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Convergent synthesis of functionalized fluoroallylamines by the Julia–Kocienski reaction

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ABSTRACT

The synthesis of β-fluoroallylamines is reported from aminofluorobenzothiazolylsulfones. These open a new route for a short synthesis of vinylic fluoride containing highly functionalized amino residues.

1. Introduction

Peptides are not suitable as therapeutic agents due to their in vivo degradation by peptidases, thus synthetic peptidomimetics, stable toward enzymatic cleavage, were designed as potential drug substance.[1] Fluorinated peptide mimics represent an important class and it is established that the replacement of a specific amide bond by a fluorinated carbon–carbon double bond acted as a surrogate of a natural peptide.[2,3] Almost synthetic routes for the preparation of fluorinated peptidomimetics and for instance the formation of the fluoroalkylidene moiety, involved the synthesis of functionalized allylamine intermediates.

These latter were obtained from α-fluoro-α,β-unsaturated esters after further chemical modifications, or from corresponding allylic alcohols through a sigmatropic rearrangement (Fig. 1A), and from *gem*-difluoroallyl unsaturated-amides, -esters through a defluorination reaction (Fig. 1B).[4]

The most straightforward and convergent approach to prepare allylamines in one step is the Wittig and related reactions. However, it has been reported that the HWE reaction cannot be applied to the direct synthesis of fluoroalkylidene derivatives from fluoroalkyl-phosphonates,[5] and up to date the derivation of fluorovinylphosphonium salts by conjugated addition of amines is the sole possibility to produce the corresponding allylamines by trapping the intermediate ylide by aldehydes.[5c] The Julia–Kocienski reaction was commonly used for the synthesis of highly functionalized intermediates involved in the total synthesis of natural products,[6] and

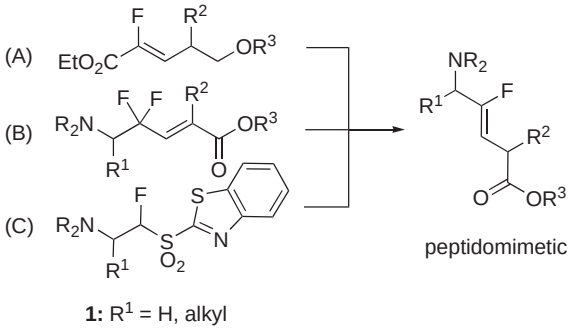

Fig. 1. Fluoroolefins as peptidomimetics.

only one example related to the preparation of alkenes as peptide mimics from tetrazolyl-aminosulfones was reported.[7] Based on the success of the Julia–Kocienski reaction to prepare fluoroethylidene derivatives in one step from heteroaromatic fluoroalkylsulfones,[8] reagents, such as benzothiazolylsulfones **1** (Fig. 1C) appeared attractive to open a new access to fluorinated allylamines and peptide mimics.

Since its first report, the modified Julia fluoroolefination reaction was extended to a large variety of π-deficient aromatic fluorosulfones substituted by an electron-withdrawing or aromatic groups to produce the corresponding α-fluoro-α,β-unsaturated esters, sulfones, nitriles, amides, and aryles.[9] The replacement of the sulfonyl moiety by a sulfoximine, or the use of pyridinylsulfone derivatives have been proposed as an alternative.[10] However, the

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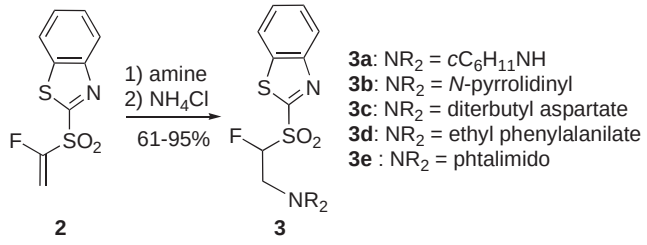
major limitation of the Julia–Kocienki reaction is the availability of functionalized reagents, such as substituted fluoroalkylsulfones, to prepare functionalized fluoroalkylidenes in one step. Previously we reported the preparation of benzothiazolyl aminosulfones **3** (Scheme 1) as potential reagents for the preparation of functionalized fluoroalkylidenes as precursors of peptidomimetics or bioconjugates through the modified Julia reaction.[11] We report our recent progress in this field, and in particular the use of these sulfones to develop a straightforward synthesis of functionalized fluoroallylamines and a short synthesis of a peptide mimic precursor.

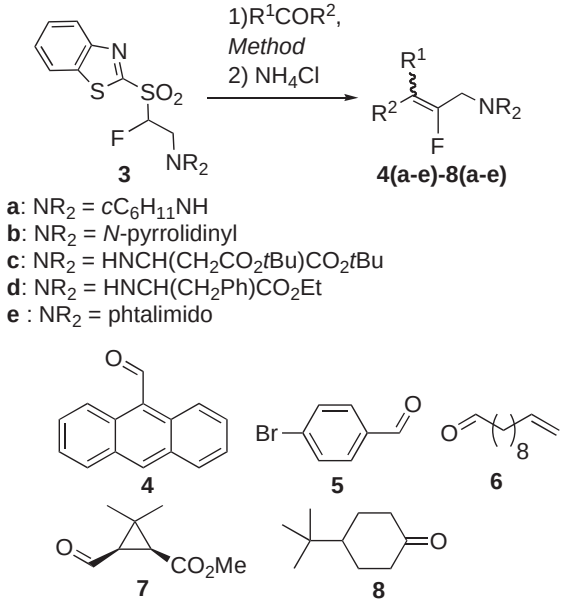


Scheme 1. Synthesis of functionalized aminosulfones by aza-Michael addition reaction.

2. Results and discussion

The synthesis of the aminosulfones **3** was not straightforward and we showed that the aza-Michael addition reaction onto vinylsulfone **2** allowed the introduction of a large variety of amines (Scheme 1).[11]

Study of the chemical behavior of functionalized fluoroalkylsulfones **3a–e** in the modified Julia reaction was investigated to prepare substituted fluoroalkylidene derivatives. Aminosulfones **3a** and **3b**, obtained from secondary and primary amines, were tested first (Scheme 2, Table 1).



Scheme 2. Julia–Kocienski reaction from aminosulfones and carbonyl compounds.

Four bases (DBU, TMG, *t*-BuOK, NaHMDS) were screened. DBU and TMG induced no reaction and the starting materials were partially recovered. However, when a solution of *t*-BuOK (1.3 equiv) in THF was slowly added to a solution of sulfone **3a** and carbonyl compound at −17 °C (method A), the reaction reached completion after 1 h of stirring. Under this Babier type conditions, no retro-Michael addition was observed and from secondary aminosulfone **3a** and aromatic aldehydes corresponding fluoroallylamines **4a** and **5a** were isolated in 68% and 88% yields, respectively (Table 1, entries 1 and 2). The addition onto aliphatic aldehydes afforded the corresponding amines **6a** and **7a** in 62–79% (Table 1, entries 3 and 4). In both cases a mixture of *Z*/*E* alkenes was obtained.

Table 1
Synthesis of aliphatic secondary and tertiary fluoroallylamines

Entry	RCOR′	Yield (%)[a] from **3a**, (method)[b]	*Z*/*E*[c]	Yield (%)[a] from **3b**, (method)[b]	*Z*/*E*[c]
1	**4**	**4a**		**4b**	
		68, (A)	85:15	60, (A)	45:55
2	**5**	**5a**		**5b**	40:60
		88, (A)	30:70	53, (A)	
				70, (B)[d]	
3	**6**	**6a**		**6b**	55:45
		79, (A)	55:45	31, (A)	
				74, (B)	
4	**7**	**7a**		**7b**	
		62, (A)	60:40	73, (B)	60:40
5	**8**	**8a**	—	**8b**	—
		24, (A)		34, (A)	
		78, (B)		95, (B)	

[a] Isolated yield by flash chromatography.
[b] (Method A) experiment realized in the presence of *t*-BuOK (1.3 equiv) at −17 °C, 1 h, THF. (Method B) experiment realized in the presence of NaHMDS (1.3–2.6 equiv) at −78 °C to 0 °C, 3 h, THF.
[c] Determined by ^{19}F NMR spectroscopy of the crude product.
[d] See Ref. 11.

The reaction with cyclic ketone **8** was more difficult, and product **8a** was isolated in low yield even after 12 h under stirring at room temperature (Table 1, entry 5). From tertiary aminosulfone **3b**, in the presence of *t*-BuOK, similar results were observed from aromatic aldehydes **4–5** (Table 1, entries 1 and 2), but not from aliphatic ones. From aldehyde **6** corresponding alkene **6b** was obtained in 31% yield, and no product was formed from sterically hindered aldehyde **7**. In theses cases, the alkene formation was improved by using NaHMDS instead of *t*-BuOK. Thus, from **3b**, in the presence of NaHMDS at −78 °C (method B), the isolated yields were increased and fluoroallylamines **4b–8b** were obtained in 73–95% yields, and good yields were observed from aliphatic aldehydes **6**, **7** (Table 1, entries 4 and 5). As shown in Table 1, even if NaHMDS is a less convenient base than *t*-BuOK, this was necessary to produce alkenes in acceptable yields.

The use of NaHMDS was also efficient when applied to 4-*tert*-butylcyclohexanone **8**. In this case the corresponding alkenes were isolated in 78–95% yields from sulfones **3a**,**b**.

