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HBTU Mediated 1-Hydroxybenzotriazole (HOBt) Conjugate Addition: Synthesis and Stereochemical Analysis of β-Benzotriazole *N*-oxide Substituted γ-Amino acids and Hybrid Peptides

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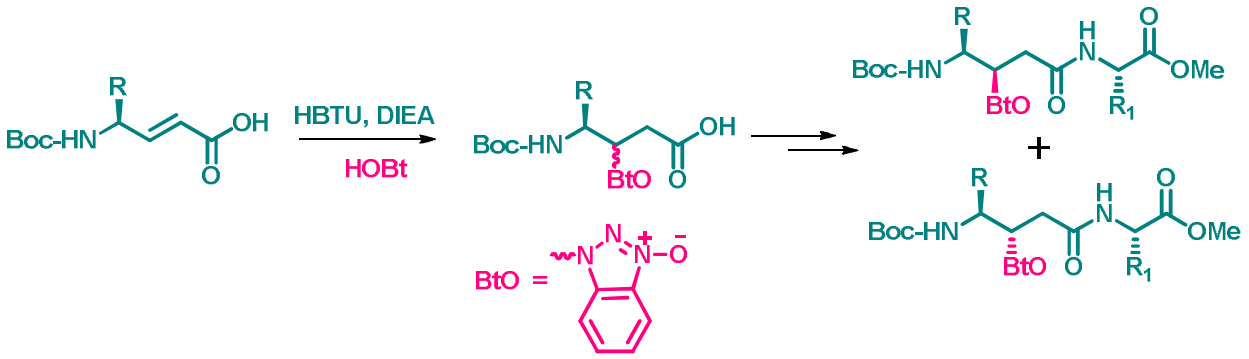
TOC



Synthesis and conformational analysis of β-benzotriazole *N*-oxide (β-BtO) substituted γ-amino acids through direct conjugate addition of HOBt to *E*-vinylogous γ-amino acids are reported.

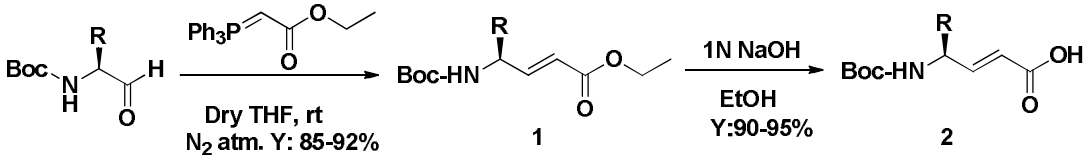
Abstract: HBTU is a standard coupling agent commonly used for the activation of free carboxylic acids during the solution and solid phase peptide synthesis. 1-Hydroxybezotriazole (HOBt) plays a significant role in reducing the racemization during peptide synthesis; hence it is regularly used as a coupling additive. Here, we are reporting the mild and facile conjugate addition of HOBt to *E*-vinylogous γ-amino acids mediated by the HBTU. The reaction is moderately diastereoselective and novel β-benzotriazole *N*-oxide (β-BtO) substituted γ-amino acids were isolated in moderate to good yields. The single crystal analysis of methyl esters of major (*anti*) and minor (*syn*) conjugate addition products infer that the formation of exclusively *N*-alkylated benzotriazole *N*-oxides instead of *O*-alkylation of HOBt. In addition, we showed the utilization of β-BtO substituted γ-amino acids in peptides synthesis and studied their conformations in single crystals.

Introduction

Nucleophilic conjugate addition is one of the most widely explored reactions in synthetic organic chemistry. The conjugate addition offers direct access to a variety of organic compounds through the C-X (X = C, N, O, S etc) bond formation.[1] The regiochemistry of 1, 2 or 1, 4- nucleophilic addition to α, β-unsaturated carbonyl compounds is generally controlled by the relative electrophilicity of the carbonyl group, steric interactions of both electrophile and nucleophile as well as hard and soft nature of the nucleophiles. Besides the organocopper reagents,[2] various other transition metals catalyzed selective conjugate addition reactions have been well documented.[3] In comparison to the α, β-unsaturated aldehydes, ketones, esters and amides, the unsaturated carboxylic acids have not been well explored in the conjugate addition reactions. However, the literature survey reveals that strong alkylating agents such as organolithium[4] and organomagnesium reagents,[5] copper reagents,[6] rhodium(I) catalyzed arylboronic acids,[7] and gold(III) catalysts[8] have been reported in the selective 1, 4 additions to α, β-unsaturated acids.

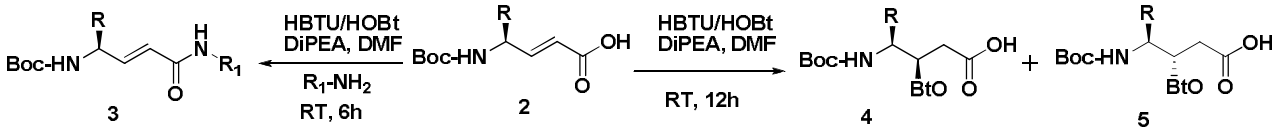
Recently we reported the synthesis, reactivity, conformational analysis and antimicrobial activities of hybrid peptides containing naturally occurring *E*-α, β-unsaturated γ-amino acids.[9] All peptide coupling reactions of these *E*-vinylogous amino acids have been performed using standard HBTU/HOBt coupling conditions. Coupling reagent HBTU consists of both carbodiimide and HOBt components and commonly used as a carboxylic acid activating reagent in both solution and solid phase peptide synthesis with or without additional equivalent of HOBt.[10] In an accidental encounter in the absence of free amine coupling partner, we observed HOBt conjugate addition product of the *E*-α, β-unsaturated γ-amino acid. As unsaturated

carboxylic acids have been proved difficult to undergo conjugate addition reactions at mild conditions, the unexpected 1, 4 addition products motivated us to investigate the HOBt conjugate addition in detail. Herein, we are reporting the 1, 4 conjugate addition of HOBt to various *E*-α, β-unsaturated γ-amino acids, stereochemical analysis of the conjugate addition products, their utility in the synthesis of peptides and the crystal conformations of β-BtO substituted γ-amino esters and peptides.



R = **a**, -CH_2-Ph; **b**, -CH-$(CH_3)_2$; **c**, -CH_2-$CH(CH_3)_2$; **d**, –CH_2-C_6H_4-OBu^t; **e,** -$CH(CH_3)$-CH_2-CH_3; **f**, α, β-unsaturated γ-proline

Scheme 1: Synthesis of α, β-unsaturated γ-amino acids

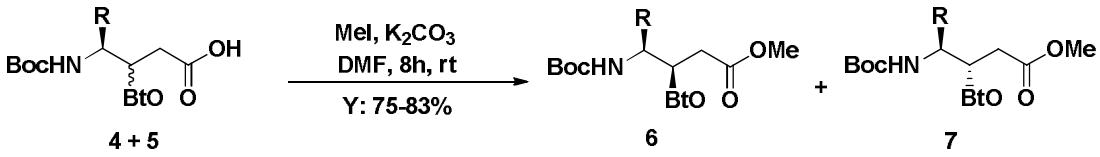


Scheme 2: Amide coupling and conjugate addition of HOBt with *E*-vinylogous γ-amino acids

Results and Discussion

Ethyl esters of *E*-vinylogous amino acids (**1**) were synthesized starting from α-amino aldehydes using the Wittig reaction as reported earlier (Scheme 1).[9a] Saponification of the ethyl esters

leads to the free *E*-vinylogous amino acids (**2**). The schematic representation of the HOBt conjugate addition in the absence and the presence of free amine coupling partner is shown in Scheme 2. In the absence of free amine coupling partner, we isolated the diastereomeric mixture of HOBt conjugate addition products (**4 + 5**) in moderate to good yields from the α, β-unsaturated γ-amino acids, **2a-f** (Scheme 2). No conjugate addition products were observed in the presence of free amine coupling partner. In addition, no HOBt conjugate addition products were observed with HBTU alone suggesting the requirement of additional HOBt for the conjugate addition. Though the β-BtO substituted γ-amino acids, (**4 + 5**) **a-f,** were isolated after the simple aqueous work-up, we found it difficult to separate the diastereomeric carboxylic acids **4** and **5** using column chromatography. In order to understand the diastereomeric ratio, we subjected all HOBt substituted diastereomeric mixtures, (**4** + **5**) **a-f,** to the esterification reaction using methyl iodide and potassium carbonate in DMF to give methyl esters **6** and **7** as shown in Scheme 3.



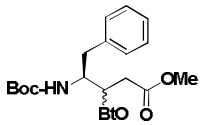
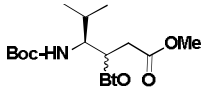
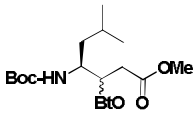
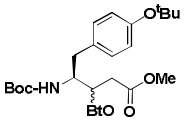
R= **a**, -CH_2-Ph; **b**, -CH-$(CH_3)_2$; **c**, -CH_2-$CH(CH_3)_2$; **d**, –CH_2-C_6H_4-OBu^t; **e,** -$CH(CH_3)$-CH_2-CH_3; **f**, α, β-unsaturated γ-proline

Scheme 3: Esterification of HOBt conjugate addition product of γ-amino acids

Out of all methyl esters of diastereoisomers in Scheme 3, we were able to separate the diastereoisomers of the compounds **6a-d** and **7a-d** using silica gel column chromatography. We

were unable to separate the diastereoisomers **6e** and **7e** as well as **6f** and **7f**. The yield and the diastereomeric ratio of the products are given in the Table 1. We observed moderate diastereoselectivity in the conjugate addition and based on the earlier reports on the Michael

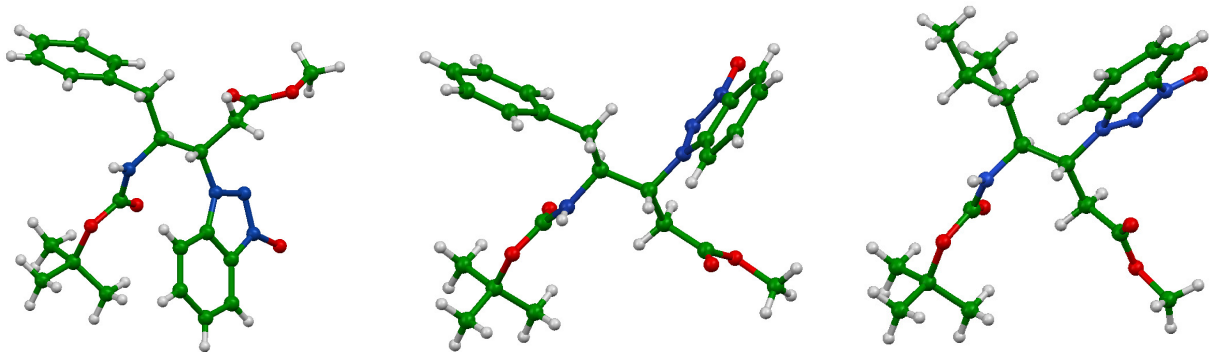
Table1: List of β-BtO substituted γ-amino acid methyl ester and their diastereomeric ratios.

