Fluorine in Peptides: The Synthesis of α-Fluoro-β-Amino Dipeptides by Direct Deoxofluorination/Rearrangement of *N*-Seryl Dipeptides

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Dedicated to Prof. *Dieter Seebach* on the occasion of his 75th birthday

This article describes the stereo- and regioselectivity of the deoxofluorination of *N*-terminal dipeptides bearing a serine residue to generate, after rearrangement, α-fluoro-β-amine-terminated dipeptides. The ratio of the rearranged α-fluorinated regioisomer is increased, relative to the non-rearranged β-fluoro isomer, with *N*-alkylated amides. Otherwise, an intramolecular H-bond between the free amine and the amide *N*H suppresses formation of the key aziridinium intermediate required for α-fluorination. *N*-Methyl and *N*-allyl amides give exclusively α-fluorination products. Subsequent deprotection of the *N*-allyl amide to give a α-fluoro-β-amino dipeptide product is demonstrated.

1. Introduction. – There has been significant interest, particularly from the *Seebach* laboratory [1][2], in the synthesis and incorporation of α-fluoro-β-amino acid moieties into β-peptides, to examine the influence of the C–F bond on the overall peptide conformation. α-Fluoro amides adopt a preferred conformation where the C–F bond aligns *anti* to the amide CO group [3][4]. This is a relatively strong effect, dictated by the stereoelectronic preference for the dipole of the amide C=O to align antiparallel to the C–F dipole. If strategically incorporated, this preference can either reinforce or disrupt the conformation of an otherwise preferred secondary structure. Indeed, *Seebach* and co-workers have shown that, by changing the stereogenicity of a single C–F bond in a relatively large tridecapeptide, this can either reinforce or disrupt the secondary conformation of the peptide [2a–2c]. Thus, despite fluorine having a very low steric impact on the overall structure, the stereoelectronic effect of the C–F bond can be significant. Therefore, methods for incorporating fluorine in a stereospecific manner into β-peptides are of interest. In this article, we report the synthesis of the α-fluoro-β-amino moiety by direct deoxofluorination of *N*-seryl dipetides, rather than the more usual approach of the deoxofluorination of serine ester **1** and then hydrolysis, followed by peptide coupling (*Scheme 1*) [5]. A key aspect of these reactions is the formation of an aziridinium intermediate **2** following activation by a deoxofluorination reagent such as *N*,*N*-diethylaminosulfur trifluoride (DAST; *Scheme 1*) [6]. The intermediate is then attacked by F^- ion to generate either an α- or β-fluorinated product (*Scheme 1*) [2d].

Following a study focused on the preparation of selectively fluorinated compounds for G-quadruplex DNA binding [7], we began to explore direct fluorination of *N*,*N*-

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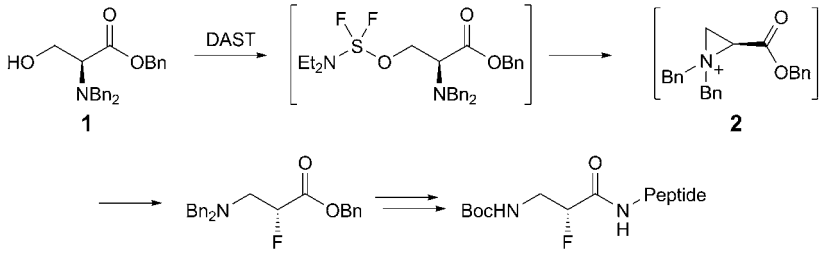
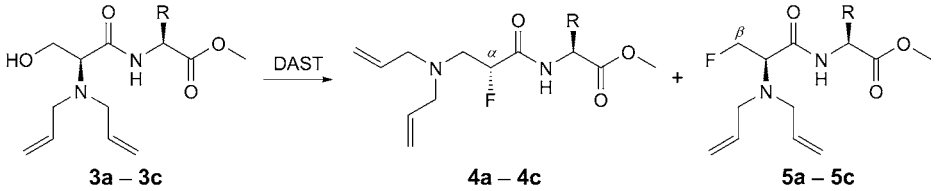
Scheme 1. *Deoxofluorination of Serine Benzyl Ester for Subsequent Incorporation into Peptides* [2b]. DAST = *N,N*-Diethylaminosulfur trifluoride (Et_2NSF_3).



Scheme 2. N-*Seryl Dipeptide Motif for Direct Fluorination with DAST.* R = Bn, Me, ^{i}Pr.



diallylseryl amides. In this article, we report our observations on the regiochemical outcome of these DAST-mediated deoxofluorination reactions (*Scheme 2*).

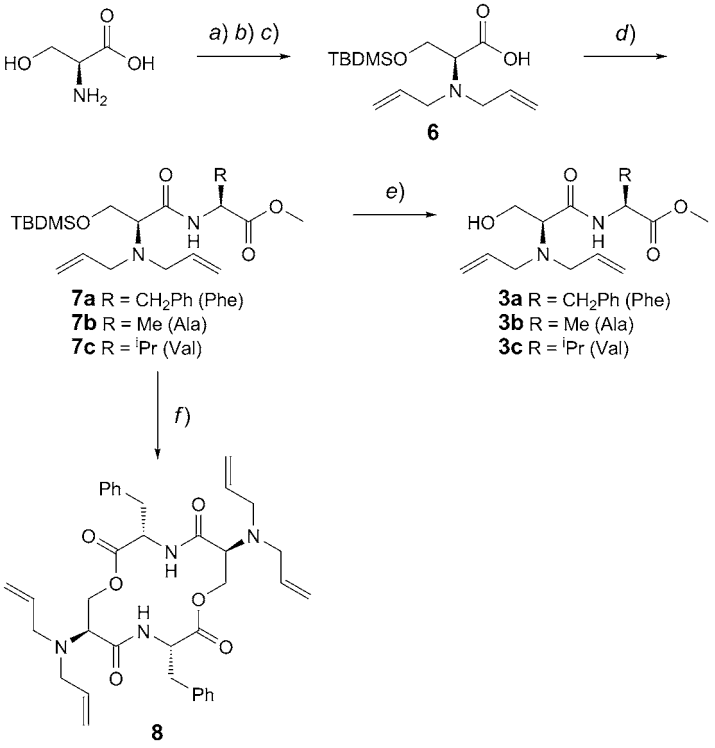
2. Results. – Three *N,N*-diallyl-seryl dipetides **3a** – **3c** were explored as substrates for direct fluorination. These dipeptides were prepared by coupling carboxylic acid **6** to L-phenylalanine, L-alanine, and L-valine amino acid methyl esters using propylphosphonic anhydride (*T3P*®; *Scheme 3*). *N,N*-Diallyl carboxylic acid **6** was synthesised in four steps starting from L-serine. The three dipeptides, **7a** – **7c**, were isolated with good diastereoselectivity, with only a very low level of epimerization at the α-C-atom (dr 95 : 5) [8]. The silyl ethers were removed using buffered TBAF solution, providing the free alcohols **3a** – **3c** in good yields (73 – 88%), and without further epimerisation (*Scheme 3*).

Interestingly, when non-buffered Bu_4NF (TBAF) was used for the silyl deprotection of **7a**, an unexpected cyclisation to the cyclic depsipeptide **8** occurred (*Scheme 3*). The structure of depsipeptide **8** was confirmed by single-crystal X-ray structure analysis (*Fig.*). The formation of the depsipeptide is clearly the consequence of a self-condensation, although the detailed sequence of events is not clear.

The fluorination of the *N*-seryl dipeptides **3a** – **3c** was investigated with DAST in THF at 0° (*Scheme 4*), typical conditions for the deoxofluorination of hydroxy amines in other motifs [2d][9][10]. The α- and β-fluorinated product ratios were determined by ^{19}F- and ^{1}H-NMR, and are compiled in *Table 1*. There is a tendency towards higher β-selectivity. By comparison, treating ester **9** under the same conditions gave a high α-selectivity (α/β 95 : 5) of product **10**, consistent with that expected from the literature (*Scheme 5*; *Table 1*, *Entry 4*) [2d][9][10].

The DAST reactions of **3b** and **3c**, with Me and ^{i}Pr groups, respectively, generated the β-products predominantly (*Table 1*, *Entries 2* and *3*) with α/β ratios of 35 : 65 and

Scheme 3



a) $SOCl_2$, MeOH, r.t., 24 h, 80%. *b*) Allyl bromide (2.5 equiv.), K_2CO_3 (4.0 equiv.), MeCN, 60°, 16 h; 57%. *c*) (*tert*-Butyl)(dimethyl)silyl trifluoromethanesulfonate (TBDMSOTf; 1.1 equiv.), Et_3N (5.0 equiv.), CH_2Cl_2, r.t., 16 h, 83%. *d*) *T3P*® (1.5 equiv.), Phe-OMe, Ala-OMe, or Val-OMe (2.0 equiv.), EtN^iPr_2 (4.0 equiv.), CH_2Cl_2, 0° to r.t., 1–12 h; 79–85%. *e*) Bu_4NF (TBAF, 4.0 equiv.; 1M THF soln.), AcOH (5.0 equiv.), THF, r.t., 12–24 h; 73–88%. *f*) TBAF (4.0 equiv.; 1M THF soln.), THF, r.t., 2 h, 27%

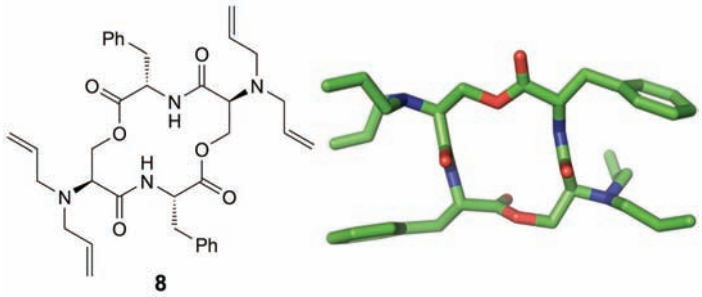
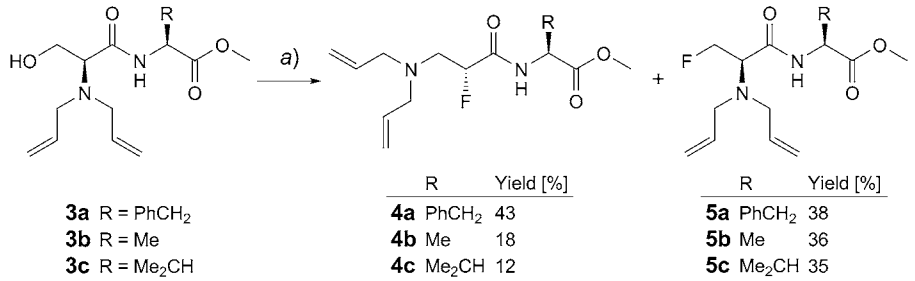


Figure. *Crystal structure of the 14-membered cyclic depsipeptide* **8**

25:75, respectively, and with good diastereocontrol. By contrast, the α/β fluorination ratio following treatment of **3a** with DAST resulted in a higher α-selectivity (*Table 1*,

Scheme 4



	R	Yield [%]
4a	$PhCH_2$	43
4b	Me	18
4c	Me_2CH	12

	R	Yield [%]
5a	$PhCH_2$	38
5b	Me	36
5c	Me_2CH	35

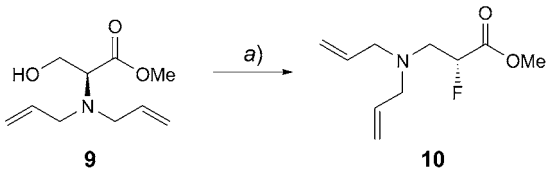
3a R = $PhCH_2$
3b R = Me
3c R = Me_2CH

a) DAST, THF; 0°, 1 h, 47–81% ($\alpha+\beta$ isomers).

Table 1. *Fluorination and Diastereoisomeric Ratios of Products* **4a**–**4c** *and* **5a**–**5c** *and Ester* **9**

Entry	Substrate	α/β ratio of **4**/**5**	δ of NH [ppm]	α dr **4**	β dr **5**
1	**3a**	60 : 40	7.75	95 : 5	95 : 5
2	**3b**	35 : 65	7.83	85 : 15	95 : 5
3	**3c**	25 : 75	7.87	92 : 8	95 : 5
4	**9**	95 : 5	N/A	N/A	N/A

Scheme 5



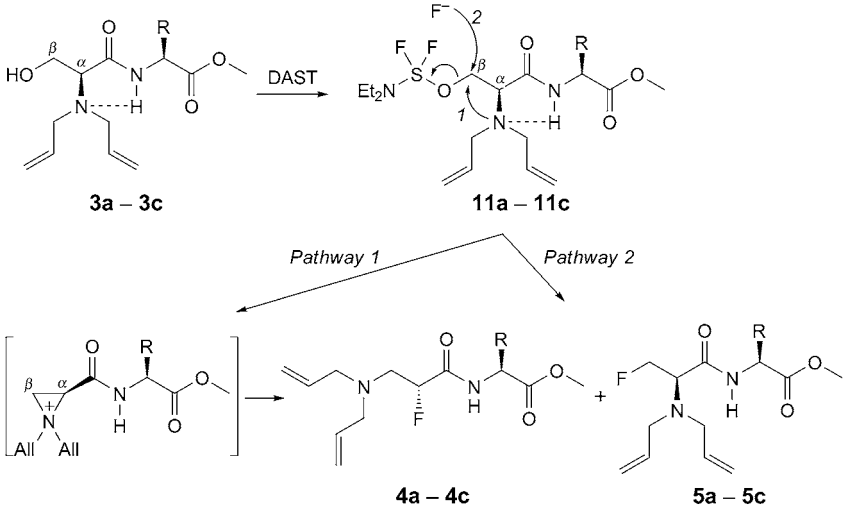
9 **10**

a) DAST, THF; 0°, 1 h, 69%.

