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Synthesis of the diazatricyclic core of the marine alkaloids madangamines

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Abstract—A new approach to synthesize the madangamine core structure is described. The synthesis involves intramolecular *N*,*O*-acetalization of the keto-aminophenol which allows rapid construction of the 2-azabicyclo[3.3.1]nonane skeleton with a quaternary carbon center at C4. This strategy also demonstrates the utility of such approach in the stereoselective construction of the central diazatricyclic core found in the madangamine alkaloids.

Madangamine A (**1**) is a novel cytotoxic alkaloid that was first isolated from the marine sponge *Xestospongia ingens* by Andersen[1] in 1994. It has been shown to exhibit inhibitory activity against a number of tumor cell lines. Subsequently, new members of this class, madangamines B–E (**2**–**5**), were also isolated from the same organism (Fig. 1).[2] This group of natural products represents the first examples of the unprecedented pentacyclic alkaloids with the basic skeleton which consists of a central diazatricyclic core, that is, 2,6-diazatricyclo[6.2.2.0^{4,9}]dodecane, and two bridges spanning N-1 to C-3 and N-7 to C-9. Structural variations in this group of alkaloids occur only in the N-7 to C-9 bridge that varies both in carbon length and in the position and degree of unsaturation. The tricyclic core of the madangamines possesses a diamond-lattice structure in which all three of the six-membered rings are in chair conformation. To date, there has been only one example directed toward the madangamine synthesis, which consisted of the construction of the diazatricyclic core ring system by adopting the Diels–Alder reaction at high pressure followed by intramolecular aminomercuration as key reactions.[3]

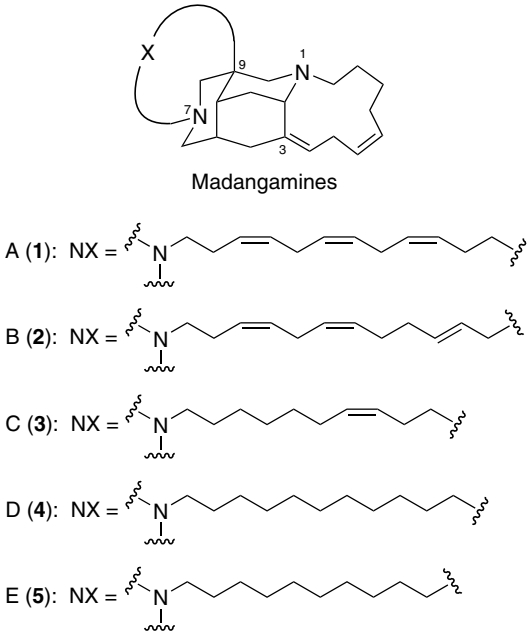

Figure 1. Structure of madangamine A–E (**1**–**5**).

In light of the interest in this class of the alkaloids, we undertook a study designed to provide a new entry to the synthesis of the core 2,6-diazatricyclo[6.2.2.0^{4,9}]-dodecane ring system of the alkaloids. The strategy we have developed for assembling this core skeleton having a quaternary carbon center at C4 as in **6** involves the construction of the 2-azabicyclo[3.3.1]nonane (morphan) ring system **8** by means of our previously reported[4] intramolecular *N*,*O*-acetalization of a

