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Synthesis of New Benzocyclotrimer Analogues: New Receptors for Tetramethylammonium Ion Recognition

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Supporting Information

ABSTRACT: Using a [2 + 2 + 2] cycloaddition/Mitsunobu reaction sequence, a convenient synthesis to access new benzocyclotrimer analogues has been developed. The new receptors have the geometry and functionality capable of recognizing the tetramethylammonium ion in the gas phase and in solution.

Benzocyclotrimers (BCTs) are C_3 symmetric fused cyclic compounds with a benzene ring at the center forming a small cavity. This class of molecules has generated new receptors for molecular recognition purposes.[1a] Fabris' and Badjić's groups have taken advantage of the BCTs structural features to develop interesting molecular capsules and baskets for gas recognition in solution.[1]

Recently, our group has reported an efficient methodology for the synthesis of BCT analogues containing oxepane (**1**) and azepane (**2**) rings (Figure 1).[2] Our method was based on a one-step process, featuring two intermolecular and one intramolecular Nicholas reaction to form a key macrocycle intermediate. This macrocycle was transformed into the corresponding BCT analogue after performing a [2 + 2 + 2] intramolecular cyclotrimerization (Scheme 1A). Besides the ease in synthesis, we demonstrated that compound **1** could recognize ammonium ions in the gas phase.[2]

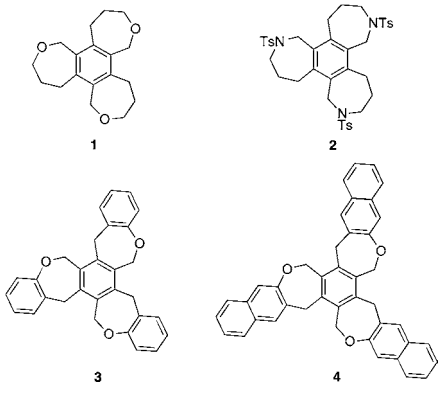
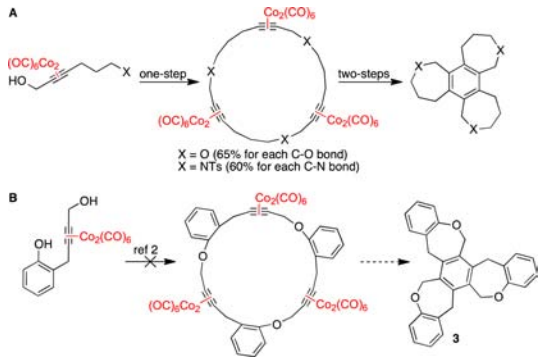


Figure 1. Benzocyclotrimers analogues.

Using compound **1** as a platform to design new hosts, we envisioned the possibility of building aromatic walls on its

Scheme 1(A) Methodology for the Synthesis of BCT Analogues Containing Oxepane (1) and Azepane (2) Rings; (B) Attempted Synthesis of Compound 3 Using Methodology[a]



[a]See ref 2 for previous methodology details; ref 2 conditions also used to synthesize **3**.

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structure to enhance noncovalent interactions such as cation−π and/or CH−π. Thus, compounds **3** and **4** were designed with the expectation to exhibit stronger affinity toward ammonium ions compared to parent molecule **1** (Figure 1).

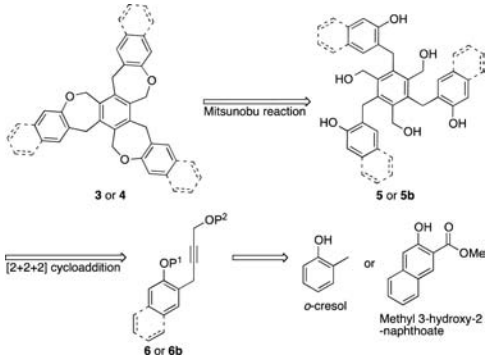
When we attempted to synthesize **3** using our previous methodology, the key macrocyclic complex suitable for the [2 + 2 + 2] cycloaddition reaction could not be obtained (Scheme 1B).

From a synthetic standpoint, adding convenient functional groups to BCTs (or BCTs analogues) can be synthetically challenging and may demand multistep synthesis. Therefore, methods allowing access to functionalized platforms in a straightforward manner are highly desirable.[3]

The present communication discloses a convenient approach to synthesizing new BCTs analogues based on a [2 + 2 + 2] cycloaddition/Mitsunobu reaction sequence. Moreover, we demonstrate the ability of the designed new hosts **3** and **4** to recognize tetramethylammonium ions (TMA^+) in the gas phase and in solution.

