JOC*Note*

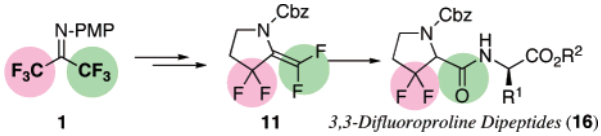
Selective Defluorination Approach to *N*-Cbz-3,3-difluoro-2-difluoromethylenepyrrolidine and Its Application to 3,3-Difluoroproline Dipeptide Synthesis

Yong Guo, Kana Fujiwara, Hideki Amii, and Kenji Uneyama*

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

uneyamak@cc.okayama-u.ac.jp

Received April 6, 2007



Mg-promoted defluorination of *N*-(*p*-methoxyphenyl)bis-(trifluoromethyl)imine **1** gave perfluoroenamine **2**, which was readily transformed to *N*-Cbz-2-trifluoromethyl-3,3-difluoropyrrolidine **10**. Chemoselective defluorination from the trifluoromethyl group of **10** by LHMDS-promoted dehydrofluorination in THF provided 3,3-difluoro-2-difluoromethylenepyrrolidine **11**. The product **11** was converted to 3,3-difluoroproline dipeptides **16** upon treatment with aminoesters.

Fluorinated amino acids have been used to effect components of modified peptides and proteins in protein engineering[1] and also find applications as potential enzyme inhibitors and antitumor and antibacterial agents.[2−4] Amino acids possessing two fluorine atoms at the β-carbon have received much attention because they can act as potent inhibitors to certain enzymes, in particular, pyridoxal phosphate-dependent enzymes where they act as and can block certain important metabolic pathways.[2a,5,6] To date, due to the potent biological activities of fluorinated α-amino acids, several synthetic methods have been reported.[7−12] Among them, fluoroproline-based molecules[13−16] have received much attention due to their application as components of bioactive oligopeptides[15i,17] and thrombin inhibitors with improved metabolic stability.[18] Fluoroproline residues contribute to stabilization of triple helix structures of collagens[19] and β-sheet structures of elastatin polypeptides.[20] Recently the relationship between the stability of collagen triple helixes and the conformation of fluoroproline residues has been vigorously investigated.[21] Therefore, incorporation of fluoroproline units into peptides is quite important for further investigation of new bioactive compounds.

Herein, we present a synthesis of a β,β-difluoroproline building block on the basis of the concept that two trifluoromethyl groups of hexafluoroacetone (HFA) imine **1** can be used differently either as a synthon of a difluoromethylene (CF_2R) group or a synthon of a carboxyl group (Scheme 1). So far in the synthetic utilization of HFA, it has been employed mostly

(1) (a) Babu, I. R.; Hamill, E. K.; Kumar, K. *J. Org. Chem.* **2004**, *69*, 5468−5470. (b) Wang, P.; Tang, Y.; Tirrell, D. A. *J. Am. Chem. Soc.* **2003**, *125*, 6900−6906.

(2) (a) Filler, R.; Kobayashi, Y. *Biomedicinal Aspects of Fluorine Chemistry*; Kodansha, Ltd.: Tokyo, Japan, 1982. (b) Ishikawa, N., Ed. *Synthesis and Speciality of Organofluorine Compounds*; CMC: Tokyo, Japan, 1987. (c) Ishikawa, N., Ed. *Biologically Active Organofluorine Compounds*; CMC: Tokyo, Japan, 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 Symp. Ser. No. 639; American Chemical Society: Washington, DC, 1996.

(3) (a) Ondetti, M. A.; Cushman, D. W.; Rubin, B. *Science* **1977**, *196*, 441−444. (b) Cushman, D. W.; Cheung, H. S.; Sabo, E. F.; Ondetti, M. A. *Biochemistry* **1977**, *16*, 5484−5491. (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*, 906−908. (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*, 2816−2819.

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

(5) (a) Abeles, R. H.; Maycock, A. L. *Acc. Chem. Res.* **1976**, *9*, 313−319. (b) Kumadaki, I. *J. Synth. Org. Chem. Jpn.* **1984**, *42*, 786−793. (c) Faraci, W. S.; Walsh, C. T. *Biochemistry* **1989**, *28*, 431−437.

(6) (a) Walsh, C. *Annu. Rev. Biochem.* **1984**, *53*, 493−535. (b) Bey, P. *Ann. Chem. Fr.* **1984**, *9*, 695−702. (c) Seiler, N.; Jung, M. J.; Kock-Weser, J. *Pharmacol. Rev.* **1984**, *36*, 111−142. (d) Rathod, A. H.; Tashjian, A. H., Jr.; Abeles, R. H. *J. Biol. Chem.* **1986**, *261*, 6461−6469. (e) Ojima, I.; Inoue, T.; Chakravarty, S. *J. Fluorine Chem.* **1999**, *97*, 3−10.

(7) (a) Uneyama, K. In *Enantiocontrolled Synthesis of Fluoro-Organic Compounds*; Soloshonok, V. A., Ed.; John Wiley & Sons, Ltd.; Chichester, UK, 1999; pp 391−418. (b) Uneyama, K.; Katagiri, T.; Amii, H. *J. Synth. Org. Chem. Jpn.* **2002**, *60*, 1069−1075.

