Pergamon

Tetrahedron. Asymmetry Vol. 5, No. 10, pp. 2009-2018, 1994
Elsevier Science Ltd
Printed in Great Britain
0957-4166/94 $7.00+0.00

0957-4166(94)00282-7

Synthesis of Optically Pure (*R*)- and (*S*)-α-Trifluoromethyl-Alanine

Pierfrancesco Bravo*, Silvia Capelli, Stefano Valdo Meille,
Fiorenza Viani and Matteo Zanda

C.N.R. - Centro di Studio per le Sostanze Organiche Naturali.
Dipartimento di Chimica del Politecnico di Milano, via Mancinelli 7, I-20131 Milano, Italy;

Valery P. Kukhar, Vadim A. Soloshonok

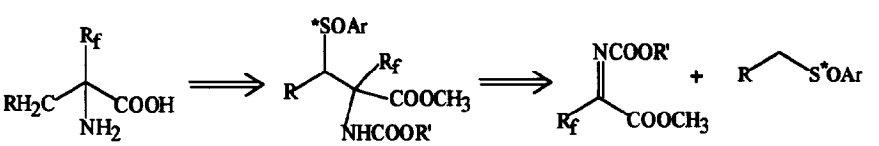
Ukrainian Academy of Sciences - Institute of Bioorganic Chemistry and Petrochemistry,
1, Murmanskaya str. Kiev-94, 252660 Ukraine

Abstract: *(+)-(R)- and (–)-(S)-3,3,3-trifluoro-2-methyl-alanine (1) were synthesized from (+)-(R)-methyl-p-tolyl-sulphoxide (5) and N-alkoxycarbonylimino derivatives 4 of methyl 3,3,3-trifluoropyruvate (3). The absolute configuration was determined by X-ray analyses of two synthetic intermediates (2S,R_S)-6a and (2R,R_S)-6c.*

Introduction

Fluorinated aminoacids have great practical application in clarifying the physiological role of specific enzymes and, therefore, a number of fluorosubstituted α-aminoacids are under intensive study. None of the different strategies applied to the synthesis of fluorinated α-aminoacids seems to have general applicability and this is particularly true for the synthesis of chiral and optically pure α-fluoroalkyl aminoacids[1].

Research in our laboratories has focused on the synthesis of optically pure fluorinated molecules of biological interest. In these syntheses, sulphoxides as stereo controlling elements[2] and fluorosubstituted acetic acid esters were used. On the basis of previous results the retrosynthetic scheme shown below was thought to be of wide applicability to obtain chiral α-fluoroalkyl aminoacids.



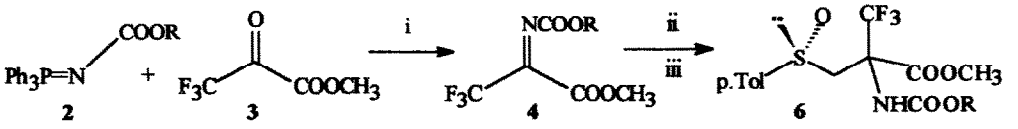
Retrosynthetic Scheme

The lithium anion of an optically active sulphoxide as synthon for the desired amino acid side chain adds to a fluorinated precursor bearing the potential amino group, the protected carboxylic group and the fluoroalkyl residue. The intermediate leads to the α-fluoroalkyl-α-aminoacid upon reductive elimination of the chiral auxiliary and hydrolysis of the protective groups.

In the present paper we report a six step synthesis of both enantiomers of 3,3,3-trifluoro-2-methyl-alanine[3] (**1**) from methyl-3,3,3-trifluoropyruvate (**3**) through its *N*-alkoxycarbonylimino derivatives (**4**) and (+)-(*R*)-methyl-*p*-tolyl-sulphoxide (**5**).

Results and discussion

The key intermediates **6** were obtained as shown on Scheme 2. Phospha-λ^5-azenes (**2a-d**) were synthesized following procedures described in literature[4a]. Methyl 3,3,3-trifluoropyruvate[5] (**3**) was chosen as α-trifluoromethyl amino acid synthon after aza-Wittig reaction[6] with compounds **2a-d** in benzene to give the trifluoro-*N*-alkoxycarbonylimino derivatives **4a-d**[3i].



6a; R = CH_3
6b; R = CH_2CH_3
6c; R = CH_2Ph
6d; R = (+)-Menthyl

Scheme 2

Reagents and Conditions: i) C_6H_6; ii) (+) or (-)-methyl-*p*-tolyl sulphoxide (**5**), LDA, THF, -60°C; iii) **4**, THF, -70°C.

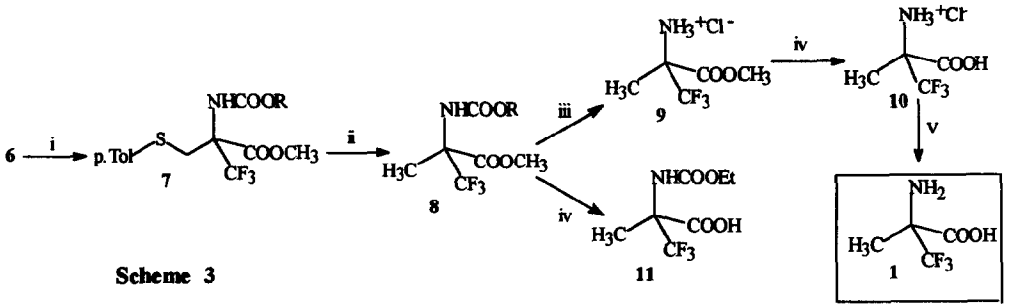
Substrates **4a-d** were treated *in situ* with the lithium derivative of (+) or (−)-methyl-*p*-tolyl sulphoxide **5**[7], after separation of the insoluble unreacted starting phospha-λ^5-azenes **2** and triphenylphosphine oxide with boiling pentane.

