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Scalable, stereoselective syntheses of α,β-difluoro-γ-amino acids

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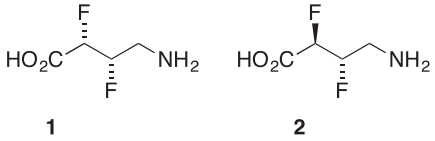
ABSTRACT

Backbone-fluorinated gamma-amino acids are novel shape-controlled building blocks that have potential utility in a variety of biological contexts. However, their synthesis poses challenges in terms of chemo-, regio- and stereoselectivity, and this has proven to be the major bottleneck in the ongoing development of their various biological applications. To address this problem, several new synthetic strategies were investigated in this work. This has led to the identification of new methods that are superior in terms of yield and stereocontrol.

1. Introduction

Selective fluorination is a well recognised tool for modulating the chemical, physical and biological properties of organic molecules.[1–10] One of the impacts of incorporating fluorine is that the molecular conformation can be affected in predictable ways, for example, due to the fluorine *gauche* effect.[10] Thus, it is possible to rationally 'program' molecules to adopt desired shapes through selective fluorination chemistry, allowing the function of the molecule (e.g., binding to a biological target) to be optimised.[11–26]

For several years we have been exploring this idea in the context of amino acids (e.g., **1** and **2**, Fig. 1).[11,13,27,28] We have examined the preferred conformations of **1** and **2**, revealing that the *syn*-isomer (**1**) adopts an extended zigzag shape, while the *anti*-isomer (**2**) adopts a bent backbone shape.[28] In both cases this can be rationalised in terms of the *gauche* effect mentioned above. We have shown that the conformational differences between **1** and **2** can be exploited in a variety of applications. For example, **1** and **2** were shown to have different selectivity patterns in GABA receptor binding assays.[11] Alternatively, **1** and **2** can be incorporated within larger molecular architectures via peptide coupling reactions, where they can dramatically affect the overall conformations of linear and even cyclic peptides.[13]



1 2

Fig. 1. α,β-Difluoro-γ-amino acids.

The ongoing development of such applications relies on an efficient and scalable method for the synthesis of **1** and **2**. Unfortunately however, the current synthetic method (Scheme 1)[28] suffers from several limitations. First, the dihydroxylation of alkene **3** proceeds in variable yield, possibly due to the instability of this (expensive) starting material. Second, in the synthesis of the *syn*-difluoro target (**1**), the fluorination of **5** is low yielding (10–21%) because the phenyl ring undergoes competing neighbouring group participation and migration to give an undesired geminal difluoro side product (**7**), rendering the purification of **6** cumbersome. Third, in the case of the *anti*-difluoro target (**2**), the fluorohydrin **8** is obtained with modest diastereoselectivity which again necessitates a laborious purification process. Overall then, there is a clear need to develop a more reliable and scalable synthesis of **1** and **2**. Our efforts to do so are detailed herein.

2. Results and discussion

2.1. Alternative starting material

To avoid the instability (and expense) of the starting material cinnamyl bromide (**3**), the cheap and readily available cinnamyl

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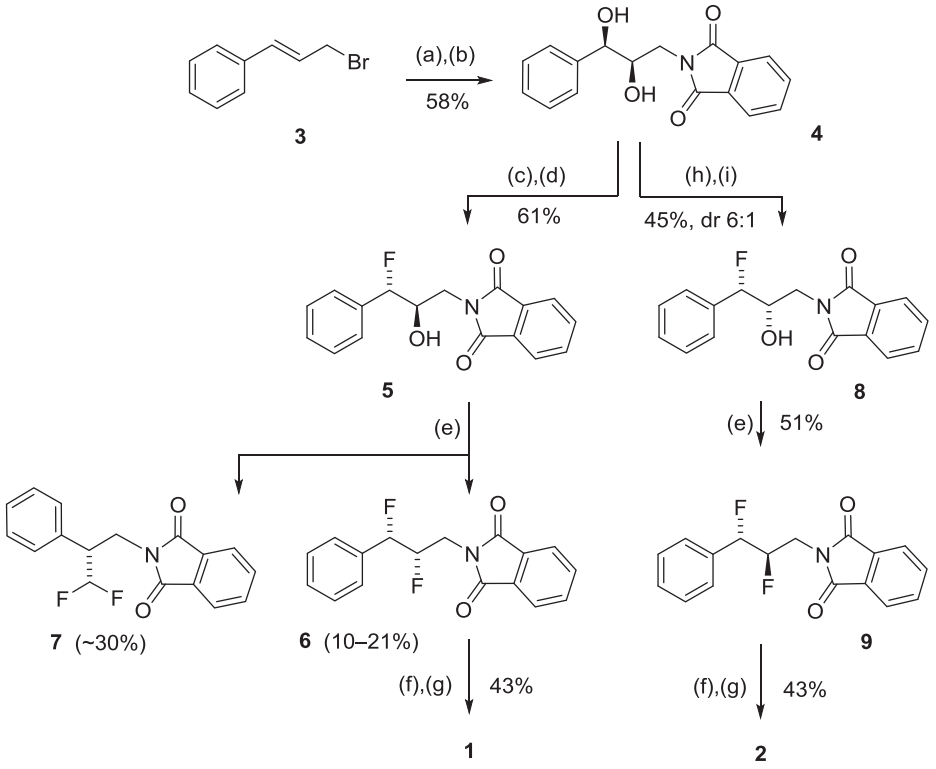
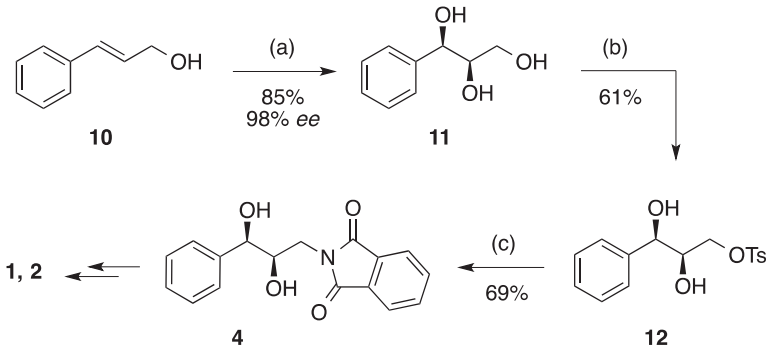


Scheme 1. [28] Previous route to α,β-difluoro-γ-amino acids. (a) AD-mix-β, $CH_3SO_2NH_2$, *t*-BuOH, H_2O, 0 °C; (b) potassium phthalimide, phthalimide, DMF, 80 °C; (c) $SOCl_2$, pyridine, CH_2Cl_2, 0 °C then $NaIO_4$, $RuCl_3$, H_2O, CH_2Cl_2, CH_3CN, 0 °C; (d) TBAF, THF, CH_3CN, 0 °C then H_2SO_4, H_2O, THF, rt; (e) DeoxoFluor® (neat), 70 °C; (f) $NaIO_4$, $RuCl_3$, H_2O, CH_2Cl_2, CH_3CN, rt; (g) $H_2NNH_2 \cdot H_2O$, EtOH, reflux; (h) $(CF_3SO_2)_2O$, 1,4-diazabicyclo[2.2.2]octane (DABCO), CH_2Cl_2, −78 °C to rt; (i) $Et_3N \cdot 3HF$, 120 °C.

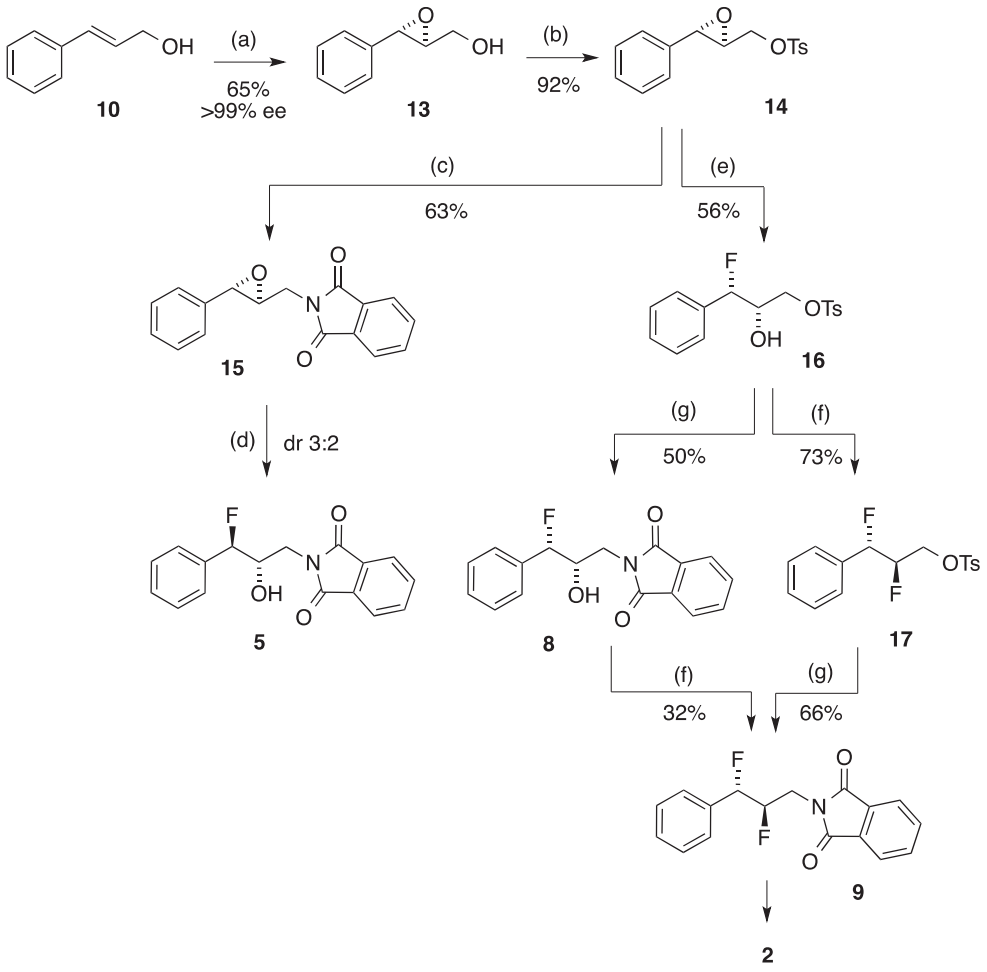
alcohol (**10**) was utilized instead (Scheme 2). Asymmetric dihydroxylation of **10** was straightforward and delivered the triol **11** in high yield.[29] Selective tosylation of the primary alcohol of triol **11** was achieved using 1.3 equiv of *p*-toluenesulfonyl chloride, furnishing the tosylate **12** in good yield.[29] Finally, the Gabriel reaction of **12** successfully provided the desired phthalimide derivative **4** (Scheme 2), which can be utilized for the synthesis of **1** and **2** according to the methods described above (Scheme 1). Although the route to **4** from cinnamyl alcohol (**10**) involved an extra step, the reproducible yields and the much lower cost of the starting material constituted a genuine improvement over the previous route from cinnamyl bromide (**3**, Scheme 1).

2.2. Sharpless epoxidation approach

Another route commencing from cinnamyl alcohol (**10**) was also investigated (Scheme 3). Asymmetric epoxidation of **10** was carried out to obtain epoxy alcohol **13** in good yield and with excellent enantioselectivity.[30] The epoxy alcohol **13** was then subjected to tosylation and a Gabriel reaction to deliver the epoxide **15**. Ring-opening of the epoxide **15** was then attempted using $Et_3N \cdot 3HF$, but unfortunately this gave the fluorohydrin **5** in only 3:2 diastereoisomeric ratio as measured by ^{19}F NMR analysis of the crude reaction mixture. The purification of **5** was laborious and hence this approach was abandoned. Alternatively, it was previously established[31] that the precursor epoxide **14** could be ring-opened with $BF_3 \cdot OEt_2$ in a highly diastereoselective manner, furnishing the pure fluorohydrin **16** in reasonable yield. In the current work, fluorohydrin **16** then underwent a Gabriel reaction to deliver compound **8** in 50% yield, thereby intercepting the previous synthesis of **2** via **9** (Scheme 1). Interestingly, it was subsequently discovered that the yield of **9** could be further increased if the order of the fluorination and Gabriel reactions was reversed. Fluorination of **16** gave the vicinal difluoride **17** in very good yield (Scheme 3), alongside a small quantity of a geminal difluoro side product (**18**; see ESI). The tosylate **17** was then subjected to a Gabriel reaction to



Scheme 2. Alternative synthesis of diol **4**. (a) $(DHQD)_2PHAL$, OsO_4, $CH_3SO_2NH_2$, $K_3Fe(CN)_6$, $NaHCO_3$, *t*-BuOH, H_2O, 0 °C; (b) Bu_2SnO, TsCl, Et_3N, CH_2Cl_2; (c) potassium phthalimide, phthalimide, DMF, 80 °C.



Scheme 3. Sharpless epoxidation route. (a) D-(−)-DET, *t*-BuOOH, Ti(O*i*-Pr)$_4$, CH_2Cl_2, −20 °C; (b) Et_3N, DMAP, TsCl, 0 °C; (c) phthalimide, potassium phtalimide, DMF, 50 °C; (d) $Et_3N{\cdot}3HF$, 120 °C; (e) $BF_3{\cdot}OEt_2$, CH_2Cl_2, −20 °C; (f) DeoxoFluor® (neat), 70 °C; (g) phthalimide, potassium phtalimide, DMF, 90 °C.

efficiently afford compound **9**. Overall, this route (Scheme 3) offers substantial improvements over the literature synthesis of target **2** in terms of yield, diastereoselectivity and ease of purifications.

