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Enantioselective Synthesis of ABCF Tetracyclic Framework of *Daphniphyllum* Alkaloid Calyciphylline N

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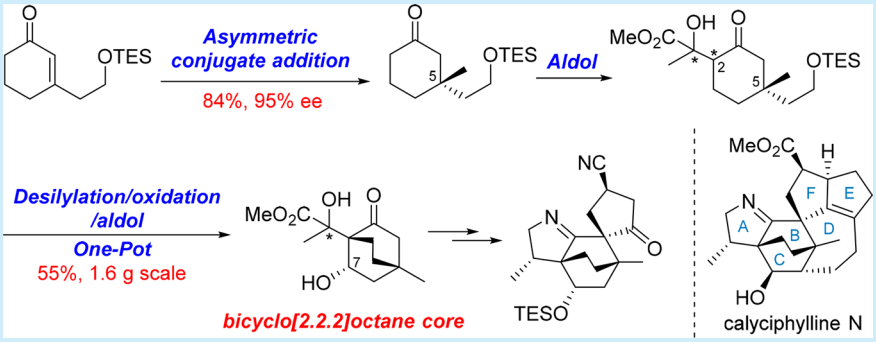
Supporting Information



ABSTRACT: Efforts toward the enantioselective synthesis of *Daphniphyllum* alkaloid calyciphylline N which leads to efficient preparation of the ABCF tetracyclic framework containing three bridgehead all-carbon quaternary stereocenters are described. This synthetic work features the utilization of an asymmetric conjugate addition to install the C5 all-carbon quaternary center, an efficient successive inter/intramolecular aldol sequence to build the critical bicyclo[2.2.2]octanone BC core, and a ring closing metathesis reaction followed by stereoselective Nagata conjugate cyanation to deliver the functionalized F ring.

The *Daphniphyllum* alkaloids are a group of highly complex polycyclic natural products with remarkable structural diversity and are mainly isolated from the genus *Daphniphyllum*.[1] Many members of this family have showed a wide range of biological activities, including anticancer, antioxidation, antiviral, vasorelaxation, nerve growth factor-regulation, anti-HIV, and antiplatelet activating factor effects.[1c,2,3] The architectural features and physiological properties of these alkaloids have attracted considerable attention from synthetic chemists for decades.[1c] In the synthesis campaigns toward these alkaloids, Heathcock and co-workers reported a series of pioneering studies and achieved the synthesis of several structural types of natural molecules within this family.[4] Then, elegant total syntheses of daphmanidin-A type alkaloids (+)-daphmanidin E (**1**)[5] (Figure 1) and (−)-calyciphylline N (**2**)[6] were achieved by Carreira and Smith, respectively. Subsequently, several impressive total syntheses of calyciphylline A-type alkaloids (e.g., **3**−**5**, Figure 1) have been accomplished successively by the groups of Li,[7] Yokoshima/Fukuyama,[8] Zhai,[9] and Paton/Dixon.[10]

The daphmanidin-A type *Daphniphyllum* alkaloids[11] feature a complex scaffold containing a highly fused 5−6−6−7−5−5 hexacyclic core (Figure 1, **1**, **2**), which includes a fused A ring dihydropyrrole and a DEF decahydrocyclopentazulene ring system arranged around a central bicyclo[2.2.2]octane BC core. Among this subfamily, (−)-calyciphylline N (**2**) was isolated in 2008 by Kobayashi and co-workers.[11b] It possesses a total of eight stereocenters, including six contiguous stereocenters, three of which are bridgehead quaternary and two are

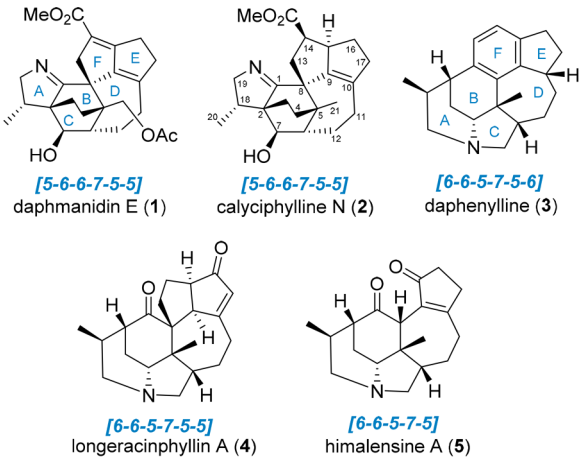


Figure 1. Structures of representative *Daphniphyllum* alkaloids.

