Asymmetric Synthesis of γ-Fluorinated α-Amino Acid Derivatives

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Asymmetric alkylation of (*S*)-Boc-BMI (**1a**, BMI = 2-*tert*-butyl-3-methylimidazolidin-4-one) and its α-methyl derivative **1b** with 2-fluoroallyl tosylate, subsequent mild acidic deprotection of the products **2a** and **2b**, and basic hydrolysis of the thus formed *N*′-methylamides **4a** and **4b** gave (*S*)-2-amino-4-fluoropent-4-enoic acid (**5a**) and (*S*)-2-amino-4-fluoro-2-methylpent-4-enoic acid (**5b**). Basic hydrolysis of compound **4a** was accompanied by partial racemization, which was overcome by applying a new stereoconservative deamidation procedure. The alkylated *cis*-configured product **2a** formed under kinetic control epimerized on refluxing with 2 N NaOH to give the thermodynamically more stable *trans* isomer **9**.

Introduction

Fluorine is one of the most abundant elements on earth, yet it occurs rarely in organic compounds as a result of its low bioavailability. Hence procedures by which fluorine can be introduced into organic molecules are well established.[1–4] During the past few decades, the development of methods for the synthesis of biologically active fluorinated compounds,[5–7] particularly fluorinated amino acids, has gained considerable attention[8–12] for various reasons. Amongst these, the unique properties and effects of fluorine as a substitute for hydrogen or hydroxy groups on the overall molecular and biological properties of a molecule have been widely reviewed.[13–15] Owing to its extreme electronegativity, fluorine is, for example, a weak hydrogen-bond acceptor.[16–19]

Recently, the growing interest in fluorinated amino acids as protein residues has created a new challenge for synthetic chemists.[20–22] Also α-substitution could lead to fluorinated compounds with specific conformations and stronger resistance to hydrolysis.[23] Our group has synthesized several saturated and unsaturated γ-fluorinated amino acids.[24–26] Fluoroolefins are well documented as isosteres of peptides (or as peptidomimetics)[27–30] and are very important, particularly in protein design.[31] The importance and synthesis of fluorinated α-amino acids have been recently reviewed.[32]

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Results and Discussion

In a recent synthetic program, we required optically pure (*S*)-2-amino-4-fluoropent-4-enoic acid (**5a**) and (*S*)-2-amino-4-fluoro-2-methylpent-4-enoic acid (**5b**) as isosteres of asparagine (Asn) and its α-methyl derivative, respectively. Amongst the methodologies developed for the preparation of chiral α-amino acids (natural as well as unnatural) based on asymmetric enolate alkylation of chiral glycine derivatives, the "self-regeneration of stereocenters" (SRS) in imidazolidinone derivatives is the most selective and efficient[33] and has been used for the synthesis of various amino acids of biological interest.[34–37] For our current synthetic plans, we used Seebach's commercially available enantiopure (*S*)-Boc-BMI (**1a**, BMI = 2-*tert*-butyl-3-methylimidazolidin-4-one).[33,38,39]

This paper reports the results of our efforts to synthesize enantiopure γ-fluoro-α-amino acid derivatives and the corresponding α-methylated analogues by using enantiopure (*S*)-Boc-BMI (**1a**) as a chiral glycine building block. 2-Fluoroallyl tosylate, synthesized[40] in 90% yield from 2-fluoroallyl alcohol[26] and tosyl chloride using $NaOH/Et_2O$, was used as the alkylating agent. By using a method similar to that described in the literature,[33] the stereoselective alkylation of **1** was carried out by using LDA as a base in dry THF in the presence of DMPU[41] as co-solvent under argon at –50 °C. The use of MeI[34] or 2-fluoroallyl tosylate as the electrophile for enolate alkylation leads selectively to one diastereomer[42] in a smooth reaction that gave the products **1b** and **2a** in 96 and 89% yields, respectively. Similarly, compounds **2b**–**f** were also prepared in good-to-excellent yields (Scheme 1).

The structures of these compounds were determined by the usual spectroscopic methods and proved by X-ray crystallography. Figure 1 shows the solid-state structure of com-

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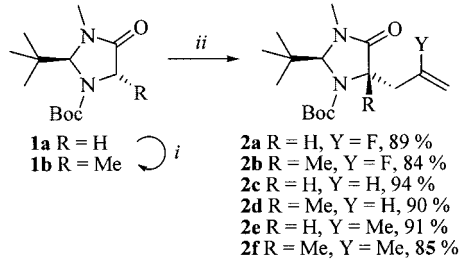


Scheme 1. Stereoselective alkylations of (*S*)-Boc-BMI −reagents and conditions: i. LDA, DMPU, THF, MeI, –50 °C, 3 h, 96%; ii. LDA, DMPU, THF, CH_2=$CYCH_2X$, –50 °C, 3 h

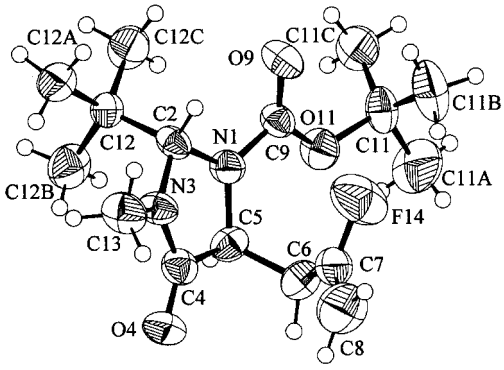


Figure 1. ORTEP diagram for *tert*-butyl (2*S*,5*S*)-2-*tert*-butyl-5-(2-fluoroallyl)-3-methyl-4-oxoimidazolidine-1-carboxylate (**2a**)

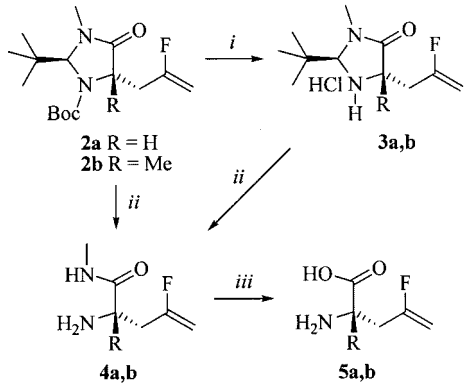
pound **2a** (for the structures of **2b**–**f**, see the Supporting Information).

Hindered rotation around the carboxamide function of compounds **2** was observed by ^{1}H NMR spectroscopy at various temperatures, but coalescence due to fluorine or methyl substitution of the double bond was not observed, even at temperatures as low as 193 K.[43]

Deprotection of the alkylation products **2** was achieved in two steps. The alkylated derivatives **2a** and **2b** were deprotected quantitatively to hydrochloride salts **3** with HCl/MeOH[44] (Scheme 2). The hydrolysis of compounds **2** to *N*′-methylamides **4** or free amino acids **5** without hydrolysis of the acid-sensitive fluorovinyl group was explored under different conditions, but the use of TFA/CH_2Cl_2 or HCl/MeOH at room temperature or at reflux (absolute conditions) always led to Boc-deprotection only. Refluxing compounds **2** in a 1:1 mixture of 1 N HCl/H_2O in MeOH (aqueous conditions) resulted in the hydrolysis of the imidazolidinone ring to *N*′-methylamides **4** in 43 and 63% yields (Scheme 2).

The hydrochlorides **3** also gave *N*′-methylamides **4** by a similar aqueous acid hydrolysis. These reactions occurred without racemization; no signals due to (*R*) enantiomers of **4** were observed in chiral GC and in NMR experiments using [Eu(hfc)$_3$] (30 mol-%) as a chiral shift reagent. No short intra- or intermolecular contact of fluorine with the NH bonds in crystal packing of compound **4a** was detected (Figure 2).

Finally the *N*′-methylamides **4** were hydrolyzed by refluxing the amides with 2 N aq. KOH for 1 hour followed



Scheme 2. Deprotection reactions of the alkylation products − reagents and conditions: i. HCl/MeOH, room temp., 1 h; ii. 1 N HCl, MeOH/H_2O, reflux, 3 h; iii. (a) 2 N KOH/H_2O, reflux, 2 h; (b) propylene oxide, EtOH, reflux, 30 min

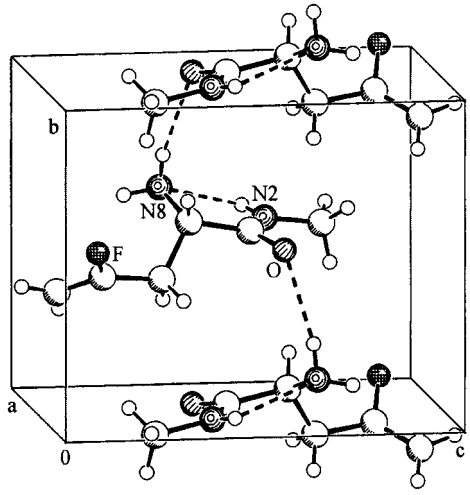
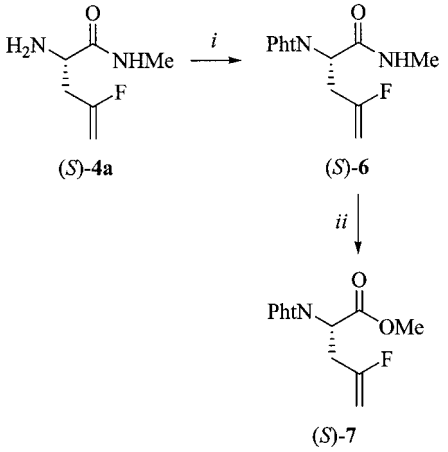


Figure 2. X-ray crystal packing for (2*S*)-2-amino-4-fluoro-*N*′-methylpent-4-enamide (**4a**)

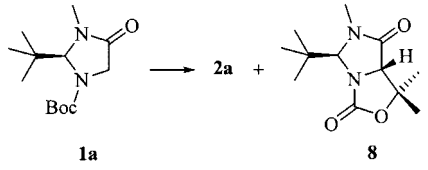
by treatment with propylene oxide in EtOH to give the corresponding free amino acids in 63–66% yields (Scheme 2). Partial racemization of **5a** occurred during basic amide hydrolysis of **4a**. Consequently, several lipases and esterases were screened for enzymatic hydrolysis in order to overcome the racemization of **4a** to the corresponding free acids **5a**, however without success.[45] Finally a nitrosative deamidation of α-amino acid amides was developed.[46] The amino group of *N*′-methylamide (*S*)-**4a** was completely protected by using phthalic anhydride (PhtA) in the presence of oxalyl chloride in $CHCl_3$/MeOH at 65 °C to yield 89% of the imide (*S*)-**6** (Scheme 3). Then the deamidation reaction was carried out by thermal decomposition of the in situ generated *N*′-nitrosoamide in a stereoconservative reaction to give the methyl ester (*S*)-**7** in 91% yield.[46] In due course the enantiopure *N*′-methylamides **4a** and **4b** will be used in peptide synthesis.[44]



Scheme 3. Stereoconservative deamidation of **4a** − reagents and conditions: i. PhtA, $C_2Cl_2O_2$, $CHCl_3$/MeOH, 0–65 °C, 7 h; ii. (a) $NaNO_2$, Ac_2O/AcOH, 0–4 °C, 14–16 h; (b) dioxane, reflux, 5 h

The fluorovinyl group in compounds **2a** and **2b** was also stable under stronger aqueous basic conditions but hydrolysis to 4-oxonorvalines occurred under stronger aqueous acidic conditions.[24–26] Thus, the alkylation reagents, 2-fluoroallylhalogenides and 2-fluoroallyl tosylate, can be seen as acetonyl cation equivalents. 4-Oxo-L-norvaline has been used as an important building block for protease inhibition studies.[47] Investigations into the synthetic use of compounds **2** are in progress and will be reported in due course.

