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J. Org. Chem., **Just Accepted Manuscript** • DOI: 10.1021/acs.joc.8b02045 • Publication Date (Web): 05 Nov 2018

ACS Publications

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Synthesis and Conformational Analysis of Alternately *N*-Alkylated Aromatic Amide Oligomers

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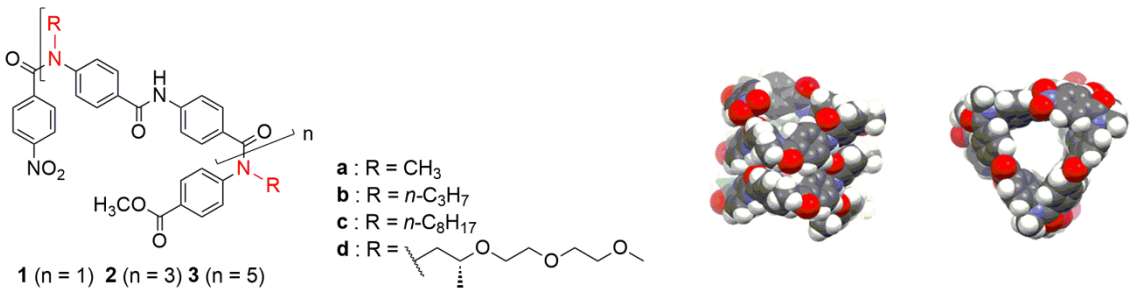


Abstract

Alternately *N*-alkylated aromatic amides such as **1** to **3** bearing various side chains were designed and synthesized as novel helical foldamers. The CD spectra of oligomers with chiral side chains showed a positive Cotton effect, which indicates that these oligomers take helical conformations in solution. The CD intensity gradually increased with increasing chain-length, and pentamer **3d** showed remarkably strong CD signals in chloroform. The absorption maxima of the UV spectra were increasingly red-shifted with increasing chain length, in contrast to the case of poly(*p*-*N*-alkylbenzamide)s. Structure optimization of the oligomers based on the crystal structure of **1a** as the monomer unit supported the formation of helical structure with a large cavity, and also suggested intramolecular hydrogen bond formation between secondary amides. The results of calculation were consistent with the observed spectroscopic features.

Introduction

Helixes are important conformational motifs in nature, as exemplified by the structures of DNA and various proteins.[1] In order to understand the relationships between the helical structures and functions of biopolymers, and to apply them to develop new functional molecules, various artificial helical polymers[2], supramolecules[3] and oligomers[4] have been synthesized. Generally, helical polymers can be classified into two types, i.e., static and dynamic. For example, PTrMA[5] and poly(*tert*-butyl isocyanide)s[6] are static helical polymers with a large reversal barrier, and they maintain one-handed helical structure even in solution. On the other hand, polyisocyanate[7] and polyacetylene[8] show rapid helical inversion; notably, the introduction of chiral element(s) into such dynamically helical molecules can lead to biased formation of one-handed helices. Oligomers with dynamic helical behavior are classified as foldamers,[9] and control of their helical conformation can afford functional molecules with interesting optical activity or liquid-crystal properties.[10] Particularly aromatic secondary amide oligomers are well-known representations of foldamer. Gong and Li introduced alkoxy group to aryl moieties, restricted the rotation of amide bond by intramolecular hydrogen bond and constructed the helical conformation.[11] Lehn and Huc developed various kinds of heterocyclic oligomers connected by secondary amide bond.[12]

We previously reported on the conformational properties of aromatic amides.[13] Aromatic secondary amides such as benzanilide exist in trans form both in the crystal and in solution, whereas their *N*-alkylated derivatives exist in cis form (Figure 1 (a)).[14] In the cis conformation, two aromatic rings lie in a face-to-face position with a dihedral angle of about 60 degrees. Poly(*N*-alkylated *p*-benzamide)s with repeating folded structure take helical conformations in solution (Figure 1 (b)).[15] The phenyl ring is oriented parallel to the helical axis with three monomer units per turn. Introduction of chiral *N*-substituents induced one-handed helical structures, whose absolute structure was determined by empirical and theoretical studies of the CD spectra. The folded structure of the aromatic *cis*-amide moiety provides a useful building block for construction of dynamic helical structures[16], and their helical properties can be tuned by modifying the aromatic structure.[17] We assumed that oligomers with longer aromatic moieties linked by a *cis*-amide bond would form helical structures with larger diameter. Such helical molecules might have a cavity that could include guest molecules having an appropriate molecular shape and size. In the case of poly(*N*-alkylated *p*-benzamide)s, the cavity is too small to include other molecules. Therefore, in this study, we designed and synthesized novel oligoamides, and obtained helical foldamers with larger diameter

and cavity size, based on the conformational properties of secondary and tertiary amide bonds.

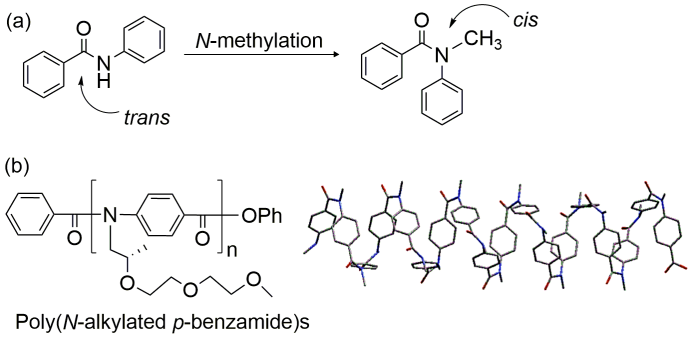


Figure 1. (a) Cis conformational preference of benzanilide caused by *N*-methylation.(b) Structures of helical Poly(*N*-alkylated *p*-benzamide)s. *N*-Substituents are omitted in the three-dimensional structures.

Results and Discussion

1. Design and syntheses of alternately *N*-alkylated amide oligomers

As novel oligoamides with larger diameter and cavity size, we designed alternately *N*-alkylated amide oligomers (Chart 1), in which we expected that the secondary benzanilides with trans conformation would be linked by *N*-alkylated amide bonds with cis conformation. Our previous studies showed that a macrocycle consisting of alternate secondary and tertiary amide bonds exists as alternate cis and trans amide moieties, forming a triangular-shaped cavity.[18] Based on those results, we anticipated that acyclic oligoamides with alternately *N*-alkylated amide bonds would form folding structures.

Using compound **1** as a monomer unit, we synthesized trimer **2** and pentamer **3**. Considering the solubility of the oligomers, methyl (**a** series), *n*-propyl (**b** series) or *n*-octyl (**c** series) groups were chosen as the *N*-alkyl groups. In addition, we synthesized oligomers possessing *N*-(*R*)-2-(methoxyethoxyethoxy)propyl, (*R*)-Tg groups, as chiral side chains (**d** series) in order to examine the possibility of bias to one-handed helix formation.

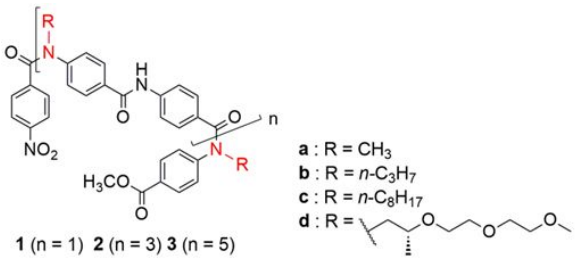
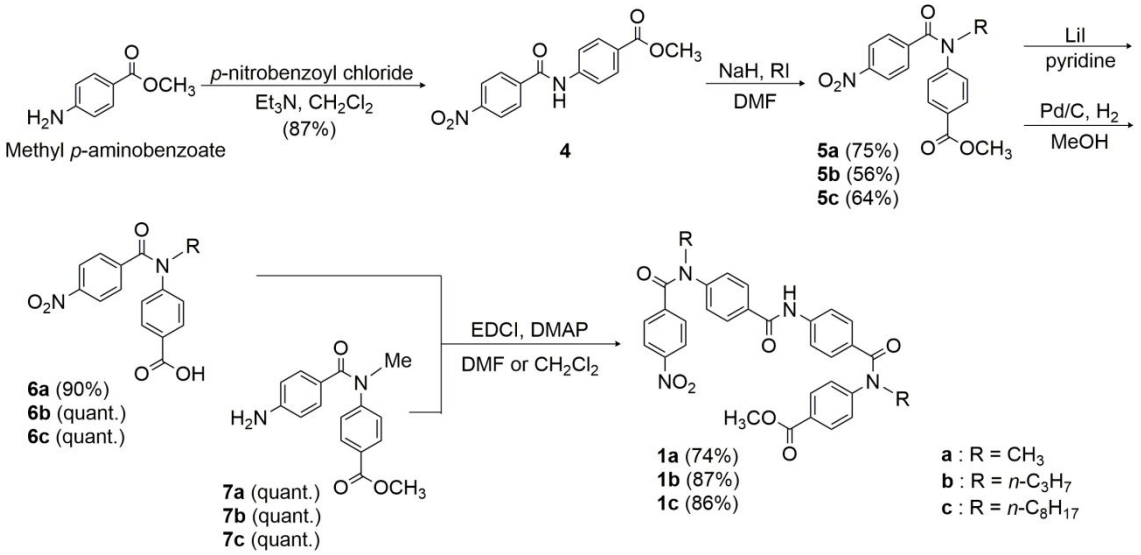


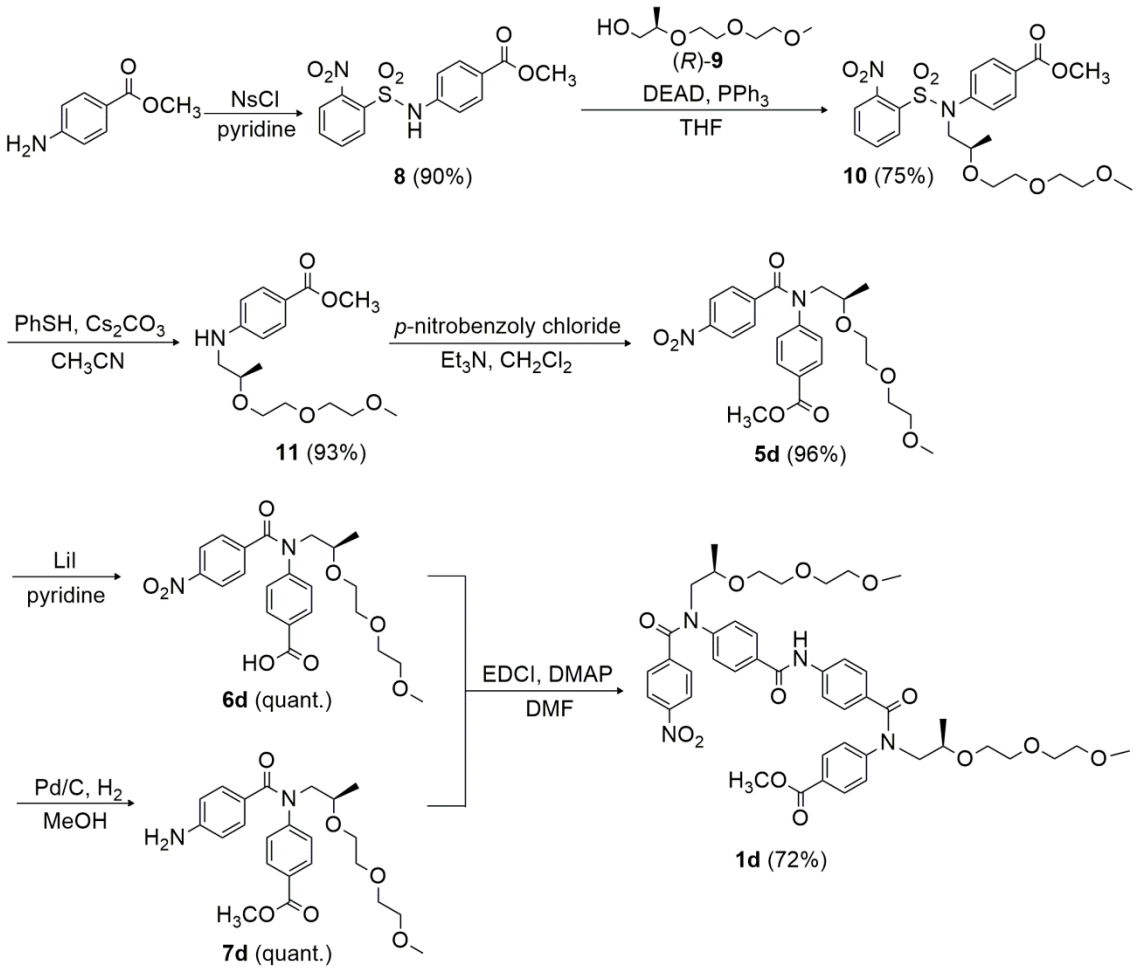
Chart 1

The monomers **1a-1c** were prepared as shown in Scheme 1. *N*-Alkylated amide **5** was prepared from methyl *p*-benzoate in two steps. Demethylation of **5** with lithium iodide afforded carboxylic acid **6** and reduction of the nitro group of **5** afforded amine **7**. Amide bond formation between these two compounds afforded key monomers **1a-1c**.



