Cryptands by One-Pot Homoacetylenic Cu-Catalyzed Coupling –Synthesis, Structure and Properties

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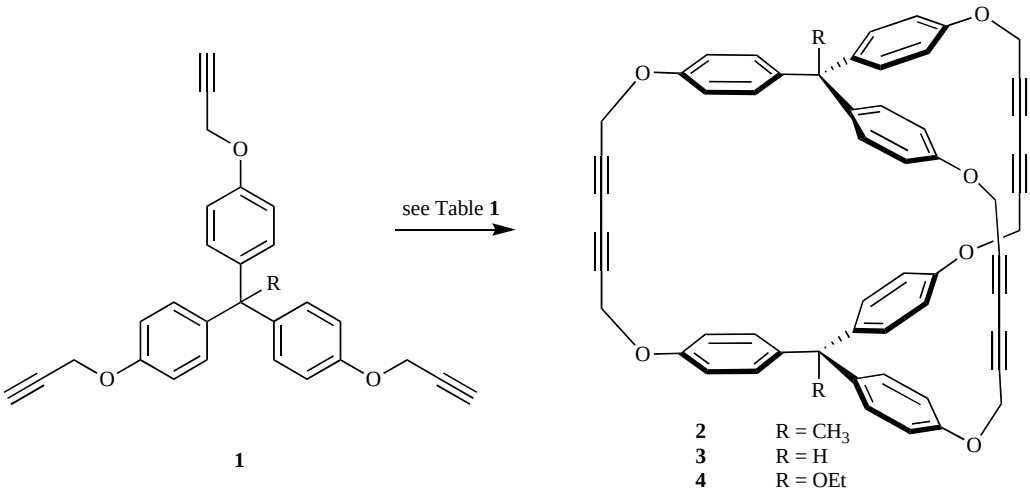
Abstract: This review presents the synthesis of macrobicyclic compounds built from triphenylmethane, triphenylphosphine oxide units and other three-dimensional molecules with an aromatic core, as well as some fullerene precursors and buta-1,3-diynediyl spacers. The dependence of the coupling yield on the solvent, catalysts (Cu^{+} and/or Cu^{2+}) and presence of oxygen is also addressed. The formation of inclusion complexes of these cage molecules with appropriately sized neutral guests such as solvent molecules (acetonitrile, benzene, dichloromethane, chloroform), cubane, benzyl cyanide and structural information of the host derivatives are also reviewed.

1. INTRODUCTION

The synthesis of three-dimensional cage-like molecules is of continuous interest in the field of supramolecular chemistry [1]. Among them, molecules with a well-defined cavity are particularly appealing for their potential binding properties [2]. We became interested to obtain such macrocyclic derivatives, starting from pre-organized half-cages with terminal triple bonds, by a one-pot three-fold oxidative homoacetylenic coupling and therefore it was considered of interest to review them.



Scheme 1. Synthesis of derivatives **2 – 4**.

2. GENERAL REMARKS ON CU-CATALYZED ACETYLENIC COUPLING

Acetylenic homocoupling represents an interesting tool for molecular construction and has been extensively used and diversified since Glaser's discovery of oxidative coupling of copper alkynylbenzene [3]. The most important and successful modifications of the initial Glaser coupling technique were reported by Eglinton [4] (the Eglinton-Galbraith method: excess $Cu(OAc)_2$ in pyridine, 20–40 % yield) and Hay [5] [the Glaser-Hay coupling: CuCl, *N,N,N',N'*-tetramethylethylendiamine (TMEDA), solvent, up to 97 % yield]. Despite the wide range of applications of alkyne coupling [6], from natural products to pharmaceuticals and macrocyclic derivatives [7], the mechanism of this reaction has not yet been elucidated. In the present review, we are summarizing the modified coupling procedures that have been used to afford cage compounds by one-pot cyclization reactions.

3. CRYPTANDS WITH AROMATIC UNITS

a. Triphenylmethane Units

The formation of three-dimensional macrobicyclic receptors with triphenylmethane units containing three buta-1,3-diynediyl spacers, by a one-pot triple-coupling reaction of two tris-ethynyl substituted half cages, has been first reported by Breslow and co-workers [8]. They have obtained the 1,1,1-triphenylethane derivative **2** by performing the triple oxidative dimerization in *dry oxygen-free pyridine* in the presence of both anhydrous Cu(I) and Cu(II) salts (Scheme **1**, Table **1**). Despite their report on complete failure when employing standard coupling conditions [Cu(II)-pyridine or Cu(I)-TMEDA-O_2], Voegtle and co-workers have later obtained compound **2** in similar yields, by using $Cu(OAc)_2$ in pyridine or acetonitrile [9].

Breslow's macrocyclization reaction was also employed for the synthesis of macrobicyclic compound **3** [10] in 35 % yields (Scheme **1**, Table **1**). The dimeric cage molecule **3** has also been synthesized following Eglinton coupling procedure with copper(II) acetate monohydrate in pyridine or acetonitrile [10b].

