

Reaction of α -Amino Esters and α -Amino Ester Imines with Thiiranium Ion Intermediates. Application to the Synthesis of New Potential Aminopeptidase Inhibitors and Mechanistic Implications.

Duncan M. Gill^a§, Neil A. Pegg^b and Christopher M. Rayner^{a*}

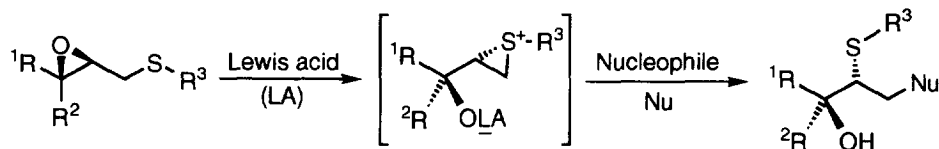
^aSchool of Chemistry, University of Leeds, Leeds LS2 9JT, U.K. (email chrism@chem.leeds.ac.uk)

^bMedicinal Chemistry I, Glaxo Research and Development Ltd., Gunnels Wood Road, Stevenage, Herts., SG1 2NY, U.K.

Abstract: Imines derived from α -amino esters react with thiiranium ions generated *in situ* from 2,3-epoxy sulfides, to give an iminium ion which can be readily hydrolysed by aqueous base to liberate a secondary amine, the product of selective monoalkylation of the primary amino group. Overall yields for this process are only moderate, but can be improved by use of α -amino esters themselves as nucleophiles at low temperature. Interesting reactivity profiles of the thiiranium ion intermediates are observed, and consequent implications for the nature of the reactive intermediates involved are discussed. The products obtained from these reactions are model systems for the synthesis of compounds related to α -thiolbestatin and other known potent aminopeptidase inhibitors. © 1997 Elsevier Science Ltd. All rights reserved.

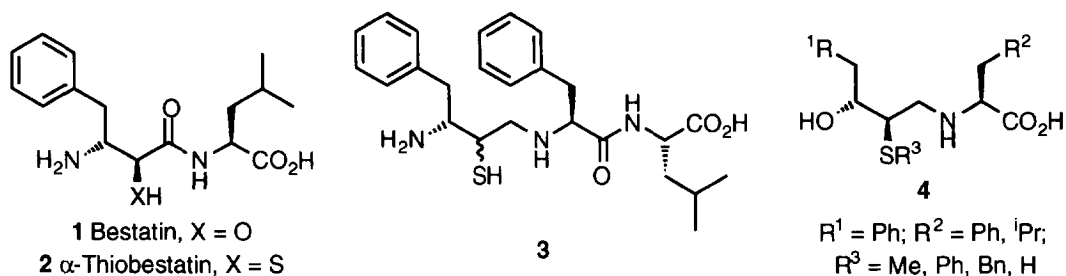
Introduction.

We are currently developing new methods for the asymmetric synthesis of organosulfur compounds, including the use of enzymatic procedures,¹ sulfur oxidation,² and alkene sulfenylation.³ In an earlier communication,⁴ we reported the conversion of homochiral 2,3-epoxy sulfides⁵ to the corresponding 3-alkoxy-1,2-thiiranium ions under Lewis acidic conditions (scheme 1). We were subsequently able to trap these species with nucleophiles, selectively at C-1 to give access to 1-substituted-3-hydroxy-2-thioethers with full control of both relative and absolute configuration at the chiral centres. This methodology also provided a mild and efficient method for the generation of a variety of thiiranium ions (or their equivalents) providing an excellent opportunity to study the reactivity of these synthetically useful⁶ and mechanistically interesting^{6,7} intermediates.



Scheme 1

We now wished to adapt this methodology to the synthesis of compounds of biological relevance, and thus became interested in the synthesis of structural analogues of the potent aminopeptidase inhibitor bestatin (1)⁸ and its superior mercapto analogue α -thiolbestatin (2).⁹ Such compounds are of considerable importance, having activity as immune response modifiers,¹⁰ analgesics by enkephalinase inhibition,¹¹ and antitumour and antimicrobial properties believed to be associated with their abilities to inhibit cell surface aminopeptidases.¹²

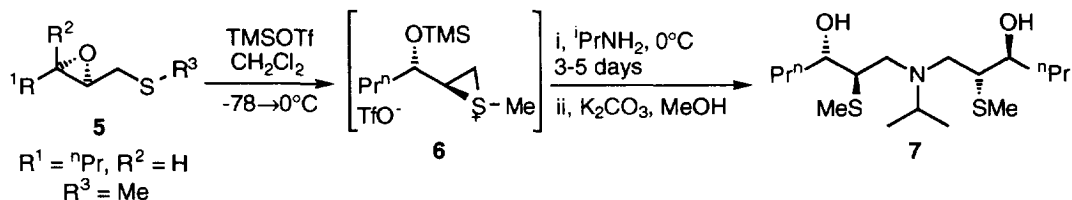


Also of importance to our work was a series of related peptide-derived diamino thiols including (3) which have also shown high activity (1nM) as aminopeptidase inhibitors.¹³ By analogy with (3) we reasoned that the amide carbonyl group of bestatin may not be necessary for activity, although it is known that the alcohol group (or presumably the thiol group) is required.⁹ Because the situation regarding binding in these types of compound remains unclear,^{9,13} we felt it would be of interest to embark on a programme to synthesise related potential novel aminopeptidase inhibitors [e.g. (4)], to further probe the structural requirements for inhibitory activity. This methodology would also provide access to novel peptide isosteres.¹⁴

Synthesis of new potential aminopeptidase inhibitors.

