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Synthesis of optically pure *N*-Boc-protected (2*R*,3*R*)- and (2*R*,3*S*)-3-fluoroprolines

Luc Demange, Jérôme Cluzeau, André Ménez and Christophe Dugave*

Département d'Ingénierie et d'Etudes des Protéines (DIEP), CEA/Saclay, 91191 Gif-sur-Yvette, France

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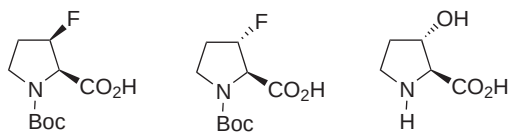
Abstract—Non-protein amino acids (2*R*,3*R*)- and (2*R*,3*S*)-3-fluoroprolines were synthesized as novel probes for studying the *cis*/*trans* isomerization of the amino acyl–proline peptide bond. The *N*-Boc-protected target compounds were obtained as optically pure material starting from (2*S*,3*S*)-3-hydroxyproline.

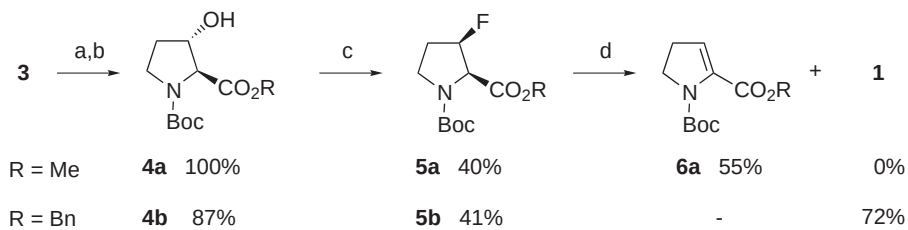
The amino acyl–proline *cis*/*trans* isomerization is a rate-limiting step of protein folding[1] and modulates the biological activity of peptides.[2] Therefore, proline plays a particular role in protein structure and peptide conformation.[3] As a consequence, many proline surrogates have been designed for the study and control of conformational transitions in peptides and proteins.[4] We focused our interest on fluorinated prolines which combine the strong electroattractive effect of fluorine with a low steric hindrance.[5] We describe herein the first synthesis of *N*-Boc-protected (2*R*,3*R*)- and (2*R*,3*S*)-3-fluoroprolines **1** and **2** (Fig. 1).



1 **2** **3**

Figure 1.

The synthesis of optically pure 3-fluoroprolines **1** and **2** was not obvious due to the marked tendency of β-activated amino acids to epimerize or to undergo an α,β-elimination. In a preliminary attempt, the (2*S*,3*S*)-3-hydroxyproline **3**[6] was protected as a Boc-methyl ester derivative **4a** and was fluorinated with DAST (Scheme 1).[7] However, saponification of the methyl ester **5a** with lithium hydroxide led exclusively to the corresponding α,β-dehydroproline **6a**. In order to ensure a complete orthogonality of protection in later steps of the synthesis, compatible with the moderately stable fluorine at Cβ, the methyl ester was replaced with a benzyl ester. Fluorination of compound **4b** with DAST yielded the corresponding 3-fluoroproline **5b** in moderate yield. Finally, the title compound **1**[8] was obtained in 26% overall yield by prolonged hydrogenolysis of the benzyl ester.



Scheme 1. R = Me; (a) $SOCl_2$ in methanol; (b) Boc_2O, NEt_3 in DCM; (c) DAST in dry DCM; (d) LiOH in acetonitrile/water; R = Bn; (a) Boc_2O, NaOH in THF; (b) Cs_2CO_3 in water then BnBr in DMF; (c) DAST in dry DCM; (d) H_2, Pd/C in methanol.

* Corresponding author. Fax: (33) 169 08 90 71; e-mail: christophe.dugave@cea.fr

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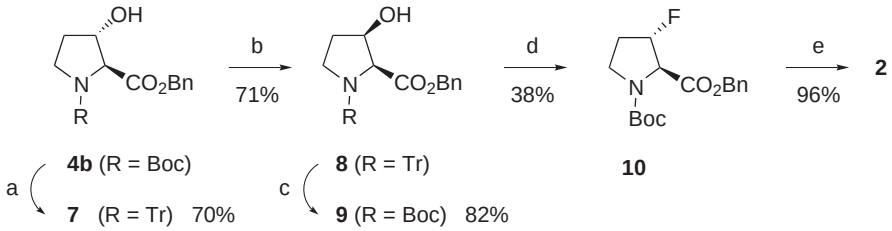

Scheme 2. (a) TFA in DCM; (b) PPh_3, DEAD, $PhCO_2H$ in toluene then KOH in methanol; (c) HCO_2H in 1,2-dichloroethane then Boc_2O, NEt_3 in DCM; (d) DAST in dry DCM; (e) H_2, Pd/C in methanol (R = Bn).

