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Synthesis of *cis*-4-Trifluoromethyl- and *cis*-4-Difluoromethyl-L-pyroglutamic Acids

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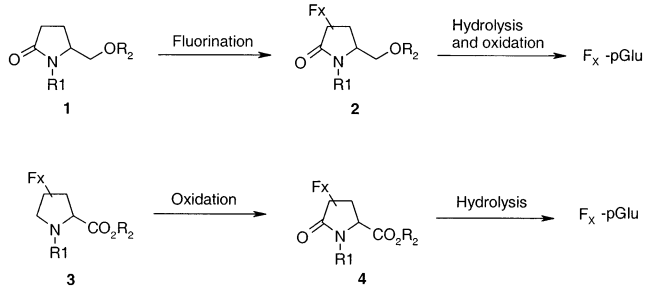
Efforts to synthesize 4-trifluoromethyl- and 4-difluoromethyl-L-pyroglutamic acids are described. After many arduous efforts, we successfully synthesized our target molecules *cis*−4-trifluoromethyl-L-pyroglutamic acid **25** and *cis*−4-difluoromethyl-L-pyroglutamic acid **26** from *trans*-4-hydroxy-L-proline through oxidation of fluorinated prolinates with RuO_4.

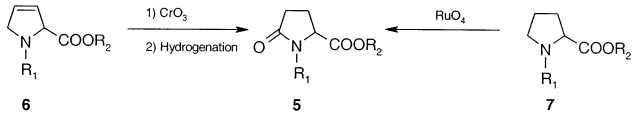
Fluorine-containing amino acids and large molecules containing them have enjoyed widespread bioorganic applications such as biological tracers, mechanistic probes, and enzyme inhibitors and medical applications including control of blood pressure, allergies, and tumor growth.[1,2] Because of these facts, fluorinated amino acids have been the object of intense synthetic activity and many fluorinated amino acids were synthesized according to the different need and aim.[2−4] Despite the synthesis of many fluorinated amino acids, there remains a strong demand for structure-constrained fluorinated amino acids as tools for investigating protein−peptide and protein−protein interactions as well as conformational transitions.

Pyroglutamic acid and its derivatives are important amino acids in many bioactive compounds such as Aza-prostaglandin analogues,[5] monocylic thienyl gamma lactam (high antibacterial activity),[6] and thyroliberin (TRH).[7]

SCHEME 1. Two Strategies for F_x-pGLu



SCHEME 2



Pyroglutamic acid and substituted pyroglutamic acid derivatives are interesting targets as they confer unique structural constraints in peptide chains[8] and hence may play a major role in protein folding and structure. Furthermore, glutamic acid, which could be derived from pyroglutamic acid, acts as one of the major neurotransmitters at excitatory synapses in the mammalian central nervous system (CNS).[9] 4-Substituted groups of pyroglutamic acids are important for conformation and activity of pyroglutamic acid derivatives and some natural and synthetic 4-substituted glutamic acids were applied to study the structure−activity relationships of excitatory effects on the nervous system.[10] Recently, there also are

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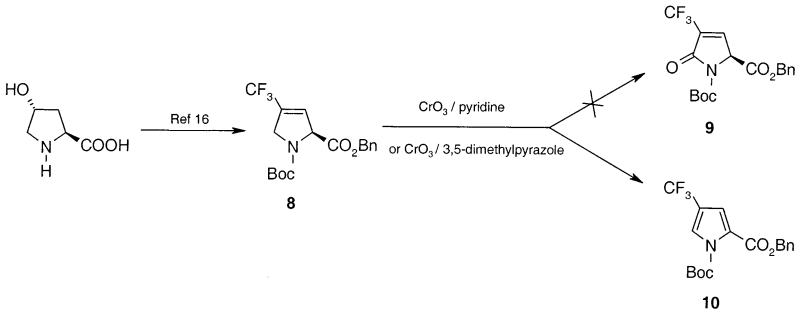
SCHEME 3



many reports[8,11] about the synthesis and characterization of substituted pyroglutamic acids and peptides containing them. Although many fluorinated pyroglutamic acids were synthesized, to the best of our knowledge, there is no report about the preparation of 4-trifluoromethyl and 4-difluoromethyl pyroglutamic acids. In connection with our studies on fluorinated amino acids, fluorinated peptides, and fluorinated nucleosides, we need an efficient synthesis of 4-trifluoromethyl and 4-difluoromethyl pyroglutamic acids, suitable for fluorinated peptides and nucleoside synthesis.

