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The Pyrrole Approach toward the Synthesis of Fully Functionalized Cup-Shaped Molecules

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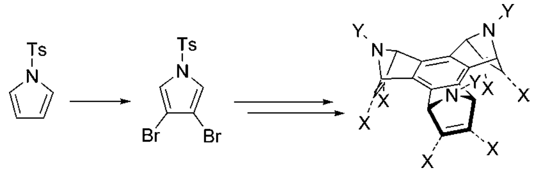
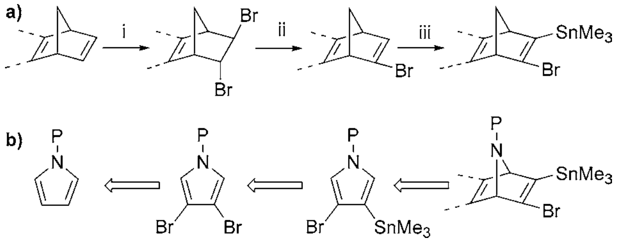
ABSTRACT



A novel method for the synthesis of new highly functionalized cyclotrimers is described. The method consists of an original synthesis of *β*-dibromosubstituted pyrroles, metalation, cycloaddition, and cyclotrimerization. The sequence is highly compatible with common functional groups and allows the construction of cup-shaped molecules functionalized both at the upper and bottom rim. This feature makes the newly formed structures useful scaffolds for the development of supramolecular receptors.

The success of supramolecular chemistry in the recent years has been characterized by the large number of original systems which were developed to meet functional requirements.[1] Calixarenes, crown ethers, resorcinarenes, just to cite a few examples, have been major actors in the scene of molecular recognition. All these systems possess common characteristics such as the ease of synthesis, a certain level of rigidity and most importantly the possibility to be smoothly functionalized. For these reasons, it was possible to use calixarenes as receptors, to bind them covalently on gold surfaces, or to use them as scaffolds for the synthesis of nanocapsules.[2] In the recent years we have been working in the synthesis of cup-shaped molecules using cyclotrimerization reactions. The synthesis of tris-annelated structures allowed a practical synthesis of fullerene fragments and of scaffolds with recognition properties.[3,4] The general approach consisted in synthesizing a vicinal halogen−metal vinyl system, which undergoes cyclotrimerization in high yield. However, this method did not appear to be applicable if functionalities other than protected alcohols are present in the substrates (Scheme 1a). For example, bromination under ionic conditions of certain bicyclic systems leads to the formation of undesired products due to Wagner-Meerwein rearrangement while bromination under radical

Scheme 1 [a]



[a] General conditions: (i) $C_2Cl_4Br_2$, CCl_4, $h\nu$; (ii) *t*-BuOK, THF, rt; (iii) (1) LDA, THF, (2) Me_3SnCl. P: protecting group.

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(2) (a) Gutsche, C. D. *Calixarenes Revisited in Monographs in Supramolecular Chemistry*; The Royal Society of Chemistry: London, 1998. (b) Jasat, A.; Sherman, J. C. *Chem. Rev.* **1999**, *99*, 931−967. (c) *Calixarenes In Action*; Mandolini, L., Ungaro, R., Eds.; Imperial College Press: London, 2000.

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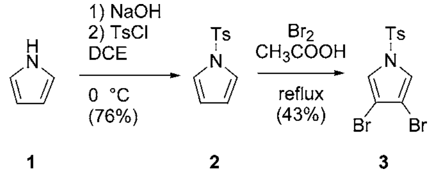
conditions in the presence of light caused decomposition of some starting materials.[5] Equally the use of strong bases in the metalation or dehydrobromination steps excludes the presence of base sensitive functional groups in the substrate.

To overcome these hurdles, we investigated the use of protected aza-bicyclic systems, which could be obtained by cycloaddition between 3,4-disubstituted pyrroles and electron deficient dienophiles (Scheme 1b). In this approach, bromination and metalation are carried out on the starting pyrrole before the cycloaddition step, allowing the presence of diverse functionalities in the dienophile. Moreover, the protected aza-bridge allows for further functionalization.

