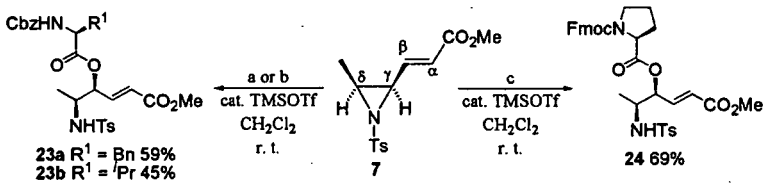
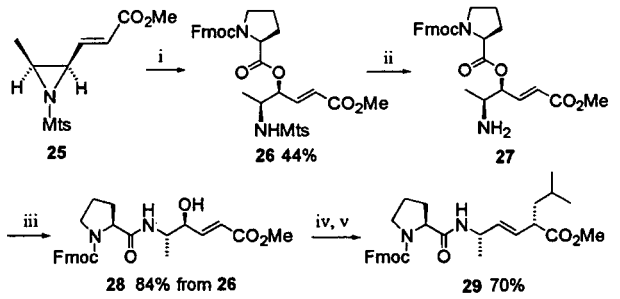


Scheme 5. Reagents: (a) Cbz–Phe–OH; (b) Cbz–Val–OH and (c) Fmoc–Pro–OH.

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**.

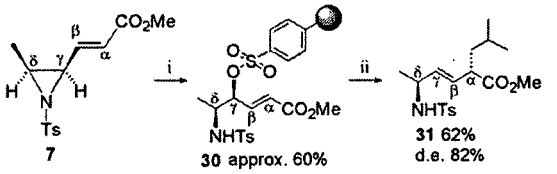
Next, this reaction was applied to the synthesis of Fmoc-Pro–Ala–ψ[(*E*)-CH=CH]–D-Leu–OMe **29** in combination with the *O*,*N*-acyl transfer reaction (Scheme 6). An *O*-acylated compound **26**, which was obtained by treatment of aziridine **25** with N^{α}-Fmoc-proline in the presence of TMSOTf, was 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, OC*H*$_2$Ph), 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 ^{t}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.

References and notes

1. (a) Duggan, M. E.; Karanewsky, D. S. *Tetrahedron Lett.* **1983**, *24*, 2935–2938; (b) Itsuno, S.; Tanaka, K.; Ito, K. *Chem. Lett.* **1986**, 1133–1136; (c) Tanner, D.; Somfai, P. *Tetrahedron Lett.* **1987**, *28*, 1211–1214; (d) Matsubara, S.; Kodama, T.; Utimoto, K. *Tetrahedron Lett.* **1990**, *31*, 6379–6380; (e) Legters, J.; Willems, J. G. H.; Thijs, L.; Zwanenburg, B. *Recl. Trav. Chim. Pays-Bas* **1992**, *111*, 59–68; (f) Tanner, D.; He, H. M.; Somfai, P. *Tetrahedron* **1992**, *48*, 6069–6078; (g) Kawabata, T.; Kiryu, Y.; Sugiura, Y.; Fuji, K. *Tetrahedron Lett.* **1993**, *34*, 5127–5130; (h) Church, N. J.; Young, D. W. *Tetrahedron Lett.* **1995**, *36*, 151–154 and references cited therein; (i) Burgaud, B. G. M.; Horwell, D. C.; Padova, A.; Pritchard, M. C. *Tetrahedron* **1996**, *52*, 13035–13050; (j) Rayner, C. M. *Synlett* **1997**, 11–21; (k) Ohno, H.; Mimura, N.; Otaka, A.; Tamamura, H.; Fujii, N.; Ibuka, T.; Shimizu, I.; Satake, A.; Yamamoto, Y. *Tetrahedron* **1997**, *53*, 12933–12946; (l) Cantrill, A. A.; Osborn, H. M. I.; Sweeney, J. *Tetrahedron* **1998**, *54*, 2181–2208; (m) Fleming, I.; Frackenpohl, J.; Ila, H. *J. Chem. Soc., Perkin Trans. 1* **1998**, 1229–1235; (n) Bongini, A.; Cardillo, G.; Orena, M.; Sandri, S.; Tomasini, C. *J. Chem. Soc., Perkin Trans. 1* **1986**, 1339–1344; (o) Bongini, A.; Cardillo, G.; Orena, M.; Sandri, S.; Tomasini, C. *J. Chem. Soc., Perkin Trans. 1* **1986**, 1345–1349; (p) Evans, D. A.; Faul, M. M.; Bilodeau, M. T.; Anderson, B. A.; Barnes, D. M. *J. Am. Chem. Soc.* **1993**, *115*, 5328–5329; (q) Coldham, I.; Collis, A. J.; Mould, R. J.; Rathmell, R. E. *J. Chem. Soc., Perkin Trans. 1* **1995**, 2739–2745; (r) Davis, F. A.; Reddy, G. V. *Tetrahedron Lett.* **1996**, *37*, 4349–4352; (s) Davis, F. A.; Zhou, P. *Tetrahedron Lett.* **1994**, *35*, 7525–7528.
2. (a) Tamamura, H.; Yamashita, M.; Muramatsu, H.; Ohno, H.; Ibuka, T.; Otaka, A.; Fujii, N. *Chem. Commun.* **1997**, 2327–2328; (b) Tamamura, H.; Yamashita, M.; Nakajima, Y.; Sakano, K.; Otaka, A.; Ohno, H.; Ibuka, T.; Fujii, N. *J. Chem. Soc., Perkin Trans. 1* **1999**, 2983–2996.
3. Oishi, S.; Tamamura, H.; Yamashita, M.; Odagaki, Y.; Hamanaka, N.; Otaka, A.; Fujii, N. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2445–2451.
4. (a) Kaltenbronn, J. S.; Hudspeth, J. P.; Lunney, E. A.; Michniewicz, B. M.; Nicolaides, E. D.; Repine, J. T.; Roark, W. H.; Stier, M. A.; Tinney, F. J.; Woo, P. K. W.; Essenburg, A. D. *J. Med. Chem.* **1990**, *33*, 838–845; (b) Tourwe, D.; Couder, J.; Ceusters, M.; Meert, D.; Burks, T. F.; Kramer, T. H.; Davis, P.; Knapp, R.; Yamamura, H. I.; Leysen, J. E.; van Binst, G. *Int. J. Peptide Protein Res.* **1992**, *39*, 131–136; (c) Christos, T. E.; Arvanitis, A.; Cain, G. A.; Johnson, A. L.; Pottorf, R. S.; Tam, S. W.; Schmidt, W. K. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 1035–1040; (d) Beresis, B.; Panek, J. S. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 1609–1614; (e) Wai, J. S.; Bamberger, D. L.; Fisher, T. E.; Graham, S. L.; Smith, R. L.; Gibbs, J. B.; Mosser, S. D.; Oliff, A. I.; Pompliano, D. L.; Rands, E.; Kohl, N. E. *Bioorg. Med. Chem.* **1994**, *2*, 939–947; (f) Bartlett, P. A.; Otake, A. *J. Org. Chem.* **1995**, *60*, 3107–3111; (g) Tamamura, H.; Hiramatsu, K.; Miyamoto, K.; Omagari, A.; Oishi, S.; Nakashima, H.; Yamamoto, N.; Kuroda, Y.; Nakagawa, T.; Otaka, A.; Fujii, N. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 923–928; (h) Tamamura, H.; Koh, Y.; Ueda, S.; Sasaki, Y.; Yamasaki, T.; Aoki, M.; Maeda, K.; Watai, Y.; Arikuni, H.; Otaka, A.; Mitsuya, H.; Fujii, N. *J. Med. Chem.* **2003**, *46*, 1764–1768; (i) Tamamura, H.; Hiramatsu, H.; Ueda, S.; Wang, Z.; Kusano, S.; Terakubo, S.; Trent, J. O.; Peiper, S. C.; Yamamoto, N.; Nakashima, H.; Otaka, A.; Fujii, N. *J. Med. Chem.* **2005**, *48*, 380–391.
5. Ibuka, T.; Mimura, N.; Ohno, H.; Nakai, K.; Akaji, M.; Habashita, H.; Tamamura, H.; Miwa, Y.; Taga, T.; Fujii, N. *J. Org. Chem.* **1997**, *62*, 2982–2991.

6. Fujii, N.; Nakai, K.; Tamamura, H.; Otaka, A.; Mimura, N.; Miwa, Y.; Taga, T.; Yamamoto, Y.; Ibuka, T. *J. Chem. Soc., Perkin Trans. 1* **1995**, 1359–1371.
7. Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092–4096.
8. McKinney, J. A.; Eppley, D. F.; Keenan, R. M. *Tetrahedron Lett.* **1994**, *35*, 5985–5988.
9. Yajima, H.; Fujii, N.; Funakoshi, S.; Watanabe, T.; Murayama, E.; Otaka, A. *Tetrahedron* **1988**, *44*, 805–819.
10. (a) Wakamiya, T.; Tarumi, Y.; Shiba, T. *Bull. Chem. Soc. Jpn.* **1974**, *47*, 2686–2689; (b) Tamamura, H.; Hori, T.; Otaka, A.; Fujii, N. *J. Chem. Soc., Perkin Trans. 1* **2002**, 577–580; (c) Sohma, Y.; Sasaki, M.; Hayashi, Y.; Kimura, T.; Kiso, Y. *Chem. Commun.* **2004**, 124–125.

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Facile Synthesis of Fluoroalkenes by Palladium-Catalyzed Reductive Defluorination of Allylic *gem*-Difluorides

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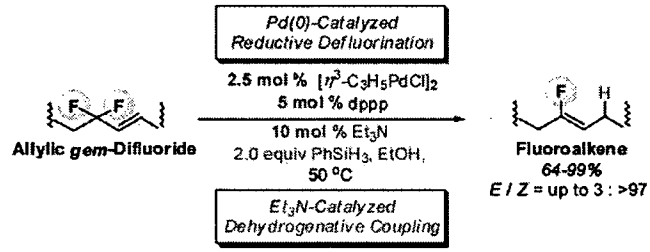
ABSTRACT



Chemo- and stereoselective synthesis of fluoroalkenes was achieved in excellent yields via Pd-catalyzed C–F bond activation. In this transformation, Et_3N plays a crucial role to produce reactive hydride species such as $Ph(EtO)SiH_2$ and $Ph(EtO)_2SiH$ by promoting dehydrogenative coupling. The reaction proceeds efficiently at 50 °C with a variety of substrates and is also useful for the synthesis of fluoroalkene peptidomimetics.

