High-Yield Macrocyclization via Glaser Coupling of Temporary Covalent Templated Bisacetylenes

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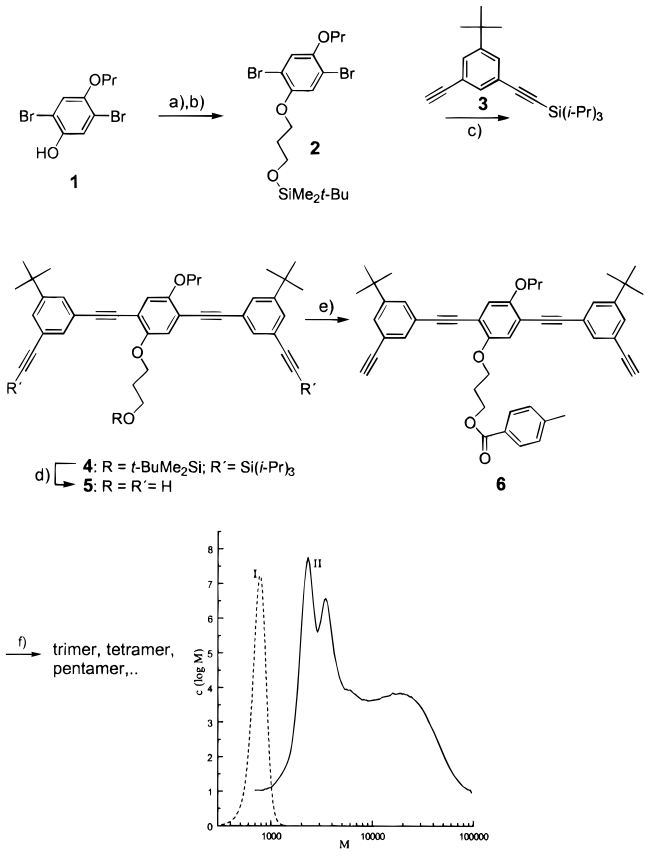
Received February 25, 1997 (Revised Manuscript Received April 8, 1997)

The synthesis of well-defined, shape-persistent nanometer-scale objects has obtained increasing attention during the last several years. Besides one-dimensional structures, those of higher dimensionality are especially interesting[1] because they can be used as host molecules if they contain appropriate binding sites.[2] Some of the most established cyclic structures are based on the phenylacetylene backbone. Two extreme synthetic strategies can be distinguished. Staab and co-workers prepared cyclic hexa-*m*-phenylacetylene in a one-pot reaction by a 6-fold Stephens−Castro coupling of 3-iodophenylacetylene in 4.6% yield.[3] Despite the low yield for the cyclization step, this method is impressive because the starting materials are readily accessible. A completely different approach was investigated by the group of Moore.[4] They prepared similar and other phenylacetylene macrocycles in good to excellent yields by an intramolecular coupling of the corresponding α-iodo-ω-ethynyl precursor; however, the synthesis of the precursors is relatively time consuming. One way to overcome this dilemma, which also occurs when the Glaser coupling is used as the bond-forming step,[5] has been investigated by the group of Sanders, using the template directed synthesis of cyclic porphyrin−acetylene structures; however, this method is restricted to metal-containing compounds.[6] We are interested in shape-persistent macrocycles containing both nonpolar and polar side groups in a switchable arrangement, which have been prepared by the intermolecular Glaser coupling of two rather large and rigid bisacetylenes. In order to reduce the number of synthetic steps, we became interested in using small and easily preparable starting materials like **6** for the cyclization step.

Scheme 1[a]



[a] Key: (a) 3-bromo-1-propanol, K_2CO_3, DMF, 70 °C (92%); (b) *t*-$BuMe_2SiCl$, imidazole, DMF, rt (87%); (c) **3**, $PdCl_2(PPh_3)_2$, CuI, piperidine, 60 °C (91%); (d) Bu_4NF, THF, rt (92%); (e) p-toluic acid chloride, pyridine, THF, rt (80%); (f) $CuCl/CuCl_2$, pyridine, rt; GPC diagram of **6** (I) and of the crude product of the cyclization of **6** (II).

