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An Organocatalytic Approach to the Construction of Chiral Oxazolidinone Rings and Application in the Synthesis of Antibiotic Linezolid and Its Analogues

Lirong Song,[†] Xiaobei Chen,[†] Shilei Zhang,*[,†] Haoyi Zhang,[†] Ping Li,[†] Guangshun Luo,[†] Wenjing Liu,[†] Wenhu Duan,*[,†,‡] and Wei Wang*[,†,§]

Department of Pharmaceutical Sciences, School of Pharmacy, East China University of Science & Technology, Shanghai 200237, People's Republic of China, Shanghai Institute of Materia Medica, Shanghai Institutes of Biological Sciences, Chinese Academy of Sciences, Graduate School of the Chinese Academy of Sciences, Shanghai 201203, People's Republic of China, and Department of Chemistry & Chemical Biology, University of New Mexico, Albuquerque, New Mexico 87131-0001

zsl103@yahoo.com.cn; whduan@mail.shcnc.ac.cn; wwang@unm.edu

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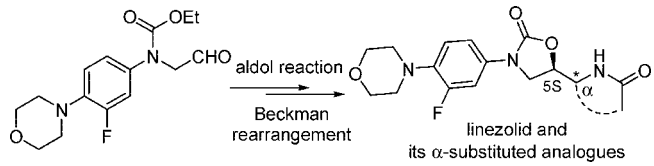
ABSTRACT



An efficient, catalytic asymmetric approach to antibacterial agent linezolid has been developed. The route features organocatalytic, highly enantioselective aldol and Beckman rearrangement reactions. The strategy has also been successfully applied for the preparation of new α-substituted analogues with high enantio- and diastereoselectivity.

Oxazolidinones are an important class of molecular architectures found in a broad range of synthetically and biologically interesting compounds. The widely used Evans chiral oxazolidinone-based auxiliaries are one of the most reliable methods in asymmetric synthesis.[1] The five-membered heterocycles display a broad spectrum of biological activities, serving as inhibitors of monoamine oxidase,[2] HIV-1 inhibitory activity,[3] NPC1L1 ligands,[4] and RNA-binding agents.[5] Moreover, the interest in this structure has recently surged significantly as a result of new antibiotic agent linezolid **1** (Zyvox) (Figure 1).[6]

[†] East China University of Science & Technology.
[‡] Graduate School of the Chinese Academy of Sciences.
[§] University of New Mexico.

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Linezolid, a new class of synthetic antibacterial with potent activity against Gram-positive nosocomial infections, was approved for use in humans in April 2000. Since then, a great deal of research effort has been devoted to the synthesis of oxazolidinone analogues aimed at seeking new antibacterials.[7] The general approach to the chiral oxazolidinone scaffold mainly relies on the use of the chiral precursors.[8] To our knowledge, a catalytic asymmetric method has not yet been described. In conjunction with our ongoing studies on the synthesis of new oxazolidinone analogues for antibacterial applications with fewer side effects, we have decided to develop an alternative, versatile catalytic enantioselective approach to the construction of the chiral architecture. It is noteworthy that both morpholine-ring and amide moieties play key roles in bioactivity.[7] As a result of the lack of an efficient catalytic method for the building of the chiral oxazolidinone framework and introducing diversity at the α-position of the amide, it is not surprising that only simple amides have been synthesized. It is realized that introducing the substituents at the α-position is a challenging task because such modification will create a new stereogenic center (Figure 1).

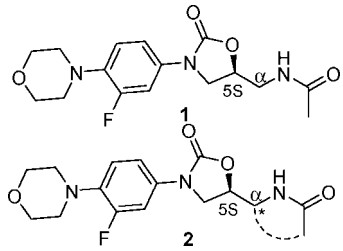


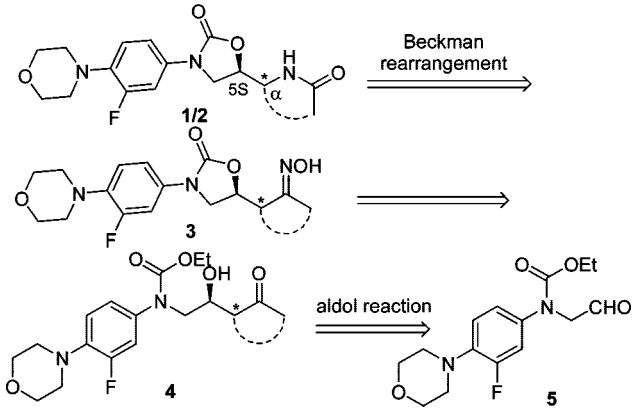
Figure 1. Structures of linezolid **1** and its α-substituted analogues **2**.

