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Quaterpyrroles as Building Blocks for the Synthesis of Expanded Porphyrins

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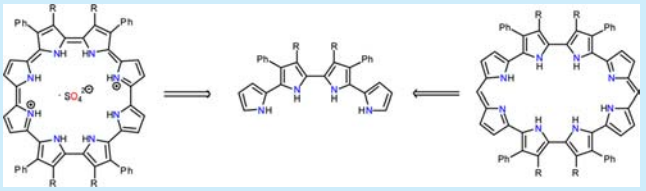
Supporting Information

ABSTRACT: A new family of quaterpyrroles and their application as building blocks for the synthesis of macrocycles is reported. The preparation of these quaterpyrroles consisted of two synthetic steps: bromination of 2,2′-bipyrroles bearing two electron-withdrawing groups followed by Suzuki coupling with 1-(*tert*-butoxycarbonyl)pyrrole-2-boronic acid. The resulting quaterpyrroles have been used to prepare an octaphyrin and a substituted cyclo[8]pyrrole. Additionally, the synthesis of a new macrocycle containing the quaterpyrrole and 2,5-di(1*H*-pyrrol-2-yl)thiophene moieties is presented.



Since the discovery of sapphyrins,[1] expanded porphyrins[2] have attracted the interest of researchers. Their unique physical and structural features have found application in fields that range from the study of aromaticity[3] to biomedicine.[4]

From a synthetic point of view, the access to new expanded porphyrins is predicated on the availability of the starting materials, pyrroles[5] or the corresponding oligopyrrole,[6] and a proper method for their condensation or coupling.[2] Usually, the limiting factor in the synthesis is the preparation of the prerequisite oligopyrrole which depends greatly on its structure. Thus, while di-, tri-, and quaterpyrranes are readily synthesized from pyrrole and the corresponding aldehyde,[7] α,α-linked oligopyrroles generally require long and difficult synthetic pathways.[8]

Fortunately, in recent years many groups have disclosed efficient and versatile methodologies to prepare the simplest α,α-linked oligopyrroles, 2,2′-bipyrroles,[9] and terpyrroles,[8] in reasonable yields. As a consequence, the chemistry of these oligomers has been studied in detail allowing the preparation of derivatives useful as starting materials to synthesize macrocycles such as porphycene[10] or amethyrin.[8] However, methods to obtain higher homologues, such as quaterpyrroles, properly functionalized to produce macrocycles are still lacking.

The first synthesis of a susbstituted quaterpyrrole was reported in 1993 by Sessler and co-workers.[11] Quaterpyrrole **1** was prepared by Ullman coupling from the corresponding monoiodobipyrrole in a four-step synthesis (Figure 1). The oligopyrrole **1** is substituted with methyl groups and esters in order to provide solubility and chemical stability. However, the removal of the esters led to the formation of a very unstable compound which decomposes easily precluding further manipulations. In 2005 the same group proposed a new general strategy to prepare β-substituted pyrrole oligomers.[12]

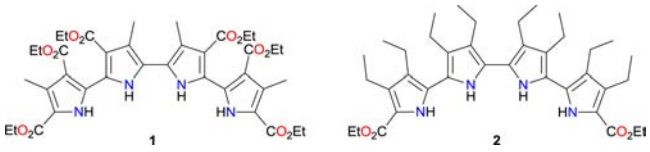


Figure 1. Quaterpyrroles synthesized by the Sessler group.

According to this synthetic scheme, quaterpyrrole **2** can be prepared very efficiently by oxidative homocoupling of the corresponding mono α-free 2,2′-bipyrrole. Quaterpyrrole **2** is isolated in its oxidized form but can be reduced with $NaBH_4$. In principle, the reduced species **2**, although quite unstable, is amenable to be functionalized. However, to the best of our knowledge there are no reports on such derivatives or the use of a quaterpyrrole for the preparation of macrocycles.

Bearing in mind the prerequisites of the ideal oligopyrrolic precursor, solubility, and stability, our group has proposed the use of 2,2′-bipyrroles **3** as starting material to prepare quaterpyrroles.[13] These precursors can be readily prepared in a one-pot procedure from a cinnamate or an enone. Unlike their alkyl or aryl substituted counterparts, α,α,-free bipyrroles **3** possess a remarkable chemical stability ascribed to the presence of two electron-withdrawing groups. On the other hand, the absence of substitution at α positions allows its direct functionalization. Another important feature of bipyrroles **3** is the possibility to be easily derivatized thanks to the presence of the β substituents.[14]

