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# Synthesis and helical properties of aromatic multilayered oligoureas

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ABSTRACT

Several aromatic multilayered oligoureas with different chain lengths and different numbers of chiral *N*-substituents were synthesized, and their helical conformation and induced handedness were examined by means of CD spectroscopy. Introduction of one chiral *N*-substituent is enough to induce handedness, and all the oligoureas examined exist predominantly as helical structures with all-*S* axial chirality. The hexaureas **6** and **7** had similar CD intensity to the tetraureas **4** and **5**, and had larger CD intensity than diurea **8**. The results indicate that the effect of a chiral *N*-substituent at the central benzene ring in inducing well-ordered handedness at the terminal positions of hexaureas **6** and **7** is relatively weak, even though these compounds mainly take the form of aromatic multilayered foldamers.



## 1. Introduction

A foldamer is a functional oligomer whose conformation generally changes dynamically between random states and a well-ordered three-dimensional structure stabilized by noncovalent interactions.[1] Various synthetic foldamers have been synthesized, and their conformational behaviors have been examined. Helicity is one of the most attractive features of foldamers, since the helix is a key structural motif in nature; for example, the double helix of DNA[2] and the α-helical structure of proteins.[3] In addition to stable helical structures with a rigid backbone, helical structures that exhibit dynamic behavior have recently been attracting much attention because of the possibility of controlling the helical handedness.[4] Induction of handedness in helical foldamers has been achieved by the introduction of chiral side chains or the addition of chiral components that interact with helical foldamers.[4–7] The dynamic behaviors of the induced handedness can be investigated by means of $^1$H NMR and CD spectroscopy in solution, and the absolute helical structure can be determined by X-ray crystallography[8] and in some cases by theoretical analysis of the CD spectra.[9]

Construction of helicity requires a folded-type monomer unit. Previously, we reported that *N*,*N*′-dimethylation of *N*,*N*′-diphenylurea (**1**) with (trans, trans) conformation generated the folded (cis, cis) conformation of **2** bearing two phenyl groups in a face-to-face orientation (Fig. 1a).[10,11] Thus, aromatic multilayered structures can be constructed by connection of aromatic rings consecutively through

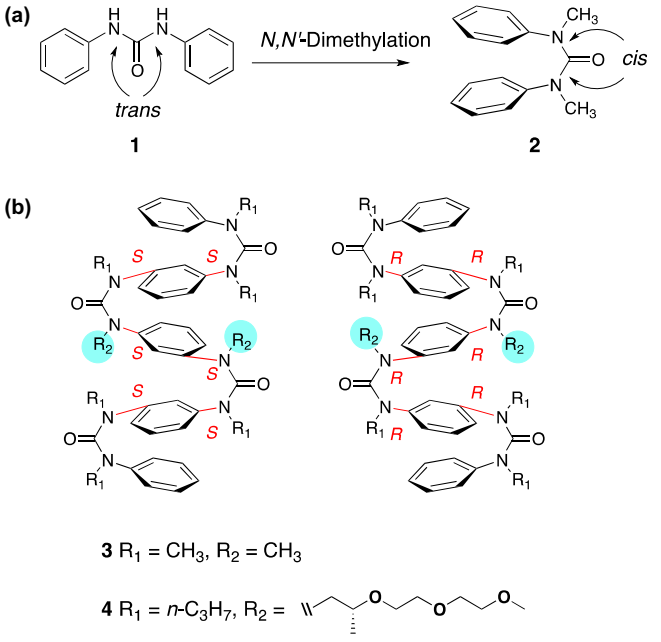


**Fig. 1.** (a) Conformational alteration of aromatic ureas by *N*,*N*′-dimethylation. (b) Helical oligoureas with aromatic multilayered structures.

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*N*,*N*′-dimethylurea bonds.[11–13] When the phenyl rings of the oligoureas are linked at the *meta* position, the oligomers **3** show well-ordered helical structure with all-*R* or all-*S* axial chirality of the phenyl–urea bonds in the crystal (Fig. 1b).[14–16] In the crystal, the enantiomeric helices exist in a 1/1 ratio, while the equilibrium between the enantiomers is very fast in solution. Clayden et al. employed an NMR technique using chiral or prochiral probes introduced at the terminal of the oligoureas to detect the chirality of the backbone.[17–19] Recently, we determined the absolute structure of oligourea **4** with chiral *N*-substituents by means of empirical and theoretical studies of the CD and VCD spectra.[15] However, the dynamic behavior of helical oligoureas remains unclear. In this study, several oligoureas with different chain lengths and different numbers of chiral *N*-substituents were designed and synthesized in order to clarify the effects of these parameters on the induction of handedness.

## 2. Results and discussion

### 2.1. Synthesis of oligoureas

In order to clarify the effect of the number of chiral substituents and the chain length on the dynamic helical properties of the oligoureas, compounds **5**–**8** were designed and synthesized (Fig. 2). Compound **5** is an analog of **4** bearing one chiral *N*-2-(methoxyethoxyethoxy)propyl group. Compounds **6** and **7** are longer oligomers with six urea bonds and two chiral groups or one, respectively, and compound **8** is a shorter oligomer with two urea bonds and one chiral group. Since the longer oligomers have poor solubility in organic solvents, *N*-*n*-pentyl groups were introduced in the compound **6** to improve the solubility.

The longer oligourea **6** was synthesized as shown in Scheme 2. The coupling reaction of *m*-nitroaniline with phenyl isocyanate afforded diarylurea **17**. After hydrogenation over Pd–C, compound **18** was reacted with *m*-nitrophenyl isocyanate to give diurea **19**. Introduction of *N*-*n*-pentylation at all urea nitrogen atoms of **19** by using sodium hydride as a base, followed by hydrogenation, afforded amine **21**. After conversion of **21** into the isocyanate by treatment with triphosgene, the isocyanate was reacted with (*R*, *R*)-*N*,*N*′-bis[2-(methoxyethoxyethoxy)propyl]-*m*-phenylenediamine (**22**)[15] to give **23**. The hexaurea **6** was obtained by *N*-*n*-pentylation at the two nitrogen atoms of **23**.

The unsymmetrical hexaurea **7** was synthesized as shown in Scheme 3. Coupling of *m*-nitrophenyl isocyanate with diamine **14** bearing a chiral *N*-substituent gave **24**. Introduction of *N*-*n*-propyl groups at the two urea nitrogen atoms, followed by hydrogenation of the nitro groups, afforded diamine **26**. Compound **26** was reacted with the isocyanate, prepared from **15** and triphosgene, followed by *N*-*n*-propylation, to give hexaurea **7**.

The shorter diurea **8** was synthesized by the coupling reaction of diamine **14** bearing a chiral *N*-substituent with phenyl isocyanate, followed by *N*-*n*-propylation (Scheme 4).

The conformation of the oligoureas in solution was examined by means of $^1$H NMR spectroscopy. The signals of the aromatic protons of **5**–**8** in $CDCl_3$ were detected at higher field (6.9–6.1 ppm), like those of **3** and **4**.[15] Thus, the $^1$H NMR spectra suggested that the oligomers synthesized here exist predominantly in aromatic multilayered form with all-*cis* urea bonds in $CDCl_3$, although the precise conformations, including the distinguishment of diastereomeric helical structures, could not be identified even at low temperature due to their rapid dynamic behavior.[21]