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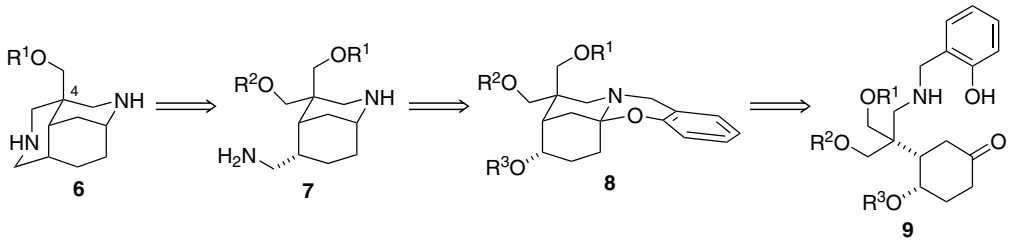
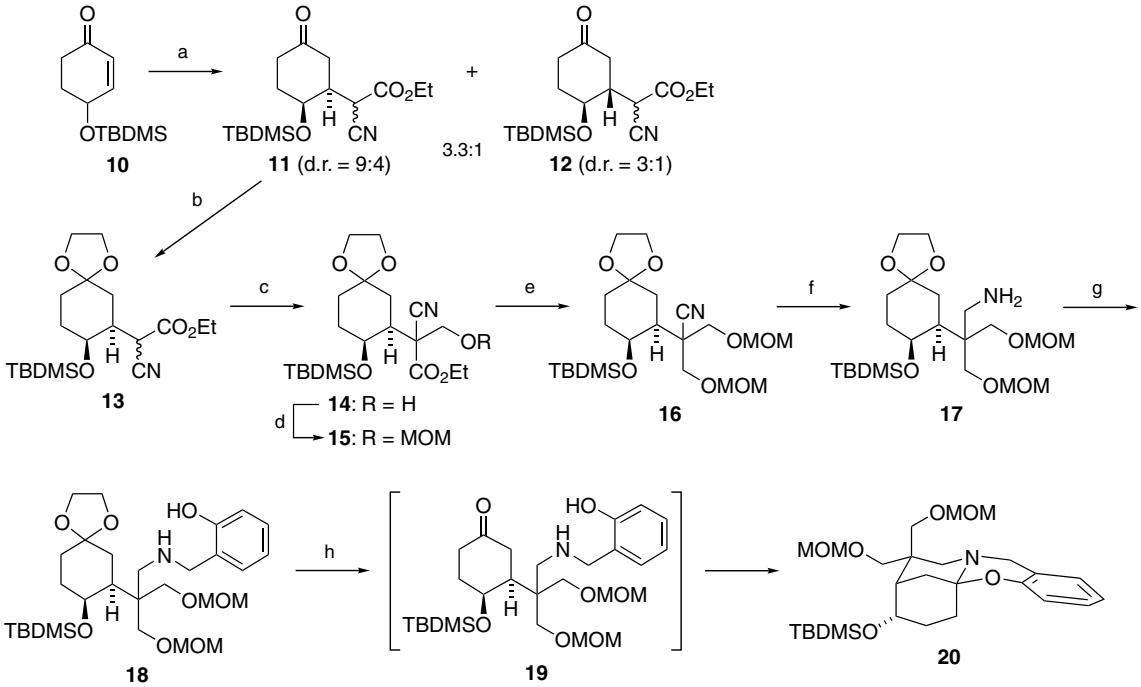


Scheme 1. Synthetic strategy for the diazatricyclic core **6** of the madangamine alkaloids.

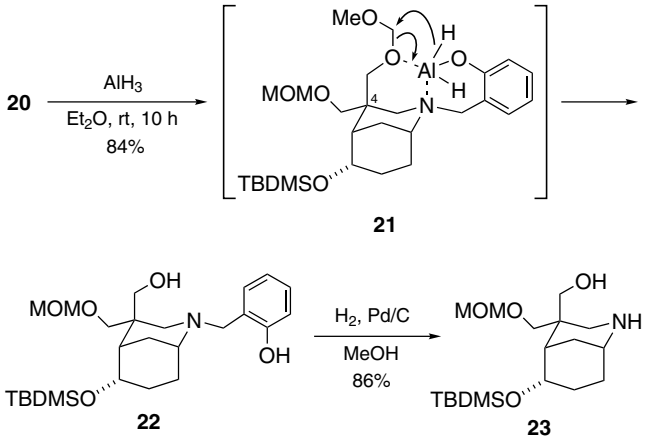
keto-aminophenol as retrosynthetically outlined below (Scheme 1).