AA	**6 + 7**	% Yield (**6 + 7**)	% *syn* (**6**)	% *anti* (**7**)
a		75	39	61
b		80	37	63
c		83	41	59
d		70	40	60

addition to the *E*-vinylogous amino esters,[9c, 11] we anticipated that *anti* addition product (**7**) may be the major product compared to the *syn* addition product (**6**). To understand whether the conjugate addition of HOBt to *E*-vinylogous amino acids is specific to the coupling additive HOBt, we performed two individual control reactions using other coupling additives,

pentafluorophenol and *N*-hydroxysuccinimide, in the presence of HBTU. Mass spectral analysis of the products reveals no conjugate addition from both pentafluorophenol as well as *N*-hydroxysuccinimide rather we isolated corresponding active esters.

In order to understand the stereochemistry and the diastereoselectivity, we subjected all major (**7**) and minor (**6**) diastereoisomers for crystallization. Out of all major and minor diastereoisomers, we were able to get the single crystals for minor (**6a**) and major (**7a**) diastereoisomers of β-BtO substituted γ-phenylalanine and the minor isomer of β-BtO-substituted γ-leucine (**6c**). The crystal structures of these diastereoisomers are shown in Figure 1.

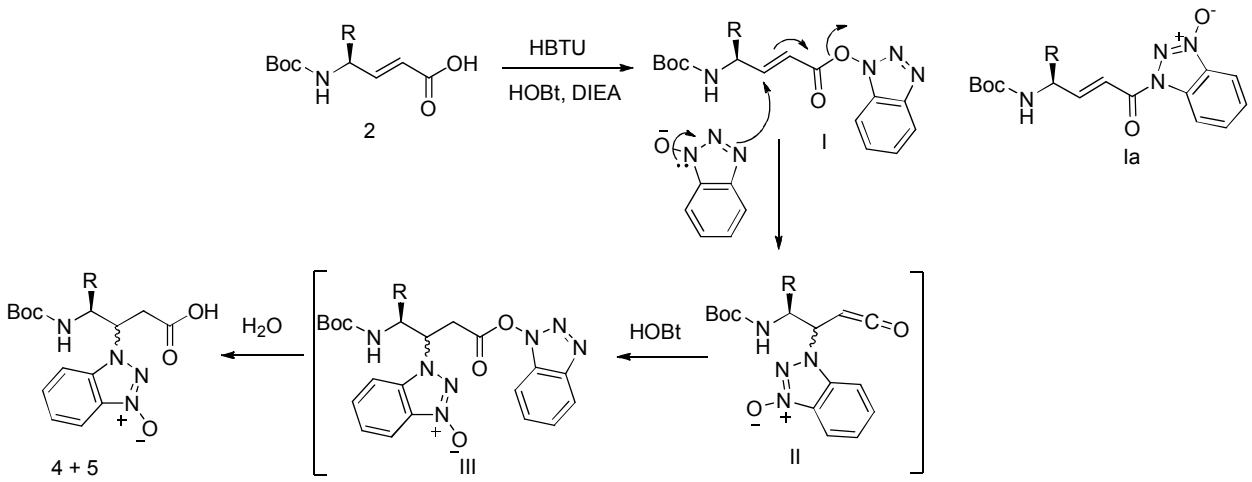


7a **6a** **6c**

Figure 1: X-ray structures of **7a**, **6a** and **6c**.

The crystal structure analysis reveals that as anticipated *anti* (**7**) is a major product and *syn* addition product (**6**) is a minor. Intriguingly, crystal structures also provide unexpected information regarding the involvement of triazole nitrogen (*N*) as a nucleophile in the conjugate addition over the *N*-hydroxyl (*N*-OH) group of HOBt. All three structures displayed *N*-alkylated benzotriazole *N*-oxides. The participation of the triazole ***N*** in the conjugate addition instead of

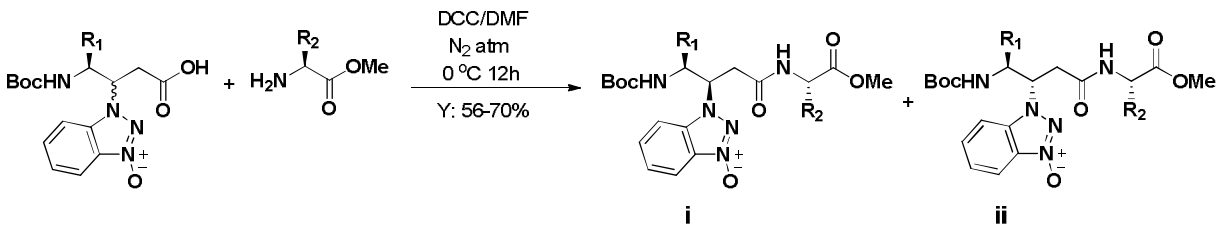
free *N*-OH group of the HOBt is not surprising as enormous attention has been paid over the decades regarding the ambidentate reactivity of HOBt. A survey of the literature reveals that both *N*-acylation and *O*-acylation properties of HOBt and their solvent dependent equilibrium properties.[12] Further, the crystal structures of HBTU, TBTU and HAPyU also suggest the formation of *N*-oxide derivatives over their uronium salts. Most of these studies convincingly suggest the *N*-acylation is an intermolecularly driven process. As we observed no HOBt conjugate addition product from the coupling reaction involving HBTU alone, supporting the intermolecular conjugate addition. Based on these experimental evidences the possible reaction mechanism of the HOBt conjugate addition is outlined in the Scheme 4.

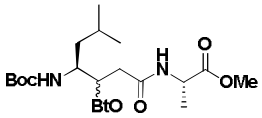
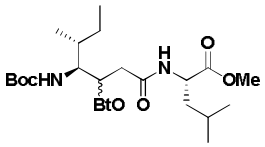
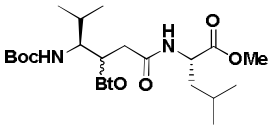
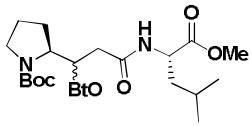
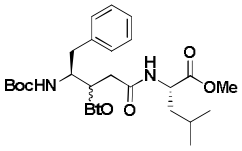


Scheme 4: Schematic representation of the conjugate addition of HOBt

We anticipate that the active ester (**I**) and/or amide (**Ia**), obtained after the treatment of HBTU in the presence of a base, will react further with the HOBt leading to the formation of diastereomeric mixture **II** which will immediately react further with HOBt to give active ester **III**. The hydrolysis of the active ester **III** during the aqueous work-up gave the diastereomeric

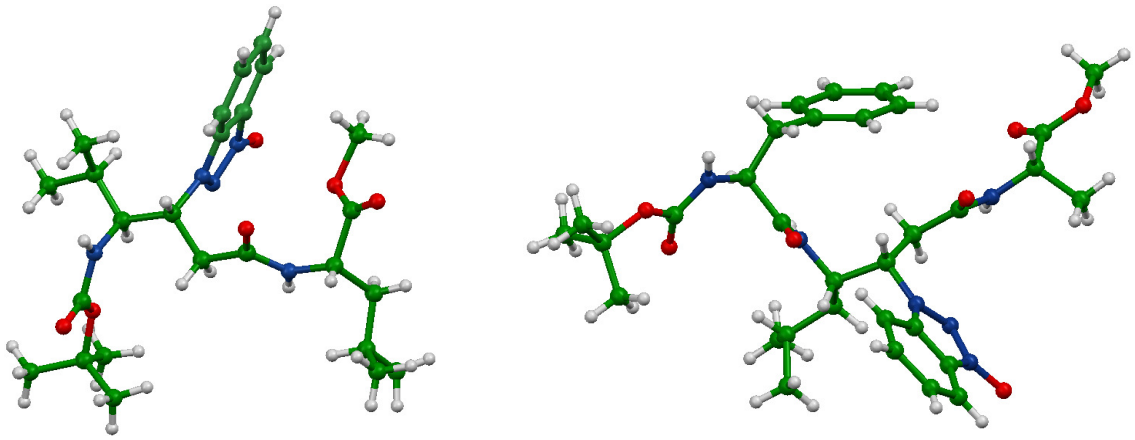
Table: 2. List of the peptides synthesized using β-BtO substituted γ-amino acids



Entry	Peptides (P)	% Yield	% **i**	% **ii**
8		70	41	59
9		62	38	62
10		67	37	63
11		58	41	59
12		56	39	61

conjugate addition products **4** and **5**. Further, we speculate that the soft nucleophilic nature of triazole nitrogen (***N***) may be preferred for the conjugate addition over the hard nucleophilc nature of the oxygen in *N*-OH. This was further supported by the 1, 2 addition of pentafluorophenol and *N*-hydroxysuccinimide. Similarly, intramolecular *N*-alkylation of unsaturated acids with various carbodiimides leading to the multisubstituted hydantoins have been recently reported.[13]

Based on the encouraging results from the methyl esters of HOBt conjugate addition products, we subjected β-BtO substituted diastereomeric mixture of **4** and **5** directly to the peptide synthesis, anticipating that it may be possible to separate the diastereomeric dipeptides once they coupled to the α-amino acid esters. In this regard, the conjugate addition products of **2c** (**4c +5c**) were directly couple with methyl ester of Ala in the presence of DCC. The two diastereomeric dipeptides **8i** and **8ii** were isolated in 70% yield and were separated using column chromatography in the ratio of 41 and 59% respectively (Table 2). The dipeptides **9i** and **9ii** were synthesized from the coupling reaction between methyl ester of Leu and diastereomeric mixture of **4e** and **5e**, respectively. Similarly, dipeptides **10** (**i** and **ii**), **11**(**i** and **ii**) and **12** (**i** and **ii**) were synthesized from the diastereomeric mixtures of BtO conjugate addition products of **2b**, **2f** and **2a**, respectively, by direct coupling with leucine methyl ester. Overall yield and the diastereomeric ratios of dipeptides are given in the Table 2.



