Synopsis

The thesis entitled “Synthesis of new β-amino acids, β-peptides, α/β-peptides, γ-boronated unsaturated amino esters and their derivatives” is divided into three chapters.

Chapter I: Synthesis of β^{2,3}-Disubstituted β-Amino Acids and their Peptides

Peptidomimetic drug design\(^1\) has emerged as an important tool for both peptide chemists and medicinal chemists. Protein folding processes that spontaneously select the most appropriate combination of backbone torsions to reach a unique and functionally active three-dimensional structure continue to puzzle the scientific community. To create such type of systems ring closing olefin metathesis has played a crucial role for the preparation of a variety of cyclic amino acids, peptides, useful in medicinal chemistry,\(^2\) ranging from simple di-,\(^3\) tri-\(^4\) and tetrapeptides\(^5\) to macrocycles.\(^6\)

β-Amino acids, part structures of several natural products and their importance, non-availability prompted the development of new and efficient strategies\(^7\) for their synthesis, enroute to peptidomimetics. Seebach \textit{et al}.\(^8\) and Gellman \textit{et al}.\(^9\) were the first to report β-peptides with novel helical structures, followed by subsequent reports\(^10\) on a variety of novel secondary structures in β-peptides with different designs.\(^11\)

Section A: Preparation of New β^{2,3}-Amino Acids and β-Dipeptides as Synthetic Precursors for Ring Closing Metathesis

This section describes the preparation of new family of β-amino esters and β-dipeptides containing allyl groups on the peptide backbone at the C\(_\alpha\), N(carbamate), positions for their conversion with the use of a ruthenium carbene catalyst through ring-closing metathesis into cyclic, medium-sized β-dipeptides and macrocyclic tetrapeptides. β-Amino esters \(4, 6\) and \(10\) were prepared from known\(^12\) α,β-unsaturated ester \(1\) and dipeptides \(12, 14, 16, 17, 19\) and \(21\) were prepared starting from β-amino acids \(3, 4\) and \(10\) containing a (D)-Xylofuranoside side chain at the C\(_\beta\) position and allyl group at C\(_\alpha\) position to understand the influence of the allylic moiety on the β-dipeptide and α/β-peptide backbone.

The DBU-mediated aza-Michael addition of benzylamine on ester \(1\) gave \(2\) (59%, 94\%\(de\)), which upon catalytic debenylation with 10\% Pd/C in methanol, followed by subsequent treatment with (Boc)\(_2\)O afforded the C-linked carbo-β-amino acid ester (β-Caa) \(3^{13}\) in 74\% yield (Scheme 1). Alkylation of ester \(3\) at the C\(_\alpha\)-position with allyl bromide in
the presence of in situ generated LDA led to the stereoselective formation of 4 in moderate yield (45%). Finally, treatment of amine 4 with CF$_3$COOH (TFA), followed by functionalization of 5 with acryloyl chloride and Et$_3$N gave acrylamide derivative 6 in 70% yield.

![Scheme 1](image)

**Scheme 1. Reagents and conditions:** (a) benzylamine, DBU, THF, rt, 8 h, 59%; (b) (i) H$_2$, 10% Pd/C, MeOH, 8 h; (ii) Et$_3$N, (Boc)$_2$O, CH$_2$Cl$_2$, 0 °C-rt, 2 h, 74% (over two steps); (c) (i) n-BuLi, iPr$_2$NH, THF, -78 °C-0 °C, 30 min; (ii) allyl bromide, -78 °C, 2 h, 45%; (d) CF$_3$COOH, CH$_2$Cl$_2$, 0 °C-rt, 1 h, quantitative; (e) Et$_3$N, acryloyl chloride, CH$_2$Cl$_2$, 70% (over two steps); (f) LiAlH$_4$, THF, 0 °C-rt, 1 h, 80%; (g) NaH, THF, 0 °C-rt, 4 h, 78%.

