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A ring expansion approach to *N*-oxy-2,5-diketopiperazines

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ABSTRACT

A ring expansion of tetramic acids (pyrrolidine-2,4-diones) to *N*-oxy-2,5-diketopiperazines (DKPs) is described. This method allows for the facile and late-stage construction of the hydroxamic acid moiety and can thereby serve as a general method for accessing *N*-oxy-2,5-DKP natural products.

Introduction

N-oxy-2,5-diketopiperazines (DKPs) are found in many biologically-relevant natural products (Fig. 1, blue highlight) [1,2], that exhibit a broad range of activities including antibacterial, antifungal, toxicity toward HeLa and HL-60 cells, anti-HCV, and antiinsectan, to name a few.

Approaches for preparing compounds possessing either a DKP or *N*-oxy-2,5-DKP core often involve the intermediacy of *N*-protected dipeptides which, upon deprotection, can undergo the desired cyclization [1a,3]. However, heating under acidic conditions or exposure to base, with the concomitant risk of racemization in chiral substrates, is often required to effect this transformation. Additionally, these approaches are often adversely affected by sterics and the propensity of most amide bonds to adopt extended conformations. The difficulties of cyclization are more acute when preparing the complex subclass of *N*-oxy-2,5-DKPs, due to the inherent lability of the *N*—*O* bond [4]. Notably, fragmentation of this bond can occur thermally, under basic conditions, or promoted by acid *via* a proposed 1,5-hydride shift such as reported by Liu (see footnote), and as observed in our studies directed toward the penicisulfuranol class of natural products [4h,5]. In considering approaches that would avoid the limitations imposed by early installation of the *N*—*O* bond in a synthesis, we were inspired by our previous efforts wherein we employed a ring expansion reaction to access the hydroxamic acid intermediate in our total synthesis of (±)-phyllantidine (Scheme 1a) [6]. Specifically, we recognized that application of this method, employing tetramic acids as substrates, held the potential for delivering *N*-oxy-2,5-DKPs (Scheme 1b).

At the outset, we anticipated that the requisite oximes (**III**) would be readily available, but their subsequent transformation to the acyloxy nitroso intermediate (**II**) and regioselective ring expansion to **I** remained very much in question. Herein, we report the realization of this ring expansion strategy in the preparation of an *N*-protected, 33 3-substituted *N*-oxy-2,5-DKP.

Results and discussion

In the forward sense, we first sought an efficient approach to the preparation of the requisite tetramic acid-derived oxime. As illustrated in Scheme 2, our point of departure was known 3,4-dimethoxybenzene *N*-protected (DMB) glycine methyl ester (**1**) [7], which was converted to amide **2** upon exposure to methyl malonyl chloride under Schotten-Baumann conditions [8]. Subsequent Dieckmann cyclization of **2** gave an intermediate tetramic acid ester (not shown), which, upon solvent exchange to wet acetonitrile and warming to 85 °C, underwent decarboalkoxylation to produce DMB-protected tetramic acid **3** in 95% yield. Although one can envision advancing **3** under a variety of direct alkylation conditions, we found that acid-promoted aldol condensation with benzaldehyde, followed by an L-proline-mediated Hantzsch ester reduction of the derived benzylidene (**4**, 1.3:1 E/Z) produced the desired tetramic acid **5** in 80% yield over the two steps. Exposure of ketone **5** to hydroxylamine hydrochloride provided the corresponding oxime **6** (structurally confirmed by X-ray analysis) in 94% yield, as a 1.7:1 inconsequential mixture of E/Z isomers, and set the stage for oxidation and subsequent ring expansion.

