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On the activation of valerolactam with triflic anhydride: the synthesis of ω-trifluorosulfonamido dipeptides using a transpeptidation reaction under mild conditions

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The activation of valerolactam with triflic anhydride is studied in detail, initially producing an *O*-triflated lactam, which rearranges, following the addition of base at higher temperatures, to an *N*-triflated derivative. This reacts with a series of nucleophiles to produce esters and amides, which are formally dipeptides of ω-amino acids.

Introduction

The amide functionality is undoubtedly one of the most important functional groups in living organisms.[1,2] All peptides and proteins are oligomers or polymers of amino acids linked by amide functionalities.[1,2] Furthermore, many natural products and drugs include the amide moiety. The amide functionality is characterised by its remarkable chemical stability, rigidity and ability to maintain protein conformation *via* hydrogen bonding. This remarkable chemical stability has resulted in the fact that amides are hardly used in synthetic organic chemistry, particularly in general carbonyl chemistry. In order to achieve cleavage of the amide group and its chemical transformation into another useful carbonyl functionality, harsh conditions are required. Nature, in contrast, has developed protease enzymes that are able to cleave the amide bond under extremely mild conditions, using electrophilic activation of the amide carbonyl in the active site of the protease, in combination with stabilisation of the transition state.[1,2]

Within our research program, we became interested in the use of amides as precursors in carbonyl chemistry. Ghosez *et al.* have described the use of triflic anhydride to activate the amide bond,[3] giving imidate intermediates which undergo cleavage under mild conditions to produce carboxylic acids.[3] The group of Charette has also used triflic anhydride for amide activation, obtaining imidate intermediates that, after nucleophilic attack with amino-thiols, yield thiazole heterocycles.[4] On the other hand, Robl reported that the reaction of amides with triflic anhydride resulted in *N*-triflation to give mixed imides.[5] Similar amide activation using diazomethane[6] and TMS triflate[7] was reported to give the *O*-activated imidates. Taking into account these literature precedents, we decided to investigate the reaction between amides and triflic anhydride in detail and exploit the activation to synthesise novel useful compounds for application in organic synthesis and medicinal chemistry.

Results and discussion

As a model amide compound for our investigation we choose valerolactam (**1**). The choice of a cyclic amide was made to ensure that activation of the amide carbonyl by the electrophile would lead to either *O*-triflated imidate or *N*-triflated imide intermediates rather than to nitrile ylids as reported previously.[8]

We started our investigation with a series of NMR experiments. The addition of triflic anhydride to valerolactam in $CDCl_3$ at different temperatures gave rise to a series of compounds formed immediately after the addition. Careful analysis by ^1H–^1H-COSY NMR spectroscopy revealed that protonated *N*-triflated lactam **2**, protonated *O*-triflated lactam **3** and *O*-protonated derivative **4** were formed in different ratios at different temperatures (Fig. 1). The latter compound arises presumably due to traces of moisture contaminating the reaction mixture during the set up of the experiment. The structure of **4** was independently confirmed by a control experiment, in which triflic acid was added to **1** in $CDCl_3$ and the resulting solution, containing protonated **4**, added to the reaction mixture above. It appears that the formation of *O*-triflated derivative **3** is disfavoured over the formation of *N*-triflated derivative **2** at all temperatures. Furthermore, increasing temperature resulted in a shift of the chemical equilibrium from the *O*-triflated imidate **3** to the *N*-triflated imide **2**, particularly at room temperature, reminiscent of the Chapman rearrangement.[9] The ratios are summarised in Table 1. Thermal rearrangements of imidates to imides have been reported, although at considerably higher temperatures.[10]

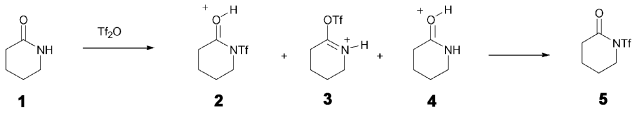

Fig. 1 Reaction of valerolactam (**1**) and triflic anhydride.

Addition of a base (either pyridine or a primary amine) at various temperatures, results in a shift of the chemical equilibrium towards the *N*-triflated imide intermediate **5**. Compound **5** could be isolated by column chromatography in an analytically pure form. After addition of an amine base, the *O*-triflated imidate intermediate **3** could not be used in a synthetically useful way under any of the studied conditions.

Unambiguous assignment of the structure of **5** proved to be rather difficult, since to distinguish it from the *O*-triflated imidate

Table 1 Ratio of **2** to **3** at variable temperatures (determined by integration in ^1H-NMR spectroscopy, 500 MHz; peak assignment by ^1H–^1H-COSY-NMR)

Temperature/K	Relative amount of **3**	Relative amount of **2**
213	1	3.6
228	1	3.1
243	1	3.0
298	1	4.2

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6 would require prior knowledge of the spectroscopic data of the two isomeric functional groups present, which were, from the literature, ambiguous .[3,4] The C=X stretching frequency in the infrared spectrum is found at 1738 cm^{-1}, which points towards compound **5**. The ^{13}C-NMR chemical shift of the carbonyl carbon appears at 170.6 ppm and the nitrogen appears at 150.3 ppm in the ^{15}N-NMR spectrum. The structural proof for **5** resulted from an accurate mass determination of a fragment ion in the CI mass spectrum. The main fragment in the CI mass spectra of **5** appears at $m/z = 174$, which could result from a fragment of $C_3HF_3O_3S$ derived from O–Tf derivative **6** or a fragment of $C_3H_3F_3NO_2S$ derived from **5** (see Fig. 2). Accurate mass determination of this fragment gave a value of $m/z = 173.9895$ indicates that it must be derived from compound **5** and therefore providing unambiguous structural proof of **5**.[11]

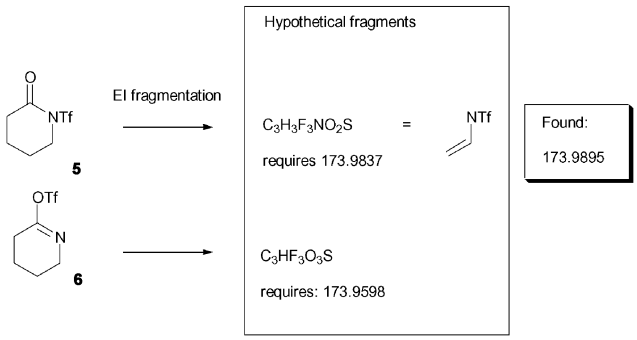

Fig. 2 Accurate mass of fragment ion of **5**.

With the *N*-triflated imide **5** in hand, we decided to investigate its reactivity towards a series of nucleophiles (Fig. 3 and Table 2). Compound **5** was generated in a one pot sequence from **1** at

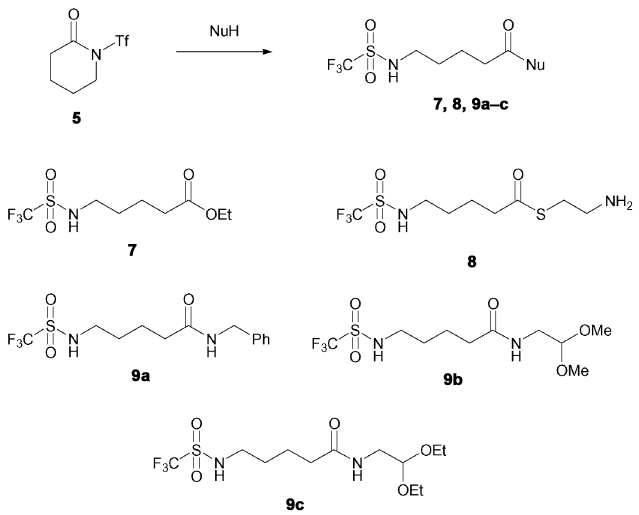

Fig. 3 Reaction of **5** with various nucleophiles.

-42 or -46 °C in dichloromethane.[12] Addition of pyridine as a base, followed by a nucleophile, gave the expected products. Ester **7** was formed from ethanol, thioester **8** was formed from amino mercaptan and amides **9a**–**c** were formed from the corresponding amines, although in poor yields. Since the yields obtained were disappointing, we decided to use isolated **5**, rather than **5** generated from the one pot sequence.