Attempts to synthesize the other diastereomer of **2b** inaone-pot or step-by-step alkylation of compound **1a** failed. Under the conditions shown in Scheme 4, besides a 65% isolated yield of compound **2a**, compound **8** was isolated as an enantiopure side-product in 20% yield (Scheme 4, Figure 3).



Scheme 4. Attempted one-pot dialkylation of (*S*)-Boc-BMI − reagents and conditions: LDA, DMPU, THF, CH_2=$CFCH_2OTs$, –50 °C, 3 h and then LDA, MeI, –50 °C, 3 h

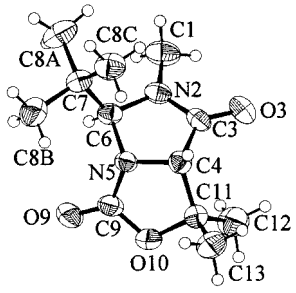
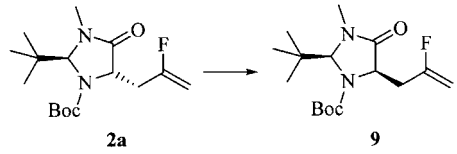


Figure 3. OPTEP diagram for (5*S*,7a*S*)-5-*tert*-butyl-1,1,6-trimethyldihydro-1*H*-imidazo[1,5-*c*][1,3]oxazole-3,7(7a*H*)-dione (**8**)

We do not have an explanation for the formation of compound **8** yet, and hence did not try to optimize the conditions for its synthesis. However, this compound may be useful in the selective synthesis of threonine analogues. These investigations will be continued.

As mentioned above, a second alkylation reaction of **2a** was not possible under the applied conditions because deprotonation of the α-position by LDA at –50 °C seems to be hindered in this *trans*-2,5-disubstituted imidazolidinone (Figure 1). The dynamics of the carbamoyl group, and probably also that of the 2-fluoroallyl function, might be the reason for the failure of the second alkylation of **2a**. An analogous failure of a similar imidazolidinone to undergo a second alkylation reaction has been reported.[48] In this case a *trans*-5-indolylmethyl group was not inverted into the position *cis* to the *tert*-butyl group largely because of steric hindrance. This suggestion is supported by the fact that second alkylation reactions of *trans*-configured **1b** proceed smoothly to form compounds **2b**, **2d**, and **2f** in high yields (Scheme 1).

In the absence of an electrophile, compound **2a**, formed by alkylation under kinetic control under strong basic conditions, isomerized mainly to the thermodynamically more stable product **9** in a 1:9 ratio, respectively, by inversion of the C-5 stereocenter (Scheme 5) Thus, in principle the synthesis of both the enantiomers of **4a** is possible by using the same auxiliary.



Scheme 5. Transformation of **2a** to **9** − reagents and conditions: 2 N KOH/H_2O, MeOH, reflux, 1 h

The assignment of the structures of **2a** and **9** is supported by investigations of the nuclear Overhauser effect (NOE). By using the frequency of the *t*Bu group at C-2, irradiation increased the intensity of the signals of 5-H_b (as well as those of H_a, and the Boc and *N*-methyl groups) for compound **2a**. On the other hand, the corresponding experiment with compound **9** resulted in an increased intensity of the signals of the 6-CH_2 and 8-CH_2 moieties (as well as those of H_a, and the Boc and *N*-methyl groups). By comparing the results of the NOE experiments, compound **9** was assigned as the *cis* isomer with a (2*S*,5*R*) configuration

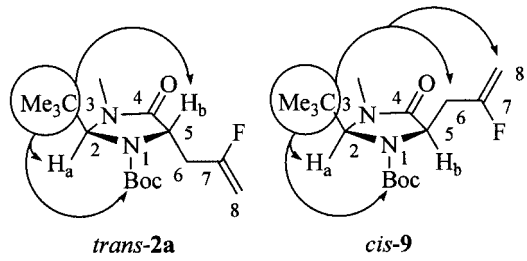


Figure 4. Significant NOE experiments for compounds **2a** and **9** by ^{1}H NMR (600 MHz) spectroscopy

(Figure 4). No dynamic effect was observed for compound **9** at room temperature.

Conclusions

We have reported herein a highly selective method, with good overall yields, for the synthesis of γ-fluoro-α-amino acid **5a** and its α-methyl analogue **5b** by using enantiopure (*S*)-Boc-BMI (**1a**) as a chiral glycine equivalent. The racemization of *N*′-methylamide **4a** under basic conditions was overcome by a new stereoconservative deamidation reaction. The fluorinated α-amino acids, as isosteres of asparagine and its α-methyl derivative, are of considerable interest as peptidomimetics and will be studied further. This study indicates that fluorine has a weak electronic effect on the overall properties of this type of molecule. Besides the dynamics of the carbamate group, no dynamic effect was observed by solution NMR spectroscopy for the fluorovinyl moiety in compounds **2a** and **2b**.

Experimental Section

General Remarks: All air- and moisture-sensitive reactions were performed under argon in flame-dried flasks using standard Schlenk-line techniques. (*S*)-Boc-BMI (**1a**) was a gift of Degussa AG, Germany. All other starting materials were obtained from Acros, Merck or Fluka. Diisopropylamine was distilled from KOH, DMPU was dried with molecular sieves (4 Å), and THF was distilled from sodium/benzophenone before use. The yields reported are those obtained after purification. Melting points are uncorrected. Optical rotations were measured in the specified solvents at 20 °C. NMR spectra: ^{1}H (300.14 and 598.98 MHz), ^{13}C (75.48 MHz), and ^{19}F NMR (282.37 and 563.58 MHz). TMS (δ = 0 ppm) for ^{1}H, $CDCl_3$ (δ = 77.00 ppm) for ^{13}C, and $CFCl_3$ (δ = 0 ppm) for ^{19}F were used as internal standards. The multiplicities of the ^{13}C NMR signals of the ^{13}C–^{1}H coupling were determined by the DEPT (90 and 135°) method. Mass spectra: GC-MS-CI by using NH_3, GC-MS-EI coupling (70 eV), and MS-EI direct inlet. Exact mass: Quattro LC method using nanospray and MicroTof Bruker Daltonics using loop injection. Elemental analysis: Mikroanalytisches Laboratorium, Organische Chemie, Universität Münster. X-ray diffraction: Data sets were collected with Enraf–Nonius CAD4 and Nonius-Kappa CCD diffractometers. Programs used: data collection EXPRESS[49] and COLLECT,[50] data reduction MolEN[51] and Denzo-SMN,[52] absorption correction for CCD data SORTAV,[53,54] structure solution SHELXS-97,[55] structure refinement SHELXL-97,[56] graphics DIAMOND[57]and SCHAKAL.[58]

General Procedure A: A solution of lithium diisopropylamide was prepared by addition of *n*-butyllithium (1.6 N solution in hexane) (7.5 mL, 12.0 mmol) to a solution of diisopropylamine (1.7 mL, 12.0 mmol) in dry THF (7.5 mL) under argon at –50 °C. The mixture was stirred for 15 min at this temperature. Then, DMPU (3.6 mL, 30.0 mmol) and (*S*)-Boc-BMI (**1a**) or (*S*)-Boc-BMI-Me (**1b**) (10.0 mmol) in dry THF (7.5 mL) were added to the above LDA solution at –50 °C. After 30 min, the corresponding electrophile (11–13 mmol) in dry THF (3.0 mL) was added in one shot at –50 °C. The resulting mixture was stirred for 2 h at this temperature and quenched with sat. aq. NH_4Cl solution (5.0 mL) and then Et_2O (30 mL) was added. After phase separation, the aqueous layer was extracted with Et_2O (3×). The combined organic layers were washed with 2 N citric acid, sat. aq. $NaHCO_3$, water and dried ($MgSO_4$). Evaporation of the solvent under vacuum followed by flash column (FC) chromatography[59] on silica gel (Et_2O/cyclohexane, 2:1) gave the respective product as a solid. Two sets of spectroscopic data corresponding to two rotamers were observed in most the cases and were differentiated as major/minor rotamers by NMR signal-to-signal integration.

