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PAPER

Synthesis of α, β-unsaturated γ-amino esters with unprecedented high (*E*)-stereoselectivity and their conformational analysis in peptides†

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Mild, efficient and racemization-free synthesis of *N*-protected α, β-unsaturated γ-amino esters with unprecedented high *E*- stereoselectivity is described. This method is found to be compatible with Boc-, Fmoc- and other side chain protecting groups. The crystal conformations of the vinylogous γ-amino esters in monomers and in homo- and mixed dipeptides are studied. Further, the vinylogous homo-dipeptide showed a β-sheet conformation, while mixed α- and α,β-unsaturated γ-hybrid dipeptide adapted an irregular structure in single crystals.

Introduction

α,β-Unsaturated γ-amino acids (insertion of –CH=CH- between $C^{\alpha}H$ and CO of α-amino acids, vinylogous amino acids) have been frequently found in many peptide natural products.[1] They have been used as starting materials for the synthesis of γ-amino acids[2] as well as substrates in a variety of organic reactions including, 1,4-conjugate addition,[3] epoxidation,[4] and Diels–Alder reaction[5] to develop the functional derivatives of γ-amino acids. The synthetic and naturally occurring peptides containing vinylogous amino acid residues (Fig. 1) have been used as inhibitors for serine and cystine proteases.[6] The *de novo* design of the folded oligomers from different sources of monomers is a very interesting field in the perspective of designing biologically relevant protein and peptidomimetics.[7] This endeavor has been elegantly described in the design of the structured peptides from the homologated derivatives of α-amino acids such as β-, γ- and ω-amino acids.[8] However, the structures of α, β- unsaturated γ-amino acids and their oligomers have been little explored. Nevertheless, preliminary work by Schreiber and colleagues gave an insight into the structures that can be formed by the vinylogous amino acids with *E*-double bond.[9] Grison *et al.* and others reported the β-turn mimetics with a nine-membered hydrogen bond using *Z*-vinylogous amino acids.[10] Recently, Hofmann *et al.* provided an overview of the helical structures formed by the vinylogous amino acids using *ab initio* MO theory.[11] These systematic conformational analyses are elucidated based on the *E* and *Z* geometry of the double bonds.

A range of methodologies including Wittig,[12] Julia,[13] Horner–Wadsworth–Emmons reaction,[14] and Peterson[15] olefination have been reported for the synthesis of α,β-unsaturated esters. However, Horner–Wadsworth–Emmons reaction, a variant of Wittig reaction has been extensively utilized for the synthesis of vinylogous amino acids.[2c,6,16] In this reaction, alkali metal bases such as BuLi and NaH are commonly used to generate the reactive metalated phosphonate intermediate and to achieve the high levels of stereoselectivity, reactions are also performed in the presence of metal salts and organic bases.[17] Seebach and co-workers reported the synthesis of methyl esters of N-Boc-protected α,β-unsaturated γ-amino acids with the *E*/*Z* ratio of 3 : 1 to 7 : 1 *via* Horner–Wadsworth–Emmons reaction using NaH as a base.[2] Grison and colleagues used Horner reagents as starting materials for the stereoselective synthesis of *E* and *Z* vinylogous amino acids.[10a,b] To achieve the major *E*-selectivity, lithiated dianion derivative of 2-diethylphosphonopropanoic acid has been used, while *Z*-stereoselectivity has been achieved by KH/ethyl 2-bis(trifluoroethyl)-phosphonopropanoate or BuLi/ethyl 2-diethyl phosphonopropanoate. However, these procedures may not be compatible for the synthesis of vinylogous amino acids containing commonly used base labile Fmoc-protecting group. Herein, we are reporting the synthesis of α, β-unsaturated γ-amino esters starting from the *N*-protected amino aldehydes using Wittig reaction with exceptional high *E*-selectivity, their solid state conformational analysis, and the conformations of homo- and mixed hybrid dipeptides in single crystals.

Results and discussions

Synthesis and characterization

As a part of our investigation to understand the structural features of vinylogous peptides, we sought to utilize the Wittig reaction, since the target vinylogous amino acids can be obtained at neutral

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† Electronic supplementary information (ESI) available: Detailed experimental procedures, characterization data, Crystallographic data, and copies of 1H and13C NMR and Mass spectra for all compounds are available. CCDC reference numbers 802255, 825100–825104. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c1ob05732d

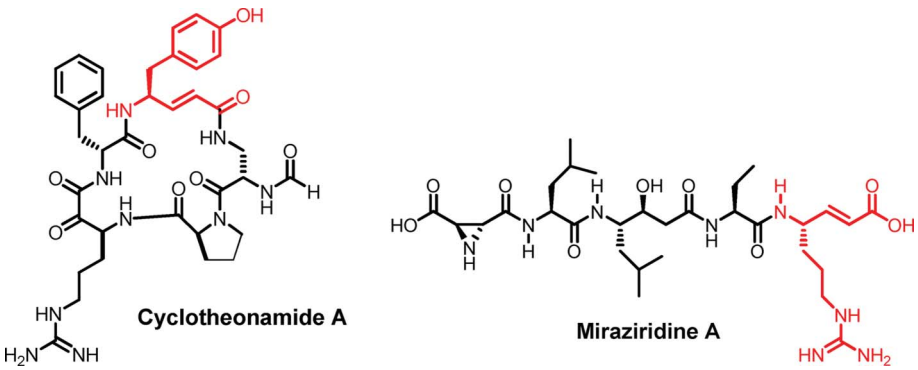
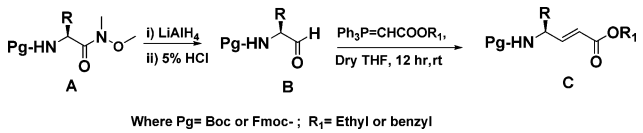


