Demonstration of *endo-cis*-(2*S*,3*R*)-Bicyclo[2.2.1]hept-5-en-2,3-dicarbonyl Unit as a Reverse-Turn Scaffold and Nucleator of Two-Stranded Parallel β-Sheets: Design, Synthesis, Crystal Structure, and Self-Assembling Properties of Norborneno Peptide Analogues

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Abstract: *endo-cis*-(2*S*,3*R*)-Bicyclo[2.2.1]hept-5-en (norbornene) dicarbonyl unit with a built-in U-architecture has been demonstrated to be an excellent reverse-turn molecular scaffold. A large variety of *endo-cis*-(2*S*,3*R*)-norborneno bispeptides containing almost all of the coded amino acids were synthesized and examined for conformational preferences by ^{1}H NMR, FT-IR, CD, and X-ray crystallographic studies. While FT-IR and ^{1}H NMR variable-temperature studies ruled out the presence of any significant amount of intramolecular hydrogen bonding in simple bispeptides (**3a**−**h**) (except in Aib bispeptide), the CD studies were clearly in favor of a β-turn type structure. Single-crystal X-ray studies on Aib, Val and Leu containing norborneno bispeptides (**3b**−**d**) provided convincing proof for the presence of reverse-turn conformation. While the interstrand $C^{\alpha}-C^{\alpha'}$ distances (5.2−5.7 Å) were well within the range of those for β-turn structures, no interstrand intramolecular hydrogen bonding was seen in Val and Leu bispeptides; the Aib bispeptide forms a seven-membered hydrogen-bonded ring, thus, showing that the norbornene (2*S*,3*R*)-dicarbonyl template assembles peptide chains in reverse-turn conformation by virtue of its built-in U-shaped architecture at these positions, and hydrogen bonding may not be necessary to stabilize the turn structure. The *endo-cis*-(2*S*,3*R*) orientation of bispeptide chains is essential for turn structure as shown by the crystal structure of *trans*-(2R, 3R) and *trans*-(2*S*,3*S*) derivative of Val bispeptide wherein the two peptide chains move away from each other with the $C^{\alpha}-C^{\alpha'}$ distance increasing to 7.1−8.2 Å. The norbornene 5,6-double bond was hydrogenated to 5,6-dihydro derivative which showed almost the same CD spectrum as its olefinic analogue. Oxidative cleavage [Ru (VIII)] of the 5,6-double bond in norborneno bispeptides, as demonstrated with Leu bispeptide, afforded novel cyclopentanoid peptide analogues. The promise of norbornene unit as a template for nucleating the formation of two-stranded parallel β-sheets with minimum structural complexity is shown by the preparation of higher members of norborneno bispeptides with the general structure NBE(Pep)$_2$ [NBE = *endo-cis*-(2*S*,3*R*)-bicyclo[2.2.1]hept-5-en (norbornene) dicarbonyl unit; Pep = peptide strand with two, three, or four (same or different) amino acid residues]. In ^{1}H NMR, the high $^3J_{HN\alpha}$ values (7.0−9.3 Hz) observed for the amide protons (Table 3) coupled with the presence of medium to strong intrastrand sequential ROE connectivities $d_{\alpha N(i,i+1)}$ spanning the entire three- or four-residue sequence in the peptide strands of **9a**−**e** and **10** and the exhibition of relatively low-temperature coefficients ($d\delta/dT = -0.2$ to -3.4 ppb/K) for amide protons in DMSO-d_6 solvent (Table 4) clearly suggested that hydrogen-bonded β-sheet conformers dominate the population. FT-IR and CD studies provided further support for parallel β-sheet structures. A particularly unique feature of the norborneno bispeptides is their strong tendency to self-assemble in the solid state. Thus, while *endo-cis*-(2*S*,3*R*)-Aib bispeptide (**3b**) forms 16-membered hydrogen bonded centrosymmetric dimers, the half-ester half-acid and the dicarboxylic acid derivatives of **3b** self-assemble to form highly ordered hydrogen-bonded molecular ribbons. The Val and Leu *cis*-(2*S*,3*R*)-bispeptides organize into hydrogen-bonded chains and the trans isomer of Val bispeptide self-assembles into hydrogen-bonded β-sheet ribbon.

Introduction

One of the important goals in peptide chemistry is to be able to design short peptides that can mimic some important aspect of protein structure or function.[1] Among the regular structures found in proteins, reverse-turns are known to account for nearly one-third of the residues in proteins of known structure.[2] The convenient location of turns on protein surface and their desirable structural compactness with the side chains projecting outward argue for the possibility that turns may participate actively in protein folding and may also serve as ideal sites for receptor binding, antibody recognition, and post-translational modification in proteins.[3] It is therefore not surprising that the

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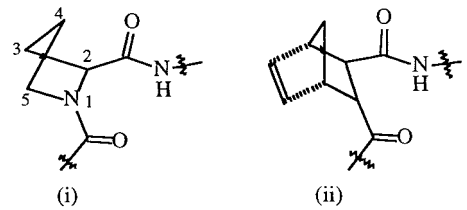
reverse-turn peptidomimetics are the most sought-after secondary structure mimetics[4] for study of molecular recognition and as probes to explore structure−function relationship of receptors and ligands.

With an ever increasing number of reports describing preformed peptides, pseudo-peptides, and non-peptide structures that can be included in polypeptide chains to mimic, induce, or stabilize various types of turn structures, a new dimension has been added in the area of constrained peptides and their use in peptide drug design.[5] However, a major breakthrough in the design of secondary structure mimetics, in particular, reverse-turn mimetics, has been the use of appropriately crafted, conformationally rigid, non-peptidic structural frameworks[4,5] which serve as ideal scaffolds for supporting the side chain functional elements in the desired reverse-turn geometry.

In this paper, we demonstrate the use of *endo-cis*-(2*S*,3*R*)-bicyclo[2.2.1]hept-5-en (norbornene) dicarbonyl unit[6] as a low molecular weight, non-peptidic molecular scaffolding for the design of reverse-turn peptide analogues and as a promising template for the nucleation of two-stranded parallel β-sheets. The *endo-cis*-(2*S*,3*R*)-norbornene scaffolding has a built-in U-architecture and appeared particularly attractive as a turn template since it has the structural elements of proline residue embedded in its framework (i) and can be considered as a carbon analogue of an N-acyl proline locked at 3,5-positions with an ethene bridge (**ii**). In that sense, use of this template would



represent the delineation of chemical simulation of protein reverse-turns in nature.[7] Additionally, the conformationally rigid and nonlinear architecture of the norbornene skeleton, apart from providing attractive models for protein folding studies,[8] may also prevent hydrophobic collapse of the peptide units in the bioactive conformation[9] and thus may serve as an ideal scaffold for the design of peptide-based drugs.

Results and Discussion

The commercially available precursor template *cis*-5-norbornene-*endo*-2,3 -dicarboxylic anhydride (**1**) was converted in an overall yield of ∼80% into a variety of *endo-cis*-(2*S*,3*R*)-norbornenobispeptides (**3a**−**h**) via a two-step sequence involving first the opening of the anhydride **1** with an appropriate amino acid ester (freshly generated in situ at 0 °C from the respective hydrochloride and triethylamine) at room temperature in dry CH_2Cl_2 or THF, followed by coupling of the product hemiamides **2a**−**i** with their respective identical amino acid partners using DCC/N−OH succinimide procedure (Scheme 1, where DCC is dicyclohexylcarbodiimide). The symmetrical *endo-cis*-(2*S*,3*R*)-norborneno bispeptides (**3a**−**h**) thus obtained were fully characterized by spectral and analytical data.

A noteworthy feature of DCC coupling of amino acid esters with hemiamides (**2a**−**i**) was that while small amounts (∼10%) of cyclic imides (**4a**−**h**) were invariably obtained as side products, the exclusive formation of imide **4b** was noticed in the case of serine condensation. The Trp imide **4e** was the exclusive product in the first step itself during the opening of precursor anhydride with Trp-OMe. Parenthetically, cyclic imides of type **4a**−**h** may provide attractive models as transition-state analogues for antibody catalysis of specific Diels−Alder reactions.[10]

In ROESY NMR spectra, strong to medium cross-peaks were seen for NH(I)−C2H and NH(II)−C3H in bispeptides **3a**−**h** (I and II denote the peptide strands at positions 2 and 3, respectively, in norbornene skeleton **3a**−**h**). The NH protons

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(7) Stereochemically constrained proline is a well-known turn-inducer in natural proteins (see ref 3). Proline may promote a β-turn or a γ-turn depending upon the flanking moieties at the *i*-position or at $i + 2$ position (for example, L, D, or Δ amino acid residue. See: (a) Aubry, A.; Marraud, M. *Biopolymers* **1989**, *28*, 109. (b) Pavone, V.; Lombardi, A.; D'Auria, G.; Saviano, M.; Nastri, F.; Paolillo, L.; DiBlastio, B.; Pedone, C. *Biopolymers* **1992**, *32*, 173. (c) Imperiali, B.; Fisher, S. L.; Moats, R. A.; Prins, T. J. *J. Am. Chem. Soc.* **1992**, *114*, 3182.

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(9) A considerable amount of effort has recently been shown in the design of scaffold peptidomimetics which can reduce or eliminate the hydrophobic collapse of peptidic chains, thus avoiding the formation of inactive conformation which appears to be the major problem during the binding of inhibitors to their receptors in aqueous solution. For a review, see ref 4f.

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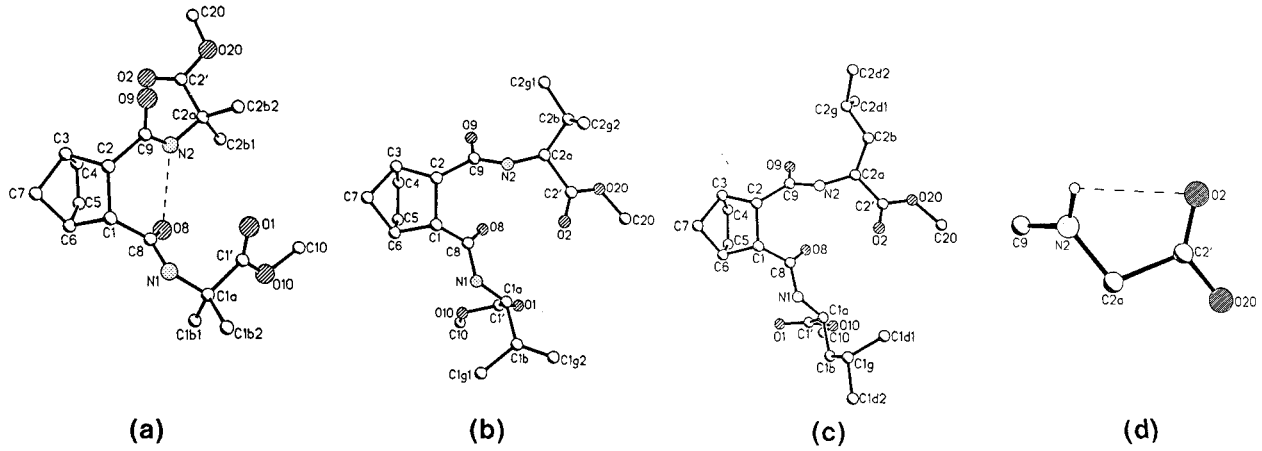
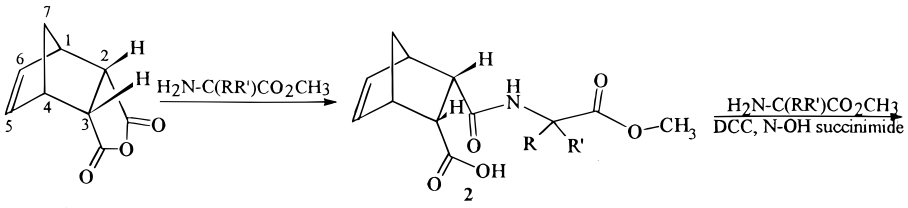


Figure 1. Crystal structure of norborneno bispeptides: (a) **3b**; (b) **3c**; (c) **3d**. All peptides adopt *endo-cis*-(2*S*,3*R*)-configuration (torsion angle C8−C1−C2−C9 = +1° (**3b**), C8−C1−C2−C9 = −10° (**3c**), and C8−C1−C2−C9 = −8° (**3d**). While the Aib bispeptide (a) exhibits a seven-membered, interstrand hydrogen-bonded ring (corresponding to γ-turn in proteins), the Val and Leu analogues show a C_5 intramolecularly hydrogen-bonded ring (d) within the same strand (II). The interstrand $C^{\alpha}-C^{\alpha'}$ distances in **3b**−**d** range between ∼5.2 and 5.7 Å.

