A Study on the Diastereoselective Synthesis of α-Fluorinated β^3-Amino Acids by α-Fluorination

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Dedicated to Professor *Dieter Seebach* in celebration of his 75th birthday

The treatment of a β^3-amino acid methyl ester with 2.2 equiv. of lithium diisopropylamide (LDA), followed by reaction with 5 equiv. of *N*-fluorobenzenesulfonimide (NFSI) at $-78°$ for 2.5 h and then 2 h at 0°, gives *syn*-fluorination with high diastereoisomeric excess (de). The de and yield in these reactions are somewhat influenced by both the size of the amino acid side chain and the nature of the amine protecting group. In particular, fluorination of *N*-Boc-protected β^3-homophenylalanine, β^3-homoleucine, β^3-homovaline, and β^3-homoalanine methyl esters, **5** and **9**–**11**, respectively, all proceeded with high de (>86% of the *syn*-isomer). However, fluorination of *N*-Boc-protected β^3-homophenylglycine methyl ester (**16**) occurred with a significantly reduced de. The use of a Cbz or Bz amine-protecting group (see **3** and **15**) did not improve the de of fluorination. However, an *N*-Ac protecting group (see **17**) gave a reduced de of 26%. Thus, a large *N*-protecting group should be employed in order to maximize selectivity for the *syn*-isomer in these fluorination reactions.

1. Introduction. – β-Amino acids and their derivatives are found in both natural and synthetic compounds that exhibit important biological activities. Naturally occurring examples include microcystins, carnosine, pantothenic acid (vitamin B_5), *Paclitaxel*, and bestatin [1]. *Paclitaxel* is an important anti-neoplastic agent used in chemotherapy for a variety of cancers [2], while bestatin is an immunological response modifier [3]. Both these agents contain a β-amino-α-hydroxy acid as a key structural feature.

Non-natural oligomers derived from β-amino acids (β-peptides) are also of significant interest because of their ability to form well-defined and stable secondary structures, such as 3_{14}-helices and hairpin turns [1][4], which can be further stabilized with the appropriate incorporation of F in their backbone as discussed below [5]. β-Peptides are reported to possess a range of biological activities, but unlike natural peptides, they are stable to common proteases and peptidases [4a][6]. Interestingly, simple fluorinated β-amino acids such as **1** and **2** (see *Fig. 1*) do in fact inhibit proteases [7].

Fluorine is an important component of many existing pharmaceuticals, with an ability to enhance metabolic stability, lipophilicity, and bioavailability, while also influencing conformation [8]. Specifically, when a F-atom is positioned α to the CO group in a β^3-amino acid, the F–C–C=O moiety adopts an *antiperiplanar* conformation, and when the F-atom is positioned β to an amide N-atom, a conformation in which C–F

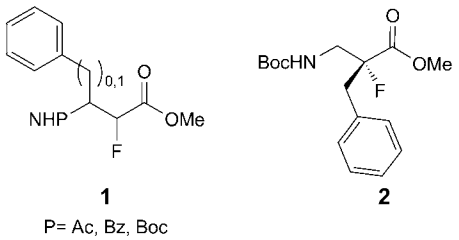
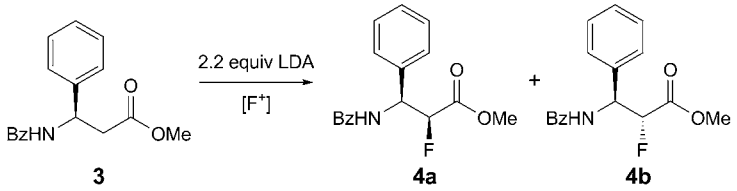


Fig. 1. *α-Fluoro β-amino acid protease inhibitors*

and C–N(CO) bonds are *gauche* is favored [5c][9]. To more widely exploit these observations in biomedical applications, we require efficient and well-defined stereoselective methods for the synthesis of α-fluoro β^3-amino acids.

Two main strategies have been reported for the synthesis of α-fluoro β^3-amino acids: direct fluorination of β-amino enolates [10] and the conversion of the OH group of an enantiomerically pure β-hydroxy α-amino acid to a F-atom [5a][6c][7b][11]. There are limited reports on this first method, with *Davis* and *Reddy* having reported the direct fluorination of the dianion of the *N*-Bz-protected methyl ester of (*R*)-β^3-homophenylglycine, **3**, to prepare the α-fluoro-β^3-homophenylglycine derivatives **4a** and **4b** as fluorinated analogues of the side chain of *Paclitaxel* (*Scheme 1*) [10]. The use of *N*-fluorobenzenesulfonimide (NFSI), as the fluorinating agent in this reaction, results in lower yields compared to *N*-fluoro-*o*-benzene-disulfonimide (NFOBS). However, NFSI does give rise to improved diastereostereoselectivity, with the ratio *syn*-**4a**/*anti*-**4b** being a respectable 81:19 in this case [10]. There is some debate as to what controls the stereochemical outcome of this reaction, with some discussion on this later on in the article.

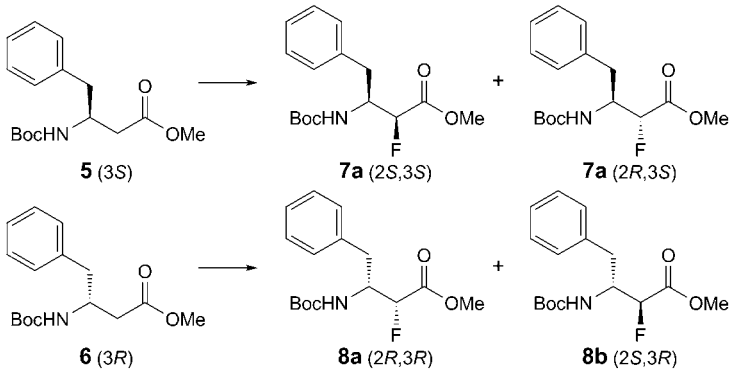
Scheme 1. *Fluorination of the Dianion of Methyl (−)-(3*R*)-3-(Benzoylamino)-3-phenylpropanoate* (**3**) *with Electrophilic Fluorinating Reagents*



The key starting β^3-amino acids used in this sequence are either commercially available, or readily prepared from the corresponding α-amino acid by *Arndt–Eistert* homologation [4a]. As such, this sequence provides a useful and direct route to α-fluoro β^3-amino acids from common α-amino acids. In this paper, we report an investigation into the scope of this methodology as a means to prepare α-fluoro β^3-amino acids. Lithium diisopropylamide (LDA) was used to generate the intermediate β-amino enolates and NFSI as the electrophilic source of F based on the earlier literature reports mentioned above.

2. Results. – 2.1. *Synthesis of α-Fluoro-β³-homophenylalanine and Optimization of Reaction Conditions.* In the first instance, a study was carried out to define the optimum conditions for the fluorination of a previously untested Boc-protected β^3-amino acid (β^3-homophenylalanine methyl ester, see (*S*)-**5** and (*R*)-**6**) with the results shown in *Table 1*. The first attempt involved generating the required lithium enolate by reacting a THF solution of (*S*)-**5** with 2.2 equiv. of LDA (freshly prepared in THF) at $-78°$ (see *Entry 1* in *Table 1*). The solution was stirred for 1 h at $-78°$, 5 equiv. of NFSI were added, and the resulting solution was stirred at $-78°$ for 2.5 h, and then for a further 2 h at 0°. The α-fluoro β^3-amino acid *syn*-**7a** (2*S*,3*S*) and its epimer *anti*-**7b** (2*R*,3*S*) were produced in a ratio of 95 : 5 (as determined from the corresponding ^{19}F-NMR spectrum of the crude product), and in a combined yield of 73% after purification by chromatography (*Entry 1* in *Table 1*).

