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Unified Total Synthesis of Madangamines A, C, and E

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Supporting Information

ABSTRACT: A stereodivergent strategy for the synthesis of skipped dienes is developed. The method consists of hydroboration of allenes and Migita−Kosugi−Stille coupling, which allows for access to all four possible stereoisomers of the skipped dienes. The hydroboration is especially useful for providing both *E*-allylic and *Z*-allylic alcohols from the same allene by simply changing the organoborane reagent. The strategy was successfully applied to a unified total synthesis of the madangamine alkaloids via a common ABCE-tetracyclic intermediate with a (*Z*,*Z*)-skipped diene. The late-stage variation of the D-ring enabled the supply of synthetic madangamines A, C, and E for the first time.

A skipped diene is an important functional group widely distributed in biologically active natural products such as madangamines,[1] corallopyronins,[2] and ripostatins[3] (Figure 1).

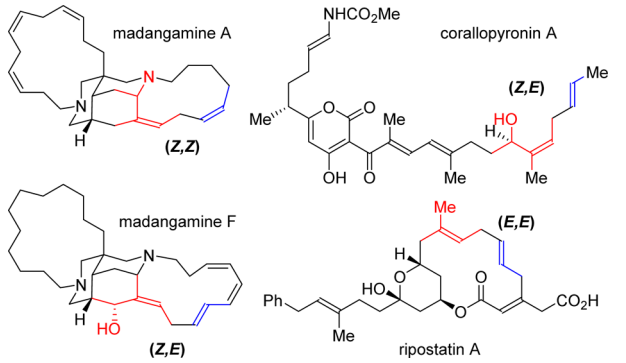
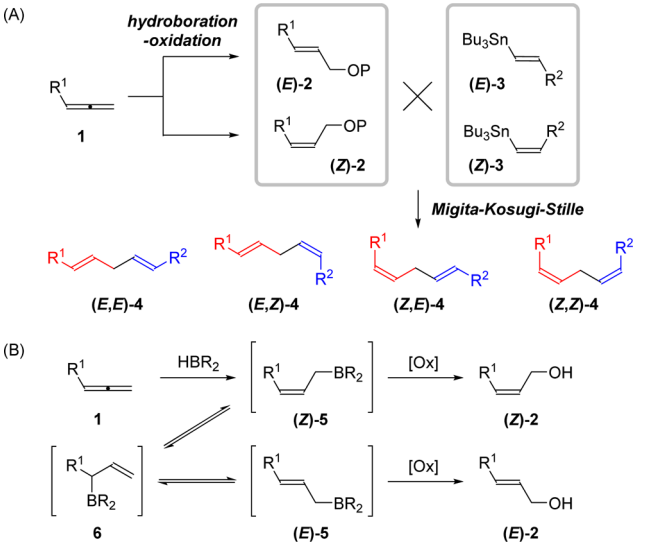


Figure 1. Representative natural products with skipped dienes.

The skipped dienes in these natural products exist as various types of stereoisomers derived from the two olefins. An ideal method to construct the skipped dienes must be stereodivergent, i.e., start from the same compound and give all four possible stereoisomers, as well as be highly convergent for the efficient synthesis of complex molecules.[4] Although a number of synthetic methods have been reported, the development of approaches to provide all four possible stereoisomers of a skipped diene still remains a major challenge in synthetic organic chemistry. In this Communication, we report a practical stereodivergent strategy that provides access to skipped dienes. The method was successfully applied to a unified total synthesis of the madangamine alkaloids.

Scheme 1. (A) Stereodivergent Approach to Skipped Dienes and (B) Mechanism for Hydroboration of Allenes



