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Direct, visible light-sensitized benzylic C–H fluorination of peptides using dibenzosuberenone: selectivity for phenylalanine-like residues

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Dedicated to Professor Gary H. Posner on the occasion of his retirement.

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ABSTRACT

A visible light-sensitized benzylic sp^3 C–H fluorination protocol using dibenzosuberenone (5 mol %) and Selectfluor® is optimized for the direct functionalization of phenylalanine-like residues in short chain peptides. Amino acids, dipeptides, and tripeptides undergo benzylic fluorination with remarkable regioselectivity in the presence of protected basic, acidic, and nonpolar side chains (including those with tertiary sites). Additionally, protecting group compatibility, a gram scale application, and competition experiments were explored.

1. Introduction

The typical procession of *synthetic method development* passes through three arenas: 1) reaction discovery, 2) optimization and mechanistic understanding, and 3) application. In the world of modern fluorine chemistry, our laboratory[1] and others[2] have discovered some of the first mild ways to effect 'radical fluorination' of sp^3 C–H bonds – transformations of high interest in the fields of medicine and agrochemistry (*arena* 1).[3] Significant strides have been made in producing and beginning to understand these reactions; however, greater selectivity and more tangible applications to the synthesis of biologically relevant molecules remain promising goals (*arenas* 2 *and* 3). Toward these efforts, we report a discrete photochemical method optimized for the site-selective fluorination of peptides.[4]

Historically, chemists have gone to great lengths to access β-fluorinated amino acids.[5] Recently, a few examples regarding direct C–H fluorination of individual amino acids have materialized in the chemical literature. For instance, palladium catalysis has proven valuable in ligand-directed syntheses of β-fluoro-α-amino acids.[6] To a much lesser extent, photochemical benzylic fluorination tactics have also emerged that include a single derivative of β-fluorophenylalanine in the substrate scope.[7] Given our interest in the latter approach, we asked: does the innate benzylic selectivity drop off when phenylalanine is incorporated into peptide chains (Fig. 1)? Would we observe competitive fluorination on the tertiary sites of valine[8] and leucine,[9] for example? To our satisfaction, we found that our newly-developed photochemical approach using Selectfluor®, catalytic dibenzosuberenone, and visible light (14-Watt CFL) is remarkably selective for the benzylic sites of phenylalanine- and tyrosine-like residues in short chain peptides that incorporate a variety of aliphatic and protected basic or acidic side chains.

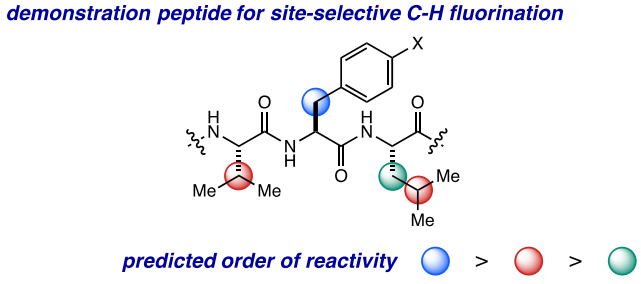

Fig. 1. Benzylic selectivity strategy toward 'directed' fluorination within peptide natural products.

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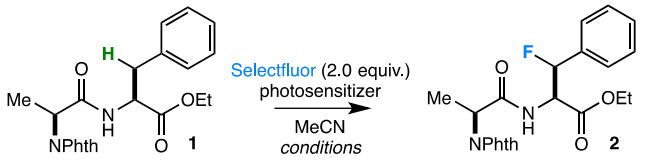
2. Results and discussion

Our initial screen included an evaluation of existing photochemical fluorination methods (developed in our laboratory[7b,10] and by others[11]) on a simple dipeptide – NPhth-Ala-Phe-OEt (**1**). Immediately, we found the methods that performed suitably in the fluorination of a single amino acid experienced a decline in product yield when applied to this dipeptide (Table 1). In some instances, increased loadings of the photosensitizers improved yields, but never above 50%. Accordingly, we expanded our survey to other potential ultraviolet and visible light photosensitizers. To our satisfaction, dibenzosuberenone[12] (5 mol %) and visible light from a 14-Watt CFL proved competent in the selective benzylic fluorination of NPhth-Ala-Phe-OEt using Selectfluor® (2.0 equiv) to provide **2** in 73% yield. We also noted that the diastereomeric ratio of the fluorinated product was ca. 2.1:1, regardless of photosensitizer.