Inversion of configuration of the alcohol was carried out starting from compound **4a** or **4b** (Scheme 2) by a three-step procedure, as previously described for 4-hydroxyproline.[5] In the methyl ester series, fluorination with DAST gave the C3 epimer of **5a**. Unexpectedly, its saponification with lithium hydroxide gave a mixture of **6a** (61%) and **2** (6%). This suggested that (2*R*,3*S*)-*N*-Boc-3-fluoroproline methyl ester exists in a twisted conformation which enables a pseudo anti-elimination of fluorine.

Starting from compound **4b**, (2*S*,3*R*)-*N*-Boc-3-hydroxyproline benzyl ester **9** was isolated in 45% overall yield. NMR analysis showed that the Mitsunobu reaction took place with a complete inversion of configuration.[9] Fluorination and hydrogenolysis led to compound **2**[10] in 36% yield (two steps).

The optical purity of compounds **5b**, **10**, **1** and **2** was investigated since the generation of a proline β-cation equivalent might cause a partial or complete racemization of both Cα and Cβ asymmetric centers. ^1H, ^{13}C and ^{19}F NMR spectra of each diastereomer clearly showed significative differences with no trace of the other isomer (Fig. 2). As already observed with Boc-4-fluoroprolines, a significative doubling of several ^1H, ^{13}C and ^{19}F NMR signals reflects the well-known urethane *cis*/*trans* equilibrium.[10,11]

Therefore, (2*R*,3*R*)- and (2*R*,3*S*)-3-fluoroprolines **1** and **2** were obtained by a straightforward synthetic route in 26% (four steps) and 13% (seven steps), respectively. A diastereomeric purity higher than 99% was assessed by NMR.

Acknowledgements

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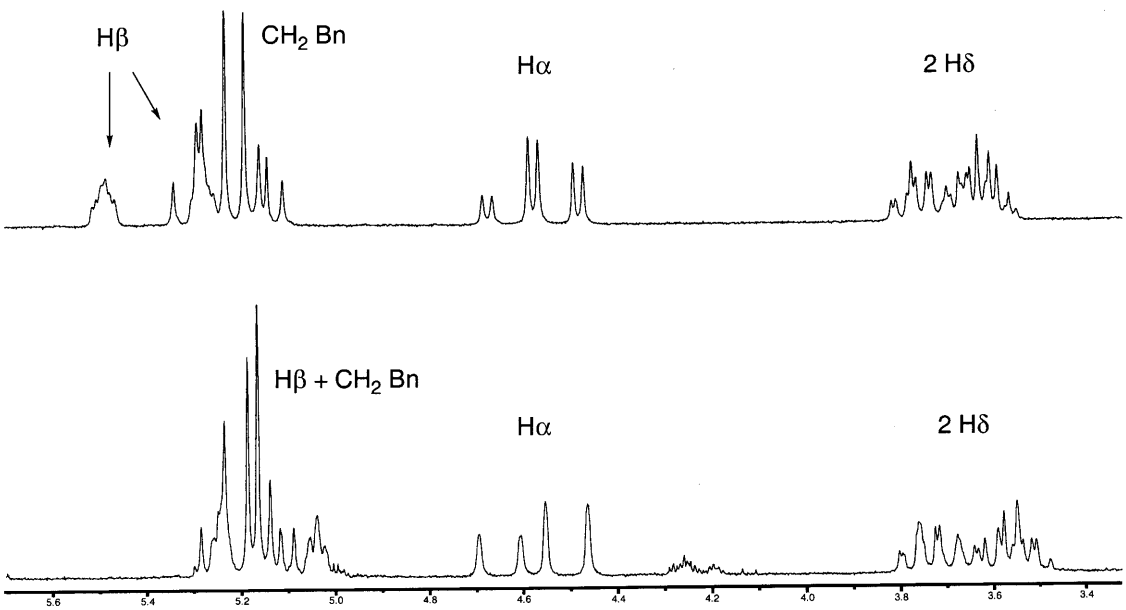

Figure 2. Comparison of ^1H NMR spectra of compounds **5b** (top) and **10** (below) at 250 MHz showed that no epimerization occurred either at Cα or Cβ during the inversion and fluorination steps.

