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Synthesis of difluorinated β- and γ-amino acids: Investigation of a challenging deoxyfluorination reaction

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ABSTRACT

Backbone-homologated amino acids containing the vicinal difluoride motif have been synthesised in a highly stereoselective manner. The key synthetic transformation is the DeoxoFluor®-mediated fluorination of a vicinal fluorohydrin. The synthetic route is amenable to the production of all possible stereoisomers of α,β-difluoro-γ-aminobutyric acid. In addition, a novel difluoromethyl-substituted β-amino acid is accessed *via* an unexpected rearrangement process.

1. Introduction

Selective fluorination chemistry is an important strategy for modulating the properties of bioactive molecules [1]. It is widely recognised that judicious incorporation of fluorine atoms can lead to desirable effects on the pharmacokinetic properties of drug candidates, including higher stability to metabolism, greater hydrophobicity, and the possibility of increased receptor binding affinity through polar intermolecular interactions [2]. In addition however, there is another impact of fluorine substitution that has been less widely appreciated in the pharmaceuticals arena: *fluorine atoms affect molecular conformation* [3]. The highly polarised C–F bond can participate in a variety of stereoelectronic interactions with neighbouring functional groups, and these can favour certain molecular conformations over others [3]. Therefore, knowledge of such effects affords the possibility of rationally "programming" molecules to adopt desired conformations through selective fluorination chemistry.

Within this context, the vicinal difluoride motif has attracted considerable interest [4]. A variety of molecules containing this motif have been created, including surface-active fatty acid derivatives [5], organic liquid crystals [6], antiretroviral nucleotide analogues [7], difluorosuccinates amenable for incorporation into pseudopeptides [8], and difluoropyrrolidine-containing peptidase inhibitors [9]. In each case the vicinal difluoride motif exerts a degree of conformational control due to the fluorine *gauche* effect [10], with important knock-on effects upon the properties of the various functional molecules containing this motif.

Building upon these previous discoveries, we recently became interested in exploring the vicinal difluoride motif within the context of backbone-homologated amino acids. Specifically, we targeted the novel molecular framework of α,β-difluoro-γ-amino acids (*e.g.* **3** and **6**, Scheme 1) [11]. We envisaged that such molecules could be valuable as conformationally restricted building blocks for the creation of shape-controlled peptides [12]. The key steps in our planned syntheses of **3** and **6** were to be the deoxyfluorination reactions [13] of vicinal fluorohydrins **1** and **4** (Scheme 1). Herein we provide full details of the outcomes of these deoxyfluorination attempts, including some challenges and unexpected discoveries that arose during the course of our synthetic efforts [11].

2. Results and discussion

The *syn*-difluoro diastereoisomeric series was targeted initially. We first investigated a two-step approach involving activation of the fluorohydrin **1** as the triflate **7**, followed by attempted substitution with fluoride (Scheme 2) [14]. The triflate **7** was

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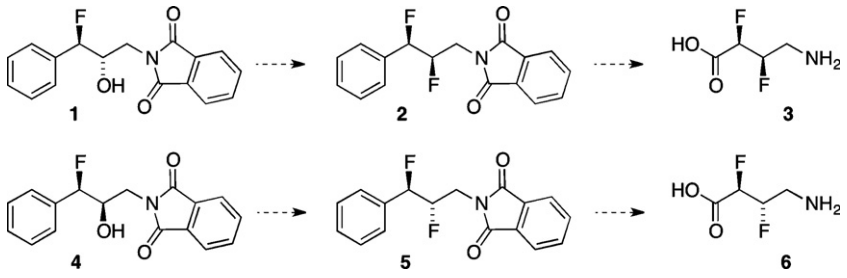
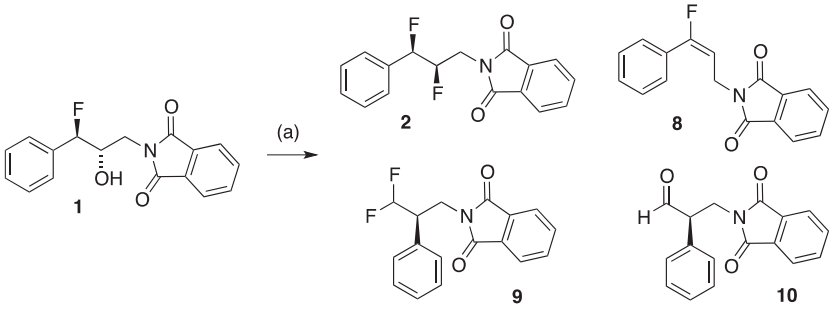


Scheme 1. Deoxyfluorination reactions (**1** → **2** and **4** → **5**) investigated in this study.

