Diastereo- and Enantioselective Synthesis of Fluorinated Threonines

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(*d,l*)-*threo* and *allo*-2-amino-4,4,4-trifluoro-3-hydroxybutanoic acids are synthesised from ethyl trifluoroacetoacetate via reduction and saponification of the 4,4,4-trifluoro-3-hydroxy-2-methoxyiminobutanoate. *threo*-Isomers are stereospecifically obtained by epimerisation of *allo*-isomers via the corresponding oxazolidinones. An acylation and stereoselective reduction sequence performed on ethyl *N,N*-dibenzylaminoacetate also leads to *threo*-isomers (**1A**) in good yields. An enantioselective synthesis of (L)-4-fluorothreonine by regiospecific opening of (2*S*),(3*R*)-3-benzyloxyoxiranecarboxylic acid is reported.

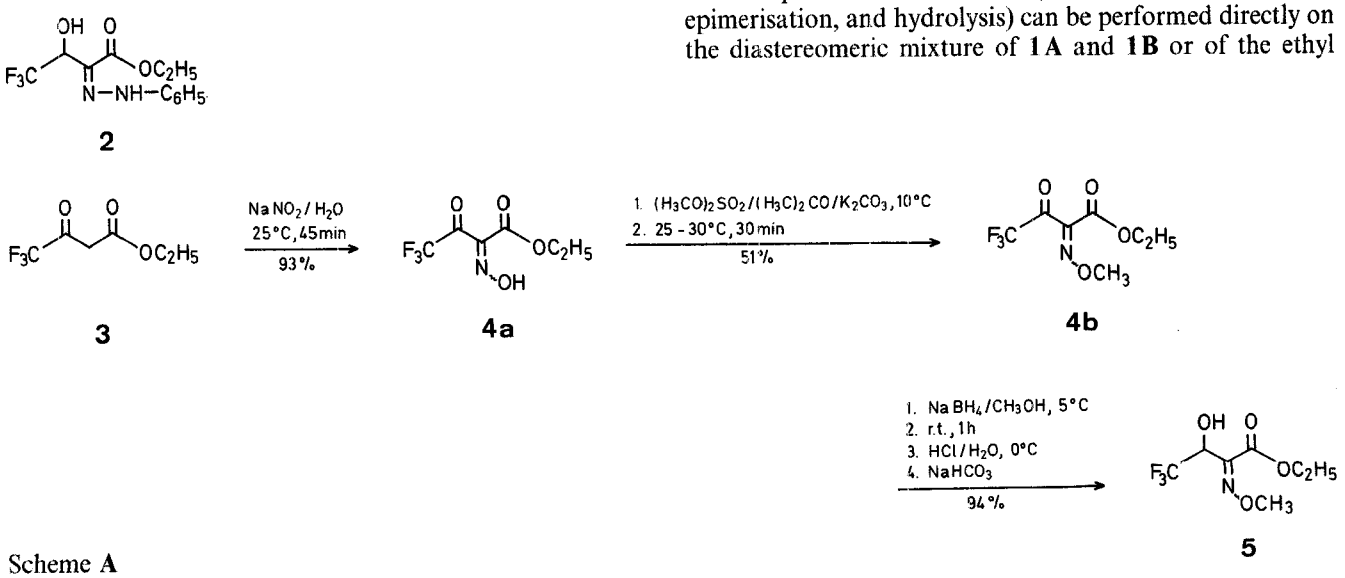
Mono- and trifluorinated threonine and *allo*-threonine are interesting products both for their potential antimetabolic activity[1] as well as their use as possible precursors for the synthesis of Aztreonam[2] analogues in which the methyl in the 4-position of the β-lactam is replaced by a monofluoromethyl or a trifluoromethyl group. Since Aztreonam has been shown to possess excellent acitivity against Gram-negative bacteria[2], it seemed interesting to evaluate whether the change of reactivity of the β-lactam ring is correlated with the antibacterial activity[3,4]. In this paper we describe two new methods for the synthesis of *(d,l)-threo*- and *allo*-(threonine nomenclature)-2-amino-4,4,4-trifluoro-3-hydroxybutanoic acids (**1A**) and (**1B**) and the enantioselective synthesis of (2*S*),(3*S*)-2-amino-4-fluoro-3-hydroxybutanoic acid (**19**).

The reported synthesis of trifluoro-*allo*-threonine (**1B**) *via* the reduction of the phenylhydrazone of 4,4,4-trifluoro-3-hydroxy-2-oxobutanoic acid (**2**)[5] (Scheme **A**)[6] gave unsatisfactory yields. Thus, we nitrosated ethyl trifluoroacetoacetate (**3**) to give the oxime **4a**, which was in turn methylated to **4b** with dimethyl sulphate in acetone in the presence of potassium carbonate, and reduced with sodium borohydride in methanol to ethyl 4,4,4-trifluoro-3-hydroxy-2-methoxyiminobutanoate (**5**).

