qinxia Xie^b, Pei Tang^{a,*}^a Key Laboratory of Drug-Targeting and Drug Delivery System of the Education Ministry, Sichuan Engineering Laboratory for Plant-Sourced Drug and Sichuan Research Center for Drug Precision Industrial Technology, West China School of Pharmacy, Sichuan University, Chengdu 610041, China^b Chongqing Key Laboratory of Natural Product Synthesis and Drug Research, School of Pharmaceutical Sciences, Chongqing University, Chongqing 401331, China^c Skaggs School of Pharmacy and Pharmaceutical Sciences, University of California San Diego, La Jolla 92093-0934, United States

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ABSTRACT

Efficient synthetic routes for the direct and rapid construction of [5-6-6] ABC tricyclic systems of daphmanidin A-type and calyciphylline A-type alkaloids have been successfully developed. For the daphmanidin A-type, the synthesis of [5-6-6] tricyclic framework utilizes a HCl-mediated intramolecular Aldol reaction to construct the bicyclo[2.2.2]octane core and a thermal condensation to afford the ABC ring system. In addition, for the calyciphylline A-type, an improved synthesis of ABC [5-6-6] tricyclic system was developed, featuring an introduction of methyl ester group at C2 before the Pd-catalyzed intramolecular oxidative alkylation to construct the desired bowl-shape tricyclic core with stereochemical control.

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Since the isolation of the first member in 1909, more than 320 *Daphniphyllum* alkaloids with a vast range of structural diversity have been isolated from the genus *Daphniphyllum* that comprises over 34 species of dioecious evergreen trees and shrubs mainly distributed from tropical to subtropical Asia [1–3]. Some of these alkaloids have shown interesting biological activities including anticancer, antioxidation, antiviral, vasorelaxation, nerve growth factor regulation, anti-HIV and anti-platelet activating factor effects [3–5]. Structurally, these triterpenoid alkaloids with highly variable polycyclic skeletons can be categorized into more than 20 different types based on the unusual ring systems [4]. Together, the extensive physiological properties and the intriguing architectural features of these alkaloids have attracted considerable attention from the synthetic chemistry community for decades [3], especially the daphmanidin A-type and the calyciphylline A-type subfamilies. Heathcock *et al.* made the seminal contributions to elegant biomimetic synthesis of several structural types of nature molecules within *Daphniphyllum* family [6]. Whilst further synthetic efforts toward these enchanting alkaloids have been

reported by Carreira [7], Smith [8,9], Li [10–12], Yokoshima/Fukuyama [13], Zhai [14], Paton/Dixon [15], Xu [16] and Gao [17].

The daphmanidin A-type [18–22] and the calyciphylline A-type [1–3,10–15,23–36] *Daphniphyllum* alkaloids, with significantly different ABC tricyclic frameworks, have characteristic structural backbone consisting of six fused rings [5-6-6-7-5-5] and [6-6-5-7-5-5], respectively (Fig. 1). Calyciohylline N (2), an emblematic daphmanidin A-type *Daphniphyllum* alkaloid, was isolated by Kobayashi *et al.* in 2008 [21], including a fused A ring dihydropyrrole and a bicyclo[2.2.2]octane BC ring. It has six contiguous stereocenters, three of which are bridgehead quaternary and two are vicinal quaternary. In addition, macropodumine D (4) and 21-deoxymacropodumine D (5) [37], the unique calyciphylline A-type alkaloids, possess an inimitable [5-6-6-7-5-5] hexacyclic system, containing an exceptional N-C3 linkage and a hydroxyl group at C4, which differ from most members of this type with N-C4 linkage. Along with seven consecutive stereocenters including the vicinal all-carbon quaternary centers, it has led to a surge in synthetic interest recently.

