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Stereocontrolled Synthesis of the Tricyclic ABC Ring System of Daphnicyclidin A

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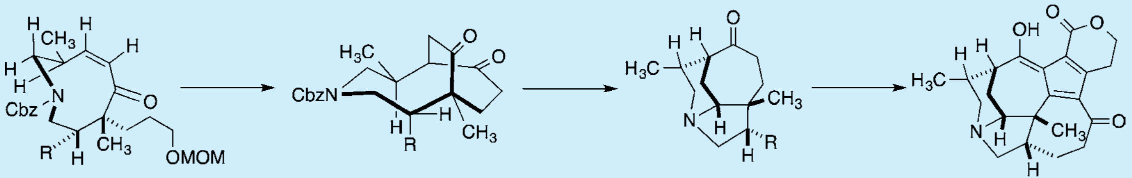
Supporting Information


29 R = $(CH_2)_3OTBDPS$ **31** R = $(CH_2)_3OTBDPS$ **7** R = $(CH_2)_3OTBDPS$ **1** (Daphnicyclidin A)

ABSTRACT: An enantiocontrolled synthesis pathway has been developed to provide formation of tricyclic amine **7**, representing the ABC ring system of the complex alkaloid daphnicyclidin A (**1**). Our efforts describe preparation of the *Z*-hexahydro-(1*H*)-azocine **29** and cyclization to construct the novel 4-azabicyclo[5.3.2]dodecane **31**. Transannular reductive amination following the deprotection of **31** gave the desired tertiary amine **7**.

Structural complexity exhibited among examples of the *Daphniphyllum* alkaloids has led to a general classification of 16 distinct types of backbone skeletons.[1] In 2001, Kobayashi and co-workers reported the discovery of the daphnicyclidins, an unprecedented class of natural products featuring fused hexa- and pentacyclic architectures.[2] These studies described the elucidation of daphnicyclidin A (**1**) based on spectroscopic data, including NMR−NOESY correlations as well as X-ray crystallography.[2] The number of *Daphniphyllum* alkaloids that have been isolated and identified has grown substantially in recent years, and as a result, the daphnicyclidins have been categorized into three subgroups based on the connectivity associated with the fulvene core. The fulvene moiety is exemplified by daphnicyclidins A−H,[2] J and K,[3] L,[4] paxiphyllines A−E,[5] daphnipaxinin,[6] daphnilongerains A−D,[7] daphcalycine,[8] and the longistylumphyllines A−C.[9] Four examples are illustrated in Figure 1. Preliminary biological evaluations have indicated that several of these alkaloids are cytotoxic against murine lymphoma L1210 and human epidermoid carcinoma KB with IC$_{50}$ values in the 0.8−10 μM range. Several polycyclic *Daphniphyllum* alkaloids are also notable constituents of plants that are used in traditional Chinese medicines for the treatment of inflammation and other diseases.[10] The significance of the biological properties and the remarkable arrangement of ring fusions and stereochemical features provide ample justification for explorations of synthesis strategy and new methodology. Studies toward the synthesis of daphnipaxinin, daphnicyclidin A, and daphenylline have been reported.[11−13] In addition, other classes of *Daphniphyllum* alkaloids have recently attracted keen interest in the synthetic community.[14]

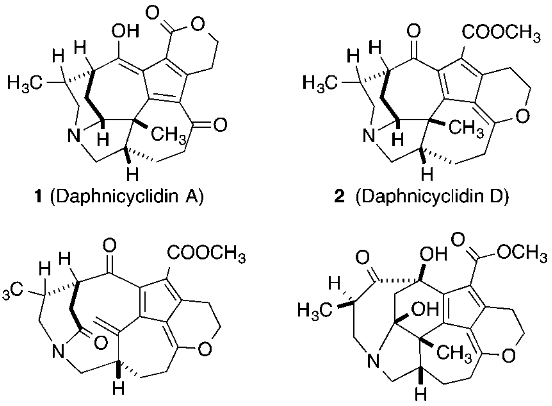

1 (Daphnicyclidin A) **2** (Daphnicyclidin D) **3** (Daphnicyclidin J) **4** (Daphnicyclidin K)

Figure 1. Examples of daphnicyclidin alkaloids.

