

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

Atsushi Suzuki, Masayuki Mae, Hideki Amii, and Kenji Uneyama*

Department of Applied Chemistry, Faculty of Engineering, Okayama University, 3-1-1 Tsushimanaka, Okayama 700-8530, Japan

uneyamak@cc.okayama-u.ac.jp

Received February 6, 2004

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 inves-

tigation 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

(7) Welch, J. T. *Tetrahedron* **1987**, 43, 3123.

(8) (a) Holmquist, B.; Bunning, P.; Babiars, J.-F. *Anal. Biochem.* **1979**, 95, 540. (b) Katagiri, T.; Akizuki, M.; Kuriyama, T.; Shinke, S.; Uneyama, K. *Chem. Lett.* **1997**, 549. (c) Katagiri, T.; Irie, M.; Uneyama, K. *Tetrahedron: Asymmetry* **1999**, 10, 2583. (d) Matsukawa, Y.; Kumar, J. S. D.; Yoneyama, Y.; Katagiri, T.; Uneyama, K. *Tetrahedron: Asymmetry* **2000**, 11, 4521. (e) Katagiri, T.; Irie, M.; Uneyama, K. *Org. Lett.* **2000**, 2, 2423. (f) Ohkura, H.; Handa, M.; Katagiri, T.; Uneyama, K. *J. Org. Chem.* **2002**, 67, 2692.

(9) (a) Abouabdellah, A.; Bégué, J.-P.; Bonnet-Delpon, D. *Synlett* **1996**, 399. (b) Prakash, G. K. S.; Yudin, A. K. *Chem. Rev.* **1997**, 97, 757. (c) Abouabdellah, A.; Bégué, J.-P.; Bonnet-Delpon, D.; Nga, T. T. *J. Org. Chem.* **1997**, 62, 8826. (d) Banks, R. E. *J. Fluorine Chem.* **1998**, 87, 1.

(10) (a) Weygand, F.; Steglich, W.; Oettmeier, W.; Maierhofer, A.; Roy, R. S. *Angew. Chem., Int. Ed. Engl.* **1966**, 5, 600. (b) Knunyants, I. L.; Shokina, V. V.; Tyuleneva, V. V. *Dokl. Acad. Nauk SSSR* **1966**, 169, 594; *Proc. Acad. Sci. USSR, Chem. Sect.* **1966**, 169, 722; *Chem. Abstr.* **1966**, 65, 15218d. (c) Metcalf, B. W.; Bey, P.; Danzin, C.; Jung, M. J.; Casara, P.; Vevert, J. P. *J. Am. Chem. Soc.* **1978**, 100, 2551. (d) Bey, P.; Vevert, J. P.; Van Dorrelaer, V.; Kolb, M. J. *Org. Chem.* **1979**, 44, 2732. (e) Burger, K.; Hubl, D.; Gertitschke, P. *J. Fluorine Chem.* **1985**, 27, 327. (f) Amii, H.; Kondo, S.; Uneyama, K. *Chem. Commun.* **1998**, 1845. (g) (**5**)–**13** was prepared by the diastereoselective bromodifluoromethylation of hydroxyppinane glycinate Schiff base as a key step: Katagiri, T.; Handa, M.; Matsukawa, Y.; Kumar, J. S. D.; Uneyama, K. *Tetrahedron: Asymmetry* **2001**, 12, 1303.

(11) (a) Hart, B. P.; Coward, J. C. *Tetrahedron Lett.* **1993**, 34, 4917. (b) Percy, J. M.; Prime, M. E.; Broadhurst, M. J. *J. Org. Chem.* **1998**, 63, 8049. (c) Gerus, I. I.; Kolomeitsev, A. A.; Kolycheva, M. I.; Kukhar, V. P. *J. Fluorine Chem.* **2000**, 105, 31.

(12) (a) Soloshonok, V. A.; Avilov, D. V.; Kukhar, V. P. *Tetrahedron: Asymmetry* **1996**, 7, 1547. (b) Osipov, S. N.; Golubev, A. S.; Sewald, N.; Michel, T.; Kolomiets, A. F.; Fokin, A. V.; Burger, K. *J. Org. Chem.* **1996**, 61, 7521. (c) Soloshonok, V. A.; Kukhar, V. P. *Tetrahedron* **1997**, 53, 8307. (d) Bravo, P.; Crucianelli, M.; Vergani, B.; Zanda, M. *Tetrahedron Lett.* **1998**, 39, 7771. (e) Percy, J. M.; Prime, M. E.; Broadhurst, M. J. *J. Org. Chem.* **1998**, 63, 8049. (f) Osipov, S. N.; Bruneau, C.; Picquet, M.; Kolomiets, A. F.; Dixneuf, P. H. *Chem. Commun.* **1998**, 2053. (g) Fustero, S.; Pina, B.; de la Torre, M. G.; Navarro, A.; de Arellano, C. R.; Simon, A. *Org. Lett.* **1999**, 1, 977.

