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Synthesis of 2-Oxazolidinones from β-Lactams: Stereospecific Total Synthesis of (−)-Cytoxazone and All of Its Stereoisomers

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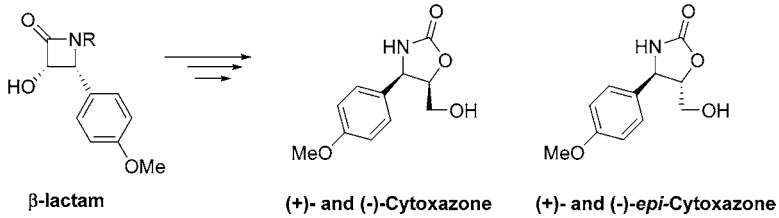
ABSTRACT



The synthetic correlation between two different antibiotic frameworks, the β-lactams and 2-oxazolidinones, is described for the first time. In this approach, 2-oxazolidinones are prepared in stereomerically pure form from 3-hydroxy β-lactams by a ring-opening−cyclization isomerization process. Application of this methodology to the total synthesis of the cytokine modulator, (−)-cytoxazone, and its three stereoisomers is demonstrated.

The β-lactam antibiotics have been the most important therapeutic agents in the 20th century, an era which began with the discovery of penicillin (Figure 1) by Alexander Fleming in 1928.[1] The key feature of penicillin and its well-known relatives, the cephalosporins, penems, carbapenems, clavulanic acids, and monobactams, is the β-lactam nucleus. Over the last 50−60 years, bacteria have been able to develop resistance to the β-lactam drugs by producing extracellular enzymes that hydrolyze the β-lactam moiety to inactive ring-opened amino acids. This resistance has spawned a renewed interest in identifying new families of antibiotics. One such class of compounds are the 2-oxazolidinones, which were discovered by researchers at Dupont in the 1980s to exert potent antibacterial properties through a unique mechanism of action.[2] Linezolid (Figure 1) was the first oxazolidinone antibiotic to be introduced into clinical trials by Pharmacia[3] and was approved in 2000 by the Food and Drug Administration for use in the treatment of infections caused by gram-positive bacteria.

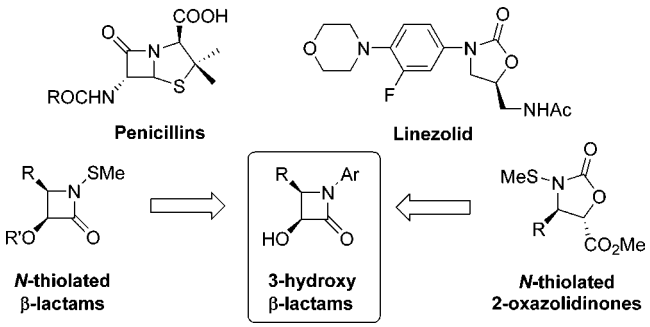


Figure 1. Structures of the penicillins and linezolid (above) and the synthetic correlation of β-lactams with 2-oxazolidinones (below).

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(2) Slee, A. M.; Wuonola, M. A.; McRipley, R. J.; Zajac, I.; Zawada, M. J.; Bartholomew, P. T.; Gregory, W. A.; Forbes, M. *Antimicrob. Agents Chemother.* **1987**, *31*, 1791.

