

# Ugi-4-Component Reaction Enabling Rapid Access to the Core Fragment of Massadine

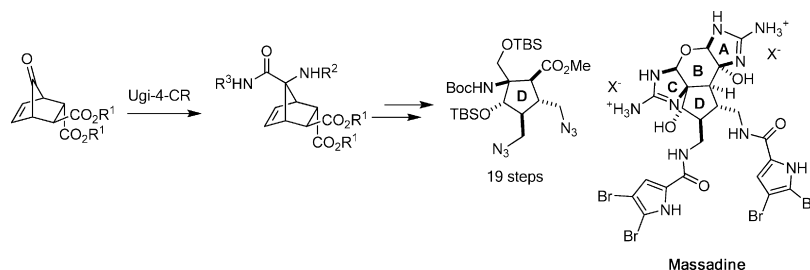
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## ABSTRACT



A rapid method to access the densely functionalized core structure of massadine (**1**) has been developed. The use of the Ugi-4-component reaction involving a convertible isonitrile and an end-group differentiating ozonolysis constitute the key operations toward the synthesis of the D-ring subunit.

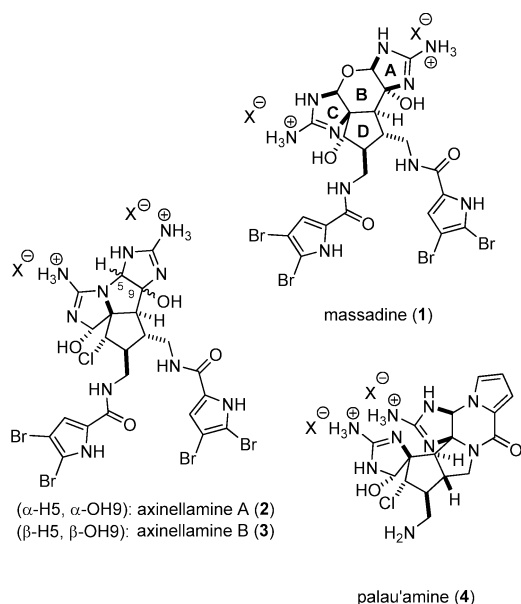
Massadine (**1**), which belongs to the class of pyrrole-imidazole alkaloids, was isolated in 2003 from the marine sponge *Stylissa aff. massa*.<sup>1</sup> The ornate and complex architecture of **1** and other congeners such as axinellamine A (**2**) and B (**3**) as well as palau'amine (**4**) (Figure 1) in combination with their potent biological activity placed these natural products into the focus of total synthesis studies.<sup>2</sup>

To date, various approaches toward the construction of the cyclopentane core of **2–4**, which all have the presence of a secondary chloro substituent in common, have been reported in the literature. Among these, the first enantioselective synthesis of such an intermediate was accomplished in our laboratories.<sup>2a</sup> In contrast, massadine (**1**) possesses a secondary hydroxyl function instead of the chloride. Apart from our previously reported approach to a similar intermediate,<sup>3</sup> there have been no reports on the enantioselective synthesis of a fully decorated core fragment of **1** possessing the correct configuration at each of the five stereogenic centers. Herein, we report the development of a facile and

enantioselective route to the core fragment of **1** involving the Ugi-4-component reaction.

From earlier studies we had learned that rapid access to an orthogonally functionalized cyclopentane ring can be gained through end-group differentiating ozonolysis of appropriately functionalized norbornene derivatives.<sup>3</sup> We were interested in harnessing the powerful discriminating characteristics of this transformation as a key step in the enantioselective synthesis of **1**. To access such an ozonolysis precursor we initially developed a strategy that involved a Strecker aminocyanation for the concomitant introduction of a carboxyl and an amino substituent at C7 of the norbornenone nucleus. However, this approach necessitated the implementation of a sequence involving various functional group interconversion steps in the synthesis. For example, the nitrogen at C7 underwent four separate operations in order to properly manage its reactivity. In order to overcome the disadvantages encountered in this approach, a reevaluation of the strategy for the elaboration of the C7 carbonyl was required. The investigations began with examination of the related Ugi-4-component reaction em-

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**Figure 1.** Oroidin alkaloids massadine (1), axinellamine A (2) and B (3), and palau'amine (4).

