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Synthesis of 4-monofluoromethylenyl- and *cis*-4-monofluoromethyl-L-pyroglutamic acids via a novel dehydrofluorination

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Abstract—Novel dehydrofluorination reactions accidentally found were used to synthesize terminal monofluoro olefin lactam analogues in good yield. The following hydrogenation of the resulting defluorinated product was systematically investigated. Two important fluorinated amino acids: 4-monofluoromethylenyl-L-pyroglutamic acid **16** and *cis*-4-monofluoromethyl-L-pyroglutamic acid **17** were synthesized using the methodology.

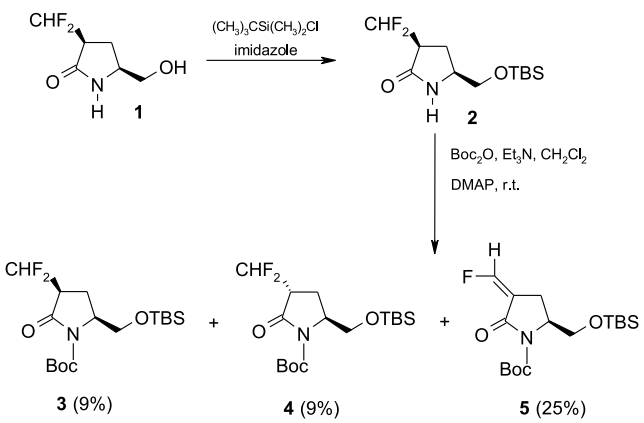
1. Introduction

In recent years, the application of the fluorinated amino acids has been progressed a great deal. As well as being used as the biological tracers and mechanistic probes for investigations on the structures and properties of enzymes, fluorinated amino acids have also played an important role in medicinal chemistry, especially in the control of blood pressure, allergies and tumor growth.[1] In particular, fluorinated amino acids have recently emerged as valuable building blocks for designing hyperstable protein folds, as well as directing highly specific protein–protein interactions.[2] For these reasons, the stereoselective synthesis of novel fluorinated amino acids is of great interest and intensive demand.[1,3,4]

Pyroglutamic acid and its derivatives are important amino acids in many bioactive compounds.[5] The 4-substituted pyroglutamic acid derivatives are important for their conformation and activities. For example, some natural and synthetic 4-substituted glutamic acids have been used to study their structure-–activity relationships of excitatory effects on the nervous system.[6] Although efficient asymmetric synthesis of fluorinated pyroglutamic acids have been reported,[7] to the best of our knowledge, there is no report on the synthesis of monofluoromethyl and monofluoromethylenyl pyroglutamic acids, probably because of the difficulties in stereoselective introduction of monofluoromethyl group into specific position of pyroglutamic acids. Herein reported is the efficient synthesis of two novel fluorinated amino acids: 4-monofluoromethylenyl-L-pyroglutamic acid and *cis*-4-monofluoromethyl-L-pyroglutamic acid via a novel dehydrofluorination reaction.

2. Results and discussion

We accidentally found that the dehydrofluorination reaction occurred when the amino group of 5-*tert*-butyldimethylsilyloxymethyl-3-difluoromethyl-pyrrolidin-2-one **2** was protected with *tert*-butoxycarbonyl group (Boc) (Scheme 1). That was: treatment of compound **2** with di-*tert*-butyl



Scheme 1.

Keywords: Fluorinated amino acids; Pyroglutamic acids; Dehydrofluorination.
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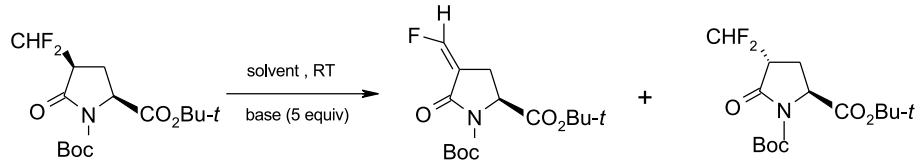
Table 1. Influence of base and solvent on dehydrofluorination reaction of **6**



6 **7** **8**

Entry	Base	Solvent	Time (h)	Product **7**[a] (%)	Product **8**[a] (%)	Conversion (%)
1	Pyridine	CH_2Cl_2	24	2.7[b]	0	10
2	*i*-Pr_2NEt	CH_2Cl_2	24	77	5	92
3	Et_3N	CH_2Cl_2	24	90	0	100
4	Et_3N	THF	24	74	15	96
5	Et_3N	DMF	24	81	0	100
6	Et_3N	CH_3CN	18	90	0	100
7	Et_3N	CH_3CN/H_2O	3	70	0	100
8	Et_3N	THF/H_2O	3	85	0	100

