Synthesis of (2*S*)-4,4-difluoroproline, (2*S*,4*R*)-4-fluoroproline and their derivatives from (*S*)-aspartic acid [1]

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Abstract

Syntheses for (2*S*)-4,4-difluoroproline, (2*S*,4*R*)-4-fluoroproline and their derivatives are described starting from (*S*)-aspartic acid, using hexafluoroacetone as the protecting reagent and DAST as the fluorinating agent.

Introduction

(*S*)-Proline is a constituent of a wide variety of peptide hormones (bradykinin, angiotensin, thyroliberin, etc.) [2], and peptide drugs (captopril, enalapril, etc.) [3]. In the tsetse fly, proline is the sole energy source for flight [4]. The first step of this energy-producing process – the oxidation of (*S*)-proline to give Δ^1-pyrroline-5-carboxylic acid – is catalyzed by proline dehydrogenase. Inhibition of this enzyme may be a strategy to control this insect [5]. Hence the development of methodology for the regio- and stereo-selective functionalization of proline is of current interest, *inter alia* for peptide modification and the design of enzyme inhibitors.

Hydrophobic interactions are known to play an important role in the binding of substrates or inhibitors to the active site of an enzyme. For considering this aspect, the substitution of hydrogen in amino acids and other biorelevant compounds by lipophilic substituents such as fluorine is a widely used strategy [6–8].

To date, the syntheses for (2*S*)-4,4-difluoroproline and (2*S*,4*R*)-4-fluoroproline start from (2*S*,4*S*)-4-hydroxyproline [2, 9, 10]. We now report on preparatively simple syntheses in reasonable yield of (2*S*)-4,4-difluoroproline, (2*S*,4*R*)-4-fluoroproline and some of their derivatives starting from (*S*)-aspartic acid, using hexafluoroacetone as the protecting reagent [11–13] and DAST [2, 14, 15] as the fluorinating agent.

Experimental

^{1}H, ^{13}C and ^{19}F NMR spectra were recorded with a Bruker AM 360 spectrometer at 360, 90 and 339 MHz or with a Bruker AC 250 spectrometer at 250, 62.5 and 235 MHz, respectively. TMS was used as reference standard for ^{1}H and ^{13}C NMR spectra (internal) and trifluoroacetic acid for ^{19}F NMR spectra (external). Infrared (IR) spectra were recorded using Perkin-Elmer 157 G or 257 spectrophotometers. Mass spectra were recorded with electron ionization (EI, 70 eV) on a Varian MAT CH5 instrument. Melting points (not corrected) were determined using a Tottoli apparatus (Büchi SMP-20). Elemental micro-analyses were carried out with a Heraeus CHN-Elemental Analyzer.

(5S)-7,7-Difluoro-2,2-bis(trifluoromethyl)-1-aza-3-oxabicyclo[3.3.0]octan-4-one (4)

DAST (1 ml, 7.5 mmol) was injected through a serum cap into a solution of 0.7 g (2.5 mmol) of **3** [16] in 20 ml dry benzene at room temperature under an argon atmosphere. The mixture was stirred for 48 h, diluted with 100 ml $CHCl_3$ and treated with ice/water. The organic layer was washed with $NaHCO_3$ solution and water. After drying with $MgSO_4$, the solvent was removed *in vacuo* and the residue purified by 'Kugelrohr' distillation.

Compound **4**: yield 53%, colourless liquid, b.p. 50 °C/1 Torr, $[\alpha]_D^{21}$: −29.0° (*c* 1.0, $CHCl_3$). IR (film) (cm^{-1}): 1830. ^{1}H NMR ($CDCl_3$) δ: 2.49–2.76 (m, 2H, CH_2); 3.59 (ddd, 1H, CH_2N, $^2J_{HH}$ = 11.9 Hz, $^3J_{HF}$ = 11.9 Hz, $^3J_{HF}$ = 11.9 Hz); 3.74 (ddd, 1H, CH_2N, $^2J_{HH}$ = 11.9 Hz, $^3J_{HF}$ = 11.9 Hz, $^3J_{HF}$ = 11.9 Hz); 4.36 (dd, 1H, CH, $^3J_{HH}$ = 7.7 Hz, $^3J_{HH}$ = 7.7 Hz) ppm. ^{13}C NMR ($CDCl_3$) δ: 36.3 (dd, CH_2, $^2J_{CF}$ = 26.1 Hz, $^2J_{CF}$ = 26.1 Hz); 54.7 (ddq, CH_2N, $^2J_{CF}$ = 31.1 Hz, $^2J_{CF}$ = 31.1 Hz, $^4J_{CF}$ = 2.7 Hz); 58.9 (CH); 91.8 (sept, $C(CF_3)_2$, $^2J_{CF}$ = 36.5 Hz); 119.8 (q, CF_3, $^1J_{CF}$ = 289.1 Hz); 121.1 (q, CF_3, $^1J_{CF}$ = 288.0 Hz); 127.4 (dd, CF_2, $^1J_{CF}$ = 251.9 Hz, $^1J_{CF}$ = 251.9 Hz);

