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Stereoselective synthesis of fluorinated β-aminoacids from ethyl *trans*-*N*-benzyl-3-trifluoromethylaziridine-2-carboxylate

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Abstract

trans-*N*-Benzyl-3-trifluoromethyl-2-ethoxycarbonylaziridine **2a**, easily obtainable in enantiopure forms by CAL-catalysed enzymatic resolution, allowed the regio- and stereoselective synthesis of chiral fluorinated *anti*-α-functionalised-β-aminoacids, such as trifluoroisoserinates or trifluoro-β-alanine, and *trans*-3-halo- or 3-hydroxy-β-lactams. Starting from the enantiomerically pure methyl analogue of the title compound, **2c**, pure enantiomers of trifluoroisoserine can be obtained in high overall chemical yield. Absolute configurations of optically active β-aminoacids were determined by chemical correlation.

1. Introduction

β-Aminoacids and their derivatives, such as α-hydroxy- or α-halocompounds, are the object of constant interest as intermediates in the synthesis of β-lactams, of Taxol® semisynthetic analogues and as peptidomimetic units.[1] In the last few years a great deal of research has been devoted to the synthesis of fluorinated analogues of non-proteinogenic β-aminoacids as highly biologically active molecules with a wide range of potential applications.[1b,2] Among these, the main source of fluorinated isoserinates and isoserines is the ring opening hydrolysis of the corresponding β-lactams;[1c,2b] these compounds, in the *syn* diastereoisomeric form, were coupled with baccatins for the synthesis of new taxoids. Nevertheless, relatively few methods for the synthesis of enantiomerically pure β-aminoacids are available: many of the procedures are known to be complicated, and by contrast with the derivatives of natural α-aminoacids, functionalised β-aminoacids are difficult to obtain in enantiomerically pure form, and often only by complex procedures.[1,2] As a consequence, new approaches to stereoselective and enantioselective synthetic methods could be of interest.

Aziridine-2-carboxylates are known to be versatile key intermediates for the synthesis of α- and β-aminoacids: the ring strain makes these compounds reactive towards a wide range of nucleophiles, often

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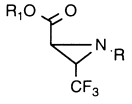
in regio- and stereoselective ways.[3] Either α- or β-aminoacids can be obtained by nucleophilic attack at the C-3 or the C-2 aziridine ring carbon atom, respectively.[4] Nevertheless, the stereoselective ring opening at C-2 is reported to be relatively rare: recently, the regiospecific C-2 nucleophilic ring opening of aziridine-2-carboxylates to β-aminoacids was achieved only after their conversion into the corresponding aziridino alcohols.[5]

Here we report the regio- and stereoselective nucleophilic ring opening of *trans*-1-benzyl-3-trifluoromethyl-2-ethoxycarbonylaziridines **2a**,**c**,**d**, allowing the regio- and stereocontrolled synthesis of chiral β-aminoacids, such as *anti*-α-halo-β-trifluoromethyl-β-alanine **3a**,**b**, β-trifluoromethyl-β-alanine **3c**, *anti*-3-(trifluoromethyl)isoserinates **3d**–**h**, as well as the synthesis of fluorinated *trans*-β-lactams **4a**,**b**.



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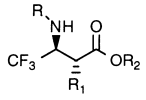
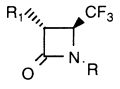
a) R = Bn; R_1 = Et
b) R = Bn; R_1 = H
c) R = Bn; R_1 = Me
d) R = H; R_1 = Et



3

	R	R_1	R_2
a	Bn	Cl	Et
b	Bn	Br	Et
c	Bn	H	Et
d	Bn	OH	Et
e	H	OH	Et
f	Bn	OH	Me
g	H	OH	Me
h	$COCF_3$	OH	Et



4

a) R_1 = Cl; R = Bn
b) R_1 = OTBDMS; R = H

anti-α-Hydroxy-β-aminoacids are known to convert into the corresponding *syn* derivatives, required by the natural products, under Mitsunobu conditions.[6] Moreover, 3-halo-β-lactam might be a possible precursor of β-lactamase inibitors[7] and a potentially useful intermediate for the synthesis of fluorinated analogues of aztreonam, 3-amino-4-trifluoromethyl-β-lactam.[8]

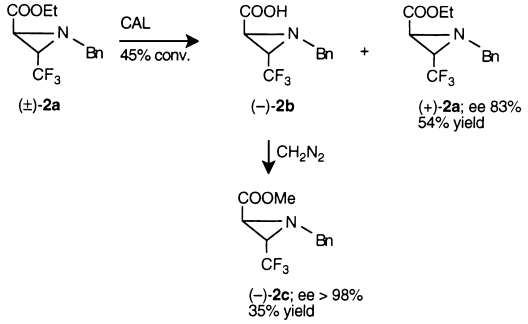
2. Results and discussion

2.1. trans-*1-Benzyl-3-trifluoromethyl-2-ethoxycarbonylaziridine* ***2a****: synthesis and enzymatic resolution*

Aziridine *trans*-**2a** was synthesised in high overall yield (90%) following the procedure described elsewhere,[9] by reaction with benzylamine from ethyl 2,3-dibromo-4,4,4-trifluorobutanoate **1**, obtained by bromination of the commercially available ethyl *trans*-4,4,4-trifluoro-2-butenoate. By hydrogenation of **2a** in the presence of Pd–C (10%), the corresponding 1*H*-aziridine **2d** was obtained in 87% yield.[9]