Table 1
Photochemical fluorination optimized for dipeptides



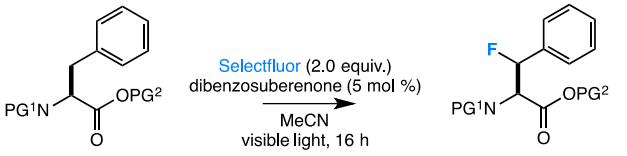
Entry	Photosensitizer	(mol %)	Light source	Yield (%)[a]
1	1,2,4,5-Tetracyanobenzene	5	300 nm	21
2		10	300 nm	33
3	Anthraquinone	10	300 nm	38
4		20	300 nm	42
5	1,4-Dicyanobenzene	10	300 nm	18
6		20	300 nm	42
7	1-Cyanonaphthalene	20	300 nm	trace
8	9,10-Phenanthrenequinone	10	300 nm	22
9		20	300 nm	21
10	Xanthone	10	300 nm	39
11		5	14-Watt CFL	39
12	2,7-Dichloro-9-fluorenone	10	300 nm	28
13		5	14-Watt CFL	29
14	9-Fluorenone	20	300 nm	10
15		5	14-Watt CFL	31
16	Benzophenone	20	300 nm	40
17		5	14-Watt CFL	46
18	2-Bromo-9-fluorenone	5	14-Watt CFL	22
19	2-Chlorothioxanthone	5	14-Watt CFL	28
20	**5-Dibenzosuberenone**	**5**	**14-Watt CFL**	**73[b]**

All reactions were irradiated in Pyrex microwave vials for 16 h while stirring, using either a 14-Watt CFL (visible light) or a Rayonet reactor (300 nm). In all cases, a 2.1:1 *dr* was observed. [a]Unless otherwise specified, ^{19}F NMR yields reported. [b]Isolated yield reported.

Control experiments revealed that 1) the reaction does not proceed in the absence of either light or dibenzosuberenone, 2) increasing the amount of Selectfluor® or dibenzosuberenone begins to have a negative impact on yield (though Selectfluor® may be decreased to 1.5 equiv in some cases with only a 5–10% decrease in yield), and 3) some benzylic fluorination is observed by heating the reaction mixture to reflux in the dark, albeit in poor yield (25%).[13] Furthermore, most photochemical fluorination methods require inert atmosphere, but this approach performs equally well in ambient air. Although anhydrous MeCN was used, rigorous exclusion of air and moisture (e.g., by degasification and Schlenck techniques) proved unnecessary – a testament to the robustness of the protocol.

Subsequently, we turned our attention to the scope of *N*- and *C*-termini protecting groups using phenylalanine derivatives (Table 2). Protecting group strategies are invaluable in peptide synthesis and may also be necessary to maintain compatibility with photochemical fluorination.[14] For instance, basic nitrogen sites have been particularly problematic in sp^3 C–H fluorination methods;[15] however, this may be circumvented through the installation of electron-withdrawing groups. Along these lines, phthalimido[16] (NPhth) and trifluoroacetate[17] (TFA) substituents at the N-terminus provided the best results (80% and 67%), and acetate groups were also competent (57%). On the other hand, Boc, Fmoc, and Cbz groups were not compatible with fluorination (0–10% yield). At the C-terminus, methyl and ethyl esters perform equally well,[18] but *tert*-butyl, trityl, and adamantyl esters decompose or undergo additional fluorination under the reaction conditions (accompanied with a decrease in yield). Moreover, we found that the C-terminus does not require a protecting group – photochemical benzylic fluorination can be achieved in good yields in the presence of carboxylic acids without competitive decarboxylative fluorination.[19]

Table 2
Protecting group compatibility



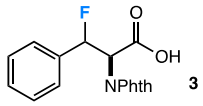
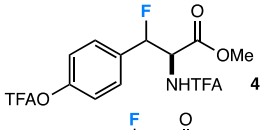
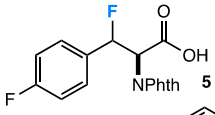
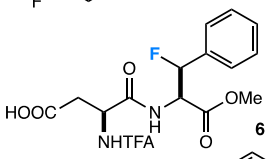
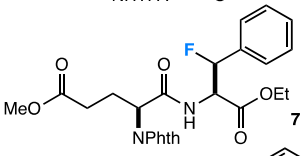
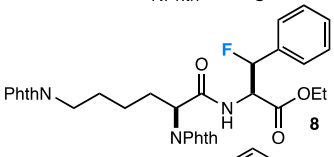
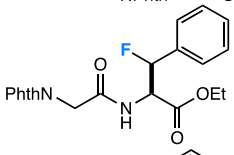
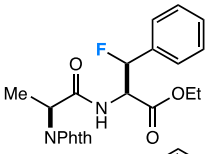
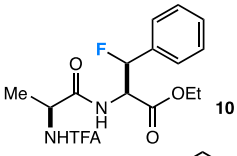
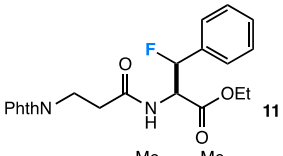
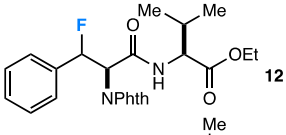
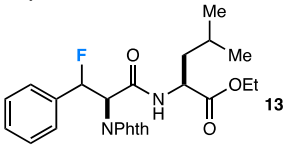
Entry	PG^1	PG^2	Yield (%)[a]
1	*tert*-butyloxycarbonyl (Boc)	-	10
2	fluorenylmethyloxycarbonyl (Fmoc)	-	0
3	carboxybenzyl (Cbz)	-	8
4	acetyl (Ac)	-	57
5	**trifluoroacetyl (TFA)**	**-**	**67**
6	**trifluoroacetyl (TFA)**	**methyl (Me)**	**74**
7	**trifluoroacetyl (TFA)**	**ethyl (Et)**	**60**
8	**phthalimide (Phth)**	**-**	**80[b]**
9	-	-	0
10	**phthalimide (Phth)**	**methyl (Me)**	**78**
11	**phthalimide (Phth)**	**ethyl (Et)**	**80**
12	phthalimide (Phth)	*tert*-butyl (*t*-Bu)	31
13	phthalimide (Phth)	trityl (Trt)	28
14	phthalimide (Phth)	1-adamantane (Ada)	20

[a]Unless otherwise specified, ^{19}F NMR yields reported. [b]Isolated yield reported.