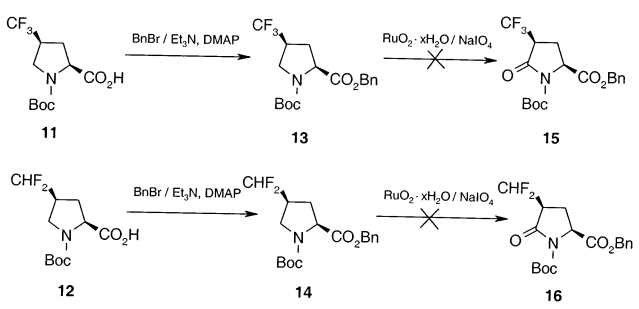
Generally speaking, there are two main effective synthetic strategies for preparation of fluorinated pyroglutamic acids (Fx-pGlu) as shown in Scheme 1. For the first strategy, compounds **1** derived from pyroglutamic acids are fluorinated with electrophilic fluorination reagents and the resulting fluorinated compounds **2** are converted to Fx-pGlu after deprotection, hydrolysis, and oxidation. Application of this strategy resulted in the synthesis of (2*S*,4*R*)-4-fluoropyroglutamic acid derivatives and (2*S*)-4,4-difluoropyroglutamic acid derivatives.[11k,12] For the second strategy, protected fluorinated prolines **3** are converted to corresponding pyroglutamate derivatives **4** via oxidation with RuO_4 and following hydrolysis of the protecting groups gives the desired fluorinated pyroglutamate derivatives. However, application of this strategy to synthesize fluorinated pyroglutamates which have strong electron-withdrawing groups in the 4-position (such as 4,4-difluoropyroglutamic acid derivatives) was unsuccessful due to the oxidation mechanism proceeding through a carbocation intermediate.[13] But application of this strategy resulted in the synthesis of (2*S*,4*S*)-4-fluoropyroglutamic acid derivatives and (2*RS*)-3,3-difluoropyroglutamic acid derivatives.[14] Herein, we described the synthesis of *cis*-4-trifluoromethyl- and *cis*-4-difluoromethyl-L-pyroglutamic acids through oxidation of fluorinated prolinates with RuO_4.

There are two methods to construct pyroglutamate skeleton **5** from the proline derivative, as shown in Scheme 2.[15] One method was realized via oxidation of 3,4-dehydroprolinate derivatives **6** with CrO_3 followed by hrdrogenation. The other method was realized via direct oxidation of prolinate derivatives **7** with RuO_4.

According to the first method, we envisioned that 4-trifluoromethyl-3,4-dehydropyroglutamate **9** could be synthesized from 4-trifluoromethyl-3,4-dehydroprolinate **8**, which was prepared recently by our group from *trans*-4-hydroxyproline in 5 steps in good yield.[16] Unfortunately, the oxidation of **8** with CrO_3 failed to furnish the desired product **9** and only gave the unexpected compound **10** in 67% yield (Scheme 3). The structure of compound **10** was determined by X-ray crystallography.

Although the RuO_4 oxidation method cannot be applied to the synthesis of (2S)-4,4-difluoropyroglutamate[17] due to the strong electron-withdrawing CF_2 group at C-4, it is reasonable to assume that this method could be applied to synthesize 4-trifluoromethyl and 4-difluoromethyl pyroglutamate because the electron-withdrawing power of trifluoromethyl and difluoromethyl was weaker than that of 4,4-difluoromethylene to the C-5 position of prolinate. Recently, we have developed a practical route to Boc-protected *cis*-4-trifluoromethyl proline **11** and Boc-protected *cis*-4-difluoromethyl proline **12**.[16] Thus, protection of carboxylic groups of **11** and **12** with the benzyl group afforded compounds **13** and **14** in 44% and 49% yield, respectively (Scheme 4). However, oxidation of **13**