Our stereodivergent strategy for the synthesis of skipped dienes is shown in Scheme 1A. Hydroboration of allene **1** would give allylic alcohols **2**.[5] The subsequent Migita−Kosugi−Stille coupling reaction[6] with vinyl stannanes **3** would lead to the formation of various skipped dienes **4**. Brown and co-workers reported that hydroboration of allene **1** with 9-BBN resulted in the formation of thermodynamically stable allyl borane (*E*)-**5** (Scheme 1B).[5c] Mechanistically, the hydroboration of **1** with 9-BBN took place from the less hindered side. The generated (*Z*)-**5** quickly underwent two allylic rearrangements via **6** under equilibrium conditions,[5,7] leading to allyl borane (*E*)-**5**, which was subsequently used as an allylating reagent with acetone. The Roush group demonstrated that the proper choice of substituents on the boron could efficiently inhibit the isomerization of kinetically favored (*Z*)-**5**.[5g−i] Based on these landmark precedents, we envisioned that, if both stereoisomers of allylic compound (*E*)-**2** and (*Z*)-**2** were accessible from the same allene **1** by simply changing the borane reagents, the overall strategy would become highly stereodivergent when associated with the Migita−Kosugi−Stille coupling.

To test the feasibility of our strategy, we evaluated the reaction sequence using 1,1-disubstituted allene **7** (Scheme 2). Treatment

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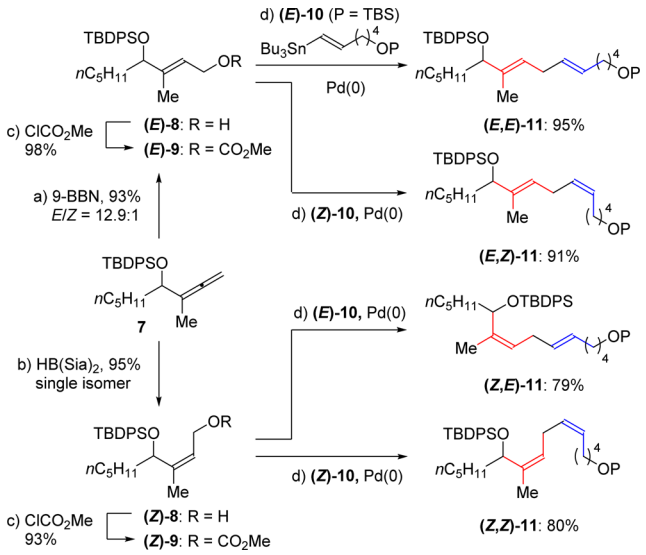
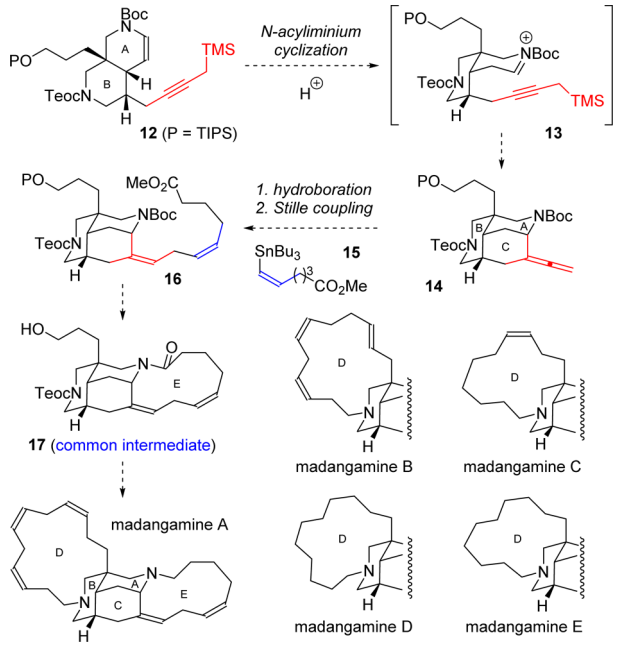
Scheme 2. Stereodivergent Syntheses of Four Skipped Dienes 11 from 1,1-Disubstituted Allene 7[a]



[a]Reagents and conditions: (a) 9-BBN, THF, rt; H_2O_2, NaOH aq; (b) $HB(Sia)_2$, THF, 0 °C; H_2O_2, NaOH aq; (c) $ClCO_2Me$, py, CH_2Cl_2, 0 °C; (d) **10**, cat. $Pd_2(dba)_3{\cdot}CHCl_3$, LiCl, DMF, rt.

