A short highly stereoselective synthesis of the fluorinated natural product (2*S*,3*S*)-4-fluorothreonine

Muhammad R. Amin,[a] **David B. Harper,**[b] **Janet M. Moloney,**[a] **Cormac D. Murphy,**[b] **Judith A. K. Howard**[a] **and David O'Hagan***[a]

[a] *Department of Chemistry, University of Durham, Science Laboratories, South Road, Durham, UK DH1 3LE*
[b] *Department of Food Science, The Queen's University of Belfast, Newforge Lane, Belfast, UK BT9 5PX*

A three step stereoselective route to the fluorinated natural product (2*S*,3*S*)-4-fluorothreonine is described; the route is amenable to the preparation of (2*S*,3*S*)-4-fluoro[3-²H]threonine and (2*S*,3*R*)-[4,4,4-²H₃]threonine.

4-Fluorothreonine **1** is a secondary metabolite of *Streptomyces cattleya* and is one of the few natural products that contain fluorine. The compound was first isolated[1] in 1986 in the course of studies aimed at improving thienamycin production by the organism. It was reported to be a single stereoisomer but the relative or absolute stereochemistry was not established at that time. Two syntheses of (2*S*,3*S*)-4-fluorothreonine **1** have been reported,[2] one prior[3] to its isolation from *S. cattleya*, and in each case the optical rotation values were close to that of the natural amino acid **1** ($[\alpha]_D$ −20) implying a 2*S*,3*S* absolute configuration. In our current programme[4–6] focused on evaluating the biosynthetic origin of fluoroacetate and 4-fluorothreonine in *S. cattleya* it proved necessary to confirm the absolute stereochemistry of **1**. As the two published syntheses are lengthy we have developed a new and more direct approach to (2*S*,3*S*)-4-fluorothreonine **1** which exploits Seebach's imidazolidinone methodology for the synthesis of α-amino-β-hydroxy acids.[7] This appeared attractive at the outset as a straightforward condensation between **2** and fluoroacetaldehyde should deliver the required framework. However, fluoroacetaldehyde is not readily prepared and despite several attempts we were not able to devise a suitable synthesis. The literature preparations[8] for fluoroacetaldehyde generated aqueous solutions which are inadequate for the current purpose.
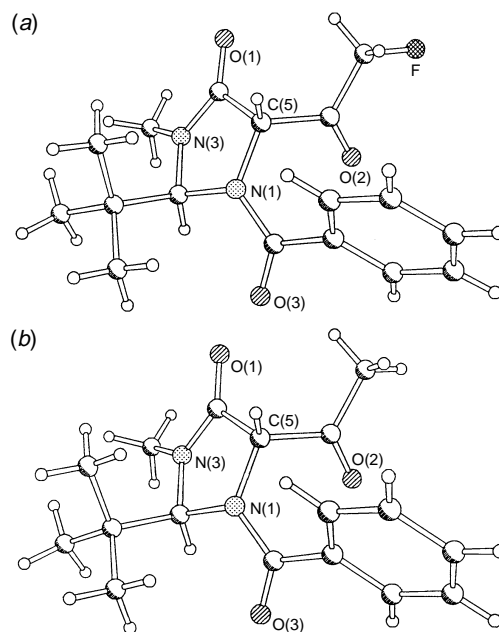
The route was therefore modified as shown in Scheme 1 such that **2** was treated with fluoroacetyl chloride[9] (**WARNING**: highly toxic) to generate the resultant β-ketone **3**,† a crystalline solid. From the X-ray structure of **3** it is noteworthy that the geometry at C-5 is fully tetrahedral and that the β-carbonyl
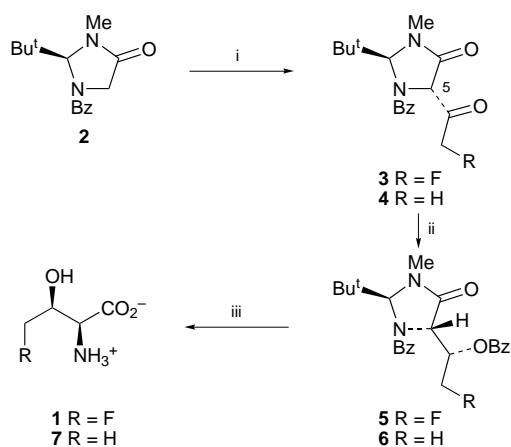
system is non-planar. This is an important feature as C-5 is rendered configurationally stable, a situation that is revealed again in the X-ray structure of the analogous defluorohydro compound **4**,‡ an intermediate in our synthesis of (2*S*,3*R*)-threonine (Fig. 1). It was not clear at the outset if the subsequent reduction of the β-carbonyls of **3** and **4** would be stereoselective and deliver the desired *threo* products, however in the event this proved to be the case. Treatment of **3** and **4** with NaBH₄ in MeOH generated the benzoate esters **5**§ and **6** respectively as single diastereoisomers. The benzoates **5** and **6** and not the *N*-benzoyl derivatives were the sole products, indicating a facile transacylation after carbonyl reduction. This transacylation is consistent with Seebach's observations[7b] after the direct condensation of **2** with acetaldehyde. The *allo*-diastereoisomers were not detectable by ¹³C, ¹H and ¹⁹F (for **5** only) NMR spectroscopy of the crude reaction products, indicating that the reduction is highly stereoselective with hydride delivered exclusively to the *si* face of **3** (*re* face of **4** due to a change in assignment priorities). If the transition state conformation of **3** bears a resemblance to the ground state structure as shown in Fig. 1 then the *si* face of the carbonyl is the more exposed of the two as the *N*-benzoyl aromatic ring hinders access to the *re* face.