The cyclohexanone **10**[5] was subjected to Michael addition with cyanoethylacetate to give the *cis*-adducts **11**[6] in 73% yield as a 9:4 diastereomeric mixture along with the *trans*-adducts **12**[7] in 22% yield as a 3:1 diastereomeric mixture (Scheme 2). After protection of the *cis*-adducts **11** as the cyclic acetal, exposure of **13** to 35% aqueous formaldehyde in the presence of a catalytic amount of $KHCO_3$ led to the hydroxymethyl ester **14**, which was protected as the MOM ether. The nitrile ester **15** thus obtained as a 9:4 diastereomeric mixture was transformed into the *o*-bis(methoxymethyl) derivative **16** as a single diastereomer via ester reduction with $LiBH_4$ followed by methoxymethylation. Reduction of the nitrile moiety of **16** with DIBAL-H yielded the primary amine **17**, which underwent reductive amination using salicylaldehyde and $NaBH_4$ to afford the aminophenol **18**. Upon treatment of **18** with pyridinium *p*-toluenesulfonate in acetone–H_2O under reflux, the transiently formed keto-aminophenol **19** was condensed to give the tetracyclic *N*,*O*-acetal **20** consisting of the 2-azabicyclo[3.3.1]nonane nucleus.[8]

Treatment of **20** with AlH_3 in ether at room temperature led to reductive C–O bond cleavage of the *N*,*O*-acetal[9] and selective deprotection of one of the two MOM ethers in one step, providing the amino alcohol **22** in good yield (Scheme 3). The latter process involves selective deprotection of the MOM ether in which the chemically equivalent MOM ethers were efficiently differentiated, being suitable to perform the subsequent cyclization for the construction of the diazatricyclic core skeleton. This process presumably occurred via a chelated phenoxyaluminum hydride intermediate such as **21** where the hydride delivery preferentially occurs at the methoxymethyl group connected to the axially oriented C4 oxymethylene group. Removal of a (2-hydroxyphenyl)methyl group from **22** was performed by catalytic



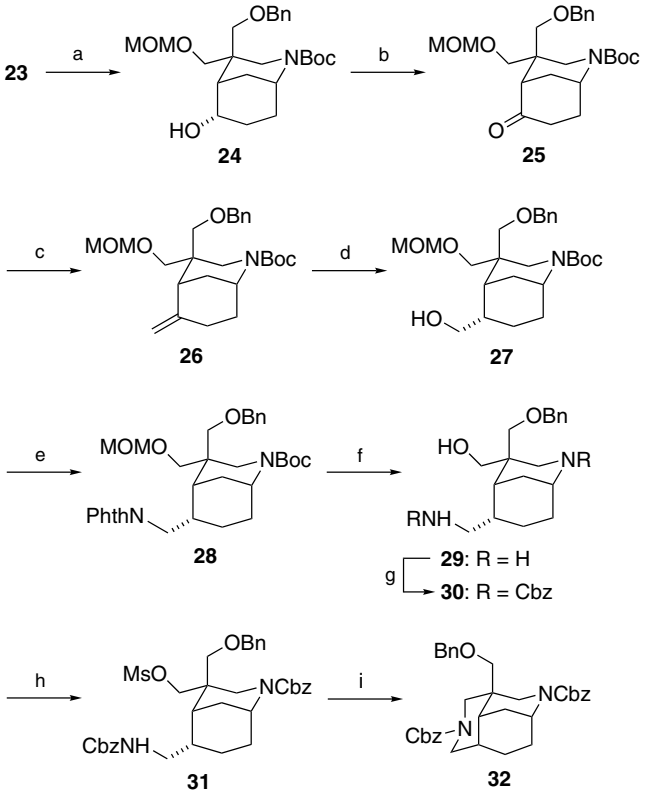
Scheme 2. Reagents and conditions: (a) $CH_2(CN)CO_2Et$, *t*-BuOK, toluene, 0 °C, 95% total yield; (b) $(CH_2OH)_2$, TsOH, benzene, reflux, 99%; (c) 35% HCHO, $KHCO_3$, rt, 90%; (d) MOMCl, *i*-Pr_2EtN, CH_2Cl_2, rt, 90%; (e) (i) $LiBH_4$ in THF, EtOH/Et_2O, reflux; (ii) MOMCl, *i*-Pr_2EtN, CH_2Cl_2, rt, 75% over two steps; (f) DIBAL-H in toluene, CH_2Cl_2, 0 °C, 83%; (g) salicylaldehyde, EtOH, rt, then $NaBH_4$, 0 °C, 98%; (h) PPTS, acetone/H_2O, reflux, 48 h, 75% for **20**.



