Asymmetric Syntheses via Heterocyclic Intermediates; XIX[1]. On the Enantioselective Synthesis of β-Fluorovaline Methyl Ester and Related α-Amino-β-fluorocarboxylic Esters

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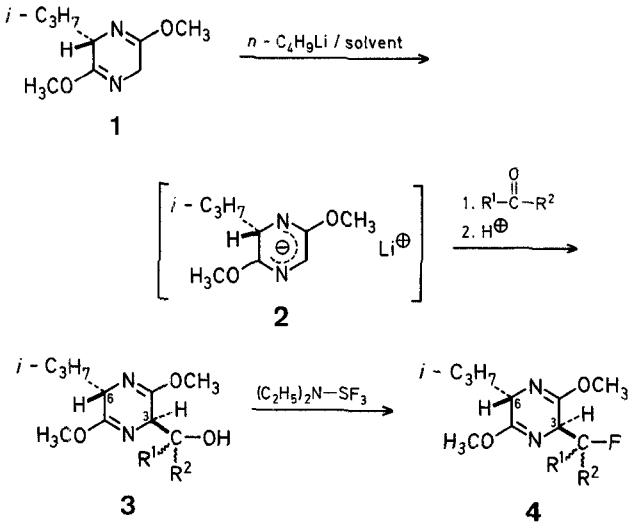
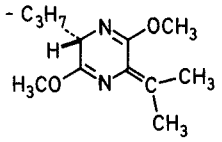
Optically active non-proteinogenic amino acids deserve attention because of their biological activity. β-Fluoro-substituted amino acids are generally regarded as potential inhibitors of pyridoxal phosphate-depending enzymes[2]. The F-atom is rather small; it is comparable to hydrogen on the size scale of enzymes. Thus, the enzyme accepts the fluorinated amino acid as a substrate but is unable to metabolize it properly[2-5].

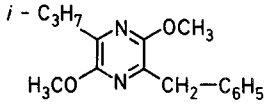
This communication describes primarily the asymmetric synthesis of optically (practically) pure methyl (*R*)-β-fluorovali-



3,4	R¹	R²
a	CH_3	CH_3
b	H	C_6H_5
c	CH_3	C_6H_5
d	H	H



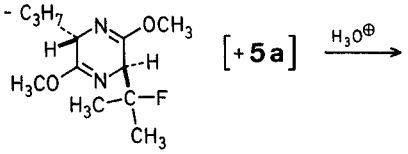
5a



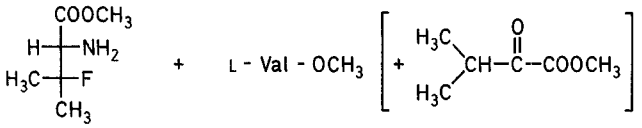
6b

nate (**7a**)[6] and methyl (2*R*)-β-fluorophenylalaninate (**7b**; ~6:1 diastereomer mixture, one diastereomer optically nearly pure). The synthesis is based on the observation[7,1] that acetone reacts with the lithiated bislactim ether **2** of cyclo(L-Val-Gly) (**1**) with essentially complete asymmetric induction[7] and with benzaldehyde with ~85% induction[1] at C-3 to give the products **3a** and **3b** with (3*R*)-configuration. These aldol-type products on treatment with diethylaminosulfur trifluoride [DAST, $(C_2H_5)_2N{-}SF_3$][8] yield the fluoro compounds **4**. Side products are the 3-isopropylidenedihydropyrazine **5a** or the pyrazine derivative **6b**, respectively.

Acid hydrolysis of **4a/5a** (81:19) affords methyl (*R*)-β-fluorovalinate (**7a**), methyl L-valinate (**8**), and (from **5a**) methyl 3-methyl-2-oxobutanoate (**9a**). Product **9a** can be extracted from the acid aqueous solution; products **7a** and **8** are separable by chromatography, **7a** being optically pure by N.M.R.-standard [^{1}H-N.M.R. in $CDCl_3$, Eu(hfc)$_3$ as chiral shift reagent].