Entry 1). The ^{1}H-NMR chemical shifts of the amide H-atom in substrate peptides **3a**–**3c** are indicative of H-bonding (*Table 1*), with higher chemical shifts corresponding to a stronger H-bond and a higher β-selectivity. The potential to form an intramolecular H-bond [11] in these substrates may compete with the formation of the key aziridinium intermediate required for α-fluorination (*Scheme 6*, *Pathway 1*) [6]. The β-product most likely arises by direct S_N2 attack of F^- to the DAST-activated **11a**–**11c** (*Scheme 6*, *Pathway 2*), a process that will be promoted if aziridinium ring formation is suppressed by H-bonding. The diastereoisomeric ratios of the α-fluorinated products **4a**–**4c** was high as determined by ^{1}H- and ^{19}F-NMR (*Table 1*). Also the diastereoisomeric ratio of the β-products **5a**–**5c** was consistent with that of the dipeptide substrate, supporting a direct S_N2 attack by F^- at the β-C-atom.

In all three α-fluorinated products, a through-space ^4J(H,F) coupling of *ca.* 4 Hz is observed between the α-F-atom and the amide NH H-atom. This ^4J(H,F) coupling has previously been reported for this motif, from the *Seebach* laboratory, in related structures [4]. Such a through-space coupling suggests a proximity in space within the

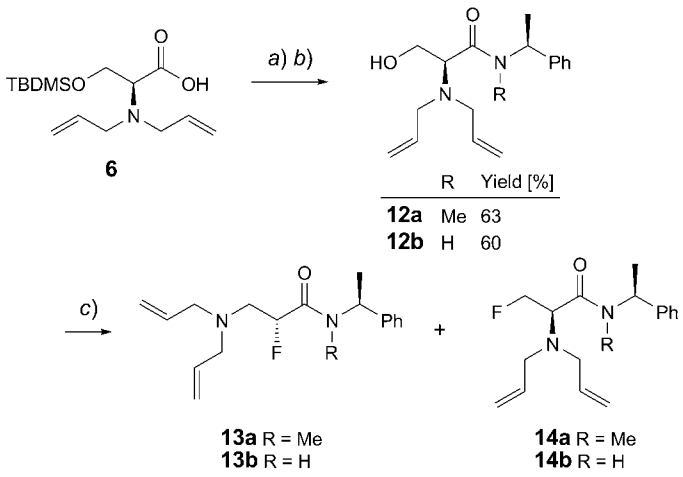
Scheme 6. *Pathways for Fluorination at Both α- and β-C-Atoms.* R = Bn, Me, ^{i}Pr. An intramolecular H-bond is shown between the amine and the amide in compounds **3** and **11**.



Van der Waals contact distance and is consistent with the predicted conformation of α-fluoroamides as a result of dipole relaxation as described in the *Introduction*.

To explore the role of intramolecular H-bonding on the α/β-fluorinated product ratio, the *N*–Me amide **12a** was explored as a substrate. Amide **12a** was prepared by coupling (1*S*)-*N*-methyl-1-phenylethanamine with carboxylic acid **6** (*Scheme 7*). The non *N*-methylated amide **12b** was also prepared as a control (*Scheme 7*).

Scheme 7



	R	Yield [%]
12a	Me	63
12b	H	60

a) *T3P*® (1.5 equiv.), amine (2.0 equiv.), Et$N^{i}Pr_2$ (4.0 equiv.), CH_2Cl_2, 0° to r.t., 1–12 h. *b*) TBAF (4.0 equiv., 1M THF soln.), AcOH (5.0 equiv.), THF, r.t., 12–24 h. *c*) DAST (1.1 equiv.), THF, 0°, 1 h.

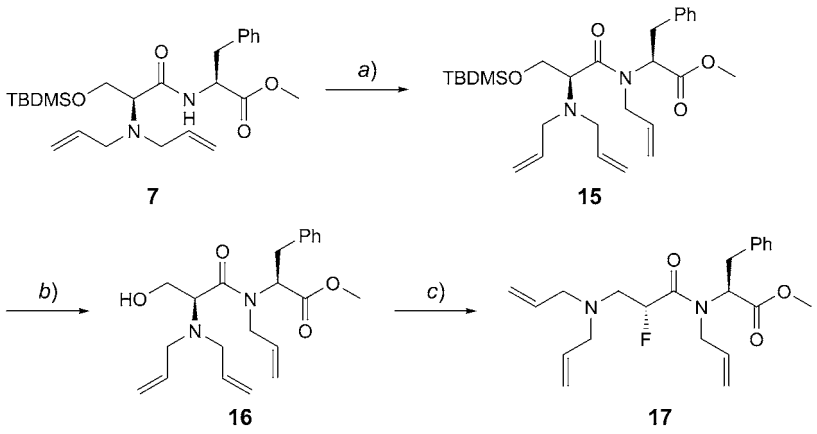
Treatment of *N*-methylated amide **12a** with DAST resulted in an almost exclusive α-fluorination (α/β 99:1) product (*i.e.*, **13a**) and with a dr of 89:11 (*Table 2*). By comparison, amide **12b** had a significantly reduced α-selectivity of 70:30 (α/β) and with a dr of 92:8 (*Table 2*). Thus, *N*-methylation significantly improved formation of the α-fluorinated product. This is consistent with the removal of an intramolecular H-bond in **12a**, competing with aziridinium ring formation (*Scheme 6*).

Table 2. *Fluorination Ratios for* N-*Me and* N-*H Amide Derivatives* **12a** *and* **12b**

Entry	Substrate	α/β ratio (**13**/**14**)	δ of NH [ppm]	α dr **13**	β dr **14**
1	**12a**	> 99:1	N/A	89:11	N/A
2	**12b**	70:30	7.63	92:8	95:5

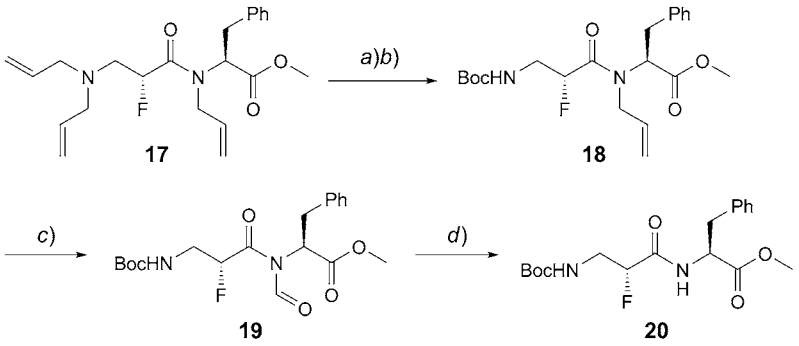
N-Methyl amides are difficult to demethylate for conversion to their corresponding amides. Therefore, in order to extend the potential of this α-fluorination method, amide *N*-alkylation was explored with a functional group that can be removed after the fluorination reaction. Thus *N*-allyl amide **16** was prepared from **7** with phosphazene P4-^{t}Bu [12][13] and allyl amide, followed *via* **15** by silyl deprotection (*Scheme 8*). Treatment of **16** with DAST gave the expected high selectivity for the α-fluorinated regioisomer (α/β 99:1) **17** and the transformation proved to be relatively efficient (73%; dr 90:10; *Scheme 8*). There was no β-fluorinated product observed by ^{19}F- and ^{1}H-NMR. Deprotection of the *N*,*N*-diallyl amine **17** was then achieved using catalytic [$Pd_2(dba)_3$] and thiosalicylic acid, following a procedure reported by *Genêt* and co-workers (*Scheme 9*) and the intermediate amine was subsequently protected as Boc derivative **18** [14].

Scheme 8



a) ^{t}Bu P4 Phosphazene (0.93 equiv.), allyl bromide (5.0 equiv.), THF, $-100°$ to $-78°$ to r.t., 20 h, 53%. *b*) TBAF (4.0 equiv.), AcOH (5.0 equiv.), THF, r.t., 12 h; 84%. *c*) DAST, THF, r.t., 1 h; 73%.

Scheme 9



a) $[Pd_2(dba)_3]$ (25 mol-%), dppb (30 mol-%), thiosalicylic acid (2.9 equiv.), THF, 60°, 3 h, 93%. *b*) Boc_2O (1.3 equiv.), EtN^iPr_2 (3.0 equiv.), aq. dioxane (25% (*v*/*v*)), r.t., 24 h; 71%. *c*) 1. $[RuHCO(PPh_3)_2]$ (10 mol-%), toluene, reflux, 3 h; 2. $RuCl_3$, $NaIO_4$, 1,2-dichloroethane, H_2O, r.t., 12 h; 59%. *d*) $NaHCO_3$ (1.0 equiv.), Na_2CO_3 (0.1 equiv.), acetone, H_2O, 10 h; 46%.

This deprotection strategy did not, however, remove the *N*-allyl amide group of **17**. The literature contains a range of methods for the removal of allyl ethers and amines; however, there are only a few examples for the removal of *N*′-allyl amides [15–17].

Selective removal of the *N*-allyl moiety of **18** was achieved by allyl isomerisation with 10 mol-% $[RuHCO(PPh_3)_2]$, followed by oxidative cleavage with $RuCl_3$ and $NaIO_4$, to generate *N*-formyl amide **19** (*Scheme 9*) [18][19]. Subsequent hydrolysis of the formamide moiety of **19** using basic aqueous acetone, furnished the desired secondary amide **20** (*Scheme 9*). Thus, successful removal of the allyl moiety in **18** is the final step in this approach to synthetically useful β-peptide stereoisomers carrying the F-atom at the α-position.

Conclusions. – A method for the preparation of α-fluoro-β-amino dipeptides is reported which generates the dipeptide moiety by direct deoxofluorination/rearrangement of *N*-seryl *N*,*N*-diallyl dipeptides with DAST. Good stereo- and regioselectivity is achieved with the *N*-methyl dipeptide; however, the *N*-methyl group cannot easily be removed after fluorination. *N*-Allyl amides also give high α-fluorinated product ratio, and can be deprotected by a Ru-mediated isomerization, followed by oxidation. Thus a new method to access α-fluoro-β-amino dipeptides is described.

We thank *Cancer Research UK* for a studentship to *D. L. S.* and *D. O'H.* thanks the *ERC* for an Advanced Investigator Award.

Experimental Part

General. All reactions involving the use of organometallic reagents were conducted by standard air-free techniques in *Schlenk* flasks. Dry THF (unstabilised) was obtained from an *mBRAUN SPS-800* solvent purification machine by passage through a drying column packed with 4-Å molecular sieves and dispensed under an inert atmosphere when required. Where appropriate, solvents were degassed by the standard freeze-pump-thaw technique at least three times with freshly dispensed dry solvent. M.p.: *Gallenkamp Griffin MPA350* or *Electrothermal 9100* digital melting point apparatus; uncorrected.

Optical rotations: *Perkin Elmer* optical rotation model *341* machine (cell path 1 dm) at 589 nm at ambient temp. (20°) and are denoted as $[\alpha]_D^{20}$ in the implied units of 10^{-1} deg cm^3 g^{-1}. IR Spectra: *Perkin-Elmer Spectrum GX FT-IR* machine either neat on NaCl plates or were recorded neat on a *Shimadzu Raffinity-1 FT-IR* machine. ^{1}H-NMR Spectra: at 300, 400, or 500 MHz *Bruker Avance/Avance II* spectrometers. ^{13}C-NMR Spectra: at 75, 101, or 126 MHz on *Bruker Avance/Avance II* spectrometers. ^{19}F-NMR Spectra: at 282, 376, or 470 MHz on *Bruker Avance/Avance II* spectrometers. NMR spectra were interpreted using iNMR or TopSpin. Resonances were assigned according to chemical shift, multiplicity, reference to 2D spectra, and the literature. Coupling constants (J) are reported to 0.1 Hz and are averaged for coupling nuclei. MS: at the *Biomedical Sciences Research Complex* (BSRC), conducted by Mrs. *Caroline Horsburgh* on a *Micromass LCT* electrospray time of flight mass spectrometer by electrospray ionisation. X-Ray analysis of single crystals was conducted by Prof. *Alexandra Slawin* at the University of St Andrews on a *Rigaku Cu MM007* high brilliance generator with *Saturn 92 CCD* and *XStream LT* accessories.

L-*Serine Methyl Ester Hydrochloride* ([20]). $SOCl_2$ (13.7 ml, 190 mmol, 1.1 equiv.) was added dropwise to MeOH (180 ml) over 30 min at r.t., followed by L-serine (18.0 g, 170 mmol, 1.0 equiv.) in a portionwise manner. Following consumption of the starting material as indicated by TLC, the solvent was removed *in vacuo*, and the solids were triturated with petroleum ether. Trituration and subsequent evaporation was repeated to remove excess $SOCl_2$. The product was recrystallized from MeOH to yield the title compound (21.3 g, 140 mmol, 80%). White crystalline solid. M.p. 162–165° ([20]: 163–166°). $[\alpha]_D^{20} = +4.3$ ($c = 4.0$, MeOH), ([20]: $[\alpha]_D^{20} = +3.7$ ($c = 4.0$, MeOH)). ^{1}H-NMR (400 MHz, CD_3OD): 4.91 (br. *s*, OH); 4.19 (*dd*, $J = 4.4$, 3.5, CHN); 4.04 (*dd*, $J = 11.9$, 4.4, CH_aH$_b$OH); 3.98 (*dd*, $J = 11.9$, 3.5, CH$_a$$H_b$OH); 3.88 (*s*, Me).

