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4-Fluoropyrrolidine-2-carbonyl Fluorides: Useful Synthons and Their Facile Preparation with 4-*tert*-Butyl-2,6-dimethylphenylsulfur Trifluoride†

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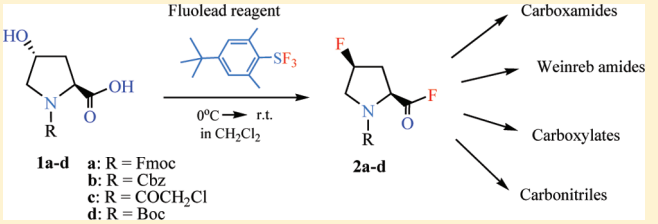
Supporting Information

ABSTRACT: 4-Fluoropyrrolidine derivatives are useful in medicinal chemistry applications such as dipeptidyl peptidase IV inhibitors. As attractive synthons for these, *N*-protected (2*S*,4*S*)-4-fluoropyrrolidine-2-carbonyl fluorides were synthesized in high yield by double fluorination of *N*-protected (2*S*,4*R*)-4-hydroxyproline with 4-*tert*-butyl-2,6-dimethylphenylsulfur trifluoride (Fluolead). The 4-fluoropyrrolidine-2-carbonyl fluorides were converted to useful intermediates such as 4-fluoropyrrolidine-2-carboxamides, -*N*-methoxy-*N*-methylcarboxamide (Weinreb amide), -carboxylate methyl esters, and -carbonitriles in excellent yields. The crystalline *N*-Fmoc-*cis*-4-fluoropyrrolidine-2-carbonyl fluoride **2a** is a particularly useful synthon due to its high yield of preparation and easy isolation as an enantiomerically pure compound by crystallization. Thus, the methodology using the synthons prepared by the stereospecific double fluorination has enabled a significant decrease in the synthetic steps needed for the preparation of the 4-fluoropyrrolidine derivatives useful for medicinal applications.



INTRODUCTION

Fluorine has an increasingly important role in medicinal chemistry and drug design, as it often imparts enhanced biological activity, metabolic stability, binding interaction, or other desirable traits in the physical properties of drug molecules.[1] Therefore, research into the biochemical applications of fluorinated compounds has been conducted extensively and actively.[1]

Recently, 4-fluoropyrrolidine derivatives **A**,[2] **B**,[3] **C**,[4] and **D**[5] as shown in Figure 1 have been developed as potent dipeptidyl peptidase (DPP) IV inhibitors for diabetes treatment. 4-Fluoropyrrolidine derivatives ***I***, ***II***, ***III***, ***IV***, and ***V*** as shown in Figure 2 have been used as key intermediates for the preparation of these DPP IV inhibitors.[2−6] In particular, carboxamide ***IV*** and carbonitrile ***V*** are important intermediates for the preparation of DPP inhibitors having a substituted acetyl group at the *N*-position such as **C** and **D**.

The conventional methodologies have been limited by the fact that the carboxyl group in 4-hydroxyprolines must be protected or changed to another functional group inactive to fluorination, such as a methoxycarbonyl or cyano, before fluorination of the 4-hydroxy group with a deoxofluorinating agent. Therefore, many synthetic steps have been required as illustrated below. In addition, diethylaminosulfur trifluoride (DAST) has been used as the deoxofluorinating agent of choice in most cases of conventional synthesis schemes. However, DAST has low thermal stability, is potentially explosive, and is not easily handled due to fuming in air and vigorous reaction on contact with water.[7]

Thus, (2*S*,4*S*)-4-fluoropyrrolidine derivatives ***I***−***V*** have been prepared as shown in Scheme 1.[2,3] A starting material, (2*S*,4*R*)-4-hydroxyproline (***VI***), was (i) esterified and (ii) *N*-protected with a group such as *tert*-butoxycarbonyl (Boc) group to give compound

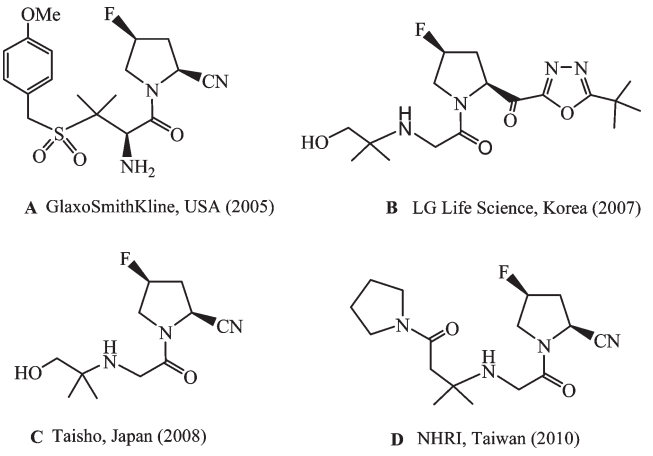


Figure 1. Potent DPP-IV inhibitors.

VIII, which was then (iii) fluorinated with DAST[2,8−10] to give ***IX***. Next, step (iv) was a careful hydrolysis of ***IX*** with lithium hydroxide giving ***X*** with the possibility of racemization. Acid ***X*** was transformed to carboxamide ***I*** in two steps, (v) a reaction with di-*tert*-butyldicarbonate followed by (vi) ammonium bicarbonate. Compound ***I*** was dehydrated to give carbonitrile ***II***. Weinreb amide ***III*** (R = Boc) was prepared by (viii) treating ***X*** with *N*,*O*-dimethylhydroxylamine hydrochloride/EDC/HOBt/Et_3N/DMF.[3,6b] (2*S*,4*S*)-*N*-Haloacetyl-4-fluoropyrrolidine-2-carboxamide ***IV*** was prepared by (ix) *N*-deprotection of carboxamide ***I***, followed by (x) haloacetylation.

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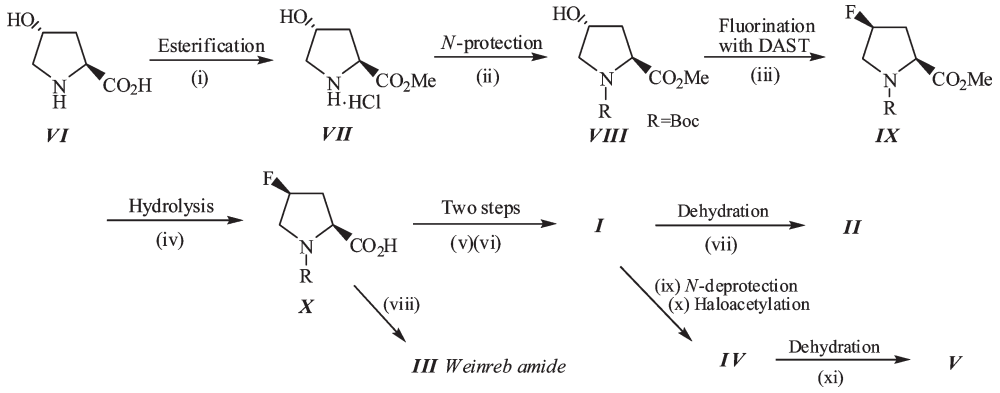
Scheme 1. Conventional Preparation of Useful Intermediates *I*−*V*



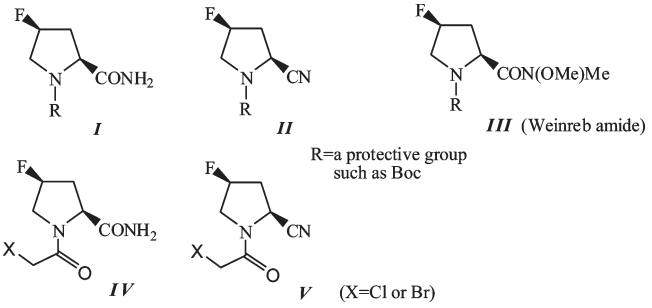


Figure 2. Useful 4-fluoropyrrolidine intermediates for DPP IV inhibitors.

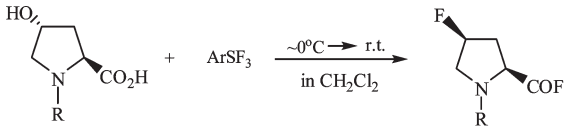
Compound ***IV*** was dehydrated (xi) to give (2*S*,4*S*)-*N*-haloacetyl-4-fluoropyrrolidine-2-carbonitrile ***V***.[2,11]

4-Fluoropyrrolidine-2-carbonitrile ***II*** was prepared alternatively.[2] The starting material ***VI*** was converted to *N*-Boc-4-hydroxyproline, which was followed by three steps, treatments with ClCOOEt/Et_3N, ammonia, and then trifluoroacetic anhydride to give *N*-Boc-4-hydroxypyrrolidine-2-carbonitrile. Fluorination of the carbonitrile with DAST afforded ***II***.

