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Linear and Cyclic Hybrids of Alternating Thiophene–Amino Acid Units: Synthesis and Effects of Chirality on Conformation and Molecular Packing

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Dedicated to Professor Hisashi Yamamoto on the occassion of his 70th birthday

Abstract: The dipeptide isostere 5-aminothiophene carboxylic acid has been combined with L-phenylalanine moieties to provide linear and cyclic hybrid oligopeptides. A suitable protecting group strategy and appropriate coupling methods have been developed to guarantee a high degree of enantiopurity of the resulting amides. Cyclic tetraamides have been efficiently obtained by macrocyclization of the linear derivatives. In the case of racemized cyclization precursors, two diastereomeric macrocycles (*S*,*S*/*R*,*R* and *meso*) have been isolated. Their crystal structures show clear effects of the stereogenic centers on the ring conformations and molecular packing.

Keywords: amino acids · crystal packing · dipeptide isosteres · macrocycles · peptidomimetics · ring conformation · thiophene

Introduction

Our research interest in this area was provoked by the discovery of biological activities of some natural cyclic compounds built up by amide bonds, for example, those extracted from marine plants.[1] Due to their multifaceted environment, marine plants have developed a variety of complex mechanisms that allow them to survive and resist infections. Studies have shown that 3.5% of marine plant extracts exhibit cytotoxic or antitumor effects.[1] For example, the calyxamides A/B[2] from the marine sponge *Discodermia calyx* proved to be cytotoxic, while solomonamide A[3] from *Theonella swinhoei* showed in vivo anti-inflammatory activity (Figure 1). Another class of bioactive cyclopeptides containing five-membered heterocycles, such as the antitumor trunkamide A[4] and the cytotoxic ascidiacyclamide[1,5] and ulicyclamide[1c,6] (all three from the *Lissoclinum*[7] class of cyclic peptides), play important roles in Nature, as they are found in many marine organisms. Most of these cyclic compounds contain at least one aromatic ring within the macrocycle. The rigidity introduced by heterocycles in the cyclopeptides could lead to a better fit in host–guest interactions. This feature is particularly shown by the

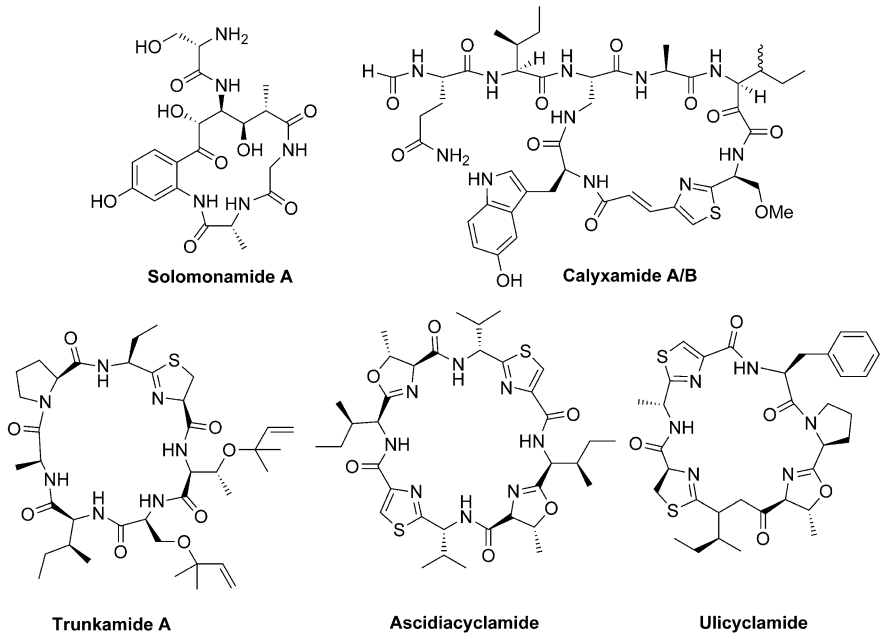

Figure 1. Bioactive natural cyclic peptides extracted from marine organisms.

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[+] Responsible for X-ray crystal structure determination

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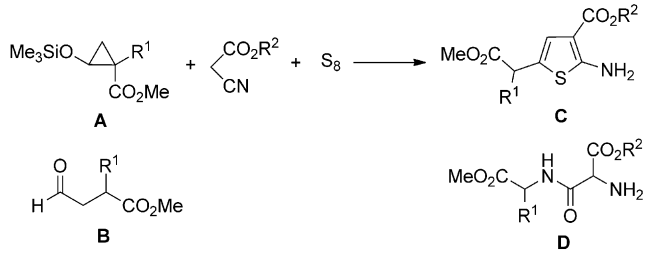
Lissoclinum class, in which five-membered heterocycles are linked by amide bonds to segments containing stereogenic centers. This alternating sequence of heterocyclic rings and amino acids containing stereogenic units led to speculation that both the heterocyclic structure and the configuration of the backbone are essential prerequisites for biological activity. These metabolites may have a role to play in vivo as host agents for metal transport,[8] and/or metals may act as templates in their biological assembly from constituent amino acids/heterocyclic rings.[9] Despite intense investigation by the scientific community, there is still a need for new synthetic methods for novel peptides or simplified and more stable peptidomimetics.[10] In particular, cyclic amides incorporating heterocyclic units other than oxazole or thiazole moieties, which are biosynthetically derived from the functionalized amino acids serine, threonine, or cysteine, should afford interesting compounds with new properties. To the best of our knowledge, no cyclic amides containing thiophene units are found in Nature, which is the key feature of the current study.

In recent years, our group has explored the synthesis and reactivity of 5-aminothiophenecarboxylic acids[11] obtained by a three-component Gewald reaction[12–15] using methyl 2-siloxycyclopropanecarboxylates **A** as equivalents of functionalized aldehydes **B** (Scheme 1).[15,16] This process gives



Scheme 1. Synthesis of 5-aminothiophenecarboxylic acids **C** by the Gewald reaction with siloxycyclopropanes **A**.

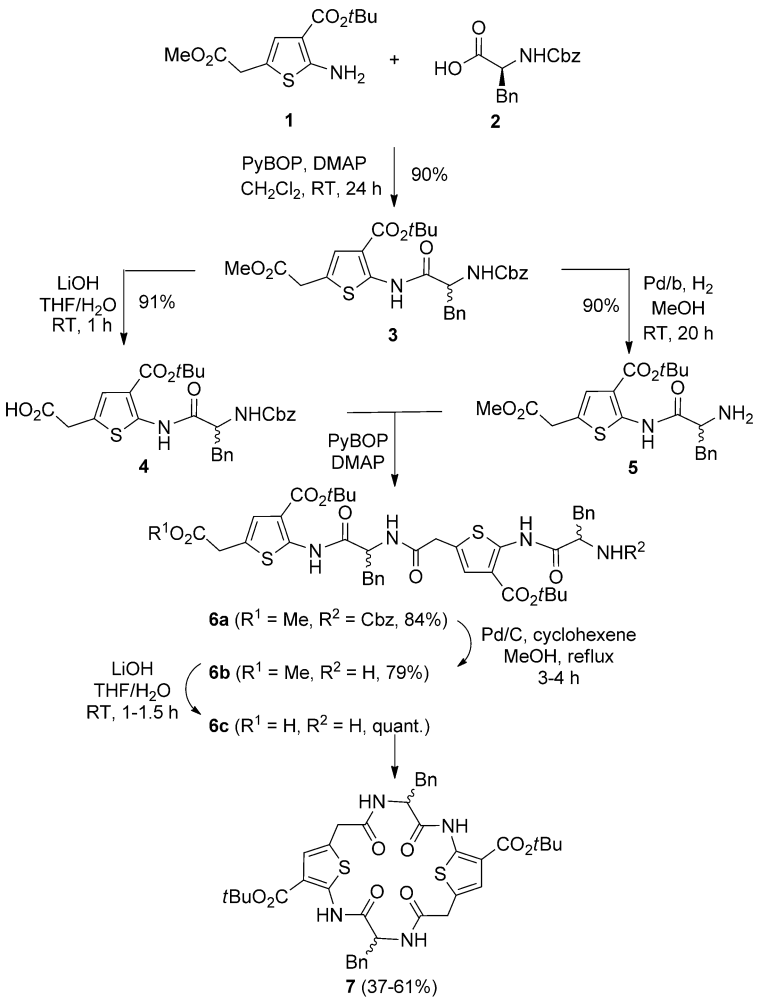
direct access to compounds **C**, which can be considered as unnatural amino acids with a thiophene backbone and as isosteres of dipeptides **D**. The ready accessibility of the unique amino acids **C** opens new prospects for the preparation of a variety of novel linear and cyclic peptidomimetics containing thiophene moieties.

