DOI: 10.1002/ejoc.200900578

Synthesis of New Trifluoromethylated Hydroxyethylamine-Based Scaffolds

Christine Philippe,[a] Thierry Milcent,[a] Tam Nguyen Thi Ngoc,[a] Benoit Crousse,*[a] and Danièle Bonnet-Delpon[a]

Keywords: Protease / Hydroxyethylamine / Fluorine / Epoxides / Amino acids / Peptidomimetics

A very easy access to new trifluoromethyl-hydroxyethylamine (Tf-HEA) derivatives by epoxide ring opening with amino-containing compounds, including aliphatic amines, aniline, aqueous ammonia, hydroxylamine, hydrazine, amino acids and a dipeptide, is described herein. The reactions were carried out in protic solvents, without the use of any catalyst or any other additive. A comparison of the efficiency of water, fluorinated and non-fluorinated alcohols as solvents is reported. Total regioselectivity is observed, and the stereochemistry of the compounds is preserved.

Introduction

A number of protease inhibitors contain in their structure a pattern able to mimic the transition state of the substrate.[1] Among them, hydroxyethylamine (HEA) dipeptide isosteres (Figure 1) have been widely used as inhibitors of HIV-1 proteases,[2] metalloproteases,[3] plasmepsines,[4–7] cathepsines D[8] and β-secretases.[9–12]

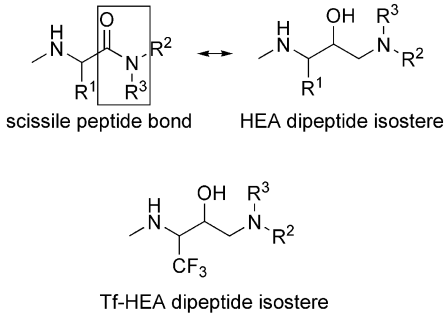
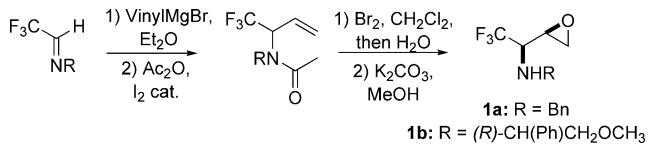


Figure 1. Replacement for the scissile peptide bond.

On the other hand, trifluoromethyl peptides and peptidomimetics play a crucial role in the development of analogues of protease inhibitors.[13–16] Due to their specific physico-chemical features (highly hydrophobic, electron–rich and sterically demanding), the fluorinated groups can greatly modify the behaviour of a molecule in a biological environment.[17–21] Indeed, the incorporation of trifluoromethyl groups into peptides and peptidomimetics can improve their resistance to metabolism and modify their structural properties and, hence, their binding with an enzyme or a receptor. The ability of a trifluoromethyl group to mimic a big lipophilic substituent (e.g. isobutyl or benzyl) allows it to efficiently replace the side chain of several amino acids (e.g. valine, leucine and phenylalanine) involved in enzyme inhibitors.[22] Furthermore, the electron-withdrawing effect of the trifluoromethyl group can decrease the pK_a of the neighbouring amino group and, thereby, increase its H-bond donating ability, leading to a putative improvement in the interaction with the enzyme. Considering that HEA is of great interest in protease inhibition and that the trifluoromethyl group offers interesting properties, we developed some new trifluoromethylated HEAs (Tf-HEAs, Figure 1). In this context, we focused our efforts on the ring-opening reactions of epoxides **1** with several nitrogen-containing compounds.

Results and Discussion

We synthesized epoxides **1** from trifluoromethyl imines using an efficient procedure previously described by our group (Scheme 1). Performing the same sequence with the aldimine substituted with the methyl ether of (*R*)-phenylglycinol, we obtained the epoxide **1b** as a single enantiomer of the (*R*,*R*) configuration.[23]



Scheme 1. Preparation of epoxides **1**.

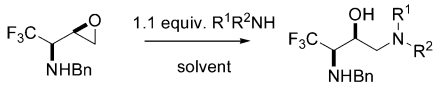
Epoxide ring opening with amines as a route to β-amino alcohols is widely described in the literature.[24,25] These reactions are usually carried out in protic solvents with an

[a] BioCIS CNRS UMR 8076, Faculté de Pharmacie, Univ. Paris Sud XI,
Rue Jean-Baptiste Clément, 92296 Châtenay-Malabry, France
Fax: +33-1-46835740
E-mail: benoit.crousse@u-psud.fr
http://www.biocis.u-psud.fr

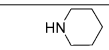
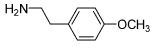
excess of amine or at elevated temperatures. In the case of poorly reactive aromatic amines, a variety of activators[26–29] have been introduced to facilitate the ring-opening reaction. Fluorinated alcohols have also been used to promote this reaction,[30] and recently, Azizi et al. reported epoxide ring opening with aliphatic amines in water without any catalyst.[31]

Thus, we investigated ring opening reactions of epoxides **1** with amines in water without catalyst, using 1.1 equiv. of the amines. In the case of aliphatic amines, we carried out reactions at room temperature. Under these mild conditions, we isolated the corresponding β-amino alcohols in good yields (Table 1, Entries 1–3). In all cases, we obtained only one regioisomer, resulting from the attack of the nucleophile at the less-hindered carbon of the epoxide. With aniline, no reaction occurred at room temperature. However, by heating the mixture at 60 °C, we produced the corresponding β-amino alcohol in good yield, albeit with a long reaction time (2 d). In this latter case, reaction conditions could be improved by changing the solvent to hexafluoropropan-2-ol (HFIP, b.p. 58 °C). Due to its H-bond donating ability, HFIP can activate oxirane ring opening with aromatic amines but not with aliphatic ones (Table 1, Entries 4 and 5).[30]

Table 1. Epoxide ring opening with amines.

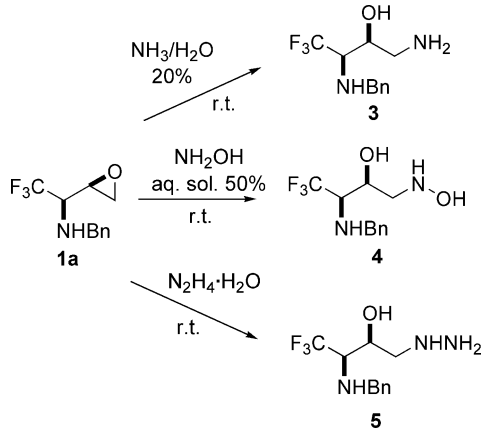


1a **2a–d**

Entry	Amine	Solvent	*T*	*t*	Yield (%)
1		H_2O	r.t.	4 h	**2a** (89)
2		H_2O	r.t.	2 d	**2b** (90)
3		H_2O	r.t.	2 d	**2c** (99)
4		H_2O	60 °C	2 d	**2d** (98)
5	–	HFIP	58 °C	3 h	**2d** (98)

The efficiency of the reaction in water prompted us to perform the oxirane ring opening of **1a** with an aqueous solution of ammonia (20%) and an aqueous solution of hydroxylamine (50%). These two reactions proceeded smoothly at room temperature and led to the corresponding β-amino alcohols **3** and **4** in quantitative yields (Scheme 2). Solvolysis with hydrazine hydrate was also successful and provided the product **5** in quantitative yield.

HEA-type inhibitors often require additional amino acids for recognition of the active site of the enzymes. In this context, a direct ring opening with amino acids or peptides is an attractive route to elaborate HEA scaffolds. Only a few examples of amino acid ring opening of oxiranes are described in the literature, in contrast to the many examples with secondary amines. In most of these cases, yields and the diversity of amino acids used were poor.[32–45] Currently, there are only two efficient methods for this reaction. The first one involves the use of $Ca(OTf)_2$ as a promoter of the



Scheme 2. Epoxide ring opening with ammonia, hydroxylamine and hydrazine.

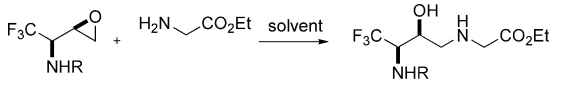
reaction.[46–47] The second one has recently been published by our group.[48] Reactions are simply performed in refluxing trifluoroethanol (TFE), which is a good H-bond donor.

Considering the above results (Table 1), we first performed the reaction in water on epoxide **1a** using 2 equiv. of glycine ethyl ester as the nucleophile. Under these conditions at room temperature, no reaction occurred, and switching to refluxing water offered no improvement. Hence, we carried out the reaction in fluorinated alcohols. HFIP proved to be unsatisfactory; ^{19}F NMR spectroscopic data indicated the formation of the desired **6a** accompanied with many side products. To maximize the yield, we stopped the reaction before its completion (Table 2, Entry 1). We made further attempts using refluxing TFE (b.p. 78 °C).[48] Under these conditions, the reaction time was decreased, and the crude product was cleaner (Table 2, Entry 2). Performing the reaction at room temperature did not decrease the amount of side products but significantly increased the reaction time (Table 2, Entry 3). To compare TFE to its non-fluorinated analogue, we investigated the epoxide ring opening in refluxing EtOH (Table 2, Entry 4). Surprisingly, we obtained product **6a** as fast as in TFE. Furthermore, the crude product was very clean. The reaction was also efficient using only 1 equiv. of glycine ethyl ester, but the reaction time increased to 10 h (Table 2, Entry 5). This observation is in accordance with our previous result.[48] With the enantiopure epoxide **1b**, we obtained similar results: reaction times in TFE and in EtOH were identical, but chemoselectivity was higher in EtOH than in TFE (Table 2, Entries 6–7). Consequently, we found EtOH to be the best solvent for this reaction.

We then explored the ring opening of epoxides **1** with other L-amino acids in refluxing EtOH. In all cases, we used 2 equiv. of amino acid. However, when the ester group of the amino acid was not an ethyl ester, transesterification occurred to a non-negligible extent (Table 3).

To overcome this problem, we used only methyl- and ethyl-ester-protected amino acids and carried out reactions in MeOH or in EtOH, respectively. We used different amino

Table 2. Optimization of the reaction.[a]



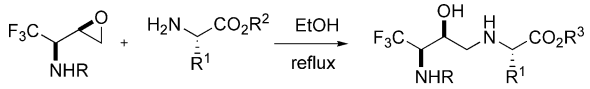
1a R = Bn
1b R = (*R*)-CH(Ph)CH$_2$OMe

6a R = Bn
6b R = (*R*)-CH(Ph)CH$_2$OMe

Entry	Epoxide	Solvent	*T* [°C]	*t* [h]	Conv. [%][b]	% Yield
1	**1a**	HFIP	58	6.25	88	45
2	**1a**	TFE	78	2	100	68
3	**1a**	TFE	r.t.	120	100	42
4	**1a**	EtOH	78	2	100	100
5	**1a**	EtOH[c]	78	10	100	100
6	**1b**	TFE	78	7.5	79	53
7	**1b**	EtOH	78	7	100	100

[a] Reactions conditions: 0.5 mmol of epoxide, 1 mmol of glycine ethyl ester. [b] Conversion was determined by ^{19}F NMR spectroscopy. [c] The reaction was performed with 1 equiv. of glycine ethyl ester.

Table 3. Transesterification.



