Synthesis of enantiomerically pure 3-fluoromethylthreonines from (*S*)-1-fluoro-3-tolylsulfinylacetone

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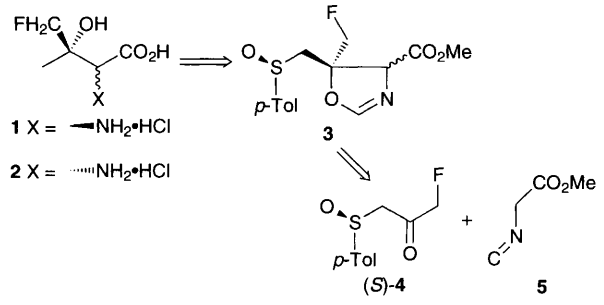
The copper(I) catalysed aldol reaction between methyl isocyanoacetate and (*S*)-3-fluoro-1-(4-methylphenyl)-sulfinylacetone affords oxazoline products which, after diastereoisomer separation, give in high yields optically pure 3-fluoromethylthreonine analogues whose absolute and relative configurations have been assigned through X-ray analyses.

Interest in fluorine containing analogues of natural amino acids originates from the peculiar and useful properties of these compounds and of the peptides and peptidomimetics containing them.[1] Fluoroamino acids afford effective ground-state[2a] and transition-state[2b] analogue enzyme inhibitors as well as mechanism-based enzyme inhibitors[3] resulting, for instance, in useful chemotherapeutic agents.[4]

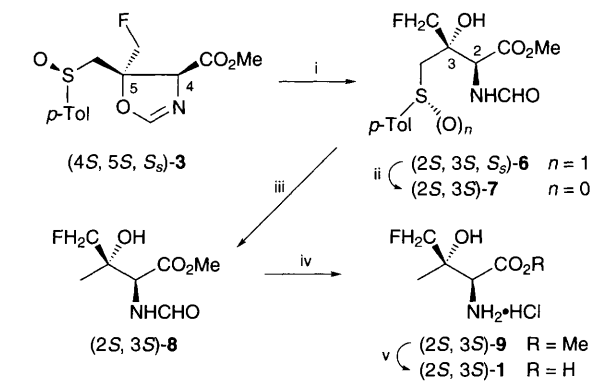
In this context, fluorinated analogues of threonine occupy a unique position. Only ten naturally occurring organofluorine metabolites have been identified[5] and (−)-4-fluorothreonine is the only fluoroamino acid found in nature.[6] It is endowed with interesting antimicrobial activity and (2*S*, 3*S*)-4,4-difluoro-[7] and (2*S*,3*S*)- 4,4,4-trifluorothreonines[8] show promising antitumour and antifungal activity.[9] This has prompted many different groups to develop approaches for the asymmetric synthesis of 3-trifluoromethyl analogues of threonine.[8–10] Here we describe the first synthesis of two new 3-fluoromethyl analogues, *i.e.* (2*S*,3*S*)-3-fluoromethylthreonine **1** and its (2*R*,3*S*) epimer **2**. The retrosynthetic Scheme 1 shows that, these compounds are obtained from oxazolines **3** which, in their turn, are formed through the aldol condensation between the chiral fluoroacetone equivalent **4** and the glycine anion equivalent **5**.

Several examples of the aldol reaction between alkyl isocyanoacetates and aldehydes have been described,[11] but the use of ketones as electrophile species is quite rare.[10b] Therefore, we were pleased to observe that the aldol condensation of methyl isocyanoacetate **5** and (*S*)-3-fluoro-1-(4-methyl phenyl)-sulfinylacetone **4** occurred at 0 °C in the presence of catalytic amounts of Cu_2O (10 mol%), despite the fact β-ketosulfoxide **4** is easily deprotoned by bases to give stable enolates (Scheme 2). While chlorinated solvents are usually employed for this reaction, higher yields were obtained by using diethyl ether. All the four possible diastereoisomers of oxazolines **3** were formed (92% isolated products) and the prevailing one (49% of product mixture), having the (4*S*,5*S*,S_S) absolute configuration, could be easily obtained in pure form by flash chromatography of the reaction mixture (AcOEt–toluene 75 : 25).† Hydrolysis of the oxazoline ring of (4*S*,5*S*,S_S)-**3** was very easy and afforded the amido-ester (2*S*,3*S*,S_S)-**6** in nearly quantitative yields when it was performed by simply stirring a chloroform–water solution of the oxazoline at room temp. Absolute and relative stereochemistry of this intermediate and, consequently, of all the other products described here, were assigned through an X-ray analysis of a crystal obtained from $CHCl_3$–hexane (Fig. 1).‡