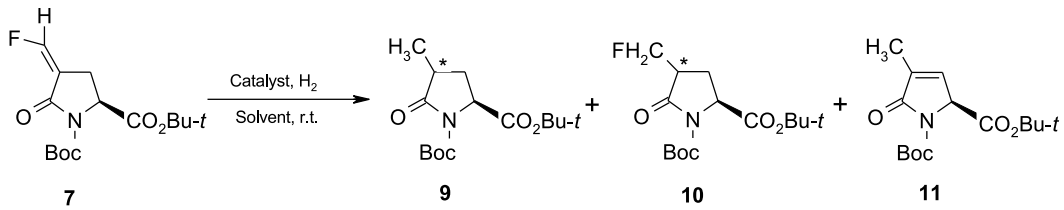
[a] Isolated yield.
[b] Determined by ^1H NMR and ^{19}F NMR.

dicarbonate (Boc_2O) and Et_3N under the catalysis of 4-(dimethylamino)pyridine (DMAP) provided the monofluoro olefin **5** in 25% yield along with desired compound **3** in very low yield (9%). The dehydrofluorination reaction was not observed during the protection of the hydroxy group of 5-hydroxymethyl-3-difluoromethyl-pyrrolidin-2-one **1** with *tert*-butyldimethylsilyl group using imidazole as a base (Scheme 1). In our opinion, dehydrofluorination reaction occurred after the desired product **3** was formed. It was induced by the enhancement of acidity of 4-H as a result of the protection of amino group of **2** by electron-withdrawing groups (Boc). Recently, the synthesis of terminal monofluoro olefins of the general structure $R^1R^2C{=}CHF$ has been summarized by Gen et al.[8] Because loss of HCl, HBr or HI seems sufficiently favorable over dehydrofluorination, only a few syntheses have applied the dehydrofluorination reaction of difluoromethyl groups.[9–11] Among these synthetic methods of terminal monofluoro olefins, all of the dehydrofluorination reactions were carried out in the presence of strong bases (NaOEt, KOH or NaOH) which could cause the racemization of some chiral substrates. The discovery of the dehydrofluorination reaction caused by weak organic amine base (Et_3N) promoted us to improve the yield of this novel dehydrofluorination for the synthesis of 4-monofluoromethylenyl-L-pyroglutamic acid.

We first studied the novel dehydrofluorination reactions with (2*S*, 4*S*)-*tert*-butyl-*N*-*tert*-butoxycarbonyl-4-difluoromethylpyroglutamate **6** as the substrate (Table 1) which was easily prepared from *trans*-4-hydroxy-L-proline.[7a] First, the effect of bases on dehydrofluorination reaction was investigated by conducting the model reaction in CH_2Cl_2 at room temperature (Table 1, entries 1–3). When pyridine was used as the base, the dehydrofluorination reaction proceeded slowly and the defluorinated compound **7** was afforded only in 2.7% yield even after 24 h (entry 1). However, when *i*-Pr_2NEt was used, the reaction rate increased dramatically and the desired compound **7** was isolated in 77% yield along with the isomeric compound **8** in 5% yield (entry 2). The reaction was performed smoothly with Et_3N as the base and compound **7** was obtained in 90% yield after 24 h without isomeric compound **8** formed (entry 3). These experiments showed that the amine bases had a profound influence. Then the investigation of the solvent effect on the reaction was followed (Et_3N as the base, entries 3–8). When the reaction was conducted in THF at room temperature for 24 h, **7** and **8** were isolated in 74 and 15% yields with a little starting material (entry 4). When DMF was used as the solvent, **7** was obtained in 81% yield without the formation of the isomeric compound **8** (entry 5). The reaction was completed in 18 h in CH_3CN to give **7** as the single product in 90% yield (entry 6). Surprisingly, H_2O had not altered the dehydrofluorination reaction, but had enhanced the reaction rate dramatically (entries 7 and 8). When reactions were conducted in a mixed solvent (CH_3CN/H_2O, v/v=2:1; THF/H_2O, v/v=2:1), the dehydrofluorination reaction was finished in 3 h to give **7** in 70 and 85% isolated yields, respectively, without a trace of compound **8** observed. It was easily concluded that Et_3N was the best amine base and THF/H_2O (v/v=2:1) was the most suitable solvent system for the novel dehydrofluorination reaction. The absolute configuration of **7** was confirmed by NOE correlation.