(8) Qiu, X.-L.; Meng, W.-D.; Qing, F.-L. *Tetrahedron* **2004**, *60*, 6711−6743.

(9) Welch, J. T. *Tetrahedron* **1987**, *43*, 3123−3197.

(10) (a) Osipov, S. N.; Golubev, A. S.; Sewald, N.; Michel, T.; Kolomiets, A. F.; Burger, K. *J. Org. Chem.* **1996**, *61*, 7521−7528. (b) Solosholok, V. A.; Kukhar, V. P. *Tetrahedron* **1997**, *53*, 8307. (c) Osipov, S. N.; Bruneau, C.; Picquet, M.; Kolomiets, A. F.; Dixneuf, P. H. *Chem. Commun.* **1998**, 2053−2054. (d) Percy, J. M.; Prime, M. E.; Broadhurst, M. J. *J. Org. Chem.* **1998**, *63*, 8049−8051. (e) Amii, H.; Kondo, S.; Uneyama, K. *Chem. Commun.* **1998**, 1845−1846. (f) Gerus, I. I.; Kolomeitsev, A. A.; Kolycheva, M. I.; Kukhar, V. P. *J. Fluorine Chem.* **2000**, *105*, 31−33. (g) Fustero, S.; Bartolomé, A.; Sanz-Cervera, J. F.; Sánchez-Roselló, M.; Soler, J. G.; Ramírez de Arellano, C.; Fuentes, A. S. *Org. Lett.* **2003**, *5*, 2523−2526.

(11) (a) Watanabe, H.; Hashizume, Y.; Uneyama, K. *Tetrahedron Lett.* **1992**, *33*, 4333−4336. (b) Amii, H.; Kishikawa, Y.; Kageyama, K.; Uneyama, K. *J. Org. Chem.* **2000**, *65*, 3404−3408. (c) Abe, H.; Amii, H.; Uneyama, K. *Org. Lett.* **2001**, *3*, 313−315.

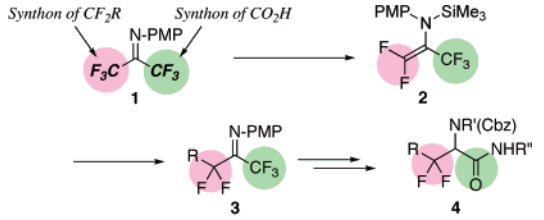
(12) (a) Soloshonok, V. A.; Avilov, D. V.; Kukhar, V. P. *Tetrahedron*: *Asymmetry* **1996**, *7*, 1547−1550. (b) Bravo, P.; Crucianelli, M.; Vergani, B.; Zanda, M. *Tetrahedron Lett.* **1998**, *39*, 7771−7774. (c) Crucianelli, M.; Bravo, P.; Arnone, A.; Corradi, E.; Meille, S. V.; Zanda, M. *J. Org. Chem.* **2000**, *65*, 2965−2971. (d) Katagiri, T.; Handa, M.; Matsukawa, Y.; Kumar. J. S. D.; Uneyama, K. *Tetrahedron*: *Asymmetry* **2001**, *12*, 1303−1331. (e) Fustereo, S.; Navorro, A.; Pina, B.; Soler, J. G.; Bartolomé, A.; Asensio, A.; Simón, A.; Bravo, P.; Fronza, G.; Volonterio, A.; Zanda, M. *Org. Lett.* **2001**, *3*, 2621. (f) Lebouvier, N.; Laroche, C.; Huguenot, F.; Brigaud, T. *Tetrahedron Lett.* **2002**, *43*, 2827−2830. (g) Wang, H.; Zhao, X. M.; Li, Y. H.; Lu, L. *Org. Lett.* **2006**, *8*, 1379−1381. (h) Li G.-Y.; van der Donk, W. A. *Org. Lett.* **2007**, *9*, 41−44.

(13) Synthesis of 3,3-difluoroproline derivatives: (a) Hart, B. P.; Coward, J. K. *Tetrahedron Lett.* **1993**, *34*, 4917−4920. (b) Shi, G. Q.; Cai, W. L. *J. Org. Chem.* **1995**, *60*, 6289−6295. (c) Hart, B. P.; Haile, W. H.; Licato, N. J.; Bolanowska, W. E.; McGuire, J. J.; Coward, J. K. *J. Med. Chem.* **1996**, *39*, 56−65. (d) Suzuki, A.; Mae, M.; Amii, H.; Uneyama, K. *J. Org. Chem.* **2004**, *69*, 5132−5134.

(14) Synthesis of 3-fluoroproline derivatives: (a) Vidal-Cros, A.; Gaudry, M.; Marquet, A. *J. Org. Chem.* **1985**, *50*, 3163−3167. (b) Demange, L.; Cluzeau, J.; Menez, A.; Dugave, C. *Tetrahedron Lett.* **2001**, *42*, 651−653. (c) Bonini, B. F.; Boschi, F.; Franchini, M. C.; Fochi, M.; Fini, F.; Mazzanti, A. Ricci, A. *Synlett* **2006**, 543−546.