The reaction took place with reasonable yields but with very low diastereoselection[8]: single diastereoisomers of adducts **6a-c** were obtained in optically pure form by easy chromatographic separation. From a synthetic point of view, **6c** showed to be the most convenient intermediate, leading to the target molecule **1** in three steps and in 55.3 % overall yield.

As shown on Scheme 3, deoxygenating of the sulphoxides **6b** and **6c** by treatment with sodium iodide and trifluoroacetic anhydride at −20°C in acetone[9] afforded the corresponding optically pure thio derivatives **7b** and **7c** in nearly quantitative yields. Starting from the benzyl-derivative **7c**, an exhaustive treatment with Raney-nickel under hydrogen atmosphere lead to simultaneous desulfurization and hydrogenolysis of the *N*-benzyloxycarbonyl moiety. The volatile 2-trifluoromethyl-alanine methyl ester[10] was isolated in optically pure form as the corresponding hydrochloride **9** in 83.3% yield.

Hydrolysis of **9** with a six to one mixture of 6N aqueous hydrochloric and glacial acetic acids at 100°C afforded the optically pure hydrochloride **10**. Ion exchange chromatography of the hydrochloride derivative **10** on strongly acidic resin DOWEX 50W afforded the unprotected, optically pure 2-trifluoromethyl-alanine **1**. Through the described procedure, both (*R*)- and (*S*)-**1** were obtained.

It can be noted that the treatment of **8c**, isolated after partial action of Raney-nickel on **7c**, with trimethylsilyl iodide in acetonitrile allowed the total conversion to the methyl ester derivative **9**, whilst the treatment of **8b** with hydrochloric\acetic acid mixture gave the *N*-ethoxycarbonyl derivative **11**.



Scheme 3

Reagents and Conditions: i) $(CF_3CO)_2O$, NaI, CH_3COCH_3, -20°C; ii) Ni-Raney, CH_3CH_2OH, 80°C, 6 h.; iii) Ni-Raney, CH_3CH_2OH, 80°C, 2 h. or $(CH_3)_3SiI$, CH_3CN; iv) 6N HCl\\CH_3COOH, 100°C, 10 h.; v) DOWEX 50W-X2.

Structural assignments

The absolute stereochemistry of the substrates **6** was determined by X-Ray crystallographic analysis on the adducts **6a** and **6c**. Fig. 1 and 2 show the corresponding ORTEP[11] drawings in the absolute configuration (2*S* and 2*R*, respectively) and with the appropriate atomic labelling.

Fig. 1 ORTEP drawing of (2*S*,*R*$_S$)-**6a**.

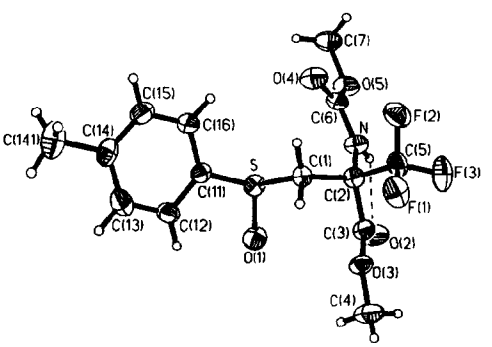
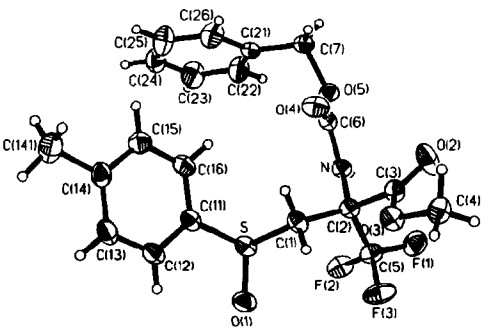


Fig. 2 ORTEP drawing of (2*R*,*R*$_S$)-**6c**



The two observed structures differ from each other for the opposite configuration at C(2), for the different substitution pattern at C(7) and for the quite different conformation of the amido-esteric and the sulphoxide moieties of the molecules. More in detail while the value of the torsion angle C(11)-S-C(1)-C(2) found in **6a** (-173.0°(2)) is close to trans planar as in other sulfoxide compound[12], in **6c** it is substantially distorted (-148.0°(2)). Similar considerations apply to bond angles C(2)-C(1)-S which measure respectively

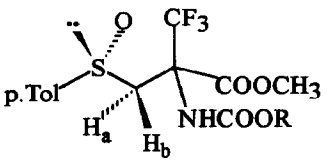
109.7°(2) in **6a** and 116.6°(2) in **6c**. The local conformation around C(2) in **6a** allows an intramolecular hydrogen bond between the carbamic hydrogen and oxygen atom O(2) similar to the one found in an isovaline derivative[13]. This interaction should be rather weak as it involves a 5-membered ring and it implies significant distortions of bond angles *N*-C(2)-C(3) (105.8°(2) for **6a** *vs* 110.1°(2) for **6c**) and C(2)-N-C(6) (126.4°(2) for **6a** *vs* 119.2°(2) for **6c**). While in the packing of **6a** no short distances are observed, in the case of **6c** hydrogen bonds are intermolecular (see Table 1). An additional close contact (F(3)···S = 3.250 Å) between fluorine atom F(3) and the S atom of the nearby molecule generated by symmetry operation (1/2-x , 2-y, -1/2+z) should be noted.

Table 1. Close contacts involving H atoms.

