# A Concise Approach to the Tricyclic Core of the Cytotoxic Marine Alkaloid Madangamine A

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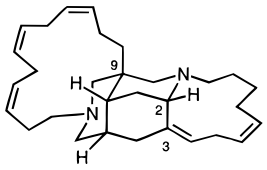
Madangamine A (**1**) is a pentacyclic alkaloid produced by the marine sponge *Xestospongia ingens*.[1] This compound is of interest both because of its unique structure and the fact that it shows significant *in vitro* cytotoxic activity toward a number of tumor cell lines, including human lung A549, brain U373, and breast MCF-7.

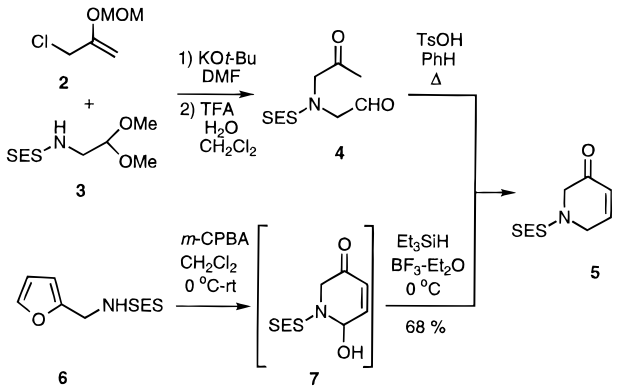


**1** madangamine A

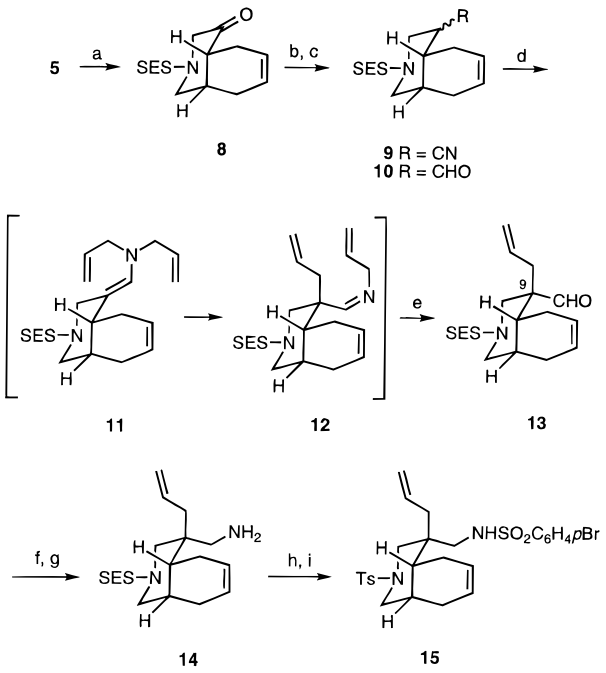
Madangamine A belongs to an ever growing class of polycyclic marine alkaloids that apparently have a common biogenetic origin from partially reduced *bis*-pyridine macrocycles.[2] Included in this group are the xestospongins, petrosins, manzamines, ircinals, sarain A, *etc.* In view of our ongoing interest in developing approaches to some of the molecules of this class,[3] we have initiated studies directed toward a total synthesis of **1**, and in this paper we outline our inital success in developing a strategy for constructing the tricyclic nucleus of the alkaloid.

A key intermediate in our approach is the enone **5**, prepared initially from known[4] chloro enol ether **2** and SES-protected amino acetal **3**[5] (Scheme 1). Base-induced condensation of **2** and **3**, followed by acetal and enol ether hydolysis with aqueous TFA, led to keto aldehyde **4**. Exposure of **4** to *p*-toluenesulfonic acid in refluxing benzene afforded the desired enone **5**. Although yields for this sequence were at times high, reproducibility problems in the aldol step, particularly on large-scale runs, prompted development of a more efficient route to **5**. Using a variation of the methodology recently described by Hiemstra and co-workers,[6] it was possible to synthesize enone **5** from SES-protected furfurylamine **6**. Thus, oxidation of furan **6** with *m*-chloroperbenzoic acid gave intermediate **7**, which without isolation could be reduced with triethylsilane *via* an *N*-sulfonyliminium species to afford **5** in good yield.

