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Studies on the synthesis of orthogonally protected azalanthionines, and of routes towards β -methyl azalanthionines, by ring opening of N-activated aziridine-2-carboxylates

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ABSTRACT

Orthogonally protected azalanthionines were successfully synthesised by the ring-opening of N-activated aziridine-2-carboxylates with protected diaminopropanoic acids (DAPs). The required DAPs were also prepared by ring-opening of N-activated aziridine-2-carboxylates with para-methoxybenzylamine, but it was found that the choice of aziridine protecting groups dictated both the success of the reaction as well as the regioselectivity of the isolated products. Attempts to extend the methodology to the preparation of the more sterically demanding β -methyl azalanthionines have, so far, been unsuccessful.

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H₂N R HO₂Č

Histidinoalanine

β-Methyl lanthionine

ŇH₂

Tetrahedron

1. Introduction

The incorporation of amino acid cross-linkers into peptide structures, which leads to the formation of cyclic peptides, is an important way that nature uses to give defined peptide and protein conformations with high biological activity. Importantly the stability of the peptides can also be increased due to their increased resistance to proteolytic cleavage.¹ There are many such crosslinkers in nature including lysinoalanine and histidinoalanine,² while the lanthipeptides contain the lanthionine or β -methyllanthionine cross-linking amino acids (Fig. 1).³ Nisin is one of the most studied lanthipeptides and is a highly active antimicrobial peptide, which has been used worldwide for decades as a food preservative (E234). The chemical synthesis of orthogonally protected lanthionines and β-methyllanthionines has been studied extensively.⁴ Vederas has also reported on the replacement of the thioether bridge of lanthionines and β -methyllanthionines with both carbon chain and oxygen bridged analogues.⁵

We recently reported on our preliminary studies on extending the range of lanthionine thioether bridge replacements that are available by preparing orthogonally protected azalanthionines, $\begin{array}{c} H_2 N \xrightarrow{R} & \int_{4} S CO_2 H \\ HO_2 \overset{i}{C} & H & NH_2 \end{array}$ Lysinoalanine

HO₂Ĉ Lanthionine



β-Methyl azalanthionine

 $H_2N \xrightarrow{R} N \xrightarrow{S} CO_2H$ $HO_2C \xrightarrow{I} H NH_2$

Fig. 1. Structures of some cross-linking amino acids.^{2,3}

which have an amine linker, which should have quite different physicochemical properties to any of the other analogues (lanthionines, oxalanthionines or carbalanthionines), including water solubility at physiological pH.⁶ To date this is the only reported method for the preparation of orthogonally protected azalanthionines though a small number of reports on the synthesis of



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azalanthionines are known, but none gave orthogonally protected compounds, which would be suitable for use in solid-phase peptide synthesis.⁷ The presence of a nitrogen atom in the cross-linker would also provide a very useful handle for further derivatisation, or conjugation, where required.

Thus, the goals of the current study were firstly to extend the range of orthogonally protected azalanthionines using our previously developed aziridine ring-opening methodology. Our initial report demonstrated the viability of the methodology but only one azalanthionine analogue was prepared with the correct stereochemistry, when compared to stereochemistry of natural lanthionine containing peptides. For the future incorporation of azalanthionines, in order to prepare lantibiotic analogues, a number of differentially protected analogues would be required with the desired stereochemistry. Since many lanthipeptides also contain the β -methyllanthionine moiety, the second goal of this study was the extension of the methodology to prepare a range of β -methyl azalanthionines, again with the correct stereochemistry at each stereocentre.

2. Results and discussion

2.1. Synthesis of orthogonally protected azalanthionines

The retrosynthetic analysis of the orthogonally protected azalanthionines shows that they could be prepared by ring-opening of *N*-activated aziridine-2-carboxylates with protected diaminopropionic acids (DAPs) (Fig. 2). In turn the DAPs could be obtained by ring-opening of differently protected aziridines with *p*methoxybenzylamine. the nature of the *N*-substituent and the ester group in the 2-position, as well as the temperature of the reaction.⁹ In all cases two molar equivalents of *p*-methoxybenzylamine was used.

Aziridine 2a gave a mixture of 4a and 5a in a 70:23 ratio at room temperature (Table 1, entry 1). However, the selectivity was reversed to give 4a and 5a in a 32:41 ratio, when the reaction was conducted at 80 °C (entry 2). Further reactions in this series were conducted at room temperature to maximise the vield of the product obtained from attack at the aziridine β -position. It was found that the *p*-Ns aziridine **2b** gave **4b** and **5b** in a 63:21 ratio (entry 3). However, the *p*-Nz substituted aziridine **2c** only gave **4c**, the product of attack at the less hindered β -carbon of the aziridine in a 66% yield (entry 4). For the N-activated aziridine allyl esters **3a**–**c** (entries 5–7), only the *N*-*p*-Nz substituted derivative **3c** underwent reaction with *p*-methoxybenzylamine, with **6c** being obtained in a 66% yield, as the sole product. The N-alloc activated aziridine 7 gave no product from attack by *p*-methoxybenzylamine (entry 10). For the unsuccessful reactions, use of Lewis acid catalysis (boron trifluoride etherate) and/or heating to 80 °C, did not lead to any of the desired products. An examination of the results of the ring-opening reactions shows that the regioselective outcome is not predictable.9

Having prepared a number of the required DAPs they were then used to prepare orthogonally protected azalanthionines by ringopening of the protected *N*-activated aziridines (Scheme 2). In these cases, it was found that there was no reaction observed at 25 °C, in the presence of 2 M equivalents of the DAP. When the reactions were heated to 80 °C, only products from attack at the less sterically hindered aziridine β -position were obtained. It is most likely that this is due to the increased steric bulk of the secondary

Fig. 2. Retrosynthetic analysis of orthogonally protected azalanthionines.

In order to prepare a range of different orthogonally protected azalanthionines suitable for solid-phase peptide synthesis the precursor *N*-activated aziridine-2-carboxylates were first prepared to explore the optimal substitution patterns for the synthesis of the required DAPs (Scheme 1). Starting with the known *N*-trityl aziridine-2-carboxylates, **1a** and **1b**,⁸ replacement of the trityl group with a number of electron-withdrawing groups gave the required *N*-activated aziridines (**2a–c**, **3a–c** and **7**). The regioselectivity of the ring-opening reaction, on treatment of the *N*-activated aziridines with *p*-methoxybenzylamine, was highly dependent on both

amine nucleophile of the DAP compared to the primary amino group of the *p*-methoxybenzylamine. Thus far a range of six diastereoisomeric azalanthionines (**8**–**12**, **17**) have been prepared using this methodology, with the stereochemistry of the diastereoisomer depending on whether L- or D-serine was used as the starting material for the precursor *N*-activated aziridines (Scheme 2 and Table 2).

The isolated yields of the azalanthionines, after aqueous workup, were 27–51%, which are comparable with those obtained for similar aziridine ring-opening reactions with protected cysteine



Reagents and conditions; (a) See Supporting Information; (b) p-methoxybenzylamine (2 molar equiv.), MeCN, rt, 24 h

Scheme 1. Synthesis of 1,2-diaminopropanoic acid derivatives (4-6).

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Table 1

Regioselectivity of the ring-opening of N-activated aziridine-2-carboxylates with p-methoxybenzylamine

	$\beta \bigvee_{\substack{N \\ EWG}}^{S} \alpha H_2 N \longrightarrow OMe$ (2 molar equiv.)	CH ₃ CN 24 h PMB N S CO ₂ R H NHEWG β-attack	$+ \frac{EWG_{N} \xrightarrow{R} CO_2 R}{\overset{i}{H} H \overset{i}{H} N_{PMB}}$ α -attack	
Entry	Aziridine	Temp (°C)	%β-attack ^a	%α-attack ^a
1	2a (R=Me, EWG=Ts)	25	70 (4a)	23 (5a)
2		80	32 (4a)	41 (5a)
3	2b (R=Me, EWG= <i>p</i> -Ns)	25	42 (4b)	32 (5b)
4	2c (R=Me, EWG=p-Nz)	25	63 (4c)	
5	3a (R=Allyl, EWG=Ts)	25 or 80 ^b	_	—
6	3b (R=Allyl, EWG=p-Ns)	25 or 80 ^b	_	_
7	3c (R=Allyl, EWG= p -Nz)	25	66 (6c)	_
10	7 (R=Allyl, EWG=alloc)	25 or 80 ^b		_

^a Product number is in parantheses.

^b No product from α - or β -attack obtained, even in the presence of BF₃·OEt₂ as Lewis acid catalyst.



Reagents and conditions; (a) **2b** (0.5 molar equiv.), MeCN, 80 °C, 24 h, (for **9** using *R*-**2b** (0.5 molar equiv.)); (b) **2a** (0.5 molar equiv.), MeCN, 80 °C, 24 h; (c) **2b** (0.5 molar equiv.), MeCN, 80 °C, 24 h, (for **12** using *R*-**2b** (0.5 molar equiv.)); (d) i) TMS-Cl, Et₃N, DCM: ii) Trt-Cl, Et₃N, MeOH, 58%; (e) i) Cs₂CO₃, MeOH: ii) allyl bromide, DMF, 91%; (f) Ref 10; (g) thiophenol, K₂CO₃, DMF, rt, 16 h, 80%; (h) **2a**, BF₃.OEt₂, CH₂Cl₂, rt, 24 h, 30%.

Scheme 2. Synthesis of azalanthionines (8-12, 17).

or serine nucleophiles, used to prepare orthogonally protected lanthionines¹¹ and oxalanthionines.^{5b,c} The mass balance in each case was made up of the starting DAP and numbers of unidentified products, which resembled ring-opened aziridines. These were possibly serine derivatives, though none were conclusively identified, either by NMR or mass spectrometric analysis. It also is worth mentioning that all of the synthesised azalanthionines were prone

to decomposition when stored at ambient temperature. Simple TLC and HPLC analysis showed that they all decomposed to a multitude of products, particularly when stored in solution (results not shown). It was necessary to store them free of solvent in a freezer at -20 °C in order to increase their stability, but even in these cases they had almost completely decomposed in a matter of weeks. The reason for the instability is most likely due to the strongly electron-

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^a % yield and stereochemistry in parantheses.

withdrawing protecting groups present on the nitrogen atoms, which increases the acidity of the α -hydrogens. This makes the molecules more prone to elimination most likely by a retro-Michael mechanism. Therefore, the same electron-withdrawing groups that are necessary for activation of the aziridine ring to nucleophilic ring-opening are also responsible for the instability of the resulting products.

