DOI: 10.1002/ange.201402310

Natural Product Synthesis

A Rapid Synthesis of 4-Oxazolidinones: Total Synthesis of Synoxazolidinones A and B**

*Nataliia V. Shymanska, Il Hwan An, and Joshua G. Pierce**

Abstract: *A five-step total synthesis of the marine natural product synoxazolidinone A was achieved through a diastereoselective imine acylation/cyclization cascade. Synoxazolidinone B and a series of analogues were also prepared to explore the potential of these 4-oxazolidinone natural products as antimicrobial agents. These studies confirmed the importance of the chlorine substituent for antimicrobial activity and revealed simplified dichloro derivatives that are equally potent against several bacterial strains.*

The continued emergence of multidrug-resistant bacteria highlights the pressing need for the development of novel antimicrobial agents.[1] Compounds that display antimicrobial activity and bear novel structural features are compelling targets for synthesis and serve as a platform for antibiotic development.[2–4] Synoxazolidinones A (**1**) and B (**2**) are recently discovered natural products isolated from the subarctic ascidian *Synoicum pulmonaria*, collected off the Norwegian coast (Figure 1).[5] The synoxazolidinones contain an unusual 4-oxazoldinone heterocycle bearing an exocyclic conjugated aromatic moiety. To our knowledge, an oxazolidinone is present in only one other class of natural products (the lipoxazolidinones; **3**, Figure 1), albeit with an alternate substitution pattern.[6] Interestingly, although rare in natural products, oxazolidinones (particularly 2-oxazolidinones) have a rich history in medicinal chemistry as highlighted by successful synthetic drugs such as linezolid.[7] A synthetic approach to these bioactive scaffolds would thus not only serve the synthesis of this class of natural products but also enable the synthesis of heterocyclic libraries.

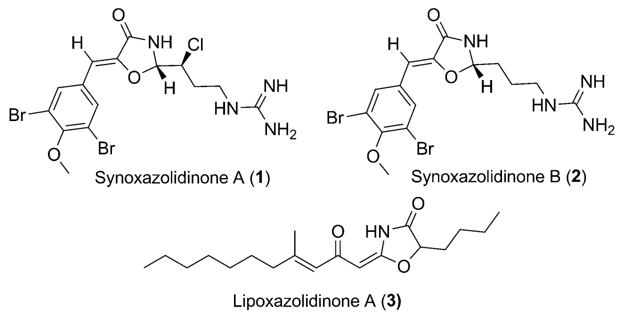
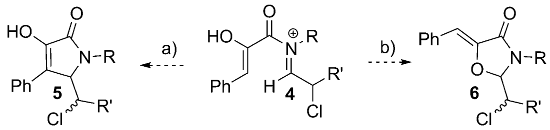


Figure 1. Natural products containing 4-Oxazolidinone.

Inspired by the proposed biosynthetic route,[5] we envisioned an imine acylation/cyclization cascade that would construct the core 4-oxazolidinone ring while stereoselectively controlling the alkene geometry and the aminal center in the process (Scheme 1 b).[8,9] The acylation of imines to generate iminium ions and subsequent trapping with



Scheme 1. Potential addition pathways for acyliminium intermediate **4**.

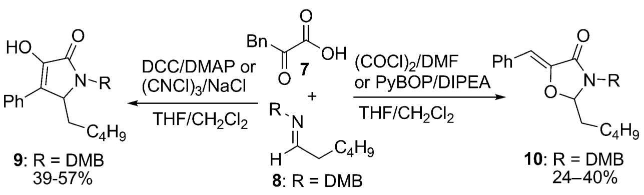
appended nucleophiles has provided rapid access to a variety of heterocyclic scaffolds.[10] Furthermore, intermolecular addition of phenylpyruvic acids to imines has been reported to prepare the biologically active but undesired 3-hydroxy-1,5-dihydro-2*H*-pyrrol-2-ones (**5**, Scheme 1 a) through an addition/cyclization/dehydration sequence.[11] Unlike these previously developed methods, the proposed reaction requires the formation of an activated enolizable α-keto carboxylic acid, subsequent reaction with an enolizable α-chloroimine[12] to generate an acyliminium ion, and finally cyclization through the oxygen atom (as opposed to the carbon atom) of the enol to generate 4-oxazolidinone **6**.

