Electronic Supplementary Material (ESI) for Nanoscale.

Programmed Hierarchical Radial Association of Anisotropic Foldamer Assemblies

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1. Characterization methods

1.1. Nuclear magnetic resonance spectroscopy (NMR)

All NMR samples were prepared in $CDCl_3$ deuterated solvent, manufactured by Cambridge isotope laboratories. Each sample was prepared by dissolving ca. 10 mg of the compound in 500 μL deuterated solvent. 1D ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance II 400 MHz, 500 MHz NMR spectrometer at the KAIST NMR Facility.

1.2. High-resolution mass spectroscopy (HRMS)

High-resolution mass spectra (HRMS) were collected with a Bruker Daltonics microTOF-Q II mass spectrometer using an ESI ion source. Methanol was used as solvent for preparing the sample solutions.

1.3. Matrix-assisted laser desorption ionization mass spectrometry (MALDI)

Matrix-assisted laser desorption ionization (MALDI) mass spectrometry was performed with Bruker Autoflex III mass spectrometer, set in the KAIST Analysis Center for Research Advancement (KARA). 2,5-dihydroxybenzoic acid (DHB) was used as the matrix. 1 mg of DHB and the stock solution (0.1 mg) were mixed in MeOH. 5 μL of the mixed solution was dropped to the steel plate and then dried in ambient condition. All MALDI-MS data were collected under negative ion mode.

1.4. Structure determination from powder x-ray diffraction pattern (SDPD)

PXRD patterns of $\mathbf{F_{C1}}$ and $\mathbf{F_S}$ were collected at 9B High-Resolution Powder Diffraction (HRPD) beamline of Pohang Accelerator Laboratory (PAL, Pohang-si, Gyeongsangbuk-do, Republic of Korea). Sufficient amounts of samples were prepared *via* the repetition of the self-assembly experiment procedure as described in Section 3 (see ahead), followed by drying the gathered foldectures *in vacuo*. The diffractometer in the beamline adopts the Bragg-Brentano geometry. The monochromatic synchrotron radiation source was used to collect the diffracted pattern, but the wavelength was varied for each sample depending on the storage ring condition of the day when the pattern collected (λ = 1.51730 Å for $\mathbf{F_{C1}}$ and λ = 1.52250 Å for $\mathbf{F_S}$, respectively). The dried samples were filled in a Polycarbonate flat-plate holder and rotated with 1 cycle sec^{-1} speed during the collection to avoid possible damage from the incident beam. The pattern was collected over the range of more than 100° in 2θ, which is enough to analyze organic material. The step size was 0.005°, and the scan time was 1 sec for each step.

For the SDPD, a semi-automated *ab initio* peak indexing process was performed. However, no appropriate unit cell parameter was obtained in the case of $\mathbf{F_S}$. Meanwhile, the peaks in $\mathbf{F_{C1}}$ pattern were successfully indexed with a trigonal unit cell, $a = b$ = 14.3353 Å, c = 21.3939 Å, α = β = 90°, γ = 120° (Figure-of-merit, $M_{(20)}$= 81.34) by using *TAUP* included in *Crysfire* suite.[1] This cell was further refined during the refinement process. We tried to obtain a structure solution *via* the direct-space method

using the *F.O.X.* program.[2] The molecular model structure for the structure solution was adopted from the previous study[3] after modifying the seventh residue to Cys from Aib. More than 10,000,000 cycles of the global optimization calculation were enough to generate the structure solution; this structure was subjected to the final Rietveld refinement process. The Rietveld refinement was carried out using the *EXPGUI/GSAS*[4] program. Due to the impurity peaks, some ranges (7.040°–7.130°, 8.200°–8.360°, 18.190°–18.380° in 2θ) of the pattern were excluded. The data up to 74.735° in 2θ were used, considering the signal-to-noise ratio. All bond length, bond angles, intramolecular hydrogen bonds and planar functional groups were subjected to be restrained during the refinement. The restraints were set based on the crystallographic data, referring to The Cambridge Structural Database (CSD).[5] The refinement resulted in the molecular packing structure in high quality (R_p = 0.0527 and R_{wp} = 0.0720). The final Rietveld plot is presented in Figure S7, and the detailed crystallographic parameters and atomic coordinates are presented in Table S1, respectively.

Table S1. Crystallographic information of $\mathbf{F_{C1}}$ structure

Crystal data	
Chemical formula*	C_{45} N_7 $O_{10}S$
M_r*	830.59
Crystal system, space group	Trigonal, $P3_2$
Temperature (K)	298
a, b, c (Å)	14.33767(6), 14.33767(6), 21.39635(14)
α, β, γ (°)	90, 90, 120
V (Å^3)	3809.15(4)
Z	3
Radiation type	Synchrotron radiation (λ = 1.5173 Å)
Specimen form, colour	Powder, white
Specimen preparation temperature	Room temperature

Data collection	
Diffractometer	9B High-resolution powder diffraction beamline at Pohang Accelerator Laboratory
Data collection method	Specimen mounting: Polycarbonate flat-plate holder, Mode: reflection mode in Bragg-Brentano geometry, Step scan method
2θ (°, range in Refinement)	$2\theta_{min}$ = 6.000, $2\theta_{max}$ = 74.735, increment = 0.005

Refinement	
Refinement on	Intensities (observed counts)
Least-squares matrix	Full-matrix
R factors and goodness-of-fit	R_p = 0.0527, R_{wp} = 0.0720, R_{exp} = 0.0341, $R(F^2)$ = 0.16238, S = 2.31
Excluded region(s)	7.040°–7.130°, 8.200°–8.360°, 18.190°–18.380°
Profile function	CW Profile function number 4 with 16 terms. Pseudo-voigt profile coefficients as parameterized in Thompson *et al.* (1987). Asymmetry correction of Finger *et al.* (1994). Microstrain broadening by Stephens (1999). #1(GU) = 0.000, #2(GV) = 0.000, #3(GW) = 0.000, #4(GP) = 0.186, #5(LX) = 1.384, #6(ptec) = 0.00, #7(trns) = -1.43, #8(shft) = -0.3853, #9(sfec) = 0.00, #10(S/L) = 0.0107, #11(H/L) = 0.0107, #12(eta) = 0.1064, #13(S_{400}) = 2.4×10^{-3},

	#14(S_{004}) = 1.2×10^{-4}, #15(S_{202}) = 3.4×10^{-4}, #16(S_{310}) = −1.6×10^{-5}, #17(S_{211}) = 0.0. Peak tails are ignored where the intensity is below 0.0010 times the peak. Anisotropic broadening axis 0.0 0.0 1.0.
No. of parameters	212
No. of restraints	193
No. of data points	13748
No. of contributing reflections	1369
H-atom treatment*	Omitted during the refinement process
Background function	GSAS background function number 1, Shifted Chebyshev function with 6 terms. 1: 647.115, 2: 1.67829, 3: 2.84180, 4: −6.55014, 5: 2.47887, 6: −4.08743.
$(\Delta/\sigma)_{max}$, $(\Delta/\sigma)_{mean}$	0.04, 0.00

* H-atoms were omitted during the structure determination process.

1.5. Scanning electron microscope (SEM)

The samples, the self-assembled structures, were prepared through the self-assembly experiment procedure explained in Section 3. For SEM measurement, a drop of the dispersed structures in water was transferred to a silicon(Si) wafer, and the droplet was dried in air. SEM images were acquired on Inspect F50, FEI at an accelerating voltage of 10 kV, after Pt coating (sputter coater 108 auto, Cressington Scientific Instruments). The hierarchically self-assembled particles were prepared as described in Section 6, and the SEM observation was performed in the same way.

1.6. Circular dichroism (CD)

CD spectra were measured using a Jasco J-815 spectrometer in 1 mm quartz cells in MeOH (1 mM). The spectra were recorded from 260 to 190 nm at a scanning rate of 20 nm min^{-1} and were averaged three scans. CD spectra were obtained at spectrometer at KARA (KAIST Analysis center for Research Advancement).

1.7. Raman spectroscopy

The Raman detection was carried out on a LabRAM HR Evolution Visible_NIR Raman microscopy system with the excitation line of 514 nm and an air cooling charge-coupled device (CCD) as the detector.

2. Experimental procedures

2.1. Materials

2.1.1. Solvents and reagents

All starting reagents were purchased from Merck and Tokyo Chemical Industry (TCI). Dichloromethane (DCM) and *N,N*-dimethylformamide (DMF) were distilled before use. DCM was distilled under the $N_{2(g)}$ atmosphere in the presence of calcium hydride. Diisopropylethylamine (DIPEA) was distilled in the presence of calcium hydride. DMF was vacuum distilled.

2.1.2. Chromatography

Thin-layer chromatography (TLC) was performed on glass plates coated with Merck 60 F254 silica. The visualization was achieved by UV light or by staining with ninhydrin, *p*-anisaldehyde solution. Flash column chromatography was carried out using Merck Kieselgel (230–400 mesh).

2.2. Synthesis

2.2.1. General details

α/β-peptides (**1Cys**, **3Cys**, $\mathbf{P_A}$, $\mathbf{P_C}$, $\mathbf{P_S}$) were prepared *via* conventional solution-phase peptide coupling by using *tert*-butyloxycarbonyl–*trans*-ACPC–benzyl (=Boc–*trans*-(*S*,*S*)-ACPC)–OBn) and commercially available Boc–Aib–OH, Boc–Cys(S*t*Bu)–OH, Boc–Ser–OH as a monomer. The optically pure, doubly protected ACPC monomer, Boc–*trans*-(*S*,*S*)-ACPC–OBn, was synthesized through the previously reported procedure.[6] Aib–ACPC hexamer acid, Boc–(Aib–*trans*-(*S*,*S*)-ACPC)$_3$–OH, was synthesized according to the literature method[7] Boc–Ser–OBn were synthesized according to the reference.[8] Other substrates were commercially purchased and used without further purification. The reduction of the disulfide bond was achieved with tris(2-carboxyethyl)phosphine (TCEP).[9]

2.2.2. *N*-*tert*-Butyloxycarbonyl–Cys(S*t*Bu)–OBn (= Boc–Cys(S*t*Bu)–OBn)

To a solution of Boc–Cys(S*t*Bu)–OH (100 mg, 0.32 mmol) in DMF (2 mL), K_2CO_3 (66 mg, 0.48 mmol) and BnBr (41 µL, 0.35 mmol) were added. After 4 h stirring, DMF was removed under vacuum to provide a white solid. The solid was washed with distilled water (3 mL). The organic layers were dried over $MgSO_4$, filtered, concentrated *in vacuo*, and purified through flash chromatography eluting with Ethyl Acetate/Hexane (99:1) to obtain the desired product as a colorless oil. (123 mg, 96%)

^{1}H NMR (400 MHz, $CDCl_3$, 23 °C): *δ* 7.38–7.32 (5H, m), 5.41 (1H, d, *J* = 6.89), 5.19 (1H, s), 4.64–4.61 (1H, m), 3.23–3.13(2H, m), 1.44(9H, s), 1.30(9H, s). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.77, 135.31, 128.73, 128.59, 128.49, 80.27, 77.48, 77.36, 77.16, 76.84, 67.59, 53.55, 48.31, 42.95, 29.89, 28.45, 15.42. HRMS: calcd. for $[M+H]^+$ $C_{19}H_{29}NO_4S_2$ = 400.1622, found: 400.16231

2.2.3. *N-tert*-Butyloxycarbonyl–(Aib–*trans*-(*S*,*S*)-ACPC)$_3$–Cys(S*t*Bu)–OBn (=P_C(S*t*Bu))

Boc–Cys(S*t*Bu)–OBn (58 mg, 0.17 mmol) was stirred with trifluoroacetic acid (TFA, 1.0 mL) at room temperature. After 2 h, the remaining TFA was removed *in vacuo* to yield the resulting amine as a TFA salt form (55 mg, 95%).