Azalanthionine **12** is considered the most useful of those prepared, as it contained five orthogonal protecting groups. The next stage in the synthesis of aza analogues of lanthipeptides would involve the deprotection of *N*-*p*-Nz protecting group of **12** and replacement with a Fmoc group. Removal of the allyl group of the ester, with Pd(PPh₃)₄, would then give a carboxylic acid, which could be attached to a resin for solid-phase peptide synthesis. Both of these deprotections have been successfully achieved by Vederas in the synthesis of analogues of the lanthipeptide lacticin 3147 A2, containing oxalanthionine linkers, so it is felt that these particular deprotections should also be possible for azalanthionine **12**. Furthermore the deprotection of the *N*-Ns group of DAP **15**, with thiophenol, has already been shown in the preparation of DAP **14**, in an isolated yield of 80% (Scheme 2).

As well as synthesising the azalanthionines two of the isomeric nor-azalanthionines (**18** and **19**) were also prepared (Scheme 3). This was achieved by treating the same *N*-activated aziridine-2-carboxylates (**2a** and **2b**) with the β -amino acid **5a**, which had been obtained as a by-product from attack of *p*-methoxybenzyl-amine at the α -position of the aziridines (Scheme 1). Again, in these cases, only attack at the less hindered β -position occurred to give nor-azalanthionines **18** and **19**, in 47% and 39% yields, respectively. The success of these reactions was somewhat surprising because of the highly hindered nature of the secondary amine nucleophiles used.



Reagents and conditions; (a) **2a** (2 molar equiv.), MeCN, 80 °C, 24 h, 47%; (b) **2b** (2 molar equiv.), MeCN, 80 °C, 24 h, 39%;

2.2. Routes towards β-methyl azalanthionines

Having successfully prepared orthogonally protected azalanthionines attempts were then made to extend the methodology to the β -methyl azalanthionines, which are the amine-linked analogues of the known β -methyllanthionines and β -methyl oxalanthionines.⁵ For the retrosynthesis of the β -methyl azalanthionines two simple disconnections were envisaged (Fig. 3). Disconnection **A** would give a route involving ring-opening of *N*-activated 3-methyl-aziridine-2carboxylates with the previously prepared DAP derivatives. The aziridines would come from suitably protected threonine derivatives, as starting materials. The alternative disconnection **B** would give *N*-activated 3-unsubstituted-aziridine-2-carboxylates and β -methyl DAPs. It was envisaged that the required β -methyl DAPs would, in turn, be prepared by ring-opening of *N*-activated 3methyl-aziridine-2-carboxylates with *p*-methoxybenzylamine.

Thus, the *N*-activated 3-methyl-aziridine-2-carboxylates were prepared in a similar manner to their des-3-methyl counterparts, with L-threonine being used in place of L-serine, as the starting material (Scheme 4). The *N*-trityl aziridine methyl and allyl esters (**20a** and **20b**) were synthesised from L-threonine in good yield.⁸ The trityl group, of each ester was removed and replaced with activating groups to promote aziridine ring-opening. The groups used were Ts, *p*-Ns and *p*-Nz, all of which had been successfully used previously in the synthesis of the azalanthionines (vide supra). In all this gave six different activated aziridines (**21a–c** and **22a–c**), which were then used for the synthesis of β -methyl azalanthionines.

The ring-opening reactions were attempted using the previously successful conditions of stirring at reflux temperature in acetonitrile using a suitably protected DAP. The DAP chosen was **6**c, which was used successfully in the preparation of the corresponding azalanthionines. However, none of the desired β -methyl azalanthionines were obtained, with only the unreacted DAP and unidentified products being recovered that appeared, from their ¹H NMR spectra, to be derived from ring-opening of the 3-methylaziridine-2-carboxylates. Use of Lewis acid catalysis, with BF₃·OEt₂ in dichloromethane at reflux temperature, again gave none of the required products.

Using the successful synthesis of the nor-azalanthionines by ring-opening of an aziridine with a relatively hindered secondary amine as a model, the synthesis of the β -methyl azalanthionines was then attempted by reaction of β -methyl DAPs with *N*-activated 3-unsubstituted aziridines. The β -methyl DAPs were prepared by ring-opening of the β -methyl aziridines (**21a**-**c** and **22a**-**c**) with *p*methoxybenzylamine (Scheme 4). For example, when aziridine **21a** was reacted with *p*-methoxybenzylamine (2 M equivalents) at room temperature in acetonitrile, again two regioisomers were obtained in a combined yield of 76% (Table 3, entry 2). In this case almost equal amounts of both regioisomers were isolated, with the product from β -attack (**23a**) being obtained in 41%, while that from

Scheme 3. Synthesis of isomeric nor-azalanthionines (18 and 19).

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Fig. 3. Retrosynthetic analysis of orthogonally protected β -methyl azalanthionines.



Reagents and conditions; (a) Ref 8; (b) see Scheme 2; (c) p-methoxybenzylamine (2 molar equiv.), MeCN, 24 h.

Scheme 4. Synthesis of β -methyl DAPs.

Table 3

Regioselectivity of the ring-opening of 3-methyl aziridines with *p*-methoxybenzylamine

	$\begin{array}{c} \overbrace{\beta}^{S-S} CO_2 R \\ \overbrace{\beta}^{N} \alpha \\ {{{}{}{}{}{}{$	CH ₃ CN PMB N R SC 24 h H NHE	$O_2R + EWG_N S CO_2R$ H H N PMB	
	2 molar equiv.	β-attack	α-attack	
Entry	Aziridine	Temp (°C)	%β-attack ^a	%α-attack ^a
1	21a (R=Me, EWG=Ts)	0	34 (23a)	32 (24a)
2		25	41 (23a)	35 (24a)
3		80	15 (23a)	62 (24a)
4	19b (R=Me, EWG= <i>p</i> -Ns)	0	42 (23b)	32 (24b)
5		25	27 (23b)	55 (24b)
6		80	21 (23b)	61 (24b)
7	19c (R=Me, EWG= <i>p</i> -Nz)	NR ^b	_	_ ` `
8	20a (R=Allyl, EWG=Ts)	0	38 (25a)	_
9		25	42 (25a)	_
10		80 ^c	_	_
11	20b (R=Allyl, EWG=p-Ns)	0	43 (25b)	35 (26b)
12		25	21 (25b)	49 (26b)
13		80 ^c	_	_ , ,
14	20c (R=Allyl, EWG= p -Nz)	0	39 (25c)	_
15		25	27 (25c)	_
16		80 ^c	_ ` `	_

^a Product number is in parantheses.

^b No reaction when conducted at 0 °C, 25 °C or 80 °C.

^c No product from α - or β -attack obtained.

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 α -attack (**24a**) was obtained in 35% yield. When the reaction was repeated at reflux temperature the ratio was ~4:1 in favour of the product from α -attack (entry 3). When the reaction was conducted at 0 °C, the ratio was ~ 1:1 (entry 1, 34% for β -attack and 32% for α -attack). All the other *N*-activated 3-methyl aziridines previously synthesised were then reacted with *p*-methoxybenzylamine at different temperatures (Table 3).

When aziridine **21b** was used similar results were obtained (entries 4–6), except for the reaction conducted at 25 °C, where the product of α -attack (55% **24b**) was obtained in preference to the product of β -attack (27%, **23b**). Surprisingly, when aziridine **21c**, which contains the N-p-Nz group, was used no products from attack at either the α - or β -positions were obtained at any of the temperatures studied (entry 7). This is in contrast to our previous study, which showed that the 3-unsubstituted N-p-Nz aziridine methyl ester (**2c**) gave the product from attack at the β -position (4c) as the sole product in a 63% isolated yield.⁹ This study had found that when the ester group was changed from methyl to allyl only the 3-unsubstituted aziridine with a *N*-*p*-Nz activating group underwent a ring-opening reaction with *p*-methoxybenzylamine, giving the product of β -attack (**6c**) as the sole product in 66% yield. However, when the corresponding 3-methyl-substituted aziridines were used strikingly different results were obtained (entries 8-16). In all cases, reactions conducted at 80 °C did not give any products from attack at the α or β positions. For aziridines **22a** and **22c** only β -attack was observed, but for **22b** products from both α - and β attack were isolated. As for the case of the 3-unsubstituted aziridines the regioselectivity is highly unpredictable. A computational study of both the 3-substituted and 3-unsubstituted aziridine derivatives is currently being undertaken in order to try to explain the observed regioselectivity outcomes.

With a selection of the required β -methyl DAPs (**23a**, **23b**, **25a**–**c**) in hand, an attempt was made to ring-open the 3unsubstituted aziridines (**2a**–**c** and **3a**–**c**) under reflux conditions in acetonitrile. A significant number of different combinations were tried but there was no evidence, in any case, for the desired β methyl azalanthionines. In every reaction only the starting β methyl DAPs were recovered after aqueous workup, along with compounds, which appeared to be derived from opening of the aziridine ring, as evidenced by the appearance of their NMR spectra compared with, for example, aziridine ring-opened precursors. As before, the use of BF₃·OEt₂ in dichloromethane at reflux temperature was also unsuccessful. These results were somewhat surprising owing to the successful synthesis of the nor-lanthionines **18** and **19**, using what appeared to be an even more sterically demanding secondary amine nucleophile.

3. Conclusions

The synthesis of a range of orthogonally protected azalanthionines, which are amine-linked analogues of the increasingly important lanthionine containing bioactive peptides, has been achieved by ring opening of N-activated 3-unsubstituted aziridines with protected DAPs. However, the azalanthionines are unstable to storage at ambient temperature, most probably due to the strongly electron-withdrawing nitrogen substitutents. Extension of the methodology to the preparation of β -methyl azalanthionines has not been achieved so far. This was attempted by two methods, which involved (i) reaction of DAPs with N-activated 3-methyl-substituted aziridines, or (ii) reaction of β -methyl DAPs with N-activated 3-unsubstituted aziridines. In all cases, there was no indication of the formation of desired β -methyl azalanthionines, even by mass spectrometry. It has also been found that the regioselectivity of the ring opening of *N*-activated aziridine-2-carboxylates with p-methoxybenzylamine is not predictable.

