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Stereoselective synthesis of the antibacterial 3-fluoro-D-alanine

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Abstract: The wide spectrum antibacterial 3-fluoro-D-alanine (*S*)-**9** has been stereoselectively synthesized *via* "chiral sulfoxide chemistry". Key steps are the azidation of the α-fluoro α′-sulfinyl alcohol (2*S*,R_S)-**1** under Mitsunobu conditions and the one-pot transformation of the *N*-Cbz α-sulfinyl amine (2*R*,R_S)-**5** into the *N*-Cbz aminoalcohol (*S*)-**7**, through a "non-oxidative Pummerer reaction". © 1997 Published by Elsevier Science Ltd

Fluorine-containing amino acids have been synthesized and studied as potential enzyme inhibitors and therapeutic agents.[1,2] Two routes are generally followed in order to obtain enantiomerically pure selectively fluorinated compounds, namely the reaction of fluorinating agents on late precursors, or the use of relatively simple fluorinated substrates already possessing some stereogenic center (usually a chiral auxiliary group), which, after appropriate elaborations, can afford the target product.

Within the later approach we have explored several synthetic ways to obtain enantiomerically pure amino acids possessing diverse fluorosubstitutions.[3] Recently we have reported that *N*-unprotected and *N*-Cbz 1-(fluoroalkyl)-2-(arylsulfinyl)enamines as well as *N*-aryl and *N*-alkyl fluoroalkyl (arylsulfinyl)methyl imines, readily obtained from the corresponding α-fluoro-α′-sulfinyl ketones and iminophosphoranes[4a] or by condensation between α-lithium (*R*)-methyl-*p*-tolylsulfoxide and fluoroacetimidoyl chlorides,[4b] are multifunctional starting compounds for the stereoselective synthesis of, *inter alia*, β-fluoro-α-amino acids. The synthesis of such starting compounds worked very well (50–100% isolated yields) with α′-sulfinyl ketones bearing on α polyfluoroalkyl residues like CF_3, $CClF_2$, CF_2CF_3, CF_2H, which are strong electron withdrawing groups. The corresponding CFH_2 derivatives could be prepared only from 1-fluoro-3-[(4-methylphenyl)sulfinyl]-2-propanone, but the reaction was sluggish, affording the desired *N*-Cbz enamine and *N*-phenylimine in 10% and 32% yield, respectively.

In this paper we describe an approach to enantiopure 3-fluoro-D-alanine, a wide spectrum antibacterial discovered by Kollonitsch,[5] which nicely complements the above described routes to β-fluoroalanine analogues. The key step of the present methodology is the conversion of the α-sulfinyl alcohol (2*S*,R_S)-**1**[6] into a nitrogen-containing derivative by a variant of the Mitsunobu reaction, which is widely employed for the conversion of primary and secondary alcohols to amines through the corresponding azides.[7]

A solution of (2*S*,R_S)-**1** (Scheme 1), Ph_3P and HN_3 in benzene was treated with DEAD at 0°C to rt,[7c] but disappointingly only a 3% yield of the corresponding azide (2*R*,R_S)-**2** was measured, whereas the main product was a 10:3 mixture of the *E* and *Z* vinyl sulfoxides (*R*)-**3** (48% yield), whose formation is favoured by the electron withdrawing sulfinyl group and fluorine atom.[8] However, when the same alcohol (2*S*,R_S)-**1** was reacted with NaN_3, Ph_3P and CBr_4 in DMF at rt,[9] the desired (2*R*,R_S)-**2** was obtained in 78% yield, along with (*R*)-**3** (22%) as a 6:1 mixture of *E* and *Z* isomers (Scheme 1).

