Access to Enantiopure Advanced Intermediates en Route to Madangamines

Celeste Are,[a] Maria Pérez,[b] Roberto Ballette,[a] Stefano Proto,[a] Federica Caso,[a] Nihan Yayik,[a] Joan Bosch,[a] and Mercedes Amat*[a]

Abstract: The synthesis of enantiopure ABCE and ABCD tetracyclic advanced intermediates en route to madangamine alkaloids and studies for the construction of the triunsaturated 15-membered D ring of madangamine B and the saturated 13-membered D ring of madangamine E are reported.

Introduction

Madangamines are a small group of pentacyclic diamine alkaloids isolated[1] from marine sponges belonging to the order Haplosclerida.[2] Six members of this family have been identified so far. Natural madangamines A and F have exhibited in vitro cytotoxicity against a variety of human cancer cell lines. Structurally, madangamines A–E share a bridged C_5N-C_5N-C_6 diazatricyclic core (rings ABC) and the eastern 11-membered ring (ring E), which incorporates two skipped (*Z*,*Z*)-configurated double bonds, one of them trisubstituted. However, they differ in the macrocyclic western D ring, both in size (13-, 14-, or 15-membered) and in the number (0, 1, or 3) and position of double bonds. Madangamine F possesses four double bonds in a 13-membered E ring and an additional hydroxy substituent at C-4 of the core ABC nucleus (Figure 1).

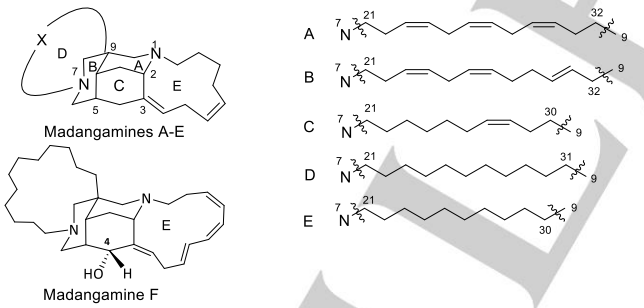

Figure 1. Madangamine alkaloids.

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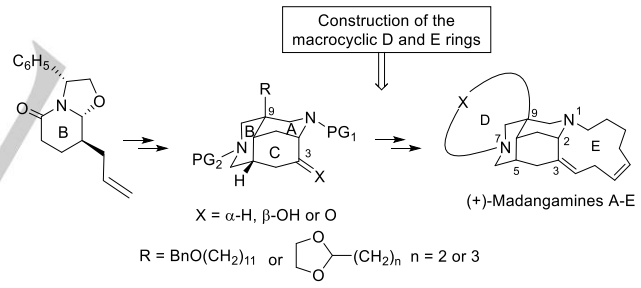
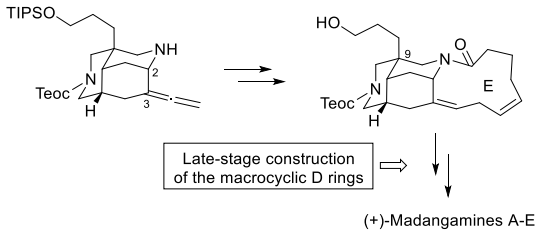
Although the isolation of madangamines A–E was reported in the 1990s[1a,b] and since then these alkaloids have been the subject of numerous synthetic studies,[3] the first total (enantioselective) synthesis of a member of this group, (+)-madangamine D, was not reported until 2014.[4] Our approach involved the use of a bridged diazatricyclic platform (rings ABC) containing the appropriate functionality, at C-3 and the C-9 substituent, for the subsequent assembly of the peripheral macrocyclic D and E rings. In this context, using a phenylglycinol-derived oxazolopiperidone lactam as the starting enantiomeric scaffold, we have developed a flexible route for the generation of the aforementioned key diazatricyclic intermediates.[3g,h,4,5] We have also developed a straightforward two-step sequence to build the 11-membered E ring, in which the skipped (*Z*,*Z*)-octadienoate chain on C-3 needed for the final macrolactamization is incorporated with acceptable stereoselectivity by using a C_8 nonstabilized ylide.[4-6]
The viability of our general strategy was recently demonstrated by the formal synthesis of (+)-madangamine A, which features a skipped (*Z*,*Z*,*Z*)-unsaturated 15-membered D ring.[5]



Scheme 1. Our general strategy for the synthesis of madangamine alkaloids.

