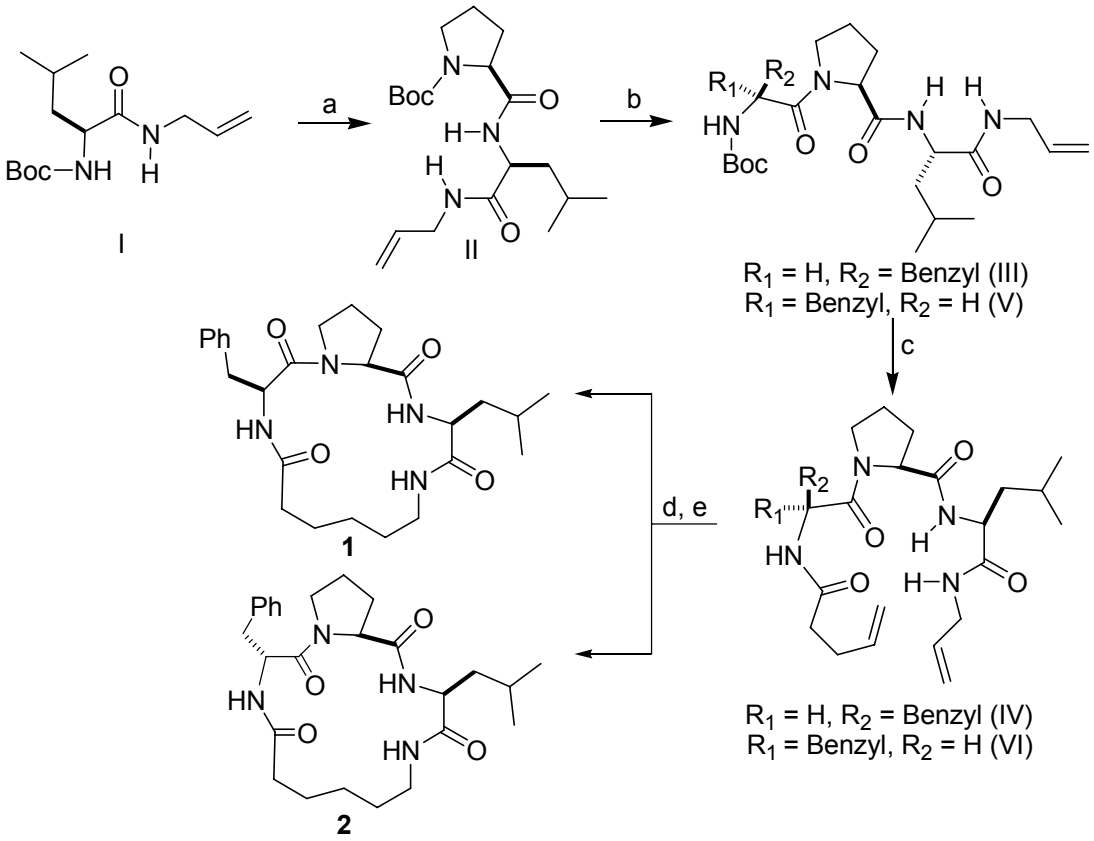
Electronic Supplementary Information (ESI)

Synthesis of tetrapeptides 1 and 2 as given in Scheme 1



Reagents and conditions: (a) i. TFA, CH_2Cl_2 0 ^oC ii. N-Boc-Pro, $ClCO_2{}^iBu$, NEt_3, CH_2Cl_2, 0 ^oC-r.t. (b) i. TFA, CH_2Cl_2 0 ^oC, ii. N-Boc Phe, EDC.HCl, HOBt, CH_2Cl_2, 0 ^oC-r.t. (c) i. TFA, CH_2Cl_2, 0 ^oC ii 4-pentenoic acid, $ClCO_2{}^iBu$, NEt_3, CH_2Cl_2, 0 ^oC-r.t. (d) 20 mol % Grubbs catalyst, Dry CH_2Cl_2, reflux, 12-24 h (e) 10 % Pd/C,MeOH, H_2

N-Boc-L-Leu allylamide (I)