Although the development of catalytic reactions involving C−F bond activation represents a great challenge in organic chemistry,[1] only a few examples of Pd-catalyzed C−F bond activation have been reported to date.[2] Recently, several groups have disclosed cross-coupling reactions of alkyl or aryl fluorides through Pd-catalyzed C−F bond activation.[3] One example of Pd-catalyzed allylic C−F bond activation is the hydrogenolysis of allyl fluorides in the presence of Pd/C,[2a] which provides a facile method for the replacement of fluorine by hydrogen atom under mild conditions. A main drawback of this transformation exists in the chemoselectivity issue: the reaction always gives a mixture of two products, one formed by replacement of the fluorine by a hydrogen atom followed by saturation of the double bond, and the other resulting from the simple hydrogenation of the double bond. On the basis of these pioneering works, we envisioned that the reaction of allylic *gem*-difluoride **1** with a homogeneous palladium catalyst in the presence of appropriate additives having an affinity to fluorine could promote the elimination of fluorine, leading to the generation of a fluorinated π-allyl palladium intermediate **2**. By a chemoselective reaction with an appropriate nucleophile, this intermediate is expected to be transformed to (*Z*)-fluoroalkene **3**,[4] which constitutes an

(1) Recent reviews for activation and functionalization of C−F bonds, see: (a) Kiplinger, J. L.; Richmond, T. G.; Osterberg, C. E. *Chem. Rev.* **1994**, *94*, 373−431. (b) Burdeniuc, J.; Jedlicka, B.; Crabtree, R. H. *Chem. Ber./Recl.* **1997**, *130*, 145−154. (c) Murai, S. *Activation of Unreactive Bonds and Organic Synthesis*; Springer: New York, 1999; pp 243−269. (d) Hiyama, T. *Organofluorine Compounds Chemistry and Applications*; Springer: New York, 2000.

(2) Pd-catalyzed C−F bond activation: (a) Hudlicky, M. *J. Fluorine Chem.* **1989**, *44*, 345−359. (b) Hintermann, L.; Läng, F.; Maire, P.; Togni, A. *Eur. J. Inorg. Chem.* **2006**, 1397−1412. (c) Torrens, H. *Coord. Chem. Rev.* **2005**, *249*, 1957−1985. (d) Ichikawa, J.; Nadano, R.; Ito, N. *Chem. Commun.* **2005**, 4425−4427.

(3) Pd-catalyzed cross coupling via C−F bond activation: (a) Widdowson, D. A.; Wilhelm, R. *Chem. Commun.* **1999**, 2211−2212. (b) Wilhelm, R.; Widdowson, D. A. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3808−3813. (c) Widdowson, D. A.; Wilhelm, R. *Chem. Commun.* **2003**, 578−579. (d) Mi, Kim, Y.; Yu, S. *J. Am. Chem. Soc.* **2003**, *125*, 1696−1697. (e) Terao, J.; Ikumi, A.; Kuniyasu, H.; Kambe, N. *J. Am. Chem. Soc.* **2003**, *125*, 5646−5647.

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important class of molecules such as peptide isosteres,[5a-d] enzyme inhibitors,[5e] and liquid-crystalline materials.[5f]

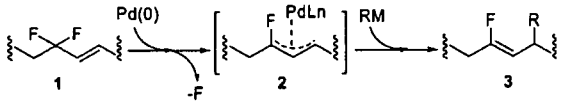
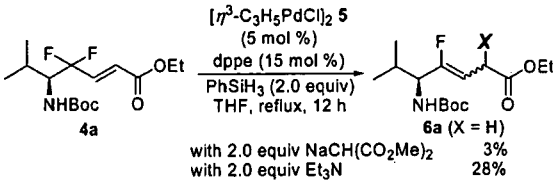


Figure 1. Synthesis of fluoroalkene via Pd catalysis.

Herein, we present a general catalytic system for the facile synthesis of fluoroalkene skeleta from readily available allylic difluorides by Pd-catalyzed reductive defluorination with phenylsilane. Some insight into the mechanistic aspect of this transformation is also described.

In an initial study, we investigated the Pd-catalyzed allylic alkylation[6] of γ,γ-difluoro-α,β-enoate **4a**, which can be readily prepared from isobutyl aldehyde[7] by modifying Honda's protocol.[8] Various additives were screened for the reaction of enoate **4a** with dimethyl sodiomalonate in the presence of a catalytic amount of $[\eta^3\text{-}C_3H_5PdCl]_2$ (**5**) and dppe. Although TMSCl, Et_4Si, $(EtO)_4Si$, or Me_3Al did not promote the desired defluorination reaction, we found that, when using $PhSiH_3$, a small amount of reductive defluorinated product **6a** was obtained (3%), without forming alkylated products **6b** [X = $CH(CO_2Me)_2$] (Scheme 1). Since

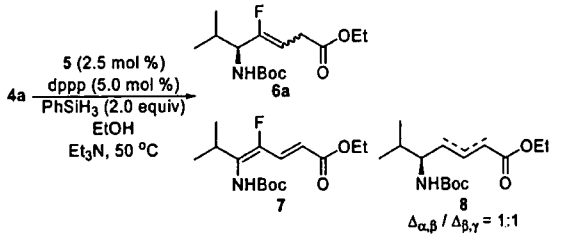
Scheme 1. Pd-Catalyzed Allylic Alkylation



the reduced product **6a** was not detected without using dimethyl sodiomalonate, we postulated that basicity of sodium malonate plays an important role in this reaction. Therefore, we tested the reaction in the presence of triethylamine instead of sodium dimethyl malonate to obtain **6a** in increased yields (28%).

After screening of the reaction conditions, we were pleased to find that the combination of dppp and EtOH at 50 °C afforded the expected products **6a** in up to 96% yield (Table 1, entry 1). However, a small amount of undesired diene **7**,

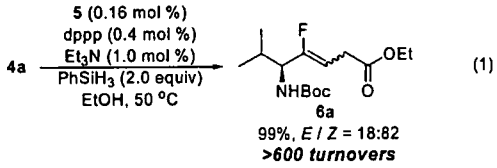
Table 1. Effect of the Amount of Et_3N[a]



entry	Et_3N [equiv]	yield of **6a**[b] [%]	*E*:*Z*[c]
1	2.0	<96	20:80
2	1.0	99	17:83
3	0.5	99	15:85
4	0.1	99	9:91
5	0.01	87	6:94

[a] Reactions were carried out with **4a** (0.13 mmol), $PhSiH_3$ (0.25 mmol), Et_3N, $[\eta^3\text{-}C_3H_5PdCl]_2$ **5** (2.5 mol %), and dppp (5.0 mol %) in EtOH (2.5 mL) at 50 °C for 2 h. [b] Yields of isolated products. [c] The ratio of *E*/*Z* isomer was determined by ^1H NMR spectroscopy.

presumably produced by Et_3N-assisted β-hydride elimination of a plausible intermediate of the type **2**, was observed in an irreproducible fashion (<10%). Therefore, we performed the reaction with 1.0 equiv of Et_3N to obtain the desired defluorinated products in 99% yield without the formation of the β-elimination product **7** (entry 2). Unexpectedly, the reduction of Et_3N to a catalytic amount improves the *E*/*Z* selectivity (entries 3−5). Of particular interest is the formation of a small amount of the bis-defluorinated product **8**, which was obtained in 8% yield when using 1 mol % of Et_3N.[9] Finally, the reaction can be conducted in quantitative conversion at catalyst loadings as low as 0.16 mol % (eq 1).



(1)

With these results in hand, we examined the scope of this reaction with readily available and synthetically useful

(4) For a recent example of the fluoroalkene synthesis: (a) Yoshida, M.; Komata, A.; Hara, S. *Tetrahedron* **2006**, *62*, 8636−8645 and references cited therein.

(5) (a) Dutheuil, G.; Couve-Bonnaire, S.; Pannecoucke, X. *Angew. Chem., Int. Ed. Engl.* **2007**, *46*, 1290−1292. (b) Narumi, T.; Niida, A.; Tomita, K.; Oishi, S.; Otaka, A.; Ohno, H.; Fujii, N. *Chem. Commun.* **2006**, 4720−4722. (c) Nakamura, Y.; Okada, M.; Sato, A.; Horikawa, H.; Koura, M.; Saito, A.; Taguchi, T. *Tetrahedron* **2005**, *61*, 5741−5753. (d) Allmendinger, T.; Felder, E.; Hungerbühler, E. *Tetrahedron Lett.* **1990**, *31*, 7301−7304. (e) Bey, P.; McCarthy, J. R.; McDonald, I. A. *ACS Symp. Ser.* **1991**, *456*, 105−133 and references cited therein. (f) Yokokoji, O.; Shimizu, T.; Kumai, S. JP 08040952, 1996 [*Chem. Abstr.* **1996**, *124*, 316586].

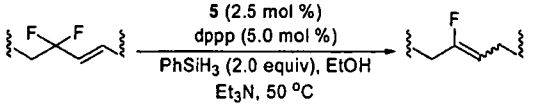
(6) For review, see: (a) Tsuji, J. *Palladium Reagents and Catalysis, Innovations in Organic Synthesis*; Wiley: New York, 1995. (b) Trost, B. M.; Van Vranken, D. L. *Chem. Rev.* **1996**, *96*, 395−422. (c) Johannsen, M.; Jorgensen, K. A. *Chem. Rev.* **1998**, *98*, 1689−1708. (d) Paquin, J.-F.; Lautens M. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer-Verlag: Berlin, Germany, 2004: Vol. 2, pp 73−95 and references cited therein. (e) Trost, B. M.; Crawley, M. L. *Chem. Rev.* **2003**, *103*, 2921−2943.