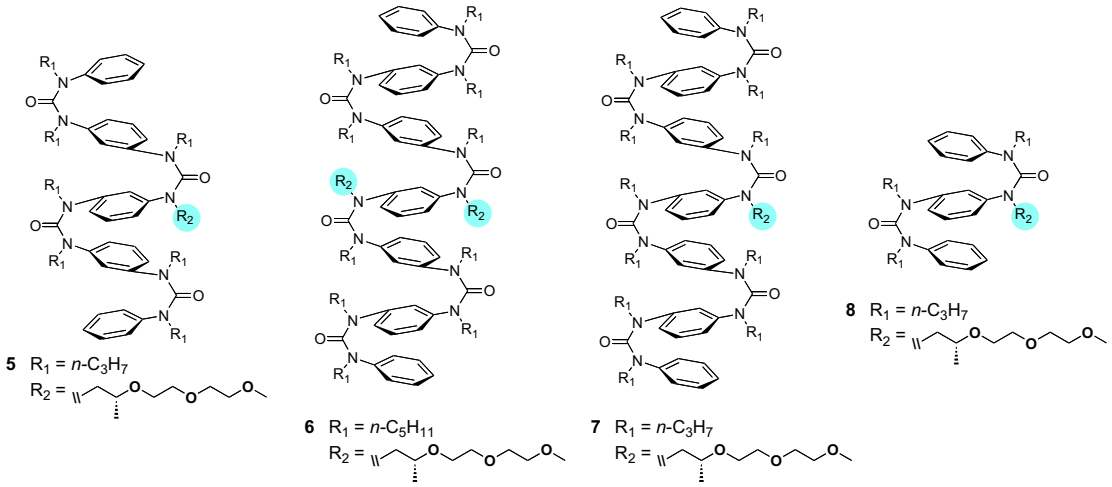
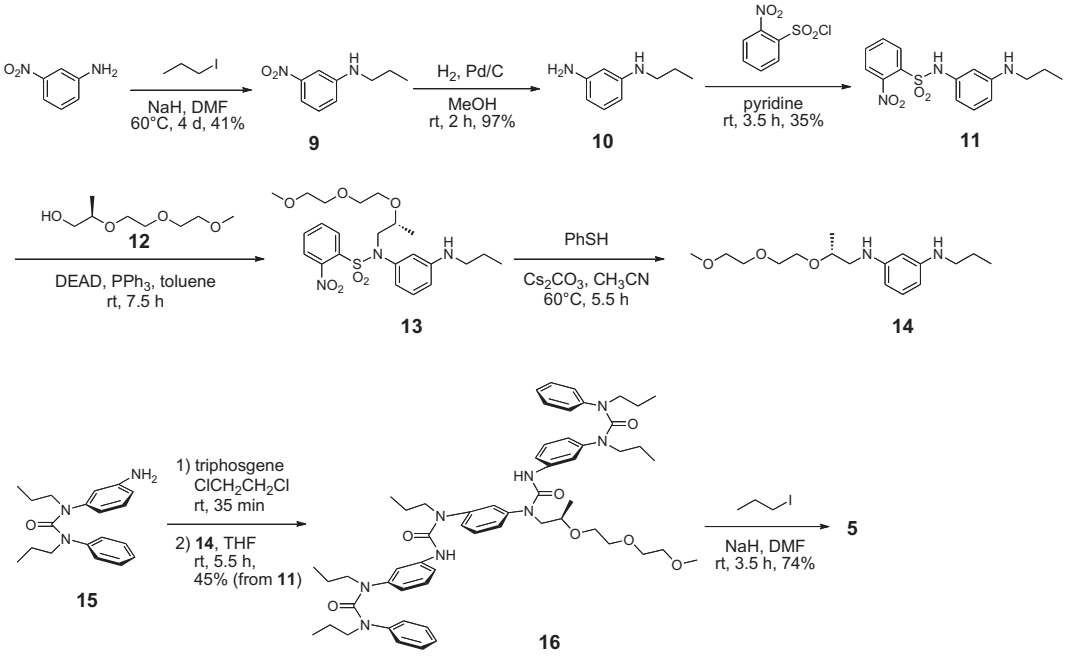



**Fig. 2.** Structures of synthesized oligoureas with various chain lengths.

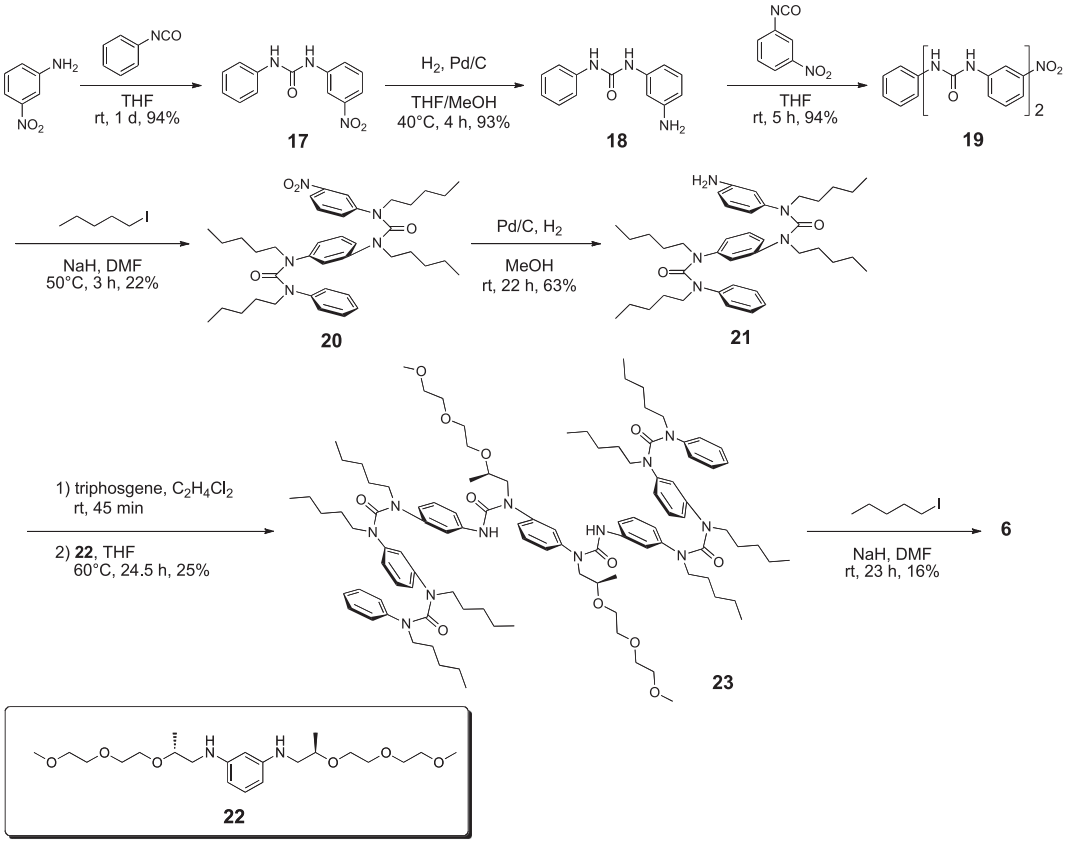
The synthetic route to unsymmetrical tetraurea **5** bearing one chiral substituent is shown in Scheme 1. Mono-*n*-propylation of *m*-nitroaniline, followed by hydrogenation afforded compound **10**. The chiral *N*-substituent was introduced by means of Fukuyama's nosyl methodology.[20] Compound **10** was treated with *o*-nitrobenzenesulfonyl chloride (NsCl) to give **11**. Alkylation of **11** under Mitsunobu conditions with chiral *R*-2-(methoxyethoxyethoxy) propanol (**12**)[15] afforded **13**. Removal of the *o*-nitrobenzenesulfonyl group was performed by treatment with benzenethiol and cesium carbonate to give diamine **14**. Coupling of diamine **14** with the isocyanate, prepared from compound **15**, afforded tetraurea **16** in 45% yield from **11**. Finally, introduction of *N*-*n*-propyl groups gave tetraurea **5**.

### 2.2. UV and CD spectra of oligoureas

UV and CD spectra of the oligoureas were analyzed in acetonitrile (Fig. 3). CD intensity was represented by ellipticity at the concentration at which the absorption at $\lambda_{max}$ of the UV spectra was 1. The UV and CD spectra of **4** were compared with those of the synthesized analogs **5**–**8**. In the UV spectra, broad electronic absorption was observed in the 190–220 and 230–310 nm regions in every case. In the CD spectra, very weak negative signals at 270–290 nm and strong positive signals at 200–270 nm were detected for every oligomer. The spectra were temperature-dependent, but not time-dependent. The UV and CD spectra of **5**–**8** were very similar to those of **4**, and therefore these oligoureas



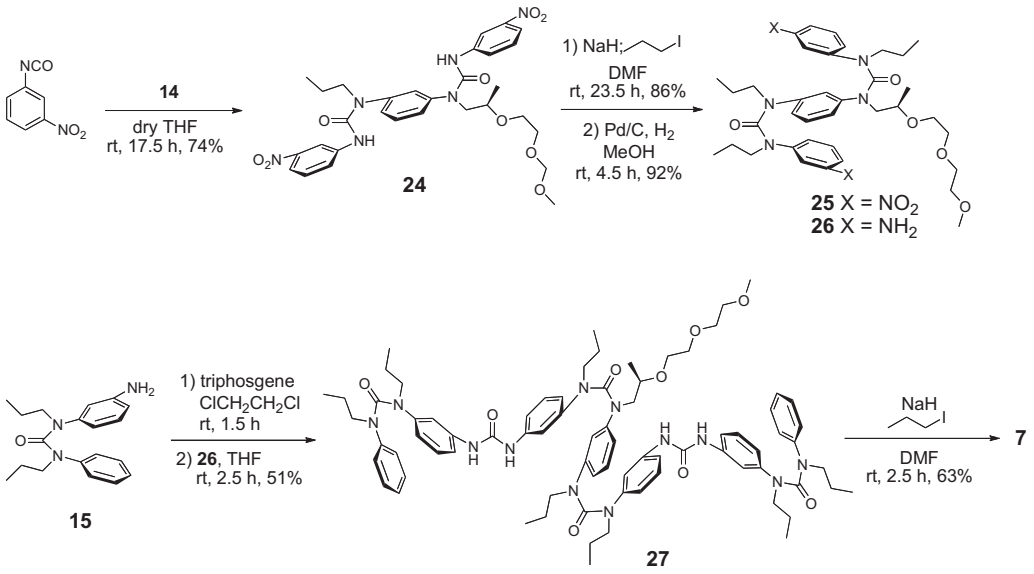

**Scheme 1.** Synthesis of **5**.



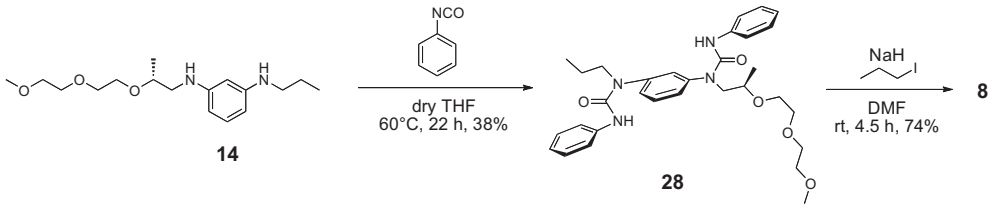

**Scheme 2.** Synthesis of **6**.

are considered to exist predominantly as a helical aromatic multilayered structure with all-*S* axial chirality.

