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## HBTU mediated 1-hydroxybenzotriazole (HOBt) conjugate addition: synthesis and stereochemical analysis of $\beta$ -benzotriazole *N*-oxide substituted $\gamma$ -amino acids and hybrid peptides†

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HBTU is a standard coupling agent commonly used for the activation of free carboxylic acids during the solution and solid phase peptide synthesis. 1-Hydroxybenzotriazole (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  $\gamma$ -amino acids mediated by the HBTU. The reaction is moderately diastereoselective and novel  $\beta$ -benzotriazole *N*-oxide ( $\beta$ -BtO) substituted  $\gamma$ -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 infers the formation of exclusively *N*-alkylated benzotriazole *N*-oxides instead of *O*-alkylation of HOBt. In addition, we showed the utilization of  $\beta$ -BtO substituted  $\gamma$ -amino acids in peptide synthesis and studied their conformations in single crystals.

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### Introduction

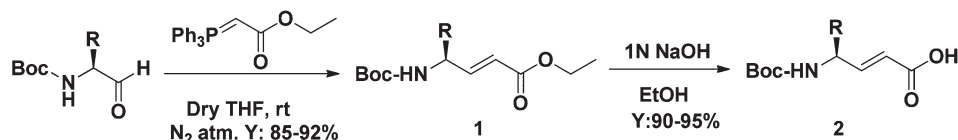
Nucleophilic conjugate addition is one of the most widely explored reactions in synthetic organic chemistry. The conjugate addition offers direct access to a variety of organic compounds by the C–X (X = C, N, O, S *etc.*) bond formation.<sup>1</sup> The regiochemistry of 1,2 or 1,4-nucleophilic addition to  $\alpha,\beta$ -unsaturated carbonyl compounds is generally controlled by the relative electrophilicity of the carbonyl group, steric interactions of both electrophiles and nucleophiles as well as the hard and soft nature of the nucleophiles. Besides the organo-copper reagents,<sup>2</sup> various other transition metal catalyzed selective conjugate addition reactions have been well documented.<sup>3</sup> In comparison with the  $\alpha,\beta$ -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<sup>4</sup> and organomagnesium reagents,<sup>5</sup> copper reagents,<sup>6</sup> rhodium(i) catalyzed arylboronic acids,<sup>7</sup> and gold(III) catalysts<sup>8</sup> have been reported for the selective 1,4 additions to  $\alpha,\beta$ -unsaturated acids.

Recently we have reported the synthesis, reactivity, conformational analysis and antimicrobial activities of hybrid peptides containing naturally occurring *E*- $\alpha,\beta$ -unsaturated  $\gamma$ -amino acids.<sup>9</sup> All peptide coupling reactions of these *E*-vinylogous amino acids have been performed using standard HBTU/HOBt coupling conditions. The 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 syntheses with or without an additional equivalent of HOBt.<sup>10</sup> In an accidental encounter in the absence of a free amine coupling partner, we observed a HOBt conjugate addition product of the *E*- $\alpha,\beta$ -unsaturated  $\gamma$ -amino acid. As unsaturated carboxylic acids have been proven difficult to undergo conjugate addition reactions under 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*- $\alpha,\beta$ -unsaturated  $\gamma$ -amino acids, stereochemical analysis of the conjugate addition products, their utility in the synthesis of peptides and the crystal conformations of  $\beta$ -BtO substituted  $\gamma$ -amino esters and peptides.

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† Electronic supplementary information (ESI) available: <sup>1</sup>H and <sup>13</sup>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**. CCDC 1012298–1012302. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c4ob01548g

### Results and discussion

Ethyl esters of *E*-vinylogous amino acids (**1**) were synthesized starting from  $\alpha$ -amino aldehydes using the Wittig reaction as reported earlier (Scheme 1).<sup>9a</sup> Saponification of the ethyl esters



**Scheme 1** Synthesis of  $\alpha,\beta$ -unsaturated  $\gamma$ -amino acids, R = a,  $-\text{CH}_2\text{-Ph}$ ; b,  $-\text{CH}-(\text{CH}_3)_2$ ; c,  $-\text{CH}_2-\text{CH}(\text{CH}_3)_2$ ; d,  $-\text{CH}_2-\text{C}_6\text{H}_4-\text{OBu}^t$ ; e,  $-\text{CH}(\text{CH}_3)-\text{CH}_2-\text{CH}_3$ ; f,  $\alpha,\beta$ -unsaturated  $\gamma$ -proline.

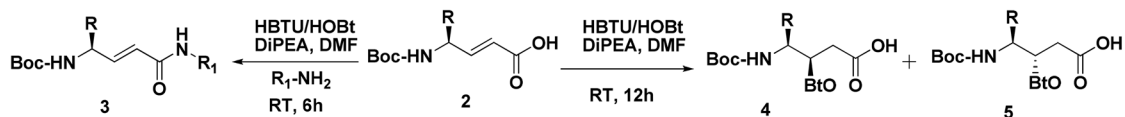
leads to the free *E*-vinylogous amino acids (2). The schematic representation of the HOBt conjugate addition in the absence and presence of the free amine coupling partner is shown in Scheme 2. In the absence of the free amine coupling partner, we isolated the diastereomeric mixture of HOBt conjugate addition products (4 + 5) in moderate to good yields from the  $\alpha,\beta$ -unsaturated  $\gamma$ -amino acids, 2a-f (Scheme 2). No conjugate addition products were observed in the presence of the free amine coupling partner. In addition, no HOBt conjugate addition products were observed with HBTU alone suggesting the requirement of an additional HOBt for the conjugate addition. Though the  $\beta$ -BtO substituted  $\gamma$ -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 by 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.

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 by 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 Table 1. We observed moderate diastereoselectivity in the conjugate addition and based on the earlier reports on the Michael addition to the *E*-vinylogous amino esters,<sup>9c,11</sup> we anticipated that the *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

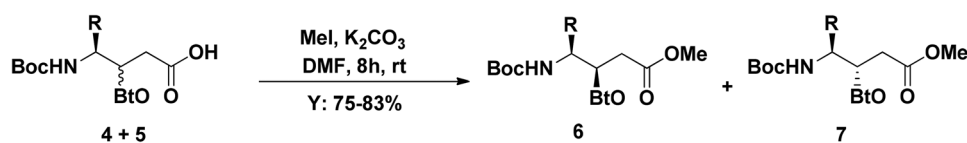
using other coupling additives, pentafluorophenol and *N*-hydroxysuccinimide, in the presence of HBTU. Mass spectral analysis of the products reveals no conjugate addition from both pentafluorophenol as well as *N*-hydroxysuccinimide rather we isolated the corresponding active esters.