Table 1
Direct fluorination of **1** under a variety of conditions.

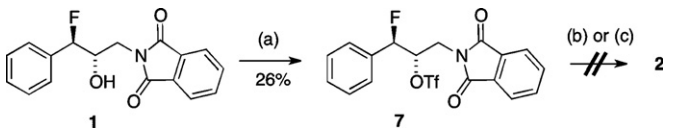


Entry	(a)	Ratio[a] **1**:**2**:**8**:**9**:**10**	Isolated yield of **2**
1	DeoxoFluor® (1.1 Equiv.), CH_2Cl_2, r.t.	1:0:0:0:0	0%
2	DeoxoFluor® (10 Equiv.), 70 °C	0:2:0:3:0	21% [11]
3	DeoxoFluor® (3 Equiv.), TMS-morpholine (3 Equiv.), CH_2Cl_2, reflux	3:1:3[b]:0:0	n/d[c]
4	PBSF (2 Equiv.), $Et_3N{\cdot}3HF$ (2 Equiv.), Et_3N (6 Equiv.), THF, r.t.	1:0:0:0:0	0%
5	PBSF (3 Equiv.), $Et_3N.3HF$ (3 Equiv.), Et_3N (9 Equiv.), CH_3CN, 95 °C	1:0:0:0:0	0%
6	XtalFluor-E® (2 Equiv.), $Et_3N{\cdot}3HF$ (2 Equiv.), Et_3N (1 Equiv.), CH_2Cl_2, reflux	3:0:0:2:3	0%
7	XtalFluor-E® (2 Equiv.), $Et_3N{\cdot}3HF$ (2 Equiv.), CH_2Cl_2, reflux	0:0:0:1:3	0%

[a] Determined by NMR analysis of the crude product mixture.
[b] Mixture of several elimination products including fluoroalkene **8**.
[c] Not determined.

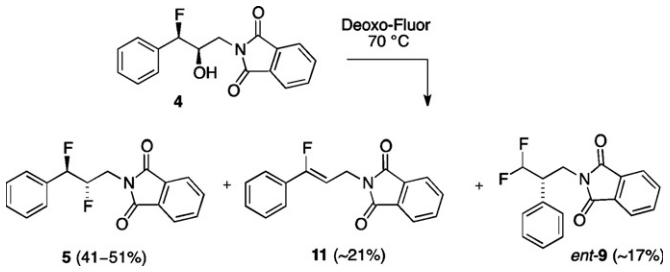
successfully prepared by treatment of **1** with triflic anhydride; the product was sufficiently stable to be purified by flash chromatography, and was characterised by IR and NMR spectrometry (notably, a long-range F–F coupling of 1.7 Hz was observed in the ^{19}F NMR spectrum of **7**). However, the apparent stability of triflate **7** proved to be a drawback in the subsequent fluorination attempts: triflate **7** was found to be surprisingly resistant to attempts at S_N2 fluorination, and was recovered intact from all reaction trials.

Having established that the stepwise approach (Scheme 2) was unsuitable for the synthesis of **2**, we next investigated the direct conversion of **1** into **2** (Table 1). Treatment of **1** with a slight excess of bis(2-methoxyethyl)aminosulfur trifluoride (DeoxoFluor®) [15] in CH_2Cl_2 led only to recovery of starting material (entry 1). More vigorous reaction conditions (entry 2) [16] led to successful formation of the desired difluoroalkane **2**, but also to a substantial quantity of the undesired difluoromethyl-containing compound **9** which presumably arose through neighbouring group participation and migration of the phenyl group (*vide infra*). Interestingly the desired difluoroalkane **2** was obtained as a single stereoisomer