1a R = Bn
1b R = (*R*)-CH(Ph)CH$_2$OMe

R^3 = R^2 or Et

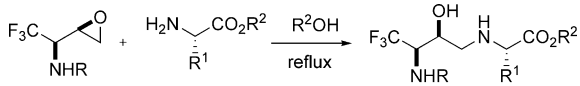
Entry	Epoxide	Amino acid	*t* [h]	R^2/Et	% Yield
1	**1a**	L-H-Phe-OBn	18	79/21	72
2	**1a**	L-H-Met-OMe	6	86/14	87
3	**1b**	L-H-Phe-OBn	18	84/16	81
4	**1b**	L-H-Met-OMe	18	72/28	71
5	**1b**	L-H-Ala-OMe	18	70/30	71

acids bearing an aliphatic, aromatic or functionalized side chain. Starting epoxides **1a**,**b**, *C*-protected amino acids, reaction times, products **6**–**12** and yields are listed in Table 4. With the epoxide **1a**, reactions were complete in less than 8 h and led to a mixture of two diastereomers (1:1), as confirmed by ^{19}F NMR spectroscopy. In most cases, 18 h were needed for a complete reaction with epoxide **1b**, probably due to steric hindrance, and we obtained only one diastereomer, indicating that no racemization occurred.

In all cases, the crude products were very clean. Chromatography on silica gel was required only for the elimination of the excess amino acid. Ring opening with amino acids afforded Tf-HEAs in good yields ranging between 65 and 94%. Using the dipeptide L-H-Phe-L-Ala-(OMe) (Table 4, Entries 7 and 14), the reaction led to the corresponding Tf-HEAs in moderate yields (45 and 38%, respectively) and a longer reaction time.

The debenzylation of **6a** provided the product **13**, which can serve as a useful platform for further peptidic coupling. Since this deprotection can be achieved in EtOH, we performed a preliminary, one-pot, ring-opening/debenzylation with **1a**. We placed this compound in refluxing EtOH with 1 equiv. of glycine ethyl ester. After 10 h, we submitted the product directly to hydrogenation. Thus, we obtained product **13**, without any purification, in a 89% yield (Scheme 3).

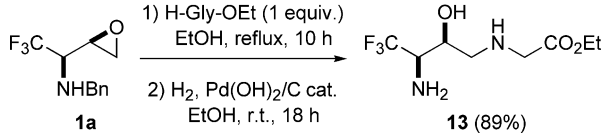
Table 4. Epoxides ring opening with amino acids and dipeptide.



1a R = Bn
1b R = (*R*)-CH(Ph)CH$_2$OMe

6–12

Entry	Epoxide	Amino acid	*t* [h]	Product	% Yield
1	**1a**	H-Gly-OEt	2	**6a**	77
2	**1a**	L-H-Ala-OMe	6.5	**7a**	65
3	**1a**	L-H-Phe-OMe	7.5	**8a**	87
4	**1a**	L-H-Tyr(Bn)-OMe	7	**9a**	84
5	**1a**	L-H-Met-OMe	6	**10a**	76
6	**1a**	L-H-Asp(OMe)-OMe	7	**11a**	89
7	**1a**	L-H-Phe-L-Ala-OMe	18	**12a**	45
8	**1b**	H-Gly-OEt	7	**6b**	76
9	**1b**	L-H-Ala-OMe	18	**7b**	67
10	**1b**	L-H-Phe-OMe	18	**8b**	94
11	**1b**	L-H-Tyr(Bn)-OMe	18	**9b**	78
12	**1b**	L-H-Met-OMe	18	**10b**	80
13	**1b**	L-H-Asp(OMe)-OMe	18	**11b**	75
14	**1b**	L-H-Phe-L-Ala-OMe	72	**12b**	38



Scheme 3. Ring opening and debenzylation in a one-pot process.

Conclusions

In summary, β-trifluoromethyl epoxide ring opening with nitrogen-containing derivatives was achieved in water or alcohol without any catalyst. Water proved to be very efficient with hydroxylamine, ammonia and aliphatic amines but less so with aromatic amines, which reacted faster in HFIP. With amino acids, reactions performed in water were unsuccessful. Better results were obtained with fluorinated alcohols; Tf-HEAs were always obtained accompanied by a variable amount of side products. Finally, EtOH and MeOH proved to be the most efficient solvents and promoters for this reaction, leading to high yields of Tf-HEAs without any additional catalyst. The corresponding fluorinated HEAs obtained are important building blocks for the synthesis of fluorinated transition-state-analogue inhibitors of proteases.

Experimental Section

General: Melting points were measured on a Stuart® SMP10 apparatus. ^{1}H, ^{13}C and ^{19}F NMR spectra were recorded with a Bruker® ARX 200 apparatus at 300, 75 and 188 MHz, respectively, in $CDCl_3$ with TMS as an internal standard for ^{1}H and ^{13}C and

$CFCl_3$ as an internal standard for ^{19}F NMR spectroscopy. Mass spectra were recorded with a Bruker® Esquire-LC apparatus. IR spectra were recorded with a Bruker® Vector 22 apparatus. Elemental analyses were carried out with an Ankersmit CAHN® 25 apparatus. Optical rotations were measured with an Optical Activity LTD Automatic polarimeter polAAr 32 apparatus at 589 nm. Column chromatography was performed on Merck® silica gel (60 μm) with cyclohexane/AcOEt or ether/cyclohexane as a system eluent.

General Procedure for the Synthesis of Products 2: Amine (1.1 equiv.) was added to a solution of epoxide **1a** (1 equiv.) in water or in HFIP. The resulting solution was stirred at room temperature or at reflux until the disappearance of the starting epoxide (monitored by ^{19}F NMR). The reaction medium was concentrated under reduced pressure, and the resulting oil was then purified by chromatography on silica gel.

3-(Benzylamino)-4,4,4-trifluoro-1-(piperidin-1-yl)butan-2-ol (2a): Epoxide **1a** (0.100 g, 0.43 mmol) and piperidine (0.040 g, 0.47 mmol) gave, after 4 h of stirring in water (3.5 mL) at room temperature and purification (ether/cyclohexane, 4:6), the product **2a** (0.121 g, 89%) as a light yellow oil. ^1H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 1.43 (m, 6 H, piperidine), 2.09 (dd, $^3J_{H,H}$ = 4.3, $^2J_{H,H}$ = 12.2 Hz, 1 H, H-1), 2.24 (m, 2 H, piperidine and H-1), 2.47 (m, 3 H, piperidine), 2.81 (qd, $^3J_{H,H}$ = 2.0, $^3J_{H,F}$ = 7.9 Hz, 1 H, H-3), 3.77 (d, $^2J_{H,H}$ = 13.2 Hz, 1 H, CH_2Ph), 3.89 (ddd, $^3J_{H,H}$ = 2.0, 4.3, 10.0 Hz, 1 H, H-2), 4.01 (d, $^2J_{H,H}$ = 13.2 Hz, 1 H, CH_2Ph), 7.22 (m, 5 H, Ar) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 24.1 (piperidine), 25.9 (2 C, piperidine), 52.1 (C-1), 54.4 (2 C, piperidine), 59.4 (q, $^2J_{C,F}$ = 28.8 Hz, C-3), 60.8 (CH_2Ph), 63.6 (C-2), 126.7 (q, $^1J_{C,F}$ = 286.4 Hz, C-4), 127.1 (Ar), 128.3 (4 C, Ar), 139.7 (Ar) ppm. ^{19}F NMR (188 MHz, $CDCl_3$, 25 °C): δ = –71.90 (d, $^3J_{F,H}$ = 7.9 Hz, 3 F) ppm. $C_{16}H_{23}F_3N_2O$ (316.36): calcd. C 60.74, H 7.33, N 8.85; found C 60.55, H 7.48, N 8.71.

1-(4-Methoxyphenethylamino)-3-(benzylamino)-4,4,4-trifluorobutan-2-ol (2b): Epoxide **1a** (0.100 g, 0.43 mmol) and 2-(4-methoxyphenyl)ethylamine (0.071 g, 0.47 mmol) gave, after 2 d of stirring in water (3.5 mL) at room temperature and purification (ether/petroleum spirit, 3:7), the product **2b** (0.148 g, 90%) as a yellow oil. ^1H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 2.40 (m, 1 H, CH_2PhOMe), 2.50 (m, 1 H, CH_2PhOMe), 2.50 (m, 2 H, H-1), 2.60 (m, 2 H, CH_2CH$_2$PhOMe), 2.82 (qd, $^3J_{H,H}$ = 4.0, $^3J_{H,F}$ = 7.8 Hz, 1 H, H-3), 3.53 (s, 3 H, OCH_3), 3.70 (d, $^2J_{H,H}$ = 13.2 Hz, 1 H, CH_2Ph), 3.75 (m, 1 H, H-2), 3.90 (d, $^2J_{H,H}$ = 13.2 Hz, 1 H, CH_2Ph), 6.75 (d, $^3J_{H,H}$ = 6.5 Hz, 2 H, Ar), 6.97 (d, $^3J_{H,H}$ = 6.5 Hz, 2 H, Ar), 7.20 (m, 5 H, Ar) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 35.3 (C-1), 50.7 (CH_2CH$_2$PhOMe), 51.9 (CH_2PhOMe), 52.0 (CH_2Ph), 54.8 (OCH_3), 59.9 (q, $^2J_{C,F}$ = 25.8 Hz, C-3), 66.2 (C-2), 126.5 (q, $^1J_{C,F}$ = 286.2 Hz, C-4), 113.9/127.1/128.3/129.5 (9 C, Ar), 131.6 (Ar), 139.6 (Ar), 158.2 (Ar) ppm. ^{19}F NMR (188 MHz, $CDCl_3$, 25 °C): δ = –71.6 (d, $^3J_{F,H}$ = 7.8 Hz, 3 F) ppm. $C_{20}H_{25}F_3N_2O_2$ (382.42): calcd. C 62.81, H 6.59, N 7.33; found C 62.85, H 6.70, N 7.28.

1,3-Bis(benzylamino)-4,4,4-trifluorobutan-2-ol (2c): Epoxide **1a** (0.060 g, 0.26 mmol) and benzylamine (0.03 mL, 0.286 mmol) gave, after 2 d of stirring in water (1 mL) at room temperature and after purification (ether/cyclohexane, 4:6), the product **2c** (0.079 g, 99%) as a yellow oil. ^1H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 3.25 (qd, $^3J_{H,H}$ = 3.2, $^3J_{H,F}$ = 7.8 Hz, 1 H, H-3), 3.96 (m, 2 H, H-1), 4.06 (m, 4 H, CH_2Ph and H-2), 4.27 (d, $^2J_{H,H}$ = 13.1 Hz, 1 H, CH_2Ph), 7.49 (m, 10 H, Ar) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 49.9 (C-1), 51.5 (CH_2Ph), 52.2 (CH_2Ph), 59.9 (q, $^2J_{C,F}$ = 25.8 Hz, C-3), 66.4 (C-2), 126.8 (q, $^1J_{C,F}$ = 286.0 Hz, C-4), 127.4/128.3/128.5 (10 C, Ar), 139.1 (Ar), 139.5 (Ar) ppm. ^{19}F NMR (188 MHz, $CDCl_3$, 25 °C): δ = –71.6 (d, $^3J_{F,H}$ = 7.8 Hz, 3 F) ppm. $C_{18}H_{21}F_3N_2O$ (338.37): calcd. C 63.89, H 6.26, N 8.28; found C 63.52, H 6.45, N 8.01.

