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Synthesis of *N*-alkylated amino acids using fluorous-tagged hydroxylamines

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ABSTRACT

The development of a new fluorous-tagged ammonia-equivalent for the synthesis of *N*-alkylated amino acids is described. The required building blocks were readily accessed in high yield and purity using F-SPE purification technique. Coupling of the fluorous-tagged hydroxylamines with a selection of boronic acids and glyoxalic acid gave the desired *N*-alkylated amino acids. Subsequent removal of the fluorous tag via catalytic hydrogenation was investigated using a number of different catalysts and solvents. A more robust de-tagging procedure involves the transformation of the amino acid to the corresponding methyl ester followed by a $Mo(CH_3CN)_3(CO)_3$ mediated N–O bond cleavage.

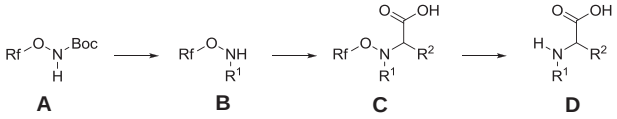
1. Introduction

Fluorous linker-facilitated chemical synthesis has evolved over the last 15 years into a well established technique.[1] It has several advantages compared to classic solid phase organic synthesis: reactions can be monitored by standard analytical methods and conventional methods for purification can be used in addition to fluorous-technologies. Furthermore, reactions proceed under solution phase reaction kinetics meaning that protocols developed in solution often can be converted to a fluorous procedure with very little optimization effort.

Multi component reactions (MCR's) are generally defined as reactions where more than two starting materials react to form a product, incorporating essentially all the atoms of the reactants.[2] Since not all reactants are used in equal molar amounts and their reactivity may be different, unreacted components may complicate the product purification. Fluorous-methods have already successfully been applied in several MCR's including the Ugi and Biginelli reaction.[3]

We recently reported the synthesis and application of a new fluorous-tagged ammonia-equivalent for the synthesis of a wide range of compound classes.[4] Herein we wish to report our efforts towards the application of this principle to the synthesis of *N*-substituted amino acids via the Petasis reaction.

The Petasis reaction provides access to amino acids under mild conditions in one step from glyoxylic acid, an amine and a boronic acid.[5] The synthetic strategy is outlined in Scheme 1.



Scheme 1. Outline of synthetic strategy towards *N*-substituted amino acids using fluorous-tagged hydroxylamines in the Petasis reaction.

Using our previously reported methodologies, fluorous-tagged primary amines **B** are readily available from Boc-protected and fluorous-tagged hydroxylamine **A**. Applying **B** in the Petasis reaction with different boronic acids and glyoxylic acid should lead to the fluorous-tagged amino acids **C**. The use of *N*-alkylhydroxylamines and *N*-alkyl-methoxyamines in the Petasis reaction has previously been reported by Naskar.[6] Finally the fluorous tag is removed providing the *N*-alkylated amino acids **D**.

The previously reported fluorous tag **E** (see Scheme 2) is readily removed in an orthogonal fashion using $Mo(CH_3CN)_3(CO)_3$.[4] However, we were concerned about possible problems with the separation of the free amino acids **D** from residual Mo-reagent, and it was decided to explore the slightly modified N–O linker **F**, where the fluorous substituent on the oxygen of the N–O bond is a perfluoro benzyl group, which would allow the traceless release via hydrogenation using a heterogeneous catalyst that could be removed by simple filtration. Thus, the deprotection would proceed

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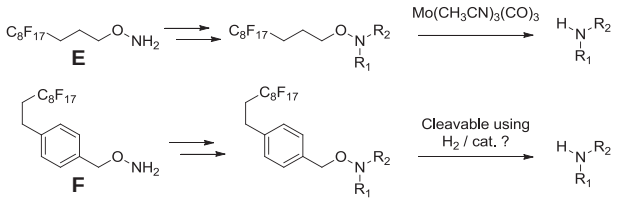
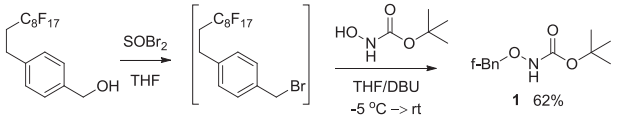
in two steps: first the benzyl group would be cleaved, leaving the *N*-hydroxy amino acid, which subsequently would be reduced in situ to the desired amino acid.



Scheme 2. Outline of the synthetic strategy towards *N*-substituted amino acids using fluorous-tagged hydroxylamines in the Petasis reaction.

2. Results and discussion

The synthesis of the Boc-protected fluorous-tagged hydroxylamine **1** is outlined in Scheme 3.



Scheme 3. Synthesis of fluorous tagged hydroxylamine **1**.

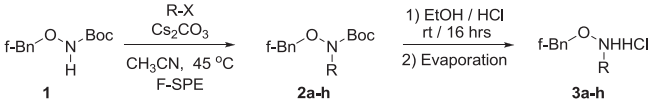
The benzyl bromide was generated in situ from the alcohol and thionyl bromide in THF. Subsequent slow cannulation of the benzyl bromide solution into a cold mixture of *N*-Boc hydroxylamine and DBU suppressed dialkylation and gave the monoalkylated product **1** in 62% yield.

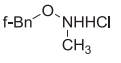
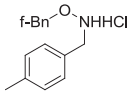
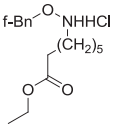
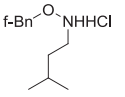
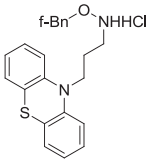
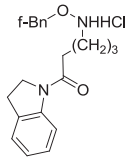
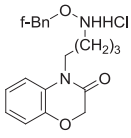
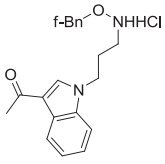
Subsequent alkylation of **1** was carried out under relatively mild conditions using Cs_2CO_3 in CH_3CN at 45 °C. Various alkyl halides were used including an alkyl chloride (for compound **2c**), alkyl bromides (for compounds **2b**, **2d**–**h**) and an alkyl iodide (for compound **2a**). Addition of the alkyl halide to a preheated mixture of **1** and Cs_2CO_3 in CH_3CN gave the best results. After 2 h at 45 °C TLC showed full conversion of **1** in most cases. The work-up of the reactions was very simple: the reaction mixture was transferred directly on to a Fluorous Solid Phase Extraction (F-SPE) cartridge together with 2 mL of water. Excess alkyl halide, Cs_2CO_3 and other non-fluorous material were then eluted with MeOH/H_2O 4:1. Subsequently, the fluorous product was eluted with MeOH, and the solvent was removed in vacuo to give the pure products **3a**–**h** in high yield. The Boc group was removed with HCl/EtOH at room temperature for 16 h. Subsequent evaporation gave the pure hydrochloride salts as shown in Table 1.