To an ice cold stirred solution of N-Boc Leucine (6.1 g, 26.4 mmol) in dry CH_2Cl_2 was added NEt_3 (11ml, 79.22 mmol) followed by the addition of isobutyl chloroformate (5.20 ml, 39.6 mmol). After 5 min at 0 °C a solution of allylamine (2.20 ml, 29.40 mmol) in dry CH_2Cl_2 was added and stirred at room temperature for 12 h. The reaction mixture was diluted with CH_2Cl_2, washed with water, dried over Na_2SO_4 and evaporated to afford crude product which was purified using 100-200 mesh silica gel and MeOH-$CHCl_3$ as the eluent to afford (6.22 g, 87.3 %) of title product as a white solid. mp. 66-70 °C, [α] = -27.00 (C, 0.5, MeOH), IR (KBr): 3352, 2966, 1666, 1535, 1244, 1174 cm^{-1} , ^1H NMR (400 MHz, $CDCl_3$): δ 6.27 (bs, 1H), 5.87-5.77 (m, 1H), 5.21-5.10 (m, 2H), 4.88 (bs, 1H), 4.10-4.09 (m, 1H), 3.87 (t, J = 5.5 Hz, 2H), 1.70-1.67 (m, 2H), 1.50-1.45 (m, 1H), 1.44 (s, 9H), 0.94 (d, J = 4.0 Hz, 3H), 0.92 (d, J = 3.7 Hz, 3H), Mass (CI method): 271 (M^++1), 215 (100), 171 (76)

N-Boc-L-Pro-L-Leu allyl amide (II)

A. To an ice cold stirred solution of N-Boc-Leu allylamide (6.22 g, 23.03 mmol) in dry CH_2Cl_2 was added trifluoroacetic acid (10 equi) at 0 °C under argon atmosphere and stirred at the same temperature for 3h. Solvent was evaporated to afford the triflate salt as a pale yellow gum, which was neutralized with NEt_3 at 0 °C to obtain the free amine (3.92 g) in quantitative yield.
B. To an ice cold stirred solution of N-Boc-L-Proline (4.95 g, 23.05 mmol) in dry CH_2Cl_2 at 0 °C was added NEt_3 (9.7 ml, 69.06 mmol) followed by the addition of isobutyl chloroformate (4.50 ml, 34.53 mmol). After 5 min at 0 °C a solution of amine (obtained in part A) (3.92 g, 23.05 mmol) in dry CH_2Cl_2 was added and stirred at room temperature for a period of 12 h. The reaction mixture was diluted with CH_2Cl_2 and washed with water and brine. Solvent evaporation under reduced pressure followed by purification using 100-200 mesh silica and MeOH-$CHCl_3$ as eluent afforded the required dipeptide as a white solid (8 g, 95 %). mp. 92-96 °C, [α] = -89.00 (C, 0.1, MeOH), IR ($CHCl_3$): 3292, 2958, 1652, 1550 cm^{-1}, ^1H NMR (400 MHz, $CDCl_3$): δ 6.78 (bs, 2H), 5.85-5.76 (m, 1H), 5.19-5.09 (m, 2H), 4.46-4.40 (m, 1H), 4.26 (bs, 1H), 3.85-3.80 (m, 2H), 3.43 (bs, 2H), 2.19-2.08 (m, 2H), 1.90-1.74 (m, 2H), 1.63-1.62 (bs, 1H), 1.62-1.49 (m, 2H), 1.46 (s, 9H), 0.97-0.88 (m, 6H), Mass (CI method): 368 (M^+ +1, 56), 312 (100), 268 (44).

N-Boc- L-Phe- L-Pro-L-Leu allyl amide (III):

A. To an ice cold stirred solution of N-Boc-Pro-Leu allylamide (2.20 g, 5.99 mmol) in dry CH_2Cl_2 was added trifluoroacetic acid (10 equi) at 0 °C under argon atmosphere and stirred at the same temperature for 3h. Solvent was evaporated to afford the triflate salt as a pale yellow gum, which was neutralized with NEt_3 at 0 °C to obtain the free amine (1.60 g) in quantitative yield.