Voegtle and co-workers have reported on the first synthesis of a new type of concave dyestuff [11] bearing a relatively large cavity

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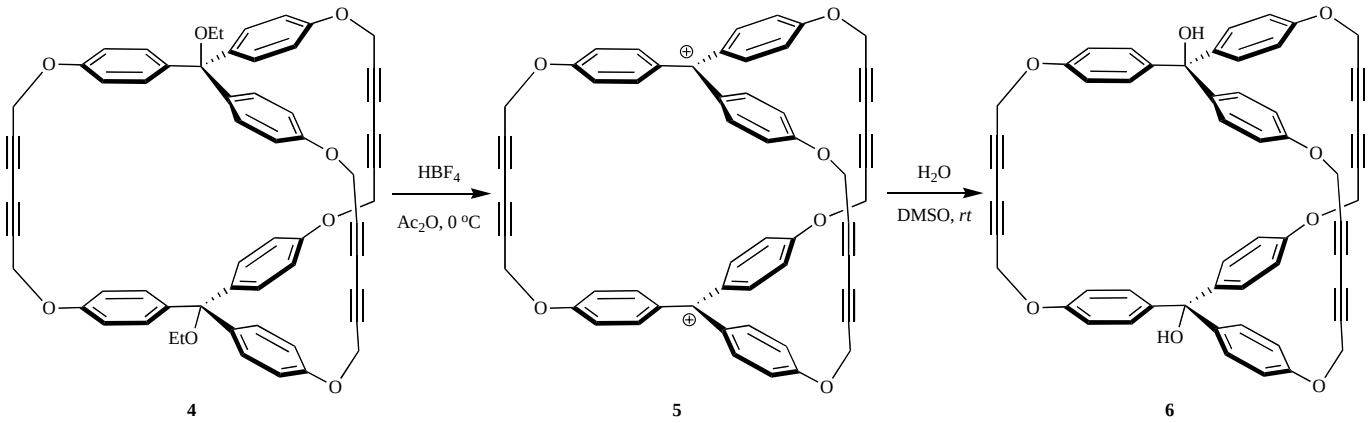
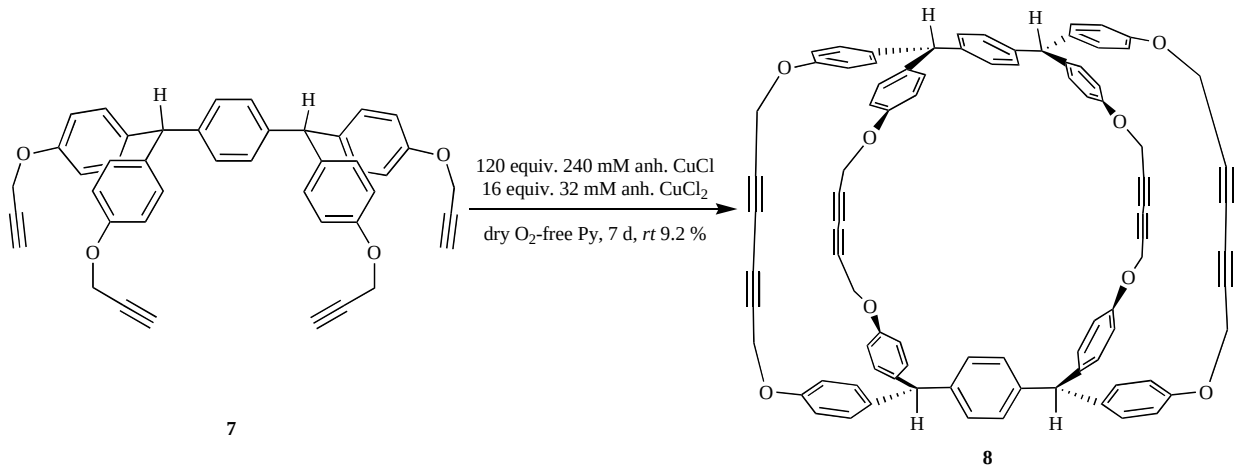
Table 1. Reaction Conditions for Cu-catalyzed Acetylenic Coupling for the Formation of Derivatives 2 – 4

Compd.	Reaction Conditions	Yield (%)	Ref.
2	100 *equiv.* 100 mM anh. CuCl/ 12.2 *equiv.* 12.2 mM anh. $CuCl_2$, dry O_2-free Py, 48 h, 0 ^oC	35	[8]
	$Cu(OAc)_2$ in Py or AcCN	17-21	[9]
3	100 *equiv.* 200 mM anh. CuCl/ 12 *equiv.* 24 mM anh. $CuCl_2$, dry O_2-free Py, 7 d, rt	35	[10]
4	10 *equiv.* 112 mM Cu(OAc)2 in AcCN, 1 h, 60 ^oC	32	[11]



4 **5** **6**

Scheme 2. Synthesis of derivatives **5** and **6**.



7 **8**

Scheme 3. Synthesis of derivative **8**.

formed from two tritylium cation units (**5**, Scheme **2**). The precursor is the diethoxy protected derivative **4**, obtained by oxidative cyclodimerization with Cu(II) in acetonitrile. The use of acetonitrile instead of pyridine had lead to a considerable yield improvement, from 18 % to 32 %, probably due to a template effect of the first.

