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Asymmetric Synthesis of Chiral δ-Lactones Containing Multiple Contiguous Stereocenters

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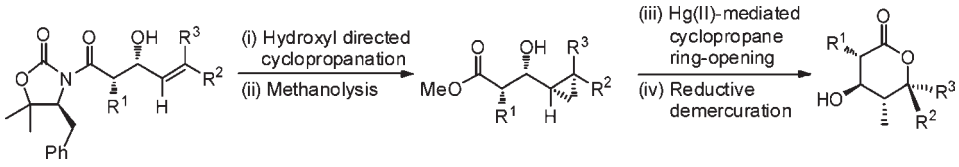
ABSTRACT



A versatile methodology for the asymmetric synthesis of chiral δ-lactones containing multiple contiguous stereocenters has been developed that relies on a series of Evans' aldol, hydroxyl-directed cyclopropanation, methanolysis, and Hg(II) mediated cyclopropane ring-opening reactions for stereocontrol.

The δ-lactone functional group appears as a fragment in many natural products that exhibit a wide range of biological activity.[1] Many of these structurally complex δ-lactones contain multiple contiguous stereocenters, which means that their asymmetric synthesis can represent a significant challenge.[2] Consequently, a wide range of methodology has been developed for their synthesis,[3] with chiral *N*-acyl-oxazolidin-2-ones having often been used to prepare δ-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[4] or stereoselective aldol reactions of chiral β-keto-*N*-acyl-oxazolidin-2-one enolates.[5] 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 δ-lactones containing up to four contiguous stereocenters with excellent levels of stereocontrol.

We have recently reported the development of novel synthetic strategies that employ the reversible generation of "temporary stereocenters" for the asymmetric synthesis of chiral aldehydes.[6] One of these protocols employs highly diastereoselective hydroxyl-directed *syn*-cyclopropanation reactions of β-alkenyl-β-hydroxyl-*N*-acyl-oxazolidin-2-ones **1** as a key reaction (Scheme 1, reaction 1) for the asymmetric synthesis of chiral cyclopropane carboxaldehydes.[7] It has

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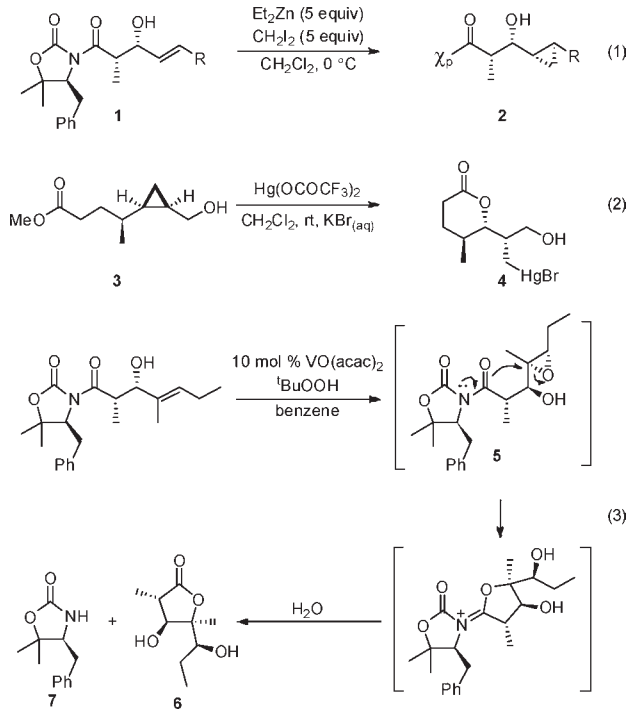
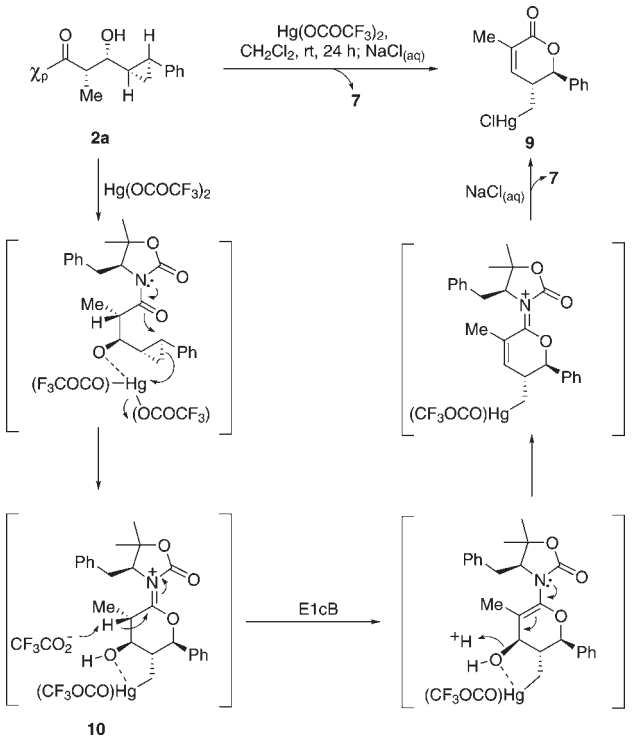
Scheme 1. Synthesis and Ring-Opening Reactions of a Range of Chiral Cyclopropanes and Epoxides