As an initial test of the proposed reaction, phenylpyruvic acid (**7**) was treated with various activating agents and imine **8** to explore the feasibility and addition chemoselectivity of this process (Scheme 2). Coupling agents such as DCC or cyanuric chloride provided the undesired carbon addition product **9** exclusively in up to 57 % yield. We cannot rule out an intermolecular imine addition process analogous to that reported;[11] however, that mechanism appears unlikely under the conditions employed. By contrast, the acid chloride generated from oxalyl chloride/DMF provided the desired 4-oxazolidinone **10** as the major product from the reaction mixture (24–40 % yield of isolated product).[13] As well as the acid chloride, PyBOP/Hunig's base also proved effective for preparing the 4-oxazolidinone products in 20–30 % yield (Scheme 2). The complete switch in selectivity is striking and is possibly accounted for by an electrocyclization mechanism

[*] N. V. Shymanska, I. H. An, Prof. J. G. Pierce
Department of Chemistry, North Carolina State University
2620 Yarbrough Drive, Raleigh NC 27695 (USA)
E-mail: jgpierce@ncsu.edu
Homepage: http://www.ncsu.edu/chemistry/jgp

[**] We thank North Carolina State University for start-up funds and the NCSU Department of Chemistry for generous support. We also thank Prof. Christian Melander and Dr. Roberta Melander for helpful discussions and assistance with initial MIC assays. Mass spectrometry data were obtained at the NCSU Mass Spectroscopy Facility.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201402310.

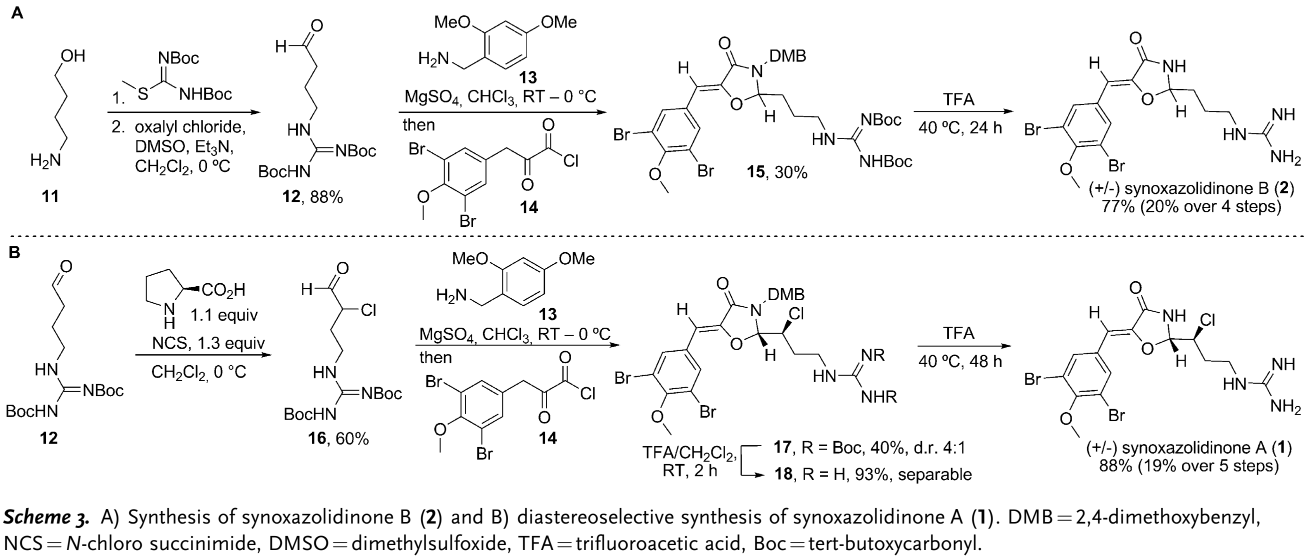


Scheme 2. Imine acylation/enol addition chemoselectivity. DMB = 2,4-dimethoxybenzyl, DCC = N,N'-dicyclohexylcarbodiimide, DMAP = 4-dimethylaminopyridine, THF = tetrahydrofuran, DMF = N,N-dimethylformamide, PyBOP = benzotriazol-1-yloxytripyrrolidinophosphonium hexafluorophosphate, DIPEA = N,N-diisopropylethylamine.

