δ,ε-Unsaturated β,β-Difluoro-α-keto Esters: Novel Synthesis and Utility as Precursors of β,β-Difluoro-α-amino Acids

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Received March 24, 1995[⊗]

Treatment of the hemiketals **6** formed from ethyl trifluoropyruvate and primary allylic alcohols with $SOCl_2$ and pyridine readily afforded a number of α-chloro-β,β,β-trifluorolactyl allyl ethers **2**. Subsequent reductive dechlorofluorination from **2** led to the formation of allyl-substituted difluoroenol pyruvyl ethers **3** whose Claisen rearrangement provided a convenient access to a variety of δ,ε-unsaturated β,β-difluoro-α-keto esters **4**. As further transformation, direct conversion of β,β-difluoro-α-keto esters to the corresponding β,β-difluoro-α-amino acids was achieved by reductive amination of the corresponding α-keto acids with $NH_3{\cdot}H_2O/NaBH_4$. Furthermore, use of the prepared β,β-difluoro-α-keto ester **4a** as a common precursor of other structurally related β,β-difluoro-α-amino acids was demonstrated by the synthesis of β,β-difluoroproline (**18**) and β,β-difluoroglutamic acid (**23**) through synthetic elaboration of its inherent double bond.

Introduction

Introduction of fluorine into pharmacologically active substances has become an important approach in the design of more potent agonists or antagonists by application of the principle of isogeometric modification of enzyme substrates with maximal shift of electron distribution.[1] In the amino acid and peptide fields, particular interest has been attracted by β-fluorinated α-amino acids which can function as highly selective and potent inhibitors of pyridoxal phosphate-dependent enzymes via a suicide-type mechanism.[2] Consequently, they have been receiving considerable attention from both mechanistic and synthetic viewpoints.[1,2] The synthesis of β-fluorinated α-amino acids has not been trivial because of the problems associated with the methods for the direct introduction of fluorine into existing amino acids or related compounds. Among several reported methods are fluorodehydoxylation of β-hydroxy-α-amino acids,[3] photofluorination of α-amino acids,[4] electrophilic fluorination of α-keto acid derivatives,[5] and ring opening of aziridine- and azirinecarboxylates,[6] of which only the last mentioned method has been aimed at the synthesis of β-difluorinated α-amino acids. Because of the necessity to use highly toxic and reactive fluorinating reagents such as SF_4, DAST, CF_3OF, F_2, and HF, most of the reported methods are not only arduous to carry out in ordinary laboratories but also necessarily limited to functional groups compatible with the reactive reagents.

β,β-Difluoro-α-keto acid derivatives can be considered as important precursors of the corresponding fluorinated amino acids. In addition, they can also be of interest as intermediates in the development of enzyme inhibitors and drugs since their nonfluorinated counterparts are often the penultimate products formed in the biosynthesis of amino acids. However, prior to the present work, the synthesis of β,β-difluoro-α-keto acids or their derivatives has virtually remained unexplored.[7] Direct introduction of two fluorines into the β-position of α-keto acid derivatives appeared to be unfeasible, for even for the synthesis of β-monofluorinated α-keto acids direct fluorination of enol-type keto esters with electrophilic fluorinating reagents has only met with limited success because of the requirement of a rate-determining enolization step that must precede the electrophilic reaction.[5] The development of a new method that can provide a convenient access to β,β-fluoro-α-keto acids or their derivatives would therefore be a worthwhile undertaking. In this paper, we wish to disclose a convenient method for the synthesis of δ,ε-unsaturated β,β-difluoro-α-keto esters as well as to demonstrate their use for the synthesis of β,β-difluoro-α-amino acids.

Results and Discussion

Recently, we have developed a convenient method for the synthesis of a variety of β,β,β-trifluorolactyl ethers **1** by means of the metal-catalyzed OH insertion reaction of a CF_3-substituted carbenoid with hydroxylic compounds.[8] A strategy based on the utilization of these fluorinated lactyl ethers for the preparation of β,β-

[⊗] Abstract published in *Advance ACS Abstracts,* September 1, 1995.

(1) (a) Filler, R., Kobayashi, Y., Eds. *Biomedicinal Aspects of Fluorine Chemistry;* Elsevier: Amsterdam, 1982. (b) Walsh, C. *Tetrahedron* **1982**, *38*, 871. (c) Welch, J. T.; Eswarakrishnan, S. *Fluorine in Biorganic Chemistry*; John Wiley & Sons: New York, 1990. (d) Filler, R., Kobayashi, Y., Yagupolski, L. M., Eds. *Organofluorine Compounds in Medicinal Chemistry and Biomedical Applications;* Elsevier Science: Amsterdam, 1993.

(2) (a) Kollonitsh, J.; Perkins, L. M.; Patchett, A. A.; Doldouras, G. A.; Marburg, S.; Duggan, D. E.; Maycock, A. L.; Aster, S. D. *Nature* **1978**, *274*, 906. (b) Bey, P. *Ann. Chim. Fr.* **1984**, *9*, 695. (c) Kollonitsh, J. *Israel J. Chem.* **1978**, *17*, 53. (d) Kawada, K.; Tsushima, T. *Kagaku Kogyo* **1987**, *38*, 164; *Chem. Abstr.* **1987**, *107*, R97067. (d) Kukhar, V. P. *J. Fluorine Chem.* **1994**, *69*, 199.

(3) (a) Kollonitsh, J.; Marburg, S.; Perkins, L. M. *J. Org. Chem.* **1979**, *44*, 771. (b) Kollonitsh, J.; Marburg, S.; Perkins, L. M. *J. Org. Chem.* **1975**, *40*, 3808. (c) Tsushima, T.; Sato, T.; Tsuji, T. *Tetrahedron Lett.* **1980**, *21*, 3591. (d) Tsushima, T.; Nishikawa, J.; Sato, T.; Tanida, H.; Tori, K.; Tsuji, T.; Misaki, S.; Suefuji, M. *Tetrahedron Lett.* **1980**, *21*, 3593. (e) Groth, U.; Schollkopf, U. *Synthesis* **1983**, 673.

(4) (a) Kollonitsh, J.; Barash, L. *J. Am. Chem. Soc.* **1970**, *92*, 7494. (b) Kollonitsh, J.; Barash, L. *J. Am. Chem. Soc.* **1976**, *98*, 5591.

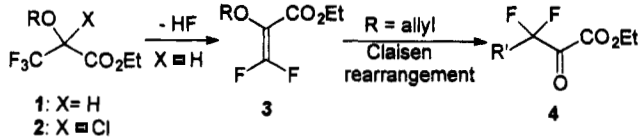
(5) (a) Tsushima, T.; Kawada, K.; Tsuji, T. *J. Org. Chem.* **1982**, *47*, 1107. (b) Tsushima, T.; Kawada, K.; Nishikawa, J.; Sato, T.; Tori, K.; Tsuji, T. *J. Org. Chem.* **1984**, *49*, 1163.