10i **13**

Figure 2: The X-ray structures of Boc-γVal(β-BtO)-Leu-OMe (**10i**) and Boc-Phe-γLeu(β-BtO)-Ala-OMe (**13**).

We further subjected dipeptide **8ii** for the synthesis of the tripeptide Boc-Phe-γLeu(β-BtO)-Ala-OMe (**13**). The Boc- group of the dipeptide was deprotected using TFA and the isolated free amine was coupled to the Boc-Phe using HBTU/HOBt to give tripeptide in good yield. Out of all the HOBt substituted peptides, we were able to get single crystals of dipeptide **10i** and tripeptide **13** and their X-ray structures are shown in Figure 2. Instructively, similar to methyl esters, the peptide crystal structures also revealed *N*-substituted conjugate addition products in the peptides.

Crystal structure analysis of the methyl esters of major (**7a,** *anti*) and minor (**6a,** *syn*) products from *N*-Boc-α, β-unsaturated γ-phenylalanine reveal that both molecules adopted unfavorable staggered conformation along the C^{β}-C^{γ} bond. Molecule **7a** adopted *t* and g^{-} conformations, while **6a** displayed g^{+} and *t* conformation along C^{β}-C^{γ} and C^{β}-C^{α} bonds, respectively. Similarly, *syn* addition products **6b** and γVal(BtO) in the dipeptide (**10i**) showed g^{+}

and *t* conformations. In contrast, *anti* γLeu(BtO) in the tripeptide **13** follow the general trend of tetra alkyl substituted ethane by adopting the *gauche* conformations[14] along C^{β}-C^{γ} bond and displayed *anti(t)* conformation along the backbone C^{β}-C^{α} bond. Recently, Alezra et al reported the conformational diversity of foldamers composed of β-substituted γ-amino acids.[15] The Michael addition of HOBt to the *E*-vinylogous amino acids reported here may serve as direct route for the synthesis of β-substituted γ-amino acids.

Conclusions

In conclusion, we have demonstrated the HBTU mediated HOBt conjugate addition to the α, β-unsaturated γ-amino acids. Using this mild and facile methodology, various β-BtO substituted γ-amino acids were synthesized and utilized in the peptide synthesis. Experimental evidences suggest that HOBt conjugate addition is an intermolecular reaction with moderate diastereoselectivity. The stereochemistry of the novel β-BtO substituted γ-amino acids were analyzed using single crystal X-ray structures from both the monomers as well as in peptides. Results also suggest the preference for the *N*-alkylation over the anticipated *O*-alkylation in the conjugate addition. As conjugate addition to the unsaturated carboxylic acids has scarcely studied due to their inherent limitations, the results reported here may provide an opportunity to extend this methodology to other α, β-unsaturated acids. The β-substituted γ-amino acids reported here can be directly utilized for the construction peptide foldamers.

Experimental Section

General Information

All amino acids, Weinreb amine hydrochloride salt, DCC, LAH, DIEA, PPh_3, Ethyl bromoacetate, di-tert-butyldicarbonate, HOBt, HBTU, THF, DCM, DMF and toluene were used as commercially available. THF was dried over sodium and distilled prior to use. Column chromatography was performed on silica gel (100-200 mesh). ^{1}H NMR spectra were recorded on 400 MHz instrument (100 MHz for ^{13}C NMR) using residual solvent as internal standard ($CDCl_3$ δ_H, 7.24 ppm, δ_c 77.0 ppm and DMSO-d_6 δ_H, 2.5 ppm δ_c 40.0 ppm). The chemical shifts (δ) were reported in ppm and coupling constant (J) in Hz. High resolution mass spectra were obtained from ESI-TOF MS spectrometer and MALDI-TOF/TOF spectrometer.

General Procedure for the Synthesis of α, β-Unsaturated γ-Amino Esters:[9a] The *N*-protected amino aldehyde (10 mmol) was dissolved in dry THF (40 mL) under the N_2 atmosphere. To this solution Wittig ylide (11.5 mmol) was added. The progress of reaction was monitored by TLC. After completion of the reaction (monitored by TLC), THF was evaporated and product was purified by column chromatography using 5:95 ethyl acetate /pet ether solvent system.

Saponification of *N*-Protected α, β-Unsaturated γ-Amino Esters:[9a] The *N*-protected vinylogous amino ester (10 mmol) was dissolved in 15 mL of ethanol. To this solution, 1*N* NaOH (10 mL) was added drop wise. The reaction mixture was allowed to stir for about 3h. The progress of reaction was monitored by TLC. After completion of reaction (3h), the solvent ethanol was evaporated and the aqueous layer was acidified (pH ~ 2) with 5% aq. HCl. This aqueous solution was then extracted with ethyl acetate (30 mL × 3). The organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give *N*-protected vinylogous amino acid in average 95% yield.

General Procedure for the Synthesis of β-BtO Substituted γ-Amino Acids: The *N*-protected *E*-vinylogous amino acid (1.6 mmol) was dissolved in 2 mL of dry DMF under N_2 atmosphere. To this solution HBTU (1.6 mmol) and HOBt (3.2 mmol) were added. The reaction mixture was cooled at 0 $^{\circ}$C prior to the addition of DIEA (3.2 mmol). This reaction mixture was allowed to stir for another 12h. After 12h, the reaction mixture was diluted with ethyl acetate and acidified to pH ~ 2 using 5% HCl. The aqueous layer was further extracted with ethyl acetate (3 × 20 mL). The combined organic layer was then washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give β-BtO substituted γ-amino acids in moderate to good yields (70-85%) and directly used for esterification as well as peptide synthesis without purification.

General Procedure for the Synthesis of Methyl Ester of β-BtO Substituted *N*-Protected γ-Amino Acids: Beta-BtO substituted γ-amino acid (1.6 mmol) was dissolved in dry DMF (2 mL). To this solution, K_2CO_3 (1.6 mmol) was added followed by methyl iodide (3.2 mmol). This reaction mixture was further stirred for 8h. After completion of reaction (monitored by TLC), the reaction mixture was diluted with water (70 mL) and extracted with ethyl acetate (25 mL × 3). The combined organic layer was washed with saturated solution of $Na_2S_2O_3$, brine and dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The two diastereoisomers **6** and **7** were separated using column chromatography using 70:30 (EtOAc : Pet Ether) solvent system.

General Procedure for the Synthesis of β-BtO Substituted *N*-Protected γ-Amino Acids Containing Dipeptides: The hydrochloride salt of amino acid methyl ester ($HCl.NH_2$-Xaa-OMe) (3 mmol) was dissolved in water and pH was adjusted to 12 by adding solid Na_2CO_3 at ice

cold condition. The aqueous solution was then extracted with ethyl acetate (30 mL × 3). The combined organic layer was then washed with brine and dried over anhydrous Na_2SO_4, concentrated to ~2 mL under reduced pressure and used in the next step.

Beta-BtO substituted *N*-protected γ-amino acid (2 mmol) was dissolved in dry DMF under N_2 atmosphere. To this solution, methyl ester of amino acid (~2 mL, from the above step) was added. The reaction mixture was cooled to 0 °C and DCC (2 mmol) was added. The reaction mixture was allowed to stir for another 12h and progress of reaction was monitored by TLC. After completion of reaction, reaction mixture was diluted with ethyl acetate (50 mL) and DCU generated in the reaction was filtered. The filtrate was then washed with 5% HCl (20 mL) and 10% Na_2CO_3 (20 mL), brine and dried over Na_2SO_4. The organic layer was concentrated under reduced pressure to get diastereomeric mixture (**i** and **ii**) of dipeptides. These dipeptides were separated through column chromatography using 2:98 (MeOH : DCM) solvent system.

Procedure for the Synthesis of Tripeptide Boc-Phe-γLeu(β-BtO)-Ala-OMe (13): NH_2-γLeu(β-BtO)-Ala-OMe: Boc-γLeu(β-BtO)-Ala-OMe (200 mg, 0.4 mmol) was dissolved in 2 mL DCM and cooled at 0 °C. To this solution TFA (4 mL) was added. After the completion of reaction (1h) (monitored by TLC), TFA was evaporated under reduced pressure. The residue was dissolved in water and pH of the solution was adjusted to ~12 in by adding solid Na_2CO_3 at ice cold conditions. This aqueous solution was then extracted with ethyl acetate (25 mL × 3), washed with brine, dried over Na_2SO_4. The organic layer was concentrated under reduced pressure to ~2 mL and used in the next step.