	D-H····A	D····A (A)	H····A (A)	D-H····A (deg)	H-D····A (deg)	Asymmetric unit of A
6a	N-H1N····O2	2.620	2.153	109.2	50.9	same
6c	N-H1N····O1	3.039	2.030	176.4	2.4	*1/2-x , 2-y, 1/2+z*
	C1-H1B····F1	3.27	2.318	165.9	10.5	*1/2-x , 2-y, -1/2+z*

The key intermediates **9** and **10** and the final product **1** were fully characterized by ^{1}H, ^{13}C, and ^{19}F NMR (see Experimental) and, in all examined cases, ^{1}H and ^{19}F NMR spectra were in complete accordance with the proposed structures. Comparison of the $\Delta\nu$ values of the two diastereotopic protons H_a and H_b in **6a** and **6c** (Figure 3) showed higher values for 2*S* epimers (160 and 165 for **6a** and **6c**, respectively) and lower ones for 2*R* epimers (135 and 137.5 for **6a** and **6c**, respectively).[14]

Figure 3



Conclusion: the synthesis of optically pure α-trifluoromethyl-alanine using the sulphinylic moiety as stereo controlling element has been accomplished. Though the diastereoselection of the method is very low, the chemical procedure allows the obtainment, in good yields and in mild conditions, of both the enantiomers in optically pure form.

Experimental

^{1}H, ^{19}F and ^{13}C NMR spectra were recorded on a Bruker CXP 300 or a Bruker AC 250L spectrometer. Chemical shifts (δ) are reported in ppm of the applied field. Me_4Si was used as internal standard (δ_H and δ_C = 0.00) for ^{1}H and ^{13}C nuclei, while C_6F_6 was used as internal standard (δ_F = −162.90) for ^{19}F nuclei. Coupling constants (*J*) are reported in hertz (Hz). Anhydrous solvents were obtained by distillation from sodium (diethyl ether, tetrahydrofuran, benzene). Diisopropylamine was distilled from calcium hydride. In all other cases

commercially available reagent-grade solvents were employed without purification. Melting points are uncorrected and were obtained on a capillary apparatus. Analytical thin-layer chromatography (TLC) was routinely used to monitor reactions. Plates precoated with E. Merck silica gel 60 F_{254} of 0.25 mm thickness were used. Merck silica gel 60 (230-400 ASTM mesh) was employed for column chromatography. HPLC was performed on a Waters 600E instrument using LiChrosorb Si60 (5 μm, Merck) prepacked columns and hexane and ethyl acetate HPLC-grade solvents (Merck). Combustion microanalyses were performed by Redox SNC, Cologno M. (Milano). Compounds **2a-b**,[4a] and **2c**[4b] were synthesized following Kricheldorf procedure[4a]. Compounds **4a-b**,[3i] **4c**,[15] and **4d, d'** (not isolated) were synthesized through Aza-Wittig reaction[7].

(1S,2R,5S)-N-(5-Methyl-2-[1-methyl-ethyl]cyclohexyloxycarbonyl)-triphenylphospha-λ⁵-azene ***(2d)***, yield 95.7 %; R_f 0.45 (hexane /ethyl acetate 3:2); $[\alpha]_D^{20}$ + 20.5 (c 1.0, $CHCl_3$), mp 151-153 °C (ethyl acetate); ^1H NMR ($CDCl_3$) δ 7.80-7.40 (m, 15 H, Ph), 4.47 (dt, 1 H, J = 5 Hz and 11 Hz, OCH), 2.03 (m, 2 H, CH' s), 1.66-0.92 (m, 7 H, CH + CH_2' s), 0.83 (d, 3 H, J = 7.0 Hz, CH_3) 0.76 (d, 3 H, J = 7.0 Hz, CH_3), 0.68 (d, 3 H, J = 7.0 Hz, CH_3).

Reaction between imino-esters 4 and optically pure methyl-p-tolyl-sulphoxide 5. General procedure. To a stirred, cooled (– 60°C) solution of 6 ml of 0.25 M LDA in THF was added a solution of 1.60 mmol of (R_S)-(+)-sulphoxide **5** in 4 ml of THF. After 5 min the resulting yellow solution was cooled to –70°C and a solution of the crude imino-derivative **4a** (1.60 mmol) in 2.5 ml of THF was added *via cannula* in 10 min. After stirring for 5 min at –70°C the reaction mixture was quenched with saturated aqueous NH_4Cl. The resulting mixture was extracted with ethyl acetate and dried over anhydrous sodium sulfate. The removal of the solvent under reduced pressure and flash chromatography on silica gel afforded the desired products **6**. Some selected chemico-physical and analytical data are reported in Table 2.

Table 2. Chemico-physical and analytical data of **6**.

Products 6		Yield[a] (%)	Conversion (%)	$[\alpha]_D^{20}$ (c, $CHCl_3$)	^1H NMR SCH_2		^{19}F NMR	m.p.[b] (°C)
R	Stereochemistries				δ	J/Hz	(δ)	
CH_3	2R,R_S	19.3	40.2	+ 103.7 (1.2)	3.78	14.0	- 75.15	oil
	2S,R_S	21.3	44.4	+ 248.7 (0.5)	3.89	13.0	- 75.70	135-137
CH_2CH_3	2R,R_S	30.0	50.0	+ 181.4 (0.2)	3.77	13.0	- 75.12	oil
	2S,R_S	27.9	46.5	+141.5 (0.5)	3.88	13.0	- 75.72	oil
CH_2Ph	2R,R_S	27.2	46.4	+ 90.2 (0.9)	3.80	13.8	- 75.07	113-114
	2S,R_S	28.1	48.0	+ 144.1 (0.4)	3.88	13.0	- 75.63	oil
Menth. (+)	2R,R_S	38.1[c]	74.0	+ 87.4 (1.0)	3.73	14.0	- 75.10	oil
	2S,R_S			+ 138.1 (2.1)	3.90	13.0	- 75.75	oil
Menth (+)	2R,S_S	38.9[c]	80.0	- 48.5 (1.2)	3.90	13.0	- 76.77	oil
	2S,S_S			- 23.3 (0.5)	3.68	13.0	- 75.28	oil

[a]From 4 for **6b**; from 2 for **6a, c,** and **d.** [b]Ethyl acetate. [c]Separation of diastereoisomers not achieved.