In addition to phenylalanine, we envisioned that other benzylic residues could be targeted, such as tyrosine or other non-natural amino acids. The hydroxy substituent on tyrosine activates the aromatic ring toward background EAS with Selectfluor®, which substantially diminishes selectivity and the extent of benzylic fluorination.[20] Acetylation reduces ring fluorination, but still results in poor desired product yields. However, transformation of the hydroxy substituent to a trifluoroacetyl group makes tyrosine residues viable candidates for direct benzylic fluorination (71% yield).[21] What is more, the phthalimide-protected *p*-fluoro-phenylalanine, an isoelectronic and isosteric replacement for tyrosine, underwent benzylic fluorination in 84% yield (Table 3).

At this juncture, we had established a visible light protocol on a prototypical dipeptide, determined the compatibility of an array of protecting groups, and investigated the viability of other phenylalanine-like residues as targets for benzylic fluorination (**3**, **4**, and **5**). The next step was to examine the regioselectivity and reaction efficiency in the presence of other amino acids. Thus, we

Table 3
Substrate scope: phenylalanine-like residues targeted for fluorination in amino acids and dipeptides

Entry	Product	dr	Yield (%)[a]
1	 **3**	1.2:1	80[b]
2	 **4**	1.4:1	71[c,d]
3	 **5**	1.2:1	84[b]
4	 **6**	1.8:1	78[b]
5	 **7**	2.1:1	71[c,d]
6	 **8**	2.2:1	61[c,d]
7	 **9**	3:1	69[c,d] **52**[d,e] gram scale
8	 **2**	2.1:1	73[c,d]
9	 **10**	2.1:1	67[b]
10	 **11**	2:1	47[b]
11	 **12**	1.4:1	62[d]
12	 **13**	1.2:1	65[d]

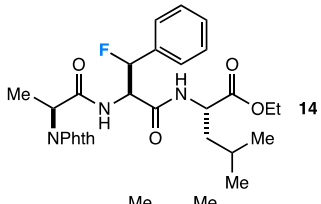
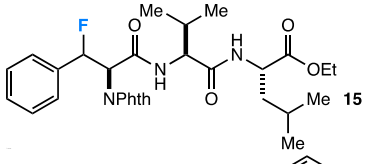
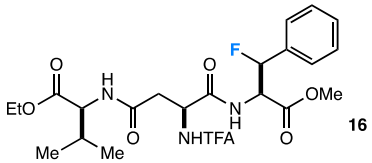
[a]Unless otherwise specified, isolated yields reported. [b]Isolated as a mixture of diastereomers. [c]Major diastereomer isolated. [d]^{19}F NMR yield reported for both diastereomers. [e]Major diastereomer isolated in 40% yield.

explored a number of dipeptides incorporating one phenylalanine-like residue (Table 3).[22] Consistent with our protecting group screen, dipeptides with carboxylic acid side chains (i.e., aspartic acid in TFA-Aspartame and glutamic acid methyl ester in NPhth-Glu-(OMe)-Phe-OEt) were competent in regioselective fluorination (**6** and **7**). Likewise, dipeptides with basic amine side chains were amenable to fluorination (**8**) after applying the same protecting group strategy discussed above (e.g., NPhth-Lys-(NPhth)-Phe-OEt). In both instances (acidic and basic side chain derivatives), benzylic fluorination was nearly site-specific; that is, only trace secondary aliphatic or α-fluorination was observed, if at all.

When it comes to nonpolar amino acids, glycine, alanine, and β-alanine derivatives intuitively are not susceptible to regioselectivity issues (**2**, **9**–**11**). Yet, valine, leucine, and isoleucine all contain tertiary sites that could conceivably compete with benzylic fluorination, assuming a radical-based mechanism.[23] (In fact, photochemical fluorination of the tertiary C–H site in valine has been reported in the literature.[8]) Fortuitously, benzylic fluorination is preferred over tertiary fluorination by more than an order of magnitude (**12** and **13**), with only 4% and trace yield of the tertiary fluoride on **12** and **13**, respectively. This is particularly exciting as NPhth-Val-OH undergoes tertiary fluorination in up to 73% yield under identical reaction conditions when not associated with phenylalanine.

