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New Strategy for the Stereoselective Synthesis of Fluorinated β-Amino Acids

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Racemic and chiral nonracemic α-substituted and α-unsubstituted β-fluoroalkyl β-amino acid derivatives **6** and **9** have been synthesized in two steps starting from fluorinated imidoyl chlorides **1** and ester enolates. This approach is based on the chemical reduction of previously obtained γ-fluorinated β-enamino esters **4** by using $ZnI_2/NaBH_4$ in a nonchelated aprotic medium (dry CH_2Cl_2) as the reducing agent. A metal-chelated six-membered model has been suggested to explain the stereochemical outcome of the reduction reaction. The process takes place with high yields and with moderate to good diastereoselectivity. The best results related to diastereoselective reduction of chiral β-enamino esters **4** were provided by the use of (−)-8-phenylmenthol as a chiral auxiliary.

Introduction

The synthesis and reactivity of 1,3-difunctionalized derivatives represent an active area of investigation in organic chemistry, especially those aspects related to the stereoselective synthesis of β-amino acids.[1] The special value of these products is due to their potential therapeutic applications and to their use as valuable intermediates in the design and construction of novel biological and medicinally important molecules.[2]

Some free β-amino acids play an important role in the biological activity of complex molecules. For example, the anticancer activity of *Taxol* mainly depends on the presence of an *N*-benzoyl-(2*R*,3*S*)-3-phenylisoserine moiety in its framework.[2,3] Furthermore, these compounds are receiving increasing attention due to the fact that β-peptides, constituted entirely by β-amino acid units as opposed to α-amino acid units, are emerging as a class of unnatural biopolymers that present interesting secondary structures, as well as increased potency and enzymatic stability.[2,4]

In addition, organofluorine chemistry is receiving remarkable interest due to the enormous utility of organofluorine compounds in several fields such as medicinal, biological, agricultural, and analytical chemistry.[5] In particular, fluorinated amino acids and amino alcohols have been shown to demonstrate extensive biological activity.[2,3c,6]

Considering the benefits of fluorine substitution for hydrogen, the development of new synthetic methodologies for preparing fluorine-containing enantiomerically pure β-amino acids is of particular interest. There are two main strategies that have been followed to synthesize these products, the direct fluorination strategy and the building block approach. Related to the former, the synthesis of α-fluoro-β-amino acids from β-hydroxy-α-amino acids has been described.[7] Furthermore, Davis

* To whom correspondence should be addressed.
† Corresponding author regarding X-ray diffraction studies.

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(5) See, for example: (a) Banks, R. E.; Tatlow, J. C.; Smart, B. E. *Organofluorine Chemistry: Principles and Commercial Applications*; Plenum Press: New York, 1994. (b) Ojima, I.; McCarthy, J. R.; Welch, J. T. *Biomedical Frontiers of Fluorine Chemistry*; ACS Symposium Series 639; American Chemical Society: Washington, DC, 1996. (c) *Houben-Weyl Methods of Organic Chemistry: Organo-Fluorine Compounds*, Workbench ed.; Georg Thieme Verlag: Stuttgart, 2000; Vols. E10a−c.

(6) For reviews, see: (a) *Fluorine-Containing Amino Acids: Synthesis and Properties*; Kukhar, V. P., Soloshonok, V. A., Eds.; Wiley: Chichester, UK, 1994. (b) Bèguè, J.-P.; Bonnet-Delpon, D. Trifluoromethylated Amino Alcohols: New Synthetic Approaches and Medicinal Targets. In *Biomedical Frontiers of Fluorine Chemistry*; Ojima, I., McCarthy, J. R., Welch, J. T., Eds.; American Chemical Society: Washington, DC, 1996; pp 59−72. (c) *Enantiocontrolled Synthesis of Fluoro-Organic Compounds*; Soloshonok, V. A., Ed.; Wiley: Chichester, UK, 1999. (d) Sutherland, A.; Wilis, C. L. *Nat. Prod. Rep.* **2000**, *17*, 621−631 and references cited therein.

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reported the electrophilic α-fluorination of nonfluorinated *β*-amino esters in moderate diastereoselectivity.[8]

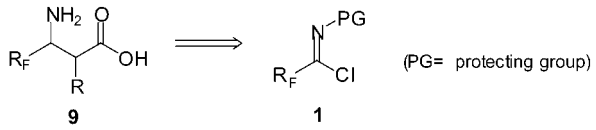
However, most of the described processes for the synthesis of fluorinated *β*-amino acids are based on the use of the building block approach. Although several synthetic routes to these derivatives have been reported, most of them suffer various limitations related to the poor diastereoselectivity observed. Bégué described the [2 + 2] cycloaddition between fluoroalkyl imines and ketenes in order to access enantiopure methyl *syn*-CF_3-isoserinates.[9] The same authors have very recently reported a new strategy based on the reaction of ethyl diazoacetate with CF_3-imines, followed by ring-opening of aziridine intermediates with various nucleophiles.[10,11]

On the other hand, strategies that imply the use of reductive and chemoenzymatic approaches are less frequent. Shen in 1995 obtained racemic *β*-amino acids by catalytic hydrogenation starting from their precursors, fluoroalkyl enamines.[12] More recently, Uneyama described the synthesis of racemic *anti*-*β*-trifluoromethyl isoserine by diastereoselective reduction of α-hydroxy-*β*-imino esters obtained via base-catalyzed intramolecular rearrangement of imino ethers.[13]

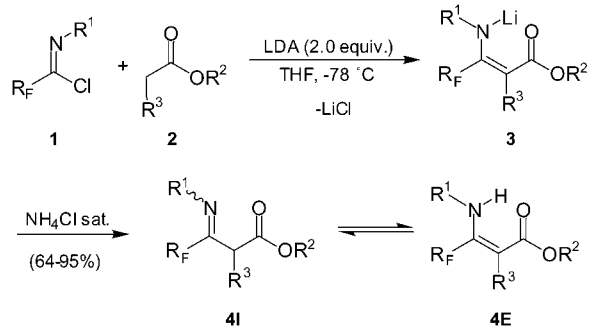
Moreover, Soloshonok designed a chemoenzymatic approach to synthesize *β*-fluoroalkyl-*β*-amino acids by stereoselective biomimetic transamination of α-alkyl-*β*-keto carboxylic esters, which implies a base catalyzed-[1,3]-proton shift reaction followed by hydrolysis and biocatalytic resolution by *Penicillin acylasa*. Alternative procedures using chiral bases and chiral amines have also been described.[14]

In the context of our ongoing study of the synthesis and reactivity of 1,3-difunctionalized fluorine-containing amino compounds,[15] we have focused our attention on the development of novel stereoselective reductive strategies for the synthesis of enantiopure fluorinated *β*-amino acids derivatives.[16] Herein, we report an efficient two-step route to prepare racemic and/or chiral nonracemic *γ*-fluorinated-*β*-amino acid derivatives through reductive processes starting from fluorinated imidoyl halides **1** and lithium enolate esters (Scheme 1).[17]

SCHEME 1



SCHEME 2



Results and Discussion

Synthesis of *γ*-Fluorinated *β*-Enamino Acid Derivatives 4 and 5. Fluorinated *β*-enamino esters **4** can be prepared from fluorinated imidoyl chlorides **1**[18] and lithium enolates of alkyl esters, as is outlined in Scheme 2. Thus, the treatment of alkyl esters **2** (1.0 equiv) with lithium diisopropylamide (LDA, 2.0 equiv) at −40 °C in tetrahydrofuran (THF) for 2 h generated a slightly yellow solution of the corresponding lithium enolate. Addition of a variety of fluorinated *N*-alkyl or *N*-aryl-imidoyl chlorides **1** (1.0 equiv) to this solution gave, after standard workup, *γ*-fluorinated-*β*-enamino esters **4** as the only products. Table 1 summarizes the obtained results.

The scope of the process described above is illustrated in Table 1. In general, the reaction works well, and good to high yields (64−99%) are obtained regardless of the nature of the starting materials **1** and **2**. No excess of the starting material is needed with the exception of the base (LDA), for which a 2-fold excess of LDA is necessary. The first equivalent is used to form the lithium ester enolate, and the second is necessary in order to ensure the presence of the intermediate **3**, avoiding possible acid/base side reactions and improving significantly the chemical yield of the process (entries 2 and 8, Table 1) as had already been postulated in related systems.[19] Chiral fluorinated *β*-enamino esters can also be obtained when starting from chiral esters[20] (entries 10−14 and 21−22) or chiral imidoyl chlorides (entries 8 and 9).

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(11) Other examples, including Mannich-type reactions and Michael additions, have also been reported. See, for example: (a) Kaneko, S.; Yamazaki, T.; Kitazume, T. *J. Org. Chem.* **1993**, *58*, 2302−2312. (b) Takaya, J.; Kagoshima, H.; Akiyama, T. *Org. Lett.* **2000**, *2*, 1577−1559. (c) Ojima, I.; Kato, K.; Nakahashi, K.; Fuchikami, T.; Fujita, M. *J. Org. Chem.* **1989**, *54*, 4511−4522. (d) Volonterio, A.; Bravo, P.; Zanda, M. *Org. Lett.* **2000**, *2*, 1827−1830. (e) Volonterio, A.; Bravo, P.; Moussier, N.; Zanda, M. *Tetrahedron Lett.* **2000**, *41*, 6517−6521.

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(14) (a) Soloshonok, V. A.; Kirilenko, A. G.; Kukhar, V. P.; Galushko, S. *Tetrahedron Lett.* **1994**, *34*, 5063−5066. (b) Soloshonok, V. A.; Ono, T.; Soloshonok, I. V. *J. Org. Chem.* **1997**, *62*, 7538−7539. (c) Soloshonok, V. A.; Svedas, V. K.; Kukhar, V. P.; Kirilenko, A. G.; Rybakova, A. V.; Solodenko, V. A.; Fokina, N. A.; Kogut, O. V.; Galaev, I. Y.; Kozlova, E. V.; Shishkina, I. P.; Galushko, S. V. *Synlett* **1993**, 339−341. (d) Soloshonok, V. A.; Soloshonok, I. V.; Kukhar, V. P.; Svedas, V. K. *J. Org. Chem.* **1998**, *63*, 1878−1884.

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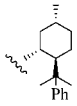
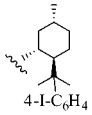
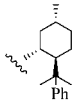
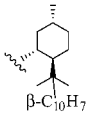
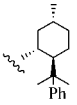
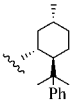
TABLE 1. Fluorinated β-Enamino Esters 4 Obtained from Imidoyl Chlorides 1 and Esters 2

entry [a]	R^1	R_F	R^2	R^3	product	ratio (**4I** / **4E**)[b]	yield (%)[c]
1	*p*-$MeOC_6H_4$	CF_3	*i*-Pr	H	**4a**	20/80	85
2	*p*-$MeOC_6H_4$	CF_3	*t*-Bu	H	**4b**	30/70	90(47)[d]
3	*p*-$MeOC_6H_4$	CF_2Cl	*i*-Pr	H	**4c**	35/65	64
4	*p*-$MeOC_6H_4$	CF_2Cl	-$(CH_2)_2$-	H	**4d**	0/100	82
5	*p*-$MeOC_6H_4$	C_2F_5	*i*-Pr	H	**4e**	70/30	100
6	*c*-C_6H_{11}	CF_3	*i*-Pr	H	**4f**	0/100	90
7	*p*-$MeOC_6H_4$	*n*-C_8F_{17}	*i*-Pr	H	**4g**	75/25	78
8	(*S*)-(+)-*c*-C_6H_{11}(Me)CH	CF_3	*t*-Bu	H	(+)-**4h**	10/90	81(51)[d]
9	(*S*)-(-)-C_6H_5(Me)CH	CF_3	*i*-Pr	H	(+)-**4i**	0/100	65
10	*p*-$MeOC_6H_4$	CF_3		H	(-)-**4j**	10/90	95
11	*p*-$MeOC_6H_4$	CF_3		H	(+)-**4k**	0/100	72
12	*p*-$MeOC_6H_4$	CF_3		H	(+)-**4l**	0/100	69
13	*p*-$MeOC_6H_4$	CF_2Cl		H	(+)-**4m**	60/40	70
14	*p*-$MeOC_6H_4$	CF_3		H	(+)-**4n**	0/100	70
15	*p*-$MeOC_6H_4$	CF_3	Me	Me	**4o**	60/40	92
16	*p*-$MeOC_6H_4$	CF_3	Et	Et	**4p**	60/40	80
17	*p*-$MeOC_6H_4$	CF_3	Et	Me	**4q**	40/60	87
19	*p*-$MeOC_6H_4$	CF_2Cl	Me	Me	**4s**	10/90	72
20	*p*-$MeOC_6H_4$	C_2F_5	Me	Me	**4t**	84/16	71
21	*p*-$MeOC_6H_4$	CF_2Cl		Me	(-)-**4u**	60/40	80
22	*p*-$MeOC_6H_4$	CF_3		Me	(-)-**4v**	65/35	85

[a] All reactions were carried out on an 8.0 mmol scale. [b] Imino/enamino tautomer ratio estimated by ^1H and ^{19}F NMR on the crude mixture. [c] Isolated yield. [d] Yield using 1.0 equiv of LDA.

Table 1 also shows that products **4** are, in general, isolated as a mixture of imino (**4I**) and enamino (**4E**) tautomers. The ratio **4I**/**4E** is influenced by the length of the perfluoroalkyl chain.[21] In general, it is observed that the longer the perfluoroalkyl substituent, the higher the ratio of imino tautomer; however, this tautomer was never isolated as the unique tautomer, opposite to the enamino tautomer form (see, for example, entries 4, 6, 9, 11, 12, and 14, Table 1).

