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J. Org. Chem., **Just Accepted Manuscript** • DOI: 10.1021/acs.joc.8b00349 • Publication Date (Web): 29 Mar 2018

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Abstract

N-Alkylbenzanilides generally exist in cis conformation both in the crystalline state and in various solvents, and this cis conformational preference can be utilized to construct dynamic helical oligoamides. Here, we synthesized the pyrrole-containing amides **2** – **5** and their oligomers **6** – **8**, and examined their conformations in the crystalline state and in solution. All the *N*-methylated amides showed cis conformational preference in solution, but the ratio of the cis isomer was decreased when the amide bond was attached at the 4-position of the pyrrole ring, probably because the destabilization of the trans conformer due to electronic repulsion between the pyrrole π electrons and the amide carbonyl lone-pair electrons is reduced due to the small torsion angle between the 5-membered *N*-pyrrole and the amide bond. In the crystalline state, *N*-methylated amides showed cis structure, except for compound **5**, and cis conformational preference was observed for the pyrrole amides. The CD spectra of oligoamides **15** – **18** bearing chiral *N*-substituents were consistent with the presence of dynamic and well-defined chiral foldamers, which were structurally distinct from *N*-alkylated poly(*p*-benzamide)s **1**.

Introduction

In the past few decades, there has been increasing interest in artificial oligomers with unique conformational behaviors and chemical functions, known as foldamers,[1] inspired by the well-known helical structures found in nature, for example in proteins and DNAs.[2] In general, well-defined structures can be constructed by utilizing a variety of specific intramolecular noncovalent interactions, such as metal coordination networks, hydrogen bonding interactions, donor-acceptor interactions, and solvophobic interactions.[3] The amide bond is a useful functional group for constructing intramolecular hydrogen-bonding interactions.[4] Among aliphatic oligoamides, various α-peptide, β-peptide,[5] γ-peptide[6] and peptidic analogue foldamers have been developed.[7] Aromatic oligoamides are also an important class of foldamers,[8] in which multiple interactions, including amide hydrogen bonds, aromatic-aromatic interactions, and the conformational properties of the bond between an aromatic ring and an amide bond, contribute to the construction of α-helix- and β-sheet-like foldamers.[9] Such foldamers can show interesting functions, such as formation of double helices,[10] conformational switching induced by environmental changes,[11] and binding ability to DNAs or proteins.[12]

We have developed aromatic oligobenzamide foldamers, based on the conformational properties of *N*-alkylbenzanilides. Thus, secondary aromatic amides such as benzanilide exist in trans form both in the crystal and in solution, whereas their *N*-methylated amides exist in cis form in the crystal and predominantly in cis form in various solvents (Fig. 1a).[13] The cis conformational preference is general for *N*-alkylated benzanilides. We found that oligo(*N*-alkyl-*p*-benzamide)s and poly(*N*-alkyl-*p*-benzamide)s, prepared by the chain-growth polycondensation of phenyl *p*-nitrobenzoate as an initiator and phenyl *p*-(alkylamino)benzoate as a monomer, adopted helical forms driven by the folded *cis*-amide structures.[14] Poly(*N*-alkyl-*p*-benzamide)s showed dynamic helical properties in solution, and polyamides **1** bearing a chiral side chain [(*S*)-2-(methoxyethoxyethoxy)propyl group] (Figure 1b) possessed a right-handed helical conformation (*P*-helix), as deduced from exciton model analysis of the absorption and CD spectra.

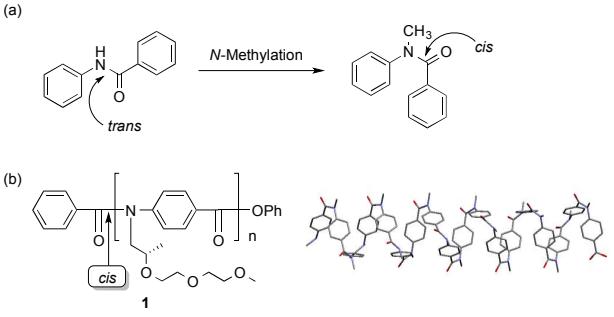


Figure 1. (a) *Cis* conformational preference of benzanilide caused by *N*-methylation. (b) Structures of helical poly(benzamide)s bearing chiral *N*-substituents. *N*-Substituents are omitted in the three-dimensional structures (right).

The dynamic helical structure of poly(*N*-alkyl-*p*-benzamide)s is unique among helical oligoamides so far known, in that there are no intramolecular noncovalent interactions, such as hydrogen bonds, and the structure is driven simply by the cis conformational properties of the *N*-alkylbenzanilide moiety. The intrinsic helical properties of poly(*N*-alkyl-*p*-benzamide)s can be applied to obtain functional helical molecules by means of further structural derivatization. For example, *N*-methylated oligoamides bearing pyridine rings also favor the cis-amide structures, and their conformations can be switched between the folded and unfolded structures simply by addition of acid.[11a] Other *N*-substituted amides have also been reported to undergo conformational switching in response to environmental changes.[15]

Various foldamers bearing pyridine- or quinolineamide backbones have been developed,[16] whereas the foldamer properties of oligoamides bearing a 5-membered heteroaromatic ring are less well known. A number of pyrrole- and imidazole-containing oligoamides have been developed, but most of them were oligomers of secondary amides developed as artificial DNA minor groove binders targeting specific sequences,[17] and there are only a few reports on the conformational properties of tertiary amides in heterocyclic rings.[11a,16c] In this study, we focused on pyrrole-containing amides and their oligomers, and investigated their conformations in the crystalline state and in solution, with the aim of applying them as building blocks for unique foldamers.

Results and Discussion

Conformational analysis of pyrrole-containing amides

Many pyrrole-containing amides have been synthesized,[18] but there is little information about the conformations of tertiary amide derivatives. Therefore, in order to clarify whether cis conformational preference holds for *N*-alkylated amide bonds on the pyrrole ring, we synthesized monoamides **2** – **5** in which one phenyl ring of benzanilide or *N*-methylbenzanilide is replaced with a pyrrole ring (Figure 2). We also synthesized *N*-methylated diamide **6**, which has a pyrrole ring as the central aromatic ring, as well as **7**, which has two terminal pyrrole rings, and triamide **8**, which has two pyrrole and two phenyl rings alternately linked by amide bonds.

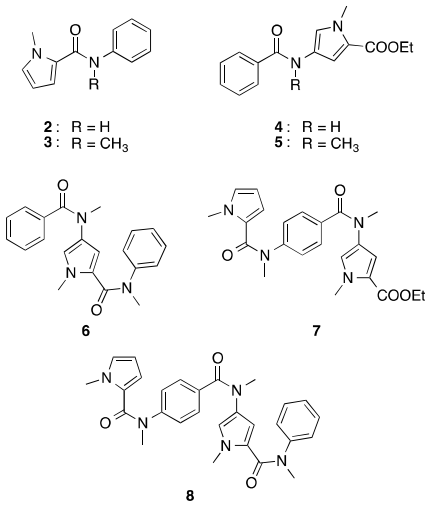
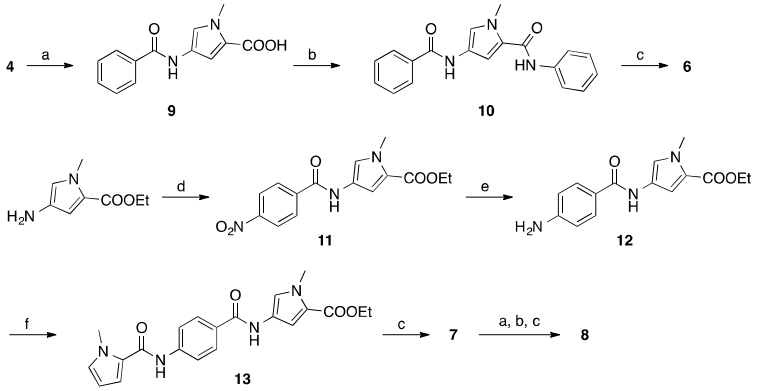


Figure 2. Structures of pyrrole-containing amide derivatives

Compound **2** was prepared in 49% yield by condensation of *N*-methylpyrrole-2-carboxylic acid with aniline in the presence of EDCI/HOBt as coupling reagents. Ethyl 4-amino-1-methylpyrrole-2-carboxylate was reacted with benzoyl chloride to afford compound **4** in 62% yield. These secondary amides were *N*-methylated to give **3** and **5**. The syntheses of diamides **6**, **7** and triamide **8** are illustrated in Scheme 1. Monoamide **4** was hydrolyzed under basic conditions to give carboxylic acid **9** (95%), which was condensed with aniline in the presence of EDCI/DIEA/HOBt to afford diamide **10**. Compound **12** was obtained via the reaction of ethyl 4-amino-*N*-methylpyrrole-2-carboxylate with *p*-nitrobenzoyl chloride, followed by catalytic hydrogenation, and was then allowed to react with *N*-methylpyyrole-2-carbonyl chloride to give **13**. *N*-Methylation of **10** and **13** afforded diamides **6** and **7**, respectively. Triamide **8** was similarly synthesized from diamide **7** by sequential hydrolysis, acylation and *N*-methylation.



Scheme 1. Synthesis of diamides **6**, **7** and triamide **8**. (a) 2 M NaOH, EtOH, rt; (b) aniline, EDCI, DIEA, HOBt, CH_2Cl_2, rt; (c) NaH, DMF; CH_3I, rt; (d) Et_3N, *p*-nitrobenzoyl chloride, CH_2Cl_2, rt; (e) H_2, Pd/C; AcOEt, rt; (f) *N*-methylpyrrole-2-carbonyl chloride, pyridine, CH_3CN, rt.

The conformations of amide compounds **3** and **5** – **8** in solution were analyzed by ^{1}H NMR spectroscopy (Figure 3). The phenyl proton chemical shifts of the secondary amides **2** and **4** were quite similar to those of benzanilide, bearing a *trans*-amide bond, in $CDCl_3$ (Table S1). *N*-Methylamide **3** afforded a simple sharp signal in CD_2Cl_2 at room temperature and retained the sharp signal even at 183 K (Figure S1). The chemical shifts of **3** in the aromatic region were shifted to higher field, compared to those of secondary amide **2**. The chemical shifts of phenyl protons of **3** were similar to those of *N*-methylbenzanilide with cis conformation. These results indicate that **3** exists predominantly in cis form in CD_2Cl_2. Compound **5** showed broad signals in CD_2Cl_2 at room temperature, and two sets of signals were observed at 218K (Figure S2). Thus, **5** exists in equilibrium between cis and trans forms in the ratio of 3 : 2 in CD_2Cl_2 at 218 K.