However, poor *E*/*Z* selectivity was observed, and no influence of the nature of the base on the selectivity was noted. Some efforts were done to control the carbon–carbon double bond geometry. By using NaHMDS in the presence of $MgBr_2$, in THF or DME no effect was observed and the *Z*/*E* ratio was found mainly unchanged. It is well known that the Julia–Kocienski reaction is substrate-dependent and the selectivity is solved on a case-by-case.[6]

The reaction with sulfones **3c**,**d** derived from racemic amino acids was then tested (Scheme 2, Table 2). As observed from sulfone **3a**,**b**, the reaction reached completion when *t*-BuOK or NaHMDS were used as base at −17 °C and −78 °C, respectively. However, these substrates seem to be more sensitive to the reaction temperature and the nature of the base and better yields were obtained with NaHMDS. In the presence of *t*-BuOK, side products appeared in the crude ^{19}F NMR analysis. In the presence of NaHMDS, from sulfone **3c** containing a ditertiobutyl aspartate residue and aliphatic or aromatic aldehydes, the corresponding fluoroalkenes **4c–7c** were isolated in moderate to excellent yields (Table 2, entries 1–4), despite some difficulties occurring during their purification by flash column chromatography. In contrast from the sulfone **3d**

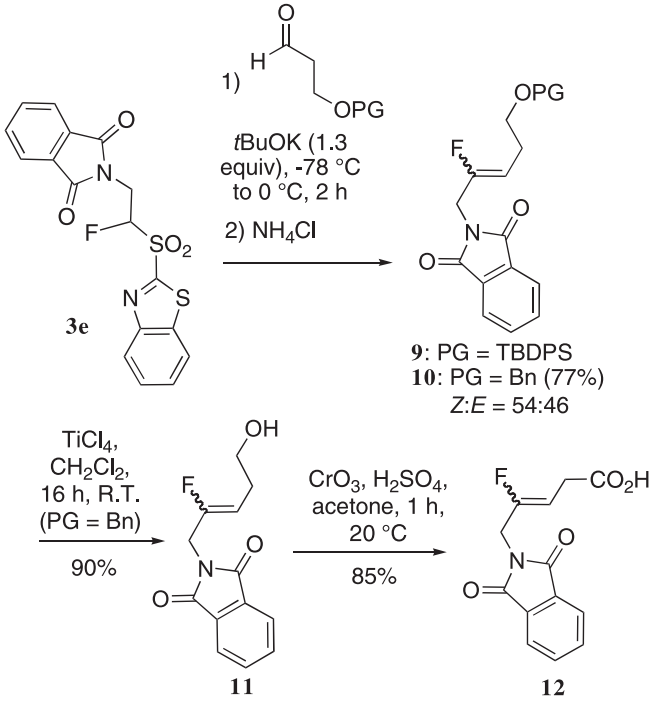
Table 2
Preparation of aminoacid and phtalimidoyl derivatives by method B

Entry	RCOR'	Yield (%) from **3c**[a]	*Z*/*E*[b]	Yield (%) from **3d**[a]	*Z*/*E*[b]	Yield (%) from **3e**[a]	*Z*/*E*[b]
1	**4**	**4c** 74	70:30	**4d** 60	20:80	**4e** 70	85:15
2	**5**	**5c** 72	60:40	**5d** 58	52:48	**5e** 56	90:10
3	**6**	**6c** 75	75:25	**6d** 21	60:40	**6e** 66	62:38
4	**7**	**7c** 77	69:41	**7d**[c] 20	70:30	**7e** 50	48:52
5	**8**	**8c** 27	—	**8d**[d]	—	**8e** 63	—

[a] Isolated yield by flash chromatography.
[b] Determined by ^{19}F NMR spectroscopy of the crude product.
[c] Not isolated.
[d] No reaction.

containing a phenylalanine residue, the reaction performed from aromatic aldehydes **4**, **5** afforded the corresponding allylamines **4d**, **5d** in 61% and 58%, but from aliphatic aldehydes **6**, **7**, compounds **6c**, **7c** were obtained in lower yields (Table 2, entries 3 and 4). Furthermore, the reaction realized with cyclic ketone **8** afforded the corresponding alkene **8c** in moderate yield from **3c**, and no product was formed from **3d**. It is noteworthy that as previously reported,[8a] no racemisation of the stereogenic center occurred during the reaction. In the crude ^{19}F NMR, from aldehyde **7** the only products formed were the corresponding *E*/*Z* alkenes.

The olefination of carbonyl compounds was extended to the phtalimidosulfone **3e** in the presence of NaHMDS at −78 °C (Table 2, entries 1–5). The reaction afforded the corresponding fluoroallylamines **4e**–**7e** in good yields (50–70%) from aliphatic and aromatic aldehydes **4**–**7**. The *E*/*Z* selectivity was poor to good. In contrast to the previous results obtained from **3c** or **3d**, the reaction performed from 4-*tert*-butylcyclohexanone afforded alkene **8e** in 63% yield, and the product was easier to purify. Having in hand the phtalimidosulfone **3e**, a short preparation of a potent glycidyl dipeptide precursor was explored from 3-alkoxy-propanal (Scheme 3).



Scheme 3. Synthesis of Gly–Gly peptidomimetic precursor.

The Julia–Kocienski reaction was realized from the protected 3-silyloxy-propanal (PG=TBDPS) and **3e**. The reaction reached completion after 2 h under stirring, however a mixture mainly composed of compound **9** and partially *O*-deprotected compound **9** was obtained. In a second approach the protected 3-benzyloxy-propanal was used, and in this case, the reaction afforded the expected olefin **10** as the sole reaction product. The compound **10** was isolated in 77% yield as a mixture of *Z*/*E* alkenes (54:46). The precursor of the Gly–Gly peptidomimetic was then prepared in two additional steps involving a deprotection of the primary alcohol in the presence of a Lewis acid ($TiCl_4$), followed by a Jones oxidation to produce the known protected acid **12** in 85% yield.[2b] This first straightforward synthesis of fluorinated allylamines from phtalimidosulfone **3e** and protected aldehyde illustrates the synthetic potential of the modified Julia reaction to prepare peptidomimetics. However, some limitations appeared due to the difficulties occurring in the preparation of sulfones containing other protected amino group (BocNH group). The aza-Michael addition onto vinylsulfone **2** is strongly dependent on the nucleophilic character of the nitrogen atom.[11] However, the deprotection and protection by a Boc protecting group will be achieved following previous method reported in the literature.[2d] Current works are underway to apply this approach for dipeptide mimics synthesis.

3. Conclusion

The first one-step synthesis of functionalized fluoroalkylidene derivatives, and in particular the synthesis of fluoroallylamines from carbonyl compounds and heterocyclic fluorosulfones by using the Julia–Kocienski reaction is reported. The preparation of the Gly–Gly peptide mimic precursor illustrates the interest of this new approach by a convergent synthesis of a dipeptide precursor in few steps. Current works are now under progress to generalize this strategy for the preparation of the most common dipeptide isosters, peptide nucleic acid mimics, and to find the most adapted heterocycle or experimental conditions to control the configuration of the alkenes.

4. Experimental section

4.1. General information

All reactions were carried out under an atmosphere of dry nitrogen in dried glassware with magnetic stirring. THF was dried by pressure filtration on a drier apparatus. HPLC grade ethyl acetate was used without further purification. Flash columns chromatography were realized on silica gel 60 (40–63 μm) and were followed by thin layer chromatography. The spots were visualized by UV-irradiation and/or $KMnO_4$ solution. NMR spectra were recorded on a 250 MHz or 400 MHz. NMR data appear in the following order: chemical shift in parts per million, multiplicity (s, singlet; d, doublet; t, triplet; q, quadruplet; m, multiplet), number of protons, coupling constant *J* in hertz. TMS and $CFCl_3$ are the internal standard for the $CDCl_3$ solutions. High-resolution mass data were recorded on a high-resolution mass spectrometer in the EI or ESI mode. All reagents are commercially available and used without further purification and aldehydes were freshly distilled prior used.

4.2. Method (A): general procedure for the preparation of fluorinated allylic amines (4a–8a) and (4b–8b) in the presence of *t*-BuOK

To a solution of aminosulfone **3a** or **3b** (1 equiv) and aldehyde (1.05 equiv) in THF at −17 °C was added slowly in 5 min a THF solution of *t*-BuOK (1.3 equiv). After 15 min at −17 °C, the mixture was stirred for 1 h at 0 °C and quenched by addition of a saturated

solution of NH_4Cl (1 mL) then extracted with CH_2Cl_2 (2×5 mL). Combined organic layers were washed with a 1 M solution of NaOH (1 mL) and brine, dried over $MgSO_4$, filtered, and evaporated under reduced pressure. The crude product was purified by flash column chromatography to give allylamines **4a**–**8a** and **4b**–**8b**.

*4.2.1. (Z/E)-N-Cyclohexyl-3-anthracen-9-yl-2-fluoro-propenamine (**4a**).* Following the method (A) from sulfone **3a** (90 mg, 0.26 mmol), anthraldehyde (57 mg, 0.27 mmol), and *t*-BuOK (38 mg, 0.34 mmol) in THF (5 mL). Purification by flash chromatography (pentane/AcOEt, gradient from 90:10 to 0:100) afforded successively alkenes (*E*)-**4a** and (*Z*)-**4a** (59 mg, 68%) as an orange oil. Compound (*E*)-**4a**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.57–0.84 (m, 6H), 1.16–1.31 (m, 4H), 1.86 (s, 1H), 2.13–2.20 (m, 1H), 3.04 (d, $^3J_{HF}$=19.5 Hz, 2H), 6.74 (d, $^3J_{HF}$=18.4 Hz, 1H), 7.37–7.39 (m, 4H), 7.89–7.91 (m, 2H), 8.05–8.08 (m, 2H), 8.32 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 23.4, 24.7, 31.7, 42.4 (d, $^2J_{CF}$=26.7 Hz), 53.5, 104.1 (d, $^2J_{CF}$=25.4 Hz), 124.2, 124.6, 124.8, 125.3, 126.0, 127.6, 129.3, 130.2, 159.7 (d, $^1J_{CF}$=258.8 Hz); ^{19}F NMR ($CDCl_3$, 376 MHz) δ −104.7 (dt, $^3J_{FH}$=18.4 , 19.5 Hz, 1F); MS (EI) *m*/*z* 334 $[M+H]^+$ (100), 235 (10); HRMS (ESI) *m*/*z* $[M+H]^+$ calcd for $C_{23}H_{25}FN$ 334.1971, found 334.1974. Compound (*Z*)-**4a**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.12–1.34 (m, 6H), 1.60–1.63 (m, 1H), 1.74–1.78 (m, 2H), 1.95–1.98 (m, 2H), 2.69–2.74 (m, 1H), 3.72 (d, $^3J_{HF}$=14.6 Hz, 2H), 6.42 (d, $^3J_{HF}$=38.6 Hz, 1H), 7.37–7.44 (m, 4H), 7.92–7.94 (m, 2H), 8.06 (d, $^3J_{HH}$=7.6 Hz, 2H), 8.35 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 24.0, 25.0, 32.3, 46.2 (d, $^2J_{CF}$=28.9 Hz), 54.5, 102.3 (d, $^2J_{CF}$=6.9 Hz), 124.1, 124.5, 124.9, 125.5, 125.9, 127.6, 128.7, 130.3, 157.2 (d, $^1J_{CF}$=268.4 Hz); ^{19}F NMR ($CDCl_3$, 376 MHz) δ −104.9 (dt, $^3J_{FH}$=38.6 , 14.6 Hz, 1F, F-9); MS (EI) *m*/*z* 334 $[M+H]^+$ (50), 235 (100); HRMS (ESI) *m*/*z* $[M+H]^+$ calcd for $C_{23}H_{25}FN$ 334.1971, found 334.1969.