Scheme 3. Treatment of **20** with AlH_3 leading to cleavage of the *N*,*O*-acetal and selective deprotection of the MOM ether.

hydrogenation using palladium on charcoal in MeOH to give the amino alcohol **23**.

Compound **23** was converted to the secondary alcohol **24** by sequential protection as the benzyl ether and the Boc carbamate followed by deprotection of the TBDPS ether with Bu_4NF (Scheme 4). The secondary alcohol **24** was oxidized with PCC and the resulting ketone **25** was converted to the exo-methylene product **26** by using the Tebbe reagent. Hydroboration of **26** with 9-BBN from the less congested convex β-face followed by an oxidative workup with basic peroxide led to the primary alcohol **27** as a single diastereomer. Mitsunobu reaction with phthalimide afforded **28**, which on acidic treatment underwent deprotection of the MOM and Boc groups, and then the phthaloyl unit was removed with hydrazine to give the amino alcohol **29**. After Cbz-protection of the primary and secondary amino groups, the primary alcohol **30** was mesylated and the resulting mesylate **31** was exposed to *t*-BuOK in THF at room temperature to produce the expecting tricyclic product **32**.[10]



Scheme 4. Reagents and conditions: (a) (i) Boc_2O, NaH, dioxane, 0 °C; (ii) BnBr, NaH, DMF, 0 °C; (iii) TBAF, THF, 0 °C → rt, 85% for three steps; (b) PCC, CH_2Cl_2, rt, 99%; (c) Tebbe reagent, THF, rt, 8 h, 73%; (d) (i) 9-BBN, THF, rt; (ii) NaOH, H_2O_2, rt, 91% over two steps; (e) PhthNH, DEAD, Ph_3P, THF, rt, 72%; (f) (i) HCl, MeOH, 60 °C; (ii) $H_2NNH_2 \cdot xH_2O$, EtOH, reflux, 72% over two steps; (g) CbzCl, Na_2CO_3, dioxane/H_2O, rt, 71%; (h) MsCl, Et_3N, CH_2Cl_2, 0 °C; (i) *t*-BuOK, THF, rt, 76% from **30**.

In summary, an efficient synthesis of the madangamine core structure has been accomplished. Our studies have shown that *N*,*O*-acetalization of the keto-aminophenol **19** allows rapid construction of the 2-azabicyclo-[3.3.1]nonane skeleton with a quaternary carbon center at C4. This strategy also demonstrates the utility of such approach in the stereoselective construction of the central diazatricyclic core found in the madangamine alkaloids. The strategy developed for stereocontrolled synthesis of **22** is amenable to the efficient synthesis of madangamines by using the keto-aminophenol with an appropriate functionality at C2, and studies directed toward this end are currently under way.

Acknowledgements

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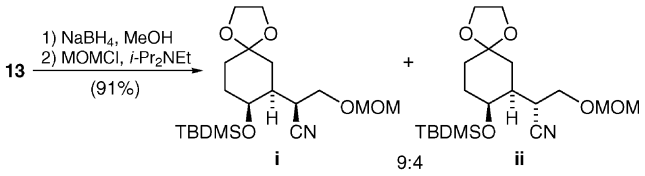
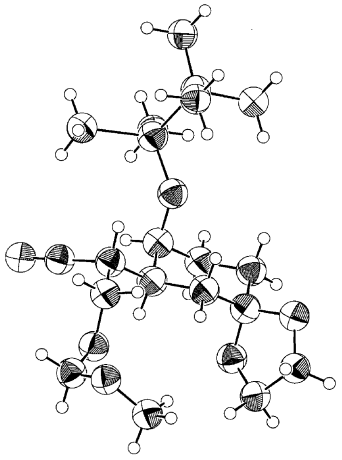
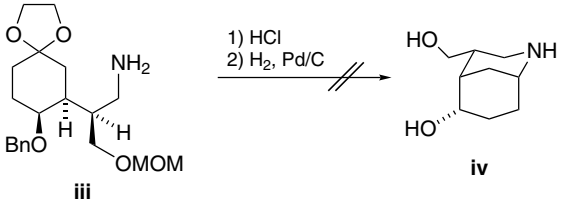
6. The *cis* stereochemistry of the major adduct **11** was established by X-ray crystallographic analysis of **ii** derived from **13** as shown below





