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A stereoselective synthesis of 1,3,4-substituted β-lactams from polymer-supported chiral oxazolidine aldehyde

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Abstract

The synthesis of a polymer supported chiral oxazolidine aldehyde is described. This intermediate has great potential for the synthesis of biologically interesting compounds. A solid phase stereoselective synthesis of an array of chirally pure β-lactams in high purity is described as a first application of the system. © 2000 Elsevier Science Ltd. All rights reserved.

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As the number of synthetic organic reactions and multi-step transformations reported on solid phase has increased, many elegant linker strategies have been developed.[1] Linkers which contain a generic core of chemical functionality that can lead to a variety of classes of interesting compounds are desirable. One such system we have been interested in is the oxazolidine aldehyde first reported by Garner.[2] Chiral oxazolidine aldehydes have the capacity to undergo a wide variety of interesting and useful transformations and also serve as a chiral directing group. Chiral oxazolidine aldehydes have been successfully employed in solution for the synthesis of several natural products (e.g. sphingosines,[3] β-amino alcohols,[4] α-amino β-hydroxy acids[5]) serving as an amino alcohol equivalent. Such systems have also been exploited as a chiral auxiliary in cycloaddition reactions for the synthesis of β-lactams bearing β-amino alcohol side chains[6] which can subsequently be rearranged to form pyrrolidinones.[7]

In this paper we describe the chemistry of generating a polymer supported chiral oxazolidine aldehyde equivalent. The linker incorporates a masked β-amino alcohol and derives its stereogenic centre from *N*-Boc-protected L-serine. A first application of this resin-bound intermediate has been exemplified with the stereoselective synthesis of an array of 1,3,4-substituted β-lactams on solid phase (Fig. 1).

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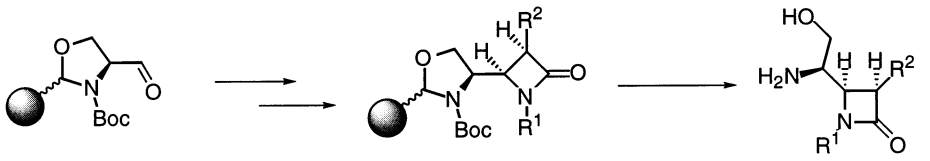
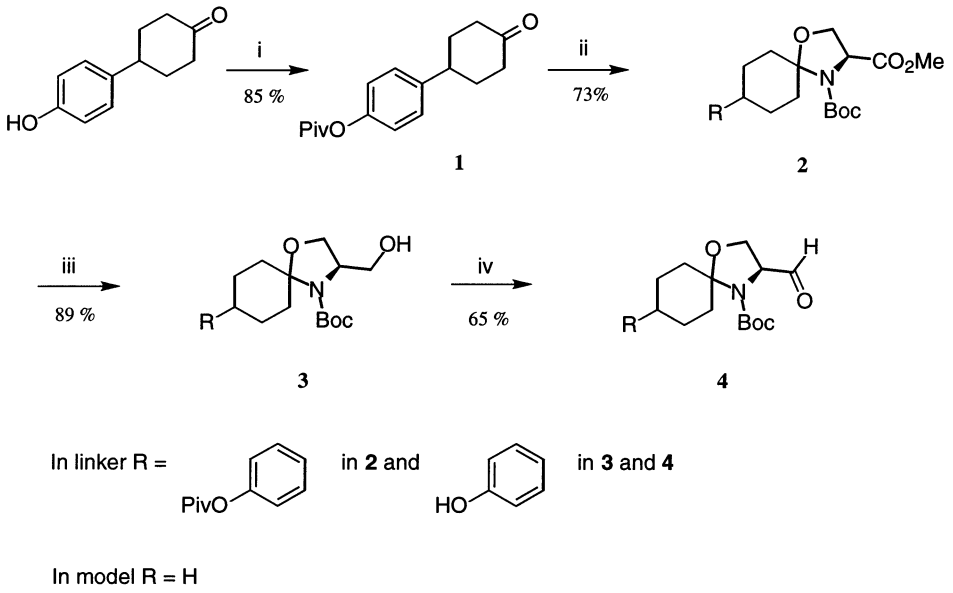


Fig. 1. A polymer supported chiral oxazolidine aldehyde approach to β-lactam synthesis

The linker was pre-assembled in solution using the pivaloyl protected ketone **1** (Scheme 1). TMS–OTf promoted ketonide formation, in the presence of isopropoxytrimethylsilane, gave the ester **2** in 73% yield using nearly equimolar quantities of ketone and amino acid.[8] Subsequent reduction of **2** with concomitant removal of the pivaloyl protecting group furnished the alcohol **3** which was oxidised to the aldehyde equivalent **4**.