The fluorous Petasis reaction was performed using the established procedure[5] with the fluorous alkoxyamine as the limiting reagent while glyoxylic acid and the boronic acids were used in excess (2–10 equiv). A selection of different Petasis products were synthesized from the hydrochloride salts in Table 1, glyoxylic acid and different boronic acids. The products were obtained in moderate to good yields (43–99%) and characterized by LC–MS before the final de-tagging reaction. The average purity by ELS was 97% and the average purity by UV was 79% (Table 2).

A range of catalysts were screened in order to optimize the cleavage: Pd/C, $Pd(OH)_2$, Ru/C, Rh/Al, Raney-Nickel, Rh[anchored], PtO_2 and Pt/C . Each reaction was carried out in EtOH at room temperature if not otherwise noted and under a hydrogen pressure of 2 bar. The reaction mixtures were analyzed by LC–MS after 5 h. Four main components were detected by LC–MS at that point: unreacted starting material **4c**, the desired product **5c**, the hydroxylamine **6** and side-product **7** resulting from cleavage of the *N*-benzyl-bond, see Scheme 4. Unfortunately, none of the catalysts screened gave clean conversion of the starting material to the desired product. Of the catalysts screened, Pd/C gave the best results, with good conversion accompanied by low (but detectable) amounts of **6** and **7** (Fig. 1).

Table 1
Alkylation products

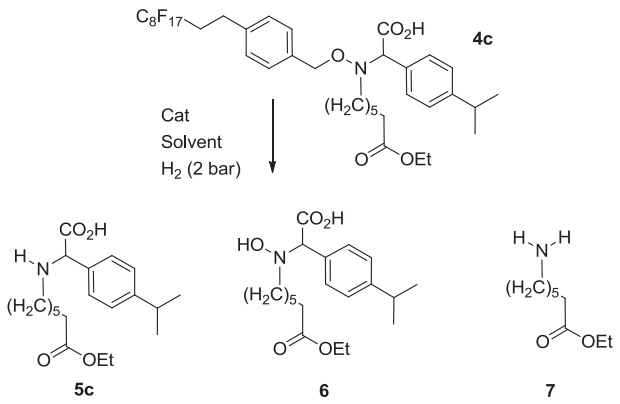


		Yield[a]			Yield[a]
3a		97	**3e**		>99
3b		96	**3f**		98
3c		41	**3g**		52
3d		87	**3h**		98

[a] Yield over two steps.

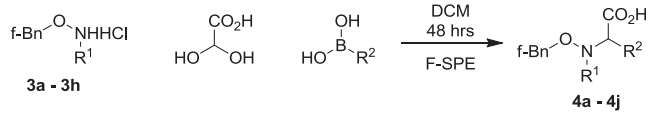
It is well-known that the solvent greatly influences the catalytic hydrogenation-process,[7] so different solvents were compared in the hydrogenation of **4c**. The reactions were carried out with 0.1 equiv Pd/C (10%) at room temperature under a hydrogen pressure of 2 bar. Each mixture was analysed by LC–MS after 16 h. The hydroxylic solvents methanol, ethanol and 2,2,3,3-tetrafluoropropanol (TEFP) worked well, whereas reactions run in THF, MeCN, $CHCl_3$, EtOAc and toluene mainly gave unchanged starting material. TEFP was found to be the solvent of choice since its high boiling point (bp=110 °C) allows for higher reaction temperatures than methanol (bp=65 °C) and ethanol (bp=78 °C).

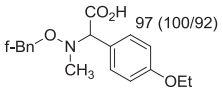
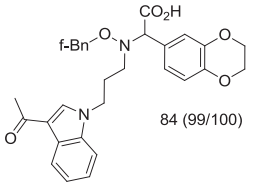
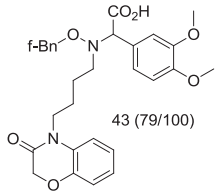
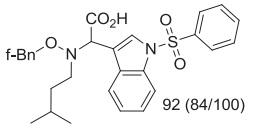
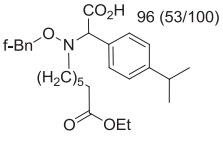
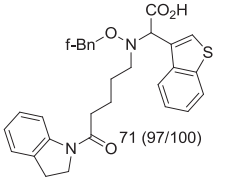
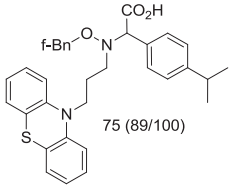
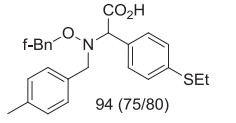
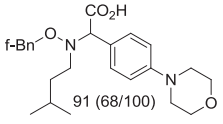
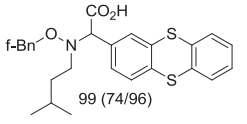
The deprotection of the fluorous tag from the series of Petasis products was a mixed success as the compounds displayed very



Scheme 4. Attempted N–O cleavage via hydrogenation.

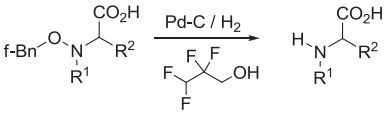
Table 2
Fluorous-tagged Petasis products

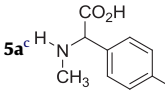
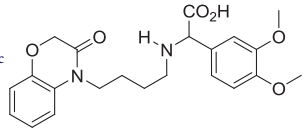
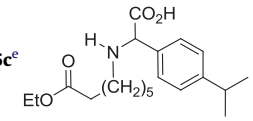
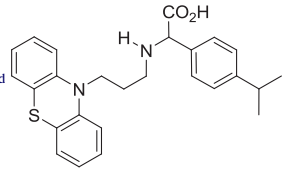
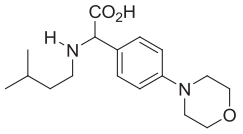
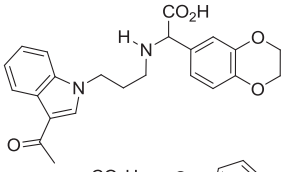
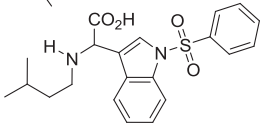


Product	Yield% (purity%)[a]	Product	Yield% (purity%)[a]
4a	 97 (100/92)	**4f**	 84 (99/100)
4b	 43 (79/100)	**4g**	 92 (84/100)
4c	 96 (53/100)	**4h**	 71 (97/100)
4d	 75 (89/100)	**4i**	 94 (75/80)
4e	 91 (68/100)	**4j**	 99 (74/96)

[a] Purity by LC–UV/ELS.

