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Helical Foldamer Containing a Combination of Cyclopentane-1,2-diamine and 2,2-Dimethylmalonic Acid

Norikazu Yamazaki,[†] Yosuke Demizu,*[,†] Yukiko Sato,[†] Mitsunobu Doi,[‡] and Masaaki Kurihara*[,†,§]

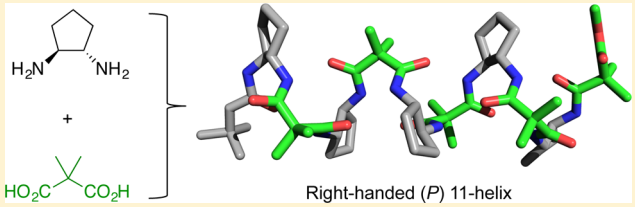
[†]Division of Organic Chemistry, National Institute of Health Sciences, Tokyo 158-8501, Japan

[‡]Osaka University of Pharmaceutical Sciences, Osaka 569-1094, Japan

[§]Graduate School of Bioscience and Biotechnology, Tokyo Institute of Technology, Yokohama 226-8501, Japan

Supporting Information

ABSTRACT: We have developed new helical oligomers using a combination of (1*S*,2*S*)-cyclopentane-1,2-diamine [(*S*,*S*)-CPDA] and 2,2-dimethylmalonic acid (DMM) residues as building blocks. In solution, the preferred secondary structure of the (*S*,*S*) tetramer **6** was a right-handed (*P*) helix, and that of the (*R*,*R*) tetramer *ent*-**6** was a left-handed (*M*) helix. In the crystalline state, both **6** and the (*S*,*S*) pentamer **7** folded into (*P*) 11-helices, and *ent*-**6** folded into an (*M*) 11-helix with hydrogen bonds that were oriented in alternating directions.



Helices are important in various fields, such as biology, chemistry, and medicinal chemistry. For instance, helical molecules are often found in numerous biopolymers, including DNA and proteins, and play important functions in living systems. Therefore, a variety of helical foldamers composed of rigidly locked molecules, such as α-peptides,[1] β-peptides,[2] γ-peptides,[3] aromatic amide oligomers,[4] urea-type oligomers,[5] and arene-based oligomers,[6] have been developed. In regard to peptide-based oligomers, the combined use of different types of amino acids (AAs) such as α-AAs and β-AAs has proved useful for designing peptides that fold into well-defined secondary structures.[7] In particular, α/β-peptides containing alternating α-AA/β-AA segments fold into 11- and 14/15-helices in solution and the crystalline state, respectively.[8] In addition to their novel structures, these α/β-peptides also exhibit unique biological activities.[9] Therefore, we speculated that novel folding oligomers that imitate α/β-peptides could be useful alternatives to biological α/β-peptides. Hence, we have designed novel oligomers that mimic α/β-peptides by replacing the β-AA residues with 1,2-diamine units and substituting the α-AA residues with malonic acid units.

We synthesized novel oligomers containing a combination of (1*S*,2*S*)-cyclopentane-1,2-diamine [(1*S*,2*S*)-CPDA], which is structurally similar to (1*S*,2*S*)-2-aminocyclopentanecarboxylic acid [(1*S*,2*S*)-ACPC], and 2,2-dimethylmalonic acid (DMM), which is structurally similar to 2-aminoisobutyric acid (Aib), and studied their preferred conformations in solution and the crystalline state. Figure 1 shows the α/β-peptides [Aib/(*S*,*S*)-ACPC-based peptides] reported by Gellman[10] and the (*S*,*S*)-CPDA/DMM-based oligomers designed by us.

The (*S*,*S*) oligomers **3**–**7** and the enantiomeric (*R*,*R*) tetramer *ent*-**6** were synthesized according to the conventional solution-phase method using *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride (EDC) as a coupling reagent (Scheme 1).[11]

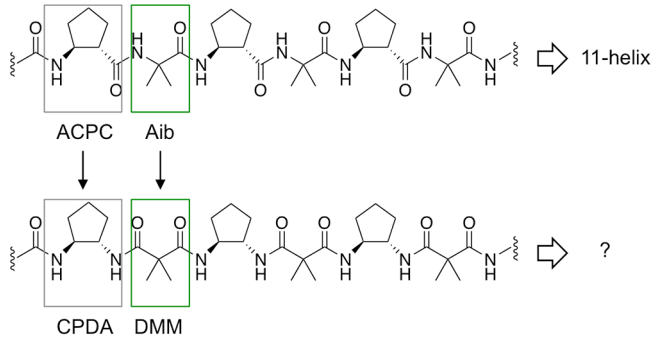


Figure 1. Chemical structures of the α/β-peptides reported by Gellman[10] and the novel folding oligomers composed of alternating (*S*,*S*)-CPDA and DMM residues.