(13) Shi, G.-Q.; Cai, W.-L. *J. Org. Chem.* **1995**, 60, 6289.

(14) (a) Tamura, K.; Mizukami, H.; Maeda, K.; Watanabe, H.; Uneyama, K. *J. Org. Chem.* **1993**, 58, 32. (b) Uneyama, K. *J. Synth. Org. Chem. Jpn.* **1995**, 53, 59. (c) Uneyama, K. *J. Fluorine Chem.* **1999**, 97, 11.

(15) (a) Watanabe, H.; Hashizume, Y.; Uneyama, K. *Tetrahedron Lett.* **1992**, 33, 4333. (b) Amii, H.; Kishikawa, Y.; Kageyama, K.; Uneyama, K. *J. Org. Chem.* **2000**, 65, 3404.

(1) (a) Filler, R.; Kobayashi, Y. *Biomedical Aspects of Fluorine Chemistry*; Kodansha, Ltd.: Tokyo, 1982. (b) Ishikawa, N., Ed. *Synthesis and Speciality of Organofluorine Compounds*; CMC: Tokyo, 1987. (c) Ishikawa, N., Ed. *Biologically Active Organofluorine Compounds*; CMC: Tokyo, 1990. (d) Welch, J. T.; Eswarakrishnan, S. *Fluorine in Bioorganic Chemistry*; John Wiley & Sons: New York, 1991. (e) Ojima, I.; McCarthy, J. R.; Welch, J. T., Eds. *Biomedical Frontiers of Fluorine Chemistry*; ACS Symposium Series 639; American Chemical Society: Washington, DC, 1996.

(2) (a) Ondetti, M. A.; Cushman, D. W.; Rubin, B. *Science* **1977**, 196, 441. (b) Cushman, D. W.; Cheung, H. S.; Sabo, E. F.; Ondetti, M. A. *Biochemistry* **1977**, 16, 5484. (c) Kollonitsch, 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. (d) Wyvratt, M. J.; Tristram, E. W.; Ikeler, T. J.; Lohr, N. S.; Joshua, H.; Springer, J. P.; Arison, B. H.; Patchett, A. A. *J. Org. Chem.* **1984**, 49, 2816.

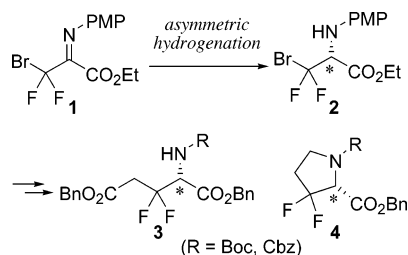
(3) Kukhar, V. P.; Soloshonok, V. A. *Fluorine-Containing Amino Acids: Synthesis and Properties*; John Wiley & Sons: New York, 1995.

(4) (a) Abeles, R. H.; Maycock, A. L. *Acc. Chem. Res.* **1976**, 9, 313. (b) Kumadaki, I. *J. Synth. Org. Chem. Jpn.* **1984**, 42, 786. (c) Faraci, W. S.; Walsh, C. T. *Biochemistry* **1989**, 28, 431.

(5) (a) Filler, R.; Kobayashi, Y. *Biomedical Aspects of Fluorine Chemistry*; Kodansha, Ltd.: Tokyo, 1982. (b) Walsh, C. *Adv. Enzymol. Relat. Areas Mol. Biol.* **1984**, 53, 493. (c) Bey, P.; *Ann. Chem. Fr.* **1984**, 9, 695. (d) Seiler, N.; Jung, M. J.; Kock-Weser, J. *Pharmacol. Rev.* **1984**, 36, 111. (e) Rathod, A. H.; Tashjian, A. H., Jr.; Abeles, R. H. *J. Biol. Chem.* **1986**, 261, 6461. (f) Ojima, I.; Inoue, T.; Chakravarty, S. *J. Fluorine Chem.* **1999**, 97, 3.

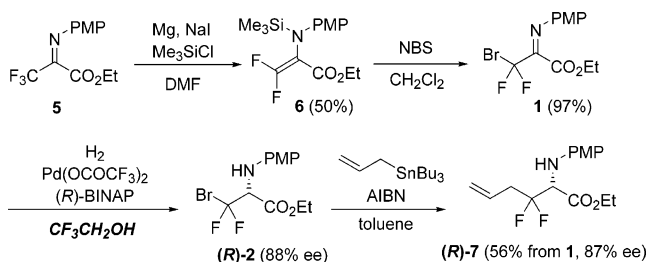
(6) (a) Uneyama, K. In *Enantiocontrolled Synthesis of Fluoro-organic Compounds*; Soloshonok, V. A., Ed.; John Wiley & Sons, Ltd.: Chichester, 1999; pp 391–418. (b) Uneyama, K.; Katagiri, T.; Amii, H. *J. Synth. Org. Chem. Jpn.* **2002**, 60, 1069.