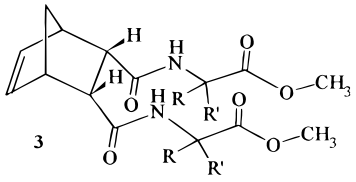
Scheme 1



1

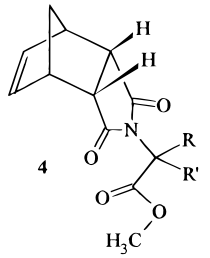
2

a: R = H; R' = CH_3; b: R = R' = CH_3; c: R = H; R' = CH_2OH
d: R = H; R' = $CH(CH_3)_2$; e: R = H; R' = $CH_2CH(CH_3)_2$
f: R = H; R' = CH_2Ph; g: R = H; R' = $(CH_2)_2SCH_3$
h: R = H; R' = CH_2COOCH_3; i: R = H; R' = $CH_2CH_2COOCH_3$

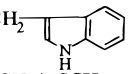


3

a: R = H; R' = CH_3
b: R = R' = CH_3
c: R = H; R' = $CH(CH_3)_2$
d: R = H; R' = $CH_2CH(CH_3)_2$
e: R = H; R' = CH_2Ph
f: R = H; R' = $(CH_2)_2SCH_3$
g: R = H; R' = CH_2COOCH_3
h: R = H; R' = $CH_2CH_2COOCH_3$



4

a: R = R' = CH_3
b: R = H; R' = CH_2OH
c: R = H; R' = $CH(CH_3)_2$
d: R = H; R' = $CH_2CH(CH_3)_2$
e: R = H; R' = 
f: R = H; R' = $(CH_2)_2SCH_3$
g: R = H; R' = CH_2COOCH_3
h: R = H; R' = $CH_2CH_2COOCH_3$

also had medium intensity ROE with C^{α} methyls in **3b** and with $C^{\beta}H_2$ protons in analogues **3c**−**3e** (Supporting Information). Although ^1H NMR variable-temperature (VT) studies (conducted with **3a**−**h** in $CDCl_3$ between 298 and 328 K) showed $d\delta/dT$ values in the range of −0.8 to −3.6 ppb/K (except in the case of **3b** which exhibited $d\delta/dT$ value of −8.5 ppb/K) indicating only small population of intramolecular hydrogen-bonded structures (also corroborated by FT-IR studies in chloroform), the presence of a strong positive band at ∼215 nm in **3c** (Figure 3) and at ∼216 nm in **3d** (Figure 4) in their circular dichroism (CD) spectra clearly suggested the type II β-turn conformation for these bispeptides.[11] Final proof for the *endo-cis*-(2*S*,3*R*)-orientation and the β-turn type conformation for norborneno bispeptides was provided by single-crystal X-ray studies.

Suitable crystals were obtained for bispeptides **3b**−**d**. The crystal structure showed that in Aib (Figure 1a), Val (Figure 1b), and Leu (Figure 1c) bispeptides, the two peptide chains are oriented in *endo-cis*-(2*S*,3*R*)-configuration and run parallel to each other (the torsion angle C8−C1−C2−C9 = +1° (**3b**), C8−C1−C2−C9 = −10° (**3c**), and C8−C1−C2−C9 = −8°

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Table 1. Torsion Angles (deg)

angle	[a]	**3b**	**3c**	**3d**	**6a**(A)	**6b**(B)
C(1)−C(2)−C(3)−C(4)		−67	−63	−63	+58	+71
C(2)−C(3)−C(4)−C(5)		+70	+67	+69	−70	−62
C(3)−C(4)−C(5)−C(6)		0	0	−1	−1	−14
C(4)−C(5)−C(6)−C(1)		−71	−73	−70	+71	+83
C(5)−C(6)−C(1)−C(2)		+67	+71	+69	−63	−55
C(6)−C(1)−C(2)−C(3)		0	−3	−4	+3	−9
C(7)−C(6)−C(1)−C(2)		−38	−34	−35	+41	+43
C(7)−C(3)−C(2)−C(1)		+37	+40	+40	−50	−25
C(8)−C(1)−C(6)−C(7)		−169	−158	−160	−73	+173
C(9)−C(2)−C(3)−C(7)		+172	+169	+168	−176	+87
O(10)−C(1′)−C(1a)−N(1)	Ψ_1	−152	−40	+153	−18	+138
C(1b)−C(1a)−N(1)−C(8)		+173	+172	+176	+125	+163
C(1′)−C(1a)−N(1)−C(8)	Φ_1	+57	−63	−63	−98	−69
C(1a)−N(1)−C(8)−C(1)	ω_{o1}	180	−176	+170	+161	+169
N(1)−C(8)−C(1)−C(2)		+120	+155	+155	+145	−162
C(8)−C(1)−C(2)−C(9)		+1[b]	−10[b]	−8[b]	−123[c]	+111[c]
C(1)−C(2)−C(9)−N(2)		+29	−66	−68	+161	−145
C(2)−C(9)−N(2)−C(2a)	ω_{o2}	+177	+168	+169	+173	+179
C(9)−N(2)−C(2a)−C(2b)		+178	+111	+105	+136	+125
C(9)−N(2)−C(2a)−C(2′)	Φ_2	−63	−127	−133	−101	−85
N(2)−C(2a)−C(2′)−O(20)	Ψ_2	+162	+164	+165	−22	−19

[a] Symbol used for torsional angles in peptides, IUPAC−IUB Commission on Biochemical Nomenclature (*Biochemistry* **1970**, *9*, 3471−3479). [b] Cis. [c] Trans.

(**3d**)) (Table 1). The interstrand $C^{\alpha}-C^{\alpha'}$ distances of 5.67 Å in **3b**, 5.20 Å in **3c**, and 5.52 Å in **3d** were also consistent with the β-turn conformation. While the crystal structures of Val (**3c**) and Leu (**3d**) bispeptides were characterized by the presence of an intrastrand C_5 type hydrogen bond (N2···O2, 2.687 Å; H2B···O2, 2.52 Å) in peptide strand II (Figure 1d), the Aib analogue (**3b**) exhibits (Figure 1a) an interstrand seven-membered hydrogen-bonded ring, (N2···O8, 2.772 Å; H2··· O8, 1.92 Å) (corresponding to γ-turn in proteins).

The presence of intramolecularly hydrogen-bonded NH in **3b** was also suggested by the ^{1}H NMR VT and FT-IR studies (Supporting Information). Thus, a $d\delta/dT$ value of −8.5 ppb/K for amide NHs in the VT spectrum of **3b** ($CDCl_3$, 298−358 K) and the presence of a broad intense band at 3309 cm^{-1} in the FT-IR ($CHCl_3$, 298 K) clearly supported the seven-membered hydrogen-bonded (NH···O═C) ring in **3b**.[12]

The notion that the reverse-turn conformation in norbornene scaffolding is controlled by *endo-cis*-(2*S*,3*R*)-orientation of the two peptide chains was firmly established by the single-crystal X-ray examination of **6a**, the trans isomer of **3c**, prepared (Scheme 2a) by neat heating of the cis peptide **3c** at ∼220 °C for 0.5 h. Interestingly, the crystal structure showed (Figure 2) the presence of two diastereomers. Molecule A (Figure 2a) with 2*R*,3*R* and molecule B (Figure 2b) with 2*S*,3*S* configurations have trans orientations of the two Val chains (torsion angle C8−C1−C2−C9 for molecule A = +111° and for molecule B = −123°). The interstrand C1aa−C2aa and C1ax−C2ax distances in molecule A and B are 8.2 and 7.4 Å, respectively (Figure 2), indicating that in trans isomers the peptide chains move away from each other. However, in both cis and trans isomers (**3c** and **6a**, respectively), the side chains on C1aa and C2aa are quite flexible and assume different conformations. Thermolysis of the Leu analogue (**3d**) gave similar results. A small amount of the olefinic product (**5**) obtained in the thermolysis reaction was identified, by comparison with authentic sample (Scheme 2b) as the trans olefin $MeO-A_{aa}-CO-CH{=}CH-CO-A_{aa}-OMe$ (E).

(12) Interestingly, peptides containing *N*-α-benzoyl-*cis*-4-amino-L-proline are recently shown to adopt γ-turn conformation in chloroform solution (Curran, T. P.; Chandler, N. M.; Kennedy, R. J.; Keaney, M. T. *Tetrahedron Lett*. **1996**, *37*, 1933).

The CD spectrum of diastereomeric mixture of trans isomer (**6a**) showed the absence of any turn features (Figure 3) and thus was in agreement with the solid-state structure. The presence of the 5,6-double bond in norbornene template did not contribute much to the turn conformation as was shown by the CD spectrum of the 5,6-dihydro derivative (obtained from **3c** by hydrogenation; Pd/C, 5%/H_2/EtOAc) which still exhibited a broad positive band although of reduced ellipticity at ∼211 nm (Figure 3).

However, the ring double bond in norbornene scaffoldings offered several advantages. Apart from acting as a marker in ^{1}H NMR, the 5,6-double bond could easily be cleaved (Scheme 3), as demonstrated with **3d**, under Ru(VIII)-catalyzed oxidative conditions[13,14] to afford a cyclopentanoid peptide analogue (**7**) with four contiguous (all cis) asymmetric centers. Interestingly, the cyclopentane scaffolding **7** retains its β-turn character as shown by the presence of a broad positive band at ∼211 nm (similar to that of **3c** and **3d**) in its CD spectrum (Figure 4). The newly generated −COOH groups offer two additional handles for attaching peptide chains thus providing attractive scaffoldings for crafting peptide dendrimers or as templates for designing artificial proteins.

From the spectral and the X-ray data, taken together, it can be concluded that *endo-cis*-(2*S*,3*R*)-bispeptides supported on a norbornene template would adopt a β-turn type conformation. The parallel orientation of the chains suggested the use of these scaffoldings as precursors for the construction of artificial, two-stranded parallel β-sheets—a secondary structural motif much sought-after in view of its potential use in the design of protease inhibitors.

Norbornene Unit as a Template for the Nucleation of Parallel β-Sheets. Recently, there has been a resurgence[15,16] of activity in the design of simple models for β-sheet structures that can provide deeper insights into the protein folding mechanism and enzyme−substrate interaction and also serve as building blocks for molecular receptors and catalysts. A strategy that has emerged as the most popular approach[17] for creating artificial β-sheets is the use of appropriately crafted

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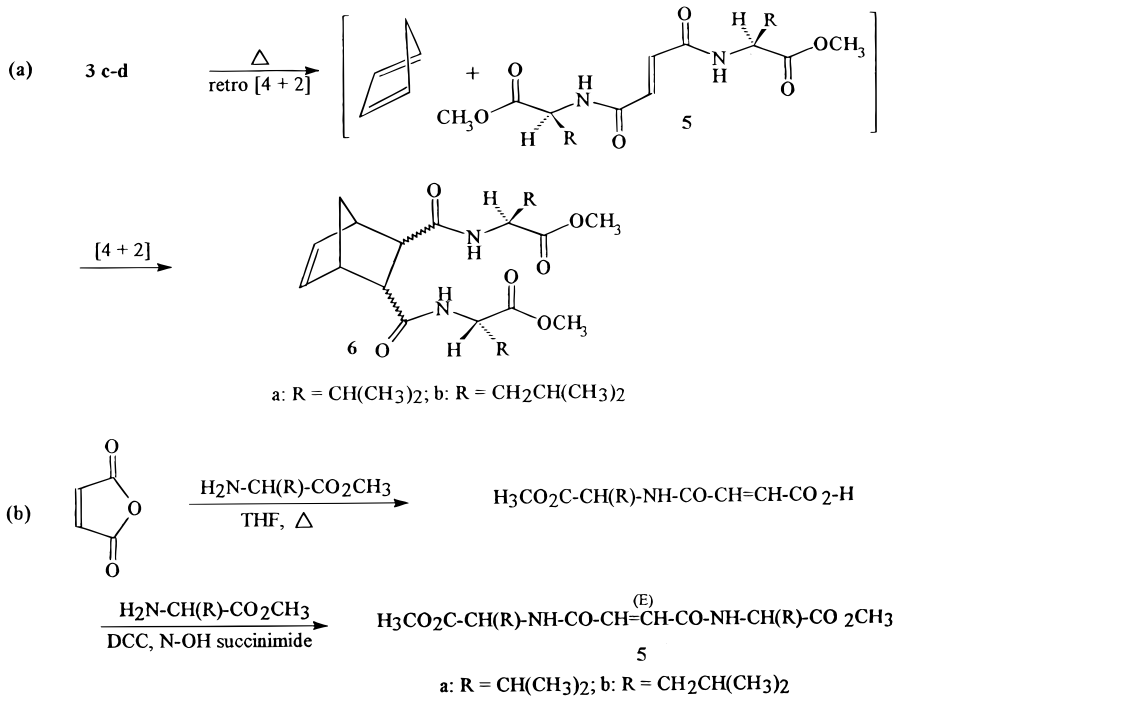
Scheme 2



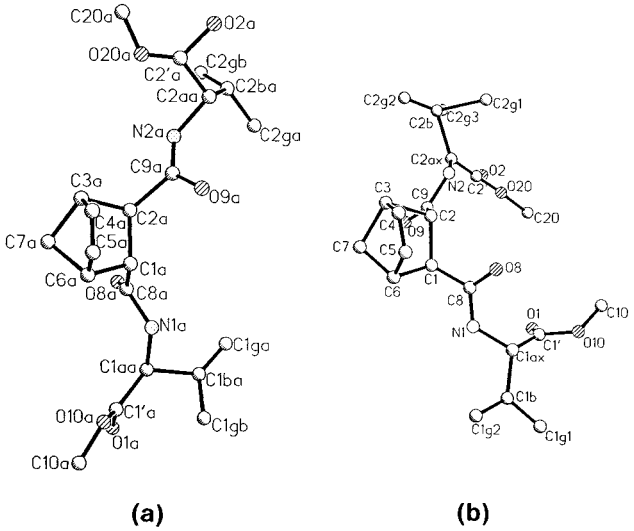


Figure 2. Crystal structure of *trans*-2,3-bis-Val peptide (**6a**). Two diastereomers are seen in the solid state. Molecule A (a) with 2*R*,3*R* and molecule B (b) with 2*S*,3*S* (the numbering of carbon atoms same as in **1**) have the trans configuration (torsional angle C8−C1−C2−C9 for molecule A = +111 Å and for molecule B = −123 Å) for the orientation of the two Val chains. The interstrand $C^{\alpha}-C^{\alpha'}$ (C9−C1aa-C2aa and $C1_{ax}-C2_{ax}$) distances in molecule A and B are 8.2 and 7.4 Å, respectively.

