

# Model Studies on the Synthesis of Madangamine Alkaloids. Assembly of the Macrocyclic Rings

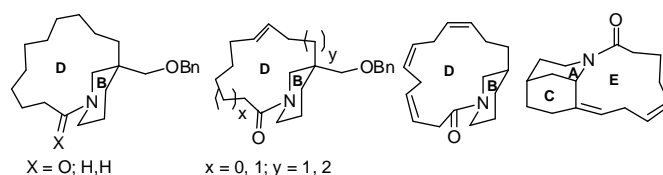
Stefano Proto, Mercedes Amat,<sup>\*</sup> Maria Pérez, Roberto Ballette, Federica Romagnoli, Andrea Mancinelli, and Joan Bosch

Laboratory of Organic Chemistry, Faculty of Pharmacy, and Institute of Biomedicine (IBUB), University of Barcelona, 08028-Barcelona, Spain

amat@ub.edu

Received Date (will be automatically inserted after manuscript is accepted)

## ABSTRACT



Using simplified model derivatives, the assembly of the macrocyclic rings of madangamines, including the 13- and 14-membered D rings of madangamines C-E, the all-*cis*-triunsaturated 15-membered D ring of madangamine A, and the (*Z,Z*)-unsaturated 11-membered E ring common to madangamines A-E, has been studied.

The marine sponges belonging to the order Haplosclerida are a source of numerous polycyclic alkaloids with a variety of skeletal structures (manzamines, sarains, nakadomarin A, ingenamines, madangamines, among others), which share a common biogenetic origin from oligomeric macrocycles bearing a partially reduced 3-alkylpyridine moiety.<sup>1</sup>

In particular, madangamines (Figure 1) possess an unprecedented diazatri-cyclic core (rings A-C) and two macrocyclic rings connecting N-7 with C-9 (ring D) and N-1 with C-3 (ring E).<sup>2</sup> Although significant *in vitro* cytotoxicity against a number of cancer cell lines has been

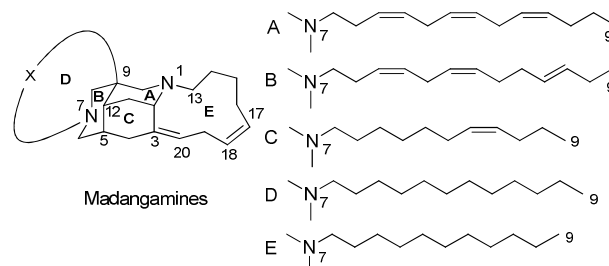


Figure 1. Madangamine alkaloids

<sup>1</sup> (a) Andersen, R. J.; van Soest, R. W. M.; Kong, F. In *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Pergamon: Oxford, U. K., 1996; Vol. 10, pp 301–355; (b) Berlinck, R. G. S. *Top Heterocycl. Chem.* **2007**, *10*, 211–238; (c) Kornprobst, J.-M. In *Encyclopedia of Marine Natural Products*; Wiley:Weinheim, 2010, Vol. 2, pp 683–723.

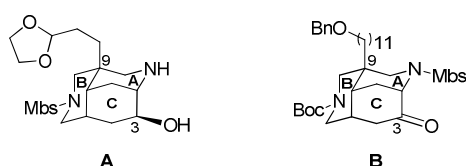
<sup>2</sup> Isolation: (a) Kong, F.; Andersen, R. J.; Allen, T. M. *J. Am. Chem. Soc.* **1994**, *116*, 6007–6008; (b) Kong, F.; Graziani, E. I.; Andersen, R. J. *J. Nat. Prod.* **1998**, *61*, 267–271; (c) de Oliveira, J. H. H. L.; Nascimento, A. M.; Kossuga, M. H.; Cavalcanti, B. C.; Pessoa, C. O.;

reported for some members of this series, further pharmaceutical research on these alkaloids has been hampered by the low quantities of available samples. As

Moraes, M. O.; Macedo, M. L.; Ferreira, A. G.; Hajdu, E.; Pinheiro, U. S.; Berlinck, R. G. S. *J. Nat. Prod.* **2007**, *70*, 538–543.

no total syntheses of madangamine alkaloids have been reported to date,<sup>3</sup> the development of synthetic routes to madangamines or synthetic analogs remains a challenging goal.