2.3. Chiral pool approach[32]

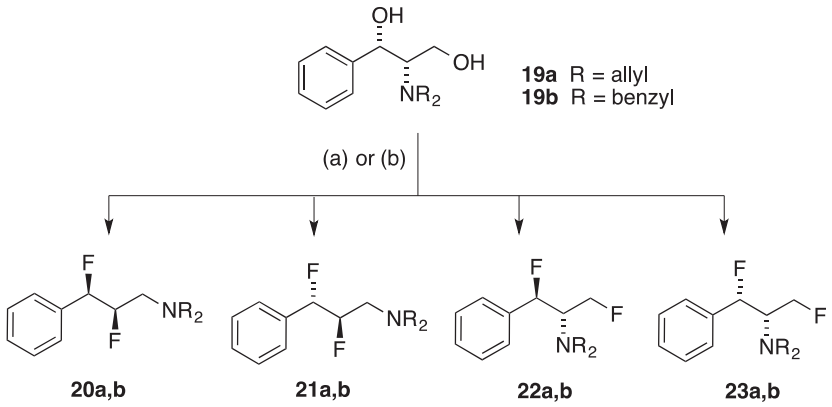
The next strategy to be investigated for the synthesis of target **1** was a chiral pool approach (Scheme 4). The commercially available compound (1*S*,2*S*)-2-amino-1-phenylpropane-1,3-diol was identified as a potential starting point for the synthesis of vicinal difluoride **20** (Scheme 4) en route to the enantiomer of target **1**. The formation of **20** would require the intermediacy of an aziridinium species arising through neighbouring group participation of the appropriately protected amino group. However, this outcome was not guaranteed because a competing direct substitution of the primary alcohol could occur to give primary alkyl fluoride products, and also substitution of the benzylic alcohol could conceivably proceed via an S_N1 mechanism to give a mixture of stereoisomers at the benzylic position.

Initially the fluorination reaction was attempted with the diallyl protected substrate **19a** (Scheme 4), using DeoxoFluor® (1–3 equiv.) at various temperatures ranging from −78 °C to 25 °C. In every case, the crude product mixture contained recovered starting material along with monofluorinated and difluorinated products (**22**, **23**); however no vicinal difluorinated products (**20**, **21**) were observed. Next, the benzyl protected substrate **19b** was investigated (Scheme 4). Fluorination with DeoxoFluor® delivered a mixture of all four products (**20**–**23**) in a ratio of 0.24: 0.23: 0.67: 1.00. In an attempt to reduce the amount of product **21** arising through substitution with retention, the fluorination reaction was re-attempted using the morpholine-DeoxoFluor® adduct (Scheme 4), since this reagent is known to disfavour unimolecular ionisation processes.[33] As expected, the diastereomeric ratio of **20**:**21** improved from ~1:1 to ~5:1. Unfortunately however, it proved extremely difficult to isolate these fluorinated compounds from the reaction mixture. Hence, this chiral pool approach was abandoned.

2.4. *N*-Halosuccinimide approach[22]

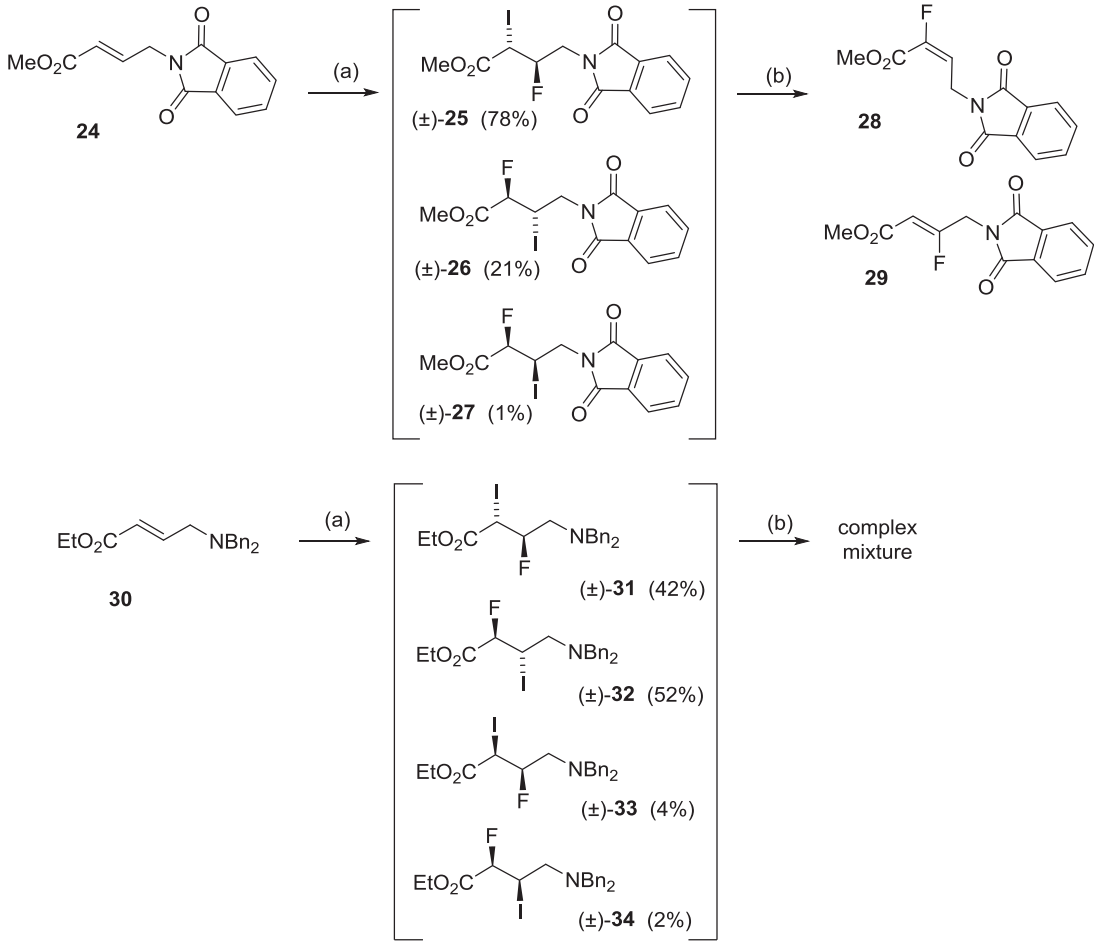
The next approach to be investigated was a racemic synthesis (Scheme 5). It was recognised that the targets **1** and **2** could still be valuable for some applications in racemic form: for example, they could conceivably be incorporated into (diastereoisomeric) peptides and separated thereafter. Several methods are known for the synthesis of racemic vicinal difluoro motifs.[34] For example, olefins can be converted via halonium intermediates into bromofluoro or iodofluoro compounds, which can subsequently be converted into difluoro compounds through nucleophilic substitution.[22,35] This was anticipated to allow a rapid and diastereoselective route to the targets **1** and **2**.

The initial substrates were olefins **24** and **30** (Scheme 5). Reaction of **24** with *N*-iodosuccinimide and Olah's reagent gave three fluoroiodo products (**25**–**27**), which were difficult to separate by



Scheme 4. Chiral pool approach. (a) DeoxoFluor®, CH_2Cl_2, rt; (b) DeoxoFluor®, TMS-morpholine, CH_2Cl_2, rt.

column chromatography. Various reaction solvents were screened (see Supplementary data), and it was discovered that acetonitrile gave the best diastereoselectivity with the β-fluoro compound **25** obtained as the major product. The stereochemistry of **25** was confirmed by X-ray crystallographic analysis (Fig. 2). Subsequently, various nucleophilic fluorination conditions were screened (including AgF, Scheme 5) in an attempt to convert the mixture of **25**–**27** into vicinal difluoro products. However, only elimination products (**28** and **29**) were observed. A similar reaction sequence was attempted using substrate **30** (Scheme 5). Iodofluorination of **30** delivered all four possible isomers of the product (**31**–**34**) as an inseparable mixture, but once again with quite good selectivity for the desired *anti*-isomers (**31**, **32**). However, addition of AgF to the reaction mixture unfortunately gave a complex mixture of products (Scheme 5), with ^{19}F NMR analysis of the crude reaction mixture suggesting that rearrangement products were present (characterised by distinctive triplet signals around −230 ppm, corresponding to primary alkyl fluorides). The reaction sequences



Scheme 5. Attempted racemic synthesis commencing with substrates **24** or **30**. (a) *N*-Iodosuccinimide, HF·pyridine, MeCN, rt; (b) AgF, MeCN, 80 °C.

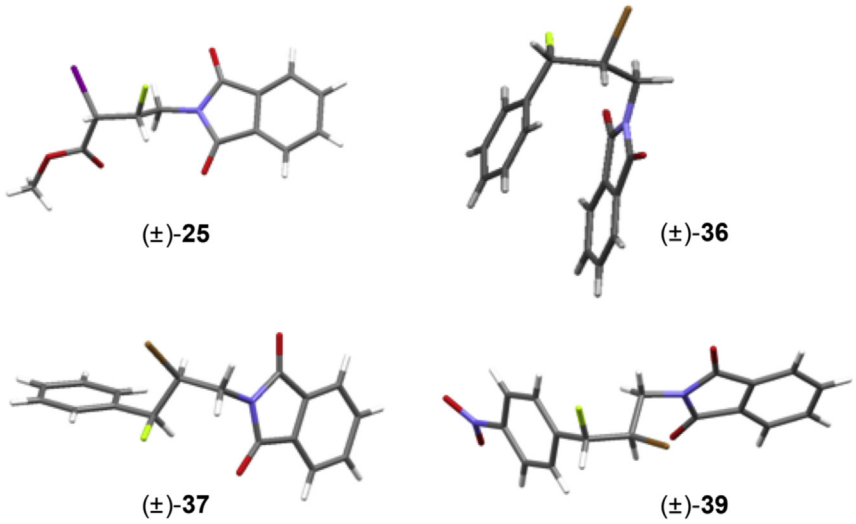


Fig. 2. X-ray crystal structures of compounds **25**, **36**, **37** and **39** (CCDC numbers: 1418490, 1418489, 1418488 and 1418491).

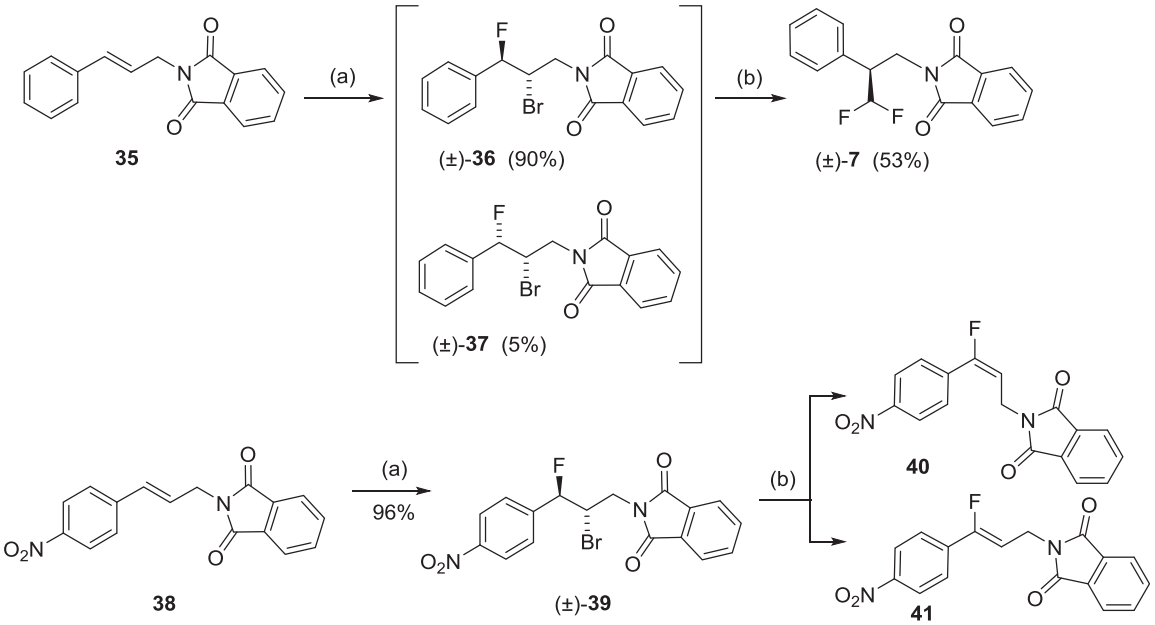
commencing from both **24** and **30** were reattempted using *N*-bromosuccinimide instead of *N*-iodosuccinimide; however, only the starting materials were recovered in both cases.

In order to improve the regioselectivity of the halofluorination reactions (Scheme 5), a phenyl group was incorporated into a new substrate (**35**, Scheme 6). When olefin **35** was treated with *N*-bromosuccinimide and Olah's reagent, the expected α-fluorinated compound **36** was formed as the major product, along with a small quantity of the diastereomer **37**. The bromofluoro intermediates **36** and **37** were separable by column chromatography. However, when the bromofluorination reaction mixture was treated with AgF (Scheme 6), the undesired rearrangement product **7** was obtained in 53% yield. This result was analogous to the rearrangement problem encountered in the first-generation synthesis of **1** (Scheme 1).[36] In order to prevent this rearrangement process, a *p*-nitro substituent was included in the modified substrate **38** (Scheme 6). The bromofluorination reaction of substrate **38** proceeded with excellent diastereoselectivity, delivering the desired bromofluoro compound **39** in high yield. However, subsequent attempts to convert **39** into a vicinal difluoro product resulted in an undesired elimination reaction, giving fluoroalkenes **40** and **41** (Scheme 6). Overall, because of the difficulties in converting the fluorohalo intermediates into difluoro species (Schemes 5 and 6) it was concluded that the racemic approach to vicinal difluorinated amino acids was not viable.

The stereochemical assignments of the fluorohalo intermediates **25**, **36**, **37** and **39** were secured using X-ray crystallographic analysis (Fig. 2).

2.5. Exploiting the p-nitro group as a tool for selectivity

Although the racemic approach (Scheme 6) was ultimately unsuccessful, the high stereoselectivity observed with substrate **38** prompted us to investigate the *p*-nitro substituent in a new context.