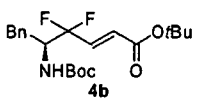
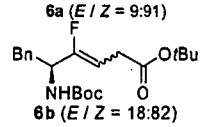
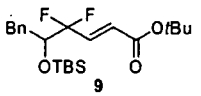
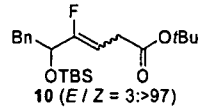
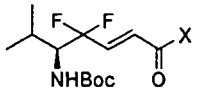
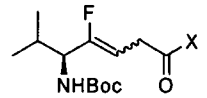
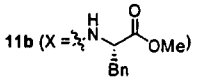
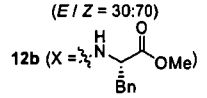
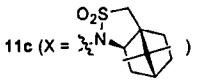
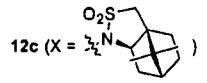
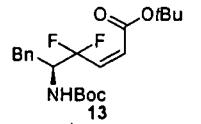
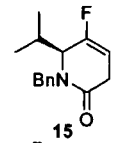
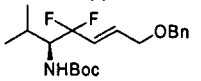
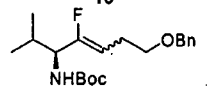
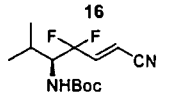
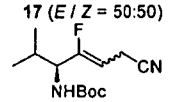
(7) (a) Otaka, A.; Watanabe, J.; Yukimasa, A.; Sasaki, Y.; Watanabe, H.; Kinoshita, T.; Oishi, S.; Tamamura, H.; Fujii, N. *J. Org. Chem.* **2004**, *69*, 1634−1645 and references cited therein.

(8) Honda, T.; Wakabayashi, H.; Kanai, K. *Chem. Pharm. Bull.* **2002**, *50*, 307−308.

(9) Formation of defluorinated product **8** could be rationalized by reaction of π-allyl Pd intermediate by hydride at the fluorinated carbon to give allyl fluoride followed by re-reductive defluorination.

Table 2. Pd- and Et_3N-Catalyzed Reductive Defluorination[a]



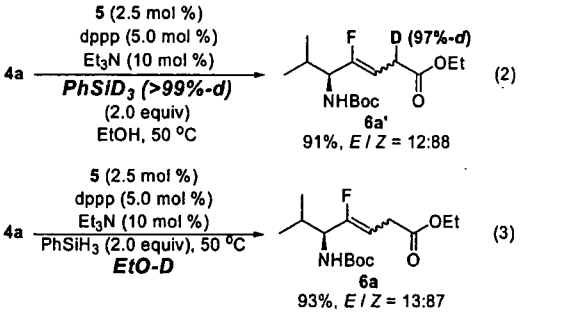
entry	substrate	product(s) (*E*:*Z*)[b]	yield [%][c]
1	**4a**	**6a** (*E* / *Z* = 9:91)	99
2	 **4b**	 **6b** (*E* / *Z* = 18:82)	97
3	 **9**	 **10** (*E* / *Z* = 3:>97)	91
4	 **11a** (X = NH_2)	 **12a** (X = NH_2) (*E* / *Z* = 30:70)	64
5	 **11b** (X =)	 **12b** (X =) (*E* / *Z* = 21:79)	97
6	 **11c** (X =)	 **12c** (X =) (*E* / *Z* = 3:>97)	76[d]
7	 **13**	**6c** (*E* / *Z* = 26:74)	99
8	 **14**	 **15**	99
9	 **16**	 **17** (*E* / *Z* = 50:50)	77
10	 **18**	 **19** (*E* / *Z* = 14:86)	73

[a] All reactions were carried out with allylic *gem*-difluoride (1.0 equiv), $PhSiH_3$ (2.0 equiv), Et_3N (10 mol %), $[\eta^3\text{-}C_3H_5PdCl]_2$ **5** (2.5 mol %), and dppp (5.0 mol %) in EtOH at 50 °C for 2 h. [b] Yields of isolated products. [c] The ratio of *E*/*Z* isomer was determined by ^1H NMR spectroscopy. [d] A trace amount of starting material was detected by ^1H NMR spectroscopy.

substrates possessing various functional groups (Table 2). In all cases, the reaction was completely chemoselective, and good to excellent yields of fluoroalkenes were obtained with modest to high selectivity. *N*-Boc amide, esters, and substituents such as alkyl and siloxy groups introduced at the δ-carbon did not affect the reaction (entries 1−3). Furthermore, amides, including a peptide, **11a−c** (entries 4−6), (*Z*)-enoate **13** (entry 7), and lactam **14** (entry 8), can be employed to give the desired fluoroalkenes **12a−c**, **6c**, and **15**. The applicability of this reaction to the substrates without a conjugated carbonyl moiety such as benzyl ether **16** and nitrile **18** (entries 9 and 10) clearly demonstrates an advantage of this reaction over the known related reduction using a single-electron donor,[7a] which is limited to α,β-unsaturated carbonyl compounds.

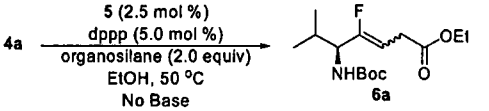
To gain some insight into the mechanism of this transformation, we examined isotopic labeling experiments (Scheme 2). The reaction with $PhSiD_3$ in EtOH induced deuterium

Scheme 2. Isotopic Labeling Experiments



incorporation at the α-position (97% -*d*) (eq 2). On the other hand, the reaction performed in EtO−D with $PhSiH_3$ promoted no deuterium incorporation (eq 3), suggesting that the introduced hydrogen originates from $PhSiH_3$. Furthermore, to determine the hydride species, we performed the reaction with $PhSiH_3$, $Ph(EtO)SiH_2$, and $Ph(EtO)_2SiH$ in the absence of Et_3N (Table 3). While no reaction was observed

Table 3. Investigation of the Hydride Species[a]



entry	organosilane	yield of **6a**[b] [%]	*E*:*Z*[c]
1	$PhSiH_3$	*d*	
2	$Ph(EtO)SiH_2$	83	13:87
3	$Ph(EtO)_2SiH$	70	45:55

[a] Reactions were carried out with **4a** (0.13 mmol), organosilane (0.25 mmol), $[\eta^3\text{-}C_3H_5PdCl]_2$ **5** (2.5 mol %), and dppp (5.0 mol %) in EtOH (2.5 mL) at 50 °C for 2 h. [b] Yields of isolated products. [c] The ratio of *E*/*Z* isomers was determined by ^1H NMR spectroscopy. [d] No reaction was observed.

with $PhSiH_3$ (entry 1), the reactions with $Ph(EtO)SiH_2$ and $Ph(EtO)_2SiH$ proceeded smoothly to provide the desired defluorinated products **6a** (entries 2 and 3). Therefore, these alkoxysilanes would be considered as the actual reactive species. On the basis of these results and Buchwald's observation,[10] Et_3N plays a crucial role for the generation of these active hydride sources such as $Ph(EtO)SiH_2$ and $Ph(EtO)_2SiH$ by promoting catalytic dehydrogenative coupling of $PhSiH_3$ with EtOH.[11] Once those active species have

been generated, they could work both as reducing agents to generate Pd^0 complexes and as hydride sources.

These results could explain the dependence of the chemical yield and stereoselectivity on the amount of Et_3N in Table 1. A catalytic amount of Et_3N would generate the reactive alkoxysilanes in an appropriate rate through dehydrogenative coupling, while the excess of Et_3N considerably accelerates this process, which would consume reactive species to cause undesired side reactions.

In summary, we have developed a novel general method for the synthesis of fluoroalkenes under mild conditions utilizing Pd-catalyzed reductive defluorination. This is an unparalleled example of a highly effective catalytic synthesis of a fluoroalkene skeleton, including peptidomimetics. Mechanistic study has proven that Et_3N promotes the dehydrogenative coupling of $PhSiH_3$ with EtOH to produce reactive species.

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Supporting Information Available: Representative procedures and spectral and analytical data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL701627V

(10) Involvement of alkoxysilane accounts for the titanium-catalyzed hydrosilylation of imine with $PhSiH_3$, see: Verdaguer, X.; Lange, U. E. W.; Reding, M. T.; Buchwald, S. L. *J. Am. Chem. Soc.* **1996**, *118*, 6784–6785.

(11) For examples of base-catalyzed dehydrogenative coupling of silanes with alcohols, see: (a) Lukevics, E.; Dzintara, M. *J. Organomet. Chem.* **1984**, *271*, 307–317. (b) Gilman, H.; Dunn, G. H.; Hartzfeld, H.; Smith, A. G. *J. Am. Chem. Soc.* **1955**, *77*, 1287–1288. (c) Bazant, V.; Chvalovsky, V.; Rathousky J. In *Organosilicon Compounds*; Publishing House of the Czechoslovak Academy of Science: Prague, Czechoslovakia, 1965: pp 54–56.

Design and synthesis of all diastereomers of cyclic pseudo-dipeptides as mimics of cyclic CXCR4 pentapeptide antagonists†

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The four diastereomers of 2,5-bis[(3-guanidino)propyl]-1-[3-(4-hydroxyphenyl)propionyl]-7-(2-naphthylacetyl)-1,4,7-triazacycloundec-9-en-3-one (**54**–**57**) and of 2,5-bis[(3-guanidino)propyl]-1-(4-hydroxyphenylacetyl)-7-(2-naphthylacetyl)-1,4,7-triazacycloundec-9-en-3-one (**58**–**61**) were synthesized by a divergent methodology from L- and D-glutamic acids. The 11-membered ring core was made by ring closing metathesis of linear bis(allylamines), and the guanidyl functions were introduced by a simultaneous double Mitsunobu reaction using bis(Boc)guanidine. These compounds were designed to mimic cyclic pentapeptide FC131 (c[Gly-D-Tyr-Arg-Arg-Nal]).