To a solution of Boc–(Aib–*trans*-(*S*,*S*)-ACPC)$_3$–OH (100 mg, 0.14 mmol) in DMF (3 mL), HATU (69 mg, 0.18 mmol) and DIPEA (61 µL, 0.35 mmol) were added. After 20 min of stirring, $TFA^-H_3N^+$–Cys(S*t*Bu)–OBn (55 mg, 0.14 mmol) was added, and the mixture was stirred at room temperature 24 h. DMF was removed under vacuum to provide a white solid. The solid was dissolved in 5 mL of chloroform and washed with 10_{wt}% citric acid aqueous solution, and *sat.*$NaHCO_3$ aqueous solution (3 mL). The organic layers were dried over $MgSO_4$, filtered, concentrated *in vacuo*, and purified through flash chromatography eluting with Ethyl Acetate/Hexane (9:1) to obtain the product as a white solid (111 mg, 80%).

^{1}H NMR (400 MHz, $CDCl_3$, 23 °C): δ 8.14–8.10 (2H, d, *J* = 8.1), 7.97 (1H, d, *J* = 9.2), 7.39–7.24 (5H, m), 7.72 (1H, s), 7.42–7.24 (5H, m), 6.39 (1H, d, *J* = 9.4), 5.27–5.17(2H, m), 5.08 (1H, s), 4.90–4.85 (1H, m), 4.39–4.24 (3H, m), 3.33–3.22 (2H, m), 2.96–2.90 (1H, m), 2.37–2.31(1H, m), 2.18–2.07 (5H, m), 2.01–1.58 (20H, m), 1.52–1.45 (18H, m), 1.14–1.16 (3H, m), 1.31 (9H, s). ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.26, 175.08, 174.87, 174.82, 174.11, 173.45, 171.08, 155.14, 136.32, 128.43, 128.34, 127.93, 81.02, 77.48, 77.36, 77.16, 76.84, 66.93, 56.97, 56.96, 56.90, 55.17, 55.12, 53.63, 53.27, 52.80, 50.92, 47.86, 42.02, 33.50, 32.98, 32.40, 30.05, 28.50, 28.25, 27.60, 27.00, 24.45, 24.36, 23.95, 23.88, 23.48. HRMS: calcd. for $[M+H]^+$ $C_{49}H_{77}N_7O_{10}S_2$ = 988.5257, found: 988.5263

2.2.4 *N-tert*-Butyloxycarbonyl–(Aib–*trans*-(*S*,*S*)-ACPC)$_3$–Cys(SH)–OBn (=P_C)

To the THF solution of Boc–(Aib–*trans*-(*S*,*S*)-ACPC)$_3$–Cys(S*t*Bu)–OBn (100 mg, 0.10 mmol), the solution of TCEP (29 mg, 1.0 mmol) in THF/MeOH/water (5:3:2) (5 mL) were added; and the mixture was stirred at room temperature for 24 h. The solvent was removed under vacuum to provide a white solid. This crude product is purified through flash chromatography of eluting with CH_2Cl_2/Acetone (7:3) to obtain the desired product (**P_C**) as a white crystalline solid (72 mg, 82%).

^{1}H NMR (400 MHz, $CDCl_3$, 23 °C): δ 8.50 (1H, d, *J* = 7.8), 8.22 (1H, d, *J* = 8.11), 7.99 (1H, d, *J* = 9.3), 7.75 (1H, s), 7.39–7.25 (6H, m), 6.41 (1H, s), 5.25–5.15 (3H, m), 4.78–4.73 (1H, m), 4.46–4.39 (1H, m), 4.34–4.24 (2H, m), 3.08–3.04 (2H, m), 2.94–2.88 (1H, m), 2.37–2.26 (2H, m), 2.18–2.04 (6H, m), 1.97–1.56 (16H, m), 1.52–1.45 (18H, m), 1.40–1.36 (9H, m). ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.72, 175.17, 175.09, 174.86, 174.01, 173.44, 170.80, 155.16, 151.68, 136.17, 135.94, 128.56, 128.41, 128.36, 128.14, 125.68, 81.24, 77.52, 77.20, 76.88, 68.14, 67.02, 57.04, 56.97, 56.87, 55.83, 55.20, 55.15, 54.90, 53.71, 53.14, 51.81,

34.39, 33.62, 32.79, 32.47, 30.49, 29.86, 28.53, 28.32, 28.13, 27.73, 27.63, 27.56, 27.50, 26.27, 25.78, 24.52, 24.46, 23.98, 23.95, 23.91, 23.47, 21.35. HRMS: calcd. for $[M+H]^+$ $C_{45}H_{69}N_7O_{10}S$ = 900.4910, found: 900.4932

2.2.5 *N-tert*-Butyloxycarbonyl–(Aib–*trans*-(*S*,*S*)-ACPC)$_3$–Ser–OBn (=P_S)

Boc–Ser–OBn (80 mg, 0.47 mmol) was stirred with 4 N HCl in dioxane (1 mL) at room temperature. After 2 h, the solvent was removed *in vacuo* to yield the resulting amine as a hydrogen chloride salt form (93 mg, 86%).

To a solution of Boc–(Aib–*trans*-(*S*,*S*)-ACPC)$_3$–OH (100 mg, 0.14 mmol) in DMF (3 mL), HATU (69 mg, 0.18 mmol) and DIPEA (61 µL, 0.35 mmol) were added. After 10 min of stirring, $Cl^-NH_3^+$–Ser–OBn (32 mg, 0.14 mmol) was added, and the mixture was stirred at room temperature for 24 h. DMF was removed under vacuum to provide a white solid. The solid was dissolved in 5 mL of chloroform and washed with 10_{wt}% citric acid aqueous solution, and *sat*.$NaHCO_3$ aqueous solution (3 mL). The organic layers were dried over $MgSO_4$, filtered, concentrated *in vacuo*, and purified through flash chromatography, eluting with Ethyl Acetate/Hexane (9:1) to obtain the desired product (**P_s**) as a white solid (71 mg, 57 %). This compound was further purified by recrystallization from THF/Ether.

^{1}H NMR (400 MHz, $CDCl_3$, 23 °C): δ 8.36 (1H, d, *J* = 9.2), 8.11 (1H, d, *J* = 7.8), 8.07 (1H, d, *J* = 9.2), 7.97 (1H, s), 7.43 (1H, s), 7.40–7.28 (5H, m), 6.54 (1H, d, *J* = 9.3), 5.35 (1H, s), 5.21 (1H, s), 4.68–4.63 (1H, m), 4.64–4.53 (1H, m), 4.31–4.22 (2H, m), 4.10–3.99 (2H, m), 2.85–2.79 (1H, m), 2.35–2.29 (1H, s) 2.15–1.91 (9H, m), 1.89–1.54 (12H, m), 1.49 (6H, d, *J* = 6.0), 1.47 (9H, s), 1.41 (6H, d, *J* = 17.8), 1.36 (6H, d, *J* = 6.4). ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.98, 175.64, 175.16, 174.77, 174.36, 173.70, 170.36, 155.25, 136.01, 128.51, 128.17, 80.59, 77.42, 77.36, 77.16, 76.91, 66.77, 62.53, 56.84, 56.81, 56.74, 56.03, 54.95, 54.92, 53.73, 53.48, 52.71, 52.36, 32.99, 32.34, 31.95, 28.51, 28.46, 28.37, 28.25, 27.36, 27.28, 24.34, 24.16, 23.84, 23.63, 23.45, 22.90. HRMS: calcd. for $[M+H]^+$ $C_{45}H_{69}N_7O_{11}$ = 884.5138, found: 884.5143.

2.2.6. *N-tert*-Butyloxycarbonyl–Cys(S*t*Bu)–(*trans*-(*S*,*S*)-ACPC–Aib)$_3$–OBn (=1Cys(S*t*Bu))

Boc–(*trans*-(*S*,*S*)-ACPC-Aib)$_3$–OBn (103 mg, 0.13 mmol) was stirred with trifluoroacetic acid (TFA, 1.0 mL) at room temperature. After 2 h, the residual TFA was removed *in vacuo* to yield the resulting amine as a TFA salt form (97 mg, 94%).

To a solution of Boc–Cys(S*t*Bu)–OH (37 mg, 0.12 mmol) in DMF (5 mL), HATU (69 mg, 0.18 mmol) and DIPEA (52 µL, 0.30 mmol) were added. After 10 min of stirring, $TFA^-H_3N^+$–(*trans*-(*S*,*S*)-ACPC–Aib)$_3$–OBn (95 mg, 0.12 mmol) was added, and the mixture was stirred at room temperature 24 h. DMF was removed under vacuum to provide a white solid. The solid was dissolved in 5 mL of chloroform and washed with 10_{wt}% citric acid aqueous solution, and *sat.*$NaHCO_3$ aqueous solution (3 mL). The organic layers were dried over $MgSO_4$, filtered, concentrated *in vacuo*, and purified through flash chromatography eluting with Ethyl Acetate/Hexane (9:1) to obtain the product as a white solid (97 mg, 82%).

^{1}H NMR (400 MHz, $CDCl_3$, 23 °C): 8.01 (1H, d, *J* = 8.7), 7.76 (1H, s), 7.68–7.66 (2H, m), 7.37–7.27 (5H, m), 6.70 (1H, s), 6.58 (1H, d, *J* = 8.3), 5.46 (1H, d, *J* = 4.0), 5.16 (2H, s), 4.41–4.25 (4H, m), 3.14–3.10 (1H, m), 3.00–2.94 (1H, m), 2.70–2.64 (1H, m), 2.38–2.32 (1H, m), 2.27–2.21 (1H, m), 2.19–2.11 (1H, m), 2.09–1.83 (6H, m), 1.84–1.67 (10H, m), 1.59 (3H, s), 1.55 (3H, s) 1.50–,1.49 (12H, m), 1.45 (3H, s), 1.38 (6H, m), 1.35 (9H, s). ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.28, 174.83, 174.38, 174.10, 173.70, 171.11, 136.84, 128.42, 128.10, 127.78, 81.73, 77.48, 77.36, 77.16, 76.84, 66.57, 57.08, 56.93, 56.08, 55.37, 55.22, 54.08, 52.99, 51.81, 49.17, 33.58, 32.94, 32.62, 30.00, 28.42, 28.16, 27.90, 27.61, 27.27, 25.52, 24.59, 24.40, 24.34, 23.89, 23.72. HRMS: calcd. for $[M+H]^+$ $C_{49}H_{77}N_7O_{10}S_2$ = 988.525, found: 988.5261

2.2.7. *N-tert*-Butyloxycarbonyl-Aib-*trans*-(*S*,*S*)-ACPC–Aib–Cys(S*t*Bu)–(*trans*-(*S*,*S*)-ACPC–Aib)$_2$–OBn (=3Cys(S*t*Bu))

Boc–Cys(S*t*Bu)–(*trans*-(*S*,*S*)-ACPC–Aib)$_2$–OBn (111 mg, 0.14 mmol) was stirred with trifluoroacetic acid (TFA, 1.0 mL) at room temperature. After 2 h, the residual TFA was removed *in vacuo* to yield the resulting amine as a TFA salt form (106 mg, 96%).

To a solution of Boc–Aib–*trans*-(*S*,*S*)-ACPC–OH (38 mg, 0.12 mmol) in DMF (5 mL), HATU (69 mg, 0.18 mmol) and DIPEA (52 µL, 0.30 mmol) were added. After 10 min of stirring, $TFA^-H_3N^+$–Cys(S*t*Bu)–(*trans*-(*S*,*S*)-ACPC–Aib)$_2$–OBn (95 mg, 0.12 mmol) was added, and the mixture was stirred at room temperature 24 h. DMF was removed under vacuum to provide a white solid. The solid was dissolved in 5 mL of chloroform and washed with 10_{wt}% citric acid aqueous solution and *sat.*$NaHCO_3$ aqueous solution (3 mL). The organic layers were dried over $MgSO_4$, filtered, concentrated *in vacuo*, and purified through flash chromatography eluting with Ethyl Acetate/Hexane (9:1) to obtain the product as a white solid (93 mg, 78%).