10.1021/jo070719q CCC: $37.00
Published on Web 10/03/2007

SCHEME 1



as protecting and activating reagents[22] or a block for a hexafluoroisopropyl group.[23] One interesting example demonstrated a transformation of one of the trifluoromethyl groups of HFA to the carboxyl group of trifluoroalanine.[23a] Meanwhile the reactions of hexafluoroacetone imine derivatives have been less studied.[24−26] On this basis, it would be important and promising from the point of synthetic organofluorine chemistry to prepare enamine **2** from **1** and to transform CF_2 and CF_3 groups of **2** selectively to a functionalized difluoromethylene moiety and a carboxamide group, respectively, leading to difluoroamino acid derivatives.

The Mg-promoted defluorination of trifluoromethyl imines and ketones converting a trifluoromethyl group to a difluoromethylene group has been systematically studied.[27−30] Recently, the defluorination protocol has been applied to the selective defluorination of imine **1** to **2**,[31] which was transformed

(15) Synthesis of 4-fluoroproline and 4,4-difluoroproline derivatives: (a) Smith, E. M.; Swiss, G. F.; Neustadt, B. R.; Gold, E. H.; Sommer, J. A.; Brown, A. D.; Chiu, P. J. S.; Moran, R.; Sybertz, E. J.; Baum, T. *J. Med. Chem.* **1988**, *31*, 875−885. (b) Karanewsky, D. S.; Badia, M. C.; Cushman, D. W.; DeForrest, J. M.; Dejneka, T.; Lee, V. G.; Loots, M. J.; Petrillo, E. W. *J. Med. Chem.* **1990**, *33*, 1459−1469. (c) Kronenthal, D. R.; Mueller, R. H.; Kuester, P. L.; Kissick, T. P.; Johnson, E. J. *Tetrahedron Lett.* **1990**, *31*, 1241−1244. (d) Hudlicky, M.; Merola, J. S. *Tetrahedron Lett.* **1990**, *31*, 7403−7406. (e) Tolman, V.; Vlasakova, V.; Nemecek, J. *J. Fluorine Chem.* **1993**, *60*, 185−191. (f) Avent, A. G.; Bowler, A. N.; Doyle, P. M.; Marchand, C. M.; Young, D. W. *Tetrahedron Lett.* **1992**, *33*, 1509−1512. (g) Hudlicky, M. *J. Fluorine Chem.* **1993**, *60*, 193−210. (h) Burger, K.; Rudolph, M.; Fehn, S.; Sewald, N. *J. Fluorine Chem.* **1994**, *66*, 87−90. (i) Tran, T. T.; Patino, N.; Condom, R.; Frogier, T.; Guedj, R. *J. Fluorine Chem.* **1997**, *82*, 125−130. (j) Demange, L.; Menez, A.; Dugave, C. *Tetrahedron Lett.* **1998**, *39*, 1169−1172. (k) Konas, D. W.; Coward, J. K. *J. Org. Chem.* **2001**, *66*, 8831−8842. (l) Doi, M.; Nishi, Y.; Kiritoshi, N.; Iwata, T.; Nago, M.; Nakano, H.; Uchiyama, S.; Nakazawa, T.; Wakamiya, T.; Kobayashi, Y. *Tetrahedron.* **2002**, *58*, 8453−8459. (m) O'Neil, I. A.; Thompson, S.; Kalindjian, S. B.; Jenkins, T. C. *Tetrahedron Lett.* **2003**, *44*, 7809−7812. (n) Filosa, R.; Holder, C.; Auberson, Y. P. *Tetrahedron Lett.* **2006**, *47*, 8929−8932. (o) Chen, L.; Kim, Y. M.; Kucera, D. J.; Harrison, K. E.; Bahmanyar, S.; Scott, J. M.; Yazbeck, D. *J. Org. Chem.* **2006**, *71*, 5468−5473. (p) Hu, S.; Martinez, C. A.; Kline, B.; Yazbeck, D.; Tao, J.; Kucera, D. J. *Org. Process Res. Dev.* **2006**, *10*, 650−654.

(16) Synthesis of fluoromethyl proline derivatives: (a) Chaume, G.; Van Severen, M.-C.; Marinkovic, S.; Brigaud, T. *Org. Lett.* **2006**, *8*, 6123−6126. (b) Zhang, X.; Qing, F.-L.; Yang, Y.; Yu, J.; Fu, X.-K. *Tetrahedron Lett.* **2000**, *41*, 2953−2955. (c) Qiu, X.-L.; Qing, F.-L. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2052−2057. (d) Qiu, X.-L.; Qing, F.-L. *J. Org. Chem.* **2002**, *67*, 7162−7164. (e) Qiu, X.-L.; Qing, F.-L. *J. Org. Chem.* **2003**, *68*, 3614. (f) Qiu, X.-L.; Meng, W.-D.; Qing, F.-L. *Tetrahedron* **2004**, *60*, 5201−5206.