Racemic aziridine **2a** was resolved by enzymatic hydrolysis, catalysed by *Candida antarctica* lipase (CAL): the ester function was hydrolysed with high enantioselectivity, as expressed by the enantiomeric ratio E >100.[10] The resolution of **2a** was carried out in phosphate buffer (0.1 mol dm^{-3} and NaCl 0.1 mol dm^{-3}; pH 7.5), at 37°C and with an enzyme/aziridine ratio (w/w) 1:50. The suspension was vigorously shaken and the reaction stopped after 30 min, when conversion reached 45%: under these conditions, the optically active unchanged ester (+)-**2a**, (ee 83%), was isolated from the reaction mixture in 54% chemical yield, by extraction with diethyl ether followed by column chromatography. The optically active hydrolysis product, aziridinecarboxylic acid (−)-**2b**, was recovered from the aqueous phase by acidification with HCl 10% until pH 1 and extraction with ethyl acetate (35% yield). The enantiomeric excess of (−)-**2b** (ee >98%) was estimated after its conversion into the corresponding methyl ester (−)-**2c**, by treatment with diazomethane (Scheme 1). Enantiomeric excesses (ees) were evaluated on a chiral B-

DEX 120 column. The conversion and *E* were determined from the values of the enantiomeric excesses of the unhydrolysed (ee_s) and hydrolysed (ee_p) products.[10]



Scheme 1.

2.2. Nucleophilic ring-opening reactions

The ring-opening reactions, to afford non-natural β-aminoacids **3a**–**h**, were performed on racemic aziridines **2a**,**d** by treatment with Brønsted acids, such as HCl, $MgBr_2$ in H_2SO_4 or trifluoroacetic acid. In particular, trifluoroacetolysis was performed on (+)-**2a** (ee 83%) and (−)-**2c** (ee >98%) to obtain trifluoromethylisoserinates in both enantiomeric forms. Moreover, the ring-opening product (+)-**3b**, obtained by treatment of (+)-**2a** with $MgBr_2$ in H_2SO_4, was correlated with the configurationally known (*R*)-(+)-4,4,4-trifluoro-3-aminobutanoic acid **5**,[2a] in order to assign absolute configurations to the β-aminoacids **3**.

The ring-opening products indicate that reactions proceed with high regio- and stereoselectivity: nucleophilic attack occurs at the C-2 ring-carbon atom affording only one regioisomer, a β-aminoacid, in a single diastereoisomeric form. Analytical and spectroscopic data of compounds **3a**–**h** are in close agreement with the structures. The results are summarised in Table 1.

By treating racemic **2a** with dry HCl in ethyl ether at room temperature for 2 h (entry 1), only one product, identified by ^{1}H NMR spectroscopy as ethyl 3-benzylamino-2-chloro-4,4,4-trifluorobutanoate **3a**, was obtained as its hydrochloride, which, after treatment with 1 M NaOH, afforded the pure α-chloro-β-trifluoromethyl-β-alanine **3a** in 94% overall yield.

The same C-2 nucleophilic attack at **2a** was observed by reaction with $MgBr_2$ in an anhydrous THF solution of H_2SO_4 (entry 2). After 10 min at −10°C, the reaction mixture yielded ethyl 3-benzylamino-2-bromo-4,4,4-trifluorobutanoate **3b** as a single stereoisomer (99%). Interestingly, when the reaction mixture was allowed to warm up or to react longer (entry 3), **3b** was obtained as a mixture of *syn/anti* stereoisomers in a variable ratio, indicative of an easy epimerisation under these reaction conditions. Hydrogenation of **3b**, with Pd–C (10%) in ethyl acetate and acetic acid, afforded ethyl 3-benzylamino-4,4,4-trifluorobutanoate **3c** in 67% yield.

Trifluoroacetolysis of **2a** at 80°C for 2 h (entry 4) produced the regioisomer ethyl 3-benzylamino-2-hydroxy-4,4,4-trifluorobutanoate **3d** in 87% yield and in a single stereoisomeric form, identified by ^{1}H NMR spectroscopy as the trifluoroacetate salt. From the salt, **3d** was recovered in 96% yield by treatment with 1 M NaOH. Hydrogenation of **3d**, with Pd–C (10%) in ethanol and acetic acid, afforded ethyl 3-amino-2-hydroxy-4,4,4-trifluorobutanoate **3e** in 83% yield.

By analogy, trifluoroacetolysis of (+)-**2a** (ee 83%) yielded (+)-**3d** which, upon debenzylation, afforded ethyl (+)-3-trifluoromethylisoserinate **3e** (ee 83%) in 73% overall yield. The corresponding levorotatory

Table 1
α-Functionalised β-aminoacids from nucleophilic ring-opening of aziridine **2a**,**c**,**d**

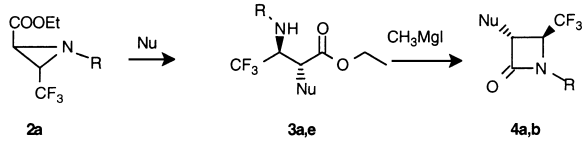
entry	aziridine	reagents	time, h (min)	T (°C)	product[a]	yield
1	**2a**	HCl/Et_2O	2	–5	**3a**	94
2	**2a**	$MgBr_2/H_2SO_4$	(10)	–10	**3b**[b]	99
3	**2a**	$MgBr_2/H_2SO_4$	1	r.t.	**3b**[c]	94
4	**2a**	CF_3COOH	2	80	**3d**[b]	83
5	**2c**[d]	CF_3COOH	2	80	**3f**[b]	91
6	**2d**	CF_3COOH	4	70	**3h**	91

[a] Recovered in a single *anti* isomer
[b] Reduction of **3b**, **3d** and **3f** with H_2/Pd-C afforded **3c** (67%), **3e** (83%) and **3g** (82%), respectively.
[c] Recovered as mixture of *syn/anti* isomer.
[d] Performed on (–)-**2c**, ee>98%

enantiomer **3g** as its methyl ester (ee >98%) was obtained in 75% overall yield from (−)-**2c** (ee >98%) following the same procedure (entry 5).

