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Fluorous (Trimethylsilyl)ethanol: A New Reagent for Carboxylic Acid Tagging and Protection in Peptide Synthesis

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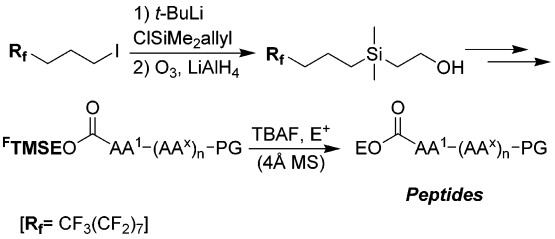
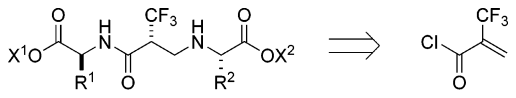


Starting with a fluorous analogue of 2-(trimethylsilyl)ethanol, we have designed an easy method for preparing a new fluorous tag (^{F}TMSE) for the protection of carboxylic acids. Because mild conditions are employed in the tag cleavage (TBAF in the presence of 4 Å molecular sieves, which prevent racemization), this tag can be advantageously used in the synthesis of peptides and modified peptides, as we have demonstrated with several examples, including the fluorous synthesis of short α- and *β*-peptides as well as of modified fluorinated retropeptides.

Fluorous chemistry is emerging as a powerful technique for the synthesis of organic molecules in a high-throughput manner[1] because the isolation of highly fluorinated (fluorous) compounds from nonfluorous reagents or byproducts can be performed by simple liquid−liquid or solid−liquid extractions with perfluorinated solvents or fluorous silica gel, respectively.[2] Moreover, since the reactions of fluorous substrates and/or reagents are conducted in solution, they constitute an alternative to established solid-phase methods. One obvious field for the application of fluorous chemistry is the preparation of peptides. Although peptide synthesis is routinely performed on solid phase, fluorous chemistry can offer numerous advantages, such as the possibility of working on a larger scale, better solution kinetics compared to solid phase, purifying intermediates by means of fluorous solid-phase extraction techniques (F-SPE), and identifying and analyzing the synthetic intermediates by means of spectroscopic methods such as NMR.[3,4]

SCHEME 1



A fluorous synthesis usually entails attaching a highly fluorinated moiety (fluorous tag) to a chosen substrate. Not only must the tag be compatible with the subsequently employed reaction conditions, but it should also be easy to remove at the end of the synthetic sequence.[5] Thus, one of the difficulties that the currently available tags present in the fluorous preparation of peptides is that of cleavage, in which a partial epimerization of the individual peptidic residues occurs. This is a serious problem that must be addressed in order to apply fluorous procedures to efficient peptide preparation. To test the usefulness of fluorous tagging in the synthesis of peptides and modified peptides, we examined its implementation in the synthesis of partially modified retropeptides (PMR) **1**, which our group had described from (α-trifluoromethyl)acryloyl chloride **2** and various amino acids, both in solution[6] and on solid phase[7] (Scheme 1). These peptidomimetic molecules contain a configurationally stable trifluoromethyl unit[8] which is, however, easily prone to epimerization under acidic or basic conditions, and thus they constitute an interesting example of the possibilities of fluorous chemistry.

In our first attempt to adapt our synthesis to fluorous techniques, we tried a simple fluorous tag derived from commercially available 3-(perfluorooctyl)propanol **3**.[9] The standard coupling of this alcohol with Fmoc-protected L-valine afforded fluorous amino acid **4** (Scheme 2).[9b] After deprotection of the Fmoc group with piperidine, free amine **5** was reacted with (α-trifluoromethyl)acryloyl chloride **2**[10] to obtain the Michael acceptor **6** in good yield. The key aza-Michael addition was tested with L-valine *tert*-butyl ester hydrochloride under what we had previously established to be optimal conditions

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(1) (a) Studer, A.; Hadida, S.; Ferritto, R.; Kim, S.-Y.; Jeger, P.; Wipf, P.; Curran, D. P. *Science* **1997**, *275*, 823−826. (b) Zhang, W. *Tetrahedron* **2003**, *59*, 4475−4489. (c) *Handbook of Fluorous Chemistry*; Gladysz, J. A., Curran, D. P., Horváth, I. T., Eds.; Wiley-VCH: Weinheim, 2004.