Since the fluorination with DAST involves a potentially serious safety issue,[7] methods have been reported using other deoxofluorinating agents such as morpholinosulfur trifluoride (Morpho-DAST),[12] Yarovenko reagent ($ClCHFCF_2NEt_2$),[13] Ishikawa reagent ($CF_3CHFCF_2NEt_2$),[13,14] and 2,2-difluoro-1,3-dimethylimidazolidine (DFI).[15] Morpho-DAST and DFI are more stable than DAST. The fluorinations with $C_8F_{17}SO_2F$/DBU[16] and with Tf_2O/pyridine followed by treatment with tetrabutylammonium fluoride[17] have also been reported. Fluorination of a related compound, *N*-benzyl-4-hydroxypyrrolidine, with Deoxo-Fluor reagent [$(MeOCH_2CH_2)_2NSF_3$] that is more thermally stable than DAST has been reported.[18]

Recently, we have developed 4-*tert*-butyl-2,6-dimethylphenylsulfur trifluoride (Fluolead) as a novel new and versatile deoxofluorinating agent that has high thermal stability and ease of handling.[19a] Fluolead reagent fluorinates alcohols,[19a−e] aldehydes, ketones, and carboxylic acids, giving the corresponding CF, CF_2, and CF_3 compounds in high yields.[19a] It also reacts with thiocarbonyl, thioester, and dithiocarbonate compounds to give the corresponding CF_2, CF_2O, and CF_3O compounds.[19a] Reactions with bifunctional compounds such as diols and amino alcohols provide stereoselective deoxofluoroarylsulfinylation products.[19a] Here, with Fluolead, we have developed a stereospecific double fluorination of (2*S*,4*R*)-4-hydroxypyrrolines as another example of bifunctional compounds, giving (2*S*,4*S*)-4-fluoropyrrolidine-2-carbonyl fluorides, as a new synthetic strategy, which significantly decreases the necessary reaction steps for the preparation of useful 4-fluorinated pyrrolidine intermediates for medicinal applications.

Scheme 2. Reaction of *trans*-4-Hydroxy-L-proline Derivatives with $ArSF_3$



1a-d
1a: R = Fmoc (9-fluorenylmethyloxycarbonyl)
1b: R = Cbz (benzyloxycarboyl)
1c: R = $COCH_2Cl$
1d: R = Boc (*tert*-butoxycarbonyl)

2a-d
2a: R = Fmoc
2b: R = Cbz
2c: R = $COCH_2Cl$
2d: R = Boc

RESULTS AND DISCUSSION

Based on literature researching we have found that there are no reports on double deoxofluorination of 4-hydroxyprolines to achieve 4-fluoropyrrolidine-2-carbonyl fluorides. The double deoxofluorination has been found by us to be a very useful methodology for reducing the number of steps required for the production of pharmaceutically useful 4-fluoropyrrolidine derivatives. This is based on 4-*tert*-butyl-2,6-dimethylphenylsulfur trifluoride (Fluolead), which has recently been developed as a deoxofluorinating reagent.[19] Fluolead is versatile, relatively highly safe, shelf-stable, and easily handled in comparison to DAST, Deoxo-Fluor, and other related deoxofluorinating agents.[19a]

With (2*S*,4*R*)-*N*-Fmoc-4-hydroxyproline (**1a**) as a substrate, the reaction of Fluolead reagent proceeded smoothly in dichloromethane at ice bath temperature (~0 °C) to room temperature to produce (2*S*,4*S*)-*N*-Fmoc-4-fluoropyrrolidine-2-carbonyl fluoride (**2a**) in 90% NMR yield (78% isolated yield), as shown in Scheme 2 and Table 1 (run 1). The fluorination of the hydroxyl group at the 4-positon proceeded in an inversion manner. Monitoring the reaction by ^{19}F NMR indicated that the formation of the carbonyl fluoride moiety was fast (<0.5 h), but the fluorination of the hydroxyl group was slow (about 60 h at rt).

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Table 1. Synthesis of 4-Fluoropyrrolidine-2-carbonyl Fluoride Derivatives with $ArSF_3$

run	substrate	$ArSF_3$[a]	solvent	T (°C), time (h)	additive[b]	product	yield[c] (%)
1	**1a**	Fluolead	CH_2Cl_2	~0 °C to rt, 1 h; rt, 60 h		**2a**	90 (78)
2	**1a**	Fluolead	CH_2Cl_2	~0 °C to rt, 1 h; rt, 22 h	HF−py, 0.1 equiv	**2a**	100 (88)
3	**1a**	Fluolead	CH_2Cl_2	~0 °C to rt, 1 h; rt, 5 h	HF−py, 0.4 equiv	**2a**	92 (84)
4	**1a**	$C_6H_5SF_3$	CH_2Cl_2	~0 °C to rt, 1 h; rt, 60 h		**2a**	68
5	**1a**	*p*-$ClC_6H_4SF_3$	CH_2Cl_2	~0 °C to rt, 1 h; rt, 60 h		**2a**	54
6	**1b**	Fluolead	CH_2Cl_2	~0 °C to rt, 1 h; rt, 60 h		**2b**	90 (75)
7	**1c**	Fluolead	CH_2Cl_2	~0 °C to rt, 1 h; rt, 72 h		**2c**	90 (76)
8	**1d**	Fluolead	CH_2Cl_2	~0 °C to rt, 1 h; rt, 45 h		**2d**	27
9	**1d**	Fluolead	CH_2Cl_2	~0 °C to rt, 1 h; rt, 45 h	pyridine, 0.5 equiv	**2d**	90
10	**1d**	Fluolead	CH_2Cl_2	~0 °C to rt, 1 h; rt, 60 h	Et_3N, 0.25 equiv	**2d**	77
11	**1d**	Fluolead	CH_2Cl_2/Et_2O(9/1)	~0 °C to rt, 1 h; rt, 20 h		**2d**	56

[a] The amount of $ArSF_3$ used was a 2.5 equimolar amount relative to a substrate except for runs 4 and 10, in which 3.8 and 3.0 equimolar amounts of $ArSF_3$ were used, respectively. Fluolead = 4-*tert*-butyl-2,6-dimethylphenylsulfur trifluoride. [b] The amount of an additive used is shown relative to a substrate. HF-py (py = pyridine) (density 1.1) (available from commercial suppliers) is a 7:3 w/w of anhydrous HF and pyridine, and its molecular weight is considered to be 263 as $C_5H_5N(HF)_{9.2}$. [c] Yields are based on ^{19}F NMR using fluorobenzene as a standard, and yields in parentheses are isolated yields.

Phenylsulfur trifluoride and *p*-chlorophenylsulfur trifluoride in place of Fluolead under the same reaction conditions provided 68% and 54% yields of the product **2a**, respectively (runs 4 and 5, Table 1). Thus, Fluolead is superior to unsubstituted and chlorine atom-substituted phenylsulfur trifluorides since multialkylated Fluolead is reactive, while electron-withdrawing group-substituted phenylsulfur trifluoride is deactivated. When HF−pyridine (7:3 w/w) was used as a catalyst, the double fluorination reaction of **1a** with Fluolead was found to be accelerated. With addition of 0.1 equiv of HF−pyridine, the reaction was complete in quantitative yield in less than 22 h (run 2). With 0.4 equiv of HF−pyridine, the reaction was greatly accelerated and almost completed around 5 h (run 3).

Similarly to **1a**, (2*S*,4*R*)-*N*-Cbz- and -*N*-chloroacetyl-4-hydroxyproline (**1b**) and (**1c**) reacted with Fluolead to give (2*S*,4*S*)-*N*-Cbz- and -*N*-chloroacetyl-4-fluoropyrroline-2-carbonyl fluoride (**2b** and **2c**) in excellent yields, respectively (runs 6 and 7). However, reaction of (2*S*,4*R*)-*N*-Boc-4-hydroxyproline (**1d**) with Fluolead gave (2*S*,4*S*)-*N*-Boc-4-fluoropyrroline-2-carbonyl fluoride (**2d**) in very low yield (27%, run 8). The low yield was due to deprotection of the acid-sensitive *tert*-butoxycarbonyl (Boc) group occurring under the reaction conditions, as ^{19}F NMR of the reaction mixture showed *tert*-butyl fluoride, a Boc-cleavage product, was formed in 43% yield. The yield of **2d** was greatly improved when a 0.5 equimolar amount of pyridine relative to a substrate was added as a HF-trap agent (90% in run 9). The reaction was slow or incomplete when pyridine was used in more than 0.5 equiv amounts, while the deprotection reaction occurred when less than 0.5 equiv of pyridine was used. When a 0.25 equimolar amount of triethylamine was used, the yield was 77% (run 10). When a 9:1 v/v mixture of dichloromethane and diethyl ether was used as a solvent instead of dichloromethane alone, the yield was increased to 56% from 27%, indicating the ether can serve as a HF-trap agent (run 11).

