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Total Syntheses of (±)-Massadine and Massadine Chloride

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The palau'amines,[1] massadines (**1**−**2**, Figure 1A),[2] axinellamines (**3**−**4**),[3] and the tetrameric stylissadines[1c,4] are pyrrole−imidazole alkaloids that express a high degree of complexity among small marine natural products. Their highly polar structures, varying modes of halogenation, dense arrangement of functionalities, and stereochemical complexity render them appealing targets for total synthesis. Additionally, many of these alkaloids possess notable biological activities, including immunosuppressant,[1b] cytotoxic,[1b] anti-inflammatory,[1c] and antifungal.[2a] As such, many elegant approaches to their syntheses have been published and reviewed.[5] Earlier this year we reported a synthesis of axinellamines A and B (**3**−**4**) enabled by a unique late-stage chemoselective oxidation.[6] This Communication reports a greatly improved version of this oxidation protocol and its application to the total syntheses of massadine (**1**) and massadine chloride (**2**).

Because of their constitutionally isomeric nature, one could envision massadine chloride (**2**) arising from the axinellamines (**3**−**4**) via aminal opening and hemiaminal closure at C7 (Figure 1A). However, such a rearrangement was not detected under a variety of thermal, acidic, and basic conditions. A distinct approach to the massadine core was therefore required. Advanced intermediates **5** and **6** (Figure 1B) were identified as plausible precursors to **1** and **2**, assuming that subsequent cyclization would occur at oxygen (massadine-type cyclization) rather than nitrogen (axinellamine-type cyclization) while the guanidine moiety was protonated. Spirocycles **5** and **6** might arise from α-chloroketone **7**, an entity available in multigram quantities.[6a]

Our initial forays toward the synthesis of the massadines revealed that the silver(II)-mediated oxidation[6b] reported earlier was not general and many routes failed because of an inability to obtain useful quantities of hemiaminal intermediates. This was addressed by optimization of the silver(II)-mediated oxidation (Figure 1C). It has since been found that conducting the reaction in the presence of TFA (10% v/v) significantly accelerates it, leads to higher conversion, and in some cases is entirely enabling (i.e., **8**−**12**). Operationally, this reaction is simple to perform (see Supporting Information for general procedure). The axinellamine precursors **13** and **14**, that previously required heating and extended reaction times,[6b] can now be prepared in 77% and 48% yield in under 3 h at ambient temperature. This reaction appears to be general for these types of systems, and five additional examples are shown in Figure 1C. With a versatile and robust oxidation of such systems in hand, rapid exploration of routes to the massadines could commence.

It was soon found that the dense functionality of these systems combined with a deliberate avoidance of complex protecting group schemes led to several dead ends. Figure 1D provides a sampling of failed routes to intermediates **5** and **6**. For example, it was found that oxidation of C9 needed to occur prior to 2-aminoimidazole formation. While preoxidized acetate **9** could be closed to the tetrahydropyran core **15**, further α-oxidation failed (**15**→**16**); formation of deacetyl-**9** also proved problematic. The α-chloro ketone **8** was also a dead-end