(17) (a) Golbik, R.; Yu, C.; Weyher-Stingl, E.; Huber, R.; Moroder, L.; Budisa, N.; Schiene-Fischer, C. *Biochemistry* **2005**, *44*, 16026−16034. (b) Naduthambi, D.; Zondlo, N. J. *J. Am. Chem. Soc.* **2006**, *128*, 12430−12434. (c) Ruzza, P.; Siligardi, G.; Donella-Deana, A.; Calderan, A.; Hussain, R.; Rubini, C.; Cesaro, L.; Osler, A.; Guiotto, A.; Pinna, L. A.; Borin, G. *J. Pept. Sci.* **2006**, *12*, 462−471.

(18) Staas, D. D.; Savage, K. L.; Sherman, V. L.; Shimp, H. L.; Lyle, T. A.; Tran, L. O.; Wiscount, C. M.; McMasters, D. R.; Sanderson, P. E. J.; Williams, P. D.; Lucas, B. J.; Krueger, J. A.; Lewis, S. D.; White, R. B.; Yu, S.; Wong, B. K.; Kochansky, C. J.; Anari, M. R.; Yan, Y.; Vacca, J. P. *Bioorg. Med. Chem.* **2006**, *14*, 6900−6916.

(19) (a) Holmgrem, S. K.; Taylor, K. M.; Bretscher, L. E.; Raines, R. T. *Nature* **1998**, *392*, 666−667. (b) Malkar, N. B.; Lauer-Fields, J. L.; Borgia, J. A.; Fields, G. B. *Biochemistry* **2002**, *41*, 6054−6064. (c) Barth, D.; Musiol, H.-J.; Schuett, M.; Fiori, S.; Milbradt, A. G.; Renner, C.; Moroder, L. *Chem. Eur. J.* **2003**, *9*, 3692−3702. (d) Hodges, J. A.; Raines, R. T. *J. Am. Chem. Soc.* **2003**, *125*, 9262−9263. (e) Doi, M.; Nishi, Y.; Uchiyama, S.; Nishiuchi, Y.; Nakazawa, T.; Ohkubo, T.; Kobayashi, Y. *J. Am. Chem. Soc.* **2003**, *125*, 9922−9923. (f) Persikov, A. V.; Ramshaw, J. A. M.; Kirkpatrick, A.; Brodsky, B. *J. Am. Chem. Soc.* **2003**, *125*, 11500. (g) Barth, D.; Milbradt, A. G.; Renner, C.; Moroder, L. *ChemBioChem* **2004**, *5*, 79−86. (h) Nishi, Y.; Uchiyama, S.; Doi, M.; Nishiuchi, Y.; Nakazawa, T.; Ohkubo, T.; Kobayashi, Y. *Biochemistry* **2005**, *44*, 6034−6042. (i) Doi, M.; Nishi, Y.; Uchiyama, S.; Nishiuchi, Y.; Nishio, H.; Nakazawa, T.; Ohkubo, T.; Kobayashi, Y. *J. Pept. Sci.* **2005**, *11*, 609−616. (j) Hodges, J. A.; Raines, R. T. *J. Am. Chem. Soc.* **2005**, *127*, 15923−15932. (k) Shoulders, M. D.; Hodges, J. A.; Raines, R. T. *J. Am. Chem. Soc.* **2006**, *128*, 8112−8113. (l) Boulègue, C.; Milbradt, A. G.; Renner, C.; Moroder, L. *J. Mol. Biol.* **2006**, *358*, 846−856.

(20) Kim, W.; McMillan, R. A.; Snyder, J. P.; Conticello, V. P. *J. Am. Chem. Soc.* **2005**, *127*, 18121−18132.

(21) (a) Eberhardt, E. S.; Panasik, N., Jr.; Raines, R. T. *J. Am. Chem. Soc.* **1996**, *118*, 12261−12266. (b) Dzakula, Z.; DeRider, M. L.; Markley, J. L. *J. Am. Chem. Soc.* **1996**, *118*, 12796−12803. (c) Bretscher, L. E.; Jenkins, C. L.; Taylor, K. M.; DeRider, M. L.; Raines, R. T. *J. Am. Chem. Soc.* **2001**, *123*, 777−778. (d) Renner, C.; Alefelder, S.; Bae, J. H.; Budisa, N.; Huber, R.; Moroder, L. *Angew. Chem., Int. Ed.* **2001**, *40*, 923−925. (e) Improta, R.; Benzi, C.; Barone, V. *J. Am. Chem. Soc.* **2001**, *123*, 12568−12577. (f) DeRider, M. L.; Wilkens, S. J.; Waddell, M. J.; Bretscher, L. E.; Weinhold, F.; Raines, R. T.; Markley, J. L. *J. Am. Chem. Soc.* **2002**, *124*, 2497−2505. (g) Jenkins, C. L.; Lin, G.; Duo, J.; Rapolu, D.; Guzei, I. A.; Raines, R. T.; Krow, G. R. *J. Org. Chem.* **2004**, *69*, 8565−8573. (h) Song, I. K.; Kang, Y. K. *J. Phys. Chem. B.* **2005**, *109*, 16982−16987. (i) Thomas, K. M.; Naduthambi, D.; Tririya, G.; Zondlo, N. J. *Org. Lett.* **2005**, *7*, 2397−2400. (j) Thomas, K. M.; Naduthambi, D.; Zondlo, N. J. *J. Am. Chem. Soc.* **2006**, *128*, 2216−2217. (k) Kim, W.; Hardcastle, K. I.; Conticello, V. P. *Angew. Chem., Int. Ed.* **2006**, *45*, 8141−8145.

