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Versatile use of acid-catalyzed ring-opening of β-aziridinyl-α,β-enoates to stereoselective synthesis of peptidomimetics

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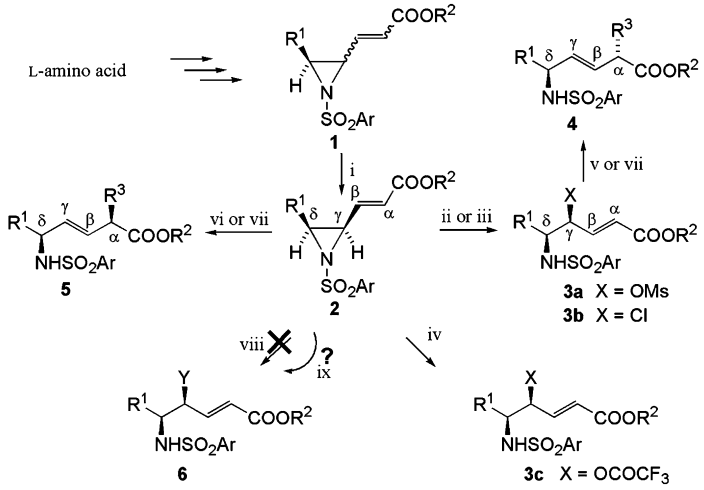
Abstract—Treatment of *N*-arylsulfonylaziridines bearing α,β-unsaturated esters with alcohols, thiols or weak acids such as AcOH in the presence of catalytic amount of Lewis acids affords regio- and stereoselectively ring-opened products, such as δ-aminated γ-alkoxy-(alkylthio or acetoxy)-α,β-enoates. In addition, the regio- and stereoselective ring-opening reactions can be performed on solid supports and applied to stereoselective synthesis of (*E*)-alkene dipeptide isosteres.

1. Introduction

Ring-opening reactions of *N*-activated aziridines have been widely used for the synthesis of various biological compounds such as β-lactams, alkaloids, dipeptide isosteres and sphingosines. Ample precedents, in which nucleophilic reagents, including acids such as HCl, AcOH, TFA and TsOH, attack either of the two carbon atoms of simple aziridines to afford the corresponding ring-opened products, have been documented to date.[1] The regiospecific ring-opening reactions of *N*-2,4,6-trimethylphenylsulfonyl (Mts)-protected (and activated) aziridines possessing α,β-unsaturated esters by strong acids, such as methanesulfonic acid (MSA), TFA or HCl (Scheme 1) have been reported by us.[2] The MSA (or HCl)-mediated ring-opening reactions of *N*-Mts-γ,δ-*cis*-γ,δ-epimino-(*E*)-α,β-enoates ((*cis*-(*E*)) **2** yield δ-aminated γ-mesyloxy (or -chloro)-α,β-enoates **3**, which can be converted into (L-amino acid, D-amino acid)-type



Scheme 1. R^1, R^2, R^3=alkyl; Ar=4-methylphenyl or 2,4,6-trimethylphenyl, Ms=methanesulfonyl; reagents: (i) $Pd(PPh_3)_4$; (ii) $MeSO_3H$ in $CHCl_3$; (iii) HCl in 1,4-dioxane; (iv) TFA; (v) $R^3Cu(CN)MgCl.BF_3$; (vi) $R^3Cu(CN)MgCl\cdot 2LiCl$; (vii) $R^3Cu(CN)ZnI\cdot 2LiCl$; (viii) YH (weak acids, alcohols or thiols) and (ix)YH, TMSOTf.

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(*E*)-alkene dipeptide isosteres (EADIs) **4** via organocopper (or organozinc-copper)-mediated *anti*-S_N2' reactions.[3] On the other hand, organocopper (or organozinc-copper)-mediated *anti*-S_N2' reactions of *cis*-(*E*) isomers **2** exclusively provide (L,L)-type EADIs **5**. The utility of EADIs as potential biomimics of amide bonds in peptides has been intensively investigated.[4] The above ring-opening reactions are proven to be useful for the stereoselective synthesis of a set of two diastereomeric EADIs starting from an L-amino acid, in the combination with the convergently transforming reactions from four stereoisomeric γ,δ-epimino-α,β-enoates **1** into the single *cis*-(*E*) isomer **2** by a Pd(0)-catalyst.[5] However, treatment of these β-aziridinyl-α,β-enoates **2** with weak acids such as AcOH, alcohols or thiols does not yield the corresponding ring-opened products **6**. It might be due to insufficient activation of *N*-arylsulfonylaziridines. Thus, in the present study, we investigated whether the catalytic amount of Lewis acids such as TMSOTf has an effect on the above ring-opening reactions of β-aziridinyl-α,β-enoates with weak acids, alcohols or thiols. In addition, the feasibility of the ring-opening reactions of β-aziridinyl-α,β-enoates bearing no side-chain group at the δ-position was examined. Furthermore, we investigated the ring-opening reactions using solid supports and their application to stereoselective synthesis of EADIs.

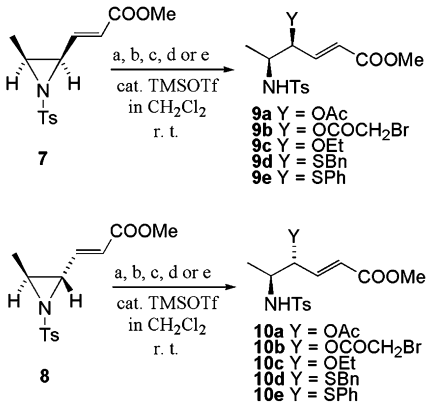
2. Results and discussion

2.1. Treatment of *N*-(4-methylphenylsulfonyl) (Ts)-γ,δ-epimino-(*E*)-α,β-enoates with weak acids, alcohols or thiols in the presence of Lewis acids

β-Aziridinyl-α,β-enoates, *cis*-(*E*)-enoate **7** and *trans*-(*E*)-enoate **8**, were prepared from Thr and D-*allo*-threonine, respectively, as previously reported by us.[6] These β-aziridinyl-α,β-enoates **7** and **8** did not react with weak acids such as AcOH, alcohols or thiols. Thus, examined was the effect of the addition of catalytic amount of Lewis acids such as TMSOTf on the ring-opening reactions with weak acids, alcohols or thiols. Treatment of **7** or **8** with AcOH, $BrCH_2COOH$, EtOH, BnSH or PhSH in the presence of catalytic amount of TMSOTf yielded the corresponding δ-aminated-γ-acyloxy (alkoxy or alkylthio)-α,β-enoates, **9a–e** or **10a–e**, exclusively and quantitatively, via the regioselective S_N2 ring-opening reaction at the γ-carbon position (Scheme 2, Table 1). Regiochemical assignments for products **9a–e** and **10a–e** were readily made by ^1H NMR (^1H–^1H COSY). The γ,δ-*syn* stereochemistry of **9a–e** and the γ,δ-*anti* stereochemistry of **10a–e** were based on X-ray analysis of **9a**. As a result, the addition of catalytic TMSOTf was proven to be efficient for the regio- and stereoselective ring-opening reactions with weak acids, alcohols or thiols as nucleophiles.

Table 1. Ring-opening reactions of β-aziridinyl-α,β-unsaturated esters by various nucleophiles in the presence of cat. TMSOTf

Substrate	YH	YH/TMSOTf (equiv)	Time (h)	Product	Yield (%)
7	AcOH	20/0.1	15	**9a**	90
7	$BrCH_2CO_2H$	10/0.1	15	**9b**	82
7	EtOH	3/0.3	7	**9c**	98
7	BnSH	10/0.1	1	**9d**	95
7	PhSH	10/0.1	1	**9e**	96
8	AcOH	20/0.1	15	**10a**	98
8	$BrCH_2CO_2H$	10/0.1	15	**10b**	86
8	EtOH	3/0.3	7	**10c**	99
8	BnSH	10/0.1	1	**10d**	90
8	PhSH	10/0.1	1	**10e**	99



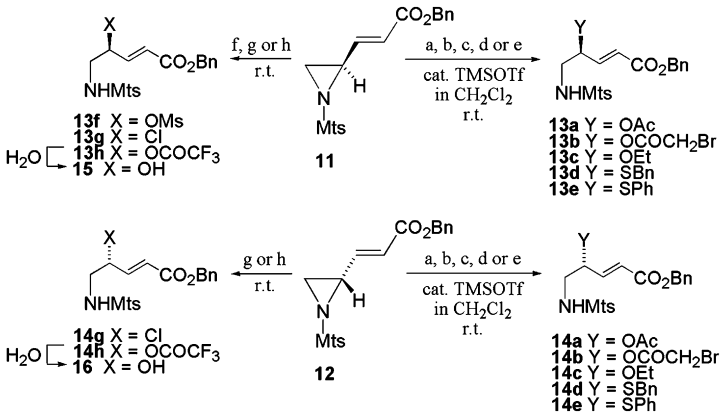
Scheme 2. Ts=4-methylphenysulfonyl; reagents: (a) AcOH; (b) $BrCH_2COOH$; (c) EtOH; (d) BnSH and (e) PhSH.

2.2. Ring-opening reactions of *N*-Mts-γ,δ-epimino-(*E*)-α,β-enoates having no side-chain group at the δ-position

Next, the feasibility of the regioselective ring-opening reactions of β-aziridinyl-α,β-enoates having no side-chain group at the δ-position was investivated. β-Aziridinyl-α,β-enoates, (4*R*,2*E*)-enoate **11** and (4*S*,2*E*)-enoate **12**, were prepared from Ser and D-Ser, respectively, according to our reported procedures. As shown in Scheme 3, exposure of **11** or **12** to several reactants afforded exclusively the corresponding δ-aminated-γ-acyloxy (alkoxy, alkylthio, mesyloxy or chloro,)-α,β-enoates, **13a–h** or **14a–h** in high yields, via the regioselective S_N2 ring-opening reaction at the γ-carbon position. Regiochemical assignments for products **13a–h** and **14a–h** were readily made by ^1H NMR. The stereochemistry at the γ-carbon position of **13a–h** and **14a–h** was based on X-ray analysis of **14g** and the analysis of **15** and **16** by the modified Mosher method.[7] As a result, the regio- and stereoselective ring-opening reactions of β-aziridinyl-α,β-enoates having no side-chain group at the δ-position were achieved by strong acids or by weak acids, alcohols or thiols in the addition of catalytic amount of TMSOTf (Table 2).