Table 1. *Results of the Fluorination of the Lithium Enolate of* **5** *and* **6** *with NFSI under Different Conditions*



Entry	Starting material	equiv. of LDA	equiv. of NFSI	Temp [°]/ time [h]	Major product	Minor product	Yield [%]	de[a]) [%]	Ratio of isomers[a])
1	**5** (3*S*)	2.2	5	– 78/2.5 0/2	**7a** (2*S*,3*S*)	**7b** (2*R*,3*S*)	73	90	95 : 5
2	**6** (3*R*)	2.2	2.5	– 78/2.5 0/2	**8a** (2*R*,3*R*)	**8b** (2*S*,3*R*)	57	90	95 : 5
3	**5** (3*S*)	2.1	2.5	– 78/3.5 – 40/1	**7a** (2*S*,3*S*)	**7b** (2*R*,3*S*)	53	86	93 : 7
4	**6** (3*R*)	2.1	1.1	– 78/2.5 – 40/1	**8a** (2*R*,3*R*)	**8b** (2*S*,3*R*)	37	94	97 : 3

[a]) Ratio of isomers and de were determined from the ^{19}F-NMR spectra of the crude products.

A number of variations to the reaction conditions were investigated using both (*S*)-**5** and its enantiomer (*R*)-**6**. In particular, a reduction in number of equiv. of either LDA or NFSI used in the reaction, or lowering the reaction temperature from 0° to $-40°$ gave reduced yields of the fluorinated product, with little effect on the observed de (see *Entries 2–4* in *Table 1*). Thus, 2.2 equiv. of LDA, 5 equiv. of NFSI, and a reaction temperature kept at $-78°$ for 2.5 h, followed by 2 h at 0°, were used as reaction

conditions for all subsequent fluorination reactions. Interestingly, the diastereoisomeric excesses (de; 86–90%), obtained in the syntheses of **7** and **8**, were higher than those reported by *Davis* and *Reddy* for the fluorination of Bz-protected β^3-homophenylglycine using either NFSI or NFOBS as the fluorinating agent (de values of 4 to 62% depending on the conditions). The relative configuration of the major isomer **8a**, (2*R*,3*R*), was assigned as *syn* based on our earlier published X-ray crystallographic structure [7a]. The absolute configuration was then assigned on the basis of the known absolute configuration of the starting β^3-amino acid. The configuration of the other isomers of **7** and **8** followed from this assignment.

Interestingly, the ^{19}F-NMR spectra obtained for purified samples of **7a** (2*S*,3*S*) and **8a** (2*R*,3*R*) revealed pairs of resonances in both $CDCl_3$ and (D_6)DMSO. In all cases, the pairs were evident in a ratio of *ca.* 9:1 (*e.g.*, see *Fig. 2* for **8a**). In the (D_6)DMSO spectrum of **8a**, each resonance of the pair was resolved as a *doublet* of *doublet*s at −199.9 (minor) and −200.9 ppm (major), with both exhibiting very similar coupling constants, *J*, of 48.8, 24.5, and 48.2, 23.3 Hz, respectively. A similar spectrum was observed for **7a** in (D_6)DMSO. This doubling of resonances is likely due to **7a** and **8a** existing as pairs of rotamers, presumably due to the presence of the *N*-Boc group as has been noted in other systems [12]. The occurrence of rotamers was consistent with variable-temperature ^{19}F-NMR spectroscopy of **8a** (in $CDCl_3$) which showed the minor and the major resonances coalescing at 55° to give a small shoulder (*Fig. 2*). The 9:1 ratio of rotamers observed for **7a** and **8a** is typical for a pair of Boc rotamers [12].

2.2. *The Effect of the Amino Acid and* N*-Protecting Group on the Diastereoselectivity of Fluorination*. Given that there were some differences in the observed de values for the fluorination of the *N*-Boc-β^3-homophenylalanine and *N*-Bz β^3-homophenylglycine methyl esters as discussed above, we decided to investigate further the influence of the amino acid containing a common *N*-Boc protecting group. A small series of *N*-Boc-protected β^3-amino acid methyl esters was used in this study, *i.e.* β^3-homoleucine, β^3-homovaline, and β^3-homoalanine, **9**–**11**, respectively (see *Scheme 2*). Fluorination of each of these β^3-amino acids, **9**–**11**, was performed under the optimum conditions established earlier. The resulting de values for all three amino acids (see *Table 2*) were similar and comparable to those obtained for *N-Boc*-protected (*R*)- and (*S*)-β^3-homophenylalanine (**5** and **6**; see *Table 1*). Based on these results the nature of the component amino acid appears to have little effect on the diastereoselectivity of the fluorination reaction, with the exception of the sterically more challenged β^3-homophenylglycine which appears to give a reduced de as discussed further below.

Given the results of the previous section, we next investigated the influence of the nature of the *N*-protecting group. Interestingly, all of the *N*-Boc-protected β^3-amino acid methyl esters used in our study to date, **5**, **6**, and **9**–**11**, gave rise to a higher diastereoselectivity (major isomer being *syn*) compared to the original study using *N*-Bz-protected β^3-homophenylglycine **3** [10]. Thus, a range of *N*-protected β^3-homophenylglycine derivatives was prepared (Bz, Cbz, Boc, and Ac, **3**, **15**–**17**, resp.), for comparative analysis relative to the previous studies. Each of these amino acids was separately fluorinated using our standard conditions, *i.e.*, 2.2 equiv. of LDA, 5 equiv. of NFSI, and a reaction temperature kept at −78° for 2.5 h, followed by 2 h at 0° (see *Scheme 3* and *Table 3*).