In the retrosynthetic analysis of **3**, a phenolic Mitsunobu reaction of hexasubstituted benzene **5** could afford the desired compound in one step. The synthesis of this key intermediate, with the substituents disposed in an alternate configuration, could be performed through [2 + 2 + 2] cycloaddition of the conveniently protected alkyne **6**. As a precursor of **6**, the commercially available *o*-cresol was anticipated as starting material (Scheme 2).

Scheme 2. Retrosynthetic Analysis for Receptor 3 and 4

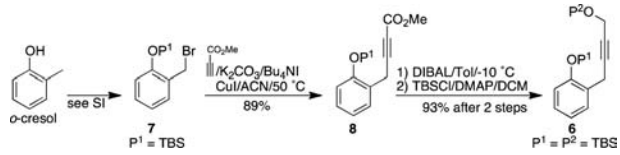


This retrosynthetic analysis can also be applied to **4**; however, the starting material for its synthesis would be the likewise commercially available methyl 3-hydroxy-2-naphthoate (Scheme 2).

Starting from the *o*-cresol, the hydroxyl group was protected as the silyl ether in excellent yield. The protected *o*-cresol was reacted with *N*-bromosuccinimide providing the benzylic bromide **7**. The coupling of the alkyne moiety was performed using methyl propiolate assisted by copper iodide providing the compound **8**.[4] The reduction of ester functionality was effected using DIBAL as a reducing agent, followed by protection of the propargylic alcohol with TBSCl giving compound **6** ($P^1 = P^2$ = TBS) (Scheme 3).

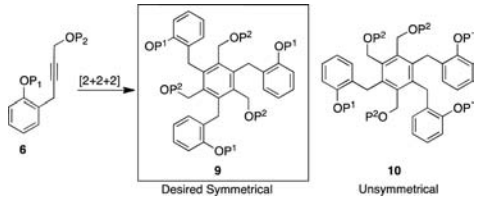
The cyclotrimerization of alkynes mediated by transition metals is a well-established strategy to obtain polysubstituted arenes in a direct way.[5] Thus, a cyclotrimerization of compound **6** would allow access to the benzene central core of the BCT analogue **3** in one step with the substituents conveniently positioned. Nevertheless, the main drawback of this approach with nonsymmetric substituted acetylenes, such as **6**, is the

Scheme 3. Synthesis of Compound 6



concurrent formation of the undesired benzene core with an unsymmetrical substitution pattern (Scheme 4).

Scheme 4. Products from the Cyclotrimerization Reaction of 6



In order to favor the formation of the symmetrical compound **9**, we decided to investigate different catalysts and the influence of the protecting groups on the acetylene **6** in the cycloaddition reaction outcome.

Initially, we investigated a range of catalysts capable of promoting the [2 + 2 + 2] cycloaddition of **6** with a view to ascertaining their selectivity to giving the symmetrical intermediate **9** (Table 1).

Table 1. Summary of the Optimization Conditions

entry	P^1/P^2	cat.	solv.	**9**:**10**	overall yield
1	TBS/TBS	$Co_2(CO)_8$	Tol	1:7	68%
2	TBS/TBS	$RhCl(Ph_3P)_3$	Tol	–	NR
3	TBS/TBS	$NiBr_2$, Mg	THF	–	NR
4	TBS/TBS	10% Pd(C), TMSCl	THF	–	NR
5	TBS/TBS	$RhCl_3{\cdot}3H_2O$	Tol	–	NR
6	TBS/TBS	$CoCp(CO)_2$	Tol	–	NR
7	TBS/TBS	$Rh_2(C_7H_{15}CO_2)_2$	Tol	–	NR
8	TBS/TBS	$[IrCl(cod)]_2$	Tol	–	NR
9	TBS/TBDPS	$Co_2(CO)_8$	Tol	1:4	71%
10[a]	TBS/Tr	$Co_2(CO)_8$	Tol	1:3	80%
11	TBDPS/TBDPS	$Co_2(CO)_8$	Tol	1:4	68%

[a]See the Supporting Information for experimental details.

To our surprise, among the eight catalysts investigated only the $Co_2(CO)_8$ promoted the cyclotrimerization reaction (Table 1, entry 1). Despite the good yield obtained with this catalyst, the ratio between the symmetrical compound **9** and the unsymmetrical product **10** was poor (1:7, respectively).

We then turned our attention to determining the influence of the protecting group on the alkyne **6**. Changing the TBS group on the propargylic position to a bulkier protecting group, such as TBDPS or trityl (Tr), improved both the reaction yield and the ratio **9**:**10** to a synthetically useful one (entries 9 and 10, Table 1). Changing both protecting groups on molecule **6** to the larger TBDPS group did not increase the yield or the selectivity (entry 11, Table 1).