(22) (a) Golubev, A.; Sewald, N.; Burger, K. *Tetrahedron Lett.* **1993**, *34*, 5879−5880. (b) Burger, K.; Windeisen, E.; Pires, R. *J. Org. Chem.* **1995**, *60*, 7641−7645. (c) Pires, P.; Burger, K. *Synthesis* **1996**, 1277−1279. (d) Burger, K.; Lange, T.; Pires, R. *J. Fluorine Chem.* **2000**, *102*, 317. (e) Schedel, H.; Dmowski, W.; Burger, K. *Synthesis* **2000**, 1681. (f) Burger, K.; Bottcher, C.; Radics, G.; Hennig, L. *Tetrahedron Lett.* **2001**, *42*, 3061−3063. (g) Spengler, J.; Schedel, H.; Sieler, J.; Quaedflieg, P. J. L. M.; Broxterman, Q. B.; Duchateau, A. L. L.; Burger, K. *Synthesis* **2001**, 1513−1518. (h) Bottcher, C.; Burger, K. *Tetrahedron Lett.* **2002**, *43*, 9711−9714. (i) Radics, G.; Pires, R.; Koksch, B.; El-Kousy, S. M.; Burger, K. *Tetrahedron Lett.* **2003**, *44*, 1059−1062. (j) Bottcher, C.; Burger, K. *Tetrahedron Lett.* **2003**, *44*, 4223−4226.

(23) Some selected papers on the synthetic application of hexafluoroacetone: (a) Burger, K.; Hubl, D.; Gertischke, P. *J. Fluorine Chem.* **1985**, *27*, 327−332. (b) Iseki, K.; Nagai, T.; Kobayashi, Y. *Chem. Pharm. Bull.* **1992**, *40*, 1346−1348. (c) Ohira, Y.; Taguchi, T.; Iseki, K.; Kobayashi, Y. *Chem. Pharm. Bull.* **1992**, *40*, 1647−1649. (d) Iseki, K.; Oishi, S.; Namba, H.; Taguchi, T.; Kobayashi, Y. *Chem. Pharm. Bull.* **1995**, *43*, 1897−1901. (e) Hilpert, H.; Wirz, B. *Tetrahedron* **2001**, *57*, 681. (f) Wu, Y.; Sabbe, K.; De Clercq, P.; Vandewalle, M.; Bouillon, R.; Verstuyf, A. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 1629−1632. (g) Wu, Y.; De Clercq, P.; Vandewalle, M.; Bouillon, R.; Verstuyf, A. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 1633−1636. (h) Anderson, J. T.; Toogood, P. L.; Marsh, E. N. G. *Org. Lett.* **2002**, *4*, 4281−4283. (i) Lateef, H.; Mullins, S. T. *J. Fluorine Chem.* **2000**, *104*, 167−171. (j) Barbarich, T. J.; Nolan, B. G.; Tsujioka, S.; Miller, S. M.; Anderson, O. P.; Strauss, S. H. *J. Fluorine Chem.* **2001**, *112*, 335−342. (k) Nolan, B. G.; Tsujioka, S.; Strauss, S. H. *J. Fluorine Chem.* **2002**, *118*, 103−106.

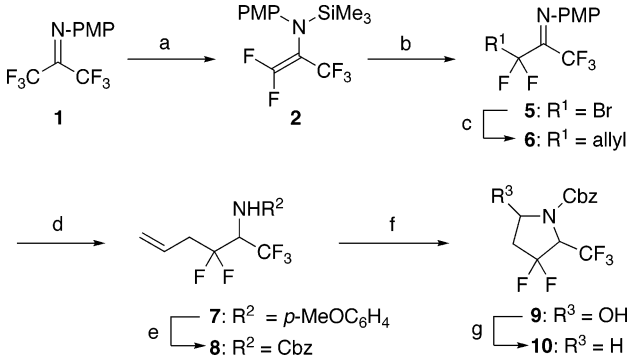
(24) Middleton, W. J.; Krespan, C. G. *J. Org. Chem.* **1965**, *30*, 1398−1402.

(25) (a) Petrov, V. A.; DesMarteau, D. D. *J. Fluorine Chem.* **1996**, *77*, 175−181. (b) Petrov, V. A.; Khasnis, D. D. *Isr. J. Chem.* **1999**, *39*, 147−150. (c) Petrov, V. A. *J. Fluorine Chem.* **2000**, *106*, 25−34. (d) Petrov, V. A. *Tetrahedron Lett.* **2000**, *41*, 6959. (e) Petrov, V. A. *J. Fluorine Chem.* **2001**, *109*, 123−128.

(26) (a) Roberts, J. D.; Hall, G. E.; Middleton, W. J. *J. Am. Chem. Soc.* **1971**, *93*, 4778−4781. (b) Steglich, W.; Burger, K.; Duerr, M.; Burgis, E. *Chem. Ber.* **1974**, *107*, 1488−1498. (c) Burger, K.; Wassmuth, U.; Penninger, S. *J. Fluorine Chem.* **1982**, *20*, 813. (d) Burger, K.; Geith, K.; Hoess, E. *Synthesis* **1990**, 352−356.