(2) Curran, D. P. *Synlett* **2001**, 1488−1496.

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(4) Fluorous moieties have also been attached to peptides at the end of a solid-phase synthesis so that fluorous techniques could be used for their purification. See: (a) de Visser, P. C.; van Helden, M.; Filippov, D. V.; van der Marel, G. A.; Drijfhout, J. W.; van Boom, J. H.; Noort, D.; Overkleeft, H. S. *Tetrahedron Lett.* **2003**, *44*, 9013−9016. (b) Montanari, V.; Kumar, K. *J. Am. Chem. Soc.* **2004**, *126*, 9528−9529.

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(6) Sani, M.; Bruché, L.; Chiva, G.; Fustero, S.; Piera, J.; Volonterio, A.; Zanda, M. *Angew. Chem., Int. Ed.* **2003**, *42*, 2060−2063.

(7) Volonterio, A.; Chiva, G.; Fustero, S.; Piera, J.; Sánchez-Roselló, M.; Sani, M.; Zanda, M. *Tetrahedron Lett.* **2003**, *44*, 7019−7022.

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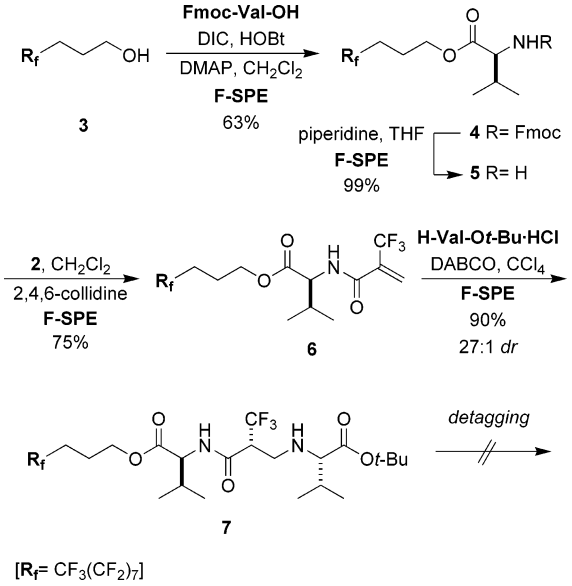
SCHEME 2

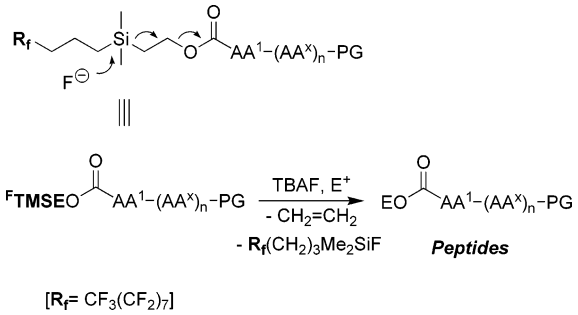


(DABCO, CCl_4)[6] to furnish compound **7** as a mixture of diastereoisomers in a 27:1 ratio. This selectivity, determined with the aid of ^{19}F NMR spectroscopy, was not only comparable to the diastereomeric ratio previously reported using the corresponding nonfluorous compound (33:1),[6] but much better than that observed on solid phase (4.8:1).[7] Obviously, both reactions in solution (fluorous and nonfluorous) benefit from the same transition state that determines the high level of diastereoselectivity, in contrast to the results obtained on solid phase. It should also be noted that all of the synthetic intermediates were easily purified through fluorous solid-phase extraction (F-SPE) to remove any excess nonfluorinated reagents, thereby speeding up and simplifying the purification steps.[11]