**Scheme 1**




**Scheme 2**[a]




[a] Key: (a) 1,3-butadiene, $CH_2Cl_2$, 12 kbar, rt, 75%; (b) TosMIC, KO-*t*-Bu, MeOH, DMF, 68%; (c) DIBALH, PhMe, −78 to 0 °C, 90%; (d) diallylamine, $PPh_3$, $Pd(OCOCF_3)_2$, PhH, reflux; (e) 5% HCl, 68% from **10**; (f) $NH_2OH$·HCl, pyr, rt, 100%; (g) $LiAlH_4$, THF, −78 °C to rt, 69%; (h) *p*-$BrC_6H_4SO_2Cl$, $NEt_3$, DMAP rt, 81%; (i) CsF, DMF, 95 °C/DMAP, $CH_2Cl_2$, $NEt_3$, TsCl, rt, 21%.

Although a [4 + 2]-cycloaddition of enone **5** with butadiene could not be effected under thermal conditions, the desired *cis* keto azadecalin derivative **8** could be formed at high pressure (12 kbar) in good yield (Scheme 2).[7] The ketone functionality in **8** could subsequently be

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(1) Kong, F.; Andersen, R. J.; Allen, T. M. *J. Am. Chem. Soc.* **1994**, *116*, 6007.

(2) Baldwin, J. E.; Whitehead, R. C. *Tetrahedron Lett.* **1992**, *33*, 2059. Baldwin, J. E.; Bischoff, L.; Claridge, T. D. W.; Heupel, F. A.; Spring, D. R.; Whitehead, R. C. *Tetrahedron* **1997**, *53*, 2271.

(3) Sisko, J; Henry, J. R.; Weinreb, S. M. *J. Org. Chem.* **1993**, *58*, 4945.

(4) Gu, X.-P.; Nishida, N.; Ikeda, I.; Okahara, M. *J. Org. Chem.* **1987**, *52*, 3192.

(5) SES = β-(trimethylsilyl)ethanesulfonyl. Prepared from commercially available aminoacetaldehyde dimethyl acetal and SES-Cl: Weinreb, S. M.; Demko, D. M.; Lessen, T. A.; Demers, J. P. *Tetrahedron Lett.* **1986**, *27*, 2099. Weinreb, S. M.; Chase, C. E.; Wipf, P.; Venkatraman, S. *Org. Synth.*, in press.

(6) Hopman, J. C. P.; van den Berg, E.; Ollero, L. O.; Hiemstra, H.; Speckamp, W. N. *Tetrahedron Lett.* **1995**, *36*, 4315. We thank Professor Hiemstra for providing experimental details.

(7) (a) The cycloaddition has been run on a scale to produce about 1 g of adduct using a Leco Model PG-200-HPC apparatus. (b) Attempted cycloaddition of enone **5** with butadiene using Lewis acids gave low yields of a mixture of *cis* and *trans* azadecalins that could only be separated by HPLC. *Cf.* Angell, E. C.; Fringuelli, F.; Minuti, L.; Pizzo, F.; Porter, B.; Taticchi, A.; Wenkert, E. *J. Org. Chem.* **1985**, *50*, 4686 and references cited therein.

