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An efficient synthesis of dehydroamino acids and dehydropeptides from *O*-Cbz and *O*-Eoc derivatives of serine and threonine

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Abstract—A simple and efficient method for the synthesis of dehydroamino acids from serine and threonine is reported. Various *O*-Cbz and *O*-Eoc derivatives of serine and threonine are prepared using CbzCl and EocCl, respectively, and are subjected to an *anti*-selective elimination on treatment with K_2CO_3 in DMF at 65 °C to afford dehydroalanine and dehydroamino butyric acid derivatives, respectively, in excellent yields. The high stability of these carbonate derivatives of serine and threonine allows their use in normal peptide synthesis as protected serine and threonine residues. Peptides synthesized by incorporating *O*-Cbz or *O*-Eoc derivatives undergo ready elimination under the reported conditions, to give the corresponding dehydropeptides in excellent yields. The reaction conditions are mild enough not to cause the racemization of other stereogenic centers present in the peptide.

1. Introduction

α,β-Dehydroamino acids are important constituents of many peptide antibiotics and play an important role in the biosynthesis of other non-proteinogenic amino acids and D-amino acids.[1] They are very useful synthetic precursors and are used widely for the synthesis of a number of unnatural amino acids and peptides.[1,2] When incorporated into peptides they induce specific folding enabling the peptides to exhibit the desired secondary structures. Studies on the self-association of α,β-dehydropeptides show that they have a greater tendency to associate than their saturated counterparts.[3] The unique properties and the increased utility of α,β-dehydroamino acids demand efficient procedures for their synthesis and effective methods to incorporate them into peptides. There are a number of procedures available for the synthesis of α,β-dehydroamino acids and α,β-dehydropeptides,[1] and most of them are based on the dehydration of β-hydroxyamino acids, which mimic their biosynthesis. The synthesis of dehydroalanine (ΔAla) and dehydroamino butyric acid (ΔAbu) derivatives from serine and threonine, respectively, either through the incorporation of a good leaving group in β-position or through direct elimination using various reagents has been widely studied.[1,4] Most of the reactions are low to moderate yielding and the active intermediates are quite reactive, which can bring about unwanted side reactions. The generation of a dehydroalanine or dehydroamino butyric acid residue within a peptide by dehydrating a serine or threonine residue faces additional problems, since the hydroxyl group has to be protected prior to peptide synthesis and has to be deprotected before elimination to the dehydroamino acid residue. The preparation of dehydroamino butyric acid derivatives from threonine is more difficult than that of the synthesis of dehydroalanine from serine, due to the formation of two different stereoisomers.

A mild and high yielding procedure for the direct elimination of serine and threonine derivatives using Boc_2O and DMAP to the corresponding dehydroamino acid derivatives has been reported by Ferreira et al.[5] The elimination reaction is selective for β-hydroxyamino acids and peptides, and proceeds via a *trans* E_2-elimination resulting in the formation of only *Z*-olefin from threonine and β-hydroxyphenylalanine. However, the procedure has the major disadvantage of leaving all the amide bonds Boc protected during the course of the reaction. Hence, the amount of Boc_2O required to bring about the reaction depends on the number of amide bonds present in the molecule. It also imposes the additional requirement of removing the Boc group from the amide nitrogen in a second step. We report here a very efficient and selective procedure for the β-elimination of serine and threonine derivatives to the corresponding α,β-dehydroamino acids. The method is based on the *anti*-selective β-elimination of *O*-Cbz and *O*-Eoc derivatives of serine and threonine, using K_2CO_3 in DMF (Scheme 1). The reactions are high yielding and the procedure is effective for the

Keywords: Dehydroamino acids; Dehydropeptides; Carbonates; Peptide synthesis; Elimination reactions.
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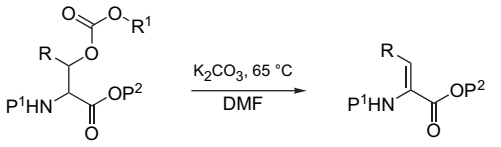
synthesis of dehydropeptides without racemization of other amino acid residues present in the peptide.



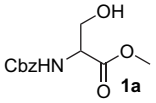
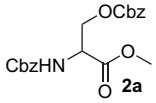
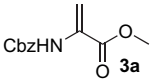
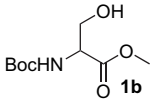
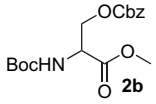
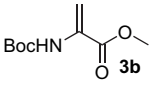
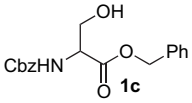
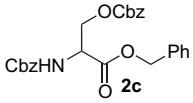
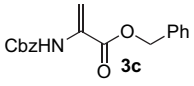
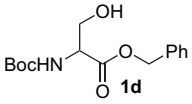
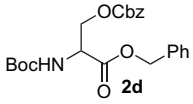
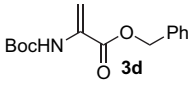
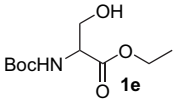
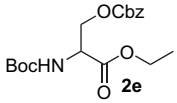
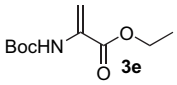
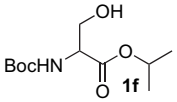
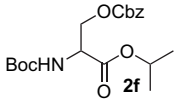
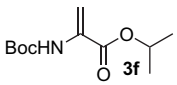
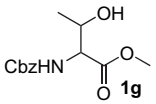
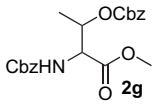
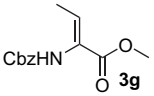
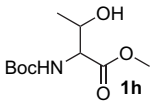
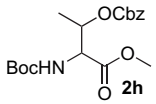
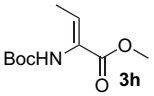
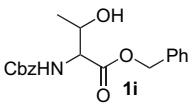
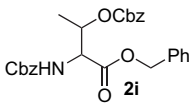
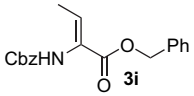
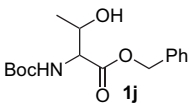
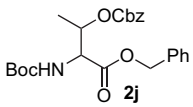
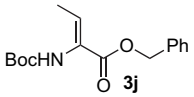
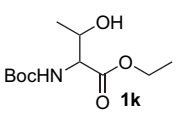
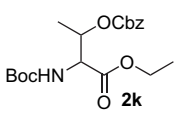
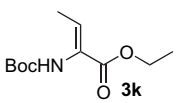
R = CH_3 or H, $P^1$and P^2 = Protecting Groups and R^1 = ethyl or benzyl

Scheme 1. Synthesis of α,β-dehydroamino acids from the carbonate derivatives of serine and threonine.

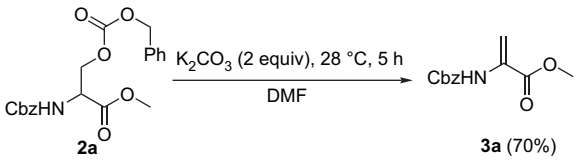
2. Results and discussion

During the course of our studies on protecting groups for peptide synthesis, we found that an *O*-Cbz derivative of serine (**2a**) undergoes ready elimination to a dehydroalanine derivative (**3a**) when treated with K_2CO_3 (2 equiv, DMF, 28 °C, 5 h, 70%, Scheme 2). The reaction was further examined toward understanding the most suitable condition for this elimination reaction. The best results were obtained when **2a** was treated with 2 equiv of K_2CO_3 in DMF (65 °C, 1 h) to get **3a** in 84% yield (Table 1, entry 1).

