Pergamon

Tetrahedron 58 (2002) 9387–9401

TETRAHEDRON

Rearrangements and racemisation during the synthesis of L-serine derived oxazolidin-2-ones

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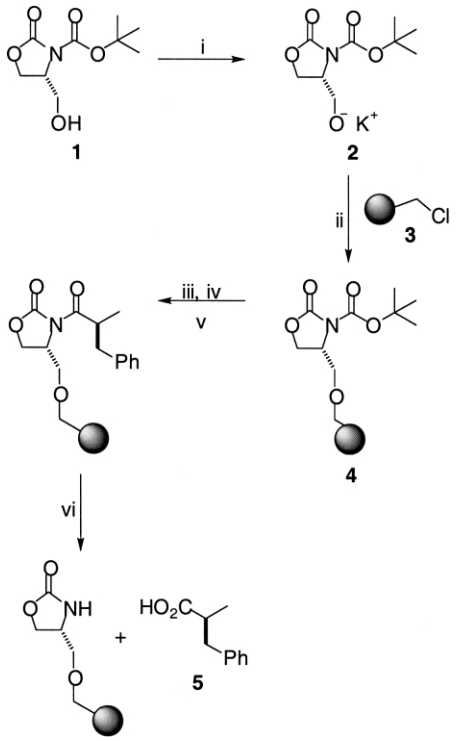
Received 12 July 2002; revised 6 September 2002; accepted 26 September 2002

Abstract—The propensity for *N*-Boc-4-hydroxymethyl-oxazolidin-2-ones to undergo rapid *O*–*O* and *N*–*O* carbonyl transfer makes these L-serine derived chiral auxiliaries unsuitable for attachment to polymers.

1. Introduction

There has recently been a concerted research effort to immobilise many of the frequently used chiral auxiliaries and reagents employed in modern synthetic organic chemistry onto polymer support.[1] Over the last 15 years, the oxazolidin-2-one auxiliaries first introduced by Evans et al. have been widely employed as chiral auxiliaries within asymmetric synthesis for utilisation in a wide range of chemistries, which have included enolate alkylations,[2] aldol reactions,[3] [4+2]-cycloadditions,[4] and conjugate addition reactions.[5] Unsurprisingly therefore, a number of groups have reported on the development and use of a range of polymer bound chiral auxiliaries derived via covalently attaching the phenolate anion of a L-tyrosine derived oxazolidin-2-one to different polymer supports. Thus, L-tyrosine derived polymer supported oxazolidin-2-ones have been employed by a number of different research groups for stereoselective enolate alkylation reactions,[6] aldol reactions,[7] [3+2]-dipolar cycloadditions,[8] and [4+2] cycloadditions.[9] In an alternative approach, Allin and Shuttleworth reported on the synthesis and use of a polymer bound L-serine derived Evans chiral auxiliary for asymmetric synthesis.[10] They reported that the L-serine derived Evans *N*-Boc protected oxazolidin-2-one **1** had been grafted onto polymer via a substitution reaction between the potassium alkoxide **2** and Merrifield resin **3**. The polymer bound chiral auxiliary **4** was then manipulated for the asymmetric synthesis of (*S*)-α-methylhydrocinnamic acid **5** in a 42% yield and 96% ee according to the protocol described in Scheme 1.



Scheme 1. *Reagents and conditions*: (i) KH (1.5 equiv.), DMF, 0°C; (ii) Merrifield resin, cat 18-crown-6, 80°C, 5 days; (iii) dil HCl, DCM, Δ, 6 h; (iv) $(CH_3CH_2CO)_2O$, DMAP (10%), Et_3N, THF, Δ, 4 days; (v) LDA (2 equiv.), THF, 0°C; BnBr (2 equiv.); NH_4Cl (aqueous); (vi) LiOH, THF, H_2O.

While these examples clearly demonstrate the potential of polymer supported Evans auxiliaries for asymmetric synthesis, they do not address the key issue of polymer recyclability. Evans oxazolidin-2-ones are not ideally suited as a class of auxiliary for the immobilisation onto polymer support. This is because of the widely recognised *endo*/*exo*-cyclic cleavage problem, whereby nucleophiles are known

Keywords: racemisation; L-serine; oxazolidin-2-one.

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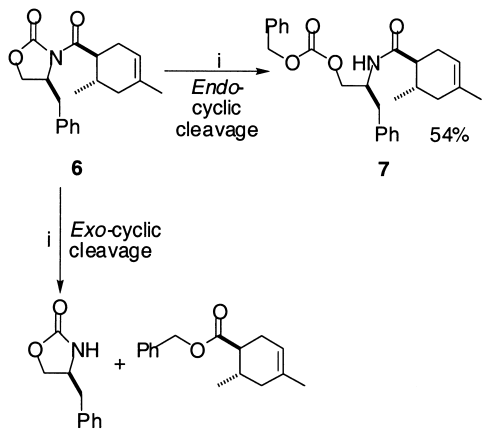
PII: S0040-4020(02)01223-1

to competitively attack both *endo* and *exo*-carbonyl groups of sterically hindered *N*-acyl-oxazolidin-2-ones, to afford *N*-acyl-amino-alcohols as competing cleavage products. For example, Evans et al. have shown that cleavage of **6** with lithium benzyloxide results in predominantly (54%) the *endo*-cyclic cleavage product **7** (Scheme 2).[11] Clearly while destruction of the oxazolidin-2-one functionality may be tolerated in 'solution phase' this competing reaction pathway will rapidly destroy any polymer bound oxazolidin-2-one, preventing recycling of the polymer and its subsequent use in asymmetric synthesis.



Scheme 2. *Reagents and conditions*: (i) $PhCH_2OLi$, THF.

Our previous work directed towards solving this *endo*-cyclic cleavage problem has resulted in the development of the SuperQuat or 5,5-*gem*-dimethyloxazolidin-2-one chiral auxiliary.[12] The SuperQuat chiral auxiliary efficiently addresses the *endo*-cyclic cleavage problem by virtue of the 5,5-*gem*-dimethyl group blocking the approach of any nucleophiles towards the oxazolidin-2-one carbonyl. Furthermore the conformational control of the 5,5-*gem*-dimethyl group on the stereocontrolling 4-alkyl substituent also serves to ensure that the stereoselectivities obtained for reactions with this class of 5,5-*gem*-dimethyloxazolidin-2-one are generally superior to those achieved with the analogous Evans type oxazolidin-2-ones.[13]

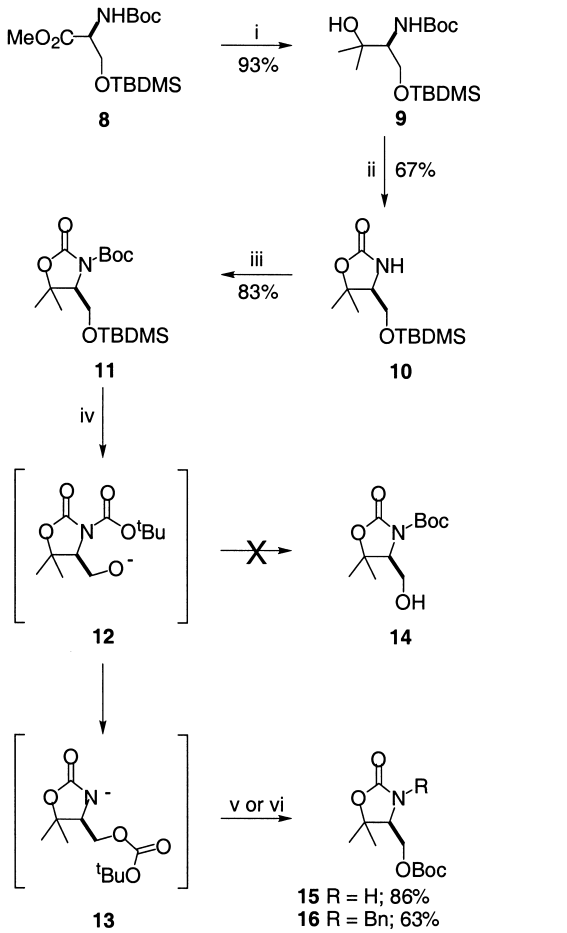
As part of a general program directed towards the transfer of SuperQuat 5,5-*gem*-dimethyloxazolidin-2-ones to polymer support we wish to describe herein our attempts to covalently attach the alkoxide anion of an L-serine-derived SuperQuat 5,5-*gem*-dimethyloxazolidin-2-one to Merrifield resin. Part of this work has been previously communicated.[14]

2. Results and discussion

2.1. Feasibility study into the attachment of L-serine derived 5,5-*gem*-dimethyloxazolidin-2-ones (SuperQuats) onto polymer support

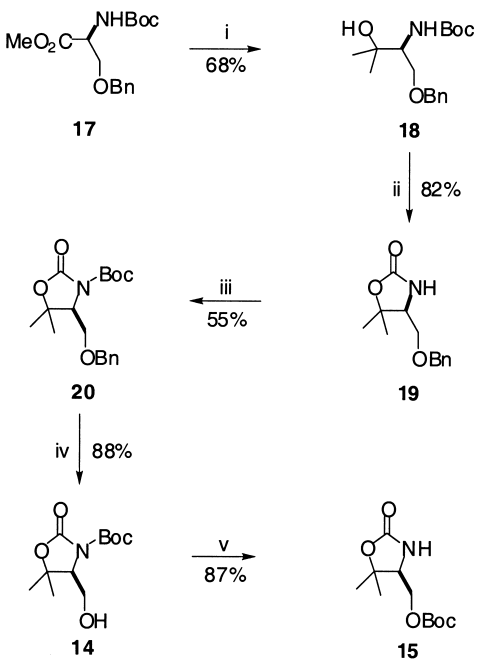
Initial synthetic attempts were directed towards the preparation of *N*-Boc-oxazolidin-2-one **14** as a monomer for immobilisation on polymer support. Towards this aim, readily available *N*-Boc-*O*-TBDMS-L-serine methyl ester **8** was treated with excess methyl magnesium bromide (4 equiv., −78°C to room temperature), yielding **9**. Treatment of **9** with potassium *tert*-butoxide afforded SuperQuat **10**, which was subsequently *N*-Boc protected to yield **11**. Treatment of *N*-Boc-*O*-TBDMS SuperQuat **11** with a 1 M solution of TBAF in THF, did not afford the desired *N*-Boc-oxazolidin-2-one **14** but gave instead (*S*)-*O*-Boc-oxazolidin-2-one **15** ($[\alpha]_D^{23}=-53.2$ (*c* 0.66, $CHCl_3$); ^1H NMR, δ 5.62 ppm, NH; ^{13}C NMR, 153.0 (C=O) and 157.8 (C=O) ppm; FT-IR, 1747 and 1720 cm^{-1}) as a clean product in which the Boc protecting group had migrated from the oxazolidin-2-one nitrogen to the oxygen of the 4-hydroxymethyl side-chain. Clearly TBAF mediated O-deprotection of the silyl protecting group on **11** afforded alkoxide intermediate **12** which readily underwent intramolecular attack at the *N*-Boc carbonyl group resulting in protecting group migration (*N*–*O*) to afford *O*-Boc-oxazolidin-2-one **15** (Scheme 3). Attempts to *O*-benzylate (as a model reaction for Merrifield resin) the intermediate alkoxide anion **12** before *N*–*O*-Boc protecting group migration could occur were unsuccessful since TBAF deprotection of **11**, followed by immediate addition of a large excess of benzyl bromide (Scheme 3) afforded (*S*)-*N*-benzyl-*O*-Boc-oxazolidin-2-one **16** ($[\alpha]_D^{22}=+11.2$ (*c* 0.82, $CHCl_3$)).

The structure of *O*-Boc-oxazolidin-2-one **15** was readily confirmed by comparison with an authentic sample of the corresponding *N*-Boc-oxazolidin-2-one **14**, prepared via



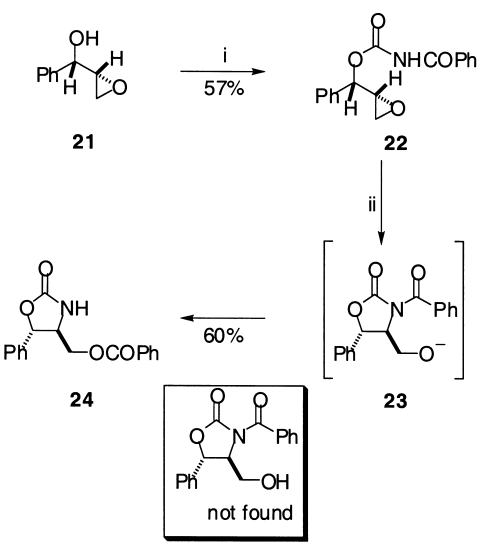
Scheme 3. *Reagents and conditions*: (i) MeMgBr (4 equiv.), THF, −78°C to room temperature; (ii) KO^{t}Bu, THF; (iii) $(Boc)_2O$, DMAP, Et_3N, DCM; (iv) TBAF, THF; (v) NH_4Cl (aqueous); (vi) BnBr.

hydrogenolysis of *N*-Boc-*O*-benzyl-oxazolidin-2-one **20**. The instability of the corresponding potassium alkoxide generated from **14** (Scheme 4) via treatment of **14** with KH in DMF at 0°C over a 2 h period, was confirmed when *O*-Boc-oxazolidin-2-one **15** (^{1}H NMR, δ 5.59 ppm, NH; ^{13}C NMR, 153.0 (C═O) and 157.8 (C═O) ppm; FT-IR, 1742 and 1720 cm^{-1}) was produced as a clean product in an excellent yield (87%).

