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Synthesis of Novel, Orthogonally Protected Multifunctional Amino Acids

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Abstract

Two synthetic strategies for the generation of differentially protected, chiral tri-amino acids have been developed. The first strategy is based on the reductive amination of a serine-derived oxazolidine aldehyde with mono *N*-protected ethylenediamine. The second approach involves reductive alkylation of an asparagine-derived *N*-protected diaminopropionate with an *N*-protected glycinal. The newly generated secondary amine functionality is derivatised to furnish structurally diverse molecules.

Keywords: Amino acids and derivatives; peptide mimetics

The development of new synthetic methodologies for generation of enantiomerically pure unnatural amino acids continues to present a challenge for the synthetic organic chemist. The utility of these non-coded chiral amino acids as building blocks in the synthesis of novel entities with interesting biological activities, such as antibacterials, metal chelators, enzyme inhibitors, *etc* have made them attractive synthetic targets [1-8]. A number of methodologies for the synthesis of anomalous α-amino acids, both by modification of the available amino acids [9-12] and by the use of enantioselective, *de-novo* approaches [1,2,13,14] have been reported.

Recently, orthogonally protected multifunctional amino acids have found valuable applications in synthetic peptides and combinatorial chemistry [10,15-18]. For example, the α- and sidechain-amino functions of available diamino acids, such as lysine, ornithine and diaminopropionic acid have been exploited in combinatorial chemistry for the design of novel structures and the generation of molecular diversity [15-18]. Furthermore, a number of strategies based on orthogonally protected lysine for the construction of multi-release resins and peptide coded libraries of non-peptidic compounds have been devised [18].

We considered that the introduction of another amine functionality at a strategic position

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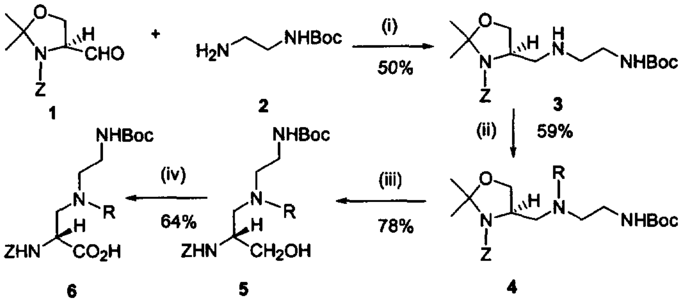
in the lysine side chain would furnish tri-amino acids. These unique amino acids were expected not only to mimic the lysine residue, but also offer opportunities for further diversification. Herein, we report two facile synthetic approaches to these novel tri-amino acids.

The serine-derived oxazolidine aldehyde (Garner's aldehyde) [19] is a popular and useful chiral synthon for the synthesis of differentially functionalized amino acids. A commonly used strategy is the modification of the aldehyde into the desired side chain followed by selective deprotection of the oxazolidine ring and oxidation of the terminal hydroxyl to the acid [20].

Thus in our first approach (**Scheme 1**), the oxazolidine aldehyde **1** was reductively aminated with *N*-(*tert*-butoxycarbonyl)ethylenediamine **2** using sodium cyanoborohydride as a reducing agent, giving compound **3** [21]. Derivatization of the secondary amine functionality of **3**, *e.g.* acylation with propionic acid in presence of *N,N'*-dicyclohexylcarbodiimide (DCCI) as an activating agent, gave the *N*-propionyl derivative **4**. However, acid catalysed removal of the acetonide protection of **4** led to partial deprotection of the Boc protecting group, which was readily re-introduced by reaction with $(Boc)_2O$ to afford the orthogonally protected tri-amino alcohol **5**. Finally, the hydroxyl functionality was oxidised to the free acid using Jones reagent giving the desired protected tri-amino acid **6** in 15% overall yield. The overall process inverts the chirality of the starting molecule, thus making D-amino acids available from naturally occurring L-serine.