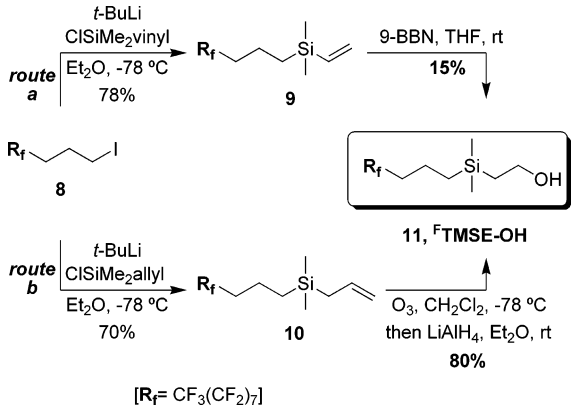
Having proved that the attachment of a simple fluorous tag was compatible with the synthetic plan and did not affect the diastereoselectivity of the aza-Michael process, we unfortunately found that its removal was an impossible task, due to the fact that mild reaction conditions were required to preserve the peptidic structure, particularly the configuration of the CF_3 group. Although several transesterification reactions were tried, they were ineffective in all cases.[12] For this reason, we embarked on the development of a new tag that would be easier to remove. We reasoned that a fluorous analogue of 2-(trimethylsilyl)-ethanol would react with carboxylic acids to afford fluorous (trimethylsilyl)ethyl (^{F}TMSE) esters, and the later removal of the resulting fluorous tag should be carried out easily by a transesterification reaction in the presence of TBAF (Scheme 3).

Thus, the reagent 2-(dimethyl-(3-(perfluorooctyl)propyl)silyl)-ethanol **11** (^{F}TMSE-OH) was prepared in two steps from

SCHEME 3



SCHEME 4



commercially available 3-(perfluorooctyl)propyl iodide **8** (Scheme 4). Metalation of **8** with *tert*-butyllithium followed by reaction with either chloro(dimethyl)vinylsilane (route *a*) or allylchlorodimethylsilane (route *b*) afforded compounds **9** and **10**, respectively. While hydroboration of **9** with several borane reagents (BH_3·SMe_2, BH_3·THF complex, 9-BBN) only produced a low yield (15% using 9-BBN, route *a*) of the desired alcohol **11**, ozonolysis of **10** and subsequent reduction of the resulting ozonide with $LiAlH_4$ was a much more effective route to synthetically useful yields of **11** (80%, route *b*).[13]

Coupling the thus-obtained fluorous alcohol **11** with *N*-Fmoc-protected L-valine or L-alanine gave compounds **12a** and **12b**, respectively, in good yield after fluorous SPE purification (Scheme 5). At this point, we decided to test the detagging conditions on **12a** and found that its treatment with TBAF in the presence of benzyl bromide removed both the fluorous tag and the Fmoc group to afford valine benzyl ester **13** with no loss of optical purity. In this case, purification by means of F-SPE served to remove the fluorinated byproducts. In contrast, deprotection of the Fmoc group with piperidine yielded free amines **14a**,**b** with the fluorous chain intact.

We next used fluorous amino acids **14** to prepare some examples of simple peptides. Thus, condensation with different *N*-Boc-protected α- or *β*-amino acids afforded compounds **15a**−**e**, which were detagged as before to produce dipeptides **16a**−**e** (Table 1). Starting from **15e**, the fluorous tag was alternatively removed in the presence of allyl bromide to afford dipeptide **16f**. It was also possible to obtain directly the corresponding carboxylic acid as demonstrated in the reaction of **15e** with TBAF solely, to produce **16g**. For the preparation of longer peptidic chains, fluorous dipeptide **15a** was deprotected with

(11) Alternatively, purification by means of standard flash column chromatography was also possible.

(12) For instance, enzymatic transesterification with *Candida rugosa* lipase (Beier, P.; O'Hagan, D. *Chem. Commun.* **2002**, 1680−1681) yielded the desired cleaved product without epimerization, but in very low conversion (between 5 and 10%), even after 3 days at rt. $(CH_3)_3SnOH$ (Nicolaou, K. C.; Estrada, A. A.; Zak, M.; Lee, S. H.; Safina, B. S. *Angew. Chem., Int. Ed.* **2005**, *44*, 1378−1382), Verkade's superbase (Ilankumaran, P.; Verkade, J. G. *J. Org. Chem.* **1999**, *64*, 3086−3089), and distannoxanes (Otera, J.; Dan-oh, N.; Nozaki, H. *J. Org. Chem.* **1991**, *56*, 5307−5311) also failed to catalyze the ester hydrolysis.

