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Efficient Asymmetric Synthesis of Chiral Hydroxy-γ-butyrolactones

Iwan R. Davies,[†] Matt Cheeseman,[†] Rachel Green,[†] Mary F. Mahon,[‡] Andrew Merritt,[§] and Steven D. Bull*,[†]

Department of Chemistry, University of Bath, BA2 7AY, U.K., Department of Chemical Crystallography, University of Bath, BA2 7AY, U.K., and GlaxoSmithKline Research and Development, Medicines Research Centre, Gunnels Wood Road, Stevenage, Hertfordshire SG1 2NY, U.K.

s.d.bull@bath.ac.uk

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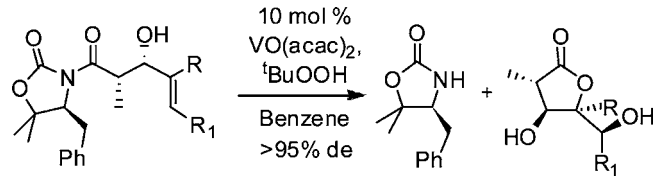
ABSTRACT



Treatment of β-vinyl-β-hydroxy-*N*-acyloxazolidin-2-ones with $VO(acac)_2$ and *tert*-butyl hydroperoxide results in formation of unstable epoxides that are ring-opened by intramolecular nucleophilic attack of their exocyclic carbonyl fragments to afford highly functionalized trisubstituted hydroxy-γ-butyrolactones in >95% de, with a polymer-supported oxazolidin-2-one having been used to transfer this methodology to the solid phase.

A large number of natural products containing chiral trisubstituted γ-butyrolactone fragments have been isolated that exhibit a broad range of activity against different biological targets.[1] Enantiopure trisubstituted γ-butyrolactones have also been used as chiral building blocks for natural product syntheses,[2] with a wide range of methodology having been developed for their asymmetric synthesis.[3] Given this interest, we now report that hydroxyl-directed epoxidation of β-hydroxy-β-vinyl-*N*-acyloxazolidin-2-ones results in a highly efficient methodology for the stereoselective synthesis of trisubstituted hydroxy-γ-butyrolactones.[4]

We have recently reported the development of novel synthetic strategies to reversibly generate "temporary stereocenters" for the asymmetric synthesis of chiral aldehydes.[5] This methodology relies on the use of highly diastereoselective substrate directable cyclopropanation and hydrogenation reactions of β-hydroxy-β-vinyloxazolidin-2-ones **2** for

[†] Department of Chemistry, University of Bath.
[‡] Department of Chemical Crystallography, University of Bath.
[§] GlaxoSmithKline Research and Development.

(1) (a) Anticancer: Popsavin, V.; Benedekovic, G.; Sreco, B.; Popsavin, M.; Francuz, J.; Kojic, V.; Bogdanovic, G. *Org. Lett.* **2007**, *9*, 4235. (b) Antibiotic: Matsumoto, N.; Tsuchida, T.; Maruyama, M.; Kinoshita, N.; Homma, Y.; Iinuma, H.; Sawa, T.; Hamada, M.; Takeuchi, T.; Heida, N.; Yoshioka, T. *J. Antibiot.* **1999**, *52*, 269. (c) Antifungal: Larrosa, I.; Da Silva, M. I.; Gomez, P. M.; Hannen, P.; Ko, E.; Lenger, S. R.; Linke, S. R.; White, A. J. P.; Wilton, D.; Barrett, A. G. M. *J. Am. Chem. Soc.* **2006**, *128*, 14042.

(2) (a) Evans, D. A.; Burch, J. D.; Hu, E.; Jaeschke, G. *Tetrahedron* **2008**, *64*, 4671. (b) Li, Y.; Hale, K. J. *Org. Lett.* **2007**, *9*, 1267. (d) Nicolaou, K. C.; Harrison, S. T. *J. Am. Chem. Soc.* **2007**, *129*, 429.