We also extended our scope to a few phenylalanine-containing tripeptides (Table 4). For instance, NPhth-Ala-Phe-Leu-OEt displayed similar propensity toward benzylic fluorination as the dipeptides, providing the desired product **14** in 63% yield and high regioselectivity. Also, in the presence of both valine and leucine in NPhth-Phe-Val-Leu-OEt, the benzylic site of phenylalanine is still highly favored for C–H fluorination (**15**).

Table 4
Regioselective fluorination showcased in tripeptides

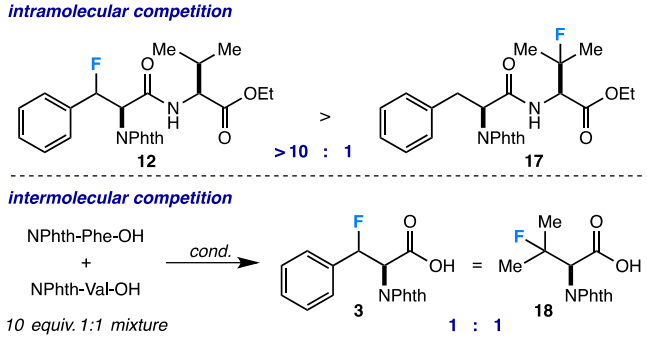
Entry	Product	dr	Yield (%)
1	 **14**	1.3:1	63[a,b]
2	 **15**	1.4:1	34[c]
3	 **16**	1.8:1	42[c]

[a]Isolated yield reported. [b]Isolated as a mixture of diastereomers. [c]^{19}F NMR yield reported.

In general, the diastereoselectivity of the fluorination reactions on amino acids and dipeptides was low (≤3:1 dr), but diastereomers were often separable by column chromatography. Regarding the tripeptides, individual fluorinated diastereomers were particularly difficult to isolate from starting material by standard column chromatography. This can be remedied, to some

extent, by resubmitting the crude reaction mixture (after workup) to the same reaction conditions, thus driving the reaction near complete conversion. However, difluorination of valine-containing peptides (i.e., at the benzylic and tertiary sites) becomes prevalent upon resubmission.

To explore the benzylic selectivity over tertiary sites further, we conducted intra- and intermolecular competition experiments between phenylalanine and valine residues (Scheme 1).[24] Under the reaction conditions, the valine- and phenylalanine-containing dipeptide, in an intramolecular competition, underwent fluorination at the benzylic position (**12**) in a ratio >10:1 over the tertiary site (**17**) by ^{19}F NMR analysis of the crude reaction mixture. On the other hand, a 1:1 mixture of phenylalanine and valine in an intermolecular competition experiment provided a somewhat unexpected result – a 1:1 mixture of benzylic:tertiary fluorinated products (**3**:**18**). Likely, there is a product-determining step that ensues the rate-determining step in the dipeptide.[25] This feature would be the culprit for our ability to target benzylic residues in small peptides, even in the presence of 'equally reactive' tertiary sites.



Scheme 1. Competition experiments.

3. Conclusion

In all, we have found that Selectfluor® (2.0 equiv), catalytic dibenzosuberenone (5 mol %), and visible light (14-Watt CFL) provide suitable photochemical conditions for the direct, sp^3 benzylic C–H fluorination of phenylalanine-like residues in amino acids and short chain peptides. Protecting group compatibility was explored at both the *C*- and *N*-termini, and the propensity for benzylic fluorination was studied in the presence of amino acids with protected basic, acidic, and nonpolar side chains (including those with tertiary sites). Despite the near equal reactivity of benzylic and tertiary sites, as shown in an intermolecular competition experiment, the benzylic sites in dipeptides and tripeptides were observed to favor C–H fluorination by over an order of magnitude.

4. Experimental section

4.1. General procedure for photochemical fluorination of peptides

The substrate (0.25 mmol), Selectfluor® (177 mg, 0.5 mmol), dibenzosuberenone (3.0 mg, 0.01 mmol), and anhydrous MeCN (3 mL) were added to an oven-dried microwave vial equipped with a stir bar under ambient air; the vial was then sealed with a septum to prevent solvent evaporation. The reaction mixture was stirred and irradiated with visible light (14-Watt CFL) for 16 h. At this time, 0.3 mL aliquots were taken for ^{19}F NMR analysis, while the remainder of the reaction mixture was diluted with Et_2O, filtered through Celite, and concentrated. Products were purified as individual diastereomers (compounds **2**, **4**, **7**, **8**, and **9**) or as mixtures of diastereomers via gradient column chromatography using a CombiFlash® Rf+Lumen™ either on silica gel eluting with 100:0 hexanes:EtOAc to 0:100 hexanes:EtOAc or on C18 eluting with 10:90 MeCN:H_2O to 100:0 MeCN:H_2O.