(13) Surprisingly, the ozonide derived from **9** was so stable that it failed to react with Me_2S or $NaBH_4$ and had to be reduced with $LiAlH_4$.

SCHEME 5

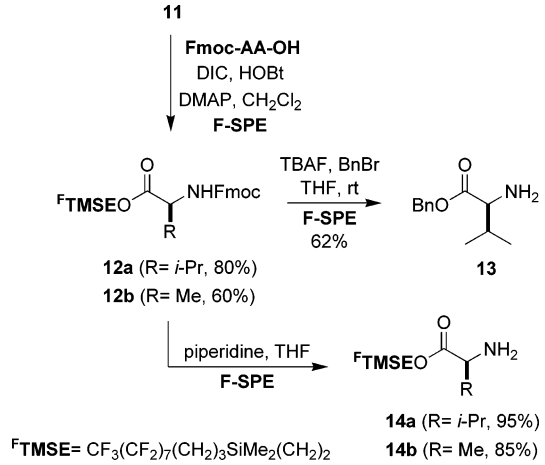
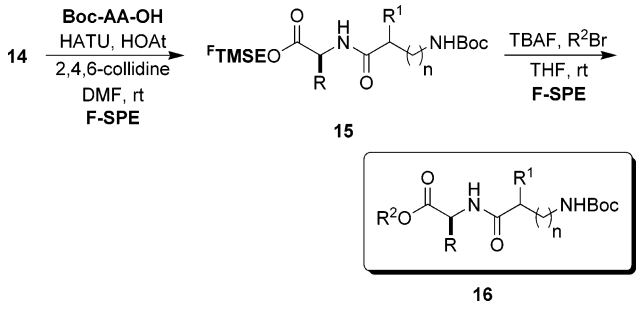


TABLE 1. Synthesis of Dipeptides 15 and 16



14	R	**15**	R^1	*n*	yield[a] (%)	**16**	R^2	yield[a] (%)
14a	*i*-Pr	**15a**	α-Me	0	80	**16a**	Bn	92
		15b	α-Ph	0	64	**16b**	Bn	79
		15c	*β*-Me	1	85	**16c**	Bn	92
14b	Me	**15d**	α-*s*-Bu	0	87	**16d**	Bn	85
		15e	α-Bn	0	80	**16e**	Bn	81
						16f	allyl	82
						16g	H[b]	78

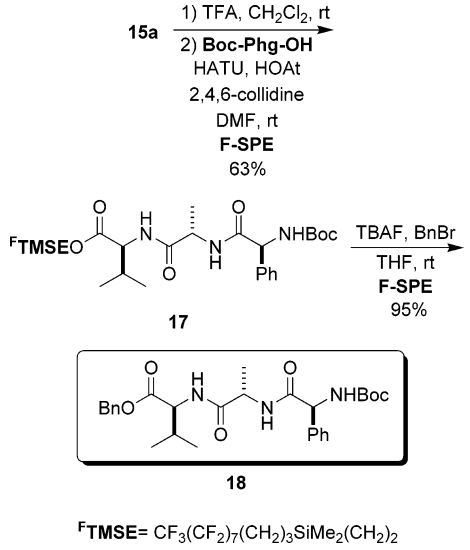
[a] Isolated yields. [b] The reaction was carried out in the presence of TBAF only. FTMSE = $CF_3(CF_2)_7(CH_3)_3SiMe_2(CH_2)_2$.

TFA and the corresponding free amine was coupled with *N*-Boc-L-phenylglycine to give **17**, which was detagged to yield tripeptide **18** (Scheme 6).

Finally, the fluorous synthesis of retropeptides **1** with the new tag was also carried out starting from compound **14a** (Scheme 7). The Michael aceptor **19** was produced in good yield under the usual conditions, and the subsequent addition of a variety of amino acids afforded fluorous retropeptides **20a**−**d** in essentially the same diastereomeric ratios as in the corresponding nonfluorous experiments[6,14] (Table 2). However, in this case the removal of the fluorous tag was more problematic because the reaction with TBAF/BnBr caused the epimerization of the CF_3 group, thus giving an almost equimolecular mixture of diastereoisomers. To circumvent this problem, we added activated 4 Å molecular sieves to minimize the presence of water, which we thought might be responsible for the epimerization.[15] Retropeptides **1a**−**d** were thus obtained with no variation in their diastereomeric ratios compared to their

(14) The same reactions on solid phase (ref 7) also showed much lower diastereoselectivities. For instance, the corresponding carboxylic acids of compounds **20a** and **20d** were obtained after release from the solid support in 15:1 and 2.1:1 diastereomeric ratios, respectively.

