ORGANIC LETTERS

2013
Vol. 15, No. 2
358–361

New and Concise Syntheses of the Bicyclic Oxamazin Core Using an Intramolecular Nitroso Diels–Alder Reaction and Ring-Closing Olefin Metathesis

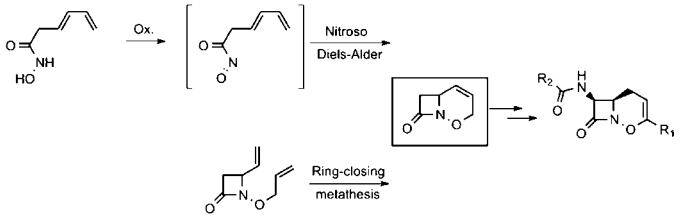
Kyle D. Watson, Serena Carosso, and Marvin J. Miller*

Department of Chemistry and Biochemistry, University of Notre Dame, 251 Nieuwland Science Hall, Notre Dame, Indiana 46556, United States

**mmiller1@nd.edu*

Received December 2, 2012

ABSTRACT



Herein two new and concise synthetic approaches for making an unsaturated bicyclic oxamazin core are reported. The first involves the use of an intramolecular Diels–Alder reaction to form both of the fused rings in one step. The second approach incorporates ring-closing olefin metathesis in the final step to form the second fused ring of the core. The scope of the second approach was also expanded further to afford larger ringed bicyclic systems.

β-Lactam antibiotics continue to play a fundamental role in the treatment of infectious diseases caused by bacteria.[1] The discovery of penicillin **1** and cephalosporin **2** (Figure 1) in the early half of the 20th century represents a crucial point in the history of human health care and their introduction into widespread use induced a dramatic improvement in the quality of life as well as a longer average life expectancy.[2] On the other hand, the era of β-lactam antibiotics is also characterized by another important phenomena: the rise of bacterial resistance.[3] For example, resistance to penicillin G was noted within one year after its introduction into clinical use.[4] Since then, numerous efforts have been directed toward the discovery and development of new molecules with improved antibacterial activity either through isolation from natural sources or synthetic methods. Nevertheless, the appearance of resistant strains of bacteria is a growing concern and, since the pipeline of available antibiotics has been diminished, the development of new drugs is becoming more and more urgent.

Oxamazins (**3**) are a class of monocyclic heteroatom activated β-lactams that shows good biological activity against Gram-negative bacteria.[5] These compounds possess a unique structure since the ionizable group is one atom further away from the β-lactam nitrogen compared to other traditional β-lactam antibiotics. Also, the presence of the oxygen atom directly bonded to the nitrogen is considered to be responsible for the electronic activation of the azetidinone ring and, therefore, the biological activity of these molecules.[6]

Our group and others have become interested in the syntheses of bicyclic oxamazins **4** and **5** (Figure 1) since the combination of the bicyclic structure and the heteroatom

(1) Dürckheimer, W.; Blumbach, J.; Lattrell, R.; Scheunemann, K. H. *Angew. Chem., Int. Ed.* **1985**, *24*, 180.
(2) Christensen, B. G. *Chem. Br.* **1989**, *25*, 371.
(3) Walsh, C. *Nature* **2000**, *406*, 775.
(4) Walsh, C. *Antibiotics: Actions, Origins, Resistance*; ASM Press: Washington, D.C., 2003.
(5) Woulfe, S. R.; Miller, M. J. *Tetrahedron Lett.* **1984**, *25*, 3293.
(6) Cohen, N. C. *J. Med. Chem.* **1983**, *26*, 259.

10.1021/ol303305u
Published on Web 12/31/2012

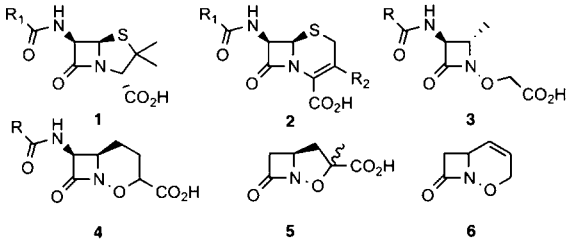


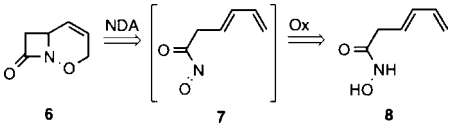
Figure 1. Representative heteroatom-activated β-lactams.

activation is envisaged to afford compounds with improved antibiotic activity.[7] Herein we report the synthesis of the unsaturated bicyclic oxamazin core **6** in which the double bond may constitute a handle for further functionalization.

Two different synthetic approaches have been used: the first involves an intramolecular nitroso Diels–Alder reaction as the key step while the second relies on a Mitsunobu cyclization followed by ring-closing olefin metathesis. We also report the application of the second methodology to the syntheses of bicyclic structures with different ring sizes and with an alkyl substituent on the double bond.