(6) (a) Wade, J. N.; Guedj, R. *Tetrahedron Lett.* **1979**, 3953. (b) Wade, T. N.; Kheribet, R. *J. Org. Chem.* **1980**, *45*, 5333. (c) Wade, T. N. *J. Org. Chem.* **1980**, *45*, 5328. (d) Ayi, A. T.; Remli, M.; Guedj, R. *J. Fluorine Chem.* **1981**, *18*, 93. (e) Guedj, R.; Ayi, A. T.; Remli, M. *Ann. Chim. Fr.* **1984**, *9*, 691. (f) Wade, T. N.; Gaymard, F.; Guedj, R. *Tetrahedron Lett.* **1979**, 2681.

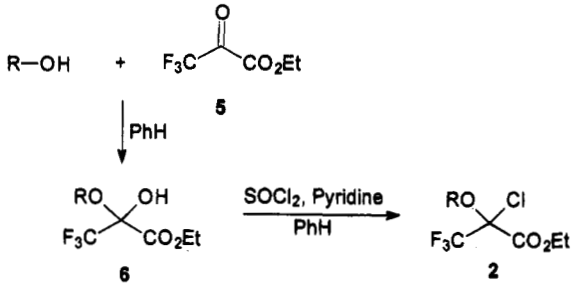
(7) A special β,β-difluoro-α-keto ester, di-*tert*-butyl difluorooxaloacetate, has been prepared by fluorination of di-*tert*-butyl oxaloacetate with $FClO_3$. Hageman, M. J. J.; Wanner, M. J.; Koomen, G.; Pandit, U. K. *J. Med. Chem.* **1977**, *20*, 1677.

0022-3263/95/1960-6289$09.00/0

Scheme 1



Scheme 2

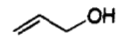
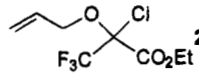
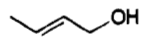
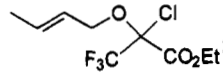
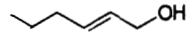
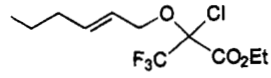
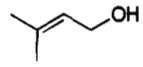
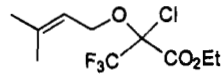
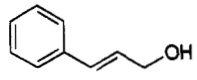
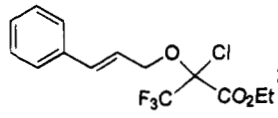
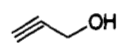
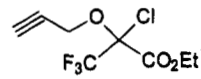
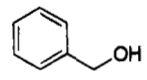
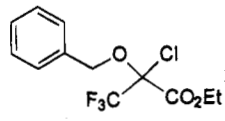


difluoro-α-keto esters **4** was then initiated. It was expected that base-promoted elimination of HF from **1** would give difluoroenol pyruvyl ether **3** which, if R is an allylic group, should be amenable to Claisen rearrangement leading to the formation of the desired product **4** (Scheme 1). Unfortunately, the elimination step was found to be accompanied by an unavoidable side reaction arising from the nucleophilic attack[9] of **3** by the base employed for the elimination of HF, such as LDA, t-BuOK, LTMP, and DBU, and hence the overall yield of **4** was rather unsatisfactory.[8]

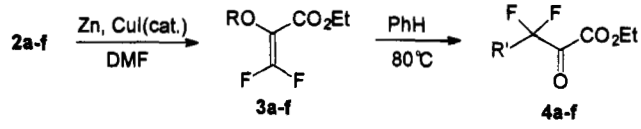
A new approach was then conceived. It involved the utilization of the readily accessible ethyl trifluoropyruvate[10] for the synthesis of the α-chlorinated lactyl ethers **2** from which reductive dechlorofluorination allowed the formation of the labile difluoroenol pyruvyl ethers **3** in non-nucleophilic media. Since allylic alcohols were employed for the preparation of **2**, the prepared difluoroenol pyruvyl ethers were found to be able to undergo facile thermal rearrangement to afford a variety of δ,ϵ-unsaturated β,β-difluoro-α-keto esters **4**. These keto esters were subsequently proved to be valuable precursors for the synthesis of a plethora of β,β-difluoro-α-amino acids.

Preparation of α-Chloro-β,β,β-trifluorolactyl Ethers. The keto carbonyl of ethyl trifluoropyruvate (**5**) is strongly electron deficient and adds alcohols readily. As outlined in Scheme 2, allylic, benzylic, and propargylic alcohols have been purposely chosen to form a stable hemiketals **6** with **5**. Conversion of the hemiketals **6** to α-chloro-β,β,β-trifluorolactyl ethers **2** was effected in one pot by treatment of **6** with 1.5 equiv of $SOCl_2$ in the presence of 3.0 equiv of pyridine. The yields of **2** were found to vary substantially with the solvent. Thus, the best yields were obtained when the reactions were carried out in a nonpolar solvent such as benzene and hexane. Unlike ordinary α-chloro ethers which are generally susceptible to hydrolysis, the α-chlorinated lactyl ethers **2** were found to be quite stable because of the strongly electron-withdrawing trifluoromethyl group, so they were easily isolated from aqueous workup and purified through distillation under reduced pressure.

Table 1. Preparation of α-Chloro-β,β,β-trifluorolactyl Ethers

entry	alcohol	product	yield, %
1		 **2a**	80
2		 **2b**	70
3		 **2c**	72
4		 **2d**	71
5		 **2e**	65
6		 **2f**	74
7		 **2g**	78

Scheme 3



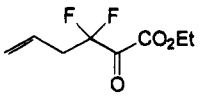
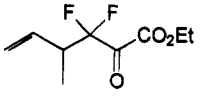
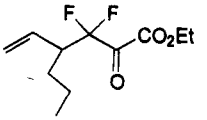
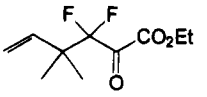
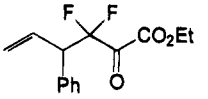
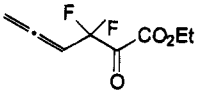
Synthesis of β,β-Difluoro-α-keto Esters. As outlined in Scheme 3, when the α-chlorolactyl ether **2** were treated with 5 equiv of freshly activated zinc in DMF, reductive dechlorofluorination occurred exothermically after an induction period to furnish the expected difluoroenol pyruvyl ethers **3** (Scheme 3) in good yield as evidenced by ^{19}F NMR analysis of the reaction mixture. A small amount of lactyl ether **1** resulting from the direct reduction of the C—Cl bond to the C—H bond was observed as the byproduct. Compound **3** could not be purified by distillation or chromatography due to their thermal lability. Therefore, they were directly subjected to the subsequent Claisen rearrangement.

(8) Shi, G.-q., Zhao, Z.-y.; Cai, W.-l. *Tetrahedron* **1995**, *51*, 5011–5018.

(9) It has been known that α,β-unsaturated β,β-difluoro carbonyl compounds are difficult to isolate in nonanhydrous or nucleophilic media due to further reactions. (a) Buxton, M. W.; Stacey, M.; Tatlow, J. C. *J. Chem. Soc.* **1954**, 366. (b) Rico, I.; Cantauzene, D.; Wakselman, C. *Tetrahedron* **1981**, *22*, 3405. (c) Ishikawa, N.; Yokozawa, T. *Bull. Chem. Soc. Jpn.* **1983**, 56, 724. (d) Kitazume, T.; Ohnogi, T. *Synthesis* **1988**, 614. (e) Ichikawa, J.; Yokota, N.; Kobayashi, M.; Minami, T. *Synlett* **1993**, 186.