Compounds **2a** and **2b** were identified by spectral and elemental analyses of the purified products. As we failed to get a pure sample of **2c**, it was derived to known compounds **5d** and **6c** as discussed below. Compound **2d** was identified by the comparison with the spectral data of an authentic sample, which was prepared by fluorination of (2*S*,4*S*)-*N*-Boc-4-fluoroproline. For further comparison, the other stereoisomers at 4-position, (2*S*,4*R*)-*N*-Fmoc-4-fluoropyrrolidine-2-carbonyl fluoride (**2a′**) and (2*S*,4*R*)-*N*-Boc-4-fluoropyrrolidine-2-carbonyl fluoride (**2d′**) were prepared by fluorination of (2*S*,4*R*)-*N*-Fmoc-4-fluoroproline and (2*S*,4*R*)-*N*-Boc-4-fluoroproline, respectively. Thus, the structural identification of **2a** and **2d** was furthermore comfirmed due to the observed definite differences in ^{19}F NMR between **2a** and **2a′**, and **2d** and **2d′**.

In the fluorination with Fluolead, 4-*tert*-butyl-2,6-dimethylphenylsulfinyl fluoride is formed as a byproduct which is derived from Fluolead. Crystalline product **2a** was easily isolated by crystallization from dichloromethane/pentane, as the byproduct is soluble in a hydrocarbon (pentane) while **2a** is insoluble in a hydrocarbon.

As shown in Scheme 3, when **1a** was allowed to react with DAST or Deoxo-Fluor, the yields of the double fluorination product **2a** were low (40% and 41%, respectively), and byproduct amides **3** and **4** were formed in 45% and 39% yields. The byproducts were isolated and confirmed by comparison with authentic samples, which were synthesized by the reaction of **2a** with diethylamine and bis(2-methoxyethyl)amine, respectively. The formation of **3** can be explained by reaction of product **2a** with diethylamine generated from decomposition of $Et_2NS(O)F$ derived from DAST during the reaction. Similarly, the formation of **4** can be explained by reaction of **2a** with bis(2-methoxyethyl)amine generated from the decomposition of $(MeOCH_2CH_2)_2NS(O)F$ during the reaction. Thus, the reactions with DAST and Deoxo-Fluor are compromised by such side reactions, which are attributed to the weak and labile N−S bonding of DAST and Deoxo-Fluor. It was reported that a similar byproduct, *N*,*N*-bis(methoxyethyl)benzamide, was obtained in 67% yield when Deoxo-Fluor was reacted with benzoic acid in the presence of *N*,*N*-diisopropylethylamine. The benzamide was presumed to be formed by reaction of benzoyl fluoride with bis(2-methoxyethyl)amine resulting from Deoxo-Fluor.[20] Similar amide products, $PhCOCONR_2$ (R = Et and $MeOCH_2CH_2$), were reported to be formed when DAST and Deoxo-Fluor reacted with phenylpyruvic acid.[21]

Another deoxofluorinating agent, 2,2-difluoro-1,3-dimethylimidazolidine (DFI), was examined. Reaction of **1a** with DFI provided product **2a** in 68% NMR yield (50% isolated) under the same reaction conditions as for Fluolead (conditions of run 1, Table 1). The yield was much less than with Fluolead.

As shown in Scheme 4, fluorination of the *cis*-isomer, (2*S*,4*S*)-*N*-Fmoc-4-hydroxyproline (**1a′**), with Fluolead was

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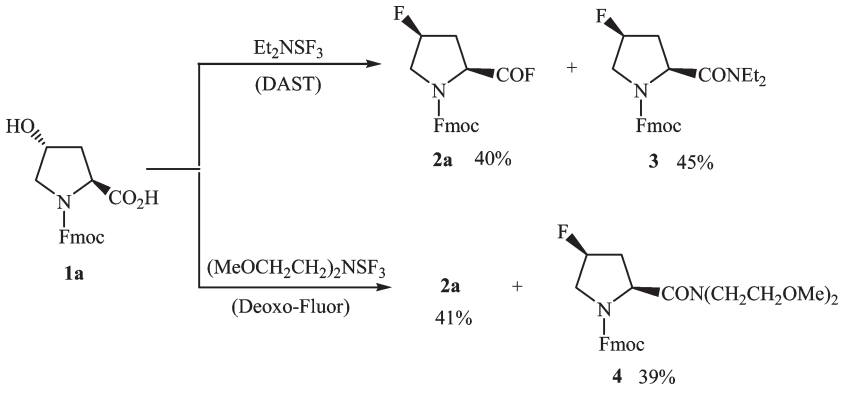
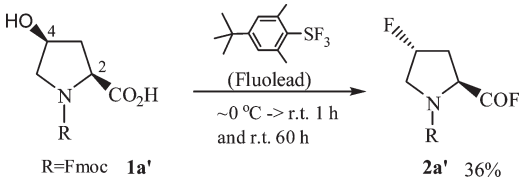
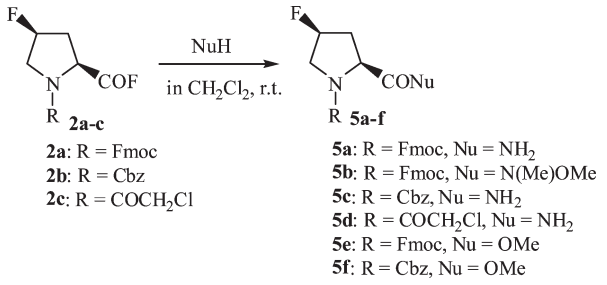
Scheme 3. Reactions of *trans*-4-Hydroxy-L-proline Derivative with DAST and Deoxo-Fluor Reagent



Scheme 4. Reaction of *cis*-4-Hydroxy-L-proline Derivative with Fluolead Reagent



Scheme 5. Reactions of 4-Fluoropyrrolidine-2-carbonyl Fluorides with Nucleophiles



also studied. This reaction produced the *trans*-isomer, (2*S*,4*R*)-*N*-Fmoc-4-fluoropyrrolidine-2-carbonyl fluoride (**2a′**), in 36% NMR yield. Fluoride **2a′** was identified by comparison with an authentic sample. The low yield of **2a′** may be explained by possible side reaction of **1a′** by the *cis*-conformation of 2-COOH and 4-OH groups although we did not examine its byproducts.

The 4-fluoropyrrolidine-2-carbonyl fluorides are useful synthons. Reactions of carbonyl fluorides **2a**−**c** with ammonia, *N*,*O*-dimethylhydroxylamine, and methanol led to the formation of the corresponding carboxamides **5a**,**c**,**d**, Weinreb amide[22] **5b**, and carboxylates **5e**,**f** in excellent isolated yields, respectively, as shown in Scheme 5 and Table 2. ^{19}F NMR showed that products **5a**,**b**,**e**,**f** were not contaminated with any diastereomers, while **5c** and **d** were contaminated with a small amount (ca. 4%) of the diastereomers. Thus, our new methodology using synthons **2** greatly decreases the necessary steps for the preparation of the useful 4-fluoropyrrolidine intermediates. For example, carboxamide **5a** and Weinreb amide **5b** were prepared in only three steps

Table 2. Reactions of 4-Fluoropyrrolidine-2-carbonyl Fluorides with Nucleophiles

entry	substrate	NuH	solvent	*T* (°C)	time (h)	product	yield[a] (%)
1	**2a**	NH_3	CH_2Cl_2	rt	1	**5a**	95
2	**2a**	HN(OMe)Me	CH_2Cl_2	rt	1	**5b**	70
3	**2b**	NH_3	CH_2Cl_2	rt	1	**5c**[b]	94
4	**2c**	NH_3	CH_2Cl_2	rt	1	**5d**[c]	85
5	**2a**	MeOH	CH_2Cl_2	rt	1	**5e**[d]	94
6	**2b**	MeOH	CH_2Cl_2	rt	1	**5f**[b]	95

[a] Yields are isolated yields. [b] Chen, H.; Chen, Y. Patent No. CN 101318922. [c] See refs 4 and 11d. [d] Tran, T. T.; Patino, N.; Frogier, T.; Guedj, R. *J. Fluorine Chem.* **1997**, *82*, 125−130.

(*N*-protection, double fluorination, and then amidation) from the starting material ***VI*** by means of our new method, while six or five steps were required to reach ***I*** or ***III*** according to the conventional methods (see Scheme 1).

The synthesis of carboxamides, Weinreb amides, and carboxylate esters may also be performed directly in a one-pot procedure by the reaction of 4-hydroxyproline **1** with Fluolead in dichloromethane followed by the addition of amines or methanol. In these cases, byproducts, 4-*tert*-2,6-dimethylphenylsulfinamides or -sulfinate methyl ester, may be formed by reaction of 4-*tert*-butyl-2,6-dimethylphenylsulfinyl fluoride, derived from Fluolead, with the amine or methanol. Therefore, it may be needed to remove the byproducts from the reaction mixture. As there is a significant difference in polarity between them, the separation of byproducts from the desired products may easily be achieved by such a method as standard chromatography on silica gel.

Carboxamides **5a**, **5c**, and **5d** were converted into the corresponding carbonitriles **6a**, **6b**,[23] and **6c**,[4,11d] respectively, in high yields by using 1.5 equiv of trifluoroacetic anhydride as a dehydrating agent in anhydrous THF[6a] (Scheme 6). Carbonitriles **6a**, **6b**, and **6c** were colorless solids and purified by crystallization from dichloromethane/pentane mixture.

