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Synthesis of the Carbocyclic Core of Massadine

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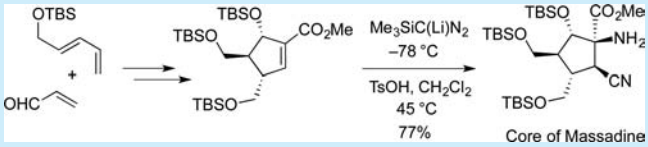
Supporting Information

ABSTRACT: The carbocyclic core of massadine has been synthesized relying on a stereoselective formal [3 + 2] cycloaddition of lithiumtrimethylsilyldiazomethane with α,β-unsaturated esters to form a Δ^2-pyrazoline moiety followed by facile N−N bond cleavage. A unique feature of the current approach is the direct installation of the tertiary α-amino center and a β-cyano group in a cis arrangement on the resulting cyclopentane framework via a previously developed formal aminocyanation protocol.



Pyrrole-imidazole alkaloids constitute a large and architecturally diverse class of natural products, which are solely found in marine sponge cultures.[1] A general characteristic of this group of molecules is the astounding high nitrogen content, which is reflected in the C/N atomic ratio of about 2:1. One of the most complex congeners of this group of metabolites is massadine **1**, which was first isolated from *Stylissa aff. massa* in 2003 by Fusetani and co-workers.[2] Other related compounds, including massadine chloride **2**, palau'amine **3**,[3] and axinellamine A **4** and B **5**,[4] are shown in Figure 1. Recently,

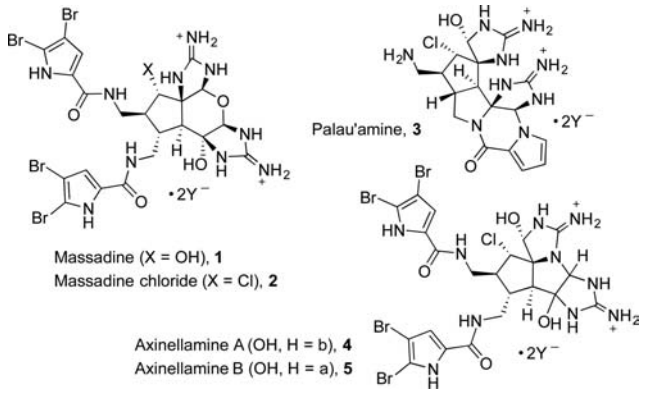


Figure 1. Pyrrole-imidazole alkaloids.

bioactivity-directed assay of extracts from marine sponge *Stylissa caribica* has led to the discovery of stylissadines, a dimeric form of massadine, which constitutes the largest pyrrole-imidazole alkaloid structure ever found.[5] These alkaloids are generally immunosuppressant,[4] cytotoxic,[6] anti-inflammatory,[3b] and antifungal.[2] It was found that massadine inhibits geranylgeranyltransferase 1 (GGTase 1), an enzyme associated with the post-translational prenylation of proteins, resulting in potent fungicidal activity.[7]

The highly polar structures, varying level of halogenation, dense array of functionalities, and stereochemical complexity, as well as the significant biological activities of these natural products, have attracted many research groups to the synthesis of their challenging molecular frameworks.[1,8] In particular, significant efforts have been directed toward the efficient construction of the highly substituted cyclopentane core common to **1**−**5**, and impressive advances have been realized by many groups.[8]

One of the first approaches to these alkaloids was the synthesis of the azabicyclo[3.3.0]octane core framework of the initially reported structure of palau'amine by Overman and co-workers in 1997, in which the stereochemical relationships within the bicyclic ring system were elegantly established through a [3 + 2]-dipolar cycloaddition of an azomethine imine intermediate. The Lovely group has also reported extensive studies in the elaboration of simple imidazoles into more complex derivatives via a novel strategy involving a Diels−Alder reaction followed by an oxidative ring contraction approach.[8d,9] The Chen group has also reported a Mn(III)-mediated radical cascade cyclization radical cyclization strategy for the construction of the highly substituted core skeletons of oroidin dimers and utilized an oxidative ring contraction protocol for the synthesis of Massadine.[10] The Romo group also independently developed and extensively studied the Diels−Alder reaction/oxidative ring contraction strategy.[11] Carreira has reported approaches to the core of massadine via the elaboration of a norbornene scaffold.[8p,12] Baran's synthesis of axinellamines **4** and **5** employed the Pauson−Khand reaction to construct the fully substituted cyclopentenone moiety followed by its elaboration to carry out aza-chlorospirocyclization to install the spiroguanidine moiety.[8v]

