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Practical Synthesis of Boc-Protected *cis*-4-Trifluoromethyl and *cis*-4-Difluoromethyl-L- prolines

Xiao-long Qiu[†] and Feng-ling Qing*[,†,‡]

Laboratory of Organofluorine Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Lu, Shanghai 200032, China, and College of Chemistry and Chemical Engineering, Donghua University, 1882 West Yanan Lu, Shanghai 200051, China

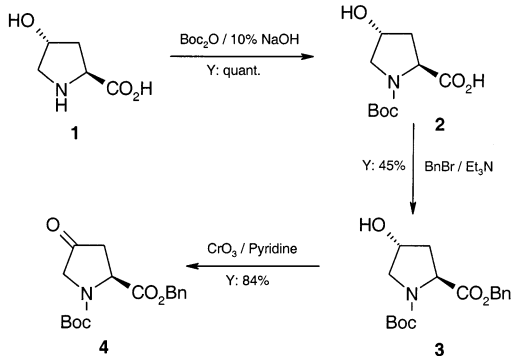
flq@pub.sioc.ac.cn

Received March 20, 2002

Abstract: A short, efficient, and diastereomerically pure synthesis of *N*-Boc-*cis*-4-trifluoromethyl-L-proline (**7**) and *N*-Boc-*cis*-4-difluoromethyl-L-proline (**9**) from *N*-Boc-4-oxo-L-proline (**4**) is described. The reaction of **4** with Me_3SiCF_3 and the conversion of the carbonyl group of **4** into the difluoromethylene group are the key steps for the synthesis of **7** and **9**, respectively.

The substitution of fluorine for hydrogen within the natural amino acids has been used as a powerful tool for bioorganic and medicinal chemists. Fluorinated amino acids and large molecules containing them have enjoyed widespread popularity and been used in applications such as biochemical probes, alternate enzyme substrates, and enzyme inhibitors.[1,2] Especially, incorporation of fluorinated amino acids provides a route to proteins and peptides with unique structural and chemical features.[3] For example, Tirrell[4] and Kumar[5] recently found that fluorinated coiled-coil protein prepared from trifluoroleucine and trifluovaline displays enhanced thermal and chemical stability. Therefore, there is a large body of literature describing methods for the synthesis of fluorinated amino acids.[6−8] Proline and its 4-substituted derivatives are a type of important amino acids in many naturally occurring bioactive peptides such as gramicidin,[9] and have been extensively used in the pharmaceutical industry as angiotensin-converting enzyme (ACE) inhibitors, including Captopril[10] and Enalapril.[11] Fluorinated prolines are useful tools for investigating protein−peptide or protein−protein interactions as well as conformations.[6] Recently, Luis Moroder et al. applied 4-fluoroproline as a tool for protein design and engineering.[12] Among the fluorinated prolines, there are a number of methods describing the preparation of 4-fluoro- and 4-difluoroprolines.[13] However, to the best of our knowledge, only one group reported the synthesis of racemic methyl *N*-*tert*-butyl-4-trifluoromethyl prolinate via (2+3) cycloaddition.[14] Herein, we report a short, efficient, and diastereomerically pure synthesis of *N*-Boc-*cis*−4-trifluoromethyl-L-proline (**7**) and *N*-Boc-*cis*-4-difluoromethyl-L-proline (**9**) from a naturally abundant amino acid L-hydroxyproline (**1**).

SCHEME 1



N-Boc-4-oxo-L-proline (**4**) is a suitable intermediate for the synthesis of fluorinated prolines **7** and **9**. *N*-Boc-4-oxo-L-proline (**4**) is derived from L-hydroxyproline (**1**) and could be obtained through a slight modification of a published procedure (Scheme 1).[15] Initially, treatment of **1** with di-*tert*-butyl dicarbonate in the presence of 10% aqueous NaOH provided *N*-*tert*-butoxycarbonyl-*trans*-4-hydroxy-L-proline (**2**). The carboxyl group of **2** was

[†] Chinese Academy of Sciences.
[‡] Donghua University.