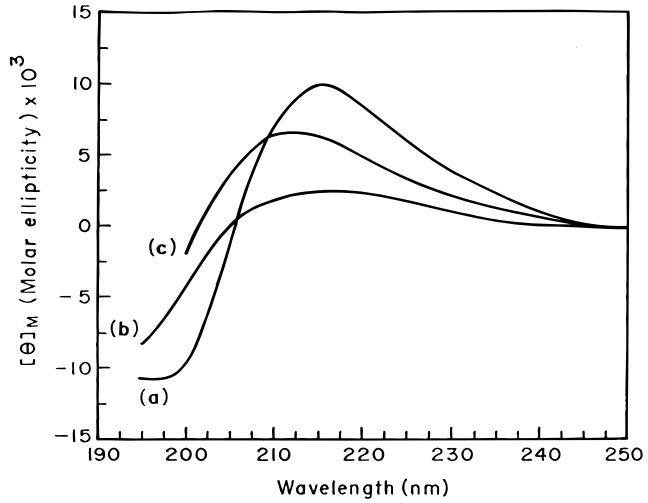
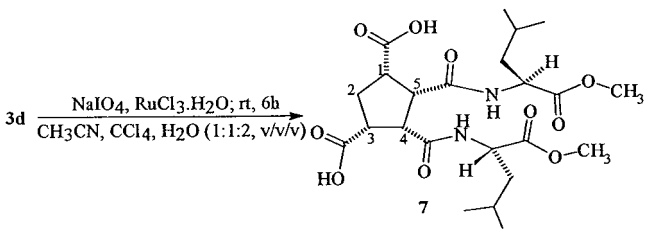


Figure 3. A comparison of the CD spectra (in TFE) of 2,3-*cis*-Val peptide **3c** (a), 2,3-*trans*-Val peptide **6a** (b) and 5,6-dihydro derivative of **3c** (c). While the cis peptide **3c** exhibits a strong band at 215 nm attributed to type-II β-turn conformation, its trans isomer **6a** shows a diffused broad band indicating loss of β-turn features in the structure. The 5,6-dihydro derivative of **3c** still shows a medium intensity positive band at ∼211 nm.

peptidic or nonpeptidic molecular scaffolds in combination with peptide strands and β-strand mimics. The function of the molecular scaffold being to bring the two peptide strands in close proximity either by virtue of its molecular geometry or by inducing intramolecular hydrogen bonding for β-sheet formation. Interestingly, although several models for antiparallel β-sheets are available,[15] the reports on the design of artificial parallel sheet structures are still scarce.[16] The above results with norbornene scaffold encouraged us to explore the potential of this unit as a possible hairpin template for the construction of simple, minimal models of two-stranded parallel β-sheets.

A large variety of higher norborneno bis-di-, -tri-, and

Scheme 3



-tetrapeptides (**8**−**10**, Chart 1) containing β-branched amino acid residues, with high β-sheet propensity, were prepared in a simple manner by bi-directional elongation of the bis-dicarboxylic acids of **3c** and **3d** precursor bispeptides using DCC/N−OH succin-

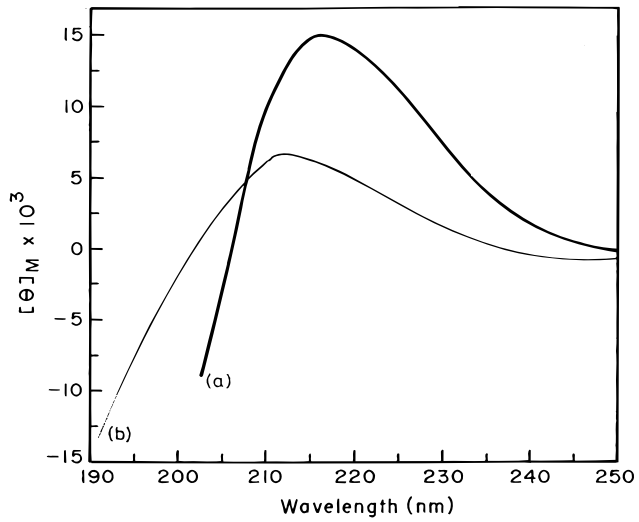
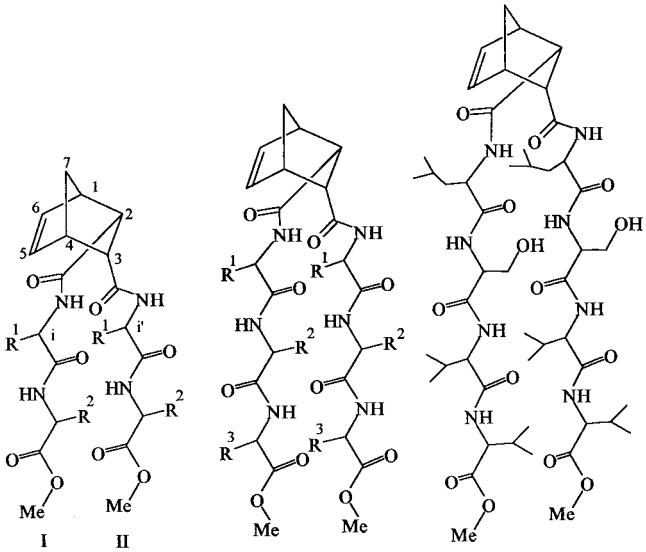


Figure 4. A comparison of the CD spectra (TFE) of 2,3-*cis*-Leu peptide **3d** (a) and cyclopentane derivatives **7** (b). The broad band at ∼211 nm in (b) shows that β-turn features are retained in **7**.

Chart 1 The Family of Norborneno Bis-di (**8a**−**c**), -tri (**9a**−**e**), and -tetra (**10**) Peptide Analogs (The Peptide Strands at Positions 2 and 3 Are Denoted by I and II, Respectively)



imide coupling procedure. Thus, for the preparation of **8a** and **8b**, the bisacid of Val analogue **3c** was coupled with Val-OMe and Phe-OMe, respectively, and **8c** was obtained from the bisacid of **3d** and Ser-OMe. The bis-tripeptides **9a**−**e** could either be obtained by two stepwise elongations of **3c** and **3d** via the intermediate bis-dipeptides **8a**−**c** as for **9a** and **9b** or by a single-step elongation of the precursor peptides **3c** and **3d** with the corresponding dipeptides, for example, Val-Val-OMe for **9a** and **9b**, Leu-Leu-OMe for **9c**, Leu-Ser-OMe for **9d**, and Ser-Leu-OMe for **9e**. For the preparation of norborneno bis-tetrapeptide **10**, the precursor Leu bisacid from **3d** was coupled with tripeptide Ser-Val-Val-OMe. The bispeptides **8**−**10** obtained in good yields were purified by column chromatography on silica gel using a gradient ($CHCl_3$/MeOH) elution and were fully characterized by ^{1}H NMR, FT-IR, and FAB MS.

Interestingly, all of the norborneno bispeptides showed high solubility[18] in a wide range of organic solvents, including the apolar chloroform. The 400 MHz ^{1}H NMR spectra of **8**−**10** (Supporting Information) in $CDCl_3$ and in DMSO-d_6 were extremely well-resolved with sharp resonances, indicating presence of well-defined conformational species in solution. Sequence-specific assignment of all backbone proton resonances was readily achieved using a combination of TOCSY and ROESY experiments. The consistently high values (7.0−9.3 Hz) observed for the $^3J_{HN\alpha}$ coupling constants (Table 3) throughout the strand segment clearly indicated[19] extended (β-strand) conformation in **8**−**10**. The presence of medium to strong intrastrand sequential ROE connectivities $d_{\alpha N(i,i+1)}$ spanning the entire three- or four-residue sequence in peptide strands of **9a**−**e** and **10** (Supporting Information) further suggested that β-sheet conformers dominate the population.[20] The temperature dependence of amide protons in **9a**, **9c**, and **10** (Supporting Information) was studied in DMSO-d_6 over the temperature range of 293−363 K. The relatively low values for temperature coefficients ($d\delta/dT$ varies between −0.2 to −3.4 ppb/K) of amide NHs (Table 4) indicate the presence of intramolecular interstrand hydrogen bonding.[21] Although weak, the presence of long-range ROEs between the NH (i+1) of strand I and the $\alpha(i)$ proton of strand II in the ROESY spectra of bis-tripeptides (**9a** and **9c**) provided further evidence for parallel β-sheet conformation.

Further support for intramolecular hydrogen bonding came from FT-IR studies (298 K, $CDCl_3$). Thus, in homologous Val series of bispeptides, steady increase in the intensity of concentration independent NH-stretch band at ∼3300 cm^{-1} (Supporting Information) with each successive addition of a pair of Val residues (**3c** → **8a** → **9a**) was clearly supportive of increasing interstrand hydrogen bonding.

CD studies of several members of norborneno bispeptides (**8**−**10**) were carried out in TFE (trifluoroethanol) as well as in MeOH solvents. The presence of a sharp −ve band at ∼218 nm in **8c** and broad −ve band at ∼220 nm in **9a**−**c** and **10** (Supporting Information) strongly supported high population of

(18) Although several non-peptidic, cyclic molecular scaffolds have been used in the recent past[15,16] for creating artificial β-sheet structures, almost all of them possessed polycyclic aromatic frameworks and had posed serious solubility problems. For example, Kemp's 2,8-diaminoepindolidione was soluble only in concentrated sulfuric acid.[15h] The parallel β-sheet models reported here on norbornene molecular scaffold have much improved solubility in organic solvents such as chloroform, ethyl acetate, and methanol indicating low tendency of these mimics to self-associate.

(19) The $^3J_{HN\alpha}$ coupling constants greater than 7 Hz are generally considered to be consistent with β-sheet structure, while values of <6 Hz are consistent with α-helical structure [(a) Kessler, H. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 512. (b) Dyson, H. J.; Wright, P. E. *Annu. Rev. Biophys. Chem.* **1991**, *20*, 519. (c) Wuthrich, K. *NMR of Proteins and Nucleic Acids*; Wiley: New York, 1986; pp 166−168)].

(20) Strong NOEs between the α-proton of one residue and the NH group of the next residue are characteristic of the β-strand (extended) conformation. (Wuthrich, K. *NMR of Proteins and Nucleic Acids*; Wiley: New York, 1986; pp 124−129).

(21) In polar aprotic solvents such as DMSO-d_6, the $-d\delta/dT$ values >5 ppb/K are interpreted for a solvent-exposed NH while values <3ppb/K suggest an amide NH that is shielded from solvent through either intramolecular hydrogen bonding or steric shielding [(a) Zerkout, S.; DuPont, V.; Aubry, A.; Vidal, J.; Collet, A.; Vicherat, A.; Marraud, M. *Int. J. Pept. Protein Res.* **1994**, *44*, 378. (b) Prasad, S.; Rao, R. B.; Balaram, P. *Biopolymers* **1995**, *35*, 11. (c) Toniolo, C.; Bonora, G. M.; Stavropoulous, G.; Cordopatis, P.; Theodoropoulos, D. *Biopolymers* **1986**, *25*, 281. (d) Aubry, A.; Chung, M. T.; Marraud, M. *J. Am. Chem. Soc.* **1985**, *107*, 1825. (e) Sakakibara, S. *Biopolymers* **1995**, *37*, 17)].

Table 2. Hydrogen Bonds in Norborneno Compounds (NBE) (Å)

3b NBE(Aib)$_2$ cis	**3c** NBE(Val)$_2$ cis	**3d** NBE(Leu)$_2$ cis	NBE(Aib)$_2$ cis half-ester; half-acid	NBE(Aib)$_2$ cis diacid	**6a** NBE(Val)$_2$ trans
			Intramolecular		
N2···O8 2.772	N2···O2 2.687	N2···O2 2.701	O2O···O8 2.623		
H···O8 1.92	H···O2 2.52	H···O2 2.50			
3 → 1	C_5	C_5	4 → 1		
			Intermolecular		
N1···O9 2.848	N1···O9 2.971	N1···O9 2.915	N1···O9 2.886	N1···O1a 3.044	N1···O8A 2.942
H···O9 1.99	H···O9 2.14	H···O9 2.04	H···O9 2.02	H···O1a 2.18	H···O8A 2.14
dimer	infinite chain	infinite chain	N2···O2 2.991	N2···O2b 2.969	N2···O9A 2.840
			H···O2 2.13	H···O2b 2.08	H···O9A 2.02
			stack in infinite	O10a···O9 2.738	N1A···O8 2.911
			ribbon	O20a···O8 2.710	H···O8 2.05
				stack in β-ribbon	N2A···O9 2.862
					H···O9 2.05
					β- sheet

Table 3. The ^{1}H NMR $^3J_{HN\alpha}$ Coupling Constants (Hz) of the NH Protons[a] of **8a**, **8b**, **9a**−**c**, and **9e** (20 °C, 1 mm in $CDCl_3$)[b] and **10** (in DMSO-d_6)

peptide	H_i	H_{i+1}	H_{i+2}	H_{i+3}	$H_{i'}$	$H_{i'+1}$	$H_{i'+2}$	$H_{i'+3}$
8a	8.9	8.3			9.4	8.3		
8b	9.3	8.6			8.7	8.3		
9a	7.0	7.9	8.7		9.2	7.9	8.7	
9b	8.2	8.0	8.9		8.4	8.4	8.2	
9c	8.3	7.4	7.9		8.1	7.9	7.9	
9e	7.5	8.2	8.0		8.0	7.7	7.8	
10	4.8	7.2	9.3	7.9	7.4	7.5	8.8	7.7

[a] *i* and *i*′ represent the first amino acid residue in strand I and II, respectively. [b] The $^3J_{HN\alpha}$ values were found to have the same profile in DMSO-d_6 also.