2.3. Synthesis of (Xaa, L-Asp)-type and (Xaa, D-Asp)-type EADIs

The stereoselective synthesis of a couple of diastereomeric EADIs from a single substrate of β-aziridinyl-α,β-enoate has been established as described in Section 1. One potential limitation to the use of these procedures for the synthesis of peptide mimetics is the introduction of various functional groups into the side chain (R^3) at the α-position. The stereoselective synthesis of (Xaa, L-Glu)-type and (Xaa, D-Glu)-type EADIs has been established by treatment of β-aziridinyl-α,β-enoates **2** and γ-chloro-α,β-enoates **3**, respectively, with organozinc-copper reagents (Scheme 1).[3] Next, we attempted to synthesize (Xaa, L-Asp)-type and (Xaa, D-Asp)-type EADIs. As shown in Scheme 4, orthoesterification of allylic alcohol **15**, which was obtained

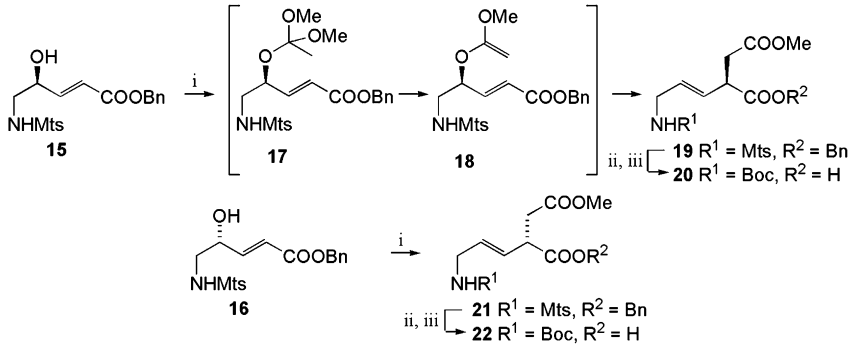


Scheme 3. Mts=2,4,6-trimethylphenysulfonyl; reagents: (a) AcOH; (b) $BrCH_2COOH$; (c) EtOH; (d) BnSH; (e) PhSH; (f) $MeSO_3H$ in $CHCl_3$; (g) HCl in 1,4-dioxane and (h) TFA.

Table 2. Ring-opening reactions of β-aziridinyl-α,β-unsaturated esters having no side-chain groups at the δ-position by various nucleophiles

Substrate	YH or XH	Solvent	YH or XH/TMSOTf (equiv)	Time	Product	Yield (%)
11	AcOH	CH_2Cl_2	20/0.1	15 h	**13a**	84
11	$BrCH_2CO_2H$	$CHCl_3$	10/0.1	15 h	**13b**	62
11	EtOH	CH_2Cl_2	3/0.3	7 h	**13c**	89
11	BnSH	CH_2Cl_2	10/0.1	1 h	**13d**	73
11	PhSH	CH_2Cl_2	10/0.1	1 h	**13e**	87
11	$MeSO_3H$	$CHCl_3$	10/—	10 min	**13f**	99
11	HCl	1,4-Dioxane	10/—	10 min	**13g**	87
11	CF_3CO_2H	—	>20/—	15 h	**13h**	72[a]
12	AcOH	CH_2Cl_2	20/0.1	15 h	**14a**	69
12	$BrCH_2CO_2H$	CH_2Cl_2	10/0.1	15 h	**14b**	69
12	EtOH	CH_2Cl_2	3/0.3	7 h	**14c**	77
12	BnSH	CH_2Cl_2	10/0.1	1 h	**14d**	69
12	PhSH	CH_2Cl_2	10/0.1	1 h	**14e**	81
12	HCl	1,4-Dioxane	10/—	10 min	**14g**	96
12	CF_3CO_2H	—	>20/—	15 h	**14h**	63[a]

[a] Isolated yield of **15** or **16**.

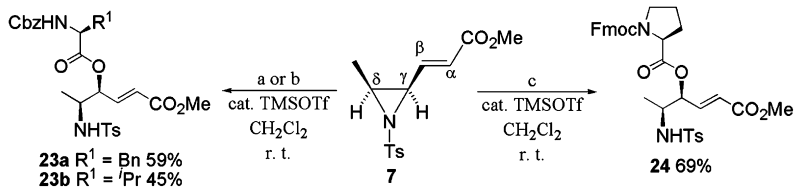


Scheme 4. Reagents: (i) $MeC(OMe)_3$, cat. PhCOOH, MS4Å, *o*-xylene; (ii) 1 M TMSBr-thioanisole/TFA; (iii) $(Boc)_2O$, Et_3N, THF.

by hydrolysis of γ-trifluoroacetate **13h** in Scheme 3, and the subsequent Claisen rearrangement[8] afforded an EADI, Mts–Gly–ψ[(*E*)-CH=CH]–L-Asp(OMe)–OBn, **19** in 34% yield. The enantiomeric EADI, Mts–Gly–ψ[(*E*)-CH=CH]–D-Asp(OMe)–OBn, **21** was also obtained from **16** in 19% yield in a similar way. The optical purities of **19** and **21** were found to be relatively low based on their HPLC analysis on chiral column: ee of **19**=33%; ee of **21**=43% on the contrary to our expectation. This might be attributable to instability of chair-like transition states. The improvement of these reactions in yields and optical purities is under investigation.

2.4. Ring-opening reactions of γ,δ-epimino-(*E*)-α,β-enoates by N^{α}-protected amino acids

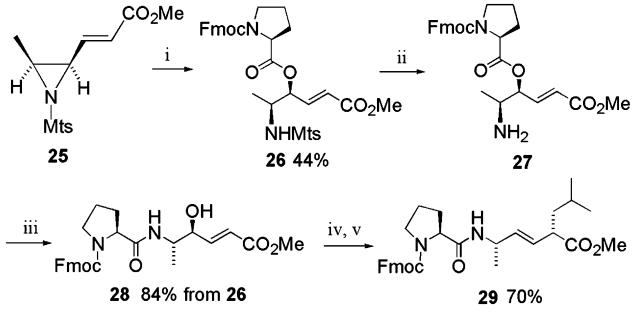
The feasibility of ring-opening reactions of γ,δ-epimino-(*E*)-α,β-enoates by N^{α}-protected amino acids was investigated, since N^{α}-protected amino acids are also weak carboxylic acids. It is thought that introduction of α-amino acids in the step of opening reactions of aziridine rings might lead to efficient synthesis of EADI-containing peptidomimetics. Treatment of aziridine **7** by N^{α}-Cbz-protected amino acids, N^{α}-Cbz-phenylalanine and N^{α}-Cbz-valine, in the



Scheme 5. Reagents: (a) Cbz–Phe–OH; (b) Cbz–Val–OH and (c) Fmoc–Pro–OH.

presence of catalytic amount of TMSOTf yielded the corresponding ring-opened products, **23a** and **b**, respectively (Scheme 5). Ring-opening reaction of **7** with N^{α}-Fmoc-proline in the presence of TMSOTf obtained **24**.

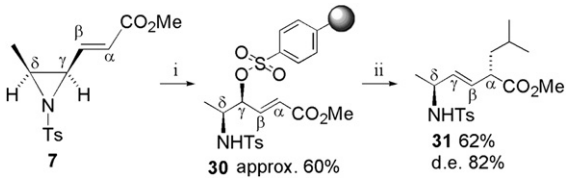
Next, this reaction was applied to the synthesis of Fmoc-Pro–Ala–ψ[(*E*)-CH=CH]–D-Leu–OMe **29** in combination with the *O*,*N*-acyl transfer reaction (Scheme 6). An *O*-acylated compound **26**, which was obtained by treatment of aziridine **25** with N^{α}-Fmoc-proline in the presence of TMSOTf, was subjected to deprotection of the N^{α}-Mts group using 1 M TMSBr-thioanisole/TFA[9] to yield **27**. Subsequent treatment of **27** with neutral phosphate buffer gave an *N*-acylated compound **28** based on the intramolecular *O*,*N*-acyl transfer.[10] *O*-Mesylation and *anti*-S_N2' type alkylation mediated by organocopper led to the stereoselective synthesis of a tripeptide mimetic **29**. The stereochemistry at the α-carbon position of **29** was determined by X-ray analysis.



Scheme 6. Reagents: (i) Fmoc–Pro–OH, cat. TMSOTf, CH_2Cl_2; (ii) 1 M TMSBr-thioanisole/TFA; (iii) pH 7.3 phosphate buffer, MeCN; (iv) MsCl, Et_3N, CH_2Cl_2 and (v) ^{t}BuCu(CN)MgCl·BF_3, THF.

2.5. Synthesis of EADIs from γ,δ-epimino-(*E*)-α,β-enoates using solid-phase techniques

To develop a convenient procedure for preparation of EADIs, simplification of isolation/purification of synthetic intermediate γ-sulfonates might be desirable and critical. Thus, ring-opening reactions of *N*-arylsulfonyl-γ,δ-epimino-(*E*)-α,β-enoates mediated by resin-bound sulfonic acid were applied to the synthesis of EADIs using solid-phase techniques. Treatment of β-aziridinyl-α,β-enoate **7** with toluenesulfonic acid resin (MP–TsOH, Argonaut Technologies) yielded a resin-bound γ-tosylate **30**, which was converted into an EADI **31** [Ts–Ala–ψ[(*E*)-CH=CH]–D-Leu–OMe] by organocopper reagents in 37% yield (Scheme 7). In this procedure, the resin-bound γ-tosylate **30** can be purified only by washing with solvents, suggesting that the present solid-phase techniques have the advantage of manipulation. However, the stereoselectivity of this reaction is not sufficiently high, compared to exceedingly high stereoselectivity in usual liquid techniques. Due to low reactivity of resin-bound γ-tosylates or basicity of organocopper reagents, **30** might partially return to the aziridine **7** via ring-closing, followed by organocopper-mediated alkylation to produce a diastereomer of **31** [Ts–Ala–ψ[(*E*)-CH=CH]–L-Leu–OMe]. The adjustment of loading amount of toluenesulfonic acid on resins and the improvement of linker/spacer units in these reactions might be required for the development of a convenient procedure for the synthesis of EADIs.



Scheme 7. Reagents: (i) MP–Ts–OH, CH_2Cl_2 and (ii) ^{t}BuCu(CN)MgCl·BF_3, THF.

3. Conclusion

In summary, the ring-opening reactions of β-aziridinyl-α,β-enoates with several nucleophiles involving alcohols, thiols and weak acids such as AcOH and N^{α}-protected amino acids in the presence of catalytic amount of Lewis acids such as TMSOTf have been fully investigated. The regio- and stereoselective S_N2' ring-opening at the γ-carbon position was observed. The combination of the ring-opening reactions with the Claisen rearrangement, the *O*,*N*-acyl transfer reaction and the organocopper-mediated *anti*-S_N2' type alkylation was efficiently applied to the synthesis of EADI-containing peptidomimetics. In addition, the ring-opening reactions of β-aziridinyl-α,β-enoates using solid-phase techniques were applied to the synthesis of EADIs.

4. Experimental

4.1. General

Melting points are uncorrected. ^{1}H NMR spectra were recorded using a JEOL EX-270, a Bruker AC 300, a JEOL AL-400 or a Bruker AM 600 spectrometer at 270, 300, 400 or 600 MHz ^{1}H frequency in $CDCl_3$, respectively. Chemical shifts are reported in parts per million downfield from internal tetramethylsilane. Nominal (LRMS) and exact mass (HRMS) spectra were recorded on a JEOL JMS-01SG-2 or JMS-HX/HX 110A mass spectrometer. Optical rotations were measured in $CHCl_3$ or H_2O with a JASCO DIP-360 digital polarimeter (Tokyo, Japan) or a Horiba high-sensitive polarimeter SEPA-200 (Kyoto, Japan). The

X-ray analysis was carried out on a Rigaku AFC5R-RU200 Fourcircle diffractometer or a Rigaku RAXIS-RAPID Imaging Plate diffractometer. For flash column chromatography, silica gel 60 H (silica gel for thin-layer chromatography, Merck) and Wakogel C-200 (silica gel for column chromatography) were employed.