Reductive removal of the sulfinyl auxiliary group from (2*S*,3*S*,S_S)-**6** was best performed in two steps: deoxygenation at sulphur with trifluoroacetic anhydride–sodium iodide[17] to give the sulfenyl-amido-ester (2*S*,3*S*)-**7** and successive hydrogenolysis of the tolylthio residue with Raney nickel to afford the diprotected 3-fluoromethylthreonine (2*S*,3*S*)-**8**. When usual reaction conditions[18] were employed in the desulfenylation step, the basicity of the Raney nickel caused partial epimerization at the nitrogen substituted stereogenic centre, but this process could be completely suppressed by using buffered reaction conditions (pH 5.2).[19]



Scheme 1



Scheme 2 *Reagents and conditions*: i, H_2O–$CHCl_3$; ii, $(CF_3CO)_2O$, NaI, acetone, −40 °C; iii, Raney-Ni, methanol-buffer pH 5.2; iv, 1M $HCl_{aq.}$; v, 12 mol dm^{-3} HCl_{aq}, reflux

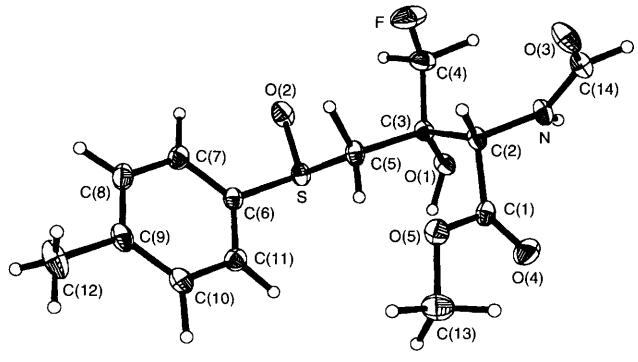


Fig. 1 ORTEP plot (2*S*,3*S*,S_S)-**6**.

Hydrolysis of the amido group of the (2*S*,3*S*)-**8** could be performed selectively (1 mol dm^{-3} hydrochloric acid, room temp.) to give the corresponding amino ester (2*S*,3*S*)-**9**. However, isolation of this intermediate was not necessary, by using more severe reaction conditions (conc. HCl, reflux) both the amide and ester functionalities were hydrolysed to give the (2*S*,3*S*)-3-fluoromethylthreonine **1** which was isolated as its hydrochloride ($[\alpha]_D^{25}$ +6.46, ethanol, *c* = 0.5, 78% overall yield from oxazoline (4*S*,5*S*,S_S)-**3**).

The other three possible stereoisomers of 3-fluoromethylthreonine can be obtained in enantiomerically and diastereoisomerically pure form by simply starting from the other three diastereoisomeric sulfinyl-amido esters **6** which are also available in pure form. For example, (2*R*,3*S*)-3-fluoromethylthreonine **2** [81% overall yield from (2*R*,3*S*,S_S)-**6**] was prepared through reductive desulfinylation of (2*R*,3*S*,S_S)-**6**§ followed by protective group removal (Scheme 3) according to the procedure described above.

The consistent steric and electronic differences existing between the methyl and trifluoromethyl groups of 3-trifluoromethylthreonines play a key role in the reported asymmetric syntheses of these compounds.[10a,c] There are no great differences between the methyl and fluoromethyl residues of 3-fluoromethylthreonines **1** and **2** and so in our synthesis we resorted to intermediates **3** and **6** bearing an enantiopure sulfinyl group on the methyl residue of final compounds **1** and **2**. The presence of this auxiliary group allowed the stereodifferentiation required for the isolation of single pure isomers to be obtained. Reductive removal (hydro-desulfinylation) of the sulfinyl residue afforded final compounds **1** and **2**.