4. Experimental

4.1. General

All isolated products were purified using column chromatography with silica gel (Aldrich, 70–230 mesh, 60 Å) in the indicated solvent systems. Melting points were determined with Stuart scientific SMP1 & Mettler FP62 melting point apparatus. Analytical thin layer chromatography (TLC) was performed on pre-coated plates (Merck Kieselgel 60 F₂₅₄) and visualised with UV light (254 nm), iodine vapour or aqueous potassium permanganate solution. Infrared spectra were recorded as KBr disks or a thin film between sodium chloride plates, on Avatar 320 and Nicolet impact 410 FT-IR spectrophotometers, run on EZ Omnic E.S.P 5.2a and 3.1a software packages, respectively. Polarimetry was carried out using an Optical Activity AA-55 series polarimeter at ambient temperature with a 2 dm, 1 ml cell. ¹H NMR and ¹³C NMR spectra were measured on a JOEL JNM-LA300 FT-NMR or a Bruker Avance III 500 MHz FT-NMR with TopSpin 2.16 Software and 5 mm PATXI 1H/ 13-C/15N Z-GRD probe, in CDCl₃ as solvent. Chemical shift values are reported relative to tetramethylsilane. Mass Spectrometry was carried out at the Centre for Synthesis and Chemical Biology in University College Dublin using Quattro micro™ LC-MS/MS and Liquid chromatography time-of-flight (LCT) mass spectrometers. Exact Mass Spectrometry analyses were carried out at the Department of Chemistry, NUI Maynooth, Co. Kildare, Ireland.

4.2. Experimental procedures

4.2.1. General procedure for ring-opening of aziridines with p-metho xybenzylamine for the preparation of DAPs 4a-c and 6c. To a solution of the relevant aziridine (2 mmol) in acetonitrile (5 ml) was added p-methoxybenzylamine (0.52 ml, 4 mmol) and the solution was stirred for 24 h at room temperature. The solvent was removed in vacuo, and then the residue was re-dissolved in ethyl acetate (20 ml), washed with brine (2×20 ml), dried over anhydrous magnesium sulfate and concentrated in vacuo. The crude product was purified by flash column chromatography on silica gel in petroleum ether—ethyl acetate (2:1).

4.2.1.1. (S)-Methyl 3-(4-methoxybenzylamino)-2-(4-methylphe nylsulfonamido) propanoate (**4a**). Colourless oil (0.54 g, 70%); *R_f*: 0.12 petroleum ether—ethyl acetate (1:1); $[\alpha]_{D}^{20}$ +13.35° (*c* 1.0 in CHCl₃); ¹H NMR (CDCl₃, δ ppm) 7.72 (d, 2H, *J*=8.8 Hz), 7.28 (d, 2H, *J*=8.8 Hz), 7.16 (d, 2H, *J*=8.8 Hz), 6.85 (d, 2H, *J*=8.8 Hz), 4.03 (t, 1H, *J*=4.8 Hz), 3.79 (s, 3H), 3.65 (d, 1H, *J*=12.9 Hz), 3.61 (d, 1H, *J*=12.9 Hz), 3.52 (s, 3H), 2.88 (d, 2H, *J*=5.2 Hz), 2.40 (s, 3H); ¹³C NMR (CDCl₃, δ ppm) 171.2, 158.7, 143.7, 136.6, 131.3, 129.6, 129.3, 127.2, 113.8, 60.4, 55.3, 52.6, 52.3, 50.0, 21.5; IR (thin film, cm⁻¹) 3347, 3089, 2981, 1744, 1188, 1150; HRMS (ES+) calculated for C₁₉H₂₅N₂O₅S, [M+H]⁺ 393.1479, found [M+H]⁺ 393.1477.

4.2.1.2. (*S*)-Methyl 3-(4-methoxybenzylamino)-2-(4-nitrophenyl sulfonamido) propanoate (**4b**). Pale yellow oil (0.53 g, 42%); R_f : 0.20 petroleum ether—ethyl acetate (1:1); $[\alpha]_D^{20}$ +16.51° (*c* 1.0 in CHCl₃); ¹H NMR (CDCl₃, δ ppm) 8.32 (d, 2H, *J*=9.0 Hz), 8.02 (d, 2H, *J*=9.0 Hz), 7.16 (d, 2H, *J*=8.7 Hz), 6.86 (d, 2H, *J*=8.7 Hz), 4.11 (t, 1H, *J*=6.1 Hz), 3.80 (s, 3H), 3.65 (s (br), 2H), 3.58 (s, 3H), 3.01–2.86 (dd, 2H, *J*=5.0, 4.9 Hz); ¹³C NMR (CDCl₃, δ ppm) 170.7, 158.9, 150.0, 145.8, 131.2, 129.5, 128.3, 124.4, 113.8, 55.5, 55.3, 52.8, 52.6, 49.9; IR (thin film, cm⁻¹) 3375, 3087, 2981, 1743, 1552, 1381, 1177; HRMS (ES+) calculated for C₁₈H₂₂N₃O₇S, [M+H]⁺ 438.1329, found [M+H]⁺ 438.1322.

4.2.1.3. (*S*)-Methyl 3-(4-methoxybenzylamino)-2-((4-nitrobenzyl oxy)carbonylamino) propanoate (**4c**). Pale yellow oil (0.46 g, 63%); *R_f*: 0.22 petroleum ether—ethyl acetate (1:1); $[\alpha]_D^{20}$ +22.48° (*c* 1.0 in

CHCl₃); ¹H NMR (CDCl₃, δ ppm) 8.20 (d, 2H, *J*=8.7 Hz), 7.50 (d, 2H, *J*=8.7 Hz), 7.20 (d, 2H, *J*=8.6 Hz), 6.86 (d, 2H, *J*=8.6 Hz), 5.19 (d, 2H, *J*=8.6 Hz), 4.43 (m, 1H), 3.78 (s, 3H), 3.75 (s (br), 2H), 3.72 (s, 3H), 3.10–2.98 (dd, 2H, *J*=4.8, 4.8 Hz); ¹³C NMR (CDCl₃, δ ppm) 171.3, 158.8, 155.3, 147.5, 143.6, 130.9, 129.5, 128.0, 123.7, 113.6, 65.3, 55.1, 53.5, 52.6, 52.3, 49.1; IR (thin film, cm⁻¹) 3341, 3065, 2981, 1744, 1680, 1212; HRMS (ES+) calculated for C₂₀H₂₄N₃O₇, [M+H]⁺ 418.1609, found [M+H]⁺ 418.1627.

4.2.1.4. (R)-Methyl 2-(4-methoxybenzylamino)-3-(4-methoxy phenylsulfonamido) propanoate (**5a**). Colourless oil (0.17 g, 41%); R_f: 0.24 petroleum ether—ethyl acetate (1:1); $[\alpha]_D^{20}$ +12.41° (*c* 1.0 in CHCl₃); ¹H NMR (CDCl₃, δ ppm) 7.70 (d, 2H, J=8.6 Hz), 7.28 (d, 2H, J=8.0 Hz), 7.15 (d, 2H, J=8.6 Hz), 6.85 (d, 2H, J=8.6 Hz), 5.15 (s (br), 1H) 3.80 (s, 3H), 3.68 (s, 3H), 3.65 (m, 2H), 3.51(d, 1H, J=12.9 Hz), 3.30 (m, 1H), 3.26 (dd, 1H, J=8.6, 8.6 Hz), 2.95 (dd, 1H, J=7.5, 7.4 Hz); ¹³C NMR (CDCl₃, δ ppm) 172.9, 158.9, 143.5, 136.6, 131.0, 129.7, 129.4, 127.0, 113.9, 59.0, 55.3, 52.3, 51.2, 44.2, 21.5; IR (thin film, cm⁻¹) 3359, 3082, 2991, 1743, 1224, 1124.

4.2.1.5. (*R*)-Methyl 2-(4-methoxybenzylamino)-3-(4-nitrophenyl sulfonamido) propanoate (**5b**). Pale yellow oil (0.17 g, 32%); *R_f*: 0.32 petroleum ether—ethyl acetate (1:1); ¹H NMR (CDCl₃, δ ppm) 8.28 (d, 2H, *J*=9.0 Hz), 7.94 (d, 2H, *J*=9.0 Hz), 7.14 (d, 2H, *J*=8.7 Hz), 6.83 (d, 2H, *J*=8.7 Hz), 3.80 (s, 3H), 3.71 (s, 3H), 3.65 (d, 1H, *J*=12.9 Hz), 3.54 (d, 1H, *J*=12.9 Hz), 3.30–3.26 (m, 2H), 3.05 (m, 1H); ¹³C NMR (CDCl₃, δ ppm) 172.5, 159.0, 149.9, 145.6, 130.8, 129.4, 128.2, 124.4, 113.9, 59.2, 55.5, 52.6, 51.3, 44.3; IR (thin film, cm⁻¹) 3401, 3065, 2971, 1745, 1542, 1371, 1196.

4.2.1.6. (S)-Allyl 3-(4-methoxybenzylamino)-2-((4-nitrobenzyloxy) carbonylamino) propanoate (**6c**). Pale yellow oil (0.58 g, 66%); *R*_f: 0.11 petroleum ether—ethyl acetate (1:1); $[\alpha]_D^{20} + 26.25^{\circ}$ (*c* 1.0 in CHCl₃); ¹H NMR (CDCl₃, δ ppm) 8.21 (d, 2H, *J*=8.7 Hz), 7.51 (d, 2H, *J*=8.7 Hz), 7.19 (d, 2H, *J*=8.6 Hz), 6.86 (d, 2H, *J*=8.6 Hz), 5.89 (m, 2H), 5.36–5.16 (m, 4H), 4.65 (d, 2H, *J*=5.9 Hz), 4.43 (m, 1H), 3.79 (s, 3H), 3.70 (s (br), 2H), 3.10–2.96 (dd, 2H, *J*=5.8, 5.7 Hz); ¹³C NMR (CDCl₃, δ ppm) 171.1, 158.8, 155.6, 147.6, 143.8, 131.6, 131.4, 129.2, 128.0, 123.7, 118.9, 113.8, 66.1, 65.4, 55.2, 54.1, 53.1, 49.5; IR (thin film, cm⁻¹) 3367, 3075, 2976, 1743, 1674; HRMS (ES+) calculated for C₂₂H₂₆N₃O₇, [M+H]⁺ 444.1765, found [M+H]⁺ 444.1754.

