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Synthesis and reactions of α-fluoro-α-amino amides

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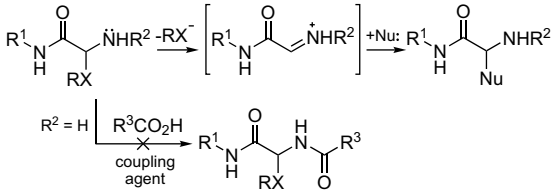
ABSTRACT

N-((*S*)-1-Phenylethyl)halofluoroethanamides have been investigated as precursors to *N*-protected α-fluoro-α-amino amides by nucleophilic displacement of halide with nitrogen nucleophiles such as potassium phthalimide, sodium succinimide, sodium glutarimide, trimethylamine and sodium azide. With single diastereoisomers of the iodofluoroethanamide, clean inversion of configuration occurs at room temperature, but subsequent epimerisation may occur as a result of the liberated iodide. The α-fluoro-α-amino amides made underwent a wide variety of reactions depending on conditions, but in many cases the carbon–fluorine bond was compromised. However, reacting trimethylamine and *N*-((*S*)-1-phenylethyl)iodofluoroethanamide gave the corresponding α-fluorobetaine amide, and subsequent acidic hydrolysis led to α-fluorobetaine as the first example of an 'unprotected' α-fluoroamino acid.

1. Introduction

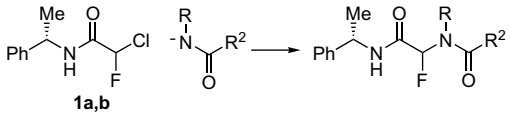
α-Amino amides in which the α-position is further substituted with a heteroatom group have both synthetic and pharmaceutical potential. The heteroatom group may be lost, by virtue of the nitrogen lone pair, resulting in an iminium ion intermediate. Such intermediates have been widely used as amino acid 'α-cation' equivalents[1] for the construction of novel amino acids and peptidomimetics (Scheme 1). In substrates analogous to biologically active peptides these derivatives may also closely bind to an enzyme or receptor, whereupon formation of the resulting iminium ion would give potential for covalent modification and inactivation of the protein.



Scheme 1.

A review of synthetic routes to α-heterosubstituted-α-amino acid derivatives[1] shows that by far the largest class of such compounds is that where the substituent XR (Scheme 1) is based on a Group 16 element. Halogenated examples are slightly less common and in the main are represented by brominated derivatives obtained by free radical processes.[2] The number of ways of accessing other such compounds is however somewhat limited.[3] We have been exploring extensions to our work[4] in this area[5] in order to discover routes to α-fluoro-α-amino amides and to investigate their stability and synthetic potential. α-Heterosubstituted-α-amino acid derivatives contain a stereogenic centre, so Takeuchi has explored the potential of similar 'multi-functional carbon' derivatives as NMR shift reagents.[6] Thus, the stereoselective synthesis of these derivatives is of particular interest too.

In considering the problem of synthesizing α-fluoroglycine-containing peptides and derivatives others have shown[5] that *N*-unprotected α-fluoro-α-amino-substituted compounds are not stable. Thus, amide bond synthesis using conventional methods is not applicable (Scheme 1). To obtain such derivatives a different approach was therefore needed and a method involving the reaction of a halofluoroethanamide derivative with an activated amide (amide anion equivalent) seemed feasible (Scheme 2).



Scheme 2.

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Other nitrogen-containing functional groups, which could be subsequently converted into an amide unit, were also considered. In a similar vein, Myers and co-workers have already investigated extensively the reaction of enolates with enantiopure iodofluoroacetic acid as a route for the stereoselective synthesis of fluorinated molecules.[7]

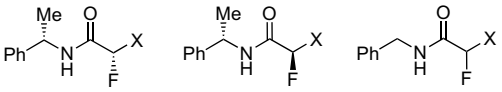
Chlorofluoroethanamide **1**[8] was identified as a key starting material for several reasons. It is a crystalline compound, and is fully separable from its epimer by silica flash chromatography and recrystallization. The choice of (*S*)-1-phenylethylamine as the chiral auxiliary, as opposed to a suitably protected amino acid, may not at first sight seem obvious. However, Molines and Wakselman[8] showed that single isomers of this amide could be converted, via the ethyl ester, to the acid chloride and that this process did not compromise the optical integrity of the chiral centre. Thus the one amide could, via the acid chloride, give access to many *N*-chlorofluoroacetylated amino amides in which the configuration of the stereogenic fluorocarbon is known. We envisaged using this as a way to extend from the carboxyl terminus of the chlorofluoroethanamide unit, before introduction of the N-terminus by a stereoselective displacement of chloride. Reported below are our latest results on the synthesis and subsequent reactions of α-amino-α-fluoroethanamide derivatives.

2. Synthesis of halofluoroethanamides

Our starting point for our synthesis was the fluorine-containing ethanamide derivatives **1**–**6** (Fig. 1). It was hoped initially that the chloro derivatives (**1**, **2**)[8] alone would give access to 'fluoroglycine' derivatives, but problems with selective halide displacement were encountered.[4] The chlorofluoroethanamides were therefore converted in high yield to the fluoroiodoethanamides **3** (91%) and **4** (98%) by heating with excess sodium iodide. Diastereoisomers of both **1** and **3** were readily separated by TLC [(9:1) benzene–ethyl acetate] and HPLC (9% ethyl acetate in hexane). Large scale separation was slightly more difficult as the best TLC resolution was obtained when the R_f values were quite high (around 0.4–0.5). However, appreciable amounts of a single isomer could be isolated by careful flash chromatography. The bromo derivatives **5a**,**b** and **6** were obtained (79% and 92%, respectively) from the iodo derivatives using the method of Willy and co-workers[9] as direct conversion from **1** or **2** needed long reaction times and gave low conversions.

Previous work had shown that conversion of either **1a** or **1b** produced a 50:50 diastereoisomeric mixture of **3**, with iodide sufficiently nucleophilic to epimerise any inverted fluoroiodoethanamide product as it is formed.[4a]

Similarly reaction of the single diastereoisomer **3a** yielded a 50:50 diastereoisomeric mixture of **5**. X-ray crystallography[4a] of the less polar diastereoisomers **1a** and **3a** showed that the fluorinated carbon in both had the (*S*) configuration. By deduction, the fluorocarbon in the less polar isomers (**1b** and **3b**) was therefore (*R*).[†] Comparison of spectral and physical data for **1**, **3** and **5** meant that we could assign the absolute configuration of the diastereoisomers **5a** and **5b** with confidence (Table 1). We therefore had access to both diastereoisomers of the three fluorohaloethanamides in which the absolute configurations of the fluorinated carbon atoms were known (Fig. 2).



(*S*,*S*) **1a** X = Cl (*S*,*R*) **1b** X = Cl **2** X = Cl
(*S*,*S*) **3a** X = I (*S*,*R*) **3b** X = I **4** X = I
(*S*,*S*) **5a** X = Br (*S*,*R*) **5b** X = Br **6** X = Br

Figure 1.

3. Substitution reactions of halofluoroethanamides

N-Alkylation of an amide using a halofluoroethanamide **1**–**6** would yield the desired α-fluoro-α-amino amide structures. However, problems were envisaged if using a simple amide in this way, as the amide anion would be quite basic as well as possibly leading to O- and N-alkylation. For this reason imides such as the phthalimide, the classical Gabriel synthesis primary amine synthon, were considered. The partial hydrolysis (or aminolysis) of the *N*-alkylated imide product to an amide acid (or bis amide) was envisaged using milder conditions due to the increased electrophilicity of the imide carbonyl group. Additionally mild reducing agents are known to convert *N*-alkylated imides to the corresponding hydroxy lactams, which would give an alternative route to a more conventional peptide structure. Succinimide and glutarimide were also identified as imides of particular interest due to their similarity to derivatives of the cyclic amino acids aspartimide and glutamimide (Fig. 3).

Reaction of potassium phthalimide with **1a**,**b** at room temperature in DMF did not proceed. Upon heating (between 40 and 90 °C) the only isolated product was found to be the diphthalimide **7** (43%) (Fig. 4). On the assumption that this was formed via the desired monophthalimide derivative, the fluoroiodoethanamide **3a**,**b** was tested, in which the better leaving group would be displaced under less forcing conditions. Reaction of **3a**,**b** at room temperature yielded the monophthalimide **8a**,**b**, which was isolated in 50% yield after only 6 h at room temperature and less than 10% of the diphthalimide **7** was formed under these conditions. The proton NMR spectrum of **8a**,**b** showed that the α-hydrogen doublets of the diastereoisomers ($^2J_{CF}$=50.3 Hz) were well resolved (Table 1), though the ^{13}C spectrum showed only small differences in the chemical shifts of the resonances for the α-carbon ($^1J_{CF}$=217 Hz). Upon repeating the reaction using the single diastereoisomer **3a**, the isolated product was found to be mainly a single diastereoisomer, but with contamination of the other epimer (d.e. 75%). Small amounts of recovered starting material were found by ^{1}H NMR to be epimerised totally. Gabriel's reagent proceeds generally via the S_N2 pathway and as the auxiliary was found not to influence the course of the reaction (i.e., **3a** goes to mainly **8a**, and **3b** goes to mainly **8b**) we concluded that the major isomer was the inverted product. This was supported by correlation of spectral and physical data (Table 1). In the light of the 0% d.e. in the recovered starting material, and the fact that the chlorine–iodine halogen exchange was stereorandom, we concluded that iodide, liberated during the course of the reaction, was sufficient to slowly epimerise the remaining starting material even under these mild conditions. This undesired epimer, **3b**, was then converted to the minor epimeric monophthalimide **8b**.

Next we investigated the reaction of sodium succinimide (1 mol equiv), generated using sodium hydride in DMF. It was found that after the addition of *N*-benzyl fluoroiodoethanamide **4** the succinimidyl derivative **11** was formed in good yield (83%).

There was no evidence for disubstitution even when the reaction was left for 24 h at room temperature. Using the bromo derivative **6** the same succinimidyl product **11** was obtained, though the reaction was lower yielding and irreproducible. This

[†] Throughout this paper each new compound, where appropriate, has a number with the suffix 'a' for the (*S*,*S*) isomer and 'b' for the (*S*,*R*) isomer. However, substitution products of derivatives **1a**, **3a** and **5a** are also given the suffix 'a' as they too are (*S*,*S*) isomers. Although the reactions go with inversion, the switch from a halogen to a nitrogen (or carbon) substituent alters the priority order of the substituents used for the assignment of configuration.

Table 1
Spectroscopic and physical properties of *N*-((*S*)-1-phenylethyl)-α-fluoro-α-substituted ethanamide derivatives[†]

No.	α-Substituent	R_f	Mp/°C	δ_H α-H	δ_C α-C	δ_F[k]
1a	–Cl	0.55[d]	74–75	6.24	94.14[h]	−144.19, −144.20[n]
1b	–Cl	0.47[d]	52–55	6.27	94.18[h]	−144.05, −144.06[n]
3a	–I	0.59[d]	83–84	7.11	62.35[h]	−157.1
3b	–I	0.51[d]	59–61	7.14	62.39[h]	−157.0
5a	–Br	0.49[m]	79–80	6.57	84.55[h]	−148.3[l]
5b	–Br	0.42[m]	n/r	6.60	84.63[h]	−148.2[l]
8a	–Phth[a]	0.41[d]	163–165	6.37	83.8[i]	−155.3
8b	–Phth[a]	0.45[d]	146–148	6.32		−154.7
9a	–Succ[b]	0.19[e]	169–172	6.13	83.5[j]	−160.5
9b	–Succ[b]		164–165	6.05		−161.2
10a	–Glut[c]	0.24[e]	142–145	6.72	85.2[h]	−163.7
10b	–Glut[c]		113–117	6.65		−163.4
13a	$-N_3$	0.60[f]	Oil	5.69	96.0[j]	n/r
13b	$-N_3$		Oil	5.51		
14a	–CN	0.48[g]	Oil	5.48	76.7[j]	−190.5
14b	–CN		Oil	5.41		
16a	$-NMe_3I$	n/r	>300	6.04	102.4[j]	−167.4
16b	$-NMe_3I$		>300	6.03		

Suffix **a** refers to the (*S*,*S*) isomer, and **b** the (*S*,*R*) isomer; n/r, not recorded.
[a] *N*-Phthaloyl.
[b] *N*-Succinimidyl.
[c] *N*-Glutarimidyl.
[d] Eluent (9:1) benzene–ethyl acetate.
[e] Eluent diethyl ether.
[f] Eluent (2:1) hexane–ethyl acetate.
[g] Eluent dichloromethane.
[h] 100 MHz.
[i] 75 MHz.
[j] 22.5 MHz.
[k] 84.5 MHz (internal reference $FCCl_3$).
[l] 376 MHz.
[m] Eluent (9:1) toluene–ethyl acetate.
[n] Due to ^{37}Cl isotope.

trend was also seen when the succinimide anion was generated in THF (NaHMDS) where the best yield (67%) was obtained with a five-fold molar excess of the nucleophile. Using the same nucleophile excess, a 50:50 diastereoisomeric mixture of either iodo **3a**,**b** or bromo **5a**,**b** gave the product in which there was a predominance of one isomer over the other (47% overall yield, 33% d.e.). Using melting point and spectral comparisons the major diastereoisomer in this mixture was the (*S*,*R*) isomer **9b**. Presumably this ratio reflects the relative rate at which the succinimide anion reacts with separate diastereoisomers of **3** or **5**. With the NaH/DMF system and 1 equiv of succinimide, the single bromo isomer **5a** gave a product with 100% d.e. though in a lower and irreproducible yield. The d.e. of the same product arising from the single iodo isomer **3a**, however, was about 75% (by ^1H NMR), though the yield in this case was excellent (93%). This result mirrors closely the result using potassium phthalimide in DMF. In both cases the product had the same absolute configuration (by NMR comparison) and since this type of nucleophile is expected to react via an S_N2 pathway it was concluded that the (major) isomer obtained was the inverted (*S*,*S*) product. This conclusion was also supported by the α-proton chemical shift data, which by now indicated a reliable trend (Table 1). By comparison, using a five-fold excess of the succinimide anion in THF, with either single isomer **3a** or **5a**, a 0% d.e. was obtained. The reactions described above were also repeated with glutarimide and, in essence, identical results were obtained. The reactions, however, were slower with succinimide and using a mixture of **3a**,**b** or **5a**,**b** gave a slightly reduced d.e. of 26% in the product. Reaction of the *N*-benzyl ethanamide **4** also gave the racemic glutarimide derivative **12**.