*4.2.2. (Z/E)-N-Cyclohexyl-3-[4-bromophenyl]-2-fluoro-propenamine (**5a**).* Following the method (A) from sulfone **3a** (70 mg, 0.20 mmol), 4-bromobenzaldehyde (39 mg, 0.21 mmol), and *t*-BuOK (30 mg, 0.26 mmol) in THF (3 mL). Purification by flash chromatography (pentane/AcOEt, gradient 98:2 to 80:20) afforded successively alkenes (*E*)-**5a** and (*Z*)-**5a** (56 mg, 88%) as an orange oil. Compound (*E*)-**5a**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.80–1.20 (m, 6H), 1.51–1.54 (m, 1H), 1.61–1.71 (m, 4H), 2.38–2.43 (m, 1H), 3.52 (d, $^3J_{HF}$=21.1 Hz, 2H), 6.18 (d, $^3J_{HF}$=20.8 Hz, 1H), 7.01 (d, $^3J_{HH}$=8.2 Hz, 2H), 7.05 (d, $^3J_{HH}$=7.2 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 24.8, 26.0, 33.1, 43.7 (d, $^2J_{CF}$=27.0 Hz), 55.8, 109.4 (d, $^2J_{CF}$=28.1 Hz), 121.0, 130.1, 131.6, 132.5 (d, $^3J_{CF}$=13.4 Hz), 160.3 (d, $^1J_{CF}$=255.0 Hz); ^{19}F NMR ($CDCl_3$, 376 MHz) δ −104.1 (dt, $^3J_{HF}$=20.8 , 21.1 Hz, 1F); MS (EI) *m*/*z* 314 $[M(C_{15}H_{20}{}^{81}BrFN)+H]^+$ (100), 312 $[M(C_{15}H_{20}{}^{79}BrFN)+H]^+$ (100), 213 (67), 134 (20); HRMS (ESI) *m*/*z* $[M+H]^+$ calcd for $C_{15}H_{20}{}^{79}BrFN$ 312.0763, found 312.0777. Compound (*Z*)-**5a**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.76–1.30 (m, 6H), 1.50–1.53 (m, 1H), 1.53–1.56 (m, 2H), 1.56–1.87 (m, 2H), 2.43–2.59 (m, 1H), 3.48 (d, $^3J_{HF}$=15.7 Hz, 2H), 5.60 (d, $^3J_{HF}$=38.7 Hz, 1H), 7.28 (d, $^3J_{HH}$=8.6 Hz, 2H), 7.36 (d, $^3J_{HH}$=8.5 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 23.8, 24.8, 31.8, 46.3 (d, $^2J_{CF}$=28.9 Hz), 54.6, 105.9 (d, $^2J_{CF}$=6.9 Hz), 120.0, 129.1, 130.5, 130.9 (d, $^3J_{CF}$=2.2 Hz), 157.2 (d, $^1J_{CF}$=268.4 Hz); ^{19}F NMR ($CDCl_3$, 376 MHz) δ −106.8 (dt, $^3J_{FH}$=38.7 , 15.7 Hz, 1F); MS (EI) *m*/*z* 314 $[M(C_{15}H_{20}{}^{81}BrFN)+H]^+$ (100), 312 $[M(C_{15}H_{20}{}^{79}BrFN)+H]^+$ (50), 213 (100), 134 (15); HRMS (ESI) *m*/*z* $[M+H]^+$ calcd for $C_{15}H_{20}{}^{79}BrFN$ 312.0763, found 312.0777.

*4.2.3. (Z/E)-N-Cyclohexyl-2-fluoro-2,12-tridecadienamine (**6a**).* Following the method (A) from sulfone **3a** (70 mg, 0.20 mmol), undecenal (43 mg, 0.21 mmol), and *t*-BuOK (30 mg, 0.26 mmol) in THF (3 mL). Purification by flash chromatography (pentane/AcOEt, gradient 98:2 to 90:10) afforded a mixture of (*Z*/*E*) **6a** (47 mg, 79%) as a yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.78–0.81 (m, 3H), 1.08–1.20 (m, 28H), 1.50–2.30 (m, 19H), 2.42–2.58 (m, 2H), 3.02–3.12 (m, 2H), 3.32 (d, $^3J_{HF}$=17.4 Hz, 2H, *Z*), 3.36 (d, $^3J_{HF}$=18.2 Hz, 2H, *E*), 4.30–4.63 (m, 2H), 4.70 (dt, $^3J_{HF}$=37.4 Hz, $^3J_{HH}$=7.5 Hz, 1H, *Z*), 4.84–4.94 (m, 4H), 5.12 (dt, $^3J_{HF}$=21.8 Hz, $^3J_{HH}$=8.0 Hz, 1H, *E*), 5.69–5.79 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 22.4, 22.5, 23.7, 23.8, 24.3, 24.5, 24.8, 24.9, 27.8, 27.9, 28.0, 28.15, 28.1, 28.2, 28.3, 28.4, 28.5, 28.6, 28.9, 31.4, 31.6, 32.7, 41.0 (d, $^2J_{CF}$=28.7 Hz, *E*), 45.4 (d, $^2J_{CF}$=29.6 Hz, *Z*), 54.1, 54.3, 107.8 (d, $^2J_{CF}$=14.1 Hz, *E*), 108.2 (d, $^2J_{CF}$=19.7 Hz, *Z*), 113.0, 113.1, 138.1, 138.2, 153.7 (d, $^1J_{CF}$=253.0 Hz, *Z*), 156.1 (d, $^1J_{CF}$=246.1 Hz, *E*); ^{19}F NMR ($CDCl_3$, 376 MHz) δ −111.5 (dt, $^3J_{FH}$=21.8 , 18.2 Hz, 1F, *E*), −117.0 (dt, $^3J_{FH}$=37.4 , 17.4 Hz, 1F, *Z*); MS (EI) *m*/*z* 296 $[M+H]^+$ (47), 214 (50), 95 (100); HRMS (ESI) *m*/*z* $[M+H]^+$ calcd for $C_{19}H_{35}FN$ 296.2754, found 296.2752.

*4.2.4. (Z/E)-(1S,3S)-Methyl-3-(3-(cyclohexylamino)-2-fluoroprop-1-enyl)-2,2-dimethyl-cyclopropane-carboxylate (**7a**).* Following the method (A) from sulfone **3a** (100 mg, 0.29 mmol), biocartol-methylester (48 mg, 0.30 mmol), and *t*-BuOK (42 mg, 0.37 mmol) in THF (5 mL). Purification by flash chromatography (pentane/AcOEt, gradient 90:10 to 0:100) afforded a mixture of (*Z*/*E*) **7a** (51 mg, 62%) as a yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.98–1.06 (m, 4H), 1.08–1.16 (m, 18H), 1.55–1.65 (m, 2H), 1.65–1.67 (m, 8H), 1.76–1.79 (m, 4H), 2.07 (t, $^3J_{HH}$=9.1 Hz, 2H), 2.37–2.42 (m, 2H), 3.29 (d, $^3J_{HF}$=17.7 Hz, 2H, *Z*), 3.43 (d, $^3J_{HF}$=21.0 Hz, 2H, *E*), 3.57–3.60 (m, 6H), 5.06 (dd, $^3J_{HF}$=36.7 Hz, $^3J_{HH}$=9.6 Hz, 1H, *Z*), 5.49 (dd, $^3J_{HF}$=20.7 Hz, $^3J_{HH}$=8.4 Hz, 1H, *E*); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.6, 24.8, 24.9, 26.0, 26.1, 26.4, 26.5, 27.8, 27.9, 28.4, 28.5, 29.0, 29.1, 30.6, 30.7, 33.1, 33.2, 33.3, 42.9 (d, $^2J_{CF}$=28.3 Hz, *Z*), 47.2 (d, $^2J_{CF}$=28.3 Hz, *E*), 51.2, 51.3, 54.9, 55.1, 101.7 (d, $^2J_{CF}$=10.0 Hz, *E*), 103.3 (d, $^2J_{CF}$=27.3 Hz, *Z*), 157.8 (d, $^1J_{CF}$=248.3 Hz, *E*), 160.3 (d, $^1J_{CF}$=256.8 Hz, *Z*), 171.0, 171.5; ^{19}F NMR ($CDCl_3$, 376 MHz) δ −107.1 (dt, $^3J_{FH}$=20.7 , 21.0 Hz, 1F, *E*), −116.9 (dt, $^3J_{FH}$=36.7 , 17.7 Hz, 1F, *Z*); MS (EI) *m*/*z* 284 $[M+H]^+$ (62), 185 (77), 125 (100), 100 (66); HRMS (ESI) *m*/*z* $[M+H]^+$ calcd for $C_{16}H_{27}FNO_2$ 284.2026, found 284.2015.

4.3. Method (B): general procedure for the preparation of fluorinated allylic amines (8a), (4b–e), (5b–e), (6b–e), (7b–e), and (8b–e) in the presence of NaHMDS

To a solution of aminosulfone **3** (1 equiv) and aldehyde (1.05 equiv) in THF at −78 °C was added slowly in 5 min a solution of NaHMDS (1.3 or 2.6 equiv, 1 M in THF). After 15 min at −78 °C, the mixture was slowly warmed-up to 0 °C under stirring over 3 h and quenched by the addition of a saturated solution of NH_4Cl (1 mL) then extracted with CH_2Cl_2 (2×5 mL). Combined organic layers were washed with a 1 M solution of NaOH (1 mL) and brine, dried over $MgSO_4$, filtered, and evaporated under reduced pressure. The crude product was purified by flash column chromatography to give allylamines **8a**, **4b**–**8b**, **4c**–**8c**, **4d**–**6d**, and **4e**–**7e**.

*4.3.1. N-[2-(4-tert-Butyl-cyclohexylidene)-2-fluoroethyl]-cyclohexyl-amine (**8a**).* Following the method (B) from sulfone **3a** (100 mg, 0.29 mmol), *tert*-butylcyclohexanone (46 mg, 0.30 mmol), and NaHMDS (380 μL, 0.38 mmol, 1 M in THF) in THF (5 mL). Purification by flash chromatography (pentane/AcOEt, gradient 90:10 to 70:30) afforded compound **8a** (64 mg, 78%) as a yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.77 (s, 9H), 0.88–1.18 (m, 9H), 1.50–1.56 (m, 2H), 1.65–1.68 (m, 2H), 1.76–1.79 (m, 4H), 1.80–2.10 (m, 1H), 2.30–2.42 (m, 2H), 2.84 (m, 1H), 3.36 (d, $^3J_{HF}$=23.2 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 24.9, 25.0, 25.6, 25.7, 26.0, 27.5, 27.6, 28.2, 28.3, 32.4, 33.0, 33.3, 42.7 (d, $^2J_{CF}$=30.3 Hz), 48.0, 55.1, 118.3 (d, $^2J_{CF}$=14.9 Hz), 148.9 (d, $^1J_{CF}$=241.7 Hz); ^{19}F NMR ($CDCl_3$, 376 MHz) δ −121.8 (t, $^3J_{FH}$=23.2 Hz, 1F); MS (EI) *m*/*z* 282 $[M+H]^+$ (100), 163 (27), 107 (28), 100 (92); HRMS (ESI) *m*/*z* $[M+H]^+$ calcd for $C_{18}H_{33}FN$ 282.2597, found 282.2589.