Reaction of isolated **5** with a series of amines and C-protected amino acids **10** gave the amides **11a**–**f** in good to excellent yields (Figs. 3, 4 and Table 2), under extremely mild conditions. The spectroscopic data were as expected. Only the ^{1}H-NMR data of amide **11b** derived from C-protected proline **10b** deserves some comment. At room temperature, two sets of signals can be observed in a ratio of 10 : 1, which we assign to the two rotamers of the proline amide **A** and **B** (in Fig. 5). At higher temperatures

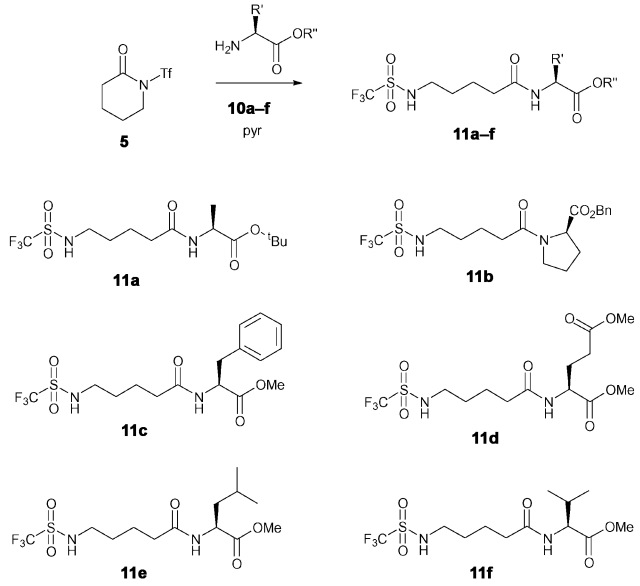

Fig. 4 Reaction of **5** with a series of C-protected amino acids.

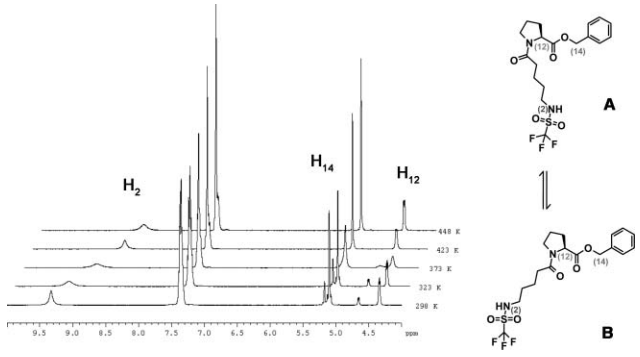

Fig. 5 Variable temperature ^{1}H-NMR spectra of amide **11b** in [D6]DMSO (expanded region, 500 MHz).

Table 2 Yields of all compound synthesised

Compound	Yield (%)	Method[a]	Compound	Yield (%)	Method
7	77	A	**11c**	99	B
8	6	A	**11d**	42	B
9a	31	A	**11e**	92	B
9b	10	A	**11f**	78	B
9c	47	A	**13a**	21	B
9c	90	B	**14**	6	B
11a	72	B	**13b**	50	B
11b	54	B	**5**	64	NA

[a] Method A uses a one pot synthesis starting from **1** without isolation and purification of **5**; method B starts from purified **5**.

in [D6]DMSO, however, the two sets of signals coalesce into one set of signals indicating rapid rotation on the NMR time scale of the C–N bond. Similar rotamers have been observed for proline derived amides.[13]

It is worth noting that addition of chiral shift reagents and CD spectra of **11** indicate that no racemisation at the amino acid carbon has occurred, as can be expected when using a relatively weak base (such as pyridine).[14]

Finally we turned our attention to the reaction between **5** and amino alcohols **12a**–**b** (Fig. 6 and Table 2), which gave the amides **13a**–**b** as expected . In the reaction with **12a** a second minor product was formed and isolated, which was shown to be the ester **14**. It appears that, in this case, both the more nucleophilic amine functionality and the less nucleophilic alcohol functionality act as nucleophiles. In all cases we achieved a transamidation under extremely mild conditions. Commonly, transamidations are carried out by intermolecular mechanisms using strong Lewis acids such as $AlCl_3$[15] or $Ti(OPr)_4$.[16] Intramolecular transamidations, otherwise known as "zipper reactions", are more facile but require strong bases.[17]

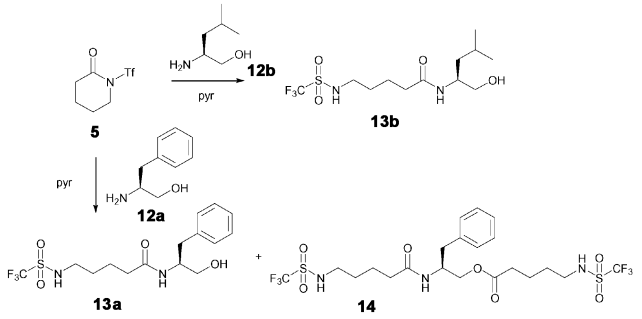

Fig. 6 Reaction of **5** with amino alcohols.

Conclusion

In conclusion, we have shown that triflic anhydride reacts with valerolactam to form *O*-triflated and *N*-triflated derivatives, depending on reaction temperature. In the presence of a basic amine nucleophile, the *O*-triflated intermediate rearranges rapidly to the *N*-triflated imide that can be isolated. The *N*-triflated imide can be used as a highly reactive carbonyl derivative to give an ester and amides in good to excellent yields under extremely mild conditions. The reaction represents a formal transamidation and proceeds (to our knowledge) under the mildest conditions known for such a synthetic transformation, which should prove useful in many areas of medicinal chemistry and organic synthesis. The novel compounds obtained using this reaction are formally dipeptides of ω-amino acids and should be useful intermediates in organic synthesis and interesting derivatives in medicinal chemistry. Furthermore, the chemistry presented offers new prospects for the use of cyclic amides as protecting groups in organic chemistry. In particular, the cyclic amides offer potential for cyclic stereocontrol in the stereoselective synthesis of other open chain amides after deprotection with triflic anhydride.

Experimental

^1H and ^{13}C NMR spectra were recorded on a Bruker Avance 500 MHz spectrometer. δ values are quoted relative to tetramethylsilane (δ_H 0.00 ppm) or chloroform (δ_H 7.26 ppm) for ^1H NMR and relative to chloroform (δ_C 77.23 ppm) for ^{13}C NMR. Coupling constants J are in Hz. All signal assignments are based on ^1H–^1H-COSY and ^1H–^{13}C-HSQC spectra. Microanalysis was carried out using a Leeman CE 440 automatic elemental analyser. Infrared spectra were determined on a Perkin Elmer 2000 Spectrometer. Optical rotations were determined on a Bellingham and Stanley ADO 220 polarimeter. Optical rotations are given in 10^{-1} deg cm^2 g^{-1} and were determined at two concentrations. The mass spectra (m/z) were recorded using a ThermoQuest Finnigan MAT 95 XL spectrometer. ESI were recorded using a Thermofinnigan DECAQPlus spectrometer. Thin layer chromatography (TLC) was carried out on commercially available pre-coated plates (Merck Kieselgel 60 F_{254} silica) using the solvent system stated: Flash column chromatography at a pressure of 1 bar was carried out on Merck Kieselgel 60 (230–400 mesh) silica. Cooled reactions at −42 °C were carried out in an acetonitrile/dry ice bath, all other cooled reactions using a cryostat. All chemicals/reagents were purchased from Lancaster, Acros or the Aldrich Chemical Company. Pet. Ether refers to petroleum ether (bp 40–60 °C).

1-Trifluoromethanesulfonylpiperidin-2-one (5)

Pyridine (0.32 ml, 0.316 g, 4 mmol) was added to piperidin-2-one (0.397 g, 4 mmol) and DCM (20 ml) in a 3-necked flask and the mixture was cooled to −40 °C. Triflic anhydride (0.67 ml, 1.129 g, 4 mmol) was added and the mixture stirred for 2 h at −40 °C.

A saturated solution of $NaHCO_3$ (aq., 80 ml) was added and the organic phase separated, then the product extracted from the aqueous phase with DCM (3 × 20 ml). The combined organic layer was washed with water (40 ml), and the organic phase separated, then the product extracted from the aqueous phase with DCM (3 × 20 ml). The combined organic layer was dried ($MgSO_4$), filtered through Celite and the solvent evaporated *in vacuo* to give a yellow liquid. This contained pyridine by TLC and so was put under high vacuum at 50 °C for 2 h to give a yellow liquid (0.593 g, 64.1%); R_f 0.6 (Pet ether : EtOAc, 55 : 45); (Found: C, 30.5%; H, 3.45%; N, 5.8%. $C_6H_8F_3NO_3S$ requires C, 31.2%; H, 3.5%; N, 6.1%); ν_{max} (neat)/cm^{-1} 1739.19 (C=O stretch of 3° amide), 1401.92 (SO_2 asym. stretch), 1225.97 (CF_3), 1135.54 (SO_2 sym. stretch); δ_H (500 MHz, $CDCl_3$): 3.85 (2H, t, J 6, CH_2N), 2.60 (2H, t, J 6.7, CH_2CO), 1.92 (4H, m, CH_2CH_2N, CH_2CH_2CO); δ_C (125 MHz, $CDCl_3$): 170.62 (CO), 119.86 (q, J 324, CF_3), 49.33 (CH_2N), 34.56 (CH_2CO), 23.10 (CH_2CH_2N), 20.20 (CH_2CH_2CO); δ_N (50.7 MHz, $CDCl_3$): 150.3; m/z (EI) 231 (M^+), 175 ($C_3H_4F_3NO_2S$), 162 ($CH_2NSO_2CF_3$ + H), 69 (CF_3).

