Pergamon

Tetrahedron, Vol. 53, No. 9, pp. 3383-3394, 1997

0040-4020/97 $17.00 + 0.00

PII: S0040-4020(97)00060-4

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.

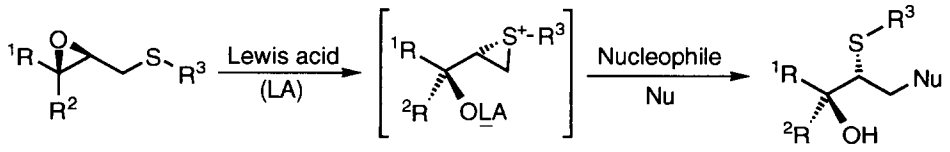
Duncan M. Gill[a§], Neil A. Pegg[b] and Christopher M. Rayner[a*]

[a]*School of Chemistry, University of Leeds, Leeds LS2 9JT, U.K. (email chrisr@chem.leeds.ac.uk)*
[b]*Medicinal 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.

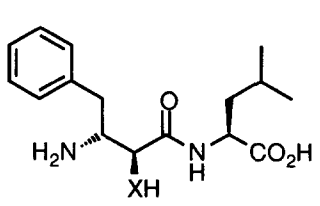
Introduction.

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 sulfides[5] 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 useful[6] and mechanistically interesting[6,7] intermediates.

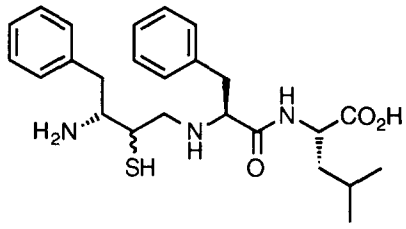


Scheme 1

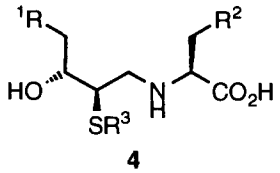
We now wished to adapt this methodology to the synthesis of compounds of biological relevance, and thus became interested in the synthesis of structural analogues of the potent aminopeptidase inhibitor bestatin (1)[8] and its superior mercapto analogue α-thiolbestatin (2).[9] Such compounds are of considerable 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]



1 Bestatin, X = O
2 α-Thiobestatin, X = S



3



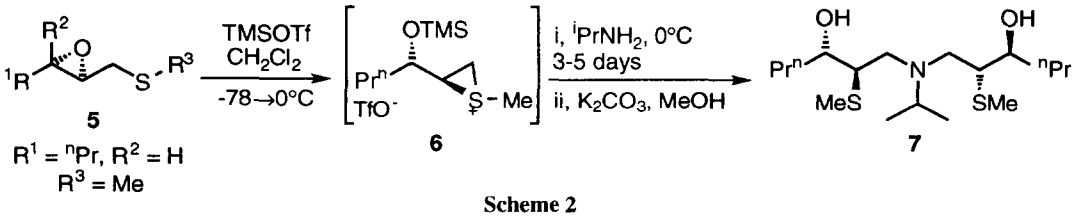
4
R^1 = Ph; R^2 = Ph, ^{i}Pr;
R^3 = Me, Ph, Bn, H

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 dialkyated 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}PrNH$_2$, Ala(OMe) and Leu(OMe).[17]



5
R^1 = ^{n}Pr, R^2 = H
R^3 = Me

6

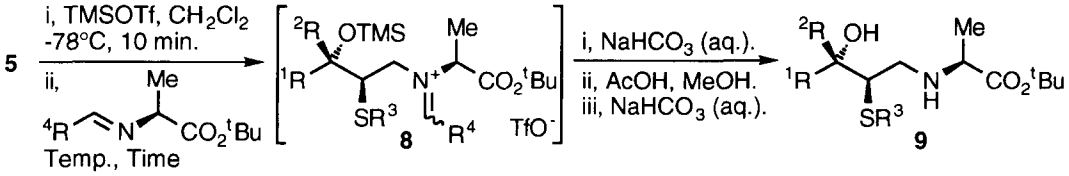
7

Scheme 2

We had also observed that sp^2 hybridised nitrogen-based nucleophiles (e.g. 2-trimethylsilyloxypyridine) 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(O^{t}Bu) were prepared according to literature procedures[19] 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 $NaHCO_3$ (aq.), followed by AcOH/MeOH to remove the trimethylsilyl group. We had previously used K_2CO_3 (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 ^{13}C NMR, indicating complete retention of stereochemical integrity throughout the reaction sequence. It was also possible to use $BF_3{\bullet}OEt_2$ instead of TMSOTf in the reaction with only slight decrease in the efficiency of the reaction (entry 3).