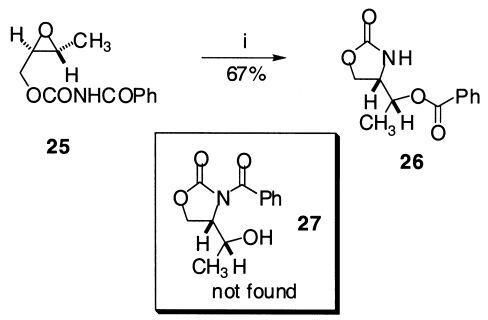


Scheme 4. *Reagents and conditions*: (i) MeMgBr, (4 equiv.) −78°C to rt, THF; (ii) KO^{t}Bu, THF, room temperature; (iii) $(Boc)_2O$, DMAP, Et_3N, DCM, room temperature; (iv) MeOH, H_2, 10% Pd on C; (v) KH, DMF, 0°C, 2 h.

There is clear literature precedent for this type of *N*–*O* carbonyl *exo*-cyclic rearrangement for *N*-carbonyl oxazolidin-2-ones. For example, Knapp et al. have reported that deprotonation of (*rac*)-(2*RS*)-3-epoxy-(1*SR*)-phenylpropyl benzoylcarbamate **22**, synthesised from (*rac*)-(2*RS*)-3-epoxy-(1*SR*)-phenylpropan-1-ol **21**, resulted in the formation of *N*-benzoyl-oxazolidin-2-one anion **23**, which spontaneously underwent a 5-*exo*-trig *N*–*O*-benzoyl migration to yield ester **24** (^{1}H NMR, δ 6.88 ppm, NH; FT-IR, 1760 and 1720 cm^{-1}) (Scheme 5).[15]



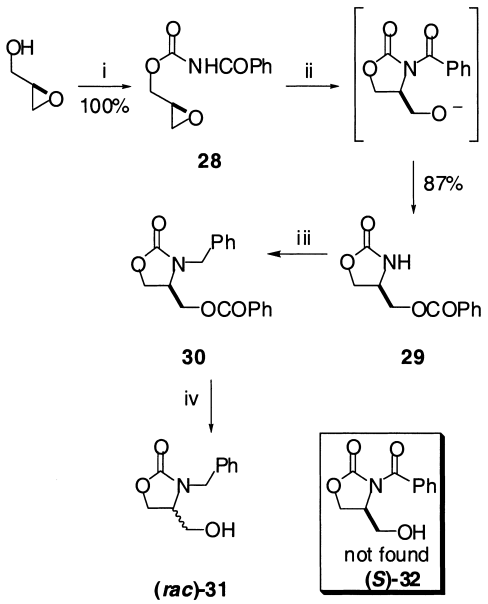
Scheme 5. *Reagents and conditions*: (i) PhCONCO, CCl_4, room temperature; (ii) NaH (0.25 equiv.), THF, reflux.



Scheme 6. *Reagents and conditions*: (i) $Al(CH_3)_3$, DCM, −15°C, 1.5 h.

Yamamoto et al. have shown that this type of *N*–*O*-benzoyl migration may also occur in the presence of Lewis acids (Scheme 6) since treatment of (2*S*,3*R*)-epoxypropyl-benzoylcarbamate **25** with trimethylaluminium gave *N*–*O*-migrated *O*-benzoyl-oxazolidin-2-one **26** (^{1}H NMR, δ 6.52 ppm, NH; ^{13}C NMR, δ 160.1 (C═O) and 165.7 ppm (C═O); FT-IR, 1740 and 1720 cm^{-1}) in a 67% yield, with no evidence of any of the corresponding *N*-benzoyl oxazolidin-2-one **27**.[16]

Definitive experiments by Katsumura et al. showed that intramolecular cyclisation of the anion derived from (*S*)-*N*-benzoyl-2,3-epoxypropylcarbamate **28** did not afford the expected (*S*)-*N*-benzoyl-oxazolidin-2-one **32** but gave instead the (*S*)-*N*–*O*-benzoyl rearrangement product **29** (Scheme 7). Furthermore, these workers demonstrated the propensity of this class of oxazolidin-2-one to racemisation. When hydrolysis of enantiomerically

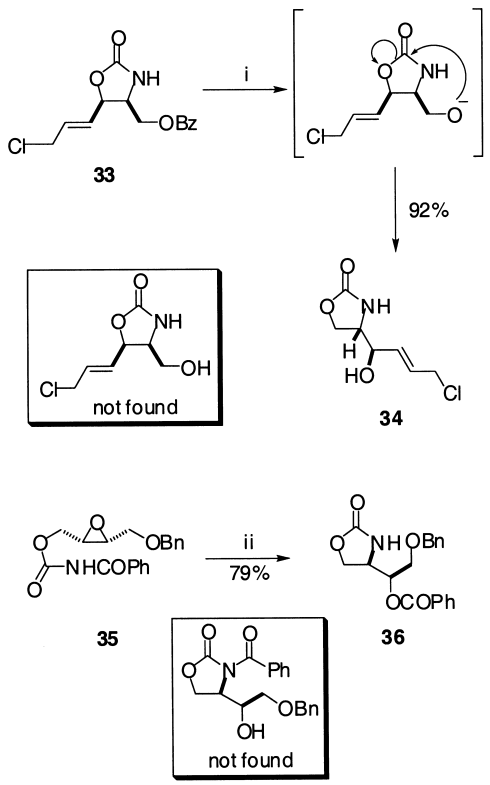


Scheme 7. *Reagents and conditions*:(i) PhCONCO, CH_2Cl_2, room temperature; (ii) K_2CO_3, $PhCH_2N(CH_2CH_3)_3Cl$, DCM/H_2O, 1:1, room temperature, 2 h; (iii) NaH, BnBr, $(CH_3CH_2)_4NI$, THF/DMF, room temperature; (iv) LiOH, H_2O, THF; Cs_2CO_3, MeOH; or K_2CO_3, MeOH.

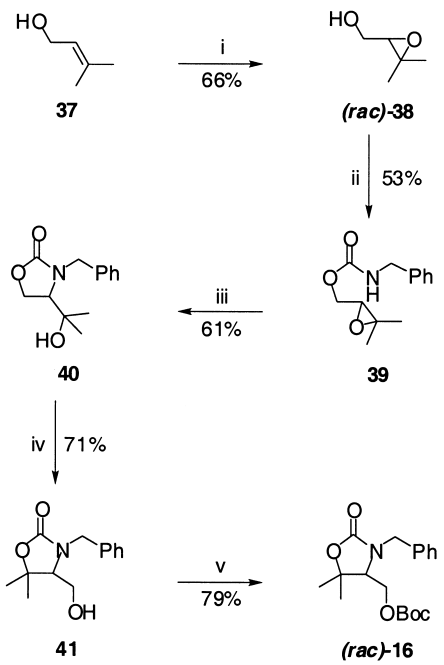
enriched (*S*)-*N*-benzyl-*O*-benzoyl-oxazolidin-2-one **30** was undertaken with a selection of inorganic bases (LiOH in H_2O/THF; or Cs_2CO_3 in MeOH; or K_2CO_3 in MeOH) the reaction afforded (*rac*)-*N*-benzyl-oxazolidin-2-one **31** presumably via an *O*–*O*-carbonyl migration pathway involving attack of the alkoxide anion of the pendant 4-hydroxymethyl group on the oxazolidin-2-one carbonyl.[17]

This *O*–*O*-carbonyl migration pathway is a common feature for this class of 4-hydroxymethyl-oxazolidin-2-one. For example, Shinozaki have shown in their studies directed towards the total synthesis of D-*erythro*-Sphingosine that treatment of *trans*-(2*S*,3*R*)-allylic chloride **33** with potassium carbonate in methanol at ambient temperatures afforded the *O*–*O*-carbonyl rearranged chloroallylic alcohol **34** in 92% yield (Scheme 8).[18] The driving force behind this rearrangement is presumably release of the 1,2-*cis*-strain of the substituents within oxazolidin-2-one ring **33**. A similar rearrangement was reported by McCombie et al. who demonstrated that treatment of (2*S*,3*R*)-2,3-epoxy carbamate **35** with potassium carbonate afforded *O*-benzoate ester **36** in 79% yield.[19]

The *O*–*O*-carbonyl rearrangement pathways described in Schemes 7 and 8 cast doubt on the structural assignment of *O*-Boc-oxazolidin-2-one **16**, since alkoxide **12** (Scheme 3) had the capacity to undergo this type of *O*–*O*-carbonyl rearrangement to afford a *N*-benzyl-oxazolidin-2-one species **40**. We decided therefore to prepare an authentic sample of oxazolidin-2-one **16**, according to the protocol described in Scheme 9, which would enable direct spectroscopic comparisons to be carried out. Thus, epoxidation of 3-methyl-but-2-ene-1-ol **37** with mCPBA gave (*rac*)-



Scheme 8. *Reagents and conditions*: (i) K_2CO_3, MeOH, room temperature, 2 h; (ii) K_2CO_3, 5 mol% $CH_3N(C_8H_{17})_3Cl$.



Scheme 9. *Reagents and conditions*: (i) mCPBA; Na_2CO_3 (aqueous), room temperature; (ii) PhCONCO, cat $[(n\text{-Bu})_2SnCl]_2O$, DCM; (iii) *n*-BuLi (1 equiv.), THF, −20°C; (iv) NaH, THF, room temperature; (v) $(Boc)_2O$, DMAP, Et_3N, DCM.

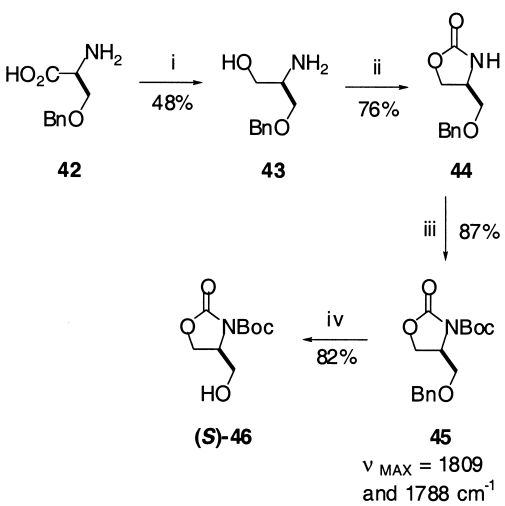
epoxide **38**,[20] which reacted with benzyl isocyanate in the presence of a catalytic amount of bis-(dibutylchlorotin)-oxide to afford (*rac*)-benzyl-carbamic acid-3,3-dimethyl-oxiranyl methyl ester **39** (53%). Cyclisation of **39** via deprotonation with *n*-BuLi afforded, after chromatographic purification, the oxazolidin-2-one tertiary alcohol **40** as a colourless oil (61%). Deprotonation of **40** with sodium hydride in THF resulted in rearrangement of oxazolidin-2-one tertiary alcohol **40** to the corresponding primary alcohol **41**.[21] A comparison of the 400 MHz ^1H NMR spectra of **40** and **41** clearly shows a significant change in the environment of the constituent protons, for example the *gem*-dimethyl groups have moved downfield from δ 1.17/1.23 to δ 1.36/1.44 ppm for **40** and **41**, respectively. Furthermore, the complexity of the $HOCH_2CHN$ ^1H–^1H coupling constants for **41** were significantly simpler than those of **40** presumably due to the freely rotating *exo*-cyclic CH_2OH group. The previously assigned structure of **16** (Scheme 3) was confirmed unambiguously by conversion of the primary alcohol **41** into the corresponding (*rac*)-*N*-benzyl-*O*-Boc-oxazolidin-2-one **16**.

We concluded therefore that the *endo* and *exo*-cyclic migrations described above render L-serine derived SuperQuat 5,5-*gem*-dimethyloxazolidin-2-ones unsuitable for attachment to polymer support via the 4-hydroxymethyl side-chain.

2.2. Investigations into *N*–*O* carbonyl migration within L-serine derived Evans' oxazolidin-2-ones

In light of the results described above, the report by Allin and Shuttleworth (Scheme 1) on the generation of an alkoxide from **1** (KH, DMF, 0°C) and clean attachment to Merrifield resin (DMF, catalytic 18-crown-6, 80°C, 5 days) without apparent racemisation (*endo*-cyclic *O*-*O* carbonyl

rearrangement), or *N*–*O*-Boc migration (*exo*-cyclic rearrangement), seemed remarkable and merited investigation. Synthesis of the key L-serine derived homochiral *N*-Boc-oxazolidin-2-one **1** was undertaken via two different protocols. Firstly, commercially available *O*-benzyl-L-serine **42** was reduced to yield the corresponding *O*-benzyl amino alcohol **43**,[22] which was subsequently transformed into *O*-benzyl-oxazolidin-2-one **44** via the phosgene equivalent, carbonyl diimidazole.[23] Subsequent *N*-Boc protection of oxazolidin-2-one **44** yielded **45** which was subjected to hydrogenolysis of the *O*-benzyl group, yielding (*S*)-*N*-Boc-oxazolidin-2-one **46** ($[\alpha]_D^{22}=+42.8$ (*c* 0.5, $CHCl_3$)) in good yield (82%, ^{13}C NMR, 149.9 (C=O) and 152.4 (C=O) ppm; FT-IR, 1798 and 1722 cm^{-1}) (Scheme 10).



Scheme 10. *Reagents and conditions*: (i) $BH_3{\cdot}SMe_2$/THF, 0°C-reflux, 12 h; H_2O_2; (ii) CDI, DCM, 12 h; (iii) $(Boc)_2O$, DMAP, Et_3N, DCM, room temperature; (iv) MeOH, H_2, 10% Pd on C.

It was considered important to confirm unequivocally the exact location of the Boc group, and as a consequence an X-ray crystal structure of (*S*)-*N*-Boc-oxazolidin-2-one **46** was obtained which clearly revealed the presence of the Boc protecting group on the nitrogen atom of the oxazolidin-2-one (Fig. 1).