Fig. 1 Representative examples of vinylogous amino acids in peptide natural products.

conditions and it can be compatible with a variety *N*-protecting groups including base labile Fmoc- group. To understand the efficacy and the stereochemical output of the Wittig reaction in the synthesis of vinylogous amino acids, initially, the Boc-alanal was subjected to the olefination reaction using the ylide, ethyl (triphenylphosphoranylidene)acetate in dry THF (tetrahydrofuran) at room temperature. The schematic representation of the synthesis is shown in Scheme 1. The Boc-amino aldehyde was synthesized from the LAH (lithium aluminium hydride) reduction of the corresponding Weinreb amide and subjected immediately to the Wittig reaction.[18] Surprisingly, no trace of *Z* product was observed in the reaction, while 100% *E*-isomer (**1C**) was isolated in high yield (93%). We speculate that there may be a chance of *cis*/*trans* isomerisation during the column chromatography, which may lead to the conversion of *Z* into *E* product.[19]

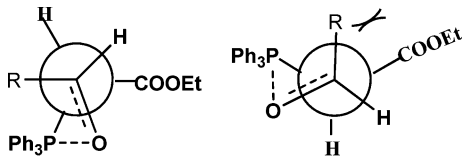


Scheme 1 Synthesis of α,β-unsaturated γ-amino esters using Wittig reaction.

To further confirm the *E*- selectivity, we subjected the crude Wittig product before the column purification to the ^{1}H NMR to observe the *cis* couplings of vinylic protons. The ^{1}H NMR shows the *trans* coupling of vinylic protons, indicating the presence of only *E*- product (**1C**) in the reaction mixture. Though it has been reported that the *E*- double bond is a major product in a verity of Wittig reactions, we are surprised to see unprecedented *E*-selectivity in the synthesis of vinylogous amino acids. Further, to understand whether the *E*-selectivity is depending upon the amino acid side chain, we subjected a variety amino aldehydes (**2B–9B**), including proline, Ser(OBu^t) and α-aminoisobutyric acid (Aib) to the Wittig reaction. In all these cases, we observed only the *E*-selectivity. In addition, except dialkyl amino acid and proline, all Wittig products (**2C–9C**) were isolated in high yields (>88%) and are given in the Table 1. All Wittig reactions of Boc-amino aldehydes proceeds very smoothly at room temperature in dry THF.

Further, to verify whether or not this method can be applicable to the synthesis of *N*-Fmoc-protected vinylogous amino acids, we subjected a variety of *N*-Fmoc-amino aldehydes (**10B–15B**) to the Wittig reaction. The *N*-Fmoc-amino aldehydes were synthesized using the corresponding Weinreb amides as described earlier. The Fmoc-amino aldehydes with a variety of orthogonal side chain protecting groups were subjected to the Wittig reaction using the ylide, benzyl (triphenylphosphoranylidene)acetate. The pure products of benzyl esters of *N*-Fmoc-vinylogous amino esters (**10C–15C**) were isolated after the column chromatography from moderate to high yields (78–94%) with 100%-(*E*)-selectivity and are given in the Table 2.

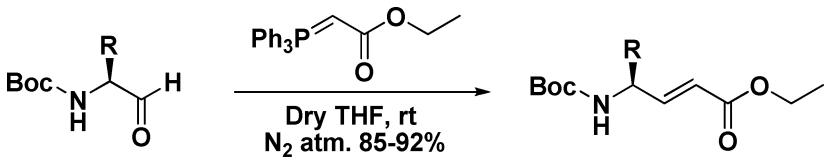
Overall, both *N*-Boc-/Fmoc-protected vinylogous amino esters were isolated in good yields with exceptional *E*-selectivity using the Wittig reaction. We speculate that the formation of *E*-product may adapted a planar transition state that leads to the less steric clash between the amino acids side-chains/NHX (**I**), while the formation of *Z*-product should adapt a energetically unfavourable puckered transition state, that leads to the steric clash between the amino acid side chains/NHX (**II**) and the incoming ethyloxycarbonyl group as shown in Scheme 2.