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vicinal quaternary. Motivated by its unique structural features and our general interest in *Daphniphyllum* alkaloids, we set out to explore the synthesis of (−)-calyciphylline N (**2**). Herein, we report our endeavors that led to the enantioselective synthesis of the ABCF tetracyclic framework of this alkaloid.

Our retrosynthetic analysis of (−)-calyciphylline N (**2**) is outlined in Figure 2. We planned to assemble the D ring at a

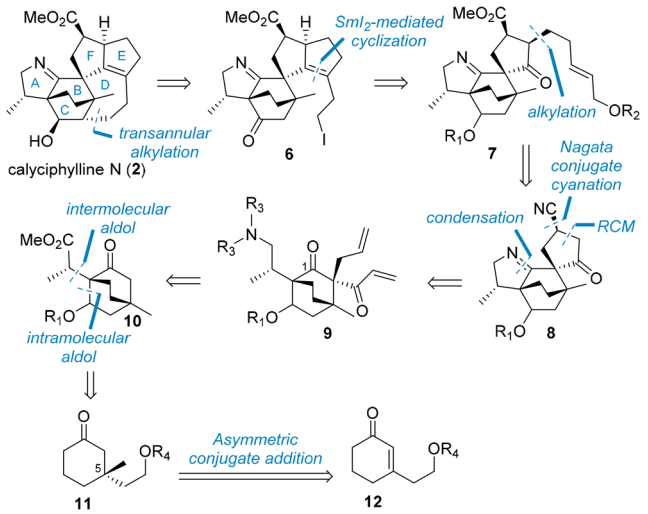


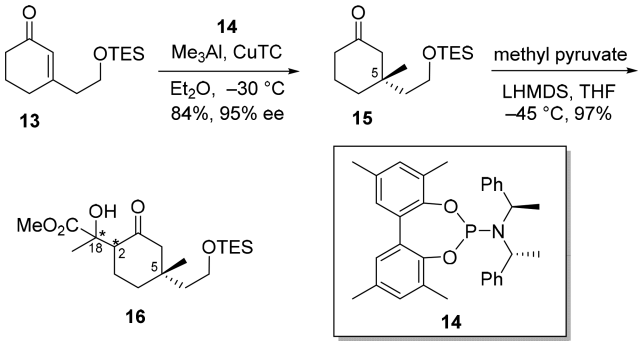
Figure 2. Retrosynthetic analysis of calyciphylline N (**2**).

later stage from primary iodide **6** by transannular alkylation. The E ring in compound **6** would be established via a SmI_2-promoted ketyl-olefin radical cyclization[12] followed by elimination from **7**, which was traced back to a simplified ABCF tetracycle **8**. The key intermediate **8** may arise from diene **9** via a sequence that includes a ring closing metathesis (RCM) reaction,[13] Nagata conjugate cyanation[14] of the resultant cyclopentenone, and condensation of the primary amine with C1 carbonyl group. In continuation of this analysis, diene **9** could be accessed through the spiro-quaternary center formation involving an aldol/oxidation/Tsuji−Trost allylation[15] sequence from bicyclo[2.2.2]octanone BC core **10**. To realize the efficient access to this key bicyclic structure, we conceived a successive inter-/intramolecular aldol[16] sequence of **11** to forge this challenging/critical bridged bicyclic structure with two bridgehead all-carbon quaternary centers. Ketone **11**, in turn, could be accessed from readily available enone **12** via an asymmetric conjugate addition[17] to build the all-carbon quaternary C5.

In our synthetic studies on 21-deoxymacropodumine D,[18] a copper-catalyzed asymmetric conjugate addition, as reported by Alexakis and co-workers,[17] was employed to prepare an enantioenriched ketone intermediate containing the C5 all-carbon quaternary center. In this work, a similar transformation of TES substrate **13** (see Supporting Information) was performed more efficiently to deliver the desired adduct **15** in 84% yield and excellent enantioselectivity up to 95% ee (Scheme 1). Subsequently, the resultant ketone was subjected to an intermolecular aldol reaction using methyl pyruvate[16a] in the presence of LHMDS in THF at −45 °C, thus affording the desired compound **16** as a mixture of four diastereoisomers in 97% combined yield.