Table 4. Temperature Dependence of the ^{1}H NMR Chemical Shifts-(ppb/K) of the NH Protons of Bispeptides **9a**, **9c**, and **10** (1 mM in DMSO-d_6)[a]

peptide	H_i	H_{i+1}	H_{i+2}	H_{i+3}	$H_{i'}$	$H_{i'+1}$	$H_{i'+2}$	$H_{i'+3}$
9a	2.3	2.2	4.3		2.3	3.1	2.9	
9c	2.3	0.9	3.1		2.6	1.7	1.0	
10	3.4	2.2	0.2	1.8	2.3	1.6	2.5	2.8

[a] VT spectra recorded at 10 °C intervals from 20 to 70 °C.

β-sheet conformers. In bis-tripeptides **9a** and **9b** a new minimum appeared at ∼205 nm which was not seen in the CD of other bispeptides.[22]

Thus, collectively, the spectroscopic (^{1}H NMR, FT-IR and CD) studies establish the parallel β-stranded nature of the two peptide chains in higher norborneno bispeptides **8**−**10** as was originally seen in the precursor bispeptides **3c** and **3d**. Furthermore, the increasing population of interstrand hydrogen-bonded structures in higher bispeptides clearly shows that norbornene unit is an effective template for nucleating parallel β-sheet structures.

Self-Assembling Properties of Norborneno Peptide Analogues. Although, in the past decade there has been virtually a near explosion in the reports describing the design of protein secondary structure mimetics,[23] an important aspect of peptidomimetics which had hitherto received scant attention is their tendency to self-associate[24] either in solid or in solution state through intermolecular hydrogen bonding. This particular aspect gains more importance in view of their preferred conformations[3] during receptor binding. Only very recently has this area been mentioned in a few reports on the self-assembling properties of core-modified small linear peptides[25] and secondary structure mimetics.[26] In the present design, the presence of norbornene unit shows the intrinsic property of promoting intermolecular hydrogen bonding with the neighbors and creates highly organized self-assemblies in the solid state as demonstrated with the crystal structure of several norborneno bispeptides.

The crystal structure of norborneno bis Aib peptide **3b** showed, in addition to an internal seven-membered hydrogen-bonded ring, the presence of dimeric structures formed through intermolecular hydrogen bonding. The internally hydrogen-bonded structure of **3b** (Figure 1a) contains an unutilized NH function on one Aib chain and a C═O group on the opposite Aib chain. The bispeptide in this conformation is self-complementary and dimerizes to form cyclic dimers (Figure 5a) through a symmetrical pair of N−H···O (N···O 2.848 Å; H···O 1.99 Å) hydrogen bonds. The 16-membered centrosymmetric dimer has a cavity with a size of 4.0 × 5.2 Å (N1···O9 and C2···C2 symmetric distances). The packing diagram of dimers is shown in Figure 5b.

Interestingly, the hydrogen-bonded dimers of **3b** are stable in solution (as shown by the molecular weight value of 805 obtained in chloroform by vapor pressure osmometry method)

(22) A shoulder at ∼210 nm in the CD of longer norborneno bispeptides was attributed to the constrained norbornene unit (ref 6).

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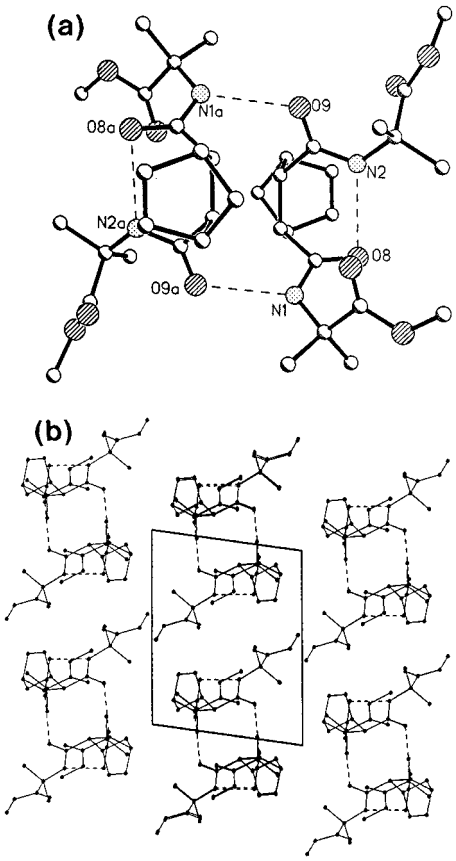

Figure 5. Hydrogen-bonded cyclic dimers of **3b** in the solid state (a) X-ray structure and (b) crystal packing.

as well as in vapor phase (FAB MS shows 6% of dimer peak). In contrast, the dicarboxylic acid of **3b** did not exhibit any intramolecular hydrogen bonds in its crystal structure (Figure 6a). There was no inter- or intramolecular hydrogen bonding between the −COOH groups as is normally found in dicarboxylic acids. As shown in Figure 6b, the U-shaped dicarboxylic acid molecules stack in an antiparallel fashion, connected to each other, through a network of N−H···O and O−H···O hydrogen bonds. Each molecule participates in a total of eight hydrogen bonds (four to each neighbor), thus utilizing all of its hydrogen-bond donors and acceptors in intermolecular hydrogen bonding which extends into an infinite double-stranded β-ribbon (Table 2). The four independent hydrogen bonds are locked in a contiguous alternating array of 11-membered and 14-membered (a characteristic feature of β-sheet) hydrogen-bonded rings in the double-stranded β-ribbon. In the dicarboxylic acid ribbon assembly, the molecules are repeated by a vertical 2-fold screw axis which directs the norbornene units toward the edges of the molecular ribbon giving the edges a very hydrophobic character. A schematic representation of the self-assembly of dicarboxylic acid is shown in Figure 6c.

The half-ester half-acid derivative of **3b** showed in its crystal structure (Figure 7a) the presence of a 10-membered intramolecularly hydrogen-bonded ring involving norbornene carbonyl and acid −OH group (O20···O8, 2.71 Å; H20···O8, 1.91 Å) as compared to a seven-membered ring involving N2···O8 in **3b**. Like the dicarboxylic acid, the cis half-ester half-acid molecules self-assemble in infinite ribbons by a pair of intermolecular N−H···O hydrogen bonds with norbornene carbonyl and carboxylic carbonyl groups acting as hydrogen-bond acceptors. The molecules alternate in orientation along the ribbon. Figures 7b and c show, respectively, the crystal

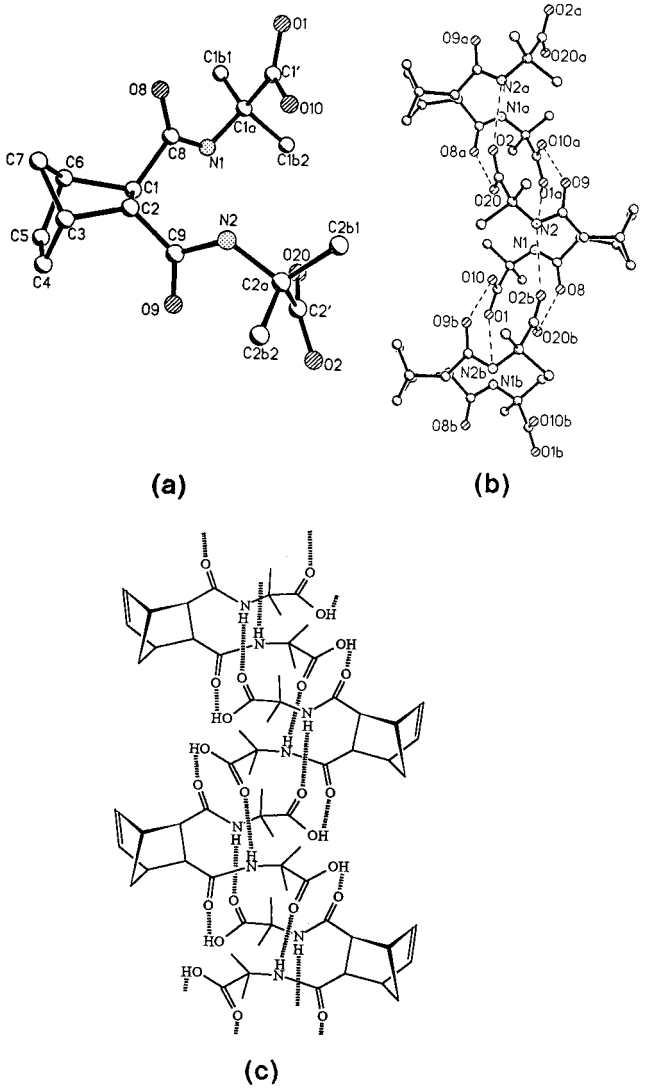

Figure 6. (a) Crystal structure of the dicarboxylic acid of **3b** (b). X-ray picture of the infinite double-stranded ribbon assembly formed by antiparallel stacking of dicarboxylic acid molecules through a network of N−H···O and O−H···O hydrogen bonds. The molecules are repeated by a vertical 2-fold screw axis which directs the norbornene units toward the edges of the ribbon (c) a schematic representation of the hydrogen-bonded molecular ribbon.

structure and the schematic representation of the self-assembly of hemiester of **3b**.

The self-assembly pattern of *endo-cis*-(2*S*,3*R*)-bis-Val peptide **3c** and its trans isomer **6a** differ from each other and from the Aib bis peptide **3b**. Thus, in *endo-cis*-peptide **3c** while one amide NH is locked in an intrachain C_5 hydrogen-bonded ring with the ester carbonyl (Figure 1d), the NH of the second Val residue participates in intermolecular hydrogen bonding with the norbornene carbonyl creating a hydrogen-bonded infinite chain wherein each molecule bonds with two neighbors through a pair of N−H···O bonds [N···O 2.971 Å, H···O 2.14 Å (Figure 8a)]. The molecules in the chain organize in an antiparallel manner with a 2-fold screw axis (schematic representation shown in Figure 8b).

The *trans*-bis-Val peptide **6a** on the other hand, by virtue of its nearly extended backbone, shows a different self-assembly. The two diastereomers 2*R*,3*R* and 2*S*,3*S* alternate in the stack to form a highly ordered β-sheet ribbon wherein each molecule is bonded to two neighbors through two pairs of symmetrical intermolecular NH···O═C hydrogen bonds forming the char-

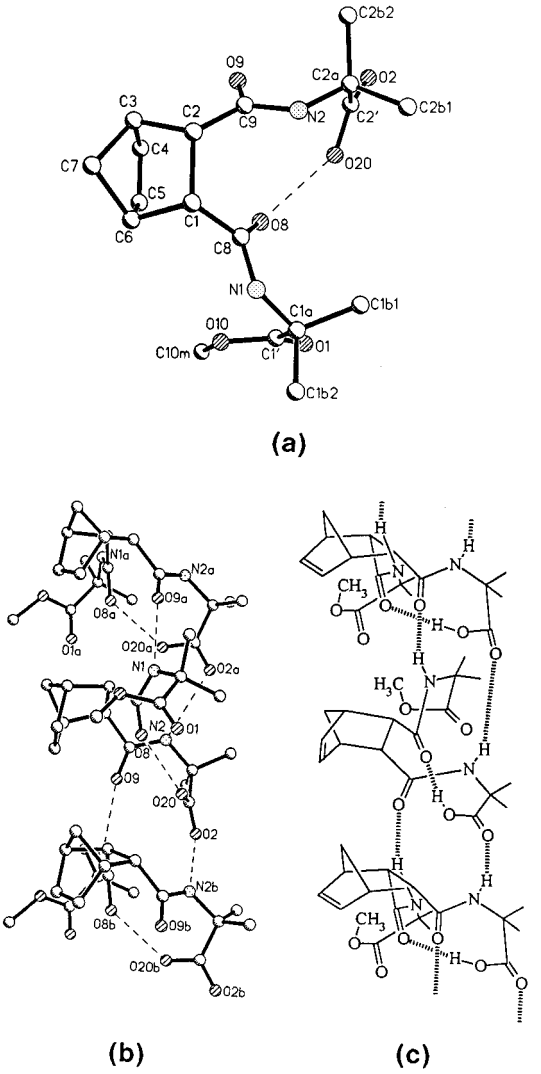

Figure 7. (a) Crystal structure of half-ester half-acid of **3b**. The molecule is locked in a 10-membered intramolecularly hydrogen-bonded ring (b), the infinite ribbon assembly formed by the molecules which alternate in orientation along the ribbon, and (c) a schematic representation of the hydrogen-bonded ribbon stabilized by a network of intramolecular (O−H···O) and intermolecular (N−H···O) hydrogen bonds.