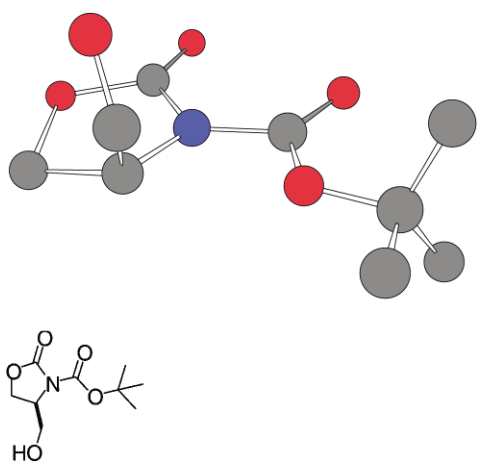
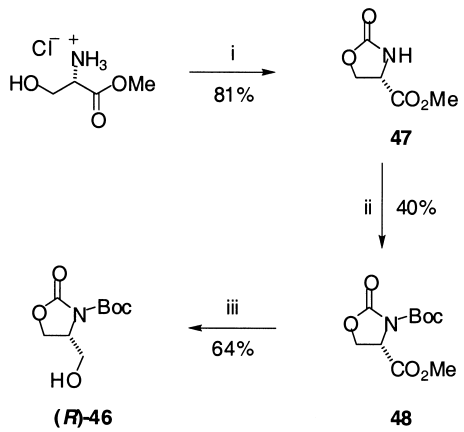


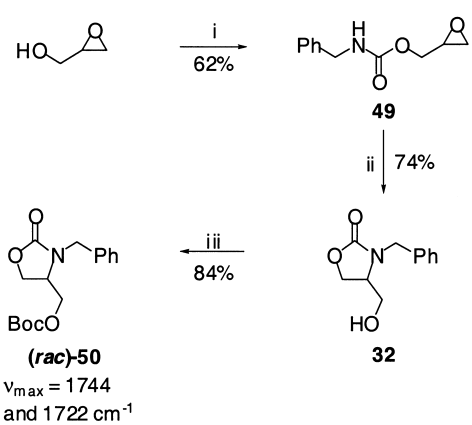
Figure 1. X-Ray crystal structure of (*S*)-4-hydroxymethyl-2-oxo-oxazolidin-3-carboxylic acid *tert*-butyl ester **46**.

Alternatively, *N*-Boc-oxazolidin-2-one **1** was prepared via a modification of the protocol originally employed by Allin and Shuttleworth for their polymer bound oxazolidin-2-one **4** (Scheme 1).[10] Thus, treatment of L-serine methyl ester hydrochloride salt with triphosgene and triethylamine yielded **47**, followed by *N*-Boc-protection to afford *N*-Boc-oxazolidin-2-one methyl ester **48**. Reduction of **48** under the original conditions of Sibi et al. ((i) $NaBH_4$, 0°C; (ii) sat. aqueous NH_4Cl) was problematic, affording only low yields of the desired (*R*)-4-hydroxymethyl-*N*-Boc-oxazolidin-2-one **46**.[24] Carrying out the reduction via inverse addition of ester **48** to an ice-cold solution of sodium borohydride (4 equiv.), followed by phosphate buffer work-up (pH 4), gave the desired (*R*)-*N*-Boc-oxazolidin-2-one **46** in a 64% yield ($[\alpha]_D^{22}=-45.6$ (*c* 0.83, $CHCl_3$)), ^{13}C NMR, 151.0 (C=O) and 152.3 (C=O) ppm; FT-IR, 1803 and 1706 cm^{-1}) (Scheme 11). The enantiomeric purity of (*R*)-**46** was determined to be >95% ee by comparison of the ^1H NMR (250 MHz) spectra of (*R*)-**46** with an authentic racemic sample of **46** in the presence of 40 mol% of (+)-Europium(tfc)$_3$.

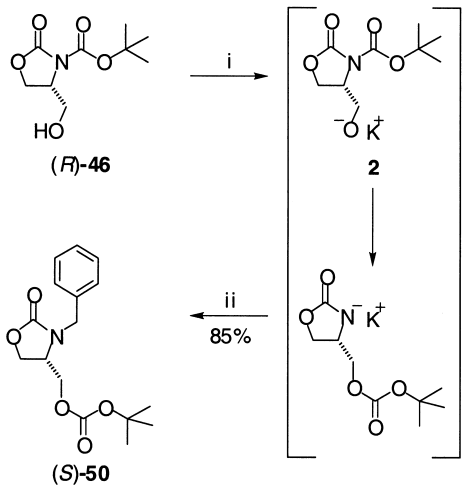


Scheme 11. *Reagents and conditions*: (i) triphosgene, DCM, Et_3N, 0°C; (ii) $(Boc)_2O$, DMAP, Et_3N; (iii) $NaBH_4$ (4 equiv.), EtOH, 0°C; phosphate buffer pH 4.

An authentic sample of **45** and (*rac*)-*N*-benzyl-*O*-Boc-oxazolidin-2-one **50** were then prepared for comparative purposes according to the protocol described in Scheme 12. Thus, (*rac*)-glycidol was treated with benzyl isocyanate in



Scheme 12. *Reagents and conditions*:(i) PhCONCO, cat $[(n\text{-}Bu)_2SnCl]_2O$, DCM; (ii) *n*-BuLi (1 equiv.), THF, −20°C; (iii) $(Boc)_2O$, DMAP, DCM.

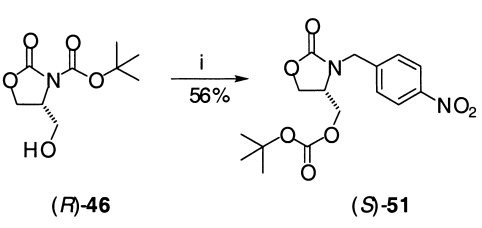


Scheme 13. *Reagents and conditions*: (i) KH, DMF, 0°C, 2 h; (ii) BnCl, cat 18-crown-6, 0°C to rt, 12 h.

the presence of catalytic amounts of bis(di-*n*-butylchlorotin) oxide, and the resulting carbamate **49** deprotonated with *n*-BuLi to afford (*rac*)-*N*-benzyl-4-hydroxymethyl-oxazolidin-2-one **32**, which was Boc protected on oxygen to afford (*rac*)-*N*-benzyl-*O*-Boc-oxazolidin-2-one **50** (Scheme 12).

With quantities of (*R*)-*N*-Boc-oxazolidin-2-one **46** in hand the reaction conditions employed by Allin and Shuttleworth could be repeated. Treatment of a solution of (*R*)-**46** in DMF at 0°C with KH presumably afforded potassium alkoxide anion **2** (Scheme 13), was followed by addition of benzyl chloride (as a mimic for Merrifield resin) and a catalytic amount of 18-crown-6. The resulting solution was heated at 80°C for 4 days to afford a complex mixture of unidentifiable reaction products. However, modification of the original reaction conditions involving generation of the corresponding potassium alkoxide of (*R*)-**46** using potassium hydride in DMF at 0°C and subsequent addition of benzyl chloride and a catalytic amount of 18-crown-6 (warming to room temperature only) afforded a crude reaction product which was shown, after flash column chromatography to be (*S*)-*N*-benzyl-*O*-Boc-oxazolidin-2-one **50** (Scheme 13, $[\alpha]_D^{23}=+10.5$ (*c* 1.54, $CHCl_3$)); ^{13}C NMR, 153.0 (C═O) and 158.2 (C═O) ppm; FT-IR, 1742 and 1724 cm^{-1}) via spectroscopic comparison with the authentic sample of (*rac*)-**50** (^{13}C NMR, 152.9 (C═O) and 158.2 (C═O) ppm; FT-IR, 1744 and 1722 cm^{-1}) previously prepared according to the protocol outlined in Scheme 12.

Further evidence for the benzyl group being located on nitrogen was sought. A sample of the crystalline (*R*)-*N*-Boc-oxazolidin-2-one **46** prepared via the synthetic route shown in Scheme 11 was treated with KH in DMF at 0°C, the resulting anion was quenched with *para*-nitrobenzyl bromide, this afforded the crystalline *O*-Boc-*N*-*para*-nitrobenzyl oxazolidin-2-one (*S*)-**51** (Scheme 14, ^{13}C NMR, 155.4 (C═O) and 160.9 (C═O) ppm; FT-IR, 1744 and 1733 cm^{-1}) which was subjected to X-ray crystallographic analysis, this clearly revealed the presence of the para-nitrobenzyl group on the nitrogen atom (Fig. 2).



Scheme 14. *Reagents and conditions*: (i) KH, DMF, 0°C, 2 h; *para*-nitrobenzyl bromide, room temperature, 12 h.

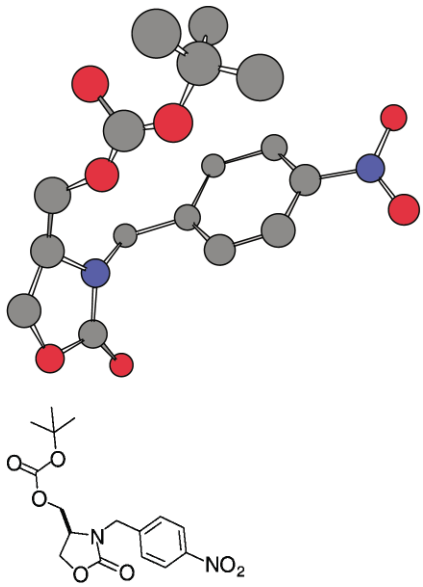
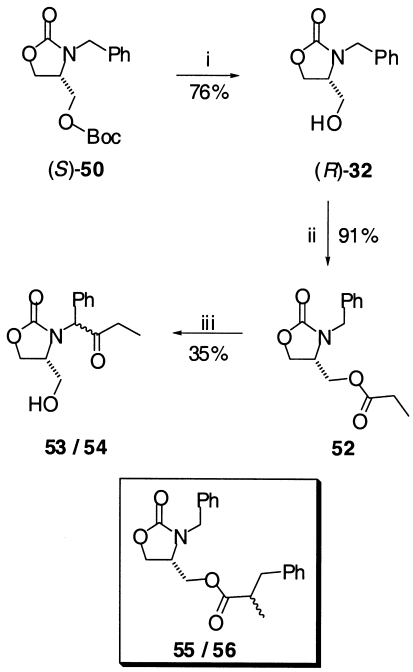


Figure 2. Crystal structure of (*S*)-carbonic acid *tert*-butyl ester-3-(4-nitrobenzyl)-2-oxo-oxazolidin-4-yl methyl ester.

With these results in hand we next investigated the possibility that *N*-benzyl-*O*-propionyl-oxazolidin-2-one **52** might prove inherently useful as a chiral auxiliary for the asymmetric synthesis of α-substituted carboxylic acids such as **5** (Scheme 1). Thus, *O*-Boc deprotection of (*S*)-*N*-benzyl-*O*-Boc-oxazolidin-2-one **50** via treatment with aqueous 1 M hydrochloric acid in refluxing THF yielded *N*-benzyl-4-hydroxymethyl-oxazolidin-2-one (*R*)-**32** (FT-IR, 1723 cm^{-1}) in a 76% yield, which was subsequently O-propionylated via the method of Ager et al to afford *N*-benzyl-*O*-propionyl-oxazolidin-2-one **52** in a 91% yield ($[\alpha]_D^{23}=+10.0$ (*c* 1.35, $CHCl_3$)); ^{13}C NMR, 158.2 (C═O) and 173.9 (C═O) ppm.[25] Treatment of *N*-benzyl-*O*-propionyl-oxazolidin-2-one **52** with 2 equiv. of LDA at −78°C followed by addition of 2 equiv. of benzyl bromide afforded a complex mixture of reaction products that contained the ketones **53/54**, with no spectroscopic evidence of any of the expected α-benzylated-propionyl-oxazolidin-2-ones **55/56** having been formed. Repeating this deprotonation reaction at −78°C, gave a cleaner reaction mixture containing the ketones **53/54** and a small amount of starting material **52** (37%), once again the 400 MHz ^1H NMR provided no evidence of the diastereoisomers **55/56**, as would have been expected from α-benzylation of the enolate derived from *O*-propionyl-*N*-benzyl-oxazolidin-2-one **52**. The absence of any resonances corresponding to the α-benzylated-*N*-propionyl-oxazolidin-2-ones **55/56** within the 400 MHz ^1H NMR spectra of these crude reaction mixtures was confirmed via spectroscopic comparison with an authentic sample of **55/56** (0% de) which was prepared

via O-acylation of the hydroxyl functionality of (R)-**32** with (*rac*)-α-methylhydrocinnamoyl chloride (Scheme 15).[26]



Scheme 15. *Reagents and conditions*: (i) 1 M HCl, THF; (ii) $(CH_3CH_2CO)_2O$, DMAP, Et_3N, DCM; (iii) LDA (2 equiv.), THF, −78°C; BnBr.

Purification of the ketones **53/54** to homogeneity was problematical, however after many attempts chromatographic separation of the crude reaction mixture was achieved using ether as the initial eluent to remove unreacted starting material **52**, followed by elution with chloroform, which resulted in partial separation of the mixture affording pure **53** in a 7.4% yield, and a mixture of **53/54** in which the minor ketone **54** was enriched. Salient spectroscopic details for the major ketone **53** include a characteristic singlet at δ 5.92 ppm (minor epimer at δ 5.48 ppm) in the ^{1}H NMR spectrum corresponding to the benzylic hydrogen; the presence of two peaks in the ^{13}C NMR spectrum corresponding to both a ketone and an oxazolidin-2-one carbonyl functionality at δ 211.8 and 158.9 ppm, respectively, and two absorbances at 1742 (oxazolidin-2-one C═O) and 1712 cm^{-1} (ketone C═O) in the FT-IR. Further confirmation of the proposed structure for the major epimer **53** was obtained from correlated ^{1}H–^{1}H and ^{1}H–^{13}C NMR (400 MHz) spectroscopic studies, the salient features of which are described in Fig. 3. Importantly, the epimeric relationship between the major and minor diastereoisomers was confirmed by undertaking a simple experiment. Dissolving pure major epimer **53** in a small amount of DCM and subsequently passing the solution through a pipette that had been charged with basic alumina allowed the emerging DCM solution to be collected, the solvent removed and a ^{1}H NMR recorded. The H NMR clearly showed the product to be a 1:1 mixture of **53/54**. With the characteristic benzylic singlets clearly identifiable at δ 5.92 and 5.48 ppm for **53/54** respectively.