B. To an ice cold stirred solution of N-Boc-L-Phenylalanine (1.60 g, 5.99 mmol) and HOBt (970 mg, 7.19 mmol) dry CH_2Cl_2 was added a solution of L-Pro-Leu allylamide (1.60 g, 5.99 mmol) in dry CH_2Cl_2. EDC.HCl (1.72 g, 9.02 mmol) was added portion wise to the reaction mixture at 0 °C and then stirred at room temperature for 12 h. The reaction mixture was diluted with CH_2Cl_2, washed with water dried over Na_2SO_4 and evaporated to obtain crude product which was purified to afford (1.84 g, 59 %) the title compound. [α] = -52 (C, 0.1, MeOH), IR (Neat): 3300, 2959, 1642 cm^{-1} , ^1H NMR (400 MHz, $DMSOd_6$): δ 7.88 (t, *J* = 5.65 Hz, 1H), 7.83 (d, *J* = 8.3 Hz, 1H), 7.30-7.17 (m, 5H), 7.03 (d, *J* = 8.3 Hz, 1H), 5.82-5.73 (m, 1H), 5.14-5.01 (m, 2H), 4.39-4.34 (m, 2H), 4.30-4.24 (m, 1H), 3.69-3.67 (t, *J* = 5.4 Hz, 2H), 3.61-3.55 (m, 2H), 2.95-2.71 (m, 2H), 2.07-2.00 (m, 1H), 1.94-1.80 (m, 3H), 1.65-1.53 (m, 1H), 1.51-1.46 (m, 2H), 1.28 (s, 9H), 0.9 (d, *J* = 6.4 Hz, 3H), 0.84 (d, *J* = 6.5 Hz, 3H), Mass (CI method): 515 (M^+ +1, 10), 514 (M^+, 65), 415 (100).

N-Pentenoyl-L-Phe-L-Pro-L-Leu allylamide (1V)

A. To a stirred solution of N-Boc-Phe-Pro-Leu allylamide (0.8g, 1.55 mmol) in dry CH_2Cl_2 was added trifluoroacetic acid (10 equi) at 0 °C under argon atmosphere and stirred at same temperature for 3h. Solvent was evaporated to afford the triflate salt as a pale yellow gum, which was neutralized with NEt_3 at 0 °C to obtain the free amine (0.64 g) in quantitative yield.
B. To an ice cold stirred solution of 4-Pentenoic acid (0.16 ml, 1.54 mmol) in dry CH_2Cl_2 at 0 °C was added NEt_3 (0.65 ml, 4.66 mmol) followed by the addition of isobutyl chloroformate (0.3 ml, 2.33 mmol). After 5 min a solution of amine (obtained in part A) (0.64 g, 1.54 mmol) in dry CH_2Cl_2 was added at 0 °C and stirred at room temperature for 12 h. The reaction mixture was diluted with CH_2Cl_2, washed with water, dried over sodium sulfate and evaporated to obtain

crude product which was purified to afford (400 mg, 53 %) of title compound as a colorless gum. [α] = -78 (C, 0.1, MeOH), IR (Neat): 3291, 2957, 1636, 1547, 1445 cm^{-1}, ^1H NMR (500 MHz, $CDCl_3$): δ 7.31-7.19 (m, 5H, aromatic), 6.47 (t, *J* = 8.8 Hz, 1H), 6.45 (dd, *J* = 5.8 Hz, 1H), 6.15 (d, *J* = 7.8 Hz, 1H), 5.86 (ddt, *J* = 17.3, 10.3, 5.6 Hz, 1H), 5.76 (ddt, *J* = 17.3, 10.3, 1.7 Hz, 1H), 5.22 (dq, *J* = 17.3, 1.6 Hz, 1H), 5.15 (dq, *J* = 10.3, 1.6 Hz, 1H), 5.03 (dq, *J* = 17.3, 1.7 Hz, 1H), 5.01 (dt, *J* = 7.8, 6.4 Hz, 1H), 4.99 (dq, *J* = 10.3, 1.7 Hz, 1H), 4.44 (dd, *J* = 8.2, 4.2 Hz, 1H), 4.41 (dt, *J* = 5.6 Hz, 1H), 3.89-3.91 (m, 2H), 3.67 (dt, *J* = 10.0, 7.4 Hz, 1H), 3.09 (ddd, *J* = 10.0, 6.8, 5.4 Hz, 1H), 3.01 (dd, *J* = 13.5, 7.8 Hz, 1H), 2.99 (dd, *J* = 13.5, 6.4 Hz, 1H), 2.33-2.21 (m, 4H), 2.12-1.90 (m, 4H), 1.85 (m, 1H), 1.57 (m,1H), 1.49 (m, 1H), 0.95 (d, *J* = 6.5 Hz, 3H), 0.91 (d, *J* = 6.5 Hz, 3H), Mass (CI method): 497 (M^++1, 100), 440 (9), 327 (16), 268 (47).

