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Assembly intermediates in polyketide biosynthesis: enantioselective syntheses of β-hydroxycarbonyl compounds

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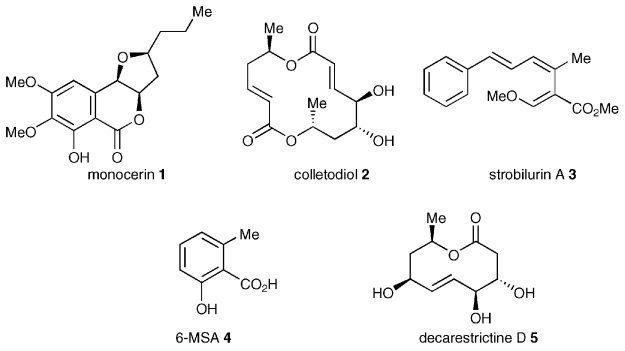
A versatile approach for the enantioselective synthesis of functionalised β-hydroxy *N*-acetylcysteamine thiol esters has been developed which allows the facile incorporation of isotopic labels. It has been shown that a remarkable reversal of selectivity occurs in the titanium mediated aldol reaction of acyloxazolidinone **7** using either (*S*)- or (*R*)-*tert*-butyldimethylsilyloxybutanal. The aldol products are valuable intermediates in the synthesis of 4-hydroxy-6-substituted δ-lactones.

Introduction

In vivo and *in vitro* studies to establish the exact sequence of events in the chain assembly phase of polyketide biosynthesis require the synthesis of putative intermediates, usually in enantioenriched form and ideally incorporating vicinal carbon-13 labels to facilitate the analysis of products from incorporation experiments by NMR spectroscopy. *N*-Acetylcysteamine thiol esters (NAC) have been shown to be recognised and processed by the polyketide biosynthetic enzymes often more efficiently than the corresponding acids or esters.[1] In addition putative assembly intermediates are required in unlabelled form as standards for analysis of culture extracts of heterologous gene expression experiments by HPLC.[2]

A common structural feature of many of the target compounds is the β-hydroxycarbonyl functionality. For example, studies on the biosynthesis of monocerin **1**[3] and colletodiol **2**[4] require the synthesis of both enantiomers of the NAC thiol esters of 3-hydroxyhexanoic and 3-hydroxybutanoic acids respectively. To elucidate the biosynthetic pathway to the important antifungal strobilurins **3**[5] access to the corresponding NAC thiol esters of 3-hydroxy-3-phenylpropanoic acid is needed whereas for studies on 6-methylsalicylic acid **4**[6] the NAC thiol esters of 3-hydroxy-5-oxohexanoic acid are required. While some of these compounds have been prepared previously,[7] the routes differ widely and are not suitable for the facile synthesis of both enantiomers or for the incorporation of vicinal ^{13}C-labelling. In a preliminary communication[8] we have described a general method for the synthesis of these β-hydroxy NAC thiol esters that fulfils the above criteria. In this paper the syntheses of these compounds are reported in full and the methodology extended to the preparation of 4-hydroxy-6-methyl-δ-lactones derived from 3,5-dihydroxyhexanoic acid which are required for biosynthetic studies on a range of polyketide derived natural products including colletodiol and the important family of decanolides, the decarestrictines *e.g.* **5**, which exhibit cholesterol lowering activity.[9] The studies have not only given access to the target putative biosynthetic intermediates but have also given a further fascinating insight into factors effecting the stereochemical outcome of the aldol reaction of more general application in synthesis.



Results and discussion

β-Hydroxycarbonyl compounds can be prepared by directed aldol methods using chiral auxiliaries such as Evans' oxazolidinones. The boron[10] and titanium[11] enolates derived from α-substituted acetyl oxazolidinones give high *syn*-selective aldol condensations. In contrast, their simple acetyl analogues give low degrees of diastereoselectivity. This is generally seen as a disadvantage which can be overcome by various ploys including for example the use of a chromium-Reformatsky reaction or *via* the thio analogues of the oxazolidinone.[12] For biosynthetic studies where both enantiomers are often required, this lack of selectivity can be used to an advantage for the efficient, cost-effective preparation of both desired biosynthetic intermediates, provided the diastereoselective aldol products are readily separable.[13]

The known[10] acetyl oxazolidinone **7** was prepared in 95% yield by acetylation of the valine-derived Evans' auxiliary **6** which in turn was synthesised by the method of McKillop and coworkers (Scheme 1).[14] The reaction may be readily modified for the efficient incorporation of carbon-13 labels at C-1′ and C-2′ of **7** using sodium [1,2-^{13}C$_2$]acetate as the source of isotopic labels.[15] Reaction of **7** with $TiCl_4$, $^{i}Pr_2EtN$ and an electrophile, either ethanal, butanal or benzaldehyde gave the aldol products **8–13** in good yields and as approximately a 2 : 1 mixture of diastereomers in each case. These were readily separated by flash chromatography. It was interesting to note that the ^{1}H-NMR spectrum of each of the minor diastereomers **9, 11** and **13**, showed a well-resolved ABX pattern for the signals assigned to 2′-H_2 whereas for the major diastereomers **8, 10** and **12** the signals assigned to these protons appeared as a poorly defined multiplet.[8] Whilst these data could be taken as diagnostic that the reaction had proceeded with similar stereofacial selectivity in each case, it was necessary to confirm this hypothesis by conversion of the aldol products to known compounds (Scheme 2). Thus the major diastereomers **8** and **10**

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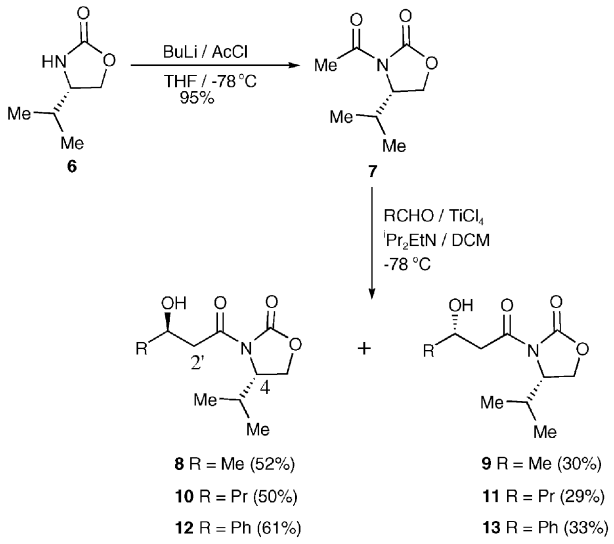


Scheme 1

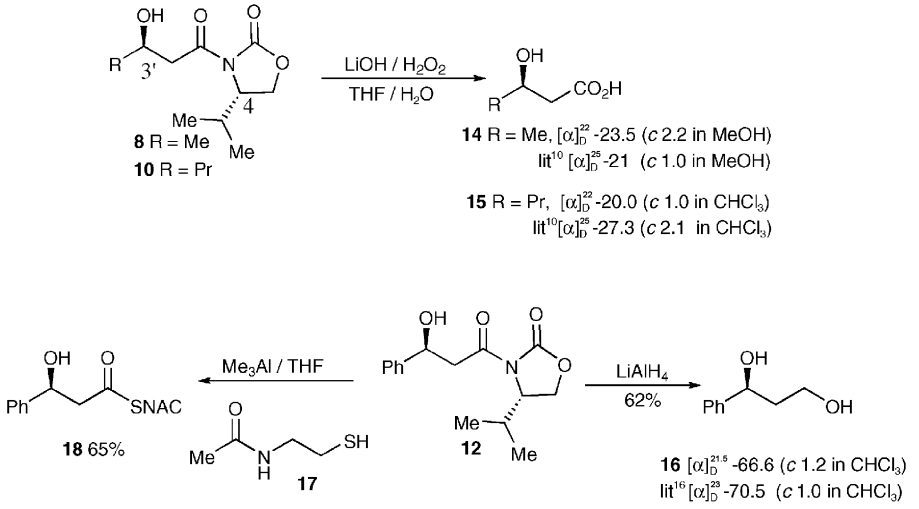
from the aldol reactions with ethanal and butanal respectively, were separately converted to the corresponding β-hydroxy acids **14** and **15** respectively using lithium hydroxide and comparison of their optical rotations with literature values[10] confirmed that the major diastereomers **8** and **10** had the absolute configuration (3′*R*,4*S*). In addition, reductive cleavage of the auxiliary in the benzaldehyde derived aldol product **12** gave the known[16] diol **16** verifying that **12** had the absolute configuration (3′*S*,4*S*). Thus it was apparent that with each electrophile, the aldol reaction had proceeded with similar stereofacial control.

Problems have been reported in the conversion of β-hydroxy acids to NAC thiol esters using standard carbodiimide coupling conditions.[7] Thus ideally a direct method for the conversion of the aldol products **8–13** to their corresponding thiol esters was required. Whilst oxazolidinones may be cleaved under a range of conditions, we found that treatment of **8** with either the lithium salt or sodium salt of *N*-acetylcysteamine **17** led to recovery of the cleaved auxiliary **6** and the starting thiol, none of the required thiol ester was detected. It has been shown that β-hydroxyacylimidazolines can be efficiently converted to the corresponding Weinreb amides using trimethylaluminium and *N*,*O*-dimethylhydroxylamine hydrochloride[17] and Corey and Beames[18] reported that esters may be converted to thiol esters using thiols in the presence of Me_3Al. In addition, Tsantrizos and coworkers[19] have converted methyl (*R*)-*tert*-butyldimethylsilyloxyheptanoate to the corresponding NAC thiol ester using Me_3Al and *N*-acetylcysteamine in benzene. Thus we were gratified to find that similar treatment of the phenyl analogue **12** with *N*-acetylcysteamine **17** and trimethylaluminium allowed direct conversion to the NAC thiol ester **18** in 65% yield (Scheme 2).

