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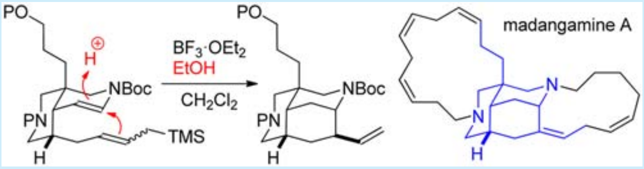
Synthesis of Diazatricyclic Common Structure of Madangamine Alkaloids

Yuta Yanagita, Takahiro Suto, Naoya Matsuo, Yasuhiro Kurosu, Takaaki Sato,* and Noritaka Chida*

Department of Applied Chemistry, Faculty of Science and Technology, Keio University, 3-14-1, Hiyoshi, Kohoku-ku, Yokohama 223-8522, Japan

Supporting Information

ABSTRACT: A general synthetic route toward a diazatricyclic core common to the madangamine family is described. Ring-closing metathesis and palladium-catalyzed cycloisomerization provided the *cis*-fused diazadecalin structure, accompanied by formation of the *N*-Boc-enamine, which was utilized as an *N*-acyliminium ion equivalent. Direct cyclization from the *N*-Boc-enamine was achieved through the in situ formation of an *N*,*O*-acetal.



In 1994, Andersen isolated the first member of the madangamine family, madangamine A, from the marine sponge *Xestospongia ingens* on the reefs off Madang, Papua New Guinea (Figure 1).[1a] Thereafter, madangamines B−E were identified from the same organism.[1b] Recently, Berlinck's team reported that a related natural product, madangamine F, was isolated from the Brazilian marine sponge *Pachychalina alcaloidifera*.[1c] Structurally, madangamine alkaloids except for madangamine F possess a common ABCE-tetracyclic system but a different D-ring moiety. Madangamine A has been shown to possess significant in vitro cytotoxicity against a variety of tumor cell lines including murine leukemia P388, human lung A549, brain U373, and breast MCF-7 cancer cell lines.[1a] Until recently, biological activities of other members of the madangamines had not been reported due to their scarcity. However, in 2014, Amat and co-workers synthesized a pure sample of madangamine D and found that it exhibited a significant, but different, antitumor spectrum from madangamine A.[2] Given these indications that the variable D-ring structure of the madangamines might play a significant role in the cytotoxic activity, our research group started a synthetic program to pursue a modular route toward the synthesis of the madangamines. The developed route would enable additional biological tests and structure−activity relationship studies. In this paper, we describe our synthetic progress toward the common diazatricyclic core (the ABC-ring) of the madangamines.

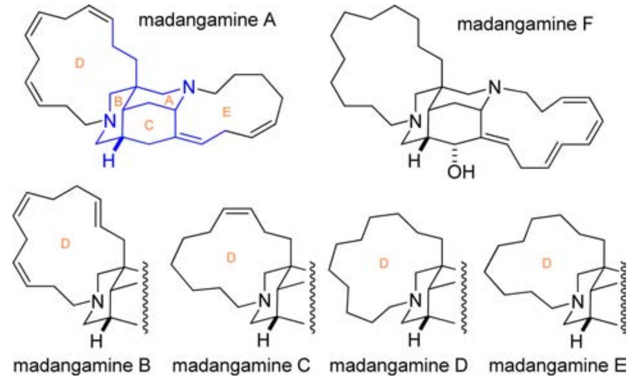
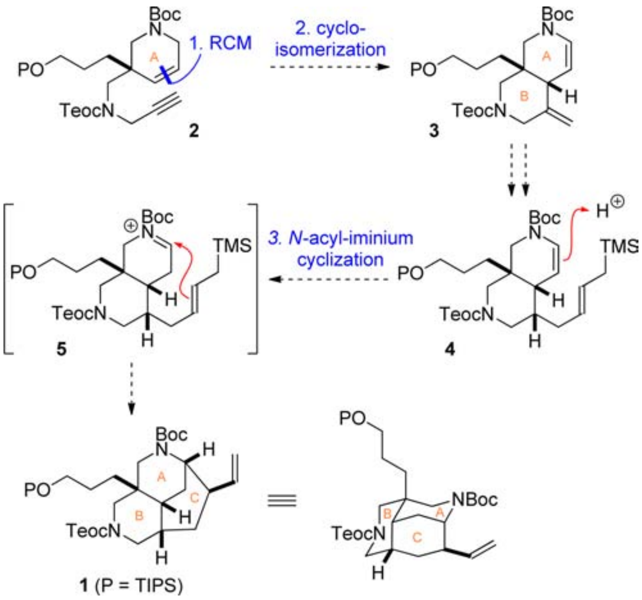


