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# Synthesis of the 11-membered ring of the marine alkaloids, madangamines

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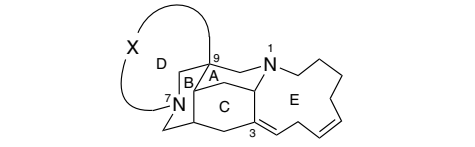
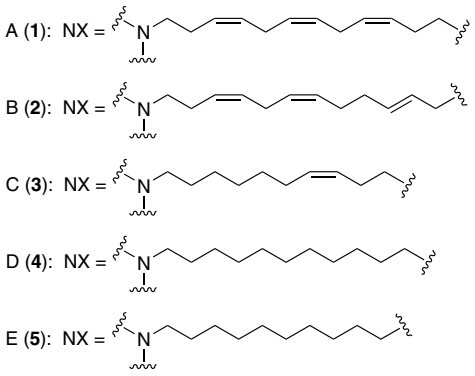
**Abstract**—The first successful attempt at synthesizing the 11-membered ring of madangamine alkaloids is described. The synthesis involves intramolecular N,O-acetalization of a cyclohexanone derivative, cross-coupling reaction with (*Z*)-vinylstannane, and intramolecular reductive amination for elaboration of the 11-membered macrocycle.


Madangamine A (**1**) is a novel pentacyclic alkaloid that was isolated from the marine sponge *Xestospongia ingens* by Andersen in 1994.[1] Soon after, new constituents of this alkaloid type, madangamines B–E (**2**–**5**), were isolated from the same organism.[2] Madangamine A exhibits cytotoxic activities against P388, A549, U373, and MCF-7 tumor cell lines. The unprecedented structure, including a diamond-lattice core (ABC-ring) and two macrocyclic rings (D- and E-rings), has attracted much attention in the fields of organic and medicinal chemistry.




Madangamines




To date, there have been reports on tricyclic ABC-ring synthesis.[3,4] By adopting the Diels–Alder reaction followed by intramolecular aminomercuration as key steps, construction of the diazatricyclic ring has been achieved[3] and, more recently, one-step construction of the tricyclic core of madangamines via condensation of dihydropyridinium salt with the sodium salt of diethyl acetonedicarboxylate has been reported.[4] In connection with our investigations, devoted to the use of *N*,*O*-acetals in alkaloid synthesis,[5] we succeeded in synthesizing the tricyclic ring system (ABC ring) of madangamines by adopting intramolecular N,O-acetalization of the corresponding keto-aminophenol for the AC-ring construction and then intramolecular cyclization for the B-ring construction.[6] To date, contrary to the case of the ABC-ring formation, there have been no reports of the synthesis of macrocyclic ring(s) (D- and/or E-ring(s)). In this context, we set out to develop a protocol for the elaboration of the 11-membered ring (E-ring) in madangamine alkaloids as a common architecture. The strategy for the construction of the E-ring, which is fused to the AC-ring, involves intramolecular reductive amination of **7** and intramolecular N,O-acetalization of **9** as shown in Scheme 1.

The Michael addition of ethyl cyanoacetate to **10** was carried out in the standard manner to give the adduct **11**[7] as a 1:1 diastereomeric mixture in an 80% yield. Protection of the keto group of **11** with 1,2-bis(hydroxymethyl)benzene

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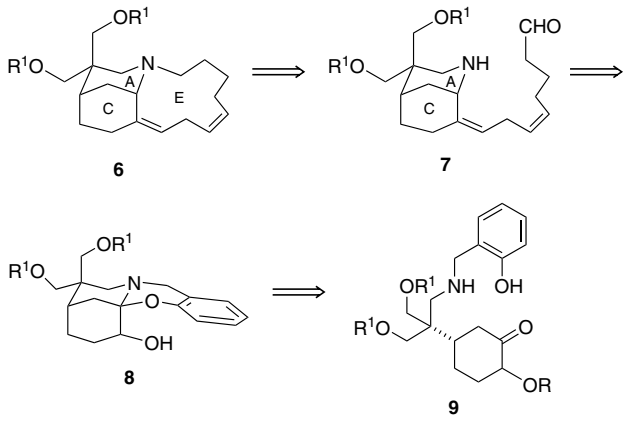