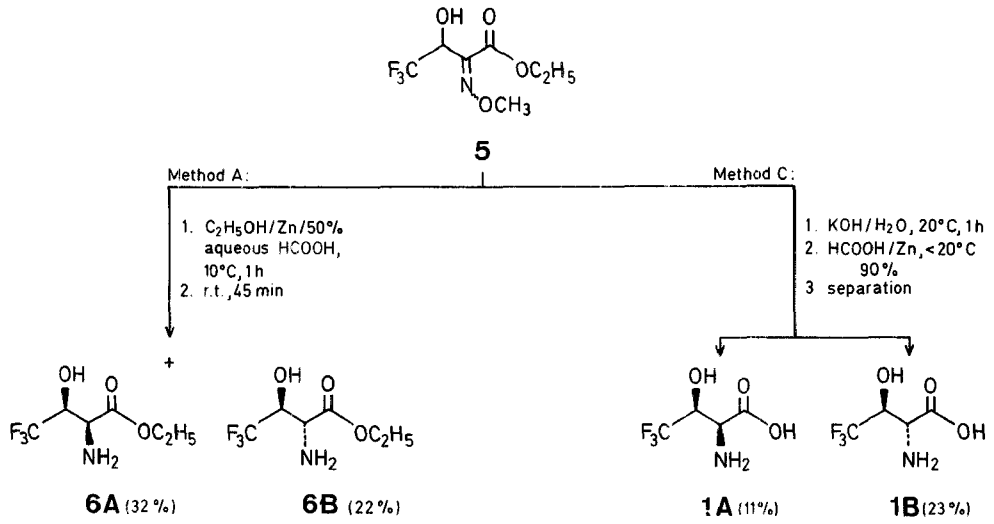
The reduction of **5** with zinc powder and 50% aqueous formic acid gave ethyl 2-amino-4,4,4-trifluoro-3-hydroxybutanoate as a diastereomeric mixture of *threo(syn)*-**6A** and *allo(anti)*-**6B** in a 1.5:1 ratio (80% yield). Compounds **6A** and **6B** could be easily separated by chromatography on silica gel (1:1 ethyl acetate/*n*-hexane) and saponified (triethylamine in aqueous ethanol) to trifluorothreonine (**1A**) and trifluoro-*allo*-threonine (**1B**). Alternatively, the methoxyimino derivative **5** could be saponified (aqueous potassium hydroxide) and reduced *in situ* by zinc powder/50% aqueous formic acid to give a mixture of **1A** and **1B** which can be separated by fractional crystallisation (Scheme **B**).

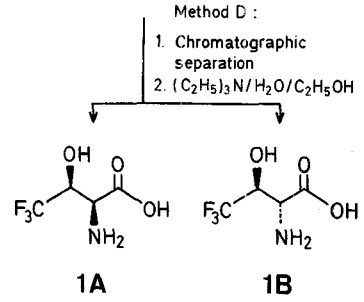
The relative configurations of **1A** and **1B** were established by their transformation (phosgene/toluene) into *trans*- and *cis*-oxazolidinones **7B** and **7A**, respectively[7], which were recognized as such by their H-4/H-5 coupling constants (3.5 and 9.1 Hz, respectively, Scheme **C**)[6]. When the *cis*-oxazolidinone **7A** was heated with two equivalents of alcoholic potassium hydroxide, the conversion to the thermodynamically more stable *trans*-oxazolidinone **7B** took place. Hydrolysis of **7B** with 6 normal hydrochloric acid yielded pure trifluorothreonine (**1A**), isolated after chromatography on DOWEX 50W ($H^{\oplus}$) (using 10% aqueous ammonia as eluent).

This sequence of reactions (oxazolidinone formation, epimerisation, and hydrolysis) can be performed directly on the diastereomeric mixture of **1A** and **1B** or of the ethyl