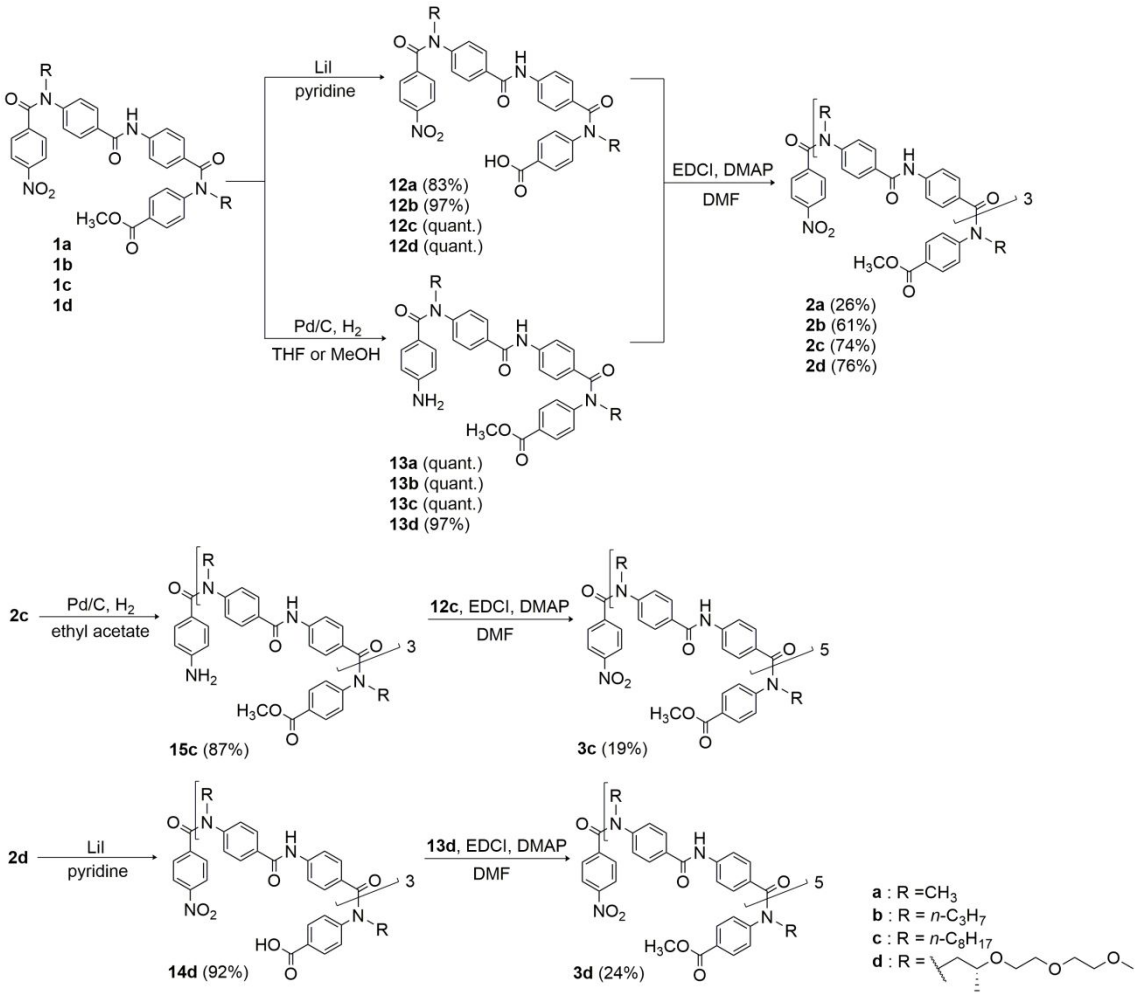
Scheme 1. Syntheses of monomers **1a - c** bearing alkyl side chains.

In the synthesis of monomer **1d**, introduction of a chiral substituent was performed by means of Fukuyama's nosyl methodology (Scheme 2).[19] Thus, methyl *p*-aminobenzoate was converted to sulfonamide **8** by treatment with *o*-nitrobenzenesulfonyl chloride. Alkylation of **8** was carried out under Mitsunobu conditions, using (*R*)-**9** synthesized from (*R*)-1,2-propanediol according to the reported method.[20] Removal of the *o*-nitrobenzenesulfonyl group of **10** was performed by treatment with PhSH and Cs_2CO_3 to give **11**. Amide bond formation with *p*-nitrobenzoyl chloride afforded alkylated amide **5d**, which was converted to the carboxyl compound **6d** and the amino compound **7d** by hydrolysis and by reduction, respectively. Condensation of **6d** and **7d** afforded monomer **1d**.



Scheme 2. Synthesis of monomer **1d** bearing chiral *N*-substituents.

Trimer **2** and pentamer **3** were synthesized similarly by condensation of the corresponding carboxylic acid and amine. However, trimers bearing *N*-methyl (**2a**) and *N*-*n*-propyl (**2b**) groups showed poor solubility. Thus, only the pentamers **3c** with *N*-*n*-octyl and **3d** with chiral Tg groups were synthesized (Scheme 3).



Scheme 3. Syntheses of trimers **2a-d** and pentamers **3c-d**.

2. ^{1}H NMR spectra of oligomers

The conformations of monomers **1** in solution were examined by comparing the ^{1}H NMR spectra with that of compound **5a**, which exists in cis conformation (Figure S1, Supporting Information). The chemical shifts of monomers **1a** and **1c** in the aromatic region were almost the same as those of the corresponding proton signals of compound **5a**. In the case of **1d** with chiral *N*-substituents, the signals of H3 and H8 were shifted to lower field (ca 0.15 ppm), while the chemical shifts of the other aromatic protons were similar to those of **5a**. These results suggest that monomers **1** predominantly exist in (*cis*, *trans*, *cis*) form in solution. This tendency was independent of the solvent (Figure S2).

To analyze the monomer conformation in more detail, VT ^{1}H NMR spectra of **1a**, **1c** and **1d** were measured in CD_2Cl_2 (Figure S3). Only monomer **1d** showed signal broadening at low temperature, and the aromatic signals were observed at higher field,

presumably due to aggregation of **1d** at low temperature as a result of interaction between the side chains, such as CH-O interaction.

In the ^{1}H NMR spectra of **1a**, minor peaks were observed downfield of the aromatic region and upfield of the aliphatic region at under 233 K, while only one set of signals was observed for **1c**, even at low temperature (Figure S4). The minor peaks of **1a** coalesced with the major peaks at 243 K, and the major and minor conformers were assigned to the (cis, trans, cis) and (trans, trans, cis) forms, respectively.

In the ^{1}H NMR spectra of the oligomers in $CDCl_3$ at 293 K, pentamer **3c** showed very broad signals, while the signals of monomer **1c** and trimer **2c** were sharp (Figure S5). However, pentamer **3c** showed relatively sharp signals in DMSO-d_6. These observations suggest that pentamer **3c** would be aggregated by intermolecular hydrogen bonding in $CDCl_3$. On the other hand, the amide NH signals of **2c** appeared at 8.5 - 9.0 ppm, while that of **3c** was shifted downfield at 10.3 ppm. These results suggest that intramolecular hydrogen bonding along the helical axis occurs only in the longer pentamer **3** with two helical turns, but not in the shorter trimer **2c** with essentially one helical turn.

3. Crystal structures of monomers

Monomer **1a** with the *N*-methyl group exhibits three polymorphs, depending on the recrystallization solvent, and each crystal contains a different conformer of **1a** (Figure 2, Table S1). In the crystal obtained from DMSO-d_6, **1a** exists in all-*trans*-amide form and the packing structure indicated the existence of intermolecular aromatic interaction and CH-O interaction (Figure S7). In the crystal obtained from CH_2Cl_2/*n*-hexane, **1a** exists in (*trans*, *trans*, *cis*) form, which corresponds to the minor conformation in CD_2Cl_2. In the packing structure, intermolecular hydrogen bonding and CH-O interaction are observed. In the crystal obtained from PhCl/*n*-hexane, **1a** exists in (*cis*, *trans*, *cis*) form, which corresponded to the major conformation in CD_2Cl_2. This crystal contains solvent of crystallization, and there are CH-Cl interaction between **1a** and the solvent molecule.

On the other hand, single crystals of **1b** obtained from DMSO-d_6 and $CHCl_3$/*n*-hexane were the same, and contained the (*cis*, *trans*, *cis*) form, as is also found in solution. Overall, it can be concluded that intermolecular interaction and solvent effects strongly influence the conformation of **1a** with the small *N*-methyl group, and the most stable conformation differs depending on the environment. Such effects should be less important for **1b** bearing the larger *N*-*n*-propyl group, and indeed, the most stable conformation depended simply on the amide conformational properties. Thus, monomers **1** with longer or larger *N*-substituents would be more useful as units for constructing helical oligomers.

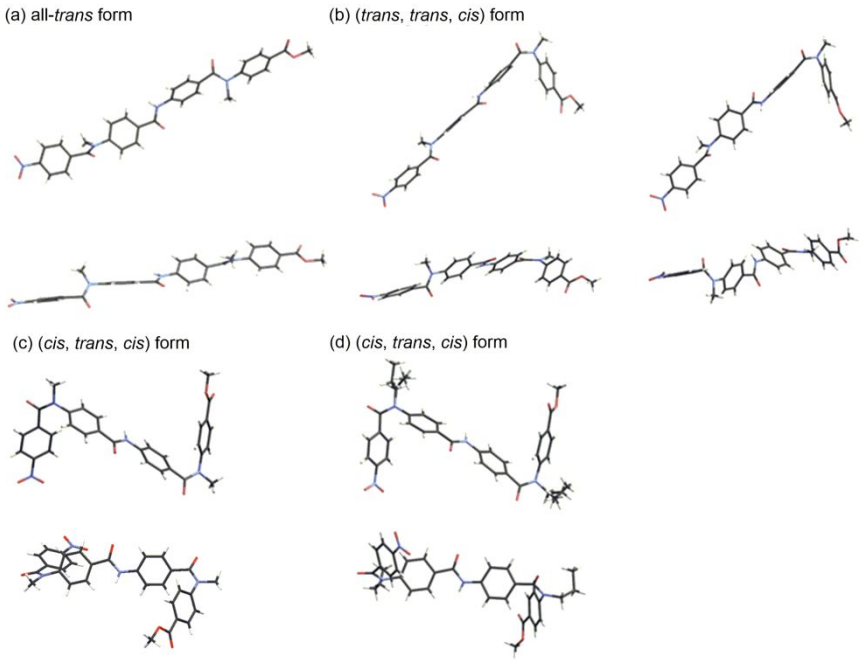


Figure 2. Crystal structures of **1a** from (a) DMSO-d_6, (b) CH_2Cl_2/*n*-hexane (two independent molecules exist in the asymmetric unit cell), (c) PhCl/*n*-hexane and **1b** (d) from $CHCl_3$ / *n*-hexane. (top : top view, bottom : side views).