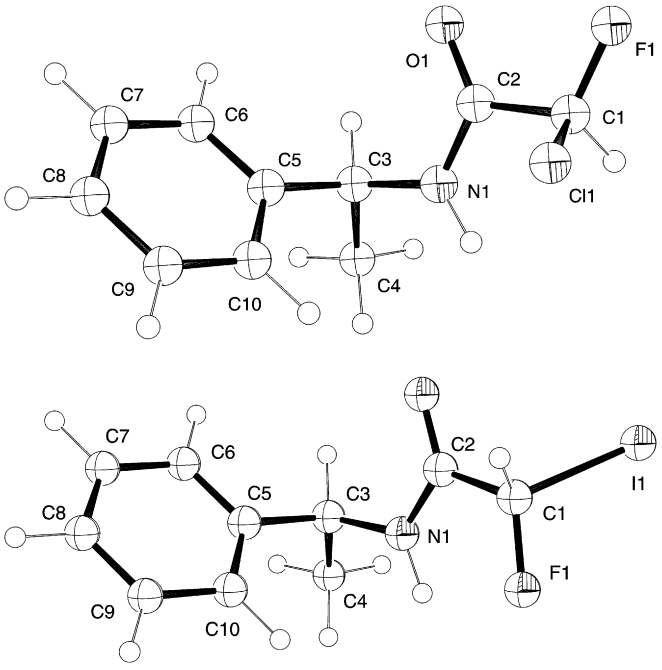


Figure 2. ORTEP view of the less polar diastereoisomers (**1a** above and **3a** below) of chlorofluoroethanamide **1** and iodofluoroethanamide **3**.

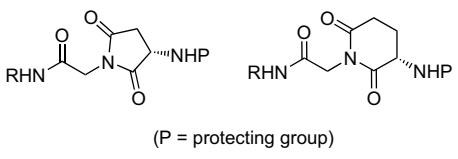


Figure 3.

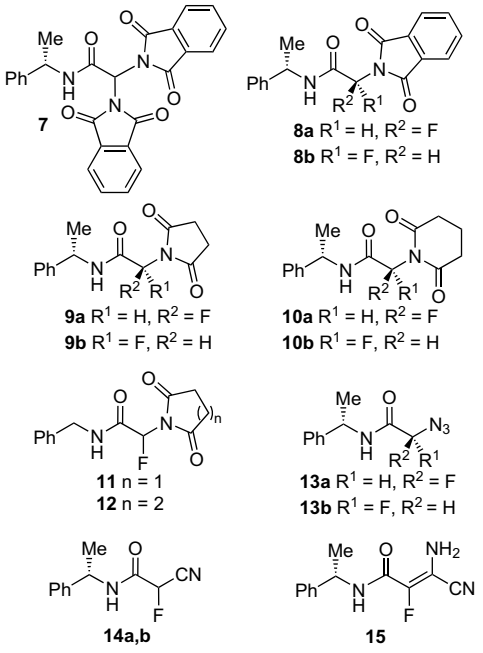
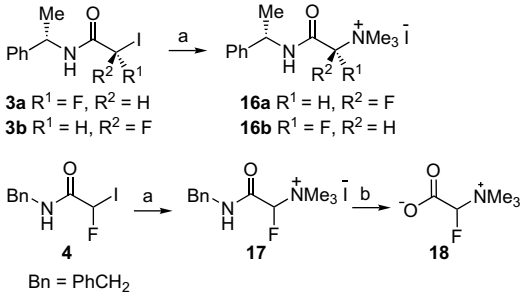


Figure 4.

Takeuchi has previously reported[5a,10] the synthesis of the azidofluoroacetate esters from ethyl bromofluoroethanoate. Azides are readily reduced to amines by a variety of methods and, although free α-fluoro-α-amino amides were predicted to be unstable, we envisaged a route to an *N*-acylated α-fluoro-α-amino amides by reduction of an azide in the presence of an acylating agent. Pleasingly, a single diastereoisomer of the fluoroiodoethanamide **3a** was rapidly converted at room temperature with clean inversion to the azido derivative **13a** and in excellent yields (95%). As azide is an excellent nucleophile we also investigated the direct conversion of chlorofluoroethanamide **1a**,**b** to the azide **13a**,**b** but at room temperature under the same conditions no product was formed.

Whilst considering other suitable nucleophiles to react with **1**–**6**, we envisaged a route to α-fluoro-β-alanine derivatives by using cyanide to form the fluoronitrile **14** followed by reduction of the CN bond. Isolation of nitrile **14** proved quite difficult due to competitive formation of a by-product. However, after carefully monitoring the reaction and quenching after 2–3 h, the nitrile **14** could be isolated in ~50% yield. Repeating the reaction with the single diastereoisomer **3a** gave a product completely epimerised at the α-carbon, but this was not surprising given that **14** is a malonic acid derivative. On investigating this reaction we found that the by-product could be made exclusively in 89% yield by reaction of **3** with an excess of potassium cyanide. Accurate mass determination of the molecular ion of this by-product matched that calculated for a molecular formula of **14** *plus* an additional mole of HCN. Only the NMR signals from the auxiliary were assignable with certainty, as other signals were weak, broad and variable. The characteristic proton and carbon doublets from the α-CHF group were not detected, and the ^{1}H NMR spectrum also indicated a change in the signal due to the CH of the auxiliary. In all products made before this proton appeared as a pseudo-quintet, as a result of coupling to the methyl and amide protons. In the ^{1}H NMR spectrum of this compound, the auxiliary CH appeared as a clean quartet, indicating that the amide had been converted into a significantly different functional group. The identity of the product was eventually assigned to structure **15** based on comparisons to the chemistry of malononitrile and its derivatives.[11] Amongst this large body of work de Vries[12] has reported that NaCN adds to the C–N triple bond in alkylamino malononitriles via the tautomeric ketenimine. Re-evaluation of the mass spectrum confirmed that the major fragmentation of the M^+ ion was at m/z=129 ([M−PhCHCH$_3$]$^+$), which was consistent with our assignment.

Betaine (*N*,*N*,*N*-trimethylglycine) is an amino acid sometimes found as the N-terminal residue in various naturally occurring peptides, and is the methylating agent used in the biosynthesis of methionine. We envisaged α-fluorobetaine as a viable synthetic target as it has no nitrogen lone pair, and so elimination to form an imine is not possible. Using just over 1 equiv of a trimethylamine solution in acetone,[13] with either **3a**,**b** or **4** dissolved in a minimum of acetone, we found that the α-fluorobetaine amides **16a**,**b** and **17** simply precipitated from solution in excellent yields (Scheme 3). A reaction using the single diastereoisomer **3a** yielded a product that was a single diastereoisomer (by NMR) so we inferred, using detailed spectroscopic comparison (Table 1), that the reaction had gone with clean inversion. The α-fluorobetaine derivative **16a** was



Scheme 3. Reagents and conditions: (a) NMe_3, acetone, rt, 3 h [**3a**→**16a** (98%), **4**→**17** (95%)]; (b) 6 M HCl (aq), heat, 48 h (22%).

therefore accessible in excellent yields, and with known absolute configuration. With the α-fluorobetaine amides in hand, we were also able to hydrolyse the amide bond to obtain the free α-fluorobetaine. Standard peptide bond hydrolysis conditions (6 M hydrochloric acid at reflux for 48 h) were applied to derivative **17**. After work-up, precipitation of the product from methanol–ether gave the product, which was 'clean' by ^{1}H and ^{13}C NMR in D_2O and near to the expected quantitative yield. However, elemental analysis indicated that the product was contaminated by ammonium chloride and iodide. Purification by cation exchange chromatography [Dowex 50X-8-100(H), elution with THF–H_2O] and freeze-drying from distilled water resulted in the isolation of the fluorobetaine **18** as a crystalline solid (22%). X-ray crystallography revealed that the product was in its zwitterionic state (Fig. 5).[4b,14]

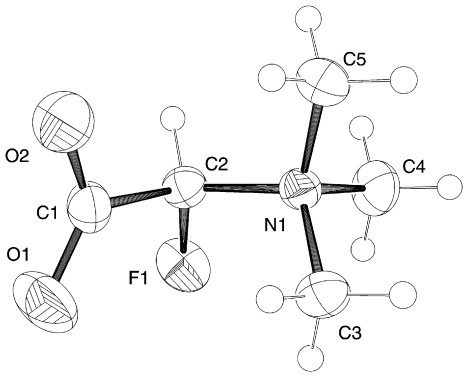
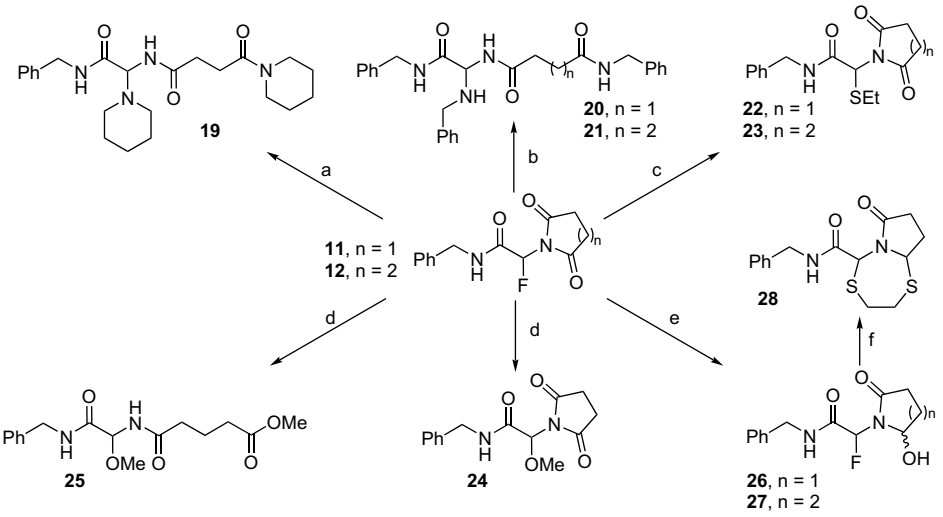


Figure 5. ORTEP view (50% probability ellipsoids) of fluorobetaine **18**.



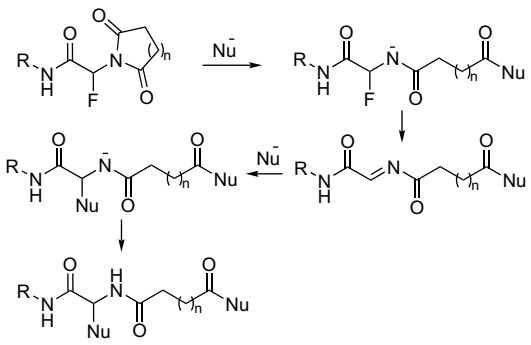
Scheme 4. Reagents and conditions: (a) 15 equiv piperidine, THF, 22 h, rt (89%); (b) 15 equiv $BnNH_2$, THF, rt [**20**, 24 h (80%); **21**, 106 h (62%)]; (c) 1.04 equiv EtSNa, DMF, rt, 24 h [**22**, 24 h (51%); **23**, 170 h (28%)]; (d) 1 equiv NaOMe, MeOH, rt, 0.1 h [**24** (77%); **25** (76%)]; (e) $LiBH_4$, THF, −15 °C, 4–8 h [**26** (59%); **27** (37%)]; (f) $HS(CH_2)_2SH$, $BF_3{\cdot}OEt_2$, $CHCl_3$, 0 °C, 3.5 h (56%).

4. Modification of α-substituted fluoroethanamides

The nucleophilic substitution reactions of halofluoroamides **1**–**6** provided useful results as to the relative reactivity of the different leaving groups and consequences for epimerisation of the fluorinated stereogenic centre. Most of the products described above were isolated as stable solids, but the stability of the substrates to further modification was of interest, especially the reactivity of the carbon–fluorine bond. No modification of the phthalimide derivative **8a**,**b** to the corresponding amine was attempted, as the harsh hydrolytic conditions normally needed to modify the phthalimide group would undoubtedly have caused decomposition of the carbon–fluorine bond.[5a] Thus attention was turned to the succinimide and glutarimide derivatives **11** and **12**. Treatment of the *N*-benzyl amide **11** with excess piperidine in THF at room temperature gave a new product **19** arising from both ring-opening and fluoride replacement (Scheme 4). An NMR-scale experiment, using less than 1 equiv of piperidine, showed in a series of spectra that no fluorine-containing products were being formed, and the only new resonances identified were those of the product. This indicated that after aminolysis of the imide the displacement of the fluoride was rapid, presumably due to assistance of the negative charge build up on the nitrogen (Scheme 5). Interestingly the glutarimide derivative **12** did not react at room temperature with piperidine, and warming led to the formation of a complex mixture. Both **11** and **12**, however, reacted cleanly with benzylamine at room temperature giving the ring-opened, fluoride-displaced products **20** and **21**. The glutarimide derivative required four times as long as the succinimide derivative (106 h vs 24 h) and gave a poorer yield (62 vs 80%), but in both cases the products were simply obtained as precipitates directly from the reaction mixture. Similar reactions were investigated using sodium ethanethiolate and sodium methoxide. Treatment of **11** and **12** with 1 equiv of sodium ethanethiolate in DMF gave only products arising from fluoride displacement (**22** and **23**). There was no evidence in these cases for ring opening and, as observed before, the reaction with the glutarimide was significantly slower (170 h) and lower yielding. However, treatment with 1 M sodium methoxide in methanol resulted in reactions, which were over in 5 min at room temperature. Surprisingly in these cases the succinimide **11** was converted to the fluoride-displaced product **24** only (77%), whereas the glutarimide **12** gave only the ring-opened, fluoride-displaced product **25** (76%).