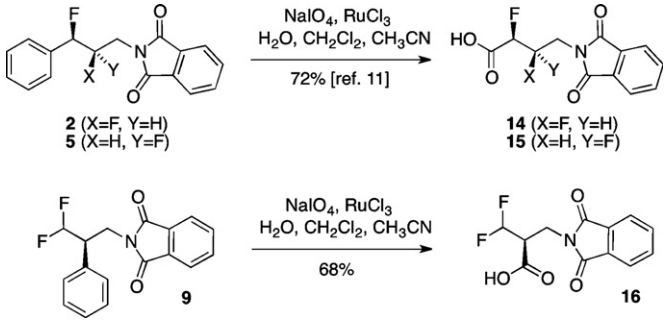


Scheme 2. First attempts to synthesise difluoroalkane **2**. Reagents and conditions: (a) Tf_2O, pyridine, CH_2Cl_2; (b) $Et_3N{\cdot}3HF$ (neat), 50 °C; (c) HF·pyridine, CH_2Cl_2, 0 °C.

(stereochemistry confirmed by X-ray crystallography, Fig. 1), indicating that the direct fluorination proceeded with pure S_N2 character and that the competing neighbouring group participation pathway resulted exclusively in rearrangement rather than epimerisation. In an attempt to suppress this rearrangement pathway, the reaction was repeated with the additive TMS-morpholine (Table 1, entry 3), which has been shown to suppress S_N1-type dissociation of the activated intermediate in DeoxoFluor®-mediated reactions [17]. In this case the presence of TMS-morpholine completely suppressed the rearrangement pathway (entry 3), but unfortunately did not lead to an increase in the yield of **2** due to the formation of several elimination products including **8** (alkene geometry confirmed by $^3J_{HF}$ = 19.6 Hz [18]). The alternative reagent perfluorobutanesulfonyl fluoride (PBSF) [19] was next investigated (entries 4 and 5). However no reaction was observed with this reagent even at elevated temperature, and the starting material **1** was recovered intact in each case. Finally, we investigated the new fluorinating reagent (diethylamino)difluorosulfonium tetrafluoroborate (XtalFluor-E®) (entries 6 and 7), which has been shown to effect direct fluorination with minimal elimination side-reactions in other systems [20]. However, when **1** was treated with XtalFluor-E® under a variety of conditions, rearrangement was once again the dominant pathway (entries 6 and 7): this time the aldehyde **10** was also formed in substantial quantities, presumably arising through neighbouring group participation of the phenyl group followed by quenching with adventitious water (*vide infra*) [21]. Such an interpretation is supported by our observation that the XtalFluor-E® reagent



Scheme 3. Synthesis of the diastereoisomeric difluoroalkane **5**. The yield of **5** refers to isolated material; the yields of **11** and *ent*-**9** are estimated from the crude NMR.



Scheme 4. Synthesis of γ-amino acid derivatives **14** and **15**, and the β-amino acid derivative **16**.

appeared to be rather hygroscopic despite our attempts to limit its exposure to air; the inclusion of molecular sieves also did not alleviate the formation of side-product **10**. Overall then, the optimal yield of difluoroalkane **2** was a modest 21%, obtained with neat DeoxoFluor® at 70 °C (entry 2).

Attention was next turned towards the alternative diastereoisomeric series (Scheme 3). For the fluorination of **4**, we employed the conditions that were previously optimised for the synthesis of **2** (*i.e.* neat DeoxoFluor®, 70 °C). When these conditions were applied to substrate **4** (Scheme 3) we were gratified to obtain a considerably higher yield of the desired difluoroalkane **5** (up to 51% yield of **5** compared to 21% yield of **2**). Rearrangement was a less prominent side-reaction in the fluorination of **4** (Scheme 3); instead the major by-product was the fluoroalkene **11** (alkene geometry confirmed by $^3J_{HF}$ = 35.3 Hz [18]).