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 obtain the single crystals for minor (6a) and major (7a) diastereoisomers of  $\beta$ -BtO substituted  $\gamma$ -phenylalanine and the minor isomer of  $\beta$ -BtO substituted  $\gamma$ -leucine (6c). The crystal structures of these diastereoisomers are shown in Fig. 1.

The crystal structure analysis reveals that as anticipated *anti* (7) is the major product and *syn* addition product (6) is the 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 the 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 both *N*-acylation and *O*-acylation properties of HOBt and their solvent dependent equilibrium properties.<sup>12</sup> Furthermore, 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 that the *N*-acylation is an intermolecularly driven process. We observed no HOBt conjugate addition product from the coupling reaction involving HBTU alone, supporting the intermolecular conjugate addition. Based on



**Scheme 2** Amide coupling and conjugate addition of HOBt with *E*-vinylogous  $\gamma$ -amino acids.



**Scheme 3** Esterification of the HOBt conjugate addition product of  $\gamma$ -amino acids, R = a,  $-\text{CH}_2\text{-Ph}$ ; b,  $-\text{CH}-(\text{CH}_3)_2$ ; c,  $-\text{CH}_2-\text{CH}(\text{CH}_3)_2$ ; d,  $-\text{CH}_2-\text{C}_6\text{H}_4-\text{OBu}^t$ ; e,  $-\text{CH}(\text{CH}_3)-\text{CH}_2-\text{CH}_3$ ; f,  $\alpha,\beta$ -unsaturated  $\gamma$ -proline.

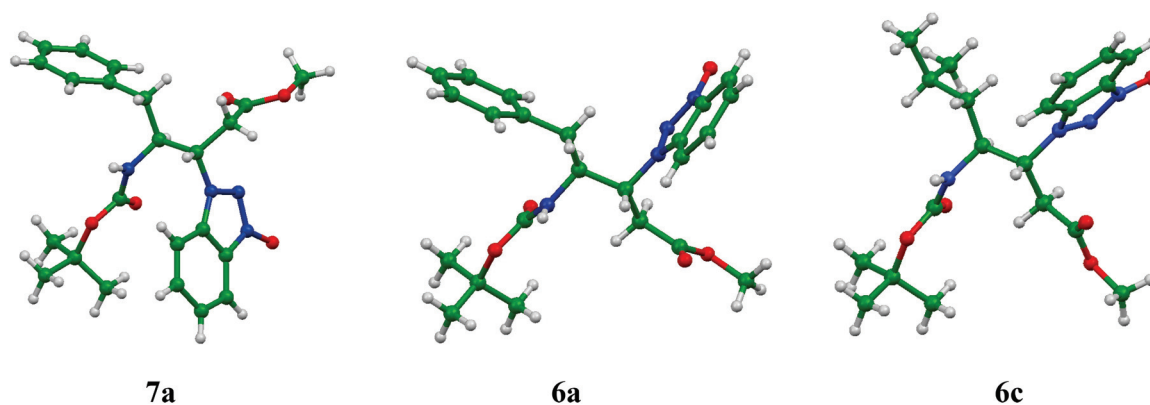
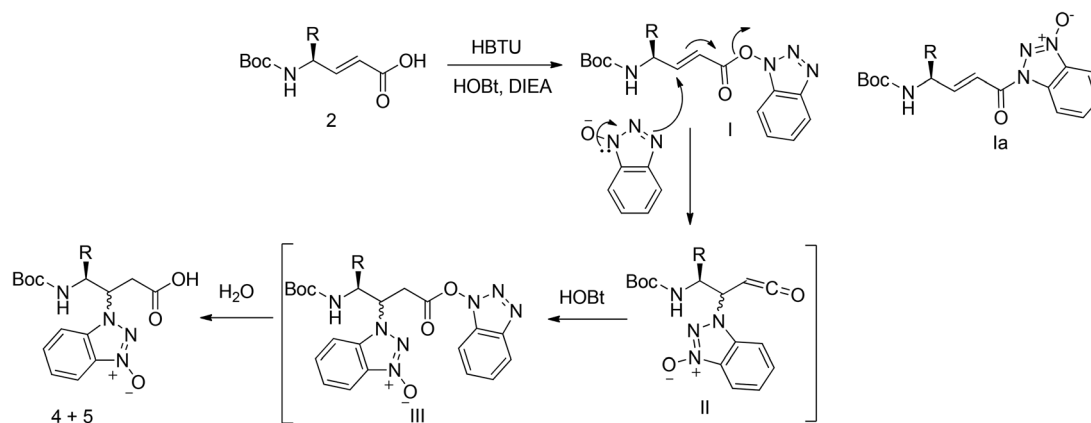
**Table 1** List of  $\beta$ -BtO substituted  $\gamma$ -amino acid methyl esters and their diastereomeric ratios

AA	6 + 7	% Yield (6 + 7)	% <i>Syn</i> (6)	% <i>Anti</i> (7)
a		75	39	61
b		80	37	63
c		83	41	59
d		70	40	60

this experimental evidence the possible reaction mechanism of the HOBt conjugate addition is outlined in Scheme 4.

We anticipate that the active ester (**I**) and/or amide (**1a**), obtained after the treatment of HBTU in the presence of a base, will react further with the HOBt leading to the formation of the diastereomeric mixture **II** which will immediately react further with HOBt to give the active ester **III**. The hydrolysis of the active ester **III** during the aqueous work-up gave the diastereomeric conjugate addition products **4** and **5**. Furthermore, we speculate that the soft nucleophilic nature of triazole nitrogen (*N*) may be preferred for the conjugate addition over the hard nucleophilic 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 hydantoin have been recently reported.<sup>13</sup>

Based on the encouraging results from the methyl esters of HOBt conjugate addition products, we subjected the  $\beta$ -BtO substituted diastereomeric mixture of **4** and **5** directly to the

**Fig. 1** X-ray structures of **7a**, **6a** and **6c**.**Scheme 4** Schematic representation of the conjugate addition of HOBt.

peptide synthesis, anticipating that it may be possible to separate the diastereomeric dipeptides once they coupled to the  $\alpha$ -amino acid esters. In this regard, the conjugate addition products of **2c** (**4c** + **5c**) were directly coupled 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 by column chromatography in the ratios of 41 and 59% respectively (Table 2). The dipeptides **9i** and **9ii** were synthesized from the coupling reaction between methyl ester of Leu and the 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. The overall yield and the diastereomeric ratios of dipeptides are given in Table 2.