From these results it was concluded that the desired ring opening of imide derivatives to given linear peptidic structures could not be achieved without loss of the fluorine. One of the possible flaws of this methodology is that cleavage of one of the imide C═O bonds leads to a negative charge on the nitrogen adjacent to the fluorine. It is likely therefore that this accelerates the loss of the fluoride via an acyl-imine intermediate, which could then add a second equivalent of the nucleophile (Scheme 5).

Attention was switched to a reductive strategy for ring opening. Partial reduction of imides to form hydroxy lactams is well documented and has been achieved with $NaBH_4$, L-Selectride, DIBAL-H and $LiEt_3BH$. Hubert[15] has shown that *N*-alkylated succinimides and glutarimides are reduced with $NaBH_4$ in ethanol. In general the succinimides give the hydroxy lactam, whereas the glutarimide derived product is in equilibrium with the ring-opened form, and so is further reduced to the amido alcohol. The electronic nature of the *N*-substituent can, however, alter the ratio of these products. Succinimide derivative **11** was reacted with $NaBH_4$ at 0 °C in methanol, and TLC showed the starting material had been consumed after 5 min. Analysis of the crude reaction mixture by H NMR indicated that the major product was the same as **24**, which resulted from displacement of fluoride. In addition there was evidence for small amounts of ring-opened α-methoxyglycyl ester analogous to the product **25**. It is most likely that methoxide, generated by the reaction of $NaBH_4$ and methanol, triggered these reactions with no reduction taking place. Other reducing agents



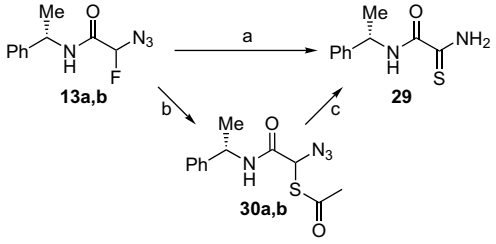
Scheme 5.

were also tried (DIBAL-H, L-Selectride, $LiEt_3BH$) but in no cases was there evidence for the desired reduction having occurred. However, success was achieved in reducing the succinimide derivative **11** with $LiBH_4$ in THF at −15 °C, albeit with a modest yield (**26**, 59%). The reaction with the glutarimide **12** was, however, particularly fickle and usually had to be worked up before the starting material had been fully consumed. This resulted in difficulties in separation of the product **27** and lower yields (best 37%). Both products **26** and **27** were relatively unstable, but could be stored at −20 °C for about 1 week.

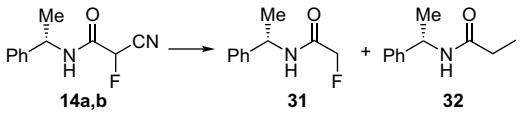
As it was known that hydroxy lactams such as **26** and **27** exist in equilibrium with the ring-opened amido aldehyde, attempts were then made to trap the aldehyde as a dithioacetal using ethane-1,2-dithiol in chloroform with $BF_3 \cdot OEt_2$ catalysis. From the reaction of **26** an essentially pure product was isolated from the mixture. It was clear from the ^1H NMR that the fluorine had been lost and a combination of ^1H, ^{13}C and 2D NMR spectra eventually showed that a single isomer of the azadithiabicyclo[5.3.0]decanone **28** had been formed. An NOE experiment showed no observable enhancement between the two protons at the stereocentres and so it was not possible to conclusively assign the relative stereochemistry.

Reduction of azides via catalytic hydrogenation in the presence of di-*tert*-butyl dicarbonate yields the carbamate-protected amines directly.[16] We reasoned that if our azido derivative **13a**,**b** was reduced under these conditions in the presence of an acid anhydride, then the 'protected' amine derivative may be formed, before decomposition of the intermediate fluoroamine. Reduction of the azide **11a**,**b** at room temperature, in the presence of Boc anhydride, was attempted using hydrogen and 10% Pd–C catalyst. Even when the catalyst was presaturated with hydrogen prior to the addition of the azide, to prevent the palladium acting as a dehydrogenation catalyst, the ^1H NMR spectrum of the recovered material was unassignable. Neither product nor starting material was identified. We also investigated variations on the reported reduction conditions, and also used the more reactive acetic anhydride, but disappointingly no products were identified in either case. Similarly a reduction at −15 °C in the presence of a mixed anhydride,[17] prepared[18] from *N*-Boc glycine and *iso*-butyl chloroformate, was attempted. After 11 h no product was identified, but there was still some starting material recovered, indicating that the lower temperatures had significantly lowered the rate of the reduction of the azide. This of course does not reflect the rate of decomposition of the free amine, which is presumably still too rapid at −15 °C for the amine to be acylated.

Rosen's reduction of azides using thiolacetic acid was of great interest, as the stable ethanamide analogues were obtained directly even when using potentially labile polyfunctional azido compounds.[19] We applied these conditions to our azide **13a**,**b** over a period of 4 h (Scheme 6). After removal of the unreacted thiolacetic acid, aqueous work-up and silica flash chromatography, the infrared spectrum of the isolated product showed no absorption due to the azido group (at 2120 cm^{-1} in **13a**,**b**), but there was a new



Scheme 6. Reagents and conditions: (a) 3–4 mol equiv MeCOSH, 4 h, rt, then aqueous work-up (90%); (b) 3–4 mol equiv MeCOSH, 4 h, rt, non-aqueous work-up (30%); (c) H_2O.



Scheme 7. Reagents and conditions: MeOH, H_2, PtO_2, rt, 24 h [**31** (16%) and **32** (13%)].

strong absorption at 1575 cm^{-1}. In the ^{13}C NMR spectrum there was a singlet at δ 191.1 in place of the fluorine doublet (at δ 96.0 in the azide). Analysis of the fragmentation patterns in the mass spectrum, and accurate mass determination of the suspected molecular ion, indicated that the interesting thioamide **29** was the product (90%). Repeating the reaction under dry conditions, and omitting the aqueous work-up, led, however, to the thioester **30a**,**b** in 30% yield. When a sample of **30a**,**b** was dissolved in diethyl ether and this solution was shaken with water for a couple of minutes, the product isolated revealed a mass and NMR spectra to match the thioamide **29**. We therefore believed that the aqueous wash hydrolysed the azido-thioester **30a**,**b** to the azido thiol, which decomposed, perhaps via a nitrene, to give the thioamide.

Although fluoronitrile **14** could not be obtained isomerically pure, attempts were nevertheless made to reduce the CN bond under an atmospheric pressure of hydrogen using platinum(IV) oxide. Many unidentified products were formed when acetic acid was used as solvent, but in ethyl acetate no reaction occurred. Switching to methanol yielded only two identifiable products, **31** and **32**, in the low yields of 16 and 13%, respectively (Scheme 7). The loss of cyanide from **14** could be aided by the +M effect of the fluorine. Under the reducing conditions **31** would be formed as the product. The propanamide **32** is probably formed via initial reduction of the nitrile to the imine and hydrolysis to the aldehyde–enol. The imine is an intermediate in the desired for reduction to β-alanine, but as yields of **32** were low this chemistry was not pursued further.

5. Conclusions

We have shown that bromofluoro- and iodofluoroethanamides are precursors to α-fluoroglycine-type derivatives by nucleophilic displacement of the halide with nitrogen nucleophiles. The corresponding chlorofluoroethanamide, if reactive at all, required elevated temperatures, longer reaction times and led to fluorine substitution as well. With single diastereoisomers of the iodofluoroethanamide clean inversion of configuration occurred with azide and trimethylamine at room temperature, but the imide-based nucleophiles produced a mixture of diastereoisomers that were sometimes produced through epimerisation of the starting material. The d.e. and yields were solvent and base-dependent and sometimes quite markedly different results were obtained with the bromofluoroethanamide. Modification of the imide derivatives **11** and **12** was investigated at length. Several interesting α-functionalised peptidic molecules were made, but in no cases could ring opening be achieved without loss of the fluorine. With the crystal structures of selected derivatives, and careful correlation of the α-CH chemical shift and R_f values, we were also able to make confident assignments of the absolute configurations for the isomers of most derivatives. With this information, the particular diastereoisomer of the halofluoroamide required to give access to any product isomer could be easily deduced. This is of particular relevance given that the 1-phenylethylamine auxiliary chosen for this work is readily available in either enantiomeric form. Finally, our synthesis of α-fluorobetaine was surprisingly straightforward and X-ray crystallography[4b,14] confirmed the synthesis of this novel amino acid. Overall, these results reveal

a flexible route to a wide range of α-heterosubstituted glycine derivatives, including access to single or separable diastereoisomers of known configuration by using the (*S*)-1-phenylethylamine auxiliary.

6. Experimental

6.1. General

Chemical shifts are measured in parts per million on the δ scale relative to $SiMe_4$ (δ_H and δ_C) or CCl_3F (δ_F) as internal standards. When the solvent was D_2O, dioxane (δ_C) and 1-(trimethylsilyl)-propane-1-sulfonic acid (δ_H) were used as external standards. ^{13}C data is quoted with ^1H multiplicities (in brackets) from off-resonance spectra, however, sometimes this information was inferred from DEPT experiments. Where a difference in chemical shift for resonances from diastereoisomeric compounds is seen, that for the (*S*,*S*) isomer is given first, and the (*S*,*R*) isomer in square brackets immediately afterwards. These assignments were made from an analysis of the spectra of a single diastereoisomer and a (1:1) mixture of diastereoisomers. If assignment to a specific diastereoisomer was not determined then the second value is given in curly brackets. Approximate diastereoisomeric excesses were determined by relative integration of the C*H*F doublets in the H NMR spectra. Mass spectra were obtained, unless stated otherwise, by electron impact ionization. FAB mass spectra were obtained using either *o*-nitrobenzyl alcohol (noba) or glycerol matrices. Infrared spectra were recorded in either chloroform solution with a chloroform reference, or a thin film, Nujol mull or KBr disc with an air reference. R_f values from thin layer chromatography were determined using Merck aluminium-backed silica gel plates ($60F_{254}$) and the compounds were visualised using either a UV lamp or iodine vapour staining.

6.2. (*S*/*R*)-*N*-[(*S*)-1-Phenylethyl]-2-chloro-2-fluoroethanamide, 1a,b[8]

(*S*)-(−)-1-Phenylethylamine (50 g, 0.413 mol) was dissolved in sodium-dried ether (200 cm^3) in a sealed 500 cm^3 steel cylinder. Chlorotrifluoroethene (50 g, 0.429 mol) was added directly from a pressurized cylinder, and the mixture was shaken for 18 h at room temperature. An additional 10 g of the ethene was then added, and shaking was continued for a further 140 h. The mixture was then filtered to remove the solid hydrofluoride salt of the unreacted amine, which was washed with ether (300 cm^3). The ether of the combined fractions was evaporated in vacuo to yield about 40 g of a golden oil. This oil was heated at reflux in 10% H_2SO_4 for 2 h and then left to cool. The organic product was extracted into ether (5×50 cm^3) and the combined ethereal extracts were washed with saturated aqueous sodium bicarbonate (10×50 cm^3), saturated brine (100 cm^3), and then dried over magnesium sulfate. Removal of the solvent in vacuo gave a golden oil, which solidified on standing. The solid was recrystallized from petroleum ether (bp 40–60 °C)–ethyl acetate (88:12) to yield 26.4 g (30%) of *the title compound* as a white crystalline solid.[8] R_f (*S*,*S*) isomer 0.55; (*S*,*R*) isomer 0.47 [(9:1) benzene–ethyl acetate]; mp (*S*,*S*) isomer 74–75 °C; (*S*,*R*) isomer 52–55 °C (diethyl ether–hexane); δ_H ($CDCl_3$, 90 MHz) 7.38–7.28 (5H, m, Ph), 6.70 (1H, br s, NH), 6.24 [6.27] (1H, d, J_{HF} 51.2, CHF), 5.16 (1H, quin, *J* 7.1, C*H*Me), 1.56 (3H, d, *J* 7.1, CH*Me*); δ_C ($CDCl_3$, 22.5 MHz) 163.4 (d, J_{CF} 23, C═O) (s), 142.0 (s, ArC), 128.7 (d, ArC), 127.6 (d, ArC), 126.1 (d, ArC), 93.9 (d, J_{CF} 255, CHF) (d), 49.5 [49.4] (d, C*H*Me), 21.3 (q, Me); ν_{max} ($CHCl_3$)/cm^{-1} 3420, 3020, 1693, 1520, 1450, 1060, 820, 700; *m*/*z* 217/215 (M^+ 14%, 37%), 200 (30), 180 (80), 105 (100), 77 (42), 51 (22).