3-(Benzylamino)-4,4,4-trifluoro-1-(phenylamino)butan-2-ol (2d): Epoxide **1a** (0.070 g, 0.30 mmol) and aniline (0.03 mL, 0.33 mmol) gave, after 3 h of refluxing in HFIP (2 mL) and purification (ether/cyclohexane, 4:6), the product **2d** (0.095 g, 98%) as a yellow light oil. ^1H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 2.75 (br. s, 2 H, NH), 3.05 (m, 1 H, H-3), 3.15 (m, 2 H, H-1), 3.78 (d, $^2J_{H,H}$ = 12.9 Hz, 1 H, CH_2Ph), 3.94 (m, 1 H, H-2), 4.08 (d, $^2J_{H,H}$ = 12.9 Hz, 1 H, CH_2Ph), 6.47 (m, 2 H, Ar), 6.63 (m, 1 H, Ar), 7.17 (m, 7 H, Ar) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 46.9 (C-1), 52.1 (CH_2Ph), 59.1 (q, $^2J_{C,F}$ = 28.8 Hz, C-3), 66.5 (C-2), 126.4 (q, $^1J_{C,F}$ = 286.1 Hz, C-4), 113.1/118.0/127.6/128.6/129.2 (10 C, Ar), 138.9 (Ar), 147.7 (Ar) ppm. ^{19}F NMR (188 MHz, $CDCl_3$, 25 °C): δ = –71.5 (d, $^3J_{F,H}$ = 7.7 Hz, 3 F) ppm. IR: $\tilde{\nu}$ = 3385, 1603, 1506 cm^{-1}. $C_{17}H_{19}F_3N_2O$ (324.34): calcd. C 62.95, H 5.90, N 8.64; found C 63.22, H 6.15, N 8.44.

General Procedure for the Synthesis of Products 3–5: An excess of the nitrogen-containing compound was added to epoxide **1a**. The resulting solution was vigorously stirred at room temperature until the disappearance of the starting epoxide (monitored by ^{19}F NMR). The removal of the excess nitrogen-containing compound was achieved under reduced pressure.

1-Amino-3-(benzylamino)-4,4,4-trifluorobutan-2-ol (3): Epoxide **1a** (0.060 g, 0.26 mmol) and NH_4OH (20%, 19.2 mL) gave, after 4 h of vigorous stirring at room temperature, the product **3** (0.064 g, 100%) as a light yellow oil. ^1H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 2.11 (br. s, 3 H, NH and NH_2), 2.69 (d, $^3J_{H,H}$ = 5.7 Hz, 2 H, H-1), 2.95 (qd, $^3J_{H,H}$ = 3.7, $^3J_{H,F}$ = 7.8 Hz, 1 H, H-3), 3.66 (m, 1 H, H-2), 3.76 (d, $^2J_{H,H}$ = 13.1 Hz, 1 H, CH_2Ph), 4.0 (d, $^2J_{H,H}$ = 13.1 Hz, 1 H, CH_2Ph), 7.22 (m, 5 H, Ar) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 44.5 (C-1), 52.1 (CH_2Ph), 59.7 (q, $^2J_{C,F}$ = 25.8 Hz, C-3), 68.5 (C-2), 126.6 (q, $^1J_{C,F}$ = 286.0 Hz, C-4), 127.3 (Ar), 128.4 (4 C, Ar), 139.3 (Ar) ppm. ^{19}F NMR (188 MHz, $CDCl_3$, 25 °C): δ = –71.6 (d, $^3J_{F,H}$ = 7.8 Hz, 3 F) ppm. MS (ESI): m/z = 249 $[M + H]^+$. IR: $\tilde{\nu}$ = 3350, 2924, 1454, 1261, 1129, 701, 629 cm^{-1}. $C_{11}H_{15}F_3N_2O$ (248.24): calcd. C 53.22, H 6.09, N 11.28; found C 53.55, H 5.80, N 10.99.

3-(Benzylamino)-4,4,4-trifluoro-1-(hydroxyamino)butan-2-ol (4): Epoxide **1a** (0.130 g, 0.56 mmol) and aqueous hydroxylamine 50% (2 mL) gave, after 16 h of vigorous stirring at room temperature, the product **4** (0.148 g, 100%) as a yellow light oil. ^1H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 2.64–2.98 (m, 3 H, H-1 and H-3), 3.71 (d, $^2J_{H,H}$ = 13.0 Hz, 1 H, CH_2Ph), 3.97 (d, $^2J_{H,H}$ = 13.0 Hz, 1 H, CH_2Ph), 4.09 (m, 1 H, H-2), 7.23 (m, 5 H, Ar) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 51.8 (C-1), 56.5 (CH_2Ph), 59.9 (q, $^2J_{C,F}$ = 25.7 Hz, C-3), 64.9 (C-2), 126.5 (q, $^1J_{C,F}$ = 286.8 Hz, C-4), 127.3 (Ar), 128.4 (4 C, Ar), 139.0 (Ar) ppm. ^{19}F NMR (188 MHz, $CDCl_3$, 25 °C): δ = –71.1 (d, $^3J_{F,H}$ = 7.5 Hz, 3 F) ppm. MS (APCI): m/z = 265 $[M + H]^+$. IR: $\tilde{\nu}$ = 3376, 2924, 1496, 1454, 1258, 1118, 1078, 1020, 978, 895, 852, 823, 659 cm^{-1}. $C_{11}H_{15}F_3N_2O_2$ (264.24): calcd. C 50.00, H 5.72, N 10.60; found C 50.38, H 5.63, N 10.43.

3-Benzylamino-4,4,4-trifluoro-1-hydrazinobutan-2-ol (5): Epoxide **1a** (0.0987 g, 0.427 mmol) and hydrazine (2 mL) gave, after 4 h of vigorous stirring at room temperature, the product **5** (0.1124 g, 100%) as a yellow oil. ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 2.61 (dd, $^3J_{H,H}$ = 3.3, $^2J_{H,H}$ = 12.6 Hz, 1 H, H-1), 2.83 (dd, $^3J_{H,H}$ = 8.7, $^2J_{H,H}$ = 12.6 Hz, 1 H, H-1), 2.90 (qd, $^3J_{H,H}$ = 3.3, $^3J_{H,F}$ = 7.8 Hz, 1 H, H-3), 3.53–3.76 (br. s, 3 H, NH), 3.73 (d, $^2J_{H,H}$ = 12.6 Hz, 1 H, CH_2Ph), 3.97 (d, $^2J_{H,H}$ = 12.6 Hz, 1 H, CH_2Ph),

3.95–4.00 (m, 1 H, H-2), 7.15–7.24 (m, 5 H, Ar) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 52.0 (C-1), 57.2 (*C*H_2Ph), 59.9 (q, $^2J_{C,F}$ = 25.6 Hz, C-3), 66.1 (C-2), 126.6 (q, $^1J_{C,F}$ = 284.6 Hz, C-4), 127.3 (Ar), 128.4 (4 C, Ar), 139.4 (Ar) ppm. ^{19}F NMR (188 MHz, $CDCl_3$, 25 °C): δ = –71.35 (d, $^3J_{F,H}$ = 7.8 Hz, 3 F) ppm. IR: $\tilde{\nu}$ = 3341, 1664, 1261, 1130, 697 cm^{-1}. $C_{11}H_{16}F_3N_3O$ (263.26): calcd. C 50.19, H 6.13, N 15.96; found C 50.57, H 5.75, N 15.70.

General Procedure for the Synthesis of Products 6–11: The *C*-protected amino acid salt (1.5 mmol) and potassium carbonate (2.5 mmol) were dissolved in water (3 mL). The free amino acid was extracted with diethyl ether (3 × 15 mL). The ethereal layer was then dried with magnesium sulphate, filtered and concentrated under reduced pressure at ambient temperature. The free amino acid (2 equiv.) was immediately introduced to an alcoholic solution of epoxide (1 equiv.). The reaction mixture was stirred at reflux until the disappearance of the starting epoxide (monitored by ^{19}F NMR). The reaction medium was concentrated under reduced pressure, and the resulting oil was then purified by chromatography on silica gel. Products **6a**–**11a** were obtained in the form of two diastereomers in a 1:1 ratio, which was determined from the ratio of integrals from ^{19}F NMR spectra. Products **6b**–**11b** were obtained in the form of one diastereomer.

Ethyl 2-[3-(Benzylamino)-4,4,4-trifluoro-2-hydroxybutylamino]acetate (6a): Epoxide **1a** (0.1156 g, 0.5 mmol) and H-Gly-OEt (0.103 g, 1.0 mmol) gave, after 2 h of refluxing in EtOH (1.25 mL) and purification (cyclohexane/AcOEt, 6:4), the product **6a** (0.128 g, 77%) as a yellow solid; m.p. 43–44 °C. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1.21 (t, $^3J_{H,H}$ = 7.2 Hz, 3 H, $CO_2CH_2CH_3$), 2.33–2.50 (br. s, 2 H, N*H*), 2.63 (dd, $^3J_{H,H}$ = 4.4, $^2J_{H,H}$ = 12.3 Hz, 1 H, CH_2CHOH), 2.71 (dd, $^3J_{H,H}$ = 7.4, $^2J_{H,H}$ = 12.3 Hz, 1 H, CH_2CHOH), 2.99 (qd, $^3J_{H,H}$ = 3.3, $^3J_{H,F}$ = 7.5 Hz, 1 H, C*H*CF_3), 3.30 (s, 2 H, H-2), 3.75–3.82 (m, 1 H, C*H*OH), 3.77 (d, $^2J_{H,H}$ = 13.1 Hz, 1 H, CH_2Ph), 4.02 (d, $^2J_{H,H}$ = 13.1 Hz, 1 H, CH_2Ph), 4.12 (q, $^3J_{H,H}$ = 7.2 Hz, 2 H, $CO_2CH_2CH_3$), 7.18–7.30 (m, 5 H, Ar) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 14.2 ($CO_2CH_2CH_3$), 50.5 (*C*H_2CHOH), 52.0 (C-2), 52.1 (*C*H_2Ph), 59.7 (q, $^2J_{C,F}$ = 25.8 Hz, *C*HCF_3), 60.9 ($CO_2CH_2CH_3$), 66.6 (*C*HOH), 126.6 (q, $^1J_{C,F}$ = 284.5 Hz, *C*F_3), 127.3 (Ar), 128.4 (2 C, Ar), 128.4 (2 C, Ar), 139.4 (Ar), 172.4 (C-1) ppm. ^{19}F NMR (188 MHz, $CDCl_3$, 25 °C): δ = –71.49 (d, $^3J_{F,H}$ = 7.5 Hz, 3 F) ppm. MS (ESI): *m*/*z* = 335.3 [M + H]$^+$, 357.3 [M + Na]$^+$. IR: $\tilde{\nu}$ = 2940, 1729, 1448, 1256, 1206, 1115, 862, 694 cm^{-1}. $C_{15}H_{21}F_3N_2O_3$ (334.33): calcd. C 53.89, H 6.33, N 8.38; found C 54.21, H 6.70, N 7.99.