*Methyl (−)-(2*S*)-(Diallylamino)-3-hydroxypropanoate* (= *Methyl* N,N-*Diprop-2-en-1-yl*-L-*serinate*; **9**). Allyl bromide (12.2 ml, 141 mmol, 2.2 equiv.) was added to a suspension of L-serine methyl ester hydrochloride (10.0 g, 64.8 mmol, 1.0 equiv.) and K_2CO_3 (35.6 g, 258 mmol, 4.0 equiv.) in MeCN (300 ml), and the resulting suspension was heated under reflux for 24 h. The mixture was cooled to r.t., diluted with H_2O (300 ml), and extracted with AcOEt (3 × 100 ml). The org. fractions were combined, washed with brine (100 ml), dried (Na_2SO_4), filtered, and the solvent was removed *in vacuo*. The resulting oil was purified by CC (SiO_2; hexane/AcOEt 95 : 5 to 90 : 10) to yield **9** (7.02 g, 36.5 mmol, 57%). Colourless oil. R_f (hexane/AcOEt 90 : 10) 0.1. $[\alpha]_D^{20} = -81.3$ ($c = 2.9$, $CHCl_3$). IR (neat): 3446 (OH), 2926 (C=CH), 1730 (C=O), 1645, 993, 920. ^{1}H-NMR (400 MHz, $CDCl_3$): 5.75 (*dddd*, $J = 17.2$, 10.1, 7.9, 4.8, 2 H–C(allyl)); 5.20 (*dddd*, $J = 17.2$, 1.8, 1.1, 1.1, 2 CH_aH$_b$(allyl)); 5.14 (*dddd*, $J = 10.1$, 1.8, 0.9, 0.9, 2 CH$_a$$H_b$(allyl)); 3.70 (*s*, MeO); 3.75 (*dd*, $J = 9.2$, 4.6, CHN); 3.67 (*dd*, $J = 14.3$, 4.6, OCH_aH$_b$); 3.64 (*d*, $J =$ 14.3, 9.2, OCH$_a$$H_b$); 3.36 (*dddd*, $J = 14.3$, 4.8, 1.1, 0.9, 2 NCH_aH$_b$(allyl)); 3.20–3.14 (*m*, 2 NCH$_a$$H_b$(allyl)); 2.63 (br. *s*, OH). ^{13}C-NMR (101 MHz, $CDCl_3$): 171.8 (*C*OOMe); 135.9 (2 CH(allyl)); 118.1 (2 CH_2(allyl)); 62.5 (CHN); 59.1 (CH_2OH); 53.7 (2 CH_2N); 51.5 (MeO). ESI-MS (pos.): 200 (100, $[M+H]^+$). HR-ESI-MS (pos.): 200.1277 ($[M+H]^+$, $C_{10}H_{18}NO_3^+$; calc. 200.1276).

*Methyl (+)-(2*R*)-3-(Diallylamino)-2-fluoropropanoate* (= *Methyl (2*R*)-3-[Di(prop-2-en-1-yl)amino]-2-fluoropropanoate*; **10**). *N,N′*-Diethylaminosulfur trifluoride (DAST; 2.5 ml, 18.9 mmol, 1.2 equiv.) was added to a soln. of **9** (3.10 g, 15.6 mmol, 1.0 equiv.) in THF (80 ml) over a period of 5 min at 0°. The resulting soln. was stirred at 0° for 1 h, and the reaction was quenched by the addition of solid K_2CO_3 (excess) and H_2O (1 ml). As the effervescence subsided, the soln. was diluted further with H_2O (20 ml), and the org. fractions were extracted with Et_2O (3 × 20 ml). The org. fractions were combined and washed with brine (20 ml), dried (Na_2SO_4), filtered, and the solvent was removed *in vacuo*. The resulting oil was purified by CC (SiO_2; hexane/AcOEt 95 : 5) to yield **10** (2.19 g, 10.9 mmol, 69%). Colourless oil. R_f (hexane/AcOEt 95 : 5) 0.15. IR (neat): 2956, 2815, 1767 (C=O), 1643, 1440, 1214, 1069, 923. $[\alpha]_D^{20} =$ +9.8 ($c = 0.97$, $CHCl_3$). ^{1}H-NMR (400 MHz, $CDCl_3$): 5.80 (*dddd*, $J = 17.2$, 10.2, 7.0, 6.0, 2 H–C(allyl)); 5.20–5.13 (*m*, 2 CH_2(allyl)); 5.05 (*ddd*, $J = 49.7$, 6.3, 3.2, CHF); 3.73 (*s*, MeO); 3.29–3.23 (*m*, 2 NCH_aH$_b$(allyl)); 3.15–3.09 (*m*, 2 NCH$_a$$H_b$(allyl)); 2.99 (*ddd*, $J = 25.8$, 14.7, 6.3, CH_aH$_b$CHF); 2.97 (*ddd*, $J = 26.6$, 14.7, 3.2, CH$_a$$H_b$CHF). ^{13}C-NMR (101 MHz, $CDCl_3$): 169.5 (*d*, $J = 23.5$, CONH); 135.3 (2 CH(allyl)); 118.0 (2 CH_2(allyl)); 89.5 (*d*, $J = 186.1$, CHF); 57.6 (2 NCH_2(allyl)); 54.2 (*d*, $J = 20.2$, *C*H_2CHF); 52.4 (MeO). ^{19}F-NMR (376 MHz, $CDCl_3$): −191.9 (*ddd*, $J = 49.7$, 26.6, 25.8, CHF). ESI-MS (pos.): 202 (100, $[M+H]^+$). HR-ESI-MS (pos.): 202.1235 ($[M+H]^+$, $C_{10}H_{17}NO_2F^+$; calc. 202.1233).

Enantiomeric excess (ee) determined by chiral HPLC (*Chiralcel OD-H* 5% ^{i}PrOH in hexane, 0.5 ml/min, t_R(major) 9.33 > 95%, t_R(minor) 9.57 min < 5%).

General Procedure 1 (*GP 1*). The appropriate quantities of *(−)-(2*S*)-3-[(*tert*-butyl)dimethylsilyloxy]-2-(*N,N*-diallylamino)propanoic acid* (= O-*[(*tert*-butyl)(dimethyl)silyl]*-N,N-*diprop-2-en-1-yl*-L-*serine*; **6**; 1.0 equiv.), $EtN^{i}Pr_2$ (4.0 equiv.), and amino ester (2.0 equiv.) in CH_2Cl_2 (1.0 ml mmol^{-1}) were cooled to 0° and propylphosphonic anhydride (*T3P*®; 50% (*w*/*w*) in AcOEt, 2.0 equiv.) was added dropwise. The soln. was maintained at 0° for a further 30 min before being warmed to r.t. and stirred until TLC indicated consumption of the starting material. The reaction was quenched by the addition of HCl (1M, 10 ml), and the aq. phase was extracted with AcOEt (2 × 10 ml). The combined org. phases were washed sequentially with HCl (1M, 3 × 10 ml), sat. aq. Na_2CO_3 (3 × 10 ml), brine (20 ml), and dried (Na_2SO_4). The solvent was removed *in vacuo* and the product purified by CC (SiO_2; AcOEt/hexane).

General Procedure 2 (*GP 2*). Bu_4NF (TBAF; 1M in THF, 4.0 equiv.) was added dropwise to silyl-protected dipeptide (1.0 equiv.) and AcOH (5.0 equiv.) in THF (8.0 ml mmol^{-1}), and the resulting mixture was stirred at r.t. The reaction was quenched by the addition of H_2O (5 ml), followed by AcOEt (10 ml). The org. phases were washed successively with H_2O (2 × 5 ml) and brine (10 ml), dried (Na_2SO_4), and the solvent was removed *in vacuo*. The product was purified by CC (SiO_2; AcOEt/hexane).

General Procedure 3 (*GP 3*). DAST (1.5 equiv.) was added dropwise to a soln. of the appropriate amino alcohol dipeptide (1.0 equiv.) in THF (5.0 ml mmol^{-1}) at 0°. The resulting soln. was stirred at 0° for 1 h before quenching the reaction by the addition of $NaHCO_3$ (solid) and H_2O, until the soln. was basic (pH > 9) and effervescence subsided. The aq. phase was extracted with Et_2O (3 × 10 ml), and the combined org. phases were washed with brine, dried (Na_2SO_4), filtered, and the solvent was removed *in vacuo*. The product mixtures were purified by CC (SiO_2; AcOEt/hexane), separating the α- and β-fluorinated regioisomers where applicable.

*Methyl (−)-(2*S*)-3-[(*tert*-Butyl)dimethylsilyloxy]-2-(*N,N*-diallylamino)propanoate* (= *Methyl* O-*[(*tert*-Butyl)(dimethyl)silyl]*-N,N-*diprop-2-en-1-yl*-L-*serinate*). Et_3N (16.0 ml, 115 mmol, 4.5 equiv.) was added dropwise over 30 min to a soln. of **9** (5.00 g, 25.1 mmol, 1.0 equiv.) and TBDMSOTf (9.00 ml, 39.1 mmol, 1.8 equiv.) in CH_2Cl_2 (230 ml) at 0°. The mixture was brought to r.t. and stirred for 16 h, and the reaction was quenched by the addition of MeOH (40 ml), followed by sat. aq. Na_2CO_3 (100 ml). The org. phase was separated and the aq. phase was extracted with CH_2Cl_2 (3 × 100 ml). The org. phases were combined, dried (Na_2SO_4), and the solvent was removed *in vacuo*. The oil was purified by CC (SiO_2; hexane/AcOEt 95:5), to yield the title compound (6.52 g, 20.8 mmol, 83%). Colourless oil. R_f (hexane/AcOEt 90:10) 0.5. $[\alpha]_D^{20} = -18.1$ ($c = 0.6$, $CHCl_3$). IR (neat): 2951, 2929, 1735 (C=O), 1251 (Si–C), 1103, 918 (Si–C). ^{1}H-NMR (400 MHz, $CDCl_3$): 5.78 (*dddd*, *J* = 17.2, 10.1, 7.0, 5.4, 2 CH(allyl)); 5.21–5.09 (*m*, 2 CH_2(allyl)); 3.93 (*dd*, *J* = 9.9, 7.0, OCH_aH_b); 3.82 (*dd*, *J* = 9.9, 5.6, OCH_aH_b); 3.61 (*dd*, *J* = 7.0, 5.6, CHN); 3.38–3.32 (*m*, 2 CH_2N); 3.15 (*s*, MeO); 0.86 (*s*, ^{t}Bu); 0.03 (*s*, 2 MeSi). ^{13}C-NMR (101 MHz, $CDCl_3$): 172.4 (*C*OOMe); 136.7 (2 CH(allyl)); 117.2 (2 CH_2(allyl)); 64.2 (CHN); 62.9 (CH_2); 54.6 (2 NCH_2(allyl)); 51.2 (MeO); 25.9 (*Me*$_3$C); 18.3 (SiC); −5.4 (2 MeSi). ESI-MS (pos.): 314 (100, $[M+H]^+$). HR-ESI-MS (pos.): 314.2156 ($[M+H]^+$, $C_{16}H_{32}NO_3Si^+$; calc. 314.2151). ee determined by chiral HPLC (*Chiralcel OD-H*, 5% ^{i}PrOH in hexane, 0.25 ml/min; t_R(major) 7.08 min).

Compound **6**. $LiOH \cdot H_2O$ (3.37 g, 80.4 mmol, 4.0 equiv.) was added portionwise to a soln. of methyl (2*S*)-3-[(*tert*-butyl)dimethylsilyloxy)-2-(*N,N*-diallylamino)propanoate (6.30 g, 20.1 mmol, 1.0 equiv.) in 150 ml of THF/H_2O/MeOH 20:20:60, and the mixture was stirred for 24 h at r.t. The reaction was quenched by neutralisation with HCl (1M, 60 ml), and the aq. phase was extracted with CH_2Cl_2 (3 × 50 ml). The combined org. phases were dried (Na_2SO_4), filtered, and the solvent was removed *in vacuo* to yield **6** (5.41 g, 18.1 mmol, 90%) as a colourless gum, which was used without any further purification. $[\alpha]_D^{20} = -3.1$ ($c = 1.7$, MeOH). IR (neat): 2927, 2856, 1635 (C=O), 1417, 1257 (Si–C), 1087, 918 (Si–C). ^{1}H-NMR (300 MHz, CD_3OD): 5.90 (*dddd*, *J* = 17.0, 10.3, 6.6, 6.6, 2 H–C(allyl)); 5.27–5.12 (*m*, 2 CH_2(allyl)); 4.01 (*dd*, *J* = 10.7, 5.2, OCH_aH_b); 3.92 (*dd*, *J* = 10.7, 6.8, OCH_aH_b); 3.47 (*dd*, *J* = 6.8, 5.2, CHN); 3.40 (*m*, 2 NCH_2(allyl)); 0.91 (*s*, ^{t}Bu); 0.08 (*s*, 2 MeSi). ^{13}C-NMR (75 MHz, CD_3OD): 178.3 (COOH); 135.0 (2 CH(allyl)); 118.5 (2 CH_2(allyl)); 68.5 (CHN); 64.4 (CH_2O); 55.5 (2 NCH_2(allyl)); 26.5 (*Me*$_3$C); 19.2 (SiC); −5.1 (2 MeSi). ESI-MS (pos.): 322 (100, $[M+Na]^+$), 300 (5, $[M+H]^+$). HR-ESI-MS (pos.): 300.2004 ($[M+H]^+$, $C_{15}H_{30}NO_3Si^+$; calc. 300.1995).