We at first envisaged that the core of bicyclic oxamazin **6** could be made in one step using an intramolecular Diels–Alder reaction of the transient nitrosocarbonyl compound **7**, which in turn could be generated through the oxidation of hydroxamic acid **8** (Scheme 1).

Scheme 1. Retrosynthetic Analysis of β-Lactam **6**

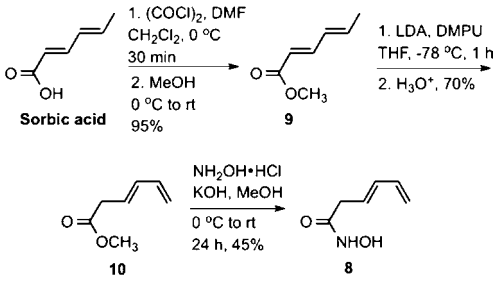


Hydroxamic acid **8** was synthesized in three steps from commercially available sorbic acid (Scheme 2). Thus, after conversion of sorbic acid to its methyl ester **9**, the diene was deconjugated from the ester by treatment with LDA and subsequent reprotonation at low temperature to afford compound **10**. Finally, treatment of the methyl ester of **10** with an excess of freshly prepared hydroxylamine in methanol gave hydroxamic acid **8** in moderate yield.

With the preparation of compound **8** being completed, we turned our attention to the key step of the synthesis: the intramolecular nitroso Diels–Alder reaction. The oxidation of hydroxamic acid **8** was initially performed in methanol at 0 °C using nBu$_4$NIO$_4$ as the oxidant. Bicyclic β-lactam **6** was obtained in 17% yield. Although the yield was low, this result was still notable since the formation of

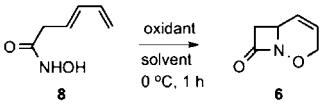
(7) (a) Kronethal, D.; Kuester, P.; Koster, W. H. Abstracts from the Tenth International Congress of Heterocyclic Chemistry, Abstract G3–25, 1985. (b) Ghosh, M.; Miller, M. J. *Tetrahedron* **1996**, *52*, 4225. (c) Zercher, C. K.; Miller, M. J. *Tetrahedron Lett.* **1989**, *30*, 7009.

Scheme 2. Synthesis of Hydroxamic Acid **8**



the β-lactam and the fused ring was obtained in a single step. Encouraged by this result, we considered the use of different oxidants and solvent systems for the oxidation reaction (Table 1).

Table 1. Nitroso Hetero Diels–Alder Reaction



entry	oxidant	solvent	yield (%)
1	nBu$_4$NIO$_4$	MeOH	17
2	nBu$_4$NIO$_4$	DCM/DMF	17
3	PhI(OAc)$_2$	CHCl$_3$	15
4	PhI(OAc)$_2$	DMF	10
5	nBu$_4$NIO$_4$	CHCl$_3$/DMF	34

Although the best yield for compound **6** was obtained using the reaction conditions shown in entry 5, it was not routinely reproducible because of the inherent instability and competitive reactivity of acylnitroso moieties.[8] For this reason, we decided to consider a different approach in which the β-lactam ring and the fused ring would be constructed in two different steps: a Mitsunobu reaction followed by ring-closing metathesis.

Several publications have reported the syntheses of strained ring systems through a ring-closing methatesis reaction using either Grubbs' first generation[9] or second generation catalyst.[10] This methodology has also been shown to be effective in the formation of the second ring of sulfactam derivatives[11] as well as larger lactam ring systems[12] and large cyclic heteroatom-containing compounds.[13]

(8) (a) Sparks, S. M.; Chow, C. P.; Zhu, L.; Shea, K. J. *J. Org. Chem.* **2004**, *69*, 3025. (b) Keck, G. E. *Tetrahedron Lett.* **1978**, *19*, 4767. (c) Keck, G. E.; Webb, R. R.; Yates, J. B. *Tetrahedron* **1981**, *37*, 4007.

(9) (a) Schwab, P.; France, M. B.; Ziller, J. W.; Grubbs, R. H. *Angew. Chem, Int. Ed.* **1995**, *34*, 2039. (b) Schwab, R.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1996**, *118*, 110.