Scheme 3. Plan for the Unified Total Synthesis of Madangamine Alkaloids



of **7** with 9-BBN at room temperature followed by oxidative workup induced *E*-selective hydroboration to afford allylic alcohol (***E*)-8** in 93% yield with *E*/*Z* = 12.9:1. Gratifyingly, we found that *Z*-selective hydroboration of allene **7** was possible when $HB(Sia)_2$ was employed at 0 °C, furnishing (***Z*)-8** as a single isomer (95%). Allylic alcohol (***E*)-8** was transformed to carbonate (***E*)-9**, which underwent the Migita–Kosugi–Stille coupling with both vinyl stannanes (***E*)-10** and (***Z*)-10**, providing skipped dienes (***E,E*)-11** and (***E,Z*)-11**, respectively. The geometry of the allylic carbonate was preserved in this palladium-catalyzed coupling reaction. Allylic alcohol (***Z*)-8** was also converted to skipped dienes (***Z,E*)-11** and (***Z,Z*)-11** through the same sequence. It is noteworthy that most of the skipped dienes seen in biologically active natural products contain a trisubstituted olefin, for which controlling the stereoselectivity is highly challenging (Figure 1). However, our stereodivergent method was applicable to syntheses of all four stereoisomers of skipped diene **11** with high levels of stereoselectivities. Indeed, the geometry of (***Z,E*)-11** corresponds to that of corallopyronin A.

Having a promising strategy to construct skipped dienes in hand, we took an interest in a unified total synthesis of the madangamine alkaloids (Scheme 3). The first isolation of the madangamine alkaloids was documented by Andersen and coworkers in 1994.[1a] They isolated madangamines A–E from the sponge *Xestospongia ingens* on the reefs of Madang, Papua New Guinea.[1b,c] These alkaloids share a common ABCE-tetracyclic structure but contain a variety of different D-rings. They also reported that madangamine A exhibited cytotoxicity against a variety of human cancer cell lines.[1a] Unfortunately, biological activities of other members of the madangamine family have not been tested due to the scarcity of the natural products. However, Amat recently achieved the landmark first total synthesis of madangamine D and provided a pure sample for biological studies.[8] These tests revealed that madangamine D also showed cytotoxicity against human cancer cell lines, but with a different cytotoxic spectrum. Further biological investigation of other members of the madangamine alkaloids has been anticipated through the supply of synthetic samples.

Significant issues in the total synthesis of the madangamine alkaloids are (i) construction of the unprecedented diazatricyclic ABC-ring and (ii) stereoselectivity of the skipped diene (Scheme 3). A number of solutions, including our racemic sequence,[9h] have been reported for the synthesis of the diazatricyclic core.[9] However, stereoselective formation of the skipped diene, especially for the trisubstituted *Z*-olefin, has remained an unsolved issue.[10] To achieve these two synthetic tasks, we planned to take advantage of *N*-acyliminium cyclization of a propargylsilane. Protonation of *N*-Boc enamine **12** would form highly electrophilic *N*-acyliminium ion **13**, which readily undergoes the cyclization to give the diazatricyclic structure **14**. The resulting 1,1-disubstituted allene of **14** would be converted to skipped diene **16** by *Z*-selective hydroboration with $HB(Sia)_2$ and the Migita–Kosugi–Stille coupling with *Z*-vinyl stannane **15**. Considering a universal route toward the madangamine alkaloids with their various D-rings, it would be reasonable to establish ABCE-tetracyclic compound **17** as the common intermediate, and construct the D-ring at the end of the synthesis.

The unified total synthesis of the madangamine alkaloids commenced with formation of propargylsilane **12** from aldehyde **18** (95% ee)[11] by a two-step procedure including the Ohira–Bestmann reaction[12] and alkylation with (iodomethyl)trimethylsilane (Scheme 4). We then investigated the pivotal *N*-acyliminium cyclization and subsequent construction of the skipped diene. Treatment of *N*-Boc enamine **12** with TFA in MeCN and EtOH at 50 °C successfully afforded the diazatricyclic structure **14** in 85% yield. The resulting allene group of **14** was subjected to *Z*-selective hydroboration with $HB(Sia)_2$. The reaction took place from the opposite side of the sterically hindered *N*-Boc group and gave allylic alcohol **20** as a kinetic product in 93% yield (*Z*:*E* = 20.4:1).[13] Allylic alcohol **20** was then converted to the carbonate, which underwent the Migita–Kosugi–Stille coupling[9d] with *Z*-vinyl stannane **15** to give (*Z,Z*)-