We next attempted to repeat the synthesis of polymer **4** (Scheme 1) according to the protocol of Allin and Shuttleworth.[10] Thus, *N*-Boc-oxazolidin-2-one **1** was dissolved in DMF, cooled to 0°C under argon and potassium hydride (oil free) added. The resulting solution was stirred for 2 h at 0°C and Merrifield resin (loading 1.7 mmol/g) was added. The resulting suspension was heated at 80°C for 5 days with a catalytic amount of 18-crown-6, after which the polymer was filtered and washed sequentially with the following solvents (in order), DMF, THF, DCM, MeOH and Et_2O to ensure removal of excess reagents from the polymer. A small portion of the polymer was subjected to FT-IR analysis (KBr), which revealed a strong broad absorbance (1785–1700 cm^{-1}) centred at 1742 cm^{-1} which is consistent with the absorption's expected for both the carbonyls of a *N*-polymer-linked-*O*-Boc-oxazolidin-2-one (compare with **50** ~1742 and ~1724 cm^{-1}), but not with the absorption's expected for a *O*-polymer-linked-*N*-Boc-oxazolidin-2-one **4** (compare with **45** ~1809 and ~1788 cm^{-1}). Removal of the Boc group from the auxiliary was achieved via treatment with 1 M aqueous hydrochloric acid in DCM at reflux. The polymer was again washed sequentially with the solvent series outlined above, i.e. DMF, THF, DCM, MeOH and Et_2O. This afforded a polymer which displayed a broad FT-IR (KBr; 1795–1705 cm^{-1}) centred at 1750 cm^{-1}. Subsequent acylation of the polymer bound serine derived oxazolidin-2-one was achieved using a mixture of propionic anhydride/triethylamine/10% DMAP in refluxing THF for 4 days. The resulting polymer possessed a broad FT-IR (KBr) absorption spanning 1780–1724 cm^{-1}, with a weak stretch at 1650 cm^{-1}. It is also noted that the corresponding FT-IR (thin film) of *N*-benzyl-*O*-propionyl-oxazolidin-2-one **52** possesses similar absorbances within the C═O region i.e. 1759–1721 cm^{-1}, centred at 1738 cm^{-1} and a weak stretch at 1643 cm^{-1}. Interestingly Allin and Shuttleworth[10] themselves reported that 'a new carbonyl band corresponding to the *N*-propionyl side chain at 1652 cm^{-1}' was observed. The polymer was washed (solvents as above), dried and suspended in THF. The suspension was cooled to −78°C and subsequently treated with LDA (2 equiv., 0.5 M in THF), after 2 h at −78°C, freshly distilled benzyl bromide was added and the resulting suspension allowed to warm to room temperature over 12 h. Attempted cleavage

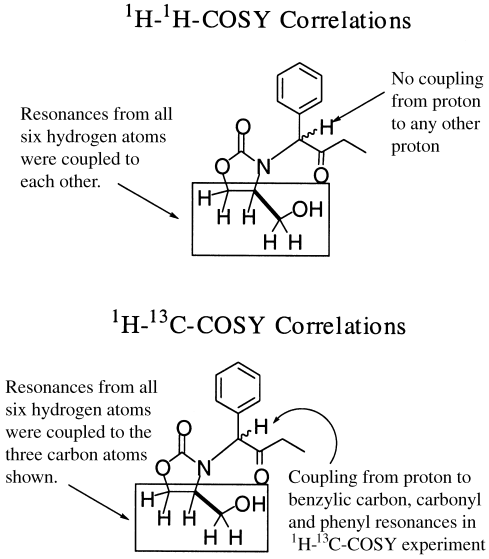


Figure 3. Selected ^{1}H–^{1}H-COSY and ^{1}H–^{13}C-COSY correlations for **53**.

of any N-acylated product from the polymer support was then undertaken using aqueous THF/lithium hydroxide solution over 12 h. Acidification (2 M HCl) of the aqueous cleavage solution followed by extraction (DCM) afforded an organic soluble product, that the corresponding ^{1}H NMR (200 MHz) revealed contained a large number of resonances none of which corresponded to α-methylhydrocinnamic acid **5**. Repetition of the above experiment at 0°C led to the same result.

In light of these observations we must conclude that the material described by Allin and Shuttleworth and described as the O-bound homochiral polymer supported *N*-Boc-oxazolidin-2-one **4** was in fact N-bound polymer supported *O*-Boc-oxazolidin-2-one **57** (Fig. 4). In light of these results we are unable to explain their success in employing polymer supported oxazolidin-2-ones for the generation of (*S*)-α-methylhydrocinnamic acid **5** in 96% ee.[10]

Figure 4.

3. Conclusion

The propensity of *N*-Boc-4-hydroxymethyl-oxazolidin-2-ones to undergo rapid *O*–*O* and *N*–*O* carbonyl transfer reactions makes these L-serine derived chiral auxiliaries unsuitable for attachment to polymer support. The successful attachment of the SuperQuat 5,5-dimethyl-oxazolidin-2-one chiral auxiliary derived from L-tyrosine to a polymer support via its phenolic hydroxyl will be reported elsewhere.

4. Experimental

4.1. General methods

All reactions were performed (under a positive pressure of argon or nitrogen) in flame dried flasks, equipped with stirrer beads unless otherwise stated. Ether and tetrahydrofuran was freshly distilled from sodium benzophenone ketyl. Dichloromethane was distilled from calcium hydride. Toluene was distilled from sodium. *N*,*N*-Dimethylformamide was stored over flame dried 4 Å molecular sieves which were allowed to cool in vacuo. Ethanol was stored over activated 4 Å molecular sieves. Water refers to distilled water. All other reagents were obtained and used 'as is' from commercial suppliers unless otherwise stated. Optical rotations were performed on a Perkin–Elmer 241 polarimeter and are quoted for spectroscopic grade chloroform (Aldrich), $[\alpha]_D^{22}$ values are given in 10^{-1} deg cm^2 g^{-1}. FT-IR spectra were recorded on a Perkin–Elmer Paragon 1000FT infrared spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on either a Bruker AM-500, AMZ-500, AC-400 or a Varian Gemini 200 and unless otherwise stated deuterated chloroform was used as solvent. The ^{1}H-spectra were recorded in ppm and referenced to residual $CHCl_3$ signal located at δ 7.26. ^{13}C NMR spectra were recorded in ppm and referenced to residual $CHCl_3$ signal found at δ 77.00. Atmospheric Pressure Chemical Ionisation (APCI) mass spectra were recorded on a Platform instrument. Major peaks are listed with the intensities quoted as percentages of the base peak. HRMS were obtained on a VG Autospec instrument, and were recorded by Mr. R. Proctor of the Dyson Perrins Laboratory. NH_3 was used as the carrier gas for CI. Melting points were obtained on either a Gallenkamp capilliary apparatus or a Leica Galen III heated stage apparatus and are uncorrected. Thin layer chromatography was performed on Merck aluminium plates coated with 0.2 mm silica gel 60 F_{254}. Flash column chromatography was performed on silica gel (Kieselgel 60).

4.1.1. {1-[(*tert*-Butyldimethylsilanoxymethyl)-2-hydroxy-2-methyl]-propyl}-(*S*)-carbamic acid *tert*-butyl ester 9. *N*-Boc-L-serine methyl ester[27] **8** (21.6 g, 71.7 mmol) was dissolved in tetrahydrofuran (300 mL) and subsequently cooled to −78°C in a CO_2/acetone bath. A solution of methyl magnesium bromide in ether (34.0 g, 95 mL, 285 mmol, 4 equiv., 3 M) was added dropwise to ester **8** over a 15 min period (care: methane evolved). The resulting solution was stirred at −78°C for a further 4 h and then allowed to warm to room temperature. After 12 h the reaction mixture was cooled to 0°C and carefully quenched with aqueous saturated ammonium chloride (200 mL). The quenched reaction was allowed to warm to room temperature over a 20 min period. The solvent was removed in vacuo and replaced with dichloromethane (200 mL). To the dichloromethane solution containing the crude reaction mixture enough aqueous saturated ammonium chloride was added so that all the magnesium salts dissolved. The aqueous layer was partitioned and the dichloromethane solution was washed with aqueous saturated ammonium chloride (2×100 mL), saturated brine (2×100 mL), aqueous saturated sodium bicarbonate (2×100 mL) and subsequently dried ($MgSO_4$). Filtration and removal of the solvent in vacuo yielded (*S*)-**9** as a pale yellow oil. The title compound was purified via flash column chromatography using *n*-pentane/ether (65:35) as the eluent, returning (*S*)-**9** as a clear oil (93%, 22.1 g); $[\alpha]_D^{22}$=+38.4 (*c* 0.75, $CHCl_3$); ν_{max} (film) (cm^{-1}) 3448, 2977, 2931, 1699 (s, C=O), 149.7, 1366, 1331, 125.6, 1173, 1099, 837; δ_H (400 MHz, $CDCl_3$) 0.077 [6H, s, $(CH_3)_2Si$], 0.89 [9H, s, $(CH_3)_3CSi$], 1.19 [3H, s, $(CH_3)_2COH$], 1.33 [3H, s, $(CH_3)_2COH$], 1.44 [9H, s, $(CH_3)_3CO$], 3.38 (1H, m, CH(NH)), 3.58 (1H, s, OH), 3.85 (1H, dd, *J*=10.7, 2.2 Hz, $CH_ACH_BOTBDMS$), 4.05 (1H, dd, *J*=10.7, 2.2 Hz, $CH_ACH_BOTBDMS$), 5.35 (1H, d, *J*=8.7 Hz, N–H); δ_C (100.6 MHz, $CDCl_3$) −5.7 [$(CH_3)_2Csi$], 18.0, 25.8 [$(CH_3)_3CSi$)], 26.8 [$(CH_3)_2COH$], 27.8 [$CH_3)_2COH$], 28.4 [$CH_3)_3CO$)], 56.8, 64.4, 73.0, 79.2, 155.9 (C=O); *m*/*z* (APCI+) 356.1 (5, M+Na$^+$), 289.1 (5), 234.1 (100%), 216.1 (5).

4.1.2. (*S*)-(*tert*-Butyldimethylsilanyloxymethyl)-5,5-dimethyloxazolidin-2-one 10. Tertiary alcohol (*S*)-**9** (19.5 g, 58.6 mmol) was dissolved in tetrahydrofuran (400 mL) whilst being stirred and cooled to −78°C. In one portion potassium *tert*-butoxide (8.0 g, 71.3 mmol) was

added, the solution quickly turning yellow. After 10 min at −78°C the reaction mixture was allowed to warm to room temperature. After 16 h at this temperature the reaction was quenched with aqueous saturated ammonium chloride (100 mL). The crude product was extracted into dichloromethane (3×75 mL). The dichloromethane solution was washed with aqueous hydrochloric acid (0.1 M, 2×100 mL), saturated brine (2×50 mL), water (2×50 mL) and subsequently dried ($MgSO_4$). Filtering the solution and removal of the solvent in vacuo yielded the title compound as a solid. Purification of (*S*)-**10** was achieved by crystallising from *n*-pentane. SuperQuat (*S*)-**10** (11.3 g, 67%) was a yellow crystalline solid with the following physical characteristics; mp 60–64°C; $[\alpha]_D^{22}=-32$ (*c* 0.52, $CHCl_3$); ν_{max} (KBr) (cm^{-1}) 3245 (N–H), 2957, 2857, 1756 (s, C=O), 1472, 1351, 1295, 1258, 1199, 1083, 840; δ_H (500 MHz, $CDCl_3$) 0.02 [6H, s, (CH_3)$_2$Si], 0.83 [9H, s, (CH_3)$_3$CSi], 1.31 (3H, s, 5-C–CH_3), 1.42 (3H, s, 5-C–CH_3'), 3.46–3.60 (3H, m, CH_ACH_BOTBDMS and 4-C*H*), 5.4 (1H, br s, N–*H*); δ_C (100.6 MHz, $CDCl_3$) −5.0 [(CH_3)$_2$Si], 18.5 [(CH_3)$_3$*C*Si], 21.8 (5-C–*C*H_3), 26.2 [(*C*H_3)$_3$CSi], 28.8 (5-C–*C*H_3'), 62.7, 62.8, 82.7, 158.9 (C=O); *m*/*z* (APCI+) 282.2 (20, M+Na^+), 260.2 (100%), 216.2 (90), 120.0 (10), 102.1 (40); HRMS (CI^+) (Found: MH^+, 260.1690. $C_{12}H_{25}NO_3Si$ requires 260.1682).

4.1.3. (*S*)-[(*tert*-Butyldimethylsilanoxymethyl]-5,5-dimethyl-2-oxo-oxazolidine-3-carboxylic acid *tert*-butyl ester 11. A flask was charged with SuperQuat (*S*)-**10** (4.94 g, 19.1 mmol) and the solid dissolved in tetrahydrofuran (100 mL). To the stirred solution was added 4-dimethylaminopyridine (1.16 g, 9.49 mmol), di-*tert*-butyl dicarbonate (8.3 g, 38.0 mmol) and triethylamine (3.84 g, 38.0 mmol). The reaction was stirred for 12 h at room temperature and the solvent removed in vacuo. Replacing the tetrahydrofuran with ether (100 mL) allowed the crude reaction mixture to be washed with aqueous hydrochloric acid (0.1 M, 3×25 mL), saturated aqueous brine (3×50 mL) and subsequently dried ($MgSO_4$). After filtration the impure product was purified via flash column chromatography using a mixture of *n*-pentane and ether (75:25) as the eluent. The purified title compound (*S*)-**11** was a white solid (5.7 g, 83%) which had the following physical characteristics; mp 110–112°C; $[\alpha]_D^{22}=+30.35$ (*c* 1.12, $CHCl_3$), ν_{max} (film) (cm^{-1}) 2930, 2857, 1808 (s, C=O), 1718 (s, C=O), 1473, 1363, 1331, 1290, 1256, 1157, 1078; δ_H (400 MHz, $CDCl_3$) 0.025 [3H, s, (CH_3)$_2$Si)], 0.04 [3H, s, (CH_3)$_2$Si)], 0.86 [9H, s, (CH_3)$_3$CSi)], 1.42 (3H, s, 5-C–CH_3), 1.53 (12H, s, [5-C–CH_3' and (CH_3)$_3$CO)], 3.78 (2H, m, CH_ACH_BOTBDMS), 3.96 (1H, dd, *J*=11.25, 4.8 Hz, 4-C*H*); δ_C (100.6 MHz, $CDCl_3$) −5.7 [(CH_3)$_2$Si], 17.9, 21.25 (5-C–*C*H_3'), 25.6 [(*C*H_3)$_3$CSi], 28.0 [(*C*H_3)$_3$CO], 28.7 (5-C–*C*H_3), 59.4, 64.0, 79.9, 83.5, 149.9 (C=O), 151.5 (C=O); *m*/*z* (APCI+) 382.3 (30, M+Na^+), 374.3 (20), 304 (20), 260 (100%), 216 (25); HRMS (CI^+) (Found: M, 360.2206. $C_{17}H_{33}NO_5Si$ requires 360.2220).