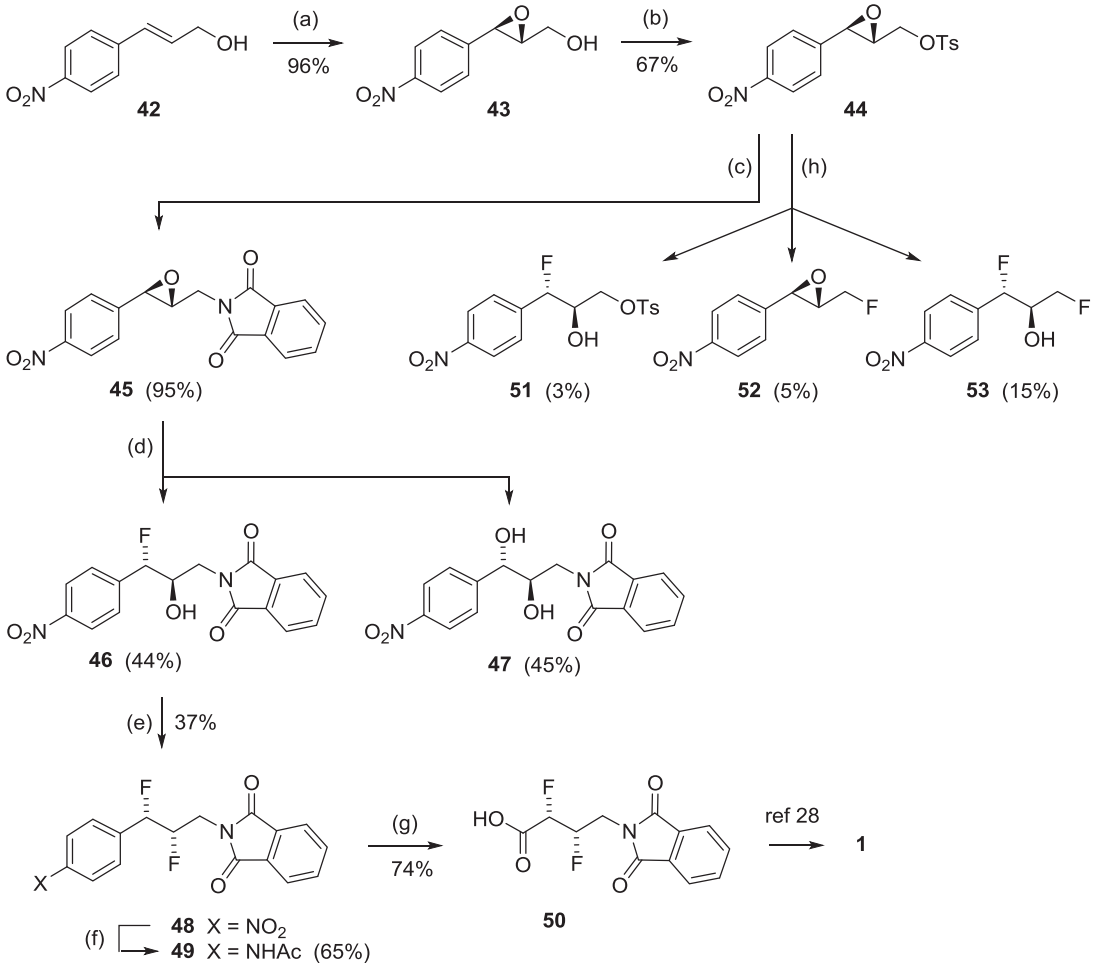
Scheme 6. Attempted racemic synthesis commencing with substrates **35** or **38**. (a) *N*-Bromosuccinimide, HF·pyridine, DCM, rt; (b) AgF.

The design of the new strategy (Scheme 7) was also informed by our recent work towards α,β,γ-trifluoro-δ-amino acids,[37] in which the *p*-nitro substituent was again shown to improve the regio- and stereoselectivity in fluorination reactions. Accordingly, the new starting material **42** (itself available in two steps from commercial materials) underwent asymmetric epoxidation followed by tosylation to give compound **44** in good yield (Scheme 7). Compound **44** then underwent a Gabriel reaction to give **45**, and subsequent epoxide ring-opening using $Et_3N{\cdot}3HF$ gave a mixture of fluorohydrin **46** and the corresponding diol **47** in 1:1 ratio with **46** in 44% yield. The enantiopurity of fluorohydrin **46** was confirmed by its derivatisation into a Mosher ester (see Supplementary data). In an attempt to improve the moderate yield of **46**, the order of the fluorination and Gabriel reactions was reversed (Scheme 7). However, this resulted mainly in formation of the undesired primary alkyl fluorides **52** and **53** rather than the desired tosylate **51**, despite the screening of several fluorinating reagents and mild reaction conditions (see Supplementary data). Nevertheless, the modest-yielding synthesis of **46** via **45** was still considered to be practical and scalable, since the diastereoselectivity was excellent. The fluorohydrin **46** was then subjected to deoxyfluorination (Scheme 7). Gratifyingly, this reaction furnished the desired difluoro compound **48** with excellent diastereoselectivity and with no evidence of rearrangement. The *p*-nitrophenyl group was then converted to the corresponding acetanilide (**49**), which was obtained in good yield alongside a small quantity of an unexpected imide product (see Supplementary data). Finally, oxidation of the aryl moiety of **49** delivered the known carboxylic acid **50**. Overall, the inclusion of the *p*-nitro group (Scheme 7) delivered significant benefits in the synthesis of target **1**, by greatly improving the chemo- and diastereoselectivity.

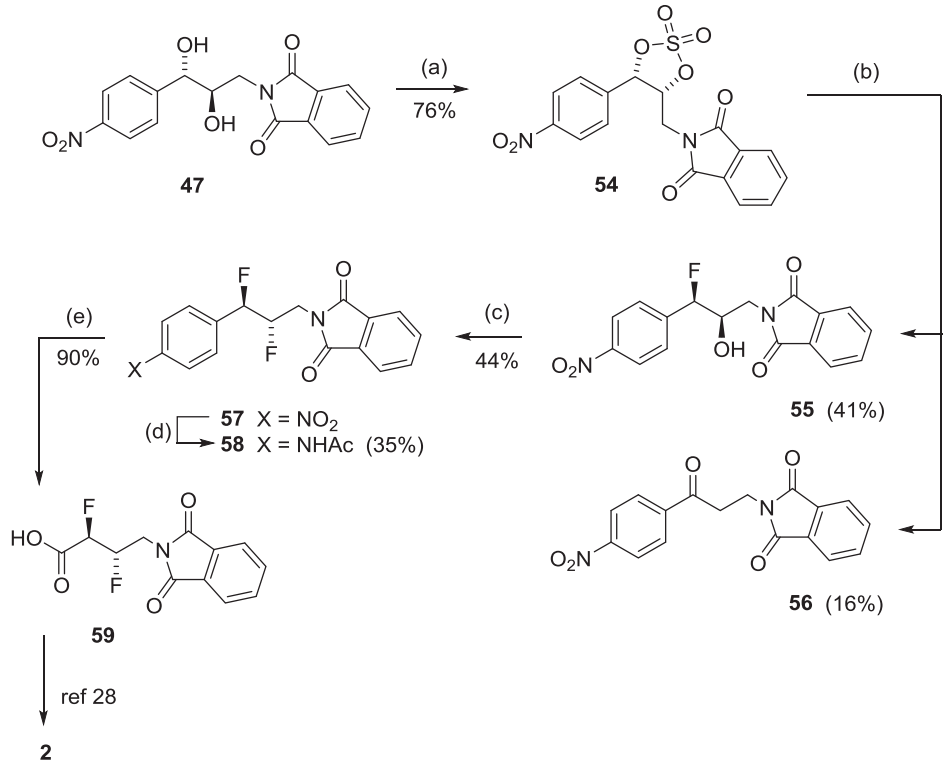
The diol **47**, which was produced as a side product in the ring-opening reaction of epoxide **45** (Scheme 7), was exploited in an alternative synthesis of the *anti*-difluoro target **2** (Scheme 8). Diol **47** was converted into the corresponding cyclic sulfate **54**,[38] then reacted with TBAF to deliver the fluorohydrin **55** along with a minor quantity of the ketone **56** which presumably arose through a competing elimination process. Next, deoxyfluorination of **55** proceeded in moderate yield, and the *anti*-difluoro compound **57** was subsequently carried through a standard sequence of transformations to deliver the target **2** (Scheme 8). The absolute stereochemistry of diol **47** was validated by an X-ray crystal structure of a chlorohydrin side product (**60**), which arose during the cyclic sulfate formation/ring-opening sequence (see Supplementary data). Overall, this route (Scheme 8) constitutes another viable synthesis of the target **2**, while also preventing wastage of the diol **47**.

3. Conclusion

Several new synthetic approaches to the backbone-fluorinated amino acids **1** and **2** were investigated, in order to address the limitations of the previous syntheses. Target **2** is now available through a robust, scalable, seven-step sequence (Scheme 3), which offers dramatic improvements in terms of diastereoselectivity and consequent ease of purifications. Target **1** remains the greater synthetic challenge; a new 10-step sequence was developed in this



Scheme 7. Exploiting the *p*-nitro group for improved selectivity. (a) D-(−)-DET, ^tBuOOH, $Ti(O^iPr)_4$, CH_2Cl_2, −20 °C; (b) Et_3N, DMAP, TsCl, 0 °C; (c) phthalimide, potassium phthalimide, DMF, 90 °C; (d) $Et_3N{\cdot}3HF$, 120 °C; (e) DeoxoFluor® (neat), 70 °C; (f) H_2, Pd/C, Ac_2O, 25 °C; (g) $NaOI_4$, $RuCl_3$, MeCN, DCM, H_2O, 25 °C; (h) $Et_3N{\cdot}3HF$, 100 °C.



Scheme 8. Conversion of diol **47** into target **2**. (a) $SOCl_2$, pyridine, CH_2Cl_2, 0 °C; then $NaIO_4$, $RuCl_3$, H_2O, CH_2Cl_2, CH_3CN, 0 °C; (b) TBAF, THF, CH_3CN, 0 °C then H_2SO_4, H_2O, THF, 25 °C; (c) DeoxoFluor® (neat), 80 °C; (d) H_2, Pd/C, Ac_2O; (e) $NaOI_4$, $RuCl_3$, MeCN, DCM, H_2O.

work (Scheme 7), and although this requires more steps than the previous synthesis, it does overcome the greatest difficulty which was to achieve good chemoselectivity and reproducibility in the second fluorination step. Overall, this work has addressed the major bottleneck in the ongoing development of biological applications of **1** and **2**, and the synthetic methods developed in this work may contribute to the wider deployment of selective fluorination chemistry as a tool for optimising the properties of bioactive molecules more generally.

4. Experimental section

4.1. Reagents and instrumentation

All reactions were performed in oven-dried glassware unless stated otherwise, under a nitrogen atmosphere with magnetic stirring. All anhydrous solvents were obtained by passage through columns of activated alumina. Triethylamine was stored over potassium hydroxide pellets. All other commercial reagents and solvents were of synthetic grade and used as received. Reactions were monitored by thin layer chromatography using Merck aluminium-backed silica gel 60 F254 (0.2 mm) TLC plates. TLC plates were visualised under short-wave UV light (254 nm) and then by staining with ceric ammonium molybdate or potassium permanganate. Flash chromatography was performed using Davisil 40–63 mesh silica gel; eluting solvents are stated as volume/volume mixtures. Nuclear magnetic resonance (NMR) spectra were obtained using a BBFO PROBE 300, TBI PROBE 400 or CRYO PROBE 600 MHzBruker Avance III spectrometer, at 300 K; chemical shifts are reported in parts per million downshift from tetramethylsilane. ^1H and ^{13}C NMR spectra were calibrated using the residual chloroform peak (δ 7.26 ppm and δ 77.16 ppm, respectively) as the internal standard. All resonances were assigned by inspection of the coupling constants and chemical shift. The multiplicities of NMR signals are denoted as follows: s=singlet, d=doublet, t=triplet, m=multiplet, br s=broad singlet. Melting points were determined using a Stanford Research Systems OptiMelt automated melting point apparatus. 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 in grams per 100 mL and specific rotations are reported in units of degrees dm^{-1} cm^3 g^{-1}. Infrared (IR) spectra were obtained using a Bruker Alpha-E FTIR 41 spectrometer. Mass spectra were recorded by the Mass Spectrometry Unit at The University of New South Wales, using a Bruker Daltonics fourier transform ion cyclotron resonance mass spectrometer (high resolution electrospray ionisation) operating in the positive ion mode; signal intensities are quoted as a percentage of the base peak. Diastereoisomeric ratios were determined by NMR. An enantiomeric or diastereomeric excess quoted as >99% indicates that no amount of the minor isomer was observed by the respective methods used.