Methyl O-*[(*tert-*Butyl)(dimethyl)silyl]*-N,N-*di(prop-2-en-1-yl)*-L-*seryl*-L-*phenylalaninate* (**7a**). Following *GP 1:* starting with **6**; 1.00 g, 3.34 mmol), L-phenylalanine methyl ester hydrochloride (1.44 g, 6.68 mmol), EtN^iPr_2 (2.30 ml, 13.2 mmol), and *T3P* (50% *w*/*w* in AcOEt, 2.33 ml), the reaction yielded **7a** (1.25 g, 2.71 mmol, 81%). Colourless oil. R_f (hexane/AcOEt 90:10) 0.35. $[\alpha]_D^{20} = +15.0$ ($c = 0.6$, $CHCl_3$). IR (neat): 3361 (NH), 2953, 1747 (C=O), 1670 (C=O), 1496 (NH), 1093, 920 (Si–C). ^{1}H-NMR (400 MHz, $CDCl_3$): 7.90 (*d*, *J* = 7.9, CONH); 7.28–7.08 (*m*, 5 arom. H); 5.61 (*dddd*, *J* = 17.0, 10.4, 6.4, 6.4, 2 CH(allyl)); 5.14–5.04 (*m*, 2 CH_2(allyl)); 4.80 (*dt*, *J* = 7.9, 6.2, CH($\alpha+1$)); 4.14 (*dd*, *J* = 11.1, 4.0, OCH_aH_b); 3.90 (*dd*, *J* = 11.1, 8.3, OCH_aH_b); 3.71 (*s*, MeO); 3.53 (*dd*, *J* = 8.3, 4.0, CH(α)); 3.21 (*m*, 2 NCH_2(allyl)); 3.17–3.02 (*m*, CH_2Ph); 0.86 (*s*, ^{t}Bu); 0.03 (*s*, 2 MeSi). ^{13}C-NMR (101 MHz, $CDCl_3$): 172.1 (CONH); 171.9 (*C*OOMe); 136.4 (arom. C); 136.2 (2 CH(allyl)); 129.3 (2 arom. CH); 128.6 (2 arom. CH); 127.1 (arom. CH); 117.3 (2 CH_2(allyl)); 63.9 (CH(α)); 61.3 (CH_2O); 53.9 (2 NCH_2(allyl)); 53.0 (CH($\alpha+1$)); 52.3 (MeO); 38.1 (CH_2Ph); 26.0 (Me_3C); 18.2 (SiC); −5.5 (MeSi). ESI-MS (pos.): 483 (30, $[M+Na]^+$), 461 (100, $[M+H]^+$). HR-ESI-MS (pos.): 483.2643 ($[M+Na]^+$, $C_{25}H_{40}N_2NaO_4Si^+$; calc. 483.2655).

Methyl O-*[(*tert-*Butyl)(dimethyl)silyl]*-N,N-*di(prop-2-en-1-yl)*-L-*seryl*-L-*alaninate* (**7b**). Following *GP 1:* starting with **6** (198 mg, 0.661 mmol), L-alanine methyl ester hydrochloride (185 mg, 1.32 mmol), EtN^iPr_2 (460 µl, 0.342 mmol), and *T3P* (460 µl, 50% (*w*/*w*) in AcOEt), the reaction yielded **7b** (215 mg, 0.559 mmol, 85%). Colourless oil. R_f (hexane/AcOEt 90:10) 0.2. $[\alpha]_D^{20} = -7.5$ ($c = 0.4$, $CHCl_3$). ^{1}H-NMR (400 MHz, $CDCl_3$): 7.94 (*d*, *J* = 7.6, CONH); 5.83 (*dddd*, *J* = 17.1, 10.3, 6.8, 5.6, 2 CH(allyl)); 5.24–5.13 (*m*, 2 CH_2(allyl)); 4.54 (*dq*, *J* = 7.6, 7.2, CH($\alpha+1$)); 4.17 (*dd*, *J* = 11.1, 4.1, OCH_aH_b); 3.97 (*dd*, *J* = 11.1, 7.6, OCH_aH_b); 3.72 (*s*, MeO); 3.53 (*dd*, *J* = 7.6, 4.1, CH(α)); 3.39–3.29 (*m*, 2 CH_2N); 1.37 (*d*, *J* = 7.2, *Me*–CH); 0.89 (*s*, ^{t}Bu); 0.06 (*s*, 2 MeSi). ^{13}C-NMR (101 MHz, $CDCl_3$): 173.5 (CONH); 171.8 (*C*OOMe); 136.2 (2 CH(allyl)); 117.5 (2 CH_2(allyl)); 64.1 (CH(α)); 61.3 (CH_2O); 54.0 (2 NCH_2(allyl)); 52.5 (MeO); 47.7 (CH($\alpha+1$)); 25.9 (Me_3C); 18.7 (*Me*CH); 18.2 (SiC); −5.4 (MeSi); −5.5 (MeSi). ESI-MS (pos.): 407 (50, $[M+Na]^+$), 385 (100, $[M+H]^+$). HR-ESI-MS (pos.): 407.2339 ($[M+Na]^+$, $C_{19}H_{36}N_2NaO_4Si^+$; calc. 407.2342).

Methyl O-*[(*tert-*Butyl)(dimethyl)silyl]*-N,N-*di(prop-2-en-1-yl)*-L-*seryl*-L-*valinate* (**7c**). Following *GP 1:* starting with **6** (205 mg, 0.685 mmol), L-valine methyl ester hydrochloride (330 mg, 1.37 mmol), EtN^iPr_2 (480 µl, 2.76 mmol), and *T3P* (480 µl, 50% (*w*/*w*) in AcOEt), the reaction yielded **7c** (224 mg, 0.590 mmol, 79%). Colourless oil: R_f (hexane/AcOEt 90:10) 0.3. $[\alpha]_D^{20} = -37.0$ ($c = 0.8$, $CHCl_3$). IR (neat): 3365 (NH), 2954, 1745 (C=O), 1680 (C=O), 1496 (NH), 920 (Si–C). ^{1}H-NMR (400 MHz, $CDCl_3$): 8.01 (*d*, *J* = 9.3, CONH); 5.83 (*dddd*, *J* = 17.2, 10.2, 7.0, 4.8, 2 CH(allyl)); 5.26–5.14 (*m*, 2 CH_2(allyl)); 4.49 (*dd*, *J* = 9.3, 4.7, CH($\alpha+1$)); 4.20 (*dd*, *J* = 11.1, 4.0, OCH_aH_b); 4.00 (*dd*, *J* = 11.1, 8.0, OCH_aH_b); 3.75 (*s*, MeO); 3.59 (*dd*, *J* = 8.0, 4.0, CH(α)); 3.43–3.30 (*m*, 2 NCH_2(allyl)); 2.21–2.13 (*m*, Me_2CH); 0.92–0.86 (*m*, Me_2CH, ^{t}Bu); 0.06 (*s*, 2 MeSi). ^{13}C-NMR (101 MHz, $CDCl_3$): 172.4 (CONH); 172.0 (*C*OOMe); 136.2 (2 CH(allyl)); 117.4 (2 CH_2(allyl)); 64.0 (CH(α)); 61.3 (CH_2O); 56.9 (CH($\alpha+1$)); 54.0 (2 NCH_2(allyl)); 52.1 (MeO); 31.3 (CH); 26.0 (Me_3C); 19.3 (Me); 18.2 (SiC); 17.8 (Me); −5.5 (2 MeSi). ESI-MS (pos.): 435 (5, $[M+Na]^+$), 413 (100, $[M+H]^+$). HR-ESI-MS (pos.): 435.2654 ($[M+Na]^+$, $C_{21}H_{40}N_2NaO_4Si^+$; calc. 435.2655).

*Cyclo(*N,N-*bisallyl-(*S*)-seryl-(*S*)-phenylalanine)* (=(*3*S,*6*S,*10*S,*13*S*)-3,10-Dibenzyl-6,13-bis[di-(prop-2-en-1-yl)amino]-1,8-dioxa-4,11-diazacyclotetradecane-2,5,9,12-tetrone*; **8**). TBAF (870 µl, 1M in THF, 4.0 equiv.) was added dropwise to **7a** (100 mg, 0.217 mmol, 1.0 equiv.) in dry THF (1.5 ml) and the mixture was stirred at r.t. for 2 h. The reaction was quenched by the addition of H_2O (5 ml), followed by AcOEt (10 ml). The org. phases were washed successively with H_2O (2 × 5 ml) and brine (10 ml), dried (Na_2SO_4), and the solvent was removed *in vacuo*. The product was purified by CC (SiO_2, AcOEt/hexane 20:80) to yield **8** (18.4 mg, 0.029 mmol, 27%). Colourless solid. M.p. 170–172° (AcOEt). $[\alpha]_D^{20} = -83.9$ ($c = 0.3$, MeOH); IR (NaCl plate); 3359 (NH), 3303, 2928, 1716 (C=O), 1663 (C=O), 1551 (NH), 1261 (C–O–C). ^{1}H-NMR (400 MHz, $CDCl_3$): 7.31–7.14 (*m*, 10 arom. H); 6.65 (*d*, *J* = 7.5, 2 NH); 5.57 (*dddd*, *J* = 17.0, 10.4, 6.6, 5.7, 4 CH(allyl)); 5.12–5.06 (*m*, 4 CH_2(allyl)); 4.52 (*dd*, *J* = 11.1, 3.3, 2 CH_aH_bCHN); 4.54–4.38 (*m*, 2 CH($\alpha+1$)); 4.40 (*dd*, *J* = 11.1, 6.2, 2 CH_aH_bCHN); 3.39 (*dd*, *J* = 6.2, 3.3, 2 CH(α)); 3.30 (*dd*, *J* = 14.3, 4.8, 2 CH_aH_bPh); 3.16 (*dd*, *J* = 14.3, 10.0, 2 CH_aH_bPh); 3.10–3.05 (*m*, 4 CH_aH_b(allyl)); 2.99–2.93 (*m*, 4 CH_aH_b(allyl)). ^{13}C-NMR (101 MHz, $CDCl_3$): 170.6 (2 *C*OOCH$_2$); 170.1 (2 CONH); 137.5 (2 arom. C); 135.8 (4 CH(allyl)); 129.3 (4 arom. CH); 128.8 (4 arom. CH); 127.0 (2 arom. CH); 117.9

(4 CH_2(allyl)); 61.4 (2 CH(α)); 60.1 (2 *C*H_2CHN); 53.9 (2 CH($\alpha+1$)); 53.7 (4 NCH_2(allyl)); 35.7 (2 *C*H_2Ph). ESI-MS (pos.): 667 (40, $[M+K]^+$), 651 (100, $[M+Na]^+$). HR-ESI-MS (pos.): 651.3154 ($[M+Na]^+$, $C_{36}H_{44}N_4NaO_6^+$; calc. 651.3153).

Methyl N,N-*Di(prop-2-en-1-yl)*-L-*seryl*-L-*phenylalaninate* (**3a**). Following *GP 2:* starting with **7a** (220 mg, 0.478 mmol), AcOH (140 µl, 2.45 mmol), and TBAF (1.88 ml, 1M in THF), the reaction yielded **3a** (121 mg, 0.349 mmol, 73%). Colourless oil: R_f (hexane/AcOEt 70:30) 0.10. $[\alpha]_D^{20} = +28.1$ ($c = 1.15$, $CHCl_3$). IR (neat): 3349 (OH), 2955, 1744 (C=O), 1659 (C=O), 1513, 1254, 1032. ^{1}H-NMR (500 MHz, $CDCl_3$): 7.75 (*d*, *J* = 7.7, CONH); 7.31–7.09 (*m*, 5 arom. H); 5.57 (*dddd*, *J* = 17.3, 10.0, 7.5, 4.5, 2 CH(allyl)); 5.16–5.10 (*m*, 2 CH_2(allyl)); 4.85 (*ddd*, *J* = 7.7, 7.3, 5.7, CH($\alpha+1$)); 3.85 (*dd*, *J* = 11.2, 7.6, OCH_aH_b); 3.76 (*s*, MeO); 3.75 (*dd*, *J* = 11.2, 4.1, OCH_aH_b); 3.41 (*dd*, *J* = 7.6, 4.1, CH(α)); 3.25 (*dd*, *J* = 14.0, 5.7, CH_aH_bPh); 3.15–3.11 (*m*, 2 CH_aH_b(allyl), CH_2OH); 3.06 (*dd*, *J* = 14.0, 7.3, CH_aH_bPh); 2.96–2.92 (*m*, 2 CH_aH_b(allyl)). ^{13}C-NMR (126 MHz, $CDCl_3$): 174.3 (CONH); 172.0 (*C*OOMe); 135.9 (arom. C); 135.5 (2 CH(allyl)); 129.2 (2 arom. CH); 128.8 (2 arom. CH); 127.3 (arom. CH); 118.1 (2 CH_2(allyl)); 62.9 (CH(α)); 58.5 (CH_2O); 53.5 (2 NCH_2(allyl)); 52.9 (CH($\alpha+1$)); 52.6 (MeO); 38.0 (*C*H_2Ph). ESI-MS (pos.): 369 (100, $[M+Na]^+$). HR-ESI-MS (pos.): 369.1782 ($[M+Na]^+$, $C_{19}H_{26}N_2NaO_4^+$; calc. 369.1790).