Also recently, outstanding synthetic work by Sato and Chida resulted in a unified total synthesis of (+)-madangamines A–E.[7] Their strategy is based on a late-stage construction of the macrocyclic D ring from a common advanced ABCE tetracyclic intermediate bearing a C-9 hydroxypropyl chain. Two crucial steps of the synthesis are the intramolecular *N*-acyliminium cyclization of a propargylsilane to assemble the vinylidene-substituted diazatricyclic ABC ring core and the stereoselective hydroboration of the 1,1-disubstituted allene to install a C-3 (*Z*)-hydroxyethylidene substituent. A subsequent Pd-coupling of the corresponding methyl carbonate with an appropriate C_6 (*Z*)-vinylstannane generates the skipped (*Z*,*Z*)-octadienoate chain required for the closure of the E ring (Scheme 2). All synthetic madangamines A–E showed antiproliferative effects against a variety of human cancer cell lines. These syntheses shed valuable light on the role of the different D rings in the bioactivity.



Scheme 2. The common ABCE tetracyclic intermediate in the Sato–Chida unified total synthesis of madangamines.

The comprehensive work of Sato and Chida prompted us to disclose our recent studies in the field of madangamines. They include the assembly of the triunsaturated 15-membered D ring of madangamine B and the saturated 13-membered D ring of madangamine E, as well as the synthesis of enantiopure ABCE and ABCD tetracyclic advanced intermediates en route to the alkaloids of this group.

Results and Discussion

Synthesis of ABCE tetracyclic precursors of madangamines A–E

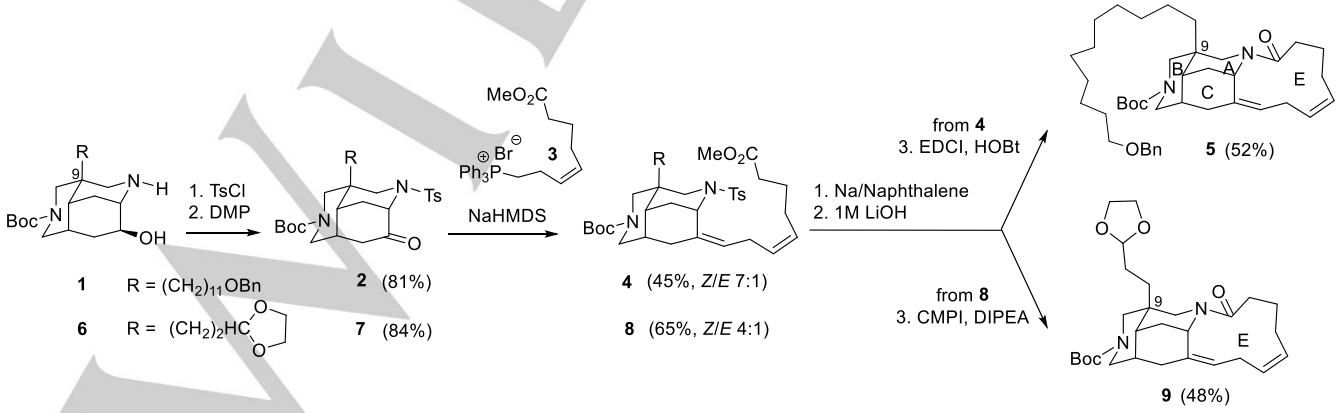
Our synthesis of (+)-madangamine D[4] involved the closure of ring E from an ABCD tetracyclic intermediate. Taking advantage of the previously reported[3g] tricyclic intermediate **1**, we envisaged a complementary approach to (+)-madangamine D, via the ABCE tetracyclic precursor **5**, which bears the C-9 benzyloxyundecyl substituent required for the final closure of the D ring.[8]

The assembly of the (*Z*,*Z*)-skipped E-ring was accomplished with excellent stereoselectivity following our previously developed Wittig/macrolactamization sequence using the eight-carbon ylide derived from phosphonium salt **3**.[9] Thus, after *N*-tosylation of **1** and Dess-Martin periodinane oxidation of the resulting tricyclic alcohol, Wittig reaction of ketone **2** with the ylide generated from **3** satisfactorily gave the expected (*Z*,*Z*)-diene **4** in 45% yield as a 7:1 mixture of *Z*/*E* isomers. Remarkably, the stereoselectivity of this reaction was higher than that observed (2.2:1) in a similar Wittig reaction from an ABCD tetracyclic ketone during our synthesis of (+)-madangamine D.[4] Removal of the *N*-tosyl protecting group, followed by alkaline hydrolysis of the ester function and EDCI-promoted macrolactamization of the resulting crude amino acid, provided tetracyclic lactam **5**, an immediate synthetic precursor of (+)-madangamine D[8] (Scheme 3).