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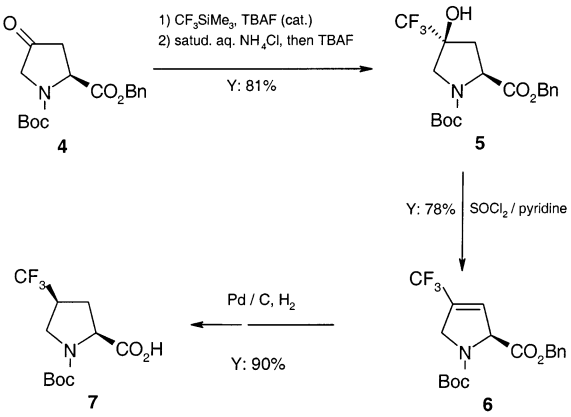
10.1021/jo0257400 CCC: $22.00
Published on Web 09/11/2002

SCHEME 2



protected in the form of benzyl ester **3**, since the benzyl ester group could be removed under hydrogenolysis. The hydroxyl group of **3** was oxidized by chromium trioxide and pyridine to give *N*-Boc-4-oxo-L-proline (**4**).

The nucleophilic trifluoromethylation reaction of the carbonyl group with (trifluoromethyl)trimethylsilane (Me_3SiCF_3) is rapidly becoming the method for introduction of a trifluoromethyl group into an organic compound.[16] It was anticipated that the treatment of **4** with Me_3SiCF_3 would lead to an intermediate **5** that could be converted to the target molecule **7**. In fact, the reaction of **4** with 1.0 equiv of Me_3SiCF_3 in the presence of catalytic tetrabutylammonium fluoride (TBAF) at room temperature overnight resulted in the total conversion of **4**. However, with the addition of TBAF to the reaction mixture for the desilylation following the usual procedure, the expected product **5** was isolated in low yield, and the byproducts were formed as indicated by the ^{19}F NMR of the reaction mixture. Fortunately, in the desilylation step, the addition of saturated aqueous NH_4Cl and stirring for 15 min followed by the addition of TBAF afforded **5** in 81% yield (Scheme 2). It seemed that saturated aqueous NH_4Cl could make the desilylation mild and reduce the formations of byproducts. It was necessary to add TBAF for total desilylation. Dehydration of **5** with thionyl chloride in pyridine under reflux provided trifluoromethylated olefin **6** in 78% yield.[17] Hydrogenation and deprotection of **6** by hydrogen with Pd/C led to a single diastereoisomer, *N*-Boc-*cis*-4-trifluoromethyl-L-proline (**7**) in 90% yield.[18] Neither high-resolution NMR nor HPLC was able to detect any of the other diastereoisomer. The X-ray structure of compound **7** and NOESY experiment demonstrated that the trifluoromethyl group is cis to the acid group (Figure 1).

The key step for the synthesis of *N*-Boc-*cis*-4-difluoromethyl-L-proline (**9**) was to convert the carbonyl group of **4** into the difluoromethylene group. Treatment of **4** with dibromodifluoromethane/Zn/HMPT[19] in THF gave the key intermediate **8** in 48% yield (Scheme 3). **8** was

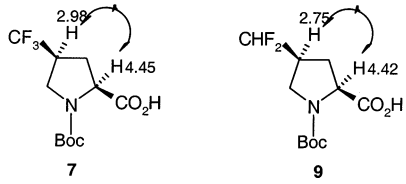
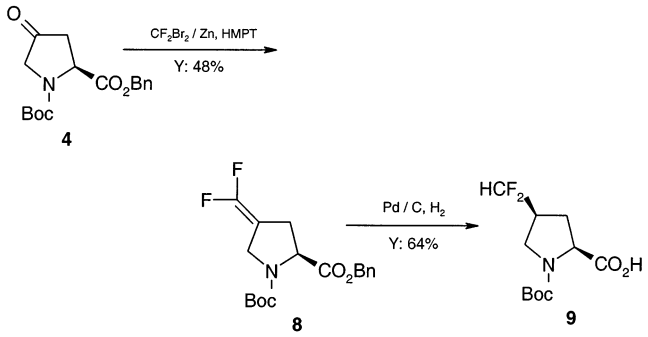


FIGURE 1. NOE correlation from NOESY spectra of **7** and **9**

SCHEME 3



hydrogenated to afford the desired product **9** in 64% yield, which was confirmed as the single diasteroisomerby ^{19}F NMR and NOESY (Figure 1). To the best of our knowledge, this is the first synthesis of *N*-Boc-*cis*-4-difluoromethyl-L-proline.

In summary, we have developed a short, efficient, and diastereoisomerically pure synthesis of *N*-Boc-*cis*−4-trifluoromethyl-L-proline (**7**) and *N*-Boc-*cis*-4-difluoromethyl-L-proline (**9**) from a naturally abundant amino acid L-hydroxyproline (**1**). The following points derived from our synthesis are noteworthy: (1) the original material is natural and cheap, (2) the synthetic route is short and efficient, (3) the diastereomeric excess is very high (almost optically pure), and (4) the preparation could be scaled up to several grams. Studies detailing the incorporation of the two building blocks into peptides and subsequent characterization are in progress.