*4.3.2. (Z/E)-N-[3-(Anthracen-9-yl)-2-fluoro-2-propenyl]-pyrrolidine (**4b**).* Following the method (B) from sulfone **3b** (100 mg, 0.32 mmol), anthraldehyde (68 mg, 0.33 mmol), and NaHMDS

(420 μL, 0.42 mmol, 1 M in THF) in THF (5 mL). Purification by flash chromatography (pentane/AcOEt, gradient 90:10 to 0:100) afforded successively alkenes (*E*)-**4b** and (*Z*)-**4b** (80 mg, 83%) as a yellow-green oil. Compound (*E*)-**4b**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.51–1.54 (m, 4H), 2.19–2.20 (m, 4H), 2.93 (d, $^3J_{HF}$=19.3 Hz, 2H), 6.74 (d, $^3J_{HF}$=18.7 Hz, 1H), 7.40–7.44 (m, 4H), 7.90–7.93 (m, 2H), 8.05–8.08 (m, 2H), 8.34 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 23.4, 52.7 (d, $^2J_{CF}$=24.1 Hz), 53.9, 105.6 (d, $^2J_{CF}$=25.2 Hz), 125.2, 125.8, 125.9, 127.0, 128.7, 130.3, 130.4, 131.3, 160.1 (d, $^1J_{CF}$=260.3 Hz); ^{19}F NMR ($CDCl_3$, 376 MHz) δ −102.3 (dt, $^3J_{FH}$=18.7 , 19.3 Hz, 1F); MS (EI) *m*/*z* 306 $[M+H]^+$ (90), 235 (100); HRMS (ESI) *m*/*z* $[M+H]^+$ calcd for $C_{21}H_{21}FN$ 306.1658, found 306.1667. Compound (*Z*)-**4b**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.81–1.85 (m, 4H), 2.73–2.76 (m, 4H), 3.51 (d, $^3J_{HF}$=15.3 Hz, 2H), 6.41 (d, $^3J_{HF}$=38.1 Hz, 1H), 7.35–7.42 (m, 4H), 7.89–7.91 (m, 2H), 8.03–8.05 (m, 2H), 8.32 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 23.7, 54.3, 56.7 (d, $^2J_{CF}$=28.0 Hz), 104.2 (d, $^2J_{CF}$=13.5 Hz), 125.1, 125.6, 126.0, 126.6, 127.0, 128.7, 129.7, 131.3, 158.3 (d, $^1J_{CF}$=265.0 Hz); ^{19}F NMR ($CDCl_3$, 376 MHz) δ −100.6 (dt, $^3J_{FH}$=38.1 , 15.3 Hz, 1F); MS (EI) *m*/*z* 306 $[M+H]^+$ (5), 235 (100); HRMS (ESI) *m*/*z* $[M+H]^+$ calcd for $C_{21}H_{21}FN$ 306.1658, found 306.1660.

*4.3.3. (Z/E)-N-(2-Fluoro-2,12-tridecadienyl)-pyrrolidine (**6b**).* Following the method (B) from sulfone **3b** (100 mg, 0.32 mmol), undecenal (56 mg, 0.33 mmol), and NaHMDS (420 μL, 0.42 mmol, 1 M in THF) in THF (5 mL). Purification by chromatography (pentane/AcOEt, gradient 90:10 to 0:100) afforded a mixture of (*Z*/*E*) **6b** (63 mg, 74%) as an orange oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.02–1.49 (m, 24H), 1.74–1.75 (m, 8H), 1.93–2.02 (m, 8H), 2.48–2.50 (m, 8H), 3.06 (d, $^3J_{FH}$=18.4 Hz, 2H, *Z*), 3.18 (d, $^3J_{HF}$=22.4 Hz, 2H, *E*), 4.63 (dt, $^3J_{HF}$=37.2 Hz, $^3J_{HH}$=7.6 Hz, 1H, *Z*), 4.84–4.94 (m, 4H), 5.17 (dt, $^3J_{HF}$=22.4 Hz, $^3J_{HH}$=8.0 Hz, 1H, *E*), 5.80 (ddt, $^4J_{HH}$=6.8 Hz, $^3J_{HH}$=10.4 Hz, $^2J_{HH}$=17.0 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 22.4, 22.5, 24.3, 24.4, 24.5, 27.9, 28.0, 28.1, 28.2, 28.3, 28.4, 28.6, 28.7, 28.8, 28.9, 32.7, 32.8, 50.5 (d, $^2J_{CF}$=27.1 Hz, *E*), 52.8, 52.9, 55.3 (d, $^2J_{CF}$=27.9 Hz, *Z*), 66.9, 107.7 (d, $^2J_{CF}$=14.5 Hz, *E*), 108.2 (d, $^2J_{CF}$=20.0 Hz, *Z*), 113.0, 113.1, 137.8, 138.1, 155.3 (d, $^1J_{CF}$=254.8 Hz, *Z*), 155.5 (d, $^1J_{CF}$=248.1 Hz, *E*); ^{19}F NMR ($CDCl_3$, 376 MHz) δ −105.7 (dt, $^3J_{FH}$=22.4 , 22.4 Hz, 1F, *E*), −113.2 (dt, $^3J_{FH}$=37.2 , 18.4 Hz, 1F, *Z*); MS (EI) *m*/*z* 268 $[M+H]^+$ (42), 208 (10), 95 (100), 93 (44), 81 (50); HRMS (ESI) *m*/*z* $[M+H]^+$ calcd for $C_{17}H_{31}FN$ 268.2441, found 268.2441.

*4.3.4. (Z/E)-(1S,3S)-Methyl3-(2-fluoro-3-(pyrrolidin-1-yl)prop-1-enyl)-2,2-dimethyl-cyclopropane-carboxylate (**7b**).* Following the method (B) from sulfone **3b** (100 mg, 0.32 mmol), biocartol-methylester (52 mg, 0.33 mmol), and NaHMDS (420 μL, 0.42 mmol, 1 M in THF) in THF (5 mL). Purification by flash chromatography (pentane/AcOEt gradient 90:10 to 0:100) afforded a mixture of (*Z*/*E*) **7b** (61 mg, 73%) as a colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.13–1.14 (m, 6H), 1.16–1.18 (m, 6H), 1.58–1.66 (m, 2H), 1.69–1.78 (m, 8H), 2.08 (t, $^3J_{HH}$=9.0 Hz, 2H), 2.49–2.51 (m, 8H), 3.11 (m, 2H, *Z*), 3.25 (d, $^3J_{HF}$=22.2 Hz, 2H, *E*), 3.54–3.61 (m, 6H), 5.08 (dd, $^3J_{HF}$=36.1 Hz, $^3J_{HH}$=9.6 Hz, 1H, *Z*), 5.53 (dd, $^3J_{HF}$=20.8 Hz, $^3J_{HH}$=9.6 Hz, 1H, *E*); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.6, 14.7, 23.5, 26.4, 26.5, 27.8, 27.9, 28.4, 28.5, 28.9, 29.1, 30.7, 30.8, 51.2, 51.3, 52.0 (d, $^2J_{CF}$=27.2 Hz, *Z*), 53.8, 56.5 (d, $^2J_{CF}$=26.7 Hz, *E*), 102.8 (d, $^2J_{CF}$=10.1 Hz, *E*), 104.3 (d, $^2J_{CF}$=27.27 Hz, *Z*), 158.1 (d, $^1J_{CF}$=250.2 Hz, *E*), 158.6 (d, $^1J_{CF}$=258.0 Hz, *Z*), 171.0, 171.5; ^{19}F NMR ($CDCl_3$, 376 MHz) δ −100.5 (dt, $^3J_{FH}$=20.8 , 22.2 Hz, 1F, *E*), −112.8 (dt, $^3J_{FH}$=36.1 , 19.1 Hz, 1F, *Z*); MS (EI) *m*/*z* 256 $[M+H]^+$ (80), 185 (53), 125 (100), 105 (16); HRMS (ESI) *m*/*z* $[M+H]^+$ calcd for $C_{14}H_{23}FNO_2$ 256.1713, found 256.1720.

*4.3.5. N-[2-(4-tert-Butyl-cyclohexylidene)-2-fluoroethyl]-pyrrolidine (**8b**).* Following the method (B) from sulfone **3b** (100 mg, 0.32 mmol), *tert*-butylcyclohexanone (50 mg, 0.33 mmol), and NaHMDS (420 μL, 0.42 mmol, 1 M in THF) in THF (5 mL). Purification by chromatography (pentane/AcOEt, gradient 90:10 to 70:30) afforded compound **8b** (76 mg, 95%) as a yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.54 (s, 9H), 0.83–0.90 (m, 1H), 0.90–0.98 (m, 2H), 1.03 (m, 1H), 1.12–1.23 (m, 1H), 1.49–1.52 (m, 1H), 1.71–1.79 (m, 6H), 2.38–2.42 (m, 1H), 2.50–2.54 (m, 3H), 2.84–2.88 (m, 1H), 3.12–3.29 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 23.4, 25.6 (d, $^3J_{CF}$=7.8 Hz), 27.5, 28.3 (d, $^3J_{CF}$=7.6 Hz), 32.4, 48.0, 51.6 (d, $^2J_{CF}$=30.3 Hz), 53.6, 119.4 (d, $^2J_{CF}$=14.9 Hz), 148.9 (d, $^1J_{CF}$=241.7 Hz); ^{19}F NMR ($CDCl_3$, 376 MHz) δ −115.0 (t, $^3J_{FH}$=23.07 Hz, 1F); MS (EI) *m*/*z* 254 $[M+H]^+$ (58), 163 (22), 135 (16), 123 (29), 121 (33), 113 (33), 107 (100), 95 (17), 93 (34); HRMS (ESI) *m*/*z* $[M+H]^+$ calcd for $C_{16}H_{29}FN$ 254.2284, found 254.2272.