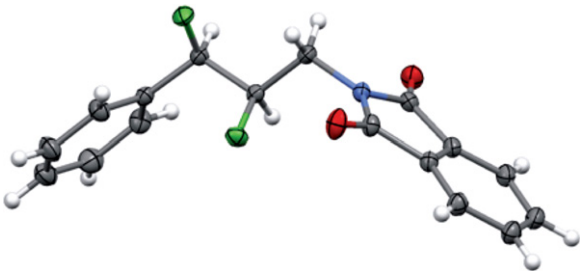


Fig. 1. X-ray crystal structure of **2** (thermal ellipsoids drawn at the 50% probability level) [11]. The observed geometry of **2** features *gauche* F–C–C–F and F–C–C–N dihedral angles (71.5° and 64.9° respectively).

The different propensities for rearrangement in the fluorination reactions of **1** (Table 1) and **4** (Scheme 3) may be rationalised by considering the likely conformations of the activated intermediates. In the fluorination of **1**, the rearrangement side-reaction is favoured because the activated intermediate **12** can readily adopt a conformation that is ideally set up for neighbouring group participation (Fig. 2). Such a conformation of **12** would be stabilised by a *gauche* F–C–C–O alignment [22]. In contrast, rearrangement is less favoured in the fluorination of **4** because the activated intermediate **13** may prefer a conformation that is not ideally set up for neighbouring group participation (Fig. 2). Such a conformation of **13** would however be susceptible to elimination, and this may explain the appearance of fluoroalkene **11** as a new side-product.

With difluoroalkanes **2** and **5** in hand, the final step to complete the syntheses of the amino acid targets was to convert the phenyl groups into the corresponding carboxylates (Scheme 4). This was achieved under standard conditions [23] to smoothly afford the difluoro γ-amino acids **14** and **15** in protected form [11], which are now ready for further development as shape-controlled GABA receptor ligands [24] or for incorporation into bioactive γ-amino acid-containing peptides [25]. The rearrangement product **9** was also converted in a similar manner to the difluoromethyl-containing β-amino acid derivative **16** (Scheme 4). This novel molecule is a potentially valuable building block for the creation of medicinally relevant entities, since the difluoromethyl group is recognised as a useful isostere of carbonyl and hydroxyl groups from a drug development perspective [26].

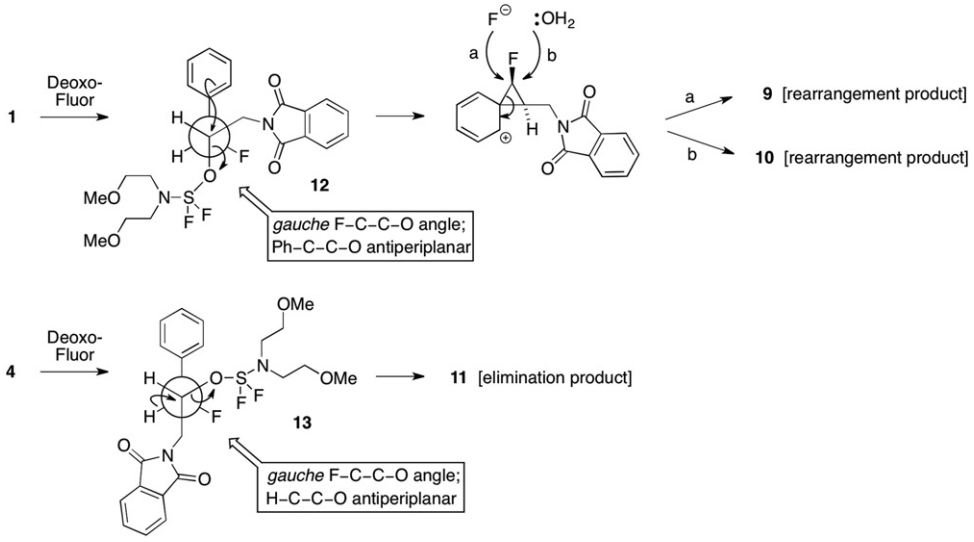


Fig. 2. In the fluorination reactions of **1** and **4** different side-products (**9–11**) are formed: rearrangement is favoured for **1** whereas elimination is favoured for **4**. This difference is explained by considering the conformations of the activated intermediates **12** and **13**.