*4.1.1. 2-((2R,3R)-2,3-Dihydroxy-3-phenylpropyl)isoindoline-1,3-dione (**4**).*[28] A mixture of tosylate **12** (0.336 g, 1.04 mmol), potassium phthalimide (0.193 g, 1.04 mmol), phthalimide (0.153 g, 1.04 mmol) and DMF (9.0 mL) was stirred at 90 °C overnight. The mixture was then cooled and concentrated to a volume of ~10 mL. Water (100 mL) was added and the mixture was extracted with DCM (4×20 mL). The combined organic layers were dried (Na_2SO_4) and concentrated onto silica. The crude product was subjected to flash chromatography eluting with 8:1→4:1 DCM/EtOAc to yield *the title compound* as a white solid (169 mg, 69%); R_f 0.22 (8:1 DCM/EtOAc); $[\alpha]_D$ +20 (*c* 0.05, EtOH) [lit.[28] for enantiomer: $[\alpha]_D$ −17 (*c* 0.69, EtOH)]; ^1H NMR (300 MHz, $CDCl_3$) δ 7.85–7.68 (m, 4H, phthalimide), 7.41–7.28 (m, 5H, Ph), 4.61 (d, *J*=5.1 Hz, 1H, Ph–C*H*), 4.06 (m, 1H, C*H*–CH_2), 3.94–3.88 (m, 2H, CH_2); spectral data in accordance with literature values.[28]

*4.1.2. (±)-(R)-2-(3,3-Difluoro-2-phenylpropyl)isoindoline-1,3-dione (**7**).*[28] *N*-Bromosuccinimide (10.0 mg, 0.052 mmol) was added to a mixture of **35** (10.0 mg, 0.038 mmol), HF/pyridine (0.04 mL) and

DCM (0.04 mL), and the resulting mixture was stirred for 3 h at 25 °C. Silver(I) fluoride (6.5 mg, 0.052 mmol) was added, and the mixture was stirred for 16 h in the dark. Water (1 mL) was added, and the mixture was partitioned between EtOAc (5 mL) and H_2O (5 mL). The organic layer was washed with saturated aqueous $NaHCO_3$ (5 mL) and brine (5 mL), dried ($MgSO_4$) and concentrated in vacuo to afford a mixture of **7**, **36** and **37** in 53:27:16 ratio.

Data for **7**: ^{19}F NMR (282 MHz, $CDCl_3$) δ −119.9 (ddd, J=283.4, 55.7, 13.7 Hz, 1F), −125.5 (ddd, J=283.4, 55.7, 16.5 Hz, 1F); ^{19}F{^{1}H} NMR (282 MHz, $CDCl_3$) δ −119.9 (d, J=283.4 Hz, 1F), −125.5 (d, J=283.4 Hz, 1F); spectral data in accordance with literature values.[28]

*4.1.3. 2-((2S,3S)-3-Fluoro-2-hydroxy-3-phenylpropyl)isoindoline-1,3-dione (**8**).*[28] A mixture of compound **16** (5.70 g, 17.5 mmol), phthalimide (3.10 g, 20.9 mmol), potassium phthalimide (3.90 g, 20.9 mmol) and DMF (100 mL) was stirred at 90 °C overnight. The mixture was concentrated, and the residue was partitioned between water (100 mL) and EtOAc (80 mL). The aqueous layer was extracted with EtOAc (5×50 mL) and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated to give *the title compound* as an off-white solid (3.98 g, 76%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.83 (m, 2H, tosyl ArH), 7.71 (m, 2H, tosyl ArH), 7.43–7.31 (m, 5H, ArH), 5.47 (dd, J=46.6, 4.7 Hz, 1H, C*H*F–CH), 4.34 (m, 1H, C*H*–OH), 3.91 (dd, J=14.1, 8.6 Hz, 1H, CH_2–NPht), 3.79 (dd, J=14.1, 4.1 Hz, 1H, CH_2–NPht), 2.63 (d, J=5.7 Hz, 1H, OH); ^{19}F NMR (282 MHz, $CDCl_3$) δ −188.9 (dd, J=46.6, 18.3 Hz, 1F); ^{19}F{^{1}H} NMR (282 MHz, $CDCl_3$) δ −188.9 (s, 1F); spectral data in accordance with literature values.[28]

*4.1.4. 2-((2R,3S)-2,3-Difluoro-3-phenylpropyl)isoindoline-1,3-dione (**9**).*[28] A mixture of compounds **17** and **18** (5.0 g, 15.5 mmol), phthalimide (2.50 g, 17.0 mmol), potassium phthalimide (3.20 g, 17.0 mmol) and DMF (100 mL) was stirred at 90 °C overnight. The mixture was concentrated, and the residue was partitioned between water (100 mL) and EtOAc (80 mL). The aqueous layer was extracted with EtOAc (5×50 mL) and the combined organic layers were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with 9:1 hexane/EtOAc to give *the title compound* as a white solid (2.70 g, 65%); $[\alpha]_D$ +40.8 (c 0.98, $CHCl_3$); mp 110–113 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.84 (m, 2H, ArH), 7.72 (m, 2H, ArH), 7.44–7.35 (m, 5H, ArH), 5.72 (ddd, J=46.4, 12.9, 4.4 Hz, 1H, C*H*F–CHF–CH$_2$), 5.14 (ddddd, J=47.6, 16.5, 8.7, 4.4, 3.6 Hz, 1H, CHF–C*H*F–CH$_2$), 4.20 (dddd, J=14.5, 12.4, 8.7, 0.7 Hz, 1H, CHF–CH_2), 3.92 (dddd, J=29.5, 14.5, 3.6, 0.7 Hz, 1H, CHF–CH_2); ^{19}F NMR (282 MHz, $CDCl_3$) δ −193.3 (ddd, J=46.4, 16.5, 16.3 Hz, 1F, CH*F*–CHF–CH$_2$), −195.2 (ddddd, J=47.6, 29.5, 16.3, 12.9, 12.4 Hz, 1F, CHF–CH*F*–CH$_2$); ^{19}F{^{1}H} NMR (282 MHz, $CDCl_3$) δ −193.3 (d, J=16.3 Hz, 1F, CH*F*–CHF–CH$_2$), −195.2 (d, J=16.3 Hz, 1F, CHF–CH*F*–CH$_2$); spectral data in accordance with literature values.[28]

*4.1.5. (1R,2R)-1-Phenylpropane-1,2,3-triol (**11**)*[29]. A mixture of potassium ferricyanide (22.1 g, 67.1 mmol), potassium carbonate (9.27 g, 67.1 mmol), sodium hydrogen carbonate (5.63 g, 67.1 mmol) and $(DHQD)_2PHAL$ (0.17 g, 0.22 mmol) in *tert*-butanol (110 mL) and water (110 mL) was stirred at 25 °C for 10 min, then cooled to 0 °C. Osmium tetroxide (2% solution in water, 1.14 mL, 0.067 mmol) was then added followed by methanesulfonamide (0.500 g, 5.26 mmol) to form a red solution. The mixture was stirred at 0 °C for 30 min prior to the addition of compound **10** (3.00 g, 22.4 mmol), and the mixture was then stirred for 48 h at 0 °C. Sodium sulfite (3.00 g) was added, and stirring continued for 1 h before extraction with EtOAc (7×75 mL) and a wash with brine. The combined organic layers were dried ($NaSO_4$) and concentrated onto silica. The crude product was purified using flash chromatography eluting with 3:7 hexane/EtOAc to yield *the title compound* as a viscous pale brown oil (3.18 g, 85%); R_f 0.20 (3:7 hexane/EtOAc); $[\alpha]_D$ −26 (c 3.52, $CHCl_3$) [lit.[29] for enantiomer: $[\alpha]_D$ +21 (c 3.68, $CHCl_3$)]; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28 (m, 5H, Ar*H*), 4.58 (d, J=7.1 Hz, 1H, Ph–C*H*), 4.56 (br s, 1H, O*H*), 4.49 (br s, 1H, O*H*), 3.83–3.73 (m, 2H, 2×C*H*–OH), 3.41 (m, 2H, CH_2); spectral data in accordance with literature values.[29]

*4.1.6. (2R,3R)-2,3-Dihydroxy-3-phenylpropyl-4-methylbenzenesulfonate (**12**).*[29] Dibutyltin oxide (0.44 g, 2 mol%) was added to a solution of triol **11** (15.0 g, 89.2 mmol) in anhydrous DCM (200 mL) and stirred for 20 min until fully dissolved. DIPEA (0.318 mL, 1.96 mmol) and *p*-toluenesulfonyl chloride (18.7 g, 98.1 mmol) were added and the mixture was stirred overnight at 0 °C then quenched with water. The mixture was extracted with DCM (3×100 mL), dried (Na_2SO_4) and concentrated. The crude product was purified by flash chromatography eluting with 9:1 DCM/ethyl acetate to yield *the title compound* as a pale yellow oil (17.5 g, 61%); R_f 0.35 (9:1 DCM/EtOAc); $[\alpha]_D$ −18 (c 2.3, $CHCl_3$) [lit.[29] for enantiomer: $[\alpha]_D$ +15 (c 1.2, $CHCl_3$)]; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78 (d, J=8.3 Hz, 2H, Ar*H*), 7.34–7.27 (m, 7H, Ar*H*), 4.68 (d, J=6.1 Hz, 1H, Ph–C*H*), 4.10–4.04 (m, 2H, CH_2), 3.94–3.88 (m, 1H, C*H*–CH$_2$), 2.45 (s, 3H, CH_3); spectral data in accordance with literature values.[29]

*4.1.7. ((2S,3S)-3-Phenyloxiran-2-yl)methanol (**13**).*[30] Titanium isopropoxide (3.81 g, 13.4 mmol), followed by 5.5 *M tert*-butyl hydroperoxide (TBHP) (17.2 mL, 179 mmol), were added to a stirred solution of molecular sieves and L-(+)-DET (4.20 g, 20.1 mmol) in dichloromethane (770 mL) at −20 °C. The mixture was allowed to stir at −20 °C for 1 h. A solution of compound **10** (12.0 g, 89.4 mmol) in dichloromethane (17 mL) was then added dropwise over 30 min. The reaction was allowed to stir overnight and then quenched at −20 °C with 10% aqueous NaOH solution saturated with NaCl (7.2 mL). Diethyl ether (100 mL) was added and the reaction mixture was warmed to 0 °C. The stirring was maintained for 15 min at 0 °C while $MgSO_4$ and Celite were added. The mixture was allowed to settle and the solution was filtered through a pad of Celite and washed with diethyl ether. Purification by flash chromatography (3:2 hexane/EtOAc) provided *the title compound* as a yellow oil (10.9 g, 81%); R_f 0.42 (7:3 hexane/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33–7.28 (m, 5H, Ar*H*), 4.06 (m, 1H, CH–*H*–OH), 3.95 (d, J=2.2 Hz, 1H, Ph–C*H*O), 3.80 (dd, J=12.7, 4.7 Hz, 1H, C*H*–H–OH), 3.28–3.25 (m, 1H, OC*H*–CH$_2$), 2.86 (br s, 1H, OH); spectral data in accordance with literature values.[30]

*4.1.8. ((2S,3S)-3-Phenyloxiran-2-yl)methyl-4-methylbenzenesulfonate (**14**).* To a solution of compound **13** (8.30 g, 55.0 mmol) in DCM (350 mL) was added triethylamine (15.3 mL, 110 mmol), DMAP (0.672 g, 5.5 mmol) and *p*-toluenesulfonyl chloride (15.7 g, 83.0 mmol). The mixture was stirred for 3 h and water was subsequently added. The mixture was extracted with DCM (2×150 mL) and the combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by flash column chromatography (9:1→3:2 hexane/EtOAc) provided *the title compound* as a colourless solid (11.0 g, 50%); R_f 0.62 (7:3 hexane/EtOAc); mp 44–48 °C; $[\alpha]_D$ −41.7 (c 1.27, $CHCl_3$); IR (neat) ν_{max} (cm^{-1}) 2987, 1730, 1594, 1439, 1352, 1271, 1170; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.84 (m, 2H, tosyl Ar*H*), 7.38–7.31 (m, 5H, Ar*H*), 7.17 (m, 2H, tosyl Ar*H*), 4.36 (dd, J=11.5, 3.6 Hz, 1H, CH–*H*–OTs), 4.14 (dd, J=11.5, 5.7 Hz, 1H, C*H*–H–OTs), 3.77 (d, J=2.0 Hz, 1H, Ar–C*H*O), 3.25 (ddd, J=5.7, 3.6, 2.0 Hz, 1H, C*H*O–CH$_2$–OTs), 2.46 (s, 3H, tosyl CH_3); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 145.3 (ArC), 135.6 (ArC), 132.7 (ArC), 130.0 (ArC), 128.7 (ArC), 128.6 (ArC), 128.0 (ArC), 125.8 (ArC), 69.5 (CH_2–OTs), 58.6

(CHO–CH_2–OTs), 58.4 (Ar–CHO), 21.7 (tosyl CH_3); HRMS (ESI, +ve) $C_{16}H_{16}O_4SNa^+$ $[M+Na]^+$ requires *m/z* 327.0769, found 327.0772.

*4.1.9. 2-(((2S,3S)-3-Phenyloxiran-2-yl)methyl)isoindoline-1,3-dione (**15**).* A mixture of compound **14** (1.50 g, 4.93 mmol), potassium phthalimide (0.91 g, 4.9 mmol), phthalimide (0.73 g, 4.9 mmol) and DMF (50 mL) was stirred at 50 °C for 16 h. The solvent was evaporated and the residue was purified by column chromatography (6:1 hexane/EtOAc) to give *the title compound* as a white solid (0.86 g, 63%); R_f 0.46 (7:3 hexane/EtOAc); mp 74–80 °C; $[\alpha]_D$ +22.9 (*c* 1.2, $CHCl_3$); IR (neat) ν_{max} (cm^{-1}) 2928, 1771, 1706, 1611, 1389, 1172, 1070; ^1H NMR (300 MHz, $CDCl_3$) δ 7.89–7.73 (m, 4H, phthalimide), 7.36–7.25 (m, 5H, Ph), 4.16 (dd, *J*=14.4, 4.6 Hz, 1H, CH–*H*–NPht), 3.88 (d, *J*=1.9 Hz, 1H, Ar–C*H*O), 3.86 (dd, *J*=14.4, 5.7 Hz, 1H, C*H*–H–NPht), 3.25 (ddd, *J*=5.7, 4.6, 1.9 Hz, 1H, C*H*O–CH_2–NPht); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 168.2 (C=O phthalimide), 134.4 (ArC),134.3 (ArC), 132.4, 128.6 (ArC), 128.5 (ArC), 125.7 (ArC), 123.6 (ArC), 59.0 (Ph–CHO), 58.1 (CHO–CH_2), 39.5 (CH_2–NPht); HRMS (ESI, +ve) $C_{17}H_{13}NO_3Na^+$ $[M+Na]^+$ requires *m/z* 302.0793, found 302.0798.