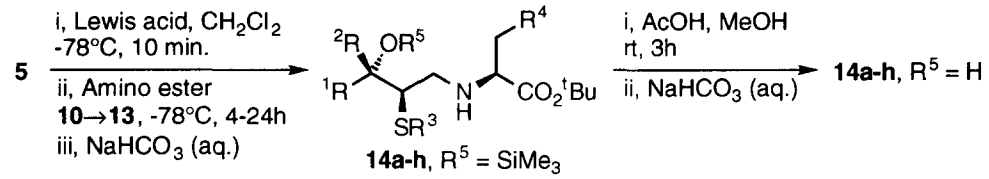
Entry	R^1	R^2	R^3	Temp. (°C)	Time (h)	R^4	Yield
1	H	^{n}Pr	Ph	0	72	(4-MeO)C_6H_4	44
2	^{n}Pr	H	Me	-78	12	Me	40[a]
3	^{n}Pr	H	Me	-78	12	Me	34[a,b]

[a]Isopropylamine added at -78°C prior to workup;
[b]$BF_3{\bullet}OEt_2$ used in place of TMSOTf.

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

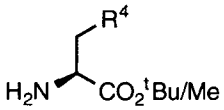
Perhaps the most interesting aspect of this chemistry is the reactivity profile observed for the nucleophilic trapping at various temperatures. If the reaction is allowed to proceed at 0 °C for 3 days then moderate yields of products are obtained. However, if the reaction is carried out at -78 °C then 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 ^{13}C 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 diasteromeric 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 $BF_3{\bullet}OEt_2$ 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	$BF_3{\bullet}OEt_2$	**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)



[a]Values in parentheses are yields based on recovered starting material; [b]Methyl 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]

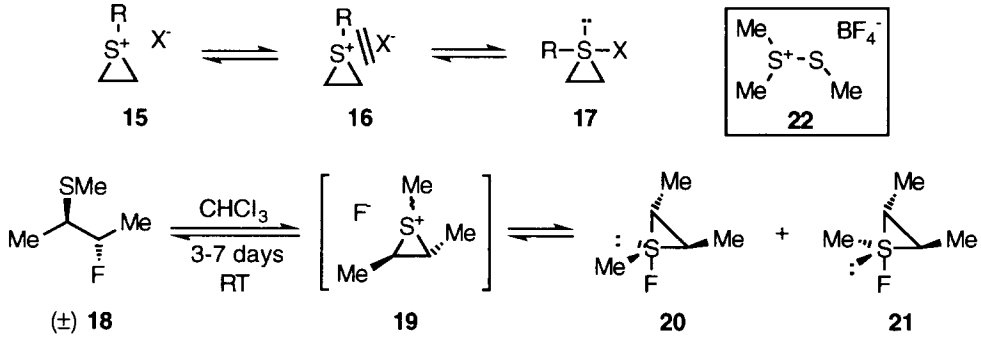
Mechanistic implications - the nature of the "thiiranium ion" intermediate.

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 days[4] 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 ^{1}H NMR, although further investigation along these lines are currently underway.

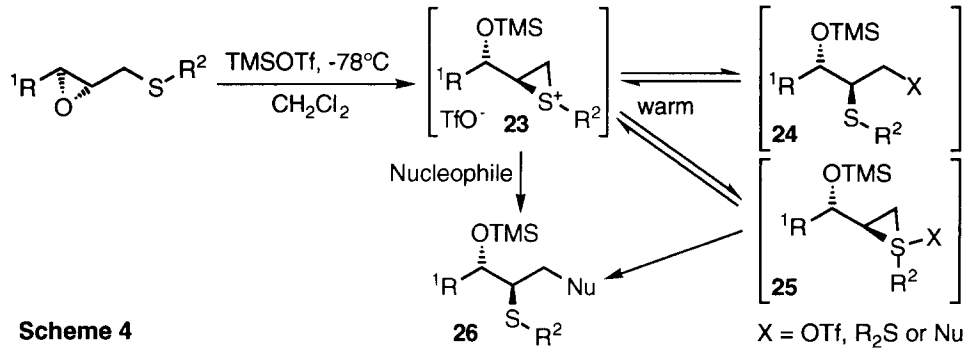
In fact, reactions of thiiranium ions are usually more complex than might at first be envisaged, mainly because of the different potential structures of the intermediates involved.[6,7] Thus, thiiranium ions (15) are one extreme possible structure, and episulfuranes (17), where the anionic counterion 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 sulfenyl 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 sulfenylating 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 sulfenylation 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.