Our retrosynthetic analysis of **1** proposes a late-stage formation of the ring-fused fulvene from the cross-conjugated ketoester **5** (Scheme 1). Our plan will explore the deprotonation of the unsaturated lactone of **5** to produce a resonance-stabilized pentadienyl carbanion which is a portion of the extended $10e^-$ system. A thermal disrotatory electrocyclization leads to ring closure for oxidation of the resulting enolate. The fulvene skeleton of **1** is formed by C-acylation of the cyclopentadienyl anion (enolate) and tautomerization. As a proof of principle, we have previously examined the electrocyclizations of cyclic pentadienyl carbanions.[15] A Stille cross-coupling reaction using the α-iodo ketone **6** is envisioned for construction of the key intermediate **5**. Thus, we have focused our efforts toward the enantiocontrolled synthesis of the novel tricyclic amine **7** as a suitable precursor which incorporates the fully elaborated ABC ring system while allowing flexibility for deployment of several tactics leading to **5**. The tricyclic framework of **7** incorporates all of the stereochemical features of daphnicyclidin A (**1**).

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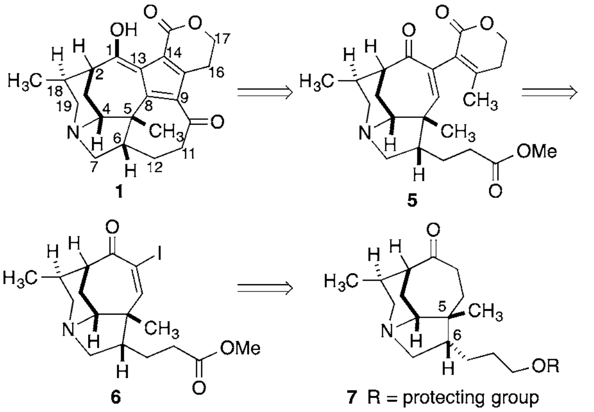
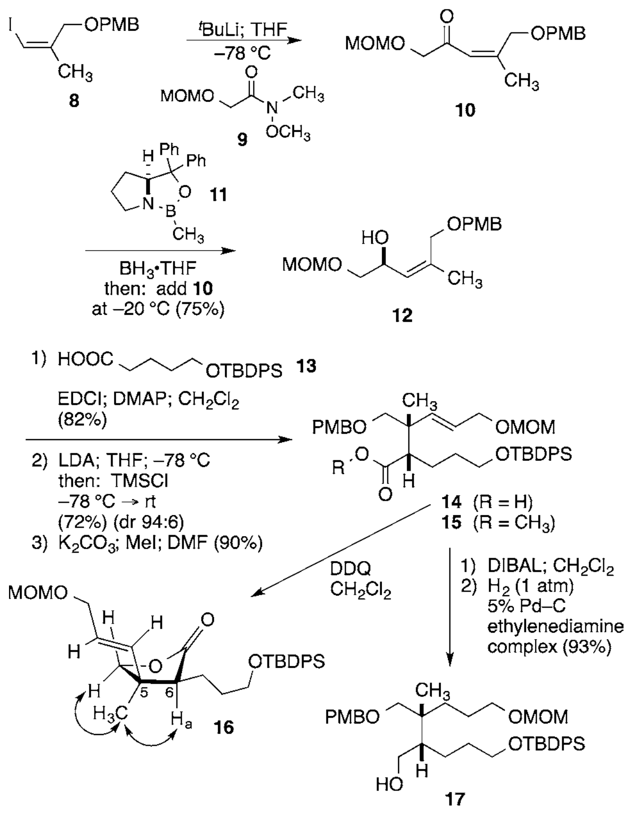
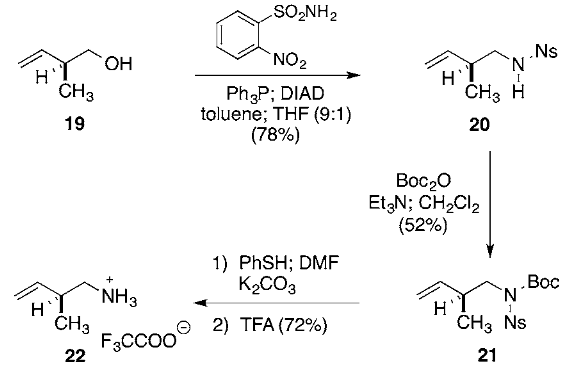
Scheme 1. Retrosynthetic Analysis