(3) (a) Yamauchi, C.; Kuriyama, M.; Shimazawa, R.; Morimoto, T.; Kakiuchi, K.; Shirai, R. *Tetrahedron* **2008**, *64*, 3133. (b) Fillion, E.; Carret, S.; Mercier, L. G.; Trepanier, V. E. *Org. Lett.* **2008**, *10*, 437. (c) Cailleau, T.; Cooke, J. W. B.; Davies, S. G.; Ling, K. B.; Naylor, A.; Nicholson, R. L.; Price, P. D.; Roberts, P. M.; Russell, A. J.; Smith, A. D.; Thomson, J. E. *Org. Biomol. Chem.* **2007**, *5*, 3922. (d) Ghosh, M. *Tetrahedron* **2007**, *63*, 11710. (e) Garnier, J. M.; Robin, S.; Guillot, R.; Rousseau, G. *Tetrahedron: Asymmetry* **2007**, *18*, 1434.

(4) (a) Chamberlin, A. R.; Dezube, M. *Tetrahedron Lett.* **1982**, *23*, 3055. (b) Chamberlin, A. R.; Dezube, M.; Reich, S. H.; Sall, D. J. *J. Am. Chem. Soc.* **1989**, *111*, 6247. (c) Honda, T.; Satoh, A.; Yamada, T.; Hayakawa, T.; Kanai, K. *J. Chem. Soc., Perkin Trans. 1* **1998**, 397. (d) Dias, L. C.; de Castro, I. B. D.; Steil, L. J.; Augusto, T. *Tetrahedron Lett.* **2006**, *47*, 213. (e) Shiina, I.; Takasuna, Y.; Suzuki, R.; Oshiumi, H.; Komiyama, Y.; Hitomi, S.; Fukui, H. *Org. Lett.* **2006**, *8*, 5279.

(5) (a) Cheeseman, M.; Feuillet, F. J. P.; Johnson, A. L.; Bull, S. D. *Chem. Commun.* **2005**, 2372. (b) Green, R.; Cheeseman, M.; Duffill, S.; Merritt, A.; Bull, S. D. *Tetrahedron Lett.* **2005**, *46*, 7931. (c) Cheeseman, M.; Bull, S. D. *Synlett* **2006**, 1119. (d) Niyadurupola, D. G.; Davies, I. R.; Wisedale, R.; Bull, S. D. *Eur. J. Org. Chem.* **2007**, 5487.

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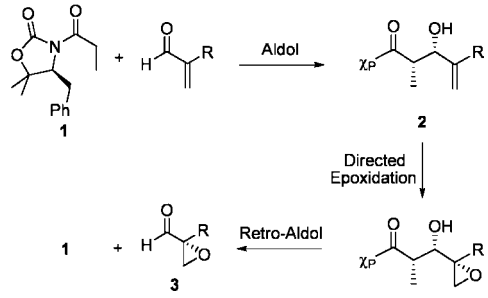
stereocontrol. Consequently, it was decided to explore whether carrying out hydroxyl-directed epoxidation reactions on these types of substrates could be used to develop a "temporary stereocenter" methodology for the asymmetric synthesis of chiral α,β-epoxy-aldehydes **3** (see Scheme 1).

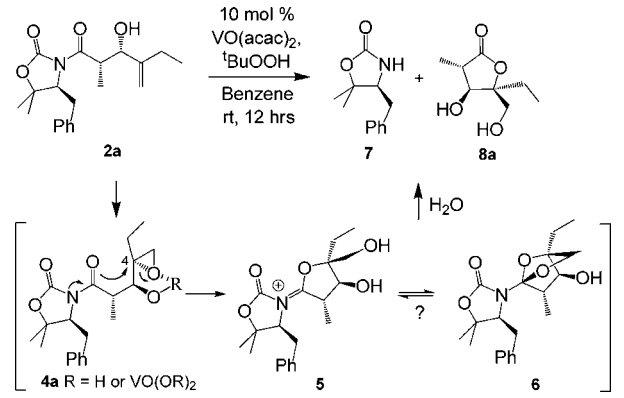
Scheme 1. Proposed "Temporary Stereocenter" Approach for the Asymmetric Synthesis of Chiral α,β-Epoxy Carboxaldehydes **3**



