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Report

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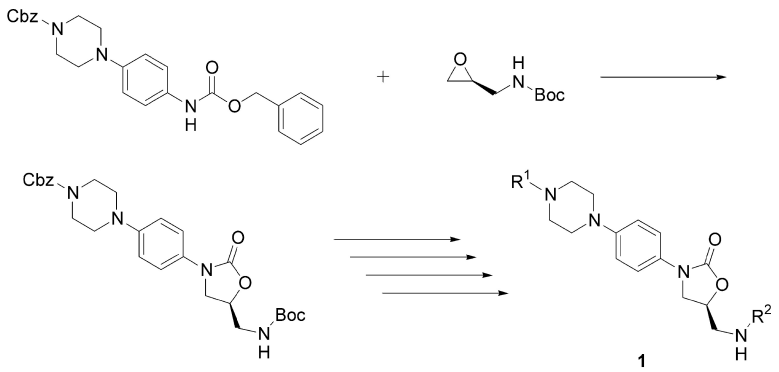

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Reports

An Efficient and Improved Route for the Preparation of (*S*)-5-Aminomethyloxazolidinone Libraries

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N-Aryloxazolidinones are a major pharmacological antibacterial class that inhibit the enzyme monoamine oxidase A.[1] New types of antibacterial compounds based on the *N*-aryloxazolidinone template have been described over the past decade. These are generally classified as oxazolidinone antibiotics[2] and have strong activity against various Gram-positive bacterial pathogens, including methicillin-resistant *Staphylococcus aureas* (MRSA) and vancomycin-resistant *Enterococci* (VRE). Oxazolidinone antibiotics inhibit bacterial protein synthesis at an early event in protein synthesis. Linezolid, Eperezolid, and Dup-721 (Figure 1) are typical examples of antibacterials released to date.[2d,3]

Oxazolidinones have attracted considerable attention because they are active against a variety of clinically important both susceptible and resistant Gram-positive organisms. Two representative routes have been developed to synthesize these compounds. In one method, shown in Scheme 1, oxazolidinone **7** is prepared from the carbamate ester **5** by reacting it with butyric acid oxiranylmethyl ester **6**.[2d,2f,4] Another method recently described is shown in Scheme 2, in which the completed 5-hydroxymethyloxazolidinone **11** is introduced as a precursor of the desired compound **12**.[5]

However, these two forms of syntheses have some disadvantages. Scheme 1 requires expensive compounds such as butyric acid oxiranylmethyl ester **6** to prepare the intermediate **7**. In addition, azides such as **9** must be handled with extreme caution. A relatively low yield seems inevitable, since there are so many steps involved in the manufacturing process from intermediate **7** to target compound **1**. As a result, the preparation of target compound **2** in Figure 1 via a 5-hydroxymethyloxazolidinone, such as **7**, also requires many steps.

To overcome some of the problems associated with the conventional preparation of 5-aminomethyloxazolidin-2-one, illustrated in Scheme 1, we developed method B, which employs a one-step reaction between carbamate ester **5** and the oxiranylmethyl carbamic acid *tert*-butyl ester **13**, as shown in Scheme 3.[6]

Employing **5** as a starting material, method B described in Scheme 3 has some similarities to Scheme 1, but method B offers a significant improvement versus the original method due to the introduction of the butyric acid oxiranylmethyl ester **6** and by eliminating the azide and the other steps shown in Scheme 1. These modifications allow the synthesis of the desired form of 5-aminomethyloxazolidin-2-one **14** through reaction between **5** and **13** in high yield.

The key reagent, the oxiranylmethyl carbamic acid *tert*-butyl ester **13** is inexpensive and easy to synthesize.[7] The new preparation method B has the advantage of fewer steps than the conventional method. This is accomplished by introducing the amine group from the first step, rather than by converting the hydroxy group to an amino group at the end of the synthesis. In addition, it uses relatively mild reaction conditions in each step, allowing a more straight-