(*S*)-Methyl 2-[3-(Benzylamino)-4,4,4-trifluoro-2-hydroxybutylamino]-propanoate (7a): Epoxide **1a** (0.1156 g, 0.5 mmol) and L-H-Ala-OMe (0.103 g, 1.0 mmol) gave, after 6.5 h of refluxing in MeOH (1.25 mL) and purification (cyclohexane/AcOEt, 7:3), the product **7a** (0.108 g, 65%) as a colourless oil. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1.19 (d, $^3J_{H,H}$ = 6.9 Hz, 3 H, H-3), 1.20 (d, $^3J_{H,H}$ = 6.9 Hz, 3 H, H-3), 2.33–2.53 (br. s, 2 H, N*H*), 2.46–2.53 (m, 2 H, CH_2CHOH), 2.65–2.75 (m, 2 H, CH_2CHOH), 2.92–3.04 (m, 2 H, C*H*CF_3), 3.20 (q, $^3J_{H,H}$ = 6.9 Hz, 1 H, H-2), 3.24 (q, $^3J_{H,H}$ = 6.9 Hz, 1 H, H-2), 3.65 (s, 3 H, CO_2Me), 3.65 (s, 3 H, CO_2Me), 3.72–3.83 (m, 2 H, C*H*OH), 3.76 (d, $^2J_{H,H}$ = 13.4 Hz, 2 H, CH_2Ph), 4.01 (d, $^2J_{H,H}$ = 13.4 Hz, 2 H, CH_2Ph), 7.18–7.27 (m, 10 H, Ar) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 19.0 (C-3), 19.2 (C-3), 50.3 (2 C, *C*H_2CHOH), 51.8 (CO_2Me), 51.9 (CO_2Me), 52.1 (*C*H_2Ph), 52.1 (*C*H_2Ph), 56.2 (C-2), 56.7 (C-2), 59.5 (q, $^2J_{C,F}$ = 25.8 Hz, *C*HCF_3), 60.0 (q, $^2J_{C,F}$ = 25.6 Hz, *C*HCF_3), 66.4 (q, $^3J_{C,F}$ = 2.4 Hz, *C*HOH), 67.0 (q, $^3J_{C,F}$ = 2.2 Hz, *C*HOH), 126.6 (q, $^1J_{C,F}$ = 284.6 Hz, 2 C, *C*F_3), 127.3 (Ar), 127.3 (Ar), 128.4/128.4/128.4 (8 C, Ar), 139.4 (Ar), 139.4 (Ar), 175.8 (C-1), 175.8 (C-1) ppm. ^{19}F NMR (188 MHz, $CDCl_3$, 25 °C): δ = –71.44 (d, $^3J_{F,H}$ = 7.7 Hz, 3 F), –71.57 (d, $^3J_{F,H}$ = 7.7 Hz, 3 F) ppm. MS (APCI): *m*/*z* = 335.2 [M + H]$^+$. IR: $\tilde{\nu}$ = 2950, 1737, 1650, 1454, 1260, 1128, 731, 698 cm^{-1}. $C_{15}H_{21}F_3N_2O_3$ (334.33): calcd. C 53.89, H 6.33, N 8.38; found C 54.23, H 6.21, N 8.37.

(*S*)-Methyl 2-[3-(Benzylamino)-4,4,4-trifluoro-2-hydroxybutylamino]-3-phenylpropanoate (8a): Epoxide **1a** (0.1156 g, 0.5 mmol) and L-H-Phe-OMe (0.179 g, 1.0 mmol) gave, after 7.5 h of refluxing in MeOH (1.25 mL) and purification (cyclohexane/AcOEt, 8:2), the product **8a** (0.178 g, 87%) as a colourless oil. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1.65–2.04 (br. s, 2 H, N*H*), 2.35–2.42 (m, 2 H, H-3), 2.63–2.77 (m, 4 H, H-3 and CH_2CHOH), 2.83–2.93 (m, 4 H, CH_2CHOH and C*H*CF_3), 3.31–3.38 (m, 2 H, H-2), 3.58 (s, 3 H, CO_2Me), 3.59 (s, 3 H, CO_2Me), 3.63–3.71 (m, 4 H, C*H*OH and CH_2Ph), 3.93 (d, $^2J_{H,H}$ = 13.2 Hz, 2 H, CH_2Ph), 7.03–7.06 (m, 4 H, Ar), 7.10–7.25 (m, 16 H, Ar) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 39.6 (C-3), 39.7 (C-3), 50.3 (*C*H_2CHOH), 50.5 (*C*H_2CHOH), 51.7 (CO_2Me), 51.7 (CO_2Me), 52.0 (*C*H_2Ph), 52.0 (*C*H_2Ph), 59.1 (q, $^2J_{C,F}$ = 25.8 Hz, *C*HCF_3), 59.7 (q, $^2J_{C,F}$ = 25.6 Hz, *C*HCF_3), 62.4 (C-2), 63.0 (C-2), 66.2 (q, $^3J_{C,F}$ = 2.2 Hz, *C*HOH), 67.0 (q, $^3J_{C,F}$ = 2.2 Hz, *C*HOH), 126.5 (q, $^1J_{C,F}$ = 284.0 Hz, 2 C, *C*F_3), 126.7/126.8/127.2/128.3/128.4/129.0 (20 C, Ar), 137.0 (2 C, Ar), 139.4 (2 C, Ar), 174.7 (C-1), 174.7 (C-1) ppm. ^{19}F NMR (188 MHz, $CDCl_3$, 25 °C): δ = –71.38 (d, $^3J_{F,H}$ = 8.5 Hz, 3 F), –71.46 (d, $^3J_{F,H}$ = 7.5 Hz, 3 F) ppm. MS (APCI): *m*/*z* = 411.2 [M + H]$^+$. IR: $\tilde{\nu}$ = 2931, 1734, 1454, 1261, 1129, 745, 698 cm^{-1}. $C_{21}H_{25}F_3N_2O_3$ (410.43): calcd. C 61.45, H 6.14, N 6.83; found C 61.57, H 6.31, N 6.66.

(*S*)-Methyl 2-[3-(Benzylamino)-4,4,4-trifluoro-2-hydroxybutylamino]-3-[4-(benzyloxy)phenyl]propanoate (9a): Epoxide **1a** (0.1156 g, 0.5 mmol) and L-H-Tyr(Bn)-OMe (0.285 g, 1.0 mmol) gave, after 7 h of refluxing in MeOH (1.25 mL) and purification (cyclohexane/AcOEt, 8:2), the product **9a** (0.217 g, 84%) as a colourless oil. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1.83–2.24 (br. s, 2 H, N*H*), 2.37–2.45 (m, 2 H, H-3), 2.65–2.95 (m, 8 H, H-3 and CH_2CHOH and C*H*CF_3), 3.28–3.35 (m, 2 H, H-2), 3.59 (s, 3 H, CO_2Me), 3.59 (s, 3 H, CO_2Me), 3.65–3.74 (m, 2 H, C*H*OH), 3.69 (d, $^2J_{H,H}$ = 12.9 Hz, 2 H, CH_2Ph), 3.95 (d, $^2J_{H,H}$ = 12.9 Hz, 2 H, CH_2Ph), 4.92 (s, 4 H, OCH_2Ph), 6.80 (d, $^3J_{H,H}$ = 8.6 Hz, 4 H, Ar), 6.96 (d, $^3J_{H,H}$ = 8.6 Hz, 4 H, Ar), 7.16–7.34 (m, 20 H, Ar) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 38.8 (C-3), 38.8 (C-3), 50.3 (*C*H_2CHOH), 50.5 (*C*H_2CHOH), 51.7 (CO_2Me), 51.8 (CO_2Me), 52.0 (2 C, *C*H_2Ph), 59.2 (q, $^2J_{C,F}$ = 25.9 Hz, *C*HCF_3), 59.8 (q, $^2J_{C,F}$ = 25.6 Hz, *C*HCF_3), 62.5 (C-2), 63.2 (C-2), 66.2 (q, $^3J_{C,F}$ = 2.4 Hz, *C*HOH), 67.0 (q, $^3J_{C,F}$ = 2.4 Hz, *C*HOH), 69.9 (2 C, O*C*H_2Ph), 126.6 (q, $^1J_{C,F}$ = 284.6 Hz, 2 C, *C*F_3), 114.8/127.3/127.3/127.4/127.9/128.3/128.4/128.4/128.5/130.1 (28 C, Ar), 129.2 (Ar), 129.3 (Ar), 136.9 (2 C, Ar), 139.4 (2 C, Ar), 157.7 (2 C, Ar), 174.7 (C-1), 174.8 (C-1) ppm. ^{19}F NMR (188 MHz, $CDCl_3$, 25 °C): δ = –71.36 (d, $^3J_{F,H}$ = 7.5 Hz, 3 F), –71.45 (d, $^3J_{F,H}$ = 7.5 Hz, 3 F) ppm. MS (APCI): *m*/*z* = 517.4 [M + H]$^+$. IR: $\tilde{\nu}$ = 2925, 1734, 1511, 1454, 1241, 1130, 1025, 735, 697 cm^{-1}. $C_{28}H_{31}F_3N_2O_4$ (516.55): calcd. C 65.10, H 6.05, N 5.42; found C 64.92, H 6.25, N 5.17.

(*S*)-Methyl 2-[3-(Benzylamino)-4,4,4-trifluoro-2-hydroxybutylamino]-4-(methylthio)butanoate (10a): Epoxide **1a** (0.1156 g, 0.5 mmol) and L-H-Met-OMe (0.163 g, 1.0 mmol) gave, after 6 h of refluxing in MeOH (1.25 mL) and purification (cyclohexane/AcOEt, 8:2), the product **10a** (0.134 g, 76%) as a colourless oil. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1.64–1.76 (m, 2 H, H-3), 1.81–1.93 (m, 2 H, H-3), 2.00 (s, 6 H, S*Me*), 2.23–2.50 (br. s, 2 H, N*H*), 2.40–2.50 (m, 6 H, H-4 and CH_2CHOH), 2.73 (dd, $^3J_{H,H}$ = 4.2, $^2J_{H,H}$ = 12.2 Hz, 1 H, CH_2CHOH), 2.77 (dd, $^3J_{H,H}$ = 6.9, $^2J_{H,H}$ = 12.2 Hz, 1 H,

CH_2CHOH), 2.97 (qd, $^3J_{H,H}$ = 2.9, $^3J_{H,F}$ = 7.6 Hz, 1 H, CHCF$_3$), 3.05 (qd, $^3J_{H,H}$ = 3.4, $^3J_{H,F}$ = 7.8 Hz, 1 H, CHCF$_3$), 3.25 (dd, $^3J_{H,H}$ = 5.1, 8.6 Hz, 1 H, H-2), 3.28 (dd, $^3J_{H,H}$ = 5.4, 8.4 Hz, 1 H, H-2), 3.66 (s, 3 H, CO$_2$*Me*), 3.66 (s, 3 H, CO$_2$*Me*), 3.71–3.83 (m, 2 H, CHOH), 3.76 (d, $^2J_{H,H}$ = 13.4 Hz, 2 H, CH_2Ph), 4.01 (d, $^2J_{H,H}$ = 13.4 Hz, 2 H, CH_2Ph), 7.16–7.27 (m, 10 H, Ar) ppm. ^{13}C NMR (75 MHz, CDCl$_3$, 25 °C): δ = 15.3 (S*Me*), 15.3 (S*Me*), 30.5 (2 C, C-4), 32.4 (C-3), 32.5 (C-3), 50.5 (*C*H$_2$CHOH), 50.5 (*C*H$_2$CHOH), 51.9 (CO$_2$*Me*), 51.9 (CO$_2$*Me*), 52.1 (*C*H$_2$Ph), 52.1 (*C*H$_2$Ph), 59.0 (q, $^2J_{C,F}$ = 25.8 Hz, *C*HCF$_3$), 59.7 (C-2), 60.0 (q, $^2J_{C,F}$ = 25.6 Hz, *C*HCF$_3$), 60.3 (C-2), 66.4 (q, $^3J_{C,F}$ = 2.2 Hz, *C*HOH), 67.2 (q, $^3J_{C,F}$ = 2.4 Hz, *C*HOH), 126.6 (q, $^1J_{C,F}$ = 284.9 Hz, *C*F$_3$), 126.6 (q, $^1J_{C,F}$ = 284.9 Hz, *C*F$_3$), 127.3 (Ar), 127.3 (Ar), 128.4 (4 C, Ar), 128.4 (4 C, Ar), 139.3 (Ar), 139.3 (Ar), 175.1 (C-1), 175.2 (C-1) ppm. ^{19}F NMR (188 MHz, CDCl$_3$, 25 °C): δ = –71.39 (d, $^3J_{F,H}$ = 7.6 Hz, 3 F), –71.48 (d, $^3J_{F,H}$ = 7.8 Hz, 3 F) ppm. MS (APCI): *m*/*z* = 395.2 [M + H]$^+$. IR: $\tilde{\nu}$ = 2919, 1733, 1454, 1260, 1128, 732, 699 cm^{-1}. $C_{17}H_{25}F_3N_2O_3S$ (394.45): calcd. C 51.76, H 6.39, N 7.10; found C 52.13, H 6.17, N 7.03.

