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Expedient Synthesis of C_3-Symmetric Hexasubstituted Benzenes via Nicholas Reaction/[2 + 2 + 2] Cycloaddition. New Platforms for Molecular Recognition

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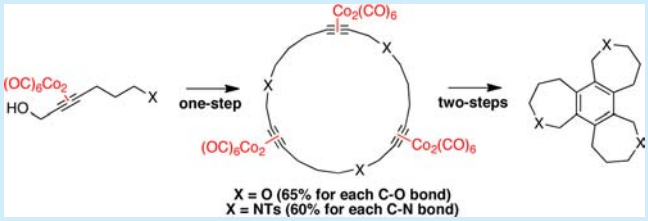
Supporting Information

ABSTRACT: An expedient methodology to synthesize macrocyclic compounds in one step based on the Nicholas reaction is disclosed. The key step features two intermolecular reactions followed by an intramolecular reaction from the starting dicobalt hexacarbonyl–propargylic complex. The macrocycles obtained were modified through [2 + 2 + 2] cycloaddition, generating two new C_3-symmetric hexasubstituted benzene structures suitable for molecular recognition purposes.



In supramolecular chemistry, molecules with a concave surface such as calixarenes, resorcinares, and cyclotriveratrylenes are canonical motifs for designing receptors for neutral or charged guests.[1] Recently, a new family of structurally simpler molecules with a concave surface, known as benzocyclotrimers, has been disclosed as a convenient architecture for molecular recognition.[2]

This class of receptors comprises fused cyclic compounds with a benzene ring at the center forming a small cavity. Fabris et al. have used benzocyclotrimers **1** and **2** with success for gas and cation recognition (Figure 1).[3] In a similar context, Dory's

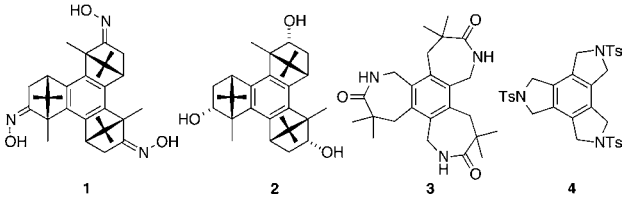


Figure 1. C_3-Symmetric structures.

group revealed a closely related benzocyclotrimer molecule **3** based on a C_3-symmetric tetracycle.[4] This molecule was able to form a tetrameric capsule in the gas phase with a guest molecule of Et_4N^+.

However, structural simplicity not always correlates with a simple synthetic approach. The receptor **3** demands a multistep process in order to obtain a key triacetylenic macrocycle intermediate prior to the final receptor.[5] Although not intended for molecular recognition purposes, Roglans et al. also used a stepwise approach to access a triacetylenic macrocycle precursor to synthesize similar C_3-symmetric tetracyclic compound **4** (Figure 1).[6]

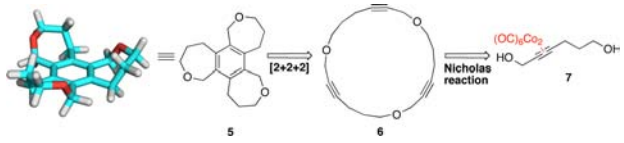
Nonetheless, building a triacetylenic macrocycle through a stepwise route is time-consuming (protection/deprotection steps) and cost inefficient. Thus, it would be highly desirable to develop a method that gains access to these macrocyles in a straightforward manner.

The present work discloses a methodology, based on the Nicholas reaction, to synthesize triacetylenic macrocyle building blocks in one step and their further modification leading to new tetracyclic structures.

Initially, we envisioned the 21-membered triacetylenic macrocycle **6** as the preliminary target. This molecule could be transformed into the tetracycle **5** containing three oxepane rings with enough conformational flexibility to generate a concave surface (Scheme 1).