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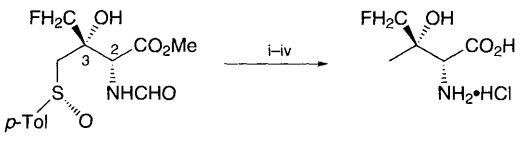

(2*R*, 3*S*, S_S)-**6** (2*R*, 3*S*)-**2**

Scheme 3 *Reagents and conditions*: i, $(CF_3CO)_2O$, NaI, acetone, −40 °C; ii, Raney-Ni, methanol-buffer pH 5.2; iii, 1M $HCl_{aq.}$; iv, 12 mol dm^{-3} $HCl_{aq.}$, reflux

Footnotes

† Diastereoisomer ratio (4*S*,5*S*,S_S)-**3**: (4*R*,5*S*,S_S)-**3**: (4*S*,5*R*,S_S)-**3**: (4*R*,5*R*,S_S)-**3** = 49 : 25 : 16 : 10. All compounds obtained gave expected ^1H, ^{13}C and ^{19}F NMR, IR and mass spectra. Selected physical and spectral data for (2*S*,3*S*)-**1**: ^1H NMR (CD_3OD, 250 MHz) δ 4.61 (dd, 1H, *J* = 46.8 and 9.9 Hz, C*H*HF), 4.45 (dd, 1H, *J* = 47.5 and 9.9 Hz, CH*H*F), 4.08 (s, 1H, H-2) and 1.25 (d, 3H, *J* = 2.4 Hz, H_3-4); ^{19}F NMR (CD_3OD) δ −226.68 (br ddq, *J* = 47.5, 46.8 and 2.4 Hz, CH_2F). For (2*R*,3*S*)-**2**: ^1H NMR (CD_3OD, 250 MHz) δ 4.47 (dd, 1H, *J* = 47.3 and 9.9 Hz, C*H*HF), 4.36 (dd, 1H, *J* = 47.0 and 9.9 Hz, CH*H*F), 3.89 (s, 1H, H-2) and 1.48 (d, 3H, *J* = 2.4 Hz, H_3-4); ^{19}F NMR (CD_3OD) δ −224.23 (br ddq, *J* = 47.3, 47.0 and 2.4 Hz, CH_2F).

‡ The relative stereochemistry at C-4 and C-5 of oxazolines **3** was also established through heteronuclear Overhauser effects. The two diastereoisomers **3** bearing the fluoromethyl residue on C-5 and the proton of C-4 in a *cis* relation showed an enhancement of H-4 on irradiation of F, while no sizeable NOE was observed for the *trans* compounds.

Crystal data for (2*S*,3*S*,S_S)-**6**: *M* = 331.35, orthorhombic, space group $P2_12_12_1$, *a* = 8.506(1), *b* = 8.816(1), *c* = 21.596(1) Å, *V* = 1619.5(3) $Å^3$, *Z* = 4. Data were collected on a P4 diffractometer, using Cu-Kα radiation. The crystal structure was solved by direct methods (SIR92),[12] and refined with full-matrix least squares on F^2 values (SHELXL-93).[13] Final *R* = 0.0351, R_w = 0.0382 for 2134 reflections with $I > 2.0\,\sigma(I)$ out of 2216 unique reflections. The highest and lowest peaks in the final difference-Fourier map were 0.242 and −0.187 e $Å^{-3}$, while the refined value of Flack's *x* parameter was 0.03(2), establishing the absolute configuration as (2*S*,3*S*,S_S). Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDC). See Information for Authors, Issue No. 1. Any request to the CCDC for this material should quote the full literature citation and the reference number 182/256. The threonine conformation in (2*S*,3*S*,S_S)-**6** is only mildly perturbed[14,15] by the sulfinyl, formamide, and fluoromethyl groups, as can be gauged by the value of 151.1° determined for the torsion angle O(5)–C(1)–C(2)–N. As in related synthetic intermediates[15,16] hydrogen bonds are not intramolecular, instead give rise to a tridimensional intermolecular network binding, respectively, the amide and the hydroxy hydrogens to the sulfoxide and the formamide oxygens of different molecules.

§ This compound could be isolated in pure form through flash chromatographic separation (AcOEt–toluene 75 : 25) of the easily available mixture containing also the stereoisomers **6** having the (4*R*,5*R*,S_S) and (4*S*,5*R*,S_S) configuration.

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