Epoxidation of the 1,1-disubstituted alkene functionalities of secondary allylic alcohols using $VO(acac)_2$ and *tert*-butyl hydroperoxide has been shown to proceed with high levels of *erythro* diastereoselectivity.[6] However, we found that treatment of β-vinyl-*syn*-aldol **2a**[7] with 10 mol % of $VO(acac)_2$ and 1 equiv of *tert*-butyl hydroperoxide in benzene at room temperature did not result in the expected *erythro*-epoxide **4a**,[8,9] but instead gave a 1:1 mixture of 5,5-dimethyloxazolidin-2-one **7** and lactone **8a** whose configuration was confirmed as (*S*,*S*,*S*) by X-ray crystallographic analysis.

This outcome is consistent with the reaction mechanism outlined in Scheme 2,[10] where hydroxyl-directed epoxidation of **2a** is predicted to afford an *erythro*-epoxide **4a**. This unstable epoxide is then ring-opened by intramolecular nucleophilic attack of the exocyclic carbonyl of its *N*-acyl fragment with inversion of configuration at C_4 to afford an unstable iminium species **5** (that may be stabilized via reversible formation of *N*,*O*,*O*-orthoester **6**) which is hydrolyzed on workup.[11] Attempts to intercept the intermediate epoxide **4a** via addition of a good nucleophile (EtSH, N_3^-) to the reaction mixture prior to workup were unsuccessful,

Scheme 2. Stereoselective Epoxidation of β-Vinyl-*syn*-aldol **2a** Affords Lactone (*S*,*S*,*S*)-**8a**



with lactone **8a** being isolated in good yield once more. This implies that intramolecular 5-*exo*-tet ring-opening of epoxide **4a** occurs very rapidly under these conditions. It was also shown that *N*-acyloxazolidin-2-one **1** was stable under these epoxidation conditions, with no oxazolidin-2-one **7** being formed, suggesting that hydrolysis of the oxazolidin-2-one fragment of aldol **2a** does not occur prior to epoxidation. Finally, we note that the ability of an *N*-acyloxazolidin-2-one fragment to participate as an intramolecular nucleophile in this manner has been invoked previously to explain the stereochemical outcome of related iodolactonization reactions of β-vinyl-*N*-acyloxazolidin-2-ones.[12]

In order to investigate the scope and limitation of this epoxidation/lactonization methodology, we prepared a series of β-vinyl-*syn*-aldols **2b**−**i** containing alkene fragments with different substitution patterns.[7] *syn*-Aldols **2b**−**h** were then treated with 10 mol % of $VO(acac)_2$ and 1 equiv of *tert*-butyl hydroperoxide in benzene to afford seven hydroxylated lactones **8b**−**h** in >90% de and 74−84% isolated yield (Table 1).[13] The diastereoselectivity observed in directed epoxidation reactions of these types of allylic alcohols is well established[14] and known to be highly dependent on the substitution pattern of their alkene functionality.[15] Therefore, $A^{1,2}$ strain is known to dominate for 1-substituted alkenes

(6) Adam, W.; Mitchell, C. M.; Saha-Moller, C. R. *J. Org. Chem.* **1999**, *64*, 3699.

(7) Aldol substrates **2a**−**i** prepared via reaction of the boron or magnesium enolate of an *N*-propionyloxazolidin-2-one with the corresponding α,β-unsaturated aldehyde: (a) Caddick, S.; Parr, N. J.; Pritchard, M. C. *Tetrahedron Lett.* **2000**, *41*, 5963. (b) Evans, D. A.; Tedrow, J. S.; Shaw, J. T.; Downey, C. W. *J. Am. Chem. Soc.* **2002**, *124*, 392.