Table 3
Petasis products



Product (reaction conditions)	Yield% (purity%)[a]
5a[c] 	93(100/100)
5b[c] 	82(99/100)
5c[e] 	95(18/91) 13(59/81)[b]
5d[d] 	74(87/100) 44(94/100)[b]
5e[c] 	50(89/100)
5f[d] 	45(46/nd)[f] 6(93/100)[b]
5g[d] 	60(34/57) 12(90/100)[b]

[a] Purity by LC–UV/ELS after F-SPE.
[b] Yield and purity after preparative LC–MS.
[c] Pressure/temp/time: 3 bar H_2/30 °C/16 h.
[d] Pressure/temp/time: 3 bar H_2/80 °C/16 h.
[e] Pressure/temp/time:1 bar H_2/22 °C/3 h.
[f] nd=not detected.

different sensitivity to catalytic hydrogenation. Thus, a general and robust procedure was not established. Nevertheless seven de-tagged products were obtained under similar conditions (Pd/C, 3 bar H_2 and TEFP). The reaction time spanned from 3 to 20 h and the temperature ranged from 22 °C to 100 °C. In two cases (**5a** and **5b**) the products were obtained in good yields and with excellent purities after purification by F-SPE.

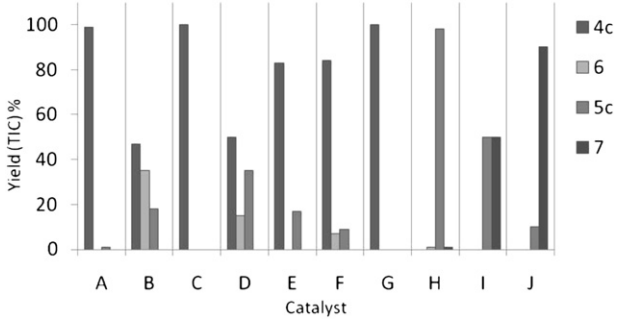
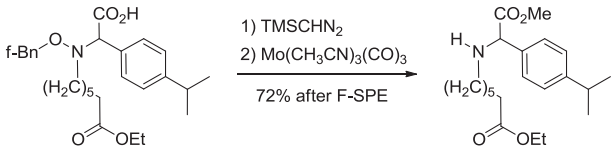


Fig. 1. Catalyst screening. (A) Pt/C, (B) PtO_2, (C) Rh(anchored), (D) $Pd(OH)_2$/C, (E) Raney-Nickel, (F) Rh/Al, (G) Ru/C, (H) Pd/C, (I) Pd/C at 50 °C, (J) Pd/C at 80 °C.

In order to address the limitations of the hydrogenation-cleavage we reverted to our previously reported $Mo(CH_3CN)_3(CN)_3$ procedure.[4] Attempted cleavage of **4c** led to a dark product after F-SPE; presumably due to contamination with Mo-residues thereby confirming our concerns about the propensity of the free amino acid to form complexes with molybdenum (Table 3).

Hence, the carboxylic acid in **4c** was esterified with trimethylsilyl diazomethane (TMS–CHN_2) in toluene/methanol. Subsequent N–O cleavage using $Mo(CH_3CN)_3(CN)_3$ at 160 °C for 15 min successfully provided **8** as a colourless material in 72% yield after

F-SPE, see Scheme 5. This cleavage procedure provides a reliable back-up in the instances where the hydrogenation protocol fails to deliver the desired product.



4c 8

Scheme 5. Esterification of **4c** followed by N–O cleavage using $Mo(CH_3CN)_3(CO)_3$.

3. Conclusion

In summary we have demonstrated that fluorous-tagged hydroxylamine **F** supplements our previously reported tag **E**. It is readily alkylated and provides access to amino acids via the Petasis reaction. Final deprotection by N–O bond cleavage via catalytic hydrogenation proved capricious, but could be executed using $Mo(CH_3CN)_3(CN)_3$ as previously reported for **E**.

4. Experimental section

4.1. General

Chemicals and solvents were obtained from commercial suppliers and used as received unless otherwise noted. THF was dried over molecular sieves (3 Å) prior to use. The molybdenum complex used for reductive N–O cleavage tris(acetonitrile)molybdenumtricarbonyl [CAS # 15,038-48-9] was purchased from AcrosOrganics and used as received. Flash column chromatography was carried out using Scharlau 60 (230–400 mesh) silica gel (sorbil) and thin-layer chromatography (TLC) was performed on Merck 60 F_{254} 0.25-μm silica gel plates. If not otherwise noted then ^{1}H NMR and ^{1}H-decoupled/^{13}C NMR spectra were recorded at 500.13 MHz and 125.67 MHz, respectively, on a Bruker Avance DRX 500 instrument using deuterated chloroform (99.8%). Chemical shifts for ^{1}H NMR are reported in parts per million with TMS as internal reference. Chemical shifts for ^{13}C NMR are reported in ppm relative to chemical shifts of $CHCl_3$. Coupling constants (*J* values) are in hertz. The following abbreviations are used for multiplicity of NMR signals: s=singlet, d=doublet, t=triplet, q=quartet, dd=double doublet, ddt=double doublet of triplets and m=multiplet. Elemental analyses were performed at H. Lundbeck A/S, with a Flash EA1112 from Thermo Fischer Scientific. HRMS were performed on an Agilent/Bruker Daltonics LC-SPE-MS at H. Lundbeck A/S. The vacuum centrifuges applied were either HT-4 or EZ2 from genevac®. Fluorous Solid Phase Extraction (F-SPE) was carried out using cartridges from Fluorous Technologies Inc. and a FlashVac-10 from Biotage designed to accommodate 10 collection tubes with 25 mm diameter vessels.

*4.1.1. tert-Butyl 4-(2-perfluoroctylethyl)benzyloxycarbamate(**1**).* A dry 250 mL round bottomed flask was added 4-(2-perfluoroctyl)ethylbenzyl alcohol (23 g, 41 mmol) and dry tetrahydrofuran (100 mL). The mix was cooled to 0 °C under argon and covered with aluminium foil. Then thionyl bromide (3.48 mL, 43.6 mmol) was added via needle through septum and the mix was heated to room temperature. After stirring for 1 h, TLC (heptane/ethyl acetate 3:1) showed full consumption of the fluorous starting material. This mix was slowly cannulated under argon through septum to a pre-cooled solution (−5 °C) of *tert*-butyl *N*-hydroxycarbamate (20.17 g, 148.4 mmol), 1,8-diazabicyclo[5.4.0]undec-7-ene (16.76 mL, 112.0 mmol) and 200 mL dry tetrahydrofuran in a 500 mL round bottomed flask covered with aluminium foil. Stirring was continued overnight with the temperature slowly rising to room temperature as the icebath melted. The reaction mixture was added 200 mL water and the product was extracted in HFE-7100. The product was purified further by flash chromatography (heptane/ethyl acetate 9:1) to give 17.2 g (62%) of **1** as a white solid. Purity by LC–UV(ELS)=100%(100%); R_f=0.38 (heptane/ethyl acetate 3:1); mp 81.1–81.3 °C; ^{1}H NMR δ 1.48 (s, 9H), 2.30–2.42 (m, 2H), 2.90–2.95 (m, 2H), 4.84 (s, 2H), 7.07 (s, 1H), 7.22 (d, *J*=7.9 Hz, 2H), 7.36 (d, *J*=7.9 Hz, 2H); ^{13}C NMR δ 26.2, 28.2, 32.9 (t, *J*=22 Hz), 78.1, 81.8, 128.4, 129.6, 134.3, 139.5, 156.7; HRMS calcd for $C_{17}H_{13}F_{17}NO^+$, 570.0726 ($-^t$Boc$^+$, $+H^+$); found 570.0733; [CHN calcd for $C_{22}H_{20}F_{17}NO_3$, C 39.48, H 3.01, N 2.09; found C 39.74, H 2.93, N 2.13].