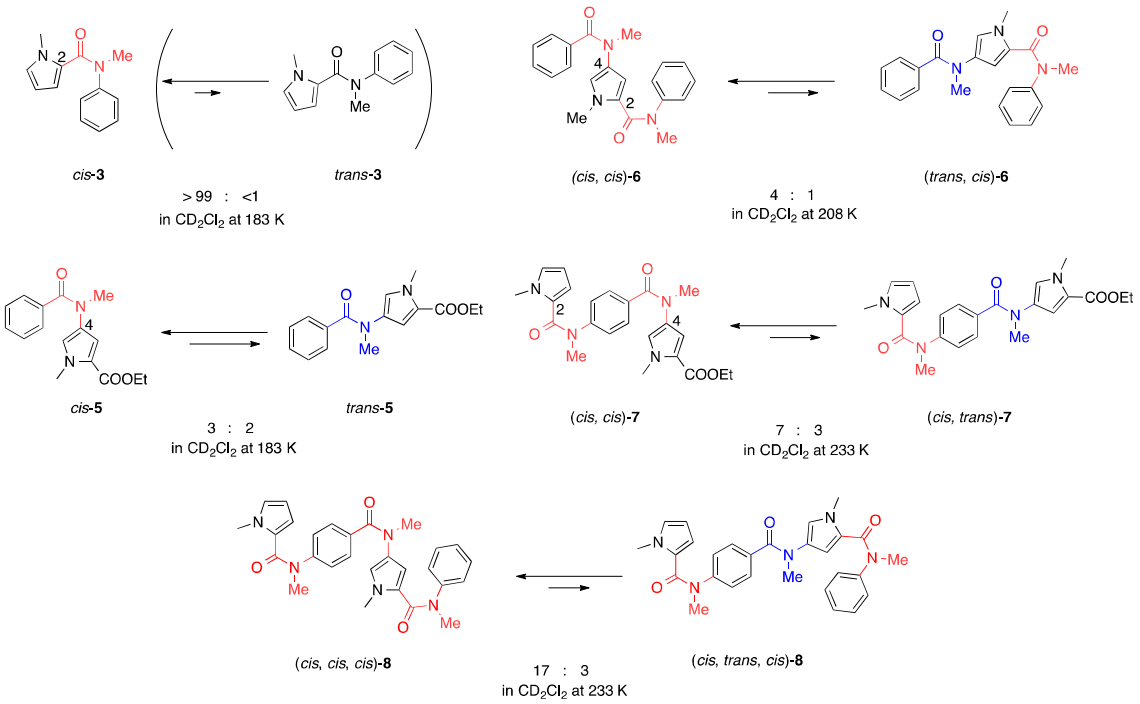


Figure 3. Conformational equilibrium of *N*-methylated amides **3** and **5** - **8**.

N-Methylated diamides **6**, **7** and triamide **8** showed broad signals at room temperature, but these split into two sets of signals at low temperature (Figures S3 – S5). The two sets of signals of diamide **6** were assigned to (cis, cis) form and (trans, cis) form in a ratio of 4 : 1 in CD_2Cl_2 at 208 K, based on a comparison of the chemical shifts with those of monoamides **2** - **5**. ^{1}H NMR signals corresponding to the (cis, trans) and (trans, trans) conformers could be estimated from the equilibrium of **3** and **5**. Similarly diamide **7** existed in equilibrium between (cis, cis) form and (cis, trans) conformers in a ratio of 7 : 3 in CD_2Cl_2 at 233 K, and triamide **8** existed in equilibrium between (cis, cis, cis) form and (cis, trans, cis) conformers in a ratio of 17 : 3 in CD_2Cl_2 at 233 K. Thus, all *N*-methylated amides on a pyrrole ring showed cis

conformational preference, like *N*-methylbenzanilide. In each case, the *N*-methylated amide bond was attached at the 2-position of the pyrrole ring, i.e. the 2-pyrrolecarboxamide bond is predominantly cis, although the ratio of cis conformation was decreased when the *N*-methylated amide bond was attached at the 4-position of the pyrrole ring. Theoretical studies on the conformation of *N*-methylacetanilide[19] showed that the trans conformer, in which the torsion angle of the bond between *N*-phenyl and the amide bond is large due to the steric repulsion, is destabilized by electronic repulsion between π electrons of *N*-phenyl ring and amide carbonyl lone pair electrons, as well as steric repulsion between the methyl group and phenyl group attached to the amide carbonyl. Similar destabilization is likely to occur in *N*-methyl-*N*-phenyl-pyyrole-2-carboxamides such as **3**. On the other hand, in the case of *N*-methyl-*N*-pyyrol-4-ylamides such as **5**, the torsion angle between *N*-pyrrole and the amide bond would be smaller than that of *N*-methylbenzanilide, because of the smaller size of the 5-membered ring. Indeed, the dihedral angle between the pyrrole ring and amide plane is small in the crystal structure of **5** (trans form) (see below). Therefore, the electronic repulsion between pyrrole π electrons and carbonyl lone pair electrons in the trans form of **5** is smaller than that in trans *N*-methylbenzanilide, and consequently the ratio of the cis form is decreased. Although the cis conformational preference of monoamide **5** is small (60%), it became larger in the corresponding amide bond in longer chains, such as diamides (80% for **6**, and 70% for **7**) and triamide (85%).

The X-ray crystal structures of pyrrole-containing amides **2** – **8** were determined, and are illustrated in Figure 4 (Table S2). Secondary monoamides **2** and **4** adopted trans form in the crystal state, as expected from the structures in solution. *N*-Methylated monoamide **3** adopted cis form in the crystal state, whereas *N*-methylated monoamide **5** existed in trans form, presumably due to the small preference for the cis conformer of **5** in solution, or some intermolecular interactions that would stabilize trans conformer in the crystal (Figure S7). As discussed above, the torsion angle between the *N*-pyrrole ring and the amide bond is small, and the pyrrole ring and the amide plane are nearly parallel.

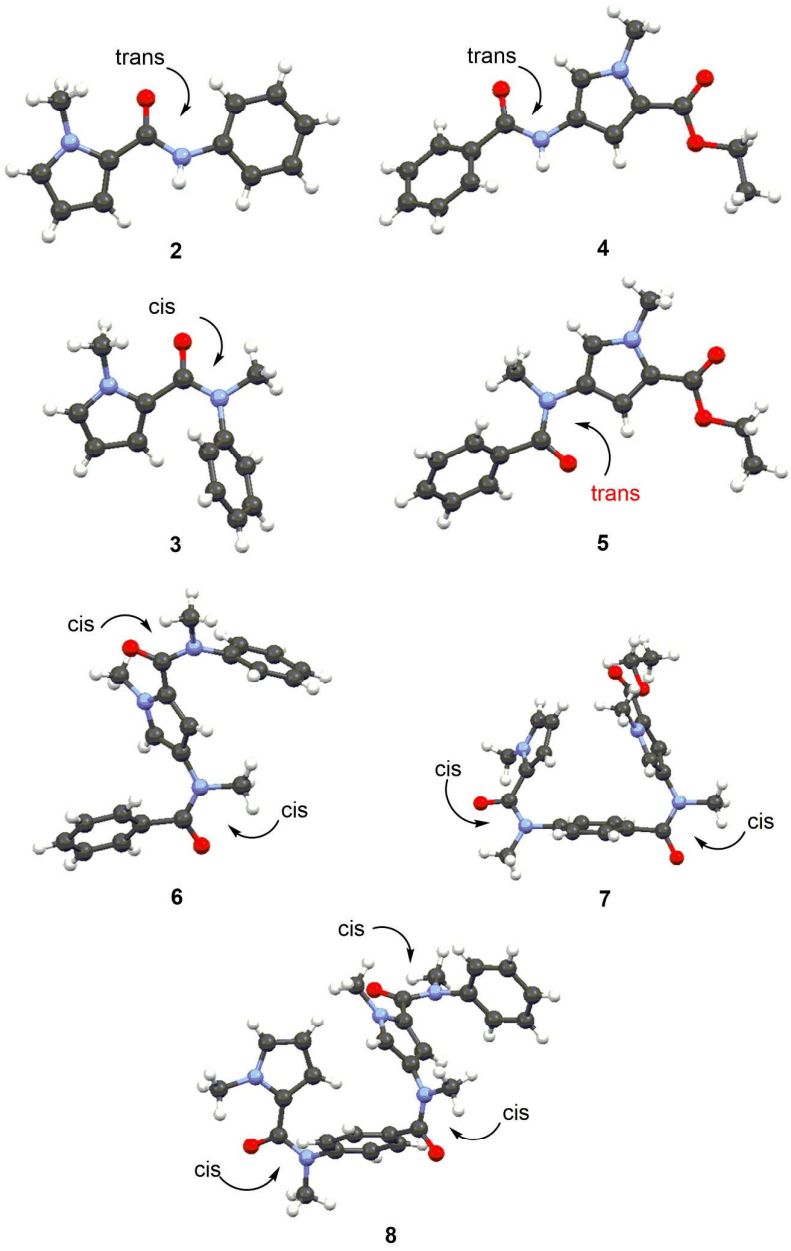


Figure 4. Crystal structures of pyrrole-containing amides **2** - **8**.

The crystal structures of **6** and **7** showed that all amide bonds adopted cis form, as expected, though the orientations of the amide bonds were different. Thus, the diamide **6** existed in anti conformation, in which two pyrrole rings are located at opposite sides of the central phenyl ring. On the other hand, the diamide **7** existed in syn conformation, in which two phenyl rings are located at the side of the central pyrrole ring. Interestingly, the conformation of triamide **8** in the crystal resembled the connected structure of the corresponding units of the crystal structures of **6** and **7** (Figure 4). Thus, the three amide

bonds are all cis, and the pyrrole-amide-phenyl-amide-pyrrole part, corresponding to the structure of **7**, takes cis conformation, while the phenyl-amide-pyrrole-amide-phenyl part, corresponding to the structure of **6**, takes anti conformation. Although the reason for the anti/syn conformational preference is unknown, pyrrole-containing amides appear to have unique folded structures based on the combination of cis-amide bonds with anti/syn conformational preference,[20] in contrast to the helical structures of poly(*N*-alkylated *p*-benzamide)s **1**, which have all-*cis*-amide bonds with all-*syn* conformation.

Next, we theoretically examined the conformational properties of pyrrole-containing monoamides **2** – **5**. Each structure was optimized by GAMESS[21] with LC-BLYP/6-31G** based on the crystal structure. In order to clarify the conformational preference, energy analysis was performed for divided fragment structures, two aromatic rings and the amide moiety. The optimized structures and the results of the conformational analysis are shown in Figure 5 and Table 1, respectively. Differences in the calculated ΔG values between cis and trans isomers showed that the trans conformer is predominant for secondary amides **2** and **4**, while the cis conformer is favored for *N*-methylamides **3** and **5**. In the case of *N*-methylamide **5**, the calculated ΔG value is smaller (-4.8 kJ/mol) than that of **3** (-9.4 kJ/mol). The theoretical results agreed well with the cis/trans population calculated from the NMR spectra. Fragment analysis of the ΔG values suggested that the cis conformational preference of the *N*-methylated amide bond reflects the stability of the amide bond itself. Comparison of the individual values between *N*-methylamides **3** and **5** revealed a difference in ΔG value in the fragment Ar^2 (aromatic ring on the amide nitrogen atom), probably due to the weak CH-π interaction of the *N*-pyrrole ring, which resulted in a decreased ratio of cis conformer of **5**.

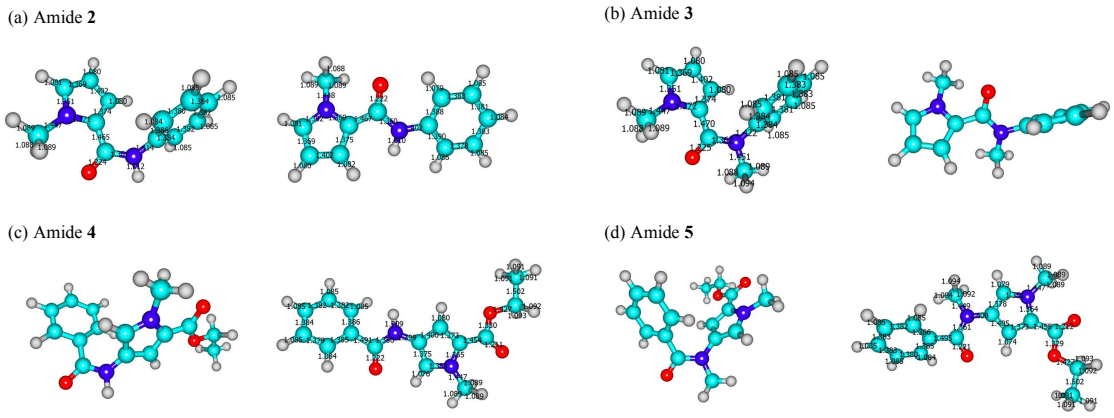
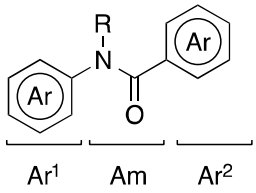


Figure 5. Optimized structures of cis and trans conformers of monoamides **2** – **5**

Table 1. Theoretical analysis of conformational properties of monoamides **2** – **5**



Compound	Calcd ΔG[a] (kJ mol^{-1})	Calcd population cis / trans	Calcd ΔG[b] (kJ mol^{-1}) of fragment structure Ar^1	Am	Ar^2
2	20.9	0.00/1.00	-6.6	27.4	0.1
3	-9.4	0.98/0.02	4.3	-14.3	0.6
4	21.0	0.00/1.00	-4.6	25.4	0.2
5	-4.8	0.60/0.40	5.5	-14.2	3.9

[a]Calcd ΔG = ΔG (cis) –ΔG (trans)

[b]Calcd by means of divide and conquer method (ref 22).

