Pergamon

Tetrahedron Letters 41 (2000) 5659–5662

TETRAHEDRON LETTERS

# A radical pathway to α-difluoromethylene containing prolines and α-aminoadipic acids†

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Received 31 March 2000; accepted 5 May 2000

**Abstract**

A new approach to the synthesis of α-difluoromethylene containing prolinates and α-aminoadipates has been developed. The method is based on intra- and intermolecular trapping reactions of in situ generated *N*-protected α-methyl difluoroalaninyl radicals. 

*Keywords:* fluoro substituted α-amino acids; α-methyl difluoroalaninyl radicals.

The design and synthesis of novel conformationally rigid amino acids as building blocks to obtain highly selective and potent peptide bioregulators is of current interest. The incorporation of α-alkylated amino acids into strategical positions of bioactive peptide ligands has proven to be a powerful tool for understanding ligand-receptor recognition and binding interactions.[1]

Among proteinogenic amino acids proline is known to be unique in its abilities to induce β-turns and initiate folding of the α-helix. Due to these structurally important properties, proline is often regarded as the primary contributor to the biological activity of several proteins, as well as having a key role in biological recognition processes.[2] Structurally modified prolines, especially containing multiple C–C bonds, have been described as potential enzyme inhibitors.[3] For example, racemic 4-methylene proline **1** is a natural product which has been isolated from seeds of loquat (*Eriobotrya japonica*).[4] It is of particular interest as an effective inhibitor of proline dehydrogenase.[5] α-Aminoadipic acid **2** is a constituent of a tripeptide δ-(L-α-aminoadipoyl)-L-cysteinyl-D-valine, which serves as a biosynthetic precursor of penicillins and cephalosporins.[6] Dieckmann cyclization of α-aminoadipate to give carbocyclic nucleoside precursors[7] has been recently described.

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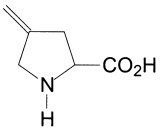
† Dedicated to Professor Horst Kessler on the occasion of his 60th birthday.

0040-4039/00/$ - see front matter 
PII: S0040-4039(00)00739-5



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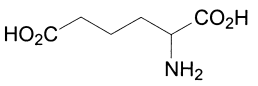

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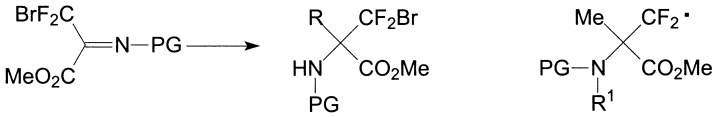
Partially fluorinated analogs of biologically active compounds often exhibit dramatic changes in their biological profiles.[8] In amino acid and peptide chemistry, particular interest has been attracted by β-fluorinated α-amino acids which can function as highly selective inhibitors of pyridoxal phosphate-dependent enzymes via a suicide-type mechanism.[9] Therefore, the development of effective methods for the synthesis of selectively fluorinated α-amino acids is of current interest.

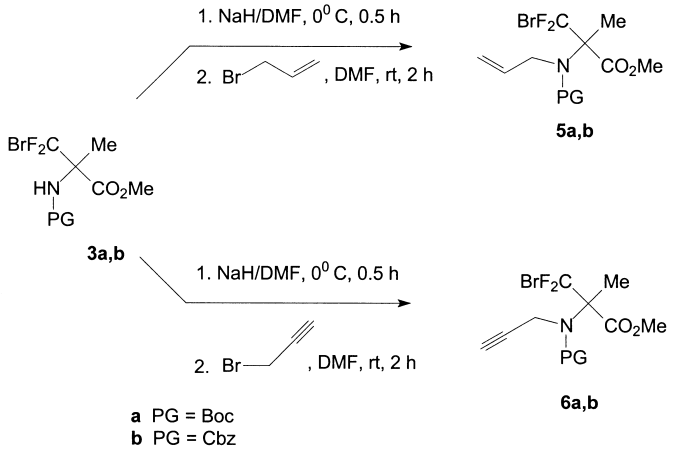
Recently we reported on a new efficient access to α-halogendifluoromethyl substituted α-amino acids based on the amidoalkylation of carbon nucleophiles with highly electrophilic imines of methyl 3-halo-3,3-difluoropyruvates.[10] This reaction offers the direct synthesis of the unknown α-bromodifluoromethyl α-amino acid derivatives **3** with orthogonal protective groups (Cbz, Boc/OMe). Now we disclose a further application of **3** to provide new α-difluoromethylene containing α-amino acids by intra- and intermolecular carbon–carbon bond formation of the in situ generated α-methyl difluoroalaninyl radicals **4** (Scheme 1).



**3** **4**

PG = Boc, Cbz; R = Alk, Ar; $R^1$ = H, Allyl, Propargyl

Scheme 1.