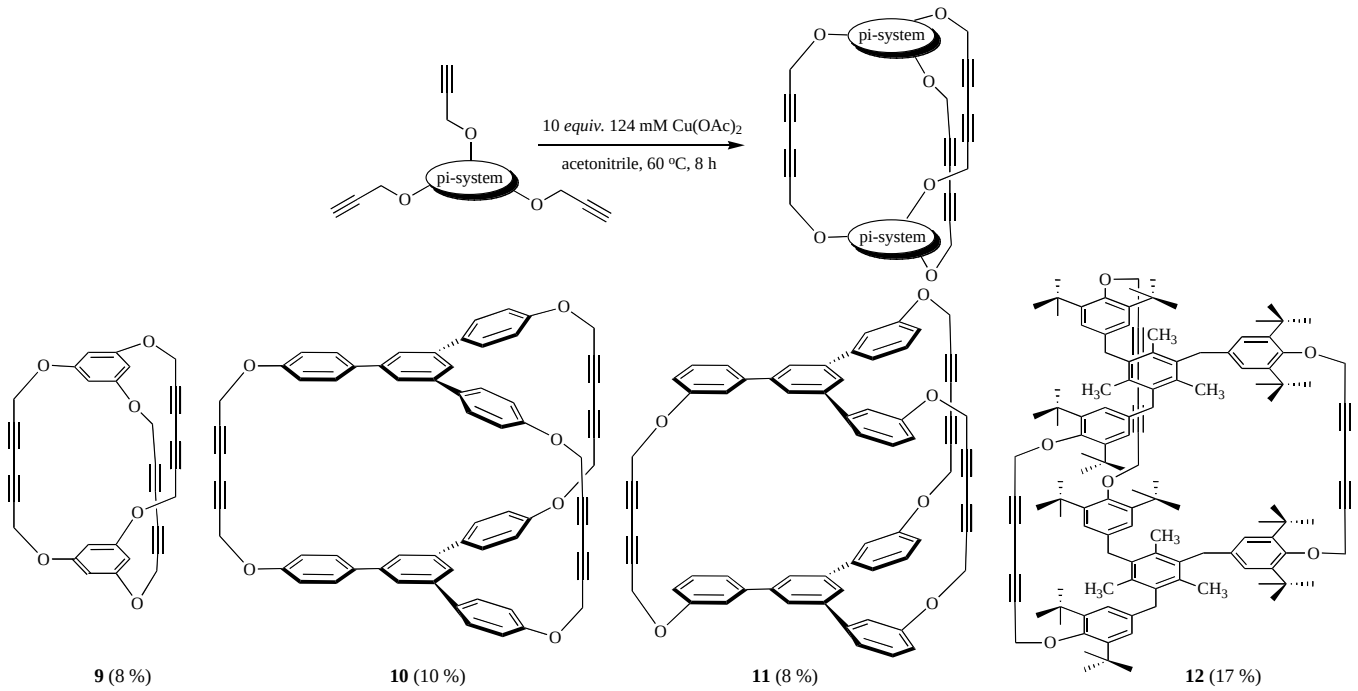
An interesting example is compound **8** (Scheme **3**), an analogue of derivative **3**, with a larger cavity formed by triphenylmethane units. Performing the four-fold oxidative Cu(I)/Cu(II)-catalyzed acetylenic coupling, a significant decrease in yield was observed when compared to the three-fold bridging (**3**) (9.2 % *vs.* 35 %).

b. Other Aromatic Units

An example of a smaller macrobicyclic cavity for the inclusion of acetonitrile was described by the same authors [12]. Derivative **9** (Scheme **4**) was synthesized in 8 % yields using $Cu(OAc)_2{\cdot}H_2O$ in pyridine under air. The larger cage compounds **10** – **12** were obtained in low yields by performing the mild, modified Eglinton acetylenic coupling in acetonitrile [13].

Structure and Properties. The multiple hexa-2,4-diyine bridges in combination with the above described aromatic units are forming cavities able to include neutral organic guests, mainly solvent molecules. The conjugated alkyne units do not show interactions for the inclusion process with the guest molecules.

The macrobicycle **3** was crystallized from acetonitrile as a 1:1 adduct and from phenylacetonitrile as a 1: 3 adduct (Fig. **1**). A comparison with the complex of **2** with benzene ($2x5C_6H_6$) shows that hosts **2** and **3** have similar torsion angles along their *pseudo* C_3 axis ($26 – 36^o$) and similar cavity sizes (Fig. **1**). These guests are not located in the center of the cavity and it was assumed that flat aromatic compounds are not sterically suitable for a spherical shaped host. This assumption has been proved later by the single-crystal X-ray structure of the inclusion complex of **2** with acetone



9 (8 %) **10** (10 %) **11** (8 %) **12** (17 %)

Scheme 4. Synthesis of derivatives **9** – **12**.

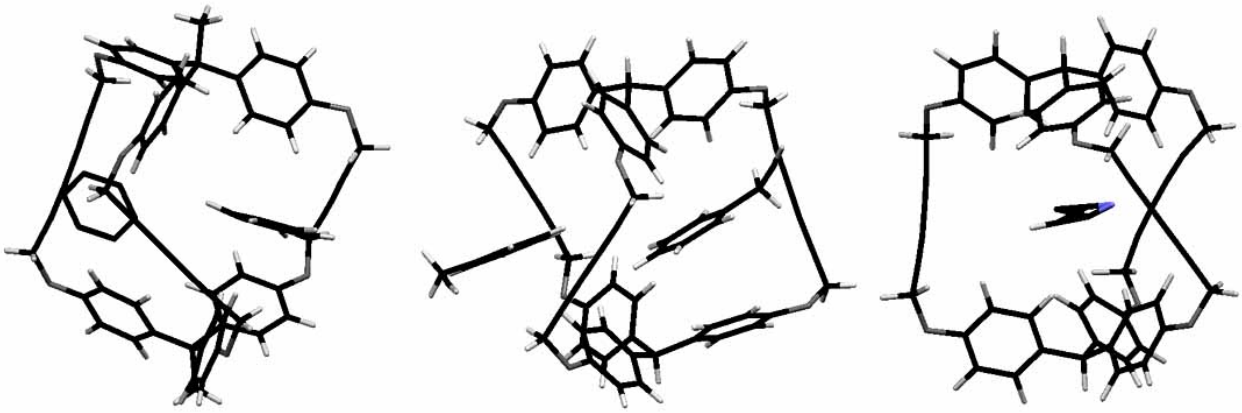


Fig. (1). X-ray structures for inclusion complexes: **a**. **2**x5 C_6H_6, **b**. **3**x3BnCN and **c**. **3**xMeCN.