^{1}H NMR (400 MHz, $CDCl_3$, 23 °C): 8.03 (1H, d, *J* = 9.8), 7.77–7.75 (2H, m), 7.38–7.27 (7H, m), 6.42 (1H, d, *J* = 9.2), 5.15 (2H, s), 5.08 (1H, s), 4.39–4.27 (4H, m), 3.22–3.18 (1H, m), 2.81–2.75 (1H, m), 2.68–2.62 (1H, m), 2.40–2.34 (1H, m), 2.26–1.84 (10H, m), 1.60 (3H, s), 1.54 (3H, s), 1.52 (3H, s), 1.49 (9H, s), 1.46 (3H, s), 1.43 (3H, s), 1.39 (3H, s), 1.35 (9H, s). ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.45, 175.25, 174.61, 174.06, 173.33, 171.45, 155.12, 136.78, 128.41, 128.06, 127.79, 81.66, 77.41, 77.36, 77.16, 77.15, 76.90, 66.55, 57.03, 56.93, 56.05, 55.51, 55.23, 53.52, 52.97, 51.85, 48.47, 40.12, 33.46, 32.99, 31.76, 30.12, 28.50, 28.24, 27.82, 27.56, 27.31, 25.54, 24.65, 24.36, 23.88, 23.86, 23.50. HRMS: calcd. for $[M+H]^+$ $C_{49}H_{77}N_7O_{10}S_2$ = 988.5257, found: 988.5262

2.2.8. *N-tert*-Butyloxycarbonyl–Cys(SH)–(*trans*-(*S*,*S*)-ACPC–Aib)$_3$–OBn (=1Cys)

To the THF solution of Boc–Cys(S*t*Bu)–(*trans*-(*S*,*S*)-ACPC–Aib)$_3$–OBn (59 mg, 0.06 mmol), the solution of TCEP (17 mg, 0.6 mmol) in THF/MeOH/water (5:3:2) (5 mL) were added; and the mixture was stirred at room temperature for 24 h. The solvent was removed under vacuum to provide a white solid. This crude product is purified through flash chromatography of eluting with CH_2Cl_2/Acetone (7:3) to obtain the desired product (**1Cys**) as a white crystalline solid (44 mg, 81%).

^{1}H NMR (400 MHz, $CDCl_3$, 23 °C): 8.07 (1H, d, *J* = 8.9), 7.89–7.87 (2H, m), 7.70 (1H, d, *J* = 7.6), 7.37–7.27 (6H, m), 6.48 (1H,s), 5.60 (1H, d, *J* = 5.4), 5.15 (2H, m), 4.36–4.21 (4H, m), 3.76–3.72 (1H, m), 3.06–2.85 (2H, m), 2.71–2.63 (1H, m), 2.37–2.31 (1H, m), 2.17–1.67 (23H, m), 1.60 (3H, s), 1.55 (3H, s), 1.51 (3H, s), 1.45 (3H, s), 1.43 (9H, s) 1.37–38 (6H, m). ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.31, 174.88, 174.55, 174.27, 173.95, 173.86, 171.01, 151.66, 136.64, 135.92, 128.46, 128.39, 128.04, 127.89, 125.66, 81.43, 77.48, 77.36, 77.16, 76.84, 68.11, 66.64, 57.02, 56.92, 56.11, 55.25, 55.15, 53.02, 52.93, 52.13, 51.22, 34.37, 33.54, 32.80, 30.46, 29.84, 28.43, 27.87, 27.64, 25.55, 24.30, 23.83, 23.69, 21.32. HRMS: calcd. for $[M+H]^+$ $C_{45}H_{69}N_7O_{10}S$ = 900.4910, found: 900.4929

2.2.9. *N*-*tert*-Butyloxycarbonyl–Aib–*trans*-(*S*,*S*)-ACPC–Aib–Cys(SH)–(*trans*-(*S*,*S*)-ACPC–Aib)$_2$–OBn (=3Cys)

To the THF solutions of Boc–Aib–*trans*-(*S*,*S*)-ACPC–Cys(S*t*Bu)–(*trans*-(*S*,*S*)-ACPC–Aib)$_2$–OBn (59 mg, 0.06 mmol), the solution of TCEP (17 mg, 0.6 mmol) in THF/MeOH/water (5:3:2, 5 mL) and the mixture was stirred at room temperature for 24 h. The solvent was removed under vacuum to provide a white solid. This crude product was purified through flash chromatography of eluting with CH_2Cl_2/Acetone (7:3) to obtain the desired product (**3Cys**) as a white crystalline solid (42 mg, 77%).

^{1}H NMR (400 MHz, $CDCl_3$, 23 °C): 8.07 (1H, d, *J* = 8.9), 7.89–7.87 (2H, m), 7.70 (1H, d, *J* = 7.6), 7.37–7.27 (6H, m), 6.48 (1H, d, *J* = 9.2), 5.15 (3H, m), 4.36–4.24 (3H, m), 4.09–3.91 (1H, m), 3.76–3.72 (1H, m), 3.08–2.74 (1H, m), 2.65–2.61 (1H, m), 2.43–2.38(1H, m), 2.33–2.29 (1H, m), 2.18–1.73 (24H, m), 1.59 (3H, s), 1.55 (3H, s), 1.51 (3H, s), 1.50–1.47 (9H, m), 1.43 (9H, s). ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.78, 175.24, 175.15, 174.93, 174.07, 173.50, 170.86, 155.22, 151.75, 136.24, 136.01, 128.62, 128.48, 128.42, 128.20, 125.74, 81.30, 77.58, 77.47, 77.26, 76.94, 68.20, 67.08, 57.11, 57.03, 56.93, 55.89, 55.27, 55.21, 54.96, 53.77, 53.20, 51.87, 34.45, 33.68, 32.85, 32.53, 30.55, 29.92, 28.59, 28.39, 28.19, 27.79, 27.69, 27.62, 27.56, 26.33, 25.84, 24.58, 24.52, 24.04, 24.01, 23.97, 23.53, 21.41. HRMS: calcd. for $[M+H]^+$ $C_{45}H_{69}N_7O_{10}S$ = 900.4910, found: 900.4930

3. General self-assembly procedure for foldecture preparation

A solution of peptide(**P_A**, **P_C**, **P_S**) in THF (200 μL, 10 g L^{-1}) was rapidly injected into an aqueous solution of P123 (1.0 mL, 0–40 g L^{-1}) under vigorous stirring for 5 min at room temperature. Then the mixture was aged for 2 h at room temperature without stirring. The resulting solution was centrifuged, and the supernatant was decanted. The remaining white powder was washed with distilled water (2 × 1 mL). About 3 μL of the solution was drop-casted on a silicon wafer and dried under air at room temperature. The remaining particles were observed with SEM.

4. Chemical structures of Cys-modified foldamers

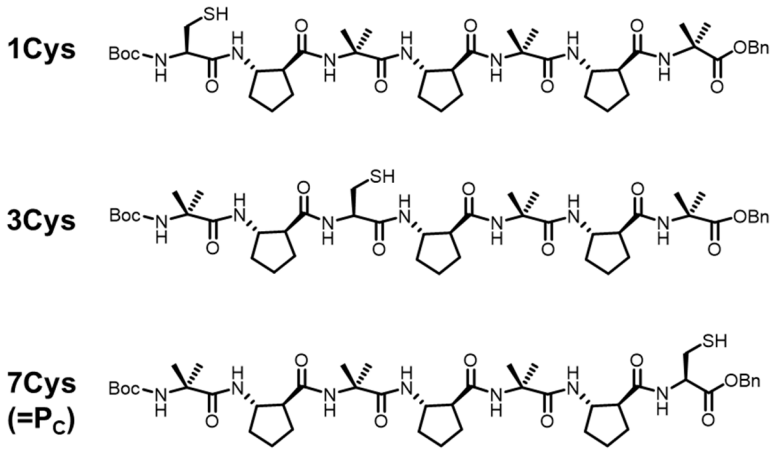


Figure S1. Chemical structures of Cys-modified foldamers, **1Cys**, **3Cys** and **7Cys** (= $\mathbf{P_C}$).

5. SEM images of foldectures F_C and F_S

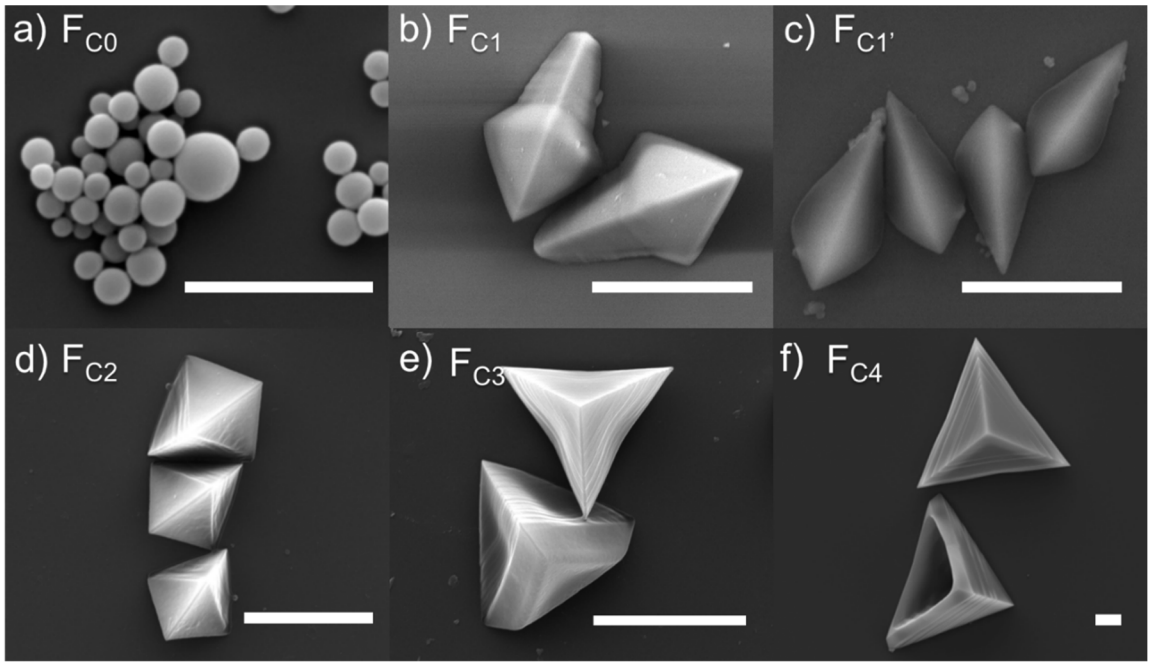


Figure S2. SEM images of $\mathbf{F_C}$ foldectures depending on P123 concentration. a) 0 g L^{-1}, b) 8 g L^{-1}, c) 16 g L^{-1}, d) 26 g L^{-1}, e) 36 g L^{-1} and f) 40 g L^{-1} (Scale bar: 3 μm)

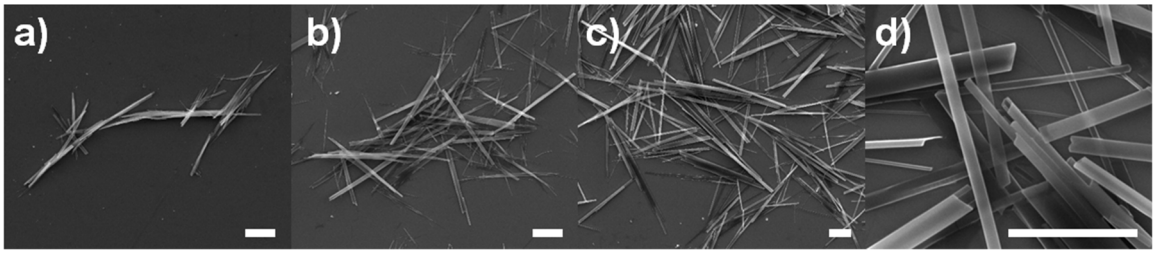
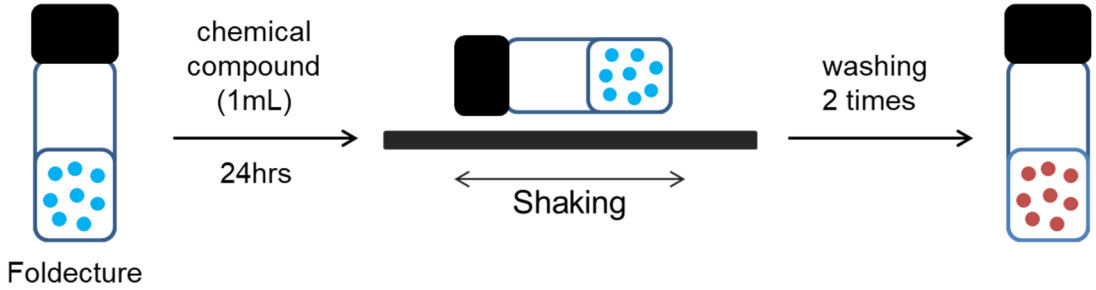


Figure S3. SEM images of $\mathbf{F_S}$ foldectures depending on P123 concentration. a) 0 g L^{-1}, b) 1 g L^{-1}, c) 16 g L^{-1} and d) 32 g L^{-1} (size bar : 5 μm)

6. Hierarchical assembly procedure

To the aqueous dispersions of $\mathbf{F_A}$ and $\mathbf{F_C}$ foldecture, 1 mL of 0.1M $NaHCO_3$ was added respectively, under the shaking for 24 h at room temperature. If necessary, basic and acidic compounds were added in this stage as additives for various chemical environments. After about 24 h, A powder that floats on the water carefully scoops into a wafer. After washing again with water, and analyzed their morphologies through SEM.