Our strategy for the synthesis of the fully functionalized cyclopentane core of massadine is depicted in Scheme 1. We envisioned that a total synthesis of massadine could be realized from an advanced intermediate such as **6**. Strategically, α-amino-β-cyanation involving a formal [3 + 2] cycloaddition and protonolytic N−N bond cleavage[13] would be implemented with α,β-unsaturated cyclopentenotate **7** to deliver **6**. The

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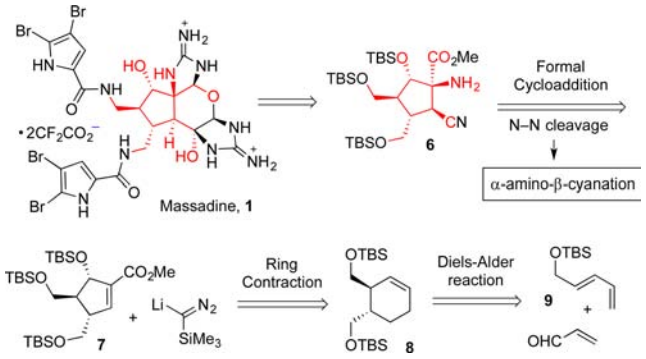
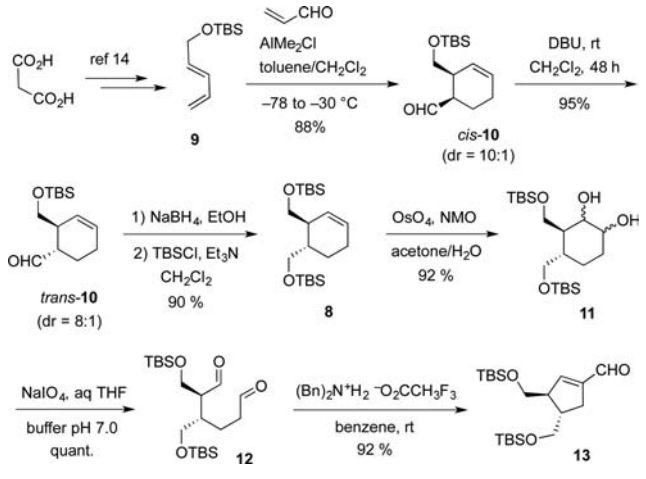
Scheme 1. Retrosynthetic Analysis



stereochemically defined functional-group-containing cyclopentenoate **7** could be derived from cyclohexene derivative **8** via ring contraction and installation of an allylic silyloxy substituent. In turn, a Diels–Alder reaction between diene **9** and acrolein followed by epimerization would set the required trans stereochemistry on the cyclohexene derivative **8**. One of the unique features of this strategy is the installation of the pivotal tertiary amino center at a later stage of the synthetic sequence, which minimizes unnecessary functional group interconversion and makes the overall synthesis efficient and concise.

The preparation of cyclopentenoate **7** commenced with the Diels–Alder reaction of known diene **9**[14] and acrolein (Scheme 2). Although the thermal reaction in refluxing toluene was

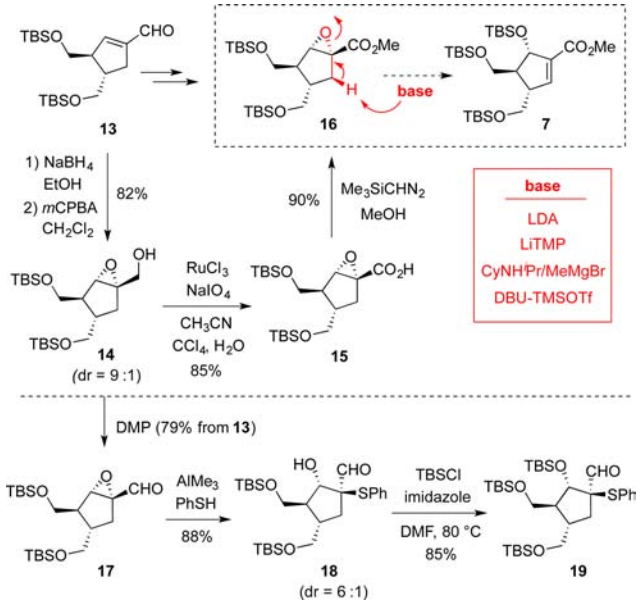
Scheme 2. Synthesis of Cyclopentene Carboxaldehyde