4.2.1.7. (S)-Methyl 3-(((S)-3-methoxy-2-(4-methylphenylsulfo namido)-3-oxopropyl)(4-methoxybenzyl)amino)-2-(4-nitrophenylsul fonamido) propanoate (8). N-p-Nosyl aziridine methyl ester 2b (0.07 g, 0.25 mmol) was dissolved in MeCN (5 ml) before adding DAP 4a (0.2 g, 0.5 mmol, 2 equiv) and the solution was stirred at reflux temperature for 24 h before removing the solvent in vacuo. The oil was dissolved in ethyl acetate (20 ml), washed with brine (2×20 ml) and dried over anhydrous magnesium sulfate before removing the solvent in vacuo. The crude product was purified by preparative TLC on silica gel (petroleum ether-ethyl acetate 4:1) to yield 8, as a pale yellow oil (0.08 g, 46%). R_{f:} 0.37 petroleum ether-ethyl acetate (1:1); ¹H NMR (CDCl₃, δ ppm) 8.33 (d, 2H, J=8.8 Hz), 8.07 (d, 2H, J=8.8 Hz), 7.70 (d, 2H, J=8.4 Hz), 7.32 (d, 2H, J=8.3 Hz), 7.08 (d, 2H, J=8.4 Hz), 6.80 (d, 2H, J=8.4 Hz), 6.20 (s (br), 1H), 4.19 (t, 1H, J=5.3 Hz), 4.03 (dd, 2H, J=7.8 Hz, 6.5 Hz) 3.79 (s, 3H), 3.74 (d, 1H, *J*=13.4 Hz), 3.50 (d, 1H, *J*=13.4 Hz), 3.46 (s, 3H), 3.41 (s, 3H), 2.97 (m, 3H), 2.71 (m, 1H), 2.40 (s, 3H); ¹³C NMR (CDCl₃, δ ppm) 171.0, 170.7, 159.0, 149.8, 146.3, 143.7, 136.5, 130.7, 130.5, 129.8, 128.5, 127.2, 124.1, 113.9, 58.4, 56.7, 56.2, 55.1, 55.1, 52.68, 52.63, 21.6; IR (thin film, cm⁻¹) 3356, 3089, 2982, 1744, 1732, 1532, 1379, 1173, 1133.

4.2.1.8. (S)-Methyl 3-(((R)-3-methoxy-2-(4-methylphenyl sulfonamido)-3-oxopropyl)(4-methoxybenzyl)amino)-2-(4-

nitrophenylsulfonamido) propanoate (9). Compound 9 was synthesised using a similar method to that used to synthesise 8, except the protected aziridine R-2b was used (0.07 g, 0.25 mmol). The crude product was purified by preparative TLC on silica gel (petroleum ether-ethyl acetate 4:1) to yield 9 as a pale yellow oil (0.09 g, 51%). R_f : 0.18 petroleum ether-ethyl acetate (1:1); $[\alpha]_D^{20}$ +32.96° (c 1.0 in CHCl₃); ¹H NMR (CDCl₃, δ ppm) 8.34 (d, 2H, *I*=8.7 Hz), 8.06 (d, 2H, *I*=8.7 Hz), 7.73 (d, 2H, *I*=8.4 Hz), 7.28 (d, 2H, I=8.3 Hz), 7.13 (d, 2H, I=8.5 Hz), 6.82 (d, 2H, I=8.5 Hz), 4.14 (d, 1H, J=6.5 Hz), 4.06 (dd, 1H, J=7.0, 6.2 Hz), 3.81 (d, 1H, *J*=12.9 Hz), 3.80 (s, 3H), 3.50 (d, 1H, *J*=12.9 Hz), 3.46 (s, 3H), 3.41 (s, 3H), 3.02 (m, 3H), 2.76 (m, 1H), 2.42 (s, 3H); ¹³C NMR (CDCl₃, δ ppm) 171.1, 170.8, 159.1, 149.9, 146.1, 143.8, 136.6, 130.8, 130.6, 129.6, 128.4, 127.2, 124.1, 113.8, 58.4, 56.7, 56.2, 55.2, 55.1, 52.7, 52.6, 21.6; IR (thin film, cm⁻¹) 3350, 3081, 2985, 1744, 1732, 1537, 1381, 1177, 1143; HRMS (ES+) calculated for C₂₉H₃₅N₄O₁₁S₂, [M+H]⁺ 679.1738, found [M+H]⁺ 679.1748.

4.2.1.9. (S)-Allyl 3-(((R)-3-methoxy-2-(4-methylphenylsulfo namido)-3-oxopropyl)(4-methoxybenzyl)amino)-2-((4-nitrobenzyloxy) carbonylamino) propanoate (10). Compound 10 was synthesised using a similar method to that used to synthesise 8, except the protected aziridine R-2a was used (0.06 g, 0.25 mmol) and the protected DAP was 6c (0.22 g, 0.5 mmol, 2 equiv). The crude product was purified by preparative TLC on silica gel (petroleum ether-ethyl acetate 4:1) to yield 10 as a pale yellow oil (0.06 g, 38%). R_f: 0.18 petroleum ether-ethyl acetate (1:1); $[\alpha]_D^{20}$ +21.31° (c 1.0 in CHCl₃); ¹H NMR (CDCl₃, δ ppm) 8.21 (d, 2H, *J*=8.3 Hz), 7.72 (d, 2H, J=8.3 Hz), 7.57 (d, 2H, J=8.0 Hz), 7.27 (d, 2H, J=8.0 Hz), 7.11 (d, 2H, *J*=8.6 Hz), 6.77 (d, 2H, *J*=8.6 Hz), 5.88 (m, 2H), 5.79 (d, 1H, *J*=8.2 Hz), 5.29 (m, 4H), 4.60 (pseudo t, 2H, *J*=5.7 Hz), 4.43 (dd, 1H, *J*=8.2, 8.1 Hz), 4.14 (m, 1H), 3.77 (s, 3H), 3.70 (d, 1H, *J*=12.9 Hz), 3.51 (s, 3H), 3.33 (d, 1H, J=13.0 Hz), 2.90-2.73 (m, 4H), 2.41 (s, 3H); ¹³C NMR (CDCl₃, δ ppm) 170.9, 170.6, 159.0, 156.0, 147.5, 143.9, 143.5, 137.1, 131.2, 130.5, 129.5, 129.2, 128.1, 127.1, 123.7, 119.3, 113.7, 66.6, 65.6, 57.6, 55.7, 55.4, 55.2, 54.3, 52.7, 52.4, 21.5; IR (thin film, cm⁻¹) 3401, 3083, 2971, 1749, 1737, 1671, 1386, 1249; HRMS (ES+) calculated for $C_{33}H_{39}N_4O_{11}S$, $[M+H]^+$ 699.2331, found [M+H]⁺ 699.2321.

4.2.1.10. (S)-Allyl 3-(((S)-3-methoxy-2-(4-nitrophenylsulfonamido)-3-oxopropyl)(4-methoxybenzyl)amino)-2-((4-nitrobenzyloxy)carbonylamino) propanoate (11). Compound 11 was synthesised using a similar method to that used to synthesise 8, except the protected aziridine 2b was used (0.07 g, 0.25 mmol) and the protected DAP was 6c (0.22 g, 0.5 mmol, 2 equiv). The crude product was purified by preparative TLC on silica gel in petroleum ether-ethyl acetate 4:1, to yield **11** as a pale yellow oil (0.05 g, 27%). *R*_f: 0.22 petroleum ether–ethyl acetate (1:1); ¹H NMR (CDCl₃, δ ppm) 8.30 (d, 2H, *J*=8.8 Hz), 8.22 (d, 2H, *J*=8.1 Hz), 8.00 (d, 2H, *J*=8.8 Hz), 7.54 (d, 2H, *J*=8.1 Hz), 7.10 (d, 2H, *J*=8.1 Hz), 6.81 (d, 2H, *J*=8.1 Hz), 6.24 (s (br), 1H), 5.94 (m, 1H), 5.43-5.24 (m, 5H), 4.60 (m, 2H, J=5.6 Hz), 4.48-4.34 (m, 1H), 4.14 (m, 1H), 3.78 (s, 3H), 3.76 (d, 1H, J=13.2 Hz), 3.51 (s, 3H), 3.46 (d, 1H, J=13.2 Hz), 2.98–2.85 (m, 2H), 2.78–2.71 (m, 2H); ¹³C NMR (CDCl₃, δ ppm) 170.6, 170.2, 159.2, 156.2, 149.9, 147.8, 146.5, 143.4, 132.4, 131.1, 130.4, 128.3, 128.1, 123.9, 123.7, 119.5, 113.9, 66.5, 65.9, 57.7, 56.6, 55.2, 54.9, 54.1, 52.8, 52.4; IR (thin film, cm⁻¹) 3347, 3074, 2991, 1749, 1733, 1677, 1547, 1386, 1192.

4.2.1.11. (S)-Allyl 3-(((R)-3-methoxy-2-(4-nitrophenylsulfonamido)-3-oxopropyl)(4-methoxybenzyl)amino)-2-((4-nitrobenzyloxy)carbonylamino) propanoate (**12**). Compound **12** was synthesised using a similar method to that used to synthesise **8**, except the protected aziridine used was R-**2b** (0.07 g, 0.25 mmol). The crude product was purified by preparative TLC on silica gel in petroleum 8

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ether—ethyl acetate 4:1, to yield **12** as a pale yellow oil (0.06 g, 32%). *Rf*: 0.22 petroleum ether—ethyl acetate (1:1); $[\alpha]_D^{20} + 67.20^{\circ}$ (*c* 1.0 in CHCl₃); ¹H NMR (CDCl₃, δ ppm) 8.30 (d, 2H, *J*=8.8 Hz), 8.26 (d, 2H, *J*=8.6 Hz), 8.06 (d, 2H, *J*=8.8 Hz), 7.57 (d, 2H, *J*=8.9 Hz), 7.14 (d, 2H, *J*=8.1 Hz), 6.78 (d, 2H, *J*=8.1 Hz), 6.51 (s (br), 1H), 5.86 (m, 1H), 5.34–5.22 (m, 5H), 4.60 (m, 2H), 4.44 (pseudo t, 1H, *J*=4.8 Hz), 4.30 (pseudo t, 1H, *J*=4.9 Hz), 3.77 (d, 1H, *J*=13.2 Hz), 3.76 (s, 3H), 3.51 (s, 3H), 3.46 (d, 1H, *J*=13.2 Hz), 2.94–2.88 (m, 2H), 2.76 (d, 2H, *J*=6.2 Hz); ¹³C NMR (CDCl₃, δ ppm) 170.6, 170.2, 159.2, 156.2, 149.9, 147.8, 146.5, 143.4, 132.4, 131.1, 130.4, 128.3, 128.1, 123.9, 123.7, 119.5, 113.9, 66.5, 65.9, 57.7, 56.6, 55.2, 54.9, 54.1, 52.8, 52.4; IR (thin film, cm⁻¹) 3359, 3079, 2998, 1748, 1734, 1678, 1551, 1381, 1199.