(*S*)-Dimethyl 2-[3-(Benzylamino)-4,4,4-trifluoro-2-hydroxybutylamino]succinate (11a): Epoxide **1a** (0.1156 g, 0.5 mmol) and L-H-Asp(OMe)-OMe (0.161 g, 1.0 mmol) gave, after 7 h of refluxing in MeOH (1.25 mL) and purification (cyclohexane/AcOEt, 7:3), the product **11a** (0.175 g, 89%) as a colourless oil. ^{1}H NMR (300 MHz, CDCl$_3$, 25 °C): δ = 2.03–2.40 (br. s, 2 H, N*H*), 2.48–2.56 (m, 4 H, CH_2CHOH and H-3), 2.60–2.69 (m, 2 H, CH_2CHOH and H-3), 2.78–2.86 (m, 2 H, CH_2CHOH and H-3), 2.96 (qd, $^3J_{H,H}$ = 3.0, $^3J_{H,F}$ = 7.8 Hz, 1 H, CHCF$_3$), 3.01 (qd, $^3J_{H,H}$ = 3.6, $^3J_{H,F}$ = 8.1 Hz, 1 H, CHCF$_3$), 3.52 (dd, $^3J_{H,H}$ = 7.8, 14.4 Hz, 1 H, H-2), 3.54 (dd, $^3J_{H,H}$ = 7.5, 14.1 Hz, 1 H, H-2), 3.60 (s, 6 H, CO$_2$*Me*), 3.67 (s, 6 H, CO$_2$*Me*), 3.70–3.82 (m, 4 H, CH_2Ph and CHOH), 4.00 (d, $^2J_{H,H}$ = 13.5 Hz, 2 H, CH_2Ph), 7.18–7.27 (m, 10 H, Ar) ppm. ^{13}C NMR (75 MHz, CDCl$_3$, 25 °C): δ = 37.8 (C-3), 37.8 (C-3), 50.5 (*C*H$_2$CHOH), 50.7 (*C*H$_2$CHOH), 51.9 (CO$_2$*Me*), 51.9 (CO$_2$*Me*), 52.1 (2 C, *C*H$_2$Ph), 52.2 (CO$_2$*Me*), 52.2 (CO$_2$*Me*), 57.2 (C-2), 58.0 (C-2), 59.3 (q, $^2J_{C,F}$ = 25.8 Hz, *C*HCF$_3$), 59.8 (q, $^2J_{C,F}$ = 25.7 Hz, *C*HCF$_3$), 66.4 (q, $^3J_{C,F}$ = 2.2 Hz, *C*HOH), 67.3 (q, $^3J_{C,F}$ = 2.1 Hz, *C*HOH), 126.6 (q, $^1J_{C,F}$ = 285.3 Hz, 2 C, *C*F$_3$), 127.3 (2 C, Ar), 128.3 (4 C, Ar), 128.4 (4 C, Ar), 139.4 (Ar), 139.4 (Ar), 171.2/171.2/173.7/173.8 (4 C, C-1 and C-4) ppm. ^{19}F NMR (188 MHz, CDCl$_3$, 25 °C): δ = –71.37 (d, $^3J_{F,H}$ = 7.8 Hz, 3 F), –71.51 (d, $^3J_{F,H}$ = 8.1 Hz, 3 F) ppm. MS (ESI): *m*/*z* = 415.1 [M + Na]$^+$. IR: $\tilde{\nu}$ = 2924, 1736, 1438, 1262, 1133, 702, 631 cm^{-1}. $C_{17}H_{23}F_3N_2O_5$ (392.37): calcd. C 52.04, H 5.91, N 7.14; found C 52.40, H 5.71, N 6.87.

Ethyl 2-{(2*S*,3*R*)-3-[(*R*)-2-Methoxy-1-phenylethylamino]-4,4,4-trifluoro-2-hydroxybutylamino}acetate (6b): Epoxide **1b** (0.4812 g, 1.75 mmol) and H-Gly-OEt (0.360 g, 3.5 mmol) gave, after 7 h of refluxing in EtOH (4.4 mL) and purification (cyclohexane/AcOEt, 1:1), the product **6b** (0.5044 g, 76%) as a yellow solid; m.p. 51–52 °C. ^{1}H NMR (300 MHz, CDCl$_3$, 25 °C): δ = 1.22 (t, $^3J_{H,H}$ = 7.2 Hz, 3 H, CO$_2$CH$_2$C*H*$_3$), 2.33–2.63 (br. s, 1 H, N*H*), 2.76 (dd, $^3J_{H,H}$ = 4.5, $^2J_{H,H}$ = 12.0 Hz, 1 H, CH_2CHOH), 2.82 (dd, $^3J_{H,H}$ = 7.8, $^2J_{H,H}$ = 12.0 Hz, 1 H, CH_2CHOH), 3.05 (qd, $^3J_{H,H}$ = 3.0, $^3J_{H,F}$ = 8.3 Hz, 1 H, CHCF$_3$), 3.29 (s, 3 H, CH$_2$O*Me*), 3.34–3.42 (m, 2 H, CH_2OMe), 3.37 (s, 2 H, H-2), 3.86 (ddd, $^3J_{H,H}$ = 3.0, 4.5, 7.8 Hz, 1 H, CHOH), 3.97–4.08 (m, 1 H, CHPh), 4.14 (q, $^3J_{H,H}$ = 7.2 Hz, 2 H, CO$_2$CH_2CH$_3$), 7.19–7.32 (m, 5 H, Ar) ppm. ^{13}C NMR (75 MHz, CDCl$_3$, 25 °C): δ = 14.2 (CO$_2$CH$_2$*C*H$_3$), 50.5 (*C*H$_2$CHOH), 52.3 (C-2), 58.8 (q, $^2J_{C,F}$ = 26.8 Hz, *C*HCF$_3$), 58.9 (CH$_2$O*Me*), 60.9 (CO$_2$*C*H$_2$CH$_3$), 61.9 (*C*HPh), 67.6 (q, $^3J_{C,F}$ = 1.6 Hz, *C*HOH), 78.0 (*C*H$_2$OMe), 126.1 (q, $^1J_{C,F}$ = 281.8 Hz, *C*F$_3$), 127.8/127.9/128.4 (5 C, Ar), 140.0 (Ar), 172.4 (C-1) ppm. ^{19}F NMR (188 MHz, CDCl$_3$, 25 °C): δ = –73.24 (d, $^3J_{F,H}$ = 8.3 Hz, 3 F) ppm. MS (APCI): *m*/*z* = 379.1 [M + H]$^+$. IR: $\tilde{\nu}$ = 2870, 1725, 1451, 1204, 1150, 1103, 865, 692, 679 cm^{-1}. $C_{17}H_{25}F_3N_2O_4$ (378.39): calcd. C 53.96, H 6.66, N 7.40; found C 54.22, H 6.78, N 7.21. $[\alpha]_D^{25}$ = –57 (*c* = 1, CH_2Cl_2).

(*S*)-Methyl 2-{(2*S*,3*R*)-3-[(*R*)-2-Methoxy-1-phenylethylamino]-4,4,4-trifluoro-2-hydroxybutylamino}propanoate (7b): Epoxide **1b** (0.1375 g, 0.5 mmol) and L-H-Ala-OMe (0.103 g, 1.0 mmol) gave, after 18 h of refluxing in MeOH (1.25 mL) and purification (cyclohexane/AcOEt, 7:3), the product **7b** (0.127 g, 67%) as a colourless oil. ^{1}H NMR (300 MHz, CDCl$_3$, 25 °C): δ = 1.25 (d, $^3J_{H,H}$ = 7.2 Hz, 3 H, H-3), 2.59 (dd, $^3J_{H,H}$ = 4.5, $^2J_{H,H}$ = 12.0 Hz, 1 H, CH_2CHOH), 2.48–2.68 (br. s, 1 H, N*H*), 2.83 (dd, $^3J_{H,H}$ = 8.1, $^2J_{H,H}$ = 12.0 Hz, 1 H, CH_2CHOH), 3.03 (qd, $^3J_{H,H}$ = 2.4, $^3J_{H,F}$ = 8.2 Hz, 1 H, CHCF$_3$), 3.28 (s, 3 H, CH$_2$O*Me*), 3.30–3.38 (m, 3 H, CH_2OMe and H-2), 3.66 (s, 3 H, CO$_2$*Me*), 3.87 (ddd, $^3J_{H,H}$ = 2.4, 4.5, 8.1 Hz, 1 H, CHOH), 4.04 (dd, $^3J_{H,H}$ = 4.8, 7.8 Hz, 1 H, CHPh), 7.16–7.31 (m, 5 H, Ar) ppm. ^{13}C NMR (75 MHz, CDCl$_3$, 25 °C): δ = 19.1 (C-3), 50.5 (*C*H$_2$CHOH), 51.8 (CO$_2$*Me*), 56.0 (C-2), 58.8 (CH$_2$O*Me*), 58.8 (q, $^2J_{C,F}$ = 26.6 Hz, *C*HCF$_3$), 61.9 (*C*HPh), 67.3 (q, $^3J_{C,F}$ = 2.1 Hz, *C*HOH), 77.9 (*C*H$_2$OMe), 126.1 (q, $^1J_{C,F}$ = 281.8 Hz, *C*F$_3$), 127.8/128.4 (5 C, Ar), 140.0 (Ar), 175.8 (C-1) ppm. ^{19}F NMR (188 MHz, CDCl$_3$, 25 °C): δ = –73.20 (d, $^3J_{F,H}$ = 8.2 Hz, 3 F) ppm. MS (APCI): *m*/*z* = 379.2 [M + H]$^+$. IR: $\tilde{\nu}$ = 2926, 1736, 1454, 1266, 1136, 701 cm^{-1}. $C_{17}H_{25}F_3N_2O_4$ (378.39): calcd. C 53.96, H 6.66, N 7.40; found C 54.36, H 6.87, N 7.02. $[\alpha]_D^{25}$ = –65 (*c* = 1, MeOH).