The formidable challenge posed by the structural intricacies presented in the ABC tricyclic systems, especially [5-6-6] tricyclic unit, with limited total synthetic reports, intrigues us to develop a unified strategy that would be applied in the synthesis of related congeners bearing the tricyclic ABC ring systems. Herein, we report

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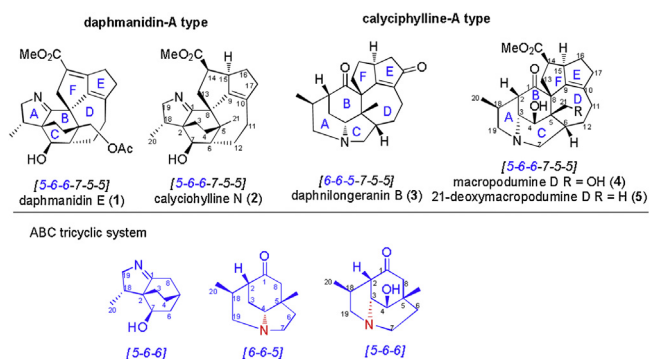


Fig. 1. Typical ABC tricyclic systems of *Daphniphyllum* alkaloids.

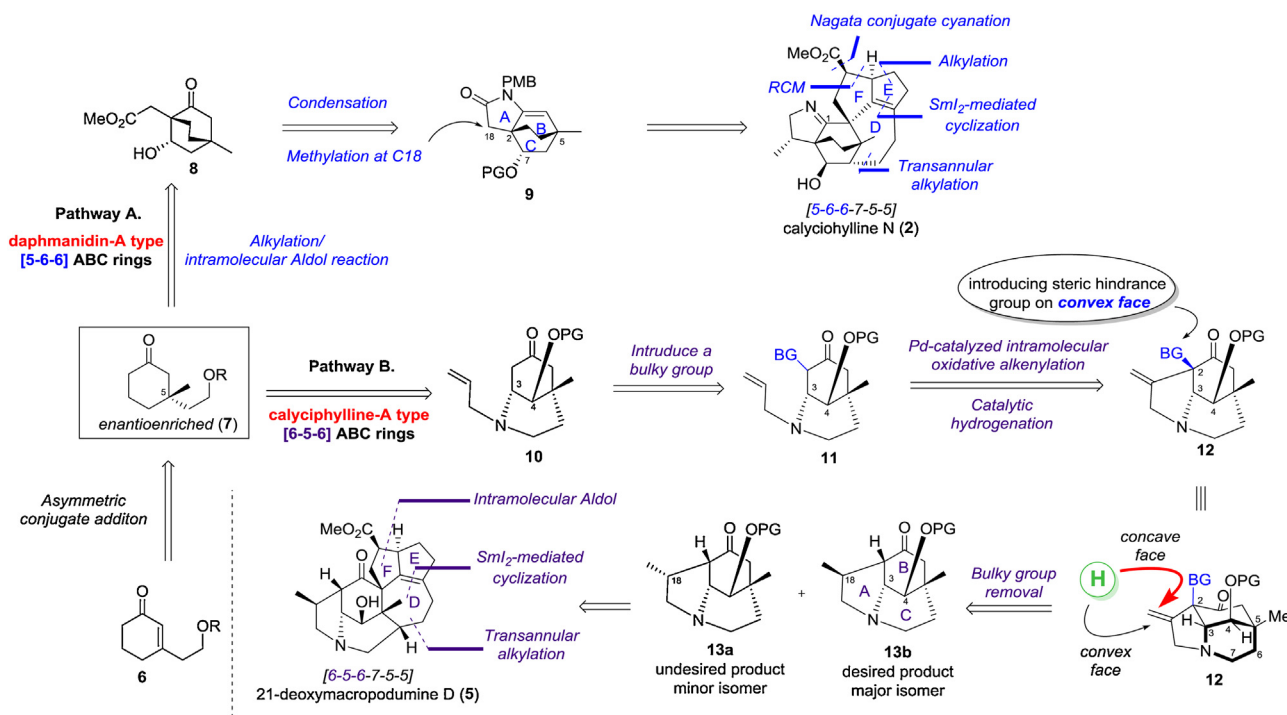
our routes of asymmetric synthesis of ABC tricyclic framework of calyciohylline N (**2**) and 21-deoxymacropodumine D (**5**).