We thus wished to develop methodology based on our recent work, where thiiranium ion intermediates are generated *in situ* from homochiral 2,3-epoxy sulfides under Lewis acidic conditions, and extend it to allow the use of α -amino acid-based nucleophiles.¹⁵ The 2,3-epoxy sulfides used in this work have been described previously.^{5,15,16} Importantly, to get the relative stereochemistry required for bestatin-like systems, 2,3-epoxy sulfides derived from *cis*-alkenes are required, although it was also of importance that the reaction be successful with substrates derived from *trans*-alkenes, which would give the opposite relative stereochemical configuration at C-2 and C-3. We initially chose isopropylamine as the amine nucleophile as we considered it to be a reasonable model system for α -amino ester nucleophiles, and had previously proven problematic.¹⁶

Under what we believed were optimised reaction conditions (0°C, 3-5 days),^{4,16} isopropylamine gave only a low yield of dialkylated product (7). If the reaction was carried out under milder conditions (-78°C, 12h), (7) was still the only isolable product, again in low yield. We had previously noted that silylated nucleophiles were generally good for reaction with thiiranium ions,⁴ however despite considerable experimentation we were unable to achieve yields of >20% for primary amine derivatives, including the stabase derivatives of $^i\text{PrNH}_2$, Ala(OMe) and Leu(OMe).¹⁷

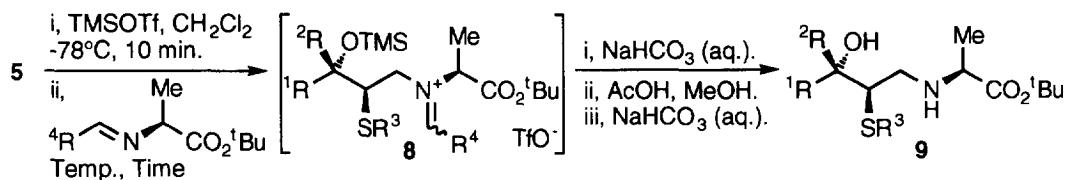


Scheme 2

We had also observed that sp^2 hybridised nitrogen-based nucleophiles (e.g. 2-trimethylsilyloxy pyridine) reacted well with our thiiranium ion intermediates.⁴ It was this observation that led us to develop methodology for the use of imines as synthetic equivalents for primary amines in the nucleophilic trapping reaction,¹⁶ the initial iminium ion products being readily hydrolysed to the corresponding secondary amine on work-up. Related procedures have previously been reported for the preparation of secondary amines using dimethyl

sulfate and alkyl halides as alkylating agents.¹⁸

Previous results had indicated that the acetaldehyde and anisaldehyde-derived imines were most efficient for this reaction.¹⁶ Such imine derivatives of Ala(OⁱBu) were prepared according to literature procedures¹⁹ and investigated in the thiiranium ion trapping reaction sequence (table 1). As can be seen from the limited number of examples, moderate yields of the desired products can be obtained using procedures slightly modified from our previous reports. In this case, iminium ion hydrolysis is carried out using NaHCO₃ (aq.), followed by AcOH/MeOH to remove the trimethylsilyl group. We had previously used K₂CO₃ (aq.) which accomplished both reactions in one step, but we felt with these more sensitive systems, racemisation and/or ester hydrolysis could be an important side reaction. Note that yields are for the 4 step reaction sequence (*viz.* thiiranium ion generation, iminium ion formation, hydrolysis, and deprotection) and purification. The desired products were obtained in reasonable yield as single diastereoisomers as determined by ¹H and ¹³C NMR, indicating complete retention of stereochemical integrity throughout the reaction sequence. It was also possible to use BF₃•OEt₂ instead of TMSOTf in the reaction with only slight decrease in the efficiency of the reaction (entry 3).



Entry	R ¹	R ²	R ³	Temp. (°C)	Time (h)	R ⁴	Yield
1	H	ⁿ Pr	Ph	0	72	(4-MeO)C ₆ H ₄	44
2	ⁿ Pr	H	Me	-78	12	Me	40 ^a
3	ⁿ Pr	H	Me	-78	12	Me	34 ^{a,b}

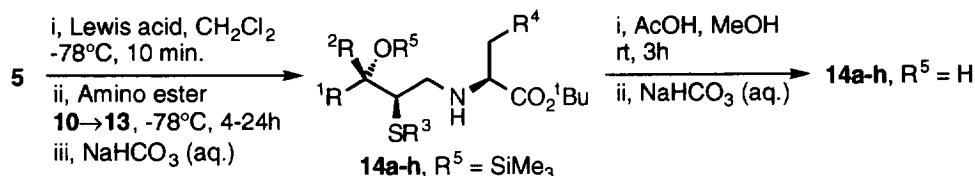
^aIsopropylamine added at -78°C prior to workup;

^bBF₃•OEt₂ used in place of TMSOTf.

Table 1: Coupling of thiiranium ions with imines derived from α -amino esters.

Perhaps the most interesting aspect of this chemistry is the reactivity profile observed for the nucleophilic trapping at various temperatures. If the reaction is allowed to proceed at 0 °C for 3 days then moderate yields of products are obtained. However, if the reaction is carried out at -78 °C then similar yields can be obtained in a much shorter reaction time. The possibility that this reaction could be carried out at such low temperature led us to reinvestigate our original reactions which had previously given only polyalkylation of primary amine nucleophiles by the thiiranium ion intermediates. To our disappointment, isopropylamine still only gave a *bis*-alkylated product under these reaction conditions, but fortunately free α -amino esters gave only products of clean monoalkylation, in better yield than using the imine systems, and with additional recovery of starting material in some cases (table 2). The reaction shows a high degree of generality. It gives moderate to good overall yields of the desired products for both *trans*-S-methyl- and *cis*-S-phenyl-2,3-epoxy sulfides. It is important to emphasise that, as with the imine-derived nucleophiles, these yields are for the multistep process, *viz.* thiiranium ion generation, nucleophilic trapping with the α -amino ester, work-up, deprotection (AcOH, MeOH) and purification by column chromatography. In all cases the products were isolated as single diastereoisomers as determined by ¹H and ¹³C NMR. Further confirmation of this came from a reaction using racemic 2,3-epoxy sulfide substrate and (+)-*L*-alanine methyl ester, which gave a mixture of diastereomeric products which could clearly be observed by NMR.

The reaction is successful for 2,3-epoxy sulfides derived from both *cis*- and *trans*-alkenes, both as the S-methyl and S-phenyl thioethers. The *tert*-butyl esters of alanine, leucine (required for bestatin-like systems), and phenyl alanine, were chosen as typical α -amino ester substrates and were found to be equally effective. In addition, for the one example investigated (entry 8), a methyl ester was as efficient as the *tert*-butyl ester. The use of $\text{BF}_3 \cdot \text{OEt}_2$ as Lewis acid in place of TMSOTf (entry 2), resulted in only marginal decrease in the efficiency of the overall process.