4. UV and CD spectra of oligomers

UV and CD spectra of monomer **1d** and oligomers **2d** and **3d** possessing the chiral Tg side chain were measured in $CHCl_3$ (Figure 3). The spectrum of simple tertiary amide **5d** with cis structure was also measured for comparison. These compounds showed broad electronic absorption in the 240-350 nm region. The absorption maxima were increasingly red-shifted with increasing chain length. This feature was also observed in the UV spectra of oligomers **1c**-**3c** bearing the *N*-*n*-octyl group (Figure 4). Such red shifts were not observed in the UV spectra of oligo(*N*-alkylated *p*-benzamide)s.[13] Therefore, this is a characteristic feature of oligomers bearing alternatively *N*-alkylated amide bonds.

In the CD spectra, a positive Cotton effect was observed in the 240-350 nm region. The CD spectrum of trimer **2d** was similar in shape to that of monomer **1d**, but different from that of **5d**. However, the intensity was much larger for **2d**, which suggested induction of chiral folded structure of the oligomer by the chiral *N*-substituent. Further, pentamer **3d** showed remarkably strong CD signals. The CD intensity of each compound gradually decreased with increase of temperature (Figure S8). Such chain- and temperature-dependence of the CD signals suggests that the oligomers take helical

conformation in solution.

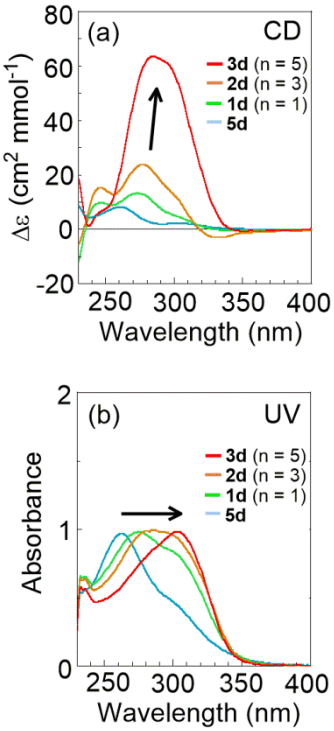


Figure 3. (a) CD and (b) UV spectra of **1d** (green line), **2d** (orange line), **3d** (red line) and **5d** (blue line), bearing (*R*)-Tg side chains in chloroform at 20°C. Concentration: [**1d**] = 143 μM, [**2d**] = 77 μM, [**3d**] = 46 μM, and [**5d**] = 262 μM.

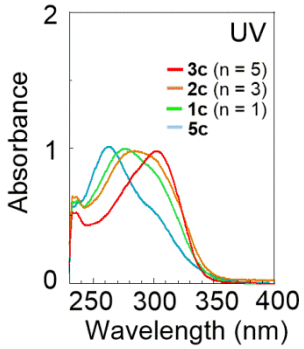


Figure 4. UV spectra of oligomers **5c** (blue line), **1c** (green line), **2c** (orange line) and **3c** (red line) bearing the *n*-octyl group in $CHCl_3$ at 20°C. Concentration: [**5c**] = 232 μM, [**1c**] = 126 μM, [**2c**] = 60 μM and [**3c**] = 37 μM.

The CD and UV spectra of oligomers in DMSO were slightly different from those in $CHCl_3$ (Figure 5). The UV spectrum of **3d** showed a red shift compared to that of **2d**,

though the change in maximum wavelength was small (302.5 nm in $CHCl_3$ and 297.5 nm in DMSO). Similarly, the CD signal also depended on the chain-length in DMSO, though the change from **2d** to **3d** was small, and no red-shift of maximum wavelength was observed in DMSO. The difference between the spectra in $CHCl_3$ and DMSO should be due to the presence or absence of hydrogen bond interactions of the secondary amides. The UV spectrum of **3c** was independent of concentration in the range of 4 - 80 μM (Figure S9). Therefore, the marked increase of CD intensity of **3d** in $CHCl_3$ is presumably due to stabilization of the helical structure by intramolecular hydrogen bond interactions. The oligomer **3d** would form two helical turns, which could make three intramolecular hydrogen bonds. Thus, pentamer **3d** with two helical turns formed a rather tight helical structure in $CHCl_3$, whereas it formed loose helical structure in DMSO, like the shorter oligomer **2d**. The red-shift in the UV spectra should be due to electronic interaction between the closely stacked aromatic groups as a result of intramolecular hydrogen bonding, which would make the HOMO-LUMO gap narrower.[21]

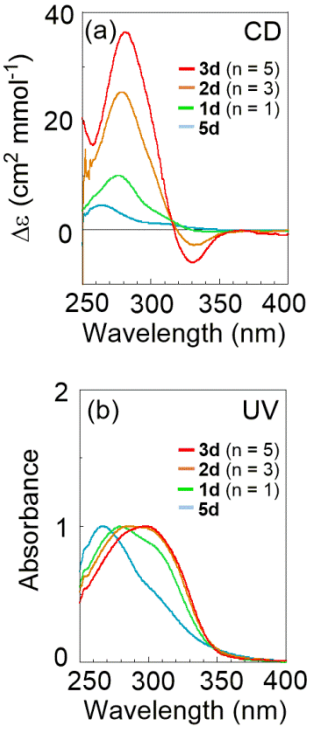


Figure 5. (a) CD and (b) UV spectra of oligomers **5d** (blue line), **1d** (green line), **2d** (orange line) and **3d** (red line) bearing (*R*)-Tg side chains in DMSO at 20°C.

5. Theoretical study on the Structural and Spectral Properties of Oligomers

NMR and UV/CD spectra indicated the helical structures of oligoamides, while the detailed structural features could not be determined. To consider the relationship between the helical structure of oligomers and the specific spectral features, we performed DFT geometry optimization of *N*-methylated oligomers **2a** and **3a** at the RI-B3LYP/def-SV(P) level, based on the crystal structure of (*cis*, *trans*, *cis*)-form monomer **1a**. The optimized conformations take helical structures and possess a cavity (Figure 6). As predicted from the CD and UV spectra of oligomers, the secondary amides form intramolecular hydrogen bonds along the helical axis. The cavity's size is approximately 9 Å.

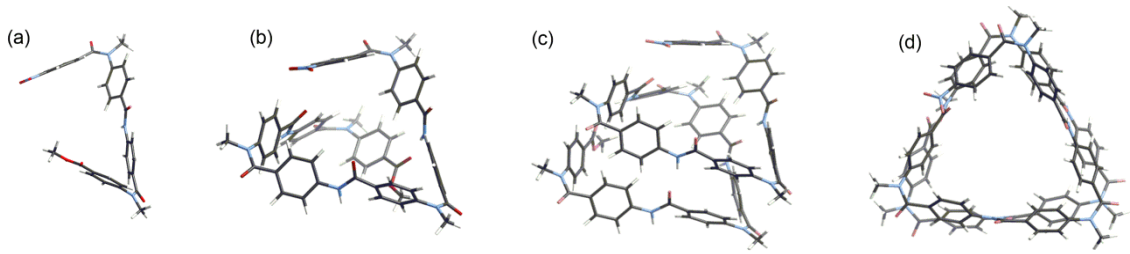


Figure 6. Optimized conformations of (a) **1a**, (b) **2a**, (c) **3a** and (d) top view of **3a**.

We also employed time-dependent DFT at the RI-B3LYP/def-SV(P) level to calculate the UV and CD spectra of the optimized conformations of monomer **1a**, and oligomers **2a** and **3a** (Figure 7). The calculated CD spectra were different from the measured spectra. In the calculated CD spectra, trimer **2a** and pentamer **3a** showed bisignate CD signals and **2a** also showed relatively strong CD intensity. The reason of difference shapes of spectra is not clear. This result suggests that trimer **2a** forms one helical turn with one intramolecular hydrogen bond, and the conformation is not stable. Thus, structural fluctuation would lower the CD intensity. On the other hand, the red-shift of the UV absorption maxima was reproduced. In the calculated UV spectra, the absorption maxima were at 190 nm for **5a**, 290 nm for **1a**, 320 nm for **2a**, and 340 nm for **3a**. Thus, the theoretical studies supported the putative helical structures of oligomers with intramolecular hydrogen bond interactions deduced from empirical experiments.

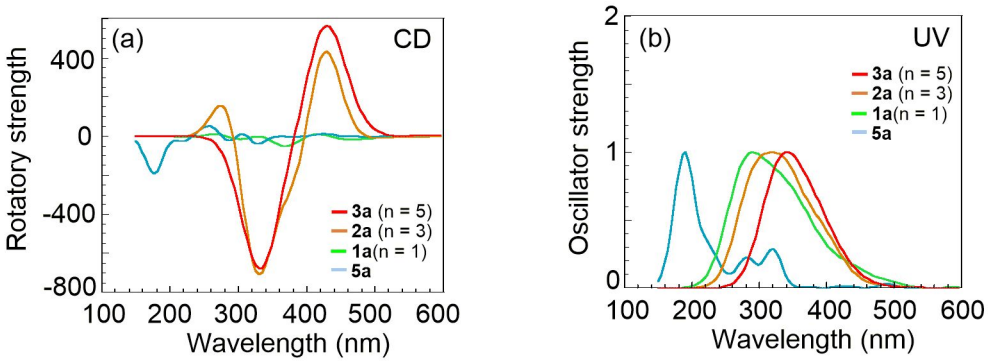


Figure 7. Calculated spectra of the optimized structures of oligomer **1a-3a**.

Conclusion

In conclusion, we synthesized alternately *N*-alkylated aromatic amide oligomers and found that the oligomers formed helical structures with a larger cavity than that of poly(*N*-alkylated *p*-benzamide)s. Introduction of a chiral *N*-substituent induced one-handed helical conformations. The NMR, UV, and CD spectra, as well as theoretical analysis, indicated intramolecular hydrogen bond interactions of secondary amides contribute the stability of the helical conformation. These novel helical oligomers are expected to have the ability to encapsulate a guest molecule in their central cavity. Studies of their potential for application in molecular recognition and chiral discrimination are in progress.

