Diastereoselective Synthesis of the Nonracemic Methyl *syn*-(3-Fluoroalkyl)isoserinates

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Cycloaddition of the (fluoroalkyl)imines **7a**−**c** with the ketene formed in situ from (benzyloxy)acetyl chloride and triethylamine provided stereoselectively *cis*-(fluoroalkyl)azetidinones **5a**−**c** in moderate yields. The corresponding *N*-Boc-isoserinates **11a**−**c** and protected synthons **12a**−**c** have been prepared from these azetidinones **5a**−**c**. Cycloaddition of the chiral imine **18** ($R_F = CF_3$) with the same ketene led to the diastereoisomeric azetidinones **19** and **20** with a poor diastereoisomeric excess (10−20%). However, the two diastereoisomers could be easily separated by crystallization and provided enantiomerically pure *N*-Boc-isoserinates **23** (*R*,*R*) and **23** (*S*,*S*) after ring opening and debenzylation.

β-Amino fluoroalkyl alcohols **1** have been used, like their nonfluorinated analogues, as peptidomimetic units, and when incorporated in peptidic substrates, they often exhibit active site directed competitive inhibitory properties toward proteases.[1] Conversely, their regioisomers, the β-hydroxy (fluoroalkyl)amines **2**, had never been described until the recent paper from Seebach *et al.*[2] The properties of these amino alcohols **2** as peptidomimetic units have never been explored, although specific features brought by the fluorinated moiety can be expected: for example, the presence of the fluoroalkyl group can increase the stability of the amide bond toward nonspecific proteolysis[3] and strongly weakens the basicity of the amine function, modifying solubility and desolvation properties.[4]

Norstatine, statine, and their analogues have been largely used as peptidomimetic units in peptide-based inhibitors of aspartyl proteases such as renin and HIV-1 protease.[5] Fluorinated analogues of these nonproteogenic α-hydroxy-β-amino acids could be of great interest, and access to fluoroalkyl derivatives **3** of isoserine had to be investigated. We have recently reported the first access to the important representative hydroxy amine of type **2**, the racemic methyl *syn*-3-(trifluoromethyl)isoserinate (**4a**), through the β-lactam **5a**.[6] This β-lactam, after suitable protection and deprotection steps, has been coupled with baccatin III, providing an analogue of docetaxel, where the 3′-phenyl group has been replaced by a CF_3 group. This compound presents a higher cytotoxicity in vitro toward human tumoral cell lines than docetaxel.[7,8] We report now the detailed preparation of **4a** and **5a**, the extension to the preparation of other fluoroalkyl β-lactams **5b** and **5c** ($R_F = CF_2H$ and CF_2-Cl), and the preparation of nonracemic β-lactams and isoserinates.

The Staudinger reaction of ketenes to aldimines is well-known to provide *cis*-β-lactams.[9] However, it had never been studied in the case of (fluoroalkyl)imines. To check the feasibility of the reaction, we first examined the [2 + 2] cycloaddition reaction between ketenes generated from propionyl, butyryl, phenylacetyl, and phenylpropionyl chlorides and the (fluoroalkyl)acetaldimine **7a**, prepared by the usual route from the corresponding ethyl hemiacetal and *p*-methoxyaniline.[10,11] In all cases, no traces of the corresponding β-lactam was detected. Fortunately, reaction of the ketene, generated from α-(benzyloxy)acetyl chloride (**6**) and triethylamine with imine **7a**, performed at 45 °C in methylene chloride, provided the expected *cis*-azetidinone **5a** in a 65% yield (Scheme 2). In azetidinone **5a**, the $^3J_{H\text{-}3,H\text{-}4}$ coupling constant of 5 Hz indicates the *cis* relative configuration. Coupling constants in parent β-lactams have been reported to be 2 Hz for the *trans* isomer and 5−6 Hz for the cis one.[12] Difluoroacetaldimine[13] **7b** and chlorodifluoroacetaldimine

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(11) It is worth noting that, unlike cyclocondensation with lithium acetate enolate, cycloaddition with ketene cannot be performed from the mixture imine and the corresponding amino ester, which always accompanies the imine **7a** in its preparation. In our hands, the treatment of this mixture with LDA did not provide the pure imine **7a**. However, a careful distillation allowed the separation and the pure imine **7a** was obtained in 60% yield.

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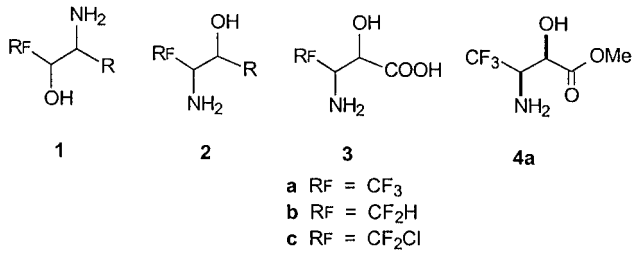
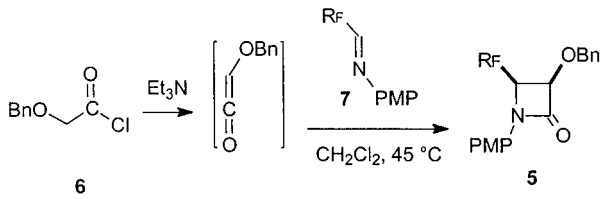
Scheme 1



a $R_F = CF_3$
b $R_F = CF_2H$
c $R_F = CF_2Cl$

Scheme 2



PMP = *p*-methoxyphenyl

a $R_F = CF_3$ (65 %)
b CF_2H (72 %)
c CF_2Cl (55 %)

7c were prepared in 60−65% yields from the corresponding ethyl hemiacetals by heating a toluene solution of hemiacetal and *p*-methoxyaniline in a Dean−Stark apparatus. These ethyl hemiacetals were obtained through the reduction of the corresponding ethyl esters with $LiAlH_4$.[13] Condensation of the aldimine **7b** with the ketene generated from **6** led to the *cis*-β-lactam **5b** in 72% yield ($^3J_{H\text{-}3,H\text{-}4} = 5.2$ Hz). The β-lactam **5c** was obtained in a satisfatory yield (55%) from aldimine **7c**, the $^3J_{H\text{-}3,H\text{-}4}$ coupling constant also indicating its *cis* relative configuration (Scheme 2).

β-Lactams **5** can be satisfactorily transformed into isoserinates. The acidic methanolysis of β-lactams **5** was very slow and often could not be reproduced. So, to prepare isoserinates **4a**−**c**, the *p*-methoxyphenyl group was first removed with ceric ammonium nitrate (CAN) (65−87%). The reaction has to be carefully monitored and stopped as soon as azetidinones **5** have reacted because of the fast degradation of azetidinones **8** in the presence of excess of CAN. The resulting azetidinones **8a**−**c** were first converted into *N*−Boc derivatives **9a**−**c**. In the case of **8c**, a low temperature of reaction (−50 °C) was absolutely required to obtain **9c** in good yield. The sodium azide catalyzed ring opening[14] by methanol provided esters **10a**−**c**. Further debenzylation by a catalytic hydrogenation followed by the Boc cleavage led to isoserinates **4a**−**c** (Scheme 3).

For the preparation of fluorinated docetaxel analogues,[7,8] azetidinones could directly react with protected baccatin III after suitable deprotection and protection steps. Azetidinones **9a**−**c** were debenzylated by catalytic hydrogenation into azetidinones **13a**−**c** and then protected again by a reaction with ethyl vinyl ether (EVE) in the presence of *p*-toluenesulfonic acid to give azetidinones **12a**−**c** (Scheme 3).

To prepare chiral azetidinones, the asymmetric Staudinger reaction, controlled by a chiral N-substituent on imines, is seldom diastereoselective, because of the relatively long distance between the chiral center and the reaction center.[15] Since the lithium ester enolate-imine

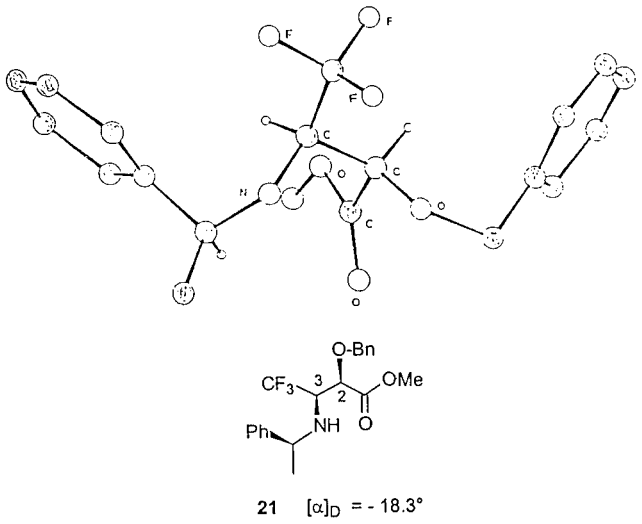


Figure 1. ORPEP stereoplot view of the crystal structure of (*R*,*R*)-methyl isoserinate **21**.

cyclocondensation has been successfully demonstrated to give *cis*-azetidinone in high yields with very high enantiomeric purity,[9b,16−19] we rather first chose this approach. We showed that the ester cyclodensation of enolate of benzyloxy esters with the trifluoroacetaldimine **7a** failed.[6] However, we finally succeeded in the preparation of the cis β-lactam **14** by using the more reactive (triisopropylsilyl)oxy esters **15**, as reported by Ojima[19] (Scheme 4). β-Lactams obtained in cyclocondensation reactions from silyloxy or alkoxy esters and aldimines have in most cases the *cis* configuration.[16a,19] However, the only reported cyclocondensation reaction involving a trifluoromethyl aldimine with an ester lithium enolate, a protected glycine, provided a *trans*-4-(trifluoromethyl)azetidinone.[10] This opposite result is probably due to a different relative stability of conformations of the enolate, the disubstituted nitrogen favoring the formation of the *Z*-enolate leading to the *trans* β-lactam.

The results were disappointing when the reaction was performed with esters **16** and **17**: azetidinone **14** was not obtained from **16** and was obtained with a very low yield from **17**.