Table 1. Synthesis of dehydroamino acids from the *O*-Cbz derivatives of serine and threonine

Entry	Protected serine and threonine derivatives	*O*-Cbz derivatives of serine and threonine	Yield[a] (%)	Dehydroamino acid derivatives	Yield[a] (%)
1	 **1a**	 **2a**	81	 **3a**	84
2	 **1b**	 **2b**	83	 **3b**	80
3	 **1c**	 **2c**	74	 **3c**	72
4	 **1d**	 **2d**	78	 **3d**	81
5	 **1e**	 **2e**	85	 **3e**	87
6	 **1f**	 **2f**	79	 **3f**	81
7	 **1g**	 **2g**	61	 **3g**	81
8	 **1h**	 **2h**	64	 **3h**	89
9	 **1i**	 **2i**	52	 **3i**	80
10	 **1j**	 **2j**	60	 **3j**	87
11	 **1k**	 **2k**	67	 **3k**	75

[a] Yields of compounds isolated after column chromatography.

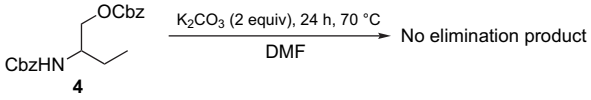


Scheme 2. Synthesis of dehydroalanine from the *O*-Cbz derivative of DL-serine.

We presumed that this observation could be developed into a very efficient methodology for the synthesis of α,β-dehydroamino acids from *O*-Cbz derivatives of serine and threonine. Though benzyloxycarbonyl (Cbz) group has been used for the protection of alcohols,[6] they are seldom used for the protection of hydroxy groups during peptide synthesis. Benzyl carbonates are very stable to mild acidic and basic conditions, and can easily be cleaved along with *N*-Cbz groups by hydrogenolysis or acidolysis with strong acids. They can easily be formed by the treatment of an alcohol with CbzCl at low temperatures in the presence of a base.[6] We prepared a number of *O*-Cbz derivatives (**2a–k**) of DL-serine and DL-threonine with the amino and carboxyl groups diversely protected by treating with CbzCl (CH_2Cl_2, −50 °C, 2–4 h). The carbonates **2a–k** were then treated with K_2CO_3 (DMF, 65 °C, 1 h) and in all cases the corresponding dehydroamino acid derivatives (**3a–k**) were obtained in excellent yields (Scheme 3, Table 1).

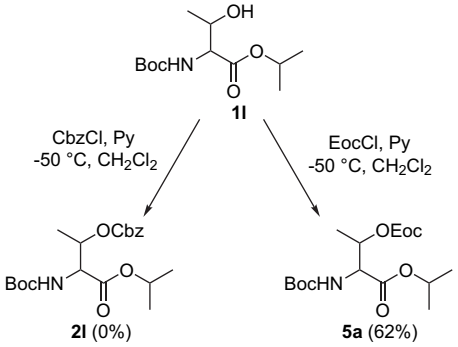
The formation of dehydroalanine derivatives (**3a–f**) from the derivatives of serine (**2a–f**) and the formation of dehydroamino butyric acid derivatives (**3g–k**) from the derivatives of threonine (**2g–k**) were equally efficient. The protecting groups used for the amino group (Boc and Cbz) or the carboxylic acid group (methyl, ethyl, benzyl, and isopropyl esters) do not have any effect on the elimination reactions. The carbamate groups present in the molecules are unaffected by the reaction conditions while the carbonates are cleanly eliminated. The elimination reactions performed on the threonine derivatives (**2g–k**) yielded the corresponding dehydroamino butyric acid derivatives (**3g–k**) as single diastereomers with the *Z*-configuration as shown by NMR spectroscopy.[7] The selective formation of the *Z*-isomer results from a *trans* E_2-elimination, which is in accordance with the results obtained by Ferreira et al.[5]

Treating the carbonates **2a–k** with organic bases such as triethylamine, pyridine, and DMAP (DMF, 65 °C, 12 h) did not result in an elimination reaction yielding the dehydroamino acid derivatives. However, treating the serine derivative **1a** with DBU (2 equiv, 65 °C, 3 h, DMF) afforded the dehydroalanine derivative **2a** in 74% yield. The elimination of the benzyl carbonate groups of the compounds **2a–k** was much faster in the presence of inorganic bases such as K_2CO_3 in DMF. Though the elimination reactions were very feasible using NaOH and KOH in DMF even at room temperatures, unwanted side reactions such as the hydrolysis of a methyl ester were also observed. The selection of the solvent is very important as the reactions were incomplete in various other solvents such as CH_3CN, CH_3OH, and THF even after refluxing for 24 h. It was also observed that the elimination occurs only when the hydrogen at the β-position of the benzyl carbonate is acidic as in amino acids. The diCbz derivative (**4**) of 2-aminobutanol did not give any elimination product when treated with K_2CO_3 (2 equiv, DMF, 70 °C) even after 24 h (Scheme 4).



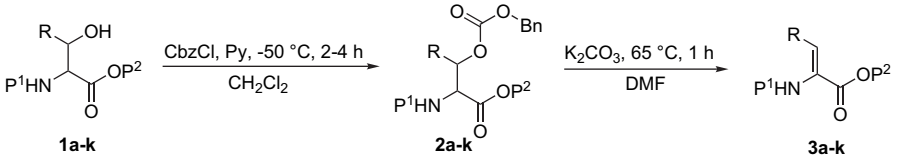
Scheme 4. Reaction of the diCbz derivative of 2-aminobutanol with K_2CO_3.

Though the elimination reactions of *O*-Cbz derivatives of threonine were efficient, the preparation of the benzyl carbonates of threonine (**2g–k**) using CbzCl was not a useful reaction, probably due to the reduced reactivity of the secondary alcoholic group in threonine as compared to the primary alcoholic group in serine. For example, the reaction between Boc–Thr–O^{i}Pr (**1l**) and CbzCl did not yield the expected carbonate Boc–Thr(Cbz)–O^{i}Pr (**2l**), but treating **1l** with ethyl chloroformate (EocCl) yielded the ethyl carbonate (**5a**) in good yield (Scheme 5).



Scheme 5. Synthesis of carbonates of DL-threonine.

We were interested in examining the possible eliminations of the ethyl carbonates that can be synthesized from protected serine and threonine derivatives using EocCl, to establish that these elimination reactions are possible with any carbonates of serine and threonine. Toward this, the ethyl carbonates (**5a–c**) were synthesized from the corresponding serine and threonine derivatives (**1l–n**) and were subjected to elimination using K_2CO_3 (DMF, 65 °C, 1 h). The dehydroamino acid residues **3l–n** were obtained in excellent yields suggesting that any carbonate derivative of serine



Scheme 3. Synthesis of dehydroamino acids from the *O*-Cbz derivatives of DL-serine and DL-threonine.

and threonine would undergo elimination under the conditions used (Scheme 6, Table 2).

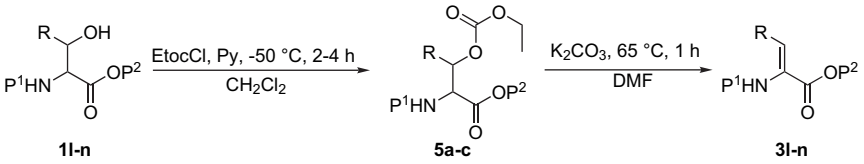
It was then decided to use the *O*-Cbz derivatives of serine and threonine for peptide synthesis. We perceived that the Cbz group would act as a protecting group for the side chain of serine and threonine during the course of peptide synthesis and could then be eliminated to incorporate a dehydroamino acid residue into a peptide. This sequence of reactions can provide a new methodology for the easy synthesis of peptides bearing dehydroamino acid residues. Accordingly, Boc–Phe–OH (**6**) and H–Ser(Cbz)–OMe (**7**) were coupled (EDC, HOBt, CH_3CN, 4 h) to get the dipeptide **8a** in very good yield (Scheme 7). The dipeptide **8a** was then treated with K_2CO_3 in DMF to get the peptide **9a**, bearing a dehydroalanine residue, in 92% yield (Scheme 7).