N-Fmoc-4-fluoropyrrolidine-2-carboxamide (**5a**) was easily deprotected using a suitable deprotecting reagent as shown in Scheme 7. Reaction of **5a** with diethylamine in dichloromethane led to the formation of deprotected **7**, which was then treated with HCl in ether to give the stable hydrochloride salt **8**[6a] in excellent yield.

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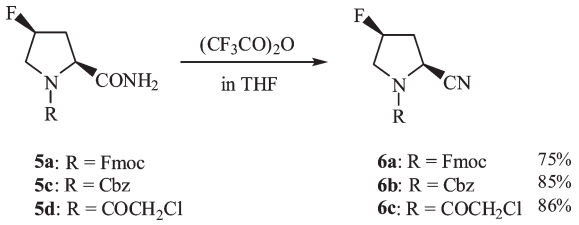
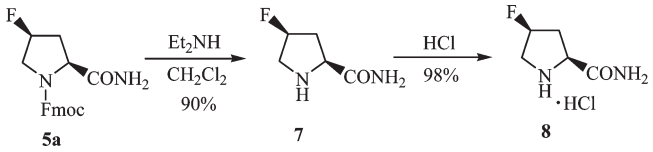
Scheme 6. Conversion of Carbamides to Carbonitriles



5a: R = Fmoc
5c: R = Cbz
5d: R = $COCH_2Cl$

6a: R = Fmoc 75%
6b: R = Cbz 85%
6c: R = $COCH_2Cl$ 86%

Scheme 7. Deprotection of Carboxamide 5a



5a **7** **8**

CONCLUSION

By employment of the stereospecific double fluorination of 4-hydroxypyrolines with Fluolead reagent, we have succeeded in synthesizing the useful synthons, *N*-protected 4-fluoropyrrolidine-2-carbonyl fluorides **2**, which can serve through very straightforward methodology in the synthesis of optically active 4-fluoropyrrolidine derivatives having different functional groups at the 2-postion, such as a carbamoyl, cyano, alkoxycarbonyl, and *N*-methoxy-*N*-methylcarbamoyl group. Significantly, *N*-Fmoc-*cis*-4-fluoropyrrolidine-2-carbonyl fluoride **2a** is a particularly useful synthon due to its high yield synthesis, convenient purification as a crystalline solid, and its utility in providing enantiomerically highly pure pharmaceutical intermediates or final products.

EXPERIMENTAL SECTION

General Methods. All experiments were performed under anhydrous conditions in an atmosphere of nitrogen with oven-dried glassware or fluoropolymer (PFA) vessels. Chemicals were purchased and used without prior purification unless otherwise noted. Solvents were dried by standard procedures. ^{1}H, ^{19}F, and ^{13}C NMR spectra were recorded at 300.53, 282.78, and 75.57 MHz, respectively. ^{19}F chemical shifts are reported in ppm with $CFCl_3$ (δ = 0.00).

Double Fluorination of 4-Hydroxyproline Derivatives 1a–d with Fluolead Reagent. *Typical Procedure.* A solution of 9.03 g (36.1 mmol) of 4-*tert*-butyl-2,6-dimethylphenylsulfur trifluoride (Fluolead) in 10 mL of dry dichloromethane was slowly added over 20 min into a stirred solution of 5.10 g (14.4 mmol) of (2*S*,4*R*)-*N*-Fmoc-4-hydroxyproline (**1a**) in 20 mL of dry dichloromethane in a fluoropolymer vessel cooled in an ice bath. After complete addition, the reaction mixture was stirred for 0.5 h, and then the ice bath was removed. It took about 1 h for the temperature of the reaction solution to get to room temperature after starting the reaction at ice bath temperature. Stirring was continued at room temperature for 60 h. Analysis of the reaction mixture by ^{19}F NMR using fluorobenzene added as a standard showed that the yield of product was 90%. After the solvent was removed at reduced pressure, diethyl ether (20 mL) and then pentane (20 mL) were added to the resulting residue. Stirring the mixture well gave a solid, which was then obtained by filtration followed by washing with pentane (25 mL × 2). The solid was dissolved in dichloromethane and precipitated out by adding pentane to the solution, giving 3.86 g (78%) of **(2*S*,4*S*)-*N*-Fmoc-4-fluoropyrrolidine-2-carbonyl fluoride** (**2a**) as white powder. An analytically pure sample of **2a** was obtained by thin-layer chromatography on silica gel using a 2:1 mixture of Et_2O and hexane as an eluent.

2a: mp 127–128 °C; ^{19}F NMR ($CDCl_3$) δ (a 56:44 mixture of two rotamers) 28.53 (s, 0.56F) and 28.34 (s, 0.44F), −172.92 (m, 1F); ^{1}H NMR ($CDCl_3$) δ (a mixture of two rotamers) 2.2–2.8 (m, 2H), 3.5–4.0 (m, 2H), 4.1–4.8 (m, 4H), 5.1–5.4 (m, 1H), 7.2–7.9 (m, 8H); ^{13}C NMR ($CDCl_3$) (a mixture of two rotamers) δ 30.8, 31.2, 35.8 (d, J = 21.7 Hz), 36.8 (d, J = 21.0 Hz), 47.2, 53.1 (d, J = 24.6 Hz), 53.5 (d, J = 25.3 Hz), 55.8 (d, J = 66.5 Hz), 56.3 (d, J = 66.5 Hz), 68.0, 68.1, 90.9 (d, J = 177.0 Hz), 92.0 (d, J = 177.7 Hz), 120.2, 125.0, 125.1, 125.2, 127.3, 128.0, 141.3, 141.4, 141.5, 141.7, 143.8, 143,9, 153.9, 154.5, 161.3 (d, J = 371.3 Hz); IR (Nujol, KBr) 1855 (COF), 1839 (COF), 1694 (NCOO) cm^{-1}; HRMS/ESI-APCI method (solvent; methanol) $(M + Na)^+$ calcd for $C_{20}H_{17}F_2NNaO_3$ 380.1070, found 380.1069. Anal. Calcd for $C_{20}H_{17}F_2NO_3$: C, 67.22; H, 4.80; N, 3.92. Found: C, 67.23; H, 5.04; N, 3.89.

(2*S*,4*S*)-*N*-Cbz-4-fluoropyrrolidine-2-carbonyl Fluoride (2b). Oil; isolated yield 75%; ^{19}F-NMR ($CDCl_3$) δ (a 47:53 mixture of two rotamers) 28.50 (s, 0.47F), 28.36 (s, 0.53F), −173.0 (m, 1F); ^{1}H NMR ($CDCl_3$) δ 2.25–2.7 (m, 2H), 3.6–4.05 (m, 2H), 4.65–4.8 (m, 1H), 5.1–5.4 (m, 3H), 7.3–7.4 (m, 5H); ^{13}C NMR ($CDCl_3$) δ (mixture of two rotamers) 35.9 (d, J = 23.8 Hz), 36.8 (d, J = 23.8 Hz), 53.1 (d, J = 26.1 Hz), 53.3 (d, J = 26.0 Hz), 55.9 (d, J = 67.2 Hz), 56.3 (d, J = 67.2 Hz), 67.9, 68.0, 90.8 (d, J = 177.5 Hz), 91.8 (d, J = 177.7 Hz), 128.2, 128.5, 128.7, 135.9, 136.0, 153.9 154.5, 161.4 (d, J = 371.0 Hz), 161.6 (d, J = 371.3 Hz); IR (neat, KBr) 1855 (COF), 1712 (NCOO) cm^{-1}; HRMS/ESI-APCI method (solvent; methanol) $(M - F + OCH_3 + Na)^+$ calcd for $C_{14}H_{16}FNNaO_4$ 304.0956, found 304.0959. Anal. Calcd for $C_{13}H_{13}F_2NO_3$: C, 57.99; H, 4.87; N, 5.20. Found: C, 57.78; H, 5.27; N, 5.51. An analytically pure sample of **2b** was obtained by thin-layer chromatography on silica gel using a 2:1 mixture of Et_2O and hexane as an eluent.

(2*S*,4*S*)-*N*-Chloroacetyl-4-fluoropyrrolidine-2-carbonyl fluoride (2c): oil; isolated yield 76%; ^{19}F NMR ($CDCl_3$) δ 28.58 (s, 1F, COF), −173.37 (m, 1F, CHF); ^{1}H NMR ($CDCl_3$) δ 2.2–2.8 (m, 2H), 3.7–4.2 (m, 4H), 4.7–5.0 (m 1H), 5.1–5.5 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 34.9 (d, J = 21.6 Hz), 41.6, 53.3 (d, J = 23.8 Hz), 56.1 (d, J = 66.5 Hz), 58.2, 91.3 (d, J = 178.4 Hz), 160.5 (d, J = 369.9 Hz), 165.9; HRMS/ESI-APCI method (solvent; methanol) $(M - F + OCH_3 + Na)^+$ calcd for $C_8H_{11}ClFNNaO_3$ 246.0304, found 246.0308.

