Stereoselective syntheses of protected β-hydroxy-α-amino acids using (arylthio)nitrooxiranes

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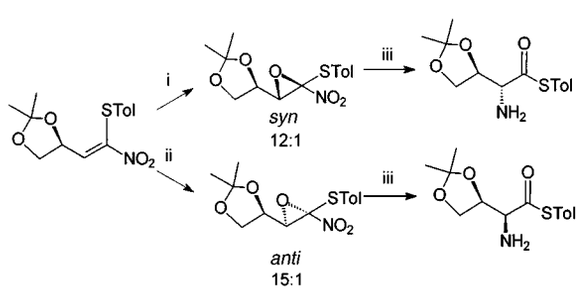
The scope and limitations of a method for the stereocontrolled synthesis of a range of protected β-hydroxy-α-amino acids have been established. The method comprises condensation of a chiral, enantiomerically pure aldehyde **6** with (4-methylphenylthio)nitromethane **7** to form a 1-arylthio-1-nitroalkene **8**; stereoselective epoxidation of this alkene with a metal alkyl peroxide; and stereospecific reaction of the arylthionitrooxirane with a nitrogen nucleophile to give an α-amino thioester. This method has been employed in the synthesis of protected derivatives of both diastereoisomers of threonine **1** and **2**, and of β-hydroxyleucine **3** and **4** and a synthesis of the *anti*-diastereoisomer of β-phenylserine **5**.

The stereoselective synthesis of β-hydroxy-α-amino acids has been extensively studied, and several excellent methods for their preparation have been established.[1,2] We have already reported an approach to the synthesis of β,γ-dihydroxy amino acids (including γ-hydroxythreonine and polyoxamic acid), in which the key step is stereoselective nucleophilic epoxidation of an appropriate 1-arylthio-1-nitroalkene, using either lithium or potassium *tert*-alkyl peroxides (Scheme 1). Subsequent reaction



Scheme 1 *Reagents and conditions*: i, ^{t}BuOOLi, toluene, −78 °C; ii, Ph_3COOK, THF, −78 °C; iii, aq. NH_3 (*d* 0.880), CH_2Cl_2.

of the (arylthio)nitrooxiranes with amine nucleophiles then leads to β-hydroxy-α-amino acids with inversion of configuration.[3] This method has the virtue that either stereoisomeric product may be obtained by appropriate choice of epoxidation reagent.

The rationalisation that we have developed for the sense of stereoselectivity observed in the key nucleophilic epoxidation by metal alkyl peroxides is based on two assumptions: (i) the 1-arylthio-1-nitroalkenes adopt a reactive conformation in which the allylic hydrogen occupies the inside position, minimising 1,3-allylic strain;[4] and (ii) the epoxidation reagent can then either coordinate to the allylic oxygen (in the case of Li), which results in preferential *syn* epoxidation, or in the absence of an appropriate cation capable of strong coordination (*e.g.* K), steric and electronic effects play a larger part, which results in preferential *anti* epoxidation (Fig. 1).

Since this model does not rely on the presence of the δ-oxygen (present in the substrates used in the syntheses of

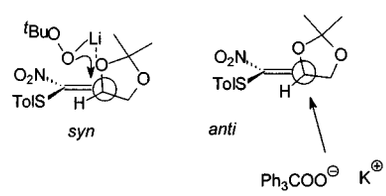
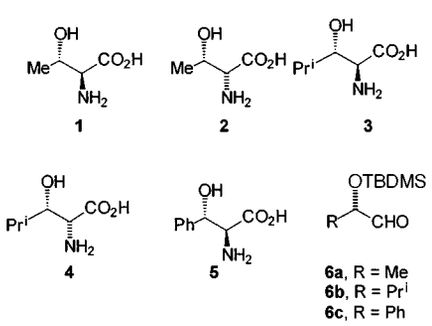


Fig. 1

γ-hydroxythreonine and polyoxamic acid),[3] it appeared worthwhile to investigate whether a similar process could be applied to the synthesis of other β-hydroxy-α-amino acids, in which there was an additional alkyl (or aryl) substituent at the β-carbon. In this paper, efforts to develop the method as a general stereoselective route to β-hydroxy-α-amino acids are reported.† This work encompasses the synthesis of one enantiomer of protected derivatives of both diastereoisomers of threonine **1** and **2**,[6–15] and β-hydroxyleucine **3** and **4**,[16–20] and



of one enantiomer of the *anti*-diastereoisomer of β-phenylserine **5**.[21]

Results and discussion

The method that we have developed for the synthesis of

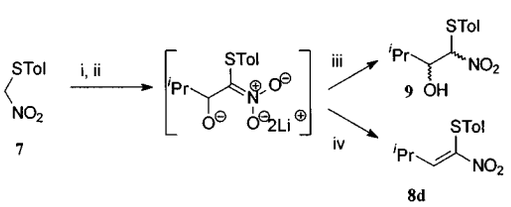
† An account of part of the work described in this manuscript has been reported in a preliminary communication.[5]

β-hydroxy-α-amino acids, which effectively emulates the Strecker reaction, involves three distinct steps: (i) condensation of a chiral, enantiomerically pure aldehyde **6** with (4-methylphenylthio)nitromethane **7** to form the 1-arylthio-1-nitroalkene **8**; (ii) stereoselective epoxidation of this alkene with a metal alkyl peroxide; and (iii) stereospecific reaction of the arylthionitrooxirane with a nitrogen nucleophile to give the α-amino thioester. Therefore the starting materials that we required for the synthesis of threonine, β-hydroxyleucine and β-phenylserine were the corresponding *tert*-butyldimethylsilyl-protected α-hydroxy aldehydes **6a–c**, which were all prepared by standard procedures.[22,23] The protecting group was selected so that the coordinating ability of the oxygen atom would be reduced (to allow the epoxidation reactions of the alkenes to occur under stereoelectronic control), and to allow easy deprotection to the free alcohol so that epoxidation of the 3-hydroxy-1-arylthio-1-nitroalkenes could be explored.

Preparation of 1-arylthio-1-nitroalkenes

There are two existing methods in the literature for the condensation of (arylthio)nitromethanes with aldehydes. The more general method involves a two-step process, comprising an initial Henry reaction mediated by potassium *tert*-butoxide, followed by an elimination using methanesulfonyl chloride in the presence of a tertiary amine.[24–27] The less general, but more straightforward, process uses piperidinium acetate to mediate a direct Knoevenagel condensation.[28] While application of the two-step Henry reaction/dehydration process to the aldehyde **6a**[22] gave an acceptable yield of the desired 1-arylthio-1-nitroalkene **8a** (40% for the two steps), this reaction failed almost completely in the case of the bulkier aldehyde **6b** (9%). Moreover, the Knoevenagel method was equally ineffective (5%). Although not firmly established, we suspect that the failure of these processes is a result of an unfavourable equilibrium in the initial condensation step, perhaps due to the bulky nature of the aldehyde. It therefore became clear that the development of a new method for the preparation of 1-arylthio-1-nitroalkenes was essential.

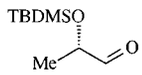
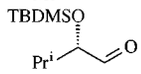
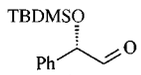
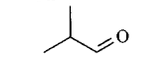
Mindful of Seebach's method of increasing the reactivity of nitroalkanes [including (phenylthio)nitromethane] as nucleophiles by double deprotonation,[29] we decided to explore the condensation of the dianion of (4-methylphenylthio)nitromethane **7** with hindered aldehydes, and chose 2-methylpropanal as a suitable model. Treatment of (4-methylphenylthio)nitromethane **7** with 2 equivalents of butyllithium, addition of 2-methylpropanal and quenching with acetic acid gave the β-hydroxy nitro compound **9** in good yield (82%). However, of more direct interest, quenching with acetic anhydride gave the desired 1-arylthio-1-nitroalkene **8d** directly (51%) (Scheme 2). Although this method was less efficient than the corresponding Knoevenagel reaction [78%, using (phenylthio)nitromethane],[30] its success encouraged us to apply it to the three aldehydes required for our study.



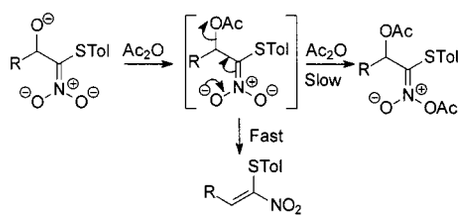
Scheme 2 *Reagents and conditions*: i, BuLi (2 equiv.), THF; ii, ^{i}PrCHO; iii, AcOH; iv, Ac_2O.

This type of elimination to give a nitroalkene does have some precedent from the work of Denmark,[31] although the example described here is more efficient. The implication of the success of this elimination is that acetylation of the more reactive alkoxide occurs first, and that elimination of acetate from this intermediate is faster than subsequent acetylation of the nitronate (Scheme 3).

Table 1 Preparation of 1-(4-methylphenylthio)-1-nitroalkenes **8** and **10**

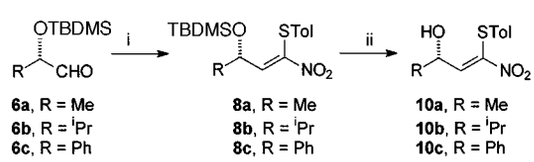
Aldehyde	Product	Yield (%)	Product	Yield (%)
	**8a**	52	**10a**	73[a]
	**8b**	73	**10b**	80[a]
	**8c**	74	**10c**	83[b]
	**8d**	51	—	—

[a] $BF_3{\cdot}Et_2O$. [b] HF–pyridine.



Scheme 3

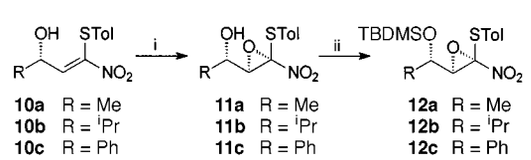
Application of this method to the three aldehydes **6a–c**, after some optimisation, allowed the preparation of each of the targets **8a–c** in moderate to good yield, Scheme 4. Our results are shown in Table 1. Each of the protected alkenes was converted into the corresponding free alcohols **10a–c**. While alkenes **8a** and **8b** could be deprotected efficiently using $BF_3{\cdot}Et_2O$,[32] treatment of **8c** with this reagent resulted in extensive decomposition, presumably due to the benzylic nature of the alcohol. However, treatment with HF–pyridine, which has been used for the same purpose in a related system,[33] resulted in smooth deprotection to the alcohol **10c**.



Scheme 4 *Reagents and conditions*: i, $TolSC(Li){=}NO_2Li$ (prepared from $TolSCH_2NO_2$ and BuLi (2 equiv.); ii, see Table 1 for reagent.

Epoxidation of 3-hydroxy-1-arylthio-1-nitroalkenes

Epoxidation of each of the hydroxyalkenes with lithium *tert*-butyl peroxide (prepared from *n*-butyllithium and *tert*-butyl hydroperoxide) in THF gave the corresponding epoxides **11a–c** as single stereoisomers as judged by ^{1}H NMR (Scheme 5). Since the stereoselectivity of the reactions in THF was so high, we did not investigate the use of toluene as solvent which had proved successful in our previous work (Scheme 1).[3] While epoxidation



Scheme 5 *Reagents and conditions*: i, ^{t}BuOOLi, THF, −100 °C; $^{t}BuMe_2SiOSO_2CF_3$, 2,6-lutidine, CH_2Cl_2, −78 °C.

Table 2 Epoxidation of 3-hydroxy-1-(4-methylphenylthio)-1-nitroalkenes, and subsequent silylation

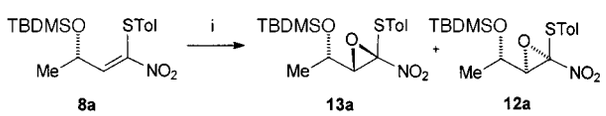
R	Conditions	Product	Yield (%)	Silylation product	Silylation yield (%)
Me	−78 °C, 10 min	**11a**	65	**12a**	83
^{i}Pr	−100 °C, 10 min	**11b**	79	**12b**	87
Ph	−100 °C, 10 min	**11c**	56	**12c**	86

of the alkene **10a** could be conducted at −78 °C, it was found that epoxidation of the alkenes **10b** and **10c** had to be conducted at −100 °C, and the reaction time restricted to ten minutes, otherwise extensive decomposition occurred to give unidentifiable products. All three epoxides **11a**–**c** were tentatively assigned *syn*-stereochemistry based on our 1,3-allylic strain model, assuming coordination between the lithium reagent and the hydroxy group. The very high rates observed for these reactions compared with rates observed for nucleophilic epoxidation of otherwise unfunctionalised 1-arylthio-1-nitroalkenes are strongly supportive of initial coordination of the lithium *tert*-butyl peroxide to the free hydroxy group. Reprotection of each of the hydroxy epoxides using *tert*-butyldimethylsilyl triflate and 2,6-lutidine[34] gave the corresponding TBDMS-protected derivatives **12a**–**c**. Our results are summarised in Table 2.