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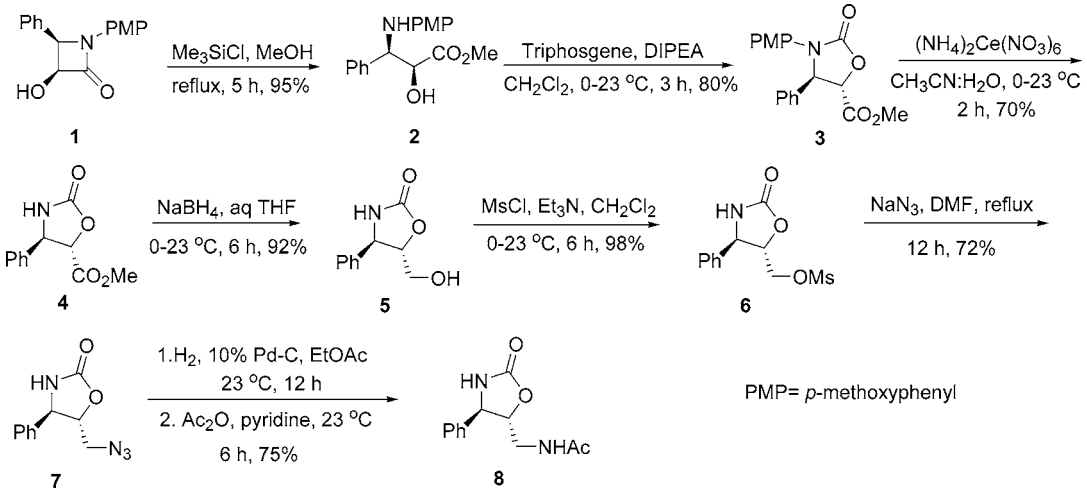
Scheme 1. Synthesis of 2-Oxazolidinones from 3-Hydroxy β-Lactam **1**



Our laboratory recently reported *N*-thiolated β-lactams which possess potent antibacterial activity against methicillin-resistant *Staphylococcus aureus* (MRSA).[4] One of the interesting features of these compounds is that the β-lactam nucleus is not required for anti-MRSA activity, which led us to the discovery of *N*-thiolated 2-oxazolidinones as a new family of antibacterial agents.[5] During the course of our studies, it occurred to us that the *N*-thiolated β-lactams and 2-oxazolidinones could perhaps both be derived from the same intermediate, 3-hydroxy β-lactam,[5] as shown in Figure 1.

Accordingly, we first developed a strategy shown in Scheme 1 to prepare a selection of racemic oxazolidinone compounds **4**−**8**, which we utilized to prepare antibacterially active *N*-methylthio-2-oxazolidinones.[5] Each of these compounds was accessed from *cis*-hydroxy β-lactam **1**. To begin the synthesis, lactam[4c] **1** was hydrolyzed with Me_3SiCl in refluxing methanol to afford the *syn*-aminol **2** in 95% yield. Upon treatment of **2** with triphosgene and Hunig's base in dichloromethane, oxazolidinone **3** was obtained in 80% yield. The *N*-methoxyphenyl moiety on the oxazolidinone ring was then cleaved with ceric ammonium nitrate in acetonitrile and water[6] to yield the *N*-protio oxazolidinone **4** in 70% yield. The ester functionality of oxazolidinone **4** was selectively reduced with sodium borohydride in aqueous THF to furnish the alcohol **5** in 92% yield. Exchange of the hydroxyl group for an azide proceeded through mesylate **6**, which gave azide **7** in 72% yield after treatment with sodium azide in DMF. Catalytic hydrogenation of the azide and subsequent acetylation afforded the acetamide **8** in 75% yield for the final one-pot conversion. Oxazolidinones **4**−**8** were each converted to their *N*-thiolated derivatives for biological evaluation, and these compounds were found to be generally quite active as antibacterials against MRSA.[5]

We were interested in adapting this sequence to the asymmetric total synthesis of (4*R*,5*R*)-(−)-cytoxazone (**9**). A microbial metabolite isolated from *Streptomyces*, cytoxazone is a selective modulator of T_H2 cytokine secretion.[7] Because of its potent biological activity, a number of research laboratories have pursued the development of efficient asymmetric routes to cytoxazone and its stereoisomers (Figure 2).[8] A sequence adapted from the one shown in Scheme 1 would provide a most convenient means to access cytoxazone and its three stereoisomers. We first set out to

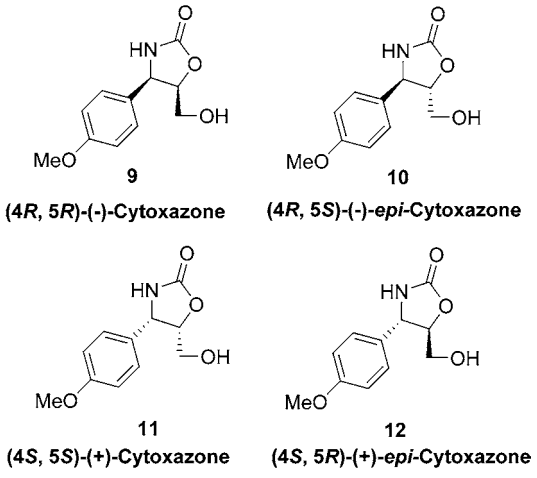


Figure 2. (−)-Cytoxazone and its stereoisomers.