NMR experiment: triflation of 1 at variable temperatures

Piperidin-2-one **1** (0.018 g, 0.186 mmol) dissolved in $CDCl_3$ (1 ml) in an NMR tube and was cooled to −70 °C. Triflic anhydride (0.031 ml, 0.052 g, 0.186 mmol) was added, the tube was shaken and ^1H NMR experiments were performed at −60, −45 and −30 °C and at room temperature. The sample was then stored in a refrigerator overnight at 4 °C.

The ^1H NMR of the sample was recorded at room temperature. 2 products were shown in each ^1H NMR experiment, but these are reported separately in this section for ease of reading; −60 °C (213 K): ratio **3** : **2** = 1 : 3.6; −45 °C (228 K): ratio **3** : **2** = 1 : 3.1; −30 °C (243 K): ratio **3** : **2** = 1 : 3.0; 25 °C (298 K): ratio **3** : **2** = 1 : 4.2; For **2**: NMR δ_H (500 MHz, $CDCl_3$): 12.70 (bs, 1H, NH^+), 3.93 (2H, bs, CH_2N), 3.17 (2H, bs, CH_2CO), 2.13 (2H, bs, CH_2CH_2CO), 2.05 (2H, bs, CH_2CH_2N). For (**3**): NMR δ_H (500 MHz, $CDCl_3$): 13.25 (1H, bs, OH), 9.95 (1H, bs, NH), 3.58 (2H, bs, CH_2N), 2.76 (2H, bs, CH_2CO), 1.94 (4H, bs, CH_2CH_2CO, CH_2CH_2N).

5-Trifluoromethanesulfonylaminopentanoic acid ethyl ester (7)

A solution of **5** (0.0216 g, 0.934 mmol) and Na_2CO_3 (0.04 g) in EtOH (10 ml) was stirred in a 3-necked flask overnight at room temperature. The solvent was evaporated *in vacuo*, the solid re-dissolved in DCM (10 ml) and H_2O (10 ml) and the organic phase separated, then the product extracted from the aqueous phase with DCM (3 × 10 ml). The combined organic phase was dried ($MgSO_4$), filtered through Celite and the solvent

evaporated *in vacuo* to give the title compound **7** as a yellow oil (0.020 g, 76.9%); one spot by TLC, R_f 0.9 (Pet ether : EtOAc, 30 : 70); (Found: C, 36.6%; H, 5.5%; N, 4.6%. $C_8H_{14}F_3NO_4S$ requires C, 34.7%; H, 5.1%; N, 5.05%); ν_{max} (neat)/cm^{-1} 3238.0 (NH stretch of 2° amide), 2853.0 (C–H stretch in ether), 1378.0 and 1148.0 (–SO_2NH–), 1233.0 and 1193.0 (CF_3), 1078.0 (CF_3 and C–O stretch in ether). δ_H (500 MHz, $CDCl_3$): 5.57 (1H, bs, NH), 4.15 (2H, q, *J* 7.1, CH_3CH_2), 3.31 (2H, m, CH_2N), 2.37 (2H, t, *J* 7, O=CCH_2), 1.72 (2H, m, O=CCH_2CH_2), 1.66 (2H, m, CH_2CH_2N), 1.27 (m, CH_3); δ_C (125 MHz, $CDCl_3$): 174.10 (C=O), 120.08 (q, *J* 321, CF_3), 61.13 (CH_3CH_2), 44.21 (CH_2N), 33.67 (O=CCH_2), 30.01 (CH_2CH_2N), 21.48 (O=CCH_2CH_2), 14.51 (CH_3); *m*/*z* (CI): 278 (M^+ + H), 232 (M^+ − OEt).

5-Trifluoromethanesulfonylaminopentanethioic acid (*S*-2-aminoethyl) ester (8)

Piperidin-2-one **1** (0.397 g, 4 mmol) in DCM (20 ml) was cooled to −40 °C in a 3-necked flask. Triflic anhydride (0.673 ml, 1.129 g, 4 mmol) and pyridine (0.323 ml, 0.316 g, 4 mmol) were added and the mixture stirred for 2 h 15 min at −40 °C. A solution of 2-aminoethanethiol hydrochloride (0.454 g, 4 mmol) and pyridine (0.646 ml, 0.632 g, 8 mmol) in DCM (20 ml) was added to the reaction which was then stirred for 1 h at −40 °C, then overnight at room temperature. A saturated solution of $NaHCO_3$ (aq., 60 ml) was added, the organic phase separated and the product extracted from the aqueous phase with DCM (3 × 20 ml). The combined organic phase was washed with water (40 ml), the organic phase separated and the product extracted from the aqueous phase with DCM (3 × 20 ml). The combined organic phase was dried ($MgSO_4$), filtered through Celite and the solvent evaporated *in vacuo* to give a yellow/orange liquid. This contained pyridine by TLC as well as 5 other products. ^{1}H NMR showed 3 major products, 1 of which was pyridine. The product was absorbed on 1.79 g silica, then separated by column chromatography (10.22 g silica), using gradient elution (first 544 ml = DCM, second 417 ml = DCM : MeOH, 98 : 2, third 400 ml = DCM : MeOH, 95 : 5) to give imide **5** as a yellow liquid (0.046 g, 5.0%) and the title compound **8** as a: pale yellow oil (0.072 g, 5.6%); one spot on TLC, R_f 0.1 (DCM : MeOH, 95 : 5); δ_H (500 MHz, $CDCl_3$): 8.20 (1H, bs, NHTf), 6.62 (2H, bs, NH_2), 3.41 (2H, m, NH_2CH_2), 3.25 (2H, m, CH_2NHTf), 3.01 (2H, t, *J* 6.3, CH_2S), 2.21 (2H, t, *J* 7.2, $SCOCH_2$), 1.73 (2H, m, $SCOCH_2CH_2$), 1.64 (2H, m, CH_2CH_2NHTf); δ_C (125 MHz, $CDCl_3$): 199.80 (CO), 120.03 (q, *J* 322, CF_3), 43.69 (NH_2CH_2), 43.55 (CH_2NHTf), 39.25 (CH_2S), 35.50 ($SCOCH_2$), 28.85 ($SCOCH_2CH_2$), 22.49 (CH_2CH_2NHTf); *m*/*z* (GCMS, EI): 308 (M^+), 232 (M^+ − $SCH_2CH_2NH_2$), 204 (M^+ − $COSCH_2CH_2NH_2$), 162 ($CH_2NHSO_2CF_3$).

5-Trifluoromethanesulfonylaminopentanoic acid benzylamide (9a)

A solution of **5** (0.022 g, 0.095 mmol) and benzylamine (0.01 ml, 0.01 g, 0.095 mmol) in DCM (10 ml) was stirred in a 3-necked flask overnight at room temperature. The product was washed with 3M HCl (aq., 10 ml) and the organic phase separated, then the product extracted from the aqueous phase with DCM (3 × 5 ml). This washing process was repeated, then the combined organic phase was dried ($MgSO_4$). The solvent was evaporated *in vacuo* to give the title compound **9a** as a yellow/orange liquid (0.010 g, 31.0%); ν_{max} (neat)/cm^{-1} 3300.0 and 3068.0 (NH stretch of 2° amide), 1650.0 (C=O stretch of 2° amide), 1538.0 (NH bend of 2° amide), 1456.0 (CH_2 scissoring bend), 1372.0 and 1148.0 (–SO_2NH–), 1230.0 and 1192.0 (CF_3), 1080.0 (CF_3). δ_H (500 MHz, $CDCl_3$): 7.29 (m, Ph), 6.93 (1H, bs, NHTf), 5.94 (1H, bs, NHCO), 4.41 (2H, bs, $PhCH_2$), 3.28 (2H, bs, CH_2NHTf), 2.26 (2H, bs, $NCOCH_2$), 1.76 (2H, bs, $NCOCH_2CH_2$), 1.65 (2H, bs, CH_2CH_2N); δ_C (125 MHz, $CDCl_3$): 173.22 (CO), 127.91 + 128.03 + 129.02 + 138.02 (Ph), 120.05 (q, *J* 322, CF_3), 44.02 ($PhCH_2$), 43.78 (CH_2NHTf), 35.46 ($NCOCH_2$), 29.58 (CH_2CH_2N), 21.83 ($NCOCH_2CH_2$); *m*/*z* (CI): 339 (M^+ + H).