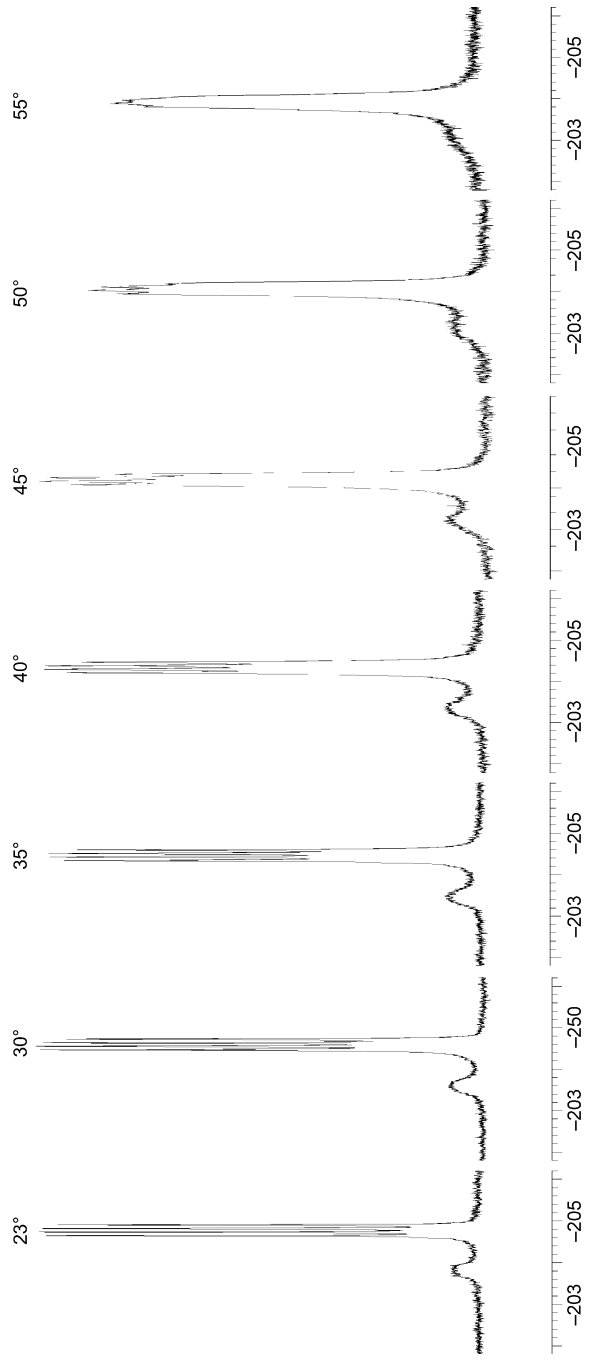
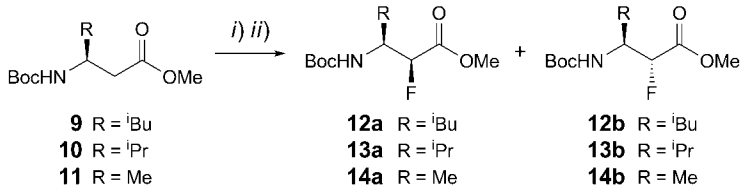


Fig. 2. *Variable-temperature* ^{19}F*-NMR of* **8a**

Scheme 2. *Fluorination of* N-*Boc-Protected* β^3*-Amino Acid Methyl Esters*



9 R = ^{i}Bu **12a** R = ^{i}Bu **12b** R = ^{i}Bu
10 R = ^{i}Pr **13a** R = ^{i}Pr **13b** R = ^{i}Pr
11 R = Me **14a** R = Me **14b** R = Me

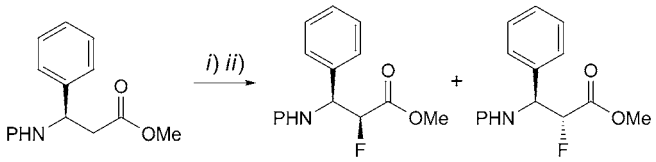
i) 2.2 equiv. lithium diisopropylamide (LDA), THF, −78°, 1 h. *ii*) 5 equiv. *N*-fluorobenzenesulfonimide (NFSI), THF, −78°, 2.5 h; 0°, 2 h.

Table 2. *Results of the Fluorination of the Lithium Enolates of* **9**–**11** *with NFSI*

Starting Material	Products	Yield [%]	de[a]) [%]	Ratio of products (**a**/**b**)[a])
9	**12a**/**12b**	60	86	93 : 7
10	**13a**/**13b**	57	91	96 : 4
11	**14a**/**14b**	45	92	96 : 4

[a]) Ratio of isomers and de were determined from the ^{19}F-NMR spectra of the crude products.

Scheme 3. *Fluorination of* N-*Protected* β^3*-Homophenylglycine Methyl Esters*



3 P = Bz **4a** P = Bz **4b** P = Bz
15 P = Cbz **18a** P = Cbz **18b** P = Cbz
16 P = Boc **19a** P = Boc **19b** P = Boc
17 P = Ac **20a** P = Ac **20b** P = Ac

i) LDA, THF, −78°, 1 h. *ii*) NFSI, THF, −78°, 2.5 h; 0°, 2 h.

Table 3. *Results of the Fluorination of the Lithium Enolates of* **3** *and* **15**–**17** *with NFSI as Shown in* Scheme 3

Starting Material	Products	Yield [%]	de[a]) [%]	Ratio of products (**a**/**b**)[a])
3	**4a**/**4b**	70	66	83 : 17
15	**18a**/**18b**	63	58	79 : 21
16	**19a**/**19b**	75	56	78 : 22
17	**20a**/**20b**	51	26	63 : 37

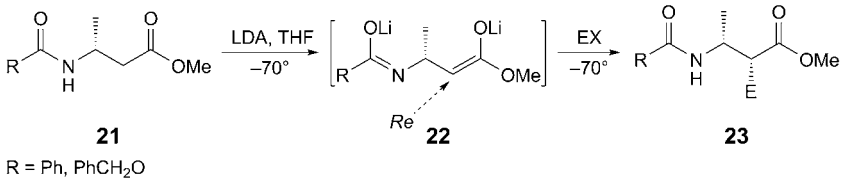
[a]) Ratio of isomers and de were determined from the ^{19}F-NMR spectra of the crude products

Fluorination of the literature *N*-Bz-protected β^3-homophenylglycine methyl ester **3**, under these conditions, gave **4a** and **4b** in a ratio of 83 : 17 (de of 66%) and a combined yield of 70% (*Scheme 3*). These values are very similar to those reported by *Davis* and *Reddy* for their synthesis of **4** (see *Scheme 1*), who reported a de of 62% and a yield of

65% [10]. We obtained similar de values and yields for the fluorination of the *N*-CBz- and *N*-Boc-protected β^3-homophenylglycine derivatives **15** and **16** (de values of 58 and 56%, and combined yields of 63 and 75%, resp., as shown in *Table 3*). However, a smaller *N*-Ac protecting group as in compound **17** gave rise to a considerably reduced de (26%) and a lower yield (51%) for the fluorination reaction. In addition, fluorination of *N*-Boc-protected β^3-homophenylglycine methyl ester (**16**) occurred with a reduced de (66%) compared to the fluorinations of the other *N*-Boc-protected β^3-amino acids, (*S*)-β^3-hPhe (**5**), (*R*)-β^3-hPhe (**6**), β^3-hLeu (**9**), β^3-hVla (**10**), and β^3-hAla (**11**), all of which proceeded with de values greater than 86%. The sterically hindered Ph side-chain of β^3-homophenylglycine is thus the least favored in these reactions.

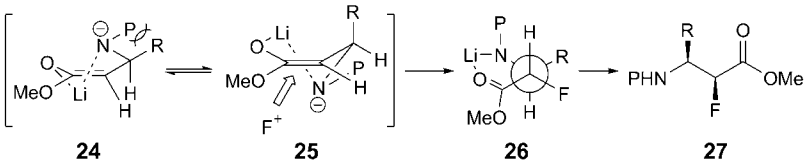
3. Discussion. – The related alkylation of β^3-amino acids is also reported to give a high *syn* diastereoselectivity [13]. These reactions have been proposed to proceed *via* a dilithiated β-amino acid intermediate (*e.g.*, **22**), which is alkylated selectively from the *Re* face to give **23** as shown in *Scheme 4* [13a]. The fluorination of β^3-amino acids shown in *Schemes 1–3* would be expected to proceed through a similar dilithiated intermediate.