4.2. General procedure A (alkylation of 1)

In a typical experiment, a mixture of **1** (1.5 mmol), caesium carbonate (3.0 mmol), and dry acetonitrile (20 mL) was heated to 45 °C and to it was added alkylbromide (2.3 mmol). The mix was stirred for 3 h at 45 °C and then cooled to room temperature. After work up with water (50 mL) and ethyl acetate (3×50 mL) the product was purified by F-SPE. The average yield was 85% and the average purity by LC–UV was 98%.

*4.2.1. tert-Butyl methyl(4-(2-perfluoroctylethyl)benzyloxy)carbamate (**2a**).* Prepared by general procedure A to give 320 mg (100%) of **2a** as a colourless oil. Purity by LC–UV=100%; =0.42 (heptane/ethyl acetate 3:1); ^{1}H NMR δ 1.50 (s, 9H), 2.29–2.42 (m, 2H), 2.90–2.94 (m, 2H), 3.05 (s, 3H), 4.81 (s, 2H), 7.21 (d, *J*=8.0 Hz, 2H), 7.37 (d, *J*=8.0 Hz, 2H); ^{13}C NMR δ 26.2, 28.2, 32.9 (t, *J*=22 Hz), 36.8, 76.1, 81.2, 106–121 (8 fluorinated carbon), 128.3, 129.9, 134.2, 139.5, 157.0; HRMS calcd for $C_{19}H_{15}F_{17}NO_3^+$, 628.0775 ($-^t$Bu$^+$, $+H^+$); found 628.0790.

*4.2.2. Ethyl 7-(tert-butoxycarbonyl(4-(2-perfluoroctylethyl)benzyloxy)amino)heptanoate (**2b**).* Prepared by general procedure A to give 3.88 g (99%) of **2b** as a colourless oil. Purity by LC–UV(ELS)=100%(98%); ^{1}H NMR δ 1.24 (t, *J*=7.1 Hz, 3H), 1.28–1.34 (m, 4H), 1.49 (s, 9H), 1.56–1.64 (m, 4H), 2.27 (t, *J*=7.5 Hz, 2H), 2.29–2.41 (m, 2H), 2.88–2.94 (m, 2H), 3.40 (t, *J*=7.2 Hz, 2H), 4.11 (q, *J*=7.1 Hz, 2H), 4.79 (s, 2H) 7.21 (d, *J*=8.0 Hz, 2H), 7.36 (d, *J*=8.0 Hz, 2H); ^{13}C NMR δ 14.2, 24.8, 26.2, 26.4, 26.9, 28.3, 28.8, 32.9 (t, *J*=22 Hz), 34.2, 49.5, 60.1, 76.5, 81.1, 106–121 (8 fluorinated carbon), 128.3, 129.8, 134.2, 139.4, 156.6, 173.7; HRMS calcd for $C_{26}H_{29}F_{17}NO_3^+$, 726.1870 (−Boc$^+$, $+H^+$); found 726.1866.

*4.2.3. tert-Butyl 3-(10H-phenothiazin-10-yl)propyl(4-(2-perfluoroctylethyl)benzyloxy)carbamate (**2c**).* Prepared by general procedure A to give 2.23 g (82%) of **2c** as a yellow oil. Purity by LC–UV(ELS)=75%(83%). Additional purification by Flash chromatography (heptane/ethyl acetate 9:1) yielded 1.13 g (41%). Purity by LC–UV(ELS)=94%(83%); ^{1}H NMR δ 1.46 (s, 9H), 2.07–2.14 (m, 2H), 2.31–2.45 (m, 2H), 2.90–2.97 (m, 2H), 3.58 (t, *J*=6.7 Hz, 2H), 3.94 (t, *J*=6.6 Hz, 2H), 4.75 (s, 2H), 6.88 (d, *J*=8.1 Hz, 2H), 6.92–6.96 (m, 2H), 7.12–7.19 (m, 6H), 7.23–7.26 (m, 2H); ^{13}C NMR δ 24.6, 26.2, 28.2, 32.9 (t, *J*=22 Hz), 44.4, 47.0, 76.2, 81.4, 115.6, 122.5, 125.5, 127.2, 127.5, 128.3, 129.9, 134.0, 139.4, 145.2, 156.4; HRMS calcd for $C_{37}H_{34}F_{17}N_2O_3S^+$, 909.2013 ($+H^+$); found 909.1991.

*4.2.4. tert-Butyl 4-(3-oxo-2H-benzo[b][1,4]oxazin-4(3H)-yl)butyl(4-(2-perfluoroctylethyl)benzyloxy)carbamate (**2d**).* Prepared by general procedure A to give 1.37 g (88%) of **2d** as a colourless oil. Purity by LC–UV(ELS)=100%(100%); ^{1}H NMR δ 1.50 (s, 9H), 1.67–1.71 (m, 4H), 2.29–2.42 (m, 2H), 2.89–2.95 (m, 2H), 3.44–3.50 (m, 2H), 3.91–3.98 (m, 2H), 4.58 (s, 2H), 4.79 (s, 2H), 6.96–7.01 (m, 4H), 7.21

(d, *J*=8.0 Hz, 2H), 7.36 (d, *J*=8.0 Hz, 2H); ^{13}C NMR δ 24.3, 24.4, 26.2, 28.3, 32.9 (t, *J*=22 Hz), 40.6, 49.0, 67.6, 76.6, 81.4, 114.9, 117.1, 122.8, 123.8, 128.4, 129.9, 134.0, 139.5, 145.4, 156.5, 164.2; HRMS calcd for $C_{29}H_{26}F_{17}N_2O_3^+$, 773.1666 ($-Boc^+$, $+$H$^+$); found 773.1674.

*4.2.5. tert-Butyl 4-methylbenzyl(4-(2-perfluoroctylethyl)benzyloxy) carbamate (**2e**).* Prepared by general procedure A to give 1.73 g (100%) of **2e** as a white solid. Purity by LC–UV(ELS)=100%(100%); ^{1}H NMR δ 1.50 (s, 9H), 2.28–2.40 (m, 5H), 2.87–2.92 (m, 2H), 4.52 (s, 2H), 4.65 (s, 2H), 7.12–7.18 (m, 4H), 7.21–7.25 (m, 4H); ^{13}C NMR δ 21.08, 26.2, 28.3, 32.9 (t, *J*=22 Hz), 53.6, 76.9, 81.5, 128.2, 128.7, 129.0, 129.9, 133.9, 134.1, 137.2, 139.4, 156.7; HRMS calcd for $C_{26}H_{21}F_{17}NO_3^+$, 718.1244 ($-^t$Bu$^+$, $+$H$^+$); found 718.1268.