(10) (a) Knunyants, I. L.; Shokina, V. V.; Tyuleneva, V. V. *Dokl. Akad. Nauk. SSSR* **1966**, *169*, 594; *Chem. Abstr.* **1966**, *65*, 15218e. (b) Sianesi, D.; Pasetti, A.; Tarli, F. *J. Org. Chem.* **1966**, *31*, 2312. (c) Francese, C.; Toxdeux, M.; Wakselman, C. *Tetrahedron Lett.* **1988**, *29*, 1029. See also: Shi, G.-q.; Xu, Y.-y. *J. Chem. Soc., Chem. Commun.* **1989**, 607. Compound **5** is now available from PCR Inc., Gainesville, FL.

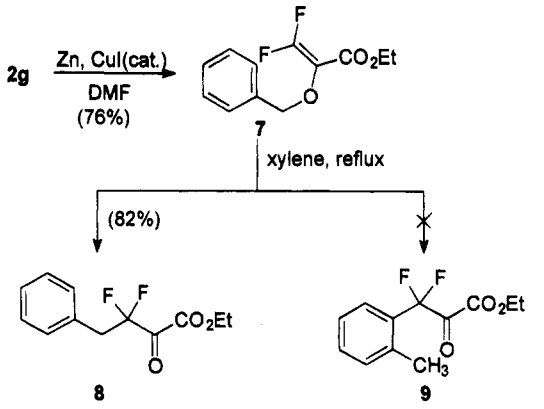
Table 2. Conversion of α-Chloro-β,β,β-trifluorolactyl Ether 2 to β,β-Difluoro-α-keto Ester 4

entry	substrate	product		yield, %
1	**2a**		**4a**	86
2	**2b**		**4b**	70
3	**2c**		**4c**	70
4	**2d**		**4d**	80
5	**2e**		**4e**	60
6	**2f**		**4f**	67

Previously, the [3,3] sigmatropic rearrangements of some fluorinated compounds have been described in the literature.[11] However, no studies have been made on the preparation and Claisen rearrangement of difluoroenolpyruvyl allyl ethers. Even in the nonfluorinated series, the rearrangement involving these particular types of compounds has remained unexplored except the unique rearrangement of chorismate, an enolpyruvyl ether, to prephenate which has been studied as an important step in the biosynthesis of aromatic amino acids.[12] To our delight, when difluoroenolpyruvyl allyl ethers **3a–e** were heated in benzene at 80 °C, a facile rearrangement[13] occurred to afford the expected β,β-difluoro-α-keto esters **4a–e**. The rearrangement has also been extended to a propargyl system which resulted in the formation of an allenyl-substituted β,β-difluoro-α-keto ester **4f** (Table 2, entry 6). All reactions were virtually completed within 1 h and the conversion of **3** to **4** was almost quantitative as revealed by ^{19}F NMR analysis of the reaction mixture.

We were also interested in performing the Claisen rearrangement of the difluoroenol pyruvyl ether **7** in which part of the aromatic ring would act as the allylic double bond. In the nonfluorinated series, the rearrangement of benzyl vinyl ethers has only met with very limited success.[14] For example, thermal rearrangement was observed only when the benzene ring was substituted with electron-donating groups[15] or when the vinyl moiety is that of a ketene acetal.[16] In the former case, the rearrangement not only required a temperature above 200 °C but also produced, in addition to the expected product, a varying amount of a product formed through a nonconcerted [1,3] shift of the benzyl group. Interestingly, when compound **7**, prepared from the corresponding α-chloro ether **2g**, was heated in refluxing xylene, a smooth rearrangement occurred to afford the β,β-difluoro-α-keto ester **8** as the only rearrangement product (Scheme 4), implying that the reaction has completely followed a nonconcerted pathway involving a [1, 3] instead of [3, 3] shift which should otherwise lead to the formation of compound **9**.

Scheme 4



Conversion of β,β-Difluoro-α-keto Esters to β,β-Difluoro-α-amino Acids. Having developed an efficient and convenient preparation of β,β-difluoro-α-keto esters, we then decided to demonstrate their synthetic viability as precursors of β,β-difluoro-α-amino acids. Our first synthetic effort aims at the direct conversion of the prepared β,β-difluoro-α-keto esters to the corresponding amino acids. The α-keto esters **4a** and **8** were chosen to be the representative substrates. They were first subjected to mild hydrolysis in aqueous 2-propanol in the presence of $NaHCO_3$ to afford the expected α-keto acids **10** and **11** in almost quantitative yield. Although the direct reductive amination of some β-*mono*fluorinated α-keto acids using either $NH_4Br/NaBH_3CN$ or $NH_3{\cdot}H_2O/NaBH_4$ has been described for the synthesis of the corresponding β-fluoro-α-amino acids,[5b,17] the feasibility of using the same protocols for the reductive amination of β,β-*di*fluoro-α-keto acids was our primary concern. The two geminal fluorine substituents, which have caused a significant change of the reactivity of the keto carbonyl, may present a potential synthetic hazard. Fortunately, when the reductive amination was carried out with $NH_3{\cdot}H_2O/NaBH_4$, the two β,β-difluoro-α-amino acids **12** and **13** were produced in 43% and 56% yield, respectively (Scheme 5). The $NH_4Br/NaBH_3CN$ protocol was, however, found to be unsuccessful, and the major reaction was the direct reduction of the keto carbonyl to a

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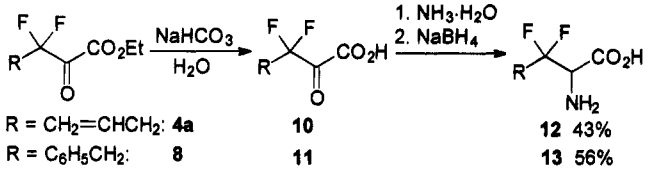
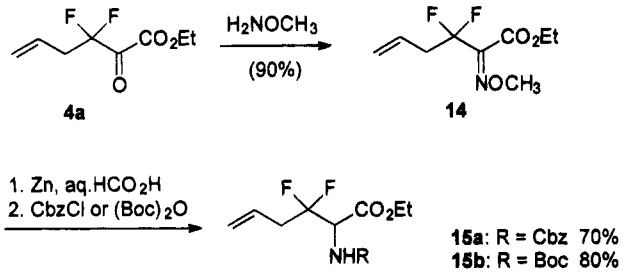
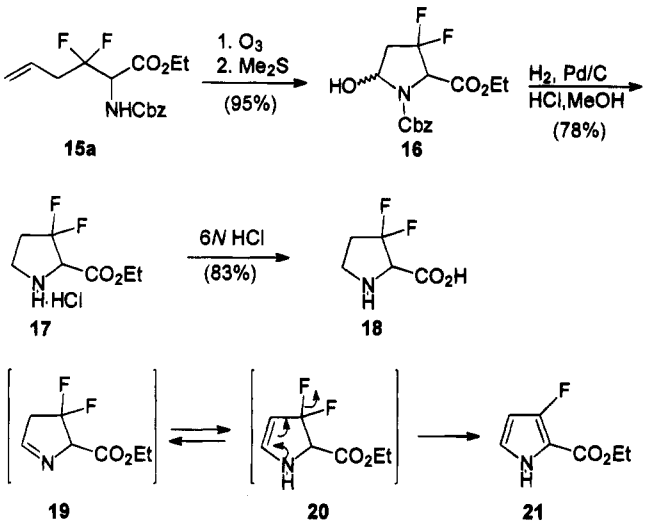
Scheme 5