Figure 1. Madangamine alkaloids.

Our synthetic plan to develop a modular route for the madangamine family is shown in Scheme 1. The variable D-ring

Scheme 1. Synthetic Plan for Diazatricyclic Structure of Madangamines



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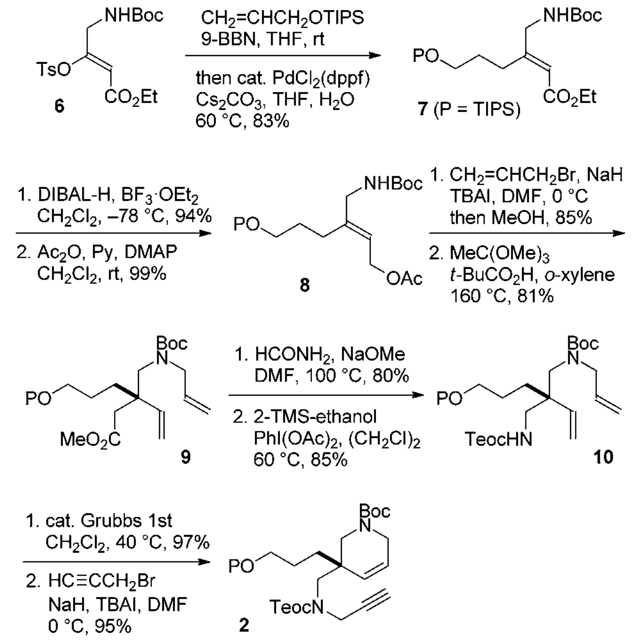
moieties would be installed by quick diversification from the common ABCE-ring structure at a late stage in the synthesis. The unprecedented diazatricyclic structure **1** embedded in the pentacyclic system has inspired a number of synthetic chemists and resulted in the development of a variety of unique approaches.[2−6] Very recently, Amat established a powerful strategy using a phenylglycinol-derived lactam, which culminated in the first total synthesis of madangamine D.[2e] We envisioned that three independent cyclizations would enable efficient synthesis of the diazatricyclic ABC-ring. The *cis*-fused diazadecalin structure **3** would be a relatively easily accessible intermediate and could be synthesized by using ring-closing metathesis and transition-metal-catalyzed cycloisomerization of **2**. This cycloisomerization would construct the B-ring, accompanied by the installation of the *N*-Boc-enamine structure, which would be utilized as an *N*-acyliminium ion equivalent in the third cyclization (**4** → **5** → **1**).[7] The highly electrophilic *N*-acyliminium ion **5** would undergo cyclization with the allylsilane, forming the bridgelike structure found in **1**.