Cyclo(L-Phe-L-Pro-L-Leu-Aha) (1)

To a stirred solution of Grubb's ruthenium catalyst (20 mol%) in dry CH_2Cl_2 (300 ml) under nitrogen was added a solution of Pentenoyl-Phe-Pro-Leu allylamide (240 mg, 0.48 mmol) in dry CH_2Cl_2 slowly over a period of 15 min and refluxed for 12 h. CH_2Cl_2 was evaporated and the residue was purified by column chromatography to afford the RCM product as a mixture of *E* and *Z* isomers (190 mg, 84 %) as an off white solid.

To a stirred solution of the unsaturated cyclic peptide (180 mg, 0.38 mmol) in 5 ml of MeOH was added 40 mg of 10 % Pd/C. The mixture was hydrogenated using a H_2 gas balloon at 20 psi for 3h. The catalyst was filtered off and the filtrate was evaporated to obtain the crude product which was purified to afford compound **1**(145 mg, 80 %). mp. 66-72 °C, [α] = -45 (C, 0.1, MeOH), IR (Neat): 3312, 2959, 1633, 754 cm^{-1}, ^1H NMR (500 MHz, $CDCl_3$): δ 7.33-7.22 (m, 5H), 6.51 (d, *J* = 8.5 Hz, 1H), 6.38 (d, *J* = 7.0 Hz, 1H), 6.23 (dd, *J* = 8.8, 4.0 Hz, 1H), 4.63 (m, 1H), 4.35 (m, 1H), 3.71 (m, 1H), 3.59 (ddd, *J* = 12.3, 8.4, 2.8 Hz, 1H), 3.45 (dd, *J* = 8.6, 1.9 Hz, 1H), 3.39 (ddd, *J* = 12.3, 9.9, 7.5 Hz, 1H), 3.21 (dd, *J* = 12.6, 4.9 Hz, 1H), 2.90 (m, 1H), 2.84 (dd, *J* = 12.6, 10.5 Hz, 1H), 2.32 (ddd, *J* = 14.1, 6.2, 3.8 Hz, 1H), 2.15 (ddd, *J* = 14.1, 10.6, 3.8 Hz, 1H), 1.84 (m, 1H), 1.70 (m, 1H), 1.68 (m,1H), 1.63 (m, 2H), 1.59 (m, 1H), 1.57-1.39 (m, 3H), 1.34 (m, 2H), 1.21 (m, 1H), 1.20 (m, 1H), 0.90 (d, *J* = 6.2 Hz, 3H), 0.88 (d, *J* = 6.2 Hz, 3H), Mass (CI method) 471 (M^++1, 100).

N-Boc-D-Phe-L-Pro-L-Leu allylamide (V):

A. To an ice cold stirred solution of N-Boc-Pro-Leu allylamide (4.95g, 13.5 mmol) in dry CH_2Cl_2 was added trifluoroacetic acid (10 equi) at 0 °C under argon atmosphere and stirred at the same temperature for 3h. Solvent was evaporated to afford the triflate salt as a pale yellow gum, which was neutralized with NEt_3 at 0 °C to obtain the free amine (3.60 g) in quantitative yields.