Aziridine **2d**, by treatment with trifluoroacetic acid at 70°C for 4 h (entry 6), yielded the regioisomer ethyl 3-trifluoroacetamino-2-hydroxy-4,4,4-trifluorobutanoate **3h** in 91% yield, as a single diastereoisomer as indicated by ^{1}H NMR spectroscopy. The isolated product **3h** suggests the formation of an α-trifluoroacetoxy intermediate followed by an intramolecular trifluoroacetyl migration from the oxygen to the nitrogen as already observed for other *N*-unsubstituted aziridines.[4b]

Since aziridine nucleophilic ring-opening reactions are reported to take place generally via S_N2 displacement,[4b] we were able to infer the *anti* relative configuration for derivatives **3a**,**b**,**d**–**h**. This assignment was unequivocally confirmed through their transformation into the β-lactam derivatives **4** (Scheme 2).



2a **3a,e** **4a,b**

Scheme 2.

2.3. β-Lactam synthesis

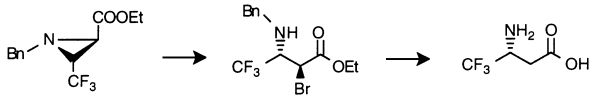
A well-known procedure, via Grignard-mediated intramolecular cyclisation,[8b,11] was followed for the synthesis of *trans*-β-lactams **4a**,**b** from β-aminoacids **3a**,**e**. For derivative **3e** in particular, the necessary protection of the hydroxy group was carried out, before cyclisation, by treatment with *t*-butyldimethylsilylchloride (TBDMSCl) in CH_2Cl_2 and in the presence of 4-*N*,*N*-dimethylaminopyridine (DMAP).

In the presence of methyl magnesium iodide at −12°C, cyclisation of **3a** occurred quickly: after 5 min, **4a** was recovered in 96% yield. By treatment of protected **3e** with methyl magnesium iodide at −12°C and then at room temperature for 12 h, **4b** was obtained in 68% chemical yield.

The structures of β-lactams **4a** and **4b** were determined by ^{1}H NMR and MS spectroscopies: the relative *trans* configuration was assigned on the basis of the $J_{H_3-H_4}$ coupling constant values (J=1.8 Hz).[7] *trans* Stereochemistry of the β-lactams confirms unambiguously the *anti* relative configurations of β-aminoacids **3** and underlines the stereoselectivity of the ring-opening reactions of *trans*-*N*-benzyl-3-trifluoromethyl-2-ethoxycarbonylaziridine **2a**. The regiospecific C-2 attack of nucleophiles at **2a** might be attributed to the strong electron-withdrawing effect of the trifluoromethyl group as well as to the electrostatic repulsion between the trifluoromethyl group and nucleophiles, which prevent C-3 attack.[12]

2.4. Chemical correlation

The absolute configurations of optically active *anti*-α-functionalised-β-aminoacids **3**, as well as of aziridine (+)-**2a**, were assigned by chemical correlation of (+)-**3b** with the configurationally known[2a] (*R*)-(+)-4,4,4-trifluoro-3-aminobutanoic acid **5** (Scheme 3).



(2*R*,3*R*)-(+)-**2a** (2*S*,3*S*)-(+)-**3b** (*R*)-(+)-**5**

Scheme 3.

Following the procedure described above for racemic **3b**, nucleophilic ring-opening of (+)-**2a** (ee 83%) with $MgBr_2$ afforded (+)-**3b** in a single *anti* stereoisomeric form. Catalytic hydrogenation of (+)-**3b**, until reductive debromination (20 min) and *N*-debenzylation (16 h) took place, yielded ethyl 4,4,4-trifluoro-3-aminobutanoate, which was hydrolysed (6N HCl, 100°C, 4 h) to obtain (+)-4,4,4-trifluoro-3-aminobutanoic acid **5**.

The absolute configuration *R* of (+)-**5** is known from the literature:[2a] since the chemical transformations reported in Scheme 3 do not involve the C-3 stereocentre of (+)-**2a** and (+)-**3b**, we must deduce for this stereocentre the same configuration as (+)-**5**, i.e. configuration 3*R* for (+)-**2a** and 3*S* for (+)-**3b**. Owing to the *trans* relative stereochemistry of aziridine (+)-**2a** and the *anti* relative stereochemistry of (+)-**3b**, we are able to infer the 2*R*,3*R*-configuration for (+)-**2a** and the 2*S*,3*S*-configuration for (+)-**3b**. Therefore, *anti*-isoserinates (+)-**3d** and (+)-**3e**, obtained from (*2R,3R*)-(+)-**2a**, must have 2*S*,3*R* absolute configurations.