(rather than a 5-endo enol addition) in which the equilibrium of keto/enol tautomers, influenced by pH value and other factors, would dictate reaction selectivity.[14] The mass balance in both the acid chloride and PyBOP reactions is high, with the remainder of the material being lost through activated-acid dimerization. Although the yields for this process are modest, the readily available starting materials, straightforward isolation, and one-step protocol allow ample material to be prepared through this approach. Furthermore, the carbon addition products, 3-hydroxy-1,5-dihydro-2*H*-pyrrol-2-ones (**9**), are commonly found in nature and possess a wide range of biological activities.[15] The imine acylation/enol addition provides a mild method to generate these heterocycles and provides compatibility with alkyl substituents that is not possible with current methods.[11]

With a route to the core heterocycle in hand, we turned our attention to the incorporation of the functional groups required for the synoxazolidinones. Being the simplest member of the family, synoxazolidinone B (**2**) was initially targeted for synthesis (Scheme 3 A). The treatment of 4-aminobutanol (**11**) with N,N'-bis(tert-butoxycarbonyl)-*S*-methylisothiourea provided a Boc-protected guanidine alcohol that was oxidized under Swern conditions to yield aldehyde **12** in 88 % yield over the two steps. Conversion of the aldehyde to the requisite benzylimine was accomplished by treatment with 2,4-dimethoxybenzyl amine (**13**) and $MgSO_4$, and the crude imine was directly subjected to the aforementioned acylation/cyclization cascade with acid chloride **14** to provide the fully functionalized synoxazolidinone B scaffold in 30 % yield over two steps. Subsequent deprotection provided compound **2** in 77 % yield after preparative reverse-phase chromatography (20 % over four steps) and the ^{1}H and ^{13}C NMR spectroscopy data are in agreement with the isolation report.[5]

In parallel to the efforts to construct synoxazolidinone B (**2**), we explored the installation of the secondary chlorine substituent present in synoxazolidinone A (**1**). To determine the potential of employing an imine acylation/cyclization cascade analogous to that employed for the deschloro product **2**, we required access to α-chloro aldehyde **16** (Scheme 3 B).[12] Although the chlorination of aldehydes is a well-established reaction, with several elegant catalytic asymmetric approaches,[16] it became apparent that a protected guanidine moiety in close proximity to the reacting aldehyde significantly complicated this reaction. All attempts at catalytic chlorination proved unsuccessful, with no reactivity observed. To overcome these difficulties, we employed stoichiometric proline to promote efficient chlorination of aldehyde **12**, thereby producing compound **16** in 60 % yield.[17] With this aldehyde in hand, we carried out the imine formation/acylation/cyclization cascade to provide compound **17** in 40 % yield and d.r. 4:1 favoring the desired diastereomer.[18] Significant efforts were made to improve this diastereoselectivity; however, no conditions provided a higher quantity of the desired product upon isolation. The presence of the dimethoxybenzyl group was essential to obtaining diastereoselectivity, with many substrates and conditions yielding a 1:1 mixture of diastereomers. With the natural product skeleton complete, removal of both the dimethoxybenzyl and Boc protecting groups was achieved with TFA (40 °C, 48 h) to yield synoxazolidinone A (**1**) as a 4:1 mixture of diastereomers in 88 % yield (19 % over 5 steps). No erosion of the diastereomeric ratio during the deprotection reactions was detected, even upon prolonged



Scheme 3. A) Synthesis of synoxazolidinone B (**2**) and B) diastereoselective synthesis of synoxazolidinone A (**1**). DMB = 2,4-dimethoxybenzyl, NCS = *N*-chloro succinimide, DMSO = dimethylsulfoxide, TFA = trifluoroacetic acid, Boc = tert-butoxycarbonyl.