Introduction

CXCR4 chemokine receptor is involved in HIV-1 infection of T cells. Attachment of virus envelope glycoprotein gp120 onto cell surface proteins CD4 and CXCR4 leads to membrane fusion and subsequent virus entry into the cell.[1,2] Thus, CXCR4 is considered an important therapeutic target. Several potent CXCR4 antagonists have been developed so far. Among these, we have previously identified a β-sheet-like 14-residue peptide[3] T140, and its down-sized analogues, cyclic pentapeptide FC131[4] (c[Gly-D-Tyr-Arg-Arg-Nal]) as potent and specific CXCR4 antagonists. These were characterized as HIV-1 entry inhibitors (Fig. 1).[5] Several other non-peptidic, low-molecular-weight CXCR4 antagonists have also been reported to inhibit HIV-1 infection through CXCR4, such as KRH2731[6] and AMD3100.[7] AMD3100 was abandoned as an anti-HIV drug[8] because of a lack of *in vivo* efficacy and undesirable side effects; nevertheless, AMD070, an orally-available derivative of AMD3100 has recently been described to be as potent as AMD3100, and it will be further investigated as an HIV drug in clinical trials.[9,10]

The use of constrained peptides or peptide mimics has become popular for increasing receptor affinity, for the development of new drugs, to investigate bioactive conformations, and to increase duration of action. On native peptides, constraints can be introduced by linkage between two points of the peptide (NH to NH,[11] NH to CO_2H[12] or disulfide bridge[13]) to fix a large secondary structure, generally a helix or sheets. The small secondary structures (turn, small helix, hairpin and *E*- or *Z*-amide bonds) can also be induced, stabilized or fixed by introduction in the sequence of one or several small constrained (Freidinger lactams[14] or azabicycloalkanes[15,16]), bulky (alkylprolines[17]) or rigid (dipeptide isosteres[18,19]) unnatural amino acids. Finally, small peptides or parts of peptides can be converted to small semi-peptidic or peptide-like structures, synthesized to mimic peptide backbones, and possessing all the necessary functional groups for activity.[20]

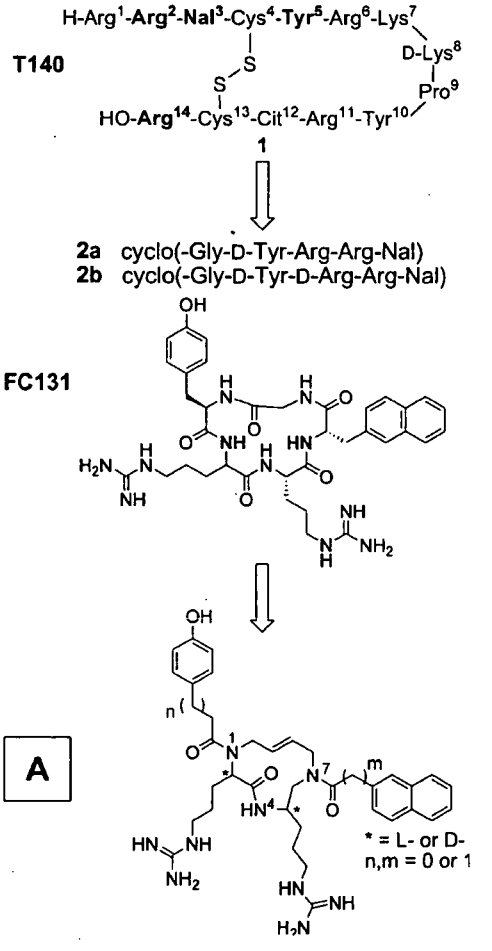

Fig. 1 Down-sizing CXCR4 antagonists.

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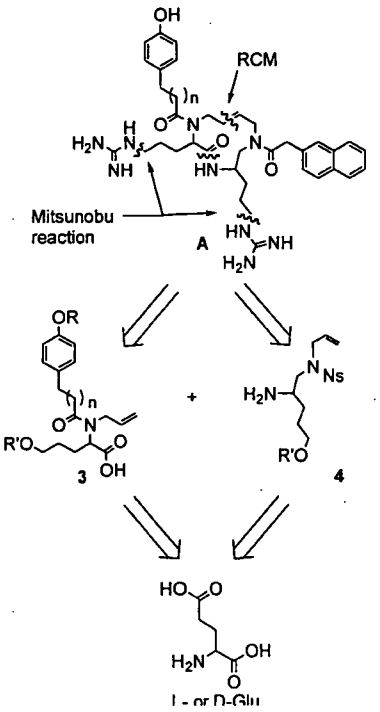
In our research on the development of new CXCR4 receptor antagonists, we are looking for compounds with a lower molecular weight than our current active peptide FC131, and with a more stable and active structure. Our previous studies on FC131 led us to modify its sequence and to use a linkage between two points of the peptide by replacing Gly[1] by an alkyl chain or disulfide bridge.[13a] Unfortunately these modifications resulted in significant loss of activity. Unnatural amino acids were also introduced to the peptide sequence to perform structure–activity relationship studies on the peptide backbone. For example, the replacement of Arg[4] by constrained amino acids *cis*- or *trans*-4-guanidino-Pro furnished peptides with similar activities to that of the parent peptide, showing the importance of the constrained structure of the peptide backbone.[13a] On the other hand, introduction of *E*-alkene dipeptide isosteres in positions 4–5 (Arg–Nal) and 5–1 (Nal–Gly) led to peptides with similar pharmacophore orientations and distances, and revealed the importance of amide bonds on the backbone of the peptide.[19] We are also interested in the synthesis of small semi-peptidic compounds containing pharmacophores of FC131. We have recently reported that a 3,6-dihydropyridin-2-one analog containing two guanidine residues and a naphthyl group retains moderate activity as a CXCR4 antagonist.[21] We are now interested in a less-rigid backbone structure, on which it would be easy to vary side-chain length and chirality. Design of compounds of type **A** was performed by removing Gly from the parent peptide and making a linkage between the nitrogens (bold) of Arg and Nal (Fig. 1). Such a structure could possess a propionyl or acetyl (*n*, $m = 0$ or 1) side chain to replace tyrosine and naphthylalanine, and propenyl linkage between nitrogens 1 and 7 to constrain dipeptides and form 11-membered ring compounds.

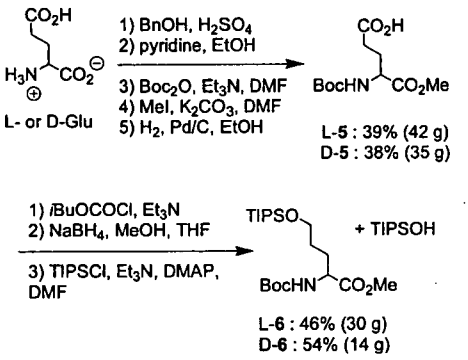
Retrosynthetically, the ring can be closed by ring closing metathesis (RCM) between two allylamine residues. RCM has been shown to be a useful method for synthesizing constrained peptides and forming 8–10-membered rings[20a,22] and 13–20-membered ring cycles.[11,12,20b,c,d] Nevertheless, the only reported example of RCM on an 11-membered, ring-constrained peptide failed,[11] but we expected that cyclization would be possible with a new generation of catalysts. Cyclization of these peptides was reported to be possible without protection of the amide bond to increase *cis* conformation for cycles of up to 10-membered rings. To simplify the synthesis, the two nucleophilic guanidyl groups should be introduced in the last steps by the Mitsunobu reaction with corresponding alcohols (Scheme 1). Our two fragments were *N*-substituted 5-hydroxynorvaline acids **3** and diamines **4**. Both of these could be synthesized from the same precursor, L- or D-glutamic acid, to give easy access to the four possible diastereomers.

Results and discussion

Synthesis of 5-hydroxynorvaline, also called pentahomoserine, has been reported many times in protected and unprotected forms.[23] We chose to use the procedure described by Kokotos[24] from glutamic acid (Scheme 2). L- and D-Glu were efficiently monobenzylated using benzyl alcohol, H_2SO_4 and pyridine;[25] the amine was protected with Boc; the α-acid was converted to a methyl ester, and the benzyl ester was removed by hydrogenation with Pd/C to give the free acids **5**, on a large scale. Reduction of acids to alcohols using the mixed anhydrides and protection with TIPSCl provided



Scheme 1 Retrosynthesis of compounds A.

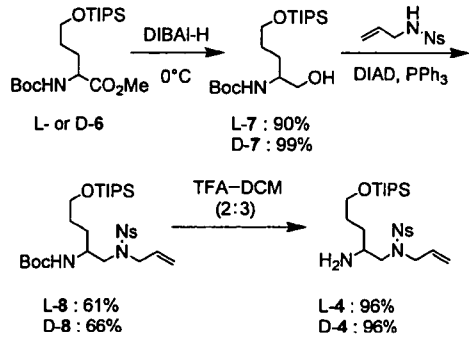


Scheme 2 Synthesis of protected L- and D-5-hydroxynorvaline.

the fully protected L-5-hydroxynorvaline L-**6** at a yield of 46% (82% brsm), and the D-5-hydroxynorvaline D-**6** in a similar manner and yield. Both amino acids **6** were obtained as inseparable mixtures with TIPSOH, but this alcohol did not interfere with the next steps, and yields were estimated by comparing ^{1}H-NMR integration of TIPS and other signals.

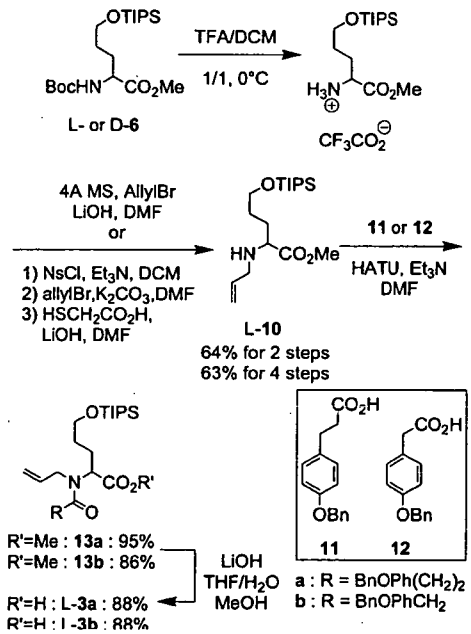
For the synthesis of diamines L- and D-**4**, esters **6** were reduced to alcohols **7** using DIBAl-H in THF (Scheme 3). Protected amines **8** were obtained by the Mitsunobu reaction between alcohols **7** and *ortho*-nitrobenzenesulfonyl allylamine (Ns-allylamine) **9**, with moderate yields. Boc removal to form both amines L- and D-**4** in TFA–DCM (2 : 3) were carried out just before coupling with acids **3**.