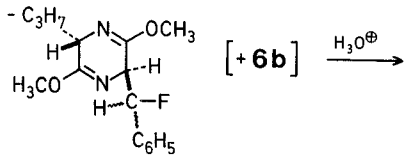


4a

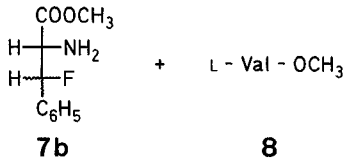


7a **8** **9a**

On hydrolysis of product **4b** + side product **6b** (ratio: 51/49), a 15.8:2.8:1 mixture of (2*R*,3*S*):(2*R*,3*R*):(2*S*,3*S*)-β-fluorophenylalanine methyl ester (**7b**) is formed together with **8**. After extraction of **6b**, the mixture of the amino acid esters **7b** and **8** are separable by bulb-to-bulb distillation.



4b



7b **8**

Compound **3c** (d.e. at C-3: >95%[8]; obtained from **2** and acetophenone) reacts with diethylaminosulfur trifluoride to give fluoro derivative **4c** as a ~12:1 mixture of (3*R*,6*S*,3′*S*)-**4c** and (3*R*,6*S*,3′*R*)-**4c**[9] (d.e. at C-3: >95%), essentially without side products. Compound **3d** (from **2** and formaldehyde[10]) cannot be converted into **4d** using diethylaminosulfur trifluoride. Product **4d** can be obtained in ~80% yield, however, from **2** and fluoroiodomethane, though with only ~45% asymmetric induction at C-3.

Compound **1** is prepared according to Ref.[11], diethylaminosulfur trifluoride (DAST) according to Ref.[8], and compounds **3a, b, c** are prepared according to Ref.[7,1].

(3*R*,6*S*)-2,5-Dimethoxy-3-(2-fluoropropyl)-6-isopropyl-3,6-dihydropyrazine (4a):

A solution of compound **3a** (1.09 g, 4.5 mmol) in dichloromethane (10 ml) is added dropwise to a stirred solution of DAST (0.81 g, 5 mmol) in dichloromethane (10 ml) at −70 °C. The mixture is then allowed to warm to room temperature and stirring is continued for 1 h. Concentrated aqueous sodium hydrogen carbonate is cautiously added with stirring until pH 7–9 is reached. The layers are separated and the aqueous layer is extracted with dichloromethane (~5 ml). The organic layers are combined, dried with magnesium sulfate, and evaporated in vacuo. The crude product **4a** (containing **5a**) thus obtained is submitted to hydrolysis.

Methyl (*R*)-β-Fluorovalinate (7a):

The crude mixture of **4a** and **5a** (see above) is suspended in 0.25 normal hydrochloric acid (36 ml, 9 mmol) and the suspension stirred for ~8 h at room temperature. The mixture is then extracted with ether (5–10 ml), the ethereal layer discharged, and the aqueous phase concentrated in vacuo to a volume of 2–3 ml. To the residue, ether (~20 ml) is added followed, under vigorous shaking, by concentrated aqueous ammonia till pH 8–10. The layers are separated and the aqueous layer is extracted with ether (3 × 10 ml). The combined ether layers are dried with magnesium sulfate and evaporated in vacuo. The residue consists of a ~1.2/1 mixture of **8** and **7a**. This mixture is low-pressure chromatographed (~1 atm; column 60 × 1.5 cm) using ethyl acetate/methanol (19/1) as eluent (**7a**: R_f = 0.41; **8**: R_f = 0.29). The eluted product **7a** is bulb-to-bulb distilled; yield: 0.31 g (46%, based on **3a**); b.p. 80–90 °C/8–10 torr; $[\alpha]_D^{20}$: −36.6° (*c* 1.4, ethanol); e.e.: >95% [only one OCH_3 signal in the ^{1}H-N.M.R. spectrum with Eu(hfc)$_3$].