*4.1.1. Ethyl (2R)-2-((S)-2-(1,3-dioxoisoindolin-2-yl)propana-mido)-3-fluoro-3-phenylpropanoate (**2**).* Following the general procedure and workup, the major diastereomer of **2** was isolated (70 mg, 49%) as a colorless oil (both diastereomers in 73% yield by ^{19}F NMR). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.85–7.82 (2H, m), 7.76–7.72 (2H, m), 7.28–7.21 (5H, m), 6.71 (1H, d, *J*=8.9 Hz), 6.04 (1H, dd, *J*=45.3, 2.5 Hz), 5.08 (1H, ddd, *J*=30.6, 9.0, 2.6 Hz), 4.84 (1H, q, *J*=7.4 Hz), 4.25 (2H, q, *J*=7.1 Hz), 1.61 (3H, d, *J*=7.4 Hz), 1.28 (3H, t, *J*=7.0 Hz); ^{13}C NMR (400 MHz, $CDCl_3$): δ 169.1, 168.5, 168.4, 167.6, 135.3, 135.1, 134.2, 131.7, 128.64, 128.63, 128.34, 128.33, 125.0, 124.9, 123.5, 92.7 (d, *J*=179.1 Hz), 62.2, 56.6 (d, *J*=22.5 Hz), 49.4, 14.9, 14.0; ^{19}F NMR (300 MHz, $CDCl_3$): δ –194.0 (1F, dd, *J*=45.9, 31.0 Hz).

*4.1.2. (2R)-2-(1,3-Dioxoisoindolin-2-yl)-3-fluoro-3-phenylpropanoic acid (**3**).* Following the general procedure and workup, **3** was isolated (63 mg, 80%) as a yellow oil (mixture of diastereomers). ^{1}H NMR (400 MHz, CD_3CN): δ 7.85–7.79 (2H, m), 7.74–7.69 (2H, m), 7.44–7.39 (1H, m), 7.37–7.30 (2H, m), 7.28–7.20 (2H, m), 6.36–6.20 (1H, m), 5.33–5.21 (1H, m); ^{13}C NMR (400 MHz, CD_3CN): δ 168.7, 168.0, 167.5, 137.8, 137.6, 137.0, 136.7, 136.5, 135.8, 135.7, 132.2, 131.9, 130.4, 130.38, 129.97, 129.95, 129.4, 129.3, 127.9, 127.8, 127.5, 127.4, 124.4, 124.3, 91.8 (d, *J*=175.1 Hz), 91.3 (d, *J*=178.8 Hz), 56.4 (d, *J*=23.2 Hz), 55.1 (d, *J*=35.8 Hz); ^{19}F NMR (300 MHz, CD_3CN): δ –170.4 (1F, dd, *J*=46.5, 15.5 Hz), –180.6 (1F, dd, *J*=45.9, 19.5 Hz).

*4.1.3. Methyl (2R)-3-fluoro-2-(2,2,2-trifluoroacetamido)-3-(4-(2,2,2-trifluoroacetoxy)phenyl)propanoate (**4**).* Following the general procedure and workup, the major diastereomer of **4** was isolated (59 mg, 41%) as a pale yellow solid (both diastereomers in 71% yield by ^{19}F NMR); mp 140–143 °C. ^{1}H NMR (400 MHz, CD_3CN): δ 8.12 (1H, d, *J*=9.3 Hz), 7.54–7.50 (2H, m), 7.36–7.32 (2H, m), 6.24 (1H, dd, *J*=44.6, 3.2 Hz), 5.11 (1H, ddd, *J*=30.4, 9.3, 3.0 Hz), 3.79 (3H, s); ^{13}C NMR (400 MHz, CD_3CN): 170.1, 167.38, 167.35, 157.1, 156.8, 155.8, 155.4, 149.6, 136.0, 134.8, 134.6, 130.8, 127.5, 127.4, 120.9, 91.5 (d, *J*=178.4 Hz), 56.8 (d, *J*=22.1 Hz), 52.8; δ ^{19}F NMR (300 MHz, CD_3CN): δ –75.1 (3F, s), –75.6 (3F, s), –190.5 (1F, dd, *J*=44.7, 31.0 Hz).

*4.1.4. (2R)-2-(1,3-Dioxoisoindolin-2-yl)-3-fluoro-3-(4-fluoro-phenyl) propanoic acid (**5**).* Following the general procedure and workup, **5** was isolated (70 mg, 84%) as a yellow oil (mixture of diastereomers). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.90 (1H, s), 7.83–7.77 (1H, m), 7.72–7.60 (3H, m), 7.42–7.24 (2H, m), 7.01–6.94 (1H, m), 6.91–6.82 (1H, m), 6.35–6.15 (1H, m), 5.29–5.18 (1H, m); ^{13}C NMR (400 MHz, $CDCl_3$): 171.1, 170.0, 167.2, 166.7, 164.27, 164.25, 164.1, 161.8, 161.78, 161.7, 134.37, 134.35, 131.3, 130.9, 128.9, 128.86, 128.83, 128.8, 128.7, 128.63, 128.55, 127.2, 123.7, 123.6, 115.5, 115.3, 90.1 (d, *J*=177.3 Hz), 89.3 (d, *J*=179.1 Hz), 55.9, 55.7, 54.6, 54.2; ^{19}F NMR (300 MHz, $CDCl_3$): δ –110.7 (3F, m), –111.5 (3F, m), –168.1 (1F, dd, *J*=46.5, 14.3 Hz), –177.7 (1F, dd, *J*=47.0, 14.9 Hz).