B. To an ice cold stirred solution of N-Boc-D-Phe (3.57 g, 13.48 mmol) and HOBt (2.18 g, 16.16 mmol) dry CH_2Cl_2 was added a solution of L-Pro-Leu allylamide (3.6 g, 13.48 mmol) in dry CH_2Cl_2. EDC.HCl (3.87 g, 20.20 mmol) was added portion wise to the reaction mixture at 0 °C and stirred at room temperature for 12 h. The reaction mixture was diluted with CH_2Cl_2, washed with water dried over Na_2SO_4 and evaporated to obtain crude product which was purified to afford (5.6 g, 81 %) of title product as a hygroscopic solid. [α] = -89.0 (C, 0.1, MeOH), IR (Neat): 3321, 2926, 1659, 1530, 1450, 11667 cm^{-1}, ^1H NMR (400 MHz, $CDCl_3$): δ 7.33-7.19 (m, 5H), 6.97 (bs, 1H), 6.85 (d, *J* = 8.9 Hz, 1H), 5.91-5.81 (m, 1H), 5.25-5.09 (m, 2H), 5.04 (d, *J* = 4.3 Hz, 1H), 4.50-4.44 (m, 1H), 4.40-4.38 (m, 1H), 4.36-4.33 (m, 1H), 3.94-3.90 (m, 1H), 3.89-3.87 (m, 1H), 3.78-3.63 (m, 1H), 3.01 (dd, *J* = 12.6 Hz and *J* = 9.4 Hz, 1H), 2.92 (dd, *J* = 12.8 Hz and *J* = 6.4 Hz, 1H), 2.61 (dd, *J* = 16.10 Hz and *J* = 8.85 Hz, 1H), 2.11-2.05 (m, 1H), 1.93-

1.85 (m, 1H), 1.78-1.71 (m, 2H), 1.62-1.55 (m, 3H), 1.38 (s, 9H), 0.91 (d, *J* = 6.5 Hz, 3H), 0.87 (d, *J* = 6.4 Hz, 3H), Mass (CI method) (m/z): 515 (M^++1, 100), 459 (M^+-t-Bu, 6)415 (M^+- Boc, 68).

Pentenoyl-D-Phe- L-Pro-L-Leu allylamide (VI):

A. To a stirred solution of N-Boc-D-Phe-Pro-Leu allylamide (4.0 g, 7.78 mmol) in dry CH_2Cl_2 was added trifluoroacetic acid (10 equi) at 0 °C under argon atmosphere and stirred at same temperature for 3h. Solvent was evaporated to afford the triflate salt as a pale yellow gum, which was neutralized with NEt_3 at 0 °C to obtain the free amine (3.22 g) in quantitative yield.

B. To an ice cold stirred solution of 4-Pentenoic acid (0.8 ml, 7.78 mmol) in dry CH_2Cl_2 at 0 °C was added NEt_3 (3.3 ml, 23.33 mmol) followed by the addition of isobutyl chloroformate (1.5 ml, 11.66 mmol). After 5 min a solution of amine (obtained in part A) (3.22 g, 7.78 mmol) in dry CH_2Cl_2 was added at 0 °C and stirred at room temperature for 12 h. The reaction mixture was diluted with CH_2Cl_2, washed with water, dried over Na_2SO_4 and evaporated to obtain crude product which was purified to afford (400 mg, 53 %) of title compound as a white solid (2.70g, 70 %). [α] = -118 (C, 0.1, MeOH), IR (KBr): 3293, 1676, 1636, 1544 cm^{-1}, ^1H NMR (500 MHz, $CDCl_3$): δ 7.19-7.31 (m, 5H), 7.03 (d, *J* = 8.6 Hz, 1H), 6.92 (t, *J* = 5.5 Hz, 1H), 6.01 (d, *J* = 4.3 Hz, 1H), 5.86 (ddt, *J* = 17.2, 10.3, 5.5 Hz, 1H), 5.79 (m, 1H), 5.20 (dq, *J* =17.2, 1.6 Hz, 1H), 5.09 (dq, *J* = 10.3, 1.6 Hz, 1H), 5.03 (dq, *J* = 17.3, 1.6 Hz, 1H), 5.00 (dq, *J* = 10.3, 1.6 Hz, 1H), 4.46 (dt, *J* = 9.6, 6.5 Hz, 1H), 4.41 (m, 1H), 4.39 (m, 1H), 3.85 (dt, J = 15, 5.5 Hz, 2H), 3.80 (m, 1H) 3.77 (m, 1H), 3.07 (dd, J = 12.8, 9.6 Hz, 1H), 2.96 (dd, J = 12.8, 6.5 Hz, 1H), 2.65 (dt, J = 9.3, 7.0 Hz, 1H), 2.33-2.17 (m, 4H), 2.07 (m, 1H), 1.87-1.65 (m, 3H), 1.83 (m, 1H), 1.72-1.60 (m, 1H), 0.95 (d, J= 6.5 Hz, 3H), 0.88 (d, J = 6.5 Hz, 3H), Mass (CI method) (m/z): 497 (100), 440 (52), 327 (100).