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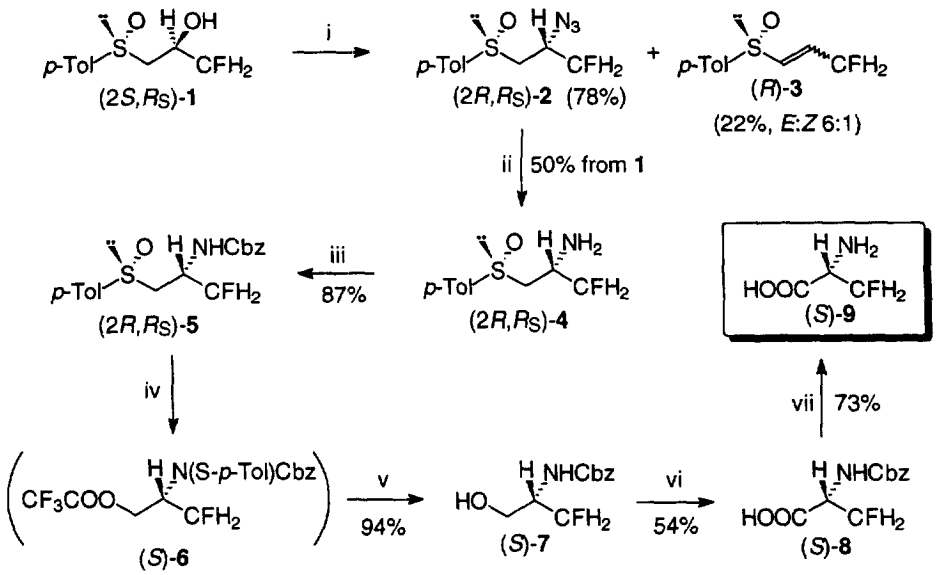

Scheme 1. Key: i) NaN_3, Ph_3P, CBr_4, DMF, 0°C; ii) $HS(CH_2)_3SH$, Et_3N, MeOH, rt; iii) ClCOOBn, K_2CO_3/H_2O 50%, dioxane, rt; iv) TFAA, *sym*-collidine, MeCN, 0°C; v) K_2CO_3, H_2O, $NaBH_4$; vi) $NaIO_4$, $RuO_2 \cdot xH_2O$, H_2O/acetone, rt; vii) Raney-Ni, H_2, abs. EtOH, rt.

As compounds (2*R*,R_S)-**2** and (*R*)-**3** have very similar R_F values (1:1 hexane/ethyl acetate) the reaction mixture was used in the next step without purification. The azido group of (2*R*,R_S)-**2** was selectively reduced to amino by 1,3-propanedithiol and Et_3N in methanol,[10] affording, after flash chromatography, the pure sulfinylamine (2*R*,R_S)-**4** in 50% overall yield from (2*S*,R_S)-**1**. After protection of the amino group by reaction with benzyl chloroformate, the corresponding *N*-Cbz derivative (2*R*,R_S)-**5** (87% yield) was submitted to the "non-oxidative Pummerer rearrangement"[4a] by reaction with TFAA and *sym*-collidine in acetonitrile at 0°C. The intermediate trifluoroacetoxy sulfenamide (*S*)-**6**, formed *via* displacement of the sulfinyl group (which undergoes reduction and intramolecular migration to the nitrogen atom) by a trifluoroacetoxy group, was treated with aqueous K_2CO_3 and then $NaBH_4$, delivering the *N*-Cbz amino alcohol (*S*)-**7**, isolated in 94% yield from (2*R*,R_S)-**5**. The hydroxymethyl group of (*S*)-**7** was oxidised by $NaIO_4/RuO_2$, affording the *N*-protected amino acid (*S*)-**8** (54% yield). Hydrogenolysis of the *N*-Cbz protection, treatment with aqueous HCl and finally ion exchange chromatography with the cationic resin DOWEX 50W, afforded pure (−)-3-fluoro-D-alanine (*S*)-**9** (73%), having $[\alpha]_D^{20}$ −10.4 (c 0.49, HCl 1N) in agreement with the literature data for the enantiopure compound.[11]

In summary, the irreversible inactivator of the bacterial alanine racemase 3-fluoro-D-alanine (*S*)-**9** is now available from fluoroacetic esters as fluorine source, and the sulfinyl group as chiral auxiliary. The protocol features excellent stereoselectivity and a synthetically useful overall yield.

Experimental

General

The instrumentation and general experimental and analytical procedures were recently described in detail.[4a] The starting α-sulfinyl alcohol (2*S*,R_S)-**1** was prepared according to literature.[6a]

Mitsunobu reaction: synthesis of (2R,RS)-2-azido-1-fluoro-3-[(4-methylphenyl)sulfinyl]propane 2

To a stirred solution of (2*S*,R_S)-**1** (0.94 g, 4.36 mmol) in DMF (45 ml) cooled at 0°C were added NaN_3 (4.25 g, 65.4 mmol), Ph_3P (3.43 g, 13.1 mmol) and finally CBr_4 (4.34 g, 13.1 mmol). The mixture was stirred at rt for 4 h, then water and ethyl ether were added and the phases were separated.