In the past decade, organocatalysis has received considerable attention due to the novelty of the concept, operational simplicity, and environmental friendliness.[9] Despite the fact that a number of highly enantioselective organocatalytic processes have been developed, their synthetic value in the application of preparation of biologically significant natural products and synthetic molecules remains to be demonstrated.[10] Toward this end, recently our group has become interested in exploring these asymmetric approaches to synthetically valuable targets. Herein, we disclose the results of an investigation that has resulted in an unprecedented organocatalytic enantioselective aldol and Beckman reactions as key steps for efficient preparation of linezolid **1**. Moreover, the strategy serves as a facile approach to its α-substituted analogues **2** (Figure 1).

A concise total synthesis of linezolid **1** and its α-substituted oxazolidinone analogues is shown in Scheme 1. We envisioned that the up to two stereogenic centers and amide moiety could be facilely constructed by organocatalytic enantioselective aldol reaction and Beckman rearrangement, respectively.

On the basis of this synthetic plan, indeed, the prerequisite aldehyde **5** could be prepared straightforwardly in four steps in an overall 70% yield (Scheme 2). Reductive amination of readily available aniline **6** with glyceraldehyde acetonide **7** in the presence of $NaBH(OAc)_3$ produced amine **8** in 82% yield. Protection of the resulting amino group **8** with ethyl chlorformate, followed by removal of the isopropylidene group of compound **9** and oxidation of corresponding diol **10** with sodium metaperiodate, afforded desired aldehyde **5** in very high yields.

Scheme 1. Retrosynthetic Analysis of Linezolid **1** and Its Analogues **2**



With the compound **5** in hand, we set the stage for the critical catalytic enantioselective aldol reaction. Despite the fact that the organocatalytic asymmetric aldol process has

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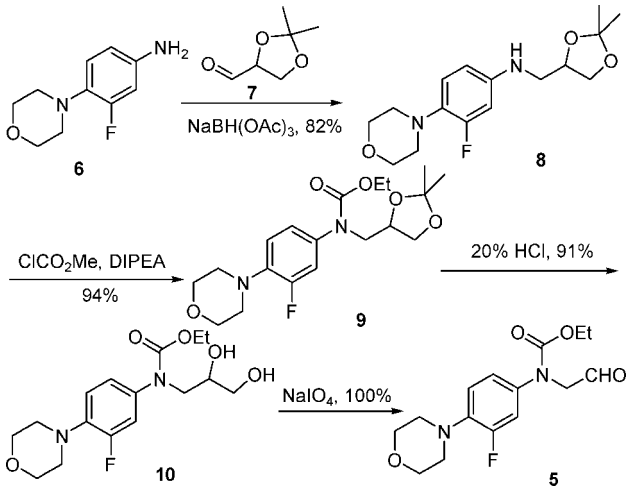
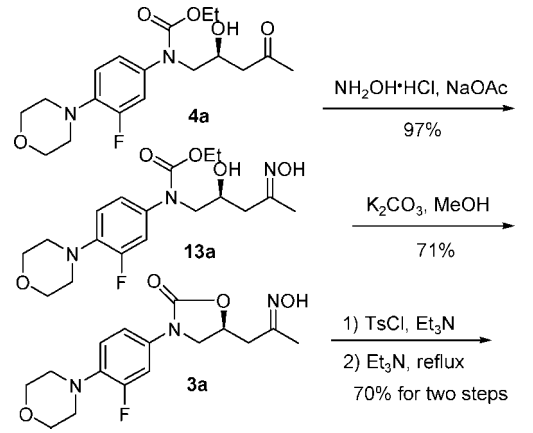
(10) For a review of application of organocatalysis in drug and total synthesis, see: de Figueiredo, R. M.; Christmann, M. *Eur. J. Org. Chem.* **2007**, 2575.