(Fig. **2a**). Acetone was located in the center of the cavity and held by multiple σ–π interactions between the methyl groups of the guest and the aromatic rings of the host.

Further evidence of the importance of topological complementarities between the shape of the host and the bonded guest has been provided by the inclusion complex of DMSO in the cavity of compound **6** (Scheme **2**). The guest molecule is situated, as acetone in **2**, in the middle of the cavity (Fig. **2b**).

The geometry of the complex formed by the smaller host **9** with acetonitrile turned out to be completely different from **3** with respect to the orientation of acetonitrile (Fig. **3**). The host phenylene rings in **3**xMeCN (Fig. **1c**) interact with the nitrile group, while in **9**xMeCN there is an interaction between the methyl group of acetonitrile and the host phenyl rings. The two aromatic rings approach each other to 7.12 Å and a torsion angle along its *pseudo* C_3 axis of 13^o was measured.

The larger host **10** did not show any endocavital complexation with flat aromatic guests, possibly because the distance between the aromatic units (8.09 Å) is far from the ideal distance for the inclusion of aromatic guests by π – π interactions (6.84 Å) [14].

Cram and co-workers [15] have reported the synthesis of chiral [1.1.1]orthocyclophane carcerand **14** by oxidative Eglinton coupling of acetylene **13** (Scheme **5**). They performed the most detailed study published so far on the employed conditions and concluded that *anaerobic conditions, even with excess Cu(II) salt gave no desired product*, while increasing the reaction temperature to 85 °C led to the formation of traces of intramolecularly coupled product **15**.

Structure and Properties. The configurations of the two diastereoisomers have been assigned by single crystal X-ray structure determinations. The crystal structure of **(±)-14** (from CH_2Cl_2) shows a compact structure with an almost spherical cavity and D_3 symmetry (Fig. **4a**). In contrast, *meso*-**14** presents a larger cavity with an approximately ellipsoidal shape (Fig. **4b**).

In order to assess the complexation properties of the diastereoisomeric carcerands **14**, ^1H NMR studies in hexachloroacetone were performed. The results demonstrated that **(±)-14** is strongly binding small neutral organic molecules with complementary shape and appropriate size. The association constants for complexing $CHCl_3$,

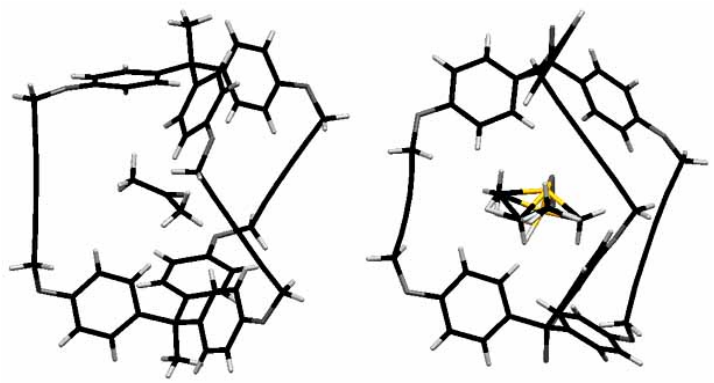


Fig. (2). X-ray structures for inclusion complexes: **a**. **2**xacetone and **b**. **6**xDMSO.

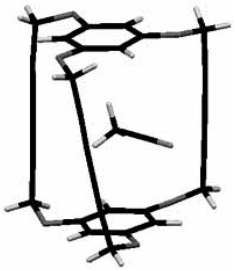
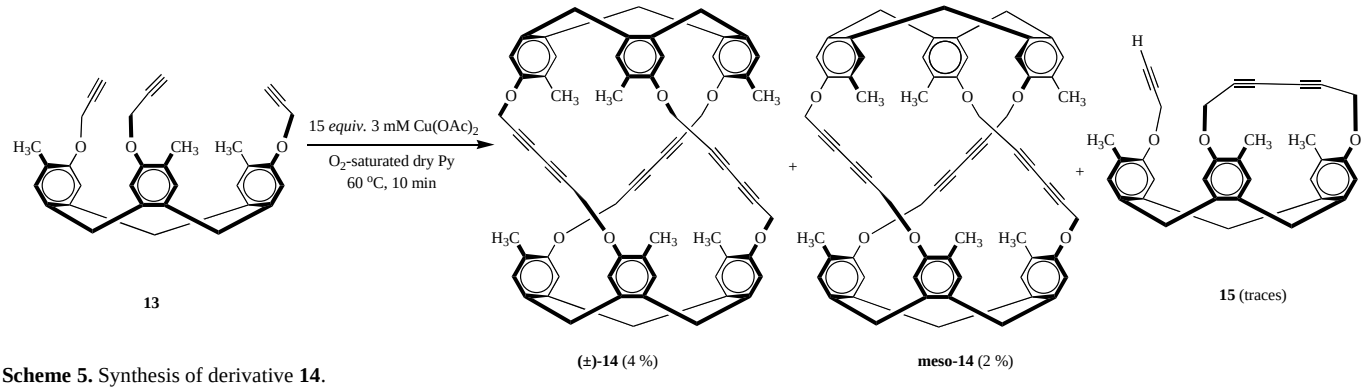


Fig. (3). X-ray structures for inclusion complex **9**xMeCN.

assumed to be due to the fact that solvent binds better to the *meso* diastereoisomer than it binds to the (±) one.

