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New Macrocyclic Peptidomimetics Containing 5-Aminothiophene Subunits

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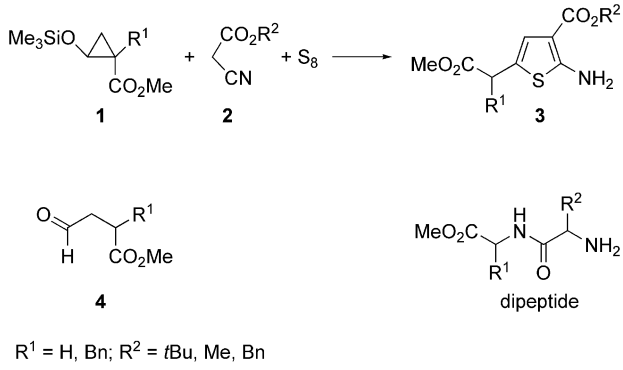
The synthesis of a new class of cyclic peptidomimetics containing 5-aminothiophene subunits in their backbone is presented. A modified Gewald reaction was applied as a key step in the synthesis of the thiophene amino acid that was used as a building block in the synthesis of linear oligomers by using standard peptide coupling protocols. Macrocyclization was achieved under high dilution by using EDCI as a coupling reagent. The conformations of an acyclic dimer and a cyclic tetramer were determined by X-ray crystallographic analyses.

Introduction

Many cyclopeptides incorporating five-membered heterocycles have been isolated from marine and other sources.[1] As a prominent example, the *Lissoclinum* class of cyclic peptides is characterized by the presence of unusual oxazole and thiazole amino acids or their reduced analogues in the macrocyclic skeleton. The structural variety of these backbone-modified cyclopeptides and their biological activities resulted in a considerable number of structural and synthetic studies.[2] These examples can be regarded as natural peptidomimetics[3] where unusual amino acids or their analogues together with the induced conformational restrictions confer new properties. This concept has also been applied to unnatural cyclic mimetics in the hope to generate molecules with new and superior (biological) activity.[4]

Our group reported simple access to new 5-aminothiophene carboxylic acids **3**, which are regarded as dipeptide isosteres (Scheme 1).[5] A three-component Gewald reaction by employing methyl 2-siloxycyclopropanecarboxylates **1**[6] smoothly afforded unusual δ-amino acids[7] **3**. Cyclopropanes **1** serve here as equivalents of carbonyl compounds **4**. Smooth in situ ring opening of **1** in methanol or in the presence of fluoride reagents generates carbonyl compounds **4** that undergo multistep condensation with **2** and sulfur.

At the beginning of this study we assumed that new macrocycles incorporating aminothiophene carboxylic acids such as **3** should have interesting chemical, structural, and biological properties. These cyclic peptidomimetics can be constructed from **3** together with proteinogenic amino acids, but alternative compounds should be available by using aminothiophene carboxylic acids as only components. The functionalized thiophene moiety should allow a variety of modifications that are of interest for the function of the resulting macrocyclic peptidomimetics. Herein, we report the synthesis of 36-membered and 24-membered cyclic peptidomimetics **13** and **14** by using 5-aminothiophene carboxylic acid **3a** as a key building block. To the best of our knowledge, no cyclopeptides containing dipeptidyl thiophenes in the backbone have been synthesized so far.



Scheme 1. Synthesis of 5-aminothiophene carboxylic acids **3** by a modified Gewald reaction by employing siloxycyclopropane **1**.