Methyl N,N-*Di(prop-2-en-1-yl)*-L-*seryl*-L-*alaninate* (**3b**). Following *GP 2:* starting with **7b** (195 mg, 0.507 mmol), AcOH (150 µl, 2.62 mmol) and TBAF (2.10 ml, 1M in THF), the reaction yielded **3b** (121 mg, 0.448 mmol, 88%). Colourless oil: R_f (hexane/AcOEt 80:20) 0.1. $[\alpha]_D^{20} = +12.0$ ($c = 0.7$, $CHCl_3$). IR (neat): 3356 (OH/NH), 3076, 2981, 1743 (C=O), 1653 (C=O), 1521 (NH), 1219, 1155. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.83 (*d*, *J* = 7.0, CONH); 5.79 (*dddd*, *J* = 17.3, 10.1, 7.3, 4.7, 2 CH(allyl)); 5.27–5.17 (*m*, 2 CH_2(allyl)); 4.57 (*dq*, *J* = 7.2, 7.0, CH($\alpha+1$)); 3.95 (*dd*, *J* = 11.2, 7.7, OCH_aH_b); 3.84–3.81 (*dd*, *J* = 11.2, 4.1, OCH_aH_b); 3.76 (*s*, MeO); 3.48 (*dd*, *J* = 7.7, 4.1, CH(α)); 3.41 (br. *s*, OH); 3.33–3.28 (*m*, 2 CH_aH_b(allyl)); 3.11–3.06 (*m*, 2 CH_aH_b(allyl)); 1.42 (*d*, *J* = 7.2, Me). ^{13}C-NMR (101 MHz, $CDCl_3$): 174.1 (CONH); 173.2 (*C*OOMe); 135.4 (2 CH(allyl)); 118.2 (2 CH_2(allyl)); 62.8 (CH(α)); 58.4 (CH_2O); 53.7 (2 CH_2(allyl)); 52.7 (MeO); 47.8 (CH($\alpha+1$)); 18.6 (*Me*CH). ESI-MS (pos.): 293 (100, $[M+Na]^+$). HR-ESI-MS (pos.): 293.1471 ($[M+Na]^+$, $C_{13}H_{22}N_2NaO_4^+$; calc. 293.1477).

Methyl N,N-*Di(prop-2-en-1-yl)*-L-*seryl*-L-*valinate* (**3c**). Following *GP 2:* starting with **7c** (201 mg, 0.487 mmol), AcOH (140 µl, 2.45 mmol), and TBAF (1.90 ml, 1M in THF), the reaction yielded **3c** (108 mg, 0.363 mmol, 75%). Colourless oil: R_f (hexane/AcOEt 80:20) 0.13. $[\alpha]_D^{20} = +6.9$ ($c = 0.5$, $CHCl_3$). IR (neat): 3361 (OH), 2960, 2821, 1741 (C=O), 1660 (C=O), 1500 (NH), 1149. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.87 (*d*, *J* = 9.0, CONH); 5.80 (*dddd*, *J* = 17.3, 10.1, 7.3, 4.4, 2 CH(allyl)); 5.30–5.18 (*m*, 2 CH_2(allyl)); 4.53 (*dd*, *J* = 9.0, 4.7, CH($\alpha+1$)); 3.99–3.83 (*m*, C*H*$_2$OH); 3.75 (*s*, MeO); 3.51 (*dd*, *J* = 7.5, 4.1, CH(α)); 3.43 (br. *s*, OH); 3.39–3.32 (*m*, 2 CH_aH_b(allyl)); 3.13–3.06 (*m*, 2 CH_aH_b(allyl)); 2.21 (*qqd*, *J* = 6.9, 6.9, 4.7, Me_2CH); 0.94 (*d*, *J* = 6.9, Me); 0.90 (*d*, *J* = 6.9, Me). ^{13}C-NMR (75.0 MHz, $CDCl_3$): 174.4 (CONH); 172.2 (*C*OOMe); 135.4 (2 CH(allyl)); 118.1 (2 CH_2(allyl)); 63.1 (CH(α)); 58.5 (CH($\alpha+1$)); 56.9 (MeO); 53.6 (2 NCH_2(allyl)); 52.3 (CH_2O); 31.3 (Me_2CH); 19.3 (*Me*CH); 17.9 (*Me*CH). ESI-MS (pos.): 321 (100, $[M+Na]^+$). HR-ESI-MS (pos.): 321.1787 ($[M+Na]^+$, $C_{15}H_{26}N_2NaO_4^+$; calc. 321.1790).

(+)-N,N-*Diallyl-(2*R*)-β²-Ala(α-F)-(2*S*)-Phe-OMe* (= *Methyl* N-*{(2*R*)-3-[Di(prop-2-en-1-yl)amino]-2-fluoropropanoyl}*-L-*phenylalaninate*; **4a**) *and (+)*-N,N-*Diallyl-(2*S*)-Ser(β-F)-(2*S*)-Phe-OMe* (= *Methyl 3-Fluoro*-N,N-*di(prop-2-en-1-yl)*-L-*alanyl*-L-*phenylalaninate*; **5a**). Following *GP 3:* starting with **3a** (181 mg, 0.522 mmol) and DAST (90.0 µl, 0.682 mmol), the reaction yielded **4a** (78.1 mg, 0.224 mmol, 43%). Colourless oil: R_f (hexane/AcOEt 70:30) 0.24. $[\alpha]_D^{20} = +69.8$ ($c = 2.3$, $CHCl_3$). IR (neat): 3429 (NH), 3070, 2924, 1747 (C=O), 1676 (C=O), 1525 (NH), 1278, 1217. ^{1}H-NMR (500 MHz, $CDCl_3$): 7.22–7.03 (*m*, 5 arom. H); 6.94 (br. *d*, *J* = 4.7, CONH); 5.71 (*dddd*, *J* = 17.0, 10.3, 6.5, 6.5, 2 CH(allyl)); 5.11–5.05 (*m*, 2 CH_2(allyl)); 4.90 (*ddd*, *J* = 49.9, 7.1, 2.8, CHF); 4.83–4.79 (*m*, CH($\alpha+1$)); 3.67 (*s*, MeO); 3.14–3.03 (*m*, 2 NCH_2(allyl), CH_2Ph); 2.94 (*ddd*, *J* = 30.1, 14.9, 2.8, CH_aH_bCHF); 2.84 (*ddd*, *J* = 23.9, 14.9, 7.1, CH_aH_bCHF). ^{13}C-NMR (125 MHz, $CDCl_3$): 171.5 (*C*OOMe); 168.6 (*d*, *J* = 20.0, CONH); 135.6 (arom. C); 135.1 (2 CH(allyl)); 129.3 (2 arom. CH); 128.7 (2 arom. CH); 127.3 (arom. CH); 118.1 (2 CH_2(allyl)); 91.2 (*d*, *J* = 187.8, CHF); 57.4 (CH($\alpha+1$)); 54.5 (*d*, *J* = 19.3, *C*H_2CHF); 52.9 (2 NCH_2(allyl)); 52.5 (MeO); 38.0 (*C*H_2Ph). ^{19}F-NMR (470 MHz, $CDCl_3$): −190.7 (*dddd*, *J* = 49.9, 30.1, 23.9, 4.0, CHF). ESI-MS (pos.): 371 (100, $[M+Na]^+$). HR-ESI-MS (pos.): 371.1741 ($[M+Na]^+$, $C_{19}H_{25}FN_2NaO_3^+$; calc. 371.1747).

Further elution of the mixture from the above preparation furnished **5a** (68.8 mg, 0.197 mmol, 38%). Colourless oil: R_f (hexane/AcOEt 70:30) 0.15. $[\alpha]_D^{20} = +21.9$ ($c = 2.8$, $CHCl_3$). IR (neat): 3360 (NH), 2951, 1743 (C=O), 1674 (C=O), 1496 (NH), 1201, 1006. ^{1}H-NMR (500 MHz, $CDCl_3$): 7.75 (*d*, *J* = 7.7, CONH); 7.21–7.02 (*m*, 5 arom. H); 5.53 (*dddd*, *J* = 17.4, 10.0, 7.5, 4.6, 2 CH(allyl)); 5.10–5.03 (*m*, 2 CH_2(allyl)); 4.89–4.70 (*m*, CH_2F, CH($\alpha+1$)); 3.68 (*s*, MeO); 3.62 (*ddd*, *J* = 23.9, 6.7, 3.5, CH(α)–CH_2F); 3.17–2.99 (*m*, 2 NCH_2(allyl), CH_2Ph). ^{13}C-NMR (125 MHz, $CDCl_3$): 172.0 (*C*OOMe); 170.1 (*d*, *J* = 10.3, CONH); 135.9 (arom. C); 135.4 (2 CH(allyl)); 129.2 (2 arom. CH); 128.7 (2 arom. CH); 127.2 (arom. CH); 118.1 (2 CH_2(allyl)); 81.1 (*d*, *J* = 171.1, CH_2F), 62.6 (*d*, *J* = 18.9, CH(α)); 53.9 (2 NCH_2(allyl)); 53.0 (CH($\alpha+1$)); 52.5 (MeO); 37.9 (CH_2Ph). ^{19}F-NMR (470 MHz, $CDCl_3$): −227.1 (*dt*, *J* = 47.2, 23.9, CH_2F). ESI-MS (pos.): 371 (100, $[M+Na]^+$). HR-ESI-MS (pos.): 371.1746 ($[M+Na]^+$, $C_{19}H_{25}FN_2NaO_3^+$; calc. 371.1747).

(+)-N,N-*Diallyl-(2*R*)-β²-Ala(α-F)-(2S)-Ala-OMe* (= *Methyl* N-*{(2*R*)-3-[Di(prop-2-en-1-yl)amino]-2-fluoropropanoyl}*-L-*alaninate*; **4b**) *and* *(−)*-N,N-*Diallyl-(2*S*)-Ser(β-F)-(2*S*)-Ala-OMe* (= *Methyl 3-Fluoro*-N,N-*di(prop-2-en-1-yl)*-L-*alanyl*-L-*alaninate*; **5b**). Following *GP 3:* starting with **3b** (98.5 mg, 0.366 mmol) and DAST (65.9 mg, 54 µl, 0.409 mmol), the reaction yielded **4b** (18.9 mg, 69.4 µmol, 18%). Colourless oil: R_f (hexane/AcOEt 80:20) 0.34. $[\alpha]_D^{20} = +15.2$ ($c = 1.8$, $CHCl_3$). ^{1}H-NMR (400 MHz, $CDCl_3$): 7.03–7.02 (*m*, CONH); 5.83 (*dddd*, *J* = 17.0, 10.3, 6.6, 6.6, 2 CH(allyl)); 5.21–5.14 (*m*, 2 CH_2(allyl)); 5.00 (*ddd*, *J* = 50.1, 7.2, 2.8, CHF); 4.63–4.59 (*dq*, *J* = 7.2, 6.7, CH($\alpha+1$)); 3.76 (*s*, MeO); 3.26–3.14 (*m*, 2 NCH_2(allyl)); 3.05 (*ddd*, *J* = 30.7, 14.9, 2.8, CH_aH_bCHF); 2.94 (*ddd*, *J* = 24.0, 14.9, 7.2, CH_aH_bCHF); 1.45 (*d*, *J* = 7.2, Me). ^{13}C-NMR (101 MHz, $CDCl_3$): 173.0 (*C*OOMe); 168.6 (*d*, *J* = 19.1, CONH); 135.2 (2 CH(allyl)); 118.2 (2 CH_2(allyl)); 91.4 (*d*, *J* = 187.9, CHF); 57.6 (2 NCH_2(allyl)); 54.7 (*d*, *J* = 19.1, CH_2); 52.7 (CH($\alpha+1$)); 47.8 (MeO); 18.5 (Me). ^{19}F-NMR (376 MHz, $CDCl_3$): −191.0 (*dddd*, *J* = 50.1, 30.7, 24.0, 3.7, CHF). ESI-MS (pos.): 273 (100, $[M+H]^+$). HR-ESI-MS (pos.): 273.1621 ($[M+H]^+$, $C_{13}H_{22}F_2N_2O_3^+$; calc. 273.1614).

Further elution of the mixture from the above preparation furnished **5b** (36.3 mg, 0.133 mmol, 36%). Colourless oil: R_f (hexane/AcOEt 80:20) 0.20. $[\alpha]_D^{20} = -1.7$ ($c = 3.6$, $CHCl_3$). IR (neat): 3365 (NH), 2983, 1745 (C=O), 1674 (C=O), 1500 (NH), 1450, 1157. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.88 (*d*, *J* = 7.2, CONH); 5.82 (*dddd*, *J* = 17.3, 10.1, 7.3, 4.9, 2 CH(allyl)); 5.28–5.18 (*m*, 2 CH_2(allyl)); 4.96 (*ddd*, *J* = 46.7, 10.3, 3.5, CH_aH_bF); 4.90 (*ddd*, *J* = 47.8, 10.3, 6.6, CH_aH_bF); 4.56 (*dq*, *J* = 7.2, 7.2, CH($\alpha+1$)); 3.75 (*s*, MeO); 3.74 (*ddd*, *J* = 23.8, 6.6, 3.5, CH(α)–CH_2F); 3.41–3.19 (*m*, 2 NCH_2(allyl)); 1.39 (*d*, *J* = 7.2, Me). ^{13}C-NMR (101 MHz, $CDCl_3$): 173.3 (*C*OOMe); 169.9 (*d*, *J* = 16.1, CONH); 135.3 (2 CH(allyl)); 118.2 (2 CH_2(allyl)); 81.1 (*d*, *J* = 170.8, CH_2F), 62.5 (*d*, *J* = 19.1, CH(α)); 54.0 (2 NCH_2(allyl)); 52.6 (CH($\alpha+1$)); 47.8 (MeO); 18.6 (Me). ^{19}F-NMR (376 MHz, $CDCl_3$): −228.9 (*ddd*, *J* = 47.8, 46.7, 23.8, CH_2F). ESI-MS (pos.): 273 (100, $[M+H]^+$). HR-ESI-MS (pos.): 273.1612 ($[M+H]^+$, $C_{13}H_{22}FN_2O_3^+$; calc. 273.1614).