3. Conclusions

The investigation of a challenging deoxyfluorination reaction has been described. DeoxoFluor® was found to be the reagent of choice for stereoselectively incorporating vicinal difluoride motifs within the densely-functionalised molecular systems **2** and **5**. This work has enabled the synthesis of novel difluorinated β- and γ-amino acids (**14**–**16**) that have a variety of potential applications in biotechnology and medicine.

4. Experimental

4.1. General methods

Tetrahydrofuran, acetonitrile, dichloromethane and *N*,*N*-dimethylformamide were purified by passage through activated alumina. Triethylamine was stored over potassium hydroxide pellets. Purified water was obtained from a Millipore Milli-Q plus system. All other reagents and solvents were purchased in the highest available quality and used as supplied. Reactions were conducted in oven-dried glassware, with magnetic stirring, under a positive pressure of nitrogen. Analytical thin layer chromatography was performed with Merck aluminium-backed TLC plates precoated with silica gel 60 F254 (0.2 mm), and visualisation was achieved by inspection under short-wave UV light followed by staining with phosphomolybdic acid or potassium permanganate dip. Flash chromatography was performed using Davisil 40–63 mesh silica gel; eluting solvents are quoted as volume/volume mixtures. Nuclear magnetic resonance spectra were recorded at 300 K using a Bruker Avance DPX400, DPX300 or DPX200 instrument; where necessary, resonances were assigned using COSY or HSQC experiments. Infrared spectra were recorded as neat thin films using a Bruker Alpha-E instrument. Mass spectra were recorded on a Finnigan MAT 900XL instrument using electrospray ionisation operating in either the positive or negative ion mode; signal intensities are quoted as a percentage of the base peak. Optical rotations were measured with a Perkin Elmer model 341 polarimeter at 589 nm with a path length of 1 dm; solution concentrations are reported as grams per 100 mL. Melting points were determined using a Stanford Research Systems Optimelt instrument.

4.2. Procedure for fluorination using neat DeoxoFluor®: synthesis of 2-((2R,3R)-2,3-difluoro-3-phenylpropyl)isoindoline-1,3-dione (**2**) and (R)-2-(3,3-difluoro-2-phenylpropyl)isoindoline-1,3-dione (**9**)

A mixture of fluorohydrin **1** (1.03 g, 3.44 mmol) and neat DeoxoFluor® (6.35 mL, 34.4 mmol) was stirred at 70 °C in a plastic reaction vessel overnight. The mixture was cooled to 0 °C, diluted with dichloromethane, and concentrated onto silica. The crude product was subjected to flash chromatography eluting with 9:1 → 1:1 hexane/ethyl acetate to give the two isolated products **2** and **9** (2:3 ratio, combined yield 54%). Characterisation data for **2** and **9** are reported elsewhere [11].

4.3. (1R,2S)-3-(1,3-dioxoisoindolin-2-yl)-1-fluoro-1-phenylpropan-2-yl trifluoromethanesulfonate (**7**)

Trifluoromethanesulfonic anhydride (114 μL, 0.685 mmol) was added to a solution of fluorohydrin **1** (41.0 mg, 0.137 mmol) in dry CH_2Cl_2 (0.5 mL) at 0 °C, and the resulting mixture was stirred at 0 °C for 3 h. The mixture was diluted with 9:1 hexane/EtOAc (~2 mL), then directly subjected to flash chromatography eluting with 9:1 → 3:2 hexane/EtOAc to afford the triflate **7** as a clear oil (15.5 mg, 26%); $[\alpha]_D$–13 (*c* 0.41, $CHCl_3$); IR (neat) ν_{max} (cm^{-1}) 1744, 1720, 1420, 1396, 1242, 1211, 1142; ^1H NMR (300 MHz, $CDCl_3$) δ 7.89–7.83 (m, 2H), 7.78–7.71 (m, 2H), 7.49–7.38 (m, 5H), 5.87 (dd, *J* = 46.1, 2.9 Hz, 1H), 5.55 (dddd, *J* = 18.6, 9.2, 2.9, 2.9 Hz, 1H), 4.25 (dd, *J* = 14.9, 9.2 Hz, 1H), 3.87 (dd, *J* = 14.9, 2.9 Hz, 1H); ^{13}C {^1H} NMR (50 MHz, $CDCl_3$) δ 167.8 (C), 134.7 (CH), 133.3 (d, *J* = 20.4 Hz, C), 131.9 (CH), 130.0 (C), 129.3 (CH), 125.9 (d, *J* = 7.9 Hz, CH), 123.9 (CH), 92.2 (d, *J* = 183.7 Hz, CH), 85.9 (d, *J* = 24.2 Hz, CH), 36.7 (d, *J* = 7.4 Hz, CH_2); ^{19}F NMR (282 MHz, $CDCl_3$) δ −75.3 (d, *J* = 1.7 Hz, 3F), −195.3 (ddq, *J* = 46.1, 18.6, 1.7 Hz, 1F); ^{19}F {^1H} NMR (282 MHz, $CDCl_3$) δ −75.3 (d, *J* = 1.7 Hz, 3F), −195.3 (q, *J* = 1.7 Hz, 1F); MS data for **7** could not be obtained due to product decomposition.