Experimental Section

All reagents were purchased from Sigma-Aldrich Chemical Co., Wako Pure Chemical Industries, Tokyo Kasei Kogyo Co., and Kanto Kagaku Co., Inc. Silica Gel 60 N (spherical, neutral) for column chromatography was purchased from Kanto Kagaku Co., Inc. ^{1}H and ^{13}C NMR spectra were recorded on JEOL JNM-ECS400 and Bruker Avance 600 spectrometers with chloroform (7.26 ppm), methylene chloride (5.32 ppm), methanol (3.31 ppm) or DMSO (2.50 ppm) as the internal standard. Mass spectral data were obtained on a Bruker Daltonics micro TOF-2focus in the positive ion detection mode. X-Ray crystallographic data for compounds **1a** and **1b** were collected at Ochanomizu University on a Bruker SMART APEX II ULTRA diffractometer equipped with a CCD detector using graphite-monochromated Mo Kα (λ = 0.71073 Å) radiation, or at the Center for Analytical Instrumentation in Chiba University on a Bruker SMART APEX II ULTRA diffractometer equipped with a CCD detector and graphite-monochromated Cu Kα (λ = 0.71073 Å) radiation. Data were corrected for absorption by the multiscan semiempirical method implemented in SADABS and the

crystal structures were solved by the intrinsic phasing method in SHELXT and refined by SHELXL-97.[22] Full-matrix least-squares refinement was performed on F2 for all unique reflections with anisotropic displacement parameters for non-hydrogen atoms. All non-hydrogen atoms were refined anisotropically. All hydrogen atoms were included at their calculated positions. UV spectra were recorded with a JASCO V-650, and CD spectra were recorded with a JASCO J-820 spectropolarimeter using a 2 mm quartz cell. The concentration of each solution in CD experiments was adjusted so that the absorbance of the oligomer was 1 at the maximum absorption wavelength in the examined solvent.

Synthesis of 4.[23]

Triethylamine (5 mL, 1.2 eq.) was added to a solution of methyl *p*-aminobenzoate (4.60 g, 30.4 mmol) in dichloromethane (70 mL), and the mixture was stirred at 0°C. A solution of *p*-nitrobenzoyl chloride (5.64 g, 1.0 eq.) in dichloromethane (70 mL) was added to the cold amine solution and the mixture was stirred at rt for 12 h, then washed successively with 2 M HCl, sat. $NaHCO_3$, and brine. The organic layer was dried over $MgSO_4$, filtered and concentrated in *vacuo*. The residue was recrystallized from ethyl acetate /*n*-hexane to give **5** (7.96 g, 26.5 mmol, 87%) as a colorless powder; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.87 (s, 1 H), 8.39 (d, J = 9.2 Hz, 2 H), 8.20 (d, J = 8.7 Hz, 2 H), 7.99 (d, J = 9.2 Hz, 2 H), 7.95 (d, J = 9.2 Hz, 2 H), 3.85 (s, 3 H).

Synthesis of 5a.[23]

A solution of **4** (299 mg, 1.00 mmol) in DMF (10 mL) was added to a suspension of NaH (60 %, 79.9 mg, 2.0 eq., washed with *n*-hexane twice) in DMF (9 mL) at 0°C. The solution was stirred at rt for 30 min, and then MeI (514 mg, 3.6 eq.) was added to it at 0°C. The resulting solution was stirred at rt for 3 h. 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 $MgSO_4$, filtered and concentrated in *vacuo.* The residue was purified by silica gel column chromatography (ethyl acetate /*n*-hexane 1:1) to give **5a** (231 mg, 0.74 mmol, 74%) as a yellow powder; ^{1}H NMR (400 MHz,$CDCl_3$) δ 8.05 (d, J = 8.8 Hz, 2 H), 7.92 (d, J = 8.8 Hz, 2 H), 7.45 (d, J = 9.2 Hz, 2 H), 7.08 (d, J = 8.7 Hz, 2 H), 3.89 (s, 3 H), 3.55 (s, 3 H) ; ^{13}C NMR (150 MHz, $CDCl_3$) δ 168.4, 166.0, 148.3, 147.9, 141.6, 131.0, 129.7, 128.8, 126.6, 123.4, 52.5, 38.2.

Synthesis of 5b.

A solution of **4** (2.52 g, 8.39 mmol) in DMF (50 mL) was added at 0°C to a suspension

of NaH (60 %, 512 mg, 1.5 eq., washed with *n*-hexane twice) in DMF (9 mL). The solution was stirred at rt for 30 min. 1-Iodopropane (4.59 g, 3.2 eq.) was added at 0°C. The resulting solution was stirred at rt for 8 h and heated at 50°C for 16 h. 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 $MgSO_4$, filtered and concentrated in *vacuo.* The residue was purified by silica gel column chromatography (ethyl acetate / *n*-hexane 1 : 5) to give **5b** (1.48 g, 4.33 mmol, 56%) as a yellow amorphous solid; ^{1}H NMR (400 MHz,$CDCl_3$) δ 8.05 (d, *J* = 8.8 Hz, 2 H), 7.92 (d, *J* = 8.8 Hz, 2 H), 7.45 (d, *J* = 9.2 Hz, 2 H), 7.08 (d, *J* = 8.7 Hz, 2 H), 3.94 (m, 2H), 3.89 (s, 3 H), 1.66 (sext, *J* = 7.4 Hz, 2 H), 0.96 (t, *J* = 7.4 Hz, 3 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 168.2, 166.0, 148.2, 146.7, 142.1, 131.0, 129.6, 129.0, 127.5, 123.4, 52.5, 52.0, 21.1, 11.4. HRMS (ESI+) m/z calcd for $C_{18}H_{19}N_2O_5$ $[M+H]^+$ 343.1288, found 343.1295.

Synthesis of 5c.

A solution of **4** (105 mg, 0.35 mmol) in DMF (2 mL) was added at 0°C to a suspension of NaH (60 %, 15.7 mg, 0.39 mmol, washed with *n*-hexane twice) in DMF (1 mL). The solution was stirred at rt for 30 min, and then 1-iodooctane (172 mg, 0.72 mmol) was added at 0°C. The resulting solution was stirred at rt for 2 h at 80°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 $MgSO_4$, filtered and concentrated in *vacuo*. The residue was purified by silica gel column chromatography (ethyl acetate / dichloromethane=1/40) to give **5c** (82.2 mg, 0.20 mmol, 57%) as a yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (d, *J* = 8.7 Hz, 2 H), 7.92 (d, *J* = 8.7 Hz, 2 H), 7.43 (d, *J* = 8.7 Hz, 2 H), 7.08 (d, *J* = 8.7 Hz, 2 H), 3.96 (dd, *J* = 7.8, 7.8 Hz, 2 H), 3.89 (s, 3 H), 1.62 (sext, *J* = 7.3 Hz, 2 H), 1.34-1.25 (m, 10 H), 0.87 (t, *J* = 6.9 Hz, 3 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 168.1, 166.0, 148.2, 146.7, 142.1, 131.0, 129.7, 129.0, 127.5, 123.4, 52.5, 50.6, 31.9, 29.4, 29.3, 27.8, 27.0, 22.7, 14.2. HRMS (ESI+) m/z calcd for $C_{23}H_{29}N_2O_5$ $[M+H]^+$ 413.2071, found 413.2077.

Synthesis of 5d.

Triethylamine (1 mL, 7.17 mmol) was added to a solution of **11** (1.0073 g, 3.24 mmol) in dichloromethane (10 mL), and the mixture was stirred at 0°C. A solution of *p*-nitrobenzoyl chloride (659.7 mg, 3.56 mmol) in dichloromethane (10 mL) was added to the cold amine solution and the mixture was stirred at rt for 6 h. The mixture was washed successively with 2 M hydrochloric acid, 2 M NaOH and brine. The organic

layer was dried over $MgSO_4$, filtered and concentrated in *vacuo* to give **5d** (1.4354 g, 3.12 mmol, 96%) as a yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (d, *J* = 8.7 Hz, 2 H), 7.87 (d, *J* = 8.7 Hz, 2 H), 7.49 (d, *J* = 8.2 Hz, 2 H), 7.27 (d, *J* = 6.8 Hz, 2 H), 4.13 (d, *J* = 12.8 Hz, 1 H), 3.94 (d, *J* = 12.8 Hz, 1 H), 3.88 (s, 3 H), 3.76-3.57 (m, 6 H), 3.53-3.49 (m, 3 H), 3.35 (s, 3 H), 1.21 (d, *J* = 6.0 Hz, 3 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 168.7, 166.2, 148.2, 142.2, 132.2, 130.7, 129.8, 128.5, 127.8, 123.4, 73.3, 72.0, 70.9, 70.6, 68.4, 59.1, 56.7, 52.4, 17.4. HRMS (ESI+) m/z calcd for $C_{23}H_{28}N_2NaO_8$ $[M+Na]^+$ 483.1738, found 483.1729.

Synthesis of 6a.[23]

LiI (870 mg, 21 eq.) was added to a solution of **5a** (96.8 mg, 0.31 mmol) in pyridine (10 mL) and the resulting mixture was stirred for 41 h at 115°C. The mixture was cooled to 0°C, diluted with CH_2Cl_2 (50 mL), and washed with 2 M HCl (70 mL). The aqueous layer was repeatedly extracted with CH_2Cl_2, and the combined organic layers were dried over $MgSO_4$, filtered and concentrated in *vacuo*. The residue was purified by silica gel column chromatography (ethyl acetate / *n*-hexane 4 : 1) to give **6a** (84.2 mg, 0.28 mmol, 90%) as a pale yellow powder; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (d, *J* = 8.7 Hz, 2H), 7.98 (d, *J* = 8.2 Hz, 2H), 7.47 (d, *J* = 8.7 Hz, 2H), 7.13 (d, *J* = 8.7 Hz, 2H), 3.56 (s, 3H).

Synthesis of 6b.

LiI (109 mg, 5.1 eq.) was added to a solution of **5b** (55.0 mg, 0.16 mmol) in pyridine (3 mL) and the resulting mixture was stirred for 4 days at 115°C. After removal of the solvent in *vacuo*, the residue was extracted with CH_2Cl_2. The organic layer was washed with 2 M HCl, dried over $MgSO_4$, filtered and concentrated in *vacuo* to give **6b** (57.2 mg, quant.) as a colorless amorphous solid; ^{1}H NMR (400 MHz,$CDCl_3$) δ 8.04 (d, *J* = 8.7 Hz, 2 H), 7.98 (d, *J* = 8.7 Hz, 2 H), 7.45 (d, *J* = 8.7 Hz, 2 H), 7.11 (d, *J* = 8.7 Hz, 2 H), 3.89 (m, 2H), 3.95 (m, 2 H), 1.67 (sext, *J* = 7.3 Hz, 2 H), 0.96 (t, *J* = 7.3 Hz, 3 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.4, 168.3, 148.3, 147.5, 142.0, 131.7, 129.7, 128.0, 127.6, 123.4, 52.1, 21.1, 11.4. HRMS (ESI+) m/z calcd for $C_{17}H_{17}N_2O_5$ $[M+H]^+$ 329.1132, found 329.1129.

Synthesis of 6c.

LiI (147 mg, 1.10 mmol) was added to a solution of **5c** (89.9 mg, 0.22 mmol) in pyridine (2.5 mL) and the resulting mixture was stirred for 3 days at 115°C. After removal of the solvent in *vacuo*, the residue was extracted with CH_2Cl_2. The organic

layer was washed with 2 M HCl, dried over $MgSO_4$, filtered and concentrated in *vacuo* to give **6c** (86.8 mg, quant.) as a brown oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (d, *J* = 8.7 Hz, 2 H), 7.97 (d, *J* = 8.7 Hz, 2 H), 7.44 (d, *J* = 8.7 Hz, 2 H), 7.10 (d, *J* = 8.7 Hz, 2 H), 3.97 (dd, *J* = 7.8, 7.8 Hz, 2 H), 1.62 (sext, *J* = 7.3 Hz, 2 H), 1.32-1.25 (m, 10 H), 0.87 (t, *J* = 6.9 Hz, 3 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.6, 168.2, 148.3, 147.5, 142.0, 131.7, 129.7, 128.0, 127.6, 123.4, 50.7, 31.9, 29.3, 29.3, 27.8, 27.0, 22.7, 14.2.; HRMS (ESI+) m/z calcd for $C_{22}H_{27}N_2O_5$ $[M+H]^+$ 399.1914, found 399.1916.