With the cyclization precursor ketone **16** in hand, the stage was set for the key transformation to construct the critical bicyclo[2.2.2]octanone BC core. An efficient intramolecular

Scheme 1. Preparation of Cyclization Precursor Ketone 16



Diels−Alder reaction had been employed for the establishment of the bicyclo[2.2.2]octane ring system in (−)-calyciphylline N (**2**) by Smith and co-workers.[6] Here, we planned to use an intramolecular aldol strategy to assemble this challenging bicyclic motif with two bridgehead all-carbon quaternary centers. Trauner's group exploited a HCl-promoted intramolecular aldol addition to assemble bicyclo[2.2.2]octane in maoecrystal V.[16b] This elegant work encouraged us to envision that HCl could be an effective promoter in our aldol-type cyclization. Pleasingly, a desilylation/oxidation sequence using HF and PCC successively on substrate **16** readily afforded an aldehyde intermediate, which was directly subjected to HCl-promoted aldol-type cyclization, thus providing the desired bicycle **17** in 32% isolated overall yield (Table 1, entry 1). Next, we integrated the three steps of desilylation, oxidation, and aldol-type cyclization into a one-pot procedure by adding the reagents successively in a reaction tube with an appropriate interval. First, the combination of HF, PCC, and HCl led to decomposition (entry 2). IBX and HCl were employed for the oxidative removal of the TES ether followed by cyclization, thus providing the trace amount of desired product (entry 3). However, the use of DMP/HCl and PCC/HCl proved to be futile (entries 4 and 5). Subsequently, the combination of *p*-TsOH, PCC, and HCl in DCM provided **17** in 6% isolated overall yield (entry 6); replacing the solvent with a mixture of DCM and acetone could increase the yield (entry 7), and changing the oxidant to DMP could not improve the efficiency (entry 8). In addition, CSA and PPTS proved to be effective desilylation reagents for this one-pot transformation, which could deliver **17** in 16−43% yields (entries 9−11), but the use of H_2SO_4 resulted in a significantly decreased yield (entry 12). Furthermore, we also investigated the base-promoted one-pot procedure. The reaction could deliver **17** in 20% yield under the conditions using PPTS, PCC, and *t*-BuOK (entry 13), but the replacement of base by NaH caused complex mixtures (entry 14). To our delight, the employment of Na_2CO_3 significantly improved the reaction efficiency up to 45% yield (entry 15), and we were pleased to find that replacing PCC with DMP could provide bicycle **17** with a reproducibly good overall yield (55%) on gram scale (entry 16). Notably, this aldol type cyclization exhibited almost unique *endo* selectivity in aforementioned reactions, and product **17** was isolated as a pair of diastereomers at C18 (ca. 1.7:1 dr).

After confirming the robust one-pot procedure to access the pivotal bicycle **17**, we then focused our attention on the elaboration of the methyl group at C18. Selective protection of the secondary alcohol in **17** was performed smoothly by treating **17** with TESCl/imidazole/DMAP. Without purification, the obtained silyl ether was subjected to elimination

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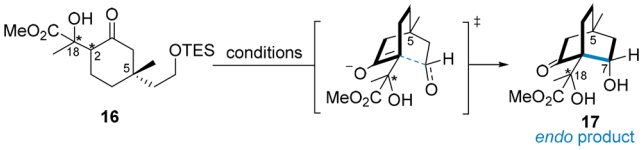
Table 1. Exploration and Optimization Studies for Synthesis of bicyclo[2.2.2]octane BC Core[a]