Scheme 2. Synthesis of Alcohol 17 via the Ireland–Claisen Process



Scheme 3. Preparation of Sulfonamide 20 and Salt 22



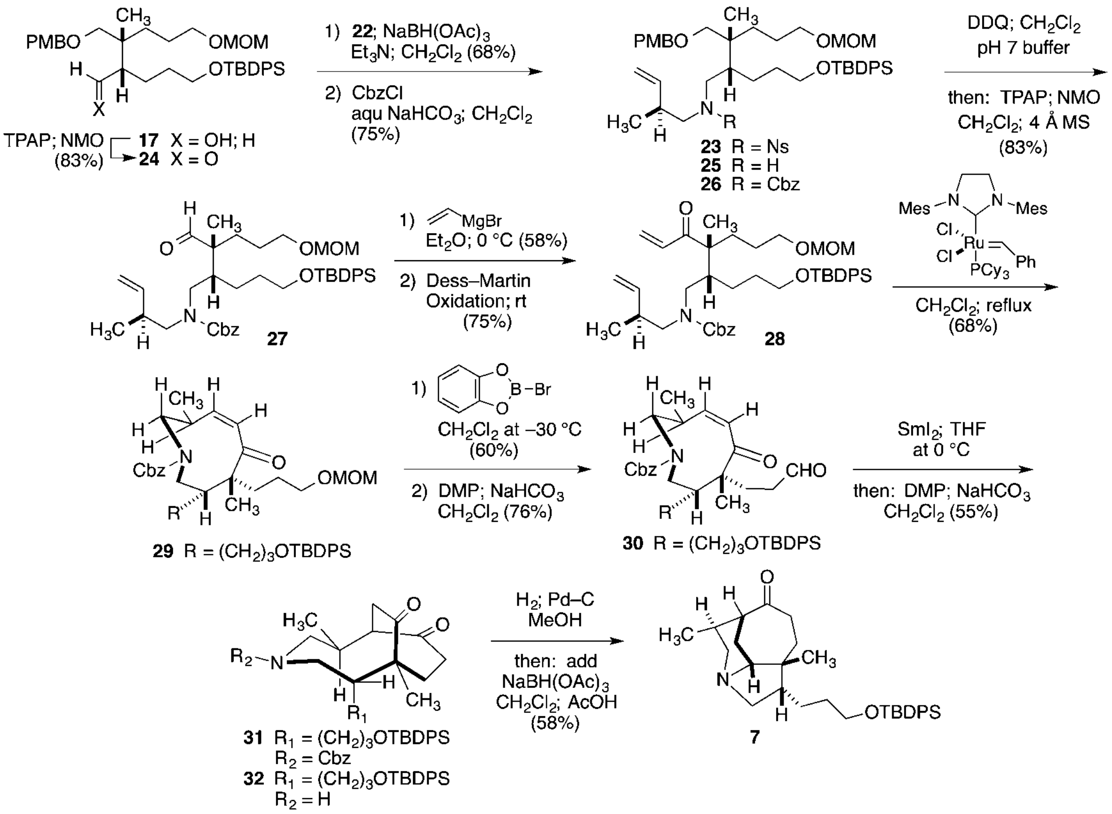
In this paper, we describe an effective, enantiocontrolled synthesis of the tricyclic ABC ring system of the tertiary amine **7** as a key component for our proposed strategy toward **1**. Our results illustrate a noteworthy ring-closing metathesis (RCM) to produce novel and relatively unexplored *Z*-hexahydro-(1*H*)-azocines. In addition, a reductive cyclization using samarium diiodide has produced an unusual aza[5.3.2]bicyclic diketone system for transannular reductive amination.

Our plan for an asymmetric synthesis sought to first introduce the chirality at C-5 and C-6 (daphnicyclidin A numbering) of **7** in an acyclic precursor to be followed by strategic cyclization events. This initial task was successfully achieved by use of the Ireland–Claisen rearrangement beginning with the known *Z*-vinylic iodide **8**, which was obtained from propargyl alcohol in two steps.[16] Metalation of **8** (Scheme 2) and acylation using the Weinreb amide **9**[17] resulted in the *Z*-enone **10** (82%). Application of the Corey–Bakshi–Shibata (CBS) reduction[18] by precomplexation of BH$_3$·THF with oxazaborolidine **11** (1.0 equiv) at 22 °C followed by introduction of **10** at −20 °C afforded the (*S*)-alcohol **11** in 75% yield. This result was confirmed by a modified Mosher ester analysis which also indicated high asymmetric induction (≥99% ee).[19] Esterification of **12** with carboxylic acid **13**, which was readily derived from valerolactone,[20] led to the kinetic deprotonation and capture of the *E*(O)-enolate as its corresponding TMS-ketene acetal at −78 °C. The facile Ireland–Claisen rearrangement occurred upon stirring the reaction mixture at rt overnight, and an aqueous workup afforded the carboxylic acid **14** in 72% yield (dr 96:4). To evaluate the stereoselectivity of the Ireland–Claisen process, the crude carboxylic acid was treated with DDQ in wet CH$_2$Cl$_2$ which directly provided the *cis*-disubstituted butyrolactone **16**. NMR studies (NOESY) leading to the observed nuclear Overhauser enhancement correlations confirmed the C-5 and C-6 stereochemistry as illustrated in **16**.[21] Further transformations and the full characterization of **14** were aided by conversion to the methyl ester **15** (90%). Methylester **15** was then reduced to the primary alcohol, and catalytic hydrogenation, using a complex derived from 5% palladium on carbon and ethylenediamine, as described by Hirota and co-workers,[22] yielded **17** (93% for two steps). This modified palladium catalyst diminished loss of the PMB ether by use of 5% Pd–C, which had led to a significant byproduct that was subsequently identified as tetrahydrofuran **18**.