With compound **7** in hand, we turned our attention to synthesize 4-monofluoromethyl pyroglutamic acid via the catalytic hydrogenations of **7** (Table 2). There are only a few reports on the catalytic hydrogenation of α- or β-fluoro-α, β-unsaturated esters and ketones.[12] This may be due to the hydrogenolyic lability of vinylic fluorine compared to the saturated counterpart.[13] The catalytic hydrogenation of **7** was first carried out under usual condition (Table 2, entries 1–3). However, the desired compound **10** was not observed, and only defluorinated compound **9** was isolated in moderate yields and good diastereoselectivities (entry 1, 10% Pd/C, 81% yield, *cis*/*trans*=19.3:1; entry 2, 10% Pt/C, 83% yield, *cis*/*trans*=5.9:1). Even with Ranney Ni as the catalyst in MeOH, compound **10** was still not observed except **9** (entry 3). In our opinion, these three catalysts caused the hydrogenolytic cleavage of carbon–fluorine bonds due to their strong catalytic activities. Thus, some weak catalysts were tried (entries 4–6). Surprisingly, *cis*-**10** was obtained in 12% yield along with **9** (77% yield) when

Table 2. Influence of catalysts and solvents on hydrogenation of **7**



Entry	Catalyst	Solvent	Time (h)	**9** Yield (%) (*cis*:*trans*)	**10** Yield (%) (*cis*:*trans*)	**11** Yield (%)	Conversion (%)
1	10% Pd/C	EtOH	5	81 (19.3:1.0)[a]	—	—	100
2	5% Pd/C	EtOH	0.5	83 (5.9:1.0)[a]	—	—	100
3	Ranney Ni	MeOH	1	96[b]	—	—	100
4	$Pd(OH)_2/C$	EtOH	0.5	77 (25.0:1.0) [a]	12[c]	—	100
5	$Pd-CaSO_4$	EtOH	0.5	74 (36.0:1.0) [a]	19[c]	—	100
6	$Pd-BaSO_4$	EtOH	1	75 (74.0:1.0) [a]	20[c]	—	100
7	$Pd-BaSO_4$	EtOH[d]	24	47[b]	1.5[e]	—	84[f]
8	$Pd-BaSO_4$	THF	24	45[b]	37[c]	9.7[g]	95[f]
9	$Pd-BaSO_4$	CH_2Cl_2	24	8[b]	29[c]	12.0[g]	88[f]
10	$Pd-BaSO_4$	EtOAc	2	20[b]	77 (>38.5:1.0)[h]	—	100
11	$Pd-BaSO_4$	Dioxane	2	13[b]	78 (>78.0:1.0)[h]	—	100

[a] *Cis*and *trans* were isolated by flash chromatography.
[b] No or trace *trans*-**9** was observed or determined.
[c] No *trans*-**10** was isolated or detected.
[d] Several drops of quinoline was added.
[e] Determined by ^1H NMR.
[f] Starting material was recovered.
[g] Isolated yield.
[h] Trace *trans*-**10** was detected or isolated.

$Pd(OH)_2/C$ was used in EtOH (entry 4). *cis*-**10** was also isolated in 19 and 20% yields, respectively, with $Pd-CaSO_4$ and $Pd-BaSO_4$ as catalysts in EtOH (entries 5 and 6). However, when $Pd-BaSO_4$ was poisoned with several drops of quinoline, **10** was observed only in 1.5% yield together with **9** (47%) and starting material even after 24 h (entry 7). Then, different solvents were investigated with $Pd-BaSO_4$ as the catalyst (entries 8–11). The usage of THF