(2R,R_S)- and (2S,R_S)-Methyl 2-methoxycarbonylamino-3-[(4-methylphenyl)sulfinyl]-2-trifluoromethyl propionate (6a): a 1.02/1.00 mixture (HPLC ratio, hexane/ethyl acetate 3:2) of two diastereoisomers was obtained. Column chromatography (hexane/ethyl acetate 7:3) gave (2*R*, R_S)-**(6a)** in 19.3%, (2*S*, R_S)-**6a** in 21.3% (40.6% from **2a**) and 52 % of unreacted (+)-**5**; (*2S,R_S*)-**6a**, R_f 0.40 (hexane/ethyl acetate 7:3); found C, 45.87; H, 4.49; N, 3.74. $C_{13}H_{16}F_3NO_5S$ requires C, 45.78; H, 4.39; N, 3.81; and (*2R,R_S*)-**5a**: R_f 0.30 (hexane/ethyl acetate 7:3); t_r 12.08 min (3:2 hexane/ethyl acetate, 1.0 ml/min).

(2S,R_S)- and *(2R,R_S)-Methyl 2-ethoxycarbonylamino-3-[(4-methylphenyl)sulfinyl]-2-trifluoromethyl propionate (6b):* a 1.00/1.14 mixture (HPLC ratio, hexane/ethyl acetate 3/2) of two diastereoisomers was obtained from distilled **4b**. Column chromatography (hexane/ethyl acetate 7:3) gave 27.9 % of *(2S, R_S)*-**6b**, 30.0 % of *(2R, R_S)*-**6b** and 40.0 % of unreacted (+)-**5**: (*2S,R_S*)-**6b**, R_f 0.40 (hexane/ethyl acetate 7:3); t_r 8.73 min (hexane/ethyl acetate 3:2, 1.0 ml/min); and (*2R,R_S*)-**6b**, R_f 0.30 (hexane/ethyl acetate 7:3); t_r 5.77 min (hexane/ethyl acetate 3:2, 1.0 ml/min).

(2S,R_S)- and *(2R,R_S)-Methyl benzyloxycarbonylamino-3-[(4-methylphenyl)sulfinyl]-2-trifluoromethyl propionate (6c).* The crude reaction mixture of the imino derivative **4c** (after solvent removal) was employed, following the general procedure. A 1.20/1.00 mixture (HPLC ratio, hexane/ethyl acetate 3:2) of two diastereoisomers was obtained. Column chromatography (hexane/ethyl acetate 3:1) gave 28.1% of *(2S, R_S)*-**6c**, 27.2% of *(2R, R_S)*-**6c** (55.3 % from **2c**) and 41.4 % of unreacted (+)-**5**: (*2S,R_S*)-**6c**, R_f 0.40 (hexane/ethyl acetate 3:1); ^{13}C NMR (All dec.) ($CDCl_3$) δ 165.45 (s, $\underline{C}OOMe$), 154.20 (s, $\underline{C}OOCH_2$) 142.14 (s, Ar), 139.52 (s, Ar), 135.65 (s, Ar), 130.15 (s, Ar), 128.67 (s, Ar), 128.62 (s, Ar), 128.41 (s, Ar), 128.12 (s, Ar), 123.89 (s, Ar), 123.44 (q, J_{C-F} = 290 Hz, $\underline{C}F_3$), 67.55 (s, $O\underline{C}H_2Ph$), 63.25 (q, J_{C-F} = 32 Hz, $\underline{C}$-CF_3), 57.11 (s, $\underline{C}H_2S$), 54.70 (s, $\underline{C}H_3OOC$), 21.47 (s, $\underline{C}H_3Ph$); EI/MS (70 eV): m/e (%) 443 (1, M^+), 335 (46, M^+– $PhCH_2OH$), 304 (8, M^+ – *p*tolSO), 246 (3, M^+ – *p*-tolSOH – $COOCH_3$), 139 (100, *p*tolSO^+), 91 (58, $C_7H_7^+$). t_r 5.47 (hexane/ethyl acetate 3:2, 1.0 ml/min); and (*2R,R_S*)-**6c**, R_f 0.35 (hexane/ethyl acetate 3:1); t_r 6.37 (hexane/ethyl acetate 3:1, 1.0 ml/min); found C, 54.17; H, 4.52; N, 3.15. $C_{20}F_3H_{20}NO_5S$ requires C, 54.17; H, 4.55; N, 3.16.

(1'S,2'R,5'S,2S,S_S)- and (1'S,2'R,5'S,2R,S_S)-Methyl 2-[5'-Methyl-2'-(1-methyl-ethyl)] cyclohexyloxycarbonylamino-3-[(4-methylphenyl)sulfinyl]-2-trifluoromethyl propionate (6d). A 1.00/1.24 mixture (HPLC ratio, hexane/ethyl acetate 3:2) of two diastereoisomers was obtained. Column chromatography (hexane/ethyl acetate 3:1) afforded 38.1% (from **2d**) of the sulphoxides (1'*S*, 2'*R*, 5'*S*, 2*S*, S_S)-**6d** and (1'*S*, 2'*R*, 5'*S*, 2*R*, S_S)-**6d** and 48.5% of unreacted (+)-**5**. A complete separation of the two diastereomers by silica gel chromatography wasn't possible: (1'*S*,2'*R*,5'*S*,2*R*,S_S)-**6d**, R_f 0.40 (hexane/ethyl acetate 3:1); found C, 56.67; H, 7.00; N, 3.06. t_r 3.95 (hexane/ethyl acetate 3:2, 1.0 ml/min); $C_{23}F_3H_{32}NO_5S$ requires C, 56.20; H, 6.56; N, 2.85; and (1'*S*,2'*R*,5'*S*,2*S*,S_S)-**6d**, R_f 0.37 (hexane/ethyl acetate 3:1); t_r 4.18 (hexane/ethyl acetate 3:2, 1.0 ml/min).