4.1.4. (*S*)-Carbonic acid *tert*-butyl ester 5,5-dimethyl-2-oxo-oxazolidin-4-yl methyl ester 15. *N*-Boc-*O*-TBDMS SuperQuat (*S*)-**11** (100 mg, 0.28 mmol) was dissolved in tetrahydrofuran (1 mL). The solution was stirred at room temperature and TBAF was added dropwise (0.58 mL, 151 mg, 0.58 mmol, 1 M solution in THF, Aldrich). The resulting yellow/orange reaction mixture was stirred for a further 12 h at room temperature. After 12 h, analysis of the reaction mixture by tlc (*n*-pentane/ether, 75/25) indicated that all of the starting material had been consumed. The solvent was removed in vacuo and replaced with dichloromethane (2 mL). The dichloromethane solution was filtered through a short column of silica. The silica was further eluted with three more aliquots of dichloromethane (2 mL). The dichloromethane fractions were combined and the solvent removed in vacuo yielding impure **15**. Purification of the title compound was readily achieved via flash column chromatography using ether as the eluent. (*S*)-*O*-Boc-SuperQuat **15** was isolated as a white solid which displayed the following physical characteristics (58 mg, 86%); mp 112–115°C; $[\alpha]_D^{23}=-53.2$ (*c* 0.66, $CHCl_3$); ν_{max} (KBr) (cm^{-1}) 3436 (N–H), 2980, 2934, 1774, 1747 (s, C=O), 1720 (s, C=O), 1455, 1393, 1370, 1276, 1256, 1157, 1090, 1002; δ_H (400 MHz) 1.39 (3H, s, 5-C–CH_3), 1.49 [9H, s, C(CH_3)$_3$], 1.51 (3H, s, 5-C–CH_3'), 3.72 (1H, m, 4-C*H*), 4.03 (1H, dd, *J*=11.0, 8.1 Hz, CH_ACH_BO), 4.18 (1H, dd, *J*=11.0, 4.6 Hz, CH_ACH_BO), 5.62 (1H, br s, N–*H*); δ_C (100.6 MHz, $CDCl_3$) 21.6 (5-C–*C*H_3), 27.6 [(*C*H_3)$_3$C], 28.0 (5-C–*C*H_3'), 59.6, 65.6, 81.8, 83.2, 153.0 (C=O), 157.8 (C=O); *m*/*z* (APCI+) 286.1 (25, M+Na^+), 236 (5), 218 (5), 212 (5), 190.1 (100%), 167.9 (5), 146 (20), 128.1 (80), 116.1 (25), 102 (10); HRMS (CI^+) (Found: MH^+, 246.1338. $C_{11}H_{20}NO_5$ requires 246.1341.

4.1.5. (*S*)-Carbonic acid 3-benzyl-5,5-dimethyl-2-oxo-oxazolidin-4-yl methyl ester *tert*-butyl ester 16 (from 11). (*S*)-*N*-Boc-*O*-silyl SuperQuat **11** (100 mg, 0.28 mmol) was dissolved in tetrahydrofuran (1 mL). The solution was stirred at room temperature and TBAF (0.58 mL, 151 mg, 0.58 mmol, 1 M solution in THF, Aldrich) was added dropwise. Immediately after the TBAF was added excess benzyl bromide was added to the flask (660 mg, 3.86 mmol). The resulting yellow/orange reaction mixture was stirred for a further 12 h at room temperature. After 12 h a tlc (eluent; *n*-pentane/ether, 75:25) indicated that all of the starting material had been consumed. The solvent was removed in vacuo and the crude reaction mixture diluted with dichloromethane (3 mL). The dichloromethane solution was filtered through a short column of silica. The silica was further eluted with three more portions of dichloromethane (3 mL). The dichloromethane fractions were combined and the solvent removed in vacuo yielding impure **16**. Purification of **16** was readily achieved via flash column chromatography using a mixture of *n*-pentane/ether (1:1) as the eluent. (*S*)-*O*-Boc-*N*-benzyl-SuperQuat **16** was isolated as a colourless oil (59 mg, 63%) which displayed the following physical characteristics; $[\alpha]_D^{22}=+11.2$ (*c* 0.82, $CHCl_3$); ν_{max} (film) (cm^{-1}) 2980, 1813 (C=O), 1744 (s, C=O), 1416, 1370, 1275, 1159; δ_H(400 MHz, $CDCl_3$) 1.35 (3H, s, 5-C–CH_3), 1.39 (3H, s, 5-C–CH_3'), 1.48 [9H, s, (CH_3)$_3$C], 3.38 (1H, t, *J*=5.5 Hz, 4-C–*H*), 4.07 (1H, dd, *J*=11.7, 5.5 Hz, CH_ACH_BO), 4.20 (2H, m, CH_ACH_BO and CH_AH_BPh), 4.84 (1H, d, *J*=15.1 Hz, CH_AH_BPh), 7.30–7.35 (5H, m, Ar-*H*); δ_C (100.6 MHz, $CDCl_3$) 21.7 (5-C–*C*H_3), 27.9 [(*C*H_3)$_3$CO], 28.5 (5-C–*C*H_3'), 46.7, 61.3, 63.8, 79.4, 82.9, 127.9 (Ar-H), 128.3 (Ar-H), 128.7 (Ar-H), 136.0 (Ar-H), 152.9 (C=O), 157.3 (C=O); *m*/*z* (APCI+) 336.2 (35), 280.2 (85), 236.1 (100%), 192.0 (50), 162.0 (30);

HRMS (CI$^+$) (Found: MNa$^+$, 358.1630. $C_{18}H_{25}NO_5Na$ requires 358.1643).

4.1.6. (*S*)-(1-Benzyloxymethyl-2-hydroxy-2-methyl-propyl)carbamic acid *tert*-butyl ester 18. (*S*)-*O*-Benzyl-*N*-Boc-L-serine methyl ester **17** (4 g, 12.9 mmol) was dissolved in tetrahydrofuran (60 mL) and the resulting solution cooled to −78°C in a CO_2/acetone bath. A solution of methyl magnesium bromide in ether (6 g, 17 mL, 50.3 mmol, 3.9 equiv., 3 M solution in ether) was added dropwise to ester **17** over a 15 min period (care: methane evolved). The resulting solution was stirred at −78°C for 4 h and then allowed to warm to room temperature. After 12 h at room temperature the reaction mixture was cooled to 0°C and carefully quenched with aqueous saturated ammonium chloride (100 mL), the reaction mixture was subsequently allowed to warm to room temperature over a 20 min period. The solvent was removed in vacuo and replaced with dichloromethane (200 mL). Transferring the solution containing the crude reaction mixture to a separating funnel, enough aqueous saturated ammonium chloride solution was added so that all the magnesium salts dissolved in the aqueous layer. The aqueous layer was partitioned from the dichloromethane. The dichloromethane was washed with aqueous saturated ammonium chloride (2×100 mL), aqueous brine (2×100 mL), saturated aqueous sodium bicarbonate (2×100 mL) and subsequently dried ($MgSO_4$). Filtering the solution and removal of the solvent in vacuo revealed the title product (*S*)-**18** as a pale yellow crystalline solid (2.7 g, 68%). Purification of product (*S*)-**18** was achieved via flash column chromatography incorporating *n*-pentane/ether (1:1) as the eluent. Pure (*S*)-**18** was returned as a white solid with the following physical characteristics; mp 52–54°C; $[\alpha]_D^{22}$=+27.3 (*c* 1.98, $CHCl_3$); ν_{max} (film) (cm^{-1}) 3432, 3346, 2982, 2934, 1709 (s, C=O), 1494, 1364, 1163; δ_H (400 MHz, $CDCl_3$) 1.19 (3H, s, 2-C–CH_3), 1.28 (3H, s, 2-C–CH_3'), 1.45 [9H, s, (CH_3)$_3$C], 3.27 (1H, s, OH), 3.55 [1H, m, C*H*(NH)], 3.66 (1H, dd, *J*=9.8, 2.7 Hz, CH_ACH$_B$O), 3.89 (1H, dd, *J*=9.8, 2.7 Hz, CH$_A$-CH_BO), 4.47 (1H, AB, *J*=11.8 Hz), 4.56 (1H, AB, *J*=11.8 Hz), 5.40 (1H, br d, *J*=9.1 Hz, N–*H*); δ_C (100.6 MHz, $CDCl_3$) 26.8, 27.6, 28.4, 56.4, 71.4, 72.9, 73.8, 79.3, 127.8, 128.0, 128.5, 137.2 (C=O), 156.1 (C=O); *m*/*z* (APCI+) 332.1 (M+Na$^+$ 20), 265.2 (M−CO_2, 10), 210.1 (M−Boc, 100%), 192 (25); HRMS (CI$^+$) (Found: MH$^+$, 310.2025. $C_{17}H_{28}NO_4$ requires 310.2018).

4.1.7. (*S*)-Benzyloxymethyl-5,5-dimethyloxazolidin-2-one 19. To a solution of tetrahydrofuran (50 mL) containing alcohol (*S*)-**18** (1.7 g, 5.5 mmol) was added potassium *tert*-butoxide in one portion (1.2 g, 10.7 mmol). The reaction was stirred at room temperature for 12 h after which time it was quenched with aqueous saturated ammonium chloride (25 mL). The tetrahydrofuran was removed in vacuo and replaced with dichloromethane (25 mL). The dichloromethane solution was transferred to a separating funnel and washed with aqueous saturated ammonium chloride (3×25 mL), saturated brine (2×25 mL), aqueous saturated sodium bicarbonate (2×25 mL) and subsequently dried ($MgSO_4$). Filtering the solution and removal of the dichloromethane in vacuo yielded a yellow oil. The oil was purified via flash column chromatography using ether as the eluent, the title compound (*S*)-**19** was a white solid (1.06 g, 82%) which displayed the following physical characteristics; mp 35–37°C; $[\alpha]_D^{22}$=−39.64 (*c* 2.5, $CHCl_3$); ν_{max} (film) (cm^{-1}) 3284 (N–H), 2973, 2875, 1744 (s, C=O), 1455, 1371, 1287, 1118, 1091, 1007; δ_H (400 MHz, $CDCl_3$) 1.35 (3H, s, 5-C–CH_3), 1.48 (3H, s, 5-C–CH_3'), 3.49 (2H, m, 4-C–CH_2CH_B), 3.67 (1H, m, 4-C-H), 4.52 (2H, m, CH_2Ph), 6.10 (1H, br s, N–*H*), 7.29–7.38 (5H, m, Ar-*H*); δ_C (100.6 MHz, $CDCl_3$) 21.5, 28.2, 60.5, 69.3, 73.6, 82.2, 127.7, 127.9, 128.5, 137.4, 158.7 (C=O); *m*/*z* (APCI+) 258.1 (100%, M+Na$^+$), 236.1 (95), 210 (10), 192 (60); HRMS (CI$^+$) (Found: MH$^+$, 236.1287. $C_{13}H_{18}NO_3$ requires 236.1287).

4.1.8. (*S*)-4-Benzyloxymethyl-5,5-dimethyl-2-oxo-oxazolidine-3-carboxylic acid *tert*-butyl ester 20. Starting material (*S*)-**19** (200 mg, 0.85 mmol) was dissolved in ether (2 mL) at room temperature. To the ethereal solution was added 4-dimethylaminopyridine (104 mg, 0.85 mmol), di-*tert*-butyl dicarbonate (370 mg, 1.69 mmol) and triethylamine (86 mg, 0.85 mmol). The reaction mixture was stirred for 12 h at room temperature and worked-up as outlined previously for (*S*)-**11**. The title compound was purified via flash column chromatography using ether as the eluent. Purified (*S*)-**20** was a colourless oil that solidified on standing to a white solid (157 mg, 55%). (*S*)-**20** displayed the following characteristics; mp 66–68°C; $[\alpha]_D^{22}$=+53.8 (*c* 0.55, $CHCl_3$); ν_{max} (film) (cm^{-1}) 2972, 1800 (s, C=O), 1718 (C=O), 1366, 1301, 1289, 1159, 1076; δ_H(400 MHz, $CDCl_3$) 1.45 (3H, s, 5-C–CH_3), 1.49 [9H, s, (CH_3)$_3$CO], 1.51 (3H, s, 5-C–CH_3'), 3.63 (1H, dd, *J*=10.0, 2.4 Hz), 3.71 (1H, m), 3.94 (1H, dd, *J*=6.1, 2.3 Hz), 4.52 (2H, s, CH_2Ph), 7.29–7.36 (5H, m, Ar-H); δ_C (100.6 MHz, $CDCl_3$) 21.5, 27.9, 28.6, 62.7, 66.4, 73.4, 80.0, 83.7, 127.65 (Ar-H), 127.9 (Ar-H), 128.5 (Ar-H), 137.3 (Ar-H), 150.0, (C=O), 151.4 (C=O); *m*/*z* (APCI+) 358.18 (50, MNa$^+$), 280.16 (20), 258.15 (65), 236.15 (100%), 192.16 (100), 145.11 (55); HRMS (CI$^+$) (Found: MNH$_4^+$, 353.2076. $C_{18}H_{29}N_2O_5$ requires 353.2083).