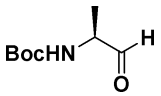
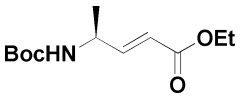
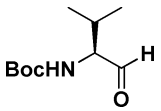
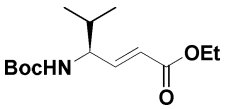
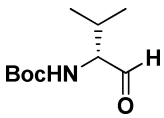
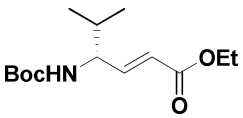
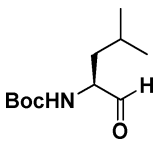
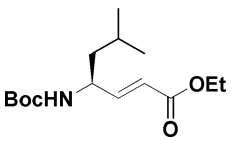
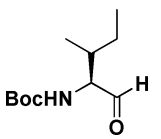
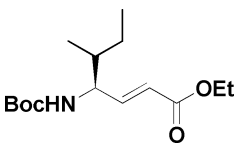
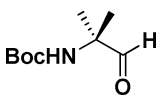
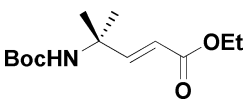
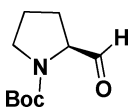
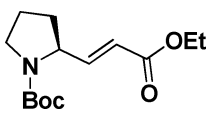
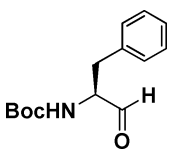
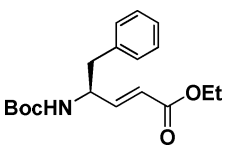
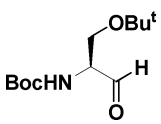
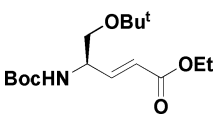
Scheme 2 Schematic representation of the transition states of the formation of *E* (I) and *Z* (II) products.

Further, to understand the chiral integrity in the synthesis of vinylogous amino esters, we synthesized *N*-Boc-protected L, D and (±) DL mixture of valinals using the protocol described earlier and then subjected to the Wittig reaction using the ylide, ethyl (triphenylphosphoranylidene)acetate. The pure ethyl esters of *N*-Boc-vinylogous amino acids were subjected to the chiral HPLC using Daicel CHIRALPAK-AI column. However, all amino ester enantiomers gave a single peak with the same retention time (t_R). Since all amino esters gave the same t_R, we further synthesized three dipeptides, Boc-Ala-dgV-OEt (**D1**), Boc-Ala-(D)dgV–OEt (**D2**) and Boc-Ala-(±DL)dgV-OEt(**D3**) by coupling of the vinylogous amino esters to the Boc-alanine using the standard DCC/HOBt coupling reaction and subjected to the chiral HPLC. The HPLC profiles of these dipeptides are shown in Fig. 2. Single peaks were

Table 1 Synthesis of *N*-Boc-α, β-dehydro γ-amino esters (dg) using Wittig reaction

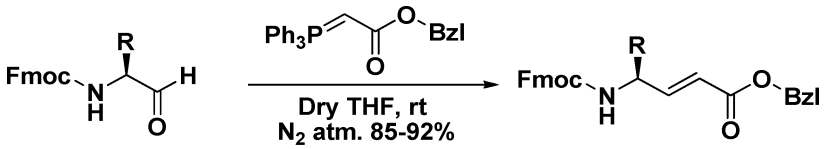


B C

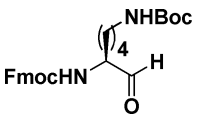
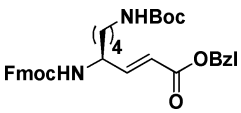
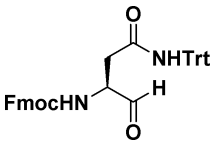
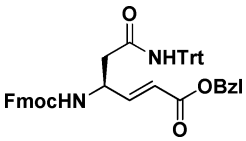
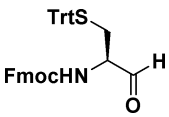
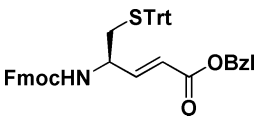
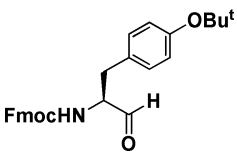
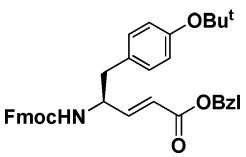
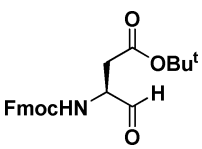
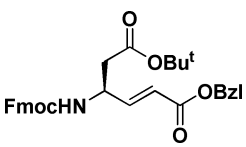
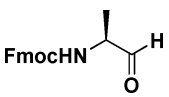
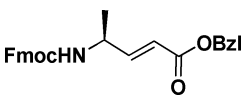
Entry	Aldehyde(B)	Product (C)	% Yield
1			93
2			90
3			90
4			95
5			92
6			75
7			83
8			88
9			81

observed for the dipeptides **D1** and **D2** at t_R 4.158 and 4.795 min respectively, whereas dipeptide **D3** showed two peaks with t_R 4.105 and 4.685 min, corresponding to the individual dipeptides **D1** and **D2**, respectively. These results indicate that the synthesis of vinylogous amino ester from Wittig reaction is free from the racemization. Further, out of all vinylogous amino esters in the Tables 1 and 2, and the dipeptides, we were able to obtain the single crystals for the amino esters **2C, 4C, 5C, 6C** and the dipeptide **D1** after slow evaporation of ethyl acetate, ethyl acetate/hexane solution as well as upon standing the pure gummy products. The crystal structure analysis of these vinylogous residues are described below.

