Pergamon

Tetrahedron: Asymmetry, Vol. 8, No. 3, pp. 391–398, 1997

Printed in Great Britain

PII: S0957-4166(96)00524-1

0957-4166/97 $17.00 + 0.00

Chemoenzymatic synthesis of enantiomerically pure 4-fluoro-3-nitro and 3-fluoro-4-nitro phenylalanine

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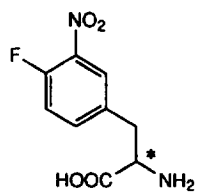
Abstract: Both antipodes of enantiomerically pure 4-fluoro-3-nitrophenylalanine and 3-fluoro-4-nitrophenylalanine were obtained from their corresponding racemates *via* enzymatic resolution. © 1997 Elsevier Science Ltd. All rights reserved.

We have recently developed an efficient macrocyclization method based on intramolecular S_NAr reaction.[1] Formation of a biaryl ether bond with concomitant ring closure characterizes this cyclization methodology.[2] To apply this approach in the synthesis of natural products such as antibiotics of vancomycin family,[3] OF49-49,[4] K-13[5] and antitumor agents RA I–XIV,[6] large quantities of enantiomerically pure 4-fluoro-3-nitrophenylalanine **1**[7] and 3-fluoro-4-nitrophenylalanine **2**[8] were required. Compounds **1** and **2** have been previously synthesized in this laboratory[7,8] *via* diastereoselective alkylation of Schöllkopf's chiral bislactam ether.[9] Although the yield was excellent using our modified procedure, the cost involved was considerable. Furthermore, the fact that both antipodes of enantiomerically pure **1** and **2** (Figure 1) were needed in our synthetic endeavour suggested us to adopt an alternative enzymatic route. Over the last few decades, the enzymatic approach to chiral building blocks has become a very important synthetic methodology due to the peculiar characteristics of the biological catalysts.[10] Here we report the synthesis of enantiomerically pure **1** and **2** in a suitably protected form by way of stereoselective enzymatic hydrolysis of racemic *N*-protected amino acid methyl esters (*RS*)-**9** and (*RS*)-**10**.

(*RS*)-*N*-Trifluoroacetyl-4-fluoro-3-nitro phenylalanine methyl ester **9** was synthesized as shown in Scheme 1.[11] Alkylation of acetamidomalonate with 4-fluoro-3-nitro benzyl bromide **3** gave compound **5** which was decarboxylated to give amino acid hydrochloride **7** in quantitative yield. It is worthy noting that displacement of fluoride *via* S_NAr mechanism was not observed in this alkylation step and this may be explained on the basis of HSAB principle.[12] Esterification of **7** followed by amide formation afforded substrate (*RS*)-**9** (85% overall yield from **3**) ready for enzymatic hydrolysis



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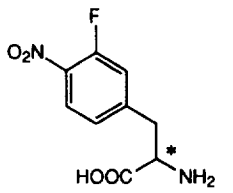

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Figure 1.

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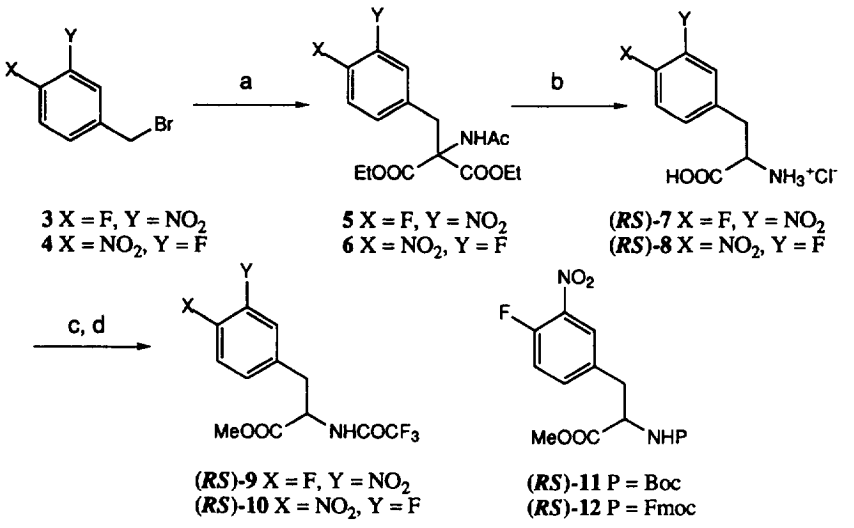