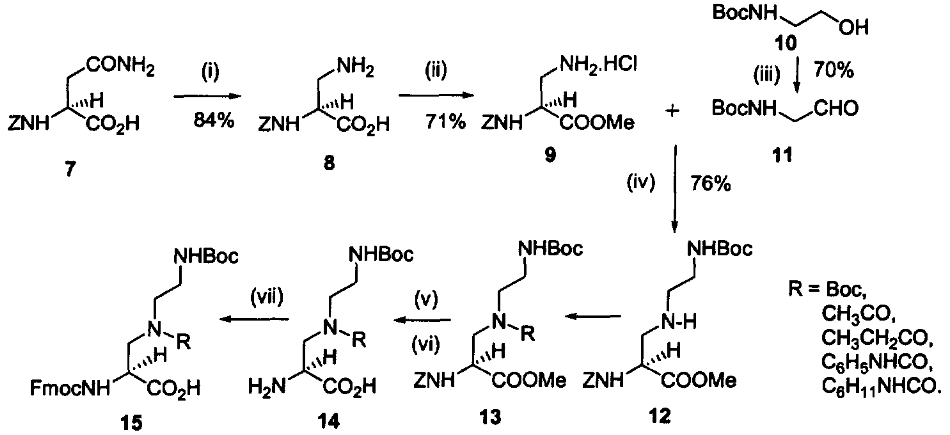
Z = benzyloxycarbonyl, Boc = *tert*-butoxycarbonyl, R = $COCH_2CH_3$

Scheme 1 Reagents and conditions : (i) $NaCNBH_3$, 1% AcOH/MeOH; (ii) propionic acid, DCCI; (iii) *(a)* MeOH, *p*-toluenesulphonic acid, *(b)* $(Boc)_2O$, $NaHCO_3$; (iv) Jones reagent.

The cumbersome reaction conditions involved in the synthesis of the aldehyde **1** and the low yielding step of mono-protection of ethylenediamine prompted us to develop a more concise route to these tri-amino acids. This approach began with commercially available N^{α}-benzyloxycarbonyl-L-asparagine **7** as outlined in **Scheme 2.**

The oxidative decarboxylation of compound **7** was carried out using the reported procedure that allows conversion of amides into amines under extremely mild conditions [22]. Thus, treatment of **7** with an excess of *bis*-(trifluoroacetoxy)phenyliodine, in the presence of pyridine, in DMF/water (1:1 *v/v*) at room temperature gave *(S)*-N^2-benzyloxycarbonyl-2,3-diaminopropionic acid **8**, which was followed by esterification with methanolic hydrochloric acid to yield methyl (*S*)-N^2-benzyloxycarbonyl-2,3-diaminopropionate hydrochloride **9**.

In parallel, *N*-(*tert*-butoxycarbonyl)glycinal **11** was prepared in two simple steps: 2-aminoethanol was protected by its reaction with $(Boc)_2O$ in acetonitrile at room temperature to give 2-(*tert*-butoxycarbonyl)aminoethanol **10** which was then smoothly oxidized to *N*-(*tert*-butoxycarbonyl)glycinal **11**[1] using *o*-iodoxybenzoic acid (IBX) [23]. The reagent IBX was prepared from the inexpensive and commercially available reagents, *o*-iodobenzoic acid and potassium bromate.



Scheme 2 *Reagents and conditions* : (i) *bis*(trifluroacetoxy)phenyliodine, pyridine, DMF/water; (ii) methanolic hydrochloric acid; (iii) *o*-iodoxybenzoic acid; (iv) $NaCNBH_3$, 1% AcOH/ MeOH; (v) NaOH, MeOH; (vi) H_2/10% Pd-C; (vii) FmocOSu, $NaHCO_3$, dioxane.

The final step in this synthetic strategy was the reductive alkylation of methyl (*S*)-N^2-benzyloxycarbonyl-2,3-diaminopropionate•HCl **9** with *N*-(*tert*-butoxycarbonyl)glycinal **11** in the presence of sodium cyanoborohydride, giving the orthogonally protected tri-amino acid **12** in an overall yield of 45% [2].