We synthesized three more peptides (**8b–d**); two of them bearing an *O*-Cbz group and one with an *O*-Eoc group and all of them were subjected to elimination reaction to get the corresponding dehydropeptides (**9b–d**) in excellent yields (Table 3). All the four peptides **8a–d** were stable compounds, and the *O*-Cbz and *O*-Eoc groups served well as protecting groups for the hydroxyl group of serine and threonine during peptide synthesis. The elimination of these carbonate groups to yield the corresponding dehydropeptides (**9a–d**) is high yielding and proceeds without the formation of byproducts.

At this stage it was important to determine the optical purity of the peptides **9a–d**, so as to check whether the methodology can be used in making enantiomerically pure dehydropeptides. Toward this, a racemic mixture of the peptide **9a** was synthesized starting from a diastereomeric mixture of **8a**, using DL-phenylalanine. The normal phase HPLC profile of the racemic mixture of **9a** showed two peaks, whereas the one prepared with optically pure **8a** showed only one peak.[8] This suggests that the methodology does not result in racemization of other amino acid residues present in a peptide, thus proving it to be a very efficient route to the synthesis of optically pure dehydropeptides.

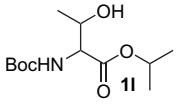
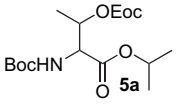
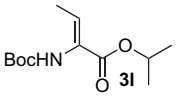
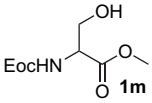
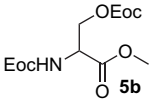
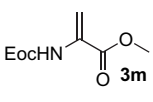
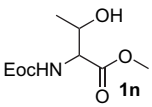
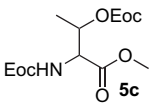
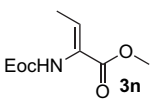
3. Conclusion

In conclusion, we have developed a novel and efficient procedure for the synthesis of dehydroamino acids from serine and threonine through their *O*-Cbz and *O*-Eoc derivatives. The procedure is selective toward amino acids and is mild enough not to cause side reactions on other protecting groups present. The elimination on threonine residues gives only the *Z*-olefins as the reactions proceed with complete *anti*-selectivity. Cbz and Eoc groups have been used as protecting groups for the side chain of serine and threonine during peptide synthesis. The peptides thus obtained were subjected to elimination reactions to get

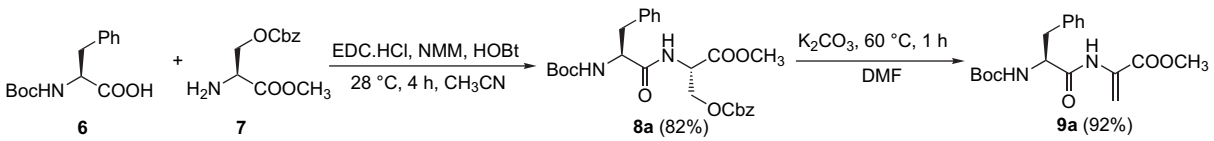


Scheme 6. Synthesis of dehydroamino acids from the *O*-Eoc derivatives of DL-serine and DL-threonine.

Table 2. Synthesis of dehydroamino acids from the *O*-Eoc derivatives of serine and threonine

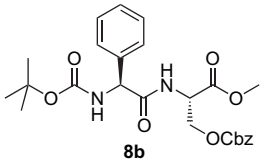
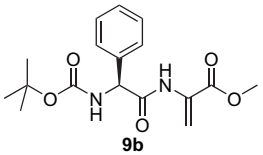
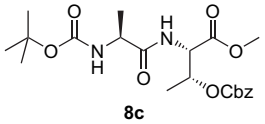
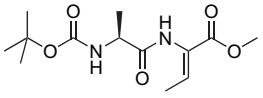
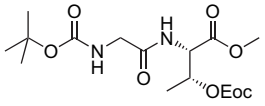
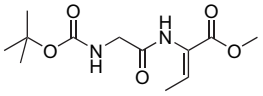
Entry	Protected serine and threonine derivatives	*O*-Eoc derivatives of serine and threonine	Yield[a] (%)	Dehydroamino acid derivatives	Yield[a] (%)
1	 **1l**	 **5a**	62	 **3l**	94
2	 **1m**	 **5b**	92	 **3m**	75
3	 **1n**	 **5c**	73	 **3n**	87

[a] Yields of compounds isolated after column chromatography.



Scheme 7. Synthesis of dehydropeptides.

Table 3. Synthesis of dehydropeptides

Entry	Peptides bearing carbonate derivatives of serine and threonine	Yield[a] (%)	Dehydropeptide derivatives	Yield[a] (%)
1	**8a**	82	**9a**	92
2	 **8b**	85	 **9b**	78
3	 **8c**	81	 **9c**	83
4	 **8d**	76	 **9d**	71

[a] Yields of compounds isolated after column chromatography.

dehydropeptides in excellent yields. The elimination reactions on these peptides did not bring about racemization of other chiral centers present in the peptides.

4. Experimental section

4.1. General

All reactions were performed in oven dry apparatus and were stirred magnetically. Melting points and optical rotation values (recorded at 25 °C) reported are uncorrected. Infrared spectra were recorded using an FTIR instrument and the frequencies are reported in wave number (cm^{-1}) and intensities of the peaks are denoted as s (strong), w (weak), m (medium). ^1H and ^{13}C NMR spectra were recorded on a 300 and 75 MHz spectrometers, respectively. Two-dimensional ^1H NMR spectra were recorded on a 400 MHz spectrometer. Chemical shifts are reported in parts per million downfield from the internal reference, tetramethylsilane (TMS). Multiplicity is indicated using the following abbreviations: s (singlet), d (doublet), t (triplet), q (quartet), qu (quintet), m (multiplet), br s (broad singlet), and br d (broad doublet). Mass spectra were recorded on a Q-TOF electrospray instrument. References for compounds reported previously are indicated against each of them along with the characterization data.

4.2. General procedure for the synthesis of the carbonates of serine and threonine (2a–k and 5a–c)

DL-Serine or DL-threonine, with the amino and carboxyl groups suitably protected (**1a**–**n**, 1 mmol) was dissolved in anhydrous CH_2Cl_2 (5 mL). The solution was cooled to −50 °C and 2.5 mmol (0.2 mL) of pyridine was added dropwise. The mixture was allowed to stir for 5 min and then 1.1 mmol of the chloroformate (CbzCl or EocCl) was added over a period of 30 min. The reaction mixture was allowed to warm to room temperature and stirred for 2 h. The crude reaction mixture was diluted with CH_2Cl_2 (50 mL), washed twice with saturated citric acid solution (25 mL), once with water (25 mL), and then with brine (25 mL). The crude solution was dried over anhydrous Na_2SO_4 and concentrated under vacuum. The carbonates (**2a**–**n** and **5a**–**c**) were isolated by silica gel (100–200 mesh) column chromatography using a solution of ethyl acetate in hexane as eluent.