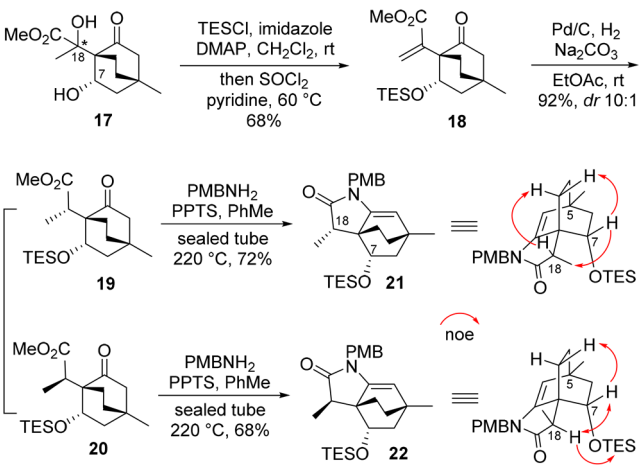


entry	reagents	solvent, t (°C)	result
1[b]	HF/PCC/HCl[c]	MeCN, 0/DCM, 25/ acetone, 50	32%
2[d]	HF, PCC, HCl[c]	DCM, 25	decomposition
3[d]	IBX, HCl[c]	EtOAc, 25→50	trace
4[d]	DMP, HCl[c]	EtOAc, 25→50	0
5[d]	PCC, HCl[c]	EtOAc, 25→50	0
6[d]	p-TsOH, PCC, HCl[c]	DCM, 25→50	6%
7[d]	p-TsOH, PCC, HCl[c]	DCM/acetone, 25→50	18%
8[d]	p-TsOH, DMP, HCl[c]	DCM/acetone, 25→50	14%
9[d]	CSA, PCC, HCl[c]	DCM/acetone, 25→50	16%
10[d]	CSA, DMP, HCl[c]	DCM/acetone, 25→50	36%
11[d]	PPTS, PCC, HCl[c]	DCM/acetone, 25→50	43%
12[d]	PPTS, PCC, H_2SO_4[e]	DCM/acetone, 25	trace
13[d]	PPTS/PCC/ t-BuOK	DCM, 25→70	20%
14[d]	PPTS/PCC/NaH	DCM, 25→70	complex mixtures
15[d]	PPTS/PCC/ Na_2CO_3	DCM, 25→70	45%
16[d,f]	**PPTS/DMP/ Na_2CO_3**	**DCM, 25→70**	**55%**

[a]Unless noted otherwise, reactions were performed on scale of 100 mg of **16**. [b]Stepwise procedure without purification of intermediates. [c]HCl: 2.0 M. [d]One-pot procedure: reactions were performed in solvent to which the reagents were added successively with an appropriate interval. [e]H_2SO_4: 2.0 M. [f]1.6 g scale.

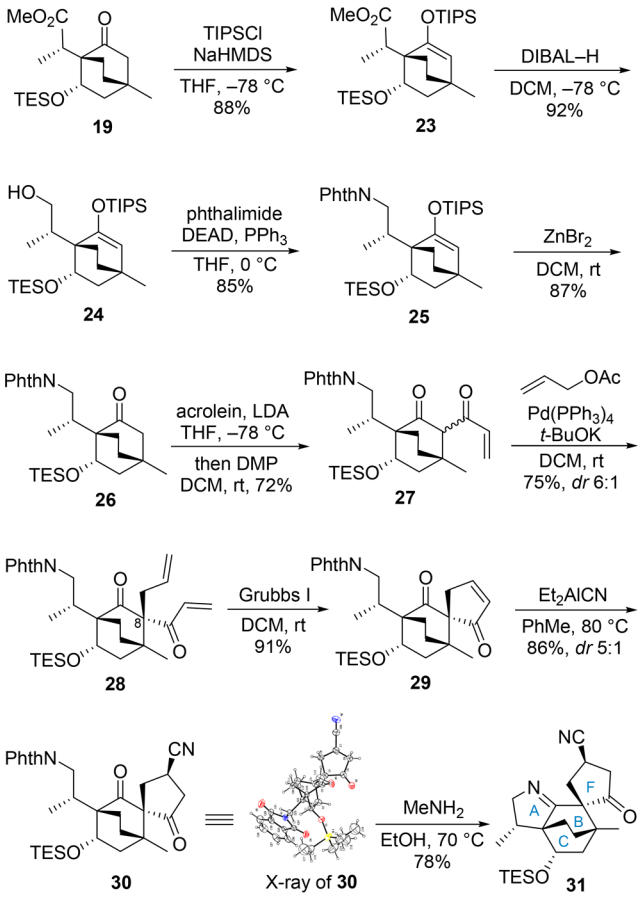
conditions using $SOCl_2$ in the heating pyridine, delivering α,β-unsaturated ester **18** in 68% overall yield (Scheme 2). Following catalytic hydrogenation of the double bond in **18** with Pd/C in the presence of Na_2CO_3 in EtOAc, two separable esters **19** and **20** were afforded in 92% combined yield with 10:1 dr. In order to determine the relative stereochemistry of C7 and C18, we converted **19** and **20** into the corresponding ABC tricyclic frameworks for NOE studies. To our delight, under the thermal condensation conditions, treating **19** and **20** with $PMBNH_2$ and PPTS in a sealed tube delivered the ABC tricycles **21** and **22** with acceptable yields, respectively. Thus, the relative stereochemistry of C7 and C18 was confirmed by the NOE correlations of the tricyclic compounds, as shown in Scheme 2 (red arrow). Unfortunately, the survey on various reductive conditions revealed that the amide groups in **21** and **22** were inert, so releasing the dihydropyrrole A ring at this stage was unsuccessful.