*4.1.10. (2S,3S)-3-Fluoro-2-hydroxy-3-phenylpropyl-4-methylbenzenesulfonate (**16**).*[31] $BF_3{\cdot}OEt_2$ (16.1 μL, 0.13 mmol) was added to a stirred 0.25 *M* solution of compound **14** (119 mg, 0.39 mmol) in dichloromethane at −20 °C over 5 min. A saturated aqueous solution of $NaHCO_3$ (5 mL) was then added, and the mixture was stirred until the two layers became clear. The aqueous layer was extracted with DCM (3×10 mL) and the combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with 4:1 hexane/EtOAc to give *the title compound* as a yellow oil (78.3 mg, 63%); $[\alpha]_D$ +0.27 (*c* 0.19, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.78 (m, 2H, ArH), 7.37–7.26 (m, 7H, ArH), 5.54 (dd, *J*=46.5, 5.3 Hz, 1H, C*H*F–CH), 4.16–4.05 (m, 2H, C*H*H–OTs and C*H*–OH), 3.95–3.88 (m, 1H, CH*H*–OTs), 2.65 (br s, 1H, OH), 2.46 (s, 3H, tosyl CH_3); ^{19}F NMR (282 MHz, $CDCl_3$) δ −192.2 (dd, *J*=46.5, 19.1 Hz, 1F); $^{19}F\{^1H\}$ NMR (282 MHz, $CDCl_3$) δ −192.2 (s, 1F); spectral data in accordance with literature values.[31]

*4.1.11. (2R,3S)-2,3-Difluoro-3-phenylpropyl-4-methylbenzenesulfonate (**17**); (R)-3,3-difluoro-2-phenylpropyl-4-methylbenzenesulfonate (**18**).* DeoxoFluor® (15.0 mL, 81.0 mmol) was added to compound **16** (6.90 g, 21.3 mmol) in a plastic reaction vessel. The mixture was stirred at 70 °C for 16 h. The mixture was cooled, diluted with DCM (25 mL), and saturated ice-cooled aqueous $NaHCO_3$ (20 mL) was added dropwise. After the bubbling ceased, the organic layer was separated, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (85:15 hexane/EtOAc) to give a 6:1 mixture of compound **17** and the rearrangement product **18** (combined yield 5.07 g, 73%) (see ESI).

Data for **17**: R_f 0.47 (7:3 hexane/EtOAc); ^1H NMR (300 MHz, $CDCl_3$) δ 7.78–7.76 (m, 2H, tosyl ArH), 7.42–7.26 (m, 7H, tosyl ArH and Ph), 5.59 (ddd, *J*=45.8, 10.9, 5.3 Hz, 1H, C*H*F–CHF–CH_2), 4.85 (ddddd, *J*=46.8, 16.6, 8.8, 5.3, 3.6 Hz, 1H, CHF–C*H*F–CH_2), 4.34 (m, 1H, CH_2–OTs), 4.26 (m, 1H, CH_2–OTs), 2.47 (s, 3H, CH_3); ^{19}F NMR (282 MHz, $CDCl_3$) δ −192.1 (ddd, *J*=46.4, 16.6, 16.6 Hz, 1F), −195.9 (m, 1F); $^{19}F\{^1H\}$ NMR (282 MHz, $CDCl_3$) δ −192.1 (d, *J*=16.6 Hz, 1F), −195.9 (d, *J*=16.6 Hz, 1F).

Data for **18**: R_f 0.47 (7:3 hexane/EtOAc); ^{19}F NMR (282 MHz, $CDCl_3$) δ −121.5 (ddd, *J*=283.3, 56.6, 16.9 Hz, 1F), −123.6 (d, *J*=283.3, 56.6, 16.9 Hz, 1F); $^{19}F\{^1H\}$ NMR (282 MHz, $CDCl_3$) δ−121.5 (d, *J*=283.3 Hz, 1F), −123.6 (d, *J*=283.3 Hz, 1F).

*4.1.12. (±)-Methyl-(2S,3R)-4-(1,3-dioxoisoindolin-2-yl)-3-fluoro-2-iodobutanoate (**25**); (±)-methyl-(2R,3S)-4-(1,3-dioxoisoindolin-2-yl)-2-fluoro-3-iodobutanoate (**26**); (±)-methyl-(2S,3S)-4-(1,3-dioxoisoindolin-2-yl)-3-fluoro-2-iodobutanoate (**27**).* To a mixture of methyl-(*E*)-4-(1,3-dioxoisoindolin-2-yl)but-2-enoate (100 mg, 0.41 mmol), HF/pyridine (0.4 mL) and MeCN (0.4 mL) at 25 °C was added *N*-iodosuccinimide (13.0 mg, 0.056 mmol), and the resulting mixture was stirred for 16 h. Water (5 mL) was added, and the mixture was partitioned between EtOAc (10 mL) and H_2O (10 mL). The organic layer was washed with saturated aqueous $NaHCO_3$ (10 mL) and brine (10 mL), dried ($MgSO_4$) and concentrated in vacuo. The residue was purified via flash chromatography eluting with 80:20 hexane/EtOAc to give colourless oil comprising a mixture of **25**, **26** and **27** in 78:21:1 ratio, as calculated from ^{19}F NMR analysis (combined yield 150 mg, 94%). A small quantity of **25** was subsequently isolated for characterisation purposes.

Data for **25**: R_f 0.23 (80:20 hexane/EtOAc); IR (neat) ν_{max} (cm^{-1}) 2900, 1747, 1740, 1640, 1310, 1280, 1240, 1110, 500; ^1H NMR (400 MHz, $CDCl_3$) δ 7.88 (m, 2H, ArH), 7.75 (m, 2H, ArH), 5.12 (dddd, *J*=47.3, 8.8, 8.2, 3.2 Hz, 1H, C*H*F), 4.50 (dd, *J*=7.9, 8.8 Hz, 1H, C*H*I), 4.35 (ddd, *J*=28.0, 14.6, 3.2 Hz, 1H, CH_2), 4.14 (ddd, *J*=14.8, 14.6, 8.2 Hz, 1H, CH_2), 3.79 (s, 3H, CH_3); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 168.9 (d, *J*=4.4 Hz, CO_2Me), 168.0 (C=O phthalimide), 134.4 (ArC), 132.0 (ArC), 123.7 (ArC), 89.6 (d, *J*=183.1 Hz, *C*HF), 53.5 (CH_3), 40.5 (d, *J*=20.8 Hz, *C*HI), 17.0 (d, *J*=24.1 Hz, CH_2); ^{19}F NMR (377 MHz, $CDCl_3$) δ −175.1 (dddd, *J*=47.3, 28.0, 14.8, 7.9 Hz, 1F, CH*F*–CH_2); $^{19}F\{^1H\}$ NMR (377 MHz, $CDCl_3$) δ −175.1 (s, 1F, CH*F*–CH_2); HRMS (ESI, +ve) $C_{13}H_{11}FINO_4Na^+$ $[M+Na]^+$ requires *m/z* 413.9609, found 413.9604.

Data for **26**: R_f 0.23 (80:20 hexane/EtOAc); ^{19}F NMR (282 MHz, $CDCl_3$) δ −186.1 (dd, *J*=46.9, 21.6 Hz, 1F); $^{19}F\{^1H\}$ NMR (282 MHz, $CDCl_3$) δ −186.1 (s, 1F).

Data for **27**: R_f 0.23 (80:20 hexane/EtOAc); ^{19}F NMR (282 MHz, $CDCl_3$) δ −202.7 (m, 1F); $^{19}F\{^1H\}$ NMR (282 MHz, $CDCl_3$) δ −202.7 (s, 1F).

*4.1.13. (±)-2-((2S,3R)-2-Bromo-3-fluoro-3-phenylpropyl)isoindoline-1,3-dione (**36**); (±)-2-((2S,3S)-2-bromo-3-fluoro-3-phenylpropyl)isoindoline-1,3-dione (**37**).* *N*-Bromosuccinimide (0.300 g, 1.547 mmol) was added to a mixture of **35** (0.300 g, 1.139 mmol), HF/pyridine (1.14 mL) and DCM (1.14 mL) at 25 °C. The mixture was stirred for 16 h. Water (10 mL) was added, and the mixture was partitioned between EtOAc (15 mL) and H_2O (5 mL). The organic layer was washed with saturated aqueous $NaHCO_3$ (15 mL) and brine (15 mL), dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by flash chromatography eluting with 85:15 hexane/EtOAc to give compound **36** as a colourless oil (0.371 g, 90%) and compound **37** as a colourless oil (20.6 mg, 5%).

Data for **36**: R_f 0.29 (85:15 hexane/EtOAc); IR (neat) ν_{max} (cm^{-1}) 2930, 1717, 1752, 1631, 1350, 1289, 1227, 1118, 510; ^1H NMR (300 MHz, $CDCl_3$) δ 7.84 (m, 2H, phthalimide), 7.72 (m, 2H, phthalimide), 7.44–7.28 (m, 5H, Ph), 5.72 (dd, *J*=46.1, 6.2 Hz, 1H, C*H*F), 4.85 (dddd, *J*=15.3, 8.9, 6.2, 5.5 Hz, 1H, C*H*Br), 4.24 (dd, *J*=14.4, 8.9 Hz, 1H, CH_2), 4.17 (dd, *J*=14.4, 5.5 Hz, 1H, CH_2); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 167.9 (C=O phthalimide), 136.3 (d, *J*=20.2 Hz, Ph quaternary C), 134.3 (phthalimide), 131.9 (phthalimide), 129.3 (d, *J*=1.9 Hz, Ph *m*–C), 128.7 (Ph *p*–C), 126.3 (d, *J*=7.1 Hz, Ph *o*–C), 123.6 (phthalimide), 94.9 (d, *J*=178.4 Hz, *C*HF), 50.4 (d, *J*=25.4 Hz, *C*HBr), 40.6 (d, *J*=5.2 Hz, CH_2); ^{19}F NMR (282 MHz, $CDCl_3$) δ −176.4 (dd, *J*=46.3, 15.4 Hz, 1F, Ph–CH*F*); $^{19}F\{^1H\}$ NMR (282 MHz, $CDCl_3$) δ −176.4 (s, 1F, Ph–CH*F*); HRMS (ESI, +ve) $C_{17}H_{13}FBrNO_2Na^+$ $[M+Na]^+$ requires *m/z* 384.0006, found 384.0001.

Data for **37**: R_f 0.23 (85:15 hexane/EtOAc); IR (neat) ν_{max} (cm^{-1}) 2939, 1726, 1759, 1622, 1363, 1281, 1241, 1118, 515; ^1H NMR (300 MHz, $CDCl_3$) δ 7.85 (m, 2H, phthalimide), 7.73 (m, 2H, phthalimide), 7.41–7.27 (m, 5H, Ph), 5.59 (dd, *J*=45.9, 4.9 Hz, 1H, C*H*F), 4.79 (m, 1H, C*H*Br), 4.22 (dd, *J*=14.3, 9.1 Hz, 1H, CH_2), 4.01 (dd, *J*=14.3, 5.6 Hz, 1H, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.9 (C=O

phthalimide), 136.4 (d, *J*=20.3 Hz, Ph quaternary C), 134.4 (phthalimide), 131.8 (phthalimide), 129.3 (d, *J*=1.3 Hz, Ph *m*–C), 128.7 (Ph *p*–C), 126.1 (d, *J*=7.1 Hz, Ph *o*–C), 123.7 (phthalimide), 92.9 (d, *J*=182.1 Hz, *C*HF), 52.3 (d, *J*=23.7 Hz, *C*HBr), 41.6 (d, *J*=3.8 Hz, CH_2); ^{19}F NMR (282 MHz, $CDCl_3$) δ −178.6 (dd, *J*=45.9, 20.3 Hz, 1F, Ph–CH*F*); $^{19}F\{^1H\}$ NMR (282 MHz, $CDCl_3$) δ −178.6 (s, 1F, Ph–CH*F*); HRMS (ESI, +ve) $C_{17}H_{13}FBrNO_2Na^+$ $[M+Na]^+$ requires *m*/*z* 384.0006, found 384.0003.

*4.1.14. (±)-2-((2S,3R)-2-Bromo-3-fluoro-3-(4-nitrophenyl)propyl) isoindoline-1,3-dione (**39**).* *N*-Bromosuccinimide (8.6 mg, 0.044 mmol) was added to a mixture of **38** (10.0 mg, 0.032 mmol), HF/pyridine (0.04 mL) and DCM (0.04 mL), and the resulting mixture was stirred at 25 °C for 16 h. Water (1 mL) was added, and the mixture was partitioned between EtOAc (5 mL) and H_2O (5 mL). The organic layer was washed with saturated aqueous $NaHCO_3$ (5 mL) and brine (5 mL), dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by flash chromatography eluting with 80:20 hexane/EtOAc to give *the title compound* as a colourless oil (12.7 mg, 96%); R_f 0.39 (80:20 hexane/EtOAc); IR (neat) ν_{max} (cm^{-1}) 2939, 1711, 1759, 1639, 1367, 1256, 1223, 1154, 525; ^1H NMR (600 MHz, $CDCl_3$) δ 8.21 (br d, *J*=8.9 Hz, 2H, $O_2NC_6H_4$), 7.84 (dd, *J*=5.6, 3.0 Hz, 2H, phthalimide), 7.73 (dd, *J*=5.6, 3.0 Hz, 2H, phthalimide), 7.61 (br d, *J*=8.9 Hz, 2H, $O_2NC_6H_4$), 5.80 (dd, *J*=46.0, 6.2 Hz, 1H, *C*HF), 4.81 (m,1H, *C*HBr), 4.21 (br d, *J*=7.3 Hz, 2H, CH_2); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ 167.8 (C=O phthalimide), 148.4 (O_2N–C), 142.9 (d, *J*=20.0 Hz, Ar*C*–CHF), 134.5 (phthalimide), 131.7 (phthalimide), 127.4 (d, *J*=8 Hz, O_2N–Ph *o*–C), 123.9 (Ph *m*–C), 123.8 (phthalimide), 93.6 (d, *J*=183.6 Hz, *C*HF), 49.1 (d, *J*=25.1 Hz, *C*HBr), 40.5 (d, *J*=5.1 Hz, CH_2); ^{19}F NMR (282 MHz, $CDCl_3$) δ −178.2 (dd, *J*=46.0, 15.5 Hz, 1F); $^{19}F\{^1H\}$ NMR (282 MHz, $CDCl_3$) δ −178.2 (s, 1F); HRMS (ESI, +ve) $C_{17}H_{12}FBrN_2O_4Na^+$ $[M+Na]^+$ requires *m*/*z* 428.9857, found 428.9852.