Early attempts to oxidize oxime **6** to the requisite acyloxy nitroso intermediate (**7**) involved exploring conditions reported by King [9], as well as those we screened in the synthesis of (±)-phyllantidine [6]. To our dismay, we were unable to isolate the oxidized compound. Based on literature reports and our own experience, our efforts were guided by the bright blue color of the derived nitroso intermediates which served as a convenient indicator of the reaction's progress. Upon screening different oxidants and conditions, we found that Bobbitt's Salt [10] (Table 1, entry 8, and Scheme 3) gave the highest conversion to the bright blue acyloxy nitroso intermediate (**7**), which was found to be quite

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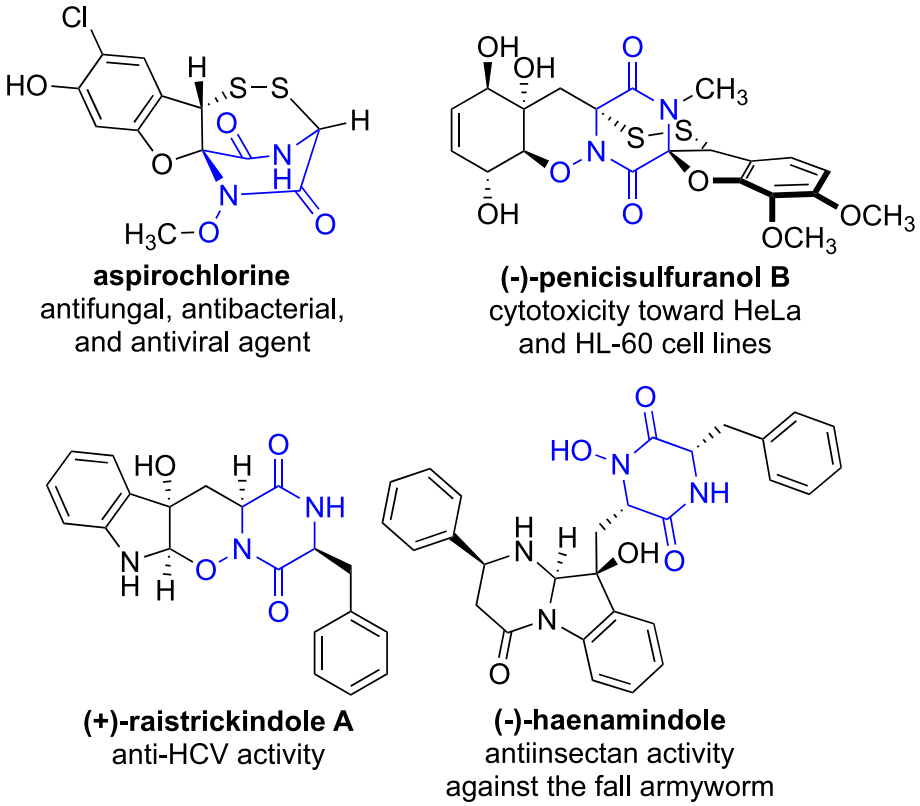
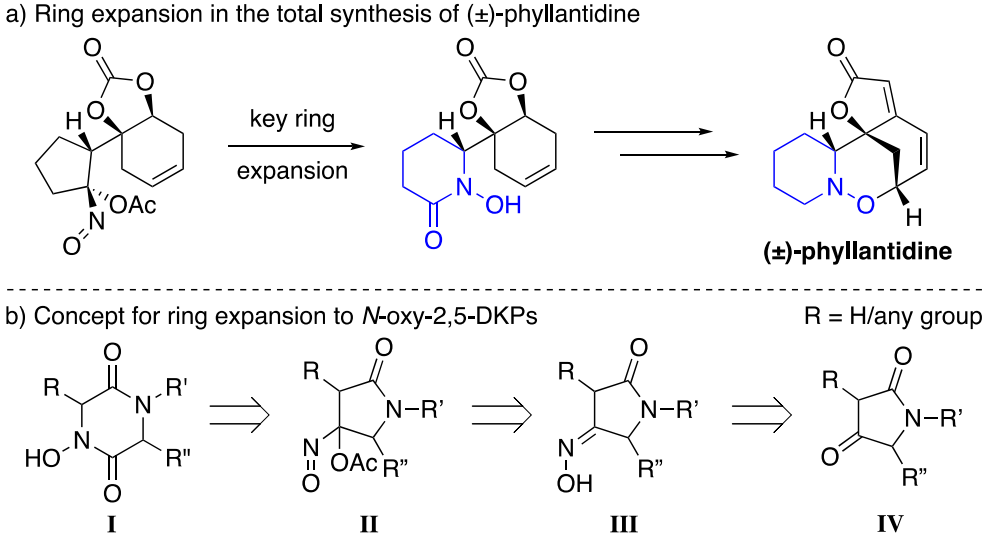