6.3. (*S*/*R*)-*N*-Benzyl-2-chloro-2-fluoroethanamide, 2[20]

Ethanamide **2** was prepared according to the method described for **1a**,**b** using benzylamine (40 g, 0.374 mol) and chlorotrifluoroethene (50 g, 0.429 mol), yielding *the title compound* as a white crystalline solid (12.9 g, 17%). R_f 0.42 [(9:1) benzene–ethyl acetate]; mp 53.5–55 °C (diethyl ether–hexane); δ_H ($CDCl_3$, 90 MHz) 7.70 (1H, br s, NH), 7.28–7.18 (5H, m, Ph), 6.27 (1H, d, J_{HF} 50.5, CHF), 4.36 (2H, d, *J* 6.0, CH_2); δ_C ($CDCl_3$, 22.5 MHz) 165.1 (d, J_{CF} 23, C═O) (s), 136.3 (s, ArC), 128.5 (d, ArC), 127.6 (d, ArC), 127.4 (d, ArC), 93.4 (d, J_{CF} 255, CHF) (d), 43.4 (t, CH_2N); ν_{max} ($CHCl_3$)/cm^{-1} 3435, 3010, 1700, 1530, 1455, 1220, 1065, 820, 700; *m*/*z* 203/201 (M^+ 10%, 32%), 166 (92), 123 (22), 106 (26), 91 (100), 77 (40), 68 (84), 45 (72).

6.4. (*S*/*R*)-*N*-[(*S*)-1-Phenylethyl]-2-fluoro-2-iodoethanamide, 3a,b

Sodium iodide (16.55 g, 110 mmol) and **1a**,**b** (3.14 g, 15 mmol) were dissolved in acetone (100 cm^3), then heated at reflux for 120 h. After cooling, the solvent was removed in vacuo, and the residue was dissolved in chloroform (50 cm^3). The chloroform solution was then washed with saturated sodium thiosulfate (2×50 cm^3) and brine (50 cm^3). After drying over magnesium sulfate, the solvent was removed in vacuo to yield *the title compound* (4.10 g, 91%) as a white solid. R_f (*S*,*S*) isomer 0.59; (*S*,*R*) isomer 0.51 [(9:1) benzene–ethyl acetate]; mp (*S*,*S*) isomer 83–84 °C; (*S*,*R*) isomer 59–61 °C (diethyl ether–hexane); found: $(M-127)^+$ 180.0825. $C_{10}H_{11}NOF$ requires 180.0825; δ_H ($CDCl_3$, 90 MHz) 7.38–7.28 (5H, m, Ph), 7.11 [7.14] (1H, d, J_{HF} 51.4, CHF), 6.50 (1H, br s, NH), 5.16 (1H, quin, *J*∼6.8, C*H*Me), 1.56 (3H, d, *J* 6.8, CH*Me*); δ_C ($CDCl_3$, 22.5 MHz), 165.7 [165.6] (d, J_{CF} 18, C═O) (s), 142.0 [141.8] (s, ArC), 128.9 [128.8] (d, ArC), 128.0 [127.7] (d, ArC), 126.3 [126.1] (d, ArC), 62.5 (d, J_{CF} 270, CHF) (d), 49.4 [49.0] (d, C*H*Me), 21.0 [21.5] (q, Me); δ_F ($CDCl_3$, 84.5 MHz) −157.1 {−157.2} (d, J_{FH} 51.4); ν_{max} ($CHCl_3$)/cm^{-1} 3420, 3020, 1685, 1520, 1450, 1040, 700; *m*/*z* 307 (M+<1%), 292 (8), 180 (100), 105 (56), 77 (22).

6.5. (*S*/*R*)-*N*-Benzyl-2-fluoro-2-iodoethanamide, 4

Ethanamide **4** was prepared according to the method described for **3a**,**b** using chloroethanamide **2** (3.00 g), sodium iodide (13.0 g) and acetone (100 cm^3). This yielded *the title compound* as a white crystalline solid (4.30 g, 98%). R_f 0.44 [(9:1) benzene–ethyl acetate]; mp 81–83 °C (diethyl ether–hexane); δ_H ($CDCl_3$, 90 MHz) 7.36–7.26 (5H, m, Ph), 7.12 (1H, d, J_{HF} 51.4, CHF), 6.80 (1H, br s, NH), 4.48 (2H, d, *J* 5.9, CH_2); δ_C ($CDCl_3$, 22.5 MHz) 166.5 (d, J_{CF} 20, C═O) (s), 137.0 (s, ArC), 130.9 (d, ArC), 128.8 (d, ArC), 127.7 (d, ArC), 62.3 (d, J_{CF} 267, CHF) (d), 43.5 (t, CH_2N); ν_{max} ($CHCl_3$)/cm^{-1} 3430, 3020, 1695, 1530, 1460, 1310, 1270, 1160, 1050, 705; *m*/*z* no M^+, 166 (M−127, 100), 123 (13), 103 (19), 91 (69).

6.6. (*S*/*R*)-*N*-[(*S*)-1-Phenylethyl]-2-fluoro-2-bromoethanamide, 5a,b

Ethanamide **5a**,**b** was prepared according to the method described for **6** using iodoethanamide **3a**,**b** (0.203 g, 0.660 mmol), sodium bromide (14 mg, 0.134 mmol), bromoethane (3.4 cm^3, 45.6 mmol, 69 equiv) in *N*-methyl-pyrrolidinone (0.5 cm^3), yielding *the title compound* as a white crystalline solid (0.136 g, 79%). R_f 0.49 [0.42] [(9:1) toluene–ethyl acetate]; mp (*S*,*S*) isomer 79–80 °C (diethyl ether–hexane); δ_H ($CDCl_3$, 400 MHz) 7.38–7.28 (5H, m, Ph), 6.57 [6.61] (1H, d, J_{HF} 51.0, CHF), 6.47 (1H, br s, NH), 5.15 (1H, quin, *J*∼6.9, CHMe), 1.58 [1.56] (3H, d, *J* 6.9, CHMe); δ_C ($CDCl_3$, 100 MHz) 163.7 (d, J_{CF} 26.3, C═O) (s), 141.6 [141.5] (s, ArC), 128.8 (d, ArC), 127.8 [127.7] (d, ArC), 126.1 [126.0] (d, ArC), 84.5 [84.6] (d, J_{CF} 267.0, CHF)

(d), 49.2 [49.0] (d, *C*HMe), 21.0 [21.4] (q, Me); δ_F ($CDCl_3$, 376 MHz) −148.3 [−148.2] (d, J_{FH} 51.0); ν_{max} (KBr)/cm^{-1} 3258, 3085, 1694, 1667, 1563, 1451, 1380, 1199, 1077, 959, 701.

6.7. (*S*/*R*)-*N*-Benzyl-2-bromo-2-fluoroethanamide, 6

Iodoethanamide **4** (0.763 g, 2.60 mmol), bromoethane (14 cm^3, 188 mmol, 72 equiv) and sodium bromide (0.054 g, 0.52 mmol) were dissolved in *N*-methyl-pyrrolidinone and heated at 60 °C for 21.5 h. After this time, the reaction mixture was allowed to cool to ambient temperature before removal of excess bromoethane under reduced pressure. The resulting orange solution was dissolved in ethyl acetate (60 cm^3) and washed with distilled water (3×60 cm^3), saturated sodium thiosulfate solution (60 cm^3) and brine (60 cm^3) before drying over $MgSO_4$. Removal of solvent under reduced pressure and purification by flash silica chromatography yielded *the title compound* as a white crystalline solid (0.569 g, 92%). R_f 0.28 [(9:1) toluene–ethyl acetate]; mp 56–58 °C (diethyl ether–hexane); δ_H ($CDCl_3$, 400 MHz) 7.38–7.28 (5H, m, Ph), 6.63 (1H, d, J_{HF} 50.9, CHF), 6.60 (1H, br s, NH), 4.54 (1H, *AB*X, *J* 14.8 and 5.8, PhCH*H*NH) and 4.50 (1H, *AB*X, *J* 14.8 and 6.0, PhC*H*HNH); δ_C ($CDCl_3$, 100 MHz) 164.5 (d, J_{CF} 20.6, C=O) (s), 136.6 (s, ArC), 128.8 (d, ArC), 127.9 (d, ArC), 127.7 (d, ArC), 84.5 (d, J_{CF} 267.0, CHF) (d), 43.5 (t, CH_2N); δ_F ($CDCl_3$, 376 MHz) −148.7 (dd, J_{FH} 50.9 and 2.4); ν_{max} (KBr)/cm^{-1} 3352, 1672, 1542, 1431, 1316, 1289, 1194, 1069, 999, 749, 707; *m*/*z* no M^+, 166 ([M−Br]$^+$, 100%), 103 (20), 91 (82), 39 (25).

6.8. *N*-[(*S*)-1-Phenylethyl]-2,2-bis(1,3-dioxo-2-isoindolinyl)ethanamide, 7

Chlorofluoroethanamide **1a**,**b** (686 mg, 3.2 mmol) and potassium phthalimide (830 mg, 4.8 mmol, 1.5 equiv) were dissolved in DMF (15 cm^3), and the resulting solution was heated under an argon atmosphere at 90 °C for 8 h. After cooling, the solvent was removed in vacuo and the residue taken up in ethyl acetate (10 cm^3). This was then washed with aqueous saturated sodium bicarbonate (10 cm^3), then saturated brine (10 cm^3) and finally dried over magnesium sulfate. After rotary evaporation of the ethyl acetate the residue was purified via silica flash chromatography [(9:1) benzene–ethyl acetate] to yield *the title compound* (623 mg, 43%) as a white solid. R_f 0.37 [(9:1) benzene–ethyl acetate]; 193–194 °C [(3:1) hexane–ethyl acetate]; found: M^+ 453.1353. $C_{26}H_{19}N_3O_5$ requires 453.1324; δ_H ($CDCl_3$+DMSO-d_6, 90 MHz) 7.73–7.63 (8H, m, NPhth), 7.32–7.22 (5H, m, Ph), 6.55 (1H, rotameric br d, *J*∼9, NH), 6.73 (1H, s, CH), 5.21 (1H, quin, *J*∼6.8, C*H*Me), 1.54 (3H, d, *J* 6.8, CH*Me*); δ_C ($CDCl_3$+DMSO-d_6, 75 MHz) 166.6 (s, C=O), 162.1 (s, C=O), 142.1 (s, ArC), 134.6 (d, ArC), 134.5 (d, ArC), 131.5 (s, ArC), 128.6 (d, ArC), 127.5 (d, ArC), 126.5 (d, ArC), 124.0 (d, ArC), 123.9 (d, ArC), 56.6 (d, ArC), 49.7 (d, C*H*Me), 20.8 (q, Me); ν_{max} ($CHCl_3$)/cm^{-1} 3420, 3020, 1775, 1740 (broad), 1515, 1470, 1390, 1345, 1320, 1220, 1130, 1090, 1035, 930, 705; *m*/*z* 453 (M^+, 2%), 306 (100), 130 (31), 120 (34), 105 (43).

6.9. (*S*)-*N*-[(*S*)-1-Phenylethyl]-2-(1,3-dioxo-2-isoindolinyl)-2-fluoroethanamide, 8a

Potassium phthalimide (118 mg, 0.60 mmol) and **3a** (174 mg, 0.57 mmol) were dissolved in DMF (7 cm^3) and stirred at ambient temperature under an argon atmosphere for 5.5 h. After this time the solvent was removed in vacuo and the residue partitioned between ethyl acetate (10 cm^3) and water (10 cm^3). The organic layer was separated, then washed with saturated solutions of sodium thiosulfate, sodium bicarbonate and brine (all 10 cm^3), and then dried over magnesium sulfate. After rotary evaporation of ethyl acetate the components of the residue were separated and purified via silica flash chromatography [(9:1) benzene–ethyl acetate] to yield unreacted starting material (18 mg, 10%, 0% d.e.), *the title compound* (92 mg, 50%, 75% d.e.) and the diphthalimide **7** (25 mg, 10%), all as white solids. R_f (*S*,*S*) isomer 0.41; (*S*,*R*) isomer 0.45 [(9:1) benzene–ethyl acetate]; mp (*S*,*S*) isomer 163–165 °C; (*S*,*R*) isomer 146–148 °C (ethyl acetate–hexane); found: M^+ 326.1069. $C_{18}H_{15}FN_2O_3$ requires 326.1066; δ_H ($CDCl_3$+DMSO-d_6, 90 MHz) 7.81–7.91 (4H, m, NPhth), 7.40–7.30 (5H, m, Ph), 7.0 (1H, br s, NH), 6.37 [6.32] (1H, d, J_{HF} 50.3, CHF), 5.25 (1H, quin, *J* 6.8, C*H*Me), 1.61 [1.67] (3H, d, *J* 6.8, CH*Me*); δ_C ($CDCl_3$+DMSO-d_6, 75 MHz) 165.8 [166.0] (s, C=O), 163.1 (d, J_{CF} 27.0, C=O) (s), 141.9 [142.1] (s, ArC), 135.0 [135.1] (d, ArC), 131.4 (s, ArC), 128.8 [128.9] (d, ArC), 127.7 [127.8] (d, ArC), 126.5 [126.4] (d, ArC), 124.3 (d, ArC), 83.8 (d, J_{CF} 217.0, CHF) (d), 49.2 [49.4] (d, C*H*Me), 21.3 [21.4] (q, Me); δ_F ($CDCl_3$, 282 MHz) −155.3 {−154.7} (d, J_{FH} 50.3); ν_{max} ($CHCl_3$)/cm^{-1} 3430, 3020, 1790, 1775, 1735, 1690, 1525, 1380, 1035, 700; *m*/*z* 326 (M^+, 1%), 180 (100), 147 (50) 105 (69), 91 (21), 76 (83), 50 (52), 32 (30).