Scheme 2. Treatment of Cyclopropane-Aldol **2a** with $Hg(OCOCF_3)_2$ Results in Intramolecular Cyclopropane Ring Opening and Dehydration To Afford α,β-Unsaturated Lactone **9**



been reported that treatment of γ-cyclopropyl carboxylic acid derivatives such as **3** with Hg(II) salts results in regioselective cyclopropane ring opening to afford δ-lactones such as **4** (Scheme 1, reaction 2).[8] We have also reported that treatment of β-alkenyl-β-hydroxy-*N*-acyloxazolidin-2-ones with $VO(acac)_2$ and *tert*-butyl hydroperoxide results in formation of unstable epoxides **5**, which are ring opened by intramolecular nucleophilic attack of their exocyclic carbonyl fragments to afford hydroxy-γ-butyrolactones **6** (Scheme 1, reaction 3).[9] Consequently, it was decided to investigate whether treatment of β-cyclopropyl-β-hydroxyl-*N*-acyl-oxazolidin-2-ones **2** with a Hg(II) species would result in regioselective intramolecular ring opening of their cyclopropane rings to afford chiral δ-lactones containing up to four contiguous stereocenters.

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/b**[10] with their corresponding α,β-unsaturated aldehydes (Table 1).[11] These aldols **1a**–**h** were then cyclopropanated *via* treatment with Et_2Zn and CH_2I_2 to afford cyclopropyl-aldols **2a**–**h** in >95% de (Table 1).[12] Treatment of cyclopropyl-aldol **2a** with 1 equiv of $Hg(OCOCF_3)_2$ in CH_2Cl_2 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 stereocenters, we decided to investigate oxymercuration of its corresponding methyl ester **11a**, with the aim of isolating a δ-lactone **12a** retaining all four stereocenters. Therefore, treatment of cyclopropyl-aldol **2a** with sodium methoxide gave ester **11a** that was subsequently treated with $Hg(OCOCF_3)_2$ to afford the desired δ-lactone **12a** in good yield (Scheme 3). Reductive demercuration[8d] of δ-lactone **12a** *via* treatment with a solution of $NaBH_4$ in aqueous NaOH/MeOH resulted in δ-lactone **14a**, whose absolute configuration was confirmed by X-ray crystallography which clearly showed the (3*S*,4*R*,5*R*,6*R*)-configuration of its four contiguous stereocenters (Figure 1).

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(9) See: Davies, I. R.; Cheeseman, M.; Green, R.; Mahon, M. F.; Merritt, A.; Bull, S. D. *Org. Lett.* **2009**, *11*, 2896–2899 and references cited therein.