4.2.1. Cbz–Ser(Cbz)–OMe, 2a. Colorless oil; column chromatography: EtOAc/hexane (1:9), R_f: 0.2; yield: 81%; FTIR (Neat): 3365 (br), 1751 (s), 1727 (s); δ_H (300 MHz, $CDCl_3$) 7.30–7.42 (m, 10H), 5.63 (br d, J=7.8 Hz, 1H), 5.14 (s, 2H), 5.12 (s, 2H), 4.61–4.66 (m, 1H), 4.54 (dd, J_1=11.1 Hz, J_2=3.9 Hz, 1H), 4.44 (dd, J_1=11.1 Hz, J_2=3.9 Hz, 1H), 3.74 (s, 3H); δ_C (75 MHz, $CDCl_3$) 169.5, 155.7, 154.6, 135.9, 134.7, 128.7, 128.6, 128.5, 128.4, 128.2, 128.1, 70.1, 67.3, 67.2, 53.3, 52.9; *m/z* (HRMS) calcd for $C_{20}H_{21}NO_7$+Na: 410.1216, found: 410.1210.

4.2.2. Boc–Ser(Cbz)–OMe, 2b. White solid; column chromatography: EtOAc/hexane (1:9), R_f: 0.2; mp: 56 °C; yield: 83%; FTIR (KBr): 3379 (br), 1752 (s), 1718 (s); δ_H (300 MHz, $CDCl_3$) 7.31–7.39 (m, 5H), 5.35 (br d, J=7.8 Hz, 1H), 5.15 (s, 2H), 4.51–4.59 (m, 2H), 4.41 (dd, J_1=10.5 Hz, J_2=3.3 Hz, 1H), 3.74 (s, 3H), 1.44 (s, 9H); δ_C (75 MHz, $CDCl_3$) 169.9, 155.1, 154.6, 134.8, 128.7, 128.6, 128.4, 80.3, 70.0, 67.5, 52.8, 28.2; *m/z* (HRMS) calcd for $C_{17}H_{23}NO_7$+Na: 376.1372, found: 376.1364.

4.2.3. Cbz–Ser(Cbz)–OBn, 2c. White solid; column chromatography: EtOAc/hexane (1:9), R_f: 0.3; mp: 61 °C; yield: 74%; FTIR (KBr): 3360 (br), 1749 (s), 1727 (s); δ_H (300 MHz, $CDCl_3$) 7.30–7.34 (m, 15H), 5.66–5.74 (m, 1H), 5.16 (s, 2H), 5.09 (s, 2H), 5.08 (s, 2H), 4.66–4.68 (m, 1H), 4.56 (dd, J_1=10.7 Hz, J_2=3.3 Hz, 1H), 4.42 (dd, J_1=10.7 Hz, J_2=3.3 Hz, 1H); δ_C (75 MHz, $CDCl_3$) 168.9, 155.6, 154.5, 135.9, 134.8, 134.7, 128.6, 128.5, 128.4,

128.3, 128.2, 128.1, 128.0, 69.9, 67.7, 67.3, 67.1, 53.4; *m/z* (HRMS) calcd for $C_{26}H_{25}NO_7$+Na: 486.1529, found: 486.1527.

4.2.4. Boc–Ser(Cbz)–OBn, 2d. White solid; column chromatography: EtOAc/hexane (1:9), R_f: 0.3; mp: 76 °C; yield: 78%; FTIR (KBr): 3380 (br), 1751 (s), 1716 (s); δ_H (300 MHz, $CDCl_3$) 7.32–7.36 (m, 10H), 5.38 (br d, J=8.1 Hz, 1H), 5.17 (s, 2H), 5.12 (s, 2H), 4.54–4.63 (m, 2H), 4.40 (dd, J_1=10.7 Hz, J_2=3 Hz, 1H), 1.43 (s, 9H); δ_C (75 MHz, $CDCl_3$) 169.3, 155.1, 154.5, 134.9, 134.8, 128.6, 128.6, 128.5, 128.4, 128.4, 128.2, 80.3, 69.9, 67.6, 60.3, 52.9, 28.2; *m/z* (HRMS) calcd for $C_{23}H_{27}NO_7$+Na: 452.1685, found: 452.1664.

4.2.5. Boc–Ser(Cbz)–OEt, 2e. Colorless oil; column chromatography: EtOAc/hexane (1:9), R_f: 0.3; yield: 85%; FTIR (Neat): 3377 (br), 1751 (s), 1718 (s); δ_H (300 MHz, $CDCl_3$) 7.35–7.38 (m, 5H), 5.37 (br d, J=7.5 Hz, 1H), 5.15 (s, 2H), 4.52–4.57 (m, 2H), 4.40 (dd, J_1=11.8 Hz, J_2=4.5 Hz, 1H), 4.20 (q, J=7.2 Hz, 2H), 1.44 (s, 9H), 1.25 (t, J=7.2 Hz, 3H); δ_C (75 MHz, $CDCl_3$) 169.3, 155.1, 154.6, 134.8, 128.6, 128.6, 128.3, 80.2, 69.9, 67.6, 61.9, 52.9, 28.2, 13.9; *m/z* (HRMS) calcd for $C_{18}H_{25}NO_7$+Na: 390.1529, found: 390.1531.

4.2.6. Boc–Ser(Cbz)-O^{i}Pr, 2f. Colorless oil; column chromatography: EtOAc/hexane (1:9), R_f: 0.3; yield: 79%; FTIR (Neat): 3376 (br), 1750 (s), 1717 (s); δ_H (300 MHz, $CDCl_3$) 7.36–7.38 (m, 5H), 5.36 (br d, J=7.5 Hz, 1H), 5.15 (s, 1H), 4.99–5.10 (m, 1H), 4.49–4.58 (m, 2H), 4.39 (dd, J_1=10.4 Hz, J_2=2.4 Hz, 1H), 1.44 (s, 9H), 1.25 (d, J=6 Hz, 3H), 1.20 (d, J=6 Hz, 3H); δ_C (75 MHz, $CDCl_3$) 168.8, 155.1, 154.6, 134.9, 128.6, 128.6, 128.3, 80.1, 69.9, 69.8, 67.7, 53.0, 28.2, 21.6, 21.5; *m/z* (HRMS) calcd for $C_{19}H_{27}NO_7$+Na: 404.1685, found: 404.1680.

4.2.7. Cbz–Thr(Cbz)–OMe, 2g. Colorless oil; column chromatography: EtOAc/hexane (2:8), R_f: 0.4; yield: 61%; FTIR (Neat): 3359 (br), 1748 (s), 1728 (s); δ_H (300 MHz, $CDCl_3$) 7.33 (br s, 10H), 5.58 (br d, J=9.31 Hz, 1H), 5.29–5.34 (m, 1H), 5.11 (s, 2H), 5.10 (s, 2H), 4.51 (br d, J=9.3 Hz, 1H), 3.66 (s, 3H), 1.33 (d, J=6.3 Hz, 3H); δ_C (75 MHz, $CDCl_3$) 169.9, 156.4, 153.9, 135.9, 134.8, 128.5, 128.4, 128.1, 128.1, 127.9, 74.3, 69.7, 67.1, 57.3, 52.6, 16.8; *m/z* (HRMS) calcd for $C_{21}H_{23}NO_7$+Na: 424.1372, found: 424.1378.

4.2.8. Boc–Thr(Cbz)–OMe, 2h. Colorless oil; column chromatography: EtOAc/hexane (2:8), R_f: 0.4; yield: 64%; FTIR (Neat): 3378 (br), 1750 (s), 1717 (s); δ_H (300 MHz, $CDCl_3$) 7.36 (s, 5H), 5.26–5.33 (m, 1H), 5.12 (s, 2H), 4.45 (dd, J_1=9.9 Hz, J_2=2.1 Hz, 1H), 3.69 (s, 3H), 1.44 (s, 9H), 1.35 (d, J=6.6 Hz, 3H); δ_C (75 MHz, $CDCl_3$) 170.3, 155.8, 153.9, 134.8, 128.5, 128.2, 126.9, 80.2, 74.6, 69.8, 56.9, 52.6, 28.1, 16.8; *m/z* (HRMS) calcd for $C_{18}H_{25}NO_7$+Na: 390.1529, found: 390.1514.

