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Synthesis of the 5,6-Dihydroxymorpholin-3-one Fragment of Monanchocidin A

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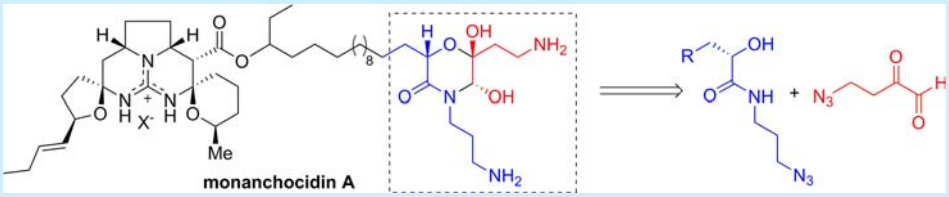
Supporting Information



ABSTRACT: Monanchocidin A is a recently isolated pentacyclic guanidinium alkaloid that contains an unusual highly oxidized morpholinone fragment. Herein we report a rapid synthesis of this heterocyclic scaffold and confirm its structure. The key reaction involves an acid promoted hemiketalization/hemiaminalization of an α-hydroxyamide and α-ketoaldehyde that proceeds with exclusive regioselectivity and high diastereoselectivity to form the natural scaffold in moderate to high yield.

Pentacyclic guanidinium alkaloids are a family of marine natural products isolated from several species of marine sponges. These complex molecules have received significant interest from the scientific community due to their complex structures and diverse biological activity.[1,2] Recently a new member of the pentacyclic guanidine family, monanchocidin A (**1**, Figure 1), was isolated from the sponge *Monanhora*

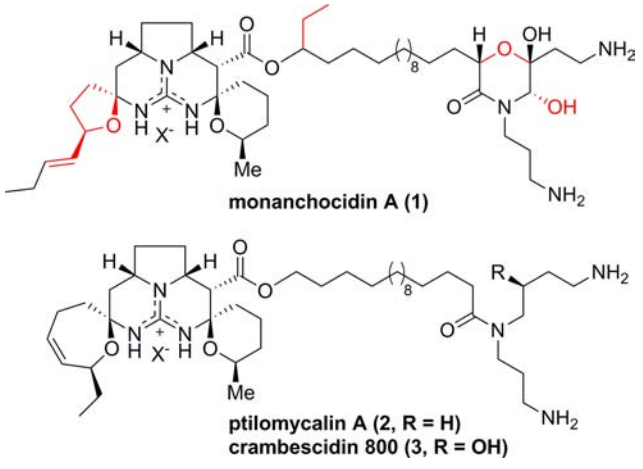


Figure 1. Structures of pentacyclic guanidine alkaloids.

pulchra.[3,4] **1** possesses several features not present in previously isolated alkaloids (for example, **2** and **3**, Figure 1), including a 1-oxa-6-azaspiro[4.5]decane in the pentacyclic guanidine domain, branching in the long chain spacer (ω-3 position vs ω-position), and a heavily oxidized and cyclized spermidine side chain (morpholinone). The heavily oxidized morpholinone is the most complex "anchor domain" observed in the pentacyclic guanidinium alkaloids to date and raises interesting questions regarding the potential role of this scaffold in the biological activity of monanchocidin A. It is known that the spermidine "anchor" is required for many of the biological properties of ptilomycalin A and the crambescidins (**2** and **3**, Figure 1); however, little is understood regarding the structural requirements or biological role of this polar tail.[2]

As part of our efforts to explore the chemistry and biology of monanchocidin A (**1**) and related marine natural products we began evaluating approaches to construct the morpholinone ring of **1**. The most straightforward approach to prepare a morpholinone such as **4** would be the coupling/cyclization of α-hydroxyamide **5** with α-ketoaldehyde **6** (Figure 2). Although