4.4. Procedure for fluorination using DeoxoFluor® + TMS-morpholine: synthesis of (E)-2-(3-fluoro-3-phenylallyl)isoindoline-1,3-dione (**8**)

TMS-morpholine (61 μL, 0.35 mmol) was added dropwise to a solution of DeoxoFluor® (64 μL, 0.35 mmol) in CH_2Cl_2 (1 mL) at 0 °C. The mixture was stirred at room temperature for 10 min then transferred *via* cannula to a flask containing fluorohydrin **1** (34 mg, 0.12 mmol). The resulting mixture was heated at reflux for 16 h, then cooled, diluted with $CDCl_3$, and directly analysed by NMR. Data for the crude fluoroalkene **8**: ^1H NMR (300 MHz, $CDCl_3$) δ 7.89–7.44 (m, 9H), 5.53 (dt, *J* = 19.6, 7.5 Hz, 1H), 4.47 (dd, *J* = 7.5, 1.5 Hz, 2H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −94.9 (d, *J* = 19.6 Hz, 1F); ^{19}F {^1H} NMR (282 MHz, $CDCl_3$) δ −94.9 (s, 1F).

4.5. Procedure for fluorination using XtalFluor-E®: synthesis of (R)-3-(1,3-dioxoisoindolin-2-yl)-2-phenylpropanal (**10**)

Triethylamine trihydrofluoride (52 mg, 0.43 mmol) was added to a solution of Xtalfluor-E® (262 mg, 1.14 mmol) in CH_2Cl_2 (0.5 mL). A solution of fluorohydrin **1** (35 mg, 0.12 mmol) in CH_2Cl_2 (0.5 mL) was added *via* cannula, and the mixture was heated to reflux overnight. The mixture was cooled and quenched by addition of 5% aqueous sodium bicarbonate solution (5 mL). The mixture was extracted with CH_2Cl_2 (2 × 5 mL) and the organic layers were dried ($MgSO_4$) and concentrated onto silica. The crude product was subjected to flash chromatography eluting with 9:1 hexane/ethyl acetate.

Data for aldehyde **10**: $[\alpha]_D$–2 (*c* 0.100, EtOH); IR (neat) ν_{max} (cm^{-1}) 1773, 1713, 1397 1359; ^1H NMR (300 MHz, $CDCl_3$) δ 9.75 (d, *J* = 0.7 Hz, 1H), 7.78 (m, 2H), 7.68 (m, 2H), 7.38–7.22 (m, 5H), 4.33–4.12 (m, 3H); ^{13}C {^1H} NMR (75 MHz, $CDCl_3$) δ 198.6 (C), 168.1 (C), 134.1 (CH), 132.9 (C), 131.9 (C), 129.4 (CH), 129.2 (CH), 128.5 (CH), 123.4 (CH), 56.9 (CH), 38.1 (CH_2); HRMS (ESI, +ve) $C_{17}H_{14}NO_3^+$ [MH^+] requires *m*/*z* 280.0968, found 280.0964; $C_{17}H_{13}NO_3Na^+$ [MNa^+] requires *m*/*z* 302.0788, found 302.0783.