(1'S,2'R,5'S,2S,R_S)- and (1'S,2'R,5'S,2R,R_S)-Methyl 2-[5'-Methyl-2'-(1-methyl-ethyl)]cyclohexyloxycarbonylamino-3-[(4-methylphenyl)sulfinyl]-2-trifluoromethyl propionate (6d'). A 1.00/1.05 mixture (HPLC ratio, hexane/ethyl acetate 7:3) of two diastereoisomers was obtained. Column chromatography (hexane/ethyl acetate 3:1) afforded 38.9 % (from **2d**) of the sulphoxides (*1'S,2'R,5'S,2S,R_S*)-**6d'** and (*1'S,2'R,5'S,2R,R_S*)-**6d'** and 51.4 % of unreacted (+)-**5**. A complete separation of the two diastereomers by silica gel chromatography wasn't possible: (1'*S,2'R,5'S,2S,R_S*)-**6d'**, R_f 0.40 (hexane/ethyl acetate 3:1); t_r 4.73 (hexane/ethyl acetate 7:3, 1.0 ml/min); and (1'*S,2'R,5'S,2R,R_S*)-**6d'**, R_f 0.37 (hexane/ethyl acetate 3:1); t_r 5.38 (hexane/ethyl acetate 7:3, 1.0 ml/min).

X-ray analyses of (2S,R$_S$)-6a and (2R,R$_S$)-6c. X-ray diffraction data for both structures were collected on a Philips PW1100 diffractometer, with graphite monochromated Cu-Kα radiation (λ = 1.5418 Å). Cell constants were obtained by least squares refinement on 2ϑ values of 24 reflections with 2ϑ > 40°. Two octants (+h,+k,+l)-(-h,-k,-l) of intensity data were collected by ϑ/2ϑ scans technique. Three standard reflections were monitored every 100 reflections measured to check crystal orientation and stability and showed no significant decay. Data were corrected for Lorentz and polarization effects but no absorption correction was applied. Both structures were solved by direct methods using SIR92[16] and refined by full matrix least squares with SHELXL93[17], establishing unambiguously the respective absolute configuration refining Flack's x parameter[18]. Non-hydrogen atoms were refined with anisotropic temperature factors. The amide hydrogen both in **6a** or in **6c**, was located by difference-Fourier map and refined, while the others were included at calculated position and refined in the riding mode with group temperature factors respectively for aromatic and aliphatic hydrogens.

Crystal data for (2*S*,R$_S$)-**6a**: $C_{14}H_{16}F_3NO_5S$, f.w. 367.34, orthorhombic, space group P $2_12_12_1$, a=17.342(7)Å, b = 16.683(2)Å, c = 5.8000(10)Å, V = 1678.0(8)Å^3, Z = 4, D_C= 1.454 Mg/m^3, μ = 2.247 mm^{-1}, F(000) = 760, crystal dimensions 0.15 x 0.15 x 1.1 mm, 2239 unique reflections in the range 4° < ϑ < 58°, final R1=0.0303, final wR2=0.0903, Flack x parameter = -0.03(2).

Crystal data for (2*R*,R$_S$)-**6c**: $C_{20}H_{20}F_3NO_5S$, f.w. 443.43, orthorhombic, space group P $2_12_12_1$, a=11.034(3)Å, b = 20.217(6)Å, c = 9.024(3)Å, V = 2013.0(11)Å^3, Z = 4, D_C = 1.463 Mg/m^3, μ = 1.981 mm^{-1}, F(000) = 920, crystal dimensions 0.2 x 0.2 x 0.7 mm , 2536 unique reflections in the range 4° < ϑ < 55°, final R1 = 0.0319, final wR2 = 0.0900, Flack x parameter = 0.01(2).

Deoxygenating reaction. General procedure. Trifluoroacetic anhydride (6.85 mmol) was added to a stirred, cooled (–20°C) mixture of sulphoxide **6c** (1.37 mmol) and sodium iodide (4.11 mmol) in acetone (9 ml). After 5 min. at the same temperature the reaction was quenched with an excess of saturated aqueous sodium sulfite and sodium hydrogen carbonate solutions. The aqueous layer was extracted with ethyl acetate and the combined organic phases were dried over anhydrous sodium sulfate. Removal of the solvent gave a residue, which, upon flash chromatography gave the enantiomerically pure sulphide 7 as a yellowish oil:

(2S)-methyl 2-ethoxycarbonylamino-3-[(4-methylphenyl)sulfenyl]-2-trifluoromethyl propionate (7b), yield 52.8 %; R_f 0.35 (hexane/ethyl acetate 85:15); $[\alpha]_D^{20}$ + 90.3 (c 0.61, $CHCl_3$), ^{1}H NMR ($CDCl_3$) δ 7.33 (d, 2 H, J = 8.0 Hz, Ar), 7.08 (d, 2 H, J = 8 Hz, Ar), 5.98 (s, 1 H, NH), 4.45 (m, 1 H, OHC<u>H</u>CH$_3$), 4.05-3.88 (m, 1 H, OHC<u>H</u>CH$_3$), 3.75 (ABq, 2 H, J_{AB} = 12 Hz, Δν = 115 Hz, SCH_2), 3.54 (s, 3 H, OCH_3), 2.33 (s, 3 H, ArC<u>H</u>$_3$), 1.23 (t, 3 H, J = 7 Hz, C<u>H</u>$_3$CH$_2$O); ^{19}F NMR ($CDCl_3$) δ –74.83; and (2*R*)-**7b**, yield 63.6 %; $[\alpha]_D^{20}$ – 94.2 (c 0.80, $CHCl_3$); R_f, ^{1}H and ^{19}F NMR ($CDCl_3$) are identical to that of the enantiomer (+)-**7b**. Analogously, *(2S)-methyl 2-benzyloxycarbonylamino-3-[(4-methylphenyl)sulfenyl]-2-trifluoromethyl propionate (7c)* was obtained: yield 97.7 %; R_f 0.35 (hexane/ethyl acetate 9:1); $[\alpha]_D^{20}$ + 85.5 (c 0.66, $CHCl_3$), ^{1}H NMR ($CDCl_3$) δ 7.42-7.30 (m, 7 H, Ar), 7.09 (d, 2 H, J = 8.0 Hz, Ar), 6.11 (s, 1 H, NH), 4.94 (ABq, 2 H, J_{AB} = 12.2 Hz, Δν = 230 Hz, OCH_2), 4.02 (ABq, 2 H, J_{AB} = 11 Hz, Δν = 230 Hz, SCH_2), 3.55 (s, 3 H, OCH_3), 2.30 (s, 3 H, ArC<u>H</u>$_3$); ^{19}F NMR ($CDCl_3$) δ –74.78; and (2*R*)-**7c**, yield 92.6 %. $[\alpha]_D^{20}$ – 83.2 (c 0.54, $CHCl_3$); R_f, ^{1}H and ^{19}F NMR ($CDCl_3$) are identical to that of the enantiomer (+)-**7c**.