*4.3.6. (Z/E)-N-[(3-Anthracen-9-yl)-2-fluoro-2-propenyl]-aspartic acid di-tert-butyl ester (**4c**).* Following the method (B) from sulfone **3c** (100 mg, 0.21 mmol), anthraldehyde (46 mg, 0.22 mmol), and NaHMDS (540 μL, 0.54 mmol, 1 M in THF) in THF (5 mL). Purification by flash chromatography (pentane/AcOEt, gradient 95:5 to 90:10) afforded a mixture of (*Z*/*E*) **4c** (74 mg, 74%) as an orange oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.03 (s, 9H), 1.28 (s, 9H), 1.37 (s, 9H), 1.44 (s, 9H), 2.23 (dd, $^2J_{HH}$=15.7 Hz, $^3J_{HH}$7.2 Hz, 1H, *E*), 2.33 (dd, $^2J_{HH}$=15.7 Hz, $^3J_{HH}$=5.8 Hz, 1H, *E*), 2.58 (dd, $^2J_{HH}$=15.7 Hz, $^3J_{HH}$=7.4 Hz, 1H, *Z*), 2.69 (dd, $^2J_{HH}$=15.7 Hz, $^3J_{HH}$=5.3 Hz, 1H, *Z*), 2.94 (dd, $^3J_{HF}$=23.5 Hz, $^3J_{HH}$=14.6 Hz, 1H, *E*), 3.13–3.21 (m, 2H, *E*), 3.54 (dd, $^3J_{HF}$=14.3 Hz, $^3J_{HH}$=13.7 Hz, 1H, *Z*), 3.74 (dd, $^3J_{HH}$=5.3 , 7.0 Hz, 1H, *Z*), 3.77 (dd, $^3J_{HF}$=14.6 Hz, $^3J_{HH}$=15.9 Hz, 1H, *Z*), 6.47 (d, $^3J_{HF}$=38.6 Hz, 1H, *Z*), 6.73 (d, $^3J_{HF}$=18.3 Hz, 1H, *E*), 7.29–7.46 (m, 9H), 7.91–7.94 (m, 3H), 8.04–8.07 (m, 3H), 8.13 (d, $^3J_{HH}$=8.4 Hz, 1H), 8.34 (s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 26.6, 26.8, 26.9, 27.0, 38.2, 38.6, 44.3, 44.6, 47.7 (d, $^2J_{CF}$=30.9 Hz, *Z*), 56.8 (d, $^2J_{CF}$=24.9 Hz, *E*), 79.8, 80.1, 80.2, 80.8, 101.9 (d, $^2J_{CF}$=13.0 Hz, *E*), 104.1 (d, $^2J_{CF}$=25.3 Hz, *Z*), 124.0, 124.2, 124.3, 124.5, 124.6, 124.8, 124.9, 125.0, 125.3, 125.4, 125.5, 125.8, 126.0, 127.6, 128.6, 130.3, 157.7 (d, $^1J_{CF}$=263.5 Hz, *Z*), 159.4 (d, $^1J_{CF}$=259.5 Hz, *E*), 168.8, 169.1, 171.0, 171.6; ^{19}F NMR ($CDCl_3$, 376 MHz) δ −103.3 (m, 1F, *Z*), −103.8 (ddd, $^3J_{HF}$=23.5 Hz, $^3J_{HF}$=18.3, 16.0 Hz, 1F, *E*); MS (EI) *m*/*z* 480 $[M+H]^+$ (67), 424 (100), 368 (74); HRMS (ESI) *m*/*z* $[M+H]^+$ calcd for $C_{29}H_{35}FNO_4$ 480.2550, found 480.2538.

*4.3.7. (Z/E)-N-[3-(4-Bromo-phenyl)-2-fluoro-2propenyl]-aspartic acid di-tert-butyl ester (**5c**).* Following the method (B) from sulfone **3c** (100 mg, 0.21 mmol), 4-bromobenzaldehyde (42 mg, 0.22 mmol), and NaHMDS (540 μL, 0.54 mmol, 1 M in THF) in THF (5 mL). Purification by flash chromatography (pentane/AcOEt, gradient 95:5 to 90:10) afforded a mixture of (*Z*/*E*) **5c** (70 mg, 72%) as an orange oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.36–1.41 (m, 36H), 2.03–2.13 (m, 2H), 2.44–2.57 (m, 4H), 3.29–3.53 (m, 6H), 5.59 (d, $^3J_{HF}$=38.9 Hz, 1H), 6.17 (d, $^3J_{HF}$=20.3 Hz, 1H), 7.03–7.10 (m, 4H), 7.17–7.35 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 26.9, 27.0, 27.1, 28.6, 38.2, 38.4, 44.2 (d, $^2J_{CF}$=12.3 Hz, *E*), 48.1 (d, $^2J_{CF}$=30.1 Hz, *Z*), 56.6, 56.8, 80.1, 80.2, 80.7, 80.8, 108.9 (d, $^2J_{CF}$=27.8 Hz, *E*), 110.8, 119.9 (d, $^2J_{CF}$=30.8 Hz, *Z*), 121.4, 122.1, 122.9, 125.4, 129.2, 130.4, 134.4, 157.6 (d, $^1J_{CF}$=267.9 Hz, *Z*), 158.7 (d, $^1J_{CF}$=255.7 Hz, *E*), 171.3, 171.5, 172.1, 172.2; ^{19}F NMR ($CDCl_3$, 376 MHz) δ −101.6 (dt, $^3J_{FH}$=20.3 , 23.7 Hz, *E*), −106.2 (dt, $^3J_{FH}$=38.9, 13.9 Hz, *Z*); MS (EI) *m*/*z* 460 $[M(C_{21}H_{30}{}^{81}BrFNO_4)+H]^+$ (90), 458 $[M(C_{21}H_{30}{}^{79}BrFNO_4)+H]^+$ (90), 402 (100), 346 (69); HRMS (ESI) *m*/*z* $[M+H]^+$ calcd for $C_{21}H_{30}{}^{79}BrFNO_4$ 458.1342, found 458.1343.

*4.3.8. (Z/E)-N-(2-Fluoro-2,12-tridecadienyl)-aspartic acid di-tert-butyl ester (**6c**).* Following the method (B) from sulfone **3c** (100 mg, 0.21 mmol), undecenal (38 mg, 0.22 mmol), and NaHMDS (540 μL, 0.54 mmol, 1 M in THF) in THF (5 mL). Purification by flash chromatography (pentane/AcOEt, 95:5) afforded a mixture of (*Z*/*E*) **6c** (71 mg, 75%) as a yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.25–1.31 (m, 31H), 1.37 (s, 18H), 1.39 (s, 18H), 1.55–1.58 (m, 1H), 1.86–1.99 (m, 6H), 2.42–2.48 (m, 2H), 3.10–3.43 (m, 4H), 4.63 (dt, $^3J_{HF}$=37.5 Hz,

$^3J_{HH}$=7.4 Hz, 1H, *Z*), 4.84–4.94 (m, 4H), 5.08 (dt, $^3J_{HF}$=21.4 Hz, $^3J_{HH}$=7.4 Hz, 1H, *E*), 5.68–5.79 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 22.4, 22.5, 24.2, 24.3, 26.9, 27.0, 27.1, 27.8, 27.9, 28.0, 28.1, 28.2, 28.3, 28.4, 28.5, 28.9, 29.0, 32.7, 38.4, 38.5, 43.3 (d, $^2J_{CF}$=28.5 Hz, *E*), 47.5 (d, $^2J_{CF}$=30.4 Hz, *Z*), 56.3, 79.9, 80.0, 80.4, 106.6 (d, $^2J_{CF}$=14.4 Hz, *E*), 107.9 (d, $^2J_{CF}$=19.9 Hz, *Z*), 113.0, 113.1, 113.2, 138.0, 138.1, 138.2, 155.5 (d, $^1J_{CF}$=253.6 Hz, *Z*), 155.8 (d, $^1J_{CF}$=247.8 Hz, *E*), 169.0, 169.1, 171.5, 171.6; ^{19}F NMR ($CDCl_3$, 376 MHz) δ −109.6 (dt, $^3J_{FH}$=21.4 , 21.5 Hz, 1F, *E*), −116.3 (dt, $^3J_{FH}$=37.5 , 15.7 Hz, 3F, *Z*); MS (EI) *m*/*z* 442 $[M+H]^+$ (50), 386 (81), 330 (100); HRMS (ESI) *m*/*z* $[M+H]^+$ calcd for $C_{25}H_{45}FNO_4$ 442.3333, found 442.3349.

*4.3.9. (Z/E)-N-[2-Fluoro-3-(3-methoxycarbonyl-2,2-dimethyl-cyclopropyl)-2-propenyl]-aspartic acid di-tert-butyl ester (**7c**).* Following the method (B) from sulfone **3c** (100 mg, 0.21 mmol), biocartolmethylester (35 mg, 0.23 mmol), and NaHMDS (540 μL, 0.54 mmol, 1 M in THF) in THF (5 mL). The purification by flash chromatography (Pentane/AcOEt, 95:5) afforded a mixture of (*Z*/*E*) **7c** (70 mg, 77%) as a yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.12–1.13 (m, 6H), 1.15 (s, 6H), 1.37 (s, 18H), 1.39–1.40 (m, 18H), 1.62–1.71 (m, 3H), 2.03–2.08 (m, 3H), 2.48–2.57 (m, 4H), 3.20–3.42 (m, 6H), 3.45 (s, 3H), 3.55 (s, 3H), 5.08 (dd, $^3J_{HF}$=36.2 Hz, $^3J_{HH}$=9.7 Hz, 1H, *Z*), 5.46 (dd, $^3J_{HF}$=20.4 Hz, $^3J_{HH}$=9.4 Hz, 1H, *E*); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.6, 26.3, 26.4, 26.5, 27.8, 27.9, 28.0, 28.1, 28.4, 28.5, 28.7, 28.8, 30.7, 30.8, 39.4, 39.5, 44.8 (d, $^2J_{CF}$=28.2 Hz, *E*), 48.8 (d, $^2J_{CF}$=28.8 Hz, *Z*), 51.2 (d, $^3J_{CF}$=8.2 Hz, *Z*), 57.4 (d, $^3J_{CF}$=4.5 Hz, *E*), 80.8, 80.9, 81.4, 81.5, 102.1 (d, $^2J_{CF}$=9.8 Hz, *E*), 103.9 (d, $^2J_{CF}$=27.1 Hz, *Z*), 158.5 (d, $^1J_{CF}$=249.5 Hz, *E*), 158.8 (d, $^1J_{CF}$=256.9 Hz, *Z*), 170.0, 170.1, 171.0, 171.3, 172.4, 172.5; ^{19}F NMR ($CDCl_3$, 376 MHz) δ −105.9 (dt, $^3J_{FH}$=20.4 , 22.2 Hz, 1F, *E*), −115.9 (dt, $^3J_{FH}$=36.2, 17.2 Hz, 1F, *Z*); MS (EI) *m*/*z* 430 $[M+H]^+$ (100), 374 (97), 318 (60); HRMS (ESI) *m*/*z* $[M+H]^+$ calcd for $C_{22}H_{37}FNO_6$ 430.2605, found 430.2609.