Scheme 6



Scheme 7



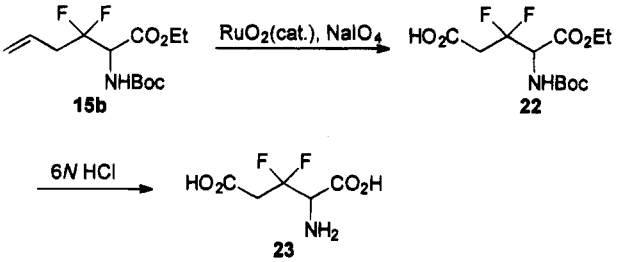
hydroxyl by $NaBH_3CN$ due to the increased electron deficiency of the carbonyl group compared with that of the monofluorinated compounds as well as the reduced nucleophilicity of NH_4Br relative to that of NH_3.

The utility of the prepared β,β-difluoro-α-keto esters as precursors for the synthesis of β,β-difluoro-α-amino acids is not confined to the above simple transformation if we realize that the inherent double bond present at the δ-position of these keto esters may serve as a surrogate for a number of other functionalities. Thus, in order to carry out various synthetic manipulations with the double bond, the α-keto ester **4a** was converted to its *O*-methyl oxime **14** in 90% yield. Subsequent reduction of **14** with Zn powder in aqueous formic acid followed by protection of the resulting amino group with Boc_2O or CbzCl afforded the *N*-protected amino ester **15a** and **15b** in 70% and 80 overall yield, respectively (Scheme 6).

The versatility of compounds **15a** and **15b** as a common intermediate of other functionalized β,β-difluoro-α-amino acids has been highlighted by two representative examples described as follows.

As the first example (Scheme 7), ozonolysis of compound **15a** followed by treatment of the resulting ozonide with Me_2S afforded the cyclic hemiaminal **16** in 95% yield. After removal of the protecting group by catalytic hydrogenation over 10% Pd/C in methanol acidified with

Scheme 8



HCl, formation of a cyclic imine was expected which was concomitantly reduced under the hydrogenation conditions to furnish the desired β,β-difluoroprolinate hydrochloride **17** in 78% yield. What should be noted here is that the catalytic hydrogenation must be conducted in the acidic medium because initial experiments performed in the absence of the acid led mostly to the formation of the pyrrole derivative **21**. The role of HCl is presumably to accelerate the reduction of the intermediate imine compound **19** and meanwhile suppress the formation of the tautomeric enamine **20** which can competitively lose HF to produce **21**. Finally, compound **17**, which was found to be unstable toward base, was subjected to hydrolysis in 6 N hydrochloric acid to furnish the desired amino acid **18** in 83% yield. To our knowledge, this is the first synthesis of a β-fluorinated analogue of proline that may find interesting applications as a potential inhibitor of enzymes related to the parent compound.

Our next example is the synthesis of β,β-difluoroglutamic acid **23** starting from **15b** (Scheme 8). The oxidative cleavage of the double bond in **15b** with RuO_2(cat.)/$NaIO_4$ cleanly afforded the fluorinated glutamic acid monoethyl ester **22**. Hydrolysis of the crude **22** in 6 N hydrochloric acid furnished the expected β,β-difluoroglutamic acid **23** in 54% overall yield. Previously, this fluorinated amino acid has been studied as an enhancer of polyglutamate chain elongation.[18] However, the reported methods for its synthesis appeared to be less attractive in terms of the overall yield and the availability of the starting material.[19]

Conclusion

We have developed a novel and convenient synthetic route to δ,ϵ-unsaturated β,β-difluoro-α-keto esters via the Claisen rearrangement of allyl-substituted difluoroenol pyruvyl ethers. The latter were readily prepared through reductive dechlorofluorination of α-chloro-β,β,β-trifluorolactyl ethers **2** which were derived from easily accessible ethyl trifluoropyruvate (**5**). We have showed that the hydrolysis of the prepared difluoro-α-keto ester so obtained followed by reductive amination could provide a direct entry to β,β-difluoro-α-amino acids. In addition, by taking advantage of the inherent double bond, we have also demonstrated the utilities of the *N*-protected β,β-difluoro-α-amino ester **15a** and **15b** as common precursors for the synthesis β,β-difluoroproline (**18**) and β,β-difluoroglutamic acid (**23**).

Experimental Section

^1H NMR spectra were recorded on a 300 MHz spectrometer with Me_4Si as internal standard. ^{19}F NMR spectra were

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obtained on a 60 MHz spectrometer using trifluoroacetic acid as external standard, downfield shifts being designated as negative. Mass spectra were obtained using EI ionization at 70 eV. All reactions were routinely monitored with the aid of TLC or ^{19}F NMR spectroscopy.

Benzene was dried over sodium wire. DMF was freshly distilled from CaH_2. Pyridine and $SOCl_2$ were distilled prior to use. Zinc powder was activated according to a standard procedure.[20] Ethyl trifluoropyruvate was prepared according to the literature methods.[9]

General Procedure for the Preparation of α-Chloro-β,β,β-trifluorolactyl Ethers 2. Ethyl trifluoropyruvate (5.1 g, 30 mmol) and an α,β-unsaturated alcohol (30 mmol) were mixed in dry benzene (30 mL). The resulting warm solution was left at room temperature under N_2 for 30 min. After addition of pyridine (7.2 mL, 90 mmol), $SOCl_2$ (3.3 mL, 45 mmol) was added dropwise over 10 min while the temperature of the reaction mixture was being maintained at 0 °C. After being stirred for 30 min at 0 °C, the reaction mixture was poured into ice–water (100 mL) and extracted with diethyl ether (3 × 50 mL). The combined organic phase was washed successively with water (100 mL), saturated $NaHCO_3$ solution (2 × 100 mL), and brine (100 mL) and dried over Na_2SO_4. After removal of the solvents, the product was purified by distillation at reduced pressure.

Ethyl 2-(2-propenyloxy)-2-chloro-3,3,3-trifluoropropanoate (2a): 80% yield; bp 52 °C/4.5 mmHg; ^1H NMR ($CDCl_3$) δ 5.92 (m, 1H), 5.38 (dq, J = 14.1, 1.4 Hz, 1H), 5.27 (dq, J = 10.3, 1.2 Hz, 1H), 4.40 (d, J = 7.1 Hz, 2H), 4.34 (m, 2H), 1.35 (t, J = 7.09 Hz, 3H); ^{19}F NMR ($CDCl_3$) δ 1.0 (s); MS (EI, m/z) 247 (8, M^+), 211 (23), 171 (99), 81 (100), 59 (46). Anal. Calcd for $C_8H_{10}ClF_3O_3$: C, 38.96; H, 4.09. Found: C, 38.83; H, 4.19.