Table 2 Synthesis of *N*-Fmoc-α, β-unsaturated γ-amino esters using Wittig reaction



B C

Entry	Aldehyde(B)	Product (C)	% Yield
10			78
11			90
12			80
13			90
14			80
15			83

Crystal structure analysis of the vinylogous amino esters and dipeptides

Crystal structures of all vinylogous residues are shown Fig. 3. The local conformations of these vinylogous residues are determined by introducing the additional torsional variables θ_1 (N–C$^{\gamma}$–C$^{\beta}$–C$^{\alpha}$) and θ_2 (C$^{\gamma}$–C$^{\beta}$═C$^{\alpha}$–C) as described by the Hofmann and colleagues.[11]

The torsional variables of all vinylogous residues are summarized in Table 3. In the case of **4C**, two molecules are appeared in the asymmetric unit with a slight variation in the torsional values. The vinylogous residues **2C** and **6C** adapted orthorhombic crystal systems, while **4C** and **5C** exhibited monoclinic crystal systems. Examination of the crystal structures of all vinylogous amino esters reveals that the torsional angle θ_1 is 0° or close to 0° suggesting the eclipsed conformation of the double bond with the N–C$^{\gamma}$ bond. In addition, the local *s-cis* conformation of the conjugated ester is observed in **2C, 4C**, and **5C**, whereas *s-trans* is observed in the dialkyl amino acid residue **6C**. The ϕ and ψ angles are found to be ~ –90 and ~ (±)180°, respectively, in the vinylogous residues **2C, 4C** and **5C**, while in the case of **6C**, the ϕ and ψ angles –63 and –3°, respectively, are observed. The torsional angle θ_2 is having the value ~ –180° in all vinylogous residues. It should be noted that the ψ value in dialkyl vinylogous amino acid is close to 0°, whereas in the other vinylogous residues it is close to 180°, indicating the rotation around the single bond in the conjugated ester is possible.

Crystals of Boc-Ala-dgV-OEt (**D1**) were obtained after slow evaporation of ethyl acetate solution and the crystal structure is shown in Fig. 4. Surprisingly, six dipeptide molecules are observed in the asymmetric unit with a significant variation in the torsional angles. The torsional values are tabulated in the Table 4. The six molecules in the asymmetric unit are held together by intermolecular H-bonds and their parameters are tabulated in the supporting information. The analysis of the torsional variables reveals the conformational flexibility of the vinylogous residue

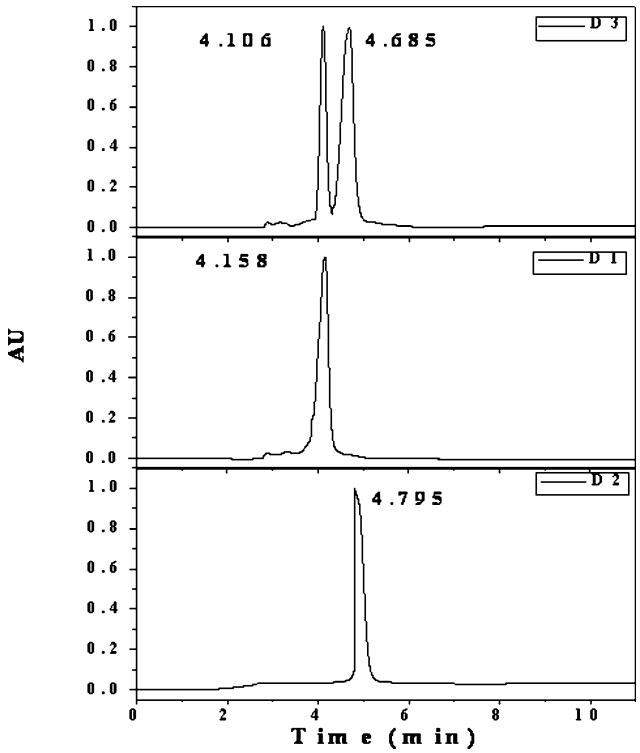
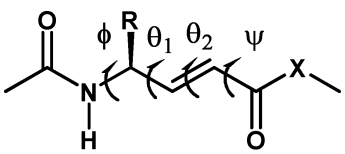


Fig. 2 Chiral HPLC of dipeptides **D1, D2**, and **D3**. The HPLC was performed on Daicel CHIRALPAK-AI column using 20% isopropanol in n-hexane as a solvent system at isocratic mode with the flow rate of 1 mL/min.

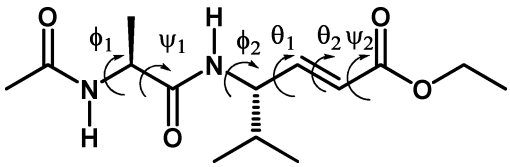
Table 3 The torsional angles (°) of vinylogous amino esters and the dipeptide **D4**