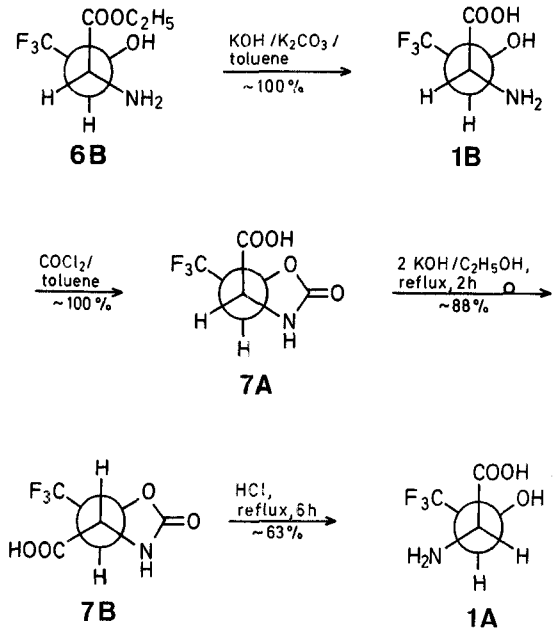


Scheme **A**





Scheme B



Scheme C

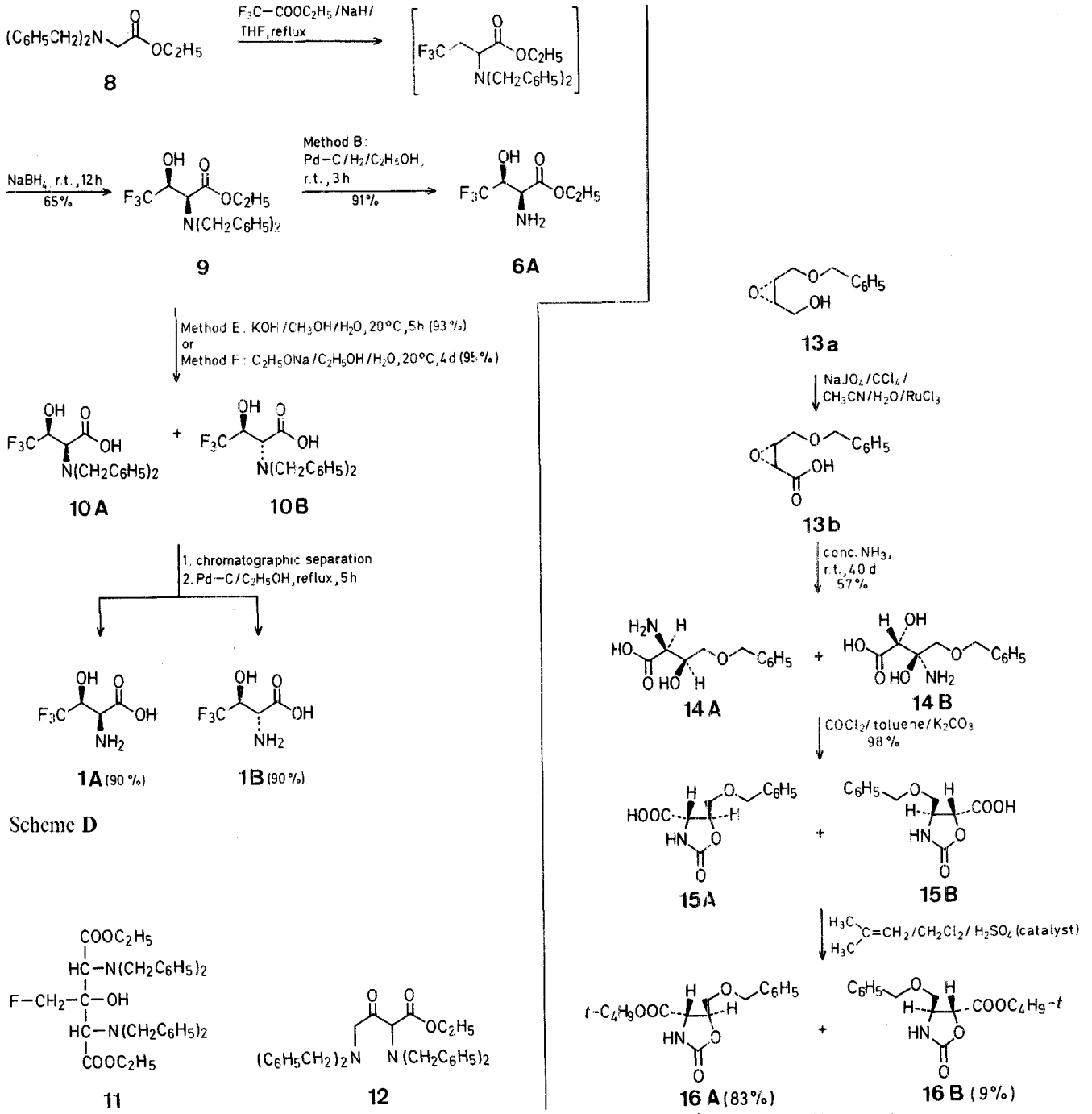
esters **6A** and **6B**, without isolation of the intermediates, in a one-pot procedure, thus allowing a stereospecific synthesis of the *threo*-isomer **1A**.

In principle, trifluorothreonine (**1A**) could also be synthesised by an aldol-type condensation between trifluoroacetaldehyde and suitably protected glycine esters. However, we were not able to obtain reasonable yields in the reaction of ethyl *N*-benzyloxycarbonylglycine with trifluoroacetaldehyde[8]. Thus, in the light of our recent report which shows the feasibility of an acylation-reduction sequence as an alternative to the aldol condensation for the stereoselective synthesis of *threo*-α-amino-β-hydroxy acids[9], we decided to apply this methodology for the synthesis of **1A** (Scheme **D**)[6].

An additional advantage of this procedure is the use of ethyl trifluoroacetate as a starting material, being much cheaper and easier to handle than trifluoroacetaldehyde. The acylation of ethyl dibenzylaminoacetate (**8**) with ethyl trifluoroacetate (sodium hydride/tetrahydrofuran, reflux) gave a very unstable β-ketoester which was reduced *in situ* with sodium borohydride to the *threo*-α-dibenzylamino-β-hydroxy derivative **9** in 65% overall yield. The reduction turned out to be very stereoselective since the *allo*-isomer could not be detected by T.L.C. or ^{1}H-N.M.R. spectrometry (d.e. > 98%). The hydrolysis of the ester group was rather problematic since **9** is prone to epimerise under basic conditions: with 0.5 normal potassium hydroxide in 7:3 methanol/water, an 85:15 mixture of **10A** and **10B** was obtained in 93% overall yield. It is noteworthy that, by carrying out the saponification with 0.4 normal sodium ethoxide in 99.8% ethanol, it was possible to obtain the *allo*-epimer as the main product in a ratio of 65:35. Compounds **10A** and **10B** could be easily separated by column chromatography and hydrogenated (10% palladium-on-carbon/ethanol, reflux) in 90% yield to afford, respectively, trifluorothreonine (**1A**) and trifluoro-*allo*-threonine (**1B**). However, the epimerisation can be avoided by carrying out the hydrogenolysis of the benzyl groups before saponification.

On the basis of this results we tried to apply the acylation-reduction sequence also to the synthesis of 4-fluorothreonine. However, using either ethyl fluoroacetate or fluoroacetyl chloride, we were not able to stop the condensation at the level of the β-ketoester, and isolated a diastereomeric mixture of **11** together with the self-condensation product **12** of ethyl dibenzylaminoacetate.

This different behaviour is probably due to the stronger acidity of the trifluoro-β-ketoester, which is rapidly deprotonated in the reaction media to give an enolate which is protectively acylated by the excess of ethyl trifluoroacetate. Actually two mol of the latter were necessary to complete the reaction.



Scheme D

Scheme E

In contrast, the carbonyl group of the less acidic monofluoro-β-ketoester is probably attacked by the dibenzylaminoacetate prior to enolate formation.