(S) and (R)-Methyl 2-benzyloxycarbonylamino-2methyl-3,3,3-trifluoromethyl propionate (8c) and (S) and (R)-2-Methyl-3,3,3-trifluoroalanine methyl ester hydrochloride (9). (Procedure a): To a solution of 0.41 g

(0.96 mmol) of (+)-**7c** in absolute ethanol (6 ml) Raney-Ni (1.5 g) was added. The slurry was heated to 80°C and stirred under hydrogen atmosphere for 6 hrs. Then Raney-Ni was filtered off and washed twice with ethanol. 2N Aqueous HCl (2 ml) was added and the mixture stirred for 5 min at room temperature. Ethanol was removed under reduced pressure. The aqueous layer was extracted with ethyl acetate. The combined organic phases were dried over anhydrous sodium sulphate and the solvent removed under reduced pressure, affording 75 mg (25.3%) of (−)-**8c** as a colourless oil: (*S*)-**8c**, R_f 0.35 (hexane/ethyl acetate 85:15); $[\alpha]_D^{20}$ − 0.8 (c 1.3, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.38-7.33 (m, 5 H, Ar), 5.48 (s, 1 H, NH), 5.10 (s, 2 H, OCH_2), 3.82 (s, 3 H, OCH_3), 1.80 (s, 3 H, CH_3C); ^{19}F NMR ($CDCl_3$) δ −77.82; and (*R*)-**8c**, $[\alpha]_D^{20}$ + 0.7 (c 1.1, $CHCl_3$); R_f, ^1H and ^{19}F NMR ($CDCl_3$) are identical to that of the enantiomer (−)-**8c**; found C, 50.62; H, 4.69; N, 4.75. $C_{13}F_3H_{14}NO_4$ requires C, 51.15; H, 4.55; N, 4.59. Following the same procedure, (*S*) and *(R)*-methyl 2-ethoxycarbonylamino-2-methyl-3,3,3-trifluoromethyl propionate (**8b**) were obtained: (*R*)-**8b**, yield 87.6 %. R_f 0.35 (hexane/ethyl acetate 4:1); $[\alpha]_D^{20}$ + 1.4 (c 1.45, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 5.37 (s, 1 H, NH), 4.13 (q, 2 H, J = 7 Hz, OCH_2), 3.85 (s, 3 H, OCH_3), 1.80 (s, 3 H, CH_3C), 1.25 (t, 3 H, J = 7 Hz, $C\underline{H}_3CH_2O$); ^{19}F NMR ($CDCl_3$) δ −77.86; and (*S*)-**8b**, $[\alpha]_D^{20}$ − 1.5 (c 1.2, $CHCl_3$); R_f, ^1H and ^{19}F NMR ($CDCl_3$) are identical to that of the enantiomer (+)-**8b**.

Removal of the solvent under reduced pressure from the aqueous layer gave 110 mg (54.2%) of (−)-**9** as a yellowish solid. If the reaction was allowed to remain at 80°C for 10 hrs. under hydrogen atmosphere 280 mg (0.66 mmol) of (+)-**7c** afforded 105 mg (76.0 %) of (−)-**9** as the only product.

(*S*) and (*R*)-*2-Methyl-3,3,3-trifluoroalanine methyl ester hydrochloride (9). (Procedure b)*: To a stirred solution of 130 mg (0.43 mmol) of (+)-**8c** in 2.5 ml of dry acetonitrile was added 0.2 ml (1.40 mmol) of iodotrimethylsilane. The resulting solution immediately became whitish. After 10 min. 0.2 ml of methanol was added to the reaction mixture, and stirring was continued 5 min. Then 0.5 ml of aqueous 2 N HCl was added and the resulting solution stirred for 5 min. The aqueous layer was washed with diethyl ether and the solvent evaporated at reduced pressure affording an orange solid, that was washed with diethyl ether. 75 mg (83.3%) of (+)-**9** was obtained as a pale yellow solid: (*R*)-**9**, $[\alpha]_D^{20}$ + 2.6 (c 0.72, H_2O); m.p. 84-86°C (water); ^1H NMR (D_2O) δ 3.93 (s, 3 H, OCH_3), 1.80 (s, 3 H, CH_3C); ^{19}F NMR ($CDCl_3$) δ −74.88; ^{13}C NMR (All dec.) (D_2O) δ 168.01 (s, $\underline{C}OO$), 124.90 (q, $J_{C\text{-}F}$ = 283.1 Hz, $\underline{C}F_3$), 64.22 (q, $J_{C\text{-}F}$ = 31.2 Hz, $\underline{C}CF_3$), 57.57 (s, OCH_3), 18.88 (s, $C\underline{C}H_3$); EI/MS (70 eV): m/e (%) 112 (100, $M^+ - COOCH_3$), 92 (13, $M^+ - COOCH_3 - HF$), 69 (3, CF_3^+); and (*S*)-**9**, $[\alpha]_D^{20}$ − 2.1 (c 0.83, H_2O); ^1H and ^{19}F NMR (D_2O) are identical to that of the enantiomer (+)-**9**.