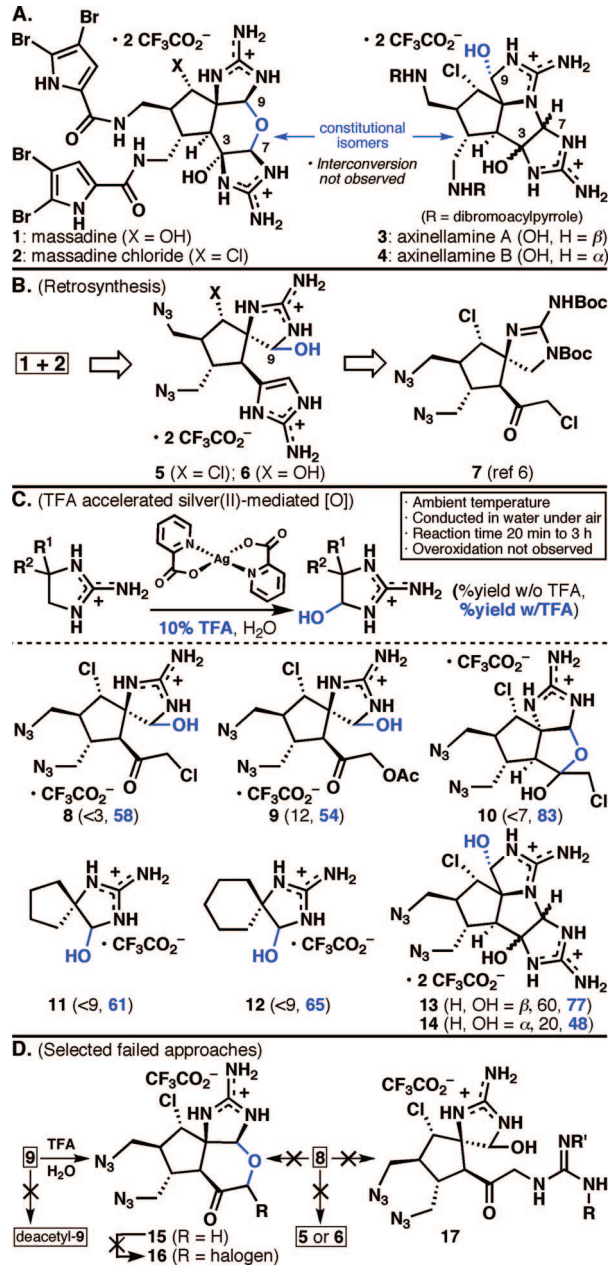
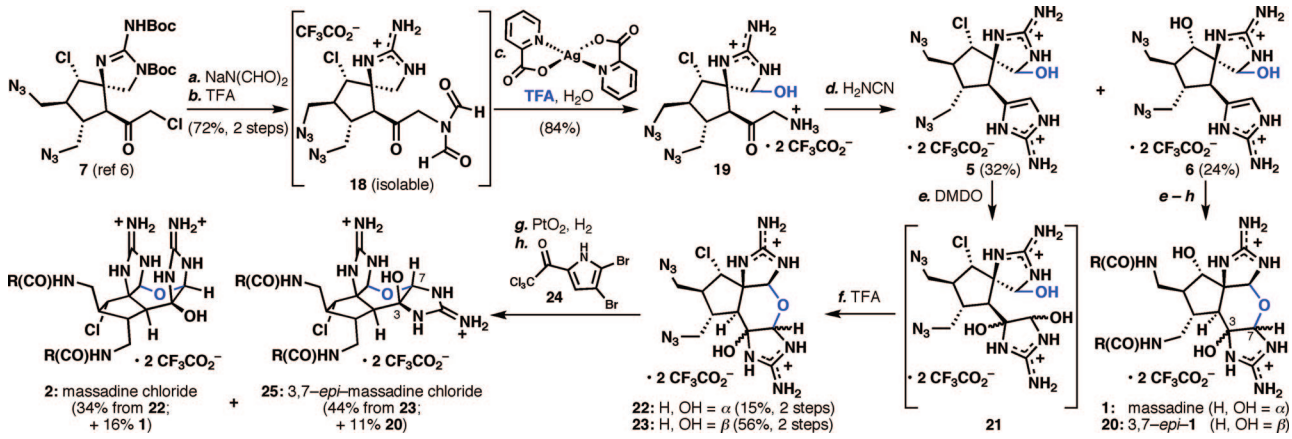


Figure 1. (A) Structures of the massadines (**1**−**2**) and axinellamines (**3**−**4**); (B) retrosynthetic analysis of the massadines (**1**−**2**); (C) chemoselective silver(II) oxidation; (D) selected failed approaches.

(due to the sensitivity of the hemiaminal moiety): closure to **15** or elaboration of the 2-aminoimidazole with guanidine equivalents failed to afford **5**, **6**, or **17**.