Compound	Residues	ϕ	θ_1	θ_2	ψ
2C	dgV	–90	0	179	177
4C	dgL	–91	–1	–179	178
5C	dgI	–94	0	180	–179
6C	dgU	–63	–10	–179	–3
Boc-dgL-dgL-OEt					
D4	dgL1	–107	116	179	171
	dgL2	–137	0	179	180

in the hybrid dipeptide. Instructively, molecules **a, c, e** and **f** in the Table 4 adapted a very similar conformations in the crystals with slight variations in the torsional values (highlighted in green in Fig.4), while dipeptides **b** and **d** adapted similar conformations different from the other four dipeptides (highlighted in blue, Fig.4). In the case of **a, c, e** and **f**, the Ala adapted a semi-extended conformation by having ϕ_1 and ψ_1 angles ~ –60° and ~140°, respectively. In addition, the vinylogous residues adapted extended conformations by having ϕ_2 ~ –120°, however, θ_1 is found to be close to 0°. Further, the local *s-cis* conformation of the conjugated

Table 4 Torsional angles (°) of the dipeptide Boc-Ala-dgV-OEt(**D1**)



	ϕ_1	ψ_1	ω	ϕ_2	θ_1	θ_2	ψ_2
a	–57	140	173	–123	9	–180	–175
b	–122	157	173	69	127	175	9
c	–60	141	169	–115	–9	179	175
d	–116	155	166	69	129	175	10
e	–61	139	177	–122	7	–179	–179
f	–60	134	175	–112	–3	177	–173

esters is observed with the ψ_2 values ~180°. Interestingly, in the case of **b** and **d**, the Ala adapted extended conformations with the ϕ_1 and ψ_1 value approximately –120, and 155°, respectively. In addition, the ϕ_2 is found to be 69° and θ_1 is having the values close to 130°. Further, the local *s-trans* conformation of the conjugated ester is observed with the ψ_2 close to 0°. It should be noted that the values of ϕ_2, θ_1 and ψ_2 are different for the two sets of the peptides in the crystals, indicating that the rotations around the single bonds are possible. In contrast to the all unsaturated γ-amino ester structures (Table 3), the θ_1 of the dipeptides **b** and **d** is having the value close to 130°.

Further, inspired by the interesting results obtained from the dipeptide **D1**, we sought to investigate the conformational behaviour of the vinylogous residues in homo-dipeptides. The dipeptide Boc-dgL-dgL-OEt (**D4**), was synthesized by coupling of *N*-Boc-vinylogous acid and the free amine of **4C** obtained after the saponification and the Boc-deprotection, respectively. The coupling reaction was mediated by DCC and HOBt. Crystals of homo-dipeptide **D4** obtained after the slow evaporation of ethyl acetate solution yield the structure shown in Fig. 5A. In contrast to the **D1**, single dipeptide molecule is observed in the asymmetric unit. Interestingly, the dipeptide **D4** adapted a partial parallel β-sheet character in the crystal structure (Fig. 5B). The torsional values are given in the Table 3. Analysis of the crystal structure reveals that the dipeptide molecules are held together by two intermolecular H-bonding between the C═O and NH groups with N–H---O distances 2.066 [N1H---O2, (N1---O2, 2.872 Å)] and 2.165 Å [N2H---O3, (N2---O3, 3.012 Å)] with N–H---O angles 156 and 168°, respectively (Fig. 5B). A fully extended conformation is observed in dgL1 of the dipeptide with ϕ, θ_1, θ_2 and ψ values –107, 116, 178 and 171°, respectively, whereas in the second residue dgL2, θ_1 is having the eclipsed conformation with the N–C$^\gamma$bond (θ_1 is 0°), leads to the deviation from the β-sheet structure. However, the other torsional variables ϕ, θ_2 and ψ showing the extended conformations with the angles of –137, 179 and 180°, respectively.

Further, to understand their conformational signature in solution, we subjected the dipeptides **D1**, **D2** and **D4** for CD analysis. The CD spectra of the dipeptides are shown Fig. 6. Instructively, dipeptide **D4** showed the CD negative maxima at 228 nm, indicating a β-sheet character in solution, while the other dipeptides **D1** and **D2** exhibiting strange characteristics by giving almost two mirror image spectra with the CD positive