5-Trifluoromethanesulfonylaminopentanoic acid (2,2-dimethoxy-ethyl)amide (9b)

Pyridine (0.105 ml, 0.103 g, 1.3 mmol) was added to a solution of piperidin-2-one **1** (0.129 g, 1.3 mmol) in DCM (7 ml) in a 3-necked flask and the mixture was cooled to −46 °C. Triflic anhydride (0.219 ml, 0.366 g, 1.3 mmol) was added and the mixture stirred for 2 h at −46 °C. Pyridine (0.105 ml, 0.103 g, 1.3 mmol), amino acetaldehyde dimethylacetal (0.143 ml, 0.137 g, 1.3 mmol), and DCM (7 ml) were added and the solution stirred for 1.5 h at −46 °C, then overnight at room temperature. A saturated solution of $NaHCO_3$ (aq., 30 ml) was added, the organic phase separated, then the product extracted from the aqueous layer with DCM (3 × 10 ml). The combined organic phase was treated with a saturated solution of $NaHCO_3$ (aq., 30 ml), the organic phase separated and the product extracted from the aqueous phase with DCM (3 × 10 ml). The combined organic phase was washed with water (20 ml), the organic phase separated and the product extracted from the aqueous layer with DCM (3 × 10 ml). The combined organic phase was dried ($MgSO_4$), filtered through Celite and the solvent evaporated *in vacuo* to give a brown/orange oil. This contained pyridine by TLC and ^{1}H NMR, so was put under high vacuum at 40 °C for 1 h to give a brown/orange oil (0.206 g). TLC and ^{1}H NMR of this crude product showed a mixture of 3 products.

The product was absorbed on 2.3 g silica, then separated by column chromatography (9.2 g silica), using gradient elution (first 187 ml = Pet. Ether : EtOAc, 40 : 60, second 220 ml = EtOAc, third 555 ml = EtOAc : MeOH, 97 : 3, fourth 400 ml = EtOAc : MeOH, 95 : 5) to give the title compound **9b** as a clear, colourless oil (0.151 g, 34.5%); one spot by TLC, R_f 0.56 (EtOAc); (Found: C, 34.9%; H, 5.6%; N, 8.35%. $C_{10}H_{19}F_3N_2O_5S$ requires C, 35.7%; H, 5.7%; N, 8.3%); ν_{max} (neat)/cm^{-1} 3432.0, 3318.0 and 3091.0 (NH stretch of 2° amide), 2946.0 (C–H stretch in ether), 1651.0 (C=O stretch of 2° amide), 1547.0 (NH bend of 2° amide), 1461.0 (CH_2 scissoring bend), 1373.0 and 1150.0 (–SO_2NH–), 1231.0 and 1192.0 (CF_3), 1077.0 (CF_3 and C–O stretch in ether); δ_H (500 MHz, $CDCl_3$): 7.45 (1H, bs, NHTf), 6.14 (1H, bs, NHCO), 4.38 (1H, t, *J* 5, CH), 3.38 (8H, m, $CHCH_2$, CH_3), 3.28 (2H, m, CH_2NHTf), 2.26 (2H, t, *J* 7, $NCOCH_2$), 1.72 (2H, m, $NCOCH_2CH_2$), 1.64 (2H, m, CH_2CH_2N); δ_C (125 MHz, $CDCl_3$): 173.70 (CO), 120.01 (q, *J* 322, CF_3), 102.64 (CH), 54.53 (CH_3), 43.74 (CH_2NHTf), 41.09 ($CHCH_2$), 35.42 ($NCOCH_2$), 29.42 ($NCOCH_2CH_2$), 22.07 (CH_2CH_2N); *m*/*z* (CI): 337 (M^+ + H), 306 (M^+ − OEt + H), 305 (M^+ − OEt).

5-Trifluoromethanesulfonylaminopentanoic acid (2,2-diethoxy-ethyl)amide (9c)

Compound **1** (0.150 g, 0.648 mmol) in DCM (3.5 ml) was cooled to −46 °C in a 3-necked flask. Pyridine (0.209 ml, 0.205 g, 2.594 mmol), amino acetaldehyde diethylacetal (0.094 ml, 0.086 g, 0.648 mmol), and DCM (3.5 ml) were added and the solution stirred for 30 min at −46 °C, then overnight at room temperature. A saturated solution of $NaHCO_3$ (aq., 15 ml) was added and the organic phase separated, then the product extracted from the aqueous phase with DCM (3 × 5 ml). The combined organic phase was washed with water (10 ml) and the organic phase separated, then the product extracted from the aqueous phase with DCM (3 × 5 ml). The combined organic phase was dried ($MgSO_4$), filtered through Celite and the solvent evaporated under high vacuum at 55 °C to give the title compound **9c** as a yellow oil (0.212 g, 89.9%); one spot by TLC, R_f 0.569 (EtOAc); (Found: C, 39.7%; H, 6.8%; N, 7.3%. $C_{12}H_{23}F_3N_2O_5S$ requires C, 39.6%; H, 6.4%; N, 7.7%,); ν_{max} (neat)/cm^{-1} 3313.1 and 3098.7 (NH stretch of 2° amide), 2886.6 (C–H stretch in ether), 1652.0

(C=O stretch of 2° amide), 1541.4 (NH bend of 2° amide), 1447.2 (CH_2 scissoring bend), 1374.7 and 1149.4 (–SO_2NH–), 1230.4 and 1190.1 (CF_3), 1074.4 (CF_3 and C–O stretch in ether); δ_H (500 MHz, $CDCl_3$): 7.20 (1H, bs, NHTf), 5.97 (1H, bs, NHCO), 4.49 (1H, t, *J* 5.0, CH), 3.69 (2H, m, CH_3CH_2), 3.53 (2H, m, CH_3CH_2'), 3.36 (2H, t, *J* 5.4, $CHCH_2NH$), 3.27 (2H, m, CH_2NHTf), 2.24 (2H, t, *J* 7, $COCH_2$), 1.72 (2H, m, $COCH_2CH_2$), 1.64 (2H, m, CH_2CH_2N), 1.20 (6H, t, *J* 7, CH_3); δ_C (125 MHz, $CDCl_3$): 173.30 (CO), 119.74 (q, *J* 321, CF_3), 100.35 (CH), 62.83 (CH_3CH_2), 43.50 (CH_2NHTf), 41.85 ($CHCH_2NH$), 35.20 ($COCH_2$), 29.20 (CH_2CH_2N), 21.72 ($COCH_2CH_2$), 15.07 (CH_3); *m*/*z* (EI): 319 (M^+ − OEt), 273 (M^+ − (2(OEt) + H)), 162 (CH_2NHTf), 103 ($CH(OEt)_2$).

5-Trifluoromethanesulfonylaminopentanoic acid (2,2-diethoxy-ethyl)amide (9c) by reaction from 5

Compound **5** (0.043 g, 0.187 mmol) in DCM (10 ml) was cooled to −46 °C in a 3-necked flask. Amino acetaldehyde diethylacetal (0.027 ml, 0.025 g, 0.187 mmol), pyridine (0.06 ml, 0.059 g, 0.748 mmol) and DCM (10 ml) were added and the solution stirred for 30 min at −46 °C, then overnight at room temperature. A saturated solution of $NaHCO_3$ (aq., 22 ml) was added and the organic phase separated, then the product extracted from the aqueous phase with DCM (3 × 10 ml). The combined organic phase was washed with water (10 ml) and the organic phase separated, then the product extracted from the aqueous phase with DCM (3 × 10 ml). The combined organic phase was dried ($MgSO_4$), filtered through Celite and the solvent evaporated under high vacuum at 40 °C to give the title compound **9c** as a yellow oil (0.032 g, 47.0%).