Theoretical analysis of the conformational properties of diamide **7** and triamide **8** was also conducted (Table 2). In the case of diamide **7**, the most stable conformer was (cis, cis). The (cis, trans) conformer had a higher ΔG value than the (cis, cis) conformer by 4.2 kJ/mol, while the (trans, cis) and (trans, trans) conformers both had much higher ΔG values. Similarly, the (cis, cis, cis) and (cis, trans, cis) conformers were the most stable among 8 possible conformers related to cis/trans amide structures. Thus, the theoretical studies agreed well with the experimental observations.

Table 2. Theoretical analysis of conformational properties of diamide **7** and triamide **8**

Diamide **7**			Triamide **8**		
Conformer[a]	Calcd ΔG[b] (kJ mol^{-1})	Calcd population	Conformer[a]	Calcd ΔG[b] (kJ mol^{-1})	Calcd population
(cis, cis)	0.0	0.84	(cis, cis, cis)	0.9	0.81
(cis, trans)	4.2	0.16	(cis, cis, trans)	10.3	0.01
(trans, cis)	14.6	0.00	(cis, trans, cis)	3.7	0.18
(trans, trans)	23.6	0.00	(cis, trans, trans)	31.2	0.00
			(trans, cis, cis)	18.6	0.00
			(trans, cis, trans)	22.7	0.00
			(trans, trans, cis)	17.7	0.00
			(trans, trans, trans)	39.8	0.00

[a]Cis and trans were assigned to the amide bonds sequentially from the left in the structures shown in Figure 2.
[b]Relative value to that of the (cis, cis) conformer.

Synthesis of pyrrole-containing oligoamides with chiral side chains.

The results of the conformational analysis of pyrrole-containing mono-, di- and triamides led us to synthesize oligoamides in which the phenyl and pyrrole rings were linked alternately by *N*-alkylated amide bonds. Thus, oligoamides **14** – **18**, bearing chiral *N*-substituents at every second amide bond were designed in order to investigate their folding structures (Figure 6). As the chiral substituent, a chiral TEG chain was chosen to ensure good

solubility in organic solvents and also in water. The chiral TEG chain was introduced onto the nitrogen atom of the pyrrole ring, not on the phenyl ring, for synthetic convenience.

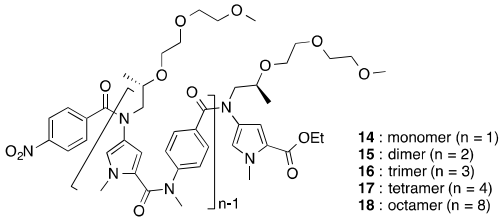
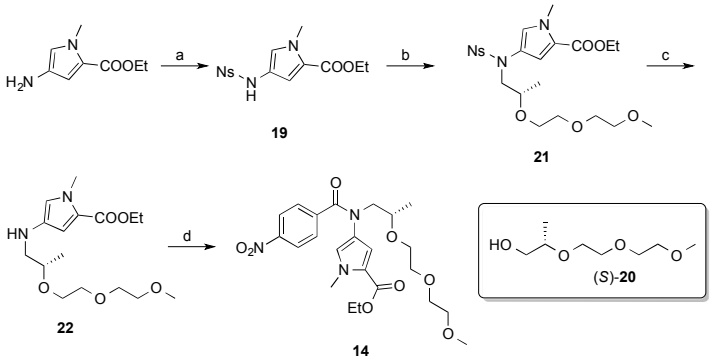


Figure 6. Structures of oligoamides **14** - **18** bearing chiral *N*-substituents

Synthesis of the monomeric building block **14** is illustrated in Scheme 2. Ethyl 4-amino-1-methylpyrrole-2-carboxylate was converted to sulfonamide **21** by treatment with *o*-nitrobenzenesulfonyl chloride in pyridine (87% yield). Alkylation of sulfonamide **19** was carried out under Mitsunobu conditions[23] with (*S*)-**20**, which was prepared by the reported procedure,[14,24] to give **21** in 87% yield. After removal of the nosyl group of **21** (77%) by treatment with thiophenol and cesium carbonate, **22** was acylated with *p*-nitrobenzoyl chloride to give **14** (quantitative). The ^{1}H NMR spectra of **14** showed that it existed in equilibrium between cis and trans conformers with a ratio of 10 : 1 in CD_2Cl_2 at 233 K (Figure S6a). The ratio of the cis conformer of **14** is much higher than that of **5** (3 : 2) bearing an *N*-methyl group. The bulkiness of the chiral *N*-substituent would increase the torsion angle between the pyrrole ring and amide bond, which would destabilize the trans conformer, while the *p*-nitro group on the benzoyl moiety would also influence the properties of the amide bond. Actually, introduction of the *p*-nitro group on the benzoyl moiety of **5** increased the ratio of cis (4 : 1) in CD_2Cl_2 at 253 K (Figure S6b). A sequential coupling strategy was used for the syntheses of the oligoamides **15-18** (Scheme S1).



Scheme 2. Synthesis of monomer **14**. (a) *o*-nitrobenzenesulfonyl chloride, pyridine, rt; (b) (*S*)-**20**, DEAD, PPh_3, THF, rt; (c) PhSH, Cs_2CO_3, CH_3CN, rt to 60°C; (d) *p*-nitrobenzoyl chloride, Et_3N,CH_2Cl_2, rt.

The conformations of oligoamides **15-18** in solution were investigated by means of

UV/vis and CD spectroscopy, and the spectra were compared with those of monomeric amide **14** and amine **22** (Figure 7a). Amides **14** – **18** showed similar UV/vis spectra in acetonitrile, exhibiting two broad bands with absorbance maxima at around 240 nm and 280-300 nm, which is different from the monomeric chiral amine **22** (maxima at 250 and 320 nm). The second band was shifted to longer wavelength in the cases of **16** – **18**, compared to the monomer **14** and dimer **15**. In the CD spectra in acetonitrile, the monomeric chiral amine **22** did not show any CD signal, while the chiral monomeric amide **14** showed a signal with a minus-to-plus-to-minus pattern in the region of 220-340 nm. The maximum wavelength was 270 nm. On the other hand, oligomers **15** – **18** showed CD signals with two maxima (around 260 nm and 310 nm) in the region of 250-330 nm. The CD intensity, especially that of the second peak (310 nm) increased as the chain length became longer. Compound **18** showed similar CD spectra in other solvents, such as chloroform and methanol, but not in water (Figure 7b). The intensity of the CD signals decreased as the temperature was raised (Figure 8). These results indicated that the chirality of the oligomers is not due to the intrinsic chirality of the chiral side chains, but rather is due to the dynamic chiral folding structures induced by the chiral side chains. The precise folding structures of oligomers **15** – **18** remain to be established. In the case of polyamides **1**, a strong CD signal was observed in aqueous methanol, and its intensity did not depend on the ratio of water (0 – 80%). The poly(*N*-alkylated 2,6-naphthalenecarboxamide)s also showed strong CD signals in aqueous methanol, and the intensity increased as the ratio of water increased (up to 60%). These polyamides bearing hydrophobic aromatic moieties showed rigid folding structures in polar solvents. In contrast, oligoamides **15** – **18** with an electron-rich pyrrole ring showed an intense CD signal in chloroform, a weaker signal in acetonitrile and methanol, and no signal in water. This indicates that the folding structure and properties of oligoamides bearing pyrrole rings are different from those of polyamides **1**, probably due to the electronic effects of pyrrole ring itself and the anti/syn conformational properties of the diamide moiety on the pyrrole ring.

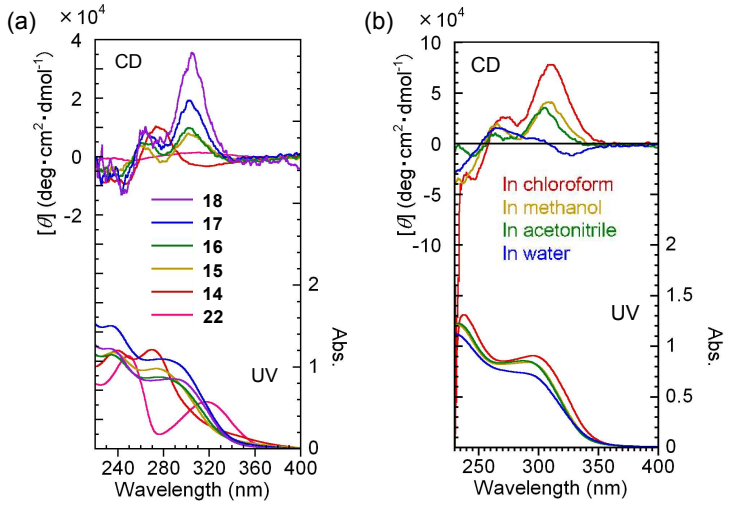


Figure 7. (a) UV and CD spectra of oligomers **14** - **18** in CD_3CN at 20°C. (b) UV and CD spectra of oligomer **18** in various solvents.

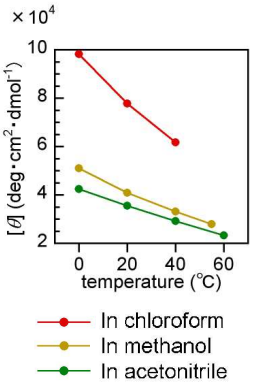


Figure 8. Temperature-dependency of CD spectra of oligomer **18** in various solvents.

Conclusion

In this study, we systematically investigated the conformational properties of *N*-methylated pyrroleamides, and established the cis conformational preference of the amide bonds on the pyrrole ring. We utilized these properties to synthesize a new type of aromatic oligoamide foldamers; these oligoamides bearing pyrrole and benzene hybrid-type structures folded into well-defined structures in solution, based on analyses of NMR and UV/CD spectra. There is no marked intramolecular interaction in these oligomers, and formation of the folded structures appears to be driven by the unique conformational properties of the aromatic amides. Oligoamides bearing a pyrrole ring showed different dynamic folding properties, as compared to known foldamers with cis-amide conformation, such as polyamides **1**. Further work is underway on applications of these unique dynamic foldamers based on amide conformational properties.

Experimental

General ^{1}H and ^{13}C NMR spectra were recorded on JEOL NHH-AL400, Bruker Advance 500 and JEOL ECA-600 spectrometers. Mass spectral data was obtained on Brucker Daltonics microTOF-2focus in the positive and negative ion detection modes. UV spectra were recorded with JASCO V-650, and CD spectra were recorded with JASCO J-820 spectropolarimeter using 2 mm quartz cell. The concentration of each solution of CD experiments was adjusted so that the absorbance of the oligoureas was 1 at the maximum absorption wavelength in the examined solvents. Crystallographic data were collected on a Bruker Apex II ultra CCD detector with graphite-monochromated Mo K□ radiation and a Bruker Apex II ultra CCD detector with graphite-monocromated Cu K□ radiation. The crystal structures were solved by direct methods using SHELXS-97 and refined by full-matrix least-squares SHELXL-97 (See: A short history of SHELX. G. M. Sheldrick *Acta Cryst.*, **2008**, *A64*, 112-122). All non-hydrogen atoms were refined anisotropically. All hydrogen atoms were included at their calculated positions.