*4.1.5. (S)-4-(((2R)-1-Fluoro-3-methoxy-3-oxo-1-phenylpropan-2-yl) amino)-4-oxo-3-(2,2,2-trifluoroacetamido)butanoic acid (**6**).* Following the general procedure and workup, **6** was isolated (80 mg, 78%) as a colorless oil (mixture of diastereomers). ^{1}H NMR (400 MHz, CD_3CN): δ 7.91–7.80 (1H, m), 7.42–7.32 (5H, m), 7.18–7.11 (1H, m), 6.13–5.79 (1H, m), 5.04–4.91 (1H, m), 4.75–4.65 (1H, m), 3.74–3.66 (3H, m), 2.83–2.77 (1H, m), 2.72–2.65 (1H, m); ^{13}C NMR (400 MHz,

CD_3CN): δ 172.1, 172.0, 170.0, 169.9, 169.83, 169.76, 169.5, 169.4, 158.0, 157.9, 157.6, 157.5, 136.8, 136.6, 136.5, 136.3, 130.09, 130.08, 129.78, 129.77, 129.5, 129.4, 127.0, 126.9, 126.63, 126.56, 93.5 (d, *J*=176.9 Hz), 93.3 (d, *J*=178.4 Hz), 57.8 (d, *J*=23.6 Hz), 53.5 (d, *J*=35.8 Hz), 50.9, 50.8, 35.53, 35.45; ^{19}F NMR (300 MHz, CD_3CN): δ −175.9 (3F, s), −185.0 (1F, dd, *J*=45.3, 16.1), −190.4 (1F, dd, *J*=45.3, 29.8 Hz).

*4.1.6. Methyl (S)-4-(1,3-dioxoisoindolin-2-yl)-5-(((2R)-1-ethoxy-3-fluoro-1-oxo-3-phenylpropan-2-yl)amino)-5-oxopentanoate (**7**).* Following the general procedure and workup, the major diastereomer of **7** was isolated (82 mg, 48%) as a colorless oil (both diastereomers in 71% yield by ^{19}F NMR). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.84–7.82 (2H, m), 7.75–7.30 (2H, m), 7.28–7.16 (5H, m), 7.08–7.06 (1H, m), 6.04 (1H, dd, *J*=45.3, 2.5 Hz), 5.07 (1H, ddd, *J*=31.1, 9.2, 2.6 Hz), 4.77 (1H, t, *J*=7.8 Hz), 4.22 (2H, q, *J*=7.1 Hz), 3.60 (3H, s), 2.45–2.40 (2H, m), 2.31–2.14 (2H, m), 1.24 (3H, m); ^{13}C NMR (400 MHz, $CDCl_3$): δ 172.6, 168.4, 168.3, 168.2, 167.7, 135.3, 135.1, 134.4, 134.3, 131.4, 129.2, 128.53, 128.52, 124.93, 124.85, 123.6, 92.7 (d, *J*=179.5 Hz), 62.1, 56.6 (d, *J*=22.1 Hz), 53.6, 51.7, 30.5, 24.0, 13.94; ^{19}F NMR (300 MHz, $CDCl_3$): δ −192.6 (1F, dd, *J*=45.3, 31.0 Hz).

*4.1.7. Ethyl (2R)-2-((S)-2,6-bis(1,3-dioxoisoindolin-2-yl)hexanamido)-3-fluoro-3-phenylpropanoate (**8**).* Following the general procedure and workup, the major diastereomer of **8** was isolated (103 mg, 42%) as a colorless oil (both diastereomers in 61% yield by ^{19}F NMR). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.84–7.813 (2H, m), 7.811–7.78 (2H, m), 7.76–7.73 (2H, m), 7.70–7.67 (2H, m), 7.30–7.25 (5H, m), 7.19–7.16 (1H, m), 6.07 (1H, dd, *J*=45.4, 2.5 Hz), 5.08 (1H, ddd, *J*=31.5, 9.1, 2.5 Hz), 4.68 (1H, dd, *J*=9.8, 6.4 Hz), 4.30–4.18 (2H, m), 3.58 (2H, t, *J*=7.3 Hz), 2.42–1.97 (3H, m), 1.75–1.54 (3H, m), 1.23 (3H, t, *J*=7.2 Hz); ^{13}C NMR (400 MHz, $CDCl_3$): δ 171.1, 168.6, 168.41, 168.38, 168.2, 167.9, 135.4, 135.2, 134.3, 133.8, 132.0, 131.5, 129.2, 128.6, 128.37, 128.35, 128.34, 125.0, 124.9, 123.6, 123.1, 92.7 (d, *J*=179.1 Hz), 62.1, 56.6 (d, *J*=22.9 Hz), 54.8, 37.3, 28.1, 27.8, 23.4, 14.0; ^{19}F NMR (300 MHz, $CDCl_3$): δ −193.1 (1F, dd, *J*=45.3, 31.0 Hz).