The configuration of the enamino double bond in tautomer **4E** (Figure 1) was also studied. NMR analyses (^1H, ^{19}F, ^{13}C) at room temperature showed that only one of the two possible geometric isomers occurs. The downfield chemical shift of the N−H proton (see Experimental

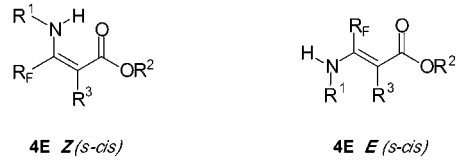
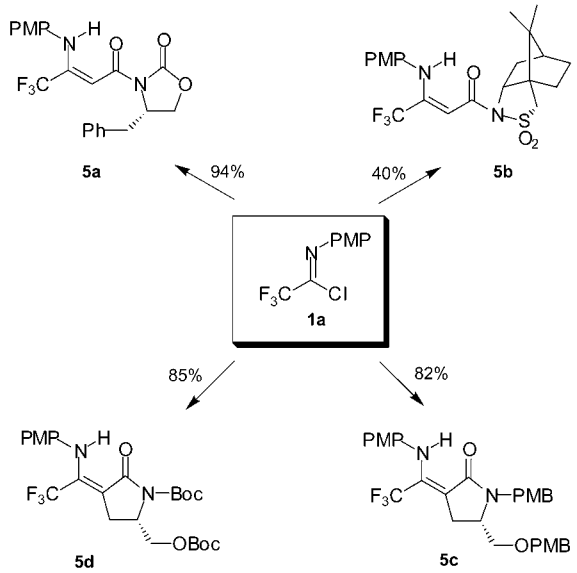


FIGURE 1.

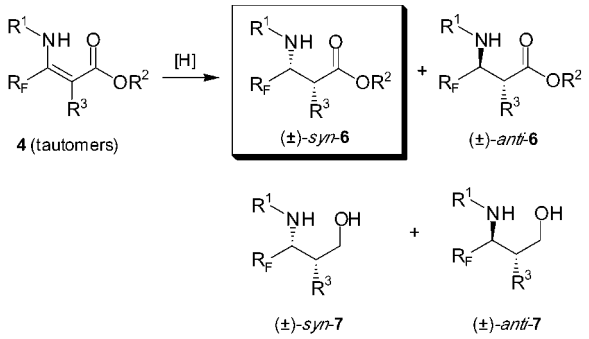
SCHEME 3



Section) is typical of a hydrogen bond with the carbonyl group oxygen, therefore suggesting a chelated configuration, *Z*, *s*-cis (Figure 1). To confirm this hypothesis, a 2D HOESY NMR $^1H-^{19}F$ experiment was carried out. For **4a**, this analysis showed (entry 1, Table 1) a cross-peak between the CF_3 moiety (δ −63.8, ^{19}F NMR) with the vinylic hydrogen (δ 5.28 ppm, ^1H NMR).[22]

Similarly, the scope of the reported approach has also been successfully extended to the synthesis of other β-enamino acids derivatives, such as fluorinated β-enamino amides **5a**−**d** derived from chiral nonracemic acyclic and cyclic amides (Scheme 3). Thus, fluorinated imidoyl chloride **1a** ($R_F = CF_3$, $R^1 = p$-$MeOC_6H_4$) reacts with a range of chiral amides,[23] under the same conditions as described above, to exclusively provide the enamino tautomers **5a**−**d** in generally good yields.

SCHEME 4



Chemo- and Stereoselective Reduction of γ-Fluorinated β-Enamino Acid Derivatives. In general, the chemoselective reduction of β-enamino acid derivatives is a simple and attractive route to β-amino acids.[1d,24] There are, however, several problems related with the chemo- and stereoselectivity that have limited the development of efficient reductive processes. In fact, to the best of our knowledge, only two reports regarding the synthesis of *racemic* γ-fluorinated β-amino acids whose key step involves the use of reductive methods have been described.[12,13]

To develop an effective process in terms of yield and chemo- and stereoselectivity to synthesize enantiopure fluorinated β-amino acids **9**, we first addressed the study of the reduction of fluorinated β-enamino esters **4** to the corresponding β-amino derivatives **6** (Scheme 4 and Tables 2 and 4).

We first carried out the reduction in different reaction conditions (Table 2). Table 2 shows a variety of reducing agents, solvents, and temperatures that were studied to produce β-fluoroalkyl β-amino esters **6**. Thus, sodium borohydride derivatives such as sodium cyanoborohydride ($NaCNBH_3$) in a 4:1 mixture of THF and methanolic HCl as a solvent at room temperature provided high chemical yields of fluorinated β-amino esters **6**; in α-substituted derivatives ($R^3 \neq H$) (entries 8−25, Table 2), a separable syn/anti mixture was obtained, although only moderate diastereoselectivity (de 30−46%) was observed (see entries 8, 20, and 22, Table 2).[25]

We next examined the behavior of sodium borohydride ($NaBH_4$) in a nonchelated aprotic medium (dry CH_2Cl_2) along with the effect of the presence of different anhydrous zinc halides as chelating agents. The reactions were performed at room temperature and gave (±)-*syn*-α-alkyl-β-fluoroalkyl-β-amino esters **6** with high yields (90%) and excellent diastereoselectivity (de up to 96%).[26]

From this study, the best diastereoselectivity was obtained using an excess of *anhydrous* ZnI_2 (3.0 equiv) and $NaBH_4$ (5.0 equiv) in dry dichloromethane at room temperature for 24 h (see, for example, entry 12, Table 2).[27] Other solvents such as diethyl ether (entry 13, Table

(20) Chiral esters have been obtained by acetylation (Ac_2O/Py) of the corresponding alcohols. See, for example: (a) Ort, O. *Org. Synth.* **1987**, *65*, 203−213. (b) D'Angelo, J.; Maddaluno, J. *J. Am. Chem. Soc.* **1986**, *108*, 8112−8114. (c) Commins, D. L.; Salvador, J. M. *J. Org. Chem.* **1993**, *58*, 4656−4661. (d) 8-(4-Iodo)phenylmenthol acetate was prepared by regioselective aromatic iodation of 8-phenylmenthol acetate with commercially available bis(pyridine)iodonium(I) tetrafluoroborate (IPy2BF4). See, for example: Barluenga, J.; González, J. M.; García-Martín, M.; Campos, P. J.; Asensio, G. *J. Org. Chem.* **1993**, *58*, 2058−2060.

(21) Portella, C.; Iznaden, M. *Tetrahedron Lett.* **1988**, *29*, 3683−3686.

(22) The signal connecting the fluorine atoms with the hydrogen of the *p*-anisidin ring at δ 7.15 ppm unequivocally corroborates the *Z*-configuration of the enamino tautomer **4b**.

(23) While (*S*)-3-acetyl-4-benzyl-2-oxazolidinone is commercially available, (1*S*)-*N*-acetyl-2,10-camphorsultam was prepared by treatment of camphor sultam with Ac_2O/Py. In the same way, γ-lactams providing **5c** and **5d** were obtained in three steps from L-pyroglutamic acid following procedures described in the literature. See: (a) Otsuka, M.; Takeshi, M.; Haupt, A.; Ohno, M.; Shiraki, T.; Sugiura, Y.; Maeda, K. *J. Am. Chem. Soc.* **1990**, *112*, 838−845. (b) Kocienski, P. J. In *Protecting Groups*; Georg Thieme Verlag: Stuttgart, 1994; Chapter 6, p 224.

(24) (a) Palmieri, M.; Bartoli, G.; Cimarelli, C.; Marcantoni, E.; Petrini, G. *J. Org. Chem.* **1994**, *59*, 5328−5335. (b) Palmieri, M.; Cimarelli, C. *J. Org. Chem.* **1996**, *61*, 5557−5563.

(25) Other reducing agents such as L-Selectride, *n*-Bu_4NBH_4, $NaBH(OAc)_3$, DIBALH, and catalytic hydrogenation (Pd/C) were much less efficient with regard to chemical yield and stereoselectivity.

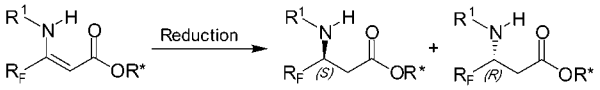
(26) Only in some instances, especially when higher temperatures and/or reaction times where used, were variable amounts of the corresponding γ-amino alcohols **7**, isolated mainly as syn isomers, detected.

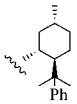
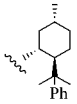
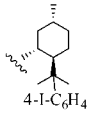
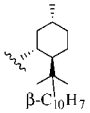
TABLE 2. Racemic β-Fluoroalkyl β-Amino Esters 6 and γ-Amino Alcohols 7 Obtained by Reduction of 4

entry	4[a]	[H]	reaction conditions	product **6** (**7**)	yield (%) of **6**[b] (syn/anti)	yield (%) of **7**[c] (syn/anti)
1	**4a**	$NaBH_3CN$	THF−AcOH, D, 24 h	**6a**	70	
2	**4a**	$NaBH_4$	THF−MeOH, 0 °C, 1.5 h	**6a**	98	
3	**4b**	$NaBH_4$	THF−MeOH, 0 °C, 2 h	**6b**	99	
4	**4e**	$NaBH_3CN$	THF−MeOH−HCl (4:1), 0 °C, 0.5 h	**6c**	98	
5	**4f**	$NaBH_3CN$	THF−MeOH−HCl (4:1), 0 °C, 1.5 h	**6d**	90	
6	**4i**	$NaBH_3CN$	THF−MeOH−HCl (4:1), 0 °C, 1.5 h	**6e**	98 (45/55)[d]	
7	**4i**	$NaBH_4$	ZnI_2 (3.0 equiv), CH_2Cl_2, rt, 15 h	**6e**	50 (45/55)[d]	
8	**4o**	$NaBH_3CN$	THF−MeOH−HCl (4:1), rt, 4 h	**6f**	90 (67/33)	
9	**4o**	$NaBH_4$	$ZnBr_2$ (1.5 equiv), CH_2Cl_2, rt, 20 h	**6f** (**7a**)	90 (93/7)	7 (99/1)
10	**4o**	$NaBH_4$	$ZnBr_2$ (1.5 equiv), CH_2Cl_2, D, 20 h	**6f** (**7a**)	43 (96/4)	57 (99/1)
11	**4o**	$NaBH_4$	$ZnCl_2$ (1.5 equiv), CH_2Cl_2, rt, 48 h	**6f**	32 (90/10)	
12	**4o**	$NaBH_4$	ZnI_2 (3.0 equiv), CH_2Cl_2, rt, 24 h	**6f** (**7a**)	90 (98/2)	10 (99/1)
13	**4o**	$NaBH_4$	ZnI_2 (3.0 equiv), Et_2O, rt, 24 h	**6f** (**7a**)	18 (83/17)	30 (89/11)
14	**4o**	$NaBH_4$	ZnI_2 (1.5 equiv), CH_2Cl_2, Δ, 8 h	**6f** (**7a**)	73 (98/2)	27 (99/1)
15	**4o**	$Zn(BH_4)_2$	CH_2Cl_2, rt, 24 h	**6f** (**7a**)	70 (96/4)	10 (99/1)
16	**4p**	$NaBH_4$	ZnI_2 (3.0 equiv), CH_2Cl_2, rt, 24 h	**6g**	94 (95/5)	
17	**4q**	$NaBH_4$	ZnI_2 (3.0 equiv), CH_2Cl_2, rt, 48 h	**6h**	92 (98/2)	
18	**4r**	$NaBH_4$	ZnI_2 (3.0 equiv), CH_2Cl_2, rt, 24 h	**6i**	71 (96/4)	
19	**4r**	$NaBH_4$	ZnI_2 (3.0 equiv), CH_2Cl_2, Δ, 24 h	**6i** (**7a**)	86 (97/3)	10 (99/1)
20	**4s**	$NaBH_3CN$	THF−MeOH·HCl (4:1), rt, 4 h	**6j**	99 (65/35)	
21	**4s**	$NaBH_4$	ZnI_2 (3.0 equiv), CH_2Cl_2, Δ, 24 h	**6j**	98 (94/6)	
22	**4t**	$NaBH_3CN$	THF−MeOH·HCl (4:1), rt, 5 h	**6k**	82 (73/27)	
23	**4t**	$NaBH_4$	ZnI_2 (3.0 equiv), CH_2Cl_2, rt, 24 h	**6k**	30 (>95/5)	
24	**4t**	$NaBH_4$	ZnI_2 (3.0 equiv), CH_2Cl_2, Δ, 24 h	**6k** (**7b**)	36 (97/3)	20 (99/1)
25	**4t**	$NaBH_4$	ZnI_2 (3.0 equiv), $PhCH_3$, Δ, 24 h	d		

[a] All reactions were carried out on a 2.0 mmol scale. [b] Yields of the crude mixture. [c] Syn/anti diastereomer ratios for **6** and **7** were determined on crude reaction mixtures by ^1H and ^{19}F NMR. [d] Complex mixture.

TABLE 3. Chiral γ-Fluorinated β-Amino Esters 6 Obtained by Reduction of 4

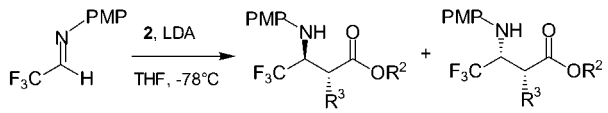


entry[a]	4[b]	R_F	R^2	t (h)	product[c]	ratio (α/β)[d]	yield (%)[e]
1	**4j**	CF_3		19	**6l**	55/45	93
2	**4k**	CF_3		48	**6m**	80/20	85
3	**4m**	CF_2Cl		28	**6n**	74/26	80
4	**4l**	CF_3		36	**6o**	72/28	75
5	**4n**	CF_3		20	**6p**	77/23	80

[a] In all cases, R^1 = *p*-$MeOC_6H_4$ (PMP) and R^3 = H. [b] Reducing conditions: ZnI_2 (3.0 equiv), $NaBH_4$ (5.0 equiv), dry CH_2Cl_2, rt. [c] All reactions were carried out on a 2.0 mmol scale. [d] α/β diastereomer ratio for **6** was determined on crude reaction mixtures by ^1H and ^{19}F NMR. [e] Yield of the crude reaction mixture.

2) and toluene (entry 25, Table 2) provided much less efficient results.

TABLE 4. β-Amino Esters 6 Obtained by Mannich Reaction with Fluorinated Imines 8



entry	R^2	yield[a] (%)	syn/anti[b] (R^3 = Me) (**6f**)	(*S*)-**6a**/(*R*)-**6b**[b] (R^3 = H) (**6m**)
1	Me	38	36/64	
2	(−)-8-phenylmenthol	58		31/69

[a] Isolated yield of the diastereomeric mixture. [b] Syn/anti and α/β diastereomer ratio was determined on crude reaction mixtures by ^{19}F NMR.