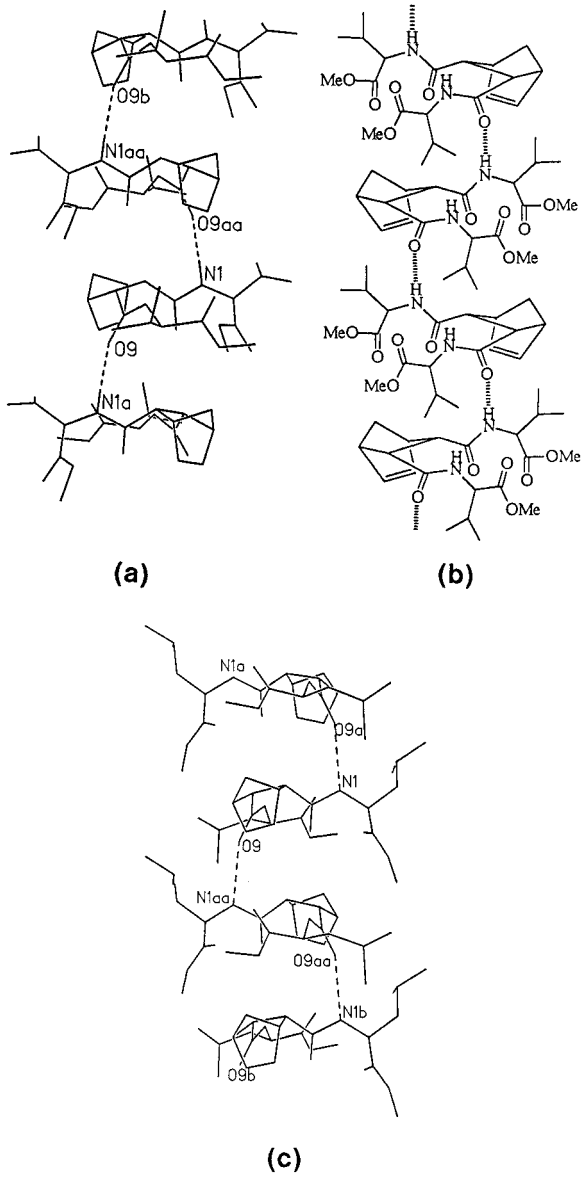

Figure 8. (a) A hydrogen-bonded chain assembly of **3c** in solid state. The molecules in the chain organize in an antiparallel manner with a 2-fold screw axis. The intramolecular C_5 hydrogen-bonded ring is not shown. (b) A schematic representation of the hydrogen-bonded molecular chains in **3c** and (c) X-ray picture of the chain assembly in structurally similar **3d**. The molecules are connected by continuous N−H···O hydrogen bonds.

acteristic 14-membered rings found in β-sheets (Figure 9a). The N−H···O hydrogen bonds are formed between NH of valine and C═O of norbornene units (N1···O1A, 2.976 Å; H1A··· O1A, 2.20 Å; N2···O4A, 2.832 Å; H2B···O4A, 2.01 Å; N1A··· O1, 2.901 Å; H1A···O1, 2.05 Å; N2A···O4, 2.952 Å, H2A··· O4, 2.13 Å) in the adjacent neighbors. A noteworthy feature of the self-assembly of *trans*-bis-Val peptide is the lining-up of the Val and carbomethoxy methyls at the edges and norbornene units in the middle of the β-sheet ribbon giving these regions a very hydrophobic character. Figure 9b shows the schematic representation of the sheet assembly.

As anticipated, the *endo-cis*-(2*S*,3*R*)-bis-Leu peptide **3d** shows strikingly similar self-assembly (Figure 8c) with a characteristic chain motif as observed in norborneno bis-Val peptide **3c**. The N1H···O9 hydrogen bonds link the molecules into a continuous string around a 2-fold screw axis (N1···O9, 2.915 Å; H···O9, 2.04 Å). The strong tendency of norborneno peptide analogues to self-assemble into contiguous ribbons or β-sheet-like structures through intermolecular hydrogen bonding is noteworthy and may have relevance in the design of protease inhibitors.[26]

Conclusion

In summary, the (2*S*,3*R*)-norbornene dicarbonyl unit with a built-in U-architecture has been demonstrated as a reliable molecular scaffold for the construction of reverse-turn peptide analogues and as a nucleator of two-stranded parallel β-sheets. A large variety of (2*S*,3*R*)-substituted norborneno bispeptides have been synthesized and examined for conformational preferences by ^{1}H NMR, FT-IR, CD, and X-ray studies. While FT-IR and VT studies are not in favor of hydrogen-bonded structures in simple bispeptides (except in Aib case), CD spectra clearly suggested the presence of β-turn type features in *endo-cis*-(2*S*,3*R*)-bispeptides **3c** and **3d**, also, supported by ROESY NMR spectra. The 5,6-double bond although not necessary for turn structure can be exploited to generate cyclopentanoid peptide analogues by Ru(VIII)-catalyzed oxidative cleavage. The reverse-turn structure has been firmly established by single-crystal X-ray studies in Aib, Val, and Leu containing norborneno

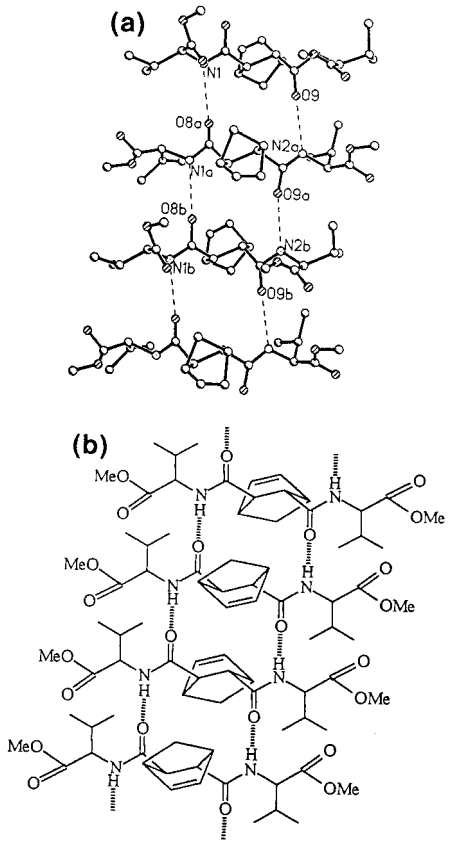

Figure 9. (a) A β-sheet ribbon assembly of 2,3-*trans*-Val bispeptides (**6a**). The two mirror-image isomers (2*R*,3*R* and 2*S*, 3*S*) alternate in the stack, each molecule bonded to the neighbor through a symmetrical pair of N−H···O hydrogen bonds forming the characteristic 14-membered rings found in β-sheets and (b) a schematic representation of the hydrogen-bonded β-sheet ribbon. A noteworthy feature of the assembly is the lining-up of the carbomethoxy methyls at the edges and norbornene units in the middle of the ribbon, giving these regions a very hydrophobic character.

bispeptides **3b**, **3c**, and **3d**, respectively. Crystal structure analyses showed that except in Aib bispeptide which has an intramolecular interstrand seven-membered ring (corresponding to a γ-turn in peptides), all bispeptides adopt open-turn structures with interstrand $C^{\alpha}-C^{\alpha'}$ distances in the range of 5.2−5.7 Å. That the *endo*-*cis*-(2*S*,3*R*)-orientation of bispeptide chains is essential for turn conformation was convincingly shown by the crystal structure of *trans*-(2*R*,3*R*)- and *trans*-(2*S*,3*S*)-Val derivatives wherein the two chains moved away from each other ($C^{\alpha}-C^{\alpha'}$, 7.2−8.2 Å). Spectroscopic studies have clearly established the parallel β-stranded nature of the peptide chains in higher norborneno bispeptides (**8**−**10**) and thus have shown that norbornene unit can act as an efficient template for the nucleation of hydrogen-bonded parallel β-sheets.

A particularly noteworthy feature of the norborneno bispeptides is their strong tendency to self-assemble in solid state. Thus, while *endo*-*cis*-(2*S*,3*R*)-Val and -Leu bispeptides self-assemble in infinite hydrogen-bonded chains, the trans isomer of Val bispeptide organizes to form an extensively hydrogen-bonded β-sheet ribbon. Interestingly, while the internally hydrogen-bonded dimethyl ester of Aib bispeptide (**3b**) forms 16-membered hydrogen-bonded centrosymmetric dimers, the half-ester half-acid and the dicarboxylic acid derivatives of **3b** form highly ordered molecular ribbons through participation of all of the available hydrogen-bonding donors and acceptors. An attractive feature of these assemblies is the lining up of norbornene units to provide strong hydrophobic regions. The demonstration of a conformationally rigid, small, low molecular weight, non-peptidic (2*S*,3*R*)-norbornene dicarbonyl unit as a molecular scaffold for the construction of minimal models of parallel two-stranded β-sheets and reverse-turn peptide analogues is particularly important in the context of designing peptide-based drugs.

Experimental Section

All amino acids used were of L-configuration. Melting points were recorded on a Fischer-Johns melting point apparatus and are uncorrected. Optical rotations were measured with an automatic JASCO polarimeter; concentrations are given in grams/100 mL. Infrared spectra were recorded on a Perkin-Elmer/1600FT spectrometer in chloroform solutions, as neat liquids, or as KBr pellets, and prominent peaks are expressed in cm^{-1}. ^1H NMR spectra were recorded on Varian UNITY-400, Bruker WM 300, Hitachi R 600 and JEOL 90 MHz instruments. The chemical shifts are reported in δ (ppm) with TMS at 0.00 as an internal reference. ROESY experiments were performed using 0.2 s mixing time with pulsed spin locking with 30° pulses and 2 kHz spin locking field. FAB MS were obtained on a JEOL SX-120/DA-6000 instrument using *m*-nitrobenzyl alcohol as the matrix. The circular dichroism (CD) spectra were recorded on JASCO J 20 spectropolarimeter in quartz cells of 1 mm path length at 25 °C. Reactions were monitored wherever possible by TLC. Silica gel G (Merck) was used for TLC, and column chromatography was done on silica gel (100−200 mesh) columns, which were generally made from a slurry in hexane or a mixture of hexane and ethyl acetate. Products were eluted (gradient) with either a mixture of ethyl acetate/hexane or chloroform/methanol.

Reaction of *cis*-5-Norbornene-*endo*-2,3-dicarboxylic Anhydride (1) with Amino Acid Esters. Preparation of *N*-[3-Carboxybicyclo-[2.2.1]hept-5-en-2-ylcarbonyl] Amino Acid Methyl Esters (2a−i). General Procedure. A well-stirred and ice-cooled solution of *cis*-5-norbornene-*endo*-2,3-dicarboxylic anhydride (**1**, 10 mmol) in dry CH_2Cl_2 (∼20 mL) was admixed with amino acid methyl ester free base (freshly generated in situ at 0 °C from corresponding methyl ester hydrochloride and triethylamine, 10 mmol each, in dry CH_2Cl_2 (∼50 mL)) and stirred at room temperature for 12 h. The reaction mixture was worked up by washing, sequentially, with ice-cold 2 N H_2SO_4 and water (20 mL each), drying (anhyd. $MgSO_4$), and evaporating in vacuo. The residue in most cases was directly crystallized from a mixture of ethyl acetate and hexane.

***N*-(3-Carboxybicyclo[2.2.1]hept-5-en-2-ylcarbonyl) alanine methyl ester (2a):** yield 86%; mp 116−118 °C; IR (KBr) 3510, 3005, 2950, 1745, 1703, 1558, 1514, 1461, 1394 cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$) δ 1.33 (3H, d, J = 7.5 Hz), 1.58 (2H, dd), 3.24 (4H, m), 3.65 (3H, s), 4.50 (1H, m), 6.02 (2H, brs), 6.43(2H, br, exchangeable with D_2O).

***N*-(3-Carboxybicyclo[2.2.1]hept-5-en-2-ylcarbonyl) Aib methyl ester (2b):** yield 94%; mp 124−128 °C; IR (KBr) 3366, 3080, 2977, 2743, 2680, 2497, 1727, 1705, 1674, 1541, 1472, 1439, 1392 cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$) δ 1.04−1.64 (8H, s+m), 3.16 (4H, m), 3.65 (3H, s), 6.19 (2H, m), 7.28 (1H, s, exchangeable).

***N*-(3-Carboxybicyclo[2.2.1]hept-5-en-2-ylcarbonyl) serine methyl ester (2c):** yield 66%; syrup; IR (KBr) 3451 (br), 2990 (br), 1750, 1712, 1574, 1544, 1524, 1435, 1395, 1340 cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$) δ 1.64 (2H, br dd), 3.33 (4H, brs), 3.68 (3H, s), 3.88 (2H, d, J = 6.0 Hz), 4.66 (1H, br t), 6.17 (3H, m).

***N*-(3-Carboxybicyclo[2.2.1]hept-5-en-2-ylcarbonyl) valine methyl ester (2d):** yield 80%; mp 114−116 °C; IR (KBr) 3549, 3375, 3279, 3088, 2978, 2672, 1727, 1657, 1571, 1531, 1469, 1440, 1388 cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$) δ 0.89 (6H, d, J = 6.0 Hz), 1.41 (2H, brs), 2.02 (1H, m), 3.20 (4H, brd), 3.65 (3H, s), 4.39 (1H, m), 5.98−6.41 (3H, m), 6.49 (1H, brd, exchangeable).