4.2.9. Cbz–Thr(Cbz)–OBn, 2i. Colorless oil; column chromatography: EtOAc/hexane (2:8), R_f: 0.5; yield: 52%; FTIR (Neat): 3358 (br), 1748 (s), 1728 (s); δ_H (300 MHz, $CDCl_3$) 7.31–7.33 (m, 15H), 5.56 (br d, J=9.9 Hz, 1H), 5.31–5.35 (m, 1H), 4.99–5.15 (m, 6H), 4.55 (dd, J_1=9.45 Hz, J_2=2.1 Hz, 1H), 1.33 (d, J=6.6 Hz, 3H); δ_C (75 MHz, $CDCl_3$) 169.3, 156.5, 153.8, 135.9, 134.9, 134.8, 128.5, 128.4, 128.4, 128.3, 128.1, 127.9, 74.4, 69.7, 67.7, 67.6, 67.2, 57.5, 16.8; *m/z* (HRMS) calcd for $C_{27}H_{27}NO_7$+Na: 478.1866, found: 478.1857.

4.2.10. Boc–Thr(Cbz)–OBn, 2j. White solid; column chromatography: EtOAc/hexane (2:8), R_f: 0.5; mp: 101 °C; yield: 60%; FTIR (KBr): 3383 (br), 1749 (s), 1719 (s); δ_H (300 MHz, $CDCl_3$) 7.32–7.35 (m, 10H), 5.30–5.35 (m, 1H), 5.25–5.28 (m, 1H), 5.02–5.13 (m, 4H), 4.48 (dd, J_1=9.75 Hz, J_2=1.8 Hz, 1H), 1.44 (s, 9H) 1.34 (d, J=6 Hz, 3H); δ_C (75 MHz, $CDCl_3$) 169.7, 155.8, 153.9, 135.0, 134.9, 128.6, 128.5, 128.4, 128.2, 80.2, 74.7, 69.8, 67.5, 57.0, 28.2, 16.8; *m/z* (HRMS) calcd for $C_{24}H_{29}NO_7$+Na: 466.1842, found: 466.1843.

4.2.11. Boc–Thr(Cbz)–OEt, 2k. Colorless oil; column chromatography: EtOAc/hexane (2:8), R_f: 0.4; yield: 67%; FTIR (Neat): 3375 (br), 1749 (s), 1718 (s); δ_H (300 MHz, $CDCl_3$) 7.35 (br s, 5H), 5.25–5.35 (m, 2H), 5.12 (s, 2H), 4.43 (dd, J_1=9.45 Hz, J_2=2.4 Hz, 1H), 4.11–4.20 (m, 2H), 1.45 (s, 9H), 1.36 (d, J=6.6 Hz, 3H), 1.20 (t, J=7.5 Hz, 3H); δ_C (75 MHz, $CDCl_3$) 169.8, 155.9, 153.9, 134.9, 128.5, 128.3, 80.1, 74.8, 69.8, 61.8, 56.9, 28.2, 16.8, 13.9; *m/z* (HRMS) calcd for $C_{19}H_{27}NO_7$+H: 382.1866, found: 382.1861.

4.2.12. Boc–Thr(Eoc)–O^{i}Pr, 5a. Colorless oil; column chromatography: EtOAc/hexane (2:8), R_f: 0.5; yield: 62%; FTIR (Neat): 3649 (br), 1748 (s), 1721 (s); δ_H (300 MHz, $CDCl_3$) 5.26–5.33 (m, 2H), 4.99–5.09 (m, 1H), 4.39 (dd, J_1=9.6 Hz, J_2=2.1 Hz, 1H), 4.16 (q, J=7.2 Hz, 2H), 1.46 (s, 9H), 1.35 (d, J=6.6 Hz, 3H), 1.21–1.31 (m, 9H); δ_C (75 MHz, $CDCl_3$) 169.2, 155.8, 153.9, 79.9, 74.4, 69.5, 64.0, 57.1, 28.1, 21.6, 21.4, 16.8, 14.1; *m/z* (HRMS) calcd for $C_{15}H_{27}NO_7$+Na: 356.1685, found: 356.1661.

4.2.13. Eoc–Ser(Eoc)–OMe, 5b. Colorless oil; column chromatography: EtOAc/hexane (2:8), R_f: 0.5; yield: 92%; FTIR (Neat): 3365 (br), 1751 (s), 1725 (s); δ_H (300 MHz, $CDCl_3$) 5.66 (br d, J=8.1 Hz, 1H), 4.61–4.66 (m, 1H), 4.52 (dd, J_1=12 Hz, J_2=3.6 Hz, 1H), 4.42 (dd, J_1=12 Hz, J_2=3.6 Hz, 1H), 4.11–4.23 (m, 4H), 3.79 (s, 3H), 1.24–1.33 (m, 6H); δ_C (75 MHz, $CDCl_3$) 169.6, 155.9, 154.5, 66.9, 64.3, 61.3, 53.1, 52.7, 14.3, 14.0; *m/z* (HRMS) calcd for $C_{26}H_{25}NO_7$+Na: 300.1059, found: 300.1052.

4.2.14. Eoc–Thr(Eoc)–OMe, 5c. Colorless oil; column chromatography: EtOAc/hexane (2:8), R_f: 0.4; yield: 73%; FTIR (Neat): 3361 (br), 1748 (s), 1727 (s); δ_H (300 MHz, $CDCl_3$) 5.45 (br d, J=9.3 Hz, 1H), 5.25–5.32 (m, 1H), 4.50 (dd, J_1=9 Hz, J_2=2.1 Hz, 1H), 4.11–4.21 (m, 4H), 3.76 (s, 3H), 1.24–1.38 (m, 9H); δ_C (75 MHz, $CDCl_3$) 170.3, 156.7, 153.9, 74.0, 64.2, 61.4, 57.2, 52.7, 16.9, 14.4, 14.1; *m/z* (HRMS) calcd for $C_{11}H_{19}NO_7$+Na: 286.0903, found: 286.0902.

4.2.15. Compound 4. White solid; column chromatography: EtOAc/hexane (1:9), R_f: 0.3; mp: 43 °C; yield: 80%; FTIR (KBr): 3335 (br), 1747 (s), 1722 (s); δ_H (300 MHz, $CDCl_3$) 7.28–7.34 (m, 10H), 5.00–5.12 (m, 5H), 4.16 (d, J=3.9 Hz, 2H), 3.81 (br s, 1H), 1.42–1.61 (m, 2H), 0.92 (t,

J=7.2 Hz, 3H); δ_C (75 MHz, $CDCl_3$) 155.9, 154.9, 136.3, 134.9, 128.5, 128.3, 128.3, 127.9, 69.7, 68.9, 66.6, 51.5, 24.3, 10.2; m/z (HRMS) calcd for $C_{20}H_{23}NO_4$+Na: 380.3901, found: 380.3906.

4.3. General procedure for the synthesis of dehydroamino acids (3a–n) from the corresponding carbonates of serine and threonine

To a solution of 1 mmol of the carbonates (**2a**–**k** and **5a**–**c**) in DMF, anhydrous K_2CO_3 (2 mmol, 0.276 g) was added. The solution was heated to 65 °C and stirred for 1 h before the reaction was found to be complete by TLC. The reaction mixture was allowed to warm to room temperature and the DMF was removed under vacuum. The residue was extracted with CH_2Cl_2 (30 mL) and filtered. The dehydroamino acids (**3a**–**n**) were then isolated from the crude solution by silica gel (100–200 mesh) column chromatography eluting with a solution of ethyl acetate in hexane.