3. Conclusion

trans-*N*-Benzyl-3-trifluoromethyl-2-ethoxycarbonylaziridine **2a**, easily obtainable in high chemical yield from the commercial *trans* ethyl γ,γ,γ-trifluorocrotonate, can be resolved by CAL-catalysed enzymatic ester-function hydrolysis in highly optically active form. This compound proved to be a versatile intermediate for the regio- and stereoselective synthesis of fluorinated *anti*-α-functionalised-β-aminoacids, such as trifluoromethylisoserinates, trifluoro-β-alanine, and for the synthesis of *trans*-trifluoromethyl-β-lactams. Starting from optically active aziridines **2**, enantiomerically pure isoserinates can be obtained in high overall chemical yield. The present synthetic method thus provides a useful entry into the stereoselective preparation of optically active fluorinated β-aminoacids and β-lactams.

4. Experimental

^{1}H NMR spectra were recorded on a Bruker AMX 400-WB or DPX-200 spectrometer. Chemical shifts are reported in δ values from TMS as internal standard (s, singlet; d, doublet; m, multiplet; q, quartet; t, triplet; br, broad signal). Coupling constants (*J*) are given in hertz. Optical rotations were measured at 20°C on a Perkin–Elmer 241 polarimeter. GLC analyses were performed on a Hewlett–Packard 5890 A gas chromatograph on a DB-1 column (30×0.53 mm I.D. and 5 μm film phase) from J&W Scientific, with helium as carrier gas. The enantiomeric excesses (ees) were evaluated on a chiral B-DEX 120 column (30×0.25 mm I.D. and 0.25 μm film phase) from Supelchem. Mass spectra were determined on a Finnigan Mat SSQA mass spectrometer (EI, 70 eV). Elemental analyses were performed with a Carlo Erba elemental analyser. Chromatographic purification of the compounds was performed on silica gel (ϕ 0.05–0.20 mm). Ethyl *trans*-4,4,4-trifluoro-2-butenoate and *Candida antarctica* lipase were purchased from Aldrich.

4.1. *Ethyl 2,3-dibromo-4,4,4*-trifluorobutanoate ***1***

To a stirred solution of ethyl *trans*-4,4,4-trifluoro-2-butenoate (5.0 g, 29.7 mmol) in carbon tetrachloride (90 mL), bromine (1.7 mL, 33.1 mmol) was slowly added at room temperature and the solution was heated at gentle reflux for 5 h. Thereafter, the solvent was removed in vacuo and the oily residue (9.0 g, 92% yield) proved to be a mixture of *syn/anti* isomers which was used without further purification. ^{1}H NMR ($CDCl_3$): major isomer (91%): 1.37 (3H, t, *J*=7.1), 4.35 (2H, q, *J*=7.1), 4.55 (1H, d, *J*=10.6), 4.72 (1H, dq, *J*=10.6, 6.3); minor isomer (9%): 1.36 (3H, t, *J*=7.1), 4.34 (2H, q, *J*=7.1), 4.74 (1H, d, *J*=6.3), 4.88 (1H, quintet, *J*=6.3). Both isomers showed the following mass fragmentation: MS, *m/z*: 331–329–327 [$(M+1)^+$], 330–328–326 (M^+), 302–300–298, 285–283–281, 257–255–253, 176–174, 157–155, 123, 110, 108, 95, 69 (100).

4.2. (±)-trans-*1-Benzyl-3-trifluoromethyl-2-ethoxycarbonylaziridine* ***2a***

Ethyl 2,3-dibromo-4,4,4-trifluorobutanoate **1** (8.96 g, 27.3 mmol) in absolute ethanol (25 mL) was slowly added to a cooled solution (−5°C) of benzylamine (10.5 mL, 96.1 mmol) in the same solvent (100 mL) with vigorous stirring over a period of 20 min. The cooling bath was then removed and the mixture allowed to react for 18 h. The solvent was removed under reduced pressure and diethyl ether (180 mL) was added to the residue; the precipitate (benzylammonium hydrobromide) was filtered off and the solution was washed with aqueous HCl (3%, 150 mL), with water (80 mL) and dried ($MgSO_4$). After filtration the solvent was removed under reduced pressure and the pale yellow oily residue was distilled (76–78°C/0.4 mmHg) to afford aziridine **2a** (6.70 g, 90% yield) as a colourless oil. ^{1}H NMR ($CDCl_3$): 1.18 (3H, t, *J*=7.1), 2.93 (1H, dq, *J*=2.3, 5.0), 2.98 (1H, d, *J*=2.3), 3.92 (1H, d, *J*=13.6), 4.07 (1H, d, *J*=13.6), 4.14 (2H, q, *J*=7.1), 7.20–7.39 (m, 5H, Ph); MS, *m/z*: 273 [M^+], 272, 244, 204, 200, 180, 158, 141, 130, 105, 104, 91 (100), 77, 65.