SCHEME 6



SCHEME 7

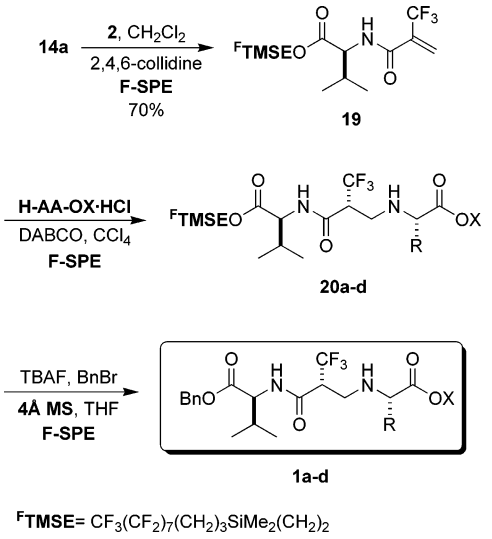


TABLE 2. Synthesis of Retropeptides 20 and 1

20	R	X	yield[a] (%)	dr (fluorous)[b]	dr (nonfluorous)[c]	**1**	yield[a] (%)
20a	*i*-Pr	Bn	87	39:1	38:1	**1a**	77
20b	*i*-Bu	Bn	99	21:1	11:1	**1b**	70
20c	*s*-Bu	*t*-Bu	92	27:1	23:1	**1c**	60[d]
20d	Me	Me	88	15:1	14:1	**1d**	81

[a] Isolated yields. [b] Determined by ^{19}F NMR spectroscopy in the crude reaction mixture. [c] Reference 6. [d] 73% brsm yield.

precursors **20**. After F-SPE extraction, standard column chromatography on silica gel was used to isolate pure retropeptides **1**, the spectroscopic data of which was identical to that for the same compounds prepared with nonfluorous precursors.[16]

In summary, we have prepared a new fluorous alcohol for the convenient protection and tagging of carboxylic acids and

(15) Rigby, J. H.; Laxmisha, M. S.; Hudson, A. R.; Heap, C. H.; Heeg, M. J. *J. Org. Chem.* **2004**, *69*, 6751−6760.

(16) Retropeptides **1a**,**b**,**d** were previously described in ref 6. Compound **1c** was also synthesized in two steps in a manner analogous to that described therein.

demonstrated its usefulness in the fluorous synthesis of peptides and retropeptides, even on substrates that are easily epimerized, thanks to the mild reaction conditions needed for the removal of the fluorous (trimethylsilyl)ethyl (^{F}TMSE) group. Further investigations on the applications of this fluorous tag are currently underway.

Experimental Section

Synthesis of Allyl(dimethyl)(3-(perfluorooctyl)propyl)silane, 10. A solution of 3-(perfluorooctyl)propyl iodide **8** (2.0 g, 3.4 mmol) in Et_2O (70 mL) was added to a flask containing a stirred solution of *t*-BuLi (1.7 M in pentane, 5.0 mL, 8.5 mmol) at −78 °C, and the mixture was warmed to −10 °C. After being stirred for 30 min, the reaction was again cooled to −78 °C and a solution of allylchlorodimethylsilane (1.2 mL, 5.1 mmol) in Et_2O (12 mL) was added. After the mixture was stirred at rt for 5 h, the reaction was quenched with water and the phases were separated. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated at reduced pressure. The crude material was purified by means of flash column chromatography with hexane to give 1.3 g of **10** as a colorless oil (70% yield). R_f = 0.96 (hexane). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.02 (s, 6H), 0.57−0.63 (m, 2H), 1.51−1.67 (m, 4H), 1.99−2.17 (m, 2H), 4.82−4.89 (m, 2H), 5.70−5.84 (m, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ −3.4, 15.2, 15.4 (t, $^3J_{CF}$ = 3.7 Hz), 23.5, 35.1 (t, $^2J_{CF}$ = 22.7 Hz), 113.6, 135.2, (the signals from the C_8F_{17} group were obscured due to their low intensity). ^{19}F NMR ($CDCl_3$, 282.4 MHz): δ −81.3 (t, $^3J_{FF}$= 8.4 Hz, 3F), −114.9 (br, 2F), −122.4 (br, 6F), −123.2 (br, 2F), −124.1 (br, 2F), −126.6 (br, 2F).