Synthesis of 6d.

LiI (899.5 mg, 6.72 mmol) was added to a solution of **5d** (460.8 mg, 1.32 mmol) in pyridine (15 mL) and the resulting mixture was stirred for 4 days at 115°C. After removal of the solvent in *vacuo*, the residue was extracted with CH_2Cl_2. The organic layer was washed with 2 M HCl, dried over $MgSO_4$, filtered and concentrated in *vacuo* to give **6d** (590.4 mg, quant.) as a brown oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (d, *J* = 8.7 Hz, 2 H), 7.92 (d, *J* = 8.7 Hz, 2 H), 7.50 (d, *J* = 8.7 Hz, 2 H), 7.31 (d, *J* = 8.2 Hz, 2 H), 4.16 (d, *J* = 12.8 Hz, 1 H), 3.98 (br, 1 H), 3.78-3.74 (m, 1 H), 3.70-3.48 (m, 8 H), 3.45 (s, 3 H), 1.22 (d, *J* = 6.4 Hz, 3 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.0, 168.7, 148.3, 142.1, 131.6, 131.3, 129.8, 127.8, 127.0, 123.4, 73.3, 72.0, 70.9, 70.6, 68.4, 59.1, 56.8, 17.4. HRMS (ESI+) m/z calcd for $C_{22}H_{26}N_2NaO_8$ $[M+Na]^+$ 469.1581, found 469.1583.

Synthesis of 7a. [24]

A solution of **5a** (199 mg, 0.63 mmol) in dry methanol (12 mL) was hydrogenated with Pd-C (10%, 20.4 mg) for 80 min at rt. The reaction mixture was filtered on Celite, and the filtrate was concentrated in *vacuo* to give **7a** (194 mg, quant.) as a pale pink solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (d, *J* = 8.7 Hz, 2H), 7.14 (d, *J* = 8.7 Hz, 2H), 7.08 (d, *J* = 8.7 Hz, 2H), 6.44 (d, *J* = 8.2Hz, 2H), 3.89 (s, 3H), 3.49 (s, 3H).

Synthesis of 7b.

A solution of **5b** (37.1 mg, 0.11 mmol) in MeOH (3 mL) was hydrogenated with Pd-C (10%, 5.3 mg) for 90 min at rt. The reaction mixture was filtered on Celite, and the filtrate was concentrated in *vacuo* to give **7b** (31.8 mg, 0.10 mmol, 94%) as a colorless amorphous solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (d, *J* = 8.7 Hz, 2H), 7.12 (d, *J* = 8.7 Hz, 2H), 7.07 (d, *J* = 8.7 Hz, 2H), 6.40 (d, *J* = 8.7 Hz, 2H), 3.89 (m, 2H), 3.89 (s, 3H), 3.78 (br, 2H), 1.64 (sext, *J* = 7.4 Hz, 2H), 0.93 (t, *J* = 7.3 Hz, 3H). ; ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.6, 166.6, 149.1, 148.3, 131.3, 130.6, 127.4, 12.0, 125.3, 113.8,

52.3, 51.1, 21.3, 11.5. HRMS (ESI+) m/z calcd for $C_{18}H_{21}N_2O_3$ $[M+H]^+$ 313.1547, found 313.1556.

Synthesis of 7c.

A solution of **5c** (1.15 g, 2.81 mmol) in dry methanol (30 mL) was hydrogenated with Pd-C (10%, 262 mg) for 5 h at rt. The reaction mixture was filtered on Celite, and the filtrate was concentrated in *vacuo* to give **7c** (1.11 g, quant.) as a yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (d, *J* = 8.7 Hz, 2 H), 7.11 (d, *J* = 8.7 Hz, 2 H), 7.07 (d, *J* = 8.7 Hz, 2 H), 6.40 (d, *J* = 8.7 Hz, 2 H), 3.91 (dd, *J* = 7.8, 7.8 Hz, 2 H), 3.79 (s, 3 H), 1.62 (sext, *J* = 7.3 Hz, 2 H), 1.34-1.25 (m, 10 H), 0.85 (t, *J* = 6.9 Hz, 3 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.3, 166.6, 149.0, 148.4, 131.2, 130.6, 127.3, 127.0, 125.1, 113.7, 52.3, 50.7, 31.9, 29.4, 29.3, 28.0, 27.1, 22.7, 14.2. HRMS (ESI+) m/z calcd for $C_{23}H_{31}N_2O_3$ $[M+H]^+$ 383.2329, found 383.2338.

Synthesis of 7d.

A solution of **5d** (48.6 mg, 0.11 mmol) in dry methanol (1.5 mL) was hydrogenated with Pd-C (10%, 5.8 mg) for 8 h at rt. The reaction mixture was filtered on Celite, and the filtrate was concentrated in *vacuo* to give **7d** (45.1 mg, quant.) as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86(d, *J* = 8.7 Hz, 2 H), 7.22 (d, *J* = 8.7 Hz, 2 H), 7.15 (d, *J* = 8.2 Hz, 2 H), 6.49 (d, *J* = 8.2 Hz, 2 H), 4.15 (dd, *J* = 14.4, 4.0 Hz, 1 H), 3.94 (m, 1 H), 3.87 (s, 3 H), 3.85-3.49 (m, 9 H), 3.45 (s, 3 H), 1.19 (d, *J* = 6.4 Hz, 3 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.7, 166.7, 150.2, 148.5, 131.3, 130.4, 127.0, 126.9, 125.0, 113.7, 74.2, 72.0, 70.8, 70.6, 68.5, 59.1, 57.0, 52.2, 17.8. HRMS (ESI+) m/z calcd for $C_{23}H_{30}N_2NaO_6$ $[M+Na]^+$ 453.1996, found 453.1985.

Synthesis of 1a.

1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (1.98 g, 1.9 eq.) and *N,N*-dimethyl-4-aminopyridine (1.24 g, 1.9 eq.) were added to a solution of **6a** (1.80 g, 5.99 mmol) and **7a** (1.55 g, 1.1 eq.) in DMF (10 mL). The resulting mixture was stirred at rt for 12 h. After removal of the solvent in *vacuo*, the residue was extracted with dichloromethane. The organic layer was washed successively with 2 M HCl, sat. $NaHCO_3$ and brine, dried over $MgSO_4$, filtered and concentrated in *vacuo*. The residue was washed with ethyl acetate to give **1a** (2.50 g, 4.41 mmol, 81%) as a white powder; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.06 (d, *J* = 8.2 Hz, 2H), 7.90 (d, *J* = 7.8Hz, 2H), 7.73 (d, *J* = 8.2 Hz, 2H), 7.69 (s, 1H), 7.46 (d, *J* = 8.7 Hz, 2H), 7.44 (d, *J* = 8.8 Hz, 2H), 7.30 (d, *J* = 7.8 Hz, 2H), 7.13 (d, *J* = 8.2 Hz, 2H), 7.08 (d, *J* = 7.8 Hz, 2H), 3.88 (s, 3H), 3.55 (s,

3H), 3.52(s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 167.0, 168.4, 166.3, 164.3, 149.2, 148.5, 147.3, 141.7, 139.3, 133.2, 131.6, 130.8, 130.3, 129.7, 128.6, 128.0, 127.1, 126.5, 123.5, 119.1, 52.4, 38.4, 38.3. HRMS (ESI+) m/z calcd for $C_{31}H_{26}N_4NaO_7$ $[M+Na]^+$ 589.1694, found 589.1685.

Synthesis of 1b.

1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (316 mg, 1.65 mmol) and *N,N*-dimethyl-4-aminopyridine (199 mg, 1.63 mmol) were added to a solution of **6b** (415 mg, 1.26 mmol) and **7b** (390 mg, 1.25 mmol) in DMF (12 mL). The resulting mixture was stirred for 4 h at rt. After removal of the solvent in *vacuo*, the residue was extracted with dichloromethane. The organic layer was washed successively with 2 M HCl, sat. $NaHCO_3$ and brine, dried over $MgSO_4$, filtered and concentrated in *vacuo*. The residue was purified by column chromatography (silica gel, ethyl acetate / *n*-hexane =1 / 5) to give **1b** (616 mg, 0.99 mmol, 87%) as a yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (d, J = 8.2 Hz, 2H), 7.89 (d, J = 8.2 Hz, 2H), 7.71 (d, J = 8.2 Hz, 2H), 7.69 (s, 1H), 7.44 (d, J = 8.7 Hz, 2H), 7.41 (d, J = 8.7 Hz, 2H), 7.28 (d, J = 7.8 Hz, 2H), 7.12 (d, J = 8.2 Hz, 2H), 7.07 (d, J = 7.8 Hz, 2H), 3.92 (m, 4H), 3.88 (s, 3H), 1.65 (sext, J = 7.3 Hz, 4H), 0.96 (t, J = 7.3 Hz, 3H), 0.94 (t, J = 7.3 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 169.7, 168.2, 166.4, 164.3, 148.2, 148.0, 142.1, 139.2, 133.3, 131.9, 130.7, 130.1, 129.6, 128.6, 128.0, 127.9, 127.3, 123.4, 119.1, 52.4, 52.1, 21.2, 21.1, 11.5, 11.4.; HRMS (ESI+) m/z calcd for $C_{35}H_{35}N_4O_7$ $[M+H]^+$ 623.2500, found 623.2486.

Synthesis of 1c.

1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (44.0 mg, 0.23 mmol) and *N,N*-dimethyl-4-aminopyridine (27.9 mg, 0.23 mmol) were added to a solution of **6c** (71.8 mg, 0.18 mmol) and **7c** (76.8 mg, 0.20 mmol) in DMF (2 mL). The resulting mixture was stirred for 5 h at rt. After removal of the solvent in *vacuo*, the residue was extracted with dichloromethane. The organic layer was washed successively with 2 M HCl, sat. $NaHCO_3$ and brine, dried over $MgSO_4$, filtered and concentrated in *vacuo*. The residue was purified by column chromatography (silica gel, ethyl acetate / dichloromethane =1 / 5) to give **1c** (117.8 mg, 0.15 mmol, 86%) as a yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (d, J = 8.7 Hz, 2 H), 7.89 (d, J = 8.2 Hz, 2 H), 7.70 (d, J = 8.7 Hz, 2 H), 7.64 (s, 1 H), 7.44 (d, J = 8.7 Hz, 2 H), 7.41 (d, J = 8.7 Hz, 2 H), 7.28 (d, J = 8.7 Hz, 2 H), 7.11 (d, J = 8.7 Hz, 2 H), 7.06 (d, J = 8.2 Hz, 2 H), 3.94 (m, 4 H), 3.88 (s, 3 H), 1.61 (m, 4 H), 1.38-1.15 (m, 20 H), 0.86 (dt, J = 7.2, 2.2 Hz, 6 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 169.6, 168.1, 166.4, 164.3, 148.3, 148.1, 146.0, 142.2, 139.2,

133.4, 132.0, 130.7, 130.2, 129.6, 128.6, 128.1, 128.0, 127.3, 123.4, 119.1, 52.4, 50.7, 31.9, 31.9, 29.4, 29.4, 29.3, 29.3, 28.0, 27.8, 27.1, 27.0, 22.7, 14.2. HRMS (ESI+) m/z calcd for $C_{45}H_{55}N_4O_7$ $[M+H]^+$ 763.4065, found 763.4048.