4.3.1. Cbz–ΔAla–OMe, 3a.[4] Colorless oil; column chromatography: EtOAc/hexane (1:9), R_f: 0.4; yield: 84%; FTIR (Neat): 3379 (br), 1739 (s), 1717 (s); δ_H (300 MHz, $CDCl_3$) 7.30–7.43 (m, 5H), 7.26 (br s, 1H), 6.25 (s, 1H), 5.79 (d, J=1.5 Hz, 1H), 5.16 (s, 2H), 3.83 (s, 3H); δ_C (75 MHz, $CDCl_3$) 164.1, 153.1, 135.8, 130.9, 128.6, 128.4, 128.2, 106.1, 67.0, 52.9; m/z (HRMS) calcd for $C_{12}H_{13}NO_4$+Na: 258.0743, found: 258.0750.

4.3.2. Boc–ΔAla–OMe, 3b.[5] Colorless oil; column chromatography: EtOAc/hexane (1:9), R_f: 0.4; yield: 80%; FTIR (Neat): 3386 (br), 1785 (s), 1751 (s), 1716 (s); δ_H (300 MHz, $CDCl_3$) 7.02 (br s, 1H), 6.16 (s, 1H), 5.73 (d, J=1.5 Hz, 1H), 3.83 (s, 3H), 1.49 (s, 9H); δ_C (75 MHz, $CDCl_3$) 164.5, 152.5, 131.2, 105.2, 80.7, 52.9, 28.2; m/z (HRMS) calcd for $C_9H_{15}NO_4$+K: 240.0638, found: 240.0842.

4.3.3. Cbz–ΔAla–OBn, 3c.[9] Colorless oil (lit. mp: 51 °C);[9] column chromatography: EtOAc/hexane (1:9), R_f: 0.5; yield: 72%; FTIR (Neat): 3411 (br), 1739 (s), 1712 (s); δ_H (300 MHz, $CDCl_3$) 7.29–7.36 (m, 11H), 6.27 (s, 1H), 5.83 (s, 1H), 5.22 (s, 2H), 5.14 (s, 2H); δ_C (75 MHz, $CDCl_3$) 163.5, 153.0, 135.7, 134.9, 130.9, 128.5, 128.5, 128.4, 128.3, 128.1, 106.2, 67.6, 66.9; m/z (HRMS) calcd for $C_{18}H_{17}NO_4$+Na: 334.1055, found: 334.1050.

4.3.4. Boc–ΔAla–OBn, 3d.[9] Colorless oil (lit. mp: 47 °C);[9] column chromatography: EtOAc/hexane (1:9), R_f: 0.5; yield: 81%; FTIR (Neat): 3419 (br), 1747 (s), 1713 (s); δ_H (300 MHz, $CDCl_3$) 7.33–7.37 (m, 5H), 7.05 (br s, 1H), 6.19 (s, 1H), 5.79 (s, 1H), 5.25 (s, 2H), 1.48 (s, 9H); δ_C (75 MHz, $CDCl_3$) 163.8, 152.5, 135.1, 131.3, 128.6, 128.4, 128.1, 105.3, 80.6, 67.5, 28.1; m/z (HRMS) calcd for $C_{15}H_{19}NO_4$+Na: 300.1212, found: 300.1218.

4.3.5. Boc–ΔAla–OEt, 3e.[10] Colorless oil; column chromatography: EtOAc/hexane (1:9), R_f: 0.4; yield: 87%; FTIR (Neat): 3422 (br), 1736 (s), 1712 (s); δ_H (300 MHz, $CDCl_3$) 7.00 (br s, 1H), 6.10 (s, 1H), 5.69 (d, J=0.9 Hz, 1H), 4.24 (q, J=7.2 Hz, 2H), 1.44 (s, 9H), 1.29 (t, J=7.2 Hz, 3H); δ_C (75 MHz, $CDCl_3$) 163.9, 152.5, 131.4, 104.8, 80.5, 61.9, 28.2, 14.0; m/z (HRMS) calcd for $C_{10}H_{17}NO_4$+Na: 238.1056, found: 238.1052.

4.3.6. Boc–ΔAla–O^{i}Pr, 3f. Colorless oil; column chromatography: EtOAc/hexane (1:9), R_f: 0.5; yield: 81%; FTIR (Neat): 3422 (br), 1738 (s), 1733 (s), 1712 (s); δ_H (300 MHz, $CDCl_3$) 7.05 (br s, 1H), 6.12 (s, 1H), 5.71 (d, J=1.2 Hz, 1H), 5.07–5.18 (m, 1H), 1.49 (s, 9H), 1.31 (d, J=6 Hz, 6H); δ_C (75 MHz, $CDCl_3$) 163.4, 152.6, 131.7, 104.5, 80.6, 69.8, 28.2, 21.6; m/z (HRMS) calcd for $C_{11}H_{19}NO_4$+Na: 252.1212, found: 252.1208.

4.3.7. Cbz–ΔAbu–OMe, 3g.[5] White solid; column chromatography: EtOAc/hexane (1:9), R_f: 0.2; mp: 68 °C (lit.: 69.5 °C);[5] yield: 81%; FTIR (KBr): 3319 (br), 1723 (s), 1716 (s); δ_H (300 MHz, $CDCl_3$) 7.32–7.38 (m, 5H), 6.75 (q, J=7.5 Hz, 1H), 6.26 (s, 1H), 5.15 (s, 2H), 3.75 (s, 3H), 1.81 (d, J=7.5 Hz, 3H); δ_C (75 MHz, $CDCl_3$) 164.9, 153.9, 135.9, 133.3, 128.5, 128.2, 128.1, 126.3, 67.3, 52.3, 14.2; m/z (HRMS) calcd for $C_{13}H_{15}NO_4$+Na: 272.0899, found: 272.0903.

4.3.8. Boc–ΔAbu–OMe, 3h.[5] Colorless oil; column chromatography: EtOAc/hexane (1:9), R_f: 0.2; yield: 89%; FTIR (Neat): 3342 (br), 1712 (s); δ_H (300 MHz, $CDCl_3$) 6.68 (q, J=6.9 Hz, 1H), 6.04 (br s, 1H), 3.77 (s, 3H), 1.80 (d, J=6.9 Hz, 3H), 1.47 (s, 9H); δ_C (75 MHz, $CDCl_3$) 165.3, 153.3, 132.1, 80.4, 65.2, 52.2, 28.1, 14.2; m/z (HRMS) calcd for $C_{10}H_{17}NO_4$+Na: 238.1055, found: 238.1050.

4.3.9. Cbz–ΔAbu–OBn, 3i.[11] White solid (lit.: yellow foam);[11] column chromatography: EtOAc/hexane (1:9), R_f: 0.3; mp: 65 °C; yield: 80%; FTIR (KBr): 3325 (br), 1716 (s); δ_H (300 MHz, $CDCl_3$) 7.35–7.38 (m, 10H), 6.81 (q, J=7.2 Hz, 1H), 6.22 (br s, 1H), 5.19 (s, 2H), 5.14 (s, 2H), 1.82 (d, J=7.2 Hz, 3H); δ_C (75 MHz, $CDCl_3$) 164.4, 153.9, 135.9, 135.4, 133.6, 128.5, 128.5, 128.3, 128.2, 128.1, 126.3, 67.3, 67.0, 65.3, 14.3; m/z (HRMS) calcd for $C_{19}H_{19}NO_4$+Na: 348.1212, found: 348.1198.