4.3. *Enzymatic resolution of (±)-****2a***

Racemic **2a** (500 mg, 1.83 mmol) was added to 0.1 mol dm^{-3} potassium phosphate buffer [40 mL containing NaCl (0.1 mol dm^{-3}), pH 7.5] at 37°C and treated with *Candida antarctica* lipase (10 mg) with vigorous mechanical stirring. After 30 min, the reaction mixture was extracted with diethyl ether (3×30 mL); the combined organic layers dried over magnesium sulphate and concentrated under reduced

pressure, yielded a crude residue which was purified by column chromatography (light petroleum:diethyl ether, 7:3, as eluent) to afford 272 mg of (2*R*,3*R*)-(+)-**2a** (54% yield), $[\alpha]_D$ +69.6 (*c* 1.7, $CHCl_3$), ee 83%. Spectroscopic data are identical to those reported for the racemic form. The aqueous phase of the enzymatic resolution was treated with HCl 10% until pH 1, extracted with ethyl acetate (4×30 mL) and dried (Na_2SO_4). After filtration, the solvent was removed under reduced pressure to afford (2*S*,3*S*)-(−)-**2b** as a fine powder (154 mg, 35%), $[\alpha]_D$ −55.3 (*c* 0.5, $CHCl_3$), ee >98%, mp 133–135°C (from methanol). ^{1}H NMR (DMSO-d_6): 2.95 (2H, dq, *J*=2.6, 0.3), 3.32 (1H, dq, *J*=2.6, 5.4), 3.99 (2H, s), 7.2–7.4 (5H, m).

The acid (2*S*,3*S*)-(−)-**2b** (154 mg, 0.60 mmol) was dissolved in ethyl acetate and treated with diazomethane in ether and concentrated under reduced pressure to afford the aziridine (2*S*,3*S*)-(−)-**2c** (163 mg, 100%) as a colourless oil, $[\alpha]_D$ −101.4 (*c* 1.5, $CHCl_3$), ee >98%. ^{1}H NMR ($CDCl_3$): 3.00 (1H, dq, *J*=2.4, 5.0), 3.04 (1H, d, *J*=2.4), 3.76 (3H, s), 3.97 (1H, d, *J*=13.6), 4.13 (1H, d, *J*=13.6), 7.33–7.39 (5H, m); MS, *m/z*: 259 [M^+], 258, 244, 228, 200, 190, 180, 158, 130, 123, 105, 104, 91 (100), 77, 69, 65.

4.4. trans-*3-Trifluoromethyl-2-ethoxycarbonylaziridine* ***2d***

A solution of **2a** (1.00 g, 3.66 mmol) in ethanol (7 mL) and acetic acid (2 mL) was stirred at room temperature with Pd 10% on carbon (50 mg) under 1 atm of hydrogen until absorption of the required volume (90 mL within 1 h). The suspension was treated with aqueous $NaHCO_3$ until gas evolution ceased, and was then filtered and extracted with diethyl ether. The collected organic phases were dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography (light petroleum:diethyl ether, 9:1, as eluent). The fractions containing aziridine were collected and concentrated at room temperature affording pure **2d** (583 mg, 87%) as a slightly volatile colourless oil. ^{1}H NMR ($CDCl_3$): 1.37 (3H, t, *J*=7.2), 1.73 (1H, br), 2.84 (1H, dd, *J*=2.2, 7.9), 2.91 (1H, ddq, *J*=7.2, 2.2, 5.0), 4.31 (2H, dq, *J*=1.6, 7.2); MS, *m/z*: 184 $[M+1]^+$, 183, 155, 138, 137, 118, 110, 109 (100), 90, 86, 82, 70.

4.5. Ethyl 3-benzylamino-2-chloro-4,4,4-trifluorobutanoate ***3a***

Anhydrous HCl was gently bubbled for 10 min into a cooled (−5°C) solution of the aziridine **2a** (1.7 g, 6.2 mmol) in anhydrous diethyl ether (80 mL). After a few minutes a precipitate appeared in the form of white crystals, and the reaction mixture was vigorously stirred until a TLC analysis showed that the aziridine had disappeared (2 h). The solvent was removed in vacuo and the crystalline residue was washed with diethyl ether, to afford compound **3a** as the hydrochloride (2.08 g, 96%). Mp 119–121°C. Anal. calcd for $C_{13}H_{16}Cl_2F_3NO_2$: C, 45.06; H, 4.62; N, 4.04%; found: C, 45.21; H, 4.71; N, 4.11.

The hydrochloride (1 g, 2.90 mmol) was treated with 1 M NaOH (5 mL) and extracted with diethyl ether (3×10 mL); the collected organic phases were dried over $MgSO_4$, filtered and the solvent removed to afford the α-chloro-β-amino-ester **3a** as a pale-yellow oil (0.88 g, 98%). ^{1}H NMR ($CDCl_3$): 1.33 (3H, t, *J*=7.1), 2.08 (1H, b), 3.83 (1H, m), 3.99 (1H, dd, *J*=6.0, 13.1), 4.06 (1H, dd, *J*=4.5, 13.1), 4.30 (2H, dq, *J*=1.3, 7.1), 4.51 (1H, d, *J*=6.2), 7.2–7.4 (5H, m); MS, *m/z*: 312–310 [M^+], 310–308, 282–280, 275–273, 242–240, 226, 204, 188 (100), 186, 160–158, 106, 91.

4.6. Ethyl 3-benzylamino-2-bromo-4,4,4-trifluorobutanoate ***3b***

A solution of H_2SO_4 in anhydrous THF (5 mL) was slowly dropped into a stirred solution of magnesium bromide (674 mg, 3.66 mmol) and aziridine **2a** (1 g, 3.66 mmol) in anhydrous THF (40 mL), the temperature being kept at below −10°C. After 10 min the reaction mixture was diluted with

diethyl ether (200 mL), washed with 5% $NaHCO_3$, with water and dried over $MgSO_4$. The solvent was removed by distillation in vacuo at room temperature and the colourless oily residue (1.29 g, 99%) proved to be **3b** in the single *anti* diastereoisomeric form. ^{1}H NMR ($CDCl_3$): 1.30 (3H, t, *J*=7.1), 2.15 (1H, b), 3.74 (1H, quintet, *J*=6.9), 3.96 (1H, d, *J*=12.8), 4.06 (1H, d, *J*=12.8), 4.26 (2H, dq, *J*=2.0, 7.1), 4.41 (1H, d, *J*=6.6), 7.2–7.4 (5H, m); MS, *m/z*: 354–356 [$(M+1)^+$], 353–355, 284–286, 274, 204, 186, 181, 158, 106, 91 (100), 69, 65.