The Fourier transform infrared (FT-IR) spectra of the (*S*,*S*) oligomers **3**–**7** were measured in the 3200–3500 cm^{-1} region (the amide-A NH stretching region) at a peptide concentration of 5.0 mM in $CDCl_3$ solution. In these spectra, the weak bands around 3430 cm^{-1} were assigned to free peptide NH groups and the strong bands at 3280–3320 cm^{-1} were assigned to peptide NH groups containing N–H···O=C intramolecular hydrogen bonds of different strengths.[12] As the length of the peptide chain increased, the wavenumber of the strong band observed at 3320 cm^{-1} in dimer **4** decreased (3280 cm^{-1} in pentamer **7**). Furthermore, the relative intensities of the bands in the 3280–3320 cm^{-1} region gradually increased (Figure 2).

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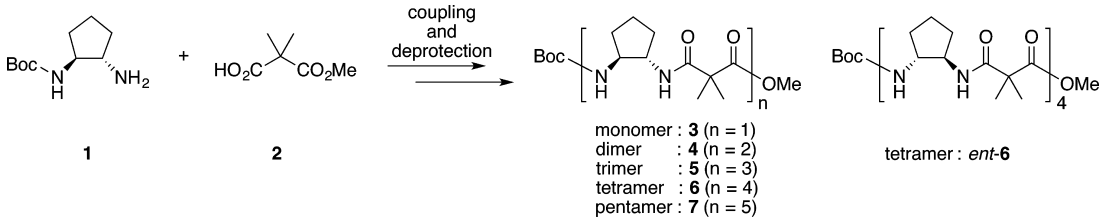
Scheme 1. Synthesis of the (*S*,*S*) Oligomers 3−7 and the Enantiomeric (*R*,*R*) Tetramer *ent*-6



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These IR spectra are similar to those of AA-based helical peptides in solution.[12]

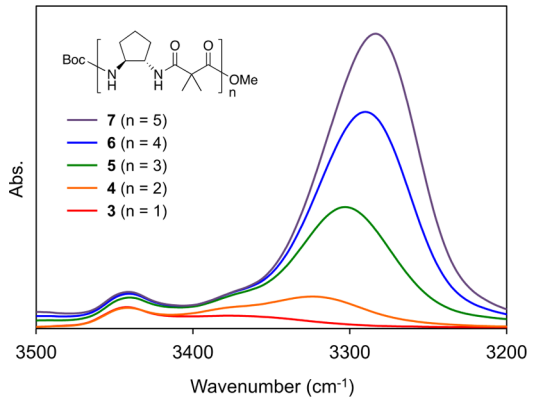

Figure 2. IR spectra of the (*S*,*S*) oligomers **3**−**7** in $CDCl_3$ solution (peptide concentration: 5.0 mM).

To obtain information about the helical screw senses of the synthetic oligomers, the circular dichroism (CD) spectra of the (*S*,*S*) tetramer **6** and the (*R*,*R*) tetramer *ent*-**6** were measured at a peptide concentration of 0.1 mM in 2,2,2-trifluoroethanol (TFE) solution. The spectrum of **6** showed a negative maximum at around 207 nm, which is similar to the negative maxima seen in the spectra of α/β-peptides that form right-handed (*P*) helical structures (Figure 3).[13] This right-handed screw sense was induced by the chirality of the (*S*,*S*)-CPDA residue. On the other hand, *ent*-**6** naturally formed a left-handed (*M*) helix, resulting in a positive peak at around 207 nm.

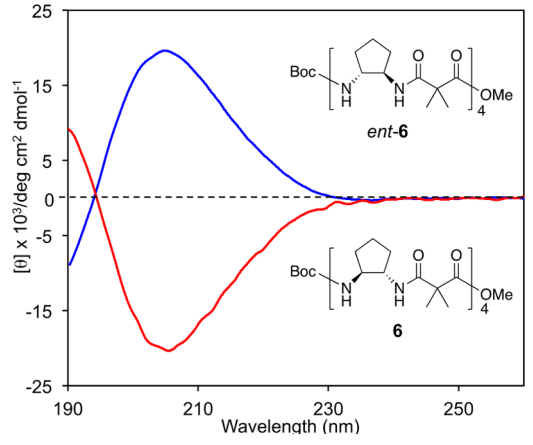

Figure 3. The 190−260 nm regions of the CD spectra of the (*S*,*S*) tetramer **6** (red) and the (*R*,*R*) tetramer *ent*-**6** (blue) (peptide concentrations: 0.1 mM in TFE solution).