4.6. Procedure for fluorination using neat DeoxoFluor®: synthesis of 2-((2S,3R)-2,3-difluoro-3-phenylpropyl)isoindoline-1,3-dione (**5**), (S)-2-(3,3-difluoro-2-phenylpropyl)isoindoline-1,3-dione (*ent*-**9**) and (Z)-2-(3-fluoro-3-phenylallyl)isoindoline-1,3-dione (**11**)

A mixture of fluorohydrin **2** (97 mg, 0.32 mmol) and neat DeoxoFluor® (0.71 g, 3.2 mmol) was stirred at 70 °C in a plastic reaction vessel overnight. The mixture was cooled to 0 °C, diluted with dichloromethane, and concentrated onto silica. The crude product was subjected to flash chromatography eluting with 9:1 → 1:1 hexane/ethyl acetate to give the isolated product **5** (40 mg, 41%) along with an inseparable mixture of the side-products *ent*-**9** (18 mg, 17%) and **11** (20 mg, 21%). Characterisation data for **5** are reported elsewhere [11]. Data for *ent*-**9**: $[\alpha]_D$–60 (*c* 0.45, $CHCl_3$) [value calculated from a mixture of **5**, *ent*-**9** and **11** of known composition]; NMR data of *ent*-**9** identical to that of **9** [11]. Data for **11**: ^1H NMR (300 MHz, $CDCl_3$) δ 7.91–7.87 (m, 2H),

7.77–7.73 (m, 2H), 5.62 (dt, J = 35.3, 7.1 Hz, 1H), 4.62 (dd, J = 7.1, 1.7 Hz, 2H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −116.4 (d, J = 35.3 Hz, 1F); HRMS (ESI, +ve) $C_{17}H_{13}FNO_2Na^+$ [MNa^+] requires m/z 282.0925, found 282.0920.

4.7. Procedure for phenyl oxidation: synthesis of (S)-2-((1,3-dioxoisoindolin-2-yl)methyl)-3,3-difluoropropanoic acid (**16**)

Ruthenium chloride hydrate (~1 mg) was added to a mixture of difluoroalkane **9** (30.1 mg, 0.100 mmol), $NaIO_4$ (0.348 g, 1.80 mmol), CH_2Cl_2 (0.75 mL), CH_3CN (0.75 mL) and H_2O (0.94 mL), and the mixture was stirred at room temperature for 3 days. The mixture was filtered through celite (EtOAc wash) and the filtrate was concentrated *in vacuo*. The crude product was subjected to flash chromatography eluting with 49:49:2 hexane/EtOAc/AcOH → 98:2 EtOAc/AcOH to afford the β-amino acid **16** as a clear oil (18.3 mg, 68%); $[\alpha]_D$ +6 (*c* 0.100, $CHCl_3$:MeOH:AcOH = 80:18:2); IR (neat) ν_{max} (cm^{-1}) 1775, 1713, 1469, 1440, 1396, 1369; ^{1}H NMR (300 MHz, CD_3CN) δ 7.91–7.80 (m, 4H), 6.20 (td, J = 54.9, 4.7 Hz, 1H), 6.03 (br s, 1H), 4.08 (dd, J = 14.4, 7.2 Hz, 1H), 4.00 (dd, J = 14.4, 6.6 Hz, 1H), 3.43 (m, 1H); ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$) δ 168.1 (t, J = 5.7 Hz, C), 167.5 (C), 134.2 (CH), 131.6 (C), 122.8 (CH), 115.1 (t, J = 240.4 Hz, CH), 47.3 (t, J = 21.7 Hz, CH), 33.5 (t, J = 5.8 Hz, CH_2); ^{19}F NMR (282 MHz, $CDCl_3$) δ−122.1 (ddd, J = 287.2, 54.9, 11.8 Hz, 1F), −125.8 (ddd, J = 287.2, 55.0, 15.4 Hz, 1F); ^{19}F {^{1}H} NMR (282 MHz, $CDCl_3$) δ −122.1 (d, J = 287.2 Hz, 1F), −125.8 (d, J = 287.2 Hz, 1F); MS (ESI, +ve) m/z 292 (MNa^+, 55%); HRMS (ESI, +ve) $C_{12}H_9F_2NO_4Na^+$ requires m/z 292.0392, found 292.0394.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.jfluchem.2012.06.016.

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