ABSTRACT
Abstract

The thesis entitled “Synthesis of mixed β-peptides, Imidazoles and Base Catalysed Condensation Reactions” is divided into two chapters. First chapter is dealt with the synthesis of (R) and (S)-β-homoserine, oxetane β-amino acid, enantiomeric C-linked carbo-β-amino acids from D- and L-arabinose and their use in the synthesis of peptides. Second chapter describes the synthesis of imidazoles and Knoevenagel condensations.

Chapter I: Synthesis of new β-amino acids and mixed β-peptides

This chapter is dealt with synthesis of (S)- and (R)-β-hSer (from L- and D-phenyl alanine), oxetane-β-amino acid and new enantiomeric C-linked carbo-β-amino acids and their use in the design and synthesis of mixed carbo-β-peptides.

Glycolipids and glycoproteins play a major role in inflammation, immune response, metastasis, fertilization and many other biomedically important processes. Majority of the natural proteins contain (oligo)-saccharide side chains and the saccharide residues are covalently linked to the protein backbone either N- (via asparagines) or O-glycosidically (via serine, threonine, or tyrosine). The incorporation of C-glycosyl amino acids in glycopeptides may serve in preparing chemically and metabolically resistant analogues that display inhibitor activity towards O- or N-glycosidases. β-Amino acids are part structures of several natural products and very important components. Due to the importance of such unusual amino acids and their nonavailability from ‘chiral pool’ work was undertaken towards their synthesis and development of non-natural peptides with new conformations.

Seebach et al.⁷a and Gellman et al.⁷b designed β-peptides with 14- and 12-helical structures by using aliphatic and constrained cyclic β-amino acids⁸ respectively. Even though sugar amino acids have been used for the peptide synthesis, synthesis of β-peptides having carbohydrates as side chains is not reported. For the synthesis of such peptides using C-linked carbo-β- and γ-amino acids (β/γ-Caa), with carbohydrate side chains, TBAF⁹ was used an efficient base in promoting the aza-Michael addition of benzylamine on sugar-based γ-alkoxy α,β-unsaturated ester¹⁰ A to result in B (Scheme 1). The continued interest in developing new bases for efficient aza-Michael addition of
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amine an α,β-unsaturated ester, revealed DBU as an efficient base to give B while reaction of A with BnNH2 gave B and C.

Scheme 1

D-Glucose → H₂CO → H₂CO → TBAF or DBU BnNH₂ → H₂CO → H₂CO → 68%

Our earlier work on the carbo-β-peptides,¹¹ prepared from (S)- and (R)- β-Caa alternately resulted in 10/12- and 12/10-mixed helices, wherein conformational constraints were observed with (S)-β-Caa. Based on the above observation, synthesis of a new set of monomers such as homoserines (S)-1 and (R)-2 (Figure 1) and small ring oxetane β-amino acids 3 were envisaged to relieve the constraints. It was assumed that, such side chains in the new β-amino acids would help in the formation of well-defined helices in the thus made peptides. Similarly, enantiomeric β-Caa 4 and 5 (Figure 1) also were prepared to study the synthesis with alternating chirality.

Figure 1

Synthesis of β-amino acids 1, 2 and 3

The requisite β-amino acids 1 and 2 were prepared from commercially available L- and D-phenyl alanine respectively. Accordingly, L-phenyl alanine 6 (Scheme 2) was treated with I₂ and NaBH₄ in dry THF to afford phenyl alaninol 7, which on reaction with (Boc)₂O in THF gave 8. Acetylation of 8 with Ac₂O and oxidative cleavage of phenyl ring in 9 afforded (S)-β-homoserine 1.
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**Scheme 2**

![Chemical structure](image)

a) NaBH₄, I₂, THF, 18 h, 0 °C-reflux; b) (Boc)₂O, Et₃N, THF, 4 h, rt; c) Ac₂O, Et₃N, CH₂Cl₂, DMAP, 30 min, rt; d) RuCl₃, NaI/O₃, CCl₄, CH₃CN : H₂O, 48 h, rt

Similar sequence of reactions on D-phenyl alanine 10 (Scheme 2) gave (R)-β-homoserine 2.