Results and Discussion

The synthesis of aminothiophene **3a** was achieved according to a literature procedure in 66% yield.[5] Compound **3a** was used both directly as the amino component and, following protective group modification to give **5**, as the carboxylic acid in the peptide coupling to furnish dimer **6** (Scheme 2). Protection of **3a** with Cbz and saponification of the resulting carbamate with lithium hydroxide gave carboxylic acid **5** in very good yield. We examined different protecting groups at the N-terminus of **3a**, but only Cbz[8] proved to be compatible with the conditions of the follow-

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[‡] Responsible for X-ray crystal structure determination.
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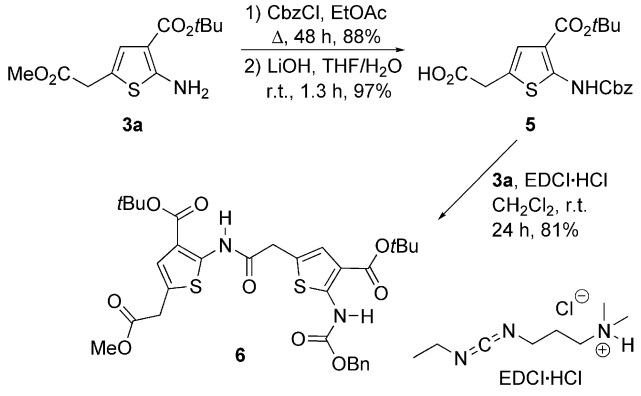
ing steps.[9] The conditions for the amide formation were carefully optimized. We found that activation of carboxylic acid **5** with 1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide (EDCI)[10] in CH_2Cl_2 was superior, affording desired dimer **6** in 81% yield.



Scheme 2. Synthesis of Cbz-protected thiophene carboxylic acid **5** and peptide coupling with 5-aminothiophene **3a**.

The solid-state structure of **6** was investigated by X-ray crystallography (Figure 1), which revealed that the conformation is dominated by two intramolecular hydrogen bonds of the amide protons to the oxygen atoms of the *tert*-butoxycarbonyl group.[11] The two thiophene rings together with the amide bonds are planar and oriented perpendicularly to the plane defined by carbon atoms C6–C5–C4 with the two thiophene sulfur atoms pointing in the same direction.

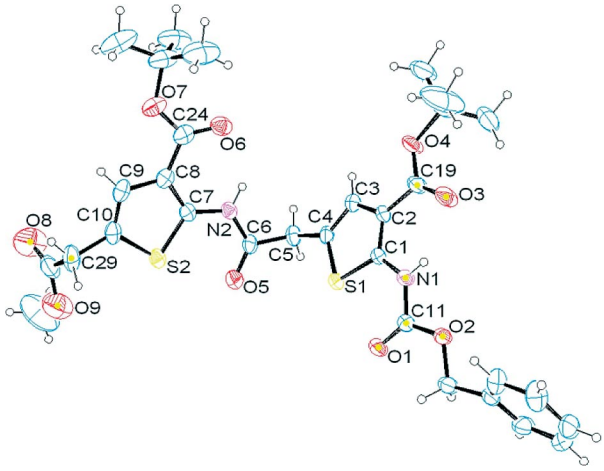
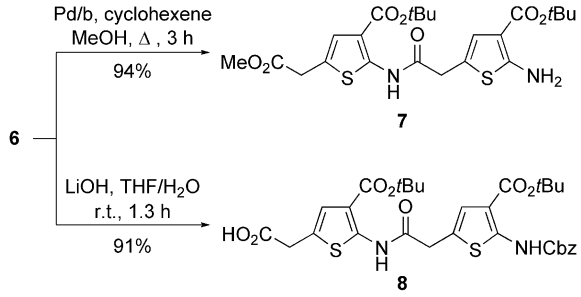


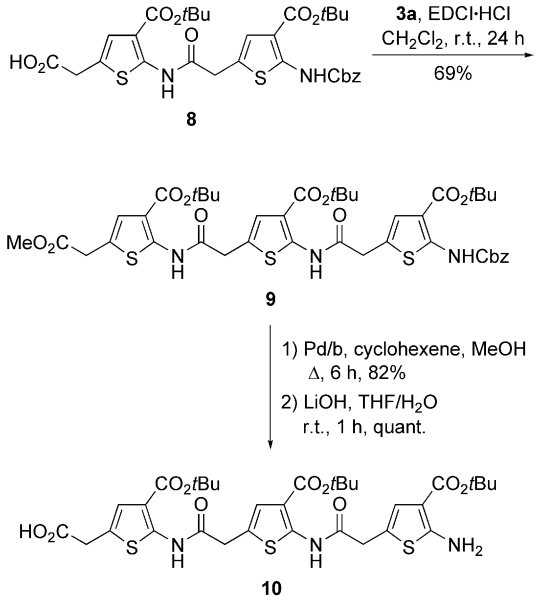
Figure 1. Molecular structure (ORTEP[12]) of dimer **6**.