Experimental Section

***N*-*tert*-Butoxycarbonyl-*trans*-4-hydroxy-L-proline (2).** A mixture of *trans*-4-hydroxy-L-proline (**1**, 25.0 g, 0.19 mol) in 380 mL of a 2:1 mixture of THF/H_2O was treated first with 10% aqueous NaOH (80 mL) and then with di-*tert*-butyldicarbonate (60 g, 0.28 mol). The reaction mixture was stirred at room temperature overnight and then the THF was removed in vacuo. The residue was adjusted to pH 2 by the addition of 10% aqueous $KHSO_4$. The acidic solution was extracted several times with ethyl acetate. The combined organic extracts were washed with H_2O and brine and then dried over anhydrous Na_2SO_4. Removal of the desiccant and evaporation of the solvent in vacuo gave **2** (44.0 g, 100%) as a syrup, which was used without further purification.

Benzyl (2*S*,4*R*)-*N*-*tert*-Butoxycarbonyl-4-hydroxyprolinate (3). To a solution of **2** (10.0 g, 43.30 mmol) in anhydrous THF (45 mL) was added dry Et_3N (8 mL). The solution was cooled to 0 °C and BnBr (7 mL, 58.50 mmol) in THF (5 mL) was added dropwise. The reaction mixture was stirred at 0 °C for 5 min, then warmed to room temperature and stirred overnight.

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The solvent was removed in vacuo and the residue was dissolved in CH_2Cl_2 (500 mL). The resultant organic phase was washed with 1 N HCl (150 mL), H_2O (150 mL), 5% aqueous Na_2CO_3 (150 mL), and H_2O (50 mL) and dried over anhydrous Na_2SO_4. The solvent was removed in vacuo and the crude product was purified by flash chromatography (hexane/ethyl acetate, 2:1) to give **3** (6.17 g, 44%) as a clear oil. $[\alpha]^{20}_D$ −58.0 (*c* 1.24, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35 (m, 5H), 5.16 (m, 2H), 4.51−4.41 (m, 2H), 3.66−3.58 (m, 2H), 2.31−2.28 (m, 1H), 2.11−2.05 (m, 1H), 1.46, 1.34 (2s, 9H); IR (thin film) 3439, 1749, 1702, 1678 cm^{-1}.

Benzyl (2*S*)-*N*-*tert*-Butoxycarbonyl-4-oxo-prolinate (4). CrO_3 (17.0 g, 0.17 mol) was added slowly with stirring over 30 min to a solution of pyridine (30 mL) in CH_2Cl_2 (80 mL) at 0 °C. The mixture was warmed to room temperature and **3** (6.0 g, 18.69 mmol) in CH_2Cl_2 (60 mL) was added. The reaction was stirred vigorously for 4 h at room temperature. The formed dark solid was decanted and washed with CH_2Cl_2 (3 × 100 mL). The organic phases were washed with saturated aqueous $NaHCO_3$, 10% aqueous critic acid, and brine and dried over anhydrous Na_2SO_4. The solvent was removed in vacuo to yield an oily residue, which was purified by flash chromatography (hexane/ethyl acetate, 3:1) to give **4** (5.0 g, 84%) as a clear oil. $[\alpha]^{20}_D$ + 0.3 (*c* 1.40, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35 (m, 5H), 5.28−5.09 (m, 2H), 4.88−4.72 (dd, *J* = 10.2, 9.3 Hz, 1H), 3.92−3.87 (d, *J* = 13.5 Hz, 2H), 2.97−2.91 (m, 1H), 2.64−2.54 (m, 1H), 1.47, 1.37 (2s, 9H); IR (thin film) 1768, 1748, 1706 cm^{-1}.