The effect of the R_F, R^2, and R^3 substituens on the diastereoselectivity was also examined. Thus, replacement of the methyl group in the ester function by ethyl or *tert*-butyl did not improve the diastereoselectivity of the process to any significant degree (entries 12, 17, 18, Table 2). In the same way, no significant effect was observed when the methyl substituent in R^3 was replaced by an ethyl group (entry 16, Table 2). On the other hand, we found that the reduction of **4t** bearing a pentafluoroethyl group with $NaBH_4/ZnI_2$ resulted in not only a lower chemical yield but also an increasing amount of the nondesired γ-amino alcohol **7** (entries 23 and 24, Table 2). In addition, the use of $Zn(BH_4)_2$ as a reducing agent did not improve the chemical yield or the diastereoselectivity (see entry 15 vs 12, Table 2).

Compounds **6** and **7** were separated and purified by flash chromatography, and their structures were corroborated by spectroscopic analyses (^1H, ^{19}F, and ^{13}C

(27) Other zinc halides salts such as $ZnCl_2$ (entry 11, Table 2) and $ZnBr_2$ (entry 9, Table 2) were less effective.

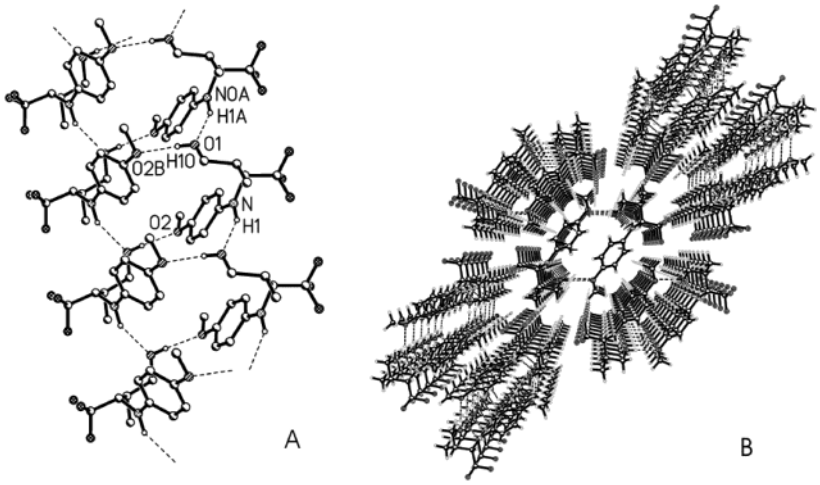
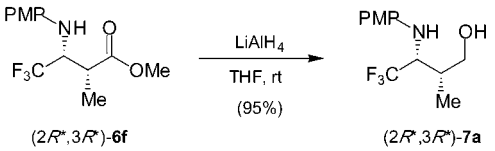


FIGURE 2. (A) Packing diagrams of (2*R**,3*R**)-**7a** showing two linear chains formed through N−H···O hydrogen bonds [N−H(1N)···O(1)#2 (#2: $x-1, y, z$) 155(4)°, H(1N)···O(1)#2 2.35(3), and N···O(1)#2 3.144(6) Å] and self-assembled through O−H···O hydrogen bonds [O(1)−H(1O)···O(2)#1 (#1: $x+1/2, -y+1/2, -z+1$) 174(8)°, H(1O)···O(2)#1 1.99(2), and O(1)···O(2)#1 2.796(6) Å]. (B) View along the *a*-axis showing the tubular superstructure with C−H···F hydrogen bonds [C(5)−H(5A)···F(2)#3 (#3: $-x+1, y-1/2, -z+1/2$) 125.8°, H(5A)···F(2)#3 2.69, and C(5)···F(2)#3 3.345(7) Å].

SCHEME 5



NMR). The relative stereochemical assignment was performed over the fluorinated derivative γ-amino alcohol **7a** obtained easily from the reduction of the corresponding major diastereomer **6f** using $LiAlH_4$ in a solution of THF at room temperature (Scheme 5).

X-ray crystallographic analysis of the γ-amino alcohol **7a** unambiguously assigned the configuration of C(2),C(3) as 2*R**,3*R**. The methyl group bonded to C(2) adopts an anti conformation with respect to both the hydroxyl group and the proton of the vicinal carbon atoms C(1) and C(3), respectively. The amino group acts as a hydrogen bond donor to the hydroxyl oxygen atom of a different molecule [N−H(1N)···O(1)#2] forming infinite linear chains along the *a*-axis. The self-assembly of two linear chains related by a screw axis through hydrogen bonds between the hydroxyl group and the methoxyl oxygen atom [O(1)−H(1O)···O(2)#1] produces a *tubular* superstructure[28] (Figure 2). A C(5)−H(5A)···F(2)#3 hydrogen bond is the closest contact between the nanotubes.

The stereochemical outcome of the reduction reaction of compounds **4** ($R^3 \neq H$) to the major diastereoisomer syn-**6** can easily be understood by assuming a cyclic model in which the ZnI_2 coordinates to the ester carbonyl oxygen and to the nitrogen imino group in a six-membered metal chelate. The hydride then attacks the imino double bond from the opposite side (*si* face) to the α-alkyl group (*ul*-1,2-addition) (Figure 3).

Considering the good results obtained in the diastereoselective reduction of **4**, we next envisaged applying the optimal reduction conditions to the synthesis of chiral nonracemic γ-fluorinated β-amino esters **6** (Table 3).

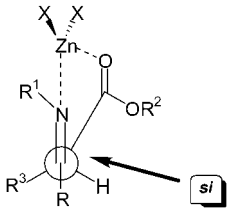


FIGURE 3.

For this purpose, several chiral γ-fluorinated β-enamino esters **4** (entries 8−14, 21, 22, Table 1) and β-enamino amides **5** (Scheme 3) were examined. However, the use of 2-benzyl-2-oxazolidinone and Oppolzer's camphor sultam as chiral auxiliaries (compounds **5a** and **5b**, respectively) was disappointing, providing either a complex mixture of products (starting from **5b**) or a moderate chemical yield with poor asymmetric induction in a nonseparable mixture of diastereoisomers in the case of **5a**. In the same way, derivatives **4** bearing the chiral auxiliary group at the nitrogen atom like (*S*)-methyl benzylamine (entry 9, Table 1) also gave a nonseparable mixture of diastereoisomers (50%, de 10%) as indicated by ^{19}F NMR spectroscopy of the crude mixture.

For this reason, the study was then centered on the reduction of systems bearing a chiral auxiliary in the ester moiety. Thus, we chose chiral auxiliaries derived from the same chiral source, (*R*)-pulegone,[20] such as (−)-8-phenylmenthol, (−)-8-(2-naphthyl)menthol, and (−)-8-(4-iodo)phenylmenthol as well as, for the sake of comparison, (−)-menthol. The reduction of the corresponding β-enamino esters **4j**−**n** was carried out as described above and provided cleanly chiral β-amino esters **6** in good yield as a mixture of two diastereoisomers **6a** and **6b** (de up to 60%) (Table 3). Surprisingly, no essential differences related to stereocontrol were observed for the pulegone derivatives used (see, for example, entry 2 vs entry 5, Table 3),[29] compound **6m** (entry 2, Table 3) being the best result, for which a 4:1 α/β ratio was attained.

(28) Philip, D.; Stoddart, J. F. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1154−1196.

(29) For related non-fluorinated systems, see: Potin, D.; Dumas, F.; d'Angelo, J. *J. Am. Chem. Soc.* **1990**, *112*, 3483−3486.

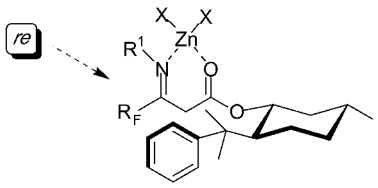
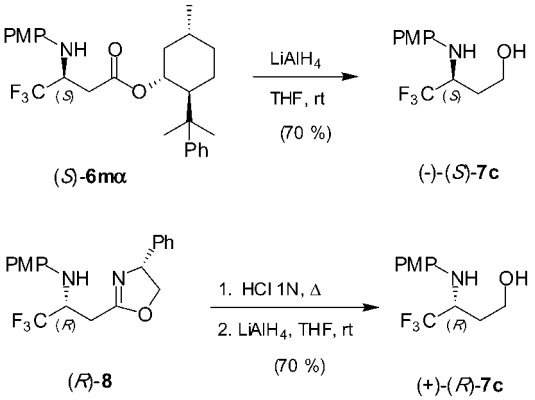
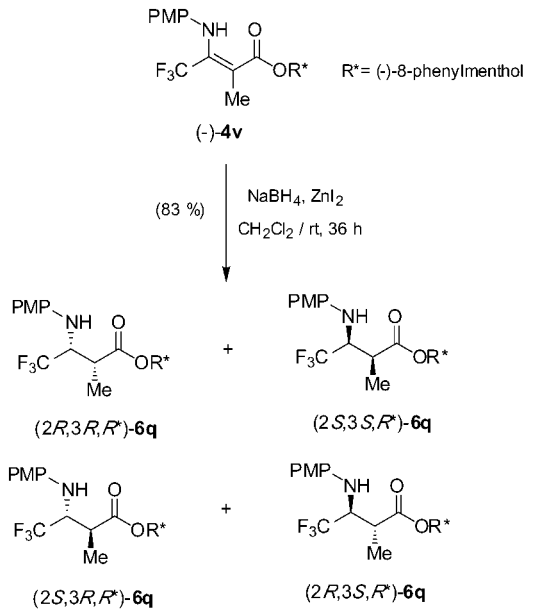


FIGURE 4.

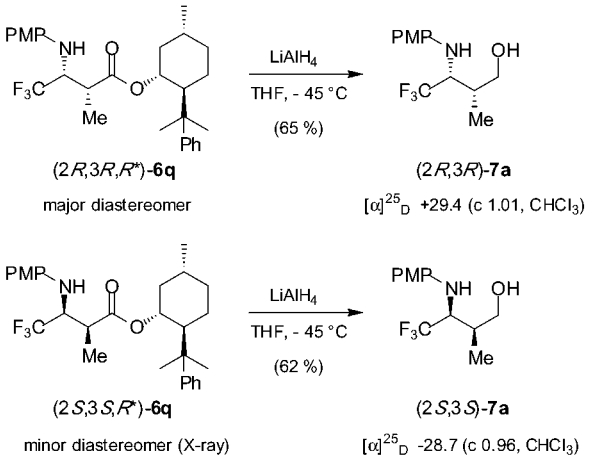
SCHEME 6



SCHEME 7



SCHEME 8



Isomers **6mα** and **6mβ** were isolated in the pure form as oily compounds by column chromatography on silica gel. Their structures were ascertained by NMR (^{1}H, ^{13}C, and ^{19}F) spectroscopy analysis and by HRMS. The absolute configuration of the newly created stereogenic center at C(3) for the major diastereomer was established as (*S*)-**6mα** through chemical correlation. This was made by comparison of the [α] absolute values of the γ-amino alcohol (−)-**7c** {[α]$^{25}_D$ −53.2 (*c* 1.03, $CHCl_3$)} obtained by LAH reduction from the major isomer **6mα** and the known compound (+)-**7c** {[α]$^{25}_D$ +52.4 (*c* 0.98, $CHCl_3$)}. Compound (+)-**7c** was alternatively prepared in two steps from the previously described[16] γ-fluorinated β-amino-D^2-oxazoline (*R*)-**8**, in which the absolute stereochemistry was ascertained by X-ray diffraction studies (Scheme 6). The absolute configuration of **6m** as 3*S* was extended to the rest of β-amino esters **6n**−**p** (Table 3).

The stereochemical outcome of the reduction of chiral β-enamino esters **4k**−**n** might be understood on the basis of a cyclic model similar to the one described above in which the hydride attack (*re*-face) is now conditioned by the presence of the 8-phenyl group of the chiral auxiliary (1,5-asymmetric induction), which effectively shields the *si*-face of the Zn(II)−**4** complex (Figure 4).

Finally, we examined the diastereoselective reduction of the α-methyl γ-fluorinated β-enaminoester (−)-**4v**. In this case, two new stereogenic centers are created at C(2) and C(3), so four diastereomers are possible (Scheme 7). The NMR analysis from the crude reduction mixture showed that only three compounds were detected in a ratio of 78/18/4. The syn diastereomers (2*R*,3*R*,*R**)-**6q** and (2*S*,3*S*,*R**)-**6q** (overall 96% of the crude reaction mixture) were isolated and purified by silica gel flash chromatography as white solids; however, only from the minor diastereomer were we able to obtain suitable crystals, and the X-ray diffraction analysis results revealed that this compound was (2*S*,3*S*,*R**)-**6q**.

To further confirm the absolute configuration of the major syn diastereomer, both isomers were separately converted into the known γ-amino alcohol **7a** (Scheme 8). Spectroscopic properties of the obtained product were identical with the racemic version described above (see Scheme 5), but the [α] value indicated that both are enantiomers. Therefore, the absolute configuration of the major syn diastereomer is (2*R*,3*R*,*R**)-**6q**.

In this case, the stereochemical outcome could be explained assuming the participation of two diastereomeric chelate models (Figure 5). Model A allowed us to explain the formation of the major (2*R*,3*R*,*R**)-**6q** diastereomer by hydride attack from the opposite side to the methyl group (*si*-face), whereas model B, which is by far less stable due to steric hindrance between the methyl and phenyl groups, provided the minor (2*S*,3*S*,*R**)-**6q** diastereomer (*re*-face hydride attack).

From the experimental results we concluded not only that model A was predominant but also that the R^3 group (R^3 = Me for **6q**) controls the hydride attack (1,2-asymmetric induction) more than the presence of the chiral auxiliary (1,5-asymmetric induction).

Parallel to this study, and for the sake of comparison, we explored an alternative one-step method for the

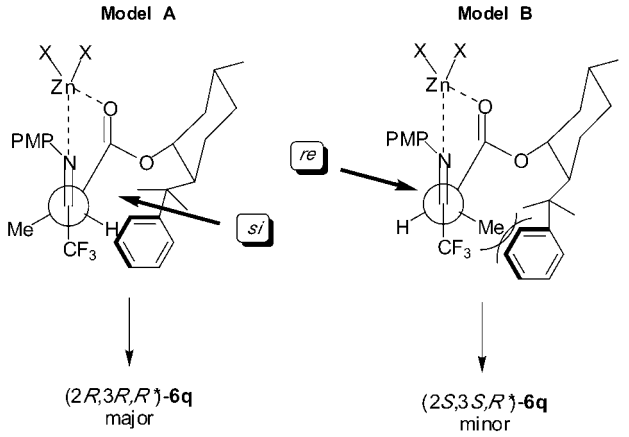
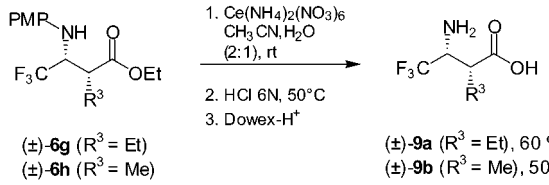


FIGURE 5.