The benzoates **5** and **6** were subjected to hydrolysis (10 M HCl at 100 °C) and the resultant (2*S*,3*S*)-4-fluorothreonine **1**¶ and (2*S*,3*R*)-threonine **7** [identical in all respects to natural (2*S*,3*R*)-threonine] were recovered after purification on Dowex H⁺. The *threo* relative stereochemistry of **1** was confirmed by an

Scheme 1 *Reagents and conditions*: i, LDA, FCH₂COCl (acetyl chloride for **4**), THF, −100 °C, 57%; ii, NaBH₄, MeOH, 20 °C, 5 min, 67%; iii, 10 M HCl, 100 °C, 72 h, 64%

Fig. 1 X-Ray structures of **3** (*a*) and **4** (*b*). The geometry at C-5 of the β-ketone is tetrahedral in each case.
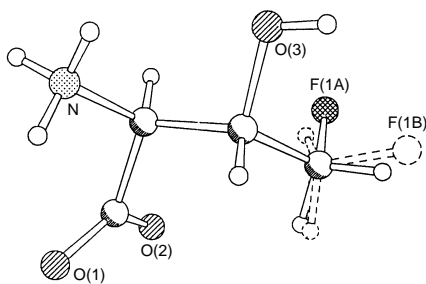
Fig. 2 X-Ray structure of synthetic (2*S*,3*S*)-4-fluorothreonine **1**, showing two positions for the disordered CH$_2$F group with occupancies of 66(2)% (solid) and 34(2)% (dashed)

X-ray structural study∥ (Fig. 2). The 2*S*,3*S* assignment for **1** follows from the structure of **3** where the known absolute stereochemistry of the auxiliary allows a 2*S* designation to be made at C-5 and subsequently at the α-position of the amino acid. All analytical data ([α]$_D$ −20, ^{19}F NMR, HPLC, GC–MS of MSTFA derivative) were identical to a sample of 4-fluoro-threonine **1** isolated[4] from *Streptomyces cattleya*, confirming the absolute stereochemistry of the natural product. Additionally this route to (2*S*,3*S*)-4-fluorothreonine is amenable to isotope labelling and (2*S*,3*S*)-4-fluoro[3-^{2}H]threonine **1a** was prepared by employing NaB^{2}H$_4$ in the reduction step. This material is being used to probe the anabolic and catabolic flux of (2*S*,3*S*)-4-fluorothreonine in *S. cattleya*.
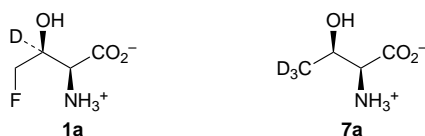
The modified methodology offers an alternative route to *threo* amino acids and it displays a higher stereoselectivity to that previously described for (2*S*,3*R*)-threonine.[7b] The method has the additional advantage of using acid chlorides in place of aldehydes when the requisite aldehyde is unavailable, as in the case of fluoroacetaldehyde, or is expensive, as in the case of isotopic labelling. For example, a sample of racemic [4,4,4-^{2}H$_3$]threonine **7a** was prepared from [^{2}H$_3$]acetyl chloride, a cheaper and more highly stereoselective route to the labelled amino acid than that using [^{2}H$_3$]acetaldehyde with racemic imidazolidinone **2**.