4.2.1.12. N-Triphenylmethyl-(S)-serine (13). To a suspension of Sserine (2.0 g, 18 mmol) in DCM (26 ml) under a nitrogen atmosphere, was added Me₃SiCl (7.5 ml, 57 mmol) and the solution was stirred at reflux temperature for 20 min. The solution was allowed to cool to 0 °C and Et₃N (8.3 ml, 57 mmol) in DCM (26 ml) was added dropwise over 10 min to the solution, which was then stirred for 45 min. The solution was cooled to 0 °C and anhydrous methanol (0.9 ml) was added dropwise. The solution was allowed to warm to room temperature, and Et₃N (7.0 ml, 18 mmol) was added followed by triphenylmethyl chloride (4.6 g, 18 mmol), and the solution was stirred for 20 h at ambient temperature. An excess of Et₃N (13 ml) and then methanol (94 ml) was added until the white solid present in the mixture was dissolved. The excess solvent was then removed in vacuo producing a white solid. The white solid was partitioned between ethyl acetate (67 ml) and citric acid (40.2 ml, 5% ag w/v), which had been pre-cooled to 4 °C. The organic layer was washed with 2 M aqueous sodium hydroxide (2×20 ml) followed by water (3×15 ml). The aqueous layers were combined, washed with ethyl acetate (15 ml) and neutralised with glacial acetic acid (3-4 ml) at 0 °C. The precipitated product was extracted with ethyl acetate $(6 \times 30 \text{ ml})$ and the organic layer was dried over anhydrous magnesium sulfate. The solvent was removed in vacuo to produce a white solid (3.1 g, 48%). Mp 109–110 °C; ¹H NMR (CDCl₃, δ ppm) 7.43 (d, 6H, J=6.0 Hz), 7.32-7.29, 7.28 (m, 3H), 3.73–3.71 (m, 1H), 3.50 (dd, 1H, J=2.9, 2.9 Hz), 2.94–2.90 (m, 1H); ¹³C NMR (CDCl₃, δ ppm) 174.9, 145.2, 129.3, 128.6, 126.2, 73.9, 67.5, 62.0; IR (KBr, cm⁻¹) 3314, 3068, 1732.

The enantiomeric *N*-trityl-(R)-serine (*R***-13**) was also prepared in a similar manner from (R)-serine.

4.2.1.13. N-Triphenylmethyl-(S)-serine allyl ester (14). N-Triphenylmethyl-(S)-serine (0.30 g, 0.87 mmol) was converted to its caesium salt by dissolving it in dry methanol (3.0 ml) containing Cs₂CO₃ (0.15 g, 0.45 mmol) under a nitrogen atmosphere. After removing the solvent in vacuo, the salt produced was re-dissolved in DMF (0.6 ml) and the resulting mixture was treated with allyl bromide (0.10 ml, 0.90 mmol). The solution was left stirring for a further 18 h at ambient temperature, after which the DMF was removed in vacuo. The mixture was then re-dissolved in ethyl acetate (3 ml) and washed with citric acid solution (1×10 ml, 5% aq w/ v). The aqueous layers were combined and extracted with ethyl acetate (2×10 ml), and the organic layers were combined and washed with water (12×10 ml). The organic layer was dried over anhydrous magnesium sulfate and the solvent was removed in vacuo producing a brown oil (0.30 g, 90%). R_f 0.73, hexane–ethyl acetate (2:1); ¹H NMR (CDCl₃, *δ* ppm) 7.50 (dd, 6H, *J*=8.4, 5.3 Hz), 7.25-7.22 (m, 9H), 5.70-5.67 (m, 1H), 5.18 (dd, 1H, J=1.5, 1.3 Hz), 5.13 (dd, 1H, J=1.5, 1.5 Hz), 4.19-4.17 (m, 1H), 4.09-4.00 (m, 1H), 3.72 (dd, 1H, *J*=6.6, 6.4 Hz), 3.54 (dd, 2H, *J*=4.2, 3.9 Hz); ¹³C NMR (CDCl₃, δ ppm) 173.1, 145.1, 131.6, 128.7, 127.9, 126.6, 118.4, 71.0, 65.7, 64.9, 57.8; IR (thin film, cm⁻¹) 3477, 3068, 2960, 1740, 1635.

The enantiomeric R-14 was also prepared in a similar manner from N-trityl-(R)-serine.

4.2.1.14. 2-(S)-Allyloxycarbonylamino-3-[(4-methoxy-benzyl)-(2nitro-benzenesulfonyl)-amino]-propionic acid allyl ester (15). To a solution of N-(p-methoxybenzyl)-2-nitrobenzenesulfonamide¹⁰ (0.22 g, 0.70 mmol) in THF (3 ml) was added PPh₃ (0.34 g, 1.4 mmol), followed by the addition of *N*-triphenylmethyl-(*S*)-serine allyl ester (0.16 g, 1.4 mmol) and then diethyl azodicarboxylate (0.19 g, 1.2 mmol). The resulting mixture was allowed to stir at room temperature, under a nitrogen atmosphere, for 10 h. The solvent was removed in vacuo giving an orange oil. Purification by flash column chromatography on silica gel in petroleum ether-ethyl acetate (4:1) gave 3-[(4-Methoxybenzyl)-(2-nitrobenzenesulfonyl)amino]-2-(S)-(tritylamino)-propanoic acid allyl ester as a white solid (0.23 g, 51%). R_f 0.36, petroleum ether-ethyl acetate (2:1); Mp 85–87 °C; ¹H NMR (CDCl₃, δ ppm) 8.01 (dd, 1H, *J*=4.6, 4.4 Hz), 7.89 (dd, 1H, J=5.1, 5.1 Hz), 7.65 (m, 6H), 7.50-7.40 (m, 2H), 7.24-7.16 (m, 9H), 7.00 (d, 2H, J=8.7 Hz), 6.70 (d, 2H, J=8.7 Hz), 5.64-5.60 (m, 1H), 5.34 (m, 1H), 5.13 (dd, 2H, J=10.2, 10.1 Hz), 4.46 (s, 2H), 4.34 (dd, 2H, J=7.1, 6.9 Hz), 3.95-3.90 (m, 1H), 3.80 (s, 3H), 3.79-3.55 (m, 2H); ^{13}C NMR (CDCl₃, δ ppm) 169.2, 159.3, 145.5, 145.0, 135.2, 134.0, 132.6, 131.1, 130.1, 129.6, 129.3, 128.0, 126.5, 125.2, 124.2, 118.8, 114.0, 67.2, 64.2, 55.3, 55.0, 49.9, 47.4. IR (KBr, cm⁻¹) 3347, 3163, 2901, 1721, 1605, 1561, 1130. MS (ES⁺) calculated for C₃₉H₃₇N₃O₇S, [M+H]⁺ 692.2, found [M+H]⁺ 692.1.

3-[(4-Methoxybenzyl)-(2-nitrobenzenesulfonyl)-amino]-2-(S)-(tritylamino)propanoic acid allyl ester (0.10 g, 0.16 mmol) was treated with 50% TFA in CHCl₃ (2.2 ml), under a nitrogen atmosphere, for 1 h. NaHCO₃ (0.10 g, 2.2 mmol) was added with water (5 ml) and stirred for 5 min, then further NaHCO₃ (0.10 g, 2.2 mmol) was added followed by allyl chloroformate (0.5 ml, 0.5 mmol). The mixture was stirred at room temperature for 12 h, diluted with ethyl acetate (20 ml) and washed with water (2×10 ml), dried over magnesium sulfate, and concentrated in vacuo producing a yellow oil. Purification by flash column chromatography on silica gel in petroleum ether-ethyl acetate (4:1) gave **15** as a yellow oil (0.050 g, 63%). $R_f 0.57$, petroleum ether–ethyl acetate (1:2); ¹H NMR (CDCl₃, δ ppm) 7.99 (d, 1H, J=7.3 Hz), 7.69–7.60 (m, 3H), 7.11 (d, 2H, J=8.6 Hz), 6.78 (d, 2H, *I*=8.6 Hz), 5.89–5.85 (m, 2H), 5.31–5.29 (m, 4H), 4.68–4.41 (m, 5H), 4.21 (s, 2H), 3.77 (s, 3H), 3.72-3.49 (m, 2H); ¹³C NMR (CDCl₃, δ ppm) 169.6, 159.5, 156.6, 147.7, 145.0, 135.1, 133.6, 132.4, 131.7, 131.2, 129.8, 126.1, 124.3, 118.9, 118.0, 117.6, 68.6, 64.1, 55.2, 51.8, 50.4, 47.8; IR (thin film, cm⁻¹) 3345, 3063, 2963, 1791, 1600, 1555, 1528, 1103; MS (ES⁺) calculated for C₂₄H₂₇N₃O₉S, [M+H]⁺ 534.1, found [M+H]⁺ 534.1.