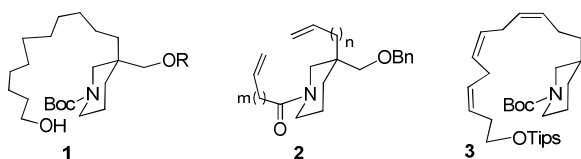
In previous work<sup>4</sup> we have reported a synthetic sequence for the enantioselective assembly of the advanced diazatricyclic intermediates **A** and **B** *en route* to madangamines, bearing rings ABC with the appropriate substitution and functionality to construct the macrocyclic D and E rings of these alkaloids (Figure 2).



**Figure 2.** Advanced enantiopure diazatricyclic intermediates *en route* to madangamines

In this letter we report the construction of saturated and (poly)unsaturated 13-, 14-, and 15-membered rings (the western D ring of madangamines) as well as the (*Z,Z*)-unsaturated 11-membered E ring common to madangamines A-E.

As model systems for the closure of the D ring we used substituted piperidines **1-3** (Figure 3), which would allow us to perform macrocyclization reactions by reductive amination or lactamization (from **1** and **3**), or by ring-closing olefin metathesis (from **2**).



**Figure 3.** Model systems

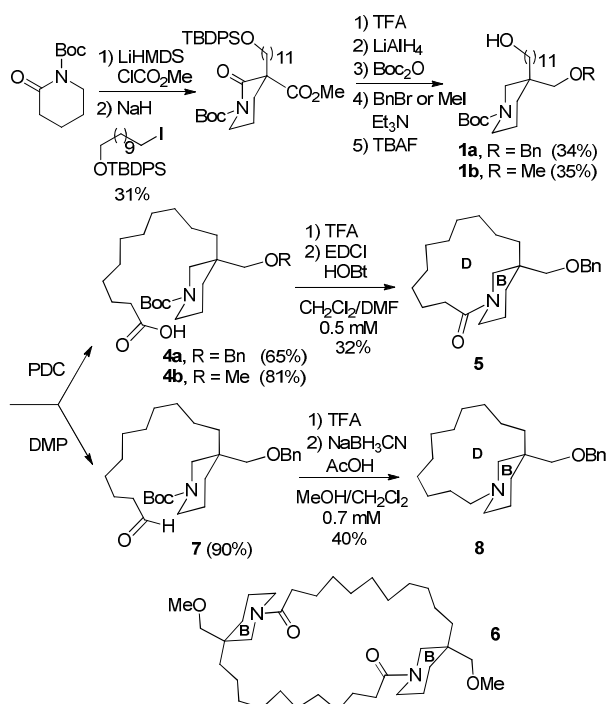
Alcohols **1**, bearing the eleven-carbon chain required to build up the 14-membered D ring of madangamine D, were prepared from *N*-Boc valerolactam, as outlined in

<sup>3</sup> For previous racemic syntheses of the diazatricyclic core of madangamines, see: (a) Matzanke, N.; Gregg, R. J.; Weinreb, S. M. *J. Org. Chem.* **1997**, *62*, 1920–1921; (b) Yamazaki, N.; Kusanagi, T.; Kibayashi, C. *Tetrahedron Lett.* **2004**, *45*, 6509–6512; (c) Yoshimura, Y.; Kusanagi, T.; Kibayashi, C.; Yamazaki, N.; Aoyagi, S. *Heterocycles* **2008**, *75*, 1329–1354; (d) Tong, H. M.; Martin, M.-T.; Chiaroni, A.; Bénéchie, M.; Marazano, C. *Org. Lett.* **2005**, *7*, 2437–2440; (e) Quirante, J.; Paloma, L.; Diaba, F.; Vila, X.; Bonjoch, J. *J. Org. Chem.* **2008**, *73*, 768–771.

<sup>4</sup> Amat, M.; Pérez, M.; Proto, S.; Gatti, T.; Bosch, J. *Chem. Eur. J.* **2010**, *16*, 9438–9441.

Scheme 1. Initial attempts to perform the macrocyclization by lactamization of carboxylic acid **4**, generated by PDC oxidation of **1**, were not satisfactory as dimer **6** was the only isolable product. When the reaction was conducted under high dilution conditions, the desired bicyclic lactam **5** was formed in acceptable yield. Alternatively, Dess–Martin oxidation of **1a**, followed by *N*-deprotection of the resulting aldehyde **7** and reductive amination under diluted conditions, satisfactorily led to the azabicyclic derivative **8** in acceptable overall yield.