According to the symmetry of bipyrrole **3**, the synthesis of quaterpyrrole **6** implies the coupling of two pyrrole units with

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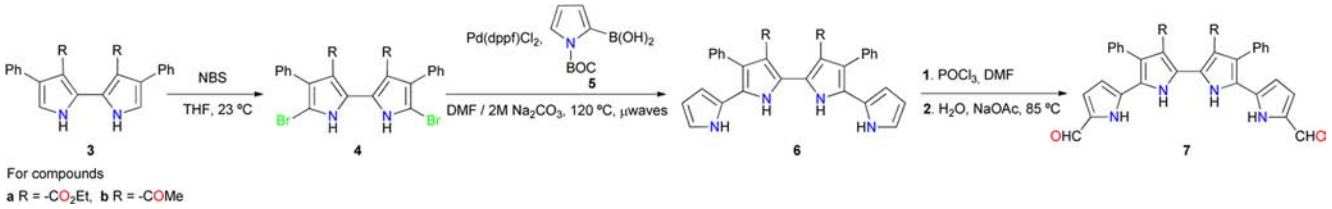
Scheme 1. Synthesis of Quaterpyrroles 6 and Formylation



bipyrrole **3** (Scheme 1). This strategy could be implemented by using a Pd-catalyzed cross-coupling such as Suzuki or Stille reactions. The ideal candidate to furnish the pyrrole fragment should be a commercially available product such as the *N*-BOC pyrrole boronic acid **5** (BOC, *tert*-butoxycarbonyl). Hence, the synthetic problem is reduced to the preparation of a dihalogenated bipyrrole. The halogenation of pyrroles is usually carried out by treatment with a *N*-halosuccinimide, typically *N*-bromosuccinimide (NBS).[15] Thus, the exposure of bipyrroles **3** to 2 equiv of NBS in tetrahydrofuran (THF) as solvent provides dibrominated bipyrrole **4a** in 87% yield and **4b** in 93% yield. Dibrominated bipyrroles **4** can be isolated without the need for chromatography as yellow solids which can be stored at room temperature without apparent decomposition. The following step is the Suzuki coupling of bipyrroles **4** with pyrrole **5** under microwave irradiation (120 °C) in the presence of [1,1′-bis(diphenylphospino)ferrocene]dichloropalladium(II) ($Pd(dppf)Cl_2$), a degassed 2 M aqueous solution of Na_2CO_3, and *N*,*N*′-dimethylformamide (DMF) as solvent. After 1.5 h, the reaction crude was purified by silica gel column chromatography to yield BOC deprotected quaterpyrroles **6a** and **6b** in 72% and 44% yield, respectively. The deprotection of the BOC groups *in situ* can be ascribed to the relatively high temperature that is required to perform the coupling.[16] Quaterpyrroles **6** are obtained as yellow-orange crystalline solids that are relatively stable at room temperature which can be stored indefinitely in the fridge. The coupling is quite robust allowing the preparation of quaterpyrroles **6** up to 400 mg per batch.

Unambiguous proof for the synthesis of quaterpyrroles **6** was provided by X-ray diffraction analyses of the diethyl ester **6a** (cf. Figure 2) and the dimethylketone **6b** (cf. Supporting Information (SI)). The solid-state structures of quaterpyrroles **6a** and **6b** are characterized by the high planarity of the heterocyclic units.

With quaterpyrroles **6** in hand, the next step is proving their usefulness in the synthesis of macrocycles. The first proposed target is octaphyrin **8**. An analogous macrocycle was previously synthesized by intramolecular oxidative closure of the corresponding oligopyrrole.[17] To this end, dialdehyde **7a** was synthesized by the Vilsmeier−Haack reaction from quaterpyrrole **6a** in 96% yield. Finally, the condensation between **7a** and **6a** was carried out in chloroform in the presence of HCl as the catalyst (Scheme 2). To our delight octaphyrin **8** was obtained in 33% yield. Additional structural evidence for octaphyrin **8** was provided by X-ray diffraction (cf. Figure 3).