Ethyl 2-[(*E*)-2-butenyloxy]-2-chloro-3,3,3-trifluoropropanoate (2b): 70% yield; bp 49 °C/0.5 mmHg; ^1H NMR ($CDCl_3$) δ 5.80 (m, 1H), 5.60 (m, 1H), 4.38 (m, 2H), 4.31 (d, J = 5.9 Hz, 2H), 1.72 (dd, J = 6.5, 1.0 Hz, 3H), 1.35 (t, J = 7.1 Hz, 3H); ^{19}F NMR ($CDCl_3$) δ 1.0 (s); MS (EI, m/z) 259 (1, M^+), 231 (1), 162 (11), 71 (53), 55 (100). Anal. Calcd for $C_9H_{12}ClF_3O_3$: C, 41.47; H, 4.64. Found: C, 41.21; H, 4.60.

Ethyl 2-[(*E*)-2-hexenyloxy]-2-chloro-3,3,3-trifluoropropanoate (2c): 72% yield; bp 64 °C/0.5 mmHg; ^1H NMR ($CDCl_3$) δ 5.80 (dt, J = 15.8, 6.6 Hz, 1H), 5.56 (dt, J = 15.8, 6.5 Hz, 1H), 4.28 –4.50 (m, 4H), 2.05 (q, J = 7.1 Hz, 2H), 1.45 (m, 2H), 1.35 (t, J = 7.1 Hz, 3H), 0.92 (t, J = 7.1 Hz, 3H); ^{19}F NMR ($CDCl_3$) δ −0.6 (s); MS (EI, m/z) 287 (1, M^+), 162 (8), 99 (36), 83 (100). Anal. Calcd $C_{11}H_{16}ClF_3O_3$: C, 46.09; H, 5.63. Found: C, 45.77; H, 5.51.

Ethyl 2-[(3-methyl-2-butenyl)oxy]-2-chloro-3,3,3-trifluoropropanoate (2d): 71% yield; bp 57 °C/0.4 mmHg; ^1H NMR ($CDCl_3$) δ 5.36 (m, 1H), 4.42 (d, J = 7.1 Hz, 2H), 4.42 (q, J = 7.1 Hz, 2H), 1.76 (s, 3H), 1.71 (s, 3H), 1.35 (t, J = 7.10 Hz, 3H); ^{19}F NMR ($CDCl_3$) δ 1.0(s); MS (EI, m/z) 260 (11, M^+), 246 (21), 144 (23), 73 (100). Anal. Calcd $C_{10}H_{14}ClF_3O_3$: C, 43.57; H, 5.12. Found: C, 43.09; H, 5.01.

Ethyl 2-[[3-phenyl-(*E*)-2-propenyl]oxy]-2-chloro-3,3,3-propanoate (2e): 65% yield; bp 105 °C/0.2 mmHg; ^1H NMR ($CDCl_3$) δ 7.20–7.45 (m, 5H), 6.68 (d, J = 15.9 Hz, 1H), 6.38 (dt, J = 15.9, 6.2 Hz, 1H), 4.53 (dd, J = 6.1, 0.8 Hz, 2H), 4.36 (q, J = 7.1 Hz, 2H), 1.33 (t, J = 7.1 Hz, 3H); ^{19}F NMR ($CDCl_3$) δ 0.0 (s); MS (EI, m/z) 324 (4, M^+ + 1), 133 (100), 117 (93), 91 (20). Anal. Calcd for $C_{14}H_{14}ClF_3O_3$: C, 52.11; H, 4.37. Found: C, 52.42; H, 4.36.

Ethyl 2-(2-propynyloxy)-2-chloro-3,3,3-trifluoropropanoate (2f): 74% yield; bp 35 °C/0.4 mmHg; ^1H NMR ($CDCl_3$) δ 4.63 (dd, J = 15.1, 2.5 Hz, 1H), 4.55 (dd, J = 15.1, 2.5 Hz, 1H), 4.37 (q, J = 7.1 Hz, 2H), 2.55 (t, J = 2.5 Hz, 1H), 1.36 (t, J = 7.1 Hz, 3H); ^{19}F NMR ($CDCl_3$) δ 1.0(s); MS (EI, m/z) 245 (9, M^+), 181 (55), 162 (63), 143 (65), 69 (100); HRMS (EI) calcd for $C_8H_8F_3O_2$ [M − Cl]$^+$ 209.0426, found 209.0410.

Ethyl 2-(benzyloxy)-2-chloro-3,3,3-trifluoropropananoate (2g): 78% yield; bp 82 °C/0.2 mmHg; ^1H NMR ($CDCl_3$) δ 7.31 (s, 5H), 4.92 (s, 2H), 4.30 (q, J = 7.1 Hz, 2H), 1.30 (t, J = 7.1 Hz, 3H); ^{19}F NMR ($CDCl_3$) δ 0.0 (s); MS (EI, m/z) 295 (2, M^+), 267 (2), 181 (15), 107 (27), 91 (100). Anal. Calcd for $C_{12}H_{12}ClF_3O_3$: C,48.58; H, 4.08. Found: C, 48.67; H, 4.09.

General Procedure for the Synthesis of δ,ω-Unsaturated β,β-Difluoro-α-keto Esters 4. To a solution of the lactyl ether **2** (10 mmol) in DMF (20 mL) was added freshly activated zinc powder (6.5 g, 0.10 mol) and a little amount of cuprous iodide (ca. 50 mg). The resulting reaction mixture was vigorously stirred while being cooled with a water bath at 25 °C. A exothermic reaction started after an induction period of 10–60 min. After the heat evolution ceased, the reaction mixture was diluted with diethyl ether (50 mL) and filtered. The filtrate was washed with water (2 × 50 mL) and dried over Na_2SO_4. After removal of the solvents, the residue was taken up in benzene (50 mL). The resulting solution was heated under reflux for 1 h. Evaporation of the solvent gave an oil which was purified by chromatography on silica gel eluting with a mixture of petroleum ether and ethyl acetate. The product so obtained was found to exist mostly in the hydrated form so that before analyses microdistillation was necessary to remove the water of hydration.

Ethyl 3,3-difluoro-2-oxo-5-hexenoate (4a): 86% yield; ^1H NMR ($CDCl_3$) δ 5.80 (m, 1H), 5.20 (m, 2H), 4.25 (q, J = 7.1 Hz, 2H), 2.80 (dt, J = 18.5, 7.0 Hz, 2H), 1.30 (t, J = 7.1 Hz, 3H); ^{19}F NMR ($CDCl_3$) δ 36.0 (t); MS (EI, m/z) 193 (9, M^+ + 1), 165 (35), 145 (32), 91 (100), 71 (32). Anal. Calcd for $C_8H_{10}F_2O_3$: C, 49.66; H, 5.47. Found: C, 50.00; H, 5.25.