Warming up the reaction mixture at room temperature for 1 h before quenching with $NaHCO_3$, the product **3b** was recovered as a mixture of *syn/anti* stereoisomers, which were separated by careful chromatography (light petroleum:diethyl ether, 6:4), to afford the previously described *anti* isomer (57%) and the *syn* isomer (37%). *syn* Isomer, ^{1}H NMR ($CDCl_3$): 1.27 (3H, t, *J*=7.3), 2.15 (1H, b), 3.85 (1H, dq, *J*=4.1, 6.9), 3.93 (1H, d, *J*=13.2), 4.02 (1H, d, *J*=13.2), 4.24 (2H, dq, *J*=2.7, 7.1), 4.66 (1H, d, *J*=4.1), 7.2–7.4 (5H, m).

*4.7. Ethyl (2S,3S)-(+)-3-benzylamino-2-bromo-4,4,4-trifluorobutanoate **3b***

The reaction of (+)-**2a** (500 mg, 1.83 mmol, ee 83%) with magnesium bromide (337 mg, 1.83 mmol), carried out as described for racemic **2a**, yielded (+)-**3b** (640 mg, 99%), $[\alpha]_D$ +12.0 (*c* 1.3, $CHCl_3$).

*4.8. Ethyl 3-benzylamino-4,4,4-trifluorobutanoate **3c***

A solution of **3b** (425 mg, 1.20 mmol) in ethyl acetate (8 mL) and acetic acid (1 mL) was stirred at room temperature with Pd 10% on carbon (50 mg) under 1 atm of hydrogen until absorption of the required volume (20 min; hydrogenation carried out for 16 h showed also *N*-debenzylation). The suspension was treated with aqueous $NaHCO_3$ until gas evolution ceased, and was then filtered and extracted with ethyl acetate. The collected organic phases were dried over Na_2SO_4 and concentrated in vacuo. The oily residue was purified by column chromatography (light petroleum:diethyl ether, 9:1, as eluent) to afford the title compound **3c** as a colourless oil (220 mg, 67%). ^{1}H NMR ($CDCl_3$): 1.27 (3H, t, *J*=7.1), 1.64 (1H, b), 2.51 (1H, dd, *J*=9.4, 15.5), 2.69 (1H, dd, *J*=4.2, 15.5), 3.66 (1H, ddq, *J*=4.2, 9.4, 7.2), 3.88 (1H, d, *J*=13.0), 4.03 (1H, d, *J*=13.0), 4.18 (2H, dq, *J*=2.2, 7.1), 7.2–7.4 (5H, m); MS, *m/z*: 276 [$(M+1)^+$], 274, 228, 206, 188, 186, 184, 159, 106 (100), 91, 77, 65.

*4.9. Ethyl 3-benzylamino-2-hydroxy-4,4,4-trifluorobutanoate **3d***

A solution of the aziridine **2a** (2 g, 7.3 mmol) in trifluoroacetic acid (15 mL) was stirred at 80°C for 2 h. The reaction mixture, concentrated in vacuo, afforded an light-brown oil which, upon treatment with wet diethyl ether immediately yielded a solid precipitate; this latter was recovered by filtration and re-crystallised from CH_2Cl_2, to afford a white crystalline compound (2.48 g, 87%), identified as the trifluoroacetate salt of the title compound, mp 94–95°C. Anal. calcd for $C_{15}H_{17}F_6NO_5$: C, 44.43; H, 4.23; N, 3.45%; found: C, 44.62; H, 4.32; N, 3.46. ^{1}H NMR (acetone-d_6): 1.26 (3H, t, *J*=7.0), 3.74 (1H, dq, *J*=4.0, 7.7), 4.11 (2H, s), 4.24 (2H, q, *J*=7.0), 4.64 (1H, dq, *J*=4.0, 1.1), 6.55 (3H, b), 7.24–7.50 (5H, m); MS, *m/z*: 292 [M^+], 291, 290, 218, 189, 188, 106, 91 (100).

The salt (1 g, 2.47 mmol) was treated with 1 M NaOH (5 mL) and the solution extracted with diethyl ether (3×10 mL); the collected organic phases were dried over $MgSO_4$, filtered and the solvent removed to afford the crystalline amino-ester **3d**, mp 96–97°C (0.69 g, 96%). ^{1}H NMR ($CDCl_3$): 1.32 (3H, t, *J*=7.1), 2.18 (1H, b), 3.23 (1H, b), 3.59 (1H, dq, *J*=3.3, 7.3), 3.98 (1H, d, *J*=13.3), 4.08 (1H, d, *J*=13.3),

4.30 (2H, dq, *J*=0.7, 7.1), 4.46 (1H, dq, *J*=3.3, 1.0), 7.25–7.45 (5H, m); MS, *m/z*: 292 [M^+], 291, 290, 218, 189, 188, 106, 91 (100).