For the confirmation of stereochemistry at Cα position in 4, it was subjected to reduction using LiAlH$_4$ to give the corresponding alcohol 7 (80%), which on reaction with NaH in THF afforded 8 in 78% yield. Similarly, ester 1 was on aza-Michael addition with allylamine gave N-allylated β-Caa 9 in 78% yield. Further, protection of 9 with (Boc)$_2$O afforded the ester 10 in 80% yield (Scheme 2).

![Scheme 2](image)

**Scheme 2. Reagents and conditions:** (a) allylamine, DBU, THF, rt, 8 h, 78%; (b) (Boc)$_2$O, Et$_3$N, CH$_2$Cl$_2$, 0 °C-rt, 8 h, 80%.

These new amino esters 4, 6 and 10 were modified and subjected for their Ring Closing Metathesis$^{14}$ to afford novel cyclic motifs.$^{15}$
Having successfully converted the new β-amino acids 4, 6 and 10 into cyclic systems by RCM, the study was then extended to use of the residues 3, 4 and 10 for the synthesis of diverse peptides in different designs. Accordingly, hydrolysis of the ester 10 on treatment with LiOH in a THF/MeOH/H₂O (3:1:1 vol. ratio) gave the acid 11 in 93% yield. The peptidic coupling of 11 with salt 5 in CH₂Cl₂ in the presence of EDCI, HOBt and DIPEA at room temperature, according to known protocol,¹⁶ furnished 12 in 60% yield. Hydrolysis of the ester 4 on treatment with LiOH in a THF/MeOH/H₂O mixture (3:1:1 vol. ratio) gave the acid 13, which on coupling with the salt 5 in the presence of EDCI, HOBt

Scheme 3. Reagents and conditions: (a) LiOH, THF:MeOH:H₂O (3:1:1), 0 °C-rt, 1 h; (b) HOBt, EDCI, DIPEA, CH₂Cl₂, 0 °C-rt, 8 h; (c) CF₃COOH, CH₂Cl₂, 0 °C-rt, 2 h.
and DIPEA in CH₂Cl₂ afforded the corresponding β-dipeptide 14 in 58% yield. Boc-deprotection of ester 3 with CF₃COOH in CH₂Cl₂ gave its salt 15. Peptidic coupling of acids 11 and 13 independently with amine salt 15 afforded the respective β-dipeptides 16 and 17 in 76% and 60% yields (Scheme 3).

Peptide 12 on RCM reaction underwent facile cyclization to give 12-membered ring, while 14 resisted to undergo RCM reaction. Peptides 16 and 17 were further transformed and subjected to RCM reaction to afford 13-membered ring and head to tail double cross metathesis products respectively.¹⁷

The results on the RCM reaction of 17 prompted us to undertake further studies on the design of new dipeptides, where in, the bulky carbohydrate side chain was removed or replaced. Accordingly, in order to get insight into the different reactivities of the above dipeptides, the dipeptides 19 and 21 were prepared, wherein, one of the monomers in 19 has a less bulky (methyl) substituent or no substituent in the peptide 21. These dipeptide derived dienes are analogues of 17 with less sterically demanding substituents on one of the amino acid fragments, were prepared specifically for a better understanding of the side chain effect on RCM in peptides.

Accordingly, the acid 13 was subjected to coupling independently with the salts 18 and 20 to give dipeptides 19 and 21 in 70% and 67% yields respectively (Scheme 4). The

\[
\text{Scheme 4. Reagents and conditions: (a) HOBt, EDCI, DIPEA, CH₂Cl₂, 0 °C-rt, 8 h.}
\]
derivatives of dipeptides 19 and 21 were subjected to RCM reaction to give head-to-tail double cross metathesis products. These results have shown that the reactivity is not driven by the steric bulk at the β-position of the amino ester end, but is likely due to intra- and/or intermolecular H-bonding interactions that drive the metathesis reaction towards the formation of large rings.

**Section B: Synthesis of α/β²⁻³-Peptides from β²⁻³-Amino Acid and L-Ala**

This section describes the design and synthesis of α/β-peptides using the β²⁻³-disubstituted β-Caa 4 to evaluate the impact of the side chain on the helix and turn formation and their stability. Earlier, we reported α/β-peptides with different conformations using C-linked carbo β³⁻Caa and L-Ala, resulting in helices and turns.