3 X = F, Y = NO_2
4 X = NO_2, Y = F

5 X = F, Y = NO_2
6 X = NO_2, Y = F

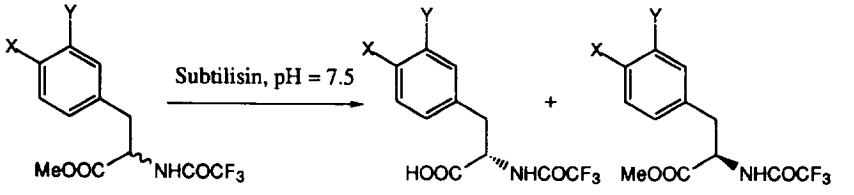
(*RS*)-**7** X = F, Y = NO_2
(*RS*)-**8** X = NO_2, Y = F

(*RS*)-**9** X = F, Y = NO_2
(*RS*)-**10** X = NO_2, Y = F

(*RS*)-**11** P = Boc
(*RS*)-**12** P = Fmoc

Reagents and Conditions: a) NaH, $AcNHCH(COOEt)_2$, DMF, room temperature; b) conc. HCl, reflux; c) $SOCl_2$, MeOH; d) $(CF_3CO)_2O$, Et_3N, CH_2Cl_2, 85% overall yield

Scheme 1.



(*RS*)-**9** X = F, Y = NO_2
(*RS*)-**10** X = NO_2, Y = F

(*S*)-**13** X = F, Y = NO_2
(*S*)-**14** X = NO_2, Y = F

(*R*)-**9** X = F, Y = NO_2
(*R*)-**10** X = NO_2, Y = F

Scheme 2.

studies. Trifluoroacetyl group, which is stable under enzymatic conditions and removable under mild conditions, was used for protecting the amino function.

Based on the literature precedents, subtilisin,[13] a serine protease of wide substrate specificity, was selected for our purpose. We have found that it catalyzes, at pH 7.5, the ester hydrolysis of racemic (*RS*)-**9** selectively to give (*S*)-*N*-trifluoroacetyl 4-fluoro-3-nitro phenylalanine **13** and unreacted (*R*)-*N*-trifluoroacetyl 4-fluoro-3-nitro phenylalanine methyl ester **9** with high enantiomeric excessScheme 2. Figure 2 shows the time course of the hydrolysis resulting from the chiral HPLC monitoring. It is seen that after 6 h at 37°C, the reaction reached 50% conversion and the enantiomeric excess of acid (*S*)-**13** and unreacted ester (*R*)-**9** was determined to be higher than 99% (chiral HPLC analysis, see experimental section). The enzyme is highly enantioselective as it only catalyzes the hydrolysis of *S* enantiomer and a longer reaction time did not affect the conversion nor the enantiomeric purity of hydrolysis product. Blank experiment shows that, without subtilisin, no noticeable hydrolysis occurred under otherwise identical experimental conditions proving the absence of any accompanying chemical hydrolysis. We would like to point out that protease type VIII-A from *Bacillus licheniformis* (Sigma) worked equally well in our present study.

(*RS*)-*N*-Boc-4-fluoro-3-nitrophenylalanine methyl ester **11** and (*RS*)-*N*-Fmoc-4-fluoro-3-