The organic phase was repeatedly washed with water in order to remove DMF and then dried over anhydrous Na_2SO_4, filtered and the solvent removed at reduced pressure. The crude mixture was submitted to flash chromatography (FC) (1:1 hexane/ethyl acetate), which afforded 0.75 g of a mixture formed by the desired azide (2*R*,*R*$_S$)-**2** (78%) and (*R*)-3-fluoro-1-[(4-methylphenyl)sulfinyl]propene **3** (22%, 6:1 mixture of *E*:*Z* isomers) as determined by ^{1}H and ^{19}F NMR analysis. The mixture was used for the next reaction without further purification.

(2*R*,*R*$_S$)-**2**: ^{1}H NMR ($CDCl_3$), δ: 7.55 (2 H, d, $J_{H,H}$=8.1 Hz), 7.38 (2 H, d, $J_{H,H}$=8.1 Hz), 4.66 (2 H, dd, $J_{H,F}$=46.7 Hz, $J_{H,H}$=4.6 Hz), 4.05–3.87 (1 H, m), 2.97 (1 H, dd, $J_{H,H}$=6.6 and 13.5 Hz), and 2.45 (3 H, s); ^{19}F NMR ($CDCl_3$), δ: −226.25 (dt, *J*=20.8 and 46.7 Hz); IR: 2117 cm^{-1}.

(*R*)-*E*-**3**: ^{1}H NMR ($CDCl_3$), δ: 7.52 and 7.33 (4 H, m), 6.63 (1 H, ddt, $J_{H,F}$=20.0, $J_{H,H}$=15.0 and 3.2 Hz), 6.54 (1 H, br dt, $J_{H,H}$=15.0 and 1.9 Hz), 5.12 and 5.06 (2 H, dddd, $J_{H,F}$=46.0, $J_{H,H}$=14.5, 3.2 and 1.9 Hz), and 2.41 (3 H, br s); ^{19}F NMR ($CDCl_3$), δ: −222.9 (1 F, br dt, *J* =20.0 and 46.0 Hz).

(*R*)-*Z*-**3**: ^{1}H NMR ($CDCl_3$), δ: 7.52 and 7.33 (4 H, m), 6.36 (1 H, br dt, $J_{H,H}$=10.5 and 1.0 Hz), 6.31 (1 H, ddt, $J_{H,F}$=15.5, $J_{H,H}$=10.5 and 4.5 Hz), 5.42 and 5.37 (2 H, dddd, $J_{H,F}$=46.5, $J_{H,H}$=13.0, 4.5 and 1.0 Hz), and 2.41 (3 H, br s); ^{19}F NMR ($CDCl_3$), δ: −214.35 (1 F, br dt, *J*=15.5 and 46.5 Hz).

*Reduction of the azido group: synthesis of (2*R,R$_S$*)-1-fluoro-3-[(4-methylphenyl)sulfinyl]-2-propanamine* **4**

The mixture (2*R*,*R*$_S$)-**2**+(*R*)-**3** (0.75 g) obtained from the Mitsunobu reaction [containing *ca.* 0.62 g (2.53 mmol) of azide (2*R*,*R*$_S$)-**2**] was dissolved in methanol (20 ml). Neat 1,3-propanedithiol (2.56 ml, 25.6 mmol) and triethylamine (3.54 ml, 25.5 mmol) were added at rt and the mixture was stirred for 4 h at rt. The solvent was carefully removed at reduced pressure and the crude mixture was purified by FC (gradient from 1:1 hexane/ethyl acetate to ethyl acetate and then 1:1 ethyl acetate/*i*-propanol) affording 0.47 g of amine (2*R*,*R*$_S$)-**4** as a yellowish oil (50% from (2*S*,*R*$_S$)-**1**). $[\alpha]_D^{20}$ +172.7 (*c* 0.89, CH_2Cl_2); IR: 3375, 1494, 1086, 1037, and 1015 cm^{-1}; MS (EI, 70 eV) m/z 216 (M$^+$, 18), 139 (26), and 76 (100); ^{1}H NMR ($CDCl_3$), δ: 7.56 (2 H, d, $J_{H,H}$=8.1 Hz), 7.35 (2 H, d, $J_{H,H}$=8.1 Hz), 4.59–4.27 (2 H, m, $^3J_{H,H}$=4.25 and 5.4 Hz, $^2J_{H,H}$=9.3 Hz, $J_{H,F}$=47.1 Hz), 3.69–3.51 (1 H, m), 2.88 (2 H, d, $J_{H,H}$=6.2 Hz), 2.43 (3 H, s), and 1.63 (2 H, br s); ^{19}F NMR ($CDCl_3$), δ: −228.85 (dt, *J*=47.1 and 19.8 Hz).