Synthesis of 2

A mixture of 1-ehtyl-3-(3-dimethylaminopropyl)carbodiimide (458 mg, 2.40 mmol), *N*,*N*-diisopropylethylamine (261 mg, 2.00 mmol), and 1-hydroxybenzotriazole (62 mg, 0.400 mmol) was added to a solution of aniline (187 mg, 2.00 mmol) in methylene chrolide. After 30 min, 1-methyl-2-pyrrolecarboxylic acid (254 mg, 2.00 mmol) was added to the mixture, and the mixture was stirred for 15 h. Solvent was removed *in vacuo*, and the residue was extracted with ethyl acetate. The organic layer was wshed with brine, dried over magnesium sulfate, filetered, and evaporated. The residue was purified by open column chromatography (silica gel, ethyl acetate/*n*-hexane = 1 : 2) to give **2** (167 mg, 49%). Compound **2**: Colorless prisms (ethyl acetate/*n*-hexane); mp 105.9-107.8°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ□7.53 (d, J = 7.2 Hz, 2 H), 7.33 (t, J = 7.6 Hz, 2 H), 7.09 (t, J = 7.6 Hz, 1 H), 7.77 (t, J = 1.6 Hz, 1 H), 6.67 (dd, J = 4.4, 2.4 Hz, 1 H), 6.13 (dd, J = 4.0, 2.8 Hz, 1 H), 3.97 (s, 3 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ□160.0, 138.2, 129.2, 129.0, 125.9, 124.2, 120.1, 112.3, 107.6, 37.0; HRMS (ESI^+, TOF) m/z Calcd for $C_{12}H_{13}N_2O$ $[M+H]^+$: 201.1022. Found: 201.1024.

Synthesis of 3

Sodium hydride (29 mg, 0.720 mmol) was washed with *n*-hexane twice. Compound **2** (63 mg, 0.316 mmol) was added to a suspension of sodium hydride in dimethylformamide (3 ml) at 0°C, and the mixture was stirred for 30 min at room temperature. Iodomethane (60 μl) was added at 0°C, and the mixture was stirred for 2 h at room temperature. After removal of the

solvent *in vacuo*, water was added to the residue, and extracted with ethyl acetate. The organic layer was wshed with brine, dried over magnesium sulfate, filtered and evaporated to give **3** (58 mg, 0.268 mmol, 85%). Compound **3**: Yellow prisms (ethyl acetate); mp 74.1-77.0°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (t, 2H, *J* = 10.0 Hz), 7.24 (t, 1H, *J* = 8.0 Hz), 7.15 (d, 2H, *J* = 7.2 Hz), 6.57 (t, 1H, *J* = 2.0 Hz), 5.77 (dd, 1H, *J* = 3.6 Hz, 3.2 Hz), 5.51 (dd, 1H, *J* = 1.6 Hz, 4.0 Hz), 3.90 (s, 3H), 3.43 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 163.2, 145.8, 129.4, 127.2, 126.9, 126.8, 125.5, 116.4, 106.8, 38.4, 36.9; HRMS (ESI^+, TOF) m/z Calcd for $C_{13}H_{15}N_2O$ $[M+H]^+$: 215.1179, Found: 215.1174.

Synthesis of 4

A solution of ethyl 4-amino-1-methylpyrrole-2-carboxylate (489 mg, 2.91 mmol) in dichloromethane (40 ml) was added to triethylamine (0.5 ml, 3.59 mmol) and benzoyl chloride (498 mg, 3.54 mmol) at 0°C, and the mixture was stirred for 13 h at room temperature. After removal of the solvent *in vacuo*, the residue was extracted with ethyl acetate. The organic layer was washed with brine, dried over magnesium sulfate, filtered and concentrated. The residue was purified by recrystallization to give **4** (489 mg, 62%). Compound **4**: Colorless prisms; mp 128.4-130.3°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (d, 2H, *J* = 6.4 Hz), 7.71 (br, 1H), 7.54 – 7.52 (m, 2H), 7.48 (t, 2H, *J* = 7.6 Hz), 6.82 (d, 1H, *J* = 2.0 Hz), 4.29 (dd, 2H, *J* = 6.8 Hz, 14.4 Hz), 3.93 (s, 3H), 1.35 (t, 3H, *J* = 6.8 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ□164.9, 161.2, 134.4, 131.7, 128.8, 127.1, 121.9, 121.4, 120.3, 108.5, 60.1, 36.9, 14.5; HRMS (ESI^+, TOF) m/z Calcd for $C_{15}H_{17}N_2O_3$ $[M+H]^+$: 273.1234, Found: 273.1240.

Synthesis of 5

Sodium hydride (32 mg, 8.13 mmol) was washed with *n*-hexane twice. Compound **4** (141 mg, 0.518 mmol) was added to a suspension of sodium hydride in dimethylformamide (5 ml) at 0°C, and the mixture was stirred for 30 min at room temperature. Iodomethane (0.3 ml) was added at 0°C, and the mixture was stirred for 2 h at room temperature. After removal of the solvent *in vacuo*, the residue was extracted with ethyl acetate. The organic layer was wshed with water, dried over magnesium sulfate, filtered and evaporated. The residue was purified by open column chromatography to give **5** (140 mg, 94%).Compound **5**: Colorless powder; mp 92.7-95.3°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (br s, 5 H), 6.70 (br s, 1 H), 6.15 (br s, 1 H), 3.99 (s, 3 H), 4.26 (q, 2 H, *J* = 7.2 Hz), 1.34 (t, 3 H, *J* = 6.6 Hz); ^{13}C NMR (150 MHz, DMSO-d_6, 353K) δ□168.9, 159.7, 136.3, 128.8, 127.4, 127.3, 127.1, 124.3, 119.9, 112.0, 59.1, 37.6, 35.7, 13.7; HRMS (ESI^+, TOF) m/z Calcd for $C_{16}H_{19}N_2O_3$ $[M+H]^+$: 287.1390,

Found: 287.1393.

Synthesis of 9

A solution of **4** (47 mg, 0.171 mmol) in ethanol (2 ml) was added to 2 M sodium hydroxide (2 ml), and the mixture was stirred for 19 h at the room temperature. After removal of the solvent *in vacuo*, the residue was extracted with ethyl acetate. Then, the aqueous layer was acidified with 2 M hydrochloric acid, and extracted with ethyl acetate. The organic layer was dried over magnesium sulfate, filtered and concentrated to afford compound **9** (40 mg, 95%). Compound **9**: Colorless powder; mp 193.7-196.8°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.3 (s, 1 H), 7.92 (d, 2 H, J = 7.2 Hz), 7.54 (t, 1 H, J = 6.4 Hz), 7.51 (t, 2 H, J = 8.0 Hz), 7.50 (d, 1 H, 2.0 Hz), 6.89 (d, 1 H, J = 1.6 Hz), 3.85 (s, 3 H); ^{13}C NMR (150 MHz, CD_3OD) δ 167.4, 164.2, 135.7, 132.7, 129.6, 128.4, 123.7, 122.6, 121.6, 110.7, 37.1; HRMS (ESI$^+$, TOF) m/z Calcd for $C_{13}H_{13}N_2O_3$ $[M+H]^+$: 245.0921, Found: 245.0920.

Synthesis of 10

A mixture of 1-ehtyl-3-(3-dimethylaminopropyl)carbodiimide (330 mg, 1.72 mmol), *N*,*N*-diisopropylethylamine (175 mg, 1.35 mmol), and 1-hydroxybenzotriazole (153 mg, 0.982 mmol) was added to a solution of aniline (230 mg, 2.47 mmol) in dry methylene chrolide. After 30 min, compound **9** (306 mg, 1.25 mmol) was added, and the mixture was stirred for 2 h at the room temperature. After removal of the solvent *in vacuo*, the residue was extracted with ethyl acetate. The Organic layer was dried over magnesium sulfate, filetered, and evaporated. The residue was purified by open column chromatography (silica gel, methylene chrolide/*n*-hexane/methanol = 4 : 1 : 0.5) to give **10** (310 mg, 79%). Compound **10**: Colorless powder; mp 192.4-195.2°C; ^{1}H NMR (400 MHz, in $CDCl_3$) δ 7.85 (d, 2 H, J = 6.8 Hz), 7.80 (br s, 1 H), 7.60 (br s, 1 H), 7.55(d, 2 H, J = 7.2 Hz), 7.55 (t, 1 H, J = 7.6 Hz), 7.48 (t, 2 H, J = 6.8 Hz), 7.35 (t, 2 H, J = 7.6 Hz), 7.27 (d, 1 H), 7.12 (t, 1 H, 6.8 Hz), 6.83 (d, 1 H, J = 2.0 Hz), 3.96 (s, 3 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ□165.1, 159.7, 138.0, 134.4, 131.9, 129.2, 129.0, 127.0, 124.3, 123.8, 121.7, 120.1, 120.1, 104.2, 37.0; HRMS (ESI$^+$, TOF) m/z Calcd for $C_{19}H_{18}N_3O_2$ $[M+H]^+$: 320.1394, Found: 320.1389.

Synthesis of 6

Sodium hydride (117 mg, 2.93 mmol) was washed with *n*-hexane twice. Compound **10** (308 mg, 0.965 mmol) was added to a suspension of sodium hydride in dimethylformamide (10 ml) at 0°C, and the mixture was stirred for 30 min at room temperature. Iodomethane (0.36 ml) was added at 0°C, and the mixture was stirred for 1 h at room temperature. After removal

of the solvent *in vacuo*, water was added to the residue, and extracted with ethyl acetate. The organic layer was wshed with water, dried over magnesium sulfate, filtered and evaporated. The residue was purified by open colmncromatography (silica gel, ethyl acetate/*n*-hexane = 1 : 1) to give **6** (292 mg, 87%). Compound **6**: Yellow oil: ^{1}H NMR (400 MHz, in $CDCl_3$) δ 7.25 (m, 10 H), 6.10 (br s, 1 H), 5. 25 (br s, 1 H), 3.67 (br s, 3 H), 3.40 (br s, 3 H), 3.17 (br s, 3 H); ^{13}C NMR (150 MHz, DMSO-d_6, 373 K) δ□168.7, 161.5, 144.5, 136.1, 128.5, 128.4, 127.0, 126.5, 126.0, 125.9, 124.0, 120.6, 109.9, 37.4, 37.0, 34.9; HRMS (ESI$^+$, TOF) m/z Calcd for $C_{21}H_{22}N_3O_2$ $[M+H]^+$: 348.1707, Found: 348.1709.

Synthesis of 11

Triethylamine (0.6 ml) and *p*-nitrobenzoyl chloride (798 mg, 4.30 mmol) wad added to a solution of ethyl 4-amino-1-methylpyrrole-2-carboxylate (720 mg, 4.28 mmol) in dichloromethane (60 ml) at 0°C, and the mixture was stirred for 30 min at room temperature. After removal of the solvent *in vacuo*, the residue was extracted with ethyl acetate. The organic layer was dried over magnesium sulfate, filtered and concentrated. The residue was purified by open column chromatography (ethyl acetate/*n*-hexane = 1 : 1) to give **11** (1.065 g, 79%). Compound **11**: Yellow powder; mp 182.2-184.2°C; ^{1}H NMR (400MHz, in $CDCl_3$) δ 8.33 (d, 2 H, J = 6.9 Hz), 7.99 (d, 2 H, J = 6.9 Hz), 7.85 (S, 1 H), 7.51 (d, 1 H, J = 1.8 Hz), 6.84 (d, 1 H, J = 1.8 Hz), 4.29 (q, 2 H, J = 7.2 Hz), 3.94 (s, 3 H), 1.35 (t, 3 H, J = 7.1 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 162.8, 161.1, 149.7, 140.0, 128.3, 124.0, 121.4, 121.3, 120.7, 108.6, 60.3, 37.1, 14.5; HRMS (ESI$^+$, TOF) m/z Calcd for $C_{15}H_{16}N_3O_5$ $[M+H]^+$: 318.1084, Found 318.1087.