The Boc-Phe-OH (110 mg, 0.4 mmol) and NH_2-γLeu(β-BtO)-Ala-OMe (from the above step) were dissolved in dry DMF. The reaction mixture was cooled at 0 °C and treated with HBTU (158 mg, 0.4 mmol) and HOBt (56 mg, 0.4 mmol), followed by DIEA (0.144 mL, 0.8 mmol). The reaction mixture was allowed to stir for overnight (12 h). After completion of reaction (12h), the reaction mixture was diluted with ethyl acetate (75 mL), washed with 5% HCl, 10% Na_2CO_3 and brine, dried over anhydrous Na_2SO_4. The organic layer was concentrated under reduced pressure to give crude tripeptide. The pure tripeptide Boc-Phe-γLeu(β-BtO)-Ala-OMe was isolated as white solid in 67 % yield after column purification in 80:20 (Ethyl acetate : Pet ether) solvent system.

*(S, E)-Ethyl 4-((tert-butoxycarbonyl)amino)-5-phenylpent-2-enoate (**1a**);* White powder (4.01g, 84%), mp 70 °C, UV (λ_{max}) 206 nm, 255 nm, $[\alpha]_D^{25}$ -2.0 (*c* 1.0, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.30-7.14 (m, 5 H), 6.89 (dd, *J* = 5.04 Hz, *J* = 11 Hz, 1 H), 5.83 (d, *J* = 17.4, 1 H), 4.59 (br, 1 H), 4.52 (m, 1 H), 4.15 (q, *J* = 6.8 Hz, 2 H), 2.92-2.85 (m, 2 H), 1.37 (s, 9 H), 1.25 (t, *J* = 7.3 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ = 166.2, 155.0, 147.6, 136.4, 129.4, 128.6, 126.9, 121.1, 79.9, 60.5, 52.3, 40.9, 28.3, 14.3 ppm. MALDI TOF/TOF *m/z* value calcd. for $C_{18}H_{25}NO_4$ [M + Na^+] 342.1681; found 342.1657.

(*S, E)-Ethyl 4-(tert-butoxycarbonylamino)-5-methylhex-2-enoate (**1b**);*White solid (yield 2.43g, 90%). mp 59 °C, UV (λ_{max}) 216 nm, $[\alpha]_D^{25}$ -3.40 (*c* 1.0, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.83 (dd, *J* = 15.8 Hz, *J* = 5.2 Hz, 1 H) 5.90 (d, *J* =15.6 Hz, 1 H), 4.55 (d, *J* = 6.8 Hz, 1 H), 4.17 (q, *J* = 6.88 Hz, 2 H), 1.86-1.84 (m, 1 H), 1.42 (s, 9 H), 1.27 (t, *J* = 7.32 Hz, 3 H), 0.90 (q, *J* = 6.4 Hz, 6 H) ppm, ^{13}C NMR (100 MHz, $CDCl_3$) δ = 166.3, 155.4, 147.4, 121.5, 79.7, 60.5,

56.7, 32.3, 28.4, 18.9, 17.0, 14.3 ppm. MALDI TOF/TOF *m/z* calcd. for $C_{14}H_{25}NO_4$ [M + Na^+] 294.1681; found 294.1686.

*(S, E)-Ethyl 4-(tert-butoxycarbonylamino)-6-methylhept-2-enoate (**1c**);* White solid (2.70g, 95%), mp 55 °C, UV (λ_{max}) 218 nm, $[\alpha]_D^{25}$ -25.50 (*c* 1.0, MeOH). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 6.83 (dd, *J* = 16 Hz, *J* = 5.5 Hz, 1 H), 5.91 (d, 1 H, *J* = 16 Hz), 4.45 (br, 1 H), 4.33 (br, 1 H), 4.19 (q, 2 H, *J* = 7 Hz), 1.72-1.67 (m, 1 H), 1.44 (s, 9 H), 1.38 (t, 2 H, *J* = 7 Hz), 1.28 (t, *J* = 7 Hz, 3 H), 0.94 (d, *J* = 6.5 Hz, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ = 166.5, 155.1, 148.0, 120.4, 79.7, 60.5, 49.8, 43.9, 28.4, 24.7, 22.7, 22.2, 14.3 ppm. MALDI TOF/TOF *m/z* calcd. for $C_{15}H_{27}NO_4$ [M + Na^+] 308.1838; found 308.1840.

*(4S, 5R, E)-Ethyl 4-(tert-butoxycarbonylamino)-5-methylhept-2-enoate (**1d**);* White solid (yield 2.62g, 92%), mp 62 °C, UV (λ_{max}) 216 nm, $[\alpha]_D^{25}$ -11.20 (*c* 1.0, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.87 (d, 1 H, *J* = 15.6 Hz), 5.92 (d, 1 H, *J* = 15.6 Hz), 4.58 (dd, 1 H, *J* = 17.9 Hz, *J* = 9.2 Hz), 4.32 (br, 1 H), 4.2 (q, *J* = 7.3 Hz, 2 H), 1.66 (m, 2 H), 1.45 (s, 9 H), 1.29 (t, *J* = 7.1 Hz, 3 H) , 1.14 (m, 1 H), 0.91-0.86 (m, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ = 166.3, 155.3, 147.1, 121.6, 79.6, 60.4, 55.7, 39.0, 28.4, 25.3, 15.3, 14.2, 11.6 ppm. MALDI TOF/TOF *m/z* calcd. for $C_{15}H_{27}NO_4$ [M + Na^+] 308.1838; found 308.1837.

*(S, E)-ethyl 5-(4-(tert-butoxy)phenyl)-4-((tert-butoxycarbonyl)amino)pent-2-enoate (**1e**);* Yellowish oil (3.2 g, 82%), UV (λ_{max}) 222 nm, 265 nm, 274 nm, 285 nm, $[\alpha]_D^{25}$ 4.0 (*c* 0.1, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.06 (d, *J* = 8 Hz, 2 H), 6.90 (m, 3 H), 5.84 (d, *J* = 16 Hz, 1 H), 4.55 (m, 2 H), 4.17 (q, *J* = 8 Hz, 2 H), 2.83 (m, 2 H), 1.40 (s, 9 H), 1.33 (s, 9 H), 1.27 (t, *J* = 8 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ = 192.3, 166.3, 155.1, 154.3, 131.3,

129.9, 124.3, 121.1, 78.5, 60.5, 28.9, 28.4, 14.3 ppm. HRMS *m/z* calcd. for $C_{22}H_{33}NO_5$ [M + Na^+] 414.2251; found 414.2259.

*(S, E)-tert-Butyl-2-(3-ethoxy-3-oxoprop-1-enyl)pyrrolidine-1-carboxylate (**1f**);*Colorless oil (2.23 g, 83%), UV (λ_{max}) 214 nm, $[\alpha]_D^{25}$ -72.0 (*c* 1.0, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.80 (d, *J* = 15.6 Hz, 1 H), 5.81 (d, *J* = 15.2 Hz, 1 H), 4.45 (br, 1 H), 4.19 (q, *J* = 6.4 Hz), 3.44 (t, *J* = 6 Hz, 2 H), 2.1 & 1.85 (m, 4 H), 1.42 (s, 9 H) 1.29 (t, *J* = 6.8 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ = 166.4, 154.3, 148.5, 120.4, 79.6, 60.3, 57.8, 46.2, 31.7, 28.3, 22.9, 14.2 ppm. MALDI TOF/TOF *m/z* calcd. for $C_{14}H_{23}NO_4$ [M + Na^+] 292.1525; found 292.1520.

*1-((3R,4S)-4-(tert-Butoxycarbonylamino)-1-methoxy-1-oxo-5-phenylpentan-3-yl)-1H-benzo[d][1,2,3]triazole 3-oxide (Boc-γPhe(β-BtO)-OMe) (**6a**)^{syn};* White solid, (0.204 g, 30%), The diastereomeric ratio of **6a**:**7a** is 39:61 respectively, mp 220-222 °C, $[\alpha]_D^{25}$ -7.4 (*c* 0.1, MeOH), UV (λ_{max}) 323 nm, 274 nm, IR (neat) ν (cm^{-1}) 3362, 2973, 2928, 1736, 1604, 1504, 1458, 1425, 1306, 1208, 1134, 748. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.99 (d, *J* = 8 Hz, 1 H), 7.55 (t, *J* = 8 Hz, 1 H), 7.42 (t, *J* = 6 Hz, 1 H), 7.24-7.21 (m, 4 H), 6.91 (dd, *J* = 4 Hz, 2 H), 5.54 (d, *J* = 8 Hz, 1 H), 5.16-5.12 (m, 1 H), 4.57-4.49 (m, 1 H), 3.51 (s, 3 H), 3.21 (dd, *J* = 4 Hz &12 Hz, 1 H), 2.98 (dd, 4 Hz & 12 Hz, 1 H), 2.76 (t, *J* = 8 Hz, 1 H), 2.41 (dd, *J* = 4 Hz & 8 Hz, 1 H), 1.42 (s, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ = 170.7, 155.7, 136.3, 130.5, 129.5, 128.7, 127.0, 124.9, 115.3, 111.7, 56.8, 54.7, 52.2, 38.5, 36.9, 29.7, 28.3 ppm. HRMS (ESI) *m/z* calcd. for $C_{23}H_{28}N_4O_5$ [M + H^+] is 441.2138; found 441.2134.

