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Enantioselective Synthesis of α-Fluorinated β²-Amino Acids

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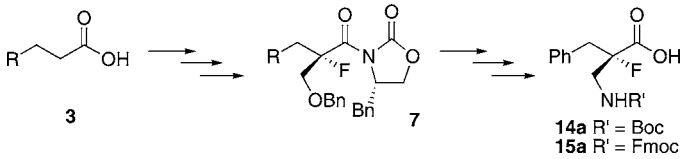
ABSTRACT



A methodology for the enantioselective synthesis of α-fluorinated β²-amino acids has been developed from readily available carboxylic acids 3. Conversion to the Evan's oxazolidinone followed by enantioselective fluorination and alkylation gave 7 in high diastereomeric excess (>95%). Subsequent removal of the oxazolidinone and amination at the Bn-protected hydroxyl center gave optically active α-fluorinated β²-amino acids.

The incorporation of fluorine into a peptide or protein is known to influence its conformation and biological activity. This can then provide fundamental insights into protein structure and function.[1,2] For example, synthetic analogues of collagen, which contain a fluorinated proline analogue (Flp) in place of hydroxyproline, show remarkable stability.[3,4] This strongly suggests that the stability of natural collagen is due to electronic effects rather than hydrogen bonding, as had been previously thought. In addition, recent reports by O'Hagan *et al.*[5,6] suggest that a fluorine suitably positioned in an amide, either α to the carbonyl or β to the N−H bond, stabilizes *anti* and *gauche* geometries, respectively. This phenomenon has been put to good effect by Seebach et al.[2] with the preparation of **2** and its incorporation (in place of **1**) into an oligo β-peptide to disrupt an inherent 3^{14} helix structure (Figure 1).

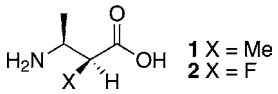


Figure 1. β-Amino acids.

While much is known about the influence of β amino acids[7] of type **1** (and hence **2**) on conformational preferences of β-peptides,[8−10] the alternative β² amino acids[7] have received less attention, partly due to difficulties in accessing

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(7) β3- and β2-amino acids possess an extra carbon between the C═O/α-C and α-C/N groups of a natural α-amino acid, respectively.

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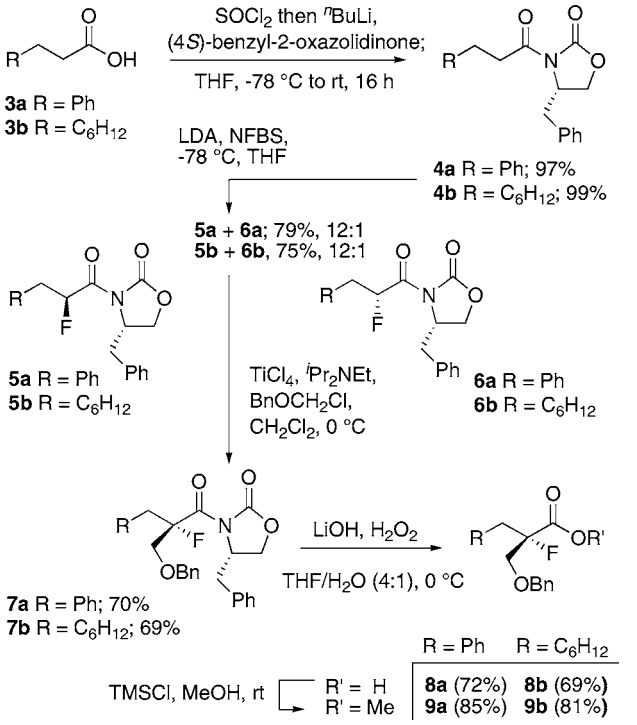
them.[11−14] However, the comparatively few reports available do reveal that oligomers derived from β^2 amino acids produce important and unusual structural motifs.[15,16] Given this, and Seebach's work on fluorinated β^3 amino acids, we now report the first synthesis of α-fluorinated β^2 amino acids for use in defining the conformation of β-peptides containing them.[17] Our methodology has been used to prepare **13a** and **13b** in high enantiomeric excess, with **13a** being converted to the *N*-protected free acids **14a** and **15a** for use in peptide synthesis.

The incorporation of fluorine at the 2 position of β^2 amino acids provided a significant synthetic challenge. Direct fluorination of β^2 amino acids was problematic due to the steric constraints involved in fluorinating an already crowded tertiary substituted C-2 center. Consequently, it was decided that fluorination of suitable 3-substituted propanoic acids (where the 3-substituent becomes the side chain of the amino acid), followed by introduction of a CH_2NH_2 group at the 2-position, would be the best approach. 3-Phenylpropanoic acid **3a** and 3-cyclohexylpropanoic acid **3b** were selected as starting materials for the development of this methodology to prepare β^2 amino acids with both "natural" (phenyl) and "unnatural" (CH_2-cyclohexyl) side chains (Schemes 1 and 2) and to access important examples for use in defining β-peptide structure.[17]

The phenyl 3-substituted propanoic acid **3a** (Scheme 1) was converted to the corresponding acid chloride, and this was reacted with the anion of (4*S*)-4-benzyl-2-oxazolidinone to give oxazolidinone **4a** in high yield. Subsequent fluorination by reaction with LDA and *N*-fluorobenzenesulfonimide (NFBS) gave **5a** in >90% de (determined by ^{1}H and ^{19}F NMR) and in a yield of 79%. Separation of **5a** from the small amount of diastereomer **6a** was not necessary given the next step involved formation and alkylation of a prochiral enolate intermediate.

