Synthesis of Functionalized Resorcin[4]arene via Click Chemistry

Ali Husain

University of South Florida

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via Click Chemistry

by

Ali Husain

A thesis submitted in partial fulfillment of the requirements for the degree of
Master of Science
Department of Chemistry
College of Arts and Sciences
University of South Florida

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<tr>
<td>CC</td>
<td>Click Chemistry</td>
<td>1</td>
</tr>
<tr>
<td>DMF</td>
<td>N,N-Dimethylformamide</td>
<td>9</td>
</tr>
<tr>
<td>IL</td>
<td>Ionic liquids</td>
<td>11</td>
</tr>
<tr>
<td>NMR</td>
<td>Nuclear magnetic resonance</td>
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<td>MW</td>
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<tr>
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<td>Azobisisobutyronitrile</td>
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<td>TLC</td>
<td>Thin layer chromatography</td>
<td>46</td>
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<tr>
<td>DCM</td>
<td>Dichloromethane</td>
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<tr>
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<tr>
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<td>Sodium hydride</td>
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<td>THF</td>
<td>Tetrahydrofuran</td>
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<td>DIPEA</td>
<td>Diisopropylethylamine</td>
<td>55</td>
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<tr>
<td>BF₃</td>
<td>Boron trifluoride</td>
<td>59</td>
</tr>
<tr>
<td>$S_{N2}$</td>
<td>Nucleophilic substitution</td>
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Synthesis of Functionalized Resorcin[4]arene via Click Chemistry

Ali Husain

ABSTRACT

Click chemistry is a very powerful chemical strategy that overcome carbon-carbon bond with carbon-heteroatom bond by joining small units with heteroatom links (C-X-C) using spring-loaded reactants. The Cu(I)-catalyzed Huisgen 1,3-dipolar cycloaddition is a major example based on the click chemistry philosophy. This method was used for the last 10 years to join different functional groups, carbohydrates, aminoacids, polymers to calix[4]arene and resorcin[4]arene cavitands by a stable 1,2,3-triazole linkages.

Herein I describe our interest in this type of click chemistry reaction in the synthesis of dimeric capsules resorcin[4]arene via four 1,2,3-triazole linkages. Two different resorcin[4]arene derivatives were synthesized in which four azide and four alkyne functional groups were attached on the upper rim of two different resorcin[4]arenes. The dimerization reaction was quite challenging due to steric factors. Each resorcin[4]arene derivative was then studied individually via click chemistry and all click reaction results were excellent and the products were isolated in good yields. These results enhanced the synthesis of the dimeric resorcin[4]arene.
CHAPTER 1
INTRODUCTION

1.1. Introduction to Click Chemistry

Click chemistry (CC)\textsuperscript{1} is a powerful strategy that depends mainly upon joining small units with heteroatom links (C-X-C) using spring-loaded reactants. The aim of this strategy is the development of an expanding set of powerful, selective, and modular blocks that work quantitatively in both small and large scale applications.\textsuperscript{1}

1.2. The Click Chemistry Approach

Click chemistry (CC)\textsuperscript{1} is a chemical philosophy that was introduced in 2001 by K. Barry Sharpless and co-workers\textsuperscript{1}. A set of standards that click chemistry (CC)\textsuperscript{1} encourage has been defined by Sharpless and co-workers- reactions must be modular, wide in scope, obtain very high yields, generates only inoffensive and safe by-products that can be easily removed, and be stereospecific. The click chemistry reaction requires simple reaction conditions, readily available starting materials and reagents, the use of benign or easily removed solvents, and simple product isolation other than chromatographic methods such as distillation and crystallization.\textsuperscript{1}

Several reactions (Scheme 1) have been identified which can be named under click chemistry such as nucleophilic substitution chemistry, specifically ring-opening
reactions of epoxides, aziridines, aziridinium ions etc.; non-aldol carbonyl chemistry: formation of ureas, oximes and hydrazones etc.; addition reactions to carbon-carbon multiple bonds, especially oxidative addition, and Michael additions of Nu-H reactants; and cycloaddition reactions: in particular the Huisgen 1,3-dipolar cycloaddition reactions, but also the Diels-Alder reactions.\textsuperscript{1,2}

![Scheme 1. A selection of reactions which match the click chemistry criteria.\textsuperscript{2}](image)
1.3. Cu(I)-catalyzed Huisgen 1,3-dipolar Cycloaddition of azide and alkyne

Cu(I)-catalyzed 1,3-dipolar cycloaddition reaction also known as the Huisgen 1,3-dipolar cycloaddition reactions\(^3\) as was first introduced as a major example of click chemistry by Sharpless and co-workers. This reaction is known as the “cream of crop” of all reactions that matches the click criteria. This type of click chemistry\(^1\) reaction takes place between an organic azide and a terminal alkyne, resulting in a five member heterocyclic 1,2,3-triazole. This reaction is irreversible and high yielding with no side products. Both alkynes and azides are stable and do not react with themselves and the reaction is tolerant of a wide range of functional groups, the trizole which results from the azide-alkyne coupling is a thermally and hydrolytically stable conjugated linkage. The reaction procedure requires no protecting groups, and proceeds with quantitative conversion and selectivity for the 1,4-disubstituted 1,2,3-triazole (\textit{anti}-1,2,3-triazole) in the presence of Cu(I) as a catalyst. In the absence of the Cu(I)-catalyst, a mixture of 1,5-disubstituted (\textit{syn}) and 1,4-disubstituted (\textit{anti}) 1,2,3-triazole is formed (Scheme 2).\(^{1,2,4}\)