(27) Short accounts: (a) Uneyama, K.; Amii, H. *J. Fluorine Chem.* **2002**, *114*, 127−131. (b) Amii, H.; Uneyama, K. Mg-Promoted Selective C-F Bond Cleavage: A General and Efficient Access to Difluoroenol Silyl Ethers and Their Derivatives. In *Fluorine-Containing Synthons*; Soloshonok, V. A., Ed.; ACS Symp. Ser. No. 911; American Chemical Society: Washington, DC, 2005; pp. 455−475.

SCHEME 2

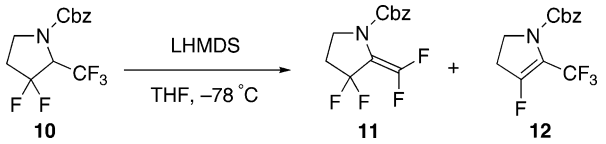


subsequently to trifluoroalanine dipeptides, where the difluoromethylene group of **2** was chemically modified to a carboxamide group, and thus the peptide synthesis involved a new entry to amide bond construction totally different from the conventional condensation of two kinds of amino acids.[32] On this basis, it is interesting to see another utilization of **2**, in which the difluoromethylene group would become the difluoromethylene moiety of difluoroproline and the trifluoromethyl group could be modified to the carbamide part of difluoroproline dipeptides.

The first defluorination of bis(trifluoromethyl)imine **1** proceeded very smoothly to provide enamine **2** in 95% yield in a 100 mmol scale on reacting **1** with 2 mol equiv of metal Mg and 4 mol equiv of chlorotrimethylsilane in anhydrous THF at 0 °C under argon atmosphere (Scheme 2).

Bromination of enamine **2** by NBS in CH_2Cl_2 at room temperature under an argon atmosphere provided the bromide **5** in 90% yield. Radical allylation of bromide **5** with allyltributyltin in toluene at 110 °C provided *C*-allylated imine **6** in 70% yield. Reduction of **6** by sodium borohydride in methanol at 0 °C gave amine **7** in 93% yield. The deprotection of the *N*-*p*-methoxyphenyl group of **7** by CAN oxidation in a mixed solvent (3/1 of CH_3CN/H_2O) at 0 °C to room temperature and subsequent reprotection with CbzCl-$NaHCO_3$ at 30 °C afforded Cbz-protected amine **8** in 58% overall yield. Ozonolysis of **8** in CH_2Cl_2 at −78 °C provided the cyclic aminal **9** in 92% yield. Dehydroxylative hydrogenation of **9** by triethylsilane/boron trifluoride ether complex[33] in anhydrous CH_2Cl_2 gave *N*-Cbz-3,3-difluoro-2-trifluoromethylpyrrolidine **10** in 74% yield.

SCHEME 3



Next, regioselective defluorination from the trifluoromethyl group of **10** was examined. The selective defluorination from the trifluoromethyl group in competition with the difluoromethylene group has been unprecedented. So far as known, the base-catalyzed dehydrofluorination always takes place at the difluoromethylene side due to the more favorable thermodynamic stability of monofluoroalkenes rather than 1,1-difluoroalkenes.[34] However, unlike the open chain compounds, it would be feasible to defluorinate selectively from the trifluoromethyl group of the cyclic compound **10**, in which there are two types of C−F bond: one is found in the conformationally fixed CF_2 group in the ring and the other belongs to the freely rotatable CF_3 group in the side chain. The latter undergoes kinetically faster dehydrofluorination, while the former is less favorable for E2 type elimination due to the conformational mismatching between C−F and C−H bonds in the five-membered ring. After a survey of bases and solvents, it was found that exocyclic difluoromethylene **11** was obtained exclusively in 82% isolated yield (92% yield based on ^{19}F NMR analysis with an internal standard) when **10** was treated with 1.6 equiv of lithium bis(trimethylsilyl)amide (LHMDS) in THF at −78 °C (Scheme 3). The reaction was fast reaching completion within 10 min. When ether, a less polar solvent than THF, was employed, geminal difluoroolefin **11** was still obtained as the major product in 77% yield with the side product **12** in 7% yield. The reaction temperature seemed to be less important for the formation of **11** since *gem*-difluoroolefin **11** was obtained in 76% yield at room temperature.

Amino esters **13** were used in the addition reaction to **11** in DMF with tertiary amine as a catalyst. The addition of the amino group of **13** to the difluoromethylene moiety of **11** occurred smoothly at room temperature, but slightly more slowly (6 h) than that of **2** (1 h).[31] Good yields of dipeptides **16** were obtained after the subsequent acid-catalyzed hydrolysis of the intermediate imidoyl fluorides **15** (Scheme 4).[31,35] The high acidity of the proton on the nitrogen of the intermediate adducts **14** might

(28) (a) Amii, H.; Kobayashi, T.; Hatamoto, Y.; Uneyama, K. *Chem. Commun.* **1999**, 1323−1324. (b) Amii, H.; Kobayashi, T.; Uneyama, K. *Synthesis* **2000**, 2001−2003. (c) Amii, H.; Kobayashi, T.; Terasawa, H.; Uneyama, K. *Org. Lett.* **2001**, *3*, 3103−3105. (d) Hata, H.; Kobayashi, T.; Amii, H.; Uneyama, K.; Welch, J. T. *Tetrahedron Lett.* **2002**, *43*, 6099−6102. (e) Uneyama, K.; Tanaka, H.; Kobayashi, S.; Shioyama, M.; Amii, H. *Org. Lett.* **2004**, *6*, 2733−2736.