*1-((3S,4S)-4-(tert-Butoxycarbonylamino)-1-methoxy-1-oxo-5-phenylpentan-3-yl)-1H-benzo[d][1,2,3]triazole 3-oxide (Boc-γPhe(β-BtO)-OMe) (**7a**)^{anti};* White solid, (0.320 g, 45%), mp 190-192 °C, $[\alpha]_D^{25}$ -0.2 (*c* 0.1, MeOH), UV (λ_{max}) 323 nm, 274 nm, IR (neat) ν (cm^{-1}) 3360,

2971, 2921, 1736, 1604, 1507, 1458, 1425, 1367, 1311, 1209, 1167, 1024, 747. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.99 (d, *J* = 12 Hz, 1 H), 7.74-7.70 (m, 1 H), 7.62-7.61 (m, 2 H), 7.54 (dd, *J* = 4 Hz, 1 H), 7.43-7.39 (m, 1 H), 7.29 (d, *J* = 8 Hz, 1 H), 7.23 (d, *J* = 6 Hz, 2 H), 7.11 (d, *J* = 8 Hz, 2 H), 5.57 (br., 1 H), 5.02-4.92 (m, 1 H), 4.22 (t, *J* = 6 Hz, 1 H), 3.57 (s, 3 H), 3.33 (dd, *J* = 8 Hz, 1 H), 3.03 (dd, *J* = 16 Hz & *J* = 4 Hz, 1 H), 2.89-2.77 (m, 2 H), 1.35 (s, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ = 170.6, 155.4, 136.7, 135.6, 130.5, 128.9, 128.6, 126.8, 124.7, 115.3, 111.1, 80.1, 57.9, 55.3, 52.2, 35.7, 29.7, 28.3 ppm. HRMS (ESI) *m/z* calcd. for $C_{23}H_{28}N_4O_5$ [M + H^+] is 441.2138; found 441.2138.

*1-((3R,4S)-4-((tert-Butoxycarbonyl)amino)-1-methoxy-5-methyl-1-oxohexan-3-yl)-1H-benzo[d][1,2,3]triazole 3-oxide (Boc-γVal(β-BtO)-OMe) (**6b**)^{syn}* White powder, (0.185 g, 32%), The diastereomeric ratio of **6b**:**7b** is 37:63 respectively; mp 164-166 °C, $[\alpha]_D^{25}$ -1.0 (*c* 0.1, MeOH), UV (λ_{max}) 323 nm, IR (neat) ν (cm^{-1}) 2968, 1736, 1707, 1605, 1503, 1460, 1423, 1390, 1366, 1303, 1241, 1199, 1165, 1109, 1022, 749. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.98 (d, *J* = 8 Hz, 1 H), 7.70-7.63 (m, *J* = 8 Hz, 2 H), 7.42 (t, *J* = 8 Hz, 1 H), 5.5 (d, *J* = 12 Hz, 1 H), 5.40-5.3 (m, 1 H), 3.90-3.8 (m, 1 H), 3.54 (s, 3 H), 3.18 (dd *J* = 10 Hz & *J* = 3.6 Hz, 1 H), 2.96 (dd, *J* = 4 Hz & 12 Hz, 1 H) 1.47 (s, 9 H), 0.89 (dd, *J* = 4 Hz, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ = 173.0, 168.9, 156.6, 135.0, 130.9, 129.3, 124.8, 115.3, 111.6, 59.1, 57.4, 52.4, 50.8, 40.9, 40.3, 30.7, 28.4, 24.6, 22.7, 21.2, 20.1, 19.4 ppm. HRMS (ESI) *m/z* calcd. for $C_{19}H_{28}N_4O_5$ [M + H^+] is 393.2138; found 393.2147.

*1-((3S,4S)-4-(tert-Butoxycarbonylamino)-1-methoxy-5-methyl-1-oxohexan-3-yl)-1H-benzo[d][1,2,3]triazole 3-oxide(Boc-γVal(β-BtO)-OMe) (**7b**)^{anti};* White powder, (0.315 g, 48%), mp 173-175 °C, $[\alpha]_D^{25}$ -7.2 (*c* 0.1, MeOH), UV (λ_{max}) 323 nm, IR (neat) ν (cm^{-1}) 3272, 2966,

2928, 1738, 1690, 1606, 1506, 1423, 1394, 1308, 1250, 1167, 1033. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.99 (d, *J* = 8.8 Hz, 1 H), 7.64-7.63 (m, 2 H), 7.43-7.38 (m, 1 H), 5.09-5.03 (m, 1 H), 4.53(d, *J* = 12 Hz, 1 H), 4.27-4.21 (m, 1 H), 3.58 (s, 3 H), 3.22-3.07 (m, 3 H), 1.45 (s, 9 H), 0.86 (dd, *J* = 6.8 Hz, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ = 171.4, 155.8, 139.3, 134.3, 130.7, 124.6, 115.8, 110.8, 57.8, 57.2, 52.2, 36.1, 31.9, 29.7, 28.3, 22.7, 20.1, 15.8, 14.1 ppm. HRMS (ESI) *m/z* calcd. for $C_{19}H_{28}N_4O_5$ [M + H^+] is 393.2138; found 393.2143.

*1-((3R,4S)-4-(tert-Butoxycarbonylamino)-1-methoxy-6-methyl-1-oxoheptan-3-yl)-1H-benzo[d][1,2,3]triazole 3-oxide (Boc-γLeu(β-BtO)-OMe) (**6c**)^{syn};* White solid, (0.220 g, 33%), The diastereomeric ratio of **6c**:**7c** is 41:59 respectively, mp 130-132 °C, $[\alpha]_D^{25}$ -7.0 (*c* 0.1, MeOH), UV (λ_{max}) 323 nm, IR (neat) ν (cm^{-1}) 3360, 3267, 2957, 1735, 1704, 1605, 1510, 1460, 1398, 1366, 1317, 1248, 1167, 1035, 749. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.97 (d, *J* = 8 Hz, 1 H), 7.69-7.62(m, 2 H), 7.41 (t, *J* = 6 Hz, 1 H), 5.20-5.15 (m, 2 H), 4.25-4.19 (m, 1 H), 3.55 (s, 3 H), 3.23 (dd *J* = 8 Hz, 1 H), 3.02 (dd, *J* = 4 Hz & 12 Hz, 1 H), 1.62-1.56 (m, 1 H), 1.43 (s, 9H), 1.02 (t, *J* = 6 Hz, 2H), 0.81 (dd, *J* = 4 Hz, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ = 170.9, 155.8, 135.3, 130.9, 129.5, 124.7, 115.5, 111.0, 79.9, 59.1, 52.1, 51.5, 40.940, 36.1, 29.7, 28.3, 24.7, 23.1, 21.7 ppm. HRMS (ESI) *m/z* calcd. for $C_{20}H_{30}N_4O_5$ [M + H^+] is 407.2294; found 407.2300.

*1-((3S,4S)-4-(tert-Butoxycarbonylamino)-1-methoxy-6-methyl-1-oxoheptan-3-yl)-1H-benzo[d][1,2,3]triazole 3-oxide (Boc-γLeu(β-BtO)-OMe) (**7c**)^{anti};* White solid, (0.317 g, 50%), mp 95-97 °C, $[\alpha]_D^{25}$ -1.6 (*c* 0.1, MeOH), UV (λ_{max}) 323 nm, IR (neat) ν (cm^{-1}) 3360, 3270, 2956, 2927, 2863, 2315, 1737, 1702, 1607, 1506, 1460, 1424, 1394, 1367, 1262, 1167, 1115, 1038, 749. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.89 (d, *J* = 4 Hz, 1 H), 7.61-7.54 (m, 2 H), 7.34 (t, *J* = 6

Hz, 1 H), 5.40 (br, 1 H), 4.72 (br, 1 H), 4.03-4.00 (m, 1 H), 3.50 (s, 3 H), 3.29 (dd, *J* = 4 H & 8 Hz, 1 H), 2.87 (dd, *J* = 4 Hz, 12 Hz, 1 H), 1.60-1.58 (m, 1 H), 1.39 (s, 9 H), 0.83 (t, *J* = 4 Hz, 8 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ = 170.5, 155.4, 135.7, 130.4, 129.8, 124.5, 115.3, 111.1, 58.3, 52.1, 38.0, 35.1, 29.7, 28.3, 24.7, 23.6, 21.1 ppm. HRMS (ESI) *m/z* calcd. for $C_{20}H_{30}N_4O_5$ [M + H^+] is 407.2294; found 407.2303.

*1-((3R, 4S)-5-(4-(tert-butoxy)phenyl)-4-((tert-butoxycarbonyl)amino)-1-methoxy-1-oxopentan-3-yl)-1H-benzo[d][1,2,3]triazole 3-oxide (Boc-Tyr(β-BtO)-OMe)(**6d**)^{syn}* :Yellowish oil, (0.152 g, 28%), The diastereomeric ratio of **6d**:**7d** is 40:60 respectively. $[\alpha]^D_{25}$ -7.0 (*c* 0.1, MeOH), UV (λ_{max}) 219 nm, 273 nm, 280 nm, 323 nm, IR (neat) ν (cm^{-1}) 3424, 2923, 1609, 1400, 1108, 740, 619. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.95 (d, *J* = 8 Hz, 1 H), 7.61-7.56 (m, 2 H), 7.39-7.36 (m, 1 H), 6.99-6.87 (m, 4 H), 5.54-5.49 (m, 1 H), 4.62-4.57 (m, 1 H), 4.24-4.18 (m, 1 H), 3.54 (s, 3 H), 3.36-2.95 (m, 2 H), 2.82-2.71 (m, 2 H), 1.33 (s, 9 H), 1.30 (s, 9 H) ppm. ^{13}C NMR δ = 170.6, 155.4, 154.3, 1135.7, 131.4, 130.6, 130.0, 129.4, 124.7, 124.5, 115.5, 111.2, 80.3, 78.6, 57.7, 55..3, 52.3, 35.5, 35.0, 29.8, 28.9, 28.3 ppm. HRMS *m/z* calcd. for $C_{27}H_{36}N_4O_6$ [M + H^+] 513.2713; found 513.2717.

