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 C6-N-C6-N-C6 diazatricyclic core (rings ABC) and the eastern 11-membered ring (ring E), which incorporates two skipped (Z,Z)-configured 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).

![Madangamine A-E](image)

**Figure 1.** Madangamine alkaloids.

Although the isolation of madangamines A–E was reported in the 1990s,[1,2,3] and since then these alkaloids have been the subject of numerous synthetic studies,[4] the first total (enantioselective) synthesis of a member of this group, (+)-madangamine D, was not reported until 2014.[5] 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.[3a,b,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 macrolactamation is incorporated with acceptable stereoselectivity by using a C6 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)-unsaturated 15-membered D ring.[6]

Also recently, outstanding synthetic work by Sato and Chida resulted in a unified total synthesis of (+)-madangamine 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 C6 (Z)-vinylstannane generates the skipped (Z,Z)-octadienoate chain required for the closure of the E ring (Scheme 2).

![Scheme 1. Our general strategy for the synthesis of madangamine alkaloids.](image)
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\(^{[9]}\) involved the closure of ring E from an ABCD tetracyclic intermediate. Taking advantage of the previously reported\(^{[9]}\) tricyclic intermediate 1, we envisaged a complementary approach to (+)-madangamine D, via the ABCE tetracyclic precursor 5, which bears the C-9 benzylxoyundecyl 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.\(^{[9]}\) 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\(^{[9]}\) (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.\(^{[9]}\) 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.
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 C9=C20 in madangamine A but E C30=C31 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[70] 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 + 4C 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[71] 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 diene 18 in 40% yield. After stereoselective Na/liq. NH₂ 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).

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 phosphazene base in the presence of nonfluorobutane-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 diene 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.

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 C7-Grignard reagent and a final macrocyclic alkylation.[7]

Illustrating the versatility of the tricyclic scaffolds 24 and 25, key intermediates in our syntheses of madanganamines 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-butynyl 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.
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 madangamines A–E produced 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

Financial support from the MINECO/FEDER, Spain (Projects CTQ2015-65384 R and RTI2018-09974-B-100) is gratefully acknowledged. We also acknowledge the networking contribution from the COST Action CM1407.

Keywords: alkaloids • macrocycles • madangamines • total synthesis • skipped dienes
[6] S. Proto, M. Amat, M. Pérez, R. Ballette, F. Romagnoli, A. Mancinelli, J. Bosch, Org. Lett. 2012, 14, 3916–3919.

[7] a) T. Suto, Y. Yanagita, Y. Nagashima, S. Takikawa, Y. Kurosu, N. Matsuo, T. Sato, N. Chida, J. Am. Chem. Soc. 2017, 139, 2952–2955; b) T. Suto, Y. Yanagita, Y. Nagashima, S. Takikawa, Y. Kurosu, N. Matsuo, K. Miura, S. Simizu, T. Sato, N. Chida, Bull. Chem. Soc. Jpn. 2019, 92, 545–571.

[8] For the closure of the 14-membered D ring from a C-9 benzyloxyundecyl-substituted ABC tricyclic derivative, see ref. [3h].

[9] J. Sandri, J. Viala, J. Org. Chem. 1995, 60, 6627–6630.

[10] L. Yet in Org. React. Vol. 89, (Ed.: S. E. Denmark), John Wiley & Sons, 2016, pp. 1–1342.

[11] L. Ravindar, R. Lekkala, K. P. Rakesh, A. M. Asiri, H. M. Marwani, H.-L. Qiu, Org. Chem. Front. 2018, 5, 1381–1391.

[12] T. Takeda, A. Tsubouchi in Org. React. Vol. 82, (Ed.: S. E. Denmark), John Wiley & Sons, 2013, pp. 1–470.

[13] R. Chinchilla, C. Nájera, Chem. Rev. 2007, 107, 874–922.

[14] Alkyne 16 was prepared in 65% overall yield by alkylation of 2-piperidone with 3-bromo-1-(trimethylsilyl)-1-propyne, followed by LiAlH₄ reduction, reaction with Boc₂O, and desilylation.

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

[16] Reaction conditions: 1,3-bis(1-adamantyl)imidazolium chloride, [[η3-allyl]PdCl]₂, CuI, Cs₂CO₃ or [[η3NN2]NiCl], CuI, Cs₂CO₃, 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.

[17] M. Lyapkalo, M. A. K.; Vogel, E. V. Bollukhina, J. Vavřík, Synlett 2009, 558–561.

[18] For model studies on the construction of the D ring of madangamine E using a ring-closing metathesis reaction, see refs. [3f] and [6].
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.