4.2.1.15. 2-(S)-Allyloxycarbonylamino-3-(4-methoxy-benzyla*mino*)-*propionic acid allyl ester* (16). Thiophenol (0.6 ml, 0.6 mmol) was dissolved in DMF (2 ml) and treated with K₂CO₃ (0.20 g, 1.6 mmol) in water (1 ml), which was then stirred at 0 °C for 10 min. Compound 15 (0.10 g, 0.53 mmol) was dissolved in DMF (1 ml) and added to the thiophenol mixture and stirred overnight at room temperature under a nitrogen atmosphere. Ethyl acetate (10 ml) was added and the mixture washed with water (2 x 10 ml), dried over magnesium sulfate and concentrated in vacuo giving a yellow oil. Purification by flash column chromatography on silica gel in DCM-diethyl ether (2:1) removed the yellow fraction. Methanol–DCM (5:95) was then added to give 16 as a light brown oil (0.15 g, 80%). R_f 0.37, DCM-diethyl ether (2:1) (stain ninhydrin, yellow spot); ¹H NMR (CDCl₃, δ ppm) 7.20 (d, 2H, *J*=8.4 Hz), 6.85 (d, 2H, J=8.7 Hz), 5.95–5.82 (m, 2H), 5.72 (d, 1H, J=6.3 Hz), 5.34–5.23 (m, 4H), 4.64-4.56 (m, 4H), 4.44-4.41 (m, 1H), 3.80 (s, 2H), 3.79 (s, 3H), 3.72 (dd, 2H, J=4.5, 3.3 Hz). ¹³C NMR (CDCl₃, δ ppm) 166.1, 159.7, 155.9, 146.7, 131.2, 128.9, 119.5, 67.9, 55.3, 52.8, 51.2, 48.7. IR (thin film, cm⁻¹) 3311, 3030, 2876, 1720, 1666, 1489; MS (ES⁺) calculated for $C_{18}H_{24}N_2O_5$, [M+1] 649.2, found [M+1] 649.2.

4.2.1.16. 2-(S)-Allyloxycarbonylamino-3-{(4-methoxy-benzyl)-[2-(S)-methoxycarbonyl-2-(toluene-4-sulfonylamino)-ethyl]-amino}-

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propionic acid allyl ester (17). Aziridine 2a (0.65 g, 0.28 mmol) and DAP 16 (0.10 g, 0.28 mmol) were dissolved in dry DCM (5 ml) and stirred at room temperature, under a nitrogen atmosphere, for 20 min. Freshly distilled BF3·OEt2 (0.01 ml, 0.1 mmol) was then added and the mixture was stirred at 40 °C for 24 h. The mixture was then diluted with DCM (10 ml) and washed with saturated aqueous NaHCO₃ solution (10 ml) and water (10 ml), dried over magnesium sulfate, and then the solvent was removed in vacuo giving a brown residue. Purification by preparative TLC in petroleum ether-ethyl acetate (2:1) gave 17 as a clear oil (48 mg, 30%). R_f 0.26, petroleum ether–ethyl aceatate (2:1); ¹H NMR (CDCl₃, δ ppm) 7.74 (d, 2H, *J*=8.2 Hz), 7.30 (d, 2H, *J*=8.0 Hz), 7.20 (d, 2H, *J*=5.3 Hz), 6.65 (d, 2H, J=6.3 Hz), 5.99-5.82 (m, 2H), 5.73 (s, 1H, J=17.4 Hz), 5.50 (d, 1H, J=12.9 Hz), 5.35–5.23 (m, 4H), 4.60 (dd, 4H, J=5.6, 5.5 Hz), 4.44–4.36 (m, 2H), 3.97 (dd, 2H, J=4.2, 3.6 Hz), 3.88 (d, 2H, J=3.6 Hz), 3.80 (s, 3H) 3.73 (d, 2H, J=3.6 Hz), 2.96 (s, 3H), 2.42 (s, 3H); MS (ES⁺) calculated for C₂₉H₃₇N₃O₉S, [M+H]⁺ 604.3, found [M+H]⁺ 604.3.

4.2.1.17. (2R)-Methyl 2-(((S)-3-methoxy-2-(4-nitrophenylsulfo namido)-3-oxopropyl)(4-methoxybenzyl)amino)-3S-(4-methylphenyl sulfonamido) propanoate (18). Compound 18 was synthesised using a similar method to that used to synthesise 8, except the protected Dap 5a and aziridine 2a were used. The crude product was purified using preparatory TLC on silica gel (petroleum ether-ethyl acetate 4:1) to yield 18 as a pale yellow oil (0.08 g, 47%). R_f: 0.29 petroleum ether–ethyl acetate (1:1); ¹H NMR (CDCl₃, δ ppm) 8.33 (d, 2H, *I*=8.9 Hz), 8.00 (d, 2H, *I*=8.7 Hz), 7.69 (d, 2H, *I*=8.0 Hz), 7.28 (d, 2H, *I*=8.1 Hz), 7.08 (d, 2H, *I*=8.4 Hz), 6.84 (d, 2H, *I*=8.4 Hz), 3.98 (t, 1H, *I*=6.5 Hz), 3.81 (s, 3H), 3.73 (s, 3H), 3.65 (d, 1H, J=13.0 Hz), 3.55 (d, 1H, J=12.9 Hz), 3.50 (s, 3H), 3.46 (m, 1H), 3.23 (m, 1H), 3.09 (m, 2H), 3.00 (m, 1H), 2.42 (s, 3H); ¹³C NMR (CDCl₃, δ ppm) 170.9, 170.7, 159.3, 150.1, 145.5, 143.6, 136.6, 130.4, 129.7, 128.4, 127.0, 124.2, 114.1, 62.7, 55.3, 55.3, 55.2, 54.5, 52.4, 52.1, 41.4, 21.5; IR (thin film, cm⁻¹) 3391, 3078, 2962, 1745, 1732, 1529, 1391, 1249, 1141.

4.2.1.18. (2R)-Methyl 3-(((S)-1-allyloxy-3-(4-methylphenyl sulfonamido)-1-oxopropan-2-yl)(4-methoxybenzyl)amino)-2-(4nitrophenylsulfonamido) propanoate (19). Compound 19 was synthesised using a similar method to that used to synthesise 18, except the protected Dap 5a and aziridine 2b were used. The crude product was purified using preparatory TLC on silica gel (petroleum ether-ethyl acetate 4:1) to yield 19 as a pale yellow oil (0.07 g, 39%). *R_f*: 0.24 petroleum ether–ethyl acetate (1:1); ¹H NMR (CDCl₃, δ ppm) 8.32 (d, 2H, J=8.8 Hz), 8.00 (d, 2H, J=8.8 Hz), 7.68 (d, 2H, J=8.7 Hz), 7.27 (d, 2H, J=8.6 Hz), 7.11 (d, 2H, J=8.7 Hz). 6.84 (d, 2H, J=8.7 Hz), 5.66 (m, 1H), 5.20 (m, 3H), 4.35 (d, 2H, J=6.0 Hz), 3.97 (t, 1H), 3.81 (s, 3H), 3.72 (s, 3H), 3.66 (d, 1H, J=13.5 Hz), 3.57 (d, 1H, J=13.5 Hz), 3.46 (m, 1H), 3.25 (m, 1H), 3.10–2.98 (m, 3H), 2.41 (s, 3H); 13 C NMR (CDCl₃, δ ppm) 170.9, 170.0, 159.3, 150.1, 145.5, 143.5, 136.7, 130.6, 130.5, 129.7, 128.5, 127.0, 124.3, 120.0, 114.1, 66.8, 62.8, 55.5, 55.4, 55.3, 54.6, 52.1, 41.5, 21.5; IR (thin film, cm⁻¹) 3376, 3065, 2963, 1751, 1732, 1684, 1524, 1391, 1247.

4.2.1.19. (ι)-Threonine methyl ester hydrochloride.⁸ A 250 ml 3necked round-bottom flask was equipped with a condenser, a dropping funnel and a rubber septum. The condenser was fitted with a calcium chloride drying tube. The dropping funnel was charged with acetyl chloride (23.0 ml, 0.33 mol). The flask was filled with 75 mls of methanol and cooled to 0 °C in an ice bath under nitrogen. The acetyl chloride is added dropwise over 5 min before Lthreonine (13.58 g, 0.11 mol) was added before heating to reflux temperature. After 2 h the solvent is removed in vacuo to yield a white fluffy solid (18.75 g, 97%), which was used without further purification. ¹H NMR (CDCl₃, δ ppm) 4.12 (d, 1H, *J*=5.8 Hz), 3.87 (d, 1H, *J*=5.8 Hz), 3.78 (dd, 1H, *J*=5.3, 5.2 Hz), 3.67 (s, 3H), 1.21 (d, 3H, J=6.0 Hz). ¹³C NMR (CDCl₃, δ ppm) 169.2, 60.9, 54.9, 52.1, 19.2. IR (KBr, cm⁻¹) 3407, 2967, 1745.

N-*trityl*-(L)-*threonine methyl ester* was synthesised using a similar method to that used to synthesise **14**, except (L)-*threonine methyl ester hydrochloride* (0.54 g, 3.2 mmol) was used, to yield a white solid (0.98 g, 82%).⁸ *R*₅: 0.50 petroleum ether—ethyl acetate (2:1). ¹H NMR (CDCl₃, δ ppm) 7.49 (m, 6H), 7.31–7.14 (m, 9H), 3.78 (m, 1H), 3.38 (d, 1H *J*=3.5 Hz), 3.15 (s, 3H), 1.22 (d, 3H *J*=6.3 Hz). ¹³C NMR (CDCl₃, δ ppm) 173.7, 145.4, 128.9, 127.9, 126.6, 69.7, 62.5, 53.4, 51.7, 18.9. **IR** (KBr, cm⁻¹) 3481, 3055, 2978, 1732, 1592.

4.2.1.20. *N*-Triphenylmethyl-(*L*)-threonine. *N*-Triphenylmethyl-(*L*)-threonine was synthesised using a similar method to that used to synthesise *N*-triphenylmethyl-(*S*)-serine (**13**), except *L*-threonine (1.13 g, 9.5 mmol) was used to yield a white solid (2.02 g, 59%). ¹H NMR (CDCl₃, δ ppm) 7.40 (d, 6H, *J*=6.0 Hz), 7.28–7.15 (m, 9H), 3.91 (m, 1H), 3.52 (dd, 1H, *J*=5.9, 5.8 Hz), 1.19 (d, 3H, *J*=5.6 Hz); ¹³C NMR (CDCl₃, δ ppm) 174.6, 145.2, 128.6, 127.7, 126.6, 70.6, 60.5, 54.8, 18.3; IR (KBr, cm⁻¹) 3341, 3082, 2977, 1737.