SCHEME 9

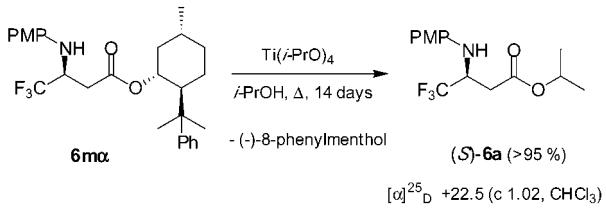


preparation of the title compounds **6**, consisting in the Mannich-like addition of lithium enolates of esters **2** to trifluoromethyl imines **8** (Table 4).[11] Two representative examples were used in this study, as it is shown in Table 4. Thus, treatment of imine **8** with lithium enolate of methyl propionate **2** (R^2, R^3 = Me) led to a racemic mixture of β-amino esters **6f** in low yield with moderate anti diastereoselectivity (de 28%) (entry 1, Table 4). On the other hand, the use of a chiral ester **2** [R^2 = (−)-8-phenylmenthyl; R^3 = H] did not provide much better results with regard to chemical yield and diastereoselectivity (entry 2, Table 4). Therefore, although the above-mentioned reaction represents an alternative to the reduction of β-enamino esters **4**, the greater effectiveness of the latter makes it the procedure of choice for the diastereoselective synthesis of fluorinated β-amino esters **6**.

Synthesis of γ-Fluorinated β-Amino Acids 9. Further conversion of **6** into β-amino acids **9** has been carried out using a standard two-step sequence (Scheme 9). For this purpose, selected examples were chosen. For racemic **6g** and **6h**, selective deprotection of the *p*-methoxyphenyl group was easily achieved with cerium ammonium nitrate (CAN) in CH_3CN-H_2O (2:1) at room temperature. The crude N-unprotected β-amino esters without isolation were then transformed into the desired β-amino acids **9** by acidic hydrolysis (6 N HCl) at 50 °C for 2 h. Isolation and purification of the free racemic β-amino acids **9** were achieved by means of ion-exchange chromatography (DOWEX-50, H^+ form).

Finally, removal of the chiral auxiliary was carried out by titanium(IV) isopropoxide-catalyzed transesterification to isopropyl esters.[30] Thus, treatment of **6m**α with

SCHEME 10



$Ti(i\text{-}PrO)_4$ in refluxing 2-propanol for 14 days cleanly gave the corresponding isopropyl β-amino ester (*S*)-(+)-**6a** in excellent yield (>95%) isolated as a yellowish solid; (−)-8-phenylmenthol was recovered by flash chromatography in ca. 91% yield (Scheme 10).

In summary, a new and effective method for the diastereoselective synthesis of γ-fluorinated β-amino acid derivatives **6** and **9** has been developed starting from imidoyl halides **1**, by means of chemical reduction. In general, the process works well and allows the preparation of enantiopure α-substituted and α-nonsubstituted β-fluoroalkyl β-amino esters **6** in a short, highly efficient way by using (−)-8-phenylmenthol as a chiral auxiliary. The use of ZnI_2 as a Lewis acid in a nonchelated aprotic medium (dry CH_2Cl_2) is the key step of the strategy to yield the desired products in a diastereoselective manner. A 1,2- more than a 1,5-asymmetric induction has been suggested to explain the stereochemical outcome of the reduction reaction in the case of chiral nonracemic α-substituted β-enamino esters **4**. Alternative and less efficient strategies have also been tested.

Experimental Section

General Methods. All reactions were run under an argon atmosphere. Solvents were dried and distilled using standard procedures before use. Chiral esters were prepared by conventional procedures.[20] Imidoyl chlorides **1**[18] and trifluoromethyl imines **8**[11a] were prepared according to the methods described in the literature. All other reagents were of the best commercial grade available and used without further purification. Thin-layer chromatography (TLC) was performed with UV active silica gel 60 F_{254}, and the plates were visualized with UV light and iodine. Flash column chromatography was carried out using silica gel 60 (0.040−0.063 mm). Melting points were uncorrected. All NMR spectra were recorded in $CDCl_3$ solution. ^1H and ^{13}C nuclei were determined using TMS (0 ppm) and the center line of the chloroform-*d* triplet (77.0 ppm) as the internal standard, respectively, while $CFCl_3$ (0 ppm) was used as the external standard for ^{19}F nuclei. *J* values are reported in hertz. Compositions of tautomeric and diasteromeric mixtures were established on the basis of ^{19}F NMR analysis. High-resolution mass spectra (HRMS) were obtained at 70 eV by electron impact. FAB mass spectra were obtained using Cs^+ as reagent ions with a *m*-nitrobenzyl alcohol (NOBA) matrix.

General Procedure for the Synthesis of β-Fluoroalkyl β-Enamino Esters 4. To a stirred solution of diisopropylamine (2.24 mL, 16.8 mmol) in THF (10 mL) at −30 °C was added *n*-butyllithium (2.5 M in hexane, 6.4 mL, 16.0 mmol) dropwise. After the reaction mixture was stirred for 30 min, the solution was cooled to −50 °C and alkyl ester **2** (0.91 mL, 8.0 mmol) in THF (10 mL) was added dropwise. The resulting mixture was stirred at −50 °C for 1.5 h and cooled to −78 °C. A solution of the corresponding imidoyl chloride **1** (8.0 mmol) in THF (10 mL) was then slowly added. The reaction mixture was monitored by TLC analysis, and after the total disappearance of the starting material (TLC), the solvents were removed under reduced pressure. The reaction was quenched with saturated

(30) Sarakinos, G.; Corey, E. J. J. *Org. Lett.* **1999**, *1*, 1741−1744 and references cited therein. See also: Seebach, D.; Hungerbüler, E.; Naef, R.; Schnurrenberger, P.; Widmann, B.; Züger, M. *Synthesis* **1982**, 138−141.

ammonium chloride solution, and the mixture was extracted with methylene chloride (2 × 25 mL). The combined organic layers were dried over anhydrous sodium sulfate. Filtration and evaporation of the solvent furnished the crude products **4**, which were purified by flash silica gel column chromatography as indicated for each example.

Isopropyl 4,4,4-Trifluoro-3-(4-methoxyanilino)-2-butenoate (4a). Flash chromatography [*n*-hexane/EtOAc (5:1)] on silica gel gave a yellow oil (85%). (*Z*)-Enamino tautomer: ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.20 (d, J = 6.2 Hz, 6H), 3.70 (s, 3H), 4.94−5.04 (m, 1H), 5.17 (s, 1H), 6.75 (d, J = 8.5 Hz, 2H), 7.0 (d, J = 8.7 Hz, 2H), 9.58 (brs, 1H); ^{13}C NMR (62.8 MHz, $CDCl_3$) δ 21.8 (q), 55.2 (q), 67.2 (d), 87.5 (q, $^3J_{CF}$ = 5.6 Hz), 113.8 (d), 120.4 (q, $^1J_{CF}$ = 277.0 Hz), 128.1 (d), 130.8 (s), 147.6 (q, $^2J_{CF}$ = 30.5), 158.3 (s), 169.3 (s); ^{19}F NMR (235 MHz, $CDCl_3$) δ −64.0 (s, 3F); HRMS calcd for $C_{14}H_{16}F_3NO_3$ 303.1089, found 303.1089. Anal. Calcd for $C_{14}H_{16}F_3NO_3$: C, 55.52; H, 5.28; N, 4.62. Found: C, 55.61; H, 5.31; N, 4.59.

Isopropyl 4-Chloro-4,4-difluoro-3-(4-methoxyanilino)-2-butenoate (4c). Flash chromatography [*n*-hexane/EtOAc (12:1)] on silica gel gave a yellow solid (64%): mp 60−62 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ ((*Z*)-enamino tautomer) 1.21 (d, J = 6.2 Hz, 6H), 3.73 (s, 3H), 5.00 (m, 1H), 5.17 (s, 1H), 6.72−7.19 (m, 4H), 9.64 (brs, 1H); (imino tautomer) 1.17 (d, J = 6.2 Hz, 6H), 3.42 (s, 2H), 3.72 (s, 3H), 4.95 (m, 1H), 6.62−7.19 (m, 4H); ^{13}C NMR (62.8 MHz, $CDCl_3$) δ ((*Z*)-enamino tautomer) 22.7 (q), 56.1 (q), 68.0 (d), 87.2 (q, $^3J_{CF}$ = 6.0 Hz), 114.5 (d), 122.8 (q, $^1J_{CF}$ = 243.4 Hz), 129.9 (d), 131.5 (s), 152.9 (q, $^2J_{CF}$ = 21.3 Hz), 159.2 (s), 170.2 (s); (imino tautomer) 22.3 (q), 35.2 (t), 56.1 (q), 70.5 (d), 114.7 (d), 121.4 (d), 122.3 (q, $^1J_{CF}$ = 231.2 Hz), 139.1 (s), 155.5 (q, $^2J_{CF}$ = 20.8 Hz), 158.6 (s), 166.9 (s); ^{19}F NMR (235 MHz, $CDCl_3$) δ ((*Z*)-enamino tautomer) −52.0 (s, 2F); (imino tautomer) −59.9 (s, 2F); HRMS calcd for $C_{14}H_{16}ClF_2NO_3$ 319.0786, found 319.0789.

3-[(*Z*)-2-Chloro-2,2-difluoro-1-(4-methoxyanilino)ethyledene]tetrahydro-2-furanone (4d). Flash chromatography [*n*-hexane/EtOAc (3:1)] on silica gel gave a yellow solid (82%): mp 59−61 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 3.07 (m, 2H), 3.73 (s, 3H), 4.34 (t, J = 7.4 Hz, 2H), 6.70 (d, J = 8.9 Hz, 2H), 7.00 (d, J = 8.7 Hz, 2H), 9.40 (brs, 1H); ^{13}C NMR (62.8 MHz, $CDCl_3$) δ 26.5 (t, $^4J_{CF}$ = 4.7 Hz), 55.3 (q), 66.0 (t), 94.7 (s), 113.9 (d), 122.4 (t, $^1J_{CF}$ = 296.4 Hz), 127.5 (d), 131.9 (s), 147.5 (t, $^2J_{CF}$ = 26.2 Hz), 158.0 (s), 174.5 (s); ^{19}F NMR (235 MHz, $CDCl_3$) δ −50.2 (s, 2F); HRMS calcd for $C_{13}H_{12}F_2NO_3Cl$ 303.0477, found 303.0473. Anal. Calcd for $C_{13}H_{12}F_2NO_3Cl$: C, 51.40; H, 3.95; N, 4.61. Found: C, 51.45; H, 3.88; N, 4.60.

Isopropyl 4,4,5,5,5-Pentafluoro-3-(4-methoxyanilino)-2-pentenoate (4e). Flash chromatography [*n*-hexane/EtOAc (10:1)] on silica gel gave a yellow oil (100%): ^{1}H NMR (250 MHz, $CDCl_3$) δ ((*Z*)-enamino tautomer) 1.20 (d, J = 6.3 Hz, 6H), 3.71 (s, 3H), 4.91−5.03 (m, 1H), 5.20 (s, 1H), 6.70−7.01 (m, 4H), 9.49 (brs, 1H); (imino tautomer) 1.17 (d, J = 6.2 Hz, 6H), 3.39 (s, 2H), 3.73 (s, 3H), 4.91−5.03 (m, 1H), 6.70−7.01 (m, 4H); ^{13}C NMR (62.8 MHz, $CDCl_3$) δ ((*Z*)-enamino tautomer) 21.8 (q), 55.2 (q), 67.5 (d), 92.6 (q, $^3J_{CF}$ = 7.0 Hz), 111.2 (tq, $^1J_{CF}$ = 264.0 Hz, $^2J_{CF}$ = 38.8 Hz), 118.7 (qt, $^1J_{CF}$ = 281.6 Hz, $^2J_{CF}$ = 37.1 Hz), 113.7 (d), 127.8 (d), 131.8 (s), 146.3 (q, $^2J_{CF}$ = 26.8 Hz), 158.1 (s), 168.6 (s); (imino tautomer) 21.4 (q), 34.9 (t), 55.3 (q), 69.7 (d), 111.2 (tq, $^1J_{CF}$ = 264.0 Hz, $^2J_{CF}$ = 38.8 Hz), 114.3 (d), 118.7 (qt, $^1J_{CF}$ = 281.6 Hz, $^2J_{CF}$ = 37.1 Hz), 120.7 (d), 139.9 (s), 153.4 (q, $^2J_{CF}$ = 26.8 Hz), 157.9 (s), 166.0 (s); ^{19}F NMR (235 MHz, $CDCl_3$) δ ((*Z*)-enamino tautomer) −83.3 (s, 3F), −112.0 (s, 2F); (imino tautomer) −81.7 (s, 3F), −117.0 (s, 2F); HRMS calcd for $C_{15}H_{16}F_5NO_3$ 353.1050, found 353.1059.

(+)-Isopropyl (*Z*)-4,4,4-Trifluoro-3-[(1*S*)-1-phenylethylamino]-2-butenoate (4i). Flash chromatography [*n*-hexane/EtOAc (10:1)] on silica gel gave a yellow oil (65%): $[\alpha]^{25}_D$ +366.3 (*c* 1.08, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.18 (d, J = 6.2 Hz, 3H), 1.19 (d, J = 6.2 Hz, 3H), 1.46 (d, J = 6.7 Hz, 3H), 4.62−4.69 (m, 1H), 4.92−5.02 (m, 1H), 5.01 (s, 1H), 7.13−7.29 (m, 5H), 8.57 (brd, J = 9.1 Hz, 1H); ^{13}C NMR (62.8 MHz, $CDCl_3$) δ 21.9 (q), 24.9 (q), 53.8 (d), 67.0 (d), 85.9 (q, $^3J_{CF}$ = 5.5 Hz), 120.2 (q, $^1J_{CF}$ = 277.0 Hz), 125.3 (d), 127.2 (d), 128.6 (d), 143.9 (s), 147.5 (q, $^2J_{CF}$ = 31.3 Hz), 169.5 (s); ^{19}F NMR (235 MHz, $CDCl_3$) δ −66.4 (s, 3F); HRMS calcd for $C_{15}H_{18}F_3NO_2$ 301.1289, found 301.1287. Anal. Calcd for $C_{15}H_{18}F_3NO_2$: C, 59.80; H, 5.98; N, 4.65. Found: C, 59.93; H, 5.95; N, 4.61.