These poor results prompted us to turn back to the [2 + 2] ketene−imine cycloaddition route to β-lactam. We investigated the reaction with the chiral imine **18**, prepared from the trifluoroacetaldehyde hemiacetal and the (*S*)-phenethylamine by the same procedure as for aldimines **7**. The cycloaddition reaction with the ketene generated from the acyl chloride **6** and the imine **18** was efficient, leading to a mixture of *cis*-azetidinones **19** and **20** (90%) accompanied by only 5−8% of *trans*-azetidinone. As expected, the chirality transfer was low since the diastereoisomeric excess was 15% only. Fortunately, crystallization of the crude mixture in ethanol allowed a

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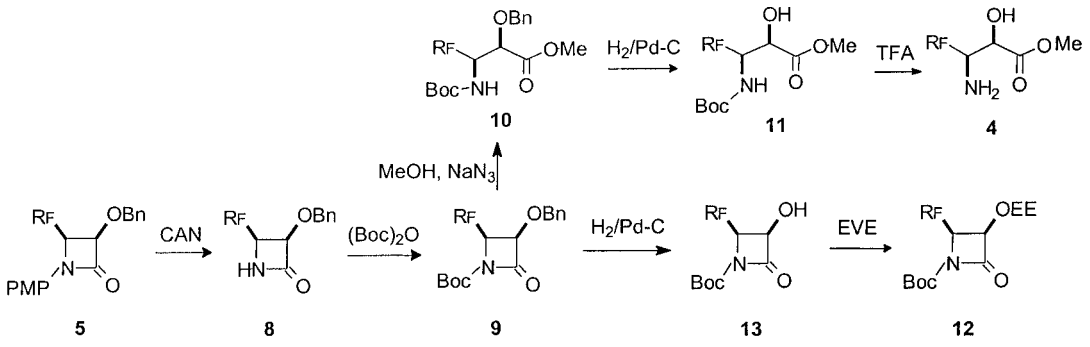
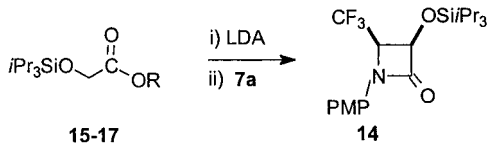
Scheme 3



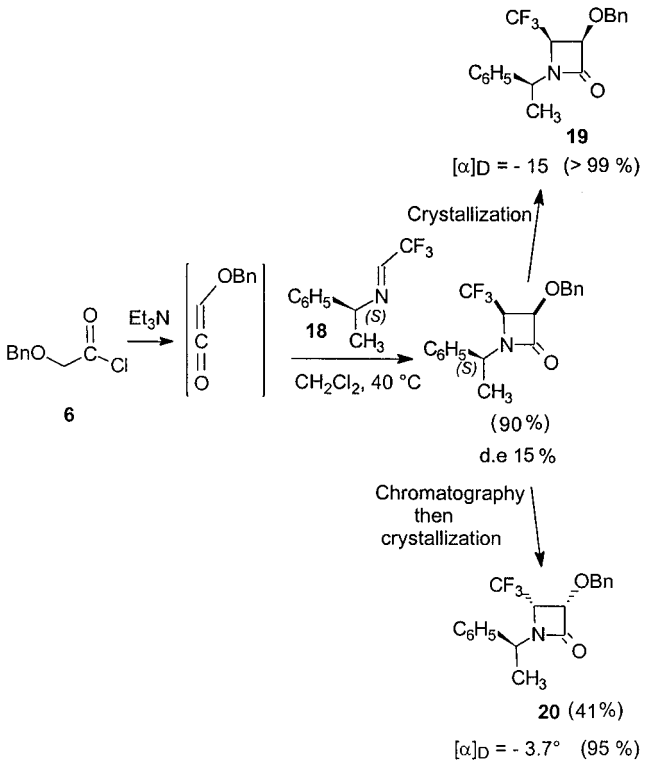
a $R_F = CF_3$, **b** $R_F = CF_2H$, **c** $R_F = CF_2Cl$

Scheme 4



15 R = Mesityl (68 %)
16 R = *(-)* Menthyl (0 %)
17 R = *(±) trans* 2-phenylcyclohexyl (20 %)

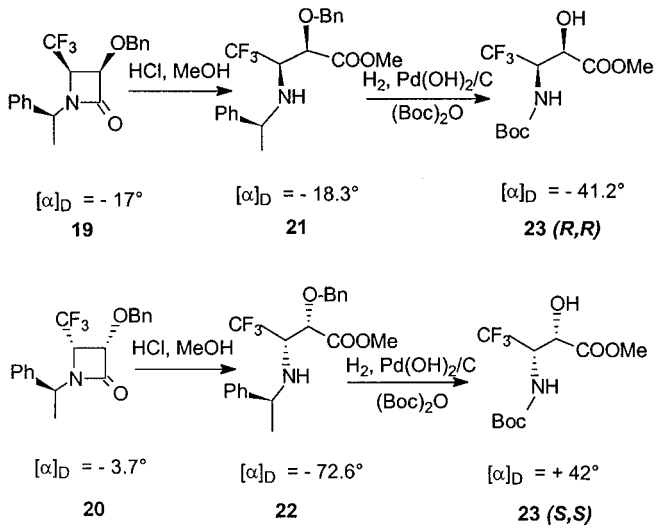
Scheme 5



fine separation of the two isomers **19** and **20**. Stereoisomer **19** crystallized and was obtained in an excellent diastereoselective purity (>99%), and stereoisomer **20** could be isolated in a 95% diastereoselective purity after SiO_2 chromatography and crystallization in pentane (Scheme 5).

In contrast to *N*-(*p*-methoxyphenyl)azetidinones **5** (*p*-methoxyphenyl = PMP), the azetidinone **19** easily underwent an acidic methanolysis leading to the isoserinate **21**. The absolute configuration has been determined for isoserinate **21**. The crystal structure of **21** indicated unambiguously the configuration (2*R*,3*R*) for this isomer

Scheme 6



(Figure 1).[20] From isoserinates **21** and **22**, a catalytic debenzylation in the presence of $(Boc)_2O$ provided the two nonracemic *N*-Boc isoserinates **23** (*R*,*R*) and (*S*,*S*) (Scheme 6).

Three fluoroalkyl (CF_3, CF_2H, and CF_2Cl) isoserine derivatives could be prepared in good yields through a [2+2] ketene−imine cycloaddition. Starting from a chiral CF_3-substituted aldimine, both pure enantiomers of the methyl *syn*-3-(trifluoromethyl)isoserinate could be obtained. These peptidomimetic units are currently under active investigation in the design of protease inhibitors.

Experimental Section

NMR spectra were performed with $CDCl_3$ solutions, on a Varian EM, FH dual probehead, a Bruker AC 200, and an ARX 400 spectrometer (^1H: 90, 200, or 400 MHz, ^{19}F: 84, 188, or 376 MHz; and ^{13}C: 50 or 100 MHz). Chemical shifts are reported in ppm relative to Me_4Si and $CFCl_3$ (for ^{19}F NMR) as internal standards. In the ^{13}C NMR data, reported signal multiplicities are related to C−F coupling. For the determination of fine coupling constants an acquisition of 16K data points, a Lorenz−Gauss transformation of the FID and a zero filling to 64K were performed in order to obtain a minimum of resolution of 0.2 Hz/pt (^1H) or 0.5 Hz/pt (^{13}C). COSY, HMQC, HMBC experiments were performed on a multinuclear

(20) The authors have deposited atomic coordinates for this structure with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

probehead equipped with a Z-gradient coil. GC analyses were performed on a capillary column SE 30, 10 or 25 m.

(2,2,2-Trifluoroethylidene)anisidine (7a). A solution of ethyl trifluoroacetaldehyde hemiacetal (15 g, 0.1 mol), *p*-methoxyaniline (10.26 g, 0.083 mol), and *p*-toluenesulfonic acid (50 mg) in toluene (120 mL) was refluxed under Ar for 1.5 h in a Dean−Stark apparatus.[11] The solution was washed with an aqueous solution of sodium hydrogenocarbonate and then with brine and dried ($MgSO_4$). The solution was evaporated under reduced pressure, and the residue was distilled (60 °C, 0.5 mmHg), leading to the *N*-(2,2,2-trifluoroethylidene)anisidine[10] (**7a**) (10.4 g, 64%): ^{19}F NMR δ −70.7 (d, $^3J_{FH}$ = 3.7 Hz); ^{1}H NMR δ 3.84 (s, 3 H), 7.1 (q, 4 H), 7.8 (q, $^3J_{HF}$ = 3.7 Hz); ^{13}C NMR δ 55.0, 119.5 (q, $^1J_{CF}$ = 279 Hz, CF_3), 114.5, 123.1, 139.8, 144.2 (q, $^2J_{CF}$ = 33 Hz, *C*CF_3), 160.0.

(2,2-Difluoroethylidene)anisidine (7b). A solution of ethyl difluoroacetate (5 g, 0.04 mol) in Et_2O (8 mL) was treated at −78 °C with a solution of $LiAlH_4$ (0.95 g, 0.025 mol) in THF (15 mL). The reaction mixture was stirred at this temperature for 3 h. EtOH (95%) (2 mL) was then added. The reaction mixture was stirred for 2 h at rt and then poured into an aqueous saturated solution of NH_4Cl and extracted with Et_2O (two times). The organic phases were dried ($MgSO_4$), evaporated, and distilled under normal pressure. Ethyl difluoroacetaldehyde hemiacetal was obtained at 90 °C (2 g, 40%): ^{19}F NMR δ −131.7 (ddd, $^2J_{FF}$ = 291 Hz, $^2J_{FH}$ = 54.8 Hz, $^3J_{FH}$ = 5.7 Hz, 1 F), −137.2 (ddd, $^2J_{FF}$ = 291 Hz, $^2J_{FH}$ = 55.3 Hz, $^3J_{FH}$ = 7.6 Hz, 1 F); ^{1}H NMR δ 1.24 (t, J = 7 Hz, 3 H), 3.80 (q, J = 7 Hz, 2 H), 4.68 (ddd, ^3J = 2.7 Hz, $^3J_{FH}$ = 5.7, 7.6 Hz, 1 H), 5.57 (ddd, ^3J = 2.7 Hz, $^2J_{FH}$ = 54.8, 55.3 Hz, 1 H). A solution of ethyl difluoroacetaldehyde hemiacetal (2 g, 0.015 mol) and *p*-methoxyaniline (1.61 g, 0.083 mol) in toluene (25 mL) was refluxed under Ar for 1.5 h in a Dean−Stark apparatus. After workup, the residue was distilled (60 °C, 1.5 mmHg) leading to the *N*-(2,2-difluoroethylidene)anisidine (**7b**)[13] (1.8 g, 60%): ^{19}F NMR δ −119.2 (dd, $^2J_{FH}$ = 55 Hz, $^3J_{FH}$ = 2.5 Hz); ^{1}H NMR δ 3.78 (s, 3 H), 7.0 (q, J_{AB} = 8.9 Hz, δ_A 6.85, δ_B 7.15, 4 H), 7.1 (ddd, $^2J_{FH}$ = 54.8, 55.3 Hz, ^3J = 5.4 Hz, 1 H, CF_2H), 7.8 (td, $^3J_{FH}$ = 2.5 Hz, ^3J = 5.4 Hz, 1 H).