Synthesis of 12

A solution of **11** (112 mg, 0.353 mmol) was hydrogenated with palladium on carbon (12 mg) in ethyl acetate (5 ml) under hydrogen atmosphere for 1.5 h at room temperature. The reaction mixture was filtrated on celite, and the filtrate was concentrated *in vacuo* to give **12** (109 mg, quant). Compound **12**: Colorless oil; ^{1}H NMR (400 MHz, in $CDCl_3$) δ 7.67 (d, 2 H, J = 8.7 Hz), 7.59 (br s, 1 H), 7.50 (d, 1 H, J = 1.8 Hz), 6.78 (d, 1 H, J = 2.3 Hz), 6.69 (d, 2 H, J = 8.7 Hz), 4.28 (q, 2 H, J = 7.2 Hz), 4.00 (br s, 2 H), 3.91 (s, 3 H), 1.34 (t, 3 H, J = 7.2 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 164.6, 161.3, 149.9, 128.8, 123.9, 122.2, 121.3, 120.2, 114.4, 108.3, 60.0, 36.9, 14.6. ; HRMS (ESI$^+$, TOF) m/z Calcd for $C_{15}H_{18}N_3O_3$ $[M+H]^+$: 288.1343, Found: 288.1336.

Synthesis of 13

2.0 M Oxalyl chloride solution in methylene chrolide (4 ml) was added to 1-methylpyrrole-2-carboxylic acid (109.9 mg, 0.878 mmol) and a catalytic amount of dimethylformamide, and the mixture was stirred at room temperature for 1 h. After removal of the solvent *in vacuo* to geive crude acid chloride. An ice-cooled mixture of **12** (251 mg, 0.874 mmol) and pyridine (81 mg, 1.02 mmol) in dry acetonitrile (7 ml) was added to the acid chloride. The mixture was stirred at 0°C for 30 min and at room temperature for 2 h. The precipitate was collected by filtration and dried to give **13** (265 mg, 0.672 mmol, 77%). Compound **13**: Colorless powder; mp 224.0-225.3°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (d, 2 H, J = 8.7 Hz), 7.72 (br s, 1 H), 7.71 (br s,1 H), 7.69 (d, 2 H, J = 8.7 Hz), 6.82 (m, 2 H), 7.52 (d, 1 H, J = 2.0 Hz), 6.74 (dd, 1 H, J = 3.9, 1.8 Hz), 6.17 (dd, 1 H, J = 4.1, 2.7 Hz), 4.28 (q, 2 H, J = 7.3 Hz), 3.99 (s, 3 H), 3.93 (s, 3 H), 1.35 (t, 3 H, J = 7.3 Hz); ^{13}C NMR (150 MHz, DMSO-d_6) δ 163.1, 160.4, 159.9, 142.3, 129.4, 128.4, 128.0, 125.1, 122.9, 120.9, 119.0, 118.9, 114.3, 108.5, 106.9, 59.4, 36.4, 36.3, 14.3; HRMS (ESI$^+$, TOF) m/z Calcd for $C_{21}H_{22}N_4NaO_4$ $[M+Na]^+$: 417.1533, Found: 417.1521.

Synthesis of 7

Sodium hydride (89 mg, 3.70 mmol) was washed with *n*-hexane twice. Compound **13** (348 mg, 0.881 mmol) was added to a suspension of sodium hydride in dimethylformamide (25 ml) at 0°C, and the mixture was stirred for 30 min at room temperature. Iodomethane (0.2 ml) was added at 0°C, and the mixture was stirred for 1 h at room temperature. After removal of the solvent *in vacuo*, water was added to the residue, and extracted with ethyl acetate. The organic layer was dried over magnesium sulfate, filtered and evaporated. The residue was purified by open column chromatography (ethyl acetate/*n* -hexane = 2 :1) to give **7** (199 mg, 53%). Compound **7**: Colorless plates (chloroform/*n*-hexane); mp 136.9-138.7°C; ^{1}H NMR (600 MHz, DMSO-d_6, at 373 K) δ 7.30 (d, 2 H, J = 8.4 Hz), 7.12 (d, 2 H, J = 7.8 Hz), 6.96 (s, 1 H), 6.72 (s,1 H), 6.67 (s, 1 H), 5.74 (dd, 1 H, J = 3.6, 2.4 Hz), 5.54 (t, 1 H, J = 1.8 Hz), 4.22 (q, 2 H, J = 7.0 Hz), 3.77 (s, 3 H), 3.75 (s, 3 H), 3.32 (s, 3 H), 3.26 (s, 3 H), 1.28 (t, 3 H, J = 7.2 Hz); ^{13}C NMR(150 MHz, DMSO-d_6, 373K) δ 168.3, 162.0, 159.6, 145.6, 133.9, 127.8, 127.2, 125.8, 125.3, 125.2, 124.4, 120.0, 114.1, 112.1, 105.8, 58.9, 37.4, 36.8, 35.6, 34.9; HRMS (ESI$^+$, TOF) m/z Calcd for $C_{23}H_{27}N_4O_4$ $[M+H]^+$: 423.2027, Found: 423.2030.

Synthesis of 8

A mixture of **7** (48.3 mg, 0.114 mmol) in ethanol (2 ml) and 2 M sodium hydroxide (2 ml) was stirred for 6.5 h at room temperature. The reaction mixture was acidified by 2 M hydrochloric acid at 0°C, extracted with ethyl acetate. The organic layer was washed with

brine, dried over magnesium sulfate, filtered and evaporated to give carboxylic acid (46 mg, quant) as colorless powder; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (br, 2 H) , 7.03 (br, 2 H) , 6.74 (br, 1 H) , 6.57 (s, 1 H) , 6.39 (br, 1 H) , 5.76 (s, 1 H), 5.51 (br, 1 H), 3.87 (s, 3 H), 3.80 (br, 3 H), 3.40 (s, 3 H), 3.37 (s, 3 H); ^{13}C NMR (150 MHz, DMSO-d_6, 373 K) δ□168.3, 162.0, 160.9, 145.6, 133.9, 127.8, 127.1, 125.8, 125.3, 125.1, 123.9, 120.8, 114.1, 112.2, 105.9, 37.4, 36.8, 35.4, 34.9; HRMS (ESI$^+$, TOF) m/z Calcd for $C_{21}H_{23}N_4O_4$ $[M+H]^+$: 395.1714, Found: 395.1725.

Aniline (0.1 ml) and *N*,*N*-diisopropylethylamine (0.2 ml) were added to a solution of the carboxylic acid (202 mg, 0.513 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (126 mg, 0.657 mmol), and 1-hydroxybenzotriazole (6 mg, 0.037 mmol) in dry methylene chrolide (3 ml), and the reaction mixture was stirred for 2.5 h at room temperature. After removal of the solvent *in vacuo*, the residue was extracted with ethyl acetate. The organic layer was dried over magnesium sulfate, filetered, and evaporated. The residue was purified by open column chromatography (silica gel, ethyl acetate/*n*-hexane = 3 : 1) to give triamide (85 mg, 35%) as colorless powder; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (d, *J*=7.8 Hz), 7.47 (br, 2 H), 7.39 (br, 1 H), 7.35 (t, *J*=7.3 Hz), 7.13 (t, *J*=7.3 Hz), 7.06 (br, 2 H), 6.55 (br, 2 H), 6.39 (br, 1 H), 5.74 (br, 1 H), 5.54 (br, 1 H), 3.86 (br, 6 H), 3.40 (br, 6 H). ; ^{13}C NMR (150 MHz, DMSO-d_6, 373 K) δ□168.3, 161.9, 158.9, 145.6, 138.5, 133.8, 127.9, 127.7, 126.7, 125.7, 125.3, 125.1, 123.6, 123.0, 122.6, 119.8, 114.0, 108.7, 105.9, 37.6, 36.8, 35.4, 34.8; HRMS (ESI$^+$, TOF) m/z Calcd for $C_{27}H_{28}N_5O_3$ $[M+H]^+$: 470.2187, Found: 470.2197.

Sodium hydride (9 mg, 0.225 mmol) was washed with *n*-hexane twice. Triamide (77 mg, 0.163 mmol) was added to a suspension of sodium hydride in dimethylformamide (1.5 ml) at 0°C, and the mixture was stirred for 30 min at room temperature. A solution of iodomethane (74 mg, 0.524 mmol) in dimethylformamide (0.3 ml) was added at 0°C, and the mixture was stirred for 2 h at room temperature. After removal of the solvent *in vacuo*, water was added to the residue, and extracted with ethyl acetate. The organic layer was dried over magnesium sulfate, filtered and evaporated to give **8** (79 mg, quant.). Compound **8**: Colorless plates (chloroform/*n*-hexane); mp 190.6-191.4°C; ^{1}H NMR (600 MHz, DMSO-d_6, at 373 K) δ 7.33 (t, 2 H, *J* = 7.4 Hz), 7.26 (t, 1 H, *J* = 7.4 Hz), 7.14 (d, 2 H, *J* = 7.3 Hz), 7.09 (d, 2 H, *J* = 8.5 Hz), 7.06 (d, 2 H, *J* = 8.5 Hz), 6.75 (t, 1 H, *J* = 2.3 Hz), 5.79 (dd, 1 H, *J* = 3.8, 2.3 Hz), 5.57 (dd, 1 H, *J* = 3.8, 2.3 Hz), 5.45 (d, 1 H, *J* = 2.3 Hz), 3.76 (s, 3 H), 3.63 (s, 3 H), 3.33 (s, 3 H), 3.31 (s, 3 H), 3.03 (s, 3 H); ^{13}C NMR (150 MHz, DMSO-d_6, 373K) δ 168.1, 162.0, 161.48, 145.5, 144.6, 133.7, 128.4, 127.9, 126.4, 126.1, 125.9, 125.9, 125.3, 125.0, 124.1, 120.8, 114.1, 109.9, 105.9, 37.3, 37.0, 36.8, 35.0, 34.9. ; HRMS (ESI$^+$, TOF) m/z Calcd for $C_{28}H_{30}N_5O_3$ $[M+H]^+$: 484.2343, Found: 484.2351.

Synthesis of 19

2-Nitrobenzenesulfonyl chloride (1.295 g, 5.84 mmol) was added to a solution of ethyl 4-amino-1-methylpyrrole-2-carboxylate (947 mg, 5.63 mmol) in dry pyridine (4 ml) at 0°C, and the reaction mixture was stirred for 20 min at room temperature. 2 M hydrochloric acid was added to the mixture, and extracted with chloroform. 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 **19** (1.729 g, 87%). Compound **19**: Yellow prisms; mp 138.0-139.4°C; ^{1}H NMR(600 MHz, $CDCl_3$) δ 7.88 (dd, 1 H, *J* = 3.7, 1.4 Hz), 7.87 (dd, 1 H, *J* = 3.7, 1.4 Hz), 7.72 (td, 1 H, *J* = 7.7, 1.3 Hz), 7.63 (td, 1 H, *J* = 7.7, 1.3 Hz), 6.89 (br s, 1 H), 6.76 (d, 1 H, *J* = 2.0 Hz), 6.57 (d, 1 H, *J* = 2.0 Hz), 4.21 (q, 2 H, *J* = 7.1 Hz), 3.84 (s, 3 H), 1.29 (t 3 H, *J* = 7.1 Hz,); ^{13}C NMR (150 MHz, $CDCl_3$) δ 160.8, 148.3, 133.9, 132.7, 132.6, 132.1, 125.4, 125.0, 121.8, 118.2, 113.3, 60.3, 37.2, 14.5; HRMS (ESI^+, TOF) m/z Calcd for $C_{14}H_{16}N_3O_6S$ $[M+H]^+$: 354.0754, Found: 354.0750.