Accordingly, coupling of acid 22 with the amine salt 5 in the presence of EDCI, HOBT and DIPEA in CH₂Cl₂ at 0 ºC to room temperature for 6 h furnished the dipeptide 23 in 80% yield. Treatment of dipeptide 23 with LiOH in a THF/MeOH/H₂O gave acid 23a, while 23 on reaction with CF₃COOH in CH₂Cl₂ gave corresponding salt 23b. Coupling
Synopsis

(EDCI, HOBT and DIPEA) of acid 23a with salt 24 in CH₂Cl₂ furnished the tripeptide 25 in 74% yield, which on reaction with CF₃COOH in CH₂Cl₂ gave amine salt 25a.

Known dipeptide 26 on base (LiOH) hydrolysis gave the acid 26a, while acid (CF₃COOH) mediated reaction of 26 in CH₂Cl₂ gave the amine salt 26b. Coupling of 26a with amine salt 25a gave pentapeptide 27 in 63% yield (Scheme 6). Similarly, acid 23a on coupling with the salt 23b in the presence of HATU and DIPEA in CH₂Cl₂ at 0 °C to room temperature for 8 h afforded tetrapeptide 28 in 69% yield (Scheme 6).

\[
\text{Scheme 6. Reagents and conditions: (a) LiOH, THF:MeOH:H₂O (3:1:1), 0 °C-rt, 1 h; (b) CF₃COOH, CH₂Cl₂, 0 °C-rt, 2 h; (c) HATU, DIPEA, CH₂Cl₂, 0 °C-rt, 8 h; (d) HATU, DIPEA, CH₂Cl₂, 0 °C-rt, 8 h.}
\]

Similarly, coupling of acid 26a with amine salt 23b gave tetrapeptide 29 (72%), which on reaction with CF₃COOH in CH₂Cl₂ gave amine salt 29a. Likewise, coupling of
acid 23a with amine salt 26b afforded tetrapeptide 30 (70%), which on reaction with CF₃COOH in CH₂Cl₂ for 1 h gave 30a. Coupling of acid 23a independently with the amine salts 29a and 30a gave hexapeptides 31 and 32 in 62% and 64% yields respectively (Scheme 7).

Scheme 7. Reagents and conditions: (a) HATU, DIPEA, CH₂Cl₂, 0 °C-rt, 8 h; (b) CF₃COOH, CH₂Cl₂, 0 °C-rt, 2 h.
The structures of all the above peptides (tri-, tetra-, penta- and hexapeptides) were analyzed by NMR (in CDCl₃), MD (Molecular Dynamics) and CD studies. These hybrid peptides showed the presence of 11/9-helices with rather weak 11-mr H-bond. Thus, it was concluded that the Cα substitution (allyl group) and carbohydrate side chain are spatially closer (Figure 1) to each other, which, is responsible for the destabilization of the realized folding, in this new class of α/β²⁻³-peptides.

Figure 1. Newman structures of peptides 27-32; in furanoside ring acetonide and OMe were removed for clarity

Chapter II: Synthesis of New β-Amino Acids and Peptides

Section A: Synthesis and Structural Studies of α/β-Peptides Derived from Fused Furano-pyran β-Amino Acid and L-Ala/D-Ala

The α/β-peptides reported from acyclic (S)-β-Caa/L-Ala¹⁸a and (S,S)-APyC/D-Ala¹⁸e resulted in 9/11-mixed helices. The APyC monomer in its constituent peptides has shown the presence of an electrostatic interaction by 5-membered H-bonding between
pyran ring ‘O’ and NH of the next residue. Further, in the preceding chapter, the Cα 
alkylation has shown the impact on helix formation and stability. Thus, based on the above 
observations, new fused furano-pyran β-amino acids 39 and 41 (Scheme 8) were designed 
and synthesized. The new fused furano-pyran β-amino acids, Boc-(S,R)-fAPyC-OMe (39) 
and Boc-(R,R)-fAPyC-OMe (41), were prepared from the known alcohol 33,19 derived 
from D-(+)-glucose.