(+)-(2*S*,5*S*,1*R*)-5-Methyl-2-(1-methyl-1-phenylethyl)-cyclohexyl (*Z*)-4,4,4-Trifluoro-3-(4-methoxyanilino)-2-butenoate (4k). Flash chromatography [*n*-hexane/AcOEt (30:1)] on silica gel gave a yellow oil (72%): $[\alpha]^{25}_D$ +64.9 (*c* 1.04, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.76−1.99 (m, 17H), 3.83 (s, 3H), 4.62 (s, 1H), 4.85 (td, J_1 = 10.6 Hz, J_2 = 4.3 Hz, 1H), 6.84−7.33 (m, 9H), 9.61 (brs, 1H); ^{13}C NMR (62.8 MHz, $CDCl_3$) δ 21.8 (q), 25.3 (d), 26.5 (t), 27.4 (d), 31.3 (q), 34.5 (t), 39.6 (s), 41.8 (t), 50.6 (d), 55.3 (q), 73.9 (d), 88.1 (q, $^3J_{CF}$ = 5.3 Hz), 113.9 (d), 120.1 (q, $^1J_{CF}$ = 277.1 Hz), 125.3 (d), 125.1 (d), 127.8 (d), 127.9 (d), 130.9 (s), 147.0 (q, $^2J_{CF}$ = 30.6 Hz), 151.3 (s), 158.2 (s), 168.7 (s); ^{19}F NMR (235 MHz, $CDCl_3$) δ −63.9 (s, 3F), −72.7 (s, 3F); HRMS calcd for $C_{27}H_{32}F_3NO_3$ 475.2334, found 475.2342. Anal. Calcd for $C_{27}H_{32}F_3NO_3$: C, 68.21; H, 6.73; N, 2.94. Found: C, 68.30; H, 6.70; N, 2.92.

(+)-(2*S*,5*S*,1*R*)-2-(1-(4-Iodophenyl)-1-methylethyl)-5-methylcyclohexyl (*Z*)-4,4,4-Trifluoro-3-(4-methoxyanilino)-2-butenoate (4l). Flash chromatography [*n*-hexane/AcOEt (30:1)] on silica gel gave a yellow oil (69%): $[\alpha]^{25}_D$ +103.4 (*c* 0.96, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.74−2.07 (m, 17H), 3.69 (s, 3H), 4.49 (s, 1H), 4.70 (dt, J_1 = 10.6 Hz, J_2 = 4.1 Hz, 1H), 6.76 (d, J = 10.0 Hz, 2H), 6.95 (d, J = 11.1 Hz, 2H), 7.03 (d, J = 8.8 Hz, 2H), 7.50 (d, J = 10.9 Hz, 2H), 9.50 (brs, 1H); ^{13}C NMR (62.8 MHz, $CDCl_3$) δ 21.7 (q), 23.8 (d), 26.4 (t), 31.2 (q), 33.8 (t), 39.2 (s), 41.7 (t), 50.6 (d), 55.3 (q), 73.8 (d), 87.5 (q, $^3J_{CF}$ = 5.2 Hz), 90.5 (s), 113.9 (d), 120.0 (q, $^1J_{CF}$ = 277.2 Hz), 127.4 (s), 127.6 (d), 128.0 (d), 130.8 (s), 136.8 (d), 147.3 (q, $^2J_{CF}$ = 30.7 Hz), 151.3 (s), 158.2 (s), 168.6 (s); ^{19}F NMR (235 MHz, $CDCl_3$) δ −33.7 (s, 3F), −72.7 (s, 3F); HRMS calcd for $C_{27}H_{31}F_3NO_3I$ 601.1300, found 601.1303.

(+)-(2*S*,5*S*,1*R*)-5-Methyl-2-(1-methyl-1-phenylethyl)-cyclohexyl(*Z*)-4-chloro-4,4-difluoro-3-(4-methoxyanilino)-2-butenoate (4m). Flash chromatography [*n*-hexane/AcOEt (30:1)] on silica gel gave a yellow oil (70%): $[\alpha]^{25}_D$ +29.9 (*c* 1.06, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.89 (d, J = 6.2 Hz, 3H), 1.27 (s, 3H), 1.61 (s, 3H), 0.91−2.06 (m, 8H), 2.75 (d, J = 16.3 Hz, 1H), 2.83 (d, J = 16.7 Hz, 1H), 3.82 (s, 3H), 4.57 (s, 3H), 4.82 (td, J_1 = 10.3 Hz, J_2 = 4.1 Hz, 1H), 6.85 (d, J = 8.8 Hz, 2H), 7.17 (d, J = 8.2 Hz, 2H), 7.29−7.31 (m, 5H), 9.58 (brs, 1H); ^{13}C NMR (62.8 MHz, $CDCl_3$) δ ((*Z*)-enamino tautomer) 21.7 (q), 25.5 (d), 26.5 (t), 27.5 (d), 31.1 (q), 35.5 (t), 39.6 (s), 41.8 (t), 50.6 (d), 55.3 (q), 73.9 (d), 86.9 (q, $^3J_{CF}$ = 7.0 Hz), 113.6 (d), 114.2 (d), 118.0 (q, $^1J_{CF}$ = 291.8 Hz), 125.3 (d), 127.8 (d), 127.9 (d), 130.8 (s), 151.3 (s), 151.4 (q, $^2J_{CF}$ = 25.1 Hz), 158.2 (s), 168.8 (s); (imino tautomer) 21.7 (q), 23.0 (d), 26.1 (t), 29.1 (d), 31.3 (q), 33.6 (t), 34.3 (t), 39.6 (s), 41.1 (t), 50.0 (d), 55.3 (q), 75.7 (d), 118.0 (q, $^1J_{CF}$ = 291.8 Hz), 120.4 (d), 123.1 (d), 125.0 (d), 125.1 (d), 128.9 (d), 139.9 (s), 151.6 (s), 155.4 (q, $^2J_{CF}$ = 27.9 Hz), 157.6 (s), 166.3 (s); ^{19}F NMR (235 MHz, $CDCl_3$) δ ((*Z*)-enamino tautomer) −51.5 (d, J = 167.8 Hz, 1F), −52.4 (d, J = 167.8 Hz, 1F); (imino tautomer) −60.4 (s, 2F); HRMS calcd for $C_{27}H_{32}F_2NO_3Cl$ 491.2038, found 491.2040. Anal. Calcd for $C_{27}H_{32}F_2NO_3Cl$: C, 65.98; H, 6.51; N, 2.85. Found: C, 65.95; H, 6.62; N, 2.92.

Methyl (*Z*)-4,4,4-Trifluoro-3-(4-methoxyanilino)-2-methyl-2-butenoate (4o). Flash chromatography [*n*-hexane/EtOAc (15:1)] on silica gel gave a yellow oil (92%): ^{1}H NMR (250 MHz, $CDCl_3$) δ ((*Z*)-enamino tautomer) 1.91 (q, $^5J_{HF}$ = 1.2 Hz, 3H), 3.63 (s, 3H), 3.58 (s, 3H), 6.71 (d, J = 8.9 Hz, 2H), 6.79 (d, J = 8.9 Hz, 2H), 9.32 (brs, 1H); (imino tautomer) 1.30 (d, J = 7.0 Hz, 3H), 3.63 (s, 3H), 3.68 (s, 3H), 3.78 (q, J = 7.3 Hz, 1H), 6.60 (d, J = 8.9 Hz, 2H), 6.79 (d, J = 8.9 Hz, 2H); ^{13}C NMR (62.8 MHz, $CDCl_3$) δ ((*Z*)-enamino tautomer) 12.9 (q), 51.9 (q), 55.3 (q), 88.9 (q, $^3J_{CF}$ = 5.7 Hz), 114.1 (d), 120.4 (q, $^1J_{CF}$ = 277.0 Hz), 126.7 (d), 127.8 (s), 135.3 (d), 156.5 (q, $^2J_{CF}$ = 24.7 Hz), 169.8 (s); (imino tautomer) 13.2 (q), 39.3 (d), 52.7

(q), 55.3 (q), 114.4 (d), 119.9 (q, $^1J_{CF}$ = 278.2 Hz), 119.9 (d), 139.8 (d), 157.4 (s), 157.6 (q, $^2J_{CF}$ = 24,7 Hz), 169.8 (s); ^{19}F NMR (235 MHz, $CDCl_3$) δ ((*Z*)-enamino tautomer) −58.6 (s, 3F); (imino tautomer) −68.1 (s, 3F); HRMS calcd for $C_{13}H_{14}F_3NO_3$ 289.0925, found 289.0915. Anal. Calcd for $C_{13}H_{14}F_3NO_3$: C, 53.97; H, 4.84; N, 4.84. Found: C, 54.01; H, 4.79; N, 4.80.

Ethyl (*Z*)-4,4,4-Trifluoro-3-(4-methoxyanilino)-2-ethyl-2-butenoate (4p). Flash chromatography [*n*-hexane/EtOAc (10:1)] on silica gel gave a yellow oil (80%): ^{1}H NMR (250 MHz, $CDCl_3$) δ ((*Z*)-enamino tautomer) 0.97 (t, *J* = 7.2 Hz, 3H), 1.21 (t, *J* = 7.1 Hz, 3H), 2.38 (q, *J* = 3.9 Hz, 2H), 3.67 (s, 3H), 4.11 (q, *J* = 7.0 Hz, 2H), 6.74 (d, *J* = 5.6 Hz, 2H), 6.80 (d, *J* = 5.6 Hz, 2H), 9.24 (brs, 1H); (imino tautomer) 0.97 (t, *J* = 7.2 Hz, 3H), 1.20 (t, *J* = 7.1 Hz, 3H), 1.70 (m, 1H), 1.95 (m, 1H), 3.62 (m, 1H), 3.71 (s, 3H), 4.11 (q, *J* = 7.0 Hz, 2H), 6.74 (d, *J* = 5.6 Hz, 2H), 6.80 (d, *J* = 5.6 Hz, 2H); ^{13}C NMR (62.8 MHz, $CDCl_3$) δ ((*Z*)-enamino tautomer) 14.1 (q), 14.5 (q), 20.9 (t), 55.5 (q), 60.8 (t), 77.2 (s), 114.5 (d), 120.0 (q, $^1J_{CF}$ = 269.6 Hz), 123.1 (d), 135.5 (s), 142.1 (q, $^2J_{CF}$ = 30.5 Hz), 157.3 (s), 169.8 (s); (imino tautomer) 11.7 (q), 13.9 (q), 20.8 (t), 47.0 (d), 55.4 (q), 61.7 (t), 114.4 (d), 119.9 (d), 120.0 (q, $^1J_{CF}$ = 269.6 Hz), 140.1 (s), 156.4 (s), 157.1 (q, $^2J_{CF}$ = 31.4 Hz), 168.8 (s); ^{19}F NMR (235 MHz, $CDCl_3$) δ ((*Z*)-enamino tautomer) −58.0 (s, 3F); (imino tautomer) −68.2 (s, 3F); HRMS calcd for $C_{15}H_{18}F_3NO_3$ 317.1238, found 317.1237.

Methyl (*Z*)-4-Chloro-4,4-difluoro-3-(4-methoxyanilino)-2-methyl-2-butenoate (4s). Flash chromatography [*n*-hexane/EtOAc (8:1)] on silica gel gave a yellow oil (72%): ^{1}H NMR (400 MHz, $CDCl_3$) δ ((*Z*)-enamino tautomer) 2.01 (q, $^5J_{HF}$ = 2.5 Hz, 3H), 3.60 (s, 3H), 3.68 (s, 3H), 6.69 (d, *J* = 5.5 Hz, 2H), 6.82 (d, *J* = 6.5 Hz, 2H), 8.89 (brs, 1H); (imino tautomer) 1.36 (d, *J* = 7.5 Hz, 3H), 3.63 (s, 3H), 3.70 (s, 3H), 3.84 (q, *J* = 7.2 Hz, 1H), 6.69 (d, *J* = 5.5 Hz, 2H), 6.82 (d, *J* = 6.5 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ((*Z*)-enamino tautomer) 17.2 (q), 51.8 (q), 52.1 (q), 106.77 (s), 114.5 (d), 119.8 (d), 120.4 (t, $^1J_{CF}$ = 277.0 Hz), 139.2 (s), 146.7 (t, $^2J_{CF}$ = 24.1 Hz), 157.3 (s), 169.8 (s); (imino tautomer) 13.8 (q), 39.6 (d), 52.5 (q), 55.3 (q), 114.0 (d), 119.3 (d), 123.5 (t, $^1J_{CF}$ = 277.0 Hz), 134.2 (t, $^2J_{CF}$ = 24.1 Hz), 135.3 (s), 156.4 (s), 169.0 (s); ^{19}F NMR (376 MHz, $CDCl_3$) δ ((*Z*)-enamino tautomer) −48.7 (s, 2F); (imino tautomer) −55.7 (d, J_{FF} = 167.2 Hz, 1F), −56.9 (d, J_{FF} = 167.2 Hz, 1F); HRMS (FAB) calcd for (M^+ + 1) $C_{13}H_{15}ClF_2NO_3$ 306.0708, found 306.0696.