(8) For a report of a 50:50 mixture of stable diastereoisomeric epoxides prepared by epoxidation of a γ,δ-unsaturated *N*-acyloxazolidin-2-one with *m*-chloroperoxybenzoic acid, see: Trova, M. P.; Wissner, A.; Casscles, W. T., Jr.; Hsu, G. C. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 903.

(9) For aldol reaction of the boron enolate of an Evans' *N*-acyloxazolidin-2-one with an α,β-epoxy aldehyde that gave a stable γ,δ-epoxy aldol product, see: Taylor, R. E.; Hearn, B. R.; Ciavarri, J. P. *Org. Lett.* **2002**, *4*, 2953.

(10) For previous reports of γ,δ-epoxides of tertiary amides cyclizing to afford γ-lactones, see: (a) Cairns, P. M.; Howes, C.; Jenkins, P. R.; Russell, D. R.; Sherry, L. *J. Chem. Soc., Chem. Commun.* **1984**, 1487. (b) Majewski, M.; Snieckus, V. *Tetrahedron Lett.* **1982**, *23*, 1343.

(11) An alternative mechanism involving intramolecular 6-*endo*-tet ring-opening of *erythro*-epoxide **4a** with retention of configuration at C4 was discounted because rearrangement of the resultant δ-lactone would have afforded a diastereoisomeric (2*S*,3*S*,4*R*)-γ-lactone; see: (a) Nacro, K.; Baltas, M.; Escudier, J. M.; Gorrichon, L. *Tetrahedron* **1997**, *53*, 659. (b) Nacro, K.; Baltas, M.; Zedde, C.; Gorrichon, L.; Jaud, J. *Tetrahedron* **1999**, *55*, 5129. (c) Nacro, K.; Gorrichon, L.; Escudier, J. M.; Baltas, M. *Eur. J. Org. Chem.* **2001**, 4247.

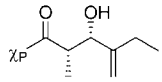
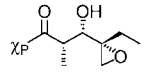
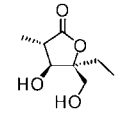
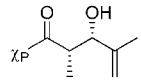
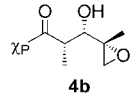
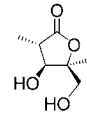
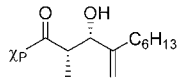
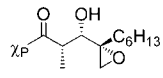
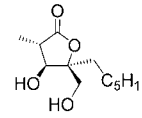
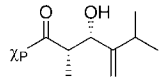
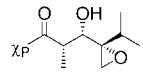
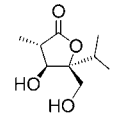
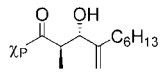
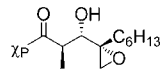
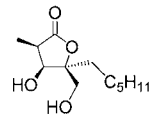
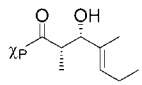
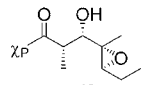
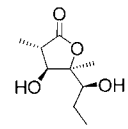
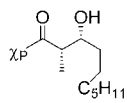
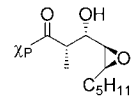
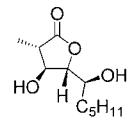
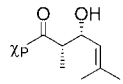
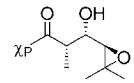
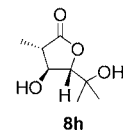
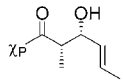
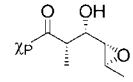
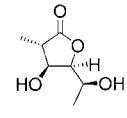
(12) See: (a) Yokomatsu, T.; Iwasawa, H.; Shibuya, S. *J. Chem. Soc., Chem. Commun.* **1992**, 728. (b) Moon, H.; Eisenberg, S. W. E.; Wilson, M. E.; Schore, N. E.; Kurth, M. J. *J. Org. Chem.* **1994**, *59*, 6504. (c) Murat, Y.; Kamino, T.; Aoki, T.; Hosokawa, S.; Kobayashi, S. *Angew. Chem., Int. Ed.* **2004**, *43*, 3175. (d) Noguchi, N.; Nakada, M. *Org. Lett.* **2006**, *8*, 2039.