heating. The diastereomers of the fully deprotected natural product proved difficult to separate without the use of HPLC, but fortunately, the partially deprotected product **18** (TFA/CH_2Cl_2, RT, 2 h) was readily separable by reverse phase chromatography. As with compound **2**, the NMR data is in full agreement with the reported data.[5]

As well as the two natural products, we prepared a small panel of compounds (**19**–**22**) to explore the impact of deleting the guanidine moiety, making the aryl ring electron deficient (**21**–**24**), or installing an additional chlorine substituent (**20**, **22**, **25**) in order to define an initial structure–activity relationship (SAR) for this class of compounds (Figure 2). All of the analogues were produced without modification to our method, thereby highlighting the straightforward nature of this approach for generating an array of 4-oxazolidinone products. It should be noted that the dichloro compounds (**20**, **22**, **25**) arise from chlorination of the crude imine (excess NCS) since purified dichloro aldehydes do not undergo our dehydration/acylation/cyclization cascade reaction.[19]

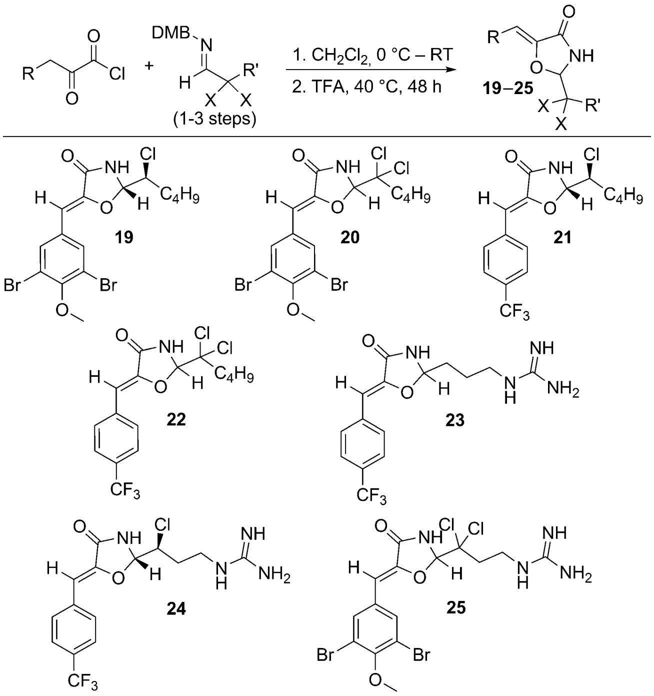


Figure 2. Analogues of synoxazolidinones A and B.

With synoxazolidinone A (**1**) and B (**2**) and their analogues in hand, we explored the antimicrobial activity of these compounds against several bacterial strains. The activities of compounds **1** and **2** are in line with those reported for the isolated natural products against both sensitive and resistant gram-positive bacteria *S. Aureus* (Table 1).[5,20] Deletion of the guanidine moiety on monochloro derivatives was detrimental to the antimicrobial activity (**19**, **21**); however, the installation of an additional chloride or an electron-withdrawing group on the aryl ring was generally beneficial. In particular, compounds **22** and **25** displayed comparable activity to that of **1** and increased activity against *A. baumannii*, a gram-negative bacterium that is resistant to many commonly employed antibiotics. These dichloro derivatives are particularly straightforward to prepare and provide a starting point for further improving the potency of these natural-product analogues and/or generating probe molecules to study the interaction of these electrophilic natural products with proteins.[21]

Table 1: Antimicrobial activity of the natural products and their analogues.

MIC [μg mL^{-1}] Compound	*S. Aureus*[a]	MRSA[b]	*A. baumannii*[c]
1	12.5	20	100
2	30	30	>100
10	>100	>100	>100
19	>100	>100	>100
20	50	60	>100
21	>100	>100	100
22	10	20	80
23	60	40	80
24	>100	>100	>100
25	12.5	20	50
vancomycin	1	1	>100
linezolid	0.5	1	>100
tetracycline	0.25	100	2

[a] ATCC 29213. [b] ATCC 33591. [c] ATCC 19606. MIC = minimum inhibitory concentration, MRSA = methicillin-resistant *Staphylococcus aureus*.