Scheme 1 illustrates the synthesis of the protected amphiphilic bisacetylene **6** and its cyclization. Protection of the free OH group of **5** as an aryl ester and cyclization of **6** by a modified Eglington−Glaser coupling using high dilution conditions gave a mixture of different oligomers, as determined by gel permeation chromatography (GPC).[7] The fact that we were not able to detect residual absorptions for acetylenic protons in the ^{1}H-NMR spectra supports the assumption that a mixture of cyclic oligomers and cyclic or noncyclic polymers was formed. The smallest cyclic product of the reaction, the cyclic trimer, was only formed in about 20−25% yield and, moreover, due to their similar physical properties we were not able to separate the reaction products by recrystallization or column chromatography.[8]

Our approach now is to circumvent the low yield of the statistical intermolecular reaction described above and still retain the advantage of small and easily preparable bisacetylenes. Therefore, we present here a template-directed synthesis of shape-persistent macrocycles based on the phenylacetylene backbone by using the Glaser coupling as the bond-forming step and a covalent linkage of the monomers to the template.[9] For this purpose, the

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(1) Selected reviews and some new examples: (a) Tour, J. M. *Chem. Rev.* **1996**, *96*, 537. (b) Bunz, U. H. F. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1073. (c) Timmermann, P.; Verboom, W.; van Veggel, F. C. J. M.; van Hoorn, W. P.; Reinhoudt, D. N. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1292. (d) Höger, S.; Enkelmann, V. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2713.

(2) Host molecules based on phenylacetylene structures: (a) Morrison, D. L.; Höger, S. *J. Chem. Soc., Chem. Commun.* **1996**, 2313. (b) Anderson, H. L.; Sanders, J. K. M. *J. Chem. Soc., Chem. Commun.* **1989**, 1714. (c) Mackeay, L. G.; Anderson, H. L.; Sanders, J. K. M. *J. Chem. Soc., Chem. Commun.* **1992**, 43. (d) Anderson, S.; Neidlein, U.; Gramlich, V.; Diederich, F. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1596.

(3) Staab, H. A.; Neunhoeffer, K. *Synthesis* **1974**, 424.

(4) Zhang, J.; Pesak, D. J.; Ludwig, J. L.; Moore, J. S. *J. Am. Chem. Soc.* **1994**, *116*, 4227.

(5) (a) de Meijere, A.; Kozhushkov, S.; Haumann, T.; Boese, R.; Puls, C.; Cooney, M. J.; Scott, L. T. *Chem. Eur. J.* **1995**, *1*, 124. (b) Boldi, A. M.; Diederich, F. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 486.

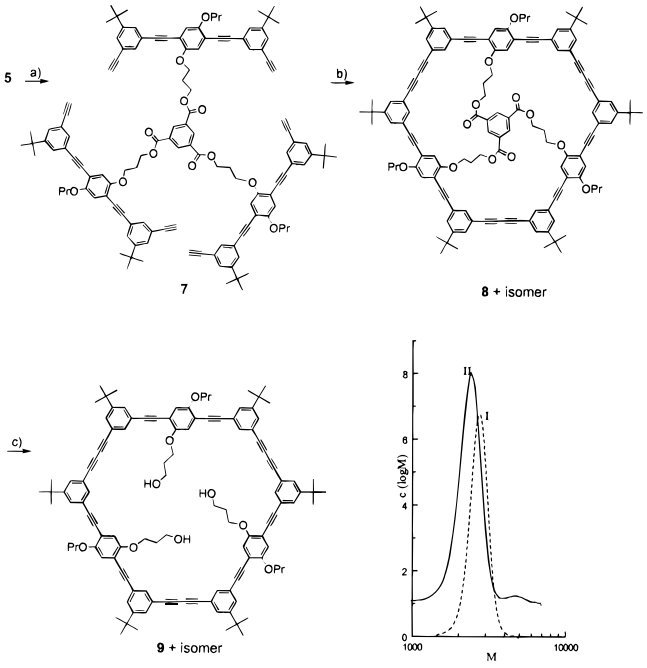
(6) For recent articles dealing with template reactions see: (a) Anderson, S.; Anderson, H. L.; Sanders, J. K. M. *Acc. Chem. Res.* **1993**, *26*, 469. (b) Hoss, R.; Vögtle, F. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 375. (c) Dietrich, B.; Viout, P.; Lehn, J.-M. *Macrocyclic Chemistry*; VCH: Weinheim, 1993; Chapter 3.3.

(7) The GPC diagrams were measured in THF, and a UV detector operating at $\lambda = 254$ nm was used. The molecular weight was obtained from polystyrene calibration of the GPC columns.

(8) To confirm that it is actually the cyclic trimer, we esterified compound **9** and compared the GPC diagram with the one obtained for the cyclization of **6**.

S0022-3263(97)00350-2 CCC: $14.00

Scheme 2[a]