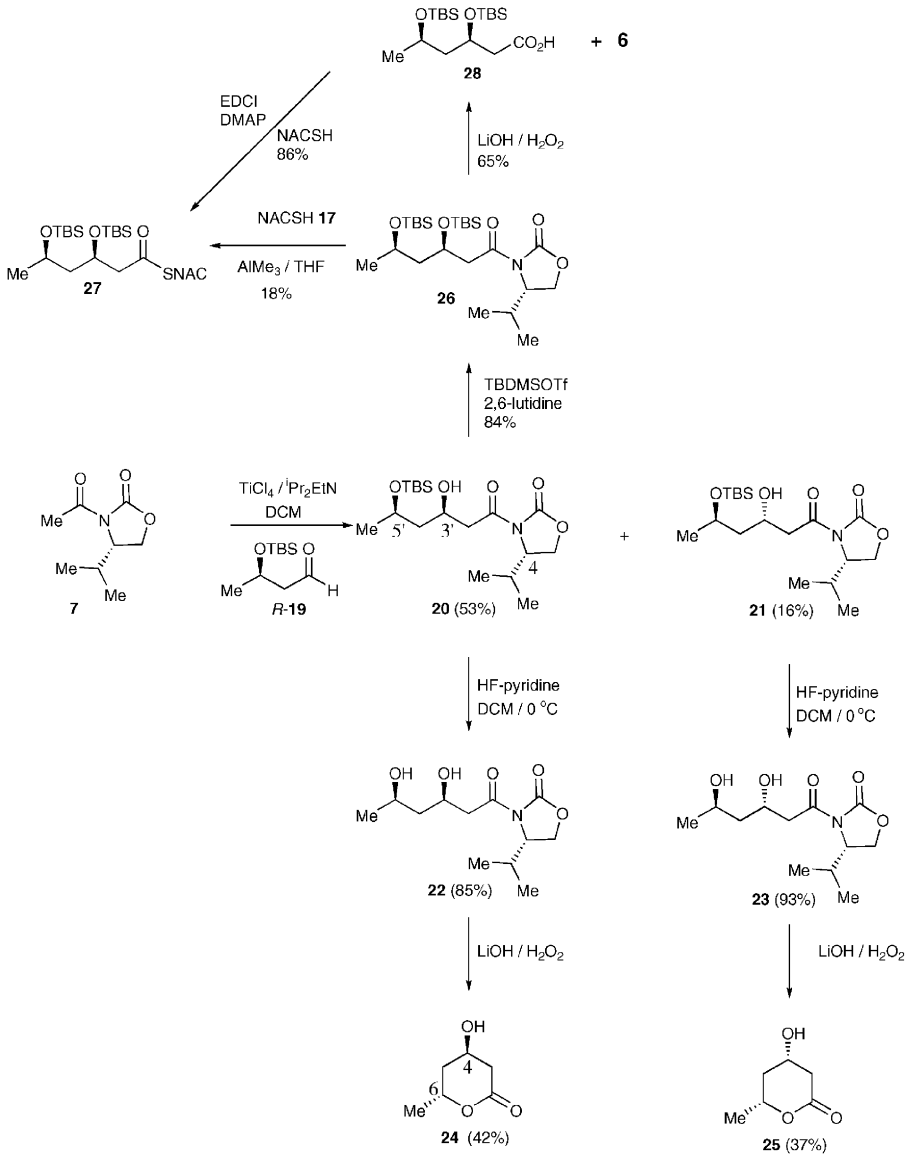
The biosynthesis of the decarestrictines (*e.g.* **5**) in *Penicillium simplicissimum* is proposed to proceed *via* reduction of polyketide synthase (PKS) bound (*R*)-5-hydroxy-3-oxohexanoate to either the (3*R*,5*R*)- or (3*S*,5*R*)-diol followed by dehydration to give the protein-bound (3*Z*,5*R*)-hydroxyhexenoate.[20] However the stereochemical outcome of the reduction is not known. A similar reduction is proposed to occur in the assembly of the 14-membered ring dilactone, colletodiol **2** in *Cytospora*.[21] In order to establish the exact sequence in both biosynthetic pathways, (3*R*,5*R*)- and (3*S*,5*R*)-dihydroxyhexanoic acids are required. It was envisaged that the aldol chemistry described herein could be used to generate the stereogenic centres at C-3.

A titanium-mediated aldol reaction of acylated auxiliary **7** with the known[22] (3*R*)-*tert*-butyldimethylsilyoxybutanal (*R*)-**19** (prepared in 92% yield *via* protection of ethyl (*R*)-3-hydroxybutanoate as the silyl ether followed by DIBAL-H reduction of the ester) gave approximately a 3 : 1 mixture of diastereomers **20** and **21** which were separated by flash chromatography (Scheme 3). In contrast to the ^{1}H-NMR spectra of the *minor* aldol products **9, 11** and **13** formed using ethanal, butanal or benzaldehyde (Scheme 1) which all displayed a well resolved ABX for the signals assigned to 2′-H_2, it was found when using protected 3-hydroxybutanal (*R*)-**19** as the electrophile that it was the *major* diastereomer **20** which gave the well-resolved ABX for the signals assigned to 2′-H_2. Whilst this may be indicative of a reversal in stereofacial selectivity in the aldol reaction, the bulky silyl ether at C-5′may alter the conformation of the side-chain and hence the coupling constants for the 2′-methylene. Thus it was necessary to convert each aldol product **20** and **21** to known compounds.

Treatment of **20** and **21** separately with HF–pyridine gave diols **22** and **23** respectively in good yields. Interestingly in the ^{1}H-NMR spectrum of diol **22**, the diastereotopic protons at C-2′ now appeared as an unresolved multiplet compared with a well resolved ABX in the parent silyl ether **20**, confirming that the coupling pattern on these signals cannot be taken as an indicator of the stereochemistry of the β-hydroxyl in the presence of a functionalised side-chain. Hydrolytic cleavage of the auxiliary from **22** and **23** with LiOH–H_2O_2 gave the known[23] β-hydroxylactones **24** and **25** respectively. Whilst the literature values for the optical rotations of the lactones are too similar to unequivocally assign their structures,[23] they were readily differentiated on the basis of their ^{1}H-NMR data. For lactone **24** the signal assigned to 6-H resonates at δ4.86 (dqd, *J* 12.0, 6.6,



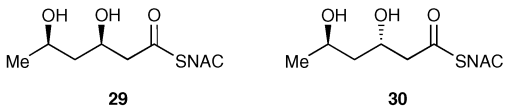
Scheme 2



Scheme 3

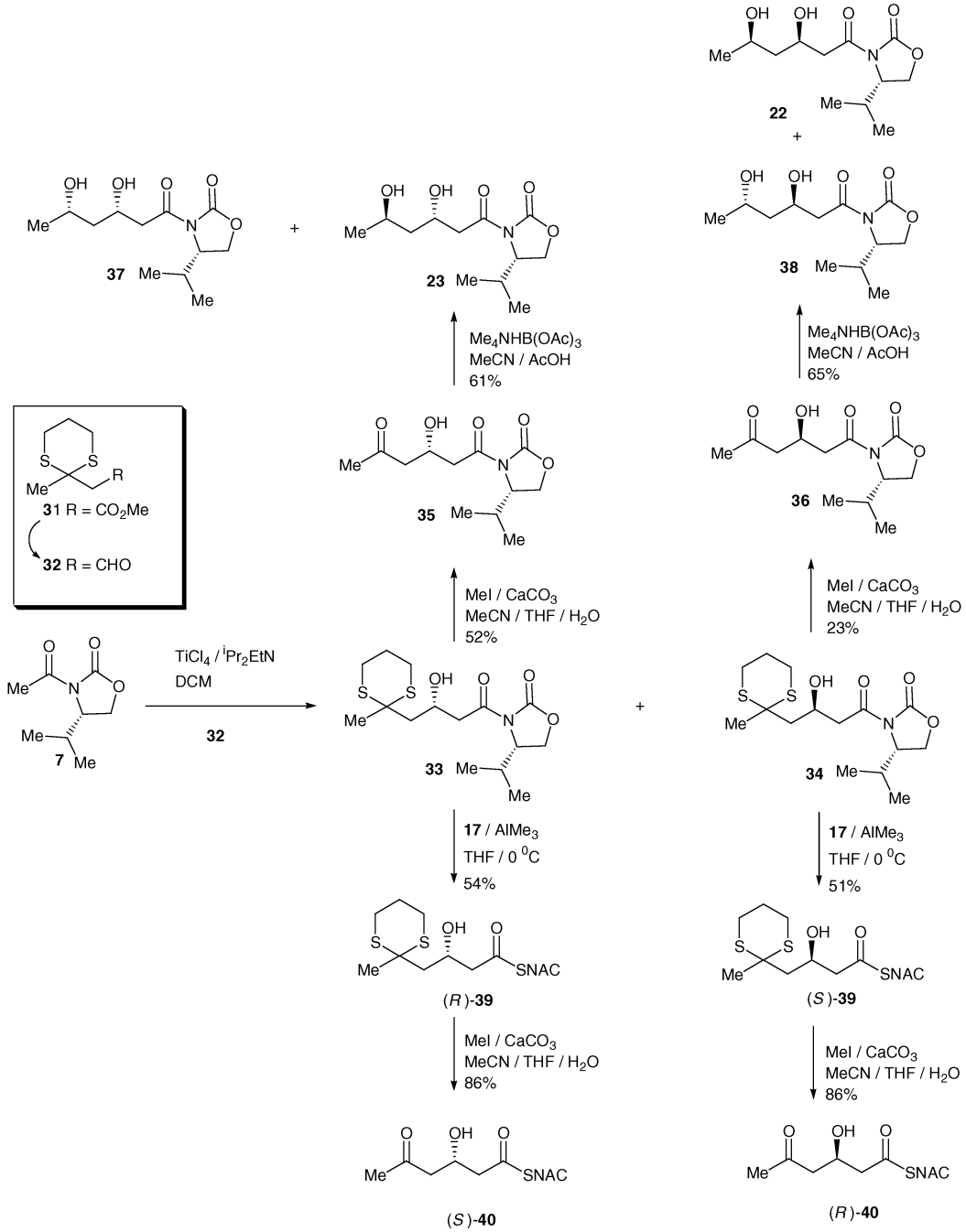
3.0) whereas in lactone **25** the signal assigned to 6-H appears at δ4.37 (dqd, *J* 12.0, 6.4, 3.0). In both isomers there is a large axial–axial coupling consistent with the 6-methyl group being in an equatorial position. The downfield shift of 6-H in the *trans* isomer **24** compared with the *cis* **25** is due the [1,3]-diaxial relationship between 6-H and the hydroxyl group at C-4. Thus it was concluded that the titanium mediated aldol reaction of **7** with aldehyde (*R*)-**19** gave approximately a 3 : 1 mixture in favour of the product **20** with the 3′-hydroxyl group *anti* to the isopropyl substituent on the oxazolidinone. This was similar stereofacial control as had been observed using the simple electrophiles, ethanal, butanal and benzaldehyde.

Whilst lactones **24** and **25** are useful standards for analysis of culture extracts of both *P. simplicissimum* and *Cytospora*, ideally the NAC thiol esters of (3*R*,5*R*)- and (3*S*,5*R*)-dihydroxyhexanoic acids **29** and **30** were required in isotopically labelled form for feeding studies. It was anticipated from an earlier report of Vederas and co-workers[24] aimed at the synthesis of the NAC thiol ester of *S*-5-hydroxyhexanoic acid (required for biosynthetic studies on dehydrocurvularin) that our targets **29** and **30** would readily lactonise and indeed this was found to be the case. Treatment of either silyl ether **20** or diol **22** with Me_3Al and *N*-acetylcysteamine **17** led to a mixture of decomposition and recovered starting material. Protection of **20** as the 3′,5′-di*tert*-butyldimethylsilyloxy ether **26** proceeded in good yield but the Me_3Al mediated conversion of **26** to the protected thiol ester gave **27** in a disappointing 18% yield (Scheme 3). An improved yield (55%) of **27** was achieved *via* a two step procedure involving hydrolytic cleavage of the auxiliary in **26** to give acid **28** followed by coupling with *N*-acetylcysteamine **17** in the presence of EDCI and DMAP.[25] Bis-silyl ether **27** was treated with HF–pyridine and cyclisation occurred to give δ-lactone **24**.