Scheme 2. Synthesis of Aldehyde **5**

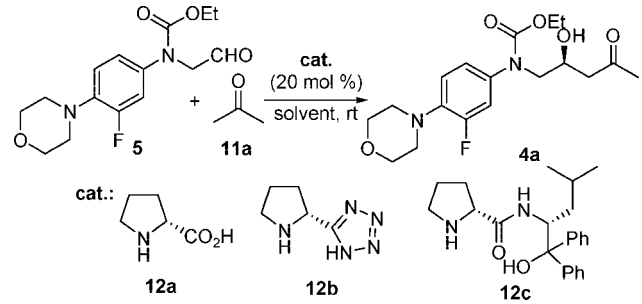


Scheme 3. Synthesis of Linezolid **1**



been intensively explored,[11−13] the utilization of the specific α-amino aldehyde **5** for the reaction has not been reported. Our experience indicated that the enantioselectivity and reaction yield of the aldol reaction is highly substrate-dependent. Accordingly, the exploration of the aldol process aimed at seeking the optimal reaction conditions was performed intensively with aldehyde **5** and acetone. The results are shown in Table 1. Commonly used organocatalysts such as (*R*)-proline **12a** and (*R*)-pyrrolidinyl tetrazole **12b** gave disappointing results in terms of reaction yields and enantioselectivity (Table 1, entries 1−4). The long reaction times and low yields made it impossible to further improve the enantioselectivities by lowering the reaction temperature. After extensive survey of a variety of chiral pyrrolidine-derived catalysts, to our delight we found that amide **12c**[11l] gave the best results. In this case, a good yield (67%) and high ee (88%) at −35 °C were achieved (Table 1, entry 5).

Table 1. Aldol Reaction of Aldehyde **5** and Acetone **11a**[a]



entry	solvent	catalyst	*t* (h)	% yield[b]	% ee[c]
1	DMF	**12a**	70	17	58
2	acetone	**12a**	70	30	67
3	DMF	**12b**	72	20	56
4	acetone	**12b**	48	40	72
5[d]	acetone	**12c**	17	67	88

[a] Unless otherwise indicated, all reactions were carried out on a 0.10 mmol scale with 0.1 mL of acetone and 0.4 mL of solvent in the presence of 20 mol % of the catalyst at room temperature. [b] Isolated yield. [c] Determined by chiral HPLC analysis. [d] Reaction performed at −35 °C.

Finally, we turned our attention to the synthesis of target molecule linezolid **1** from compound **4a**. The synthesis is straightforward. Treatment of β-hydroxyketone **4a** with hydroxylamine hydrochloride gave oxime **13a** in a nearly quantitative yield (97%). Subsequent cyclization in the presence of K_2CO_3/MeOH to provide oxazolidinone **3a** was followed by a two-step Beckman rearrangement to afford linezolid **1** in 50% yield (Scheme 3). The spectral data of the synthetic substance **1** were in full agreement with those described in the literature.[14]

The generality of the synthetic strategy was further explored in the synthesis of the analogues **2** of linezolid **1**.

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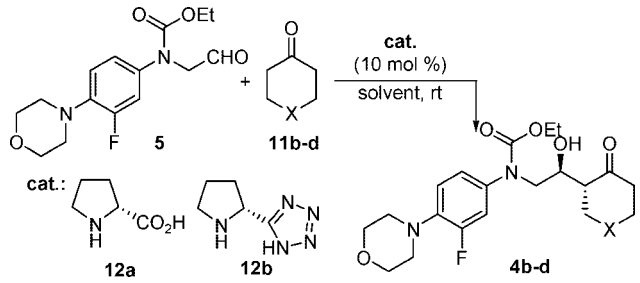
Table 2. Aldol Condensation of Aldehyde **5** and Cycloketones **11a−c**[a]



entry	X	solvent	catalyst	t (h)	% yield[b]	% ee[c]
1	CH_2, **11b**	**11b**	**12a**	20	96	95
2	O, **11c**	**11c**	**12a**	48	95	97
3[d]	NBoc, **11d**	DMF	**12a**	21	61	90
4[d]	NBoc, **11d**	DMSO	**12a**	28	77	93
5[d]	NBoc, **11d**	DMSO	**12b**	48	55	93