The basic knowledge for this approach is the widely explored chemistry of pyrroles usually directed at the synthesis of aza-bicycles included in alkaloids.[6] Recently, Tidwell et al. reported a method to prepare β-dibromo substituted pyrroles which could be useful starting materials for our approach.[7] The method uses the steric properties of triisopropylsilyl (TIPS) protected nitrogen to force the formation of β-substituted compounds. Disappointedly, the reaction of benzine on *N*-TIPS-3,4-dibromopyrrole failed to afford the expected cycloadduct. These preliminary data prompted us to investigate different *N*-protecting groups aimed at favoring the cycloaddition step, focusing our attention on electron-withdrawing groups, that are known to diminish the aromatic character of pyrroles. From the literature it is also known that α substituted *N*-protected pyrroles rearrange at β position under acidic conditions due to the higher thermodynamic stability of the β adducts.[8] On this basis, we submitted the *N*-tosyl-protected pyrrole **2** (prepared in multigram scale using a procedure described in the literature for the benzene sulfonyl chloride) to 2-fold bromination (Scheme 2).[9,10] The tosyl group provides the necessary electron-withdrawing feature and stability to the acidic conditions.

Scheme 2

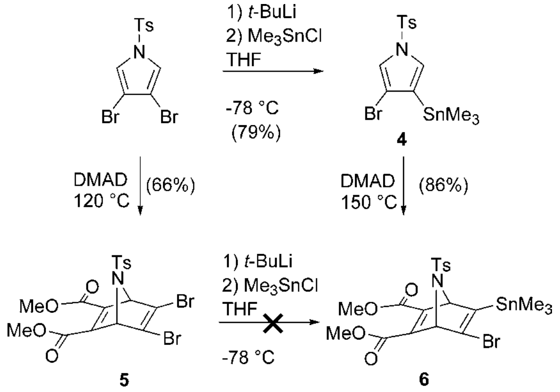


Several conditions for the bromination were used. The use of a catalytic amount of trifluoro acetic acid in DCM with 1 or 2 equiv of bromine led to mixtures of monosubstituted and disubstituted products. The selective dibromination in α position using NBS at low temperatures and the subsequent rearrangement with 10% of trifluoroacetic acid gave complex mixtures.[11] Better results were obtained using acetic acid as solvent. Under these conditions, two equivalents of bromine at reflux furnished mainly the desired product. GC−MS analysis of the crude mixture revealed that in the course of the reaction the $\alpha-\alpha'$ dibromide rearranges to the $\beta-\beta'$ isomer in 1 h under reflux. Filtration over silica and subsequent recrystallization in DCM/Et$_2$O gave 43% of **3** as a colorless solid.[12,13] Possibly, the hydrobromic acid produced under the reaction conditions led to a certain degree of tosyl group deprotection.

Despite the moderate productivity, the procedure gives the possibility to selectively synthesize and easily isolate mono- and dibromo-substituted pyrroles starting from inexpensive reagents.[14]

The synthesis of **4** was accomplished via metal−halogen exchange with *t*-BuLi and subsequent quenching with trimethyltin chloride in high yield (Scheme 3).[15] Compounds **3** and **4** were then used in the Diels−Alder reaction with dimethyl acetylene dicarboxylate (DMAD). They both

Scheme 3



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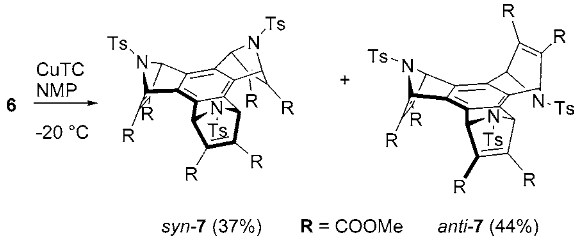
(12) **General Procedure for the Synthesis of 3.** A solution of bromine (7.4 mL, 0.14 mol) in acetic acid (80 mL) was slowly added to a solution of **2** (13.5 g, 0.06 mol) in acetic acid (200 mL) over 30 min. After addition was completed the mixture was heated to reflux for 1.5 h. The reaction mixture was warmed to room temperature and the solvent removed under reduced pressure. The black oil was filtered through a column of silica using DCM as eluant. The resulting oil was recrystallised in a DCM/ether mixture giving **3** (6.5 g) as colorless crystals. The remaining oil was then purified using silica flash chromatography (DCM) affording further 3.5 g of product with an overall yield of 43%.