***tert*-Butyl (2*S*,5*S*)-2-*tert*-Butyl-3,5-dimethyl-4-oxoimidazolidine-1-carboxylate (1b):** Following general procedure A, (*S*)-Boc-BMI (**1a**) (1.28 g, 5.0 mmol) and MeI (0.44 g, 7.0 mmol) yielded **1b** as a pale yellowish crystalline solid (1.3 g, 96%): m.p. 103 °C (Et_2O/pentane). $[\alpha]_D^{20}$ = –14.9 (*c* = 1.09, Et_2O). The spectral data agree with those reported previously.[38]

***tert*-Butyl (2*S*,5*S*)-2-*tert*-Butyl-5-(2-fluoroallyl)-3-methyl-4-oxoimidazolidine-1-carboxylate (2a):** Following general procedure A, (*S*)-Boc-BMI (**1a**) (2.56 g, 10.0 mmol) and 2-fluoroallyl tosylate (2.53 g, 11.0 mmol), prepared from 2-fluoroallyl alcohol[26] by tosylation, gave title compound **2a** as a white crystalline solid (2.8 g, 89 %): m.p. 79 °C (Et_2O/pentane). $[\alpha]_D^{20}$ = –16.5 (*c* = 0.515, CH_2Cl_2). ^{1}H NMR (300.14 MHz, $CDCl_3$): δ = 0.98 (3 × s, 9 H, CH-C(CH_3)$_3$), 1.48 (3 × s, 9 H, CO-C(CH_3)$_3$), 2.77–2.97 (m, 1 H, CH-CH_2-CF), 3.01 (s, 3 H, N-Me), 3.30–3.60 (m, 1 H, CH-CH_2-CF), 4.12 (d, ^3J(H,H) = 5.4 Hz, 1 H, CO-C*H*-N), 4.27 (dd, $^2J_{H,H}$ = 2.1, $^3J_{H,F}$ = 50.0 Hz, 1 H, CF=CH_Z), 4.57 (dd, $^2J_{H,H}$ = 2.1, $^3J_{H,F}$ = 17.8 Hz, 1 H, CF=CH_E), 4.95 ppm (br. s, 1 H, C*H*-C(CH$_3$)$_3$). ^{13}C NMR (75.48 MHz, $CDCl_3$): δ = 26.4 (3 × q, CH-C(*C*H$_3$)$_3$), 28.1 (3 × q, CO-C(*C*H$_3$)$_3$), 31.6 (ddd, $^2J_{C,F}$ = 26.9 Hz, H_2C=*C*F), 32.0 (q, N-CH$_3$), 40.8 (s, CH-*C*(CH$_3$)$_3$), 57.5 (d, N-*C*H-CO), 80.6 (s + d, CO-*C*(CH$_3$)$_3$ + *C*H-C(CH$_3$)$_3$), 93.6 (ddd, $^2J_{C,F}$ = 18.7 Hz, CF-*C*H$_2$), 152.6 (s, N-*C*O-O*t*Bu), 162.3 (d, $^1J_{C,F}$ = 258.5 Hz, *C*F=CH$_2$), 171.1 ppm (s, H_2C-*C*O-NMe). ^{19}F NMR (282.37 MHz, $CDCl_3$) major rotamer: δ = –96.73 ppm (m, 1 F, CF=CH$_2$); minor rotamer: δ = –93.17 ppm (m, 1 F, CF=CH$_2$). MS-ES: *m*/*z* = 315.3 [M + H]. GC-MS: *m*/*z* (%) = 257 (5) [M$^+$ – C_4H_9], 241 (7) [M$^+$ – $C_4H_{10}O$], 201 (63), 181 (20), 157 (73), 131 (38), 110 (28), 88 (50), 69 (42), 57 (70), 42 (100). $C_{16}H_{27}FN_2O_3$ (314.4): calcd. C 61.12, H 8.66, N 8.91; found: C 61.14, H 8.91, N 9.01.

***tert*-Butyl (2*S*,5*S*)-2-*tert*-Butyl-5-(2-fluoroallyl)-3,5-dimethyl-4-oxoimidazolidine-1-carboxylate (2b):** Following general procedure A, slow addition of 2-fluoroallyl tosylate (0.97 g, 7 mmol) to (*S*)-Boc-BMI-Me (**1b**) (1.35 g, 5.0 mmol) gave **2b** as a white crystalline solid (1.3 g, 84%): m.p. 68 °C (Et_2O/pentane). $[\alpha]_D^{20}$ = –8.7 (*c* =1.09, Et_2O). ^{1}H NMR (300.14 MHz, $CDCl_3$) major rotamer: δ = 0.98 (3 × s, 9 H, CH-C(CH_3)$_3$), 1.51 (3 × s, 9 H, CO-C(CH_3)$_3$), 1.53 (s, 3 H, C*-Me), 2.97 (s, 3 H, N-Me), 2.98–3.20 (m, 1 H, CH-CH_2-CF), 3.38–3.54 (m, 1 H, CH-CH_2-CF), 4.25 (dd, $^2J_{H,H}$ = 2.7, $^3J_{H,F}$ = 49.7 Hz, 1 H, CF=CH_Z), 4.55 (dd, $^2J_{H,H}$ = 2.7, $^3J_{H,F}$ = 17.5 Hz, 1 H, CF=CH_E), 5.00 ppm (s, 1 H, N-CH-NMe); minor rotamer: δ = 1.00 (3 × s, 9 H, CH-C(CH_3)$_3$), 1.48 (3 × s, 9 H, CO-C(CH_3)$_3$), 1.58 (s, 3 H, C*-Me), 2.45–2.73 (m, 2 H, CH-CH_2-CF), 2.97 (s, 3 H, N-Me), 4.29 (dd, $^2J_{H,H}$ = 2.5, $^3J_{H,F}$ = 49.8 Hz, 1 H, CF=CH_Z), 4.53 (dd, $^2J_{H,H}$ = 2.4, $^3J_{H,F}$ = 17.3 Hz, 1 H, CF=CH_E), 4.87 ppm (s, 1 H, N-CH-NMe). ^{13}C NMR (75.48 MHz, $CDCl_3$) major rotamer: δ = 23.8 (s, C*-*C*H$_3$), 26.9 (3 × q, CH-C(*C*H$_3$)$_3$), 28.3 (3 × q, CO-C(*C*H$_3$)$_3$), 31.7 (q, N-CH$_3$), 38.7 (s, CH-*C*(CH$_3$)$_3$), 39.7 (ddd, $^2J_{C,F}$ = 25.6 Hz, H_2C-CF), 63.77 (s, N-*C*-CO), 80.5 (d, N-CH-N), 81.0 (s, CO-*C*(CH$_3$)$_3$), 93.7 (ddd, $^2J_{C,F}$ = 20.2 Hz, CF=*C*H$_2$), 153.1 (s, N-*C*O-O*t*Bu), 163.0 (d, $^1J_{C,F}$ = 258.1 Hz, *C*F=CH$_2$), 172.8 ppm (s, *C*O-NMe); minor rotamer: δ = 23.6 (q, C*-*C*H$_3$), 27.2 (3 × q, CH-C(*C*H$_3$)$_3$), 28.1 (3 × q, CO-C(*C*H$_3$)$_3$), 31.9 (q, N-CH$_3$), 38.2 (ddd, $^2J_{C,F}$ = 26.2 Hz, H_2C-CF), 39.0 (s,

CH-*C*(CH_3)$_3$), 64.1 (s, N-*C**-CO), 81.0 (d, N-CH-N), 81.1 (s, CO-*C*(CH_3)$_3$), 94.1 (ddd, $^2J_{C,F}$ = 20.0 Hz, CF=*C*H_2), 154.2 (s, N-*C*O-O*t*Bu), 162.6 (d, $^1J_{C,F}$ = 258.8 Hz, *C*F=CH_2), 173.1 ppm (s, *C*O-NMe). ^{19}F NMR (282.37 MHz, $CDCl_3$) major rotamer: δ = –94.77 ppm (dddd, $^3J_{H,F}$ = 7.6, $^3J_{H,F}$ = 17.3, $^3J_{H,F}$ = 22.6, $^3J_{H,F}$ = 49.6 Hz, 1 F, CF=CH_2); minor rotamer: δ = –97.98 ppm (dddd, $^3J_{H,F}$ = 8.4, $^3J_{H,F}$ = 16.9, $^3J_{H,F}$ = 25.1, $^3J_{H,F}$ = 50.1 Hz, 1 F, CF=CH_2). MS-ES: *m*/*z* = 329.2 [M + H]. GC-MS: *m*/*z* (%) = 271 (6) [M^+ – C_4H_8], 255 (3) [M^+ – $C_4H_{10}O$], 215 (84), 195 (2), 171 (43), 143 (3), 123 (2), 111 (35), 87 (5), 57 (100), 42 (58). $C_{17}H_{29}FN_2O_3$ (328.4): calcd. C 62.17, H 8.90, N 8.53; found: C 62.23, H 8.93, N 8.40.

***tert*-Butyl (2*S*,5*S*)-5-Allyl-2-*tert*-butyl-3-methyl-4-oxoimidazolidine-1-carboxylate (2c):** Following general procedure A, the reaction of **1a** (1.28 g, 5.0 mmol) with allyl bromide (0.85 g, 7.0 mmol) gave compound **2c** as a white crystalline solid (1.39 g, 94%): m.p. 63 °C (Et_2O/pentane). $[\alpha]_D^{20}$ = +1.2 (*c* = 1.005, Et_2O). The spectral data agree with those reported previously.[33]

