

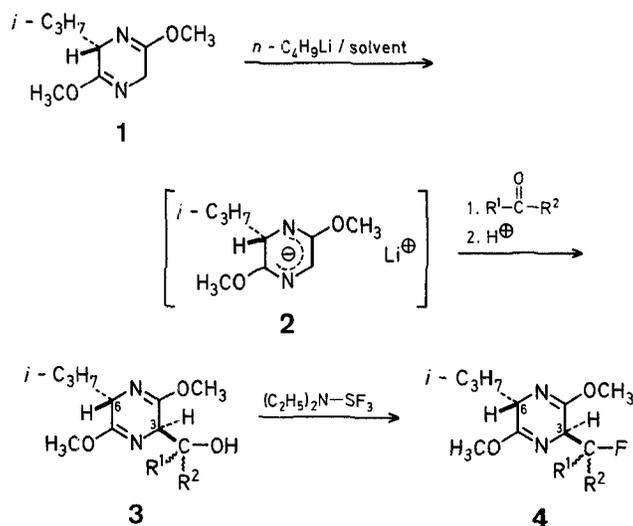
**Asymmetric Syntheses via Heterocyclic Intermediates;
XIX¹. On the Enantioselective Synthesis of β -
Fluorovaline Methyl Ester and Related α -Amino- β -
fluorocarboxylic Esters**

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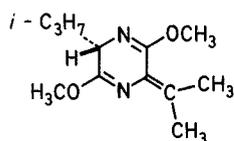
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Optically active *non-proteinogenic amino acids* deserve attention because of their biological activity. β -Fluoro-substituted amino acids are generally regarded as potential inhibitors of pyridoxal phosphate-dependent enzymes². The F-atom is rather 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 properly²⁻⁵.

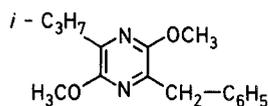
This communication describes primarily the asymmetric synthesis of optically (practically) pure methyl (*R*)- β -fluorovali-



3,4	R ¹	R ²
a	CH ₃	CH ₃
b	H	C ₆ H ₅
c	CH ₃	C ₆ H ₅
d	H	H



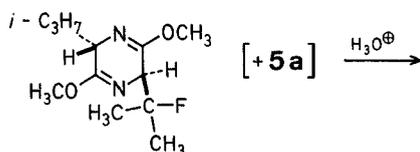
5a



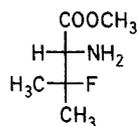
6b

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 induction⁷ and with benzaldehyde with ~85% induction¹ at C-3 to give the products **3a** and **3b** with (3*R*)-configuration. These aldol-type products on treatment with diethylaminosulfur trifluoride [DAST, (C₂H₅)₂N-SF₃]⁸ yield the fluoro compounds **4**. Side products are the 3-isopropylidenedihydropyrazine **5a** or the pyrazine derivative **6b**, respectively.

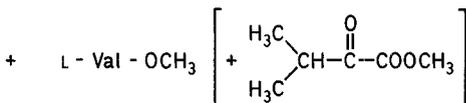
Acid hydrolysis of **4a/5a** (81:19) affords methyl (*R*)- β -fluorovalinate (**7a**), methyl L-valinate (**8**), and (from **5a**) methyl 3-methyl-2-oxobutanoate (**9a**). Product **9a** can be extracted from the acid aqueous solution; products **7a** and **8** are separable by chromatography, **7a** being optically pure by N.M.R.-standard [¹H-N.M.R. in CDCl₃, Eu(hfc)₃ as chiral shift reagent].



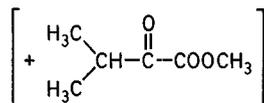
4a



7a

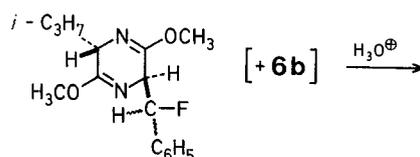


8

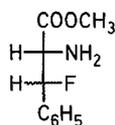


9a

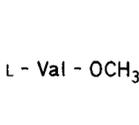
On hydrolysis of product **4b** + side product **6b** (ratio: 51/49), a 15.8:2.8:1 mixture of (2*R*,3*S*):(2*R*,3*R*):(2*S*,3*S*)- β -fluorophenylalanine methyl ester (**7b**) is formed together with **8**. After extraction of **6b**, the mixture of the amino acid esters **7b** and **8** are separable 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 formaldehyde¹⁰) cannot be converted into **4d** using diethylaminosulfur trifluoride. Product **4d** can be obtained in ~80% yield, however, from **2** and fluoriodomethane, 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 x 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 x 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; [α]_D²⁰: -36.6° (c 1.4, ethanol); e.e.: >95% [only one OCH₃ signal in the ¹H-N.M.R. spectrum with Eu(hfc)₃].

C ₆ H ₁₂ FNO ₂	calc.	C 48.31	H 8.11
(149.2)	found	48.42	8.21

I.R. (film): ν =3500-3200 (NH₂); 1735 (C=O); 1600 cm⁻¹ (br., NH₂).