Preparation of (2*S*,4*S*)-*N*-Boc-4-fluoropyrrolidine-2-carbonyl Fluoride (2d) as an Authentic Sample. (2*S*,4*S*)-*N*-Boc-4-fluoroproline (1.17 g, 5 mmol) and sodium fluoride (0.63 g, 15 mmol) were placed in a fluoropolymer vessel, and 10 mL of dry dichloromethane was added into the vessel. The mixture was cooled with an ice bath. A solution of 2,2-difluoro-1,3-dimethylimidazolidine (817 mg, 6 mmol) in 2 mL of dry dichloromethane was added slowly. After the addition, the mixture was stirred for 5 min. The ice bath was removed and the mixture warmed to room temperature. The reaction mixture was stirred for a total of 20 min. ^{19}F NMR analysis of the reaction mixture showed that (2*S*,4*S*)-*N*-Boc-4-fluoropyrrolidine-2-carbonyl fluoride (**2d**) was produced in 85% yield. The mixture was diluted with 10 mL of dichloromethane and washed with water. The organic layer was dried over anhydrous magnesium sulfate and filtered. Removal of solvent followed by washing with a small amount of water and then drying gave 846 mg (yield 72%) of **2d**: oil; ^{19}F NMR ($CDCl_3$) (a 6:4 mixture of two rotamers) δ 28.22 (s, 0.6F, COF), 28.14 (s, 0.4F, COF), −173.18 (m, 1F, CF); ^{1}H NMR ($CDCl_3$) δ (mixture of two rotamers) 1.40 (s, 0.55 × 9H, *t*-Bu), 1.43 (s, 0.45 × 9H, *t*-Bu), 2.2–2.6 (m, 2H), 3.45–3.95 (m, 2H), 4.5–4.7 (m, 1H), 5.22 (br d, J = 51.9 Hz, 1H, CHF); ^{13}C NMR ($CDCl_3$) δ (mixture of two rotamers) 90.9 (d, J = 177.0 Hz, 1H, CF), 92.0 (d, J = 177.0 Hz, CF), 153.1 (s, CON), 153.8 (s, CON), 161.5 (d, J = 372.1 Hz, COF), 161.7 (d, J = 372.8 Hz, COF); IR (neat, KBr) 1849

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(COF), 1694 (NCOO) cm^{-1}; HRMS/ESI-APCI method (solvent; methanol) $(M - F + OCH_3 + Na)^+$ calcd for $C_{11}H_{18}FNNaO_4$ 270.1112, found 270.1109. Anal. Calcd for $C_{10}H_{15}F_2NO_3$: N, 5.95. Found: N, 6.07.[24]

Preparation of (2*S*,4*R*)-*N*-Boc-4-fluoropyrrolidine-2-carbonyl Fluoride (2d′) as an Authentic Sample. Compound **2d′** was prepared in 90% isolated yield using (2*S*,4*R*)-*N*-Boc-4-fluoroproline in the same way as for **2d**. Compound **2d′**: oil; ^{19}F NMR ($CDCl_3$) (a 4:6 mixture of rotamers) δ 28.66 (s, 0.4F, COF), 28.10 (s, 0.6F, COF), −177.16 (m, 0.4F, CF), −177.83 (m, 0.6F, CF); ^1H NMR ($CDCl_3$) (a mixture of rotamers) δ 1.42 (s, 0.6 × 9H, *t*-Bu), 1.44 (s, 0.4 × 9H, *t*-Bu), 2.0−2.8 (m, 2H), 3.45−4.0 (m, 2H), 4.51 (m. 1H), 5.22 (dm, 1H, J = 51.6 Hz); ^{13}C NMR ($CDCl_3$) (mixture of two rotamers) δ 90.7 (d, J = 179.9 Hz, CF), 91.6 (d, J = 179.9 Hz, CF), 153.1 (s, CON), 154.2 (s, CON), 161.9 (d, J = 368.4 Hz, COF), 162.1 (d, J = 368.4 Hz, COF); IR (neat, KBr) 1849 (COF), 1702 (NCOO), 1664 (NCOO) cm^{-1}; HRMS/ESI-APCI method (solvent; methanol) $(M - F + OCH_3 + Na)^+$ calcd for $C_{11}H_{18}FNNaO_4$ 270.1112, found 270.1114. Anal. Calcd for $C_{10}H_{15}F_2NO_3$: C, 51.06; H, 6.43; N, 5.95. Found: C, 50.79; H, 6.64; N, 5.97.

Reaction of (2*S*,4*R*)-*N*-Fmoc-4-hydroxyproline (1a) with Diethylaminosulfur Trifluoride (DAST). A solution of 591 mg (3.67 mmol) of diethylaminosulfur trifluoride (DAST) in 2 mL of dry dichloromethane was slowly added to a stirred solution of 518 mg (1.47 mmol) of **1a** in 3 mL of dry dichloromethane in a fluoropolymer vessel cooled in an ice bath. After complete addition, the reaction mixture was stirred for 1 h in an ice bath, and then the ice bath was removed and the reaction mixture was stirred for 60 h at room temperature. ^{19}F NMR analysis of the reaction mixture showed that **2a** and **3** were formed in 40% and 45% yield, respectively. After some amount of dichloromethane was added into the reaction mixture, the mixture was washed with water, dried over anhydrous magnesium sulfate, and filtered. Removal of solvent at reduced pressure gave a residue, which was then thin-layer chromatographed on silica gel using ethyl acetate as an eluent to give **2a** and **3**, which were identified by comparison with each of authentic samples.

Reaction of (2*S*,4*R*)-*N*-Fmoc-4-hydroxyproline (1a) with Bis(2-methoxyethyl)aminosulfur Trifluoride (Deoxo-Fluor). The reaction was carried out in the same way as that of **1a** with DAST as shown above except that Deoxo-fluor was used in place of DAST. After the reaction, ^{19}F NMR analysis of the reaction mixture showed that **2a** and amide **4** were formed in 41% and 39% yield, respectively. Products **2a** and **4** were isolated in the same way as with DAST and identified by comparison with each of authentic samples.

Preparation of (2*S*,4*S*)-*N*-Fmoc-4-fluoropyrrolidine-4-*N*,*N*-diethylcarbamide (3) as an Authentic Sample. Diethylamine (73 mg, 1.0 mmol) was added into a stirred solution of 178 mg (0.50 mmol) of **2a** in 1 mL of dry dichloromethane. The mixture was stirred at room temperature for 45 min. After some additional amount of dichloromethane was added, the mixture was washed with water, dried over anhydrous magnesium sulfate, and filtered. Solvent was removed at reduced pressure, and the resulting residue was thin-layer chromatographed on silica gel using ethyl acetate as an eluent to give 174 mg (85%) of **3**: oil; ^{19}F NMR ($CDCl_3$) (a 36:64 mixture of rotamers) δ −171.90 (m, 0.36F), −172.52 (m, 0.64F); ^1H NMR ($CDCl_3$) δ 1.0−1.4 (m, 6H), 2.1−2.7 (m, 2H), 3.1−4.8 (m, 10H), 5.1−5.4 (m, 1H), 7.2−7.9 (m, 8H); ^{13}C NMR ($CDCl_3$) (mixture of rotamers) δ 13.0, 14.3, 36.7 (d, J = 21.7 Hz), 37.9 (d, J = 22.4 Hz), 40.4, 40.6, 41.2, 41.5, 47.2, 47.5, 53.1 (d, J = 26.0 Hz), 53.8 (d, J = 25.3 Hz), 56.2, 56.4, 67.3, 67.7, 90.5 (d, J = 179.9 Hz), 91.5 (d, J = 180.6 Hz), 120.0, 125.2, 125.4, 127.1, 127.2, 127.8, 141.3, 141.4, 143.8, 144.3, 144.4, 154.4, 154.7, 169.6, 169.8; HRMS/ESI-APCI method (solvent; methanol) $(M + Na)^+$ calcd for $C_{24}H_{27}FN_2NaO_3$ 433.1898, found 433.1899. Anal. Calcd for $C_{24}H_{27}FN_2O_3$: C, 70.22; H, 6.63; N, 6.82. Found: C, 69.91; H, 6.74; N, 6.72.