Scheme 4. *Stereochemistry of the Alkylation of β-Aminobutanoic Acid Derivatives* via *a Dilithiated Enolate* [13a]



Intramolecular chelation of the Li^+ cation with the enolate O-atom and the deprotonated amino group in such an intermediate would give rise to the cyclic chelates **24** and **25** (see *Scheme 5*). A structure of this type has been proposed to explain the *syn* selectivity in the alkylation reactions [13e][14]. Such a six-membered chelate ring has been characterized by X-ray crystallography, with the enolate rings forming prismatic hexamers [15]. The proposed chelated enolate intermediate preferentially adopts a half-chair conformation in which the R group occupies a pseudo-axial position (see **25**), because of a steric clash in the alternative conformer **24** as indicated [13e][14]. Fluorination would then take place from the face opposite to the axial R group in **25** to give the *syn*-product **27** as shown.

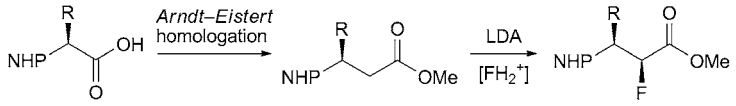
Scheme 5. *Possible Lithium-Enolate Intermediate*



Interestingly, we observed that fluorination of the β^3-homophenylglycine methyl ester (**3**) occurred with a reduced de value compared to those of the other amino acids investigated (see **5**, **6**, **9**–**11**). This is surprising given that the extra steric bulk[1]) of a Ph group would be expected to enhance the facial selectivity in the halogenation of **25**. However, it may be the case that this sterically demanding axial group destabilizes conformer **25** relative to **24**, with an associated decrease in stereoselectivity. The Bz-, Cbz-, and Boc-protected β^3-homophenylglycines were all fluorinated with similar de values, *i.e.*, 56–66%. However, an *N*-Ac protecting group, as in derivative **17**, gave rise to a significantly reduced de of 26%. A smaller protecting group (P = Ac in *Scheme 5*) would be expected to diminish the steric clash in structure **24**, such that the thermodynamic preference for **25** relative to **24** is decreased (see *Scheme 5*). The net result would again be decreased facial selectivity on fluorination.

4. Conclusions. – The method devised by *Davis* and *Reddy* (*Scheme 1*) [10] has been shown to be suitable for the preparation of a number of α-fluoro-β^3-amino acids. The reactions occur in good yield and with high *syn* diastereoselectivity. This methodology allows the stereoselective conversion of an α-amino acid to an α-fluoro-β^3-amino acid in two steps: *Arndt–Eistert* homologation of the α-amino acid to generate the β^3-amino acid, which is fluorinated on treatment with LDA and NFSI (see *Scheme 6*).

Scheme 6. *Stereoselective Conversion of an α-Amino Acid to an α-Fluoro-β³-amino Acid*



It is important to note that the stereoselectivity of fluorination is influenced by both the size of the amino acid side chain and the nature of the amine protecting group. In particular, fluorination of *N*-Boc-protected β^3-homophenylalanine, β^3-homoleucine, β^3-homovaline, and β^3-homoalanine methyl esters, **5** and **9**–**11**, respectively, all proceeded with high de values (> 86% de of the *syn* isomer). However, fluorination of the *N*-Boc-protected β^3-homophenylglycine (**16**) occurred with a reduced de of 66%. The use of a *N*-Cbz or *N*-Bz protecting group (see **3** and **15**) in place of Boc did not improve the de value of fluorination reaction. However an Ac protecting group (see **17**) gave rise to a

[1]) The *Winstein–Holness A* values (or axial strain values) provide a measure of the conformational preference of a substituent (R) in a monosubstituted cyclohexane to be equatorial rather than axial [16]. It is defined as the *Gibbs* free energy between the equatorial and axial conformers. These values provide a measure of steric bulk, with the literature values shown in *Table 4* indicating that a Ph substituent has the greatest steric bulk of these four substituents.

Table 4. Winstein–Holness A *Values for Selected Substituents*

Substituent	*A* Value [kcal mol^{-1}]
Me	1.74 [17]
^{i}Pr	2.21 [17]
Ph	2.8 [18]
$PhCH_2$	1.68 [19]

reduced de value of 26%. Thus, in order to maximize selectivity for the *syn*-isomer in these fluorination reactions one should employ a large *N*-protecting group.

We gratefully acknowledge financial support from the *Australian Research Council* (ARC) and the *Tertiary Education Commission of New Zealand*.

Experimental Part

1. *General.* *N*-Fluorobenzenesulfinimide (NFSI) was purchased from *Sigma–Aldrich*. Dry THF was distilled from Na and benzopheneone. All moisture-sensitive reactions were carried out under a positive pressure of N_2 or Ar in oven-dried glassware (140°). The β^3-amino acids **3**, **5**, **6**, **9**–**11**, **15**–**17** were synthesized according to published procedures [7a][20]. TLC: Plastic-backed *Merck-Kieselgel KG60F254* or *Polygram Sil G/UV254* plates. Flash chromatography (FC; positive pressure of anh. N_2): 230–400 mesh *Merck* silica gel *60*. Radial chromatography (RC): *Chromatotron*™ apparatus with silica plates (silica gel *60* PF_{254} with gypsum) of 5-, 2-, and 1-mm thickness. M.p.: electrothermal melting-point apparatus, or a *Reichert* hot-stage melting-point apparatus; not corrected. Optical rotations: *Perkin–Elmer 341* polarimeter or *Polaar 2001* polarimeter, with a 1.0-dm cell length, at 21–23° in HPLC-grade solvents at $\lambda = 589$ nm; $[\alpha]_D$ values are given in deg ml g^{-1} dm^{-1}; the sample concentration values are in 10 mg ml^{-1}. IR Spectra: *Shimadzu 9201PC* series FT-IR spectrophotometer or a *Perkin–Elmer 1600* Series FT-IR spectrophotometer. ^{1}H-spectra (300, 500, and 600 MHz) and ^{13}C-NMR spectra (75, 126, and 151 MHz): *Varian Unity 300*, *Varian Inova 500*, or *Varian Inova 600* spectrometers. ^{19}F-NMR spectra (282 MHz): *Varian Unity 300* spectrometer, chemical shifts (δ) in ppm and coupling constants *J* in Hz. ESI-MS: *Micromass/Waters LCT* TOF mass spectrometer or an *Agilent G1969A LC-TOF* spectrometer. Elemental analyses for C, N, H, and F: at the University of Otago Microanalytical Laboratory.

2. *General Procedure 1* (*GP 1*). *Fluorination of β^3-Amino Acids.* A soln. of BuLi (1.6M in hexane, 2.2 equiv.) was added to a soln. of freshly distilled ^{i}Pr$_2$NH (2.2 equiv.) in anh. THF (0.5M) at −78° under N_2. The reaction was stirred at −78° for 1 h, and then a soln. of the amino acid (1 equiv.) in anh. THF (0.5M) was added. The mixture was stirred for 1 h at −78°, NFSI (5 equiv.) in anh. THF (1M) was added dropwise, and the resulting yellow mixture was stirred for 2.5 h at −78° and for 2 h at 0°. Sat. aq. NH_4Cl was added, and the aq. layer was extracted with CH_2Cl_2 (3×). The combined org. phases were dried ($MgSO_4$), and the solvent was removed *in vacuo*. Petroleum ether (PE)/AcOEt 4:1 was added to give a white precipitate that was removed by filtration. The filtrate was concentrated *in vacuo*, and the crude mixture was purified as specified for each compound.