Our synthetic plan is illustrated in Scheme 1, with calyciohylline N (**2**) and 21-deoxymacropodumine D (**5**) as exemplary targets. We designed pathway A and B to construct [5-6-6] tricyclic frameworks from enantioenriched ketone **7** with all-carbon quaternary C5, which could be accessed from readily available enone **6** via an asymmetric conjugate addition [38]. For construction of the bicyclo[2.2.2]octanone B/C core **8**, we conceived that alkylation/intramolecular Aldol tandem reaction of **7** could forge the rudimentary/Critical bridged bicyclic structure with two bridgehead all-carbon quaternary centers (Scheme 1, pathway A). The formation of A ring could be enabled by the condensation of the primary amine with C1 carbonyl group. Furthermore, calyciohylline N (**2**) could be assembled from the key tricyclic [5-6-6] intermediate **9** via sequential reactions that includes methylation at C18, ring closing metathesis (RCM) reaction [39,40], Nagata conjugate cyanation [41–44], Sml₂-mediated cyclization [45] and transannular alkylation.

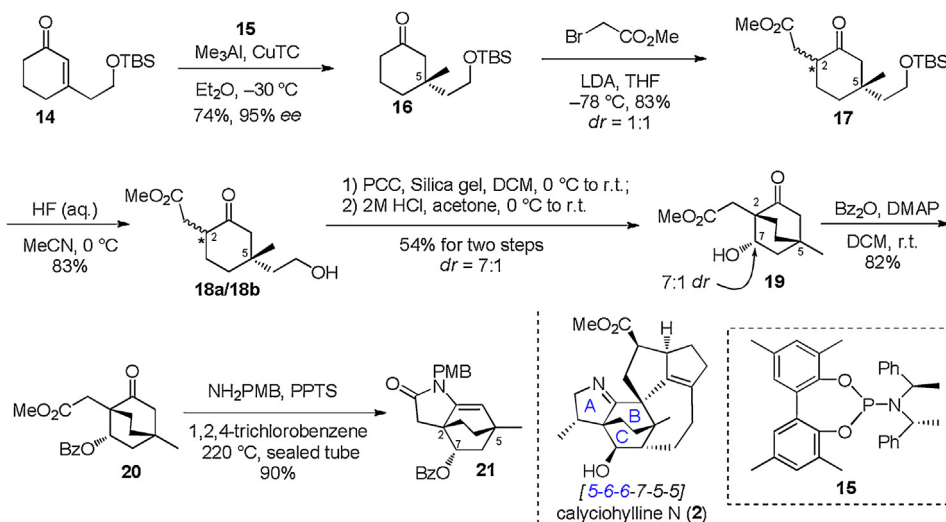
In our initial attempt [36], we obtained the desired key intermediate **13b** with tricyclic [5-6-6] structure in low yield and

unsatisfied stereoselectivity at C18. According to our analysis, the hydrogenation of double bond at C18, occurring dominantly from convex face of the alkene substrate, might lead to the poor stereoselectivity. We anticipated to derive stereochemical control from introducing a sterically bulky and easily removable group at C2 of bicyclic intermediate **10** (Scheme 1, pathway B). Formation of the desired ABC [5-6-6] tricyclic core **13b** would be achieved through Pd-catalyzed intramolecular oxidative alkylation [46–48], catalytic hydrogenation from concave face of the alkene and bulky group removal in sequential. In this event, the steric hindrance of the bulky group on convex face could promote the catalytic hydrogenation occurring from concave face of the tricyclic alkene **12**. Additionally, the DEF rings of 21-deoxymacropodumine D (**5**) could be built via intramolecular Aldol reaction, Sml₂-mediated cyclization and transannular alkylation, which was similar with the strategy of synthesis of calyciohylline N (**2**).