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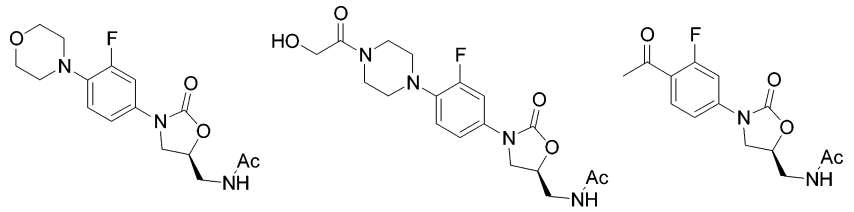
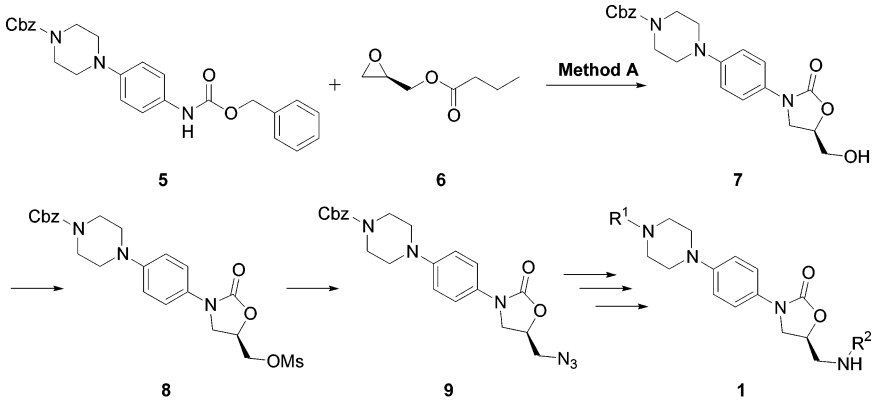
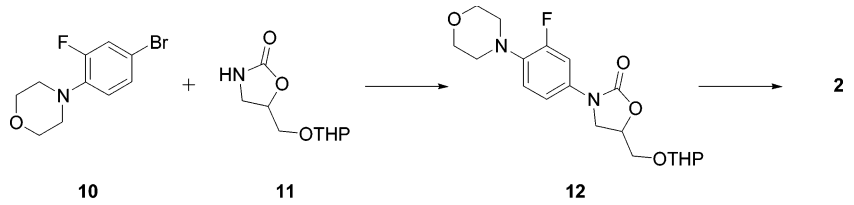


Figure 1.

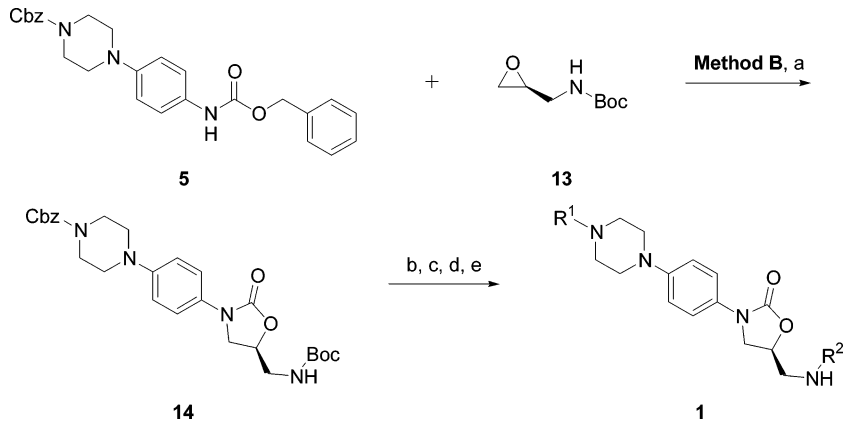
Scheme 1



Scheme 2

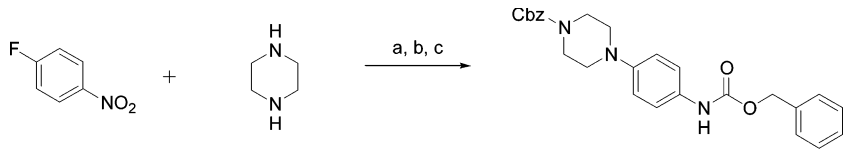


Scheme 3[a]



[a] Reagents: (a) *n*-BuLi, THF, −78 °C to RT; (b) Pd/C, EtOH, H_2; (c) R^1-Cl, 2-ethoxyethanol, DIPEA, 100 °C; (d) 10% TEA in MC; (e) R^2−X, MC, TEA (R^2= R^2SO_2−, R^2CO−).