Scheme 1. The schematic image of experimental procedure for the hierarchical self-assembly of foldectures ($\mathbf{F_A}$, $\mathbf{F_C}$).

7. SEM image of hierarchically assembled structures

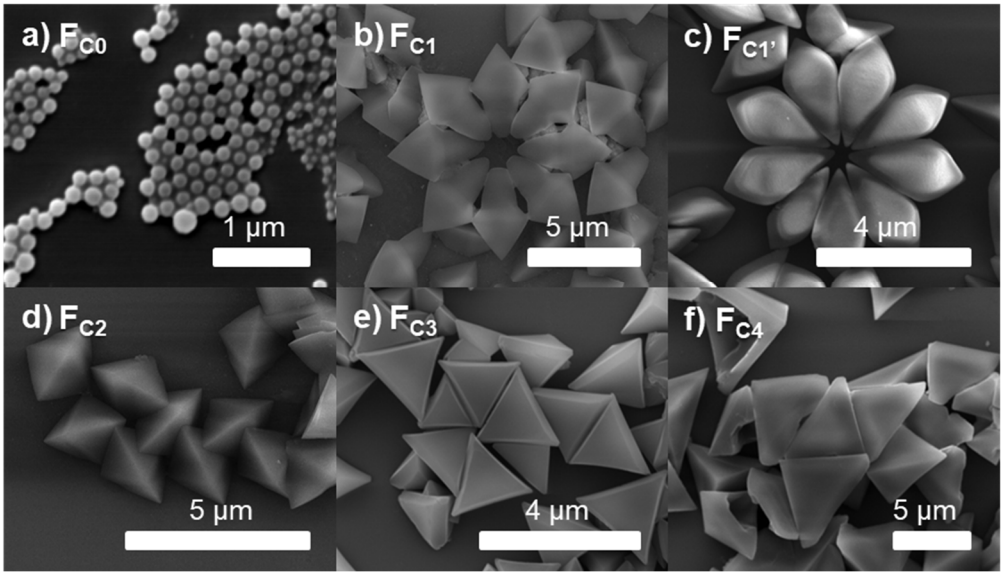


Figure S4. SEM images representing the hierarchical assembly of $\mathbf{F_C}$ foldecture in 0.1 M $NaHCO_3$. a) $\mathbf{F_{C0}}$, b) $\mathbf{F_{C1}}$c) $\mathbf{F_{C1'}}$, d) $\mathbf{F_{C2}}$, e) $\mathbf{F_{C3}}$ and f) $\mathbf{F_{C4}}$

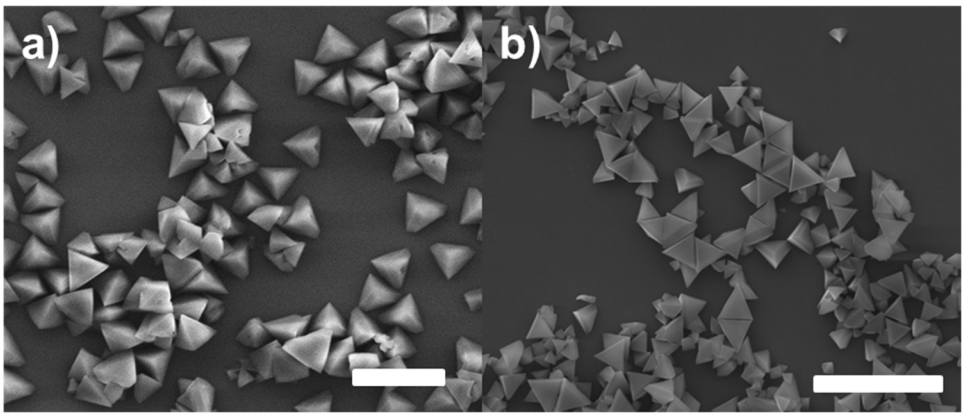


Figure S5. SEM images of hierarchical assembly of a) $\mathbf{F_{A3}}$ and b) $\mathbf{F_{C3}}$ with 0.1 M $NaHCO_3$. (scale bar: 10 μm)

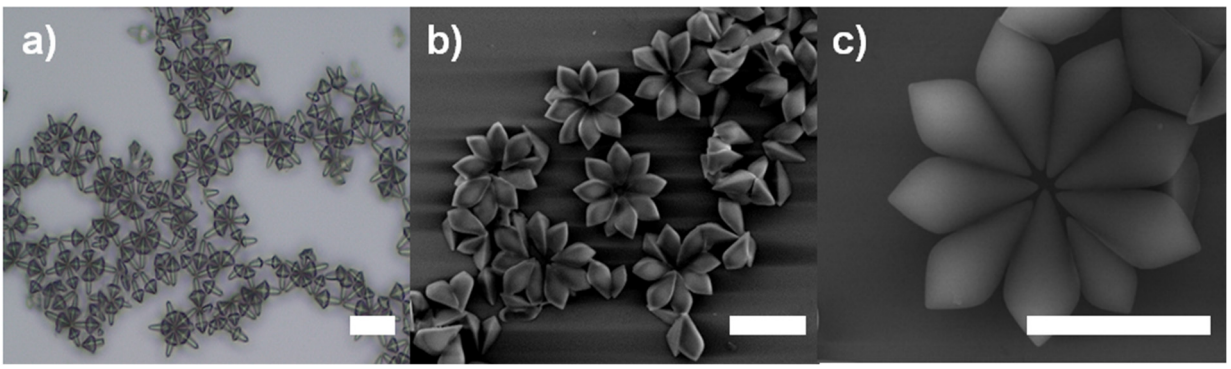


Figure S6. a) Optical image of hierarchical assembly of $\mathbf{F_{C1}}$ with $NaHCO_3$. b, c) SEM images of hierarchical assembly of $\mathbf{F_{C1'}}$ with $NaHCO_3$. (scale bar: 5 μm)

8. Structure determination from powder diffraction data

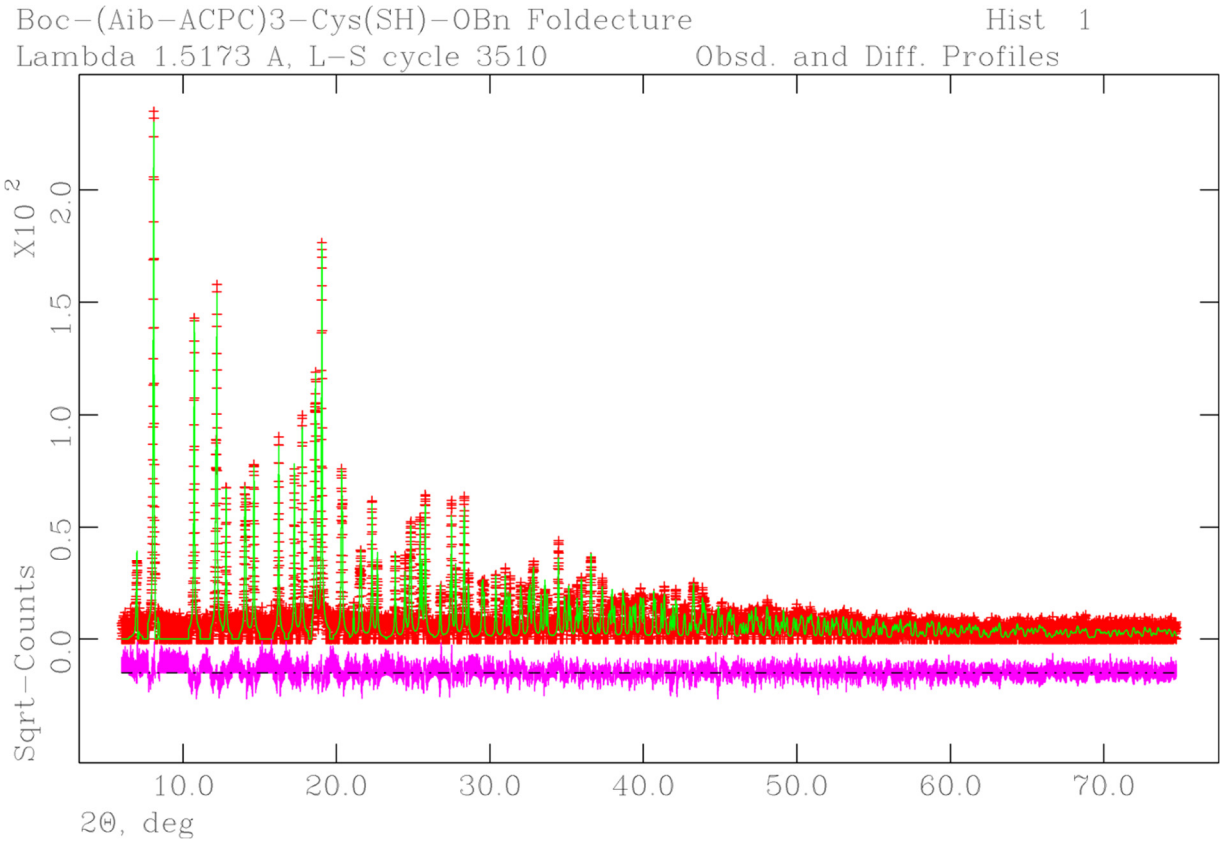


Figure S7. The final Rietveld plot of $\mathbf{F_C}$ foldecture. Observed data points, the calculated pattern, and the difference pattern are represented red crosses, green and magenta solid line, respectively. The square root of the intensity was plotted to clearly show weak peaks of high-angle region.

Table S2. Atomic coordinates and displacement and population parameters for the PXRD structure of foldecture $\mathbf{F_C}$.

No.	Label	*fractional coordinated*			Occupancy	B factor type	U_{equiv}
		x (esd)	*y (esd)*	*z (esd)*			
1	C1	−0.30660(18)	1.07399(24)	0.4886(7)	1	Isotropic	0.458
2	C2	−0.41140(15)	1.05409(33)	0.48438(8)	1	Isotropic	0.458
3	C3	−0.47637(17)	0.99385(30)	0.43563(11)	1	Isotropic	0.458
4	C4	−0.43715(19)	0.95263(24)	0.39153(9)	1	Isotropic	0.458
5	C5	−0.33266(15)	0.97210(31)	0.39588(9)	1	Isotropic	0.458
6	C6	−0.26581(13)	1.03403(21)	0.44410(8)	1	Isotropic	0.458
7	C7	−0.15371(22)	1.05272(18)	0.44884(12)	1	Isotropic	0.259
8	C8	−0.05462(14)	0.97653(18)	0.40736(11)	1	Isotropic	0.259
9	C9	−0.06443(13)	0.87942(15)	0.37276(8)	1	Isotropic	0.0777
10	C10	−0.14367(18)	0.84979(19)	0.31864(8)	1	Isotropic	0.0777
11	C11	−0.07357(24)	0.79181(13)	0.47531(7)	1	Isotropic	0.0777
12	C12	−0.10729(19)	0.68510(16)	0.50733(7)	1	Isotropic	0.0777
13	C13	−0.1029(4)	0.6923(4)	0.57952(10)	1	Isotropic	0.0777