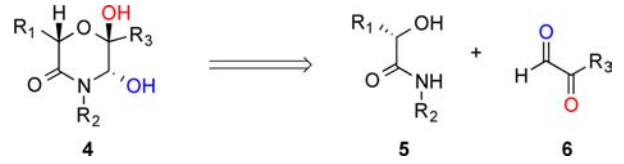


Figure 2. Retrosynthetic approach to morpholinone **4**.

this disconnection would conceptually provide the necessary ring structure, key questions regarding regiochemistry, stereochemistry, and overall stability were present at the outset of our efforts.[5]

To evaluate the potential of our planned approach we screened a series of acids and solvents for their ability to promote the formation of morpholinone **9** from hydroxyamide **7** and ketoaldehyde **8** (Table 1). Strong acids such as TFA and HCl provided only trace amounts of product even after extended reaction periods, which may be attributed to the

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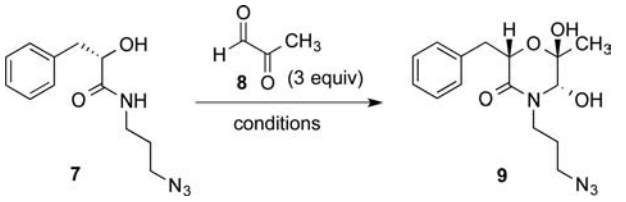
Table 1. Optimization of Morpholinone Formation



no.	acid (1 M)[a]	conditions	9 (%)[b,c]	brsm (%)[e]
1	TFA	$CHCl_3$, rt, 96 h	<10[d]	–
2	HCl	THF, rt, 96 h	<10[d]	–
3	*p*-TsOH	$CHCl_3$, rt, 96 h	<10[d]	–
4	PPTS	$CHCl_3$, rt, 96 h	<10[d]	–
5	CSA	CH_2Cl_2, rt, 48 h	29	45
6	CSA	CH_3CN, rt, 48 h	56	77
7	CSA	dioxane, rt, 48 h	50	80
8	CSA	$CHCl_3$, rt, 48 h	43	52
9	CSA	toluene, rt, 48 h	59	82
10	CSA	DMF, rt, 96 h	<10[d]	–
11	CSA	MeOH, rt, 96 h	0	–

[a]TFA = trifluoroacetic acid; PPTS = pyridinium *p*-toluenesulfonate; CSA = camphorsulfonic acid. [b]One isomer isolated after column chromatography. [c]Isolated yields unless otherwise noted. [d]<10% Yields determined by integration of UV peaks (254 nm). [e]Calculated based on recovery of 7.

decomposition of starting material under the harsh reaction conditions (entries 1 and 2). To explore the effect of acid strength we next screened *p*-TsOH, PPTS, and CSA (entries 3–5, Table 1). Surprisingly, while *p*-TsOH and PPTS were mostly ineffective for the reaction, CSA in dichloromethane provided the morpholinone product in 29% yield (45% brsm) after stirring for 96 h.[6] Further screening of solvents revealed toluene to be the best solvent for this substrate with acetonitrile, dioxane, and chloroform also providing moderate yields of the desired product (entries 6–9, Table 1). Compound **9** was not formed in polar aprotic solvents such as DMF and polar protic solvents such as methanol (entries 10 and 11, Table 1). It is interesting to note that in no case did we observe complete conversion, even upon addition of additional ketoaldehyde or acid. Fortunately, the unreacted hydroxyamide could be isolated in most cases, which will be particularly important for more complex systems required for preparation of monanchocidin A.

Having straightforward access to the morpholinone heterocycle, we sought to confirm the regiochemistry and stereochemistry of this unusual scaffold. As shown in Figure 3, HMBC (a) and NOESY (b) correlations are in agreement with the proposed structure and match the data reported by the isolation group. Additionally, carbon and proton NMR data are in agreement with the morpholinone region reported for **1**.[7]

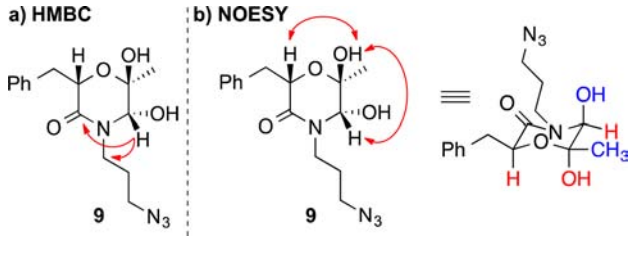


Figure 3. HMBC (a) and NOESY (b) correlations of **9**.

