COMMUNICATION

Enantioselective Formal Synthesis of (+)-Madangamine A

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An enantioselective formal synthesis of the marine alkaloid madangamine A using phenylglycinol-derived lactam 1 as the starting enantiomeric scaffold is reported. The synthesis involves the construction of the C-9 substituted diazatricyclic ABC core and the final closure of D and E rings from the polyunsaturated skipped intermediate 19.

Madangamine alkaloids[1] are a small family (six members isolated so far) of complex marine natural products isolated from sponges of the order Haplosclerida.[2] They are biogenetically derived from partially reduced bis-3-alkylpyridine macrocycles through a pathway that involves a skeletal rearrangement of ingenamine-type precursors.[3] Structurally, madangamines are pentacyclic diamines embodying a diazatricyclic core (ABC rings) and two peripheral macrocyclic rings. In madangamines A–E, ring E is an 11-membered ring that incorporates a (*Z*,*Z*)-skipped diene with a trisubstituted double bond, whereas ring D differs in each one, both in size (13-, 14-, or 15-membered) and in the number and position of double bonds. Madangamine F features a tetraunsaturated 13-membered E ring and an additional C-4 hydroxy substitutent (Figure 1). Madangamines A, D, and F have exhibited significant in vitro cytotoxicity against a variety of human cancer cell lines. The unique structure of madangamines has attracted considerable synthetic interest, resulting in a number of model studies for the construction of the diazatricyclic ABC core[4] and for the assembly of the macrocyclic E[5] and D rings.[6] These studies have culminated in the first total enantioselective syntheses of madangamine D[7] and madangamines A, C, and E.[8] Our synthesis of (+)-madangamine D allowed the absolute configuration of this alkaloid family to be confirmed.[7]

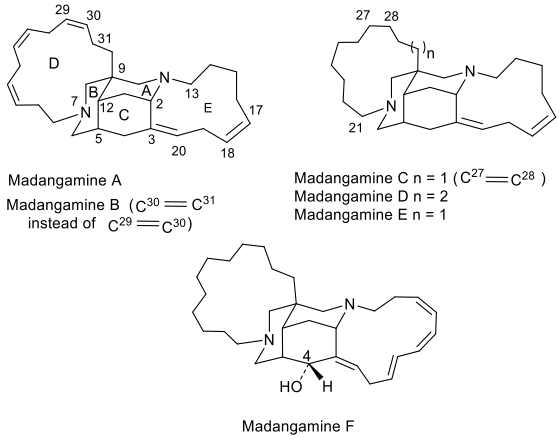

Fig. 1 Alkaloids of the madangamine group.

We present herein an enantioselective formal synthesis of (+)-madangamine A. Our general synthetic approach to mandangamines takes advantage of the versatility of phenylglycinol-derived lactams as enantiomeric scaffolds[9] to build enantiopure complex polycyclic nitrogen-containing derivatives.[10] The initial construction of an appropriately substituted and functionalized diazatricyclic platform embodying rings ABC of the alkaloids is followed by the assembly of the peripheral macrocyclic D and E rings.

For the synthesis of the target madangamine A, starting from the same bicyclic lactam **1** as in our previous synthesis of madangamine D, we initially envisaged the generation of a C-9[11] 3-butynyl-substituted diazatricylic intermediate **A**, which would allow the incorporation of the unsaturated eight-carbon fragments, on C-29 and C-3, needed for the construction of the 15-membered D ring and the 11-membered E ring (Scheme 1).

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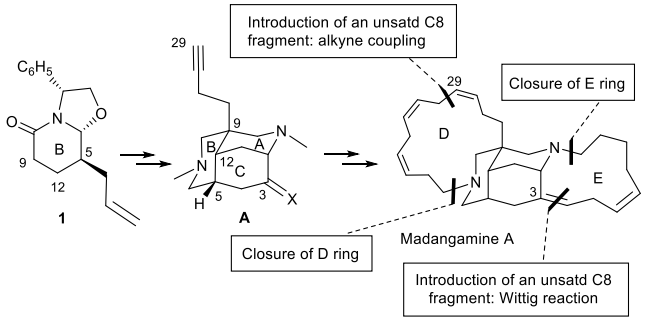


Scheme 1 Synthetic strategy.