***tert*-Butyl (2*S*,5*S*)-5-Allyl-2-*tert*-butyl-3,5-dimethyl-4-oxoimidazolidine-1-carboxylate (2d):** Following general procedure A, the reaction of **1b** (1.35 g, 5.0 mmol) with allyl bromide (0.85 g, 7.0 mmol) gave compound **2d** as a white crystalline solid (1.4 g, 90%): m.p. 57 °C (Et_2O-pentane). $[\alpha]_D^{20}$ = –15.2 (*c* = 1.0, Et_2O). ^{1}H NMR(300.14 MHz, $CDCl_3$) major rotamer: δ = 0.97 (3 × s, 9 H, CH-C(CH_3)$_3$), 1.51 (3 × s, 9 H, CO-C(CH_3)$_3$), 1.51 (s, 3 H, C*-Me), 2.48 (dd, $^3J_{H,H}$ = 7.8, $^2J_{H,H}$ = 13.9 Hz, 1 H, CH_2-CH=CH_2), 2.90–3.00 (dd, overlapped, 1 H, CH_2-CH=CH_2), 2.95 (s, 3 H, N-Me), 4.96 (br. s, 1 H, N-CH-N), 4.98–5.13 (m, 2 H, CH_2-CH=CH_2), 5.26–5.48 ppm (m, 1 H, CH_2-CH=CH_2); minor rotamer: δ = 0.99 (3 × s, 9 H, CH-C(CH_3)$_3$), 1.48 (3 × s, 9 H, CO-C(CH_3)$_3$), 1.57 (s, 3 H, C*-Me), 2.41 (dd, $^3J_{H,H}$ = 7.8, $^2J_{H,H}$ = 13.9 Hz, 1 H, CH_2-CH=CH_2), 2.97 (2 × s, 3 H, N-Me), 3.26 (dd, $^3J_{H,H}$ = 8.4, $^2J_{H,H}$ = 13.9 Hz, 1 H, CH_2-CH=CH_2), 4.81 (br. s, 1 H, N-CH-N), 4.98–5.13 (m, 2 H, CH_2-CH=CH_2), 5.26–5.48 ppm (m, 1 H, CH_2-CH=CH_2). ^{13}C NMR (75.48 MHz, $CDCl_3$) major rotamer: δ = 23.6 (q, C*-*C*H_3), 26.7 (3 × q, CH-C(*C*H_3)$_3$), 28.3 (3 × q, CO-C(*C*H_3)$_3$), 31.4 (q, N-Me), 38.9 (s, CH-*C*(CH_3)$_3$), 42.1 (dd, *C*H_2-CH=CH_2), 65.0 (s, N-*C**-Me), 80.6 (d, N-CH-N), 80.7 (s, CO-*C*(CH_3)$_3$), 119.4 (dd, CH_2-CH=CH_2), 131.7 (d, CH_2-*C*H=*C*H_2), 155.0 (s, *C*O-C(CH_3)$_3$), 173.6 ppm (s, *C*O-NMe); minor rotamer: δ = 23.5 (q, C*-*C*H_3), 27.1 (3 × q, CH-C(*C*H_3)$_3$), 28.1 (3 × q, CO-C(*C*H_3)$_3$), 31.4 (q, N-Me), 38.6 (s, CH-*C*(CH_3)$_3$), 40.3 (dd, *C*H_2-CH=CH_2), 65.5 (s, N-*C**-Me), 80.8 (s, CO-*C*(CH_3)$_3$), 81.0 (d, N-CH-N), 119.4 (dd, CH_2-CH=CH_2), 132.2 (d, CH_2-*C*H=*C*H_2), 154.6 (s, *C*O-C(CH_3)$_3$), 173.7 ppm (s, *C*O-NMe). MS-ES: *m*/*z* = 311 [M + H]. GC-MS: *m*/*z* (%) = 253 (5) [M^+ – C_4H_9], 197 (78) [M^+ – C_8H_{18}], 179 (30), 169 (43), 153 (45), 136 (10), 125 (15), 112 (58), 94 (32), 84 (54), 69 (64), 57 (94), 42 (100). $C_{17}H_{30}N_2O_3$ (310.4): calcd. C 65.77; H 9.74, N 9.02; found: C 65.72; H 9.70, N 8.87.

***tert*-Butyl (2*S*,5*S*)-2-*tert*-Butyl-3-methyl-5-(2-methylallyl)-4-oxoimidazolidine-1-carboxylate (2e):** Following general procedure A, the reaction of **1a** (1.28 g, 15.0 mmol) with 2-methallyl chloride (0.63 g, 7.0 mmol) gave compound **2e** as a white crystalline solid (1.41 g, 91%): m.p. 82 °C (Et_2O/pentane). $[\alpha]_D^{20}$ = –16.3 (*c* = 1.0, Et_2O). ^{1}H NMR (300.14 MHz, $CDCl_3$): δ = 0.98 (3 × s, 9 H, CH-C(CH_3)$_3$), 1.47 (3 × s, 9 H, CO-C(CH_3)$_3$), 1.66 (s, 3 H, H_2C=CH-CH_3), 2.65 (d, $^2J_{H,H}$ = 15.8 Hz, 1 H, CH-CH_2-CMe), 3.00 (s, 3 H, N-Me), 3.13 (dd, $^4J_{H,H}$ = 4.9, $^2J_{H,H}$ = 15.7 Hz, 1 H, CH-CH_2-CMe), 4.12 (dd, $^3J_{H,H}$ = 1.8, $^3J_{H,H}$ = 3.3 Hz, 1 H, CO-C*H*-CH_2), 4.56 (d, 1 H, MeC=CH_Z), 4.78 (d, 1 H, MeC=CH_E), 4.94 ppm (br. s, 1 H, N-CH-N). ^{13}C NMR (75.48 MHz, $CDCl_3$): δ = 23.7 (q, H_2C=CH-*C*H_3), 26.5 (3 × q, CH-C(*C*H_3)$_3$), 28.1 (3 × q, CO-C(*C*H_3)$_3$), 32.0 (q, N-Me), 35.6 (s, CH-*C*(CH_3)$_3$), 40.8 (dd, H_2*C*-CCH$_3$), 58.6 (d, CO-*C*H-N), 80.7 (s, CO-*C*(CH_3)$_3$), 81.0 (d, N-CH-N), 112.8 (dd, H_2*C*=*C*-CH_3), 140.4 (s, H_2C=C-CH_3), 152.9 (s, *C*O-O*t*Bu), 172.0 ppm (s, *C*O-NMe). MS-ES: *m*/*z* = 311.3 [M + H]. GC-MS: *m*/*z* (%) = 253 (5) [M^+ – C_4H_9], 237 (2), 207 (7), 197 (71) [M^+ – C_8H_{18}], 179 (35), 167 (2), 153 (67), 134 (25), 127 (33), 110 (44), 94 (82), 84 (76), 69 (94), 57 (94), 41 (100). $C_{17}H_{30}N_2O_3$ (310.4): calcd. C 65.77, H 9.74, N 9.02; found: C 65.88, H 9.71, N 8.82.

***tert*-Butyl (2*S*,5*S*)-2-*tert*-Butyl-3,5-dimethyl-5-(2-methylallyl)-4-oxoimidazolidine-1-carboxylate (2f):** Following general procedure A, the reaction of **1b** (1.0 g, 3.7 mmol) with 2-methallyl chloride (0.47 g, 5.2 mmol) gave compound **2f** as a white crystalline solid (1.02 g, 85%): m.p. 62 °C (Et_2O/pentane). $[\alpha]_D^{20}$ = –34.4 (*c*= 1.01, Et_2O). ^{1}H NMR (300.14 MHz, $CDCl_3$) major rotamer: δ = 0.99 (3 × s, 9 H, CH-C(CH_3)$_3$), 1.51 (3 × s, 9 H, CO-C(CH_3)$_3$), 1.52 (s, 3 H, C*-Me), 1.62 (s, 3 H, CH_2=C-CH_3), 2.43 (d, $^2J_{H,H}$ = 14.4 Hz, 1 H, CH-CH_2-CMe), 2.94 (s, 3 H, N-Me), 2.95 (d, $^2J_{H,H}$ = 14.4 Hz, 1 H, CH-CH_2-CMe), 4.62 (d, $^2J_{H,H}$ = 10.6 Hz, 1 H, H_ZC=CMe), 4.79 (d, $^2J_{H,H}$ = 7.2 Hz, 1 H, H_EC=CMe), 4.94 ppm (br. s, 1 H, N-CH-N); minor rotamer: δ = 1.01 (3 × s, 9 H, CH-C(CH_3)$_3$), 1.47 (3 × s, 9 H, CO-C(CH_3)$_3$), 1.57 (s, 3 H, C*-Me), 1.59 (s, 3 H, CH_2=C-CH_3), 2.40 (d, $^2J_{H,H}$ = 14.4 Hz, 1 H, CH-CH_2-CMe), 2.95 (s, 3 H, N-Me), 3.26 (d, $^2J_{H,H}$ = 14.4 Hz, 1 H, CH-CH_2-CMe), 4.62 (d, $^2J_{H,H}$ = 10.6 Hz, 1 H, H_ZC=CMe), 4.79 (d, $^2J_{H,H}$ = 7.2 Hz, 1 H, H_EC=CMe), 4.81 ppm (2 × br. s, 1 H, N-CH-N). ^{13}C NMR (75.48 MHz, $CDCl_3$) major rotamer: δ = 23.7 (q, C*-*C*H_3), 24.9 (q, CH_2-C-*C*H_3), 27.0 (3 × q, CH-C(*C*H_3)$_3$), 28.3 (3 × q, CO-C(*C*H_3)$_3$), 31.5 (q, N-Me), 39.1 (s, CH-*C*Me$_3$), 44.2 (dd, C-*C*H_2-CMe), 64.3 (s, CO-*C**-Me), 80.5 (d, N-CH-N), 80.7 (s, CO-O*C*Me$_3$), 114.4 (dd, H_2*C*=*C*Me), 140.4 (s, H_2C=CMe), 154.5 (s, *C*O-O*t*Bu), 173.3 ppm (s, *C*O-NMe);minor rotamer: δ = 23.2 (q, C*-*C*H_3), 24.8 (q, CH_2-C-*C*H_3), 27.3 (3 × q, CH-C(*C*H_3)$_3$), 28.1 (3 × q, CO-C(*C*H_3)$_3$), 31.5 (q, N-Me), 38.6 (s, CH-*C*Me$_3$), 42.9 (dd, C-*C*H_2-CMe), 64.8 (s, CO-*C**-Me), 80.8 (s, CO-O*C*Me$_3$), 80.9 (d, N-CH-N), 114.84 (dd, H_2*C*=*C*Me), 140.7 (s, H_2C=CMe), 152.7 (s, *C*O-O*t*Bu), 173.6 ppm (s, *C*O-NMe). MS-ES: *m*/*z* = 325.3 [M + H]. GC-MS: *m*/*z* (%) = 267 (3) [M^+ – C_4H_9], 251 (1), 223 (1), 211 (64) [M^+ – C_8H_{18}], 193 (27), 167 (42), 151 (23), 112 (83), 108 (28), 98 (24), 82 (24), 69 (35), 57 (98), 41 (100). $C_{18}H_{32}N_2O_3$ (324.5): calcd. C 66.63, H 9.94, N 8.63; found: C 66.37, H 10.04, N 8.60.

General Procedure B: The alkylation product **2** (5.0 mmol), dissolved in anhydrous MeOH (5.0 mL), was treated with the anhydrous HCl/MeOH[44] (10.0 mL) and the mixture was stirred at room temp. for 1 h. The solvent and excess reagent were removed under vacuum and the residue was stirred in Et_2O. The white powder formed was isolated by filtration and washed with Et_2O. The solid was dried in vacuo and with P_2O_5 in a desiccator.