*4.3.10. N-[2-(4-tert-Butyl-cyclohexylidene)-2-fluoro-2-propenyl]-aspartic acid di-tert-butyl ester (**8c**).* Following the method (B) from sulfone **3c** (100 mg, 0.21 mmol), 4-*tert*-butylcyclohexanone (35 mg, 0.23 mmol), and NaHMDS (540 μL, 0.54 mmol, 1 M in THF) in THF (5 mL). Purification by flash chromatography (pentane/AcOEt, 95:5) afforded compound **8c** (25 mg, 27%) as a yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.84 (s, 9H), 0.92–0.99 (m, 2H), 1.01–1.12 (m, 1H), 1.45 (s, 9H), 1.50 (s, 9H), 1.55–1.63 (m, 2H), 1.82–1.87 (m, 3H), 2.53–2.56 (m, 1H), 2.60–2.61 (m, 2H), 2.89–2.92 (m, 1H), 3.38–3.50 (m, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 25.5, 25.6, 27.5, 28.0, 28.1, 32.4, 39.6, 44.5 (d, $^2J_{CF}$=30.1 Hz), 57.3, 80.9, 81.3, 81.4, 118.8 (d, $^2J_{CF}$=14.5 Hz), 148.7 (d, $^1J_{CF}$=243.2 Hz), 170.0, 172.7; ^{19}F NMR ($CDCl_3$, 470 MHz) δ −119.6 (m, 1F); MS (EI) *m*/*z* 428 $[M+H]^+$ (100), 372 (83), 316 (43), 211 (43); HRMS (ESI) *m*/*z* $[M+H]^+$ calcd for $C_{24}H_{43}FNO_4$ 428.3176, found 428.3188.

*4.3.11. (Z/E)-N-[3-(Anthracen-9-yl)-2-fluoro-2-propenyl]-phenylalanine ethyl ester (**4d**).* Following the method (B) from sulfone **3d** (100 mg, 0.23 mmol), anthraldehyde (49 mg, 0.24 mmol), and NaHMDS (600 μL, 0.60 mmol, 1 M in THF) in THF (5 mL). Purification by flash chromatography (pentane/AcOEt, gradient 95:5 to 70:30) afforded (*E*)-**4d** (59 mg, 60%) as an orange oil, the *Z* alkene appeared as traces. Compound (*E*)-**4d**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.76 (t, $^3J_{HH}$=7.1 Hz, 3H), 1.65 (s, 1H), 2.64 (d, $^3J_{HH}$=6.8 Hz, 2H), 2.85–3.11 (m, 2H), 3.22 (t, $^3J_{HF}$=6.8 Hz, 1H), 3.55–3.69 (m, 2H), 6.72 (d, $^3J_{HF}$=18.4 Hz, 1H, *E*), 6.82–6.87 (m, 2H), 7.06–7.10 (m, 3H), 7.36–7.41 (m, 4H), 7.91–7.93 (m, 3H), 8.00–8.02 (m, 1H), 8.07–8.10 (m, 1H), 8.34 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 12.7, 38.3, 44.3 (d, $^2J_{CF}$=26.3 Hz, *E*), 59.3, 60.5, 104.2 (d, $^2J_{CF}$=25.2 Hz, *E*), 124.2, 124.6, 124.9, 125.0, 125.5, 126.0, 127.2, 127.7, 128.0, 129.3, 130.3, 135.9, 159.3 (d, $^1J_{CF}$=259.2 Hz, *E*), 172.5; ^{19}F NMR ($CDCl_3$, 376 MHz) δ −103.8 (m, 1F, *E*); MS (EI) *m*/*z* 428 $[M+H]^+$ (100), 235 (90); HRMS (ESI) *m*/*z* $[M+H]^+$ calcd for $C_{28}H_{27}FNO_2$ 428.2026, found 428.2018.

*4.3.12. (Z/E)-N-[3-(4-Bromo-phenyl)-2-fluoro-2propenyl]-phenylalanine ethyl ester (**5d**).* Following the method (B) from sulfone **3d** (100 mg, 0.23 mmol), 4-bromobenzaldehyde (45 mg, 0.24 mmol), and NaHMDS (600 μL, 0.60 mmol, 1 M in THF) in THF (5 mL). Purification by flash chromatography (pentane/AcOEt, 95:5) afforded successively alkenes (*E*)-**5d** and (*Z*)-**5d** (54 mg, 58%) as an orange oil. Compound (*E*)-**5d**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.05 (t, $^3J_{HH}$=7.2 Hz, 3H), 1.12–1.22 (m, 1H), 2.83 (dd, $^2J_{HH}$=13.5 Hz, $^3J_{HH}$=7.9 Hz, 1H), 2.91 (dd, $^2J_{HH}$=13.5 Hz, $^3J_{HH}$=6.1 Hz, 1H), 3.27–3.46 (m, 3H), 3.94–4.03 (m, 2H), 6.16 (d, $^3J_{FH}$=20.2 Hz, 1H), 6.93–6.96 (m, 2H), 7.09–7.11 (m, 2H), 7.15–7.23 (m, 3H), 7.29–7.36 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.1, 39.7, 45.3 (d, $^2J_{CF}$=27.4 Hz), 60.8, 61.9, 110.1 (d, $^2J_{CF}$=27.7 Hz), 121.2, 126.8, 128.4, 129.2, 130.1, 130.9, 132.2, 137.1, 159.5 (d, $^1J_{CF}$=255.7 Hz), 173.8; ^{19}F NMR ($CDCl_3$, 376 MHz) δ −101.9 (dt, $^3J_{FH}$=20.2 , 23.7 Hz, 1F); MS (EI) *m*/*z* 408 $[M(C_{20}H_{22}{}^{81}BrFNO_2)+H]^+$ (100), 406 $[M(C_{20}H_{22}{}^{79}BrFNO_2)+H]^+$ (100), 213 (48), 134 (7); HRMS (ESI) *m*/*z* $[M+H]^+$ calcd for $C_{20}H_{22}{}^{79}BrFNO_2$ 406.0818, found 406.0821. Compound (*Z*)-**5d**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.10 (t, $^3J_{HH}$=7.1 Hz, 3H), 1.43–1.63 (m, 1H), 2.86 (dd, $^2J_{HH}$=13.7 , 7.4 Hz, 1H), 2.94 (dd, $^2J_{HH}$=13.7 , 7.4 Hz, 1H), 3.18–3.44 (m, 2H), 3.50 (t, $^3J_{HH}$=6.9 Hz, 1H), 4.04 (q, $^3J_{HH}$=7.1 Hz, 2H), 5.39 (d, $^3J_{FH}$=38.8 Hz, 1H), 7.12–7.15 (m, 2H), 7.16–7.24 (m, 5H), 7.33–7.34 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.1, 39.4, 48.9 (d, $^2J_{CF}$=27.3 Hz), 60.9, 61.9, 106.1 (d, $^2J_{CF}$=16.5 Hz), 120.8, 126.8, 128.4, 129.3, 129.9, 130.0, 132.0, 137.1, 159.4 (d, $^1J_{CF}$=255.8 Hz), 174.1; ^{19}F NMR ($CDCl_3$, 376 MHz) δ −106.4 (dt, $^3J_{FH}$=38.8 , 13.4 Hz, 1F); MS (EI) *m*/*z* 408 $[M(C_{20}H_{22}{}^{81}BrFNO_2)+H]^+$ (82), 406 $[M(C_{20}H_{22}{}^{79}BrFNO_2)+H]^+$ (82), 213 (100), 134 (9); HRMS (ESI) *m*/*z* $[M+H]^+$ calcd for $C_{20}H_{22}{}^{79}BrFNO_2$ 406.0818, found 406.0807.

*4.3.13. (Z/E)-N-(2-Fluoro-2,12-tridecadienyl)-phenylalanine ethyl ester (**6d**).* Following the method (B) from sulfone **3d** (100 mg, 0.23 mmol), undecenal (41 mg, 0.24 mmol), and NaHMDS (600 μL, 0.60 mmol, 1 M in THF) in THF (5 mL). Purification by flash chromatography (pentane/AcOEt, 95:5) afforded a mixture of (*Z*/*E*) **6d** (19 mg, 21%) as a yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.08 (t, $^3J_{HH}$=7.1 Hz, 3H), 1.09 (t, $^3J_{HH}$=7.1 Hz, 3H), 1.18–1.30 (m, 26H), 1.69 (s, 2H), 1.81 (q, $^3J_{HH}$=8.0 Hz, 2H), 1.94–1.99 (m, 5H), 2.87–2.90 (m, 3H), 3.03–3.29 (m, 4H), 3.48 (t, $^3J_{HH}$=6.9 Hz, 2H), 4.03 (q, $^3J_{HH}$=7.1 Hz, 2H), 4.04 (t, $^3J_{HH}$=7.1 Hz, 2H), 4.54 (dt, $^3J_{FH}$=37.1 Hz, $^3J_{HH}$=7.5 Hz, 1H, *Z*), 4.83–4.96 (m, 4H), 5.05 (dt, $^3J_{FH}$=21.3 Hz, $^3J_{HH}$=8.0 Hz, 1H, *E*), 5.69–5.77 (m, 2H), 7.10–7.20 (m, 10H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 13.0, 21.9, 22.3, 22.4, 22.7, 24.1, 24.2, 27.7, 27.8, 27.9, 28.0, 28.1, 28.2, 28.3, 28.4, 28.5, 28.6, 28.9, 32.7, 32.8, 38.6, 38.7, 43.1 (d, $^2J_{CF}$=28.6 Hz, *E*), 47.3 (d, $^2J_{CF}$=30.7 Hz, *Z*), 60.4, 60.6, 106.7 (d, $^2J_{CF}$=14.3 Hz, *Z*), 108.1 (d, $^2J_{CF}$=19.7 Hz, *Z*), 113.0, 113.1, 125.7, 125.8, 127.3, 127.4, 128.1, 128.2, 136.0, 136.1, 138.1, 138.2, 155.3 (d, $^1J_{CF}$=253.6 Hz, *Z*), 155.7 (d, $^1J_{CF}$=247.8 Hz, *E*), 172.9, 173.1; ^{19}F NMR ($CDCl_3$, 376 MHz) δ −109.9 (dt, $^3J_{FH}$=21.3 , 21.6 Hz, 1F, *E*), −116.5 (dt, $^3J_{FH}$=37.1 , 15.8 Hz, 1F, *Z*); MS (EI) *m*/*z* 390 $[M+H]^+$ (100), 316 (50), 194 (12); HRMS (ESI) *m*/*z* $[M+H]^+$ calcd for $C_{24}H_{37}FNO_2$ 390.2808, found 390.2824.