The (*S*,*S*) tetramer **6**, the (*R*,*R*) tetramer *ent*-**6**, and the (*S*,*S*) pentamer **7** all formed crystals suitable for X-ray crystallographic analysis after the slow evaporation of the relevant solvent (1,2-dichloroethane for **6**, $CHCl_3$/*n*-hexane for **7**, and CH_2Cl_2/*n*-hexane for *ent*-**6**) at room temperature. Their structures were solved by direct methods using SHELXS 97[14] and expanded with the Fourier technique.[15] Selected backbone and side-chain torsion angles and intra- and intermolecular hydrogen-bond parameters are listed in the Supporting Information.[11,16]

The structure of **6** was solved with the space group *P*21. It forms a right-handed (*P*) 11-helix, as do Aib/(*S*,*S*)-ACPC-based peptides (Figure 4).[10] However, **6** exhibits a different

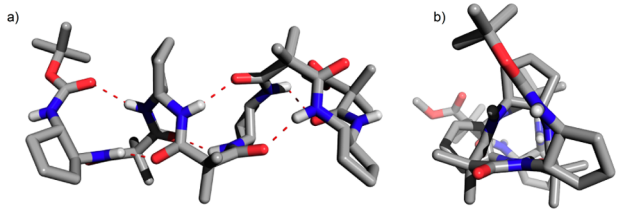

Figure 4. X-ray diffraction structure of **6** as viewed (a) perpendicular to the helical axis and (b) along the helical axis. Intramolecular hydrogen bonds are indicated by the red dashed lines.

hydrogen-bonding pattern from Aib/(*S*,*S*)-ACPC-based peptides: Aib/(*S*,*S*)-ACPC-based peptides possess *i*, *i* + 3 type C═O···H−N hydrogen bonds in their 11-atom rings (Figure 5a), whereas the hydrogen bonds in the 11-atom rings of the (*S*,*S*)-CPDA/DMM-based tetramer **6** are arranged in alternating directions, as indicated by the black and red arrows in Figure 5b. Figure 5c shows the overlaid structures of the tetramer **6** fragment [from DMM(1) to CPDA(4)] and the Aib/(*S*,*S*)-ACPC-based octamer fragment [from Aib(1) to ACPC(6), CCDC 273778].[8a] The main-chain conformations of the two are well-matched, but there are differences in the conformations of their side chains. In packing mode, **6** is connected by intermolecular hydrogen bonds arranged in a head-to-tail manner.

The (*S*,*S*) pentamer **7** also formed a right-handed (*P*) 11-helix, with each pentamer unit bound to three $CHCl_3$ molecules (Figure 6). The hydrogen-bonding patterns were the same as those of the tetramer **6**. On the other hand, a left-handed (*M*) 11-helical structure was present in the asymmetric unit of the (*R*,*R*) tetramer *ent*-**6**. The detailed crystallographic data for *ent*-**6** are summarized in the Supporting Information.

MacroModel and the OPLS_2005 force field were used to calculate the global minimum-energy conformation of **6**, and the calculated structure was similar to the conformer of **6** seen in the crystalline state.[11]

In summary, we have designed and synthesized new α/β-peptide-mimicking oligomers, (*S*,*S*)-CPDA/DMM-based

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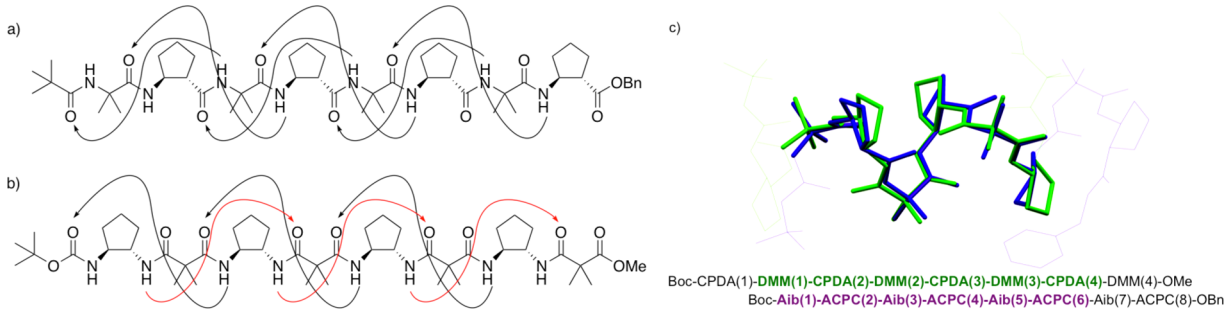