A proposed key step in the biosynthesis of 6-MSA **4** is reduction of a C_6-triketide to 3-hydroxy-5-oxohexanoate. The stereochemistry of the alcohol is unknown as the next stage is a dehydration.[26] In a further example to demonstrate the utility of the aldol approach for the synthesis of putative polyketide-derived β-hydroxycarbonyl assembly intermediates, the preparation of the NAC thiol esters of 3-hydroxy-5-oxohexanoic acid (*S*)-**40** and (*R*)-**40** was examined (Scheme 4). The synthesis of (*S*)-**40** and (*R*)-**40** was outlined in our preliminary communication[8] and more recently Shoolingin-Jordan and coworkers have used a resolution to access these enantiomers.[26]

Our approach to the syntheses of the enantiomers of **40** began with dithiane **32** prepared in 91% yield by DIBAL-H reduction

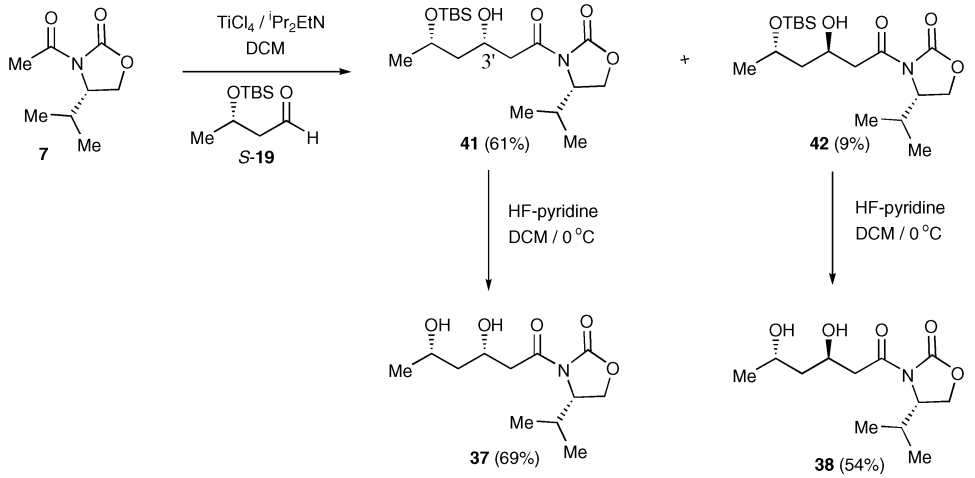


Scheme 4

of the analogous known[27] methyl ester **31** (Scheme 4). Treatment of acylated oxazolidinone **7** with aldehyde **32** in the presence of $TiCl_4$ and $iPrEt_2N$ gave a 2 : 1 mixture of diastereomers **33** and **34** which were separated by flash chromatography.[28] The stereochemistry of the products was assigned by first conversion of each dithiane **33** and **34** to the corresponding hydroxy-ketones **35** and **36** respectively using methyl iodide and calcium carbonate.[29] A directed reduction of the major diastereomer **35** with tetrabutylammonium triacetoxyborohydride[30] gave a 3 : 1 mixture of the *anti* (3′*S*,5′*R*)- and *syn* (3′*S*,5′*S*)-diols **23** and **37** which were separated by flash chromatography. The spectral data of diastereomer **23** correlated well with those of the derivative prepared *via* the aldol reaction of acylated oxazolidinone **7** with (*R*)-3-*tert*butyldimethylsilyloxybutanal (*R*)-**19** followed by deprotection of the silyl ether (Scheme 3). Similarly reduction of the minor β-hydroxy ketone **36** with tetrabutylammonium triacetoxyborohydride gave a 3 : 1 mixture of the *anti* (3′*R*,5′*S*)- and *syn* (3*R*,5′*R*)-diols **38** and **22** and the spectral data for **22** were in accord that of this diastereomer prepared as outlined in Scheme 3.

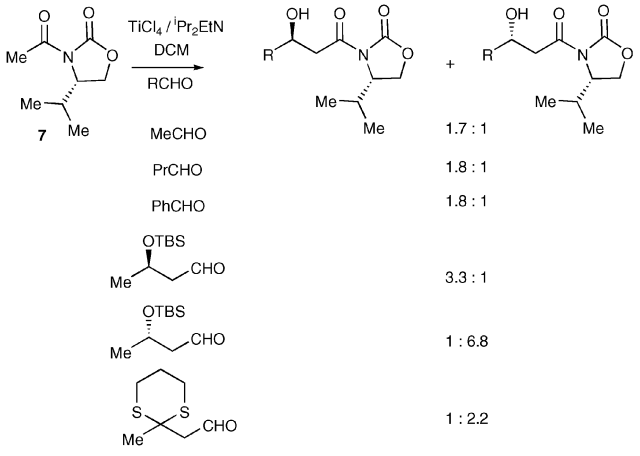
Following confirmation of the structures of the alcohols **33** and **34**, each was separately converted to the protected NAC thiol esters (*R*)-**39** and (*S*)-**39** respectively using Me_3Al and *N*-acetylcysteamine. Finally the 5-oxo functionality was released by removal of the dithiane protection to give the desired enantiomers (*S*)-**40** and (*R*)-**40** in approximately 45% overall yield from the aldol products **33** and **34** respectively.[31]

The stereochemical outcome of the aldol reactions of the enolate of **7** observed with simple aldehydes (ethanal, butanal and benzaldehyde) is consistent with Zimmerman–Traxler models of the transition states of these aldol reactions.[32] However, in the case of aldehyde (*R*)-**19** the β-silyl ether may also influence the stereochemical outcome of the reaction. In order to probe the effect of substrate control in these aldol reactions and to prepare the diastereomers **37** and **38** as a further confirmation of the stereochemical assignments shown in Scheme 4, the reaction



Scheme 5

of acyloxazolidinone **7** and aldehyde (*S*)-**19** was examined. The substrate (*S*)-**19** was prepared from ethyl (3*S*)-hydroxybutanoate by an analogous three step procedure to that used for the (*R*)-enantiomer (Scheme 5). Interestingly the titanium mediated aldol reaction of (*S*)-**19** with **7** gave approximately a 7 : 1 mixture of alcohols **41** and **42**, which were separated by flash chromatography. This remarkable selectively indicates that the reagent and substrate are matched in this case favouring formation of the product with the 3′-hydroxy *syn* to the isopropyl group in contrast to *ca.* 3 : 1 selectivity observed on reaction of acyloxazolidinone **7** with the enantiomer (*R*)-**19** in favour of the diastereomer with the 3′-hydroxy *anti* to the isopropyl group (Scheme 6). Treatment of each silyl ether **41** and **42** (Scheme 5) with HF–pyridine gave the corresponding diols **37** and **38** with spectral data in accord with that of these diols prepared *via* reduction of the β-hydroxyketones **35** and **36** respectively (Scheme 4).



Scheme 6 Summary of the aldol reactions.

In conclusion, a versatile and efficient approach for the enantioselective synthesis of functionalised β-hydroxy *N*-acetylcysteamine thiol esters has been developed which allows the facile incorporation of [1,2-$^{13}C_2$] from commercially available sodium [1,2-$^{13}C_2$]acetate. It has been shown that a remarkable reversal of selectivity is observed in the titanium mediated aldol reaction of acyloxazolidinone **7** using either (*S*)- or (*R*)-*tert*-butyldimethylsilyloxybutanal (*S*)-**19** and (*R*)-**19**. The aldol products are valuable intermediates in the synthesis of 4-hydroxy-6-substituted δ-lactones (*e.g.* **24** and **25**).

Experimental

General procedure 1: aldol condensation of acetyl oxazolidinone 7

A 1 M solution of titanium(IV) chloride in DCM (2 equiv.) was added to a stirred solution of acetyl oxazolidinone **7** in DCM (5 ml mmol^{-1}) at −78 °C under nitrogen. After 10 min diisopropylethylamine (2 equiv.) was added followed 1 h later by the aldehyde (2–5 equiv.). The reaction mixture was maintained at −78 °C for 5 h and allowed to warm to room temperature overnight. Saturated ammonium chloride solution was added (20 ml) and the mixture was extracted with DCM (3 × 100 ml). The DCM was washed with water (50 ml), dried over magnesium sulfate and concentrated *in vacuo* to give the diastereomers which were separated by flash chromatography.

With acetaldehyde. The reaction was carried out according to general procedure 1 using acetyl oxazolidinone **7** (0.60 g, 3.51 mmol). Eluting the column with 15% ethyl acetate in petrol gave (*3′R,4S*)-*3*-(*3′-hydroxybutanoyl*)-*4*-(*1-methylethyl*)-*2-oxazolidinone* **8** as a colourless oil (395 mg, 52%); $[\alpha]_D^{23}$ + 25.9 (*c* 1.8 in $CHCl_3$); ν_{max}/cm^{-1} 3506, 2965, 1782, 1697 and 1466; δ_H (300 MHz) 0.89 (3H, d, *J* 7.0, CHC*H*$_3$), 0.93 (3H, d, *J* 7.1, CHC*H*$_3$), 1.28 (3H, d, *J* 6.2, 4′-H$_3$), 2.39 (1H, m, C*H*(CH$_3$)$_2$), 3.08 (2H, m, 2′-H$_2$), 4.26 (1H, m, 3′-H), 4.23 (1H, dd, *J* 9.1 and 3.3, 5-H*H*), 4.30 (1H, t, *J* 9.1, 5-*H*H) and 4.46 (1H, dt, *J* 9.1 and 3.3, 4-H), OH not observed; δ_C (68 MHz) 14.6 and 17.9 (CH(*C*H$_3$)$_2$), 22.4 (C-4′), 28.4 (*C*H(CH$_3$)$_2$), 43.9 (C-2′), 58.3 (C-5), 63.5 (C-4), 64.1 (C-3′), 154.0 (C-2) and 172.7 (C-1′); *m/z* (EI) 215 (M$^+$, 1%), 198 (5), 182 (4), 171 (4), 83 (100) and 69 (19). Found (M + 1)$^+$, 216.1242, $C_{10}H_{18}NO_4$ requires (M + 1) 216.1236.

Further elution with 20% ethyl acetate in petrol gave (*3′S,4S*)-*3*-(*3′-hydroxybutanoyl*)-*4*-(*1-methylethyl*)-*2-oxazolidinone* **9** as a colourless oil (225 mg, 30%); $[\alpha]_D^{23}$ +99.5 (*c* 1.0 in $CHCl_3$); ν_{max}/cm^{-1} 3454, 2965, 1781, 1701 and 1465; δ_H (300 MHz) 0.89 (3H, d, *J* 7.0, CHC*H*$_3$), 0.93 (3H, d, *J* 7.0, CHC*H*$_3$), 1.28 (3H, d, *J* 6.4, 4′-H$_3$), 2.38 (1H, m, C*H*(CH$_3$)$_2$), 2.48 (1H, br s, OH), 2.94 (1H, dd, *J* 17.5 and 9.2, 2′-H*H*), 3.21 (1H, dd, *J* 17.5 and 2.5, 2′-*H*H), 4.23 (1H, dd, *J* 9.0 and 3.1, 5-H*H*), 4.27–4.35 (1H, m, 3′-H), 4.30 (1H, t, *J* 9.0, 5-*H*H) and 4.43–4.48 (1H, m, 4-H); δ_C (68 MHz) 14.6 and 17.9 (CH(*C*H$_3$)$_2$), 22.4 (C-4′), 28.4 (*C*H(CH$_3$)$_2$), 44.0 (C-2′), 58.4 (C-5), 63.5 (C-4), 64.1 (C-3′), 154.0 (C-2) and 172.7 (C-1′); *m/z* 215 (M$^+$, 1%), 198 (6), 182 (6), 171 (6), 83 (100) and 69 (27). Found (M + 1)$^+$, 216.1242, $C_{10}H_{18}NO_4$ requires (M + 1) 216.1236.

With butanal. The reaction was carried out according to general procedure 1 using acetyl oxazolidinone **7** (0.40 g, 2.34 mmol). Eluting the column with 20% ethyl acetate in

petrol gave (*3′*R,*4*S)-*3*-(*3′-hydroxyhexanoyl*)-*4*-(*1-methylethyl*)-*2-oxazolidinone* **10** as a colourless oil (285 mg, 50%); $[\alpha]_D^{23}$ +36.5 (*c* 1.6 in $CHCl_3$); ν_{max}/cm^{-1} 3510, 2960, 1782, 1697 and 1466; δ_H (300 MHz) 0.89 (3H, d, *J* 7.0, $CHCH_3$), 0.93 (3H, d, *J* 7.1, $CHCH_3$), 0.94 (3H, t, *J* 7.0, 6′-H_3), 1.36–1.59 (4H, m, 4′-H_2 and 5′-H_2), 2.39 (1H, m, $CH(CH_3)_2$), 2.81 (1H, br s, OH), 3.07 (2H, m, 2′-H_2), 4.08 (1H, m, 3′-H), 4.23 (1H, dd, *J* 9.0 and 3.1, 5-H*H*), 4.29 (1H, t, *J* 9.0, 5-*H*H) and 4.46 (1H, dt, *J* 9.0 and 3.1, 4-H); δ_C (68 MHz) 13.9 (C-6′), 14.6 and 17.9 ($CH(CH_3)_2$), 18.6 (C-5′), 28.3 ($CH(CH_3)_2$), 38.7 (C-4′), 42.5 (C-2′), 58.3 (C-5), 63.4 (C-4), 67.7 (C-3′), 154.1 (C-2) and 172.8 (C-1′); *m/z* (E.I.) 243 (M^+, 1%), 226 (9), 200 (42), 182 (8), 171 (8), 130 (100) and 86 (63). Found $(M + 1)^+$, 244.1558 $C_{12}H_{22}NO_4$ requires (M + 1) 244.1549.