(2,2,2-Chlorodifluoroethylidene)anisidine (7c). A solution of ethyl chlorodifluoroacetate (5 g, 3.16 mmol) in Et_2O (5 mL) was treated at −78 °C with a solution of DIBAL (solution 1 M in CH_2Cl_2, 38 mL, 0.038 mol) in THF (15 mL). The reaction mixture was stirred at this temperature for 5 h. EtOH (95%) (2 mL) was then added, and the reaction mixture was stirred 2 h at rt and then poured into an aqueous saturated solution of NH_4Cl and extracted with Et_2O (two times). The organic phases were dried ($MgSO_4$) and evaporated under reduced pressure (5 mmHg). Ethyl chlorodifluoroacetaldehyde hemiacetal was obtained at 18 °C (1.67 g, 33%): ^{19}F NMR δ −69.0 (dd, $^2J_{FF}$ = 8.6 Hz, $^3J_{FH}$ = 3.5 Hz); ^{1}H NMR δ 1.28 (t, J = 7 Hz, 3 H), 2.55 (s, 1 H, OH), 3.83 (dq, J_{AB} = 9.8 Hz, ^3J = 7 Hz, 2 H), 4.79 (t, $^3J_{FH}$ = 3.5 Hz, 1 H). A solution of ethyl chlorodifluoroacetaldehyde hemiacetal (1.67 g, 10 mmol) and *p*-methoxyaniline (1.28 g, 0.01 mol) in toluene (20 mL) was refluxed under Ar for 1.5 h in a Dean−Stark apparatus. After workup, the residue was distilled (70 °C, 6 mmHg) leading to the *N*-(2,2,2-chlorodifluoroethylidene)anisidine (**7c**) (1.9 g, 64%): ^{19}F NMR δ −59.0 (d, $^3J_{FH}$ = 5 Hz); ^{1}H NMR δ 3.78 (s, 3 H), 7.1 (q, 4 H), 7.81 (t, $^3J_{FH}$ = 5 Hz); ^{13}C NMR δ 55.0, 111.6 (q, $^1J_{CF}$ = 272 Hz, CF_2Cl), 114.8, 123.5, 138.7, 139.9, 147.8 (q, $^2J_{CF}$ = 31 Hz, *C*CF_2Cl), 160.

[2 + 2] Ketene−Imine Condensation: *cis*-*N*-(4-Methoxyphenyl)-3-(benzyloxy)-4-(trifluoromethyl)azetidin-2-one (5a). A solution of *N*-(2,2,2-trifluoroethylidene)-4-methoxyaniline (**7a**) (6 g, 0.03 mol) and α-(benzyloxy)acetyl chloride (**6**) (11.07 g, 0.06 mol) in freshly distilled CH_2Cl_2 (40 mL) was treated slowly with NEt_3 (9.1 g, 0.09 mol). The resulting mixture was then stirred for 26 h at 45 °C. The solution was poured into water (20 mL) and extracted with EtOAc (2 × 50 mL). The organic phase was washed with brine and dried over $MgSO_4$. After evaporation of solvent, the crude product was purified by crystallization in cold ethanol to give **5a** as a white solid (6.72 g, 65%): mp 132 °C (EtOH): ^{19}F NMR δ −68.9 (d, $^3J_{FH}$ = 5.5 Hz); ^{1}H NMR δ 3.8 (s, 3 H), 4.6 (qd, $^3J_{FH}$ = 5.5 Hz, ^3J = 5.0 Hz, 1 H, H-4), 4.83 (q, J_{AB} = 11.8 Hz, δ_A 4.80, δ_B 4.86, 2 H, OCH_AH_BC$_6$H$_5$), 4.98 (d, ^3J = 5.0 Hz, 1 H, H-3), 7.2 (q, J = 10 Hz, δ_A 6.8, δ_B 7.4, 4 H, C_6H_4); ^{13}C NMR δ 55.6, 57.8 (q, $^2J_{CF}$ = 33 Hz, C-4), 73.9, 80.4, 114.6, 119.6, 123.8 (q, $^1J_{CF}$ = 280 Hz, CF_3), 128.0, 128.4, 128.7, 129.5, 136.3, 157.4, 163.9. Anal. Calcd for $C_{18}H_{16}F_3NO_3$: C, 61.54; H, 4.59; N, 4.0. Found: C, 60.77; H, 4.91; N, 3.81.

***cis*-*N*-(4-Methoxyphenyl)-3-(benzyloxy)-4-(difluoromethyl)azetidin-2-one (5b).** A solution of *N*-(2,2-difluoromethylidene)-4-methoxyaniline (**7b**) (1.8 g, 9.7 mmol) and α-(benzyloxy)acetyl chloride (**6**) (3.69 g, 0.02 mol) in freshly distilled CH_2Cl_2 (25 mL) was treated slowly with NEt_3 (2.95 g, 0.029 mol). The resulting mixture was then stirred 17 h at 45 °C. Workup and purification by crystallization in cold ethanol afforded **5b** as a white solid (2.35 g, 72%): mp 91 °C (EtOH); ^{19}F NMR δ − 119.0 (ddd, $^2J_{FF}$ = 301 Hz, $^2J_{FH}$ = 56 Hz, $^3J_{FH}$ = 7.6 Hz, 1 F), −122.6 (ddd, $^2J_{FF}$ = 301 Hz, $^2J_{FH}$ = 54 Hz, $^3J_{FH}$ = 6 Hz, 1 F); ^{1}H NMR δ 3.7 (s, 3 H), 4.32 (dddd, $^3J_{FH}$ = 7.6, 6 Hz, ^3J = 5.2, 5.7 Hz, 1 H, H-4), 4.7 (q, J_{AB} = 12 Hz, δ_A 4.60, δ_B 4.80, 2 H, OCH_AH_BC$_6$H$_5$), 4.84 (d, ^3J = 5.2 Hz, 1 H, H-3), 6.0 (ddd, $^2J_{HF}$ = 56, 54 Hz, ^3J = 5.7 Hz, 1 H, CHF_2), 7.1 (q, J = 10 Hz, δ_A 6.85, δ_B 7.4, 4 H, C_6H_4), 7.3 (m, 5 H); ^{13}C NMR δ 55.6, 57.9 (dd, $^2J_{CF}$ = 20.6, 32 Hz, C-4), 73.8 (d, $^5J_{CF}$ = 1.2 Hz), 80.3 (dd, $^3J_{CF}$ = 1.1 Hz, C-3), 114.0 (t, $^1J_{CF}$ = 243 Hz, CF_2H), 114.5, 119.3, 128.2, 128.5, 128.8, 130.4, 136.4, 157.1, 164.1. Anal. Calcd for $C_{18}H_{17}F_2NO_3$: C, 64.86; H, 5.14; N, 4.20. Found: C, 64.71; H, 5.27; N, 4.15.

***cis*-*N*-(4-Methoxyphenyl)-3-(benzyloxy)-4-(chlorodifluoromethyl)azetidin-2-one (5c).** A solution of *N*-(2,2,2-chlorodifluoroethylidene)-4-methoxyaniline (**7c**) (1.9 g, 8.5 mmol) and α-(benzyloxy)acetyl chloride (**6**) (3.2 g, 17.4 mmol) in freshly distilled CH_2Cl_2 (24 mL) was treated slowly with NEt_3 (2.6 g, 25.5 mmol). The resulting mixture was then stirred for 26 h at 45 °C. The solution was poured into water (10 mL) and extracted with EtOAc (2 × 30 mL). The organic phase was washed with brine and dried over $MgSO_4$. After evaporation of solvent, the crude product was purified by crystallization in cold ethanol to give **5c** as a white solid (1.76 g, 55%): mp 140 °C (EtOH); ^{19}F NMR δ −54.9 (dd, $^2J_{FF}$ = 173 Hz, $^3J_{FH}$ = 2.4 Hz, 1 F), − 56.4 (ddd, $^2J_{FF}$ = 173 Hz, $^3J_{FH}$ = 11 Hz, 1 F); ^{1}H NMR δ 3.8 (s, 3 H), 4.75 (ddd, $^3J_{FH}$ = 11, 2.4 Hz, ^3J = 5 Hz, 1 H, H-4), 4.85 (q, J_{AB} = 12.2 Hz, δ_A 4.81, δ_B 4.89, 2 H, OCH_AH_BC$_6$H$_5$), 4.97 (d, ^3J = 5 Hz, 1 H, H-3), 7.1 (q, J_{AB} = 9 Hz, 4 H, C_6H_4), 7.4 (m, 5 H); ^{13}C NMR δ 55.6, 62.3 (dd, $^2J_{CF}$ = 28.5, 25.9 Hz, C-4), 74.0, 80.6 (t, $^3J_{CF}$ = 2 Hz, C-3), 119.9, 127.2 (dd, $^1J_{CF}$ = 294, 296 Hz, CF_2Cl), 127.8, 128.0, 128.5, 128.6, 129.0, 136.0, 157.1, 164.1. Anal. Calcd for $C_{18}H_{16}ClF_2NO_3$: C, 58.79; H, 4.39; N, 3.81. Found: C, 58.81; H, 4.43; N, 3.85.

***cis*-3-(Benzyloxy)-4-(trifluoromethyl)azetidin-2-one (8a).** A solution of ceric ammonium nitrate (CAN) (39 g, 71 mmol) in water (180 mL) was added slowly at 0 °C to a solution of azetidinone **5a** (5 g, 14.2 mmol) in acetonitrile (90 mL). The reaction mixture was stirred until the disappearance of starting material (TLC) (about 1 h) at 0 °C. Then water and ethyl acetate were added for extraction (twice). Organic phases were washed with $NaHCO_3$ 5% aqueous solution and brine and then dried ($MgSO_4$) and concentrated. Purification on a SiO_2 column (pentane/EtOAc 70:30) provided the azetidinone **8a** as a yellow solid (2.23 g, 64%): mp 91 °C (EtOAc); ^{19}F NMR d −72.4 (d, $^3J_{FH}$ = 6.2 Hz); ^{1}H NMR δ 4.04 (qd, $^3J_{FH}$ = 6.0 Hz, ^3J = 4.9 Hz, 1 H, H-4), 4.65 (q, J_{AB} = 12 Hz, δ_A 4.62, δ_B 4.69, 2 H, OCH_AH_BC$_6$H$_5$), 4.78 (dd, ^3J = 4.9 Hz, $^4J_{FH}$ = 2 Hz, 1 H, H-3), 6.57 (s, 1 H, NH), 7.28 (m, 5 H, C_6H_5); ^{13}C NMR δ 54.4 (q, $^2J_{CF}$ = 37 Hz, C-4), 73.8, 82.3, 124.0 (q, $^1J_{CF}$ = 279 Hz, CF_3), 128.1, 128.7, 128.8, 136.3, 167.6. Anal. Calcd for $C_{11}H_{10}F_3NO_2$: C, 53.88; H, 4.11; N, 5.71. Found: C, 53.75; H, 4.25; N, 5.63.

