

Asymmetric Synthesis of Trisubstituted Oxazolidinones by the Thiourea-Catalyzed Aldol Reaction of 2-Isocyanatomalonate Diester

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(5) Supporting Information

ABSTRACT: A new method has been developed for the synthesis of chiral 4-carboxyl oxazolidinones by the catalytic asymmetric aldol reaction of an isocyanatomalonate diester with an aldehyde in the presence of a thiourea catalyst. The resulting chiral 4-carboxyl oxazolidinones are the equivalent of β -hydroxy- α -amino acids bearing a tri- or tetrasubstituted carbon center at their α position. With this in mind, this procedure was successfully applied to the first total synthesis of



procedure was successfully applied to the first total synthesis of mycestericin C, which was completed in 12 steps and represents one of the shortest reported sequences for the construction of natural products of this type.

O xazolidinones are a fundamental structural class in organic chemistry, where they have been used successfully as chiral auxiliaries, 1 and in medicinal chemistry (e.g., Linezolid, Figure 1).² This structure bearing an ester moiety (i.e., 4-carboxyl



Figure 1. Biologically active compounds containing an oxazolidinone or β -hydroxy- α -amino acid moiety.

oxazolidinones) is synthetically equivalent to β -hydroxy- α -amino acids, which can be found in various biologically active compounds, including peptides and β -lactams, as well as natural products such as mycestericin C and polyoxin J.³ For this reason, considerable research efforts have been directed toward the development of synthetic methods for the enantioselective construction of oxazolidinone systems.⁴ Oxazolidinones have traditionally been synthesized from chiral β -hydroxy- α -amino acids, and this particular method is generally both convenient and robust when it is applied to natural amino acid substrates. Several stepwise methods have also been developed for the synthesis of chiral oxazolidinones, including catalytic asymmetric reactions such as the Sharpless asymmetric aminohydroxylation⁵ and asymmetric aldol reaction.⁶ Chiral oxazolidinones can also be accessed using dynamic kinetic resolution techniques.⁷⁻⁹ Although a variety of different methods have been reported for the asymmetric synthesis of oxazolidinones, reports pertaining to the direct asymmetric synthesis of 4-carboxyl oxazolidinone have been scarce, with research in this area being focused predominantly on the preparation of mono- and disubstituted oxazolidinones.10

The direct catalytic asymmetric aldol reaction¹¹ is a powerful method for the construction of 4-carboxy oxazoline¹² and thiooxazolidinone¹³ scaffolds (Figure 2a and b). In 1986, Ito and



Figure 2. Synthetic strategy for 4-carboxyl oxazolidinone based on catalytic asymmetric aldol reaction.

Hayashi^{12a} reported their pioneering work toward the catalytic asymmetric synthesis of oxazolines from isocyanoacetates using a gold catalyst with a phenylphosphine ligand. In 2008, Seidel^{13a} developed a method for the catalytic enantioselective aldol addition of α -isothiocyanato esters to aldehydes and ketones to give the corresponding thiooxazolidinones using an organo-catalyst. Furthermore, Shibasaki and Feng^{13b,c} reported the asymmetric aldol reactions of α -isothiocyanato esters and aldehydes and ketones for the synthesis of tri- and tetrasub-

Received: July 25, 2014 Published: September 9, 2014 stituted thiooxazolidinones using Mg, Ag, and Ni catalysts. Asymmetric aldol reactions involving the reaction of isocyanoacetates with aldehydes or ketones in the presence of organocatalysts have also been developed by Dixon and Gong.^{12b,c} Although several methods have been reported in the literature for the asymmetric synthesis of oxazoline and thiooxazolidinone systems, there have, to the best of our knowledge, been no reports concerning the use of a direct catalytic enantioselective aldol reaction for the synthesis of 4-carboxyl oxazolidinones. For this reason, di- and trisubstituted oxazolidinones have generally been accessed by performing additional transformations with the oxazoline and thiooxazolidinone systems described above. There is therefore an urgent need for the development of new methods allowing for the direct construction of oxazolidinones.

It was envisaged that the coupling of an isocyanatomalonate diester with an aldehyde in the presence of a thiourea catalyst (TUC)^{14,15} would allow for the direct asymmetric construction of the corresponding oxazolidinone (Figure 2c). To date, isocyanatomalonate diesters bearing both nucleo- and electrophilic groups have only been used as electrophiles for the preparation of ureas,¹⁶ and the properties of these compounds have never been reported in any great detail. Because the isocyanate group is more reactive than the isothiocyanate group, its application as a nucleophile in an aldol reaction would be challenging. Compared with previously reported methods for the direct catalytic synthesis of oxazolidinones, this method is at a distinct advantage because trisubstituted oxazolidinones are readily available. Furthermore, the resulting oxazolidinones could be converted to $syn-\beta$ -hydroxyl- α -amino acids derivatives by decarboxylation, as well as anti- β -hydroxyl- α -amino acids derivatives bearing a tetrasubstituted carbon center, which have never before been synthesized from oxazolines and thiooxazolidinones. Herein, we report the first catalytic asymmetric aldol reaction of isocyanatomalonate diesters with aldehydes for the synthesis of oxazolidinones, and the application of this method to the total synthesis of mycestericin C, which contains an *anti-\beta*-hydroxyl- α -amino acid structure with a tetrasubstituted carbon center.