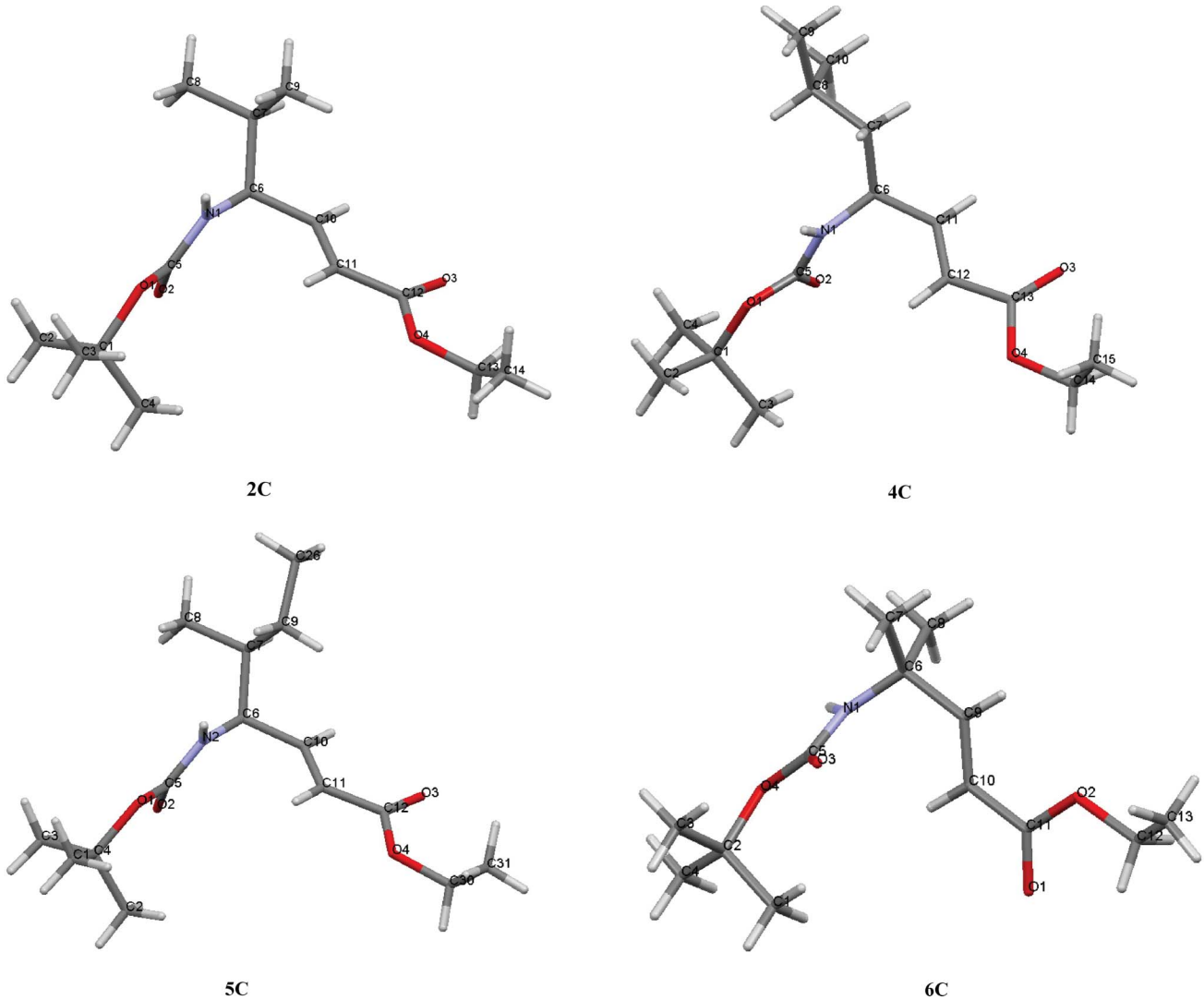


Fig. 3 Crystal structures of vinylogous amino esters, Boc-(*S*, *E*)-dgV-OEt (2C), Boc-(*S*, *E*)-dgL-OEt (4C), Boc-(*S*, *E*)-dgI-OEt (5C) and Boc-(E)-dgU-OEt(6C).

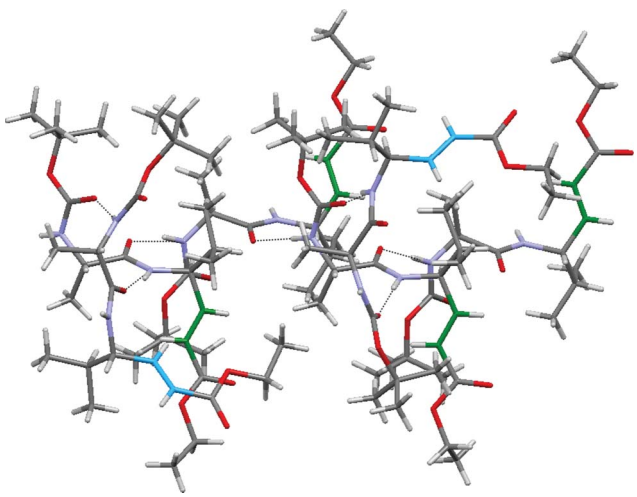


Fig. 4 Crystal structure of dipeptide Boc-Ala-dgV-OEt. Six molecules are appeared in the asymmetric unit. The intermolecular H-bonding between the dipeptide units are shown in dotted lines. The types of conformations with significant variation in the torsional values of vinylogous residues are highlighted in different colours.

and negative maxima at around 205 and 202 nm, respectively. For a comparison, the CD spectrum of the α-dipeptide, Boc-Leu-Leu-OMe (**D5**) is also shown in Fig. 6. The CD analysis, however, suggests that the lack of secondary structural elements in dipeptide **D5**. We speculate that the red shift of the CD negative maxima at 228 nm for the dipeptide **D4** and the anomalous CD spectra of the dipeptides **D1** and **D2** may be due to the conjugated enamides and esters of vinylogous residues.