Further elution with 25% ethyl acetate in petrol gave (*3S′*,*4S*)-*3*-(*3′-hydroxyhexanoyl*)- *4*-(*1-methylethyl*)-*2-oxazolidinone* **11** as a colourless oil (165 mg, 29%); $[\alpha]_D^{23}$ +83.9 (*c* 1.2 in $CHCl_3$); ν_{max}/cm^{-1} 3513, 2961, 1781, 1696 and 1466; δ_H (300 MHz) 0.82 (3H, d, *J* 7.0, $CHCH_3$), 0.86 (3H, d, *J* 7.0, $CHCH_3$), 0.87 (3H, t, *J* 6.2, 6′-H_3), 1.30–1.55 (4H, m, 4′-H_2 and 5′-H_2), 2.31 (1H, m, $CH(CH_3)_2$), 2.80 (1H, br s, OH), 2.88 (1H, dd, *J* 17.4 and 9.5, 2′-H*H*), 3.10 (1H, dd, *J* 17.4 and 2.6, 2′-*H*H), 4.04 (1H, m, 3′-H), 4.16 (1H, dd, *J* 9.1 and 3.1, 5-H*H*), 4.23 (1H, t, *J* 9.1, 5-*H*H) and 4.38 (1H, dt, *J* 9.1 and 3.1, 4-H); δ_C (68 MHz) 13.9 (C-6′), 14.6 and 17.9 ($CH(CH_3)_2$), 18.6 (C-5′), 28.4 ($CH(CH_3)_2$), 38.6 (C-4′), 42.6 (C-2′), 58.3 (C-5), 63.5 (C-4), 67.6 (C-3′), 154.0 (C-2) and 172.8 (C-1′); *m/z* (E.I.) 243 (M^+, 1%), 200 (36), 182 (8), 171 (7), 130 (100) and 86 (91). Found $(M+1)^+$, 244.1558, $C_{12}H_{22}NO_4$ requires (M + 1) 244.1549.

With benzaldehyde. The reaction was carried out according to general procedure 1 using acetyl oxazolidinone **7** (0.67 g, 3.92 mmol). Eluting the column with 20% ethyl acetate in petrol gave (*3′R*,*4S*)-*3*-(*3′-hydroxy-3′-phenylpropionyl*)-*4*-(*1-methylethyl*)-*2-oxazolidinone* **13** (360 mg, 33%) as a colourless oil; $[\alpha]_D^{22}$ + 45.1 (*c* 1.2 in $CHCl_3$); ν_{max}/cm^{-1} 3507, 2961, 1782, 1697, 1452 and 756; δ_H (300 MHz) 0.86 (3H, d, *J* 7.0, $CHCH_3$), 0.92 (3H, d, *J* 7.1, $CHCH_3$), 2.37 (1H, m, $CH(CH_3)_2$), 3.23 (1H, br s, OH), 3.28 (1H, dd, *J* 17.2 and 3.1, 2′-H*H*), 3.49 (1H, dd, *J* 17.2 and 9.4, 2′-*H*H), 4.22 (1H, dd, *J* 9.2 and 3.5, 5-H*H*), 4.27 (1H, t, *J* 9.2, 5-*H*H), 4.46 (1H, dt, *J* 9.2 and 3.5, 4-H), 5.19 (1H, m, 3′-H) and 7.27–7.42 (5H, m, C_6H_5); δ_C (68 MHz) 14.6 and 17.9 ($CH(CH_3)_2$), 28.3 ($CH(CH_3)_2$), 44.1 (C-2′), 58.4 (C-5), 63.5 (C-4), 70.2 (C-3′), 125.7 (CH), 127.7(CH), 128.4 (CH), 142.4 (C_0), 154.0 (C-2) and 172.2 (C-1′); *m/z* (E.I.) 277 (M^+, 39%), 259 (24), 171 (20), 131 (100), 105 (75), 83 (96) and 68 (21). Found M^+, 277.1313, $C_{15}H_{19}NO_4$ requires 277.1314.

Further elution with 25% ethyl acetate in petrol gave (3′*S*,4*S*)-3-(3′-hydroxy-3′-phenylpropionyl)-4-(1-methylethyl)-2-oxazolidinone **12** (660 mg, 61%) as a white crystalline solid; mp 115–117 °C (from EtOAc–petrol) (lit.[33] 115–117 °C); $[\alpha]_D^{22}$ + 114.2 (*c* 0.5 in $CHCl_3$) [lit.[33] +131.0 (*c* 0.001 in CH_2Cl_2)]; ν_{max}/cm^{-1} 3500, 3027, 2966, 1781, 1697, 1455 and 766; δ_H (300 MHz) 0.80 (3H, d, *J* 7.0, $CHCH_3$), 0.85 (3H, d, *J* 7.1, $CHCH_3$), 2.30 (1H, m, $CH(CH_3)_2$), 3.15 (1H, br s, OH), 3.29 (2H, m, 2′-H_2), 4.13 (1H, dd, *J* 9.2 and 3.4, 5-H*H*), 4.19 (1H, t, *J* 9.2, 5-*H*H), 4.37 (1H, dt, *J* 9.2 and 3.4, 4-H), 5.16 (1H, m, 3′-H) and 7.18–7.35 (5H, m, C_6H_5); δ_C (68 MHz) 15.1 and 18.3 ($CH(CH_3)_2$), 28.9 ($CH(CH_3)_2$), 44.7 (C-2′), 58.8 (C-5), 64.0 (C-4), 70.6 (C-3′), 126.2 (CH), 128.1 (CH), 128.9 (CH), 142.8 (C_0), 154.4 (C-2) and 172.4 (C-1′); *m/z* (E.I.) 277 (M^+, 72%), 171 (35), 130 (100), 107 (86), 79 (81) and 68 (39). Found M^+, 277.1313 $C_{15}H_{19}NO_4$ requires 277.1314.

With (*R*)-3-*tert*-butyldimethylsilyloxybutanal *R*-19. The reaction was carried out according to general procedure 1 using acetyl oxazolidinone **7** (0.6 g, 3.51 mmol). Eluting the column with 25% ethyl acetate in petrol gave (*3′R*,*4S*,*5′R*)-*N*-(*5′-tert-butyldimethylsilyloxy*)-*3′-hydroxyhexanoyl-4-isopropyl-2-oxazolidinone* **20** as a colourless oil (0.7 g, 53%); $[\alpha]_D^{22}$ + 34.7 (*c* 3.3 in $CHCl_3$); ν_{max}/cm^{-1} 3482 (OH), 1782 and 1699, 1388, 1209; δ_H (400 MHz; $CDCl_3$) 0.09 (6H, s, $Si(CH_3)_2$), 0.88 (3H, d, *J* 7.0, $CHCH_3$), 0.88 (9H, s, $C(CH_3)_3$), 0.93 (3H, d, *J* 7.0, $CHCH_3$), 1.20 (3H, d, *J* 6.3, 6′-H_3), 1.60 (1H, ddd, *J* 13.9, 5.1, 3.7, 4′-*H*H), 1.75 (1H, ddd, *J* 13.9, 8.8, 7.7, 4′-H*H*), 2.40 (1H, septd, *J* 7.0, 3.7, 6-H), 3.06 (1H, dd, *J* 16.6, 4.4, 2′-*H*H), 3.15 (1H, dd, *J* 16.6, 7.8, 2′-H*H*), 3.45 (1H, br s, OH), 4.20 (1H, m, 5′-H), 4.22 (1H, dd, *J* 9.0, 2.9, 5-*H*H), 4.25 (1H, m, 3′-H), 4.28 (1H, t, *J* 9.0, 5-H*H*), 4.46 (1H, m, 4-H); $\delta^{13}C$ (75 MHz; $CDCl_3$) −5.1 ($Si(CH_3)_2$), −4.5 ($Si(CH_3)_2$), 14.7 and 17.9 ($CH(CH_3)_2$), 18.0 ($(CH_3)_3C$), 23.5 (CH_3), 25.8 ($(CH_3)_3C$), 28.5 ($CH(CH_3)_2$), 43.2 (C-2′), 44.6 (C-4′), 58.4 (C-4), 63.5 (C-5), 64.7 (C-3′), 66.4 (C-5′), 154.1 (C-2), 172.1 (C-1′); *m/z* (CI) 374.2284 (MH^+, $C_{18}H_{36}SiO_5N$ requires MH^+ 374.2284, 5%), 145 (100) and 75 (95).

Further elution gave (*3′S*, *4S*, *5′R*)-*N*-(*5′-tert-butyldimethylsilyloxy*)-*3′-hydroxyhexanoyl-4-isopropyl-2oxazolidinone* **21** as a yellow oil (0.21 g, 16%); $[\alpha]_D^{22}$ + 45.9 (*c* 3 in $CHCl_3$); ν_{max}/cm^{-1} 3463 (OH), 1781 and 1697 (C=O), 1388 (O–H), 1207 (C–O); δ_H (400 MHz; $CDCl_3$) 0.08 and 0.10 (each 3H, s, $SiCH_3$), 0.88 (3H, d, *J* 7.0, $CHCH_3$), 0.88 (9H, s, $C(CH_3)_3$), 0.92 (3H, d, *J* 7.0, $CHCH_3$), 1.21 (3H, d, *J* 6.4, 6′-H_3), 1.55 (1H, ddd, *J* 14.0, 7.1, 2.4, 4′-*H*H), 1.69 (1H, ddd, 14.0, 10.0, 3.3, 4′-H*H*), 2.39 (1H, septd, *J* 7.0, 3.7, 6-H), 3.1 (2H, m, 2′-H_2), 3.44 (1H, br s, OH), 4.18 (1H, m, 5′-H), 4.21 (1H, dd, *J* 8.8, 2.9, 5-*H*H), 4.27 (1H, t, *J* 8.8, 5-H*H*), 4.43 (2H, m, 4-H and 3′-H); $\delta^{13}C$ (75 MHz; $CDCl_3$) −4.8 ($Si(CH_3)_2$), −4.1 ($Si(CH_3)_2$), 14.6 and 17.9 ($CH(CH_3)_2$), 18.0 ($(CH_3)_3C$), 23.9 (CH_3), 25.7 ($(CH_3)_3C$), 28.3 ($CH(CH_3)_2$), 42.8 (C-2′), 45.7 (C-4′), 58.4 (C-4), 63.5 (C-5), 66.8 (C-5′), 67.9 (C-3′), 154.1 (C-2), 172.1 (C-1′); *m/z* (CI) 374.2287 $C_{18}H_{36}SiO_5N$ requires MH^+ 374.2284, 40%), 159 (70) and 130 (100).