Synthesis of 2-(Dimethyl-(3-(perfluorooctyl)propyl)silyl)-ethanol, 11. Ozone was bubbled into a cold (−78 °C) solution of **10** (1.02 g, 1.82 mmol) in CH_2Cl_2 (90 mL) until a blue color appeared. The reaction mixture was then concentrated at reduced pressure. The residue was dissolved in Et_2O (45 mL) and cooled to 0 °C, and $LiAlH_4$ (270 mg, 7.2 mmol) was added. After the mixture was stirred at rt for 16 h, the reaction was quenched with 0.27 mL of water, followed by 0.27 mL of NaOH (10% aq) and 1.08 mL of water. The suspension was filtered, dried over Na_2SO_4, and concentrated at reduced pressure. The crude material was purified by means of flash chromatography (hexane/EtOAc 4:1) to give 820 mg of **11** as a white solid (80% yield). R_f = 0.36 (hexane/EtOAc 4:1). Mp: 41−42 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.04 (s, 6H), 0.57−0.63 (m, 2H), 0.95−1.01 (m, 2H), 1.39 (br, 1H), 1.56−1.67 (m, 2H), 1.99−2.16 (m, 2H), 3.71−3.77 (m, 2H). ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ −3.0, 15.2 (t, $^3J_{CF}$= 3.7 Hz), 15.7, 20.8, 34.9 (t, $^2J_{CF}$= 21.9 Hz), 60.2, (the signals from the C_8F_{17} group were obscured due to their low intensity). ^{19}F NMR ($CDCl_3$, 282.4 MHz): δ -81.3 (t, $^3J_{FF}$= 10.5 Hz, 3F), −114.9 (br, 2F), −122.4 (br, 6F), −123.2 (br, 2F), −124.1 (br, 2F), −126.6 (br, 2F).

General Procedure for the Detagging of Fluorous Peptides (General Procedure A). To a stirred solution of the corresponding fluorous peptide (1.0 equiv) in THF (0.01 M) were added TBAF (1 M in THF, 1.3 equiv) and benzyl or allyl bromide (1.5 equiv). After the mixture was stirred at rt for 1 h, the crude was concentrated at reduced pressure and purified by means of F-SPE.

Synthesis of Boc-Phe-Ala-OBn, 16e. Following general procedure A (employing BnBr), from **15e** (13 mg, 0.015 mmol), 5 mg of **16e** was obtained as a colorless oil (81% yield). $[\alpha]^{25}_D$ = −6.0 (*c* 1.35, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.29 (d, *J* = 7.2 Hz, 3H), 1.33 (s, 9H), 2.99 (d, *J* = 7.0 Hz, 2H), 4.32 (br, 1H), 4.45−4.55 (m, 1H), 5.02 (br, 1H), 5.08 (s, 2H), 6.52 (d, *J* = 6.6 Hz, 1H), 7.11−7.30 (m, 10H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 18.5, 28.4, 38.6, 48.4, 55.8, 67.3, 80.4, 127.1, 128.3, 128.6, 128.8, 129.5, 135.5, 136.7, 155.6, 171.1, 172.5. HRMS (FAB): calcd for $C_{24}H_{31}N_2O_5$ (M^+ + 1) 427.2233, found 427.2233.