4.1.1. Methyl (2*E*,4*S*,5*S*)-4-acetyloxy-5-(((4-methylphenyl)sulfonyl)amino)hex-2-enoate 9a. To a stirred solution of the (*E*)-enoate **7** (50 mg, 0.169 mmol) in CH_2Cl_2 (0.5 cm^3) were added dropwise CH_3COOH (0.194 cm^3, 3.38 mmol) and CF_3SO_3TMS (0.00306 cm^3, 16.9 μmol) at rt, and the stirring was continued for 15 h. The mixture was purified by flash column chromatography over silica gel with *n*-hexane–EtOAc (3:1) to yield 54.2 mg (0.152 mmol, 90%) of compound **9a**, as colourless crystals, mp 108–110 °C [from *n*-hexane–Et_2O (3:1)] (Found: C, 53.95; H, 5.94; N, 3.76. $C_{16}H_{21}NO_6S$ requires C, 54.07; H, 5.96; N, 3.94%); $[\alpha]_D^{28}$ −22.1 (*c* 1.220 in $CHCl_3$); δ_H (300 MHz; $CDCl_3$) 1.09 (3H, d, *J* 6.8, CMe), 2.05 (3H, s, CMe), 2.43 (3H, s, CMe), 3.59 (1H, m, 5-H), 3.72 (3H, s, OMe), 4.81 (1H, d, *J* 8.8, NH), 5.33 (1H, m, 4-H), 5.90 (1H, dd, *J* 15.8 and 1.6, CH═), 6.68 (1H, dd, *J* 15.8 and 5.5, CH═), 7.29 (2H, d, *J* 7.9, ArH), 7.74 (2H, d, *J* 8.3, ArH).

4.1.2. Methyl (2*E*,4*S*,5*S*)-4-(2-bromoacetyloxy)-5-(((4-methylphenyl)sulfonyl)amino)hex-2-enoate 9b. By use of a procedure similar to that described for the preparation of **9a** from **7**, the (*E*)-enoate **7** (50 mg, 0.169 mmol) was converted into the γ-bromoacetyloxy-α,β-enoate **9b** (60.2 mg, 0.139 mmol, 82% yield) by treatment with $BrCH_2COOH$ (235 mg, 1.69 mmol) and CF_3SO_3TMS (0.00306 cm^3, 16.9 μmol) in CH_2Cl_2 (0.5 cm^3) at rt for 15 h.

Compound **9b**, colourless oil [Found (FAB): $(M+H)^+$, 434.0278. $C_{16}H_{21}BrNO_6S$ requires *M*+H, 434.0273]; $[\alpha]_D^{25}$ −42.7 (*c* 0.445 in $CHCl_3$); δ_H (300 MHz; $CDCl_3$) 1.12 (3H, d, *J* 6.8, CMe), 2.43 (3H, s, CMe), 3.60–3.67 (1H, m, 5-H), 3.74 (3H, s, OMe), 3.79 (2H, s, CCH_2Br), 4.59 (1H, d, *J* 8.8, NH), 5.37 (1H, m, 4-H), 5.98 (1H, dd, *J* 15.8 and 1.5, CH═), 6.70 (1H, dd, *J* 15.7 and 5.6, CH═), 7.31 (2H, d, *J* 7.9, ArH), 7.74 (2H, d, *J* 8.3, ArH); *m*/*z* (FABLRMS) 436, 434 (MH^+, base peak), 391, 296, 259, 198, 167, 149 and 136.

4.1.3. Methyl (2*E*,4*S*,5*S*)-4-ethoxy-5-(((4-methylphenyl)sulfonyl)amino)hex-2-enoate 9c. By use of a procedure similar to that described for the preparation of **9a** from **7**, the (*E*)-enoate **7** (50 mg, 0.169 mmol) was converted into the γ-ethoxy-α,β-enoate **9c** (56.4 mg, 0.165 mmol, 98% yield) by treatment with EtOH (0.0296 cm^3, 0.508 mmol) and CF_3SO_3TMS (0.00919 cm^3, 50.8 μmol) in CH_2Cl_2 (0.5 cm^3) at rt for 7 h.

Compound **9c**, colourless oil [Found (FAB): $(M+H)^+$, 342.1384. $C_{16}H_{24}NO_5S$ requires *M*+H, 342.1375]; $[\alpha]_D^{25}$ −20.8 (*c* 2.662 in $CHCl_3$); δ_H (300 MHz; $CDCl_3$) 1.10–1.17 (6H, m, 2×CMe), 2.42 (3H, s, CMe), 3.26–3.41 (1H, m, 5-H and OC*H*HMe), 3.43–3.57 (1H, m, OCH*H*Me), 3.72 (3H, s, OMe), 3.77 (1H, m, 4-H), 4.87 (1H, d, *J* 7.5, NH), 5.93 (1H, dd, *J* 15.8 and 1.3, CH═), 6.64 (1H, dd, *J* 15.8 and 6.2, CH═), 7.28 (2H, d, *J* 7.9, ArH), 7.72 (2H, d, *J* 8.3, ArH); *m*/*z* (FABLRMS) 342 (MH^+), 296 (base peak), 279, 198, 184, 155 and 154.

4.1.4. Methyl (2*E*,4*S*,5*S*)-5-(((4-methylphenyl)sulfonyl)amino)-4-(phenylmethylthio)hex-2-enoate 9d. By use of a procedure similar to that described for the preparation of **9a** from **7**, the (*E*)-enoate **7** (50 mg, 0.169 mmol) was converted into the γ-phenylmethylthio-α,β-enoate **9d** (68.0 mg, 0.162 mmol, 96% yield) by treatment with BnSH (0.198 cm^3, 1.69 mmol) and CF_3SO_3TMS (0.00306 cm^3, 16.9 μmol) in CH_2Cl_2 (0.5 cm^3) at rt for 1 h.

Compound **9d**, colourless crystals, mp 100 °C [from *n*-hexane–Et_2O (3:1)] (Found: C, 60.05; H, 6.10; N, 3.32. $C_{21}H_{25}NO_4S_2$ requires C, 60.12; H, 6.01; N, 3.34%); $[\alpha]_D^{27}$ +73.2 (*c* 3.045 in $CHCl_3$); δ_H (300 MHz; $CDCl_3$) 1.08 (3H, d, *J* 6.8, CMe), 2.42 (3H, s, CMe), 3.21 (1H, ddd, *J* 10.0, 5.2 and 0.5, 4-H), 3.47–3.58 (1H, m, 5-H), 3.49–3.68 (2H, m, SCH_2Ph), 3.74 (3H, s, OMe), 4.67 (1H, d, *J* 7.7, NH), 5.62 (1H, dd, *J* 15.5 and 0.7, CH═), 6.67 (1H, dd, *J* 15.5 and 10.0, CH═), 7.22–7.28 (7H, m, ArH and Ph), 7.66 (2H, d, *J* 8.3, ArH).

4.1.5. Methyl (2*E*,4*S*,5*S*)-5-(((4-methylphenyl)sulfonyl)amino)-4-phenylthiohex-2-enoate 9e. By use of a procedure similar to that described for the preparation of **9a** from **7**, the (*E*)-enoate **7** (50 mg, 0.169 mmol) was converted into the γ-phenylthio-α,β-enoate **9e** (66.0 mg, 0.163 mmol, 96%) by treatment with PhSH (0.174 cm^3, 1.69 mmol) and CF_3SO_3TMS (0.00306 cm^3, 16.9 μmol) in CH_2Cl_2 (0.5 cm^3) at rt for 1 h.

Compound **9e**, colourless crystals, mp 99–101 °C [from *n*-hexane–Et_2O (3:1)] (Found: C, 59.07; H, 5.49; N, 3.17. $C_{20}H_{23}NO_4S_2$ requires C, 59.23; H, 5.72; N, 3.45%); $[\alpha]_D^{28}$ +1.38 (*c* 3.610 in $CHCl_3$); δ_H (300 MHz; $CDCl_3$) 1.16 (3H, d, *J* 6.8, CMe), 2.42 (3H, s, CMe), 3.58–3.68 (1H, m, 5-H), 3.70 (3H, s, OMe), 3.74 (1H, ddd, *J* 10.3, 5.6 and 0.8, 4-H), 4.80 (1H, d, *J* 7.8, NH), 5.63 (1H, dd, *J* 15.5 and 0.8, CH═), 6.75 (1H, dd, *J* 15.5 and 9.5, CH═), 7.26–7.32 (7H, m, ArH and Ph), 7.68 (2H, d, *J* 8.3, ArH).

4.1.6. Methyl (2*E*,4*R*,5*S*)-4-acetyloxy-5-(((4-methylphenyl)sulfonyl)amino)hex-2-enoate 10a. By use of a procedure identical with that described for the preparation of **9a** from **7**, the (*E*)-enoate **8** (50 mg, 0.169 mmol) was converted into the γ-acetyloxy-α,β-enoate **10a** (58.8 mg, 0.165 mmol, 98% yield).

Compound **10a**, colourless crystals, mp 99–101 °C [from *n*-hexane–Et_2O (3:1)] (Found: C, 54.03; H, 5.87; N, 3.85. $C_{16}H_{21}NO_6S$ requires C, 54.07; H, 5.96; N, 3.94%); $[\alpha]_D^{29}$ −8.80 (*c* 1.590 in $CHCl_3$); δ_H (300 MHz; $CDCl_3$) 1.06 (3H, d, *J* 6.9, CMe), 2.02 (3H, s, CMe), 2.43 (3H, s, CMe), 3.61–3.67 (1H, m, 5-H), 3.73 (3H, s, OMe), 5.11 (1H, d, *J* 8.9, NH), 5.26 (1H, m, 4-H), 5.93 (1H, dd, *J* 15.8 and 1.7, CH═), 6.74 (1H, dd, *J* 15.8 and 5.1, CH═), 7.29–7.32 (2H, d, *J* 8.0, ArH), 7.74 (2H, d, *J* 8.4, ArH).

4.1.7. Methyl (2*E*,4*R*,5*S*)-4-(2-bromoacetyloxy)-5-(((4-methylphenyl)sulfonyl)amino)hex-2-enoate 10b. By use of a procedure identical with that described for the preparation of **9b** from **7**, the (*E*)-enoate **8** (50 mg, 0.169 mmol) was converted into the γ-bromoacetyloxy-α,β-enoate **10b** (63.6 mg, 0.146 mmol, 87% yield).

Compound **10b**, colourless oil [Found (FAB): $(M+H)^+$, 434.0262. $C_{16}H_{21}BrNO_6S$ requires *M*+H, 434.0273]; $[\alpha]_D^{26}$ −18.5 (*c* 3.085 in $CHCl_3$); δ_H (300 MHz; $CDCl_3$) 1.06 (3H, d, *J* 6.9, CMe), 2.44 (3H, s, CMe), 3.64–3.70 (1H, m, 5-H), 3.73 (3H, s, OMe), 3.81 (2H, d, *J* 2.6, CCH_2Br), 5.27 (1H, d, *J* 9.0, NH), 5.32 (1H, m, 4-H), 6.02 (1H, dd, *J* 15.8 and 1.7, CH═), 6.75 (1H, dd, *J* 15.8 and 5.1, CH═), 7.32 (2H, d, *J* 7.9, ArH), 7.74 (2H, d, *J* 8.3, ArH); *m*/*z* (FABLRMS) 436, 434 (MH^+), 391, 296, 264, 250 (base peak), 198, 167, 155 and 110.