The Nicholas reaction has proven to be a valuable tool to generate heterocycles of different size based on the nucleophilic attack of a heteroatom on the stabilized carbocation.[8] Therefore, we hypothesized that depending on the reaction conditions compound **6** could result from a convenient

Scheme 1. Retrosynthetic Analysis of Compound 5[7]



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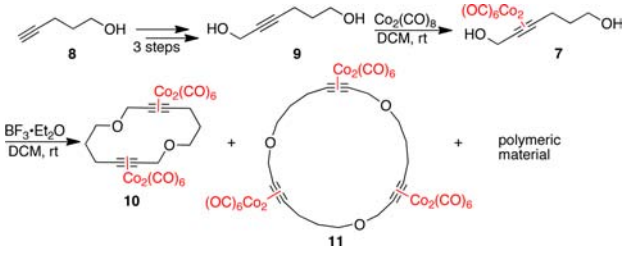
nucleophilic substitution sequence of three units of the dicobalt hexacarbonyl complex **7** (Scheme 1).

To verify our hypothesis, we synthesized the known compound **9**[9] according to the literature protocol in three synthetic steps from the commercially available alcohol **8**. Its complexation with dicobalt octacarbonyl led to the model compound **7**.

Using $CH_2Cl_2/BF_3{\cdot}Et_2O$ to trigger the Nicholas reaction, we were able to isolate the dimer **10** (26% yield) and the desired macrocycle **11** (9% yield), along with polymeric material (Scheme 2).

Scheme 2. Synthesis of Model Molecule 8 and Nicholas Reaction



This initial result encouraged us to search for different reaction conditions in order to improve the overall conversion and the ratio between **10** and **11** (Table 1).[10] Changing the nature of the acid and keeping dichloromethane as solvent, there was a slighlt improvement in the yield and in the **10**/**11** ratio (entries 1−3). From these experiments, the TMSOTf gave the best results (entry 2).

Table 1. Optimization of Reaction Conditions[a]

7 → 10 + 11

entry	acid[b]	solvent	conversion (%) (**10**:**11** ratio)
1	$BF_3{\cdot}Et_2O$	CH_2Cl_2	30 (3.5:1)
2	TMSOTf	CH_2Cl_2	34 (2.4:1)
3	HOTf	CH_2Cl_2	34 (3:1)
4	$BF_3{\cdot}Et_2O$	toluene	47 (1.7:1)
5	**TMSOTf**	**toluene**	**56 (1:1)**
6	HOTf	toluene	48 (1:1)

[a]The reaction time and the temperature in all cases were 90 min and 25 °C, respectively. [b]The best results were obtained when 1.2 equiv of acid was used.

Previous work from our group has demonstrated that toluene is a convenient solvent to perform Nicholas reaction.[11] Accordingly, we decided to study if toluene could influence the reaction outcome in the present case.

We were pleased to find that independently of the acid nature, toluene improved not only the yield but also the product ratio (entries 4−6). From table 1, we can extract that the best conditions were the combination of TMSOTf and toluene (entry 5). Considering that 3 new C−O bond are formed in the whole process, the average is 65% yield for each bond.

Recently, the syntheses of crown ether and natural product based macrocycles using the Nicholas reaction have established the convenience of this reaction as a tool for the dynamic covalent chemistry (DCC) toolbox.[12]

The DCC concept relies on the reversible nature of some reactions leading to products under thermodynamic control. The reversibility of these reactions allows an error-checking/proof-reading event to afford the "right" product.[13] We postulated that perhaps, in the presence of the right stimulus, the dimeric compound **10** could rearrange into the "correct" trimeric compound **11**.

Considering the resemblance of the desired product **11** with a crown ether structure, we imagined that under acidic conditions and the presence of alkali metal salts as template the transformation of **10** into **11** could be promoted. Thus, the dimer **10** was exposed to Nicholas reaction condition in the presence of Li^+, Na^+, and K^+ salts and also in the absence of template (Table 2).

Table 2. Dimer 10 Conversion into Trimer 11

10 → 10 + 11 + polymeric material

entry	acid	solvent[a]	salt	conversion[b] (%) (**10**:**11** ratio)
1	$BF_3{\cdot}Et_2O$	CH_2Cl_2		20 (1:1)
2	$BF_3{\cdot}Et_2O$	CH_2Cl_2	$LiBF_4$	35 (1:1.2)
3	$BF_3{\cdot}Et_2O$	CH_2Cl_2	$NaBF_4$	50 (1:1.31)
4	$BF_3{\cdot}Et_2O$	CH_2Cl_2	KBF_4	50 (1:1.3)
5	TMSOTf	toluene	NaOTf[c]	*d*
6	TMSOTf	toluene		*d*

[a]The starting concentration of the dimer was 0.05 M (at 0.01 M the reaction took longer time without improving the conversion yield). [b]Conversion in this case refers to the total of **10** and **11** recovered after the reaction, and the ratio was calculated by ^1H NMR.[14] [c]In toluene, the $^-BF_4$ salts are unsoluble. [d]The starting material was recovered.