Scheme 4

Summary.

In summary, we have succeeded in developing new methodology for coupling α-amino esters with thiiranium ions, and we are now exploiting this new chemistry for the synthesis of potential aminopeptidase inhibitors, the results of which will be reported in due course. This chemistry is also providing useful insight on the nature of the reactive species involved in this reaction, and is currently under further investigation.

Experimental Section.

General Procedures and Instrumentation.

Nuclear magnetic resonance spectra were recorded on a General Electric QE 300 spectrometer or a Bruker AM400 spectrometer. Chemical shifts are expressed in parts per million (ppm) downfield of tetramethylsilane for ^1H resonances, and referenced to the central peak of the deuterated chloroform triplet for ^{13}C resonances. Infrared spectra were recorded on a Philips PU 8706 infrared spectrophotometer and signals were referenced to the polystyrene 1601 cm^{-1} absorbtion. Mass spectra were recorded on a VG Autospec mass spectrometer. Optical rotations were measured on an Optical Activity AA-1000 polarimeter and calibrated using a solution of camphor in ethanol of known rotation, $[\alpha]_D^{20}$ +44.1° (*c* 10, ethanol). Flash chromatography signifies column chromatography on Merck silica gel (230-400) or equivalent according to the method of Still[28]. All glassware was washed with acetone, oven dried overnight at 125°C and allowed to cool under a stream of dry nitrogen prior to use. Reactions were carried out under a positive pressure of dry oxygen - free nitrogen. Solvents were removed under reduced pressure using a Buchi rotary evaporator at water aspirator pressure, followed by drying under high vacuum at 0.5 mm Hg. Solvents were purified prior to use by established procedures[29] and other reagents used as received. Trimethylsilyl trifluoromethanesulfonate was obtained from Aldrich Chemical Company Ltd. and used immediately upon opening. Petroleum ether refers to petroleum ether (b.p. 40-60°C) unless otherwise stated. 2,3-Epoxy sulfide substrates were prepared according to our previously published procedures.[4,5] α-Amino esters were liberated from commercial samples of their hydrochloride salts as follows, illustrated for (+)-(R)-Alanine *tert*-butyl ester: (+)-(R)-Alanine *tert*-butyl ester hydrochloride was shaken with saturated aqueous sodium hydrogen carbonate solution (10ml) for 2 min, then washed with chloroform (5x50cm^3). The combined washings were dried ($MgSO_4$), filtered and concentrated to give (+)-(R)-alanine *tert*-butyl ester as a colourless oil which was used without further purification.

Experimental details.

(+)-L-Alanine tert-butyl ester anisylidene imine

Alanine *tert*-butyl ester (2.00g, 13.8mmol) was heated under reflux with *p*-anisaldehyde (1.88g,