Synthesis of 1d.

1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (30.3 mg, 0.16 mmol) and *N,N*-dimethyl-4-aminopyridine (21.1 mg, 0.17 mmol) were added to a solution of **6d** (36.2 mg, 0.08 mmol) and **7d** (45.1 mg, 0.10 mmol) in DMF (2 mL). The resulting mixture was stirred for 20 h at rt. After removal of the solvent in *vacuo*, the residue was extracted with dichloromethane. The organic layer was washed successively with 2 M HCl, sat. $NaHCO_3$ and brine, dried over $MgSO_4$, filtered and concentrated in *vacuo*. The residue was purified by column chromatography (silica gel, ethyl acetate/methanol =15/1) to give **1d** (45.9 mg, 0.06 mmol, 72%) as a yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (d, *J* = 8.7 Hz, 2 H), 7.85 (d, *J* = 8.7 Hz, 2 H), 7.82 (s, 1 H), 7.69 (d, *J* = 8.7 Hz, 2 H), 7.49 (d, *J* = 8.2 Hz, 2 H), 7.42 (d, *J* = 8.7 Hz, 2 H), 7.31 (d, *J* = 8.7 Hz, 2 H), 7.23 (d, *J* = 8.7 Hz, 2 H), 4.16(dd, *J* = 10.5, 3.7 Hz, 2 H), 3.96 (m, 2 H),3.87 (s, 3 H), 3.75-3.47 (m, 18 H), 3.36 (s, 3 H), 3.33 (s, 3 H), 1.21 (m, 6 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.0, 166.5, 164.6, 149.3, 148.3, 142.2, 139.5, 133.0, 131.8, 130.5, 130.3, 129.8, 128.3, 128.2, 127.7, 127.4, 123.4, 119.0, 73.9, 73.5, 72.0, 70.9, 70.9, 70.6, 70.5, 68.5, 68.3, 59.2, 59.1, 56.8, 56.6, 52.3, 17.7, 17.4. HRMS (ESI+) m/z calcd for $C_{45}H_{54}N_4NaO_{13}$ $[M+Na]^+$ 881.3580, found 881.3577.

Synthesis of 8. [25]

2-Nitrobenzenesulfonyl chloride (1.4687 g, 6.63 mmol) was added to a solution of methyl *p*-aminobenzoate (1.0069 g, 6.66 mmol) in dry pyridine (5 mL) at 0°C, and the reaction mixture was stirred for 1 h at room temperature. The solvent was removed in *vacuo*, then the residue was poured into 2 M hydrochloric acid, and extracted with chloroform. The organic layer was washed with brine, dried over $MgSO_4$, filtered, and evaporated to give **8** (2.0189 g, 6.00 mmol, 90%) as a red solid; ^{1}H NMR (400 MHz,DMSO-d_6) δ 11.3 (s, 1 H), 8.04 (d, *J* = 6.4 Hz, 1 H), 8.01 (d, *J* = 8.2 Hz, 1 H), 7.89 (d, *J* = 7.2 Hz, 1 H), 7.87 (d, *J* = 8.7 Hz, 2 H), 7.82 (d, *J* = 7.3 Hz, 1 H), 7.24 (d, *J* = 8.7 Hz, 2 H), 3.79 (s, 3 H).

Synthesis of 10.

Diethyl azodicarboxylate (40% in toluene, 345.6 mg, 0.79 mmol) in dry tetrahydrofuran (1 mL) was added to a mixture of **8** (132.0 mg, 0.39 mmol), (*R*)-**9** (73.5

mg, 0.41 mmol), and triphenylphosphine (210.2 mg, 0.80 mmol) in dry tetrahydrofuran (3 mL) under an argon atmosphere at 0°C. The reaction mixture was stirred for 2 days at room temperature, then the solvent was removed in *vacuo*, and the residue was purified by column chromatography (silica gel, ethyl acetate/*n*-hexane=2/1) to give **10** (146.7 mg, 0.30 mmol, 75%) as a yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, J = 8.4 Hz, 2 H), 7.61 (m, 2 H), 7.52 (d, J = 7.2 Hz, 1 H), 7.44 (td, J = 6.4, 2.3 Hz, 1 H), 7.38 (d, J = 8.8 Hz, 2 H), 3.91 (s, 3 H), 3.87 (m, 2 H), 3.63-3.39 (m, 9 H), 3.37 (s, 3 H), 1.18 (t, J = 6.4 Hz, 3 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 166.3, 148.0, 143.5, 133.9, 132.1, 131.8, 131.3, 130.7, 129.6, 129.0, 124.1, 74.9, 72.0, 70.7, 70.6, 68.3, 59.2, 57.0, 52.5, 17.4. HRMS (ESI+) m/z calcd for $C_{22}H_{28}N_2NaO_9S$ $[M+Na]^+$ 519.1408, found 519.1407.

Synthesis of 11.

A solution of **10** (1.7309 g, 3.49 mmol) in dry acetonitrile (20 mL) and cesium carbonate (1.4856 g, 4.57 mmol) were added to a solution of benzenethiol (0.5 mL, 4.90 mmol) in acetonitrile (10 mL). The mixture was stirred for 1 h at 45°C, then poured into water, and extracted with ethyl acetate. The organic layer was washed with brine, dried over $MgSO_4$, filtered, and evaporated. The residue was purified by column chromatography (silica gel, ethyl acetate/n-hexane=1/1) to give **11** (1.0073 g, 3.27 mmol, 93%) as a yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, J = 8.7 Hz, 2 H), 6.56 (d, J = 8.7 Hz, 2 H), 4.88 (br, 1 H), 3.84 (s, 3 H), 3.79-3.71 (m, 2 H), 3.70-3.60 (m, 4 H), 3.59-3.55 (m, 3 H), 3.39 (s, 3 H), 3.30-3.25 (m, 1 H), 3.11-3.05 (m, 1 H), 1.23 (d, J = 6.4 Hz, 3 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 167.5, 152.3, 131.6, 118.0, 111.7, 74.3, 72.0, 70.8, 70.6, 68.0, 59.2, 51.6, 48.4, 17.9. HRMS (ESI+) m/z calcd for $C_{16}H_{25}NNaO_5$ $[M+Na]^+$ 334.1625, found 334.1628.

Synthesis of **12a**.

LiI (123.4 mg, 5.1 eq.) was added to a solution of **1a** (99.8 mg, 0.18 mmol) in pyridine (5 mL), and the resulting mixture was stirred for 4 days at 115°C. After removal of the solvent in vacuo, the residue was dissolved in water and the solution was poured into 2 M HCl. The gray precipitate was collected and dried to give **12a** (82.3 mg, 0.15 mmol, 83%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.2 (s, 1H), 8.10 (d, J = 8.7 Hz, 2H), 7.80 (d, J = 8.2 Hz, 4H), 7.59 (d, J = 8.7 Hz, 2H), 7.57 (d, J = 8.7 Hz, 2H), 7.37 (d, J = 8.7 Hz, 2H), 7.25 (d, J = 8.8 Hz, 2H), 7.24 (d, J = 8.8Hz, 2H), 3.43 (s, 3H), 3.40 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 169.2, 167.7, 166.6, 164.7, 148.7, 147.6, 146.5, 142.5, 140.3, 132.6, 130.7, 130.1, 129.5, 129.2, 128.8, 128.0, 126.9, 126.6, 123.2, 119.1, 37.6. HRMS (ESI+) m/z calcd for $C_{30}H_{25}N_4O_7$ $[M+H]^+$ 553.1718, found 553.1706.

Synthesis of **12b**.

LiI (55.2 mg, 5.1 eq) was added to a solution of **1b** (51.4 mg, 0.08 mmol) in pyridine (1.5 mL) and the resulting mixture was stirred for 4 days at 115°C. After removal of the solvent in vacuo, the residue was poured into 2 M HCl and the precipitate was collected by filtration to give **12b** (48.6 mg, 97%) as a yellow-brown solid; ^{1}H NMR (400 MHz,$CDCl_3$) δ 8.02 (d, *J* = 8.7 Hz, 2 H), 7.93 (d, *J* = 8.7 Hz, 2 H), 7.76 (s, 1 H), 7.71 (d, *J* = 8.7 Hz, 2 H), 7.43 (d, *J* = 6.9 Hz, 4 H), 7.29 (d, *J* = 8.7 Hz, 2 H), 7.11 (d, *J* = 8.7 Hz, 2 H), 7.10 (d, *J* = 8.7 Hz, 2 H), 3.93 (m, 4 H), 3.95 (m, 2 H), 1.65 (m, 4 H), 0.94 (m, 6 H). ^{13}C NMR (150 MHz, DMSO-d_6) 169.0, 167.8, 166.7, 164.8, 147.5, 147.4, 145.0, 142.8, 140.2, 132.9, 131.1, 130.2, 129.4, 129.3, 128.8, 128.3, 127.9, 127.5, 125.8, 123.3, 119.2, 50.9, 50.9, 20.6, 20.5, 11.2, 11.2. HRMS (ESI+) m/z calcd for $C_{34}H_{33}N_4O_7$ $[M+H]^+$ 609.2344, found 609.2343.

Synthesis of **12c**.

LiI (36.2 mg, 0.27 mmol) was added to a solution of **1c** (34.7 mg, 0.05 mmol) in pyridine (1.5 mL) and the resulting mixture was stirred for 4 days at 115°C. After removal of the solvent in *vacuo*, the residue was extracted with CH_2Cl_2 and washed with 2 M HCl. The organic layer was dried over $MgSO_4$, filtered and concentrated in *vacuo* to give **12c** (34.1 mg, quant.) as a brown oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (d, *J* = 8.7 Hz, 2 H), 7.93 (d, *J* = 8.2 Hz, 2 H), 7.72 (d, *J* = 8.7 Hz, 2 H), 7.43 (d, *J* = 8.7 Hz, 2 H), 7.29 (d, *J* = 8.7 Hz, 2 H), 7.11 (d, *J* = 8.7 Hz, 2 H), 7.09 (d, *J* = 8.7 Hz, 2 H), 3.97 (m, 4 H), 1.61 (m, 4 H), 1.38-1.15 (m, 20 H), 0.86 (t, *J* = 6.8 Hz, 6 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 169.8, 169.3, 168.2, 164.5, 148.2, 146.8, 142.1, 139.6, 139.3, 133.3, 131.8, 131.2, 130.1, 129.6, 128.7, 128.0, 127.9, 127.3, 125.1, 123.4, 119.2, 50.7, 31.9, 31.9, 29.4, 29.4, 29.3, 29.3, 27.9, 27.8, 27.0, 27.0, 22.7, 14.2. HRMS (ESI+) m/z calcd for $C_{44}H_{53}N_4O_7$ $[M+H]^+$ 749.3909, found 749.3903.

Synthesis of 12d.