**Scheme 1.** Model Annulation Studies. The Macrocyclic D Ring of Madangamine D



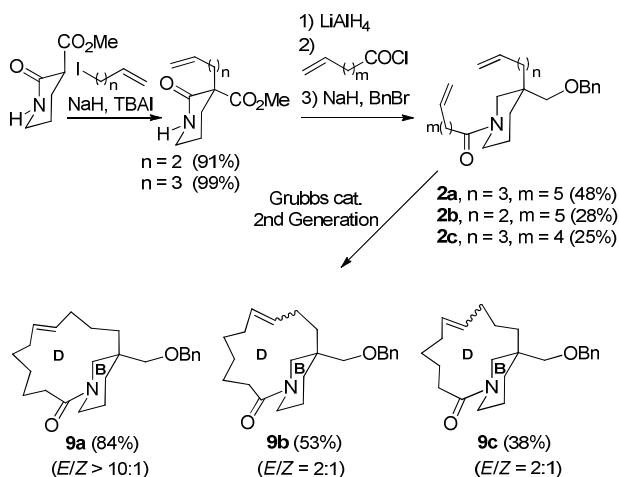
We then focused our attention on macroannulations involving ring-closing metathesis reactions.<sup>5</sup> The required dienes **2**, bearing unsaturated chains of different length, were prepared from 3-methoxycarbonyl-2-piperidone by successive *C*-alkylation and *N*-acylation reactions, as outlined in Scheme 2. Gratifyingly, diene **2a** underwent a ring-closing metathesis reaction on treatment with the second-generation Grubbs catalyst, leading to the 14-membered (*E*)-unsaturated lactam **9a** in excellent yield.<sup>6</sup> Cyclization of dienes **2b** and **2c** to the corresponding 13-

<sup>5</sup> For reviews on the construction of macrocyclic rings by RCM reactions, see: (a) Meng, Q.; Hesse, M. *Top. Curr. Chem.* **1991**, *161*, 109–176; (b) Deiters, A.; Martin, S. F. *Chem. Rev.* **2004**, *104*, 2199–2238; (c) Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem. Int. Ed.* **2005**, *44*, 4490–4527; (d) Gradillas, A.; Pérez-Castells, J. *Angew. Chem. Int. Ed.* **2006**, *45*, 6068–6101.

<sup>6</sup> Only trace amounts of the *Z*-isomer in compound **9a** were detected by <sup>1</sup>H NMR.

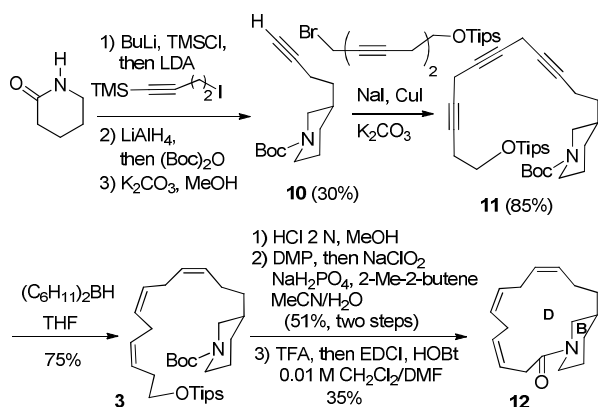
membered ring alkenes **9b** and **9c** were also satisfactory, although the yields were lower.<sup>7</sup>

**Scheme 2.** Model Annulation Studies. Construction of the Macrocyclic D Rings of madangamines C, D, and E by Ring-Closing Metathesis



Having achieved model macrocyclizations to construct 13- and 14-membered rings, like those present in madangamines C-E, we then explored the construction of the skipped (*Z,Z,Z*)-unsaturated 15-membered ring characteristic of madangamine A. The required twelve-carbon chain was installed sequentially, by *C*-alkylation of  $\delta$ -valerolactam with 4-iodo-1-(trimethylsilyl)but-1-yne<sup>8</sup> followed by cuprous iodide-catalyzed coupling of the