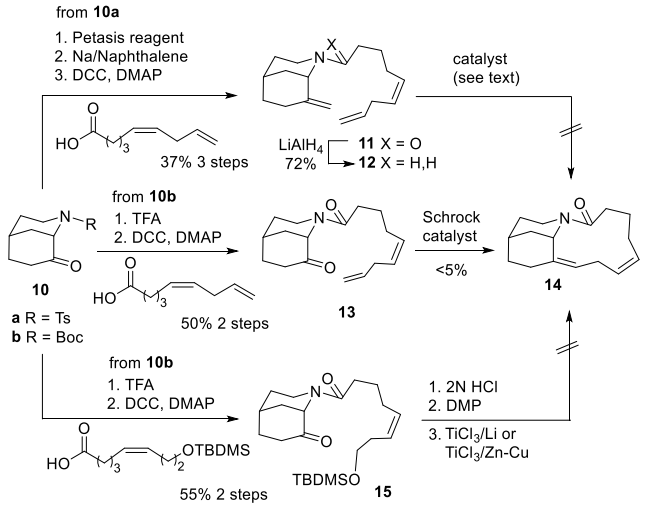
The above satisfactory results spurred us to apply the same methodology for the construction of the E ring from tricyclic ketone **7**, an intermediate in our synthesis of (+)-madangamine A.[5] After Wittig reaction of **7** with the ylide derived from **3** (65%; *Z*/*E*, 4:1 ratio), the closure of the E ring was accomplished in 48% overall yield from **8**, providing the C-9 3,3-(ethylenedioxy)propyl substituted tetracycle **9**, a potential ABCE tetracyclic intermediate for the synthesis of (+)-madangamines A–E. The corresponding *N*-Teoc alcohol and (in some cases) aldehyde are common intermediates in the Sato–Chida unified total synthesis of madangamine alkaloids.[7]

In an attempt to develop alternative procedures for the closure of the E ring common to madangamines A–E, we focused our attention on macroannulations from model azabicyclic ketones **10**, based on olefin ring-closing metathesis (RCM),[10] carbonyl–olefin metathesis,[11] or McMurry[12] reactions.

Scheme 4 outlines the preparation of the required substrates, by *N*-deprotection of **10** followed by acylation with the appropriate unsaturated acid. Unfortunately, all attempts to induce RCM, using a variety of catalysts (Grubbs I and II, Hoveyda-Grubbs, Schrock), either from amide **11** or amine **12** were ineffective. In some runs, products arising from a cross-metathesis were detected. Similar disappointing results were obtained in the cyclization of **13** using the Schrock catalyst, although in this case trace amounts of the tricyclic lactam **14** were detected. Nor did the desired cyclization occur when the unstable aldehyde resulting from deprotection/oxidation of the silyl derivative **15** was subjected to McMurry reaction conditions.



Scheme 3. Access to ABCE tetracyclic precursors of (+)-madangamines A–E.

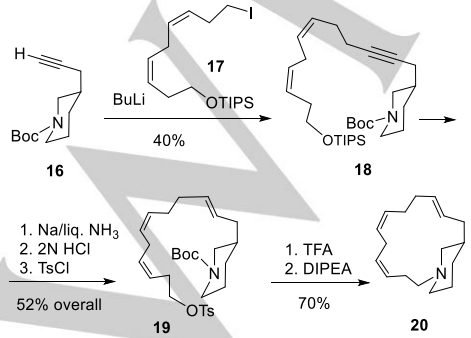


Scheme 4. Model studies on the closure of the E ring.