(−)-(2*S*,5*S*,1*R*)-5-Methyl-2-(1-methyl-1-phenylethyl)-cyclohexyl (*Z*)-4-Chloro-4,4-difluoro-3-(4-methoxyanilino)-2-methyl-2-butenoate (4u). Flash chromatography [*n*-hexane/EtOAc (30:1)] on silica gel gave a yellow oil (80%): $[\alpha]^{25}_D$ −113.9 (*c* 0.89, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ (imino tautomer) 0.66 (d, *J* = 7.3 Hz, 3H), 0.81 (d, *J* = 6.6 Hz, 3H), 1.06 (s, 3H), 1.14 (s, 3H), 0.83−1.92 (m, 7H), 1.98 (td, J_1 = 12.0 Hz, J_2 = 3.5 Hz, 1H), 3.15 (q, *J* = 7.3 Hz, 1H), 3.77, (s, 3H), 4.77 (td, J_1 = 10.7 Hz, J_2 = 4.5 Hz, 1H), 6.72 (d, *J* = 9.0 Hz, 2H), 6.84−6.86 (m, 2H), 6.91 (d, *J* = 8.8 Hz, 2H), 7.01−7.04 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (imino tautomer) 14.3 (q), 22.7 (q), 23.4 (d), 27.2 (t), 30.7 (q), 32.2 (q), 35.4 (t), 39.2 (s), 42.0 (d), 42.2 (t), 51.2 (d), 56.5 (q), 76.5 (d), 115.4 (d), 120.9 (d), 123.3 (t, $^1J_{CF}$ = 226.7 Hz), 125.9 (d), 126.0 (d), 128.8 (d), 140.5 (s), 152.0 (s), 157.4 (s), 161.6 (t, $^2J_{CF}$ = 26.2 Hz), 168.8 (s); ^{19}F NMR (282 MHz, $CDCl_3$) δ ((*Z*)-enamino tautomer) −48.7 (s, 2F); (imino tautomer) −55.2 (d, *J* = 166.7 Hz, 1F), −56.4 (d, *J* = 166.7 Hz, 1F); HRMS calcd for $C_{28}H_{34}F_2NO_3Cl$ 505.2197, found 505.2195.

(−)-(2*S*,5*S*,1*R*)-5-Methyl-2-(1-methyl-1-phenylethyl)-cyclohexyl (*Z*)-4,4,4-Trifluoro-3-(4-methoxyanilino)-2-methyl-2-butenoate (4v). Flash chromatography [*n*-hexane/EtOAc (30:1)] on silica gel gave a yellow oil ((*Z*)-enamino tautomer)/solid (imino tautomer) (85%): mp (imino tautomer) 122−123 °C; $[\alpha]^{25}_D$ −165.5 (*c* 1.03, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ ((*Z*)-enamino tautomer) 0.79 (d, *J* = 6.3 Hz, 3H), 0.82−1.97 (m, 14H), 1.39 (q, $^4J_{FH}$ = 6.3 Hz, 3H), 3.72, (s, 3H), 4.87 (td, J_1 = 10.7 Hz, J_2 = 4.3 Hz, 1H), 6.76 (d, *J* = 9.2 Hz, 2H), 6.83 (d, *J* = 9.0 Hz, 2H), 7.07−7.19 (m, 5H), 9.29 (brs, 1H); (imino tautomer) 0.65 (d, *J* = 7.3 Hz, 3H), 0.78−2.03 (m, 17H), 3.14 (q, *J* = 7.3 Hz, 1H), 3.75, (s, 3H), 4.77 (td, J_1 = 10.7 Hz, J_2 = 4.3 Hz, 1H), 6.74 (d, *J* = 8.8 Hz, 2H), 6.92 (d, *J* = 8.8 Hz, 2H), 6.85−7.19 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ((*Z*)-enamino tautomer) 13.5 (q), 24.9 (q), 26.0 (d), 26.5 (t), 29.5 (q), 31.3 (q), 34.2 (t), 39.6 (s), 39.9 (d), 41.8 (t), 55.4 (q), 74.6 (d), 75.9 (d), 114.2 (d), 120.3 (d), 123.1 (q, $^1J_{CF}$ = 297.0 Hz), 125.1 (d), 128.0 (d), 138.1 (s), 151.8 (s), 157.5 (s), 158.2 (q, $^2J_{CF}$ = 31.9 Hz), 168.8 (s); (imino tautomer) 12.6 (q), 21.6 (q), 22.6 (d), 26.2 (t), 29.5 (q), 31.2 (q), 34.4 (t), 39.2 (s), 40.5 (d), 41.2 (t), 50.2 (d), 55.4 (q), 75.6 (d), 114.4 (d), 119.9 (d), 123.1 (q, $^1J_{CF}$ = 297.0 Hz), 124.9 (d), 127.7 (d), 140.4 (s), 151.9 (s), 157.5 (s), 158.2 (q, $^2J_{CF}$ = 31.9 Hz), 168.7 (s); ^{19}F NMR (235 MHz, $CDCl_3$) δ ((*Z*)-enamino tautomer) −59.0 (s, 3F); (imino tautomer) −67.9 (s, 3F). HRMS calcd for $C_{28}H_{34}F_3NO_3$ 489.2490, found 489.2491.

General Procedure for the Synthesis of β-Trifluoromethyl β-Enamino Amides 5. To a stirred solution of LDA (12.6 mmol) in THF (10 mL) at −60 °C was added dropwise a solution of the corresponding amide (6.3 mmol) in THF (10 mL), and the resulting mixture was stirred for 2 h. The temperature of the reaction was brought to −78 °C prior to the additon of a solution of imidoyl chloride **1a** (1.5 g, 6.3 mmol) in THF (15 mL). After the total disappearance of the starting materials (TLC), the reaction was quenched with saturated NH_4Cl (1 mL) and the solvent was removed under reduced pressure. The residue was dissolved in dichloromethane and washed with brine. The organics were dried with $MgSO_4$, filtered, and concentrated to furnish the crude products. Column chromatography on silica gel (prewashed with a 2% solution of Et_3N in *n*-hexanes) gave the pure enamino amides **5**.

(+)-(*Z*)-[(4*S*)-4-Benzyl-2-oxo-1,3-oxazolan-3-ilo]-4,4,4-trifluoro-3-(4-methoxyanilino)-2-buten-1-ona (5a). Flash chromatography [*n*-hexane/EtOAc (3:1)] on silica gel gave a yellow oil (94%): $[\alpha]^{25}_D$ +60.2 (*c* 1.36, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.73 (dd, J_1 = 13.3 Hz, J_2 = 9.7 Hz, 1H), 3.31 (dd, J_1 = 13.3 Hz, J_2 = 3.2 Hz, 1H), 3.75 (s, 3H), 4.08−4.13 (m, 2H), 4.65−4.70 (m, 1H), 6.76−7.30 (m, 10H), 10.68 (brs, 1H); ^{13}C NMR (62.8 MHz, $CDCl_3$) δ 38.0 (t), 55.0 (d), 55.3 (q), 65.7 (t), 85.6 (q, $^3J_{CF}$ = 5.5 Hz), 113.9 (d), 119.9 (q, $^1J_{CF}$ = 277.6 Hz), 127.2 (d), 128.0 (d), 128.8 (d), 129.3 (d), 130.0 (s), 135.3 (s), 149.6 (q, $^2J_{CF}$ = 30.7 Hz), 153.0 (s), 158.5 (s), 167.2 (s); ^{19}F NMR (235 MHz, $CDCl_3$) δ −63.5 (s, 3F); HRMS calcd for $C_{21}H_{19}F_3N_2O_4$ 420.1295, found 420.1294.

(+)-(5*S*)-(4-Methoxybenzyl)-5-(4-methoxybenzyloxymethyl)-3-[(*Z*)-2,2,2-trifluoro-1-(4-methoxyanilino)etiliden]-azolan-2-ona (5c). Recrystallization [*n*-hexane/EtOH (50:1)] gave a white solid (82%): mp 85−86 °C; $[\alpha]^{25}_D$ +261.4 (*c* 1.08, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.58−2.69 (m, 1H), 2.80−2.93 (m, 1H), 3,36 (dd, J_1 = 4.4 Hz, J_2 = 1.7 Hz, 2H), 3.65 (m, 1H), 3.71 (s, 6H), 3.73 (s, 3H), 4.04 (d, *J* = 14.7 Hz, 1H), 4.32 (s, 2H), 4.81 (d, *J* = 14.7 Hz, 1H), 6.71−7.17 (m, 12H), 9.42 (brs, 1H); ^{13}C NMR (62.8 MHz, $CDCl_3$) δ 26.8 (t), 44.3 (d), 54.3 (q), 55.1 (q), 55.2 (q), 70.6 (t), 72.6 (t), 108.0 (q, $^3J_{CF}$ = 1.7 Hz), 113.7 (d), 113.8 (d), 113.9 (d), 121.3 (q, $^1J_{CF}$ = 288.2 Hz), 124.8 (d), 128.5 (s), 129.3 (d), 129.4 (d), 129.6 (s), 134.8 (s), 137.2 (q, $^2J_{CF}$ = 31.8 Hz), 156.7 (s), 158.91 (s), 159.2 (s), 170.7 (s); ^{19}F NMR (235 MHz, $CDCl_3$) δ −61.1 (s, 3F); HRMS calcd for $C_{30}H_{31}N_2O_5F_3$ 556.2185, found 556.2185. Anal. Calcd for $C_{30}H_{31}F_3N_2O_5$: C, 64.69; H, 5.57; N, 5.03. Found: C, 64.72; H, 5.55; N, 4.89.

General Procedure for the Synthesis of γ-Fluorinated β-Amino Esters (6). To a solution of anhydrous zinc iodide (1.91 g, 6.0 mmol) in dry CH_2Cl_2 (20 mL) at 0 °C were added the corresponding β-fluoroalkyl β-amino esters **4** (2.0 mmol). The resulting mixture was stirred at the same temperature for 1 h after which $NaBH_4$ (0.375 g, 10 mmol) was added, also at 0 °C. The solution was allowed to reach room temperature and then monitored by means of TLC. The reaction was then quenched with saturated ammonium chloride solution, and the reaction mixture was extracted with dichloromethane (3 × 20 mL). The organic layers were combined, washed with brine,

and dried over sodium sulfate. After filtration, the solvents were removed under reduced pressure to provide the crude reaction mixture consisting of **6** and/or **7**. Purification was carried out as indicated in each example.

(±)-Isopropyl 4,4,4-Trifluoro-3-(4-methoxyanilino)-butanoate (6a). Flash chromatography [*n*-hexane/EtOAc (10:1)] on silica gel gave a white solid (70%): mp 76−78 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.06 (d, J = 6.2 Hz, 3H), 1.12 (d, J = 6.2 Hz, 3H), 2.48 (dd, J_1 = 15.4 Hz, J_2 = 9.0 Hz, 1H), 2.70 (dd, J_1 = 15.4 Hz, J_2 = 4.4 Hz, 1H), 3.37 (brd, J = 10.0 Hz, 1H), 3.66 (s, 3H), 4.22−4.32 (m, 1H), 4.87−4.97 (m, 1H), 6.61 (d, J = 9.1 Hz, 2H), 6.70 (d, J = 9.0 Hz, 2H); ^{13}C NMR (62.8 MHz, $CDCl_3$) δ 21.5 (q), 21.6 (q), 35.3 (t), 54.7 (q, $^2J_{CF}$ = 29.7 Hz), 55.6 (q), 68.9 (d), 114.7 (d), 115.7 (d), 125.6 (q, $^1J_{CF}$ = 282.9 Hz), 139.7 (s), 153.3 (s), 169.0 (s); ^{19}F NMR (235 MHz, $CDCl_3$) δ −76.3 (d, J = 7.1 Hz, 3F); HRMS calcd for $C_{14}H_{18}F_3NO_3$ 305.1238, found 305.1250. Anal. Calcd for $C_{14}H_{18}F_3NO_3$: C, 55.34; H, 5.92; N, 4.50. Found: C, 55.28; H, 5.81; N, 4.43.

(+)-(3*S*)-Isopropyl 4,4,4-Trifluoro-3-(4-methoxyanilino)-butanoate ((*S*)-6a). Obtained from **6m**α by transesterification with *i*-PrOH following the procedure described in the literature.[30] Flash chromatography [*n*-hexane/EtOAc (10:1)] on silica gel gave a white solid (99%): $[\alpha]^{25}_D$ +22.5 (*c* 1.02, $CHCl_3$); mp 77−78 °C. Spectroscopic data (^{1}H, ^{13}C, ^{19}F NMR) and HRMS are identical to those of (±)-**6a**.

(±)-Isopropyl 4,4,5,5,5-Pentafluoro-3-(4-methoxyanilino)-pentanoate (6c). Flash chromatography [*n*-hexane/EtOAc (10:1)] on silica gel gave a yellow oil (98%): ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.05 (d, J = 6.2 Hz, 3H), 1.11 (d, J = 6.2 Hz, 3H), 2.52 (dd, J_1 = 15.4 Hz, J_2 = 8.3 Hz, 1H), 2.75 (dd, J_1 = 15.3 Hz, J_2 = 4.7 Hz, 1H), 3.50 (brd, J = 10.8 Hz, 1H), 3.67 (s, 3H), 4.45 (m, 1H), 4.89 (m, 1H), 6.62 (d, J = 9.0 Hz, 2H), 6.72 (d, J = 8.9 Hz, 2H); ^{13}C NMR (62.8 MHz, $CDCl_3$) δ 21.5 (q), 34.7 (t), 53.1 (q, $^2J_{CF}$ = 21.1 Hz), 55.5 (q), 68.9 (d), 114.7 (d), 115.5 (d), 110.0−123.0 (signals of the group C_2F_5 are obscured due to their low intensity) 139.2 (s), 154.1 (s), 168.1 (s); ^{19}F NMR (235 MHz, $CDCl_3$) δ −81.6 (s, 3F), −119.5 (dd, J_{FF} = 274.2 Hz, J_{FH} = 7.0 Hz, 1F), −126.9 (dd, J_{FF} = 274.0 Hz, J_{FH} = 17.8 Hz, 1F); HRMS calcd for $C_{15}H_{18}F_5NO_3$ 355.1206, found 355.1201.

Isopropyl 4,4,4-Trifluoro-3-[(1*S*)-1-phenylethylamino]-butanoate (6e). Pale yellow oil, obtained as a mixture of diastereomers that were not separated. Data were taken from the crude diastereomeric mixture (de 10%): yield 50%; ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.14 (d, J = 6.2 Hz, 3H), 1.17−1.21 (d, 3 × 3H), 1.25 (d, J = 6.2 Hz, 3H), 1.28 (d, J = 6.2 Hz, 3H), 1.58 (brs, 2 × 1H), 2.21−2.63 (m, 2 × 2H), 3.35 (m, 1H), 3.48 (m, 1H), 3.94−4.03 (m, 2 × 1H), 4.86−5.01 (m, 2 × 1H), 7.15−7.29 (m, 2 × 5H); ^{19}F NMR (235 MHz, $CDCl_3$) δ −74.4 (d, J = 7.1 Hz, 3F), −75.5 (d, J = 7.1 Hz, 3F).