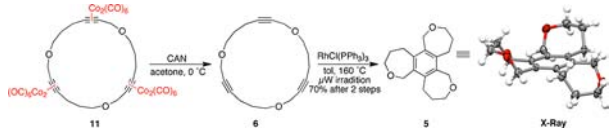
The conversion of the dimeric product **10** into compound **11** took place in all the conditions using $BF_3{\cdot}Et_2O/CH_2Cl_2$ (entries 1−4). However the presence of a template was important to the overall yield and the transformation ratio. The reaction without any cation after 1 h led to a mixture of **10** and **11** in 1:1 ratio along with polymeric material as main product (entry 1). The amount of polymeric material was considerably lower and a better conversion ratio was obtained when Na^+ was present in the reaction media (entry 3, table 2).

These results strongly support the use of the Nicholas reaction in a dynamic covalent chemistry approach.[15] Combining the results from the starting diol **7** and from dimer **10**, the overall yield for **11** is 36%.

The key macrocyle **5** was obtained through decomplexation with CAN, and the [2 + 2 + 2] reaction was performed under microwave irradiation in the presence of Wilkinson's catalyst.[16] As expected, the final product **5** was obtained with 70% yield, which conveniently crystallized for X-ray analysis (Scheme 3).

The mass spectrometry (ESI-MS) is an excellent tool to probe host−guest complex formation in the gas phase.[17] This technique is well suited in cases where the recognition event is not strong enough to overcome the solvation effect in solution phase.[18]

Scheme 3. Cobalt Decomplexation and [2 + 2 + 2] Cycloaddition



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Considering the bowl size and the structural elements of **5**, we envisaged that tetramethylammonium cation would be a convenient substrate to study host–guest complex formation in gas phase. Moreover, dicationic compounds such as *N*,*N*′-dimethyl DABCO or dimethyl viologen could lead to complexes with higher stoichiometry. Therefore, guest solutions were prepared dissolving the respective hexafluorophosphate salts in acetonitrile and the host **5** in dichloromethane. After mixing host and guest solutions in a 2:1 ratio, the complexation was investigated in positive electrospray mass spectrometry (50 μM complex concentration).

The mass spectrometry of the Me_4N^+–host mixture revealed a 1:1 complexation stoichiometry.[14] However the base peak corresponds to the complex formation between host **5** and sodium ion in 2:1 stoichiometry, suggesting that under these conditions Na^+ is a better guest for **5**. We have also identified minor peaks corresponding to host–sodium 1:1 and host–NH_4^+ complexes in 1:1 and 2:1 stoichiometry. The 2:1 stoichiometry for host–Me_4N^+ was not observed.[14]

Surprisingly, with the dication substrates (*N*,*N*′-dimethyl-DABCO and dimethylviologen) the receptor was able to form complexes in higher stoichiometry. In the case where dimethylviologen was the guest, we could identify complex formation in 1:1, 2:1, and 3:1 stoichiometry. Among these complexes, the 1:1 supramolecular peak was the most prominent.[14] The *N*,*N*′-dimethyl-DABCO complexation followed a pattern similar to that of dimethylviologen; nonetheless, the 2:1 host–guest complex (359.2401) was the favored structure. The doubly charged complex can be unequivocally characterized by the 0.5 mass unit increments in the isotopic distribution (Figure 2). Moreover, the host–guest complex 2:1