4.2.1.21. *N*-Triphenylmethyl-(*L*)-threonine allyl ester. *N*-Triphenylmethyl-(*L*)-threonine allyl ester was synthesised using a similar method to that used to synthesise *N*-trityl-(*L*)-serine methyl ester, except *N*-triphenylmethyl-(*L*)-threonine (0.31 g, 0.87 mmol) was used to yield a brown oil (0.31 g, 90%). *R_f*: 0.60 petroleum ether--ethyl acetate (2:1); ¹H NMR (CDCl₃, δ ppm) 7.49 (m, 6H), 7.28–7.12 (m, 9H), 5.63 (m, 1H), 5.16 (m, 2H), 4.06 (m, 1H), 3.82 (m, 2H), 3.40 (d, 1H *J*=7.3 Hz), 1.22 (d, 3H *J*=6.1 Hz); ¹³C NMR (CDCl₃, δ ppm) 173.0, 145.5, 131.6, 129.0, 127.9, 126.7, 118.8, 70.8, 69.8, 62.5, 53.5, 19.0; IR (thin film, cm⁻¹) 3446, 3058, 2931, 1732, 1674.

4.2.1.22. (2S,3R)-Methyl-1-(trityl)-aziridine-2-carboxylic acid methyl ester (**20a**). Compound **20a** was synthesised using a similar method to that used to synthesise **1a**, except *N*-trityl-(L)-threonine methyl ester (2.06 g, 5.5 mmol) was used, to yield a cloudy oil (1.79 g, 91%). *R*_f: 0.82 petroleum ether—ethyl acetate (2:1); ¹H NMR (CDCl₃, δ ppm) 7.53 (m, 6H), 7.28–7.13 (m, 9H), 3.67 (s, 3H), 1.90 (dd, 1H, *J*=3.8, 3.7 Hz), 1.66 (m, 1H), 1.36 (d, 3H, *J*=6.2 Hz); ¹³C NMR (CDCl₃, δ ppm) 170.8, 144.2, 129.5, 127.7, 127.0, 75.1, 51.9, 36.1, 35.0, 13.4; IR (thin film, cm⁻¹) 3069, 2947, 1739.

4.2.1.23. (2S,3R)-Methyl-1-trityl-aziridine-2-carboxylic acid allyl ester (**20b**). Compound **20b** was synthesised using a similar method to that used to synthesise **1b**, except *N*-triphenylmethyl-(L)-threonine allyl ester (2.07 g, 5.16 mmol) was used to yield **20b** as a yellow oil (1.72 g, 87%). *R*_f: 0.90 petroleum ether—ethyl acetate (2:1); ¹H NMR (CDCl₃, δ ppm) 7.45 (m, 6H), 7.31–7.19 (m, 9H), 5.88 (m, 1H), 5.24 (m, 2H), 4.59 (m, 2H), 1.84 (d, 1H *J*=6.5 Hz), 1.55 (m, 1H), 1.27 (d, 3H *J*=5.5 Hz); ¹³C NMR (CDCl₃) δ ppm; 170.0, 143.9, 132.2, 129.4, 128.3, 126.6, 118.5, 82.0, 65.4, 36.0, 35.0, 13.4; IR (thin film, cm⁻¹) 3080, 2975, 1742, 1641.

4.2.1.24. (2S,3R)-Methyl-1-(*p*-tosyl)-aziridine-2-carboxylic acid methyl ester (**21a**). Compound **21a** was synthesised using a similar method to that used to synthesise **2a**, except **20a** (2.07 g, 5.8 mmol) was used to yield a clear oil (1.26 g, 81%). $R_{\rm f}$: 0.47 petroleum ether—ethyl acetate (2:1); ¹H NMR (CDCl₃, δ ppm) 7.85 (d, 2H, *J*=8.4 Hz), 7.35 (d, 2H, *J*=8.3 Hz), 3.73 (s, 3H), 3.39 (d, 1H, *J*=7.5 Hz), 3.10 (m, 1H), 2.44 (s, 3H), 1.32 (d, 3H, *J*=5.6 Hz); ¹³C NMR (CDCl₃, δ ppm) 166.2, 145.0, 136.6, 129.8, 128.0, 53.0, 41.4, 40.1, 21.6, 12.4; IR (thin film, cm⁻¹) 3072, 2979, 1741, 1214.

4.2.1.25. (2S,3R)-Methyl-1-(p-nosyl)-aziridine-2-carboxylic acid methyl ester (**21b**). Compound **21b** was synthesised using a similar method to that used to synthesise **2b**, except **20a** (2.07 g, 5.8 mmol) was used to yield a yellow oil (1.39 g, 80%). *R*_f: 0.51 petroleum

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ether—ethyl acetate (2:1); ¹H NMR (CDCl₃, *δ* ppm) 8.35 (d, 2H, *J*=8.8 Hz), 8.14 (d, 2H, *J*=8.8 Hz), 3.68 (s, 3H), 3.44 (d, 1H, *J*=7.5 Hz), 3.18 (m, 1H), 1.21 (d, 3H, *J*=5.7 Hz); ¹³C NMR (CDCl₃, *δ* ppm) 165.6, 150.8, 145.4, 129.2, 124.4, 52.8, 42.2, 40.7, 12.4; IR (thin film, cm⁻¹) 3080, 2967, 1747, 1540, 1379, 1276.

4.2.1.26. (2S,3R)-Methyl-1-(*p*-nitrobenzyloxycarbony)-aziridine-2-carboxylic acid methyl ester (**21c**). Compound **21c** was synthesised using a similar method to that used to synthesise **2c**, except **20a** (2.07 g, 5.8 mmol) was used to yield a yellow oil (1.33 g, 78%). *R_f*: 0.45 petroleum ether—ethyl acetate (2:1); ¹H NMR (CDCl₃, δ ppm) 8.08 (d, 2H, *J*=8.8 Hz), 7.44 (d, 2H, *J*=8.8 Hz), 5.12 (d, 2H, *J*=3.1 Hz), 3.67 (s, 3H), 3.18 (d, 1H, *J*=6.7 Hz), 2.78 (m, 1H), 1.27 (d, 3H, *J*=5.6 Hz); ¹³C NMR (CDCl₃, δ ppm) 171.4, 161.2, 147.6, 143.9, 129.2, 123.4, 66.8, 53.6, 39.8, 39.0, 12.6; IR (thin film, cm⁻¹) 3065, 2981, 1744, 1680, 1528, 1397, 1212.

4.2.1.27. (2S,3R)-Methyl-1-(p-tosyl)-aziridine-2-carboxylic acid allyl ester (**22a**). Compound **22a** was synthesised using a similar method to that used to synthesise **3a**, except **20b** (2.07 g, 5.4 mmol) was used to yield a clear oil (1.34 g, 84%). *R*_f: 0.47 petroleum ether—ethyl acetate (2:1); ¹H NMR (CDCl₃, δ ppm) 7.85 (d, 2H, *J*=8.8 Hz), 7.35 (d, 2H, *J*=8.8 Hz), 5.88 (m, 1H), 5.22 (m, 2H), 4.65 (d, 2H, *J*=6.0 Hz), 3.39 (d, 1H, *J*=6.6 Hz), 3.10 (m, 1H), 2.44 (s, 3H), 1.32 (d, 3H, *J*=5.8 Hz); ¹³C NMR (CDCl₃, δ ppm) 166.2, 145.0, 136.6, 131.1, 129.8, 128.0, 119.0, 66.5, 41.4, 40.1, 21.6, 12.4; IR (thin film, cm⁻¹) 3090, 2992, 1740, 1621, 1220.

4.2.1.28. (2S,3R)-Methyl-1-(p-nosyl)-aziridine-2-carboxylic acid allyl ester (**22b**). Compound **22b** was synthesised using a similar method to that used to synthesise **3b**, except **20b** (2.07 g, 5.4 mmol) was used to yield a yellow oil (1.35 g, 77%). *R*_f: 0.54 petroleum ether—ethyl acetate (2:1); ¹H NMR (CDCl₃, δ ppm) 8.35 (d, 2H, *J*=9.0 Hz), 8.14 (d, 2H, *J*=8.9 Hz), 5.86 (m 1H), 5.26 (m, 2H), 4.57 (d, 2H, *J*=5.8 Hz), 3.48 (d, 1H, *J*=7.5 Hz), 3.20 (m, 1H), 1.29 (d, 3H*J*=5.7 Hz); ¹³C NMR (CDCl₃, δ ppm) 164.8, 150.8, 143.5, 130.9, 129.2, 124.4, 119.5, 66.5, 42.0, 40.7, 12.3; IR (thin film, cm⁻¹) 3077, 2954, 1742, 1538, 1371, 1242.

4.2.1.29. (2S,3R)-Methyl-1-(*p*-nitrobenzyloxycarbony)-aziridine-2-carboxylic acid allyl ester (**22c**). Compound **22c** was synthesised using a similar method to that used to synthesise **3c**, except **20b** (2.07 g, 5.4 mmol) was used to yield a yellow oil (1.29 g, 75%). *R_f*: 0.42 petroleum ether—ethyl acetate (2:1); ¹H NMR (CDCl₃, δ ppm) 8.25 (d, 2H, *J*=8.8 Hz), 7.55 (d, 2H, *J*=8.8 Hz), 5.90 (m, 1H), 5.38–5.19 (m, 4H), 4.70 (d, 2H, *J*=5.8 Hz), 3.23 (d, 1H, *J*=6.7 Hz), 2.88 (m, 1H), 1.39 (d, 3H, *J*=5.6 Hz); ¹³C NMR (CDCl₃, δ ppm) 166.6, 161.1, 147.8, 142.4, 131.3, 128.5, 123.8, 119.2, 66.9, 66.2, 39.9, 39.1, 12.7; IR (thin film, cm⁻¹) 3068, 2982, 1741, 1681, 1640, 1209.

DAPs **23a**, **24a**, **23b**, **24b**, **25a**–**c** and **26** were prepared by ringopening of 3-methyl aziridines with *p*-methoxybenzylamine using the general procedure used to prepare DAPs **4a**–**c** and **6c**.

