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A Facile Synthesis of Cyclononatripyrroles

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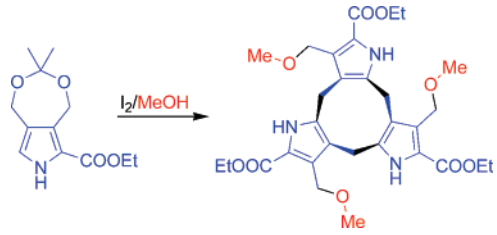
ABSTRACT



A facile synthesis of a functionalized cyclononatripyrrole derivative is described. It involves the iodine-catalyzed cyclotrimerization of ethyl 3,3-dimethyl-5,7-dihydro[1,3]dioxepino[5,6-*c*]pyrrole-6-carboxylate in methanol. The product obtained in this way exists solely in the crown conformation typical of cyclononatripyrroles. However, in contrast to previously reported compounds of this class, it possesses three labile methoxymethyl arms that can be further functionalized under acidic conditions.

Bowl-shaped molecules are ubiquitous in supramolecular chemistry because of their ability to act as receptors and provide high levels of supramolecular organization.[1] Many of the systems studied to date, including inter alia calixarenes[2] and calixpyrroles,[3] contain 1,3-connected aromatic subunits, thus providing inner receptor/functionalization sites. On the other hand, cyclotriveratrylenes (CTVs, **1**),[4] which are constructed from 1,2-connected arene subunits, contain no inner functionalities but retain a bowl-like shape. CTVs are easily synthesized and have been used as receptors of spherical guests, such as fullerenes and carboranes,[5−7] and as the central core motifs for discotic liquid crystals.[8−11] Despite the continued interest in cyclotriveratrylenes, few of their heterocyclic analogues are known. Analogues studied to date include the cyclononatripyrroles (**2**)[12−14] and cyclononatriindoles (**3**).[15,16] These systems are of interest because their bowl conformations are chiral and because they contain external donor sites, which are absent in **1**. So far, cyclononatripyrroles have been synthesized via acid-catalyzed cyclotrimerization reactions of appropriately substituted monopyrroles, possessing one free α position and a reactive

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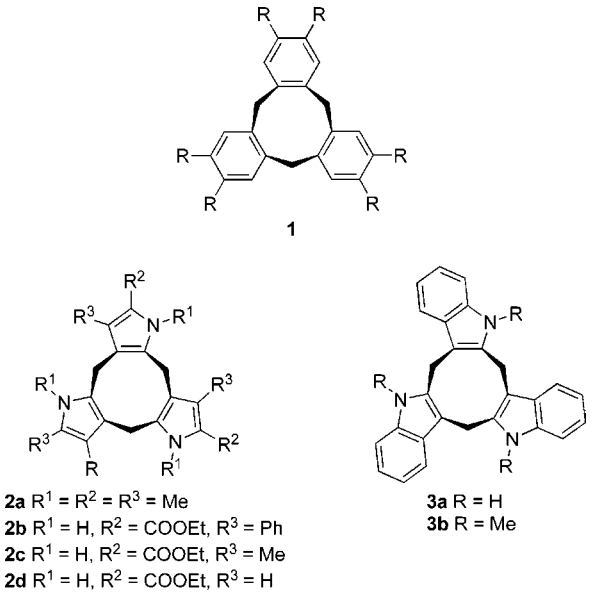
Chart 1



hydroxymethyl group in the adjacent β position. Similar strategies, based on gramine and its derivatives, have been used to prepare cyclononatriindoles.[16] Here we show that the cyclononatripyrrole skeleton can be easily accessed from a monopyrrolic precursor containing two latent carbinol groups by treating with molecular iodine, which apparently functions as an extremely mild Lewis acid catalyst.

The pyrrolic precursor in question, ethyl 3,3-dimethyl-5,7-dihydro[1,3]dioxepino[5,6-*c*]pyrrole-6-carboxylate (**4**),[17] was initially investigated as a potential source of the dicarbinol **5**. As pyrrole carbinols are known to be acid-sensitive, a particularly mild procedure was sought to deprotect the acetonide function. Acetonides are cleaved by a methanolic solution of diiodine.[18] We thus decided to try this method, encouraged by the very low Lewis acidity of I_2.[19,20] Accordingly, **4** was dissolved in a 1% methanolic solution of I_2 and stirred for 16 h. To our surprise, a large amount of precipitate was formed, with TLC analysis of the reaction mixture revealing the presence of several nonpolar products. It was soon established that the major product formed was the cyclononatripyrrole **6**, accompanied by smaller amounts of the monopyrrole **7** and the dipyrromethane derivative **8** (Scheme 1). To the best of our knowledge, none of these compounds has been reported previously. The outcome of the above reaction is a result of three processes that presumably take place consecutively. First, the acetonide is cleaved. This results in the formation of the dicarbinol **5**. While not characterized explicitly, a transient, very polar intermediate is observed by TLC during the early stages of the reaction.