During the past few years, we have focused on the development of methods for constructing unnatural oligoamides by peptide coupling reactions between the carboxylic acid derived from **C** and the notoriously unreactive 5-amino group at the thiophene ring. Hence, different synthetic procedures have been tested involving both traditional methodology (conventional stirring) and ultrasound activation, in conjunction with various coupling reagents, to achieve the optimal reaction conditions for linear and cyclic oligoamides with a thiophene backbone.[11b,17] Initial studies clearly indicated that under conventional stirring the coupling reagent *N*-ethyl-*N*′-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDCI·HCl) gave the best results, though a clear trend of decreasing yields with higher homologues was observed.[11b] The same reaction conditions were applied to achieve macrocyclization under high dilution affording low to moderate yields. In our last report, we revealed an optimized procedure for our systems employing propylphosphonic anhydride (T3P)[18] as a coupling reagent combined with ultrasound activation.[17] These proved to be excellent reaction conditions for fast and high-yielding (up to quantitative) amide couplings, including those of higher homologues that gave fairly low yields under conventional conditions. This optimized procedure was applied to prepare cyclic amides in high yields; the selectivity in terms of the size of the macrocycles could be controlled by the choice of dilution level.

These promising results encouraged us to expand the scope of our developed methods toward linear and cyclic oligoamides with alternating 5-aminothiophene carboxylic acids and natural amino acids, introducing stereogenic centers into the backbone. In this report, we disclose different reaction conditions and synthetic pathways for the construction of these new peptidomimetics. The high tendency of intermediates and products to undergo racemization is discussed, as well as the conformations of macrocyclic products in the solid state, including their crystal packing.

Results and Discussion

For the construction of such hybrid oligoamides with alternating 5-aminothiophene carboxylic acids and natural amino acids, L-phenylalanine was chosen as an enantiopure component to introduce a stereogenic center. In the initial period of our investigation, we focused on yield optimization of the chain elongation and cyclization reactions of oligoamides. The peptide coupling between 5-aminothiophene carboxylic acid **1** and carboxybenzyl-protected (Cbz) L-phenylalanine **2** was carried out under conditions of conventional stirring. PyBOP-mediated amide coupling in the presence of DMAP (see footnote to Table 1 for abbreviations) proved to be a good synthetic method for obtaining the desired monoamide **3** (90%, Scheme 2). Deprotection of **3** according to the literature procedures afforded the desired carboxylic acid **4** and amine **5** in excellent yields of 91 and 90%, respectively. By combining these two components under the same coupling conditions, we obtained a high yield (84%) of triamide **6a**. After deprotections of the reactive termini, precursor **6a** was ready for the cyclization step. Remarkably, the above described synthetic sequence occurred with high to quantitative yields in each step. At the stage of the acyclic intermediates, there was no evidence that (partial) racemization had occurred, which would have led to diastereomers for compounds **6a–c**. The cyclization step was carried out with different coupling reagent systems, for example, BOP with DMAP or PyBroP with DIPEA (Scheme 2, Table 1). Under high-dilution reaction conditions ($c = 0.004\ \mathrm{mol\,L^{-1}}$) with BOP/DMAP, 61% of the desired cyclic tetraamide **7** was obtained after 2 days (Table 1, entry 1). By changing the sol-



Scheme 2. Synthesis of macrocyclic tetraamide **7**, affording a mixture of the (*S*,*S*)/(*R*,*R*), and (*R*,*S*) isomers (Bn = benzyl, Pd/b = palladium/black)

Table 1. Synthesis of macrocyclic tetraamide **7** from precursor **6c**.

Entry	Coupling reagent[a]	Solvent	Yield [%]
1	BOP/DMAP	CH_2Cl_2	61
2	BOP/DMAP	DMF	49
3	BOP/DMAP	DMF/CH_2Cl_2	59
4	PyBroP/DIPEA	CH_2Cl_2	37

[a] PyBOP = benzotriazol-1-yloxy(tripyrrolidino)phosphonium hexafluorophosphate, BOP = benzotriazol-1-yloxytris(dimethylamino)-phosphonium hexafluorophosphate, DMAP = 4-(dimethylamino)pyridine, PyBroP = bromo(tripyrrolidino)phosphonium hexafluorophosphate, DIPEA = *N*,*N*-diisopropylethylamine.

vent system from CH_2Cl_2 to DMF or a mixture of DMF and CH_2Cl_2, the yields dropped to 49 and 59%, respectively. When PyBroP and DIPEA were employed in CH_2Cl_2, only a 37% yield of the macrocyclic product **7** was isolated.

NMR data for macrocycle **7** obtained by the BOP/DMAP method are displayed in Figure 2. The observation of a double set of signals in a ratio of 1:1 indicates that the 18-membered macrocycle did not show the expected symmetry and that two diastereomers were probably present in the mixture. Two sets of signals in a ratio of 1:3 were likewise observed in the ^{1}H NMR spectrum of the product derived from the cyclization with PyBroP/DIPEA, indicating that mixtures of diastereomers were generated in the reaction sequence.

After careful purification by HPLC, two fractions were isolated and characterized. Their ^{1}H NMR spectra in [D$_6$]DMSO clearly showed single sets of signals (Figure 3). The compounds in these fractions were characterized as two diastereomers (*S*,*S*)/(*R*,*R*)-**7** = *rac*-**7** and (*S*,*R*)-**7** = *meso*-**7**. Evidently, racemization at the stereogenic centers had occurred during our synthetic sequence. After crystallization of the separated macrocycles, the solid-state structures revealed the expected C_2-symmetry for each of the enantiomers of *rac*-**7** and C_i-symmetry for *meso*-**7**. The solid-state structures are discussed in detail below.

The spectroscopic data and solid-state structures clearly proved that during our synthesis of tetraamide **7** extensive racemization occurred, ultimately resulting in the production of diastereomers. In the second part of this work, we therefore investigated pathways toward enantiomerically pure macrocyles and resumed our synthesis with the same precursors once more.

We first sought the optimal reaction conditions for the initial coupling of amine **1** with L-phenylalanine derivative **2** to afford amide (*S*)-**3** with regard to yield and enantiopurity (Scheme 3, Table 2). The choice of base not only affected the yield, but also influenced the extent of racemization. When the amount of DMAP was reduced from three (Table 2, entry 1) to two equivalents with PyBOP as the coupling reagent, a decreased yield of 60% and a low *ee* (22%) were observed (Table 2, entry 2). By changing the base to DIPEA or 2,4,6-collidine,[18] the degree of racemization was reduced, but the yield decreased to 36 and 6%, respectively (Table 2, entries 3 and 4). In the case of the coupling reagent TFFH[20] (see footnote to Table 2), better *ee* values (85–97%) were achieved, but the yields were only moderate to low (47–73%), depending on the base (Table 2, entries 5 and 6). A similar influence of the base was also ob-

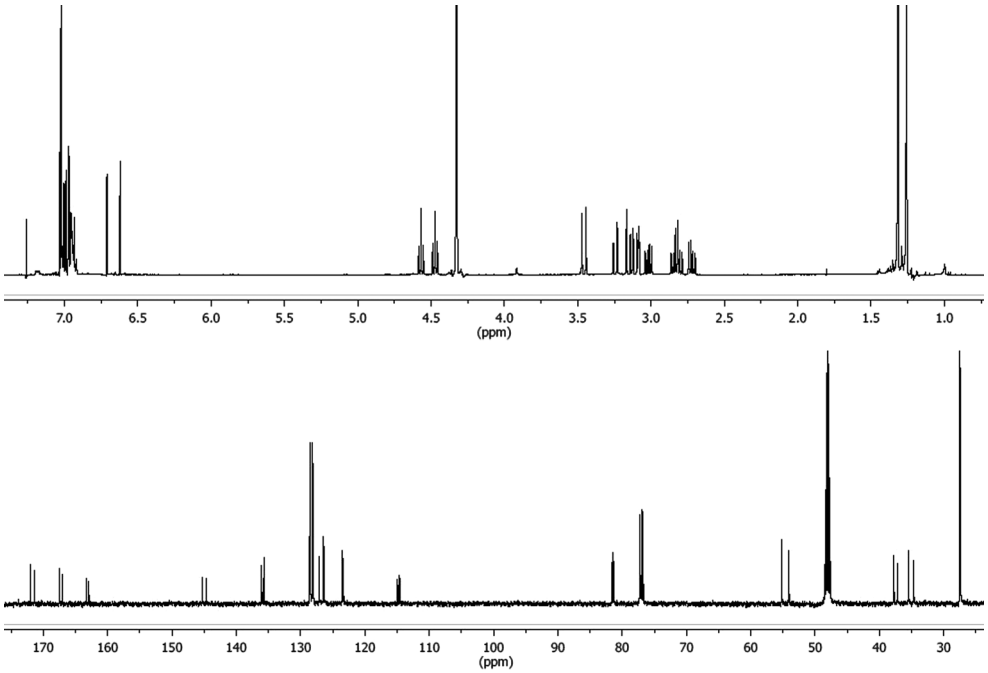


Figure 2. ^{1}H NMR (500 MHz, CD_3OD, $CDCl_3$) and ^{13}C NMR (126 MHz, CD_3OD, $CDCl_3$) spectra of tetraamide **7** obtained by cyclization according to the BOP/DMAP method (Table 1, entry 1).