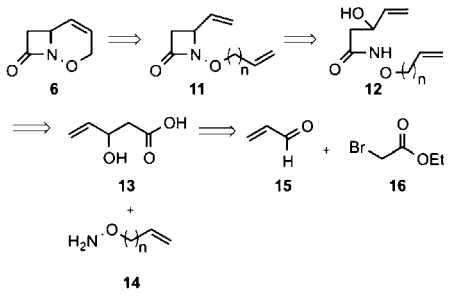
(10) (a) Barrett, A. G. M.; Baugh, S. P. D.; Braddock, C.; Flack, K.; Gibson, V. C.; Giles, M. R.; Marshall, E. L.; Procopiou, P. A.; White, A. J. P.; Williams, D. J. *J. Org. Chem.* **1998**, *63*, 7893. (b) Alcaide, B.; Almendros, P.; Alonso, J. M.; Redondo, M. C. *J. Org. Chem.* **2003**, *68*, 1426.

(11) Frietag, D.; Schwab, P.; Metz, P. *Tetrahedron Lett.* **2004**, *45*, 3589.

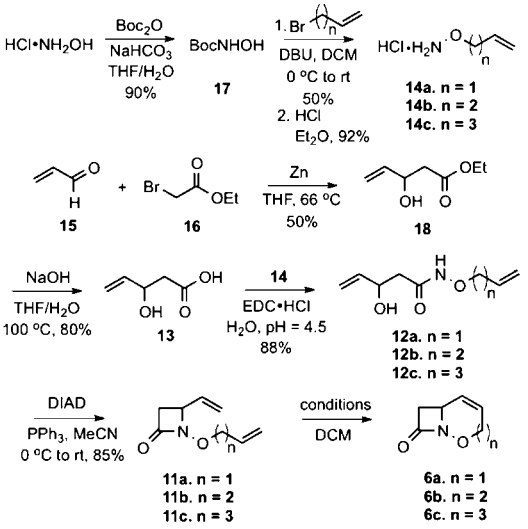
(12) Lennartz, M.; Steckhan, E. *Synlett* **2000**, *3*, 319.

(13) Yang, Y.-K.; Tae, J. *Synlett* **2003**, *7*, 1043.

Scheme 3. Revised Route for the Synthesis of β-Lactam **6**



Scheme 4. Syntheses of Bicyclic β-Lactams **6a**–**c**



Our revised approach for the synthesis of the bicyclic oxamazin core **6** (n = 1) is displayed in Scheme 3 and involves a ring-closing metathesis reaction as the final step. We anticipated that the cyclization precursor **11** would be obtained from the corresponding hydroxamate **12** using methodology developed in our group.[14] We planned to prepare linear hydroxamate **12** by our standard water-soluble carbodiimide-mediated coupling of Reformatsky-derived carboxylic acid **13** with allyl protected hydroxylamine **14** (n = 1). It is worth noting the wider scope of this methodology since the use of a protected hydroxylamine with a longer alkyl chain (n > 1) would allow the synthesis of β-lactams fused with larger ring systems.

To initiate the syntheses, hydroxylamines **14a**–**c** (Scheme 4) were prepared starting from hydroxylamine hydrochloride by Boc protection followed by O-alkylation and subsequent acidic removal of the Boc protecting group to give the corresponding hydrochloride salts. Carboxylic acid **13** was obtained in two steps: a Reformatsky reaction between acrolein **15** and ethyl bromoacetate **16**, which afforded ethyl ester **18** in moderate yield, followed by saponification to the carboxylic acid.

Standard coupling between carboxylic acid **13** and amines **14a**–**c** under aqueous conditions afforded compounds **12a**–**c**, which were cyclized under Mitsunobu conditions[14c,15] to afford β-lactams **11a**–**c**. It should be noted that no δ-lactams were observed from allylic reactions during the Mitsunobu process.

Formation of the targeted bicyclic β-lactams **6a**–**c** using Grubbs' second generation catalyst[9] for ring-closing metathesis was then studied and yields were found to depend on ring size (Table 2). It should be noted that attempted metathesis reactions involving Grubbs' first generation catalyst gave no product formation.

Encouraged by these results, we considered subtle structural modifications to further expand the scope of this methodology. The replacement of acrolein with an appropriate unsaturated aldehyde was envisaged to allow the syntheses of bicyclic structures containing a trisubstituted double bond (Scheme 5). Thus, we opted to first incorporate

Table 2. Ring-closing Metathesis on Precursors **11a**–**c**

entry	SM	temp	product	yield (%)
1	**11a**	rt	**6a**	45
2		40 °C		80
3	**11b**	rt	**6b**	62
4		40 °C		81
5	**11c**	rt	**6c**	7
6		40 °C		47

a methyl group into the bicyclic system. While this might seem to be a simple change, it should be pointed out that similar incorporation of a methyl substituent in carbapenems had a dramatic impact in antibiotic development. Appropriately, placement of a β-methyl group in imipenem analogs improved their efficacy and circumvented their susceptibility to human renal peptidases.[16] Thus, use of methacrolein **19** in the Reformatsky reaction, followed by saponification, gave carboxylic acid **21**. Coupling of **21** with amines **14a**–**c** afforded the late intermediates **22a**–**c**, which underwent cyclization under Mitsunobu conditions to give β-lactams **23a**–**c**. The ring-closing metathesis step was then again attempted using the Grubbs' second generation catalyst (Table 3).