(2*R*,5*S*)-5-(2-Allyl)-2-*tert*-butyl-3-methylimidazolidin-4-one Hydrochloride (3a): Following general procedure B, starting from alkylation product **2a** (1.57 g, 5.0 mmol) the HCl salt of **3a** was isolated as a white powder (0.91 g, quant.): m.p. 130–135 °C (decomposition, Et_2O/MeOH). $[\alpha]_D^{20}$ = –52.4 (*c* = 0.965, MeOH). ^{1}H NMR (300.14 MHz, CD_3OD): δ = 1.16 (3 × s, 9 H, CH-C(CH_3)$_3$), 2.76–3.12 (m, 2 H, CH-CH_2-CF), 3.08 (s, 3 H, N-Me), 4.37 (dd, $^2J_{H,H}$ = 2.1, $^3J_{H,H}$ = 8.8 Hz, 1 H, CF=CH_Z), 4.65–4.90 ppm (m, overlapped for 5 H, CF=CH_E, CO-C*H*-N, N-CH-N, CH-N*H*-CH). ^{13}C NMR (75.48 MHz, CD_3OD): δ = 25.3 (3 × q, CH-C(*C*H_3)$_3$), 32.6 (q, N-Me), 33.2 (ddd, $^2J_{C,F}$ = 27.9 Hz, CH-CH_2-CF), 37.5 (s, CH-*C*(CH_3)$_3$), 56.0 (d, NH-*C*H-CO), 82.7 (d, NH-*C*H-NMe), 95.5 (ddd, $^2J_{C,F}$ = 18.0 Hz, CF=*C*H_2), 161.4 (d, $^1J_{C,F}$ = 256.8 Hz, CH_2-

*C*F=CH_2), 169.2 ppm (s, *C*O-NMe). ^{19}F NMR (282.37 MHz, CD_3OD) major rotamer: δ = –97.73 ppm (dddd, $^3J_{H,F}$ = 15.5, $^3J_{H,F}$ = 16.0, $^3J_{H,F}$ = 20.0, $^3J_{H,F}$ = 51.4 Hz, 1 F, CH_2-CF=CH_2); minor rotamer: δ = –96.25 ppm (m, 1 F, CH_2-CF=CH_2). MS-ES: *m*/*z* = 215.1 [M – Cl]. MS-EI: *m*/*z* (%) = 198 (5) [M^+ – (Cl + CH_3)], 171 (89) [M^+ – (Cl + CHF=CH_2)], 157 (52) [M^+ – (Cl + C_4H_8)], 88 (100), 57 (26). $C_{11}H_{20}ClFN_2O$ (250.7): calcd. C 52.69, H 8.04, N 11.17; found: C 52.14, H 8.08, N 11.08.

(2*R*,5*S*)-2-*tert*-Butyl-5-(2-fluoroallyl)-3,5-dimethylimidazolidin-4-one Hydrochloride (3b): Following general procedure B, starting from dialkylated product **2b** (230 mg, 0.7 mmol) the HCl salt **3b** was isolated as a white powder (182 mg, quant.): m.p. 131–133 °C (decomposition, Et_2O/MeOH). $[a]_D^{20}$ = –38.0 (*c* = 0.84, MeOH). ^{1}H NMR (300.14 MHz, CD_3OD, major/minor): δ = 1.19/1.22 (2 × 3 × s, 9 H, CH-C(C*H*$_3$)$_3$), 1.67/1.57 (2 × s, 3 H, C*-Me), 2.88–2.93 (m, 1 H, CH-C*H*$_2$-CF), 2.97–3.08 (m, 1 H, CH-C*H*$_2$-CF), 3.05 (s, 3 H, N-Me), 4.65–4.92 ppm (m, overlapped for 4 H, CF=C*H*$_Z$, CF=C*H*$_E$, N-CH-N, CH-N*H*-CH). ^{13}C NMR (75.48 MHz, CD_3OD, major/minor): δ = 22.3 (q, C*-*C*H$_3$), 25.4/25.7 (2 × 3 × q, CH-C(*C*H$_3$)$_3$), 32.1/31.4 (2 × q, N-Me), 36.0/35.5 (2 × s, CH-*C*(CH$_3$)$_3$), 39.3 (ddd, $^2J_{C,F}$ = 28.7 Hz, *C*H$_2$-CF=CH_2), 64.5 (s, CO-*C**-NH), 81.7 (d, N-*C*H-N), 97.2 (ddd, $^2J_{C,F}$ = 17.7 Hz, CH_2-CF=*C*H$_2$), 161.3 (d, $^1J_{C,F}$ = 234.8 Hz, CH_2-*C*F=CH_2), 172.4 ppm (s, MeN-*C*O-C*). ^{19}F NMR (282.37 MHz, CD_3OD) major rotamer: δ = –94.55 ppm (dddd, $^3J_{H,F}$ = 7.9, $^3J_{H,F}$ = 19.0, $^3J_{H,F}$ = 19.8, $^3J_{H,F}$ = 50.2 Hz, 1 F, CH_2-CF=CH_2); minor rotamer: δ = –93.51 ppm (m, 1 F, CH_2-CF=CH_2). MS-ES: *m*/*z* = 229.1 [M – Cl]. MS-ES, daughters of 229.1: *m*/*z* (%) = 228 (7) [M^+ – HCl], 168 (100) [M^+ – (HCl + CH_3F=CH_2)], 150 (10) [M^+ – (HCl + HF + C_4H_8)], 143 (5) [M^+ – (HCl + $C_5H_{11}N$)], 126 (10) [M^+ – (HCl + $C_7H_{13}NO$)], 112 (70) [M^+ – (HCl + C_4H_8 + C_2H_3NO)], 108 (25), 101 (90), 99 (80), 101 (90); 85 (25), 68 (20), 157 (3), 42 (22). $C_{12}H_{22}ClFN_2O$ (264.8): calcd. C 54.44, H 8.38, N 10.58; found: C 53.22, H 8.22, N 10.54.

General Procedure C: The alkylation product **2** (4.72 g, 15.0 mmol) was dissolved in dry methanol (80 mL) and 1 N HCl solution (80 mL) was added at room temp. and the mixture refluxed for 3 h. The solvent was removed under vacuum and the residue was diluted with CH_2Cl_2 (100 mL). The pH of the aqueous phase was adjusted to 7–8 with 2 N KOH solution. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (5×). The combined organic layers were dried over Na_2SO_4 and the solvent was evaporated in vacuo to give a dark oil. After purification by column chromatography (CH_2Cl_2/MeOH, 9:1), *N*′-methylamides **4** were isolated as a single enantiomer (see Results and Discussion).

(*S*)-2-Amino-4-fluoropent-4-enoic*N*′-Methylamide (4a): Following general procedure C, alkylation product **2a** (4.72 g, 15.0 mmol) after crystallization from CH_2Cl_2/pentane in a freezer gave pale yellowish crystals of **4a** (1.38 g, 63%): m.p. 39 °C (Et_2O/pentane). $[a]_D^{20}$ = –60.6 (*c* = 1.04, CH_2Cl_2). ^{1}H NMR (300.14 MHz, $CDCl_3$): δ = 1.63 (br. s, 2 H, CH-N*H*$_2$), 2.31 (ddd, $^3J_{H,H}$ = 5.4, $^3J_{H,F}$ = 9.9, $^2J_{H,H}$ = 15.3 Hz, 1 H, CH-C*H*$_2$-CF), 2.82 (d, 3 H, $^3J_{H,H}$ = 5.0 Hz, N-Me), 2.88 (dddd, $^4J_{H,H}$ = 0.9, $^3J_{H,H}$ = 3.9, $^3J_{H,F}$ = 10.4, $^2J_{H,H}$ = 15.3 Hz, 1 H, CH-C*H*$_2$-CF), 3.57 (dd, $^3J_{H,H}$ = 3.9, $^3J_{H,H}$ = 9.5 Hz, 1 H, CO-C*H*-CH_2), 4.37 (ddd, $^4J_{H,H}$ = 0.7, $^2J_{H,H}$ = 2.8, $^3J_{H,F}$ = 49.6 Hz, 1 H, CH_2-CF=C*H*$_Z$), 4.67 (dd, $^2J_{H,H}$ = 2.8, $^3J_{H,F}$ = 17.1 Hz, 1 H, CH_2-CF=C*H*$_E$), 7.46 ppm (br. s, 1 H, N*H*-Me). ^{13}C NMR (75.48 MHz, $CDCl_3$): δ = 25.7 (q, N-Me), 37.6 (ddd, $^2J_{C,F}$ = 27.6 Hz, CH-*C*H$_2$-CF), 52.22 (d, CO-*C*H-CH_2), 92.9 (ddd, $^2J_{C,F}$ = 20.2 Hz, CH_2-CF=*C*H$_2$), 163.3 (d, $^1J_{C,F}$ = 257.8 Hz, CH_2-*C*F=CH_2), 174.0 ppm (s, *C*O-NHMe). ^{19}F NMR (282.37 MHz, $CDCl_3$): δ = –96.43 ppm (ddt, $^3J_{H,F}$ = 6.4, $^3J_{H,F}$ = 22.5, $^3J_{H,F}$ = 50.5 Hz, 1 F, CH_2-CF=CH_2). MS-ES: *m*/*z* = 147.2 [M + H]. GC-MS: *m*/*z* (%) = 99 (2) [M^+ – C_2H_3F], 88 (100) [M^+ – C_2H_5NO], 69 (12) [M^+ – (HF + C_2H_5NO)], 61 (36), 58 (10), 41 (25), 39 (7). $C_9H_{11}FN_2O$ (146.2): calcd. C 49.30, H 7.59, N 19.17; found: C 49.19, H 7.62, N 19.15.