Studies on the construction of the D ring of madangamine B

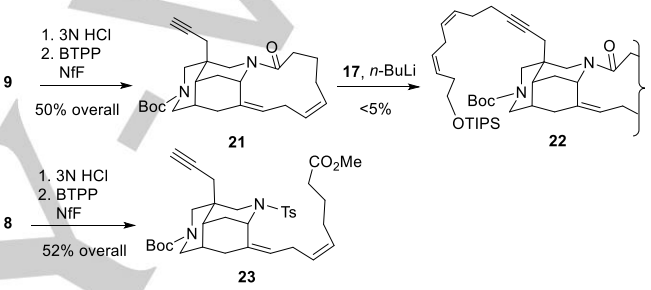
Madangamine B features a 15-membered D ring embodying a skipped (*Z*,*Z*)-diene and an isolated double bond. It differs from madangamine A only in the position and stereochemistry of one double bond (*Z* C^{29}=C^{30} in madangamine A but *E* C^{30}=C^{31} in madangamine B). To date, there is only one report on the construction of the D ring of madangamine B. In the Sato–Chida synthesis of this alkaloid[7b] the (*Z*,*Z*,*E*)-dodecatriene chain needed for the ring closure was assembled stepwise from a C-9 3-oxopropyl substituent by a sequence involving a one-carbon dehomologation, a Takai olefination, and a Wittig reaction (3C – 1C + 4C + 6C strategy).

Using a model 3-(2-propynyl)piperidine derivative, we devised a straightforward procedure based on the coupling reaction of an alkyne with an unactivated nonadienyl halide (3C + 9C strategy). Although the Pd- or Ni-catalyzed Sonogashira coupling[13] of alkyne **16**[14] with the unactivated halide **17**[15] took place in only moderate yield (<25%),[16] alkylation under basic conditions (*n*-BuLi, THF, reflux, 24h) afforded the desired dienyne **18** in 40% yield. After stereoselective Na/liq. NH_3 reduction of the alkyne to an (*E*)-alkene and exchange of the TIPS protecting group for a tosylate, removal of the Boc group in the resulting (*Z*,*Z*,*E*)-triene **19** followed by intramolecular alkylation provided compound **20**, the AD ring moiety of madangamine B (Scheme 5).



Scheme 5. Model studies for the construction of the D ring of madangamine B.

In view of the above results, we decided to apply the methodology to the tetracyclic alkynyl derivative **21**, which was prepared in 50% overall yield from the advanced intermediate **9** in two steps: acid hydrolysis of the acetal function and subsequent reaction of the resulting somewhat unstable aldehyde with a phosphozene base in the presence of nonafluorobutane-1-sulfonyl fluoride (NfF)[17]. Unfortunately, the *n*-BuLi-promoted coupling of **21** with the unactivated iodide **17** under the previously established conditions occurred with abundant decomposition, affording the desired dienyne **22** in negligible yield (Scheme 6). Extensive decomposition, or recovery of the starting material, was also observed in the attempts to induce the coupling from tricyclic alkyne **23**, which was prepared from **8** by the procedure previously used for **21**. The strong nucleophilic character of *n*-BuLi combined with the presence of a lactam or ester carbonyl group could account for the failure of the above coupling reactions.

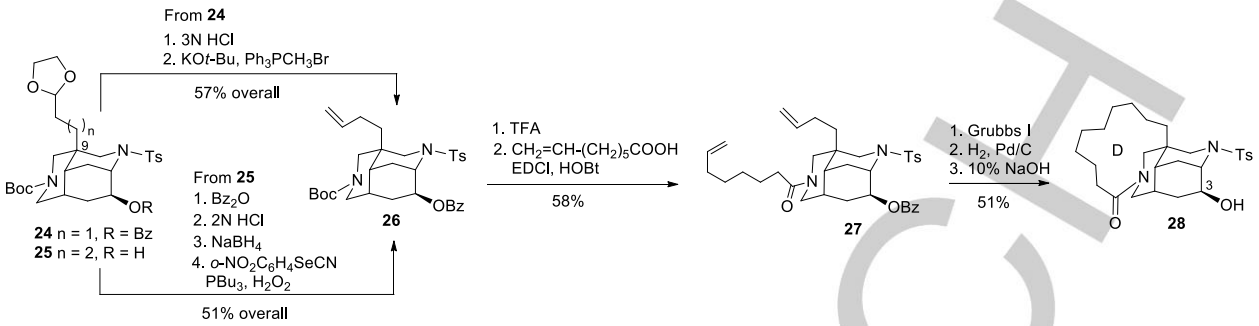


Scheme 6. Attempted construction of the D ring of madangamine B from tricyclic or tetracyclic precursors.