Accordingly, reaction of 33 with methyl 2-bromomethylacrylate20 in the presence of 
NaH in THF at 0 °C to room temperature for 1 h afforded bis-olefin 34 in 90% yield. 
Although RCM14 of 34 with Grubbs 1st generation catalyst in CH2Cl2 (room temperature) 
and in toluene (reflux) failed to give 35, a facile RCM reaction on 34 with Grubbs 2nd 
generation catalyst in toluene at reflux for 18 h furnished the ester 35 in 80% yield. Aza-
Michael addition of 35 with benzylamine in THF under N2 atmosphere at 40 °C gave a 
mixture of esters 36 (56%) and 37 (28%) in 2:1 ratio. Both the esters (36 and 37) were 
independently subjected to debenzylation with 10% Pd/C in MeOH, followed by 
subsequent treatment of the corresponding amines 38 and 40 with (Boc)2O and Et3N in 
CH2Cl2 afforded 39 (74%) and 41 (72%) respectively (Scheme 8).

\[ \text{Scheme 8. Reagents and conditions: (a) NaH, methyl-2-(bromomethyl)acrylate, THF, 0 °C-rt, 1 h; (b) G-II generation catalyst, toluene, reflux, 18 h; (c) BnNH2, THF, 40 °C, 6 h; (d) Pd/C-H2, MeOH, 8 h; (e) (Boc)2O, Et3N, CH2Cl2, 6 h.} \]
The major β-amino acid 39 was converted into α/β-peptides. Accordingly, reaction of 39 with CF$_3$COOH in CH$_2$Cl$_2$ for 1 h gave the corresponding amine salt 39a. Coupling of acid 40 with salt 39a in the presence of EDCI, HOBT and DIPEA in CH$_2$Cl$_2$ at 0 ºC to room temperature for 8 h furnished dipeptide 41 in 85% yield, which on base hydrolysis with LiOH gave acid 41a. Coupling (EDCI, HOBT and DIPEA) of acid 41a with 40a in CH$_2$Cl$_2$ furnished tripeptide 42 (76%), which, on acid treatment with CF$_3$COOH gave salt 42a (Scheme 9).

**Scheme 9. Reagents and conditions:** (a) CF$_3$COOH, dry CH$_2$Cl$_2$, 0 ºC-rt, 2 h; (b) HOBT, EDCI, DIPEA, CH$_2$Cl$_2$, 0 ºC-rt, 8 h; (c) LiOH, THF:MeOH:H$_2$O (3:1:1), 0 ºC-rt, 1 h.

Coupling of acid 41a in CH$_2$Cl$_2$ with the salt 42a furnished pentapeptide 43 (68%). Treatment of pentapeptide 43 with CF$_3$COOH in CH$_2$Cl$_2$ gave salt 43a, which, on coupling

**Scheme 10. Reagents and conditions:** (a) HOBT, EDCI, DIPEA, CH$_2$Cl$_2$, 0 ºC-rt, 8 h; (a) CF$_3$COOH, dry CH$_2$Cl$_2$, 0 ºC-rt, 2 h.
with dimeric acid 41a in the presence of EDCI, HOBT and DIPEA in CH₂Cl₂, afforded heptapeptide 44 in 59% yield (Scheme 10).

Likewise, treatment of dipeptide 41 with CF₃COOH in CH₂Cl₂ afforded salt 41b. Coupling of acid 41a with salt 41b afforded tetrapeptide 45 in 70% yield, which, on reaction with CF₃COOH, furnished amine salt 45a. Further, coupling of acid 41a with salt 45a afforded hexapeptide 46 in 65% yield (Scheme 11).