We further subjected dipeptide **8ii** for the synthesis of the tripeptide Boc-Phe- $\gamma$ Leu( $\beta$ -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 the 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 Fig. 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- $\alpha,\beta$ -unsaturated  $\gamma$ -phenylalanine reveals that both molecules adopted the unfavorable staggered conformation along the  $C^\beta-C^\gamma$  bond. Molecule **7a** adopted *t* and  $g^-$  conformations, while **6a** displayed  $g^+$  and *t* conformations along  $C^\beta-C^\gamma$  and  $C^\beta-C^\alpha$  bonds, respectively. Similarly, *syn* addition products **6b** and  $\gamma$ Val(BtO) in the dipeptide (**10i**) showed  $g^+$  and *t* conformations. In contrast, *anti*  $\gamma$ Leu(BtO) in the tripeptide **13** follows the general trend of tetra alkyl substituted ethane by adopting the *gauche* conformations<sup>14</sup> along the  $C^\beta-C^\gamma$  bond and displayed the *anti(t)* conformation along the backbone  $C^\beta-C^\alpha$  bond. Recently, Alezra *et al.* reported the conformational diversity of foldamers composed of  $\beta$ -substituted  $\gamma$ -amino acids.<sup>15</sup> The Michael addition of HOBt to the *E*-vinylogous amino acids reported here may serve as the direct route for the synthesis of  $\beta$ -substituted  $\gamma$ -amino acids.

Table 2 List of the peptides synthesized using  $\beta$ -BtO substituted  $\gamma$ -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

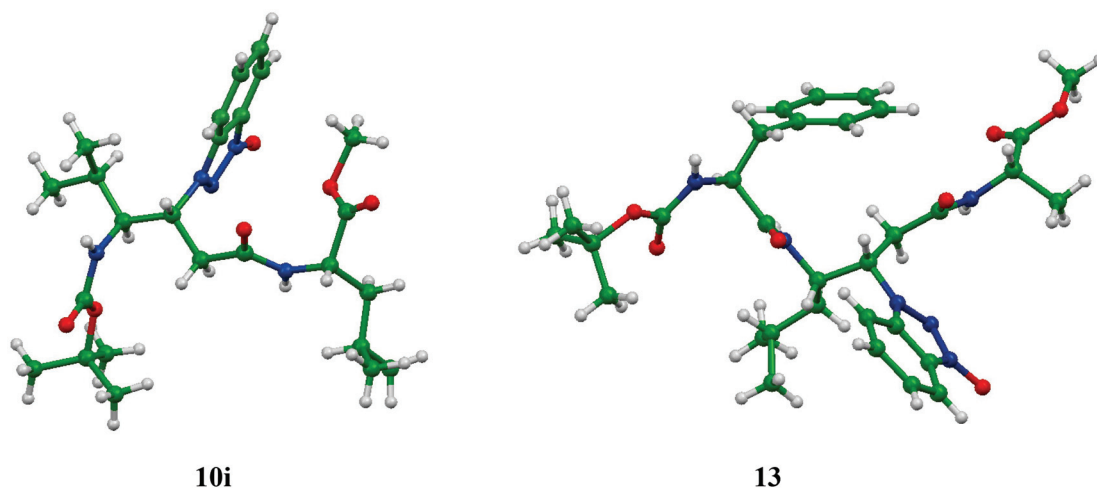


Fig. 2 The X-ray structures of Boc- $\gamma$ Val( $\beta$ -BtO)-Leu-OMe (**10i**) and Boc-Phe- $\gamma$ Leu( $\beta$ -BtO)-Ala-OMe (**13**).

## Conclusions

In conclusion, we have demonstrated the HBTU mediated HOBt conjugate addition to the  $\alpha,\beta$ -unsaturated  $\gamma$ -amino acids. Using this mild and facile methodology, various  $\beta$ -BtO substituted  $\gamma$ -amino acids were synthesized and utilized in the peptide synthesis. Experimental evidence suggests that HOBt conjugate addition is an intermolecular reaction with moderate diastereoselectivity. The stereochemistry of the novel  $\beta$ -BtO substituted  $\gamma$ -amino acids was analyzed using single crystal X-ray structures from both the monomers as well as 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 been studied due to their inherent limitations, the results reported here may provide an opportunity to extend this methodology to other  $\alpha,\beta$ -unsaturated acids. The  $\beta$ -substituted  $\gamma$ -amino acids reported here can be directly utilized for the construction of peptide foldamers.

## Experimental section

### General information

All amino acids, Weinreb amine hydrochloride salt, DCC, LAH, DIEA, PPh<sub>3</sub>, 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). <sup>1</sup>H NMR spectra were recorded on a 400 MHz instrument (100 MHz for <sup>13</sup>C NMR) using residual solvent as the internal standard (CDCl<sub>3</sub>  $\delta_{\text{H}}$ , 7.24 ppm,  $\delta_{\text{C}}$  77.0 ppm and DMSO-*d*<sub>6</sub>  $\delta_{\text{H}}$ , 2.5 ppm  $\delta_{\text{C}}$  40.0 ppm). The chemical shifts ( $\delta$ ) were reported in ppm and the coupling constant (*J*) in Hz. High resolution mass spectra were obtained using an ESI-TOF MS spectrometer and a MALDI-TOF/TOF spectrometer.

**General procedure for the synthesis of  $\alpha,\beta$ -unsaturated  $\gamma$ -amino esters.**<sup>9a</sup> The *N*-protected amino aldehyde (10 mmol) was dissolved in dry THF (40 mL) under a N<sub>2</sub> 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 the product was purified by column chromatography using the 5 : 95 ethyl acetate–pet ether solvent system.

**Saponification of *N*-protected  $\alpha,\beta$ -unsaturated  $\gamma$ -amino esters.**<sup>9a</sup> The *N*-protected vinyllogous 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 3 h. The progress of reaction was monitored by TLC. After completion of reaction (3 h), 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  $\times$  3). The organic layer was washed with brine, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure to give the *N*-protected vinyllogous amino acid in average 95% yield.