The enantioselective synthesis of L-4-fluorothreonine (**19**) was performed starting from the known (2*S*),(3*R*)-3-benzyloxymethyl-2-(hydroxymethyl)-oxirane (**13a**)[10] (Scheme E). Oxidation of **13a** to (2*S*),(3*R*)-3-benzyloxyoxiranecarboxylic acid (**13b**) was performed with sodium metaperiodate in carbon tetrachloride/acetonitrile/water in the presence of a catalytic amount of ruthenium(III) chloride[11]. Treatment of **13b** with concentrated ammonia at room temperature for 40 days gave a 57% yield of the regioisomers **14A** and **14B** in a 9:1 ratio. This mixture was resolved by conversion of the amino acids **14A** and **14B** into the corresponding 4- and 5-oxazolidinecarboxylic acids **15A** and **15B** (phosgene in toluene/potassium carbonate) followed by es-

terification with isobutene (dichloromethane, catalytic amount of sulphuric acid), to give the *t*-butyl esters **16A** and **16B**. These were separated by flash chromatography[12] and **16A** was then hydrogenated (palladium-on-carbon/methanol) to afford *t*-butyl (4*S*),(5*S*)-5-hydroxymethyl-2-oxo-4-oxazolidinecarboxylate **(17)**. The fluorination of **17** in dichloromethane solution, carried out with diethylaminosulphur trifluoride at −78 °C, gave *t*-butyl (4*S*),(5*S*)-5-fluoromethyl-2-oxo-4-oxazolidinecarboxylate **(18)** in 53% yield. Finally, hydrolysis of **18** with aqueous 6 normal hydrochloric acid for 7 h followed by ion-exchange chromatography on DOWEX 50W ($H^{\oplus}$) gave L-4-fluoro-threonine **(19)** in 62% yield.

I.R. spectra were recorded with a Perkin-Elmer 457 spectrophotometer. ^{1}H-N.M.R. spectra were recorded with Varian FT-80 (80 MHz) or with Bruker WP-80 (80 MHz) instruments, using tetramethylsilane as internal standard. ^{19}F-N.M.R. were recorded with a Varian XL-100 instrument, using hexafluorobenzene (C_6F_6) as an internal standard. Microanalyses were performed with a Perkin-Elmer 240 instrument. Optical rotations were measured in 1 dm cells of 1 ml capacity using a Perkin-Elmer 141 polarimeter. 270–400 Mesh silica gel (Merck) was used for flash chromatography[12].

Ethyl 4,4,4-Trifluoro-2-hydroxyimino-3-oxobutanoate (4a):
To a solution of ethyl 4,4,4-trifluoroacetoacetate (**3**; 130 g, 0.91 mol) in acetic acid (200 ml), a solution of sodium nitrite (56 g, 0.81 mol) in water (120 ml) is added dropwise over 45 min at 20 °C. Then the mixture is poured into brine (800 ml) and extracted with ether (3 × 200 ml). The extract is washed with brine (400 ml) and aqueous sodium hydrogen carbonate (100 ml) until pH = 6.8. The aqueous phase is extracted again with ether (4 × 200 ml). The organic extracts are dried with sodium sulphate and evaporated under reduced pressure to give the crude ester **4a** as an oily mixture of the two geometric isomers, which can be directly used for the next step, yield: 140 g (93%); a sample is purified by column chromatography (silica gel, *n*-hexane/ethyl acetate, 6:4).

$C_6H_6F_3NO_4$	calc.	C 33.82	H 2.84	N 6.57
(213.1)	found	33.89	2.88	6.54

I.R. (neat): ν = 3600–3000, 1730, 1630 cm^{-1}.

^{1}H-N.M.R. ($CDCl_3$): δ = 1.25 (t, 3 H, CH_3CH_2, J = 7 Hz); 3.65 (q, 2 H, CH_2CH_3, J = 7 Hz); 4.1–5.8 ppm (br.s, 1 H, OH).

Ethyl 4,4,4-Trifluoro-2-methoxyimino-3-oxo-butanoate (4b):
Crude **4a** (139.6 g, 0.655 mol) and dimethyl sulphate (100 g, 0.794 mol) are dissolved in acetone (800 ml). To the stirred solution, potassium carbonate (50 g) is added portionwise at 10 °C. The mixture is allowed to stand at 25–30 °C for 30 min, and then is filtered and evaporated. The resulting yellow oil is dissolved in ether (500 ml) and washed with brine (2 × 100 ml) and water (50 ml). The organic extract is dried with sodium sulphate and evaporated. The residue (185 g) is distilled to afford pure **4b**; yield: 76 g (51%); b.p. 45–46 °C/0.7 torr.

$C_7H_8F_3NO_4$	calc.	C 37.01	H 3.55	N 6.17
(227.1)	found	37.12	3.63	6.11

I.R. (neat): ν = 1760, 1735, 1595 cm^{-1}.

^{1}H-N.M.R. ($CDCl_3$): δ = 1.45 (t, 3 H, CH_2CH_3, J = 7 Hz); 4.45 (q, 2 H, CH_2CH_3, J = 7 Hz); 4.30 ppm (s, 3 H, OCH_3).

Ethyl 4,4,4-Trifluoro-3-hydroxy-2-methoxyiminobutanoate (5):
To a solution of **4b** (13 g, 0.057 mol) in methanol (70 ml) sodium borohydride (1 g) is added portionwise at 5 °C. The mixture is stirred for 1 h at room temperature, and then cooled to 0 °C. 6 Normal hydrochloric acid until pH < 4, and sodium hydrogen carbonate until pH = 8 are added in sequence. The mixture is filtered and the filtrate is evaporated under vacuum. The residue is dissolved in ether (200 ml) and washed with brine (2 × 75 ml). The organic extract is evaporated to dryness to afford pure **5**; yield: 12.4 g (94%); b.p. 66–68 °C/1 torr.

$C_7H_{10}F_3NO_4$	calc.	C 36.69	H 4.40	N 6.11
(229.2)	found	36.82	4.53	5.98

I.R. (neat): ν = 3600–3000, 1740, 1625 cm^{-1}.