*Protection of the amino group: synthesis of (2*R,R$_S$*)-N-benzyloxycarbonyl-1-fluoro-3-[(4-methylphenyl)sulfinyl]-2-propanamine* **5**

To a solution of (2*R*,*R*$_S$)-**4** (0.40 g, 1.86 mmol) in 2.5 ml of dioxane were added 0.40 ml of 50% aqueous K_2CO_3 and benzyl chloroformate (0.28 ml, 1.86 mmol). The mixture was stirred at rt for 1 h (separation of KCl was observed). After separation of the organic solvent the residue was diluted with water (5 ml) and extracted with ethyl acetate. The collected organic phases were dried over anhydrous Na_2SO_4 and filtered, and the solvent was removed under reduced pressure. FC of the crude mixture (4:6 hexane/ethyl acetate) afforded 0.57 g of (2*R*,*R*$_S$)-**5** as a white solid (87.3%). M.p. 98.0–98.5°C (*i*-Pr_2O/AcOEt); $[\alpha]_D^{20}$ +87.9 (*c* 0.71, $CHCl_3$); IR: 3433, 1692, 1541, 1385, 1269, and 1024 cm^{-1}; MS (EI, 70 eV) m/z 350 (M$^+$, 4), 210 (21), 139 (22), and 91 (100); ^{1}H NMR ($CDCl_3$), δ: 7.55 (2 H, d, $J_{H,H}$=7.8 Hz), 7.38–7.29 (7 H, m), 5.35 (1 H, br d, $J_{H,H}$ *ca.* 5 Hz), 5.09 (2 H, s), 4.76–4.37 (2 H, m, $^3J_{H,H}$=4.25 and 3.86 Hz, $^2J_{H,H}$=9.65 Hz, $J_{H,F}$=46.9 Hz), 4.35–4.15 (1 H, m), 3.09 (2 H, d, $J_{H,H}$=7.0 Hz), and 2.42 (3 H, s); ^{13}C NMR ($CDCl_3$) δ: 155.5, 142.0, 139.7, 136.0, 130.2, 128.5, 128.2, 128.1, 124.1, 83.7 (d, $J_{C,F}$=173.9 Hz), 67.0, 57.4, 47.7 (d, $J_{C,F}$=20.4 Hz), 21.4; ^{19}F NMR ($CDCl_3$) δ: −230.9 (dt, *J*=24.0 and 46.9 Hz). Anal. Calcd. for $C_{18}H_{20}FNO_3S$: C, 61.87; H, 5.77; N, 4.01%. Found: C, 61.86; H, 5.81; N, 4.00.

*Pummerer rearrangement performed on (2*R,R$_S$*)-5: synthesis of (*S*)-2-(N-benzyloxycarbonyl)amino-3-fluoro-1-propanol* **7**

To a stirred solution of (2*R*,*R*$_S$)-**5** (0.40 g, 1.20 mmol) and *sym*-collidine (0.48 ml, 3.59 mmol) in 4.0 ml of acetonitrile, under nitrogen at 0°C, was added TFAA (0.84 ml, 5.98 mmol). The reaction mixture was stirred at 0°C and after 10 min 0.5 ml of water were added, followed by solid K_2CO_3 until pH 7

was reached. After 10 min an excess of $NaBH_4$ (about 3 equiv.) was added portionwise at 0°C. The reaction was warmed up at rt and stirred for 20 min, then quenched with a saturated aqueous solution of NH_4Cl and extracted with ethyl acetate. The collected organic layers were treated twice with a 1 N aqueous solution of HCl (4 ml) in order to remove the excess of *sym*-collidine and then washed with aqueous $NaHCO_3$. The collected organic phases were dried over anhydrous Na_2SO_4 and filtered, and the solvent was removed under reduced pressure. FC of the crude mixture (6:4 hexane/ethyl acetate) afforded 0.26 g of (*S*)-**7** as a white solid (94.2%). M.p. 82.5–83.0°C (*i*-Pr_2O); $[\alpha]_D^{20}$ +1.89 (*c* 1.35, $CHCl_3$); IR: 3460, 3350, 3302, 1691, 1549, 1354, 1307, and 1275 cm^{-1}; MS (EI, 70 eV) m/z 228 (M^+, 30), 184 (9), 152 (9), 108 (89), and 91 (100); ^1H NMR ($CDCl_3$), δ: 7.40–7.34 (5 H, m), 5.33–5.24 (1 H, br signal), 5.13 (2 H, s), 4.73–4.39 (2 H, m, $^3J_{H,H}$=3.7 and 4.6 Hz, $^2J_{H,H}$=9.2 Hz, $J_{H,F}$=47.3 Hz), 4.07–3.70 (3 H, m), and 2.14 (1 H, br t); ^{19}F NMR ($CDCl_3$), δ: −232.8 (dt, *J*=22.9 and 47.3 Hz). Anal. Calcd. for $C_{11}H_{14}FNO_3$: C, 58.14; H, 6.21. Found: C, 57.91; H, 6.24; N, 6.10.; N, 6.16.