4.1.9. (*S*)-4-Hydroxy-5,5-dimethyl-2-oxo-oxazolidine-3-carboxylic acid-*tert*-butyl ester 14. A solution of (*S*)-*N*-Boc-*O*-benzyl-SuperQuat **20** (100 mg, 0.30 mmol) was dissolved in anhydrous methanol (2 mL). To this was added a catalytic amount of 10% palladium on carbon (~10 mg). The resulting solution was vigorously stirred under an atmosphere of hydrogen contained within two balloons inside each other. After stirring for 12 h the solution was filtered through Celite®. The Celite® was eluted with methanol (2×5 mL), the methanol fractions were combined and the solvent evaporated in vacuo. The title compound (*S*)-**14** was returned as a white solid (64 mg, 88%) which displayed the following physical characteristics; mp 133–135°C; $[\alpha]_D^{22}$=+10.2 (*c* 0.5, $CHCl_3$); ν_{max} (KBr) (cm^{-1}) 2979, 1787 (s, C=O), 1700 (C=O), 1395, 1372, 1319; δ_H (400 MHz, $CDCl_3$) 1.49 (3H, s, 5-C–CH_3), 1.51 (3H, s, 5-C–CH_3'), 1.56 [9H, s, (CH_3)$_3$CO], 2.80 (1H, br s, O*H*), 3.83–3.93 (3H, m, 4-C(*H*)CH_ACH_BOH); δ_C (100.6 MHz, $CDCl_3$) 21.4, 27.9, 28.3, 60.4, 65.0, 80.1, 84.5, 150.8 (C=O), 151.4 (C=O); *m*/*z* (APCI+) 268.1 (10, M+Na$^+$), 246.1 (5), 208.1 (5), 190.1 (60), 167.9 (10), 146.1 (100%), 128.1 (20), 116.1 (50); HRMS (CI$^+$) (Found: MNa$^+$, 268.1161. $C_{11}H_{19}NO_5Na$ requires 268.1165).

4.1.10. (*S*)-Carbonic acid *tert*-butyl ester-5,5-dimethyl-2-oxo-oxazolidin-4-yl methyl ester 15. A flask was charged with DMF (2 mL). To the flask was added (*S*)-*N*-Boc-oxazolidin-2-one **14** (23 mg, 0.094 mmol), the resulting solution was stirred and cooled to 0°C in an ice bath. To the cold DMF solution was added oil free potassium hydride (washed with *n*-pentane, 3×5 mL; 5.5 mg, 0.14 mmol). The resulting solution was stirred at 0°C for 2 h, and then quenched at 0°C with a saturated aqueous ammonium chloride solution (2 mL). The aqueous DMF was removed in vacuo, water was added (5 mL) and the organic material extracted with dichloromethane (3×10 mL). The dichloromethane extracts were combined, dried ($MgSO_4$) and filtered. The resulting product was purified via flash column chromatography using ether as the eluent. (*S*)-*O*-Boc-SuperQuat **15** was a white solid (20 mg, 87%) which had essentially the same physical characteristics as the identical compound synthesised previously from (*S*)-**11**; ν_{max} (KBr) (cm^{-1}) 3341 (br), 2917, 1742 (br s, C=O), 1370, 1257; δ_H (400 MHz, $CDCl_3$) 1.43 [3H, s, 5-C–CH_3), 1.49 (9H, s, (CH_3)$_3$CO), 1.51 (3H, s, (5-C–CH'_3), 3.72 (1H, dd, *J*=8.0, 4.5 Hz, 4-C(*H*)N), 4.03 (1H, dd, *J*=11.0, 8.2 Hz, 4-C(H)CH_ACH$_B$O), 4.19 (1H, dd, *J*=11.0, 4.5 Hz, 4-C(H)CH$_A$CH_BO), 5.59 (1H, br s, N–*H*); δ_C (100.6 MHz, $CDCl_3$) 21.6 (5-C–*C*H$_3$), 27.6 [(*C*H$_3$)$_3$CO], 28.0 (5-C–*C'*H$_3$), 59.6, 65.7, 81.8, 83.2, 153.0 (C=O), 157.8 (C=O); HRMS (CI^+) (Found: MH^+, 246.1349. $C_{11}H_{20}NO_5$ requires 246.1341).

4.1.11. (±)-Benzyl-carbamic acid-3,3-dimethyl-oxiranyl methyl ester 39. (*rac*)-Epoxide[20] **38** (573 mg, 5.41 mmol) synthesised from 3-methyl-2-butene-1-ol **37** was dissolved in anhydrous dichloromethane (5 mL), to the dichloromethane solution was added benzyl isocyanate (1.0 g, 7.51 mmol) and a catalytic amount (31 mg, 0.056 mmol, 1 mol%) of bis(dibutylchlorotin) oxide. The reaction was stirred at room temperature. After 48 h removal of the solvent was undertaken in vacuo and the impure carbamate **39** purified via flash column chromatography using a mixture of *n*-pentane/ether as eluent (25:75). The title compound **39** was isolated as a colourless oil (694 mg, 53%); ν_{max} (film) (cm^{-1}) 3336 (br, N–H), 2970, 2932, 1797 (C=O), 1719 (C=O), 1528, 1244, 1148; δ_H (400 MHz, $CHCl_3$) 1.33 (3H, s, 3-C–CH_3), 1.35 (3H, s, 3-C–CH'_3), 3.01 (1H, dd, *J*=7.0, 4.1 Hz, 2-C*H*O), 4.03 (1H, dd, *J*=12.0, 7.0 Hz, 1-OCH_AH$_B$), 4.43 (3H, m, 1-OCH$_A$$H_B$ and CH_A-CH_BPh), 5.12 (1H, br, s, N–*H*), 7.27–7.37 (5H, m, Ar-*H*); δ_C (100.6 MHz, $CDCl_3$) 18.9 (3-C–*C*H$_3$), 24.6 (3-C–*C*H$'_3$), 45.1 (*C*H$_2$Ph), 58.2 (3-*C*–CH$_3$), 60.9 (1-CH$_2$O), 64.0 (2-*C*HO), 127.6 (Ar-H), 128.6 (Ar-H), 128.7 (Ar-H), 138.3 (Ar-H), 156.25 (C=O); *m/z* (APCI+) 236.1 ($M^{++}H^+$, 100%), 218.1 (65), 152 (30) 103.1 (95); HRMS (CI^+) (Found: MH^+, 236.1287. $C_{13}H_{18}NO_3$ requires 236.1291).

4.1.12. (±)-3-Benzyl-4-(1-hydroxy-1-methylethyl)-oxazolidin-2-one 40. A flask was charged with racemic **39** (115 mg, 0.87 mmol) and the carbamate dissolved in tetrahydrofuran (2 mL). The resulting solution was stirred and cooled until the solution reached −20°C. Whilst at −20°C, *n*-BuLi was added dropwise (0.195 mL, 31 mg, 0.48 mmol, 2.5 M solution in hexanes). The reaction mixture was stirred at −20°C for 2 h, after which it was quenched at −20°C with aqueous saturated ammonium chloride (3 mL) and allowed to warm to room temperature over 15 min. The quenched reaction was transferred to a separating funnel and the organic products extracted into ether (3×15 mL). The organic fractions were combined, dried ($MgSO_4$) and filtered. Removal of the solvent in vacuo revealed an oil, the purification of which was undertaken via flash column chromatography using ether as the eluent. The title compound **40** was obtained as a colourless oil (70 mg, 61%) with the following physical characteristics; ν_{max} (film) (cm^{-1}) 3424 (s), 2976, 2933, 1732 (s, C=O), 1428, 1368, 1235, 1149; δ_H (400 MHz, $CDCl_3$) 1.17 (3H, s, CH_3), 1.23 (3H, s, CH'_3), 2.07 (1H, s, OH), 3.55 (1H, dd, *J*=9.3, 5.2 Hz, 5-CH_ACH$_B$), 4.03 (1H, dd, *J*=9.3, 5.2 Hz, 5-CH_ACH$_B$), 4.20 (1H, t, *J*=9.3 Hz, 4-CH), 4.48 (1H, d, *J*=15.0 Hz, PhCH_ACH$_B$), 4.92 (1H, d, *J*=15.0 Hz, PhCH$_A$CH_B); 7.25–7.36 (5H, m, Ar-*H*); δ_C (100.6 MHz, $CDCl_3$) 23.6 [(CH$_3$)$_2$C], 26.5 [(CH$_3$)$_2$C], 48.2, 62.0, 64.6, 73.2, 127.8 (Ar-H), 128.4 (Ar-H), 128.7 (Ar-H), 136.4 (Ar-H), 159.6 (C=O); *m/z* (APCI+) 258.1. (10, M+Na^+), 236.1 (100%), 192 (5); HRMS (CI^+) (Found: MH^+, 236.1287. $C_{13}H_{18}NO_3$ requires 236.1294).

4.1.13. (±)-3-Benzyl-4-hydroxymethyl-5,5-dimethyl-oxazolidin-2-one 41. A flask was charged with alcohol **40** (47 mg, 0.2 mmol) and the oil dissolved in tetrahydrofuran (2 mL). To the cooled (0°C) solution was added oil free sodium hydride (washed with *n*-pentane 3×5 mL, 5.3 mg, 0.22 mmol). The reaction was allowed to warm to room temperature over a 24 h period and then quenched with aqueous saturated ammonium chloride (2 mL). The aqueous tetrahydrofuran was removed in vacuo and replaced with dichloromethane (5 mL), the dichloromethane was washed with aqueous hydrochloric acid (3×5 mL, 1 M), brine (10 mL), water (10 mL) and subsequently dried ($MgSO_4$). Removing the solvent in vacuo allowed the resulting oil to be purified via flash column chromatography using ether as the eluent. The title compound **41** was a colourless oil (33 mg, 71%) with the following physical characteristics; ν_{max} (film) (cm^{-1}) 3410, 2971, 2920, 1720 (s, C=O), 1425; δ_H (400 MHz, $CDCl_3$) 1.36 (3H, s, 5-C–CH_3), 1.44 (3H, s, 5-C–CH'_3), 2.28 (1H, br s, OH), 3.25 (1H, t, *J*=4.7 Hz, 4-CH), 3.72 (2H, br s, CH_ACH_BOH), 4.31 (1H, d, *J*=15.2 Hz, PhCH_ACH$_B$), 4.74 (1H, d, *J*=15.2 Hz, PhCH$_A$-CH_B), 7.27–7.4 (5H, Ar-*H*); δ_C (100.6 MHz, $CDCl_3$) 21.65, 28.6, 46.7, 59.6, 64.0, 79.7, 128.0 (Ar-H), 128.0 (Ar-H), 128.7 (Ar-H), 136.5 (Ar-H), 158.0 (C=O); *m/z* (APCI+) 236.1 (100%), 218.1 (5), 206.1 (10), 192.1 (30), 162.1 (10); HRMS (CI^+) (Found: MH^+ 236.1287. $C_{13}H_{18}NO_3$ requires 236.1293).

4.1.14. (±)-Carbonic acid-3-benzyl-5,5-dimethyl-2-oxo-oxazolidin-4-yl methyl ester *tert*-butyl ester 16 (from 41). A stirred solution of (*rac*)-*N*-benzyl SuperQuat **41** (38 mg, 0.16 mmol) was dissolved in dichloromethane (3 mL). The solution was stirred and 4-dimethylaminopyridine (9.8 mg, 0.08 mmol), di-*tert*-butyl dicarbonate (71 mg, 0.325 mmol) and triethylamine (0.045 mL, 33 mg, 0.33 mmol) were added. The reaction was stirred at room temperature for 12 h and worked-up as for **11**. The title product (*rac*)-**16** was purified via flash column chromatography using *n*-pentane/ether (1:1), **16** was returned as a colourless oil (42 mg, 79%) and possessed essentially the same spectroscopic

characteristics as (*S*)-**16**, the identical compound synthesised previously.

4.1.15. (*S*)-4-Benzyloxymethyl-2-oxo-oxazolidine-3-carboxylic acid *tert*-butyl ester 45. To dichloromethane (20 mL) was added (*S*)-**44** (1.17 g, 5.65 mmol). The resulting solution was stirred whilst 4-dimethylaminopyridine (345 mg, 2.82 mmol), di-*tert*-butyl dicarbonate (2.54 g, 11.64 mmol) and triethylamine (571 mg, 5.64 mmol) were added. The reaction mixture was stirred at room temperature. After 4 h the reaction was diluted with dichloromethane (20 mL) and subsequently washed with aqueous hydrochloric acid (0.1 M, 3×25 mL), aqueous saturated sodium bicarbonate (2×25 mL), water (25 mL) and dried ($MgSO_4$). The solution was filtered and the solvent removed in vacuo. The title compound (*S*)-**45** (1.5 g, 87%) possessed the following physical characteristics; mp 93–96°C; $[\alpha]_D^{22}=+56.3$ (*c* 0.4, $CHCl_3$); ν_{max} (film) (cm^{-1}) 2971, 2929, 2869, 1809 (s, C=O), 1788 (s, C=O), 1713, 1365 (s), 1331, 1285, 1259, 1158 (s), 1082; δ_H (400 MHz, $CDCl_3$) 1.50 [9H, s, $(CH_3)_3CO$], 3.65 [2H, m, 4-C(H)CH_A-CH_BO], 4.35 (3H, m, 4-C*H* and 5-CH_ACH_B), 4.56 (2H, m, PhCH_ACH_B), 7.29–7.38 (5H, m, Ar-*H*); δ_C (100.6 MHz, $CDCl_3$) 27.9 [$(CH_3)_3$C], 54.2 [$(CH_3)_3C$], 64.7, 68.4, 73.45, 83.9, 127.7 (Ar-H), 128.0 (Ar-H), 128.6 (Ar-H), 137.3 (Ar-H), 149.2 (C=O), 152.2 (C=O); *m/z* (APCI+) 330.1 (5, M+Na^+), 252.1 (12). 236.1 (10), 208.1 (45), 182 (100%), 149.9 (15); HRMS (CI^+) (Found: MNH_4 325.1763. $C_{16}H_{25}N_2O_5$ requires 325.1759).