6.10. (*S*)-*N*-[(*S*)-1-Phenylethyl]-2-(2,5-dioxo-1-pyrrolidinyl)-2-fluoroethanamide, 9a

Sodium hydride (80% suspension in mineral oil, 13.3 mg, 0.44 mmol) was suspended in DMF (2 cm^3) under an argon atmosphere, and to this was added a DMF solution (2 cm^3) of succinimide (44 mg, 0.44 mmol). Stirring was continued until effervescence had ceased, and the solution was clear and homogeneous. Then a DMF solution (3 cm^3) of **3a** (123 mg, 0.40 mmol) was added dropwise into the reaction flask. Stirring was continued at ambient temperature for 20 h. The DMF was then removed in vacuo, and the residue taken up in chloroform (20 cm^3). This was washed with saturated solutions of sodium bicarbonate, sodium thiosulfate and brine (all 20 cm^3), and then dried over magnesium sulfate. The chloroform was removed and the crude product purified via silica flash chromatography (chloroform), yielding *the title compound* (104 mg, 93%, 75% d.e.) as a white solid. R_f 0.19 for both isomers (diethyl ether); mp (*S*,*S*) isomer 169–172 °C, (*S*,*R*) isomer 164–165 °C [(1:6) chloroform–diethyl ether]; (*S*,*S*) isomer [α] −195.0 (*c* 0.23, $CHCl_3$); (*S*,*R*) isomer [α] −48.3 (*c* 0.38, $CHCl_3$); found: M^+ 278.1074. $C_{14}H_{15}FN_2O_3$ requires 278.1067; δ_H ($CDCl_3$, 90 MHz) 7.39–7.29 (5H, m, Ph), 7.25 (1H, br s, NH), 6.13 [6.05] (1H, d, J_{HF} 49.1, CHF), 5.17 (1H, quin, *J*∼7.0, C*H*Me), 2.70 [4H, s, $(CH_2)_2$], 1.55 [1.57] (3H, d, *J* 7.0, CH*Me*); δ_C ($CDCl_3$, 22.5 MHz) 174.8 (s, C=O), 162.7 (d, J_{CF} 23, C=O) (s), 141.9 [142.1] (s, ArC), 128.3 [128.5] (d, ArC), 127.2 [127.3] (d, ArC), 126.2 [126.1] (d, ArC), 83.5 (d, J_{CF} 218, CHF) (d), 48.8 [49.0] (d, C*H*Me), 27.9 (t, CH_2), 21.1 (q, Me); δ_F ($CDCl_3$, 84.5 MHz) −160.6 {−161.2} (d, J_{FH} 49.1); ν_{max} ($CHCl_3$)/cm^{-1} 3430, 3020, 1795, 1735, 1695, 1530, 1380, 1255, 1180, 1035, 700; *m*/*z* 278 (M^+, 5%), 263 (6), 120 (100), 105 (65), 77 (23), 55 (32).

6.11. (*S*/*R*)-*N*-[(*S*)-1-Phenylethyl]-2-(2,6-dioxo-1-piperidinyl)-2-fluoroethanamide, 10a,b

Sodium bis(trimethylsilyl)amide (1.0 M in THF, 2.4 cm^3, 2.4 mmol) was added dropwise to a solution of glutarimide (0.341 g, 3.01 mmol, 5 equiv) in anhydrous THF (15 cm^3) at −78 °C. The mixture stirred for 0.25 h, before being allowed to warm to room temperature. After re-cooling to −78 °C, a solution of iodoethanamide **3a**,**b** (0.185 g, 0.601 mmol) in anhydrous THF (3 cm^3) was added dropwise. After allowing the mixture to warm to room temperature, stirring was continued for 42 h before being quenched by addition of saturated ammonium chloride. The organic layer was extracted with ethyl acetate (3×20 cm^3) and the combined organic extracts were washed with saturated sodium bicarbonate (2×20 cm^3), saturated sodium thiosulfate (20 cm^3) and brine (20 cm^3) before drying over magnesium sulfate. After evaporation of the solvent, purification of the crude product was achieved by flash silica chromatography (diethyl ether) to give *the title*

compound as a white solid (0.078 g, 45%). R_f 0.24 both isomers (diethyl ether); mp (*S*,*S*) isomer 142–145 °C; (*S*,*R*) isomer 113–117 °C (dichloromethane–hexane); (*S*,*S*) isomer [α] −167.1 (*c* 0.35, $CHCl_3$); (*S*,*R*) isomer [α] −52.9 (*c* 0.73, $CHCl_3$); found: M^+ 292.1216. $C_{15}H_{17}FN_2O_3$ requires 292.1223; δ_H ($CDCl_3$, 200 MHz) 7.38–7.28 (5H, m, Ph), 6.72 [6.65] (1H, d, J_{HF} 47.8, CHF), 6.62 (1H, br s, NH) 5.15 (1H, quin, *J*∼6.7, CH*Me*), 2.72 [2.75] (4H, t, *J* 6.5, $CH_2CH_2CH_2$), 2.00 [2.04] (2H, quin, *J* 6.5, $CH_2CH_2CH_2$), 1.58 [1.59] (3H, d, *J* 6.9, CH*Me*); δ_C ($CDCl_3$, 100 MHz) 171.3 [171.5] (s, C=O), 164.4 (d, J_{CF} 24.1, C=O) (s), 142.1 [142.4] (s, ArC), 128.8 (d, ArC), 127.5 [127.6] (d, ArC), 126.3 (d, ArC), 85.2 (d, J_{CF} 218.3, CHF) (d), 48.9 [49.1] (d, C*H*Me), 32.6 (t, $COCH_2$), 21.6 [21.2] (q, Me), 16.5 [16.6] (t, CH_2); δ_F ($CDCl_3$, 376 MHz) −163.71 [−163.38] (d, J_{FH} 47.8, CHF); ν_{max} (KBr)/cm^{-1} 3313, 3287, 1750, 1705, 1672, 1539, 1347, 1239, 1172, 1126, 1050, 1013; *m*/*z* 292 (M^+, 2%), 144 (21), 120 (100), 105 (100), 55 (99).

6.12. (*S*/*R*)-*N*-Benzyl-2-(2,5-dioxo-1-pyrrolidinyl)-2-fluoroethanamide, 11

Ethanamide **11** was prepared according to the method described for **9a** using **4** (117 mg, 0.40 mmol), succinimide (44 mg, 0.44 mmol) and sodium hydride (13.3 mg, 0.44 mmol) in a total of 7 cm^3 of DMF. This yielded *the title compound* (88 mg, 83%) as a white solid. R_f 0.37 [(1:1) chloroform–ethyl acetate]; mp 123–126 °C [(1:6) chloroform–diethyl ether]; found: M^+ 264.0919. $C_{13}H_{13}FN_2O_3$ requires 264.0910; δ_H ($CDCl_3$, 300 MHz) 7.65 (1H, br s, NH), 7.35–7.25 (5H, m, Ph), 6.12 (1H, d, J_{HF} 48.7, CHF), 4.49 (2H, ABX, J_{AB} 14.9, J_{AX} 6.4 and J_{BX} 5.5, CH_2), 2.81 [4H, s, $(CH_2)_2$]; δ_C ($CDCl_3$, 22.5 MHz) 175.1 (s, C=O), 163.6 (d, J_{CF} 26, C=O) (s), 137.1 (s, ArC), 128.5 (d, ArC), 127.4 (d, ArC), 127.6 (d, ArC), 83.6 (d, J_{CF} 217, CHF) (d), 43.2 (t, CH_2N), 27.9 (t, CH_2); ν_{max} ($CHCl_3$)/cm^{-1} 3440, 3020, 1795, 1735, 1700, 1535, 1380, 1255, 1180, 1050, 700; *m*/*z* 264 (M^+, 9%) 166 (20), 106 (100), 91 (94), 65 (20), 55 (35).

6.13. (*S*/*R*)-*N*-Benzyl-2-(2,6-dioxo-1-piperidinyl)-2-fluoroethanamide, 12

Ethanamide **12** was prepared according to the procedure described above for **10a**,**b**, using glutarimide (2.819 g, 24.9 mmol), sodium bis(trimethylsilyl)amide (1.0 M in THF, 19.9 cm^3, 19.9 mmol) and ethanamide **4** (1.459 g, 4.98 mmol) in anhydrous THF (100 cm^3) yielding *the title compound* as a white crystalline solid (0.601 g, 54%). R_f 0.24 (diethyl ether); mp 164–167 °C (diethyl ether–hexane); found: M^+ 278.1058. $C_{14}H_{15}FN_2O_3$ requires 278.1067; found: C, 60.41; H, 5.54; N, 9.91%. $C_{14}H_{15}FN_2O$ requires C, 60.43; H, 5.43; N, 10.07%; δ_H ($CDCl_3$, 200 MHz) 7.38–7.28 (5H, m, Ph), 6.70 (1H, br s, NH), 6.69 (1H, d, J_{HF} 50.0, CHF), 4.58 (1H, A*B*X, *J* 14.8 and 5.7, PhC*H*HNH) and 4.48 (1H, *A*BX, *J* 14.8 and 5.7, PhCH*H*NH), 2.71 (4H, t, *J* 6.5, $CH_2CH_2CH_2$), 2.02 (2H, quin, *J* 6.5, $CH_2CH_2CH_2$); δ_C ($CDCl_3$, 75 MHz) 171.4 (s, C=O), 165.2 (d, J_{CF} 24.8, C=O) (s), 137.3 (s, ArC), 128.8 (d, ArC), 127.9 (d, ArC), 127.7 (d, ArC), 85.2 (d, J_{CF} 218.0, CHF) (d), 43.5 (t, CH_2N), 32.6 (t, $COCH_2$), 16.5 (t, CH_2); δ_F ($CDCl_3$, 188 MHz) −165.6 (dd, J_{FH} 50.0 and 3.5); ν_{max} (KBr)/cm^{-1} 3324, 1747, 1704, 1674, 1552, 1345, 1174, 1120, 1042, 743, 701; *m*/*z* 278 (M^+, 8%), 106 (100), 91 (65).

6.14. (*S*)-*N*-[(*S*)-1-Phenylethyl]-2-azido-2-fluoroethanamide, 13a

Sodium azide (108 mg, 1.67 mmol) and **3a** (32 mg, 0.10 mmol) were dissolved in DMF (5 cm^3) and then stirred at ambient temperature for 3 h. Next DMF was removed in vacuo to leave a white solid, which was triturated thoroughly with diethyl ether (2×20 cm^3), then filtered. The ether was removed from the filtrate to leave a residue, which was purified via silica flash chromatography [(3:1) hexane–ethyl acetate] to yield *the title compound* (22 mg, 95%, 100% d.e.) as a colourless, viscous oil. R_f 0.60 for both isomers [(2:1) hexane–ethyl acetate]; δ_H ($CDCl_3$, 90 MHz) 7.37–7.27 (5H, m, Ph), 6.60 (1H, br s, NH), 5.69 [5.51] (1H, d, J_{HF} 55.5, CHF), 5.13 (1H, quin, *J*∼7.0, C*H*Me), 1.54 (3H, d, *J* 6.8, CH*Me*); δ_C ($CDCl_3$, 22.5 MHz) 162.6 (d, J_{CF} 25.6, C=O) (s), 141.8 (s, ArC), 128.8 (d, ArC), 127.8 (d, ArC), 126.3 (d, ArC), 96.0 (d, J_{CF} 224.0, CHF) (d), 49.1 (d, *C*HMe), 21.4 [21.5] (q, Me); ν_{max} ($CHCl_3$)/cm^{-1} 3430, 2930, 2120 (N_3), 1690, 1500, 1310, 1005; *m*/*z* no M^+, 174 (50%), 159 (59), 132 (58), 104 (74), 77 (100), 51 (72), 42 (39).

6.15. (*S*/*R*)-*N*-[(*S*)-1-Phenylethyl]-2-cyano-2-fluoroethanamide, 14a,b

Fluoroethanamide **3a**,**b** (122 mg, 0.40 mmol) and potassium cyanide (25 mg, 0.40 mmol) were dissolved in DMF (4 cm^3) under an argon atmosphere. The mixture was stirred at ambient temperature for 2 h, and then the solvent was removed in vacuo. The residue was purified via silica flash chromatography (dichloromethane) to yield *the title compound* as a colourless oil [35 mg, 42% yield or 65% after correction for recovered starting material (43 mg, 35%)]. R_f 0.48 (both isomers, CH_2Cl_2); found: M^+ 206.0855. $C_{11}H_{11}FN_2O$ requires 206.0855; δ_H ($CDCl_3$, 90 MHz) 7.38–7.28 (5H, m, Ph), 6.60 (1H, br s, NH), 5.48 {5.41} (1H, d, J_{HF} 47.0, CHF), 5.16 (1H, quin, *J*∼7.0, C*H*Me), 1.59 {1.57} (3H, d, *J* 7.0, CH*Me*); δ_C ($CDCl_3$, 22.5 MHz) 159.3 (d, J_{CF} 19.5, C=O) (s), 141.3 (s, ArC), 128.9 (d, ArC), 128.1 (d, ArC), 126.2 (d, ArC), 76.7 (d, J_{CF} 201.0, CHF) (d), 49.7 (d, C*H*Me), 21.2 (q, Me), CN signal not observed; δ_F ($CDCl_3$, 84.5 MHz) −190.5 (both isomers) (d, J_{FH} 47.0); ν_{max} ($CHCl_3$)/cm^{-1} 3420, 3020, 1705, 1520, 1450, 1070, 700; *m*/*z* 206 (M^+, 95%), 191 (100), 180 (34), 148 (34), 105 (92), 77 (48), 51 (52).