*4.1.15. (E)-2-(3-Fluoro-3-(4-nitrophenyl)allyl)isoindoline-1,3-dione (**40**); (Z)-2-(3-fluoro-3-(4-nitrophenyl)allyl)isoindoline-1,3-dione (**41**).* *N*-Bromosuccinimide (8.6 mg, 0.044 mmol) was added to a mixture of **38** (10.0 mg, 0.032 mmol), HF/pyridine (0.04 mL) and DMF (0.04 mL), and the resulting mixture was stirred for 3 h at 25 °C. Silver(I) fluoride (5.6 mg, 0.044 mmol) was added, and the mixture was stirred for 16 h at 80 °C in the dark. Water (1 mL) was added, and the mixture was partitioned between EtOAc (5 mL) and H_2O (5 mL). The organic layer was washed with saturated aqueous $NaHCO_3$ (5 mL) and brine (5 mL), dried ($MgSO_4$) and concentrated in vacuo to afford a mixture of **40**, **41** and **38** in 18:1:1 ratio.

Data for **40**: ^{19}F NMR (282 MHz, $CDCl_3$) δ −96.3 (d, *J*=19.9 Hz, 1F); $^{19}F\{^1H\}$ NMR (282 MHz, $CDCl_3$) δ −96.3 (s, 1F).

Data for **41**: ^{19}F NMR (282 MHz, $CDCl_3$) δ −115.8 (d, *J*=35.2 Hz, 1F); $^{19}F\{^1H\}$ NMR (282 MHz, $CDCl_3$) δ −115.8 (s, 1F).

*4.1.16. ((2R,3R)-3-(4-Nitrophenyl)oxiran-2-yl)methanol (**43**).*[39] An oven dried 500 mL three neck round bottom flask was charged with 3 Å activated molecular sieves (1.0 g) and dry DCM (100 mL). The mixture was cooled to −20 °C and then (−)-DET (258 mg, 1.25 mmol), Ti(O-*i*-Pr)$_4$ (236 mg, 0.83 mmol) and 5.5 *M* TBHP (6.1 mL, 33 mmol) were added. After 30 min, a solution of compound **42** (2.99 g, 16.7 mmol) in dry DCM (50 mL) was added slowly via cannula and the mixture was stirred for 2 h at −20 °C. The mixture was quenched at −20 °C by the addition of a 10% aqueous NaOH solution saturated with NaCl (1.5 mL). Diethyl ether (10% v/v) was added, and the mixture was warmed to 10 °C. The mixture was then stirred for an additional 10 min at 10 °C and then $MgSO_4$ (1.5 g) and Celite (200 mg) were added, and stirred for another 15 min.The mixture was allowed to settle, and the clear solution was filtered through a pad of Celite and washed with diethyl ether (40 mL). The volatiles were removed under reduced pressure to afford a crude residue which was recrystallised from hexane/EtOAc to give *the title compound* as yellow needles (3.12 g, 96%); mp 114–115 °C; $[\alpha]_D$ −6.49 (*c* 0.133, MeCN); ^1H NMR (400 MHz, $CDCl_3$) δ 8.21 (d, *J*=8.8 Hz, 2H, ArH), 7.45 (d, *J*=8.8 Hz, 2H, ArH), 4.08 (dd, *J*=12.9, 2.3 Hz, 1H, CH_2OH), 4.05 (d, *J*=2.1 Hz, 1H, Ar–*C*HO), 3.86 (dd, *J*=12.9, 3.3 Hz, 1H, CH_2OH), 3.19 (dt, *J*=3.3, 2.2 Hz, 1H, *C*HO–CH_2), 1.82 (br s, 1H, CH_2O*H*); spectral data in accordance with literature values.[39]

*4.1.17. ((2R,3R)-3-(4-Nitrophenyl)oxiran-2-yl)methyl-4-methylbenzenesulfonate (**44**).* Triethylamine (1.6 mL, 12 mmol) and DMAP (74.5 mg, 0.61 mmol) were added to a solution of compound **43** (1.20 g, 6.10 mmol) in DCM (30 mL) at 0 °C. *p*-Toluenesulfonyl chloride (1.70 g, 9.15 mmol) was then added in portions and the mixture was stirred for 1 h. The reaction mixture was partitioned between water (50 mL) and EtOAc (50 mL). The organic layer was washed with water (25 mL) and brine (25 mL), and dried over $MgSO_4$. The volatiles were removed under reduced pressure and the residue was purified by flash chromatography eluting with 85:15→60:40 hexane/EtOAc to afford *the title compound* as a brown solid (1.4 g, 67%); R_f 0.4 (70:30 hexane/EtOAc); $[\alpha]_D$ −12.3 (*c* 0.071, MeCN); mp 105–106 °C; IR (neat) ν_{max} (cm^{-1}) 1512, 1344, 963, 835; ^1H NMR (300 MHz, $CDCl_3$) δ 8.21 (d, *J*=8.8 Hz, 2H, $C_6H_4NO_2$), 7.82 (d, *J*=8.3 Hz, 2H, $C_6H_4NO_2$), 7.42–7.35 (m, 4H, $C_6H_4CH_3$), 4.32 (dd, *J*=11.7, 3.9 Hz, 1H, CH_2), 4.22 (dd, *J*=11.7, 5.4 Hz, 1H, CH_2), 3.91 (d, *J*=1.9, 1H, $O_2NC_6H_4$–*C*HO), 3.23 (ddd, *J*=5.4, 3.9, 1.9 Hz, 1H, *C*HO–CH_2), 2.46 (s, 3H, $C_6H_4CH_3$); $^{13}C\{^1H\}$ NMR (300 MHz, $CDCl_3$) δ 148.3 (C–NO_2), 145.5 (C–S), 143.2 (*C*–CHO), 132.7 (*C*–CH_3), 130.2 (ArC), 128.2 (ArC), 126.6 (ArC), 124.0 (ArC), 68.6 (CH_2), 59.3 (*C*HO–CH_2), 55.6 ($O_2NC_6H_4$–*C*HO), 21.8 (CH_3); HRMS (ESI, +ve) $C_{16}H_{15}NO_6Na^+$ $[M+Na]^+$ requires *m*/*z* 372.0512, found 372.0511.

*4.1.18. 2-(((2R,3R)-3-(4-Nitrophenyl)oxiran-2-yl)methyl)isoindoline-1,3-dione (**45**).* A solution of tosylate **44** (8.64 g, 24.7 mmol) and potassium phthalimide (5.50 g, 4.02 mmol) in DMF (100 mL) was stirred overnight at 55 °C. The mixture was cooled and concentrated to dryness. The residue was dissolved in ethyl acetate (400 mL) and the solution was washed with water (3×400 mL) and brine (1×200 mL). The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure to yield *the title compound* as a yellow solid (7.75 g, 97%); R_f 0.3 (70:30 hexane/EtOAc); $[\alpha]_D$ +25.9 (*c* 0.039, MeCN); mp 176–178 °C; IR (neat) ν_{max} (cm^{-1}) 1699, 1509, 1338, 936; ^1H NMR (300 MHz, $CDCl_3$) δ 8.18 (d, *J*=8.8 Hz, 2H, $C_6H_4NO_2$), 7.89 (m, 2H, phthalimide), 7.75 (m, 2H, phthalimide), 7.43 (d, *J*=8.8 Hz, 2H, $C_6H_4NO_2$), 4.21 (dd, *J*=14.5, 4.3 Hz, 1H, CH_2), 3.99 (d, *J*=1.9 Hz, 1H, $O_2NC_6H_4$–*C*HO), 3.86 (dd, *J*=14.5, 5.9 Hz, 1H, CH_2), 3.21 (ddd, *J*=5.9, 4.3, 1.9 Hz, 1H, *C*HO–CH_2); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 168.1 (C=O), 147.9 (O_2N–C), 144.0 (C–CHO), 134.5 (ArC), 132.0 (ArC), 126.5 (ArC), 123.9 (ArC), 123.8 (ArC), 59.6 (*C*HO–CH_2), 57.2 ($O_2NC_6H_4$–*C*HO), 39.2 (CH_2); HRMS (ESI, +ve) $C_{17}H_{12}N_2O_5Na^+$ $[M+Na]^+$ requires *m*/*z* 347.0638, found 347.0633.

*4.1.19. 2-((2R,3S)-3-Fluoro-2-hydroxy-3-(4-nitrophenyl)propyl)isoindoline-1,3-dione (**46**); 2-((2R,3S)-2,3-dihydroxy-3-(4-nitrophenyl) propyl)isoindoline-1,3-dione (**47**).* In an oven dried pressure flask, a mixture of compound **45** (54.9 mg, 0.17 mmol) and $Et_3N{\cdot}3HF$ (1.0 mL) was stirred overnight at 120 °C. The mixture was diluted with DCM (50 mL) and washed with saturated aqueous $NaHCO_3$ (3×30 mL). The organic layer was dried over $MgSO_4$ and purified by column chromatography eluting with 80:20 hexane/EtOAc to afford compound **46** as an off-white powder (25.5 mg, 44%) and compound **47** as a yellow powder (26.4 mg, 45%).

Data for **46**: R_f 0.5 (95:5 DCM/EtOAc); $[\alpha]_D$ +1.17 (*c* 0.223, MeCN); mp 225–226 °C; IR (neat) ν_{max} (cm^{-1}) 3334, 1694, 1515, 1341,1001; ^1H NMR (600 MHz, $CDCl_3$) δ 8.26 (d, *J*=8.3 Hz, 2H, $C_6H_4NO_2$), 7.86 (dd, *J*=5.4, 3.1 Hz, 2H, phthalimide), 7.75 (dd, *J*=5.5,

3.0 Hz, 2H, phthalimide), 7.61 (d, *J*=8.9 Hz, 2H, $C_6H_4NO_2$), 5.54 (dd, *J*=46.6, 6.1 Hz, 1H, C*H*F), 4.23 (m, 1H, CHF–C*H*OH), 3.99–3.96 (m, 2H, CHOH–CH_2), 3.08 (d, *J*=6.6 Hz, 1H, CHO*H*); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ 169.0 (C=O), 148.3 (O_2N–C), 143.3 (d, *J*=20.0 Hz, Ar*C*–CHF), 134.6 (ArC), 134.6 (ArC), 131.9 (ArC), 127.2 (d, *J*=8.3 Hz, *m*-$NO_2C_6H_4$), 123.8 (d, *J*=11.5 Hz, *o*-$NO_2C_6H_4$), 93.2 (d, *J*=179.1 Hz, *C*HF), 72.5 (d, *J*=25.2 Hz, *C*HOH), 40.3 (d, *J*=5.0 Hz, *C*H_2); ^{19}F NMR (282 MHz, $CDCl_3$) δ −191.9 (dd, *J*=46.4, 13.8 Hz, 1F); $^{19}F\{^1H\}$ NMR (282 MHz, $CDCl_3$) δ −191.9 (s, 1F); HRMS (ESI, +ve) $C_{17}H_{13}FN_2O_5Na^+$ $[M+Na]^+$ requires *m/z* 367.0701, found 367.0696.

Data for **47**: R_f 0.1 (95:5 DCM/EtOAc); $[\alpha]_D$ −3.1 (*c* 0.285, MeCN); mp 92–93 °C; IR (neat) ν_{max} (cm^{-1}) 3470, 1770, 1703, 1518, 1397; ^1H NMR (600 MHz, CD_3Cl_3) δ 8.20 (d, *J*=8.9 Hz, 2H, $O_2NC_6H_4$), 7.86 (dd, *J*=5.5, 3.1 Hz, 2H, phthalimide), 7.56 (dd, *J*=5.4, 3.0 Hz, 2H, phthalimide), 7.61 (d, *J*=8.7 Hz, 2H, $O_2NC_6H_4$), 4.74 (dd, *J*=6.2, 4.5 Hz, 1H, $O_2NC_6H_4CHOH$), 4.09 (ddd, *J*=9.3, 5.5, 3.5 Hz, 1H, C*H*OHCH$_2$), 4.01 (dd, *J*=14.8, 5.7 Hz, 1H, CH_2), 3.91 (dd, *J*=14.8, 3.4 Hz, 1H, CH_2), 3.51 (d, *J*=4.3 Hz, 1H, ArCHO*H*), 2.81 (d, *J*=4.8 Hz, 1H, CHO*H*CH$_2$); $^{13}C\{^1H\}$ NMR (150 MHz, CD_3Cl_3) δ 169.5 (*C*=O), 147.7 (O_2N–C), 147.6 (Ar*C*–CHOH), 134.6 (ArC), 131.8 (ArC), 127.5 (ArC), 123.8 (ArC), 123.7 (ArC), 74.2 (*C*HOH–CH$_2$), 73.9 (ArC–*C*HOH), 40.0 (*C*H$_2$); HRMS (ESI, +ve) $C_{17}H_{14}N_2O_6Na^+$ $[M+Na]^+$ requires *m/z* 365.0744, found 365.0727.

*4.1.20. 2-((2S,3S)-2,3-Difluoro-3-(4-nitrophenyl)propyl)isoindoline-1,3-dione (**48**).* A mixture of fluorohydrin **46** (0.75 g, 2.2 mmol) and DeoxoFluor® (4.1 mL, 22 mmol) was heated at 70 °C for 16 h. The mixture was cooled to 0 °C and diluted with DCM (10 mL) before washing with saturated aqueous $NaHCO_3$ (10 mL). The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with 30:70 DCM/hexane to afford *the title compound* as a yellow solid (277 mg, 37%), plus recovered starting material (289 mg, 38%).

