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Stereocontrolled Construction of ABCD Tetracyclic Ring System with Vicinal All-Carbon Quaternary Stereogenic Centers of Calyciphylline A Type Alkaloids

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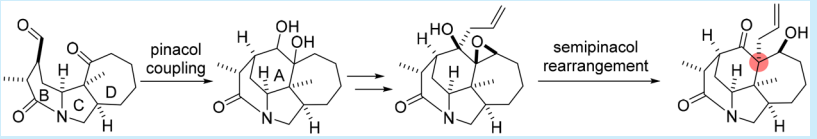
Supporting Information



ABSTRACT: A unique approach to the synthesis of an ABCD tetracyclic core bearing the vicinal all-carbon quaternary stereogenic centers of the calyciphylline A type alkaloids is reported. The synthesis features two C−C bond formations at a sterically congested position: one is an intramolecular pinacol coupling to construct the central A ring; the other is a semipinacol rearrangement to construct a quaternary stereogenic center adjacent to another quaternary center.

Daphniphyllum alkaloids, more than 300 species of which have been isolated, have unique polycyclic fused ring systems that are classified into 14 different structural types.[1] One of these is the calyciphylline A type, which possesses an unprecedented fused penta- or hexacyclic ring system that contains more than six stereogenic centers, some of which are vicinal all-carbon quaternary stereogenic centers (Figure 1). A member of this

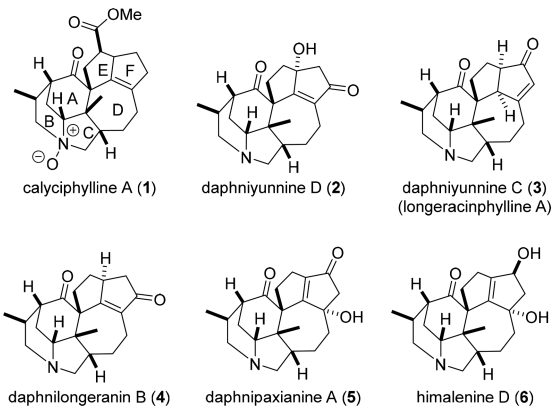
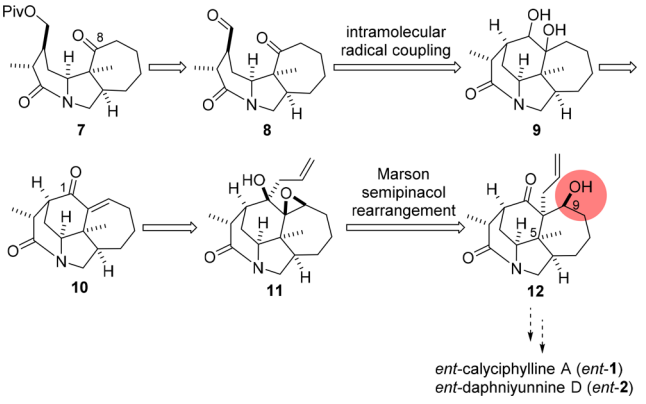


Figure 1. Calyciphylline A type alkaloids.

class of alkaloids, namely, daphniyunnine D (**2**), exhibits antitumor activity.[2] However, further investigations into the biological activities of this class of alkaloids have not been carried out because of their poor availability in Nature. Owing to their interesting biological effects and highly complex structures, calyciphylline A type alkaloids have attracted the interest of synthetic organic chemists; to date, more than 15 synthetic studies on these alkaloids have been reported.[3] Very recently, four reports of the total syntheses of calyciphylline A type alkaloids have been published.[4,5] In this paper, we report a unique approach to the synthesis of a common ABCD tetracyclic structure bearing the vicinal all-carbon quaternary stereogenic centers of calyciphylline A type alkaloids. Two reactions have been employed for the construction of the C−C bonds at a sterically congested position: SmI_2-promoted pinacol coupling to construct the central A ring and semipinacol rearrangement to introduce an all-carbon quaternary stereogenic center adjacent to another quaternary center.

Our synthetic plan is shown in Scheme 1. We set the BCD tricyclic lactam **7** as the platform for our feasibility study, the