^{1}H-N.M.R. ($CDCl_3$): δ = 1.33 (t, 3 H, CH_2—CH_3, J = 7 Hz); 3.50 (s, 1 H, OH); 4.05 (s, 3 H, OCH_3); 4.40 (q, 2 H, CH_2CH_3, J = 7 Hz); 4.85 (q, 1 H, CF_3—CH, J = 6 Hz).

Ethyl 2-Amino-4,4,4-trifluoro-3hydroxybutanoates (6A) and (6B):
Method A: To a solution of **5** (131.9 g, 5.76 mol) in ethanol (330 ml), and 50% aqueous formic acid (200 ml), zinc powder (640 g, 9.79 mol) is added portionwise over 60 min at 10 °C. The mixture is then allowed to stand at room temperature for 45 min. The salts are filtered off and washed with water. The aqueous phase is treated with concentrated ammonia (2000 ml) until pH = 8 and then extracted with ethyl acetate (4 × 1000 ml). The organic phase is dried with sodium sulphate, filtered, and evaporated to dryness under reduced pressure. Separation by column chromatography (silica gel, acetate/*n*-hexane, 1:1) gives **6A** [yield: 36.5 g (32%)] and **6B** [yield: 26 g (22%)] which are purified by trituration in *n*-pentane; m.p. 87–89 °C **(6A)** and 77–79 °C **(6B)**.

$C_6H_{10}F_3NO_3$	calc.	C 35.83	H 5.01	N 6.96
(201.2)	found **(6A)**	35.97	5.15	6.82
	found **(6B)**	35.90	5.09	6.80

I.R. ($CHCl_3$) **(6A)**: ν = 3360, 3280, 1730, 1600, 1465 cm^{-1}.
I.R. ($CHCl_3$) **(6B)**: ν = 3390, 3325, 1735, 1590, 1465 cm^{-1}.

^{1}H-N.M.R. ($CDCl_3/D_2O$) **(6A)**: δ = 1.30 (t, 3 H, CH_2CH_3, J = 7 Hz); 3.87 (d, 1 H, $CHNH_2$, J = 1.8 Hz.); 4.05–4.52 ppm (m, 3 H, CH_2—CH_3 and CH—CF_3).
^{1}H-N.M.R. ($CDCl_3/D_2O$) **(6B)**: δ = 1.33 (t, 3 H, CH_3CH_2, J = 7 Hz); 3.78 (d, 1 H, CH—NH_2, J = 5 Hz); 4.07–4.54 ppm (m, 3 H, CH_2CH_3 and CH—CF_3).

Method B: A solution of **9** (100 mg, 0.262 mmol) in absolute ethanol (10 ml) is hydrogenated over 10% palladium-on-carbon (20 mg) for 3 h at room temperature. Filtration of the catalyst and evaporation of the filtrate to dryness give a white solid corresponding to pure **6A** (T.L.C., ^{1}H-N.M.R.); yield: 48 mg (91%); m.p. 88–89 °C.

2-Amino-4,4,4-trifluoro-3-hydroxybutanoic Acids (1A) and (1B):
Method C: To a solution of potassium hydroxide (8.8 g, 0.157 mol) in water (50 ml), **5** (14.6 g, 63.7 mmol) is added over 15 min at 20 °C. After 1 h at room temperature, formic acid (55 ml) is added. The solution is then cooled with an ice bath and, keeping the temperature below 20 °C, zinc powder (7.08 g, 0.108 mol) is added portionwise. The mixture is allowed to stand at room temperature for 3 h and is then filtered and evaporated. The residue (36 g) is dissolved in water (100 ml) and purified by ion-exchange chromatography on DOWEX 50W-X4 ($H^{\oplus}$) (330 ml) eluting with 10% aqueous ammonia; yield: 9.9 g (90%); Crystallisation from methanol (480 ml) affords the *anti*-isomer **1B** [yield: 2.5 g (23%)] and, after concentration of mother liquors, by cooling, the *syn*-isomer **1B** [yield: 1.2 g (11%)] is obtained: m.p. 212–214 °C dec. **(1A)** and 191–193 °C dec. **(1B)**.

$C_4H_6F_3NO_3$	calc.	C 27.76	H 3.49	N 8.09
(173.09)	found **(1A)**	27.78	3.50	7.98
	found **(1B)**	27.80	3.50	7.96

^{1}H-N.M.R. (DMSO-d_6) **(1A)**: δ = 3.40 (d, 1 H, CHCOOH, J = 1.8 Hz); 4.70 ppm (dq, 1 H, $CHCF_3$, J = 1.8 Hz, 8.4 Hz).
^{1}H-N.M.R. (DMSO-d_6) **(1B)**: δ = 3.36 (d, 1 H, CH—COOH, J = 5.7 Hz); 4.20 ppm (m, 1 H, $CHCF_3$, J = 5.7 Hz, 7.0 Hz).

Method D: To a solution of **6** (10 g, 49.7 mmol) in 1:2 ethanol/water (100 ml), triethylamine (42 ml) is added. After 24 h the mixture is evaporated to dryness. The residue is dissolved in water (50 ml) and hydrochloric acid is added until pH = 4.5. The mixture is then evaporated and the residue is tritured in methanol. After 30 min at 5 °C the precipitated **1A** is filtered and washed with methanol and diethyl ether; yield: 7.1 g (83%); m.p. 210–213 °C (dec.).