***cis*-3-(Benzyloxy)-2-(difluoromethyl)azetidin-2-one (8b).** A solution of ceric ammonium nitrate (CAN) (13.2 g, 0.024 mmol) in water (60 mL) was added slowly at 0 °C to a solution of azetidinone **5b** (1.6 g, 4.8 mmol) in acetonitrile (30 mL). The reaction mixture was stirred until disappearance of the starting material (about 3 h) at 0 °C. Workup and evaporation of the solvents provided, after chromatography on SiO_2 (pentane/EtOAc 60:40), the azetidinone **8b** as a white solid (840 mg, 72%): mp 67 °C (pentane/EtOAc); ^{19}F NMR δ −121.5 (ddd,

$^2J_{FF}$ = 301 Hz, $^2J_{FH}$ = 57 Hz, $^3J_{FH}$ = 11.5 Hz, $^4J_{FH}$ not observed, 1 F), −128 (ddd, $^2J_{FF}$ = 301 Hz, $^2J_{FH}$ = 53.4 Hz, $^3J_{FH}$ = 7.6 Hz); ^{1}H NMR δ 3.89 (dddd, $^3J_{FH}$ = 11.5, 7.6 Hz, ^3J = 7, 4.8 Hz, 1 H, H-4), 4.72 (q, J_{AB} = 11.5 Hz, δ_A 4.68, δ_B 4.76, 2 H, OCH_AH_BC$_6$H$_5$), 4.8 (ddd, ^3J = 4.8 Hz, $^4J_{FH}$ = 2, 1.1 Hz, 1 H, H-3), 5.9 (ddd, $^2J_{FH}$ = 57, 54 Hz, ^3J = 6.5 Hz, 1 H, CF_2H), 6.2 (s, 1 H, NH), 7.3 (m, 5 H, C$_6$H$_5$); ^{13}C NMR δ 55.4 (dd, $^2J_{CF}$ = 34 Hz, C-4), 74.3 (d, $^5J_{CF}$ = 1.3 Hz), 83.1 ($^3J_{CF}$ = 6.3 Hz, C-3), 116.2 (t, $^1J_{CF}$ = 246 Hz, CF_2H) 124.0, 128.2, 128.5, 128.7, 136.3, 167.7. Anal. Calcd for $C_{11}H_{11}F_2NO_2$: C, 58.16; H, 4.88; N, 6.16. Found: C, 58.11; H, 4.97; N, 6.09.

***cis*-3-(Benzyloxy)-4-(chlorodifluoromethyl)azetidin-2-one (8c).** A solution of ceric ammonium cerium nitrate (CAN) (2.3 g, 4.09 mmol) in water (28 mL) was slowly added at 0 °C to a solution of azetidinone **5c** (300 mg, 0.82 mmol) in acetonitrile (14 mL). The reaction mixture was stirred for 3.5 h at this temperature. The workup and evaporation of the solvents provided, after SiO_2 chromatography (pentane/EtOAc 70:30), the azetidinone **8c** (186 mg, 87%): mp 58 °C (pentane/EtOAc); ^{19}F NMR δ −60.7 (dd, $^2J_{FF}$ = 167.5 Hz, $^3J_{FH}$ = 8.5 Hz, $^4J_{FH}$ not observed, 1 F), −62.3 (dd, $^2J_{FF}$ = 167.5 Hz, $^2J_{FH}$ = 9 Hz, 1 F); ^{1}H NMR δ 4.3 (ddd, $^3J_{FH}$ = 8.5, 9 Hz, ^3J = 4.8 Hz, 1 H, H-4), 4.8 (q, J_{AB} = 11.8 Hz, δ_A 4.75, δ_B 4.82, 2 H, OCH_AH_BC$_6$H$_5$), 4.90 (dd ^3J = 4.8 Hz, $^4J_{FH}$ = 1.8 Hz, 1 H, H-3), 6.3 (s, 1 H, NH), 7.3 (m, 5 H); ^{13}C NMR δ 59.5 (dd, $^2J_{CF}$ = 27, 30 Hz, C-4), 73.7, 82.2 (d, $^3J_{CF}$ = 1.5 Hz, C-3), 126.8 (dd, $^1J_{CF}$ = 294, 296 Hz, CF_2Cl), 127.8, 128.2, 128.5, 132.7, 167.8. Anal. Calcd for $C_{11}H_{10}ClF_2NO_2$: C, 50.49; H, 3.85; N, 5.35. Found: C, 50.38; H, 3.94; N, 5.23.

***cis*-*N*-(*tert*-Butoxycarbonyl)-3-(benzyloxy)-4-(trifluoromethyl)azetidin-2-one (9a).** Triethylamine (1.6 mL, 11.6 mmol) and 4-(*N*-dimethylamino)pyridine (DMAP) (100 mg) were added at −20 °C under Ar to a solution of the azetidinone **8a** (1.14 g, 4.65 mmol) and $(Boc)_2O$ (1.52 g, 6.97 mmol) in THF (12 mL). After 2 h, water was added, and the organic phase was extracted (EtOAc), washed (brine), and dried ($MgSO_4$). Evaporation of the solvents and filtration on silica gel (pentane−EtOAc) provided the *N*-Boc derivative **9a** as a white solid (1.205 g, 75%): mp 100 °C (AcOEt/pentane); ^{19}F NMR δ −69.8 (d, $^3J_{FH}$ = 6 Hz); ^{1}H NMR δ 1.45 (s, 9 H), 4.42 (qd, $^3J_{FH}$ = 6.0 Hz, ^3J = 6.0 Hz, 1 H, H-4), 4.7 (q, J_{AB} = 11 Hz, δ_A 4.67, δ_B 4.74, 2 H), 4.80 (d, ^3J = 6.0 Hz, 1 H, H-3), 7.30 (m, 5 H); ^{13}C NMR δ 27.8, 56.6 (q, $^2J_{CF}$ = 34 Hz, C-4), 73.9, 80.0, 84.9, 123.1 (q, $^1J_{CF}$ = 280 Hz, CF_3), 128.0, 128.5, 128.7, 135.7, 146.8, 163.4. Anal. Calcd for $C_{16}H_{18}F_3NO_4$: C, 55.65; H, 5.25; N, 4.05. Found: C, 55.46; H, 5.32; N, 4.01.

***cis*-*N*-(*tert*-Butoxycarbonyl)-3-(benzyloxy)-4-(difluoromethyl)azetidin-2-one (9b).** Triethylamine (1.2 mL, 8.7 mmol) and DMAP (50 mg) were added at −20 °C under Ar to a solution of the azetidinone **8b** (0.79 g, 3.48 mmol) and $(Boc)_2O$ (1.17 g, 5.36 mmol) in THF (8 mL). After 2 h, workup and filtration on silica gel (pentane/EtOAc 70:30) provided the *N*-Boc derivative **9b** as a white solid (718 mg, 63%): mp 48 °C (EtOAc/pentane); ^{19}F NMR δ −123.3 (ddd, $^2J_{FF}$ = 300 Hz, $^2J_{FH}$ = 54 Hz, $^3J_{FH}$ = 9.4 Hz, 1 F), −127.1 (ddd, $^2J_{FF}$ = 300 Hz, $^2J_{FH}$ = 54.5 Hz, $^3J_{FH}$ = 7.4 Hz, $^4J_{FH}$ = 1 Hz, 1 F); ^{1}H NMR δ 1.50 (s, 9 H), 4.29 (dddd, $^3J_{HF}$ = 9.4, 7.4 Hz, ^3J = 6.0, 4.8 Hz, 1 H, H-4), 4.79 (q, J_{AB} = 11.8 Hz, δ_A 4.76, δ_B 4.82, 2 H, OCH_AH_BC$_6$H$_5$), 4.83 (dd, ^3J = 6.0 Hz, $^4J_{FH}$ = 1 Hz, 1 H, H-3), 6.04 (ddd, $^2J_{FH}$ = 54, 54.5 Hz, $^3J_{FH}$ = 4.8 Hz, 1 H, CHF_2), 7.37 (m, 5 H); ^{13}C NMR δ 28.0, 56.8 (dd, $^2J_{CF}$ = 30.7, 22.9 Hz, C-4), 73.8, 80.1 (dd, $^3J_{CF}$ = 4.4, 1.7 Hz, C-3), 84.7, 113.4 (t, $^1J_{CF}$ = 245 Hz, CHF_2), 128.0, 128.6, 128.8, 136.0, 151.4, 163.8. Anal. Calcd for $C_{16}H_{19}F_2NO_4$: C, 58.70; H, 5.85; N, 4.28. Found: C, 58.57; H, 5.94; N, 4.22.

***cis*-*N*-(*tert*-Butoxycarbonyl)-3-(benzyloxy)-4-(chlorodifluoromethyl)azetidin-2-one (9c).** Triethylamine (0.2 mL, 1.39 mmol) and DMAP (10 mg) were added at −50 °C under Ar to a solution of azetidinone **8c** (243 mg, 0.93 mmol) and $(Boc)_2O$ (304 mg, 1.39 mmol) in THF (3 mL). After 2 h at −50 °C and then 2 h at 0 °C, water was added, and the organic phase was extracted (EtOAc), washed (brine), and dried ($MgSO_4$). Evaporation of the solvents and filtration on silica gel provided the *N*-Boc-azetidinone **9c** as a white solid (247 mg, 74%): mp 120 °C (EtOAc/pentane); ^{19}F NMR δ −55.5 (dd, $^2J_{FF}$ = 171 Hz, $^3J_{FH}$ = 3.7 Hz, 1 F), −57.5 (dd, $^2J_{FF}$ = 171 Hz, $^3J_{FH}$ = 10.6 Hz, 1 F); ^{1}H NMR δ 1.43 (s, 9 H), 4.62 (ddd, $^3J_{HF}$ = 3.8, 10.6 Hz, $^3J_{HH}$ = 5.5 Hz, 1 H, H-4), 4.79 (q, J_{AB} = 12 Hz, δ_A 4.74, δ_B 4.83, 2 H, OCH_AH_BC$_6$H$_5$), 4.88 (d, $^3J_{HH}$ = 5.9, 1 H, H-3), 7.3 (m, 5 H); ^{13}C NMR δ 27.8, 61.2 (dd, $^2J_{CF}$ = 27.3, 29 Hz, C-4), 74.0, 80.4, 84.8, 126.3 (dd, $^1J_{CF}$ = 294.5, 296 Hz, CF_2-Cl), 127.9, 128.4, 128.6, 135.7, 146.8, 163.6. Anal. Calcd for $C_{16}H_{18}ClF_2NO_4$: C, 53.12; H, 5.02; N, 3.87. Found: C, 53.07; H, 5.13; N, 3.80.