*4.1.8. Ethyl (2R)-2-(2-(1,3-dioxoisoindolin-2-yl)acetamido)-3-fluoro-3-phenylpropanoate (**9**).* Following the general procedure and workup, the major diastereomer of **9** was isolated (75 mg, 52%) as a white solid (both diastereomers in 69% yield by ^{19}F NMR); mp 172–176 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.90–7.84 (2H, m), 7.76–7.70 (2H, m), 7.35–7.25 (5H, m), 6.54 (1H, d, *J*=9.2 Hz), 6.00 (1H, dd, *J*=45.2, 2.7 Hz), 5.08 (1H, ddd, *J*=29.3, 9.1, 2.8 Hz), 4.38–4.23 (4H, m), 1.29 (3H, t, *J*=7.1 Hz); ^{13}C NMR (400 MHz, $CDCl_3$): δ 168.44, 168.42, 167.4, 166.1, 135.2, 135.0, 134.2, 131.9, 128.84, 128.83, 128.46, 128.45, 125.2, 125.1, 123.6, 92.7 (d, *J*=179.5 Hz), 62.3, 56.6 (d, *J*=22.9 Hz), 40.47, 14.0; ^{19}F NMR (300 MHz, $CDCl_3$): δ −191.3 (1F, dd, *J*=45.3, 28.7 Hz).

*4.1.9. Ethyl (2R)-3-fluoro-3-phenyl-2-((S)-2-(2,2,2-trifluoroacetamido)propanamido)propanoate (**10**).* Following the general procedure and workup, **10** was isolated (64 mg, 67%) as a colorless solid (mixture of diastereomers); mp 96–98 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40–7.27 (5H, m), 7.09 (1H, d, *J*=7.1 Hz), 6.89–6.82 (1H, m), 6.13–5.79 (1H, m), 5.19–5.03 (1H, m), 4.66–4.50 (1H, m), 4.30 (1H, q, *J*=7.1 Hz), 4.16–4.08 (1H, m), 1.45–1.39 (3H, m), 1.33–1.10 (3H, m); ^{13}C NMR (400 MHz, $CDCl_3$): δ 170.7, 168.5, 168.4, 167.9, 167.8, 157.2, 157.0, 156.81, 156.75, 156.7, 156.4, 156.3, 156.1, 155.9, 135.09, 135.06, 134.88, 134.85, 128.99, 128.98, 128.92, 128.91, 128.51, 128.50, 128.47, 128.46, 125.17, 125.15, 125.09, 125.07, 117.04, 116.96, 114.2, 114.1, 93.0 (d, *J*=179.1 Hz), 92.6 (d, *J*=182.8 Hz), 62.5, 62.2, 57.3, 57.0, 56.9, 56.7, 49.1, 48.9, 18.4, 18.2, 14.0, 13.8; ^{19}F NMR (300 MHz, $CDCl_3$): δ −75.31 (3F, s), −75.35 (3F, s), −190.9 (1F, dd, *J*=45.9, 20.7 Hz), −192.1 (1F, dd, *J*=45.3, 30.4 Hz).

*4.1.10. Ethyl (2R)-2-(3-(1,3-dioxoisoindolin-2-yl)propanamido)-3-fluoro-3-phenylpropanoate (**11**).* Following the general procedure and workup, **11** was isolated (49 mg, 47%) as a beige solid (mixture of diastereomers); mp 134–138 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.80–7.76 (2H, m), 7.69–7.65 (2H, m), 7.33–7.18 (5H, m), 6.69–6.59 (1H, m), 6.04–5.7 (1H, m), 5.18–5.04 (1H, m), 4.23–4.16 (1H, m), 4.05–3.92 (2H, m), 3.86–3.75 (1H, m), 2.72–2.52 (2H, m), 1.25–1.00 (3H, m); ^{13}C NMR (400 MHz, $CDCl_3$): δ 171.4, 169.7, 169.6, 169.3, 168.74, 168.71, 168.3, 168.07, 168.02, 167.95, 167.9, 135.8, 135.6, 135.41, 135.37, 135.2, 133.9, 133.8, 131.9, 129.2, 128.58, 128.57, 128.53, 128.52, 128.3, 128.22, 128.21, 128.20, 125.13, 125.05, 125.04, 125.0, 123.18, 123.15, 92.9 (d, *J*=182.1 Hz), 92.8 (d, *J*=178.8 Hz), 62.0, 61.6, 57.0, 56.8, 56.3, 56.1, 34.5, 34.4, 34.1, 34.0, 33.8, 13.9, 13.6; ^{19}F NMR (300 MHz, $CDCl_3$): δ −191.2 (1F, dd, *J*=45.3, 29.8 Hz), −192.5 (1F, dd, *J*=45.9, 22.4 Hz).