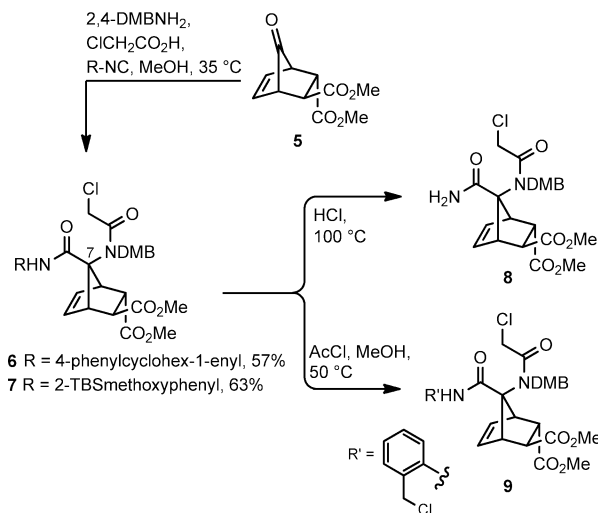
employing “convertible isonitriles”. In the typical Ugi-4-component sequence the amide bonds formed during the reaction are difficult to further elaborate, as harsh conditions are required for the subsequent synthetic manipulations. These conditions, however, would be incompatible with a complex structure containing sensitive functionalities. Thus, we became interested in examining the use of “convertible isonitriles” that would lead to amides amenable to subsequent facile and mild manipulation.

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Ketone **5**, the Ugi precursor, was accessed in enantioenriched form by a four-step procedure as reported previously by us.<sup>3</sup> With norbornenone **5** in hand, the stage was set for investigating the Ugi-4-component reaction. In preliminary experiments racemic **5** was reacted with 4-phenyl-1-isocyanocyclohexene, chloroacetic acid, and dimethoxybenzylamine (DMBNH<sub>2</sub>) to give the corresponding Ugi-adduct **6** (Scheme 1).

**Scheme 1.** Attempted Amide Manipulations



Diamides similar to **6** have been reported to be susceptible to nucleophilic attack in acidic media through the intermediacy of a münchnone.<sup>4</sup> However, when **6** was subjected to HCl in ether, we merely recorded the loss of the cyclohexenyl group leading to primary amide **8** as the sole product (Scheme 1).

The use of 2-(*tert*-butyldimethylsilyloxymethyl)phenyl-isonitrile under otherwise identical conditions for the Ugi-reaction gave **7** in 63% yield. The aniline moiety within **7** was shown to undergo intramolecular transesterification in related systems under acidic conditions.<sup>5</sup> Thus, **7** was exposed to acidic methanol at 35 °C, which resulted in an overall displacement of the TBS ether with chloride at the benzylic position (**9**, Scheme 1). After screening several other isonitriles, we found 2-nitrophenylisonitrile to efficiently participate in the Ugi-reaction (79%, Scheme 2). More importantly, subsequent conversion of amide **11** to alcohol **13** proceeded without any difficulty.<sup>6</sup> The reduction of the amide was realized in two steps starting with SnCl<sub>2</sub> mediated reduction of the nitro group within the Boc-carbamate derived from **11** (70%). In the second operation the arylamino function was allowed to react with isoamyl nitrite to give the corresponding benzotriazole intermediate **A**, which upon

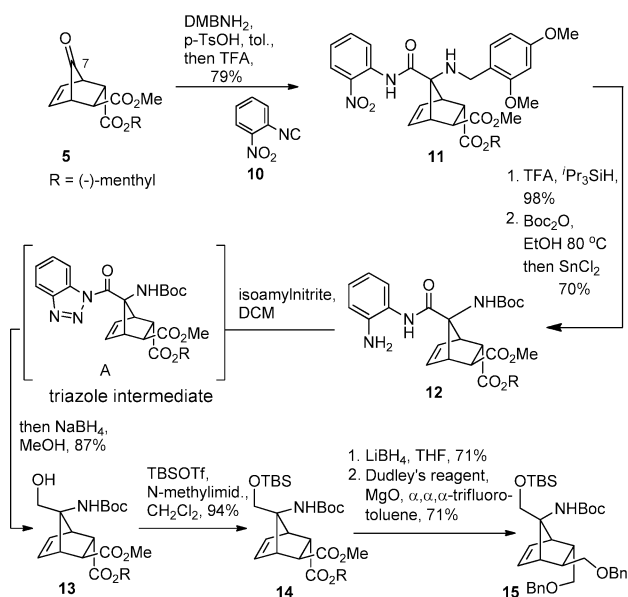
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treatment with NaBH<sub>4</sub> furnished **13** (87%) in a total number of four steps from ketone **5**. Further elaboration of **13**

**Scheme 2.** Synthesis of the Ozonolysis Precursor **15**



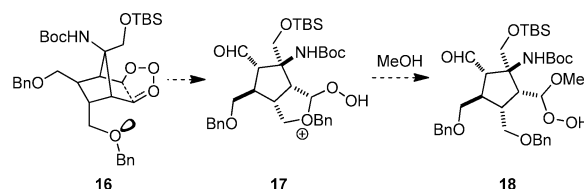
included silylation of the primary alcohol, LiBH<sub>4</sub> mediated reduction of the esters, and protection of the resulting diol using Dudley's reagent to afford norbornene **15** in good yield (71%).<sup>7</sup>