Ethyl 2,2-difluoro-4-methyl-2-oxo-5-hexenoate (4b): 70% yield; ^1H NMR ($CDCl_3$) δ 5.80 (m,1H), 5.20 (m, 2H), 4.38 (m, 2H), 3.15 (m, 1H), 1.35 (t, J = 7.1 Hz, 3H), 1.20 (d, J = 7.0 Hz, 3H); ^{19}F NMR ($CDCl_3$) δ 34.5 (dd), 39.0 (dd); MS (EI, m/z) 207 (96, M^+ + 1), 187 (55), 159 (82), 105 (75), 77 (100); HRMS (EI) calcd for $C_9H_{12}F_2O_3$ 206.0755, found 206.0792.

Ethyl 3,3-difluoro-4-propyl-2-oxo-5-hexenoate (4c): 70% yield; ^1H NMR ($CDCl_3$) δ 5.53 (m, 1H), 5.20 (m, 2H), 4.37 (q, J = 7.1 Hz, 2H), 3.05 (m, 1H), 1.40 (t, J = 7.1 Hz, 3H), 1.20–1.72 (m, 4H), 0.91 (t, J = 7.1 Hz, 3H); ^{19}F NMR ($CDCl_3$) δ 31.6 (dd), 37.5 (dd); MS (EI, m/z) 234 (13, M^+), 214 (44), 161 (25), 43 (100). Anal. Calcd for $C_{11}H_{16}F_2O_3$: C, 56.40; H, 6.88. Found: C, 56.20; H, 6.68.

Ethyl 3,3-difluoro-4,4-dimethyl-2-oxo-5-hexenoate (4d): 80% yield; ^1H NMR ($CDCl_3$) δ 5.96 (dd, J = 17.4 Hz, 10.8 Hz, 1H), 5.21 (d, J = 10.8 Hz, 1H), 5.16 (d, J = 17.4 Hz, 1H), 4.35 (q, J = 7.1 Hz, 2H), 1.36 (t, J = 7.1 Hz, 3H), 1.22 (s, 6H); ^{19}F NMR ($CDCl_3$) δ 35.8 (m); MS (EI, m/z) 220 (34, M^+), 119 (44), 77 (51), 69 (100). Anal. Cacld for $C_{10}H_{14}F_2O_3$: C, 54.54; H, 6.41. Found: C, 54.23; H, 6.64.

Ethyl 3,3-difluoro-4-phenyl-2-oxo-5-hexenoate (4e): 60% yield; ^1H NMR ($CDCl_3$) δ 7.25–7.42 (m, 5H), 6.22 (m, 1H), 5.31 (m, 2H), 4.42 (dt, J = 8.5, 17.2 Hz, 2H), 4.35 (q, J = 7.1 Hz, 2H), 1.35 (t, J = 7.1 Hz, 3H); ^{19}F NMR (CCl_4) δ 36.6 (m); MS (EI, m/z) 250 (12, $M^+ - H_2O$), 205 (8), 174 (11), 117 (100), 91 (14). Anal. Calcd for $C_{14}H_{14}F_2O_3$: C, 62.68; H, 5.26. Found: C, 62.45; H, 5.26.

Ethyl 3,3-difluoro-2-oxo-4,5-hexadienoate (4f): 67% yield; ^1H NMR ($CDCl_3$) δ 5.58 (m, 1H), 5.19 (m, 2H), 4.46 (q, J = 7.1 Hz, 2H), 1.33 (t, J = 7.1 Hz, 3H); ^{19}F NMR ($CDCl_3$) δ 36.2 (m); MS (EI, m/z) 191 (13, M^+ + 1), 171 (29), 143 (57), 115 (59), 89 (100); HRMS (EI) calcd for $C_8H_8F_2O_3$ 191.0520, found 191.0567.

Ethyl 2-(Benzyloxy)-3,3-difluoropropenoate (7). A mixture of **4g** (2.96 g, 10 mmol) and freshly activated zinc powder (6.5 g, 0.10 mol) and cuprous iodide (ca. 50 mg) in DMF (20 mL) was stirred under N_2 until the heat evolution ceased. The reaction mixture was then diluted with diethyl ether (50 mL) and fitered. The filtrate was washed with water (2 × 50 mL) and dried over Na_2SO_4. Evaporation of the solvents gave a residue which was purified by flash chromatography eluting with a 2:8 mixture of ethyl acetate and petroleum ether to afford 1.8 g (76%) of **7** as an oil: ^1H NMR ($CDCl_3$) δ 7.21 (s, 5H), 4.82 (s, 2H), 4.25 (q, J = 7.1 Hz, 2H), 1.30 (t, J = 7.1 Hz, 3H); ^{19}F NMR ($CDCl_3$) d 4.1 (d), 9.4 (d); MS (EI, m/z) 242 (5, M^+), 197 (8), 169 (15). Anal. Calcd for $C_{12}H_{12}F_2O_3$: C, 59.50; H, 4.99. Found: C, 59.89; H, 4.68.

Ethyl 3,3-difluoro-2-oxo-4-phenylbutanoate (8). A solution of **7** (1.2 g, 5.0 mmol) in xylene was heated under reflux for 72 h. Evaporation of the solvent gave a residue from which 1.0 g (82%) of **8** was separated by flash chromatography on silica gel eluting with a 2:8 mixture of ethyl acetate and

petroleum ether: ^{1}H NMR ($CDCl_3$) δ 7.23 (s, 5H), 4.25(q, J = 7.1 Hz, 2H), 3.31 (t, J = 18.0 Hz, 2H), 1.30 (t, J = 7.1 Hz, 3H); ^{19}F NMR ($CDCl_3$), δ 36.4 (t); MS (EI, m/z) 242 (8, M^+), 225 (40), 141 (60), 91 (100). Anal. Calcd for $C_{12}H_{12}F_2O_3$: C, 41.28; H, 4.99. Found: C, 41.32; H, 5.03.

3,3-Difluoro-2-oxo-5-hexenoic Acid (10). A mixture of keto ester **4a** (2.9 g, 15 mmol) and $NaHCO_3$ (8.0 g, 95 mmol) in 50% (v/v) aqueous 2-propanol (300 mL) was stirred at 40 °C for 48 h. After being diluted with water (300 mL) and washed with diethyl ether (50 mL), the reaction mixture was acidified to pH 1 with 2 N HCl solution, saturated with NaCl, and extracted with diethyl ether (3 × 50 mL). The ether extracts were washed with brine (50 mL) and concentrated to give 2.3 g (95%) of **10** as a semisolid (partly hydrated): ^{1}H NMR ($CDCl_3$) δ 5.80 (m, 1H), 5.27 (m, 2H), 2.88 (dt, J = 6.90, 16.5 Hz, 2H); ^{19}F NMR ($CDCl_3$) δ 35.0 (t, J = 16.5 Hz).