***N*-(3-Carboxybicyclo[2.2.1]hept-5-en-2-ylcarbonyl) leucine methyl ester (2e):** yield 90%; mp 94−96 °C; IR (KBr) 3532, 3418, 3274, 3096, 2971, 2620, 1730, 1657, 1569, 1393 cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$) δ 0.96 (6H, d, J = 5.0 Hz), 1.51 (5H, m), 3.14 (4H, m), 3.70 (3H, s), 4.53 (1H, m), 6.03−6.79 (4H, m); FAB MS *m*/*z* 310 $(MH)^+$.

***N*-(3-Carboxybicyclo[2.2.1]hept-5-en-2-ylcarbonyl) phenylalanine methyl ester (2f):** yield 90%; mp 98−100 °C; IR (KBr) 3531, 3417,

3283, 3092, 2978, 2647, 1721, 1666, 1565, 1504, 1452, 1387 cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$) δ 1.32 (2H, brs), 2.77−3.33 (6H, m), 3.62 (3H, s), 4.57 (1H, m), 5.72 (2H, brs), 6.27 (1H, brd), 7.04 (5H, brs); FAB MS *m*/*z* 344 $(MH)^+$.

***N*-(3-Carboxybicyclo[2.2.1]hept-5-en-2-ylcarbonyl) methionine methyl ester (2 g):** yield 54%; mp 102−104 °C; IR (KBr) 3525, 3390, 3287, 3087, 2978, 2950, 2660, 1726, 1656, 1561, 1436, 1387 cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$) δ 1.39 (2H, brs), 2.03 (5H, s+m), 2.46 (2H, m), 3.19 (4H, brd), 3.66 (3H, s), 4.51 (1H, m), 6.21 (3H, m), 7.31 (1H, brd).

***N*-(3-Carboxybicyclo[2.2.1]hept-5-en-2-ylcarbonyl) aspartic acid dimethyl ester (2h):** yield 73%; syrup; IR (KBr) 3403, 3072, 3025, 3003, 2959, 2702, 2487, 1733, 1654, 1523, 1446, 1400, 1380 cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$) δ 1.30 (2H, brs), 2.75 (2H, brd), 3.15 (4H, brd), 3.61 (6H, s), 4.65 (1H, m), 6.20 (2H, br), 7.85 (1H, brd).

***N*-(3-Carboxybicyclo[2.2.1]hept-5-en-2-ylcarbonyl) glutamic acid dimethyl ester (2i):** yield 71%; syrup; ^1H NMR (60 MHz, $CDCl_3$) δ 1.35 (2H, brs), 2.25 (4H, m), 3.30 (4H, m), 3.65 (6H, s), 4.50 (1H, m), 6.10 (2H, br), 7.85 (1H, br).

Norbornenyl Cyclic Imides (4a−h) of Amino Acid Methyl Esters Isolated during the DCC/N−OH Succinimide Coupling of Monocarboxylic Acid Derivatives 2a−i. *N*-(*endo*-Bicyclo[2.2.1]hept-5-en-2,3-diyldicarbonyl) Aib methyl ester (4a): yield 10%; mp 140−142 °C; IR (KBr) 3077, 2996 (br), 2878, 1778 (sh), 1745, 1713, 1551 (sh), 1458, 1439 (sh), 1365, 1287 cm^{-1}; ^1H NMR (90 MHz,$CDCl_3$) δ 1.35−1.65 (8H, s+m), 3.20 (2H, brs), 3.30 (2H,brs), 3.65 (3H, s), 6.09 (2H, brs); ^{13}C NMR (22.40 MHz, $CDCl_3$) δ 177.3, 172.8, 134.3, 60.1, 52.2, 51.7, 45.3, 45.0, 23.3; FAB MS *m*/*z* 264 $(MH)^+$.

***N*-(*endo*-Bicyclo[2.2.1]hept-5-en-2,3-diyldicarbonyl) serine methyl ester (4b):** yield 90%; mp 127−129 °C; IR (KBr) 3336, 2933, 2856, 1777 (sh), 1750, 1704, 1629, 1575, 1551, 1473 (sh), 1436, 1396 cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$) δ 1.60 (2H, dd), 3.33 (4H, brs), 3.68 (3H, s), 3.87 (2H, d, J = 5.0 Hz), 4.60 (1H, t), 6.03 (2H, s); FAB MS *m*/*z* 266 $(MH)^+$. Anal. Calcd. for $C_{13}H_{15}NO_5$ (mol wt 265): C, 58.86; H, 5.66; N, 5.28. Found: C, 58.42; H, 5.32; N, 4.88.

***N*-(*endo*-Bicyclo[2.2.1]hept-5-en-2,3-diyldicarbonyl) valine methyl ester (4c):** yield 10%; mp 58−59 °C; IR (KBr) 3068, 2989, 2955, 2881, 1775 (sh), 1756, 1705, 1628, 1579, 1547, 1458, 1434, 1388, 1353, 1286 cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$) δ 0.80 (3H, d, J = 6.0 Hz), 1.03 (3H, d, J = 6.0 Hz), 1.65 (2H, dd,), 2.55 (1H, m), 3.37 (4H, brd), 3.68 (3H, s), 4.24 (1H, d, J = 9 Hz), 6.15 (2H, s); FAB MS *m*/*z* 278 $(MH)^+$. Anal. Calcd. for $C_{15}H_{19}NO_4$ (mol wt 277): C, 64.98; H, 6.85. Found: C, 65.28; H, 6.84.

***N*-(*endo*-Bicyclo[2.2.1]hept-5-en-2,3-diyldicarbonyl) leucine methyl ester (4d):** yield 9%; mp 75−77 °C; IR (KBr) 3070, 2969, 2876, 1779 (sh), 1746, 1708, 1550, 1509, 1439, 1386 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 0.90 (6H, d, J = 5.0 Hz), 1.45−2.05 (5H, m), 3.36 (4H, brd), 3.70 (3H, s), 4.60 (1H, m), 6.13 (2H, s); FAB MS *m*/*z* 292 $(MH)^+$. Anal. Calcd. for $C_{16}H_{21}NO_4$ (mol wt 291: C, 65.97; H, 7.21, N, 4.81; Found: C,65.88; H, 7.26; N, 5.07.

***N*-(*endo*-Bicyclo[2.2.1]hept-5-en-2,3-diyldicarbonyl) tryptophan methyl ester (4e):** yield 88%; mp 144−146 °C; $[\alpha]_D^{26}$ −87.21 (*c* 3.13, $CHCl_3$); IR (KBr) 3422, 3376, 3133, 3066, 2991, 2939, 2870, 1767 (sh), 1748, 1693, 1575, 1557, 1488, 1455, 1392 cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$) δ 1.43 (2H, dd), 3.00 (2H, m), 3.37 (2H, brs), 3.52 (2H, brs), 3.66 (3H, s), 4.91 (1H, t), 5.40 (2H, s), 6.65−7.50 (5H, m), 8.15 (1H, s exchangeable); FAB MS *m*/*z* 365 $(MH)^+$.

***N*-(*endo*-Bicyclo[2.2.1]hept-5-en-2,3-diyldicarbonyl) methionine methyl ester (4f):** yield 12%; syrup; $[\alpha]_D^{26}$ −35.61 (c 4.45, $CHCl_3$); IR (KBr) 3070, 2993, 2957, 2925, 2877, 1779 (sh), 1750, 1710, 1638, 1440, 1387 cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$) δ 1.60 (2H, dd), 1.95 (3H, s), 2.07−2.60 (4H, m), 3.22 (4H, brs), 3.60 (3H, s), 4.60 (1H, t), 5.99 (2H, s); FAB MS *m*/*z* 310 $(MH)^+$.

***N*-(*endo*-Bicyclo[2.2.1]hept-5-en-2,3-diyldicarbonyl) aspartic acid methyl ester (4 g):** yield 12%; syrup; IR (KBr) 2985 (br), 1770 (sh), 1745, 1710, 1440, 1391 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 1.70 (2H, br), 2.80 (2H, brd), 3.40 (4H, brs), 3.70 (6H, s), 5.10 (1H, m), 6.11 (2H, brs); FAB MS *m*/*z* 308 $(MH)^+$.

***N*-(*endo*-Bicyclo[2.2.1]hept-5-en-2,3-diyldicarbonyl) glutamic acid dimethyl ester (4h):** yield 9.5%; syrup; IR (KBr) 3003, 2961, 2883, 1771 (sh), 1745, 1710, 1543, 1442, 1387 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 1.60 (2H, br), 2.27 (4H, m), 3.32 (4H, brd), 3.61, 3.63 (3H, s; 3H, s), 4.52 (1H, m), 6.10 (2H, s); FAB MS *m*/*z* 322 $(MH)^+$.

Preparation of *endo*-*cis*-(2*S*,3*R*)-diyl-norborneno Bispeptides (3a−h). General Procedure. Solid *N*-hydroxy succinimide (1 mmol) and dicyclohexylcarbodiimide (DCC, 1 mmol) were added sequentially at 0 °C to a stirred solution of *N*-(3-carboxy bicyclo[2.2.1]hept-5-en-2-ylcarbonyl) amino acid methyl ester (**2a**−**i**, 1 mmol) in dry CH_2Cl_2 (∼20 mL) or in a mixture of dry DMF and CH_2Cl_2 in cases where solubility was poor in CH_2Cl_2. After a period of ∼0.25 h, the reaction mixture was admixed with the amino acid methyl ester, prepared in situ at 0 °C from the corresponding methyl ester hydrochloride and triethylamine (1.2 mmol each) in dry CH_2Cl_2 or in a mixture of dry DMF and CH_2Cl_2. The combined mixture was stirred at room temperature for 2 days, the precipitated dicyclohexyl urea filtered, and the residue washed with CH_2Cl_2 (2 × 10 mL), and the combined filtrates were washed sequentially with cold 2 N H_2SO_4 (∼20 mL), water (∼20 mL), and saturated bicarbonate solution (∼20 mL). The organic extract was dried ($MgSO_4$) and evaporated in vacuo. The residue in most cases was directly crystallized from EtOAc/hexane or purified on a short column of silica gel using EtOAc/hexane as eluents.

***N*,*N*′-(*endo*-Bicyclo[2.2.1]hept-5-en-2,3-diyldicarbonyl) bis-alanine methyl ester (3a):** yield 88%; mp 125−127 °C; $[\alpha]_D^{26}$ −27.56 (*c* 1.70, $CHCl_3$); IR (KBr) 3350, 2950, 1743 (br), 1637, 1574, 1551, 1453, 1389 cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$) δ 1.34 (3H, d, J = 6.5 Hz), 1.38 (3H, d, J = 6.5 Hz), 1.53 (2H, dd), 3.35 (4H, m), 3.67 (6H, brs), 4.48 (2H, m), 6.05 (2H, m), 6.34 (1H, m), 6.83 (1H, m); FAB MS *m*/*z* 353 $(MH)^+$. Anal. Calcd. for $C_{17}H_{24}N_2O_6$ (mol wt 352): C, 57.95; H, 6.82; N, 7.95. Found: C, 57.80; H, 7.12; N, 7.58.

***N*,*N*′-(*endo*-Bicyclo[2.2.1]hept-5-en-2,3-diyldicarbonyl) bis-Aib methyl ester (3b):** yield 88%; mp 154−155 °C; IR (KBr) 3320, 3290 (sh), 3067, 2997, 2962 (sh), 2875 (sh), 1741, 1689, 1650, 1633 (sh), 1554, 1531, 1465, 1441 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.33 (1H, d, J = 8.4 Hz), 1.43 (1H, d, J = 8.4 Hz), 1.47 (12H, s), 3.12 (4H, s), 3.71 (6H, s), 6.36 (2H, s), 7.18 (2H, s); FAB MS *m*/*z* 381 $(M + H)^+$ (100%), 761 $(2 \times M + H)^+$ (6%). Anal. Calcd. for $C_{19}H_{28}N_2O_6$ (mol wt 380): C, 60.00; H, 7.36; N, 7.36. Found: C, 60.14; H, 7.48; N, 7.67.

Hydrolysis (2 N aqueous NaOH) of bis methyl ester afforded a mixture of half-ester half-acid [mp 208−210 °C; IR (KBr) 3338, 3286, 3087, 2999, 2880, 1745 (br), 1642, 1556, 1532, 1475, 1458, 1393 cm^{-1}; FAB MS *m*/*z* 367, $(MH)^+$, 389 $(M + Na^+)$] and diacid [mp 238−240 °C; IR (KBr) 3357, 3077, 2997, 1725, 1646, 1556, 1467, 1405, 1367 cm^{-1}; FAB MS *m*/*z* 353 $(MH)^+$].

***N*,*N*′-(*endo*-Bicyclo[2.2.1]hept-5-en-2,3-diyldicarbonyl) bis-valine methyl ester (3c):** yield 88%; mp 158−160 °C; $[\alpha]_D^{26}$ −5.39 (*c* 4.92, $CHCl_3$); IR (KBr) 3405, 3375, 3333, 3067, 2978, 2882, 1749, 1663, 1539, 1505, 1463, 1441 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.88-(12H, m), 1.33 (1H, d, J = 8.4 Hz), 1.47 (1H, d, J = 8.4 Hz), 2.06 (2H, m), 3.16 (2H, brs), 3.27 (2H, m), 3.68 (6H, s), 4.34 (2H, m), 6.27 (1H, d, J = 8.1 Hz), 6.38 (1H, m), 6.43 (1H, m), 6.47 (1H, d, J = 7.7 Hz); ^{13}C NMR (22.40 MHz, $CDCl_3$) δ 172.53, 172.41, 172.05, 135.41, 57.448, 51.70, 51.46, 51.34, 49.40, 47.82, 47.55, 30.87, 30.63, 18.73, 18.10, 17.89; FAB MS *m*/*z* 409 $(MH)^+$. Anal. Calcd. for $C_{21}H_{32}N_2O_6$ (mol wt 408): C, 61.76, H, 7.84, N, 6.86. Found: C, 61.97; H, 7.63; N, 6.88.