Preparation of (2*S*,4*S*)-*N*-Fmoc-4-fluoropyrrolidine-4-*N*,*N*-bis(2′-methoxyethyl)carbamide (4) as an Authentic Sample. Bis(2-methoxyethyl)amine (133 mg, 1.0 mmol) was added into a stirred solution of 178 mg (0.50 mmol) of **2a** in 1 mL of dry dichloromethane. The mixture was stirred at room temperature for 45 min. After some amount of dichloromethane was added, the mixture was washed with water, dried over anhydrous magnesium sulfate, and filtered. Solvent was removed at reduced pressure, and the resulting residue was thin-layer chromatographed on silica gel using ethyl acetate as an eluent to give 211 mg (90%) of **4**: oil; ^{19}F NMR ($CDCl_3$) (a 4:6 mixture of rotamers) δ −171.71 (m, 0.4F), −172.68 (m, 0.6F); ^1H NMR ($CDCl_3$) δ 2.2−2.7 (m, 2H), 3.1−4.1 (multiplets with singlet of methyl groups, 16H), 4.2−4.5 (m, 3H), 4.8−4.9 (m, 1H), 5.1−5.4 (m, 1H), 7.2−7.8 (m, 8H); ^{13}C NMR ($CDCl_3$) (mixture of rotamers) δ 36.8 (d, J = 21.7 Hz), 38.1 (d, J = 22.4 Hz), 46.6, 47.0, 47.2, 47.5, 48.5, 48.7, 53.2 (d, J = 26.0 Hz), 53.9 (d, J = 26 Hz), 56.2, 59.0, 59.1, 59.3, 67.7, 70.4, 70.5, 71.0, 90.6 (d, J = 179.2 Hz), 91.4 (d, J = 181.3 Hz), 119.9, 120.0, 125.2, 125.3, 127.1, 127.2, 127.7, 127.8, 141.3, 141.4, 143.8, 144.2, 144.4, 154.4, 154.7, 171.2, 171.4; HRMS/ESI-APCI method (solvent; methanol) $(M + H)^+$ calcd for $C_{26}H_{31}FN_2O_5$ 471.2290, found 471.2289. Anal. Calcd for $C_{26}H_{31}FN_2O_5$: N, 5.95. Found: N, 5.75.[24]

Preparation of (2*S*,4*R*)-*N*-Fmoc-4-fluoropyrrolidine-2-carbonyl Fluoride (2a′) as an Authentic Sample. A solution of Fluolead (10.5 mmol) in 5 mL of dry dichloromethane was added slowly to a stirred solution of (2*S*,4*R*)-*N*-Fmoc-4-fluoroproline (7 mmol) in 15 mL of dry dichloromethane in a fluoropolymer vessel cooled in an ice bath. After complete addition, the ice bath was removed and the reaction mixture was stirred at room temperature for 0.5 h. ^{19}F NMR analysis of the reaction mixture showed that **2a′** was produced in 97% yield. All of the volatiles were removed at reduced pressure, and dichloromethane (2 mL) was added to the residue, followed by the addition of pentane (30 mL). After stirring well, the supernatant liquid was removed and the residue (solid) was washed with pentane (25 mL × 2). Product **2a′** (1.75 g, 70% yield) was obtained as white powder by dissolving the solid in dichloromethane and precipitating with pentane. **2a′**: mp 110−111 °C; ^{19}F NMR ($CDCl_3$) (a 6:4 mixture of two rotamers) δ 29.69 (s, 0.6F, COF), 29.39 (s, 0.6F, COF), −177.05 (m, 0.6F, CF), −177.99 (m, 0.4F, CF); ^1H NMR ($CDCl_3$) δ (mixture of rotamers) 2.0−2.9 (m, 2H), 3.4−4.8 (m, 6H), 5.1−5.45 (m, 1H), 7.2−8.0 (m, 8H); ^{13}C NMR ($CDCl_3$) (mixture of two rotamers) δ 35.9 (d, J = 22.4 Hz), 37.0 (d, J = 22.4 Hz), 47.1, 53.1 (d, J = 22.4 Hz), 53.6 (d, J = 23.1 Hz), 55.9 (d, J = 66.5 Hz), 56.5 (d, J = 66.5 Hz), 57.9, 68.3, 90.4 (d, J = 177.9 Hz), 91.4 (d, J = 180.6 Hz), 120.2, 124.8, 124.9, 127.3, 128.0, 141.4, 143.7, 154.2, 154.8, 161.5 (d, J = 367.8 Hz); IR (Nujol, KBr) 1855 (COF), 1840 (COF), 1695 (NCOO) cm^{-1}; HRMS/ESI-APCI method (solvent; methanol) $(M - F + OCH_3 + Na)^+$ calcd for $C_{21}H_{20}FNNaO_4$ 392.1269, found 392.1272. Anal. Calcd for $C_{20}H_{17}F_2NO_3$: C, 67.22; H, 4.80; N, 3.92. Found: C, 66.92; H, 4.98; N, 3.84.

Preparation of (2*S*,4*S*)-*N*-Fmoc-4-fluoropyrrolidine-2-carboxamide (5a). Compound **2a** (355 mg, 1 mmol) was dissolved in 5 mL of dichloromethane. Into the solution was added an aqueous 28−30% ammonia solution (NH_3, 2.2 mmol) dropwise at room temperature. The reaction mixture was stirred at room temperature for 0.5 h. The mixture was extracted with dichloromethane. The organic layer was separated, washed with water, dried over anhydrous magnesium sulfate, and filtered. Removal of solvent at reduced pressure gave a solid, which was then crystallized from a 1:3 mixture of dichloromethane and pentane to give 335 mg (95%) of **5a** as white crystals: mp 106−107 °C; ^{19}F NMR ($CDCl_3$) δ (a 52:48 mixture of two rotamers) δ −174.50 (m, 0.52F), −173.02 (m, 0.48F); ^1H NMR ($CDCl_3$) δ 2.0−2.8 (m, 2H), 3.35−3.9 (m, 2H), 4.1−4.7 (m, 4H), 5.16 (d, 1H, J = 52.3 Hz), 5.9−6.4 (m, 2H), 7.2−7.9 (m, 8H); ^{13}C NMR ($CDCl_3$) δ (mixture of two rotamers) δ 35.6 (d, J = 21.0 Hz), 37.5 (d, J = 19.5 Hz), 47.3, 53.9 (d, J = 25.3 Hz), 54.3 (d, J = 23.8 Hz), 59.6, 67.7, 68.0, 91.6 (d,

J = 175.5 Hz), 92.2 (d, J = 177.0 Hz), 120.2, 124.9, 125.0, 127.2, 127.3, 128.0, 141.5, 143.6, 143.7, 155.3, 155.8, 173.8, 174.3; HRMS/ESI-APCI method (solvent; methanol) $(M + Na)^+$ calcd for $C_{20}H_{19}FN_2NaO_3$ 377.1272, found 377.1277. Anal. Calcd for $C_{20}H_{19}FN_2O_3 \cdot {}^1/_4H_2O$: C, 66.93; H, 5.48; N, 7.81. Found: C, 66.88; H, 5.41; N, 7.91.

Preparation of (2*S*,4*S*)-*N*-Fmoc-4-fluoropyrrolidine-2-*N*-methoxy-*N*-methylcarboxamide (5b). Compound **2a** (714 mg, 2.0 mmol) was dissolved in 5 mL of dichloromethane. The solution was cooled in an ice bath. Into the solution was added a dichloromethane solution of *N,O*-dimethylhydroxylamine (in situ prepared from 4.0 mmol of *N,O*-dimethylhydroxylamine hydrochloride and 4.0 mmol of diisopropylethylamine in 5 mL of dichloromethane at ice bath temperature). The reaction mixture was stirred at ice bath temperature for 1 h. The mixture was washed with water, dried over anhydrous magnesium sulfate, and filtered. Removal of solvent at reduced pressure gave a solid, which was then chromatographed on silica gel using ethyl acetate as an eluent to give 589 mg (74%) of **5b**: mp 64−65 °C; ^{19}F NMR ($CDCl_3$) δ −171.39 (m, 1F); ^{1}H NMR ($CDCl_3$) δ (a 6:4 mixture of two rotamers) 2.22−2.6 (m, 2H), 3.13 (s, 0.4 × 3H, NCH_3), 3.24 (s, 0.6 × 3H, NCH_3), 3.48 (s, 0.4 × 3H, OCH_3), 3.77 (s, 0.6 × 3H, OCH_3), 3.7−4.9 (m, 6H except a peak at 3.77), 5.18 (dm, J = 53.3 Hz, 0.4H, CHF), 5.27 (dm, J = 53.3 Hz, 0.6H, CHF), 7.25−7.8 (m, 8H); ^{13}C NMR ($CDCl_3$) δ (mixture of two rotamers) 32.5, 36.2 (d, J = 21.7 Hz), 37.3 (d, J = 22.4 Hz), 47.3, 47.5, 53.3 (d, J = 25.3 Hz), 53.9 (d, J = 25.3 Hz), 56.6, 56.8, 61.0, 61.2, 66.8, 67.7, 90.8 (d, J = 179.2 Hz), 91.8 (d, J = 179.9 Hz), 119.9, 120.1, 125.0, 125.1, 125.4, 127.1, 127.2, 127.6, 127.7, 127.8, 141.3, 141.4, 143.9, 144.2, 144.2, 154.4, 154.7, 171.1, 171.3. HRMS/ESI-APCI method (solvent; methanol) $(M + H)^+$ calcd for $C_{22}H_{24}FN_2O_4$ 399.1715, found 399.1714. Anal. Calcd for $C_{22}H_{23}FN_2O_4$: C, 66.32; H, 5.82; N, 7.03. Found: C, 66.18; H, 5.86; N, 6.96.