***d,l-cis*-5-Trifluoromethyl-2-oxo-4-oxazolidinecarboxylic Acid (7A):**
The racemic compound **1B** (100 mg, 5.85 mmol) is dissolved in 0.25 normal aqueous potassium hydroxide (2.5 ml); potassium carbonate (330 mg, 2.39 mmol) is added to the solution which is covered with toluene (1 ml). Then a 20% solution of phosgene in toluene (0.98 ml) is added dropwise at 0°C. The mixture is stirred for further 2 h and then the excess of phosgene is removed. The solution is extracted with ethyl acetate (5 ml). The aqueous phase is acidified (pH = 2) with 6 normal hydrochloric acid and extracted again with ethyl acetate (3 × 2 ml). The organic phase is dried with sodium sulphate and evaporated under reduced pressure to afford practically pure **7A** which can be recrystallised from ethyl acetate/*n*-hexane; yield: 115 mg (99%); m.p. 180–185°C (dec.).

$C_5H_4F_3NO_4$	calc.	C 30.15	H 2.01	N 7.03
(199.1)	found	30.31	2.03	7.00

^{1}H-N.M.R. (DMSO-d_6): δ = 4.75 (d, 1H, CH—COOH, J = 9.1 Hz); 5.55 ppm (dq, 1H, CH—CF_3, J = 9.1 Hz, J = 7.2 Hz).

***d,l-trans*-5-Trifluoromethyl-2-oxo-4-oxazolidinecarboxylic Acid (7B):**
The carboxylic acid **7A** (1.052 g, 5.28 mmol) is dissolved in a 0.59 normal solution of potassium hydroxide in ethanol (17.5 ml). The mixture is refluxed for 5 h and then the solvent is evaporated. The residue is dissolved in water (15 ml) and washed with ethyl acetate (5 ml). The aqueous phase is acidified with 6 normal hydrochloric acid until pH = 2 and again extracted with ethyl acetate (3 × 15 ml). The organic extract is dried with sodium sulphate and then evaporated to dryness under reduced pressure; yield: 905 mg (88%); m.p. 105–107°C.

$C_5H_4F_3NO_4$	calc.	C 30.15	H 2.01	N 7.03
(199.1)	found	30.01	2.00	6.90

^{1}H-N.M.R. (DMSO-d_6): δ = 4.55 (d, 1H, CH—COOH, J = 3.5 Hz); 4.45 ppm (dq, 1H, CH—CF_3, J = 3.5 Hz, 6.8 Hz).

2-Amino-4,4,4-trifluoro-3-hydroxybutanoic Acid (1A):
Compound **7B** (300 mg, 1.51 mmol) is refluxed with 6 normal hydrochloric acid (4.5 ml) for 6 h. The solution is concentrated and then washed with ethyl acetate (6 ml). The product is purified by ion-exchange chromatography on DOWEX 50W ($H^{\oplus}$) (eluting first with water until pH = 7 and then with 5% aqueous ammonia) and crystallised from ethanol; yield: 140 mg (63%).

Ethyl Dibenzylaminoacetate (8):
To a solution of dibenzylamine (13.8 ml, 71.9 mmol) in absolute ethanol (50 ml), ethyl chloroacetate (7 ml, 65.4 mmol) is added. The resulting solution is refluxed for 12 h. After evaporation under vacuum of most of the ethanol, 1 normal sodium hydroxide (100 ml) and dichloromethane (700 ml) are added, and the phases separated. The organic layer is dried with sodium sulphate and evaporated to dryness, to give a product which, after crystallisation from ethanol/water affords 8.3 g of **8**. Additional 3 g are obtained from the mother liquors by column chromatography on silica gel (*n*-hexane/ether); yield 11.3 g (61%); m.p. 54–55°C.

$C_{18}H_{21}NO_2$	calc.	C 76.30	H 7.47	N 4.94
(283.4)	found	76.45	7.60	4.80

^{1}H-N.M.R. ($CDCl_3$): δ = 1.27 (t, 3H, CH_3CH_2, J = 7.2 Hz); 3.29 (s, 2H, $CH_2COOC_2H_2$); 3.81 (s, 4H, $CH_2C_6H_5$); 4.15 (q, 2H, CH_2CH_3, J = 7.2 Hz); 7.50–7.20 ppm (m, 10 H_{arom}).

***(syn)* Ethyl 2-Dibenzylamino-4,4,4-trifluoro-3-hydroxybutanoate (9):**
To a solution of **8** (2 g, 7.06 mmol) and ethyl trifluoroacetate (1.85 ml, 15.53 mmol) in tetrahydrofuran (15 ml), sodium hydride (50% suspension in mineral oil) (1.02 g, 21.18 mmol) is added. The resulting suspension is refluxed for 5 h (after this time it becomes deep red) and then cooled to 0°C and treated with acetic acid (1.42 ml, 24.71 mmol). Sodium borohydride (668 mg, 17.66 mmol) is then added and the suspension is stirred overnight at room temperature, treated with 1 normal hydrochloric acid to pH = 5, stirred for 10 min, and treated with 1 normal potassium hydroxide to pH = 10. Extraction with diethyl ether (3 × 150 ml) gives, after drying of the extract sodium sulphate and evaporation to dryness, 3.3 g of a crude product. This is purified by flash[12] chromatography (*n*-hexane/ether) to give pure **9** as a white solid which is crystallised from ether/*n*-hexane; yield: 1.75 g (65%); m.p. 78–79°C.

$C_{20}H_{22}F_3NO_3$	calc.	C 62.98	H 5.81	N 3.67
(381.4)	found	62.85	5.95	3.65

I.R. ($CHCl_3$): ν = 1730, 1170, 1145 cm^{-1}.

^{1}H-N.M.R. ($CDCl_3$): δ = 1.40 (t, 3H, CH_3CH_2, J = 7.1 Hz); 3.52 (d, 1H, CH—N, J = 9.4 Hz); 3.44, 3.96 (AB-system, 4H, $CH_2C_6H_5$, J_{AB} = 13 Hz); 4.33, 4.34 (ABX$_3$-system, 2H, CH_2CH_3, $J_{AX} \approx J_{BX}$ = 7.1 Hz); 4.35 (br.s, 1H, OH); 4.10–4.65 (m, 1H, CH—CF_3); 7.30 ppm (s, 10 H_{arom}).

