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

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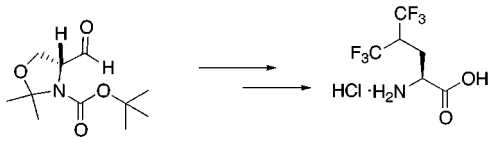
ABSTRACT



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-

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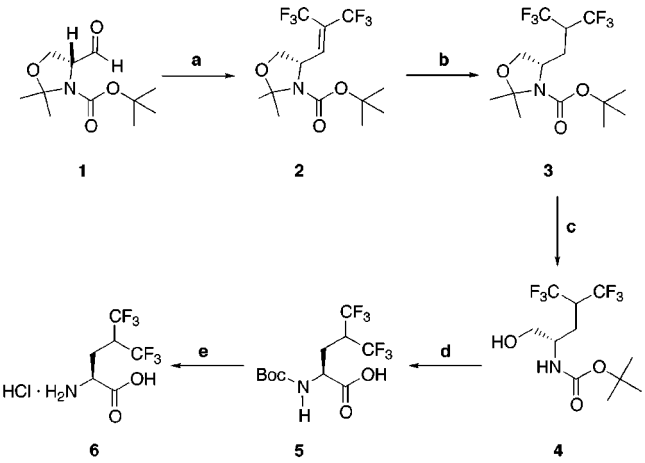
ethyl olefin **2** by a Wittig reaction in 92% yield (Scheme 1).[11] The ylide for this reaction is the phosphonium analogue

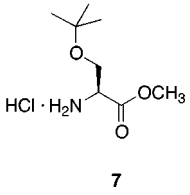
Scheme 1[a]



[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



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.

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(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).