Footnotes

† *Selected data* for **3**: mp 197 °C; [α]$_D$ +140 (*c* 1, CHCl$_3$); ν$_{max}$(CDCl$_3$)/cm^{-1} 3360m, 2960s, 1715s, 1695s, 1665m; δ$_H$(CDCl$_3$) 7.60–7.35 (5 H, m, Ar), 5.75 [1 H, s, HC(2)], 5.39 [1 H, s, HC(5)], 4.45 (2 H, m, FCH$_2$), 3.06 (3 H, s, NMe), 1.08 (9 H, s, Bu^t); δ$_C$(CDCl$_3$) 197.7 (C-1′, d, *J*$_{CF}$ 18.6), 170.6 (*C*OPh), 165.0 (C-4), 135.8 (Ar), 131.6 (Ar), 128.8 (Ar), 127.6 (Ar), 83.8 (C-2′, d, *J* 187), 80.4 (C-2), 66.2 (C-5), 40.3 [*C*(CH$_3$)$_3$], 32.2 (NMe), 26.1 [C(*C*H$_3$)$_3$]; δ$_F$(CDCl$_3$) −230.8 (t, *J* 46.3); Found: C, 63.52; H, 6.63; N, 8.63. C$_{17}$H$_{21}$N$_2$O$_3$F requires: C, 63.68; H, 6.55; N, 8.74%.

‡ *Selected data* for **4**: mp 188–189 °C (decomp.); [α]$_D^{25}$ +120 (*c* 0.01, CHCl$_3$); ν$_{max}$(CDCl$_3$)/cm^{-1} 2984s (br), 2940s (br), 2287s (br), 1732s, 1700s, 1397s; δ$_H$(CDCl$_3$) 7.60–7.23 (5 H, m, Ar), 5.64 (1 H, s, HC-2), 5.11 [1 H, s, HC(5)], 3.00 (3 H, s, NMe), 1.82 (3 H, s, CH$_3$CO), 0.99 (9 H, s, Bu^t); δ$_C$(CDCl$_3$) 199.7 (C-1″), 171.3 (*C*OPh), 165.3 (C-4), 136.3 (Ar), 131.3

(Ar), 128.6 (Ar), 127.7 (Ar), 79.9 (C-2′), 70.5 (C-5), 40.3 [*C*(CH$_3$)$_3$], 32.1 (NMe), 28.7 (C-2′), 26.1 [C(*C*H$_3$)$_3$]; Found: C, 56.18; H, 7.27; N, 9.21. C$_{17}$H$_{22}$N$_2$O$_3$ requires: C, 56.29; H, 7.28; N, 9.27%.

§ *Selected data* for **5**: (0.32 g, 67%): an oil; [α]$_D$ −13 (*c* 1, CHCl$_3$); ν$_{max}$(CDCl$_3$)/cm^{-1} 3360m (br), 2958s, 1675s, 1645m; δ$_H$(CDCl$_3$) 8.10–7.60 (5 H, m, Ar), 5.62 (1 H, m, HCObz), 4.91 (2 H, dm, *J* 47, FH$_2$C), 4.31 [1 H, d, *J* 2.1, HC(2)], 4.15 [1 H, m, HC(5)], 3.02 (3 H, s, NMe), 1.15 (9 H, s, Bu^t; δ$_C$(CDCl$_3$) 172.5 (*C*OPh), 165.4 (CO), 133.2 (Ar), 129.6 (Ar), 129.4 (Ar), 128.3 (Ar), 83.7 (C-2), 81.8 (C-2′, d, *J* 172.4, CH$_2$F), 72.1 (C-1′, d, *J* 19.4, *C*OBz), 58.2 (C-5), 37.2 [*C*(CH$_3$)$_3$], 31.1 (NMe), 25.3 [C(*c*H$_3$)$_3$]; δ$_F$(CDCl$_3$) −233.1 (dt, *J* 47.4, 25); Found: 323.17628. C$_{17}$H$_{23}$N$_2$O$_3$F requires: 323.17709 (M + H$^+$).