SCHEME 4



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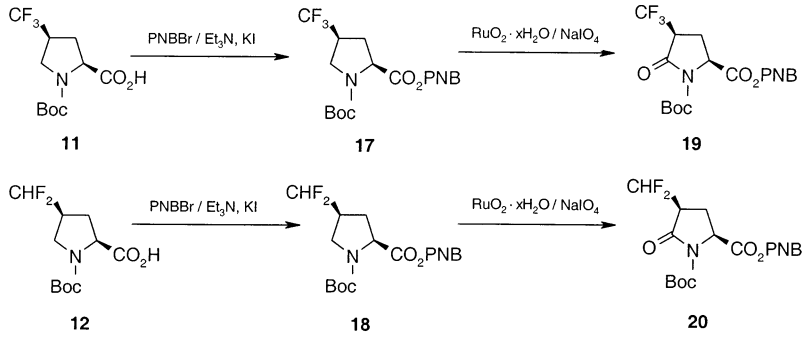
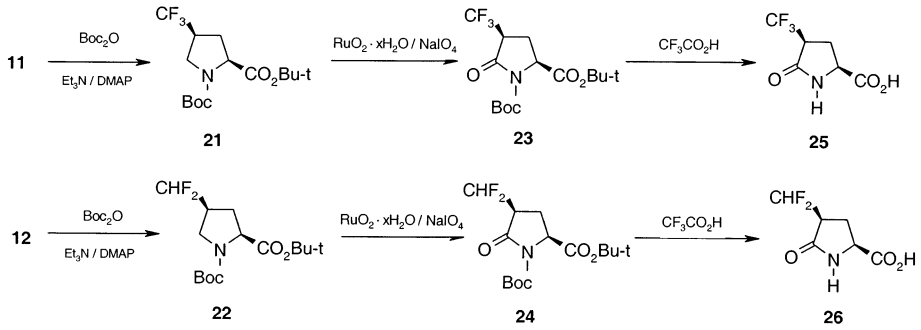
SCHEME 5



SCHEME 6



and **14** with $RuO_2 \cdot xH_2O/NaIO_4$ under ethyl acetate/water biphase condition[18] failed to furnish the corresponding lactam **15** and **16** because of simultaneous oxidative cleavage of the benzyl group.

The benzyl group was replaced with the *p*-nitrobenzyl group acting as a deactivated protecting group to afford **17** and **18** in 95% and 95% yield, respectively (Scheme 5). The oxidation of **17** and **18** with $RuO_2 \cdot xH_2O/NaIO_4$ proceeded smoothly to afford the desired lactam compounds **19** and **20** in 22% and 58% yield, respectively. To improve the yield of the oxidation reaction, protection of the carboxylic group of **11** and **12** with the *tert*-butyl group instead of the *p*-nitrobenzyl group provided the corresponding ester **21** and **22** in 89% and 94% yield. To our delight, the oxidation of **21** and **22** with $RuO_2 \cdot xH_2O/NaIO_4$ under EtOAc/H_2O biphase condition afforded the expected products **23** and **24** in 58% and 78% yield, respectively (Scheme 6). Finally, one-step removal of protective groups with trifluoroacetic acid in CH_2Cl_2 successfully afforded the target compounds *cis*-4-trifluoromethyl-L-pyroglutamic acid **25** and *cis*-4-difluoromethyl-L-pyroglutamic acid **26**.

In summary, we have described our attempts on the synthesis of *cis*-4-trifluoromethyl-L-pyroglutamic acid **25** and *cis*-4-difluoromethyl-L-pyroglutamic acid **26**. After numerous arduous efforts, we successfully synthesized our target molecules *cis*-4-trifluoromethyl-L-pyroglutamic acid **25** and *cis*-4-difluoromethyl-L-pyroglutamic acid **26**. Studies on detailing the incorporation of two fluorinated amino acids into peptides and peptidomimetics and on the synthesis of fluorinated nucleosides from them are in progress.