4. CRYPTANDS WITH TRIPHENYLPHOSPHINE UNITS

As phosphine oxides can serve as hydrogen–bond acceptors, Whitlock and Friedrichsen [16, 17] have considered this moiety for the synthesis of this type of well defined three-dimensional host molecules. Treatment of **16** in pyridine at 60 °C with $Cu(OAc)_2 \cdot H_2O$ provided a mixture of isomeric diyne-bridged bis-phosphoryl macrocycles **17** (*exo-exo*) and **18** (*endo-exo*) in 14 % and 7 % yield, respectively (Scheme **6**).



Scheme 5. Synthesis of derivative **14**.

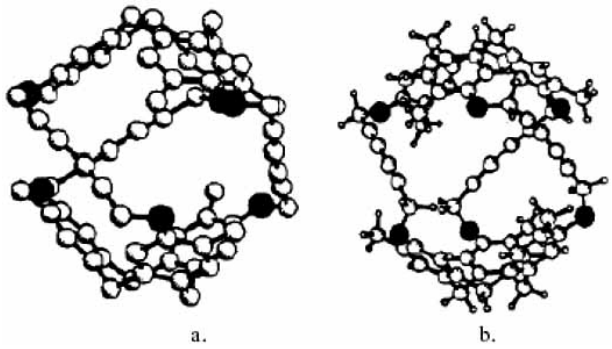
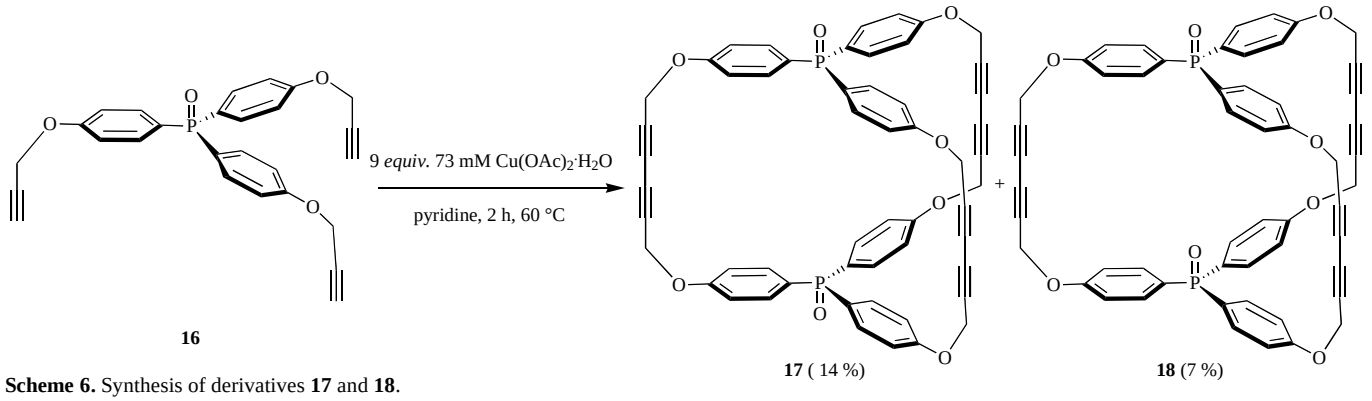


Fig. (4). X-ray structures for the free diastereoisomeric carcerands: **a**. (±)-**14** and **b**. *meso*-**14** (Permission to reprint is granted by the American Chemical Society).

$(CH_3)_3COH$, CH_2Cl_2, cubane, propylene oxide and benzene were determined in $(CCl_3)_2CO$ at −20 °C.

The ^1H NMR spectra of ***meso*-14** in $(CCl_3)_2CO$ showed no signs of complexation with any of the guests, from −20 to −40 °C. It was

Structure and Properties. The X-ray structures of compound **17** (from chloroform, Fig. **5a**) and **18** (from anisole, Fig. **5b**) showed the orientation of the phosphoryl groups and the helical nature of both species. Complete ^1H and ^{31}P NMR studies were



16 **17** (14 %) **18** (7 %)

Scheme 6. Synthesis of derivatives **17** and **18**.