In conclusion, we have developed a rapid and diasteroselective synthesis for the synoxazolidinone family of natural products. Through these efforts, we have gained insight into the chemistry of these unusual heterocycles and provided new lead compounds for antimicrobial development. Efforts to increase the potency and selectivity of this class of compounds are underway, as well as studies aimed at identifying their intracellular targets.

Received: February 11, 2014
Revised: March 6, 2014
Published online: April 7, 2014

Keywords: antimicrobial agents · heterocycles · natural products · stereoselectivity · total synthesis

[1] Infectious Diseases Society of America (IDSA), *Clin. Infect. Dis.* **2011**, *52*, S397 – S428.
[2] J. W. H. Li, J. C. Vederas, *Science* **2009**, *325*, 161 – 165.
[3] a) C. T. Walsh, T. A. Wencewicz, *J. Antibiot.* **2013**, 1 – 16; b) K. M. G. O'Connell, J. T. Hodgkinson, H. F. Sore, M. Welch, G. P. C. Salmond, D. R. Spring, *Angew. Chem.* **2013**, *125*, 10904 – 10932; *Angew. Chem. Int. Ed.* **2013**, *52*, 10706 – 10733; c) T. Böttcher, M. Pitscheider, S. A. Sieber, *Angew. Chem.* **2010**, *122*, 2740 – 2759; *Angew. Chem. Int. Ed.* **2010**, *49*, 2680 – 2698.
[4] D. J. Newman, G. M. Cragg, *J. Nat. Prod.* **2007**, *70*, 461 – 477.
[5] a) M. Tadesse, M. B. Strøm, J. Svenson, M. Jaspars, B. F. Milne, V. Tørfoss, J. H. Andersen, E. Hansen, K. Stensvåg, T. Haug, *Org. Lett.* **2010**, *12*, 4752 – 4755; b) M. Tadesse, J. Svenson, M. Jaspars, M. B. Strøm, M. H. Abdelrahman, J. H. Andersen, E. Hansen, P. E. Kristiansen, K. Stensvåg, T. Haug, *Tetrahedron Lett.* **2011**, *52*, 1804 – 1806; c) K. H. Hopmann, J. Šebestík, J.