4.3.10. Boc–ΔAbu–OBn, 3j.[12] White solid; column chromatography: EtOAc/hexane (1:9), R_f: 0.3; mp: 61 °C (lit.: 84 °C);[12] yield: 87%; FTIR (KBr): 3342 (br), 1721 (s), 1710 (s); δ_H (300 MHz, $CDCl_3$) 7.33–7.38 (m, 5H), 6.73 (q, J=7.2 Hz, 1H), 6.04 (br s, 1H), 5.19 (s, 2H), 1.80 (d, J=7.2 Hz, 3H), 1.45 (s, 9H); δ_C (75 MHz, $CDCl_3$) 164.7, 153.4, 135.6, 132.5, 128.5, 128.2, 128.2, 126.7, 80.4, 66.9, 28.1, 14.2; m/z (HRMS) calcd for $C_{16}H_{21}NO_4$+Na: 314.1368, found: 314.1363.

4.3.11. Boc–ΔAbu–OEt, 3k.[13] Colorless oil; column chromatography: EtOAc/hexane (1:9), R_f: 0.3; yield: 75%; FTIR (Neat): 3341 (br), 1724 (s), 1710 (s); δ_H (300 MHz, $CDCl_3$) 6.67 (q, J=6.9 Hz, 1H), 6.03 (br s, 1H), 4.22(q, J=7.2 Hz, 2H), 1.80 (d, J=6.9 Hz, 3H), 1.45 (s, 9H), 1.30 (t, J=7.2 Hz, 3H); δ_C (75 MHz, $CDCl_3$) 164.9, 153.1, 131.6, 126.8, 80.4, 61.2, 28.1, 14.2; m/z (HRMS) calcd for $C_{16}H_{21}NO_4$+Na: 252.1212, found: 252.1217.

4.3.12. Boc–ΔAbu–O^{i}Pr, 3l. Colorless oil; column chromatography: EtOAc/hexane (1:9), R_f: 0.4; yield: 94 %; FTIR (Neat): 3346 (br), 1727 (s), 1715 (s); δ_H (300 MHz, $CDCl_3$) 6.57 (q, J=6.9 Hz, 1H), 6.04 (br s, 1H), 4.94–5.06 (m, 1H), 1.73 (d, J=6.9 Hz, 3H), 1.40 (s, 9H), 1.21 (d, J=6.3 Hz, 6H); δ_C (75 MHz, $CDCl_3$) 164.3, 153.1, 131.0,

127.1, 80.2, 68.7, 28.1, 21.7, 14.2; *m/z* (HRMS) calcd for $C_{12}H_{21}NO_4$+Na: 266.1368, found: 266.1364.

4.3.13. Eoc–ΔAla–OMe, 3m. Colorless oil; column chromatography: EtOAc/hexane (1:9), R_f: 0.4; yield: 75%; FTIR (Neat): 3416 (br), 1738 (s), 1718 (s); δ_H (300 MHz, $CDCl_3$) 7.17 (br s, 1H), 6.22 (s, 1H), 5.77 (d, J=1.5 Hz, 1H), 4.19 (q, J=6.9 Hz, 2H), 3.84 (s, 3H), 1.29 (t, J=6.9 Hz, 3H); δ_C (75 MHz, $CDCl_3$) 164.3, 153.4, 130.9, 105.7, 61.2, 52.3, 14.4; *m/z* (HRMS) calcd for $C_7H_{11}NO_4$+Na: 196.0586, found: 196.0588.

4.3.14. Eoc–ΔAbu–OMe, 3n. Colorless oil; column chromatography: EtOAc/hexane (1:9), R_f: 0.2; yield: 87%; FTIR (Neat): 3327 (br), 1724 (s); δ_H (300 MHz, $CDCl_3$) 6.75 (q, J=7.2 Hz, 1H), 6.20 (br s, 1H), 4.17 (q, J=7.2 Hz, 1H), 3.78 (s, 3H), 1.82 (d, J=7.2 Hz, 3H), 1.28 (t, J=7.2 Hz, 3H); δ_C (75 MHz, $CDCl_3$) 165.1, 154.2, 133.1, 126.4, 61.6, 52.3, 23.8, 14.4; *m/z* (HRMS) calcd for $C_8H_{13}NO_4$+Na: 188.0923, found: 118.0913.

4.4. Procedure for the synthesis of the dipeptide Boc–Phe–Ser(Cbz)–OMe, 8a

A solution of Boc–Phe–OH (0.265 g, 1 mmol), HCl·H–Ser(Cbz)–OCH_3 (0.289 g, 1 mmol), *N*-methyl morpholine (0.33 mL, 3 mmol), and *N*-hydroxy benzotriazole (0.135 g, 1 mmol) in acetonitrile was cooled to 0 °C and EDC·HCl (0.288 g, 1.5 mmol) was added in small portions. The reaction mixture was brought to room temperature (28 °C) and stirred for 4 h. Acetonitrile was removed under vacuum and the reaction mixture was extracted with ethyl acetate (50 mL), washed with saturated citric acid solution (25 mL), saturated Na_2CO_3 (25 mL), and saturated brine solution (25 mL). Ethyl acetate was removed under vacuum and the peptide **8a** was purified by silica gel (230–400 mesh) column chromatography eluting with a solution of ethyl acetate in hexane (3:7, R_f: 0.3), as colorless oil in 82% yield. $[\alpha]_D$ +2.3 (*c* 1, MeOH); FTIR (Neat): 3315 (br), 1751 (s); δ_H (300 MHz, $CDCl_3$) 7.41–7.43 (m, 5H), 7.22–7.33 (m, 5H), 7.03 (br s, 1H), 5.18 (s, 3H), 4.84–4.89 (m, 1H), 4.41–4.57 (m, 3H), 3.74 (s, 3H), 3.08–3.19 (m, 2H), 1.43 (s, 9H); δ_C (75 MHz, $CDCl_3$) 171.4, 168.9, 155.2, 154.4, 136.2, 134.7, 129.2, 128.6, 128.5, 128.4, 126.7, 80.0, 69.9, 66.9, 55.3, 52.7, 51.5, 38.1, 28.1; *m/z* (HRMS) calcd for $C_{26}H_{32}N_2O_8$+Na: 523.2056, found: 523.2056.

The dipeptides **8b–d** were prepared using the same procedure.

4.4.1. Boc–Phg–Ser(Cbz)–OMe, 8b. Colorless gummy solid; column chromatography: EtOAc/hexane (3:7), R_f: 0.4; yield: 85%; $[\alpha]_D$ +18 (*c* 1, MeOH); FTIR (Neat): 3318 (br), 1751 (s), 1712 (s), 1675 (s); δ_H (300 MHz, $CDCl_3$) 7.26–7.35 (m, 10H), 6.86 (br d, J=6.6 Hz, 1H), 5.26 (br s, 1H), 5.12 (s, 2H), 4.75–4.85 (m, 1H), 4.40–4.52 (m, 2H), 3.63 (s, 3H); δ_C (75 MHz, $CDCl_3$) 170.2, 168.9, 154.9, 154.5, 137.5, 134.7, 128.8, 128.6, 128.5, 128.4, 128.3, 127.2, 80.0, 70.0, 66.7, 52.8, 51.7, 28.1; *m/z* (HRMS) calcd for $C_{25}H_{30}N_2O_8$+Na: 509.1900, found: 509.1904.