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169.4 (CO) ppm. ^{19}F NMR ($CDCl_3$) δ: −2.79 (q, 3F, CF_3, $^4J_{FF}$ = 9.5 Hz); −5.51 to −5.62 (m, 3F, CF_3); −25.36 to −25.70 (m, 2F, CF_2) ppm. Analysis: Calc. for $C_8H_5F_8NO_2$ (299.12); C, 32.12; H, 1.68; N, 4.68%. Found: C, 32.15; H, 1.80; N, 4.72% MS *m/e*: 230 $(M-CF_3)^+$; 202 $(230-CO)^+$; 69 $(CF_3)^+$.

(2S)-4,4-Difluoroproline (5)

A solution of 0.70 g (2.3 mmol) **4** in 20 ml of a 1:1 2-propanol/water mixture (v/v) was stirred at room temperature for 24 h. The progress of the reaction was monitored by ^{19}F NMR spectroscopy. The reaction mixture was evaporated to dryness *in vacuo*. The residue was triturated with 20 ml ether (3×) and recrystallized from ethanol/water.

Compound **5**: yield 44%, colourless solid, m.p. 247 °C (dec.) after recrystallization from ethanol/water, $[\alpha]_D^{21}$: −35.0° (*c* 1.0, H_2O); lit. value [9]: m.p. 252–256 °C (dec.), $[\alpha]_D^{29}$: −34.5° (*c* 1.0, H_2O). IR (KBr) (cm^{-1}): 3200−2500; 1620; 1595. ^{1}H NMR (D_2O) δ: 2.76 (m_c, 1H, CH_2); 2.97 (m_c, 1H, CH_2); 3.80–3.99 (m, 2H, CH_2N); 4.52 (dd, 1H, CH, $^3J_{HH}$ = 7.4 Hz, $^3J_{HH}$ = 9.2 Hz) ppm. ^{13}C NMR (D_2O) δ: 39.4 (dd, CH_2, $^2J_{CF}$ = 24.7 Hz, $^2J_{CF}$ = 24.7 Hz); 53.1 (dd, CH_2N, $^2J_{CF}$ = 34.7 Hz, $^2J_{CF}$ = 34.7 Hz); 61.9 (CH); 129.2 (dd, CF_2, $^1J_{CF}$ = 248.8 Hz, $^1J_{CF}$ = 248.8 Hz); 174.6 (CO) ppm. ^{19}F NMR (D_2O) δ: −20.13 (CF_a, CF_2, $^2J_{FaFb}$ = 238.8 Hz); −21.65 (CF_b, CF_2, $^2J_{FaFb}$ = 238.8 Hz) ppm; multiplets of higher order. Analysis: Calc. for $C_5H_7F_2NO_2$ (151.10): C, 39.74; H, 4.67; N, 9.27%. Found: C, 39.73; H, 4.67; N, 9.23%. MS *m/e*: 151 $(M)^+$; 107 $(M-CO_2)^+$; 106 $(M-CO_2H)^+$; 86 $(106-HF)^+$.

(S)-4,4-Difluoroproline methyl ester hydrochloride (6)

Compound **4** (0.55 g, 1.8 mmol) was dissolved in 8 ml of dry methanol saturated with HCl gas. The mixture was stirred at room temperature until the reaction was complete (^{19}F NMR analysis). The solvent was removed *in vacuo*, the crude product crystallizing on addition of ethyl acetate.