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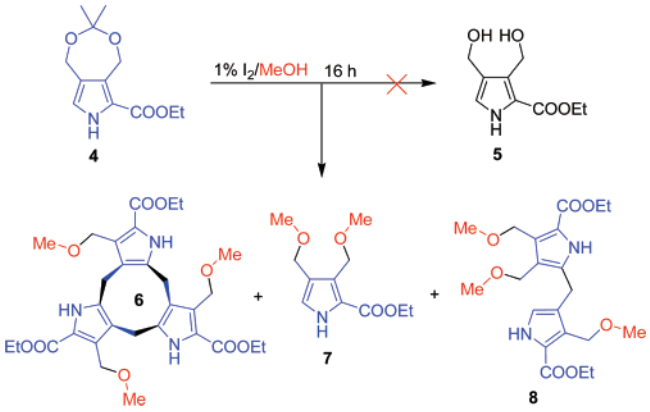
Scheme 1



Next, the labile OH groups of the putative intermediate **5** are converted to the corresponding methyl ether derivatives, yielding compound **7**. This species, however, is still reactive in the presence of iodine and undergoes self-condensation to produce the "N-confused" dipyrromethane **8** and, ultimately, the cyclononapyrrole product **6**. The reactivity of **7** was verified in a separate experiment, in which it was converted to **6** (along with small amounts of the higher tetrameric analogue) under identical reaction conditions. Interestingly, the pseudobenzylic CH_2 group adjacent to the free α-position reacts preferentially; presumably, this is the basis of the observed regioselectivity.

The identity of **6** was confirmed by ^1H and ^{13}C NMR spectroscopy, high-resolution mass spectrometry, and elemental analysis. In addition, 2D $^1H-^1H$ and $^1H-^{13}C$ correlation spectra were recorded; this enabled a complete assignment of the NMR signals and provided insight into the three-dimensional structure of the molecule. In the ^1H NMR spectrum (Figure 1), all three pyrrole rings give rise to a single set of signals, thus confirming the threefold symmetry of **6**. The molecule contains three nonequivalent types of CH_2 groups, corresponding to the methylene bridge, the methoxymethyl substituent, and the ethoxy group. Each of these is diastereotopic, indicating that **6** exists in the crown conformation characteristic of both previously reported cyclononatripyrroles[13,14] and CTVs.[4,21] The functionalized system **6** is thus nonplanar, with pseudoinversion either not taking place or being too slow to be observed on the NMR time scale. Protons *a* and *b* show very weak allylic coupling (^4J of ca. 0.6 Hz based on the differences in line widths) to the NH proton (signal *k*, Figure 1), as observed in a COSY spectrum (see Supporting Information).

Compound **6** was not affected by heating with *p*-toluenesulfonic acid in benzene at reflux, a finding that we interpret in terms of this cyclononatripyrrole being resistant to acid-catalyzed ring opening. However, the pendant methoxy substituents of **6** are labile and can be replaced with other alcoholic groups under conditions of acid catalysis. For

(21) See, for instance: Zimmermann, H.; Tolstoy, P.; Limbach, H.-H.; Poupko, R.; Luz, Z. *J. Phys. Chem. B* **2004**, *108*, 18772 and references therein.

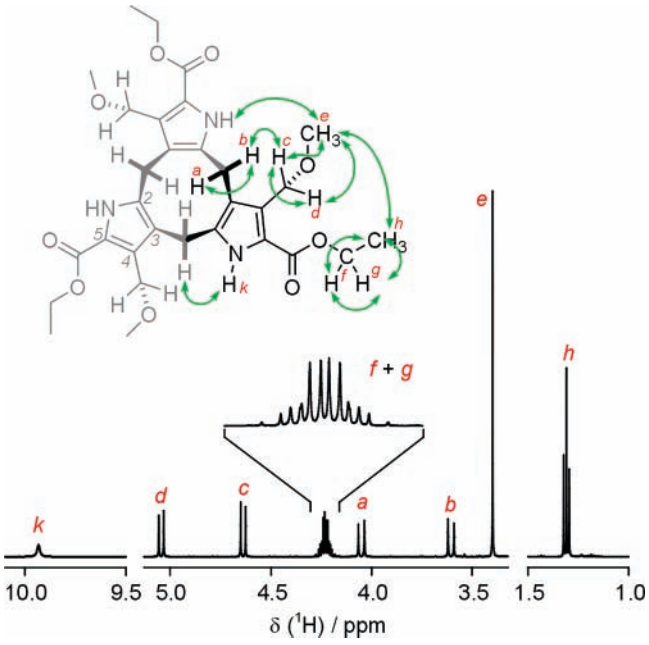
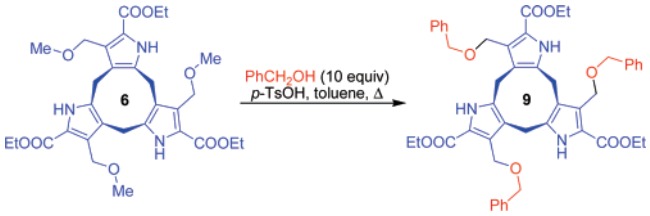


Figure 1. ^{1}H NMR spectrum of compound **6** (500 MHz, $CDCl_3$, 298 K). Green arrows correspond to dipolar couplings observed in the NOESY spectrum.

example, reacting **6** with 10 equiv of benzyl alcohol (toluene, *p*-TsOH, heating) afforded the benzyl-substituted derivative **9** in 78% yield (Scheme 2).

In conclusion, we have developed a facile synthesis of cyclononatripyrroles. The requisite C−C bond formation is catalyzed by molecular iodine, an extremely mild Lewis acid. Although frequently used as an oxidant, to the best of our knowledge, such Lewis acid catalysis has no precedent in pyrrole chemistry. We thus believe that, with further refinements, the present approach could find general use in condensations involving acid-sensitive pyrroles. In the present case, the condensation proceeds with surprising regioselectivity, something that results in the preferential formation of cyclononatripyrroles. The macrocycle obtained in this way can be easily modified by replacing the labile methoxy substituents. This is a feature that makes cyclononatripyrrole **6** and its derivatives of interest as potential building blocks for supramolecular chemistry. Studies designed to explore this possibility are currently in progress.

Scheme 2



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Supporting Information Available: Experimental details and 1D and 2D NMR spectral data for compounds **6**−**9**. This material is available free of charge via the Internet at http://pubs.acs.org.

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