For the synthesis of acids **3**, conversion of Boc carbamate to allyl amine was carried out on a small scale with a two-step procedure. Boc removal with TFA and selective mono-allylation of the free amine using the Kim protocol gave allyl amine **10**.[26] Unfortunately, we were not able to obtain a good yield of monoallylamine on the



Scheme 3 Synthesis of amines 4.

5 g scale (35%) by this method, and diallylamine became the major product. We decided to use a longer but more reliable method using an *ortho*-nitrobenzenesulfonyl (Ns) protecting group (Scheme 4). Boc carbamate was removed with TFA and replaced by a nosyl group by reaction with NsCl and Et_3N in DMF. Nosyl amine was easily allylated using allyl bromide and potassium carbonate in DMF, and the nosyl group was removed using mercaptoacetic acid under basic conditions to give **10**, with a 63% yield, from **6** on a 5 g scale. Allylamine **10** was then coupled with acids **11** and **12** using *O*-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HATU)[27] in DMF to give allylamides **13a** and **13b**, with 95 and 86% yields, respectively. Saponification of the methyl esters with LiOH furnished the desired acids L-**3a** and L-**3b**.[28]

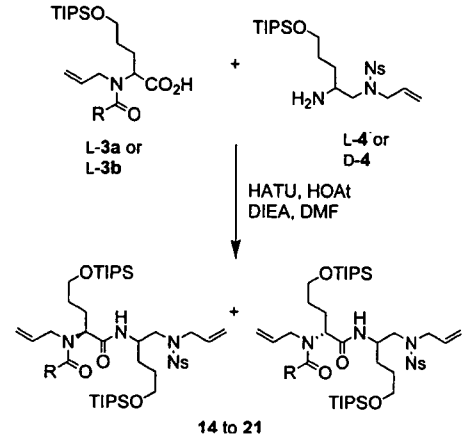


Scheme 4 Synthesis of acids 3a and 3b.

The amino acid coupling of acid L-**3a** and amine L-**4** proceeded completely using HATU, 1-hydroxy-7-azabenzotriazole (HOAt) and DIEA in DMF, but gave a 1 : 1 mixture of two inseparable diastereomers, **14** and **15** (Scheme 5, Table 1, entry 1). We were not able to suppress epimerization of the acid during the coupling step. We decided to use this epimerization to our advantage for the synthesis of the different diastereomers. Acid L-**3a** was coupled

Table 1 Amino acid coupling of compounds 3 and 4

	Acid	Amine	R	Products (yield)
1	L-**3a**	L-**4**	$BnOPh(CH_2)_2$	**14/15** (88%)
2	L-**3a**	D-**4**	$BnOPh(CH_2)_2$	**16/17** (91%)
3	L-**3b**	L-**4**	$BnOPhCH_2$	**18** (43%)
				19 (48%)
4	L-**3b**	D-**4**	$BnOPhCH_2$	**20** (37%)
				21 (53%)



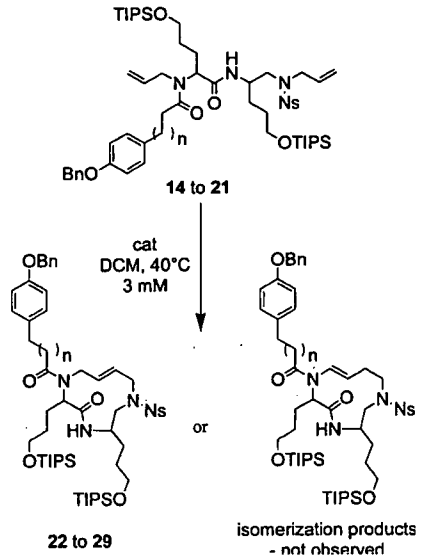
Scheme 5 Synthesis of dienes 14 to 21.

with amine D-**4** using the same conditions and gave a mixture of **16** and **17**. Acid L-**3b** was coupled with amines L-**4** and D-**4** to give separable mixtures of diastereomers **18/19** and **20/21** in good yields.

RCM of allylamines has been reported to react differently depending on the temperature and the catalyst used. Grubb's I and Grubb's II catalysts have been reported to lead to partial or total isomerization of the olefin, depending on reaction temperature and substrates, to give cyclic or acyclic enamides.[22e,29] This isomerization process does not seem to be general, indeed normal reactivity has also been reported on similar substrates with both catalysts.[30] We first attempted RCM on the diene mixture **14/15** using 0.2 eq. of Grubb's catalysts of first and second generation, in CH_2Cl_2 at reflux and high dilution (6 to 3 mM, Scheme 6). Reaction with Grubb's I catalyst proceeded slowly and was not completed within 24 h. A low yield of the desired separable 11-membered ring diastereomers **22** and **23** was nevertheless obtained (Table 2, entry 1). Surprisingly, in contrast to the reported observation of RCM with allylamines, reaction with Grubb's II catalyst was completed after 12 h and gave a good yield of diastereomers **22** and **23**. (Table 2, entry 2). The structures of **22** and **23** were confirmed using COSY NMR spectra of **22** and **39** (derived from **23**). Both

Table 2 RCM of linear dienes

	Diene	*n*	Grubb's catalyst	Product (yield)
1	**14/15**	1	I	**22** (13%) + **23** (25%)
2	**14/15**	1	II	**22** (43%) + **23** (42%)
3	**16/17**	1	II	**24** (38%) + **25** (35%)
4	**18**	0	II	**26** (69%)
5	**19**	0	II	**27** (65%)
6	**20**	0	II	**28** (71%)
7	**21**	0	II	**29** (67%)

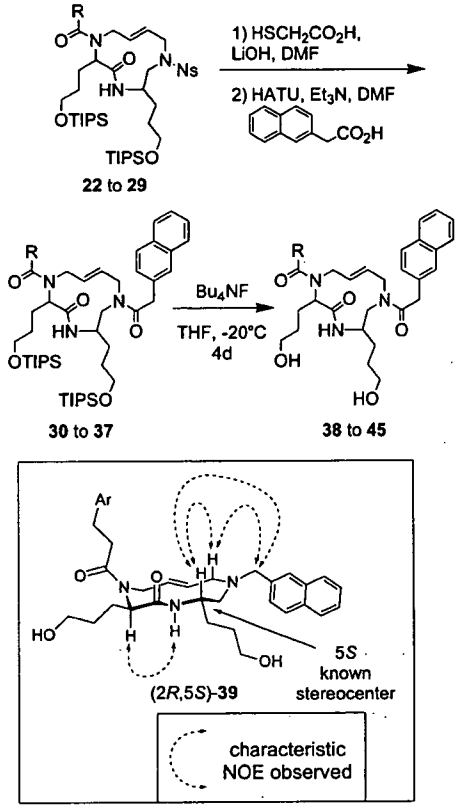


Scheme 6 RCM of diallylamines **14–21** to 11-membered rings **22–29**.

compounds had the desired but-2-ene-1,4-diamine structure, but enamide structures coming from olefin isomerization anticipated for the reaction with Grubb's II catalyst at high temperature were not observed.[31]

The diastereomeric mixture **16/17** and the single diastereomers **18–21** were then cyclized using Grubb's II catalyst in DCM at 40 °C, to give products **24–29** in good yields. All the compounds appeared to have *E*-olefins; *Z*-olefins were not observed.

Introduction of naphthylacetyl side chains was easily achieved by removal of nosyl groups using mercaptoacetic acid under basic conditions on cycles **22–29** to form the free amines, which were directly acylated with naphthylacetic acid using HATU and triethylamine, to give compounds **30–37** (Scheme 7, Table 3). These compounds were then submitted to tetrabutylammonium fluoride (TBAF) solution at −20 °C to remove both TIPS groups. The first TIPS group was completely removed in less than 24 h (by TLC), but removal of the second TIPS appeared to be very slow and needed a large excess of TBAF. Increasing the temperature up to −20 °C accelerated the rate of deprotection but led to formation of unidentified side products on TLC and coloration of the solution. After 72–96 h at −20 °C with 6 eq. TBAF, diols **38–45** were isolated in moderate to good yields. The structures and relative stereochemistry of diastereomers were established based on the known stereochemistry at carbon 5 and one- and two-dimensional NMR experiments. The majority of the NMR signals were well resolved at distinct chemical shifts for product



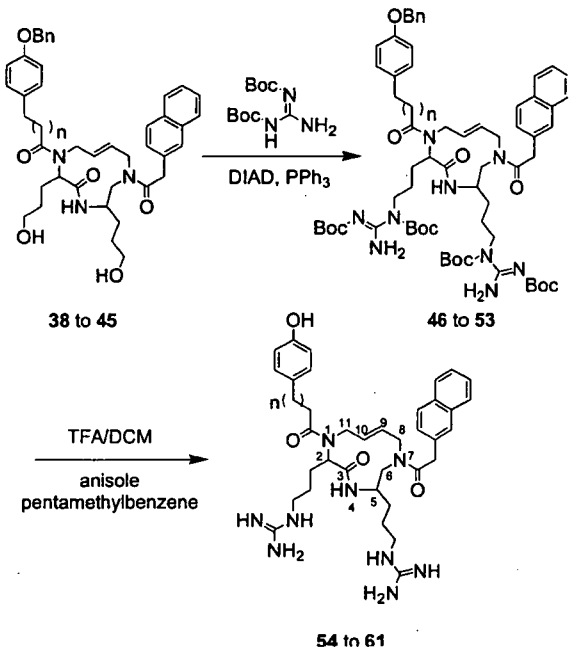
Scheme 7 Introduction of naphthylacetyl side chain and removal of TIPS protecting groups. Expected structure of compound **39** using NOE correlation.

39. All protons were assigned using the COSY experiment, which established their linear sequence around the macrocycle. A large coupling constant for NH proton (J_{NH} 9.5 Hz),[32] indicating a dihedral angle of −130° or −110°, and observation in the NOESY spectra of a correlation between C_2 proton and NH allowed us to attribute the (2*R*,5*S*) stereochemistry to compound **39**, and therefore to other diastereomers. Unfortunately, we were not able to get clearer proof of the stereochemistry at C_2.