Synthesis of 21

Diethyl azodicarboxylate (40% in toluene, 3.2133 g, 7.38 mmol) in dry tetrahydrofuran (7 ml) was added to a mixture of **19** (1.321 g, 3.74 mmol), *(S)*-**20** (665 mg, 3.73 mmol), and triphenylphosphine (2.057 g, 7.84 mmol) in dry tetrahydrofuran (23 ml) under argon atmosphere at 0°C. The reaction mixture was stirred for 1 h at room temperature. After removal of the solvent *in vacuo*, the residue was purified by column chromatography (silica gel, ethyl acetate/*n*-hexane = 1 : 1) to give **21** (1.658 g, 87%). Compoud **21**: Yellow oil; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.74 (dd, 1 H, *J* = 7.9, 1.3 Hz), 7.64 (td, 1 H, *J* = 7.3, 1.4 Hz), 7.60 (dd, 1 H, *J* = 7.9, 1.3 Hz), 7.55 (td, 1 H, *J* = 7.9, 1.4 Hz), 6.88 (, 1 H d, *J* = 2.0 Hz), 6.66 (d, 1 H, *J* = 2.0 Hz), 4.23 (q, 2 H, *J* = 7.1 Hz), 3.86 (s, 3 H), 3.75-3.51 (m, 11 H), 3.37 (s, 3 H), 1.31 (t, , 3 H *J* = 7.1 Hz), 1.18 (d, 3H, *J* = 5.9 Hz); ^{13}C NMR(150 MHz, $CDCl_3$) δ 160.9, 148.3, 133.5, 132.3, 131.9, 131.3, 128.1, 124.0, 121.7, 121.5, 115.0, 74.1, 72.1, 70.8, 70.7, 68.4, 60.3, 59.1, 57.0, 37.3, 17.5, 14.5; HRMS (ESI^+, TOF) m/z Calcd for $C_{22}H_{32}N_3O_9S$ $[M+H]^+$: 514.1854, Found: 514.1859.

Synthesis of 22

A solution of **21** (90 mg, 0.175 mmol) in dry acetonitrile (1.5 ml) and cesium carbonate (75 mg, 0.230 mmol) were added to a solution of benzenethiol (22 mg, 0.202 mmol) in acetonitrile (0.5 ml), and the mixture was stirred for 3 h at room temperature. The mixture 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 = 3 : 1) to give **22** (44 mg, 77%). Compound **22**: Brown oil; ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.44 (d, 1 H, *J* = 2.2 Hz), 6.29 (d, 1 H, *J* = 2.2 Hz), 4.24 (q, 2 H, *J* = 7.1 Hz), 3.82 (s, 3 H), 3.75 (m, 1 H), 3.65 (m, 5 H), 3.55 (m, 3 H), 3.39 (s, 3 H), 2.98 (dd, 1 H, *J* = 12.4, 3.6 Hz), 2.92 (dd, 1 H, *J* = 12.4, 8.0 Hz), 1.32 (t, 3 H, *J* = 7.1 Hz), 1.18 (d, 3 H, *J* = 6.2 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 161.3, 120.6, 115.6, 106.0, 100.0, 74.4, 72.0, 70.8, 70.5, 68.0, 59.6, 59.0, 53.0, 36.4, 17.7, 14.5); HRMS (ESI^+, TOF) m/z Calcd for $C_{16}H_{28}N_2NaO_5$ $[M+Na]^+$: 351.1890, Found: 351.1885.

Synthesis of 14

Triethylamine (0.5 ml) and *p*-nitrobenzoyl chloride (345.9 mg, 1.86 mmol) was added to a solution of **22** (720 mg, 4.28 mmol) in dry dichloromethane (15 ml) at 0°C, and the mixture was stirred for 30 min at room temperature. After removal of the solvent *in vacuo*, the residue was extracted with ethyl acetate. The organic layer was dried over magnesium sulfate, filtered, and concentrated. The residue was purified by column chromatography (silica gel, ethyl acetate/n-hexane = 3 : 1) to give **14** (907 mg, quant). Compound **14**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (d, 2 H, *J* = 8.1 Hz), 7.53 (d, 2 H, *J* = 8.2 Hz), 4.21, (m, 2 H), 3.92 (m, 2 H), 3.77 (m, 4 H), 3.64 (m, 5 H), 3.55 (m, 3 H), 3.35 (s, 3 H), 1.31 (t, 3 H, *J* = 7.3 Hz), 1.21 (d, 3 H, *J* = 5.5 Hz); ^{13}C NMR (150 MHz, DMSO-d_6, 363 K) δ 167.7, 159.6, 147.1, 143.0, 128.3, 126.7, 122.4, 120.4, 114.2, 72.3, 71.0, 69.8, 69.2, 67.2, 59.1, 57.5, 54.6, 35.7, 17.0, 13.6; HRMS (ESI^+, TOF) m/z Calcd for $C_{23}H_{32}N_3O_8$ $[M+H]^+$: 478.2184, Found: 478.2190.

Synthesis of 23

A solution of **14** (417 mg, 0.874 mmol) was hydrogenated with palladium on carbon (42 mg) in ethyl acetate (16 ml) under hydrogen atmosphere for 4 h at room temperature. The reaction mixture was filtrated on celite, and the filtrate was concentrated *in vacuo* to give **23** (386 mg, 99%). Compound **23**: Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (d, 2 H *J* = 8.7 Hz), 6.68 (br s, 1 H), 6.60 (br s, 1 H), 6.47 (d, 2 H, *J* = 8.7 Hz), 4.24 (qd, 2 H, *J* = 7.6, 2.3 Hz), 3.93 (br s, 2 H), 3.78 (s, 3 H), 3.73 (m, 1 H), 3.64 (m, 4 H), 3.58 (m, 2 H), 3.53 (m, 2 H), 3.36 (s, 3 H), 1.32 (t, 3 H, *J* = 6.9 Hz), 1.17 (d, 3 H, *J* = 5.9); ^{13}C NMR (150 MHz, DMSO-d_6, 373 K) δ □169.4, 159.7, 149.3, 129.3, 127.9, 125.6, 119.9, 113.7, 112.0, 72.8, 70.9, 69.7, 69.2, 67.2, 58.9, 57.4, 55.1, 35.5, 17.1, 13.5; HRMS (ESI^+, TOF) m/z Calcd for $C_{23}H_{34}N_3O_6$ $[M+H]^+$: 448.2442, Found 448.2448.

Synthesis of 24

A mixture of **14** (422 mg, 0.883 mmol) in ethanol (16 ml) and 2 M sodium hydroxide (16 ml) was stirred for 18 h at room temperature. The reaction mixture was acidified by 2 M hydrochloric acid (18 ml), and extracted with ethyl acetate. The organic layer was washed with brine, dried over sodium sulfate, filtered and evaporated to give **24** (401 mg, quant). Compound **24**: Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (d, 2 H, *J* = 8.7 Hz), 7.53 (d, 2 H, *J* = 8.7 Hz), 6.79 (s, 1 H), 6.74 (s, 1 H), 3.97 (m, 2 H) , 3.80 (br s, 1 H), 3.76 (s, 3 H), 3.68 (m, 4 H), 3.56 (m, 4 H), 3.35 (s, 3 H), 1.21 (d, 3 H, *J* = 5.9 Hz); ^{13}C NMR (150 MHz, DMSO-d_6, 373 K) δ 167.6, 160.7, 147.1, 142.9, 130.0, 128.2, 126.0, 122.9, 122.2, 121.1, 72.3, 70.9, 69.7, 69.2, 67.1, 57.4, 54.5, 35.4, 16.9; HRMS (ESI^+, TOF) m/z Calcd for $C_{21}H_{27}N_3NaO_8$ $[M+Na]^+$: 472.1690, Found: 472.1685.

Synthesis of 25

A solution of **23** (381 mg, 0.851 mmol) and **24** (394 mg, 0.876 mmol) in dimethylformamide (9 ml) was treated with 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride (339.1 mg, 1.77 mmol) and *N,N*-dimethyl-4-aminopyridine (270.5 mg, 2.21 mmol) and the resulting solution was stirred for 19 h at room temperature. The reaction mixture was poured into ethyl acetate, washed with 2 M hydrochrolide, and saturated sodium hydrogen carbonate. The organic layer was dried over sodium sulfate, filtered, and evaporated to give **25** (651 mg, 87%). Compound **25**: Yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.32 (br, 1 H), 8.06 (d, 2 H, *J* = 8.7 Hz), 7.57 (d, 2 H, *J* = 8.7 Hz), 7.44 (br s, 2 H), 7.39 (br s, 2 H), 7.12 (s, 1 H), 6.67 (br s, 1 H), 6.58 (br s, 1 H), 6.43 (s, 1 H), 4.24 (m, 2 H), 3.97 (m, 4 H), 3.76 (m, 10 H), 3.65 (m, 6 H), 3.55 (m, 8 H), 3.36 (s, 3 H), 3.19 (s, 3 H), 1.34 (t, 3 H, *J* = 6.9 Hz), 1.221 (br s, 6 H). ; ^{13}C NMR (150 MHz, DMSO-d_6, 373 K) δ 168.9, 167.6, 159.6, 158.8, 147.1, 142.8, 139.2, 131.1, 128.3, 127.8, 126.9, 126.0, 125.5, 124.9, 123.7, 122.2, 120.1, 118.5, 114.0, 110.6, 72.6, 72.2, 70.9, 69.7, 69.2, 67.1, 67.1, 58.9, 57.4, 57.4, 54.8, 54.6, 35.5, 17.0, 13.5; HRMS (ESI^+, TOF) m/z Calcd for $C_{44}H_{59}N_6O_{13}$ $[M+H]^+$: 879.4135, Found: 879.4121.

Synthesis of 15

Sodium hydride (4 mg, 0.098 mmol) was washed with *n*-hexane twice. Compound **25** (30 mg, 0.034 mmol) was added to a suspension of sodium hydride in dimethylformamide (1 ml) at 0°C, and the mixture was stirred for 30 min at room temperature. A solution of iodomethane (27 mg, 0.192 mmol) in dimethylformamide (0.2 ml) was added t the mixture, and the mixture was stirred for 1 h at room temperature. After removal of the solvent *in vacuo*, water was added to the residue, and extracted with ethyl acetate. The organic layer was dried over magnesium sulfate, filtered and evaporated. The residue was purified by open column

chromatography (silica gel. ethyl acetate/methanol = 10 :1) to give **15** (29 mg, 94%). Compound **15**: Yellow oil; ^{1}H NMR (600 MHz, DMSO-d_6, at 353 K) δ 8.07 (d, 2 H, J = 8.4 Hz), 7.36 (br s, 2 H), 7.28 (d, 2 H, J = 8.3 Hz), 7.04 (d, 2 H, J = 8.3 Hz), 6.92 (s, 1 H), 6.64 (br s, 2 H), 6.57 (br s, 1 H), 4.24 (m, 2 H), 3.97 (m, 4 H), 3.876 (m, 10 H), 3.65 (m, 6 H), 3.55 (m, 8 H), 3.36 (s, 3 H), 3.19 (s, 3 H), 1.34 (t, 3 H, J = 6.9 Hz), 1.21 (br s, 6 H); ^{13}C NMR (150 MHz, DMSO-d_6, 373 K) δ □168.4, 167.4, 161.3, 159.6, 147.0, 145.0, 142.8, 134.1, 128.1, 128.0, 126.5, 125.8, 124.8, 124.6, 124.3, 122.8, 122.1, 120.2, 113.7, 111.4, 72.5, 72.0, 70.9, 70.9, 69.7, 69.2, 67.1, 67.0, 58.9, 57.4, 54.8, 54.2, 36.9, 35.5, 34.8, 17.0, 16.9, 13.5; HRMS (ESI$^+$, TOF) m/z Calcd for $C_{45}H_{61}N_6O_{13}$ $[M+H]^+$: 893.4291, Found: 893.4291.