***N*,*N*′-(*endo*-Bicyclo[2.2.1]heptane-2,3-diyl dicarbonyl) bis-valine methyl ester, 5,6-dihydro derivative of 3c:** prepared by hydrogenation of **3c** in EtOAc with Pd/C, 5%, H_2; yield 98%; mp172−173 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 0.93 (12H, m), 1.47 (4H, m), 1.90 (2H, d, J = 7.3 Hz), 2.15 (2H, m), 2.54 (2H, brs), 2.88 (2H, s), 3.72 (6H, s), 4.55 (2H, m), 6.49 (1H, d, J = 8.33 Hz), 6.72 (1H, d, J = 8.34 Hz); FAB MS *m*/*z* 411 $(MH)^+$.

***N*,*N*′-(bicyclo[2.2.1]hept-5-ene-*trans*-2,3-diyldicarbonyl) bis-valine methyl ester (6a):** prepared by neat heating of endo isomer (**3c**) at ∼220 °C for 30 min, followed by purification on a small column of silica gel using a mixture of ethyl acetate/hexane (60:40) as eluents; yield 35%; mp 175−177 °C; IR (KBr) 3316, 3071, 2976, 2883, 1748, 1648, 1544 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 0.90 (12H, m), 1.61 (2H, m), 1.90−2.60 (4H, m), 3.03 (2H, m), 3.67 (6H, s), 4.46 (2H, m), 6.20 (2H, m), 6.68 (1H, brd), 7.03 (1H, brd).

Further elution with the same solvent afforded core fumaroyl bis-Val peptide (**5a**) arising from the retro-Diels−Alder of **3c**: yield 15%; mp 225−227 °C; $[\alpha]_D^{26}$ −50.89 (c 1.29, MeOH); IR (KBr) 3309, 3078, 2973, 2938, 2858, 1748, 1643, 1552, 1442 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 0.95 (12H, dd, J = 9.0 Hz, 2.0 Hz), 2.20 (2H, m), 3.75 (6H, s), 4.70 (2H, q), 7.13 (2H, s), 7.35 (2H, d, J = 11.25 Hz); FAB MS m/z 343 $(MH)^+$.

Authentic MeO−Val−CO−CH═CH−CO−Val-OMe (E). To a well-stirred and ice-cooled mixture of MeO−Val−CO−CH═CH−COOH (1 mmol, prepared from maleic anhydride and Val-OMe), DCC, and N−OH succinimide (1 mmol each) in dry CH_2Cl_2 was added a solution of freshly generated Val-OMe (from 1 mmol each of Val-OMe hydrochloride and triethylamine in CH_2Cl_2) and stirred for 24 h. The reaction mixture was worked up by washing, sequentially with ice-cold 2 N H_2SO_4, water, and saturated bicarbonate solution (20 mL each), drying (anhydrous $MgSO_4$), and evaporating *in vacuo*. Purification on a small column of silica gel and elution with a mixture of ethyl acetete and hexane (80:20) afforded the trans isomer in 70% yield; found identical in all respects with the olefinic product (**5a**) obtained by the thermolysis of **3c**. A small amount (∼ 20%) of cis isomer MeO−Val-CO−CH═CH− CO−Val−OMe (Z) was also obtained in the above reaction: syrup; IR (KBr) 3274, 3033, 2974, 1748, 1677, 1645, 1618, 1541 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 1.00 (12H, d, J = 7.5 Hz), 2.20 (2H, m), 3.74 (6H, s), 4.55 (2H, m), 6.32 (2H, s), 9.43 (2H, d, J = 8.0 Hz); FAB MS m/z 343 $(MH)^+$.

***N,N′*-(*endo*-Bicyclo[2.2.1]hept-5-en-2,3-diyldicarbonyl) bis-leucine methyl ester (3d):** yield 89%; mp 138−140 °C; $[\alpha]_D^{26}$ −4.50 (*c* 4.30, $CHCl_3$); IR (KBr) 3405, 3351, 2961, 2876, 1749, 1665, 1574, 1532, 1513, 1468, 1440 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.90 (12H, d, J = 4.5 Hz), 1.34 (1H, d, J = 8.7 Hz), 1.49 (1H, d, J = 8.7 Hz), 1.62 (6H, m), 3.22 (4H, m), 3.73 (6H, s), 4.45 (2H, m), 6.27 (1H, d, J = 7.6 Hz), 6.40 (2H, m), 6.55 (1H, d, J = 7.4 Hz); ^3C NMR (22.40 MHz, $CDCl_3$) δ 173.09, 172.50, 172.23, 135.47, 135.17, 51.87, 51.81, 51.58, 51.13, 50.98, 49.28, 47.88, 47.64, 41.16, 41.01, 24.67, 22.46, 22.10, 21.98; FAB MS m/z 437 $(MH)^+$.

***N,N′*-(Bicyclo[2.2.1]hept-5-ene-*trans*-2,3-diyldicarbonyl) bis-leucine methyl ester (6b):** prepared by neat heating of **3d** at ∼220 °C using identical conditions as with **3c**. Chromatography yielded a mixture of two products identified as trans isomer **6b**; [yield 33%; mp 184−186 °C; IR (KBr) 3302, 3076, 2965, 1751, 1649, 1557, 1474, 1443 cm^{-1}; ^1H NMR ($CDCl_3$, 90 MHz) δ 0.96 (12H, m), 1.67 (8H, m), 3.11 (4H, m), 3.74 (6H, s), 4.62 (2H, m), 6.10−6.60 (3H, m), 7.30 (1H, br); FAB MS m/z 437 $(MH)^+$] and core fumaryl retro bis peptide MeO−Leu−CO−CH═CH−CO−Leu−OMe (**5b**); [yield; 10%; mp 196−198 °C; IR (KBr) 3321, 2957, 1738, 1633, 1536, 1437 cm^{-1}; ^1H NMR (80 MHz, $CDCl_3$) δ 0.93 (12H, d, J = 5.0 Hz), 1.71 (6H, br), 3.81 (6H, s), 4.75 (2H, m), 7.03 (2H, s), 7.28 (2H, d, J = 7.5 Hz); FAB MS (m/z) 371 $(MH)^+$].

The authentic sample prepared from maleic anhydride and Leu-OMe by procedure described as under Val case was found to be identical with the thermolysis product.

***N,N′*-(*endo*-Bicyclo[2.2.1]hept-5-en-2,3-diyldicarbonyl) bis-phenylalanine methyl ester (3e):** yield 91%; mp 154−156 °C; $[\alpha]_D^{26}$ +56.40 (*c* 3.95, $CHCl_3$); IR (KBr) 3437, 3326, 3030, 3001, 2955, 1756, 1664, 1536, 1501, 1440, 1366 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.28 (1H, d, J = 8.5 Hz); 1.42 (1H, d, J = 8.5 Hz); 3.05 (6H, m), 3.18 (2H, s), 3.66 (3H, s), 3.69 (3H, s), 4.66 (1H, m), 4.73 (1H, m), 5.93 (1H, m), 6.17 (1H, m), 6.24 (1H, d, J = 7.3 Hz), 6.28 (1H, d, J = 7.2 Hz), 7.13 (4H, m), 7.30 (6H, m); ^{13}C NMR (22.40 MHz, $CDCl_3$) δ 172.11, 171.99, 171.90, 171.81, 136.16, 135.98, 135.44, 135.17, 129.27, 129.12, 128.40, 128.31, 126.91, 53.63, 53.46, 51.87, 51.22, 49.37, 47.16, 37.67, 37.49; FAB MS m/z 505 $(MH)^+$. Anal. Calcd. for $C_{29}H_{32}N_2O_6$ (mol wt 504): C, 69.04; H, 6.34; N, 5.55; Found: C, 69.22; H, 6.43; N, 5.27.

***N,N′*-(*endo*-Bicyclo[2.2.1]hept-5-en-2,3-diyldicarbonyl) bis-methionine methyl ester (3f):** yield 70%; mp 90−92 °C; −5.30 (c 4.53, $CHCl_3$); IR (KBr) 3412, 3363, 2978, 2923, 1743, 1659, 1574, 1552, 1531, 1439 cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$) δ 1.32 (2H, m), 1.69−2.19 (10H, s+m), 2.39 (4H, m), 3.09 (2H, brs), 3.24 (2H, brs); 3.58 (6H, brs), 4.64 (2H, m), 6.26 (2H, brs), 6.84 (2H, m, exchangeable); FAB MS m/z 473 $(MH)^+$. Anal. Calcd. for $C_{21}H_{32}N_2O_6S_2$: C, 53.38; H, 6.77; N, 5.93. Found: C, 53.80; H, 7.18; N, 6.13.

***N,N′*-(*endo*-Bicyclo[2.2.1]hept-5-en-2,3-diyldicarbonyl) bis-aspartic acid methyl ester (3 g):** yield 58%; syrup; IR (KBr) 3391, 2960, 1743 (br), 1689, 1521, 1441, 1373 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 1.40 (2H, brs), 2.81 (4H, m), 3.29 (4H, m), 3.62, 3.64 (6H, s; 6H, s), 4.60 (2H, m), 6.20 (2H, brs), 7.10 (2H, brd).

***N,N′*-(*endo*-Bicyclo[2.2.1]hept-5-en-2,3-diyldicarbonyl) bis-glutamic acid methyl ester (3h):** yield 75%; syrup; IR (KBr) 3382, 2965, 1743, 1677, 1542, 1444, 1379 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 1.40 (2H, brd), 2.05−2.81 (8H, m), 3.28 (4H, m), 3.70, 3.73 (6H, s; 6H, s), 4.55 (2H, m), 6.40 (2H, brs), 6.80 (2H, brd); FAB MS m/z 497 $(MH)^+$.

***N,N′*-(1*S*,3*R*)-dicarboxy-(4*S*,5*R*)-dicarbonyl)cyclopentane bis-leucine methyl ester (7):** Oxidative cleavage of **3d**. A solution of **3d** (4 mmol) in MeCN (16 mL) was admixed with CCl_4/H_2O (1:2, 48 mL), $NaIO_4$ (15.4 g, 72 mmol), and $RuCl_3 \cdot 3H_2O$ (0.030 g, 2.2 mol %), sealed, and left shaken for 6 h at room temperature, cautiously opened and filtered, and the residue washed with CCl_4 (3 × 10 mL). The filtrates were combined and evaporated without heating in vacuo, and the residue was digested with saturated aqueous $NaHCO_3$ (∼40 mL) for 3 h. The bicarbonate extract was adjusted to pH ≈3 with 2 N H_2SO_4, saturated with NaCl, extracted with EtOAc (3 × 25 mL), dried, and evaporated to yield the dicarboxylic acid **7**: yield 50%; mp 168−170 °C; $[\alpha]_D^{26}$ −44.76 (*c* 3.60, $CHCl_3$); IR (KBr) 3386, 3324, 2968, 2499, 1756, 1724, 1690, 1605, 1563, 1445 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$ + DMSO-d_6) δ 0.90 (12H, m), 1.57 (6H, m), 2.48 (2H, m), 3.44 (4H, m), 3.68 (6H, s), 4.42 (2H, m), 7.63 (1H, d, J = 7.9 Hz), 7.92 (1H, d, J = 7.9 Hz); FAB MS m/z 523 $(M + Na^+)$, 501 $(MH)^+$. Anal. Calcd. for $C_{23}H_{36}N_2O_{10}$ (mol wt 500): C, 55.20; H, 7.20; N, 5.60. Found: 54.98; H, 7.37; N, 5.08.

Preparation of Higher Norborneno Bispeptides 8−10 Listed in Chart 1. General Procedure. (a) Preparation of precursor biscarboxylic acids from bismethyl esters 3c and 3d: An ice-cooled solution of bisester **3c**/**3d** (1 mmol, in 2 mL of MeOH) was admixed with 2 N aqueous NaOH (4 mmol) and stirred at room temperature for 4 h (TLC). The reaction mixture was concentrated to half the volume in vacuo (without heating), acidified to pH ≈3 with ice-cold 2 N H_2SO_4, saturated with solid NaCl, extracted with ethyl acetate (3 × 20 mL), dried (anhydrous $MgSO_4$), and evaporated in vacuo to give near quantitative yield of the biscarboxylic acid which was pure enough for direct use in the next reaction.

(b) Bidirectional coupling of biscarboxylic acids of 3c/3d with amino acids/dipeptides or tripeptides: To a well-stirred and ice-cooled solution of biscarboxylic acid (1 mmol) in dry dichloromethane (∼10 mL) or a mixture of dry DMF (∼0.5 mL) and dichloromethane (∼10 mL) was added, sequentially, N−OH succinimide and DCC (2 mmol each). After 15 min of stirring, the reaction mixture was treated with freshly prepared free base of an amino acid ester (generated at 0 °C from 2.5 mmol each of the corresponding ester hydrochloride and triethylamine in dry CH_2Cl_2) or an N^{α}-deprotected dipeptide or tripeptide ester and left stirred at room temperature for 24 h. The precipitated DC-urea was filtered, the residue was washed with CH_2Cl_2 (3 × 20 mL), and the combined filtrates were washed sequentially with ice-cold 2 N H_2SO_4, H_2O and saturated aqueous bicarbonate (20 mL each), dried (anhydrous $MgSO_4$) and solvent removed in vacuo. The residue was purified by column chromatography on silica gel and eluted with either a mixture of ethyl acetate/hexane or chloroform/methanol (gradient) to afford the higher bispeptides **8−10**.