**General procedure for the synthesis of  $\beta$ -BtO substituted  $\gamma$ -amino acids.** The *N*-protected *E*-vinyllogous amino acid (1.6 mmol) was dissolved in 2 mL of dry DMF under a N<sub>2</sub> atmosphere. To this solution HBTU (1.6 mmol) and HOBt (3.2 mmol) were added. The reaction mixture was cooled at 0 °C prior to the addition of DIEA (3.2 mmol). This reaction mixture was allowed to stir for another 12 h. After 12 h, 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  $\times$  20 mL). The combined organic layer was then washed with brine, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure to give  $\beta$ -BtO substituted  $\gamma$ -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  $\beta$ -BtO substituted *N*-protected  $\gamma$ -amino acids.** Beta-BtO substituted



$\gamma$ -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 8 h. After completion of reaction (monitored by TLC), the reaction mixture was diluted with water (70 mL) and extracted with ethyl acetate (25 mL  $\times$  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 by column chromatography using the 70 : 30 (EtOAc–pet ether) solvent system.

**General procedure for the synthesis of  $\beta$ -BtO substituted *N*-protected  $\gamma$ -amino acids containing dipeptides.** The hydrochloride salt of amino acid methyl ester (HCl-NH<sub>2</sub>-Xaa-OMe) (3 mmol) was dissolved in water and pH was adjusted to 12 by adding solid  $Na_2CO_3$  under ice cold conditions. The aqueous solution was then extracted with ethyl acetate (30 mL  $\times$  3). The combined organic layer was then washed with brine and dried over anhydrous  $Na_2SO_4$ , concentrated to  $\sim$ 2 mL under reduced pressure and used in the next step.

The beta-BtO substituted *N*-protected  $\gamma$ -amino acid (2 mmol) was dissolved in dry DMF under a  $N_2$  atmosphere. To this solution, methyl ester of the amino acid ( $\sim$ 2 mL, from the above step) was added. The reaction mixture was cooled to 0 °C and then DCC (2 mmol) was added. The reaction mixture was allowed to stir for another 12 h and progress of the reaction was monitored by TLC. After completion of reaction, the 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), 10%  $Na_2CO_3$  (20 mL), and brine and dried over  $Na_2SO_4$ . The organic layer was concentrated under reduced pressure to obtain a diastereomeric mixture (**i** and **ii**) of dipeptides. These dipeptides were separated by column chromatography using the 2 : 98 (MeOH–DCM) solvent system.

**Procedure for the synthesis of tripeptide Boc-Phe- $\gamma$ Leu ( $\beta$ -BtO)-Ala-OMe (**13**).** NH<sub>2</sub>- $\gamma$ Leu( $\beta$ -BtO)-Ala-OMe: Boc- $\gamma$ Leu( $\beta$ -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 (1 h) (monitored by TLC), TFA was evaporated under reduced pressure. The residue was dissolved in water and pH of the solution was adjusted to  $\sim$ 12 by adding solid  $Na_2CO_3$  under ice cold conditions. This aqueous solution was then extracted with ethyl acetate (25 mL  $\times$  3), washed with brine, and dried over  $Na_2SO_4$ . The organic layer was concentrated under reduced pressure to  $\sim$ 2 mL and used in the next step.

The Boc-Phe-OH (110 mg, 0.4 mmol) and NH<sub>2</sub>- $\gamma$ Leu( $\beta$ -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 overnight (12 h). After completion of reaction (12 h), the reaction mixture was diluted with ethyl acetate (75 mL), washed with 5% HCl, 10%  $Na_2CO_3$  and brine, and dried over anhydrous  $Na_2SO_4$ . The organic layer was concentrated under

reduced pressure to give the crude tripeptide. The pure tripeptide Boc-Phe- $\gamma$ Leu( $\beta$ -BtO)-Ala-OMe was isolated as a white solid in 67% yield after column purification in the 80 : 20 (Ethyl acetate–Pet ether) solvent system.

*(S,E)*-Ethyl 4-((*tert*-butoxycarbonyl)amino)-5-phenylpent-2-enoate (**1a**). White powder (4.01 g, 84%), mp 70 °C, UV ( $\lambda_{max}$ ) 206 nm, 255 nm,  $[\alpha]_D^{25}$   $-2.0$  (*c* 1.0, MeOH). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  = 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. <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  = 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<sub>18</sub>H<sub>25</sub>NO<sub>4</sub> [*M* + Na<sup>+</sup>] 342.1681; found 342.1657.

*(S,E)*-Ethyl 4-((*tert*-butoxycarbonyl)amino)-5-methylhex-2-enoate (**1b**). White solid (yield 2.43 g, 90%). mp 59 °C, UV ( $\lambda_{max}$ ) 216 nm,  $[\alpha]_D^{25}$   $-3.40$  (*c* 1.0, MeOH). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  = 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. <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  = 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<sub>14</sub>H<sub>25</sub>NO<sub>4</sub> [*M* + Na<sup>+</sup>] 294.1681; found 294.1686.

*(S,E)*-Ethyl 4-((*tert*-butoxycarbonyl)amino)-6-methylhept-2-enoate (**1c**). White solid (2.70 g, 95%), mp 55 °C, UV ( $\lambda_{max}$ ) 218 nm,  $[\alpha]_D^{25}$   $-25.50$  (*c* 1.0, MeOH). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  = 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. <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  = 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<sub>15</sub>H<sub>27</sub>NO<sub>4</sub> [*M* + Na<sup>+</sup>] 308.1838; found 308.1840.

*(4S,5R,E)*-Ethyl 4-((*tert*-butoxycarbonyl)amino)-5-methylhept-2-enoate (**1d**). White solid (yield 2.62 g, 92%), mp 62 °C, UV ( $\lambda_{max}$ ) 216 nm,  $[\alpha]_D^{25}$   $-11.20$  (*c* 1.0, MeOH). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  = 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. <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  = 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<sub>15</sub>H<sub>27</sub>NO<sub>4</sub> [*M* + Na<sup>+</sup>] 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 ( $\lambda_{max}$ ) 222 nm, 265 nm, 274 nm, 285 nm,  $[\alpha]_D^{25}$  4.0 (*c* 0.1, MeOH). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  = 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. <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  = 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<sub>22</sub>H<sub>33</sub>NO<sub>5</sub> [*M* + Na<sup>+</sup>] 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 ( $\lambda_{max}$ ) 214 nm,

$[\alpha]_{\text{D}}^{25}$   $-72.0$  ( $c$  1.0, MeOH).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  = 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.  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  = 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  $\text{C}_{14}\text{H}_{23}\text{NO}_4$   $[\text{M} + \text{Na}^+]$  292.1525; found 292.1520.