$C_6H_{12}FNO_2$	calc.	C 48.31	H 8.11
(149.2)	found	48.42	8.21

I.R. (film): ν = 3500–3200 (NH_2); 1735 (C=O); 1600 cm^{-1} (br., NH_2).

^{1}H-N.M.R. ($CDCl_3$/TMS_{int}): δ = 1.43, 1.47 [2d, $^3J_{HF}$ = 22 Hz, $(CH_3)_2CF$]; 1.86 (s, NH_2); 3.61 (d, $^3J_{HF}$ = 11 Hz, α-H); 3.78 ppm (s, OCH_3).

^{19}F-N.M.R. ($CDCl_3$/$C_6F_{6\,int}$): δ = +16.75 ppm (dsp, J_{HF} = 11.6 Hz, 21.9 Hz).

(3*R*,6*S*,3′*S*,*R*)-2,5-Dimethoxy-3-(α-fluorobenzyl)-6-isopropyl-3,6-dihydropyrazine (4b):

Prepared in the same manner as **4a** from compound **3b**[1] (0.96 g, 3.3 mmol) and DAST (0.58 g, 3.6 mmol). A 45/55 mixture of **4b** and **6b** (0.89 g) is obtained and submitted to hydrolysis.

^{1}H-N.M.R. ($CDCl_3$/TMS_{int}) of **4b**: δ = 5.89 ppm (dd, *J* = 3 Hz, 46 Hz, CHF).

Methyl (2*R*)-β-Fluorophenylalaninate (7b):

The crude mixture **4b** + **6b** (see above) is suspended in 0.25 normal hydrochloric acid (26.4 ml, 6.6 mmol) and the suspension stirred for 5 h at room temperature. Work-up is as described for **7a**. The crude product is bulb-to-bulb distilled and methyl L-valinate (**8**) removed as forerun; yield of **7b**: 0.24 g (40% based on **3b**); b.p. 130–140 °C (bath)/0.2 torr. The product has the following composition [determined ^{1}H-N.M.R.-spectrometrically using Eu(hfc)$_3$]: (2*R*,3*S*)-**7b**/(2*R*,3*R*)-**7b**/(2*S*,3*S*)-**7b** = 15.8/2.8/1; the isomer (2*S*,3*R*)-**7b** was not detectable, i.e., the main diastereoisomer (2*R*,3*S*)-**7b** (*threo*) is >95% optically pure.

$C_{10}H_{12}FNO_2$	calc.	C 60.91	H 6.13
(179.2)	found	60.96	6.09

I.R. (film): ν = 3450–3200 (NH_2); 1740 cm^{-1} (C=O).

^{1}H-N.M.R. ($CDCl_3$/TMS_{int}): δ = 3.79 (s, OCH_3); 3.83 (dd, *J* = 3.5 Hz, 26 Hz, α-H); 5.85 ppm (dd, *J* = 3.5 Hz, 46 Hz, CHF).

^{19}F-N.M.R. ($CDCl_3$/$C_6F_{6\,int}$): δ = −20.19 [dd, *J* = 4.5 Hz, 11.4 Hz, C_6H_5—CHF, (2*R*,3*R*/2*S*,3*S*)]; 33.48 ppm [dd, *J* = 46.2 Hz, 26.2 Hz, CHF, (2*R*,3*S*)]; intensity ratio ~1:4.

(3*R*,6*S*,3'*SR*)-2,5-Dimethoxy-3-(1-fluoro-1-phenylethyl)-6-isopropyl-3,6-dihydropyrazine (4c):

Prepared in the same manner as **4a** from compound **3c**[1] (0.55 g, 1.8 mmol; d.e. at C-3: >95%) and DAST (0.32 g, 2 mmol); yield of **4c**: 0.53 g (96%); b.p. 120–130 °C (bath)/0.5 torr; (3*R*,6*S*,3'*S*)-**4c**/(3*R*,6*S*,3'*R*)-**4c** ≈ 12/1; the (3*S*)-diastereoisomer is not detectable (^{1}H- and ^{13}C-N.M.R.).