Entry	R ¹	R ²	R ³	R ⁴	Lewis Acid	Amino ester	Product	% Yield ^a
1	ⁿ Pr	H	Me	H	TMSOTf	10	14a	54 (74)
2	ⁿ Pr	H	Me	H	$\text{BF}_3 \cdot \text{OEt}_2$	10	14a	49
3	ⁿ Pr	H	Ph	H	TMSOTf	10	14b	48 (84)
4	ⁿ Pr	H	Me	ⁱ Pr	TMSOTf	11	14c	54
5	ⁿ Pr	H	Ph	ⁱ Pr	TMSOTf	11	14d	58 (87)
6	H	ⁿ Pr	Me	H	TMSOTf	10	14e	44
7	H	ⁿ Pr	Ph	H	TMSOTf	10	14f	43 (78)
8	ⁿ Pr	H	Me	H	TMSOTf	12	14g	53 ^b
9	ⁿ Pr	H	Me	Ph	TMSOTf	13	14h	49

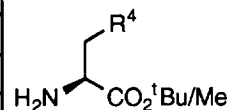
Amino esters:

10, Ala(O^tBu)

11, Leu(O^tBu)

12, Ala(OMe)

13, Phe(O^tBu)



^aValues in parentheses are yields based on recovered starting material; ^bMethyl ester

Table 2: Coupling of thiiranium ions with α -amino esters

This methodology now demonstrates the potential of using α -amino acid-based nucleophiles for reactions with thiiranium ion intermediates, and we are currently developing this chemistry further to prepare systems more closely related to bestatin (**1**) and other biologically active systems.²⁰

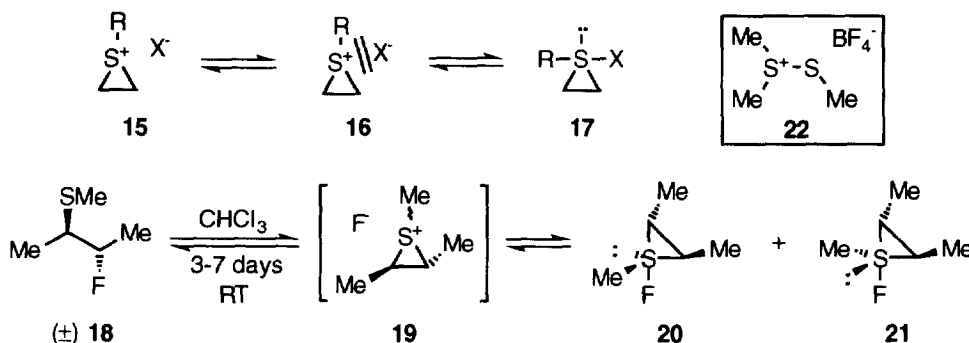
Mechanistic implications - the nature of the "thiiranium ion" intermediate.

This chemistry is also beginning to shed further light on the nature of the reactive species in the reaction, the "thiiranium ion" intermediate.^{6,7} It is of interest to note that in most of the examples involving S-phenyl thiiranium ions, the reaction did not go to completion, and considerable quantities (up to 36%) of starting material could be recovered. Despite much experimentation, it was not possible to significantly improve on this. In comparison, for reactions involving the S-methyl thiiranium ions, recovery of starting material was observed in only one case (entry 1), the material balance in the other examples being mainly decomposition products. This is likely to be a reflection of the greater reactivity of S-alkyl thiiranium ions relative to S-phenyl systems, due to stabilisation of the positive charge on sulfur in the latter.

The surprising effect of temperature on the reactivity of our thiiranium ion system is particularly worthy of comment. We have for some time been concerned that although thiiranium ions are generally considered to be highly electrophilic species,^{6,7} our original optimum reaction conditions of 0°C over a period of days⁴ were consistent with the intermediacy of a much less reactive intermediate. The surprising observation that similar, if

not better yields could be obtained after shorter reaction times (4-24h) at considerably lower temperatures (-78°C), would tend to indicate that the nature of the reacting species (the "thiiranium ion intermediate") is different in either case. Despite our recent success in related systems,²¹ we have so far been unsuccessful in characterising the inferred thiiranium ion intermediate at 0°C or room temperature by ^1H NMR, although further investigation along these lines are currently underway.

In fact, reactions of thiiranium ions are usually more complex than might at first be envisaged, mainly because of the different potential structures of the intermediates involved.^{6,7} Thus, thiiranium ions (15) are one extreme possible structure, and episulfuranes (17), where the anionic counterion is covalently bonded to the sulfur atom, lies at the other end of the spectrum, with various degrees of ion pairing in between. Episulfuranes are proposed as intermediates in reactions of halogens with episulfides,²² halide ions with thiiranium ions,²³ and sulfonyl halides with alkenes.^{23a,24} Molecular orbital calculations have indicated that in the gas phase, an episulfurane structure is more stable than the corresponding sulfonium salt.²⁵ The stable fluoroepisulfuranes (20) and (21) have recently been isolated as a mixture of diastereoisomers at sulfur, and are sufficiently stable to allow characterisation at room temperature.²⁶ They are considered to be the thermodynamically favoured products of rearrangement of a β -fluorosulfide, the reaction proceeding *via* a thiiranium ion (scheme 3).



Scheme 3

Alternatively, it has been proposed that with suitable alkene sulfonylating agents, the thiiranium ion may be in equilibrium with a ring opened intermediate. This has been noted previously using reagents such as dimethyl(methylthio)sulfonium tetrafluoroborate (DMTSF) (22),²⁷ where the thiiranium ion formed by formal addition of MeS^+ to an alkene, is believed to be in equilibrium with a sulfonium salt, formed as a result of reversible nucleophilic ring opening by dimethyl sulfide which is a byproduct of the sulfonylation reaction.^{27c} Reformation of the thiiranium ion and irreversible nucleophilic ring opening gives the final product. This reaction requires a few days to reach completion, which is of the same order of magnitude observed with our systems.

We believe possible explanations for our observations are that at -78°C , the intermediate in the reaction is essentially a free thiiranium ion (scheme 4). On warming, some interaction with the nucleophile, a thioether (*e.g.* 5 or 26), or counterion (CF_3SO_3^-) occurs either by formation of some kind of episulfurane-like intermediate (25),⁷ or by reversible ring opening of the thiiranium ion to give (24), which reacts with an external nucleophile *via* a small equilibrium concentration of the thiiranium ion. We are currently investigating both these hypotheses further, the results of which will be reported in due course.