It is noteworthy that this approach enables access to **15** in only 11 steps, which constitutes a significant improvement in step economy when compared to the synthesis of an analogous structure reported previously (15 steps).<sup>3</sup> In order to convert **15** to the necessary cyclopentane ring, it was subjected to ozonolytic conditions entailing an oxidative workup protocol. This procedure provided ester/aldehyde **19** in 76% yield as the only isolable isomer (Scheme 4).<sup>8</sup> We speculate that the *endo*-oriented benzyloxy group influences the breakdown of primary ozonide **16**, which leads to the formation of methylhydroperoxy hemiacetal **18**.<sup>3</sup> This intermediate is further converted to corresponding methyl ester **19** upon treatment with Ac<sub>2</sub>O and base (Scheme 3).

For the introduction of the secondary hydroxyl function present in the D-ring subunit of massadine (**1**), we envisioned the application of Barton's radical decarboxylation/oxygenation chemistry.<sup>9</sup>

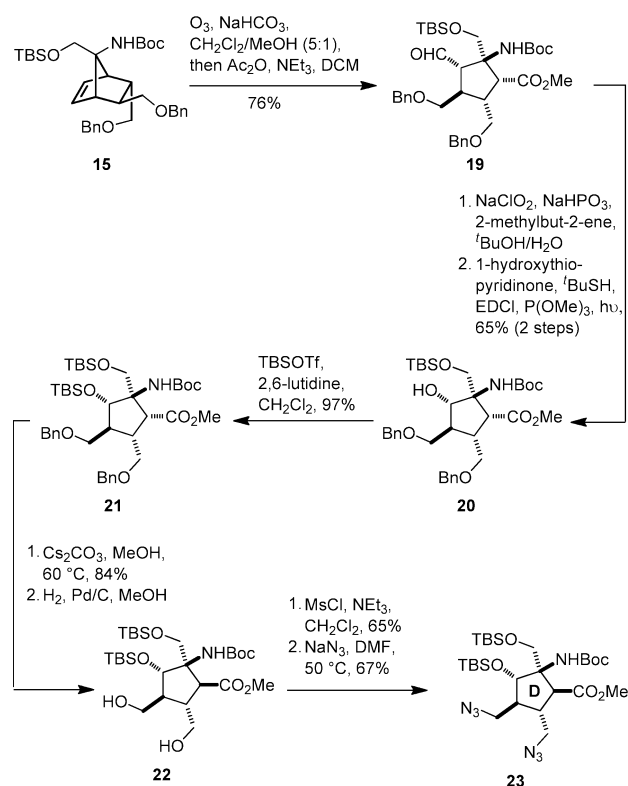
From preliminary studies in this direction we found that hydroxyl installation through oxidative radical decarboxyl-

**Scheme 3.** Mechanistic Proposal for the Regioselective Breakdown of the Primary Ozonide



ation in an atmosphere of oxygen occurs with net retention of configuration most likely controlled by the *endo*-oriented benzyloxymethyl group. Hence, following Pinnick oxidation of ester/aldehyde **19**, the resulting ester/acid was subjected to Barton's decarboxylation conditions furnishing alcohol **20** in 65% yield (Scheme 4).<sup>10</sup> At this point

**Scheme 4.** Completion of the Core Fragment of **1**



remaining operations for completion of the core structure of **1** included conversion of the benzyl ethers into protected amino groups and epimerization of the ester

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(10) Compounds **20–23** have been synthesized by a nonasymmetric route, starting from ketone ( $\pm$ )-**5** (R = Me).

bearing stereogenic center. Accordingly, silyl protection of **20** was followed by base-induced epimerization of the methyl ester group using  $\text{Cs}_2\text{CO}_3$  in methanol (84%) and hydrogenolytic removal of the benzyl ethers, affording diol **22** in good yields. Finally, introduction of the nitrogen substituents was accomplished by mesylation of **22** (65%) and subsequent  $\text{S}_{\text{N}}2$ -displacement of the mesylates with azides (67%), which completed the enantioselective synthesis of the D-ring subunit **23**.

In summary, we have disclosed a concise approach to the core fragment of massadine (**1**). The application of an Ugi-4-component reaction involving a convertible isonitrile enables the facile C7 functionalization of a norbornenone.

The enantioselective route toward core fragment **20** consists of only 19 linear steps, which underscores the efficiency applied in this synthesis.

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**Supporting Information Available:** Experimental procedures and characterization for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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