(3) Ford, C. W.; Zurenko, G. E.; Barbachyn, M. R. *Curr. Drug. Targets: Infect. Disord.* **2001**, *1*, 181−199.

(4) (a) Heldreth, B.; Long, T. E.; Jang, S.; Reddy, G. S. K.; Turos, E.; Dickey, S.; Lim, D. V. *Bioorg. Med. Chem.* **2006**, *14*, 3775−3784. (b) Turos, E.; Long, T. E.; Heldreth, B.; Leslie, J. M.; Reddy, G. S. K.; Wang, Y.; Coates, C.; Konaklieva, M.; Dickey, S.; Lim, D. V.; Alonso, E.; Gonzalez, J. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 2084−2090. (c) Turos, E.; Coates, C.; Shim, J. Y.; Wang, Y.; Leslie, J. M.; Long, T. E.; Reddy, G. S. K.; Ortiz, A.; Culberth, M.; Dickey, S.; Lim, D. V.; Alonso, E.; Gonzalez, J. *Bioorg. Med. Chem.* **2005**, *13*, 6289−6308. (d) Long, T. E.; Turos, E.; Konaklieva, M. I.; Blum, A. L.; Amry, A.; Baker, E. A.; Suwandi, L. S.; McCain, M. D.; Rahman, M. F.; Dickey, S.; Lim, D. V. *Bioorg. Med. Chem.* **2003**, *11*, 1859−1863. (e) Coates, C.; Long, T. E.; Turos, E.; Dickey, S.; Lim, D. V. *Bioorg. Med. Chem.* **2003**, *11*, 193−196. (f) Turos, E.; Long, T. E.; Konaklieva, M. I.; Coates, C.; Shim, J. Y.; Dickey, S.; Lim, D. V.; Cannons, A. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 2229−2231.

(5) Mishra, R. K.; Revell, K. D.; Coates, C. M.; Turos, E.; Dickey, S.; Lim, D. V. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 2081−2083.