3. *Synthesis of Methyl Esters of α-Fluoro-β^3-homophenylalanine* **7** *and* **8**, *and Optimization of Reaction Conditions.* 3.1. *Methyl (2*S*,3*S*)- and (2*R*,3*S*)-3-[(*tert*-Butoxycarbonyl)amino]-2-fluoro-4-phenylbutanoate* ((2*S*,3*S*)-**7a** and (2*R*,3*S*)-**7b**, resp.). *Table 1*, *Entry 1.* Amino acid **5** (66 mg, 0.23 mmol) was treated with BuLi (0.31 ml, 0.50 mmol, 1.6M in hexane), ^{i}Pr$_2$NH (70 ml, 0.50 mmol), and NFSI (425 mg, 1.3 mmol) according to *GP 1*. The crude product was purified by RC (silica gel; 5-mm plate; PE/AcOEt 1:9) to give a mixture (2*S*,3*S*)-**7a**/(2*R*,3*S*)-**7b** (51 mg, 73%). White solid. The diastereoisomeric ratio (dr) 95:5 (^{19}F-NMR). Recrystallization (AcOEt/PE) gave the single diasteroisomer (2*S*,3*S*)-**7a** as white needles.

Table 1 Entry 3. BuLi (0.56 ml, 0.89 mmol, 2.1 equiv, 1.6M in hexane) was added to a soln. of freshly dist. ^{i}Pr$_2$NH (120 µl, 0.89 mmol, 2.1 equiv.) in anh. THF (2.75 ml) at −78° under N_2. The mixture was stirred at −78° for 1 h, then a soln. of (*S*)-**5** (124 mg, 0.42 mmol) in anh. THF (1 ml) under N_2 was added. The mixture was stirred for 1 h at −78° and then NFSI (333 mg, 1.1 mmol, 2.5 equiv.) in anh. THF (1 ml), under N_2, was added dropwise. The resulting yellow mixture was stirred for 3.5 h at −78° then allowed to slowly warm to −40° over 1 h. Sat. aq. NH_4Cl soln. was added to quench the reaction, and the aq. layer was extracted with CH_2Cl_2 three times. The combined org. phases were dried ($MgSO_4$), and the solvent was removed *in vacuo* to give an orange oil. PE/AcOEt 4:1 was added to give a white precipitate that was removed by filtration. The filtrate was concentrated *in vacuo* to give an orange oil that was purified by RC (silica gel, 1-mm plate; 1:9 AcOEt/PE) to give a mixture (2*S*,3*S*)-**7a**/(2*R*,3*S*)-**7b** (70 mg, 53%). White solid. The dr 93:7 (^{19}F-NMR).

*Data of (2S,3S)-***7a** (isolated). M.p. 86–87°. $[\alpha]_D^{22} = +13.1$ ($c = 0.82$ in $CHCl_3$). IR (KBr): 3374, 1736, 1682, 1515, 1273, 1161, 1048, 1010, 740. ^{1}H-NMR (500 MHz, $CDCl_3$): 7.32–7.19 (*m*, 5 arom. H); 5.03 (*dd*, $J = 48.5, 3.0$, CHF); 4.73 (*d*, $J = 8.0$, NH); 4.52–4.41 (*m*, NCH); 3.65 (*s*, MeO); 2.90–2.81 (*m*, PhCH_2); 1.38 (*s*, ^{t}Bu). ^{13}C-NMR (126 MHz, $CDCl_3$): 167.9 (*d*, $J = 23.8$); 154.9; 136.1; 129.4; 128.5; 126.8; 89.6 (*d*, $J = 188.9$); 80.0; 52.8 (*d*, $J = 20.2$); 52.4; 35.2; 28.2. ^{19}F-NMR (282 MHz, $CDCl_3$): −203.4 – −203.9 (*m*, minor rotamer); −204.7 (*dd*, $J = 48.4, 24.9$, major rotamer). HR-ESI-MS: 334.1425 ($[M+H]^+$, $C_{16}H_{22}FNNaO_4^+$; calc. 334.1430). Anal. calc. for $C_{16}H_{22}NO_4F$ (311.35): C 61.72, H 7.12, F 6.10, N 4.50; found C 61.61, H 7.07, F 6.01, N 4.44.

*Selected Data for Minor Isomer (2S,3R)-***7b** *from the Mixture.* ^{19}F-NMR (282 MHz, $CDCl_3$: −208.3 (*dd*, $J = 47.3, 28.8$).

3.2. *Methyl (2R,3R)- and (2S,3R)-3-[(*tert*-Butoxycarbonyl)amino]-2-fluoro-4-phenylbutanoate* ((2*R*,3*R*)-**8a** and (2*S*,3*R*)-**8b**, resp.). *Table 1*, *Entry 2*. BuLi (1.23 ml, 2.0 mmol, 2.2 equiv, 1.6M in hexane) was added to a soln. of freshly dist. ^{i}Pr$_2$NH (270 µl, 2.0 mmol, 2.2 equiv.) in anh. THF (6 ml) at −78° under N_2. The mixture was stirred at −78° for 1 h, a soln. of (*R*)-**6** (262 mg, 0.89 mmol) in anh. THF (2 ml) was added, and the mixture was stirred under N_2 for 1 h at −78°. NFSI (4.05 g, 2.2 mmol, 2.5 equiv.) in anh. THF (2 ml) was added dropwise, and the resulting yellow mixture was stirred for 2.5 h at −78° and then for 2 h at 0°. Sat. aq. NH_4Cl soln. was added to quench the reaction, and the aq. layer was extracted with CH_2Cl_2 three times. The combined org. phases were dried ($MgSO_4$), and the solvent was removed *in vacuo* to give an orange oil. PE/AcOEt 4:1 was added to give a white precipitate that was removed by filtration. The filtrate was concentrated *in vacuo* to give an orange oil that was purified by RC (silica gel, 1-mm plate; AcOEt/PE 1:9) to give a mixture (2*R*,3*R*)-**8a**/(2*S*,3*R*)-**8b** (158 mg, 57%). White solid. The dr 95:5 (^{19}F-NMR). Recrystallization (PE/AcOEt) gave the single diasteroisomer **8a** as white needles.

Table 1, *Entry 4*. BuLi (0.59 ml, 0.94 mmol, 2.1 equiv, 1.6M in hexane) was added to a soln. of freshly distilled ^{i}Pr$_2$NH (130 µl, 0.94 mmol, 2.1 equiv.) in anh. THF (2.75 ml) at −78° under N_2. The mixture was stirred at −78° for 1 h, a soln. of (*R*)-**6** (131 mg, 0.45 mmol) in anh. THF (1 ml) was added, and the mixture was stirred for 1 h at −78°. NFSI (155 mg, 0.49 mmol, 2.5 equiv.) in anh. THF (0.5 ml) was added dropwise, and the resulting yellow mixture was stirred for 2.5 h at −78°. After slowly warming to −40° over 1 h, sat. aq. NH_4Cl soln. was added to quench the reaction, and the aq. layer was extracted with CH_2Cl_2 three times. The org. phases were combined, dried ($MgSO_4$), and the solvent was removed *in vacuo* to give an orange oil. PE/AcOEt 4:1 was added to give a white precipitate that was removed by filtration. The filtrate was concentrated *in vacuo* to give an orange oil that was purified by RC (silica gel, 1-mm plate; AcOEt/PE 1:9) to give a mixture (2*R*,3*R*)-**8a**/(2*S*,3*R*)-**8b** (38 mg, 37%). White solid. dr 97:3 (^{19}F-NMR).