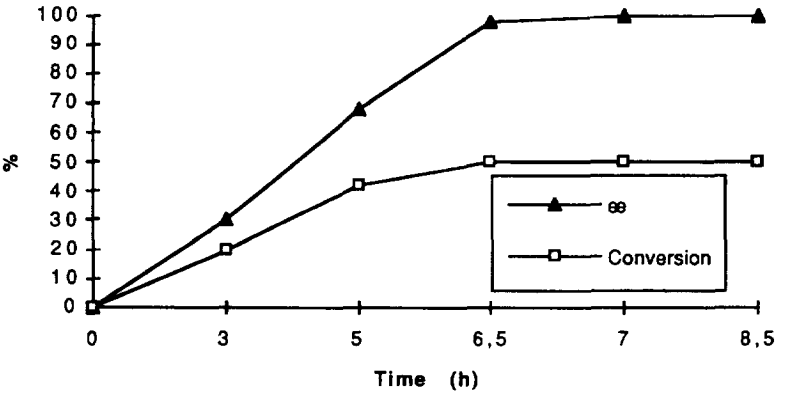


Figure 2. Time course for the subtilisin-catalyzed hydrolysis of (*RS*)-*N*-trifluoroacetyl-4-fluoro-3-nitrophenylalanine methyl ester **9**. The conversion was followed by C18 HPLC while enantiomeric excess of unreacted (*R*)-**9** was analyzed by chiral HPLC: Column: OD, DAICEL; Eluent: heptane/isopropanol=10/1; Flow rate: 1 mL/min; Detection: UV 254 nm.

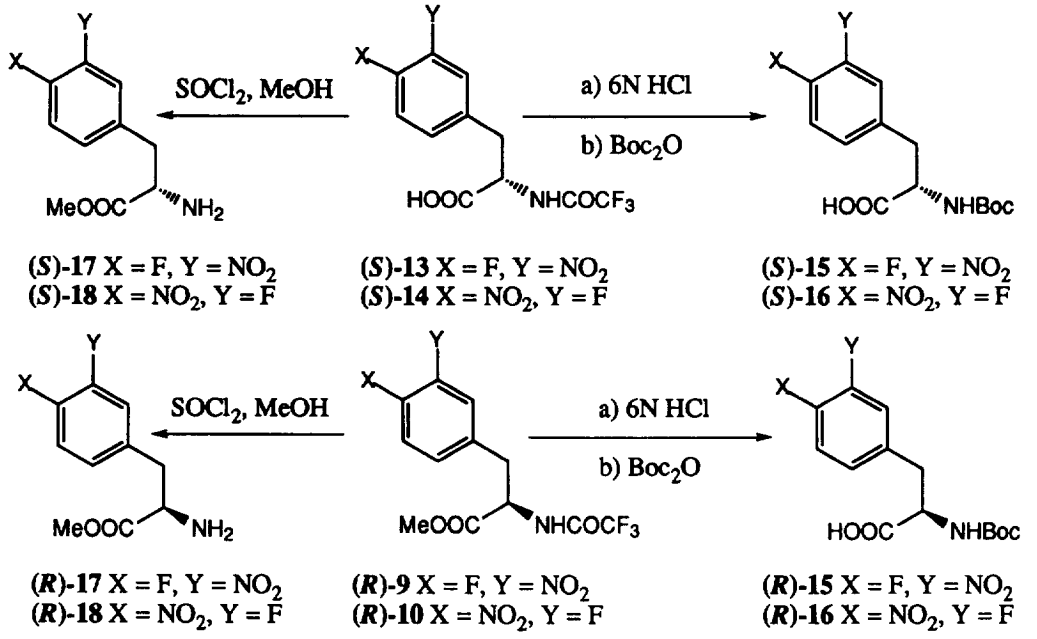
nitrophenylalanine methyl ester **12** (Scheme 1) have also been prepared and tested in the enzymatic process. While the former (*RS*)-**11** experienced enantioselective enzymatic hydrolysis, the overall yield was low due to the partial removal of *N*-Boc group. No hydrolysis of compound (*RS*)-**12** was, however, observed under the conditions employed in these studies. The steric hindrance around ester function of (*RS*)-**12** may be responsible for its inactivity towards the enzyme.