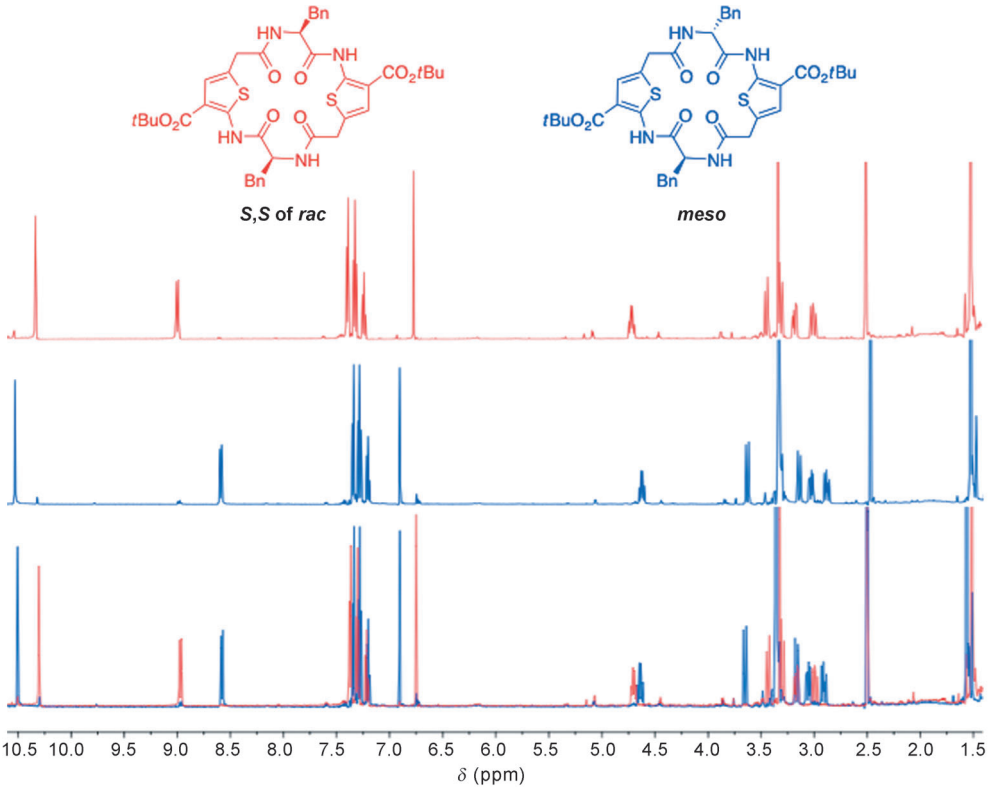
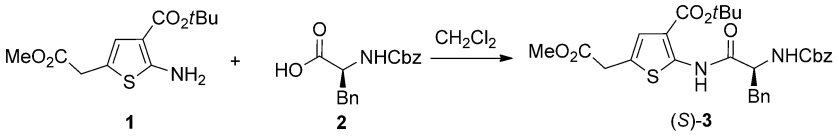


Figure 3. ^{1}H NMR (500 MHz, [D_6]DMSO) spectra of purified cyclic oligoamides *rac*-**7** [in red, (*S*,*S*)-enantiomer shown only)] and *meso*-**7** (in blue).

served with PyBOP as the coupling reagent. DIPEA appeared to induce less racemization, but gave lower yields than DMAP. When EDCI·HCl[21] was employed without a base, a high *ee* value (96%) was obtained with moderate yield (47%, Table 2, entry 7). This coupling reagent gave no racemization in the presence of HOBt,[22] but the observed yields decreased significantly to 8–10% (Table 2, entries 8 and 9). In all cases, the enantiomeric excesses were deter-



Scheme 3. Peptide coupling of **1** and **2** in order to prepare enantiopure amide (*S*)-**3**.

Table 2. Synthesis of monoamide (*S*)-**3** by coupling of **1** with **2** under different conditions.

Entry	Coupling reagent[a]	Base ([equiv])	Conditions	Yield [%]	*ee* [%]
1	PyBOP	DMAP (3)	RT, 1 d	90	46
2	PyBOP	DMAP (2)	RT, 1 d	60	22
3	PyBOP	DIPEA (2)	RT, 1 d	36	76
4	PyBOP	2,4,6-collidine (2)	RT, 1 d	6	97
5	TFFH	DIPEA (2)	0 °C, 30 min→RT, 8 h	47	97
6	TFFH	DMAP (2)	0 °C, 30 min→RT, 8 h	73	85
7	EDCI·HCl	–	0 °C, 30 min→RT, 8 h	47	96
8	EDCI·HCl/HOBt	–	0 °C, 30 min→RT, 8 h	8	>99
9	EDCI·HCl/HOBt	–	RT, 1 d	10	>99

[a] TFFH = *N*,*N*,*N*′,*N*′-tetramethylfluoroformamidinium hexafluorophosphate, HOBt = 1-hydroxybenzotriazole.

mined by HPLC using an enantiopure stationary phase (Chiralpak IA column).

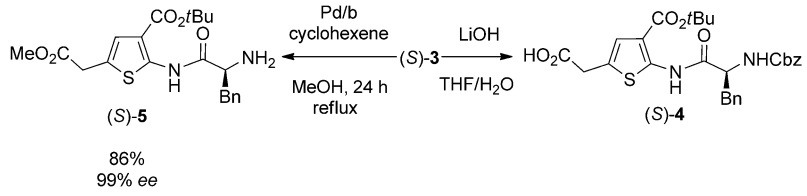
The above mentioned experimental data reveal that either the yield of (*S*)-**3** is good but there is considerable racemization, or else the enantiopurity is fair to excellent but the yields are low. In spite of this conundrum, moderate yields in the first step would be tolerable if the subsequent steps of our synthesis could be achieved without problems. Therefore, the TFFH/DIPEA- and EDCI·HCl-promoted amide couplings (Table 2, entries 5 and 7) might have been acceptable for further elongation and cyclization steps employing (*S*)-**3**. However, we encountered a severe setback in the next step, namely the deprotection of the carboxylic acid moiety of amide (*S*)-**3** (Scheme 4, Table 3). While deprotection of the amino group by removal of the Cbz group of (*S*)-**3** to furnish (*S*)-**5** could be smoothly achieved in high yield and without racemization by reduction with palladium in cyclohexene, saponification of the ester moiety of (*S*)-**3** proved more challenging. Due to the acidic protons in the α-position with respect to the amide moiety, the saponification occurred with remarkably facile racemization at the stereogenic center. By using 3 equivalents of LiOH, a yield of 88% was obtained, but only a moderate *ee* was observed (Table 3, entry 1). By decreasing the amount of base to 1.1 equivalents, a higher *ee* value was obtained with a slight loss of yield (84%, Table 3, entry 2). Lowering the temperature to 0 °C favored the *ee* (91%), but the yield decreased further to 75% (Table 3, entry 3). A good yield was achieved with H_2O_2 as an additive,[23] but again a higher degree of racemization was observed (Table 3, entry 4). When the reaction temperature was reduced to −78 °C and then slowly increased to 0 °C in the presence of 1.3 equivalents of LiOH, both the yield and *ee* decreased (Table 3, entry 5). All of these experiments indicated the significant effects of temperature and amount of base. Other reaction conditions reported in the literature were also examined, but they gave no satisfactory results. Saponifications mediated by PhSH/KF[24] and bis(tributyltin) oxide (BBTO)[25] gave poor yields and low *ee* values (Table 3, entries 6 and 9), and no reaction was observed when NaI and LiCl[26] were employed (Table 3, entries 7 and 8).