(29) (a) Uneyama K.; Kato T. *Tetrahedron Lett.* **1998**, *39*, 587−590. (b) Mae, M.; Amii, H.; Uneyama, K. *Tetrahedron Lett.* **2000**, *41*, 7893−7896. (c) Mae, M.; Matsuura, M.; Amii, H.; Uneyama, K. *Tetrahedron Lett.* **2002**, *43*, 2069−2072. (d) Kobayashi, T.; Nakagawa, T.; Amii, H.; Uneyama, K. *Org. Lett.* **2003**, *5*, 4297−4300. (e) Amii, H.; Ichihara, Y.; Nakagawa, T.; Kobayashi, T.; Uneyama, K. *Chem. Commun.* **2003**, 2902−2903. (f) Amii, H.; Kohda, M.; Katagiri, T.; Uneyama, K. *J. Fluorine Chem.* **2006**, *127*, 505−509.

(30) (a) Prakash, G. K. S.; Hu, J.; Olah, G. A. *J. Fluorine Chem.* **2001**, *112*, 355−360. (b) Prakash, G. K. S.; Hu, J.; Alauddin, M. M. *J. Fluorine Chem.* **2003**, *121*, 239−243.

(31) Guo, Y.; Fujiwara, K.; Uneyama, K. *Org. Lett.* **2006**, *8*, 827−829.

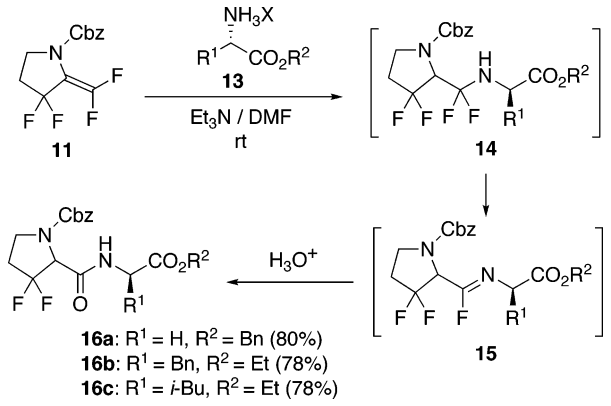
(32) The standard synthetic approaches to dipeptides: (a) Jones, J. *Amino Acid and Peptide Synthesis*, 2nd ed.; Oxford University Press: Oxford, UK, 2002. (b) Kusumoto, S. Ed. *Experimental Chemistry*, 4th ed.; Maruzen: Tokyo, Japan, 1990; No. 22. (c) Hodgson, D. R. W.; Sanderson, J. M. *Chem. Soc. Rev.* **2004**, *33*, 422−430.

(33) He, B. Y.; Wu, T. J.; Yu, X. Y.; Huang, P. Q. *Tetrahedron: Asymmetry* **2003**, *14*, 2101−2108.

(34) Several reports on selective defluorination of CF_2 groups in the presence of CF_3 groups: (a) Collins, D.; Stephens, R.; Tatlow, J. C. *J. Fluorine Chem.* **1986**, *32*, 213−227. (b) Burdon, J.; Ezmirly, S. T.; Huckerby, T. N. *J. Fluorine Chem.* **1988**, *40*, 283−318. (c) Qian, C. P.; Nakai, T.; Dixon, D. A.; Smart, B. E. *J. Am. Chem. Soc.* **1990**, *112*, 4602−4604. (d) van der Puy, M. *J. Org. Chem.* **1997**, *62*, 6466−6468. (e) Brisdon, A. K.; Crossley, I. R. *Chem. Commun.* **2002**, 2420−2421. (f) Brisdon, A. K.; Crossley, I. R.; Pritchard, R. G.; Sadig, G.; Warren, J. E. *Organometallics* **2003**, 22, 5534−5542.

(35) We have isolated imidoyl fluorides **15** through column chorography on silica gel and we obtained some data for identification, but we did not achieve satisfactory consistency of elemental analysis for these compounds which were moderately unstable. Data of imidoyl fluoride **15a**: ^1H NMR ($CDCl_3$) δ 2.28−2.64 (m, 2H), 3.59−3.68 (m, 1H), 3.80 (td, J = 9.6, 3.0 Hz, 1H), 4.11 (dd, J = 24, 17.4 Hz, 1H), 4.28 (dd, J = 43.5, 17.4 Hz, 1H), 4.61−4.71 (m, 1H), 5.05−5.22 (m, 4H), 7.24−7.40 (m, 10H); ^{19}F NMR ($CDCl_3$) δ 51.6−54.5 (m, 1F), 64.8−66.2 (m, 1F), 129.3 (s, 0.53F), 130.8 (s, 0.47F). Data of imidoyl fluoride **15b**: IR (neat) 2968, 2350, 1726, 1418, 1352 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.79−0.94 (m, 6H), 1.21−1.30 (m, 3H), 1.38−1.76 (m, 3H), 2.30−2.74 (m, 2H), 3.55−3.84 (m, 1H), 3.85−3.97 (m, 1H), 4.10−4.20 (m, 2H), 4.45−4.60 (m, 1H), 4.60−4.72 (m, 1H), 5.03−5.28 (m, 2H), 7.26−7.35 (m, 5H); ^{19}F NMR ($CDCl_3$) δ 51.0−55.1 (m, 1F), 64.9−66.4 (m, 1F), 126.7−130.1 (m, 1F); MS (EI) (*m*/*z*) 428 (M^+, 0.4), 355 (4), 91 (100).