Introduction of a guanidyl group *via* the Mitsunobu reaction can be achieved using bis- or tris-Boc- or Cbz-guanidine (Scheme 8).[23c,33] We decided to use the bis-Boc-guanidine for the acidic cleavage of the Boc group and because bis-Boc has only one reactive site while tris-Boc has the possibility to react twice. The reaction worked well with simple alcohols, with yields up to 90%,[33c] but gave average results on amino acids, with yields of 40–63%. In

Table 3 Introduction of naphthyl side chain and TIPS deprotection

	Ns amine	R	Acyl product (yield, 2 steps)	Diol (yield)
1	(2*S*,5*S*)-**22**	$BnOPh(CH_2)_2$	**30** (63%)	**38** (78%)
2	(2*R*,5*S*)-**23**	$BnOPh(CH_2)_2$	**31** (80%)	**39** (74%)
3	(2*R*,5*R*)-**24**	$BnOPh(CH_2)_2$	**32** (44%)	**40** (72%)
4	(2*S*,5*R*)-**25**	$BnOPh(CH_2)_2$	**33** (65%)	**41** (72%)
5	(2*S*,5*S*)-**26**	$BnOPhCH_2$	**34** (63%)	**42** (59%)
6	(2*R*,5*S*)-**27**	$BnOPhCH_2$	**35** (66%)	**43** (98%)
7	(2*R*,5*R*)-**28**	$BnOPhCH_2$	**36** (58%)	**44** (89%)
8	(2*S*,5*R*)-**29**	$BnOPhCH_2$	**37** (68%)	**45** (78%)



Scheme 8 Synthesis of final compounds.

our case, the double reaction occurred, but products **46–53** were isolated as inseparable mixtures with triphenylphosphine oxide. The reaction was not completed in the case of products **38** and **41** (Table 4, entries 1 and 4). Starting materials were recovered and resubmitted to Mitsunobu conditions. Enantiomers **42** and **44** were not soluble in THF, so the reaction was carried out in THF–toluene–DMF (6 : 1 : 1) solutions (Table 4, entries 5 and 7). The mixtures of products and Ph_3PO were directly submitted to acidic cleavage of the protecting groups. All protecting groups, including benzyl ether, could be cleaved in acidic conditions using TFA–CH_2Cl_2 (3: 1), with a large excess of anisole and pentamethylbenzene as scavengers of benzyl cations.[34] Products **54–61** were purified by semi-preparative HPLC and were isolated in 9–40% yields from diols **38–45**.

These compounds were tested as CXCR4 receptor antagonists using inhibition of [^{125}I]-SDF-1 binding to CXCR4 transfectants. Compounds **54** and **55** retained activity against CXCR4 receptor (IC_{50} 3.4 and 3.2 μM), despite significant loss of activity when compared to the native peptide (FC131, IC_{50} 0.004 μM).[44] As observed in cyclic pentapeptides, diastereomers **56** and **57**, containing a D configuration for the second Arg, showed no activity. This confirms the importance of this chiral center for antagonist activity. The four compounds containing the less flexible phenol side chain, **58–61**, lost all antagonist activity.

Conclusion

We report here the divergent synthesis of tetra-substituted 11-membered ring compounds **54–61** from L- and D-glutamic acids. Two of these compounds, **54** and **55**, showed antagonist activity against CXCR4 receptors, and could be potential scaffolds for the development of novel low-molecular-weight CXCR4 antagonists.

Experimental

Methyl (*S*)-2-(*N*-Boc-amino)-5-(triisopropylsilyloxy)pentanoate (L-6) [Boc-Hnv(TIPS)-OMe]

Methyl (*S*)-2-(*N*-Boc-amino)-5-hydroxypentanoate (18.4 g, 74.5 mmol) was dissolved in DMF (100 ml) and was treated with triethylamine (20.8 ml, 2 eq.) and TIPSCl (19.1 ml, 1.2 eq.) and stirred for 5 h at rt. The reaction was partitioned between ether and HCl 0.5 M. The organic layer was washed twice with HCl (0.5 M). The combined aqueous layers were extracted with ether. The combined ether fractions were washed with water and brine, dried over $MgSO_4$ and concentrated. The oil was purified by flash chromatography using 90 : 10 hexane–ethyl acetate to afford an inseparable mixture (3 : 1) of L-**6** and TIPSOH (29.9 g, 87%). ^{1}H NMR ($CDCl_3$) δ 5.20 (d, 1H, $J = 7.8$ Hz), 4.30 (q, 1H, $J = 7.5$ Hz), 3.73 (s, 3H), 3.70 (t, 2H, $J = 6.3$ Hz), 1.90 (m, 1H), 1.75 (m, 1H), 1.59 (m, 2H), 1.44 (s, 9H), 1.06 (m, 27 H (21H + TIPSOH)). ^{13}C ($CDCl_3$) δ 174.3, 156.2, 80.1, 62.8, 53.6, 52.4, 29.2, 28.8, 28.4, 18.0, 17.8, 12.3, 12.0. FTIR (cm^{-1}) 2941, 2865, 1717, 1503, 1462, 1365, 1166, 1104, 1012, 881. MS (FAB$^+$) : $m/z = 404$ (M + H$^+$).

(*S*)-2-(*N*-Boc-amino)-5-(triisopropylsilyloxy)pentan-1-ol (L-7). The 3 : 1 mixture of L-**6** and TIPSOH (10 g, 24.8 mmol of **6**) was dissolved in THF (250 ml) and cooled down to −5 °C. DIBAl-H 1M in toluene (87 ml, 4 eq.) was added dropwise over 20 min. The reaction was stirred for an hour at 0 °C. The reaction was quenched by AcOH (5 ml), diluted with HCl 0.5 M (200 ml) and extracted 3 times with EtOAc (100 ml). The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated. The oil was purified by flash chromatography using hexane–EtOAc (80 : 20 to 50 : 50) to furnish L-**7** (6.46 g, 79%). ^{1}H NMR ($CDCl_3$) δ 4.89

Table 4 Introduction of guanidyl groups and final deprotection

	Diol	*n*	Final product	Yield (2 steps)	*m/z* (calcd), (MH$^+$)	*m/z* (MH$^+$)
1	(2*S*,5*S*)-**38**	1	**54**	9%	684.3986	684.3984
2	(2*R*,5*S*)-**39**	1	**55**	19%	"	684.3992
3	(2*R*,5*R*)-**40**	1	**56**	26%	"	684.3993
4	(2*S*,5*R*)-**41**	1	**57**	10%	"	684.3973
5[a]	(2*S*,5*S*)-**42**	0	**58**	40%	670.3829	670.3822
6	(2*R*,5*S*)-**43**	0	**59**	19%	"	670.3821
7[a]	(2*R*,5*R*)-**44**	0	**60**	27%	"	670.3820
8	(2*S*,5*R*)-**45**	0	**61**	15%	"	670.3835

[a] Mitsunobu reaction was done in THF–toluene–DMF (6 : 1 : 1).

(br s, 1H), 3.70–3.56 (m, 5H), 2.71 (br s, 1H), 1.62 (m, 3H), 1.44 (m, 10H), 1.06 (m, 21H). ^{13}C ($CDCl_3$) δ 157.6, 80.0, 66.7, 63.2, 53.1, 29.3, 28.5, 27.8, 18.1, 12.0. FTIR (cm^{-1}) 3339, 2942, 2866, 1687, 1506, 1461, 1390, 1365, 1246, 1170, 1102, 881. $[\alpha]_D^{24}$ −7.9 (c = 5.0, $CHCl_3$), MS (FAB$^+$) m/z 376 (M + H$^+$); HRMS calcd for $C_{19}H_{42}NO_4Si^+$ (MH$^+$) 376.2883, found 376.2887.

***N*-Allyl(*o*-nitrobenzene)sulfonamide.** Nosyl chloride (5.54 g, 25 mmol) was dissolved in DCM (25 ml) and was cooled down to 0 °C. Allylamine (4.7 ml, 62.5 mmol) was added dropwise. The reaction was stirred at rt for 2 h. The solution was washed twice with 10% citric acid solution, with brine, dried over $MgSO_4$ and concentrated to give pure *N*-allyl(*o*-nitrobenzene)sulfonamide (4.42 g, 73%). ^{1}H NMR ($CDCl_3$) δ 8.13 (m, 1H), 7.88 (dd, 1H, J = 3.4 Hz, J = 5.6 Hz), 7.75 (m, 2H), 5.74 (ddt, 1H, J_{d1} = 17.1 Hz, J_{d2} = 10.5 Hz, J_t = 5.6 Hz), 5.41 (br s, 1H), 5.21 (d, 1H, J = 17.1 Hz), 5.11 (d, 1H, J = 10.2 Hz), 3.78 (t, 2H, J = 6.0 Hz).

(*S*)-*N*^{1}-Allyl-*N*^{2}-Boc-*N*^{1}-(*o*-nitrobenzenesulfonyl)-5-(triisopropylsilyloxy)pentane-1,2-diamine (L-8). To a stirred mixture of alcohol L-7 (6.40 g, 17 mmol), triphenylphosphine (5.36 g, 1.2 eq.) and *N*-allyl(*o*-nitrobenzene)sulfonamide (8.26 g, 2 eq.) in toluene–THF (7 : 1, 40 ml) at 0 °C was added dropwise DIAD solution 1.9 M in toluene (11.7 ml, 1.3 eq.). The reaction was warmed up to rt and stirred for 3 h. The reaction was concentrated and purified by flash chromatography using hexane–EtOAc (90 : 10 to 70 : 30) to furnish product L-8 (6.25 g, 61%). ^{1}H NMR ($CDCl_3$) δ 8.03 (d, 1H, J = 6.8 Hz), 7.65 (m, 3H), 5.61 (m, 1H), 5.25 (d, 1H, J = 17.0 Hz), 5.16 (d, 1H, J = 10.2 Hz), 4.62 (d, 1H, J = 9.0 Hz), 4.09 (m, 1H), 3.92 (dd, 1H, J = 7.5 Hz, J = 16.3 Hz), 3.83 (m, 1H), 3.68 (m, 2H), 3.45 (dd, 1H, J = 10.2 Hz, J = 14.4 Hz), 3.21 (dd, 1H, J = 4.9 Hz, 14.6 Hz), 1.61 (m, 3H), 1.41 (m, 10H), 1.05 (m, 21H). ^{13}C ($CDCl_3$) δ 155.8, 147.9, 134.0, 133.4, 132.0, 131.7, 130.9, 124.1, 119.9, 79.2, 62.8, 50.4, 49.6, 47.6, 29.3, 29.1, 28.3, 18.0, 12.0. FTIR (cm^{-1}) 2942, 2866, 1707, 1545, 1509, 1454, 1365, 1244, 1163. MS (FAB$^+$) m/z 600 (M + H$^+$); HRMS calcd for $C_{28}H_{50}N_3O_7SSi^+$ (MH$^+$) 600.3133, found 600.3146. $[\alpha]_D^{21}$ −22.3° (c = 1.04).