Table 3. Saponification of amide (*S*)-**3** to form carboxylic acid (*S*)-**4**.

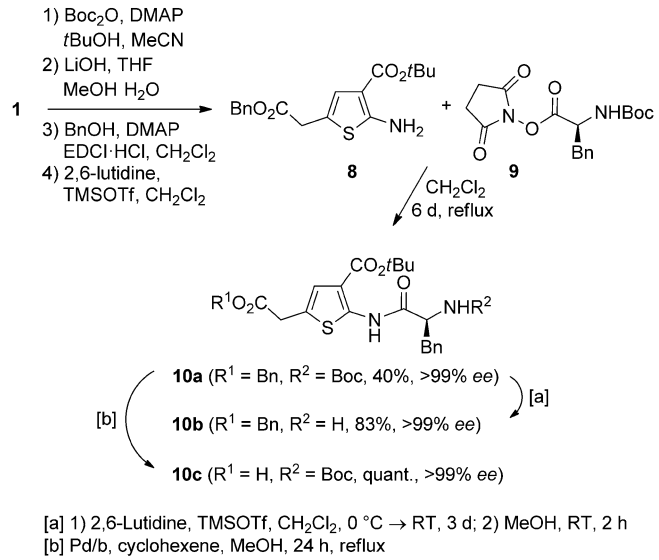
Entry	Conditions ([equiv])	Yield [%]	*ee* [%][a]
1	LiOH (3), RT, 1 h	88	74
2	LiOH (1.1), RT, 2.5 h	84	89
3	LiOH (1.1), 0 °C, 2.5 h	75	91
4	LiOH (3), H_2O_2 (9 eq), RT, 80 min	91	63
5	LiOH (1.3), −78→0 °C, 6 h	69	64
6	PhSH (1), KF (0.1), NMP, 4 h	30	58
7	NaI (2), DMSO, 80 °C, overnight	–	–
8	LiCl, DMF, microwave, 2 h	–	–
9	BBTO (2), toluene, 80 °C, overnight	54	83

[a] Determined by HPLC.

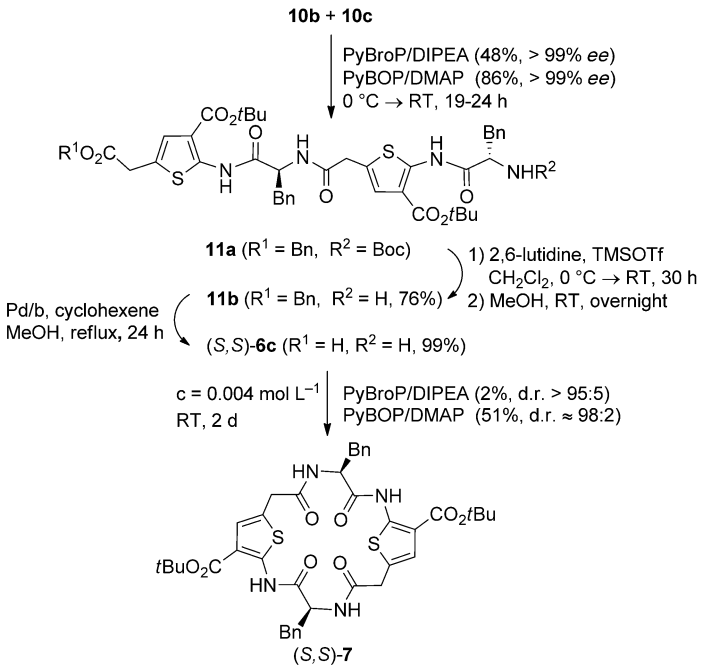
The results collected above indicate that a considerable degree of racemization in each of the steps will lower the *ee* of the final cyclic oligoamide **7**. Therefore, an alternative strategy for the synthesis of enantiomerically pure **7** was explored (Scheme 5). To avoid the racemization during liberation of the carboxylic acid, a benzyl group was chosen for protection of this moiety, whereas a *tert*-butoxycarbonyl (Boc) group was introduced at the amino unit as an orthogonal protecting unit, allowing for selective deprotections at later stages. The required 5-aminothiophene **8** was prepared by routine operations



Scheme 4. Selective deprotections of the amino and carboxylic acid groups of amide (*S*)-**3**.



Scheme 5. Synthesis of enantiopure monoamides **10a–c**



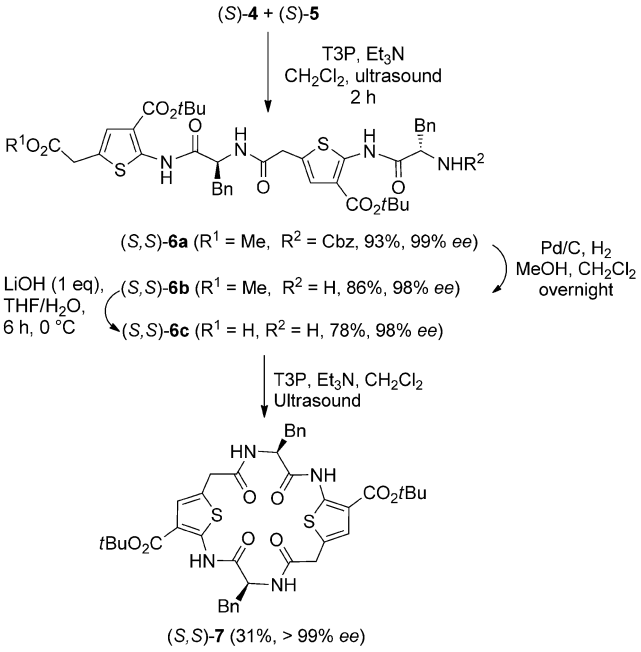
Scheme 6. Synthesis of enantiopure cyclic tetraamide (*S*,*S*)-**7**.

(see the Supporting Information). Boc-protection of 5-aminothiophene **1** was followed by saponification and subsequent esterification of the carboxylic acid moiety with benzyl alcohol. The amino group was finally deprotected affording aminothiophene **8** in reasonable quantities (Scheme 5). Although the yield of the coupling generating amide **10a** from thiophene derivative **8** and commercially available L-phenylalanine-derived active ester **9** was only moderate, racemization could essentially be avoided. The protective groups were easily and selectively removed by palladium-mediated hydrogenation with cyclohexene and treatment with trimethylsilyl triflate in the presence of 2,6-lutidine, respectively, to afford the deprotected products in high to quantitative yields, again without racemization.[27]

To couple the obtained monoamides **10b** and **10c**, the PyBroP/DIPEA and PyBOP/DMAP methods were tested (Scheme 6). The first approach provided an acceptable yield of 48%, whereas the yield of the second method was much higher (86%). Both procedures were essentially free of racemization (HPLC control). The obtained triamide **11a** was easily deprotected by the same procedures as described above, providing the precursor for the cyclization, (*S*,*S*)-**6c**, in high to near-quantitative yield. Under high-dilution conditions ($c = 0.004$ M), cyclic tetraamide (*S*,*S*)-**7** was obtained by the PyBroP/DIPEA method in only 2% yield and with a diastereomeric ratio (d.r.) of 95:5. Better results were achieved when the PyBOP/DMAP method was applied; the yield increased to a more impressive 51% and the d.r. was 98:2, demonstrating that essentially no racemization had occurred in any of the relevant steps.

In a recent publication, we reported a high-yielding synthesis of linear and cyclic oligoamides with a thiophene backbone under ultrasound activation, employing T3P (1-propanephosphonic acid cyclic anhydride) as a coupling reagent in the presence of triethylamine.[17] These findings prompted us to investigate the above described steps toward cyclic tetraamide (*S*,*S*)-**7** employing these reaction conditions.

