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A Nitron Dipolar Cycloaddition Strategy toward an Enantioselective Synthesis of Massadine

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Abstract

An enantioselective route to the C,D-bicycle of massadine is reported. Enantiopure intermediates were generated by a single stereoselective reduction using the Corey–Bakshi–Shibata reagent. This initial stereoreduction was translated into the five contiguous stereocenters of the massadine D-ring by a synthetic route that features a diastereoselective and stereospecific Ireland–Claisen rearrangement of a trianionic enolate followed by a diastereoselective nitron dipolar cycloaddition of a highly electron-poor oxime.

Graphical Abstract

The pyrrole-imidazole alkaloids are a large, structurally diverse, and bioactive family of marine-isolated natural products constructed of oroidin units.^{1–5} Of this family, the

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Supporting Information

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Experimental details, ¹H and ¹³C NMR spectra of new compounds, and crystallographic data for *syn*-**15a** and **26** (PDF)

Accession Codes

CCDC 1839960–1839961 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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molecules derived from the oxidative dimerization of oroidin are the most structurally complex and synthetically challenging.^{6,7} Massadine (**1**)⁸ and related natural products axinellamine⁹ and palau'amine^{10,11} have been the subject of much synthetic work,^{12–25} although only the Baran, Chen, and Namba groups have published completed syntheses of any of these molecules.^{26–32} Central to the synthetic challenge posed by these molecules is the high heteroatom content (approximately 2:1 C/N), especially the proximal arrangement of two positively charged guanidinium functional groups. Massadine, in particular, contains a highly congested and stereochemically rich tetracyclic core. The central tetrahydropyran B-ring is flanked by two cationic aminoimidazoline units in addition to the fully substituted cyclopentanol D-ring. Its eight contiguous stereocenters contain a fully substituted amine center (C13) as well as trans-oriented vicinal aminomethyl groups that require special synthetic attention. The high heteroatom count presents a further challenge for the chemoselectivity of the current synthetic methods.

These natural products are proposed to have a shared biosynthesis that stems from a “pre-axinellamine” structure that contains the shared central cyclopentane flanked by two oxidized aminoimidazole units.¹ This biosynthetic proposal indicates that a synthesis of these molecules that focuses on the early assembly of the core cyclopentane has the potential to be broadly applicable to the family at large. A strategy that utilizes pericyclic reactions might take advantage of the inherent stereoselectivity of their highly organized transition states. This approach was inspired by work from the Overman laboratory, where an azomethine ylide was used to construct advanced intermediates toward palau'amine.^{33–36} It was thought, therefore, that the sequential use of pericyclic reactions that take advantage of massadine's functional density could enable an enantioselective synthesis where a single initial stereocenter could be relayed to the remaining seven centers.

The retrosynthetic analysis of massadine (**1**) aimed to use the high heteroatom count as an asset toward both stereo-selectivity and chemoselectivity (Scheme 1). The inherent functionality of the natural product could therefore be utilized as a set of handles to direct the desired transformations. The retrosynthetic analysis followed some of the precedent from the Baran and Chen groups as well as our own model studies, which suggested that the central tetrahydropyran B-ring could be formed from a structure such as **2** by reduction of a glycoamidinium followed by oxidative cyclization onto the aminoimidazole.^{28,30,31} The guanidine functionality would then be installed onto a cyclopentanol precursor such as **3**. Construction of the cyclopentanol was envisioned to arise from intramolecular nitron dipolar cycloaddition of ene–nitron **4** followed by cleavage of the isoxazolidine N–O bond.^{37–40} Preferential pseudoequatorial orientation of the substituents in the chairlike cycloaddition transition structure would establish the C2 and C13 stereocenters. This reaction would also directly install heteroatom functionality where it would be needed for late-stage guanidine installation. Cycloaddition substrate **4** could be synthesized from carboxylic acid **5**, which in turn would be produced by a stereospecific Ireland–Claisen rearrangement of an allylic ester. It was thought that the nature of the nitrogen protecting groups at this stage would be critical in controlling the diastereoselectivity of this rearrangement. The Ireland–Claisen rearrangement substrate could be derived from alcohol **6** by acylation with a β -alanine derivative. One salient feature of this strategy was that the

forward synthesis could be easily rendered enantioselective with the single stereoisomer of allylic alcohol **6** directing the establishment of all eight stereocenters in massadine (**1**).