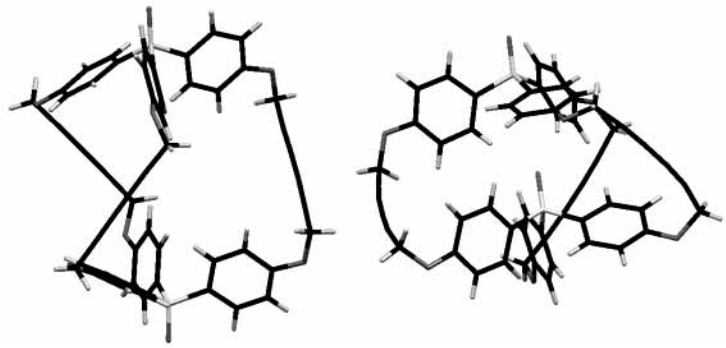
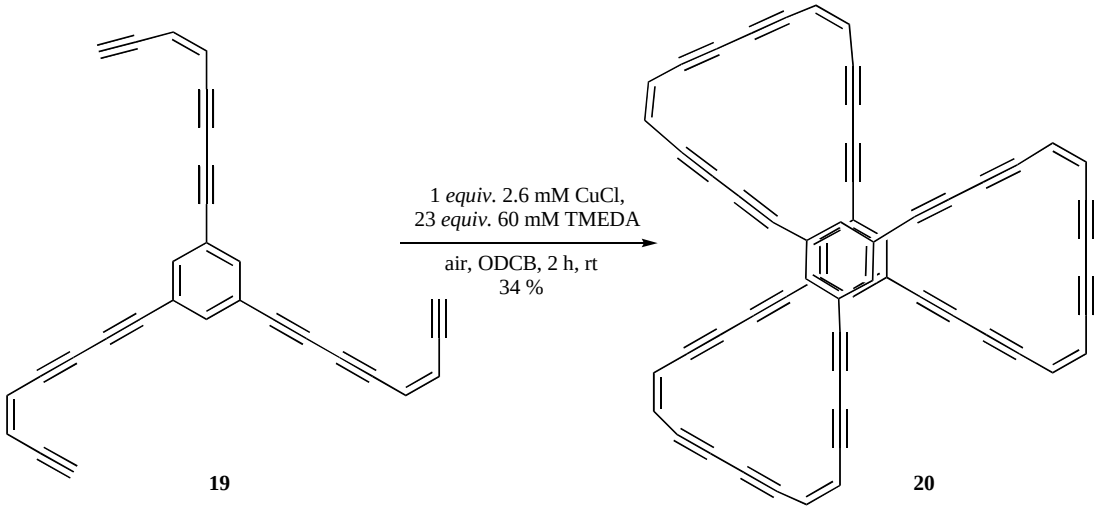


Fig. (5). X-ray structures for the free cryptands: **a**. **17** and **b**. **18**.



19 **20**

Scheme 7. Synthesis of derivative **20**.

undertaken and proved that *exo-exo* host **17** forms only extracavity complexes, while *endo-exo* host **18** allows also intracavity complexation.

The 1:2 complexation mechanism of **18** with a variety of guests has been studied by ^{1}H NMR spectroscopy. The calculated chemical shifts for the 1:1 and 1:2 complexes have evidenced the initial *endo* complexation of most of the guests. The association constants were modest and range from 18 M^{-1} (for phenol) to 354 M^{-1} (for *p*-nitrophenol) for the formation of the 1:1 complex with mono- and unsubstituted phenols, while the association constants for 1:2 complexes range from 1 M^{-1} to 320 M^{-1}. Surprisingly, even larger hosts such as 4-[(*p*-nitrophenyl)-azo]phenol and 6-nitro-2-naphtol showed preference for the initial *endo* complexation. The exception from this mechanism was proved for pentafluorophenol, which prefers to complex with **18** by initial *exo* pathway. No complexation was observed for 2,4-dinitrophenol, 4-nitrothiophenol, benzoic acid and pyridine hydrochloride.

The ^{31}P NMR studies allowed calculation of the association constants for the *exo*cavital complexes of **17** and brought further information regarding the complexation of **18**. It has been shown that 2,6-dimethyl-4-nitrophenol, acetic acid and pentafluorophenol prefer initial *exo* complexation with the *endo-exo* phosphine oxide moieties.

5. FULLERENE PRECURSORS

The first approach to the unconventional synthesis of buckminsterfullerene (C_{60}) and heterofullerenes from polyalkynyl precursors was reported by Rubin [18]. Cyclization of **19** under Hay conditions, in *o*-dichlorobenzene at 25°C, afforded the corresponding macrocyclic cyclophane **20** in 34% yield (Scheme **7**).