(13) Selected data for **3**: ^{1}H NMR (300 MHz, CDCl$_3$, 25 °C) $\delta = 7.80-7.75$ (m, 2 H, $^1/_2$ AB), 7.37−7.32 (m, 2 H, $^1/_2$ AB), 7.19 (s, 2 H, H-2 and H-5), 2.44 (s, 3 H); ^{13}C NMR (CDCl$_3$, 75 MHz) $\delta = 146.4$, 135.9, 130.8, 127.6, 120.4, 105.6, 22.1; IR (KBr, cm^{-1}) 3137, 1594, 1520, 1455, 1376, 1172, 1057, 782. MS (EI+) *m/z* 379 (7) [M$^+$], 155 (74) [C$_7$H$_7$O$_2$S$^+$], 91 (100) [C$_7$H$_7^+$].

underwent cycloaddition smoothly using the dienophile as solvent. Interestingly, the tin atom seems to offer d-retrodonation favoring the reaction conditions. As expected, compound **5** did not give metalation due to decomposition of the starting cycloadduct.

The cyclotrimerization reaction was performed using copper thiophenecarboxylate (CuTC)[16] at −20 °C for 1 h (Scheme 4).[3] The reaction afforded the cyclotrimers *anti*-**7** and *syn*-**7** in 82% yield in 1:1.2 ratio. The two isomers were isolated using column chromatography.[17] The structures of the *syn*-**7** and *anti*-**7** were assigned according to symmetry consideration.[18]

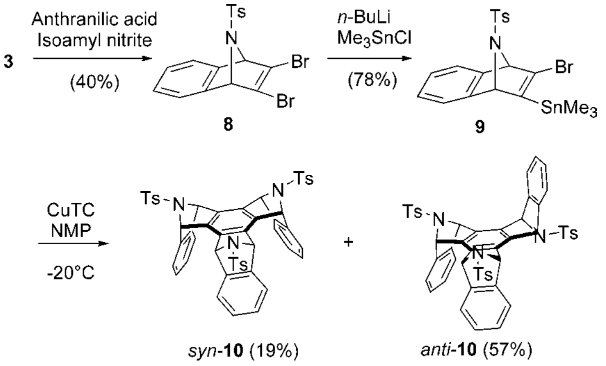
Scheme 4



syn-**7** (37%) **R** = COOMe *anti*-**7** (44%)

To prove the viability of the method, the synthesis of cyclotrimer **10** was performed (Scheme 5). The precursor of the cyclotrimerization **9** was prepared by metalation of the dibromo derivative **8**, which in turn was obtained by cycloddition of β-dibromopyrrole **3** and benzine generated from anthranilic acid and isoamylnitrite.[19] With the metalated cycloadduct **9** in hands, the trimerization was performed using standard conditions to obtain the trimers *syn*-**10** and *anti*-**10** in a 1:3 statistical ratio.[20,21] Both products were separated using flash chromatography. Interestingly, the ^{1}H NMR spectrum for compound *anti*-**10** shows unexpected high field chemical shifts of the tosyl group protons (Figure 1). In the compound, the pocket formed by the two contiguous aromatic rings generates a cleft in which the electron-poor tosyl group forms a double edge-to-face interaction.[22]

Scheme 5



syn-**10** (19%) *anti*-**10** (57%)

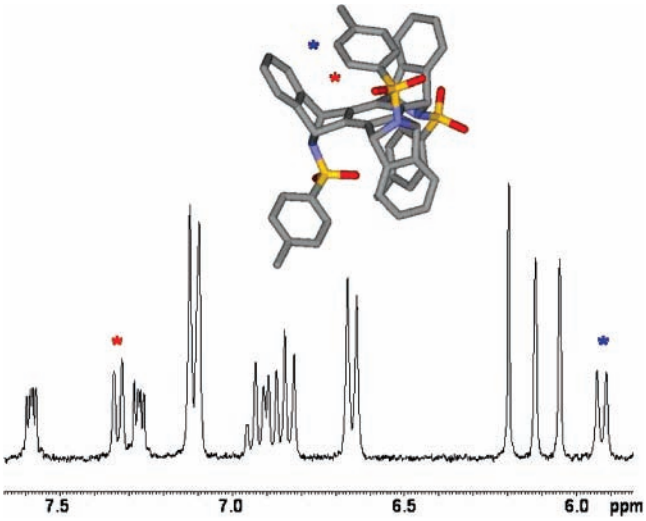


Figure 1. Partial ^{1}H NMR spectrum of the compound *anti*-**10** in acetone-d_6 and MM2-minimized structure showing edge-to-face interaction between the tosyl group and the aromatic cleft.