Three allylic esters were prepared to study the Ireland–Claisen rearrangement (Scheme 2). An allylic ester with basic amine functionality was prepared by Horner–Wadsworth–Emmons olefination of the aldehyde derived from ethanolamine (7). Reduction of ketone **8** to alcohol **9** was followed by acylation with acryloyl chloride and conjugate addition onto the resultant acrylate with dibenzylamine to provide ester **10**. Two Boc-protected allylic esters were also synthesized: one with an unsubstituted side chain (**13a**) and another with additional oxidation at the terminal carbon (**13b**). These substrates would present fully anionic nitrogen atoms under the Ireland–Claisen conditions. Both were obtained from Wittig olefination of Bocglycinal with the requisite ketophosphorane (**11**).⁴¹ Reduction of ketone **12a** followed by nucleophilic ring-opening reaction of *N*-Boc- β -lactam provided racemic ester **13a**. Ketone **12b** was reduced enantioselectively with the (*S*)-CBS-oxazaborolidine reagent and was acylated by carbodiimide coupling with *N*-Boc- β -alanine to provide allylic ester **13b**. A stoichiometric amount of oxazaborolidine was required to ensure both high yield and enantioselectivity were achieved. The enantiopurity and absolute configuration of **13b** were confirmed by Mosher ester analysis of the intermediate alcohol.

The Ireland–Claisen strategy hinged around transmitting easily established carbon–oxygen stereochemistry to the C1–C15 bond in massadine. The C1 stereocenter would be set by the absolute stereochemistry of the allylic ester, but the C15 center would necessitate selectively synthesizing the *Z*-enolate of the appropriate ester (i.e., **14**, Table 1).⁴² We anticipated that the nearby nitrogen atoms would allow the use of natural functionality to direct the stereochemistry of deprotonation. Specifically, chelation of the β -nitrogen atom would force deprotonation to provide a *Z*-enolate such as **14**.^{43,44} Rearrangement of enolate **14** would then stereoselectively provide a γ,δ -unsaturated carboxylic acid (**15**).

Benzyl-protected diaminoester **10** was initially used to study the Ireland–Claisen rearrangement (Table 1). For all rearrangements, it was found that productive reactions only occurred when base was added to freshly distilled TMSCl premixed with the ester. Addition of TMSCl after deprotonation resulted in decomposition to the alcohol, presumably through ketene elimination. Under standard rearrangement conditions, lithium diisopropylamide (LDA) and TMSCl, rearrangement of **10** occurred in good yield to provide a 30:70 mixture of diastereomers, favoring the undesired *syn* isomer of **15a** (entry 1). The preferential formation of *syn*-**15a** indicated that the *E*-enolate was generated predominantly, and this product is the expected major diastereomer for these kinetic deprotonation conditions.⁴⁵ Therefore, the hypothesis that the Lewis basic nitrogen atoms would enforce *Z*-selectivity in enolate synthesis does not hold for this substrate. Conditions that typically favor *Z*-enolate formation, such as addition of HMPA (entry 2), did reverse the selectivity to the desired diastereomer (*anti*-**15a**) but failed to produce synthetically useful yields or diastereoselectivities. Other additives, such as ZnCl₂, or lithium salts also failed to improve the diastereoselectivity.^{43,44,46}