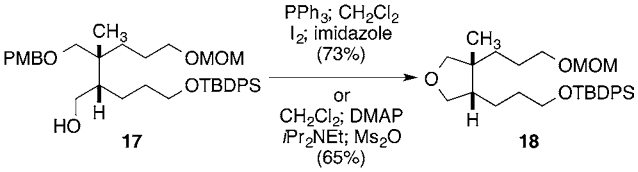
For introduction of the amino moiety of **7**, the nonracemic 2-nitrobenzenesulfonamide **20** (Ns = 2-nitrobenzenesulfonyl) was prepared for application of the Fukuyama–Mitsunobu protocol[23] beginning with the known (2*S*)-2-methyl-3-buten-1-ol (**19**).[24] The reactions summarized in Scheme 3 permitted access to the sulfonamide **20** as well as the ammonium trifluoroacetate salt **22**. The salt **22** was directly obtained as a solid under anhydrous conditions following the deprotection of **21** with benzenethiol followed by TFA. This route avoided problems associated with the volatility of the corresponding primary amine itself.

Our initial attempts for *N*-alkylation of the sulfonamide **20** (from Scheme 4) planned to explore the anionic displacement of a reactive halide derived from alcohol **17** (Scheme 3). Unfortunately, efforts to convert **17** into a suitable leaving group afforded a facile cyclization to yield the tetrahydrofuran **18**, as exemplified by treatment with triphenylphosphine and iodine or by standard conditions for mesylation. Subsequent studies examined several variations of the Fukuyama–Mitsunobu procedure in an attempt to prepare **23** (R = Ns) (Scheme 4) by

Scheme 4. Synthesis of Tricyclic Amine 7



directly utilizing alcohol **17**. In these cases, only starting **17** and THF **18** (5−15%) were obtained.



To circumvent these difficulties, we successfully implemented a reductive amination of aldehyde **24**, prepared via oxidation[25] of **17** (TPAP; NMO; CH_2Cl_2; 4 Å MS, 83% yield), using the ammonium trifluoroacetate **22** and sodium triacetoxyborohydride. Formation of the secondary amine **25** was followed by Cbz protection to give **26**. PMB cleavage and oxidation produced the aldehyde of **27** and led to the addition of vinylmagnesium bromide to yield a mixture of diastereomeric allylic alcohols. Subsequent oxidation produced the ketone **28** as a substrate for RCM. RCM cyclizations that yield 9-membered rings are very rare.[26] Moreover, our search of the literature has indicated that **29** features an unusual and unexplored *Z*-hexahydro-(1*H*)-azocine system.[27] Studies of enone **28** using the Grubbs II catalyst[28] provided the desired *Z*-enone **29** in 68% yield, whereas the Grubbs I catalyst was ineffective. More reactive catalysts resulted in faster consumption of starting **28** with increasing amounts of intermolecular C═C products. On the other hand, the precursor allylic alcohols of **28** proved to be much less effective substrates, leading to poor yields of RCM product.

The construction of a bridging seven-membered ring was undertaken by the application of a reductive cyclization. Thus, the cleavage of the methoxymethyl (MOM) acetal of **29** and Dess−Martin oxidation[29] gave the ketoaldehyde **30**, which was subjected to SmI_2 in THF at 0 °C.[30] Rapid cyclization yielded a mixture of alcohol diastereomers which were immediately treated with the Dess−Martin periodinane leading to the isolation of the diketone **31** (55%).[31] Finally, hydrogenolysis of **31** in methanol at 22 °C provided the secondary amine **32** in addition to small amounts of a hemiaminal resulting from transannular attack, as well as the reduced tricycle **7**. This mixture was directly treated with acetic acid and the addition of sodium borohydride to complete conversion to the desired amino ketone **7** (58%).

In summary, an enantiocontrolled pathway has resulted in the synthesis of tricyclic amine **7** as a significant motif representing the ABC ring system of daphnicyclidin A (**1**). These efforts have documented the preparation of a nine-membered *Z*-hexahydro-(1*H*)-azocine and the reductive cyclization to form a novel 4-azabicyclo[5.3.2]dodecane system. Further studies to incorporate our findings for a convergent total synthesis of **1** are planned.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures, spectroscopic data, and ^1H and ^{13}C NMR spectra for compounds **10−31** and tricyclic amine **7**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(31) To the best of our knowledge, the aza[5.3.2]bicyclic system of **31**/**32** is unique and has not previously been described in the synthesis literature.