13.8mmol) and pyridine (1.09g, 13.8mmol) in toluene (10cm^3) 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, $CDCl_3$) 1.45 (9 H, s, ^tBu), 1.47 (3 H, d, J 6.8, 3-H), 3.81 (3 H, s, CH_3OAr), 3.98 (1 H, q, *J* 6.8, 2-H), 7.30 (4 H, AB system, *J* 8.8, Δν 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 (0.159cm^3, 0.822mmol) was added to epoxy sulfide (-)-2-[(methylthio)methyl]-(2S,3S)-3-propyloxirane (100mg, 0.685mmol) in dichloromethane (2cm^3) 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 (3cm^3) was added, the mixture shaken and the layers separated. The aqueous layer was extracted with dichloromethane (5x5cm^3) and the combined organic portions dried ($MgSO_4$), filtered and concentrated. The crude mixture was stirred at room temperature with glacial acetic acid (0.04cm^3, 0.685mmol) in methanol (3cm^3) for 3 hours at room temperature then concentrated. Saturated aqueous sodium hydrogen carbonate solution (3cm^3) was added, the mixture shaken and the layers separated. The aqueous layer was extracted with dichloromethane (5x5cm^3) and the combined organic portions dried ($MgSO_4$), 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, $CDCl_3$) 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, $CDCl_3$) 14.07 (C-6' + MeS), 19.07 (C-5'), 19.12 (C-3), 28.01 ($(CH_3)_3C$), 38.32 (C-4'), 47.48 (C-1'), 50.72 (C-2'), 56.86 (C-3'), 74.38 (C-2), 81.20 ($(CH_3)C$), 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 $C_{14}H_{30}NO_3S$: *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 (0.111cm^3, 0.577mmol) was added to epoxy sulfide (-)-2-[(phenylthio)methyl]-(2S,3S)-3-propyloxirane (100mg, 0.481mmol) in dichloromethane (2cm^3) 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 (3cm^3) was added, the mixture shaken and the layers separated. The aqueous layer was extracted with dichloromethane (5x5cm^3) and the combined organic portions dried ($MgSO_4$), filtered and concentrated. The crude mixture was stirred at room temperature with glacial acetic acid (0.04cm^3, 0.685mmol) in methanol (3cm^3) for 3 h at room temperature then concentrated. Saturated aqueous sodium hydrogen carbonate solution (3cm^3) was added, the mixture shaken and the layers separated. The aqueous layer was extracted with dichloromethane (5x5cm^3) and the combined organic portions dried ($MgSO_4$), 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 (($\underline{C}H_3)_3C$), 38.45 (CH_2-4'), 48.54 (CH_2-1'), 52.64 (CH-2'), 57.02 (CH-3'), 74.60 (CH-2), 81.26 (($CH_3)\underline{C}$), 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 $C_{19}H_{32}NO_3S$: *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 (0.159cm^3, 0.822mmol) was added to epoxy sulfide (-)-2-[(methylthio)methyl]-(2S,3S)-3-propyloxirane (100mg, 0.685mmol) in dichloromethane (2cm^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 (3cm^3) was added, the mixture shaken and the layers separated. The aqueous layer was extracted with dichloromethane (5x5cm^3) and the combined organic portions dried ($MgSO_4$), filtered and concentrated. The crude mixture was stirred at room temperature with glacial acetic acid (0.040cm^3, 0.685mmol) in methanol (3cm^3) for 3 hours at room temperature then concentrated. Saturated aqueous sodium hydrogen carbonate solution (3cm^3) was added, the mixture shaken and the layers separated. The aqueous layer was extracted with dichloromethane (5x5cm^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, $(CH_3)_2CH$), 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 $(CH_3)_2CH$), 22.78 (remaining $(CH_3)_2CH$), 24.87 (($CH_3)_2CH$), 28.10 (($CH_3)C$), 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 (($CH_3)C$), 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: (M+1), 334.2418. Calculated for $C_{17}H_{36}NO_3S$: *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 (0.111cm^3, 0.577mmol) was added to epoxy sulfide (-)-2-[(phenylthio)methyl]-(2S,3S)-3-propyloxirane (100mg, 0.481mmol) in dichloromethane (2cm^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 (3cm^3) was added, the mixture shaken and the layers separated. The aqueous layer was extracted with dichloromethane (5x5cm^3) and the combined organic portions dried ($MgSO_4$), filtered and concentrated. The crude mixture was stirred at room temperature with glacial acetic acid (0.04cm^3, 0.685mmol) in methanol (3cm^3) for 3 hours at room temperature then concentrated. Saturated aqueous sodium hydrogen carbonate solution (3cm^3) was added, the mixture shaken and the layers separated. The aqueous layer was extracted with dichloromethane (5x5cm^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,$(CH_3)_2CH$), 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 $(CH_3)_2CH$), 22.78 (remaining $(CH_3)_2CH$), 24.86 ($(CH_3)_2CH$), 27.97 ($(CH_3)C$), 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 ($(CH_3)C$), 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 $C_{22}H_{37}NO_3S$: *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 (0.159cm^3, 0.822mmol) was added to epoxy sulfide (+)-2-[(methylthio)methyl]-(2R,3S)-3-propyloxirane (100mg, 0.685mmol) in dichloromethane (2cm^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 (3cm^3) was added, the mixture shaken and the layers separated. The aqueous layer was extracted with dichloromethane (5x5cm^3) and the combined organic portions dried ($MgSO_4$), filtered and concentrated. The crude mixture was stirred at room temperature with glacial acetic acid (0.04cm^3, 0.685mmol) in methanol (3cm^3) for 3 h at room temperature then concentrated. Saturated aqueous sodium hydrogen carbonate solution (3cm^3) was added, the mixture shaken and the layers separated. The aqueous layer was extracted with dichloromethane (5x5cm^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, $(CH_3)_2CH$), 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_3S), 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 $(CH_3)_2CH$), 22.76 (remaining $(CH_3)_2CH$), 24.85 ($(CH_3)_2(CH_3)_2CH$), 28.05 ($(CH_3)C$), 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 ($(CH_3)C$), 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 $C_{17}H_{36}NO_3S$: *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 (0.111cm^3, 0.577mmol) was added to epoxy sulfide (+)-2-[(phenylthio)methyl]-(2R,3S)-3-propyloxirane (100mg, 0.481mmol) in dichloromethane (2cm^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 (3cm^3) was added, the mixture shaken and the layers separated. The aqueous layer was extracted with dichloromethane (5x5cm^3) and the combined organic portions dried ($MgSO_4$), filtered and concentrated. The crude mixture was stirred at room temperature with glacial acetic acid (0.04cm^3, 0.685mmol) in methanol (3cm^3) for 3 h at room temperature then concentrated. Saturated aqueous sodium hydrogen carbonate solution (3cm^3) was added, the mixture shaken and the layers separated. The aqueous layer was extracted with dichloromethane (5x5cm^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,$(CH_3)_2CH$), 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,remaining1'-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 $(CH_3)_2CH$), 22.71 (remaining $(CH_3)_2CH$), 24.90 ($(CH_3)_2(CH_3)_2CH$), 27.95 ($(CH_3)C$), 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 ($(CH_3)C$), 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 $C_{22}H_{38}NO_3S$: *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 (0.159cm^3, 0.822mmol) was added to epoxy sulfide (-)-2-[(methylthio)methyl]-(2S,3S)-3-propyloxirane (100mg, 0.685mmol) in dichloromethane (2cm^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 (3cm^3) was added, the mixture shaken and the layers separated. The aqueous layer was extracted with dichloromethane (5x5cm^3) and the combined organic portions dried ($MgSO_4$), filtered and concentrated. The crude mixture was stirred at room temperature with glacial acetic acid (0.04cm^3, 0.685mmol) in methanol (3cm^3) for 3 hours at room temperature then concentrated. Saturated aqueous sodium hydrogen carbonate solution (3cm^3) was added, the mixture shaken and the layers separated. The aqueous layer was extracted with dichloromethane (5x5cm^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 $C_{11}H_{24}NO_3S$: *m/z* 250.1477] *m/z* 250 (M^++1, 100%); α_D^{20} -52.6° (*c* 1.22, EtOH).