Methyl (*S*)-2-(*N*-allylamino)-5-(triisopropylsilyloxy)pentanoate (L-10) [allyl-Hnv(TIPS)-OMe]. Method 1: L-6 (500 mg, 1.24 mmol) was dissolved in DCM (9 ml) and cooled down to 0 °C. TFA (8 ml) was added dropwise and the reaction was stirred for an hour at 0 °C. The reaction was diluted with toluene and was concentrated. The oil was diluted again in toluene and concentrated to give the TFA salt, which was used without further purification. Dried, powdered 4 Å molecular sieves (2.5 g) were suspended in DMF (13 ml). LiOH (100 mg, 2.13 eq.) was added and the mixture was it stirred for 20 min. Amine was added and the reaction was stirred for 45 additional min. Allyl bromide (100 µl, 1.0 eq.) was finally added and the reaction was stirred overnight. The reaction was filtered, diluted in EtOAc and washed 3 times with water. The combined aqueous layers were extracted twice with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated. The oil was purified by flash chromatography using DCM–EtOAc (90 : 10) to furnish L-10 (246 mg, 64%).

Method 2: the 3 : 1 mixture of L-6 L-6 and TIPSOH (5.5 g, 13.6 mmol of L-6) was dissolved in DCM (70 ml) and cooled down to 0 °C. TFA (60 ml) was added dropwise and the reaction was stirred for an hour at 0 °C. The reaction was diluted with toluene (60 ml) and DCM was removed under reduced pressure. To the solution was carefully added saturated $NaHCO_3$ solution. The aqueous layer was extracted twice with ethyl acetate. The combined organic fractions were washed with brine, dried over $MgSO_4$ and concentrated. The oil was used without further purification. The free amine was dissolved in DCM (20 ml) and was treated with Et_3N (1 ml, 1.2 eq.) followed by nosyl chloride (2.92 g, 1.1 eq.) in solution in DCM (20 ml). The reaction was stirred overnight and was then washed twice with 10% citric acid solution, with brine, dried over $MgSO_4$ and concentrated. The oil was purified by flash chromatography using hexane–EtOAc (90 : 10 to 60 : 40) to furnish methyl (*S*)-2-[*N*-(*o*-nitrobenzenesulfonyl)amino)-5-(triisopropylsilyloxy]pentanoate [Ns-Hnv(TIPS)-OMe] (4.95 g, 85%). ^{1}H NMR ($CDCl_3$) δ 8.07 (m, 1H), 7.92 (m, 1H), 7.73 (m, 2H), 6.10 (d, 1H, J = 9.0 Hz), 4.22 (ddd, 1H, J = 5.4 Hz, J = 8.0 Hz, J = 13.2 Hz), 3.70 (t, 2H, J = 6.1 Hz), 3.47 (s, 3H), 1.99 (m, 1H), 1.82 (m, 1H), 1.63 (m, 2H), 1.05 (m, 21H). ^{13}C ($CDCl_3$) δ 171.6, 136.5, 133.6, 132.9, 130.5, 125.6, 125.3, 62.1, 56.6, 52.3, 29.9, 28.4, 18.0, 12.0. FTIR (cm^{-1}) 2943, 2866, 1742, 1542, 1441, 1358, 1170, 1104.MS (FAB$^+$) m/z 489 (M + H$^+$); HRMS calcd for $C_{21}H_{37}N_2O_7SSi^+$ (MH$^+$) 489.2085, found 489.2096. Nosyl amide (4.90 g, 10 mmol) was dissolved in DMF (40 ml). Allyl bromide (1.3 ml, 1.5 eq.) and K_2CO_3 (1.80 g, 1.3 eq.) were successively added and the reaction was stirred for 3 h at rt. The reaction was partitioned between ether and water. The aqueous phase was extracted twice with ether. The combined organic phases were successively washed with water and brine, dried over $MgSO_4$ and concentrated. The oil was purified by flash chromatography using hexane–EtOAc (90 : 10 to 80 : 20) to furnish methyl (2*S*)-2-[*N*-(*o*-nitrobenzenesulfonyl)-*N*-allylamino]-5-(triisopropylsilyloxy)pentanoate (4.34 g, 82%). ^{1}H NMR ($CDCl_3$) δ 8.06 (m, 1H), 7.67 (m, 2H), 7.59 (m, 1H), 5.93 (ddt, 1H, J_t = 6.8 Hz, J_{d1} = 10.2 Hz, J_{d2} = 17.1 Hz), 5.21 (dd, 1H, J = 1.2 Hz, J = 17.1 Hz), 5.10 (d, 1H, J = 10.2 Hz), 4.66 (dd, 1H, J = 5.4 Hz, J = 10.0 Hz), 4.10 (dd, 1H, J = 5.9 Hz, J = 16.3 Hz), 3.92 (dd, 1H, J = 7.2 Hz, J = 16.3 Hz), 3.71 (t, 2H, J = 5.7 Hz), 3.57 (s, 3H), 2.14 (m, 1H), 1.83 (m, 1H), 1.66 (m, 2H), 1.05 (m, 21H). ^{13}C ($CDCl_3$) δ 171.4, 148.4, 134.9, 133.4, 131.4, 131.2, 124.0, 118.0, 62.3, 60.4, 52.1, 48.8, 29.5, 26.5, 18.0, 11.9. FTIR (cm^{-1}) 2943, 2865, 1743, 1544, 1461, 1437, 1354, 1164, 1101. MS (FAB$^+$) m/z 529 (M + H$^+$); HRMS calcd for $C_{24}H_{41}N_2O_7SSi^+$ (MH$^+$) 529.2398, found 529.2396. The allylnosylamide (4.34 g, 8.21 mmol) was dissolved in DMF (95 ml) and was treated with mercaptoacetic acid (2.8 ml, 5 eq.) and $LiOH{\cdot}H_2O$ (3.40 g, 9.85 eq.). The reaction was stirred for an hour at rt. The reaction was diluted in EtOAc and $NaHCO_3$. Aqueous layer was extracted twice with EtOAc. Combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated. The oil was purified by flash chromatography using hexane–EtOAc (80 : 20) to furnish L-10 (2.55 g, 90%, 63% from L-6). ^{1}H NMR ($CDCl_3$) δ 5.85 (ddt, 1H, J_{d1} = 16.8 Hz, J_{d2} = 10.2 Hz, J_t = 6.1 Hz), 5.17 (dt, 1H, J_d = 17.3 Hz, J_t = 1.5 Hz), 5.08 (dt, 1H, J_d = 10.2 Hz, J_t = 1.5 Hz), 3.72 (s, 3H), 3.68 (t, 2H, J = 6.0 Hz), 3.31–3.24 (m, 2H), 3.11 (ddd, 1H, J = 1.2 Hz, J = 6.1 Hz, J = 13.7 Hz), 1.79 (br s, 1H), 1.72 (m, 2H), 1.59 (m, 2H), 1.05 (m, 21H). ^{13}C ($CDCl_3$) δ 175.9, 136.3, 116.2, 62.9, 60.4, 51.6, 50.7, 29.9, 29.0, 18.0, 11.9. FTIR (cm^{-1}) 2943, 2865, 1737, 1462, 1196, 1171, 1103. MS (FAB$^+$) m/z 344 (M + H$^+$); HRMS calcd for $C_{18}H_{38}NO_3Si^+$ (MH$^+$) 344.2615, found 344.2620.

Methyl (*S*)-2-[*N*-allyl-3-(4-benzyloxyphenyl)propamido]-5-(triisopropylsilyloxy)pentanoate (13a). Amine L-**10** (1.97 g, 5.73 mmol), 3-(4-benzyloxyphenyl)propanoic acid **11** (2.94 g, 2 eq.) and HATU (4.36 g, 2 eq.) were dissolved in DMF (55 ml). Et_3N (2.4 ml, 3 eq.) was added dropwise and the reaction was stirred for 3 h at rt. The reaction was partitioned between ether and HCl 0.5M solution. The aqueous phase was extracted twice with ether. The combined organic phases were successively washed with water and brine, dried over $MgSO_4$ and concentrated. The oil was purified by flash chromatography using hexane–EtOAc (90 : 10 to 80 : 20) to furnish **13a** (3.18 g, 95%). ^{1}H NMR ($CDCl_3$) δ 7.43–7.26 (m, 5H), 7.12 (m, 2H), 6.89 (m, 2H), 5.78 (m, 1H), 5.19–5.13 (m, 2H), 5.03 (s, 2H), 4.87 (dd, 1H, J = 6.1 Hz, J = 9.0 Hz), 3.95 (dd, 1H, J = 5.6 Hz, J = 17.6 Hz), 3.81 (dd, 1H, J = 5.4 Hz, J = 17.8 Hz), 3.68 (m, 5H), 2.92 (m, 2H), 2.62 (dd, 1H, J = 6.6 Hz, J = 8.8 Hz), 2.06 (m, 1H), 1.82 (m, 1H), 1.53 (m, 2H), 1.06 (m, 21H). ^{13}C ($CDCl_3$) δ 173.4, 172.1, 157.2, 137.1, 134.1, 133.6, 132.9, 129.3, 128.6, 127.9, 127.4, 117.2, 114.8, 70.0, 62.7, 57.3, 52.0, 48.8, 35.6, 30.4, 29.8, 25.6, 18.0, 11.9. FTIR (cm^{-1}) 2943, 2865, 1738, 1649, 1611, 1510, 1455, 1238, 1175, 1105.