First, the reaction of 5-aminothiophene **1** and L-phenylalanine derivative **2** was carried out under conventional stirring and the conversion was monitored by TLC (Scheme 3). With T3P and 1.3 equivalents of triethylamine, the reaction proceeded slowly at room temperature. After five days, 94% of the desired monoamide (*S*)-**3** had been obtained with an *ee* of 98%. We then reduced the amount of base to one equivalent and applied ultrasound activation to speed up the reaction. Slow addition of triethylamine to the reaction mixture ensured a low concentration of base and minimized the racemization process. After six hours, the conversion was complete and (*S*)-**3** was isolated in 92% yield. Much to our delight, no racemization was observed under these conditions. The two termini were deprotected as described above, with slight modification of the saponification (Scheme 4, Table 3). Since the extent of racemization decreases with lower amounts of base, we used only 1.0 equivalent of LiOH, performing the reaction at 0°C. LiOH solution was added dropwise to the solution of the ester to ensure a high excess of the precursor. This small, but important modification raised the *ee* value to 94% with an acceptable yield of 67%. The deprotected monoamides (*S*)-**4** and (*S*)-**5** were subjected to further peptide coupling (Scheme 7). After two hours of sonication in the presence of T3P and triethylamine, 93% of the desired product (*S*,*S*)-**6a** was isolated. HPLC showed a high *ee* of 99%. Applying the same deprotection procedures as previously, the cyclization pre-



Scheme 7. Ultrasound-mediated synthesis of enantiopure cyclic oligoamide (*S*,*S*)-**7** by starting from (*S*)-**4** and (*S*)-**5** with T3P as the coupling reagent.

cursor (*S*,*S*)-**6c** was obtained in reasonable yield and with high *ee*. Under high-dilution conditions, precursor (*S*,*S*)-**6c** provided cyclic tetraamide (*S*,*S*)-**7** in good yield and with high diastereomeric and enantiomeric purity.

The above described synthetic work shows three pathways toward the desired cyclic amides **7** with different stereogenic centers. In the first stage, a mixture of *rac*-**7** and *meso*-**7** was obtained in high yields by using BOP and PyBroP as coupling reagents. By changing the protecting groups of the termini of the precursors (from Me to Bn for the carboxylic acid group and from Cbz to Boc for the amine group), racemization during the synthetic sequence was avoided. The combination of T3P as a coupling agent under ultrasound activation and a lower amount of LiOH during the saponification also contributed to affording the desired cyclic tetraamide (*S*,*S*)-**7** in acceptable yield and with high *ee* value.

Solid-state structures: Slow diffusion of hexanes into solutions of the macrocycles *rac*-**7** and *meso*-**7** in dichloromethane afforded crystals suitable for X-ray analyses. From the crystal structure data, both diastereomers *rac*-**7** (*S*,*S*+*R*,*R*) and *meso*-**7** (*S*,*R*=*R*,*S*) could be unequivocally assigned. The racemic macrocycle crystallized in the centrosymmetric orthorhombic space group *Pbcn* with eight molecules in the unit cell. Figure 4a shows one of the four *RR* units with all of its substituents.

When all external substituents are removed, the side view of (*R*,*R*)-**7** with the stereogenic centers marked in violet gives a clearer picture (Figure 4c,d). One can recognize the C_2-symmetry of the 18-membered ring and the angle of 71.2° defined by the two thiophene planes. These features combined with the fixing of the sulfur in the same direction give the unit molecule a crown-like overall conformation (Figure 4c). The two enantiomeric molecules (*S*,*S* and *R*,*R*) are significantly offset against each other, creating a void between the two (Figure 4d).

The second diastereomer *meso*-**7** crystallized in the centrosymmetric monoclinic space group $P2_1/n$. Half of the molecule forms the asymmetric unit, which is complemented by the crystallographic center of symmetry to the complete molecule. The entire molecule with all of its substituents is depicted in Figure 4b, whereas the side view without exter-

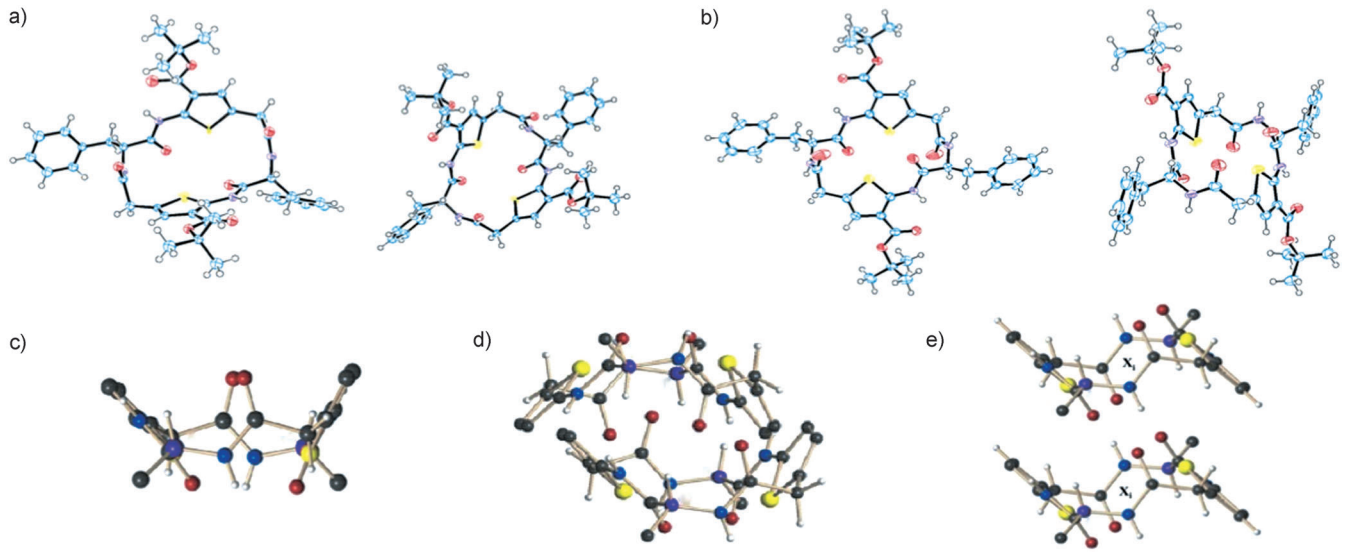


Figure 4. a) Crystal structure of (*R*,*R*)-**7** of the racemic mixture *rac*-**7** (ORTEP-3; ellipsoids drawn at the 50% probability level); b) crystal structure of *meso*-**7** (ORTEP-3; ellipsoids drawn at the 50% probability level); c) side view of (*R*,*R*)-**7** (being part of *rac*-**7**) without external substituents (XSHELL); d) intermolecular stacking of (*R*,*R*)-**7** and (*S*,*S*)-**7** (XSHELL); and e) side view of *meso*-**7** without external substituents with X_i as the inversion center (XSHELL).

nal substituents given in Figure 4e displays the 18-membered macrocycle with antiparallel bonds. The same can be said for the two thiophene planes, which are oriented in an antiparallel manner. The full molecule shows a double-boat conformation. This conformation leads to parallel intermolecular stacking of the macrocycles.

Not only do the individual molecules of *rac*-**7** and *meso*-**7** have different conformations, but this dissimilarity also affects their intermolecular packing within the unit cells. In the case of *rac*-**7** enantiomers, four (*R*,*R*)- and four (*S*,*S*)-macrocycles fill the unit cell. The two enantiomers are arranged in pairs, one above the other (Figure 5a).

The unit cell of *meso*-**7** shows the packing as rows of identically arranged cycles with a linear sequence of inversion centers in between rows with a different orientation of the ring (Figure 5b).

Unfortunately, no suitable crystals of enantiopure macrocycle (*S*,*S*)-**7** could be obtained. Different crystallization methods were applied, but none proved to be successful. The crystal packing of (*S*,*S*)-**7** most likely differs from that of the racemic compound.