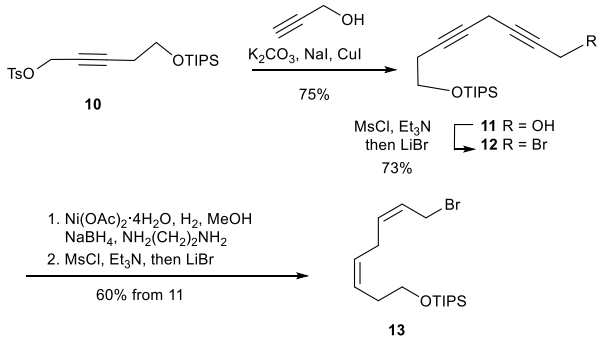
Scheme 2 outlines the preparation of the key intermediate **8** and our initial attempts to incorporate the skipped (*Z*,*Z*,*Z*)-dodecatriene chain required for the closure of the D ring. Lactam **1** was stereoselectively converted to *cis*-octahydroisoquinolone **2** in five steps and 62% overall yield, as previously reported.[12] This multistep sequence involves the initial generation of an unsaturated lactam bearing an additional methoxycarbonyl activating substituent, a stereoselective conjugate addition of an allyl group to create the C-12 stereocenter, a ring-closing metathesis reaction to construct the carbocyclic C-ring, and a stereoselective alkylation of the β-dicarbonyl moiety to generate the C-9 quaternary stereocenter.

After reductive cleavage of the benzylic C–N bond, simultaneous $LiAlH_4$ reduction of the hemiaminal and carbonyl groups, and *N*-Boc protection, the closure of the piperidine A ring from *cis*-octahydroisoquinoline **3** was efficiently accomplished (54% overall yield) via an intermediate azido epoxide generated by a mesylation-azidation-epoxidation sequence. Reduction of the azido group under Staudinger reaction conditions provided a transient amino epoxide that underwent smooth in situ cyclization to give a tricyclic amino alcohol, which was protected as the *N*-tosyl derivative **5**.

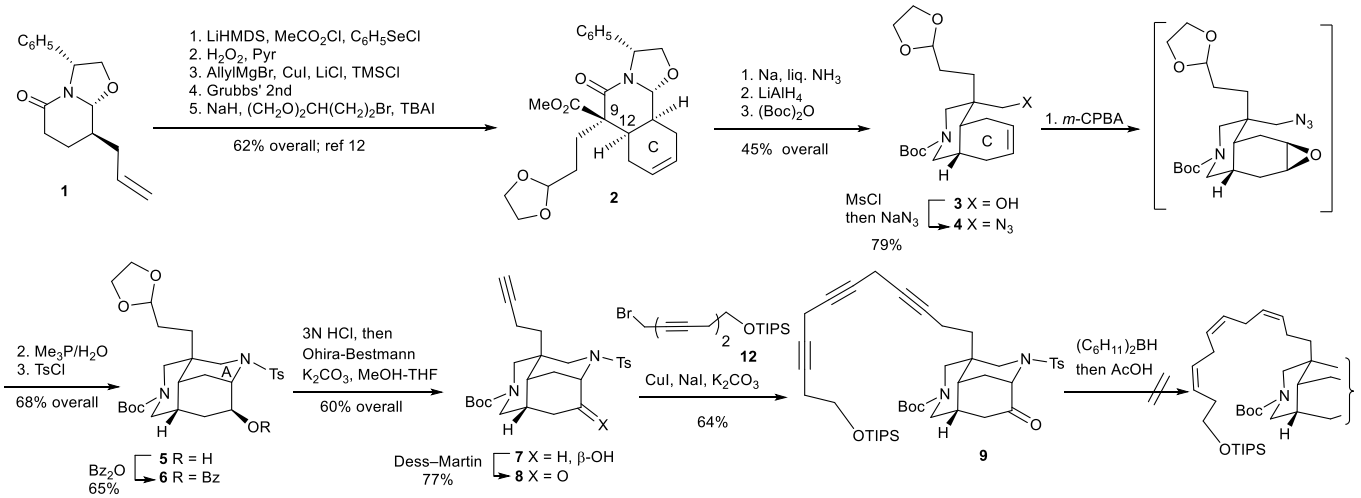
The next step of the synthesis was the generation of the alkynyl moiety needed for the incorporation of the eight-carbon fragment en route to the closure of the D ring. After protection of the hydroxy function of **5** as a benzoate (**6**) and acid hydrolysis of the acetal group, homologation of the resulting crude aldehyde with the Ohira-Bestmann reagent (dimethyl 1-diazo-2-oxopropylphosphonate) in the presence of potassium carbonate and methanol generated the required butynyl appendage.[13] The basic reaction conditions of the homologation reaction also brought about deprotection of the hydroxy group, leading to alkynyl alcohol **7**, which was then oxidized to tricyclic ketone **8**.