After cleavage of the terminal *N*-Cbz group of dimer **6** under catalytic transfer hydrogenolysis[13] with palladium black (Pd/b),[14] amine **7** was isolated in excellent yield, and the hydrolysis of methyl ester **6** with lithium hydroxide provided carboxylic acid **8** in 91% yield (Scheme 3).



Scheme 3. Synthesis of *C*-protected dimer **7** and *N*-Cbz-protected dimer **8**.

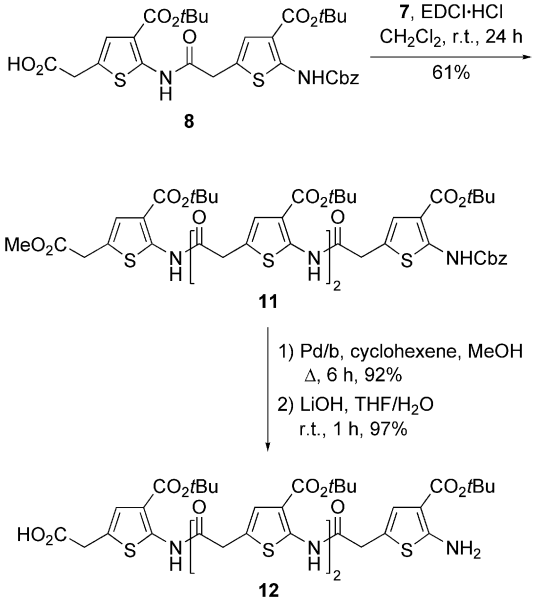
Carboxylic acid **8** was successfully coupled to monomer amine **3a** by using carbodiimide methodology to furnish trimer **9** in 69% yield (Scheme 4). Removal of the *N*-Cbz group of **9** was followed by treatment with LiOH in a mixture of tetrahydrofuran/water to give the fully deprotected trimer **10**, which was used without further purification in the subsequent attempted macrocyclization.



Scheme 4. Synthesis of *C*- and *N*-deprotected trimer **10**.

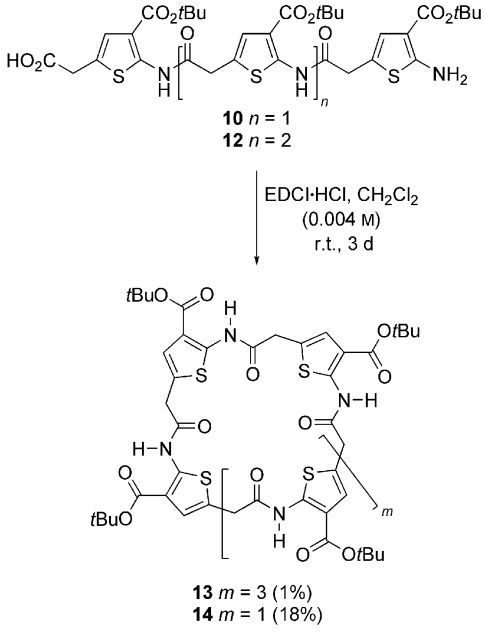
The EDCI-mediated coupling of carboxylic acid **8** with amine **7** furnished tetramer **11** in good yield (Scheme 5). Cleavage of the terminal *N*-Cbz group and subsequent saponification utilizing the conditions described for the conversion of **9** into **10** also provided cyclization precursor **12** in good overall yield.

We examined several condensation reagents for the macrocyclization of acyclic precursor compounds **10** and **12**. EDCI proved to be the most advantageous peptide coupling reagent in these examples. These macrocyclization experiments were performed under high-dilution conditions (0.004 M) at room temperature for 3 d (Scheme 6). Acyclic tetramer precursor **12** was successfully converted into the desired 24-membered cyclic peptide **14** in 18% yield. In contrast, no cyclization of trimer **10** to the corresponding



Scheme 5. Synthesis of acyclic tetrameric precursor **12**.