(+)-N,N-*Diallyl-(2*R*)-β²-Ala(α-F)-(3*S*)-Val-OMe* (= *Methyl* N-*{(2*R*)-3-[Di(prop-2-en-1-yl)amino]-2-fluoropropanoyl}*-L-*valinate*; **4c**) *and* *(+)*-N,N-*Diallyl-(2*S*)-Ser(β-F)-(3*S*)-Val-OMe* (= *Methyl 3-Fluoro*-N,N-*di(prop-2-en-1-yl)*-L-*alanyl*-L-*valinate*; **5c**). Following *GP 3:* starting with **3c** (136 mg, 0.455 mmol) and DAST (65.0 µl, 0.492 mmol), the reaction yielded **4c** (12.7 mg, 42.3 µmol, 12%). Colourless oil. R_f (hexane/AcOEt 80:20) 0.50. $[\alpha]_D^{20} = +24.1$ ($c = 1.3$, $CHCl_3$). ^{1}H-NMR (400 MHz, $CDCl_3$): 6.97 (br. *d*, *J* = 5.3, CONH); 5.83 (*dddd*, *J* = 17.0, 10.3, 6.6, 6.6, 2 CH(allyl)); 5.21–5.14 (*m*, 2 CH_2(allyl)); 5.04 (*ddd*, *J* = 50.1, 7.0, 2.8, CHF); 4.56 (*dd*, *J* = 8.9, 5.3, CH($\alpha+1$)); 3.75 (*s*, MeO); 3.26–3.14 (*m*, 2 NCH_2(allyl)); 3.05 (*ddd*, *J* = 29.4, 14.9, 2.8, CH_aH_bCHF); 2.95 (*ddd*, *J* = 24.9, 14.9, 7.0, CH_aH_bCHF); 2.24–2.16 (*m*, Me_2CH); 0.95 (*d*, *J* = 6.9, Me); 0.93 (*d*, *J* = 6.9, Me). ^{13}C-NMR (101 MHz, $CDCl_3$): 172.0 (*C*OOMe); 169.0 (*d*, *J* = 19.1, CONH); 135.2 (2 CH(allyl)); 118.2 (2 CH_2(allyl)); 91.5 (*d*, *J* = 187.9, CHF); 57.6 (2 NCH_2(allyl)); 56.9 (CH($\alpha+1$)); 54.6 (*d*, *J* = 19.1, CH_2CHF); 52.4 (MeO); 31.5 (Me_2CH); 19.1 (Me); 17.9 (Me). ^{19}F-NMR (376 MHz, $CDCl_3$): −190.8 (*dddd*, *J* = 50.1, 29.4, 24.9, 4.3, CHF). ESI-MS (pos.): 301 (100, $[M+H]^+$). HR-ESI-MS (pos.): 301.1925 ($[M+H]^+$, $C_{15}H_{26}FN_2O_3^+$; calc. 301.1927).

Further elution of the mixture from the above preparation furnished **5c** (50.8 mg, 0.169 mmol, 35%). Colourless oil. R_f (hexane/AcOEt 80:20) 0.4. $[\alpha]_D^{20} = +2.1$ ($c = 5.0$, $CHCl_3$). IR (neat): 3367 (NH), 2962, 1741 (C=O), 1680 (C=O), 1500 (NH), 1149. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.91 (br. *d*, *J* = 9.2, CONH); 5.83 (*dddd*, *J* = 17.3, 10.2, 7.3, 4.6, 2 CH(allyl)); 5.30–5.19 (*m*, 2 CH_2(allyl)); 4.96 (*ddd*, *J* = 46.8, 10.3, 3.5, CH_aH_bF); 4.92 (*ddd*, *J* = 47.8, 10.3, 6.3, CH_aH_bF); 4.53 (*dd*, *J* = 9.2, 4.6, CH($\alpha+1$)); 3.74 (*ddd*, *J* = 24.8,

6.3, 3.5, CH(α)–CH_2F); 3.74 (*s*, MeO); 3.45–3.39 (*m*, 2 NCH_aH$_b$(allyl)); 3.25–3.20 (*m*, 2 NCH$_a$$H_b$(allyl)); 2.25–2.15 (*m*, Me_2CH); 0.92 (*d*, *J* = 6.9, *Me*CH); 0.87 (*d*, *J* = 6.9, *Me*CH). ^{13}C-NMR (101 MHz, $CDCl_3$): 172.3 (*C*OOMe); 170.2 (*d*, *J* = 10.1, CONH); 135.3 (2 CH(allyl)); 118.2 (2 CH_2(allyl)); 81.1 (*d*, *J* = 171.5, CH_2F); 62.8 (*d*, *J* = 11.1, CH_2FC_αH); 56.9 (CH(α+1)); 53.9 (2 NCH_2(allyl)); 52.3 (MeO); 31.3 (Me_2CH); 19.2 (Me); 17.7 (Me). ^{19}F-NMR (376 MHz, $CDCl_3$): −227.6 (*ddd*, *J* = 47.8, 46.8, 24.8, CH_2F). ESI-MS (pos.): 301 (100, $[M+H]^+$). HR-ESI-MS (pos.): 301.1921 ($[M+H]^+$, $C_{15}H_{26}FN_2O_3^+$; calc. 301.1927).

*(−)-*O*-[(*tert*-Butyl)(dimethyl)silyl]-*N*-methyl-*N*-[(1*S*)-1-phenylethyl]-*N*^{2},*N*^{2}-diprop-2-en-1-yl-*L*-serinamide.* Following *GP 1:* starting with **6** (205 mg, 0.685 mmol), (−)-(*S*)-*N*,α-dimethylbenzylamine (=(1*S*)-*N*-methyl-1-phenylethanamine; 188 mg, 200 µl, 1.39 mmol), EtN^iPr_2 (450 µl, 2.58 mmol), and *T3P* (470 µl, 50% (*w*/*w*) in AcOEt), the reaction yielded the title compound (231 mg, 0.561 mmol, 82%). Colourless oil: R_f (hexane/AcOEt 90:10) 0.25. $[\alpha]_D^{20} = -87.0$ (*c* = 1.3, $CHCl_3$). IR (neat): 2927, 2854, 1635 (C=O), 1404, 1095, 920 (Si–C). ^{1}H-NMR (400 MHz, $CDCl_3$): (major rotamer) 7.34–7.21 (*m*, 5 arom. H); 6.07 (*q*, *J* = 7.1, CH(α+1)); 5.84–5.73 (*m*, 2 CH(allyl)); 5.18–5.03 (*m*, 2 NCH_2(allyl)); 4.07 (*dd*, *J* = 9.5, 7.6, OCH_aH$_b$); 3.91 (*dd*, *J* = 9.5, 5.4, OCH$_a$$H_b$); 3.84 (*dd*, *J* = 7.6, 5.4, CH(α)); 3.32–3.28 (*m*, 2 NCH_2(allyl)); 2.70 (*s*, MeN); 1.44 (*d*, *J* = 7.1, *Me*CH); 0.85 (*s*, ^{t}Bu); 0.05 (*s*, MeSi); 0.03 (*s*, MeSi). ^{13}C-NMR (101 MHz, $CDCl_3$): 172.0 (CONH); 140.8 (arom. C); 137.2 (2 CH(allyl)); 128.4 (2 arom. CH); 127.5 (2 arom. CH); 117.5 (arom. CH); 116.9 (2 CH_2(allyl)); 62.1 (CH_2); 60.9 (CH(α)); 54.0 (2 NCH_2(allyl)); 50.3 (CH(α+1)); 29.6 (MeN); 26.0 (Me_3C); 18.4 (SiC); 15.7 (*Me*CH); −5.3 (MeSi); −5.4 (MeSi). ESI-MS (pos.): 417 (100, $[M+H]^+$). HR-ESI-MS (pos.): 417.2941 ($[M+H]^+$, $C_{24}H_{41}N_2O_2Si^+$; calc. 417.2937).

*(−)-*O*-[(*tert*-Butyl)(dimethyl)silyl]-*N*-[(1*S*)-1-phenylethyl]-*N*^{2},*N*^{2}-diprop-2-en-1-yl-*L*-serinamide.* Following *GP 1:* starting with (2*S*)-3-[(*tert*-butyl)dimethylsilyloxy]-2-(diallylamino)propanoic acid (104 mg, 0.347 mmol), (−)-(*S*)-α-methylbenzylamine (=(1*S*)-1-phenylethanamine; 85.0 µl, 0.668 mmol), EtN^iPr_2 (230 µl, 1.34 mmol), and *T3P* (390 µl, 50% (*w*/*w*) in AcOEt), the reaction yielded the title compound (109 mg, 0.270 mmol, 78%). Colourless oil: R_f (hexane/AcOEt 80:20) 0.5. $[\alpha]_D^{20} = -50.3$ (*c* = 1.0, $CHCl_3$). IR (neat): 3365 (NH), 2953, 1747 (C=O), 1674 (C=O), 1498 (NH), 1259, 920 (Si–C). ^{1}H-NMR (400 MHz, $CDCl_3$): 7.73 (*d*, *J* = 8.0, CONH); 7.33–7.20 (*m*, 5 arom. H); 5.81–5.71 (*m*, 2 CH(allyl)); 5.18–5.08 (*m*, 2 CH_2(allyl)); 5.02 (*dq*, *J* = 8.0, 6.9, CH(α+1)); 4.20 (*dd*, *J* = 11.1, 4.2, OCH_aH$_b$); 3.98 (*dd*, *J* = 11.1, 7.8, OCH$_a$$H_b$); 3.51 (*dd*, *J* = 7.8, 4.2, CH(α)); 3.36–3.27 (*m*, 2 NCH_2(allyl)); 1.42 (*d*, *J* = 6.9, *Me*CH); 0.88 (*s*, ^{t}Bu); 0.05 (*s*, MeSi); 0.04 (*s*, MeSi). ^{13}C-NMR (101 MHz, $CDCl_3$): 171.2 (CONH); 143.6 (arom. C); 136.2 (2 CH(allyl)); 128.7 (2 arom. CH); 127.3 (arom. CH); 126.1 (2 arom. CH); 117.5 (2 CH_2(allyl)); 64.1 (CH(α)); 61.5 (CH_2O); 54.0 (2 NCH_2(allyl)); 48.4 (CH(α+1)); 26.0 (Me_3C); 22.5 (Me); 18.2 (SiC); −5.4 (MeSi); −5.5 (MeSi). ESI-MS (pos.): 425 (30, $[M+Na]^+$), 403 (100, $[M+H]^+$). HR-ESI-MS (pos.): 403.2787 ($[M+H]^+$, $C_{23}H_{39}N_2O_2Si^+$; calc. 403.2781).

N-*Methyl*-N-*[(1S)-1-phenylethyl]*-N^2,N^2-*diprop-2-en-1-yl*-L-*serinamide* (**12a**). Following *GP 2:* starting with (−)-[(*tert*-butyl)(dimethyl)silyl]-*N*-[(1*S*)-1-phenylethyl]-*N*^{2},*N*^{2}-diprop-2-en-1-ylserinamide (102 mg, 0.245 mmol), AcOH (60.0 µl, 1.00 mmol), and TBAF (1.00 ml, 1M in THF), the reaction yielded **12a** (58 mg, 0.192 mmol, 78%). Colourless oil: R_f (hexane/AcOEt 80:20) 0.15. $[\alpha]_D^{20} = -54.2$ (*c* = 0.8, $CHCl_3$). IR (neat): 3419 (OH), 2926, 1630 (C=O), 1404, 1282, 1122, 995. ^{1}H-NMR (500 MHz, $CDCl_3$): (major rotamer): 7.31–7.17 (*m*, 5 arom. H); 5.98 (*q*, *J* = 7.1, CH(α+1)); 5.74–5.61 (*m*, 2 CH(allyl)); 5.15–5.11 (*m*, 2 CH_2(allyl)); 3.94 (*dd*, *J* = 10.9, 6.9, CH(α)); 3.76–3.70 (*m*, CH_2OH); 3.41 (br. *s*, CH_2O*H*); 3.40–3.29 (*m*, 2 NCH_aH$_b$(allyl)); 3.18–3.12 (*m*, 2 NCH$_a$$H_b$(allyl)); 2.70 (*s*, MeO); 1.41 (*d*, *J* = 7.1, Me). ^{13}C-NMR (126 MHz, $CDCl_3$): 172.5 (CONH); 140.2 (arom. C); 136.1 (2 CH(allyl)); 128.8 (2 arom. CH); 127.5 (2 arom. CH); 118.4 (arom. CH); 117.8 (2 CH_2(allyl)); 60.8 (CH(α)); 58.0 (CH_2O); 53.8 (2 NCH_2(allyl)); 50.7 (CH(α+1)); 29.7 (MeN); 15.7 (Me). ESI-MS (pos.): 325 (100, $[M+Na]^+$). HR-ESI-MS (pos.): 325.1885 ($[M+Na]^+$, $C_{18}H_{26}N_2NaO_2^+$; calc. 325.1892).