(13) *ent*-Lactones **8b** and **8f** have been prepared previously via directed epoxidation of β-vinyl-*syn*-aldol esters; see: (a) McCarthy, P. A. *Tetrahedron Lett.* **1982**, *23*, 4199. (b) Nakata, T.; Fukui, M.; Oishi, T. *Tetrahedron Lett.* **1988**, *29*, 2219. (c) Reference 4b.

(14) Adam, W.; Wirth, T. *Acc. Chem. Res.* **1999**, *32*, 703.

(15) Repeated attempts to epoxidize a monosubstituted *syn*-aldol product derived from acrolein under these conditions were unsuccessful, affording only recovered starting material.

Table 1. Epoxidation of Aldols **2a**−**i** Using $VO(acac)_2$ and *tert*-Butyl Hydroperoxide To Afford Hydroxy-γ-butyrolactones **8a**−**i**

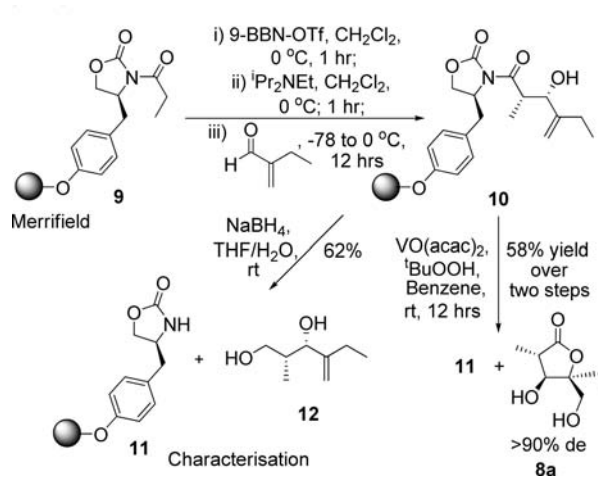
entry	aldols **2a-i**	epoxides **4a-i** (not isolated)	lactones **8a-i**	de (%)[a]	yield (%)[b]
1	 **2a**	 **4a**	 **8a**	>95	78
2	 **2b**	 **4b**	 **8b**	>95	76
3	 **2c**	 **4c**	 **8c**	>95	83
4[c]	 **2d**	 **4d**	 **8d**	>95	74
5	 **2e**	 **4e**	 **8e**	>95	74
6	 **2f**	 **4f**	 **8f**	>95	83
7	 **2g**	 **4g**	 **8g**	>95	84
8	 **2h**	 **4h**	 **8h**	>90	78
9	 **2i**	 **4i**	 **8i**	33	54[d]

[a] All de's determined by ^{1}H NMR spectroscopic analysis of crude reaction products. [b] Yields of lactones **8a**−**i** calculated from aldols **2a**−**i**. [c] χ_P = Evans' (*S*)-4-benzyloxazolidin-2-one. [d] Yield of pure diastereoisomer **8i** after chromatographic purification.