(*S*)-Methyl 2-{(2*S*,3*R*)-3-[(*R*)-2-Methoxy-1-phenylethylamino]-4,4,4-trifluoro-2-hydroxybutylamino}-3-phenylpropanoate (8b): Epoxide **1b** (0.1375 g, 0.5 mmol) and L-H-Phe-OMe (0.179 g, 1.0 mmol) gave, after 18 h of refluxing in MeOH (1.25 mL) and purification (cyclohexane/AcOEt, 7:3), the product **8b** (0.214 g, 94%) as a colourless oil. ^{1}H NMR (300 MHz, CDCl$_3$, 25 °C): δ = 2.52 (dd, $^3J_{H,H}$ = 4.5, $^2J_{H,H}$ = 12.3 Hz, 1 H, CH_2CHOH), 2.38–2.55 (br. s, 1 H, N*H*), 2.78–2.97 (m, 4 H, CH_2CHOH and H-3 and CHCF$_3$), 3.24 (s, 3 H, CH$_2$O*Me*), 3.27–3.47 (m, 3 H, CH_2OMe and H-2), 3.59 (s, 3 H, CO$_2$*Me*), 3.75 (ddd, $^3J_{H,H}$ = 2.7, 4.5, 7.5 Hz, 1 H, CHOH), 3.95–4.02 (m, 1 H, CHPh), 7.07–7.26 (m, 10 H, Ar) ppm. ^{13}C NMR (75 MHz, CDCl$_3$, 25 °C): δ = 39.6 (C-3), 50.5 (*C*H$_2$CHOH), 51.7 (CO$_2$*Me*), 58.7 (q, $^2J_{C,F}$ = 26.6 Hz, *C*HCF$_3$), 58.7 (CH$_2$O*Me*), 61.8/62.1 (*C*HPh/C-2), 67.0 (q, $^3J_{C,F}$ = 1.6 Hz, *C*HOH), 77.9 (*C*H$_2$OMe), 126.0 (q, $^1J_{C,F}$ = 281.8 Hz, *C*F$_3$), 126.8/127.8/127.8/128.3/128.4/129.0 (10 C, Ar), 137.0 (Ar), 139.9 (Ar), 174.6 (C-1) ppm. ^{19}F NMR (188 MHz, CDCl$_3$, 25 °C): δ = –73.15 (d, $^3J_{F,H}$ = 8.3 Hz, 3 F) ppm. MS (APCI): *m*/*z* = 455.1 [M + H]$^+$. IR: $\tilde{\nu}$ = 2933, 1734, 1455, 1266, 1134, 700 cm^{-1}. $C_{23}H_{29}F_3N_2O_4$ (454.48): calcd. C 60.78, H 6.43, N 6.16; found C 60.41, H 6.54, N 5.79. $[\alpha]_D^{25}$ = –37 (*c* = 1, MeOH).

(*S*)-Methyl 2-{(2*S*,3*R*)-3-[(*R*)-2-Methoxy-1-phenylethylamino]-4,4,4-trifluoro-2-hydroxybutylamino}-3-[4-(benzyloxy)phenyl]propanoate (9b): Epoxide **1b** (0.1375 g, 0.5 mmol) and L-H-Tyr(Bn)-OMe (0.285 g, 1.0 mmol) gave, after 18 h of refluxing in MeOH (1.25 mL) and purification (cyclohexane/AcOEt, 8:2), the product **9b** (0.217 g, 78%) as a colourless oil. ^{1}H NMR (300 MHz, CDCl$_3$, 25 °C): δ = 2.26–2.56 (br. s, 1 H, N*H*), 2.53 (dd, $^3J_{H,H}$ = 4.5, $^2J_{H,H}$ = 12.3 Hz, 1 H, CH_2CHOH), 2.74–2.90 (m, 3 H, CH_2CHOH and H-3), 2.96 (qd, $^3J_{H,H}$ = 2.4, $^3J_{H,F}$ = 8.3 Hz, 1 H, CHCF$_3$), 3.26 (s, 3 H, CH$_2$O*Me*), 3.29–3.44 (m, 3 H, CH_2OMe and H-2), 3.60 (s, 3 H, CO$_2$*Me*), 3.77 (ddd, $^3J_{H,H}$ = 2.4, 4.5, 7.5 Hz, 1 H, CHOH), 3.98 (dd, $^3J_{H,H}$ = 4.5, 8.2 Hz, 1 H, CHPh), 4.94 (s, 2 H, OCH_2Ph), 6.82 (d, $^3J_{H,H}$ = 8.6 Hz, 2 H, Ar), 7.01 (d, $^3J_{H,H}$ = 8.6 Hz, 2 H, Ar), 7.15–7.36 (m, 10 H, Ar) ppm. ^{13}C NMR (75 MHz, CDCl$_3$, 25 °C): δ = 38.8 (C-3), 50.5 (*C*H$_2$CHOH), 51.8 (CO$_2$*Me*), 58.8 (q, $^2J_{C,F}$ =

26.5 Hz, *C*HCF$_3$), 58.8 (CH$_2$O*Me*), 61.9/62.2 (2 C, *C*HPh and C-2), 67.0 (q, $^3J_{C,F}$ = 1.7 Hz, *C*HOH), 69.9 (O*C*H$_2$Ph), 77.9 (*C*H$_2$OMe), 126.0 (q, $^1J_{C,F}$ = 281.6 Hz, *C*F$_3$), 114.8/127.4/127.8/127.9/128.4/128.5/130.1 (14 C, Ar), 129.2 (Ar), 136.9 (Ar), 139.9 (Ar), 157.7 (Ar), 174.7 (C-1) ppm. ^{19}F NMR (188 MHz, CDCl$_3$, 25 °C): δ = –73.14 (d, $^3J_{F,H}$ = 8.3 Hz, 3 F) ppm. MS (APCI): *m*/*z* = 561.4 [M + H]$^+$. IR: $\tilde{\nu}$ = 2923, 1734, 1511, 1454, 1240, 1136, 1109, 734, 699 cm^{-1}. $C_{30}H_{35}F_3N_2O_5$ (560.60): calcd. C 64.27, H 6.29, N 5.00; found C 64.16, H 6.47, N 4.77. $[a]_D^{25}$ = –30 (*c* = 1, CH$_2$Cl$_2$).

(*S*)-Methyl 2-{(2*S*,3*R*)-3-[(*R*)-2-Methoxy-1-phenylethylamino]-4,4,4-trifluoro-2-hydroxybutylamino}-4-(methylthio)butanoate (10b): Epoxide **1b** (0.1375 g, 0.5 mmol) and L-H-Met-OMe (0.163 g, 1.0 mmol) gave, after 18 h of refluxing in MeOH (1.25 mL) and purification (cyclohexane/AcOEt, 8:2), the product **10b** (0.176 g, 80%) as a colourless oil. ^{1}H NMR (300 MHz, CDCl$_3$, 25 °C): δ = 1.76–1.88 (m, 1 H, H-3), 1.90–1.99 (m, 1 H, H-3), 2.03 (s, 3 H, S*Me*), 2.55 (t, $^3J_{H,H}$ = 7.4 Hz, 2 H, H-4), 2.62 (dd, $^3J_{H,H}$ = 4.5, $^2J_{H,H}$ = 12.3 Hz, 1 H, C*H*$_2$CHOH), 2.78–3.10 (br. s, 1 H, N*H*), 2.92 (dd, $^3J_{H,H}$ = 7.5, $^2J_{H,H}$ = 12.3 Hz, 1 H, C*H*$_2$CHOH), 3.06 (qd, $^3J_{H,H}$ = 3.0, $^3J_{H,F}$ = 8.3 Hz, 1 H, C*H*CF$_3$), 3.30 (s, 3 H, CH$_2$O*Me*), 3.34–3.44 (m, 3 H, C*H*$_2$OMe and H-2), 3.69 (s, 3 H, CO$_2$*Me*), 3.92 (ddd, $^3J_{H,H}$ = 3.0, 4.5, 7.5 Hz, 1 H, C*H*OH), 4.04 (dd, $^3J_{H,H}$ = 4.7, 8.0 Hz, 1 H, C*H*Ph), 7.19–7.31 (m, 5 H, Ar) ppm. ^{13}C NMR (75 MHz, CDCl$_3$, 25 °C): δ = 15.3 (S*Me*), 30.5 (C-4), 32.2 (C-3), 50.8 (*C*H$_2$CHOH), 52.1 (CO$_2$*Me*), 58.8/59.6 (2 C, CH$_2$O*Me* and C-2), 59.0 (q, $^2J_{C,F}$ = 26.2 Hz, *C*HCF$_3$), 61.8 (*C*HPh), 67.0 (q, $^3J_{C,F}$ = 1.6 Hz, *C*HOH), 78.0 (*C*H$_2$OMe), 126.0 (q, $^1J_{C,F}$ = 282.3 Hz, *C*F$_3$), 127.8 (2 C, Ar), 127.9 (Ar), 128.4 (2 C, Ar), 139.9 (Ar), 174.6 (C-1) ppm. ^{19}F NMR (188 MHz, CDCl$_3$, 25 °C): δ = –73.04 (d, $^3J_{F,H}$ = 8.3 Hz, 3 F) ppm. MS (APCI): *m*/*z* = 439.2 [M + H]$^+$. IR: $\tilde{\nu}$ = 2920, 1733, 1454, 1266, 1134, 1101, 701 cm^{-1}. $C_{19}H_{29}F_3N_2O_4S$ (438.51): calcd. C 52.04, H 6.67, N 6.39; found C 52.09, H 6.61, N 6.02. $[a]_D^{25}$ = –55 (*c* = 1, MeOH).

(*S*)-Dimethyl 2-{(2*S*,3*R*)-3-[(*R*)-2-Methoxy-1-phenylethylamino]-4,4,4-trifluoro-2-hydroxybutylamino}succinate (11b): Epoxide **1b** (0.1375 g, 0.5 mmol) and L-H-Asp(OMe)-OMe (0.161 g, 1.0 mmol) gave, after 18 h of refluxing in MeOH (1.25 mL) and purification (cyclohexane/AcOEt, 8:2), the product **11b** (0.163 g, 75%) as a yellow oil. ^{1}H NMR (300 MHz, CDCl$_3$, 25 °C): δ = 2.32–2.73 (br. s, 1 H, N*H*), 2.54–2.73 (m, 1 H, C*H*$_2$CHOH), 2.58 (dd, $^3J_{H,H}$ = 7.8, $^2J_{H,H}$ = 15.9 Hz, 1 H, H-3), 2.70 (dd, $^3J_{H,H}$ = 5.1, $^2J_{H,H}$ = 15.9 Hz, 1 H, H-3), 2.93 (dd, $^3J_{H,H}$ = 8.1, $^2J_{H,H}$ = 12.3 Hz, 1 H, C*H*$_2$CHOH), 3.02 (qd, $^3J_{H,H}$ = 3.0, $^3J_{H,F}$ = 8.3 Hz, 1 H, C*H*CF$_3$), 3.28 (s, 3 H, CH$_2$O*Me*), 3.33–3.38 (m, 2 H, C*H*$_2$OMe), 3.58 –3.62 (m, 1 H, H-2), 3.62 (s, 3 H, CO$_2$*Me*), 3.68 (s, 3 H, CO$_2$*Me*), 3.87 (ddd, $^3J_{H,H}$ = 3.0, 4.2, 8.1 Hz, 1 H, C*H*OH), 4.00–4.05 (m, 1 H, C*H*Ph), 7.16–7.30 (m, 5 H, Ar) ppm. ^{13}C NMR (75 MHz, CDCl$_3$, 25 °C): δ = 37.8 (C-3), 50.7 (*C*H$_2$CHOH), 51.9 (CO$_2$*Me*), 52.2 (CO$_2$*Me*), 56.9/58.7 (2 C, CH$_2$O*Me* and C-2), 58.8 (q, $^2J_{C,F}$ = 26.5 Hz, *C*HCF$_3$), 61.8 (*C*HPh), 67.1 (q, $^3J_{C,F}$ = 1.8 Hz, *C*HOH), 77.9 (*C*H$_2$OMe), 126.0 (q, $^1J_{C,F}$ = 281.8 Hz, *C*F$_3$), 127.8 (Ar), 127.8 (2 C, Ar), 128.3 (2 C, Ar), 140.0 (Ar), 171.2/173.7 (2 C, C-1 and C-4) ppm. ^{19}F NMR (188 MHz, CDCl$_3$, 25 °C): δ = –72.75 (d, $^3J_{F,H}$ = 8.3 Hz, 3 F) ppm. MS (ESI): *m*/*z* = 459.2 [M + Na]$^+$. IR: $\tilde{\nu}$ = 2954, 1736, 1438, 1267, 1138, 704, 630 cm^{-1}. $C_{19}H_{27}F_3N_2O_6$ (436.42): calcd. C 52.29, H 6.24, N 6.42; found C 52.67, H 6.14, N 6.24. $[a]_D^{25}$ = –27 (*c* = 0.5, MeOH).