Both compounds (*S*)-**13** and (*R*)-**9** can be easily converted into the corresponding (*S*) or (*R*)-4-fluoro-3-nitrophenylalanine methyl ester and (*S*) or (*R*)-*N*-Boc-4-fluoro-3-nitrophenylalanine in high yields Scheme 3. Thus, simultaneous hydrolysis of methyl ester and trifluoroacetamide (6N HCl, 65°C) of (*R*)-**9** followed by *N-tert* butyloxycarbamate formation under classic conditions (Dioxane–H_2O, Na_2CO_3) afforded (*R*)-**15** in 90% overall yield. When hydrolysis was performed under basic conditions (K_2CO_3, MeOH–H_2O, 60°C) which is frequently used for removal of trifluoroacetyl group, displacement of fluoride by methoxy group occurred as a side reaction. Treament of (*S*)-**13** with $SOCl_2$ in methanol allows for the protection of carboxyl group and deprotection of trifluoroacetamide in a single operation affording the corresponding amino ester (*S*)-**17** in 84% yield. Compounds (*S*)-**15** and (*R*)-**17** were prepared in an identical way. Enantiomeric purities of (*S*)-**15** and (*R*)-**15** were determined (ee >95% by NMR) by its transformation into the corresponding (*S*)-(−)-α-methyl benzamide.

Enantiomerically pure compounds (*R*) and (*S*)-**15** to **18** have been synthesized previously by chemical method and their stereochemistry have been determined unambiguously.[7,8] Thus, the above transformations also led us to assign the absolute configurations of (*R*)-**9**, (*R*)-**10** and (*S*)-**13**, (*S*)-**14** by comparison of the specific rotation with the authentic samples.

(*RS*)-*N*-trifluoroacetyl-3-fluoro-4-nitro phenyl alanine methyl ester **10** was prepared in the same fashion as detailed for (*RS*)-**9** (Scheme 1). In spite of the structural similarity, a significant kinetic difference between **9** and **10** was observed. Thus, while subtilisin only hydrolyzes the (*S*)-**9**, it can hydrolyze both (*R*) and (*S*)-**10** if the reaction time was prolonged (Figure 3). Fortunately, the kinetic preference is great enough so that compounds (*S*)-**14** and (*R*)-**10** can be obtained in high enantiomeric purity when the reaction is quenched at 50% conversion (1.5 h).

In conclusion, we have developed a chemoenzymatic approach for large scale syntheses of enantiomerically pure amino acids **1** and **2**, which constitute useful building blocks for natural product synthesis. The process might also be applicable for preparation of other enantiomeric pure nitro[14] or fluoro[15] substituted aromatic amino acids required for diverse purposes.



Scheme 3.

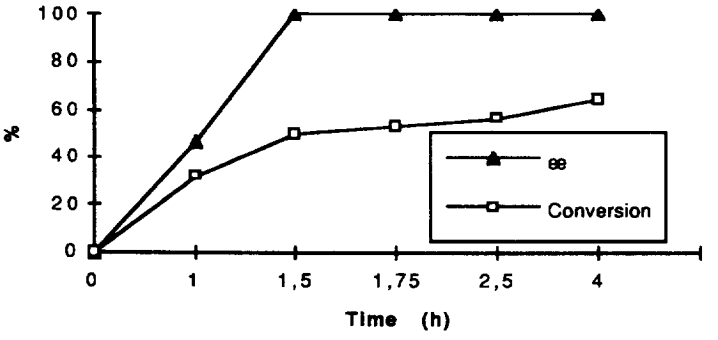


Figure 3. Time course for the subtilisin-catalyzed hydrolysis of *(RS)-N*-trifluoroacetyl-3-fluoro-4-nitrophenylalanine methyl ester **10**. The conversion was followed by C18 HPLC while enantiomeric excess of unreacted *(R)*-**10** was analyzed by chiral HPLC: Column: OD, DAICEL; Eluent: heptane/isopropanol=10/1; Flow rate: 1 mL/min; Detection: UV 254 nm; Temperature: 10°C.