6.16. (*E*)-3-Amino-3-cyano-2-fluoro-*N*-[(*S*)-1-phenylethyl]-acrylamide, 15

Fluoroiodoethanamide **3a**,**b** (126 mg, 0.41 mmol) and potassium cyanide (60 mg, 0.92 mmol) were dissolved in DMF (5 cm^3) under an argon atmosphere, and stirred at ambient temperature for 20 h. After removal of the solvent in vacuo, the residue was purified via silica flash chromatography (diethyl ether) to yield *the title compound* (85 mg, 89%) as a dark red oil. R_f 0.18 (CH_2Cl_2); found: M^+ 233.0964. $C_{12}H_{12}FN_3O$ requires 233.0964; δ_H ($CDCl_3$, 90 MHz) 7.38–7.28 (5H, m, Ph), 5.44 (1H, q, *J* 7.2, C*H*Me), 4.56 (1H, br s, OH), 1.71 (3H, d, *J* 7.2, CH*Me*) (no other signals clearly observed); δ_C ($CDCl_3$, 22.5 MHz) 139.6 (s, ArC), 128.8 (d, ArC), 127.8 (d, ArC), 126.5 (d, ArC), 47.8 (d, C*H*Me), 17.3 (q, Me) from the auxiliary, plus four weak signals at 164.5, 163.4, 154.0 and 153.5, all of which are singlets in the off-resonance spectrum; ν_{max} ($CHCl_3$)/cm^{-1} 3500, 3390, 3310, 3000, 1750, 1715, 1655, 1585, 1420, 1390, 1265, 1190, 1135, 905, 860, 700; *m*/*z* 233 (M^+, 22%), 129 (73), 105 (100), 77 (19).

6.17. (*S*)-*N*-[(*S*)-1-Phenylethyl]-α-fluorobetainamide, 16a

Ethanamide **3a** (100 mg 0.33 mmol) was dissolved in distilled acetone (3 cm^3), then cooled to 0 °C. To this was added a 4.5 M solution of trimethylamine in acetone (75 μL, 0.34 mmol) and the mixture was stirred at ambient temperature for 3 h. The solvent and excess amine were then removed in vacuo to yield *the title compound* (117 mg, 98%, 100% d.e.) as a white solid. Mp>300 °C; δ_H (DMSO-d_6, 300 MHz) 9.62 (1H, br s, NH), 7.38–7.24 (5H, m, Ph), 6.04 [6.03] (1H, d, J_{HF} 45.0, CHF), 5.03 (1H, quin, *J*∼7.2, C*H*Me), 3.24 [3.22] (9H, d, J_{HF} 1.3, NMe_3), 1.48 [1.47] (3H, d, *J* 6.8, CH*Me*); δ_C (DMSO-d_6, 22.5 MHz) 162.4 (d, J_{CF} 22, C=O) (s), 146.4 [146.5] (s, ArC), 132.5 (d, ArC), 131.2 (d, ArC), 130.1 (d, ArC), 102.4 (d, J_{CF} 232, CHF) (d), 54.0 (q, NMe_3), 52.8 (d, C*H*Me), 25.4 (q, Me); δ_F (DMSO-d_6, 84.5 MHz) −167.4 (both isomers) (d, J_{FH} 45.0); ν_{max} (Nujol)/cm^{-1} 3280, 1700, 1540, 1470, 1400, 1380, 1250, 1220, 1155, 1105, 1090, 960,

885, 750, 700; *m*/*z* (FAB, glycerol) 240 ([M−I+H]$^+$, 51%), 239 ([M−I]$^+$, 100).

6.18. (*S*/*R*)-*N*-Benzyl-α-fluorobetainamide, 17

Fluorobetainamide **17** was prepared according to the method described for **16a**, using **4** (1.340 g, 4.57 mmol), 7.0 M trimethylamine in acetone (0.7 cm^3) and acetone (10 cm^3). On this scale the product precipitated from the reaction mixture as a white solid (1.53 g, 95%). Mp>300 °C; δ_H (DMSO-d_6, 90 MHz) 9.70 (1H, br s, NH), 7.38–7.28 (5H, m, Ph), 6.09 (1H, d, J_{HF} 44.5, CHF), 4.42 (2H, br d, *J* 5.0, CH_2), 3.26 (9H, d, J_{HF} 1.0, NMe_3); δ_C (DMSO-d_6, 22.5 MHz) 163.3 (d, J_{CF} 22, C=O) (s), 141.1 (s, ArC), 132.4 (d, ArC), 131.6 (d, ArC), 131.3 (d, ArC), 102.6 (d, J_{CF} 233, CHF) (d), 54.1 (q, NMe_3), 46.6 (t, CH_2N); ν_{max} (Nujol)/cm^{-1} 3200, 3070, 1705, 1565, 1475, 1425, 1380, 1265, 1155, 1110, 975, 955, 725; *m*/*z* (FAB, glycerol) 226 ([M−I+H]$^+$, 44%), 225 ([M−I]$^+$, 100).

6.19. (*S*/*R*)-α-Fluorobetaine, 18

A solution of fluorobetaine amide **17** (0.295 g, 0.838 mmol) in 6 M hydrochloric acid was heated at reflux for 48 h. After cooling, the solvent and excess acid were removed in vacuo leaving a residue, which was dissolved in de-ionized water (50 cm^3). This solution was taken to pH 10 with 25% aqueous ammonia solution, and washed with dichloromethane (10×15 cm^3) to remove the benzylamine. The pH of the aqueous solution was adjusted to pH 7 with 1 M hydrochloric acid then the solvent was removed in vacuo. Purification by anion-exchange chromatography (Dowex 50X-8-100) yielded the product, after freeze-drying, as a white crystalline solid (0.025 g, 22%, mp 218–222 °C), which was shown to be the zwitterion by X-ray diffraction methods. Found: M$^+$ 136.0780. $C_5H_{11}FNO_2$ requires 136.0774; δ_H (D_2O, 90 MHz) 5.53 (1H, d, J_{HF} 48.0, CHF), 3.26 (9H, d, J_{HF} 1.7, NMe_3); δ_C (D_2O, 22.5 MHz) 164.9 (d, J_{CF} 22, C=O) (s), 100.7 (d, J_{CF} 235, CHF) (d), 51.0 (q, NMe_3); δ_F (D_2O, 84.5 MHz) −159.4 (d, J_{FH} 48.0); ν_{max} (Nujol)/cm^{-1} 3140, 3030, 1645, 1405, 1310, 1145, 1090, 980, 950, 890, 815, 750; *m*/*z* (FAB, noba) 136 (M$^+$, 100%). Attempted crystallisation of the residue (methanol–diethyl ether) before ion exchange chromatography yielded a buff precipitate, which was contaminated with ammonium chloride and iodide [mp 160–165 °C (dec)].

6.20. (*S*/*R*)-*N*-Benzyl-2-piperidinyl-2-(4-oxo-4-piperidinylbutaneamido)ethanamide, 19

(*S*/*R*)-*N*-Benzyl-2-(2,5-dioxopyrrolidiny1)-2-f1uoroethanamide (**11**) (0.106 g, 0.400 mmol) was dissolved in dry THF (10 cm^3) and piperidine (0.6 cm^3, 6.07 mmol, 15 equiv) was added. The reaction mixture was allowed to stir at ambient temperature for 22 h and was then worked up via removal of the excess piperidine and solvent under reduced pressure The crude residue was purified by flash silica chromatography (ethyl acetate) to yield *the title compound* as a white solid (0.148 g, 89%). R_f 0.27 (ethyl acetate); mp 126–128 °C (diethyl ether); found: C, 66.27; H, 8.60, N, 13.49%. $C_{23}H_{35}N_4O_3$ requires C, 66.48; H, 8.49; N, 13.48%; δ_H ($CDCl_3$, 400 MHz) 7.38 (1H, AB*X*, *J* 6.5, $PhCH_2NH$), 7.20–7.35 (5H, m, Ph), 6.80 (1H, d, *J* 8.0, CHN*H*), 5.24 (1H, d, *J* 8.0, *CH*NH), 4.52 (1H, *ABX*, *J* 14.9 and 6.5, PhC*H*HNH) and 4.41 (1H, A*B*X, *J* 14.9 and 5.6, PhCH*H*NH), 3.53 (2H, d, *J* 5.5, $COCH_2CH_2CO$), 3.41 (2H, d, *J* 5.5, $COCH_2CH_2CO$), 2.40–2.80 (8H, m, 4×CH_2N), 1.40–1.70 (12H, m, 2×$(CH_2)_3$); δ_C ($CDCl_3$, 100 MHz) 174.1 (s, C=O), 169.8 (s, C=O), 169.4 (s, C=O), 138.2 (s, ArC), 128.7 (d, ArC), 127.6 (d, ArC), 127.5 (d, ArC), 71.0 (d, CHN), 49.7 (t, CH_2N), 46.4 (t, CH_2N), 43.7 (t, CH_2N), 42.9 (t, CH_2N), 31.5 (t, CH_2), 28.7 (t, CH_2), 26.3 (t, CH_2), 26.1 (t, CH_2), 25.5 (t, CH_2), 24.5 (t, CH_2), 23.9 (t, CH_2); ν_{max} (KBr)/cm^{-1} 3363, 3268, 3088, 2931, 1692, 1655, 1618, 1477, 1351, 1251, 1190, 1010, 720; *m*/*z* (FAB, noba) 416 (MH$^+$, 30%), 280 (10), 231 (100), 84 (22), 41 (19), 31 (20).

6.21. (*S*/*R*)-*N*-Benzyl-2-benzylamino-2-(4-benzylamino-4-oxo-butaneamido)ethanamide, 20

(*S*/*R*)-*N*-Benzyl-2-(2,5-dioxopyrrolidinyl)-2-fluoroethanamide (**11**) (0.107 g, 0.406 mmol) was dissolved in anhydrous THF (10 cm^3) and benzylamine (0.7 cm^3, 6.41 mmol, 15 equiv) was added. The reaction mixture was allowed to stir at ambient temperature for 24 h. The white precipitate was filtered from the reaction mixture to give *the title compound* (0.150 g, 80%). R_f 0.48 (ethyl acetate); mp 168–171 °C (dec, without further purification); δ_H (DMSO-d_6, 400 MHz) 8.56 (1H, t, *J* 6.1, $PhCH_2NHCOCH_2$), 8.41 (1H, t, *J* 5.8, $PhCH_2NHCOCH$), 8.28 (1H, d, *J* 8.2, $PhCH_2NHCH$), 7.46–7.20 (15H, m, Ph), 4.98 (1H, d, *J* 8.2, $PhCH_2NHCH$), 4.29 (2H, d, *J* 6.1, $PhCH_2NHCOCH_2$), 4.27–4.23 (2H, m, $PhCH_2NHCOCH$), 3.73 (1H, *AB*, *J* 13.5, PhC*H*HNHCH) and 3.63 (1H, A*B*, *J* 13.5, PhCH*H*NHCH), 2.44 (4H, s, CH_2CH_2); δ_C (DMSO-d_6, 100 MHz) 172.4 (s, C=O), 171.7 (s, C=O), 169.8 (s, C=O), 140.3 (s, ArC), 139.8 (s, ArC), 139.5 (s, ArC), 128.5 (d, ArC), 128.4 (2×d, ArC), 128.3 (d, ArC), 128.0 (d, ArC), 127.4 (d, ArC), 127.3 (d, ArC), 127.2 (d, ArC), 126.9 (d, ArC), 64.7 (d, CHN), 48.8 (t, CH_2N), 42.4 (t, CH_2N), 42.3 (t, CH_2N), 31.0 (t, CH_2), 30.9 (t, CH_2); ν_{max} (KBr)/cm^{-1} 3275, 1636, 1559, 1532, 1454, 1420, 1343, 749, 695; *m*/*z* (FAB, noba) 459 (MH$^+$, 8%), 324 (9), 253 (19), 207 (44), 190 (44), 108 (20), 91 (100).

6.22. (*S*/*R*)-*N*-Benzyl-2-benzylamino-2-(4-benzylamino-4-oxo-pentaneamido)ethanamide, 21

Ethanamide **21** was prepared according to the method described for **20** using (*S*/*R*)-*N*-benzyl-2-(2,6-dioxopiperidinyl)-2-fluoroethanamide (**12**) (0.083 g, 0.299 mmol) and benzylamine (0.5 cm^3, 4.58 mmol, ~15 equiv) in dry THF (10 cm^3). The reaction mixture was allowed to stir for 106 h, before filtration of the white precipitate (0.088 g, 62%). R_f 0.45 (ethyl acetate); mp 181–184 °C (dec); δ_H (DMSO-d_6, 400 MHz) 8.52–8.50 (1H, m, $PhCH_2NHCO$), 8.31 (1H, br t, *J*~5.7, $PhCH_2NHCO$), 8.18 (1H, d, *J* 8.2, CHN*H*), 7.46–7.20 (15H, m, Ph), 4.97 (1H, d, *J* 8.2, *CH*NH), 4.26–4.30 (4H, m, 2×$PhCH_2NHCO$), 3.72 (1H, A*B*, *J* 13.5, PhCH*H*NHCH) and 3.63 (1H, *AB*, *J* 13.5, PhC*H*HNHCH), 2.16–2.22 (4H, m, $CH_2CH_2CH_2$), 1.80–1.78 (2H, m, *J*~7.5, $CH_2CH_2CH_2$); δ_C (DMSO-d_6, 100 MHz) 172.4 (s, C=O), 171.8 (s, C=O), 169.6 (s, C=O), 140.1 (s, ArC), 139.7 (s, ArC), 139.3 (s, ArC), 128.4 (2×d, ArC), 128.3 (d, ArC), 128.2 (d, ArC), 127.3 (d, ArC), 127.2 (d, ArC), 126.9 (2×d, ArC), 126.8 (d, ArC), 64.4 (d, CHN), 48.6 (t, CH_2N), 42.1 (t, CH_2N), 42.0 (t, CH_2N), 34.8 (t, CH_2), 34.7 (t, CH_2), 21.6 (t, $CH_2CH_2CH_2$); ν_{max} (KBr)/cm^{-1} 3285, 3267, 1641, 1546, 1454, 1382, 1239, 1134, 1079, 1030, 1009, 744, 693; *m*/*z* (FAB, noba) 473 (MH$^+$, 7%), 338 (12), 221 (36), 91 (100).