Encouraged by the preparation of octaphyrin **8**, a novel macrocycle **10** containing a thiophene ring in its structure was envisioned. These mixed pyrrole−thiophene macrocycles have attracted interest because of their unique physical properties.[18] The precursors for the formation of macrocycle **10** are quaterpyrrole **6a** and dialdehyde **9**. The latter can be easily prepared in a two-step procedure from commercially available

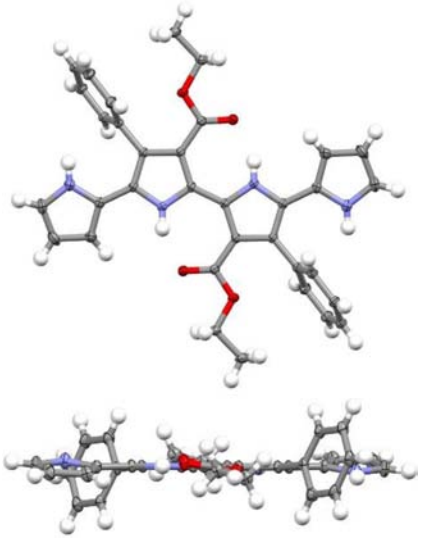
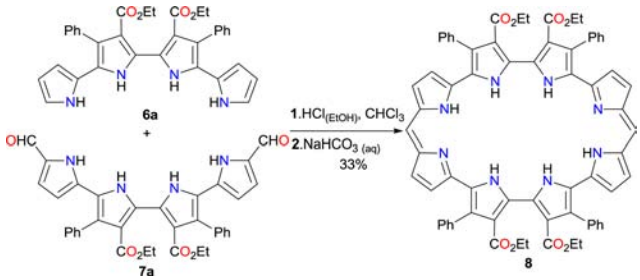


Figure 2. Crystal structure of quaterpyrrole **6a**. Displacement ellipsoids are scaled to the 40% probability level.

Scheme 2. Synthesis of Octaphyrin 8



reagents which consists of the Suzuki coupling of *N*-Boc-pyrrole-2-boronic acid MIDA ester and 2,5-dibromo-3,4-dihexylthiophene and formylation of the resulting intermediate. The synthesis of **10** is an acid catalyzed condensation of the precursors **6a** and **9**. The thiophene-containing macrocycle **10** can be isolated in 71% yield as a dark microcrystalline solid (Scheme 3).

^{1}H NMR spectroscopic studies of **10** and its HCl and H_2SO_4 salts have been carried out. The relevant signals in the ^{1}H NMR spectrum of **10** are four doublets in the 5.6−6.6 ppm region, attributable to the pyrrolic protons, a singlet at 6.3 ppm corresponding to the proton at the *meso* position, and a broad deuterable signal at 4.1 ppm.[19a] Upon the addition of HCl, a dramatic upfield shift of the pyrrolic signals of about 1 ppm takes place and three signals, corresponding to the N*H* protons, emerge at 20.6, 19.6, and 19.12 ppm in an integral ratio of 1:1:1. The observation of inner N*H* signals at low field is considered diagnostic of an antiaromatic system[3c,19b] (cf. SI).

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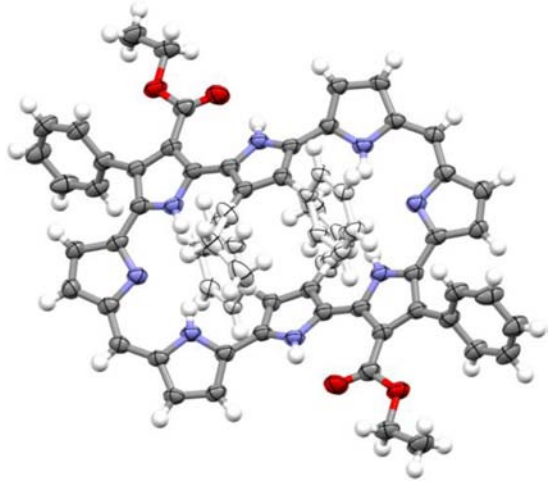
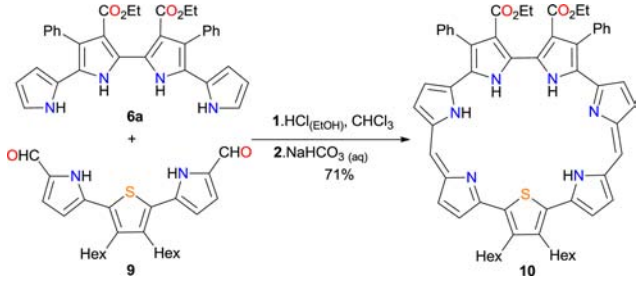


Figure 3. Crystal structure of octaphyrin **8**. Inner phenyl and ester groups have been colored in white for clarity. Displacement ellipsoids are scaled to the 40% probability level.