3,3-Difluoro-2-oxo-4-phenylbutanoic Acid (11). Following the same procedure as described for the preparation of **10**, 1.0 g (95%) of **11** was obtained from **8** (1.2 g, 5.0 mmol): mp 62 °C; ^{1}H NMR (CD_3COCD_3) δ 7.25 (s, 5H), 3.40 (t, J = 19.8 Hz, 2H); ^{19}F NMR (CD_3COCD_3) δ 36.5 (t, J = 19.8 Hz); MS (EI, m/z) 214 (4, M^+) 194 (30), 149 (20), 141 (32), 91 (100). Anal Calcd for $C_{10}H_8F_2O_3$: C, 56.68; H, 3.76. Found: C, 56.64; H, 3.53.

2-Amino-3,3-difluoro-5-hexenoic Acid (12). A solution of keto acid **10** (1.0 g, 5 mmol) in 25% aqueous ammonia (10 mL) was kept at 40 °C for 5 h. After the solution was cooled to 10 °C, $NaBH_4$ (0.57 g, 15 mmol) was added in one portion. The reaction flask was then evacuated with a water pump for 30 min, while a stream of nitrogen was bubbled into the stirred reaction mixture. After being stirred for an additional 3 h at room temperature, the reaction mixture was acidified to pH 1 with concentrated HCl solution and poured onto a column packed with Dowex 50W-X8 (H^+). The column was successively eluted with 50% (v/v) aqueous 2-propanol, water, and 1 N aqueous ammonia. Removal of the solvents from the last fraction gave 0.35 g (43%) of **12** as a white solid: mp 194–196 °C; ^{1}H NMR (D_2O) δ 5.84 (m, 1H), 5.26 (m, 2H), 3.53 (t, J = 13.3 Hz, 1H), 2.72 (m, 2H); ^{19}F NMR ($CDCl_3$) δ 26.0 (m); MS (EI, m/z) 149 (15), 81 (58), 74 (77), 69 (100), 44 (99). Anal. Calcd for $C_6H_9F_2NO_2$: C, 43.64; H, 5.49; N, 8.48. Found: C, 42.31; H, 5.38; N, 8.27.

2-Amino-3,3-difluoro-4-phenylbutanoic Acid (13). Following the same procedure as described for the synthesis of **12**, 0.48 g (56%) of **13** was obtained from **11** (0.86 g, 4.0 mmol): mp 188–189 °C; ^{1}H NMR (D_2O) δ 7.23 (s, 5H), 4.62 (dd, J = 22.3, 3.8 Hz, 1H) 3.40 (m, 2H); ^{19}F NMR (D_2O) δ 21.3 (dm), 27.5 (dm); MS (EI, m/z) 215 (10, M^+), 195 (21), 171 (45), 91 (100). Anal. Calcd for $C_{10}H_{11}F_2NO_2$: C, 55.81; H, 5.15. Found: C, 55.46; H, 5.25.

Ethyl 3,3-Difluoro-2-(methoxyimino)-5-hexenoate (14). A mixture of keto ester **4a** (12.0 g, 60 mmol) and *O*-methylhydroxyamine hydrochloride (7.1 g, 84 mmol) in ethanol (150 mL) was stirred at 40 °C for 48 h. After removal of the solvent, the residue was taken up in diethyl ether (100 mL), and the resulting solution was washed with brine and dried over Na_2SO_4. Distillation under reduced pressure gave 12 g (90%) of **14** as a colorless liquid: bp 78 °C/1.5 mmHg; ^{1}H NMR ($CDCl_3$) δ 5.72 (m, 1H), 5.20 (m, 2H), 4.26 (q, J = 7.1 Hz, 2H), 3.93 (s, 3H), 2.87 (dt, J = 6.9, 18.5 Hz), 1.32 (t, J = 7.1 Hz, 3H); ^{19}F NMR ($CDCl_3$) δ 18.8 (t, J = 18.5 Hz); MS (EI, m/z) 221 (M^+), 201 (18), 135 (30), 94 (24), 91 (100). Anal. Calcd for $C_9H_{13}F_2NO_3$: C, 48.87; H, 5.92; N,6.33. Found: C, 48.65; H, 5.97; N, 6.32.

Ethyl 2-[*N*-(Benzyloxycarbonyl)amino]-3,3-difluoro-5-hexenoate (15a). To a vigorously stirred solution of **14** (9.5 g, 40 mmol) in 70% aqueous formic acid (750 mL) cooled with an ice bath was added zinc powder (78 g, 1.2 mol) portionwise over 30 min. After being stirred overnight at 25 °C, the reaction mixture was filtered. The filtrate was neutralized with concentrated ammonia solution to pH 8 and then extracted with ethyl acetate (3 × 100 mL). The organic phase was washed with brine, dried over Na_2SO_4, and concentrated. The residue was redissolved in ethyl acetate (50 mL). To the resulting solution was added simultaneously benzyl chloroformate (8.5 mL, 10.2 g, 60 mmol) and 1 N aqueous $KHCO_3$ (60 mL) over 30 min while the reaction mixture was stirred and cooled with an ice bath. After the reaction mixture was stirred for an additional 30 min, the organic phase was separated and the aqueous phase extracted with ethyl acetate (2 × 25 mL). The combined organic phase was washed with brine, dried over Na_2SO_4, and concentrated. The residue was subjected to chromatography on silica gel eluting with a 1:3 (v/v) mixture of ethyl acetate and petroleum ether to afford 8.5 g (70%) of **15a** as a colorless syrup: ^{1}H NMR ($CDCl_3$) δ 7.35 (m, 5H), 5.81 (m, 2H), 5.61 (d, J = 8.8 Hz, 1H), 5.28 (m, 2H), 5.15 (s, 2H), 4.79 (dt, J = 8.8, 10.8 Hz, 1H), 4.18 (m, 2H), 2.72 (dt, J = 7.1, 16.7 Hz, 2H), 1.30 (t, J = 7.1 Hz, 3H); ^{19}F NMR ($CDCl_3$) δ 26.7 (m); MS (EI, m/z) 328 (5, M^+ + 1), 284 (22), 181 (18), 108 (11), 91 (100). Anal. Calcd for $C_{16}H_{19}F_2NO_4$: C, 58.71; H, 5.85; N, 4.28. Found: C, 58.49; H, 5.76; N, 4.32.

Ethyl 2-[*N*-(*tert*-Butyloxycarbonyl)amino]-3,3-difluoro-5-hexenoate (15b). The residue obtained after reduction of **14** (2.4 g, 10 mmol) with zinc as described above was dissolved in diethyl ether (20 mL), then di-*tert*-butyl dicarbonate (3.1 g, 15 mmol) was added. The resulting mixture was stirred at room temperature overnight and then concentrated. The residue was purified by flash chromatography on silica gel eluting with a 1:10 mixture of ethyl acetate and petroleum ether to afford 2.3 g (80%) of **15b** as a colorless syrup: ^{1}H NMR ($CDCl_3$) δ 5.82 (m, 1H), 5.30 (m, 3H), 4.72 (dt, J = 15.0, 10.4 Hz, 1H), 4.28 (m, 2H), 2.75 (dt, J = 16.7, 7.1 Hz, 2H), 1.49 (s, 9H), 1.30 (t, J = 7.1 Hz, 3H); ^{19}F NMR ($CDCl_3$) δ 27 (m); MS (EI, m/z) 294 (2, M^+ + 1), 238 (45), 194 (76), 120 (33), 102 (22), 57 (100). Anal. Calcd for $C_{13}H_{21}F_2NO_4$: C, 53.23; H, 7.22; N, 4.78. Found: C, 53.28; H, 7.17; N, 4.82.