Oxidation of the primary alcoholic group: synthesis of (S)*-2-*(N*-benzyloxycarbonyl)amino-3-fluoropropanoic acid* **8**

To a solution of (*S*)-**7** (0.19 g, 0.84 mmol) in 5 ml of a 3:2 acetone/water mixture was added solid $NaIO_4$ (0.36 g, 1.7 mmol) followed by $RuO_2 \cdot xH_2O$ (52 mg, 0.25 mmol). The mixture was stirred at rt for 2 h and then quenched with 4 ml of *i*-PrOH. The suspension was filtered through a Celite pad, and the filtrate was concentrated under reduced pressure. The crude product was dissolved in ethyl acetate (4 ml) and extracted 3 times with 4 ml of a 5% aqueous solution of $NaHCO_3$. The collected aqueous phases were treated with 1 N HCl until an acidic pH was reached. The mixture was then extracted with ethyl acetate, then the solvent was removed at reduced pressure. The residue was purified by FC (hexane/ethyl acetate from 3:2 to 2:3) affording 110 mg of (*S*)-**8** as a solid (54%). M.p. 106–108°C (hex/AcOEt); $[\alpha]_D^{20}$ −26.5 (*c* 0.93, $CHCl_3$); IR: 3362, 3140, 1740, 1648, 1542, 1207, 1067, and 1025 cm^{-1}; MS (EI, 70 eV) m/z 241 (M^+, 6), 198 (5), 108 (90), and 91 (100); ^1H NMR ($CDCl_3$), δ: 8.57 (1 H, br signal), 7.42–7.32 (5 H, m), 5.67 (1 H, d, $J_{H,H}$=8.2 Hz), 5.15 (2 H, s), and 5.02–4.53 (3 H, m); ^{19}F NMR ($CDCl_3$), δ: −231.8 (dt, *J*=33.6 and 45.8 Hz).

Deprotection of the amino group of (S)*-8: synthesis of* (S)*-2-amino-3-fluoropropanoic acid (3-fluoro-*D*-alanine)*

To a stirred solution of (*S*)-**8** (77 mg, 0.32 mmol) in 4 ml of absolute ethanol about 300 mg of Raney Ni were added, and the slurry was vigorously stirred for 4 h under hydrogen at rt. About 5 ml of water were added and Raney Ni was removed by filtration on a Celite pad. A 1 N HCl solution was added to the filtrate until an acidic pH was reached. The solvent was removed under reduced pressure and the resulting residue was purified with DOWEX 50W X8-400 resins, eluting with water until the collected fractions (2 ml) reached an almost neutral pH, then with a 7.5% aqueous ammonia solution. The first two fractions contained (*S*)-**9** (purple spot with ninhydrin), which was obtained as a white crystalline solid (25 mg, 73%). M.p. 167–168°C dec. (H_2O);[11] $[\alpha]_D^{20}$ −10.41 (*c* 0.49, 1 N HCl);[11] ^1H NMR (D_2O), δ: 4.97 (1 H, ddd, $^3J_{H,H}$=4.8 Hz, $^2J_{H,H}$=10.8 Hz, $J_{H,F}$=46.1 Hz), 4.89 (1 H, ddd, $^3J_{H,H}$=2.8 Hz, $^2J_{H,H}$=10.8 Hz, $J_{H,F}$=47.3 Hz), and 4.11 (1 H, ddd, $^3J_{H,H}$=4.8 and 2.8 Hz, $J_{H,F}$=29.3 Hz); ^{19}F NMR (D_2O), δ: −227.93 (ddd, $J_{H,F}$=29.3, 46.1 and 47.3 Hz.

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