LiI (199.7 mg, 1.49 mmol) was added to a solution of **1d** (240.6 mg, 0.28 mmol) in pyridine (3 mL) and the resulting mixture was stirred for 4 days at 115°C. After removal of the solvent in *vacuo,* the residue was extracted with CH_2Cl_2 and washed with 2 M HCl. The organic layer was dried over $MgSO_4$, filtered and concentrated in *vacuo* to give **12d** (272.8 mg, quant.) as a brown oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (d, *J* = 8.7 Hz, 2 H), 7.95 (s, 1H), 7.88 (d, *J* = 8.7 Hz, 2 H), 7.69 (d, *J* = 8.7 Hz, 2 H), 7.49 (d, *J* = 8.2 Hz, 2 H), 7.44 (d, *J* = 8.2 Hz, 2 H), 7.33-7.25 (m, 6 H), 4.17 (d, *J*

= 11.4 Hz, 2 H), 3.97 (m, 2 H), 3.75-3.47 (m, 18 H),3.36 (s, 3 H), 3.33 (s, 3 H), 1.21 (d, J = 6.0 Hz, 6 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.6, 169.0, 165.1, 163.1, 149.2, 148.1, 146.0, 142/1. 140.0, 131.1, 131.0, 130.1, 129.8, 128.8, 128.0, 127.5, 127.4, 123.4, 119.4, 73.9, 73.4, 71.9, 71.8, 70.8, 70.7, 70.4, 70.4, 68.2, 68.1, 59.1, 59.0, 56.6, 56.4, 53.6, 36.8, 31.7, 17.6, 17.4. HRMS (ESI+) m/z calcd for $C_{44}H_{52}N_4NaO_{13}$ $[M+Na]^+$ 867.3423, found 867.3426.

Synthesis of **13a**.

A solution of **1a** (41.2 mg, 0.07 mmol) in THF (5 mL) was hydrogenated with Pd-C (10%, 4.9 mg) for 19 h at rt. The reaction mixture was filtered on Celite, and the filtrate was concentrated in vacuo to give **13a** (38.0 mg, quant.) as a white powder; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (d, J = 8.7 Hz, 2H), 7.75 (s, 1H), 7.70 (d, J = 8.7 Hz, 2H), 7.46 (d, J = 8.7 Hz, 2H), 7.31 (d, J = 8.7 Hz, 2H), 7.13 (d, J = 8.2 Hz, 2H), 7.12 (d, J = 8.2 Hz, 2H), 7.09 (d, J = 8.7 Hz, 2H), 6.42 (d, J = 8.7 Hz, 2H), 3.88 (s, 3H), 3.53 (s, 3H), 3.49 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.1, 166.4, 164.9, 161.5, 149.2, 148.6, 139.7, 131.6, 131.2, 131.1, 130.8, 130.2, 128.2, 127.9, 126.6, 126.5, 126.5, 124.5, 119.1, 113.8, 52.4, 38.4, 38.3. HRMS (ESI+) m/z calcd for $C_{31}H_{29}N_4O_5$ $[M+H]^+$ 537.2132, found 537.2123.

Synthesis of **13b**.

A solution of **1b** (63.9 mg, 0.10 mmol) in MeOH (5 mL) was hydrogenated with Pd-C (10%, 9.7 mg) for 90 min at rt. The reaction mixture was filtered on Celite, and the filtrate was concentrated in vacuo to give **13b** (62.8 mg, 0.10 mmol, quant.) as a white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (d, J = 8.7 Hz, 2H), 7.71 (s, 1 H), 7.68 (d, J = 8.7 Hz, 2 H), 7.44 (d, J = 8.7 Hz, 2 H), 7.29 (d, J = 8.7 Hz, 2 H), 7.10 (m, 6 H), 6.40 (d, J = 8.7 Hz, 2 H), 3.90 (m, 4 H), 3.88 (s, 3 H), 3.86 (br, 2H), 1.63 (m, 4 H), 0.93 (m, 6 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.5, 149.9, 166.4, 165.0, 148.5, 148.0, 148.0, 139.8, 131.7, 131.4, 131.1, 130.7, 130.0, 128.2, 128.0, 127.3, 127.2, 124.9, 119.1, 113.7, 52.4, 52.2, 52.1, 21.2, 21.2, 11.5, 11.5.

HRMS (ESI+) m/z calcd for $C_{35}H_{37}N_4O_5$ $[M+H]^+$ 593.2758, found 593.2744.

Synthesis of 13c.

A solution of **1c** (356.4 mg, 0.47 mmol) in dry ethyl acetate (5 mL) was hydrogenated with Pd-C (10%, 61.7 mg) for 7 h at rt. The reaction mixture was filtered on Celite, and the filtrate was concentrated in *vacuo* to give **13c** (342.3 mg, quant.) as a white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (d, J = 8.7 Hz, 2 H), 7.81 (s, 3 H), 7.68 (d, J = 8.2 Hz,

2 H), 7.43 (d, *J* = 8.7 Hz, 2 H), 7.28 (d, *J* = 8.7 Hz, 2 H), 7.09 (m, 6 H), 6.39 (d, *J* = 8.7 Hz, 2 H), 3.93 (m, 4 H), 3.88 (s, 3 H), 1.61 (m, 4 H), 1.38-1.15 (m, 20 H), 0.85 (dt, *J* = 6.7, 2.3 Hz, 6 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.4, 169.7, 166.4, 164.9, 148.4, 148.1, 148.1, 139.6, 131.7, 131.6, 131.2, 130.7, 130.2, 128.1, 127.9, 127.3, 127.3, 125.1, 119.0, 113.8, 52.4, 50.8, 50.6, 31.9, 29.4, 29.4, 29.3, 29.3, 28.0, 27.9, 27.1, 27.0, 22.7, 14.2. HRMS (ESI+) m/z calcd for $C_{45}H_{57}N_4O_5$ $[M+H]^+$ 733.4323, found 733.4307.

Synthesis of 13d.

A solution of **1d** (246.3 mg, 0.29 mmol) in dry ethyl acetate (4 mL) was hydrogenated with Pd-C (10%, 30.6 mg) for 24 h at rt. The reaction mixture was filtered on Celite, and the filtrate was concentrated in *vacuo* to give **13d** (231.1 mg, 0.28 mmol, 97%) as a yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (s, 1 H), 7.86 (d, *J* = 8.7 Hz, 2 H), 7.66 (d, *J* = 8.7 Hz, 2 H), 7.46(d, *J* = 8.7 Hz, 2 H), 7.30 (d, *J* = 8.2 Hz, 2 H), 7,24 (m, 4 H), 7.13 (d, *J* = 8.7 Hz, 2 H), 6.39 (d, *J* = 8.7 Hz, 2 H), 4.15 (m, 2 H), 3.97 (m, 2 H), 3.88 (s, 3 H), 3.82 (s, 2 H), 3.75-3.46 (m, 18 H), 3.36 (s, 3 H), 3.33 (s, 3 H), 1.20 (t, *J* = 6.4 Hz, 6 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.7, 170.2, 166.5, 165.2, 149.4, 148.6, 139.9, 131.4, 131.3, 130.5, 130.3, 128.0, 127.6, 127.4, 124.8, 119.0, 113.7, 74.4, 73.9, 72.0, 72.0, 71.0, 70.9, 70.6, 70.4, 68.5, 68.4, 60.6, 59.2, 59.1, 56.8, 52.3, 21.2, 17.7, 17.7, 14.3. HRMS (ESI+) m/z calcd for $C_{45}H_{56}N_4NaO_{11}$ $[M+Na]^+$ 851.3838, found 851.3832.

Synthesis of **2a**.

1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (40.5 mg, 0.21 mmol) and *N*,*N*-dimethyl-4-aminopyridine (25.2 mg, 0.21 mmol) were added to a solution of **12a** (89.3 mg, 0.16 mmol) and **13a** (85.1 mg, 0.16 mmol) in DMF (1 mL). The resulting mixture was stirred for 31 h at rt and heated at 50°C for 19 h. After removal of the solvent in vacuo, the residue was extracted with THF. The organic layer was washed successively with 2 M HCl, sat. $NaHCO_3$ and brine, dried over $MgSO_4$, filtered and concentrated in *vacuo*. THF was added to the residue and the resulting pale yellow precipitate was collected and dried to give **2a** (45.4 mg, 26%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.3 (s, 1H), 10.3 (s, 1H), 10.3 (s, 1H), 8.09 (d, *J* = 8.7 Hz, 2H), 7.80 (m, 8H), 7.59 (m, 8H), 7.35 (d, *J* = 8.2 Hz, 2H), 7.27 (m, 12H), 3.79 (s, 3H), 3.42 (s, 3H), 3.40 (s, 3H), 3.40 (s, 3H), 3.39 (s, 3H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 169.2, 167.8, 165.6, 164.9, 149.1, 147.9, 147.6, 146.5, 142.5, 140.5, 140.4, 140.3, 132.6, 131.9, 130.9, 130.8, 130.6, 130.0, 129.5, 128.8, 128.7, 126.9, 126.9, 126.8, 126.6, 123.2, 119.2, 119.2, 119.1, 52.2, 37.8, 37.6. HRMS (ESI+) m/z calcd for $C_{61}H_{50}N_8NaO_{11}$

$[M+Na]^+$ 1093.3491, found 1093.3463.

Synthesis of **2b**.

1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (138 mg, 0.72 mmol) and *N*,*N*-dimethyl-4-aminopyridine (89.8 mg, 0.74 mmol) were added to a solution of **12b** (223 mg, 0.37 mmol) and **13b** (234 mg, 0.39 mmol) in DMF (4 mL). The resulting mixture was stirred for 5 day. After removal of the solvent in vacuo, the residue was extracted with dichloromethane. The organic layer was washed successively with 2 M HCl, sat. $NaHCO_3$ and brine, dried over $MgSO_4$, filtered and concentrated in *vacuo*. The residue was purified by column chromatography (silica gel, ethyl acetate / n-hexane = 4 / 1) to give **2b** (264 mg, 0.22 mmol, 61%) as a yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.10 (s, 1 H), 8.83 (s, 1 H), 8.65 (s, 1 H), 8.00 (d, *J* = 8.7 Hz, 2 H), 7.88 (d, *J* = 8.7 Hz, 2 H), 7.76 (m, 4 H), 7.59 (d, *J* = 8.2 Hz, 2 H), 7.46 (d, *J* = 8.2 Hz, 2 H), 7.43 (d, *J* = 8.7 Hz, 2 H), 7.44 (m, 6 H), 7.07 (m, 12 H), 3.87 (m, 8 H), 3.86 (s, 3 H), 1.63 (m, 8 H), 0.92 (m, 12 H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 169.1, 167.7, 165.6, 165.0, 147.8, 147.6, 146.4, 142.8, 140.4, 140.3, 140.2, 132.9, 132.2, 131.2, 130.9, 130.1, 129.4, 129.3, 128.8, 128.7, 127.9, 127.6, 127.4, 127.1, 123.2, 119.2, 119.1, 52.2, 51.0, 50.9, 20.6, 20.6, 20.5, 11.2, 11.2. HRMS (ESI+) m/z calcd for $C_{69}H_{66}N_8NaO_{11}$ $[M+Na]^+$ 1205.4743, found 1205.4719.

Synthesis of 2c.