10.1021/ja8074852 CCC: $40.75

Scheme 1. Total Syntheses of the Massadines[a]



[a] Reagents and conditions: (a) sodium diformylamide (1.2 equiv), TBAI (0.1 equiv), THF, 23 °C, 2 h, 72%; (b) 2:1 TFA/DCM, 23 °C, 2 h, quant; (c) silver(II)picolinate (2.5 equiv), 9:1 H_2O/TFA, 23 °C, 35 min, then TFA (to 1:1 v:v), 38 °C, 18 h, 84%; (d) cyanamide (excess), 0.2 M NaOH (to pH 5.0), 78 °C, 2 h, 32% **5**, 24% **6**; (e) DMDO (1.3 equiv), 9:1 H_2O/TFA, 0 °C, 1 h; (f) TFA, 23 °C, 3 h, 71% over two steps, 1:3.7 **22**:**23**, (65% for −OH series, 1:1.9); (g) PtO_2 (0.3 equiv), H_2 (1 atm), 19:1 H_2O/TFA, 1 h, 23 °C; (h) **24** (16 equiv), $^iPr_2NEt$ (16 equiv), DMF, 14 h, 23 °C, 34% (**22**→**2**), 44% (**23**→**25**) (40% for **1** and 40% for **20**, −OH series). TBAI = tetrabutylammonium iodide, TFA = trifluoroacetic acid, DMDO = dimethyldioxirane, R = 5-(2,3-dibromopyrrole).

Ultimately, an iterative formation[7] of the 2-aminoimidazole allowed access to **5** and **6**, which could be converted into massadine chloride (**2**) and massadine (**1**) as outlined in Scheme 1. Thus, displacement of the α-chlorine in **7** with sodium diformylamide followed by Boc−removal with TFA provided **18** in 72% yield (two steps). Oxidation with silver(II)picolinate in 10% TFA/H_2O installed the C9 hemiaminal in 84% isolated yield after deformylation (100 mg scale). Treatment with cyanamide under carefully controlled pH constructed the desired 2-aminoimidazole **5** (32%) along with its hydroxy analogue **6** (24%), resulting from the displacement of the chloride with retention of configuration in a manner similar to the known conversion of massadine chloride (**2**) to massadine (**1**).[2b]

Unlike the axinellamines (**3**−**4**), the massadines (**1**−**2**) were not isolated in nature with their C3,C7 epimers. Thus, we had postulated that the natural configuration was favored thermodynamically, perhaps due to a π-stacking or the hydrogen-bonding effect between the two guanidine moieties (compare **2** and **25**, Scheme 1). To our surprise, when 2-aminoimidazole **5** was exposed to a variety of oxidative conditions followed by acid-mediated closure, the C3,C7-*epi* products were favored. After extensive optimization, it was found that a 1:3.7 (**22**:**23**) ratio of diastereomers could be achieved with dimethyldioxirane in water followed by ring closure in neat TFA. Careful control of the pH during the oxidation was required to suppress N-cyclization (axinellamine mode).[8] Reduction of the azide moieties in **22** and **23** with PtO_2 under H_2 followed by exposure to bromopyrrole **24** provided massadine chloride (**2**, 34%) and 3,7-*epi*-massadine chloride (**25**, 44%).[8] The identical sequence with the hydroxy-analogue **6** provided access to massadine (**1**) and 3,7-*epi*-massadine (**20**) in a 1:1.9 ratio.[8] Notably, **25** could be converted into **20** in warm water,[8] analogous to the known conversion of **2** to **1**.[2b] Equilibration from **2** and **1** to **25** and **20**, respectively (or vice versa), was not observed under acidic conditions.

In summary, the discovery and optimization of a robust method to chemoselectively oxidize a variety (**8**−**14**, **19**) of unprotected guanidines has enabled a synthetic entry to the massadines (**1**−**2**) without recourse to a complicated orthogonal protecting group scheme. As a side note, the diastereoselectivity of oxidative closure using 9-deoxy-**5** in the total synthesis of the axinellamines, is 1:1, and both isomers are found in nature.[6] The stereochemistry expressed in **1** and **2** at C3 and C7 correlates with that of axinellamine B (**4**), yet no *epi*-series has been isolated for the massadines (**1**−**2**). The stability and ease of formation of the C3,C7-*epi*-massadines begs the question: could there be a natural *epi*-series of the massadines (e.g., **20**, **25**), analogous to axinellamine A (**3**)?

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Supporting Information Available: Detailed experimental procedures, copies of all spectral data, and full characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

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(8) See Supporting Information for details. Synthetic material was spectroscopically identical to natural samples provided by Prof. Matthias Köck.

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