Compound **6**: yield 55%, colourless solid, m.p. 109 °C, $[\alpha]_D^{21}$: −13.0° (*c* 1.0, H_2O). IR (KBr) (cm^{-1}): 1755. ^{1}H NMR (CD_3OD) δ: 2.80 (m_c, 1H, CH_2); 3.00 (m_c, 1H, CH_2); 3.81–3.87 (m, 2H, CH_2N); 3.89 (s, 3H, OCH_3); 4.87 (dd, 1H, CH, $^3J_{HH}$ = 8.7 Hz, $^3J_{HH}$ = 8.7 Hz) ppm. ^{13}C NMR (CD_3OD) δ: 37.4 (dd, CH_2, $^2J_{CF}$ = 26.2 Hz, $^2J_{CF}$ = 26.2 Hz); 52.1 (dd, CH_2N, $^2J_{CF}$ = 34.7 Hz, $^2J_{CF}$ = 34.7 Hz); 54.4 (OCH_3); 58.8 (dd, CH, $^3J_{CF}$ = 3.8 Hz, $^3J_{CF}$ = 3.8 Hz); 127.6 (dd, CF_2, $^1J_{CF}$ = 249.0 Hz, $^1J_{CF}$ = 249.0 Hz); 168.5 (CO) ppm. ^{19}F NMR (CD_3OD) δ: −21.33 (CF_a, CF_2, $^2J_{FaFb}$ = 240.0 Hz); (CF_b, CF_2, $^2J_{FaFb}$ = 240.0 Hz) ppm; multiplets of higher order. Analysis: Calc. for $C_6H_{10}ClF_2NO_2$ (201.60): C, 35.75; H, 5.00; N, 6.95%. Found: C, 35.30; H, 5.03; N, 6.97%. MS *m/e*: 165 $(M-HCl)^+$; 145 $(165-HF)^+$; 106 $(165-CO_2CH_3)^+$; 86 $(106-HF)^+/(145-CO_2CH_3)^+$.

(S)-4,4-Difluoroprolyl-(S)-phenylalanine t-butyl ester (7)

A solution of 0.45 g (1.5 mmol) **4** and 0.66 g (3 mmol) (*S*)-PheOBu^t was stirred in 5 ml acetonitrile at room temperature until the reaction had reached completion (^{19}F NMR analysis). The solvent was removed *in vacuo* and the crude product purified by chromatography on silica gel (eluent, Et_2O).

Compound **7**: yield 66%, colourless solid, m.p. 119–120 °C, $[\alpha]_D^{21}$: +33.5 (*c* 1.0, $CHCl_3$). IR (KBr) (cm^{-1}): 3360; 2990; 1750; 1655. ^{1}H NMR ($CDCl_3$) δ: 1.44 (s, 9H, $C(CH_3)_3$); 2.23 (m_c, 1H, CH_{2Pro}); 2.30 (brs, 1H, NH); 2.55 (m_c, 1H, CH_{2Pro}); 2.83 (m_c, 1H, CH_2N); 3.04 (dd, 1H, CH_{2Phe}, $^2J_{HH}$ = 13.8 Hz, $^3J_{HH}$ = 6.6 Hz); 3.16 (m_c, 1H, CH_2N); 3.18 (dd, 1H, CH_{2Phe}, $^2J_{HH}$ = 13.8 Hz, $^3J_{HH}$ = 6.1 Hz); 3.88 (dd, 1H, CH_{Pro}, $^3J_{HH}$ = 9.7 Hz, $^3J_{HH}$ = 6.5 Hz); 4.73 (m_c, 1H, CH_{Phe}); 7.13–7.16 (m, 2H, arom.); 7.23–7.30 (m, 3H, arom.); 7.87 (d, 1H, NH, $^3J_{HH}$ = 8.0 Hz) ppm. ^{13}C NMR ($CDCl_3$) δ: 27.9 ($C(CH_3)_3$); 38.0 (CH_{2Phe}); 38.3 (dd, CH_{2Pro}, $^2J_{CF}$ = 25.2 Hz, $^2J_{CF}$ = 25.2 Hz); 52.9 (CH_{Phe}); 53.0 (dd, CH_2N, $^2J_{CF}$ = 29.1 Hz, $^2J_{CF}$ = 29.1 Hz); 58.4 (dd, CH_{Pro}, $^3J_{CF}$ = 2.4 Hz, $^3J_{CF}$ = 6.2 Hz); 82.3 ($C(CH_3)_3$); 127.0, 128.3, 129.4 (C, arom.); 130.3 (dd, CF_2, $^1J_{CF}$ = 247.7 Hz, $^1J_{CF}$ = 253.6 Hz); 136.0 (C, arom.); 170.6, 171.8 (CO, ester, amide) ppm. ^{19}F NMR ($CDCl_3$) δ: −21.90 (dm, CF_a, CF_2, $^2J_{FaFb}$ = 230.0 Hz); −28.15 (ddddd, CF_b, CF_2, $^2J_{FaFb}$ = 230.0 Hz, $^3J_{FH}$ = 12.6 Hz, $^3J_{FH}$ = 6.3 Hz, $^3J_{FH}$ = 6.3 Hz, $^3J_{FH}$ = 6.3 Hz) ppm. Analysis: Calc. for $C_{18}H_{24}F_2N_2O_3$ (354.40): C, 61.00; H, 6.83; N, 7.90%. Found: C, 60.99; H, 6.93; N, 7.83%. MS *m/e*: 298 $(M-CH_2=C(CH_3)_2)^+$; 253 $(M-CO_2Bu^t)^+$; 193 $(298-C_4H_5F_2N)^+$; 192 $(298-C_4H_6F_2N)^+$; 148 $(253-C_4H_5F_2N)^+$; 120 $(148-CO)^+$; 106 $(C_4H_6F_2N)^+$; 86 $(106-HF)^+$; 57 $(Bu^t)^+$.