A similar reaction performed using (±)-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 (0.159cm^3, 0.822mmol) was added to epoxy sulfide (-)-2-[(methylthio)methyl]-(2S,3S)-3-propyloxirane (100mg, 0.685mmol) in dichloromethane (2cm^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 (3cm^3) was added, the mixture shaken and the layers separated. The aqueous layer was extracted with dichloromethane (5x5cm^3) and the combined organic portions dried ($MgSO_4$), filtered and concentrated. The crude mixture was stirred at room temperature with glacial acetic acid (0.04cm^3, 0.685mmol) in methanol (3cm^3) for 3 hours at room temperature then concentrated. Saturated aqueous sodium hydrogen carbonate solution (3cm^3) was added, the mixture shaken and the layers separated. The aqueous layer was extracted with dichloromethane (5x5cm^3) and the combined organic portions dried ($MgSO_4$), 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, $CDCl_3$) 0.90 (3 H, t, *J* 6.8, $C\underline{H}_3$-6'), 1.22-1.51 (4 H, m, 4'-H and 5'-H), 1.39 (9 H, s, ^{t}Bu), 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, $CDCl_3$) 14.05 (C-6' + MeS), 19.06 (C-5'), 27.97 ((*C*H$_3$)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 ((CH$_3$)*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 $C_{20}H_{34}NO_3S$: *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).

References and notes.