(±)-Methyl 4,4,4-Trifluoro-3-(4-methoxyanilino)-2-methylbutanoate (6f): (2*R,3*R**)-6f.** Flash chromatography [*n*-hexane/EtOAc (7:1)] on silica gel gave a yellow solid (90%): mp 64−66 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.23 (d, J = 7.1 Hz, 3H), 2.88 (m, 1H), 3.45 (brd, J = 11.1 Hz, 1H), 3.58 (s, 3H), 3.67 (s, 3H), 4.31−4.41 (m, 1H), 6.63 (d, J = 8.8 Hz, 2H), 6.70 (d, J = 9.0 Hz, 2H); ^{13}C NMR (62.8 MHz, $CDCl_3$) δ 11.5 (q), 39.6 (d), 52.2 (q), 55.6 (q), 58.4 (q, $^2J_{CF}$ = 28.1 Hz), 114.7 (d), 115.8 (d), 122.3 (q, $^1J_{CF}$ = 282.5 Hz), 139.9 (s), 153.3 (s), 173.2 (s); ^{19}F NMR (235 MHz, $CDCl_3$) δ −73.4 (d, J = 7.3 Hz, 3F); HRMS calcd for $C_{13}H_{16}F_3NO_3$ 291.1081, found 291.1079. Anal. Calcd for $C_{13}H_{16}F_3NO_3$: C, 53.61; H, 5.54; N, 4.81. Found: C, 53.66; H, 5.52; N, 4.80. **(2*S**,3*R**)-6f**. Obtained and purified from the crude mixture in the reduction reaction of **4o** with $NaBH_3CN$ (entry 8, Table 2). Flash chromatography [*n*-hexane/EtOAc (7:1)] on silica gel gave a yellow oil (17%): ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.22 (d, J = 7.1 Hz, 3H), 2.87−2.96 (m, 1H), 3.63 (s, 3H), 3.66 (s, 3H), 3.84−3.92 (m, 1H), 4.37 (brd, J = 9.8 Hz, 1H), 6.59 (d, J = 9.0 Hz, 2H), 6.72 (d, J = 9.8 Hz, 2H); ^{13}C NMR (62.8 MHz, $CDCl_3$) δ 14.7 (q), 38.7 (d), 52.1 (q), 55.6 (q), 59.6 (q, $^2J_{CF}$ = 28.9 Hz), 114.8 (d), 114.9 (d), 125.5 (q, $^1J_{CF}$ = 282.5 Hz), 140.5 (s), 152.9 (s), 174.2 (s); ^{19}F NMR (235 MHz, $CDCl_3$) δ −73.8 (d, J = 7.3 Hz, 3F). HRMS calcd for $C_{13}H_{16}F_3NO_3$ 291.1082, found 291.1087.

(±)-Ethyl (2*R,3*R**)-2-Ethyl-4,4,4-trifluoro-3-(4-methoxyanilino)-butanoate (6g).** Flash chromatography [*n*-hexane/EtOAc (10:1)] on silica gel gave a yellow oil (94%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.85 (t, J = 5.6 Hz, 3H), 1.16 (t, J = 5.2 Hz, 3H), 1.65 (m, 1H), 1.75 (m, 1H), 2.52−2.58 (m, 1H), 3.60 (brs, 1H), 3.66 (s, 3H), 4.08 (q, J = 7.0 Hz, 2H), 4.14 (m, 1H), 6.58 (d, J = 6.3 Hz, 2H), 6.70 (d, J = 6.7 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.5 (q), 14.0 (q), 21.4 (t), 47.6 (d), 55.6 (q), 58.4 (q, $^2J_{CF}$ = 28.9 Hz), 61.0 (t), 114.8 (d), 115.1 (d), 125.7 (q, $^1J_{CF}$ = 282.0 Hz), 140.2 (s), 153.1 (s), 172.4 (s); ^{19}F NMR (235 MHz, $CDCl_3$) δ −74.0 (d, J = 7.0 Hz, 3F); HRMS calcd for $C_{15}H_{20}F_3NO_3$ 319.1395, found 319.1399.

(±)-Methyl (2*R,3*R**)-4-Chloro-4,4-difluoro-3-(4-methoxyanilino)-2-methyl-butanoate (6j).** Flash chromatography [*n*-hexane/AcOEt (8:1)] on silica gel gave a yellow solid (98%): mp 43−45 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.22 (d, J = 7.0 Hz, 3H), 2.93−3.00 (m, 1H), 3.51 (brd, J = 11.0 Hz, 1H), 3.57 (s, 3H), 3.66 (s, 3H), 4.41−4.50 (m, 1H), 6.63 (d, J = 9.0 Hz, 2H), 6.70 (d, J = 9.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.9 (q), 40.5 (d), 55.2 (q), 55.6 (q), 63.5 (t, $^2J_{CF}$ = 24.1 Hz), 114.7 (d), 115.5 (d), 130.2 (t, $^1J_{CF}$ = 297.5 Hz), 140.1 (s), 153.2 (s), 173.5 (s); ^{19}F NMR (376 MHz, $CDCl_3$) δ −59.6 (dd, J_{FF} = 168.4 Hz, J_{FH} = 9.1 Hz, 1F), −58.0 (dd, J_{FF} = 163.8 Hz, J_{FH} = 9.1 Hz, 1F); HRMS calcd for $C_{13}H_{16}ClF_2NO_3$ 307.0786, found 307.0798. Anal. Calcd for $C_{13}H_{16}ClF_2NO_3$: C, 50.73; H, 5.20; N, 4.55. Found: C, 50.87; H, 5.14; N, 4.67.

(2*S*,5*S*,1*R*)-5-Methyl-2(1-methyl-1-phenylethyl)cyclohexyl 4,4,4-Trifluoro-3-(4-methoxyanilino)-butanoate (6m). Flash chromatography [*n*-hexane/AcOEt (50:1)] on silica gel gave a yellow oil (85%). **(3*S*,*R**)-6m (major diastereomer)**: $[\alpha]^{25}_D$ +18.8 (*c* 1.03, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.43 (q, J = 11.1 Hz, 1H), 0.65 (d, J = 6.6 Hz, 3H), 1.08 (s, 3H), 1.18 (s, 3H), 0.67−2.01 (m, 7H), 1.83 (dd, J_1 = 15.8 Hz, J_2 = 10.1 Hz, 1H), 2.01 (dd, J_1 = 15.6 Hz, J_2 = 4.1 Hz, 1H), 3.20 (brd, J = 6.4 Hz, 1H), 3.65 (m, 1H), 3.66 (s, 3H), 4.64 (td, J_1 =10.7 Hz, J_2 = 4.3 Hz, 1H), 6.47 (d, J = 9.0 Hz, 2H), 6.68 (d, J = 8.8 Hz, 2H), 7.04−7.23 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.5 (q), 21.3 (d), 25.0 (t), 28.8 (q), 30.0 (q), 33.3 (t), 34.2 (t), 38.2 (s), 39.8 (t), 48.9 (d), 52.9 (q, $^2J_{CF}$ = 29.7 Hz), 54.6 (q), 74.1 (d), 113.6 (d), 114.2 (d), 124.1 (d), 125.4 (q, $^1J_{CF}$ = 281.5 Hz), 126.8 (d), 138.9 (s), 151.1 (s), 152.0 (s), 167.3 (s); ^{19}F NMR (282 MHz, $CDCl_3$) δ −76.6 (d, J_{FH} = 6.1 Hz, 3F); HRMS calcd for $C_{27}H_{34}F_3NO_3$ 477.2490, found 477.2495. **(3*R*,*R**)-6m (minor diastereomer)**: $[\alpha]^{25}_D$ −21.1 (*c* 0.96, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.65−1.73 (m, 16H), 1.74 (dd, J_1 = 15.9 Hz, J_2 = 8.6 Hz, 1H), 1.97 (dd, J_1 = 15.8 Hz, J_2 = 4.3 Hz, 1H), 3.37 (brd, J = 6.8 Hz, 1H), 3.46 (td, J_1 = 9.9 Hz, J_2 = 3.9 Hz, 1H), 3.66 (s, 3H), 3.99 (s, 1H), 4.72 (td, J_1 =10.7 Hz, J_2 = 4.3 Hz, 1H), 6.55 (d, J = 8.8 Hz, 2H), 6.69 (d, J = 9.0 Hz, 2H), 7.02−7.20 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.6 (q), 23.1 (d), 26.2 (t), 29.2 (q), 31.1 (q), 34.3 (t), 41.3 (s), 45.3 (t), 50.1 (t), 54.1 (d), 54.7 (q, $^2J_{CF}$ = 30.8 Hz), 55.5 (q), 74.0 (d), 114.6 (d), 115.6 (d), 125.0 (d), 125.2 (d), 125.9 (q, $^1J_{CF}$ = 221.4 Hz), 127.4 (d), 139.8 (s), 151.7 (s), 153.2 (s), 169.0 (s); ^{19}F NMR (282 MHz, $CDCl_3$) δ −76.3 (d, J = 7.1 Hz, 3F); HRMS calcd for $C_{27}H_{34}F_3NO_3$ 477.2490, found 477.2495.

(2*S*,5*S*,1*R*)-5-Methyl-2(1-methyl-1-phenylethyl)cyclohexyl 4-Chloro-4,4-difluoro-3-(4-methoxyanilino)-butanoate (6n). Flash chromatography [*n*-hexane/AcOEt (50:1)] on silica gel gave a colorless oil (80%). **(3*S*,*R**)-6n (major diastereomer)**: $[\alpha]^{25}_D$ +3.2 (*c* 1.06, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.49 (q, J = 11.1 Hz, 1H), 0.74 (d, J = 6.4 Hz, 3H), 1.28 (s, 3H), 1.92 (s, 3H), 0.75−2.17 (m, 7H), 1.97 (dd, J_1 = 15.6 Hz, J_2 = 10.5 Hz, 1H), 2.20 (dd, J_1 = 15.4 Hz, J_2 = 3.7 Hz, 1H), 3.38 (brd, J = 6.4 Hz, 1H), 3.76 (s, 3H), 3.86 (m, 1H), 4.74 (td, J_1 =10.7 Hz, J_2 = 4.3 Hz, 1H), 6.60 (d, J = 9.0 Hz, 2H), 6.78 (d, J = 9.0 Hz, 2H), 7.18 (m, 1H), 7.30 (brs, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.5 (q), 22.4 (d), 26.0 (t), 29.8 (q), 30.9 (q), 34.3 (t), 36.3 (t), 39.2 (s), 40.7 (t), 49.9 (d), 55.5 (q), 59.0 (q, $^2J_{CF}$ = 25.1 Hz), 75.1 (d), 114.5 (d), 115.1 (d), 125.2

(d), 126.2 (d), 130.2 (q, $^1J_{CF}$ = 297.5 Hz), 139.8 (s), 152.0 (s), 153.0 (s), 168.3 (s); ^{19}F NMR (282 MHz, $CDCl_3$) δ −60.1 (dd, J_{FF} = 161.6 Hz, J_{FH} = 7.1 Hz 1F), −60.9 (dd, J_{FF} = 161.6 Hz, J_{FH} = 7.1 Hz 1F); HRMS calcd for $C_{27}H_{34}ClF_2NO_3$ 493.2195, found 493.2186.

(2*S*,5*S*,1*R*)-2[1-(4-Iodophenyl)-1-methylethyl]-5-methylcyclohexyl 4,4,4-Trifluoro-3-(4-methoxyanilino)-butanoate (6o). Flash chromatography [*n*-hexane/AcOEt (10:1)] on silica gel gave a yellow solid (75%). **(3*S*,*R**)-6o (major diastereomer)**: mp 38−40 °C; $[\alpha]^{25}_D$ +42.3 (*c* 0.08, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.56 (q, *J* = 11.8 Hz, 1H), 0.67 (d, *J* = 6.4 Hz, 3H), 1.06 (s, 3H), 1.15 (s, 3H), 0.70−1.84 (m, 7H), 1.90 (dd, J_1 = 15.7 Hz, J_2 = 9.1 Hz, 1H), 2.06 (dd, J_1 = 15.7 Hz, J_2 = 4.3 Hz, 1H), 3.26 (brd, *J* = 10.2 Hz, 1H), 3.67 (s, 3H), 4.64 (td, J_1 = 10.5 Hz, J_2 = 4.1 Hz, 2H), 6.53 (d, *J* = 8.8 Hz, 2H), 6.70 (d, *J* = 8.8 Hz, 2H), 6.95 (d, *J* = 8.5 Hz, 2H), 7.49 (d, *J* = 8.3 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.5 (q), 22.8 (d), 26.1 (t), 29.2 (q), 31.0 (q), 34.3 (t), 35.2 (t), 39.3 (s), 40.9 (t), 50.0 (d), 54.2 (q, $^2J_{CF}$ = 30.0 Hz), 55.6 (q), 75.1 (d), 90.1 (s), 114.7 (d), 115.4 (d), 127.6 (d), 125.4 (q, $^1J_{CF}$ = 281.5 Hz), 136.9 (d), 139.7 (s), 151.7 (s), 153.2 (s), 168.4 (s); ^{19}F NMR (235 MHz, $CDCl_3$) δ −76.4 (d, *J* = 7.0 Hz, 3F); HRMS calcd for $C_{27}H_{34}F_3INO_3$ 604.1535, found 604.1487.