Synthesis of 26

A solution of **25** (263.0 mg, 0.299 mmol) was hydrogenated with palladium on carbon (26.9 mg) in ethyl acetate (10 ml) under hydrogen atmosphere for 32 h at room temperature. The reaction mixture was filtrated on celite, and the filtrate was concentrated *in vacuo* to give **26** (260 mg, quant). Compound **26**: Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31 (br s, 1 H), 7.48 (d, 2 H, J = 8.7 Hz), 7.37 (d, 2 H, J = 8.7 Hz), 7.28 (d, 2 H, J = 8.2 Hz), 7.03 (d, 1 H, J = 1.3 Hz), 6.68 (br s, 1 H), 6.56 (br s, 2 H), 6.45 (d, 2 H, J = 8.2 Hz), 4.24 (m, 2 H), 3.47-4.05 (m, 27 H), 3.82 (s, 3 H), 3.36 (s, 3 H), 3.20 (s, 3 H), 1.32 (t, 3 H, J = 6.9 Hz), 1.20 (br s, J= 6 H); ^{13}C NMR (150 MHz, DMSO-d_6, 373 K) δ □169.3, 168.9, 159.6, 159.0, 149.3, 139.4, 130.9, 129.4, 129.2, 127.8, 127.3, 126.9, 126.0, 124.7, 123.1, 123.1, 120.1, 118.4, 113.9, 111.9, 110.5, 72.8, 72.6, 70.9, 70.9, 69.7, 69.2, 69.1, 67.1, 67.1, 58.9, 57.4, 55.1, 54.8, 35.5, 17.2, 17.0, 13.5; HRMS (ESI$^+$, TOF) m/z Calcd for $C_{44}H_{61}N_6O_{11}$ $[M+H]^+$: 849.4393, Found: 849.4396.

Synthesis of 27

A solution of **26** (39 mg, 0.0462 mmol) and **24** (23 mg, 0.0512 mmol) in dimethylformamide (1 mL) was treated with 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride (19.4 mg, 0.101 mmol) and *N,N*-dimethyl-4-aminopyridine (14.2 mg, 0.116 mmol), and the resulting solution was stirred for 24 h at room temperature. The reaction mixture was poured into ethyl acetate, and washed with 2 M hydrochloric acid and saturated aqueous sodium hydrogen carbobate. The organic layer was dried with sodium sulfate, filtered, and concentrated. The residue was purified by open column chromatography (silica gel, ethyl acetate/methanol = 10 :1) to give **27** (38 mg, 66%). Compound **27**: Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.35 (br, 1 H), 8.32 (br, 1H), 8.05 (d, 2 H, J = 7.8 Hz), 7.57 (d, 2 H, J = 7.8 Hz), 7.42 (m, 8 H), 7.11 (s, 1 H), 7.06 (s, 1 H), 6.68 (br s, 1 H), 6.56 (br s, 1 H), 6.42 (br s,

2 H), 4.23 (br s, 2 H), 3.54-4.00 (m, 42 H), 3.36 (s, 3 H), 3.21 (s, 3 H), 3.19 (s, 3 H), 1.32 (t, 3 H, J = 6.9 Hz), 1.20 (br s, 9 H); ^{13}C NMR (150 MHz, DMSO-d_6, 373 K) δ 168.9, 167.6, 159.6, 158.9, 158.8, 147.2, 142.8, 139.4, 139.3, 131.0, 131.0, 128.3, 128.0, 127.8, 126.9, 126.3, 126.0, 125.1, 124.9, 123.7, 123.3, 122.2, 120.1, 118.6, 118.5, 114.0, 110.6, 110.6, 72.6, 72.6, 72.2, 70.9, 69.7, 69.2, 69.1, 67.2, 67.1, 67.1, 58.9, 57.4, 57.4, 54.8, 54.6, 35.5, 17.2, 17.0, 17.0, 13.5; HRMS (ESI$^+$, TOF) m/z Calcd for $C_{65}H_{86}N_9O_{18}$ $[M+H]^+$: 1280.6085, Found: 1280.6051.

Synthesis of 16

Sodium hydride (3 mg, 0.075 mmol) was washed with *n*-hexane twice. Compound **27** (22 mg, 0.0174 mmol) was added to a suspension of sodium hydride in dimethylformamide (1 ml) at 0°C, and the mixture was stirred for 30 min at room temperature. A solution of iodomethane (27.8 mg, 0.196 mmol) in dimethylformamide (0.2 ml) was added, and the mixture was stirred for 1 h at room temperature. After removal of the solvent *in vacuo*, the residue was extracted with ethyl acetate. The organic layer was dried over magnesium sulfate, filtered and evaporated. The residue was purified by open column chromatography (silica gel ethyl acetate/methanol = 10 :1) to give **16** (18 mg, 80%). Compound **16**: Yellow oil; ^{1}H NMR(400 MHz, $CDCl_3$) δ 8.03 (d, 2 H, J = 8.2 Hz), 7.52 (br s, 2 H), 7.28 (br s, 2 H), 7.15 (br s, 2 H), 6.91 (br s, 2 H), 6.86 (br s, 2 H), 6.64 (br s, 1 H), 6.60 (br s, 1 H), 6.50 (br s, 1 H), 6.45 (br s, 1 H), 5.45 (br s, 1 H), 5.31 (br s, 1 H), 4.24 (q, 2H, J = 7.3 Hz), 3.32-3.88 (m, 57 H), 1.32 (t, 3 H, J = 7.3 Hz), 1.19 (br s, 3 H), 1.10 (d, 6 H, J = 6.9 Hz); ^{13}C NMR (150 MHz, DMSO-d_6, 373 K) δ 168.4, 168.3, 167.5, 161.5, 161.3, 159.6, 147.0, 145.0, 144.8, 142.9, 134.2, 133.9, 128.1, 128.0, 126.5, 125.8, 125.6, 124.7, 124.6, 124.3, 124.1, 123.0, 122.1, 120.1, 113.7, 111.4, 111.2, 72.5, 72.3, 72.0, 70.8, 69.7, 69.2, 67.1, 67.1, 58.9, 57.4, 54.8, 54.5, 54.2, 37.0, 37.0, 35.5, 34.8, 34.8, 17.0, 17.0, 16.9, 13.5; HRMS (ESI$^+$, TOF) m/z Calcd for $C_{67}H_{90}N_9O_{18}$ $[M+H]^+$: 1308.6398, Found: 1308.6379.

Synthesis of 28

A mixture of **25** (277 mg, 0.315 mmol) in ethanol (10 ml) and 2 M sodium hydroxide (10 ml) was stirred for 17 h at room temperature. The reaction mixture was acidified by 2 M hydrochloric acid (12 ml) at 0°C, extracted with ethyl acetate and THF. The organic layer was washed with brine, dried over sodium sulfate, filtered and evaporated to give **28** (333 mg, quant). Compound **28**: Yellow solid; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.34 (br s, 1 H), 8.05 (d, 2 H, J = 8.4 Hz), 7.57 (d, 2 H, J = 8.4 Hz), 7.46 (br s, 2 H), 7.38 (br s, 2 H), 7.10 (br s, 1 H), 6.76 (br s, 1 H), 6.70 (br s, 1 H), 6.42 (br s, 1 H), 3.54-4.00 (m, 28 H), 3.36 (s, 3 H), 3.20 (s, 3 H), 1.32 (t, 3 H, J = 6.9 Hz), 1.19 (br s, 6 H); ^{13}C NMR (150 MHz, DMSO-d_6, 373 K) δ 168.9,

167.7, 160.9, 158.8, 147.2, 142.8, 139.2, 131.2, 128.3, 127.8, 126.7, 125.5, 124.9, 123.7, 122.2, 120.7, 118.5, 113.9, 110.6, 72.6, 72.2, 70.9, 69.7, 69.2, 69.2, 67.2, 67.1, 57.4, 57.4, 54.8, 54.6, 35.5, 35.4, 17.1, 17.0; HRMS (ESI^+, TOF) m/z Calcd for $C_{42}H_{54}N_6NaO_{13}$ $[M+Na]^+$: 873.3641, Found: 873.3660.

Synthesis of 29

A solution of **26** (254 mg, 0.299 mmol) and **28** (326 mg) in dimethylformamide (6 mL) was treated with 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride (120 mg, 0.628 mmol) and *N,N*-dimethyl-4-aminopyridine (97 mg, 0.793 mmol), and the resulting solution was stirred for 22.5 h at room temperature. The reaction mixture was poured into ethyl acetate, and washed with 2 M hydrochloride and saturated sodium hydrogen carbonate. The organic layer was dried with sodium sulfate, filtered, and concentrated. The residue was purified by open column chromatography (silica gel ethyl acetate/methanol = 10 :1) to give **29** (257 mg, 52%). Compound **29**: Yellow oil; ^1H NMR (400 MHz, $CDCl_3$) δ 8.33 (br s, 1 H), 8.26 (br s, 1H), 8.24 (br s, 1H), 8.05 (d, 2 H, *J* = 8.7 Hz), 7.57 (d, 2 H, *J* = 8.7 Hz), 7.40 (m, 12 H), 7.10 (br s, 1 H), 7.07 (br s, 1 H), 7.06 (br s, 1 H), 6.68 (br s, 1 H), 6.56 (br s, 1 H), 6.43 (br s, 3 H), 4.23 (m, 2 H), 3.53-4.00 (m, 56 H), 3.36 (s, 3 H), 3.21 (s, 3 H), 3.19 (s, 3 H), 3.18 (s, 3 H), 1.32 (t, 3 H, *J* = 7.3 Hz), 1.20 (br s, 12 H); ^{13}C NMR (150 MHz, DMSO-d_6, 373 K) δ 168.9, 167.6, 159.6, 158.9, 158.8, 147.1, 142.8, 139.4, 139.3, 131.0, 130.9, 130.9, 128.3, 128.0, 127.9, 126.9, 126.3, 126.0, 125.4, 124.1, 124.9, 123.7, 123.3, 122.2, 120.1, 118.6, 118.5, 118.5, 115.0, 113.9, 110.6, 72.6, 72.6, 72.2, 70.9, 69.7, 69.2, 69.1, 67.2, 67.1, 67.1, 58.9, 57.4, 57.4, 54.8, 54.6, 35.5, 17.1, 17.0, 17.0, 13.5; HRMS (ESI^+, TOF) m/z Calcd for $C_{86}H_{113}N_{12}O_{23}$ $[M+H]^+$: 1681.8036, Found: 1681.8027.