*4.3.14. (Z/E)-N-[3-(Anthracen-9-yl)-2-fluoro-2-propenyl]-isoindole-1,3-dione (**4e**).* Following the method (B) from sulfone **3e** (90 mg, 0.23 mmol), anthraldehyde (49 mg, 0.24 mmol), and NaHMDS (300 μL, 0.3 mmol, 1 M in THF) in THF (4 mL). The crude product was purified by flash chromatography (pentane/AcOEt, gradient 95:5 to 70:30) to afford a mixture of (*Z*/*E*) **4e** (62 mg, 70%) as a yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.16 (d, $^3J_{HF}$=11.7 Hz, 2H), 4.19 (d, $^3J_{HF}$=12.0 Hz, 2H), 6.55 (d, $^3J_{HF}$=37.2 Hz, 1H, *Z*), 6.88 (d, $^3J_{HF}$=18.4 Hz, 1H, *E*), 7.36–7.48 (m, 9H), 7.52–7.53 (m, 5H), 7.69–7.71 (m, 2H), 7.86–7.93 (m, 6H), 8.03–8.04 (m, 2H), 8.09–8.13 (m, 2H), 8.24 (s, 1H, *E*), 8.33 (s, 1H, *Z*); ^{13}C NMR ($CDCl_3$, 100 MHz)

δ 38.7 (d, $^2J_{CF}$=33.5 Hz), 105.2 (d, $^2J_{CF}$=12.9 Hz), 123.6, 123.7, 125.2, 125.9, 126.0, 127.3, 128.6, 129.7, 131.3, 132.0, 134.4, 152.6 (d, $^1J_{CF}$=264.4 Hz), 167.6; ^{19}F NMR ($CDCl_3$, 376 MHz) δ −104.3 (dt, $^3J_{FH}$=18.4 , 11.7 Hz, 1F, *E*), −106.5 (dt, $^3J_{FH}$=37.2 , 12.0 Hz, 1F, *Z*); MS (EI) *m*/*z* 382 $[M+H]^+$ (100), 362 (26), 215 (11); HRMS (ESI) *m*/*z* $[M+H]^+$ calcd for $C_{25}H_{18}FNO_2$ 382.1243, found 382.1254.

*4.2.15. (Z/E)-N-[3-(4-Bromo-phenyl)-2-fluoro-2-propenyl]-isoindole-1,3-dione (**5e**).* Following the method (B) from sulfone **3e** (100 mg, 0.25 mmol), 4-Bromobenzaldehyde (49 mg, 0.26 mmol), and NaHMDS (320 μL, 0.32 mmol, 1 M in THF) in THF (4 mL). The crude product was purified by flash chromatography (pentane/AcOEt, gradient 95:5 to 90:10) to afford successively alkenes (*E*)-**5e** and (*Z*)-**5e** (50 mg, 56%) as a yellow oil. Compound (*E*)-**5e**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.54 (d, $^3J_{HF}$=15.4 Hz, 2H), 6.30 (d, $^3J_{HF}$=20.1 Hz, 1H), 7.24–7.27 (m, 2H), 7.41–7.42 (m, 2H), 7.65–7.67 (m, 2H), 7.77–7.79 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 35.5 (d, $^2J_{CF}$=28.6 Hz), 110.4 (d, $^2J_{CF}$=25.8 Hz), 121.5, 123.5, 130.5, 131.5, 131.8, 131.9, 134.2, 154.6 (d, $^1J_{CF}$=256.0 Hz), 167.5; ^{19}F NMR ($CDCl_3$, 376 MHz) δ −107.5 (dt, $^3J_{FH}$=15.4 , 20.1 Hz, 1F). Compound (*Z*)-**5e**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.44 (d, $^3J_{HF}$=15.3 Hz, 2H), 5.70 (d, $^3J_{HF}$=37.3 Hz, 1H), 7.23–7.25 (m, 2H), 7.32–7.35 (m, 2H), 7.65–7.67 (m, 2H), 7.79–7.81 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 35.5 (d, $^2J_{CF}$=28.6 Hz), 110.5 (d, $^2J_{CF}$=25.8 Hz), 121.6, 123.5, 130.5, 131.4, 131.8, 131.9, 134.2, 154.6 (d, $^1J_{CF}$=256.0 Hz), 167.6; ^{19}F NMR ($CDCl_3$, 376 MHz) δ −108.3 (dt, $^3J_{FH}$=15.3 , 37.3 Hz, 1F); HRMS not analyzable.

*4.3.16. (Z/E)-N-(2-Fluoro-2,12- tridecadienyl)-isoindole-1,3-dione (**6e**).* Following the method (B) from sulfone **3e** (90 mg, 0.23 mmol), undecenal (41 mg, 0.24 mmol), and NaHMDS (300 μL, 0.30 mmol, 1 M in THF) in THF (4 mL). The crude product was purified by flash chromatography (pentane/AcOEt, 95:5) to afford successively alkenes (*E*)-**6e** and (*Z*)-**6e** (52 mg, 66%) as a yellow oil. Compound (*E*)-**6e**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.18–1.52 (m, 12H), 1.94–2.00 (m, 2H), 2.12–2.16 (m, 2H), 4.38 (d, $^3J_{HF}$=19.2 Hz, 2H), 4.84–4.95 (m, 2H), 5.18 (dt, $^3J_{HH}$=8.1 Hz, $^3J_{HF}$=20.7 Hz, 1H), 5.69–5.78 (m, 1H), 7.64–7.67 (m, 2H), 7.78–7.80 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 25.3 (d, $^3J_{CF}$=7.6 Hz), 28.9, 29.1, 29.3, 29.4, 29.7, 29.8, 33.8, 34.5 (d, $^2J_{CF}$=30.4 Hz), 110.5 (d, $^2J_{CF}$=18.0 Hz), 114.1, 123.4, 132.0, 134.0, 139.2, 152.8 (d, $^1J_{CF}$=248.3 Hz), 167.6; ^{19}F NMR ($CDCl_3$, 376 MHz) δ −112.1 (dt, $^3J_{FH}$=19.2 , 20.7 Hz, 1F); MS (EI) *m*/*z* 344 $[M+H]^+$ (100), 324 (74), 172 (65); HRMS (ESI) *m*/*z* $[M+H]^+$ calcd for $C_{21}H_{27}FNO_2$ 344.2026, found 344.2025. Compound (*Z*)-**6e**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.26–1.37 (m, 12H), 2.01–2.09 (m, 4H), 4.37 (d, $^3J_{HF}$=14.9 Hz, 2H), 4.92–5.01 (m, 3H), 5.77–5.85 (m, 1H), 7.73–7.75 (m, 2H), 7.87–7.89 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 23.5 (d, $^3J_{CF}$=3.8 Hz), 28.9, 29.0, 29.1, 29.2, 29.3, 29.4, 33.8, 38.4 (d, $^2J_{CF}$=33.5 Hz), 109.6 (d, $^2J_{CF}$=13.6 Hz), 114.1, 123.5, 132.0, 134.1, 139.2, 152.7 (d, $^1J_{CF}$=254.6 Hz), 167.5; ^{19}F NMR ($CDCl_3$, 376 MHz) δ −118.0 (dt, $^3J_{FH}$=14.9 , 36.3 Hz, 1F); MS (EI) *m*/*z* 344 $[M+H]^+$ (100), 324 (74), 172 (65); HRMS (ESI) *m*/*z* $[M+H]^+$ calcd for $C_{21}H_{27}FNO_2$ 344.2026, found 344.2033.

*4.3.17. (Z/E)-3-[3-(1,3-Dioxo-1,3-dihydro-isoindol-2-yl)-2-fluoro-propenyl]-2,2-dimethyl-cyclopropane carboxylic acid methyl ester (**7e**).* Following the method (B) from sulfone **3e** (90 mg, 0.23 mmol), biocarptolmethylester (37 mg, 0.24 mmol), and NaHMDS (300 μL, 0.30 mmol, 1 M in THF) in THF (4 mL). The crude product was purified by flash chromatography (pentane/AcOEt, gradient 95:5 to 90:10) to afford a mixture of (*Z*/*E*) **7e** (38 mg, 50%) as a yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.08–1.22 (m, 12H), 1.65 (d, $^3J_{HH}$=8.5 Hz, 1H), 1.75 (d, $^3J_{HH}$=8.6 Hz, 1H), 1.96–2.09 (m, 2H), 3.57 (s, 6H), 4.26–4.45 (m, 4H), 5.28 (dd, $^3J_{HH}$=9.7 Hz, $^3J_{HF}$=35.5 Hz, 1H, *Z*), 5.61 (dd, $^3J_{HH}$=9.4 Hz, $^3J_{HF}$=19.7 Hz, 1H, *E*), 7.63–7.68 (m, 4H), 7.76–7.81 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.7, 26.6, 26.7, 26.8, 27.5, 27.6, 28.3, 28.4, 28.5, 28.6, 30.8, 31.0, 35.0 (d, $^2J_{CF}$=30.6 Hz, *E*), 38.6 (d, $^2J_{CF}$=31.3 Hz, *Z*), 51.2, 51.3, 104.3 (d, $^2J_{CF}$=7.8 Hz, *E*), 105.8 (d, $^2J_{CF}$=25.1 Hz, *Z*), 123.4, 132.0, 134.0, 134.1, 154.5 (d, $^1J_{CF}$=257.5 Hz, *Z*), 154.6 (d, $^1J_{CF}$=250.1 Hz, *E*), 167.4, 167.5, 171.1, 171.2; ^{19}F NMR ($CDCl_3$, 376 MHz) δ −107.4 (dt, $^3J_{FH}$=19.6 , 19.7 Hz, 1F, *E*), −118.0 (ddd, $^3J_{FH}$=13.4 , 18.4 , 35.5 Hz, 1F, F*Z*); MS (EI) *m*/*z* 332 $[M+H]^+$ (100), 318 (38), 300 (93), 280 (7); HRMS (ESI) *m*/*z* $[M+H]^+$ calcd for $C_{18}H_{19}FNO_4$ 332.1298, found 332.1290.