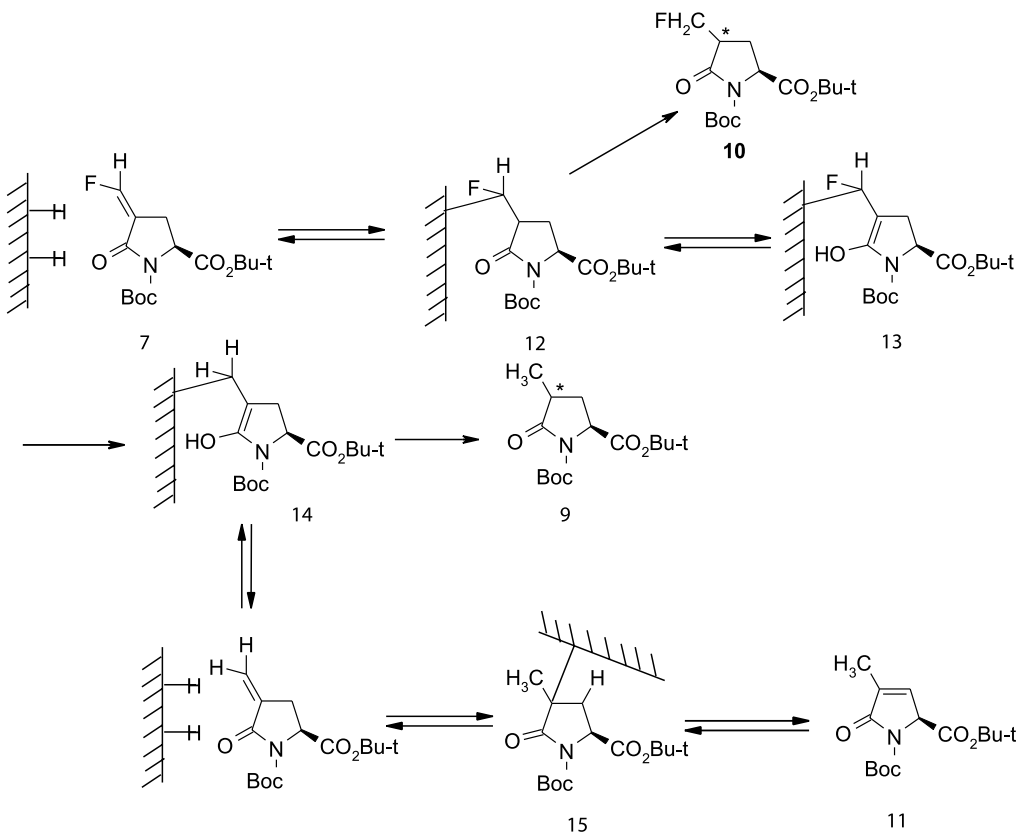


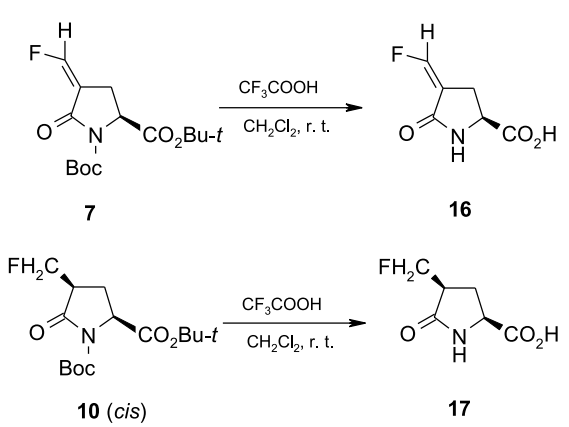
Figure 1. Mechanism of hydrogenation of compound **7**.

and CH_2Cl_2 gave **10** in 37 and 29% yields, respectively, together with **9** (entries 8 and 9), to our surprise, the unexpected defluorinated compound **11** was also observed in 9.7 and 12.0% yields, respectively. The best results were obtained when EtOAc and dioxane were used as the solvents. **10** was isolated in 77 and 78% yields, respectively, with a small amount of **9** formed (entries 10 and 11). It was concluded from these results that the catalysts and solvents had great effects on the hydrogenation of **7**. The absolute configuration of *cis*-**10** was confirmed by X-ray diffraction.

How to explain the hydrogenation mechanism was a challenge for us. According to the different products, the reaction probably proceeded through the following mechanism (Fig. 1). Attachment of **7** to Pd carrier gave the intermediate **12** which could be directly hydrogenated to give the desired compound **10**. **12** could also transform to **13** due to the enolization of lactam. Elimination of HF from **13** by rearranging the enol followed by reattachment of Pd afforded the intermediate **14** that could be reductive eliminated to furnish **9**. **14** could be converted to **15** via reduction elimination followed by re-attachment to Pd carrier. Finally, compound **11** was provided via elimination of 3-H of **15**.

With **7** and *cis*-**10** in hand, one-step removal of protective groups with trifluoroacetic acid in CH_2Cl_2 successfully afforded two important fluorine-containing amino acids: 4-monofluoromethylenyl-L-pyroglutamic acid **16** and *cis*-4-monofluoromethyl-L-pyroglutamic acid **17** in 72 and 66% yields, respectively, (Scheme 2).