¶ *Selected data* for **1** (90 mg, 64%): white crystalline solid; mp 182–183 °C (lit.,[1,2] 181–182 °C); [α]$_D$ −20 (*c* 5, H$_2$O) [lit.,[2] −20 (*c* 0.06, H$_2$O]; ν$_{max}$(KBr)/cm^{-1} 3500s, 3000s, 2800s, 1435m, 1130m; δ$_H$ (D$_2$O) 4.52 (2 H, ddd, *J* 46.5, 10.5, 3.9, CH$_2$F), 4.22 (1 H, dq, *J* 25, 4.6, HC(3)), 3.72 [1 H, d, *J* 4.8, HC(2)]; δ$_C$(D$_2$O) 175.5 (C-1), 87.8 (d, *J* 167.5, C-4), 70.8 (d, *J* 19.1, C-3), 59.2 (C-2); δ$_F$(D$_2$O) −229.7 (dt, *J* 47, 25).

∥ X-Ray diffraction experiments were performed on a Rigaku AFC6S 4-circle diffractometer (graphite-monochromated Cu-Kα radiation, λ = 1.54184 Å, ω scan mode) for **1** and on a Siemens SMART 3-circle diffractometer with a CCD area detector (graphite-monochromated Mo-Kα radiation, λ = 0.71073 Å, ω scan mode in 0.3° frames) for **3** and **4**. The structures were solved by direct methods and refined by full-matrix least-squares (non-H atoms anisotropic, H isotropic) against F^2 of all data, using SHELXTL ver. 5/VMS software (G. M. Sheldrick, Siemens Analytical X-Ray Instruments Inc., Madison, WI, USA, 1995). Absolute configurations were assigned according to those of the starting materials. CCDC 182/499.

Crystal data for **1**: C$_4$H$_8$FNO$_3$, *M* = 137.1, *T* = 296 K, orthorhombic, space group P2$_1$2$_1$2$_1$ (No. 19), *a* = 5.231(1), *b* = 7.870(2), *c* = 13.603(3) Å, *U* = 560.0(2) Å^3, *Z* = 4, *D*$_x$ = 1.63 g cm^{-3}, μ = 13.9 cm^{-1}, crystal size 0.15 × 0.15 × 0.05 mm, 730 data total (2θ ⩽ 100°), 549 unique, 447 observed with *I* > 2σ(*I*), *R*$_{int}$ = 0.029, 93 variables, *R* (*F*, obs. data) = 0.059, *wR* (*F*^{2}, all data) = 0.163, goodness-of-fit *S* = 1.02, Δρ$_{min,max}$ = 0.27, −0.22 e Å^{-3}.

For **3**: C$_{17}$H$_{21}$FN$_2$O$_3$, *M* = 320.4, *T* = 296 K, orthorhombic, space group P2$_1$2$_1$2 (No. 18), *a* = 13.294(1), *b* = 21.437(2), *c* = 6.037(1) Å, *U* = 1720.5(3) Å^3, *Z* = 4, *D*$_x$ = 1.24 g cm^{-3}, μ = 0.9 cm^{-1}, crystal size 0.4 × 0.2 × 0.15 mm, 12 388 data total (2θ ⩽ 55°), 3916 unique, 2909 observed, *R*$_{int}$ = 0.041, 225 variables, *R* = 0.050, *wR* = 0.142, *S* = 1.14, Δρ$_{min,max}$ = 0.19, −0.19 e Å^{-3}.

For **4**: C$_{17}$H$_{22}$N$_2$O$_3$, *M* = 302.4, *T* = 150 K, orthorhombic, space group P2$_1$2$_1$2 (No. 18), *a* = 12.636(1), *b* = 21.459(2), *c* = 6.059(1) Å, *U* = 1642.9(3) Å^3, *Z* = 4, *D*$_x$ 1.22 g cm^{-3}, μ = 0.8 cm^{-1}, crystal size 0.4 × 0.2 × 0.1 mm, 9842 data total (2θ ⩽ 50°), 2866 unique, 2289 observed, *R*$_{int}$ = 0.064, 216 variables, *R* = 0.050, *wR* = 0.115, *S* = 1.14, Δρ$_{min,max}$ = 0.15, −0.19 e Å^{-3}.

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