Cyclo(D-Phe-L-Pro-L-Leu-Aha) (2):

To a stirred solution of Grubb's ruthenium catalyst (20 mol%) in dry CH_2Cl_2 (300 ml) under nitrogen was added a solution of N-Pentenoyl-D-Phe-L-Pro-Leu allylamide (250 mg, 0.50 mmol) in dry CH_2Cl_2 over a period of 15 min and refluxed for 12 h. CH_2Cl_2 was evaporated and the residue was purified by column chromatography to afford the RCM product as a mixture of *E* and *Z* isomers (150mg, 64 %) as an off white solid.

To a stirred solution of the unsaturated cyclic peptide (110 mg, 0.23 mmol) in 5 ml of MeOH was added 25 mg of 10 % Pd/C. The mixture was hydrogenated using a H_2 gas balloon at 20 psi for 3h. The catalyst was filtered off and the filtrate was evaporated to obtain the crude product which was purified to afford compound **2** (98 mg, 88.7 %). [α] = (C, 0.1, MeOH), IR (KBr): 3422, 1635, 1451cm^{-1}, ^1H NMR (500 MHz, $CDCl_3$): δ 7.36-7.21 (m, 5H), 7.03 (d, *J* = 9.4 Hz, 1H), 6.92 (dd, *J* = 7.9 Hz, 4.4 Hz, 1H), 6.07 (d, *J* = 4.2 Hz, 1H), 4.50 (m, 1H), 4.48 (m, 1H), 4.42 (dd, *J* = 8.7 Hz and *J* = 2.7 Hz, 1H), 3.75 (m, 1H), 3.73 (m, 1H), 3.08 (dd, *J* = 12.9 Hz and *J* = 9.7 Hz, 1H), 2.99 (dd, *J* = 12.9 Hz and *J* = 6.4 Hz, 1H), 2.77 (m, 1H), 2.57 (dt, *J* = 9.5 Hz and *J* = 6.9 Hz, 1H), 2.28 (m, 1H), 2.16 (m, 1H), 2.07 (m, 1H), 1.94 (m, 1H), 1.85 (m, 1H), 1.74 (m, 1H), 1.70 (m, 1H), 1.63 (m, 1H), 1.62-1.36 (m, 6H), 1.56 (m, 1H), 0.94 (d, *J* = 6.6 Hz, 3H), 0.88 (d, *J* = 6.6 Hz, 3H), Mass (CI method) 471 (M^++1, 100).

CSD search methods to retrieve Refcodes tabulated in Tables 3 and 4

CSD was searched for cyclic peptides having cavities (nanotube) in the class of molecules 'amino acids, peptides and complexes'. Any cyclic peptides with water, R-factor < 0.1, organic structure, 3D coordinates determined were extracted from CSD version 5.27, ConQuest 1.9, November 2006 release, May 2007 update. Crystal structures were visualized in Mercury 1.4.1. Total of 210 crystals structures are analyzed manually, out of which 58 crystal structures contain cyclic peptides with water (Table 3). Based on the contacts between the two backbones of cyclic peptides, they are further divided into three sub-classes. Peptide backbones directly connected with each other, peptide rings connected via water and peptides connected to each other and also through water molecules.

The CSD was searched for DL pairs of cyclic peptides assembling in nanotube architecture. All cyclic peptides, which belong to the class of 'D-Amino-acids, peptides and complexes', were retrieved from CSD version 5.27, ConQuest 1.9, November 2006 release, May 2007 update to give 141 hits. These structures were manually analyzed and 12 sets are extracted and presented in Table 4. Refcodes CBBLPB10/ BIPVUR10 and VOPYOO/ VOPYUU are hydrate/anhydrate pairs, a case similar to cyclic tetrapeptides **2** and **1**. CAHWEN/ PHLEGL10 and FAQYEC/ FAQYIG have different hydrate stoichiometry.