Scheme 2. Elaborations of the Methyl Group at C18 and ABC Tricyclic Frameworks



In accord with our synthetic plan, we turned our attention to the installment of the requisite nitrogen at an appropriate reduction state of C19. At this point, we envisaged using a silyl enol ether as a masked C1 carbonyl group to prevent the probable ketone carbonyl reduction in the subsequent reductive operations. Thus, as shown in Scheme 3, ketone **19** was subjected to silyl enol ether formation employing TIPSCl/NaHMDS, leading to **23** in 88% yield. The latter was converted into primary alcohol **24** with DIBAL-H in 92% yield. Pleasingly, the introduction of the requisite nitrogen with protection by treatment of **24** with phthalimide under Mitsunobu conditions[19] produced **25** in 85% yield. Subsequent selective desilylation using $ZnBr_2$[20] released the desired ketone **26**, which was a suitable precursor for the assembly of a C8 spiro-quaternary center. Inspired by Smith's seminal work,[6] the construction of the C8 center began with an aldol condensation of **26** with acrolein, followed by DMP oxidation

Scheme 3. Synthesis of ABCF Tetracyclic Framework



The construction of the C8 center began with an aldol condensation of **26** with acrolein, followed by DMP oxidation

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to form diketone **27** in 72% yield. The subsequent Tsuji–Trost allylation[15] installed the allyl group, thus delivering diene **28** as the dominant stereoisomer (dr 6:1). Moving forward, the obtained diene was subjected to standard metathesis conditions using Grubbs I catalyst,[13] thus completing the cyclopentenone motif formation with an excellent efficiency (91% yield). Subsequently, a CN group, the surrogate of CO_2Me in the target molecule, was set to be introduced onto enone **29** by Nagata conjugate cyanation.[14] Fortunately, we found that 1,4-hydrocyanation of **29** using Nagata's reagent (Et_2AlCN) proceeded smoothly in heated toluene with ca. 5:1 selectivity in favor of the desired C14 diastereomer and afforded tricycle **30** containing the functionalized F ring in good yield, the structure of which was confirmed unambiguously by X-ray diffraction analysis. Ultimately, the exposure of **30** to $MeNH_2$ in EtOH[21] at 70 °C readily led to removal of the phthalimide followed by spontaneous ring closure via imine formation, thus accomplishing the ABCF tetracyclic framework **31** in 78% yield.

In conclusion, the ABCF tetracyclic framework of *Daphniphyllum* alkaloid calyciphylline N (**2**), which comprises three bridgehead all-carbon quaternary stereocenters of the natural product, was synthesized in 14 steps from readily obtained enone **13**. A successive inter-/intramolecular aldol sequence was systematically investigated, in which a robust one-pot procedure involving desilylation/oxidation/aldol-type cyclization was particularly employed to construct the critical bridged bicyclo[2.2.2]octanone BC core. Efficient RCM reaction followed by stereoselective Nagata conjugate cyanation forged the functionalized F ring for the subsequent studies. Efforts toward the total synthesis of calyciphylline N (**2**) are currently under investigation.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b02202.

Detailed experimental procedures, spectral data, and X-ray crystallography (PDF)

Accession Codes

CCDC 1855186 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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