*1-((3S, 4S)-5-(4-(tert-butoxy)phenyl)-4-((tert-butoxycarbonyl)amino)-1-methoxy-1-oxopentan-3-yl)-1H-benzo[d][1,2,3]triazole 3-oxide (Boc-Tyr(β-BtO)-OMe) (**7d**)^{anti} :* Yellowish oil, (0.240 g, 42%), $[\alpha]^D_{25}$ + 0.2 (*c* 0.1, MeOH), UV (λ_{max}) 219 nm, 273 nm, 280 nm, 323 nm, IR (neat) ν (cm^{-1}) 3395, 2923, 1723, 1683, 1609, 1512, 1418, 1370, 1304, 1162, 1108, 895, 740, 618. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.98 (d, *J* = 8 Hz, 1 H), 7.55-7.39 (m, 2 H), 7.24-7.19 (m, 1 H), 6.89-6.77 (m, 4 H), 5.52 (d, *J* = 8 Hz, 1 H), 5.12 (m, 1 H), 4.51 (m, 1 H), 3.51 (s, 3 H), 3.10 (m, 2 H), 2.54 (m, 2 H), 1.42 (s, 9 H), 1.33 (s, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.7, 155.7,

154.3, 135.4, 131.1, 130.5, 129.4, 124.8, 124.5, 115.3, 111.8, 80.1, 78.6, 56.7, 54.6, 52.1, 37.9, 36.9, 29.7, 28.8, 28.3 ppm. HRMS *m/z* calcd. for $C_{27}H_{36}N_4O_6$ [M + H^+] 513.2713; found 513.2730.

*1-((4S,8R,9S)-9-Isobutyl-4,13,13-trimethyl-3,6,11-trioxo-2,12-dioxa-5,10-diazatetradecan-8-yl)-1H-benzo[d][1,2,3]triazole 3-oxide (Boc-γLeu(β-BtO)-Ala-OMe) (**8i**);* White solid, (0.273 g, 28%), The diastereomeric ratio of **8i**:**8ii** is 41:59 respectively, mp 135-137 °C, $[\alpha]^D_{25}$ -62.0 (*c* 0.1, MeOH), UV(λ_{max}) 323 nm, IR (neat) ν (cm^{-1}) 3281, 2960, 2378, 2312, 2112, 1741, 1668, 1525, 1458, 1423, 1367, 1208, 1164, 1114, 1052, 996, 748. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.91 (d, *J* = 4 Hz, 1 H), 7.68 (d, *J* = 8 Hz, 1 H), 7.59 (t, *J* = 6 Hz, 1 H), 7.38 (t, *J* = 8 Hz, 1 H), 6.85 (d, *J* = 8 Hz, 1 H), 5.26 (d, *J* = 8 Hz, 1 H), 5.24-5.21 (m, 1 H), 4.35-4.30 (m, 1 H), 4.29-4.25 (m, 1 H), 3.66 (s, 3 H), 3.03-2.93 (m, 2 H), 1.61-1.54 (m, 1 H), 1.41 (s, 9 H), 1.07 (d, *J* = 4 Hz, 3 H), 0.79 (t, *J* = 4 Hz, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ = 173.1, 168.7, 155.1, 135.3, 130.8, 129.4, 124.8, 115.2, 111.4, 60.0, 52.5, 51.6, 48.1, 41.2, 38.5, 28.3, 24.8, 23.1, 21.7, 17.5 ppm. MALDI TOF/TOF m/z calcd. for $C_{23}H_{35}N_5O_5$ [M + Na^+] is 500.2485; found 500.2491.

*1-((4S,8S,9S)-9-Isobutyl-4,13,13-trimethyl-3,6,11-trioxo-2,12-dioxa-5,10-diazatetradecan-8-yl)-1H-benzo[d][1,2,3]triazole 3-oxide (Boc-γLeu(β-BtO)-Ala-OMe) (**8ii**);* White solid, (0.393 g, 42%), mp 98-100 °C, $[\alpha]^D_{25}$ -66.0 (*c* 0.1, MeOH), UV (λ_{max}) 323 nm, IR (neat) ν (cm^{-1}) 3276, 2958, 2873, 2313, 1740, 1710, 1661, 1532, 1458, 1423, 1368, 1208, 1166, 1114, 953, 749. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 8.52 (d, *J* = 8 Hz, 1 H), 7.85 (d, *J* = 8 Hz, 1 H), 7.67 (t, *J* = 8 Hz, 1 H), 7.60 (d, *J* = 8 Hz, 1 H), 7.41 (t, *J* = 8 Hz, 1 H), 6.94 (d, *J* = 8 Hz, 1 H), 5.17-5.13 (m, 1 H), 3.95-3.88 (m, 1 H), 3.23 (s, 3 H), 3.03 (dd, *J* = 4 Hz &12 Hz, 1 H), 2.75 (dd *J* = 4 Hz &12 Hz, 1 H), 1.36 (s, 9 H), 1.12(d, *J* = 8 Hz, 3 H), 0.77 (t, *J* = 8 Hz, 6 H) ppm. ^{13}C NMR (100 MHz,

DMSO-d_6) δ = 173.0, 169.1, 155.8, 135.3, 130.6, 129.6, 124.5, 115.1, 112.0, 78.5, 59.7, 51.7, 48.0, 36.1, 28.6, 24.7, 23.9, 21.4, 17.1 ppm. MALDI TOF/TOF m/z calcd. for $C_{23}H_{35}N_5O_5$ [M + Na^+] is 500.2485; found 500.3464.

1-((4S,8R,9S)-9-sec-Butyl-4-isobutyl-13,13-dimethyl-3,6,11-trioxo-2,12-dioxa-5,10-diazatetradecan-8-yl)-1H-benzo[d][1,2,3]triazole 3-oxide (Boc-γIle(β-BtO)-Leu-OMe) ***(9i);*** White solid, (0.254 g, 25%), The diastereomeric ratio of **9i**:**9ii** is 39:61 respectively, mp 230-232 °C, $[\alpha]^D_{25}$ +20.0 (*c* 0.1, MeOH), UV (λ_{max}) 323 nm, IR (neat) ν (cm^{-1}) 2963, 2381, 2313, 2112, 1738, 1660, 1509, 1459, 1424, 1368, 1310, 1207, 1167, 749. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.96 (d, *J* = 8 Hz, 1 H), 7.66-7.58 (m, 2 H), 7.39 (t, *J* = 8 Hz, 1 H), 6.08 (d, *J* = 8 Hz. 1 H), 5.47-5.43 (m, 2 H), 4.42-4.36 (m, 1 H), 4.01-3.95 (m, 1 H), 3.44 (s, 3 H), 2.99 (dd, *J* = 4 Hz &12 Hz, 1 H), 2.87 (dd, *J* = 4 Hz & *J* = 12 Hz, 1 H), 1.61-1.50 (m, 2 H), 1.45 (s, 9 H), 1.17-1.11 (m, 2 H), 0.89 (d, *J* = 4 Hz, 6 H), 0.76 (dd, *J* = 8 Hz, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ = 172.4, 168.7, 156.3, 135.1, 130.8, 129.5, 124.6, 115.4, 111.3, 57.3, 52.2, 50.9, 41.2, 39.6, 36.6, 29.7, 28.4, 26.3, 24.8, 22.7, 21.8, 14.9, 10.6 ppm. MALDI TOF/TOF m/z calcd. for $C_{26}H_{41}N_5O_6$ [M + Na^+] is 542.2955; found 542.2957.

1-((4S,8S,9S)-9-sec-Butyl-4-isobutyl-13,13-dimethyl-3,6,11-trioxo-2,12-dioxa-5,10-diazatetradecan-8-yl)-1H-benzo[d][1,2,3]triazole 3-oxide (Boc-γIle(β-BtO)-Leu-OMe) ***(9ii);*** White solid, (0.397 g, 37%), mp 193-195 °C, $[\alpha]^D_{25}$ + 32.0 (*c* 0.1, MeOH), UV (λ_{max}) 323 nm, IR (neat) ν (cm^{-1}) 2964, 2875, 2314, 2259, 2124, 1740, 1707, 1664, 1545, 1460, 1425, 1369, 1207, 1168, 1022, 992, 825, 754, ^{1}H NMR (400 MHz, DMSO-d_6) δ = 8.49 (d, *J* = 8 Hz, 1 H), 7.84 (d, *J* = 8 Hz, 1 H), 7.67 (d, *J* = 4 Hz, 2 H), 7.42-7.38 (m, 1 H), 7.03 (d, *J* = 8 Hz, 1 H), 5.28-5.22 (m, 1 H), 4.05-4.0 (m, 1 H), 3.86-3.80 (m, 1 H), 3.22 (s, 3 H), 3.05 (dd, *J* = 4 Hz &12

Hz, 1 H), 2.69 (dd, *J* = 4 Hz &12 Hz,1 H), 1.33 (s, 9 H), 0.84 (d, *J* = 8 Hz, 3 H), 0.73 (dd, *J* = 4 Hz &12 Hz, 6 H), 0.56 (t, *J* = 8 Hz 3 H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6) δ = 172.8, 169.5, 156.1, 134.5, 130.6, 129.7, 124.5, 115.2, 112.0, 78.4, 57.5, 51.9, 50.8, 35.7, 35.2, 28.6, 24.5, 23.1, 21.5, 16.5, 11.4 ppm. MALDI TOF/TOF m/z calcd. for $C_{26}H_{41}N_5O_6$ [M + Na^+] is 542.2955; found 542.2950.