*4.2.6. tert-Butyl isopentyl(4-(2-perfluoroctylethyl)benzyloxy)carbamate (**2f**).* Prepared by general procedure A to give 3.19 g (99%) of **2f** as a colourless oil. Purity by LC–UV(ELS)=100%(100%); ^{1}H NMR δ 0.89 (d, *J*=6.6 Hz, 6H), 1.45–1.63 (m, 12H), 2.29–2.42 (m, 2H), 2.89–2.95 (m, 2H), 3.42 (t, *J*=7.5 Hz, 2H), 4.81 (s, 2H), 7.21 (d, *J*=7.8 Hz, 2H), 7.37 (d, *J*=7.8 Hz, 2H); ^{13}C NMR δ 22.4, 25.7, 26.2, 28.3, 32.9 (t, *J*=22 Hz), 35.8, 48.2, 76.5, 81.1, 128.3, 129.8, 134.3, 139.4, 156.6; HRMS calcd for $C_{23}H_{23}F_{17}NO_3^+$, 684.1401 ($-^t$Bu$^+$, $+$H$^+$); found 684.1381.

*4.2.7. tert-Butyl 5-(indolin-1-yl)-5-oxopentyl(4-(2-perfluoroctylethyl)benzyloxy)carbamate (**2g**).* Prepared by general procedure A to give 681 mg (52%) of **2g** as a white solid. Purity by LC–UV(ELS)=96%(100%); ^{1}H NMR δ 1.50 (s, 9H), 1.69–1.81 (m, 4H), 2.28–2.47 (m, 4H), 2.88–2.94 (m, 2H), 3.17 (t, *J*=8.4 Hz, 2H), 3.48 (t, *J*=6.5 Hz, 2H), 4.02 (t, *J*=8.4 Hz, 2H), 4.82 (s, 2H), 6.98–7.03 (m, 1H), 7.15–7.21 (m, 4H), 7.37 (d, *J*=7.8 Hz, 2H), 8.23 (d, *J*=7.9 Hz, 1H); ^{13}C NMR δ 21.7, 26.2, 26.7, 28.0, 28.3, 32.9, 35.3, 47.9, 49.3, 76.6, 81.3, 117.0, 123.5, 124.5, 127.5, 128.4, 129.9, 131.0, 134.1, 139.4, 143.0, 156.6, 170.9; HRMS calcd for $C_{35}H_{36}F_{17}N_2O_4^+$, 871.2398 ($+H^+$); found 871.2410.

*4.2.8. tert-Butyl (3-(3-acetyl-1H-indol-1-yl)propyl)((4-(2-perfluoroctylethyl)benzyl)oxy)carbamate (**2h**).* Prepared by general procedure A to give 1.266 g (98%) of **2h** as a white solid. Purity by LC–UV(ELS)=100%(100%); ^{1}H NMR δ 1.50 (s, 9H), 2.13–2.19 (m, 4H), 2.29–2.41 (m, 2H), 2.49 (s, 3H), 2.89–2.93 (m, 2H), 3.47 (t, *J*=6.4 Hz, 2H), 4.18 (t, *J*=7.0 Hz, 2H), 4.79 (s, 2H), 7.17–7.21 (m, 2H), 7.25–7.33 (m, 5H), 7.78 (s, 1H), 8.37–8.40 (m, 2H); ^{13}C NMR δ 27.5, 28.2, 32.8 (t, *J*=22 Hz), 44.4, 46.6, 76.5, 81.9, 109.7, 117.0, 122.5, 122.7, 123.2, 126.4, 128.4, 129.8, 133.7, 135.0, 136.6, 139.7, 156.4, 192.9; HRMS calcd for $C_{35}H_{34}F_{17}N_2O_4^+$, 869.2242 ($+H^+$); found 869.2251.

4.3. General procedure B (Boc-deprotection of fBnO–NRBoc)

A mixture of absolute ethanol (15 mL) was slowly added acetyl chloride (2.5 mL, 34 mmol) and stirred for 5 min. To it was added Boc-protected substrate (2–3 mmol) and the mix was stirred under argon overnight. TLC (heptane/ethyl acetate 3:1) showed completion of the reaction in all cases except **3b** in this case stirring for 48 h was necessary. The solvent and excess HCl was removed in vacuo to give the hydrochloride salts of the perfluorobenzyloxyamines. The average purity by LC–UV was 98%.

*4.3.1. N-Methyl-O-(4-(2-perfluoroctylethyl)benzyl)hydroxylamine hydrochloride (**3a**).* Prepared by general procedure B to give 119 mg (97%) of **3a** as a white solid. One spot by TLC R_f(free base)=0.24 (heptane/ethyl acetate 3:1). Purity by NMR >90%; ^{1}H NMR (CD$_3$OD) δ 2.28–2.39 (m, 2H), 2.86–2.91 (m, 2H), 2.98 (s, 3H), 5.26 (s, 2H), 7.24 (d, *J*=8.0 Hz, 2H), 7.41 (d, *J*=8.0 Hz, 2H); ^{13}C NMR (CD$_3$OD) δ 25.4, 31.2 (t, *J*=22 Hz), 34.7, 74.1, 128.5, 129.6, 131.8, 140.0; HRMS calcd for $C_{18}H_{15}F_{17}NO^+$, 584.0877 ($+$H$^+$); found 584.0855.

*4.3.2. N-(3-(10H-phenothiazin-10-yl)propyl)-O-(4-(2-perfluoroctylethyl)benzyl)hydroxylamine hydrochloride (**3c**).* Prepared by general procedure B to give 791 mg (99%) of **3c** as a grey solid. Purity by LC–UV(ELS)=91%(nd); ^{1}H NMR (CD$_3$OD) δ 2.19–2.26 (m, 2H), 2.42–2.55 (m, 2H), 2.94–3.00 (m, 2H), 3.43–3.48 (m, 2H), 4.13 (t, *J*=6.2 Hz, 2H), 4.95 (s, 2H), 6.96–7.00 (m, 2H), 7.03–7.06 (m, 2H), 7.17–7.24 (m, 4H), 7.28 (d, *J*=8.0 Hz, 2H), 7.3 (d, *J*=8.0 Hz, 2H); ^{13}C NMR (CD$_3$OD) δ 22.5, 27.1, 33.4 (t, *J*=22 Hz), 44.9, 48.2, 76.8, 106–121 (8 fluorinated carbon), 117.2, 124.2, 127.5, 128.6, 128.7, 130.1, 130.9, 132.3, 142.5, 146.4; HRMS calcd for $C_{32}H_{26}F_{17}N_2OS^+$, 809.1489 ($+H^+$); found 809.1473.