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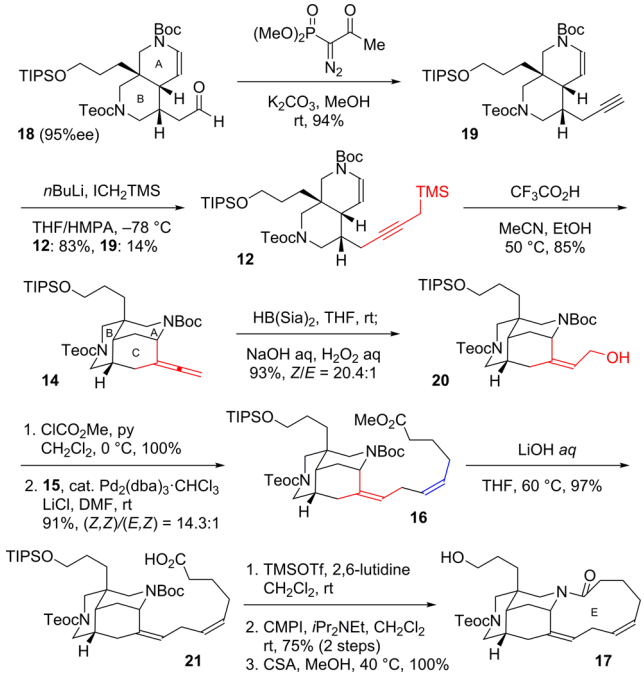
Scheme 4. Synthesis of the Common Intermediate by Stereoselective Synthesis of the Skipped Diene

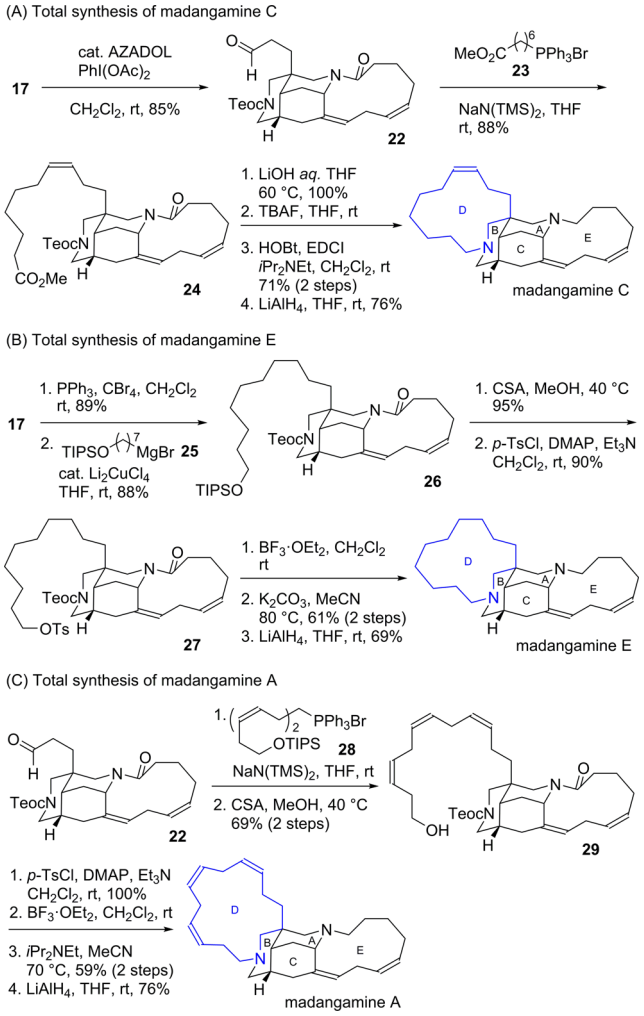


skipped diene **16** in high yield. Thus, we achieved the first stereoselective control of the skipped diene of the madangamine alkaloids as a fully functionalized intermediate. After hydrolysis of methyl ester **16**, TMSOTf-mediated removal of the Boc group provided the amino acid. After extensive investigations of the macrolactamization, the best result was obtained with the Mukaiyama reagent (2-chloro-1-methylpyridinium iodide, CMPI)[14] to form the E-ring of the madangamine alkaloids in 75% yield over two steps. The TIPS group was selectively removed in the presence of the Teoc group with CSA in MeOH at 40 °C, giving the common intermediate **17** in quantitative yield.