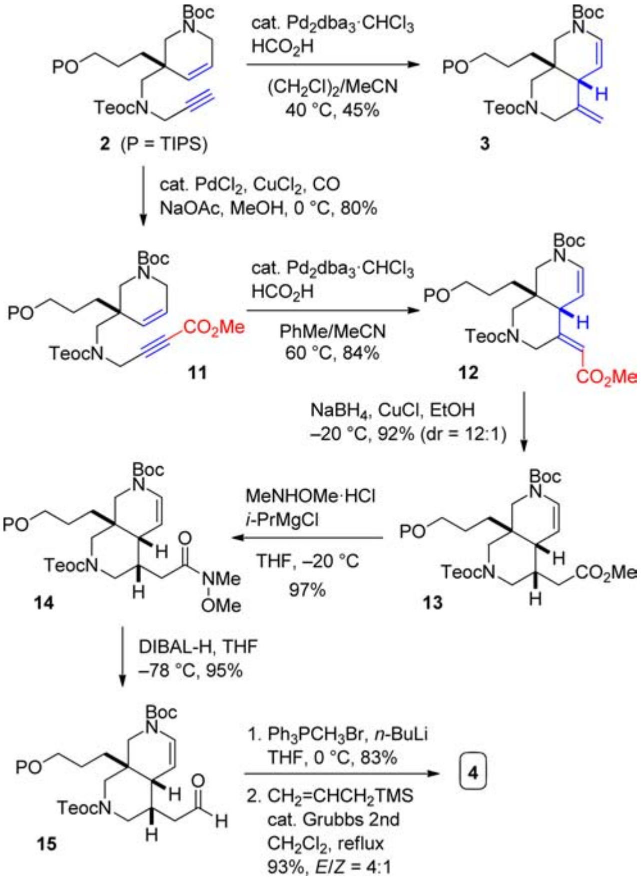
Our synthesis began with the Suzuki−Miyaura coupling of the known enol tosylate **6** to give **7** (Scheme 2).[8] DIBAL-H reduction in the presence of $BF_3{\cdot}Et_2O$ induced the 1,2-reduction of unsaturated ester **7** in 94% yield.[9] The resulting alcohol was then protected as an acetate, giving allylic acetate **8**. The *N*-allylation of **8** with NaH and TBAI, followed by methanolysis, provided the allylic alcohol in a one-pot sequence. The subsequent Johnson-type Claisen rearrangement with $MeC(OMe)_3$ in the presence of 10 mol % of pivalic acid installed the quaternary carbon center of the madangamines in 81% yield. The resulting methyl ester **9** was then converted to Teoc-protected amine **10** by a two-step sequence including direct amidation of the methyl ester[10] and Hofmann rearrangement with $PhI(OAc)_2$ and 2-TMS-ethanol.[11] Diene **10** underwent the ring-closing metathesis,[12] followed by subsequent *N*-propargylation to afford enyne **2** in high yield.

Scheme 2. Synthesis of the A-Ring Moiety 2



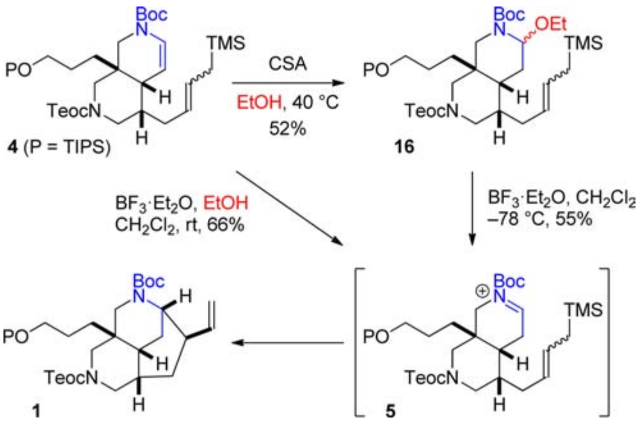
With enyne substrate **2** in hand, we then turned our attention to the palladium-catalyzed cycloisomerization originally developed by Trost (Scheme 3).[13] Treatment of **2** with 20 mol % of $Pd_2dba_3{\cdot}CHCl_3$ and HCO_2H in $(CH_2Cl)_2$/MeCN = 49[14] at 40 °C resulted in the construction of the *cis*-fused AB-ring system **3** in 45% yield (not optimized). Unfortunately, the terminal olefin in **3** could not be functionalized in the presence of the *N*-Boc-enamine under a number of attempted conditions such as hydroboration. We therefore examined different functional groups at the terminal position of the alkyne for further transformations. After extensive investigations, the methyl ester was proved to be the best functional group in regard to both the cyclization itself and the subsequent transformations. While carbonylation of alkyne **2** resulted in significant decomposition under standard basic conditions such as *n*-BuLi and methyl chloroformate, the palladium-catalyzed oxidative carbonylation provided alkynoate **11** in 80% yield.[15] Cycloisomerization of alkynoate **11** provided the *cis*-fused AB-ring system **12** in the presence of 2 mol % of $Pd_2dba_3{\cdot}CHCl_3$ and HCO_2H in PhMe/MeCN = 49 at 60 °C in 84% yield. Methyl enoate **12** was selectively functionalized without affecting the relatively reactive *N*-Boc-enamine. Treatment of methyl enoate **12** with $NaBH_4$ and CuCl induced the highly diastereoselective 1,4-reduction, resulting in the establishment of the three contiguous stereocenters in the madangamines.[16] Methyl ester **13** was then transformed to aldehyde **15** via Weinreb amide **14**[17] in two steps. The Wittig reaction and the cross-metathesis reaction[18] with allyltrimethyl silane provided **4** in 93% yield (*E*/*Z* = 4:1).