Scheme 1. Synthetic Plan for Calyciphylline A Type Alkaloids



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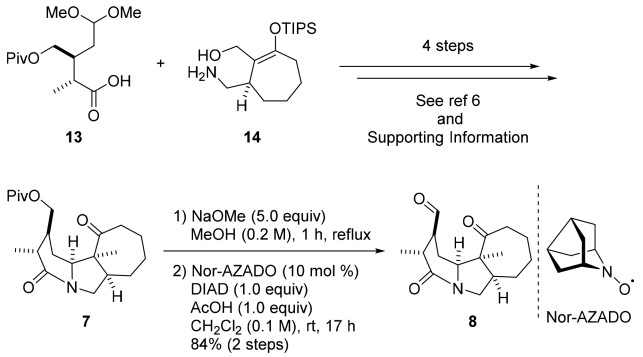
synthesis of which we previously reported as a synthetic intermediate for other *Daphniphyllum* alkaloids, namely, daphnicyclidins.[6] (Note: The antipodes of natural products were selected as the targets considering the ready availability of the starting material, namely, (−)-8-phenylmenthol. The synthetic studies of natural enantiomers of the natural products are underway.) As a preliminary investigation, we examined C−C bond formation at the C8 ketone of **7** to secure a synthetic platform for the E-ring. As a result, it was proven that the introduction of the C−C bond at this position is a formidable challenge, likely due to the steric hindrance of this position adjacent to the all-carbon quaternary stereogenic center: Neither the attempted nucleophilic addition of an organometallic reagent nor the transition-metal-catalyzed coupling of the corresponding enol triflate gave us sufficient materials to continue the synthesis. On the basis of these results, we planned to adopt an intramolecular reductive radical coupling of ketoaldehyde **8**, which is readily obtainable from **7** and allows the expedient construction of the A-ring of the calyciphylline A type alkaloids.[7] The subsequent construction of the all-carbon quaternary stereogenic center at the C8 position adjacent to another quaternary stereogenic center at the C5 position was anticipated as another challenge. We envisaged that enone **10**, potentially securable from diol **9** via a conventional set of transformations, offered a possible platform from where to achieve this demanding task: the cage-shaped skeleton would govern 1,2-addition of an allyl group onto the C1 ketone from the convex face and the resulting *endo*-alcohol would direct *syn*-selective epoxidation to give epoxy alcohol **11**, setting up the subsequent Marson semipinacol rearrangement.[8] Product **12** has a versatile allyl group at C8 and a hydroxy group at the C9 position, which would serve as promising levers for construction of the E- and F-rings.

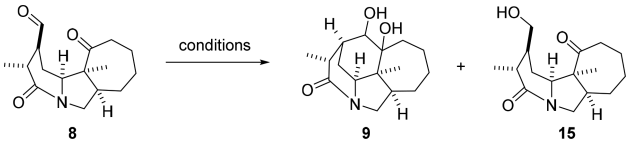
Our synthetic study began with an examination of the construction of the ring A. The substrate for the intramolecular pinacol coupling, ketoaldehyde **8**, was synthesized from **7**[6] in 84% yield in two steps, namely, by deprotection of the pivaloyl group and mild oxidation of the resulting alcohol with Nor-AZADO and DIAD (Scheme 2).[9] In the case of using IBX for

Scheme 2. Synthesis of Ketoaldehyde 8



alcohol oxidation, the alcohol was excessively oxidized to the corresponding carboxylic acid.[10] Next, the key intramolecular pinacol coupling was examined (Table 1). Mg induced no reaction (entry 1).[11] The use of AIBN and Bu_3SnH did not lead to the expected C−C bond formation between the two carbonyl groups, but led to reduction of the aldehyde group with recovery of the starting material (entry 2).[12] Then, SmI_2 was examined. Gratifyingly, tetracyclic diol **9** was obtained in

Table 1. Intramolecular Pinacol Coupling

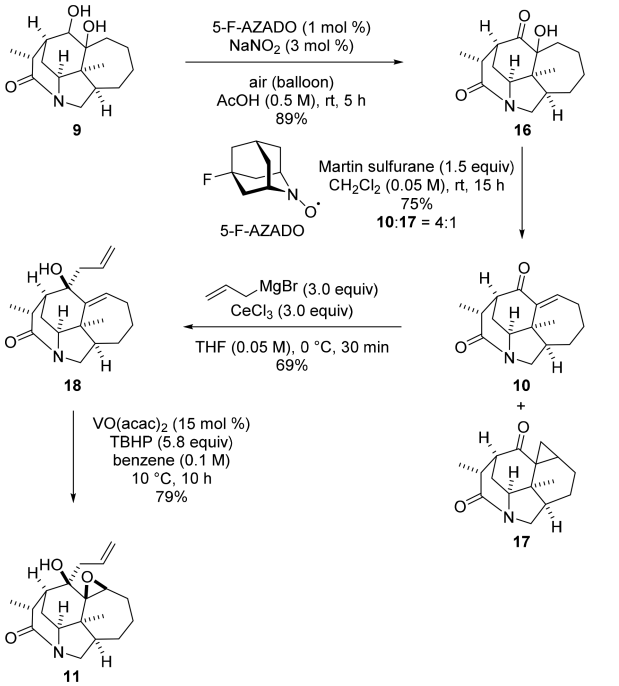


entry	conditions	results
1	Mg (5.0 equiv), TMSCl (5.0 equiv), DMF (0.03 M), rt, 12 h	no reaction
2	AIBN (20 mol %), Bu_3SnH (1.5 equiv), benzene (0.01 M), reflux, 16 h	**15** (44%), **8** (47%)
3	SmI_2 (5.0 equiv), THF (0.03 M), rt, 3 h	**9** (71%)
4	SmI_2 (5.0 equiv), HMPA (20 equiv), THF (0.03 M), rt, 1.5 h	**15** (62%)
5	SmI_2 (5.0 equiv), LiCl (20 equiv), THF (0.03 M), rt, 1.5 h	**15** (51%)

71% yield as a single diastereomer (entry 3: the stereochemistry of **9** was not determined). HMPA and LiCl were examined as additives for the SmI_2-induced pinacol coupling; however, the coupling product **9** was not obtained (entries 4 and 5).[13] It is likely that the strong oxophilicity of SmI_2 forced the two carbonyl groups into close proximity to one another to promote the coupling reaction. The addition of HMPA and LiCl might reduce the interaction between the SmI_2 and the carbonyl groups.