(2*S*,5*S*,1*R*)-5-Methyl-2(1-methyl-1-phenylethyl)cyclohexyl 4,4,4-Trifluoro-3-(4-methoxyanilino)-2-methylbutanoate (6q). Flash chromatography [*n*-hexane/AcOEt (50:1)] on silica gel gave two white solids (83%). **(2*R*,3*R*,*R**)-6q (major diastereomer)**: mp 96−98 °C; $[\alpha]^{25}_D$ −30.4 (*c* 1.17, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.74 (d, *J* = 6.6 Hz, 3H), 0.76 (d, *J* = 7.1 Hz, 3H), 1.10 (s, 3H), 1.21 (s, 3H), 0.78−1.63 (m, 7H), 1.97 (td, J_1 = 10.7 Hz, J_2 = 4.8 Hz, 1H), 2.22 (qd, J_1 = 7.1 Hz, J_2 = 4.3 Hz, 1H), 3.37 (brd, *J* = 10.7 Hz, 1H), 3.64 (s, 3H), 4.30−4.38 (m, 1H), 4.74 (td, J_1 = 10.7 Hz, J_2 = 4.3 Hz, 1H), 6.66 (d, *J* = 9.2 Hz, 2H), 6.68 (d, *J* = 9.2 Hz, 2H), 7.04−7.10 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.0 (q), 21.6 (q), 24.3 (d), 26.4 (t), 28.2 (q), 31.1 (d), 34.4 (t), 39.2 (s), 41.2 (t), 50.0 (d), 55.3 (q), 57.3 (q, $^2J_{CF}$ = 27.8 Hz), 75.4 (d), 114.7 (d), 115.6 (d), 125.1 (d), 125.2 (d), 125.9 (q, $^1J_{CF}$ = 283.2 Hz), 127.9 (d), 140.2 (s), 151.6 (s), 153.1 (s), 172.2 (s); ^{19}F NMR (282 MHz, $CDCl_3$) δ −73.3 (d, *J* = 7.2 Hz, 3F); HRMS calcd for $C_{28}H_{36}F_3NO_3$ 491.2647, found 491.2663. Anal. Calcd for $C_{28}H_{36}F_3NO_3$: C, 68.43; H, 7.33; N, 2.85. Found: C, 68.31; H, 7.21; N, 2.76. **(2*S*,3*S*,*R**)-6q (minor diastereomer)**: mp 110−112 °C; $[\alpha]^{25}_D$ +9.4 (*c* 0.52, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.25 (q, *J* = 12.9 Hz, 1H), 0.59 (d, *J* = 6.4 Hz, 3H), 0.98 (d, *J* = 7.1 Hz, 3H), 1.08 (s, 3H), 1.18 (s, 3H), 0.96−1.17 (m, 6H), 1.50−1.57 (m, 1H), 1.72−178 (m, 1H), 1.88−1.97 (m, 2H), 3.65 (s, 3H), 4.61 (td, J_1 = 10.9 Hz, J_2 = 4.1 Hz, 1H), 6.44 (d, *J* = 8.8 Hz, 2H), 6.65 (d, *J* = 8.8 Hz, 2H), 7.05−7.23 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 9.5 (q), 21.5 (q), 22.4 (d), 26.1 (t), 29.8 (q), 30.9 (d), 34.4 (t), 38.8 (s), 40.5 (t), 50.1 (d), 55.6 (q), 57.1 (q, $^2J_{CF}$ = 28.3 Hz), 75.2 (d), 114.5 (d), 115.4 (d), 125.1 (d), 125.5 (q, $^1J_{CF}$ = 282.7 Hz), 127.8 (d), 140.0 (s), 152.1 (s), 153.1 (s), 171.3 (s); ^{19}F NMR (282 MHz, $CDCl_3$) δ −72.5 (d, *J* = 7.1 Hz, 3F); HRMS calcd for $C_{28}H_{36}F_3NO_3$ 491.2647, found 491.2663. Anal. Calcd for $C_{28}H_{36}F_3NO_3$: C, 68.43; H, 7.33; N, 2.85. Found: C, 68.41; H, 7.29; N, 2.89.

Crystal Data for (2*S*,3*S*,*R)-6q:** Colorless prism with dimensions 0.66 × 0.53 × 0.53 mm, orthorhombic, $P2_12_12_1$, *a* = 8.905(2), *b* = 10.655(2), *c* = 28.662(6) Å, *V* = 2719.5(10) Å^3, *Z* = 4, D_c = 1.201 g/cm^3, F(000) = 1048, 2θmax = 56°, Mo Kα (λ = 0.71073 Å), ω-scan, *T* = 293(2) K, 7553 reflections collected of which 6549 were independent (R_{int} = 0.024), direct primary solution and refinement on F^2 using the SHELX97 program,[31] 318 refined parameters, amino group hydrogen atom located in a difference Fourier synthesis and refined with restrained N−H bond lengths, other hydrogen atoms riding, $R_1[I > 2\sigma(I)]$ = 0.0519, R_2 (all data) = 0.1328, residual electron density 0.139 (−0.159) e/Å^3, absolute structure could not be determined.

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General Procedure for the Synthesis of γ-Fluorinated γ-Amino Alcohols 7. $LiAlH_4$ (69 mg, 1.8 mmol) was added to a solution of β-amino ester **6** (177 mg, 0.6 mmol) in THF (12 mL) at −50 °C. The resulting mixture was stirred for 2 h at room temperature under an argon atmosphere. The reaction was quenched with saturated ammonium chloride solution. A similar workup as described in the synthesis of β-fluoroalkyl-β-amino esters **6** yielded crude **7** as a solid.

(+)-(2*R*,3*R*)-4,4,4-Trifluoro-3-(4-methoxyanilino)-2-methylbutan-1-ol (7a). Obtained from (2*R*,3*R*,*R**)-**6q**. Flash chromatography [*n*-hexane/AcOEt (3:1)] on silica gel followed by recrystallization [*n*-hexane/$CHCl_3$ (5:1)] gave a white solid (65%): mp 120−121 °C; $[\alpha]^{25}_D$ +29.4 (*c* 1.01, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.90 (d, *J* = 7.0 Hz, 3H), 1.62 (brs, 1H), 2.19 (m, 1H), 3.44 (dd, J_1 = 15.3 Hz, J_2 = 10.5 Hz, 1H), 3.51 (dd, J_1 = 15.5 Hz, J_2 = 4.9 Hz, 1H), 3.66 (s, 3H), 4.19 (m, 1H), 6.64 (d, *J* = 9.2 Hz, 2H), 6.70 (d, *J* = 9.2 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 10.2 (q), 35.0 (d), 55.6 (q), 56.2 (q, $^2J_{CF}$ = 27.0), 64.5 (t), 114.8 (d), 115.4 (d), 126.6 (q, $^1J_{CF}$ = 283.3 Hz), 140.8 (s), 153.0 (s); ^{19}F NMR (282 MHz, $CDCl_3$) δ −72.6 (d, *J* = 7.2 Hz, 3F); HRMS calcd for $C_{12}H_{16}F_3NO_2$ 263.1133, found 263.1121. Anal. Calcd for $C_{12}H_{16}F_3NO_2$: C, 54.75; H, 6.13; N, 5.31. Found: C, 54.80; H, 6.16; N, 5.41.

(−)-(2*S*,3*S*)-4,4,4-Trifluoro-3-(4-methoxyanilino)-2-methylbutan-1-ol (7a). Obtained from (2*S*,3*S*,*R**)-**6q**. Flash chromatography [*n*-hexane/AcOEt (3:1)] on silica gel followed by recrystallization [*n*-hexane/$CHCl_3$(5:1)] gave a white solid (62%): mp 119−121 °C; $[\alpha]^{25}_D$ −28.7 (*c* 0.96, $CHCl_3$). Spectroscopic data (^{1}H, ^{13}C,^{19}F NMR) and HRMS are identical to those of (2*R*,3*R*)-**7a**.

Crystal Data for (±)-7a. Obtained from (2*R**,3*R**)-**6f**. Colorless lath with dimensions 0.73 × 0.20 × 0.08 mm, orthorhombic, $P2_12_12_1$, *a* = 5.404(1), *b* = 8.133(1), *c* = 30.115-(5) Å, *V* = 1323.6(4) Å^3, *Z* = 4, D_c = 1.321 g/cm^3, F(000) = 552, 2θmax = 50°, Mo Kα (λ = 0.71073 Å), ω-scan, *T* = 291(2) K, 3302 reflections collected of which 2342 were independent (R_{int} = 0.047), direct primary solution and refinement on F^2 using the SHELX97 program,[31] 173 refined parameters, amino and OH group hydrogen atoms located in a difference Fourier synthesis and refined with restrained N−H and O−H bond lengths, other hydrogen atoms riding, $R_1[I > 2\sigma(I)]$ = 0.0676, wR_2 (all data) = 0.1497, residual electron density 0.136 (−0.133) e/Å^3, absolute structure could not be determined.

(±)-(2*S,3*S**)-4,4,5,5,5-Pentafluoro-3-(4-methoxyanilino)-2-methyl Pentan-1-ol (7b).** Obtained by reduction of **4t** (entry 23, Table 2). Flash chromatography [*n*-hexane/AcOEt (5:1)] on silica gel gave a white solid (20%): mp 70−72 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.90 (d, *J* = 5.2 Hz, 3H), 1.55 (brs, 1H), 2.27 (m, 1H), 3.37 (dd, J_1 = 15.4 Hz, J_2 = 7.9 Hz, 1H), 3.40 (brs, 1H), 3.48 (dd, J_1 = 15.5 Hz, J_2 = 3.7 Hz, 1H), 3.67 (s, 3H), 4.40 (m, 1H), 6.62 (d, *J* = 6.7 Hz, 2H), 6.70 (d, *J* = 6.7 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 10.2 (q), 35.2 (d), 53.0 (t, $^2J_{CF}$ = 20.3 Hz), 55.6 (q), 64.3 (t), 114.6 (d), 114.9 (d), 115.0−125.0 (signals of the group CF_2CF_3 are obscured due to their low intensity), 140.8 (s), 152.7 (s); ^{19}F NMR (282 MHz, $CDCl_3$) δ −82.4 (s, 3F), −119.4 (dd, $^1J_{FF}$ = 272.8 Hz, $^2J_{FH}$ = 8.2 Hz, 1F), −123.4 (dd, $^1J_{FF}$ = 273.0 Hz, $^2J_{FH}$ = 21.3 Hz, 1F); HRMS calcd for $C_{13}H_{16}F_5NO_2$ 313.1101, found 313.1103. Anal. Calcd for $C_{13}H_{16}F_5NO_2$: C, 49.84; H, 5.11; N, 4.47. Found: C, 49.57; H, 4.98; N, 4.35.

(−)-(3*S*)-4,4,4-Trifluoro-3-(4-methoxyanilino)-butan-1-ol (7c). Obtained from (3*S*,*R**)-**6m**. Flash chromatography [*n*-hexane/AcOEt (1:1)] on silica gel gave a white solid (70%): mp 107−109 °C; $[\alpha]^{25}_D$ −53.2 (*c* 1.03, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.66 (m, 1H), 2.00 (m, 1H), 3.60 (brs, 1H), 3.68 (s, 3H), 3.78 (m, 2H), 3.90 (m, 1H), 6.72 (d, *J* = 8.9 Hz, 2H), 6.72 (d, *J* = 9.0 Hz, 2H); ^{13}C NMR (62.8 MHz, $CDCl_3$) δ 31.7 (t), 54.9 (q, $^2J_{CF}$ = 28.9 Hz), 55.6 (q), 58.8 (t), 114.8 (d), 115.4 (d), 126.2 (q, $^1J_{CF}$ = 283.4 Hz), 140.4 (s), 153.1 (s); ^{19}F NMR (235 MHz, $CDCl_3$) δ −76.2 (d, *J* = 7.1 Hz, 3F); HRMS calcd for $C_{11}H_{14}F_3NO_2$ 249.0976, found 249.0987.

General Procedure for the Synthesis of β-Amino Acids 9. A solution of ceric ammonium nitrate (CAN) (2.74 g, 5 mmol) in water (4 mL) at 0 °C was added to a solution of **6g** or **6h** (0.29 g, 1 mmol) in acetonitrile (8 mL). The reaction mixture was stirred at 0 °C until TLC showed no starting material (2 h). The aqueous phase was extracted with ethyl acetate (5 × 20 mL). The organic phases were pooled together and washed in sequence with aqueous solutions of Na_2SO_3 (20%), $NaHCO_3$ (5%), and brine. The resulting organic layer was then dried over anhydrous sodium sulfate and concentrated under reduced pressure to yield the crude N-unprotected β-amino esters, which were then used in the next step without further purification. The crude mixture (ca. 1.0 mmol) was dissolved in 5 mL of 6 N HCl. The mixture was heated at 50 °C and stirred for 2 h. The reaction mixture was cooled at room temperature and extracted with ether (3 × 4 mL). The aqueous layer was evaporated in vacuo to dryness. Standard Dowex-50 column chromatography of the residue afforded the free amino acid **9**.

(2*S,3*S**)-3-Amino-2-ethyl-4,4,4-trifluoro-butanoic Acid (9a).** A Dowex-50 chromatographic column gave a white solid (60%): mp 71−73 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.79 (t, J = 7.3 Hz, 3H), 1.28−1.43 (m, 1H), 1.51−1.62 (m, 1H), 2.37 (dt, J_1 = 8.8 Hz, J_2 = 4.3 Hz, 1H), 3.75−3.86 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) 11.0 (q), 21.0 (t), 46.8 (d), 54.2 (q, $^2J_{CF}$ = 30.3 Hz), 123.9 (q, $^1J_{CF}$ = 280.0 Hz), 178.0 (s); ^{19}F NMR (235 MHz, $CDCl_3$) δ −74.0 (d, J = 7.1 Hz, 3F); HRMS calcd for (M^+ + 1) $C_6H_{10}F_3NO_2$ 186.0741, found 186.0742.

(2*S,3*S**)-3-Amino-4,4,4-trifluoro-2-methylbutanoic Acid (9b).** A Dowex-50 chromatographic column gave a white solid (50%): mp 155−157 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.04 (d, J = 7.3 Hz, 3H), 2.63 (m, 1H), 4.07 (m, 1H); ^{13}C NMR (62.8 MHz, $CDCl_3$) δ 13.3 (q), 39.7 (d), 54.8 (q, $^2J_{CF}$ = 30.3 Hz), 124.7 (q, $^1J_{CF}$ = 280.6 Hz), 180.2 (s); ^{19}F NMR (235 MHz, $CDCl_3$) δ −70.1 (d, J = 7.5 Hz, 3F); HRMS calcd for (M^+ + 1) $C_5H_8F_3NO_2$ 172.0585, found 172.0583.

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Supporting Information Available: Characterization data for the new compounds **4b**, **4f**−**h**, **4j**, **4n**, **4q**−**r**, **4t**, **5b**, **5d**, **6b**−**c**, **6h**−**i**, **6k**−**l**, and **6p** and ORTEP diagrams and crystallographic data for compounds (2*S*,3*S*,*R**)-**6q** and (2*R**,3*R**)-**7a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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