***cis*-*N*-(*tert*-Butoxycarbonyl)-3-hydroxy-4-(trifluoromethyl)azetidin-2-one (13a).** A solution of azetidinone **9a** (0.32 g, 0.93 mmol) in EtOAc, freshly distilled on CaH_2 (10 mL), was stirred overnight under H_2 over 10% Pd/C. The mixture was filtered through a Celite pad (CH_2Cl_2) and evaporated to dryness to give the crude azetidinone **13a** (0.21 g, 88%). This compound has not been purified because of its instability on silica gel: mp 128 °C; ^{19}F NMR δ −69.9 (d, $^3J_{FH}$ = 6.2 Hz); ^{1}H NMR δ 1.50 (s, 9 H), 3.4 (bs, 1 H,OH), 4.50 (dq, $^3J_{FH}$ = 6.2 Hz, $^3J_{HH}$ = 6.0 Hz, 1 H, H-4), 4.80 (d, $^3J_{HH}$ = 6 Hz, 1 H, H-3); ^{13}C NMR δ 27.8, 58.6 (q, $^2J_{CF}$ = 32 Hz, C-4), 76.8, 86.4, 123.9 (q, $^1J_{CF}$ = 279 Hz, CF_3), 148.7, 167.5. Anal. Calcd for $C_9H_{12}F_3NO_4$: C, 42.36; H, 4.74; N, 5.49. Found: C, 42.25; H, 4.92; N, 5.36.

***cis*-*N*-(*tert*-Butoxycarbonyl)-3-hydroxy-4-(difluoromethyl)azetidin-2-one (13b).** A solution of azetidinone **9b** (0.200 g, 0.6 mmol) in freshly distilled EtOAc (3 mL) was stirred under H_2 over 10% Pd/C (100 mg) for 23 h. The mixture was filtered through a Celite pad and evaporated to dryness to give crude azetidinone **13b** (0.118 g, 78%): mp 149 °C (EtOAc−pentane); ^{19}F NMR δ −120.8 (ddd, $^2J_{FF}$ = 296 Hz, $^2J_{FH}$ = 54 Hz, $^3J_{FH}$ = 9.7 Hz, 1 F), −125.1 (dddd, $^2J_{FF}$ = 296 Hz, $^2J_{FH}$ = 55 Hz, $^3J_{FH}$ = 10 Hz, $^4J_{FH}$ = 0.6 Hz, 1 F); ^{1}H NMR δ 1.42 (s, 9 H), 4.20 (tdd, $^3J_{HF}$ = 9.8 Hz, ^3J = 6.0, 3.8 Hz, 1 H, H-4), 5.0 (dd, ^3J = 6.0 Hz, ^4J = 0.6 Hz, 1 H, H-3), 5.97 (ddd, $^2J_{FH}$ = 55, 54 Hz, ^3J = 3.8 Hz, 1 H, CHF_2); ^{13}C NMR δ 28.0, 59.0 (q, $^2J_{CF}$ = 28 Hz, C-4), 76.4 (t, $^3J_{CF}$ = 3.5 Hz, C-3), 85.0, 111.5 (t, $^1J_{CF}$ = 295 Hz, CF_2H), 149.2, 168.0. Anal. Calcd for $C_9H_{13}F_2NO_4$: C, 45.57; H, 5.50; N, 5.90. Found: C, 45.65; H, 5.67; N, 5.80.

***cis*-*N*-(*tert*-Butoxycarbonyl)-3-hydroxy-4-(chlorodifluoromethyl)azetidin-2-one (13c).** A solution of azetidinone **9c** (0.200 g, 0.55 mmol) in freshly distilled EtOAc (3 mL) was stirred under H_2 over 10% Pd/C (80 mg) for 16 h. The mixture was filtered through a Celite pad and evaporated to dryness to give crude azetidinone **13c** (0.135 g, 87%): mp 106 °C (EtOAc/pentane); ^{19}F NMR (CD_3OD) δ −51.5 (d, $^2J_{FF}$ = 168 Hz, 1 F), −56.7 (dd, $^2J_{FF}$ = 168 Hz, $^3J_{FH}$ = 13 Hz, $^4J_{FH}$ not observed, 1 F); ^{1}H NMR (MeOD) δ 1.50 (s, 9 H), 4.70 (ddd, $^3J_{FH}$ = 13 Hz, ^3J = 6 Hz, ^4J = 2 Hz, 1 H, H-4), 4.80 (d, ^4J = 2 Hz, 1 H, OH); 5.23 (dd, ^3J = 6 Hz, $^4J_{FH}$ = 2 Hz, 1 H, H-3); ^{13}C NMR (MeOD) δ 28.2, 63.2 (dd, $^2J_{CF}$ = 25.2, 26 Hz, C-4), 77.0 (dd, $^3J_{CF}$ = 1.5, 2.5 Hz, C-3), 85.4, 128.1 (dd, $^1J_{CF}$ = 294, 295 Hz, CF_2Cl), 148.8, 167.9. Anal. Calcd for $C_9H_{12}F_2NO_4$: C, 39.79; H, 4.45; N, 5.16. Found: C, 39.95; H, 4.67; N, 5.03.

***cis*-*N*-(*tert*-Butoxycarbonyl)-2-(ethoxyethylenoxy)-4-(trifluoromethyl)azetidin-2-one (12a).** Ethyl vinyl ether (EVE) (78 mg, 1.1 mmol) was added at 0 °C to a solution of the azetidinone **13a** (140, 0.55 mmol) and *p*-toluenesulfonic acid (5 mg) in THF (3 mL). The reaction was stirred for 5 h at 0 °C. Diethyl ether was added, and the solution was washed with a saturated aqueous solution of $NaHCO_3$ (2 × 15 mL). The organic layer was dried ($MgSO_4$) and then evaporated. Chromatography on SiO_2 (petroleum ether/EtOAc 75:25) of the residue led to the diastereoisomeric azetidinones **12a** (140 mg, 80%) as a liquid: ^{19}F NMR δ − 70.2 (d, $^3J_{FH}$ = 5.7 Hz) and −70.3 (d, $^3J_{FH}$ = 5.7 Hz); ^{1}H NMR δ 1.17 (t, ^3J = 7.1 Hz) and 1.18 (t, ^3J = 7.1 Hz) (3 H), 1.28 (d, ^3J = 5.3 Hz) and 1.35 (d, ^3J = 5.4 Hz) (3 H), 1.45 (s, 9 H), 3.58 (q, ^3J = 7.1 Hz, δ_A 3.53, δ_B 3.63) and 3.67 (q, ^3J = 7.1 Hz, δ_A 3.47, δ_B 3.87), (2 H), 4.45 (dq, $^3J_{FH}$ = 5.7 Hz, $^3J_{HH}$ = 6.0 Hz, 1 H, H-4) and 4.50 (dq, $^3J_{HF}$ = 5.7 Hz, $^3J_{HH}$ = 6.0 Hz, H-4), 4.85 (q, $^3J_{HH}$ = 5.4 Hz) and 4.92 (q, $^3J_{HH}$ = 5.3 Hz) (1 H), 5.22 (d, $^3J_{HH}$ = 6.0 Hz, H-3) and 5.23 (d, $^3J_{HH}$ = 6.1 Hz, H-3); ^{13}C NMR δ 14.8 and 15.0, 19.5 and 19.9, 27.8, 56.5 (q, $^2J_{CF}$ = 33.6 Hz, C-4) and 56.8 (q, $^2J_{CF}$ = 33.4 Hz, C-4), 61.0 and 62.0, 73.3 and 73.4, 83.7, 123.1 (q, $^1J_{CF}$ = 280 Hz, CF_3), 146.7 and 146.8, 167.1 and 164.4. Anal. Calcd

for $C_{13}H_{20}F_3NO_5$: C, 47.66; H, 6.16; N, 4.28. Found: C, 47.50; H, 6.28; N, 4.22.

***cis*-*N*-(*tert*-Butoxycarbonyl)-2-(ethoxyethylenoxy)-4-(difluoromethyl)azetidin-2-one (12b).** Ethyl vinyl ether (EVE) (58 mg, 0.8 mmol) was added at 0 °C to a solution of the azetidinone **13b** (100, 0.4 mmol) and *p*-toluenesulfonic acid (10 mg) in THF (7 mL). The reaction mixture was stirred for 2 h at 0 °C and then 3 h at rt. Diethyl ether was added, and the solution was washed with a saturated aqueous solution of $NaHCO_3$ (2 × 15 mL). The organic phases were dried ($MgSO_4$) and then evaporated. Chromatography of the residue on SiO_2 (petroleum ether/EtOAc 75:25) led to the diastereoisomeric azetidinones **12b** (80 mg, 62%) as a liquid: ^{19}F NMR δ −124.8 (ddd, $^2J_{FF}$ = 245 Hz, $^2J_{FH}$ = 55.6 Hz, $^3J_{FH}$ = 6.8 Hz) and −125.1 (ddd, $^2J_{FF}$ = 245 Hz, $^2J_{FH}$ = 54 Hz, $^3J_{FH}$ = 9.8 Hz) (1 F), −122.8 (ddd, $^2J_{FF}$ = 297 Hz, $^2J_{FH}$ = 54.2 Hz, $^3J_{FH}$ = 9.8 Hz) and −127.0 (ddd, $^2J_{FF}$ = 297 Hz, $^2J_{FH}$ = 55 Hz, $^3J_{FH}$ = 7.9 Hz) (1 F); ^{1}H NMR δ 1.20 (t, ^3J = 7 Hz) and 1.21 (t, ^3J = 7 Hz) (3 H), 1.5 (s, 9 H), 1.32 (d, ^3J = 5.3 Hz) and 1.38 (d, ^3J = 5.4 Hz) (3 H), 3.47 (q, ^3J = 7 Hz) and 3.63 (q, ^3J = 7 Hz) (2 H), 4.29 (m, 1 H, H-4), 4.92 (q, ^3J = 5.3 Hz) and 4.97 (q, ^3J = 5.4 Hz) (1 H), 5.1 (d, ^3J = 6.0 Hz) and 5.2 (d, ^3J = 6.1 Hz) (1 H, H-3), 6.2 (ddd, $^2J_{FH}$ = 55, 54 Hz, ^3J = 4.4 Hz, 1 H, C*H*F$_2$); ^{13}C NMR δ 15.9 and 16.0, 20.8 and 21.2, 27.8, 57.5 (t, $^2J_{CF}$ = 29.8 Hz, C-4) and 57.9 (t, $^2J_{CF}$ = 29.4 Hz, C-4), 61.6 and 62.9, 74.3 (dd, $^3J_{CF}$ = 3.9, 2.4 Hz, C-3) and 74.6 (dd, $^3J_{CF}$ = 4.4, 1.5 Hz, C-3), 84.3 and 84.4, 111.5 (t, $^1J_{CF}$ = 300 Hz, CF$_2$H), 165.4. Anal. Calcd for $C_{13}H_{21}F_2NO_5$: C, 50.48; H, 6.84; N, 4.53. Found: C, 50.56; H, 6.89; N, 4.58.