13.8mmol) and pyridine (1.09g, 13.8mmol) in toluene (10cm³) for 4h, allowed to cool and concentrated to give crude (+)-*L*-alanine *tert*-butyl ester anisylidene imine (2.84g, 13.9mmol, 100% yield) as a yellow oil used without further purification: δ_{H} (300MHz, CDCl₃) 1.45 (9 H, s, ^tBu), 1.47 (3 H, d, *J* 6.8, 3-H), 3.81 (3 H, s, CH₃OAr), 3.98 (1 H, q, *J* 6.8, 2-H), 7.30 (4 H, AB system, *J* 8.8, $\Delta\nu$ 241.8, ArH), 8.20 (1 H, s, CH=N); ν_{max} (thin film)/cm⁻¹ 1731s (C=N); MS (CI), *m/z* 264 (*M*⁺+1, 100%); α_{D}^{20} +5.39° (*c* 1.15, EtOH).

Typical details of thiiranium ion couplings with imines derived from simple primary amines can be found in an earlier full paper.⁴

Coupling of thiiranium ions with α -amino esters (table 2).

(-)-*N*-[(2'*S*,3'*S*)-2'-Methylthio-3'-hydroxyhexyl]-(*R*)-alanine *tert*-butyl ester (**14a**).

Trimethylsilyl trifluoromethane sulfonate (0.159cm³, 0.822mmol) was added to epoxy sulfide (-)-2-[(methylthio)methyl]-(2*S*,3*S*)-3-propyloxirane (100mg, 0.685mmol) in dichloromethane (2cm³) at -78°C, stirred for 5 mins then alanine *tert*-butyl ester (120mg, 0.822mmol) added and stirring continued for 3 h at this temperature. Saturated aqueous sodium hydrogen carbonate solution (3cm³) was added, the mixture shaken and the layers separated. The aqueous layer was extracted with dichloromethane (5x5cm³) and the combined organic portions dried (MgSO₄), filtered and concentrated. The crude mixture was stirred at room temperature with glacial acetic acid (0.04cm³, 0.685mmol) in methanol (3cm³) for 3 hours at room temperature then concentrated. Saturated aqueous sodium hydrogen carbonate solution (3cm³) was added, the mixture shaken and the layers separated. The aqueous layer was extracted with dichloromethane (5x5cm³) and the combined organic portions dried (MgSO₄), filtered and concentrated. Flash chromatography [silica (10g); eluant 3% ethyl acetate / petroleum ether followed by 30% ethyl acetate / 1% ethanol / petroleum ether] gave epoxy sulfide starting material (20mg, 0.137mmol, 20% yield) and (-)-*N*-[(2'*S*,3'*S*)-2'-methylthio-3'-hydroxyhexyl]-(*R*)-alanine *tert*-butyl ester as a colourless oil (107mg, 0.368mmol, 54% yield, 74% yield based on recovered starting material): δ_{H} (300MHz, CDCl₃) 0.94 (3 H, t, *J* 6.9, 6'-H), 1.27 (3 H, d, *J* 7.8, 3-H), 1.30-1.60 (4 H, m, 4'-H + 5'-H), 1.47 (9 H, s, ^tBu), 2.12 (3 H, s, MeS), 2.63 (1 H, ddd, *J* 5.1, 7.2, 5.7, 4.0, 2'-H), 2.91 (1 H, dd, *J* 12.0, 4.0, one of 1'-H), 3.00 (1 H, dd, *J* 12.0, 5.7, remaining 1'-H), 3.26 (1 H, q, *J* 7.8, 2-H), 3.76 (1 H, dt, *J* 7.2, 4.8, 3'-H); δ_{C} (100MHz, CDCl₃) 14.07 (C-6' + MeS), 19.07 (C-5'), 19.12 (C-3), 28.01 ((CH₃)₃C), 38.32 (C-4'), 47.48 (C-1'), 50.72 (C-2'), 56.86 (C-3'), 74.38 (C-2), 81.20 ((CH₃)₃C), 174.14 (C-1); ν_{max} (thin film)/cm⁻¹ 3650-3000 (br, O-H, N-H), 2920 (s, C-H), 2885 (s, C-H), 2820 (s, C-H), 1700 (s, C=O), 1350 (s), 1130 (s); MS (CI) [Found: (*M*+1), 292.1951. Calculated for C₁₄H₃₀NO₃S: *m/z* 292.1946] *m/z* 292 (*M*⁺+1, 100%); α_{D}^{20} -57.7° (*c* 1.02, ethanol).

(-)-*N*-[(2'*S*,3'*S*)-2'-Phenylthio-3'-hydroxyhexyl]-(*R*)-alanine *tert*-butyl ester (**14b**).

Trimethylsilyl trifluoromethane sulfonate (0.111cm³, 0.577mmol) was added to epoxy sulfide (-)-2-[(phenylthio)methyl]-(2*S*,3*S*)-3-propyloxirane (100mg, 0.481mmol) in dichloromethane (2cm³) at -78°C, stirred for 5 min, then alanine *tert*-butyl ester (84mg, 0.577mmol) added and stirring continued for 18 h at this temperature. Saturated aqueous sodium hydrogen carbonate solution (3cm³) was added, the mixture shaken and the layers separated. The aqueous layer was extracted with dichloromethane (5x5cm³) and the combined organic portions dried (MgSO₄), filtered and concentrated. The crude mixture was stirred at room temperature with glacial acetic acid (0.04cm³, 0.685mmol) in methanol (3cm³) for 3 h at room temperature then concentrated. Saturated aqueous sodium hydrogen carbonate solution (3cm³) was added, the mixture shaken and the layers separated. The aqueous layer was extracted with dichloromethane (5x5cm³) and the combined organic portions dried (MgSO₄), filtered and concentrated. Flash chromatography [silica (10g); eluant 3% ethyl acetate / petroleum ether followed by 30% ethyl acetate / 1% ethanol / petroleum ether] gave epoxy sulfide starting