At this stage, the structure of the epoxide **12c** was unambiguously determined by X-ray crystallography,‡ which confirmed that the product was the *syn*-isomer as expected from our model. This result, and the result of subsequent ring-opening reactions of the epoxides **12a** and **12b**, confirmed that *syn*-epoxidation had occurred in all cases.

Having established the generality of epoxidation of the hydroxyalkenes **10**, we turned our attention to the epoxidation of the silyl-protected derivatives **8**, which we expected would occur with the opposite stereochemical sense. However, we were mindful of the results of epoxidation of related silyl-protected γ-hydroxy vinyl sulfones,[35] where the size of the alkyl substituent at the γ-centre had a strong influence on the stereochemical outcome of nucleophilic epoxidation reactions.

In the event, epoxidation of the silyl-protected alkene **8a** (R = Me) with potassium triphenylmethyl peroxide (prepared from potassium hydride and triphenylmethyl hydroperoxide) led to the formation of two epoxides **13a** and **12a** in a ratio of 15 : 1 (total 74%) (Scheme 6). The minor epoxide was identical

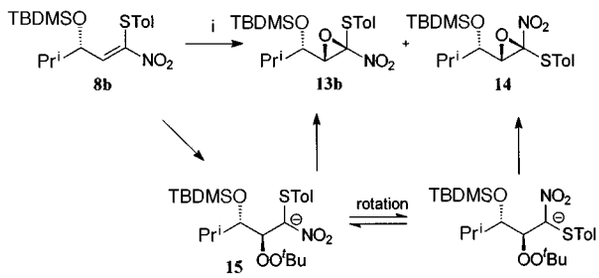


Scheme 6 *Reagents and conditions*: i, Ph_3COOK, THF, −78 °C.

to the compound derived by silylation of the product of epoxidation of the 3-hydroxy-1-(4-methylphenylthio)-1-nitroalkene **10a**. Thus, the reagent based stereocontrol that we had first identified in the synthesis of γ-hydroxythreonine also appears to be operating in this case.

Epoxidation of the two silyl-protected alkenes **8b** (R = ^{i}Pr) and **8c** (R = Ph) was much more problematic. The best conditions (among a range explored) for epoxidation of the alkene **8b** (R = ^{i}Pr) involved treatment with lithium *tert*-butyl peroxide in THF at 0 °C for 24 hours (Scheme 7). Under these conditions, besides the isolation of the expected compound **13b** (53%), another epoxide isomer **14** (11%) was also isolated. A similar result was obtained when potassium triphenylmethyl peroxide was employed as the oxidant, but the overall yield of each of the products was slightly lower. The minor component was *not* identical to that derived by silylation of the

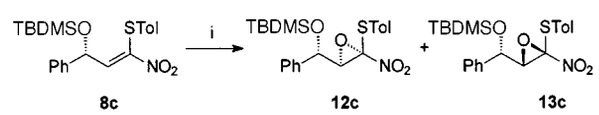
‡ M. R. J. Elsegood and W. Clegg, unpublished results.



Scheme 7 *Reagents and conditions*: i, ^{t}BuOOLi, THF, 0 °C.

product of epoxidation of the 3-hydroxy-1-(4-methylphenylthio)-1-nitroalkene **10b**. Subsequent ring-opening of this unexpected product (*vide infra*) established that the relative stereochemistry of the epoxidation was *anti*, which implied that the compound must be stereoisomeric about the epoxide and therefore have structure **14**. These results are consistent with a high level of stereoselectivity in the initial conjugate addition of *tert*-butyl peroxide anion, but it appears that the initial adduct **15** has a sufficiently long lifetime that rotation about the C(1)–C(2) bond can occur, and that the reaction is not stereospecific. Under milder reaction conditions, it proved possible to isolate compounds derived from protonation of **15**.

Epoxidation of alkene **8c** was carried out using either lithium *tert*-butyl peroxide or potassium triphenylmethyl peroxide. In the latter case, epoxidation was much quicker than had been observed for the corresponding ^{i}Pr example **8b**, but the *syn*-epoxide **12c** was isolated in poor yield (39%), together with unidentified material. When the oxidant was lithium *tert*-butyl peroxide, the reaction had to be conducted at 0 °C, and led to a mixture of *syn*-**12c** and *anti*-epoxides **13c** in a ratio of 15 : 8 (52% combined yield) (Scheme 8).



Scheme 8 *Reagents and conditions*: i, ^{t}BuOOLi, THF, 0 °C.

It is clear that our model for epoxidation of the silyl-protected 3-hydroxy-1-(4-methylphenylthio)-1-nitroalkenes is simply not applicable to the alkene **8c**. Anomalous results have been reported by Barrett for the addition of other nucleophiles to a very closely related alkene, in which the *syn*-isomer is also generally observed as the major product.[36] These results have been rationalised by the suggestion that the influence of 1,3-allylic strain is not the dominant factor, and that conformer (**a**) below (Fig. 2) in which the phenyl group occupies the 'inside' position (credible due to the long C–S bond and the ability of both the S–Ph group and the allylic phenyl group to rotate) is the reactive conformer.[36] When lithium *tert*-butyl peroxide is used as the nucleophile, it is clear that there is little difference between the two possibilities (**a**) and (**b**).

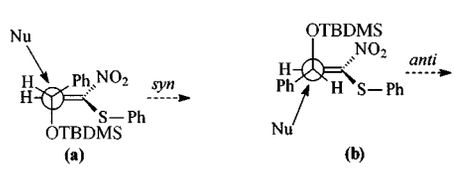


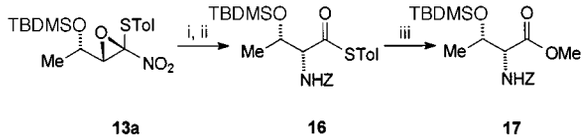
Fig. 2

Preparation of protected β-hydroxy-α-amino acids

Having established stereoselective routes to five of the six 2-arylthio-2-nitrooxiranes (**12a**–**c**, **13a** and **13b**) required for the synthesis of our targets, we now set about exploring the reactions of these epoxides with nitrogen nucleophiles.

Threonine derivatives

Treatment of the *anti*-epoxide **13a** with aqueous ammonia according to our previous procedures,[35] followed by cooling to 0 °C and addition of benzyl chloroformate, gave the Z-protected threonine derivative **16** (82% overall from **13a**) (Scheme 9). Treatment of this thioester with mercury(II) acetate

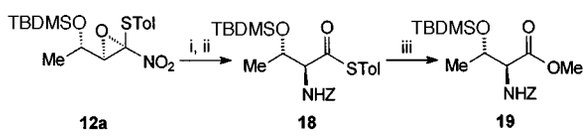


13a **16** **17**

Scheme 9 *Reagents and conditions*: i, aq. NH_3 (*d* 0.880), CH_2Cl_2, room temperature; ii, $PhCH_2OCOCl$; iii, $Hg(OAc)_2$, MeOH, room temperature.

in methanol gave the methyl ester **17** (86%), which was identified as protected D-threonine by comparison of its ^1H NMR with authentic data in the literature.[37] The measured optical rotation for **17** also compared favourably with the literature value for *ent*-**17**.[37] Since the ring-opening reaction with ammonia proceeds with inversion of configuration, this confirms that the initial epoxidation process did give the *anti*-epoxide **13a**.

Treatment of the *syn*-epoxide **12a** with aqueous ammonia, followed by addition of benzyl chloroformate, gave the Z-protected L-*allo*-threonine thioester **18** (65%) (Scheme 10).



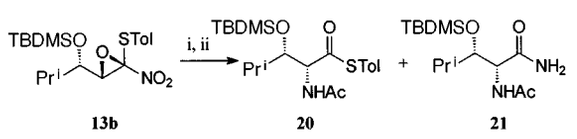
12a **18** **19**

Scheme 10 *Reagents and conditions*: i, aq. NH_3 (*d* 0.880), CH_2Cl_2, room temperature; ii, $PhCH_2OCOCl$; iii, $Hg(OAc)_2$, MeOH, room temperature.

Treatment of **18** with mercury(II) acetate in methanol (65%) gave fully protected L-*allo*-threonine methyl ester **19** (Scheme 10), which was clearly distinct from the protected D-threonine derivative **17**. Since both compounds **17** and **19** are derived from a common precursor **8a**, and there is no evidence for racemisation in the conversion of this precursor into **17**, the enantiomeric purity of **19** is assured.

3-Hydroxyleucine derivatives

Reaction of the (arylthio)nitrooxiranes **12b** and **13b** with ammonia proved to be a difficult process. Reaction of the *anti*-epoxide **13b** with aqueous ammonia under the optimised conditions developed for the threonine chemistry was much slower and less efficient (Scheme 11). After quenching with acetic

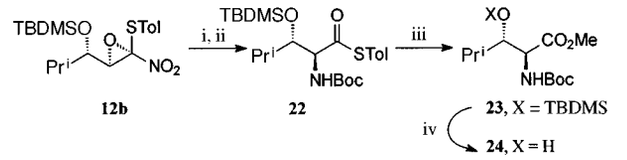


13b **20** **21**

Scheme 11 *Reagents and conditions*: i, aq. NH_3 (*d* 0.880), CH_2Cl_2, room temperature; ii, Ac_2O.

anhydride, the desired thioester **20** was isolated in poor yield (26%). There was evidence for the formation of the primary amide **21**, presumably formed by reaction of thioester **20** with excess ammonia.

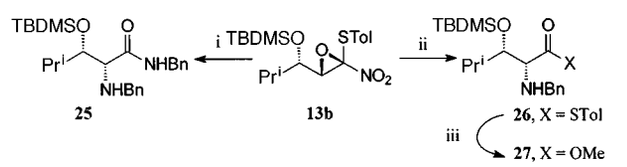
Reaction of the *syn*-epoxide **12b** with ammonia proved to be an even more difficult process, and the optimum conditions, amongst many tried, involved treatment with *d* 0.88 aqueous ammonia in a two-phase system with toluene at 80 °C (Scheme 12). These conditions maximised the amount of thioester **22** isolated (31%), whilst minimising the amount of the corresponding amide formed by reaction of this thioester with ammonia. In this case the reaction mixture was treated with $(Boc)_2O$, both to aid product isolation and to allow subsequent comparison with a known derivative. The starting epoxide **12b** (38%) was also isolated. Thioester **22** was then converted into the known methyl ester **24**,[38] for comparison of its optical rotation with the literature value. This transformation was achieved by reaction with lithium methoxide to give the ester **23** (85%) followed by removal of the silyl ether using HF–pyridine to give the target compound **24** (87%). The specific rotation of our material ($[\alpha]_D^{25}$ +18.1) was slightly lower than that reported in the literature ($[\alpha]_D^{25}$ +23.6).[38]



12b **22**

Scheme 12 *Reagents and conditions*: i, aq. NH_3 (*d* 0.880), toluene, 80 °C; ii, Boc_2O, room temperature; iii, MeOLi (1.2 equiv.), MeOH, room temperature; iv, HF–py, THF, room temperature.

Following the disappointing results with ammonia, we decided to treat the epoxides **12b** and **13b** with a different nitrogen nucleophile. Benzylamine was chosen because it had been used successfully before[3] and because ^1H NMR data are available in the literature for the *anti N*-benzyl, TBDMS-protected methyl ester **30**.[39] Treatment of the *anti*-epoxide **13b** with two equivalents of benzylamine gave the amide **25** in excellent yield (97%) (Scheme 13). The reaction was repeated using one

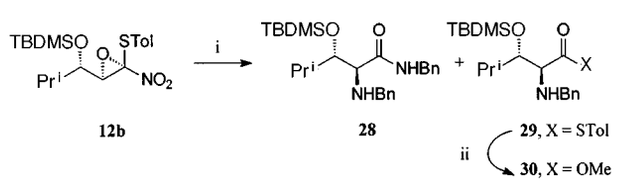


25 **13b**

Scheme 13 *Reagents and conditions*: i, $PhCH_2NH_2$ (2 equiv.), CH_2Cl_2, room temperature; ii, $PhCH_2NH_2$ (1 equiv.), $NaHCO_3$ (aq.), CH_2Cl_2, reflux; iii, MeOLi (1.2 equiv.), MeOH, room temperature.

equivalent of benzylamine, with aqueous sodium hydrogen carbonate as base. The best results were obtained at reflux in a two-phase dichloromethane–aqueous ammonia system which yielded the desired thioester **26** (66%). Conversion of thioester **26** into the corresponding methyl ester **27** was achieved using a solution of lithium methoxide in methanol (73%). There was no evidence of any epimerisation under these conditions (*vide infra*).