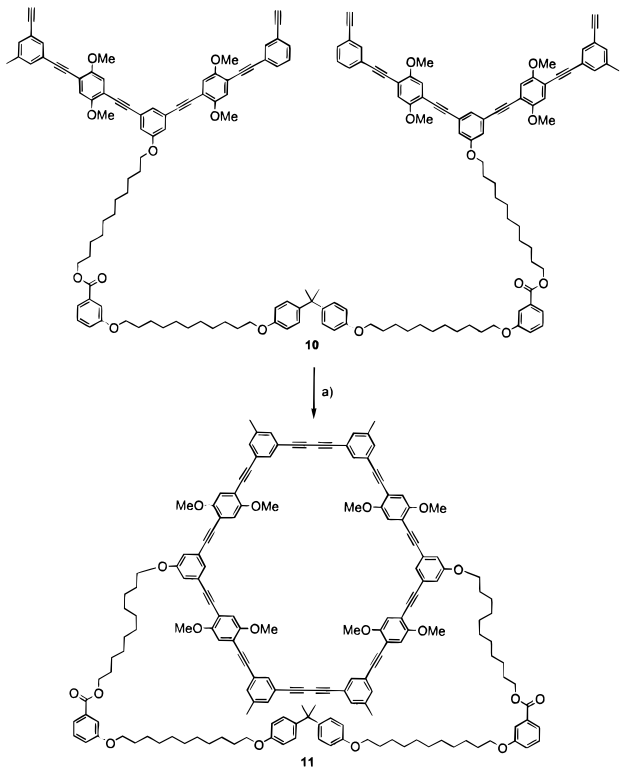
[a] Key: (a) 1,3,5-benzenetricarboxylic acid, DEAD, PPh_3, THF, rt (79%); (b) $CuCl/CuCl_2$, pyridine, rt; (c) NaOH, LiOH, MeOH, H_2O, THF, 80 °C (95%); GPC diagram of **7** (I) and of the crude product of the cyclization of **7** (II).

bisacetylene **5** was protected with 1,3,5-benzenetricarboxylic acid under Mitsunobu conditions to give the triester **7** in good yields (Scheme 2).

Cyclization was carried out under the same conditions used for the coupling of **6**, except that the crude product of the reaction (94% yield) now contained more than 95% of the template-bound cyclic trimer (according to the GPC data). If instead of the 3-hydroxypropyl ether **5** the corresponding 11-hydroxyundecyl ether was used for the cyclization under the same conditions, the crude product (88%) again contained more than 95% of the desired templated macrocycle. This result is quite important since it shows that for a high-yield intramolecular coupling of the monomers it is not necessary to arrange them in a special preorganized geometry. Rather, the high yield of the cyclization process can be attributed to an overall low triester concentration in the reaction mixture (as a result of the high dilution conditions) together with a high local concentration of terminal acetylenes (as a result of the intramolecular nature of the coupling reaction).

Both templated products show, probably due to their restricted flexibility, complex NMR spectra. Contrary to our expectations, we could not observe, even in the case of the undecyl derivative, any simplification of the spectra upon heating, even up to 130 °C in tetrachloroethane. Base-catalyzed hydrolysis of **8** gave the macrocycle **9** in nearly quantitative yield. **9**, as well as the undecyl compound, now show the expected simple NMR spectra.

Scheme 3[a]



[a] Key: (a) $CuCl/CuCl_2$, pyridine, rt.

Both macrocycles are probably a mixture of two isomers. One of these corresponds to the case where the polar side groups of a ring point in the same direction, while in the other case one of the polar groups points in an opposite direction. We were not able to separate these mixtures by simple column chromatography.

The results shown above motivated us to extend our strategy and prepare the tetraacetylene **10** (Scheme 3).[10]

Under conditions identical to those used above, the crude product (92%) contained **11** in ~86−88% yield. The reason for the lower yield compared to the cyclization of **7** is at the present not clear, and future variations of the spacer geometry will show if steric restrictions after the first diyne formation prevent a fast intermolecular second reaction.

In summary, we can say that macrocyclic geometries of well-defined size and shape can be easily prepared by cyclization of relatively small and readily accessible monomers if they are temporarily covalently bound to a template. The length of the spacer betwen the template and the monomer is of only minor importance, and even attachement of the template at the outside of the final ring works well.

Supporting Information Available: Preparation of all the starting materials including spectral data (^1H NMR and ^{13}C NMR). Experimental procedures for the preparation of **6** and **9**, including copies of the ^1H NMR spectra (10 pages).

JO970350C

(9) The preparation of C_3 macrocyclic receptors by a templated triple macrolactamization (Hong, J.-I.; Namgoong, S. K.; Bernardi, A.; Still, W. C. *J. Am. Chem. Soc.* **1991**, *113*, 5111) and the formation of macrocyclic tetraesters by reaction on a porphyrin template (Mackey, L. G.; Bonar-Law, R. P.; Sanders, J. K. M. *J. Chem. Soc., Perkin Trans. 1* **1993**, 1377) are also reported. However, in both cases the yields are relatively low, and the template was not removed after cyclization.

(10) **10** was prepared using our convergent strategy for the preparation of arylacetylene oligomers with ethynyl end groups (Höger, S.; Müller, S.; Karcher, L.; *Polym. Prepr. (Am. Chem. Soc. Div. Polym. Chem.)* **1997**, *38*(1), 72). A detailed experimental procedure for the preparation of **10** as well as the functionalization of the detemplated macrocycle will be published elsewhere.