In the light of our model studies from a simple (3-butynyl)piperidine,[5b] the construction of the skipped[14] (*Z*,*Z*,*Z*)-unsaturated 15-membered ring of madangamine A was attempted by cross-coupling of terminal alkyne **8** with octadiynyl bromide **12** and subsequent stereoselective reduction of the resulting triyne derivative **9**. Unfortunately, although the coupling reaction satisfactorily afforded the skipped triyne **9**, the hydroboration/protonolysis of **9** with dicyclohexylborane and AcOH resulted in the degradation of the starting material, in contrast with the results obtained in the model series.

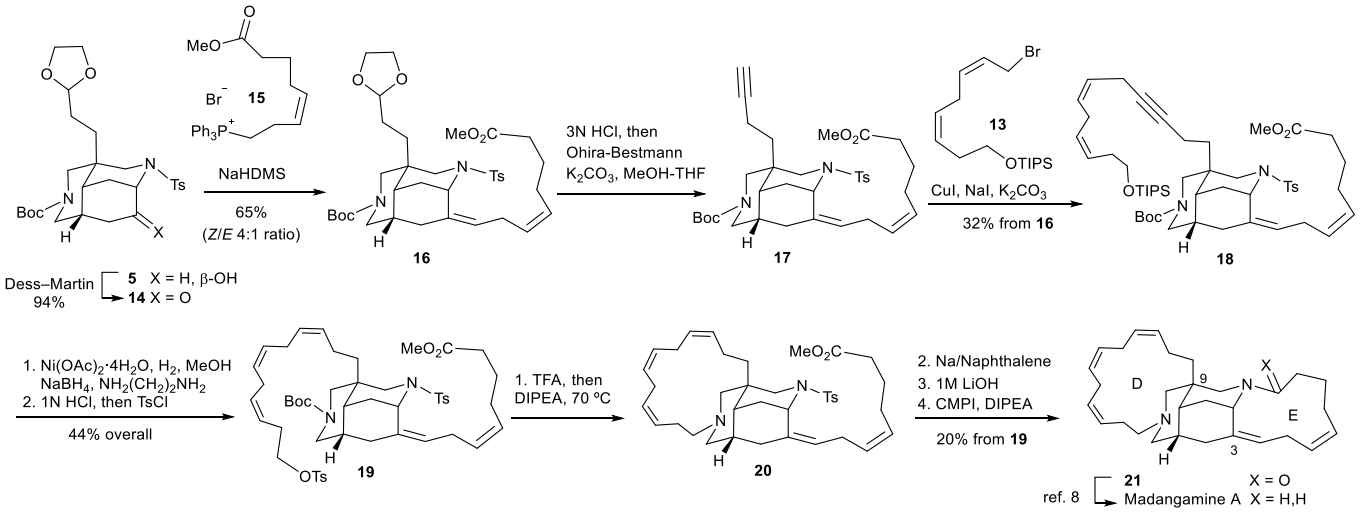
The required octadiyne **12** was prepared in excellent overall yield by cuprous iodide catalyzed coupling of propargyl alcohol with the orthogonally protected pentynediol **10**, followed by functional group interconversions, as outlined in Scheme 3.[15]



Scheme 3 Synthesis of the skipped octadiyne **12** and octadiene **13**.