4.1.8. Methyl (2*E*,4*R*,5*S*)-4-ethoxy-5-(((4-methylphenyl)-sulfonyl)amino)hex-2-enoate 10c. By use of a procedure identical with that described for the preparation of **9c** from **7**, the (*E*)-enoate **8** (50 mg, 0.169 mmol) was converted into the γ-ethoxy-α,β-enoate **10c** (57.4 mg, 0.168 mmol, 99% yield).

Compound **10c**, colourless oil [Found (FAB): $(M+H)^+$, 342.1367. $C_{16}H_{24}NO_5S$ requires *M*+H, 342.1375]; $[\alpha]_D^{23}$ −24.2 (*c* 2.768 in $CHCl_3$); δ_H (300 MHz; $CDCl_3$) 0.98 (3H, d, *J* 6.8, CMe), 1.13 (3H, t, *J* 7.0, CMe), 2.43 (3H, s, CMe), 3.19–3.29 (1H, m, OC*H*HMe), 3.39–3.52 (2H, m, OCH*H*Me and 5-H), 3.74 (3H, s, OMe), 3.85 (1H, m, 4-H), 4.91 (1H, d, *J* 8.9, NH), 5.95 (1H, dd, *J* 15.8 and 1.5, CH═), 6.70 (1H, dd, *J* 15.8 and 5.6, CH═), 7.30 (2H, d, *J* 7.9, ArH), 7.76 (2H, d, *J* 8.3, ArH); *m*/*z* (FABLRMS) 342 (MH^+), 310, 296, 282, 264, 256 (base peak), 198, 186, 155, 144 and 110.

4.1.9. Methyl (2*E*,4*R*,5*S*)-5-(((4-methylphenyl)sulfonyl)-amino)-4-(phenylmethylthio)hex-2-enoate 10d. By use of a procedure identical with that described for the preparation of **9d** from **7**, the (*E*)-enoate **8** (50 mg, 0.169 mmol) was converted into the γ-phenylmethylthio-α,β-enoate **10d** (64.1 mg, 0.153 mmol, 90% yield).

Compound **10d**, colourless oil [Found (FAB): $(M+H)^+$, 420.1298. $C_{21}H_{26}NO_4S_2$ requires *M*+H, 420.1303]; $[\alpha]_D^{27}$ −144.2 (*c* 3.210 in $CHCl_3$); δ_H (300 MHz; $CDCl_3$) 1.06 (3H, d, *J* 6.7, CMe), 2.42 (3H, s, CMe), 3.13 (1H, ddd, *J* 9.4, 4.3 and 0.5, 4-H), 3.44–3.67 (2H, m, SCH_2Ph), 3.47–3.54 (1H, m, 5-H), 3.73 (3H, s, OMe), 4.90 (1H, d, *J* 9.0, NH), 5.68 (1H, dd, *J* 15.4 and 0.9, CH═), 6.65 (1H, dd, *J* 15.4 and 9.4, CH═), 7.21–7.34 (7H, m, ArH and Ph), 7.66 (2H, d, *J* 8.3, ArH); *m*/*z* (FABLRMS) 420 (MH^+), 391, 249, 222 (base peak), 198, 155, 149 and 109.

4.1.10. Methyl (2*E*,4*R*,5*S*)-5-(((4-methylphenyl)sulfonyl)-amino)-4-phenylthiohex-2-enoate 10e. By use of a procedure identical with that described for the preparation of **9e** from **7**, the (*E*)-enoate **8** (50 mg, 0.169 mmol) was converted into the γ-phenylthio-α,β-enoate **10e** (68.6 mg, 0.169 mmol, 99%).

Compound **10e**, colourless oil [Found (FAB): $(M+H)^+$, 406.1133. $C_{20}H_{24}NO_4S_2$ requires *M*+H, 406.1147]; $[\alpha]_D^{28}$ −117.7 (*c* 3.730 in $CHCl_3$); δ_H (300 MHz; $CDCl_3$) 1.15 (3H, d, *J* 6.8, CMe), 2.41 (3H, s, CMe), 3.59 (1H, ddd, *J* 8.8, 4.0 and 1.0, 4-H), 3.66–3.77 (1H, m, 5-H), 3.70 (3H, s, OMe), 5.07 (1H, d, *J* 9.2, NH), 5.66 (1H, dd, *J* 15.4 and 1.1, CH═), 6.76 (1H, dd, *J* 15.4 and 8.8, CH═), 7.19–7.27 (7H, m, ArH and Ph), 7.73 (2H, d, *J* 8.3, ArH); *m*/*z* (FABLRMS) 406 (MH^+), 391 (base peak), 374, 296, 235, 198, 175, 155 and 149.

4.1.11. Phenylmethyl (2*E*,4*S*)-4-acetyloxy-5-(((2,4,6-trimethylphenyl)sulfonyl)amino)pent-2-enoate 13a. By use of a procedure similar to that described for the preparation of **9a** from **7**, the (*E*)-enoate **11** (50 mg, 0.130 mmol) was converted into the γ-acetyloxy-α,β-enoate **13a** (48.3 mg, 0.108 mmol, 84%) by treatment with CH_3COOH (0.149 cm^3, 2.60 mmol) and CF_3SO_3TMS (0.00235 cm^3, 13.0 μmol) in CH_2Cl_2 (0.5 cm^3) at rt for 15 h.

Compound **13a**, colourless crystals, mp 106 °C [from *n*-hexane–Et_2O (3:1)] (Found: C, 62.14; H, 6.10; N, 2.84. $C_{23}H_{27}NO_6S$ requires C, 62.00; H, 6.11; N, 3.14%); $[\alpha]_D^{26}$ +1.65 (*c* 1.208 in $CHCl_3$); δ_H (300 MHz; $CDCl_3$) 2.03 (3H, s, CMe), 2.29 (3H, s, CMe), 2.60 (6H, s, 2×CMe), 3.08–3.17 (1H, m, C*H*H), 3.19–3.28 (1H, m, CH*H*), 4.75 (1H, t, *J* 6.4, NH), 5.17 (2H, s, OCH_2Ph), 5.33–5.39 (1H, m, 4-H), 5.96 (1H, dd, *J* 15.8 and 1.6, CH═), 6.72 (1H, dd, *J* 15.8 and 5.1, CH═), 6.94 (2H, s, ArH), 7.33–7.39 (5H, m, Ph).

4.1.12. Phenylmethyl (2*E*,4*S*)-4-(2-bromoacetyloxy)-5-(((2,4,6-trimethylphenyl)sulfonyl)amino)pent-2-enoate 13b. By use of a procedure similar to that described for the preparation of **9b** from **7**, the (*E*)-enoate **11** (200 mg, 0.519 mmol) was converted into the γ-bromoacetyloxy-α,β-enoate **13b** (167.7 mg, 0.320 mmol, 62%) by treatment with $BrCH_2COOH$ (1.44 g, 10.4 mmol) and CF_3SO_3TMS (0.00940 cm^3, 51.9 μmol) in $CHCl_3$ (5 cm^3) at rt for 15 h.

Compound **13b**, colourless crystals, mp 91–93 °C [from *n*-hexane–Et_2O (3:1)] (Found: C, 52.70; H, 5.07; N, 2.69. $C_{23}H_{26}BrNO_6S$ requires C, 52.68; H, 5.00; N, 2.67%); $[\alpha]_D^{29}$ +3.29 (*c* 4.250 in $CHCl_3$); δ_H (300 MHz; $CDCl_3$) 2.29 (3H, s, CMe), 2.60 (6H, s, 2×CMe), 3.13–3.22 (1H, m, C*H*H), 3.26–3.34 (1H, m, CH*H*), 3.78 (2H, s, CCH_2Br), 4.91 (1H, t, *J* 6.6, NH), 5.18 (2H, s, OCH_2Ph), 5.39–5.45 (1H, m, 4-H), 6.04 (1H, dd, *J* 15.8 and 1.6, CH═), 6.73 (1H, dd, *J* 15.8 and 5.2, CH═), 6.95 (2H, s, ArH), 7.36–7.38 (5H, m, Ph).

4.1.13. Phenylmethyl (2*E*,4*S*)-4-ethoxy-5-(((2,4,6-trimethylphenyl)sulfonyl)amino)pent-2-enoate 13c. By use of a procedure similar to that described for the preparation of **9c** from **7**, the (*E*)-enoate **11** (50 mg, 0.130 mmol) was converted into the γ-ethoxy-α,β-enoate **13c** (49.9 mg, 0.117 mmol, 89%) by treatment with EtOH (0.0227 cm^3, 0.390 mmol) and CF_3SO_3TMS (0.00235 cm^3, 13.0 μmol) in CH_2Cl_2 (0.5 cm^3) at rt for 7 h.

Compound **13c**, colourless oil [Found (FAB): $(M+H)^+$, 432.1859. $C_{23}H_{30}NO_5S$ requires *M*+H, 432.1844]; $[\alpha]_D^{25}$ +14.66 (*c* 1.705 in $CHCl_3$); δ_H (300 MHz; $CDCl_3$) 1.16 (3H, t, *J* 7.0, CMe), 2.29 (3H, s, CMe), 2.62 (6H, s, 2×CMe), 2.74–2.83 (1H, m, C*H*H), 3.07–3.16 (1H, m, CH*H*), 3.21–3.31 (1H, m, OC*H*HMe), 3.44–3.54 (1H, m, OCH*H*Me), 3.91 (1H, m, 4-H), 4.95 (1H, br, NH), 5.16 (2H, dd, *J* 13.7 and 12.4, OCH_2Ph), 6.00 (1H, dd, *J* 15.8 and 1.3, CH═), 6.69 (1H, dd, *J* 15.8 and 6.0, CH═), 6.94 (2H, s, ArH), 7.31–7.38 (5H, m, Ph); *m*/*z* (FABLRMS) 432 (MH^+), 324 (base peak), 302, 261, 212, 183, 149 and 119.

4.1.14. Phenylmethyl (2*E*,4*S*)-4-(phenylmethylthio)-5-(((2,4,6-trimethylphenyl)sulfonyl)amino)pent-2-enoate 13d. By use of a procedure similar to that described for the preparation of **9d** from **7**, the (*E*)-enoate **11** (50 mg, 0.130 mmol) was converted into the γ-phenylmethylthio-α,β-enoate **13d** (48.0 mg, 0.0942 mmol, 73%) by treatment with BnSH (0.152 cm^3, 1.30 mmol) and CF_3SO_3TMS (0.00235 cm^3, 13.0 μmol) in CH_2Cl_2 (0.5 cm^3) at rt for 1 h.