(*S*)- *and* (*R*)-*2-Methyl-3,3,3-trifluoroalanine hydrochloride (10). General procedure.* An HCl 6N/glacial acetic acid 6:1 mixture (3.5 ml) was added to 95 mg (0.46 mmol) of (+)-**9** and the resulting mixture stirred and heated to 100°C for 8 hrs. The solvent was evaporated at reduced pressure affording 75 mg (88.6 %) of the amino acid hydrochloride (+)-**10** as a yellowish solid: (*R*)-**10**, $[\alpha]_D^{20}$ + 11.4 (c 1.04, H_2O); m.p. > 220°C; ^1H NMR (D_2O) δ 1.76 (s, 3 H, CH_3); ^{19}F NMR (D_2O) δ −74.70; ^{13}C NMR (All dec.) (D_2O) δ 170.29 (s, $\underline{C}OOH$), 125.91 (q, $J_{C\text{-}F}$ = 281 Hz, $\underline{C}F_3$), 64.74 (q, $J_{C\text{-}F}$ = 28 Hz, $\underline{C}CF_3$), 19.22 (s, $\underline{C}H_3$); EI/MS (70 eV): m/e (%) 158 (1, $M^+ + 1$), 142 (4, $M^+ - CH_3$), 112 (100, $M^+ - COOH$), 96 (7, $M^+ - COOH - NH_2$), 92 (25, $M^+ - COOH - HF$), 88 (7, $M^+ - CF_3$), 69 (10, CF_3^+); and (*S*)-**10**, $[\alpha]_D^{20}$ − 10.50 (c 0.58, H_2O); m.p. > 220°C; ^1H, ^{13}C and ^{19}F NMR (D_2O) are identical to that of the enantiomer (+)-**10**.

(S) and (R)-2-Methyl-3,3,3-trifluoroalanine (1). General procedure. The hydrochloride (+)-**10** (65 mg, 0.34 mmol) was dissolved in 2 ml of water and chromatographed on 2.5 g of ion-exchange acidic resin DOWEX 50W-X2 (H^+ form), eluting first with water until pH was about 5 and then with 7.5 % aqueous ammonia. Solvent removal at reduced pressure (65°C) from the collected ammonia fractions, afforded 45 mg (84.2 %) of the free aminoacid (+)-**1** as a white powder, that was readily sublimated by moderate heating under high vacuum: (*R*)-**1**, $[\alpha]_D^{20}$ + 15.8 (c 0.57, H_2O) (lit. + 13.2[3a], c not reported, H_2O); m.p. > 230°C (lit. 252°C)[3a]; ^1H NMR (D_2O) δ 1.55 (s, 3 H, CH_3); ^{19}F NMR (D_2O) δ −75.85; ^{13}C NMR (All dec.) (D_2O) δ 174.67 (s, COOH), 127.48 (q, J_{C-F} = 281 Hz, CF_3), 64.14 (q, J_{C-F} = 27 Hz, CCF_3), 20.93 (s, CH_3). Found C, 29.71; H, 4.17; N, 9.37. $C_4F_3H_6NO_2$ requires C, 30.58; H, 3.85; N, 8.92; and (*S*)-**1**, $[\alpha]_D^{20}$ − 13.9 (c 0.54, H_2O) (lit. − 13.2[3a], c not reported, H_2O); m.p. > 230°C, (lit. 252°C)[3a]; ^1H, ^{13}C and ^{19}F NMR (D_2O) are identical to that of the enantiomer (+)-**1**.

N-Ethoxycarbonyl-2-methyl-3,3,3-trifluoroalanine (11b). An HCl 6N/glacial acetic acid 6:1 mixture (3.5 ml) was added to 40 mg (0.17 mmol) of (−)-**8b** and the resulting mixture stirred and heated to 100°C for 10 hrs. The solvent was evaporated at reduced pressure affording 28 mg (74.3 %) of the *N*-ethoxycarbonyl-aminoacid (**11b**) as a yellowish solid: ^1H NMR (D_2O) ($CDCl_3$) δ 4.18-4.04 (m, 2 H, OCH_2), 1.63 (s, 3 H, OCH_3), 1.22 (q, 3 H, J = 6.5 Hz, OCH_2CH_3); ^{19}F NMR (D_2O) δ − 74.45.

Acknowledgements: *Financial support from Consiglio Nazionale delle Ricerche. "Progetto Finalizzato Chimica Fine II" and "Comitato per le Ricerche Tecnologiche" are gratefully acknowledged. Dr. Matteo Zanda and Dr. Silvia Capelli thank Politecnico di Milano for a scholarship.*

References and Notes

1. a) Kollonitsch, J. Suicide Substrate Enzyme Inactivators of Enzymes Dependent on Pyridoxal-Phosphate: β-Fluoro Amino Acids and β-Fluoro Amines. Design, Synthesis and Application: a Contribution to Drug Design. In *Biomedicinal Aspects of Fluorine Chemistry*; Filler, R.; Kobayashi, Y. Eds.; Kodansha Ltd.. Tokyo, 1981; pp 93-122; b) Welch, J.T.; Eswarakrishnan, S., *Fluorine in Bioorganic Chemistry*, John Wiley & Son Inc.: New York, 1991. c) Resnati, G. Synthesis of Chiral and Bioactive Fluoroorganic Compounds; *Tetrahedron*, **1993**,*42*, 9385-9445; for comprehensive reviews on α-fluoroalkyl aminoacids see: d) Kukhar', V.P.; Yagupol'skii, Yu.L.; Soloshonok, V.A., β-Fluoro-Substituted Amino Acids *Russ. Chem. Rev.*, **1990**, *59 (1)*, 149-175; e) Kukhar, V.P.; Resnati, G.; Soloshonok, V. Asymmetric Synthesis of Fluorine Containing Amino Acids in *Fluorine-containing Amino Acids;* Kukhar, V.P.; Soloshonok, V.eds; John Wiley & Son, 1994.
2. For the synthesis of: a) fluoro muscarines: Bravo, P.; Resnati, G.; Angeli, P.; Frigerio, M.; Viani, F.; Arnone, A.; Marucci, G.; Cantalamessa, F., *J. Med. Chem.*, **1992**, *35*, 3102-3110; b) fluoro sugars: Bravo, P.; Piovosi, E.; Resnati, G.; Fronza, G. *J. Org. Chem.* **1989**, *54*, 5171-5176; c) fluoro nucleosides: Bravo, P.; Resnati, G.; Viani, F., *Tetrahedron*, **1993**, *49*, 713-720.
3. a) Keller, J.W.; Hamilton, B.J., *Tetrahedron Lett.*, **1986**, *27*, 1249-1250; b) Lontz, J.F.; Raasch, M.S., U.S. Patent 266915/C.A. **1954**, *48*, 12795a; c) Watanabe, H.; Hashizume, Y.; Uneyama, K., *Tetrahedron Lett.*, **1992**, *33*, 4333-4336; d) Keller J.W.; O' Leary, M.H., *Biochem. Biophys. Res. Commun.*, **1979**, *90*,