Conclusion

In conclusion, we have demonstrated the facile and racemization-free synthesis of α,β-unsaturated γ-amino esters with exceptional high *E*-stereoselectivity using Wittig reaction. In addition, this method was found to compatible with Boc-, Fmoc- and other side chain protecting groups. Further, the crystal conformations of vinylogous amino esters and dipeptides were analyzed. The homo-vinylogous dipeptide **D4** showed the partial extended β-sheet characters in single crystals. The knowledge from this work can be further utilized to construct higher ordered structures of

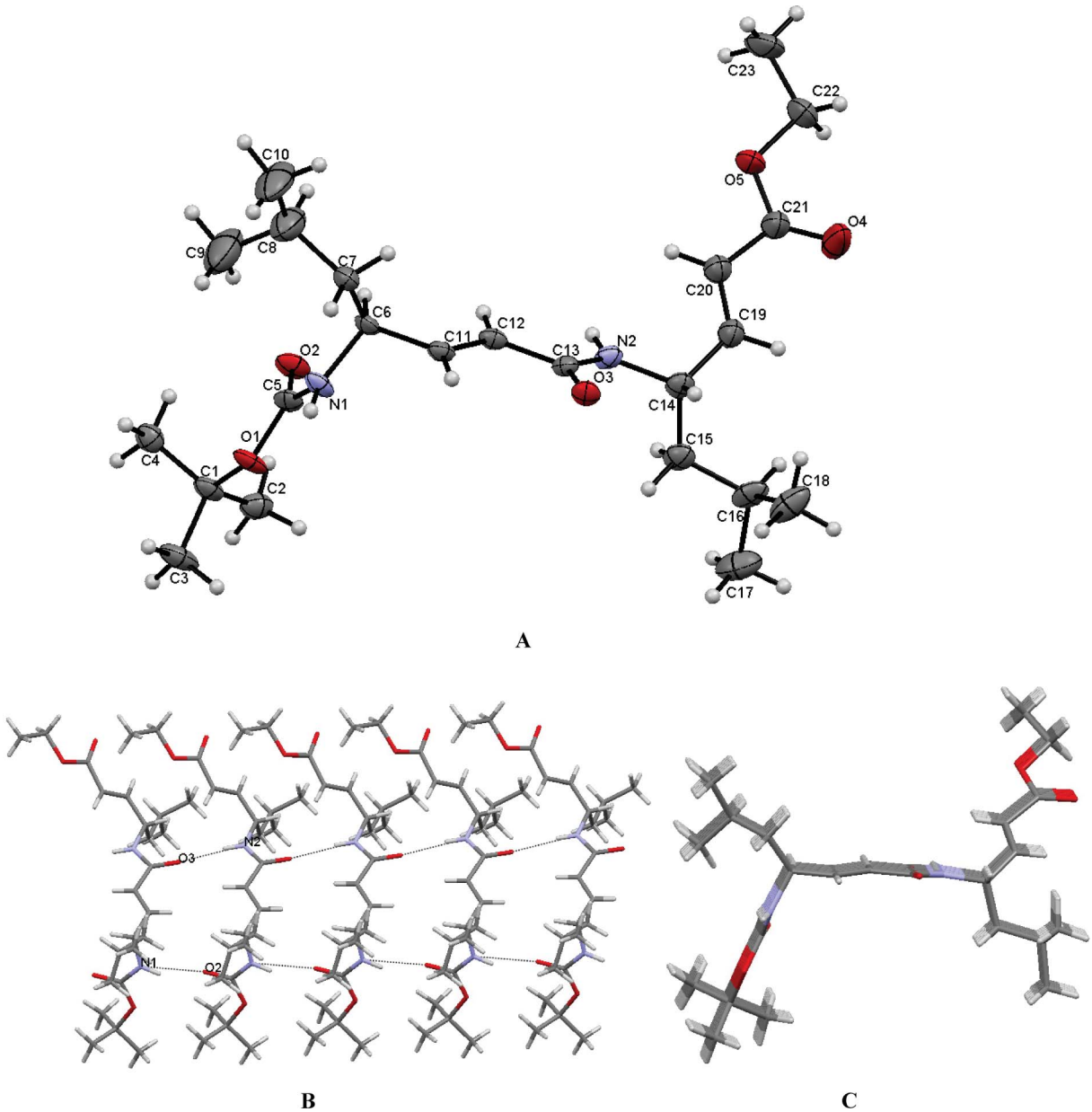


Fig. 5 Crystal structure of dipeptide Boc-dgL-dgL-OEt (D4). **A**. The ORTEP diagram of the dipeptide. **B**. The partial β-sheet of character exhibited by the dipeptide in crystals. **C**. The side view of the β-sheets.

vinylogous residues as well as for the synthesis biologically active peptides.

Experimental section

General procedure for the synthesis of *N*-protected-α, β-unsaturated-γ-amino esters

The solution of *N*-protected amino acid Weinreb amide (20 mmol) in 130 mL of THF was cooled to 0 °C under N_2 atmosphere. To this solution, $LiAlH_4$ (22 mmol) was added slowly and the reaction mixture was stirred for further 20 min. After the completion of reaction, as indicated by the TLC, the reaction mixture was quenched with 5% HCl. The organic layer was evaporated under reduced pressure and product was isolated by extracting with ethyl acetate (50 mL × 3). The combined organic layer was then washed with brine and dried over Na_2SO_4. The oily product of N-protected amino aldehyde was isolated after evaporating ethyl acetate under reduced pressure and used immediately for next step without purification. The Wittig ylide, alkyl(triphenylphosphoranylidene)acetate (22 mmol) was added to the solution of N-protected amino aldehyde dissolved in 40 mL dry THF under the N_2 atmosphere. The reaction mixture was stirred overnight and the progress of reaction was monitored by TLC. After the completion of reaction (~8h) the THF was evaporated and product was purified by coloumn chromatography