sluggish and low yielding, dimethylaluminum chloride promoted the reaction to give *endo*-selective product *cis*-**10** in 88% yield (dr = 10:1).[15] Epimerization of *cis*-**10** with DBU readily occurred to generate thermodynamically more stable *trans*-isomer *trans*-**10** in a 8:1 ratio. Standard functional group manipulations involving the reduction of aldehyde with $NaBH_4$ followed by TBS-protection of the resulting primary alcohol afforded **8** in 92% yield. Dihydroxylation of **8** (cat. OsO_4, NMO) followed by the oxidative cleavage of the resulting diol **11** ($NaIO_4$, aq THF, pH 7 buffer) afforded dialdehyde **12** which was used for the next step without further purification because it is extremely sensitive and thus decomposed on silica gel. Among several conditions screened, a *trans*-3-hydroxy-L-proline-mediated reaction afforded desired product **13** but only with a marginal yield. We finally found that treating **12** with a catalytic amount of dibenzylammonium trifluoroacetate provided cyclopentene carboxaldehyde **13** in excellent yield (92% in two steps).[16]

To install the required allylic hydroxyl group, we envisioned a base-mediated epoxide opening with **16** (Scheme 3). To test

Scheme 3. Synthesis of α,β-Epoxy Ester and α-Thiophenyl Aldehyde



this seemingly straightforward approach, cyclopentene carboxaldehyde **13** was converted to epoxy alcohol **14** in 82% (dr = 9:1) yield via reduction ($NaBH_4$, EtOH) followed by *m*CPBA treatment.[17] Oxidation of the primary alcohol to the corresponding carboxylic acid **15** (5 mol % $RuCl_3$, $NaIO_4$)[18] and a subsequent esterification (trimethylsilyldiazomethane, MeOH) delivered **16** in 90% yield (two steps).[19] Unfortunately, however, all attempts to open the epoxide under various conditions failed, returning the **16** intact.

Eventually, the installation of the allylic hydroxyl group was realized via the conversion of epoxy alcohol to the corresponding aldehyde **17** followed by treating it with dimethylaluminum thiophenoxide generated *in situ* by mixing $AlMe_3$ and thiophenol at 0 °C,[20] which afforded α-phenylthio aldehyde **18** in 88% yield (dr = 6:1). The resulting free hydroxyl group was then protected as TBS-ether (TBSCl, imidazole, DMF, 80 °C) to generate **19**. Having installed the phenylthio group on the α-carbon of the formyl group in **19**, its oxidation to the corresponding sulfoxide **20** followed by its elimination was examined under various conditions (Table 1). While treating **19** with $NaIO_4$ in aqueous MeOH[21] returned the starting material untouched (Table 1, entry 1), H_2O_2 and catalyst scandium triflate[22] led to complete decomposition (Table 1, entry 2). Typical *m*CPBA conditions under different temperatures and solvents did afford the desired sulfoxide with moderate diastereoselectivity (3:1–5:1). Unfortunately, however, in a subsequent elimination step, only the minor isomer was eliminated to provide **21** and the major sulfoxide remained intact even after a long reaction time or at higher temperature (Table 1, entries 3 and 4). To our delight, it was found that treating **19** with H_2O_2 in an acidic media[23] furnished sulfoxide **20** with excellent diastereoselectivity (>19:1), which underwent