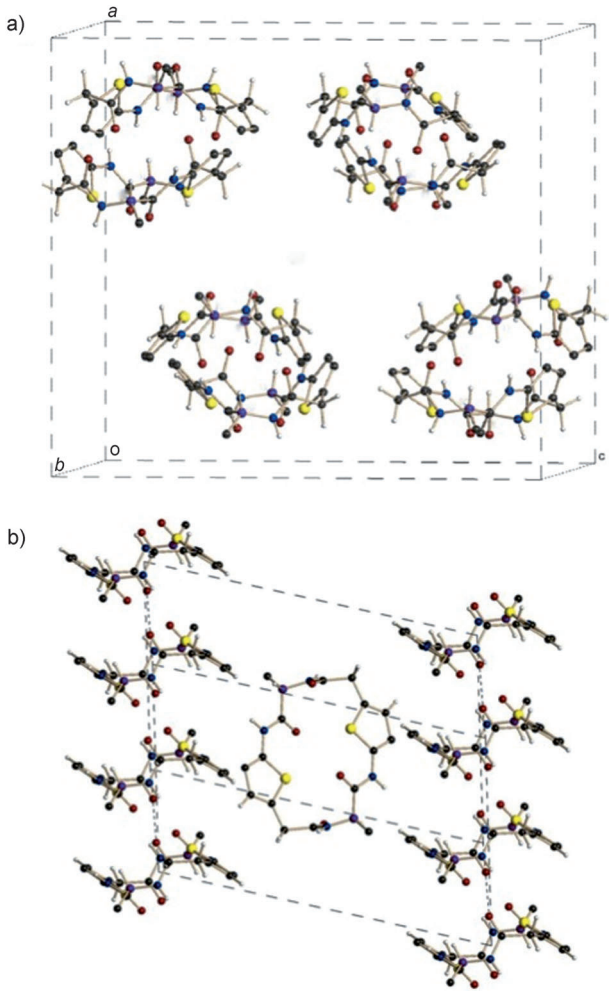


Figure 5. a) Molecular packing of *rac*-**7** in the unit cell (XSHELL, picture without external substituents); b) molecular packing of *meso*-**7** in the unit cell (XSHELL, picture without external substituents).

Conclusion

Our first synthetic approach to linear and cyclic peptides afforded the alternating peptides as mixtures of diastereomers due to extensive racemization of the L-amino acid derived units during the synthetic sequence. Different synthetic strategies were investigated and after analysis and optimization of each reaction step an improved synthetic sequence was established for which racemization at the stereogenic centers was essentially avoided. Encouraged by our earlier discovery, ultrasound-activated amide coupling of thiophene and L-phenylalanine with T3P as a coupling reagent was applied, which afforded the enantiopure tetraamide in high yield and with excellent enantiomeric excess.

The solid-state structures of two diastereomeric cyclic tetrapeptides (*SS*/*RR* and *meso*) were elucidated by X-ray crystallographic analysis. The solid-state conformations show a crown-like (*SS*/*RR*) or a double-boat (*meso*) shape. Depending on the stereogenic centers, the packing of the two diastereomers within the unit cells defines box-like subunits constructed from two enantiomers of *rac*-**7** or perfectly arranged rows of parallel-stacked *meso*-**7** macrocycles.

Experimental Section

General information: ^{1}H and ^{13}C NMR spectra were recorded on commercial 250, 400, 500, and 700 MHz instruments from samples in $CDCl_3$; chemical shifts (δ) are reported in parts per million (ppm) referenced to tetramethylsilane or the internal (NMR) solvent signals. Detailed NMR peak assignments were obtained by analysis of DEPT, HMQC, HMBC, and COSY NMR spectra. NMR signals indicating the presence of diastereomers are given by "/". NMR signals indicating the presence of rotamers are indicated by "*". High-resolution mass spectra were obtained on an ESI-TOF spectrometer. Silica gel (0.040–0.063 mm) was used for column chromatography. HPLC separations were carried out with 5 μm Nucleosil 50 as the stationary phase. Chiral HPLC analyses were performed on a Chiralpak IA column. Melting points are uncorrected.

X-ray crystallography: Single crystals for X-ray diffraction experiments were selected by using a microscope and mounted on the top of a glass fiber. Crystallographic data were collected on a diffractometer by using $Mo_{K\alpha}$ radiation ($\lambda = 0.71073$ Å, graphite monochromator) at low temperature. CCDC-942503 (*meso*-**7**) and 942504 (*rac*-**7**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. IR spectra were recorded on an FTIR spectrometer with a DTGS detector and a Nicolet Smart DuraSamp1IR ATR device. An ultrasound bath set at 35 kHz, 100% power, was used for syntheses.

Synthesis of cyclic tetraamides *meso*-7 and *rac*-7: BOP (0.059 g, 0.134 mmol) and DMAP (0.033 g, 0.267 mmol) were added to a solution of precursor **6c** (0.070 g, 0.089 mmol) in CH_2Cl_2 (23 mL). The reaction mixture was stirred for 3 d at room temperature, then diluted with CH_2Cl_2, and the organic phase was washed with 1 M HCl, saturated $NaHCO_3$, and saturated NaCl solutions, and dried with Na_2SO_4. The solvent was evaporated under reduced pressure. Chromatographic purification (silica gel; hexanes/EtOAc, 2:1) yielded **7** (42 mg, 61%, d.r. ≈ 4:6) as a mixture of *rac*-**7** (*R*,*R* and *S*,*S*) and *meso*-**7** as a colorless solid. The d.r. was determined by HPLC (5% isopropanol in hexanes, 2.0 mL min^{-1}). After preparative HPLC purification, *meso*-**7** (22 mg, 31%) and *rac*-**7** (16 mg, 24%) were isolated.

Data for the mixture of diastereomers: IR (ATR): $\tilde{\nu} = 3325$–3265 (N–H), 3085–2855 (=C–H, C–H), 1670 (C=O), 1560–1525 cm^{-1} (C=C); HRMS

(ESI-TOF): *m/z* calcd for $C_{40}H_{44}N_4O_8S_2$+Na^+: 795.2493 [*M*+Na]$^+$; found: 795.2493; *rac*-**7**: ^{1}H NMR (500 MHz, $CDCl_3$, CD_3OD): δ = 1.26 (s, 18H; *t*Bu), 2.81, 3.02 (2dd, *J* = 7.8, 14.2 Hz and 7.8, 14.2 Hz, 2H each; C*H*$_2$Ph), AB system (δ_A = 3.15, δ_B = 3.24, J_{AB} = 13.0 Hz, 4H; CH_2), 4.80 (t, *J* = 7.8 Hz, 2H; COCHN), 6.62 (s, 2H; H_{thioph}), 6.92–7.03 ppm (m, 10H; Ph); ^{13}C NMR (126 MHz, $CDCl_3$, CD_3OD): δ = 27.4 (q; *t*Bu), 34.7 (t; *C*H$_2$Ph), 37.2 (t; CH_2), 54.1 (d; CO*C*HN), 81.3 (s; *t*Bu), 114.9 (s; *C*CO$_2$-*t*Bu), 123.3 (d; CH_{thioph}), 126.4 (s; S*C*CH$_2$), 127.12, 128.1, 128.6, 136.1 (3d, s; Ph), 144.7 (s; SCN), 162.9 (s; *C*O$_2$*t*Bu), 167.0 (s; N*C*OCH), 171.3 ppm (s; NH*C*OCH$_2$); *meso*-**7**: ^{1}H NMR (500 MHz, $CDCl_3$, CD_3OD): δ = 1.32 (s, 18H; *t*Bu), 2.72, 2.84 (2dd, *J* = 7.8, 14.2 Hz for both, 2H each; C*H*$_2$Ph), AB system (δ_A = 3.108/3.110, δ_B = 3.45, J_{AB} = 13.8 Hz, 4H; CH_2), 4.70 (t, *J* = 7.8 Hz, 2H; COCHN), 6.71 (s, 2H; H_{thioph}), 6.92–7.03 ppm (m, 10H; Ph); ^{13}C NMR (126 MHz, $CDCl_3$, CD_3OD): δ = 27.5 (q; *t*Bu), 35.5 (t; *C*H$_2$Ph), 37.8 (t; CH_2), 55.2 (d, CO*C*HN), 81.5 (s; *t*Bu), 114.6 (s; *C*CO$_2$*t*Bu), 123.5 (d; CH_{thioph}), 126.5 (s; S*C*CH$_2$), 127.08, 128.08, 128.5, 135.7 (3d, s; Ph), 145.2 (s; SCN), 163.4 (s; CO$_2$*t*Bu), 167.5 (s; N*C*OCH), 172.0 ppm (s; NH*C*OCH$_2$).

Data for the individual diastereomers:

Compound rac-**7**: Melting range 76–81 °C; $[\alpha]_D^{22}$ = +4.7 (*c* = 0.11 in $CHCl_3$); ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 1.51 (s, 18H; *t*Bu), 2.99, 3.17 (2dd, *J* = 8.1, 13.8 Hz for both, 2H each; C*H*$_2$Ph), AB system (δ_A = 3.30, δ_B = 3.43, J_{AB} = 12.7 Hz, 4H; CH_2), 4.68–4.72 (m, 2H; COCHN), 6.75 (s, 2H; H_{thioph}), 7.20–7.23, 7.29–7.32, 7.36–7.38 (3m, 2H, 4H, 4H; Ph), 8.97 (d, *J* = 7.2 Hz, 2H; NH), 10.30 ppm (s, 2H; NH); ^{13}C NMR (101 MHz, [D$_6$]DMSO): δ = 27.9 (q; *t*Bu), 34.4 (t; *C*H$_2$Ph), 37.0 (t; CH_2), 54.3 (d; CO*C*HN), 81.2 (s; *t*Bu), 114.0 (s; *C*CO$_2$*t*Bu), 123.0 (d; CH_{thioph}), 126.5 (s; S*C*CH$_2$), 128.2, 128.3, 129.3, 137.6 (3d, s; Ph), 145.1 (s; SCN), 162.6 (s; *C*O$_2$*t*Bu), 167.8 (s; N*C*OCH), 170.4 ppm (s; NH*C*OCH$_2$).