Compound **13d**, colourless oil [Found (FAB): $(M+H)^+$, 510.1765. $C_{28}H_{32}NO_4S_2$ requires *M*+H, 510.1772]; $[\alpha]_D^{25}$ +81.8 (*c* 1.198 in $CHCl_3$); δ_H (600 MHz; $CDCl_3$) 2.28 (3H, s, CMe), 2.55 (6H, s, 2×CMe), 3.00–3.13 (2H, m, CH_2), 3.23 (1H, br, 4-H), 3.53 (1H, d, *J* 13.6, SC*H*HPh), 3.53 (1H, d, *J* 13.5, SCH*H*Ph), 4.83 (1H, t, *J* 6.3, NH), 5.17 (2H, dd, *J* 15.2 and 12.3, OCH_2Ph), 5.63 (1H, d, *J* 15.5, CH═), 6.64 (1H, dd, *J* 15.5 and 9.0, CH═), 6.90 (2H, s, ArH), 7.20–7.30 (5H, m, Ph), 7.34–7.40 (5H, m, Ph); *m*/*z* (FABLRMS) 531, 510 (MH^+), 402, 298, 282, 256 (base peak), 207, 183, 154 and 119.

4.1.15. Phenylmethyl (2*E*,4*S*)-4-phenylthio-5-(((2,4,6-trimethylphenyl)sulfonyl)amino)pent-2-enoate 13e. By use of a procedure similar to that described for the preparation of **9e** from **7**, the (*E*)-enoate **11** (50 mg, 0.130 mmol) was converted into the γ-phenylthio-α,β-enoate **13e** (55.7 mg, 0.112 mmol, 87%) by treatment with PhSH (0.133 cm^3, 1.30 mmol) and CF_3SO_3TMS (0.00235 cm^3, 13.0 μmol) in CH_2Cl_2 (0.5 cm^3) at rt for 1 h.

Compound **13e**, colourless crystals, mp 96–97 °C [from *n*-hexane–Et_2O (3:1)] [Found (FAB): $(M+H)^+$, 496.1629. $C_{27}H_{30}NO_4S_2$ requires *M*+H, 496.1616]; $[\alpha]_D^{25}$ +42.8 (*c* 1.495 in $CHCl_3$); δ_H (300 MHz; $CDCl_3$) 2.28 (3H, s, CMe), 2.59 (6H, s, 2×CMe), 3.06–3.24 (2H, m, CH_2), 3.59–3.66 (1H, m, 4-H), 5.08 (1H, t, *J* 6.4, NH), 5.56 (2H, s, OCH_2Ph), 5.58 (1H, dd, *J* 15.6 and 1.0, CH═), 6.71 (1H, dd, *J* 15.6 and 8.7, CH═), 6.92 (2H, s, ArH), 7.22–7.29 (5H, m, Ph), 7.29–7.39 (5H, m, Ph); *m*/*z* (FABLRMS) 496 (MH^+), 444, 388, 386, 330, 296 (base peak), 284, 256, 207, 183, 149 and 119.

4.1.16. Reaction of phenylmethyl (2*E*,4*R*)-3-(2-((2,4,6-trimethylphenyl)sulfonyl)-2-aziridinyl)prop-2-enoate 11 with MSA in $CHCl_3$.

4.1.16.1. Phenylmethyl (2*E*,4*S*)-4-(methylsulfonyloxy)-5-(((2,4,6-trimethylphenyl)sulfonyl)amino)pent-2-enoate 13f. To a stirred solution of (*E*)-enoate **9** (7 mg, 0.0182 mmol) in $CHCl_3$ (0.182 cm^3) was added dropwise MSA (0.0118 cm^3, 0.182 mmol) at rt, and the stirring was continued for 10 min. The mixture was extracted with EtOAc and the extract was washed successively with aq 5% citric acid, brine, aq 5% $NaHCO_3$, brine, and dried over $MgSO_4$. Concentration under reduced pressure gave the crude mesyl compound **13f**, as a colourless oil (crude), δ_H (300 MHz; $CDCl_3$) 2.29 (3H, s, CMe), 2.61 (6H, s, 2×CMe), 3.07 (3H, s, SMe), 3.13–3.30 (2H, m, CH_2), 5.04 (1H, t, *J* 6.7, NH), 5.18 (2H, s, OCH_2Ph), 5.22–5.30 (1H, m, 4-H), 6.13 (1H, dd, *J* 15.7 and 1.5, CH═), 6.78 (1H, dd, *J* 15.7 and 5.7, CH═), 6.95 (2H, s, ArH), 7.33–7.39 (5H, m, Ph); *m*/*z* (FABLRMS) 482 (MH^+), 391, 363, 296 (base peak), 279, 261, 212, 167 and 149.

4.1.17. Reaction of phenylmethyl (2*E*,4*R*)-3-(2-((2,4,6-trimethylphenyl)sulfonyl)-2-aziridinyl)prop-2-enoate 11 with HCl-1,4-dioxane.

4.1.17.1. Phenylmethyl (2*E*,4*S*)-4-chloro-5-(((2,4,6-trimethylphenyl)sulfonyl)amino)pent-2-enoate 13g. The (*E*)-enoate **11** (50 mg, 0.130 mmol) was dissolved in 4 M HCl-1,4-dioxane (0.325 cm^3, 1.30 mmol) at rt, and the solution was stirred for 10 min followed by extraction with EtOAc. The extract was washed successively with aq 5% citric acid, brine, aq 5% $NaHCO_3$, brine and dried over $MgSO_4$. Concentration under reduced pressure gave a crystalline residue, which was purified by chromatography over silica gel with *n*-hexane–EtOAc (3:1) to yield 47.5 mg (0.113 mmol, 87%) of compound **13g** as colourless crystals, mp 78–79 °C [from *n*-hexane–Et_2O (3:1)] (Found: C, 59.60; H, 5.92; N, 3.21. $C_{13}H_{17}NO_4S$ requires C, 59.78; H, 5.73; N, 3.32%); $[\alpha]_D^{25}$ −26.2 (*c* 1.185 in $CHCl_3$); δ_H (300 MHz; $CDCl_3$) 2.29 (3H, s, CMe), 2.62 (6H, s, 2×CMe), 3.14–3.23 (1H, m, C*H*H), 3.30–3.38 (1H, m, CH*H*), 4.45–4.52 (1H, m, 4-H), 4.97 (1H, t, *J* 5.8, NH), 5.18 (2H, s, OCH_2Ph), 6.04 (1H, dd, *J* 15.4 and 1.2, CH═), 6.77 (1H, dd, *J* 15.4 and 7.4, CH═), 6.95 (2H, s, ArH), 7.33–7.39 (5H, m, Ph).

4.1.18. Reaction of phenylmethyl (2*E*,4*R*)-3-(2-((2,4,6-trimethylphenyl)sulfonyl)-2-aziridinyl)prop-2-enoate 11 with TFA.

4.1.18.1. Phenylmethyl (2*E*,4*S*)-4-hydroxy-5-(((2,4,6-trimethylphenyl)sulfonyl)amino)pent-2-enoate 15. The (*E*)-enoate **11** (1 g, 2.60 mmol) was dissolved in TFA (10 cm^3) at rt, and the solution was stirred for 15 h. Concentration under reduced pressure gave a crude product **13h** as an oil. Hydrolysis and purification by flash chromatography over silica gel with *n*-hexane–EtOAc (4:1) afforded the hydrolyzate **15** (752 mg, 1.86 mmol, 72% yield based on **11**) as an oil.

Compound **13h**, colourless oil (crude), δ_H (300 MHz; $CDCl_3$) 2.29 (3H, s, CMe), 2.59 (6H, s, 2×CMe), 3.26–3.32 (2H, br, CH_2), 5.14 (1H, t, *J* 6.7, NH), 5.17 (2H, s, OCH_2Ph), 5.47–5.53 (1H, m, 4-H), 6.03 (1H, dd, *J* 15.8 and 1.5, CH═), 6.74 (1H, dd, *J* 15.8 and 5.8, CH═), 6.95 (2H, s, ArH), 7.31–7.38 (5H, m, Ph); *m*/*z* (FABLRMS) 500 (MH^+), 404, 302 (base peak), 212, 183, 137 and 119.

Compound **15**, colourless oil [Found (FAB): $(M+H)^+$, 404.1527. $C_{21}H_{26}NO_5S$ requires *M*+H, 404.1532]; $[\alpha]_D^{22}$ −2.59 (*c* 3.855 in $CHCl_3$); δ_H (300 MHz; $CDCl_3$) 2.28 (3H, s, CMe), 2.60 (6H, s, 2×CMe), 2.83 (1H, m, C*H*H), 3.13 (1H, m, CH*H*), 4.12 (1H, m, 4-H), 5.16 (2H, s, OCH_2Ph), 5.22 (1H, t, *J* 5.8, NH), 6.13 (1H, dd, *J* 15.7 and 1.8, CH═), 6.82 (1H, dd, *J* 15.6 and 4.4, CH═), 6.94 (2H, s, ArH), 7.31–7.36 (5H, m, Ph); *m*/*z* (FABLRMS) 404 (MH^+), 302, 212, 183, 167, 149 (base peak) and 119.

4.1.19. Phenylmethyl (2*E*,4*R*)-4-acetyloxy-5-(((2,4,6-trimethylphenyl)sulfonyl)amino)pent-2-enoate 14a. By use of a procedure identical with that described for the preparation of **13a** from **11**, the (*E*)-enoate **12** (50 mg, 0.130 mmol) was converted into the γ-acetyloxy-α,β-enoate **14a** (39.9 mg, 0.0896 mmol, 69%).

Compound **14a**, colourless crystals, mp 84–86 °C [from *n*-hexane–Et_2O (3:1)] (Found: C, 61.73; H, 6.05; N, 2.95.

$C_{23}H_{27}NO_6S$ requires C, 62.00; H, 6.11; N, 3.14%); $[\alpha]_D^{26}$ −2.00 (*c* 0.998 in $CHCl_3$); δ_H (270 MHz; $CDCl_3$) 2.03 (3H, s, CMe), 2.29 (3H, s, CMe), 2.60 (6H, s, 2×CMe), 3.10–3.23 (2H, m, CH_2), 4.92 (1H, m, NH), 5.16 (2H, s, CH_2), 5.35 (1H, m, 4-H), 5.96 (1H, dd, *J* 15.8 and 1.7, CH═), 6.72 (1H, dd, *J* 15.8 and 5.3, CH═), 6.94 (2H, s, ArH), 7.37 (5H, m, ArH).

4.1.20. Phenylmethyl (2*E*,4*R*)-4-(2-bromoacetyloxy)-5-(((2,4,6-trimethylphenyl)sulfonyl)amino)pent-2-enoate 14b. By use of a procedure similar to that described for the preparation of **13b** from **11**, the (*E*)-enoate **12** (100 mg, 0.260 mmol) was converted into the γ-bromoacetyloxy-α,β-enoate **14b** (93.6 mg, 0.178 mmol, 69%) by treatment with $BrCH_2COOH$ (721 mg, 5.19 mmol) and CF_3SO_3TMS (0.00470 cm^3, 26.0 μmol) in CH_2Cl_2 (1 cm^3) at rt for 15 h.