Methyl *N*-[3-(Benzylamino)-4,4,4-trifluoro-2-hydroxybutyl]-L-phenylalanyl-L-alaninate (12a): L-Cbz-Phe-L-Ala-OMe (768 mg, 1.0 mmol, 2 equiv.) was dissolved in 5 mL of MeOH. Pd/C (10% in mass, 0.077 g) was added. The mixture was then placed under an atmosphere of H$_2$. After 30 min of vigorous stirring, the mixture was filtered over Celite, and the filtrate was concentrated under reduced pressure. The L-H-Phe-L-Ala-OMe thus obtained and epoxide **1a** (0.1156 g, 0.5 mmol, 1 equiv.) were dissolved in 1.25 mL of MeOH. After 18 h of refluxing and purification (cyclohexane/AcOEt, 8:2 then 1:1), the product **12a** (0.107 g, 45%, 2 diastereomers, 1:1) was obtained as a yellow oil. ^{1}H NMR (300 MHz, CDCl$_3$, 25 °C): δ = 1.26 (d, $^3J_{H,H}$ = 7.5 Hz, 3 H, CH*Me*), 1.28 (d, $^3J_{H,H}$ = 7.5 Hz, 3 H, CH*Me*), 1.73–2.09 (br. s, 2 H, N*H*), 2.44–2.70 (m, 6 H, C*H*$_2$CHOH and CHC*H*$_2$Ph), 2.78 (qd, $^3J_{H,H}$ = 3.4, $^3J_{H,F}$ = 7.7 Hz, 1 H, C*H*CF$_3$), 2.91 (qd, $^3J_{H,H}$ = 3.4, $^3J_{H,F}$ = 7.7 Hz, 1 H, C*H*CF$_3$), 3.06 (dd, $^3J_{H,H}$ = 4.2, $^2J_{H,H}$ = 14.0 Hz, 2 H, CHC*H*$_2$Ph), 3.19 (dd, $^3J_{H,H}$ = 4.2, 9.0 Hz, 1 H, C*H*CH$_2$Ph), 3.25 (dd, $^3J_{H,H}$ = 4.2, 9.3 Hz, 1 H, C*H*CH$_2$Ph), 3.60 (s, 3 H, CO$_2$*Me*), 3.61 (s, 3 H, CO$_2$*Me*), 3.64–3.73 (m, 3 H, C*H*OH and C*H*$_2$Ph), 3.75–3.80 (m, 1 H, C*H*OH), 3.92 (d, $^2J_{H,H}$ = 12.6 Hz, 1 H, C*H*$_2$Ph), 3.96 (d, $^2J_{H,H}$ = 13.2 Hz, 1 H, C*H*$_2$Ph), 4.51 (qi, $^3J_{H,H}$ = 7.5 Hz, 2 H, C*H*Me), 7.09–7.22 (m, 20 H, Ar), 7.60 (d, $^3J_{H,H}$ = 7.5 Hz, 1 H, N*H*CO), 7.62 (d, $^3J_{H,H}$ = 7.5 Hz, 1 H, N*H*CO) ppm. ^{13}C NMR (75 MHz, CDCl$_3$, 25 °C): δ = 18.1 (CH*Me*), 18.2 (CH*Me*), 39.2 (CH*C*H$_2$Ph), 39.3 (CH*C*H$_2$Ph), 47.4 (2 C, *C*HCH$_2$Ph), 51.4/51.9/52.1 (4 C, *C*H$_2$CHOH and *C*H$_2$Ph), 52.4 (2 C, CO$_2$*Me*), 59.5 (q, $^2J_{C,F}$ = 26.1 Hz, *C*HCF$_3$), 60.0 (q, $^2J_{C,F}$ = 25.8 Hz, *C*HCF$_3$), 63.7 (*C*HMe), 63.9 (*C*HMe), 67.1 (q, $^3J_{C,F}$ = 1.7 Hz, *C*HOH), 67.4 (q, $^3J_{C,F}$ = 2.0 Hz, *C*HOH), 126.3 (q, $^1J_{C,F}$ = 282.9 Hz, *C*F$_3$), 126.4 (q, $^1J_{C,F}$ = 282.1 Hz, *C*F$_3$), 126.9 (Ar), 126.9 (Ar), 127.3 (Ar), 127.3 (Ar), 128.2 (2 C, Ar), 128.3 (2 C, Ar), 128.3 (2 C, Ar), 128.4 (2 C, Ar), 128.6 (2 C, Ar), 128.7 (2 C, Ar), 129.0 (2 C, Ar), 129.0 (2 C, Ar), 137.1 (Ar), 137.1 (Ar), 139.1 (Ar), 139.1 (Ar), 173.3/173.3/173.7/173.7 (4 C, *C*O$_2$Me and NH*C*O) ppm. ^{19}F NMR (188 MHz, CDCl$_3$, 25 °C): δ = –71.48 (d, $^3J_{F,H}$ = 7.7 Hz, 3 F), –71.69 (d, $^3J_{F,H}$ = 7.7 Hz, 3 F) ppm. MS (ESI): *m*/*z* = 482.3 [M + H]$^+$, 504.3 [M + Na]$^+$. IR: $\tilde{\nu}$ = 3330, 2930, 2019, 1867, 1742, 1581, 1356, 1132 cm^{-1}. $C_{24}H_{30}F_3N_3O_4$ (481.51): calcd. C 59.87, H 6.28, N 8.73; found C 59.49, H 6.24, N 8.37.

Methyl *N*-((2*S*,3*R*)-4,4,4-Trifluoro-2-hydroxy-3-{[(1*R*)-2-methoxy-1-phenylethyl]amino}butyl)-L-phenylalanyl-L-alaninate (12b): L-Cbz-Phe-L-Ala-OMe (768 mg, 1.0 mmol, 2 equiv.) was dissolved in 5 mL of MeOH. Pd/C (10% in mass, 0.077 g) was added. The mixture was then placed under an atmosphere of H$_2$. After 30 min of vigorous stirring, the mixture was filtered over Celite, and the filtrate was concentrated under reduced pressure. The L-H-Phe-L-Ala-OMe thus obtained and epoxide **1b** (0.1375 g, 0.5 mmol, 1 equiv.) were dissolved in 1.25 mL of MeOH. After 72 h of refluxing and purification (cyclohexane/AcOEt, 8:2 then 1:1), the product **12b** (0.100 g, 38%, 1 diastereomer) was obtained as a yellow oil. ^{1}H NMR (300 MHz, CDCl$_3$, 25 °C): δ = 1.31 (d, $^3J_{H,H}$ = 7.5 Hz, 3 H, CH*Me*), 1.90–2.34 (br. s, 1 H, N*H*), 2.61–2.75 (m, 3 H, C*H*$_2$CHOH and CHC*H*$_2$Ph), 3.06 (qd, $^3J_{H,H}$ = 3.0, $^3J_{H,F}$ = 8.3 Hz, 1 H, C*H*CF$_3$), 3.13 (dd, $^3J_{H,H}$ = 3.9, $^2J_{H,H}$ = 13.8 Hz, 1 H, CHC*H*$_2$Ph), 3.22 (s, 3 H, CH$_2$O*Me*), 3.30–3.35 (m, 3 H, C*H*CH$_2$Ph and C*H*$_2$OMe), 3.65 (s, 3 H, CO$_2$*Me*), 3.68–3.73 (m, 1 H, C*H*OH), 4.00 (dd, $^3J_{H,H}$ = 5.4, 7.2 Hz, 1 H, C*H*Ph), 4.55 (qi, $^3J_{H,H}$ = 7.5 Hz, 1 H, C*H*Me), 7.15–7.28 (m, 10 H, Ar), 7.67 (d, $^3J_{H,H}$ = 7.5 Hz, 1 H, N*H*CO) ppm. ^{13}C NMR (75 MHz, CDCl$_3$, 25 °C): δ = 18.1 (CH*Me*), 39.4 (CH*C*H$_2$Ph), 47.4 (*C*HCH$_2$Ph), 52.0 (*C*H$_2$CHOH), 52.4 (CO$_2$*Me*), 58.7 (CH$_2$O*Me*), 58.8 (q, $^2J_{C,F}$ = 26.3 Hz, *C*HCF$_3$), 61.3 (*C*HPh), 63.7 (*C*HMe), 68.3 (q, $^3J_{C,F}$ = 1.6 Hz, *C*HOH), 78.1 (*C*H$_2$OMe), 126.2 (q, $^1J_{C,F}$ = 276.7 Hz, *C*F$_3$), 127.0 (Ar), 127.7 (2 C, Ar), 127.9 (Ar), 128.4 (2 C, Ar), 128.7 (2 C, Ar), 129.1 (2 C, Ar), 137.2 (Ar), 139.9 (Ar), 173.3/173.8 (2 C, *C*O$_2$Me and NH*C*O) ppm. ^{19}F NMR (188 MHz, CDCl$_3$, 25 °C): δ = –73.24 (d, $^3J_{F,H}$ = 8.3 Hz, 3 F) ppm. MS (ESI): *m*/*z* = 548.3 [M + Na]$^+$. IR: $\tilde{\nu}$ = 3324,

2930, 1742, 1653, 1520, 1454, 1209, 1136, 732, 700 cm^{-1}. $C_{26}H_{34}F_3N_3O_5$ (525.56): calcd. C 59.42, H 6.52, N 8.00; found C 59.11, H 6.45, N 7.67. $[\alpha]_D^{25} = -58$ (c = 1, CH_2Cl_2).