We initially investigated the aldol reaction of isocyanates 1a-d with benzaldehyde (2a) in the presence of (R,R)-TUC 4a (Table 1). The aldol reaction of **1a** proceeded smoothly in toluene at rt to give oxazolidinone 3a in 87% yield with an enantiomeric excess (ee) of 88%. This reaction also afforded a small amount of the byproduct 3a' (11%), resulting from the reaction of the product 3a with 1a. It is noteworthy that higher ee values were observed with the smaller ester groups (Table 1, entries 1-4). Based on the ee values of the products, as well as the stabilities and prices of the starting materials, diethyl 2-isocyanatomalonate (1b) was selected for further investigation. The temperature of the reaction was then examined, and it was found that the formation of the byproduct could be suppressed at lower temperatures. The use of a lower temperature also resulted in an improved yield, although the reaction required 72 h to proceeded to completion with the complete consumption of benzaldehyde 2a (Table 1, entries 5–8). The use of aliphatic aldehydes resulted in lower ee values compared with aromatic aldehydes, and it was therefore decided to optimize the TUC 4 using an aliphatic aldehyde in the interest of developing a process with the broadest possible substrate scope.¹⁷ The aldol reaction of 3-phenylpropanal (2b) with diethyl 2-isocyanatomalonate 1b in the presence of 10 mol % of the TUC 4a at -60 °C gave oxazolidinone 3e quantitatively with 65%ee (Table 1, entry 9). Several di-n-alkyl amines were then introduced to the TUC

NCO RO ₂ C CO ₂ R 1a, R = Me 1b, R = Et 1c, R = <i>i</i> Pr 1d, R = Bn		CHO (2a) (2b) (R,R)-TUC (4a-g) (10 mol %) Toluene, temp, time		0 2b) RO ₂ C g) RO ₂ C me 3a, R = Me, R 3b, R = Et, R' 3c, R = <i>P</i> , R' 3c, R = <i>P</i> , R' 3c, R = <i>P</i> , R' 3c, R = <i>R</i> , R' 3c, R = <i>R</i> , R'	$RO_{2}C$ $RO_{2}C$ $RO_{2}C$ $RO_{2}C$ R'' R''' R''' R''''''''''	
F ₃ C	CF ₃		4a, F 4b, F 4c, F 4d, F 4e, F 4f, F	$\begin{array}{l} R = NMe_{2} \\ R = N(nC_{5}H_{11})_{2} \\ R = N(nC_{6}H_{13})_{2} \\ R = N(nC_{7}H_{15})_{2} \\ R = N(nC_{7}H_{15})_{2} \\ R = N(nC_{8}H_{17})_{2} \\ R = \frac{5}{2} - N \\ \end{array} \qquad \qquad$	CF ₃ N H 4g	Ph Ph Ph NMe ₂
entry	1a-d	2a-b	cat.	temp, time	yield $(\%)^a$	ee (%)
1	1a	2a	4a	rt, 24 h	87 ^b	88
2	1b	2a	4a	rt, 24 h	82	83
3	1c	2a	4a	rt, 24 h	88	61
4	1d	2a	4a	rt, 24 h	80	78
5	1b	2a	4a	0 °C, 24 h	84	87
6	1b	2a	4a	−20 °C, 24 h	88	88
7	1b	2a	4a	−40 °C, 24 h	85	87
8	1b	2a	4a	−60 °C, 72 h	90	87
9	1b	2b	4a	−60 °C, 72 h	quant	65
10	1b	2b	4b	−60 °C, 72 h	66	78
11	1b	2b	4c	−60 °C, 72 h	72	77
12	1b	2b	4d	−60 °C, 72 h	60	71
13	1b	2b	4e	−60 °C, 72 h	36	54
14	1b	2b	4f	−60 °C, 72 h	62	54
15	1b	2b	4g	−60 °C, 72 h	76	19
^a Isolated yield. b The yield was estimated by 1 H NMR.						

Table 1. Investigation of the Conditions for the Reaction of

the Aldehydes with the Isocyanates

instead of the dimethylamine moiety. In the case of the TUCs containing di-*n*-pentyl- and di-*n*-hexylamine groups (4a and 4b), the enantioselectivity was improved to 78%ee, although further increases in the length of the alkyl side chain were ineffective (Table 1, entries 10-13). Based on these results, steric factors appeared to be particularly important to the outcome of this reaction. However, TUCs 4f and 4g did not give satisfactory results (Table 1, entries 14-15), and catalyst 4b bearing a dipentylamine side chain was selected as the optimum TUC for the reaction.