Experimental Section

(2*S*,4*S*)-*tert*-Butyl-*N*-*tert*-butoxycarbonyl-4-trifluoromethylprolinate (21). Boc_2O (950 mg, 4.35 mmol) in CH_2Cl_2 (5 mL) was added to a cooled solution of **11** (300 mg, 1.06 mmol), Et_3N (0.75 mL, 5.39 mmol), and DMAP (45 mg, 0.37 mmol) in CH_2Cl_2 (10 mL). After being stirred at room temperature overnight, the reaction was quenched with H_2O, then the resulting solution was extracted with CH_2Cl_2 three times. The combined organic phases were washed with H_2O and brine and dried over anhydrous Na_2SO_4. After removal of the solvent in vacuo, the resulting residue was purified by silica gel chromatography (hexane/ethyl acetate, 10:1) to give **21** as a white solid (318 mg, 89%). Mp 58−60 °C; $[\alpha]^{20}_D$ −72.4 (*c* 0.80, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.31−4.19 (m, 1H), 3.95−3.76 (tt, J = 36.0, 9.8 Hz, 1H), 3.48−3.42 (t, J = 10.2 Hz, 1H), 2.99−2.87 m, 1H), 2.62−2.50 (m, 1H), 2.11−2.02 (m, 1H), 1.47, 1.44 (2s, 18H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −67.6 (s, 3F); IR (thin film) 1740, 1691 cm^{-1}; MS (EI) *m*/*z* 57 (100). Anal. Calcd for $C_{15}H_{24}F_3NO_4$: C, 53.10; H, 7.08; N, 4.13. Found: C, 53.09; H, 6.95; N, 4.06.

(2*S*,4*S*)-*tert*-Butyl-*N*-*tert*-butoxycarbonyl-4-trifluoromethylpyroglutamate (23). To a solution of $NaIO_4$ (380 mg, 1.78 mmol) in H_2O (6 mL) was added $RuO_2 \cdot xH_2O$ (18 mg, 0.13 mmol) under the protection of nitrogen. The resulting green-yellow solution was stirred for 5 min followed by addition of **21** (183 mg, 0.54 mmol) in EtOAc (6 mL) in one portion. The mixture was heated to 50 °C and stirred vigorously. Additional aliquots of 10% aqueous $NaIO_4$ were added to maintain a yellow-colored solution during the reaction. After 29 h, the resulting mixture was then diluted with EtOAc and filtered. The filtrate was washed with saturated aqueous $NaHSO_3$. The organic layer was washed with brine and dried over anhydrous Na_2SO_4. After removal of the solvent in vacuo, the resulting residue was purified by silica gel chromatography (hexane/ethyl acetate, 10:1, then 7:1) to give **23** as a white solid (110 mg, 58%). Mp 143−144 °C; $[\alpha]^{20}_D$ −53.6 (*c* 0.51, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.53−4.48 (dd, J = 5.7, 5.4 Hz, 1H),

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3.38−3.30 (m, 1H), 2.74−2.63 (m, 1H), 2.22−2.13 (m, 1H), 1.53, 1.48 (2s, 18H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −68.4 (d, J = 9.0 Hz, 3F); IR (thin film) 1775, 1742, 1700, 1163 cm^{-1}; MS (EI) *m*/*z* 57 (100). Anal. Calcd for $C_{15}H_{22}F_3NO_5$: C, 50.99; H, 6.23; N, 3.97. Found: C, 51.04; H, 6.36; N, 3.80.

(2*S*,4*S*)-4-Trifluoromethylpyroglutamic Acid (25). TFA (0.5 mL) was added to a solution of **23** (110 mg, 0.31 mmol) in CH_2Cl_2 (6 mL) at 0 °C. The mixture was allowed to warm to room temperature and stirred for 6 h. The reaction mixture was concentrated in vacuo (last traces of TFA being removed under high vacuum) to give **25** as an off-white solid (61 mg, 100%). $[\alpha]^{20}_D$ −53.8 (*c* 0.38, HOAc); ^{1}H NMR (300 MHz, D_2O) δ 4.44−4.39 (dd, J = 6.3, 6.3 Hz, 1H), 3.62−3.53 (m, 1H), 2.95−2.84 (m, 1H), 2.39−2.30 (m, 1H); ^{19}F NMR (282 MHz, D_2O) δ −69.0 (d, J = 8.7 Hz, 3F); ^{13}C NMR (75.5 MHz, CD_3OD) δ 172 (q, J = 2.5 Hz), 171.8 (d, J = 1.2 Hz), 126.5 (q, J = 276.7 Hz), 55.2, 46.6 (q, J = 29.0 Hz), 26.6 (d, J = 1.7 Hz); IR (thin film) 3291, 1751, 1724, 1658, 1131 cm^{-1}; MS (EI) *m*/*z* 197 (M^+, 2), 152 (M^+ − COOH, 100); EI-HRMS *m*/*z* 197.02539 (M^+, $C_6H_6F_3NO_3$ required 197.02534). Anal. Calcd for $C_6H_6F_3NO_3$: C, 36.55; H, 3.05; N, 7.10. Found: C, 36.98; H, 3.30; N, 6.52.