**Scheme 1.** Retrosynthetic analysis of the 11-membered ring in the madangamine alkaloids.

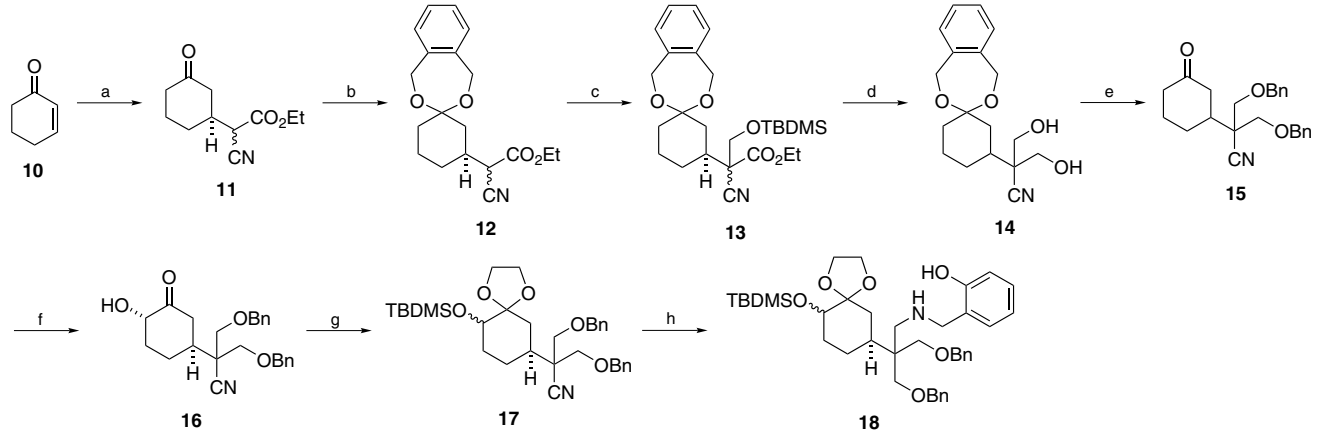
yielded the seven-membered cyclic acetal **12**. Potassium-carbonate mediated hydroxymethylation followed by TBDMS protection led to ester **13** having a quaternary carbon center in a 98% yield over two steps. Conversion of the diastereomeric mixture of **13** to the bis(hydroxymethyl)nitrile **14** was carried out in the standard manner by lithium borohydride reduction in an ether–ethanol solution, and subsequent desilylation with TBAF. After the protection of the two hydroxy groups of **14** as their benzyl ethers, the cyclic acetal was cleaved with pyridinium *p*-toluenesulfonate in a mixture of acetone and water at reflux to give the 3-substituted cyclohexanone **15** in excellent yields.

Application of the modified Rubottom oxidation protocol to **15** with *tert*-butyldimethylchlorosilane in the presence of NHMDS followed by osmium tetroxide in the presence of a stoichiometric amount of *N*-methylmorpholine oxide gave the secondary α-alcohol **16** in a 65% yield as a single diastereomer.[8]

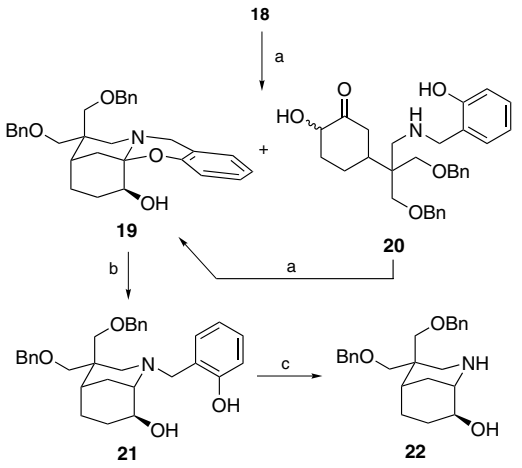
With α-hydroxylated cyclohexanone in hand, we next examined its conversion to the tetracyclic *N*,*O*-acetal. Sequential treatment of **16** with ethylene glycol and trimethylsilylchloride followed by TBDMSOTf in the presence of 2,6-lutidine gave **17** in an 81% yield as a 3:1 diastereomeric mixture over two steps.[9] After reduction of nitrile **17** with DIBAL-H, the resulting primary amine was treated with salicylaldehyde and sodium borohydride to give the reductive amination product **18** in a 96% yield (Scheme 2).