**Scheme 3.** Model Annulation Studies. Construction of the Macrocyclic D Ring of Madangamine A



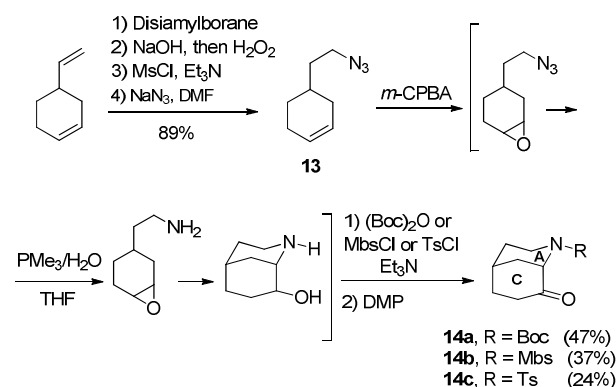
<sup>7</sup> *E/Z* mixtures of isomers (2:1 ratio) were formed in these reactions. In the cyclization of **2b**, the corresponding dimer was isolated in 12% yield.

<sup>8</sup> Duthéuil, G.; Webster, M. P.; Worthington, P. A.; Aggarwal, V. K. *Angew. Chem. Int. Ed.* **2009**, *48*, 6317–6319

terminal alkyne **10** with 8-bromo-1-(triisopropylsilyloxy)octa-3,6-diyne.<sup>9</sup> Reduction of the resulting triyne **11** with dicyclohexylborane<sup>10</sup> stereoselectively provided the unstable all-*cis* model triene **3**. In this series the final annulation to **12** was performed by macrolactamization, as outlined in Scheme 3.

To study how to assemble the (*Z,Z*)-unsaturated 11-membered eastern E ring of madangamines A-E, we used azabicyclic ketones **14**, which embody rings A and C of the alkaloids and mimic our advanced diazatricyclic intermediate **B**. These model 8-oxomorphan derivatives **14** were prepared from 4-vinylcyclohexene by a straightforward route involving the generation of azide **13**, epoxidation of the cyclohexene double bond, and a Staudinger reduction of the azide functionality (Scheme 4). The initially formed amino epoxide underwent a smooth *in situ* cyclization, directly leading to an intermediate amino alcohol, which was then *N*-protected and oxidized.

**Scheme 4.** Synthesis of the Model Azabicyclic Ketones **14**



Hoping to stereoselectively install the exocyclic *Z* double bond characteristic of madangamines A-E, we initially used the Still-Gennari modification<sup>11</sup> of the Horner-Wadsworth-Emmons reaction, a protocol that has been employed<sup>12</sup> with excellent *Z* stereoselectivity from a related 8-oxomorphan derivative (Scheme 5). However, disappointingly, all attempts to induce the same stereoselectivity from ketones **14a** and **14b**, either under the original<sup>12</sup> or slightly modified<sup>13</sup> reaction conditions, resulted in the generation of *Z/E* mixtures of alkenes **15**,

<sup>9</sup> Gueugnot, S.; Aiami, M.; Linstrumeile, G.; Mambu, L.; Petit, Y.; Larchevêque, M. *Tetrahedron* **1996**, *52*, 6635–6646.

<sup>10</sup> For a review on the construction of (*Z,Z*) skipped 1,4-dienes, see: Durand, S.; Parrain, J.-L.; Santelli, M. *J. Chem. Soc., Perkin Trans I*, **2000**, 253–273.

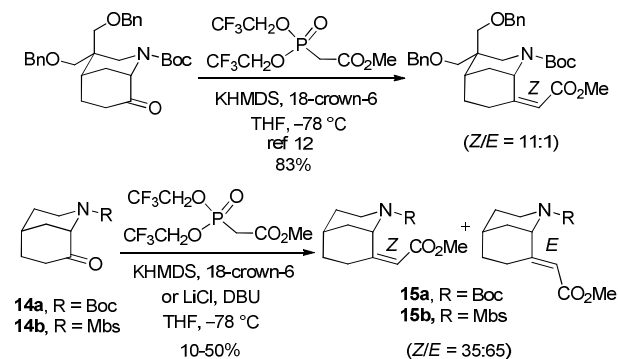
<sup>11</sup> Still, W. C.; Gennari, C. *Tetrahedron Lett.* **1983**, *24*, 4405–4408.

<sup>12</sup> Yoshimura, Y.; Inoue, J.; Yamazaki, N.; Aoyagi, S.; Kibayashi, C. *Tetrahedron Lett.* **2006**, *47*, 3489–3492.

<sup>13</sup> Blanchette, M. A.; Choy, W.; Davis, J. T.; Essensfeld, A. P.; Masamune, S.; Roush, W. R.; Sakai, T. *Tetrahedron Lett.* **1984**, *25*, 2183–2186.