material (33mg, 0.149mmol, 36% yield) and (-)-*N*-[(2'*S*,3'*S*)-2'-phenylthio-3'-hydroxyhexyl]-(*R*)-alanine *tert*-butyl ester as a colourless oil (77mg, 0.218mmol, 48% yield, 84% yield based on recovered starting material): δ_{H} (300MHz, CDCl_3) 0.94 (3 H, t, J 8.3, 6'-H), 1.25 (3 H, d, J 6.0, 3-H), 1.33-1.64 (4 H, m, 4'-H and 5'-H), 1.38 (9 H, s, ^tBu), 2.89 (1 H, dd, J 12.0, 4.2, one of 1'-H), 2.96 (1 H, dd, J 12.0, 5.5, remaining 1'-H), 3.12 (1 H, ddd, J 7.5, 5.5, 4.2, 2'-H), 3.20 (1 H, q, J 6.0, 2-H), 3.86 (1H, ddd, J 7.5, 4.5, 1.9, 3-H), 7.23-7.46 (5H, m, ArH); δ_{C} (100MHz, CDCl_3) 14.09 (CH_3 -6'), 19.06 (CH_2 -5'), 19.09 (CH_3 -3), 27.96 ($(\text{CH}_3)_3\text{C}$), 38.45 (CH_2 -4'), 48.54 (CH_2 -1'), 52.64 (CH -2'), 57.02 (CH -3'), 74.60 (CH -2), 81.26 ($(\text{CH}_3)_3\text{C}$), 127.24 (Ar-CH), 128.97 (Ar-CH), 132.41 (Ar-CH), 134.29 (Ar-C), 174.05 (C-1); ν_{max} (thin film)/ cm^{-1} 3700-3090 (br, O-H, N-H), 2960 (s, C-H), 2920 (s, C-H), 2860 (s, C-H), 1740 (s, C=O), 1490 (s), 1470 (s), 1445 (s), 1155 (s); MS (EI) [Found: (M^+), 354.2135. Calculated for $\text{C}_{19}\text{H}_{32}\text{NO}_3\text{S}$: m/z 354.2103] m/z 354 (M^+ , 0.5%), 178 (90), 102 (100); α_{D}^{20} -66.7° (c 1.11, EtOH).

(-)-*N*-[(2'*S*,3'*S*)-2-Methylthio-3-hydroxyhexyl]-(*R*)-leucine *tert*-butyl ester (**14c**).

Trimethylsilyl trifluoromethane sulfonate (0.159 cm^3 , 0.822mmol) was added to epoxy sulfide (-)-2-[(methylthio)methyl]-(2*S*,3*S*)-3-propyloxirane (100mg, 0.685mmol) in dichloromethane (2 cm^3) at -78°C, stirred for 5 min, then leucine *tert*-butyl ester (154mg, 0.822mmol) added and stirring continued for 4 h at this temperature. Saturated aqueous sodium hydrogen carbonate solution (3 cm^3) was added, the mixture shaken and the layers separated. The aqueous layer was extracted with dichloromethane (5 \times 5 cm^3) and the combined organic portions dried (MgSO_4), filtered and concentrated. The crude mixture was stirred at room temperature with glacial acetic acid (0.040 cm^3 , 0.685mmol) in methanol (3 cm^3) for 3 hours at room temperature then concentrated. Saturated aqueous sodium hydrogen carbonate solution (3 cm^3) was added, the mixture shaken and the layers separated. The aqueous layer was extracted with dichloromethane (5 \times 5 cm^3) and the combined organic portions dried (MgSO_4), filtered and concentrated. Flash chromatography [silica (10g); eluant 3% ethyl acetate / petroleum ether followed by 10% ethyl acetate / 1% ethanol / petroleum ether] gave (-)-*N*-[(2'*S*,3'*S*)-2-methylthio-3-hydroxyhexyl]-(*R*)-leucine *tert*-butyl ester as a colourless oil (120mg, 0.372mmol, 54% yield): δ_{H} (300MHz, CDCl_3) 0.92 (6 H, t, J 6.9, $(\text{CH}_3)_2\text{CH}$), 0.94 (3 H, t, J 6.9, 6'-H), 1.34-1.60 (6 H, m, 4'-H, 5'-H and 3-H), 1.48 (9 H, s, ^tBu), 1.68-1.75 (1 H, m, 4-H), 2.12 (3H, s, MeS), 2.65 (1 H, ddd, J 6.0, 5.1, 3.0, 2'-H), 2.87 (1 H, dd, J 12.3, 3.0, one of 1'-H), 3.01 (1 H, dd, J 12.3, 5.1, remaining 1'-H), 3.17 (1 H, t, J 6.9, 2-H), 3.77 (1 H, q, J 6.0, 3'-H); δ_{C} (100MHz, CDCl_3) 14.08 (C-6'), 14.11 (MeS), 19.13 (C-5'), 21.98 (one of $(\text{CH}_3)_2\text{CH}$), 22.78 (remaining $(\text{CH}_3)_2\text{CH}$), 24.87 ($(\text{CH}_3)_2\text{CH}$), 28.10 ($(\text{CH}_3)_3\text{C}$), 38.57 (C-4'), 42.53 (C-3), 47.22 (C-1'), 50.61 (C-2'), 60.23 (C-3'), 74.46 (C-2), 81.23 ($(\text{CH}_3)_3\text{C}$), 174.27 (C-1); ν_{max} (thin film)/ cm^{-1} 3650-3000 (br, O-H, N-H), 2920 (s, C-H), 2885 (s, C-H), 2820 (s, C-H), 1700 (s, C=O), 1350 (s), 1130 (s); MS (CI) [Found: ($\text{M}+1$), 334.2418. Calculated for $\text{C}_{17}\text{H}_{36}\text{NO}_3\text{S}$: m/z 334.2415] m/z 334 (M^++1 , 100%); α_{D}^{20} -52.6° (c 1.02, EtOH).

(-)-*N*-[(2'*S*,3'*S*)-2-Phenylthio-3'-hydroxyhexyl]-(*R*)-leucine *tert*-butyl ester (**14d**).

