ORGANIC LETTERS

2002
Vol. 4, No. 24
4281−4283

A Short and Efficient Synthesis of L-5,5,5,5′,5′,5′-hexafluoroleucine from *N*-Cbz-L-Serine

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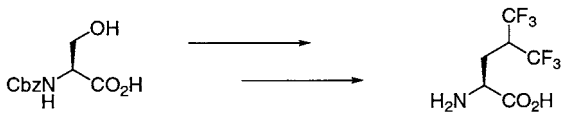
Received September 17, 2002

ABSTRACT



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5,5,5,5′,5′,5′-Hexafluoroleucine (6), a fluorous analogue of leucine, is of considerable interest as a building block in the design of fluorous proteins and peptides. We report a short and efficient synthesis of 6, which is obtained from *N*-Cbz-L-serine (1) in 50% overall yield, 99% enantiomeric excess, and in multigram quantities. Key steps are addition of a serine-derived organozincate to hexafluoroacetone to construct the hexafluoroleucine side chain, followed by radical-mediated deoxygenation of the resulting tertiary alcohol.

Fluorocarbons have long been known for their chemical inertness, and their unique physicochemical properties have found industrial and medical applications in fire retardants, refrigerants, anesthetics, and biologically inert polymers. The tendency of extensively fluorinated, or fluorous, organic molecules to partition into perfluorinated solvents has been exploited in organic synthesis to facilitate the purification of products from reaction mixtures.[1−4] Recently, there has been much interest in whether the novel properties exhibited by fluorocarbon polymers can be exploited in the design of biological macromolecules. We predicted that extensively fluorinated analogues of hydrophobic amino acids, when substituted into proteins and peptides, should pack into the hydrophobic core of the protein to produce "Teflon" proteins that may combine novel physicochemical properties with biological activity.[5] This idea is supported by recent reports describing the properties of peptides designed to form dimeric coiled-coil structures, based either on the "leucine zipper" domain of the transcription factor GCN4 or de novo designed sequences that incorporate (4*R*,4*S*)-L-trifluoroleucine,[6] (3*R*,3*S*)-L-trifluorovaline,[7] or L-hexafluoroleucine.[8,9]

To facilitate further development of these novel biomaterials, short, efficient syntheses of fluorous amino acids in chiral form are needed. Hexafluoroleucine (hFLeu) is a particularly attractive target as a highly fluorinated analogue of leucine, an amino acid that has been demonstrated to play an important role in the folding of many proteins. A racemic synthesis of hexafluoroleucine was reported in 1968,[10] and it is perhaps surprising that the first chiral synthesis of this amino acid was not reported until 1998;[11] however, this synthesis only achieved an enantiomeric excess of 81%,

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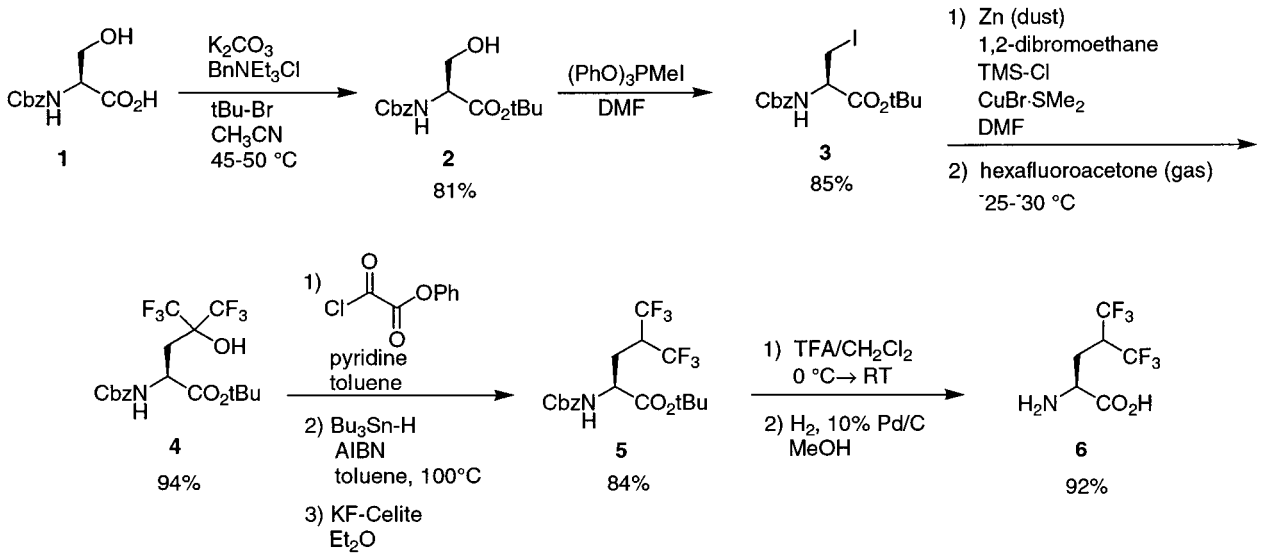
10.1021/ol026922j CCC: $22.00
Published on Web 10/26/2002