The cyclic ketal **18** was treated with hydrochloric acid in methanol to give the tetracyclic *N*,*O*-acetal **19** as a single diastereomer[10] in a 51% yield with the accompanying uncyclized **20** in a 42% yield. The uncyclized product **20** was converted to **19** under the same acidic conditions (3 M HCl–MeOH) in a 65% yield. Reductive cleavage of the *N*,*O*-acetal **19** with alane in ether provided the 2-azabicyclo[3.3.1]nonane (morphan) derivative **21** in an 84% yield. Removal of the (2-hydroxyphenyl)methyl group of **21** was accomplished by hydrogenation using palladium hydroxide as a catalyst to give **22** in a 50% yield along with a 49% recovery of **21** (Scheme 3).[11]

The next stage of our synthesis involved macrocyclization between the secondary amine and the carbinol carbon via the retrosynthesis (Scheme 1). After protection of the secondary amine of **22** as a *tert*-butyl carbamate, treatment of Dess–Martin periodinane gave ketone **23** in a 99% yield in two steps. The application of Still's *Z*-selective Wittig–Horner olefination[12] to **23** employing KHMDS as a base in the presence of 18-crown-6 yielded the (*Z*)-exo-olefin **24** as a major product with the accompanying undesired (*E*)-isomer in a ratio of 11:1. This inseparable geometrical mixture (11:1) was treated with DIBAL-H in dichloromethane at −78 °C to give (*Z*)-allylic alcohol **25** in an 85% yield after chromatographic removal of a small amount of the (*E*)-isomer. Methoxycarbonylation of the allylic alcohol **25** with methyl chloroformate in the presence of pyridine at 0 °C gave **26** in an 88% yield. Palladium-catalyzed coupling of **26** with the (*Z*)-vinylstannane, (1,1-dimethylethyl)(dimethyl){[(5*Z*)-6-(tributylstannanyl)hex-5-enyl]oxy}silane, in



**Scheme 2.** Reagents and conditions: (a) $CH_2(CN)CO_2Et$, NaOEt, EtOH, rt, 80%; (b) *o*-$C_6H_4(CH_2OH)_2$, *p*-TsOH, benzene, reflux, 99%; (c) (i) HCHO, $K_2CO_3$, THF, rt, 99%; (ii) TBDMSCl, imidazole, DMF, rt, 99%; (d) (i) $LiBH_4$, $Et_2O$–EtOH, reflux, 95%; (ii) TBAF, THF, rt, 99%; (e) (i) BnBr, NaH, DMF, rt, 95%; (ii) PPTS, acetone–$H_2O$, reflux, 98%; (f) (i) TBDMSCl, NHMDS, THF, rt 96%; (ii) $OsO_4$, NMO, MeCN–$H_2O$, rt, 65%; (g) (i) $HO(CH_2)_2OH$, TMSCl, $CH_2Cl_2$, rt, 83%; (ii) TBDMSOTf, 2,6-lutidine, $CH_2Cl_2$, 0 °C, 99%; (h) (i) DIBAL-H, $CH_2Cl_2$, 0 °C, 82%; (ii) *o*-$(OH)C_6H_4CHO$, $NaBH_4$, MeOH, rt, 96%.




**Scheme 3.** Reagents and conditions: (a) 3 M HCl, MeOH, reflux, 51% for **19** from **18**, 42% for **20** from **18**, 65% for **19** from **20**; (b) $LiAlH_4$–$AlCl_3$, $Et_2O$, rt, 84%; (c) $H_2$, $Pd(OH)_2$, MeOH–THF, rt, 50%, 98% based on recovered **21**.