(2*S*) 2-(5-Trifluoromethanesulfonylaminopentanoylamino)-propionic acid *tert*-butyl ester (11a)

A solution of **5** (0.231 g, 1 mmol) in DCM (5 ml) was cooled to −40 °C in a 3-necked flask. Pyridine (0.08 ml, 0.079 g, 1 mmol) and L-alanine *t*-butyl ester hydrochloride **10a** (0.182 g, 1 mmol) were added and the solution stirred for 30 min at −40 °C, then overnight at room temperature. A saturated solution of $NaHCO_3$ (aq., 20 ml) was added, the organic phase separated and the product extracted from the aqueous phase with DCM (3 × 5 ml). The combined organic phase was washed with water (10 ml), the organic layer separated and the product extracted from the aqueous phase with DCM (3 × 5 ml). The combined organic phase was dried ($MgSO_4$), filtered through Celite and the solvent evaporated *in vacuo* to give a yellow/orange oil. This contained pyridine by TLC and ^{1}H NMR, so was put under high vacuum at 55 °C for 1.5 h to give a pale yellow oil (0.336 g). TLC and ^{1}H NMR of this crude product showed 2 main products, with two further impurities. The crude product was absorbed on 1.176 g silica, then separated by column chromatography (6.72 g silica), using gradient elution (first 70 ml = Pet. Ether, second 270 ml = Pet. Ether : EtOAc 70 : 30, third 50 ml = Pet. Ether : EtOAc 50 : 50, fourth 255 ml = EtOAc) to give the title compound **11a** as a clear, colourless oil (0.270 g, 71.7%); $[\alpha]_D^{25}$ − 49.38 [*c* 0.08, CH_2Cl_2, 1-dl]; (Found: C, 41.4%; H, 6.3%; N 7.3%. $C_{13}H_{23}F_3N_2O_5S$ requires C, 41.5%; H, 6.2%; N, 7.4%); ν_{max} (neat)/cm^{-1} 3403.0 (NH stretch of amine), 3303.0 and 3093.0 (NH stretch of 2° amide), 2982.0 and 2881.0 (CH_3), 2940.0 and 2830.0 (CH_2), 1728.0 (C=O stretch of ester), 1651.0 (C=O of 2° amide), 1536.0 (NH bend of acyclic 2° amide), 1371.0 and 1152.0 (–SO_2NH–), 1231.0, 1192.0 and 1081.0 (CF_3); δ_H (500 MHz, $CDCl_3$): 7.21 (1H, bs, NHTf), 6.34 (1H, d, *J* 7.29, CONH), 4.43 (1H, m, CH), 3.29 (2H, t, *J* 6.3, $NHCH_2$), 2.28 (2H, t, *J* 7, CH_2CO), 1.74 (2H, m, CH_2CH_2CO), 1.65 (2H, m, $NHCH_2CH_2$), 1.47 (9H, s, *t*-butyl), 1.36 (3H, d, *J* 7.2, $CHCH_3$); δ_C (125 MHz, $CDCl_3$): 172.84 ($CHCO_2$), 172.78 (CH_2CO), 120.04 (q, *J* 322, CF_3), 82.57 ($OC(CH_3)_3$), 48.89 (CH), 43.81 ($NHCH_2$), 35.32 (CH_2CO), 29.36 ($NHCH_2CH_2$), 28.06 ($OC(CH_3)_3$), 21.92 (CH_2CH_2CO), 18.47 ($CHCH_3$); *m*/*z* (CI): 377 (M^+ + H), 361 (M^+ − CH_3), 321 (M^+ − $C(CH_3)_3$ + 2H).

1-(5-Trifluoromethanesulfonylaminopentanoyl)pyrrolidine-2-carboxylic acid benzyl ester (11b)

A solution of **5** (0.108 g, 0.467 mmol) in DCM (2.5 ml) was cooled to −40 °C in a 3-necked flask. Pyridine (0.038 ml, 0.037 g, 0.467 mmol) and L-proline benzyl ester hydrochloride **10b** (0.113 g, 0.467 mmol) were added and the solution stirred for 30 min at −40 °C, then overnight at room temperature. A saturated solution of $NaHCO_3$ (aq., 10 ml) was added, the organic phase separated and the product extracted from the aqueous phase with DCM (3 × 2.5 ml). The combined organic phase was washed with water (5 ml), the organic phase separated and the product extracted from the aqueous phase with DCM (3 × 2.5 ml). The combined organic phase was dried ($MgSO_4$), filtered through Celite and the solvent evaporated *in vacuo* to give a yellow/orange oil. This contained pyridine by TLC and ^{1}H NMR so was put under high vacuum at 55 °C for 2 h to give a yellow/orange oil (0.165 g).

The crude product was absorbed on 0.5 g silica, then separated by column chromatography (3.75 g silica), using gradient elution (first 25 ml = Pet. Ether, second 170 ml = Pet. Ether : EtOAc 90 : 10, third 50 ml = Pet. Ether : EtOAc 70 : 30, fourth 188 ml = Pet. Ether : EtOAc 40 : 60, fifth 136 ml = EtOAc, sixth 519 ml = EtOAc : MeOH 97 : 3) to give crude **11b** as a clear, colourless oil (0.130 g, 63.8%). This was crystallised from DCM, then the solid washed with hexane on a sintered filter funnel to give the title compound **11b** as a white powder (0.110 g, 54.0%); mp 80–82 °C; $[\alpha]_D^{25}$ − 41.67 [*c* 0.12, CH_2Cl_2, 1-dl]; One spot by TLC, R_f 0.4 (Pet. ether : EtOAc, 40 : 60); ν_{max} (nujol mull)/cm^{-1} 3110.0 (NH stretch of 2° amide), 1740.0 (C=O stretch of ester), 1630.0 (C=O stretch of 2° amide), 1456.0 (CH_2 scissoring bend), 1376.0 and 1159.0 (–SO_2NH–), 1232.0, 1182.0 and 1065.0 (CF_3), 757.2 and 705.8 (oop bend of aromatic ring CH); δ_H (500 MHz, [D6]DMSO, 298 K): (ratio rotamer **A** : **B** = 1 : 4) 9.33 (1H, bs, NH [**A** + **B**]), 7.34–7.39 (5H, m, Ph [**A** + **B**]), 5.18 (2H, bs, OCH_2 [**B**]), 5.11 (2H, m, OCH_2 [**A**]), 4.66 (1H, m, CH [**B**]), 4.34 (1H, m, CH [**A**]), 3.52 (2H, m, $CONCH_2$ [**A** + **B**]), 3.13 (2H, bs, $NHCH_2$ [**A**]), 3.08 (2H, bs, $NHCH_2$ [**B**]), 2.30 (2H, m, CH_2CO [**A**]), 2.23 (2H, m, CH_2CO [**B**]), 2.18 (2H, m, CH_2CH [**A**]), 2.06 (2H, m, CH_2CH [**B**]), 1.91 (2H, m, CH_2CH_2CH [**A**]), 1.84 (2H, m, CH_2CH_2CH [**B**]), 1.52 (4H, bs, CH_2CH_2CO, $NHCH_2CH_2$ [**A**]), 1.44 (4H, m, CH_2CH_2CO, $NHCH_2CH_2$ [**B**]); NMR δ_H (500 MHz, [D6]DMSO, 423 K): 8.61 (1H, bs, NH), 7.32–7.38 (5H, m, Ph), 5.15 (2H, bs, OCH_2), 4.48 (1H, m, CH), 3.55 (2H, m, $CONCH_2$), 3.16 (2H, bs, $NHCH_2$), 2.28 (2H, m, CH_2CO), 2.23 (2H, m, CH_2CH), 1.94 (2H, bs, CH_2CH_2CH), 1.61 (4H, bs, CH_2CH_2CO, $NHCH_2CH_2$); δ_C (125 MHz, $CDCl_3$, 298 K): 172.34, 135.85 (CO [**A**]), 172.10, 135.38 (CO [**B**]), 128.36–128.98 (Ph [**A** + **B**]), 120.14 (q, *J* 320, CF_3 [**A** + **B**]), 67.66 (OCH_2 [**B**]), 67.15 (OCH_2 [**A**]), 59.78 (CH [**B**]), 59.15 (CH [**A**]), 47.34 ($OCNCH_2$ [**A**]), 46.84 ($OCNCH_2$ [**B**]), 43.66 ($NHCH_2$ [**A** + **B**]), 33.52 (CH_2CO [**A**]), 33.37 (CH_2CO [**B**]), 31.59 ($NHCH_2CH_2$ [**B**]), 29.58 ($CHCH_2$ [**B**]), 29.49 ($NHCH_2CH_2$ [**A**]), 29.34 ($CHCH_2$ [**A**]), 24.94 ($CHCH_2CH_2$ [**A**]), 22.72 ($CHCH_2CH_2$ [**B**]), 20.74 (CH_2CH_2CO [**B**]), 20.57 (CH_2CH_2CO [**A**]); Found (CI): 437.1360 (M^+ + H), $C_{18}H_{23}F_3N_2O_5S$ + H requires 437.1353; *m*/*z* (CI): 438 (M^+ + 2H), 437 (M^+ + H), 301 (M^+ − CO_2CH_2Ph).