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7. **General procedure of fluorination using DAST**: 5 equiv. of DAST were added dropwise to a solution of Boc-3-fluoroproline benzyl ester (1 mmol) in dry dichloromethane under argon at −78°C. The mixture was stirred for 5 hours at room temperature. The reaction was quenched with 1 M sodium bicarbonate and the aqueous layer was extracted with dichloromethane. The combined organic layers were washed with 10% citric acid and brine and were dried over sodium sulfate. Purification by silica gel flash chromatography (eluent: ethyl acetate:hexane 20:80) gave the product along with the corresponding Boc-3-chloroprolines (up to 60% from **4b** and 22% from **9**; DCI/NH_3: m/z=340+342 (MH^+)) as the major by-product.
8. **1**: $[\alpha]_D^{21}=-86$ ($c=1$, $CHCl_3$); ^1H ($CDCl_3$): δ (ppm) 7.8 (s, 1H), 5.41 (d, 1H, $^2J_{H\text{-}F}=55$ Hz), 4.53–4.45 (m, 1H), 3.82–3.55 (m, 2H), 2.34–1.95 (m, 2H), 1.46 (minor) and 1.42 (major); ^{13}C ($CDCl_3$): δ (ppm) 172.5 (major) and 171.6 (minor), 154.4 (minor) and 153.7 (major), 93.1(major, d, $^1J_{C\text{-}F}=185$ Hz) and 92.2 (minor, d, $^1J_{C\text{-}F}=182$ Hz), 81.0 (major) and 80.8 (minor), 64.1 (d, $^2J_{C\text{-}F}=22$ Hz), 44.6 (minor) and 44.1 (major), 32.0 (minor, d, $^2J_{C\text{-}F}=23$ Hz) and 31.4 (major, d, $^2J_{C\text{-}F}=21$ Hz), 29.2 (minor) and 28.1 (major); ^{19}F NMR ($CDCl_3$): δ (ppm)= −182.6 (major) and −183.0 (minor); MS (DCI, NH_3): m/z 251 (MNH_4^+, 26%), 234 (MH^+, 85%), 195 (MNH_4^+–C_4H_8, 30%), 178 (MH^+–C_4H_8, 100%). Anal. ($C_{10}H_{16}FNO_4$) calcd: C, 51.50; H, 6.91; N, 6.0. Found: C, 52.15; H, 7.14; N, 5.88.
9. Comparison of ^1H NMR spectra of the corresponding 3-hydroxyprolines showed significative differences with no traces of the other isomer, see: Jurczac, J.; Prokopowicz, P.; Golebiowski, A. *Tetrahedron Lett.* **1993**, *34*, 7107–7110.
10. **2**: $[\alpha]_D^{21}=-69$ ($c=0.75$, $CHCl_3$); ^1H NMR ($CDCl_3$): δ (ppm) 8.15 (bs, 1H), 5.43 (major, d, 1H, $^2J_{H\text{-}F}=52$ Hz) and 5.24 (minor, d, 1H, $^2J_{H\text{-}F}=48$ Hz), 4.59 (major, d, 1H, $^3J_{H\text{-}F}=22$ Hz) and 4.50 (minor, d, 1H, $^3J_{H\text{-}F}=23$ Hz), 3.80–3.48 (m, 2H), 2.24–1.83 (m, 2H), 1.50 (major, s) and 1.43 (minor, s) (9H); ^{13}C NMR ($CDCl_3$): δ (ppm) 174.3 (minor) and 171.2 (major), 156.7 (major) and 153.6 (minor), 95.0 (minor, d, $^1J_{C\text{-}F}=186$ Hz) and 93.7 (major, d, $^1J_{C\text{-}F}=182$ Hz), 82.5 (major) and 81.0 (minor), 59.9 (minor) and 58.4 (major), 44.8 (major) and 44.6 (minor), 34.2 (major) and 33.7 (minor), 28.2; ^{19}F NMR ($CDCl_3$): δ (ppm) −171.1 (major), −176.7 (minor); MS (DCI, NH_3): m/z 251 (MNH_4^+, 53%), 234 (MH^+, 100%), 216 (MH^+–H_2O, 35%), 195 (MNH_4^+–C_4H_8, 41%), 178 (MH^+–C_4H_8, 85%). Anal. ($C_{10}H_{16}FNO_4$) calcd: C, 51.50; H, 6.91; N, 6.0. Found: C, 51.38; H, 7.01; N, 6.10.
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