4.4.2. Boc–Ala–Thr(Cbz)–OMe, 8c. White solid; column chromatography: EtOAc/hexane (3:7), R_f: 0.2; mp: 108 °C; yield: 81%; $[\alpha]_D$ +14 (*c* 1, MeOH); FTIR (KBr): 3344 (br), 1749 (s), 1714 (s), 1694 (s), 1682 (s); δ_H (300 MHz, $CDCl_3$) 7.36 (br s, 5H), 6.94 (br d, J=5.1 Hz, 1H), 5.26–5.40 (m, 2H), 5.13 (s, 2H), 4.82 (dd, J_1=9.2 Hz, J_2=2.4 Hz, 1H), 4.25–4.29 (m, 1H), 3.67 (s, 1H), 1.42 (s, 9H), 1.36 (d, J=7.2 Hz, 3H), 1.30 (d, J=6.6 Hz, 3H); δ_C (75 MHz, $CDCl_3$) 173.4, 169.5, 155.3, 153.9, 134.8, 128.5, 128.2, 79.9, 74.4, 69.7, 55.1, 52.6, 50.0, 28.1, 17.9, 16.6; *m/z* (HRMS) calcd for $C_{21}H_{30}N_2O_8$+Na: 461.1900, found: 461.1896.

4.4.3. Boc–Gly–Thr(Eoc)–OMe, 8d. Colorless gummy solid; column chromatography: EtOAc/hexane (4:6), R_f: 0.2; yield: 76%; $[\alpha]_D$ +19 (*c* 1, MeOH); FTIR (Neat): 3354 (br), 1748 (s), 1722 (s), 1695 (s); δ_H (300 MHz, $CDCl_3$) 7.05 (br d, J=8.4 Hz, 1H), 5.55 (br s, 1H), 5.28–5.33 (m, 1H), 4.83 (dd, J_1=9.5 Hz, J_2=2.4 Hz, 1H), 4.30–4.35 (m, 1H), 4.11–4.30 (m, 2H), 3.90 (t, J=6.6 Hz, 2H), 3.75 (s, 3H), 1.47 (s, 9H), 1.25–1.33 (m, 6H); δ_C (75 MHz, $CDCl_3$) 170.2, 169.7, 155.9, 153.9, 80.1, 73.9, 64.1, 55.0, 52.6, 44.0, 28.1, 16.7, 14.3; *m/z* (HRMS) calcd for $C_{15}H_{26}N_2O_8$+Na: 385.1587, found: 385.1593.

4.5. Procedure for the synthesis of Boc–Phe–ΔAla–OMe, 9a

The peptide **8a** (1 mmol, 0.500 g) was dissolved in DMF (5 mL), 2 mmol of K_2CO_3 (0.276 g) was added, and the solution was heated to 60 °C for 1 h. The reaction mixture was allowed to cool to room temperature and DMF was removed under vacuum. The residue was extracted with CH_2Cl_2 (30 mL) and filtered. CH_2Cl_2 was then removed and the crude product was purified by silica gel (230–400 mesh) column chromatography eluting with a solution of ethyl acetate in hexane (1:9, R_f: 0.2) to get the dehydropeptides **9a** as a white solid in 92% yield. $[\alpha]_D$ −63 (*c* 1, MeOH); FTIR (KBr): 3376 (br), 3345 (br), 1723 (s), 1704 (s), 1693 (s); δ_H (300 MHz, $CDCl_3$) 7.17–7.35 (m, 5H), 6.59 (s, 1H), 5.89 (s, 1H), 5.18 (br s, 1H), 4.46 (br s, 1H), 3.77 (s, 3H), 3.06–3.17 (m, 2H), 1.39 (s, 9H); δ_C (75 MHz, $CDCl_3$) 170.3, 163.9, 155.3, 136.2, 130.5, 129.1, 128.6, 126.8, 109.4, 80.4, 56.4, 52.8, 38.0, 28.1; *m/z* (HRMS) calcd for $C_{18}H_{24}N_2O_5$+Na: 371.1583, found: 371.1576.

The dehydropeptides **9b–d** were prepared using the same procedure.

4.5.1. Boc–Phg–ΔAla–OMe, 9b. Colorless gummy solid; column chromatography: EtOAc/hexane (1:9), R_f: 0.2; yield: 78%; $[\alpha]_D$ +38 (*c* 1, MeOH); FTIR (Neat): 3337 (br), 1710 (s), 1683 (s); δ_H (300 MHz, $CDCl_3$) 8.10 (br s, 1H), 7.35–7.39 (m, 5H), 6.59 (s, 1H), 5.89 (d, J=1.2 Hz, 1H), 5.73 (br s, 1H), 5.25 (br s, 1H), 3.79 (s, 3H), 1.42 (s, 9H); δ_C (75 MHz, $CDCl_3$) 168.8, 164.1, 154.9, 137.4, 130.5, 129.2, 128.6, 127.2, 109.3, 80.3, 59.6, 52.9, 28.2; *m/z* (HRMS) calcd for $C_{17}H_{22}N_2O_5$+Na: 357.1426, found: 357.1418.

4.5.2. Boc–Ala–ΔAbu–OMe, 9c.[14] White solid; column chromatography: EtOAc/hexane (2:8), R_f: 0.3; mp: 114 °C (lit.: 116 °C);[14] yield: 83%; $[\alpha]_D$ −21 (*c* 1, MeOH); FTIR (KBr): 3310 (br), 1724 (s), 1679 (s), 1519 (s); δ_H (300 MHz, $CDCl_3$) 7.81 (br s, 1H), 6.82 (q, J=7.2 Hz, 1H), 5.30 (d, J=7.2 Hz, 1H), 4.35 (br s, 1H), 3.75 (s, 3H), 1.76 (d, J=7.2 Hz, 3H), 1.45 (a doublet and a singlet

merging, 12H); δ_C (75 MHz, $CDCl_3$) 171.2, 164.7, 155.5, 134.5, 125.9, 80.1, 52.2, 50.2, 28.2, 18.2, 14.3; *m/z* (HRMS) calcd for $C_{13}H_{22}N_2O_5$+Na: 309.1426, found: 309.1427.

4.5.3. Boc–Gly–ΔAbu–OMe, 9d.[14] White solid; column chromatography: EtOAc/hexane (2:8), R_f: 0.2; mp: 100 °C (lit.: 103 °C);[14] yield: 71%; FTIR (KBr): 3320 (br), 1724 (s), 1714 (s), 1701 (s), 1682 (s); δ_H (300 MHz, $CDCl_3$) 7.94 (br s, 1H), 6.83 (q, *J*=6.9 Hz, 1H), 5.66 (br s, 1H), 3.95 (d, *J*=2.1 Hz, 2H), 3.75 (s, 3H), 1.77 (d, *J*=7.5 Hz, 3H), 1.45 (s, 9H); δ_C (75 MHz, $CDCl_3$) 168.2, 164.7, 156.1, 134.7, 125.8, 80.0, 53.3, 52.2, 44.3, 28.2, 14.3; *m/z* (HRMS) calcd for $C_{12}H_{20}N_2O_5$+Na: 295.1270, found: 295.1264.

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Supplementary data

^1H and ^{13}C NMR spectra for all the new compounds and HPLC profile for the dehydropeptide **9a**. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2007.07.094.

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7. The NOESY spectrum of compound **3g** showed no interactions between the two methyl groups, which confirm the *Z*-configuration. The ^1H NMR data for the compounds **3g–k** are in agreement with those reported in the literature.
8. HPLC of compound **9a** and a racemic mixture of **9a** (prepared separately) was carried out on a normal phase chiralcel OD (250×4.6 mm) column with 10% isopropanol in hexane using a flow rate of 1 mL/min. The racemic mixture resolved into two different peaks with t_Rs of 5.3 and 6.2, respectively, whereas the optically pure **9a** showed only one peak in the chromatogram with a t_R of 6.3.
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