**Scheme 3**

![Chemical structure](image)

a) NaBH₄, I₂, THF, 18 h, 0 °C-reflux; b) (Boc)₂O, Et₃N, THF, 4 h, rt; c) Ac₂O, Et₃N, CH₂Cl₂, DMAP, 30 min, rt; d) RuCl₃, NaI/O₃, CCl₄, CH₃CN : H₂O, 48 h, rt

The oxetane-β-amino acid (3, β-Oaa) was prepared from D-mannitol. Accordingly, mannitol diacetone, prepared from D-mannitol, on oxidative cleavage gave (R)-glyceraldehyde 14 (Scheme 4). Reaction of 14 with allyl bromide and zinc dust¹² in THF at room temperature for 4 h afforded homoallylic alcohol 15, which on osmylation with catalytic amount of OsO₄ and NMO in acetone:water (4:1) at room temperature for 24 h afforded 16. Further, cleavage of 1,2-diol 16 using NaIO₄ in CH₂Cl₂ and catalytic sat. NaHCO₃ at 0 °C to room temperature for 5 h afforded aldehyde 17, which was used as such for the next reaction. Aldehyde 17 was treated with NaBH₄ in MeOH at 0 °C for 30 min to furnish alcohol 18. Primary alcohol 18 on tosylation with p-TsCl and Et₃N in CH₂Cl₂ and catalytic amount of DMAP at room temperature for 12 h afforded 19, which was reacted with NaH in DMF at room temperature for 12 h to give 20 in. Acetonide deprotection in compound 20, on reaction with 60% aq. AcOH at room temperature for 12 h afforded the diol 21.
Further, cleavage of 1,2-diol in 21 using NaIO₄ in MeOH-H₂O at room temperature for 1 h gave aldehyde 22, which was immediately treated with (methoxycarbonylmethylene)triphenyl phosphorane in MeOH at room temperature for 2 h to give 23. Reaction of Michael acceptor 23 with benzyl amine (2.5 equivalents) at room temperature gave oxetane-β-amino acid ester 24. Ester 24 was subjected to hydrogenation with 10% Pd/C in methanol under hydrogen atmosphere and the amine was treated with (Boc)₂O and Et₃N in THF to result in 3.

In our reported studies on the carbo-β-peptides, the epimeric β-Caas were utilized with ‘alternating chirality’. It was planned to synthesise enantiomeric β-Caas and use them in the peptide design with alternating chirality. In this direction, enantiomeric β-Caas were prepared from D- and L-arabinose. Accordingly, the new C-linked carbo-β-amino acid 4 was prepared from L-arabinose as shown in Scheme 5. Readily available L-(-)-arabinose was selectively silylated using TBDPSCI in DMF at 0 °C to room temperature for 18 h to afford 25, which was treated with dry acetone, CuSO₄ and catalytic amount of conc. H₂SO₄ at room temperature for 5 h to furnish 26. Compound 26 was subjected to alkylation using MeI and NaH in THF at 0 °C to room temperature for 12 h to give 27, which on desilylation using TBAF at 0 °C to room temperature for 14 h
gave 28. Oxidation of 28 with IBX in DMSO gave aldehyde 29, which on Witting reaction in C₆H₆ at reflux for 5 h gave 30. Reaction of 30 with benzyl amine (2.5 equivalents) at room temperature for instance gave a separable mixture of C-linked carbo-ß-amino acid esters 31 and 32. Ester 31 was subjected to hydrogenolysis with 10% Pd-C in methanol under hydrogen atmosphere to give the amine, which on treatment with (Boc)₂O and Et₃N in CH₂Cl₂ afforded 4.

In a similar way, as described for 4, readily available D- (+)-arabinose was selectively silylated using TBDPSCI in DMF to afford 33 (Scheme 6). Compound 33 was treated with dry acetone, CuSO₄ and H₂SO₄ (cat) to furnish 34, which was subjected to alkylation with MeI and NaH in THF to give 35. Deprotection of 35 using TBAF gave 36, which on oxidation with IBX in DMSO gave aldehyde 37; Witting olefination on 37 in C₆H₆ at reflux temperature for 5 h gave 38. Reaction of 38 with benzyl amine gave a separable mixture of Caas 39 and 40. Compound 39 was subjected hydrogenation with 10% Pd/C and resultant amine was treated with (Boc)₂O and Et₃N in CH₂Cl₂ to result in 5.