Fig. 1. Selected biologically-active *N*-oxy-2,5-DKPs.

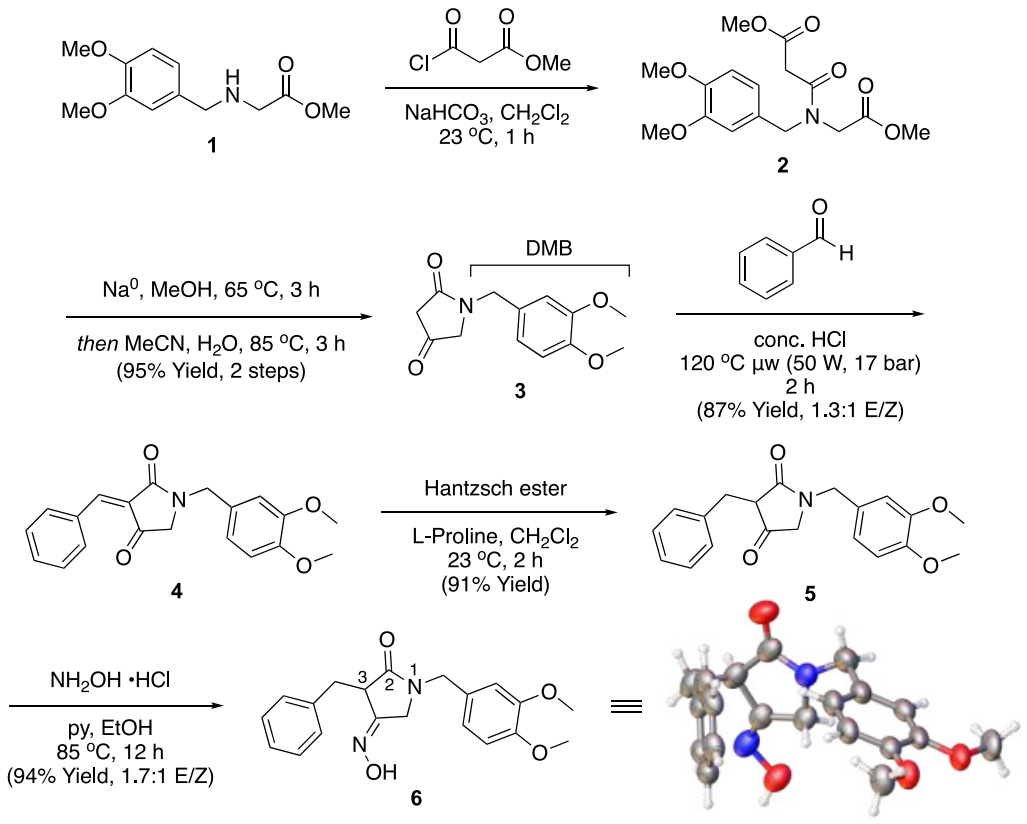


Scheme 1.

unstable and best advanced directly to the ring expansion step following rapid filtration through a short pad of silica gel.