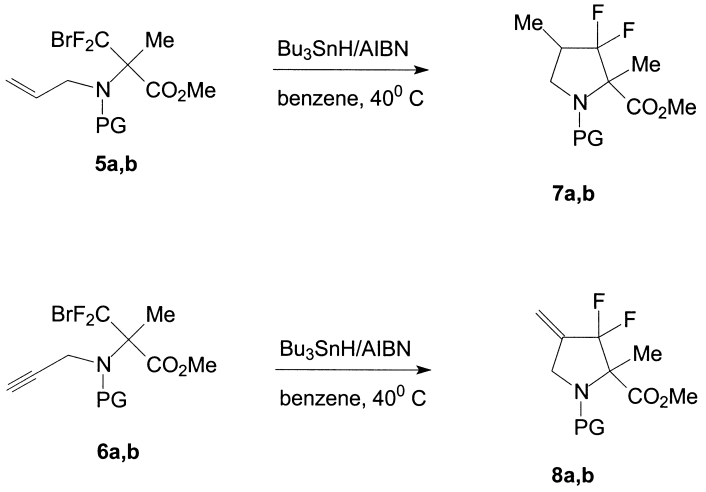
**3a,b** **5a,b** **6a,b**

**a** PG = Boc
**b** PG = Cbz

Scheme 2.

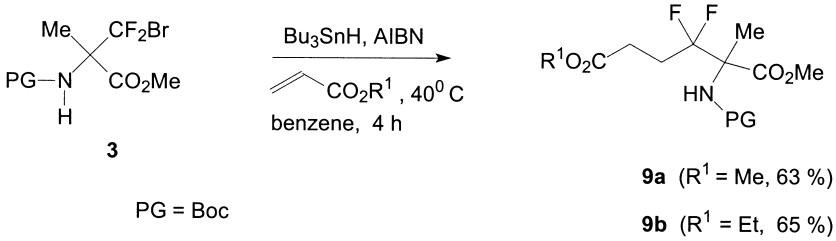
Thus, we were successful in obtaining novel proline derivatives **7** and **8** via a two-step procedure starting from **3**. The *N*-allylated and *N*-propargylated α-$BrCF_2$-alaninates **5**, **6** were obtained in 71–75% yield on deprotonation with NaH in DMF and subsequent alkylation with allyl- or propargyl bromide (Scheme 2).

The intramolecular free radical ring closure of **5**, **6** (Scheme 3) proceeded at 40°C in benzene within 3–4 h in the presence of 1.1 equivalents of $Bu_3SnH$ and 15 mol% of AIBN to give **7**, **8** [11] in acceptable yields (40–45%).




Scheme 3.

Following the same procedure, **3** underwent a radical intermolecular C–C bond formation with methyl and ethyl acrylates leading to the corresponding α-aminoadipic acid derivatives **9**[11] (Scheme 4). Satisfactory yields were obtained when four equivalents of acrylate were used for trapping the radical species **4**.




Scheme 4.

To the best of our knowledge, this is the first application of a radical α-methyl difluoroalanine synthon for the synthesis of β-fluorinated α-amino acids. Scope and limitation of the new method are under current investigation.

## Acknowledgements

This work was supported by the Deutsche Forschungsgemeinschaft (Innovationskolleg), Stiftung Volkswagenwerk, and the Fonds der Chemischen Industrie.

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11. Satisfactory spectroscopic data and elemental analyses were obtained for compounds **5**–**9**. *Selected data* for **5a**: $^1$H NMR ($CDCl_3$) $\delta$ 1.42 (s, 9H, $CMe_3$), 1.71 (s, 3H, Me), 3.71 (m, 1H, $NCH_2$), 3.78 (s, 3H, OMe), 4.25 (m, 1H, $NCH_2$), 5.25 (m, 2H, $CH_2$=CH-), 5.83 (m, 1H, $CH_2$=C*H*-); $^{19}$F NMR ($CDCl_3$) $\delta$ 25.86 (br.s, $CF_2Br$). For **8a**: $^1$H NMR ($CDCl_3$) $\delta$ 1.44 (s, 9H, $CMe_3$), 1.65 and 1.71 (two s, 3H, Me), 3.75 (s, 3H,OMe), 4.15 ($d_{AB}$, $J_{AB}$ 14.0 Hz, 1H, $NCH_2$), 4.28 ($d_{AB}$, $J_{AB}$ 14.0 Hz, 1H, $NCH_2$), 5.44 (s, 1H, =$CH_2$), 5.67 (s, 1H, =$CH_2$); $^{19}$F NMR ($CDCl_3$) $\delta$ –28.50 (m, $CF_2$). For **9b**: $^1$H NMR ($CDCl_3$) $\delta$ 1.25 (t, $^2J_{H-H}$ 7.5 Hz, 3H, $OCH_2$*Me*), 1.43 (s, 9H, $CMe_3$), 1.69 (s, 3H, Me), 2.48 (m, 4H, -$C_2H_4$-), 3.78 (s, 3H, OMe), 4.13 (q, $^2J_{H-H}$ 7.5 Hz, $OCH_2$Me), 5.19 (s, 1H, NH); $^{19}$F NMR ($CDCl_3$) $\delta$ –32.25 (m, $CF_2$).