*Data of (2R,3R)-***8a** (isolated). M.p. 88–89°. $[\alpha]_D^{22} = -10.0$ ($c = 1.05$ in $CHCl_3$). IR (KBr): 3380, 1736, 1682, 1515, 1273, 1161, 1048, 1010, 740. ^{1}H-NMR (500 MHz, $CDCl_3$): 7.32–7.20 (*m*, 5 arom. H); 5.04 (*dd*, $J = 48.4, 2.6$, CHF); 4.73 (*d*, $J = 7.7$, NH); 4.52–4.40 (*m*, NCH); 3.65 (*s*, MeO); 2.88–2.82 (*m*, CH_2Ph); 1.38 (*s*, Me_3C). ^{13}C-NMR (126 MHz, $CDCl_3$): 168.0 (*d*, $J = 23.8$); 154.9; 136.2; 129.4; 128.5; 126.9; 89.6 (*d*, $J = 189.1$); 80.1; 52.8 (*d*, $J = 21.0$); 52.4; 35.2; 28.2. ^{19}F-NMR (23°, 282 MHz, (D_6)DMSO): −199.9 (*dd*, $J = 48.8, 24.5$, minor rotamer); −200.9 (*dd*, $J = 48.2, 23.3$, major rotamer). ^{19}F-NMR (23°, 282 MHz, $CDCl_3$): −203.4 to −203.8 (*m*, minor rotamer); −204.7 (*dd*, $J = 48.5, 24.8$, major rotamer). ^{19}F-NMR (30°, 282 MHz, $CDCl_3$): −203.4 to −203.8 (*m*, minor rotamer); −204.6 (*dd*, $J = 48.5, 24.6$, major rotamer). ^{19}F-NMR (35°, 282 MHz, $CDCl_3$): −203.2 to −203.7 (*m*, minor rotamer); −204.5 (*dd*, $J = 48.4, 24.4$, major rotamer). ^{19}F-NMR (40°, 282 MHz, $CDCl_3$): −203.0 to −203.7 (*m*, minor rotamer); −204.3 (*dd*, $J = 48.2, 24.0$, major rotamer). ^{19}F-NMR (45°, 282 MHz, $CDCl_3$): −202.9 to −203.7 (*m*, minor rotamer); −204.2 (*dd*, $J = 47.6, 23.9$, major rotamer). ^{19}F-NMR (50°, 282 MHz, $CDCl_3$): −202.8 to −204.4 (*m*, major + minor rotamers). ^{19}F-NMR (55°, 282 MHz, $CDCl_3$): −202.8 to −204.1 (*m*, major + minor rotamers). HR-ESI-MS: 334.1425 ($[M+Na]^+$, $C_{16}H_{22}FNNaO_4^+$; calc. 334.1431). Anal. calc. for $C_{16}H_{22}FNO_4$ (311.35): C 61.72, H 7.12, F 6.10, N 4.50; found C 61.58, H 7.39, F 5.90, N 5.37.

*Selected Data for Minor Isomer (2S,3R)-***8b** *from Mixture:* ^{19}F-NMR (282 MHz, $CDCl_3$): −208.3 (*dd*, $J = 47.9, 28.6$).

4. *Synthesis of Methyl Esters of β³-Homoleucine, β³-Homovaline, and β³-Homoalanine* **12**, **13**, *and* **14**, *Respectively.* (**14**). 4.1. *Methyl (2*S,*3*S*)- and (2*R,*3*S*)-3-[(*tert-*Butoxycarbonyl)amino]-2-fluoro-5-methylhexanoate* (**12a** and **12b**, resp.). The amino acid **9** (119 mg, 0.46 mmol) was treated with BuLi (0.63 ml, 1.0 mmol, 1.6M in hexane), $^{i}Pr_2NH$ (0.14 ml, 3.9 mmol), and NFSI (724 mg, 2.3 mmol) according to *GP 1*. The crude product was purified by CC (SiO_2; AcOEt/CH_2Cl_2 0:1 → 1:9) to give a mixture **12a**/**12b** (76 mg, 60%). White solid. dr 93:7 (^{19}F-NMR). Recrystallisation from PE gave the single diasteroisomer **12a** as white block crystals.

Data for **12a** (isolated). M.p. 65–66°. $[\alpha]_D^{22} = -15.6$ ($c = 0.22$ in $CHCl_3$). IR (KBr): 3473, 3411, 1762 1679, 1639, 1618, 1532, 1251, 1174, 1073. ^{1}H-NMR (300 MHz, $CDCl_3$): 5.04 (*dd*, *J* = 49.2, 2.7, CHF); 4.63 (*d*, *J* = 8.8, NH); 4.28–4.08 (*m*, NCH); 3.81 (*s*, MeO); 1.73–1.59 (*m*, Me_2CH); 1.50–1.43 (*m*, 1 H, $CHCH_2$); 1.45 (*s*, ^{t}Bu); 1.18–1.07 (*m*, 1 H, $CHCH_2$); 0.93 (*d*, *J* = 6.7, 1 Me of Me_2CH); 0.90 (*d*, *J* = 6.5, 1 Me of Me_2CH). ^{13}C-NMR (126 MHz, $CDCl_3$): 168.2 (*d*, *J* = 24.2); 155.2; 90.8 (*d*, *J* = 187.5), 80.0; 52.4; 50.3 (*d*, *J* = 20.0); 37.6; 28.3; 24.5; 23.4; 21.3. ^{19}F-NMR (282 MHz, $CDCl_3$): −204.8 – −205.2 (*m*, minor rotamer); −206.6 (*dd*, *J* = 49.2, 27.0, major rotamer). HR-ESI-MS: 278.1761 ($[M+H]^+$, $C_{13}H_{25}FNO_4^+$; calc. 278.1768). Anal. calc. for $C_{13}H_{24}FNO_4$ (277.33): C 56.30, H 8.72, F 6.85, N 5.05; found C 56.11, H 8.83, F 6.65, N 4.98.

Selected Data for Minor Diastereoisomer **12b** *from the Mixture.* ^{19}F-NMR (282 MHz, $CDCl_3$): −206.2 (*dd*, *J* = 48.1, 27.0).

4.2. *Methyl (2*S,*3*S*)- and (2*R,*3*S*)-3-[(*tert-*Butoxycarbonyl)amino]-2-fluoro-4-methylpentanoate* (**13a** and **13b**, resp.). Compound **10** (235 mg, 0.96 mmol) was treated with BuLi (1.32 ml, 2.1 mmol, 1.6M in hexane), $^{i}Pr_2NH$ (0.29 ml, 2.1 mmol), and NFSI (1.51 g, 4.8 mmol) according to *GP 1*. The crude product was purified by CC (SiO_2; AcOEt/CH_2Cl_2, 0:1 → 1:19) to give a mixture **13a**/**13b** (144 mg, 57%). Colorless oil. dr 96:4 (^{19}F-NMR). $[\alpha]_D^{22}$ (mixture) = −7.6 ($c = 0.97$ in $CHCl_3$). IR (KBr) 3352, 2967, 1764, 1713, 1514, 1367, 1240, 1171.