The tetraurea **5** bearing only one chiral *N*-substituent showed similar CD intensity at each temperature to the tetraurea **4** bearing two chiral *N*-substituents. A similar tendency was observed with hexaureas **6** and **7**. Therefore, one chiral *N*-substituent is enough to induce handedness, and the second chiral *N*-substituent at the same phenylenediamine moiety seems to be relatively unimportant. This is reasonable, in view of the (cis, cis) conformational preference of the *N*,*N*′-dimethylurea bond and the anti




**Scheme 3.** Synthesis of **7**.




**Scheme 4.** Synthesis of **8**.

conformation between adjacent urea groups. Comparison of the oligomers with different chain lengths showed that tetraurea **5** had a larger CD intensity than diurea **8** at each temperature, while hexaurea **7** had a similar CD intensity to the tetraurea **5**. The situation was similar for hexaurea **6** and tetraurea **4** with two chiral *N*-substituents. These results indicate that the effect of a chiral *N*-substituent at the central benzene ring in inducing well-ordered handedness at the terminal positions of hexaureas **6** and **7** is relatively weak. Clayden et al. conducted a $^1$H NMR study of oligoureas bearing a chiral probe at the terminal phenyl ring, and suggested that the diastereotopic probe could distinguish prochirality separated by about 24 bond lengths (corresponding to the tetraureas), which is consistent with the results of our CD spectral study. Dynamic helical features of the hexaurea **6** were next examined by measuring the CD spectra at lower temperature. Interestingly, the CD intensity of **6** in methanol increased as the temperature was lowered down to −85 °C (Fig. 4), although it is rather small, compared with the typical polymers with dynamic helical properties. Thus, the oligoureas appear to exist mainly as aromatic multilayered foldamers, but the well-ordered helical structure with induced handedness remained in a dynamic state over the whole temperature range examined.

## 3. Conclusion

Several aromatic layered oligoureas were synthesized, and the handedness induced by chiral *N*-substituents was examined by means of CD spectroscopy. The results indicate that the effect of a chiral *N*-substituent(s) at the central benzene ring in inducing well-ordered handedness at the terminal positions of hexaureas **6** and **7** is relatively weak. The CD signal intensity of hexaurea **6** increased as the temperature was lowered. Our results indicate that the folded aromatic multilayered structures of *N*,*N*′-dimethylated oligoureas are stable and predominant in solution, though dynamic changes of the helical structures are rapid even at low temperature. Further studies of the dynamic helical properties of the oligoureas are in progress.

## 4. Experimental section

### 4.1. General methods

$^1$H and $^{13}$C NMR spectra were recorded on a JNN-AL 400 or a Bruker Avance 600 spectrometer. Chemical shifts for $^1$H NMR are reported in parts per million (ppm) relative to the centerline of a singlet signal of the solvent molecule (7.26 ppm for chloroform); coupling constants are given in hertz (Hz). Chemical shifts for $^{13}$C NMR are reported in ppm relative to the centerline of a triplet at 77.16 ppm for $CDCl_3$. UV/vis and CD spectra were recorded in a 0.2-mm quartz cell on a JASCO V-650 spectrophotometer and a JASCO J-820 spectropolarimeter, respectively. Mass spectra were recorded on Bruker Daltonics microTOF-2focus spectrometer in the positive ion detection mode. All reagents were purchased from Sigma–Aldrich Chemical Co., Tokyo Kasei Kogyo Co., Wako Pure Chemical Industries, or Kanto Kagaku Co., Inc.. Open column chromatography was performed on Silica gel 60 N (spherical, neutral, particle size 100–210 mm; Kanto). Preparative thin-layer chromatography (PTLC) was performed on silica gel 60 $F_{254}$ plates (Merck, Germany). Compounds **12**, **15**, and **22** were synthesized as reported previously.[15]

### 4.2. Synthesis

*4.2.1. Synthesis of* ***9****.* Sodium hydride (685 mg, 17.1 mmol) was washed with *n*-hexane, and suspended in dry dimethylformamide

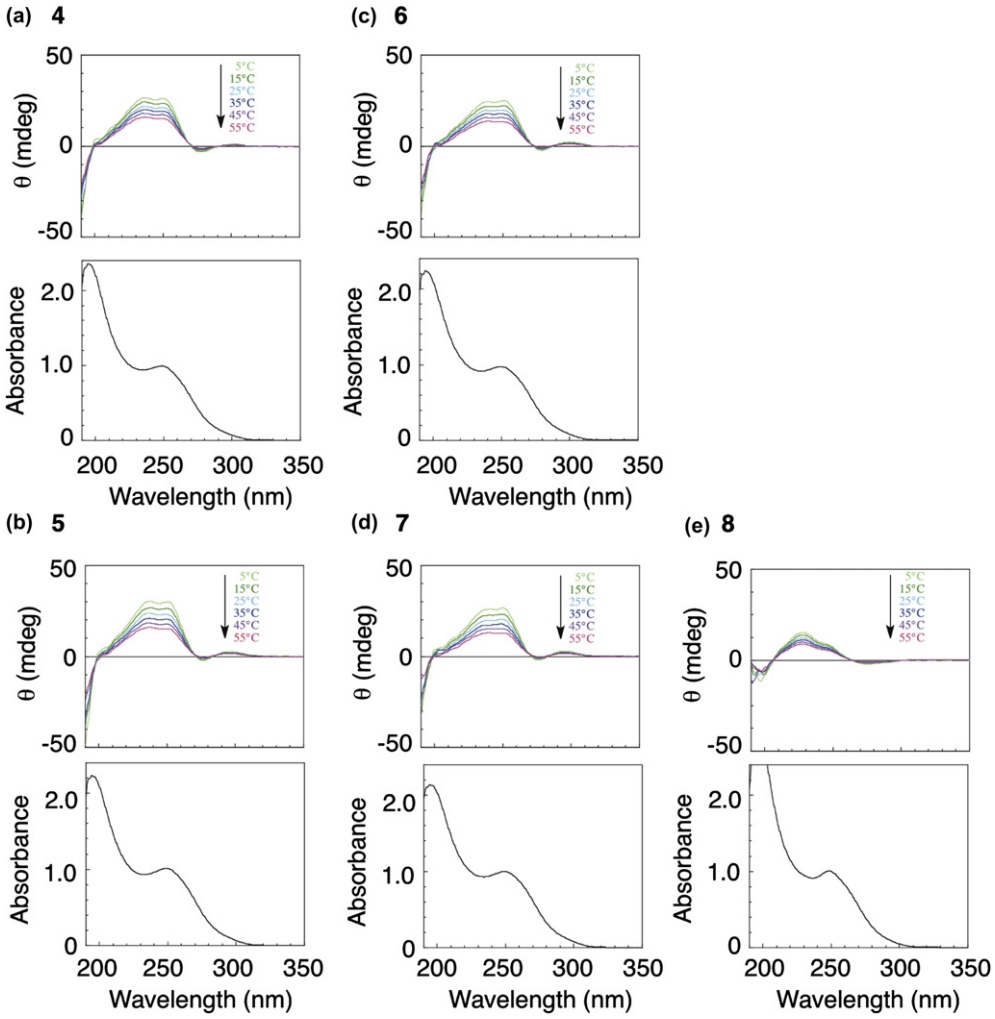



**Fig. 3.** CD (upper) and UV (lower) spectra of oligoureas (a) **4**, (b) **5**, (c) **6**, (d) **7**, and (e) **8** in acetonitrile. UV/CD spectra of each oligomer were measured at the concentration at which the absorption at $\lambda_{max}$ of the UV spectra was 1.

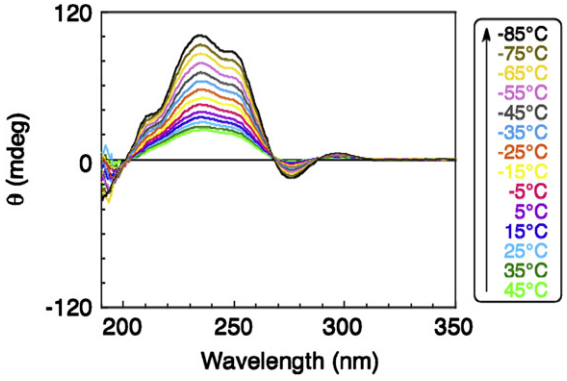



**Fig. 4.** CD spectra of oligourea **6** in methanol at various temperatures. CD spectra were measured at the concentration at which the absorption at $\lambda_{max}$ of the UV spectra was 1.

(20 mL). A solution of *m*-nitroaniline (2.004 g, 14.5 mmol) in dry dimethylformamide (40 mL) was added to the suspension at 0 °C. The reaction mixture was stirred for 1 h at room temperature, then 1-iodopropane (2.0 mL, 20.6 mmol) was added, and stirring was continued for 4 days at 60 °C. After removal of the solvent in vacuo, the residue was poured into water, and extracted with ethyl acetate. The organic layer was washed with brine, dried over magnesium sulfate, filtered, and evaporated. The residue was purified by column chromatography (silica gel, ethyl acetate/*n*-hexane=1/7) to give **9** (1.076 g, 5.97 mmol, 41%) as a yellow solid.

$^1$H NMR (600 MHz, $CDCl_3$) $\delta$ 7.49 (d, $J$=8.1 Hz, 1H), 7.37 (s, 1H), 7.26 (t, $J$=8.2 Hz, 1H), 6.85 (d, $J$=8.3 Hz, 1H), 3.13 (t, $J$=7.1 Hz, 2H), 1.67 (sextet, $J$=7.3 Hz, 2H), 1.02 (t, $J$=7.4 Hz, 3H); $^{13}$C NMR (150 MHz, $CDCl_3$) $\delta$ 149.5, 149.2, 129.8, 118.8, 111.7, 106.2, 45.7, 22.5, 11.7.

*4.2.2. Synthesis of* ***10****.* 10% Pd on carbon (201 mg) was added to a solution of **9** (960 mg, 5.33 mmol) in dry methanol (45 mL), and the mixture was stirred for 2 h under a hydrogen atmosphere. The reaction mixture was filtered through Celite, and the filtrate was evaporated to give **10** (776 mg, 5.17 mmol, 97%) as a brown oil.

$^1$H NMR (600 MHz, $CDCl_3$) $\delta$ 6.96 (t, $J$=7.9 Hz, 1H), 6.06 (d, $J$=8.0 Hz, 2H), 5.96 (s, 1H), 3.56 (br s, 3H), 3.05 (br t, $J$=6.9 Hz, 2H), 1.63 (sextet, $J$=7.3 Hz, 2H), 0.99 (t, $J$=7.5 Hz, 3H); $^{13}$C NMR (150 MHz, $CDCl_3$) $\delta$ 149.8, 147.6, 130.1, 104.7, 104.1, 99.4, 45.9, 22.8, 11.7.

*4.2.3. Synthesis of* ***11****.* 2-Nitrobenzenesulfonyl chloride (3.715 g, 16.8 mmol) was added to a solution of **10** (2.076 g, 13.8 mmol) in dry pyridine (10 mL) at 0 °C, and the reaction mixture was stirred for 3.5 h at room temperature, then poured into 2 M hydrochloric acid, and extracted with chloroform. The organic layer was washed with brine, dried over magnesium sulfate, and filtered. The solvent

was removed in vacuo to afford **11** (1.624 g, 4.84 mmol, 35%) as an orange solid.

$^1$H NMR (600 MHz, $CDCl_3$) $\delta$ 7.88 (d, $J$=7.9 Hz, 1H), 7.84 (d, $J$=8.0 Hz, 1H), 7.68 (t, $J$=7.7 Hz, 1H), 7.58 (t, $J$=7.7 Hz, 1H), 7.11 (br s, 1H), 6.99 (t, $J$=8.0 Hz, 1H), 6.48 (s, 1H), 6.42 (d, $J$=7.8 Hz, 1H), 6.38 (d, $J$=8.1 Hz, 1H), 3.71 (br s, 1H), 3.01 (t, $J$=7.1 Hz, 2H), 1.59 (sextet, $J$=7.3 Hz, 2H), 0.97 (t, $J$=7.4 Hz, 3H); $^{13}$C NMR (150 MHz, $CDCl_3$) $\delta$ 149.6, 148.3, 136.6, 133.9, 132.6, 132.5, 132.1, 130.1, 125.3, 111.2, 111.0, 107.0, 45.7, 22.7, 11.7.

*4.2.4. Synthesis of **13**.* Diethyl azodicarboxylate (40% in toluene, 1.871 g, 4.30 mmol) in dry tetrahydrofuran (4 mL) was added to a mixture of **11** (603 mg, 1.80 mmol), **12** (350 mg, 1.96 mmol), and triphenylphosphine (1.082 g, 4.13 mmol) in dry tetrahydrofuran (12 mL) under an argon atmosphere at 0 °C. The reaction mixture was stirred for 7.5 h at room temperature, then the solvent was removed in vacuo, and the residue was purified by column chromatography (silica gel, ethyl acetate/*n*-hexane=1/1) to give **13** (956 mg) as a yellow oil.

$^1$H NMR (600 MHz, $CDCl_3$) $\delta$ 7.61–7.56 (m, 3H), 7.44 (t, $J$=7.5 Hz, 1H), 7.02 (t, $J$=8.0 Hz, 1H), 6.59 (br s, 1H), 6.50 (br d, $J$=7.2 Hz, 1H), 6.46 (d, $J$=7.7 Hz, 1H), 3.86 (dd, $J$=14.3, 7.0 Hz, 1H), 6.39 (dd, $J$=14.3, 5.3 Hz, 1H), 3.65–3.62 (m, 3H), 3.57–3.46 (m, 6H), 3.37 (s, 3H), 2.99 (t, $J$=7.1 Hz, 2H), 1.63 (br s, 1H), 1.58 (sextet, $J$=7.3 Hz, 2H), 1.18 (d, $J$=6.2 Hz, 3H), 0.96 (t, $J$=7.4 Hz, 3H); $^{13}$C NMR (150 MHz, $CDCl_3$) $\delta$ 149.2, 148.2, 139.9, 133.3, 132.4, 132.4, 131.0, 129.9, 123.7, 117.3, 114.3, 112.7, 74.3, 72.1, 70.8, 70.7, 68.4, 59.1, 56.9, 22.6, 17.6, 14.6, 11.7.

*4.2.5. Synthesis of **14**.* A solution of **13** (918 mg, 1.85 mmol) in dry acetonitrile (15 mL) and cesium carbonate (901 mg, 2.77 mmol) was added to a solution of benzenethiol (0.23 mL, 2.24 mmol) in acetonitrile (5 mL). The mixture was stirred for 5.5 h at 60 °C, then poured into water, and extracted with ethyl acetate. The organic layer was washed with brine, dried over magnesium sulfate, filtered, and evaporated. The residue was purified by column chromatography (silica gel, ethyl acetate/*n*-hexane=1/1) to give **14** (564 mg) as a brown oil.

$^1$H NMR (600 MHz, $CDCl_3$) $\delta$ 6.96 (t, $J$=7.0 Hz, 1H), 6.01–5.99 (m, 2H), 5.89 (s, 1H), 3.75–3.70 (m, 2H), 3.67–3.62 (m, 4H), 3.60–3.56 (m, 3H), 3.39 (s, 3H), 3.19 (dd, $J$=12.5, 3.7 Hz, 1H), 3.05 (t, $J$=7.1 Hz, 2H), 3.03 (dd, $J$=12.6, 7.6 Hz, 1H), 1.62 (sextet, $J$=7.3 Hz, 2H), 1.21 (d, $J$=6.2 Hz, 3H), 0.99 (t, $J$=7.3 Hz, 3H); $^{13}$C NMR (150 MHz, $CDCl_3$) $\delta$ 149.9, 149.8, 130.0, 103.1, 103.0, 97.6, 74.6, 72.2, 71.0, 70.7, 68.1, 59.2, 49.4, 46.0, 23.0, 18.0, 11.8.

*4.2.6. Synthesis of **16**.* A solution of **15** (100 mg, 0.321 mmol) in 1,2-dichloroethane (2 mL) was added to a solution of triphosgene (39 mg, 0.130 mmol) in 1,2-dichloroethane (1 mL), and the mixture was stirred at room temperature for 35 min. After concentration, the residual isocyanate was dissolved in dry tetrahydrofuran (1 mL). A solution of **14** (45 mg, 0.146 mmol) in dry tetrahydrofuran (2.5 mL) was added to the isocyanate solution, and the mixture was stirred for 5.5 h at room temperature, then poured into saturated sodium bicarbonate, and extracted with ethyl acetate. The organic layer was dried over magnesium sulfate, filtered, and evaporated. The residue was purified by column chromatography (silica gel, ethyl acetate/*n*-hexane=1/1 then 1/0) to give **16** (75 mg, 0.0757 mmol, 45% from **11**) as a brown oil.

$^1$H NMR (600 MHz, $CDCl_3$) $\delta$ 7.58 (br s, 1H), 7.50 (t, $J$=8.0 Hz, 1H), 7.34 (d, $J$=8.0 Hz, 1H), 7.28 (s, 1H), 7.17 (d, $J$=7.9 Hz, 1H), 6.99 (t, $J$=7.7 Hz, 2H), 6.97 (t, $J$=7.7 Hz, 2H), 6.89–6.84 (m, 4H), 6.82–6.78 (m, 4H), 6.74–6.71 (m, 4H), 6.37–6.33 (m, 2H), 6.32 (s, 1H), 3.86–3.79 (m, 3H), 3.74–3.66 (m, 3H), 3.60–3.42 (m, 15H), 3.24 (s, 3H), 1.60 (sextet, $J$=7.5 Hz, 2H), 1.57–1.49 (m, 8H), 1.18 (d, $J$=6.1 Hz, 3H), 0.92 (t, $J$=7.3 Hz, 3H), 0.84 (t, $J$=7.4 Hz, 3H), 0.83 (t, $J$=7.5 Hz, 3H), 0.82 (t, $J$=7.4 Hz, 3H), 0.82 (t, $J$=7.5 Hz, 3H); $^{13}$C NMR (150 MHz, $CDCl_3$) $\delta$ 160.7, 160.7, 155.3, 153.8, 145.2, 145.0, 144.8, 144.5, 144.4, 143.0, 139.5, 139.3, 131.0, 128.6, 128.5, 128.4, 128.4, 127.4, 127.2, 127.1, 126.3, 126.0, 124.7, 124.7, 121.6, 121.5, 118.5, 118.0, 116.2, 115.7, 75.8, 72.0, 70.6, 70.5, 68.5, 59.0, 56.4, 53.4, 53.4, 53.4, 53.4, 51.3, 21.9, 21.6, 21.6, 21.6, 17.2, 11.5, 11.5, 11.3.

*4.2.7. Synthesis of **5**.* Sodium hydride (5 mg, 0.125 mmol) was washed with *n*-hexane, and suspended in dry dimethylformamide (0.3 mL). A solution of **16** (28 mg, 0.0285 mmol) in dry dimethylformamide (0.9 mL) was added to the suspension at 0 °C. The reaction mixture was stirred for 1 h at room temperature, then 1-iodopropane (0.03 mL, 0.309 mmol) was added, and stirring was continued for 3.5 h at room temperature. The solvent was removed in vacuo, and the residue was poured into water, and extracted with ethyl acetate. The organic layer was washed with brine, dried over magnesium sulfate, filtered, and evaporated. The residue was purified by open column chromatography (ethyl acetate/*n*-hexane=1/2 then 2/1) to give **5** (22.6 mg, 0.0211 mmol, 74%) as a colorless oil.

$^1$H NMR (600 MHz, $CDCl_3$) $\delta$ 6.93 (t, $J$=7.6 Hz, 2H), 6.92 (t, $J$=7.5 Hz, 2H), 6.84 (t, $J$=7.3 Hz, 1H), 6.83 (t, $J$=7.3 Hz, 1H), 6.61 (t, $J$=8.0 Hz, 2H), 6.59 (d, $J$=7.5 Hz, 2H), 6.58 (d, $J$=7.3 Hz, 2H), 6.53 (t, $J$=7.8 Hz, 1H), 6.40 (d, $J$=7.9 Hz, 1H), 6.32 (d, $J$=8.5 Hz, 1H), 6.30 (d, $J$=7.9 Hz, 1H), 6.24 (d, $J$=8.0 Hz, 1H), 6.22 (d, $J$=8.1 Hz, 1H), 6.17 (s, 1H), 6.16 (d, $J$=7.5 Hz, 1H), 5.90 (s, 1H), 5.90 (s, 1H), 3.77–3.70 (m, 2H), 3.67–3.59 (m, 4H), 3.56–3.49 (m, 4H), 3.45–3.35 (m, 4H), 3.38 (s, 3H), 3.28–3.11 (m, 9H), 2.90–2.86 (m, 1H), 1.52–1.23 (m, 15H), 1.11 (d, $J$=6.2 Hz, 3H), 0.87 (t, $J$=7.4 Hz, 3H), 0.85 (t, $J$=7.4 Hz, 3H), 0.85 (t, $J$=7.3 Hz, 3H), 0.81 (t, $J$=7.6 Hz, 12H); $^{13}$C NMR (150 MHz, $CDCl_3$) $\delta$ 160.3, 160.3, 159.8, 159.1, 146.1, 145.2, 145.0, 144.9, 144.7, 144.4, 144.3, 144.3, 128.4, 128.0, 127.6, 127.4, 126.6, 126.6, 125.0, 123.8, 123.6, 123.4, 123.3, 123.3, 123.0, 122.6, 122.3, 74.0, 72.1, 71.0, 70.7, 67.9, 59.2, 58.1, 53.6, 53.5, 53.5, 53.5, 53.3, 29.8, 21.8, 21.8, 21.7, 21.7, 21.6, 17.6, 11.5, 11.5, 11.5; HRMS (ESI$^+$) calcd for $C_{63}H_{89}N_8O_7$ $(M+Na)^+$ 1069.6849, found 1069.6816.

*4.2.8. Synthesis of **17**.* Phenyl isocyanate (7.2 mL, 66.5 mmol) was added to a solution of *m*-nitroaniline (9.00 g, 65.2 mmol) in dry tetrahydrofuran (68 mL), and the reaction mixture was stirred for 1 day at room temperature. The solvent was removed in vacuo, then the residue was precipitated in ethyl acetate and collected by filtration to give **17** (15.8 g, 61.4 mmol, 94%) as a white powder.

$^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 9.19 (s, 1H), 8.82 (s, 1H), 8.55 (s, 1H), 7.81 (d, $J$=8.3 Hz, 1H), 7.70 (d, $J$=8.3 Hz, 1H), 7.56 (t, $J$=8.3 Hz, 1H), 7.47 (d, $J$=7.3 Hz, 2H), 7.29 (t, $J$=7.3 Hz, 2H), 6.99 (t, $J$=7.3 Hz, 1H).

*4.2.9. Synthesis of **18**.* 10% Pd on carbon (502 mg) was added to a solution of **17** (3.11 g, 12.1 mmol) in a 1/1 mixture of dry tetrahydrofuran and dry methanol (200 mL). The reaction mixture was stirred for 4 h at 40 °C under a hydrogen atmosphere, then filtered through Celite, and the filtrate was concentrated. The residue was precipitated in dichloromethane/*n*-hexane, and collected by filtration to give **18** (2.56 g, 11.3 mmol, 93%) as a white powder.

$^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 8.53 (s, 1H), 8.34 (s, 1H), 7.43 (d, $J$=7.3 Hz, 2H), 7.26 (t, $J$=7.8 Hz, 2H), 6.96 (t, $J$=7.3 Hz, 1H), 6.88 (t, $J$=7.8 Hz, 1H), 6.76 (s, 1H), 6.54 (d, $J$=7.3 Hz, 1H), 6.18 (d, $J$=7.8 Hz, 1H), 5.01 (s, 2H).

*4.2.10. Synthesis of **19**.* A solution of **18** (2.20 g, 8.56 mmol) in dry tetrahydrofuran (60 mL) was added to a solution of *m*-nitrophenyl isocyanate (2.12 g, 12.9 mmol) in dry tetrahydrofuran (40 mL). The mixture was stirred for 5 h at room temperature, then filtered, and the solid was washed with ethyl acetate to give **19** (3.15 g, 8.04 mmol, 94%) as a white powder.

$^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 9.13 (s, 1H), 8.87 (s, 1H), 8.72 (s, 1H), 8.59 (s, 1H), 8.58 (s, 1H), 7.83 (d, $J$=8.3 Hz, 1H), 7.72 (s, 1H), 7.70

(d, *J*=8.3 Hz, 1H), 7.57 (t, *J*=7.8 Hz, 1H), 7.45 (d, *J*=8.8 Hz, 2H), 7.28 (t, *J*=8.3 Hz, 2H), 7.19 (t, *J*=7.8 Hz, 1H), 7.10 (d, *J*=7.8 Hz, 1H), 7.08 (d, *J*=7.8 Hz, 1H), 6.97 (t, *J*=7.3 Hz, 1H).

*4.2.11. Synthesis of **20**.* Sodium hydride (123 mg, 3.08 mmol) was washed with *n*-hexane, and suspended in dry dimethylformamide (1.0 mL). The suspension was added to a mixture of **19** (198 mg, 0.506 mmol) and 1-iodopentane (0.7 mL, 5.34 mmol) in dry dimethylformamide (2.0 mL) at 0 °C. The reaction mixture was stirred for 3 h at 50 °C, then the solvent was removed in vacuo. The residue was poured into water, and extracted with ethyl acetate. The organic layer was washed with brine, dried over magnesium sulfate, filtered, and evaporated. The residue was purified by column chromatography (silica gel, ethyl acetate/*n*-hexane=1/5) and preparative thin-layer chromatography (ethyl acetate/*n*-hexane=1/5, three times) to give **20** (73.5 mg, 0.109 mmol, 22%) as a yellow oil.

$^1$H NMR (600 MHz, $CDCl_3$) $\delta$ 7.71 (d, *J*=8.3 Hz, 1H), 7.51 (s, 1H), 7.16 (t, *J*=8.0 Hz, 1H), 7.02 (d, *J*=7.9 Hz, 1H), 6.97 (t, *J*=7.6 Hz, 2H), 6.88 (t, *J*=7.3 Hz, 1H), 6.67 (t, *J*=8.0 Hz, 1H), 6.63 (d, *J*=7.4 Hz, 2H), 6.32 (d, *J*=7.0 Hz, 1H), 6.30 (d, *J*=7.4 Hz, 1H), 6.04 (s, 1H), 3.54–3.51 (m, 2H), 3.48–3.46 (m, 2H), 3.37–3.34 (m, 2H), 3.26–3.24 (m, 2H), 1.57–1.28 (m, 24H), 0.96 (t, *J*=7.2 Hz, 3H), 0.94 (t, *J*=7.3 Hz, 3H), 0.85 (t, *J*=7.1 Hz, 3H), 0.84 (t, *J*=7.3 Hz, 3H); $^{13}$C NMR (150 MHz, $CDCl_3$) $\delta$ 160.2, 159.4, 148.2, 145.6, 145.5, 144.4, 144.2, 131.8, 129.2, 128.5, 128.4, 126.7, 125.1, 123.7, 123.7, 123.0, 121.0, 119.3, 52.2, 52.1, 51.9, 51.6, 29.5, 29.4, 29.3, 29.2, 28.4, 28.3, 28.2, 28.1, 22.7, 22.7, 22.5, 22.5, 14.4, 14.3, 14.2, 14.2.

*4.2.12. Synthesis of **21**.* 10% Pd on carbon (15 mg) was added to a solution of **20** (96 mg, 0.143 mmol) in dry methanol (2.0 mL), and the reaction mixture was stirred for 22 h at room temperature under a hydrogen atmosphere, then filtered through Celite. The filtrate was concentrated, and the residue was purified by column chromatography (silica gel, ethyl acetate/*n*-hexane=1/3) to give **21** (58 mg, 0.0904 mmol, 63%) as a yellow oil.

$^1$H NMR (600 MHz, $CDCl_3$) $\delta$ 6.97 (t, *J*=7.6 Hz, 2H), 6.88 (t, *J*=7.4 Hz, 1H), 6.72 (t, *J*=7.9 Hz, 1H), 6.70 (t, *J*=8.0 Hz, 1H), 6.66 (d, *J*=7.3 Hz, 2H), 6.39–6.36 (m, 2H), 6.19 (d, *J*=7.9 Hz, 1H), 6.05 (s, 1H), 6.03 (d, *J*=7.9 Hz, 1H), 5.94 (s, 1H), 3.48 (t, *J*=7.7 Hz, 2H), 3.42 (t, *J*=7.8 Hz, 2H), 3.33 (t, *J*=7.7 Hz, 2H), 3.27 (t, *J*=7.7 Hz, 2H), 1.55–1.18 (m, 24H), 0.93 (t, *J*=7.2 Hz, 3H), 0.93 (t, *J*=7.2 Hz, 3H), 0.84 (t, *J*=7.0 Hz, 6H); $^{13}$C NMR (150 MHz, $CDCl_3$) $\delta$ 160.5, 160.4, 146.6, 145.3, 145.2, 145.2, 144.4, 129.0, 128.5, 127.8, 126.7, 125.0, 124.2, 123.6, 123.3, 117.1, 113.5, 111.9, 52.1, 52.0, 51.9, 51.8, 29.6, 29.5, 29.4, 29.4, 28.4, 28.3, 28.2, 28.2, 22.8, 22.6, 22.6, 14.4, 14.2, 14.2.

*4.2.13. Synthesis of **23**.* A solution of **21** (58 mg, 0.090 mmol) in 1,2-dichloroethane (0.8 mL) was added to a solution of triphosgene (10 mg, 0.033 mmol) in 1,2-dichloroethane (0.4 mL), and the reaction mixture was stirred at room temperature for 45 min. After concentration, the residual isocyanate was dissolved in dry tetrahydrofuran (0.4 mL). A solution of **22** (17 mg, 0.041 mmol) in dry tetrahydrofuran (0.8 mL) was added to the isocyanate solution, and this mixture was stirred for 24 h at 60 °C, then poured into saturated sodium bicarbonate, and extracted with ethyl acetate. The organic layer was dried over magnesium sulfate, filtered, and evaporated. The residue was purified by column chromatography (silica gel, ethyl acetate/*n*-hexane=3/1) and preparative thin-layer chromatography (ethyl acetate/*n*-hexane=3/1) to give **23** (18 mg, 0.010 mmol, 25%) as a colorless oil.

$^1$H NMR (600 MHz, $CDCl_3$) $\delta$ 7.48 (br s, 2H), 7.43 (t, *J*=8.0 Hz, 1H), 7.3 (s, 1H), 7.25 (d, *J*=8.7 Hz, 2H), 6.96 (t, *J*=7.9 Hz, 4H), 6.96 (s, 2H), 6.87 (t, *J*=7.3 Hz, 2H), 6.79 (t, *J*=8.0 Hz, 2H), 6.75 (d, *J*=8.2 Hz, 2H), 6.67 (t, *J*=8.0 Hz, 2H), 6.64 (d, *J*=7.5 Hz, 4H), 6.39 (d, *J*=8.0 Hz, 2H), 6.33 (d, *J*=7.9 Hz, 2H), 6.24 (d, *J*=7.7 Hz, 2H), 6.08 (s, 2H), 3.82–3.75 (m, 5H), 3.70–3.66 (m, 2H), 3.58–3.41 (m, 22H), 3.33 (t, *J*=7.6 Hz, 2H), 3.29 (t, *J*=7.7 Hz, 2H), 3.27 (s, 6H), 1.53–1.54 (m, 6H), 1.38–1.32 (m, 8H), 1.29–1.18 (m, 27H), 1.16 (d, *J*=6.2 Hz, 6H), 0.92 (t, *J*=7.3 Hz, 6H), 0.92 (t, *J*=7.2 Hz, 6H), 0.84 (t, *J*=7.1 Hz, 6H), 0.82 (t, *J*=7.1 Hz, 6H); $^{13}$C NMR (150 MHz, $CDCl_3$) $\delta$ 160.4, 160.2, 155.0, 145.2, 145.0, 144.7, 144.5, 144.3, 139.7, 130.5, 128.4, 128.4, 128.0, 126.8, 126.4, 125.9, 125.0, 124.1, 123.6, 123.1, 120.7, 117.8, 115.7, 75.6, 72.0, 70.7, 70.5, 68.5, 59.1, 56.2, 52.1, 52.0, 51.9, 29.5, 29.5, 29.3, 29.3, 28.5, 28.2, 28.1, 22.7, 22.6, 17.4, 14.4, 14.4, 14.2, 14.2.

*4.2.14. Synthesis of **6**.* Sodium hydride (2 mg, 0.055 mmol) was washed with *n*-hexane, and suspended in dry dimethylformamide (0.1 mL). A solution of **23** (16 mg, 0.0088 mmol) in dry dimethylformamide (0.2 mL) was added to the suspension at 0 °C. The reaction mixture was stirred for 45 min at room temperature, then 1-iodopentane (0.015 mL, 0.114 mmol) was added, and stirring was continued for 23 h at room temperature. The solvent was removed in vacuo, and the residue was poured into water, and extracted with ethyl acetate. The organic layer was washed with brine, dried over magnesium sulfate, filtered, and evaporated. The residue was purified by preparative thin-layer chromatography (ethyl acetate/*n*-hexane=1/1) to give **6** (3 mg, 0.0014 mmol, 16%) as a colorless oil.

$^1$H NMR (600 MHz, $CDCl_3$) $\delta$ 6.93 (t, *J*=7.6 Hz, 4H), 6.84 (t, *J*=7.3 Hz, 2H), 6.60 (d, *J*=7.5 Hz, 4H), 6.58 (t, *J*=8.0 Hz, 2H), 6.57 (t, *J*=7.9 Hz, 2H), 6.47 (t, *J*=7.9 Hz, 1H), 6.34 (d, *J*=7.9 Hz, 2H), 6.29 (d, *J*=8.1 Hz, 2H), 6.28 (s, 1H), 6.25 (d, *J*=7.9 Hz, 2H), 6.15 (d, *J*=8.7 Hz, 2H), 6.12 (d, *J*=7.9 Hz, 2H), 5.97 (s, 2H), 5.95 (s, 2H), 3.73–3.60 (m, 12H), 3.57–3.53 (m, 6H), 3.45 (t, *J*=7.7 Hz, 4H), 3.38 (s, 6H), 3.34–3.07 (m, 20H), 1.51–1.16 (m, 50H), 1.08 (d, *J*=6.2 Hz, 6H), 0.91 (t, *J*=7.3 Hz, 18H), 0.90 (t, *J*=7.6 Hz, 6H), 0.83 (t, *J*=7.1 Hz, 6H); $^{13}$C NMR (150 MHz, $CDCl_3$) $\delta$ 160.2, 159.8, 159.2, 145.9, 145.3, 145.2, 144.9, 144.5, 144.3, 128.5, 128.4, 127.9, 127.9, 127.7, 126.7, 125.0, 123.8, 123.2, 123.2, 123.1, 122.8, 122.6, 122.4, 73.9, 72.1, 70.9, 70.7, 68.0, 59.2, 57.7, 52.1, 52.0, 51.9, 29.8, 29.5, 29.4, 29.4, 29.4, 29.3, 28.5, 28.4, 28.1, 22.7, 22.7, 22.6, 22.5, 18.0, 14.3, 14.3, 14.3, 14.1; HRMS ($ESI^+$) calcd for $C_{114}H_{174}N_{12}NaO_{12}$ $(M+Na)^+$ 1926.3266, found 1926.3251.

*4.2.15. Synthesis of **24**.* A solution of *m*-nitrophenyl isocyanate (427 mg, 2.60 mmol) in dry tetrahydrofuran (8 mL) was added to a solution of **14** (401 mg, 1.29 mmol) in dry tetrahydrofuran (2 mL), and the reaction mixture was stirred for 18 h at room temperature. The solvent was removed in vacuo, and the residue was purified by column chromatography (silica gel, ethyl acetate/*n*-hexane=1/1) to give **24** (577 mg, 0.904 mmol, 74%) as a yellow oil.

$^1$H NMR (600 MHz, $CDCl_3$) $\delta$ 8.72 (br s, 1H), 8.33 (s, 1H), 8.23 (s, 1H), 7.89 (d, *J*=8.1 Hz, 1H), 7.87 (d, *J*=7.8 Hz, 1H), 7.85 (d, *J*=8.2 Hz, 1H), 7.82 (d, *J*=8.2 Hz, 1H), 7.55 (t, *J*=8.0 Hz, 1H), 7.44 (t, *J*=8.2 Hz, 1H), 7.39 (t, *J*=8.2 Hz, 1H), 7.37 (s, 1H), 7.33 (d, *J*=7.9 Hz, 1H), 7.23 (d, *J*=8.0 Hz, 1H), 6.99 (br s, 1H), 3.93–3.86 (m, 4H), 3.77 (t, *J*=7.5 Hz, 2H), 3.68–3.65 (m, 2H), 3.63–3.59 (m, 1H), 3.57–3.50 (m, 2H), 3.36 (t, *J*=4.3 Hz, 2H), 3.20 (s, 3H), 1.64 (sextet, *J*=7.6 Hz, 2H), 1.23 (d, *J*=5.5 Hz, 3H), 0.94 (t, *J*=7.4 Hz, 3H); $^{13}$C NMR (150 MHz, $CDCl_3$) $\delta$ 156.0, 153.7, 148.8, 148.7, 144.9, 142.2, 140.8, 140.6, 131.4, 129.8, 129.5, 128.1, 125.6, 125.5, 125.4, 125.2, 117.5, 117.5, 114.3, 113.9, 76.3, 71.9, 70.5, 70.5, 68.7, 59.0, 56.4, 51.4, 21.9, 17.1, 11.4.

*4.2.16. Synthesis of **25**.* Sodium hydride (145 mg, 3.63 mmol) was washed with *n*-hexane, and suspended in dry dimethylformamide (2 mL). A solution of **24** (577 mg, 0.904 mmol) in dry dimethylformamide (7 mL) was added to the suspension at 0 °C. The reaction mixture was stirred for 50 min at room temperature, then 1-iodopropane (0.5 mL, 5.15 mmol) was added, and stirring was continued for 24 h at room temperature. The solvent was removed in vacuo, and the residue was poured into water, and extracted with ethyl acetate. The organic layer was washed with brine, dried over magnesium sulfate, filtered, and evaporated. The residue was

purified by column chromatography (ethyl acetate/*n*-hexane=1/1) to give **25** (561 mg, 0.777 mmol, 86%) as a yellow oil.

$^1$H NMR (600 MHz, $CDCl_3$) $\delta$ 7.72 (d, $J$=8.2 Hz, 1H), 7.70 (d, $J$=7.6 Hz, 1H), 7.47 (s, 1H), 7.45 (s, 1H), 7.20 (t, $J$=7.9 Hz, 1H), 7.19–7.17 (m, 2H), 7.03 (d, $J$=7.4 Hz, 1H), 6.66 (t, $J$=7.9 Hz, 1H), 6.47 (d, $J$=8.1 Hz, 1H), 6.29 (d, $J$=8.4 Hz, 1H), 6.27 (s, 1H), 3.84–3.77 (m, 2H), 3.70–3.48 (m, 12H), 3.37 (s, 3H), 3.33–3.28 (m, 2H), 2.92 (dd, $J$=14.2, 8.8 Hz, 1H), 1.60–1.39 (m, 6H), 1.18 (d, $J$=6.2 Hz, 3H), 0.92 (t, $J$=7.4 Hz, 3H), 0.88 (t, $J$=7.4 Hz, 3H), 0.86 (t, $J$=7.4 Hz, 3H); $^{13}$C NMR (150 MHz, $CDCl_3$) $\delta$ 159.4, 159.0, 148.4, 148.3, 146.3, 145.5, 145.1, 144.5, 132.3, 132.0, 129.4, 129.2, 128.7, 124.0, 123.4, 121.0, 120.5, 119.5, 119.4, 73.8, 72.1, 71.0, 70.7, 67.8, 59.1, 58.4, 53.6, 53.3, 53.2, 21.7, 17.3, 11.5.

*4.2.17. Synthesis of* ***26****.* 10% Pd on carbon (21 mg) was added to a solution of **25** (103 mg, 0.142 mmol) in dry methanol (2 mL), and the reaction mixture was stirred for 4.5 h at room temperature under a hydrogen atmosphere, then filtered through Celite. The filtrate was concentrated to give **26** (86 mg, 0.130 mmol, 92%) as a colorless oil.

$^1$H NMR (600 MHz, $CDCl_3$) $\delta$ 6.74 (t, $J$=8.0 Hz, 1H), 6.73 (t, $J$=7.9 Hz, 1H), 6.70 (t, $J$=7.9 Hz, 1H), 6.52 (d, $J$=7.9 Hz, 1H), 6.46 (d, $J$=7.9 Hz, 1H), 6.21 (d, $J$=7.9 Hz, 1H), 6.20 (s, 1H), 6.17 (d, $J$=7.9 Hz, 1H), 6.07 (s, 1H), 6.03 (d, $J$=7.4 Hz, 1H), 6.02 (d, $J$=7.4 Hz, 1H), 5.96 (s, 1H), 3.82–3.76 (m, 2H), 3.70–3.62 (m, 5H), 3.55 (br s, 2H), 3.55 (t, $J$=4.7 Hz, 4H), 3.50–3.39 (m, 5H), 3.36 (s, 3H), 3.31 (t, $J$=7.8 Hz, 2H), 3.19 (dd, $J$=14.0, 7.8 Hz, 1H), 1.72 (br s, 2H), 1.57–1.46 (m, 4H), 1.18 (d, $J$=6.2 Hz, 3H), 0.90 (t, $J$=7.4 Hz, 3H), 0.84 (t, $J$=7.4 Hz, 3H), 0.83 (t, $J$=7.4 Hz, 3H); $^{13}$C NMR (150 MHz, $CDCl_3$) $\delta$ 160.4, 160.1, 146.9, 146.8, 146.4, 145.3, 144.9, 144.7, 129.1, 128.9, 127.6, 124.7, 123.7, 123.4, 116.8, 116.5, 113.6, 113.5, 112.0, 111.7, 74.2, 72.0, 71.1, 70.6, 68.0, 59.1, 57.8, 53.4, 53.3, 21.7, 21.7, 21.7, 17.8, 11.6, 11.5, 11.5.

*4.2.18. Synthesis of* ***27****.* A solution of **15** (131 mg, 0.421 mmol) in 1,2-dichloroethane (1.0 mL) was added to a solution of triphosgene (43 mg, 0.146 mmol) in 1,2-dichloroethane (0.5 mL), and the reaction mixture was stirred at room temperature for 1.5 h. After concentration, the residual isocyanate was dissolved in dry tetrahydrofuran (0.5 mL). A solution of **26** (94 mg, 0.142 mmol) in dry tetrahydrofuran (1.0 mL) was added to the isocyanate solution, and this mixture was stirred for 2.5 h at room temperature, then poured into saturated sodium bicarbonate, and extracted with ethyl acetate. The organic layer was dried over magnesium sulfate, filtered, and evaporated. The residue was purified by column chromatography (ethyl acetate/*n*-hexane=3/1) to give **27** (97 mg, 0.0727 mmol, 51%) as a white solid.

$^1$H NMR (600 MHz, $CD_3OD$) $\delta$ 7.08–7.04 (m, 6H), 6.99–6.87 (m, 13H), 6.80 (d, $J$=7.6 Hz, 4H), 6.62 (d, $J$=7.9 Hz, 1H), 6.56 (d, $J$=7.9 Hz, 1H), 6.41–6.39 (m, 2H), 6.36 (d, $J$=7.6 Hz, 1H), 6.28 (d, $J$=7.9 Hz, 1H), 6.24 (s, 1H), 3.82 (t, $J$=8.8 Hz, 1H), 3.78–3.70 (m, 5H), 3.64–3.42 (m, 16H), 3.32 (s, 3H), 3.30 (t, $J$=7.9 Hz, 2H), 2.97–2.95 (m, 1H), 1.61–1.48 (m, 14H), 1.13 (d, $J$=6.3 Hz, 3H), 0.97 (t, $J$=7.4 Hz, 3H), 0.91–0.85 (m, 18H); $^{13}$C NMR (150 MHz, $CD_3OD$) $\delta$ 162.5, 161.9, 161.8, 154.2, 147.6, 145.9, 145.9, 145.8, 145.5, 145.2, 141.0, 141.0, 141.0, 140.8, 130.0, 129.9, 129.7, 129.6, 129.3, 128.1, 128.1, 126.3, 126.3, 126.0, 125.1, 124.8, 122.1, 121.9, 121.8, 121.1, 118.6, 118.4, 118.3, 118.1, 116.7, 116.6, 116.4, 75.7, 72.8, 72.5, 71.7, 68.8, 59.1, 59.1, 54.6, 54.5, 54.5, 54.4, 54.4, 54.3, 22.8, 22.6, 22.6, 22.5, 17.6, 12.0, 11.8, 11.8, 11.7.

*4.2.19. Synthesis of* ***7****.* Sodium hydride (19 mg, 0.788 mmol) was washed with *n*-hexane, and suspended in dry dimethylformamide (0.3 mL). A solution of **27** (97 mg, 0.073 mmol) in dry dimethylformamide (0.6 mL) was added to the suspension at 0 °C. The reaction mixture was stirred for 30 min at room temperature, then 1-iodopropane (0.08 mL, 0.82 mmol) was added, and stirring was continued for 2.5 h at room temperature. The solvent was removed in vacuo, and the residue was poured into water, and extracted with ethyl acetate. The organic layer was washed with brine, dried over magnesium sulfate, filtered, and evaporated. The residue was purified by column chromatography (ethyl acetate/*n*-hexane=2/1) to give **7** (69 mg, 0.0458 mmol, 63%) as a colorless oil.

$^1$H NMR (600 MHz, $CD_3OD$) $\delta$ 7.00 (t, $J$=7.6 Hz, 4H), 6.90 (t, $J$=7.4 Hz, 2H), 6.74 (t, $J$=7.4 Hz, 1H), 6.73 (t, $J$=7.9 Hz, 3H), 6.68 (d, $J$=8.1 Hz, 4H), 6.67 (t, $J$=8.3 Hz, 1H), 6.50 (d, $J$=7.9 Hz, 1H), 6.43 (d, $J$=8.0 Hz, 1H), 6.40 (d, $J$=8.0 Hz, 2H), 6.35–6.31 (m, 4H), 6.26 (s, 1H), 6.25 (d, $J$=7.3 Hz, 1H), 6.02 (s, 1H), 6.00 (s, 1H), 5.98 (s, 1H), 5.95 (s, 1H), 3.79–3.76 (m, 1H), 3.72–3.61 (m, 5H), 3.58–3.55 (m, 3H), 3.53–3.49 (m, 1H), 3.46–3.42 (m, 4H), 3.37 (s, 3H), 3.37–3.33 (m, 1H), 3.27–3.09 (m, 16H), 2.85–2.82 (m, 1H), 1.52–1.27 (m, 24H), 1.13 (d, $J$=6.2 Hz, 3H), 0.90–0.81 (m, 33H); $^{13}$C NMR (150 MHz, $CDCl_3$) $\delta$ 161.9, 161.4, 161.4, 161.4, 160.5, 147.2, 146.2, 146.0, 145.9, 145.9, 145.8, 145.6, 145.5, 145.1, 129.7, 129.6, 129.4, 129.4, 129.1, 129.0, 127.6, 126.4, 125.1, 124.8, 124.7, 124.6, 124.5, 124.3, 124.3, 124.2, 124.2, 124.1, 124.1, 124.1, 123.9, 75.1, 73.1, 72.1, 71.6, 69.0, 59.4, 59.2, 54.7, 54.6, 54.6, 54.5, 54.5, 54.4, 54.3, 22.9, 22.8, 22.8, 22.7, 22.7, 22.6, 22.5, 17.6, 11.8, 11.8, 11.7, 11.7, 11.7, 11.7.

*4.2.20. Synthesis of* ***28****.* Phenyl isocyanate (0.024 mL, 0.222 mmol) was added to a solution of **14** (34 mg, 0.108 mmol) in dry tetrahydrofuran (1 mL), and the mixture was stirred for 22 h at 60 °C, then poured into saturated sodium bicarbonate, and extracted with ethyl acetate. The organic layer was washed with brine, dried over magnesium sulfate, filtered, and evaporated. The residue was purified by column chromatography (silica gel, ethyl acetate/*n*-hexane=1/1) to give **28** (26 mg, 0.0478 mmol, 38%) as a colorless oil.

$^1$H NMR (600 MHz, $CDCl_3$) $\delta$ 7.74 (br s, 1H), 7.50 (t, $J$=8.0 Hz, 1H), 7.39–7.34 (m, 6H), 7.27–7.21 (m, 5H), 7.01 (t, $J$=7.4 Hz, 1H), 6.98 (t, $J$=7.5 Hz, 1H), 6.40 (br s, 1H), 3.90–3.81 (m, 3H), 3.76–3.72 (m, 3H), 3.60 (t, $J$=4.6 Hz, 2H), 3.57–3.50 (m, 3H), 3.41 (t, $J$=4.6 Hz, 2H), 3.25 (s, 3H), 1.62 (sextet, $J$=7.5 Hz, 2H), 1.18 (d, $J$=6.1 Hz, 3H), 0.92 (t, $J$=7.4 Hz, 3H); $^{13}$C NMR (150 MHz, $CDCl_3$) $\delta$ 155.7, 154.2, 145.2, 142.9, 139.3, 139.1, 131.1, 129.0, 128.8, 127.7, 126.4, 126.1, 123.0, 119.7, 119.3, 75.8, 71.9, 70.6, 70.5, 68.6, 59.0, 56.4, 51.3, 21.9, 17.2, 11.4.

*4.2.21. Synthesis of* ***8****.* Sodium hydride (7 mg, 0.175 mmol) was washed with *n*-hexane, and suspended in dry dimethylformamide (0.3 mL). A solution of **28** (22 mg, 0.040 mmol) in dry dimethylformamide (0.3 mL) was added to the suspension at 0 °C. The reaction mixture was stirred for 1 h at room temperature, then 1-iodopropane (0.04 mL, 0.412 mmol) was added, and stirring was continued for 4.5 h at room temperature. The solvent was removed in vacuo, and the residue was poured into water, and extracted with ethyl acetate. The organic layer was washed with brine, dried over magnesium sulfate, filtered, and evaporated. The residue was purified by preparative thin-layer chromatography (ethyl acetate/*n*-hexane=1/1) to give **8** (19 mg, 0.029 mmol, 74%) as a colorless oil.

$^1$H NMR (600 MHz, $CDCl_3$) $\delta$ 6.95 (t, $J$=7.5 Hz, 2H), 6.94 (t, $J$=7.6 Hz, 2H), 6.87 (t, $J$=7.3 Hz, 1H), 6.85 (t, $J$=7.3 Hz, 1H), 6.66 (d, $J$=7.3 Hz, 2H), 6.64 (t, $J$=8.0 Hz, 1H), 6.61 (d, $J$=7.4 Hz, 2H), 6.43 (d, $J$=7.9 Hz, 1H), 6.35 (d, $J$=7.9 Hz, 1H), 6.08 (s, 1H), 3.81–3.65 (m, 6H), 3.63–3.59 (m, 1H), 3.57 (t, $J$=4.6 Hz, 2H), 3.52–3.42 (m, 5H), 3.39 (s, 3H), 3.27 (t, $J$=7.6 Hz, 2H), 3.04 (dd, $J$=14.1, 8.0 Hz, 1H), 1.58–1.43 (m, 6H), 1.17 (d, $J$=6.2 Hz, 3H), 0.90 (t, $J$=7.4 Hz, 3H), 0.84 (t, $J$=7.3 Hz, 3H), 0.83 (t, $J$=7.4 Hz, 3H); $^{13}$C NMR (150 MHz, $CDCl_3$) $\delta$ 160.5, 160.0, 146.4, 144.7, 144.4, 144.0, 128.5, 128.3, 127.9, 126.8, 126.7, 125.0, 124.9, 124.4, 123.5, 123.2, 74.2, 72.2, 71.1, 70.8, 68.1, 59.2, 57.9, 53.5, 53.4, 21.7, 21.7, 21.7, 17.8, 11.5, 11.5.

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