Ethyl 1-(Benzyloxycarbonyl)-3,3-difluoro-(*cis*/*trans*)-5-hydroxy-2-pyrrolidinecarboxylate (16). A solution of **15a** (1.5 g, 5.0 mmol) in CH_2Cl_2 (50 mL) was treated with ozone at −78 °C until the blue color persisted. After the reaction system was purged with N_2, Me_2S (5.0 mL) was added and the reaction mixture was allowed to warm to room temperature over 2 h. Evaporation of the volatiles gave a residue which was purified by flash chromatography on silica gel eluting with a 2:5 mixture of ethyl acetate and petroleum ether to afford 1.4 g (95%) of **16** as a syrup: ^{1}H NMR ($CDCl_3$) δ 7.25–7.45 (m, 5H), 5.86 (d, J = 6.5 Hz, 0.7 × 1H), 5.76 (d, J = 6.5 Hz, 0.3 × 1H), 5.22 (d, J = 12.3 Hz, 0.7 × 2H), 5.18 (d, J = 12.3 Hz, 0.3 × 2H), 4.70 (d, J = 16.0 Hz, 0.3 × 1H), 4.66 (d, J = 16.0 Hz, 0.7 × 1H), 4.29 (m, 0.3 × 2H), 4.11 (q, J = 7.1 Hz, 0.7 × 2H), 2.39–2.81 (m, 2H), 1.80 (br s, 2H), 1.30 (t, J = 7.1 Hz, 0.3 × 3H), 1.16 (t, J = 7.1 Hz, 0.7 × 3H); ^{19}F NMR (CCl_4) δ 9.4 (dm, 0.7 × 1F), 27.4 (dm, 0.7 × 1F), 18.7 (dm, 0.3 × 1F), 29.4 (dm, 0.3 × 1F); MS (EI, m/z) 311 (4, $M^+ - H_2O$), 267 (11), 177 (15), 91 (100).

Ethyl 3,3-Difluoro-DL-prolinate Hydrochloride (17). A mixture of **16** (1.0 g, 3.3 mmol), 10% Pd/C (0.40 g), and concentrated HCl (0.40 mL) in ethanol (20 mL) was stirred at 25 °C under H_2 (3.5 atm) for 30 min. Evaporation of the solvent gave a residue which was triturated with diethyl ether to afford 0.45 g (78%) of **17** as a sticky solid which could not be recrystallized: ^{1}H NMR (D_2O) δ 4.8 (dd, J = 15.0, 10.5 Hz, 1H), 4.32 (q, J = 7.0 Hz, 2H), 3.62 (t, J = 7.5 Hz, 2H), 2.95 (m, 2H), 1.61 (t, J = 7.0 Hz, 3H); ^{19}F NMR (D_2O) δ 24.7 (m); MS (EI, m/z) 180 (12, M^+ − Cl), 160 (6), 106 (100), 86 (13).

Ethyl 3-Fluoro-2-pyrrolecarboxylate (21). This compound was obtained as the major product when the above reaction described for the preparation of **17** was run in the absence of HCl: ^{1}H NMR ($CDCl_3$) δ 9.7 (br s, 1H), 6.67 (dd, J = 7.2, 3.3 Hz, 1H), 5.87 (dd, J = 6.0, 3.3 Hz, 1H), 4.30 (q, J = 7.1 Hz, 2H), 1.33 (t, J = 7.1 Hz, 3H); ^{19}F NMR ($CDCl_3$) δ 71.3 (dd); MS (EI, m/z) 157 (94, M^+), 129 (39), 112 (98), 111 (100). Anal. Calcd for $C_7H_8FNO_2$: C, 53.50; H, 5.13; N, 8.91. Found: C, 53.56; H, 4.93; N, 8.79.

***β,β*-Difluoro-DL-proline (18).** A solution of **17** (0.35 g, 2.0 mmol) in 6 N HCl solution (10 mL) was refluxed for 7 h. Concentration of the solution gave a residue which was purified with Dowex 50-X8 (H^+) by successively using 50% aqueous 2-propanol, water, and 0.5 N aqueous ammonia as the eluent. Concentration of the last fraction below 30 °C afforded 0.25 g (83%) of **18** as a brown solid: mp 140–145 °C

dec; ^{1}H NMR (D_2O) δ 4.40 (dd, J = 15.3, 11.1 Hz, 1H), 3.59 (t, J = 7.8 Hz, 2H), 2.62 (m, 2H); ^{19}F NMR (D_2O) δ 22.7(m); ^{13}C NMR (D_2O) δ 171.7, 130.3 (t), 67.6 (dd), 61.5, 36.3 (dd); MS (EI, *m/z*) 151 (4, M^+), 106 (100), 86 (17), 77 (14), 59 (13), 44 (12). Anal. Calcd for $C_5H_7F_2NO_2$: C, 39.74; H, 4.67; N, 9.26. Found: C, 41.08; H, 5.07; N, 8.91.

3,3-Difluoro-DL-glutamic Acid (23). A solution of **15b** (1.5 g, 5.0 mmol) in ethyl acetate (20 mL) was mixed with RuO_2xH_2O (0.10 g) and a 20% aqueous solution of $NaIO_4$ (25 mL) at room temperature. The resulting biphasic mixture was stirred at 25 °C for 7 days during which several additional aliquots (5.0 mL each) of aqueous $NaIO_4$ solution was added from time to time to maintain the yellow color of RuO_4. The aqueous phase was then separated and extracted with ethyl acetate (3 × 20 mL). The combined organic phase was treated with 2-propanol (2.0 mL) for 30 min, and the precipitate was removed by filtration. After removal of the solvents from the filtrate, the residue was dissolved in 6 N HCl solution (20 mL). The resulting solution was refluxed for 8 h before it was concentrated to a small volume. The residue was purified with Dowex 1 × 2 (formate form) using successively 50% 2-propanol, water, and formic acid as the eluent. Concentration of the last fraction afforded 0.41 g (54%) of **23** as a white solid: mp 170–175 °C dec; ^{1}H NMR (D_2O) δ 4.62 (dd, J = 24.5, 3.7 Hz, 1H), 3.42–3.62 (m, 2H); ^{19}F NMR (D_2O) δ 20.2 (dm), 26.1 (dm); ^{13}C NMR (D_2O) δ 173.2 (d), 169.8 (d), 121.9 (t), 60.1 (dd), 42.5 (t); MS (EI, *m/z*) 185 (2, M^+ + 2,), 161 (6), 105 (100), 77 (38), 44 (9). The NMR data are fully in accord with the reported values.[19]

Acknowledgment. This work was supported by grants from the National Natural Science Foundation of China and Shanghai Municipal Scientific Committee.

JO9505740