4.1.16. (*S*)-4-Hydroxymethyl-2-oxo-oxazolidine-3-carboxylic acid *tert*-butyl ester 46. (*S*)-*N*-Boc-*O*-benzyl-oxazolidin-2-one **45** (78 mg, 0.25 mmol) was treated with a catalytic amount of 10% palladium on carbon (~10 mg) in anhydrous methanol (5 mL) and placed under hydrogen (balloon). After the reaction was complete the methanol solution was filtered through Celite. The Celite was subsequently washed with methanol (3×5 mL), the combined organic fractions had the solvent removed in vacuo yielding (*S*)-*N*-Boc-4-hydroxymethyl-oxazolidin-2-one **46** as a white solid (64 mg, 82%). (*S*)-**46** had the following characteristics; mp 101–104°C; $[\alpha]_D^{22}=+42.8$ (*c* 0.54, $CHCl_3$); ν_{max} (film) (cm^{-1}) 3489, 2980, 2934, 2361, 1798 (s, C=O), 1722 (s, C=O), 1478, 1371, 1299, 1257, 1158; δ_H (400 MHz, $CDCl_3$) 1.55 [9H, s, $(CH_3)_3CO$], 3.78 (1H, m), 3.88 (1H, m), 4.28–4.41 (3H, m); δ_C (100.6 MHz, $CDCl_3$) 27.9 [$(CH_3)_3$C], 53.2, 62.3, 64.2, 84.5, 149.9 (C=O), 152.4 (C=O); *m/z* (APCI+) 236.1 (5, M^++Na), 218.0 (12). 182.0 (20), 176.0 (100%), 160 (20), 135.8 (20).

4.2. X-Ray crystal structure determination for (*S*)-46

Data were collected using an Enraf-Nonius CAD4 diffractometer with graphite monochromated Mo Kα radiation using standard procedures at room temperature. The structure was solved by direct methods (Sir92), all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.[28]

X-Ray crystal structure data for (*S*)-**46**: $[C_{18}H_{30}N_2O_{10}]$; M=434.44, monoclinic, space group $P1211$, a=9.6450(4) Å, b=11.2679(5) Å, c=11.2357(5) Å, β=114.111(4)°, U=1114.59(9) $Å^3$, Z=2, μ=0.106 cm^{-1}, colourless block, crystal dimensions=0.4×0.4×0.4 mm^3. A total of 2384 unique reflections were measured for $1.99<\theta<26.33$ and 2272 reflections were used in the refinement. The final parameters were wR_2=0.0402 and R_1=0.0335 [$I>3\sigma(I)$].

Crystallographic data (excluding structure factors) has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC189191. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].

4.2.1. (*S*)-2-Oxo-oxazolidine-3,4-dicarboxylic acid-3-*tert*-butyl ester-4-methyl ester 48. A solution of (*S*)-**47**[24b] (3.00 g, 20.7 mmol) was dissolved in dichloromethane (50 mL) and the stirred solution subsequently cooled to 0°C. To this solution was added 4-dimethylaminopyridine (2.3 g, 18.8 mmol), di-*tert*-butyl dicarbonate (9.00 g, 41.4 mmol) and triethylamine (4.1 g, 41 mmol). The reaction was stirred for 12 h and allowed to warm to room temperature where upon it was worked-up as outlined for (*S*)-**11**. The title product (*S*)-**48** was crystallised from ether (2.0 g, 40%) and possessed the following physical characteristics; mp 100–102°C (ether), $[\alpha]_D^{22}=-65.5$ (*c* 0.7, $CHCl_3$); ν_{max} (KBr) (cm^{-1}) 3011, 2978, 2950, 1806 (s, C=O), 1748 (s, C=O), 1724 (s, C=O), 1486, 1442, 1400, 1351, 1295, 1260, 1212, 1189, 1078, 771; δ_H (400 MHz, $CDCl_3$) 1.51 [9H, s, $(CH_3)_3CO$], 3.83 (3H, s, CO_2CH_3), 4.27 (1H, dd, J=9.3, 3.8 Hz, 5-CH_ACH$_B$), 4.51 (1H, t, J=9.3 Hz, 4-C(*H*)N), 4.79 (1H, dd, J=9.3, 3.8 Hz, 5-CH$_A$CH_B); δ_C (100.6 MHz, $CDCl_3$) 27.8 [$(CH_3)_3$C], 53.1, 56.1, 63.6, 84.7, 148.5 (C=O), 151.1 (C=O), 169.3 (C=O); *m/z* (APCI+) 268.0 (20, M+Na^+), 245.9 (10), 235.9 (10), 189.9 (80), 145.8 (100%); HRMS (CI^+) (Found: MNH_4 263.1243. $C_{10}H_{19}N_2O_6$ requires 263.1243).

4.2.2. (*R*)-4-Hydroxymethyl-2-oxo-oxazolidine-3-carboxylic acid *tert*-butyl ester 46. A flask was charged with anhydrous ethanol (3 mL) and subsequently cooled to 0°C in an ice bath. To the cold ethanol was added sodium borohydride (62 mg, 1.64 mmol). A separate flask was charged with ester (*S*)-**48** (100 mg, 0.41 mmol) and ethanol (2 mL) this solution was stirred and cooled to 0°C in an ice bath. The cold ester (*S*)-**48** solution was added dropwise to the ethanolic sodium borohydride solution at 0°C, the resulting mixture was stirred at 0°C until tlc analysis (eluent: ether) indicated all the starting material had been consumed. Whilst at 0°C the reaction mixture was quenched by adding the resulting ethanolic solution to an excess of pH 4 phosphate buffer, ensuring that the pH of the resulting solution did not go above pH 6, by adding, if necessary more pH 4 buffer. Allow the quenched reaction mixture to stir for a further 2 h at room temperature and then remove the ethanol in vacuo. Extract the organic components into ethyl acetate (4×10 mL). Dry the combined ethyl acetate fractions ($MgSO_4$), filter the solution and remove the ethyl acetate in vacuo. (*R*)-**46** was purified via flash column chromatography using ether as the eluent. The title compound was a colourless oil (56 mg, 64%), which

solidified on standing. The product could be further purified by crystallisation from ether; mp 106–108°C (ether); $[\alpha]_D^{22}=-45.6$ (*c* 0.83, $CHCl_3$); ν_{max} (KBr) (cm^{-1}) 3523, 2985, 2935, 1803 (s, C=O), 1706 (C=O), 1407, 1370, 1307, 1261, 1163, 1084, 1047; δ_H (400 MHz, d_6-benzene) 1.41 [9H, s, $(CH_3)_3CO$], 2.19 (1H, br t, O*H*, *J*=5.5 Hz), 3.13 (1H, m), 3.29 (1H, m), 3.41 (1H, m), 3.56 (2H, m); δ_C (100.6 MHz, d_6-benzene) 28.1 [$(CH_3)_3CO$], 56.3, 62.2, 63.9, 83.7, 151.0 (C=O), 152.3 (C=O); *m/z* (APCI+) 240.03. (80, $M+Na^+$), 183.9 (25), 161.8 (40), 139.8 (100%), 117.8 (70).

4.2.3. (±)-Benzylcarbamic acid oxiranylmethyl ester 49. (*rac*)-Glycidol (573 mg, 7.73 mmol) was dissolved in dichloromethane (5 mL) to this solution was added benzyl isocyanate (1.0 g, 7.51 mmol) and a catalytic amount of bis(dibutylchlorotin) oxide (43 mg, 1 mol%). The resulting solution was stirred for 48 h at room temperature. The reaction mixture was subsequently washed with aqueous hydrochloric acid (0.5 M, 3×25 mL), water (3×25 mL) and dried ($MgSO_4$). Removal of the solvent in vacuo yielded a pale yellow oil which was purified via flash column chromatography using a mixture of *n*-pentane and ether as the eluent (25:75). The title compound was isolated as a colourless oil (992 mg, 62%) with the following physical characteristics; ν_{max} (film) (cm^{-1}) 3328 (br, N–H), 2945, 1707 (s, C=O), 1528, 1248, 1148; δ_H (400 MHz, $CDCl_3$) 2.64 (1H, m), 2.83 (1H, t, *J*=4.5 Hz), 3.21 (1H, m), 3.90 (1H, dd, *J*=12.2, 6.4 Hz), 4.37 (2H, d, *J*=6.0 Hz), 4.46 (1H, dd, *J*=12.2, 2.9 Hz), 5.40 (1H, br s, N–*H*), 7.26–7.36 (5H, m, Ar-H); δ_C (100.6 MHz, $CDCl_3$) 44.6, 45.0, 49.8, 65.5, 127.5 (Ar-H), 128.4 (Ar-H), 128.6 (Ar-H), 138.3 (Ar-H), 156.1 (C=O); *m/z* (APCI+) 208.1 ($M^{++}H^+$, 100%), 152 (5), 108.9 (5).

4.2.4. (±)-3-Benzyl-4-hydroxymethyl-oxazolidine-2-one 32. (*rac*)-*N*-Benzyl carbamate **49** (210 mg, 1.0 mmol) was added to a flask and the solid dissolved in tetrahydrofuran (2 mL), the resulting solution was cooled to 0°C in an ice bath. To the carbamate solution was added *n*-BuLi (65 mg, 1.01 mmol, 2.5 M solution in hexanes, Aldrich). The resulting mixture was stirred for 2 h at 0°C. Whilst at 0°C the reaction mixture was quenched by adding saturated aqueous ammonium chloride (2 mL). The majority of the solvent was removed in vacuo, and the remaining aqueous phase extracted with dichloromethane (3×10 mL). The combined organic layers were washed with aqueous hydrochloric acid (1 M, 3×25 mL), saturated brine (2×25 mL), water (2×25 mL) and dried ($MgSO_4$). Filtering the solution and removal of the solvent in vacuo, yielded a yellow oil. Purification of oxazolidin-2-one **32** was achieved via flash column chromatography using ether as the eluent. (*rac*)-*N*-Benzyl-oxazolidin-2-one **32** (155 mg, 74%) had the following physical characteristics; ν_{max} (film) (cm^{-1}) 3415 (br s, OH), 2922, 1726 (s, C=O), 1479, 1444, 1252, 1093, 1035; δ_H(400 MHz, $CDCl_3$) 3.20 (1H, br s, O*H*), 3.52 (1H, br d, *J*=10.4 Hz), 3.71 (2H, m), 4.28 (3H, m), 4.72 (1H, d, *J*=15.3 Hz, $PhCH_ACH_B$), 7.27–7.36 (5H, m, Ar-H); δ_C(100.6 MHz, $CDCl_3$) 46.2, 55.7, 60.3, 64.6, 128.0 (×2, Ar-H), 128.9 (Ar-H), 136.0 (Ar-H), 159.1 (C=O); *m/z* (APCI+) 208 (M^+H^+, 100%), 164 (5), 130 (5); HRMS (CI^+) (Found: MH^+ 208.0974. $C_{11}H_{14}NO_3$ requires 208.0973).

4.2.5. (±)-Carbamic acid 3-benzyl-2-oxo-oxazolidin-4-yl methyl ester *tert*-butyl ester 50 (from 32). To a stirred solution of dichloromethane (5 mL) was added (*rac*)-**32** (87 mg, 0.42 mmol). To the resulting solution was added 4-dimethylaminopyridine (25 mg, 0.2 mmol), di-*tert*-butyl dicarbonate (183 mg, 0.84 mmol) and triethylamine (85 mg, 0.84 mmol). The reaction mixture was stirred at room temperature for 5 h. After which the reaction was diluted with dichloromethane (5 mL) and subsequently washed with aqueous hydrochloric acid (0.1 M, 3×10 mL), aqueous saturated sodium bicarbonate (2×10 mL), water (10 mL) and dried ($MgSO_4$). The solution was filtered and the solvent removed in vacuo. The title compound (*rac*)-**50** (108 mg, 84%) possessed the following physical characteristics; ν_{max} (film) (cm^{-1}) 2982, 2911, 1740 (br s, C=O), 1724 (C=O), 1455, 1278, 1251; δ_H (400 MHz, $CDCl_3$) 1.48 [9H, s, $(CH_3)_3CO$], 3.81 (1H, m), 4.03 (1H, dd, *J*=11.7, 4.3 Hz), 4.12–4.21 (3H, m), 4.33 (1H, t, *J*=9.0 Hz), 4.83 (1H, d, *J*=15.2 Hz, $PhCH_ACH_B$), 7.29–7.375 (5H, m, Ar-H); δ_C (100.6 MHz, $CDCl_3$) 27.6 [$(CH_3)_3CO$], 46.5, 53.1, 64.3, 64.7, 83.1, 128.0 (Ar-H), 128.2 (Ar-H), 128.8 (Ar-H), 135.6 (Ar-H), 152.9 (C=O), 158.2 (C=O); *m/z* (APCI+) 330.3 (5, $M+Na^+$), 308.3 (5, $M+H^+$), 252.2 (100%), 208.25 (45). HRMS (CI^+) (Found: MNa^+ 330.1318. $C_{16}H_{21}NO_5Na$ requires 330.1317).