N-*[(1S)-1-Phenylethyl]*-N^2,N^2-*diprop-2-en-1-yl*-L-*serinamide* (**12b**). Following *GP 2:* starting with (−)-[(*tert*-butyl)(dimethyl)silyl]-*N*-[(1*S*)-1-phenylethyl]-*N*^{2},*N*^{2}-diprop-2-en-1-ylserinamide (93 mg, 0.231 mmol), AcOH (66 µl, 1.16 mmol), and TBAF (900 µl, 1 M in THF), the reaction yielded **12b** (51.0 mg, 0.180 mmol, 77%). Colourless oil: R_f (hexane/AcOEt 80:20) 0.11. $[\alpha]_D^{20} = -25.2$ (*c* = 0.7, $CHCl_3$). IR (neat): 3325 (OH/NH), 3064, 2926, 1647 (C=O), 1521 (NH), 1494, 1280, 1128, 993. ^{1}H-NMR (300 MHz, $CDCl_3$): (major rotamer): 7.63 (*d*, *J* = 7.8, CONH); 7.35–7.22 (*m*, 5 arom. H); 5.74 (*dddd*, *J* =

17.3, 10.1, 7.3, 4.6, 2 CH(allyl)); 5.23–5.12 (*m*, 2 CH_2(allyl)); 5.06 (*dq*, *J* = 7.8, 6.9, CH(α + 1)); 3.94 (*dd*, *J* = 11.1, 7.9, OCH_aH_b); 3.79 (*dd*, *J* = 11.1, 3.9, OCH_aH_b); 3.58 (br. *s*, OH); 3.42 (*dd*, *J* = 7.9, 3.9, CH(α)); 3.34–3.26 (*m*, 2 NCH_aH_b(allyl)); 3.08–3.01 (*m*, 2 NCH_aH_b(allyl)); 1.45 (*d*, *J* = 6.9, Me). ^{13}C-NMR (75 MHz, $CDCl_3$): 173.6 (CONH); 143.1 (arom. C); 135.4 (2 CH(allyl)); 128.9 (2 arom. CH); 127.5 (arom. CH); 126.0 (2 arom. CH); 118.1 (2 NCH_2(allyl)); 62.7 (CH(α)); 58.2 (MeO); 53.7 (2 CH_2(allyl)); 48.5 (CH(α + 1)); 22.4 (*Me*). HR-ESI-MS (pos.): 311.1739 ($[M+Na]^+$, $C_{17}H_{24}N_2NaO_2^+$; calc. 311.1735). ESI-MS (pos.): 311 (100, $[M+Na]^+$), 289 (20, $[M+H]^+$).

(−)-N,N-*Diallyl-(2*R*)-β²-Ala(α-F)-N′(Me)-(*S*)-α-methylbenzylamide* (=*(2*R*)-3-[Di(prop-2-en-1-yl)amino]-2-fluoro*-N-*methyl*-N-*[(1*S*)-1-phenylethyl]propanamide*; **13a**). Following *GP 3:* starting with **12a** (50.0 mg, 0.165 mmol) and DAST (25 µl, 0.189 mmol), the reaction yielded **13a** (41.0 mg, 0.135 mmol, 81%). Colourless oil: R_f (hexane/AcOEt 90:10) 0.09. $[\alpha]_D^{20} = -125$ (*c* = 1.8, $CHCl_3$). ^{1}H-NMR (400 MHz, $CDCl_3$): (major rotamer): 7.32–7.18 (*m*, 5 arom. H); 5.96 (*qq*, *J* = 7.1, 1.6, CH(α + 1)); 5.83–5.70 (*m*, 2 CH(allyl)); 5.48–5.23 (*m*, CHF); 5.16–5.03 (*m*, 2 CH_2(allyl)); 3.20–3.10 (*m*, 2 NCH_2(allyl)); 3.04–2.90 (*m*, CH_2CHF); 2.63 (*d*, *J* = 1.6, MeN); 1.43 (*d*, *J* = 7.1, Me). ^{13}C-NMR (101 MHz, $CDCl_3$): 168.2 (*d*, *J* = 20.0, CONH); 139.9 (arom. C); 135.3 (2 CH(allyl)); 128.6 (2 arom. CH); 127.5 (2 arom. CH); 126.8 (arom. CH); 118.2 (2 CH_2(allyl)); 89.0 (*d*, *J* = 181.3, CH(α)F); 57.9 (2 NCH_2(allyl)); 54.4 (*d*, *J* = 21.9, CH_2CHF); 51.0 (CH(α + 1)); 28.5 (MeN); 15.5 (Me). ^{19}F-NMR (376 MHz, $CDCl_3$): −184.5 (*ddd*, *J* = 50.3, 28.9, 21.0, CHF (minor)); −186.8 (*ddd*, *J* = 49.3, 28.3, 20.6, CHF (major)). ESI-MS (pos.): 327 (100, $[M+Na]^+$), 305 (30, $[M+Na]^+$). HR-ESI-MS (pos.): 327.1844 ($[M+Na]^+$, $C_{18}H_{25}FN_2NaO_3^+$; calc. 327.1849).

Methyl O-*[*tert*-Butyl(dimethyl)silyl]*-N,N-*di(prop-2-en-1-yl)*-L-*seryl*-N-*prop-2-en-1-yl*-L-*phenylalaninate* (**15**). Phosphazene P4-^{t}Bu (1M in hexanes, 1.00 ml, 1.00 mmol, 0.93 equiv.) was gradually added dropwise to a soln. of **7** (500 mg, 1.09 mmol, 1.0 equiv.) and allyl bromide (500 µl, 5.79 mmol, 5.3 equiv.) in THF (15 ml) at −100°. The resulting mixture was gradually warmed to −78° and stirred at this temp. for 20 h before being diluted with AcOEt (10 ml), and washed with HCl (1M, 2 × 10 ml). The org. fractions were dried (Na_2SO_4), filtered, and the solvent was removed *in vacuo*. The mixture was purified by CC (SiO_2; hexane/AcOEt (90:10) to yield **15** (286 mg, 0.57 mmol, 53%). Colourless oil: R_f (hexane/AcOEt 90:10) 0.10. $[\alpha]_D^{20} = -102.3$ (*c* = 2.3, $CHCl_3$). IR (neat): 2951, 2856, 1747 (C=O), 1670 (C=O), 1259, 1093, 920 (Si–C). ^{1}H-NMR (300 MHz, $CDCl_3$): (major rotamer): 7.30–7.17 (*m*, 5 arom. H); 5.79–5.67 (*m*, 2 CH(allyl)); 5.66–5.58 (*m*, CH(allyl)); 5.17–5.06 (*m*, 2 CH_2(allyl)); 5.09–4.96 (*m*, CH_2(allyl)); 4.19 (*dd*, *J* = 9.6, 5.4, CH(α + 1)); 4.06–3.88 (*m*, OCH_2, N′CH_2(allyl)); 3.71–3.67 (*m*, CH(α)); 3.64 (*s*, MeO); 3.40–3.08 (*m*, 2 NCH_2(allyl), CH_2Ph); 0.91 (*s*, ^{t}Bu); 0.10 (*s*, MeSi); 0.08 (*s*, MeSi). ^{13}C-NMR (101 MHz, $CDCl_3$): 171.4 (CONH); 171.3 (*C*OOMe); 138.5 (arom. C); 136.7 (2 CH(allyl)); 134.5 (CH(allyl)); 129.6 (2 arom. CH); 128.6 (2 arom. CH); 126.6 (arom. CH); 118.0 (CH_2(allyl)) 117.5 (2 CH_2(allyl)); 61.3 (CH(α)); 60.4 (CH(α + 1)); 59.9 (CH_2O); 53.6 (2 NCH_2(allyl)); 52.0 (MeO); 51.3 (N′CH_2(allyl)); 34.9 (CH_2Ph); 26.1 (Me_3C); 18.5 (SiC); −5.2 (MeSi); −5.3 (MeSi). ESI-MS (pos.): 523 (100, $[M+Na]^+$), 501 (80, $[M+H]^+$). HR-ESI-MS (pos.): 523.2969 ($[M+Na]^+$, $C_{28}H_{44}N_2NaO_4Si^+$; calc. 523.2968).

Methyl N,N-*Di(prop-2-en-1-yl)*-L-*seryl*-N-*prop-2-en-1-yl*-L-*phenylalaninate* (**16**). Following *GP 2:* starting with **15** (206 mg, 0.411 mmol), AcOH (120.0 µl, 2.06 mmol), and TBAF (1.6 ml, 1M in THF), the reaction yielded **16** (133 mg, 0.345 mmol, 84%). Colourless oil: R_f (hexane/AcOEt 70:30) 0.12. $[\alpha]_D^{20} = -124$ (*c* = 1.2, $CHCl_3$). IR (neat): 3446 (OH), 3078, 2949, 1743 (C=O), 1635 (C=O), 1436, 1274, 1195, 993. ^{1}H-NMR (400 MHz, $CDCl_3$): (major rotamer): 7.25–7.06 (*m*, 5 arom. H); 5.63 (*dddd*, *J* = 17.3, 10.0, 7.4, 5.4, 2 CH(allyl)); 5.59–5.50 (*m*, H–C(allyl)); 5.11–5.03 (*m*, 2 CH_2(allyl)); 5.03–4.92 (*m*, CH_2(allyl)); 4.12 (*dd*, *J* = 10.2, 5.2, CH(α + 1)); 4.00–3.94 (*m*, N′CH_aH_b(allyl)); 3.88 (*dd*, *J* = 11.3, 7.3, OCH_aH_b); 3.69 (*dd*, *J* = 11.3, 5.0, OCH_aH_b); 3.62 (*s*, MeO); 3.60 (*dd*, *J* = 7.3, 5.0, CH(α)); 3.32 (*dd*, *J* = 14.0, 5.2, CH_aH_bPh); 3.22–3.04 (*m*, CH_aH_bPh, 2 NCH_2(allyl), N′CH_aH_b(allyl)); 2.27 (br. *s*, OH). ^{13}C-NMR (101 MHz, $CDCl_3$): 172.5 (CONH); 170.9 (*C*OOMe); 138.0 (arom. C); 136.1 (2 CH(allyl)); 133.8 (CH(allyl)); 129.4 (2 arom. CH); 128.8 (2 arom. CH); 126.9 (arom. CH); 118.8 (CH_2(allyl)); 118.1 (2 CH_2(allyl)); 60.8 (CH(α)); 60.4 (CH(α + 1)); 57.8 (CH_2O); 53.5 (2 NCH_2(allyl)); 52.2 (MeO); 51.6 (N′CH_2(allyl)); 34.7 (CH_2Ph). ESI-MS (pos.): 409 (100, $[M+Na]^+$). HR-ESI-MS (pos.): 409.2090 ($[M+Na]^+$, $C_{22}H_{30}N_2NaO_4^+$; calc. 409.2103).

(−)-N,N-*Bisallyl-(2*R*)-β²-Ala(α-F)*-N′*-allyl-(3*S*)-Phe-OMe* (= *Methyl* N-*{(2*R*)-3-[Di(prop-2-en-1-yl)amino]-2-fluoropropanoyl}*-N-*prop-2-en-1-yl*-L-*phenylalaninate*; **17**). Following *GP 3:* starting with **16** (76.3 mg, 0.197 mmol) and DAST (30.0 µl, 0.265 mmol), the reaction yielded **17** (56 mg, 0.144 mmol, 73%). Colourless oil: R_f (hexane/AcOEt 90:10) 0.1. $[\alpha]_D^{20} = -39.2$ ($c = 1.3$, $CHCl_3$). IR (neat): 3076, 2949, 1743 (C=O), 1653 (C=O), 1436, 1222, 1166, 993. ^{1}H-NMR (500 MHz, $CDCl_3$): (major rotamer): 7.25–7.09 (*m*, 5 arom. H); 5.74 (*dddd*, *J* = 17.0, 10.3, 6.6, 6.6, 2 CH(allyl)); 5.52–5.44 (*m*, CH(allyl)); 5.12–5.04 (*m*, 3 × CH_2(allyl)); 5.06 (*ddd*, *J* = 49.7, 8.0, 3.2, CHF); 4.31 (*dd*, *J* = 10.3, 5.3, CH(α+1)); 3.86–3.82 (*m*, N′CH_2(allyl)); 3.64 (*s*, MeO); 3.30 (*dd*, *J* = 14.1, 5.3, C$H_a$$H_b$Ph); 3.17 (*dd*, *J* = 14.1, 10.3, CH_aH_bPh); 3.13–3.03 (*m*, 2 NCH_2(allyl)); 2.82 (*ddd*, *J* = 18.1, 15.0, 8.0, C$H_a$$H_b$CHF); 2.68 (*ddd*, *J* = 31.8, 15.0, 3.2, CH_aH_bCHF). ^{13}C-NMR (125 MHz, $CDCl_3$): 170.5 (*C*OOMe); 168.5 (*d*, *J* = 20.4, CONH); 137.6 (arom. C); 135.3 (2 CH(allyl)); 133.1 (CH(allyl)); 129.4 (2 arom. CH); 128.7 (2 arom. CH); 126.9 (arom. CH); 118.4 (CH_2(allyl)); 118.1 (2 CH_2(allyl)); 88.4 (*d*, *J* = 180.7, CHF); 60.8 (CH(α+1)); 57.7 (2 NCH_2(allyl)); 54.3 (*d*, *J* = 21.6, *C*H_2CHF); 52.4 (MeO); 50.8 (*d*, *J* = 4.1, N′CH_2(allyl)); 34.8 (*C*H_2Ph). ^{19}F-NMR (470 MHz, $CDCl_3$): −185.4 (*ddd*, *J* = 49.6, 33.5, 19.0, CHF (minor rotamer)); −187.2 (*ddd*, *J* = 49.7, 31.8, 18.1, CHF (major rotamer)). ESI-MS (pos.): 411 (100, $[M+Na]^+$). HR-ESI-MS (pos.): 411.2058 ($[M+Na]^+$, $C_{22}H_{29}N_2NaO_3F^+$; calc. 411.2060).