Compound **14b**, colourless crystals, mp 87–88 °C [from *n*-hexane–Et_2O (3:1)] (Found: C, 52.70; H, 5.26; N, 2.75. $C_{23}H_{26}BrNO_6S$ requires C, 52.68; H, 5.00; N, 2.67%); $[\alpha]_D^{28}$ −2.56 (*c* 3.905 in $CHCl_3$); δ_H (270 MHz; $CDCl_3$) 2.29 (3H, s, CMe), 2.60 (6H, s, 2×CMe), 3.16–3.28 (2H, m, CH_2), 3.79 (2H, s, CCH_2Br), 5.17 (2H, s, OCH_2Ph), 5.29 (1H, br, NH), 5.43 (1H, m, 4-H), 6.04 (1H, dd, *J* 15.8 and 1.7, CH═), 6.74 (1H, dd, *J* 15.8 and 5.3, CH═), 6.94 (2H, s, ArH), 7.36 (5H, m, Ph); *m*/*z* (FAB-LRMS) 432 (MH^+), 324, 302, 250 (base peak), 212, 183, 149 and 119.

4.1.21. Phenylmethyl (2*E*,4*R*)-4-ethoxy-5-(((2,4,6-trimethylphenyl)sulfonyl)amino)pent-2-enoate 14c. By use of a procedure identical with that described for the preparation of **13c** from **11**, the (*E*)-enoate **12** (50 mg, 0.130 mmol) was converted into the γ-ethoxy-α,β-enoate **14c** (43.1 mg, 0.0999 mmol, 79%).

Compound **14c**, colourless oil [Found (FAB): $(M+H)^+$, 432.1856. $C_{23}H_{29}NO_5S$ requires *M*+H, 431.1766]; $[\alpha]_D^{25}$ −14.51 (*c* 2.205 in $CHCl_3$); δ_H (270 MHz; $CDCl_3$) 1.16 (3H, t, *J* 6.9, CMe), 2.29 (3H, s, CMe), 2.62 (6H, s, 2×CMe), 2.77 (1H, m, C*H*H), 3.11 (1H, m, CH*H*), 3.22–3.28 (1H, m, OC*H*HMe), 3.46–3.52 (1H, m, OCH*H*Me), 3.91 (1H, m, 4-H), 4.98 (1H, m, NH), 5.16 (2H, s, OCH_2Ph), 6.00 (1H, dd, *J* 15.8 and 1.3, CH═), 6.69 (1H, dd, *J* 15.8 and 6.3, CH═), 6.95 (2H, s, ArH), 7.37 (5H, m, Ph); *m*/*z* (FABLRMS) 432 (MH^+), 324, 302, 250 (base peak), 212, 183, 149 and 119.

4.1.22. Phenylmethyl (2*E*,4*R*)-4-(phenylmethylthio)-5-(((2,4,6-trimethylphenyl)sulfonyl)amino)pent-2-enoate 14d. By use of a procedure similar to that described for the preparation of **13d** from **11**, the (*E*)-enoate **12** (50 mg, 0.130 mmol) was converted into the γ-phenylmethylthio-α,β-enoate **14d** (45.9 mg, 0.0901 mmol, 69%).

Compound **14d**, colourless oil [Found (FAB): $(M+H)^+$, 510.1760. $C_{28}H_{32}NO_4S_2$ requires *M*+H, 510.1772]; $[\alpha]_D^{25}$ −74.2 (*c* 1.145 in $CHCl_3$); δ_H (400 MHz; $CDCl_3$) 2.28 (3H, s, CMe), 2.55 (6H, s, 2×CMe), 3.01–3.12 (2H, m, CH_2), 3.20–3.26 (1H, m, 4-H), 3.52–3.67 (2H, m, SCH_2Ph), 4.84 (1H, t, *J* 6.3, NH), 5.18 (2H, s, OCH_2Ph), 5.63 (1H, d, *J* 15.4, CH═), 6.64 (1H, dd, *J* 15.6 and 8.8, CH═), 6.90 (2H, s, ArH), 7.21–7.29 (5H, m, Ph) 7.38 (5H, m, Ph); *m*/*z* (FABLRMS) 510 (MH^+), 408, 402 (base peak), 311, 302, 221, 207, 183, 149 and 119.

4.1.23. Phenylmethyl (2*E*,4*R*)-4-phenylthio-5-(((2,4,6-trimethylphenyl)sulfonyl)amino)pent-2-enoate 14e. By use of a procedure similar to that described for the preparation of **13e** from **11**, the (*E*)-enoate **12** (50 mg, 0.130 mmol) was converted into the γ-phenylthio-α,β-enoate **14e** (55.7 mg, 0.112 mmol, 87%).

Compound **14e**, colourless crystals, mp 99 °C [from *n*-hexane–Et_2O (3:1)] (Found: C, 65.19; H, 5.71; N, 2.82. $C_{27}H_{29}NO_4S_2$ requires C, 65.43; H, 5.90; N, 2.83%); $[\alpha]_D^{26}$ −41.2 (*c* 2.575 in $CHCl_3$); δ_H (400 MHz; $CDCl_3$) 2.29 (3H, s, CMe), 2.60 (6H, s, 2×CMe), 3.08–3.20 (2H, m, CH_2), 3.62 (1H, m, 4-H), 5.02 (1H, t, *J* 6.4, NH), 5.14 (2H, s, OCH_2Ph), 5.59 (1H, dd, *J* 15.5 and 1.0, CH═), 6.71 (1H, dd, *J* 15.4 and 8.8, CH═), 6.93 (2H, s, ArH), 7.24–7.27 (5H, m, Ph), 7.35 (5H, m, Ph).

4.1.24. Reaction of phenylmethyl (2*E*,4*S*)-3-(2-((2,4,6-trimethylphenyl)sulfonyl)-2-aziridinyl)prop-2-enoate 12 with HCl-1,4-dioxane.

4.1.24.1. Phenylmethyl (2*E*,4*R*)-4-chloro-5-(((2,4,6-trimethylphenyl)sulfonyl)amino)pent-2-enoate 14g. By use of a procedure identical with that described for the preparation of **13g** from **11**, the (*E*)-enoate **12** (50 mg, 0.130 mmol) was converted into the γ-chloro-α,β-enoate **14g** (52.7 mg, 0.125 mmol, 96%).

Compound **14g**, colourless crystals, mp 80–81 °C [from *n*-hexane–Et_2O (3:1)] (Found: C, 59.53; H, 5.73; N, 3.40. $C_{13}H_{17}NO_4S$ requires C, 59.78; H, 5.73; N, 3.32%); $[\alpha]_D^{25}$ +25.9 (*c* 1.390 in $CHCl_3$); δ_H (270 MHz; $CDCl_3$) 2.30 (3H, s, CMe), 2.62 (6H, s, 2×CMe), 3.13–3.23 (1H, m, C*H*H), 3.28–3.38 (1H, m, CH*H*), 4.46 (1H, m, 4-H), 5.03 (1H, t, *J* 7.3, NH), 5.18 (2H, s, CH_2), 6.04 (1H, dd, *J* 15.5 and 1.0, CH═), 6.78 (1H, dd, *J* 15.5 and 7.6, CH═), 6.95 (2H, s, ArH), 7.37 (5H, m, ArH).

4.1.25. Reaction of phenylmethyl (2*E*,4*S*)-3-(2-((2,4,6-trimethylphenyl)sulfonyl)-2-aziridinyl)prop-2-enoate 12 with TFA.

4.1.25.1. Phenylmethyl (2*E*,4*R*)-4-hydroxy-5-(((2,4,6-trimethylphenyl)sulfonyl)amino)pent-2-enoate 16. By use of a procedure identical with that described for the preparation of **13h** from **11**, the (*E*)-enoate **12** (200 mg, 0.519 mmol) was converted into the hydrolyzate **16** (131 mg, 0.325 mmol, 63% yield based on **12**) via the γ-trifluoroacetoxy-α,β-enoate **14h**.

Compound **14h**, colourless oil (crude), δ_H (300 MHz; $CDCl_3$) 2.29 (3H, s, CMe), 2.59 (6H, s, 2×CMe), 3.20–3.38 (2H, m, CH_2), 4.99 (1H, t, *J* 6.7, NH), 5.18 (2H, s, CH_2), 5.46–5.52 (1H, m, 4-H), 6.03 (1H, dd, *J* 15.8 and 1.5, CH═), 6.73 (1H, dd, *J* 15.8 and 5.8, CH═), 6.94 (2H, s, ArH), 7.32–7.40 (5H, m, ArH); *m*/*z* (FABLRMS) 500 (MH^+), 404, 398, 302, 273 (base peak), 212, 183, 167 and 119.

Compound **16**, colourless oil [Found (FAB): $(M+H)^+$, 404.1521. $C_{21}H_{26}NO_5S$ requires *M*+H, 404.1532]; $[\alpha]_D^{22}$ +2.56 (*c* 2.340 in $CHCl_3$); δ_H (300 MHz; $CDCl_3$) 2.29 (3H, s, CMe), 2.62 (6H, s, 2×CMe), 2.85 (1H, m, C*H*H), 3.16 (1H, m, CH*H*), 4.42 (1H, m, 4-H), 4.98 (1H, s, NH), 5.17 (2H, s, CH_2), 6.13 (1H, dd, *J* 15.7 and 1.7, CH═),

6.82 (1H, dd, *J* 15.6 and 4.5, CH=), 6.95 (2H, s, ArH), 7.32–7.38 (5H, m, ArH); *m/z* (FABLRMS) 426, 404 (MH^+), 391, 302, 222 (base peak), 212, 183, 149 and 119.

4.1.26. Mts-Gly–ψ[(*E*)-CH=CH]–L-Asp(OMe)–OBn [methyl phenylmethyl (1*E*,2*R*)-2-(3-(((2,4,6-trimethylphenyl)sulfonyl)amino)prop-1-enyl)butane-1,4-dioate] 19. Allylic acetate **15** (2.30 g, 5.69 mmol), trimethyl orthoacetate (7.25 cm^3, 56.9 mmol), benzoic acid (139 mg, 1.14 mmol), and dried molecular sieves (4 Å, powder, 2.85 g) were mixed in 75 cm^3 *o*-xylene and then refluxed for 3 days. The mixture was cooled to rt and purified by chromatography over silica gel with *n*-hexane–EtOAc (3:1) to give 896 mg (1.95 mmol, 34%) of the mixture of Mts–Gly–ψ[(*E*)-CH=CH]–L-Asp(OMe)–OBn **19** and its enantiomer **21** (66.5: 33.5) as a colourless oil [Found (FAB): $(M+H)^+$, 460.1802. $C_{24}H_{30}NO_6S$ requires *M*+H, 460.1794]; δ_H (400 MHz; $CDCl_3$) 2.29 (3H, s, CMe), 2.37–2.43 (1H, dd, *J* 16.6 and 5.9, C*H*H), 2.60 (6H, s, 2×CMe), 2.63–2.76 (1H, dd, *J* 16.6 and 8.5, CH*H*), 3.45–3.51 (3H, m, CH and CH_2), 3.62 (3H, s, OMe), 4.44 (1H, t, *J* 6.1, NH), 5.11 (2H, s, OCH_2Ph), 5.45–5.50 (1H, m, CH=), 5.57–5.63 (1H, dd, *J* 15.6 and 7.6, CH=), 6.94 (2H, s, ArH), 7.33 (5H, m, Ph); *m/z* (FABLRMS), 460 (MH^+), 352 (base peak), 183, 136, 119.