14	C14	−0.2185(4)	0.6409(6)	0.59993(12)	1	Isotropic	0.0777
15	C15	−0.2797(4)	0.55137(30)	0.55362(9)	1	Isotropic	0.0777
16	C16	−0.22490(17)	0.59838(17)	0.49065(7)	1	Isotropic	0.0777
17	C17	−0.27776(14)	0.49589(20)	0.39238(8)	1	Isotropic	0.0777
18	C18	−0.24967(15)	0.43035(17)	0.34781(8)	1	Isotropic	0.0777
19	C19	−0.2914(4)	0.4324(4)	0.28200(11)	1	Isotropic	0.0777
20	C20	−0.3007(5)	0.31487(30)	0.37261(12)	1	Isotropic	0.0777
21	C21	−0.06578(12)	0.58040(13)	0.33100(11)	1	Isotropic	0.0777
22	C22	0.05177(14)	0.62097(18)	0.34366(8)	1	Isotropic	0.0777
23	C23	0.12736(33)	0.72636(32)	0.30893(11)	1	Isotropic	0.0777
24	C24	0.2223(5)	0.7793(5)	0.35017(12)	1	Isotropic	0.0777
25	C25	0.17541(32)	0.76384(26)	0.41447(11)	1	Isotropic	0.0777
26	C26	0.07813(17)	0.64880(15)	0.41393(8)	1	Isotropic	0.0777
27	C27	0.03041(14)	0.50170(18)	0.48884(10)	1	Isotropic	0.0777
28	C28	0.05613(16)	0.41476(17)	0.51044(8)	1	Isotropic	0.0777
29	C29	0.12922(35)	0.4556(5)	0.56775(11)	1	Isotropic	0.0777
30	C30	−0.04870(33)	0.3122(5)	0.52642(12)	1	Isotropic	0.0777
31	C31	0.07523(12)	0.37338(23)	0.40098(7)	1	Isotropic	0.0777
32	C32	0.14304(15)	0.35455(20)	0.35337(8)	1	Isotropic	0.0777
33	C33	0.0773(4)	0.28630(33)	0.29658(10)	1	Isotropic	0.0777
34	C34	0.1268(5)	0.3584(7)	0.23958(12)	1	Isotropic	0.0777
35	C35	0.24164(32)	0.4304(4)	0.25687(9)	1	Isotropic	0.0777
36	C36	0.23460(15)	0.46042(21)	0.32469(8)	1	Isotropic	0.0777
37	C37	0.37185(14)	0.57747(18)	0.40071(9)	1	Isotropic	0.0777
38	C38	0.47561(15)	0.60075(15)	0.43497(8)	1	Isotropic	0.0777
39	C39	0.57331(32)	0.6805(5)	0.39649(12)	1	Isotropic	0.0777
40	C40	0.4767(4)	0.6474(4)	0.49948(11)	1	Isotropic	0.0777
41	C41	0.39721(12)	0.41322(14)	0.46878(11)	1	Isotropic	0.107
42	C42	0.34458(19)	0.22646(21)	0.49562(10)	1	Isotropic	0.107
43	C43	0.3521(5)	0.2440(8)	0.56542(12)	1	Isotropic	0.107
44	C44	0.3870(4)	0.15225(33)	0.47779(13)	1	Isotropic	0.107
45	C45	0.23116(32)	0.1875(7)	0.47245(13)	1	Isotropic	0.107
46	N46	−0.09274(31)	0.78640(18)	0.41317(9)	1	Isotropic	0.0777
47	N47	−0.22941(16)	0.51710(19)	0.44795(9)	1	Isotropic	0.0777
48	N48	−0.13257(14)	0.47715(23)	0.34572(12)	1	Isotropic	0.0777
49	N49	0.09806(16)	0.57138(18)	0.44684(10)	1	Isotropic	0.0777
50	N50	0.11197(16)	0.39237(31)	0.46002(9)	1	Isotropic	0.0777
51	N51	0.33614(14)	0.49948(27)	0.35765(10)	1	Isotropic	0.0777
52	N52	0.47865(14)	0.50086(18)	0.44229(11)	1	Isotropic	0.0777
53	O53	−0.15088(18)	0.96206(18)	0.42110(12)	1	Isotropic	0.259
54	O54	0.02773(30)	1.0630(4)	0.41114(13)	1	Isotropic	0.259
55	O55	−0.0260(5)	0.87728(26)	0.50405(11)	1	Isotropic	0.0777

56	O56	−0.34196(24)	0.52445(30)	0.37709(12)	1	Isotropic	0.0777
57	O57	−0.09808(28)	0.64180(21)	0.31446(13)	1	Isotropic	0.0777
58	O58	−0.05172(22)	0.50056(33)	0.50578(12)	1	Isotropic	0.0777
59	O59	−0.00543(22)	0.3771(4)	0.38539(11)	1	Isotropic	0.0777
60	O60	0.31928(25)	0.61887(26)	0.41800(12)	1	Isotropic	0.0777
61	O61	0.31435(21)	0.40696(29)	0.48768(13)	1	Isotropic	0.107
62	O62	0.41752(21)	0.33145(17)	0.46613(11)	1	Isotropic	0.107
63	S63	−0.0987(7)	0.95015(30)	0.25691(11)	1	Isotropic	0.247

9. Solid-state structure from PXRD analysis of compound F_{C1}, F_{A1} and F_S

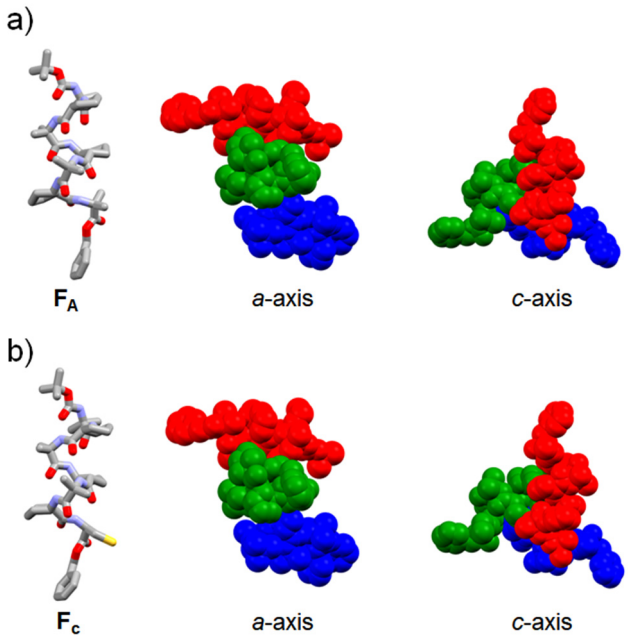


Figure S8. Comparison of the molecular packing motifs based on the PXRD structures of a) F_A and b) F_C.

10. Raman spectra of self-assembled structures F_{C1}

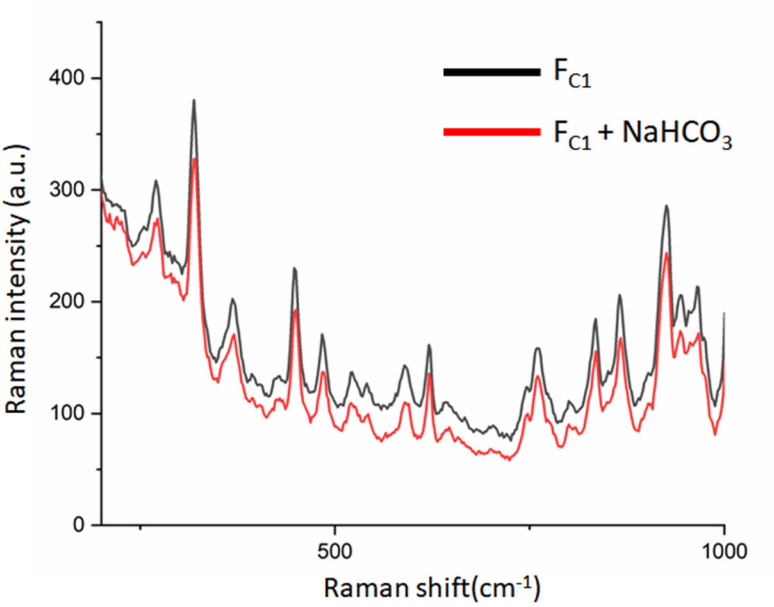


Figure S9. Raman spectra of $\mathbf{F_{C1}}$ and the hierarchically assembled $\mathbf{F_{C1}}$ with 0.1 M $NaHCO_3$.

11. SEM and optical microscope image of hierarchically-assembled structures F_{C1}

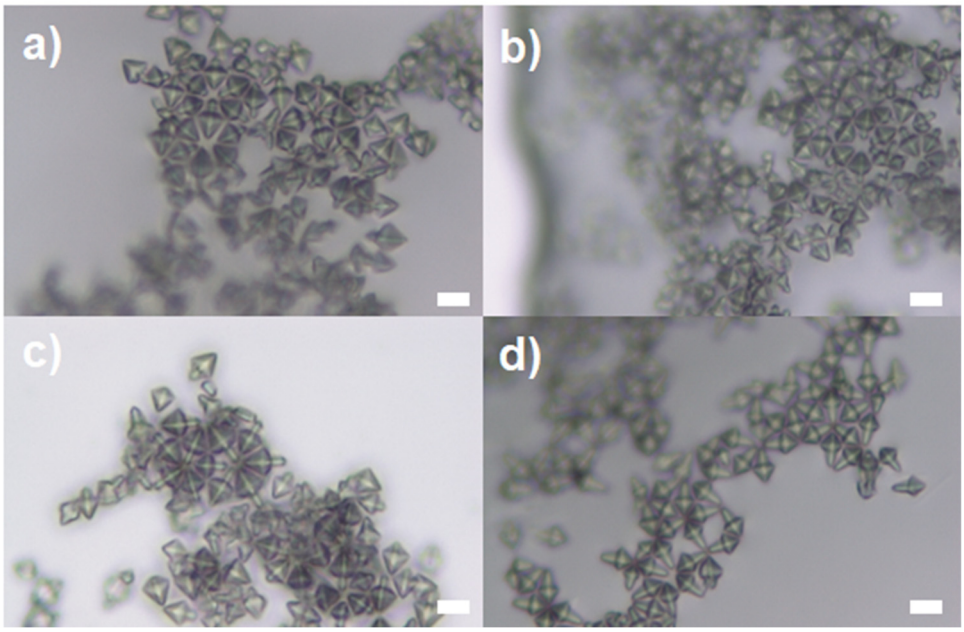


Figure S10. Optical microscope images of hierarchically assembled $\mathbf{F_{C1}}$ with different salt, a) 0.1 M $Ca(HCO_3)_2$ b) 0.1 M NH_4HCO_3 c) 0.1 M Na_2HPO_4 and d) 0.1 M NaCl. (scale bar : 5 μm)

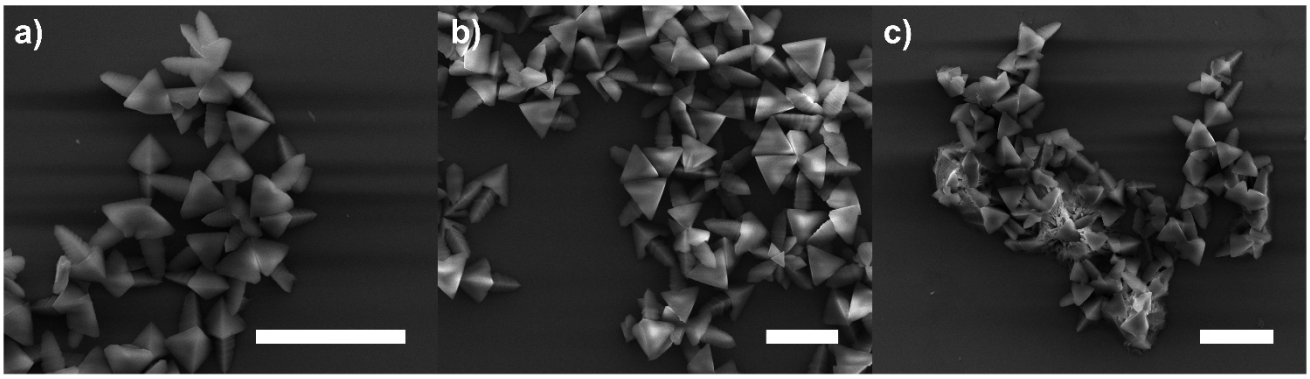


Figure S11. SEM images of the hierarchical assembly of $\mathbf{F_{c1}}$ in acidic conditions; a) 0.1 M acetic acid, b) 0.01 M acetic acid and c) 0.1 M NH_4Cl. (scale bar : 10 μm)