*4.3.18. N-[2-(4-tert-Butyl-cyclohexylidene)-2-fluoro-ethyl]-isoindole-1,3-dione (**8e**).* Following the method (B) from sulfone **3e** (90 mg, 0.23 mmol), 4-*tert*-butylcyclohexanone (37 mg, 0.24 mmol), and NaHMDS (300 μL, 0.30 mmol, 1 M in THF) in THF (4 mL). The crude product was purified by flash chromatography (pentane/AcOEt, 95:5) to afford compound **8e** (48 mg, 63%) as a yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.92 (s, 9H), 0.97–1.04 (m, 1H), 1.11–1.29 (m, 2H), 1.59–1.63 (m, 1H), 1.82–1.83 (m, 1H), 1.92–1.97 (m, 2H), 2.79 (m, 1H), 2.87 (m, 1H), 4.49 (d, $^3J_{HF}$=20.9 Hz, 2H), 7.72–7.37 (m, 2H), 7.85–7.87 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 25.7 (d, $^3J_{CF}$=7.8 Hz), 27.6, 28.4 (d, $^3J_{CF}$=4.6 Hz), 32.5, 34.9 (d, $^2J_{CF}$=32.0 Hz), 47.9, 120.7 (d, $^2J_{CF}$=13.1 Hz), 123.4, 132.1, 134.0, 145.2 (d, $^1J_{CF}$=243.1 Hz), 167.7; ^{19}F NMR ($CDCl_3$, 376 MHz) δ −121.9 (t, $^3J_{FH}$=20.9 Hz, 1F); HRMS not analyzable.

4.4. Preparation of dipeptide precursor 12

*4.4.1. (Z/E)-N-(5-Benzyloxy-2-fluoro-2-pentenyl)-isoindole-1,3-dione (**10**).* To a solution of sulfone **3e** (150 mg, 0.38 mmol, 1 equiv) and 3-benzyloxy-propionaldehyde (66 mg, 0.40 mmol, 1.05 equiv) in THF (6 mL) at −17 °C was added *t*-BuOK (0.056 g, 0.49 mmol, 1.3 equiv). After 5 min at −17 °C, the mixture was stirred for 2 h at 20 °C, quenched with a saturated solution of NH_4Cl (1 mL) and extracted with CH_2Cl_2 (2×5 mL). Combined organic layers were washed with a 1 M solution of NaOH, dried over $MgSO_4$, filtered, and evaporated under reduced pressure. The crude residue was purified by flash silica gel chromatography (pentane/AcOEt, 9:1) to afford a mixture of (*Z*/*E*)-*N*-(5-benzyloxy-2-fluoro-2-pentenyl)-isoindole-1,3-dione **10** (100 mg, 77%) as a yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.33 (q, $^3J_{HH}$=6.6 Hz, 2H), 2.46 (q, $^3J_{HH}$=6.8 Hz, 2H), 3.39 (t, $^3J_{HH}$=6.7 Hz, 2H), 3.49 (t, $^3J_{HH}$=6.8 Hz, 2H), 4.29 (d, $^3J_{HF}$=14.3 Hz, 2H, *E*), 4.38 (d, $^3J_{HF}$=20.7 Hz, 2H, *Z*), 4.41 (s, 2H), 4.45 (s, 2H), 4.91 (dt, $^3J_{HF}$=36.1 Hz, $^3J_{HH}$=7.4 Hz, 1H, *Z*), 5.27 (dt, $^3J_{HF}$=19.7 Hz, $^3J_{HH}$=6.2 Hz, 1H, *E*), 7.18–7.29 (m, 10H), 7.63–7.66 (m, 4H), 7.75–7.80 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 23.3 (d, $^3J_{CF}$=4.1 Hz, *E*), 25.1 (d, $^3J_{CF}$=8.0 Hz, *Z*), 33.6 (d, $^2J_{CF}$=30.2 Hz, *E*), 37.2 (d, $^2J_{CF}$=33.5 Hz, *Z*), 67.9 (d, $^4J_{CF}$=1.9 Hz, *E*), 68.4 (d, $^4J_{CF}$=2.7 Hz, *Z*), 71.8, 71.9, 104.7 (d, $^2J_{CF}$=13.1 Hz, *E*), 106.1 (d, $^2J_{CF}$=20.2 Hz, *Z*), 122.4, 122.5, 126.5, 126.6, 127.3, 127.4, 127.5, 130.9, 133.0, 133.1, 133.2, 134.1, 137.3, 137.4, 152.8 (d, $^1J_{CF}$=256.6 Hz, *Z*), 153.2 (d, $^1J_{CF}$=250.1 Hz, *E*), 166.4, 166.5; ^{19}F NMR ($CDCl_3$, 376 MHz) δ −109.6 (dt, $^3J_{FH}$=19.7 Hz, $^3J_{FH}$=20.7 Hz, 1F, *E*), −115.6 (dt, $^3J_{FH}$=36.1 , 14.3 Hz, 1F, *Z*); MS (EI) *m*/*z* 340 $[M+H]^+$ (49), 302 (100), 173 (45), 160 (99), 155 (42); HRMS (ESI) *m*/*z* $[M+H]^+$ calcd for $C_{20}H_{19}O_3NF$ 340.1349, found 340.1344.

*4.4.2. (Z/E)-N-(2-Fluoro-5-hydroxy-pent-2-enyl)-isoindole-1,3-dione (**11**).* To a solution of compound **10** (84 mg, 0.25 mmol, 1 equiv) in CH_2Cl_2 (14 mL) was added $TiCl_4$ (0.28 mL, 2.55 mmol, 10 equiv) at 20 °C. After 16 h under stirring, the mixture was added to a solution of $NaHCO_3$/Et_2O (1:9, 10 mL) and stirred over 30 min then the resulting mixture was dried and filtered on Celite. The filtrate was evaporated under reduced pressure to afford a mixture of (*Z*/*E*) **11** (56 mg, 90%) as a colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.05 (s, 2H), 2.26 (q, $^3J_{HH}$=6.0 Hz, 2H), 2.42 (q, $^3J_{HH}$=6.0 Hz, 2H), 3.57 (t, $^3J_{HH}$=6.3 Hz, 2H), 3.67 (t, $^3J_{HH}$=5.6 Hz, 2H), 4.31 (d, $^3J_{HF}$=14.3 Hz, 2H, *E*), 4.36 (d, $^3J_{HF}$=13.0 Hz, 2H, *Z*), 4.90 (dt, $^3J_{HF}$=36.1 Hz, $^3J_{HH}$=7.4 Hz, 1H, *Z*), 5.25 (dt, $^3J_{HF}$=20.3 Hz, $^3J_{HH}$=8.2 Hz, 1H, *E*), 7.66–7.67 (m, 4H), 7.78–7.79 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 29.0 (d, $^3J_{CF}$=5.2 Hz, *E*), 31.9 (d, $^3J_{CF}$=7.8 Hz, *Z*), 34.7 (d,

$^{2}J_{CF}$=29.6 Hz, *E*), 38.4 (d, $^{2}J_{CF}$=33.3 Hz, *Z*), 61.7 (d, $^{4}J_{CF}$=3.0 Hz, *E*), 61.8 (d, $^{4}J_{CF}$=2.6 Hz, *Z*), 105.4 (d, $^{2}J_{CF}$=13.0 Hz, *E*), 107.3 (d, $^{2}J_{CF}$=19.8 Hz, *Z*), 123.6, 126.0, 129.7, 129.9, 131.9, 134.2, 154.8 (d, $^{1}J_{CF}$=262.4 Hz, *Z*), 154.9 (d, $^{1}J_{CF}$=242.6 Hz, *E*), 167.5, 167.6; ^{19}F NMR ($CDCl_3$, 376 MHz) δ −109.1 (dt, $^{3}J_{FH}$=20.3 , 13.0 Hz, 1F, *E*), −115.4 (dt, $^{3}J_{FH}$=36.1 , 14.3 Hz, 1F, *Z*); MS (EI) *m*/*z* 250 $[M+H]^+$ (37), 232 (10), 230 (100), 104 (13); HRMS (ESI) *m*/*z* $[M+H]^+$ calcd for $C_{13}H_{13}O_3NF$ 250.0879, found 250.0873.

*4.4.3. (Z/E)-5-Phtalimido-4-fluoro-pent-3-enoic acid (**12**).* To a solution of compound **11** (20 mg, 0.08 mmol, 1 equiv) in acetone (0.6 mL) was added Jones oxidant (0.1 mL) at 0 °C. After 1 h at 20 °C, the mixture was diluted in AcOEt and water (9:1, 5 mL) and extracted with CH_2Cl_2 (3×5 mL). Combined organic layers were washed with a saturated solution of NaCl, dried over $MgSO_4$, filtered, and evaporated under reduced pressure to afford a mixture of (*Z*/*E*)-5-phtalimido4-fluoro-pent-3-enoic acid **12** (18 mg, 85%) as a yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.13 (d, $^{3}J_{HH}$=15.4 Hz, 2H, *Z*), 3.32 (d, $^{3}J_{HH}$=7.7 Hz, 2H, *E*), 4.35 (d, $^{3}J_{HF}$=14.2 Hz, 2H, *Z*), 4.39 (d, $^{3}J_{HF}$=20.0 Hz, 2H, *E*), 5.11 (dt, $^{3}J_{HH}$=7.1 Hz, $^{3}J_{HF}$=34.7 Hz, 1H, *Z*), 5.42 (dt, $^{3}J_{HH}$=7.1 Hz, $^{3}J_{HF}$=18.9 Hz, 1H, *E*), 7.64–7.71 (m, 4H), 7.77–7.85 (m, 4H), 9.4–9.8 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 27.9 (d, $^{3}J_{CF}$=5.0 Hz, *E*), 29.5 (d, $^{3}J_{CF}$=9.2 Hz, *Z*), 33.5 (d, $^{2}J_{CF}$=30.2 Hz, *E*), 36.9 (d, $^{2}J_{CF}$=32.6 Hz, *Z*), 99.8 (d, $^{2}J_{CF}$=11.9 Hz, *E*), 101.9 (d, $^{2}J_{CF}$=25.7 Hz, *Z*), 110.6, 121.6, 122.3, 122.5, 125.5, 130.8, 133.2, 153.8 (d, $^{1}J_{CF}$=260.3 Hz, *Z*), 154.5 (d, $^{1}J_{CF}$=253.5 Hz, *E*), 166.4, 166.5, 174.4, 174.5; ^{19}F NMR ($CDCl_3$, 376 MHz) δ −106.3 (dt, $^{3}J_{FH}$=20.0 Hz, $^{2}J_{FH}$=18.9 Hz, 1F, *E*), −112.6 (dt, $^{3}J_{FH}$=14.2 Hz, $^{2}J_{FH}$=34.7 Hz, 1F, *Z*); MS (EI) *m*/*z* 262 $[M-H]^-$ (100), 242 (71), 218 (9), 146 (98), 114 (22); HRMS (ESI) *m*/*z* $[M-H]^-$ calcd for $C_{13}H_9O_4NF$ 262.0516, found 262.0517.

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Supplementary data

Copies of ^{1}H, ^{13}C NMR spectra of compounds **4a**–**e** to **8a**–**e**, **10**–**12** are available. Supplementary data associated with this article can be found in online version at doi:10.1016/j.tet.2010.12.061. These data include MOL files and InChIKeys of the most important compounds described in this article.

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