In conclusion, we have described a novel dehydrofluorination reaction caused by weak organic amino base and have systematically investigated the effects of the different bases and solvents on the reaction. The process of this reaction was simple operated with readily available and cheap reagents and occurred under very mild condition. We have also described the hydrogenation of the resulting desired compound **7** in view of different catalysts and solvents, and have proposed a corresponding hydrogenation mechanism. Finally, we have synthesized two important fluorine-containing amino acids: 4-monofluoromethylenyl-L-pyroglutamic acid **16** and *cis*-4-monofluoromethyl-L-pyroglutamic acid **17**. We believe that the novel dehydrofluorination reaction and hydrogenation of corresponding defluorinated compounds could be applied to synthesize other α-monofluoromethylenyl amide analogues and corresponding α-monofluoromethyl amide analogues. Studies on detailing the application of this novel reaction to other substrates and incorporation of these two novel important fluorine-containing amino acids into peptides, domimetics and potential bioactive molecules are in intensive progress.



Scheme 2.

3. Experimental

3.1. General procedure for dehydrofluorination of comound 6

To a solution of **6** (around 100 mg) in the different solvent (10 mL), organic base (5.0 equiv.) was added dropwise. Then, the mixture was stirred at room temperature. The reaction was quenched with H_2O (5 mL) and the resulted mixture was extracted with CH_2Cl_2. The combined organic phases were washed with brine and dried over anhydrous Na_2SO_4. Filtration and removal of the solvent gave a residue, which was purified by silica gel chromatography to afford the corresponding products.

3.1.1. (2*S*)-*tert*-Butyl-*N*-*tert*-butoxycarbonyl-4-monofluoromethylenylpyroglutamate 7. White solid; Mp 104–105 °C; $[\alpha]_D^{20}$ −17.1 (*c* 0.5, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.51 (dt, *J*=78.4, 3.0 Hz, 1H), 4.52 (dd, *J*=3.3, 2.7 Hz, 1H), 3.02 (m, 1H), 2.72 (dq, *J*=17.6, 3.0 Hz, 1H), 1.53 (s, 9H), 1.48 (s, 9H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −120.6–120.8 (dq, *J*=78.3, 3.0 Hz, 1F); IR (thin film) ν_{max} 1784, 1772, 1747, 1711, 1690, 1294, 1149 cm^{-1}; MS (ESI) *m*/*z* 338 (M^++Na); Anal. Calcd for $C_{15}H_{22}FNO_5$: C, 57.13; H, 7.03; N, 4.44. Found: C, 57.18; H, 7.12; N 4.33.

3.1.2. (2*S*,4*R*)-*tert*-Butyl-*N*-*tert*-butoxycarbonyl-4-difluoromethylpyroglutamate 8. White solid; Mp 66–68 °C; $[\alpha]_D^{20}$ −21.1 (*c* 0.6, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 6.23 (td, *J*=55.4, 2.1 Hz, 1H), 4.51 (dd, *J*=1.8, 2.1 Hz, 1H), 3.30–3.12 (m, 1H), 2.58–2.47 (m, 1H), 2.12 (ddd, *J*=13.8, 1.8, 1.8 Hz, 1H), 1.52 (s, 9H), 1.49 (s, 9H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −124.0 to −125.2 (dd, *J*=277.5, 54.1 Hz, 1F), −127.3–128.6 (ddd, *J*=286.2, 25.0, 27.6 Hz, 1F); IR (thin film) ν_{max} 1758, 1739, 1717, 1327, 1158 cm^{-1}; MS (ESI) *m*/*z* 353 (M^++NH_4); Anal. Calcd for $C_{15}H_{23}F_2NO_5$: C, 53.72; H, 6.91; N, 4.18. Found: C, 53.92; H, 6.99; N, 4.02.

3.2. General procedure for hydrogenation of compound 7

To a solution of compound **7** in the solvent, Pd-catalyst (5–10% mmol) was added. The mixture was hydrogenated at room temperature. Filtration and removal of the solvent gave a residue that was purified by silica gel chromatography to afford the corresponding products.

3.2.1. (2*S*,4*S*)-*tert*-Butyl-*N*-*tert*-butoxycarbonyl-4-methylpyroglutamate 9 (*cis*). White solid; Mp 58–60 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 4.41–4.36 (m, 1H), 2.67–2.50 (m, 2H), 1.62–2.56 (m, 1H), 1.51 (s, 9H), 1.49 (s, 9H), 1.23 (d, *J*=6.9 Hz, 3H); ^{13}C NMR spectra was identical to that of literature (*J. Chem. Soc., Perkin Trans. 1* **1996**, 507).