***cis*-*N*-(*tert*-Butoxycarbonyl)-2-(ethoxyethylenoxy)-4-(dichlorofluoromethyl)azetidin-2-one (12c).** Ethyl vinyl ether (EVE) (100 mg, 1.39 mmol) was added at 0 °C to a solution of the azetidinone **13c** (180 mg, 0.66 mmol) and *p*-toluenesulfonic acid (5 mg) in THF (6 mL). The reaction was stirred for 5 h at 0 °C. Diethyl ether was added, and the solution was washed with a saturated aqueous solution of $NaHCO_3$ (2 × 15 mL). The organic layer was dried ($MgSO_4$) and then evaporated. Chromatography of the residue on SiO_2 (petroleum ether/EtOAc 75:25) led to the diastereoisomeric azetidinones **12c** (137 mg, 60%) as a liquid: ^{19}F NMR δ −56.5 (d, $^3J_{FH}$ = 7 Hz, 2 F) and −55.8 (dd, $^2J_{FF}$ = 171 Hz, J_{FH} = 4 Hz, 1 F), −58.2 (dd, $^2J_{FF}$ = 171 Hz, J_{FH} = 11 Hz, 1 F); ^{1}H NMR δ 1.17 (t ^3J = 7 Hz, 3 H), 1.29 and 1.34 (d, ^3J = 5.4 Hz, 3 H), 1.45 (s, 9 H), 3.51, 3.65 (dq, ^3J = 9.5, 7.0 Hz) and 3.47, 3.93 (dq, ^3J = 9.5, 7.0 Hz) [CH$_2$], 4.61 (dt, $^3J_{FH}$ = 7.1 Hz, $^3J_{HH}$ = 7 Hz) and 4.62 (ddd, $^3J_{HF}$ = 11.0, 4.0 Hz, $^3J_{HH}$ = 7 Hz) (1 H, H-4), 4.85 and 4.92 (q, $^3J_{HH}$ = 5.4 Hz, 1 H), 5.20 and 5.22 (d, $^3J_{HH}$ = 7 Hz, H-3); ^{13}C NMR δ 14.8 and 15.0, 19.6 and 19.8, 27.8, 61.2 and 63.4, 62.0 (q, $^2J_{CF}$ = 27.5 Hz, C-4) and 62.5 (q, $^2J_{CF}$ = 28 Hz, C-4), 73.6 and 75.2, 84.5 and 84.6, 101.0 and 101.1, 127.4 (q, $^1J_{CF}$ = 295 Hz, *C*F$_2$Cl), 146.7 and 146.8, 164.8 and 167.4. Anal. Calcd for $C_{13}H_{20}ClF_2NO_5$: C, 45.42; H, 5.86; N, 4.07. Found: C, 45.55; H, 5.96; N, 4.03.

Methyl *syn*-2-(Benzyloxy)-4,4,4-trifluoro-3-[(*tert*-butoxycarboxyl)amino]butanoate (10a). A solution of the azetidinone **9a** (315 mg, 0.912 mmol) in DMF (1.7 mL) was stirred with NaN_3 (67 mg, 1.03 mmol) and MeOH (1 mL) under Ar for 20 h at rt. After dilution with EtOAc and washing with brine, the extracts were dried ($MgSO_4$) and concentrated. The residue was purified on silica gel column (pentane/EtOAc, 75:25) to give the ester **10a** as a liquid (300 mg, 88%): ^{19}F NMR δ −73.5 (d, $^3J_{FH}$ = 7.6 Hz); ^{1}H NMR δ 1.42 (s, 9 H), 3.77 (s, 3 H, OCH$_3$) 4.3 (d, ^3J = 1.5 Hz, 1 H, H-2), 4.65 (q, J_{AB} = 11 Hz, δ_A 4.48, δ_B 4.82, 2 H), 4.75 (dq, $^3J_{HF}$ = 7.6 Hz, ^3J = 1.5 Hz, 1 H, H-3), 5.25 (s, 1 H, NH), 7.35 (m, 5 H); ^{13}C NMR δ 27.9, 52.5, 53.8 (q, $^2J_{CF}$ = 32 Hz, C-3), 73.0, 74.1 (q, $^3J_{CF}$ = 1.3 Hz), 80.8, 124.1 (q, $^1J_{CF}$ = 283 Hz, CF$_3$), 128.2, 128.4, 136.1, 154.6, 169.1. Anal. Calcd for $C_{17}H_{22}F_3NO_5$: C, 54.11; H, 5.87; N, 3.71. Found: 54.01; H, 5.86; N, 3.69.

Methyl *syn*-2-(Benzyloxy)-4,4-difluoro-3-[(*tert*-butoxycarboxyl)amino]butanoate (10b). A solution of the azetidinone **9b** (180 mg, 0.55 mmol) in DMF (1.5 mL) was stirred with NaN_3 (43 mg, 0.65 mmol) and MeOH (1 mL) under Ar for 18 h at rt. After workup, the crude product was purified on a silica gel column (pentane/EtOAc, 75:25) to give the ester **10b** as a liquid (138 mg, 70%): ^{19}F NMR δ −125.9 (ddd, $^2J_{FF}$ = 284 Hz, $^2J_{FH}$ = 56 Hz, $^3J_{FH}$ = 10 Hz, 1 F), −128.7 (ddd, $^2J_{FF}$ = 284 Hz, $^2J_{FH}$ = 56 Hz, $^3J_{FH}$ = 10 Hz, 1 F); ^{1}H NMR δ 1.45 (s, 9 H), 3.75 (s, 3 H, OCH$_3$), 4.2 (bs, 1 H, H-2), 4.35 (ddd, $^3J_{FH}$ = 10, 10 Hz, ^3J = 5.3 Hz, 1 H, H-3), 4.62 (q, $^3J_{AB}$ = 11 Hz, δ_A 4.43, δ_B 4.80, 2 H), 5.1 (d, ^3J = 10 Hz, 1 H, NH), 5.75 (ddd, $^3J_{HF}$ = 56, 56 Hz, ^3J = 5.3 Hz, 1 H, CF$_2$H), 7.35 (m, 5 H); ^{13}C NMR δ 28.0, 53.3, 53.3 (t, $^2J_{CF}$ = 26 Hz, C-3), 74.1, 75.6 (dd, $^3J_{CF}$ = 1.5 Hz, C-2), 81.4, 113.3 (t, $^1J_{CF}$ = 258 Hz, CF$_2$H), 129.3, 129.4, 137.3, 155.9, 170.7. Anal. Calcd for $C_{17}H_{23}F_2NO_5$: C, 56.82; H, 6.45; N, 3.90. Found: 56.68; H, 6.51; N, 3.88.

Methyl *syn*-2-(Benzyloxy)-4-(chloro-4,4-difluoro-3-[(*tert*-butoxycarboxyl)amino]butanoate (10c). A solution of the azetidinone **9c** (150 mg, 0.4 mmol) in DMF (1 mL) was stirred with NaN_3 (31 mg, 0.47 mmol) and MeOH (0.8 mL) under Ar for 16 h at rt. After workup, the crude product was purified on a silica gel column (pentane/EtOAc, 75:25) to give the ester **10c** as a liquid (136 mg, 83%): ^{19}F NMR δ −59.7 (d, $^3J_{FH}$ = 10 Hz); ^{1}H NMR δ 1.35 (s, 9 H), 3.70 (s, 3 H, OCH$_3$), 4.48 (d, ^3J = 0.9 Hz, 1 H, H-2), 4.64 (q, J_{AB} = 11 Hz, δ_A 4.43, δ_B 4.80, 2 H), 4.80 (tdd, $^3J_{FH}$ = 10 Hz, ^3J = 0.9, 10 Hz, 1 H, H-3), 5.25 (d, ^3J = 10 Hz, 1 H, NH), 7.30 (m, 5 H); ^{13}C NMR δ 28.2, 52.7, 58.8 (t, $^2J_{CF}$ = 26 Hz, C-3), 73.4, 74.6, 80.9, 127.8 (t, $^1J_{CF}$ = 293 Hz, CF$_2$Cl), 128.4, 128.5, 128.7, 136.3, 154.8, 169.5. Anal. Calcd for $C_{17}H_{22}ClF_2NO_5$: C, 51.85; H, 5.63; N, 3.56. Found: 51.77; H, 5.72; N, 3.49.

Methyl *syn*-2-Hydroxy-4,4,4-trifluoro-3-[(*tert*-butoxycarboxyl)amino]butanoate (11a). A solution of the amino ester **10a** (250 mg, 0.66 mmol) in anhydrous EtOAc (5 mL) was stirred under H_2 atmosphere in the presence of Pd/C (5%) (60 mg) for 18 h. After filtration on Celite and evaporation of the solvent, purification by SiO_2 chromatography (pentane−EtOAc, 60/40) provided the ester **11a** (190 mg, 98%): mp 69 °C (EtOAc); ^{19}F NMR δ −74.0 (d, $^3J_{FH}$ = 8 Hz); ^{1}H NMR δ 1.40 (s, 9 H), 3.24 (s, 1 H, O*H*), 3.82 (s, 3 H), 4.6 (d, ^3J = 1 Hz, 1 H, H-2), 4.70 (ddq, $^3J_{FH}$= 8 Hz, ^3J = 10, 1 Hz, 1 H, H-3), 5.18 (d, J = 10 Hz, 1 H, NH); ^{13}C NMR δ 28.1, 53.6, 53.7 (q, $^2J_{CF}$ = 31 Hz, C-3), 67.8 (d, $^3J_{CF}$ = 1 Hz, C-2), 81.1, 124.1 (q, $^1J_{CF}$ = 283 Hz, CF$_3$), 154.5, 171.9. Anal. Calcd for $C_{10}H_{16}F_3NO_5$: C, 41.81; H, 5.61; N, 4.87. Found: 42.02; H, 5.79; N, 4.76.