Experimental section

Ethyl 2-(acetylamino)-2-(ethoxycarbonyl)-3-(4'-fluoro-3'-nitrophenyl) propanoate **5**

Sodium hydride (60% in oil, 0.88 g, 22 mmol) was washed with pentane and suspended in DMF (6 mL). A solution of diethyl acetamidomalonate (5.1 g, 23.5 mmol) in DMF (15 mL) and a solution of 4-fluoro-3-nitrobenzyl bromide (**3**, 5 g, 21.36 mmol) in DMF (5 mL) were added successively and the reaction mixture was stirred for 4 h at room temperature. The solvent was removed under reduced pressure. The residue was dissolved in CH_2Cl_2, washed with water, dried over Na_2SO_4, evaporated and purified by flash chromatography (SiO_2, hexane/ether=1/1) to give quantitative yield of **5** as white needles (7.9 g, 21.35 mmol): mp 125°C (CH_2Cl_2/heptane); IR ($CHCl_3$) ν_{max} 3400, 1750, 1680, 1620, 1540, 1500, 1350, 1300 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.30 (t, J=7.0 Hz, 6H, 2 x OCH_2CH_3);

2.06 (s, 3H, $NCOCH_3$), 3.72 (s, 2H, $ArCH_2$), 4.29 (q, J=7.0 Hz, 4H, 2 x OCH_2CH_3); 6.62 (s, 1H, NH), 7.20 (dd, J=10.5, 8.4 Hz, 1H, H-5′), 7.27 (m, 1H, H-6′), 7.72 (dd, J=7.0, 1.8 Hz, H-2′); ^{13}C NMR ($CDCl_3$) δ 14.0, 23.0, 36.7, 63.1, 66.9, 118.4, 127.0 (d, J=18.0 Hz), 132.6 (d, J=3.5 Hz), 137.2, 154.8 (d, J=263 Hz), 167.0, 169.7; MS *m/z* (CI): 371 (M+1), 356, 341, 299; Anal. Calcd for $C_{16}H_{19}FN_2O_7$: C, 51.89; H, 5.17; N, 7.56; Found: C, 52.01; H, 5.08; N, 7.52.

Ethyl 2-(acetylamino)-2-(ethoxycarbonyl)-3-(3′-fluoro-4′-nitrophenyl) propanoate ***6***

Compound **6** was prepared as described for **5**: mp 170–172°C; IR ($CHCl_3$) ν_{max} 3400, 1750, 1680, 1610, 1532, 1490, 1350, 1300 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.23 (t, J=7.5 Hz, 6H, 2×OCH_2CH_3); 2.00 (s, 3H, $NCOCH_3$), 3.67 (s, 2H, $ArCH_2$), 4.21 (q, J=7.5 Hz, 4H, 2×OCH_2CH_3); 6.69 (br s, 1H, NH), 6.90 (m, 2H, H-2′, H-6′), 7.90 (t, J=8.0 Hz, 1H, H-5′); ^{13}C NMR ($CDCl_3$) δ 13.9, 22.9, 37.5, 63.0, 66.7, 119.5, 125.8, 125.9, 136.1, 144.9, 155.0 (d, J=263 Hz), 166.8, 169.7; Ms *m/z* (CI): 371 (M+1), 341, 299; Anal. Calcd for $C_{16}H_{19}FN_2O_7$: C, 51.89; H, 5.17; N, 7.56; Found: C, 52.16; H, 5.38; N, 7.52.