Analogous treatment of the *syn*-epoxide **12b** with benzylamine proved to be problematic, due to the very low reactivity of this compound towards nucleophiles, which we had already encountered. Using the conditions developed above for the *anti*-epoxide resulted in a greater proportion of the amide **28**, in addition to small amounts of the desired thioester **29**. However, by changing the co-solvent to hexane, it proved possible to isolate the desired thioester **29** in reasonable yield (42%), along with the amide **28** (12%) and starting epoxide **12b** (29%) (Scheme 14). The *anti*-methyl ester **30** was prepared from the thioester **29** in an analogous manner to the *syn*-isomer **27**.



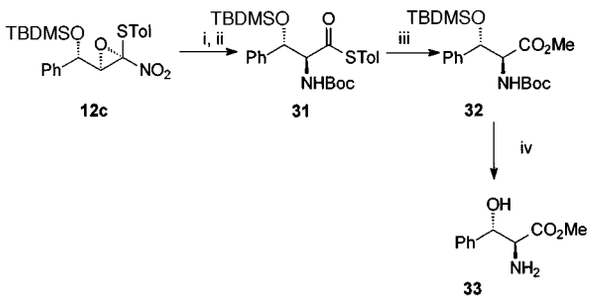
12b **28**

Scheme 14 *Reagents and conditions*: i, $PhCH_2NH_2$ (1 equiv.), $NaHCO_3$ (aq.), hexane, reflux; ii, MeOLi (1.2 equiv.), MeOH, room temperature.

The ^{1}H NMR spectrum of the *anti*-isomer **30** correlated well with the literature.[39] Therefore the other isomer, **27**, must be *syn* as expected. These results also show that the assignments of the C(2) configurations of epoxides **12b** and **13b** were correct, assuming that the ring opening reactions proceed with inversion of configuration, as has previously been established for other (arylthio)nitrooxiranes.[3]

3-Phenylserine derivatives

Armed with the experience from the 3-hydroxyleucine derivatives, optimisation of the ring opening of *syn*-epoxide **12c** with ammonia was much more straightforward. Treatment with aqueous ammonia at 80 °C in toluene gave the desired product **31** (65%), in a much reduced reaction time of six hours (Scheme 15). Conversion of thioester **31** into methyl ester **32** (86%) using



Scheme 15 *Reagents and conditions*: i, aq. NH_3 (*d* 0.880), toluene, 80 °C; ii, Boc_2O, room temperature; iii, MeOLi (1.2 equiv.), MeOH, room temperature; iv, HF–py, THF, room temperature.

lithium methoxide followed by removal of both the silyl ether and Boc group with HF–pyridine complex (65%) gave 3-phenylserine methyl ester **33**. Physical and optical rotation data for **33** ($[\alpha]_D^{20}$ +32.4) compared satisfactorily with that reported ($[\alpha]_D^{20}$ +34.1)[21] showing that there had been no epimerisation at C(2) or C(3) during the synthesis. Since we already knew that epoxide **12c** was *syn* from the X-ray crystal structure, this confirmed that the ring opening reaction had proceeded with inversion of configuration.

Conclusions

The scope and limitations of an approach to the synthesis of β-hydroxy-α-amino acids by the combination of the stereoselective epoxidation of 3-hydroxy-1-arylthio-1-nitroalkenes, followed by ring-opening of the epoxides with nitrogen nucleophiles, have been established. The process can be used to prepare either diastereoisomer of β-alkyl-β-hydroxy-α-amino acids with high stereoselectivity, although with branched alkyl substituents, the slow rate of ring opening of the intermediate epoxides does reduce the overall efficiency. In the case of β-aryl-β-hydroxy-α-amino acids, the *anti*-epoxide cannot be prepared stereoselectively using the reagents which work satisfactorily for the corresponding β-alkyl-β-hydroxy-α-amino acids, so access to the *syn*-β-aryl-β-hydroxy-α-amino acids is not at present possible.

Experimental

General experimental procedures and instrumentation are as previously described.[3] NMR spectra were recorded in $CDCl_3$ and *J* values are given in Hz. $[\alpha]_D$ Values are given in units of 10^{-1} deg cm^2 g^{-1}. Light petroleum refers to that fraction with boiling point range 40–60 °C. All organic extracts were dried over anhydrous $MgSO_4$, and solvent was removed using a rotary evaporator. The following compounds were prepared by the literature methods: (2*S*)-2-(*tert*-butyldimethylsilyloxy)propanal **6a**,[22] (2*S*)-2-(*tert*-butyldimethylsilyloxy)-2-phenylethanal **6c**.[23]

(2*S*)-2-*tert*-Butyldimethylsilyloxy-3-methylbutanal 6b[40]

Diisobutylaluminium hydride (20 cm^3 of a 1 M solution in hexanes, 20 mmol) was added dropwise to a solution of methyl (2*S*)-2-*tert*-butyldimethylsilyloxy-3-methylbutanoate (2.35 g, 9.6 mmol) in toluene (70 cm^3) at −90 °C under nitrogen. The reaction was stirred at −78 °C for 24 h then quenched at this temperature with methanol (10 cm^3). A solution of Rochelle salt (20.5 g in 80 cm^3 water) was added to the reaction. The mixture was stirred at 0 °C for 2½ hours until two separate layers formed. The organic layer was separated and the aqueous layer was washed with diethyl ether (2 × 100 cm^3). The organic portions were combined, dried and concentrated to give aldehyde **6b** (1.65 g, 80%) as a colourless oil. ^{1}H NMR analysis confirmed the absence of any starting ester or over-reduced alcohol. $[\alpha]_D^{20}$ −18.7 (*c* 1.35 in CH_2Cl_2) (Found: M^+ − CHO 187.1512, $C_{10}H_{23}OSi$ requires 187.1518); ν_{max}/cm^{-1} (film) 1730, 1254; δ_H (200 MHz) 0.07 (s, 6H, $Si(CH_3)_2$), 0.92 (d, 3H, *J* 7.0, C(4)H_3), 0.94 (s, 9H, $SiC(CH_3)_3$), 1.00 (d, 3H, *J* 7.0, C(4)H_3), 2.03 (m, 1H, C(3)H), 3.73 (dd, 1H, *J* 2.1 and 4.9, C(2)H), 9.55 (d, 1H, *J* 2.1, CHO); δ_C (50 MHz) −5.0, −4.5, 16.8, 18.3, 18.7, 25.8, 31.5, 82.0, 205.1; *m*/*z* (EI) 187 (M^+ − CHO, 30%), 159 (M^+ − ^{t}Bu, 35), 75 (100).

(1*Z*,3*S*)-3-*tert*-Butyldimethylsilyloxy-1-(4′-methylphenylthio)-1-nitrobut-1-ene 8a

^{t}BuOK (1.94 cm^3, 1 M solution in ^{t}BuOH, 0.1 equiv.) was added to a solution of (4-methylphenylthio)nitromethane **7** (3.55 g, 19.39 mmol) in 1:1 ^{t}BuOH–THF (100 cm^3) at 0 °C. After 15 min the aldehyde **6a** (3.68 g, 19.39 mmol) in THF (20 cm^3) was added, the reaction was allowed to warm to room temperature and stirred for a further 3 h, by which time all the aldehyde had reacted (as judged by TLC). The reaction was quenched by pouring into pH 7.0 phosphate buffer (100 cm^3). The organic layer was removed and the aqueous layer was extracted with ether (3 × 50 cm^3). The organic layers were combined, dried, filtered and the solvent removed under reduced pressure. The residue was purified by flash chromatography using 25:1 light petroleum–ethyl acetate as eluent to yield a mixture of diastereoisomeric alcohols (4.43 g, 61%) that were not characterised but used directly in the next step. The alcohols (1.0 g, 2.69 mmol) were dissolved in dichloromethane (25 cm^3) and cooled to −78 °C. Methanesulfonyl chloride (0.63 cm^3, 8.09 mmol, 3 equiv.) was added at −78 °C followed by diisopropyl(ethyl)-amine (1.41 cm^3, 8.09 mmol, 3 equiv.) The solution was allowed to warm to room temperature over 3 h and was stirred at this temperature for a further 1 h resulting in a yellow solution. The reaction was quenched by pouring into saturated aqueous $NaHCO_3$ (10 cm^3) and the organic layer was washed with $NaHCO_3$ (2 × 10 cm^3). The aqueous layers were combined and extracted with dichloromethane (10 cm^3). The organic layers were combined, dried, filtered and the solvent removed under reduced pressure. The residue was purified by flash chromatography using 180:1 light petroleum–ethyl acetate as eluent to yield the alkene **8a** (0.40 g, 42%) as a yellow oil. $[\alpha]_D$ −12.4 (*c* 1 in CH_2Cl_2); ν_{max}/cm^{-1} (film) 2955, 2930, 2859, 1539, 1327, 1256, 1109, 1087, 831, 810, 779; δ_H (200 MHz) 0.07 (s, 3H, $SiCH_3$), 0.09 (s, 3H, $SiCH_3$), 0.90 (s, 9H, $C(CH_3)_3$), 1.29 (d, 3H, *J* 6.4, C(4)H_3), 2.32 (s, 3H, $SArCH_3$), 4.95 (dq, 1H, *J* 6.4, 8.0, C(3)H), 7.08–7.29 (AA′BB′, 4H, ArH), 7.48 (d, 1H, *J* 8.0, C(2)H); δ_C (50 MHz) 149.1, 138.3, 130.3, 129.8, 67.2, 25.8, 23.7, 21.1, 18.0, −4.5, −4.6; *m*/*z* (EI) 296 (M^+ − ^{t}Bu, 74%), 159 (^{t}BuMe$_2$SiOCHCH$_3$, 25), 57 (^{t}Bu, 23). Anal. Calcd for $C_{17}H_{27}NO_3SSi$: C 57.8, H 7.9, N 4.0. Found: C 58.3, H 7.7, N 4.1%.

Dianion method

(4-Methylphenylthio)nitromethane **7** (0.37 g, 2 mmol) was dissolved in THF (15 cm^3) and cooled to −90 °C under nitrogen.

n-Butyllithium (1.9 cm^3 of a 2.13 M solution in hexanes, 4 mmol, 2 eq.) was added dropwise. The reaction was allowed to warm to −78 °C for 1 h before adding aldehyde **6a** (0.56 g, 3 mmol, 1.5 eq.). After stirring at −78 °C for 3 h, the reaction was quenched with acetic anhydride (0.38 cm^3, 4 mmol, 2 eq.) and allowed to warm to room temperature. The solution was washed with water (4 × 30 cm^3) and the aqueous portions extracted with dichloromethane (3 × 30 cm^3). The organic extracts were combined, dried and concentrated. The resulting green oil was purified immediately by flash chromatography with light petroleum–toluene (10 : 1) as eluent to yield alkene **8a** (0.362 g, 52%) as a yellow oil, which exhibited identical spectroscopic data and specific rotation to that of the compound prepared by the two-step method.

(1*Z*,3*R*)-3-*tert*-Butyldimethylsilyloxy-4-methyl-1-(4′-methylphenylthio)-1-nitropent-1-ene 8b

(4-Methylphenylthio)nitromethane **7** (0.37 g, 2 mmol) was dissolved in THF (15 cm^3) and cooled to −90 °C under nitrogen. *n*-Butyllithium (1.9 cm^3 of a 2.13 M solution in hexanes, 4 mmol, 2 eq.) was added dropwise. The reaction was allowed to warm to −78 °C for 1 h before the aldehyde **6b** (0.66 g, 3 mmol, 1.5 eq.) was added. After stirring at −78 °C for 3 days, the reaction was quenched with acetic anhydride (0.23 cm^3, 2.4 mmol, 1.2 eq.) and allowed to warm to room temperature. The solution was washed with water (4 × 30 cm^3) and the aqueous portions extracted with dichloromethane (3 × 30 cm^3). The organic extracts were combined, dried and concentrated. The resulting green oil was purified by flash chromatography with light petroleum–toluene (10 : 1) as eluent to yield alkene **8b** (0.57 g, 73%) as a yellow oil. $[\alpha]_D^{20}$ −38.1 (*c* 1.01 in CH_2Cl_2) (Found: $M^+ - {}^t$Bu 324.1091, $C_{15}H_{22}NO_3SSi$ requires 324.1090); ν_{max}/cm^{-1} (film) 2960, 2932, 1539; δ_H (500 MHz) 0.04 (s, 3H, $SiCH_3$), 0.08 (s, 3H, $SiCH_3$), 0.91 (s, 9H, $SiC(CH_3)_3$), 0.96 (d, 6H, *J* 6.8, C(5)H_3), 1.83 (m, 1H, C(4)H), 2.32 (s, 3H, $SArCH_3$), 4.55 (dd, 1H, *J* 5.1, 8.6, C(3)H), 7.16 (AA′BB′, 4H, Ar), 7.39 (d, 1H, *J* 8.6, C(2)H); δ_C (125 MHz) −4.8, −4.1, 17.4, 18.2, 18.7, 21.1, 25.8, 35.4, 75.2, 127.8, 129.9, 130.3, 132.3, 138.4, 146.7; *m*/*z* (EI) 324 ($M^+ - {}^t$Bu, 71%), 73 (100). Anal. Calcd for $C_{19}H_{31}NO_3SSi$: C 59.8, H 8.1, N 3.7. Found: C 59.6, H 8.4, N 3.6%.