***(syn)* and *(anti)* 2-Dibenzylamino-4,4,4-trifluoro-3-hydroxybutanoic Acids (10A) and (10B):**
Method E: A suspension of **9** (100 mg, 0.262 mmol) in 0.5 normal potassium hydroxide in 7:3 methanol/water (3.15 ml, 1.57 mmol) is stirred at 20°C for 5 h. The resulting solution is treated with 0.3 molar aqueous potassium dihydrogen phosphate (5.24 ml), evaporated to dryness, taken up with ethyl acetate (10 ml) and brine (5 ml), and extracted with ethyl acetate (15 ml) to give, after drying with sodium sulphate and evaporation to dryness, a crude mixture of **10A** and **10B** in an 85:15 ratio, as judged by ^{1}H-N.M.R. Column chromatography on silica gel (ethyl acetate) gives pure **10A** [yield: 75 mg (80%); R_f: 0.45] and **10B** [yield: 12 mg (13%); R_f: 0.21] as oils; total yield: 87 mg (93%).

$C_{18}H_{18}H_{18}F_3NO_3$	calc.	C 61.19	H 5.13	N 3.96
(353.3)	found (**10A**)	61.31	5.19	3.80
	found (**10B**)	61.30	5.27	3.75

^{1}H-N.M.R. (DMSO-d_6) (**10A**): δ = 3.54 (d, 1H, CH—N, J = 8.3 Hz); 3.77, 4.03 (AB-system, 4H, $CH_2C_6H_5$, J_{AB} = 13.5 Hz); 4.61 (dq, 1H, CH—CF_3, J = 6 Hz, 8.3 Hz); 7.15–7.60 ppm (m, 10 H_{arom}).
^{1}H-N.M.R. (DMSO-d_6) (**10B**): δ = 3.53 (d, 1H, CH—N, J = 6 Hz); 3.72, 3.97 (AB-system, 4H, $CH_2C_6H_5$, J_{AB} = 13.5 Hz); 4.44 (dq, 1H, CH—CF_3, J = 6 Hz, 7.7 Hz); 7.15–7.60 ppm (10 H_{arom}).

Method F: Compound **9** (100 mg, 0.26 mmol) is treated with a 0.4 normal solution of sodium ethoxide in 99.8:0.2 ethanol/water (7.9 ml, 0.79 mmol). The resulting solution is stirred at 20°C for 4 days and then worked up as above described to give a crude mixture of **10A** and **10B** in the ratio 65:35 (^{1}H-N.M.R.). Silica gel chromatography gives pure **10A** [yield: 30 mg (32%)] and **10B** [yield: 58 mg (63%)] by T.L.C. and ^{1}H-N.M.R.; total yield: 88 mg (95%).

***(syn)* 2-Amino-4,4,4-trifluoro-3-hydroxybutanoic Acid (1A):**
A solution of **10A** (100 mg, 0.28 mmol) in 95% ethanol (10 ml) is hydrogenated over 10% palladium-on-carbon (30 mg) for 5 h at reflux. After filtration of the catalyst, the solution is evaporated to dryness to give pure **1A** by T.L.C. and ^{1}H-N.M.R.; yield: 44 mg (90%).

***(anti)* 2-Amino-4,4,4-trifluoro-3-hydroxybutanoic Acid (1B):**
Prepared from **10B** (50 mg, 0.14 mmol) as described above for **1A**; yield: 22 mg (90%).

(2*S*),(3*S*)-2-Amino-4-benzyloxy-3-hydroxy-butanoic Acid (14A) and (2*R*),(3*S*)-3-Amino-4-benzyloxy-2-hydroxy-butanoic Acid (14B):
The epoxide **13b** (4.7 g, 22.5 mmol) is dissolved in concentrated ammonia (67 ml) and the solution is allowed to stand for 40 days at room temperature. The mixture is then evaporated to dryness under reduced pressure. The residue is triturated in 1:4 methanol/ethyl acetate (25 ml) and then filtered under vacuum to give a mixture of **14A** and **14B**; yield: 2.9 g (57%).

$C_{11}H_{15}NO_4$	calc.	C 58.66	H 6.70	N 6.22
(225.3)	found	58.32	6.69	6.09

I.R. (KBr): ν = 3460, 3180–3000, 1670, 1640, 1580, 1530 cm^{-1}.

^{1}H-N.M.R. (DMSO-d_6): δ = 3.10 (d, 1H, CH—COOH, J = 5.4 Hz); 3.30 (m, 2H, $CH_2OCH_2C_6H_5$); 3.73 (m, 1H, CH—OH); 4.62 ppm (s, 2H, $CH_2C_6H_5$); the peaks of **14B** are not identifiable.

t-Butyl (4S),(5R)-5-Benzyloxy-2-oxo-4-oxazolidinecarboxylate (16A) and t-Butyl (4S),(5R)-4-Benzyloxy-2-oxo-4-oxazolidinecarboxylate (16B):

A mixture of **14A** and **14B** (1000 g, 4.44 mmol) is subjected to the reaction with phosgene as above described for the preparation of **7A** to give a mixture of **15A** and **15B**; yield: 1.088 g (98%).

I.R. ($CHCl_3$): ν = 3500–3000, 1750, 1610, 1275 cm^{-1}.