*4.3.3. 4-(4-(((4-(2-Perfluoroctylethyl)benzyl)oxy)amino)butyl)-2H-benzo[b][1,4]oxazin-3(4H)-one hydrochloride (**3d**).* Prepared by general procedure B to give 1.22 g (99%) of **3d** as a white solid. Purity by LC–UV(ELS)=100%(100%); ^{1}H NMR (CD$_3$OD) δ 1.77–1.81 (m, 4H), 2.42–2.55 (m, 2H), 2.95–3.00 (m, 2H), 3.36–3.44 (m, 2H), 4.03–4.09 (2 m, H), 4.59 (s, 2H), 5.07 (s, 2H), 6.99–7.10 (m, 3H), 7.18–7.22 (m, 1H), 7.36 (d, *J*=8.0 Hz, 2H), 7.41 (d, *J*=8.0 Hz, 2H); ^{13}C NMR (CD$_3$OD) δ 22.0, 25.2, 27.2, 33.4, 40.8, 50.2, 68.5, 77.0, 106–121 (8 fluorinated carbon), 116.5, 118.1, 124.1, 125.4, 129.3, 130.1, 131.0, 132.4, 142.6, 147.1, 166.7; HRMS calcd for $C_{29}H_{26}F_{17}N_2O_3^+$, 773.1666 ($+H^+$); found 733.1669.

*4.3.4. N-(4-methylbenzyl)-O-(4-(2-perfluoroctylethyl)benzyl)hydroxylamine hydrochloride (**3e**).* Prepared by general procedure B to give 1.57 g (101%) of **3e** as a white solid. Purity by LC–UV(ELS)= 100%(100%); ^{1}H NMR (MeOD) δ 2.38 (s, 3H), 2.43–2.55 (m, 2H), 2.95–3.00 (m, 2H), 4.48 (s, 2H), 5.07 (s, 2H), 7.29 (d, *J*=7.8 Hz, 2H), 7.34–7.41 (m, 6H); ^{13}C NMR (CD$_3$OD) δ 21.3, 27.2, 33.4 (t, *J*=22 Hz), 54.5, 77.1, 106–121 (8 fluorinated carbon), 126.9, 130.0, 130.8, 130.9, 131.8, 132.5, 141.5, 142.5; HRMS calcd for $C_{25}H_{21}F_{17}NO^+$, 674.1346 ($+$H$^+$); found 674.1335.

*4.3.5. N-Isopentyl-O-(4-(2-perfluoroctylethyl)benzyl)hydroxylamine hydrochloride (**3f**).* Prepared by general procedure B to give 2.66 g (99%) of **3f** as a white solid. Purity by ^{1}H NMR >90%; ^{1}H NMR (CD$_3$OD) δ 0.91 (d, *J*=6.6 Hz, 6H), 1.69 (hept, *J*= Hz, 1H), 1.77–1.83 (m, 2H), 2.27–2.39 (m, 2H), 2.84–2.90 (m, 2H), 3.23–3.30 (m, 2H), 5.32 (s, 2H), 7.21 (d, *J*=8 Hz, 2H), 7.39 (d, *J*=8 Hz, 2H); HRMS calcd for $C_{22}H_{23}F_{17}NO^+$, 640.1503 ($+$H$^+$); found 640.1492.

*4.3.6. 1-(Indolin-1-yl)-5-(((4-(2-perfluoroctylethyl)benzyl)oxy)amino)pentan-1-one hydrochloride (**3g**).* Prepared by general procedure B to give 481 mg (100%) of **3g** as a white solid. Purity by LC–UV(ELS)=98%(100%); ^{1}H NMR (CD$_3$OD) δ 1.77–1.90 (m, 4H), 2.41–2.54 (m, 2H), 2.61 (t, *J*=6.5 Hz, 2H), 2.94–2.99 (m, 2H), 3.20 (t, *J*=8.4 Hz, 2H), 3.41 (t, *J*=7.2 Hz, 2H), 4.11 (t, *J*=8.4 Hz, 2H), 5.11 (s, 2H), 7.01–7.05 (m, 1H), 7.13–7.18 (m, 1H), 7.21–7.25 (m, 1H), 7.35 (d, *J*=8.0 Hz, 2H), 7.43 (d, *J*=8.0 Hz, 2H), 8.11 (d, *J*=8.1 Hz, 1H); ^{13}C NMR δ 20.9, 23.6, 26.2, 28.1, 32.5, 32.7, 32.8, 32.4, 33.4, 35.1, 48.3, 76.4, 106–121 (8 fluorinated carbon), 117.1, 124.1, 124.7, 127.5, 128.7, 130.4, 131.2, 131.3, 140.6, 142.6, 171.1; HRMS calcd for $C_{30}H_{28}F_{17}N_2O_2^+$, 771.1874 ($+H^+$); found 771.1862.

*4.3.7. 1-(1-(3-(((4-(2-Perfluoroctylethyl)benzyl)oxy)amino)propyl)-1H-indol-3-yl)ethanone hydrochloride (**3h**).* Prepared by general procedure B to give 203 mg (100%) of **3h** as a pink solid. Purity by LC–UV(ELS)=98%(100%); ^{1}H NMR (CD$_3$OD) δ 1.26–1.35 (m, 2H), 2.26–2.38 (m, 2H), 2.43–2.50 (m, 3H), 2.84–2.89 (m, 2H), 3.24 (t, *J*=6.9 Hz, 2H), 4.34 (t, *J*=6.7 Hz, 2H), 5.24 (s, 3H), 7.19 (d, *J*=8.0 Hz, 2H), 7.25–7.29 (m, 1H), 7.31–7.35 (m, 3H), 7.95 (s, 1H), 8.29–8.32 (m, 1H); ^{13}C NMR (CD$_3$OD) δ 24.1, 26.2, 32.5 (t, *J*=22 Hz), 43.8, 46.5,

76.5, 109.6, 106–121 (8 fluorinated carbon), 117.5, 122.7, 122.8, 123.6, 126.3, 128.9, 130.1, 130.6, 134.9, 136.4, 141.1, 193.5; HRMS calcd for $C_{30}H_{26}F_{17}N_2O_2^+$, 769.1717 ($+H^+$); found 769.1714.

*4.3.8. 2-(4-Ethoxyphenyl)-2-(methylamino)acetic acid (**5a**).* A mixture of **3a** (106 mg, 0.17 mmol), 4-ethoxyphenylboronic acid (37 mg, mmol), dihydroxy-acetic acid (19 mg, mmol) in dichloromethane (4 mL) was stirred for 20 h at room temperature. Evaporation of the solvent and purification by F-SPE gave 126 mg (97%) of intermediate **4a** as a white solid. Purity by LC–UV(ELS)=100%(100%). Intermediate **4a** (47 mg) was dissolved in 2,2,3,3-tetrafluoropropanol (2 mL), added Pd/C 10% (20 mg, 19 mmol), and hydrogenated under 3 bar H_2 at 30 °C for 16 h in an Argonaut Endeavor apparatus. The mixture was filtered through Celite and purified by F-SPE to give 12 mg (93%) of **5a** as a white solid. Purity by LC–UV(ELS)=100%(100%); ^{1}H NMR (CD_3OD) 1.38, (t, J=7.0 Hz, 3H), 2.54 (s, 3H), 4.04 (q, J=7.0 Hz, 2H), 4.39 (s, 1H), 6.95 (d, J=8.8 Hz, 2H), 7.39 (d, J=8.8 Hz, 2H); ^{13}C NMR (CD_3OD): 15.1, 31.7, 64.6, 68.1, 116.0, 131.1, 131.2, 161.3, 172.5; HRMS calcd for $C_{11}H_{16}NO_4^+$, 210.1130 ($+H^+$); found 210.1122.