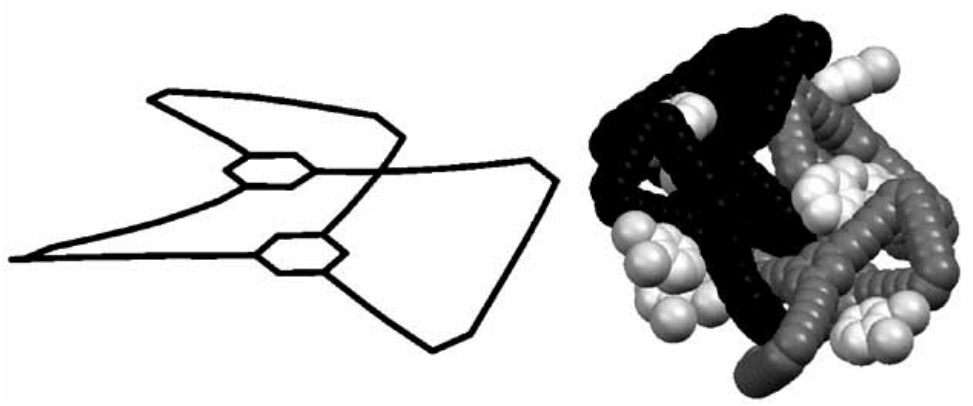
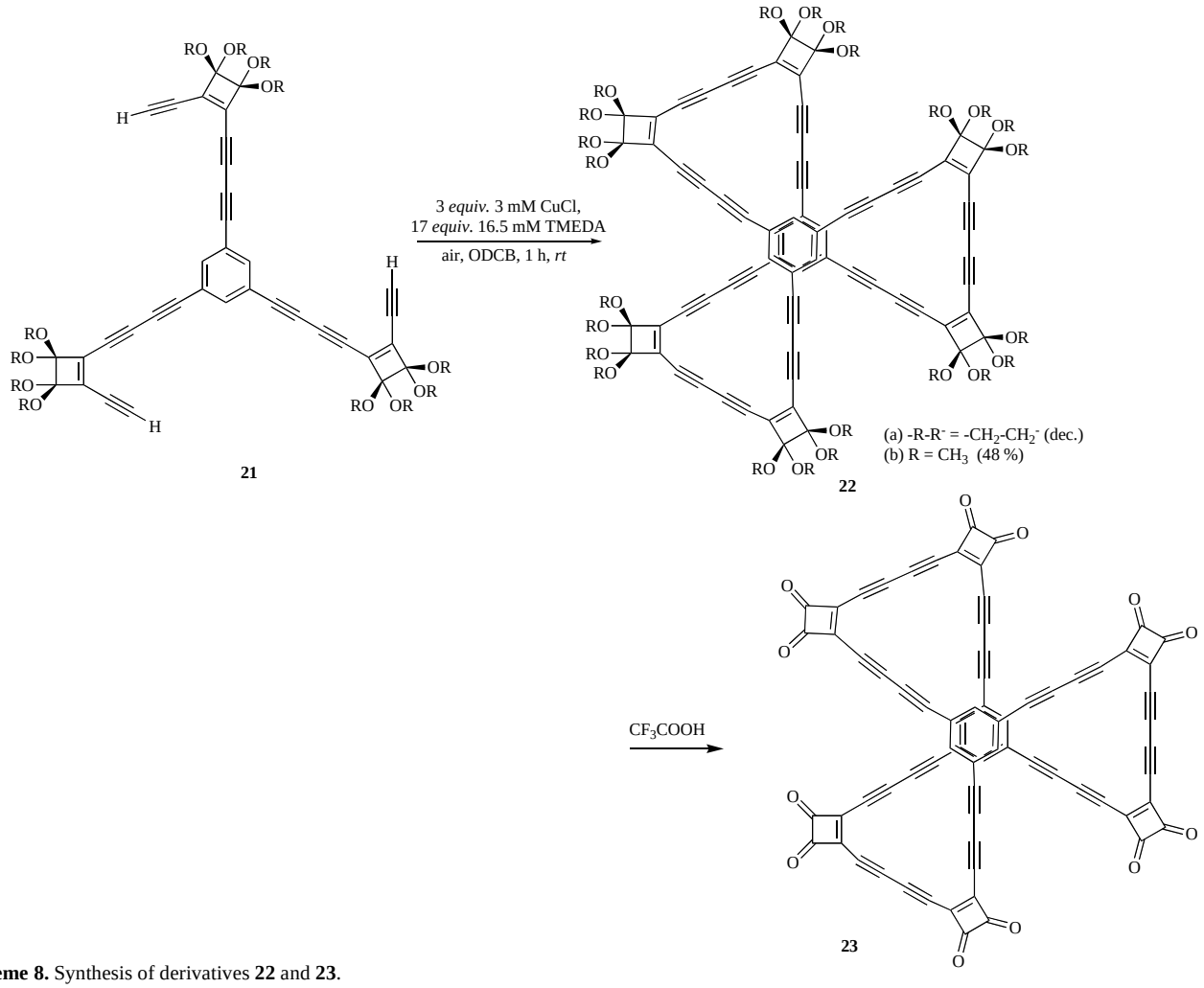


Fig. (6). X-ray structure (**a**) and crystal packing (**b**) for the free cage **20**.