Data for **48**: R_f 0.2 (70:30 hexane/EtOAc); $[\alpha]_D$ −9.6 (*c* 0.094, MeCN); mp 202–203 °C; IR (neat) ν_{max} (cm^{-1}) 1706, 1513, 1004; ^1H NMR (400 MHz, CD_3CN) δ 8.25 (d, *J*=8.4 Hz, 2H, $C_6H_4NO_2$), 7.86 (m, 2H, phthalimide), 7.80 (m, 2H, phthalimide), 7.68 (d, *J*=8.7 Hz, 2H, $C_6H_4NO_2$), 5.90 (ddd, *J*=45.4, 23.7, 2.8 Hz, 1H, C_6H_4–C*H*F), 5.09 (ddddd, *J*=46.6, 23.7, 8.0, 4.5, 2.8 Hz, 1H, CHF–C*H*F–CH$_2$), 4.13 (ddd, *J*=14.4, 13.1, 8.0, 0.6 Hz, 1H, CH_2), 3.96 (ddd, *J*=26.5, 14.4, 4.5 Hz, 1H, CH_2); $^{13}C\{^1H\}$ NMR (150 MHz, CD_3CN) δ 168.9 (*C*=O), 149.3 (O_2N–C), 143.3 (dd, *J*=21.0, 4.0 Hz, Ar*C*–CHF), 135.4 (ArC), 133.0 (ArC), 128.4 (d, *J*=8.1 Hz, *o*–$NO_2C_6H_4$), 124.6 (ArC), 124.1 (ArC), 91.8 (dd, *J*=179.4, 18.7 Hz, Ar–*C*HF), 91.4 (dd, *J*=183.3, 20.6 Hz, *C*HF–CH$_2$), 38.7 (dd, *J*=25.7, 6.9 Hz, *C*H$_2$); ^{19}F NMR (376 MHz, CD_3CN) δ −199.0 (dddd, *J*=45.4, 23.7, 10.0, 0.6 Hz, 1F, Ph–CH*F*), −203.4 (ddddd, *J*=46.6, 26.5, 23.7, 13.1, 10.0 Hz, 1F, C*H*F–CH$_2$); $^{19}F\{^1H\}$ NMR (376 MHz, CD_3CN) δ −199.0 (d, *J*=10.0 Hz, 1F, Ph–CH*F*), −203.4 (dd, *J*=10.0 Hz, 1F, CHF–CH*F*); HRMS (ESI, +ve) $C_{17}H_{12}F_2N_2O_4Na^+$ $[M+Na]^+$ requires *m/z* 369.0657, found 369.0673.

*4.1.21. N-(4-((1S,2S)-3-(1,3-Dioxoisoindolin-2-yl)-1,2-difluoropropyl)phenyl)acetamide (**49**).* To a solution of compound **48** (326 mg, 0.94 mmol) in freshly distilled acetic anhydride (15 mL) was added Pd/C (5%, 250 mg), and the mixture was stirred under a H_2 balloon for 5 h. The mixture was filtered through a small pad of Celite, washed with methanol and concentrated under reduced pressure. The residue was purified by column chromatography eluting with 97:3→80:20 DCM/EtOAc to afford *the title compound* as a white solid (218 mg, 65%); R_f 0.43 (5:95 EtOAc/DCM); $[\alpha]_D$ −7.15 (*c* 0.118, MeCN); mp 138–140 °C; IR (neat) ν_{max} (cm^{-1}) 1796, 1715, 1388; ^1H NMR (400 MHz, CD_3CN) δ 7.84–7.77 (m, 4H, $C_6H_4NO_2$), 7.54–7.49 (m, 4H, phthalimide), 5.74 (ddd, *J*=45.7, 21.6, 3.9 Hz, 1H, Ar–C*H*F), 5.06 (ddddd, *J*=47.4, 21.6, 8.3, 3.9, 3.9 Hz, 1H, C*H*F–CH$_2$), 4.07 (ddd, *J*=14.4, 13.5, 8.3 Hz, 1H, CH_2), 3.82 (ddd, *J*=27.4, 14.4, 3.9 Hz, 1H, CH_2), 2.21 (s, 3H, COCH_3); $^{13}C\{^1H\}$ NMR (150 MHz, CD_3CN) δ 168.9 (C=O phthalimide), 168.9 (*C*OCH$_3$), 141.2 (d, *J*=2.0 Hz, ArC), 135.4 (ArC), 135.4 (ArC), 133.0 (ArC), 128.3 (ArC), 124.1 (ArC), 124.1 (ArC), 92.5 (dd, *J*=177.0, 19.0 Hz, *C*HF), 91.7 (dd, *J*=183.4, 21.4 Hz, *C*HF), 38.9 (dd, *J*=24.6, 6.3 Hz, CH$_2$), 18.6 (*C*OCH$_3$); ^{19}F NMR (376 MHz, CD_3CN) δ −192.5 (br s, 1F, Ar–CH*F*), −201.7 (br s, 1F, C*H*F–CH$_2$); $^{19}F\{^1H\}$ NMR (376 MHz, CD_3CN) δ −192.5 (br s, 1F, Ar–CH*F*), −201.7 (br s, 1F, C*H*F–CH$_2$); HRMS (ESI, +ve) $C_{19}H_{17}F_2N_2O_3^+$ $[M+H]^+$ requires *m/z* 359.1202, found 359.1181.

*4.1.22. (2S,3S)-4-(1,3-Dioxoisoindolin-2-yl)-2,3-difluorobutanoic acid (**50**).*[28] To a stirred mixture of compound **49** (10.8 mg, 30.1 μmol), acetonitrile (0.9 mL), DCM (0.9 mL) and H_2O (1.1 mL) was added $NaIO_4$ (184 mg, 0.86 mmol) followed by $RuCl_3$ (8 mg, 30 μmol), and the resulting mixture was stirred for 5 d. The mixture was filtered through Celite and washed with EtOAc. The filtrate was concentrated under reduced pressure, and the residue was purified by flash chromatography eluting with 97:3 DCM/EtOAc followed by 100:10:0.5 DCM/MeOH/CH_3COOH to afford *the title compound* as a white solid (3.8 mg, 74%), plus recovered starting material (2.7 mg, 25%).

Data for **50**: R_f 0.1 (5:95:0.1 EtOAc/DCM/CH_3COOH); ^1H NMR (400 MHz, CD_3CN) δ 7.84–7.80 (m, 4H, phthalimide), 5.29–5.10 (m, 2H, C*H*F–C*H*F), 4.10–4.01 (m, 2H, CH_2); ^{19}F NMR (376 MHz, CD_3CN) δ −202.2 (m, 1F, Ph–CH*F*), −210.5 (m, 1F, C*H*F–CH$_2$); $^{19}F\{^1H\}$ NMR (376 MHz, CD_3CN) δ −202.2 (br s, 1F, Ph–CH*F*), −210.5 (br s, 1F, CHF–CH*F*); spectral data in accordance with literature values.[28]

*4.1.23. (2S,3R)-3-Fluoro-2-hydroxy-3-(4-nitrophenyl)propyl-4-methylbenzenesulfonate (**51**); (2R,3S)-2-(fluoromethyl)-3-(4-nitrophenyl)oxirane (**52**); (1R,2S)-1,3-difluoro-1-(4-nitrophenyl) propan-2-ol (**53**).* In an oven dried pressure flask, a mixture of epoxide **44** (60.0 mg, 0.17 mmol) and $Et_3N\cdot 3HF$ (2.8 mL) was stirred for 16 h at 100 °C. The reaction mixture was cooled to room temperature, diluted with DCM (50 mL) and quenched with saturated aqueous $NaHCO_3$ at 0 °C. The organic layer was washed with water (3×30 mL), dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash chromatography eluting with 80:20 hexane/EtOAc to afford compound **51** as a white solid (2.0 mg, 3%), plus compound **52** as a white solid (3.5 mg, 5%), plus compound **53** as a white solid (5.4 mg, 15%).

Data for **51**: R_f 0.33 (EtOAc/hexane 80:20); IR (solution in DCM) ν_{max} (cm^{-1}) 3520, 2954, 1600, 1523, 1348, 1175, 1096, 990, 815; ^1H NMR (600 MHz, CD_3CN) δ 8.19 (d, *J*=8.5 Hz, 2H, $C_6H_4NO_2$), 7.77 (d, *J*=8.1 Hz, 2H, $C_6H_4CH_3$), 7.54 (d, *J*=8.5 Hz, 2H, $C_6H_4NO_2$), 7.43 (d, *J*=8.1 Hz, 2H, $C_6H_4CH_3$), 5.48 (dd, *J*=46.0, 5.8 Hz, 1H, C*H*F), 4.09 (m, 2H, CHOH–CH_2), 4.06 (m, 1H, C*H*OH–CH$_2$), 3.73 (d, *J*=5.8 Hz, 1H, CHO*H*), 2.45 (s, 3H, $C_6H_4CH_3$); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ 149.2 (O_2N–C), 146.7 (C–S), 144.6 (d, *J*=19.3 Hz, Ar*C*–CHF), 133.3 (Ar*C*–CH_3), 131.1 (*o*–$CH_3C_6H_4$), 128.9 (*m*–$CH_3C_6H_4$), 128.8 (d, *J*=7.4 Hz, *m*–$NO_2C_6H_4$), 124.3 (*o*–$NO_2C_6H_4$), 92.7 (d, *J*=175.3 Hz, *C*HF), 71.5 (dd, *J*=26.7 Hz, *C*HOH), 71.1 (d, *J*=4.2 Hz, CHO–*C*H$_2$–OTs), 21.8 (*C*H$_3$); ^{19}F NMR (564 MHz, $CDCl_3$) δ −188.8 (dd, *J*=46.0, 11.0 Hz, 1F, Ph–CH*F*), $^{19}F\{^1H\}$ NMR (282 MHz, $CDCl_3$) δ −188.8 (s, 1F, Ph–CH*F*); HRMS (ESI, +ve) $C_{16}H_{16}FNO_6SNa^+$ $[M+Na^+]$ requires *m/z* 392.0575, found 392.0570.

Data for **52**: R_f 0.40 (80:20 EtOAc/hexane); IR (solution in DCM) ν_{max} (cm^{-1}) 3495, 3114, 2963, 1741, 1603, 1518, 1459, 1350, 1250, 1109, 984, 858, 763; ^1H NMR (300 MHz, $CDCl_3$) δ 8.23 (d, *J*=8.7 Hz, 2H, $C_6H_4NO_2$), 7.47 (d, *J*=8.7 Hz, 2H, $C_6H_4NO_2$), 4.75 (ddd, *J*=47.6, 11.0, 2.6 Hz, 1H, C*H*H), 4.57 (ddd, *J*=47.6, 11.0, 4.7 Hz, 1H, CH*H*), 3.99 (br s, 1H, $O_2NC_6H_4$–C*H*O), 3.30 (dddd, *J*=14.1, 4.7, 2.6, 2.1 Hz, 1H, C*H*O–CH$_2$); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 148.2 (C–NO_2), 143.7 (*C*–CHO), 126.6 (ArC), 124.1 (ArC), 81.6 (d, *J*=173.1 Hz, CH$_2$–F), 60.4 (d, *J*=23.3 Hz, *C*HO–CH$_2$), 54.5 (d, *J*=8.3 Hz, $O_2NC_6H_4$–*C*HO); ^{19}F NMR (282 MHz, $CDCl_3$) δ −229.5 (dt, *J*=47.3, 14.3 Hz, 1F); $^{19}F\{^1H\}$

NMR (282 MHz, $CDCl_3$) δ −229.5 (s, 1F); HRMS (ESI, +ve) $C_9H_8FNO_3Na^+$ [M+Na^+] requires *m/z* 220.0380, found 220.0381.

Data for **53**: R_f 0.43 (80:20 EtOAc/hexane); IR (solution in DCM) ν_{max} (cm^{-1}) 3361, 2958, 1605, 1519, 1344, 1290, 1203, 1106, 1011, 734; ^1H NMR (300 MHz, $CDCl_3$) δ 8.28 (d, *J*=8.9 Hz, 2H, $C_6H_4NO_2$), 7.59 (d, *J*=8.9 Hz, 2H, $C_6H_4NO_2$), 5.55 (dd, *J*=45.8, 6.9 Hz, 1H, C*H*F), 4.70 (dddd, *J*=25.0, 14.9, 5.0, 2.1 Hz, 1H, C*H*H), 4.54 (dddd, *J*=24.8, 14.9, 5.0, 2.1 Hz, 1H, CH*H*), 4.13 (m, 1H, C*H*OH−CH_2), 2.26 (d, *J*=6.1 Hz, 1H, CHO*H*); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 148.4 (O_2N−C), 143.3 (d, *J*=19.2 Hz, ArC−CHF), 127.4 (d, *J*=7.5 Hz, *m*−$NO_2C_6H_4$), 123.9 (d, *J*=8.9 Hz, *o*−$NO_2C_6H_4$), 91.3 (dd, *J*=177.5, 6.6 Hz, *C*HF), 82.9 (dd, *J*=170.1, 4.5 Hz, *C*H_2), 72.3 (dd, *J*=26.8, 19.3 Hz, *C*HOH); ^{19}F NMR (282 MHz, $CDCl_3$) δ −189.7 (dd, *J*=46.0, 9.9 Hz, 1F, CH*F*), −236.2 (dt, *J*=46.7, 19.9 Hz, 1F, CH_2F); $^{19}F\{^1H\}$ NMR (282 MHz, $CDCl_3$) δ −189.7 (s, 1F, CH*F*), −236.2 (s, 1F, CH_2F); HRMS (ESI, +ve) $C_9H_9F_2NO_3Na^+$ [M+Na^+] requires *m/z* 240.0443, found 240.0439.