(*S*)-2-Amino-4-fluoro-2-methylpent-4-enoic*N*′-Methylamide (4b): Following general procedure C, hydrolysis of **2b** (4.36 g, 13.3 mmol) gave compound **4b** as a colorless oil (0.92 g, 43 %). $[a]_D^{20}$ = –29.4 (*c* = 1.32, CH_2Cl_2). ^{1}H NMR (300.14 MHz, $CDCl_3$): δ = 1.35 (s, 3 H, C*-Me), 1.61 (br. s, 2 H, C*-NH_2), 2.46 (dd, $^3J_{H,F}$ = 8.4, $^2J_{H,H}$ = 14.6 Hz, 1 H, CH-C*H*$_2$-CF), 2.78 (dd, $^3J_{H,F}$ = 5.1, $^2J_{H,H}$ = 14.6 Hz, 1 H,), 2.79 (d, $^3J_{H,H}$ = 4.9 Hz, 3 H, NH-Me), 4.34 (dd, $^3J_{H,F}$ = 50.0, $^2J_{H,H}$ = 2.7 Hz, 1 H, CF=C*H*$_Z$), 4.66 (dd, $^3J_{H,F}$ = 17.3, $^2J_{H,H}$ = 2.7 Hz, 1 H, CF=C*H*$_E$), 7.69 ppm (br. s, 1 H, N*H*-Me). ^{13}C NMR (75.48 MHz, $CDCl_3$): δ = 25.9 (q, C*-Me), 27.3 (q, N-Me), 42.9 (ddd, $^2J_{C,F}$ = 24.2 Hz, -C*-*C*H$_2$-CF), 56.7 (d, $^3J_{C,F}$ = 1.8 Hz, CO-*C**-Me), 93.7 (ddd, $^2J_{C,F}$ = 19.5 Hz, CH_2-CF=*C*H$_2$), 163.5 (d, $^1J_{C,F}$ = 257.2 Hz, CH_2-*C*F-CH_2), 176.3 ppm (s, C*-*C*O-NHMe). ^{19}F NMR (282.37 MHz, $CDCl_3$): δ = –91.12 ppm (dddd, $^3J_{H,F}$ = 4.5, $^3J_{H,F}$ = 7.9, $^3J_{H,F}$ = 19.1, $^3J_{H,F}$ = 49.9 Hz, 1 F, CH_2-CF-CH_2). MS-ES: *m*/*z* = 161 [M + H]. MS-EI: *m*/*z* (%) = 140 (2) [M^+ – HF], 123 (8) [140–CH_3], 102 (72) [M^+ – C_2H_5NO], 101 (15) [C_3H_4F], 94 (5), 86 (6), 80 (7), 66 (8), 61 (9), 59 (22), 55 (15), 42 (100). ES-EM for [$C_7H_{13}FN_2O$ + H]: calcd. 161.1085; found: 161.1038.

General Procedure D: The respective *N*′-methylamide **4** (5 mmol) was dissolved in 2 N KOH (20 mL) at room temp. and the solution was then refluxed for 2 h. The pH of the solution was adjusted to 5–6 with stirring by using 2 N HCl at room temp. The water was removed under vacuum, the residue diluted with anhydrous EtOH (20 mL), and the precipitate (KCl) filtered. Propylene oxide (10 mL) was added to the filtrate and the solution was refluxed for 30 min. After cooling in a freezer for 2 h the precipitated solid was collected by filtration.

(2*S*)-2-Amino-4-fluoropent-4-enoic Acid (5a): Following general procedure D, starting from *N*′-methylamide **4a** (702 mg, 4.8 mmol) title compound **5a** was isolated as a white powder (400 mg, 63%). $[a]_D^{20}$ = –5.3 (*c* = 1.03, H_2O) [lit.[22] $[a]_D^{20}$ = –18.0 (*c* = 1.78, H_2O)]. The spectroscopic data for the racemate agree with previously published values.[26]

(2*S*)-2-Amino-4-fluoro-2-methylpent-4-enoic Acid (5b): Following general procedure D, starting from *N*′-methylamide **4b** (140 mg, 0.87 mmol) title compound **5b** was isolated as a white powder (85 mg, 66%). $[a]_D^{20}$ = –3.7 (*c* = 1.04, H_2O). The spectroscopic data for the racemate agree with previously published values.[26]

(*S*)-4-Fluoro-2-(1,3-dioxaisoindolin-2-yl)pent-4-enoic *N*-Methylamide (6):[46] Phthalic anhydride (3.6 mmol, freshly recrystallized from $CHCl_3$) was added to a solution of *N*-methylamide (*S*)-**4a** (438 mg, 3 mmol in $CHCl_3$/MeOH (2:1, 30 mL) at 0 °C. After 10 min, oxalyl chloride (4.5 mmol) was added dropwise at 0 °C. This solution was refluxed for 5 h and then cooled to room temp. The solvent was evaporated under vacuum and the residue was recrystallized from CH_2Cl_2/pentane (2:1) in a freezer to give the title compound **6** as white prisms (738 mg, 89%). In the X-ray structure determination, 0.5 equiv. CH_2Cl_2 was used as the solvent of crystallization: m.p. 169 °C (CH_2Cl_2/pentane). $[a]_D$ = –64.6 (*c* = 1.02, CH_2Cl_2). ^{1}H NMR (300.14 MHz, $CDCl_3$): δ = 2.78 (d, $^3J_{H,H}$ = 4.9 Hz, 3 H, NH-Me), 3.03–3.14 (m, 1 H, CH-C*H*$_2$-CF), 3.14–3.32 (m, 1 H, CH-C*H*$_2$-CF), 4.28 (ddd, $^4J_{H,H}$ = 0.5, $^3J_{H,F}$ = 49.1, $^2J_{H,H}$ = 3.0 Hz, 1 H, C*H*-CH_2-CF), 4.50 (dd, $^3J_{H,F}$ = 16.8, $^2J_{H,H}$ = 3.0 Hz, 1 H, CH_2-CF=C*H*$_Z$), 5.02 (dd, $^3J_{H,H}$ = 4.9, $^3J_{H,H}$ = 10.9 Hz, 1 H, CH_2-CF=C*H*$_E$), 6.32 (br. s, 1 H, N*H*-Me), 7.76 (2 × dd, $^4J_{H,H}$ = 3.0, $^3J_{H,H}$ = 5.5 Hz, 2 H, C*H*-Ar$_{meta}$), 7.86 ppm (2 × dd, $^4J_{H,H}$ = 3.0,

$^3J_{H,H}$ = 5.5 Hz, 2 H, C*H*-Ar$_{ortho}$). ^{13}C NMR (75.48 MHz, $CDCl_3$): δ = 26.51 (q, N-Me), 31.42 (ddd, $^2J_{C,F}$ = 27.2 Hz, *C*H$_2$-CF-CH$_2$), 51.17 (d, *C*H-CH$_2$-CF), 93.34 (ddd, $^2J_{C,F}$ = 19.4 Hz, CF=*C*H$_2$), 123.58 (2 × d, *C*H-Ar$_{ortho}$), 131.51 (2 × s, *C*-Ar), 134.40 (2 × d, *C*H-Ar$_{meta}$), 162.28 (d, $^1J_{C,F}$ = 258.0 Hz, CH$_2$-*C*F=CH$_2$), 167.67 (2 × s, C(Ar)-CO-N), 168.15 ppm (s, CH-*C*O-OMe). ^{19}F NMR (282.41 MHz, $CDCl_3$): δ = –98.13 ppm (dddd, $^3J_{H,F}$ = 12.1, $^3J_{H,F}$ = 16.8, $^3J_{H,F}$ = 17.0, $^3J_{H,F}$ = 49.1 Hz, 1 F, CH$_2$-CF=CH$_2$). MS-ES: *m*/*z* = 277 [M + H], 299 [M + Na]. GC-MS-EI: *m*/*z* (%) = 276 (17) [M$^+$], 256 (15) [M$^+$ – HF], 245 (7), 218 (65) [M$^+$ – C$_2$H$_4$NO or M$^+$ – C$_3$H$_4$F], 198 (100) [218 – HF], 189 (10), 171 (13), 160 (41) [218 – C$_2$H$_4$NO], 148 (12), 130 (41) [M$^+$ – C$_8$H$_4$NO$_2$], 104 (70) [160 – C$_2$H$_2$NO], 76 (96), 58 (55), 50 (68), 42 (49). GC-HRMS for [C$_{14}$H$_{12}$FN$_2$O$_3$]: calcd. 276.0910; found: 276.0915; for [C$_{14}$H$_{12}$FN$_2$O$_3$ – HF]: calcd. 256.0848; found: 256.0856.

Methyl (*S*)-4-Fluoro-2-(1,3-dioxaisoindolin-2-yl)pent-4-enoate (7): Granular $NaNO_2$ (1.53 g, 22 mmol) was added in portions over 2 h to a solution of the *N*-phthaloyl *N*′-methylamide **6** (276 mg, 1 mmol) in a 2:1 mixture of Ac_2O and AcOH (7.5 mL) at 0–4 °C. Evolution of a brown gas occurred, the solution changed color, and a solid precipitated. After 14–16 h, the mixture was warmed to room temperature in less than 20 min, added to ice–water (10 mL), and extracted with Et_2O (3 × 20 mL). The combined organic layers were washed (carefully!) with 5% Na_2CO_3 (3 × 20 mL) and then H_2O and dried (Na_2SO_4). Evaporation of the solvent gave a yellowish liquid. GC shows complete conversion of the *N*-phthalimido-*N*′-methylamide **6**. Anhydrous 1,4-dioxane (10 mL) was added to this residue, and the solution was refluxed. The yellowish color of the solution disappeared in the first 1 h, but refluxing was continued for 5 h. Then, the solution was cooled to room temperature and the solvent was removed under vacuum to give a colorless oil. GC of the crude product as such shows high purity (252 mg, 91%): $[a]_D$ = –67.9 (*c* = 1.1, CH_2Cl_2). ^{1}H NMR (300.14 MHz, $CDCl_3$): δ = 3.04–3.24 (m, 2 H, C*H*$_2$-CF=CH$_2$), 3.68 (s, 3 H, CO-OMe), 4.22 (dd, $^3J_{H,F}$ = 49.2, $^2J_{H,H}$ = 3.0 Hz, 1 H, CH$_2$-CF=C*H*$_Z$), 4.45 (dd, $^3J_{H,F}$ = 16.8, $^2J_{H,H}$ = 3.1 Hz, 1 H, CH$_2$-CF=C*H*$_E$), 5.09 (dd, $^3J_{H,H}$ = 5.7, $^3J_{H,H}$ = 10.3 Hz, 1 H, CO-C*H*-CH$_2$), 7.67 (2 × dd, $^4J_{H,H}$ = 3.1, $^3J_{H,H}$ = 5.5 Hz, 2 H, C*H*-Ar$_{meta}$), 7.79 ppm (2 × dd, $^4J_{H,H}$ = 3.1, $^3J_{H,H}$ = 5.4 Hz, 2 H, C*H*-Ar$_{ortho}$). ^{13}C NMR (75.48 MHz, $CDCl_3$): δ = 31.70 (ddd, $^2J_{C,F}$ = 27.7 Hz, CH-*C*H$_2$-CF), 49.01 (q, CO-OMe), 52.87 (d, CO-*C*H-CH$_2$), 93.22 (ddd, $^2J_{C,F}$ = 20.2 Hz, CF=*C*H$_2$), 123.58 (2 × d, *C*H-Ar$_{ortho}$), 131.66 (2 × s, *C*-Ar), 134.31 (2 × d, *C*H-Ar$_{meta}$), 161.87 (d, $^1J_{C,F}$ = 258.6 Hz, CH$_2$-*C*F=CH$_2$), 167.22 (2 × s, C(Ar)-CO-N), 168.64 ppm (s, CH-*C*O-OMe). ^{19}F NMR (282.37 MHz, $CDCl_3$): δ = –98.26 ppm (dddd, $^3J_{H,F}$ = 12.9, $^3J_{H,F}$ = 15.9, $^3J_{H,F}$ = 16.6, $^3J_{H,F}$ = 49.2 Hz, 1 F, CH$_2$-CF CH$_2$). MS-ES: *m*/*z* = 278 [M + H], 300 [M + Na]. GC-MS-EI: *m*/*z* (%) = 257 (1) [M$^+$ – HF], 245 (3) [M$^+$ – CH$_4$O], 218 (45) [M$^+$ – C$_2$H$_4$O$_2$ or M$^+$ – C$_3$H$_5$F], 198 (100) [218 – HF], 190 (40) [218 – CH$_4$O], 172 (7) [M$^+$ – 104], 163 (9), 143 (5), 130 (100) [M$^+$ – C$_8$H$_5$NO$_2$], 115 (15), 104 (40) [M$^+$ – C$_7$H$_6$O], 76 (47), 59 (20), 50 (51). ES-EM for [C$_{14}$H$_{12}$FNO$_4$+H]: calcd. 278.0823; found: 278.0801.