Scheme 4[a]



[a] Reagents: (a) CH_3CN; (b) Pd/C, THF, H_2, 100 psi; (c) benzyl chloroformate, 1,4-dioxane, $NaHCO_3$, 0 °C to RT.

Scheme 5

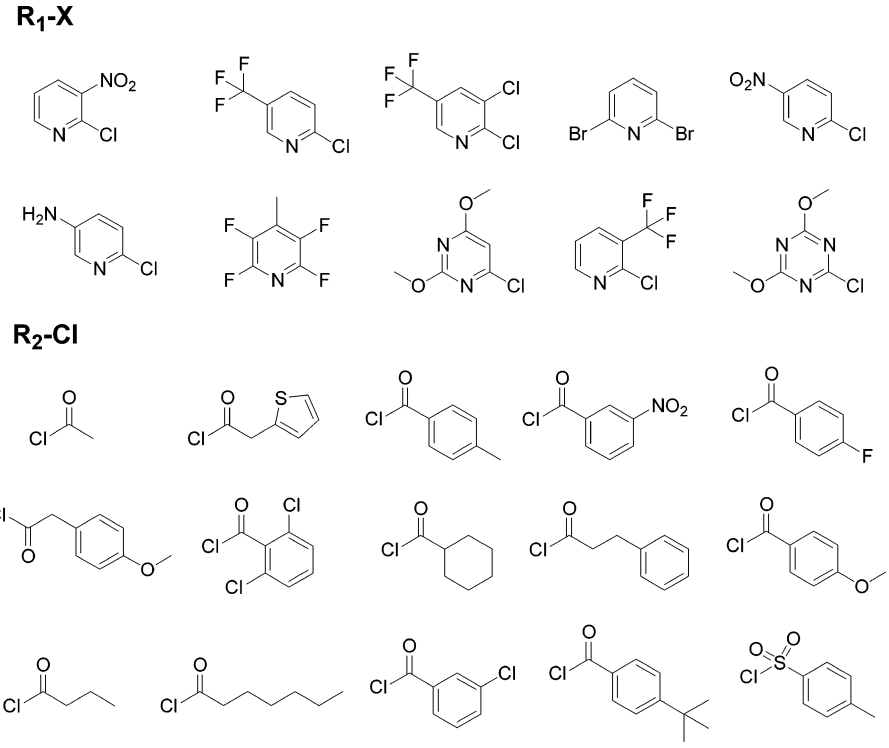
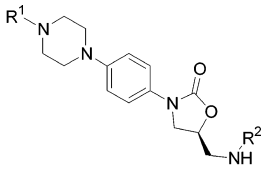
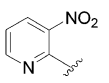
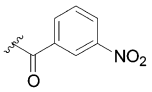
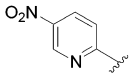
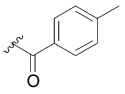
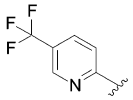
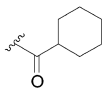
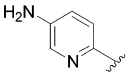
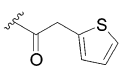
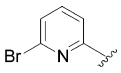
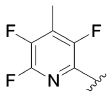
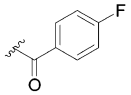
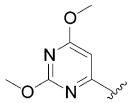
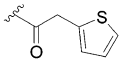
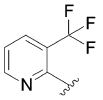
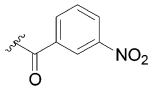
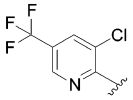
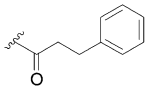
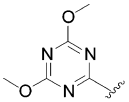
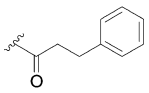


Table 1. Examples of the Chemical Libraries Produced Using Method B



1

compound	R^1	R^2	Yield(%)[a]	compound	R^1	R^2	Yield(%)[a]
22			88	**27**			84
23			81	**28**			79
24			72	**29**			80
25			79	**30**			81
26			81	**31**			87

[a] Purification yield.

forward synthesis of 5-aminomethyloxazolidin-2-one. The synthesis of carbamate ester **5** was accomplished by modifying a well-known method (Scheme 4).[2d,8] The target compound **5** was obtained by reducing 1-(4-nitrophenyl)-

piperazine, which was previously obtained by reacting 1-fluoro-4-nitrobenzene **15** and piperazine **16** by Pd/C−H_2 reduction, followed by reaction with benzyl chloroformate. The compound **5** obtained was reacted with the synthesized compound **13** and *n*-BuLi in THF at −78 °C to give compound **14** (Scheme 3).

The parallel synthesis of a chemical library was performed using the method, shown in Scheme 3. A Cbz protecting group was removed from the oxazolidinone **14** using Pd/C and hydrogen in MeOH/MC (3:1 v/v) as solvent, and this was divided into 10 equal volumes and reacted with 10 different aryl halides (pyridines, pyrimidine, and triazine) to substitute different R_1 groups in **1**. Scheme 5 shows the structures of R_1 and R_2. The 10 different reaction mixtures were refluxed for 12 h in a screw reactor[9] in a sea sand bath. The yields of these 10 compounds were generally 80−90%. Each product was divided into 15 equal volumes, and 15 different acyl or sulfonyl chlorides were the added to the reactor to give in total 150 disubstituted derivates ($10 \times 15 = 150$). The yields of the desired derivatives were ∼70−90% after purification. Table 1 shows some of the compounds synthesized on the basis of using this parallel method.

This paper provided many chemical libraries easily by changing the methodology and employing (*S*)-oxiranylmethylcarbamic acid *tert*-butyl ester to make the oxazolidinone scaffold. We synthesized more than 150 derivatives conveniently. Moreover, this methodology can be applied to the development of diverse drugs by introducing various functional groups to the 5-aminomethyl group of oxazolidinone.

In summary, we describe a method for the rapid synthesis of antibiotics based on a (S)-oxazolidine template. We believe this method will be helpful for identifying lead compounds for drug development.

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Supporting Information Available. Preparation and characterization of the compounds in Schemes 3 and 4 and in Table 1. This material is available free of charge via the Internet at http://pubs.acs.org.

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(6) Preparation of (*S*)-4-{4-[5-(*tert*-butoxycarbonylamino-methyl)-2-oxo-oxazolidin-3-yl]phenyl}piperazin-1-carboxylic acid benzyl ester (**14**). To a solution of *n*-BuLi (1.6 M in hexane, 23.2 mL, 37.04 mmol) in THF (150 mL) at −78 °C was added dropwise benzyl ester **5** (15 g, 33.67 mmol) over 30 min, and then the solution was stirred for at least 3 h. Butyl ester **13** (6.4 g, 37.04 mmol) dissolved in THF (100 mL) was added dropwise over 30 min, and the temperature was maintained below −78 °C for 3 h. The mixture was then stirred for 15 h and poured into aqueous NH_4Cl (100 mL). The organic layer was separated with ethyl acetate (100 mL × 3) and washed with brine. The solvent was dried ($MgSO_4$), concentrated, and chromatographed (silica gel; 230−400 mesh) to afford 10.5 g (61%) of the benzyl ester **14**. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.40 (m, 5H), 7.26 (s, 2H), 6.93 (t, 2H, $J = 7.52$ Hz), 5.17 (d, 2H, $J = 6.06$ Hz), 4.95 (m, 1H), 4.67 (m, 1H), 4.02 (m, 1H), 3.82 (m, 1H), 3.67 (t, 4H, $J = 5.03$ Hz), 3.52 (t, 2H, $J = 5.90$ Hz), 3.12 (s, 4H), 1.42 (s, 9H).

(7) Prepared from (*S*)-3-hydroxybutyrolactone. See: Roh, K. R.; Lee, J. H.; Hwang, D. I.; Lee, W. J.; Kim, K. I. U.S. Patent 6,417,403 B1, 2002 (80% yield). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 4.83 (br, 1H), 3.54 (m, 1H), 3.20 (m, 1H), 3.08 (m, 1H), 2.77 (m, 1H), 2.58 (m, 1H), 1.43 (s, 9H).

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