Benzyl (2*S*,4*S*)-*N*-*tert*-Butoxycarbonyl-4-hydroxy-4-trifluoromethyl-L-prolinate (5). A solution of **4** (3.0 g, 9.40 mmol) in THF (45 mL) was cooled to 0 °C, then $CF_3Si(CH_3)_3$ (1.62 mL, 10.04 mmol) and TBAF (330 μL, 1.0 M in THF) were added. The mixture was warmed to room temperature and stirred overnight. The saturated aqueous NH_4Cl (15 mL) was added and the mixture was stirred for 15 min, then TBAF (15 mL, 1.0 M in THF) was added and the mixture was stirred for 1 h. The organic layer was separated and the aqueous layer was extracted with Et_2O (3 × 100 mL). The combined organic phases were washed with water and brine and dried over anhydrous Na_2SO_4. Filtration and removal of the solvent in vacuo gave the residue. The residue was purified by flash chromatography (hexane/ethyl acetate, 10:1) to give **5** (2.97 g, 81%) as a white solid. Mp 68−70 °C; $[\alpha]^{20}_D$ −12.0 (*c* 1.54, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37−7.36 (m, 5H), 5.30−5.13 (m, 2H), 4.62−4.47 (dd, *J* = 9.3, 9.3 Hz, 1H), 3.78−3.68 (m, 2H), 2.63−2.49 (m, 1H), 2.26−2.18 (t, *J* = 13.0 Hz, 1H), 1.47, 1.33 (2s, 9H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −81 (d, *J* = 16.6 Hz); IR (KBr) 3377, 2980, 1757, 1707, 1682, 1500, 1479, 1457, 1418, 1178, 1113, 698 cm^{-1}; MS (EI) *m*/*z* 389 (M^+, 1), 290 (24), 91 (98), 57 (100). Anal. Calcd for $C_{18}H_{22}F_3NO_5$: C, 55.53; H, 5.66; N, 3.60. Found: C, 55.77; H, 5.98; N, 3.50.

Benzyl (2*S*)-*N*-*tert*-Butoxycarbonyl-4-trifluoromethyl-3,4-dehydroprolinate (6). A mixture of **5** (123 mg, 0.32 mmol), dry pyridine (4 mL), and $SOCl_2$ (300 μL) was refluxed under nitrogen for 20 min. The H_2O (1 mL) was added to quench the reaction. The aqueous layer was extracted with Et_2O (3 × 20 mL). The combined organic phases were washed with 1 N HCl (20 mL), saturated aqueous $NaHCO_3$ (10 mL), water (10 mL), and brine and dried over anhydrous Na_2SO_4. After removal of the solvent in vacuo, the residue was purified by flash chromatography (hexane/ethyl acetate, 30:1) to give **6** (92 mg, 78%) as a clear oil. $[\alpha]^{20}_D$ −175.7 (*c* 0.92, $CHCl_3$); ^{1}H NMR(300 MHz, $CDCl_3$) δ 7.38−7.35 (m, 5H), 6.29−6.24 (dt, *J* = 10.8, 2.1 Hz, 1H), 5.29−5.11 (m, 2H), 5.15−5.11 (m, 1H), 4.43−4.36 (m, 2H), 1.48, 1.34 (2s, 9H);^{19}F NMR (282 MHz, $CDCl_3$) δ −66 (d, *J* = 15 Hz); IR (thin film) 2979, 1757, 1708, 1674, 1500, 1458, 1400, 1168, 1128, 697 cm^{-1}; MS (EI) *m*/*z* 373 (M^+ + 2, 0.3), 372 (M^+ + 1, 1), 316 (32), 270 (M^+ − Boc, 2), 91 (78), 57 (100). Anal. Calcd for $C_{18}H_{20}F_3NO_4$: C, 58.22; H, 5.39; N, 3.77. Found: C, 58.43; H,5.62; N, 3.98.

(2*S*,4*S*)-*N*-*tert*-Butoxycarbonyl-4-trifluoromethyl-proline (7). Pd/C (490 mg, 10%Pd) was added to a solution of **6** (394 mg, 1.39 mmol) in EtOH (25 mL), then the solution was hydrogenated at room temperature overnight. After filtration and removal of the solvent in vacuo, the residue was purified by flash chromatography (hexane/ethyl acetate, 1:1) to give **7** (360 mg, 90%) as a white solid. Mp 124.5−126.5 °C; $[\alpha]^{20}_D$ −77.6 (*c* 0.70, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.98−8.91 (bs, 1H), 4.48−4.33 (dt, *J* = 29, 7.8 Hz, 1H), 3.96−3.82 (m, 1H), 3.53−3.45 (m, 1H), 3.04−2.90 (m, 1H), 2.67−2.53 (m, 1H), 2.41−2.19 (m, 1H), 1.49, 1.43 (2s, 9H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −71.2 (d, *J* = 4.8 Hz); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 177.3, 175.7, 154.6, 153.4, 127.6, 123.9, 81.7, 81.4, 58.3, 58.2, 45.9, 45.6, 41.8, 41.5, 41.2, 40.8, 29.9, 28.6, 28.2, 28.0; IR (thin film) 3000−2500, 1726, 1647, 1481, 1445, 1407, 1280, 1164, 699 cm^{-1}; MS(EI) *m*/*z* 238 (M^+ − COOH, 3), 182 (M^+ − Boc, 23), 138 (M^+ − Boc − COOH, 37), 69 (2), 57 (100).; Anal. Calcd for $C_{11}H_{16}F_3NO_4$: C, 46.64; H, 5.65; N, 4.95. Found: C, 46.80; H, 5.65; N, 4.92.