It was then hypothesized that an anionic nitrogen might more strongly enforce *Z*-enolate intermediate **14** in the Ireland–Claisen rearrangement. Under standard rearrangement

conditions, allylic ester **13a** reacted in modest yield to provide γ,δ -unsaturated acid **15b** as a single diastereomer (entry 3). A survey of bases identified LHMDs as the optimal base for this transformation, providing **15b** in 58% yield (entry 4). Attempts to improve conversion by either increasing the reaction temperature or by influencing potential lithium aggregates with additives failed to increase the yield of **15b** (e.g., entry 5); however, nearly quantitative recovery of unreacted starting material was possible under the optimized conditions. These conditions were also ideal for the rearrangement of silyloxy-substituted ester **13b** (entry 6). It is important to note that under all conditions tested, only a single diastereomer of acid **15b/c** was produced, with no evidence of the *syn* diastereomer visible by ¹H NMR analysis. These results indicate high selectivity for the *Z*-enolate stereoisomer, directed by intramolecular chelation of the nearby carbamate. The fully anionic nature of the carbamate group appears to be required to enforce the stereoselectivity of this deprotonation as compared to the neutral tertiary amine substituents that were initially investigated.

γ,δ -Unsaturated acids **15b** and **15c** were then elaborated to the oxime substrate for intramolecular nitron-dipolar cyclo-addition (Scheme 3). Acids **15** could be activated as the acyl imidazole derivatives by reaction with 1,1'-carbonyldiimidazole (CDI). Reaction of these acyl imidazoles with the lithium enolate of *tert*-butylacetate afforded β -ketoesters **16** in good yield. β -Ketoesters **16** could then be nitrosated with sodium nitrite under acidic conditions to provide key cycloaddition substrates **17**.

Reduction of the ketone of **17a** followed by thermal nitron dipolar cycloaddition successfully provided a fully substituted cyclopentane (eq 1). However, this reduction provided the epimeric alcohol at C14 (**18**). This configuration was confirmed by NOESY studies and by chemical correlation. It appeared that the hydride reduction of ketone **17a** selectively provided the undesired configuration, which is the predicted product of both Felkin- and chelation-controlled hydride addition models.

(1)

In order to circumvent this issue with stereoselectivity, the order of cycloaddition and reduction was reversed. Nitron dipolar cycloadditions of double electron-withdrawing oximes are not well preceded,^{47,48} and indeed, nitron **17** proved to be a more challenging substrate for dipolar cycloaddition than its corresponding C14 alcohol (Table 2). Thermal cycloaddition provided variable yields of cyclopentanone **19** in only modest diastereoselectivities (entry 1). Furthermore, these conditions were not amenable to scale, as **19** decomposed under the reaction conditions. Lewis acids were then investigated as they have been shown to accelerate cycloaddition reactions of electron-poor dipoles.⁴⁹ A survey

of Lewis acids found that magnesium bromide was uniquely useful for the desired cycloaddition (entries 2 and 3). The reduced temperatures allowed by MgBr₂ catalysis enabled reproducible production of isoxazolidine **19a** in good yield and high diastereoselectivity. Interestingly, nitron **17b**, with additional oxidation at the allylic position was more effectively cyclized with ZnCl₂ (entries 4 and 5). Diastereoselectivities for this substrate were also noticeably lower, but the two diastereomers were readily separated by chromatographic methods.

The resulting cyclopentanones were reduced stereoselectively and protected to give alcohols **20** (Scheme 4). Diastereoselective reduction of ketone **19** was likely directed by the adjacent amine in conjunction with the bulky *tert*-butyl ester to give hydride addition to the concave face of the bicyclooctane. This is supported by the observation that diastereoselectivity was reduced if the amine was protected before ketone reduction. Cleavage of the N–O bond with samarium diiodide to **21** followed by chemoselective oxidation of the resulting alcohol provided fully substituted cyclopentanols **22**, representing the complete massadine D-ring.

Initial studies to elaborate carbocycles **22** focused on conversion to a bromoketone (e.g., **3**) in order to intercept model studies that identified such a compound as a promising intermediate. Unfortunately, neither methyl ketone **22a** or silyloxyketone **22b** was a suitable substrate for this conversion. Both α -oxidation strategies and attempts to convert the silyl ether to a bromide were challenged by the steric congestion and functional group density of ketones **22**.