4.2.6. (*S*)-Carbonic acid-3-benzyl-2-oxo-oxazolidin-4-ylmethyl ester *tert*-butyl ester 50 (from 46). A flask was charged with DMF (2 mL). To this was added (*R*)-*N*-Boc-oxazolidin-2-one **46** (57 mg, 0.26 mmol), the resulting solution was stirred and cooled to 0°C in an ice bath. To the cold DMF solution was added oil free potassium hydride (washed with *n*-pentane, 3×5 mL; 16 mg, 0.40 mmol). The resulting solution was stirred at 0°C for 2 h, then benzyl chloride (freshly distilled) was added (35 mg, 0.27 mmol) and a catalytic amount (50 mg) of 18-crown-6. The solution was stirred for a further 12 h warming from 0°C to room temperature. The reaction was quenched with aqueous saturated ammonium chloride (1 mL). The aqueous DMF was removed in vacuo, water was added (5 mL) and the organic products extracted with dichloromethane (3×10 mL). The dichloromethane was dried ($MgSO_4$), filtered and the crude product purified via flash column chromatography using ether/*n*-pentane (1:1) to give the title compound (*S*)-**50** (68 mg, 85%); mp 110–113°C; $[\alpha]_D^{22}=+10.5$ (*c* 1.54, $CHCl_3$).

4.2.7. (*S*)-Carbonic acid *tert*-butyl ester-3-(4-nitro-benzyl)-2-oxo-oxazolidin-4-yl methyl ester 51. A flask was charged with DMF (1 mL). To the flask was added (*R*)-*N*-Boc-oxazolidin-2-one **46** (25 mg, 0.12 mmol), the resulting solution was stirred whilst being cooled to 0°C. To the cold DMF solution was added oil free potassium hydride (washed with *n*-pentane, 5 mg, 0.13 mmol). The resulting solution was stirred at 0°C for 2 h and 4-nitrobenzyl bromide was added in one portion (50 mg, 0.23 mmol). The reaction was allowed to warm to room temperature over 12 h under argon and then quenched with aqueous saturated ammonium chloride (1 mL). The aqueous DMF was removed in vacuo, water was added (5 mL) and the crude product extracted with dichloromethane (3×10 mL). The dichloromethane fractions were combined, dried ($MgSO_4$), filtered and the crude product purified via flash column

chromatography using a mixture of ether and *n*-pentane (75:25) as the eluent. The title compound (*S*)-**51** was a white solid (23 mg, 56%) which displayed the following physical characteristics; ν_{max} (KBr) (cm^{-1}) 2980, 2921, 1744 (s, C=O), 1733 (s, C=O), 1606, 1518, 1409, 1347, 1258, 1158; δ_H (400 MHz, $CDCl_3$) 1.46 [9H, s, $(CH_3)_2CO$], 3.87 (1H, m), 4.01 (1H, dd, J=11.8, 5.0 Hz), 4.17 (2H, m), 4.43 (2H, m), 4.78 (1H, d, J=15.8 Hz, $PhCH_ACH_B$), 7.52 (2H, d, J=8.7 Hz, Ar-*H*), 8.23 (2H, d, J=8.7 Hz, Ar-H *ortho* to nitro); δ_C (100.6 MHz, $CDCl_3$) 30.3 [$(CH_3)_3CO$], 48.9, 56.5, 67.0, 67.75, 81.8, 86.1, 126.7, 131.6, 146.1, 150.4, 155.4 (C=O), 160.9 (C=O); *m/z* (APCI+) 297.0 (10), 253.0 (10), 221.0 (25), 195.0 (10), 161.9 (30), 121.9 (65), 118.1 (100%), 106.1 (90).

4.3. X-Ray crystal structure determination for (*S*)-51

Data were collected using an Enraf-Nonius CAD4 diffractometer with graphite monochromated Cu Kα radiation using standard procedures at room temperature. The structure was solved by direct methods (Sir92), all non-hydrogen atoms were refined with anisotropic thermal parameters. The carbonate residue was modelled as disordered equally over two sites. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.[28]

X-Ray crystal structure data for (*S*)-**51**: [$C_{16}H_{16}N_2O_7$]; M=348.31, orthorhombic, space group $P212121$, a=6.0043(5) Å, b=10.846(1) Å, c=26.727(3) Å, U=1740.61(3) Å^3, Z=4, β=0.902 cm^{-1}, colourless block, crystal dimensions=0.2×0.4×0.8 mm. A total of 2081 unique reflections were measured for $3.31<\theta<74.23$ and 1907 reflections were used in the refinement. The final parameters were wR_2=0.0748 and R_1=0.0599 [$I>1\sigma(I)$].

Crystallographic data (excluding structure factors) has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC189192. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].

4.3.1. (*R*)-3-Benzyl-4-hydroxymethyloxazolidin-2-one 32. A flask was charged with (*S*)-*N*-benzyl-*O*-Boc-oxazolidin-2-one **50** (46 mg, 0.15 mmol) dissolved in tetrahydrofuran (5 mL). To the tetrahydrofuran solution was added aqueous hydrochloric acid (2 mL, 1 M). The resulting solution was heated at reflux for 30 min. Removing the solvent in vacuo and extracting the solution with dichloromethane (3×10 mL) allowed the *N*-benzyl oxazolidin-2-one to be washed with water (10 mL) and dried ($MgSO_4$). Filtering and removal of the solvent in vacuo yielded an oil which was purified via flash column chromatography using ether as the eluent. The purified title product (*R*)-**32** (24 mg, 76%) was isolated as an oil and possessed the following physical characteristics; $[\alpha]_D^{23}$=+29.0 (c 0.17, $CHCl_3$). Lit[17b] +29.8, (c 1.0, $CHCl_3$); ν_{max} (KBr) (cm^{-1}) 3376 (s), 2931, 2880, 1723 (s, C=O), 1448, 1252, 1087; δ_H (400 MHz, d_6-benzene) 2.58 (1H, m, O*H*), 2.84–2.94 (2H, m), 3.18–3.23 (1H, m), 3.52 (1H, t, J=8.7 Hz), 3.82 (1H, dd, J=8.5, 5.8 Hz), 4.02 (1H, d, J=15.3 Hz, $PhCH_ACH_B$), 4.67 (1H, d, J=15.3 Hz, $PhCH_ACH_B$), 7.00–7.15 (5H, Ar-*H*); δ_C NMR (100 MHz, d_6-benzene) 46.5, 55.9, 60.5, 64.3, 137.3 (Ar-H), rest of the Ar-H peaks obscured by C_6D_6 solvent peaks, 159.4 (C=O); *m/z* (APCI+) 208.2 (100%, $M+H^+$), 164.1 (5), 130.1 (25), 122.0 (5); HRMS (CI^+) (Found: MH^+ 208.0972. $C_{11}H_{14}NO_3$ requires 208.0973).

4.3.2. (*R*)-Propionic acid 3-benzyl-2-oxo-oxazolidin-4-yl methyl ester 52. (*R*)-*N*-Benzyl-oxazolidin-2-one **32** (130 mg, 0.63 mmol) was dissolved in dichloromethane (5 mL). To this solution was added propionic anhydride (164 mg, 1.26 mmol), 4-dimethylaminopyridine (77 mg, 0.63 mmol) and triethylamine (0.26 mL, 190 mg, 1.88 mmol). The solution was stirred for 12 h at room temperature and then worked-up as outlined for (*S*)-**11**. The crude product was purified via flash column chromatography using *n*-pentane/ether (1:1) as the eluent. The title compound (*R*)-**52** was a colourless oil (150 mg, 91%) with the following physical characteristics; $[\alpha]_D^{23}$=+10.0 (c 1.35, $CHCl_3$); ν_{max} (film) (cm^{-1}) 2983, 2940, 1759–1721 (br s, C=O), 1643, 1419, 1234, 1178; δ_H (400 MHz, $CDCl_3$) 1.14 [3H, t, J=7.6 Hz, CH_3CH_2CO], 2.35 (2H, q, J=7.6 Hz, CH_3CH_2CO), 3.83 (1H, m), 4.05 (1H, dd, J=12.0, 3.6 Hz), 4.14–4.21 (2H, m), 4.25 (1H, dd, J=12, 4 Hz), 4.35 (1H, t, J=9.0 Hz), 4.82 (1H, d, J=15.3 Hz, $PhCH_ACH_B$), 7.27–7.39 (5H, m, Ar-H); δ_C (100 MHz, $CHCl_3$) 8.9 (CH_3CH_2), 27.3 (CH_3CH_2), 46.4, 53.2, 61.8, 64.5, 128.0 (Ar-H), 128.9 (×2, Ar-H), 135.6 (Ar-H), 158.2 (C=O), 173.9 (C=O); *m/z* (APCI+) 264.2 (100%), 208.0 (30), 164 (10).

4.3.3. 4-Hydroxymethyl-3-(2-oxo-1-phenylbutyl)-oxazolidin-2-one 53/54. A flask was charged with oxazolidin-2-one **52** (108 mg, 0.21 mmol) and the solid dissolved in tetrahydrofuran (1 mL). The tetrahydrofuran solution was cooled to −78°C (acetone/CO_2) and a solution of LDA in tetrahydrofuran (0.84 mL, 44 mg, 0.42 mmol, 2 equiv., 0.5 M solution) was added dropwise. The reaction mixture changes from a clear to yellow solution within 15 min. After 30 min benzyl bromide (70 mg, 0.41 mmol) was added and the reaction was left stirring at −78°C for a further 2.5 h whereupon it was quenched with an aqueous saturated ammonium chloride solution (3 mL). The quenched reaction mixture was allowed to warm to room temperature over 15 min. The organic components of the reaction mixture were extracted with dichloromethane (3×10 mL), the combined dichloromethane fractions were dried ($MgSO_4$), filtered and the solvent removed in vacuo. The resulting mixture of products (tlc analysis, eluent; ether) were separated via flash column chromatography using, in the first instance, ether as the eluent to remove unreacted starting material **52** (37%). After which changing the solvent from ether to chloroform allowed the partial separation of the ketones **53/54** (38 mg, 35%). Of this mixture the major component **53** was separated and isolated as a white solid (8 mg, 7.4%). The impure minor fraction **54** (contaminated with the major fraction **53**) was isolated as an oily liquid. The major component (**53**) had the following physical characteristics; mp 110–113°C; ν_{max} (KBr) (cm^{-1}) 3468, 2942, 2881, 1742 (s, C=O), 1712 (s, C=O), 1418, 1246, 1117; δ_H (400 MHz, $CDCl_3$) 1.14 [3H, t, J=7.3 Hz, CH_3CH_2CO], 2.60 (2H, m, CH_3CH_2CO), 3.21 (2H, m), 3.58 (1H, br d, J=12.3 Hz), 4.24 (1H, t, J=8.4 Hz), 4.44 (2H, m), 5.92 (1H, s, NC*H*CO), 7.18–7.49 (5H, m, Ar-*H*); δ_C

(100 MHz, $CDCl_3$) 8.0 (CH_3CH_2), 34.3, 55.8, 61.6, 65.3, 67.5, 129.8, 129.9, 129.9, 131.6, 159.1 (C═O), 211.8 (C═O); *m/z* (APCI+) 264.2 (50%), 246.2 (15), 220.1 (5), 147.1 (100%); HRMS (CI^+) (Found: MNa^+ 286.1055). $C_{14}H_{17}NO_4Na$ requires 286.1068). Key ^1H NMR data for ketone **54** that is significantly different to **53** δ_H (400 MHz, $CDCl_3$) 3.01 (1H, br m), 5.48 (1H, s).

4.3.4. 2-Methyl-3-phenylpropionic acid-3-benzyl-2-oxo-oxazolidin-4-yl methyl ester 55/56. A flask was charged (*R*)-*N*-benzyl-oxazolidin-2-one **32** (5.5 mg, 0.026 mmol) the solid was dissolved in dichloromethane (0.5 mL) and the flask cooled to 0°C in an ice bath. To the dichloromethane was added α-methylhydrocinnamoyl chloride[26] (0.008 mL, 5.4 mg, 0.03 mmol) followed by dropwise addition of triethylamine (5.4 mg, 0.05 mmol). The resulting solution was stirred for 12 h, and allowed to warm to room temperature. After 12 h the reaction was quenched by the addition of aqueous saturated ammonium chloride (2 mL) and diluted with dichloromethane (5 mL). The dichloromethane layer was separated and the aqueous layer further extracted with dichloromethane (2×3 mL). The combined organic layers were washed with aqueous hydrochloric acid (0.1 M, 3×10 mL), saturated brine (3×10 mL), saturated aqueous sodium bicarbonate and dried ($MgSO_4$). Filtering the solution and removing the solvent in vacuo yielded ester **55/56**. The product was purified via flash column chromatography using a mixture of ether and *n*-pentane (75:25) as the eluent. A mixture of epimers **55/56** were isolated as a pale yellow oil (5.8 mg, 64%) with the following physical characteristics; ν_{max} (film) (cm^{-1}) 2971, 2924, 1744 (s, C═O), 1728 (s, C═O), 1492, 1452, 1417, 1255, 1149, 1082; δ_H (400 MHz, $CDCl_3$) 1.12 (3H, m), 2.58–2.71 (3H, m), 2.85 [1H, dd, J=13.8, 7.8 Hz), 3.56 (1H, m), 3.80–3.98 (3H, m), 4.02–4.16 (1H, m), 4.67 (1H, t, J=15.4 Hz), 7.05–7.29 (10H, m, Ar-H); δ_C (100.6 MHz, $CDCl_3$) 17.4 (CH_3), 40.4, 41.8, 46.7, 53.5, 62.2, 65.0, 126.9 (Ar-H), 127.0 (Ar-H), 128.5 (Ar-H), 128.9 (Ar-H), 129.4 (Ar-H), 136.0 (Ar-H), 139.4 (Ar-H), 139.5 (Ar-H), 158.6 [OC(O)N], 176.1 [OC(O)CH]; *m/z* (APCI+) 354.3 ($M^{++}H^+$, 100%), 237.2 (10), 208.2 (70), 190.1 (5); HRMS (CI^+) (Found: MH^+ 354.1705. $C_{21}H_{24}NO_4$ requires 354.1713).

Acknowledgements

We are grateful to Drs T. M. Claridge and B. O'Dell (Dyson Perrins Laboratory, University of Oxford) for invaluable help and assistance with providing and interpretation of NMR data.

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