Scheme 1



making it unsuitable for the production of material for peptide synthesis. More recently, a nine-step synthesis of L-hFLeu from D-serine with high enantiomeric excess has been reported that uses Garner's aldehyde as a key intermediate.[12] We have developed a shorter synthesis of L-hFLeu that uses Cbz-protected L-serine as a chiral building block and hexafluoroacetone as the source of the fluorocarbon portion. We chose to exploit the organozinc chemistry developed by Jackson that has been used to extend the side chain of serine with a wide variety of functional groups without racemization of the α-carbon.[13] The complete synthetic route is outlined in Scheme 1. *N*-Cbz-L-serine **1** was converted to its corresponding *tert*-butyl ester, **2**, using a modified procedure from Martinez.[14] The protected iodoalanine compound **3** was formed in one step from **2** by reaction with $(PhO)_3PMeI$.[15] Following a procedure similar to that described by Jackson and co-workers[16] led to the conversion of iodide **3** to the organozincate, and, after the addition of a catalytic quantity of $CuBr{\cdot}SMe_2$, the organozincate was reacted in situ with hexafluoroacetone gas at −25 °C to give, upon workup, the desired fluorine-containing carbon skeleton, compound **4**, as the only product in 94% yield. We note that alkylzincates are not usually sufficiently reactive to undergo addition to ketones;[17] however, the extremely electrophilic nature of hexafluoroacetone results in an efficient reaction in this case. If $CuBr{\cdot}SMe_2$ was omitted, lower yields of **4** were obtained and Cbz-alanine-*tert*-butyl ester was formed as a byproduct.

Subsequent deoxygenation of compound **4** to give the hFLeu side-chain was ultimately achieved by using a modification of the radical deoxygenation methodology developed by Dolan and MacMillan.[18] Thus, the phenyl oxalate ester of **4** (rather than the methyl oxalate analog[19] as in the original procedure) was formed by reaction with phenyl oxalyl chloride[20] and pyridine in dry toluene at room temperature for 3 h. The oxalate ester was unstable to silica gel and was not isolated. The reaction mixture was filtered to remove the precipitated pyridinium chloride, and the toluene was removed by rotary evaporation to azeotrope away most of the excess pyridine. Careful removal of pyridinium chloride and pyridine appears to be important to obtain good yields in the subsequent reduction step. To effect reduction, a solution of the phenyl oxalate ester in toluene was heated in the presence of a small excess of Bu_3SnH and a catalytic amount of AIBN. This resulted in an efficient reaction to give the protected hexafluoroleucine **5** in 84% overall yield after purification. Interestingly, the deoxygenation did not proceed if Et_3N was used as the base. The treatment of the products of the deoxygenation reaction with KF−Celite resulted in the efficient removal of organo-tin compounds from the reaction mixture[21] so that compound **5** could be purified straightforwardly by column chromatography.

Final deprotection of **5** by standard methods proceeded to give hFLeu **6** in 92% yield. The enantiomeric excess of the

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L-isomer of **6**[22] was determined to be 96% by NMR analysis of the Mosher amide.[23] Subsequent recrystallization of **6** from methanol yielded material with an ee greater than 99%.

In summary, the synthesis of L-hFLeu from *N*-Cbz-L-serine has been achieved with an overall yield of 50%. Each step proceeds in better than 80% yield, and only two chromatographic purifications are required. All the steps in the reaction can be performed on a multigram scale (>10 g per reaction) to produce pure L-hFLeu in large quantities.

(22) Xing et al. (ref 12) previously determined the ee of **6** by NMR analysis of the dipeptide of **6** formed with serine. However, in our hands, this method proved to be unreliable, as the major proton peaks of the two diastereomers were insufficiently resolved to allow accurate integration of the peaks.

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Acknowledgment. J.T.A. thanks Pfizer Global Research and Development, Ann Arbor, for support through a postdoctoral fellowship.

Supporting Information Available: Detailed procedures and spectral characterization of compounds for **2**−**5**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL026922J