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

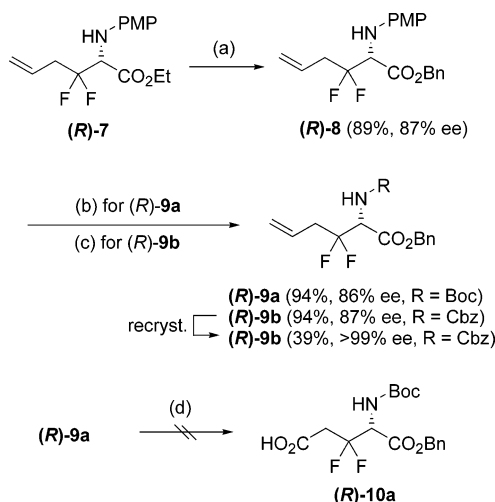


of a bromo group is considered to be of great advantage to further transformations of **6**, since chiral bromoester **2** is a versatile building block of enantioenriched β,β -difluorinated amino acid. Enaminoester **6** was treated with NBS to provide the corresponding bromodifluoromethyl iminoester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

Until now, most of optically active β,β -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 $\text{Pd}(\text{OCOCF}_3)_2$ and $(R)\text{-BINAP}$ 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 $\text{Pd}(\text{OCOCF}_3)_2$ and $(R)\text{-BINAP}$ in TFE, the catalytic asymmetric hydrogenation of **1** proceeded smoothly at room temperature to yield aminoester $(R)\text{-2}$ in 88% ee. The absolute configuration of $(R)\text{-2}$ was confirmed by its transformation to the known $(R)\text{-11}$.²² Notably, the bromo functionality was compatible with the present reaction conditions; the hydrogenolysis of $\text{C}-\text{Br}$ bonds in **1** and **2** did not occur. Subsequently, the allylation of $(R)\text{-2}$, a versatile precursor of optically active β,β -difluoroamino acids, was carried out via a radical substitution reaction. Upon treatment with allyltributyltin and a catalytic amount of AIBN as a radical initiator, $(R)\text{-2}$ underwent radical allylation to afford C -allylated aminoester $(R)\text{-7}$ in 56% yield with 87% ee for two steps from bromoiminoester **1**.

Using chiral aminoester $(R)\text{-7}$, we tried to synthesize highly enantioenriched β,β -difluoroglutaric acid derivatives. In previous work done by Shi et al., the synthesis of racemic β,β -difluoroglutaric 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 $(R)\text{-7}$ with benzyl alcohol using a catalytic amount of 3-chloro-1-hydroxytetrahydrodistannoxane (CHTD)²³ afforded the corresponding benzyl ester $(R)\text{-8}$ in high yield (Scheme 3).

SCHEME 3^a

^a Reagents: (a) CHTD , BnOH , toluene. (b) (i) CAN , CH_3CN ; (ii) $\text{Na}_2\text{S}_2\text{O}_3$ then $(\text{Boc})_2\text{O}$, NaHCO_3 . (c) (i) CAN , CH_3CN ; (ii) $\text{Na}_2\text{S}_2\text{O}_3$, then Cbz-Cl , NaHCO_3 . (d) $\text{RuO}_4 \cdot x\text{H}_2\text{O}$, 10% NaIO_4 aq, AcOEt .

(22) For $(R)\text{-12}$ (87% ee): $[\alpha]^{25}_D = 21.8$ (c 0.91, CHCl_3). For $(S)\text{-12}^{108}$ (>95% ee): $[\alpha]^{25}_D = -22.6$ (c 0.62, CHCl_3).

(23) (a) Otera, J.; Yano, T.; Okawa, R. *Chem. Lett.* **1985**, 901. (b) Otera, J.; Yano, T.; Okawa, R. *Organometallics* **1986**, 5, 1167. (c) Otera, J.; Dan-oh, N.; Nozaki, H. *J. Org. Chem.* **1991**, 56, 5307.

(16) A short account: Uneyama, K.; Amii, H. *J. Fluorine Chem.* **2002**, 114, 127.

(17) (a) Amii, H.; Kobayashi, T.; Hatamoto, Y.; Uneyama, K. *Chem. Commun.* **1999**, 1323. (b) Amii, H.; Kobayashi, T.; Uneyama, K. *Synthesis* **2000**, 2001. (c) Amii, H.; Hatamoto, Y.; Seo, M.; Uneyama, K. *J. Org. Chem.* **2001**, 66, 7216. (d) Amii, H.; Kobayashi, T.; Terasawa, H.; Uneyama, K. *Org. Lett.* **2001**, 3, 3103. (e) Hata, H.; Kobayashi, T.; Amii, H.; Uneyama, K.; Welch, J. T. *Tetrahedron Lett.* **2002**, 43, 6099.