The conformational analysis of above peptides (tri-, tetra-, penta-, hexa-, and heptamers) inferred that the α/β-peptides derived from the newly designed fused furanopyran β-amino acid (39) and L-Ala resulted in the formation of a left-handed 9/11-helix, with rather weak 9-mr H-bonds. The peptides (43 and 44) with an “α-β-α” sequence at the C-terminus revealed a 12-mr turn at the C-terminus. This turn was akin to those in α/β-peptides (45 and 46) with “β-α-β” sequence at the C-terminus, for which 7-mr and 13-mr H-bonds stabilized the structure. In both cases, the 9/11-helix was associated with a 7-mr (γ-turn) H-bond at the N-terminus, stabilizing the helix.²¹
The synthesis of peptides 48-50 from Boc-(S,R)-fAPyC-OMe (39) and D-Alanine (Scheme 12), was achieved by adopting the similar protocols described above. Accordingly, acid 47 on coupling (EDCI, HOBt and DIPEA) with salt 39a in CH₂Cl₂ at 0 °C to room temperature for 8 h furnished the dipeptide 48 (79%), which on base (LiOH) hydrolysis gave the acid 48a. Coupling of acid 48a with salt 47a in the presence of EDCI, HOBT and DIPEA in CH₂Cl₂ furnished the tripeptide 49 (66%). Reaction of 49 with CF₃COOH in CH₂Cl₂ gave the salt 49a, which on coupling with acid 48a in CH₂Cl₂ gave the pentapeptide 50 in 60% yield.

Scheme 12. Reagents and conditions: (a) HOBt, EDCI, DIPEA, CH₂Cl₂, 0 °C-rt, 8 h; (b) LiOH, THF:MeOH:H₂O (3:1:1), 0 °C-rt, 1 h; (c) CF₃COOH, CH₂Cl₂, 0 °C-rt, 2 h.

Exclusive NMR studies on above synthesized peptides (di-, tri- and pentamers) revealed that these peptides are showing aggregation properties, which was supported by TEM and SEM images (Figure 2).

Figure 2. A and B are TEM images for 50 and C is the SEM image for 50
**Section B: Synthesis of β-Peptides from Fused Furano-pyran β-Amino Acid and β-hGly**

Having observed interesting results in α/β-peptides derived from the new constrained β-amino acid 39, the study was then extended to the β-peptides from 39 and β-hGly. Accordingly, coupling of acid 51 with the salt 39a in the presence of EDCI, HOBT and DIPEA in CH$_2$Cl$_2$ at room temperature for 6 h furnished the dipeptide 52 in 78% yield. Hydrolysis of 52 with LiOH at 0 ºC afforded the acid 52a (95%), while 52 on reaction with TFA in CH$_2$Cl$_2$ gave the salt 52b. Acid 52a on coupling (EDCI, HOBT, DIPEA) with amine 52b in CH$_2$Cl$_2$ for 6 h furnished the tetrapeptide 53 (69%), which on reaction with CF$_3$COOH in CH$_2$Cl$_2$ for 1 h gave salt 53a. Coupling of acid 52a with 53a under the above reaction conditions afforded the hexapeptide 54 in 58% yield (Scheme 13).

**Scheme 13. Reagents and conditions:** (a) HOBT, EDCI, DIPEA, CH$_2$Cl$_2$, 0 °C-rt, 6 h; (b) LiOH, THF-MeOH:H$_2$O (3:1:1), 0 °C-rt, 1 h; (c) CF$_3$COOH, CH$_2$Cl$_2$, 0 °C-rt, 2 h.
Similarly, ester 39 was subjected to hydrolysis with LiOH at 0 °C to afford the acid 39b (96%), which on coupling with the salt 51a in the presence of EDCI, HOBt and DIPEA in CH$_2$Cl$_2$ at room temperature for 6 h furnished the dipeptide 55 in 79% yield.

Base (LiOH) hydrolysis of 55 gave the acid 55a, while, 55 on exposure to CF$_3$COOH in CH$_2$Cl$_2$ for 1 h gave 55b. Acid 55a was then coupled (EDCI, HOBt, DIPEA) with amine 55b in CH$_2$Cl$_2$ for 6 h to furnish the tetrapeptide 56 in 67% yield, which on reaction with

**Scheme 14. Reagents and conditions:** (a) HOBt, EDCI, DIPEA, CH$_2$Cl$_2$, 0 °C-rt, 6 h; (b) LiOH, THF:MeOH:H$_2$O (3:1:1), 0 °C-rt, 1 h; (c) CF$_3$COOH, CH$_2$Cl$_2$, 0 °C-rt, 2 h.
CF₃COOH in CH₂Cl₂ for 1 h gave salt 56a. Coupling of the acid 55a with salt 56a under the above reaction conditions afforded the hexapeptide 57 in 56% yield (Scheme 14).