Last year, we synthesized the ABCF tetracyclic framework of *Daphniphyllum* alkaloid calyciohylline N (**2**) by serving the inter/intramolecular aldol sequence and the stereoselective Nagata conjugate cyanation as the key reactions [22]. Here, we plan to use an alternative strategy to assemble the challenge of constructing the bicyclo[2.2.2]octane BC ring with two bridgehead all-carbon quaternary centers. Our synthesis of ABC [5-6-6] tricyclic unit of calyciohylline N (**2**) commenced with the copper-catalyzed asymmetric conjugate addition developed by Vuagnoux-d'Augustin and Alexakis [38], affording an enantioenriched ketone intermediate **16** with C5 all-carbon quaternary center in 74% yield and excellent enantioselectivity up to 95% ee (Scheme 2). Whereafter, the resultant ketone **16** was subjected to alkylation with methyl 2-bromoacetate in the presence of LDA in THF at –78 °C, affording the desired product **17** as a mixture of two diastereoisomers (1:1 ratio) in 83% combined yield. After the deprotection of TBS group, compound **18** was then transformed into the key bicyclo[2.2.2]octanone B/C core **19** by sequential oxidation of resulting alcohol with PCC and acid-mediated intramolecular Aldol reaction in 54% yield for two steps with high stereoselectivity at C7 (7:1 dr). It is worthwhile to mention that this acid-mediated



Scheme 1. An initial strategy for constructing ABC tricycle of calyciohylline N (**2**) and 21-deoxymacropodumine D (**5**). PG = protecting group. BG = bulky group.



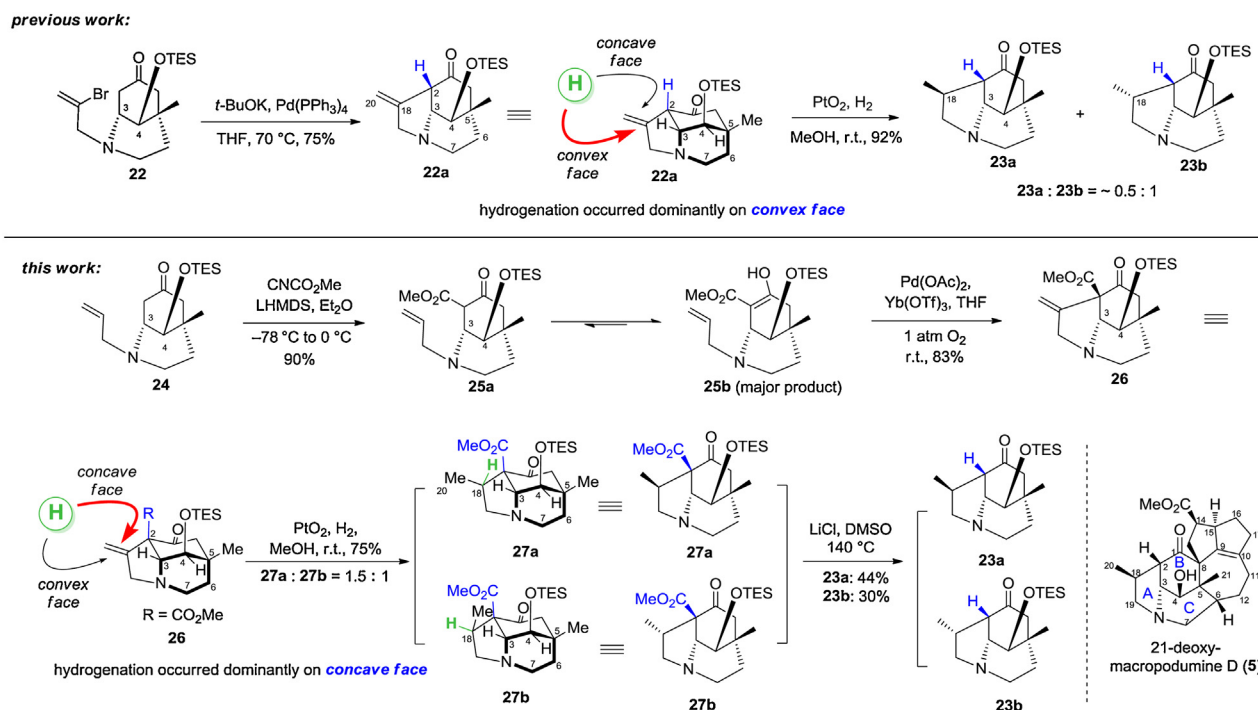
Scheme 2. Preparation of ABC tricyclic [5-6-6] system of calyciohylline N (2).