(18) (a) Uneyama, K.; Kato, T. *Tetrahedron Lett.* **1998**, 39, 587. (b) Mae, M.; Amii, H.; Uneyama, K. *Tetrahedron Lett.* **2000**, 41, 7893. (c) Mae, M.; Matsuura, M.; Amii, H.; Uneyama, K. *Tetrahedron Lett.* **2002**, 43, 2069. (d) Kobayashi, T.; Nakagawa, T.; Amii, H.; Uneyama, K. *Org. Lett.* **2003**, 5, 4297. (e) Amii, H.; Ichihara, Y.; Nakagawa, T.; Kobayashi, T.; Uneyama, K. *Chem. Commun.* **2003**, 2902.

(19) (a) Prakash, G. K. S.; Hu, J.; Olah, G. A. *J. Fluorine Chem.* **2001**, 112, 355. (b) Prakash, G. K. S.; Hu, J.; Alauddin, M. M. *J. Fluorine Chem.* **2003**, 121, 239.

(20) (a) Sakai, T.; Yan, F.; Uneyama, K. *Synlett* **1995**, 753. (b) Sakai, T.; Yan, F.; Kashino, S.; Uneyama, K. *Tetrahedron* **1996**, 52, 233.

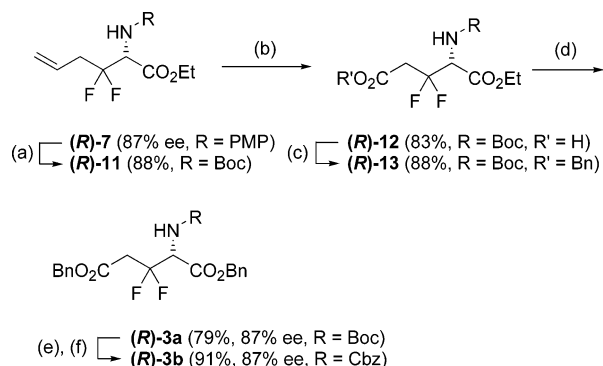
(21) Abe, H.; Amii, H.; Uneyama, K. *Org. Lett.* **2001**, 3, 313.

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 $\text{RuO}_2 \cdot \text{H}_2\text{O}/\text{NaIO}_4$ 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*-methoxy-

SCHEME 4^a

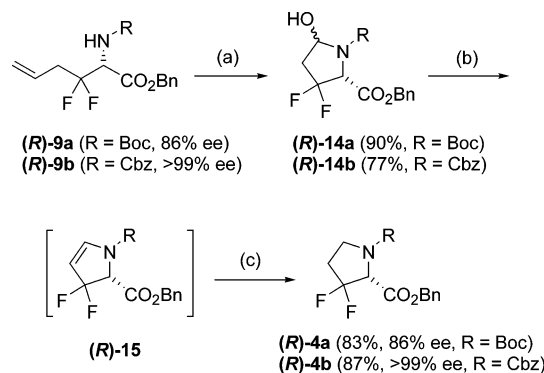


^a Reagents: (a) (i) CAN, CH_3CN ; (ii) $\text{Na}_2\text{S}_2\text{O}_3$, then $(\text{Boc})_2\text{O}$, NaHCO_3 . (b) $\text{RuO}_2 \cdot x\text{H}_2\text{O}$, 10% NaIO_4 aq, AcOEt . (c) BnBr , CsF , DMF . (d) CHTD, BnOH . (e) TFA , CH_2Cl_2 . (f) Cbz-Cl , NaHCO_3 , 1,4-dioxane– H_2O .

phenyl 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 ($\text{RuO}_2 \cdot \text{H}_2\text{O}/\text{NaIO}_4$), ethyl ester (*R*)-**11** was converted to the desired product β,β -difluoroglutamic acid derivative (*R*)-**12** in 83% yield. CsF -mediated esterification²⁴ 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.

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) $\text{PPh}_3 \cdot \text{Cl}_2$, DMF . (c) H_2 (1 atm), $\text{RhCl}(\text{PPh}_3)_3$, 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.

Acknowledgment. This work has been supported by the Ministry of Education, Culture, Sports, Science and Technology of Japan (Grant-in-Aid for Scientific Research (B), No. 13555254, Grant-in-Aid for Young Scientists (B), No. 14750684, and Grant-in-Aid for Scientific Research on Priority Areas (“Reaction Control of Dynamic Complexes”), No. 16033621). H.A. received a research grant from Okayama Prefecture. We also thank the SC-NMR laboratory of Okayama University for ^{19}F NMR analysis.

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>.

(24) Sato, T.; Otera, J.; Nozaki, H. *J. Org. Chem.* **1992**, *57*, 2166.