With dithiane 32[8]. The reaction was carried out according to general procedure 1 using acetyl oxazolidinone **7** (0.08 g, 0.45 mmol). Eluting the column with 15% ethyl acetate in petrol gave (4*S*,3′*R*)-3-[3′-hydroxy-4-(2-methyl-1,3-dithianyl)]butanoate-4-isopropyloxazolidin-2-one **34** as a pale yellow oil (35 mg, 23%). $[\alpha]_D^{21}$ + 59.1 (*c* 2.1 $CHCl_3$); ν_{max}/cm-1 3522, 2963, 1783, 1693, δ_H (300 MHz) 0.89 (3H, d, *J* 7, $CHCH_3$), 0.92 (3H, d, *J* 7, $CHCH_3$), 1.69 (3H, s, 6′-H_3), 1.90–2.05 (2H, m, 3″-H_2), 2.07 (1H, dd, *J* 15, 2, 4′-HH), 2.36 (1H, dd, *J* 15, 9, 4′-HH), 2.39 (1H, m, $CH(CH_3)_2$), 2.79–2.95 (4H, m, 2″-H_2 and 4″-H_2), 2.98 (1H, dd, *J* 17, 4, 2′-HH), 3.27 (1H, dd, *J* 17, 8.5, 2′-HH), 4.22 (1H, dd, *J* 9, 3, 5-HH), 4.29 (1H, t, *J* 9, 5-HH), 4.46 (1H, dt, *J* 9, 3, 4-H), 4.46 (1H, m, 3′-H); δ_C 14.66 (CH_3CH), 17.98 (CH_3CH), 24.69 ($CH(CH_3)_2$), 24.77 (C-3″), 26.55 (C-2″ or C-4″), 26.65 (C-2″ or C-4″), 28.26 (C-6′), 43.24 (C-4′), 46.76 (C-2′), 47.56 (C-5′), 58.44 (C-4), 63.48 (C-5), 65.64 (C-3′), 153.50 (C-1′), 171.41 (C-2); *m/z* (EI), 347.1223 (M^+, $C_{15}H_{25}NO_4S_2$ requires 347.1225), 347 (M^+, 62%), 264 (32), 133 (100), 83 (75) and 59 (2).

Further elution gave (*4S*,*3′S*)-*3*-[*3′-hydroxy-4*-(*2-methyl-1*,*3-dithianyl*)]*butanoate-4-isopropyloxazolidin-2-one* **33** as a yellow oil (80 mg, 52%). $[\alpha]_D^{21}$ + 37.5 (*c* 3 $CHCl_3$); δ_H (300 MHz) 0.89 (3H, d, *J* 7, CH_3CH), 0.92 (3H, d, *J* 7, CH_3CH), 1.69 (3H, s, 6′-H_3), 1.85–2.08 (1H, m, 3″-H_2), 2.06 (1H, dd, *J* 15, 3.5, 4′-*H*H), 2.40 (1H, dd, *J* 15, 7, 4′-H*H*), 2.42 (1H, m, $CHCH_3$), 2.80–2.97 (4H, m, 2″-H_2 and 4″-H_2), 3.12 (2H, m, 2′-H_2), 4.25 (1H, dd, *J* 9, 3, 5-*H*H), 4.29 (1H, t, *J* 9, 5-H*H*), 4.47 (1 H, dt, *J* 9, 3, 4-H), 4.50 (1H, m, 3′-H); *m/z* (EI), 347.1228 (M^+, $C_{15}H_{25}NO_4S_2$ requires 347.1225), 347 (M^+, 45%), 264 (28), 133 (100), 83 (56) and 59 (8).

With (*S*)-3-*tert*-butyldimethylsilyloxybutanal *S*-19. The reaction was carried out according to general procedure 1 using acetyl oxazolidinone **7** (0.846 g, 4.95 mmol). Eluting the column with 25% ethyl acetate in petrol gave (*5′S*, *3′S*, *4S*)-*3*-[*5*-(*tert-butyldimethylsilanyloxy*)-*3-hydroxyhexanoyl*]-*4-isopropyloxazolidin-2-one* **41** as a yellow oil (1.12 g, 3.00 mmol, 61%). $[\alpha]_D^{22}$ +57.0 (*c* 1.09, $CHCl_3$); ν_{max}(film)/cm^{-1} 3524 (OH), 1780 (C=O), 1698 (C=O); δ_H (400 MHz, $CDCl_3$) 0.09 (6H, s, $Si(CH_3)_2$), 0.88 (9H, s, *t*-butyl), 0.91 (6H, m, $CH(CH_3)_2$), 1.19

(3H, d, *J* 6, 6′-H_3), 1.60 (1H, m, 4′-*H*H), 1.73 (1H, m, 4′-H*H*), 2.39 (1H, m, C*H*(CH_3)$_2$), 3.01 (1H, dd, *J* 16, 9, 2′-*H*H), 3.16 (1H, dd, *J* 16, 4, 2′-H*H*), 4.09 (1H, m, 5′-H), 4.22 (1H, dd, *J* 9, 4, 5-*H*H), 4.29 (1H, t, *J* 9, 5-H*H*) 4.29 (1H, m, 3′-H), 4.46 (1H, dt, *J* 9, 4, 4-H); δ_C (100 MHz, $CDCl_3$) −4.8 ($SiCH_3$), −4.1 ($SiCH_3$), 14.7 (CH*C*H_3), 17.9 (CH*C*H_3), 24.1 (C-6′), 25.9 (3C, SiC(*C*H_3)$_3$) 28.6 (C-6) 43.0 (C-2′), 45.7 (C-4′), 58.4 (C-4), 63.6 (C-5), 66.9 (C-3′), 68.2 (C-5′) 154.1 (C-1′), 171.5 (C-2), 207.5 (C-5′); *m*/*z* (CI) 242.1394 (M^+ − OTBDMS, $C_{12}H_{21}NO_4$ requires 242.1392) 242 (2%), 224 (8), 130 (72) and 61 (100).

Further elution gave (*5′S,3′R,4S*)-*3*-[*5*-(*tert-butyldimethylsilanyloxy*)-*3-hydroxyhexanoyl*]-*4-isopropyloxazolidin-2-one* **42** as a yellow oil (164 mg, 0.44 mmol, 9%). $[a]_D^{22}$ +36.1 (*c* 0.7, $CHCl_3$); ν_{max}(film)/cm^{-1} 3514 (OH), 1781 (C=O), 1698 (C=O); δ_H (400 MHz, $CDCl_3$) 0.09 (3H, s, Si(C*H*$_3$)$_2$), 0.10 (3H, s, Si(C*H*$_3$)$_2$), 0.88 (9H, s, *t*-butyl), 0.91 (6H, m, CH(C*H*$_3$)$_2$), 1.21 (3H, d, *J* 6, 6′-H_3), 1.54 (1H, m, 4′-*H*H), 1.68 (1H, m, 4′-H*H*), 2.40 (1H, m, C*H*(CH_3)$_2$), 3.02 (1H, dd, *J* 17, 3, 2′-*H*H), 3.13 (1H, dd, J 17, 9, 2′-H*H*), 4.14 (1H, m, 5′-H), 4.23 (1H, dd, *J* 9, 4, 5-*H*H), 4.28 (1H, t, *J* 9, 5-H*H*), 4.39 (1H, m, 3′-H), 4.46 (1H, dt, *J* 8, 4, 4-H); δ_C (100 MHz, $CDCl_3$) −4.9 ($SiCH_3$), −4.4 ($SiCH_3$), 14.7 (CH*C*H_3), 18.0 (CH*C*H_3), 23.6 (C-6′), 25.9 (3C, SiC(*C*H_3)$_3$), 28.3 (C-6), 43.3 (C-2′), 44.9 (C-4′), 58.5 (C-4), 63.5 (C-5), 66.1 (C-3′), 66.2 (C-5′), 154.1 (C-1′), 172.4 (C-2); *m*/*z* (CI) 242.1393 (M^+ − OTBDMS, $C_{12}H_{21}NO_4$ requires 242.1392) 242 (1%), 224 (3), 130 (44) and 61 (100).

General procedure 2

A 2 M solution of trimethylaluminium in hexanes (1.4–5 equiv.) was added to a stirred solution of *N*-acetylcysteamine (1.5–5 equiv.) in THF at the indicated temperature under nitrogen. After 1.5 h a solution of oxazolidinone in THF was added and the solution was stirred at the indicated temperature for the required time. The reaction mixture was acidified to pH 5 using dilute hydrochloric acid and extracted using ethyl acetate. The ethyl acetate was washed with brine, dried over magnesium sulfate and concentrated *in vacuo* to give an oil which was purified by flash chromatography.

With oxazolidinone 12. The reaction was carried out according to the general procedure 2. Trimethylaluminium (4.4 equiv.) was added to a solution of *N*-acetylcysteamine (5 equiv.) in THF at −10 °C. The reaction mixture was stirred at −10 °C for 1.5 h. A solution of oxazolidinone **12** (100 mg, 0.36 mmol) in THF (10 ml) was added and the solution was allowed to warm to room temperature overnight. Elution the column with 50% ethyl acetate in petrol gave (*S*)-*3-hydroxy-3-phenylpropionic acid S*-[*2*-(*acetylamino*)*ethyl*] *ester* **18** (62 mg, 65%) as a colourless oil; $[a]_D^{22}$ +25.6 (*c* 4.3 in $CHCl_3$); ν_{max}/cm^{-1} 3299, 2928, 1657 and 760; δ_H (300 MHz) 1.96 (3H, s, $COCH_3$), 2.89–3.12 (5H, m, CH_2S, 2-H_2 and OH), 2.42 (2H, m, CH_2N), 5.20 (1H, m, 3-H), 6.13 (1H, br s, NH) and 7.28–7.38 (5H, m, C_6H_5); δ_C (75 MHz) 23.0 (CH_3), 28.8 (CH_2S), 39.2 (CH_2N), 52.8 (C-2), 70.9 (C-3), 125.7 (CH), 127.9 (CH), 128.6 (CH), 142.4 (C_0), 170.8 (CON) and 198.7 (COS); *m*/*z* (E.I.) 267 (M^+, 0.3%), 259 (3), 207 (3), 172 (33), 131 (100) and 77 (74). Found M^+, 267.0917 $C_{13}H_{17}NO_3S$ requires M 267.0929.

With oxazolidinone 26. The reaction was carried out according to the general procedure 2. Trimethylaluminium (5 equiv.) was added to a solution of *N*-acetylcysteamine (5 equiv.) in THF at 0 °C. The reaction mixture was stirred at room temperature for 1.5 h. A solution of oxazolidinone **26** (150 mg, 0.31 mmol) in THF (2 ml) was added and the reaction mixture was stirred at RT for 1 day and then heated at 40 °C for 9 h. Eluting the column with 30% ethyl acetate–petrol afforded the (*3R,5R*)-*3,5*-(*di-tert-butyldimethylsilyloxy*)*hexanoic acid S-2*-(*acetylaminoethyl*) *ester* **27** as a colourless oil (27 mg, 18%); $[a]_D^{20}$ −31.6 (*c* 0.7 in $CHCl_3$); ν_{max}/cm^{-1} (neat) 3289 (NH), 1693 (COS), 1656 (CON), 1554 (NH), 1257 (Si(CH_3)$_2$), 1085 (C-O); δ_H (400 MHz; $CDCl_3$) 0.03 (3H, s, $SiCH_3$), 0.06 (6H, s, Si(CH_3)$_2$), 0.07 (3H, s, $SiCH_3$), 0.86 and 0.89 (each 9H, s, C(CH_3)$_3$), 1.14 (3H, d, *J* 5.8, 6-H_3), 1.54 (1H, m, 4-*H*H), 1.71 (1H, m, 4-H*H*), 1.97 (3H, s, CH_3C=O), 2.71 (1H, dd, *J* 14.3, 6.9, 2-*H*H), 2.76 (1H, dd, *J* 14.3, 4.8, 2-H*H*), 3.02 (2H, m, SCH_2), 3.43 (2H, m, CH_2N), 3.87 (1H, m, 5-H), 4.23 (1H, m, 3-H), 5.90 (1H, br s, NH); δ_C (100 MHz; $CDCl_3$) −4.7, −4.5, −4.2 and −4.1 (2 × Si(CH_3)$_2$), 18.1 (2 × *C*(CH_3)$_3$), 23.3 (*C*H_3C=O), 24.1 (C-6), 25.9 (2 × C(*C*H_3)$_3$), 28.7 (SCH_2), 39.7 (CH_2N), 47.5 (C-4), 51.6 (C-2), 65.5 (C-3), 67.3 (C-5), 170.3 (CONH), 198.2 (C-1); *m*/*z* (CI) 478.2842 (MH^+, $C_{22}H_{48}NO_4SSi_2$ requires 478.2843), 478 (MH^+, 20%), 346 (22) and 214 (100).

