Asymmetric Synthesis of Chiral \( \delta \)-Lactones Containing Four Contiguous Stereocentres

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ABSTRACT

Versatile methodology for the asymmetric synthesis of chiral \( \delta \)-lactones containing four contiguous stereocentres has been developed that relies on a series of Evans’ aldol, hydroxyl-directed cyclopropanation and Hg(II)-mediated cyclopropane ring-opening reactions for stereocontrol.

The \( \delta \)-lactone functional group appears as a fragment in many natural products that exhibit a wide range of biological activity.† Many of these structurally complex \( \delta \)-lactones contain multiple contiguous stereocentres, which means that their asymmetric synthesis can represent a significant challenge.‡ Consequently, a wide range of methodology has been developed for their synthesis,§ with chiral \( N \)-acyl-oxazolidin-2-ones having often been used to prepare \( \delta \)-lactones as intermediates for natural product synthesis. These protocols are generally based on the stereoselective addition of enolates of chiral \( N \)-acyl-oxazolidin-2-ones to enantiopure electrophiles,¶ or stereoselective aldol reactions of chiral \( \beta \)-keto-\( N \)-acyl-oxazolidin-2-ones enolates.¶ We now report herein an alternative strategy that employs a chiral \( N \)-acyl-oxazolidin-2-one to prepare enantiomerically pure cyclopropane-esters that undergo regioselective Hg(II) ring-opening reactions to afford \( \delta \)-lactones containing four contiguous stereocentres with excellent levels of stereocontrol.

We have recently reported the development of novel synthetic strategies that employ the reversible generation of “temporary stereocentres” for the asymmetric synthesis of chiral aldehydes.¶ One of these protocols employs highly diastereoselective hydroxyl-directed \( \textit{syn} \)-cyclopropanation reactions of \( \beta \)-alkenyl-\( \beta \)-hydroxy-\( N \)-acyl-oxazolidin-2-ones \( \delta \) as a key reaction (Scheme 1, reaction 1) for the asymmetric synthesis of chiral cyclopropane carboxaldehydes.¶ It has been reported that treatment of \( \gamma \)-cyclopropyl carboxylic acid derivatives such as \( \delta \) with Hg(II) salts results in regioselective cyclopropane ring-opening to afford \( \delta \)-lactones such as \( \delta \) (Scheme 1, reaction 2).¶ We have also reported that treatment of \( \beta \)-alkenyl-\( \beta \)-hydroxy-\( N \)-acyloxazolidin-2-ones with VO(acac)\( \delta \) and tert-butyl hydroperoxide results in formation of unstable epoxides \( \delta \), which are ring-opened by intramolecular nucleophilic attack of their exocyclic carbonyl fragments to afford hydroxy-\( \gamma \)-butyrolactones \( \delta \) (Scheme 1, reaction 3).¶ Consequently, it was decided to investigate whether treatment of \( \beta \)-cyclopropyl-\( \beta \)-hydroxy-\( N \)-acyl-oxazolidin-2-ones \( \delta \) with a Hg(II) species would result in regioselective intramolecular ring-opening of their cyclopropane rings to afford chiral \( \delta \)-lactones containing four contiguous stereocentres.
Scheme 1. Synthesis and ring-opening reactions of a range of chiral cyclopropanes and epoxides

A series of (syn)- and (anti)-aldols 1a-h were prepared via literature procedures, involving reaction of boron or magnesium enolates of 5,5-dimethyl-N-acyl-oxazolidin-2-ones 8a/b10 with their corresponding α,β-unsaturated aldehydes (Table 1).11 These aldols 1a-h were then cyclopropanated via treatment with Et₂Zn and CH₂Cl₂ to afford cyclopropyl-aldols 2a-h in >95% de (Table 1).12 Treatment of cyclopropyl-aldol 2a with one equivalent of Hg(OOCOCF₃)₂ in CH₂Cl₂ resulted in regioselective ring-opening of the cyclopropane ring to afford a 50:50 mixture of the organomercurial α,β-unsaturated lactone 9 and the parent oxazolidin-2-one 7 (Scheme 2). It is proposed that coordination of Hg(II) to the cyclopropane ring of 2a facilitates intramolecular nucleophilic attack by the endocyclic carbonyl group, resulting in regioselective ring-opening of the cyclopropane ring. This affords an iminium species 10 that undergoes a rapid E1cb elimination reaction to afford α,β-unsaturated lactone 9 (Scheme 2).

Since oxymercuration of β-cyclopropyl-β-hydroxy-N-acyl-oxazolidin-2-one 2a had resulted in the loss of two stereocentres, we decided to investigate oxymercuration of its corresponding methyl ester 11a, with the aim of isolating a δ-lactone 12a retaining all four stereocentres. Therefore, treatment of cyclopropyl-aldol 2a with sodium methoxide gave ester 11a that was subsequently treated with Hg(OOCOCF₃)₂ to afford the desired δ-lactone 12a in good yield (Scheme 3). Reductive demercuration14 of δ-lactone 12a via treatment with a solution of NaBH₄ in aqueous NaOH/MeOH resulted in δ-lactone 14a, whose absolute configuration was confirmed by X-ray-crystallography which clearly showed the (3S,4R,5R,6R)-configuration of its four contiguous stereocentres (Figure 1). It is proposed that the oxymercuration reaction of ester 11a proceeds via a different mechanism to 2a involving nucleophilic attack of the trifluoroacetate counterion at its cyclopropane ring to afford intermediate 13, which is hydrolysed upon work-up to afford the observed δ-lactone 12a (Scheme 3).13 This occurs because the ester group of 11a is a poorer nucleophile than the corresponding N-acyl-oxazolidin-2-one fragment of 2a and therefore less likely to participate as an anionic nucleophile to facilitate intramolecular cyclopropane ring-opening.