*4.1.11. Ethyl ((2R)-2-(1,3-dioxoisoindolin-2-yl)-3-fluoro-3-phenylpropanoyl)-L-valinate (**12**).* Following the general procedure and workup, **12** was isolated (68 mg, 62%) as a colorless oil (mixture of diastereomers). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.94–7.87 (1H, m), 7.80–7.74 (1H, m), 7.73–7.67 (1H, m), 7.64–7.60 (1H, m), 7.55–7.50 (1H, m), 7.41–7.36 (2H, m), 7.29–7.24 (2H, m), 7.21–7.15 (1H, m), 6.56–6.33 (1H, m), 5.36–5.30 (1H, m), 4.63–4.36 (1H, m), 4.31–4.18 (1H, m), 4.15–4.01 (1H, m), 2.30–2.02 (1H, m), 1.32–1.16 (3H, m), 0.98–0.77 (6H, m); ^{13}C NMR (400 MHz, $CDCl_3$): δ 171.2, 170.9, 167.8, 167.2, 165.84, 165.81, 165.0, 164.9, 135.7, 135.5, 135.4, 135.0, 134.8, 134.1, 131.5, 131.3, 129.83, 129.80, 129.77, 128.8, 128.62, 128.61, 127.32, 127.27, 127.1, 127.0, 123.8, 123.5, 91.9 (d, *J*=169.9 Hz), 89.6 (d, *J*=179.9 Hz), 61.4, 61.2, 59.3, 59.1, 57.7, 57.4, 56.4, 56.0, 31.3, 31.1, 18.9, 18.7, 17.6, 17.5, 14.1, 14.0; ^{19}F NMR (300 MHz, $CDCl_3$): δ −164.0 to −164.2 (1F, m), −174.4 (1F, dd, *J*=47.0, 11.5 Hz).

*4.1.12. Ethyl ((2R)-2-(1,3-dioxoisoindolin-2-yl)-3-fluoro-3-phenylpropanoyl)-L-leucinate (**13**).* Following the general procedure and workup, **13** was isolated (74 mg, 65%) as a colorless oil (mixture of diastereomers). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.94–7.88 (1H, m), 7.81–7.75 (1H, m), 7.72–7.69 (1H, m), 7.65–7.60 (1H, m), 7.54–7.50 (1H, m), 7.43–7.35 (2H, m), 7.29–7.24 (2H, m), 7.08–6.67 (1H, m), 6.55–6.32 (1H, m), 5.35–5.26 (1H, m), 4.73–4.41 (1H, m), 4.29–4.02 (2H, m), 1.75–1.59 (2H, m), 1.57–1.42 (1H, m), 1.32–1.15 (3H, m), 0.98–0.92 (3H, m), 0.86–0.79 (3H, m); ^{13}C NMR (400 MHz, $CDCl_3$): δ 172.3, 172.1, 167.8, 167.2, 165.61, 165.59, 164.8, 164.7, 135.6, 135.4, 135.0, 134.8, 134.5, 134.1, 131.5, 131.4, 129.85, 129.82, 129.80, 129.78, 128.80, 128.64, 128.63, 127.33, 127.27, 127.10, 127.05, 123.8, 123.5, 92.0 (d, *J*=169.9 Hz), 89.5 (d, *J*=179.9 Hz), 61.5, 61.3, 59.3, 59.1, 56.2, 55.9, 51.5, 51.1, 41.7, 41.4, 26.9, 24.9, 24.7, 22.7, 22.6, 22.0, 21.8, 14.1, 14.0; ^{19}F NMR (300 MHz, $CDCl_3$): δ −165.0 (1F, ddd, *J*=47.6, 13.8, 9.2 Hz), −176.2 (1F, dd, *J*=47.0, 11.5 Hz).

*4.1.13. Ethyl ((2R)-2-((S)-2-(1,3-dioxoisoindolin-2-yl)propanamido)-3-fluoro-3-phenylpropanoyl)-L-leucinate (**14**).* Following the general procedure and workup, **14** was isolated (83 mg, 63%) as a white solid (mixture of diastereomers); mp 138–141 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.86–7.78 (2H, m), 7.76–7.69 (2H, m), 7.39–7.22 (5H, m), 6.96–6.33 (2H, m), 6.24–5.86 (1H, m), 5.07–4.80 (2H, m), 4.58–4.42 (1H, m), 4.20–4.06 (2H, m), 1.73–1.65 (2H, m), 1.64–1.45 (4H, m), 1.28–1.14 (3H, m), 0.98–0.82 (6H, m); ^{13}C NMR (400 MHz, $CDCl_3$): δ 171.9, 171.7, 168.9, 168.7, 167.5, 167.43, 167.41, 167.26, 167.25, 167.03, 166.98, 135.5, 135.33, 135.27, 135.1, 134.3, 134.2, 131.7, 131.6, 129.0, 128.9, 128.7, 128.6, 128.5, 128.4, 125.7, 125.6, 125.2, 125.1, 123.48, 123.45, 92.2 (d, *J*=180.2 Hz), 91.8 (d, *J*=178.0 Hz), 61.19, 61.15, 57.6, 57.4, 57.3, 57.2, 51.30, 51.27, 49.0,

48.9, 40.9, 40.8, 24.7, 24.6, 22.7, 22.6, 21.81, 21.77, 14.9, 14.8, 14.0; ^{19}F NMR (300 MHz, $CDCl_3$): δ −189.0 (1F, dd, J=45.3, 18.4 Hz), −192.4 (1F, dd, J=45.3, 24.7 Hz).

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Supplementary data

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