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

1. Milton, J.; Brand, S.; Jones, M.F.; Rayner, C.M. *Tetrahedron Asymm.*, **1995**, *6*, 1903-1906; *idem*, *Tetrahedron Lett.*, **1995**, *36*, 6961-6964; Brand, S.; Jones, M.F.; Rayner, C.M. *Tetrahedron Lett.*, **1995**, *36*, 8493-8496.
2. Procter, D.J.; Lovell, S.J.; Rayner, C.M. *Synlett*, **1994**, 204-206; Procter, D.J.; Rayner, C.M. *Tetrahedron Lett.*, **1994**, *35*, 1449-1452; Procter, D.J.; Thornton Pett, M.; Rayner, C.M. *Tetrahedron*, **1996**, *52*, 1841-1854.
3. Archer, N.J.; Rayner, C.M.; Bell, D.; Miller, D. *Synlett*, **1994**, 617-619; see also: Lucchini, V.; Modena, G.; Pasquato, L. *J. Chem. Soc., Chem. Commun.*, **1994**, 1565-1566.
4. a) Gill, D.M.; Pegg, N.A.; Rayner, C.M. *J. Chem. Soc., Perkin Transactions 1*, **1993**, 1371-1372; b) *idem*, *Tetrahedron*, **1996**, *52*, 3609-3630.
5. Westwell, A.D.; Thornton-Pett, M.; Rayner, C.M. *J. Chem. Soc., Perkin Trans. 1*, **1995**, 847-859 and refs. cited therein.
6. a) Rayner, C. M. in "Organosulfur Chemistry Series", ed. Page, P.C.B., Pergamon Press, 1995, chapter 3; b) Capozzi, G.; Modena, G.; Pasquato, L. in "The chemistry of sulphenic acids and their derivatives", ed. Patai, S., J. Wiley, Chichester, 1990, chapter 10; c) for recent examples of reactions involving thiiranium ions and nitrogen nucleophiles, see ref. 4b and: Toshimitsu, A.; Abe, H.; Hirosawa, C.; Tamao, K. *J. Chem. Soc., Perkin Trans. 1*, **1994**, 3465-3471; Brownridge, P. *Tetrahedron Lett.*, **1984**, *25*, 3759-3762; Benati, L.; Montevecchi, P.C.; Spagnolo, P. *Tetrahedron*, **1986**, *42*, 1145-1155; Capozzi, G.; Ottana, R.; Romeo, G. *Heterocycles*, **1986**, *24*, 583-587; Coldham, I.; Warren, S. *Tetrahedron Lett.*, **1989**, *30*, 5937-5940; Ohsawa, T.; Ihara, M.; Fukumoto, K. *J. Org. Chem.*, **1983**, *48*, 3644-3648.
7. For a review on the chemistry of sulfuranes see: Hayes, R.A.; Martin, J.C. "Organic Sulfur Chemistry", eds. Bernadi, F.; Csizmadia, I.G.; Mangini, A., Elsevier, 1985, chapter 8. See also ref. 9b.
8. Nishizawa, R.; Saino, T.; Takita, T.; Suda, H.; Aoyagi, T.; Umezawa, H. *J. Med. Chem.*, **1977**, *20*, 510-