Trimethylsilyl trifluoromethane sulfonate (0.111 cm^3 , 0.577mmol) was added to epoxy sulfide (-)-2-[(phenylthio)methyl]-(2*S*,3*S*)-3-propyloxirane (100mg, 0.481mmol) in dichloromethane (2 cm^3) at -78°C, stirred for 5 min then leucine *tert*-butyl ester (108mg, 0.577mmol) added and stirring continued for 18 h at this temperature. Saturated aqueous sodium hydrogen carbonate solution (3 cm^3) was added, the mixture shaken and the layers separated. The aqueous layer was extracted with dichloromethane (5 \times 5 cm^3) and the combined organic portions dried (MgSO_4), filtered and concentrated. The crude mixture was stirred at room temperature with glacial acetic acid (0.04 cm^3 , 0.685mmol) in methanol (3 cm^3) for 3 hours at room temperature then concentrated. Saturated aqueous sodium hydrogen carbonate solution (3 cm^3) was added, the mixture shaken and the layers separated. The aqueous layer was extracted with dichloromethane (5 \times 5 cm^3) and the combined organic portions dried (MgSO_4), filtered and concentrated. Flash chromatography [silica (10g); eluant 2% ethyl acetate /

petroleum ether followed by 5% ethyl acetate / petroleum ether, then 10% ethyl acetate / 1% ethanol / petroleum ether] gave epoxy sulfide starting material (29mg, 0.139mmol, 29% yield) and (-)-*N*-[(2'*S*,3'*S*)-2'-phenylthio-3'-hydroxyhexyl]-(*R*)-leucine *tert*-butyl ester as a colourless oil (107mg, 0.279mmol, 58% yield, 87% yield based on recovered starting material): δ_{H} (300MHz, CDCl_3) 0.91 (3 H, t, J 6.0, $(\text{CH}_3)_2\text{CH}$), 0.94 (3 H, t, J 6.9, 6'-H), 1.25-1.73 (7 H, m, 4'-H, 5'-H, 3-H and 4-H), 1.37 (9 H, s, ^tBu), 2.85 (1 H, dd, J 12.6, 3.6, one of 1'-H), 2.95 (1 H, dd, J 12.6, 4.5, remaining 1'-H), 3.13 (2 H, m, 2'-H and 2-H), 3.89 (1 H, ddd, J 7.5, 4.5, 2.9, 3'-H), 7.21-7.48 (5 H, m, ArH); δ_{C} (100MHz, CDCl_3) 14.10 (C-6'), 19.08 (C-5'), 22.01 (one of $(\text{CH}_3)_2\text{CH}$), 22.78 (remaining $(\text{CH}_3)_2\text{CH}$), 24.86 ($(\text{CH}_3)_2\text{CH}$), 27.97 ($(\text{CH}_3)_2\text{CH}$), 38.63 (C-4'), 42.50 (C-3), 48.17 (C-1'), 52.63 (C-2'), 60.41 (C-3'), 74.60 (C-2), 81.23 ($(\text{CH}_3)_2\text{CH}$), 127.26 (CHAr), 128.96 (CHAr), 132.55 (CHAr), 134.28 (CAr), 174.27 (C-1); ν_{max} (thin film)/ cm^{-1} 3700-3100 (br, O-H, N-H), 3060 (s, C-H), 2980 (m, C-H), 1780 (s, C=O), 1535 (s), 1490 (s), 1420 (s), 1445 (s), 1210 (s); MS (CI) [Found: (M+1), 396.2567. Calculated for $\text{C}_{22}\text{H}_{37}\text{NO}_3\text{S}$: m/z 396.2572] m/z 396 (M^+ +1, 100%); α_{D}^{20} -52.8° (c 1.11, EtOH).

(-)-*N*-[(2'*R*,3'*S*)-2'-Methylthio-3'-hydroxyhexyl]-(*R*)-leucine *tert*-butyl ester (**14e**).

Trimethylsilyl trifluoromethane sulfonate (0.159 cm^3 , 0.822mmol) was added to epoxy sulfide (+)-2-[(methylthio)methyl]-(2*R*,3*S*)-3-propyloxirane (100mg, 0.685mmol) in dichloromethane (2 cm^3) at -78°C, stirred for 5 min then leucine *tert*-butyl ester (154mg, 0.822mmol) added and stirring continued for 4 h at this temperature. Saturated aqueous sodium hydrogen carbonate solution (3 cm^3) was added, the mixture shaken and the layers separated. The aqueous layer was extracted with dichloromethane (5 \times 5 cm^3) and the combined organic portions dried (MgSO_4), filtered and concentrated. The crude mixture was stirred at room temperature with glacial acetic acid (0.04 cm^3 , 0.685mmol) in methanol (3 cm^3) for 3 h at room temperature then concentrated. Saturated aqueous sodium hydrogen carbonate solution (3 cm^3) was added, the mixture shaken and the layers separated. The aqueous layer was extracted with dichloromethane (5 \times 5 cm^3) and the combined organic portions dried (MgSO_4), filtered and concentrated. Flash chromatography [silica (10g); eluant 3% ethyl acetate / petroleum ether followed by 10% ethyl acetate / 1% ethanol / petroleum ether] gave (-)-*N*-[(2'*R*,3'*S*)-2'-methylthio-3'-hydroxyhexyl]-(*R*)-leucine *tert*-butyl ester as a colourless oil (71mg, 0.300mmol, 44% yield): δ_{H} (300MHz, CDCl_3) 0.92 (6 H, t, J 6.9, $(\text{CH}_3)_2\text{CH}$), 0.94 (3 H, t, J 6.9, CH_3 -6'), 1.30-1.75 (7 H, m, 4'-H, 5'-H, 3-H and 4-H), 1.47 (9 H, s, ^tBu), 2.09 (3 H, s, CH_3 S), 2.66 (1 H, dd, J 11.4, 2.7, one of 1'-H), 2.72 (1 H, ddd, J 7.5, 3.9, 2.7, 2'-H), 3.19 (1 H, t, J 7.2, 2-H), 3.21 (1 H, dd, J 11.4, 3.9, remaining 1'-H), 3.97 (1 H, ddd, J 7.5, 5.0, 2.0, 3-H); δ_{C} (100MHz, CDCl_3) 13.78 (C-6'), 14.09 (MeS), 19.11 (C-5'), 22.01 (one of $(\text{CH}_3)_2\text{CH}$), 22.76 (remaining $(\text{CH}_3)_2\text{CH}$), 24.85 ($(\text{CH}_3)_2\text{CH}$), 28.05 ($(\text{CH}_3)_2\text{CH}$), 36.94 (C-4'), 42.69 (C-3), 49.97 (C-1'), 52.20 (C-2'), 60.36 (C-3'), 75.72 (C-2), 81.17 ($(\text{CH}_3)_2\text{CH}$), 174.25 (C-1); ν_{max} (thin film)/ cm^{-1} 3650-3000 (br, O-H, N-H), 2920 (s, C-H), 2885 (s, C-H), 2820 (s, C-H), 1700 (s, C=O), 1420 (m), 1350 (s), 1130 (s); MS (CI) [Found: (M+1), 334.2419. Calculated for $\text{C}_{17}\text{H}_{36}\text{NO}_3\text{S}$: m/z 334.2416] m/z 334 (M^+ +1, 100%); α_{D}^{20} -35.1° (c 1.02, EtOH).