It was thought that installation of the glycoamidine C ring might alleviate some of the steric congestion that plagued these attempts (Scheme 5). Reduction of ketone **19b** was followed by silver-mediated guanylation of the isoxazolidine to provide differentially substituted guanidine **23**. Hydrogenolysis of the Cbz protecting group initiated cyclization to tricycle **24**. Hydrogenation of the N–O bond required the addition of base and provided C,D-bicycle **25** in good yield. Under these basic conditions, however, the TBS protecting group migrated between the two vicinal alcohols. This equilibrium favored the primary silyl ether **25** and occurred in the absence of the palladium catalyst. Minor isomer **26** was crystalline, allowing for the unambiguous determination of the relative stereo-chemical configuration of the fully substituted cyclopentane. This sequence provided the spirocyclic C,D ring system with the proper functionalization and stereochemical arrangement for the eventual elaboration to the natural product (**1**).

A concise and stereoselective route to the fully substituted cyclopentane ring of the dimeric pyrrole-imidazole alkaloids massadine, axinellamines A–B, and palau'amine has been developed. The present route takes advantage of two key stereospecific transformations to synthesize complex enantio-pure intermediates. Challenging Ireland–Claisen rearrangements of trianionic intermediates (**13**) were shown to proceed with high diastereoselectivity. The templating effect of the nearby nitrogen functionality was found to rely on this anionic character. Additionally, an unprecedented 1,3-dipolar cyclo-addition of an α -nitroso- β -ketoester (**17**) generated the fully substituted cyclopentane. Lewis acid catalysis of this cyclo-addition improved the yield, diastereoselectivity, and reproducibility of this reaction.

This strategy utilized the intrinsic functionality of massadine to affect the selective synthesis of functionally dense and stereochemically rich polycycles.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Scheme 1.
Retrosynthetic Analysis

Scheme 2.
Allylic Ester Synthesis

Scheme 3.
Synthesis of Oxime Substrates

Scheme 4.
Conversion to Functionalized Cyclopentane

Scheme 5.
Synthesis of C-Ring

Table 1.

Ireland–Claisen Rearrangement^a

entry	R, N	base (equiv)	yield (15) (%)	anti/syn ^b
1	H, NBn ₂ (10)	LDA (2)	75 (15a)	30:70
2 ^c	H, NBn ₂ (10)	LDA (2)	66 (15a)	62:38
3	H, NHBoc (13a)	LDA (4)	33 ^d (15b)	>20:1
4	H, NHBoc (13a)	LHMDS (4)	58 ^d (15b)	>20:1
5 ^e	H, NHBoc (13a)	LHMDS (4)	42 ^d (15b)	>20:1
6	OTBS, NHBoc (13b)	LHMDS (4)	48 ^d (15c)	>20:1

^a[**10/13**] = 0.1 M, 4 equiv TMSCl, –78 to +40°C.^bDetermined by ¹H NMR analysis of the unpurified reaction mixture. The configuration of *syn*-**15a** was confirmed by X-ray crystallographic analysis (see the SI for details).^cSolvent: 23% HMPA in THF.^dQuantitative recovery of starting material.^eWith 6 equiv of LiCl.

Table 2.

Nitron Dipolar Cycloaddition^a

entry	R	Lewis acid	temp (°C)	yield (%) ^b	dr ^c
1	H		150 ^d	0–60	3:1
2	H	Zn(OTf) ₂ ^e	23	0	
3	H	MgBr ₂ · OEt ₂	50	55	10:1
4	OTBS	MgBr ₂ · OEt ₂	60 ^d	40	3:1
5 ^e	OTBS	ZnCl ₂	50 ^d	46	3:1

^a[**17**] = 0.05 M, 0.1 equiv of Lewis acid.^bIsolated yield of diastereomerically pure **19**.^cDetermined by ¹H NMR analysis of the unpurified reaction mixture.^dConducted in a microwave reactor.^e0.5 equiv of Lewis acid.