Compound 8a: prepared from dicarboxylic acid of **3c** and Val-OMe; yield 67%; hygroscopic solid; $[\alpha]_D^{26}$ −49.52 (*c* 4.08, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 0.87 (24 H, m), 1.40 (1H, d, J = 8.4 Hz), 1.57 (1H, d, J = 8.4 Hz), 2.11 (1H, m), 2.16 (1H, m), 2.25 (1H, m), 2.34 (1H, m), 3.12 (2H, brs), 3.29 (2H, m), 3.69 (3H, s), 3.71 (3H, s), 4.34 (1H, m), 4.44 (3H, m), 6.12 (1H, d, J = 9.4 Hz), 6.32 (1H, m), 6.47 (1H, m), 6.50 (1H, d, J = 8.8 Hz), 7.40 (1H, d, J = 8.3 Hz), 7.57 (1H, d, J = 8.3 Hz); FAB MS m/z 607 $(MH)^+$. Anal. Calcd. for $C_{31}H_{50}O_8N_4$ (mol wt 606): C, 61.38; H, 8.25; N, 9.24. Found: C, 61.74; H, 7.88; N, 9.06.

Compound 8b: prepared from dicarboxylic acid of **3c** and Phe-OMe; yield 62% sticky solid; $[\alpha]_D^{26}$ +6.02 (*c* 5.5, $CHCl_3$); ^1H NMR

(400 MHz, $CDCl_3$) δ 0.87 (12 H, m), 1.47 (1H, d, J = 8.7 Hz), 1.63 (1H, d, J = 8.7 Hz), 2.10 (1H, m), 2.35 (1H, m), 3.05−3.22 (6H, m), 3.33 (2H, m), 3.49 (3H, s), 3.60 (3H, s), 4.47 (1H, m), 4.56 (1H, m), 4.86 (2H, m), 5.84 (1H, d, J = 9.3 Hz), 6.33 (1H, m), 6.42 (1H, d, J = 8.7 Hz), 6.53 (1H, m), 7.30 (10H, m), 7.62 (1H, d, J = 8.3 Hz), 7.86 (1H, d, J = 8.6 Hz); FAB MS m/z 703 $(MH)^+$.

Compound 8c: prepared from dicarboxylic acid of **3d** and Ser-OMe; yield 77% syrup; $[\alpha]_D^{26}$ −65.05 (c 4.35, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.94 (12 H, m), 1.43−1.84 (8H, m), 3.09 (2H, m), 3.30 (2H, m), 3.79 (6H, s), 3.97 (4H, m), 4.42 (2H, m), 4.68 (2H, m), 6.07 (1H, d, J = 8.3 Hz), 6.27 (2H, m), 6.82 (1H, d, J = 7.5 Hz), 7.67 (1H, d, J = 7.5 Hz), 7.74 (1H, d, J = 8.3 Hz). Anal. Calcd. for $C_{24}H_{46}N_4O_{10}$ (mol wt 550): C, 57.04; H, 7.54; N, 9.18. Found: C, 57.02; H, 7.29; N, 9.00.

Compound 9a: prepared from dicarboxylic acid of **3c** and Val-Val-OMe; yield 52%; mp 254−256 °C; $[\alpha]_D^{26}$ −80.03 (c 1.80, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (36 H, m), 1.38 (1H, d, J = 8.4 Hz), 1.54 (1H, d, J = 8.4 Hz), 2.13 (4H, m), 2.33 (2H, m), 3.14 (2H, brs), 3.24 (2H, brs), 3.69 (6H, s), 3.98 (1H, m), 4.11 (1H, m), 4.40 (1H, m), 4.44 (1H, m), 4.49 (1H, m), 4.50 (1H, m), 6.24 (1H, d, J = 9.2 Hz), 6.30 (1H, m), 6.39 (1H, m), 6.65 (1H, d, J = 7.0 Hz), 6.87 (2H, d, J = 8.7 Hz); 7.69 (1H, d, J = 7.9 Hz), 7.94 (1H, d, J = 7.9 Hz); FAB MS m/z 805 $(MH)^+$. Anal. Calcd. for $C_{41}H_{68}O_{10}N_6$ (mol wt 804): C, 61.19; H, 8.45; N, 10.45. Found: C, 60.97 H, 8.28; N, 10.95.

Compound 9b: prepared from dicarboxylic acid of **3d** and Val-Val-OMe; yield 55%; mp 155−157 °C; $[\alpha]_D^{26}$ −73.66 (c 3.80, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.89 (36 H, m), 1.36 (1H, d, J = 8.3 Hz), 1.44−1.80 (7H, m), 2.13 (3H, m), 2.29 (1H, m), 3.14 (2H, brs), 3.25 (2H, m), 3.72 (6H, s), 4.09 (2H, m), 4.36 (1H, m), 4.51 (2H, m), 4.60 (1H, m), 6.29 (2H, m), 6.33 (1H, d, J = 8.2 Hz), 6.51 (1H, d, J = 8.2 Hz), 7.01 (1H, d, J = 8.9 Hz), 7.10 (1H, d, J = 8.4 Hz), 7.63 (1H, d, J = 8.4 Hz), 7.75 (1H, d, J = 8.0 Hz); FAB MS m/z 833 $(MH)^+$.

Compound 9c: prepared from dicarboxylic acid of **3d** and Leu-Leu-OMe; yield 45%; mp 143−144 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (36 H, m), 1.38 (1H, m), 1.43−1.87 (19H, m), 3.12 (2H, brs), 3.21 (1H, dd, J = 3.1, 10.6 Hz), 3.27 (1H, dd, J = 2.9, 10.6 Hz), 3.70 (6H, s), 4.36 (3H, m), 4.49 (3H, m), 6.04 (1H, d, J = 8.1 Hz), 6.23 (1H, d, J = 8.3 Hz), 6.27 (1H, m), 6.35 (1H, m), 6.68 (1H, d, J = 7.9 Hz), 6.78 (1H, d, J = 7.9 Hz), 7.65 (1H, d, J = 7.9 Hz); 7.78 (1H, d, J = 7.4 Hz); FAB MS m/z 889 $(MH)^+$.

Compound 9d: prepared from dicarboxylic acid of **3d** and Leu-Ser-OMe; yield 59%; syrup; $[\alpha]_D^{26}$ −59.53 (c 0.55, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.93 (24 H, m), 1.35−2.1 (14H, m), 3.12 (2H, brs), 3.26 (2H, brs), 3.75 (6H, s), 3.80 (4H, m), 4.37 (4H, m), 4.60 (2H, m), 6.05 (2H, brd), 6.27 (2H, brs), 6.50 (1H, brd), 7.26 (1H, brd), 7.41 (1H, brd), 8.02 (2H, m); FAB MS m/z 837 $(MH)^+$.

Compound 9e: prepared from dicarboxylic acid of **3d** and Ser-Leu-OMe; yield 52%; mp 97−99 °C; $[\alpha]_D^{26}$ −48.24 (c 0.65, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.89 (24 H, m), 1.39 (1H, d, J = 8.6 Hz), 1.47−1.80 (13H, m), 3.15 (2H, brs), 3.29 (2H, m), 3.72 (6H, s), 3.85 (4H, m), 4.27 (1H, m), 4.36 (1H, m), 4.44 (1H, m), 4.55 (2H, m), 4.64 (1H, m), 6.28 (2H, m), 6.54 (1H, d, J = 7.5 Hz), 6.77 (1H, d, J = 7.8 Hz), 7.32 (1H, d, J = 8.0 Hz), 7.36 (1H, d, J = 8.0 Hz), 7.80 (1H, d, J = 8.2 Hz), 7.85 (1H, d, J = 7.7 Hz); FAB MS m/z 837 $(MH)^+$.

Compound 10: prepared from dicarboxylic acid of **3d** and Ser-Val-Val-OMe which in turn was obtained by $^{\alpha}$N−Z deprotection (Pd/C, 5%, H_2) of Z-Ser-Val-Val-OMe [prepared by coupling Z-Ser with Val-Val-OMe in 69% yield; mp 168−169 °C, $[\alpha]_D^{26}$ −17.59 (c 2.9, $CHCl_3$)]. Selected data for **10**: yield 35%; hygroscopic solid; ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.68−0.98 (36 H, m), 1.24 (2H, m), 1.44 (4H, m), 1.68 (2H, m), 2.02 (4H, m), 2.93 (1H, brs), 3.12 (1H, m), 3.16 (1H, m), 3.38 (1H, m), 3.48 (1H, m), 3.56 (1H, m), 3.60 (6H, s), 3.69 (2H, m), 3.90 (1H, m), 4.14 (5H, m), 4.34 (2H, m), 4.68 (1H, m), 4.90 (1H, m), 5.92 (1H, m), 6.19 (1H, m), 7.25 (1H, d, J = 9.3 Hz), 7.67 (1H, d, J = 7.5 Hz), 7.75 (1H, d, J = 8.8 Hz), 7.80 (1H, d, J = 7.9 Hz), 7.91 (1H, d, J = 4.8 Hz), 8.12 (1H, d, J = 7.7 Hz), 8.17 (1H, d, J = 7.2 Hz), 8.26 (1H, d, J = 7.4 Hz); FAB MS m/z 1007 $(MH)^+$.

X-ray Structure Analyses of Norborneno Bispeptides. (1) *cis*-bis-Aib methyl ester **3b**: $C_{19}H_{28}N_2O_6$, space group $P\bar{1}$, a = 8.891(1) Å, b = 10.526(0) Å, c = 11.751(0) Å, α = 71.25(0)°, β = 79.09(0)°, γ = 79.03(0)°, V = 1012.6 Å^3, Z = 2, d_{calcd} = 1.248 g/cm^3, R = 5.18%. (2) *cis*-bis-Val methyl ester **3c**: $C_{21}H_{32}N_2O_6$, space group $P2_12_12_1$, a = 10.076(1) Å, b = 11.147(1) Å, c = 20.118(1) Å, V = 2259.6 Å^3, Z = 4, d_{calcd} = 1.201 g/cm^3, R = 8.75%. (3) *cis*-bis-Leu methyl ester **3d**: $C_{23}H_{36}N_2O_6$, space group $P2_1$, a = 10.66(2) Å, b = 9.951(8) Å, c = 12.39(2) Å, β = 106.31(12)°, V = 1261.3 Å^3, Z = 2, d_{calcd} = 1.150 g/cm^3, R = 11.1%. (4) *trans*-bis-Val methyl ester **6a**: $C_{21}H_{32}N_2O_6$, space group $P2_12_12_1$, a = 9.626(1) Å, b = 16.659(4) Å, c = 29.847(7) Å, V = 4786.1 Å^3, Z = 8 (contains a pair of diastereomers), d_{calcd} = 1.132 g/cm^3, R = 14.0%. (5) Diacid of **3b**: $C_{17}H_{25}N_2O_6$, space group Cc, a = 16.257(2) Å, b = 9.192(1) Å, c = 11.875(1) Å, β = 97.72(1)°, V = 1758.4 Å^3, Z = 4, d_{calcd} = 1.327 g/cm^3, R = 5.43%. (6) Half-acid half-ester of **3b**: $C_{36}H_{52}N_4O_{12}$, space group Cc, a = 12.047(1) Å, b = 16.556(2) Å, c = 11.427(2) Å, β = 120.09(1)°, V = 1971.8(5) Å^3, Z = 2, d_{calcd} = 1.234 g/cm^3, R = 4.47%.

X-ray data were collected with Cu Kα radiation (λ = 1.54178 Å) on a Siemens automated diffractometer in the $\theta/2\theta$ mode, constant scan speed of 10 deg/min, 2° scan width, and $2\theta_{max}$ = 115° (0.9 Å resolution). Crystal structures were determined by direct phase determination. Full-matix, anisotropic least-squares refinement was performed on the parameters for all atoms except the H atoms. Hydrogen atoms involved in hydrogen bonding were located in electron density maps. The remainder of the H atoms were placed in idealized positions and allowed to ride with the C atoms to which each was bonded.

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Supporting Information Available: ^{1}H NMR spectra of **3b**−**e**, **8a**, **8b**, **9a**, **9b**, **9c**, **9e**, and **10**, ^{1}H NMR VT spectra of **3b**−**e**, **8a**, **8b**, **9a**−**c**, **9e**, and **10**, ROESY NMR spectra of **3b**−**e**, **8a**, **8b**, **9a**−**c**, **9e**, and **10**, FT-IR spectra (NH stretch region in $CHCl_3$) of **3b**, **9b**, and **9c**, comparison of FT-IR for **3c**, **8a**, and **9a**, FAB MS of **8a**, **9a**−**c**, and **10**, CD spectra of **8c**, **9c**, and **10**, X-ray diffraction structure determination summaries and tables of atomic coordinates, bond lengths, bond angles, anisotropic thermal coefficients and hydrogen atom coordinates for compounds **3b**−**d**, **6a**, **3b** (diacid), and **3b** (half-acid half-ester) (90 pages, print/PDF). See any current masthead page for ordering information and Web access instructions.

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