Synthesis of 17

Sodium hydride (6 mg, 0.16 mmol) was washed with *n*-hexane twice. Compound **29** (36 mg, 0.022 mmol) was added to a suspension of sodium hydride in dimethylformamide (0.9 ml) at 0°C, and the mixture was stirred for 30 min at room temperature. A solution of iodomethane (55 mg, 0.384 mmol) in dimethylformamide (0.1 ml) was added, and the mixture was stirred for 1.5 h at room temperature. After removal of the solvent *in vacuo*, the residue was extracted with ethyl acetate. The organic layer was dried over magnesium sulfate, filtered and evaporated. The residue was purified by open column chromatography (silica gel, ethyl acetate/methanol = 10 :1) to give **17** (22 mg, 58%). Compound **17**: Yellow oil; ^1H NMR (600 MHz, DMSO-d_6, 373K) δ 8.06(d, 2 H, *J* = 8.6 Hz), 7.38 (d, 2 H, *J* = 8.2 Hz), 7.30 (d, 2 H, *J* = 8.4 Hz), 7.15 (d, 2 H, *J* = 8.3 Hz), 7.14 (d, 2 H, *J* = 8.3 Hz), 7.06 (d, 2 H, *J* = 8.5 Hz), 7.03 (d,

2 H, *J* = 8.5 Hz), 7.01 (d, 2 H, *J* = 8.4 Hz), 6.88 (s, 1 H), 6.64 (m, 2 H), 6.60 (s, 1 H) 6.57 (s, 1 H), 5.61 (d, 1 H, *J* = 1.6 Hz), 5.60 (d, 1 H, *J* = 1.6 Hz), 5.58 (s, 1H), 4.19 (q, 2 H, *J* = 7.1 Hz), 3.37-3.73 (m, 56 H), 3.29 (s, 3 H), 3.26 (s, 3 H), 3.26 (s, 3 H), 3,26 (s, 3 H), 3.24 (s, 3 H), 3.23 (s, 3 H), 1.26 (t, 3 H, *J* = 7.1 Hz), 1.10 (d, 3 H, *J* = 5.8 Hz), 1.03 (d, 3 H, *J* = 5.8 Hz), 1.01 (d, 3 H, *J* = 5.8 Hz), 1.00 (d, 3 H, *J* = 5.8 Hz); ^{13}C NMR (150 MHz, DMSO-d_6, 373 K) δ 168.4, 168.3, 168.3, 167.4, 161.5, 161.5, 161.3, 159.6, 147.0, 145.0, 144.8, 144.7, 142.8, 134.2, 134.0, 133.9, 128.1, 128.0, 128.0, 126.5, 125.7, 125.6, 125.6, 124.7, 124.6, 124.5, 124.3, 124.1, 122.8, 122.8, 122.1, 120.2, 113.8, 113.7, 111.3, 111.1, 111.0, 72.5, 72.3, 72.0, 70.9, 69.7, 69.1, 67.1, 67.1, 67.0, 58.9, 57.4, 54.8, 54.5, 54.5, 54.2, 54.0, 37.0, 37.0, 37.0, 35.5, 34.8, 34.7, 17.0, 17.0, 16.9, 13.5; HRMS (ESI$^+$, TOF) m/z Calcd for $C_{89}H_{119}N_{12}O_{23}$ $[M+H]^+$: 1723.8506, Found: 1723.8466.

Synthesis of 30

A solution of **29** (72 mg, 0.0426 mmol) was hydrogenated with palladium on carbon (9 mg) in ethyl acetate (1.5 ml) under hydrogen atmosphere for 29 h at room temperature. The reaction mixture was filtrated on celite, and the filtrate was concentrated. The residue was purified by open column chromatography (silica gel, ethyl acetate/methanol = 20 : 3) to give **30** (52 mg, 74%). Compound **30**: Colorless solid; ^{1}H NMR (600 MHz, $CDCl_3$, 323K) δ 8.03 (br, 1 H), 8.02 (br, 1H), 8.00 (br, 1H), 7.40 (m, 14 H), 6.91 (s, 1 H), 6.88 (s, 1 H), 6.67 (s, 1 H), 6.60 (br s, 1 H), 6.50 (br s, 3 H), 6.45 (d, 2 H, *J* = 8.4 Hz), 4.24 (m, 2 H), 3.49-4.00 (m, 56 H), 3.36 (s, 3 H), 3.26 (s, 3 H), 3.25 (s, 3 H), 3.24 (s, 3 H), 1.32 (t, 3 H, *J* = 7.2 Hz), 1.20-1.17 (br s, 12 H); ^{13}C NMR (150 MHz, DMSO-d_6, 373 K) δ 169.3, 168.9, 159.6, 159.0, 158.9, 149.4, 139.4, 139.4, 131.0, 130.9, 130.8, 129.4, 128.0, 127.8, 127.3, 126.9, 126.3, 126.0, 125.1, 124.7, 123.3, 123.1, 123.1, 120.1, 118.5, 118.5, 113.9, 111.9, 110.6, 110.6, 110.5, 72.8, 72.6, 72.6, 70.9, 69.7, 69.2, 69.1, 67.2, 67.1, 58.9, 57.4, 57.4, 55.1, 54.9, 35.5, 17.2, 17.1, 17.0, 13.5; HRMS (ESI$^+$, TOF) m/z Calcd for $C_{86}H_{115}N_{12}O_{21}$ $[M+H]^+$: 1651.8294, Found: 1651.8304.

Synthesis of 31

A mixture of **29** (37 mg, 0.222 mmol) in ethanol (0.8 ml) and 2 M sodium hydroxide (0.8 ml) was stirred for 20 h at room temperature. The reaction mixture was acidified by 2 M hydrochloric acid at 0°C, extracted with ethyl acetate and THF. The organic layer was washed with brine, dried over sodium sulfate, filtered and evaporated to give **31** (40 mg, quant). Compound **31**: Yellow solid; ^{1}H NMR (600 MHz, $CDCl_3$, 323K) δ 8.20 (br s, 1 H), 8.05 (br s, 2 H), 8.03 (br s, 1H), 7.94 (br s, 1H), 7.57 (br s, 2 H), 7.39 (m, 12 H), 6.96 (br s, 1 H), 6.88 (br s, 1 H), 6.75 (br s, 1 H), 6.71 (br s, 1 H), 6.65 (br s, 1 H), 6.57 (br s, 1 H), 6.51 (br s, 1 H),

3.50-4.00 (m, 56 H), 3.36 (s, 3 H), 3.26 (s, 3 H), 3.23(br s, 6 H), 3.18 (s, 3 H), 1.32 (t, 3 H, *J* = 7.3 Hz), 1.20 (br s, 12 H); ^{13}C NMR (150 MHz, DMSO-d_6, 373 K) δ 168.9, 167.6, 160.9, 158.9, 158.8, 147.1, 142.8, 139.4, 139.3, 139.2, 131.0, 130.9, 128.3, 128.0, 127.8, 126.7, 126.3, 125.5, 125.1, 124.9, 124.9, 123.6, 123.3, 123.3, 122.2, 120.7, 118.6, 118.5, 118.5, 113.9, 110.6, 110.6, 72.6, 72.6, 72.2, 70.9, 69.7, 69.2, 69.1, 67.1, 67.1, 57.4, 57.4, 54.8, 54.8, 54.6, 35.5, 35.4, 17.1, 17.1, 17.0; HRMS (ESI$^+$, TOF) m/z Calcd for $C_{84}H_{109}N_{12}O_{23}$ $[M+H]^+$: 1653.7723, Found: 1653.7733.

Synthesis of 32

A solution of **30** (49 mg, 0.0297 mmol) and **31** (49 mg, 0.0297 mmol) in dimethylformamide (2.1 ml) was treated with 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride (12 mg, 0.0636 mmol) and *N,N*-dimethyl-4-aminopyridine (9 mg, 0.074 mmol), and the resulting solution was stirred for 44 h at room temperature. The reaction mixture was poured into ethyl acetate, and washed with 2 M hydrochloric acid and saturated sodium hydrogen carbonate. The organic layer was dried with sodium sulfate, filtered, and concentrated. The residue was purified by open column chromatography (silica gel, ethyl acetate/methanol = 5 :1) and preparative TLC (silica gel, ethyl acetate/methanol = 5 :1) to give **32** (43 mg, 44%). Compound **32**: Yellow solid; ^{1}H NMR (600 MHz, DMSO-d_6, 373K) δ 9.40 (m, 7 H), 8.09 (d, 2 H, *J* = 8.7 Hz), 7.56 (m, 16 H), 7.34 (m, 12 H), 7.28 (d, 2 H, *J* = 8.6 Hz), 6.88 (m, 9 H), 6.82 (br s, 6 H), 6.63 (d, 1 H, *J* = 2.0 Hz), 4.19 (q, 2 H, *J* = 7.1 Hz), 3.42-3.79 (m, 112 H), 3.26 (s, 3 H), 3.24 (m, 18 H), 1.25 (t, 3 H, *J* = 7.1 H), 1.13 (m, 24 H); ^{13}C NMR (150 MHz, DMSO-d_6, 373 K) δ 168.9, 158.9, 158.8, 147.1, 142.8, 139.4, 139.2, 131.0, 130.9, 128.3, 128.0, 127.8, 126.3, 126.0, 125.1, 125.0, 123.3, 122.2, 120.1, 118.6, 118.5, 118.5, 113.9, 110.6, 110.5, 72.6, 72.2, 70.9, 69.7, 69.1, 67.2, 67.1, 58.9, 57.4, 54.9, 54.6, 35.5, 17.1, 17.0, 17.0, 13.5; HRMS (ESI$^+$, TOF) m/z Calcd for $C_{170}H_{221}N_{24}O_{43}$ $[M+H]^+$: 3286.5839, Found: 3286.5902.

Synthesis of 18

Sodium hydride (6 mg, 0.138 mmol) was washed with *n*-hexane twice. Compound **32** (25 mg, 0.0076 mmol) was added to a suspension of sodium hydride in dimethylformamide (1.5 ml) at 0°C, and the mixture was stirred for 30 min at room temperature. Iodomethane (56 mg, 0.392 mmol) was added, and the mixture was stirred for 1 h at room temperature. After removal of the solvent *in vacuo*, the residue was extracted with ethyl acetate. The organic layer was dried over magnesium sulfate, filtered and evaporated. The residue was purified by preparative TLC (methylene chrolide/methanol = 20 : 1) to give **18** (15 mg, 58%). Compound **18**: Yellow

oil; ^{1}H NMR (600 MHz, DMSO-d_6, 373K) δ 8.06 (d, 2 H, J = 8.7 Hz), 7.37 (d, 2 H, J = 8.6 Hz), 7.29 (d, 2 H, J = 8.5 Hz), 7.15 (m, 12 H), 7.03 (m, 14 H), 6.88 (br s, 1 H), 6.58 (m, 2 H), 6.57 (m, 6 H), 5.60 (m, 7 H), 4.20 (q, 2 H, J = 7.0 Hz), 3.35-3.74 (m, 112 H), 3.25 (m, 45 H), 1.26 (t, 3 H, J = 7.0 Hz), 1.10 (d, 3 H, J = 5.9 Hz), 1.01 (m, 21 H); ^{13}C NMR (150 MHz, DMSO-d_6, 373 K) δ 168.4, 168.3, 168.3, 167.5, 161.6, 161.5, 161.4, 159.6, 147.0, 145.0, 144.8, 142.9, 134.2, 134.0, 128.2, 128.1, 128.0, 128.0, 125.8, 125.6, 124.7, 124.7, 124.6, 124.1, 122.2, 122.1, 120.1, 111.1, 72.5, 72.3, 72.0, 70.9, 69.7, 69.2, 67.2, 67.1, 67.1, 58.9, 57.4, 54.8, 54.5, 54.3, 40.1, 37.1, 37.0, 37.0, 35.5, 34.8, 34.8, 28.4, 28.0, 17.0, 16.9, 13.5; HRMS (MALDI-TOF) m/z Calcd for $C_{177}H_{234}N_{24}O_{43}$ $[M+Na]^+$: 3406.6754, Found: 3406.6536.

Acknowledgements

This work was partly supported by JSPS KAKENHI Grant No 16K08318 (to AT) and JSPS Core-to-Core Program, A. Advanced Research Networks. AT gratefully acknowledge funding from The Sumitomo Foundation and The Naito Foundation. KU is grateful for financial support from JSPS Research Fellow for Young Scientists.

Supporting Information Available: ^{1}H and ^{13}C NMR spectra, synthetic scheme of oligomers, crystal data and structures and cartesian coordinates of the calculation. This material is available free of charge via the Internet at http://pubs.acs.org.

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