3.2.2. (2*S*,4*R*)-*tert*-Butyl-*N*-*tert*-butoxycarbonyl-4-methylpyroglutamate 9 (*trans*). White solid; Mp 63–64 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.43 (dd, J=1.5, 1.8 Hz, 1H), 2.73–2.59 (m, 1H), 2.28–2.20 (m, 1H), 1.95–1.84 (m, 1H), 1.51 (s, 9H), 1.48 (s, 9H), 1.23 (d, J=7.2 Hz, 1H) (literature reported: 4.42 (d, J=9.5 Hz, 1H), 2.65 (m, 1H), 2.24 (ddd, J=13.5, 8.7, 1.0 Hz, 1H), 1.89 (m, 1H), 1.51 (s, 9H), 1.48 (s, 9H), 1.21 (t, J=7.0 Hz, 1H). *J. Chem. Soc., Perkin Trans. 1* **2001**, 2367.)

3.2.3. (2*S*,4*S*)-*tert*-Butyl-*N*-*tert*-butoxycarbonyl-4-monofluoromethylpyroglutamate 10 (*cis*). White solid; Mp 68–70 °C; $[\alpha]_D^{20}$ −35.7 (c 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.73 (ddd, J=21.4, 5.1, 5.0 Hz, 1H), 4.58 (ddd, J=20.9, 5.1, 5.0 Hz, 1H) 4.48 (dd, J=5.4, 5.7 Hz, 1H), 3.01–2.84 (m, 1H), 2.62–2.51 (m, 1H), 2.08–2.00 (m, 1H), 1.52 (s, 9H), 1.48 (s, 9H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −227.9 (m, 1F); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 171.5 (d, J=9.6 Hz), 170.1, 149.2, 83.8, 83.2, 81.7 (d, J=112.6 Hz), 58.0, 44.0 (d, J=21.7 Hz), 29.7, 27.9, 27.8, 23.9 (d, J=3.2 Hz); IR (thin film) ν_{max} 1757, 1740, 1713, 1321, 1156 cm^{-1}; MS (ESI) m/z 657 ($2M^+$ +Na), 652 ($2M^+$+NH_4), 335 (M^++NH_4); Anal. Calcd for $C_{15}H_{24}FNO_5$: C, 56.77; H, 7.62; N, 4.41. Found: C, 56.93; H, 7.69; N 4.12.

3.3. X-ray crystal structures of 10 (*cis*)

A white crystal having approximate dimension of 0.36×0.26×0.20 mm^3 was used for X-ray study. The data were collected on Bruker Smart APEX CCD diffractometer. The crystal structure has been deposited at the Cambridge crystallographic Data center and allocated the deposition number CCDC 236000.

Crystal data: $C_{15}H_{24}FNO_5$, M=317.35, Orthorhombic, Space group $P2(1)2(1)2(1)$, α=8.7047(13), β=11.2204(16), c=17.628 (3) Å, V=1721.7(4) Å^3, Z=4, D_{calc}=1.224 mg cm^{-3}, μ=0.098 mm^{-1}, $F(000)$=680, T=293 K, 2θmax=56.56°, 4036 independent reflections scanned, 1716 reflections observed ($I \geqq 2\sigma(I)$), 296 parameters, $R1$=0.0420, $wR2$=0.0654.

3.3.1. (2*S*)-*tert*-Butyl-*N*-*tert*-butoxycarbonyl-4-methyl-3,4-dehydropyroglutamate 11. White solid; Mp 59–61 °C; $[\alpha]_D^{20}$ −218.1 (c 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.71–6.69 (m, 1H), 4.91–4.89 (m, 1H), 1.92 (t, J=4.8 Hz, 3H), 1.55 (s, 9H), 1.48 (s, 9H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 169.1, 165.9, 148.8, 136.8, 135.9, 83.2, 83.1, 63.2, 28.0, 27.9, 11.0; IR (thin film) ν_{max} 3082, 2982, 1787, 1747, 1721, 1657, 1160 cm^{-1}; MS (ESI) m/z 617 ($2M^+$+Na), 612 ($2M^+$+NH_4); Anal. Calcd for $C_{15}H_{23}NO_5$: C, 60.59; H, 7.80; N, 4.71. Found: C, 60.88; H, 7.78; N, 4.59.