(5*S*,7a*S*)-5-*tert*-Butyl-1,1,6-trimethyldihydro-1*H*-imidazo[1,5-*c*][1,3]-oxazole-3,7(7a*H*)-dione (8): In a reaction similar to general procedure A, **1a**, LDA (2 equiv.), DMPU (3 equiv.), 2-fluoroallyl tosylate (1.1 equiv.), and MeI (1.5 equiv.) gave a mixture of **2a** (65% yield) and **8** as a side-product (20% yield, see the Results and Discussion). The crude solid **8** was crystallized from Et_2O/pentane in a freezer to give white prisms: m.p. 144 °C (Et_2O/pentane). $[a]_D^{20}$ = –21.0 (*c* = 1.02, CH_2Cl_2). ^{1}H NMR (300.14 MHz, $CDCl_3$): δ = 1.04 (3 × s, 9 H, CH-C(C*H*$_3$)$_3$), 1.44 (s, 3 H, C-Me), 1.63 (s, 3 H, C-Me), 3.00 (s, 3 H, N-Me), 3.96 (s, 1 H, CO-C*H*-CMe$_2$), 4.71 ppm (s, 1 H, N-CH-N). ^{13}C NMR (75.48 MHz, $CDCl_3$): δ = 23.9 (q, C-Me), 25.6 (3 × q, CH-C(*C*H$_3$)$_3$), 29.2 (q, C-Me), 31.1 (q, N-Me), 38.1 (s, CH-*C*(CH$_3$)$_3$), 66.3 (d, CO-*C*H-CMe$_2$), 83.9 (s + d, CH-*C*Me$_2$, N-CH-N), 160.6 (s, N-CO-O), 169.1 ppm (s, CH-*C*O-NMe). MS-ES: *m*/*z* = 263.4 [M + Na]. GC-MS: *m*/*z* (%) = 183 (27) [M$^+$ – C$_4$H$_8$], 169 (2) [M$^+$ – (C$_4$H$_8$ + CH$_3$)], 153 (3) [M$^+$ – (CO$_2$ + C$_3$H$_6$)], 139 (100) [M$^+$ – (CO$_2$ + C$_4$H$_8$)], 111 (5), 98 (5), 82 (78), 70 (18), 55 (28), 42 (75). C$_{12}$H$_{20}$N$_2$O$_3$ (240.3): calcd. C 59.98, H 8.39, N 11.66; found: C 59.71, H 8.47, N 11.42.

***tert*-Butyl (2*S*,5*R*)-2-*tert*-Butyl-5-(2-fluoroallyl)-3-methyl-4-oxoimidazolidine-1-carboxylate (9):** 2 N KOH (10 mL) was added to a solution of compound **2a** (314 mg, 1.0 mmol) in MeOH (10 mL) at room temp. The solution was refluxed for 2 h and MeOH was removed under vacuum. The residual aqueous phase was neutralized carefully with 2 N HCl solution at 0 °C and extracted with EtOAc (3×). The combined organic layers were dried ($MgSO_4$) and the solvents evaporated under vacuum to give a colorless oil of **9** and **2a** in a 9:1 ratio. The product *cis*-**9** (90%) was separated from *trans*-**2a** (10%) by column chromatography (cyclohexane/EtOAc, 4:1) to give a colorless oil (277 mg, 88%). $[a]_D^{20}$ = –25.6 (*c* = 1.1, CH_2Cl_2). ^{1}H NMR (300.14 MHz, $CDCl_3$): δ = 1.02 (3 × s, 9 H, CH-C(C*H*$_3$)$_3$), 1.47 (3 × s, 9 H, CO-C(C*H*$_3$)$_3$), 2.51 (ddd, $^3J_{H,H}$ = 8.8, $^3J_{H,F}$ = 22.7, $^2J_{H,H}$ = 14.7 Hz, 1 H, CH-C*H*$_2$-CF), 2.78 (dddd, $^4J_{H,H}$ = 2.0, $^3J_{H,H}$ = 5.1, $^3J_{H,F}$ = 17.8, $^2J_{H,H}$ = 14.7 Hz, 1 H, CH-C*H*$_2$-CF), 3.00 (s, 3 H, N-Me), 4.39 (dd, $^3J_{H,H}$ = 2.9, $^3J_{H,F}$ = 48.3 Hz, 1 H, CH$_2$-CF=C*H*$_E$), 4.38 (dd, $^3J_{H,H}$ = 4.9, $^3J_{H,H}$ = 8.7 Hz, 1 H, C*H*-CH$_2$-CF), 4.61 (dd, $^2J_{H,H}$ = 2.9, $^3J_{H,F}$ = 16.5 Hz, 1 H, CH$_2$-CF=C*H*$_Z$), 4.99 ppm (br. s, 1 H, N-CH-N). ^{13}C NMR (75.48 MHz, $CDCl_3$): δ = 26.6 (3 × q, CH-C(*C*H$_3$)$_3$), 28.0 (3 × q, CO-C(*C*H$_3$)$_3$), 31.31 (q, N-Me), 36.3 (ddd, $^2J_{C,F}$ = 27.1 Hz, C*H*$_2$-CF=CH$_2$), 37.1 (s, CH-*C*(CH$_3$)$_3$), 57.5 (d, CO-C*H*-CH$_2$), 81.6 (s, CO-O*C*(CH$_3$)$_3$), 82.3 (d, N-CH-N), 92.4 (ddd, $^2J_{C,F}$ = 19.6 Hz, CF=C*H*$_2$), 155.8 (s, *C*O-O*t*Bu), 162.7 (d, $^1J_{C,F}$ = 258.8 Hz, CH$_2$-*C*F-CH$_2$), 170.7 ppm (s, CH-*C*O-NMe). ^{19}F NMR (282.37 MHz, $CDCl_3$): δ = –94.67 ppm (dddd, $^3J_{H,F}$ = 17.2, $^3J_{H,F}$ = 17.3, $^3J_{H,F}$ = 22.5, $^3J_{H,F}$ = 48.1 Hz, 1 F, CH$_2$-CF=CH$_2$). MS-ES: *m*/*z* = 315.3 [M + H]. GC-MS: *m*/*z* (%) = 257 (5) [M$^+$ – C$_4$H$_8$], 241 (7) [M$^+$ – C$_4$H$_{10}$O], 201 (63), 181 (20), 157 (73), 131 (38), 110 (28), 88 (50), 69 (42), 57 (70), 42 (100). ES-EM for [C$_{16}$H$_{26}$FN$_2$O$_3$ + H]: calcd. 315.2078; found: 315.2047.

X-ray Crystal Structure Analysis for 2a: Formula C$_{16}$H$_{27}$FN$_2$O$_3$, *M* = 314.40, colorless crystal, 0.65 × 0.05 × 0.05 mm, *a* = 9.515(1), *b* = 6.067(1), *c* = 16.305(1) Å, β = 106.19(1)°, *V* = 903.9(1) Å^3, $\rho_{calcd.}$ = 1.155 g cm^{-3}, μ = 7.11 cm^{-1}, empirical absorption correction 0.655 ≤ *T* ≤ 0.965, *Z* = 2, monoclinic, space group *P*2$_1$ (No. 4), λ = 1.54178 Å, *T* = 223 K, ω and φ scans, 4229 reflections collected (±*h*, ±*k*, ±*l*), [(sin θ)/λ] = 0.59 Å^{-1}, 1855 independent (R_{int} = 0.038) and 1252 observed reflections [$I \geq 2\sigma(I)$], 206 refined parameters, *R* = 0.053, wR_2 = 0.124, Flack parameter –0.6(5), max. residual electron density 0.19 (–0.14) e Å^{-3}; hydrogen atoms were calculated and all refined as riding atoms.

X-ray Crystal Structure Analysis for 4a: Formula C$_6$H$_{11}$FN$_2$O, *M* = 146.17, colorless crystal, 0.20 × 0.15 × 0.05 mm, *a* = 5.121(1), *b* = 8.129(1), *c* = 9.538(1) Å, β = 99.50(1)°, *V* = 391.6(1) Å^3, $\rho_{calcd.}$ = 1.240 g cm^{-3}, μ = 8.65 cm^{-1}, empirical absorption correction 0.846 ≤ *T* ≤ 0.958, *Z* = 2, monoclinic, space group *P*2$_1$ (No. 4), λ = 1.54178 Å, *T* = 223 K, ω and φ scans, 1350 reflections collected (±*h*, ±*k*, ±*l*), [(sin θ)/λ] = 0.59 Å^{-1}, 891 independent (R_{int} = 0.012) and 763 observed reflections [$I \geq 2\sigma(I)$], 105 refined parameters, *R* = 0.037, wR_2 = 0.075, Flack parameter –0.1(4), max. residual electron density 0.14 (–0.17) e Å^{-3}; hydrogen atoms bonded to nitrogen atoms were obtained from difference Fourier calculations, others were calculated and all refined as riding atoms.