Using the optimized conditions (entry 10, Table 1), the receptor **3** could be easily obtained after deprotection of compound **9**, leading to the hexaol **5**, followed by the

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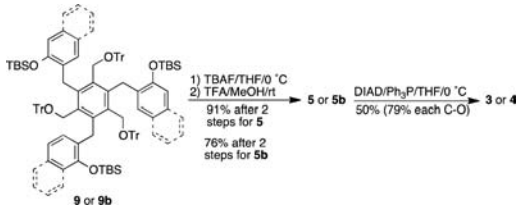
Mitsunobu reaction (Scheme 5). It is important to highlight that, in this step, three C−O bonds are formed in one step with an average 79% yield in each oxepane formed.

Scheme 5. Synthesis of Receptor 3 and 4



For the synthesis of receptor **4** we have applied a slightly different synthetic route to access the alkyne intermediate previous to the cyclotrimerization reaction (see the Supporting Information (SI)).

Using the [2 + 2 + 2] cycloaddition conditions developed previously, the reaction proceeded with good conversion (78% yield) and better selectivity (1:2.2, symmetrical/unsymmetrical; see the SI). Following the same reaction conditions used for receptor **3**, the desired receptor **4** was obtained from **9b** (Scheme 5).

Some groups have developed new receptors for recognition of TMA^+ as a potential tool toward understanding and identifying methylated lysine residues in proteins modified post-translationally.[6] In the protein−protein interaction of these modified proteins, the methylated lysine residue binds to a pocket rich in aromatic amino acids, also known as an "aromatic box".[7]

Considering that BCT analogues **3** and **4** have the flexibility to adopt a vase-type conformation (Figure 2) and the presence

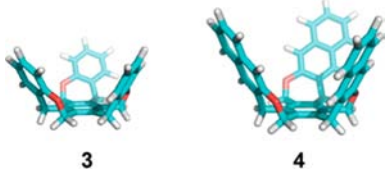


Figure 2. Computational models generated using SPARTAN 14 DFT/B3LYP/6-31G*.

of aromatic walls (4 and 7 respectively), we focused our attention on investigating their ability to emulate an "aromatic box" and recognize the TMA^+. It is worth mentioning that **3** and **4** are chiral molecules depending on the direction of the vase conformation adopted (*P*/*M*) and at room temperature both molecules are present as a racemic mixture. Recently, the synthesis and resolution of twisted baskets with similar chirality have been reported.[8]

We began the recognition studies performing a series of ESI-MS experiments using the receptors **3** and **4** to recognize the TMA^+ in gas phase. A series of solutions of tetramethylammonium acetate (TMAAc) and either receptor **3** or **4** were prepared separately. For each receptor molecule, three solutions with TMAAc at different host−guest stoichiometries (1:1, 2:1 and 4:1; see the Supporting Information) were analyzed. Both receptors, independently of the stoichiometry, gave clean ESI-mass spectra where the supramolecular complexes 1:1 host−guest were the most intense signal. Apart from the 1:1 host−guest complexes (*m*/*z* 506-TMA^+@**3** and *m*/*z* 656-TMA^+@**4**), the 2:1 host−guest complexes are also formed (*m*/*z* 938-TMA^+@$\mathbf{3}_2$ and *m*/*z*-1238 TMA^+@$\mathbf{4}_2$), suggesting a pseudocapsule formation (Figure 3).

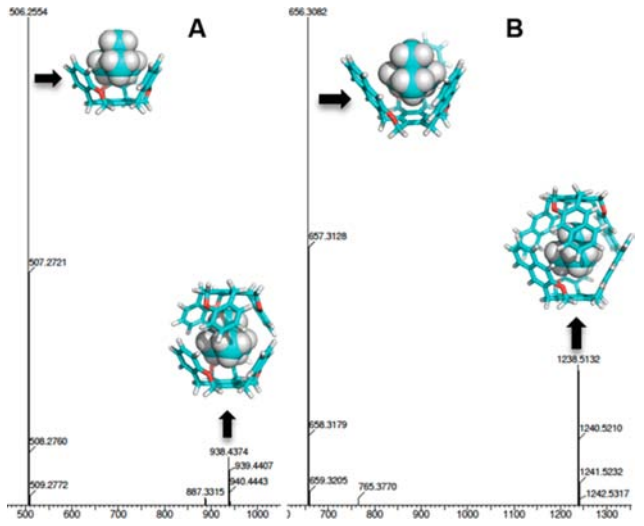


Figure 3. (A) ESI-MS experiment with **3**:TMAAc (1:1) at 50 μM. (B) ESI-MS with **4**:TMAAc (1:1) at 50 μM. The computational models were generated using SPARTAN 14 DFT/B3LYP/6-31G*.