6.23. (*S*/*R*)-*N*-Benzyl-2-(2,5-dioxopyrrolidinyl)-2-ethylthioethanamide, 22

Sodium hydride (60% dispersion in mineral oil, 8 mg, 0.200 mmol) was dispersed in anhydrous DMF (5 cm^3) and ethanethiol (14 μL, 0.2 mmol) was added. The reaction was allowed to stir until effervescence ceased and the mixture had become homogeneous. (*S*/*R*)-*N*-Benzyl-2-(2,5-dioxopyrrolidinyl)-2-fluoroethanamide (**11**) (0.051 g, 0.193 mmol) in DMF (5 cm^3) was added via cannulation and the reaction mixture was allowed to stir at ambient temperature and monitored by TLC. After 24 h the reaction was worked up via removal of solvent under reduced pressure. The resulting residue was partitioned between ethyl acetate (20 cm^3) and distilled water (20 cm^3) and the organic layer was then washed with brine before drying over $MgSO_4$. The crude product was purified by flash silica chromatography (diethyl ether) to yield the

product as an oil, which solidified on standing (0.031 g, 51%). R_f 0.47 (diethyl ether); mp 115 °C (dec); δ_H ($CDCl_3$, 300 MHz) 7.56 (1H, br s, NH), 7.38–7.28 (5H, m, Ph), 5.56 (1H, s, C*H*(SEt)N), 4.52 (1H, A*B*X, *J* 14.9 and 5.9, PhCH*H*NH) and 4.47 (1H, *A*BX, *J* 14.9 and 5.9, PhC*H*HNH), 2.80 (4H, s, CH_2CH_2), 2.74 (2H, q, *J* 7.4, SCH_2CH_3), 1.31 (3H, t, *J* 7.4, SCH_2CH_3); δ_C ($CDCl_3$, 75 MHz) 175.5 (s, C=O), 164.6 (s, C=O), 137.4 (s, ArC), 128.8 (d, ArC), 127.8 (d, ArC), 127.6 (d, ArC), 56.2 (d, CHS), 44.6 (t, CH_2N), 28.2 (t, CH_2), 28.1 (t, CH_2), 15.1 (q, Me); ν_{max} (KBr)/cm^{-1} 3370, 1778, 1703, 1672, 1515, 1388, 1230, 1176, 822, 758, 702; *m*/*z* (FAB, noba) 307 (MH^+, 22%), 149 (40), 109 (15), 91 (63), 81 (31), 69 (52), 55 (83), 43 (100), 27 (27).

6.24. (*S*/*R*)-*N*-Benzyl-2-(2,6-dioxopiperidinyl)-2-ethylthio-ethanamide, 23

Ethanamide **23** was prepared according to the method described for **22** using (*S*/*R*)-*N*-benzyl-2-(2,6-dioxopiperidinyl)-2-fluoroethanamide (**12**) (0.055 g, 0.198 mmol), sodium hydride (8 mg, 0.200 mmol) and ethanethiol (14 μL, 0.200 mmol). Stirring was continued for 170 h at ambient temperature to yield, after work-up and purification [flash silica chromatography, (1:1) ethyl acetate–hexane], *the title compound* as a white solid (0.017 g, 0.053 mmol, 28%). R_f 0.12 [(1:1) ethyl acetate–hexane]; mp 128 °C (dec); δ_H ($CDCl_3$, 200 MHz) 7.62 (1H, br s, NH), 7.31–7.21 (5H, m, Ph), 6.02 (1H, s, C*H*(SEt)N), 4.44 (1H, A*B*X, *J* 14.3 and 5.8, PhCH*H*NH) and 4.38 (1H, *A*BX, *J* 14.3 and 6.4, PhC*H*HNH), 2.76–2.56 (6H, m, $CH_2CH_2CH_2$+SCH_2CH_3), 1.95 (2H, quin, *J* 6.2, $CH_2CH_2CH_2$), 1.23 (3H, t, *J* 7.4, SCH_2CH_3); δ_C ($CDCl_3$, 75 MHz) 171.7 (s, C=O), 166.6 (s, C=O), 137.9 (s, ArC), 128.8 (d, ArC), 127.7(d, ArC), 127.6 (d, ArC), 57.7 (d, CHS), 44.4 (t, CH_2N), 32.6 (t, CH_2), 28.5 (t, CH_2), 16.9 (t, $CH_2CH_2CH_2$), 15.5 (q, Me); ν_{max} (KBr)/cm^{-1} 3370, 1728, 1668, 1517, 1360, 1174; *m*/*z* (FAB, noba) 321 (MH^+, 5%), 279 (6), 259 (8), 176 (13), 149 (34), 131 (14), 108 (53), 89 (61), 77 (73), 65 (33), 39 (100).

6.25. (*S*/*R*)-*N*-Benzyl-2-(2,5-dioxopyrrolidinyl)-2-methoxyethanamide, 24

(*S*/*R*)-*N*-Benzyl-2-(2,5-dioxopyrrolidinyl)-2-fluoroethanamide (**11**) (0.080 g, 0.304 mmol) was dissolved in dry methanol (8 cm^3) and 1 M NaOMe solution (0.30 cm^3, 0.300 mmol) was added [NaOMe solution prepared freshly from sodium (0.245 g) and MeOH (10 cm^3)]. After 0.1 h TLC showed that all starting materials have been consumed, and the reaction was worked up via removal of methanol under reduced pressure. The resulting residue was partitioned between ethyl acetate and distilled water (15 cm^3 each). The organic extract was separated and washed with brine before drying over $MgSO_4$. The solvent was removed under reduced pressure and the resulting residue was purified by flash silica chromatography [(1:1) ethyl acetate–petroleum ether (bp 40–60 °C)] to yield *the title compound* as a white solid (0.065 g, 77%). R_f 0.33 (ethyl acetate); mp 125–127 °C (ethyl acetate–hexane); found: M^+ 276.1105. $C_{14}H_{16}N_2O_4$ requires 276.1110; δ_H ($CDCl_3$, 200 MHz) 7.38–7.28 (5H, m, Ph), 7.16 (1H, br s, NH), 5.40 (1H, s, C*H*OCH_3), 4.55 (1H, A*B*X, *J* 14.8 and 6.2, PhCH*H*N) and 4.43 (1H, *A*BX, *J* 14.8 and 5.8, PhC*H*HN), 3.40 (3H, s, CHOCH_3), 2.77 (4H, s, CH_2CH_2); δ_C ($CDCl_3$, 50 MHz) 176.3 (s, C=O), 165.1 (s, C=O), 137.5 (s, ArC), 128.6 (d, ArC), 127.8 (d, ArC), 127.4 (d, ArC), 79.1 (d, CH), 57.6 (q, OMe), 43.4 (t, CH_2N), 29.1 (t, CH_2); ν_{max} (KBr)/cm^{-1} 3379, 1784, 1717, 1685, 1541, 1454, 1385, 1362, 1288, 1247, 1201, 1179, 1103, 700; *m*/*z* 276 (M^+, 10%), 244 (4), 177 (75), 142 (100), 128 (21), 106 (46), 100 (27), 91 (53), 60 (37), 28 (33).

6.26. (*S*/*R*)-*N*-Benzyl-2-methoxy-(5-methoxy-5-oxo-pentaneamido)-ethanamide, 25

(*S*/*R*)-*N*-Benzyl-2-(2,6-dioxopiperidinyl)-2-fluoroethanamide (**12**) (0.057 g, 0.206 mmol) was dissolved in dry methanol (8 cm^3) and 1 M NaOMe solution (0.2 cm^3, 0.2 mmol) was added [NaOMe solution prepared freshly from sodium (0.245 g) and MeOH (10 cm^3)]. After 0.1 h, TLC showed that all starting materials have been consumed and the reaction was worked up via removal of the solvent under reduced pressure. The resulting residue was partitioned between ethyl acetate and distilled water (15 cm^3 each). The organic layer was washed with brine (15 cm^3) and dried over $MgSO_4$. Solvent was removed under reduced pressure and purified by flash silica chromatography (diethyl ether) to yield *the title compound* as a white solid (0.050 g, 76%). R_f 0.18 (diethyl ether); mp 122–124 °C (diethyl ether–hexane); δ_H ($CDCl_3$, 300 MHz) 7.38–7.28 (5H, m, Ph), 7.08 (1H, br t, $PhCH_2NH$), 6.83 (1H, d, *J* 8.6, CH(OMe)N*H*, 5.52 (1H, d, *J* 8.6), C*H*(OMe)NH), 4.54–4.34 (2H, m, PhCH_2NH), 3.66 (3H, s, CO_2CH_3), 3.39 (3H, s, CHOCH_3), 2.38 (2H, t, *J* 7.2, $CH_2CH_2CH_2$), 2.35 (2H, t, *J* 7.2, $CH_2CH_2CH_2$), 1.93 (2H, quin, *J* 7.2, $CH_2CH_2CH_2$); δ_C ($CDCl_3$, 75 MHz) 173.6 (s, C=O), 173.5 (s, C=O), 167.8 (s, C=O), 137.5 (s, ArC), 128.8 (d, ArC), 127.8 (d, ArC), 127.7 (d, ArC), 79.0 (d, CH), 56.1 (q, OMe), 51.6 (q, OMe), 43.6 (t, CH_2N), 35.1 (t, $COCH_2$), 33.0 (t, $COCH_2$), 20.5 (t, $CH_2CH_2CH_2$); ν_{max} (KBr)/cm^{-1} 3289, 1732, 1642, 1555, 1531, 1194, 1080; *m*/*z* (FAB, noba) 323 (MH^+, 33%), 291 (12), 188 (15), 163 (15), 149 (31), 129 (100).

6.27. (*S*/*R*)-*N*-Benzyl-2-(2-[*S*/*R*]-hydroxy-5-oxo-pyrrolidinyl)-2-fluoroethanamide, 26

(*S*/*R*)-*N*-Benzyl-2-(2,5-dioxopyrrolidinyl)-2-fluoroethanamide (**11**) (0.309 g, 1.17 mmo1) was dissolved in anhydrous THF (30 cm^3) in a flame dried glass round-bottomed flask and cooled to −15 °C (ethylene glycol–dry ice). Lithium borohydride (2 M in THF) (0.6 cm^3, 1.2 mmol) was added via syringe and the reaction mixture was allowed to stir at −15 °C for 7.5 h. The reaction was quenched with saturated NaCl solution and extracted with ethyl acetate (3×20 cm^3). The combined organic extracts were washed with brine (60 cm^3) and dried over $MgSO_4$. Solvent was removed under reduced pressure and the resulting residue was purified by flash silica chromatography [(2:1) ethyl acetate–petroleum ether (bp 40–60 °C)] to yield *the title compound* as a colourless oil (0.184 g, 59%). R_f 0.56 (ethyl acetate); δ_H ($CDCl_3$, 400 MHz, −15 °C) (major isomer first) 7.38–7.28 (5H, m, Ph protons), 6.05 {6.30} (1H, J_{HF} 52.7, CHF), 5.53–5.23 (1H, m, C*H*CH_2CH_2), 4.70 {4.87} (1H, br s, $PhCH_2NH$), 4.56–4.38 (2H, m, $PhCH_2$), 1.90–2.62 (4H, m, CHCH_2CH_2); δ_C ($CDCl_3$, 100 MHz, −15 °C) (major isomer first) 176.0 {176.9} (s, C=O), 165.2 {166.1} (d, J_{CF} 28.0, C=O), 136.9 {136.5} (s, ArC), 129.2 {129.3} (d, ArC), 128.2 {128.4} (d, ArC), 128.2 {128.3} (d, ArC), 87.7 {87.6} (d, J_{CF} 211.0, CHF) (d), 82.0 {80.9} (d, CHOH), 43.5 {43.7} (t, CH_2N), 29.1 {29.0} (t, CH_2), 28.9 {28.8} (t, CH_2); δ_F ($CDCl_3$, 376 MHz) −150.41 {−150.25} (d, J_{FH} 52.7); ν_{max} (thin film)/cm^{-1} 3435, 3333 (broad), 1721, 1684, 1541, 1454, 1409, 1280, 1074, 1029, 983, 699.

6.28. (*S*/*R*)-*N*-Benzyl-2-(2-[*S*/*R*]-hydroxy-6-oxo-piperidinyl)-2-fluoroethanamide, 27

Hydroxylactam **27** was prepared according to the method described for **26** using 100 μL of $LiBH_4$ (2 M in THF) with (*S*/*R*)-*N*-benzyl-2-(2,6-dioxopiperidiny1)-2-fluoro-ethanamide (**12**) (0.057 g, 0.203 mmol) in anhydrous THF (7 cm^3) for 3.5 h at −15 °C to yield *the title compound* as a colourless oil (0.021 g, 37%). R_f 0.38 (ethyl acetate); δ_H ($CDCl_3$, 400 MHz, −15 °C) 7.35–7.25 (5H, m, Ph), 7.10 and 7.00 (2H, 2×br s, N*H*/O*H*), 5.85 {6.75} (1H, d, J_{HF} 50.0, CHF), 5.20–4.90 (1H, m, C*H*OH), 4.59–4.41 (2H, m $PhCH_2$), 3.00–1.50 (6H, m, $CH_2CH_2CH_2$); δ_C ($CDCl_3$, 100 MHz, −15 °C) 172.9 {173.2} (s, C=O), 167.3 {167.4} (d, J_{CF} 27.8, C=O) (s), 137.3 {136.9} (s, ArC), 129.3 {129.5} (d, ArC), 128.4 {128.6} (d, ArC), 128.2 {128.3} (d, ArC), 92.7 {90.9} (d, J_{CF} 216.0, CHF) (d), 81.1 {78.4} (d, CHOH), 43.9 {44.0} (t, CH_2N), 33.1 {32.1} (t, CH_2), 30.9 {29.6} (t, CH_2), 16.9 {16.1} (t, CH_2CH_2CH), δ_F

($CDCl_3$, 376 MHz, −15 °C) −149.88 (d, J_{FH} 50.0); ν_{max} ($CHCl_3$)/cm^{-1} 3437, 3333 (broad), 1679, 1540, 1455, 1332, 1281, 1086, 699.