Preparation of (2*S*,4*S*)-*N*-Cbz-4-fluoropyrrolidine-2-carboxamide (5c). Compound **2b** (807 mg, 2 mmol) was dissolved in 5 mL of dichloromethane. Into the solution was added an aqueous 28−30% ammonia solution (NH_3, 6.6 mmol) dropwise at room temperature. The mixture was stirred at room temperature for 0.5 h. The reaction mixture was extracted with dichloromethane, and the organic layer was separated, washed with water, dried over anhydrous magnesium sulfate, and filtered. Removal of solvent at reduced pressure gave a solid, which was then crystallized from a 1:3 mixture of dichloromethane and pentane to give 751 mg (94%) of **5c** as white crystals: ^{19}F NMR ($CDCl_3$) δ (a 1:1 mixture of two rotamers) −172.75 (m, 0.5F), −174.32 (m, 0.5F); ^{1}H NMR ($CDCl_3$) δ 2.0−2.8 (m, 2H), 3.4−4.0 (m, 2H), 4.43 (m, 1H), 4.8−5.4 (m, 3H), 6.2−6.7 (m, 2H), 7.2−7.5 (m, 5H); ^{13}C NMR ($CDCl_3$) δ (mixture of two rotamers) 35.7 (d, J = 20.2 Hz), 37.5 (d, J = 21.8 Hz), 54.1(m), 59.7, 67.8, 91.7 (d, J = 176.3 Hz), 92.3 (d, J = 178.4 Hz), 128.1, 128.4, 128.7, 136.1, 155.3, 155.8, 174.1, 174.7. ^{19}F NMR showed that **5c** was contaminated with a small amount (ca. 4%) of its diastereomer, as two small peaks at −176.8 (m) and −177.8 (m) with a 2:3 ratio that may correspond to two rotamers of the diastereomer were observed in the ^{19}F NMR of **5c**.

Preparation of (2*S*,4*S*)-*N*-Chloroacetyl-4-fluoropyrrolidine-2-carboxamide (5d). An aqueous 28−30% ammonia solution (NH_3, 10 mmol) was added to a stirred solution of 1.06 g (5.0 mmol) of **2c** in 10 mL of dichloromethane cooled in an ice bath. After 10 min, the ice bath was removed, and stirring was continued for another 20 min at room temperature. Water (10 mL) was added to the reaction mixture. The reaction mixture was shaken well and then the dichloromethane layer removed. The aqueous layer was mixed with a saturated brine aqueous solution and extracted with ethyl acetate (25 mL × 3). Ethyl acetate layers were combined, dried over anhydrous magnesium sulfate, and filtered. Removal of solvent at reduced pressure gave 886 mg (85%) of **5d** as a white solid: ^{19}F NMR (CD_3CN) (a 1:3 mixture of two rotamers) δ −173.20 (m, 0.25F), −173.85 (m, 0.75F); ^{1}H NMR (CD_3CN) δ 2.2−2.6 (m, 2H), 3.6−4.25 (m, 4H), 4.45 (m, 1H), 5.1−5.4 (m, 1H), 5.8−6.7 (m, 2H); ^{13}C NMR (CD_3CN) (a major rotamer) δ 35.6 (d, J = 21.0 Hz), 42.9, 53.5 (d, J = 23.8 Hz), 59.7, 93.2 (d, J = 175.6 Hz), 166.1, 173.1. ^{19}F NMR showed that **5d** was contaminated with a small amount (ca. 4%) of its diastereomer, as a small peak at −178.6 ppm (m) which may correspond to the diastereomer was observed in the ^{19}F NMR of **5d**.

Preparation of Methyl (2*S*,4*S*)-*N*-Fmoc-4-fluoropyrrolidine-2-carboxylate (5e). Compound **2a** (1 mmol) was dissolved in 5 mL of dichloromethane. Into the reaction, an excess of methanol was added at room temperature. The reaction mixture was stirred at room temperature for 1 h. After addition of some amount of dichloromethane, the reaction mixture was washed with water, dried over anhydrous magnesium sulfate and filtered. Removal of solvent at reduced pressure gave a solid, which was then crystallized from a 1:3 mixture of dichloromethane and pentane to give 345 mg (94%) of **5e** as white crystals: mp 120−121 °C; ^{19}F NMR δ ($CDCl_3$) −172.70 (m, 1F); ^{1}H NMR ($CDCl_3$) (a 54:46 mixture of two rotamers) δ 2.2−2.7 (m, 2H), 3.6−4.0 (m, 5H; including two CH_3 singlets at 3.67 as a minor rotamer and 3.76 as a major rotamer), 4.15−4.7 (m, 4H), 5.20 (dm, J = 52.3 Hz, 0.46H), 5.25 (dm, J = 52.6 Hz, 0.54H), 7.2−7.9 (m, 8H); ^{13}C NMR ($CDCl_3$) (a mixture of two rotamers) δ 36.7 (d, J = 21.7 Hz), 37.8 (d, J = 21.7 Hz), 47.3, 52.7, 53.3 (d, J = 24.6 Hz), 53.6 (d, J = 24.6 Hz), 57.5, 57.8, 67.6, 67.8, 91.2 (d, J = 177.7 Hz), 92.2 (d, J = 177.7 Hz), 120.1, 127.2, 127.9, 141.4, 143.8, 144.1, 154.4, 155.6, 171.8; HRMS/ESI-APCI method (solvent; methanol) $(M + Na)^+$ calcd for $C_{21}H_{20}FNNaO_4$ 392.1269, found 392.1272. Anal. Calcd for $C_{21}H_{20}FNO_4$: N, 3.79. Found: N, 3.78.[24]

Preparation of Methyl (2*S*,4*S*)-*N*-Cbz-4-fluoropyrrolidine-2-carboxylate (5f). Into a solution of 269 mg (1.0 mmol) of **2b** in 5 mL of dichloromethane was added 320 mg (10 mmol) of methanol at room temperature, followed by the addition of 152 mg (1.5 mmol) of triethylamine. The mixture was stirred at room temperature for 1 h. After addition of some amount of dichloromethane, the reaction mixture was washed with water, dried over anhydrous magnesium sulfate, and filtered. Removal of solvent at reduced pressure gave 266 mg (95%) of **5f**: oil; ^{19}F NMR ($CDCl_3$) δ −172.8 (m, 1F); ^{1}H NMR ($CDCl_3$) δ (a 53:47 mixture of two rotamers) 2.2−2.6 (m, 2H), 3.6−4.0 (m, 5H, including two CH_3 singlet peaks at 3.63 as a minor rotamer and 3.74 as a major rotamer), 4.53 (d, J = 9.3 Hz, 0.47H), 4.60 (d, J = 9.6 Hz, 0.53H), 5.0−5.4 (m, 3H), 7.2−7.5 (m, 5H); ^{13}C NMR ($CDCl_3$) (mixture of two rotamers) δ 36.5 (d, J = 21.7 Hz), 37.5 (d, J = 21.7 Hz), 52.3, 52.4, 53.2 (d, J = 31.1 Hz), 53.5 (d, J = 30.3 Hz), 57.5, 57.8, 67.1, 67.2, 91.3 (d, J = 177.0 Hz), 92.2 (d, J = 177.0 Hz), 127.9, 128.0, 128.1, 128.2, 128.5, 128.6, 136.6, 154.2, 154.6, 171.6, 171.9.

Preparation of (2*S*,4*S*)-*N*-Fmoc-4-fluoropyrrolidine-2-carbonitrile (6a). Into a solution of 354 mg (1.0 mmol) of **5a** in 3 mL of dry tetrahydrofuran (THF) cooled in an ice bath was slowly added trifluoroacetic anhydride (315 mg, 1.5 mmol). The reaction mixture was stirred under ice bath cooling for 2 h. After reaction, all the volatiles were removed on vacuum to give a solid, which was then crystallized from an ether/pentane mixture to give 250 mg (75%) of **6a**: mp 106−107 °C; ^{19}F NMR ($CDCl_3$) δ −174.70 (m, 1F); ^{1}H NMR ($CDCl_3$) δ 2.15−2.75 (m, 2H), 3.4−4.0 (m, 2H), 4.15−4.85 (m, 4H), 5.30 (d, J = 51.6 Hz, 1H), 7.2−7.9 (m, 8H); ^{13}C NMR ($CDCl_3$) (mixture of two rotamers) δ 37.0 (d, J = 21.7 Hz), 38.0 (d, J = 21.7 Hz), 45.4, 45.8, 47.1, 52.9 (d, J = 23.8 Hz), 53.3 (d, J = 23.8 Hz), 68.2, 68.6, 90.9 (d, J = 179.9 Hz), 91.9 (d, J = 179.9 Hz), 117.9, 118.1, 120.2, 125.0, 125.2, 127.3, 128.0, 141.5, 143.6, 143.7, 143.8, 153.5, 154.0; IR (neat, KBr) 2243 (CN), 1714 (NCOO) cm^{-1}; HRMS/ESI-APCI method (solvent; methanol) $(M + Na)^+$ calcd for $C_{20}H_{17}FN_2NaO_2$ 359.1166, found 359.1164. Anal. Calcd for $C_{20}H_{17}FN_2O_2$: N, 8.33. Found: N, 8.32.[24]