Construction of the D ring of madangamine E

In the reported synthesis of (+)-madangamine E, the saturated 13-membered D ring was constructed by copper-mediated alkylation of a C-9 bromopropyl-substituted ABCE tetracyclic derivative with a C_7-Grignard reagent and a final macrocyclic alkylation.[7]

Illustrating the versatility of the tricyclic scaffolds **24** and **25**, key intermediates in our syntheses of madangamines A[5] and D,[4] respectively, we have developed an alternative procedure for the closure of the D ring of madangamine E, via the 3-butenyl derivative **26**, using a ring-closing metathesis reaction[18] (Scheme 7). After acid hydrolysis of the acetal function, the terminal double bond of **26** was introduced by a Wittig reaction from **24** or following the Grieco dehydration protocol via a C-9 4-hydroxybutyl derivative starting from **25**. Removal of the *N*-Boc protecting group followed by acylation with 7-octenoic acid provided diene **27**, which underwent RCM with excellent yield using the Grubbs 1st generation catalyst. Hydrogenation of the resulting *Z*/*E* mixture of alkenes (2:1 ratio) followed by deprotection of the hydroxy substituent led to alcohol **28**, an advanced ABCD tetracyclic intermediate towards (+)-madangamine E.



Scheme 7. Access to an ABCD tetracyclic intermediate for the synthesis of (+)-madangamine E.

Conclusions

The synthesis of the ABCE tetracyclic derivatives **5** and **9** from ABC tricyclic precursors further illustrates the usefulness of the straightforward Wittig/macrolactamization sequence we had developed for the assembly of the *Z*,*Z*-unsaturated 11-membered E ring shared by madangamines A–E. Alternative strategies for the closure of the E ring, involving RCM, carbonyl-olefin metathesis, or McMurry reactions met with no success. Tetracyclic intermediate **5** can be envisaged as an immediate synthetic precursor of madangamine D, whereas tetracyclic derivatives closely related to acetal **9** have been used as common intermediates in the Sato–Chida unified synthesis of madangamines A–E.

On the other hand, although a procedure for the construction of the (*Z*,*Z*,*E*)-unsaturated D ring characteristic of madangamine B has been established operating from a model piperidine system, its application to carbonyl-bearing ABC tricyclic or ABCE tetracyclic derivatives was unsuccessful.

Finally, the ABC tricyclic intermediates **24** and **25**, each one bearing a different functionalized chain at C-9, have served as platforms for the construction of the saturated D ring of madangamine E using a ring-closing metathesis reaction. Taking advantage of the functionalization at C-3 in the advanced tetracyclic intermediate **28**, the E ring could be assembled using the methodology applied in the above preparation of ABCE tetracycles **5** and **9** as well as previously in our synthesis of madangamines A and D.

All the above results confirm the viability and versatility of our general strategy for the synthesis of madangamine alkaloids. We now have in hand efficient procedures for the construction of the functionalized ABC core of madangamines with appropriate substituents at C-9 for the subsequent assembly of the peripheral D and E rings.

Acknowledgements

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Keywords: alkaloids • macrocycles • madangamines • total synthesis • skipped dienes

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[15] Iodide **17** was prepared by treatment of the corresponding mesylate[7] with NaI.

[16] Reaction conditions: 1,3-bis(1-adamantyl)imidazolium chloride, $[(\pi\text{-allyl})PdCl]_2$, CuI, Cs_2CO_3 or $[(^{Me}NN_2)NiCl]$, CuI, Cs_2CO_3, as reported by a) M. Eckhardt, C. G. Fu, *J. Am. Chem. Soc*. **2003**, *125*, 13642–13643; b) G. Altenhoff, S. Wurtz, F. Glorius, *Tetrahedron Lett.* **2006**, *47*, 2925–2928; c) O. Vechorkin, D. Barmaz, V. Proust, X. Hu, *J. Am. Chem. Soc.* **2009**, *131*, 12078–12079; d) X. Hu, *Chimia* **2010**, *64*, 231–234.

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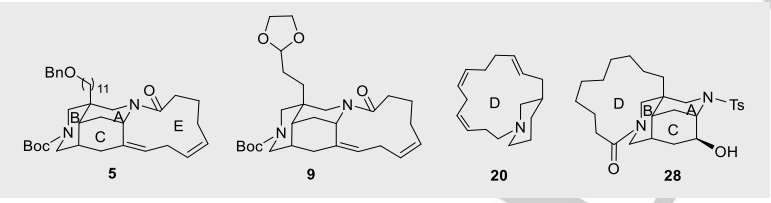

Valuable tetracyclic synthetic precursors of (+)-madangamines A–E and model studies for the construction of the triunsaturated 15-membered D ring of Madangamine B are reported.

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