(-)-*N*-[(2'*R*,3'*S*)-2'-Phenylthio-3'-hydroxyhexyl]-(*R*)-leucine *tert*-butyl ester (**14f**).

Trimethylsilyl trifluoromethane sulfonate (0.111 cm^3 , 0.577mmol) was added to epoxy sulfide (+)-2-[(phenylthio)methyl]-(2*R*,3*S*)-3-propyloxirane (100mg, 0.481mmol) in dichloromethane (2 cm^3) at -78°C, stirred for 5 min then leucine *tert*-butyl ester (108mg, 0.577mmol) added and stirring continued for 24 h at this temperature. Saturated aqueous sodium hydrogen carbonate solution (3 cm^3) was added, the mixture shaken and the layers separated. The aqueous layer was extracted with dichloromethane (5 \times 5 cm^3) and the combined organic portions dried (MgSO_4), filtered and concentrated. The crude mixture was stirred at room temperature with glacial acetic acid (0.04 cm^3 , 0.685mmol) in methanol (3 cm^3) for 3 h at room temperature then concentrated. Saturated aqueous sodium hydrogen carbonate solution (3 cm^3) was added, the mixture shaken and the layers separated. The aqueous layer was extracted with dichloromethane (5 \times 5 cm^3) and the combined organic portions

dried (MgSO_4), filtered and concentrated. Flash chromatography [silica (10g); eluant 2% ethyl acetate / petroleum ether followed by 5% ethyl acetate / petroleum ether then 30% ethyl acetate / 1% ethanol / petroleum ether] gave epoxy sulfide starting material (35mg, 0.168mmol, 35% yield) and *(-)-N-[(2'R,3'S)-2'-phenylthio-3'-hydroxyhexyl]-(R)-leucine tert-butyl ester* as a colourless oil (82mg, 0.208mmol, 43% yield, 78% yield based on recovered starting material): δ_{H} (300MHz, CDCl_3) 0.91 (3 H, t, J 6.0, $(\text{CH}_3)_2\text{CH}$), 0.94 (3 H, t, J 6.9, 6'-H), 1.25-1.73 (7 H, m, 4'-H, 5'-H, 3-H and 4-H), 1.37 (9 H, s, ^tBu), 2.66 (1 H, dd, J 11.4, 2.1, one of 1'-H), 3.14 (1 H, dd, J 11.4, 3.6, remaining 1'-H), 3.10-3.20 (2 H, m, 2'-H and 2-H), 4.07 (1 H, ddd, J 7.5, 5.7, 1.5, 3-H), 7.21-7.35 (5 H, m, ArH); δ_{C} (100MHz, CDCl_3) 14.13 (C-6'), 19.08 (C-5'), 22.18 (one of $(\text{CH}_3)_2\text{CH}$), 22.71 (remaining $(\text{CH}_3)_2\text{CH}$), 24.90 ($(\text{CH}_3)_2(\text{CH}_3)_2\text{CH}$), 27.95 ($(\text{CH}_3)_2\text{C}$), 37.05 (C-4'), 42.70 (C-3), 51.34 (C-1'), 54.35 (C-2'), 60.77 (C-3'), 75.81 (C-2), 81.17 ($(\text{CH}_3)_2\text{C}$), 127.11 (CHAr), 128.93 (CHAr), 132.69 (CHAr), 134.44 (CAr), 174.12 (C-1); ν_{max} (thin film)/ cm^{-1} 3700-3100 (br, O-H, N-H), 3060 (s, C-H), 2980 (m, C-H), 1780 (s, C=O), 1535 (s), 1490 (s), 1420 (s), 1445 (s), 1210 (s); MS (CI) [Found: (M+1), 396.2562. Calculated for $\text{C}_{22}\text{H}_{38}\text{NO}_3\text{S}$: m/z 396.2572] m/z 396 (M^+ +1, 100%); α_{D}^{20} -66.7° (c 1.11, EtOH).

(-)-N-[(2'S,3'S)-2'-Methylthio-3'-hydroxyhexyl]-(R)-alanine methyl ester (14g).

Trimethylsilyl trifluoromethane sulfonate (0.159 cm^3 , 0.822mmol) was added to epoxy sulfide *(-)-2-[(methylthio)methyl]-(2S,3S)-3-propyloxirane* (100mg, 0.685mmol) in dichloromethane (2 cm^3) at -78°C, stirred for 5 mins then alanine methyl ester (85.0mg, 0.822mmol) added and stirring continued for 3 h at this temperature. Saturated aqueous sodium hydrogen carbonate solution (3 cm^3) was added, the mixture shaken and the layers separated. The aqueous layer was extracted with dichloromethane (5x5 cm^3) and the combined organic portions dried (MgSO_4), filtered and concentrated. The crude mixture was stirred at room temperature with glacial acetic acid (0.04 cm^3 , 0.685mmol) in methanol (3 cm^3) for 3 hours at room temperature then concentrated. Saturated aqueous sodium hydrogen carbonate solution (3 cm^3) was added, the mixture shaken and the layers separated. The aqueous layer was extracted with dichloromethane (5x5 cm^3) and the combined organic portions dried (MgSO_4), filtered and concentrated. Flash chromatography [silica (10g); eluant 10% ethyl acetate / petroleum ether followed by 40% ethyl acetate / 1% ethanol / petroleum ether] gave *(-)-N-[(2'S,3'S)-2'-methylthio-3'-hydroxyhexyl]-(R)-alanine methyl ester* as a colourless oil (84mg, 0.361mmol, 53% yield): δ_{H} (300MHz, CDCl_3) 0.94 (3 H, t, J 6.9, 6'-H), 1.33 (3 H, d, J 7.8, 3-H), 1.40-1.60 (4 H, m, 4'-H and 5'-H), 2.10 (3 H, s, MeS), 2.64 (1 H, ddd, J 7.2, 5.4, 3.6, 2'-H), 2.89 (1 H, dd, J 12.3, 3.6, one of 1'-H), 3.00 (1 H, dd, J 12.3, 5.4, remaining 1'-H), 3.35-3.52 (2 H, s, br, NH and OH), 3.42 (1 H, q, J 7.8, 2-H), 3.74 (3 H, s, CO_2Me), 3.40-3.79 (1 H, m, 3'-H); δ_{C} (100MHz, CDCl_3) 14.10 (C-6' + MeS), 19.14 (C-5' + C-3), 38.21 (C-4'), 47.36 (C-1'), 50.97 (C-2'), 51.93 (MeO_2C), 56.14 (C-3'), 74.24 (C-2), 175.29 (C-1); ν_{max} (thin film)/ cm^{-1} 3620-3060 (br, O-H, N-H), 2960 (s, C-H), 2930 (s, C-H), 2880 (s, C-H), 1740 (s, C=O), 1560 (s), 1540 (s), 1200 (s), 1160 (s), 975 (m); MS (CI) [Found: (M+1), 250.1483. Calculated for $\text{C}_{11}\text{H}_{24}\text{NO}_3\text{S}$: m/z 250.1477] m/z 250 (M^+ +1, 100%); α_{D}^{20} -52.6° (c 1.22, EtOH).