*4.1.24. 2-(((4R,5S)-5-(4-Nitrophenyl)-2,2-dioxido-1,3,2-dioxathiolan-4-yl)methyl) isoindoline-1,3-dione (**54**).* Diol **47** (500 mg, 1.46 mmol) was dissolved in DCM (15 mL) and the solution was cooled to 0 °C. Pyridine (0.35 mL, 4.4 mmol) and thionyl chloride (0.21 mL, 2.9 mmol) were then added dropwise, and the resulting mixture stirred for 30 min. Saturated aqueous $CuSO_4$ (20 mL) was added and stirring continued for a further 15 min prior to extraction with DCM (3×15 mL). The combined organic layers were dried and concentrated under reduced pressure to yield a pale yellow film. The residue was redissolved in acetonitrile (10 mL) and DCM (10 mL) and cooled to 4 °C to produce a deep red solution. A solution of $RuCl_3$ (5 mg, 20 μmol) dissolved in water (10 mL) was added, followed by sodium metaperiodate (624 mg, 2.92 mmol). The mixture was stirred for 5 min at 0 °C before addition of diethyl ether (80 mL) and washing with water (80 mL), saturated $NaHCO_3$ (2×80 mL) and brine (2×80 mL). The organic layer was dried ($NaSO_4$) and concentrated to yield *the title compound* as a white foam (446 mg, 76%), which was carried onto the next step without purification or characterization.

*4.1.25. 2-((2R,3R)-3-Fluoro-2-hydroxy-3-(4-nitrophenyl)propyl)isoindoline-1,3-dione (**55**); 2-(3-(4-Nitrophenyl)-3-oxopropyl)isoindoline-1,3-dione (**56**).* A mixture of compound **54** (446 mg, 1.06 mmol), TBAF (1 M solution in THF, 2.59 mL, 2.59 mmol) and anhydrous acetonitrile (23 mL) was stirred at 0 °C for 1 h. The mixture was concentrated to yield a brown oil. This residue was redissolved in a mixture of concentrated sulfuric acid (0.44 mL), water (80 μL) and THF (80 mL) and the resultant solution was stirred at room temperature overnight. The reaction was quenched with brine (50 mL) and water (50 mL), and then extracted with DCM (100 mL, 50 mL). The combined organic layers were dried ($MgSO_4$) and concentrated onto silica. The crude product was subjected to flash chromatography eluting with 4:1 hexane/EtOAc to give compound **55** as a white solid (167 mg, 41%), compound **56** as a white solid (66 mg, 16%) and a mixture of compounds **60a** and **60b** as transparent needles (9.8 mg, 3%).

Data for **55**: R_f 0.31 (4:1 hexane/EtOAc); $[\alpha]_D$ −11 (*c* 0.14, CH_3CN); mp 158–160 °C; IR (neat) ν_{max} (cm^{-1}) 3471, 1767, 1699, 1519, 1342, 794; ^1H NMR (300 MHz, $CDCl_3$) δ 8.30–8.20 (m, 2H, Ph), 7.90–7.70 (m, 4H, phthalimide), 7.60–7.50 (m, 2H, Ph), 5.63 (dd, *J*=46.2, 3.4 Hz, 1H, CHF), 4.35–4.21 (m, 1H, C*H*OH), 3.97–3.95 (m, 2H, CH_2); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ 168.0 (C=O), 147.6 (C−NO_2), 143.7 (d, *J*=20.8 Hz, Ph*C*−CF), 133.8 (ArC), 131.7 (ArC), 126.9 (d, *J*=8.0 Hz, ArC), 123.1 (ArC), 122.9 (ArC), 92.7 (d, *J*=179.5 Hz, C−F), 70.5 (d, *J*=21.2 Hz, C−OH), 40.2 (d, *J*=5.0 Hz, CH_2); ^{19}F NMR (282 MHz, $CDCl_3$) δ −196.1 (dd, *J*=45.7, 20.6 Hz, 1F); $^{19}F\{^1H\}$ NMR (282 MHz, $CDCl_3$) δ −196.1 (s, 1F); HRMS (ESI, +ve) $C_{17}H_{14}FN_2O_5^+$ [M+H^+] requires *m/z* 345.0881, found 345.0833.

Data for **56**: R_f 0.44 (4:1 hexane/EtOAc); mp 166–168 °C; IR (neat) ν_{max} (cm^{-1}) 2942, 1767, 1702, 1517, 1344, 988, 853, 761; ^1H NMR (300 MHz, $CDCl_3$) δ 8.09–7.87 (m, 4H, phthalimide), 7.86–7.72 (m, 4H, Ph), 4.19–4.14 (m, 2H, $COCH_2$), 3.50–3.45 (m, 2H, CH_2); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 196.1 (Ph−C=O), 168.5 (N−C=O), 150.9 (C−NO_2), 141.0 (Ph*C*−CO), 134.5 (ArC), 134.5 (ArC), 129.4 (ArC), 124.3 (ArC), 123.7 (ArC), 37.7 (CO−CH_2), 33.6 (CH_2−Pht); HRMS (ESI, +ve) $C_{17}H_{12}N_2O_5Na^+$ [M+Na^+] requires *m/z* 347.0638, found 347.0635.

*4.1.26. 2-((2S,3R)-2,3-Difluoro-3-(4-nitrophenyl)propyl)isoindoline-1,3-dione (**57**); (Z)-2-(3-fluoro-3-(4-nitrophenyl)allyl)isoindoline-1,3-dione (**41**).* Neat DeoxoFluor® (0.107 mL, 0.581 mmol) was added to fluorohydrin **55** (20 mg, 0.058 mmol) and the mixture was stirred at 80 °C in a sealed plastic reaction vessel overnight. The mixture was cooled to 0 °C, diluted with DCM (3.5 mL) and quenched with saturated aqueous $NaHCO_3$ (5 mL). The aqueous layer was extracted with DCM (2×10 mL). The combined organic layers were dried ($MgSO_4$) and concentrated, and the residue was subjected to flash chromatography eluting with 4:1 hexane/EtOAc to yield compound **57** as a yellow oil (9.0 mg, 45%) plus compound **41** as a white solid (3.8 mg, 20%).

Data for **57**: R_f 0.21 (4:1 hexane/EtOAc); $[\alpha]_D$ +0.26 (*c* 0.16, CH_3CN); IR (neat) ν_{max} (cm^{-1}) 1774, 1715, 1524, 1391, 1347; ^1H NMR (300 MHz, $CDCl_3$) δ 8.27–8.24 (m, 2H, Ph), 7.86–7.72 (m, 4H, phthalimide), 7.64–7.61 (m, 2H, Ph), 5.71 (ddd, *J*=45.9, 12.6, 4.6 Hz, 1H, α−CHF), 5.12 (ddddd, *J*=47.0, 15.3, 8.0, 4.6, 4.4 Hz, 1H, β−CHF), 4.15 (dddd, *J*=14.6, 13.0, 8.0, 1.0 Hz, 1H, C*H*H), 3.93 (dddd, *J*=25.9, 14.6, 4.4, 0.8 Hz, 1H, CH*H*); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 167.9 (N−C=O), 148.5 (C−NO_2), 141.4 (dd, *J*=20.0, 4.0 Hz, Ph*C*−CF), 134.5 (ArC), 131.8 (ArC), 127.2 (d, *J*=8.0 Hz, ArC), 124.0 (ArC), 123.7 (ArC), 91.2 (dd, *J*=181.7, 24.0 Hz, Ph−CF), 89.7 (dd, *J*=183.1, 26.4 Hz, *C*F−CH_2), 38.0 (dd, *J*=25.1, 6.0 Hz, CH_2); ^{19}F NMR (282 MHz, $CDCl_3$) δ −194.1 (ddd, *J*=45.9, 16.2, 16.2 Hz, 1F), −195.3 (m, 1F); $^{19}F\{^1H\}$ NMR (282 MHZ, $CDCl_3$) δ −194.1 (d, *J*=16.2 Hz, 1F), −195.3 (d, *J*=16.2 Hz, 1F); HRMS (ESI, +ve) $C_{17}H_{12}F_2N_2O_4^+$ [M+H^+] requires *m/z* 347.0838, found 347.0836.

Data for **41**: R_f 0.31 (4:1 hexane/EtOAc); mp 98–100 °C; IR (neat) ν_{max} (cm^{-1}) 1708, 1511, 1397, 1325; ^1H NMR (300 MHz, $CDCl_3$) δ 8.36–8.18 (m, 2H, Ph), 7.92–7.71 (m, 4H, phthalimide), 7.71–7.58 (m, 2H, Ph), 5.79 (ddd, *J*=35.2, 7.3, 7.1 Hz, 1H, CFC*H*), 4.62 (dd, *J*=7.1, 1.8 Hz, 2H, CH_2); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 168.1 (C=O), 148.5 (C−NO_2), 137.8 (ArC), 134.5 (ArC), 132.4 (ArC), 125.6 (ArC), 124.3 (ArC), 123.9 (ArC), 104.5 (d, *J*=15.1 Hz, CF=*C*), 32.5 (d, *J*=7.5 Hz, CH_2); ^{19}F NMR (282 MHz, $CDCl_3$) δ −115.8 (d, *J*=35.2 Hz, 1F); $^{19}F\{^1H\}$ NMR (282 MHZ, $CDCl_3$) δ 115.8 (s, 1F); HRMS (ESI, +ve) $C_{17}H_{11}FN_2O_4Na^+$ [M+Na^+] requires *m/z* 349.0595, found 349.0597.

*4.1.27. N-(4-((1R,2S)-3-(1,3-Dioxoisoindolin-2-yl)-1,2-difluoropropyl)phenyl) acetamide (**58**).* Palladium on charcoal (10%, ~10 mg) was added to a solution of compound **57** (14.2 mg, 0.041 mmol) in freshly distilled acetic anhydride (4 mL). The mixture was stirred at room temperature under a balloon of H_2 gas for 6 h. The reaction mixture was filtered through a pad of Celite (EtOAc wash) and concentrated under reduced pressure. The residue was subjected to flash chromatography eluting with 95:5 DCM/EtOAc to yield *the title compound* as an off white solid (5.1 mg, 35%); R_f 0.20 (95:5 DCM/EtOAc); ^1H NMR (600 MHz, $CDCl_3$) δ 7.90–7.55 (m, 4H, phthalimide), 7.54–7.53 (m, 4H, Ph), 5.58 (ddd, *J*=45.9, 12.2, 4.6 Hz, 1H, Ph−CHF), 5.11 (ddddd, *J*=47.8, 13.8, 8.0, 4.6, 3.7 Hz, 1H, C*H*F−CH_2), 4.20 (dddd, *J*=14.8, 13.0, 8.0, 1.5 Hz, 1H, C*H*H), 3.92 (dddd, *J*=28.7, 14.8, 3.7, 0.8 Hz, 1H, CH*H*), 2.25 (s, CH_3); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ 168.0 (C=O), 140.1 (*C*−NHCOCH_3), 134.4 (ArC), 134.2 (ArC), 132.3 (ArC), 131.9 (ArC), 123.7 (ArC), 123.5 (ArC), 91.7 (dd, *J*=179.2, 21.8 Hz, Ph−CF), 90.1 (dd, *J*=182.3, 27.3 Hz, *C*F−CH_2), 37.9–37.6 (m, 1C, CH_2), 21.7 (CH_3); ^{19}F NMR (376 MHz, $CDCl_3$)

δ −191.2 (m, 1F), −195.6 (m, 1F); $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$) δ −191.2 (br s, 1F), −195.6 (d, J=16.3 Hz, 1F); HRMS (ESI, +ve) $C_{21}H_{19}F_2N_2O_5^+$ [M+AcOH+H^+] requires m/z 417.1262, found 417.1251.

*4.1.28. (2R,3S)-4-(1,3-Dioxoisoindolin-2-yl)-2,3-difluorobutanoic acid (**59**).*[28] Sodium metaperiodate (34 mg, 0.161 mmol) and ruthenium chloride hydrate (1 mg, 3.8 μmol) were added to a stirred mixture of **58** (3 mg, 0.008 mmol), DCM (0.2 mL), acetonitrile (0.2 mL) and water (0.4 mL). The resulting mixture was stirred at room temperature for 5 d. The mixture was filtered through a pad of Celite (EtOAc wash) and the filtrate was concentrated under reduced pressure. The residue was subjected to flash chromatography eluting with 90:9.5:0.5 DCM/MeOH/CH_3COOH to give *the title compound* as a pale brown oil (1 mg, 90%); R_f 0.1 (95:4.5:0.5 DCM/EtOAc/CH_3COOH); ^1H NMR (400 MHz, CD_3CN) δ 7.85–7.78 (m, 4H, phthalimide), 5.45–5.08 (m, 2H, CHF×2), 4.22–4.08 (m, 1H, C*H*H), 3.98–3.80 (m, 1H, CH*H*); $^{13}C\{^1H\}$ NMR (150 MHz, CD_3CN) δ 168.8 (C=O), 135.3 (phthalimide), 132.9 (phthalimide), 124.1 (phthalimide), 90.6 (dd, J=181.5, 21.3 Hz, HOOC−*C*HF), 88.9 (dd, J=188.6, 23.1 Hz, HFC−CH_2), 37.8 (dd, J=24.9, 9.1 Hz, CH_2), (1×C=O signal obscured); ^{19}F NMR (376 MHz, CD_3CN) δ −196.8 (m, 1F), −201.6 (m, 1F); $^{19}F\{^1H\}$ NMR (376 MHz, CD_3CN) δ −196.8 (d, J=14.1 Hz, 1F), −201.6 (m, 1F); spectral data in accordance with literature values.[28]

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Supplementary data

Reproductions of the NMR spectra of all new compounds, and further details of selected fluorination reaction trials, are provided as Supplementary data. This material is available free of charge via the Internet at http://dx.doi.org/10.1016/j.tet.2016.04.070.

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