12. ^{1}H and ^{13}C NMR Spectra

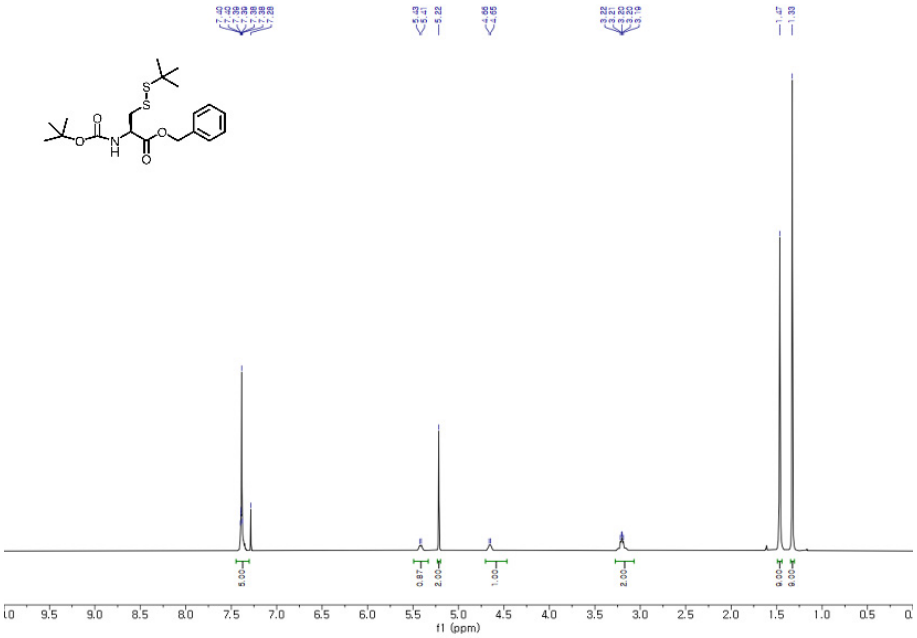


Figure S12.1. ^{1}H NMR spectrum (400 MHz, $CDCl_3$, 23 ˚C) of compound Boc-Cys(S*t*Bu)-OBn

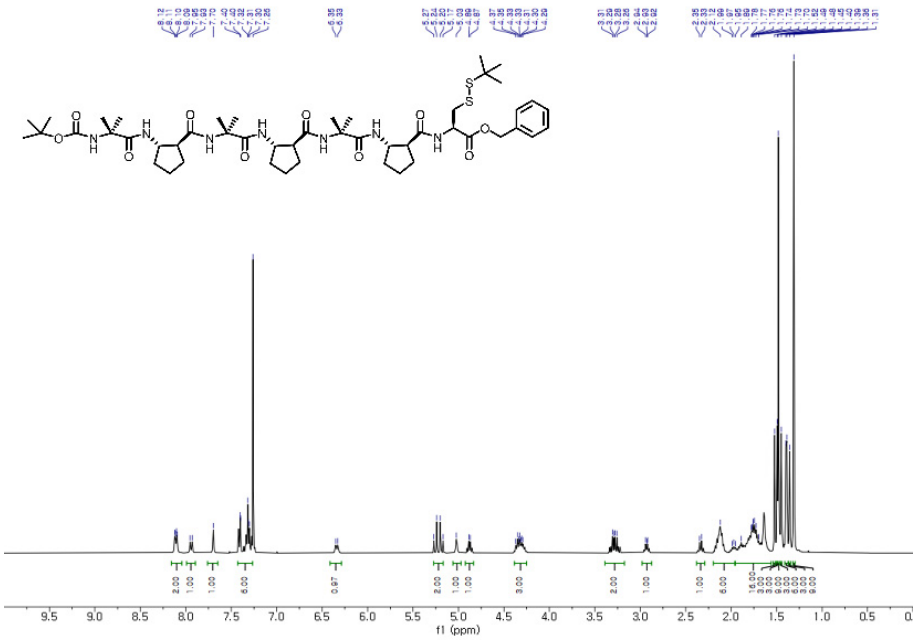


Figure S12.2. ^{1}H NMR spectrum (400 MHz, $CDCl_3$, 23 ˚C) of compound Boc-(Aib-ACPC)$_3$-Cys(S*t*Bu)-OBn

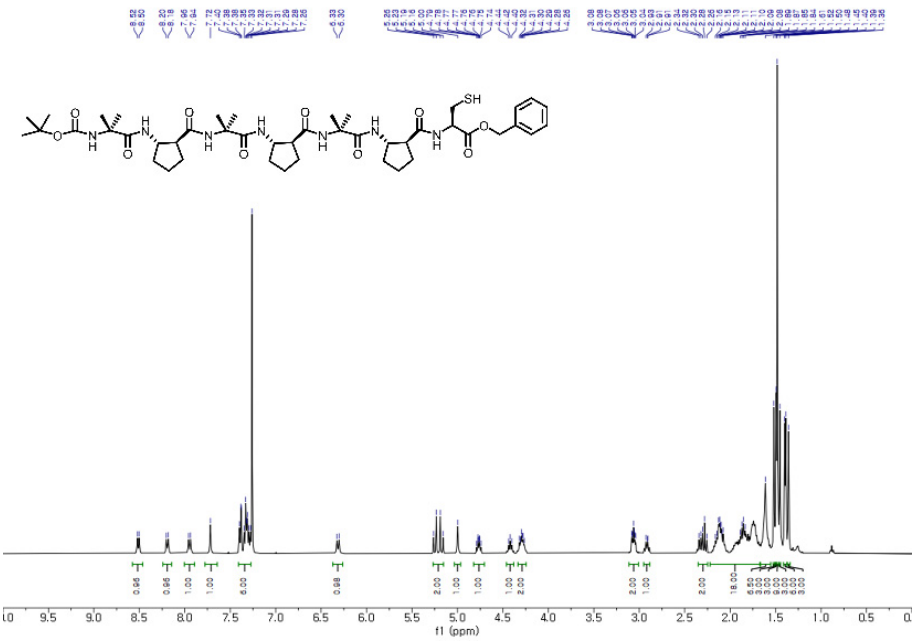


Figure S12.3. ^{1}H NMR spectrum (400 MHz, $CDCl_3$, 23 ˚C) of compound Boc-(Aib-ACPC)$_3$-Cys(SH)-OBn (**P$_C$**)

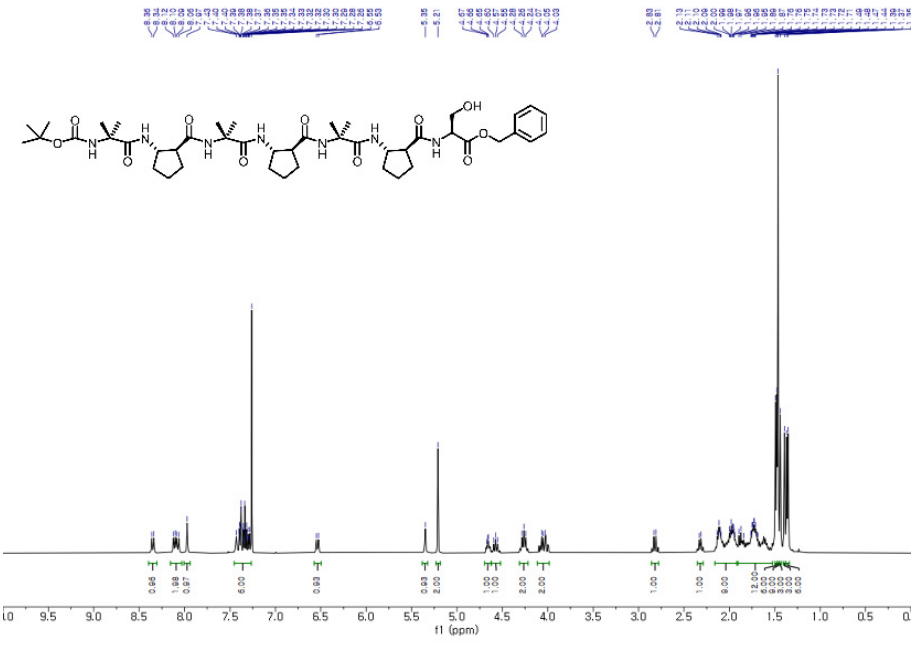


Figure S12.4. ^{1}H NMR spectrum (400 MHz, $CDCl_3$, 23 ˚C) of compound Boc-(Aib-ACPC)$_3$-Ser-OBn (**P$_S$**)

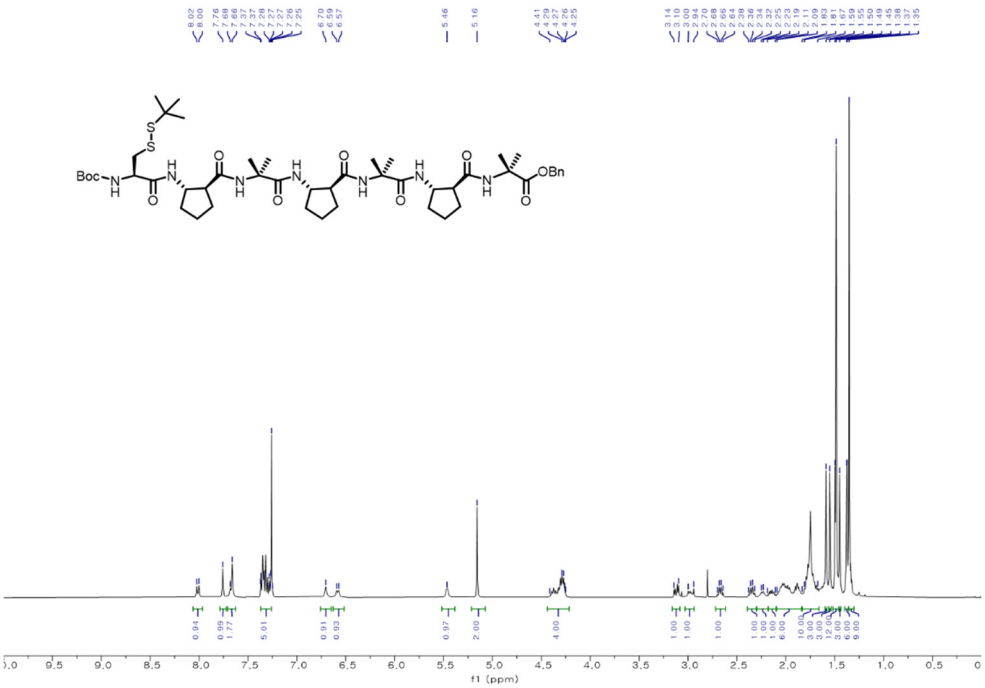


Figure S12.5. ^{1}H NMR spectrum (400 MHz, $CDCl_3$, 23 ˚C) of compound Boc–Cys(S*t*Bu)–(ACPC–Aib)$_3$–OBn (=1Cys(S*t*Bu))

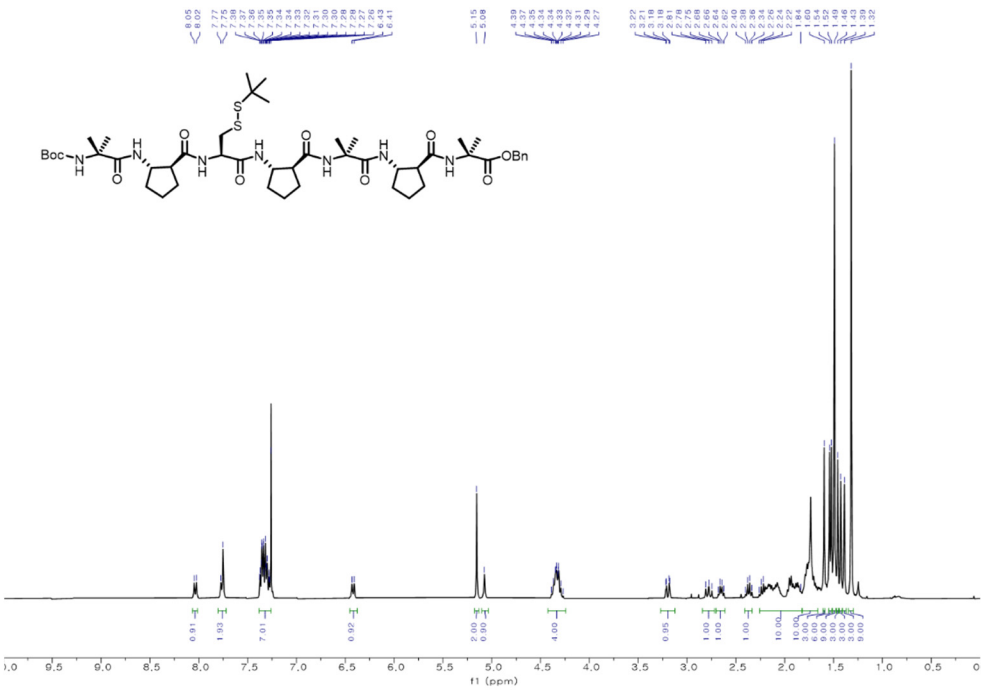


Figure S12.6. ^{1}H NMR spectrum (400 MHz, $CDCl_3$, 23 ˚C) of compound Boc–Aib–ACPC–Aib–Cys(S*t*Bu)–(ACPC–Aib)$_2$–OBn (=3Cys(StBu))