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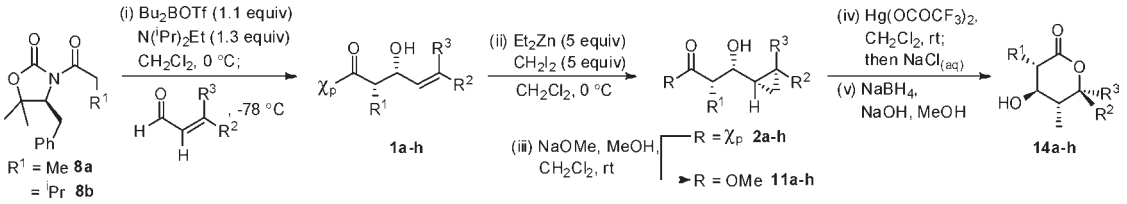
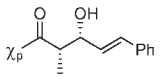
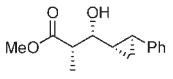
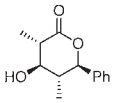
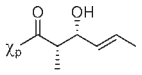
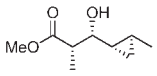
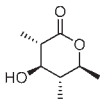
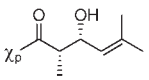
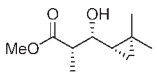
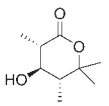
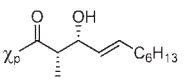
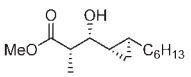
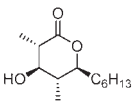
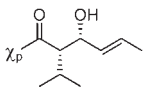
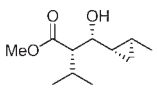
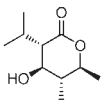
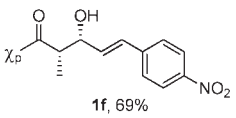
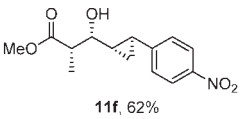
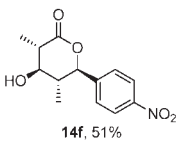
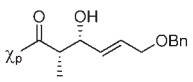
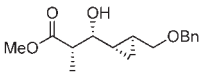
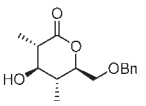
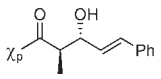
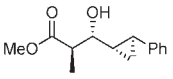
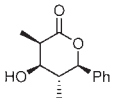
Table 1. Asymmetric Synthesis of Chiral δ-Lactones Containing Multiple Contiguous Stereocenters

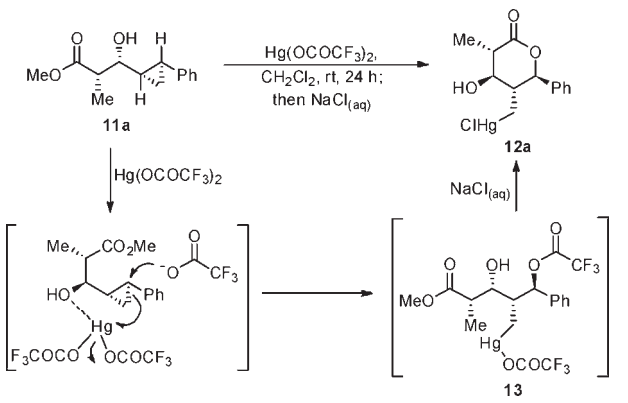


entry	aldol **1a-h**[a]	cyclopropane ester **11a-h**[b]	δ-lactone **14a-h**[a]
1	 **1a**, 86%	 **11a**, 92%	 **14a**, 81%
2	 **1b**, 95%	 **11b**, 64%	 **14b**, 71%
3	 **1c**, 81%	 **11c**, 87%	 **14c**, 58%
4	 **1d**, 66%	 **11d**, 73%	 **14d**, 66%
5	 **1e**, 82%	 **11e**, 80%	 **14e**, 72%
6[15]	 **1f**, 69%	 **11f**, 62%	 **14f**, 51%
7[16]	 **1g**, 89%	 **11g**, 84%	 **14g**, 82%
8[17]	 **1h**, 82%	 **11h**, 77%	 **14h**, 77%

[a] Isolated yields. [b] Isolated yields over two steps.