515.
9. Ocain, T.D.; Rich, D. *J. Med. Chem.*, **1988**, *31*, 2193-2199.
10. Dunlap, B.E.; Dunlap, S.A.; Rich, D.H. *Scand. J. Immunol.*, **1984**, *20*, 237-245; Schorlemmer, H.; Basslet, K.; Sedlacek, H. *Cancer Res.*, **1983**, *43*, 4148-4153; see also ref. 9.
11. Barclay, R.K.; Phillipps, M.A. *Biochem. Biophys. Res. Commun.*, **1980**, *96*, 1732-1738; Roques, B.P.; Fournie-Zaluski, M.C.; Soroca, E.; Lecomte, J.M.; Malfroy, B.; Lloreus, C.; Schwartz, J.-C. *Nature (London)*, **1980**, *288*, 286-288.
12. Norman, B.H.; Morris, M.L. *Tetrahedron Lett.*, **1992**, *33*, 6803-6806 and refs. cited therein.
13. Gordon, E.M.; Godfrey, J.D.; Delaney, N.G.; Asaad, M.M.; Von Langen, D.; Cushman, D.W. *J. Med. Chem.*, **1988**, *31*, 2199-2211.
14. For other examples see: Askin, D.; Wallace, M.A.; Vacca, J.P.; Reamer, R.A.; Volante, R.P.; Shinkai, I. *J. Org. Chem.*, **1992**, *57*, 2771-2773; Fincham, C.I.; Higginbottom, M.; Hill, D.R.; Horwell, D.C.; O'Toole, J.C.; Ratcliffe, G.S.; Rees, D.C.; Roberts, E. *J. Med. Chem.*, **1992**, *35*, 1472-1484; Hoffman, R.V.; Kim, H.-O. *Tetrahedron Lett.*, **1992**, *33*, 3579-3582; Thompson, W.J.; Ball, R.G.; Darke, P.L.; Zugay, J.A.; Thies, J.E. *Tetrahedron Lett.*, **1992**, *33*, 2957-2960; Baker, W.R.; Condon, S.L. *Tetrahedron Lett.*, **1992**, *33*, 1581-1584; Poss, M.A.; Reid, J.A. *Tetrahedron Lett.*, **1992**, *33*, 1411-1415.
15. Gill, D.M.; Pegg, N.A.; Rayner, C.M. *Tetrahedron Lett.*, **1995**, *36*, 8327-8330.
16. Gill, D.M.; Pegg, N.A.; Rayner, C.M. *Synlett*, **1995**, 1275-1277.
17. Djuric, S.; Venit, J.; Magnus, P. *Tetrahedron Lett.*, **1981**, *22*, 1787-1790. Other silylated nucleophiles such as $(Me_3Si)_3N$ and $(Me_3Si)_2NMe$ were equally unsuccessful.
18. Lucier, J.J.; Harris, A.D.; Korosec, P.S. *Org. Synth., Coll. Vol. 5*, **1973**, 736-739; Wawzonek, S.; McKillip, W.; Peterson, C.J. *Org. Synth., Coll. Vol. 5*, **1973**, 758-761.
19. Stork, G.; Leong, A.Y.W.; Touzin, A.M. *J. Org. Chem.*, **1976**, *41*, 3491-3493.
20. Gill, D.M.; Pegg, N.A.; Rayner, C.M.; Fletcher, S. unpublished results.
21. Liu, Q.; Simms, M.J.; Boden, N.; Rayner, C.M. *J. Chem. Soc., Perkin Trans. 1*, **1994**, 1363-1365; Liu, Q.; Marchington, A.P.; Boden, N.; Rayner, C.M. *Synlett*, **1995**, 1037-1039; *idem*, *J. Chem. Soc., Perkin Trans. 1*, in press.
22. Villa, J.L. *Chem. Abstr.*, **1973**, *79*, 19734v, U.S. 3725337 (cl. 260145. 8R; C 08g).
23. a) Owsley, P.C.; Helmkamp, G.K.; Rettig, F.M. *J. Amer. Chem. Soc.*, **1969**, *91*, 5239-5242; b) Bakker, S.; Kellog, R.M.; Raynolds, P.; Zonnebelk, S. *J. Amer. Chem. Soc.*, **1974**, *96*, 3146-3154.
24. Smit, W.A.; Zefirov, N.S.; Bodrikiv, I.V. in "Organic Sulphur Chemistry", Ed. Freidlina, R.K.; Skorava, A.E., Pergamon, Oxford, **1981**, 159.
25. Csizmadia, V.M.; Schmid, G.H.; Mezey, P.G.; Csizmadia, I.G. *J. Chem. Soc., Perkin Trans. II*, **1977**, 1019-1024.
26. Carretero, J.C.; Garcia Ruano, J.L.; Rodriguez, J.H. *Tetrahedron Lett.*, **1987**, *28*, 4593-4596.
27. a) Trost, B.M.; Shibata, T. *J. Am. Chem. Soc.*, **1982**, *104*, 3225-3228; b) Trost, B.M.; Shibata, T.; Martin, S.J. *J. Am. Chem. Soc.*, **1982**, *104*, 3228-3230; c) Caserio, M.C.; Kim, J.K. *J. Am. Chem. Soc.*, **1982**, *104*, 3231-3230.
28. Still, W.C.; Khan, M.; Mitra, A; J. Org. Chem., **1978**, *43*, 2923-2925; see also: Leonard, J.; Lygo, B.; Procter, G. *Advanced Practical Chemistry*, Blackie, 1990.
29. Perrin, D. D.; Armarego, W. L. F.; Perrin, D. R. *Purification of Laboratory Chemicals*, Pergamon, 1980.

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