Encouraged by the results obtained in the gas phase, we analyzed the recognition process in solution performing a ^{1}H NMR titration experiment.

Starting with the receptor **3**, and/while keeping the TMAAc concentration constant, increased amounts of **3** were added to the salt solution. The continuous upfield shift of the methyl group resonance due to the shielding effect of the aromatic walls present on the host indicates a fast exchange recognition process on the NMR time scale (Figure 4). The stoichiometry

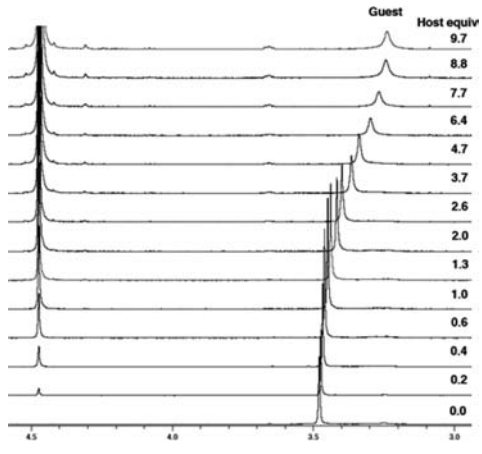


Figure 4. ^{1}H NMR titration experiment adding host **3** to a constant concentration of guest (1.25 mM, $CDCl_3$, 298 K).

of the process was determined through a Job's plot experiment, and its analysis suggested a mixture of complexes (1:1 and 2:1) with 2:1 host/guest stoichiometry being more favored (see the SI).

To calculate the binding constant, WinEQNMR[9] was used to fit the experimental data into a model containing 1:1 and 2:1 species. We were pleased to observe that experimental values are in good agreement with the theoretical ones, resulting in a

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K_1 constant of 32 ± 4 M^{-1} and K_1K_2 product of 5320 ± 806 M^{-2} (see the SI).

In the case of receptor **4**, its low solubility in $CDCl_3$ required a titration in which the concentration of **4** was kept constant, while increased amounts of TMAAc were added to the host solution. At these experimental conditions, the ammonium methyl group resonance suffered a relatively small downfield shift when increasing the guest concentration. In contrast to receptor **3**, the Job's plot experiment suggested the presence of a mixture of 1:1 and 2:1 host–guest complexes, but with a tendency to a 1:1 stoichiometry at higher guest concentration (see the SI).

Unfortunately, perhaps due to the presence of both complexes, 1:1 and 2:1, a reliable binding constant could not be obtained.

To understand the difference in the complexation stoichiometry tendency between hosts **3** and **4**, it is important to bear in mind that although TMAAc is soluble in $CDCl_3$, due to the low dielectric constant of the solvent, it is extensively ion paired. In such circumstances the ion pair can be considered as being a single species.[10] Thus, in the recognition event involving the host **3**, there are two molecules of **3** and one ion paired species. The computational model suggests a distorted pseudocapsule partially opened with enough room to accommodate the ion pair (Figure 5).

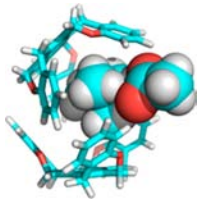

Figure 5. Computational models were generated using SPARTAN 14 DFT/B3LYP/6-31G*.

In the case of the receptor **4**, a plausible explanation for the more favored 1:1 host–guest stoichiometry could be the larger size of the naphthalene wall. In order to accommodate the ion pair in a pseudocapsule, the two-receptor halves have to tilt to make room for both ions (Figure 5). In an eventual situation where a pseudocapsule is formed by receptor **4**, there is no room for tilting the halves without causing unfavorable steric and electrostatic interactions between the naphthalene walls and the anion.

In summary, we have developed a useful method to access new BCT analogues through a simple synthetic route. The receptors **3** and **4** have demonstrated to be suitable for recognition of the TMA^+ in the gas phase and in organic solvent ($CDCl_3$) as an ion pair. We are currently working on a water-soluble version of the receptors presented here, and the results will be published in due course.

■ ASSOCIATED CONTENT

Supporting Information

Full experimental details, spectroscopic data, and copies of NMR spectra. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01058.

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Notes

The authors declare no competing financial interest.

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