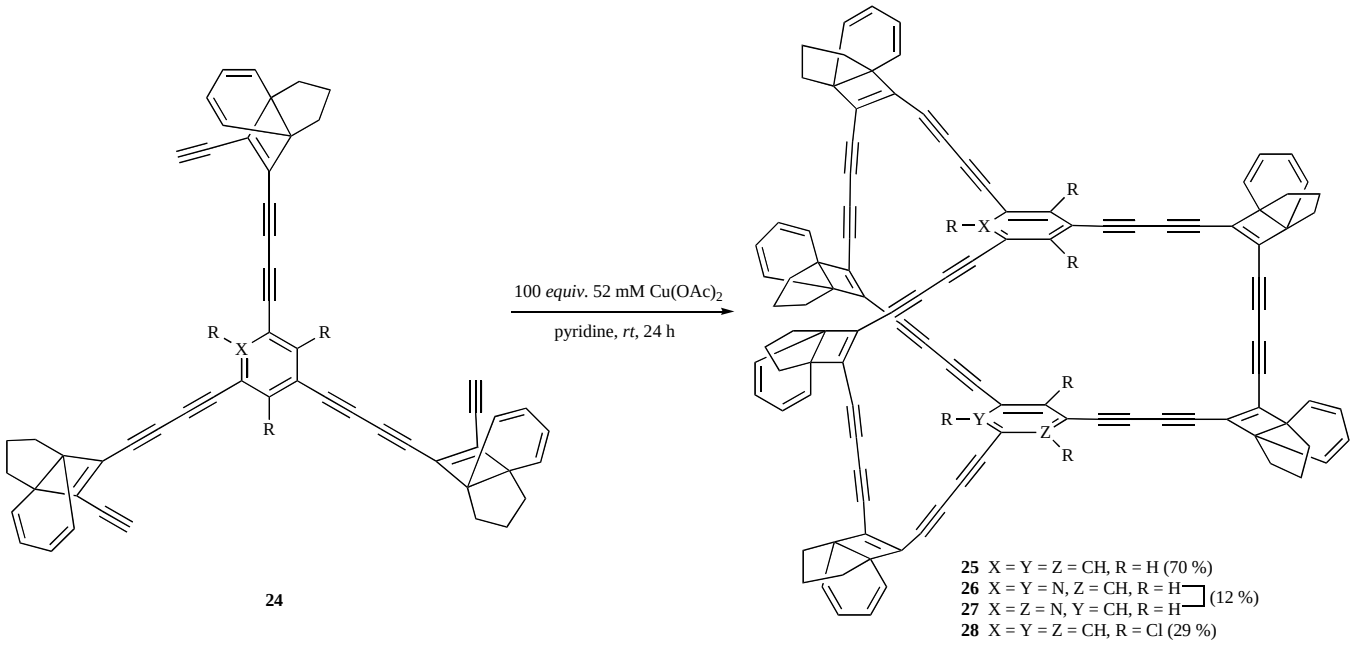


Scheme 8. Synthesis of derivatives **22** and **23**.

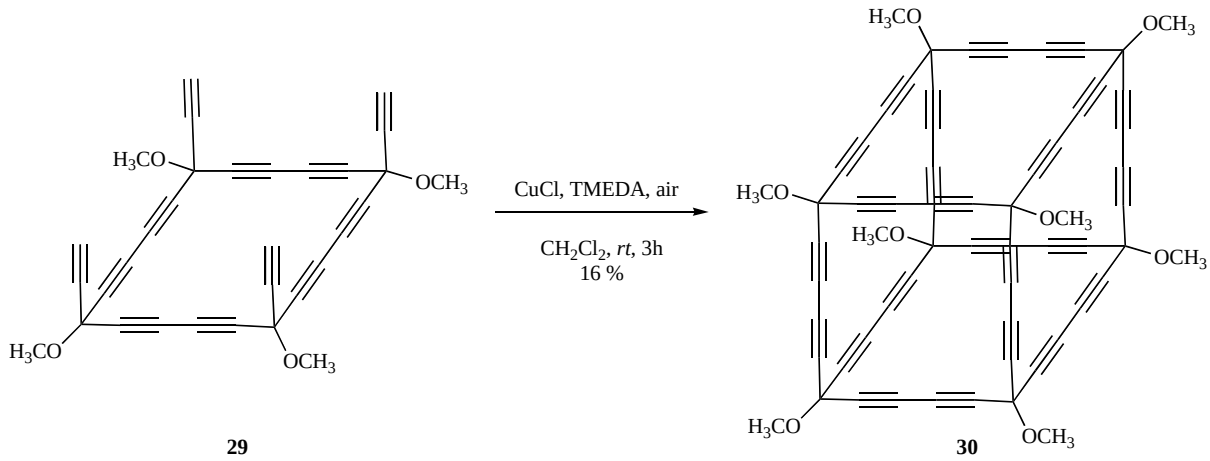
Structure. The single crystal X-ray structure of macrobicyclic compound **20**, together with the partial packing diagram is showing the helical chirality of the structure (Fig. **6**). The only solvent that resulted in well defined crystals was *o*-dichlorobenzene, forming co-crystals with the cyclophane by separating the right handed helices from the opposite-handed partner.

Thermochemical studies on macrocycle **20** have shown an unexpected stability of the parent molecular ion ($C_{60}H_{18}$). Therefore, Rubin and co-workers have synthesized the cyclobutanedione **23** (Scheme **8**) that would rearrange to the more highly unsaturated precursor $C_{60}H_6$ and generates C_{60} ions in mass spectrometric experiments. Cyclization of dimethoxyacetal alkyne **21** [19] (R = CH_3) by a modified Hay procedure (Scheme **8**) has lead to the formation of macrocycle **22** as a solid in a very good yield (48 %).

A different approach in the formation of fullerenes was reported by Tobe and co-workers [20-22]. Cage molecule **25** was synthesized in an impressive 70 % yield by oxidative homoacetylenic coupling under high dilution modified Eglinton conditions (Scheme



Scheme 9. Synthesis of derivatives **25** – **28**.



Scheme 10. Synthesis of derivative **30**.

9). The analogue tris(propellane)trichloro-substitued benzene macrocyclic derivative **28** was obtained in only 29 % yield, probably due to its increased instability.

The same dimerization conditions were followed for the synthesis of macrocyclic polyynes $C_{58}H_4N_2$ (**26** and **27**) as precursors to diazafullerene [23]. The nitrogen substitution of one carbon atom in the benzene ring has lead to the formation of a mixture of both regioisomers in a rather low yield (12 %).

Diederich and co-workers [24] have successfully applied Hay's acetylenic homocoupling conditions for the synthesis of expanded cubane **30** (Scheme **10**). The four-fold oxidative coupling cyclization afforded **30** in a quite low yield (16 %), reasonable when considering its instability.

CONCLUSIONS

The procedures for the one-pot formation of cage molecules by Cu-catalyzed acetylenic coupling uses both Cu (I) and Cu (II) catalysts and acetonitrile, dichlorobenzene, pyridine or dichloromethane as solvents. The yields of these reactions vary from fair to good in agreement with the preorganization and the steric complementarities of the reacting molecules, but the mechanism of this coupling reaction is not yet elucidated. The target cryptands successfully bind neutral molecules such as solvents and aromatic compounds. The host guest interactions are ensured by the participation of the aromatic core of the cryptands and no evidence of the participation of the diyne bridges to this process was revealed. Some of the target molecules were used for the synthesis of fullerenes and heterofullerenes.

ACKNOWLEDGEMENTS

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