$C_{17}H_{23}FN_2O_2$	calc.	C 66.65	H 7.57
(306.4)	found	67.14	7.67

^{1}H-N.M.R. ($CDCl_3$/TMS_{int}): δ = 0.66, 1.06 [2d, $CH(CH_3)_2$]; 1.27 [d, J = 1.5 Hz, 3'-CH_3, (3*R*,6*S*,3'*S*)]; 1.64 [d, J = 1.5 Hz, 3-CH_3, (3*R*,6*S*,3'*R*)]; 3.68, 3.75 [2s, OCH_3, (3*R*,6*S*,3'*S*)]; 3.71, 3.79 [2s, OCH_3, (3*R*,6*S*,3'*R*)]; 5.54 [d, J = 45 Hz, CHF, (3*R*,6*S*,3'*S*)]; 5.63 ppm [d, J = 45 Hz, CHF, (3*R*,6*S*,3'*R*)].

^{13}C-N.M.R. ($CDCl_3$/TMS_{int}) [of (3*R*,6*S*,3'*S*)-**4c**]: δ = 16.68, 19.38 [$CH(CH_3)_2$]; 24.34 (d, 3'-CH_3); 60.71 (6-CH); 61.24 (d, C-3); 96.98 ppm (d, CHF); [of (3*R*,6*S*,3'*R*)-**4c**]: δ = 24.72 (d, 3'-CH_3); 60.66 (6-C); 96.16 ppm (d, CHF).

^{19}F-N.M.R. ($CDCl_3$/$C_6F_{6\,int}$): δ = −18.12 ppm [dq, J = 44.9 Hz, 1.5 Hz, CHF, (3*R*,6*S*,3'*S*)-**4c**].

(3*RS*,6*S*)-2,5-Dimethoxy-3-fluoromethyl-6-isopropyl-3,6-dihydropyrazine (4d):

A solution of compound **2** in tetrahydrofuran (4 ml) is prepared from dihydropyrazine **1** (0.22 g, 1.2 mmol) and 1.8 normal butyllithium in hexane (0.8 ml) as described in Ref.[11]. To this, a solution of fluoroiodomethane (0.19 g, 1.2 mmol) in tetrahydrofuran (2 ml) is added by syringe and the mixture is stirred for 8 h at −70 °C. The solvent is then evaporated in vacuo and the residue shaken with ether (10 ml) + water (10 ml). The layers are separated and the aqueous layer is extracted with ether (2 × 10 ml). The combined organic layers are dried with magnesium sulfate, the solvent is evaporated, and the residual product is submitted to bulb-to-bulb distillation; yield: 0.21 g (80%); b.p. 80–90 °C (bath)/0.2 torr. The product **4d** thus obtained is not analytically pure (it was clearly identified by mass-, ^{1}H-N.M.R., and ^{13}C-N.M.R. spectrometry, however).

$C_{10}H_{17}FN_2O_2$ (216.3)

M.S. (70 eV): m/e = 216 ($M^{\oplus}$).

I.R. (film): ν = 1685 cm^{-1} (C=N).

^{1}H-N.M.R. ($CDCl_3$/TMS_{int}): δ = 0.74, 1.01 [2d, $CH(CH_3)_2$]; 4.59, 4.77 (AB of ABXY, CH_2F); 3.70, 3.7 ppm (2s, OCH_3).

^{13}C-N.M.R. ($CDCl_3$/TMS_{int}): δ = 16.96, 19.07; 16.58, 19.01 [$CH(CH_3)_2$ of (3*R*) and (3*S*)], 56.63, 56.87 [2d, J = 20 Hz, 3-C, (3*R*), (3*S*)]; 83.75, 84.18 ppm [2d, J = 174 Hz, CHF, (3*S*), (3*R*)].

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9 The (3*R*,6*S*,3'*S*)/(3*R*,6*S*,3'*R*) ratio of **3c** is different from the one of **4c**. Some epimerisation takes place at C-3'. This indicates a carbenium ion-pair mechanism for the "fluorodehydroxylation" with DAST, cf. Ref.[8].

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