Data of **13a** *from the Mixture.* ^{1}H-NMR (500 MHz, $CDCl_3$): 4.95 (*dd*, *J* = 48.4, 2.6, CHF); 4.75 (*d*, *J* = 9.2, NH); 4.08–3.97 (*m*, NCH); 3.81 (*s*, MeO); 1.97–1.89 (*m*, Me_2CH); 1.46 (*s*, ^{t}Bu), 0.99–0.94 (*m*, Me_2CH). ^{13}C-NMR (126 MHz, $CDCl_3$: 168.6 (*d*, *J* = 23.5); 155.5; 90.0 (*d*, *J* = 189.3); 79.9; 56.0 (*d*, *J* = 20.5); 52.5; 28.6; 28.3; 20.1; 17.5. ^{19}F-NMR (282 MHz, $CDCl_3$): −199.4 (*dd*, *J* = 48.6, 22.0, minor rotamer); −201.0 (*dd*, *J* = 48.4, 23.5, major rotamer). HR-ESI-MS: 286.1437 ($[M+Na]^+$, $C_{12}H_{22}FNNaO_4^+$; calc. 286.1431).

Selected Data of Minor Diastereoisomer **13b** *from the Mixture.* ^{19}F-NMR (282 MHz, $CDCl_3$): −206.8 (*dd*, *J* = 48.2, 30.9).

4.3. *Methyl (2*S,*3*S*)- and (2*R,*3*S*)-3-[(*tert-*Butoxycarbonyl)amino]-2-fluorobutanoate* (**14a** and **14b**, resp.). Compound **11** (302 mg, 1.4 mmol) was treated with BuLi (1.88 ml, 3.0 mmol, 1.6M in hexane), $^{i}Pr_2NH$ (0.52 ml, 3.0 mmol), and NFSI (2.19 g, 7.0 mmol) according to *GP 1*. The crude product was purified by CC (SiO_2; AcOEt/CH_2Cl_2 0:1 → 1:19) to give a mixture **14a**/**14b** (134 mg, 41%). Colorless oil. dr 96:4 (^{19}F-NMR). M.p. 59–60°. $[\alpha]_D^{20}$ (mixture) = −1.4 ($c = 0.91$ in $CHCl_3$). IR (KBr) 3370, 2981, 1766, 1713, 1519, 1367, 1247, 1168, 1061.

Data of **14a** *from the Mixture.* ^{1}H-NMR (300 MHz, $CDCl_3$): 5.03 (*dd*, *J* = 49.4, 2.0, CHF); 4.74 (*d*, *J* = 5.4, NH); 4.33–4.10 (*m*, NCH); 3.80 (*s*, MeO); 1.44 (*s*, ^{t}Bu); 1.14 (*d*, *J* = 7.0, *Me*CH). ^{13}C-NMR (126 MHz, $CDCl_3$): 168.2 (*d*, *J* = 23.9); 154.8; 90.2 (*d*, *J* = 188.1); 80.0; 52.5; 47.8 (*d*, *J* = 20.5); 28.3; 14.2. ^{19}F-NMR (282 MHz, $CDCl_3$): −207.3 to −207.9 (*m*, minor rotamer); −208.2 (*dd*, *J* = 49.3, 26.9, major rotamer). HR-ESI-MS: 236.1298 ($[M+H]^+$, $C_{10}H_{19}FNO_4^+$; calc. 236.1298). Anal. calc. for $C_{10}H_{18}FNO_4$ (235.25): C 51.05, H 7.71, F 8.08, N 5.95; found C 51.11, H 7.71, F 7.96, N 5.86.

Selected Data of Minor Diastereoisomer **14b** *from the Mixture.* ^{19}F-NMR (282 MHz, $CDCl_3$): −205.9 (*dd*, *J* = 48.0, 27.0).

5. *Synthesis of the Fluorinated β-Homophenylglycine Methyl Esters* **4** *and* **18**–**20**. 5.1. *Methyl (2*S,*3*S*)- and (2*R,*3*S*)-3-(Benzoylamino)-2-fluoro-3-phenylpropanoate* (**4a** and **4b**, resp.). The ester **3** (196 mg, 0.69 mmol) was treated with BuLi (0.96 ml, 1.5 mmol, 1.6M in hexane), $^{i}Pr_2NH$ (0.21 ml, 1.5 mmol), and NFSI (1.09 g, 3.5 mmol) according to *GP 1*. dr 83:17 (^{19}F-NMR). The mixture was purified by RC (silica gel, 5-mm plate; AcOEt/CH_2Cl_2 0:1 → 1:9) to give a fraction containing a mixture **4a**/**4b** (112 mg, 54%) and a pure fraction of **4a** (34 mg, 16%). Both fractions were an off-white solid and gave a total yield of 70%.

Data of **4a** (isolated). M.p. 133–135° ([10]: 138–140°). $[\alpha]_D^{20} = -3.3$ ($c = 1.14$ in $CHCl_3$). IR (KBr) 3412, 1764, 1713, 1521, 1456, 1289, 1231, 1107, 1048, 700. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.84–7.78 (*m*, 2 arom. H); 7.58–7.33 (*m*, 8 arom. H); 6.86 (*d*, $J = 8.0$, NH); 5.75 (*ddd*, $J = 26.7, 8.0, 3.7$, NCH); 5.47 (*dd*, $J = 48.8, 3.6$, CHF); 3.67 (*s*, MeO). ^{13}C-NMR (75 MHz, $CDCl_3$): 167.4 (*d*, $J = 23.6$); 166.8; 135.2; 133.7; 132.0; 129.0; 128.8; 128.7; 127.8; 127.1; 89.6 (*d*, $J = 191.4$); 54.9 (*d*, $J = 18.6$); 52.5. ^{19}F-NMR (282 MHz, $CDCl_3$): −202.45 (*dd*, $J = 48.8, 26.8$). HR-ESI-MS: 302.1180 ($[M+H]^+$, $C_{17}H_{17}FNO_3^+$; calc. 302.1192).

Selected Data of Minor Diastereoisomer **4b** *from the Mixture.* ^{1}H-NMR (300 MHz, $CDCl_3$): 6.95 (*d*, $J = 10.2$, NH); 5.94–5.87 (*m*, NCH); 5.32 (*dd*, $J = 47.4, 1.8$, CHF); 3.82 (*s*, MeO). ^{13}C-NMR (75 MHz, $CDCl_3$): 168.0 (*d*, $J = 25.1$); 166.8; 90.0 (*d*, $J = 191.0$); 54.0 (*d*, $J = 19.3$); 52.7. ^{19}F-NMR (282 MHz, $CDCl_3$): −202.8 (*dd*, $J = 47.2, 27.8$).

5.2. *Methyl (2*S*,3*S*)- and (2*R*,3*S*)-3-{[(Benzyloxy)carbonyl]amino}-2-fluoro-3-phenylpropanoate* (**18a** and **18b**, resp.). The ester **15** (226 mg, 0.72 mmol) was treated with BuLi (1.00 ml, 1.6 mmol, 1.6M in hexane), ^{i}Pr$_2$NH (0.22 ml, 1.6 mmol), and NFSI (1.14 g, 3.6 mmol) according to *GP 1*. The crude product was purified by RC (silica gel, 5-mm plate; AcOEt/CH_2Cl_2 0:1 → 1:9) to give a mixture **18a**/**18b** (150 mg, 63%). Off-white solid. dr 79:2 (^{19}F-NMR).