*(2*R*)-β²-Ala(α-F)*-N′*-allyl-(2*S*)-Phe-OMe* (= *Methyl* N-*[(2*R*)-3-Amino-2-fluoropropanoyl]*-N-*prop-2-en-1-yl*-L-*phenylalaninate*). 1,4-Bis(phenylphosphino)butane (16.5 mg, 37.3 µmol, 30.0 mol%) was added to a soln. of tris(dibenzylideneacetone)dipalladium (22.2 mg, 24.2 µmol, 25.0 mol%) in THF (5 ml) and stirred for 15 min until the soln. turned yellow. This soln. was added *via* canula to a soln. of **17** (51.6 mg, 0.133 mmol, 1.0 equiv.) and 2-sulfanylsalicylic acid (60.0 mg, 0.389 mmol, 2.9 equiv.) in THF (7.0 ml), and the soln. was brought to reflux for 3 h. The mixture was cooled to r.t., and H_2O (10 ml) and HCl (1M, 0.2 ml) were added. The precipitate was isolated by filtration and washed repeatedly with H_2O, with the filtrate collected and the solvent removed *in vacuo* to furnish a yellow solid. This solid was reconstituted in H_2O and re-filtered, and the sample was lyophilised to yield the title compound (41 mg, 0.20 mmol, 93%). Colourless solid which was used without further purification: $[\alpha]_D^{20} = -41.7$ ($c = 1.0$, D_2O). ^{1}H-NMR (500 MHz, D_2O): (major rotamer) 7.36–7.22 (*m*, 5 arom. H); 5.62 (*ddd*, *J* = 48.0, 7.4, 3.4, C(α)HF); 5.58–5.51 (*m*, CH(allyl)); 5.18–5.14 (*m*, CH_2(allyl)); 4.65 (*dd*, *J* = 10.7, 5.1, CH(α+1)); 3.96–3.92 (*m*, N′C$H_a$$H_b$(allyl)); 3.71 (*s*, MeO); 3.41–3.32 (*m*, CH_2CHF); 3.29–3.16 (*m*, CH_2Ph, N′CH_aH_b(allyl). ^{13}C-NMR (101 MHz, D_2O): 172.2 (*C*OOMe); 167.5 (*d*, *J* = 19.8, CONH); 136.9 (arom. C); 131.6 (CH(allyl)); 129.4 (2 arom. CH); 128.8 (2 arom. CH); 127.1 (arom. CH); 119.3 (CH_2(allyl)); 84.3 (*d*, *J* = 179, CHF); 61.3 (CH(α+1)); 53.0 (MeO); 51.5 (N′CH_2(allyl)); 40.0 (*d*, *J* = 21.3, *C*H_2CHF); 33.5 (*C*H_2Ph). ^{19}F-NMR (376 MHz, D_2O): −193.9 (*ddd*, *J* = 48.0, 27.9, 20.2, CHF (minor rotamer)); −194.7 (*ddd*, *J* = 48.0, 26.8, 21.5, CHF (major rotamer)). ESI-MS (pos.): 331 (50, $[M+Na]^+$), 309 (100, $[M+H]^+$). HR-ESI-MS (pos.): 309.1621 ($[M+H]^+$, $C_{16}H_{22}FN_2O_3^+$; calc. 309.1614).

(−)-N-*Boc-(2*R*)-β²-Ala(α-F)*-N′*-allyl-(2*S*)-Phe-OMe* (= *Methyl* N-*{(2*R*)-3-[(*tert*-*Butoxycarbonyl)-amino]-2-fluoropropanoyl}*-N-*prop-2-en-1-yl*-L-*phenylalaninate*; **18**). EtN^iPr_2 (40.0 µl, 0.230 mmol, 3.0 equiv.) and Boc_2O (22.0 mg, 0.101 mmol, 1.3 equiv.) were added to a soln. of (2*R*)-β²-Ala(α-F)-*N*′-allyl-(2*S*)-Phe-OMe (24.0 mg, 69.6 µmol, 1.0 equiv.) in aq. dioxane (2 ml, 25% *v*/*v*), and the mixture was stirred at r.t. for 24 h. The reaction was quenched by the addition of sat. aq. Na_2CO_3 (2 ml), and the aq. phase was extracted with AcOEt (2 × 2 ml). The org. extracts were combined, dried (Na_2SO_4), filtered, and the solvent was removed *in vacuo* to yield an oil. The product was purified by CC (SiO_2; hexane/AcOEt 90:10), to yield **18** (20.1 mg, 49.2 µmol, 71%). Colourless oil. $[\alpha]_D^{20} = -52.1$ ($c = 2.0$, $CHCl_3$). ^{1}H-NMR (400 MHz, $CDCl_3$): (major rotamer): 7.31–7.16 (*m*, 5 arom. H); 5.55–5.46 (*m*, CH(allyl)); 5.17–5.10 (*m*, CH_2(allyl)); 5.15–5.02 (*m*, CH(α)F); 4.93 (*t*, *J* = 6.3, N*H*Boc); 4.40 (*dd*, *J* = 10.4, 5.1, CH(α+1)); 3.96–3.87 (*m*, N′C$H_a$$H_b$(allyl)); 3.73 (*s*, MeO); 3.58–3.29 (*m*, CH_2CHF, N′CH_aH_b(allyl)); 3.38 (*dd*, *J* = 14.2, 5.1, C$H_a$$H_b$Ph); 3.24 (*dd*, *J* = 14.2, 10.4, CH_aH_bPh); 1.44 (*s*, ^{t}Bu). ^{13}C-NMR (75 MHz, $CDCl_3$): 170.5 (*C*OOMe); 167.8 (*d*, *J* = 20.3, CONH); 156.0 (O*C*O^{t}Bu); 137.5 (arom. C); 132.8 (CH(allyl)); 129.5 (2 arom. CH); 128.7 (2 arom. CH); 127.0 (arom. CH); 119.0 (CH_2(allyl)); 86.4 (*d*, *J* = 181, CHF); 60.9 (CH(α+1)); 52.5 (MeO); 51.1 (NCH_2(allyl)); 41.7 (*d*, *J* = 23.8, *C*H_2CHF); 34.8 (*C*H_2Ph); 30.0 (Me_3C); 28.5 (*Me*$_3$*C*). ^{19}F-NMR (376 MHz, $CDCl_3$): −191.5 (*ddd*, *J* = 47.3, 25.4, 19.6, CHF (minor rotamer)); −192.5 (*ddd*, *J* = 48.0, 22.9, 17.4, CHF (major rotamer)). ESI-MS (pos.): 431 (100, $[M+Na]^+$). HR-ESI-MS (pos.): 431.1948 ($[M+Na]^+$, $C_{21}H_{29}FN_2NaO_5^+$; calc. 431.1958).

*N-Boc-(2*R*)-β²-Ala(α-F)-N′-formyl-(2*S*)-Phe-OMe* (= *Methyl N-{(2*R*)-3-[(*tert*-Butoxycarbonyl)-amino]-2-fluoropropanoyl}-*N*-formyl-*L*-phenylalaninate*; **19**). [RuH(CO)Cl(PPh_3)$_3$] (4.7 mg, 4.9 μmol, 10 mol-%) was added to a soln. of **18** (20 mg, 48.9 μmol, 1.0 equiv.) in toluene (2 ml), and the mixture was brought to reflux for 3 h. The soln. was cooled to r.t. and the solvent removed *in vacuo*. $RuCl_3$ (1.0 mg, 1.7 μmol, 3.5 mol-%) and $NaIO_4$ (20.8 mg, 97.8 μmol, 2 equiv.) in aq. 1,2-dichloroethane (50% (*v*/*v*), 1 ml) were added to the isomerised product, and the mixture was stirred at r.t. for 24 hr. The reaction was quenched by the addition of sat. aq. Na_2CO_3 (1 ml), and the org. phases were extracted with AcOEt (2 × 2 ml). The org. phases were combined and washed with brine (1 ml), dried (Na_2SO_4), filtered, and the solvent was removed *in vacuo* to yield an oil. The product was purified by CC (SiO_2) to yield **19** (11.5 mg, 29 μmol, 59%). Colourless oil. $[\alpha]_D^{20} = -30.2$ (*c* = 1.1, $CHCl_3$). ^{1}H-NMR (500 MHz, $CDCl_3$): 8.97 (*s*, CHO); 7.29–7.10 (*m*, 5 arom. H); 5.49 (*dd*, *J* = 10.2, 5.2, N*H*Boc); 5.35–5.26 (*m*, CHF); 4.74 (*m*, CH(α + 1)); 3.76 (*s*, MeO); 3.52 (*dd*, *J* = 14.2, 5.4, CH_aH$_b$Ph); 3.54–3.34 (*m*, CH_aH$_b$CHF); 3.28 (*dd*, *J* = 14.2, 11.1, CH$_a$$H_b$Ph); 3.32–3.23 (*m*, CH$_a$$H_b$CHF); 1.44 (*s*, ^{t}Bu). ^{13}C-NMR (126 MHz, $CDCl_3$): 169.1 (*C*OOMe); 168.8 (*C*HO), 161.3 (*d*, *J* = 9.6, CONH); 155.7 (O*CO*^{t}Bu); 136.3 (arom. C); 129.2 (2 arom. CH); 128.6 (2 arom. CH); 127.1 (arom. CH); 87.0 (*d*, *J* = 186, CHF); 60.4 (*s*, HC(α + 1)); 52.8 (MeO); 41.8 (*d*, *J* = 23.1, *C*H$_2$CHF); 34.3 (*C*H$_2$Ph); 29.7 (Me$_3$*C*); 28.3 (*Me*$_3$C). ^{19}F-NMR (470 MHz, $CDCl_3$): −190.1 to −190.7 (br. *m*, CHF (minor rotamer)); −191.1 to −191.8 (br. *m*, CHF (major rotamer)). ESI-MS (pos.): 419 (100, $[M + Na]^+$). HR-ESI-MS (pos.): 419.1588 ($[M + Na]^+$, $C_{19}H_{25}FN_2NaO_6^+$; calc. 419.1594).

*(+)-N-Boc-(2*R*)-β²-Ala(α-F)-(2*S*)-Phe-OMe* (= *Methyl N-{(2*R*)-3-[(*tert*-Butoxycarbonyl)amino]-2-fluoropropanoyl}-*L*-phenylalaninate*; **20**). Sat. aq. Na_2CO_3 (0.5 ml) was added to a soln. of $NaHCO_3$ (1.0 mg, 9.4 μmol, 0.33 equiv.) and **19** (11.0 mg, 28 μmol, 1.0 equiv.) in aq. acetone (25% (*v*/*v*), 1 ml), and the mixture was stirred vigorously for 12 h at r.t. The mixture was diluted with H_2O (1 ml) and AcOEt (2 ml), the org. phase was separated, and the aq. layer was further extracted with AcOEt (2 ml). The org. phases were combined, washed with brine (1 ml), dried with Na_2SO_4, filtered, and the solvent was removed *in vacuo*. The oil was purified by CC (SiO_2) to yield **20** (4.7 mg, 12 μmol, 46%). Colourless solid. $[\alpha]_D^{20} = -26.1$ (*c* = 0.1, $CHCl_3$). ^{1}H-NMR (500 MHz, $CDCl_3$): 7.34–7.11 (*m*, 5 arom. H); 6.70 (br. *d*, *J* = 4.9, CONH); 4.95–4.84 (*m*, CHF, CH(α + 1), N*H*Boc); 3.82–3.72 (*m*, CH_aH$_b$CHF); 3.75 (*s*, MeO); 3.54–3.44 (*m*, CH$_a$$H_b$CHF); 3.19 (*dd*, *J* = 14.0, 5.7, CH_aH$_b$Ph); 3.12 (*dd*, *J* = 14.0, 6.5, CH$_a$$H_b$Ph); 1.43 (*s*, ^{t}Bu). ^{13}C-NMR (126 MHz, $CDCl_3$): 171.2 (*C*OOMe); 167.9 (*d*, *J* = 20.7, CONH); 155.7 (O*CO*^{t}Bu); 135.3 (arom. C); 129.1 (2 arom. CH); 128.8 (2 arom. CH); 127.4 (arom. C); 90.0 (*d*, *J* = 194.5, CHF); 52.8 (CH(α + 1)); 52.6 (MeO); 42.1 (*d*, *J* = 21.1, *C*H$_2$CHF); 37.7 (*C*H$_2$Ph); 29.7 (Me$_3$*C*); 28.3 (*Me*$_3$C). ^{19}F-NMR (470 MHz, $CDCl_3$): −195.3 (*ddd*, *J* = 48.1, 23.7, 23.7, CHF). ESI-MS (pos.): 391 (100, $[M + Na]^+$). HR-ESI-MS (pos.): 391.1645 ($[M + Na]^+$, $C_{18}H_{25}FN_2NaO_5^+$; calc. 391.1645).

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