The secondary amine functionality can now be derivatised with an appropriate reagent, *e.g.* acetic anhydride, propionic acid–DCCI or isocyanates, giving a diverse range of molecules **13**. Saponification of the methyl ester to the free acid, and cleavage of the Z group by catalytic

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[1] *Preparation of N-(tert-butoxycarbonyl)glycinal* **11**: A solution of 2-(*tert*-butoxycarbonyl)aminoethanol **10** (0.805 g, 5.0 mmol) in DMSO (3 ml) was added to a stirred solution of *o*-iodoxybenzoic acid (2.79 g, 10.0 mmol) in DMSO (20 ml) and the stirring continued at room temperature overnight. The reaction mixture was then diluted with water (200 ml) and filtered. The filtrate was extracted with EtOAc (2 x 100 ml) and the pooled extracts were washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed on a silica column using EtOAc as eluant, to yield the desired aldehyde **11** (0.53 g, 70% yield). R_f (50% EtOAc/hexane) 0.38; *m/z* (ES-MS) 160 (M+H); δ_H (250 MHz, $CDCl_3$) 1.28 (9H, s, $(CH_3)_3$), 3.80 (2H, d, *J* 6.0 Hz, CH_2), 5.42 (1H, br s, NH), 9.44 (1H, s, CHO); δ_C (62.9 MHz, $CDCl_3$) 28.55 ($C(CH_3)_3$), 51.31 (CH_2), 80.04 ($C(CH_3)_3$), 156.35 (CONH), 198.89 (CHO).

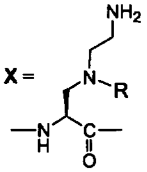
[2] *Preparation of methyl N^2-benzyloxycarbonyl-N^6-tert-butoxycarbonyl-2(S),6-diamino-4-azahexanoate* **12**: *N*-(*tert*-Butoxycarbonyl) glycinal **11** (0.29 g, 1.85 mmol) was dissolved in 1% acetic acid/methanol (12 ml) containing methyl *N*-benzyloxycarbonyl-2,3-diaminopropionate• HCl **9** (0.48 g, 1.68 mmol). Sodium cyanoborohydride (133 mg) was added portionwise over a period of 45 min. The reaction mixture was then stirred overnight. The mixture was cooled in an ice bath, and a saturated sodium bicarbonate solution (80 ml) was added with stirring followed by ethyl acetate (150 ml). The organic extract was washed with water, dried and concentrated *in vacuo*. Silica column chromatography (EtOAc) of the residue gave the pure compound **12** (0.50 g, 76% yield). R_f (EtOAc) 0.23; *m/z* (ES-MS) 396 (M+H); δ_H (250 MHz, $CDCl_3$) 1.37 (9H, s, $(CH_3)_3$), 2.65 (2H, m, 5-CH_2), 2.90 (2H, m, 3-CH_2), 3.10 (2H, m, 6-CH_2), 3.68 (3H, s, $COOCH_3$), 4.38 (1H, br m, α-H), 5.05 (2H, s, $PhCH_2$), 5.15 (1H, m, 6-NH), 6.06 (1H, d, *J* 8.0 Hz, 2-NH), 7.30 (5H, s, Ph); δ_C (62.9 MHz, $CDCl_3$) 28.73 ($(CH_3)_3$), 40.33 (CH_2), 49.07 (CH_2), 50.38 (CH_2), 52.76 ($COOCH_3$), 54.42 (CH), 67.27 (Ph-CH_2), 79.35 ($C(CH_3)_3$), 128.47, 128.81 & 136.60 (aromatic C), 156.59 (2 x CONH), 172.44 ($COOCH_3$).

hydrogenolysis gave the free amino acids **14**. The α-amino function was then protected by the Fmoc group affording the N^{α}-Fmoc amino acids **15** for use in the Fmoc/^{t}Bu-based solid phase peptide synthesis. To establish the potential of the synthesized α-amino acids, these were successfully incorporated into a hexapeptide sequence **16**, which were obtained in *ca* 80% purities when assessed by RP-HPLC.

H-Arg-Arg-Trp-Trp-**X**-Phe-NH$_2$

16

X =



R = H (M+H found 978.4);
CH_3CO (M+H found 1018.8);
CH_3CH_2CO (M+H found 1035.6).

In conclusion, we have accomplished the synthesis of fully protected chiral tri-amino acids *via* two synthetic approaches, utilizing nature's 'chiral pool' of α-amino acids. Both methodologies developed are generic in nature and can easily be adapted to introduce functionalities other than ε-amino in the side chain. The strategically placed secondary amine functionality in the molecule could be used for introducing molecular diversity within the context of combinatorial chemistry and in the construction of heterocyclic libraries. Moreover, as a lysine surrogate, these unique tri-amino acids can be incorporated into bioactive peptides giving sequences with modified structural and functional properties.

Acknowledgements

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