*4.3.9. 2-(3,4-Dimethoxyphenyl)-2-((4-(3-oxo-2H-benzo[b][1,4]-oxazin-4(3H)-yl)butyl)amino)acetic acid (**5b**).* A mixture of **3d** (273 mg, 0.34 mmol), 3,4-dimethoxyphenylboronic acid (123 mg, 0.68 mmol), dihydroxy-acetic acid (84 mg, 0.91 mmol) in dichloromethane (6 mL) was stirred for 48 h at room temperature. Evaporation of the solvent and purification by F-SPE gave 141 mg (43%) of intermediate **4b** as a yellow solid. Purity by LC–UV(ELS)=79%(100%). Intermediate **4b** (77 mg) was dissolved in 2,2,3,3-tetrafluoropropanol (2 mL), added Pd/C 10% (20 mg, 19 mmol), and hydrogenated under 3 bar H_2 at 30 °C for 16 h in an Argonaut Endeavor apparatus. The mixture was filtered through Celite and purified by F-SPE to give 27 mg (82%) of **5b** as a white solid. Purity by LC–UV(ELS)=99%(100%); ^{1}H NMR (CD_3OD, 600 MHz) δ 1.66–1.80 (m, 4H), 2.82–2.87 (m, 1H), 2.94–3.00 (m, 1H), 3.82 (s, 3H), 3.83 (s, 3H), 3.98–4.01 (m, 2H), 4.42 (s, 1H), 4.57 (s, 2H), 6.95–7.08 (m, 4H), 7.11 (d, J=2.0 Hz, 1H), (dd, J_1=8.0 Hz, J_2=1.5 Hz, 1H); ^{13}C NMR (CD_3OD, 150 MHz) δ 24.4, 25.4, 41.0, 47.2, 56.40, 56.43, 67.3, 68.5, 112.7, 112.8, 116.5, 118.1, 123.0, 124.1, 125.3, 127.4, 129.3, 147.0, 150.8, 151.3, 166.6, 172.4; HRMS calcd for $C_{22}H_{27}N_2O_6^+$, 415.1869 ($+H^+$); found 415.1871.

*4.3.10. 2-((7-Ethoxy-7-oxoheptyl)amino)-2-(4-isopropylphenyl)acetic acid (**5c**).* The Boc-group of compound **2b** was removed by general procedure B to give 2.1 g (97%) of ethyl 7-(((4-(2-perfluoroctylethyl)benzyl)oxy)amino)heptanoate hydrochloride (**3b**) as a white solid. Purity by LC–UV(ELS)=100%(100%). A mixture of **3b** (960 mg, 1.2 mmol), 4-isopropylphenylboronic acid (361 mg, 2.20 mmol), dihydroxy-acetic acid (310 mg, 3.4 mmol) in dichloromethane (30 mL) was stirred for 48 h at room temperature. Evaporation of the solvent and purification by F-SPE gave 1095 mg (96%) of intermediate **4c** as a colourless solid. Purity by LC–UV(ELS)=53%(100%). Purity by NMR >90%. HRMS calcd for $C_{37}H_{41}F_{17}NO_{5+}$, 902.2708($+H^+$); found 902.2733. Intermediate **4c** (100 mg, 0.11 mmol) was dissolved in 2,2,3,3-tetrafluoropropanol (2 mL), added Pd/C 10% (2 mg, 2 mmol), and hydrogenated under 1 bar H_2 at room temperature for 3 h in an Argonaut Endeavor apparatus. The mixture was filtered through Celite and purified by F-SPE to give 37 mg (95%) of **5c** as a white solid. Purity by LC–UV(ELS)=18%(91%). Additional purification by preparative LC–MS yielded 5 mg of a white solid. Purity by LC–UV(ELS)=59%(81%). HRMS calcd for $C_{20}H_{32}NO_4^+$, 350.2331 ($+H^+$); found 350.2335.

*4.3.11. 2-((3-(10H-Phenothiazin-10-yl)propyl)amino)-2-(4-isopropylphenyl)acetic acid (**5d**).* A mixture of **3c** (241 mg, 0.27 mmol), boronic acid (86 mg, 0.52 mmol), dihydroxy-acetic acid (68 mg, 0.74 mmol) in dichloromethane (20 mL) was stirred for 48 h at room temperature. Evaporation of the solvent and purification by F-SPE gave 203 mg (75%) of intermediate **4d** as a brown sticky solid. Purity by LC–UV(ELS)=89%(100%). Intermediate **4d** was dissolved in 2,2,3,3-tetrafluoropropanol (2 mL), Pd/C 10% (7 mg, 7 mmol) was added, and hydrogenated under 3 bar H_2 at 100 °C for 16 h in an Argonaut Endeavor apparatus. The mixture was filtered through Celite and purified by F-SPE to give 15 mg (74%) of **5d** as a brown sticky solid. Purity by LC–UV(ELS)=87%(100%). Additional purification of 12 mg by preparative LC–MS yielded 9 mg of a yellow oil. Purity by LC–UV(ELS)=94%(100%); ^{1}H NMR (CD_3OD) δ 1.26 (d, J=6.7 Hz, 6H), 2.05–2.15 (m, 1H), 2.15–2.26 (m, 1H), 2.88–3.07 (m, 3H), 4.04–4.07 (m, 2H), 4.74 (s, 1H), 6.94–7.01 (m, 4H), 7.12–7.14 (m, 2H), 7.18–7.28 (m, 4H); ^{13}C NMR (CD_3OD) δ 24.3, 24.4, 35.2, 45.1, 45.2, 65.0, 117.1, 124.1, 127.5, 128.6 (high intensity), 128.7, 129.7, 129.9, 146.3, 152.4, 170.8; HRMS calcd for $C_{26}H_{29}N_2O_2S^+$, 433.1950 ($+H^+$); found 433.1952.

*4.3.12. 2-(Isopentylamino)-2-(4-morpholinophenyl)acetic acid (**5e**).* A mixture of **3f** (38 mg, 56 mmol), boronic acid (35 mg, 0.17 mmol), dihydroxy-acetic acid (21 mg, 0.23 mmol) in dichloromethane (5 mL) was stirred for 48 h at room temperature. Evaporation of the solvent and purification by F-SPE gave 44 mg (91%) of intermediate **4e** as a brown solid Purity by LC–UV(ELS)=68%(100%). Intermediate **4e** was dissolved in 2,2,3,3-tetrafluoropropanol (2 mL), added Pd/C 10% (12 mg, 11 mmol), and hydrogenated under 3 bar H_2 at 30 °C for 16 h in an Argonaut Endeavor apparatus. The mixture was filtered through Celite and purified by F-SPE to give 8 mg (50%) of **5e** as a yellow solid. Purity by LC–UV(ELS)=89%(100%). HRMS calcd for $C_{17}H_{27}N_2O_{3+}$, 307.2022 ($+H^+$); found 307.2016.