Novotná, W. Stensen, M. Urbanová, J. Svenson, J. S. Svendsen, P. Bouř, K. Ruud, *J. Org. Chem.* **2012**, *77*, 858–869.
[6] V. R. Macherla, J. Liu, M. Sunga, D. J. White, J. Grodberg, S. Teisan, K. S. Lam, B. C. M. Potts, *J. Nat. Prod.* **2007**, *70*, 1454–1457.
[7] M. R. Barbachyn, C. W. Ford, *Angew. Chem.* **2003**, *115*, 2056–2070; *Angew. Chem. Int. Ed.* **2003**, *42*, 2010–2023.
[8] For singular examples of similar 4-oxazolidinone synthesis, see: a) W. R. Roush, A. P. Essenfeld, J. S. Warmus, B. B. Brown, *Tetrahedron Lett.* **1989**, *30*, 7305–7308; b) Y. S. Laxmi, D. S. Iyengar, *J. Chem. Soc. Perkin Trans. 1* **1995**, 3043–3045.
[9] P.-L. Shao, X.-Y. Chen, S. Ye, *Angew. Chem.* **2010**, *122*, 8590–8594; *Angew. Chem. Int. Ed.* **2010**, *49*, 8412–8416.
[10] a) W. P. Unsworth, G. Coulthard, C. Kitsiou, R. J. K. Taylor, *J. Org. Chem.* **2014**, *79*, 1368–1376; b) W. P. Unsworth, C. Kitsiou, R. J. K. Taylor, *Org. Lett.* **2012**, *15*, 258–261; c) W. P. Unsworth, K. A. Gallagher, M. Jean, J. P. Schmidt, L. J. Diorazio, R. J. K. Taylor, *Org. Lett.* **2012**, *15*, 262–265; d) O. Sieck, M. Ehwald, J. R. Liebscher, *Eur. J. Org. Chem.* **2005**, 663–672; e) K. T. Wanner, U. Weber, *Synthesis* **1994**, 387–390.
[11] a) S. V. Ryabukhin, D. M. Panov, A. S. Plaskon, O. O. Grygorenko, *ACS Comb. Sci.* **2012**, *14*, 631–635; b) Y. I. Sakhno, S. V. Shishkina, O. V. Shishkin, V. I. Musatov, E. V. Vashchenko, S. M. Desenko, V. A. Chebanov, *Mol. Diversity* **2010**, *14*, 523–531.
[12] For preparation and reaction of α-chloro aldimines, see: G. R. Stanton, M. Göllü, R. M. Platoff, C. E. Rich, P. J. Carroll, P. J. Walsh, *Adv. Synth. Catal.* **2013**, *355*, 757–764 and references therein. For a recent example of intermolecular Cl-controlled aldehyde addition, see: W. J. Chung, J. S. Carlson, D. K. Bedke, C. D. Vanderwal, *Angew. Chem.* **2013**, *125*, 10236–10239; *Angew. Chem. Int. Ed.* **2013**, *52*, 10052–10055.
[13] Reverse phase purification was required for these substrates and yields of isolated product were significantly lower than expected by inspection of crude ^{1}H NMR or LC–MS analysis; however, isolated, purified products were stable to long-term storage.
[14] For a discussion of related Nazarov-type cyclizations of enols to enones: W. A. Batson, D. Sethumadhavan, M. A. Tius, *Org. Lett.* **2005**, *7*, 2771–2774. Also see: T. Vaidya, R. Eisenberg, A. J. Frontier, *ChemCatChem* **2011**, *3*, 1531–1548; K. K. S. Sai, M. J. O'Connor, D. A. Klumpp, *Tetrahedron Lett.* **2011**, *52*, 2195–2198.
[15] For example: C. Intaraudom, N. Boonyuen, R. Suvannakad, P. Rachtawee, P. Pittayakhajonwut, *Tetrahedron Lett.* **2013**, *54*, 744–748.
[16] For an example: M. P. Brochu, S. P. Brown, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2004**, *126*, 4108–4109. For a review: S. France, A. Weatherwax, T. Lectka, *Eur. J. Org. Chem.* **2005**, 475–479.
[17] The most successful asymmetric chlorination we have achieved provides aldehyde **16** in 56% *ee* (2 equiv proline amide, 2 equiv NCS, dioxane, 0°C); however, the crude product can not be successfully carried forward and all attempts at aldehyde purification provided racemic product in low yield. New catalyst development, a multistep work-around, or a substrate lacking the guanidine functionality would likely be required to overcome these obstacles.
[18] The diastereomeric ratio ranges from 5:1 to 2.5:1 depending on the batch of acid chloride and conditions employed; 4:1 is the most commonly observed diastereoselectivity. The ^{1}H NMR spectra for the two diastereomers are significantly different (chemical shifts and coupling constants) for both the protected and deprotected **1**, thus allowing straightforward assignment of the isolated diastereomers (see compound **17** in the Supporting Information).
[19] N. De Kimpe, R. Verhe, L. De Buyck, H. Hasma, N. Schamp, *Tetrahedron* **1976**, *32*, 2457–2466. For detailed procedures and yields, see the Supporting Information.
[20] The compounds tested herein are racemic; although the numbers reported are within the error of those reported in Ref. [5] for enantiomerically enriched compounds, we do not currently have accesses to purified enantiomers of the natural products for a direct comparison of the impact of stereochemistry on activity. These efforts are underway.
[21] For a discussion of the value of electrophilic natural product scaffolds: a) M. Gersch, J. Kreuzer, S. A. Sieber, *Nat. Prod. Rep.* **2012**, *29*, 659–682; b) A. W. Puri, M. Bogyo, *Biochemistry* **2013**, *52*, 5985–5996.