4.1.27. Mts–Gly–ψ[(*E*)-CH=CH]–D-Asp(OMe)–OBn [methyl phenylmethyl (1*E*,2*S*)-2-(3-(((2,4,6-trimethylphenyl)sulfonyl)amino)prop-1-enyl)butane-1,4-dioate] 21. By use of a procedure identical with that described for the preparation of **19** from **15**, the allylic acetate **16** (1.88 g, 4.64 mmol) was converted into the mixture (398 mg, 0.866 mmol, 19%) of Mts–Gly–ψ[(*E*)-CH=CH]–D-Asp-(OMe)–OBn **21** and its enantiomer **19** (71.5: 28.5) as a colourless oil [Found (FAB): $(M+H)^+$, 460.1801. $C_{24}H_{30}NO_6S$ requires *M*+H, 460.1794]; δ_H (300 MHz; $CDCl_3$) 2.29 (3H, s, CMe), 2.41 (1H, dd, *J* 16.6 and 5.8, C*H*H), 2.60 (6H, s, 2×CMe), 2.73 (1H, dd, *J* 16.7 and 8.7, CH*H*), 3.43–3.47 (1H, m, CH), 3.48–3.52 (2H, t, *J* 6.3, CH_2), 3.62 (3H, s, OMe), 4.41 (1H, t, *J* 6.4, NH), 5.12 (2H, s, OCH_2Ph), 5.42–5.51 (1H, m, CH=), 5.61 (1H, dd, *J* 15.5 and 7.6, CH=), 6.95 (2H, s, ArH), 7.29–7.39 (5H, m, Ph); *m/z* (FABLRMS), 460 (MH^+, base peak), 307, 289, 243, 154, 136.

4.1.28. Boc–Gly–ψ[(*E*)-CH=CH]–L-Asp(OMe)–OH [(3*E*,2*R*)-5-((*tert*-butoxy)carbonylamino)-2-((methoxycarbonyl)methyl)pent-3-enoic acid] 20. Mts–Gly–ψ[(*E*)-CH=CH]–L-Asp(OMe)–OBn **19** (48.7 mg, 0.106 mmol, the enantiomixture with **21**, ee=33%) was treated with 1 M TMSBr-thioanisole/TFA (2.5 cm^3) in the presence of *m*-cresol (0.122 cm^3, 1.17 mmol) and 1,2-ethanedithiol (0.050 cm^3, 0.595 mmol) at 0 °C with warming to rt for 15 h. After concentration with N_2 gas, ice-cold Et_2O was added. The resulting precipitate was collected by centrifugation, and the precipitate was washed three times with Et_2O, and dissolved with H_2O (0.150 cm^3). The solution was treated with 3 M $(Boc)_2O$ in THF (0.050 cm^3) in the presence of Et_3N (0.0334 cm^3, 0.240 mmol) at 0 °C with warming to rt for 15 h. The mixture was extracted with EtOAc, and the extract was washed with saturated aq citric acid, brine and dried over $MgSO_4$. Concentration under reduced pressure followed by chromatography over silica gel with CH_3Cl–MeOH (9:1) gave 14.0 mg (0.0487 mmol, 46%) of Boc–Gly–ψ[(*E*)-CH=CH]–L-Asp(OMe)–OH **20** accompanied with its enantiomer **22** as a colourless oil [Found (CI): $(M+H)^+$, 288.1453. $C_{13}H_{22}NO_6$ requires *M*+H, 288.1447]; δ_H (600 MHz; $CDCl_3$) 1.27 (9H, s, 3×CMe), 2.54–2.58 (1H, dd, *J*=16.6 and 5.2, C*H*H), 2.82–2.86 (dd, *J*=16.7 and 8.2, CH*H*), 3.55 (1H, m, 2-H), 3.69 (3H, s, OMe), 3.70 (2H, br, CH_2), 4.63 (1H, br, NH), 5.63–5.67 (2H, m, 2×CH=); *m/z* (CILRMS), 288 (MH^+, base peak), 260, 242, 232, 214, 188, 171.

4.1.29. Boc–Gly–ψ[(*E*)-CH=CH]–D-Asp(OMe)–OH [(3*E*,2*S*)-5-((*tert*-butoxy)carbonylamino)-2-((methoxycarbonyl)methyl)pent-3-enoic acid] 22. By use of a procedure identical with that described for the preparation of **20** from **19**, the allylic dioate **21** (58.1 mg, 0.126 mmol, the enantiomixture with **19**, ee=43%) was converted into Boc–Gly–ψ[(*E*)-CH=CH]–D-Asp(OMe)–OH **22** accompanied with its enantiomer **20** (16.0 mg, 0.0557 mmol, 44%) as a colourless oil [Found (CI): $(M+H)^+$, 288.1442. $C_{13}H_{22}NO_6$ requires *M*+H, 288.1447]; δ_H (270 MHz; $CDCl_3$) 1.45 (9H, s, 3×CMe), 2.52–2.60 (1H, dd, *J*=16.8 and 5.9, C*H*H), 2.80–2.89 (1H, dd, *J*=16.8 and 8.2, CH*H*), 3.53 (1H, m, 2-H), 3.69 (3H, s, OMe), 3.74 (2H, br, CH_2), 4.63 (1H, br, NH), 5.65–5.67 (2H, m, 2×CH=); *m/z* (CILRMS), 288 (MH^+, base peak), 272, 260, 242, 232, 214, 188, 171.

4.1.30. Methyl (2*E*,2*S*,4*S*,5*S*)-5-(((4-methylphenyl)sulfonyl)amino)-4-(3-phenyl-2-((phenylmethoxy)carbonylamino)propanoyloxy)hex-2-enoate 23a. By use of a procedure similar to that described for the preparation of **9a** from **7**, the (*E*)-enoate **7** (50 mg, 0.169 mmol) was converted into the γ-acyloxy-α,β-enoate **23a** (59.7 mg, 0.100 mmol, 59%) by treatment with Cbz–L-Phe–OH (507 mg, 1.69 mmol) and CF_3SO_3TMS (0.00920 cm^3, 50.8 μmol) in CH_2Cl_2 at rt for 15 h.

Compound **23a**, colourless crystals, mp 60–62 °C [from *n*-hexane–Et_2O (3:1)] (Found: C, 62.33; H, 5.77; N, 4.50. $C_{31}H_{34}N_2O_8S$ requires C, 62.61; H, 5.76; N, 4.71%); $[\alpha]_D^{29}$ +17.9 (*c* 0.335, $CHCl_3$); δ_H (600 MHz; $CDCl_3$) 0.87–0.89 (3H, m, CMe), 2.41 (3H, s, CMe), 3.09 (2H, d, *J* 6.4, CCH_2Ph), 3.47 (1H, br, 5-H), 3.71 (3H, s, OMe), 4.63 (1H, q, *J* 7.2, 2-H), 4.72 (1H, d, *J* 8.7, NH), 5.06–5.12 (2H, m, OCH_2Ph), 5.25 (1H, d, *J* 8.0, NH), 5.33 (1H, br, 4-H), 5.84 (1H, d, *J* 15.8, CH=), 6.62 (1H, dd, *J* 15.8 and 5.5, CH=), 7.22–7.35 (12H, m, ArH and 2×Ph), 7.71 (2H, d, *J* 8.2, ArH).

4.1.31. Methyl (2*E*,2*S*,4*S*,5*S*)-4-(3-methyl-2-((phenylmethoxy)carbonylamino)butanoyloxy)-5-(((4-methylphenyl)sulfonyl)amino)hex-2-enoate 23b. By use of a procedure similar to that described for the preparation of **9a** from **7**, the (*E*)-enoate **7** (100 mg, 0.339 mmol) was converted into the γ-acyloxy-α,β-enoate **23b** (83.2 mg, 0.152 mmol, 45%) by treatment with Cbz–L-Val–OH (852 mg, 3.39 mmol) and CF_3SO_3TMS (0.0184 cm^3, 0.102 mmol) in CH_2Cl_2 at rt for 15 h.

Compound **23b**, colourless crystals, mp 51–52 °C [from *n*-hexane–Et_2O (3:1)] (Found: C, 59.52; H, 6.44; N, 4.85. $C_{27}H_{34}N_2O_8S$ requires C, 59.32; H, 6.27; N, 5.12%); $[\alpha]_D^{29}$ −49.0 (*c* 0.490, $CHCl_3$); δ_H (600 MHz; $CDCl_3$) 0.89 (3H,

d, *J* 6.6, CMe), 1.00 (3H, d, *J* 6.8, CMe), 1.05 (3H, d, *J* 6.7, CMe), 2.17–2.24 (1H, m, 3-H), 2.42 (3H, s, CMe), 3.61 (1H, m, 5-H), 3.72 (3H, s, OMe), 4.30 (1H, dd, *J* 8.6 and 4.6, 2-H), 4.67 (1H, d, *J* 8.7, NH), 5.09–5.16 (2H, m, OCH_2Ph), 5.19 (1H, m, NH), 5.37 (1H, br, 4-H), 5.92 (1H, d, *J* 15.7, CH=), 6.66 (1H, dd, *J* 15.7 and 5.5, CH=), 7.29 (2H, d, *J* 8.1, ArH), 7.32–7.36 (5H, m, Ph), 7.73 (2H, d, *J* 8.2, ArH).

4.1.32. Methyl (2*E*,2*S*,4*S*,5*S*)-4-(1-((fluoren-9-ylmethyl)-oxycarbonyl)pyrrolidin-2-ylcarbonyloxy)-5-(((4-methylphenyl)sulfonyl)amino)hex-2-enoate 24. By use of a procedure similar to that described for the preparation of **9a** from **7**, the (*E*)-enoate **7** (50 mg, 0.169 mmol) was converted into the γ-acyloxy-α,β-enoate **24** (73.9 mg, 0.117 mmol, 69%) by treatment with Fmoc–L-Pro–OH (852 mg, 3.39 mmol) and CF_3SO_3TMS (0.0184 cm^3, 0.102 mmol) in CH_2Cl_2 at rt for 6 h.

Compound **24**, colourless amorphous semisolid [Found (FAB): (M+H)$^+$, 633.2261. $C_{34}H_{37}N_2O_8S$ requires *M*+H, 633.2270]; $[\alpha]_D^{20}$ −38.6 (*c* 1.346, $CHCl_3$); δ_H (600 MHz; $CDCl_3$) 1.03 (3H, d, *J* 6.8, CMe), 1.93–2.32 (4H, m, 2×CH_2), 2.39 (3H, s, CMe), 3.51–3.66 (2H, m, CH_2), 3.59–3.66 (1H, m, 5-H), 3.72 (3H, s, OMe), 4.29–4.38 (2H, m, CH_2), 4.46 (1H, dd, *J* 8.6 and 3.9, 2-H), 4.58 (1H, dd, *J* 10.4 and 6.5, 9-H), 5.04 (1H, d, *J* 9.1, NH), 5.42 (1H, m, 4-H), 5.96 (1H, dd, *J* 15.7 and 1.4, CH=), 6.72 (1H, dd, *J* 15.8 and 5.2, CH=), 7.20–7.43 (6H, m, ArH), 7.63–7.78 (6H, m, ArH); *m*/*z* (FABLRMS), 633 (MH$^+$), 411, 296, 292 (base peak), 225, 179, 178 and 91.