1-((3*R*,4*S*)-4-(*tert*-Butoxycarbonylamino)-1-methoxy-1-oxo-5-phenylpentan-3-yl)-1*H*-benzo[*d*][1,2,3]triazole 3-oxide (Boc- $\gamma$ Phe( $\beta$ -BtO)-OMe) (**6a**)<sup>syn</sup>. White solid (0.204 g, 30%), the diastereomeric ratio of **6a** : **7a** is 39:61, mp 220–222 °C,  $[\alpha]_{\text{D}}^{25}$   $-7.4$  ( $c$  0.1, MeOH), UV ( $\lambda_{\text{max}}$ ) 323 nm, 274 nm, IR (neat)  $\nu$  ( $\text{cm}^{-1}$ ) 3362, 2973, 2928, 1736, 1604, 1504, 1458, 1425, 1306, 1208, 1134, 748.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  = 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.  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  = 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  $\text{C}_{23}\text{H}_{28}\text{N}_4\text{O}_5$   $[\text{M} + \text{H}^+]$  is 441.2138; found 441.2134.

1-((3*S*,4*S*)-4-(*tert*-Butoxycarbonylamino)-1-methoxy-1-oxo-5-phenylpentan-3-yl)-1*H*-benzo[*d*][1,2,3]triazole 3-oxide (Boc- $\gamma$ Phe( $\beta$ -BtO)-OMe) (**7a**)<sup>anti</sup>. White solid (0.320 g, 45%), mp 190–192 °C,  $[\alpha]_{\text{D}}^{25}$   $-0.2$  ( $c$  0.1, MeOH), UV ( $\lambda_{\text{max}}$ ) 323 nm, 274 nm, IR (neat)  $\nu$  ( $\text{cm}^{-1}$ ) 3360, 2971, 2921, 1736, 1604, 1507, 1458, 1425, 1367, 1311, 1209, 1167, 1024, 747.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  = 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.  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  = 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  $\text{C}_{23}\text{H}_{28}\text{N}_4\text{O}_5$   $[\text{M} + \text{H}^+]$  is 441.2138; found 441.2138.

1-((3*R*,4*S*)-4-((*tert*-Butoxycarbonyl)amino)-1-methoxy-5-methyl-1-oxohexan-3-yl)-1*H*-benzo[*d*][1,2,3]triazole 3-oxide (Boc- $\gamma$ Val( $\beta$ -BtO)-OMe) (**6b**)<sup>syn</sup>. White powder (0.185 g, 32%), the diastereomeric ratio of **6b** : **7b** is 37:63; mp 164–166 °C,  $[\alpha]_{\text{D}}^{25}$   $-1.0$  ( $c$  0.1, MeOH), UV ( $\lambda_{\text{max}}$ ) 323 nm, IR (neat)  $\nu$  ( $\text{cm}^{-1}$ ) 2968, 1736, 1707, 1605, 1503, 1460, 1423, 1390, 1366, 1303, 1241, 1199, 1165, 1109, 1022, 749.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  = 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.  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  = 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  $\text{C}_{19}\text{H}_{28}\text{N}_4\text{O}_5$   $[\text{M} + \text{H}^+]$  is 393.2138; found 393.2147.

1-((3*S*,4*S*)-4-(*tert*-Butoxycarbonylamino)-1-methoxy-5-methyl-1-oxohexan-3-yl)-1*H*-benzo[*d*][1,2,3]triazole 3-oxide (Boc- $\gamma$ Val( $\beta$ -BtO)-OMe)

(**7b**)<sup>anti</sup>. White powder (0.315 g, 48%), mp 173–175 °C,  $[\alpha]_{\text{D}}^{25}$   $-7.2$  ( $c$  0.1, MeOH), UV ( $\lambda_{\text{max}}$ ) 323 nm, IR (neat)  $\nu$  ( $\text{cm}^{-1}$ ) 3272, 2966, 2928, 1738, 1690, 1606, 1506, 1423, 1394, 1308, 1250, 1167, 1033.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  = 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.  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  = 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  $\text{C}_{19}\text{H}_{28}\text{N}_4\text{O}_5$   $[\text{M} + \text{H}^+]$  is 393.2138; found 393.2143.

1-((3*R*,4*S*)-4-(*tert*-Butoxycarbonylamino)-1-methoxy-6-methyl-1-oxoheptan-3-yl)-1*H*-benzo[*d*][1,2,3]triazole 3-oxide (Boc- $\gamma$ Leu( $\beta$ -BtO)-OMe) (**6c**)<sup>syn</sup>. White solid (0.220 g, 33%), the diastereomeric ratio of **6c** : **7c** is 41:59, mp 130–132 °C,  $[\alpha]_{\text{D}}^{25}$   $-7.0$  ( $c$  0.1, MeOH), UV ( $\lambda_{\text{max}}$ ) 323 nm, IR (neat)  $\nu$  ( $\text{cm}^{-1}$ ) 3360, 3267, 2957, 1735, 1704, 1605, 1510, 1460, 1398, 1366, 1317, 1248, 1167, 1035, 749.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  = 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.  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  = 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  $\text{C}_{20}\text{H}_{30}\text{N}_4\text{O}_5$   $[\text{M} + \text{H}^+]$  is 407.2294; found 407.2300.

1-((3*S*,4*S*)-4-(*tert*-Butoxycarbonylamino)-1-methoxy-6-methyl-1-oxoheptan-3-yl)-1*H*-benzo[*d*][1,2,3]triazole 3-oxide (Boc- $\gamma$ Leu( $\beta$ -BtO)-OMe) (**7c**)<sup>anti</sup>. White solid (0.317 g, 50%), mp 95–97 °C,  $[\alpha]_{\text{D}}^{25}$   $-1.6$  ( $c$  0.1, MeOH), UV ( $\lambda_{\text{max}}$ ) 323 nm, IR (neat)  $\nu$  ( $\text{cm}^{-1}$ ) 3360, 3270, 2956, 2927, 2863, 2315, 1737, 1702, 1607, 1506, 1460, 1424, 1394, 1367, 1262, 1167, 1115, 1038, 749.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  = 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.  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  = 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  $\text{C}_{20}\text{H}_{30}\text{N}_4\text{O}_5$   $[\text{M} + \text{H}^+]$  is 407.2294; found 407.2303.