X-ray Crystal Structure Analysis for 8: Formula C$_{12}$H$_{20}$N$_2$O$_3$, *M* = 240.30, colorless crystal, 0.40 × 0.30 × 0.07 mm, *a* = 7.006(1), *b* =

9.889(1), c = 19.362(1) Å, V = 1341.4(2) Å^3, $\rho_{calcd.}$ = 1.190 g cm^{-3}, μ = 7.01 cm^{-1}, empirical absorption correction 0.767 ≤ T ≤ 0.953, Z = 4, orthorhombic, space group $P2_12_12_1$ (No. 19), λ = 1.54178 Å, T = 223 K, ω and φ scans, 5409 reflections collected (±h, ±k, ±l), [(sin θ)/λ] = 0.58 Å^{-1}, 2063 independent (R_{int} = 0.030) and 1670 observed reflections [$I \geq 2\sigma(I)$], 160 refined parameters, R = 0.038, wR_2 = 0.086, Flack parameter –0.1(4), max. residual electron density 0.12 (–0.10) e Å^{-3}, hydrogen atoms were calculated and all refined as riding atoms.

CCDC-246723 to -246730 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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[1] G. A. Olah, R. D. Chambers, G. K. S. Prakash (Eds.), *Synthetic Fluorine Chemistry*, Wiley Interscience, New York, **1992**.
[2] J. Mann, *Chem. Soc. Rev.* **1987**, *16*, 381–436.
[3] B. Baasner, H. Hagemann, J. C. Tatlow (Eds.), *Methods of Organic Chemistry (Houben-Weyl)*, 4th ed., George Thieme-Verlag, Stuttgart and New York, **2000**, vols. 10a–c.
[4] M. Hudlický, A. E. Pavlath (Eds.), *Chemistry of Organic Fluorine Compounds II. A Critical Review*, ACS Monograph 187, American Chemical Society, Washington, DC, **1995**, chapter 3, pp. 41–293.
[5] J. T. Welch (Ed.), *Selective Fluorination in Organic and Bioorganic* Chemistry, ACS Symposium Series 456, American Chemical Society, Washington, DC, **1991**.
[6] R. Filler, Y. Kobayashi, L. M. Yagripolskii (Eds.), *Organofluorine Compounds in Medicinal Chemistry and Biomedical Applications*, Elsevier, Amsterdam, **1993**.
[7] K. L. Kirk, R. Filler in *Biomedical Frontiers of Fluorine Chemistry* (Eds.: I. Ojima, J. R. McCarthy, J. T. Welch), ACS Symposium Series 639, American Chemical Society, Washington, DC, **1996**, pp. 1–24.
[8] J. T. Welch, S. Eswarakrishnan, *Fluorine in Bioorganic Chemistry*, John Wiley & Sons, New York, **1991**, pp. 7–65.
[9] J. T. Welch, A. Gyenes, M. J. Jung in *Fluorine-containing Amino Acids: Synthesis and Properties* (Eds.: V. P. Kukhar′, V. A. Soloshonok), John Wiley & Sons, Chichester, **1995**, pp. 311–331.
[10] K. L. Kirk in *Fluorine-containing Amino Acids: Synthesis and Properties* (Eds.: V. P. Kukhaf, V. A. Soloshonok), John Wiley & Sons, Chichester, **1995**, pp. 343–401.
[11] V. Soloshonok in *Biomedical Frontiers of Fluorine Chemistry* (Eds.: I. Ojima, J. R. McCarthy, J. T. Welch), ACS Symposium Series 639, American Chemical Society, Washington, DC, **1996**, pp. 26–41.
[12] K. Uneyama in *Enantiocontrolled Synthesis of Fluoro-Organic Compounds: Stereochemical Challenges and Biomedical Targets* (Ed.: V. A. Soloshonok), John Wiley & Sons, Chichester, **1999**, pp. 391–418.
[13] B. C. Smart, *J. Fluorine Chem.* **2001**, *109*, 3–11.
[14] D. O'Hagan, H. S. Rzepa, *Chem. Commun.* **1997**, 645–652.
[15] M. Schlosser, D. Michel, *Tetrahedron* **1996**, *52*, 99–108.
[16] J. A. K. Howard, V. J. Hoy, D. O'Hagan, G. T. Smith, *Tetrahedron* **1996**, *52*, 12 613–12 622.
[17] I. Alkorta, I. Rozas, J. Elguero, *J. Fluorine Chem.* **2000**, *101*, 233–238.
[18] G. Haufe, T. C. Rosen, O. G. J. Meyer, R. Fröhlich, K. Rissanen, *J. Fluorine Chem.* **2002**, *114*, 189–198.
[19] I. Hyla-Kryspin, G. Haufe, S. Grimme, *Chem. Eur. J.* **2004**, *10*, 3411–3422.
[20] K. G. Grozinger, R. W. Kriwacki, S. F. Leonard, T. P. Pitner, *J. Org. Chem.* **1993**, *58*, 709–713.
[21] D. Winkler, N. Sewald, K. Burger, N. N. Chung, P. W. Schiller, *J. Pept. Sci.* **1998**, *4*, 496–501.
[22] K. W. Laue, S. Kröger, E. Wegelius, G. Haufe, *Eur. J. Org. Chem.* **2000**, 3737–3743.
[23] L. Zhang, J. M. Finn, *J. Org. Chem.* **1995**, *60*, 5719–5720 and references cited therein.
[24] K. W. Laue, C. Mück-Lichtenfeld, G. Haufe, *Tetrahedron* **1999**, *55*, 10 413–10 424.
[25] G. Haufe, K. W. Laue, M. W. Triller, Y. Takeuchi, N. Shibata, *Tetrahedron* **1998**, *54*, 5929–5938.
[26] K. W. Laue, G. Haufe, *Synthesis* **1998**, 1453–1456.
[27] J. T. Welch, J. Lin, L. G. Boros, B. De Corte, K. Bogmann, R. Gimi in *Frontiers of Fluorine Chemistry* (Eds.: I. Ojima, J. R. McCarthy, J. T. Welch), ACS Symposium Series 639, American Chemical Society, Washington, DC, **1996**, pp. 129–142.
[28] T. Allmendinger, E. Felder, E. Hungerbühler, *Tetrahedron Lett.* **1990**, *31*, 7301–7304.
[29] L. G. Boros, B. De Corte, R. H. Gimi, J. T. Welch, Y. Wu, R. E. Handschumacher, *Tetrahedron Lett.* **1994**, *35*, 6033–6036.
[30] R. J. Abraham, S. L. R. Ellison, P. Schonholzer, W. A. Thomas, *Tetrahedron***1986**, *42*, 2101–2110.
[31] N. S. Yoder, K. Kumar, *Chem. Soc. Rev.* **2002**, *31*, 335–341.
[32] X.-L. Qui, W.-D. Meng, F.-L. Qing, *Tetrahedron* **2004**, *60*, 6711–6745 and references cited therein.
[33] R. Fitzi, D. Seebach, *Tetrahedron* **1988**, *44*, 5277–5292 and references cited therein.
[34] M. J. Al-Darwich, A. Plenevaux, C. Lemaire, G. D. Fiore, L. Christiaens, D. Comar, A. Luxen, *J. Fluorine Chem.* **1996**, *80*, 117–124.
[35] P. Damhaut, C. Lemaire, A. Plenevaux, C. Bihaye, L. Christiaens, D. Comar, *Tetrahedron* **1997**, *53*, 5785–5796.
[36] A. Mazón, C. Nájera, *Tetrahedron: Asymmetry* **1997**, *8*, 1855–1859.
[37] H. Pajouhesh, M. Hosseini-Meresht, S. H. Pajonhesh, K. Curry, *Tetrahedron: Asymmetry* **2000**, *11*, 4955–4958.
[38] D. Seebach, E. Dziadulewicz, L. Behrendt, S. Cantoreggi, R. Fitzi, *Liebigs Ann. Chem.* **1989**, 1215–1232.
[39] D. Seebach, A. R. Sting, M. Hoffmann, *Angew. Chem.* **1996**, *108*, 2880–2921; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2708–2748 and references cited therein.
[40] M. Lübke, Ph. D. Dissertation, Universität Münster, Germnany, **2002**.
[41] T. Mukhopadhyay, D. Seebach, *Helv. Chim. Acta* **1982**, *65*, 385–391.
[42] The diastereomeric purity of the crude products was checked by GC and confirmed by ^{19}F NMR spectroscopy.
[43] See the Supporting Information for dynamic NMR studies.
[44] The reagent HCl/MeOH was prepared by bubbling HCl gas through cooled dry MeOH for 5 hours.
[45] In collaboration with Prof. Dr. A. Liese, Institute of Biochemistry, University of Münster, Germany, and Prof. Dr. F. P. J. T. Rutjes, Department of Organic Chemistry, University of Nijmegen, Nijmegen, The Netherlands.
[46] D. M. Shendage, R. Fröhlich, G. Haufe, *Org. Lett.* **2004**, *6*, 3675–3678.
[47] R. Marshall, O. Shokek, J. T. Davis, *J. Org. Chem.* **1997**, *62*, 8243–82–46 and references cited therein.
[48] S. Mezengeza, T. K. Venkatachalam, M. Diksic, *Amino Acids* **2000**, *18*, 81–88.
[49] B. V. Nonius, *EXPRESS*, **1994**.
[50] B. V. Nonius, *COLLECT*, **1998**.
[51] K. Fair, B. V. Enraf–Nonius, *MolEN*, **1990**.
[52] Z. Otwinowski, W. Minor, *Methods Enzymol.* **1997**, *276*, 307–326.
[53] R. H. Blessing, *Acta Crystallogr. Sect. A* **1995**, *51*, 33–37.
[54] R. H. Blessing, *J. Appl. Crystallogr.* **1997**, *30*, 421–426.

[55] G. M. Sheldrick, *Acta Crystallogr. Sect. A* **1990**, *46*, 467–473.
[56] G. M. Sheldrick, *SHELXL-97*, University of Göttingen, **1997**.
[57] K. Brandenburg, *DIAMOND*, University of Bonn, **1997**.
[58] E. Keller, *SCHAKAL*, University of Freiburg, **1997**.
[59] W. C. Still, M. Kahn, A. Mitra, *J. Org. Chem.* **1978**, *43*, 2923–2925.

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