(1*Z*,3*R*)-3-*tert*-Butyldimethylsilyloxy-1-(4′-methylphenylthio)-1-nitro-3-phenylpropene 8c

A solution of (4-methylphenylthio)nitromethane **7** (0.55 g, 3 mmol) in THF (10 cm^3) was cooled to −90 °C under nitrogen. *n*-Butyllithium (2.6 cm^3 of a 2.27 M solution in hexanes, 6 mmol, 2 eq.) was added dropwise. The reaction was allowed to warm to −78 °C for 1 h then aldehyde **6c** (1.12 g, 4.5 mmol, 1.5 eq.) was added. After stirring at −78 °C for 3 days, the reaction was quenched with acetic anhydride (0.57 cm^3, 6 mmol, 2 eq.) and allowed to warm to room temperature. The solution was washed with water (3 × 40 cm^3) and the aqueous portions extracted with dichloromethane (2 × 15 cm^3). The organic extracts were combined, dried and concentrated. The resulting green oil was purified by flash chromatography with light petroleum–toluene (10 : 1) as eluent to yield alkene **8c** (0.92 g, 74%) as a yellow oil. $[\alpha]_D^{21}$ −106.5 (*c* 0.68 in CH_2Cl_2) (Found: $M^+ - H$ 414.1540, $C_{22}H_{28}NO_3SSi$ requires 414.1559); ν_{max}/cm^{-1} (film) 2955, 2929, 2857, 1538, 1325, 1089, 1066, 839, 779, 699; δ_H (500 MHz) 0.00 (s, 3H, $SiCH_3$), 0.09 (s, 3H, $SiCH_3$), 0.90 (s, 9H, $SiC(CH_3)_3$), 2.34 (s, 3H, $SArCH_3$), 5.87 (d, 1H, *J* 8.9, C(3)H), 7.08–7.18 (AA′BB′, 4H, S*Ar*CH_3), 7.28–7.40 (m, 5H, *Ph*CH), 7.53 (d, 1H, *J* 8.9, C(2)H); δ_C (125 MHz) −4.6, −4.3, 18.3, 21.2, 25.8, 72.9, 126.4, 127.8, 128.5, 129.0, 129.7, 130.4, 138.4, 141.1, 145.8, 146.6; *m*/*z* (EI) 414 ($M^+ - H$, 2%), 358 ($M^+ - {}^t$Bu, 28), 221 (18), 210 (23), 148 (42), 131 (^{t}BuMe$_2$SiO$^+$, 18), 123 (TolS$^+$, 35), 115 (^{t}BuMe$_2$Si$^+$, 35), 91 (Tol$^+$, 100), 73 (65), 57 (^{t}Bu$^+$, 33). Anal. Calcd for $C_{22}H_{29}NO_3SSi$: C 63.6, H 7.0, N 3.4. Found: C 63.5, H 6.8, N 2.8%.

(1*Z*,3*S*)-3-Hydroxy-1-(4′-methylphenylthio)-1-nitrobut-1-ene 10a

Boron trifluoride–diethyl ether (0.11 cm^3, 0.89 mmol, 1.5 equiv.) was added to a solution of the silyl ether **8a** (0.210 g, 0.59 mmol) in dichloromethane (7 cm^3) at −78 °C. The reaction was allowed to warm to room temperature over 2 h then stirred for a further 2 h. Another 1 equiv. (0.07 cm^3, 0.59 mmol) of boron trifluoride–diethyl ether was added and the reaction stirred for 1 h. The reaction mixture was washed with saturated aqueous sodium carbonate (10 cm^3) and the aqueous layer was extracted with dichloromethane (2 × 10 cm^3). The organic layers were combined, dried, filtered and the solvent removed under reduced pressure. The residue was purified by flash chromatography using 4 : 1 light petroleum–ethyl acetate as eluent to yield the free hydroxyalkene **10a** (0.103 g, 73%) as a yellow waxy solid, mp 34–35 °C; $[\alpha]_D$ −32.4 (*c* 0.885 in CH_2Cl_2) (Found: M^+ 239.0625, $C_{11}H_{13}NO_3S$ requires 239.0616); ν_{max}/cm^{-1} (film) 3395, 3032, 2928, 1736, 1535, 1493, 1327, 1086, 1064, 810; δ_H (200 MHz) 1.41 (d, 3H, *J* 6.5, C(4)H_3), 2.31 (s, 3H, $SArCH_3$), 2.58 (br s, 1H, OH), 5.01 (dq, 1H, *J* 8.0, 6.5, C(3)H), 7.09–7.26 (AA′BB′, 4H, Ar), 7.52 (d, 1H, *J* 8.0, C(2)H); δ_C (50 MHz) 147.7, 147.1, 138.7, 130.4, 130.3, 127.6, 66.4, 22.7, 21.2; *m*/*z* (EI) 239 (M^+, 15%), 149 (MH^+ − Tol, 95), 123 (STol, 22), 115 (M^+ − HSTol, 24), 91 (Tol, 62), 45 (CH_3CHOH, 100).

(1*Z*,3*R*)-3-Hydroxy-4-methyl-1-(4′-methylphenylthio)-1-nitropent-1-ene 10b

Boron trifluoride–diethyl ether (0.13 cm^3, 1.00 mmol, 3 equiv.) was added to a solution of alkene silyl ether **8b** (0.131 g, 0.34 mmol) in dichloromethane (5 cm^3) under nitrogen at −78 °C. The reaction was allowed to warm to room temperature and stirred overnight. The reaction mixture was diluted with dichloromethane (10 cm^3) and washed with saturated aqueous sodium hydrogen carbonate (10 cm^3). The aqueous layer was extracted with dichloromethane (2 × 10 cm^3). The organic layers were combined, dried and the solvent removed under reduced pressure. Purification by flash chromatography using 9 : 1 light petroleum–ethyl acetate as eluent yielded hydroxy alkene **10b** (0.073 g, 80%) as a yellow oil. $[\alpha]_D^{22}$ −67.6 (*c* 1.2 in CH_2Cl_2) (Found: M^+ 267.0294, $C_{13}H_{17}NO_3S$ requires 267.0929); ν_{max}/cm^{-1} (film) 3600–3200, 2965, 1536; δ_H (500 MHz) 0.99 (d, 3H, *J* 6.7, C(5)H_3), 1.03 (d, 3H, *J* 7.0, C(5)H_3), 1.93 (m, 2H, *J* 6.7, 13.3, C(4)H and OH), 2.32 (s, 3H, $ArCH_3$), 4.60 (dd, 1H, *J* 6.2, *J* 8.6, C(3)H), 7.19 (AA′BB′, 4H, Ar), 7.50 (d, 1H, *J* 8.6, C(2)H); δ_C (125 MHz) 17.6, 18.3, 21.1, 34.4, 74.8, 127.6, 130.2, 130.4, 138.6, 145.0 (1 Ar-C obscured); *m*/*z* (EI) 267 (M^+, 3.4%), 43 (100).

(1*Z*,3*R*)-3-Hydroxy-1-(4′-methylphenylthio)-1-nitro-3-phenylpropene 10c

Hydrogen fluoride–pyridine complex (approx. 0.5 cm^3) was transferred by Pasteur pipette to a solution of silyl-protected alkene **8c** (0.111 g, 0.27 mmol) in THF (5 cm^3) in a HF-resistant container under nitrogen. The reaction was covered with a plastic lid and stirred overnight. Chromatographic grade alumina (200 mg) was added and the reaction was stirred for a further 30 minutes. The alumina was removed by filtration through a glass sinter and the solvent was removed under reduced pressure. Purification by flash chromatography using dichloromethane as eluent yielded hydroxyalkene **10c** (0.067 g, 83%) as a yellow oil. The unstable hydroxyalkene was used as soon as possible in the next reaction. $[\alpha]_D^{25}$ −64.8 (*c* 0.5 in CH_2Cl_2); δ_H (500 MHz) 2.31 (s, 3H, $SArCH_3$), 2.38 (br, 1H, OH), 5.93 (d, 1H, *J* 8.6, C(3)H), 7.07–7.21 (AA′BB′, 4H, S*Ar*CH_3), 7.32–7.44 (m, 5H, *Ph*CH), 7.68 (d, 1H, *J* 8.6, C(2)H);

δ_C (125 MHz) 21.1, 72.3, 126.4, 127.4, 129.0, 129.21, 130.2, 130.4, 138.6, 140.2, 145.1, 147.7.

(1′*S*,2*R*,3*R*)-3-(1′-Hydroxyethyl)-2-(4″-methylphenylthio)-2-nitrooxirane 11a

ⁿBuLi (0.24 cm³, 0.52 mmol, 1.2 equiv.) was added to a solution of *tert*-butyl hydroperoxide (0.17 cm³, 0.65 mmol, 1.5 equiv.) in THF (5 cm³) at −78 °C. The alkene **10a** (0.103 g, 0.431 mmol) in THF (3 cm³) was added dropwise at −78 °C. The reaction was stirred at −78 °C for 10 min then quenched at −78 °C with saturated aqueous NH_4Cl (10 cm³). The organic layer was separated and washed with 10% sodium sulfite solution (10 cm³), then dried, filtered and the solvent removed under reduced pressure. The residue was purified by flash chromatography using 4:1 light petroleum–ethyl acetate as eluent to yield the *syn*-epoxide **11a** (0.072 g, 65%) as a colourless oil. $[\alpha]_D$ −28.3 (*c* 3.6 in CH_2Cl_2) (Found: MH^+ − Tol 165.0092, $C_4H_7NO_4S$ requires 165.0096); ν_{max}/cm⁻¹ (film) 3393, 3027, 2978, 1566, 1493, 1342, 1157, 1087, 814, 772; δ_H (200 MHz) 1.36 (d, 3H, *J* 7.6, C(2′)H_3), 2.35 (s, 3H, SArCH_3), 2.62 (br s, 1H, OH), 3.61 (d, 1H, *J* 7.6, C(3)H), 4.09 (m, 1H, C(1′)H), 7.16–7.48 (AA′BB′, 4H, Ar); δ_C (50 MHz) 140.9, 134.7, 130.6, 122.0, 95.8, 68.3, 66.6, 21.4, 19.1; *m*/*z* (EI) 254 (M^+ − H, 5%), 165 (MH^+ − Tol, 32), 123 (STol, 100), 91 (Tol, 95).

(1′*S*,2*R*,3*R*)-3-(1′-Hydroxy-2′-methylpropyl)-2-(4″-methylphenylthio)-2-nitrooxirane 11b

A solution of *tert*-butyl hydroperoxide (0.14 cm³ of a 3.91 M solution in toluene, 0.53 mmol, 1.5 eq.) in THF (5 cm³) was cooled to −100 °C under nitrogen. *n*-Butyllithium (0.17 cm³ of a 2.27 M solution in hexanes, 0.39 mmol, 1.1 eq.) was added, followed by a solution of alkene **10b** (94 mg, 0.35 mmol, 1 eq.) in THF (5 cm³). The reaction was stirred at −100 °C for 15 min before quenching with saturated aqueous NH_4Cl (10 cm³) and allowing to warm to room temperature. The reaction was poured into 10% aqueous sodium sulfite (10 cm³). The aqueous layer was extracted with ethyl acetate (3 × 10 cm³). The combined organic portions were dried and concentrated. Purification by flash chromatography using light petroleum–ethyl acetate (10:1) as eluent gave *syn*-epoxide **11b** (77 mg, 79%) as a pale cream oil; $[\alpha]_D^{22}$ −54.4 (*c* 0.1 in CH_2Cl_2) (Found: M^+ − HNO_2 236.0859, $C_{13}H_{16}O_2S$ requires 236.0871); ν_{max}/cm⁻¹ (film) 3600–3100, 2965, 1565; δ_H (500 MHz) 1.05 (d, 3H, *J* 6.9, C(3′)H_3), 1.09 (d, 3H, *J* 6.8, C(3′)H_3), 1.90 (m, 1H, C(2′)H), 2.36 (s, 3H, ArCH_3), 3.59 (d, 1H, *J* 7.9, C(3)H), 3.67 (dd, 1H, *J* 7.0, 7.9, C(1′)H), 7.33 (AA′BB′, 4H, Ar); δ_C (125 MHz) 17.8, 18.1, 21.3, 31.8, 67.1, 74.3, 96.7, 122.1, 130.6, 134.7, 140.9; *m*/*z* (EI) 236 (M^+ − HNO_2, 2.8%), 123 (STol, 100).