With morpholinone **9** in hand our attention turned to the installation of the other amino group present in the natural product. To prepare this more complex system would require *β*-amino ketoaldehyde **10** (Figure 4). The preparation of **10**

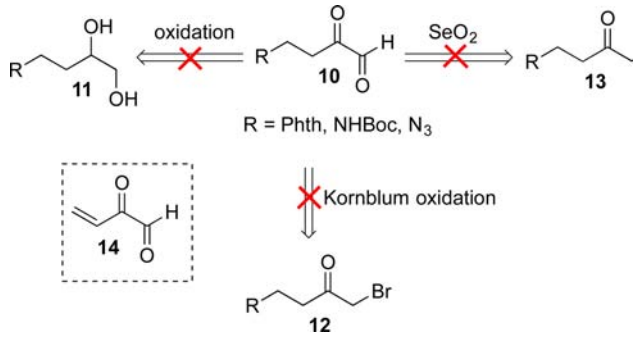
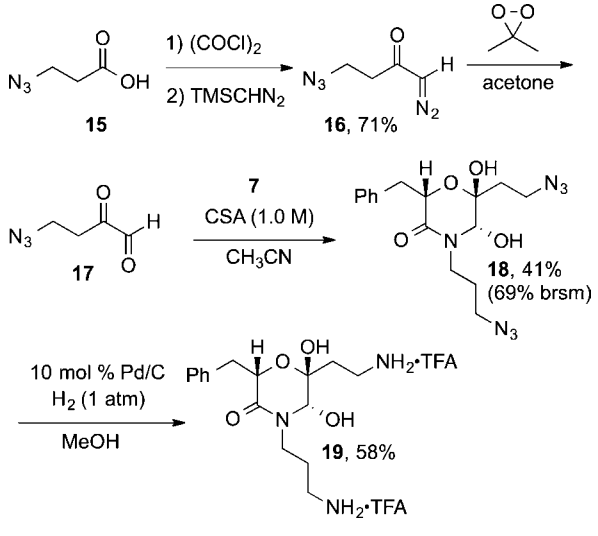


Figure 4. Attempted preparation of ketoaldehyde **10**.

was challenging due to the presence of a *β*-amino group and the proximity of the amino functionality to the reactive ketoaldehyde. A variety of protected substrates underwent elimination of the protected *β*-amino group during attempted installation of the ketoaldehyde to presumably give **14**[8] or were otherwise incompatible with the harsh oxidation conditions employed (Figure 4). A subset of the attempted reaction conditions includes oxidation of diol **11** with a variety of oxidants,[9] Kornblum-type oxidations of *α*-bromoketone **12**,[10] and Riley oxidation (SeO_2) of ketone **13**.[11] Installation of the amino group at a later stage of the synthesis failed, and a variety of protecting group strategies also did not allow for preparation of **10**.

It was finally found that the combination of an azide as the amine precursor and mild dimethyldioxirane (DMDO) oxidation of an *α*-diazoketone was successful for the preparation of *β*-amino ketoaldehydes.[5c,12] To this end, acid **15** was treated with oxalyl chloride followed by (trimethylsilyl)diazomethane to generate *α*-diazoketone **16** in 71% yield (Scheme 1). With **16** in hand the diazo moiety was oxidized with DMDO and the resulting ketoaldehyde **17** (3 equiv) was reacted with amide **7** under our optimized conditions

Scheme 1. Synthesis of the Morpholinone Heterocycle of Monanchocidin A (19)