Methyl *syn*-2-Hydroxy-4,4-difluoro-3-[(*tert*-butoxycarboxy)amino]butanoate (11b). A solution of the amino ester **10b** (138 mg, 0.38 mmol) in anhydrous EtOAc (5 mL) was stirred under H_2 atmosphere in the presence of Pd/C (5%) (25 mg) for 18 h. After filtration on Celite and evaporation of the solvent, purification by SiO_2 chromatography (pentane−EtOAc, 60/40) of the residue provided the ester **11b** (100 mg, 97%): mp 69 °C (pentane/EtOAc); ^{19}F NMR δ −126.2 (ddd, $^2J_{FF}$ = 286 Hz, $^2J_{FH}$ = 59 Hz, $^3J_{FH}$ = 11 Hz, 1 F), −128.8 (ddd, $^2J_{FF}$ = 286 Hz, $^2J_{FH}$ = 56 Hz, $^3J_{FH}$ = 11 Hz, 1 F); ^{1}H NMR δ 1.42 (s, 9 H), 3.6 (s, 1 H, OH), 3.8 (s, 3 H, OCH$_3$), 4.37 (m, 1 H, H-3), 4.49 (s, 1 H, H-2), 5.22 (d, ^2J = 10 Hz, 1 H, NH), 5.80 (ddd, $^3J_{FH}$ = 59 Hz, $^3J_{FH}$ = 56 Hz, ^3J = 5 Hz, 1 H, CF$_2$H); ^{13}C NMR δ 28.0, 53.1, 54.2 (t, $^2J_{CF}$ = 25 Hz, C-3), 68.2 (d, $^3J_{CF}$ = 4.2 Hz, C-2), 80.5, 117.5 (t, $^1J_{CF}$ = 286 Hz, CF$_3$), 155.0, 172.5. Anal. Calcd for $C_{10}H_{17}F_3NO_5$: C, 44.61; H, 6.36; N, 5.20. Found: 44.49; H, 6.47; N, 5.03.

Methyl *syn*-2-Hydroxy-4-chloro-4,4-difluoro-3-[(*tert*-butoxycarboxyl)amino]butanoate (11c). A solution of the amino ester **10c** (136 mg, 0.35 mmol) in anhydrous EtOAc (4 mL) was stirred under H_2 atmosphere in the presence of Pd/C (10%) (65 mg) for 18 h. After filtration on Celite and evaporation of the solvent, the crude product was purified by SiO_2 chromatography (pentane−EtOAc, 60/40) and provided the ester **11c** (78 mg, 75%): mp 87 °C (pentane−EtOAc); ^{19}F NMR δ −60.3 (d, $^3J_{FH}$ = 10.6 Hz); ^{1}H NMR δ 1.45 (s, 9 H), 3.23 (d, ^3J = 4.1 Hz, 1 H, OH), 3.87 (s, 3 H, OCH$_3$), 4.69 (d, ^3J = 4.1 Hz, 1 H, H-2), 4.78 (dd, $^3J_{HF}$ = 10.6 Hz, ^3J = 10.5 Hz, 1 H, H-3), 5.25 (d, ^3J = 10.5 Hz, 1 H, NH); ^{13}C NMR δ 28.2, 53.4, 58.8 (t, $^2J_{CF}$ = 26 Hz, C-3), 68.2, 80.9, 127.8 (t, $^1J_{CF}$ = 298 Hz, CF$_2$Cl), 154.6 172.2. Anal. Calcd for $C_{17}H_{22}ClF_2NO_5$: C, 39.55; H, 5.31; N, 4.61. Found: 39.38; H, 5.52; N, 4.58.

Methyl *syn*-2-Hydroxy-4,4,4-trifluoro-3-aminobutanoate (4a). Trifluoroacetic acid (0.16 mL, 2.18 mmol) was added, under Ar, to a solution of *N*-Boc-amino ester **11a** (150 mg, 0.52 mmol) in CH_2Cl_2 (3 mL). The reaction mixture was stirred at

rt for 2 h, Et_2O was added (5 mL), and *N*-methylmorpholine was added until pH 7. After extraction with Et_2O, the organic phase was washed with brine, dried ($MgSO_4$), and evaporated to give the amino ester **4a**: ^{19}F NMR δ −76.1 (d, $^3J_{FH}$ = 7.4 Hz); ^1H NMR δ 1.7 (s, 2 H, NH_2), 3.55 (bs, 1 H, OH), 3.61 (dq, $^3J_{HF}$ = 7.4 Hz, ^3J = 1.2 Hz, 1 H, H-3), 3.85 (s, 3 H, OCH_3), 4.52 (d, ^3J = 1.2 Hz,1 H, H-2); ^{13}C NMR δ 53.5, 55.0 (q, $^2J_{CF}$ = 29 Hz, C-3), 68.9 (q, $^3J_{CF}$ = 2.0 Hz), 125.5 (q, $^1J_{CF}$ = 283 Hz, CF_3), 172.7. Anal. Calcd for $C_5H_9F_3NO_3$: C, 31.90; H, 4.82; N, 7.44. Found: 31.48; H, 5.07; N, 7.19.

***syn*-Methyl 2-Hydroxy-4,4-difluoro-3-aminobutanoate (4b).** Trifluoroacetic acid (0.16 mL, 2.18 mmol) was added, under Ar, to a solution of *N*-Boc-amino ester **11b** (150 mg, 0.52 mmol) in CH_2Cl_2 (3 mL). The reaction mixture was stirred at rt for 2 h, Et_2O was added (5 mL), and *N*-methylmorpholine was added until pH 7. After extraction with Et_2O, the organic phase was washed with brine, dried ($MgSO_4$), and evaporated to give the amino ester **4b** (40 mg, 64%): mp 60 °C (CH_2Cl_2−pentane); ^9F NMR δ −124.8 (ddd, $^2J_{FF}$ = 286 Hz, $^2J_{FH}$ = 56 Hz, $^3J_{FH}$ = 7 Hz, 1 F), −139.6 (dddd, $^2J_{FF}$ = 286 Hz, $^2J_{FH}$ = 57.5 Hz, $^3J_{FH}$ = 11 Hz, $^4J_{FH}$ = 1.3 Hz, 1 F); ^1H NMR δ 2.1 (bs, 3 H, NH_2 and OH), 3.83 (s, 3 H, OCH_3), 3.3 (dddd, $^3J_{FH}$ = 11, 7 Hz, ^3J = 6.3, 2 Hz, 1 H, H-3), 4.39 (m, ^3J = 2 Hz, $^4J_{FH}$ = 1.3 Hz, ^3J = 1 Hz, 1 H, H-2), 5.72 (ddd, $^3J_{HF}$ = 56, 57.5 Hz, ^3J = 6.4 Hz, 1 H, CF_2H); ^{13}C NMR δ 53.1, 55.7 (t, $^2J_{CF}$ = 23 Hz, C-3), 69.3 (dd, $^3J_{CF}$ = 6.7, 2 Hz), 116.2 (t, $^1J_{CF}$ = 291 Hz, CF_3), 173.1. Anal. Calcd for $C_5H_9F_2NO_3$: C, 35.51; H, 5.36; N, 8.28. Found: 37.34; H, 5.64; N, 7.81.

Reaction of the *N*-(2,2,2-Trifluoroethylidene)-4-methoxyaniline (6a) with Ester 15−17 Enolates: General Procedure. To a solution of LDA in THF, prepared at 0 °C from diisopropylamine (1.1 mmol) and BuLi (1.1 mol equiv of a 1.5 M solution in hexanes) in THF (2 mL), was added, after 30 min at −78 °C, the (silyloxy)acetate **15**−**17** (1.1 mol equiv). After 2 h, trifluoroacetaldimine **7a** (1.1 mole equiv) in solution in THF (1 mL) was added. The solution was stirred for 3 h at −78 °C and then allowed to warm to rt overnight. The resulting reaction mixture was then poured into a saturated ammonium chloride solution (10 mL) and extracted with diethyl ether (3 × 25 mL). The combined organic extracts were washed (brine), dried ($MgSO_4$), and evaporated to give a residue that was purified by chromatography on silica gel (pentane−EtOAc, 95:5).

Reaction with the Mesityl (Triisopropylsilyl)oxy Ester 15: *cis*-*N*-(4-Methoxyphenyl)-3-[(triisopropylsilyl)oxy]-4-(trifluoromethyl)azetidin-2-one (14). The reaction performed from **15** (500 mg, 1.18 mmol), trifluoroaldimine **7a** (240 mg, 1.18 mmol), and LDA (1.3 mmol equiv) afforded, after workup and purification, the *cis*-*N*-(4-methoxyphenyl)-3-[(triisopropylsilyl)oxy]-4-(trifluoromethyl)azetidin-2-one (**14**) (400 mg, 68%): ^{19}F NMR δ −68.8 (d, $^3J_{FH}$ = 5.5 Hz); ^1H NMR δ 0.82 (m, 3 H), 1.1 (bs, 18 H), 3.7 (s, 3 H), 4.5 (m, 1 H, H-4), 5.13 (d, ^3J = 5.1 Hz, 1 H, H-3), 7.0 (q, J = 10 Hz, 4 H, C_6H_4). Anal. Calcd for $C_{18}H_{16}F_3NO_3$: C, 61.54; H, 4.59; N, 4.0. Found: C, 61.17; H, 4.83; N, 3.81.

Reaction with the Menthyl (Triisopropylsilyl)oxy ester 16. The same reaction performed from ester **16** gave an unidentified mixture. Azetidinone **14** was not detected.

Reaction with the 2-Phenylcyclohexyl (Triisopropylsilyl)oxy ester 17. The reaction performed from **17** (355 mg, 1.15 mmol), trifluoroaldimine **7a** (230 mg, 1.15 mmol), and LDA (1.3 mmol equiv) afforded, after workup and purification, the azetidinone **14** (117 mg, 20%).

(*S*)-*N*-(2,2,2-Trifluoroethylidene)phenethylamine (18). A solution of ethyl trifluoroacetaldehyde hemiacetal (15 g, 0.1 mol), (*S*) phenylethylamine (9 g, 0.074 mol), and *p*-toluenesulfonic acid in toluene (150 mL) was refluxed under Ar for 1.5 h in a Dean−Stark apparatus. Et_2O (100 mL) was added, and the solution was washed with an aqueous solution of sodium hydrogenocarbonate and then with brine and dried ($MgSO_4$). The solution was evaporated under reduced pressure, and the residue was distilled leading to the (*S*)-*N*-(2,2,2-trifluoroethylidene)phenethylamine (**18**) (13.6 g, 55%): ^{19}F NMR δ −71.8 (d, $^3J_{FH}$ = 3.5 Hz); ^1H NMR δ 1.56 (d, ^3J = 6.6 Hz, 3 H, CH_3), 4.57 (q, ^3J = 6.6 Hz, 1 H), 7.3 (m, 5 H, C_6H_5), 7.6 (q, $^3J_{FH}$ = 3.5 Hz, 1 H); ^{13}C NMR δ 23.8, 68.6, 118.9 (q, ^1J = 284 Hz, CF_3), 126.5, 127.5, 128.6, 142.0, 147.9 (q, $^2J_{CF}$ = 38 Hz, *C*-CF_3).