Synthesis of Boc-Phe-Ala-OCH$_2$CH=CH$_2$, 16f. Following general procedure A (employing allyl bromide), from **15e** (26 mg, 0.029 mmol), 9 mg of **16f** was obtained as a colorless oil (82% yield). $[\alpha]^{25}_D$ = −25.0 (*c* 0.4, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.31 (d, *J* = 7.2 Hz, 3H), 1.35 (s, 9H), 3.00−3.03 (m, 2H), 4.29 (br, 1H), 4.43−4.56 (m, 3H), 4.91 (br, 1H), 5.18−5.29 (m, 2H), 5.76−5.89 (m, 1H), 6.35 (d, *J* = 6.9 Hz, 1H), 7.13−7.27 (m, 5H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 18.5, 28.2, 38.3, 48.2, 55.7, 66.0, 80.3, 118.8, 127.0, 128.7, 129.4, 131.4, 136.5, 155.3, 170.7, 172.1. HRMS (FAB): calcd for $C_{20}H_{29}N_2O_5$ (M^+ + 1) 377.2076, found 377.2065.

Synthesis of Boc-Phe-Ala-OH, 16g. Following general procedure A (employing TBAF only), from **15e** (17 mg, 0.019 mmol), 5 mg of **16g** was obtained as a white solid (78% yield). Mp: 92−93 °C. $[\alpha]^{25}_D$ = +0.7 (*c* 0.5, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.22−1.32 (m, 12H), 2.97 (br, 2H), 4.41 (br, 2H), 5.29 (br, 1H), 6.88 (br, 1H), 7.11−7.20 (m, 5H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 18.2, 28.4, 38.6, 48.7, 55.8, 80.7, 127.2, 128.8, 129.6, 136.7, 156.0, 171.8, 176.1. HRMS (FAB): calcd for $C_{17}H_{25}N_2O_5$ (M^+ + 1) 337.1763, found 337.1757.

General Procedure for the Detagging of Fluorous Retropeptides (General Procedure B). A 0.01 M solution of TBAF (1.3 equiv) in THF was stirred over powdered, activated 4 Å molecular sieves (ca. 200 mg/mL of TBAF solution) for 20 min, after which a solution of the corresponding fluorous retropeptide (1.0 equiv) in THF (0.1 M) and BnBr (1.5 equiv) was added. After the mixture was stirred at rt for 1.5 h, the crude was filtered, concentrated at reduced pressure, and purified by means of F-SPE. The resulting mixture of retropeptides was separated with the aid of flash column chromatography.

Synthesis of BnO-Val-CF$_3$-Ile-OtBu, 1c. Following general procedure B, from **20c** (22 mg, 0.023 mmol), 7 mg of **1c** was obtained as a white solid (60% yield, 73% brsm yield). Mp: 48−50 °C. $[\alpha]^{25}_D$ = +7.1 (*c* 1.1, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.77−0.82 (m, 9H), 0.88 (d, *J* = 6.9 Hz, 3H), 1.00−1.14 (m, 1H), 1.33−1.45 (m, 1H), 1.49 (s, 9H), 1.53−1.63 (m, 1H), 1.77 (br, 1H), 2.11−2.22 (m, 1H), 2.91−3.03 (m, 4H), 4.55 (dd, *J* = 8.8, 4.7 Hz, 1H), 5.05 (d, *J* = 12.2 Hz, 1H), 5.14 (d, *J* = 12.2 Hz, 1H), 7.24−7.32 (m, 5H), 7.49 (d, *J* = 8.8 Hz, 1H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 12.0, 15.8, 17.9, 19.4, 25.9, 28.4, 31.2, 38.9, 45.8 (q, $^3J_{CF}$ = 2.9 Hz), 51.3 (q, $^2J_{CF}$ = 24.7 Hz), 57.7, 67.4, 67.5, 81.9, 124.9 (q, $^1J_{CF}$ = 280.0 Hz), 128.7, 128.8, 128.9, 135.7, 166.8 (q, $^3J_{CF}$ = 1.7 Hz), 172.1, 172.0, 174.9; ^{19}F NMR ($CDCl_3$, 282.4 MHz) δ −66.7 (d, J_{HF} = 8.7 Hz, 3F). HRMS (FAB): calcd for $C_{26}H_{40}F_3N_2O_5$ (M^+ + 1) 517.2889, found 517.2901.

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Supporting Information Available: Experimental procedures and characterization data for compounds **1a**−**b, 1d**, **4**−**7**, **9**, **12**−**15**, **16a**−**d**, and **17**−**20** and copies of NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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