18-membered cyclic peptide was observed. Surprisingly, 1% of the unexpected 36-membered cyclohexapeptide **13** was isolated. Despite the high-dilution conditions, dimerization followed by cyclization was the pathway leading to the only low molecular mass product. The missing material apparently was consumed by the formation of higher (acyclic) oligomers.[15]



Scheme 6. Synthesis of 36-membered and 24-membered cyclic peptidomimetics **13** and **14**.

^{1}H and ^{13}C NMR spectra of cyclic peptides **13** and **14** in $CDCl_3$ are very similar at room temperature. The spectra indicate the presence of symmetric compounds, showing just four signals for the four different types of protons attached to each subunit. The definite number of subunits in macrocycles **13** and **14** was confirmed by mass spectrometry.

X-ray quality crystals of **14** were obtained by slow diffusion of hexane into a dichloromethane solution of the cyclic peptide, which allowed detailed analysis of the solid-state structure (Figure 2). Remarkably, the macrocycle includes one molecule of hexane. Apparently, the cavity of the cyclotetramer has a diameter of ca. 8 Å and hence is sufficiently wide to extract a hexane molecule from the solvent mixture. Half of molecule **14** (strongly resembling dimer **6**, see Figure 1) and half of a hexane molecule form the asymmetric unit. The molecule is completed by a crystallographic inversion center resulting in an up/up/down/down arrangement of the four sulfur atoms. The structure shows that **14** is a fairly rigid molecule with a diamond core close to a square (angles of 84.9 and 95.1°), in which the sp^3-hybridized carbon atoms C5–C11–$C5_i$–$C11_i$ form the corners. The thiophene rings are oriented almost perpendicular to the plane defined by these four carbon atoms. Intramolecular hydrogen bonds exist again between the amide protons and the oxygen atoms of the *tert*-butoxycarbonyl groups. This is consistent with the values determined by ^{1}H NMR spectroscopy, where the signals of the amide protons are shifted downfield.

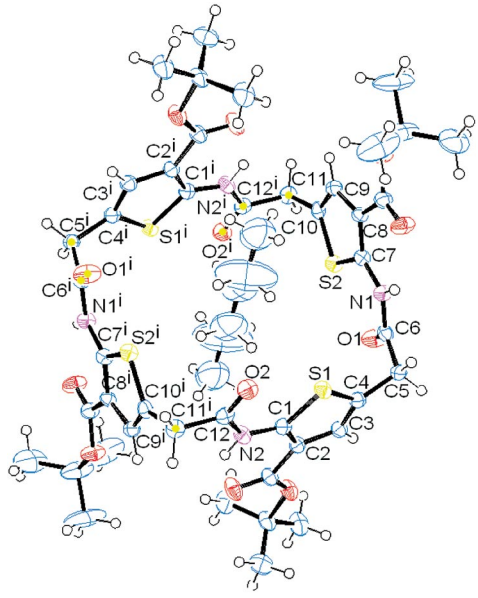


Figure 2. Molecular structure (ORTEP[12]) of macrocyclic peptidomimetic **14** including one molecule of hexane.

Conclusions

In conclusion, we have demonstrated the synthesis of new 36-membered and 24-membered macrocyclic peptidomimetics **13** and **14** based on new thiophene amino acid **5**. These compounds are the first macrocycles incorporating aminothiophene subunits. Studies of the properties of these peptidomimetics and preparation of chiral macrocycles also incorporating proteinogenic amino acids are currently been performed.

CCDC-780179 (for **6**) and -780180 (for **14**) 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.

Supporting Information (see footnote on the first page of this article): Detailed description of all experimental procedures and analytical data for all compounds.

Acknowledgments

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[15] A similar cyclodimerization was observed for **12** under modified reaction conditions (TFFH, 2,4,6-collidine). Together with 3% of **14**, 3% of the cyclic compound with eight thiophene subunits was obtained.

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