(1′*S*,2*R*,3*R*)-3-(1′-Hydroxy-1′-phenylmethyl)-2-(4″-methylphenylthio)-2-nitrooxirane 11c

A solution of *tert*-butyl hydroperoxide (0.17 cm³ of a 4.45 M solution in toluene, 0.76 mmol, 1.5 eq.) in THF (5 cm³) was cooled to −100 °C under nitrogen. *n*-Butyllithium (0.21 cm³ of a 2.68 M solution in hexanes, 0.56 mmol, 1.1 eq.) was added, followed by a solution of hydroxyalkene **10c** (152 mg, 0.50 mmol, 1 eq.) in THF (2 cm³). The reaction was stirred at −100 °C for 15 min before quenching with saturated aqueous NH_4Cl (10 cm³) and allowing to warm to room temperature. The reaction was poured into 10% aqueous sodium sulfite (10 cm³). The aqueous layer was extracted with ethyl acetate (2 × 10 cm³). The combined organic portions were dried and concentrated. Purification by flash chromatography using dichloromethane as eluent gave *syn*-epoxide **11c** (90 mg, 56%) as a pale yellow oil. $[\alpha]_D^{19}$ −28.8 (*c* 1.3 in CH_2Cl_2) (Found: M^+ 317.0735, $C_{16}H_{15}NO_4S$ requires 317.0722); ν_{max}/cm⁻¹ (film) 3600–2500, 3064, 3034, 1695, 1597, 1559, 1493, 1452, 1177, 811, 700; δ_H (500 MHz) 2.35 (s, 3H, SArCH_3), 2.67 (br, 1H, OH), 3.85 (d, 1H, *J* 7.9, C(3)H), 5.02 (d, 1H, *J* 7.7, C(1′)H), 7.15–7.55 (m, 9H, Ar); δ_C (125 MHz) 21.3, 67.7, 72.1, 96.2, 122.0, 126.2, 129.1, 129.2, 130.6, 134.7, 137.4, 140.9; *m*/*z* (EI) 317 (M^+, 0.3%), 270 (M^+ − HNO_2, 2), 225 (M^+ − TolH, 3.4), 195 (MH^+ − TolS, 2), 124 ($TolSH^+$, 100), 123 ($TolS^+$, 91), 91 (Tol^+, 86), 77 (Ph^+, 40).

(1′*S*,2*R*,3*R*)-3-[1′-(*tert*-Butyldimethylsilyloxy)ethyl]-2-(4″-methylphenylthio)-2-nitrooxirane 12a

2,6-Lutidine (0.047 cm³, 0.4 mmol, 4 equiv.) was added to a solution of the free hydroxy epoxide **11a** (0.025 g, 0.01 mmol) in dichloromethane (1 cm³) at −78 °C. *tert*-Butyldimethylsilyl trifluoromethanesulfonate (0.049 cm³, 0.22 mmol, 2.2 equiv.) was added and the reaction was stirred at −78 °C for 2.5 h. The reaction was diluted with dichloromethane (10 cm³) and washed with 10% citric acid (5 cm³) followed by saturated aqueous sodium bicarbonate (5 cm³). The organic layer was dried, filtered and the solvent removed under reduced pressure. The residue was purified by flash chromatography using 80:1 light petroleum–ethyl acetate as eluent to yield the *syn*-epoxide **12a** (0.03 g, 83%) as a colourless oil. $[\alpha]_D$ −60.1 (*c* 1.25 in CH_2Cl_2); ν_{max}/cm⁻¹ (film) 2957, 2930, 2858, 1568, 1257, 1111, 997, 831, 812, 779; δ_H (200 MHz) 0.12 (s, 3H, $SiCH_3$), 0.14 (s, 3H, $SiCH_3$), 0.92 (s, 9H, $SiC(CH_3)_3$), 1.30 (d, 3H, *J* 6.5, C(2′)H), 2.36 (s, 3H, $ArCH_3$), 3.56 (d, 1H, *J* 7.8, C(3)H), 3.98 (dq, 1H, *J* 7.8, 6.5, C(1′)H), 7.17–7.48 (AA′BB′, 4H, Ar); *m*/*z* (EI) 238 (M^+ − ᵗBuMe₂SiO, 82%), 123 (STol, 80), 91 (Tol, 58), 57 (ᵗBu, 65).

(1′*S*,2*R*,3*R*)-3-(1′-*tert*-Butyldimethylsilyloxy-2′-methylpropyl)-2-(4″-methylphenylthio)-2-nitrooxirane 12b

A solution of hydroxy epoxide **11b** (84 mg, 0.30 mmol) in dichloromethane (5 cm³) was cooled to −78 °C under nitrogen. 2,6-Lutidine (0.14 cm³, 1.2 mmol, 4 equiv.) was added, followed by *tert*-butyldimethylsilyl trifluoromethanesulfonate (0.15 cm³, 0.65 mmol, 2.2 equiv.). The reaction was allowed to warm to room temperature and stirred for 80 min. The reaction mixture was washed with 10% aqueous citric acid (10 cm³) followed by saturated aqueous sodium hydrogen carbonate (10 cm³). The organic layer was dried and concentrated under reduced pressure. Purification by flash chromatography using light petroleum–ethyl acetate (10:1) as eluent gave epoxide **12b** (94 mg, 79%) as a pale cream oil. $[\alpha]_D^{22}$ −51.4 (*c* 1.7 in CH_2Cl_2) (Found: M^+ − NO_2 351.1804, $C_{19}H_{31}O_2SSi$ requires 351.1814); ν_{max}/cm⁻¹ (film) 2959, 2930, 2858, 1567, 1253, 1125, 1096, 1058, 839, 812, 779; δ_H (500 MHz) 0.11 (s, 3H, $SiCH_3$), 0.16 (s, 3H, $SiCH_3$), 0.93 (s, 9H, $SiC(CH_3)_3$), 1.02 (d, 6H, *J* 6.7, C(3′)H_3), 1.85 (m, 1H, C(2′)H), 2.36 (s, 3H, ArCH_3), 3.54 (d, 1H, *J* 8.3, C(3)H), 3.63 (dd, 1H, *J* 5.3, *J* 8.3, C(1′)H), 7.32 (AA′BB′, 4H, Ar); δ_C (125 MHz) −4.8, −4.1, 17.5, 18.3, 18.6, 21.4, 25.9, 32.7, 67.5, 75.3, 96.9, 122.3, 130.6, 134.8, 140.9; *m*/*z* (EI) 351 (M^+ − NO_2, 0.2%), 340 (M^+ − ᵗBu, 0.2), 268 (MH_2^+ − ᵗBuMe₂SiO, 100), 238 (55), 123 ($STol^+$, 29), 115 ($^tBuMe_2Si^+$, 5), 91 (Tol^+, 8), 73 (73), 57 ($^tBu^+$, 13).

(1′*S*,2*R*,3*R*)-3-(1′-*tert*-Butyldimethylsilyloxy-1′-phenylmethyl)-2-(4″-methylphenylthio)-2-nitrooxirane 12c

A solution of hydroxy epoxide **11c** (82 mg, 0.26 mmol) in dichloromethane (5 cm³) was cooled to −100 °C under nitrogen. 2,6-Lutidine (0.06 cm³, 0.52 mmol, 2 equiv.) was added, followed by *tert*-butyldimethylsilyl trifluoromethanesulfonate (0.18 cm³, 0.78 mmol, 3 equiv.) and the reaction was stirred for 15 min. The reaction mixture was washed with 10% aqueous citric acid (5 cm³) followed by saturated aqueous sodium hydrogen carbonate (10 cm³). The organic layer was dried and concentrated under reduced pressure. Purification by flash chromatography using light petroleum–dichloromethane (5:1) as eluent gave epoxide **12c** (96 mg, 86%) as a white solid, mp

70–72 °C; $[a]_D^{18}$ −28.8 (*c* 0.16 in CH_2Cl_2) (Found: $M^+ - NO_2$ 385.1657, $C_{22}H_{29}O_2SSi$ requires 385.1658); ν_{max}/cm^{-1} (film) 2958, 2928, 2856, 1570, 1105, 1087, 1059, 850, 838, 815; δ_H (500 MHz) 0.06 (s, 3H, $SiCH_3$), 0.17 (s, 3H, $SiCH_3$), 0.94 (s, 9H, $SiC(CH_3)_3$), 2.37 (s, 3H, $SArCH_3$), 3.74 (d, 1H, *J* 8.0, C(3)H), 4.95 (d, 1H, *J* 8.0, C(1′)H), 7.19–7.51 (m, 9H, Ar); δ_C (125 MHz) −5.0, −4.8, 18.1, 21.2, 25.6, 68.3, 73.1, 96.3, 122.2, 125.9, 128.6, 128.8, 130.4, 134.6, 138.5, 140.7; *m*/*z* (EI) 385 ($M^+ - NO_2$, 0.5%), 374 ($M^+ - {}^tBu$, 0.5), 341 (MH^+ − Tol, 3), 328 ($M^+ - NO_2 - {}^tBu$, 1) 310 (4), 268 (100), 238 (92), 123 ($STol^+$, 94), 91 (Tol^+, 23), 73 (82); Anal. Calcd for $C_{22}H_{29}NO_4SSi$: C 61.2, H 6.8, N 3.2. Found: C 61.2, H 6.6, N 3.1%.

(1′*S*,2*S*,3*S*)-3-[1′-(*tert*-Butyldimethylsilyloxy)ethyl]-2-(4″-methylphenylthio)-2-nitrooxirane 13a

Triphenylmethyl hydroperoxide (0.234 g, 0.85 mmol, 1.5 equiv.) in THF (7 cm^3) was added to a solution of KH (35 wt% dispersion in mineral oil) (0.284 g, 0.736 mmol, 1.3 equiv.) in THF (7 cm^3) at −78 °C. The reaction was allowed to warm slightly to enable the KH and triphenylmethyl hydroperoxide to react before being cooled back to −78 °C. The alkene **8a** (0.200 g, 0.567 mmol) in THF (3 cm^3) was added dropwise at −78 °C and the reaction mixture was allowed to warm to −60 °C for 10 min during which time the reaction colour changed from yellow to colourless. The reaction was quenched with saturated aqueous NH_4Cl (10 cm^3). The organic layer was separated and washed with 10% sodium sulfite solution (10 cm^3), then dried, filtered and the solvent removed under reduced pressure. The residue was purified by flash chromatography using pure light petroleum then 40:1 light petroleum–ethyl acetate as eluent to yield an inseparable 15:1 *anti*:*syn* mixture of epoxides **13a**,**12a** (0.155 g, 74%) as a colourless oil. $[a]_D$ +33.4 (*c* 1.1 in CH_2Cl_2) (Found: $M^+ - {}^tBuMe_2SiO$ 238.0543, $C_{11}H_{12}NO_3S$ requires 238.0538); ν_{max}/cm^{-1} (film) 2955, 2930, 2859, 1568, 1471, 1464, 1339, 1260, 1115, 1005, 831, 812, 779; δ_H (200 MHz) 0.14 (s, 3H, $SiCH_3$), 0.17 (s, 3H, $SiCH_3$), 0.91 (s, 9H, $SiC(CH_3)_3$), 1.37 (d, 3H, *J* 6.4, C(2′)H), 2.35 (s, 3H, $ArCH_3$), 3.49 (d, 1H, *J* 7.6, C(3)H), 4.07 (dq, 1H, *J* 6.4, *J* 7.5, C(1′)H), 6.98–7.30 (AA′BB′, 4H, Ar); δ_C (50 MHz) 140.6, 134.7, 130.5, 122.5, 96.9, 68.0, 66.1, 25.8, 21.3, 21.2, 18.0, −4.2, −4.4; *m*/*z* (EI) 238 ($M^+ - {}^tBuMe_2SiO$, 20%), 123 (STol, 80), 91 (Tol, 58), 57 (^tBu, 75).

(1′*S*,2*S*,3*S*)-3-(1′-*tert*-Butyldimethylsilyloxy-2′-methylpropyl)-2-(4″-methylphenylthio)-2-nitrooxirane 13b

A solution of *tert*-butyl hydroperoxide (0.11 ml of a 3.91 M solution in toluene, 0.43 mmol, 1.5 eq.) in THF (5 cm^3) was cooled to −78 °C under nitrogen. *n*-Butyllithium (0.13 cm^3 of a 2.4 M solution in hexanes, 0.31 mmol, 1.1 eq.) was added, followed by a solution of alkene **8b** (108 mg, 0.28 mmol, 1 eq.) in THF (2 cm^3). The reaction was allowed to warm to 0 °C and held at that temperature overnight. The reaction was quenched with saturated aqueous ammonium chloride (10 cm^3) and allowed to warm to room temperature. The THF layer was washed with 10% aqueous sodium sulfite (10 cm^3). The combined aqueous layers were extracted with dichloromethane (10 cm^3). The organic portions were dried and concentrated under reduced pressure. Purification by flash chromatography using light petroleum–toluene (10:1) as eluent gave epoxide **13b** (60 mg, 53%) as a pale cream oil, as well as a compound tentatively identified as the epoxide stereoisomer **14** (12 mg, 11%). Data for *anti*-epoxide **13b**, $[a]_D^{23}$ +42.3 (*c* 0.2 in CH_2Cl_2) (Found: M^+ 397.1730, $C_{19}H_{31}NO_4SSi$ requires 397.1743); ν_{max}/cm^{-1} (film) 2959, 2930, 1567, 1060, 856, 839, 778; δ_H (500 MHz) 0.16 (s, 3H, $SiCH_3$), 0.18 (s, 3H, $SiCH_3$), 0.93 (s, 9H, $SiC(CH_3)_3$), 1.00 (d, 3H, *J* 6.7, C(3′)H_3), 1.02 (d, 3H, *J* 6.9, C(3′)H_3), 1.93 (m, 1H, C(2′)H), 2.35 (s, 3H, $ArCH_3$), 3.54 (d, 1H, *J* 7.7, C(3)H), 3.83 (dd, 1H, *J* 3.1 and *J* 7.7, C(1′)H), 7.31 (AA′BB′, 4H, Ar); δ_C (125 MHz) −4.7, −4.0, 15.8, 18.1, 18.5, 21.2, 25.7, 34.0, 66.3, 72.4, 96.5, 122.5, 130.4, 134.7, 140.6; *m*/*z* (EI) 397 (M^+, 0.05%), 340 ($M^+ - {}^tBu$, 2), 293 (2), 268 ($MH_2^+ - {}^tBuMe_2SiO$, 63), 246 (M^+ − COSTol, 12), 232 (35), 149 (53), 107 (100), 91 (Tol, 27), 73 (79).

(1′*S*,2*R*,3*R*)- 12c and (1′*S*,2*S*,3*S*)-3-(1′-*tert*-Butyldimethylsilyloxy-1′-phenylmethyl)-2-(4″-methylphenylthio)-2-nitrooxirane 13c

A solution of *tert*-butyl hydroperoxide (0.16 ml of a 3.55 M solution in toluene, 0.56 mmol, 1.5 eq.) in THF (5 cm^3) was cooled to −78 °C under nitrogen. *n*-Butyllithium (0.18 cm^3 of a 2.27 M solution in hexanes, 0.41 mmol, 1.1 eq.) was added, followed by a solution of alkene **8c** (156 mg, 0.38 mmol, 1 eq.) in THF (2 cm^3). The reaction was allowed to warm to 0 °C and held at that temperature overnight. The reaction was quenched with saturated aqueous ammonium chloride (10 cm^3), allowed to warm to room temperature and poured into 10% aqueous sodium sulfite (10 cm^3). The layers were separated and the aqueous layer was extracted with ethyl acetate (10 cm^3). The organic portions were dried and concentrated under reduced pressure. The crude material was purified twice by flash chromatography using light petroleum–ethyl acetate (25:1) then light petroleum–ethyl acetate (50:1) as eluent to give an inseparable mixture of *syn*- and *anti*-epoxides (**12c** and **13c**) (84 mg, 52%) as a pale cream oil. Data for *anti*-epoxide **13c**, δ_H (500 MHz) −0.03 (s, 3H, $SiCH_3$), 0.19 (s, 3H, $SiCH_3$), 0.93 (s, 9H, $SiC(CH_3)_3$), 2.36 (s, 3H, $SArCH_3$), 3.70 (d, 1H, *J* 7.6, C(3)H), 4.90 (d, 1H, *J* 7.6, C(1′)H), 7.12–7.53 (m, 9H, Ar).

S-(4′-Methylphenyl) (2*R*,3*S*)-2-benzyloxycarbonylamino-3-(*tert*-butyldimethylsilyloxy)butanethioate 16

Aqueous ammonia (0.163 cm^3, 2.61 mmol, 5 equiv., 16 M soln.) was added to a solution of the *anti*-epoxide **13a** (0.193 g, 0.523 mmol) in dichloromethane (1.5 cm^3). The reaction was stirred at room temperature for 7 h then cooled to 0 °C and benzyl chloroformate (0.74 cm^3, 5.23 mmol, 10 equiv.) was added. The reaction was allowed to warm to room temperature and stirred for a further 30 min. Dichloromethane (10 cm^3) was added and the reaction was dried, filtered and the solvent removed under reduced pressure. The residue was purified by flash chromatography using 20:1 light petroleum–ethyl acetate as eluent to yield the Z-protected α-amino thioester **16** (0.202 g, 82%) as a colourless oil. $[a]_D$ +57.4 (*c* 1.11 in CH_2Cl_2) (Found: $M^+ - {}^tBu$ 416.1339, $C_{21}H_{26}NO_4SSi$ requires 416.1352); ν_{max}/cm^{-1} (film) 3432, 3057, 2930, 1726, 1495, 1385, 1265, 1099, 738, 704, 275; δ_H (200 MHz) 0.01 (s, 3H, $SiCH_3$), 0.04 (s, 3H, $SiCH_3$), 0.88 (s, 9H, $SiC(CH_3)_3$), 1.22 (d, 3H, *J* 6.2, C(4)H_3), 2.38 (s, 3H, $ArCH_3$), 4.36 (d, 1H, *J* 9.6, C(2)H), 4.55 (m, 1H, C(3)H), 5.24 (m, 2H, CH_2Ph), 5.70 (d, 1H, *J* 9.7, NH), 7.18–7.44 (m, 9H, ArH); δ_C (50 MHz) 200.1, 157.0, 139.7, 134.6, 130.1, 128.7, 128.4, 128.3, 124.1, 68.5, 67.5, 66.6, 25.9, 21.4, 21.1, 18.0, −4.3, −5.1 (1 Ar-C not resolved); *m*/*z* (EI) 416 ($M^+ - {}^tBu$, 16%), 350 (M^+ − STol, 80), 322 (M^+ − COSTol, 40), 159 ($^tBuMe_2SiO$-$CHCH_3$, 79), 91 (Tol, 100).

Methyl (2*R*,3*S*)-2-benzyloxycarbonylamino-3-(*tert*-butyldimethylsilyloxy)butanoate 17

Mercuric acetate (0.198 g, 0.621 mmol, 3 equiv.) was added to a solution of the Z-protected thioester **16** (0.098 g, 0.207 mmol) in methanol (3 cm^3). The reaction was stirred at room temperature for 1 h then poured into saturated aqueous KI (10 cm^3) which was extracted with diethyl ether (3 × 5 cm^3). The organic layers were combined, dried, filtered and the solvent removed under reduced pressure. The residue was purified by flash chromatography using 15:1 light petroleum–ethyl acetate as eluent to yield the Z-protected α-amino methyl ester **17** (0.068 g, 86%) as a colourless oil; $[a]_D$ +9.0 (*c* 1 in $CHCl_3$) {lit.,[37] $[a]_D$ −7.31 (*c* 3.55 in $CHCl_3$) for enantiomer} (Found: $M^+ - {}^tBu$

324.1258, $C_{15}H_{22}NO_5SSi$ requires 324.1267); ν_{max}/cm^{-1} (film) 3449, 2955, 2930, 1730, 1508, 1315, 1256, 1208, 1101, 1070, 964, 839, 777; δ_H (200 MHz) 0.01 (s, 3H, $SiCH_3$), 0.03 (s, 3H, $SiCH_3$), 0.83 (s, 9H, $SiC(CH_3)_3$), 1.20 (d, 3H, *J* 6.2, C(4)H_3), 3.72 (s, 3H, OCH_3), 4.28 (dd, 1H, *J* 1.8, 9.7, C(2)H), 4.44 (dq, 1H, *J* 1.8, 6.2, C(3)H), 5.14 (s, 2H, CH_2Ph), 5.44 (d, 1H, *J* 9.7, NH), 7.33–7.41 (m, 5H, Ar); δ_C (50 MHz) 171.4, 157.0, 136.3, 128.6, 128.3, 128.2, 68.8, 67.2, 60.0, 52.3, 25.7, 20.9, 17.9, −4.3, −5.3; *m*/*z* (EI) 324 (M^+ − ^{t}Bu, 61%), 159 (^{t}BuMe$_2$SiOCHCH$_3$, 81), 115 (^{t}BuMe$_2$Si, 43), 91 (Tol, 100), 57 (^{t}Bu, 38).

S-(4′-Methylphenyl) (2*S*,3*S*)-2-benzyloxycarbonylamino-3-(*tert*-butyldimethylsilyloxy)butanethioate 18

Aqueous ammonia (0.05 cm^3, 0.34 mmol, 5 equiv., 16 M soln.) was added to a solution of the *syn*-epoxide **12a** (0.025 g, 0.068 mmol) in dichloromethane (1 cm^3). The reaction mixture was stirred at room temperature for 7 h then cooled to 0 °C and benzyl chloroformate (0.1 cm^3, 0.68 mmol, 10 equiv.) was added. The reaction was allowed to warm to room temperature and stirred for a further 30 min. Dichloromethane (10 cm^3) was added and the reaction was dried, filtered and the solvent removed under reduced pressure. The residue was purified by flash chromatography using 20:1 light petroleum–ethyl acetate as eluent to yield the Z-protected α-amino thioester **18** (0.021 g, 65%) as a colourless oil. $[\alpha]_D$ −34.7 (*c* 1.15 in CH_2Cl_2) (Found: M^+ − ^{t}Bu 416.1357, $C_{21}H_{26}NO_4SSi$ requires 416.1352); ν_{max}/cm^{-1} (film) 3331, 2955, 2930, 2857, 1730, 1703, 1495, 1254, 1132, 1117, 1045, 1013, 835, 777; δ_H (200 MHz) 0.07 (s, 6H, $Si(CH_3)_2$), 0.90 (s, 9H, $SiC(CH_3)_3$), 1.23 (d, 3H, *J* 6.4, C(4)H_3), 2.37 (s, 3H, $ArCH_3$), 4.20 (m, 1H, C(3)H), 4.51 (dd, 1H, *J* 4.6, 9.1, C(2)H), 5.18 (s, 2H), 5.45 (d, 1H, *J* 9.1, NH), 7.19–7.40 (m, 9H, Ar); δ_C (50 MHz) 197.9, 155.9, 139.8, 134.5, 130.1, 128.6, 128.3, 128.2, 123.8, 69.3, 67.4, 66.0, 25.8, 21.4, 19.7, 18.1, −4.4, −5.0 (1 Ar-C not resolved); *m*/*z* (EI) 416 (M^+ − ^{t}Bu, 39%), 350 (M^+ − STol, 40), 322 (M^+ − COSTol, 28), 159 (^{t}BuMe$_2$SiOCHCH$_3$, 37), 91 (Tol, 100).

Methyl (2*S*,3*S*)-2-benzyloxycarbonylamino-3-(*tert*-butyldimethylsilyloxy)butanoate 19

Mercuric acetate (0.042 g, 0.133 mmol, 3 equiv.) was added to a solution of the Z-protected thioester **18** (0.021 g, 0.044 mmol) in methanol (2 cm^3). The reaction mixture was stirred at room temperature for 1 h then poured into saturated aqueous KI solution (10 cm^3) which was extracted with diethyl ether (3 × 5 cm^3). The organic layers were combined, dried, filtered and the solvent removed under reduced pressure. The residue was purified by flash chromatography using 15:1 light petroleum–ethyl acetate as eluent to yield the Z-protected α-amino methyl ester **19** (0.011 g, 65%) as a colourless oil. $[\alpha]_D$ +27.3 (*c* 0.55 in CH_2Cl_2) (Found: M^+ − ^{t}Bu 324.1274, $C_{15}H_{22}NO_5Si$ requires 324.1267); ν_{max}/cm^{-1} (film) 3439, 3352, 2955, 2932, 2857, 1728, 1506, 1257, 1207, 1134, 1111, 837, 777, 738; δ_H (200 MHz) 0.02 (s, 3H, $SiCH_3$), 0.04 (s, 3H, $SiCH_3$), 0.85 (s, 9H, $SiC(CH_3)_3$), 1.24 (d, 3H, *J* 6.4, C(4)H_3), 3.75 (s, 3H, OCH_3), 4.08 (dq, 1H, *J* 3.8, 6.4, C(3)H), 4.31 (dd, 1H, *J* 3.8, 8.4, C(2)H), 5.11 (s, 2H, CH_2Ph), 5.51 (d, 1H, *J* 8.4, NH), 7.30–7.38 (m, 5H, ArH); *m*/*z* (EI) 324 (M^+ − ^{t}Bu, 42%), 159 (^{t}BuMe$_2$SiOCHCH$_3$, 71), 115 (^{t}BuMe$_2$Si, 40), 91 (Tol, 100).