Figure 5. Intramolecular hydrogen-bonding patterns of (a) an Aib/(*S*,*S*)-ACPC-based peptide and (b) (*S*,*S*)-CPDA/DMM-based tetramer **6**. The arrows indicate hydrogen-bonding interactions. (c) Overlay of the structures of the (*S*,*S*)-CPDA/DMM-based tetramer **6** [from DMM(1) to CPDA(4), green] and the Aib/(*S*,*S*)-ACPC-based octamer [from Aib(1) to ACPC(6), purple].

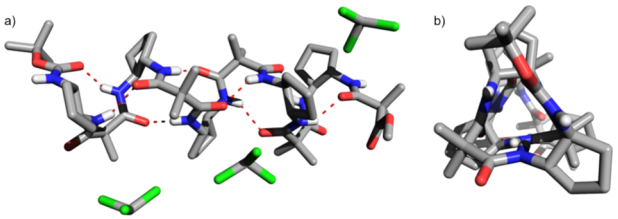

Figure 6. X-ray diffraction structure of **7** as viewed (a) perpendicular to the helical axis and (b) along the helical axis. Intramolecular hydrogen bonds are indicated by the red dashed lines.

oligomers, which contain a combination of (*S*,*S*)-CPDA and DMM residues, and we have investigated their preferred conformations in solution and in the crystalline state. The (*S*,*S*) oligomers predominantly fold into right-handed (*P*) helical structures in solution. In the crystalline state, (*P*) 11-helices are present in the (*S*,*S*) tetramer **6** and the pentamer **7**, and an (*M*) 11-helical structure was detected in the (*R*,*R*) tetramer *ent*-**6**. The right-handed screw sense of the (*S*,*S*)-CPDA/DMM-based oligomers is induced by their (*S*,*S*)-CPDA residues, indicating that (*S*,*S*)-CPDA generates the same screw sense as (1*S*,2*S*)-ACPC. Although the 11-helical structures of the CPDA/DMM-based oligomers are similar to those seen in Aib/ACPC-based peptides, differences between the hydrogen-bonding patterns of the two types of oligomer were observed. Namely, the hydrogen bonds in the 11-atom rings in the Aib/ACPC-based peptides' 11-helices are all oriented in the same direction, whereas the hydrogen bonds in the 11-atom rings of the CPDA/DMM-based oligomers' 11-helices are arranged in alternating directions. The alternating directions of the above-mentioned hydrogen bonds results from the alternating directions of the amide bonds in the CPDA/DMM-based oligomers. Therefore, their dipole moments should differ from those of AA-based peptides, and we hope to investigate their physicochemical properties in the future. The novel α/β-peptide-mimicking folding oligomers described in this study are expected to be valuable for the design of foldamer scaffolds and as new peptide materials.

EXPERIMENTAL SECTION

Synthesis of Monomer 3. A mixture of EDC (2.95 g, 15.4 mmol), 1-hydroxybenzotriazole (HOBt, 2.1 g, 15.4 mmol), amine **1** (765 mg, 3.8 mmol), and carboxylic acid **2** (2.3 g, 15.4 mmol) in DMF (35 mL) was stirred at rt for 3 days. CH_2Cl_2 was added into the solution, which was then washed with 3% aqueous HCl, 5% aqueous $NaHCO_3$, and brine and dried over $MgSO_4$. After removal of the solvent, the residue was purified by column chromatography on silica gel (2:1 *n*-hexane/EtOAc) to give monomer **3** (1.15 g, 92%) as colorless crystals. Mp: 113−115 °C. $[\alpha]_D^{24} = -17.0$ (*c* 1.0, $CHCl_3$). IR ($CDCl_3$, cm^{-1}): 3444, 2956, 2931, 2873, 1723, 1703, 1664. ^1H NMR (400 MHz, $CDCl_3$): δ 7.00 (br s, 1H), 4.74 (br s, 1H), 3.75 (br, 2H), 3.73 (s, 3H), 2.07−2.30 (m, 2H), 1.69−1.74 (m, 2H), 1.57 (s, 3H), 1.27−1.44 (m, 14H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.9, 173.1, 156.8, 79.7, 58.4, 56.7, 52.7, 50.2, 29.9, 29.3, 28.5, 23.7, 23.4, 19.7. HR-ESI(+)-TOF MS *m*/*z*: calcd for $C_{16}H_{28}N_2O_5Na$ $[M + Na]^+$, 351.1896; found, 351.1894.

Synthesis of Dimer 4. A solution of monomer **3** (280 mg, 0.85 mmol) and 1 M aqueous NaOH (2.5 mL, 2.5 mmol) in MeOH (6 mL) was stirred at room temperature for 20 h. The solution was then neutralized with 1 M aqueous HCl, and MeOH was evaporated. The aqueous solution was extracted with EtOAc and dried over Na_2SO_4. Removal of the solvent afforded the monomer carboxylic acid as colorless crystals, which were used for the next reaction without further purification. Trifluoroacetic acid (1 mL) was added to a solution of monomer **3** in CH_2Cl_2 (6 mL) at 0 °C, and the whole was stirred at room temperature for 2 h. Removal of the solvent afforded a crude N-terminal-free monomer, which was used without further purification. A mixture of EDC (613 mg, 3.2 mmol), HOBt (414 mg, 3.1 mmol), *N*,*N*-diisopropylethylamine (DIPEA, 656 μL, 3.9 mmol), and the above amine and carboxylic acid in CH_2Cl_2 (16 mL) and DMF (4 mL) was stirred at rt for 3 days. The solution was washed with 3% aqueous HCl, 5% aqueous $NaHCO_3$, and brine and then dried over $MgSO_4$. After removal of the solvent, the residue was purified by column chromatography on silica gel (1:1 *n*-hexane/EtOAc) to give dimer **4** (521 mg, 79%). Mp: 175−176 °C. $[\alpha]_D^{24} = -59.5$ (*c* 1.0, $CHCl_3$). IR ($CDCl_3$, cm^{-1}): 3443, 3327, 2976, 2878, 1697, 1664. ^1H NMR (400 MHz, $CDCl_3$): δ 7.44 (br s, 1H), 7.11 (br s, 1H), 6.80 (br s, 1H), 4.74 (d, J = 7.6 Hz, 1H), 4.04−4.11 (m, 2H), 3.91−3.97 (m, 2H), 3.75 (s, 3H), 2.02−2.20 (m, 4H), 1.68−1.77 (m, 4H), 1.56 (s, 9H), 1.35−1.45 (m, 16H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.3, 174.9, 174.6, 173.0, 156.7, 79.7, 57.9, 57.7, 57.3, 56.3, 52.9, 50.2, 50.1, 30.2, 30.1, 29.6, 28.8, 28.6, 24.9, 24.7, 23.7, 20.3. HR-ESI(+)-TOF MS *m*/*z*: calcd for $C_{26}H_{44}N_4O_7Na$ $[M + Na]^+$, 547.3108; found, 547.3111.

Synthesis of Trimer 5. Trimer **5** was prepared using a method similar to that described for the preparation of **4**. Colorless crystals, 93% yield. Mp: 181−183 °C. $[\alpha]_D^{24} = -103.1$ (*c* 1.0, $CHCl_3$). IR ($CDCl_3$, cm^{-1}): 3443, 3302, 2976, 2937, 2878, 1698, 1666, 1633. ^1H NMR (400 MHz, $CDCl_3$): δ 7.65 (br s, 1H), 7.64 (br s, 1H), 7.44 (d, J = 8.4 Hz, 1H), 7.08 (d, J = 8.0 Hz, 1H), 6.61 (d, J = 7.6 Hz, 1H), 4.71 (d, J = 8.8 Hz, 1H), 3.97−4.40 (m, 6H), 3.76 (s, 3H), 1.68−2.17 (m, 14H), 1.59 (s, 6H), 1.26−1.44 (m, 25H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.5, 175.4, 175.2, 174.5, 174.0, 172.8, 156.7, 79.5, 57.8, 57.4, 57.3, 57.2, 56.5, 52.9, 50.8, 50.7, 50.2, 30.8, 30.3, 29.3, 29.2, 29.1, 28.6, 28.4, 25.3, 25.2, 25.1, 25.0, 23.9, 23.7, 21.0, 20.5, 20.4. HR-ESI(+)-TOF MS *m*/*z*: calcd for $C_{36}H_{60}N_6O_9Na$ $[M + Na]^+$, 743.4319; found, 743.4322.

Synthesis of Tetramer 6. Tetramer **6** was prepared using a method similar to that described for the preparation of **4**. Colorless crystals, 78% yield. Mp: 204−205 °C. $[\alpha]_D^{24} = -109.5$ (*c* 1.0, $CHCl_3$). IR ($CDCl_3$, cm^{-1}): 3443, 3289, 2976, 2936, 2878, 1698, 1666, 1630.

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^{1}H NMR (400 MHz, $CDCl_3$): δ 7.93 (d, J = 8.4 Hz, 1H), 7.87 (d, J = 7.6 Hz, 1H), 7.79 (d, J = 8.4 Hz, 1H), 7.74 (d, J = 8.4 Hz, 1H), 7.46 (d, J = 8.4 Hz, 1H), 7.06 (d, J = 8.0 Hz, 1H), 6.61 (d, J = 8.0 Hz, 1H), 4.73 (d, J = 9.2 Hz, 1H), 3.98−4.44 (m, 8H), 3.76 (s, 3H), 1.70−2.14 (m, 21H), 1.23−1.48 (m, 36H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.7, 175.6, 175.3, 175.2, 174.6, 172.8, 156.7, 79.5, 57.9, 57.5, 57.4, 56.5, 53.0, 51.0, 50.9, 50.8, 50.2, 30.9, 30.4, 29.3, 29.2, 29.1, 29.0, 28.8, 28.7, 28.4, 25.4, 25.3, 25.2, 25.1, 25.0, 23.9, 23.7, 21.1, 21.0, 20.6, 20.5. HR-ESI(+)-TOF MS m/z: calcd for $C_{46}H_{76}N_8O_{11}Na$ $[M + Na]^+$, 939.5531; found, 939.5526.

Synthesis of Pentamer 7. Pentamer **7** was prepared using a method similar to that described for the preparation of **4**. Colorless crystals; 65% yield. Mp: 272−273 °C. $[\alpha]_D^{24}$ = −103.4 (c 1.0, $CHCl_3$). IR ($CDCl_3$, cm^{-1}): 3443, 3283, 2977, 2937, 2878, 1698, 1665, 1628. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.03 (d, J = 8.0 Hz, 1H), 8.01 (d, J = 8.0 Hz, 1H), 7.95 (d, J = 7.6 Hz, 1H), 7.91 (d, J = 7.6 Hz, 1H), 7.81 (d, J = 8.4 Hz, 1H), 7.77 (d, J = 8.4 Hz, 1H), 7.46 (d, J = 8.8 Hz, 1H), 7.04 (d, J = 8.0 Hz, 1H), 6.61 (d, J = 7.6 Hz, 1H), 4.72 (d, J = 9.2 Hz, 1H), 4.01−4.46 (m, 10H), 3.70 (s, 3H), 1.69−2.17 (m, 26H), 1.24−1.61 (m, 43H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.7, 175.6, 175.4, 175.3, 175.2, 175.2, 174.6, 174.0, 172.8, 156.7, 79.5, 57.9, 57.5, 57.4, 56.5, 53.0, 51.0, 50.9, 50.8, 50.2, 30.9, 30.4, 29.9, 29.3, 29.2, 29.1, 28.8, 28.7, 28.4, 25.5, 25.4, 25.3, 25.2, 25.1, 25.0, 24.0, 23.7, 21.1, 21.0, 20.6, 20.5. HR-ESI(+)-TOF MS m/z: calcd for $C_{56}H_{92}N_{10}O_{13}Na$ $[M + Na]^+$, 1135.6743; found, 1135.6743.

Synthesis of Tetramer *ent*-6. The tetramer *ent*-**6** was prepared using a method similar to that described for the preparation of **6**. Colorless crystals. Mp: 204−205 °C. $[\alpha]_D^{24}$ = +109.4 (c 1.0, $CHCl_3$).

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Crystallographic data (CIF) and copies of the ^{1}H NMR and ^{13}C NMR spectra of the oligomers. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Authors

*Tel: + 81-3-3700-1141. Fax: + 81-3-3707-6950. E-mail: demizu@nihs.go.jp.

*E-mail: masaaki@nihs.go.jp.

Notes

The authors declare no competing financial interest.

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