intramolecular Aldol type cyclization performed with high *endo* selectivity. With the desired bicyclic key intermediate **19** in hand, the late stage was set for the key transformation to construct the critical ABC [5-6-6] tricyclic unit. Protection of the secondary alcohol in **19** followed by thermal condensation delivered the A/B/C tricycle **21** in the presence of PMBNH₂ and PPTS with high yield. Thus, the A/B/C tricyclic framework of calyciphylline N (2), which comprises bicyclo[2.2.2]octanone and three quaternary stereocenters, was synthesized in 7 steps from the known unsaturated ketone **14**.

Then, we turned our attention to investigate the synthesis of ABC tricyclic [5-6-6] unit of 21-deoxymacropodumine D (5). Since the strategy of Pd-catalyzed enolate α -alkylation lead to ABC tricyclic [5-6-6] framework **23a** with unacceptable yield and disappointing approximate 0.5:1 ratio of diastereomers (Scheme 3), we focused on improving the stereoselectivity at

C18 *via* introducing a suitable bulky group at C2 (as previously mention in retro synthetic analysis, Scheme 1, pathway B).

Our optimized synthesis commenced with bicyclic ketone **24**, which we previously utilized for the synthetic studies of 21-deoxymacropodumine D (5) *via* radical cyclization strategy [38]. Regioselective deprotonation of **24** with LiHMDS followed by quenching of the anion with Mander's reagent provided enol **25b** as the major product. To implement the Pd-catalyzed intramolecular oxidative alkylation, enol **25b** was treated with Pd(OAc)₂ and Yb(OTf)₃ in THF under O₂ atmosphere [46–48], generating the C2-C18 ligated compound **26** in 83% yield. Catalytic hydrogenation of the double bond in **26** with PtO₂ in MeOH afforded an inseparable mixture of two diastereoisomers in a 1.5:1 ratio determined by the ¹H NMR spectrum. The relative stereochemistry of **27a** and **27b** was determined by comparing the NMR spectrum of the Krapcho decarboxylation products **23a** and **23b**. The relative



Scheme 3. Improved preparation of ABC tricyclic [5-6-6] system of 21-deoxymacropodumine D (5).

stereochemistry of compounds **23a** and **23b** was determined by the NOE correlations, which indicates that the major isomer is our desired product **23a**. Therefore, the ABC tricyclic unit of 21-deoxymacropodumine D (**5**) with five consecutive stereogenic centers including an all-carbon quaternary center was successfully synthesized, which improves the stereoselectivity at C18 from 0.5:1 to acceptable 1.5:1 ratio of diastereomers.

In summary, we have established an efficient synthetic route of ABC [5-6-6] ring systems, which is a potential useful method in the total synthesis of daphmanidin A-type and calyciphylline A-type alkaloids. The asymmetric synthesis of ABC [5-6-6] tricyclic frame of calyciohylline N (**2**) *via* acid-mediated intramolecular Aldol reaction to construct the desired bicyclo[2.2.2]octane core and a thermal condensation to afford the ABC tricyclic framework was achieved. Meanwhile, the improved synthesis of ABC [5-6-6] tricyclic system of 21-deoxymacropodumine D (**5**) was also achieved. It features a Pd-catalyzed intramolecular oxidative alkylation as the key reaction to construct the desired bowl-shaped tricyclic core and promising stereoselectivity at C18 (1.5:1 ratio of diastereomers) by introducing a steric repulsion on convex face. Inspired by these initial studies, the total synthesis of daphmanidin A-type and calyciphylline A-type alkaloids are undergoing in our lab.

Acknowledgments

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:<https://doi.org/10.1016/j.cclet.2019.08.033>.

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