The above mixture of **15A** and **15B** is directly dissolved in dichloromethane (30 ml), cooled to 0°C, and treated with a catalytic amount of sulphuric acid. Isobutene is then bubbled into the solution until saturation. The mixture is allowed to stand at 0°C overnight. The excess of isobutene is then removed and 10% aqueous sodium carbonate solution is added until pH = 9. The mixture is extracted with dichloromethane (3 × 70 ml), the organic phases are dried with sodium sulphate, and evaporated under reduced pressure to afford pure **16A** and **16B** (yield: 1.22 g) which are separated by flash chromatography[12] on silica gel with 4:6 ethyl acetate/*n*-hexane as eluent: **16A**; yield: 1.09 g (83%); m.p. 119–120°C; $[\alpha]_D^{20}$: +43.9°C (*c* 1, chloroform); **16B**; yield: 0.12 g (9%); m.p. 92–94°C; $[\alpha]_D^{20}$: −38.4 (*c* 1, chloroform).

$C_{16}H_{21}NO_5$	calc.	C 62.54	H 6.84	N 4.56
(307.4)	found **(16A)**	62.62	6.91	4.60
	found **(16B)**	62.60	6.87	4.54

I.R. ($CHCl_3$) **(16A)**: ν = 3460, 1766, 1740, 1370, 1155 cm^{-1}

I.R. (KBr) **(16B)**: ν = 3200, 1765, 1730, 1380 cm^{-1}.

^{1}H-N.M.R. ($CDCl_3$) **(16A)**: δ = 1.46 (s, 9H, *t*-C_4H_9); 3.50–3.90 (m, 2H, $CH_2OCH_2C_6H_5$); 4.21 (dd, 1H, $CHCOOC_4H_9$-*t*, J = 5.5 Hz, 0.7 Hz); 4.60 (s, 2H, $CH_2C_6H_5$); 4.55–4.87 (m, 1H, $CHCH_2$); 5.95 (br.s, 1H, NH); 7.30 ppm (s, 5 H_{arom}).

^{1}H-N.M.R. ($CDCl_3$) **(16B)**: δ = 1.50 (s, 9H, *t*-C_4H_9); 3.38–3.72 (m, 2H, $CH_2COCH_2C_6H_5$); 4.63 (s, 2H, $CH_2C_6H_5$); 4.65 (d, 1H, CHOCO, J = 0.5 Hz); 6.18 (br.s, 1H, NH); 7.30 ppm (s, 5 H_{arom}).

t-Butyl (4S),(5R)-5-Hydroxymethyl-2-oxo-4-oxazolidinecarboxylate (17):

The oxazolidinone **16** (954 mg, 3.10 mmol) is dissolved in methanol (31 ml) and hydrogenated on 10% palladium-on-carbon (493 mg) for 15 h at room temperature. After filtration of the catalyst, the solution is evaporated, and the crude product **17** is crystallised from ethyl acetate/*n*-hexane; yield: 650 mg (96%); m.p. 122–123°C; $[\alpha]_D^{20}$: +47.5°C (*c* 1, chloroform).

$C_9H_{15}NO_5$	calc.	C 49.77	H 6.91	N 6.51
(217.2)	found	49.85	6.85	6.4

I.R. ($CHCl_3$): ν = 3600, 3450, 1780, 1740, 1370 cm^{-1}.

^{1}H-N.M.R. ($CDCl_3/D_2O$): δ = 1.48 (s, 9H, *t*-C_4H_9); 3.50–4.15 (m, 2H, CH_2OH); 4.29 (dd, 1H, $CHCOOC_4H_9$-*t*, J = 5.8 Hz, 0.6 Hz); 4.50–4.77 ppm (m, 1H, $CHCH_2OH$).

(2S),(S)-2-Amino-4-fluoro-3-hydroxybutanoic Acid (19):

To a solution of **17** (140 mg, 0.645 mmol) in dry dichloromethane (4 ml) under nitrogen at −78°C, diethylaminosulphur trifluoride (0.085 ml, 0.695 mmol) is added. The mixture is stirred for 30 min, then allowed to warm to room temperature over 1 h, and 10% aqueous sodium hydrogen carbonate solution (0.8 ml, 0.95 mmol) is added. The water layer is then extracted with dichloromethane (3 × 4 ml) and the combined organic layers are dried with sodium sulphate and evaporated under vacuum. The crude product is partialy purified by flash chromatography[12] on silica gel with ethyl acetate/*n*-hexane (4:6) as eluent to afford crude **18** which is used as such in the next step; yield: 75 mg (53%).

I.R. (KBr): ν = 3450, 1775, 1725, 1370 cm^{-1}.

^{1}H-N.M.R. ($CDCl_3$): δ = 1.55 (s, 9H, *t*-C_4H_9); 4.10–5.10 (m, 4H, $CHCOOC_4H_9$-*t* and $CH{-}CH_2F$); 5.95 ppm (br. s, 1H, NH).

^{19}F-N.M.R. ($CHCl_3$): δ = −243.16 ppm (dt, J_{FCH_2} = 50.8 Hz, J_{FCH_2CH} = 25.6 Hz).

The crude compound **18** (75 mg) is hydrolysed following the procedure given above for **7B**; crystallisation from ethanol gives pure **19**; yield: 25 mg (62%); m.p. 182–183°C (dec.); $[\alpha]_D^{25}$: −18.4 (*c* 1, water).

$C_4H_8FNO_3$	calc.	C 35.03	H 5.84	N 10.22
(137.1)	found	34.86	5.94	10.09

I.R. (KBr): ν = 3600, 3400–3000, 1620, 1595 cm^{-1}.

^{1}H-N.M.R. (DMSO-d_6): δ = 3.23 (d, 1H, CHCOOH, J = 5.0 Hz); 3.90–5.00 (m, 3H, CH_2F and CHOH); 5.00–7.25 ppm (br.s, 4H, OH, NH_2, COOH).

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