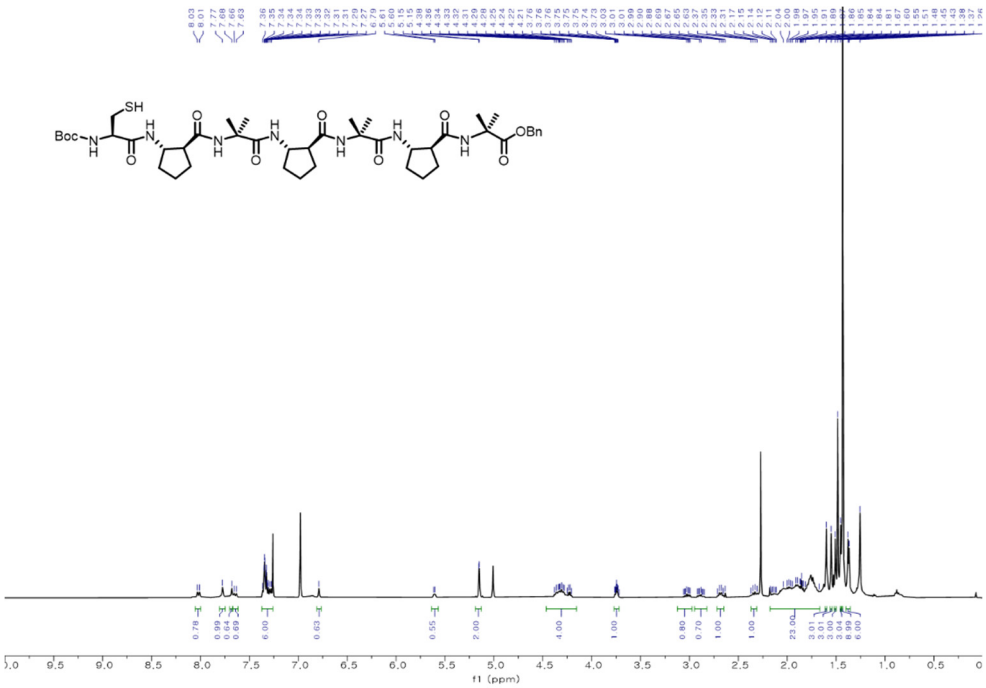


Figure S12.7. ^{1}H NMR spectrum (400 MHz, $CDCl_3$, 23 ˚C) of compound Boc–Cys(SH)–(ACPC–Aib)$_3$–OBn (=1Cys)

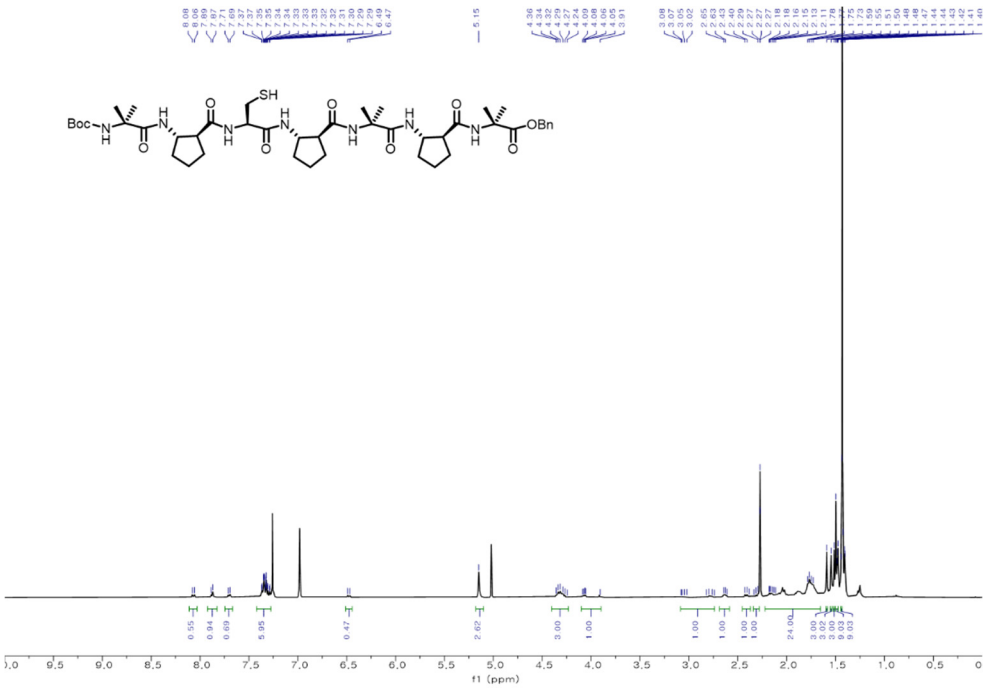


Figure S12.8. ^{1}H NMR spectrum (400 MHz, $CDCl_3$, 23 ˚C) of compound Boc–Aib–ACPC–Aib–Cys(SH)–(ACPC–Aib)$_2$–OBn (=3Cys)

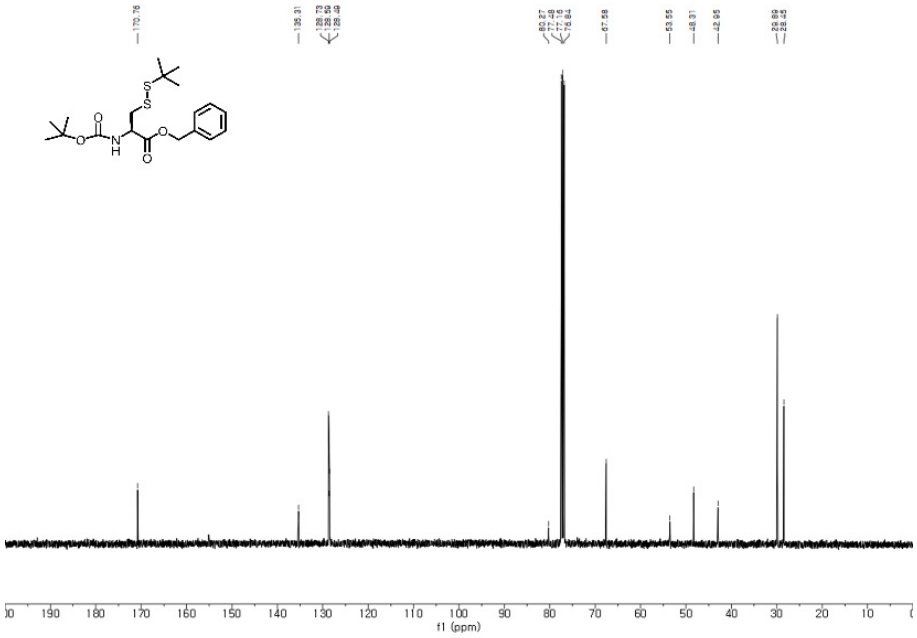


Figure S12.9. ^{13}C NMR spectrum (100 MHz, $CDCl_3$, 23 ˚C) of compound Boc -Cys(S*t*Bu)-OBn

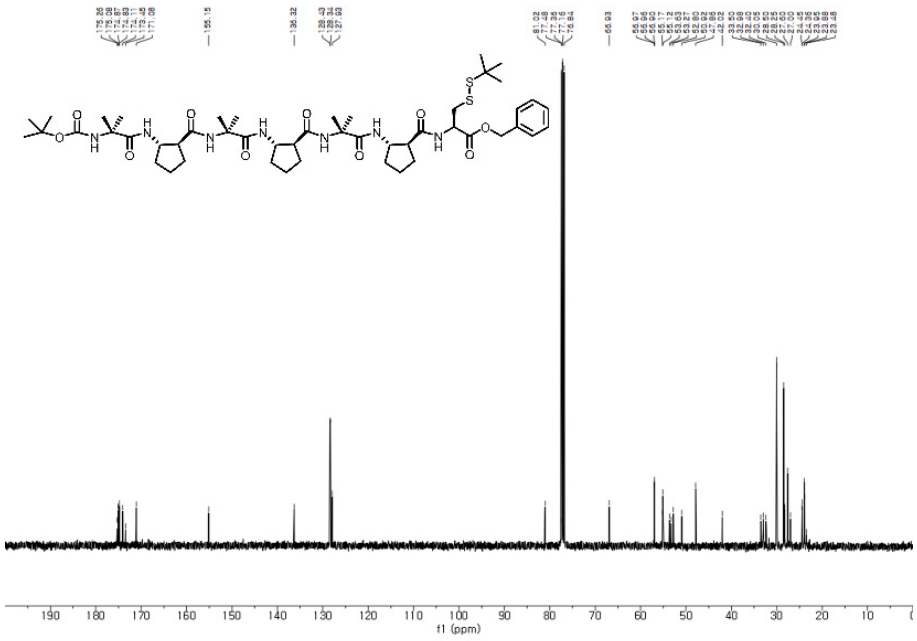


Figure S12.10. ^{13}C NMR spectrum (100 MHz, $CDCl_3$, 23 ˚C) of compound Boc-(Aib-ACPC)$_3$-Cys(S*t*Bu)-OBn (P_C(S*t*Bu))

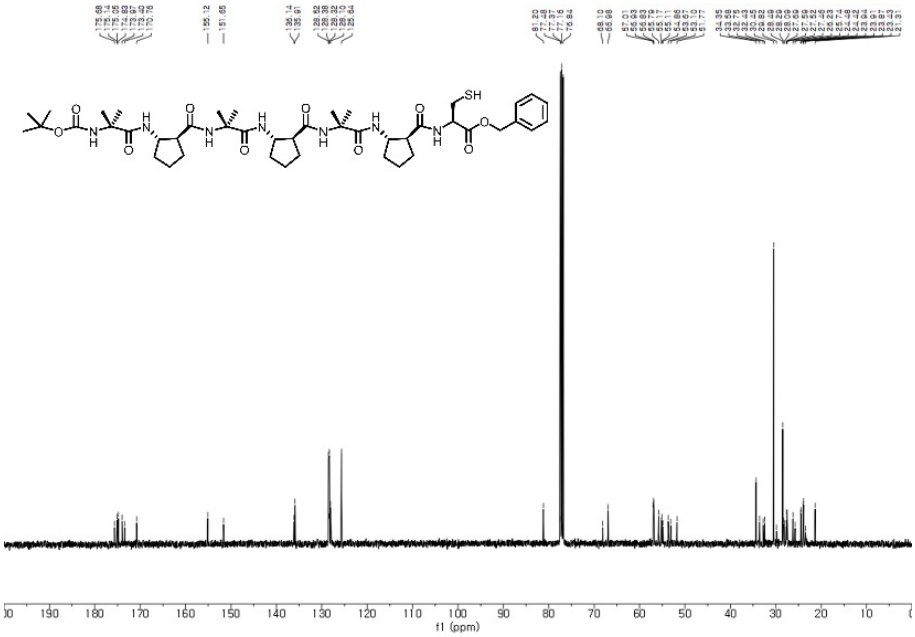


Figure S12.11. ^{13}C NMR spectrum (100 MHz, $CDCl_3$, 23 ˚C) of compound Boc-(Aib-ACPC)$_3$-Cys(SH)-OBn (**P$_C$**)