Scheme 2 First approach to (+)-madangamine A.



Scheme 4 Formal synthesis of (+)-madangamine A.

To avoid the manipulation of highly unstable polyacetylenic intermediates, we devised an alternative approach in which the eight-carbon fragment used in the cross-coupling reaction with the terminal alkyne would be a skipped octadiene. To also minimize the manipulation of sensitive skipped dienyne or triene intermediates, the coupling reaction was performed from a more advanced intermediate already incorporating the octadienoate chain required for the closure of the E ring.

For this reason, tricyclic alcohol **5** was oxidized to ketone **14**, which was treated under strictly anhydrous conditions with the nonstabilized ylide generated from the phosphonium salt **15**,[16] previously used in our synthesis of madangamine D (Scheme 4). The resulting inseparable mixture (*Z*,*Z*/*E*,*Z*, 4:1 ratio) of dienes **16** was then converted to C-9 butynyl derivative **17** following the previously used hydrolysis/Ohira–Bestmann homologation sequence.

The skipped *Z*,*Z*-octadienyl bromide **13**, required for the cross-coupling reaction with **17**, was stereoselectively prepared from diyne **11** as shown in Scheme 3. A partial *cis*-hydrogenation of **11** with Brown's P2-Ni catalyst (generated by in situ reduction of nickel acetate tetrahydrate with sodium borohydride in methanol in a hydrogen atmosphere),[17] in the presence of 1,2-diaminoethane as a catalyst modifier to increase the *cis*-selectivity, afforded a *Z*,*Z*-dienyl alcohol intermediate, which was converted to bromide **13** via the corresponding mesylate.

As expected, the cuprous iodide catalyzed coupling of terminal alkyne **17** with allyl bromide **13**, followed by stereoselective reduction of the resulting dienyne **18** using the Brown P2-Ni catalyst system, generated the required skipped *Z*,*Z*,*Z*-triene moiety.[18] A subsequent exchange of the TIPS protecting group for tosyl, able to act as a leaving group, provided the advanced intermediate **19**, which incorporates all the skeletal atoms of the target madangamine A.

At this point, only the closure of the macrocyclic D and E rings was required to complete the synthesis. This was accomplished without purification of the potentially sensitive polyunsaturated intermediates. Closure of the D ring was effected by intramolecular alkylation, after acid removal of *N*-Boc protecting group. Finally, deprotection of the *N*-tosyl group, followed by alkaline hydrolysis and macrolactamization of the resulting crude amino acid, furnished the known pentacyclic lactam **21**, which had previously been converted[8] to (+)-madangamine A.

In conclusion, the above synthesis of (+)-madangamine A confirms the viability of the general strategy we are exploring to access the various members of this alkaloid family, using phenylglycinol-derived lactam **1** as the common starting enantiomeric scaffold. The tactically versatile functionality of **1** enables the elaboration of the diazatricyclic core (rings ABC) of the target alkaloids, which serves as a platform to construct the macrocyclic D and E rings. Thus, the macrocyclic E ring common to madangamines A-E can be built taking advantage of the C-3 carbonyl group using a straightforward Wittig/macrolactamization sequence with an eight-carbon ylide, whereas the different D rings present in madangamines can be assembled by manipulating the length and adjusting the functionality of the chain at the quaternary C-9 stereocenter. In the synthesis of madangamine A, the assembly of the triunsaturated 15-membered D ring is accomplished by cyclization of a skipped (*Z*,*Z*,*Z*)-dodecatrienyl tosylate **19**, generated from a diazatricyclic intermediate bearing a 3-butynyl substituent at C-9.

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Conflicts of interest

There are no conflicts to declare.

Notes and references

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