1-((3*R*, 4*S*)-5-(4-(*tert*-butoxy)phenyl)-4-((*tert*-butoxycarbonyl)amino)-1-methoxy-1-oxopentan-3-yl)-1*H*-benzo[*d*][1,2,3]triazole 3-oxide (Boc-Tyr( $\beta$ -BtO)-OMe)(**6d**)<sup>syn</sup>. Yellowish oil (0.152 g, 28%), the diastereomeric ratio of **6d** : **7d** is 40:60.  $[\alpha]_{\text{D}}^{25}$   $-7.0$  ( $c$  0.1, MeOH), UV ( $\lambda_{\text{max}}$ ) 219 nm, 273 nm, 280 nm, 323 nm, IR (neat)  $\nu$  ( $\text{cm}^{-1}$ ) 3424, 2923, 1609, 1400, 1108, 740, 619.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  = 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.  $^{13}\text{C}$  NMR  $\delta$  = 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  $\text{C}_{27}\text{H}_{36}\text{N}_4\text{O}_6$   $[\text{M} + \text{H}^+]$  513.2713; found 513.2717.

1-((3*S*, 4*S*)-5-(4-(*tert*-butoxy)phenyl)-4-((*tert*-butoxycarbonyl)amino)-1-methoxy-1-oxopentan-3-yl)-1*H*-benzo[*d*][1,2,3]triazole

3-oxide (*Boc-Tyr*( $\beta$ -*BtO*)-*OMe*) (**7d**)<sup>anti</sup>. Yellowish oil (0.240 g, 42%),  $[\alpha]_{\text{D}}^{25} +0.2$  (c 0.1, MeOH), UV ( $\lambda_{\text{max}}$ ) 219 nm, 273 nm, 280 nm, 323 nm, IR (neat)  $\nu$  ( $\text{cm}^{-1}$ ) 3395, 2923, 1723, 1683, 1609, 1512, 1418, 1370, 1304, 1162, 1108, 895, 740, 618.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta = 7.98$  (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.  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  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  $\text{C}_{27}\text{H}_{36}\text{N}_4\text{O}_6$  [ $\text{M} + \text{H}^+$ ] 513.2713; found 513.2730.

1-((4*S*,8*R*,9*S*)-9-*Isobutyl*-4,13,13-trimethyl-3,6,11-trioxo-2,12-dioxo-5,10-diazatetradecan-8-yl)-1*H*-benzo[d][1,2,3]triazole 3-oxide (*Boc- $\gamma$ Leu*( $\beta$ -*BtO*)-*Ala*-*OMe*) (**8i**). White solid (0.273 g, 28%), The diastereomeric ratio of **8i** : **8ii** is 41:59, mp 135–137 °C,  $[\alpha]_{\text{D}}^{25} -62.0$  (c 0.1, MeOH), UV ( $\lambda_{\text{max}}$ ) 323 nm, IR (neat)  $\nu$  ( $\text{cm}^{-1}$ ) 3281, 2960, 2378, 2312, 2112, 1741, 1668, 1525, 1458, 1423, 1367, 1208, 1164, 1114, 1052, 996, 748.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta = 7.91$  (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.  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta = 173.1$ , 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  $\text{C}_{23}\text{H}_{35}\text{N}_5\text{O}_5$  [ $\text{M} + \text{Na}^+$ ] is 500.2485; found 500.2491.

1-((4*S*,8*S*,9*S*)-9-*Isobutyl*-4,13,13-trimethyl-3,6,11-trioxo-2,12-dioxo-5,10-diazatetradecan-8-yl)-1*H*-benzo[d][1,2,3]triazole 3-oxide (*Boc- $\gamma$ Leu*( $\beta$ -*BtO*)-*Ala*-*OMe*) (**8ii**). White solid (0.393 g, 42%), mp 98–100 °C,  $[\alpha]_{\text{D}}^{25} -66.0$  (c 0.1, MeOH), UV ( $\lambda_{\text{max}}$ ) 323 nm, IR (neat)  $\nu$  ( $\text{cm}^{-1}$ ) 3276, 2958, 2873, 2313, 1740, 1710, 1661, 1532, 1458, 1423, 1368, 1208, 1166, 1114, 953, 749.  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-d_6$ )  $\delta = 8.52$  (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.  $^{13}\text{C}$  NMR (100 MHz,  $\text{DMSO}-d_6$ )  $\delta = 173.0$ , 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  $\text{C}_{23}\text{H}_{35}\text{N}_5\text{O}_5$  [ $\text{M} + \text{Na}^+$ ] is 500.2485; found 500.3464.

1-((4*S*,8*R*,9*S*)-9-*sec-Butyl*-4-*isobutyl*-13,13-dimethyl-3,6,11-trioxo-2,12-dioxo-5,10-diazatetradecan-8-yl)-1*H*-benzo[d][1,2,3]triazole 3-oxide (*Boc- $\gamma$ Ile*( $\beta$ -*BtO*)-*Leu*-*OMe*) (**9i**). White solid, (0.254 g, 25%), The diastereomeric ratio of **9i** : **9ii** is 39:61, mp 230–232 °C,  $[\alpha]_{\text{D}}^{25} +20.0$  (c 0.1, MeOH), UV ( $\lambda_{\text{max}}$ ) 323 nm, IR (neat)  $\nu$  ( $\text{cm}^{-1}$ ) 2963, 2381, 2313, 2112, 1738, 1660, 1509, 1459, 1424, 1368, 1310, 1207, 1167, 749.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta = 7.96$  (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.  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta = 172.4$ , 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  $\text{C}_{26}\text{H}_{41}\text{N}_5\text{O}_6$  [ $\text{M} + \text{Na}^+$ ] is 542.2955; found 542.2957.

1-((4*S*,8*S*,9*S*)-9-*sec-Butyl*-4-*isobutyl*-13,13-dimethyl-3,6,11-trioxo-2,12-dioxo-5,10-diazatetradecan-8-yl)-1*H*-benzo[d][1,2,3]triazole 3-oxide (*Boc- $\gamma$ Ile*( $\beta$ -*BtO*)-*Leu*-*OMe*) (**9ii**). White solid (0.397 g, 37%), mp 193–195 °C,  $[\alpha]_{\text{D}}^{25} +32.0$  (c 0.1, MeOH), UV ( $\lambda_{\text{max}}$ ) 323 nm, IR (neat)  $\nu$  ( $\text{cm}^{-1}$ ) 2964, 2875, 2314, 2259, 2124, 1740, 1707, 1664, 1545, 1460, 1425, 1369, 1207, 1168, 1022, 992, 825, 754,  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-d_6$ )  $\delta = 8.49$  (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.  $^{13}\text{C}$  NMR (100 MHz,  $\text{DMSO}-d_6$ )  $\delta = 172.8$ , 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  $\text{C}_{26}\text{H}_{41}\text{N}_5\text{O}_6$  [ $\text{M} + \text{Na}^+$ ] is 542.2955; found 542.2950.