Extensive NMR studies on the above β-peptides (52-57) revealed the presence of unprecedented left-handed 10/12- and 12/10-helices with additional hydrogen bonding when compared with the β-peptides derived from β³-Caa and β-hGly units.¹³

Chapter III: Regio- and Stereocontrolled access to γ-Boronated Unsaturated Amino Esters and Derivatives from (Z)-Alkenyl 1,2-Bis(boronates)

Alkenyl boronates are versatile synthons for carrying out diverse coupling reactions. Even though these systems are well studied, a regioselctive Petasis reaction of the same has not been studied. The present work undertakes the synthesis of four different alkenyl bis boronates and their use in regioselective Petasis reaction to give diverse amino acid derivatives. The thus prepared amino acid derivative were then subjected to Suzuki coupling for the creation of diversily substituted olefinic amino acid systems.

(Z)-Alkenyl 1,2-bis boronates (58) were prepared by known protocol²² from the corresponding alkynes. 1-Hexyne, propargyl trimethyl silane, phenyl acetylene and 3-hexyne using tetrakis triphenyl phosphine platinum as catalyst and bis pinacol boronate in DMF and toluene at 80 °C for 18 h gave their respective bis boronates in good yields. Bis boronates 58 were subjected for regioselctive Petasis reaction using different amines and glyoxylic acid in HFIP (1,1,1,3,3,3-hexafluoropropan-2-ol) at room temperature for 8 h to give the corresponding γ-boronated unsaturated amino acids, which were directly subjected for esterification with CH₂N₂ for 2 h to afford the corresponding esters 59a-i, with diversity in 50-69% yield (over two steps) (Scheme 15).²³

![Scheme 15](attachment:image.png)

58a R = n-Bu, R¹ = H
58b R = CH₃TMS, R¹ = H
58c R = Ph, R¹ = H
58d R = Et, R¹ = Et

Scheme 15. A borono-Mannich route to γ-boronated unsaturated amino esters 59
Thus obtained esters 59 were subjected to Suzuki coupling\textsuperscript{24} with different aromatic halides in the presence of Pd catalyst and potassium phosphate tribasic monohydrate in THF/H\textsubscript{2}O at reflux to give the corresponding olefinic amino esters \textbf{60a-j} in 69-89\% yield (Scheme 16).\textsuperscript{23}

\begin{scheme}
\centering
\includegraphics[width=\textwidth]{scheme16.png}
\caption{Suzuki coupling with \textgreek{g}-Boryl Amino Esters}
\end{scheme}
Further, Petasis product 59a engaged in different synthetic transformations. Accordingly, γ-borylated amino ester 59a on oxidation with sodium perborate in THF:H2O afforded γ-oxo-α-aminoester 61 in 74% yield (Scheme 17). Similarly, 59a on treatment with NaN3 in the presence of copper catalyst (CuSO4) in MeOH gave alkenyl azide 62 in 71% yield. Further, the alkenyl azide 62 on reaction with phenyl acetylene and sodium ascorbate under ‘click’ reaction conditions resulted a trizole derivative 63 in 36% yield (over two steps) (Scheme 17).

![Scheme 17. Synthetic transformations of 59a](image)

In conclusion, it is pertinent to mention that a regioselective Petasis reaction has been for the first time performed on bis-boronates to give amino esters. The esters were then subjected to Suzuki coupling with the second boronate moiety of bis-boronate to give the complex products. This protocol provides an opportunity for the conversion of bis-boronates into not only Petasis/Suzuki products, but to diverse systems that can undergo reactions with bis-boronates. The utilization of the products of the present protocol is in progress.

REFERENCES:


