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A Novel Synthesis of Enantiomerically Pure 5,5,5,5′,5′,5′-Hexafluoroleucine

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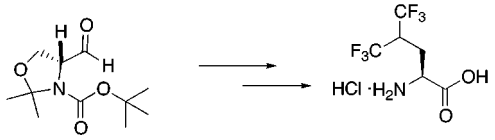
ABSTRACT



1 **6**

A novel, short, and efficient synthesis of (*S*)-5,5,5,5′,5′,5′-hexafluoroleucine (6) in greater than 99% ee starting from the protected oxazolidine aldehyde 1 is described. The enantiomeric excess of the product was calculated from an NMR analysis of a dipeptide formed by reaction with a protected L-serine derivative. Furthermore, a racemic sample of *N*-acylated hexafluoroleucine was enzymatically resolved by treatment with porcine kidney acylase I and was found to have the same optical rotation as a synthetic sample of 6.

Selective fluorination of biologically active compounds is often accompanied by dramatic changes in physiological activities.[1] Fluorinated amino acids have been synthesized[1c−h,7] and studied as potential inhibitors of enzymes and as therapeutic agents.[2] Trifluoromethyl-containing amino acids acting as potential antimetabolites have also been reported.[3]

We have recently described the de novo design of peptides based on the coiled coil motif[4] where the residues lining the interface between helices have highly fluorinated side chains.[5] These peptides form well-defined coiled coil structures with higher thermal stability than their natural hydrocarbon counterparts. To create protein structures with very highly fluorinated cores, we required an efficient and inexpensive synthesis of **6** in enantiomerically pure form.

Herein, we report a novel and efficient synthesis of (*S*)-5,5,5,5′,5′,5′-hexafluoroleucine starting from commerically available D-serine.[6] While there is one existing report of the synthesis of racemic hexafluoroleucine[7] and another recent report detailing the preparation of **6** in 81% ee,[8] we sought a better method to obtain hexafluoroleucine in >99% ee for direct use in solid-phase peptide synthesis. Our synthesis commenced from the oxazolidine aldehyde **1** (Garner aldehyde) which served as a chiral, nonracemic synthon.[9] Aldehyde **1** is derived from D-serine, was obtained using a slight modification of a published procedure, and is exceptionally stable toward racemization in subsequent steps.[10] In a key step, aldehyde **1** was converted to the bis-trifluorom-

(1) (a) Welch, T.; Eswarakrishnan, S. *Fluorine in Bioorganic Chemistry*; Wiley-Interscience: New York, 1991 and references therein. (b) *Fluorine-containing Amino Acids*; Kukhar′, V. P., Soloshonok, V. A., Eds.; John Wiley & Sons: Chichester, 1994. (c) Williams, R. M. *Synthesis of Optically Active α-Amino Acids*; Pergamon Press: Oxford, 1989. (d) Ojima, I.; Kato, K.; Nakahashi, K.; Fuchikami, T.; Fujita, M. *J. Org. Chem.* **1989**, *54*, 4511−4522. (e) Tsushima, T.; Kawada, K.; Ishihara, S.; Uchida, N.; Shiratori, O.; Higaki, J.; Hirata, M. *Tetrahedron* **1988**, *44*, 5375−5387. (f) Weinges, K.; Kromm, E. *Liebigs Ann. Chem.* **1985**, 90−102. (g) Eberle, M. K.; Keese, R.; Stoeckli-Evans, H. *Helv. Chim. Acta* **1998**, *81*, 182−186. (h) Tolman, V. *Amino Acids* **1996**, *11*, 15−36.

(2) Kollonitsch, J.; Patchett A. A.; Marburg, S.; Maycock, A. L.; Perkins, L. M.; Doldouras, G. A.; Duggan, D. E.; Aster, S. D. *Nature* **1978**, *274*, 906−908.

(3) (a) Walborsky, H. M.; Baum, M. E. *J. Am. Chem. Soc.* **1958**, *80*, 187−192. (b) Walborsky, H. M.; Baum, M.; Loncrini, D. F. *J. Am. Chem. Soc.* **1955**, *77*, 3637−3640. (c) Hill, H. M.; Towne, E. B.; Dickey, J. B. *J. Am. Chem. Soc.* **1950**, *72*, 3289−3289.

(4) (a) Crick, F. H. C. *Acta Cyrstallogr.* **1953**, *6*, 689. (b) O'Shea, E. K.; Rutkowski, R.; Kim, P. S. *Science* **1989**, *243*, 538. (c) Lupas, A. *Trends Biochem. Sci.* **1996**, *21*, 375−382. (d) Kohn, W. D.; Hodges, R. S. *Trends Biotechnol.* **1998**, *16*, 379−389.

(5) Bilgiçer, B.; Fichera, A.; Kumar, K. *J. Am. Chem. Soc.*, in press.

(6) For synthesis of α-amino acids derived from D-serine using a serine aldehyde equivalent, see: Blaskovich, M. A.; Lajoie, G. A. *J. Am. Chem. Soc.* **1993**, *115*, 5021−5030.

(7) Lazar, J.; Sheppard, W. A. *J. Med. Chem.* **1968**, *11*, 138.

(8) Zhang, C.; Ludin, C.; Eberle, M. K.; Stoeckli-Evans, H.; Keese, R. *Helv. Chim. Acta* **1998**, *81*, 174−181.

(9) (a) Garner, P.; Park, J. M. *J. Org. Chem.* **1987**, *52*, 2361−2364. (b) Garner, P.; Park, J. M. *J. Org. Chem.* **1988**, *53*, 2979−2984. (c) Garner, P.; Park, J. M.; Malecki, E. *J. Org. Chem.* **1988**, *53*, 4395−4398. (d) Angrick, M. *Montash. Chem.* **1985**, *116*, 645−649.

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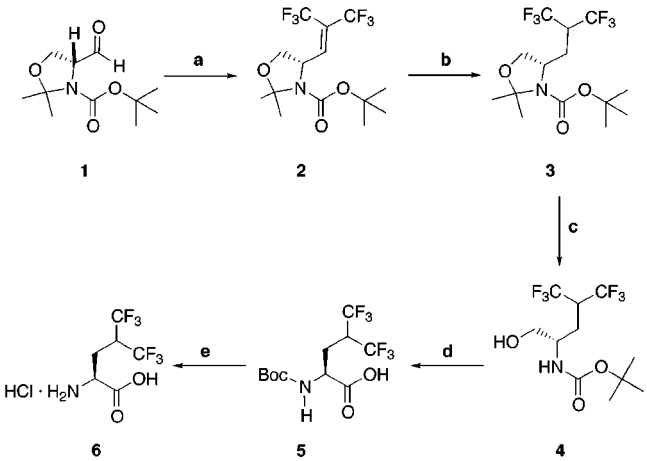
ethyl olefin **2** by a Wittig reaction in 92% yield (Scheme 1).[11] The ylide for this reaction is the phosphonium analogue

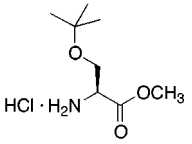
Scheme 1[a]



[a] Reagents and conditions: (a) PPh_3, $[(CF_3)_2C]_2S_2$, Et_2O, −78 °C → rt, 3 d, 92%; (b) H_2, 10% Pd/C, THF, 98%; (c) TsOH, MeOH, rt, 1 d, 80%; (d) PDC, DMF, 18 h, 75%; (e) 40% CF_3CO_2H/CH_2Cl_2; HCl, 10 min, rt, >95%.

of Middleton's phosphorane,[12] generated in situ from tetrakis-(trifluoromethyl)-1,3-dithietane[13] and triphenylphosphine.[14,15] The olefin **2** was reduced by catalytic hydrogenation over Pd/C to give the suitably substituted oxazolidine **3** in 98% yield. Next, the oxazolidine was subjected to acid-catalyzed ring cleavage unmasking the alcohol **4**. Alcohol **4** was oxidized to the carboxylic acid **5** using pyridinium dichromate, and in the final step, the *tert*-butyloxycarbonyl group was removed using trifluoroacetic acid to yield the hydrochloride salt of the desired α-amino acid **6**. While the last deprotection step was carried out in order to verify the optical purity of **6**, the Boc-protected amino acid **5** could be directly used for solid-phase synthesis of peptides.