and (*E*)-1,2-disubstituted alkenes resulting in formation of *erythro*-epoxy alcohols, while A[1,3] strain dominates for (*Z*)-1,2-disubstituted and 1,2,2-trisubstituted alkenes to afford their corresponding *threo*-epoxy alcohols. Consequently, the configuration of unstable epoxides **4b**−**f** (not isolated) were assigned as *erythro*, while unstable epoxides **4g**,**h** (not isolated) were assigned as *threo*. Therefore, it follows that subsequent intramolecular ring-opening of epoxides **4b**−**h** (via mechanism shown in Scheme 2) proceeds with inversion of configuration at their C_4 carbons to afford their corresponding lactones **8b**−**h**.[16] All lactones **8b**−**h** were formed with excellent levels of diastereocontrol (>90% de), as expected for the high diastereoselectivity predicted for vanadium-catalyzed hydroxyl-directed epoxidation reactions of their corresponding β-vinyl-*syn*-aldols **2a**−**h**. Conversely, lactone **8i** was formed with poorer diastereoselectivity (33% de) as expected for epoxidation of β-vinylaldol **2i**, whose (*E*)-1,2-disubstituted alkene functionality is known to be epoxidized with poor levels of *erythro* diastereocontrol under these conditions.[6]

We then demonstrated that this epoxidation/lactonization methodology could be transferred to solid support using a polymer-supported Evans oxazolidin-2-one **9**[17] for synthesis. Therefore, the boron enolate of polymer **9** was treated with 2-ethylacrolein to afford polymer-supported *syn*-aldol **10**,[18] which was characterized by reductive cleavage of the *N*-acyl side chain of a small portion of resin with $NaBH_4$ in THF/H_2O to afford chiral alcohol **12** in >95% de. Subsequent treatment of polymer **10** with 10 mol % of $VO(acac)_2$ and 1 equiv of *tert*-butyl hydroperoxide in benzene at room temperature for 3 h, followed by filtration to remove polymer **11** and evaporation of the filtrate, gave a clean sample of lactone **8a** in 58% yield over two steps (Scheme 3).[19]

Scheme 3. Sequential Polymer-Supported Aldol/Epoxidation/Lactonization Reactions for the Asymmetric Synthesis of Lactone (*S*,*S*,*S*)-**8a**



In conclusion, a novel three-step aldol/epoxidation/intramolecular lactonization strategy has been developed for the synthesis of highly functionalized trisubstituted hydroxy-γ-butyrolactones with excellent levels of diastereocontrol.

Acknowledgment. We thank the EPSRC and GlaxoSmithKline for funding.

Supporting Information Available: Experimental details and spectroscopic characterization for compounds **2a**−**i**/**8a**−**i** and crystal data for **8a** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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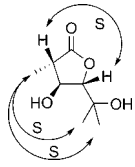
(16) A NOESY ^{1}H NMR experiment revealed strong (*S*) interactions consistent with the proposed (*S*,*S*,*S*) configuration of γ-lactone **8h**, which implies that all of the epoxides **4a**−**i** are ring-opening via the intramolecular 5-*exo*-tet pathway shown in Scheme 2.[11]



(17) See: (a) Green, R.; Taylor, P. J. M.; Bull, S. D.; James, T. D.; Mahon, M. F.; Merritt, A. T. *Tetrahedron: Asymmetry* **2003**, *14*, 2619. (b) Green, R.; Merritt, A. T.; Bull, S. D. *Chem. Commun.* **2008**, 508.

(18) For other polymer-supported oxazolidin-2-one aldol reactions, see: (a) Purandare, A. V.; Natarajan, S. *Tetrahedron Lett.* **1997**, *38*, 8777. (b) Phoon, C. W.; Abell, C. *Tetrahedron Lett.* **1998**, *39*, 2655.

(19) For asymmetric syntheses of chiral lactones using other polymer-supported chiral auxiliaries, see: (a) Moon, H. S.; Schore, N. E.; Kurth, M. J. *J. Org. Chem.* **1992**, *57*, 6088. (b) Moon, H. S.; Schore, N. E.; Kurth, M. J. *Tetrahedron Lett.* **1994**, *35*, 8915. (c) Kerrigan, N. J.; Hutchinson, P. C.; Heightman, T. D.; Procter, D. J. *Chem. Commun.* **2003**, 1402. (d) Kerrigan, N. J.; Hutchinson, P. C.; Heightman, T. D.; Procter, D. J. *Org. Biomol. Chem.* **2004**, *2*, 2476.