(*S*)-2-[*N*-Allyl-3-(4-benzyloxyphenyl)propanamido]-5-(triisopropylsilyloxy)pentanoic acid (3a). Ester **13a** (3.18 g, 5.46 mmol) was dissolved in THF–H_2O–MeOH (3 : 1 : 1, 55 ml), cooled down to 0 °C and treated with LiOH·H_2O (688 mg, 3 eq.). The reaction was stirred for 3 h at 0 °C and was diluted with EtOAc and 0.5 M HCl solution. The aqueous phase was extracted with EtOAc. The combined organic phases were washed with brine, dried over $MgSO_4$ and concentrated. The oil was purified by flash chromatography using hexane–EtOAc (90 : 10 to 60 : 40) to furnish **3a** (2.72 g, 88%). ^{1}H NMR ($CDCl_3$) δ 7.43–7.29 (m, 5H), 7.10 (m, 2H), 6.89 (m, 2H), 5.78 (ddt, 1H, J_{d1} = 17.1 Hz, J_{d2} = 10.2 Hz, J_t = 4.9 Hz), 5.18 (m, 2H), 5.02 (s, 2H), 4.64 (dd, 1H, J = 6.3 Hz, J = 8.5 Hz), 3.96 (dd, 1H, J = 5.6 Hz, J = 17.6 Hz), 3.80 (dd, 1H, J = 5.4 Hz, J = 17.6 Hz), 3.69 (m, 2H), 2.92 (m, 2H), 2.63 (dd, 1H, J = 7.3 Hz, J = 9.0 Hz), 2.12 (m, 1H), 1.87 (m, 1H), 1.56 (m, 2H), 1.05 (m, 21H). ^{13}C ($CDCl_3$) δ 175.7, 174.2, 157.2, 137.1, 134.1, 133.6, 132.9, 129.3, 128.6, 127.9, 127.4, 117.2, 114.8, 69.9, 62.6, 59.0, 50.0, 35.7, 30.4, 29.8, 25.5, 18.0, 11.9. FTIR (cm^{-1}) 2942, 2865, 1731, 1649, 1610, 1545, 1510, 1462, 1239, 1176, 1105. MS (FAB$^+$) m/z 568 (M + H$^+$); HRMS calcd for $C_{33}H_{50}NO_5Si^+$ (MH$^+$) 568.3453, found 568.3454.

(2*R*,*S*)-2-[*N*-Allyl-3-(4-benzyloxyphenyl)propanamido]-*N*-[(2*S*)-1-(*N*-allyl-*o*-nitrophenylsulfonamido)-5-triisopropylsilyloxypentan-2-yl]-5-triisopropylsilyloxypentanamide [(2*R*,*S*,2′*S*)-(14/15)]. L-**8** (3.00 g, 5 mmol) was dissolved in DCM (30 ml) and cooled down to 0 °C. TFA (20 ml) was then added dropwise and the reaction was stirred for an hour at 0 °C. Toluene (30 ml) was added and DCM and TFA were removed under reduced pressure. Toluene solution was diluted with EtOAc and saturated $NaHCO_3$ solution was carefully added. Aqueous phase was extracted twice with EtOAc. Combined organic phases were washed with brine, dried over $MgSO_4$ and concentrated as an oil. L-**4** (2.40 g, 96%) was used without further purification. Acid **3a** (2.00 g, 3.50 mmol), amine L-**4** (2.29 g, 1.3 eq.), HOAt (0.815 g, 1.70 eq.) and HATU (2.68 g, 2.00 eq.) were dissolved in DMF (35 ml) and DIEA (1.23 ml, 2.00 eq.) was added dropwise. The reaction was stirred overnight at room temperature. The reaction was partitioned between ether and HCl 0.5 M. The ether phase was washed again with HCl 0.5 M. The combined aqueous phases were reextracted twice with ether. The combined organic phases were washed with water, brine, dried over $MgSO_4$ and concentrated. Purification by flash chromatography using hexane–EtOAc (75 : 25) furnished **(14 + 15)** (3.24 g, 88%) as a 1 : 1 mixture of two diastereomers. MS (FAB$^+$) m/z 1049 (M + H$^+$), 1071 (M + Na$^+$); HRMS calcd for $C_{56}H_{89}N_4O_9SSi_2^+$ (MH$^+$) 1049.5889, found 1049.5879. Analytical HPLC on CHIRACEL OD–H 0.46 × 25 cm in hexane–*i*PrOH (90 : 10 to 5 : 95 in 30 min) give *rt*1 = 9.27 min and *rt*2 = 10.61 min.

(2*R*)- and (2*S*)-2-[*N*-Allyl-(4-benzyloxyphenyl)acetamido]-*N*-[(2*S*)-1-(*N*-allyl-*o*-nitrophenylsulfonamido)-5-triisopropylsilyloxypentan-2-yl]-5-triisopropylsilyloxypentanamide [(2*S*,2′*S*)-18 and (2*R*,2′*S*)-19]. Acid **3b** (1.38 g, 2.49 mmol) and amine L-**4** (1.62 g, 1.3 eq.) were coupled as described for the synthesis of **14/15**. Purification by flash chromatography using hexane–EtOAc (75 : 25) furnished two diastereomers (2*S*,2′*S*)-**18** (1.11 g, 43%) and (2*R*,2′*S*)-**19** (1.23 g, 48%). First to elute (2*S*,2′*S*)-**18**: ^{1}H NMR ($CDCl_3$) δ (signal for major rotamer) 8.01 (m, 1H), 7.66 (m, 3H), 7.46–7.32 (m, 5H), 7.15 (d, 2H, J = 7.5 Hz), 6.93 (d, 2H, J = 7.5 Hz), 6.52 (br d, 1H, J = 9.0 Hz), 5.77 (m, 1H), 5.55 (m, 1H), 5.25–5.08 (m, 4H), 5.04 (s, 2H), 4.57 (br s, 1H), 4.13–3.87 (m, 4H), 3.65 (m, 7H), 3.45 (dd, 1H, J = 10.0 Hz, J = 14.9 Hz), 3.16 (dd, 1H, J = 4.9 Hz, J = 14.9 Hz), 2.01 (m, 1H), 1.89 (m, 1H), 1.48 (m, 6H), 1.05 (m, 42H). MS (FAB$^+$) m/z 1035 (M + H$^+$), 1057 (M + Na$^+$); HRMS calcd for $C_{55}H_{87}N_4O_9Si_2S^+$ (MH$^+$) 1035.5727, found 1035.5726. Second to elute (2*R*,2′*S*)-**19**: ^{1}H NMR ($CDCl_3$) δ 7.96 (m, 1H), 7.68–7.60 (m, 3H), 7.43–7.31 (m, 5H), 7.17 (d, 2H, J = 8.5 Hz), 6.91 (d, 2H, J = 8.5 Hz), 6.28 (d, 1H, J = 9.8 Hz), 5.86 (m, 1H), 5.50 (m, 1H), 5.28 (m, 3H), 5.14 (d, 1H, J = 10.3 Hz), 5.07 (t, 1H, J = 7.8 Hz), 5.03 (s, 2H), 4.12 (m, 2H), 3.99 (dd, 1H, J = 8.0 Hz, J = 16.3 Hz), 3.91 (dd, 1H, J = 4.6 Hz, J = 18.0 Hz), 3.78–3.60 (m, 7H), 3.44 (dd, 1H, J = 10.5 Hz, J = 14.4 Hz), 3.11 (dd, 1H, J = 4.1 Hz, J = 14.4 Hz), 2.01 (m, 1H), 1.74 (m, 1H), 1.50 (m, 6H), 1.04 (m, 42H). MS (FAB$^+$) m/z 1035 (M + H$^+$), 1057 (M + Na$^+$); HRMS calcd for $C_{55}H_{87}N_4O_9SSi_2^+$ (MH$^+$) 1035.5732, found 1035.5743.

(2*S*,5*S*,6*E*)-2,5-Bis[3-(triisopropylsilyloxy)propyl]-1-[3-(4-benzyloxyphenyl)propionyl]-7-(*o*-nitrobenzenesulfonyl)-1,4,7-triazacycloundec-9-en-3-one [(2*S*,5*S*,6*E*)-22] and its (2*R*,5*S*,6*E*)-isomer (23). The diastereomeric mixture **14/15** (3.2 g, 3.05 mmol) was dissolved in DCM (500 ml, 6 mM). The solution was degassed 5 min by bubbling argon and Grubb's I catalyst (250 mg, 0.1 eq.) was added. The reaction was stirred for 12 h under reflux. The catalyst (250 mg, 0.1 eq.) was added again and the reaction was stirred for 12 h under reflux. Volatile compounds were removed and the products were purified by flash chromatography using hexane–EtOAc (70 : 30 to 60 : 40) and furnished two diastereomers, (2*S*,5*S*,6*E*)-**22** (0.406 g, 13%) and (2*R*,5*S*,6*E*)-**23** (0.752 g, 25%). First to elute (2*S*,5*S*,6*E*)-**22** : ^{1}H NMR ($CDCl_3$) δ 7.91 (d, 1H, J = 7.6 Hz), 7.71–7.60 (m, 3H), 7.44–7.29 (m, 5H), 7.13 (d, 2H, J = 8.3 Hz), 6.91 (d, 2H, J = 8.5 Hz), 6.21 (d, 1H, J = 5.9 Hz), 5.57 (d, 1H, J = 16.1 Hz), 5.45 (m, 1H), 5.13 (t, 1H, J = 7.8 Hz), 5.05 (s, 2H), 4.30 (d, 1H, J = 11.5 Hz), 3.92 (d, 1H, J = 9.3 Hz), 3.76 (dd, 1H, J = 5.1 Hz, J = 17.8 Hz), 3.68–3.51 (m, 5H), 3.29 (m, 2H), 3.14 (dd, 1H, J = 9.8 Hz, J = 12.9 Hz), 2.96 (t, 2H, J = 8.5 Hz), 2.65 (t, 2H, J = 8.5 Hz), 2.00 (m, 1H), 1.77 (m, 1H), 1.40 (m, 6H), 1.05 (m, 42H). MS (FAB$^+$) m/z 1021 (M$^+$),