(S)-4,4-Difluoroprolyl-azaglycine methyl ester (8)

Compound **4** (0.59 g, 2 mmol) and 0.36 g (4 mmol) hydrazinocarboxylic acid methyl ester were stirred in 50 ml acetonitrile. Compound **8** precipitated within 24 h and was obtained analytically pure after filtration and drying *in vacuo*.

Compound **8**: yield, 71%, colourless solid, m.p. 129–130 °C, $[\alpha]_D^{21}$: −27.5° (*c* 1.0, H_2O). IR (KBr) (cm^{-1}): 3270; 3060–2940; 1750; 1670. ^{1}H NMR (CD_3CN) δ: 2.24–2.67 (m, 3H, NH_{Pro}, CH_2); 2.97–3.34 (m, 2H, CH_2N); 3.65 (s, 3H, OCH_3); 3.96 (dd, 1H, CH, $^3J_{HH}$ = 9.3 Hz, $^3J_{HH}$ = 6.1 Hz); 7.24 (brs, 1H, NH); 8.87 (brs, 1H, NH) ppm. ^{13}C NMR (CD_3CN) δ: 39.4 (dd, CH_2, $^2J_{CF}$ = 25.6 Hz, $^2J_{CF}$ = 25.6 Hz); 53.3 (OCH_3); 54.1 (dd, $^2J_{CF}$ = 29.1 Hz, $^2J_{CF}$ = 29.1 Hz); 58.9 (dd, CH_2, $^3J_{CF}$ = 4.0 Hz, $^3J_{CF}$ = 4.0 Hz); 132.6 (dd, CF_2, $^1J_{CF}$ = 247.9 Hz, $^1J_{CF}$ = 247.9 Hz); 157.7 (CO, carbamate); 173.3 (CO,

amide) ppm. ^{19}F NMR (CD_3CN) δ: −20.9 (CF_a, CF_2, $^2J_{FaFb}$ = 229.9 Hz); −24.4 (CF_b, CF_2, $^2J_{FaFb}$ = 229.9 Hz) ppm; multiplets of higher order. Analysis: Calc. for $C_7H_{11}F_2N_3O_3$ (223.18): C, 37.67; H, 4.97; N, 18.83%. Found: C, 37.49; H, 5.06; N, 18.78%. MS *m/e*: 223 $(M)^+$; 106 $(M-CONHNHCO_2CH_3)^+$; 86 $(106-HF)^+$.

(5S,7R)-7-Fluoro-2,2-bis(trifluoromethyl)-1-aza-3-oxabicyclo[3.3.0]octan-4-one (10)

DAST (1 ml, 7.5 mmol) was injected through a serum cap into a solution of 0.7 g (2.5 mmol) **9** [16] in 20 ml dry CH_2Cl_2 at room temperature under an argon atmosphere. The mixture was stirred for 16 h, diluted with 100 ml $CHCl_3$ and treated with ice/water. The organic layer was washed with $NaHCO_3$ solution and water. After drying with $MgSO_4$, the solvent was removed *in vacuo* and the residue purified by 'Kugelrohr' distillation.