3.3.2. (2*S*)-4-Monofluoromethylenylpyroglutamic acid (16). TFA (0.85 mL) was added to a solution of **7** (205 mg, 0.65 mmol) in CH_2Cl_2 (15 mL) at 0 °C. The mixture was allowed to warm to room temperature and stirred for 24 h. The reaction mixture was concentrated in vacuo and the residue was triturated with Et_2O–petroleum ether to precipitate white solid, which was washed several times with Et_2O–petroleum ether. Remaining of the resulted solid was dried under high vacuum at 60 °C for several hours to give **16** (75 mg, 72%) as an off-white solid. Mp 153–154.5 °C; $[\alpha]_D^{20}$+37.6 (c 1.1, H_2O); ^{1}H NMR (300 MHz, MeOH-d_4) δ 7.44 (dt, J=78.3, 3.0 Hz, 1H), 4.50 (dd, J=4.2, 4.2 Hz, 1H), 3.37–3.26 (m, 1H), 3.04–2.97 (m, 1H); ^{19}F NMR (282 MHz, MeOH-d_4) δ −123.5 to −123.8 (dt, J=78.5, 3.9 Hz, 1F); ^{13}C NMR (75.5 MHz, MeOH-d_4) δ 176.6, 173.6 (d, J=19.5 Hz), 154.2 (d, J=270.3 Hz), 116.1 (d, J=13.4 Hz), 54.7, 26.6; IR (thin film) ν_{max} 3370, 3319, 3101, 2471, 1918, 1726, 1703, 1642, 1257, 1087 cm^{-1}; MS (EI) m/z 159 (M^+, 2), 114 (M^+ −COOH, 100); Anal. Calcd for $C_6H_6FNO_3$: C, 45.29; H, 3.80; N, 8.80. Found: C, 45.17; H, 3.78; N, 8.54.

3.3.3. (2*S*,4*S*)-4-Monofluoromethylpyroglutamic acid (17). Compound **17** (66 mg, 66%) was prepared as an off-white solid from compound **10** (*cis*) (198 mg, 0.625 mmol) following the procedure described for compound **16**. Mp 110–112 °C; $[\alpha]_D^{20}$ −28.4 (c 0.60, H_2O); ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.87 (s, 1H), 8.15 (s, 1H), 4.61 (ddd, J=34.9, 4.5, 4.5 Hz, 1H), 4.51 (ddd, J=34.9, 3.0, 3.0 Hz, 1H) 4.11 (t, J=7.2 Hz, 1H), 2.80–2.55 (m, 2H), 1.95–1.85 (m, 1H); ^{19}F NMR (282 MHz, DMSO-d_6) δ −227.8 (m, 1F); ^{13}C NMR (75.5 MHz, MeOH-d_4) δ 189.6, 186.4, 93.2 (d, J=165.6 Hz), 65.2, 53.4 (d, J=20.5 Hz), 37.4 (d, J=4.0 Hz); IR (thin film) ν_{max} 3366, 1716, 1664, 1642, 1265, 948 cm^{-1}; MS (EI) m/z 161 (M^+, 2), 116 (M^+ −COOH, 100); Anal. Calcd for $C_6H_8FNO_3$: C, 44.72; H, 5.00; N, 8.69. Found: C, 44.46; H, 4.95; N, 8.56.

Acknowledgements

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References and notes

1. (a) Welch, J. T.; Eswarakrishnan, S. *Fluorine in Bioorganic Chemistry*; Wiley: New York, 1991. (b) Kukhar, V. P.; Soloshonok, V. A. *Fluorine Containing Amino Acids: Synthesis and Properties*; Wiley: New York, 1995. (c) Filler, R.; Kobayashi, Y.; Yagupolski, L. M. *Biomedical Aspects of Fluorine Chemistry*; Elsevier: Amsterdam, 1993.
2. For a recent review, see: Yoder, N. C.; Kumar, K. *Chem. Soc. Rev.* **2002**, *31*, 335–341.
3. For reviews, see: (a) Haufe, G.; Kroger, S. *Amino Acids* **1996**, *11*, 409–424. (b) Tolman, V. *Amino Acids* **1996**, *11*, 15–36. (c) Sutherland, A.; Willis, C. L. *Nat. Prod. Rep.* **2000**, *17*, 621–631.
4. For recent examples, see: (a) Vera-Ayoso, Y.; Borrachero, P.; Cabrera-Escribano, F.; Diánez, M. J.; Estrada, M. D.; Gómez-Guillén, M.; López-Castro, A.; Pérez-Garrido, S. *Tetrahedron: Asymmetry* **2001**, *12*, 2031–2041. (b) Xing, X.; Fichera, A.; Kumar, K. *Org. Lett.* **2001**, *3*, 1285–1286. (c) Fustero, S.; Navarro, A.; Pina, B.; Soler, J. G.; Bartolomé, A.; Asensio, A.; Simon, A.; Bravo, P.; Fronza, G.; Volonterio, A.; Zanda, M. *Org. Lett.* **2001**, *3*, 2621–2624. (d) Abe, H.; Amii, H.; Uneyama, K. *Org. Lett.* **2001**, *3*, 313–315. (e) Lebouvier, N.; Laroche, C.; Huguenot, F.; Brigaud, T. *Tetrahedron Lett.* **2002**, *43*, 2827–2830. (f) Xing, X.; Fichera, A.; Kumar, K. *J. Org. Chem.* **2002**, *67*, 1722–1725. (g) Staas, D. D.; Savage, K. L.; Homnick, C. F.; Tsou, N. N.; Ball, R. G. *J. Org. Chem.*