Compound meso-**7**: M.p. 173–176 °C; $[\alpha]_D^{22}$ = +5.4 (*c* = 0.37 in $CHCl_3$/CH_3OH, 1:1); ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 1.56 (s, 18H; *t*Bu), 2.91, 3.06 (2dd, *J* = 9.3, 13.7 Hz and 6.2, 13.7 Hz, 2H each; C*H*$_2$Ph), AB system (δ_A = 3.17, δ_B = 3.65, J_{AB} = 13.2 Hz, 4H; CH_2), 4.62–4.66 (m, 2H; COCHN), 6.90 (s, 2H; H_{thioph}), 7.19–7.22, 7.27–7.30, 7.33–7.35 (3m, 2H, 4H, 4H; Ph), 8.58 (d, *J* = 8.4 Hz, 2H; NH), 10.50 ppm (s, 2H; NH); ^{13}C NMR (101 MHz, [D$_6$]DMSO): δ = 28.0 (q; *t*Bu), 34.9 (t; *C*H$_2$Ph), 37.8 (t; CH_2), 55.4 (d; CO*C*HN), 81.3 (s; *t*Bu), 113.8 (s; *C*CO$_2$*t*Bu), 123.2 (d; CH_{thioph}), 126.6 (s; S*C*CH$_2$), 127.9, 128.3, 129.3, 137.3 (3d, s; Ph), 145.5 (s; SCN), 163.1 (s; *C*O$_2$*t*Bu), 168.3 (s; N*C*OCH), 171.2 ppm (s; NH*C*OCH$_2$).

Synthesis of enantiomerically pure (*S*,*S*)-7: PyBOP (0.157 g, 0.302 mmol) and DMAP (0.062 g, 0.504 mmol) were added to a solution of triamide (*S*,*S*)-**6c** (0.199 g, 0.252 mmol) in CH_2Cl_2 (63 mL) at 0 °C. The mixture was stirred for 2 d at room temperature. It was then diluted with CH_2Cl_2, and the organic phase was washed with 1 M HCl, saturated $NaHCO_3$, and saturated NaCl solutions, and then dried with Na_2SO_4. The solvent was then evaporated under reduced pressure. Purification by column chromatography (silica gel; hexanes/EtOAc, 2:1→1:1) afforded (*S*,*S*)-**7** (0.094 g, 51%, d.r. ≈ 98:2) as a colorless solid. The ratio of diastereomers was determined by HPLC (5% isopropanol in hexanes, 1.5 mL min^{-1}). Traces of the *meso*-**7** diastereomer (4 mg, 2%) could be separated by an additional HPLC purification together with 0.087 g of the desired (*S*,*S*)-**7** (45%) with a d.r. > 99:1. M.p. 162–166 °C; $[\alpha]_D^{22}$ = +162.8 (*c* = 1.03 in $CHCl_3$); ^{1}H NMR (700 MHz, [D$_6$]DMSO): δ = 1.52 (s, 18H; *t*Bu), 2.30, 3.17 (2dd, *J* = 9.8, 13.7 Hz and 5.4, 13.7 Hz, 2H each; C*H*$_2$Ph), AB system (δ_A = 3.30, δ_B = 3.44, J_{AB} = 12.8 Hz, 4H; CH_2), 4.68–4.72 (m, 2H; COCHN), 6.75 (s, 2H; H_{thioph}), 7.20–7.23, 7.29–7.32, 7.36–7.37 (3m, 2H, 4H, 4H; Ph), 8.95 (d, *J* = 9.2 Hz, 2H; NH), 10.28 ppm (s, 2H; NH); ^{13}C NMR (126 MHz, [D$_6$]DMSO): δ = 27.8 (q; *t*Bu), 34.4 (t; *C*H$_2$Ph), 37.0 (t; CH_2), 54.2 (d; CO*C*HN), 81.1 (s; *t*Bu), 113.9 (s; *C*CO$_2$*t*Bu), 122.9 (d; CH_{thioph}), 126.4 (s; S*C*CH$_2$), 128.1, 128.2, 129.2, 137.5 (3d, s; Ph), 145.0 (s; SCN), 162.5 (s; *C*O$_2$*t*Bu), 167.7 (s; N*C*OCH), 170.3 ppm (s; N*C*OCH$_2$); IR (ATR): $\tilde{\nu}$ = 3280 (N–H), 3110–2930 (=C–H, C–H), 1670 (C=O), 1560–1525 cm^{-1} (C=C); HRMS (ESI-TOF): *m/z* calcd for $C_{40}H_{44}N_4O_8S_2$+Na^+: 795.2493 [*M*+Na]$^+$; found: 795.2509.

Synthesis of enantiopure oligoamides (*S*)-3, (*S*)-4, (*S*)-5, (*S*,*S*)-6a, (*S*,*S*)-6b, (*S*,*S*)-6c, and (*S*,*S*)-7 by employing the ultrasound and T3P-promoted protocol:

*Amide (*S*)-**3***: A solution of aminothiophene **1** (1.00 g, 3.69 mmol), L-phenylalanine derivative **2** (1.30 g, 4.34 mmol), and T3P (2.00 g, 6.46 mmol) in CH_2Cl_2 (25 mL) was ultrasonicated and Et_3N (0.359 g, 3.66 mmol) was slowly added. Following the addition, the mixture was further sonicated for 6 h. EtOAc was then added and the mixture was washed with water. The organic phase was dried with Na_2SO_4 and the solvent was removed under reduced pressure. Purification of the residue by column chromatography (silica gel; hexanes/EtOAc, 4:1) gave amide (*S*)-**3** (1.79 g, 92%, > 99% *ee*) as a colorless solid. The enantiomeric excess was determined by HPLC analysis (20% isopropanol in hexanes, 0.7 mL min^{-1}). M.p. 41–44 °C; $[\alpha]_D^{22}$ = −31.5 (*c* = 0.75 in $CHCl_3$); the NMR data were consistent with those of racemic **3**; HRMS (ESI): *m/z* calcd for $C_{29}H_{32}N_2O_7S$+Na^+: 575.1828 [*M*+Na]$^+$; found: 575.1852.

*Amide (*S*)-**4***: LiOH (36.4 mg, 1.52 mmol) was added in small portions to a solution of enantiopure (*S*)-**3** (0.840 g, 1.52 mmol) in THF (10 mL) and H_2O (4 mL) at 0 °C and the mixture was stirred for 6 h at 0 °C. It was then acidified to pH 2–3 with HCl (1 M) and extracted with EtOAc. The organic phase was washed with water until the washings were neutral and dried with Na_2SO_4. The solvent was removed under reduced pressure and the residue was purified by column chromatography (silica gel; CH_2Cl_2/MeOH, 9:1) to afford amide (*S*)-**4** (0.550 g, 67%, 94% *ee*) as a colorless solid. The enantiomeric excess was determined by HPLC analysis (30% isopropanol in hexanes, 0.7 mL min^{-1}). M.p. 68–71 °C; $[\alpha]_D^{22}$ = −35.4 (*c* = 0.98 in $CHCl_3$); the NMR data were consistent with those of racemic **4**; HRMS (ESI): *m/z* calcd for $C_{28}H_{30}N_2O_7S$+Na^+: 561.1666 [*M*+Na]$^+$; found: 561.1687.

*Amide (*S*)-**5***: Cyclohexene (3.5 mL) and Pd/b (98%, 0.200 g) were added to a solution of enantiopure (*S*)-**3** (0.940 g, 1.70 mmol) in MeOH (3.5 mL) and the mixture was heated at reflux for 24 h. After cooling, it was filtered through Celite and the solvent was removed under reduced pressure. Chromatographic purification of the residue (silica gel; CH_2Cl_2/EtOAc, 9:1) afforded (*S*)-**5** (0.614 g, 86%, 99% *ee*) as a yellow solid. The enantiomeric excess was determined by HPLC analysis (20% isopropanol in hexanes, 0.7 mL min^{-1}). $[\alpha]_D^{22}$ = −39.6 (*c* = 1.0 in $CHCl_3$); the NMR data were consistent with those of racemic **5**.