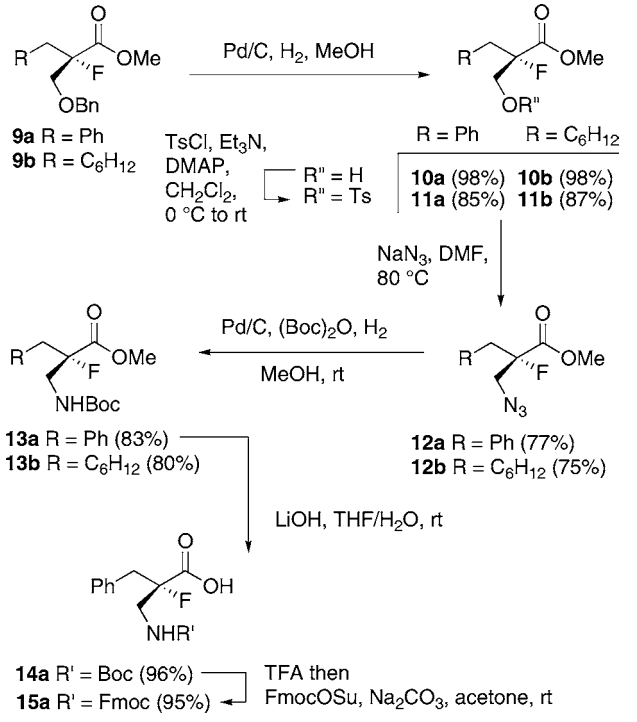
The direct addition of a CH_2NHZ group to nonfluorinated analogues of **5a** has been reported using $MeOCH_2NHZ$ as an alkylating reagent.[14] However, this approach was unsuccessful in our system, perhaps due to deactivation of the intermediate enolate by the electronegative fluorine atom. In support, other alkylating reagents including CH_3I and CH_3OCH_2I were also unreactive toward the anion derived from **5**, a result consistent with literature reports.[18] Hence, a new

Scheme 1. Establishing a Fluorinated Chiral Center



approach was necessary. To this end, alkylation of the sample of **5a** with $TiCl_4$, ^{i}Pr$_2$Et, and benzyl chloromethyl ether as the alkylating agent gave **7a** in 70% yield and >95% de (as determined by ^{1}H and ^{19}F NMR), where the benzyl-protected hydroxylmethyl group is suitable for subsequent conversion into the desired amine functionality (Scheme 2).

Scheme 2. Synthesis of α-Fluorinated β^2-Amino Acids



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Treatment of **7a** with LiOOH (generated in situ) removed the bulky oxazolidinone chiral auxiliary to give the free acid **8a**.[19] Esterification of this acid, using TMSCl in MeOH, then gave methyl ester **9a**. The benzyl group of **9a** was removed by hydrogenation (Scheme 2) to give the free alcohol **10a**, which was converted to tosylate **11a** in good yield on treatment with tosyl chloride, Et_3N, and DMAP. Reaction of the tosylate **11a** with NaN_3 gave the azide **12a**. Hydrogenation then gave the free amine, which was *N*-Boc-protected by in situ reaction with the $(Boc)_2O$ to give **13a,** an α-fluorinated β^2-analogue of phenylalanine. The cyclohexyl-substituted β^2 amino acid **13b** was similarly prepared in high enantiomeric excess (>95%) from **3b** (see Schemes 1 and 2).

Hydrolysis of the methyl ester of **13a** with LiOH gave the Boc-protected free acid **14a**. Treatment with TFA followed by *N*-(9*H*-fluoren-2-ylmethoxycarbonyloxy)succinimide (FmocOSu) gave the Fmoc-protected α-fluorinated β^2-analogue of phenylalanine **15a**, which is suitable for solid-phase synthesis. The incorporation of **15a** into a β-heptapeptide and its effect on molecular conformation is discussed elsewhere.[17]

In conclusion, we present the first synthesis of α-fluorinated β^2-amino acids suitable for incorporation into β-peptides by either solution or solid-phase chemistry. Ongoing work is directed at applying this methodology to a wide range of natural and unnaturally substituted α-fluorinated β^2-amino acids as well as investigating the structure and properties of β-peptides containing these units.[17]

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Supporting Information Available: Experimental details for all new compounds and copies of the ^1H and ^{13}C NMR spectra for key new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(19) Attempts to convert ozazolidinone protected **7a** directly into the desired amino acid were unsuccessful. As such, the large oxazolidinone group was replaced with a smaller methyl ester to minimize unfavorable steric interactions.