¹H-N.M.R. (CDCl₃/TMS_{int}): δ =1.43, 1.47 [2d, ³J_{HFF}=22 Hz, (CH₃)₂CF]; 1.86 (s, NH₂); 3.61 (d, ³J_{HFF}=11 Hz, α -H); 3.78 ppm (s, OCH₃).

¹⁹F-N.M.R. (CDCl₃/C₆F₆_{int}): δ =+16.75 ppm (dsp, J_{HFF}=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.

¹H-N.M.R. (CDCl₃/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 ¹H-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 (NH₂); 1740 cm⁻¹ (C=O).

¹H-N.M.R. (CDCl₃/TMS_{int}): δ =3.79 (s, OCH₃); 3.83 (dd, J=3.5 Hz, 26 Hz, α -H); 5.85 ppm (dd, J=3.5 Hz, 46 Hz, CHF).

¹⁹F-N.M.R. (CDCl₃/C₆F₆_{int}): δ =-20.19 [dd, J=4.5 Hz, 11.4 Hz, C₆H₅-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.

(3R,6S,3'S)-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; (3R,6S,3'S)-**4c**/(3R,6S,3'R)-**4c** ≈ 12/1; the (3S)-diastereoisomer is not detectable (¹H- and ¹³C-N.M.R.).

C ₁₇ H ₂₃ FN ₂ O ₂	calc.	C 66.65	H 7.57
(306.4)	found	67.14	7.67

¹H-N.M.R. (CDCl₃/TMS_{int}): δ = 0.66, 1.06 [2 d, CH(CH₃)₂]; 1.27 [d, J = 1.5 Hz, 3'-CH₃, (3R,6S,3'S)]; 1.64 [d, J = 1.5 Hz, 3-CH₃, (3R,6S,3'R)]; 3.68, 3.75 [2 s, OCH₃, (3R,6S,3'S)]; 3.71, 3.79 [2 s, OCH₃, (3R,6S,3'R)]; 5.54 [d, J = 45 Hz, CHF, (3R,6S,3'S)]; 5.63 ppm [d, J = 45 Hz, CHF, (3R,6S,3'R)].

¹³C-N.M.R. (CDCl₃/TMS_{int}) [of (3R,6S,3'S)-**4c**]: δ = 16.68, 19.38 [CH(C₂H₅)₂]; 24.34 (d, 3'-CH₃); 60.71 (6-CH); 61.24 (d, C-3); 96.98 ppm (d, CHF); [of (3R,6S,3'R)-**4c**]: δ = 24.72 (d, 3'-CH₃); 60.66 (6-C); 96.16 ppm (d, CHF).

¹⁹F-N.M.R. (CDCl₃/C₆F_{6int}): δ = -18.12 ppm [dq, J = 44.9 Hz, 1.5 Hz, CHF, (3R,6S,3'S)-**4c**].

(3RS,6S)-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-, ¹H-N.M.R., and ¹³C-N.M.R. spectrometry, however).

C₁₀H₁₇FN₂O₂ (216.3)

M.S. (70 eV): m/e = 216 (M⁺).

I.R. (film): ν = 1685 cm⁻¹ (C=N).

¹H-N.M.R. (CDCl₃/TMS_{int}): δ = 0.74, 1.01 [2 d, CH(CH₃)₂]; 4.59, 4.77 (AB of ABXY, CH₂F); 3.70, 3.7 ppm (2 s, OCH₃).

¹³C-N.M.R. (CDCl₃/TMS_{int}): δ = 16.96, 19.07; 16.58, 19.01 [CH(CH₃)₂ of (3R) and (3S)], 56.63, 56.87 [2 d, J = 20 Hz, 3-C, (3R), (3S)]; 83.75, 84.18 ppm [2 d, J = 174 Hz, CHF, (3S), (3R)].

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¹ For part XVIII, see: U. Schöllkopf, U. Groth, M. R. Gull, J. Nozulak, *Liebigs Ann. Chem.* **1983**, in press.

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⁴ A. I. Ayi, M. Remli, R. Guedj, *Tetrahedron Lett.* **1981**, 1505.

⁵ C. Walsh, *Tetrahedron* **38**, 871 (1982).

⁶ For a synthesis of *racem*-β-fluorovaline, see Ref.⁴; for a synthesis of (*R*)-β-fluorovaline (from D-penicillamine), see Ref.³.

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⁸ S. P. v. Halasz, O. Glemser, *Chem. Ber.* **103**, 594 (1970).

W. J. Middleton, *J. Org. Chem.* **40**, 574 (1975).

⁹ The (3R,6S,3'S)/(3R,6S,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.

¹⁰ U. Groth, *Dissertation*, Universität Göttingen, 1981.

¹¹ U. Schöllkopf, U. Groth, C. Deng, *Angew. Chem.* **93**, 791 (1981); *Angew. Chem. Int. Ed. Engl.* **20**, 798 (1981).