Compound **10**: yield 50%, colourless liquid, b.p. 55 °C/0.3 Torr, $[\alpha]_D^{21}$: −86.5° (*c* 1.3, $CHCl_3$). IR (film) (cm^{-1}) 1840. ^{1}H NMR ($CDCl_3$) δ: 2.09 (dddd, 1H, CH_2, $^3J_{HF}$ = 38.8 Hz, $^3J_{HH}$ = 10.1 Hz, $^3J_{HH}$ = 3.9 Hz, $^2J_{HH}$ = 14.3 Hz); 2.60 (ddd, 1H, CH_2, $^3J_{HF}$ = 17.3 Hz, $^3J_{HH}$ = 7.5 Hz, $^2J_{HH}$ = 14.3 Hz); 3.53 (m_c, 1H, CH_2N); 3.61 (m_c, 1H, CH_2N); 4.45 (dd, 1H, CH, $^3J_{HH}$ = 10.0 Hz, $^3J_{HH}$ = 7.5 Hz); 5.41 (dm, CHF, $^2J_{HF}$ = 52.9 Hz) ppm. ^{13}C NMR ($CDCl_3$) δ: 35.2 (d, CH_2, $^2J_{CF}$ = 22.3 Hz); 54.6 (dq, CH_2N, $^2J_{CF}$ = 23.6 Hz, $^4J_{CF}$ = 3.0 Hz); 60.4 (CH); 91.2 (sept, $C(CF_3)_2$, $^2J_{CF}$ = 31.3 Hz); 94.1 (d, CHF, $^1J_{CF}$ = 181.5 Hz); 119.9 (q, CF_3, $^1J_{CF}$ = 289.8 Hz); 120.9 (q, CF_3, $^1J_{CF}$ = 287.5 Hz); 170.3 (CO) ppm. ^{19}F NMR ($CDCl_3$) δ: 5.24 (q, 3F, CF_3, $^4J_{FF}$ = 9.6 Hz); −3.05 (q, 3F, CF_3, $^4J_{FF}$ = 9.6 Hz); −99.91 (m, 1F, CHF) ppm. Analysis: calc. for $C_8H_6F_7NO_2$ (281.13): C, 34.18; H, 2.15; N, 4.98%. Found: C, 34.13; H, 2.23; N, 4.98%. MS *m/e*: 281 $(M)^+$; 237 $(M-CO_2)^+$; 212 $(M-CF_3)^+$; 184 $(212-CO)^+$; 164 $(184-HF)^+$; 69 $(CF_3)^+$; 43 $(CH_2NHCH_2)^+$.

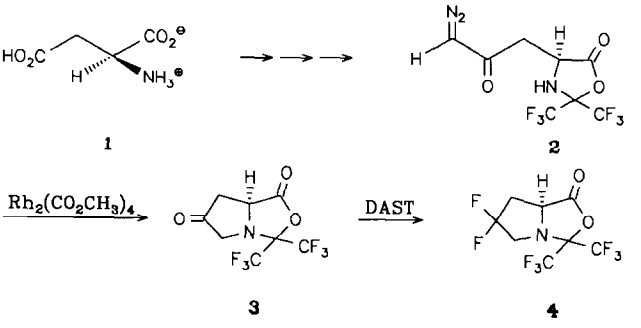
(2S,4R)-4-Fluoroproline (11)

A solution of 0.37 g (1.3 mmol) **10** in 10 ml of a 1:1 2-propanol/water mixture (v/v) was stirred at room temperature until the reaction was complete (^{19}F NMR analysis). The reaction mixture was evaporated to dryness *in vacuo*. The residue was triturated with 10 ml ether and recrystallized from ethanol.

Compound **11**: yield 58%, colourless solid, m.p. 240–241 °C (dec.), $[\alpha]_D^{21} = -92°$ (*c* 1.0, H_2O); lit. value [10]: m.p. 243–245 °C (dec.), $[\alpha]_D^{21} = -87.5 + 1.0°$ (*c* 1.0, H_2O).