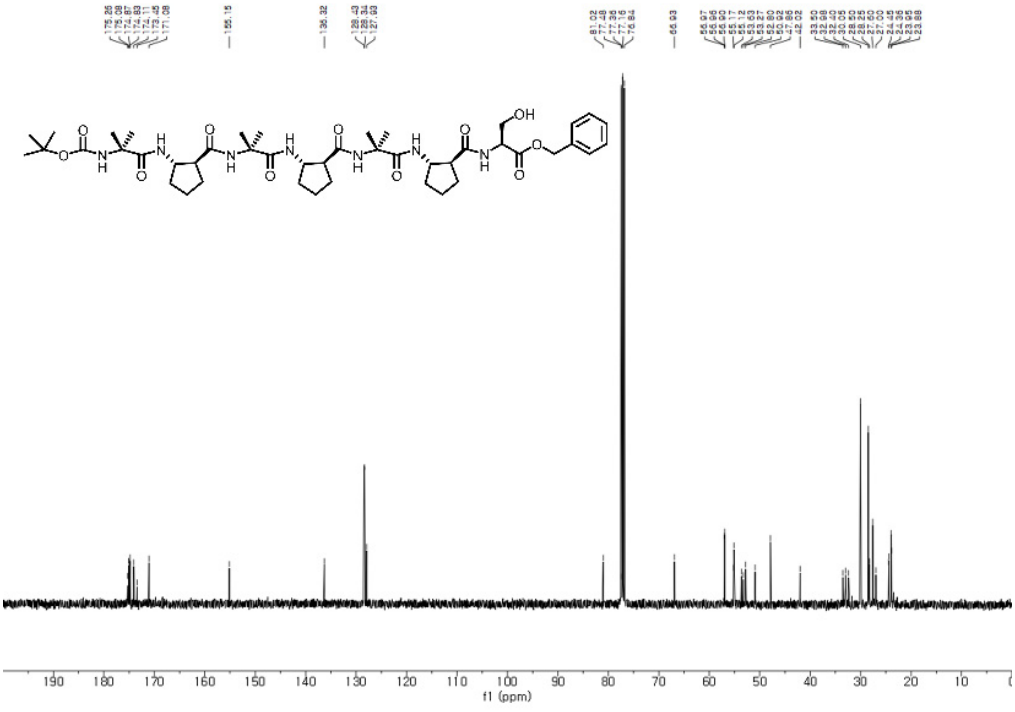


Figure S12.12. ^{13}C NMR spectrum (125 MHz, $CDCl_3$, 23 ˚C) of compound Boc-(Aib-ACPC)$_3$-Ser-OBn (**P$_S$**)

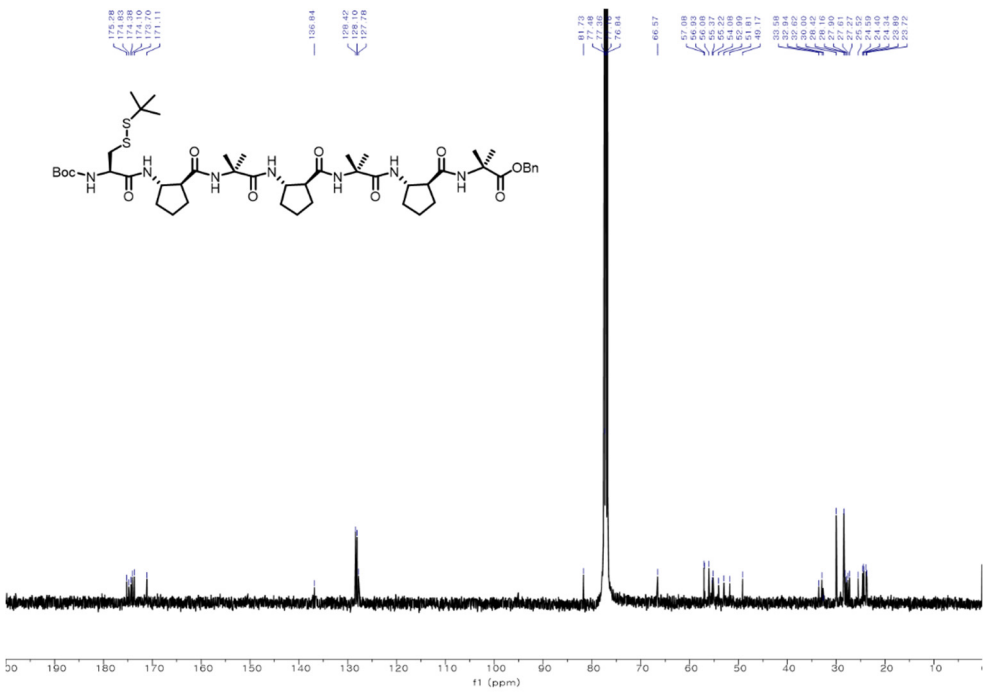


Figure S12.13. ^{13}C NMR spectrum (100 MHz, $CDCl_3$, 23 ˚C) of compound Boc–Cys(S*t*Bu)–(ACPC–Aib)$_3$–OBn (=1Cys(S*t*Bu))

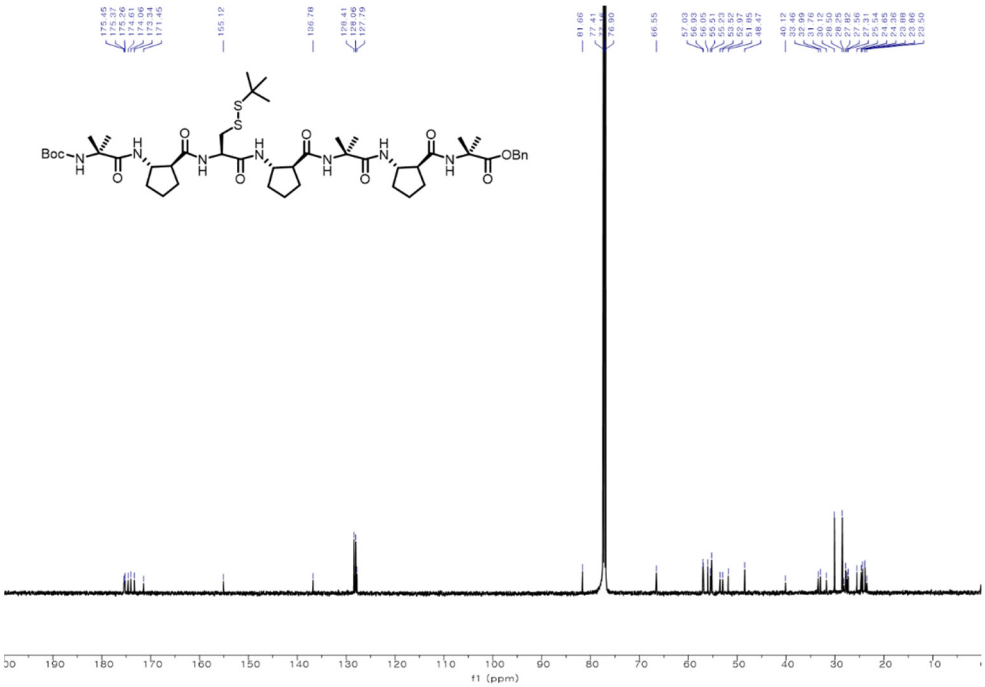


Figure S12.14. ^{13}C NMR spectrum (125 MHz, $CDCl_3$, 23 ˚C) of Boc–Aib–ACPC–Aib–Cys(S*t*Bu)–(ACPC–Aib)$_2$–OBn (=3Cys(StBu))

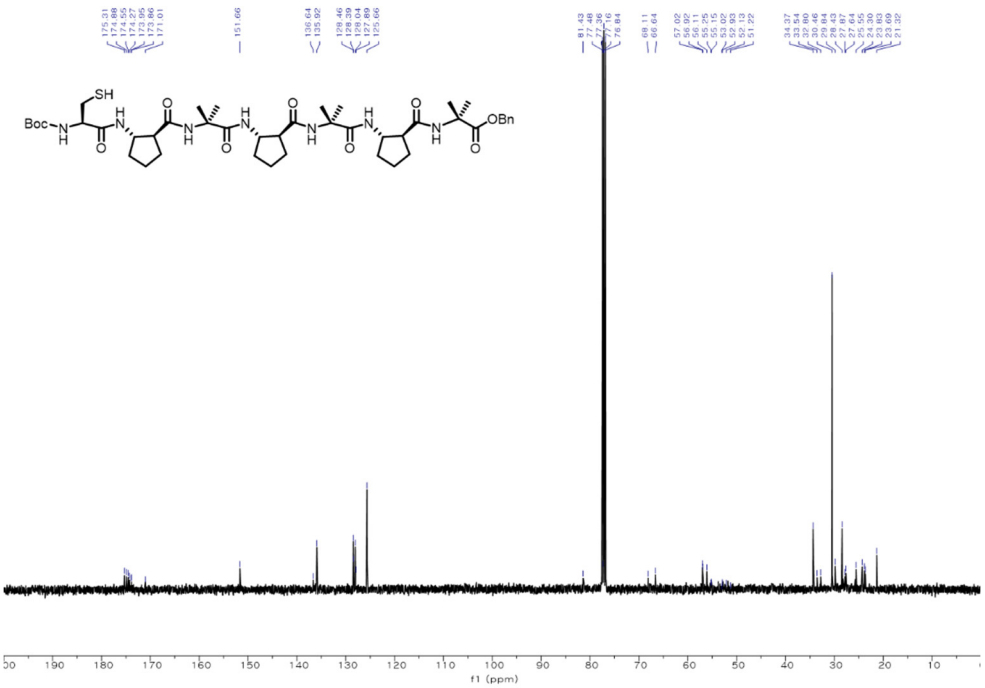


Figure S12.15. ^{13}C NMR spectrum (100 MHz, $CDCl_3$, 23 ˚C) of compound Boc–Cys(SH)–(ACPC–Aib)$_3$–OBn (=1Cys)

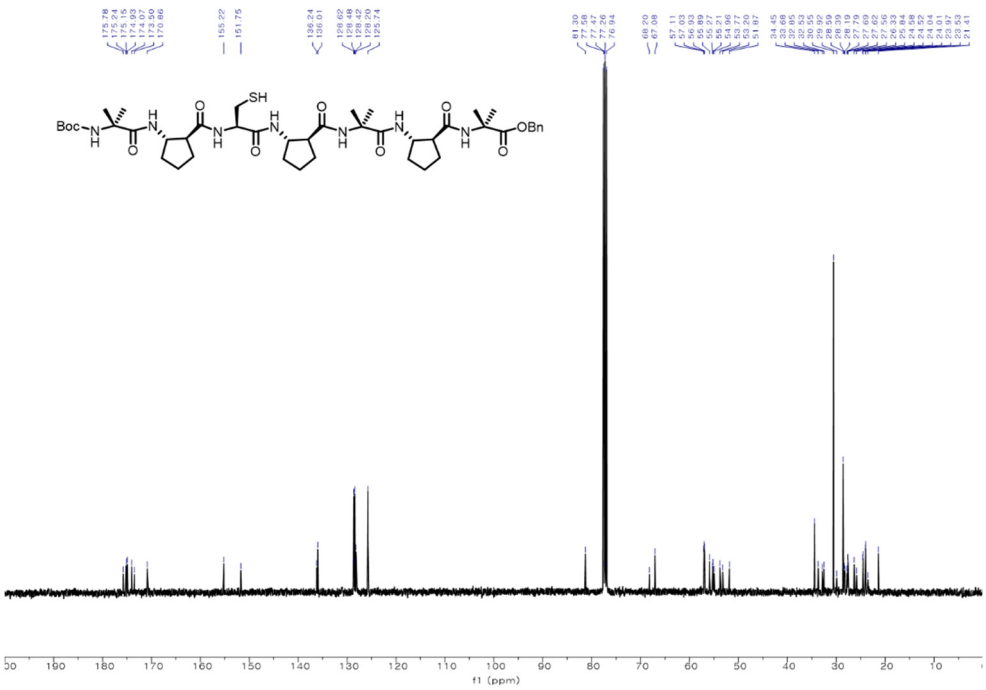


Figure S12.16. ^{13}C NMR spectrum (125 MHz, $CDCl_3$, 23 ˚C) of Boc–Aib–ACPC–Aib–Cys(SH)–(ACPC–Aib)$_2$–OBn (=3Cys)

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