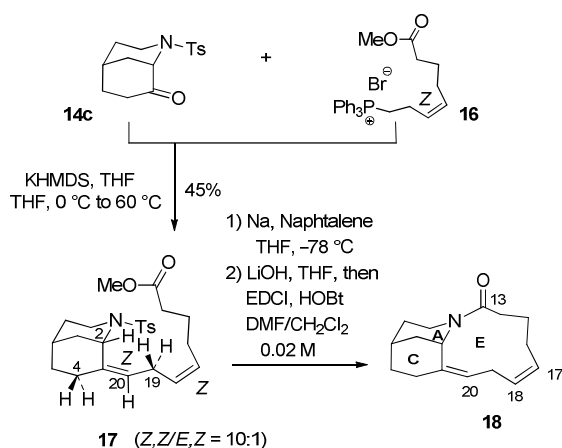
in which the undesired *E*-isomer was predominant (35:65 ratio).

**Scheme 5.** Still-Gennari Olefination from 8-Oxomorphan Derivatives



At this point, we reasoned that the use of a nonstabilized ylide could reverse the stereoselectivity of the Wittig reaction, leading to the required *Z*-isomer.<sup>14</sup> Additionally, we envisaged a more direct approach using a eight-carbon phosphonium salt, such as **16** (Scheme 6), already containing the central *Z* C<sub>17</sub>-C<sub>18</sub> double bond present in the *E* ring of madangamines and the ester functionality required for the final macrolactamization. After some experimentation, to our delight, treatment of bicyclic ketone **14c** with the ylide generated from

**Scheme 6.** Model Annulation Studies. Straightforward Assembly of the Macrocyclic *E* Ring of Madangamines A-E



phosphonium bromide **16**<sup>15</sup> and KHMDS in THF (0.75 M) under strictly anhydrous conditions led to a highly enriched mixture (*Z/E*, 10:1 ratio) of alkenes **17** in 45% yield. The desired *Z* stereochemistry for the major product was deduced by a 2D NOESY experiment, which showed two sharp cross-peaks resulting from the spatial interactions between H-4/H-20 and H-2/H-19. After removal of the protecting tosyl substituent, alkaline hydrolysis followed by macrolactamization of the resulting crude amino acid provided a single tricyclic lactam **18**, bearing the (*Z,Z*)-unsaturated eleven-membered ring of the target alkaloids.

In summary, using appropriate simplified model derivatives, we have developed synthetic routes to construct the 13- and 14-membered D rings of madangamines C-E, the all-*cis*-triunsaturated 15-membered D ring of madangamine A, and the (*Z,Z*)-unsaturated 11-membered E ring common to madangamines A-E.

**Acknowledgment** Financial support from the MICINN, Spain (Project CTQ2009-07021/BQU), and the AGAUR, Generalitat de Catalunya (Grant 2009-SGR-1111) is gratefully acknowledged. Thanks are also due to the Ministry of Education (Spain) for a fellowship to R.B. and to the Leonardo da Vinci programme (Unipharma Graduates-6 and 7) for mobility grants to F.R. and A.M., respectively.

**Supporting Information Available** Full experimental and <sup>1</sup>H and <sup>13</sup>C NMR description of new compounds. <sup>1</sup>H NMR spectra for compounds **1-5**, and **7-14c**, and **16-18**; <sup>13</sup>C NMR spectra for compounds **2, 3, 9-14c**, and **16, 17**; mass spectra for compounds **5, 8, 18**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

<sup>14</sup> (a) Vedejs, E.; Cabaj, J.; Peterson, M. J. *J. Org. Chem.* **1993**, *58*, 6509–6512; For a review on Wittig reaction, see: (b) Vedejs, E.; Peterson, M. J. *Top. Stereochem.* **1994**, *21*, 1–157.

<sup>15</sup> The synthesis of the phosphonium salt **16** was accomplished by modification of known procedures: (a) Zamboni, R.; Milette, S.; Rokach, J. *Tetrahedron Lett.* **1983**, *24*, 4899–4902; (b) Wang, S. S.; Rokach, J.; Powell, W. S.; Dekle, C.; Feinmark, S. J. *Tetrahedron Lett.* **1994**, *35*, 4051–4054; (c) Sandri, J.; Viala, J. *J. Org. Chem.* **1995**, *60*, 6627–6630.