(2*S*) 3-Phenyl-2-(5-trifluoromethanesulfonylamino-pentanoylamino)-1-propionic acid methyl ester (11c)

Pyridine (0.070 ml, 0.068 g, 0.865 mmol) was added to a solution of **5** (0.2 g, 0.865 mmol) in DCM (2 ml) in a reaction vessel and the mixture was cooled to −42 °C. L-Phenylalanine methyl ester hydrochloride **10c** (0.205 g, 0.952 mmol) was added and the solution stirred for 30 min at −40 °C, then overnight at room temperature. A saturated solution of $NaHCO_3$ (aq., 17.5 ml) was added, the organic phase separated and the product extracted

from the aqueous phase with DCM (3 × 4 ml). The combined organic phase was washed with water (8 ml), the organic phase separated and the product extracted from the aqueous phase with DCM (3 × 4 ml). The combined organic phase was dried ($MgSO_4$), filtered through Celite and the solvent evaporated *in vacuo* to give a yellow liquid. This contained pyridine by TLC, so it was evaporated using a Genevac EZ-2 at 52 °C on setting "med b.p." for 1.5 h to give the title compound **11c** as a yellow oil (0.35 g, 98.6%); $[\alpha]_D^{27.3}$ + 22.22 [*c* 0.18, CH_2Cl_2, 1-dl]; (Found C, 48.25%; H, 5.4%; N, 6.7%. $C_{16}H_{21}F_3N_2O_5S$ requires C, 46.8%; H, 5.2%; N, 6.8%); ν_{max} (neat)/cm^{-1} 3298.0 and 3066.0 (NH stretch of 2° amide), 2955.0 (CH_2 asymmetric stretch), 2879.0 (CH_2 symmetric stretch), 1742.0 (C=O stretch in aliphatic ester), 1652.0 (C=O stretch of 2° amide), 1532.0 (NH bend of 2° amide), 1439.0 (CH_2 scissoring bend), 1373.0 and 1149.0 (–SO_2NH–), 1230.0, 1191.0 and 1081.0 (CF_3), 746.1 and 702.3 (oop bend of aromatic ring CH); NMR δ_H (500 MHz, [D6]DMSO, 298 K): (ratio rotamer **A** : **B** = 1 : 4) 8.29 (1H, d, *J* 7.8, NHCH [**A** + **B**]), 7.17–7.29 (5H, m, Ph [**A** + **B**]), 6–7.1 (1H, bs, NHTf [**A** + **B**]), 4.46 (1H, m, CH [**A** + **B**]), 3.59 (3H, s, CH_3 [**A**]), 3.58 (3H, s, CH_3 [**B**]), 3.07 (3H, t, *J* 6.8, NHCH_2 [**A** + **B**]), 3.02 (1H, d of d, *J* 5.4, 13.7, CH_2Ph′ [**A**]), 2.87 (1H, d of d, *J* 9.7, 13.7, CH_2Ph [**A**], CH_2Ph′ [**B**]), 2.79 (1H, d of d, *J* 7.2, 13.4, CH_2Ph [**B**]), 2.07 (2H, m, CH_2CO [**A** + **B**]), 1.44 (2H, m, C$H_2$$CH_2$CO [**A** + **B**]), 1.36 (2H, m, NHCH_2CH_2 [**A** + **B**]); NMR δ_H (500 MHz, [D6]DMSO, 398 K): 7.66 (1H, bs, NHCH), 7.17–7.26 (5H, m, Ph), 5.9–6.5 (1H, bs, NHTf), 4.55 (1H, m, CH), 3.60 (3H, s, CH_3), 3.09 (2H, t, *J* 6.3, NHCH_2), 3.04 (1H, d of d, *J* 5.9, 14.0, CH_2Ph′), 2.92 (1H, d of d, *J* 8.4, 14.1, CH_2Ph), 2.10 (2H, m, CH_2CO), 1.49 (4H, m, C$H_2$$CH_2CO, NHCH_2CH_2$); δ_C (75.5 MHz, $CDCl_3$): 172.61 (*C*O[**A** + **B**]), 172.30 (CO[**A** + **B**]), 126.88 + 127.28 + 128.61 + 128.72 + 129.16 + 129.28 + 135.69 + 137.20 (Ph [**A** + **B**]), 119.81 (q, *J* 321, CF_3 [**A** + **B**]), 55.81 (CH [**B**]), 53.07 (CH [**A**]), 52.53 (CH_3 [**A**]), 52.00 (CH_3 [**B**]), 43.49 ($NHCH_2$ [**A** + **B**]), 41.11 (CH*C*H_2 [**B**]), 37.76 (CH*C*H_2 [**A**]), 34.84 (*C*H_2CO [**A** + **B**]), 28.97 (NHCH_2*C*H_2 [**A** + **B**]), 21.26 (*C*$H_2$$CH_2$CO [**A** + **B**]); Found (CI) 411.1196 (M^+ + H), $C_{16}H_{21}F_3N_2O_5S$ + H requires 411.1196; LCMS: 1 fraction, *m*/*z* (ESI): 449 (M^+ + K), 433 (M^+ + Na), 411 (M^+ + H).

2-(5-Trifluoromethanesulfonylaminopentanoylamino)-1,5-pentanedioic acid dimethyl ester (11d)

A solution of **5** (0.108 g, 0.467 mmol) in DCM (2.5 ml) was cooled to −40 °C in a 3-necked flask. Pyridine (0.038 ml, 0.037 g, 0.467 mmol), L-glutamic acid dimethyl ester hydrochloride (0.099 g, 0.467 mmol) were added and the solution stirred for 30 min at −40 °C, then overnight at room temperature. A saturated solution of $NaHCO_3$ (aq., 10 ml) was added, the organic phase separated and the product extracted from the aqueous phase with DCM (3 × 2.5 ml). The combined organic phase was washed with water (5 ml), the organic phase separated and the product extracted from the aqueous phase with DCM (3 × 2.5 ml). The combined organic phase was dried ($MgSO_4$), filtered through Celite and the solvent evaporated *in vacuo* to give a yellow/orange oil. This contained pyridine by TLC and ^{1}H NMR so was put under high vacuum at 55 °C for 2 h to give a yellow/orange wax (0.112 g). The crude product was absorbed on 0.39 g silica, then separated by column chromatography (2.5 g silica), using gradient elution (first 50 ml = Pet. Ether, second 290 ml = Pet. Ether : EtOAc 70 : 30, third 136 ml = Pet. Ether : EtOAc 60 : 40, fourth 250 ml = EtOAc) to give the title compound **11d** as a: clear, colourless oil (0.080 g, 42.2%); $[\alpha]_D^{24.1}$ + 11.63 [*c* 0.43, CH_2Cl_2, 1-dl]; one spot by TLC, R_f 0.2 (Pet ether : EtOAc, 40 : 60); (Found C, 38.7%; H, 5.45%; N, 6.4%. $C_{13}H_{21}F_3N_2O_7S$ requires C, 38.4%; H, 5.2%; N, 6.9%); ν_{max} (neat)/cm^{-1} 3278.0 and 3089.0 (NH stretch of 2° amide), 2957.0 (CH_2 asymmetric stretch), 2868.0 (CH_2 symmetric stretch), 1741.0 (C=O stretch of ester), 1653.0 (C=O stretch of 2° amide), 1538.0 (NH bend of acyclic 2° amide), 1440.0 (CH_2 scissoring bend), 1374.0 and 1150.0 (–SO_2NH–), 1230.0, 1188.0 and 1080.0 (CF_3); δ_H (500 MHz, $CDCl_3$): 6.72 (1H, bs, NHTf), 6.55 (1H, d, *J* 7.55, CONH), 4.59 (1H, m, CH), 3.76 (3H, s, $CHCO_2C$*H*$_3$), 3.69 (3H, s, CH_2CO_2C*H*$_3$), 3.30 (2H, t, *J* 6.4, NHCH_2), 2.41 (2H, m, CH_2CO_2), 2.31 (2H, t, *J* 6.9, CH_2CONH), 2.19 (1H, m, CHCH_2), 2.02 (1H, m, CHCH_2′), 1.75 (2H, m, C$H_2$$CH_2$CONH), 1.65 (2H, m, NHC$H_2CH_2$); δ_C (125 MHz, $CDCl_3$): 173.81 (CH*C*O_2), 173.40 (CH_2*C*O_2), 172.65 (CONH), 120.04 (q, *J* 321, CF_3), 52.83 ($CHCO_2$*C*H_3), 52.19 (CH_2CO_2*C*H_3), 52.02 (CH), 43.80 ($NHCH_2$), 35.22 (*C*H_2CONH), 30.28 (*C*$H_2$$CO_2$), 29.32 ($NHCH_2$*C*$H_2$), 27.04 (CH*C*$H_2$), 21.82 (*C*$H_2$$CH_2$CON); *m*/*z* (CI): 408 (M^+ + 2H), 407 (M^+ + H), 375 (M^+ − OMe).