1104-1110; e) Christensen, H.N.; Oxender, D.L., *Biochim. Biophys. Acta*, **1963**, *74*, 385-391; f) Keller, J.W.; Day, C.S., *Acta Crystallogr.*, **1984**, *40*, 1224-1226; g) Schierlinger, C.; Burger, K., *Tetrahedron Lett.*, **1992**, *33*, 193-194; h) Soloshonok, V.A.; Kukhar, V. P.; Yagupol'skii, Yu.L., *Zh. Org. Khim.*, **1986**, *22*, 517-521; i) Soloshonok, V.A.; Gerus, I.I.; Yagupol'skii, Yu.L.; Kukhar', V.P., *Zh. Org. Khim.*, **1987**, *23*, 2308-2313; l) Taylor, J.S.; Deutsch, C., *Biophys. J.*, **1983**, *43*, 261-267.

4. a) Kricheldorf, H.R., *Synthesis*, **1972**, 695-697; b) Jung, M.E.; Shishido, K.; Light, L.; Davies, L. *Tetrahedron Lett.*, **1981**, *22*, 4607-4610; c) for overviews on the synthesis of imino phosphoranes and related compounds see: *Ylides and Imines of Phosphorus;* Johnson, A.W.; John Wiley and Sons Eds., 1993; d) Barluenga, J.; Palacios, F. Synthesis and Reactivity of λ^5-phosphazenes. Uses as Synthetic Intermediates; *Org. Prep. and Proc. Int.* **1991**, *23(1)*, 1-65.
5. a) Knunyants, I.L.; Shokina, V.V.; Tyuleneva, V.V., *Dokl. Akad. Nauk.*, **1966**, *169*, 594-597; b) Knunyants, I.L.; Yakobson, G.G. *Synthesis of Fluoroorganic Compounds*, Springer Eds., 68-69.
6. Eguchi, S.; Matsushita, Y.; Yamashita, K. The Aza-Wittig Reaction in Heterocyclic Synthesis. In *Org. Prep. and Proc. Int.;* **1992**, 211-243.
7. For the reaction of sulphoxide-stabilized carbanions with imines see: Walker, A.J. In Asymmetric Carbon-Carbon Bond Formation Using Sulphoxide-Stabilized Carbanions, *Tetrahedron: Asymmetry* **1992**, *3*, 961-996.
8. The addition of sulphinyl anions to aldimines is described to be highly diastereoselective (Pyne, S.G. and Boche, G. *J. Org. Chem.* **1989**, *54*, 2663-2667). The diastereoselection of the herewith described process was not affected by differences in the protecting groups at the iminic nitrogen and in the addition rate of both partners, as well as by the use of chelating agents ($AlEt_3$ and $MgCl_2$). An unremarkable diastereoselection (9.8 % d.e. for **4d** and (-)-(*S*)-**5**; 2.4 % for **4d** and (+)-(*R*)-**5**) was observed when the chiral imine **4d** was reacted with both (*R*)-**5** and (*S*)-**5**.
9. Drabowicz, J.; Oae, S. *Synthesis* **1977**, *6*, 404-405.
10. Burger, K.; Schierlinger, C.; Mütze K. *J. Fluorine Chem.* **1993**, *65*, 149-152.
11. Johnson, C. K. (1976) ORTEPII. Report ORNL-5138. Oak Ridge National Laboratory, Tennesee.
12. Bravo, P; Farina, A.; Frigerio, M.; Meille, S.V.; Viani, F.; Soloshonok, V.A. *Tetrahedron Asymmetry* **1994**, in press.
13. Bosh, R.; Bruckner, H.; Jung, G.; Winter, W. *Tetrahedron* **1982**, *38*, 3579-3583.
14. This trend was general for **6b** and **6d'** couples, being $155<\Delta\nu<175$ for 2*S* and $115<\Delta\nu<137.5$ for 2*R*. Similar trends were supported both by polarities ($R_f = 0.40$ for 2*S* and ≤ 0.37 for 2*R*) and ^{19}F δ values ($\Delta\nu \leq -75.63$ and ≥ -75.28 for 2*S* and 2*R* respectively) (see Experimental). For **6d**, being the stereochemistry at sulphur *S*, the trend is observed but on enantiomeric couples. On this basis, the stereochemistry of the three couples **6b**, **6d**, and **6d'** was, in every case, tentatively assigned.
15. Burgher, V.K.; Gaa, K. *Chem. Ztg.* **1990**, *114(3)*, 101-104.
16. Altomare, A.; Cascarano, G.; Giacovazzo, G.; Guagliardi, A. *J. Appl. Cryst.* **1993**, *26*, 343.
17. Sheldrick, G.M. *J.Appl.Cryst.* **1994**, in preparation.
18. Flack, H.D. *Acta Cryst.* **1983**, *A 39*, 876-880.

(*Received in UK* 8 *August* 1994)