1-((4*S*,8*R*,9*S*)-4-*Isobutyl*-9-*isopropyl*-13,13-dimethyl-3,6,11-trioxo-2,12-dioxo-5,10-diazatetradecan-8-yl)-1*H*-benzo[d][1,2,3]triazole 3-oxide (*Boc- $\gamma$ Val*( $\beta$ -*BtO*)-*Leu*-*OMe*) (**10i**). White solid (0.249 g, 26%), The diastereomeric ratio of **10i** : **10ii** is 37:63, mp 200–202 °C,  $[\alpha]_{\text{D}}^{25} +18.0$  (c 0.1, MeOH), UV ( $\lambda_{\text{max}}$ ) 323 nm, IR (neat)  $\nu$  ( $\text{cm}^{-1}$ ) 2964, 2312, 2117, 1740, 1542, 1425, 1368, 1311, 1210, 1092, 748.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta = 7.95$  (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.  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta = 173.0$ , 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  $\text{C}_{25}\text{H}_{39}\text{N}_5\text{O}_6$  [ $\text{M} + \text{Na}^+$ ] is 528.2798; found 528.2780.

1-((4*S*,8*S*,9*S*)-4-*Isobutyl*-9-*isopropyl*-13,13-dimethyl-3,6,11-trioxo-2,12-dioxo-5,10-diazatetradecan-8-yl)-1*H*-benzo[d][1,2,3]triazole 3-oxide (*Boc- $\gamma$ Val*( $\beta$ -*BtO*)-*Leu*-*OMe*) (**10ii**). White solid (0.425 g, 41%), mp 230–232 °C,  $[\alpha]_{\text{D}}^{25} +40.0$  (c 0.1, MeOH), UV ( $\lambda_{\text{max}}$ ) 323 nm, IR (neat)  $\nu$  ( $\text{cm}^{-1}$ ) 2962, 2928, 2314, 1737, 1543, 1459, 1424, 1368, 1310, 1208, 1169, 1089, 1038, 747.  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-d_6$ )  $\delta = 8.47$  (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.  $^{13}\text{C}$  NMR (100 MHz,  $\text{DMSO}-d_6$ )  $\delta = 172.7$ , 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  $\text{C}_{25}\text{H}_{39}\text{N}_5\text{O}_6$  [ $\text{M} + \text{Na}^+$ ] 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, mp 110–112 °C,  $[\alpha]_{\text{D}}^{25}$  –22.0 (c 0.1, MeOH), UV ( $\lambda_{\text{max}}$ ) 323 nm, IR (neat)  $\nu$  (cm<sup>-1</sup>) 2966, 2313, 1740, 1687, 1544, 1507, 1455, 1368, 1210, 1164, 907, 748. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  = 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. <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  = 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<sub>25</sub>H<sub>37</sub>N<sub>5</sub>O<sub>6</sub> [M + Na<sup>+</sup>] 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,  $[\alpha]_{\text{D}}^{25}$  –18.0 (c 0.1, MeOH), UV ( $\lambda_{\text{max}}$ ) 323 nm, IR (neat)  $\nu$  (cm<sup>-1</sup>) 3023, 2967, 2129, 1739, 1653, 1509, 1443, 1368, 1221, 1022, 990, 763. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  = 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. <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  = 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<sub>25</sub>H<sub>37</sub>N<sub>5</sub>O<sub>6</sub> [M + Na<sup>+</sup>] is 526.2642; found 526.2639.

1-((4S,8R,9S)-9-Benzyl-4-isobutyl-13,13-dimethyl-3,6,11-trioxo-2,12-dioxo-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, mp 175–177 °C,  $[\alpha]_{\text{D}}^{25}$  +42.0 (c 0.1, MeOH), UV ( $\lambda_{\text{max}}$ ) 323 nm, 274, IR (neat)  $\nu$  (cm<sup>-1</sup>) 2960, 2130, 1739, 1655, 1526, 1505, 1458, 1425, 1368, 1209, 1164, 1022, 991, 749. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  = 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. <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  = 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<sub>29</sub>H<sub>39</sub>N<sub>5</sub>O<sub>6</sub> [M + Na<sup>+</sup>] is 576.2798; found 576.2814.

1-((4S,8S,9S)-9-Benzyl-4-isobutyl-13,13-dimethyl-3,6,11-trioxo-2,12-dioxo-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,  $[\alpha]_{\text{D}}^{25}$  +32.0 (c 0.1, MeOH), UV ( $\lambda_{\text{max}}$ ) 323 nm, 274 nm, IR (neat)  $\nu$  (cm<sup>-1</sup>) 3026, 2966, 2313, 1739, 1653, 1542, 1524, 1456, 1425, 1368, 1210, 1022, 992, 757. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  = 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. <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  = 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<sub>29</sub>H<sub>39</sub>N<sub>5</sub>O<sub>6</sub> [M + Na<sup>+</sup>] 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-dioxo-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 ( $\lambda_{\text{max}}$ ) 323 nm, <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  = 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. <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  = 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<sub>32</sub>H<sub>44</sub>N<sub>6</sub>O<sub>7</sub> [M + Na<sup>+</sup>] 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 a loop with a small amount of the paraffin oil. The X-ray data were collected at 173 K on a Bruker APEX DUO CCD diffractometer using Cu K<sub>α</sub> radiation ( $\lambda$  = 1.54178 Å),  $\omega$ -scans ( $2\theta$  = 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<sup>3</sup>, orthorhombic P, *Z* = 4 for the chemical formula C<sub>23</sub>H<sub>29</sub>N<sub>4</sub>O<sub>5</sub> with one molecule in the asymmetric unit;  $\rho_{\text{calcd}}$  = 1.428 g cm<sup>-3</sup>,  $\mu$  = 0.781 mm<sup>-1</sup>, *F*(000) = 968, *R*<sub>int</sub> = 0.0201. The structure was obtained by direct methods using SHELXS-97. The final *R* value was 0.0831 (*wR*<sub>2</sub> = 0.2275), 3712 observed reflections (*F*<sub>0</sub> ≥ 4σ(|*F*<sub>0</sub>|)) and 281 variables, *S* = 1.224. The largest difference peak and holes were 1.376 and –0.726 e Å<sup>-3</sup>, respectively.