The remaining issue toward the unified total synthesis is the construction of a variety of macrocyclic D-rings from the common intermediate **17**. The synthesis of madangamine C was achieved through a conventional macrolactamization (Scheme 5A). Iwabuchi oxidation of **17** with AZADO[15] and subsequent Wittig reaction with **23** gave *cis*-olefin **24** bearing the D-ring carbon unit. After cleavage of the methyl and Teoc groups, the macrolactamization with EDCI and HOBt provided the pentacyclic compound in 71% yield (2 steps).[8c] Finally, the total synthesis of madangamine C was achieved by $LiAlH_4$ reduction of the two macrolactams.

The synthesis of madangamine E with the saturated D-ring was not trivial because it has no functional bias such as a *cis*-olefin to assist the macrocyclization (Scheme 5B). Indeed, the attempted macrolactamization used in the synthesis of madangamine C resulted in the formation of a significant amount of the dimer through intermolecular coupling. However, we found that the following macrocyclic alkylation was most effective in the case of madangamine E. First, the saturated D-ring carbon unit was installed by bromination of alcohol **17** and copper-mediated alkylation under Cahiez's conditions.[16] The TIPS-protected hydroxy group of **26** was then converted to tosylate **27** in two steps. After removal of the Teoc group with $BF_3{\cdot}Et_2O$, the macrocyclic alkylation took place in the presence of K_2CO_3 at 80

Scheme 5. Unified Total Synthesis of Madangamine Alkaloids



°C in 61% yield (2 steps). The total synthesis of madangamine E was accomplished by reduction of the amide carbonyl.

We then turned our attention to the synthesis of madangamine A (Scheme 5C). The skipped triene unit was installed by the Wittig reaction of aldehyde **22** and the cleavage of the TIPS group, giving **29** in 69% yield over two steps. Although a number of approaches have been reported for the construction of macrocyclic compounds, the case including the skipped triene proved to be highly challenging. For example, attempted oxidation of primary alcohol **29** to the corresponding carboxylic acid for the subsequent macrolactamization[8c] resulted in significant decomposition due to the sensitive skipped triene. However, we found that the macrocyclic alkylation was also effective for madangamine A. After the formation of the tosylate from primary alcohol **29**, cleavage of the Teoc group with $BF_3{\cdot}Et_2O$ provided the secondary amine, which underwent macrocyclic alkylation with iPr_2NEt at 70 °C. Finally, the total synthesis of madangamine A was accomplished by $LiAlH_4$ reduction of the remaining macrolactam.

In conclusion, we have developed a stereodivergent strategy to yield all four possible stereoisomers of a skipped diene by combination of the hydroboration of an allene and the Migita–Kosugi–Stille coupling. The method was successfully applied to a unified total synthesis of the madangamine alkaloids with the high stereocontrol of a skipped diene including the challenging trisubstituted olefin. Our synthetic route via a common ABCE-

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tetracyclic intermediate enabled the late-stage installation of various macrocyclic D-rings, and supplied sufficient amounts of madangamines A, C, and E for the first time for biological tests, which are now ongoing.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.7b00807.

Experimental procedures and ^{1}H and ^{13}C NMR spectra of new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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(10) Kibayashi reported that the Still−Gennari olefination of a simple bicyclic model provided the trisubstituted olefin with almost complete *Z*-selectivity (ref 9d). However, Amat disclosed that the Still−Gennari olefination showed *E*-selectivity in their model synthesis, and then developed a convergent method using the nonstabilized ylide (ref 8c). Unfortunately, the stereoselectivity was not high enough in their landmark first total synthesis of madangamine D (ref 8e, *E*/*Z* = 1:2.2).

(11) Previously, we reported racemic synthesis of aldehyde **18** (ref 9h). In this Communication, we developed a newed enantioselective route to **18** from benzylamine in 15 steps; see the Supporting Information for details.

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(13) Hydroboration of allene **14** with 9-BBN provided the *E*-allylic alcohol corresponding to madangamine F in 83% yield (*E*:*Z* = 6.1:1).

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