(2*S*,4*S*)-*tert*-Butyl-*N*-*tert*-butoxycarbonyl-4-difluoromethylprolinate (22). Compound **22** (1.34 g, 94%) was prepared as a white solid from **12** (1.18 g, 4.47 mmol), using the same conditions as for compound **21**. Mp 108−110 °C; $[\alpha]^{20}_D$ −48.8 (*c* 1.58, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.00−5.60 (td, J = 56.7, 6.0 Hz, 1H), 4.26−4.41 (m, 1H), 3.77−3.63 (m, 1H), 3.51−3.41 (m, 1H), 2.69−2.61(m, 1H), 2.52−2.40 (m, 1H), 2.04−1.95 (m, 1H), 1.48, 1.44 (2s, 18H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −120 (m); IR (thin film) 1745, 1691, 1407, 1149 cm^{-1}; MS (EI) *m*/*z* 120 (50), 57 (100). Anal. Calcd for $C_{15}H_{25}F_2NO_4$: C, 56.07; H, 7.79; N, 4.36. Found: C, 55.92; H, 7.82; N, 4.16.

(2*S*,4*S*)-*tert*-Butyl-*N*-*tert*-butoxycarbonyl-4-difluoromethylpyroglutamate (24). Compound **24** (768 mg, 78%) was prepared as a white solid from **22** (942 mg, 2.93 mmol), using the same conditions as for compound **23**. Mp 116−118 °C; $[\alpha]^{20}_D$ −30.3 (*c* 0.45, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.36−5.99 (td, J = 55.4, 1.8 Hz, 1H), 4.53−4.48 (dd, J = 4.5, 5.1 Hz, 1H), 3.18−3.07 (m, 1H), 2.59−2.47 (m, 1H), 2.27−2.19 (m, 1H), 1.52, 1.49 (2s, 18H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −121.02 to −122.26 (ddd, J = 278.0, 6.8, 6.2 Hz, 1F), −124.62 to −125.92 (ddd, J = 285.0, 29.6, 26.4 Hz, 1F); IR (thin film) 1771, 1743, 1696, 1154 cm^{-1}; MS (EI) 57 (100). Anal. Calcd for $C_{15}H_{23}F_2NO_5$: C, 53.73; H, 6.87; N, 4.18. Found: C, 53.92; H, 6.96; N, 4.19.

(2*S*,4*S*)-4-Difluoromethylpyroglutamic Acid (26). Compound **26** (220 mg, 100%) was prepared as an off-white solid from **24** (413 mg, 1.23 mmol) using the same conditions as for compound **25**. Mp 134.5−135.5 °C; $[\alpha]^{20}_D$ −32.0 (*c* 0.34, AcOH);^{1}H NMR (300 MHz, D_2O) δ 6.29−5.91 (td, J = 55.0, 2.7 Hz, 1H), 4.41−4.36 (dd, J = 6.0, 6.0 Hz, 1H), 3.20 (m, 1H), 2.73 (m, 1H), 2.28 (m, 1H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −123 (m); ^{13}C NMR (75.5 MHz, CD_3OD) δ 175.2 (dd, J = 2.7, 2.0 Hz), 174.7, 116.5 (t, J = 240.0 Hz), 55.1, 46.7 (t, J = 23.0 Hz), 24.5 (dd, J = 3.0, 2.7 Hz); IR (thin film) 3361, 1713, 1668, 1251 cm^{-1}; MS (EI) *m*/*z* 179 (M^+, 1), 134 (M^+ − COOH, 100). Anal. Calcd for $C_6H_7F_2NO_3$: C, 40.22; H, 3.91; N, 7.82. Found: C, 40.16; H, 4.00; N, 7.53.

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Supporting Information Available: Experimental procedures and analytical data for compounds **10**, **13**, **14**, **17**, **18**, **19**, and **20** as well as an ORTEP drawing of the X-ray crystallographic structure of **10**, and crystallographic data for compounds **10** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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