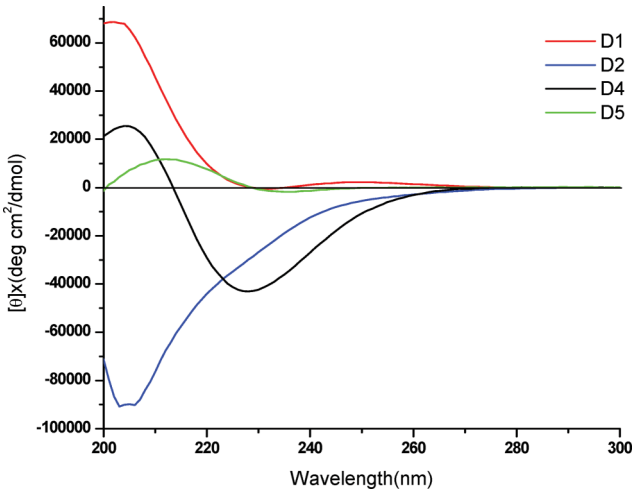


Fig. 6 Circular Dichroism spectra of dipeptides **D1, D2, D4** and **D5** in methanol.

using 5 : 95 ethyl acetate/pet ether solvent system. The pure products were isolated with an average 85% yield. Individual yield, ^{1}H, ^{13}C and mass spectra of all Wittig products are given the supporting information.

Synthesis of Boc-dgL-dgL-OEt (D4)

(*S*,*E*)-4-(*tert*-butoxycarbonylamino)-6-methylhept-2-enoic acid-(Boc-dgL-OH). Boc-dgL-OEt, **4C** (1.86 g, 6.8 mmol) was dissolved in 4 mL of ethanol followed by 10 mL of 1 N NaOH was added slowly to the solution. The reaction mixture was then stirred for about 8h. The progress of reaction was monitored by TLC. After completion of the reaction, the solvent was evaporated under reduced pressure. The aqueous layer was diluted with water (50 mL) and then acidified (~pH 3.0) with 5% HCl and extracted with ethyl acetate (3 × 50 mL). The combined organic layer was then washed with brine and dried over anhydrous Na_2SO_4. Product was concentrated under reduced pressure to get 1.67 g (95%) of oily Boc-dgL-OH.

(*S*,*E*)-Ethyl 4-amino-6-methylhept-2-enoate(H_2N-dgL-OEt). The solution of Boc-dgL-OEt (1.95 g, 7.2 mmol) in 5 mL of DCM was cooled to 0 °C followed by 5 mL of neat TFA was added. The reaction mixture was stirred for about 1.5 h at the same temperature. The progress of the reaction was monitored by TLC. After completion of the reaction (1.5 h), the solvent was evaporated under reduced pressure. The residue was then treated with saturated Na_2CO_3 solution in cold condition. This aqueous layer was extracted with ethyl acetate (3 × 50 mL). The combined organic layer was washed with brine and dried over anhydrous Na_2SO_4. The organic layer was concentrated under reduced pressure to 4 mL.

The solution of H_2N-dgL-OEt in ethyl acetate (4 mL) was added to the ice-cold solution of Boc-dgL-OH (1.67 g, 6.5 mmol) in DMF (4 ml). The reaction mixture was then treated with DCC (1.34 g, 6.5 mmol) followed by HOBt (0.884 g, 6.5 mmol). The reaction mixture was stirred for about 12 h at room temperature and the progress of the reaction was monitored by TLC. After completion of reaction, the reaction mixture was diluted with ethyl acetate (100 mL) and DCU formed in reaction was filtered. This filtrate was washed with brine (3 × 50 mL), 5% HCl (3 × 50 mL), 10% Na_2CO_3(3 × 50 mL), brine (30 mL) and dried over Na_2SO_4. The organic layer was concentrated under reduced pressure and the crude product was purified by column chromatography using ethyl acetate/pet ether to get 1.2 g (40%) of the pure dipeptide D4.

Crystal structure analysis of Boc-dgV-OEt. Crystals of Boc-dgV-OEt were grown by slow evaporation from a solution of EtOAc and Hexane. A single crystal (0.50× 0.35 × 0.20 mm) was mounted on loop with a small amount of the paraffin oil. The X-ray data were collected at 200 K temperature on a Bruker APEX DUO CCD diffractometer using Mo-Kα radiation (λ = 0.71073 Å), ω-scans (2θ = 55.84), for a total of 3650 independent reflections. Space group $P2_1$, 2(1), 2(1), a = 9.978(4), b = 10.083(3), c = 16.904(6), V = 1700.7(10) Å^3, Orthorhombic P, Z = 4 for chemical formula $C_{14}H_{25}NO_4$, with one molecule in asymmetric unit; ρ calcd = 1.060gcm^{-3}, μ = 0.077 mm^{-1}, $F(000)$ = 592, R_{int} = 0.0268. The structure was obtained by direct methods using SHELXS-97.[20] The final R value was 0.0581 (wR_2 = 0.1589) 1978 observed reflections ($F_0 \geq 4\sigma$ (|F_0|)) and 178 variables, S = 1.011. The largest difference peak and hole were 0.344 and –0.160eÅ^3, respectively.

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