S-(4′-Methylphenyl) (2*R*,3*S*)-2-acetylamino-3-*tert*-butyldimethylsilyloxy-4-methylpentanethioate 20

Aqueous ammonia (2 cm^3, *d* 0.88, 28% w/v) was added to a solution of *anti*-epoxide **13b** (0.209 g, 0.53 mmol) in dichloromethane (5 cm^3). The reaction mixture was stirred at room temperature for 4 days then cooled to −78 °C before adding acetic anhydride (3 cm^3, 32 mmol, 60 eq.). The reaction was allowed to warm to room temperature and stirred for a further hour. Dichloromethane (10 cm^3) and water were added and the reaction was washed with saturated aqueous sodium hydrogen carbonate (50 cm^3). The aqueous layer was extracted with dichloromethane (5 × 10 cm^3). The combined organic layers were dried and concentrated. Purification by flash chromatography using light petroleum–ethyl acetate (20:1 then 10:1) as eluent gave thioester **20** (56 mg, 26%) as a colourless oil, and di-*p*-tolyl disulfide (46 mg, 36%). Data for thioester **20**, $[\alpha]_D^{22}$ +86.1 (*c* 0.6 in CH_2Cl_2) (Found: M^+ − ^{t}Bu 352.1390, $C_{17}H_{26}NO_3SSi$ requires 352.1403); ν_{max}/cm^{-1} (film) 3434, 2958, 2930, 1696, 1494, 1472, 1255, 1078, 834; δ_H (300 MHz) 0.01 (s, 3H, $SiCH_3$), 0.02 (s, 3H, $SiCH_3$), 0.90 (d, 3H, *J* 7.0, C(5)H_3), 0.94 (s, 9H, $SiC(CH_3)_3$), 0.95 (d, 3H, *J* 7.0, C(5)H_3), 1.78 (m, 1H, C(4)H), 2.15 (s, 3H, $COCH_3$), 2.37 (s, 3H, $ArCH_3$), 4.12 (d, 1H, *J* 6.0, C(3)H), 4.82 (d, 1H, *J* 9.0, C(2)H), 6.38 (d, 1H, *J* 9.0, NH), 7.19–7.24 (AA′BB′ system, 4H, Ar); *m*/*z* (EI) 352 (M^+ − ^{t}Bu, 11%), 286 (M^+ − STol, 32), 258 (M^+ − COSTol, 80), 123 ($STol^+$, 39), 91 (Tol^+, 36), 73 (100).

S-(4′-Methylphenyl) (2*S*,3*S*)-2-*tert*-butoxycarbonylamino-3-*tert*-butyldimethylsilyloxy-4-methylpentanethioate 22

Aqueous ammonia (5 cm^3, *d* 0.88, 28% w/v) was added to a solution of *syn*-epoxide **12b** (60 mg, 0.15 mmol) in toluene (5 cm^3). The reaction was stirred at 80 °C for 11 days then allowed to cool to room temperature. A solution of di-*tert*-butyl dicarbonate (66 mg, 0.30 mmol, 2 equiv.) in toluene (1 cm^3) was added and the reaction was stirred for 2 hours. Water (20 cm^3) and ethyl acetate (20 cm^3) were added and the layers were separated. The aqueous layer was extracted with ethyl acetate (3 × 10 cm^3) and the combined organic layers were dried and concentrated. Purification by flash chromatography using hexane–toluene (10:1) then hexane–ethyl acetate (10:1) as eluent gave Boc-protected α-amino thioester **22** (22 mg, 31%) as a colourless oil. $[\alpha]_D^{25}$ −41.3 (*c* 0.55 in CH_2Cl_2) (Found: M^+ − 2′Bu 354.1202, $C_{16}H_{24}NO_4SSi$ requires 354.1195); δ_H (250 MHz) 0.00 (s, 3H, $SiCH_3$), 0.04 (s, 3H, $SiCH_3$), 0.84 (s, 9H, $SiC(CH_3)_3$), 0.87 (d, 3H, *J* 8.4, C(5)H_3), 0.93 (d, 3H, *J* 8.4, C(5)H_3), 1.41 (s, 9H, $CO_2C(CH_3)_3$), 1.77–1.88 (m, 1H, C(4)H), 2.29 (s, 3H, $ArCH_3$), 3.76 (dd, 1H, *J* 4.5, 6.0, C(3)H), 4.56 (dd, 1H, *J* 4.5, 8.9, C(2)H), 5.1 (d, 1H, *J* 8.9, NH), 7.10–7.22 (m, 4H, Ar); *m*/*z* (EI) 354 (M^+ − 2′Bu, 31%), 288 (M^+ − ^{t}Bu − STol, 43), 260 (M^+ − ^{t}Bu − COSTol, 38), 124 ($TolSH^+$, 100).

Methyl (2*S*,3*S*)-2-*tert*-butoxycarbonylamino-3-*tert*-butyldimethylsilyloxy-4-methylpentanoate 23

n-Butyllithium (1 cm^3 of a 2.27 M solution in hexanes, 2.27 mmol) was added to methanol (20 cm^3) at room temperature under nitrogen. A portion of this solution (0.43 cm^3, 1.2 eq.) was added to a solution of thioester **22** (19 mg, 0.04 mmol, 1 eq.) in methanol (1 cm^3). The reaction was stirred at room temperature for three days. The methanol was evaporated, dichloromethane (5 cm^3) was added and the mixture was washed with saturated aqueous ammonium chloride (5 cm^3). The dichloromethane layer was dried and concentrated. Purification by flash chromatography using hexane–ethyl acetate (10:1) as eluent gave methyl ester **23** (13 mg, 85%) as a colourless oil. $[\alpha]_D^{25}$ +21.7 (*c* 0.65 in CH_2Cl_2) (Found: M^+ − O′Bu 302.1787, $C_{14}H_{28}NO_4Si$ requires 302.1788); δ_H (250 MHz) 0.06 (s, 3H, $SiCH_3$), 0.09 (s, 3H, $SiCH_3$), 0.89 (s, 9H, $SiC(CH_3)_3$), 0.94 (d, 3H, *J* 6.7, C(5)H_3), 1.00 (d, 3H, *J* 6.8, C(5)H_3), 1.45 (s, 9H, $CO_2C(CH_3)_3$), 1.91 (m, 1H, C(4)H), 3.59 (dd, 1H, *J* 2.9 and 7.4, C(2)H), 3.74 (s, 3H, OCH_3), 4.49 (dd, 1H, *J* 2.9 and 7.9, C(3)H), 5.30 (d, 1H, *J* 7.4, NH); *m*/*z* (EI) 302 (M^+ − O′Bu, 4%), 262 (M^+ − 113, 26), 187 (M^+ − 188, 75), 91 (Tol^+, 45), 73 (O′Bu$^+$, 100), 57 (^{t}Bu$^+$, 100).

Methyl (2*S*,3*S*)-2-*tert*-butoxycarbonylamino-3-hydroxy-4-methylpentanoate 24

Hydrogen fluoride–pyridine complex (approx. 0.5 cm^3) was

quickly transferred by Pasteur pipette to a solution of silyl ether **23** (12.6 mg, 0.034 mmol) in THF (4 cm^3) in a plastic HF-resistant container at room temperature. The reaction was followed by TLC. After stirring overnight, a further 0.5 cm^3 of hydrogen fluoride–pyridine complex was added. After 1 hour, saturated aqueous sodium carbonate (5 cm^3) was cautiously added and the reaction was stirred for a further hour. The product was extracted with ethyl acetate (3 × 10 cm^3). The combined organic portions were dried and concentrated. Purification by flash chromatography using hexane–ethyl acetate (10:1) as eluent gave hydroxy compound **24** (7.6 mg, 87%) as a colourless oil. $[a]_D^{25}$ +18.1 (*c* 0.105 in $CHCl_3$) {lit.,[38] $[a]_D$ +23.6 (*c* 0.45)} (Found: $MH_2^+ - {}^t$Bu 206.1019, $C_8H_{16}NO_5$ requires 206.1028); δ_H (500 MHz) 0.98 (d, 3H, *J* 6.7, C(5)H_3), 1.01 (d, 3H, *J* 6.7, C(5)H_3), 1.45 (s, 9H, $CO_2C(CH_3)_3$), 1.72 (m, 1H, C(4)H), 2.05 (br, 1H, OH), 2.49 (d, 1H, *J* 6.4, C(3)H), 3.46 (dd, 1H, *J* 8.0 and 3.4, C(2)H), 3.78 (s, 3H, OCH_3), 4.46 (br, 1H, C(3)H), 5.47 (br, 1H, NH); δ_C (125 MHz) 18.7, 19.1, 28.3, 29.7, 31.2, 52.4, 56.2, 78.7, 80.3, 155.3, 171.8; *m*/*z* (EI) 206 ($MH_2^+ - {}^t$Bu, 1%), 189 ($MH^+ - O^t$Bu, 17), 133 (85), 128 (59), 101 (83), 73 ($O^t Bu^+$, 50), 57 ($^tBu^+$, 100).

S-(4′-Methylphenyl) (2*R*,3*S*)-2-benzylamino-3-*tert*-butyldimethylsilyloxy-4-methylpentanethioate 26

Benzylamine (34 µl, 0.31 mmol, 1 eq.) and saturated aqueous sodium hydrogen carbonate (1 cm^3) were added to a solution of *anti*-epoxide **13b** (0.123 g, 0.31 mmol, 1 eq.) in dichloromethane (1 cm^3) at room temperature under nitrogen. The reaction was heated to reflux and stirred for 24 hours, then quenched with saturated aqueous ammonium chloride (10 cm^3) and extracted with dichloromethane (10 cm^3). The organic layer was dried and concentrated. Purification by flash chromatography using light petroleum–ethyl acetate (40:1) as eluent gave benzyl protected α-amino thioester **26** (0.093 g, 66%) as a colourless oil. $[a]_D^{24}$ +44.0 (*c* 1.2 in CH_2Cl_2) (Found: $M^+ - {}^t$Bu 400.1755, $C_{22}H_{30}NO_2SSi$ requires 400.1767); ν_{max}/cm^{-1} (film) 3363, 2957, 2929, 2857, 1697, 1076, 837, 807, 778; δ_H (500 MHz) 0.00 (s, 3H, $SiCH_3$), 0.03 (s, 3H, $SiCH_3$), 0.88 (s, 9H, $SiC(CH_3)_3$), 0.89 (d, 3H, *J* 7.0, C(5)H_3), 0.91 (d, 3H, *J* 7.1, C(5)H_3), 1.88 (br, 1H, C(4)H), 2.36 (s, 3H, ArCH_3), 3.45 (br, 1H, C(2)H), 3.89 (br, 2H, CH_2Ph), 4.09 (br, 1H, NH), 7.19–7.36 (m, 9H, CH_2Ph and S*Ar*CH_3); *m*/*z* (EI) 400 ($M^+ - {}^t$Bu, 2%), 306 ($M^+ -$ COSTol, 80), 248 (55), 91 (Tol^+, 100), 73 (90).