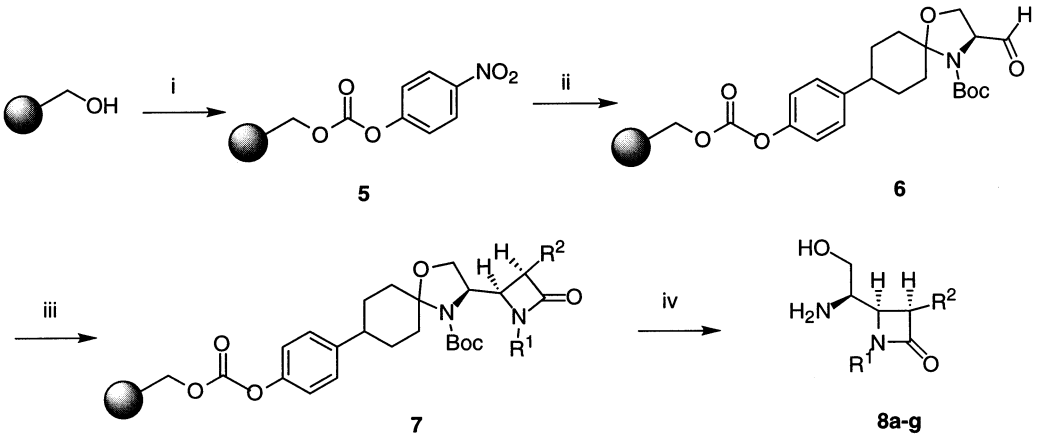
Scheme 1. Linker assembly. Reagents and conditions: (i) Piv–Cl/DMAP/Pyr; (ii) *N*-Boc-protected L-serine methyl ester/1% TMSOTf/Isopropoxytrimethyl silane/DCM; (iii) $LiBH_4$/THF; (iv) $(COCl)_2$/DMSO/DCM/Et_3N

The chiral integrity of all key intermediates was confirmed throughout the synthesis.[†] This was augmented by a Mosher ester study of the synthesis of a non-diastereomeric model aldehyde derived from *N*-Boc-L-serine under identical conditions, using cyclohexanone as the protecting group. The Mosher esters were formed from the corresponding alcohols after reduction of the ester (model of **2**) and the target aldehyde (model of **4**). Both esters gave single peaks when analysed by ^{19}F NMR spectroscopy, whereas when racemic *N*-Boc-L-serine was used as a control, two ^{19}F peaks were clearly visible in the ^{19}F NMR spectrum in a 1:1 ratio.

The aldehyde **4** was subsequently attached to resin via a carbonate linkage under mild conditions (Scheme 2). Hydroxymethyl polystyrene resin was activated by formation of its 4-nitrophenol carbonate **5** and was then substituted by reaction with the phenolic group of **4** to give the immobilised chiral equivalent **6** (loading 0.932 mmol/g, based on nitrogen elemental

[†] Optical rotations of intermediates: **2** $[\alpha]_D$ −19 (MeOH, $c=1$), **3** $[\alpha]_D$ −18 (MeOH, $c=1$), **4** $[\alpha]_D$ −12 (MeOH, $c=1$).

analysis of **5**). The reaction was monitored by the disappearance of the NO_2 peaks in the FTIR spectrum (1596 and 1348 cm^{-1}) and was characterised by the appearance of three resolvable carbonyl absorbances (1764, 1758, 1710 cm^{-1}). A study in solution with the model aldehyde (model of **4**) confirmed that the stereogenic centre was preserved under the coupling conditions (DIPEA and DMAP) as judged by analysis of the corresponding Mosher ester. Coupling of the aldehyde using a stronger base (e.g. NaH) led to epimerisation and some degree of decomposition as judged from the observation of by-products by TLC.