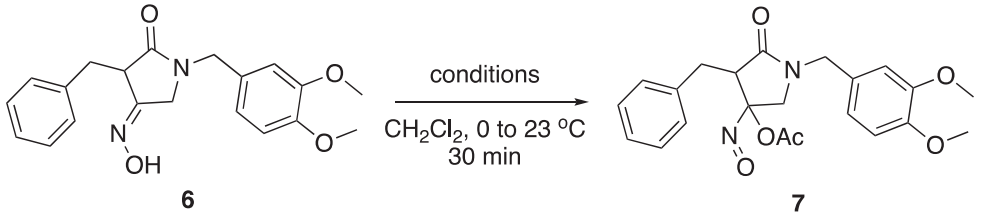
Once the optimal oxidant was found, we focused our efforts toward defining viable conditions for ring expansion to the desired *N*-oxy-2,5-DKP **8** (i.e., nucleophilic cleavage of the acetate group). To this end, we performed a brief screen of conditions and found that both those employed by King (KOH) and by our group in the synthesis of phyllantidine (LiOMe) were equally effective in promoting the desired transformation to **8** (31% yield from **6**, Table 2, entries 2 and 6, and Scheme 3) [6,9].

The modest yield of **8** results from the formation of ketone **5**, a major by-product deriving *via* loss of HNO from the acyloxy nitroso intermediate **7**; the mass balance is accounted for by the observed 1:3 ratio of **8** to **5** in the crude ^{1}H NMR. Similar results were observed in the original reports by King.[9] The likely mechanisms of both by-product and DKP formation are illustrated in Scheme 4.



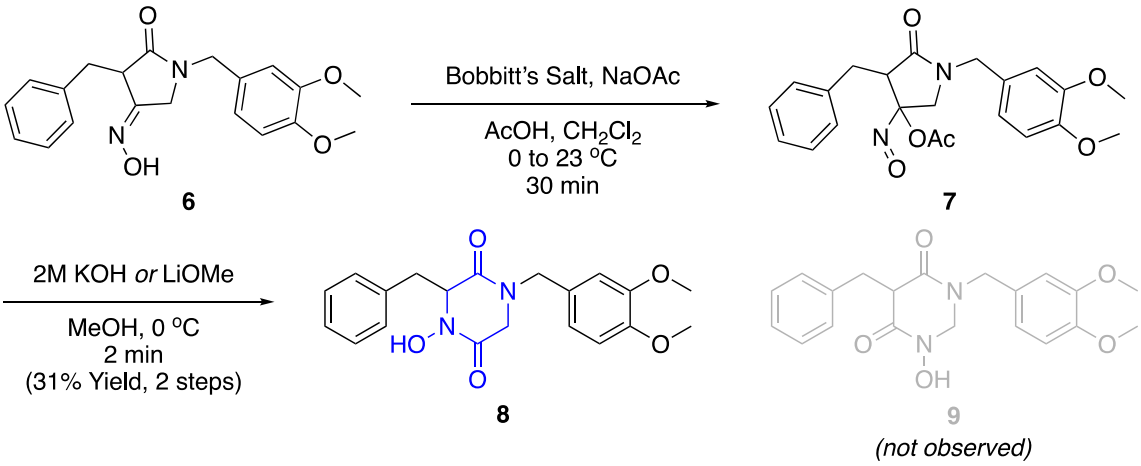
Scheme 2. Formation of the functionalized ring expansion precursor.

Table 1
Oxidation of oxime to the acyloxy nitroso intermediate.



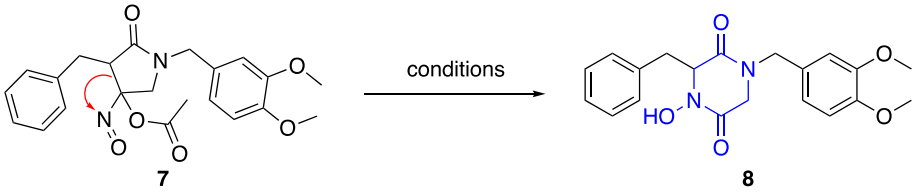
Entry	Oxidant (equiv)	Additive	Yield[a]
1	$Pb(OAc)_4$ (1.0)	-	complex mixture
2	PIDA (1.0)	-	trace
3	PIDA (1.5)	AcOH	16%
4	PIDA (1.25)	AcOH	24%
5	PIDA (1.25)	AcOH	49%
6	Bobbitt's Salt[b] (2.0)	AcOH, py	trace
7	Bobbitt's Salt (2.5)	AcOH, NaOAc	77%
8	**Bobbitt's Salt (5.0)**	**AcOH, NaOAc**	**85%**

[a]Crude yield recorded after filtration through silica.
[b]4-acetamido-2,2,6,6-tetramethylpiperidine.