*4.3.13. 2-((3-(3-Acetyl-1H-indol-1-yl)propyl)amino)-2-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)acetic acid (**5f**).* A mixture of **3h** (160 mg, 0.20 mmol), 1,4-benzodioxane-6-boronic acid (108 mg, 0.6 mmol), dihydroxy-acetic acid (56 mg, mmol) in dichloromethane (6 mL) was stirred for 48 h at room temperature. Evaporation of the solvent and purification by F-SPE gave 180 mg (84%) of intermediate **4f** as a light brown sticky solid. Purity by LC–UV(ELS)=99%(100%). Intermediate **4f** (84 mg, 87 mmol) was dissolved in 2,2,3,3-tetrafluoropropanol (2 mL), added Pd/C 10% (28 mg, 26 mmol), and hydrogenated under 3 bar H_2 at 80 °C for 16 h in an Argonaut Endeavor apparatus. The mixture was filtered through Celite and purified by F-SPE to give 16 mg (45%) of **5f** as a white solid. Purity by LC–UV(ELS)=46%(ND). Additional purification of 12 mg by preparative LC–MS yielded 2 mg of yellow oil. Purity by LC–UV(ELS)=93%(100%). HRMS calcd for $C_{23}H_{25}N_2O_5^+$, 409.1763 ($+H^+$); found 409.1751.

*4.3.14. 2-(Isopentylamino)-2-(1-(phenylsulfonyl)indolin-3-yl)acetic acid (**5g**).* A mixture of **3f** (171 mg, 0.25 mmol), 1-(phenylsulfonyl)-3-indoleboronic acid (761 mg, 2.5 mmol), dihydroxy-acetic acid (349 mg, 3.8 mmol) in dichloromethane (6 mL) was stirred for 48 h at room temperature. Evaporation of the solvent and purification by F-SPE gave 222 mg (92%) of intermediate **4g** as a brown oil. Purity by LC–UV(ELS)=84%(100%). Intermediate **4g** (218 mg) was dissolved in 2,2,3,3-tetrafluoropropanol (2 mL), added Pd/C 10% (54 mg, 51 mmol), and hydrogenated under 3 bar H_2 at 80 °C for 16 h in an Argonaut Endeavor apparatus. The mixture was filtered through Celite and purified by F-SPE to give 61 mg (60%) of **5f** as a yellow solid. Purity by LC–UV(ELS)=34%(57%). Additional purification of 57 mg by preparative LC–MS yielded 12 mg (12%) of a yellow solid. Purity by LC–UV(ELS)=90%(100%); ^{1}H NMR (CD_3OD) δ 0.88–0.99 (m,6H), 1.49–1.69 (m, 3H), 2.89–3.01 (m, 2H), 3.87–3.92 (m, 1H), 3.98–4.13 (m, 3H), 7.04–7.08 (m, 1H), 7.27–7.35

(m, 2H), 7.52–7.67 (m, 4H), 7.84–7.88 (m, 2H). HRMS calcd for $C_{21}H_{27}N_2O_4S^+$, 403.1692 ($+H^+$); found 403.1688.

*4.3.15. Ethyl 7-((1-(4-isopropylphenyl)-2-methoxy-2-oxoethyl) amino)heptanoate (**8**). Esterification using TMS-CH_2N_2*: A mixture of **4c** (626 mg, 0.694 mmol), dry toluene (30 mL), and dry methanol (15 mL), was added 2 M trimethylsilyl diazomethane in hexane (690 μL, 1.4 mmol) and stirred for 1 h. The reaction mixture was then quenched with acetic acid (1.5 mL), transferred to a product vial and evaporated to give 619 mg (97%) of the methyl ester of **4c** as a yellow oil. Purity by LC–UV(ELS)=52%(100%); ^{1}H NMR δ 1.22–1.37 (m, 13H), 1.56 (m, 4H), 2.25 (t, J=7.5 Hz, 2H), 2.28–2.40 (m, 2H), 2.53–2.61(m, 1H), 2.62–2.70(m, 1H), 2.86–2.95 (m, 3H), 3.68 (s, 3H), 4.11 (q, J=7.1 Hz, 2H), 4.41 (s, 1H), 4.62–4.70 (m, 1H), 4.89–4.96 (m, 1H), 7.14–7.22 (m, 6H), 7.42 (d, J=8.1 Hz, 2H); ^{13}C NMR δ 14.2, 23.87, 23.92, 24.9,26.2, 26.6, 26.8, 29.0, 33.0 (t, J=22 Hz), 33.8, 34.3, 51.9, 56.7, 60.2, 75.4, 126.7, 128.3, 128.8, 129.2, 132.6, 135.5, 138.8, 149.5, 171.2, 173.7; HRMS calcd for $C_{38}H_{43}F_{17}NO_5^+$, 916.2864 ($+H^+$); found 916.2825. *N–O cleavage using Mo(CH_3CN)$_3$(CO)$_3$*: A microwave vial was added the methyl ester of **4c** (105 mg, 0.115 mmol), tris(acetonitrile)molybdenumtricarbonyl (52 mg, 0.172 mmol), methanol (2.5 mL), flushed with argon and sealed with a cap. The mixture was sonicated with ultrasound for 15 min and then heated in a microwave for 15 min at 160 °C. The mixture was then added satd aq Bicarbonate (3 mL), water (3 mL), ethyl acetate (6 mL) and stirred overnight with no lid on the tube. It was then extracted with ethyl acetate (3×20 mL) and washed with water (20 mL). The combined organic phases were evaporated and purified by F-SPE. The non-fluorous fraction was concentrated in vacuo and dried in a vacuum centrifuge to give 31 mg (74%) of **8** as a yellow sticky solid. Purity by LC–UV(ELS)=100%(100%); ^{1}H NMR δ 1.22–1.26 (m, 9H), 1.29–1.35 (m, 4H), 2.01 (br s, 1H), 2.27 (t, J=7.6 Hz, 2H), 2.45–2.51 (m, 1H), 2.54–2.59 (m, 1H), 2.89 (hept, J=6.9 Hz, 1H), 3.69 (s, 3H), 4.11 (q, J=7.2 Hz, 2H), 4.33 (s, 1H), 7.19 (d, J=8.1 Hz, 2H), 7.27(d, J=8.1 Hz, 2H); ^{13}C NMR δ 14.2, 23.8, 24.8, 26.8, 28.9, 29.8, 33.7, 34.2, 47.7, 52.1, 60.1, 65.3, 126.7, 127.2, 135.4, 148.6, 173.73, 173.75; HRMS calcd for $C_{21}H_{34}NO_{4+}$, 364.2482 ($+H^+$); found 364.2480.

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