Scheme 2. Utilisation of the chiral oxazolidine aldehyde in the synthesis of a β-lactam library. Reagents and conditions: (i) 4-nitrophenylchloroformate/DIPEA/DMAP/DCM; (ii) Linker **4**/DIPEA/DMAP/DMF; (iii) R^1NH_2/DCM/4 Å sieves then DCM/Et_3N/R^2CH_2COCl/DCM; (iv) 10% TFA/DCM

β-Lactam library synthesis

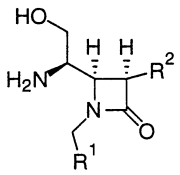
To explore the application of the resin-bound chiral oxazolidine aldehyde equivalent **6**, the synthesis of a small array of β-lactams was carried out. Such compounds are renowned for their biological activity but surprisingly, have received scant attention by solid phase chemists.[9–12] A versatile reaction for the synthesis of this heterocycle involves a cycloaddition reaction of an imine and a ketene. The reaction is believed to occur via a two-step mechanism which can be controlled to exclusively yield β-lactams with *cis* stereochemistry.[6] The aldehyde **6** was thus condensed with four amines chosen to represent different electronic and steric properties. The resulting resin-bound imines subsequently underwent cycloaddition reactions with ketenes, which were formed in situ from their corresponding acid chlorides. Acid chlorides, with α-heteroatoms (oxygen or nitrogen) were chosen, to achieve control of stereochemistry. The resulting resin-bound β-lactams **7a–g** were treated with 10% TFA in DCM to remove the *N*-Boc protecting group and cleave the now unstable oxazolidine moiety to unmask the amino alcohol functionality (Scheme 2).

A simple extraction of the final products into H_2O generated the expected lactams **8a–g** in generally excellent purity (~90%) and reasonable yields (53–62%) as judged by HPLC and ^1H NMR spectroscopy (Table 1).[‡] All products **8a–g** gave a coupling constant of $J = 5$–5.5 Hz for the methine protons on the β-lactam ring which is consistent with *cis*-stereochemistry.[13] The absolute stereochemistry of the β-lactam products (as their TFA salts) was evaluated by

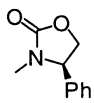
[‡] No rearrangement to pyrrolidinone was observed in the cleavage conditions given. This reaction has been investigated but remains to be optimised.

polarimetry. An optical rotation was measured for each β-lactam and β-lactam **8e** was de-salted and its optical rotation ($[\alpha]_D = -38$) was comparable to the literature value ($[\alpha]_D = -36.5$).[6] The opposite antipode to β-lactam **8f** ($[\alpha]_D = -23$) was also synthesised in solution and had an opposite but equal rotation ($[\alpha]_D = +22$ MeOH, $c = 1$). It would thus appear that both the relative and absolute stereochemistries were controlled in all steps from the solid phase equivalent assembly to the chiral β-lactam products.

Table 1



8

8	R^1	R^2	LCMS	% Purity[c]	% Yield[a]	$[\alpha]_D$ ($c = 1$)
a	Bn	OPh	313	93	54	−26 (MeOH)
b	Cyclohexyl	OPh	306	92	53	−79 (MeOH)
c	PMP[d]	OPh	329	95	62	−72 (MeOH)
d	nBu	OPh	279	77[b]	45	−85 (MeOH)
e	Bn	OBn	327	93	60	−38 (DCM)[e]
f	PMP	OBn	343	89	59	−23 (MeOH)
g	Bn		382	96	58	+83 (MeOH)

[a] Yields are based on the loading of resin **5** as determined by elemental analysis (N).
[b] The main impurity in this case was the *N*-Boc-protected β-lactam.
[c] Purity based on HPLC with UV detection at 220 nm.
[d] PMP = *p*-methoxyphenyl.
[e] Literature value −36.5[6].

Conclusion

A polymer-supported synthesis of an array of a chirally pure β-lactams in high purity has been demonstrated. There are many possibilities for further exploitation of the resin-bound chiral oxazolidine aldehyde **6**, which will be explored in due course.

Acknowledgements

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