*1-((4S,8R,9S)-4-Isobutyl-9-isopropyl-13,13-dimethyl-3,6,11-trioxo-2,12-dioxa-5,10-diazatetradecan-8-yl)-1H-benzo[d][1,2,3]triazole 3-oxide (Boc-γVal(β-BtO)-Leu-OMe) (**10i**);* White solid, (0.249 g, 26%), The diastereomeric ratio of **10i**:**10ii** is 37:63 respectively, mp 200-202 °C, $[\alpha]^D_{25}$ +18.0 (*c* 0.1, MeOH), UV (λ_{max}) 323 nm, IR (neat) ν (cm^{-1}) 2964, 2312, 2117, 1740, 1542, 1425, 1368, 1311, 1210, 1092, 748. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.95 (d, *J* = 8 Hz, 1 H), 7.70 (d, *J* = 8 Hz, 1 H), 7.62 (t, *J* = 8 Hz, 1 H), 7.40 (t, *J* = 8 Hz,1 H), 6.54 (d, *J* = 8 Hz, 1 H), 5.55 (d, *J* = 12 Hz, 1 H), 5.46-5.42 (m, 1 H), 4.39-4.33 (m, 1 H), 3.99-3.93 (m, 1 H), 3.70 (s, 3 H), 2.89 (d, *J* = 8 Hz, 2 H), 1.48 (s, 9 H), 1.28-1.24 (m, 2 H), 0.90 (t, *J* = 8 Hz, 6 H), 0.69 (d, *J* = 8 Hz, 3 H) 0.53 (d, *J* = 4 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ = 173.0, 168.9, 156.6, 135.0, 130.9, 129.3, 124.8, 115.3, 111.6, 59.1, 57.4, 52.4, 50.8, 40.9, 40.3, 30.7, 28.4, 24.6, 22.7, 21.2, 20.1, 19.4 ppm. MALDI TOF/TOF m/z calcd. for $C_{25}H_{39}N_5O_6$ [M + Na^+] is 528.2798; found 528.2780.

*1-((4S,8S,9S)-4-Isobutyl-9-isopropyl-13,13-dimethyl-3,6,11-trioxo-2,12-dioxa-5,10-diazatetradecan-8-yl)-1H-benzo[d][1,2,3]triazole 3-oxide (Boc-γVal(β-BtO)-Leu-OMe) (**10ii**);* White solid, (0.425 g, 41%), mp 230-232 °C, $[\alpha]^D_{25}$ +40.0 (*c* 0.1, MeOH), UV (λ_{max}) 323 nm, IR (neat) ν (cm^{-1}) 2962, 2928, 2314, 1737, 1543, 1459, 1424, 1368, 1310, 1208, 1169, 1089, 1038, 747. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 8.47 (d, *J* = 8 Hz, 1 H), 7.84 (d, *J* = 8 Hz, 1 H),

7.697-7.662 (m, 2 H), 7.40 (t, *J* = 8 Hz, 1 H), 7.08 (d, *J* = 8 Hz, 1 H), 5.17 (t, *J* = 8 Hz, 1 H), 4.032-3.98 (m, 1 H), 3.91-3.86 (m, 1 H), 3.19 (s, 3 H), 3.00 (t, *J* = 12 Hz, 1 H), 2.70 (d, *J* = 20 Hz, 1 H), 1.37 (s, 9 H), 0.91-0.85 (m, 2 H) 0.82 (d, *J* = 8 Hz, 3 H), 0.75 (d, *J* = 4 Hz, 3 H), 0.71 (d, *J* = 4 Hz, 6 H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6) δ = 172.7, 169.5, 156.3, 134.6, 130.7, 129.6, 124.5, 115.2, 112.1, 78.5, 57.8, 51.9, 50.8, 36.5, 28.6, 24.5, 23.1, 21.6, 20.4, 17.2 ppm. MALDI TOF/TOF m/z calcd. for $C_{25}H_{39}N_5O_6$ [M + Na^+] is 528.2798; found 528.2535.

*1-((R)-1-((S)-1-(tert-Butoxycarbonyl)pyrrolidin-2-yl)-3-((S)-1-methoxy-4-methyl-1-oxopentan-2-ylamino)-3-oxopropyl)-1H-benzo[d][1,2,3]triazole 3-oxide (Boc-γPro(β-BtO)-Leu-OMe) (**11i**);* White solid, (0.242 g, 23%), The diastereomeric ratio of **11i**:**11ii** is 41:59 respectively, mp 110-112 °C, $[\alpha]^D_{25}$ -22.0 (*c* 0.1, MeOH), UV =(λ_{max}) 323 nm, IR (neat) ν (cm^{-1}) 2966, 2313, 1740, 1687, 1544, 1507, 1455, 1368, 1210, 1164, 907, 748. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.94 (d, *J* = 8 Hz, 1 H), 7.62 (d, *J* = 8 Hz, 1 H), 7.52 (t, *J* = 6 Hz, 1 H), 7.37 (t, *J* = 8 Hz, 1 H), 6.39 (d, *J* = 8 Hz,1 H), 5.87-5.83 (m, 1 H), 4.41-4.36 (m, 1 H), 4.27-4.23 (m, 1 H), 3.40 (s, 3 H), 3.23-3.21 (m, 2 H), 2.87 (dd, *J* = 4 Hz &12 Hz, 1 H), 2.24-2.20 (m, 1 H), 2.05-2.00 (m, 4 H), 1.45 (s, 9 H), 0.88 (t, *J* = 4 Hz, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ = 172.6, 168.5, 157.0, 155.2, 139.3, 135.7, 130.3, 124.6, 115.0, 114.1, 111.6, 60.5, 57.0, 52.1, 51.0, 47.0, 41.0, 37.4, 33.8, 31.9, 29.7, 28.4, 25.8, 24.8, 22.8, 21.8, 14.1 ppm. MALDI TOF/TOF m/z calcd. for $C_{25}H_{37}N_5O_6$ [M + Na^+] is 526.2642; found 526.2652.

*1-((S)-1-((S)-1-(tert-Butoxycarbonyl)pyrrolidin-2-yl)-3-((S)-1-methoxy-4-methyl- 1-oxopentan-2-ylamino)-3-oxopropyl)-1H-benzo[d][1,2,3]triazole 3-oxide (Boc-γPro(β-BtO)-Leu-OMe) (**11ii**)* ; White solid, (0.349 g, 35%), mp 132-134 °C, $[\alpha]^D_{25}$ -18.0 (*c* 0.1, MeOH), UV (λ_{max}) 323 nm, IR (neat) ν (cm^{-1}) 3023, 2967, 2129, 1739, 1653, 1509, 1443, 1368, 1221, 1022, 990, 763. ^{1}H

NMR (400 MHz, DMSO-d_6) δ = 8.50 (d, J = 8 Hz, 1 H), 7.79 (br. 2 H), 7.63 (t, J = 8 Hz, 1 H), 7.36 (t, J = 8 Hz, 1 H), 5.12-5.05 (br. 1 H), 4.11-4.09 (m, 2 H), 3.53 (s, 3 H), 3.19 (dd, J =12 Hz, 1 H), 2.84 (d, J = 16 Hz, 1 H), 1.97-1.81(m, 4 H), 1.08 (s, 9 H), 0.71 (d, J = 4 Hz, 3 H), 0.33 (d, J = 4 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6) δ = 173.2, 169.0, 135.1, 124.4, 114.9, 111.9, 58.7, 52.2, 50.2, 31.8, 29.5, 28.0, 24.3, 24.2, 20.7 ppm. MALDI TOF/TOF m/z calcd. for $C_{25}H_{37}N_5O_6$ [M + Na^+] is 526.2642; found 526.2639.

1-((4S,8R,9S)-9-Benzyl-4-isobutyl-13,13-dimethyl-3,6,11-trioxo-2,12-dioxa-5,10-diazatetradecan-8-yl)-1H-benzo[d][1,2,3]triazole 3-oxide (Boc-γPhe(β-BtO)-Leu-OMe) (***12i***) ; White solid, (0.240 g, 23%), The diastereomeric ratio of **12i**:**12ii** is 39:61 respectively, mp 175-177 °C, $[\alpha]^D_{25}$ +42.0 (*c* 0.1, MeOH), UV (λ_{max}) 323 nm, 274, IR (neat) ν (cm^{-1}) 2960, 2130, 1739, 1655, 1526, 1505, 1458, 1425, 1368, 1209, 1164, 1022, 991, 749. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 8.50 (d, J = 8 Hz, 1 H), 7.86 (d, J = 8 Hz, 1 H), 7.70-7.61 (m, 2 H), 7.42 (t, J = 8 Hz, 1 H), 7.25-7.16(m, 5 H), 7.07-7.05 (d, J = 8 Hz 1 H), 5.33-5.28 (m, 1 H), 4.14-4.05 (m, 2 H), 3.54 (s, 3 H), 3.18 (dd, J = 4 Hz &12 Hz, 1 H), 2.88 (dd, J 4 Hz, & J = 12 Hz, 1 H), 2.69-2.66 (m, 2 H), 1.25 (s, 9 H), 0.67 (d, J = 8 Hz, 3 H) 0.28 (d, J = 8 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6) δ = 173.2, 169.1, 155.4, 138.9, 135.3, 130.3, 129.5, 128.4, 126.5, 124.4, 114.9, 112.6, 78.1, 60.2, 55.9, 52.2, 50.2, 28.4, 24.3, 23.3, 20.6, 14.5 ppm. MALDI TOF/TOF m/z calcd. for $C_{29}H_{39}N_5O_6$ [M + Na^+] is 576.2798; found 576.2814.

1-((4S,8S,9S)-9-Benzyl-4-isobutyl-13,13-dimethyl-3,6,11-trioxo-2,12-dioxa-5,10-diazatetradecan-8-yl)-1H-benzo[d][1,2,3]triazole 3-oxide (Boc-γPhe(β-BtO)-Leu-OMe) (***12ii***) ; White solid, (0.377 g, 33%), mp 153-155 °C, $[\alpha]^D_{25}$ +32.0 (*c* 0.1, MeOH), UV (λ_{max}) 323 nm, 274 nm, IR (neat) ν (cm^{-1}) 3026, 2966, 2313, 1739, 1653, 1542, 1524, 1456, 1425, 1368, 1210,

1022, 992, 757. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 8.53 (d, J = 8 Hz, 1 H), 7.86 (d, J = 8 Hz, 1 H), 7.69-7.61 (m, 2 H), 7.42 (t, J = 6 Hz, 1 H), 7.23 (t, J = 8 Hz, 3 H), 7.16 (d, J = 4 Hz, 4 H), 7.03 (d, J = 12 Hz, 1 H), 5.34-5.29 (m, 1 H), 4.10.4.06 (m, 2 H), 3.28 (s, 3 H), 3.16 (dd, J = 4 Hz &12 Hz, 1 H), 2.94 (dd, J = 4 Hz &12 Hz, 1 H), 2.73-2.65 (m, 2 H), 1.24 (s, 9 H), 0.79 (d, J = 8 Hz, 3 H), 0.74 (d, J = 8 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6) δ = 172.9, 169.3, 155.6, 138.9, 135.3, 130.5, 129.4, 128.5, 126.5, 124.4, 115.2, 112.0, 78.5, 60.2, 59.4, 55.3, 52.0, 50.8, 36.0, 35.5, 28.6, 24.5, 23.2, 21.5, 14.5 ppm. MALDI TOF/TOF m/z calcd. for $C_{29}H_{39}N_5O_6$ [M + Na^+] is 576.2798; found 576.4337.