4.1.33. Methyl (2*E*,2*S*,4*S*,5*S*)-4-(1-((fluoren-9-ylmethyl)-oxycarbonyl)pyrrolidin-2-ylcarbonyloxy)-5-(((2,4,6-trimethylphenyl)sulfonyl)amino)hex-2-enoate 26. By use of a procedure similar to that described for the preparation of **9a** from **7**, the (*E*)-enoate **25** (723 mg, 2.24 mmol) was converted into the γ-acyloxy-α,β-enoate **26** (657 mg, 0.994 mmol, 44%) by treatment with Fmoc–L-Pro–OH (5.20 g, 15.5 mmol) and CF_3SO_3TMS (0.121 cm^3, 0.669 mmol) in CH_2Cl_2 at rt for 15 h.

Compound **26**, colourless crystals, mp 77–79 °C [from *n*-hexane–Et_2O (3:1)] (Found: C, 63.80; H, 6.11; N, 4.20. $C_{36}H_{40}N_2O_8S\cdot H_2O$ requires C, 63.70; H, 6.24; N, 4.13%); $[\alpha]_D^{22}$ +14.88 (*c* 0.739, $CHCl_3$); δ_H (600 MHz; $CDCl_3$) 1.08 (3H, d, *J* 6.8, CMe), 1.92–2.17 (4H, m, 2×CH_2), 2.27 (3H, s, CMe), 2.61 (6H, s, 2×CMe), 3.50–3.57 (2H, m, C*H*H and 5-H), 3.61–3.67 (1H, m, CH*H*), 3.70 (3H, s, OMe), 4.27–4.56 (4H, m, CH_2, 2-H and 9-H), 5.08 (1H, d, *J* 9.3, NH), 5.42 (1H, m, 4-H), 5.91 (1H, dd, *J* 15.7 and 1.5, CH=), 6.64 (1H, dd, *J* 15.8 and 5.0, CH=), 6.89 (2H, s, ArH), 7.30–7.33 (2H, m, ArH), 7.36–7.42 (2H, m, ArH), 7.65 (2H, t, *J* 7.2, ArH), 7.73–7.78 (2H, m, ArH).

4.1.34. Methyl (2*E*,2*S*,4*S*,5*S*)-5-((1-((fluoren-9-ylmethyl)-oxycarbonyl)pyrrolidin-2-yl)carbonylamino)-4-hydroxyhex-2-enoate 28. The γ-acyloxy-α,β-enoate **26** (250 mg, 0.378 mmol) was treated with 1 M TMSBr-thioanisole/TFA (12.5 cm^3) in the presence of *m*-cresol (0.610 cm^3, 5.83 mmol) at 0 °C with warming to rt for 15 h. After thorough concentration under reduced pressure, the residue **27** was dissolved with CH_3CN (20 cm^3). To the solution was added dropwise PBS (20 cm^3) and saturated aq Na_2HPO_4 (3.4 cm^3) at 0 °C, and the mixture was allowed to warm to rt for 30 min. Concentration under reduced pressure gave an oily residue, which was purified by chromatography over silica gel with *n*-hexane–EtOAc (1:3) to yield 152 mg (0.318 mmol, 84%) of compound **28** as colourless crystals, mp 85–87 °C [from *n*-hexane–Et_2O (3:1)] (Found: C, 67.50; H, 6.25; N, 5.67. $C_{27}H_{30}N_2O_6$ requires C, 67.77; H, 6.32; N, 5.85%); $[\alpha]_D^{23}$ −21.9 (*c* 1.097, $CHCl_3$); δ_H (600 MHz; $CDCl_3$) 1.25–1.27 (3H, m, CMe), 1.91–1.96 (3H, br, CH_2 and C*H*H), 2.28 (1H, br, CH*H*), 3.32 (2H, m, CH_2), 3.70 (3H, s, OMe), 3.87 (1H, br, 5-H), 4.25 (3H, br, 2-H, 4-H and 9-H), 4.33 (2H, br, CH_2), 6.12 (1H, d, *J* 11.0, CH=), 6.82 (1H, br, NH), 6.90 (1H, d, *J* 12.7, CH=), 7.30–7.34 (2H, m, ArH), 7.41 (2H, t, *J* 5.7, ArH), 7.60 (2H, d, *J* 7.0, ArH), 7.77 (2H, d, *J* 7.5, ArH).

4.1.35. Fmoc–L-Pro–L-Ala–ψ[(*E*)-CH=CH]–D-Leu–OMe 29. To a stirred solution of the γ-hydroxy-α,β-enoate **28** (53.1 mg, 0.111 mmol) in CH_2Cl_2 (2 cm^3) were added dropwise MsCl (0.0859 cm^3, 1.11 mmol) and Et_3N (0.153 cm^3, 1.11 mmol) at 0 °C, and the mixture was stirred at this temperature for 3 h. To ice-cold saturated aq citric acid was added the mixture followed by stirring for 10 min. The mixture was extracted with EtOAc, and the extract was washed successively with aq 5% citric acid and brine and dried over $MgSO_4$. Concentration under reduced pressure gave an oily residue of the crude γ-mesyloxy-α,β-enoate, which was utilized for the next reaction without purification.

To a stirred slurry of CuCN (79.9 mg, 0.888 mmol) in THF (1 cm^3) was added a solution of ^{i}BuMgCl in THF (1.3 M, 0.683 cm^3, 0.888 mmol) at −78 °C under argon, and the mixture was stirred at 0 °C for 15 min. $BF_3\cdot Et_2O$ (0.109 cm^3, 0.888 mmol) was added to the above mixture at −78 °C. After 10 min of stirring at −78 °C, a solution of the crude γ-mesyloxy-α,β-enoate in dry THF (2 cm^3) was added to the above mixture at −78 °C under argon. The stirring was continued at −78 °C for 30 min followed by quenching with saturated aq NH_4Cl at 0 °C. The mixture was extracted with Et_2O, and the extract was washed with water and dried over $MgSO_4$. Concentration under reduced pressure gave a colourless oil, which was purified by chromatography over silica gel with *n*-hexane–EtOAc (1:1) to yield 40.2 mg (0.0775 mmol, 70%) of **29** as colourless crystals, mp 158–159 °C [from EtOAc] (Found: C, 71.53; H, 7.38; N, 5.33. $C_{31}H_{38}N_2O_5$ requires C, 71.79; H, 7.16; N, 5.40%); $[\alpha]_D^{23}$ −22.8 (*c* 0.832, $CHCl_3$); δ_H (600 MHz; $CDCl_3$) 0.87–0.89 (6H, br, 2×CMe), 1.18 (3H, d, *J* 5.8, CMe), 1.36 (1H, br, CH), 1.50 (1H, br, C*H*H), 1.60 (1H, br, CH*H*), 1.92 (2H, br, CH_2), 2.17 (2H, m, CH_2), 3.07 (1H, br, 2-H), 3.43 (1H, br, C*H*H), 3.54 (1H, br, CH*H*), 3.64 (3H, s, OMe), 4.22–4.45 (4H, br, CH_2, 2-H and 9-H), 4.52 (1H, br, 5-H), 5.45–5.54 (2H, br, 2×CH=), 6.57 (1H, br, NH), 7.30–7.33 (2H, m, ArH), 7.40 (2H, t, *J* 7.4, ArH), 7.59 (2H, d, *J* 3.8, ArH), 7.76 (2H, d, *J* 7.4, ArH).

4.1.36. Methyl (2*E*,4*S*,5*S*)-5-(((4-methylphenyl)sulfonyl)-amino)-4-(phenylsulfonyloxy)hex-2-enoate resin 30. The (*E*)-enoate **7** (1.05 g, 3.56 mmol) was treated with MP–Ts–OH resin (Argonaut Technologies, California, U.S.A., 1.27 mmol/g, 933 mg, 1.19 mmol) in CH_2Cl_2 (12 cm^3) at rt, and the mixture was stirred for 15 h. The resin was filtered

and washed with dried THF (1 $cm^3 \times 7$) to give resin-bound enoate **30** (1.26 g). The filtrate was concentrated under reduced pressure and chromatographed by flash column over silica gel with *n*-hexane–EtOAc (4:1) to recover excess of **7** (0.84 g, 2.84 mmol).

4.1.37. Ts–L-Ala–ψ[(*E*)-CH=CH]-D-Leu–OMe [methyl (2*E*,2*S*,5*S*)-5-(((4-methylphenyl)sulfonyl)amino)-2-(2-methylpropyl)hex-3-enoate] 31. To a stirred slurry of CuCN (122 mg, 1.35 mmol) in THF (3 cm^3) was added a solution of ^{t}BuMgCl in THF (1.2 M, 1.13 cm^3, 1.35 mmol) at −78 °C under argon, and the mixture was stirred at 0 °C for 15 min. $BF_3 \cdot Et_2O$ (0.167 cm^3, 1.35 mmol) was added to the above mixture at −78 °C. After 10 min of stirring at −78 °C, the dried resin-bound enoate **30** (180 mg) was added to the above mixture at −78 °C. The stirring was continued at −78 °C for 30 min and then at 0 °C for 15 h followed by quenching with 2 cm^3 of saturated aq NH_4Cl-aq 28% NH_4OH (1:1 (v/v)). The mixture was extracted with Et_2O, and the extract was washed with water and dried over $MgSO_4$. Concentration under reduced pressure gave a colourless oil, which was purified by chromatography over silica gel with *n*-hexane–EtOAc (5:1) to yield 22.4 mg (0.0634 mmol, 37% based on **7**) of **31** accompanied with its 2*R*-isomer.

Compound **31**, colourless oil [Found (FAB): $(M+H)^+$, 354.1746. $C_{18}H_{28}NO_4S$ requires *M*+H, 354.1739]; $[\alpha]_D^{27}$ −7.14 (*c* 1.680, $CHCl_3$); $\Delta\varepsilon$+2.833 (227 nm, isooctane); δ_H (600 MHz; $CDCl_3$) 0.81–0.86 (6H, m, 2×CMe), 1.17 (3H, d, *J* 6.8, CMe), 1.19–1.24 (1H, m, C*H*H), 1.37–1.42 (1H, m, CH), 1.48–1.55 (1H, m, CH*H*), 2.43 (3H, s, CMe), 2.95 (1H, q, *J* 7.9, 2-H), 3.65 (3H, s, OMe), 3.85–3.95 (1H, m, 5-H), 4.40 (1H, d, *J* 7.6, NH), 5.33–5.37 (1H, m, CH=), 5.40–5.45 (1H, m, CH=), 7.23–7.30 (2H, m, ArH), 7.72–7.74 (2H, m, ArH); *m*/*z* (FABLRMS), 354 (MH^+, base peak), 352, 338, 322, 294, 198, 183, 155, 123.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2007.06.029.

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