***cis*-1-(*S*)-(Phenylethyl)-3-(benzyloxy)-4-(trifluoromethyl)azetidin-2-ones 19 and 20.** A solution of *N*-(2,2,2-trifluoroethylidene)phenethylamine **18** (7.6 g, 0.038 mol) and α-(benzyloxy)acetyl chloride (12 mL, 75.9 mmol) in freshly distilled CH_2Cl_2 (30 mL) was treated with NEt_3 (15.3 mL, 0.11 mol). The resulting mixture was then stirred overnight at 40 °C. The solution was poured into water (20 mL) and extracted with EtOAc (2 × 50 mL). The organic phase was washed with brine and dried over $MgSO_4$. After evaporation of solvent, the crude product was purified by crystallization in cold ethanol. The white solid was crystallized again (Et_2O/2-propanol) to give the pure azetidinone **19** (3.8 g, 29%, 99% of purity). The filtrate was evaporated, and the residue was purified by chromatography on a SiO_2 column (pentane−EtOAc 75:25) and by crystallization (pentane) to give the pure isomer **20** (5.5 g, 41%).

(*S*)-1-Phenylethyl-3(*R*)-(benzyloxy)-4(*R*)-(trifluoromethyl)azetidin-2-one (19): mp 108 °C (Et_2O-2-propanol); $[\alpha]^{25}_D$ −17.0° (*c* = 3, EtOAc); ^{19}F NMR δ − 69.2 (d, $^3J_{FH}$ = 7 Hz); ^1H NMR δ 1.57 (d, ^3J = 7.4 Hz, 3 H, CH_3), 3.7 (qd, $^3J_{HF}$ = 7 Hz, ^3J = 6.2 Hz, 1 H, H-4), 4.6 (d, ^3J = 6.2 Hz, 1 H, H-3), 4.66 (q, J_{AB} = 11.8 Hz, 2 H, $OCH_2C_6H_5$), 5.0 (q, J = 7.4 Hz, 1 H) 7.3 (m, 10 H, C_6H_5); ^{13}C NMR δ 18.2, 51.7, 56.7 (q, $^2J_{CF}$ = 34 Hz, C-4), 73.5, 80.3, 124.7 (q, $^1J_{CF}$ = 280 Hz, CF_3), 127.3, 127.9, 128.2, 128.3, 128.6, 129.0, 136.3, 138.1, 166.5. Anal. Calcd for $C_{20}H_{18}F_3NO_3$: C, 65.32; H, 5.19; N, 4.00. Found: 65.17; H, 5.27; N, 4.00.

(*S*)-1-(Phenylethyl)-3(*S*)-(benzyloxy)-4-(*S*)-(trifluoromethyl)azetidin-2-one (20): mp 44 °C (pentane); $[\alpha]^{25}_D$ −3.7° (*c* = 3, EtOAc); ^{19}F NM δ − 69.4 (d, $^3J_{FH}$ = 6 Hz); ^1H NMR δ 1.8 (d, ^3J = 7.2 Hz, 3 H, CH_3), 3.8 (qd, $^3J_{HF}$ = 6 Hz, ^3J = 6.0 Hz, 1 H, H-4), 4.5 (q, ^3J = 7.2 Hz, 1 H), 4.67 (d, ^3J = 6.0 Hz, 1 H, H-3), 4.69 (q, J_{AB} = 11.8 Hz, δ_A 4.73, δ_B 4.66, 2 H, $OCH_AH_BC_6H_5$), 7.3 (m, 10 H, C_6H_5); ^{13}C NMR δ 19.6, 55.7, 56.5 (q, $^2J_{CF}$ = 32.8 Hz, C-4), 73.4, 79.9, 124.0 (q, $^1J_{CF}$ = 280 Hz, CF_3), 126.6, 127.8, 128.2, 128.5, 129.0, 129.1, 136.3, 140.3, 166.6. Anal. Calcd for $C_{20}H_{18}F_3NO_3$: C, 65.32; H, 5.19; N, 4.00. Found: 65.10; H, 5.35; N, 4.15

Methyl 2-(*R*)-Benzyloxy-4,4,4-trifluoro-3(*R*)-[[(*S*)-phenylethyl]amino]butanoate (21). Azetidinone **19** (1 g, 3.03 mmol) was stirred in a methanol solution of HCl gas (3 M) (20 mL) at rt for 24 h. After evaporation of MeOH under reduced pressure at rt and treatment with *N*-methylmorpholine and extraction (CH_2Cl_2), the organic phases were washed with water (2 × 15 mL) and then with brine. After solvent evaporation, the residue was purified by SiO_2 chromatography and provided the amino ester **21** (910 mg, 84%): mp 68 °C (pentane); $[\alpha]^{25}_D$ −18.3° (*c* = 3, EtOAc); ^{19}F NMR δ − 72.6 (d, $^3J_{FH}$ = 7.5 Hz); ^1H NMR δ 1.1 (d, ^3J = 6.4 Hz, 3 H, CH_3), 2.25 (bs, 1 H, NH), 3.5 (m, $^3J_{FH}$ = 7.5 Hz, 1 H, H-3), 3.73 (s, 3 H), 3.85 (q, ^3J = 6.4 Hz, 1 H); 4.2 (d, ^3J = 1.7 Hz, 1 H, H-2); 4.6 (q, J_{AB} = 11.2 Hz, δ_A 4.45, δ_B 4.8, 2 H), 7.3 (m, 10 H); ^{13}C NMR δ 24.0, 52.0, 55.2, 58.2 (q, $^2J_{CF}$ = 28 Hz, C-3), 73.2, 74.6 (d, $^3J_{CF}$ = 2 Hz, C-2), 125.2 (q, $^1J_{CF}$ = 284 Hz, CF_3), 126 to 128, 136.7, 144.3, 171.0. Anal. Calcd for $C_{20}H_{22}F_3NO_3$: C, 63.00; H, 5.80; N, 3.70. Found: 62.96; H, 5.91; N, 3.69.

Methyl 2(*S*)-(Benzyloxy)-4,4,4-trifluoro-3(*S*)-[[(*S*)-phenylethyl]amino]butanoate (22). Following the same procedure, azetidinone **20** led to isoserinate **22**: mp 85 °C (pentane); $[\alpha]^{25}_D$ −72.7° (*c* = 3, EtOEt); ^{19}F NMR δ −69.1 (d, $^3J_{FH}$ = 6.5 Hz); ^1H NMR δ 1.23 (d, ^3J = 6.5 Hz, 3 H, CH_3), 2.15 (bs, 1 H, NH), 3.3 (q, $^3J_{HF}$ = 7.7 Hz, 1 H, H-3), 3.60 (s, 3 H, OCH_3), 3.97 (qd, $^3J_{HF}$ = 6.5 Hz, $^3J_{HH}$ = 1.4 Hz, 1 H, H-3); 4.11 (d, ^2J = 2.1 Hz, 1 H, H-2), 4.56 (q, J_{AB} = 11.2 Hz, δ_A 4.36, δ_B 4.76, 2 H), 7.3 (m, 10 H); ^{13}C NMR δ 25.0, 51.9, 55.0, 57.9 (q, $^2J_{CF}$ = 26.5 Hz, C-3), 73.3, 76.1 (d, $^3J_{CF}$ = 2.7 Hz, C-2), 125.9 (q, $^1J_{CF}$ = 289 Hz, CF_3), 127.2, 127.3, 128.0, 128.2, 128.3 128.4, 136.6, 143.9, 169.6. Anal. Calcd for $C_{20}H_{22}F_3NO_3$: C, 63.00; H, 5.80; N, 3.70. Found: 63.06; H, 5.95; N, 3.68.

Methyl 2(*R*)-Hydroxy-4,4,4-trifluoro-3(*R*)-[(*tert*-butoxycarbonyl)amino]butanoate (23). A solution of the amino ester **21** (930 mg, 2.44 mmol) and $(Boc)_2O$ (640 mg, 2.9 mmol) in anhydrous EtOAc (20 mL) was stirred under H_2 atmosphere

in the presence of $Pd(OH)_2/C$ (300 mg) for 24 h. After filtration on Celite and evaporation of the solvent, purification by SiO_2 chromatography (pentane−EtOAc, 60:40) provided the ester **23** (2*R*,3*R*) (526 mg, 75%): mp 96 °C (EtOAc, pentane); $[\alpha]^{25}_D$ −41.2° (*c* = 2, EtOAc); ^{19}F NMR δ −74.0 (d, $^3J_{FH}$ = 7.5 Hz); ^{1}H NMR δ 1.35 (s, 9 H), 3.25 (d, ^3J = 3.5 Hz, 1 H, H-2), 3.82 (s, 3 H), 4.57 (d, J = 3.5 Hz, 1 H, OH), 4.73 (dq, $^3J_{FH}$ = 7.8 Hz, ^3J = 10 Hz, 1 H, H-3); 5.18 (d, J = 10 Hz, 1 H, NH); ^{13}C NMR δ 27.9, 53.5, 53.6 (q, $^2J_{CF}$ = 31 Hz, C-3), 67.8, 81.0, 124.1 (q, $^1J_{CF}$ = 283 Hz, CF_3), 155.0, 172.0. Anal. Calcd for $C_{16}H_{16}NO_4$: C, 41.81; H, 5.61; N, 4.87. Found: 41.76; H, 5.74; N, 4.83.

Methyl 2(*S*)-Hydroxy-4,4,4-trifluoro-3(*S*)-[(*tert*-butoxycarbonyl)amino]butanoate (23). Following the same procedure, the compound **22** (930 mg, 2.44 mmol) led after workup to the ester **23** (2*S*,3*S*) (505 mg, 72%): mp 98 °C (EtOAc, pentane); $[\alpha]^{25}_D$ +42° (*c* = 2.5, EtOAc); ^{19}F NMR δ − 73.9 (d, $^3J_{FH}$ = 7.5 Hz); ^{1}H NMR δ 1.35 (s, 9 H), 3.25 (d, ^3J = 3.0 Hz, 1 H, H-2), 3.82 (s, 3 H), 4.57 (d, J = 3.0 Hz, 1 H, OH), 4.73 (dq, $^3J_{HF}$ = 7.5 Hz, ^3J = 10 Hz, 1 H, H-3), 5.18 (d, J = 10 Hz, 1 H, NH); ^{13}C NMR δ 27.9, 53.4, 53.6 (q, $^2J_{CF}$ = 31 Hz, C-3), 67.8, 81.0, 124.1 (q, $^1J_{CF}$ = 283 Hz, CF_3), 154.6, 172.0. Anal. Calcd for $C_{16}H_{16}F_3NO_4$: C, 41.81; H, 5.61; N, 4.87. Found: 41.87; H, 5.73; N, 4.84.

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Supporting Information Available: Crystal data for **21** (3 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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