With the optimized conditions in hand, we proceeded to investigate the scope of the reaction using TUC 4a or 4b as the catalyst with a broad range of aryl aldehydes 2f-p. All of the reactions were conducted with isocyanate 1b (10 mol %) in toluene at -60 °C and proceeded smoothly to give the corresponding oxazolidinones 3f-p in high yields with good enantioselectivities (Scheme 1). Various aldehydes reacted successfully under the optimized conditions, including electron-rich and -deficient aryl aldehydes, as well as heteroaromatic aldehydes. The use of catalyst 4b instead of 4a led to improvements in the ee in some cases (89–92%ee for 3g–i, k, 1), whereas 4a gave satisfactory ee values in other cases (87-95%ee for 3f, j, m-p). The reactions of α -branched aliphatic aldehydes including isopropyl aldehyde (2q) and cyclohexanecarboxaldehyde (2r) gave the corresponding oxazolidinones 3qand 3r in moderate yields with high ee values. In contrast, the reactions of *trans*-cinnamaldehyde, *n*-heptaldehyde, and isobutyl aldehyde resulted in moderate ee values (65-82%ee, 3s-u), even when catalyst 4b was used. Furthermore, the use of a bulky

Scheme 1. Scope and Limitations^a



aldehyde such as pivalaldehyde (2v) resulted in no reaction under the optimized conditions. These results indicated that the stereoselectivity of the reaction resulted from the recognition of the α position of the aldehyde by the catalyst. The trisubstituted oxazolidinone **3** could be converted to a disubstituted oxazolidinone by decarboxylation. For example, a hydrolysis of compound **3b** followed by treatment of the resulting acid with DBU gave the *trans*-disubstituted oxazolidinone **5**, which is a precursor for the synthesis of *syn-β*-hydroxyl- α -amino acid (Scheme 2).^{10c,17} The absolute stereochemistry of the newly formed chiral center in **5** was confirmed to be the *R* configuration by comparing its optical rotation with the literature data.^{8b}



To demonstrate of the synthetic utility of our newly developed asymmetric aldol reaction, it was applied to the total synthesis of mycestericin C. Mycestericins are potent immunosuppressant agents that were originally isolated from the culture broth of *Mycelia sterilia* by Fujita et al. in 1994 (Figure 1).¹⁸ Although there have been no reports in the literature concerning the total synthesis of mycestericin C, several related synthetic studies have revealed that the construction of the β -hydroxy- α -amino acid moiety requires several challenging manipulations, including the diastereo- and enantioselective synthesis of a tetrasubstituted carbon center.^{19,20} It was envisaged that our newly developed

enantioselective aldol reaction could be used to construct an oxazolidinone, which could be converted to a β -hydroxy- α -amino acid bearing a tetrasubstituted carbon center for a concise synthesis of mycestericin C.

The commercially available α,β -unsaturated aldehyde **6** was subjected to an aldol reaction with diethyl isocyanatomalonate **1b** under the optimized conditions using (*R*,*R*)-TUC **4a** to give oxazolidinone 7 in 91% yield with high enantioselectivity (88% ee, Scheme 3).²¹ Treatment of 7 with aqueous KOH gave





carboxylic acid 8 as a single product following the nucleophilic attack of the hydroxide anion at the least hindered ester. The subsequent formation of an acid chloride followed by reduction with $Zn(BH_4)_4$ gave alcohol 9 in 96% yield, which was protected with TBSCl to give the corresponding silyl ether. The carboncarbon double bond was cleaved by ozonolysis, followed by reduction with NaBH₄ to give lactone 10 as a 4:1 mixture of diastereomers. Oxidation of 10 followed by a Wittig reaction gave 11, which was coupled with compound 12^{21} using Grubbs first generation catalyst.^{20c,22,23} Subsequent hydrogenation and removal of the TBS group gave the protected mycestericin C 13, and the minor isomer was removed by silica gel column chromatography at this stage. The treatment of 13 with aq. NaOH completed the first total synthesis of mycestericin C. This material was treated with Ac₂O to give the corresponding triacetylated mycestericin C, which was subjected to spectroscopic analysis and found to be identical to the reported material.^{17,18} The longest liner sequence in this synthesis was 12 steps from the commercially available aldehyde 6, which demonstrates that this protocol is preferable to the other synthetic methods currently available for mycestericins.

In summary, we have developed a catalytic asymmetric aldol reaction for the synthesis of 4-carboxyl oxazolidinone. This reaction represents the first reported example of the use of isocyanatomalonate diester in an aldol reaction, which is critical to the success of this transformation. By tuning the TUC, we have enhanced the scope of this reaction so that it can be applied to a broad range of aldehydes, including aryl and branched alkyl aldehydes. The resulting oxazolidinones are equivalent to β -

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hydroxy- α -amino acids, and this process was therefore successfully applied to the total synthesis of mycestericin C. This synthesis not only represents the first reported total synthesis of mycestericin C but also is one of the shortest reported sequences for the synthesis of related natural products. We believe that this method could be used for the preparation of chiral 4-carboxyl oxazolidinones, and further studies toward the application of this transformation are currently underway in our laboratory.

ASSOCIATED CONTENT

Supporting Information

Experimental procedure, spectroscopic data, ¹H, ¹³C NMR spectra were described. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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