A similar reaction performed using (\pm) -2-[(methylthio)methyl]-(2S,3S)-3-propyloxirane gave an inseparable mixture of *(-)-N-[(2'S,3'S)-2'-methylthio-3'-hydroxyhexyl]-(R)-alanine methyl ester* and *(-)-N-[(2'R,3'R)-2'-methylthio-3'-hydroxyhexyl]-(R)-alanine methyl ester*: δ_{H} (300MHz, CDCl_3) 0.94 (3 H, t, J 6.9, 6'-H), 1.31 (3 H, d, J 7.8, 3-H), 1.40-1.60 (4 H, m, 4'-H and 5'-H), 2.11 (3 H, s, MeS), 2.56 (1 H, ddd, J 7.2, 5.4, 3.6, 2'-H), 2.80 (1 H, dd, J 12.3, 3.6, one of 1'-H), 3.04 (1 H, dd, J 12.3, 5.4, remaining 1'-H), 3.40 (1 H, q, J 7.8, 2-H), 3.74 (3 H, s, CO_2Me), 3.70-3.80 (1 H, m, 3'-H).

(-)-N-[(2'S,3'S)-2'-Methylthio-3'-hydroxyhexyl]-(R)-phenylalanine tert-butyl ester (14h).

Trimethylsilyl trifluoromethane sulfonate (0.159 cm^3 , 0.822mmol) was added to epoxy sulfide *(-)-2-[(methylthio)methyl]-(2S,3S)-3-propyloxirane* (100mg, 0.685mmol) in dichloromethane (2 cm^3) at -78°C,

stirred for 5 min then phenylalanine *tert*-butyl ester (182mg, 0.822mmol) added and stirring continued for 4 h at this temperature. Saturated aqueous sodium hydrogen carbonate solution (3cm³) was added, the mixture shaken and the layers separated. The aqueous layer was extracted with dichloromethane (5x5cm³) and the combined organic portions dried (MgSO₄), filtered and concentrated. The crude mixture was stirred at room temperature with glacial acetic acid (0.04cm³, 0.685mmol) in methanol (3cm³) for 3 hours at room temperature then concentrated. Saturated aqueous sodium hydrogen carbonate solution (3cm³) was added, the mixture shaken and the layers separated. The aqueous layer was extracted with dichloromethane (5x5cm³) and the combined organic portions dried (MgSO₄), filtered and concentrated. Flash chromatography [silica (10g); eluant 3% ethyl acetate / petroleum ether followed by 8% ethyl acetate / petroleum ether then 10% ethyl acetate / 1% ethanol / petroleum ether] gave (-)-*N*-[(2'*S*,3'*S*)-2'-methylthio-3'-hydroxyhexyl]-(*R*)-phenylalanine *tert*-butyl ester as a colourless oil (122mg, 0.332mmol, 49% yield): δ_{H} (300MHz, CDCl₃) 0.90 (3 H, t, *J* 6.8, CH₃-6'), 1.22-1.51 (4 H, m, 4'-H and 5'-H), 1.39 (9 H, s, ^tBu), 2.06 (3 H, s, MeS), 2.58 (1 H, ddd, *J* 7.5, 5.0, 3.8, 2'-H), 2.82-2.99 (4 H, m, 3-H + 1'-H), 3.40 (1 H, t, *J* 7.3, 2-H), 3.68 (1 H, br m, 3'-H), 7.16-7.30 (5 H, m, ArH); δ_{C} (100MHz, CDCl₃) 14.05 (C-6' + MeS), 19.06 (C-5'), 27.97 ((CH₃)C), 38.14 (C-4'), 39.73 (C-3), 47.48 (C-1'), 50.96 (C-2'), 63.18 (C-3'), 74.06 (C-2), 81.48 ((CH₃)C), 126.64 (CHAr), 128.34 (CHAr), 129.17 (CHAr), 137.14(CAr), 172.95 (C-1); ν_{max} (thin film)/cm⁻¹ 3650-3000 (br, O-H, N-H), 2920 (s, C-H), 2885 (s, C-H), 2820 (s, C-H), 1700 (s, C=O), 1420 (m), 1350 (s), 1130 (s); MS (CI) [Found: (M+1), 368.2265. Calculated for C₂₀H₃₄NO₃S: *m/z* 368.2259] *m/z* 368 (M⁺+1, 100%); α_{D}^{20} -26.7° (c 1.02, EtOH).

Acknowledgements: We thank Glaxo Research and Development for a studentship (DMG), the Nuffield Foundation for an award under its Scheme for Newly Appointed Science Lecturers (CMR), and the Royal Society and ICI Strategic Research Fund for Research Grants (CMR).

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§ Current address: University of Salford, Department of Chemistry and Applied Chemistry, Salford, Manchester, M5 4WT, U.K.

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(Received in UK 9 December 1996; revised 13 January 1997; accepted 16 January 1997)