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# Catalytic Route to the Synthesis of Optically Active *β,β*-Difluoroglutamic Acid and *β,β*-Difluoroproline Derivatives

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**Abstract:** *β,β*-Difluorinated amino acid derivatives were synthesized via Mg(0)-promoted defluorination of α-trifluoromethyl iminoester. Bromination of the difluoroenamine afforded the bromodifluoromethyl iminoester in good yield. Pd-catalyzed asymmetric hydrogenation of the bromodifluoromethyl iminoester and the subsequent transformations provided optically active *β,β*-difluoroglutamic acid and *β,β*-difluoroproline derivatives.

Among various organofluorine compounds, fluorinated amino acids have been studied as potential enzyme inhibitors and therapeutic agents.[1−3] Recently, in amino acid and peptide chemistry, amino acids possessing two fluorine atoms at the *β*-carbon have been paid much attention because they can act as potent inactivators of certain enzymes, in particular, highly selective inhibitors of pyridoxal phosphate-dependent enzymes via a suicide-type mechanism, and can block certain important metabolic pathways.[4,5]

To date, despite the potent biological activities of fluorinated α-amino acids, few examples of synthetic methods have been reported.[6−10] Toward further investigation of new biological activities of fluorinated amino acids,[11] a more practical and general route to fluorinated α-amino acids, particularly for their optical pure enantiomers,[12] is quite attractive. In 1995, Shi et al. reported the divergent synthesis of *racemic β,β*-difluoroglutamic acid and *β,β*-difluoroproline.[13] Key features of their pioneering work are follows: (i) the use of *β,β*-difluoro-α-aminoesters as a common precursor, which were prepared from trifluoropyruvate via reductive dechlorofluorination, Claisen rearrangement, and the subsequent reductive amination and (ii) the application of oxidative cleavage of C−C double bonds in fluorinated aminoesters, which provided difluoroglutamic acid and difluoroproline selectively.

Herein, we present an enantioselective synthesis of *β,β*-difluoroglutamic acid derivatives (**3**) and *β,β*-difluoroproline derivatives (**4**) possessing general N- and O-protecting groups by the use of the *chiral common precursor* **2**, which was prepared via the catalytic asymmetric hydrogenation of bromodifluoromethylated iminoester **1** (Scheme 1).

Trifluoromethyl iminoester **5**[14,15] underwent reductive defluorination upon treatment with metallic magnesium

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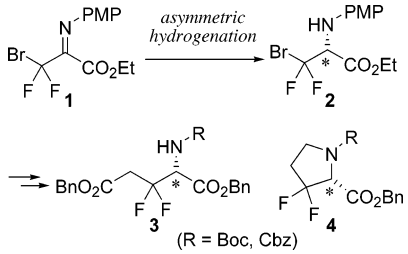
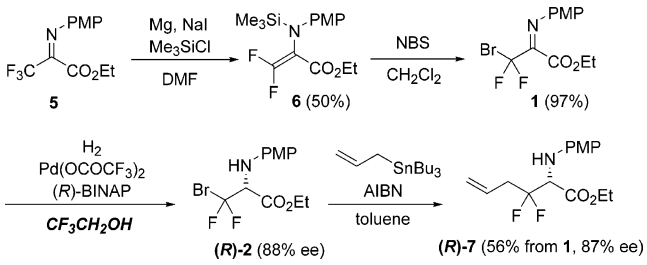
**SCHEME 1**




and trimethylsilyl chloride,[16−19] leading to enaminoester **6**. A gram-scale preparation of difluoroacrylate **6** (10 mmol scale) was executed under basic conditions, and the selective defluorination proceeded smoothly at 0 °C to afford **6** in 50% isolated yield (Scheme 2). Introduction

**SCHEME 2**

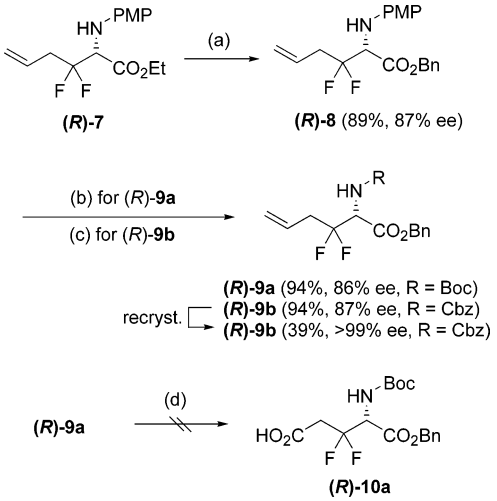



of a bromo group is considered to be of great advantage to further transformations of **6**, since chiral bromoester **2** is a versatile building block of enantioenriched $\beta,\beta$-difluorinated amino acid. Enaminoester **6** was treated with NBS to provide the corresponding bromodifluoromethyl iminoester **1** in excellent yield.