(2*S*) 4-Methyl-2-(5-trifluoromethanesulfonylaminopentanoylamino)-1-pentanoic acid methyl ester (11e)

Pyridine (0.070 ml, 0.068 g, 0.865 mmol) was added to a solution of **5** (0.2 g, 0.865 mmol) in DCM (2 ml) in a reaction vessel and the mixture was cooled to −42 °C. L-Leucine methyl ester hydrochloride **10e** (0.173 g, 0.952 mmol) was added and the solution stirred for 30 min at −42 °C, then overnight at room temperature. A saturated solution of $NaHCO_3$ (aq., 17.5 ml) was added, the organic phase separated and the product extracted from the aqueous phase with DCM (3 × 4 ml). The combined organic phase was washed with water (8 ml), the organic phase separated and the product extracted from the aqueous phase with DCM (3 × 4 ml). The combined organic phase was dried ($MgSO_4$), filtered through Celite and the solvent evaporated *in vacuo* to give a yellow liquid. This contained pyridine by TLC so it was evaporated using a Genevac EZ-2 at 50 °C on setting "med b.p." for 2 h to give the title compound **11e** as a yellow oil (0.298 g, 91.5%); $[\alpha]_D^{27.3}$ + 9.09 [*c* 0.11, CH_2Cl_2, 1-dl]; one spot by TLC, R_f 0.2 [Heptane 50: EtOAc 50]; ν_{max} (neat)/cm^{-1} 3289.0 and 3085.0 (NH stretch of 2° amide), 2961.0 (CH_2 asymmetric stretch), 2872.0 (CH_2 symmetric stretch), 1733.0 (C=O stretch in aliphatic ester), 1650.0 (C=O stretch of 2° amide), 1536.0 (NH bend of 2° amide), 1440.0 (CH_2 scissoring bend), 1373.0 and 1149.0 (–SO_2NH–), 1261.0 (C–C(=O)–O stretch of ester), 1230.0, 1188.0 and 1081.0 (CF_3); δ_H (500 MHz, $CDCl_3$): 6.56 (1H, bs, NHTf), 5.94 (1H, d, *J* 8.1, CONH), 4.61 (1H, m, NHC*H*), 3.75 (3H, s, OCH_3), 3.30 (2H, m, $NHCH_2$), 2.31 (2H, t, *J* 6.7, CH_2CO), 1.80 (2H, m, C$H_2$$CH_2$CO), 1.66 (4H, m, $NHCH_2$CH_2, CHCH_2, C*H*$(CH_3)_2$), 1.54 (1H, m, CHCH_2′), 0.94 (6H, m, $CHCH_3$, $CHCH_3$′); δ_C (125 MHz, $CDCl_3$): 174.20 (*C*O_2CH_3), 173.19 (CONH), 119.99 (q, *J* 321, CF_3), 52.72 (OCH_3), 51.05 (NHCH), 43.72 ($NHCH_2$), 41.48 (CH*C*H_2), 35.04 (*C*H_2CO), 29.92 ($NHCH_2$*C*H_2), 25.14 (*C*H$(CH_3)_2$), 22.99 (CH_3), 21.99 (CH_3′), 21.59 ($NHCH_2CH_2$*C*H_2); Found (CI) 377.1353 (M^+ + H), $C_{13}H_{23}F_3N_2O_5S$ + H requires 377.1353; *m*/*z* (CI) 377 (M^+ + H), 345 (M^+ − OMe), 317 (M^+ − CO_2Me); LCMS: 1 fraction, *m*/*z* (ESI): 377 (M^+ + H), 399 (M^+ + Na), 415 (M^+ + K).

(2*S*) 3-Methyl-2-(5-trifluoromethanesulfonylaminopentanoylamino)-1-butyric acid methyl ester (11f)

Pyridine (0.070 ml, 0.068 g, 0.865 mmol) was added to a solution of **5** (0.2 g, 0.865 mmol) in DCM (2 ml) in a reaction vessel and the mixture was cooled to −42 °C. L-Valine methyl ester hydrochloride **10f** (0.160 g, 0.952 mmol) was added and the solution stirred for 30 min at −42 °C, then overnight at room temperature. A saturated solution of $NaHCO_3$ (aq., 17.5 ml) was added, the organic phase separated and the product extracted from the aqueous phase with DCM (3 × 4 ml). The combined organic phase was washed with water (8 ml), the organic phase separated and the product extracted from the aqueous phase with DCM (3 × 4 ml). The combined organic phase was dried ($MgSO_4$), filtered through Celite and the solvent evaporated *in vacuo* to give a yellow liquid. This contained pyridine by TLC

so it was evaporated using a Genevac EZ-2 at 52 °C on setting "med b.p." for 1.5 h to give the title compound **11f** as a yellow oil (0.244 g, 77.9%); $[a]_D^{27.6}$ − 5.00 [*c* 0.20, CH_2Cl_2, 1-dl]; one spot by TLC, R_f 0.3 [Pet ether : EtOAc, 50 : 50]; ν_{max} (neat)/cm^{-1} 3300.0 and 3094.0 (NH stretch of 2° amide), 2965.0 (CH_2 asymmetric stretch), 2880.0 (CH_2 symmetric stretch), 1733.0 (C=O stretch in aliphatic ester), 1651.0 (C=O stretch of 2° amide), 1535.0 (NH bend of 2° amide), 1439.0 (CH_2 scissoring bend), 1374.0 and 1150.0 (–SO_2NH–), 1264.0 (C–C(=O)–O stretch of ester), 1230.0, 1188.0 and 1081.0 (CF_3); δ_H (500 MHz, $CDCl_3$): 7.24 (1H, bs, TfNH), 6.43 (1H, d, *J* 8.8, N*H*CH), 4.52 (1H, d of d, *J* 5.2, 8.8, NHC*H*), 3.74 (3H, s, OCH_3), 3.28 (2H, t, *J* 6.5, NHCH_2), 2.31 (2H, t, *J* 7.1, CH_2CO), 2.15 (1H, m, C*H*$(CH_3)_2$), 1.73 (2H, m, CH_2CH_2CO), 1.64 (2H, m, NHCH_2CH_2), 0.93 (3H, d, *J* 6.9, CHCH_3), 0.90 (3H, d, *J* 6.9, CHCH_3'); δ_C (75.5 MHz, $CDCl_3$): 173.03 (CO_2CH_3), 172.82 (CONH), 119.81 (q, *J* 244, CF_3), 57.18 (NHCH), 52.33 (OCH_3), 43.55 ($NHCH_2$), 34.97 (CH_2CO), 31.03 ($CH(CH_3)_2$), 29.06 (NHCH_2CH_2), 21.37 (CH_2CH_2CO), 18.97 (CH_3), 17.79 (CH_3'); Found (CI) 363.1173 (M^+ + H), $C_{12}H_{21}F_3N_2O_5S$ + H requires 363.1196; *m*/*z* (CI) 363 (M^+ + H), 331 (M^+ − OMe), 303 ((M^+ − CO_2Me).