Methyl (2*R*,3*S*)-2-benzylamino-3-*tert*-butyldimethylsilyloxy-4-methylpentanoate 27

A portion of the lithium methoxide solution (0.80 cm^3, 1.2 eq.) used in the preparation of methyl ester **23** was added to a solution of thioester **26** (34.5 mg, 0.08 mmol, 1 eq.) in methanol (1 cm^3). The reaction was stirred at room temperature for three days. The methanol was evaporated, dichloromethane (5 cm^3) was added and the mixture was washed with saturated aqueous ammonium chloride (5 cm^3). The aqueous phase was extracted with dichloromethane (2 × 5 cm^3). The combined organic layers were dried and concentrated. Purification by flash chromatography using light petroleum–ethyl acetate (50:1) as eluent gave methyl ester **27** (20 mg, 73%) as a colourless oil. $[a]_D^{22}$ +16.9 (*c* 0.6 in CH_2Cl_2) (Found: $M^+ - {}^i$Pr 322.1841, $C_{17}H_{28}NO_3Si$ requires 322.1838); ν_{max}/cm^{-1} (film) 2956, 2930, 2857, 1744, 1254, 1152, 1077, 836, 776; δ_H (500 MHz) −0.04 (s, 3H, $SiCH_3$), 0.03 (s, 3H, $SiCH_3$), 0.85 (d, 3H, *J* 6.7, C(5)H_3), 0.88 (s, 9H, $SiC(CH_3)_3$), 0.89 (d, 3H, *J* 6.7, C(5)H_3), 1.99 (m, 1H, C(4)H), 3.33 (s, 1H, C(3)H), 3.70 (br, 2H, C(2)H and NH), 3.73 (s, 3H, OCH_3), 3.97 (br, 2H, CH_2Ph), 7.23–7.37 (m, 5H, Ar); *m*/*z* (EI) 322 ($M^+ - {}^i$Pr, 8%), 308 ($M^+ - {}^t$Bu, 34), 293 (40), 187 (88) 115 ($^tBuMe_2Si^+$, 47), 91 (Tol^+, 96), 73 (100).

S-(4′-Methylphenyl) (2*S*,3*S*)-2-benzylamino-3-*tert*-butyldimethylsilyloxy-4-methylpentanethioate 29

Benzylamine (25 µl, 0.23 mmol, 1 eq.) and saturated aqueous sodium hydrogen carbonate (1 cm^3) were added to a solution of *syn*-epoxide **12b** (92 mg, 0.23 mmol, 1 eq.) in *n*-hexane (1 cm^3) under nitrogen. The reaction was heated to reflux and stirred for 5 days. Diethyl ether (10 cm^3) was added and the reaction was washed with saturated aqueous ammonium chloride (10 cm^3). The aqueous layer was extracted with dichloromethane (10 cm^3). The combined organic layers were dried and concentrated. Purification by flash chromatography using light petroleum–ethyl acetate (40:1) as eluent gave benzyl protected α-amino thioester **29** (44 mg, 42%) as a colourless oil together with the amide **28** (12%) and starting epoxide **12b** (29%). Data for thioester **29**; $[a]_D^{22}$ −9.3 (*c* 0.6 in CH_2Cl_2) (Found: $M^+ - {}^t$Bu 400.1762, $C_{22}H_{30}NO_2SSi$ requires 400.1767); ν_{max}/cm^{-1} (film) 3345, 2958, 2929, 2857, 1696, 1472, 1253, 1056, 838, 777; δ_H (500 MHz) 0.03 (s, 3H, $SiCH_3$), 0.08 (s, 3H, $SiCH_3$), 0.90 (s, 9H, $SiC(CH_3)_3$), 0.93 (d, 3H, *J* 6.8, C(5)H_3), 1.00 (d, 3H, *J* 6.8, C(5)H_3), 2.03 (m, 1H, C(4)H), 2.38 (s, 3H, ArCH_3), 3.64 (br, 1H, C(3)H), 3.83 (br, 1H, C(2)H), 3.91 (br, 1H, NH) 4.01 (d, 2H, *J* 12.9, CH_2Ph), 7.18–7.47 (m, 9H, CH_2Ph and S*Ar*CH_3); *m*/*z* (EI) 400 ($M^+ - {}^t$Bu, 8%), 306 ($M^+ -$ COSTol, 95), 187 (60), 91 (Tol^+, 100), 73 (97).

Methyl (2*S*,3*S*)-2-benzylamino-3-*tert*-butyldimethylsilyloxy-4-methylpentanoate 30

Transesterification of thioester **29** to give methyl ester **30** (21 mg, 73%) as a colourless oil was carried out using the same procedure as for the preparation of ester **27** from thioester **26**. $[a]_D^{22}$ −18.3 (*c* 0.3 in CH_2Cl_2) (Found: $M^+ - {}^t$Bu 308.1672, $C_{16}H_{26}NO_3Si$ requires 308.1682); ν_{max}/cm^{-1} (film) 3340, 2957, 2930, 2857, 1738, 1252, 1078, 1059, 838, 777; δ_H (500 MHz) 0.00 (s, 3H, $SiCH_3$), 0.06 (s, 3H, $SiCH_3$), 0.85 (s, 9H, $SiC(CH_3)_3$), 0.90 (d, 6H, *J* 7.0, C(5)H_3), 1.99 (m, 1H, C(4)H), 3.48 (br, 2H, C(2)H and C(3)H), 3.74 (s, 3H, OCH_3), 3.82 (br, 2H, CH_2Ph), 3.85 (br, 1H, NH), 7.26–7.40 (m, 5H, Ar); *m*/*z* (EI) 322 ($M^+ - {}^i$Pr, 6%), 308 ($M^+ - {}^t$Bu, 22), 293 (28), 187 (87), 115 ($^tBuMe_2Si^+$, 38), 91 (Tol^+, 94), 73 (100).

S-(4′-Methylphenyl) (2*S*,3*S*)-2-*tert*-butoxycarbonylamino-3-*tert*-butyldimethylsilyloxy-3-phenylpropanethioate 31

Aqueous ammonia (1 cm^3, *d* 0.88, 28% w/v) was added to a solution of *syn*-epoxide **12c** (73 mg, 0.17 mmol) in toluene (5 cm^3). The reaction was stirred at 80 °C for 6 hours then allowed to cool to room temperature. The aqueous phase was removed using a glass pipette. A solution of di-*tert*-butyl dicarbonate (185 mg, 0.30 mmol, 5 equiv.) in toluene (1 cm^3) was added and the reaction was stirred overnight. Water (10 cm^3) and ethyl acetate (10 cm^3) were added and the layers were separated. The aqueous layer was extracted with ethyl acetate (2 × 10 cm^3) and the combined organic layers were dried and concentrated. Purification by flash chromatography using light petroleum–ethyl acetate (40:1) then ethyl acetate as eluent gave Boc-protected α-amino thioester **31** (55 mg, 65%) as white needles, mp 97–101 °C; $[a]_D^{21}$ −29.5 (*c* 1.8 in CH_2Cl_2) (Found: MH^+ 502.2466, $C_{27}H_{40}NO_4SSi$ requires 502.2473); ν_{max}/cm^{-1} (KBr disc) 3421, 2927, 1721, 1696, 1491; δ_H (500 MHz) −0.09 (s, 3H, $SiCH_3$), 0.09 (s, 3H, $SiCH_3$), 0.91 (s, 9H, $SiC(CH_3)_3$), 1.43 (s, 9H, $CO_2C(CH_3)_3$), 2.38 (s, 3H, SArCH_3), 4.79 (dd, 1H, *J* 5.0 and 9.5, C(2)H), 4.97 (d, 1H, *J* 9.5, C(3)H), 5.21 (d, 1H, *J* 5.0, NH), 7.16–7.24 (AA′BB′, 4H, S*Ar*CH_3), 7.29–7.39 (m, 5H, *Ar*CH); δ_C (125 MHz) −5.3, −4.9, 18.1, 21.3, 25.7, 28.3, 66.3, 74.6, 80.2, 123.9, 126.7, 128.1, 128.3, 130.0, 134.4, 139.3, 139.7, 155.0, 198.1; *m*/*z* (EI) 502 (MH^+, 0.1%), 322 ($MH^+ - {}^t$Bu − STol, 11), 294 ($MH^+ - {}^t$Bu − COSTol, 11), 282 (25), 250 ($MH^+ - CO_2{}^t$Bu − COSTol, 23), 221 ($MH^+ - {}^t$Bu − $CO_2{}^t$Bu − STol, 100), 192 ($MH^+ - {}^t$Bu − $CO_2{}^t$Bu − COSTol,

9), 124 (TolSH$^+$, 32), 91 (Tol$^+$, 12), 73 (^{t}BuO$^+$, 47), 57 (^{t}Bu$^+$, 50). Anal. Calcd for $C_{26}H_{40}NO_4SSi$: C 64.6, H 7.8, N 2.8. Found: C 64.8, H 8.2, N 2.8%.

Methyl (2*S*,3*S*)-2-*tert*-butoxycarbonylamino-3-*tert*-butyldimethylsilyloxy-3-phenylpropanoate 32

n-Butyllithium (1 cm^3 of a 2.68 M solution in hexanes, 2.68 mmol) was added to dry methanol (20 cm^3) at room temperature under nitrogen; 0.64 cm^3 of this solution (0.086 mmol, 1.2 eq.) was added to a solution of thioester **31** (35.7 mg, 0.071 mmol, 1 eq.) in methanol (1 cm^3). The reaction was stirred at room temperature for 2$\frac{1}{2}$ hours. The reaction was quenched by adding water (1 cm^3) and the methanol was evaporated. Saturated aqueous ammonium chloride (10 cm^3) was added and the mixture was extracted with ethyl acetate (3 × 10 cm^3). The organic portion was dried and concentrated. Purification by flash chromatography using light petroleum–ethyl acetate (20 : 1) as eluent gave methyl ester **32** (25 mg, 86%) as a colourless oil. $[a]_D^{23}$ +67.4 (*c* 0.86 in CH_2Cl_2) (Found: M$^+$ − O^{t}Bu 336.1619, $C_{17}H_{26}NO_4Si$ requires 336.1631); ν_{max}/cm^{-1} (KBr disc) 3448, 2955, 2930, 2858, 1746, 1718, 1495, 1366, 1255, 1167; δ_H (500 MHz) −0.12 (s, 3H, $SiCH_3$), 0.07 (s, 3H, $SiCH_3$), 0.90 (s, 9H, $SiC(CH_3)_3$), 1.42 (s, 9H, $CO_2C(CH_3)_3$), 3.62 (s, 3H, OCH_3), 4.54 (dd, 1H, *J* 4.5 and 8.3, C(2)H), 5.04 (d, 1H, *J* 4.5, C(3)H), 5.21 (d, 1H, *J* 8.3, NH), 7.31–7.34 (m, 5H, Ar); δ_C (125 MHz) −5.1, −4.6, 18.3, 25.9, 28.5, 52.0, 61.0, 75.8, 80.0, 126.5, 127.9, 128.2, 140.7, 155.1, 170.6; *m*/*z* (EI) 336 (M$^+$ − O^{t}Bu, 3.5%), 296 (MH$^+$ − 2^{t}Bu, 20), 252 (MH$^+$ − ^{t}Bu − $CO_2{}^t$Bu, 6), 221 (MH$^+$ − ^{t}Bu − $CO_2{}^t$Bu − OMe, 100), 190 (10), 146 (14), 73 (O^{t}Bu$^+$, 48), 57 (^{t}Bu$^+$, 14).

Methyl (2*S*,3*S*)-2-amino-3-hydroxy-3-phenylpropanoate 33

Hydrogen fluoride–pyridine complex (approx. 0.25 cm^3) was transferred by Pasteur pipette to a solution of silyl ether **32** (12.6 mg, 0.034 mmol) in THF (5 cm^3) in a plastic HF-resistant container at room temperature. After stirring overnight, a further 0.5 cm^3 of hydrogen fluoride–pyridine complex was added. After 2 days total reaction time, chromatographic grade alumina (200 mg) was added and the reaction was stirred for a further 30 minutes. The alumina was removed by filtration through a glass sinter and the solvent was removed under reduced pressure. The residue was suspended in ethyl acetate, dried ($MgSO_4$), filtered and concentrated to give a white solid (8 mg) which was not the expected product (by ^{1}H NMR). The $MgSO_4$ and alumina residues were suspended in water (pH 3) and the pH adjusted to pH 10 with concentrated aqueous ammonia. The product was extracted with ethyl acetate (3 × 10 cm^3), dried and concentrated to give β-hydroxy-α-amino acid ester **33** (7.7 mg, 65%) as a colourless oil. $[a]_D^{20}$ +32.4 (*c* 0.74 in MeOH) {lit.,[21] $[a]_D$ +34.1, *c* 2} (Found: M$^+$ − OH 178.0876, $C_{10}H_{12}NO_2$ requires 178.0868); δ_H (500 MHz) 2.1–2.2 (br, 3H, OH and NH_2), 3.69 (s, 3H, OCH_3), 3.85 (br, 1H, C(3)H), 4.97 (d, 1H, *J* 4.5, C(2)H), 7.24–7.37 (m, 5H, Ar); δ_C (125 MHz) 51.8, 59.5, 74.0, 126.0, 127.9, 128.1, 139.4; *m*/*z* (EI) 178 (M$^+$ − OH, 29%), 177 (M$^+$ − H_2O, 35), 118 (M$^+$ − H_2O − CO_2Me, 100), 105 (PhCO$^+$, 57), 91 (PhCH$_2^+$), 77 (Ph$^+$).

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