(RS)-N-trifluoroacetyl-4-fluoro-3-nitrophenylalanine methyl ester ***9***

A solution of **5** (7.9 g, 21.35 mmol) in concentrated HCl (50 mL) was refluxed for 20 h. The volatile was evaporated and the residue was dried over P_2O_5 under reduced pressure (4 h). The crude amino acid hydrochloride **7** was added to a solution of $SOCl_2$ (7 mL) in methanol (40 mL) and heated at 40°C for 5 h. The solvent was removed and the crude ester was dissolved in CH_2Cl_2 (40 mL). To this solution were added triethylamine (3 mL, 21.38 mmol) and trifluoroacetic anhydride (3.3 mL, 23.4 mmol). The reaction mixture was stirred for 3 h at room temperature. The solvent was then evaporated under reduced pressure and the residue was purified by flash chromatography (SiO_2, CH_2Cl_2) to afford the racemic amino acid derivative (*RS*)-**9** (6.14 g 18.16 mmol, 85% overall yield from the alkylation step): mp: 113–115°C; IR ($CHCl_3$) ν_{max} 3464, 3395, 1736, 1540 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 3.20 (dd, J=5.9, 14.2 Hz, 1H, $ArCH_2$), 3.35 (dd, J=5.7, 14.2 Hz, 1H, $ArCH_2$), 3.84 (s, 3H, OMe), 4.89 (q, J=5.8 Hz, 1H, $ArCH_2CH$), 7.09 (br s, 1H, NH), 7.27 (dd, J=8.5, 12.1 Hz, 1H, H-5′), 7.41 (m, 1H, H-6′), 7.83 (dd, J=7.0, 2.1 Hz, H-2′); ^{13}C NMR ($CDCl_3$) δ 36.3, 53.3, 53.6, 118.9 (d, J=20.0 Hz), 120 (q, J=280 Hz), 126.8, 132.4 (d, J=5.0 Hz), 136.4, 154.9 (d, J=263 Hz), 170.0; MS *m/z* (CI): 339 (M+1); Anal. Calcd for $C_{12}H_{10}F_4N_2O_5$: C, 42.61; H, 2.98; N, 8.28; Found: C, 42.36; H, 3.06; N, 8.37.

(RS)-Methyl-N-trifluoroacetyl-3-fluoro-4-nitrophenyl alanate ***10***

Compound (*RS*)-**10** was prepared as described for (*RS*)-**9**: mp 76–78°C; IR ($CHCl_3$) ν_{max} 3400, 1755, 1730, 1610, 1535, 1435, 1348 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 3.23 (dd, J=5.8, 14.0 Hz, 1H, $ArCH_2$), 3.40 (dd, J=5.9, 14.0 Hz, 1H, $ArCH_2$), 3.82 (s, 3H, OMe), 4.90 (q, J=5.9, 1H, $ArCH_2CH$), 7.07 (m, 3H, NH, H-2′, H-6′), 8.00 (t, J=7.0 Hz, 1H, H-5′); ^{13}C NMR ($CDCl_3$) δ 37.0, 53.2, 53.4, 115.0 (q, J=284 Hz), 119.0, 125.0, 126.0, 136.0 (d, J=5.0 Hz), 144.0 (d, J=8.7 Hz), 155.0 (d, J=263 Hz), 169.0; MS *m/z* (IC): 339 (M+1); Anal. Calcd for $C_{12}H_{10}F_4N_2O_5$: C, 42.61; H, 2.98; N, 8.28; Found: C, 42.13; H, 3.11; N, 8.16.

Enzymatic resolution of (RS)-N-trifluoroacetyl-4-fluoro-3-nitrophenylalanine methyl ester ***9***

To a biphasic solution of racemic (*RS*)-**9** (3.0 g, 8.87 mmol) in phosphate buffer (pH 7.5, 500 mL) and CH_2Cl_2 (75 mL) was added a solution of subtilisin carlsberg (*Bacillus subtilis*, 40 mL). The mixture was vigorously stirred at 37°C and the reaction course was monitored by HPLC (column: hypersil ODS, 5 μm (250×4.6 mm), eluent: 0.1% of TFA in MeCN, detection: UV 250 nm). The reaction was stopped at the 50%-of-hydrolysis point (6 h) by addition of methanol. The precipitated enzyme was filtered, the volatile was removed under reduced pressure and the aqueous solution was extracted with EtOAc. The organic phases were washed with brine, dried and evaporated to afford the unhydrolysed ester: (*R*)-*N*-trifluoroacetyl-4-fluoro-3-nitrophenylalanine methyl ester **9**, (1.43 g, 47.7%): $[\alpha]_D^{20}$=−86 (*c* 0.5, $CHCl_3$). The aqueous phase was then acidified with citric acid to