the presence of lithium chloride in DMF led to the skipped diene **27** as a single stereoisomer.[13] It is noteworthy that the (*Z*)-geometry of the starting material was clearly retained in the product as (*Z*)-exo olefin via the $^3\eta$-allylpalladium intermediate.[13] Deprotection of the TBDPS group from **27** by treatment of TBAF gave the primary alcohol **28** in a 97% yield. Finally, the 11-membered ring was constructed by a sequential reaction involving oxidation of **28** with Dess–Martin periodinane followed by deprotection of the Boc group with trifluoroacetic acid and intramolecular reductive amination giving rise to the expected tricyclic product **29** in a 35% yield over three steps. The product thus obtained exhibited the satisfactory spectral data (Scheme 4).[14]

In summary, an efficient construction of the madangamine tricyclic ring, 4-azatricyclo[11.2.2.0$^{4,14}$]heptadec-12-ene, including an 11-membered macrocycle has been accomplished via construction of the morphan skeleton by N,O-acetalization of a cyclohexanone derivative, geometry-retained cross-coupling reaction, and intramolecular reductive amination. Because we have already established the ABC-ring construction starting from 4-hydroxycyclohex-2-en-1-one, our future studies will be focused on the construction of a 15-membered macrocycle (D-ring) for the total synthesis of madangamine A.

## Acknowledgements

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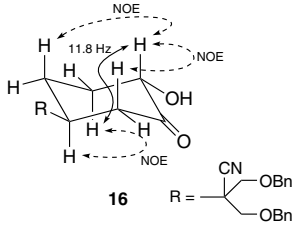
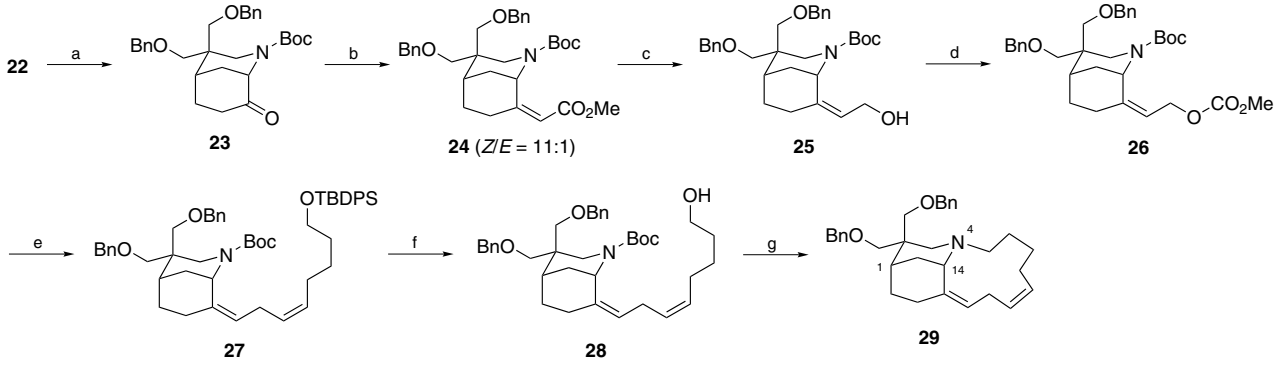
## References and notes

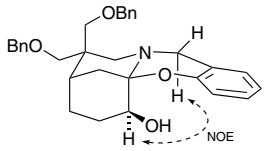
1. Kong, F.; Andersen, R. J.; Allen, T. M. *J. Am. Chem. Soc.* **1994**, *116*, 6007–6008.
2. Kong, F.; Graziani, E. I.; Andersen, R. J. *J. Nat. Prod.* **1998**, *61*, 267–271.
3. Matzanke, N.; Gregg, R. J.; Weinreb, S. M.; Parvez, M. *J. Org. Chem.* **1997**, *62*, 1920–1921.
4. Tong, H.-M.; Martin, M.-T.; Chiaroni, A.; Bénéchle, M.; Marazano, C. *Org. Lett.* **2005**, *7*, 2437–2440.
5. Yamazaki, N.; Suzuki, H.; Kibayashi, C. *J. Org. Chem.* **1997**, *62*, 8280–8281; Suzuki, H.; Yamazaki, N.; Kibayashi, C. *Tetrahedron Lett.* **2001**, *42*, 3013–3015.
6. Yamazaki, N.; Kusanagi, T.; Kibayashi, C. *Tetrahedron Lett.* **2004**, *45*, 6509–6512.
7. For other methods of synthesis of **11** see: Macquarrie, D. J. *Tetrahedron Lett.* **1998**, *39*, 4125–4128; Subba Rao, Y. V.; De Vos, D. E.; Jacobs, P. A. *Angew. Chem., Int. Ed.* **1997**, *36*, 2661–2663; Manickam, G.; Sundararajan, G. *Tetrahedron* **1999**, *55*, 2721–2736; Ranu, B. C.; Saha, M.; Bhar, S. *Synth. Commun.* **1997**, *27*, 621–626.
8. The configuration and conformation of **16** were determined by the coupling constants and NOESY spectra as shown below:




**Scheme 4.** Reagents and conditions: (a) (i) $(Boc)_2O$, 1 M NaOH, dioxane, rt, quant; (ii) Dess–Martin periodinane, $CH_2Cl_2$, rt, 99%; (b) $(CF_3CH_2O)_2P(=O)CH_2CO_2Me$, KHMDS, 18-crown-6, THF, rt, 83%, $Z/E = 11:1$; (c) DIBAL-H, $CH_2Cl_2$, −78 °C, 85%; (d) $ClCO_2Me$, pyridine, $CH_2Cl_2$, 0 °C, 88%; (e) (*Z*)-$Bu_3SnCH{=}CH(CH_2)_4OTBDPS$, $Pd(dba)_2$, LiCl, DMF, rt, 92%; (f) TBAF, THF, rt, 97%; (g) (i) Dess–Martin periodinane, $CH_2Cl_2$, rt; (ii) TFA, $CH_2Cl_2$, rt; (iii) $NaBH(OAc)_3$, MeOH–THF, rt; 35% from **28**.

9. During acetalization by acidic treatment (TMSCl–ethylene glycol), no regioisomerization of the α-hydroxy ketone was observed, but epimerization of carbinol carbon at C-2 occurred to result in a diastereomeric mixture of **17**.
10. The configuration of **19** was determined by NOESY spectra as shown below:




Selected NOE correlation for **19**.