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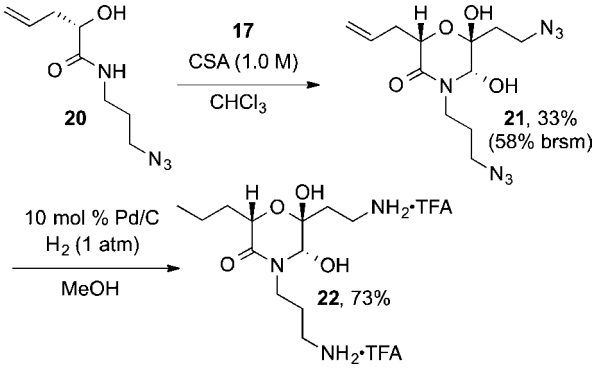
(acetonitrile employed for solubility of this substrate) to provide morpholinone **18** in 41% yield (69% brsm) (crude material was a 9:1 mixture of diastereomers, but only the major diastereomer was isolated after chromatography). Reduction of the bis-azide was accomplished via hydrogenation over Pd/C to reveal morpholinone diamine **19** in 58% yield after reversed phase chromatography. We found it to be essential to use heterogeneous reduction conditions, as **18** is not stable to extended treatment with PPh_3; however, it is important to note that the final product is stable to reversed phase chromatography (0.1% TFA) and is stable to storage at room temperature for several weeks without significant decomposition.

In addition to phenyl substituted derivative **19** we also targeted allyl-functionalized morpholinone **21**, as this moiety contained a handle for future incorporation into the natural product and could be reduced to provide the diamine required for monanchocidin A. Analogous to the preparation of **19**, **21** was prepared from amide **20** and ketoaldehyde **17** in 33% yield (58% brsm, [crude material was a 4:1 mixture of diastereomers, but only the major diastereomer was isolated after chromatography[13]]) followed by reduction of both azides and the terminal alkene to give **22** in 73% yield (Scheme 2).

Scheme 2. Synthesis of a Propyl-Containing Derivative (22)



In conclusion, we have developed a synthetic approach to the unusual and heavily oxidized morpholinone heterocycle contained in monanchocidin A. These initial studies have revealed key insights into the chemical properties and stability of these heterocycles and pave the way for their further study. Exploration into the role of these scaffolds in biology, particularly as probes to explore polyamine signaling pathways,[14] is ongoing and will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, characterization of products, ^1H, ^{13}C, and 2D-NMR spectra are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

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(4) The absolute stereochemistry of **1** was not assigned in the isolation report, and we have chosen to draw the absolute configuration analagous to that of ptilomycalin A.

(5) For related reactions of 1,2-dicarbonyls, see: (a) Ley, S. V.; Diez, E.; Dixon, D. J.; Guy, R. T.; Michel, P.; Nattrass, G. L.; Sheppard, T. D. *Org. Biomol. Chem.* **2004**, *2*, 3608. (b) Giovenzana, G. B.; Palmisano, G.; Del Grosso, E.; Giovannelli, L.; Penoni, A.; Pilati, T. *Org. Biomol. Chem.* **2005**, *3*, 1489. (c) Groarke, M.; McKervey, M. A.; Nieuwenhuyzen, M. *Bioorg. Med. Chem. Lett.* **2000**, *41*, 1275. (d) Lerouzic, A.; Raphalen, D.; Papillon, D.; Kerfanto, M. *Tetrahedron Lett.* **1985**, *26*, 1853.

(6) Additional product was not observed if the reaction was allowed to proceed for longer reaction times; however, if purified **9** was resubjected to the reaction conditions amide **7** was observed (~25% after 18 h) suggesting that the reaction is reversible and may reach equilibrium under the employed conditions.

(7) A comparison of the ^1H and ^{13}C NMR data of our natural product fragment (**22**) to that of the morpholine region of **1** is presented in the Supporting Information.

(8) Tentative assignment as this compound was not stable to isolation and purification.

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(13) **22** Contains trace ammounts of starting material **21**.
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