With oxazolidinone 33[8]. The reaction was carried out according to the general procedure 2. Trimethylaluminium (1.4 equiv.) was added to a solution of *N*-acetylcysteamine (1.5 equiv.) in THF at 0 °C. The reaction mixture was stirred at room temperature for 1.5 h. It was then cooled to −5 °C and a solution of oxazolidinone **33** (210 mg, 0.60 mmol) in THF was added. The mixture was stirred at −5 °C for 5 h, then stored at −20 °C overnight. Eluting the column with 70% ethyl acetate in petroleum ether followed by 0.5% methanol in ethyl acetate gave the desired thioester (*R*)-**39** as an opaque oil (109 mg, 54%). $[a]_D^{20}$ − 17.4 (*c* 1.0, $CHCl_3$), δ_H (270 MHz) 1.67 (3H, s, 6-H_3), 1.88–2.11 (2H, m, 3′-H_2), 1.92 (1H, dd, *J* 15, 2, 4-*H*H), 2.21 (3H, s, CH_3CO), 2.38 (1H, dd, *J* 15, 9, 4-H*H*), 2.71–2.81 (2H, m, 2-H_2), 2.75–2.99 (4H, m, 2′-H_2 and 4′-H_2), 3.07 (2H, m, CH_2S), 3.20 (1H, br s, OH), 3.45 (2H, dt, *J* 6.5, 6, CH_2N), 4.45 (1H, m, 4-H), 6.24 (1H, br s, NH); *m*/*z* (CI) 338.0916 (MH^+, $C_{13}H_{24}NO_3S_3$ requires 338.0918), 338 (MH^+, 16%), 320 (66), 278 (28), 133 (100) and 60 (22).

With oxazolidinone 34[8]. The reaction was carried out according to the general procedure 2. Trimethylaluminium (1.4 equiv.) was added to a solution of *N*-acetylcysteamine (1.5 equiv.) in THF at 0 °C. The reaction mixture was stirred at room temperature for 1.5 h. It was then cooled to −5 °C and a solution of oxazolidinone **34** (200 mg, 0.58 mmol) in THF was added. The mixture was stirred at −5 °C for 5 h, then stored at −20 °C overnight. Eluting the column with 70% ethyl acetate in petroleum ether followed by 0.5% methanol in ethyl acetate to give the title compound (*S*)-**39** as an opaque oil (75 mg, 51%). $[a]_D^{23}$ + 20.1 (*c* 1.1, $CHCl_3$), ν_{max}/cm-1 3324, 2933, 1781, 1694, 1667, 1650; δ_H (270 MHz) 1.67 (3H, s, 6-H_3), 1.88–2.11 (2H, m, 3′-H_2), 1.92 (1H, dd, *J* 15, 2, 4-*H*H), 1.99 (3H, s, CH_3CO), 2.38 (1H, dd, *J* 15, 9, 4-H*H*), 2.71–2.81 (2H, m, 2-H_2), 2.75–2.99 (4H, m, 2′-H_2 and 4′-H_2), 3.07 (2H, m, CH_2S), 3.20 (1H, br s, OH), 3.45 (2H, dt, *J* 6.5, 6, CH_2N), 4.45 (1H, m, 3-H), 6.24 (1H, br s, NH); δ_C 23.07 (*C*H_3CO), 24.49 (C-3′), 26.53 (C-2′ or C-4′), 26.74 (C-2′ or C-4′), 28.39 (C-6), 28.68 (SCH_2), 39.40 (NCH_2), 46.62 (C-2), 47, 30 (C-5), 51.44 (C-4), 66.24 (C-3), 170.68 (C-1), 197.96 (CO); *m*/*z* (CI) 338.0908 (MH^+, $C_{13}H_{24}NO_3S_3$ requires 338.0918), 338 (MH^+, 12%), 320 (76), 278 (88), 133 (100), 120 (92) and 61 (92).

General procedure 3

A solution of HF–pyridine (70% HF, 0.17–0.25 ml per mmol) was added to a solution of oxazolidinone in DCM (20–40 ml per mmol) at 0 °C. After 0.5–2.5 h of stirring, water (20–40 ml $mmol^{-1}$) was added. The mixture was then thoroughly extracted with DCM, the organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. The crude material was purified by column chromatography.

With oxazolidinone 20. The reaction was carried out by following the general procedure 3. A solution of HF–pyridine (70% HF, 0.1 ml) was added to a solution of oxazolidinone **20** (0.15 g, 0.4 mmol) in DCM (10 ml) at 0 °C and was stirred at this temperature for 1 h. Purification by column chromatography, eluting with 60% ethyl acetate–petrol afforded (*3′R,5′R,4S*)-*N-3′,5′*-(*dihydroxyhexanoyl*)-*4-isopropyl-2-oxazolidinone* **22** as

white crystals (0.88 g, 85%); mp 95–97 °C; $[\alpha]_D^{22}$ + 47.1 (*c* 1 in $CHCl_3$); ν_{max}/cm^{-1} 3424 (OH), 1779 and 1701 (C=O), 1388 (O-H), 1208 (C-O); δ_H (400 MHz; $CDCl_3$) 0.89 (3H, d, *J* 7.0, CHC*H*$_3$), 0.93 (3H, d, *J* 7.0, CHC*H*$_3$), 1.20 (3H, d, *J* 6.2, 6′-H$_3$), 1.60 (1H, m, 4′-*H*H), 1.68 (1H, m, 4′-H*H*), 2.39 (1H, septd, *J* 7.0, 4.0, 6-H), 3.10 (2H, m, 2′-H$_2$), 3.45 (1H, br s, 5′-OH), 3.68 (1H, br s, 3′-OH), 4.08 (1H, m, 5′-H), 4.24 (1H, dd, *J* 9.0, 2.9, 5-*H*H), 4.30 (1H, t, 9.0, 5-H*H*), 4.35 (1H, m, 3′-H), 4.45 (1H, m, 4-H); δ_C (100 MHz; $CDCl_3$) 14.8 and 18.1 (C-7 and C-8), 23.8 (C-6′), 28.4 (C-6), 42.9 (C-2′), 44.2 (C-4′), 58.5 (C-4), 63.7 (C-5), 68.3 (C-5′), 69.1 (C-3′), 154.0 (C-2), 172.2 (C-1′); *m*/*z* (CI) 260.1484 (MH^+, $C_{12}O_5NH_{22}$ requires 260.1498), 260 (MH^+, 2%), 242 (32), 224 (47) and 130 (100).

With oxazolidinone 21. The reaction was carried out by following the general procedure 3. A solution of HF–pyridine (70% HF, 0.05 ml) was added to a solution of oxazolidinone **21** (0.1 g, 0.27 mmol) in DCM (8 ml) at 0 °C and was stirred at this temperature for 2.5 h. Purification by column chromatography, eluting with 60% ethyl acetate–petrol afforded (*3′S,5′R,4S*)-*N*-*3′,5′*-(*dihydroxyhexanoyl*)-*4-isopropyl-2-oxazolidinone* **23** as a pale yellow oil (47 mg, 79%); $[\alpha]_D^{22}$ + 85.4 (*c* 1 in $CHCl_3$); ν_{max}/cm^{-1} 3411 (OH), 1779 and 1698 (C=O), 1389 (O-H), 1209 (C-O); δ_H (400 MHz; $CDCl_3$) 0.88 (3H, d, *J* 7.0, CHC*H*$_3$), 0.93 (3H, d, *J* 7.0, CHC*H*$_3$), 1.26 (3H, d, *J* 6.4, 6′-H$_3$), 1.65 (1H, ddd, *J* 14.5, 8.5, 3.5, 4′-*H*H), 1.71 (1H, ddd, *J* 14.5, 8.5, 3.0, 4′-H*H*), 2.37 (1H, septd, *J* 7.0, 4.0, 6-H), 2.53 (1H, br s, OH), 3.10 (2H, dd, *J* 17.6, 9.5, 2′-*H*H), 3.17 (1H, dd, *J* 17.6, 2.9, 2′-H*H*), 3.42 (1H, br s, OH), 4.17 (1H, m, 5′-H), 4.23 (1H, dd, *J* 8.5, 2.9, 5-*H*H), 4.30 (1H, t, 8.5, 5-H*H*), 4.44 (2H, m, 3′-H and 4-H); *m*/*z* (CI) 260.1488 (MH^+, $C_{12}O_5NH_{22}$ requires 260.1498), 260 (MH^+, 50%), 242 (100) and 224 (40).

With oxazolidinone 41. The reaction was carried out by following the general procedure 3. A solution of HF–pyridine (70% HF, 0.25 ml) was added to a solution of oxazolidinone **41** (0.5 g, 1.34 mmol) in DCM (30 ml) at 0 °C and was stirred at this temperature for 0.5 h. Purification by column chromatography, eluting with 60% ethyl acetate–petrol afforded (*5′S,3′S,4S*)-*3*-(*3′,5′-dihydroxyhexanoate*)-*4-isopropyl-2-oxazolidinone* **37** as a white solid (240 mg, 0.93 mmol, 69%). Mp 75–76 °C; $[\alpha]_D$ +117.4 (*c* 1.28, $CHCl_3$); anal calcd for $C_{12}H_{21}O_5N$: C 55.58, H 8.16, N 5.40. Found: C 55.82, H 8.04, N 5.11%; ν_{max}(film)/cm^{-1} 3388 (OH), 1773 (C=O), 1708 (C=O), 1690 (C=O); δ_H (400 MHz, $CDCl_3$) 0.88 (3H, d, *J* 7, CHC*H*$_3$), 0.94 (3H, d, *J* 7, CHC*H*$_3$), 1.21 (3H, d, *J* 6, 6′-H$_3$), 1.60 (1H, m, 4′-*H*H), 1.79 (1H, m, 4′-H*H*), 2.37 (1H, m, C*H*(CH$_3$)$_2$), 2.99 (1H, dd, *J* 18, 9, 2′-*H*H), 3.20 (1H, dd, *J* 18, 3, 2′-H*H*), 3.56 (1H, br, OH), 3.72 (1H, br, OH), 4.08 (1H, m, 5′-H), 4.24 (1H, dd, *J* 9, 3, 5-*H*H), 4.28 (1H, t, *J* 9, 5-H*H*), 4.38 (1H, m, 3′-H), 4.45 (1H, dt, *J* 8, 3, 4-H); δ_C (100 MHz, $CDCl_3$) 14.8 (CH*C*H$_3$), 18.0 (CH*C*H$_3$), 23.8 (C-6′), 28.6 (C-6), 43.0 (C-2′), 44.3 (C-4′), 58.5 (C-4), 63.7 (C-5), 68.2 (C-5′), 68.9 (C-3′), 154.1 (C-1′), 172.3 (C-2); *m*/*z* (CI) 242 (M^+ − H_2O, 1%), 224 (4), 130 (51) and 61 (100).

With oxazolidinone 42. The reaction was carried out by following the general procedure 3. A solution of HF–pyridine (70% HF, 0.03 ml) was added to a solution of oxazolidinone **42** (67 mg, 0.18 mmol) in DCM (7 ml) at 0 °C and was stirred at this temperature for 0.5 h. Purification by column chromatography, eluting with 60% ethyl acetate–petrol afforded (*5′S,3′R,4S*)-*3*-(*3′,5′-dihydroxyhexanoate*)-*4-isopropyl-2-oxazolidinone* **38** as a clear oil (25 mg, 0.1 mmol, 54%). $[\alpha]_D$ +68.7 (*c* 1.39, $CHCl_3$); ν_{max}(film)/cm^{-1} 3402 (OH), 1772 (C=O), 1694 (C=O); δ_H (400 MHz, $CDCl_3$) 0.89 (3H, d, *J* 7, CHC*H*$_3$), 0.94 (3H, d, *J* 7, CHC*H*$_3$), 1.25 (3H, d, *J* 6, 6′-H$_3$), 1.66 (2H, m, 4′-H$_2$), 2.39 (1H, m, C*H*(CH$_3$)$_2$), 3.10 (1H, dd, *J* 17, 4, 2′-*H*H), 3.20 (1H, dd, J 17, 9, 2′-H*H*), 4.14 (1H, m, 5′-H), 4.24 (1H, dd, *J* 9, 3, 5-*H*H), 4.29 (1H, t, *J* 9, 5-H*H*), 4.43 (1H, m, 3′-H), 4.47 (1H, dt, *J* 9, 3, 4-H); δ_C (100 MHz, $CDCl_3$) 14.8 (CH*C*H$_3$), 18.1 (CH*C*H$_3$), 23.7 (C-6′), 28.4 (C-6), 42.5 (C-2′), 43.7 (C-4′), 58.5 (C-4), 63.6 (C-5), 65.1 (C-5′), 68.9 (C-3′), 154.1 (C-1′), 172.8 (C-2); *m*/*z* (CI) 242.1389 (M^+ − H_2O, $C_{12}H_{21}NO_4$ requires 242.1392) 242 (M^+ − H_2O, 2%), 224 (4), 130 (100) and 61 (73).