Data of the mixture **18a**/**18b**. M.p. 53–55°. $[\alpha]_D^{22}$ (mixture) = +19.5 ($c = 1.04$ in $CHCl_3$). IR (KBr) 3412, 1764, 1712, 1521, 1456, 1289, 1231,1107, 1048, 700. ^{1}H-NMR (500 MHz, $CDCl_3$): 7.47–7.20 (*m*, each 10 arom. H, major + minor); 5.68–5.55 (*m*, NH, major + minor), 5.44–5.06 (*m*, CHF, NCH, PhCH_2O, major + minor); 3.78 (*s*, MeO, minor); 3.64 (*s*, MeO, major). ^{13}C-NMR (126 MHz, $CDCl_3$): 167.7 (*d*, $J =$ 25.0, minor); 167.1 (*d*, $J = 23.4$, major); 155.5 (minor); 155.3 (major); 137.0 (minor); 135.9 (minor); 135.9 (major); 135.2 (major); 128.6; 128.6; 128.5;128.3; 128.3; 128.1; 128.1; 128.0; 127.9; 127.5; 126.8; 126.6; 90.2 (*d*, $J = 191.4$, minor); 89.7 (*d*, $J = 192.1$, major); 67.0 (major); 67.0 (minor); 56.1 (*d*, $J = 18.8$, major); 55.7 (*d*, $J = 19.3$, minor); 52.5 (minor); 52.1 (major). ^{19}F-NMR (282 MHz, $CDCl_3$: −203.2 (*dd*, $J = 48.5$, 27.4, major); −203.5 (*dd*, $J = 47.4$, 27.8, minor). HR-ESI-MS: 332.1284 ($[M+H]^+$, $C_{18}H_{19}FNO_4^+$; calc. 332.1298).

5.3. *Methyl (2*S*,3*S*)- and (2*R*,3*S*)-3-[(*tert*-Butoxycarbonyl)amino]-2-fluoro-3-phenylpropanoate* (**19a** and **19b**, resp.). The ester **16** (214 mg, 0.77 mmol) was treated with BuLi (1.06 ml, 1.7 mmol, 1.6M in hexane), ^{i}Pr$_2$NH (0.24 ml, 1.7 mmol), and NFSI (1.20 g, 3.8 mmol) according to *GP 1*. dr 78:22 (^{19}F-NMR). The mixture was purified by RC (silica gel, 5-mm plate; AcOEt/CH_2Cl_2 0:1 → 1:9) to give a fraction containing a mixture **19a**/**19b** (157 mg, 68%) and a pure fraction of **19a** (13 mg, 6%). Both fractions were an off-white solid and gave a total yield of 74%.

Data of **19a** (isolated). M.p. 82–84°. $[\alpha]_D^{20} = +32.4$ ($c = 0.89$ in $CHCl_3$). IR (KBr) 3389, 2978, 1767, 1712, 1497, 1368, 1293, 1250, 1167, 702.^{1}H-NMR (300 MHz, $CDCl_3$): 7.38–7.27 (*m*, 5 arom. H); 5.43–5.13 (*m*, NH, CHF, NCH); 3.65 (*s*, MeO); 1.44 (*s*, *Me*$_3$C). ^{13}C-NMR (75 MHz, $CDCl_3$): 167.4 (*d*, $J = 23.5$); 154.7; 135.6; 128.8; 128.6; 127.6; 90.0 (*d*, $J = 192.0$); 80.4; 55.9 (*d*, $J = 18.0$); 52.3; 28.3.^{19}F-NMR (282 MHz, $CDCl_3$): −203.5 (*dd*, $J = 49.1, 26.4$). HR-ESI-MS: 298.1443 ($[M+H]^+$, $C_{15}H_{21}FNO_4^+$; calc. 298.1455).

Data of the Minor Diastereoisomer **19b** *from the Mixture.* ^{1}H-NMR (300 MHz, $CDCl_3$): 7.52–7.17 (*m*, 5 arom. H); 5.49–5.05 (*m*, NH, CHF, NCH); 3.81 (*s*, MeO); 1.43 (*s*, *Me*$_3$C). ^{13}C-NMR (75 MHz, $CDCl_3$: 167.9 (*d*, $J = 25.1$); 154.8; 137.4; 128.7; 128.1; 126.6; 90.4 (*d*, $J = 190.8$); 80.2; 55.3 (*d*, $J = 18.3$); 52.6; 28.1. ^{19}F-NMR (282 MHz, $CDCl_3$): −204.0 (*dd*, $J = 47.3, 27.8$).

5.4. *Methyl (2*S*,3*S*)- and (2*R*,3*S*)-3-(Acetylamino)-2-fluoro-3-phenylpropanoate* (**20a** and **20b** resp.). The ester **17** (200 mg, 0.90 mmol) was treated with BuLi (1.24 ml, 2.0 mmol, 1.6M in hexane), ^{i}Pr$_2$NH (0.28 ml, 2.0 mmol), and NFSI (1.43 g, 4.5 mmol) according to *GP 1*. The crude product was purified by RC (silica gel, 5-mm plate; AcOEt/CH_2Cl_2 0:1 → 1:9) to give a mixture **20a**/**20b** (111 mg, 51%). Colorless oil. dr 63:37 (^{19}F-NMR).

Data of the Mixture of **20a**/**20b**. IR (KBr) 3289, 3065, 2957, 1763, 1659, 1536, 1295, 1222, 1101, 732, 711. ^{1}H-NMR (500 MHz, $CDCl_3$): 7.54 (*d*, $J = 8.3$, NH, major); 7.47 (*d*, $J = 9.3$, NH, minor); 7.38–7.25 (*m*, 10 arom. H); 5.64 (*ddd*, $J = 28.9, 9.3, 2.1$, NCH, minor); 5.51 (*ddd*, $J = 28.1, 8.3, 3.7$, NCH, major); 5.21 (*dd*, $J = 48.9, 3.7$, CHF, major); 5.16 (*dd*, $J = 47.4, 2.3$, CHF, minor); 3.72 (*s*, MeO, minor); 3.59 (*s*, MeO, major); 2.02 (*s*, MeC, minor); 2.00 (*s*, MeC, major). ^{13}C-NMR (126 MHz, $CDCl_3$): 170.1 (major + minor); 167.7 (*d*, $J = 25.3$, minor); 167.2 (*d*, $J = 23.7$, major); 136.8; 135.0; 128.4;128.3; 128.1; 127.8; 127.6; 126.6; 90.0 (*d*, $J = 190.3$, minor); 89.4 (*d*, $J = 191.4$, major); 54.1 (*d*, $J = 18.9$, major); 53.5 (*d*, $J = 19.0$,

minor); 52.3 (minor); 52.0 (major); 22.4 (major); 22.3 (minor).^{19}F-NMR (282 MHz, $CDCl_3$): -203.0 (*dd*, $J = 47.4$, 29.1, minor), -203.1 (*dd*, $J = 48.9$, 28.1, major). HR-ESI-MS: ($[M+H]^+$, $C_{12}H_{15}FNO_3^+$: 240.1036; found 240.1027.

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