Preparation of (2*S*,4*S*)-*N*-Cbz-4-fluoropyrrolidine-2-carbonitrile (6b). Dehydration of **5c** (266 mg, 1 mol) was conducted

in the same manner as that of **5a** with trifluoroacetic anhydride in THF, as mentioned above. The solid obtained by removal of all the volatiles was crystallized from an ether/pentane mixture to give 211 mg (85%) of **6b**: ^{19}F NMR ($CDCl_3$) δ −174.93 (m, 1F); ^{1}H NMR ($CDCl_3$) δ 2.1−2.7 (m, 2H), 3.4−4.0 (m, 2H), 4.69 (t, J = 10.3 Hz, 1H), 5.05−5.4 (m, 3H), 7.2−7.5 (m, 5H); ^{13}C NMR ($CDCl_3$) (mixture of two rotamers) (major rotamer) δ 36.9 (d, J = 21.7 Hz), 45.9, 52.9 (d, J = 23.8 Hz), 68.0, 92.2 (d, J = 178.5 Hz), 118.3, 128.3, 128.5, 128.7, 135.9, 154.1, (minor rotamer) δ 37.8 (d, J = 20.9 Hz), 45.4, 53.3 (d, J = 24.6 Hz), 68.1, 91.2 (d, J = 178.5 Hz), 118.4, 128.2, 128.5, 128.7, 135.9, 153.4.

Praparation of (2*S*,4*S*)-*N*-Chloroacetyl-4-fluoropyrrolidine-2-carbonitrile (6c). Into a solution of 209 mg (1.0 mmol) of **5d** in 4 mL of dry THF was slowly added 315 mg (1.5 mmol) of trifluoroacetic anhydride at room temperature. The reaction mixture was stirred for 0.5 h at room temperature and evaporated to dryness under vacuum. The resulting solid was crystallized from a dichloromethane/pentane mixture, giving 164 mg (86% yield) of **6c** as a white solid: mp 139−140 °C (lit.[4] mp 140−141 dec); ^{19}F NMR ($CDCl_3$) δ −174.63 (m, 1F); ^{1}H NMR ($CDCl_3$) (mixture of rotamers) δ 2.2−2.9 (m, 2H), 3.65−4.35 (m, 4H), 4.9−5.1 (m, 1H), 5.25−5.6 (m, 1H); ^{13}C NMR ($CDCl_3$) (major rotamer) δ 36.5 (d, J = 21.7 Hz), 41.3, 45.5, 53.2 (d, J = 24.6 Hz), 92.0 (d, J = 182.0 Hz), 117.0, 165.3.

Preparation of (2*S*,4*S*)-4-Fluoropyrrolidine-2-carboxamide hydrochloride (8). Compound **5a** (354 mg, 1 mmol) was dissolved in 12 mL of a 1:1 mixture of diethylamine and dichloromethane at room temperature. After the mixture was stirred for 1.5 h, all the volatiles were removed under reduced pressure. To the resulting residue was added 10 mL of ethyl acetate and 5 mL of water, and the mixture was stirred well and left standing. The aqueous layer was separated, washed with 10 mL of ethyl acetate, and evaporated to dryness by a vacuum pump. The residue was dissolved in 2 mL of 2-propanol and mixed with ether. The resulting precipitates were collected, washed with ethyl acetate, and dried in vacuum to give 119 mg (90%) of (2*S*,4*S*)-4-fluoropyrrolidine-2-carboxamide (**7**) as crystals: ^{19}F NMR (D_2O) δ −172.40 (m, 1F); ^{1}H NMR (D_2O) δ 2.0−2.5 (m, 2H), 2.8−3.35 (m, 2H), 3.80 (dd, J = 14.1, 4.1 Hz, 1H), 5.16 (dt, J = 53.2, 4.1 Hz, 1H); ^{13}C NMR (D_2O) δ 37.5 (d, J = 21.7 Hz), 52.7 (d, J = 23.1 Hz), 58.5, 94.6 (d, J = 171.2 Hz), 177.7.

Compound **7** (119 mg, 0.90 mmol) was dissolved in 5 mL of 2-propanol, and 1.5 mL (HCl 1.5 mmol) of 1.0 M HCl in ether was added into the solution. After the mixture was stirred for 10 min, all of the volatiles were removed under reduced pressure. The resulting solid was dried in vacuum at 50 °C for 2 h, giving 148 mg (98%) of **8** as solid powder. The product was identified by comparison with an authentic sample (OmegaChem).

Preparation of (2*S*,4*R*)-*N*-(Chloroacetyl)-4-hydroxypyrrolidine-2-carboxylic Acid (1c). *Step 1.* A flask with a condenser was charged with 20.0 g (152 mmol) of (2*S*,4*R*)-4-hydroxyproline and 130 mL (517 mmol) of *N*,*O*-bis(trimethylsilyl)acetamide, and the mixture was heated at 90−100 °C under nitrogen atmosphere for 6 h, during which time the initial slurry became a clear solution. A byproduct, *O*-(trimethylsily)acetamide, was completely removed from the reaction mixture by distillation under 4 mmHg at a maximum temperature of 150 °C (oil bath). The resulting residue was 45.6 g (86%) of trimethylsilyl (2*S*,4*R*)-*N*-trimethylsilyl-4-(trimethylsilyloxy)pyrrolidine-2-carboxylate[25] as a clear yellow oil.

Step 2. Into a stirred solution of 5.22 g (15.0 mmol) of the product of step 1 in 15 mL of dry dichloromethane was added dropwise a solution of 1.45 g (15.0 mmol) of chloroacetyl fluoride[26] in 5 mL of dry dichloromethane at room temperature. Exothermic reaction occurred with liberation of Me_3SiF. The reaction mixture was stirred at room temperature for 2 h. Complete removal of solvent in vacuum gave 5.02 g (95%) of trimethylsilyl (2*S*,4*R*)-*N*-(chloroacetyl)-4-(trimethylsilyloxy)-pyrrolidine-2-carboxylate as off-white solid: ^{1}H NMR ($CDCl_3$) δ 0.02 (m, 9H), 0.19 (m, 9H), 1.8−2.4 (m, 2H), 3.3−3.8 (m, 2H), 3.8−4.0 (m, 2H), 4.2−4.6 (m, 2H); ^{13}C NMR ($CDCl_3$) δ −0.3, −0.1, 37.9, 41.8, 55.3, 59.2, 70.3, 165.1, 171.8.

Step 3. Anhydrous HF gas with nitrogen gas was bubbled into a stirred solution of 4.70 g (15.0 mmol) of the product of step 2 in 20 mL of dry acetonitrile in a fluoropolymer vessel [HF was generated by heating 10 g (100 mmol) of NaF·HF at 215 °C in a fluoropolymer vessel and carried with nitrogen flow into the solution]. After that, the reaction mixture was stirred at room temperature for 15 h and then evaporated to dryness in vacuum. The resulting solid was washed with 100 mL of dry ether and dried in vacuum to give 2.67 g (92%) of **1c** as a off-white solid: mp 123−124 °C dec; ^{1}H NMR (D_2O) δ 1.9−2.4 (m, 2H), 3.4−3.7 (m, 2H), 3.9−4.2 (m, 2H), 4.3−4.5 (m, 2H); ^{13}C NMR ($CDCl_3$) (mixture of two rotamers) major rotamer δ 36.7, 41.9, 54.9, 58.4, 69.8, 168.3, 175.3; IR (Nujol, KBr) 3310 (OH), 1713 (COOH), 1644 (CON) cm^{-1}; HRMS/ESI-APCI method (solvent; methanol) $(M + H)^+$ calcd for $C_7H_{11}ClNO_4$ 208.0371, found 208.0369; $(M + Na)^+$ calcd for $C_7H_{10}ClNNaO_4$ 230.0191, found 230.0189. Anal. Calcd for $C_7H_{10}ClNO_4$: C, 40.50; H, 4.85; N, 6.75. Found: C, 40.51; H, 4.94; N, 6.59.

■ ASSOCIATED CONTENT

Supporting Information. ^{19}F, ^{1}H, and ^{13}C NMR spectra of new compounds **1c**, **2a**−**d**, **2a′**,**d′**, **3**, **4**, **5a**,**b**, and **6a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

†Synthesis of 4-fluoropyrrolidine-2-carbonyl fluorides with Fluolead has been published as our patent, WO/2010/081014 A1.

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(26) Chloroacetyl fluoride was prepared in 93% yield by reaction of chloroacetic acid (0.15 mol) with an equimolar amount of Fluolead reagent with no solvent in a fluoropolymer vessel at ice-bath temperature to room temperature for 2 h, followed by addition of powdered KF (0.2 mol) as a HF-trap. The volatile product was collected to a receiver cooled on a liquid nitrogen under vacuum (1∼4 mmHg) at a maximum temperature of 90 °C (oil bath). The liquid product (room temperature) was microfiltered through a small amount of KF to remove any last traces of HF that may have been present.