Scheme 3. Synthesis of the AB Bicyclic Moiety 4



The stage was now set for the crucial *N*-acyliminium ion cyclization (Scheme 4). The direct cyclization of *N*-Boc-enamine **4** to diazatricyclic core **1** with a variety of Brønsted acids in aprotic solvents caused complete decomposition,

Scheme 4. *N*-Acyliminium Ion Cyclization via the in Situ formation of the *N*,*O*-Acetal



probably because of the instability of the transient *N*-acyliminium ion **5**. A stepwise cyclization was then examined via *N*,*O*-acetal **16** on the assumption that the labile *N*-acyliminium ion **5** could be stabilized by equilibrium with *N*,*O*-acetal **16**. Thus, *N*-Boc-enamine **4** was first converted to *N*,*O*-acetal **16** upon treatment with CSA and EtOH at 40 °C in 52% yield. As expected, the subsequent cyclization of *N*,*O*-acetal **16** took place in the presence of $BF_3{\cdot}Et_2O$, giving diazatricyclic core **1** in 55% yield. Although **1** was successfully obtained in this two-step procedure, the need to isolate the unstable *N*,*O*-acetal **16** led to a low yield (29%, two steps). Therefore, the one-step procedure was reinvestigated on the basis of the results using *N*,*O*-acetal **16**. We finally found that the direct cyclization from *N*-Boc-enamine **4** smoothly took place in the presence of $BF_3{\cdot}Et_2O$ and EtOH, affording **1** in 66% yield in a single operation. TLC analysis of this reaction indicated that *N*,*O*-acetal **16** was formed first and then was consumed as the reaction proceeded. Thus, we succeeded in the practical *N*-acyliminium ion cyclization to assemble the common diazatricyclic structure **1** in the madangamine alkaloids.

In conclusion, we have developed a unified route to a common diazatricyclic core found in the madangamine family, which would enable efficient modular syntheses of the madangamines and their derivatives. The *cis*-fused diazadecalin structure (AB-ring) was synthesized by palladium-catalyzed cycloisomerization of a methyl alkynoate. The direct *N*-acyliminium ion cyclization from an *N*-Boc-enamine was successfully established through in situ formation of an *N*,*O*-acetal. The resulting ABC-ring system possesses all functional groups to install the macrocyclic E- and D-rings. Efforts toward the unified total synthesis of the madangamine family as well as development of an enantioselective version are ongoing.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures and copies of ^1H NMR and ^{13}C NMR spectra of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: takaakis@applc.keio.ac.jp.
*E-mail: chida@applc.keio.ac.jp.

Notes

The authors declare no competing financial interest.

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