4.2.1.30. (2S,3R)-Methyl 3-(4-methoxybenzylamino)-2-(4methylphenylsulfonamido) butanoate (**23a**). Cloudy oil (0.08 g, 41%); R_{f} : 0.18 petroleum ether—ethyl acetate (1:1); $[\alpha]_{D}^{20}$ +16.55° (*c* 1.0 in CHCl₃); ¹H NMR (CDCl₃, δ ppm) 7.71 (d, 2H, *J*=8.1 Hz), 7.28 (d, 2H, *J*=8.0 Hz), 7.13 (d, 2H, *J*=8.4 Hz), 6.82 (d, 2H, *J*=8.4 Hz), 3.81 (d, 1H, *J*=3.6 Hz), 3.80 (s, 3H), 3.68 (d, 1H, *J*=12.8 Hz), 3.55 (d, 1H, *J*=12.8 Hz), 3.45 (s, 3H), 3.09 (m, 1H), 2.41 (s, 3H), 1.13 (d, 3H, *J*=6.2 Hz); ¹³C NMR (CDCl₃, δ ppm) 171.1, 158.7, 143.5, 136.7, 131.8, 129.5, 129.3, 127.2, 113.7, 60.4, 55.2, 53.9, 52.3, 50.3, 21.5, 17.6; IR (thin film, cm⁻¹) 3411, 3077, 2977, 1733, 1213, 1126; HRMS (ES+) calculated for C₂₀H₂₇N₂O₅S, [M+H]⁺ 407.1635, found [M+H]⁺ 407.1628.

4.2.1.31. (2S,3R)-Methyl 3-(4-methoxybenzylamino)-2-(4nitrophenylsulfonamido) butanoate (23b). Pale yellow oil (0.09 g, 42%); *R*₅: 0.45 petroleum ether–ethyl acetate (1:1); $[\alpha]_D^{20} +7.10^{\circ}$ (*c* 1.0 in CHCl₃); ¹H NMR (CDCl₃, δ ppm) 8.32 (d, 2H, *J*=8.7 Hz), 8.03 (d, 2H, *J*=8.7 Hz), 7.13 (d, 2H, *J*=8.4 Hz), 6.83 (d, 2H, *J*=8.5 Hz), 3.88 (d, 1H, *J*=3.2 Hz), 3.78 (s, 3H), 3.65 (d, 2H, *J*=12.6 Hz), 3.49 (d, 1H, *J*=12.7 Hz), 3.47 (s, 3H), 3.18 (m, 1H), 1.17 (d, 2H, *J*=5.6 Hz); ¹³C NMR (CDCl₃, δ ppm) 170.8, 158.9, 149.9, 145.9, 131.0, 129.4, 128.4, 124.6, 113.8, 60.2, 55.3, 53.8, 52.6, 50.6, 18.0; IR (thin film, cm⁻¹) 3352, 3066, 2967, 1741, 1521, 1386, 1191; HRMS (ES+) calculated for C₁₉H₂₄N₃O₇S, [M+H]⁺ 438.1329, found [M+H]⁺ 438.1330.

4.2.1.32. (2R,3S)-Methyl 2-(4-methoxybenzylamino)-3-(4-methylphenylsulfonamido) butanoate (**24a**). R_f : 0.29 petroleum ether—ethyl acetate (1:1); ¹H NMR (CDCl₃, δ ppm) 7.64 (d, 2H, J=8.4 Hz), 7.20 (d, 2H, J=8.4 Hz), 7.10 (d, 2H, J=8.6 Hz), 6.78 (d, 2H, J=8.6 Hz), 3.73 (s, 3H), 3.65–3.50 (dd, 2H, J=12.6, 12.6 Hz), 3.56 (s, 3H), 3.50 (d, 1H, J=12.6 Hz), 3.43 (m, 1H), 3.01 (d, 1H, J=5.1 Hz), 2.33 (s, 3H), 1.02 (d, 3H, J=6.5 Hz). ¹³C NMR (CDCl₃, δ ppm) 172.8, 158.9, 143.3, 137.5, 130.7, 129.6, 129.6, 127.2, 113.8, 64.2, 55.3, 52.4, 52.0, 51.5, 21.5, 17.6; IR (thin film, cm⁻¹) 3365, 3089, 2982, 1738, 1194, 1133.

4.2.1.33. (2*S*,3*R*)-*Allyl* 3-(4-*methoxybenzylamino*)-2-(4-*methylphenylsulfonamido*) *butanoate* (**25a**). Pale yellow oil (0.09 g, 42%); *R_f*: 0.2 petroleum ether—ethyl acetate (1:1); $[\alpha]_D^{20}$ +21.83° (*c* 1.0 in CHCl₃); ¹H NMR (CDCl₃, δ ppm) 7.72 (d, 2H, *J*=8.3 Hz), 7.27 (d, 2H, *J*=8.3 Hz), 7.15 (d, 2H, *J*=8.4 Hz), 6.83 (d, 2H, *J*=8.4 Hz), 5.66 (m, 1H), 5.16 (m, 2H), 4.38–4.25 (dd, 2H, *J*=6.0, 6.0 Hz), 3.82 (d, 1H, *J*=13.2 Hz), 3.12 (m, 1H), 2.40 (s, 3H), 1.15 (d, 3H, *J*=6.5 Hz); ¹³C NMR (CDCl₃, δ ppm) 170.3, 158.7, 143.5, 136.7, 131.7, 131.1, 129.6, 129.3, 127.2, 119.0, 113.7, 66.1, 60.1, 55.2, 54.0, 50.3, 21.5, 17.5; IR (thin film, cm⁻¹) 3346, 3081, 2962, 1744, 1612, 1201, 1152; HRMS (ES+) calculated for C₂₂H₂₉N₂O₅S, [M+H]⁺ 433.1792, found [M+H]⁺ 433.1796.

4.2.1.34. (2S,3R)-Allyl 3-(4-methoxybenzylamino)-2-(4-nitrophenylsulfonamido) butanoate (**25b**). Pale yellow oil (0.1 g, 43%); R_{f} : 0.41 petroleum ether—ethyl acetate (1:1); $[\alpha]_{D}^{20}$ +12.37° (*c* 1.0 in CHCl₃); ¹H NMR (CDCl₃, δ ppm) 8.31 (d, 2H, *J*=8.8 Hz), 8.01 (d, 2H, *J*=8.8 Hz), 7.12 (d, 2H, *J*=8.5 Hz), 6.84 (d, 2H, *J*=8.5 Hz), 5.63 (m, 1H), 5.18 (m, 2H) 4.42 (dd, 1H, *J*=12.8, 6.1 Hz), 4.30 (dd, 1H, *J*=12.7, 6.1 Hz), 3.88 (d, 1H, *J*=4.6 Hz), 3.78 (s, 3H), 3.68 (d, 1H, *J*=12.8 Hz), 3.51 (d, 1H, *J*=12.8 Hz), 3.21 (m, 1H), 1.19 (d, 3H, *J*=6.3 Hz); ¹³C NMR (CDCl₃, δ ppm) 170.1, 158.8, 149.9, 145.9, 131.6, 130.0, 129.2, 128.4, 124.6, 119.5, 113.8, 66.4, 60.3, 55.2, 53.9, 50.8, 18.2; IR (thin film, cm⁻¹) 3397, 3069, 2981, 1738, 1612, 1557, 1379, 1176; HRMS (ES+) calculated for C₂₁H₂₆N₃O₇S, [M+H]⁺ 464.1486, found [M+H]⁺ 464.1504.

4.2.1.35. (2S,3R)-Allyl 3-(4-methoxybenzylamino)-2-((4nitrobenzyloxy)carbonylamino) butanoate (**25c**). Pale yellow oil (0.09 g, 39%); R_f : 0.50 petroleum ether—ethyl acetate (1:1); $[\alpha]_D^{20}$ +29.62° (*c* 1.0 in CHCl₃); ¹H NMR (CDCl₃, δ ppm) 8.19 (d, 2H J=8.8 Hz), 7.51 (d, 2H J=8.8 Hz), 7.17 (d, 2H J=8.9 Hz), 6.85 (d, 2H, J=8.8 Hz), 6.08 (s (br), 1H), 5.90 (m, 1H), 5.36–5.25 (m, 2H), 4.80 (s, 2H), 4.64 (d, 2H, J=6.0 Hz), 4.27 (pseudo t, 2H, J=4.3 Hz), 3.79 (s, 3H), 3.24 (d, 1H J=7.2 Hz), 2.78 (m, 1H), 1.29 (d, 3H J=5.6 Hz); ¹³C NMR (CDCl₃, δ ppm) 167.8, 163.1, 159.0, 148.5, 147.5, 131.4, 129.8, 129.2, 126.9, 123.6, 119.1, 114.0, 66.2, 63.8, 55.3, 44.4, 40.5, 39.4, 13.0; IR (thin film, cm⁻¹) 3380, 3071, 2980, 1742, 1666, 1206; HRMS: (ES+) calculated for C₂₃H₂₈N₃O₇, calculated [M+H]⁺ 458.1943, found [M+H]⁺ 458.1922.

4.2.1.36. (2R,3S)-Allyl 2-(4-methoxybenzylamino)-3-(4-nitrophenylsulfonamido) butanoate (**26b**). R_{f} : 0.52 petroleum ether-–ethyl acetate (1:1). ¹H NMR (CDCl₃, δ ppm) 8.28 (d, 2H, J=8.8 Hz),

7.96 (d, 2H, *J*=8.7 Hz), 7.07 (d, 2H, *J*=8.4 Hz), 6.80 (d, 2H, *J*=8.4 Hz), 5.63 (m, 1H), 5.18 (m, 2H), 4.26 (dd, 2H, *J*=6.2, 6.1 Hz), 3.80 (s, 3H), 3.72 (d, 1H, *J*=12.9 Hz), 3.58 (d, 1H, *J*=12.9 Hz), 3.28 (m, 1H), 2.98 (d, 1H, *J*=7.4 Hz), 1.07 (d, 2H, *J*=5.8 Hz). ¹³C NMR (CDCl₃, δ ppm) 172.8, 158.8, 149.9, 147.6, 131.5, 130.9, 129.0, 128.5, 124.1, 119.2, 113.8, 66.5, 63.8, 55.2, 52.9, 51.1, 18.1. IR (thin film, cm⁻¹) 3368, 3068, 2979, 1739, 1622, 1552, 1378, 1165.

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Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2014.06.011.

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