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 hydrolyzed upon workup 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*-acyloxazolidin-2-one fragment of **2a** and therefore is less likely

Scheme 3. Treatment of Methyl Ester **11a** with $Hg(OCOCF_3)_2$ Results in Intramolecular Cyclopropane Ring Opening To Afford δ-Lactone **12a**



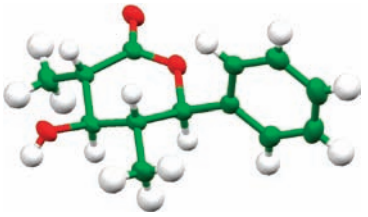
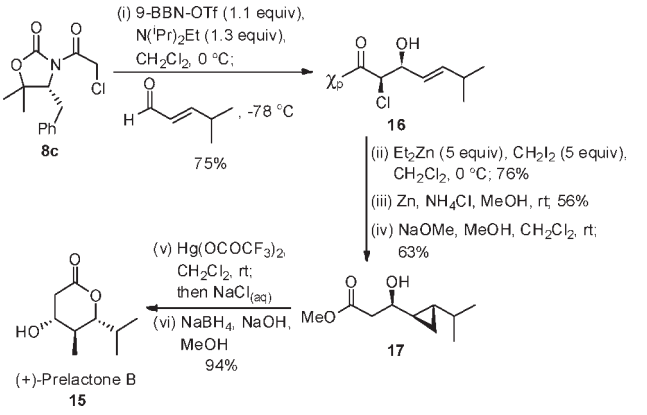


Figure 1. X-ray crystal structure of (3*S*,4*R*,5*R*,6*R*)-δ-lactone **14a**.

to participate as an anchimeric 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 since its terminal *O*-benzyl group will enable it to function as a bifunctional chiral building block for introducing (*syn*)-(*syn*)-(*anti*)-stereotetrad fragments into analogues of numerous polyketide natural products.[14]

Scheme 4. Asymmetric Synthesis of (+)-Prelactone B



We have used this methodology to prepare (+)-Prelactone B **15**, which is a highly functionalized δ-lactone that has been isolated as a shunt metabolite of polyketide metabolism from the bafilomycin-producing organism *Streptomyces griseus*.[18] Therefore, the boron enolate of α-chloropropionyl-*N*-acyl-oxazolidin-2-one **8c** 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,[19] and methanolysis reactions. Subsequent treatment of **17** with $Hg(OCOCF_3)_2$/$NaCl_{(aq)}$, followed by reductive demercuration with alkaline $NaBH_4$, resulted in formation of (+)-Prelactone B **15** in >95% de (Scheme 4).[20]

In conclusion, we have developed a versatile methodology for the asymmetric synthesis of chiral δ-lactones containing up to four contiguous stereocenters. This approach relies on a combination of Evans' aldol, cyclopropanation and Hg(II)-mediated cyclopropane ring-opening reactions for stereocontrol, 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 http://pubs.acs.org.

(11) See: (a) Ref 7. (b) Evans, D. A.; Tedrow, J. S.; Shaw, J. T.; Downey, C. W. *J. Am. Chem. Soc.* **2002**, *124*, 392–393. (c) Caddick, S.; Parr, N. J.; Pritchard, M. C. *Tetrahedron Lett.* **2000**, *41*, 5963–5966.

(12) See: (a) Ref 7. (b) Son, J. B.; Hwang, M. H.; Lee, W.; Lee, D. H. *Org. Lett.* **2007**, *9*, 3897–3900.

(13) For a report where the trifluoroacetate counterion of $Hg(OCOCF_3)_2$ acts as a nucleophile to facilitate ring opening of a cyclopropane ester, see: Ref 8d.

(14) Koskinen, A. M. P.; Karisalmi, K. *Chem. Soc. Rev.* **2005**, *34*, 677–690.

(15) It was found that 5,5-dimethyloxazolidin-2-one **7** (SuperQuat) coeluted with methyl ester **11f**, therefore Evans auxiliary was used.

(16) An alternative method was used for the synthesis of aldol **1g** using Et_3N instead of $N(^iPr)_2Et$. For synthesis of (*E*)-4-(benzyloxy)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*-acyl-oxazolidin-2-one **8a** with cinnamaldehyde, see ref 11b.

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(20) For previous syntheses of (+)-Prelactone B see: Li, Y.-J.; Hung, H-Y; Liu, Y.-W.; Lin, P.-J.; Huang, H.-J. *Tetrahedron*, 2011, *67*, 927-935 and references cited therein.