6.29. 1-Aza-2-(*S*/*R*)-(*N*-benzylformamido)-3,6-dithiabicyclo[5.3.0]deca-10-one, 28

(*S*/*R*)-*N*-Benzyl-2-(2-(*S*/*R*)-hydroxy-5-oxopyrrolidinyl)-2-fluoroethanamide (**26**) (0.088 g, 0.330 mmol) was dissolved in anhydrous chloroform (5 cm^3) and ethane-l,2-dithiol (0.5 cm^3, 5.96 mmol, 18 equiv) was added. The reaction mixture was cooled to 0 °C and boron trifluoride diethyl etherate (0.3 cm^3, 2.44 mmol, 7 equiv) was added. After 7.5 h the reaction was worked up via dilution with chloroform (15 cm^3), washing with saturated sodium bicarbonate solution (15 cm^3) and brine (15 cm^3) before drying over $MgSO_4$. The solvent was removed under reduced pressure to give the product in the excess ethane-1,2-dithiol. The mixture was then partitioned between toluene (15 cm^3) and saturated sodium bicarbonate solution (15 cm^3), and then the toluene solution was washed with brine (15 cm^3) before drying over $MgSO_4$. Solvent was removed under reduced pressure and the product was purified by flash silica chromatography [(2:1) ethyl acetate–petroleum ether (bp 40–60 °C)] to yield *the title compound* as a white solid (0.060 g, 56%). R_f 0.17 [(2:1) ethyl acetate–petroleum ether (bp 40–60 °C)]; mp 176–178 °C (ethyl acetate–hexane); found: M^+ 322.0839. $C_{15}H_{18}N_2O_2S_2$ requires 322.0810; δ_H ($CDCl_3$, 400 MHz) 7.38–7.28 (5H, m, Ph), 6.83 (1H, br s, NH), 5.60 (1H, s, SC*H*N), 5.35–5.31 (1H, m, C*H*CH_2CH_2), 4.56 (1H, A*B*X, *J* 14.9 and 5.9, PhCH*H*NH) and 4.51 (1H, *A*BX, *J* 14.9 and 5.7, PhC*H*HNH), 3.10–3.02 (2H, m, SCH_2CH_2S), 2.98–2.87 (2H, m, SCH_2CH_2S), 2.65–2.45 (3H, m, CHCH*HCH*$_2$), 1.98–1.88 (1H, m, CHC*H*HCH_2); δ_C ($CDCl_3$, 100 MHz) 173.6 (s, C=O), 166.1 (s, C=O), 137.8 (s, ArC), 128.6 (d, ArC), 127.7 (d, ArC), 127.4 (d, ArC), 68.0 (d, CO*C*HS), 59.2 (d, CH_2*C*HS), 44.1 (t, CH_2N), 35.6 (t, CH_2), 34.9 (t, CH_2), 31.2 (t, CH_2), 28.0 (t, CH_2); ν_{max} (KBr)/cm^{-1} 3331, 1681, 1666, 1525, 1373, 1285, 1265, 1237, 813, 746, 700, 616; *m*/*z* 322 (M^+, 9%), 294 (30), 188 (53), 105 (100), 91 (64), 84 (18).

6.30. 2-[(*S*)-1-Phenylethylamino]-2-oxo-1-thioethanamide, 29

The azide **13a**,**b** (75 mg, 0.34 mmol) and thiolacetic acid (0.2 mL, 200 mg, 2.9 mmol) were stirred under an argon atmosphere for 4 h. The excess thiolacetic acid was removed in vacuo, then the residue dissolved in ethyl acetate, washed with water and dried over magnesium sulfate. After removal of ethyl acetate, the residue was purified via silica flash chromatography [(1:3) ethyl acetate–petroleum ether (bp 40–60 °C)] to yield *the title compound* (63 mg, 90%) as a bright yellow solid. R_f 0.44 [(2:1) hexane–ethyl acetate]; found: M^+ 208.0677. $C_{10}H_{12}N_2OS$ requires 208.0670; mp 108–112 °C (diethyl ether–hexane); δ_H ($CDCl_3$, 90 MHz) 7.38–7.28 (5H, m, Ph), 7.8, 8.40 and 8.90 (3H, 3×bs, NHs), 5.09 (1H, quin, *J* 7.0, C*H*Me), 1.57 (3H, d, *J* 6.8, CH*Me*); δ_C ($CDCl_3$, 22.5 MHz) 191.1 (s, C=S), 157.2 (s, C=O), 142.1 (s, ArC), 128.8 (d, ArC), 127.7 (d, ArC), 126.0 (d, ArC), 50.7 (d, CH_2N), 21.8 (q, Me); ν_{max} ($CHCl_3$)/cm^{-1} 3490, 3350, 3030, 1690, 1575, 1525, 1410, 710; *m*/*z* 208 (M^+, 40%), 120 (100), 105 (70), 91 (24), 77 (26), 60 (26).

6.31. (*S*/*R*)-*N*-[(*S*)-1-Phenylethyl]-*S*-ethanoyl-2-azido-2-mercaptoethanamide, 30a,b

The azide **13a**,**b** (186 mg, 0.84 mmol) and thiolacetic acid (0.3 cm^3, 297 mg, 3.93 mmol) were stirred at ambient temperature, under an argon atmosphere and in an oven-dried flask. After 4 h the excess acid was removed in vacuo, and the residue purified via silica flash chromatography [(3:1) hexane–ethyl acetate] to yield *the title compound* (64 mg, 30%) as a viscous yellow oil, which solidified to a paste on standing. R_f 0.47 [(2:1) hexane–ethyl acetate]; δ_H ($CDCl_3$, 90 MHz) 7.36–7.26 (5H, m, Ph), 6.70 (1H, br s, NH), 5.79 {5.73} (1H, s, CHN_3), 5.08 (1H, quin, *J* 6.8, C*H*Me), 2.45 (3H, s, SCOMe), 1.50 (3H, d, *J* 6.8, CH*Me*); δ_C ($CDCl_3$, 22.5 MHz) 193.3 (s, SC=O), 164.1 (s, NC=O), 142.2 (s, ArC), 128.8 (d, ArC), 127.6 (d, ArC), 126.0 (d, ArC), 64.3 (d, CHS), 49.6 (d, CH_2N), 30.3 (q, CO*Me*), 21.5 (q, CH*Me*); ν_{max} ($CHCl_3$)/cm^{-1} 3400, 2990, 2120 (N_3), 1685, 1515, 1120, 905; *m*/*z* no M^+, 180 (20%), 159 (26), 132 (33), 105 (100), 77 (31), 43 (72), 32 (30).

6.32. *N*-[(*S*)-1-Phenylethyl]-2-fluoroethanamide, 31, and *N*-[(*S*)-1-phenylethyl]propanamide, 32

The fluoronitrile **14a**,**b** (90 mg, 0.43 mmol) was dissolved in distilled methanol (10 cm^3), and to this was added platinum(IV) oxide (13 mg). This mixture was stirred vigorously under a hydrogen atmosphere for 24 h at room temperature, and then the solution was diluted, filtered and evaporated to dryness. The residue was purified via silica flash chromatography (dichloromethane, then diethyl ether) to yield *the title compounds* **31** (13 mg, 16%) and **32** (10 mg, 13%). (**31**) R_f 0.65 (diethyl ether); found: M^+ 181.0909. $C_{10}H_{12}NOF$ requires 181.0903; δ_H ($CDCl_3$, 90 MHz) 7.38–7.28 (5H, m, Ph), 6.50 (1H, br s, NH), 5.20 (1H, quin, *J* 7.0, C*H*Me), 4.79 (2H, d, J_{HF} 48.0, CH_2F), 1.55 (3H, d, *J* 7.0, CH*Me*); δ_C ($CDCl_3$, 22.5 MHz) 166.7 (d, J_{CF} 17) (s, C=O), 142.5 (s, ArC), 128.9 (d, ArC), 128.2 (d, ArC), 127.8 (d, ArC), 80.3 (d J_{CF} 185, CH_2F) (t), 48.4 (d, C*H*Me), 21.8 (q, Me); ν_{max} ($CHCl_3$)/cm^{-1} 3430, 3000, 1675, 1530, 1050, 705; *m*/*z* 181 (M^+, 70%), 166 (84), 120 (17), 106 (100), 91 (10), 77 (58), 51 (34), 42 (36). (**32**) R_f 0.56 (diethyl ether); found: M^+ 177.1172. $C_{11}H_{15}NO$ requires 177.1155; δ_H ($CDCl_3$, 90 MHz) 7.36–7.26 (6H, m, Ph+NH), 5.10 (1H, quin, *J* 7.0, C*H*Me), 2.21 (2H, q, 7.4, CH_2Me), 1.49 (3H, d, *J* 6.9, CH*Me*), 1.16 (3H, t, *J* 7.4, CH_2*Me*); δ_C ($CDCl_3$, 22.5 MHz) 167.0 (s, C=O), 143.3 (s, ArC), 128.7 (d, ArC), 127.4 (d, ArC), 126.2 (d, ArC), 48.6 (d, C*H*Me), 25.6 (t, CH_2Me), 21.7 (q, CH*Me*), 9.80 (q, CH_2*Me*); *m*/*z* 177 (M^+, 41%), 162 (8), 120 (30), 106 (100), 91 (22), 77 (33), 57 (20), 44 (24).

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References and notes

1. Bailey, P. D.; Boa, A. N.; Clayson, J. *Contemporary Org. Synth.* **1995**, *2*, 173–187.
2. (a) Kober, R.; Hammes, W.; Steglich, W. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 203–204; (b) Kober, R.; Steglich, W. *Liebigs Ann. Chem.* **1983**, 599–609; (c) Easton, C. J.; Hay, M. P.; Love, S. G. *J. Chem. Soc., Perkin Trans. 1* **1988**, 265–268; (d) See also citations 2–11 in Ref. 1 of this paper.
3. (a) Baba, D.; Fuchigami, T. *Tetrahedron Lett.* **2002**, *43*, 4805–4808; (b) Mohar, B.; Sterk, D.; Ferron, L.; Cahard, D. *Tetrahedron Lett.* **2005**, *46*, 5029; (c) Huber, D. P.; Stanek, K.; Togni, A. *Tetrahedron: Asymmetry* **2006**, *17*, 658–664.
4. (a) Bailey, P. D.; Boa, A. N.; Crofts, G. A.; van Diepen, M.; Helliwell, M.; Gammon, R. E.; Harrison, M. J. *Tetrahedron Lett.* **1989**, *30*, 7457–7460 (X-ray data deposited with the Cambridge Crystallographic Data Centre: for **1a** CSD Ref. KAVWEJ11; for **3a** CSD Ref. SEHDAK); (b) Bailey, P. D.; Baker, S. R.; Boa, A. N.; Clayson, J.; Rosair, G. M. *Tetrahedron Lett.* **1998**, *39*, 7755–7758.
5. (a) Takeuchi, Y.; Nabetani, M.; Takagi, K.; Hagi, T.; Koizumi, T. *J. Chem. Soc., Perkin Trans. 1* **1991**, 49–53; (b) Takeuchi, Y.; Kamezaki, M.; Kirihara, K.; Haufe, G.; Laue, K. W.; Shibata, N. *Chem. Pharm. Bull.* **1998**, *46*, 1062–1064; (c) Takeuchi, Y.; Kirihara, K.; Kirk, K. L.; Shibata, N. *Chem. Commun.* **2000**, 785–786; (d) Annedi, S. C.; Li, W.; Samson, S.; Kotra, L. P. *J. Org. Chem.* **2003**, *68*, 1043–1049.
6. Takeuchi, Y.; Itoh, N.; Satoh, T.; Koizumi, T.; Yamaguchi, K. *J. Org. Chem.* **1993**, *58*, 1812–1820.
7. Myers, A. G.; Barbay, J. K.; Zhong, B. *J. Am. Chem. Soc.* **2001**, *123*, 7207–7219.
8. Molines, H.; Wakselman, C. *Synthesis* **1984**, 838–839.
9. Willy, W. E.; McKean, D. R.; Garcia, B. A. *Bull. Chem. Soc. Jpn.* **1976**, *49*, 1989–1995.
10. Takeuchi, Y.; Takagi, K.; Nagata, K.; Koizumi, T. *Chem. Pharm. Bull.* **1991**, *39*, 3120–3122.
11. (a) Fatiadi, A. J. *Synthesis* **1978**, 165–204; (b) Fatiadi, A. J. *Synthesis* **1978**, 241–282.

12. de Vries, L. *J. Org. Chem.* **1973**, *38*, 2604–2613.
13. Adams, R.; Brown, B. K. *Org. Synth., Coll. Vol. 1* **1941**, 528–530. The trimethylamine solution was titrated with 0.10 M hydrochloric acid before use, and the concentration was typically in the range of 4–6 M.
14. X-ray data for **18** deposited with the Cambridge Crystallographic Data Centre, reference CCDC 665739.
15. Hubert, J. C.; Wijnberg, B. P.; Speckamp, W. N. *Tetrahedron* **1975**, *31*, 1437–1441.
16. Saito, S.; Nakajima, H.; Inaba, M.; Moriwake, T. *Tetrahedron Lett.* **1989**, *30*, 837–838.
17. Kawai, M.; Neogi, P.; Khattri, P. S.; Butsugan, Y. *Chem. Lett.* **1990**, 577–580.
18. Mori, K.; Ebata, T.; Sakakibara, M. *Tetrahedron* **1981**, *37*, 709–713.
19. Rosen, T.; Lico, I. M.; Chu, D. T. W. *J. Org. Chem.* **1988**, *53*, 1580–1582.
20. Verniest, G.; Colpaert, F.; Van Hende, E.; De Kimpe, N. *J. Org. Chem.* **2007**, *72*, 8569–8572.