*1-((4S,8S,9S,12S)-12-Benzyl-9-isobutyl-4,16,16-trimethyl-3,6,11,14-tetraoxo-2,15-dioxa-5,10,13-triazaheptadecan-8-yl)-1H-benzo[d][1,2,3]triazole 3-oxide (Boc-Phe-γLeu(β-BtO)-Ala-OMe) (**13**);* White solid, (0.175 g, 67%), UV (λ_{max}) 323 nm, ^{1}H NMR (400 MHz, DMSO-d_6) δ = 8.52 (d, J = 8 Hz, 1 H), 7.91 (d, J = 8 Hz, 2 H), 7.80 (d, J = 8 Hz, 1 H), 7.68 (t, J = 8 Hz, 1 H), 7.35 (t, J = 6 Hz, 1 H), 7.22 (t, J = 8 Hz, 3 H), 7.15 (d, J = 8 Hz, 1 H), 6.93 (d, J = 8 Hz, 1 H), 5.15-5.10 (m, 1 H), 4.27 (d, J = 8 Hz, 1 H), 4.06-4.99 (m, 1 H), 3.86-3.80 (m, 1 H), 3.50 (s, 3 H), 3.17-3.03 (m, 1 H), 2.79 (dd, J = 4 Hz &12 Hz, 1 H), 2.38 (dd, J = 4 Hz &12 Hz, 1 H), 2.07 (dd, J = 4 Hz & 8 Hz, 1 H), 1.67-1.59 (m, 1 H), 1.27 (s, 9 H), 1.10 (d, J = 4 Hz, 3 H), 0.82(d, J = 4 Hz, 3 H), 0.74 (d, J = 8 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6) = 173.3, 172.2, 168.9, 155.7, 138.8, 135.3, 129.5, 128.4, 124.5, 115.0, 112.6, 78.4, 59.8, 56.5, 48.0, 36.1, 28.5, 24.1, 21.3 ppm. MALDI TOF/TOF m/z calcd. for $C_{32}H_{44}N_6O_7$ [M + Na^+] is 647.3169; found 647.3171.

Crystal structure analysis: Crystal structure analysis of Boc-γF(β-BtO)-OMe (7a): Crystals of peptide were grown by slow evaporation from a solution of 2-propanol. A single

crystal (0.15× 0.04 × 0.012 mm) was mounted on loop with a small amount of the paraffin oil. The X-ray data were collected at 173K temperature on a Bruker APEX DUO CCD diffractometer using Cu K_α radiation (λ = 1.54178Å), ω-scans (2θ = 65.16), for a total of 3950 independent reflections. Space group P2(1) 2(1) 2(1) , a = 5.2262(5), b = 10.1445(9), c = 41.525(3), V= 2201.5(3) Å^3, Orthorhombic P, Z=4 for chemical formula C_{23} H_{29} N_4 O_5 with one molecule in asymmetric unit; ρ calcd = 1.428 gcm^{-3}, μ= 0.781 mm^{-1}, F(000)= 968, R_{int}=0.0201. The structure was obtained by direct methods using SHELXS-97.The final R value was 0.0831 (wR2= 0.2275) 3712 observed reflections ($F_0 \geq 4\sigma$ ($|F_0|$)) and 281 variables, S = 1.224. The largest difference peak and hole were 1.376 and -0.726 eÅ^3, respectively.

Crystal structure analysis of Boc-γF(β-BtO)-OMe (6a): Crystals of peptide were grown by slow evaporation from a solution of Toluene and Methanol. A single crystal (0.15× 0.04 × 0.012 mm) was mounted on loop with a small amount of the paraffin oil. The X-ray data were collected at 100K temperature on a Bruker APEX DUO CCD diffractometer using Cu K_α radiation (λ = 1.54178Å), ω-scans (2θ = 72.28), for a total of 3950 independent reflections. Space group P2(1) 2(1) 2(1) , a = 9.0179 (3), b = 11.9971 (4), c = 21.7378 (7), V= 2351.78 (13) Å^3, Orthorhombic P, Z=4 for chemical formula C_{23} H_{29} N_4 O_5 with one molecule in asymmetric unit; ρ calcd = 1.247 gcm^{-3}, μ= 0.731 mm^{-1}, F(000)= 940, R_{int}=0.056. The structure was obtained by direct methods using SHELXS-97.The final R value was 0.0479 (wR2= 0.1263) 4083 observed reflections ($F_0 \geq 4\sigma$ ($|F_0|$)) and 293 variables, S = 1.049. The largest difference peak and hole were 0.213 and -0.219 eÅ^3, respectively.

Crystal structure analysis of Boc-γL(β-BtO)-OMe (6c): Crystals of peptide were grown by slow evaporation from a solution of EtOAc. A single crystal (0.2× 0.05 × 0.01 mm) was

mounted on loop with a small amount of the paraffin oil. The X-ray data were collected at 100K temperature on a Bruker APEX DUO CCD diffractometer using Mo K_α radiation (λ = 0.71073 Å), ω-scans (2θ = 56.56), for a total of 5506 independent reflections. Space group P2(1) 2(1) 2(1) , a = 9.730(5), b = 10.761(5), c = 21.944(10), V= 2297.7(19) Å^3, Orthorhombic P, Z=4 for chemical formula C_{20} H_{30} N_4 O_5 with one molecule in asymmetric unit; ρ calcd = 1.172 gcm^{-3}, μ= 0.085 mm^{-1}, F(000)= 868, R_{int}=0.2494. The structure was obtained by direct methods using SHELXS-97.The final R value was 0.0791 (wR2= 0.1449) 5506 observed reflections ($F_0 \geq 4\sigma$ ($|F_0|$)) and 268 variables, S = 0.887. The largest difference peak and hole were 0.305 and -0.289 eÅ^3 respectively.

Crystal structure analysis of Boc-γV(β-BtO)-L-OMe (10i): Crystals of peptide were grown by slow evaporation from a solution of EtOAc. A single crystal (0.12× 0.04 × 0.015 mm) was mounted on loop with a small amount of the paraffin oil. The X-ray data were collected at 200K temperature on a Bruker APEX DUO CCD diffractometer using Mo K_α radiation (λ = 0.71073 Å), ω-scans (2θ = 56.56), for a total of 5643 independent reflections. Space group Triclinic P1, a = 10.152 (9), b = 12.510 (11), c = 12.604 (11), V= 1425 (2) Å^3, Triclinic P1, Z=1 for chemical formula C_{25} H_{39} N_5 O_6 with two molecules in asymmetric unit; ρ calcd = 1.178 gcm^{-3}, μ= 0.085 mm^{-1}, F(000)= 544, R_{int}=0.1355. The structure was obtained by direct methods using SHELXS-97.The final R value was 0.0954 (wR2= 0.2236) 5943 observed reflections ($F_0 \geq 4\sigma$ ($|F_0|$)) and 665 variables, S = 0.889. The largest difference peak and hole were 0.503 and -0.378eÅ^3 respectively. Though we diffracted the crystal up to 0.75 A resolution, the crystal still diffracted quite weekly. We could get only small crystals on thorough crystallization process.

Crystal structure analysis of (Boc-Phe-γLeu(β-BtO)-Ala-OMe) (13): Crystals of peptide were grown by slow evaporation from a solution of methanol. A single crystal (0.34 × 0.28 × 0.26 mm) was mounted in a loop with a small amount of the mother liquor. The X-ray data were collected at 100 K temperature on a Bruker AXS SMART APEX CCD diffractometer using MoK_α radiation (λ = 0.71073 Å), ω-scans (2θ = 56.56°), for a total number of 8114 independent reflections. Space group *P2(1),2(1),2(1)* a = 9.002(3), b = 14.970(4), c = 24.507(7) Å, α = 90.00 , β = 90, γ = 90.00, V= 2894.6(9) $Å^3$ Orthorhombic P, Z=4 for chemical formula $C_{32}H_{44}N_6O_7$, with one molecule in asymmetric unit; ρ_{calcd} = 1.256 g cm^{-3}, μ= 0.090 mm^{-1}, F(000) = 1336, R_{int}= 0.0486. The structure was obtained by direct methods using SHELXS-97.[1] All non-hydrogen atoms were refined anisotropically. The hydrogen atoms were fixed geometrically in the idealized position and refined in the final cycle of refinement as riding over the atoms to which they are bonded. The final R value was 0.0451 ($wR2$= 0.0917) for 6805 observed reflections ($F_0 \geq 4\sigma(|F_0|)$) and 413 variables, S = 1.083. The largest difference peak and hole were 0.225 and -0.217 e $Å^3$, respectively.

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Supporting Information Available ^1H and ^{13}C NMR spectra of **1a-f, 6a-d, 7a-d,** dipeptides**, 8 (i, ii)-12(i, ii)** and **13,** and ORTEP diagrams for **7a**, **6a**, **6c**, **10i** and **13**. This material available free of charge via the Internet at htpp:// pubs.acs.org.

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