11. An extended reaction time resulted in the cleavage of the *O*-benzyl groups.
12. Still, W. C.; Gennari, C. *Tetrahedron Lett.* **1983**, *24*, 4405–4408.
13. Valle, L. D.; Stille, J. K.; Hegedus, L. S. *J. Org. Chem.* **1990**, *55*, 3019–3023.
14. NMR data for selected compounds: Compound **16**: $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 1.43 (1H, qd, $J = 12.9$, 3.5 Hz), 1.75 (1H, qd, $J = 13.1$, 3.3 Hz), 1.91–1.97 (1H, m), 2.21 (1H, tt, $J = 12.7$, 3.7 Hz), 2.41–2.47 (2H, m), 2.61–2.67 (1H, m), 3.53 (1H, br s), 3.58 (1H, 1/2ABq, $J = 9.2$ Hz), 3.63 (1/2ABq, $J = 9.2$ Hz), 3.69 (1H, 1/2ABq, $J = 9.2$ Hz), 3.74 (1H, 1/2ABq, $J = 9.2$ Hz), 4.12 (1H, dd, $J = 11.8$, 7.1 Hz), 4.49–4.59 (4H, m), 7.27–7.38 (10H, m); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 24.9 ($CH_2$), 33.9 ($CH_2$), 39.7 (CH), 40.9 ($CH_2$), 47.0 (C), 67.9 ($CH_2$), 68.0 ($CH_2$), 73.6 ($CH_2$), 73.7 ($CH_2$), 74.8 (CH), 119.3 (C), 127.7 (two carbons, CH), 127.8 (two carbons, CH), 128.1 (two carbons, CH), 128.6 (four carbons, CH), 137.0 (C), 137.1 (C), 209.0 (C). Compound **19**: $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 1.48–1.92 (5H, m), 2.21–2.32 (2H, m), 2.65 (1H, 1/2 ABq, $J = 12.4$ Hz), 3.16 (1H, 1/2ABq, $J = 12.4$ Hz), 3.52 (2H, s), 3.68 (1H, 1/2ABq, $J = 15.4$ Hz), 3.77 (1H, 1/2ABq, $J = 15.4$ Hz), 3.765 (1H, s), 3.773 (1H, s), 4.14 (1H, s), 4.43–4.58 (4H, m), 6.85–6.92 (2H, m), 6.98 (1H, t, $J = 7.1$ Hz), 7.13 (1H, t, $J = 7.4$ Hz), 7.24–7.33 (10H, m); $^{13}$C NMR (100.6 MHz, $CDCl_3$) $\delta$ 21.4 ($CH_2$), 28.1 ($CH_2$), 30.0 ($CH_2$), 32.1 (CH), 41.4 (C), 48.8 ($CH_2$), 56.4 ($CH_2$), 64.4 ($CH_2$), 71.1 ($CH_2$), 72.1 ($CH_2$), 73.2 ($CH_2$), 73.4 ($CH_2$), 88.2 (C), 117.0 (CH), 120.6 (C), 120.8 (CH), 126.6 (CH), 127.4 (five carbons, CH), 127.5 (CH), 128.0 (CH), 128.25 (two carbons, CH), 128.30 (two carbons, CH), 150.6 (C). Compound **22**: $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 1.65–1.92 (9H, m), 2.01–2.12 (1H, m), 2.82–2.92 (3H, m), 3.38 (1H, 1/2ABq, $J = 8.8$ Hz), 3.41 (1H, 1/2ABq, $J = 8.8$ Hz), 3.62 (1H, 1/2ABq, $J = 8.9$ Hz), 3.71 (1H, 1/2ABq, $J = 8.9$ Hz), 3.91 (1H, s), 4.48 (2H, s), 4.51 (1H, 1/2ABq, $J = 12.2$ Hz), 4.55 (1H, 1/2ABq, $J = 12.2$ Hz), 7.24–7.33 (10H, m); $^{13}$C NMR (100.6 MHz, $CDCl_3$) $\delta$ 22.9 ($CH_2$), 25.1 ($CH_2$), 28.7 (CH), 30.2 ($CH_3$), 40.6 (C), 45.4 ($CH_2$), 52.1 (CH), 70.8 ($CH_2$), 70.9 ($CH_2$), 72.5 ($CH_2$), 73.2 ($CH_2$), 73.3 ($CH_2$), 127.36 (two carbons, CH), 127.39 (CH), 127.41 (CH), 127.5 (two carbons, CH), 128.28 (two carbons, CH), 128.31 (two carbons, CH), 138.8 (C), 138.9 (C). Compound **29**: $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 1.30–1.52 (7H, m), 1.95–2.17 (8H, m), 2.22–2.29 (1H, m), 2.54–2.58 (1H, m), 2.75 (1H, d, $J = 12.1$ Hz), 2.82 (1H, quint, $J = 6.8$ Hz), 3.00 (1H, s), 3.44 (1H, 1/2ABq, $J = 8.0$ Hz), 3.48 (1H, 1/2ABq, $J = 8.0$ Hz), 3.70 (1H, 1/2ABq, $J = 10.0$ Hz), 3.80 (1H, 1/2ABq, $J = 10.0$ Hz), 4.47–4.53 (4H, m), 4.95 (1H, m), 5.32–5.43 (2H, m), 7.23–7.33 (10H, m); $^{13}$C NMR (100.6 MHz, $CDCl_3$) $\delta$ 25.2 ($CH_2$), 26.3 ($CH_2$), 26.5 ($CH_2$), 26.8 ($CH_2$), 27.0 ($CH_2$), 27.4 ($CH_2$), 28.8 (CH), 32.3 ($CH_2$), 41.8 (C), 53.4 ($CH_2$), 54.9 ($CH_2$), 60.7 (CH), 71.4 ($CH_2$), 72.5 ($CH_2$), 73.1 ($CH_2$), 73.3 ($CH_2$), 125.5 (CH), 127.17 (two carbons, CH), 127.25 (two carbons, CH), 127.29 (two carbons, CH), 127.9 (CH), 128.16 (two carbons, CH), 128.19 (two carbons, CH), 134.4 (C), 138.9 (C), 139.2 (C).