To conclude, a new approach to the synthesis of cup-shaped molecules has been developed. This method is based on original synthesis of a β-dibromopyrrole, its metalation and subsequent cycloaddition. The cyclotrimers represent highly functionalized structures for future derivatization and

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(14) One equivalent of bromine in the same condition led to the formation of the β bromo isomer **11** in 72% yield.

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(17) Selected data for *syn*-**7**: ^{1}H NMR (300 MHz, CDCl$_3$, 25 °C) δ 7.59−7.54 (m, 6 H, $^1/_2$ AB), 7.29−7.24 (m, 6 H, $^1/_2$ AB), 5.76 (s, 6 H), 3.65 (s, 18 H), 2.40 (s, 9 H); ^{13}C NMR (CDCl$_3$, 75 MHz) δ 161.6, 147.1, 145.1, 134.3, 133.6, 130.6, 128.3, 68.1, 52.7, 21.9.

(18) Selected data for *anti*-**7**: ^{1}H NMR (300 MHz, CDCl$_3$, 25 °C) δ 7.56−7.46 (m, 2 H, $^1/_2$ AB), 7.42−7.37 (m, 4 H, $^1/_2$ AB), 7.17−7.12 (m, 6 H, 2 $^1/_2$ AB), 5.72 (s, 2 H), 5.66 (s, 4 H), 3.96 (s, 6 H), 3.76 (s, 6 H), 3.74 (s, 6 H), 2.34 (s, 3H), 2.34 (s, 6 H); ^{13}C NMR (CDCl$_3$, 75 MHz) δ 161.7, 161.6, 161.4, 147.9, 147.6, 145.3, 145.0, 134.3, 134.2, 134.0, 133.5, 133.4, 130.6, 130.3, 128.3, 128.0, 68.3, 68.1, 67.8, 53.3, 53.0, 52.9, 21.9 (2 carbons).

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(20) Selected data for *syn*-**10**: ^{1}H NMR (300 MHz, CDCl$_3$, 25 °C) δ 7.45−7.44 (m, 6 H, $^1/_2$ AB), 7.12−7.08 (m, 6 H, $^1/_2$ AB), 6.82−6.79 (m, 6 H, $^1/_2$ AA′BB′), 6.63−6.59 (m, 6 H, $^1/_2$ AA′BB′), 5.79 (s, 6 H), 2.32 (s, 9H); ^{13}C NMR (CDCl$_3$, 75 MHz) δ 144.8, 144.1, 134.5, 134.1, 130.0, 128.2, 126.7, 121.1, 66.4, 21.9.

(21) Selected data for *anti*-**10**: ^{1}H NMR (300 MHz, CD$_3$COCD$_3$, 25 °C) δ 7.60−7.56 (m, 2 H, $^1/_2$ AA′BB′), 7.35−7.31 (m, 2 H, $^1/_2$ AB), 7.29−7.25 (m, 2 H, $^1/_2$ AA′BB′), 7.13−7.08 (m, 8 H, $^1/_2$ AB), 6.67−6.63 (m, 8 H, $^1/_2$ AB), 6.20 (s, 2 H), 6.12 (s, 2 H), 6.05 (s, 2 H), 5.95−5.91 (m, 2 H, $^1/_2$ AB), 2.87 (s, 3H), 2.83 (s, 6H); ^{13}C NMR (CDCl$_3$, 75 MHz) δ 146.8, 146.3, 146.0, 143.4, 142.4, 135.1, 135.0, 134.6, 134.5, 134.3, 129.7, 129.2, 127.7, 127.2, 126.8, 126.6, 126.4, 122.0, 121.9, 121.5, 66.6, 66.3, 66.0, 20.8, 20.7.

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application in supramolecular chemistry. Further functionalizations of these molecules are under development.

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Supporting Information Available: Experimental procedures and full characterization for compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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