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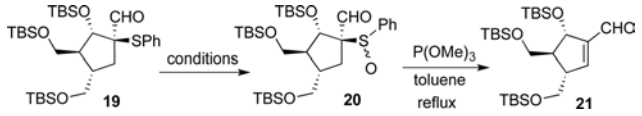
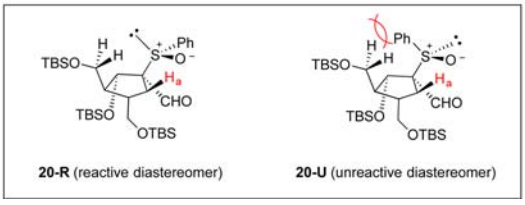
Table 1. Oxidation of the Phenylsulfide and Its Elimination



entry	conditions	dr of **20**	result
1	$NaIO_4$, aq MeOH, rt	—	Recovering starting material
2	$Sc(OTf)_3$, H_2O_2, CH_2Cl_2/EtOH	—	Complex reaction mixture
3	*m*CPBA, CH_2Cl_2, –78 °C to rt	3:1	Only the minor isomer eliminated
4	*m*CPBA, MeOH, 0 °C	5:1	Only the minor isomer eliminated
5	H_2O_2, AcOH/CH_2Cl_2, rt	>1:19	76% in 2 steps

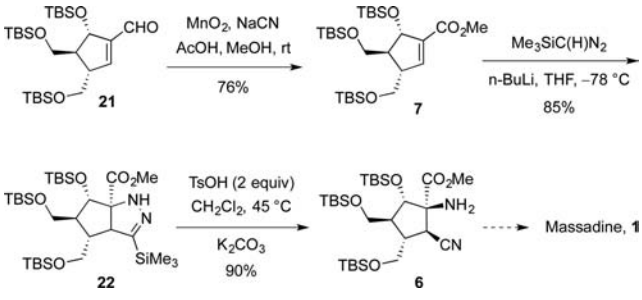


smooth elimination upon heating in the presence of $P(OMe)_3$ to deliver **21** in 76% yield over two steps (Table 1, entry 5).

At this point, it is beyond our understanding how simple conditions such as H_2O_2/AcOH can achieve such high selectivity for diastereomeric sulfoxide **20** compared to other conditions. However, based on the behavior of sulfoxide diastereomers for elimination, we tentatively propose that isomer **20-R** would be the one undergoing facile elimination whereas **20-U** is the unreactive isomer as shown in the inset in Table 1. We infer that diastereomer **20-R** may easily assume a reactive conformation for elimination with close proximity between the sulfoxy moiety and the β-proton H_a. On the other hand, diastereomer **20-U** may suffer from achieving the reactive conformation as shown because of the steric interaction between the phenyl group pointing to the top face of the cyclopentane core and the CH_2OTBS group.[23]

Securing a sizable amount of aldehyde **21** sets the stage to explore the key α-amino-β-cyanation through a formal cycloaddition with lithiumtrimethylsilyldiazomethane and a subsequent N–N bond cleavage (Scheme 4). Toward this goal,

Scheme 4. Completion of the Fully Functionalized Cyclopentane Core of Massadine



cyclopentene carboxaldehyde **21** was converted to the corresponding methyl ester **7** under Corey–Ganem conditions. Treatment of cyclopentenoate **7** with lithium trimethylsilyldiazomethane, *in situ* generated from *n*-BuLi and trimethylsilyldiazomethane at −78 °C, furnished Δ^2-pyrazoline **22** in 85% yield as a single diastereomer. The subsequent N–N bond cleavage was achieved by treating pyrazoline **22** with toluenesulfonic acid (2 equiv) in CH_2Cl_2 at 45 °C, affording the free primary amine-containing cyclopentane carboxylate **6** in 90% yield.

In conclusion, we have developed an efficient strategy to access the highly substituted carbocyclic core of massadine and other structurally related pyrrole-imidazole alkaloids. One of the salient features in the present synthetic approach is the stereoselective installation of the tertiary α-amino center along with the required cyano group at the β-position in a cis relationship using a formal [3 + 2] cycloaddition between lithium trimethylsilyldiazomethane and α,β-unsaturated esters. An operational advantage to the relatively late-stage implementation of this key transformation of the synthetic sequence is that unnecessary protecting group manipulations can be avoided. Further elaboration of the carbocyclic core is underway toward a total synthesis of massadine.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02709.

Detailed experimental procedures, characterization data and spectroscopic data of all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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