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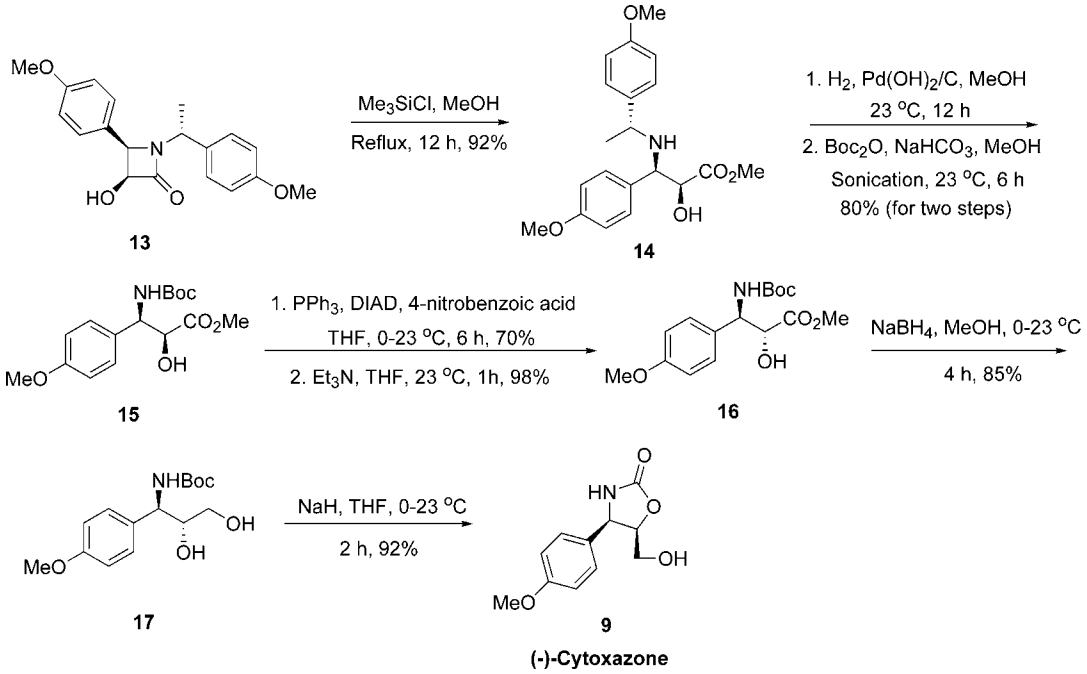
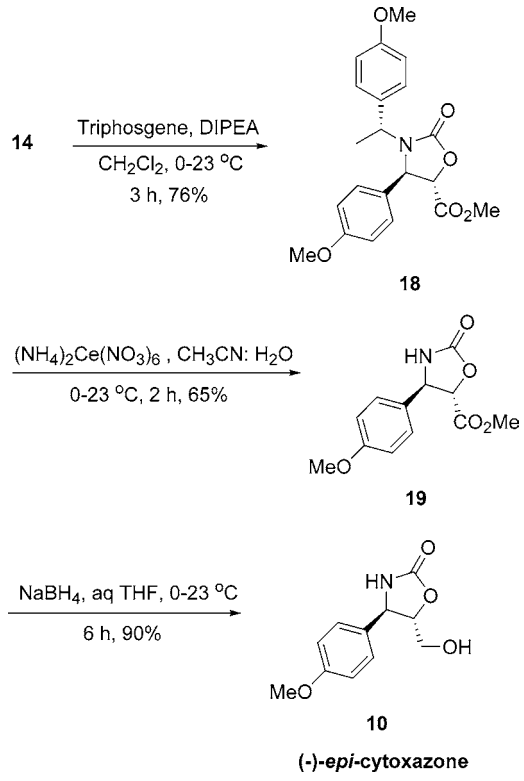
Scheme 2. Stereospecific Total Synthesis of (−)-Cytoxazone (**9**)



prepare the naturally occurring form, (4*R*,5*R*)-cytoxazone (**9**), from optically pure hydroxy lactam **13**, as shown in Scheme 2.[9] Methanolysis of **13** with Me_3SiCl in refluxing methanol yielded a 92% yield of *syn*-amino alcohol **14**, which was subjected to hydrogenation with Pearlman's catalyst in methanol to chemoselectively cleave the α-methyl-(4-methoxybenzyl) moiety. The resultant amine was protected as its *tert*-butyl carbamate derivative **15** using di-*tert*-butyl carbonate and $NaHCO_3$ in MeOH under sonication. The hydroxyl group was inverted under Mitsunobu conditions to afford

Scheme 3. Stereospecific Synthesis of (−)-*epi*-Cytoxazone (**10**)



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the *anti*-amino alcohol **16**. Borohydride reduction and base-promoted cyclization of the diol **17** completed the synthesis of (−)-cytoxazone (**9**). NMR spectral data and optical rotation values confirmed a match to the natural product.[8]

Our next task was to complete a stereospecific synthesis of (−)-*epi*-cytoxazone, which we carried out by first intercepting amino alcohol **14** with triphosgene and Hunig's base to form the trans-disubstituted oxazolidinone **18** (Scheme 3). The α-methyl-(4-methoxybenzyl) moiety was chemoselectively cleaved with ceric ammonium nitrate to furnish the *N*-protio oxazolidinone **19** in 65% yield. The ester was reduced with $NaBH_4$ in MeOH to afford (−)-*epi*-cytoxazone, whose spectral and physical properties matched those reported.[8]

In a similar fashion, (+)-cytoxazone (**11**) and (+)-*epi*-cytoxazone (**12**) were synthesized from the enantiomeric stereoisomer of hydroxy lactam **13**. Thus, this protocol afforded access to all four stereoisomers of the oxazolidinone.

In summary, we have demonstrated the value of β-lactams as building blocks for the stereospecific synthesis of substituted 2-oxazolidinones, compounds which are of broad interest both as synthetic intermediates and as commercial pharmaceutical products. We believe that this methodology provides unique flexibility and opportunities to the synthesis of stereochemically pure oxazolidinones that are needed for biological studies and drug development.

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

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