*Triamide (*S*,*S*)-**6a***: T3P (0.501 g, 1.62 mmol) was added to a solution of enantiopure (*S*)-**4** (0.500 g, 0.928 mmol) and enantiopure (*S*)-**5** (0.466 g, 1.11 mmol) in CH_2Cl_2 (25 mL). The solution was activated by ultrasound and Et_3N (0.094 g, 0.928 mmol) was added dropwise. The mixture was sonicated for 2 h. EtOAc was then added and the mixture was washed with water. The organic phase was dried with Na_2SO_4 and the solvent was removed under reduced pressure. Purification of the residue by column chromatography (silica gel; CH_2Cl_2/EtOAc, 9:1) gave enantiopure (*S*,*S*)-**6a** (0.808 g, 93%, 99% *ee*) as a colorless solid. The enantiomeric excess was determined by HPLC analysis (30% isopropanol in hexanes, 0.7 mL min^{-1}). M.p. 83–86 °C; $[\alpha]_D^{22}$ = −13.9 (*c* = 0.38 in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.53, 1.54 (2s, 9H each; *t*Bu), 3.07–3.11, 3.19–3.26 (2m, 1H, 3H; C*H*$_2$Ph), AB system (δ_A = 3.64, δ_B = 3.64/3.78, J_{AB} = 17.2 Hz, 2H; CH_2), 3.70 (s, 2H; CH_2), 3.72 (s, 3H; OMe), 4.73–4.77, 4.88–4.92 (m, 1H each; COCHN), AB system (δ_A = 5.10, δ_B = 5.14, J_{AB} = 12.3 Hz, 2H; C*H*$_2$Ph), 5.42–5.45, 6.19–6.22 (2m, 1H each; NH), 6.93, 6.96 (2s, 1H each; H_{thioph}), 6.98–7.00, 7.13–7.14, 7.18–7.22, 7.25–7.26, 7.28–7.34 (5m, 2H, 3H, 3H, 2H, 5H; Ph), 11.37, 11.39 ppm (brs, s, 2H; NH); ^{13}C NMR (126 MHz, $CDCl_3$): δ = 28.3, 28.4 (2q; *t*Bu), 35.0, 36.8 (2t; CH_2-thioph), 37.5, 38.3 (2t; *C*H$_2$Ph), 52.5 (q; OMe), 54.3, 56.4 (2d; CO*C*HNH), 67.5 (t; O*C*H$_2$Ph), 81.95, 82.0 (2s; *t*Bu), 114.9, 115.2 (2s; *C*-CO$_2$*t*Bu), 123.8, 124.8 (2d; CH_{thioph}), 125.0, 125.3 (2s; S*C*CH$_2$), 127.3, 127.4, 128.2, 128.3, 128.6, 128.9, 129.0, 129.2, 129.3, 135.3, 135.7, 136.1 (9d, 3s; Ph), 146.8, 147.0 (2s; SCNH), 156.0 (s; Cbz), 164.5, 164.8 (2s; *C*O$_2$*t*Bu), 167.8, 168.4, 169.5 (3s; CH*C*ONH), 170.7 ppm (s, *C*O$_2$Me); HRMS (ESI): *m/z* calcd for $C_{49}H_{54}N_4O_{11}S_2$+Na^+: 961.3123 [*M*+Na]$^+$; found: 961.3129.

*Triamide (*S*,*S*)-**6b***: Hydrogen gas was flushed through a suspension of 10% Pd/C (0.500 g) in MeOH (15 mL) for 15 min. A solution of carbamate (*S*,*S*)-**6a** (0.890 g, 0.948 mmol) in CH_2Cl_2 (5 mL) was then added and hydrogen gas was flushed through the mixture for 16 h (TLC control). The mixture was then filtered through Celite and the solvent was removed under reduced pressure. Chromatographic purification (silica

gel; CH_2Cl_2/EtOAc, 9:1) afforded (*S*,*S*)-**6b** (0.656 g, 86%, 98% *ee*) as a colorless solid. The enantiomeric excess was determined by HPLC analysis (20% isopropanol in hexanes, 0.7 mL min^{-1}). M.p. 81–84 °C; $[\alpha]_D^{22} = +7.2$ ($c = 1.05$ in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 1.55$, 1.57 (2s, 9H each; *t*Bu), 2.86/2.88, 3.36/3.39 (2dd, $J = 9.4$, 13.8 Hz and $J = 3.9$, 13.8 Hz, 1H each; CH_2Ph), 3.09/3.12, 3.23/3.26 (2dd, $J = 6.3$, 13.9 Hz for both, 1H each; CH_2Ph), AB system ($\delta_A = 3.67$, $\delta_B = 3.81$, $J_{AB} = 17.2$ Hz, 2H; CH_2), 3.71 (s, 2H; CH_2), 3.72 (s, 3H; OMe), 3.86–3.89 (m, 1H; COCHN), 4.89–4.93 (m, 1H; COCHN), 6.30 (d, $J = 7.8$ Hz, 1H; NH), 6.96, 6.99 (2s, 1H each; H_{thioph}), 7.00–7.02, 7.14–7.16, 7.23–7.27, 7.31–7.34 (4m, 2H, 3H, 3H, 2H; Ph), 11.40, 12.16 ppm (2s, 1H each; NH); ^{13}C NMR (126 MHz, $CDCl_3$): $\delta = 28.4$, 28.5 (2q; *t*Bu), 35.0, 36.9 (2t; CH_2-thioph), 37.5 (t; CH_2Ph), 40.8 (t; CH_2Ph), 52.5 (q; OMe), 54.3, 56.5 (2d; CO*C*HN), 81.7, 81.9 (2s; *t*Bu), 114.8, 115.3 (2s; *C*-CO_2*t*Bu), 123.7, 124.9 (2d; CH_{thioph}), 125.0, 125.1 (2s; S*C*CH_2), 127.1, 127.2, 128.8, 128.9, 129.2, 129.4, 135.5, 137.4 (6d, 2s; Ph), 146.8, 147.2 (2s, SCN), 164.1, 164.8 (2s, *C*O_2*t*Bu), 167.8, 169.7, 170.7 (3s; CH*C*ONH), 172.3 ppm (s; CO_2Me); HRMS (ESI): *m*/*z* calcd for $C_{41}H_{48}N_4O_9S_2+H^+$: 805.2940 $[M+H]^+$; found: 805.2941.

Triamide (S,S)-***6c***: LiOH (0.013 g, 0.542 mmol) was added in small portions to a solution of triamide (*S*,*S*)-**6b** (0.426 g, 0.545 mmol) in THF (10 mL) and H_2O (4 mL) at 0 °C and the mixture was stirred at this temperature for 6 h. It was then acidified to pH 2–3 with HCl (1 M) and extracted with EtOAc. The organic phase was washed with water until the washings were neutral and dried with Na_2SO_4. The solvent was removed under reduced pressure and purification of the residue by column chromatography (silica gel; CH_2Cl_2/MeOH, 9:1) afforded (*S*,*S*)-**6c** (0.335 g, 78%, 98% *ee*) as a colorless solid. The enantiomeric excess was determined by chiral HPLC analysis (30% isopropanol in hexanes, 0.7 mL min^{-1}). The spectroscopic and physical properties were in agreement with those recorded above.

(S,S)-***7***: Et_3N (16.6 mg, 0.928 mmol) was added dropwise to a solution of enantiopure (*S*,*S*)-**6c** (0.130 g, 0.164 mmol) and T3P (0.200 g, 0.656 mmol) in CH_2Cl_2 (50 mL) activated by ultrasound. The mixture was sonicated for 6 h. EtOAc was then added and the mixture was washed with water. The organic phase was dried with Na_2SO_4 and the solvent was removed under reduced pressure. Purification by column chromatography (silica gel; CH_2Cl_2/EtOAc, 9:1) afforded enantiopure (*S*,*S*)-**7** (0.040 g, 31%, >99% *ee*) as a colorless solid. The enantiomeric excess was determined by HPLC analysis (30% isopropanol in hexanes, 0.7 mL min^{-1}). The spectroscopic data were in agreement with those recorded above. M.p. 160–164 °C; $[\alpha]_D^{22} = +159.8$ ($c = 0.95$ in $CHCl_3$).

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