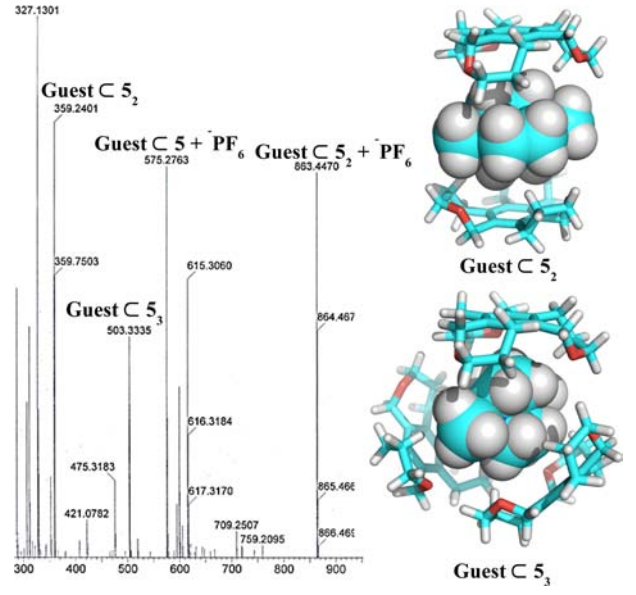


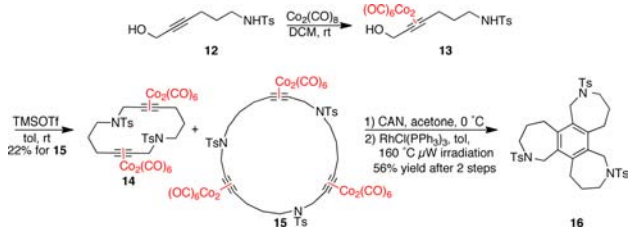
Figure 2. Complex formation in gas phase with *N*,*N*′-dimethyl-DABCO. The computational models were minimized using MM+ force field (HyperChem 8.0.3 Molecular Modeling).

was detected with and without the PF_6^- anion. Based on the experimental evidence, we propose computational models for 2:1 and 3:1 host–guest complexes (Figure 2). Similar experimental observations were reported for a 2:1 complex formation with resorcinarene: *N*,*N*′-dimethyl-DABCO in gas phase.[19]

Having established the synthetic conditions for compound **5**, we decided to extend our protocol to a nitrogenated version.

It is known that sulfonamide can act as suitable nucleophile in the Nicholas reaction.[8c] Thus, we synthesized compound **12** as described in the literature.[20] After cobalt complexation, the Nicholas reaction was performed with the optimized conditions (Table 1, entry 5). To our delight, the compound **13** behaved almost identically to its oxygenated homologous, leading to the desired trimeric compound **15** with 22% yield (60% yield for each C–N bond) along with the dimer **14** (20%) (Scheme 4).

Scheme 4. Nitrogenated Version



The dimeric compound **14** could not be converted into the trimer **15**. This was not completely unexpected, since for the Nicholas reaction to proceed, it is necessary to have an alcohol, ether or acetate derivative at the propargylic position.

Cobalt decomplexation and [2 + 2 + 2] cycloaddition were identical as described for the **11**. The new tetracycle compound **16** containing three azepane rings fused to the benzene core was obtained with 56% overall yield after two steps (Scheme 4). From a synthetic standpoint, the new tetracycle **16** is a valuable scaffold to build more complex receptors, since the sulfonamide deprotection would unmask the amine functionality conveniently for further derivatization.

In conclusion, we have developed an expedient protecting group free methodology for macrocyclization based on the Nicholas reaction. The present method highlights the suitability of the Nicholas reaction for a dynamic combinatorial chemistry concept and generates in one-step triacetylenic macrocycles in moderate yield. The final tetracycles were efficiently achieved through a [2 + 2 + 2] cycloaddition reaction, completing a synthetic route in a few steps. Finally, the tetracycles obtained here present important features for molecular recognition purposes and modifications on the nitrogenated scaffold are currently in progress in our laboratory and will be published in due time.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details and characterization data for all new compounds. 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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(14) For details, see the Supporting Information
(15) Curiously, the optimized conditions found previously (Table 1, entry 5) did not promote the conversion, and the starting material was completely recovered (entries 5 and 6, Table 2). This result indicates that these conditions are less harsh for generating the Nicholas carbocation than $BF_3{\cdot}Et_2O/CH_2Cl_2$ conditions.
(16) We have tried the [2 + 2 + 2] reaction with the compound **11**; however, we did not obtain the desired compound **5**. This result can be explained on the basis of the [2 + 2 + 2] mechanism, where two uncomplexed alkynes are necessary to form the key intermediate with the dicobalt complex in order to access the corresponding arene. See: Baxter, J. R.; Nox, G. R.; Pauson, P. L.; Spicer, M. D. *Organometallics* **1999**, *18*, 197.
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