SCHEME 4



contribute to the selective dehydrofluorination of **14** to the intermediates **15** exclusively. The result demonstrated that difluoromethylene moiety of *gem*-difluoroolefin **11** was an excellent counterpart of the active carboxyl compound, which could be used in peptide synthesis under mild conditions.

In summary, two trifluoromethyl groups of imine **1** could be successfully differentiated: one for a synthon of the difluoromethylene moiety (CF_2R) and another for that of the carbamide group. Also an exploratory application for the synthesis of β,β-difluoroproline dipeptides has been demonstrated. The *gem*-difluoroenamine moiety of **11** proved to be a good precursor of the amide bond in the peptide synthesis.

Experimental Section

***N*-Benzyloxycarbonyl-2-difluoromethylene-3,3-difluoropyrrolidine (11).** A solution of compound **10** (289 mg, 1 mmol) in 10 mL of anhydrous THF was cooled at −78 °C. LHMDS (1.6 mmol) in THF was dropped into the solution. The mixture was allowed to stir for 10 min. After adding cold hexane, all of the solvent was removed by evaporation. The residue was purified by silica gel column chromatography (hexane/AcOEt = 20/1) to afford **11** as an exclusive product (237 mg, 0.82 mmol, 82%). Mp 30−31 °C; IR (neat) 1778, 1728, 1408, 1344 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.40−2.52 (m, 2H), 3.80 (t, J = 7.0 Hz, 2H), 5.20 (s, 2H), 7.30−7.41 (m, 5H); ^{19}F NMR ($CDCl_3$) δ 64.6 (s, 2F), 65.9 (s, 1F), 81.6 (s, 1F). Anal. Calcd for $C_{13}H_{11}F_4NO_2$: C, 53.99; H, 3.83; N, 4.84. Found: C, 54.28; H, 4.22; N, 5.01.

***N*-Benzyloxycarbonyl-3,3-difluoroprolylglycine Benzyl Ester (Z-3,3-Difluoro-Pro-Gly-Obn, 16a).** Under argon atmosphere, to a solution of **11** (100 mg, 0.35 mmol) in DMF (0.5 mL) subsequently were added glycine benzyl ester **13a** (350 mg, 1.04 mmol) and triethylamine (161 mg, 1.60 mmol). The mixture was stirred at room temperature for 6 h. The reaction was monitored by both TLC and ^{19}F NMR analyses. Then, the mixture was cooled to 0 °C and water (1 mL) was added and then hydrochloric acid was dropped into the solution until the pH was 1.0. After stirring for 2.5 h, the mixture was poured into water (10 mL) and extracted with ether. The combined organic phase was washed with saturated sodium hydrogen carbonate aqueous solution and saturated brine and dried over anhydrous magnesium sulfate. After removal of the solvent, the residue was subjected to column chromatography on silica gel (hexane/EtOAc = 4/1 to 3/1) to afford **16a** (119 mg, 0.28 mmol, 80%) as a viscous colorless oil. IR (neat) 3340, 1752, 1716, 1696, 1676, 1418, 1188 cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.20−2.60 (m, 2H), 3.38−3.58 (m, 1H), 3.62−3.78 (m, 1H), 3.85−4.09 (m, 2H), 4.60 (dd, J = 14.1, 17.1 Hz, 1H), 5.01−5.18 (m, 4H), 7.24−7.42 (m, 10H), 8.97 (t, J = 5.7 Hz, 1H); ^{19}F NMR (DMSO-d_6) δ 54.6 (d, J = 236 Hz, 0.48F), 53.4 (d, J = 218 Hz, 0.52F), 69.5−70.0 (including app. d, J = 230 Hz, 1F). Anal. Calcd for $C_{22}H_{22}F_2N_2O_5$: C, 61.11; H, 5.13; N, 6.48. Found: C, 61.19; H, 5.25; N, 6.63.

Acknowledgment. This work is dedicated to the late Professor Yoshihiko Ito. The financial support of the Ministry of Education, Culture, Sports, Science and Technology of Japan (Grant-in-Aid for Scientific Research (C), No. 17550104) is gratefully acknowledged. We also thank the SC-NMR laboratory of Okayama University for ^{19}F NMR analysis.

Supporting Information Available: Detailed descriptions of the synthetic methods for compounds **2**, **5**−**12**, and **16a**−**c** and NMR spectra (^1H, ^{19}F) for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JO070719Q