The optical purity of synthetic **6** was verified in two ways. A racemic sample of **5** (prepared using a different route) and **5** obtained through the scheme described here were separately coupled to a protected methyl ester of L-serine (**7**), and the resulting dipeptide was analyzed using ^{1}H NMR



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spectroscopy. In the case of the dipeptide obtained from racemic **5**, three signals corresponding to the *t*-Boc group, the methyl ester, and the *tert*-butyl ether were split into two peaks presumably due to formation of two diastereomers, whereas **5** from the present synthesis yielded a dipeptide with only one set of signals for the three sets of protons described above. Furthermore, racemic **6** was *N*-acylated and enzymatically resolved using porcine kidney acylase I [EC 3.5.1.14] to yield the α-*S* isomer exclusively.[16] The optical rotation of **6** obtained in this manner and that of the synthetic sample were identical. Thus, as far as we can tell, the synthesis proceeds in >99% ee. The NMR data for **6** agree with those reported previously.[8,17] The construction of 5,5,5,5′,5′,5′-(*R*)-hexafluoroleucine is similarly achieved from L-serine.

In summary, we have developed an efficient synthesis of enantiomerically pure 5,5,5,5′,5′,5′-hexafluoroleucine. Studies detailing the incorporation of this building block into peptides and subsequent characterization will be reported shortly.

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Supporting Information Available: Spectral characterization of compounds **2**−**6** and dipeptide **8** obtained from the reaction of **7** and **6**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL015567E

(10) Campbell, A. D.; Raynham, T. M.; Taylor, R. J. K. *Synthesis* **1998**, 1707−1709.

(11) Korhummel, C.; Hanack, M. *Chem. Ber.* **1989**, *122*, 2187−2192. **Typical procedure for the coupling reaction:** To a stirred solution of the Garner aldehyde **1** (7.0 g, 31.0 mmol) and PPh_3 (57 g, 217 mmol) in dry Et_2O (300 mL) was added 2,2,4,4-tetrakis(trifluoromethyl)-1,3-dithietane (39.5 g, 108.5 mmol) at −78 °C under argon. The mixture was stirred for 3 d while being slowly warmed to room temperature. The reaction slowly accumulated an insoluble white solid which was filtered, and the filtrate was concentrated. The residue was further dissolved in *n*-pentane (300 mL) and filtered again to remove insoluble impurities. After removal of the solvent, the residue was subjected to flash column chromatography using *n*-pentane/Et_2O (6/1) as eluant to give pure **2** as a pale yellow oil (10.4 g, 92%).

(12) Middleton, W. J.; Sharkey, W. H. *J. Org. Chem.* **1965**, *30*, 1384.

(13) Anello, L. G.; Vanderpuy, M. *J. Org. Chem.* **1982**, *47*, 377−378.

(14) (a) Burton, D. J.; Yang, Z. Y.; Qiu, W. M. *Chem. Rev.* **1996**, *96*, 1641−1715. (b) Dixon, D. A.; Smart, B. E. *J. Am. Chem. Soc.* **1986**, *108*, 7172−7177. (c) Burton, D. J.; Inouye, Y. *Tetrahedron Lett.* **1979**, 3397−3400.

(15) Kobayashi, Y.; Nakajima, M.; Nakazawa, M.; Taguchi, T.; Ikekawa, N.; Sai, H.; Tanaka, Y.; Deluca, H. F. *Chem. Pharm. Bull.* **1988**, *36*, 4144−4147.

(16) (a) Chenault, H. K.; Dahmer, J.; Whitesides, G. M. *J. Am. Chem. Soc.* **1989**, *111*, 6354−64. (b) Fu, S. C. J.; Birnbaum, S. M. *J. Am. Chem. Soc.* **1953**, *75*, 918−920.

(17) Both the synthetic sample and the enzyme-resolved samples of **6** had $[\alpha]^{26.0}_D = +5.6°$ (*c* 1, CH_3OH), a value smaller in magnitude than that reported previously (ref 8).