General procedure 4

Methyl iodide (32 equiv.) and calcium carbonate (12 equiv.) were added to a solution of thiolester in acetonitrile (4 ml per mmol), water (20 ml per mmol) and tetrahydrofuran (2.5 ml per mmol). The mixture was heated to reflux for 4 h. It was left to cool to room temperature, then extracted with EtOAc (3 × 10 ml). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo* to give a yellow oil.

With thiol ester (*S*)-39[8,26]. The reaction was carried out by following the general procedure 4 using thiol ester (*S*)-**39** (65 mg, 0.19 mmol) to give (*S*)-3-hydroxy-5-oxohexanoic acid-*S*-[2-(acetylamino ester)ethyl]thiol ester (*R*)-**40** as a yellow oil (40 mg, 86%). $[\alpha]_D^{21}$ +2.8 (*c* 0.47, $CHCl_3$); δ_H (300 MHz) 1.89 (3H, s, 6-H$_3$), 2.20 (3H, s, CH_3CON), 2.45 (1H, br s, OH), 2.60–2.77 (4H, m, 2-H$_2$ and 4-H$_2$), 3.01 (2H, t, *J* 6, CH_2S), 3.48 (2H, dt, *J* 6.5, 6, CH_2N), 4.48 (1H, m, 3-H), 6.05 (1H, br s, NH); *m*/*z* (EI) 248.0954 (M^+, $C_{10}H_{18}NO_4S$ requires 248.0950), 248 (M^+, 30%), 230 (34), 119 (100), 89 (48), 72 (40), 60 (78).

With thiol ester (*R*)-39[8,26]. The reaction was carried out by following the general procedure 4 using thiol ester (*R*)-**39** (84 mg, 0.248 mmol) to give (*R*)-3-hydroxy-5-oxohexanoic acid-*S*-[2-(acetylamino ester)ethyl]thiol ester (*S*)-**40** as a yellow oil (52 mg, 86%). $[\alpha]_D^{20}$ −3.3 (*c* 0.90, $CHCl_3$); ν_{max}/cm^{-1} 3418, 2361, 1652, 1552, 1433, 1094; δ_H (300 MHz) 1.89 (3H, s, 6-H$_3$), 2.07 (3H, s, CH_3CON), 2.45 (1H, br s, OH), 2.60–2.77 (4H, m, 2-H$_2$ and 4-H$_2$), 3.01 (2H, t, *J* 6, CH_2S), 3.48 (2H, dt, *J* 6.5, 6, CH_2N), 4.43 (1H, m, 3-H), 6.09 (1H, br s, NH); δ_C 23.1 (C-6), 28.8 (SC), 30.7 (CH_3CON), 39.1 (CN), 48.9 (C-2), 50.0 (C-4), 64.7 (C-3), 170.6 (C-1), 197.9 (NCO), 208.3 (C-5); *m*/*z* (EI) 248.0956 (M^+, $C_{10}H_{18}NO_4S$ requires 248.0950), 248 (M^+, 84%), 230 (44), 119 (100), 72 (40), 60 (78).

With oxazolidinone 33. The reaction was carried out by following the general procedure 4 using oxazolidinone **33** (200 mg, 0.58 mmol). The crude material was purified by column chromatography, eluting with 60% EtOAc–petrol to give (*3′S,4S*)-*3*-(*3′-hydroxy-5′-oxohexanoate*)-*4-isopropyl-2-oxazolidinone* **35** (80 mg, 0.31 mmol, 54%). $[\alpha]_D$ +64.9 (*c* 1.31, $CHCl_3$); ν_{max}(film)/cm^{-1} 3507 (OH), 1773 (C=O), 1697 (C=O); δ_H (400 MHz, $CDCl_3$) 0.89 (3H, d, *J* 7, CHC*H*$_3$), 0.92 (3H, d, *J* 7, CHC*H*$_3$), 2.20 (3H, s, 6′-H$_3$), 2.38 (1H, m, C*H*CH$_3$), 2.67 (1H, dd, *J* 17, 4, 4′-*H*H), 2.75 (1H, dd, *J* 17, 8, 4′-H*H*), 3.06 (1H, dd, *J* 17, 9, 2′-*H*H), 3.16 (1H, dd, *J* 17, 4, 2′-H*H*), 3.34 (1H, d, *J* 3, OH), 4.23 (1H, dd, *J* 9, 3, 5-*H*H), 4.30 (1H, t, *J* 9, 5-HH), 4.45 (1H, dt, *J* 9, 3, 4-H), 4.60 (1H, m, 3′-H); δ_C (100 MHz, $CDCl_3$) 14.8 (CH*C*H$_3$), 18.0 (CH*C*H$_3$), 28.6 (*C*HCH$_3$), 30.7 (C-6′), 42.0 (C-2′), 49.4 (C-4′), 58.5 (C-4), 63.7 (C-5), 64.3 (C-3′), 154.1 (C-1′), 171.5 (C-2), 207.5 (C-5′); *m*/*z* (CI) 258.1353 (MH^+, $C_{12}H_{19}NO_5$ requires 258.1341), 258 (MH^+, 14%), 240 (MH^+ − H_2O, 50) and 130 (auxiliary, 100).

With oxazolidinone 34. The reaction was carried out by following the general procedure 4 using oxazolidinone **34** (767 mg, 2.21 mmol). The crude material was purified by column chromatography, eluting with 60% EtOAc–petrol to give (*3′R,4S*)-*3*-(*3′-hydroxy-5′-oxohexanoate*)-*4-isopropyl-2-oxazolidinone* **36** (258 mg, 1.00 mmol, 45%). $[\alpha]_D$ +49.6 (*c* 1.00, $CHCl_3$); ν_{max}(film)/cm^{-1} 3502 (OH), 1772 (C=O), 1695 (C=O); δ_H (400 MHz, $CDCl_3$) 0.88 (3H, d, *J* 7, CHC*H*$_3$), 0.93 (3H, d, *J* 7, CHC*H*$_3$), 2.20 (3H, s, 6′-H$_3$), 2.39 (1H, m, C*H*CH$_3$), 2.63 (1H, dd, *J* 17, 8, 4′-*H*H), 2.76 (1H, dd, *J* 17, 5, 4′-H*H*), 3.12 (2H, m, 2′-H$_2$), 4.23 (1H, dd, *J* 9, 3, 5-*H*H), 4.31 (1H, t, *J* 9, 5-H*H*), 4.45 (1H, m, 4-H), 4.56 (1H, m, 3′-H); δ_C (100 MHz, $CDCl_3$) 14.7 (CH*C*H$_3$), 18.0 (CH*C*H$_3$), 28.5 (*C*HCH$_3$), 30.7 (C-6′), 42.0 (C-2′), 49.4 (C-4′), 58.5 (C-4), 63.6 (C-5), 64.3 (C-3′), 154.1 (C-1′),

171.5 (C-2), 207.5 (C-5′); *m/z* (CI) 258.1343 (MH^+, $C_{12}H_{19}NO_5$ requires 258.1341), 258 (MH^+, 30%), 240 (26) and 130 (100).

General procedure 5

Acetic acid (3.8 ml $mmol^{-1}$) was added to a solution of tetramethylammonium triacetoxyborohydride (5 equiv.) in MeCN (3.8 ml $mmol^{-1}$) at −40 °C. The oxazolidinone was then added in MeCN (1.3 ml) and the mixture was stirred at −40 °C for 10 minutes, before it was allowed to warm to room temperature. After 1 h the reaction was quenched by addition of 0.5 N aqueous sodium potassium tartrate (15 ml $mmol^{-1}$). The mixture was stirred for 0.5 h and then diluted with dichloromethane. The organic layer was washed with saturated aqueous sodium hydrogen carbonate. The aqueous layer was extracted with dichloromethane and the combined organics were washed with saturated aqueous sodium hydrogen carbonate again. The aqueous layer was back extracted with dichloromethane. All the organic layers were combined, dried over sodium sulfate and concentrated. The residue was purified by column chromatography (80% EtOAc–petrol) to give a 3 : 1 mixture of diastereomers.

With oxazolidinone 35. The general procedure 5 was followed, using **35** (200 mg, 0.78 mmol) to give a 3 : 1 mix of (5′*R*,3′*S*,4*S*)-3-(3′,5′-dihydroxyhexanoate)-4-isopropyl-2-oxazolidinone **23** and (5′*S*,3′*S*,4*S*)-3-(3′,5′-dihydroxyhexanoate)-4-isopropyl-2-oxazolidinone **37** as a clear oil (123 mg, 0.47 mmol, 61%). Data as before.

With oxazolidinone 36. The general procedure 5 was followed, using **36** (151 mg, 0.57 mmol) to give a 3 : 1 mix of (5′*S*,3′*R*,4*S*)-3-(3′,5′-dihydroxyhexanoate)-4-isopropyl-2-oxazolidinone **38** and (5′*R*,3′*R*,4*S*)-3-(3′,5′-dihydroxyhexanoate)-4-isopropyl-2-oxazolidinone **22** as a clear oil (99 mg, 0.38 mmol, 65%). Data as before.

General procedure 6

A solution of oxazolidinone in a mixture of THF–water (4 : 1) at 0 °C was treated with hydrogen peroxide (30% w/v, 3.5 equiv.) and lithium hydroxide monohydrate (1.1 equiv.). The reaction mixture was stirred for the time indicated. Water (1 ml) and sodium sulfite (2 equiv.) were added, then the solvent was evaporated under reduced pressure. The remaining aqueous layer was extracted with DCM (3 × 5 ml) and the pH was adjusted to 1 with 2 M HCl. The mixture was extracted with ethyl acetate (5 × 5 ml), dried over $MgSO_4$ then evaporated *in vacuo* to give a colourless oil, which was purified by flash chromatography.

With oxazolidinone 8. The general procedure 6 was followed, using **8** (0.10 g, 0.47 mmol) in THF–water (2.5 ml). The reaction mixture was stirred for 1 h to give **14** as a colourless oil (30 mg, 62%). $[\alpha]_D^{22}$ −23.5 (*c* 2.2, MeOH), [lit.[10] $[\alpha]_D^{25}$ −21 (*c* 1.0, MeOH)]; ν_{max}(film)/cm^{-1} 3365, 2973, 1720; δ_H (2700 MHz, $CDCl_3$) 1.25 (3H, d, *J* 7, 4-H_3), 2.52 (2H, m, 2-H_2), 4.23 (1H, m, 3-H), 5.20 (1H, br s, OH).