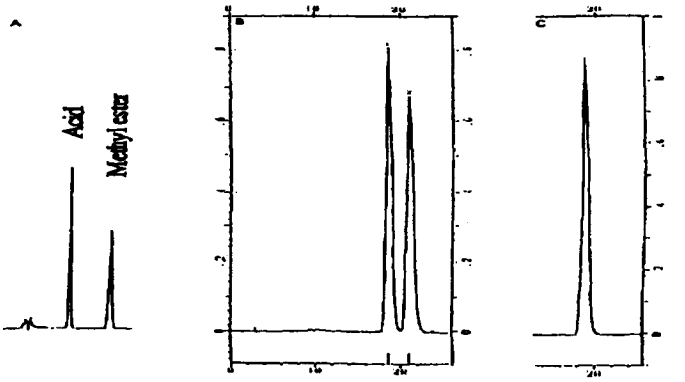


Figure 4. C18 HPLC was used to follow the reaction course (Trace A); Chiral HPLC was used to determine the enantiomeric excess of unhydrolyzed ester (Trace B shows the racemic ester (*RS*)-**9** while trace C shows the enantiomerically pure ester (*R*)-**9** obtained by enzymatic hydrolysis).

pH=4 and extracted with EtOAc. The organic extracts were washed, dried and evaporated to give (*S*)-*N*-trifluoroacetyl-4-fluoro-3-nitrophenylalanine **13** whose enantiomeric purity was determined by conversion into (*S*)-*N*-trifluoroacetyl-4-fluoro-3-nitrophenylalanine methyl ester **9** (1.48 g, 49.3%): $[\alpha]_D^{20}$=+86 (*c* 0.96, $CHCl_3$).

The enantiomeric purity was analyzed on chiral HPLC column [OD, DAICEL (250 x 4.6 mm), eluent: heptane/isopropanol (10/1), detection: UV 250 nm]. The HPLC trace is shown in Figure 4.

Enzymatic resolution of (RS)-N-*trifluoroacetyl-3-fluoro-4-nitrophenylalanine methyl ester* ***10***

Protease type VIII-A from *Bacillus licheniformis* (Sigma) was used for the resolution of **10**. The same procedure detailed above for (*RS*)-**9** was used but the reaction time was reduced to 1.5 h. The (*R*)-*N*-trifluoroacetyl-3-fluoro-4-nitrophenylalanine methyl ester **10** was obtained in 45% yield (*ee*=100% according to chiral HPLC analysis). $[\alpha]_D^{20}$=−80 (c 1.4, $CHCl_3$). (*S*)-*N*-trifluoroacetyl-3-fluoro-4-nitrophenylalanine **14** was obtained in 45% yield whose enantiomeric excess was determined (chiral HPLC analysis) to be 98% and confirmed by its transformation into (*S*)-**18** (*vide supra*).

(R)-N-*Boc-4-fluoro-3-nitrophenylalanine* ***15***

A solution of (*R*)-*N*-trifluoroacetyl-4-fluoro-3-nitrophenylalanine methyl ester **9** (1.00 g, 2.96 mmol) in 6 N HCl (20 mL) was heated to 65°C for 7 h. The volatile was removed under reduced pressure to give analytically pure amino acid hydrochloride (*R*)-**7**. To the solution of so obtained crude product in dioxane (40 mL) and water (20 mL) was added Na_2CO_3 (941 mg, 9 mmol) and Boc_2O (710 mg, 3.2 mmol). After being stirred for 3 h at room temperature, the reaction was diluted with water (120 mL) and extracted with CH_2Cl_2 to remove the neutral species. The aqueous phases were then acidified with citric acid (pH=2–3) and extracted with EtOAc. The organic extracts were washed, dried and evaporated. Purification by flash chromatography (SiO_2, eluent: Heptane/AcOEt/AcOH=20/10/0.5) afforded (*R*)-**15** (0.88 g, 90%): mp 136–138°C; $[\alpha]_D^{20}$=−14 (*c* 0.2, MeOH); IR ($CHCl_3$) 3442, 3300, 2997, 1722, 1650, 1620, 1536, 1500, 1343, 1250, 1170 cm^{-1}; ^1H NMR (200 MHz, CD_3COCD_3) δ 1.32 (s, 9H, ^tBu), 3.08 (dd, *J*=4.6, 14.1 Hz, 1H, ArCH_2), 3.34 (dd, *J*=9.4, 14.1 Hz, 1H, ArCH_2), 4.66 (m, 1H, $ArCH_2CH$), 7.40 (dd, *J*=8.7, 11.0 Hz, 1H, H5′), 7.72 (m, 1H, H6′), 8.03 (d, *J*=6.9 Hz, 1H, H2′); ^{13}C NMR (CD_3COCD_3) δ 31.7, 38.5, 56.6, 80.9, 120.2 (d, *J*=20 Hz), 129.4, 133.8, 137.5 (d, *J*=16 Hz), 139.0, 156.3 (d, *J*=266 Hz), 157.7, 174.7; MS *FAB (NaCl)* 373 ($M+2Na^+-1$); Anal. Calcd for $C_{14}H_{17}FN_2O_6$: C, 51.22; H, 5.22; N, 8.53; Found: C, 50.88; H, 5.60; N, 8.22.