Scheme 3. Synthesis of 10 (one tautomer is shown)

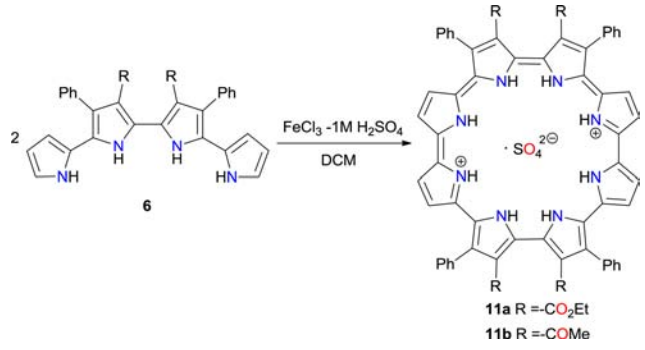


To gain further insight into the structure of macrocycle **10**, DFT calculations have been carried out. The geometry optimization of the free base **10** displays a quite distorted structure. However, as expected, complexation of **10** with H_2SO_4 enhances the molecular planarity of the ligand (cf. SI).

Another family of macrocycles suitable to be prepared from quaterpyrroles are cyclo[8]pyrroles.[20] These macrocycles show application as SO_4^{2-} anion extractants,[21] G-quadruplex binders,[22] and liquid crystals.[23] Typically, cyclo[8]pyrroles are easily synthesized by oxidative coupling of the corresponding substituted 2,2′-bipyrroles. However, the high symmetry of these cyclo[8]pyrroles hampers their regioselective functionalization, precluding the preparation of complex systems such as polymers[24] or ditopic[25] receptors. In principle, this limitation could be overcome by using quaterpyrroles **6** given their substitution pattern. Bearing this in mind, the synthesis of **11** was proposed. Thus, the slow addition of quaterpyrroles **6** to a biphasic mixture of dichloromethane (DCM) and $FeCl_3$/1 M H_2SO_4 provides macrocycles **11a** and **11b** in 38% and 83% yield respectively (Scheme 4). The crystal structure of cyclo[8]pyrrole **11a** clearly shows the presence of two sets of ester groups at opposite sides of the macrocycle (Figure 4).

To conclude, the preparation of a new family of quaterpyrroles **6** in two steps from 2,2′-bipyrroles **3** has been presented. These oligopyrroles are characterized by excellent chemical stability and high solubility in organic solvents. These features make quaterpyrroles **6** ideal building blocks for the preparation of macrocycles by McDonald type condensations and oxidative ring closures. The presence of β substituents on the central bipyrrole unit of **6** gives access to functionalized

Scheme 4. Synthesis of Cyclo[8]pyrroles 11



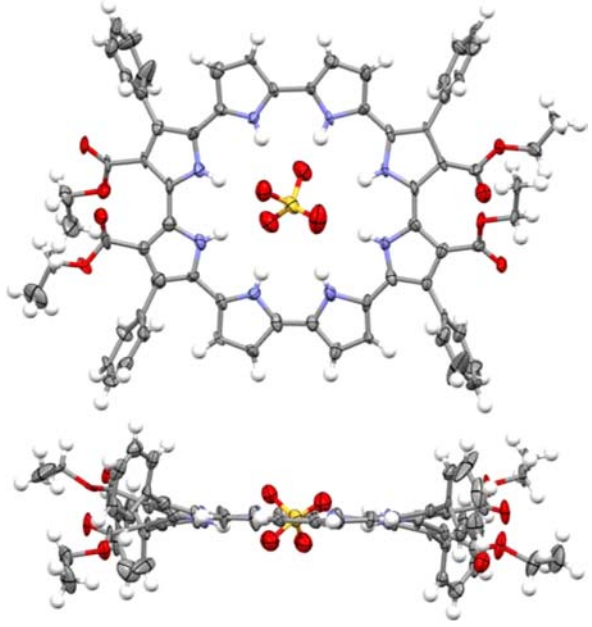


Figure 4. Crystal structure of cyclo[8]pyrrole **11a**. Displacement ellipsoids are scaled to the 40% probability level. Although omitted for clarity, the molecule crystallized with a molecule of DCM.

macrocycles, enabling the development of complex systems. Currently, the preparation of such new systems is being explored.

■ ASSOCIATED CONTENT

Supporting Information

Detailed synthetic procedures and spectroscopic characterization of compounds. X-ray crystallographic files (CIF) for compounds **6a**, **6b**, **8** and **11a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(19) (a) Selected NICS(0) values for **10**·H_2SO_4, obtained with the GIAO method, can be found in the SI. The results are in good agreement with the experimental values. (b) Accordingly, the signals corresponding to the peripheral protons of **10**, and its salts are shifted upfield as compared to the linear precursor **9** (cf. SI).

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