(2*S*) 5-Trifluoromethanesulfonylaminopentanoic acid (1-benzyl-2-hydroxyethyl)amide (13a)

Pyridine (0.052 ml, 0.051 g, 0.641 mmol) was added to a solution of **5** (0.148 g, 0.641 mmol) in DCM (1.6 ml) in a reaction vessel and the mixture was cooled to −42 °C. L-Phenylalaninol **12a** (0.097 g, 0.641 mmol) was added and the solution stirred for 30 min at −42 °C, then overnight at room temperature. A saturated solution of $NaHCO_3$ (aq., 13 ml) was added, the organic phase separated and the product extracted from the aqueous phase with DCM (3 × 3 ml). The combined organic phase was washed with water (6 ml), the organic phase separated and the product extracted from the aqueous phase with DCM (3 × 3 ml). The combined organic phase was dried ($MgSO_4$), filtered through Celite and the solvent evaporated *in vacuo* to give a clear, pale yellow liquid. This contained pyridine by TLC so was put under high vacuum at 50 °C for 4 h to give a clear very pale yellow oil (0.160 g). TLC showed 3 products and NMR showed the product to be impure, so the crude product was absorbed onto a preparative TLC plate (20 cm × 20 cm SiO_2) and developed using EtOAc as the eluant to give the title compound **13a** as a clear, colourless oil (0.052 g, 21.2%); $[a]_D^{27.1}$ − 10.53 [*c* 0.38, CH_2Cl_2, 1-dl]; one spot by TLC, R_f 0.4 [EtOAc]; ν_{max} (neat)/cm^{-1} 3308.0 and 3089.0 (NH stretch of 2° amide), 2939.0 (CH_2 asymmetric stretch), 2878.0 (CH_2 symmetric stretch), 1649.0 (C=O stretch of 2° amide), 1537.0 (NH bend of 2° amide), 1371.0 and 1148.0 (–SO_2NH–), 1230.0, 1191.0 and 1080.0 (CF_3), 748.3 and 702.1 (oop bend of aromatic ring CH); δ_H (500 MHz, $CDCl_3$): 7.17–7.30 (5H, m, Ph), 6.05 (1H, d, *J* 8.2, CONH), 4.23 (1H, s, CH), 3.75 (1H, s, SO_2NH), 3.68 (1H, dd, *J* 3.3 and 11, CH_2OH), 3.53 (1H, dd, *J* 5.9 and 11, CH_2OH), 3.18 (2H, m, NHCH_2), 2.84 (1H, dd, *J* 6.9 and 13.8, CH_2Ph), 2.78 (1H, dd, *J* 7.7 and 13.8, CH_2Ph), 2.16 (2H, m, CH_2CO), 1.62 (2H, m, CH_2CH_2CO), 1.49 (2H, m, NHCH_2CH_2); δ_C (125 MHz, $CDCl_3$): 174.04 (CO), 137.66, 129.34, 128.83, 126.92 (Ph), 120.05 (q, *J* 322, CF_3), 64.06 (CH_2OH), 52.76 (CH), 43.74 ($NHCH_2$), 37.28 (CH_2Ph), 35.50 (CH_2CO), 29.02 (NHCH_2CH_2), 22.06 (CH_2CH_2CO); Found (CI) 383.1243 (M^+ + H), $C_{15}H_{21}F_3N_2O_4S$ + H requires 383.1247; *m*/*z* (CI) 384 (M^+ + 2H), 383 (M^+ + H), 365 (M^+ − OH).

(2*S*) 5-Trifluoromethanesulfonylaminopentanoic acid (1-hydroxymethyl-3-methylbutyl)amide (13b)

Pyridine (0.052 ml, 0.051 g, 0.641 mmol) was added to a solution of **5** (0.148 g, 0.641 mmol) in DCM (1.6 ml) in a reaction vessel and the mixture was cooled to −40 °C. L-Leucinol (0.075 g, 0.641 mmol) was added and the solution stirred for 30 min at −40 °C, then overnight at room temperature. A saturated solution of $NaHCO_3$ (aq., 13 ml) was added, the organic phase separated and the product extracted from the aqueous phase with DCM (3 × 3 ml). The combined organic phase was washed with water (6 ml), the organic phase separated and the product extracted from the aqueous phase with DCM (3 × 3 ml). The combined organic phase was dried ($MgSO_4$), filtered through Celite and the solvent evaporated *in vacuo* to give the title compound **13b** as a clear very pale yellow liquid (0.111 g, 49.7%); $[a]_D^{27.8}$ − 20.45 [*c* 0.44, CH_2Cl_2, 1-dl]; one spot by TLC, R_f 0.3 (EtOAc); ν_{max} (neat)/cm^{-1} 3300.0 and 3092.0 (NH stretch of 2° amide), 2959.0 (CH_2 asymmetric stretch), 2878.0 (CH_2 symmetric stretch), 1651.0 (C=O stretch of 2° amide), 1543.0 (NH bend of 2° amide), 1470.0 (CH_2 scissoring bend), 1371.0 and 1149.0 (–SO_2NH–), 1230.0, 1193.0 and 1080.0 (CF_3); δ_H (500 MHz, $CDCl_3$): 5.90 (1H, d, *J* 8.6, CONH), 5 (1H, bs, TfNH), 4.09 (1H, m, NHC*H*), 3.70 (1H, d of d, *J* 3.5, 11.3, CH_2OH), 3.45 (1H, d of d, *J* 6.9, 11.3, CH_2OH′), 3.28 (2H, m, NHCH_2), 2.26 (2H, m, CH_2CONH), 1.73 (2H, m, NHCH_2CH_2CH_2), 1.62 (3H, m, C*H*$(CH_3)_2$, NHCH_2CH_2), 1.31 (1H, m, OH), 1.30 (2H, m, CHCH_2CH), 0.92 (6H, t, *J* 7, CH_3); δ_C (125 MHz, $CDCl_3$): 174.23 (CONH), 120.07 (q, *J* 321, CF_3), 65.78 (CH_2OH), 50.05 (NHCH), 43.81 ($NHCH_2$), 40.37 (CHCH_2CH), 35.57 (CH_2CONH), 29.17 (NHCH_2CH_2), 25.09 (NHCH_2CH_2CH_2), 23.17 (*C*H$(CH_3)_2$), 22.26 (CH_3), 22.19 (CH_3'); Found (CI): 349.1405 (M^+ + H), $C_{12}H_{23}F_3N_2O_4S$ + H requires 349.1403. *m*/*z* (CI): 350 (M^+ + 2H), 349 (M^+ + H), 331 (M^+ − OH), 317 (M^+ − CH_2OH).

(2*S*) 5-Trifluoromethanesulfonylaminopentanoic acid 3-phenyl-2-(5-trifluoromethanesulfonylamino-1-pentanoylamino)-propyl ester (14)

Under the same conditions as above for **13a** column chromatography gave the title compound **14** as a clear, colourless oil (0.025 g, 6.4%); one spot by TLC, R_f 0.4 [Pet. Ether : EtOAc 50 : 50]; ν_{max} (neat)/cm^{-1} 3306 and 3089 (NH stretch of 2° amide), 2953 (CH_2 asymmetric stretch), 2857 (CH_2 symmetric stretch), 1721 (C=O stretch of ester), 1652 (C=O stretch of 2° amide), 1536 (NH bend of 2° amide), 1371 and 1148 (–SO_2NH–), 1229, 1190 and 1079 (CF_3), 749 and 702 (oop bend of aromatic ring CH); δ_H (500 MHz, $CDCl_3$): 7.17–7.33 (5H, m, Ph), 6.63 (1H, bs, NHTf), 6.13 (1H, bs, NHTf), 5.67 (1H, d, *J* 8.9, OCNH), 4.52 (1H, m, CH_2O), 4.51 (1H, m, CH), 4.25 (1H, m, CH_2O'), 3.21 (2H, m, NHCH_2), 3.19 (2H, m, NHCH_2), 2.87 (1H, d of d, *J* 14.0, 6.6, CH_2Ph), 2.76 (1H, d of d, *J* 14.0, 7.9, CH_2Ph′), 2.39 (2H, m, $COCH_2$), 2.15 (2H, m, $COCH_2$), 1.81 (2H, bs, NHCH_2CH_2), 1.70 (2H, m, $COCH_2$CH_2), 1.61 (2H, m, $COCH_2$CH_2), 1.46 (2H, bs, NHCH_2CH_2); δ_C (125 MHz, $CDCl_3$): 173.39 (CO), 173.27 (CO), 127.04–136.44 (Ph), 119.81 (q, *J* 321, CF_3), 119.76 (q, *J* 321, CF_3), 65.71 (CH_2O), 49.49 (CH), 43.90 ($NHCH_2$), 43.57 ($NHCH_2$), 37.48 (CH_2Ph), 35.47 (CO*C*H$_2$), 33.48 (CO*C*H$_2$), 28.94 (NHCH_2CH_2), 28.86 (NHCH_2CH_2), 21.79 ($COCH_2CH_2$), 21.50 ($COCH_2CH_2$); Found (CI) 614.1462 (M^+ + H), $C_{21}H_{29}F_6N_3O_7S_2$ + H requires 614.1424; *m*/*z* (CI) 615 (M^+ + 2H), 614 (M^+ + H), 365 (M^+ − OCO$(CH_2)_4$NHTf).

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