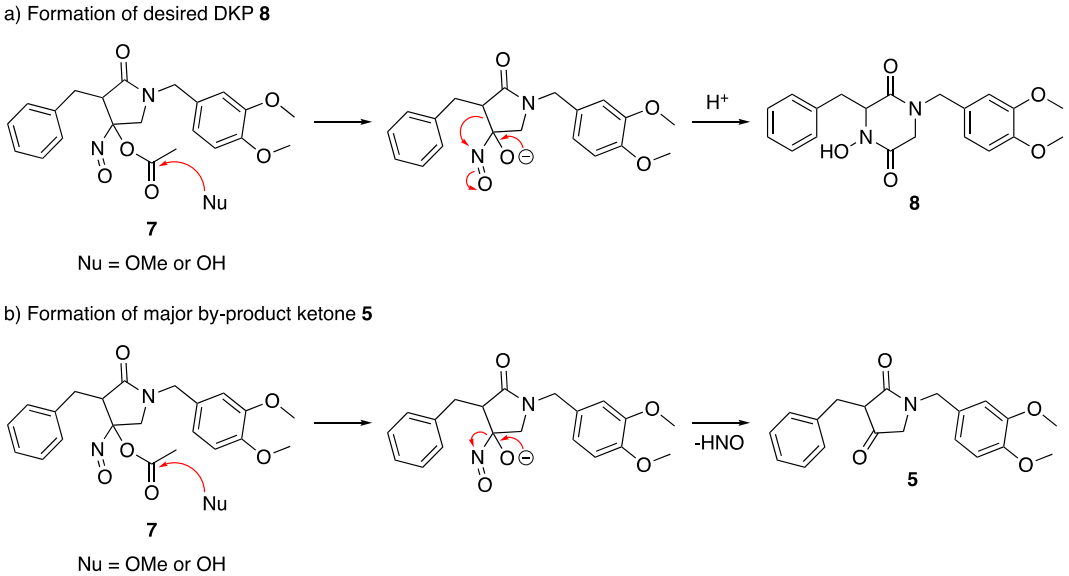


Scheme 3. Regioselective ring expansion to *N*-oxy-2,5-DKP.

Table 2
Ring expansion of acyloxy nitroso compound to *N*-oxy-2,5-DKP.



Entry	Base	Solvent	Yield (over 2 steps)
1	LiOMe	THF	complex mixture
2	**LiOMe**	**MeOH**	**31%**
3	NaOMe	MeOH	complex mixture
4	NaOH	MeOH	19%
5	LiOH	MeOH	18%
6	**KOH**	**MeOH**	**31%**
7	$(n\text{Bu})_4\text{NOH}$	MeOH	complex mixture
8	$Ca(OH)_2$	MeOH	trace
9	K_2CO_3	MeOH	29%



Scheme 4. Mechanism of both DKP and major by-product formation.

Conclusions

In conclusion, we report the first example of a tetramic acid ring expansion as a means of accessing *N*-oxy-2,5-DKPs. This strategy allows for late-stage installation of the labile *N—O* bond and provides a unique approach to the preparation of *N*-oxy-2,5-DKP-containing natural products.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2022.153851.

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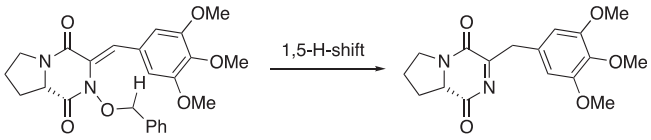

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