With tetracyclic compound **9** obtained, we focused our efforts on installation of the quaternary stereogenic center at the C8 position. Epoxy alcohol **11**, the precursor of the semipinacol rearrangement, was synthesized as shown below (Scheme 3): The secondary alcohol of diol **9** was successfully oxidized under 5-F-AZADO/NO_x-catalyzed aerobic oxidation to afford α-hydroxyketone **16** in 89% yield without cleavage of the vicinal diol.[14] Dehydration of α-hydroxyketone using Martin sulfurane gave enone **10** and cyclopropane **17** in 75% yield as a 4:1 inseparable mixture.[15] The use of thionyl chloride

Scheme 3. Synthesis of Epoxy Alcohol 11



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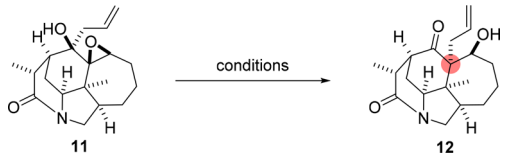
in a pyridine solution gave enone **10** in lower (23%) yield concomitant with a chloride, which is generated in 4% yield by the substitution of the hydroxy group of **16** for a Cl group. The spectral data of enone **10** were consistent with those of Bonjoch's product, whose synthesis was completely different from ours.[3d] An allyl group was introduced onto the C1 ketone using allylMgBr in the presence of $CeCl_3$ to afford allylic alcohol **18** in 69% yield, which was obtained as a single diastereomer. Stereoselective epoxidation of allylic alcohol **18** with a vanadium catalyst afforded epoxy alcohol **11** in 79% yield.

With precursor **11** obtained, the key Marson semipinacol rearrangement was examined (Table 2). The use of concd HCl

Table 2. Semipinacol Rearrangement



11 12

entry	acid (equiv)	solvent	temp (°C)	times	results
1	concd HCl (1 drop)	CH_2Cl_2	rt	1 d	no reaction
2	$TiCl_4$ (45)	CH_2Cl_2	−78	20 min	unidentified product
3	$BF_3{\cdot}OEt_2$ (2.0)	CH_2Cl_2	−78 to rt	2 h	**12** (<63%)
4	$LiBF_4$ (2.0)	MeCN	60	11 h	**12** (96%)

as the Brønsted acid induced no reaction (entry 1). Then, several Lewis acids were examined. Although $TiCl_4$ afforded an unidentified product (entry 2), $BF_3{\cdot}OEt_2$ afforded the desired product **12** in moderate yield (entry 3). Eventually, it was found that Lipshutz's conditions using $LiBF_4$ in MeCN achieved a high yield of **12**, which was obtained as a single stereoisomer (entry 4).[16] The stereochemistry of **12** was verified by X-ray crystallographic analysis (Figure 2).

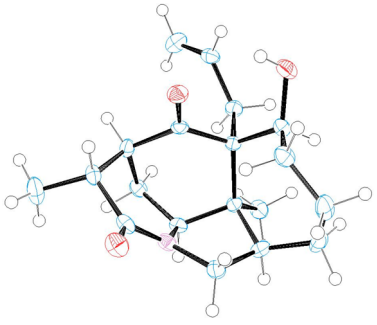


Figure 2. ORTEP structure of **12**.

In conclusion, we have achieved an enantiocontrolled construction of an ABCD tetracyclic system of calyciphylline A type alkaloids bearing six chiral centers, including vicinal all-carbon quaternary centers. This is the first example of the construction of the A-ring after the BCD rings have been constructed. This study provides some useful solutions to the construction of C−C bonds in sterically congested positions. The intramolecular pinacol coupling with SmI_2 enables the construction of a C−C bond on the ketone moiety in the neopentyl position of **8**, likely due to the high reactivity of the radical intermediate and the strong oxophilicity of the Sm ion. The semipinacol rearrangement with $LiBF_4$ in MeCN has enabled the construction of the all-carbon quaternary stereogenic center adjacent to the other quaternary center. The final product, **12**, having allyl and hydroxy groups, could serve as a synthetic scaffold for constructing the EF rings. Investigations into the total synthesis of calyciphylline A type alkaloids are underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b01087.

Synthetic scheme for **7**, detailed experimental procedures, spectral data, and X-ray crystallographic data (PDF)

Accession Codes

CCDC 1833117 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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