In order to demonstrate the scope and limitation of this methodology, the remaining cyclopropyl aldols 2b-h were converted into their corresponding methyl esters 11b-h and subjected to oxymercuration/reductive demercuration to afford a series of δ-lactones 14b-h in >95% de (Table 1). Access to δ-lactone 14g is particularly noteworthy.

Figure 1. X-ray crystal structure of (3S,4R,5R,6R)-δ-lactone 14a
since its terminal O-benzyl group will enable it to function as a bifunctional chiral building block for introducing 

\[(\text{syn})-(\text{syn})-(\text{anti})\text{-stereotetrad fragments into analogues of numerous polyketide natural products}^{14}\]

Table 3. Asymmetric synthesis of chiral $\delta$-lactones containing four contiguous stereocentres

<table>
<thead>
<tr>
<th>entry</th>
<th>aldol 1a-h$^a$</th>
<th>cyclopropane ester 11a-h$^b$</th>
<th>$\delta$-lactone 14a-h$^c$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>$X_\alpha$</td>
<td>MeO-OH-Ph</td>
<td>14a, 81%</td>
</tr>
<tr>
<td>2</td>
<td>$X_\alpha$</td>
<td>MeO-OH-Ph</td>
<td>14b, 71%</td>
</tr>
<tr>
<td>3</td>
<td>$X_\alpha$</td>
<td>MeO-OH-Ph</td>
<td>14c, 52%</td>
</tr>
<tr>
<td>4</td>
<td>$X_\alpha$</td>
<td>MeO-OH-Ph</td>
<td>14d, 66%</td>
</tr>
<tr>
<td>5</td>
<td>$X_\alpha$</td>
<td>MeO-OH-Ph</td>
<td>14e, 72%</td>
</tr>
<tr>
<td>6$^{15}$</td>
<td>$X_\alpha$</td>
<td>MeO-OH-Ph</td>
<td>14f, 51%</td>
</tr>
<tr>
<td>7$^{16}$</td>
<td>$X_\alpha$</td>
<td>MeO-OH-Ph</td>
<td>14g, 82%</td>
</tr>
<tr>
<td>8$^{17}$</td>
<td>$X_\alpha$</td>
<td>MeO-OH-Ph</td>
<td>14h, 77%</td>
</tr>
</tbody>
</table>

$^a$ Isolated yields. $^b$ Isolated yields over two steps.
We have used this methodology to prepare (+)-Prelactone B 15, which is a highly functionalised δ-lactone that has been isolated as a shunt metabolite of polyketide metabolism from the batfowlmuc-producing organism Streptomyces griseus. Therefore, the boron enolate of α-chloropropionyl-N-acetyl-oxalidin-2-one 8e was reacted with (E)-4-methylpent-2-enal to afford (syn)-aldol 16, which was converted into cyclopropyl-ester 17 via a series of cyclopropanation, dechlorination 18 and methanolysis reactions. Subsequent treatment of 17 with Hg(OCCF$_3$)$_2$/NaCl($\text{aq}$) followed by reductive demercuration with alkaline NaBH$_4$, resulted in formation of (+)-Prelactone B 15 in >95% de. 19

In conclusion, we have developed versatile methodology for the asymmetric synthesis of chiral δ-lactones containing four contiguous stereocentres. This approach relies on a combination of Evans’ aldol, cyclopropanation and Hg(II)-mediated cyclopropane ring-opening reactions for stereocore, with its utility having been demonstrated for the asymmetric synthesis of (+)-Prelactone B.

Acknowledgment. We would like to thank the EPSRC and the University of Bath for funding.

Supporting Information Available: Experimental details, spectroscopic data, and crystal data. This material is available free of charge via the Internet at pubs.acs.org.

13. (a) For a report where the trifluoroacetate counterion of Hg(OCCF$_3$)$_2$ acts as a nucleophile to facilitate ring-opening of a cyclopropane ester see: Ref 9d.
15. It was found that 5,5-dimethylzolazidin-2-one 7 (SuperQuat) co-olated with methyl ester 11f, therefore Evans auxiliary was used.
16. (a) An alternative method was used for the synthesis of aldol 1g using Et$_3$N instead of N(P$_2$Et)$_3$. For synthesis of (E)-4-(benzoyloxy)but-2-enal see: Anderson, J. C.; McDermott, B. P.; Griffin, E. J. Tetrahedron 2000, 56, 8747-8767.
17. (anti)-Aldol 1h was prepared via treatment of the magnesium enolate of N-acetyl-oxalidin-2-one 8a with chiralaldimide, see Ref 11b.