Until now, most of optically active $\beta,\beta$-difluoro-α-amino acids have been mostly synthesized via diastereoselective routes by the use of chiral auxiliaries but rarely done via catalytic asymmetric routes, to our knowledge.[20] Enantioselective transformations of fluorinated α-iminoesters are one of the useful methods for the asymmetric synthesis of fluorinated α-amino acids. Recently, we reported the Pd-catalyzed hydrogenation of α-trifluoromethyl iminoesters.[21] Under a hydrogen pressure, a catalytic amount of $Pd(OCOCF_3)_2$ and (*R*)-BINAP promoted the asymmetric hydrogenation of trifluoromethylated iminoester **5** to afford the highly enantioenriched trifluoroalanine derivative. Very interestingly, both the yield and ee of this catalytic hydrogenation were dramatically improved (up to 91% ee) by employing fluorinated alcohols such as 2,2,2-trifluoroethanol (TFE) as a solvent. Thus, we examined asymmetric hydrogenation of bromodifluoromethyl iminoester **1** catalyzed by a chiral palladium complex. When iminoester **1** was subjected to a hydrogen pressure in the presence of a small amount of $Pd(OCOCF_3)_2$ and (*R*)-BINAP in TFE, the catalytic asymmetric hydrogenation of **1** proceeded smoothly at room temperature to yield aminoester (*R*)-**2** in 88% ee. The absolute configuration of (*R*)-**2** was confirmed by its transformation to the known (*R*)-**11**.[22] Notably, the bromo functionality was compatible with the present reaction conditions; the hydrogenolysis of C−Br bonds in **1** and **2** did not occur. Subsequently, the allylation of (*R*)-**2**, a versatile precursor of optically active $\beta,\beta$-difluoroamino acids, was carried out via a radical substitution reaction. Upon treatment with allyltributyltin and a catalytic amount of AIBN as a radical initiator, (*R*)-**2** underwent radical allylation to afford C-allylated aminoester (*R*)-**7** in 56% yield with 87% ee for two steps from bromoiminoester **1**.

Using chiral aminoester (*R*)-**7**, we tried to synthesize highly enantioenriched $\beta,\beta$-difluoroglutamic acid derivatives. In previous work done by Shi et al., the synthesis of racemic $\beta,\beta$-difluoroglutamic acid was accomplished via hydrolysis of the corresponding ethyl esters under severe conditions (refluxing in 6 N HCl). For the asymmetric synthesis of amino acids, the choice of the N- and O-protecting groups is of significant importance. We sought to introduce general and easily removable protecting groups such as benzyl groups into the enantioenriched difluoro amino acids. Transesterification of ethyl ester (*R*)-**7** with benzyl alcohol using a catalytic amount of 3-chloro-1-hydroxytetrabutyldistannoxane (CHTD)[23] afforded the corresponding benzyl ester (*R*)-**8** in high yield (Scheme 3).

**SCHEME 3**[a]




[a] Reagents: (a) CHTD, BnOH, toluene. (b) (i) CAN, $CH_3CN$; (ii) $Na_2S_2O_3$ then $(Boc)_2O$, $NaHCO_3$. (c) (i) CAN, $CH_3CN$; (ii) $Na_2S_2O_3$, then Cbz-Cl, $NaHCO_3$. (d) $RuO_2 \cdot xH_2O$, 10% $NaIO_4$ aq, AcOEt.

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(22) For (*R*)-**12** (87% ee): $[\alpha]^{25}_D = 21.8$ (*c* 0.91, $CHCl_3$). For (*S*)-**12**[10g] (>95% ee): $[\alpha]^{25}_D = -22.6$ (*c* 0.62, $CHCl_3$).

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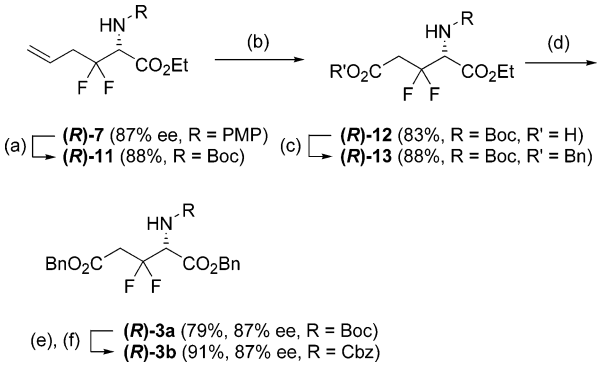
Subsequently, the *p*-methoxyphenyl (PMP) group on the amino nitrogen of (*R*)-**8** was removed, and then *tert*-butoxycarbonyl (Boc) and benzyloxycarbonyl (Cbz) groups were introduced as common protecting groups of amino nitrogen, to provide N-protected *β*,*β*-difluoroaminoesters (*R*)-**9a** and (*R*)-**9b**, respectively. Fortunately, the optical purity of *N*-Cbz derivative **9b** increased by simple recrystallization, affording enantiomerically pure (*R*)-**9b** (>99% ee).