As shown in Table 3, the attempted cyclization of compound **23a** to afford the [4.2.0] bicyclic system **24a**, the methyl substituted analog of **6a**, proved to be problematic since only starting material was reisolated under different reaction conditions. This could be a result of the inherent strain of the intermediate. On the other hand,

(14) (a) Miller, M. J.; Mattingly, P. G.; Morrison, M. A.; Kerwin, J. F., Jr. *J. Am. Chem. Soc.* **1980**, *102*, 7026. (b) Miller, M. J.; Mattingly, P. G. *Tetrahedron* **1983**, *39*, 2563. (c) Miller, M. J. *J. Acc. Chem. Res.* **1986**, *19*, 49.

(15) Mitsunobu, O. *Synthesis* **1981**, 1.

(16) Humphrey, G. R.; Miller, R. A.; Pye, P. J.; Rossen, K.; Reamer, R. A.; Miliakal, A.; Ceglia, S. S.; Grabowski, E. J. J.; Volante, R. P; Reider, P. J. *J. Am. Chem. Soc.* **1999**, *121*, 11261.

Scheme 5. Syntheses of Bicyclic β-Lactams **24a**–**c**

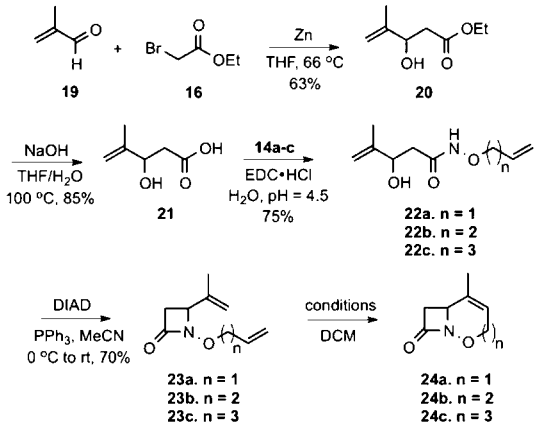


Table 3. Ring-closing Metathesis on Compounds **23a**–**c**

entry	SM	temp	product	yield (%)
1	**23a**	rt	**24a**	0[a]
2		40 °C		0[a]
3	**23b**	rt	**24b**	50
4		40 °C		73
5	**23c**	rt	**24c**	10
6		40 °C		55

[a] Only monocyclic β-lactam starting material was recovered.

under the same conditions, the larger bicyclic systems **24b** (n = 2) and **24c** (n = 3) were obtained in moderate yield from the cyclization of compounds **23b** and **23c**, respectively.

Although monocyclic β-lactams **11a**–**c** and **23a**–**c** and the corresponding bicyclic systems **6a**–**c** and **24a**–**c** lack the standard peripheral substituents needed for recognition by antibiotic targeted enzymes, we screened them against a panel of Gram-negative and Gram-positive bacteria via agar-diffusion assays. Not surprisingly, none of the compounds were active. However, with the methodology in hand for formation of the key bicyclic oxamazins, further studies are focused on preparation of precursors with appropriate recognition elements, including pendant acylamino and ionizable groups.

Herein we have reported the synthesis of the bicyclic oxamazin core **6** using two different synthetic approaches. The first involved an intramolecular nitroso Diels–Alder reaction as the key step and afforded the desired compound **6a**, despite the inherent competitive reactivity of the acylnitroso moiety. The second strategy involved the formation of the β-lactam ring under Mitsunobu conditions followed by the formation of the second ring using a ring-closing metathesis reaction. We also demonstrated that the second strategy could be used for the construction of larger [5.2.0] and [6.2.0] ring systems and as well as the introduction of an alkyl substituent on the double bond. Since all the β-lactams synthesized did not have biological activity, further work will be focused on the functionalization of bicyclic systems **6a**–**c** and **24a**–**c**.

Acknowledgment. We gratefully acknowledge Patricia Miller (UND) for biological data, Nonka Sevova and Dr. Bill Bogges (Mass Spectrometry and Proteomics Facility, UND) for mass spectroscopic analyses, Dr. Jaroslav Zajicek (Lizzadro Magnetic Resonance Research Center, UND) for NMR assistance, and Ms. Kathleen Peterson (UND) for use of IR instrumentation. We acknowledge the University of Notre Dame, Rempex Pharmaceuticals, Inc., and NIH (1R21 AI098689) for support of this work. K.D.W. acknowledges a Grace Fellowship (2011-2012, UND).

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

The authors declare no competing financial interest.