Ethyl 2-(3-Amino-4,4,4-trifluoro-2-hydroxybutylamino)acetate (13): Epoxide **1a** (115.6 mg, 0.5 mmol, 1 equiv.) and H-Gly-OEt (51.5 mg, 0.5 mmol, 1 equiv.) were dissolved in EtOH (1.25 mL). After 10 h of refluxing, $Pd(OH)_2$ (30% in mass, 50 mg) and EtOH (15.75 mL) were added to the mixture, which was then placed under an atmosphere of H_2. After one night of vigorous stirring, the mixture was filtered over celite. The filtrate was concentrated under reduced pressure and gave product **13** (108.7 mg, 89%) as white needless; m.p. 60–62 °C. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1.27 (t, $^3J_{H,H}$ = 7.2 Hz, 3 H, $CO_2CH_2CH_3$), 1.59–2.51 (br. s, 3 H, N*H* and NH_2), 2.80 (dd, $^3J_{H,H}$ = 4.5, $^2J_{H,H}$ = 12.6 Hz, 1 H, CH_2CHOH), 2.86 (dd, $^3J_{H,H}$ = 8.1, $^2J_{H,H}$ = 12.6 Hz, 1 H, CH_2CHOH), 3.11 (qd, $^3J_{H,H}$ = 2.4, $^3J_{H,F}$ = 8.1 Hz, 1 H, $CHCF_3$), 3.42 (s, 2 H, H-2), 3.89–3.93 (m, 1 H, C*H*OH), 4.19 (q, $^3J_{H,H}$ = 7.2 Hz, 2 H, $CO_2CH_2CH_3$) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 14.1 ($CO_2CH_2CH_3$), 50.5 (CH_2CHOH), 52.1 (2-C), 55.4 (q, $^2J_{C,F}$ = 27.6 Hz, $CHCF_3$), 60.9 ($CO_2CH_2CH_3$), 66.2 (q, $^3J_{C,F}$ = 1.7 Hz, $CHOH$), 126.1 (q, $^1J_{C,F}$ = 280.7 Hz, CF_3), 172.4 (1-C) ppm. ^{19}F NMR (188 MHz, $CDCl_3$, 25 °C): δ = –76.28 (d, $^3J_{F,H}$ = 8.1 Hz, 3 F) ppm. MS (ESI): m/z = 245 $[MH]^+$, 267 $[M + Na]^+$. IR: $\tilde{\nu}$ = 3309, 1726, 1661, 1260, 1110, 1023, 796 cm^{-1}. $C_8H_{15}F_3N_2O_3$ (244.21): calcd. C 39.35, H 6.19, N 11.47; found C 39.74, H 5.93, N 11.13.

Acknowledgments

Central Glass is thanked for the kind gift of fluoral hydrate and HFIP. DSM company is also thanked for the donation of (*R*)-phenylglycine. C. P. thanks the French Ministère de l'Enseignement Supérieur et de la Recherche (MESR) for awarding a PhD student fellowship. We thank A. Solgadi for performing mass spectra analysis (SAMM platform, Châtenay-Malabry).

[1] D. Leung, G. Abbenante, D. P. Fairlie, *J. Med. Chem.* **2000**, *43*, 305–341.
[2] A. K. Ghosh, G. Bilcer, G. Schiltz, *Synthesis* **2001**, *15*, 2203–2229.
[3] C. S. T. Oost, M. Brewer, M. Goodnough, W. Tepp, E. A. Johnson, D. H. Rich, *Pept. Sci.* **2003**, *71*, 602–619.
[4] D. Muthas, D. Noteberg, Y. A. Sabnis, E. Hamelink, L. Vrang, B. Samuelsson, A. Karlen, A. Hallberg, *Bioorg. Med. Chem.* **2005**, *13*, 5371–5390.
[5] D. Noteberg, E. Hamelink, J. Hulten, M. Wahlgren, L. Vrang, B. Samuelsson, A. Hallberg, *J. Med. Chem.* **2003**, *46*, 734–746.
[6] T. S. Haque, A. G. Skillman, C. E. Lee, H. Habashita, I. Y. Gluzman, T. J. A. Ewing, D. E. Goldberg, I. D. Kuntz, J. A. Ellman, *J. Med. Chem.* **1999**, *42*, 1428–1440.
[7] D. Nöteberg, W. Schaal, E. Hamelink, L. Vrang, M. Lahred, *J. Comb. Chem.* **2003**, *5*, 456–464.
[8] R. M. McConnell, A. W. Green, C. J. Trana, M. S. McConnell, J. F. Lindley, K. Sayyar, W. E. Godwin, S. E. Hatfield, *Med. Chem.* **2006**, *2*, 27–38.
[9] N. Charrier, B. Clarke, L. Cutler, E. Demont, C. Dingwall, R. Dunsdon, P. East, J. Hawkins, C. Howes, I. Hussain, P. Jeffrey, G. Maile, R. Matico, J. Mosley, A. Naylor, A. Brien, S. Redshaw, P. Rowland, V. Soleil, K. J. Smith, S. Sweitzer, P. Theobald, D. Vesey, D. S. Walter, G. Wayne, *J. Med. Chem.* **2008**, *51*, 3313–3317.
[10] J. N. Freskos, Y. M. Fobian, T. E. Benson, M. J. Bienkowski, D. L. Brown, T. L. Emmons, R. Heintz, A. Laborde, J. J. McDonald, B. V. Mischke, J. M. Molyneaux, J. B. Moon, P. B. Mullins, D. B. Prince, D. J. Paddock, A. G. Tomasselli, G. Winterrowd, *Bioorg. Med. Chem. Lett.* **2007**, *17*, 73–77.
[11] J. N. Freskos, Y. M. Fobian, T. E. Benson, J. B. Moon, M. J. Bienkowski, D. L. Brown, T. L. Emmons, R. Heintz, A. Laborde, J. J. McDonald, B. V. Mischke, J. M. Molyneaux, P. B. Mullins, D. B. Prince, D. J. Paddock, A. G. Tomasselli, G. Winterrowd, *Bioorg. Med. Chem. Lett.* **2007**, *17*, 78–81.
[12] M. C. Maillard, R. K. Hom, T. E. Benson, J. B. Moon, S. Mamo, M. Bienkowski, A. G. Tomasselli, D. D. Woods, D. B. Prince, D. J. Paddock, T. L. Emmons, J. A. Trucker, M. S. Dappen, L. Brogley, E. D. Thorsett, N. Jewett, S. Sinha, V. John, *J. Med. Chem.* **2007**, *50*, 776–781.
[13] M. Sani, A. Volonterio, M. Zanda, *ChemMedChem* **2007**, *2*, 1693–1700.
[14] H. Meng, K. Kumar, *J. Am. Chem. Soc.* **2007**, *129*, 15615–15622.
[15] I. Ojima, K. Kato, F. A. Jameison, J. Conway, *Bioorg. Med. Chem. Lett.* **1992**, *2*, 219–222.
[16] I. Ojima, F. A. Jameison, *Bioorg. Med. Chem. Lett.* **1991**, *1*, 581–584.
[17] J. P. Bégué, D. Bonnet-Delpon, *J. Fluorine Chem.* **2006**, *127*, 992–1012.
[18] C. Isanbor, D. O'Hagan, *J. Fluorine Chem.* **2006**, *127*, 303–319.
[19] K. L. Kirk, *J. Fluorine Chem.* **2006**, *127*, 1013–1029.
[20] J. P. Bégué, D. Bonnet-Delpon, *Bioorganic and Medicinal Chemistry of Fluorine*, John Wiley & Sons, Hoboken, **2008**.
[21] P. Kirsch, *Modern Fluoroorganic Chemistry: Synthesis Reactivity, Applications*, Wiley-VCH, Weinheim, **2004**.
[22] M. Zanda, *New J. Chem.* **2004**, *28*, 1401–1411.
[23] N. T. N. Tam, G. Magueur, M. Ourevitch, B. Crousse, J. P. Bégué, D. Bonnet-Delpon, *J. Org. Chem.* **2005**, *70*, 699–702.
[24] D. M. Hodgson, A. R. Gibbs, G. P. Lee, *Tetrahedron* **1996**, *52*, 14361–14384.
[25] R. M. Hanson, *Chem. Rev.* **1991**, *91*, 437–475.
[26] K. Fagnou, M. Lautens, *Org. Lett.* **2000**, *2*, 2319–2321.
[27] G. Sekar, V. K. Singh, *J. Org. Chem.* **1999**, *64*, 287–289.
[28] R. H. Fan, X. L. Hou, *J. Org. Chem.* **2003**, *68*, 726–730.
[29] A. Procopio, M. Gaspari, M. Nardi, M. Oliverio, O. Rosati, *Tetrahedron Lett.* **2008**, *49*, 2289–2293.
[30] U. Das, B. Crousse, V. Kesavan, D. Bonnet-Delpon, J. P. Bégué, *J. Org. Chem.* **2000**, *65*, 6749–6751.
[31] N. Azizi, M. R. Saidi, *Org. Lett.* **2005**, *7*, 3649–3651.
[32] P. W. Erhardt, C. M. Woo, R. J. Gorczynski, W. G. Anderson, *J. Med. Chem.* **1982**, *25*, 1402–1407.
[33] P. W. Erhardt, C. M. Woo, W. G. Anderson, R. J. Gorczynski, *J. Med. Chem.* **1982**, *25*, 1408–1412.
[34] S. Higashibayashi, T. Mori, K. Shinko, K. Hashimoto, M. Nakata, *Heterocycles* **2002**, *57*, 111–122.
[35] H. Kotsuki, T. Shimanouchi, M. Teraguchi, M. Kataoka, A. Tatsukawa, H. Nishizawa, *Chem. Lett.* **1994**, 2159–2162.
[36] S. Rodriguez-Escrich, D. Popa, C. Jimeno, A. Vidal-Ferran, M. A. Pericas, *Org. Lett.* **2005**, *7*, 3829–3832.
[37] K. C. Nicolaou, M. Zak, B. S. Safina, S. H. Lee, A. A. Estrada, *Angew. Chem. Int. Ed.* **2004**, *43*, 5092–5097.
[38] C. Coudures, R. Pastor, S. Szonyi, A. Cambon, *J. Fluorine Chem.* **1984**, *24*, 105–115.
[39] N. Vaiana, L. Rizzi, S. Romeo, *Chem. Lett.* **2007**, *36*, 648–649.
[40] F. Saitoh, T. Mukaihira, H. Nishida, T. Satoh, A. Okano, Y. Yumiya, M. Ohkouchi, R. Johka, T. Matsusue, I. Shiromizu, Y. Hosaka, M. Matsumoto, S. Ohnishi, *Chem. Pharm. Bull.* **2006**, *54*, 1535–1544.
[41] S. Kiyohara, M. Sasaki, K. Saito, K. Sugita, T. Sugo, *J. Membr. Sci.* **1996**, *109*, 87–92.
[42] J. W. Janetka, P. Raman, K. Satyshur, G. R. Flentke, D. H. Rich, *J. Am. Chem. Soc.* **1997**, *119*, 441–442.
[43] L. Kolaczkowski, D. M. Barnes, *Org. Lett.* **2007**, *9*, 3029–3032.
[44] C. Gravier-Pelletier, M. Milla, Y. Le Merrer, J. C. Depezay, *Eur. J. Org. Chem.* **2001**, 3089–3096.
[45] T. Tashiro, S. Fushiya, S. Nozoe, *Chem. Pharm. Bull.* **1988**, *36*, 893–901.

[46] M. Sova, A. Babic, S. Pecar, S. Gobec, *Tetrahedron* **2007**, *63*, 141–147.
[47] A. Babic, M. Sova, S. Gobec, S. Pecar, *Tetrahedron Lett.* **2006**, *47*, 1733–1735.
[48] C. Philippe, T. Milcent, B. Crousse, D. Bonnet-Delpon, *Org. Biomol. Chem.* **2009**, *7*, 2026–2028.

Received: May 25, 2009
Published Online: September 3, 2009