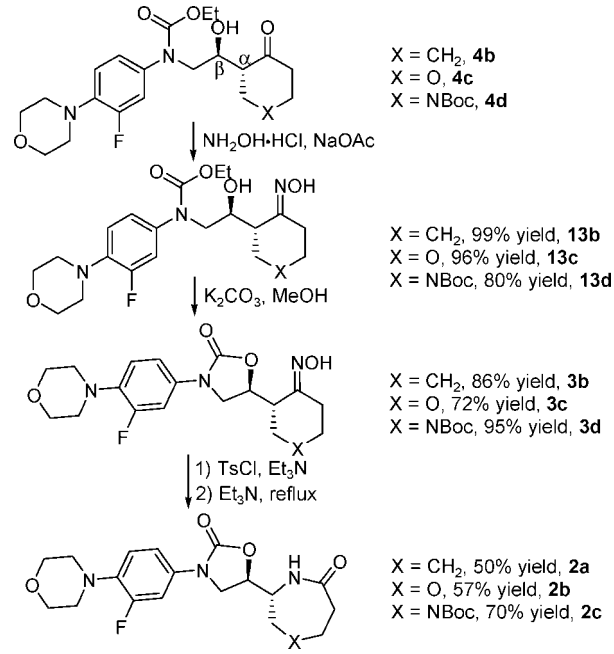
[a] Unless otherwise indicated, all reactions were carried out on a 0.10 mmol scale with 0.1 mL of acetone and 0.4 mL of solvent in the presence of 10 mol % of the catalyst at room temperature. [b] Isolated yield. [c] Determined by chiral HPLC analysis. [d] 2.5 mmol **11d** used.

As demonstrated, the strategy serves as a powerful tool for the efficient preparation of the new α-substituted analogues of linezolid **1** in high yields and with enantio- and diastereoselectivities. It is anticipated that the reaction efficiency of the organocatalyzed aldol reaction of aldehyde **5** with cyclic ketones **11b−d** highly depends on organocatalysts and reaction conditions. After the optimization of reaction conditions, it was found that the best outcomes were obtained with (*R*)-proline **12a** as catalyst for cyclohexanone **11b** and tetrahydropyran-4-one **11c**. In both cases, high yields and excellent levels of enantioselectivity were achieved (Table 2, entries 1 and 2). When solid ketone **11d** was employed as aldol donor, a solvent was necessary for the process (entries 3−5). Although (*R*)-pyrrolidinyl tetrazole **12b** gave a similar level of enantioselectivity (93% ee, entry 5) in DMSO, a higher yield was obtained with (*R*)-proline **12a** (77% yield, Table 2, entry 4).

The highly enantio-enriched aldol adducts **4b−d** were smoothly transformed into the α-substituted analogs of linezolid **2** according to the established synthetic protocols described above (Scheme 4). It is known that the chiral center at the α-position of the carbonyl group is prone to racemization under a basic condition. This is particularly problematic for *β*-hydroxy ketones. To minimize the problem, we first converted the ketones in **4b−d** to oximes **13b−d**.

(14) See Supporting Information and Brickner, S. J.; Hutchinson, D. K.; Barbachyn, M. R.; Manninen, P. R.; Ulanowicz, D. A.; Garmon, S. A.; Grega, K. C.; Hendges, S. K.; Toops, D. S.; Ford, C. W.; Zurenko, G. E. *J. Med. Chem.* **1996**, *39*, 673.

Scheme 4. Synthesis of Analogues **2** of Linezolid



Then compound **13** was exposed to K_2CO_3/MeOH to give cyclic oxazolidinone **3**. Finally two-step Beckman rearrangement furnished the amides **2a−c** in good yields. During these transformations, no racemization was observed.[15]

In conclusion, we have developed a concise and flexible asymmetric approach to the antibacterial agent linezolid and its analogues in an efficient way. The route features organocatalytic, highly enantioselective aldol and Beckman rearrangement reactions. The strategy, reported for the first time, serves as a powerful tool for synthesis of analogues of linezolid with branches at the α-position. Further elaboration of the method for preparation of more analogues and their biological activity studies are currently in progress in our laboratory.

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Supporting Information Available: Experimental procedures and spectra data for compounds **1−10** and **13**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) Chiral HPLC analysis of final products showed no racemization occurred during these transformations (see Supporting Information for product **2a**).