4.10. Ethyl 3-amino-2-hydroxy-4,4,4-trifluorobutanoate ***3e***

A solution of **3d** (2.48 g, 6.12 mmol) in ethanol (10 mL) and acetic acid (5 mL) was stirred at room temperature with Pd 10% on carbon (125 mg) under 1 atm of hydrogen until absorption of the required volume (150 mL within 2 h). The catalyst was then removed by filtration, the solution was poured into aqueous $NaHCO_3$ (60 mL) and solid $NaHCO_3$ was added until gas evolution ceased. The resulting suspension was extracted with diethyl ether (3×50 mL) and the collected organic phases were dried ($MgSO_4$). The solvent was removed in vacuo and the residue purified by column chromatography (*n*-hexane:diethyl ether, 1:1, as eluent) to yield **3e** (1.02 g, 83%) as white crystals, mp 50–51°C. Anal. calcd for $C_6H_{10}F_3NO_3$: C, 35.81; H, 5.01; N, 6.96%; found: C, 36.02; H, 5.14; N, 6.83. ^{1}H NMR ($CDCl_3$): 1.36 (3H, t, *J*=7.2), 2.25 (3H, b), 3.65 (1H, dq, *J*=3.5, 7.4), 4.32 (2H, dq, *J*=0.6, 7.2), 4.41 (1H, dq, *J*=3.5, 1.1); MS, *m/z*: 202 [$(M+1)^+$], 128, 104 (100), 98, 80, 76, 59, 58.

*4.11. Ethyl (2*S*,3*R*)-(+)-3-amino-2-hydroxy-4,4,4-trifluorobutanoate* ***3e***

The reaction of (2*R*,3*R*)-(+)-**2a** (135 mg, 0.51 mmol, ee 83%) with trifluoroacetic acid (2 mL), carried out as described for racemic **2a**, yielded (2*S*,3*R*)-(+)-**3d** as a crystalline white solid, $[\alpha]_D$ +11.8 (*c* 1.7, $CHCl_3$). Subsequent debenzylation of (2*S*,3*R*)-(+)-**3d**, following the same procedure described for racemic **3d**, afforded (2*S*,3*R*)-(+)-**3e** (72 mg, 73% overall yield) as a low-melting solid, mp 32–35°C, $[\alpha]_D$ +15.8 (*c* 1.6, $CHCl_3$), ee 83%.

*4.12. Methyl (2*R*,3*S*)-(−)-3-benzylamino-2-hydroxy-4,4,4-trifluorobutanoate* ***3f***

Trifluoroacetolysis of (2*S*,3*S*)-(−)-**2c** (130 mg, 0.5 mmol), ee >98%, carried out as described for the synthesis of **3d**, afforded (2*R*,3*S*)-(−)-**3f** (170 mg, 91%) as a crystalline white solid, mp 86–87°C, $[\alpha]_D$ −11.3 (*c* 0.6, $CHCl_3$), ee >98%. ^{1}H NMR ($CDCl_3$): 2.04 (1H, b), 3.01 (1H, b), 3.73 (1H, dq, *J*=3.3, 7.3), 4.04 (1H, d, *J*=13.6), 4.16 (1H, d, *J*=13.6), 4.53 (1H, dq, *J*=3.3, 0.8), 7.20–7.45 (5H, m); MS, *m/z*: 278 [$(M+1)^+$], 218, 216, 208, 188, 106, 91 (100), 65.

*4.13. Methyl (2*R*,3*S*)-(−)-3-amino-2-hydroxy-4,4,4-trifluorobutanoate* ***3g***

Debenzylation of (2*R*,3*S*)-(−)-**3f** (170 mg, 0.45 mmol, ee >98%) in methanol (0.75 mL) and acetic acid (0.45 mL) was stirred at room temperature with Pd 10% on C (15 mg) under 1 atm of hydrogen until absorption of the required volume (4 h). Following the work-up procedure described for the synthesis of **3e**, (2*R*,3*S*)-(−)-**3g** was obtained (70 mg, 82%), $[\alpha]_D$ −22.4 (*c* 0.7, $CHCl_3$), ee >98%. ^{1}H NMR ($CDCl_3$): 1.68 (3H, b), 3.65 (1H, dq, *J*=3.4, 7.4), 3.94 (3H, s), 4.43 (1H, d, *J*=3.4); MS, *m/z*: 188 [$(M+1)^+$], 170, 128, 108, 98, 90 (100), 78, 59.

4.14. Ethyl 3-trifluoroacetamino-2-hydroxy-4,4,4-trifluorobutanoate ***3h***

A solution of the aziridine **2d** (100 mg, 0.55 mmol) in trifluoroacetic acid (2 mL) was stirred at 70°C for 4 h; the reaction mixture was concentrated in vacuo and the residue purified by column chromatography (*n*-hexane:diethyl ether, 4:6, as eluent) to afford the title compound (147 mg, 91%) as a white solid, mp

73–74°C. Anal. calcd for $C_8H_9F_6NO_4$: C, 32.32; H, 3.03; N, 4.71%; found: C, 31.85; H, 3.08; N, 4.41. ^{1}H NMR ($CDCl_3$): 1.39 (3H, t, *J*=7.2), 3.32 (1H, b), 4.39 (2H, dq, *J*=0.8, 7.2), 4.43 (1H, dq, *J*=3.2, 1.5), 5.11 (1H, ddq, *J*=10.2, 3.2, 6.7), 7.13 (1H, b); MS, *m/z*: 298 [$(M+1)^+$], 280, 241, 224, 204, 186, 175, 158, 114, 103 (100), 75, 68.

