ORGANIC LETTERS

2008
Vol. 10, No. 5
885−887

Enantioselective Synthesis of α-Fluorinated β²-Amino Acids

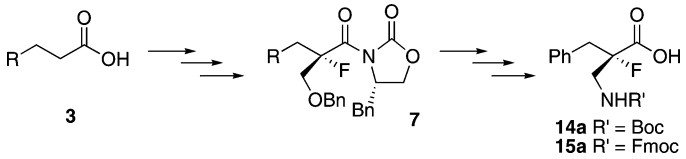
Michael K. Edmonds,[†] Florian H. M. Graichen,[‡] James Gardiner,[§] and Andrew D. Abell*,[||]

School of Applied Science, Christchurch Polytechnic Institute of Technology, Christchurch, New Zealand, Department of Chemistry, University of Canterbury, Christchurch, New Zealand, Eidgenössische Technische Hochschule, Zurich, Switzerland, and School of Chemistry and Physics, University of Adelaide, Australia

andrew.abell@adelaide.edu.au

Received December 19, 2007

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).

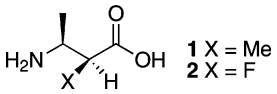


Figure 1. β-Amino acids.

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

[†] Christchurch Polytechnic Institute of Technology.
[‡] Postdoctoral Fellow with Prof. Andrew Abell, University of Canterbury.
[§] Postdoctoral fellow with Prof. Dr. Dieter Seebach, ETH Zürich, 2004−2007.
[||] University of Adelaide.

(1) Jäckel, C.; Koksch, B. *Eur. J. Org. Chem.* **2005**, 4483.
(2) Mathad, R. I.; Gessier, F.; Seebach, D.; Jaun, B. *Helv. Chim. Acta* **2005**, 266.
(3) Barth, D; Milbradt, A. G.; Renner, C.; Moroder, L. *ChemBioChem* **2004**, *5* 79.
(4) Hodges, J. A.; Raines, R. T. *J. Am. Chem. Soc.* **2003**, *125*, 9262.
(5) Briggs, R. S.; O'Hagan, D.; Howard, J. A. K.; Yufit, D. S. *J. Fluorine Chem.* **2003**, *119*, 9.
(6) Schüler, M.; O'Hagan, D.; Slawin, A. M. Z. *Chem. Commun.* **2005**, 4324.

(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.

(8) Seebach, D.; Matthews, J. L. *J. Chem. Soc., Chem. Commun.* **1997**, *21*, 2105.

10.1021/ol703045z CCC: $40.75
Published on Web 01/31/2008

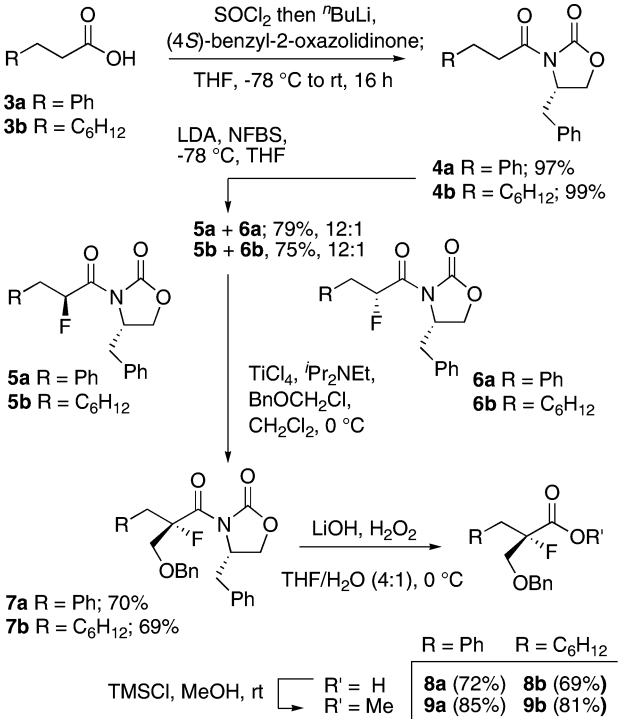
them.[11−14] However, the comparatively few reports available do reveal that oligomers derived from β^2 amino acids produce important and unusual structural motifs.[15,16] Given this, and Seebach's work on fluorinated β^3 amino acids, we now report the first synthesis of α-fluorinated β^2 amino acids 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.