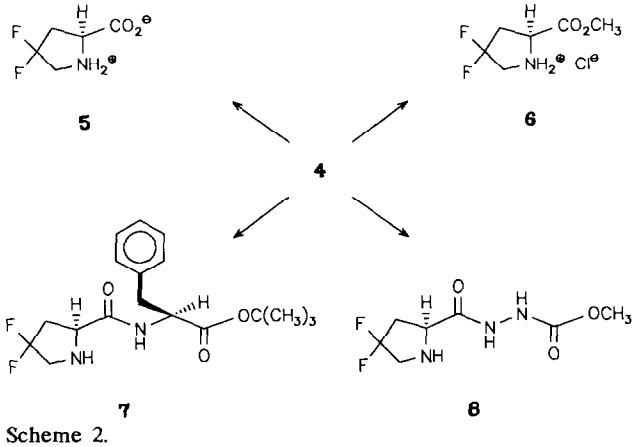
Results and discussion

The diazoketone **2** can be obtained from (*S*)-aspartic acid (**1**) in a three-step procedure [17]. The complete skeleton of (2*S*)-4-ketoproline is already present in **2**, only one single CN bond has to be formed. Compound **2** is transformed into the (2*S*)-4-ketoproline derivative **3** in 73% yield on treatment with dirhodium tetraacetate [16]. Fluorination of **3** can be accomplished in benzene at room temperature using DAST as the fluorinating agent.



Scheme 1.

Compound **4** is an amino-protected, carboxy-activated derivative of (2*S*)-4,4-difluoroproline. (2*S*)-4,4-Difluoroproline (**5**) is obtained from **4** on deprotection under neutral conditions at room temperature with 2-propanol/water. The physical and spectral data are in agreement with literature data [9]. With methanol/HCl, **4** reacts to give the amino acid ester hydrochloride **6** in high yield. Dipeptides e.g. **7** and azadipeptides e.g. **8** are formed on reaction with the appropriate amino compounds. Functionalization of the carboxylic group and deprotection of the amino group are achieved in one step. In this reaction sequence the stereochemistry at C-2 of proline is retained, as shown earlier for similar reactions [13].

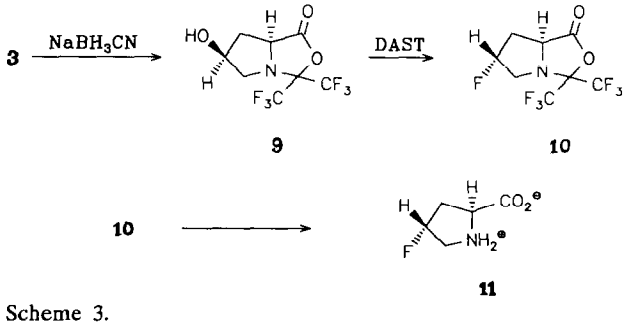


Scheme 2.

Compound **3** has a concave shape, the inside of the 'bowl' being 'filled' with one of the trifluoromethyl groups. Consequently, addition reactions to the carbonyl group occur preferentially from the pro-*R* side. The (2*S*,4*S*)-4-hydroxyproline derivative **9** is the main product of the reduction of **3** with $NaBH_3CN$ (*de* > 86%) [16], which can be transformed into the 4-fluoroproline

derivative **10** on treatment with DAST at room temperature.

The displacement reactions of the hydroxy functions by fluorine on treatment with DAST are S_N2 processes [18]. Hence, the stereochemistry of the bicyclic system **10** should be 5*S*,7*R*. This has been confirmed by a NOESY experiment. Since the absolute configuration at C_α was not changed, the crosspeaks between the proline-H_α ($\delta = 4.45$ ppm) and one H_β ($\delta = 2.60$ ppm) and between the second H_β ($\delta = 2.09$ ppm) and the single H_γ ($\delta = 5.41$ ppm) confirm the postulated stereochemistry of **10**.



Scheme 3.

On stirring in 2-propanol/water, **10** gives the amino acid **11**. The physical and spectra data of **11** are in agreement with literature data [10], proving that all steps of the reaction sequence described occur with retention of configuration at C_α. With amines, the corresponding amides are formed [19].

When the reaction sequence is performed with (*R*)-aspartic acid, the enantiomeric (2*R*)-4,4-difluoro- and (2*R*,4*S*)-4-fluoro-proline derivatives are obtained.

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