X-ray crystallographic structure of **ii.**

7. The *trans* stereochemistry of the minor adduct **12** was supported by a diaxial H_3–H_4 couplig constant ($J = 10.0$ Hz) for both diastereomers.
8. Preliminary studies using the ketal-protected amino ketone **iii** lacking the *o*-hydroxybenzyl substitution at nitrogen indicated that deprotection followed by exposure to reductive amination conditions did not result in cyclization to the expected azabicyclo skeleton **iv**, but instead gave a complex mixture



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10. NMR data for selected compounds: Compound **20**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.06 (3H, s), 0.09 (3H, s), 0.91 (9H, s), 1.56 (1H, td, $J = 14.0$, 6.8 Hz), 1.75–1.83 (2H, m), 1.91 (1H, qd, $J = 13.5$, 5.9 Hz), 2.25 (1H, dt, $J = 13.0$, 3.5 Hz), 2.42 (1H, dt, $J = 14.0$, 3.7 Hz), 2.50 (1H, br d, $J = 2.9$ Hz), 2.98 (1H, A part of ABq, $J = 12.8$ Hz), 3.03 (1H, B part of ABq, $J = 12.8$ Hz), 3.34 (3H, s), 3.35 (3H, s), 3.72 (1H, A part of ABq, $J = 10.2$ Hz), 3.76 (2H, s), 3.78 (1H, A part of ABq, $J = 9.8$ Hz), 3.98 (1H, B part of ABq, $J = 9.8$ Hz), 4.06 (1H, B part of ABq, $J = 10.2$ Hz), 4.08–4.14 (1H, m), 4.58 (2H, s), 4.63 (2H, s), 6.76 (1H, d, $J = 8.1$ Hz), 6.84 (1H, t, $J = 7.4$ Hz), 6.99 (1H, d, $J = 7.4$ Hz), 7.09 (1H, t, $J = 7.6$ Hz); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ −4.9 (CH_3), −4.7 (CH_3), 18.0 (C), 25.9 (3 carbons, CH_3), 27.8 (CH_2), 31.3 (CH_2), 36.3 (CH_2), 38.4 (CH), 42.4 (C), 49.5 (CH_2), 55.0 (CH_3), 55.2 (CH_3), 58.6 (CH_2), 68.5 (CH_2), 71.0 (CH_2), 74.9 (CH_2), 86.0 (C), 96.8 (CH_2), 96.9 (CH_2), 116.7 (CH), 119.9 (C), 120.0 (CH), 126.6 (CH), 127.7 (CH), 151.8 (C). Compound **32**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.40 (1H, br t, $J = 14.5$ Hz), 1.50–2.12 (7H, m), 2.81–3.03 (2H, m), 3.15–3.52 (3H, m), 3.71 and 3.80 (total 1H in 1:1 ratio, d, $J = 14.5$ Hz each), 3.84–4.14 (2H, m), 4.25 and 4.32 (total 1H in 1:1 ratio, br s each), 4.40–4.54 (2H, m), 5.00–5.28 (4H, m), 7.26–7.45 (15H, m); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 24.1 (CH_2), 28.7 (CH_2), 29.7 and 30.5 (total 1 carbon, CH_2), 31.0 and 31.8 (total 1 carbon, CH), 34.1 (CH), 36.8 and 37.0 (total 1 carbon, C), 44.4 and 44.6 (total 1 carbon, CH), 45.8 and 46.4 (total 1 carbon, CH_2), 49.4 (CH_2), 49.8 (CH_2), 66.9 (CH_2), 67.1 (CH_2), 73.2 (CH_2), 73.3 (CH_2), 127.3 (CH), 127.4 (CH), 127.6 (2 carbons, CH), 127.7 (2 carbons, CH), 127.8 (2 carbons, CH), 127.9 (2 carbons, CH), 128.3 (2 carbons, CH), 128.4 (3 carbons, CH), 136.8 (C), 136.9 (C), 138.1 (C), 156.2 (2 carbons, C).