Oxidative cleavage of C−C double bond in (*R*)-**9a** by the use of $RuO_2 \cdot H_2O/NaIO_4$ was examined. However, the desired product (*R*)-**10a** was not obtained selectively, but a complex mixture was provided (Scheme 3). It can be explained that there existed the competition of oxidation of the terminal olefin moiety of **9a** with that of the benzylic carbon of the benzyl ester even at a low temperature (−30 °C), because the benzylic position of **9a** was quite sensitive to the oxidative conditions.

Thus, to avoid the oxidation of the benzylic carbon, ethyl ester (*R*)-**7** (87% ee) was used for the oxidative transformation (Scheme 4). At first, the *N*-*p*-methoxyphenyl group of ethyl ester (*R*)-**7** was removed; then, a *t*-butoxycarbonyl (Boc) group was introduced to the substrate as an N-protecting group, and the desired N-protected-*β*,*β*-difluoroamino ester (*R*)-**11** was afforded in 84% yield. Then, under the oxidative condition ($RuO_2 \cdot H_2O/NaIO_4$), ethyl ester (*R*)-**11** was converted to the desired product *β*,*β*-difluoroglutamic acid derivative (*R*)-**12** in 83% yield. CsF-mediated esterification[24] to the *γ*-carboxyl group of (*R*)-**12** proceeded smoothly, and the desired dibenzyl ester (*R*)-**13** was obtained without any loss of enantiomeric excess. At last, the transesterification reaction by the use of CHTD smoothly proceeded, affording the final target compound, enantioenriched N- and O-protected difluoroglutamic acid (*R*)-**3a** in good yield. After the deprotection−protection sequence, a Cbz group was introduced as an alternative N-protecting group to afford *N*-Cbz derivative (*R*)-**3b** in good yield.

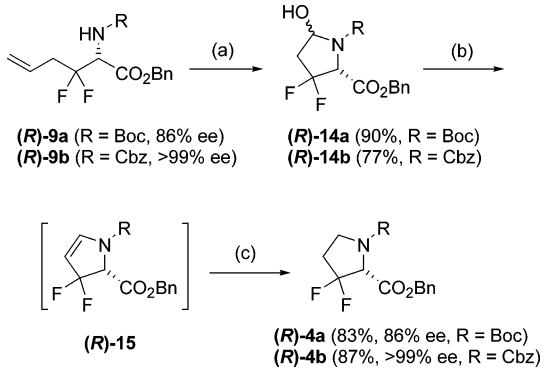
**SCHEME 4**[a]




[a] Reagents: (a) (i) CAN, $CH_3CN$; (ii) $Na_2S_2O_3$, then $(Boc)_2O$, $NaHCO_3$. (b) $RuO_2 \cdot xH_2O$, 10% $NaIO_4$ aq, AcOEt. (c) BnBr, CsF, DMF. (d) CHTD, BnOH. (e) TFA, $CH_2Cl_2$. (f) Cbz-Cl, $NaHCO_3$, 1,4-dioxane−$H_2O$.

The next target was the synthesis of optically pure *β*,*β*-difluoroproline derivatives **4** by the use of the chiral common precursors **9** (Scheme 5).

**SCHEME 5**[a]




[a] Reagents: (a) (i) $O_3/O_2$, $CH_2Cl_2$; (ii) $Me_2S$. (b) $PPh_3 \cdot Cl_2$, DMF. (c) $H_2$ (1 atm), $RhCl(PPh_3)_3$, benzene.

Ozonolysis of N-protected *β*,*β*-difluoroamino esters (*R*)-**9** followed by the reductive treatment of the resulting ozonide with $Me_2S$ afforded cyclic hemiaminal (*R*)-**14** in high yields (as a mixture of the diastereomers). When benzyl ester (*R*)-**14a** was treated with dichlorotriphenylphosphorane, an elimination reaction took place to afford olefin **15a** in quantitative yield. Fortunately, the purity of **15a** was high enough for the next step. The subsequent Rh(I)-catalyzed hydrogenation of olefin (*R*)-**15a** proceeded smoothly to give the desired compound (*R*)-**4a**, and *N*-(Boc)-protected difluoroproline was obtained in high yield (83% from (*R*)-**14a**). Moreover, by the use of enantiomerically pure precursor (*R*)-**9b** (>99% ee), *N*-(Cbz)-protected difluoroproline (*R*)-**4b** was obtained in high optical purity (>99% ee).

In conclusion, we have demonstrated the enantioselective divergent synthesis of N- and O-protected *β*,*β*-difluoroglutamic acids (**3**) and *β*,*β*-difluoroprolines (**4**). A Pd/BINAP/TFE system was found to be effective for the catalytic asymmetric hydrogenation of bromodifluoromethylated iminoesters **1**, providing aminoesters **2** (88% ee), which served as general precursors of enantioenriched *β*,*β*-difluorinated α-amino acids. Furthermore, *N*-(Cbz)-protected difluoroproline (**4b**) was obtained in high optical purity (>99% ee) via simple recrystallization. We believe that these results make a great contribution toward further potential biological and chemical applications.

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**Supporting Information Available:** Experimental procedures and compound characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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