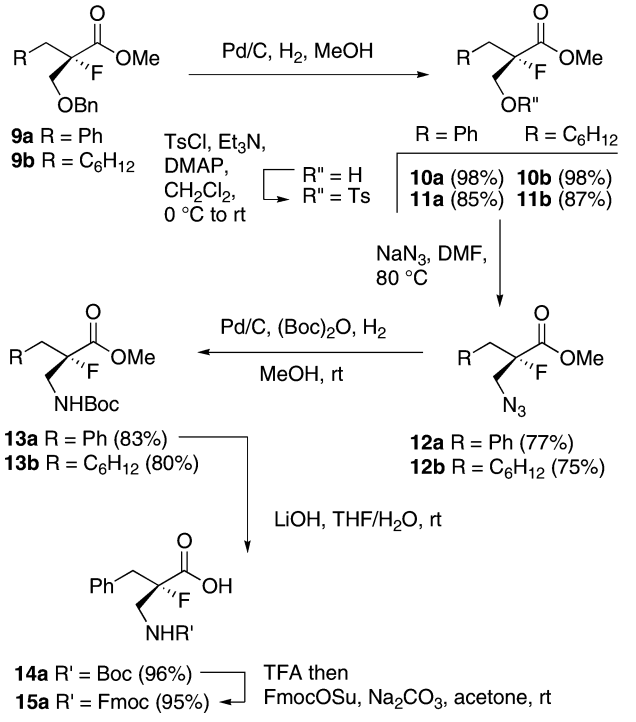
The direct addition of a CH_2NHZ group to nonfluorinated analogues of **5a** has been reported using $MeOCH_2NHZ$ as an alkylating reagent.[14] However, this approach was unsuccessful in our system, perhaps due to deactivation of the intermediate enolate by the electronegative fluorine atom. In support, 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 $TiCl_4$, $^iPr_2Et$, 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



(9) Seebach, D.; Beck, A. K.; Bierbaum, D. J. *Chem. Biodivers.* **2004**, *1*, 1111.
(10) Cheng, R. P.; Gellman, S. H.; DeGrado, W. F. *Chem. Rev.* **2001**, *101*, 3219.
(11) Moumne, R.; Lelais, G.; Seebach, D. *Biopolymers* **2004**, *76*, 206.
(12) Chi, Y. G.; Denise, B.; Guitot, K.; Rudler, H.; Lavielle, S.; Karoyan. P. *Eur. J. Org. Chem.* **2007**, *12*, 1912.
(13) Gellman, S. H. *J. Am. Chem. Soc.* **2006**, *128*, 6804.
(14) Seebach, D.; Schaeffer, L.; Gessier, F.; Bindschädler, P.; Jäger, C.; Josien, D.; Lelais, G.; Kopp, S.; Mahajan, Y. R.; Micuch, P.; Sebesta, R.; Schweizer, B. W. *Helv. Chim. Acta* **2003**, *86*, 1852.
(15) Gessier, F.; Noti, C.; Rueping, M.; Seebach, D. *Helv. Chim. Acta* **2003**, *86*, 1862.
(16) Takeuchi, Y.; Nabetani, M.; Takagi, K.; Hagi, T.; Koizumi, T. *J. Chem. Soc., Perkin Trans. 1* **1991**, 49.
(17) Mathad, R. I.; Jaun, B.; Flögel, O.; Löweneck, M.; Gardiner, J.; Seebach, D.; Graichen, F. H. M; Edmonds, M. K.; Abell, A.D. *Helv. Chim. Acta* **2007**, *90*, 2251.
(18) Less, S. L.; Handa, S.; Millburn, K.; Leadlay, P. F.; Dutton, C. J.; Staunton, J. *Tetrahedron Lett.* **1996**, *37*, 3515.

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]

Acknowledgment. This research was supported, in part, by the New Zealand Marsden Fund, the New Zealand Foundation for Research, Science and Technology, and the Australian Research Council. J.G. was supported by the New Zealand Foundation for Research, Science & Technology, Project No. SWSS0401.

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.

OL703045Z

(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.