Benzyl (2*S*)-*N*-*tert*-Butoxycarbonyl-4-difluoromethyl-eneprolinate (8). CF_2Br_2 (0.30 mL, 3.06 mmol) and HMPT (0.67 mL, 3.06 mmol) were added at 0 °C to a solution of **4** (229 mg, 0.72 mmol) in THF (7 mL). The mixture was warmed to room temperature and zinc dust (200 mg, 3.06 mmol) and HMPT (40 μL) were added. The reaction mixture was refluxed for 3.5 h. Then H_2O (20 mL) and Et_2O (20 mL) were added. The aqueous layer was extracted with Et_2O (3 × 30 mL). The combined organic phases were washed with saturated aqueous $CuSO_4$, water, and brine and dried over anhydrous Na_2SO_4. After removal of the solvent in vacuo, the residue was purified by flash chromatography (hexane/ethyl acetate; 30:1) to give **8** (122 mg, 48%) as a colorless oil. $[\alpha]^{20}_D$ −25.1 (*c* 1.96, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39 (m, 5H), 5.26−5.09 (m, 2H), 4.62−4.45 (dd, *J* = 9.3, 9.3 Hz, 1H), 4.14−4.08 (m, 2H), 2.97−2.85 (m, 1H), 2.70−2.62 (m, 1H), 1.47, 1.34 (2s, 9H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −88 (m, 1F), −91 (m, 1F); IR (thin film) 2978, 1787, 1749, 1705, 1499, 1456, 1393, 1274, 1064, 698 cm^{-1}; MS (EI) *m*/*z* 354 (M^+ + 1, 2), 353 (M^+, 1) 254 (32), 162 (34), 91 (80), 69 (1), 57 (100). Anal. Calcd for $C_{18}H_{21}F_2NO_4$: C, 61.19; H, 5.95; N, 3.97. Found: C, 61.15; H, 6.07; N, 4.03.

(2*S*,4*S*)-*N*-*tert*-Butoxycarbonyl-4-difluoromethyl-proline (9). Pd/C (520 mg, 10% Pd) was added to a solution of **8** (321 mg, 0.91 mmol) in EtOH (20 mL) and the solution was hydrogenated at room temperature overnight. After filtration and removal of the EtOH in vacuo, the residue was purified by flash chromatography (hexane/ethyl acetate, 1:1) to give **9** (155 mg, 64.3%) as a white solid. Mp 96.5−98.5 °C; $[\alpha]^{20}_D$ −77.6 (*c* 0.56, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.02−8.88 (bs, 1H), 6.02−5.60 (tt, *J* = 56, 7.8 Hz; 1H), 4.44−4.28 (dt, *J* = 32, 7.5 Hz, 1H), 3.77−3.67 (m, 1H), 3.52−3.42 (m, 1H), 2.78−2.64 (m, 1H), 2.58−2.42 (m, 1H), 2.33−2.09 (m, 1H), 1.49, 1.42 (2s, 9H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −120 (m); ^{13}C NMR($CDCl_3$, 75.5 MHz) δ 177.9, 176.0, 154.9, 153.5, 119.4, 116.2, 113.0, 81.5, 81.2, 58.3, 46.3, 46.0, 42.2, 41.8, 41.5, 41.2, 40.9, 30.1, 28.8, 28.2, 28.1; IR (thin film) 3000−2500, 1733, 1637, 1481, 1445, 1370, 1267, 1167, 1151 cm^{-1}; MS (EI) *m*/*z* 266 (M^+ + 1, 0.5), 265 (M^+, 0.4), 220 (M^+ − COOH, 3), 164 (M^+ − Boc, 47), 120 (M^+ − Boc − COOH, 100), 57 (99). Anal. Calcd for $C_{11}H_{17}F_2NO_4$: C, 49.81; H, 6.24; N, 5.28. Found: C, 49.97; H, 6.31 N, 5.16.

Supporting Information Available: ORTEP drawing of the X-ray crystallographic structure of **7**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0257400