With oxazolidinone 22. The general procedure 6 was followed, using **22** (0.11 g, 0.42 mmol) in THF–water (3 ml). The reaction mixture was stirred for 5 h. The crude material was purified by column chromatography, eluting with 100% EtOAc to give lactone **24** as a colourless oil (23 mg, 42%). $[\alpha]_D^{22}$ +30.1 (*c* 1.3, $CHCl_3$) [lit.[23] $[\alpha]_D$ +23.1 (*c* 1.0, $CHCl_3$)]; ν_{max}(film)/cm^{-1} 3417 (OH), 1713 (C=O), 1073 (C–O); δ_H (400 MHz, $CDCl_3$) 1.40 (3H, d, *J* 6.6, CH_3), 1.72 (1H, ddd, *J* 14.7, 12.0, 3.3, 7, 5-*H*H), 2.00 (1H, dddd, *J* 14.7, 3.7, 2.9, 1.5, 5-H*H*), 2.67 (1H, ddd, *J* 17.6, 3.3, 1.5, 3-*H*H), 2.71 (1H, dd, *J* 17.6, 4.7, 3-H*H*), 4.38 (1H, m, 4-H), 4.86 (1H, dqd, *J* 12.0, 6.6, 2.9, 6-H); δ_C (100 MHz; $CDCl_3$) 21.4 (CH_3), 37.5 and 38.3 (C-5 and C-3), 62.6 (C-4), 72.7 (C-6), 171.3 (C-2).

With oxazolidinone 23. The general procedure 6 was followed, using **23** (0.13 g, 0.5 mmol) in THF–water (4 ml). The reaction mixture was stirred for 4 h. The crude material was purified by column chromatography, eluting with 100% EtOAc to give lactone **25** as a colourless oil (24 mg, 37%). $[\alpha]_D^{22}$ +27.8 (*c* 0.94, $CHCl_3$), [lit.[23] enant. $[\alpha]_D$ −20.7 (*c* 0.92, $CHCl_3$)]; ν_{max}(film)/cm^{-1} 3408 (OH), 1722 (C=O), 1081 (C–O); δ_H (400 MHz, $CDCl_3$) 1.42 (3H, d, *J* 6.4, CH_3), 1.59 (1H, ddd, *J* 13.7, 12.0, 9.3, 7, 5-*H*H), 2.28 (1H, dddd, *J* 13.7, 5.5, 3.0, 1.5, 5-H*H*), 2.46 (1H, dd, *J* 17.2, 7.8, 3-*H*H), 2.90 (1H, ddd, *J* 17.2, 5.5, 1.5, 3-H*H*), 4.26 (1H, dd, br t, *J* 9.3, 7.8, 5.5, 4-H), 4.37 (1H, dqd, *J* 12.0, 6.4, 3.0, 6-H); δ_C (100 MHz; $CDCl_3$) 21.4 (CH_3), 39.2 and 39.5 (C-5 and C-3), 63.8 (C-4), 73.8 (C-6), 171.0 (C-2).

(*R*)-3-Hydroxyhexanoic acid 15[10]

A solution of lithium hydroxide (60 mg, 1.43 mmol) in water (5 ml) was added to a stirred solution of oxazolidinone **10** (163 mg, 0.67 mmol) in THF (5 ml) at room temperature. After stirring overnight the mixture was acidified to pH 4 using dilute hydrochloric acid and extracted using ethyl acetate (3 × 50 ml). The solvent was dried over magnesium sulfate and concentrated *in vacuo* to give an oil which was purified by flash chromatography. Elution with 40% ethyl acetate in petrol gave the title compound **15** (69 mg, 78%) as a colourless oil; $[\alpha]_D^{22}$ −20.0 (*c* 3.0 in $CHCl_3$) [lit.[10] −27.3 (*c* 2.1 in $CHCl_3$)]; δ_H (300 MHz) 0.94 (3H, t, *J* 6.9, CH_3), 1.36–1.64 (4H, m, 4-H_2 and 5-H_2), 2.47 (1H, dd, *J* 16.5 and 8.8, 2-H*H*), 2.57 (1H, dd, *J* 16.5 and 3.3, 2-*H*H), 4.06 (1H, m, 3-H) and 7.06 (1H, br s, CO_2H); *m/z* (C.I.) 133 (M^++1, 21%), 115 (92), 104 (17) and 97 (100).

(3*R*,5*R*)-3,5-(Di-*tert*-butyldimethylsilyloxy)hexanoic acid 28

A solution of oxazolidinone **26** (0.27 g, 0.56 mmol) in a mixture of THF and water (4:1, 3.5 ml) at 0 °C was treated with hydrogen peroxide (30% w/v, 0.23 ml, 2 mmol) and lithium hydroxide monohydrate (47 mg, 1.1 mmol). The reaction mixture was stirred for 4 h. Water (1 ml) and sodium sulfite (80 mg, 0.72 mmol) were added, the mixture was then extracted with DCM (3 × 5 ml). The pH of the remaining aqueous layer was adjusted to 1 with 2 M HCl. The mixture was extracted with ethyl acetate (3 × 5 ml). Both organic layers were dried over $MgSO_4$ concentrated *in vacuo* to give a yellow oil which was purified by flash chromatography, eluting with 20% ethyl acetate–petrol to give (*3*R,*5*R)-*3,5*-(*di*-tert-*butyldimethylsilyloxy*)*hexanoic acid* **28** as a pale yellow oil (0.14 g, 65%); $[\alpha]_D^{22}$ − 7.8 (*c* 2 in $CHCl_3$); ν_{max}/cm^{-1} (neat) 2500–3000 (CO_2H), 1714 (C=O), 1258 ($SiMe_2$), 1103 (C–O); δ_H (400 MHz; $CDCl_3$) 0.05, 0.06, 0.09 and 0.11 (each 3H, s, $SiCH_3$), 0.83 and 0.84 (each 9H, s, $C(CH_3)_3$), 1.10 (3H, d, *J* 6.1, 6-H_3), 1.55 (1H, ddd, *J* 13.6, 8.5, 4.4, 4-*H*H), 1.71 (1H, ddd, *J* 13.6, 8.3, 4.9, 4-H*H*), 2.44 (1H, dd, *J* 14.8, 5.8, 2-*H*H), 2.56 (1H, dd, *J* 14.8, 4.9, 2-H*H*), 3.81 (1H, m, 5-H), 4.21 (1H, m, 3-H); δ_C (100 MHz; $CDCl_3$) −4.94, −4.81, −4.58 and −4.13 (2 × $Si(CH_3)_2$), 17.9 (2 × $C(CH_3)_3$), 24.1 (C-6), 25.7 and 25.8 ($C(CH_3)_3$), 41.2 (C-2), 46.7 (C-4), 65.6 (C-3), 66.9 (C-5), carbonyl signal not observed; *m/z* (CI) 245.1536 (MH^+ − TBSOH, $C_{12}H_{25}O_3Si$ requires 245.1573), 245 (MH^+ − TBSOH, 10%), 113 (20) and 57 (100).

(3′*R*,4*S*,5′*R*)-*N*-(3′,5′-Di-*tert*-butyldimethylsilyloxy)hexanoyl-4-isopropyl-2-oxazolidinone 26

To a solution of oxazolidinone **20** (0.21 g, 0.55 mmol) in DCM (1 ml) was added 2,6-lutidine (0.13 ml, 1.1 mmol) and *tert*-butyldimethylsilyltrifluoromethanesulfonate (0.19 ml, 0.83 mmol) simultaneously at 0 °C. After 0.5 h, 1 M HCl (2 ml) was added and the reaction mixture was then extracted with DCM (5 × 5 ml), the combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo* to give

a yellow oil. Purification by column chromatography eluting 20% ethyl acetate–petrol yielded (*3′*R,*4*S,*5′*R)-N-(*3′*,*5′-di*-tert-*butyldimethylsilyloxy)hexanoyl-4-isopropyl-2-oxazolidinone* **26** as a pale yellow oil (0.23 g, 84%); $[\alpha]_D^{20}$ + 27.3 (*c* 1 in $CHCl_3$); ν_{max}/cm^{-1} (neat) 1786, 1705 (C=O), 1254 ($SiMe_2$), 1062 (C–O); δ_H (400 MHz; $CDCl_3$) 0.04, 0.046, 0.05 and 0.09 (each 3H, s, $SiCH_3$), 0.86 (9H, s, $C(CH_3)_2$), 0.86 (3H, d, *J* 7.0, $CHCH_3$), 0.88 (9H, s, $C(CH_3)_2$), 0.91 (3H, d, *J* 7.0, $CHCH_3$), 1.16 (3H, d, *J* 5.9, 6′-H_3), 1.57 (1H, ddd, *J* 12.7, 7.0, 5.6, 4′-*H*H), 1.75 (1H, ddd, *J* 12.7, 6.8, 5.9, 4′-H*H*), 2.39 (1H, septd, *J* 7.0, 4.0, 6-H), 3.35 (1H, dd, *J* 14.5, 4.9, 2′-*H*H), 3.20 (1H, dd, *J* 14.5, 7.1, 2′-H*H*), 3.90 (1H, m, 5′-H), 4.19 (1H, dd, *J* 9.3, 3.4, 5-*H*H), 4.25 (1H, t, *J* 9.3, 5-H*H*), 4.35 (1H, m, 3′-H), 4.43 (1H, m, 4-H); δ_C (100 MHz; $CDCl_3$) −4.7, −4.6, −4.5 and −4.4 (2 × $Si(CH_3)_2$), 14.4 and 17.9 (C-7 and C-8), 17.9 ($C(CH_3)_3$), 23.8 (C-6′), 25.8 and 25.9 (2 × $C(CH_3)_3$), 28.1 (C-6), 42.9 (C-2′), 47.5 (C-4′), 58.4 (C-4), 63.0 (C-5), 65.7 (C-3′), 66.0 (C-5′), 154.0 (C-2), 170.9 (C-1′); *m/z* (CI) 488.3238 (MH^+, $C_{24}H_{50}NO_5Si_2$ requires 488.3228), 488 (MH^+, 2%), 356 (40), 224 (84) and 130 (100).

(3*R*,5*R*)-3,5-(Di-*tert*-butyldimethylsilyloxy)hexanoic acid *S*-2-(acetylamino ethyl) ester 27

Acid **28** (0.14 g, 0.36 mmol) and *N*-acetylcysteamine (52 mg, 0.43 mmol) were dissolved in DCM (3 ml) at 0 °C. A mixture of EDCI (90 mg, 0.47 mmol) and DMAP (catalytic amount) in DCM (2 ml) was added slowly and the reaction mixture was stirred overnight at RT. Water (3 ml) was then added and the mixture was extracted with DCM (4 × 5 ml). The combined organic layers were dried over $MgSO_4$, and concentrated *in vacuo*. The oil was purified by flash chromatography, eluting with 45% ethyl acetate–petrol to give thiol ester **27** as a colourless oil (0.15 g, 86%); Spectroscopic data as before.

(*S*)-3-Hydroxy-3-phenylpropanol (*S*)-16[16]

A solution of oxazolidinone **12** (89 mg, 0.32 mmol) in THF (10 ml) was added dropwise to a stirred suspension of lithium aluminium hydride (19 mg, 0.50 mmol) in THF (10 ml) at 0 °C under nitrogen. After stirring overnight saturated aqueous potassium sodium tartrate solution (10 ml) was added and the reaction mixture was stirred for 1 h before the reaction mixture was then extracted with ethyl acetate (4 × 50 ml). The ethyl acetate was washed with brine (20 ml), dried over magnesium sulfate and concentrated *in vacuo* to give an oil which was purified by flash chromatography. Elution with 40% ethyl acetate in petrol returned the title compound (*S*)-**16** (33 mg, 68%) as a colourless oil; $[\alpha]_D^{23}$ −66.6 (*c* 1.2 in $CHCl_3$) [lit.,[16] −70.5 (*c* 1.0 in $CHCl_3$)]; δ_H (300 MHz) 1.90–2.07 (2H, m, 2-H_2), 2.47 (2H, br s, 2 × OH), 3.87 (2H, t, *J* 5.1, 1-H_2), 4.97 (1H, dd, *J* 8.4 and 4.0, 3-H) and 7.27–7.39 (5H, m, C_6H_5); *m/z* (E.I.) 152 (M^+, 14%), 134 (30), 133 (34), 117 (58), 105 (100) and 77 (76).

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