**Crystal structure analysis of Boc-γF(β-BtO)-OMe (6a).** Crystals of peptides 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 a loop with a small amount of the paraffin oil. The X-ray data were collected at 100 K on a Bruker APEX DUO CCD diffractometer using Cu K<sub>α</sub> radiation ( $\lambda$  = 1.54178 Å),  $\omega$ -scans ( $2\theta$  = 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<sup>3</sup>, orthorhombic P, *Z* = 4 for the chemical formula C<sub>23</sub>H<sub>29</sub>N<sub>4</sub>O<sub>5</sub> with one molecule in the asymmetric unit;  $\rho_{\text{calcd}}$  = 1.247 g cm<sup>-3</sup>,  $\mu$  = 0.731 mm<sup>-1</sup>, *F*(000) = 940, *R*<sub>int</sub> = 0.056. The structure was

obtained by direct methods using SHELXS-97. The final  $R$  value was 0.0479 ( $wR_2 = 0.1263$ ) 4083 observed reflections ( $F_0 \geq 4\sigma(|F_0|)$ ) and 293 variables,  $S = 1.049$ . The largest difference peak and holes were 0.213 and  $-0.219 \text{ e } \text{\AA}^{-3}$ , respectively.

**Crystal structure analysis of Boc- $\gamma$ L( $\beta$ -BtO)-OMe (6c).** Crystals of peptides were grown by slow evaporation from a solution of EtOAc. A single crystal ( $0.2 \times 0.05 \times 0.01 \text{ mm}$ ) was mounted on a loop with a small amount of the paraffin oil. The X-ray data were collected at 100 K on a Bruker APEX DUO CCD diffractometer using Mo  $K_\alpha$  radiation ( $\lambda = 0.71073 \text{ \AA}$ ),  $\omega$ -scans ( $2\theta = 56.56^\circ$ ), for a total of 5506 independent reflections. Space group  $P2(1)2(1)2(1)$ ,  $a = 9.730(5)$ ,  $b = 10.761(5)$ ,  $c = 21.944(10)$ ,  $V = 2297.7(19) \text{ \AA}^3$ , orthorhombic  $P$ ,  $Z = 4$  for the chemical formula  $C_{20}H_{30}N_4O_5$  with one molecule in the asymmetric unit;  $\rho_{\text{calcd}} = 1.172 \text{ g cm}^{-3}$ ,  $\mu = 0.085 \text{ mm}^{-1}$ ,  $F(000) = 868$ ,  $R_{\text{int}} = 0.2494$ . The structure was obtained by direct methods using SHELXS-97. The final  $R$  value was 0.0791 ( $wR_2 = 0.1449$ ) for 5506 observed reflections ( $F_0 \geq 4\sigma(|F_0|)$ ) and 268 variables,  $S = 0.887$ . The largest difference peak and holes were 0.305 and  $-0.289 \text{ e } \text{\AA}^{-3}$  respectively.

**Crystal structure analysis of Boc- $\gamma$ V( $\beta$ -BtO)-L-OMe (10i).** Crystals of the peptide were grown by slow evaporation from a solution of EtOAc. A single crystal ( $0.12 \times 0.04 \times 0.015 \text{ mm}$ ) was mounted on a loop with a small amount of the paraffin oil. The X-ray data were collected at 200 K on a Bruker APEX DUO CCD diffractometer using Mo  $K_\alpha$  radiation ( $\lambda = 0.71073 \text{ \AA}$ ),  $\omega$ -scans ( $2\theta = 56.56^\circ$ ), for a total of 5643 independent reflections. Space group triclinic  $P1$ ,  $a = 10.152(9)$ ,  $b = 12.510(11)$ ,  $c = 12.604(11)$ ,  $V = 1425(2) \text{ \AA}^3$ , triclinic  $P1$ ,  $Z = 1$  for the chemical formula  $C_{25}H_{39}N_5O_6$  with two molecules in the asymmetric unit;  $\rho_{\text{calcd}} = 1.178 \text{ g cm}^{-3}$ ,  $\mu = 0.085 \text{ mm}^{-1}$ ,  $F(000) = 544$ ,  $R_{\text{int}} = 0.1355$ . The structure was obtained by direct methods using SHELXS-97. The final  $R$  value was 0.0954 ( $wR_2 = 0.2236$ ) for 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  $-0.378 \text{ e } \text{\AA}^{-3}$  respectively. Though we diffracted the crystal up to  $0.75 \text{ \AA}$  resolution, the crystal still diffracted quite weakly. We could get only small crystals on the thorough crystallization process.

**Crystal structure analysis of (Boc-Phe- $\gamma$ Leu( $\beta$ -BtO)-Ala-OMe (13).** Crystals of the peptide were grown by slow evaporation from a solution of methanol. A single crystal ( $0.34 \times 0.28 \times 0.26 \text{ mm}$ ) was mounted in a loop with a small amount of the mother liquor. The X-ray data were collected at 100 K on a Bruker AXS SMART APEX CCD diffractometer using Mo  $K_\alpha$  radiation ( $\lambda = 0.71073 \text{ \AA}$ ),  $\omega$ -scans ( $2\theta = 56.56^\circ$ ), for a total number of 8114 independent reflections. Space group  $P2(1)2(1)2(1)$ ,  $a = 9.002(3)$ ,  $b = 14.970(4)$ ,  $c = 24.507(7) \text{ \AA}$ ,  $\alpha = 90.00$ ,  $\beta = 90$ ,  $\gamma = 90.00$ ,  $V = 2894.6(9) \text{ \AA}^3$  Orthorhombic  $P$ ,  $Z = 4$  for the chemical formula  $C_{32}H_{44}N_6O_7$ , with one molecule in the asymmetric unit;  $\rho_{\text{calcd}} = 1.256 \text{ g cm}^{-3}$ ,  $\mu = 0.090 \text{ mm}^{-1}$ ,  $F(000) = 1336$ ,  $R_{\text{int}} = 0.0486$ . The structure was obtained by direct methods using SHELXS-97.<sup>1</sup> 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 ( $wR_2 = 0.0917$ ) for 6805 observed reflections ( $F_0 \geq 4\sigma(|F_0|)$ ) and 413 variables,  $S = 1.083$ . The largest difference peak and holes were 0.225 and  $-0.217 \text{ e } \text{\AA}^{-3}$ , respectively.

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