4.15. trans-*1-Benzyl-3-chloro-4-trifluoromethyl-2-azetidinone* ***4a***

A freshly prepared solution of methyl magnesium iodide (4.29 mmol) in anhydrous diethyl ether (10 mL), was slowly added to a stirred solution of **3a** (884 mg, 2.86 mmol) in anhydrous diethyl ether (10 mL) under a stream of nitrogen, at a carefully controlled temperature of −12°C. The mixture was stirred for a further 5 min, thereafter the slurry was quenched with satd NH_4Cl, and extracted with diethyl ether; the collected organic phases were washed with aqueous $NaHCO_3$, with water and dried over Na_2SO_4. The filtered solution was concentrated under reduced pressure and the residue purified by column chromatography (light petroleum:diethyl ether, 8:2, as eluent) to yield **4a** as a colourless oil (723 mg, 96%). ^{1}H NMR ($CDCl_3$): 3.86 (1H, dq, *J*=1.8, 5.7), 4.07 (1H, d, *J*=15.1), 4.86 (1H, d, *J*=1.8), 4.95 (1H, d, *J*=15.1), 7.2–7.5 (5H, m); MS, *m/z*: 265–263 [M^+], 245–243, 227, 133, 132, 123, 105, 104, 92, 91 (100), 77, 65.

4.16. trans-*3-(*t*-Butyldimethylsilyloxy)-4-trifluoromethyl-2-azetidinone* ***4b***

Before cyclisation, **3e** was protected as TBDMS-ether as follows: *t*-butyldimethylsilylchloride (280 mg, 1.85 mmol) in CH_2Cl_2 (1 mL) was added to a solution of **3e** (107 mg, 0.53 mmol) and 4-*N*,*N*-dimethylaminopyridine (273 mg, 2.23 mmol) in anhydrous CH_2Cl_2 (2 mL) at −5°C, and the solution was stirred for 15 min. Thereafter the solution was diluted with CH_2Cl_2 (5 mL), washed with water and dried ($MgSO_4$). The solvent was removed in vacuo and the residue purified by column chromatography (light petroleum:diethyl ether, 8:2, as eluent), to afford ethyl 3-amino-2-(*t*-butyldimethylsilyloxy)-4,4,4-trifluorobutanoate (117 mg, 70%) as a colourless oil.

A freshly prepared solution of methyl magnesium iodide (0.76 mmol) in anhydrous diethyl ether (5 mL) was slowly added to a stirred solution of the TBDMS-ether (117 mg, 0.37 mmol) in anhydrous diethyl ether (5 mL) at −12°C under a stream of nitrogen. The mixture was warmed at room temperature and stirred overnight; thereafter, the slurry was quenched with satd NH_4Cl, and extracted with diethyl ether; the collected organic phases were washed with aqueous $NaHCO_3$, then with water and dried over Na_2SO_4. The filtered solution was concentrated under reduced pressure and the residue purified by column chromatography (light petroleum:diethyl ether, 6:4, as eluent) to yield **4b** as a colourless oil (68 mg, 68%).

Ethyl 3-amino-2-(*t*-butyldimethylsilyloxy)-4,4,4-trifluorobutanoate: ^{1}H NMR ($CDCl_3$): 0.12 (3H, s), 0.13 (3H, s), 0.95 (9H, s), 1.33 (3H, t, *J*=7.1), 1.61 (2H, b), 3.65 (1H, m), 4.26 (2H, dq, *J*=0.7, 7.1), 4.36 (1H, dq, *J*=4.3, 0.6); MS, *m/z*: 316 [$(M+1)^+$], 300, 259, 258, 242, 230, 218, 212, 184 (100), 133, 103, 75, 73.

trans 3-(*t*-Butyldimethylsilyloxy)-4-trifluoromethyl-2-azetidinone **4b**: ^{1}H NMR ($CDCl_3$): 0.20 (3H, s), 0.21 (3H, s), 0.96 (9H, s), 3.94 (1H, dq, 1.8, 6.2), 4.98 (1H, t, 1.8), 5.98 (1H, b); MS, *m/z*: 270 [$(M+1)^+$], 254, 241, 226, 212 (100), 184, 169, 157, 90, 88, 77, 73.

4.17. Chemical correlation

A solution of (+)-**3b** (500 mg, 1.41 mmol), $[\alpha]_D$ +12.0, ee 83%, in ethyl acetate (8 mL) and acetic acid (1 mL) was stirred at room temperature with Pd 10% on carbon (55 mg) under 1 atm of hydrogen until absorption of the required volume (70 ml within 16 h). The catalyst was removed by filtration and the solution washed with aqueous $NaHCO_3$, dried ($MgSO_4$) and filtered; the complete reductive debromination and debenzylation to ethyl 3-amino-4,4,4-trifluorobutanoate was confirmed by GC/MS analysis. Ms, *m/z*: 186 [$(M+1)^+$], 165, 140, 116, 98, 93, 78, 74, 69.

Owing to the high volatility of the aminoester, the organic solution was extracted with 6N HCl (4 mL), and the aqueous phase heated at reflux for 4 h. Thereafter, the solvent was removed under reduced pressure to afford 4,4,4-trifluoro-3-aminobutanoic acid **5** as a crystalline solid (43% yield), showing $[\alpha]_D$ +21.4 (*c* 1.6, 6N HCl) (lit:[2a] (*R*)-(+)-**5** $[\alpha]_D$ +27.6, ee >95%).

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