1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (175.5 mg, 0.92 mmol) and *N,N*-dimethyl-4-aminopyridine (110.2 mg, 0.90 mmol) were added to a solution of **12c** (330.0 mg, 0.44 mmol) and **13c** (342.2 mg, 0.47 mmol) in DMF (5 mL). The resulting mixture was stirred for 2 days at rt. After removal of the solvent in *vacuo*, the residue was extracted with dichloromethane. The organic layer was washed successively with 2 M HCl, sat. $NaHCO_3$ and brine, dried over $MgSO_4$, filtered and concentrated in *vacuo*. The residue was purified by column chromatography (silica gel, ethyl acetate/*n*-hexane=2/1) to give **2c** (480.2 mg, 0.33 mmol, 74%) as a yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.64 (br, 1 H), 8.41 (br, 1 H), 8.33 (br, 1 H), 8.00 (d, *J* = 8.7 Hz, 2 H), 7.89 (d, *J* = 8.7 Hz, 2 H), 7.73 (d, *J* = 8.2 Hz, 4 H), 7.63 (d, *J* = 8.7 Hz, 2 H), 7.46 (d, *J* = 8.2 Hz, 2 H), 7.43 (d, *J* = 6.8 Hz, 2 H), 7.30-7.20 (m, 4 H), 7.16-7.01 (m, 12 H), 3.90 (m, 8 H), 3.86 (s, 3 H), 1.61 (m, 8 H), 1.40-1.20 (m, 40 H), 0.86 (m, 12 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 169.9, 166.4, 165.6, 165.1, 164.9, 148.1, 148.0, 146.7, 142.3, 140.2, 139.4, 139.2, 132.9, 132.8, 132.0, 131.7, 131.2, 131.0, 130.7, 130.1, 130.0, 129.6, 128.9, 128.8, 128.6, 128.2, 128.0, 127.8, 127.6, 127.4, 127.3, 127.2, 123.4, 120.1,

119.8, 119.2, 119.0, 52.4, 50.8, 50.8, 50.7, 31.9, 29.4, 29.4, 29.4, 29.4, 29.3, 27.9, 27.9, 27.8, 27.1, 27.0, 27.0, 22.8, 14.3. HRMS (ESI+) m/z calcd for $C_{89}H_{107}N_8O_{11}$ $[M+H]^+$ 1463.8054, found 1463.8035.

Synthesis of 2d.

1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (108.8 mg, 0.57 mmol) and *N,N*-dimethyl-4-aminopyridine (70.0 mg, 0.57 mmol) were added to a solution of **12d** (236.7 mg, 0.28 mmol) and **13d** (231.1 mg, 0.28 mmol) in DMF (4 mL). The resulting mixture was stirred for 24 h at rt. After removal of the solvent in *vacuo*, the residue was extracted with dichloromethane. The organic layer was washed successively with 2 M HCl, sat. $NaHCO_3$ and brine, dried over $MgSO_4$, filtered and concentrated in *vacuo*. The residue was purified by column chromatography (silica gel, ethyl acetate/methanol =10/1) to give **2d** (353.6 mg, 0.21 mmol, 76%) as a pale yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.46 (br, 1 H), 8.43 (br, 1 H), 8.33 (br, 1 H), 8.02 (d, J = 8.7 Hz, 2 H), 8.75 (d, J = 8.7 Hz, 2 H), 7.69 (d, J = 8.7 Hz, 4 H), 7.61 (d, J = 8.7 Hz, 2 H), 7.47 (d, J = 8.2 Hz, 4 H), 7.38 (m, 4 H), 7.22 (m, 12 H), 4.13 (m, 4 H), 3.92 (m, 4 H), 3.85 (s, 3 H), 3.75-3.40 (m, 36 H), 3.35 (s, 3 H), 3.31 (s, 3 H), 3.30 (s, 3 H), 3.28 (s, 3 H), 1.19 (d, J = 6.0 Hz , 12 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.4, 170.2, 170.2, 166.5, 165.8, 165.2, 162.7, 149.2, 148.2, 142.2, 140.3, 139.8, 139.7, 132.7, 132.2, 132.0, 131.6, 131.5, 131.1, 130.5, 130.3, 130.1, 129.9, 129.8, 128.6, 128.5, 128.4, 128.0, 127.6, 127.5, 127.3, 123.4, 119.7, 119.1, 77.4, 77.2, 76.9, 74.0, 73.9, 72.0, 71.9, 71.9, 71.9, 70.9, 70.9, 70.9, 70.6, 70.5, 70.5, 70.4, 68.4, 68.3, 68.3, 68.2, 60.5, 59.2, 59.1, 59.0, 59.0, 56.8, 56.7, 56.5, 52.3, 36.7, 31.6, 29.8, 21.2, 17.7, 17.6, 17.4, 14.3. HRMS (ESI+) m/z calcd for $C_{89}H_{107}N_8O_{23}$ $[M+H]^+$ 1655.7444, found 1655.7416.

Synthesis of **14d**.

LiI (33.0 mg, 0.25 mmol) was added to a solution of **2d** (79.0 mg, 0.05 mmol) in pyridine (2 mL) and the resulting mixture was stirred for 6 days at 115°C. After removal of the solvent in *vacuo*, the residue was extracted with CH_2Cl_2 and washed with 2 M HCl. The organic layer was dried over $MgSO_4$, filtered and concentrated in *vacuo* to give **14d** (71.9 mg, 88%) as a brown oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.00 (br, 2 H), 8.83 (br, 1 H), 8.00 (m, 2 H), 7.78 (m, 6 H), 7.50 (m, 8 H), 7.18 (m, 16 H), 4.12 (m, 8H), 3.95 (m, 8 H), 3.70-3.50 (m, 36 H), 3.33-3.26 (m, 12 H), 1.20-1.10 (m, 12 H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.7, 170.4, 165.3, 148.1, 142.2, 140.1, 132.2, 131.3, 131.0, 130.8, 130.0, 129.9, 129.8, 129.0, 128.7, 128.2, 127.8, 127.6, 127.4, 127.3, 123.4, 120.0, 119.7, 119.3, 74.0, 71.8, 71.7, 71.6, 70.8, 70.7, 70.6, 70.5, 70.4, 70.3, 68.3,

68.1, 59.1, 59.1, 59.0, 59.0, 56.5, 56.5, 56.4, 17.6, 17.6, 17.4. HRMS (ESI+) m/z calcd for $C_{88}H_{104}N_8NaO_{23}$ $[M+Na]^+$ 1663.7107, found 1663.7100.

Synthesis of 15c.

A solution of **2c** (51.9 mg, 0.04 mmol) in dry ethyl acetate (6 mL) was hydrogenated with Pd-C (10%, 10.5 mg) for 24 h at rt. The reaction mixture was filtered on Celite, and the filtrate was concentrated in *vacuo* to give **15c** (44.2 mg, 0.03 mmol, 87%) as a white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.70 (br, 2 H), 8.43 (br, 1 H), 7.88 (d, J = 8.7 Hz, 2 H), 7.73 (d, J = 8.7 Hz, 2 H), 7.65 (d, J = 8.2 Hz, 4 H), 7.62 (d, J = 8.7 Hz, 2 H), 7.45 (d, J = 8.2 Hz, 2 H), 7.31 (d, J = 6.8 Hz, 2 H), 7.31-7.18 (m, 8 H), 7.18-7.01 (m, 12 H), 6.38 (d, J = 8.7 Hz, 2 H), 3.89 (m, 8 H), 3.86 (s, 3 H), 1.61 (m, 8 H), 1.40-1.20 (m, 40 H), 0.86 (m, 12 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.6, 170.0, 169.8, 166.4, 165.7, 165.2, 148.6, 148.0, 140.1, 139.5, 139.4, 131.8, 131.6, 131.2, 131.0, 130.7, 129.9, 129.6, 128.7, 128.6, 128.4, 127.9, 127.5, 127.2, 124.9, 120.0, 119.9, 119.2, 113.7, 52.4, 50.8, 50.7, 31.8, 29.4, 29.4, 29.3, 29.3, 28.1, 27.9, 27.8, 27.1, 27.0, 22.7, 22.7, 14.2. HRMS (ESI+) m/z calcd for $C_{89}H_{109}N_8O_9$ $[M+H]^+$ 1433.8312, found 1433.8313.

Synthesis of 3c.

1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (30.6 mg, 0.16 mmol) and *N,N*-dimethyl-4-aminopyridine (19.5 mg, 0.16 mmol) were added to a solution of **12c** (84.6 mg, 0.11 mmol) and **15c** (117.9 mg, 0.08 mmol) in DMF (4 mL). The resulting mixture was stirred for 36 h at rt. After removal of the solvent in *vacuo*, the residue was extracted with dichloromethane. The organic layer was washed successively with 2 M HCl, sat. $NaHCO_3$ and brine, dried over $MgSO_4$, filtered and concentrated in *vacuo*. The residue was purified by GPC to give **3c** (33.1 mg, 0.02 mmol, 19%) as a pale brown solid; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.28-10.24(m, 5 H), 8.06 (d, J = 7.8 Hz, 2 H), 7.81-7.75 (m, 12 H), 7.57-7.55 (m, 12 H), 7.33 (d, J = 7.8 Hz, 2 H), 7.25-7.19 (m, 20 H), 3.85 (br, 12 H), 3.77 (s, 3 H), 1.48(br, 12 H), 1.19 (br, 60 H), 0.83-0.81 (m, 18 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 172.9, 166.4, 164.9, 144.8, 144.5, 142.1, 132.6, 130.7, 130.1, 129.4, 127.9, 127.4, 126.9, 124.1, 123.5, 119.9, 119.3, 52.3, 52.2, 50.8, 50.7, 31.9, 31.8, 29.8, 29.4, 29.4, 29.4, 29.3, 29.2, 29.0, 28.9, 28.7, 28.2, 28.0, 27.1, 27.0, 26.9, 26.5, 26.4, 22.8, 22.8, 22.6, 14.3, 14.2. HRMS (ESI+) m/z calcd for $C_{133}H_{158}N_{12}NaO_{15}$ $[M+Na]^+$ 2186.1867 , found 2186.1862.

Synthesis of 3d.

1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (12.7 mg, 2.4 eq.) and

N,N-dimethyl-4-aminopyridine (9.0 mg, 2.7 eq.) were added to a solution of **14d** (43.6 mg, 0.027 mmol) and **13d** (29.5 mg, 1.3 eq.) in DMF (2 mL). The resulting mixture was stirred for 3 days at rt. After removal of the solvent in *vacuo*, the residue was extracted with dichloromethane. The organic layer was washed successively with 2 M HCl, sat. $NaHCO_3$ and brine, dried over $MgSO_4$, filtered and concentrated in *vacuo*. The residue was purified by preparative-TLC (ethyl acetate / methanol = 8 / 1) to give **3d** (15.9 mg, 6.5 μmol, 24%) as a pale yellow solid; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.24 (s, 5 H), 8.07 (br, 2 H), 7.79-7.74 (m, 12 H), 7.58-7.40 (m, 10 H), 7.40 (br, 4 H), 7.34 (m, 10 H), 7.33-7.20 (m, 10 H), 3.99 (m, 6 H), 3.78 (s, 3 H), 3.70-3.68 (m, 14 H), 3.56 (m, 6 H), 3.46-3.31 (m, 36 H), 3.31-3.17 (m, 18 H), 1.10 (s, 18 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 173.1, 164.8, 144.1, 141.6, 132.6, 130.4, 129.9, 129.2, 129.0, 127.2, 123.3, 119.8, 71.9, 71.6, 70.8, 70.6、70.5, 70.4, 68.2, 59.2, 59.1, 59.0, 59.0, 56.7, 52.1, 29.7, 16.9. HRMS (ESI+) m/z calcd for $C_{133}H_{158}N_{12}NaO_{33}$ $[M+Na]^+$ 2474.0946, found 2474.0897.

Supporting Information

^{1}H NMR spectra of **1** and **5a**, X-ray crystallography data of **1a** and **1b**, CD and UV spectra of **5d** and **1d-3d**, computational data and NMR spectra of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

Acknowledgments

This work was partly supported by JSPS KAKENHI Grant No 16K08318 (to A.T.), 17J00036 (to K.U.) and JSPS Core-to-Core Program, A. Advanced Research Networks. A.T. gratefully acknowledges funding from The Sumitomo Foundation and The Naito Foundation. K.U. is grateful for financial support from JSPS (Research Fellowship for Young Scientists).

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