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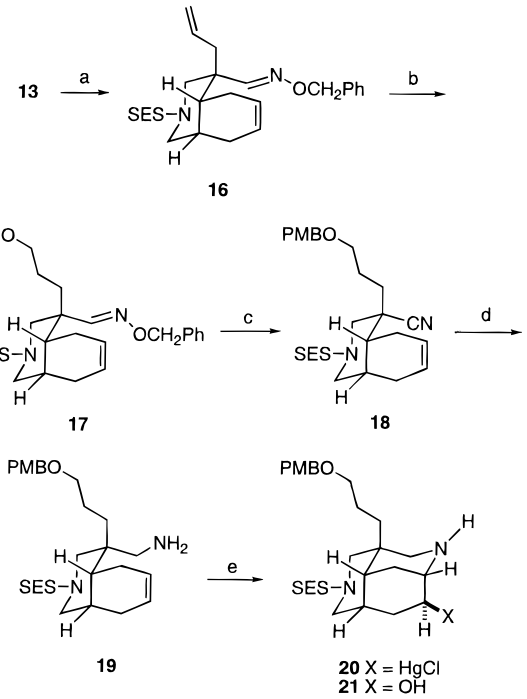
homologated to nitrile **9** using TosMIC.[8] Reduction of the nitrile group then produced aldehyde **10** as a 1:1 mixture of epimers. We next opted to establish the requisite quaternary center and attendant stereochemistry at C-9 (madangamine A numbering) *via* application of the palladium-promoted aza-Claisen methodology of Murahashi *et al*.[9,10] Therefore, aldehyde **10** was treated with diallylamine and $Pd(O_2CCF_3)_2/PPh_3$ to initially generate enamine **11**, which underwent stereospecific [3,3]-sigmatropic rearrangement from the less congested convex face of the molecule to afford imine **12**.[11] Acidic hydrolysis of this imine gave a single stereoisomeric aldehyde **13** having the appropriate madangamine C-9 stereochemistry. The configuration at this quaternary center was confirmed by first converting aldehyde **13** to amine **14** *via* reduction of the corresponding oxime. Further transformation of **14** to bis-sulfonamide **15**, whose structure was established as shown by X-ray crystallography,[12] confirmed that the aza-Claisen rearrangement of **11** had proceeded as expected.

Continuing the synthesis, aldehyde **13** was first transformed into *O*-benzyl oxime **16** (Scheme 3), which could be hydroborated to yield alcohol **17**, having functionality that will be used for eventual construction of the "western" macrocyclic ring.[13] This alcohol was protected with *p*-methoxybenzyl chloride and NaH to produce the *p*-methoxybenzyl ether (PMB). Interestingly, under these conditions, the oxime also underwent elimination to produce nitrile **18**. Hydride reduction of the nitrile then afforded primary amine **19**. The remaining ring of the tricyclic core of **1** was established by treating amino alkene **19** with mercuric trifluoroacetate, followed by NaCl, to provide aminomercuration product **20**. Exposure of organomercury compound **20** to oxygen and sodium borohydride[14] yielded a single tricyclic amino alcohol **21** whose stereochemistry has tentatively been assigned as shown. This product has the N/C-2 bond of **1** and possesses suitable functionality at C-3 for construction of the "eastern" macrocyclic ring. We intend to use compound **21**, which can be prepared in approximately 12 steps from inexpensive furfurylamine, in a total synthesis of madangamine A. Further studies in this area will be communicated in due course.

**Scheme 3**[a]




[a] Key: (a) $NH_2OCH_2Ph{\cdot}HCl$, pyr, $CH_2Cl_2$, 0 °C to rt, 97%; (b) disiamylborane, THF, 0 °C/$H_2O_2$, NaOH, 84%; (c) NaH, TBAI, THF, *p*-$OMeC_6H_4CH_2Cl$, reflux, 73%; (d) $LiAlH_4$, THF, −78 °C to rt, 74%; (e) $Hg(OCOCF_3)_2$, THF, 0 °C/NaCl/$O_2$, $(CF_3)_2CHOH$, $NaBH_4$, rt, 39%.

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**Supporting Information Available:** Experimental procedures along with spectral data for all new compounds and an ORTEP drawing of compound **15** (9 pages).

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(8) Oldenziel, O. H.; van Leusen, D.; van Leusen, A. M. *J. Org. Chem.* **1977**, *42*, 3114.

(9) Murahashi, S.-I.; Makabe, Y.; Kunita, K. *J. Org. Chem.* **1988**, *53*, 4489.

(10) Attempts to deprotonate nitrile **9**, followed by alkylation with allyl bromide, were unsuccessful. *Cf.* Sisk, S. A.; Hutchinson, C. R. *J. Org. Chem.* **1979**, *44*, 3500.

(11) Imine **12** could be reduced *in situ* with sodium borohydride to afford the *N*-allyl analog of amine **14**.

(12) The author has deposited atomic coordinates for this structure with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

(13) Hydroboration of various *N*-protected derivatives of primary amine **14** proceeded in low yields.

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