(S)-4-Fluoro-3-nitrophenylalanine methyl ester 17

A solution of (*S*)-*N*-trifluoroacetyl-4-fluoro-3-nitrophenyl alanine **13** (1.00 g, 3 mmol) in MeOH (7 ml) and excess of $SOCl_2$ (1.3 mL) was refluxed for 15 h. The volatile was evaporated and the residue dissolved in water and basified with aqueous K_2CO_3 (pH=7–8). The aqueous solution was extracted with EtOAc. The organic phase was washed, dried and evaporated to give pure (*S*)-4-fluoro-3-nitrophenyl alanine methyl ester **17** in 80% yield: $[\alpha]_D^{20}$=+14.8 (*c* 0.1, $CHCl_3$); IR ($CHCl_3$) 1735, 1537, 1356 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.60 (br s, 2H, NH_2), 2.90 (dd, *J*=13.8, 7.8 Hz, 1H, ArCH_2), 3.13 (dd, *J*=13.8, 5.1 Hz, 1H, ArCH_2), 3.70 (m, 1H, ArCH_2CH), 3.73 (s, 3H), 7.23 (dd, *J*=10.6, 8.5 Hz, 1H, H5′), 7.50 (m, 1H, H6′), 7.93 (dd, *J*=7.1, 2.2 Hz, 1H, H2′); ^{13}C NMR ($CDCl_3$) δ 39.7, 52.3, 55.4, 118.5 (d, *J*=21 Hz), 126.0, 134.0, 136.0, 154.5 (d, *J*=262 Hz), 174; MS *m/z* (CI) 243 (M^++1); Anal. Calcd for $C_{10}H_{11}FN_2O_4$: C, 49.59; H, 4.58; Found: C, 49.36; H, 4.64.

(S)-3-Fluoro-4-nitrophenylalanine methyl ester (18)

$[\alpha]_D^{20}$=+14.6 (*c* 0.7, $CHCl_3$, Lit[8b], $[\alpha]_D^{20}$=+15.0); IR ($CHCl_3$) 3450, 2988, 1738, 1613, 1531, 1269, 1063 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.62 (br s, 2H, NH_2), 2.93 (dd, *J*=7.9, 13.7 Hz, 1H, CH_2Ar), 3.15 (dd, *J*=5.3, 13.7 Hz, 1H,CH_2Ar), 3.73 (m, 1H, ArCH_2CH), 3.74 (s, 3H, OMe), 7.17 (m, 2H, H2′, H6′), 8.02 (t, *J*=8.2 Hz, 1H, H5′); ^{13}C NMR ($CDCl_3$) δ 40.6, 55.3, 68.1, 119.2 (d, *J*=17.0 Hz), 125.5 (d, *J*=30.5 Hz), 126.1, 147.3, 155.5 (d, *J*=211.0 Hz), 174.8; MS *m/z* (CI) 243 (M^++1), 242 (M^+), 189.

Acknowledgements

One of us (C. Vergne) thanks "Ministère de la Recherche et de l'Enseignement Superieur" for a doctoral fellowship.

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(*Received in UK 11 November 1996; accepted 11 December 1996*)