2002, *67*, 8276–8279. (h) Del Valle, J. R.; Goodman, M. *Angew. Chem., Int. Ed.* **2002**, *41*, 1600–1602. (i) Fustero, S.; Pina, B.; Salavert, E.; Navarro, A.; Ramírez de Arellano, C.; Fuentes, A. S. *J. Org. Chem.* **2002**, *67*, 4667–4679. (j) Anderson, J. T.; Toogood, P. L.; Marsh, E. N. G. *Org. Lett.* **2002**, *4*, 4281–4283. (k) Sani, M.; Bruche, L.; Chiva, G.; Fustero, S.; Piera, J.; Volonterio, A.; Zanda, M. *Angew. Chem., Int. Ed.* **2003**, *42*, 2060–2063. (l) Fustero, S.; Bartolome, A.; Sanz-Cervera, J. F.; Sanchez-Rosello, M.; Soler, J. G.; Ramírez de Arellano, C.; Fuentes, A. S. *Org. Lett.* **2003**, *5*, 2523–2526.

5. (a) Barco, A.; Benetti, S.; Pollini, G. P.; Baraldi, P. G.; Guarneri, M.; Gandolfi, C.; Ceserani, R.; Longiave, D. *J. Med. Chem.* **1981**, *24*, 625–628. (b) Kar, G. K.; Roy, B. C.; Adhikari, S. D.; Ray, J. K.; Brahma, N. K. *Bioorg. Med. Chem.* **1998**, *6*, 2397–2403.
6. Hon, Y.-S.; Chang, Y.-C.; Gong, M.-L. *Heterocycles* **1990**, *31*, 191–195.
7. (a) Qiu, X.-L.; Qing, F.-L. *J. Org. Chem.* **2003**, *68*, 3614–3617. (b) Hudlickú, M. *J. Fluorine Chem.* **1993**, *60*, 193–210. (c) Tolman, V.; Vlasáková, V.; Němeček, J. *J. Fluorine Chem.* **1993**, *60*, 185–191. (d) Tolman, V.; Sedmera, P. *J. Fluorine Chem.* **2000**, *101*, 5–10. (e) Doyle, M. P.; Hu, W.; Phillips, I. M.; Moody, C. J.; Pepper, A. G.; Slawin, A. M. Z. *Adv. Synth. Catal.* **2001**, *343*, 112–117. (f) Vidal-Cros, A.; Gaudry, M.; Marquet, A. *J. Org. Chem.* **1985**, *50*, 3163–3167. (g) Hart, B. P.; Coward, J. K. *Tetrahedron Lett.* **1993**, *34*, 4917–4920. (h) Hart, B. P.; Haile, W. H.; Licato, N. J.; Bolanowska, W. E.; McGuire, J. J.; Coward, J. K. *J. Med. Chem.* **1996**, *39*, 56–65.
8. van Steenis, J. H.; van der Gen, A. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2117–2133.
9. Komatsu, Y.; Sakamoto, T.; Kitazume, T. *J. Org. Chem.* **1999**, *64*, 8369–8374.
10. Bornstein, J.; Blum, M. S.; Pratt, Jr. J. J. *J. Org. Chem.* **1957**, *22*, 1210–1213.
11. McDonald, I. A.; Lacoste, J. M.; Bey, P.; Palfreyman, M. G.; Zreika, M. *J. Med. Chem.* **1985**, *28*, 186–193.
12. (a) Martinet, P.; Sauvetre, R.; Normant, J.-F. *J. Fluorine Chem.* **1991**, *52*, 419–432. (b) Allmendinger, T.; Dandois, C.; Walliser, B. *Tetrahedron Lett.* **1991**, *32*, 2735–2736. (c) Zheng, G.-C.; Yoshihara, K.; Kobayashi, Y.; Taguchi, T. *Chem. Express* **1990**, *5*, 577–580.
13. (a) Hudlicky, M. *J. Fluorine Chem.* **1979**, *14*, 189–199. (b) Hudlickú, M. *J. Fluorine Chem.* **1983**, *23*, 241–259.