The Cu(I)-catalyzed Huisgen reaction, an example of [3+2] cycloaddition, is one of the most widely studied reactions based on the click chemistry philosophy. This highly efficient reaction occurs under benign conditions and has formed bai of ingenious methodologies for constructing materials that have found use in many applications in a relatively short period of time.\(^{1,2,4}\)
Scheme 2. Cu(I)-catalyzed Huisgen 1,3-dipolar cycloaddition of azide and alkyne.²

The reaction mechanism of the Cu(I) catalyzed 1,3-dipolar Huisgen cycloaddition between an azide and an alkyne is drawn in (Scheme 3). The copper(I) first coordinates to the triple bond of the alkyne to form a Cu(I)-acetylide complex via π-complex making the alkyne proton more acidic which can be easily abstracted in the presence of a base to form the copper acetylide intermediate. In the transition state, two copper ions are involved- the first copper ion is bonded to the acetylide while the other activates the azide by coordinating with the electrons on the nitrogen atom in the azide compound. The azide then displaces one of the ligands to generate copper-azide-acetylide complex. Furthermore, cyclization takes place followed by protonation to form 1,2,3-triazole.⁴,⁵
Scheme 3. Copper(I)-catalyzed click chemistry mechanism.

1.4.1. **Synthesis of Sugar-Calix[4]arene via Click Chemistry**

Sugars were first attached to calix[4]arenes via copper(I)-catalyzed azide-alkyne cycloaddition by Santoyo-Gonzalez and coworkers.\(^6\) Santoyo-Gonzalez synthesized glycoconjugate as a mixture of 1,4- and 1,5-disubstituted 1,2,3-triazole rings (Scheme 4).

![Chemical structure](image)


Obviously, the product was obtained as a mixture of 1,4- and 1,5-disubstituted 1,2,3-triazole and the long period of time reaction is due to the absence of Cu(I)-catalyst.
Dondoni and Marra\textsuperscript{7} reported the use of click reaction for multiple carbohydrate calix[4]arene scaffolds. Two divalent and four tetravalent sugar-calix[4]arene derivatives were synthesized successfully (Table 1). The click reactions were carried out using CuI, DIPEA in toluene at room temperature. Interestingly, the peracetoxy sugar’s coupling was higher yielding than the perbenzylated; due to the steric factors- the perbenzylated sugar is bulkier than the peracetoxy sugar. Similarly, the divalent sugar-calix[4]arene derivatives were formed in higher yield than the tetravalent because of the increased steric bulk of the four sugars connected and pointing at the same direction on the upper rim of the calix[4]arene is considerably higher than the two sugars.
**Table 1.** Divalent and tetravalent sugar-calix[4]arenes.

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<tr>
<td><img src="image1" alt="Calix[4]arene structure" /></td>
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<td><img src="image3" alt="Sugar-calix[4]arene structure" /></td>
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<td><img src="image4" alt="Calix[4]arene structure" /></td>
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<td><img src="image7" alt="Calix[4]arene structure" /></td>
<td><img src="image8" alt="Sugar structure" /></td>
<td><img src="image9" alt="Sugar-calix[4]arene structure" /></td>
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R = Bn, Ac
Bew and co-workers\(^8\) have described the application of click chemistry (CC)\(^1\) for the synthesis of hybrid calix[4]arenes with \(N,C\)-protected \(\alpha\)-amino acids and carbohydrates (Scheme 5) on the upper rim. Several hybrid calix[4]arenes were synthesized including disaccharides listed in (Table 2) and reaction conditions was optimized. The use of copper(II) sulfate and sodium ascorbate to generate Cu(I) \textit{in-situ} in anhydrous DMF at 90\(^0\)C using microwave irradiation led to faster reaction and higher product yield.

Scheme 5: “Click” Chemistry Derived upper Rim Hybrid Calix[4]arene
Table 2. Hybrid calix[4]arenes.

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<tr>
<td><img src="image7" alt="Diagram 7" /></td>
<td><img src="image8" alt="Diagram 8" /></td>
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More recently, Dondoni, Marra and co-workers\textsuperscript{9} have reported the click reaction using ionic liquids (ILs). Ionic liquids (ILs) have the ability to solve many problems including safety and environmental concerns. The ILs are good microwave (MW) absorbers and their use in microwave may yield a new and green synthetic method.\textsuperscript{10} Indeed the click reaction under MW heating was much faster than under thermal heating, i.e., 2 h vs 16 h in 65 to 90 \% product yield (Scheme 6).


Calix[4]arene-based C-glycosides were synthesized by taking the advantages of the expertise of an Italian team on calix[4]arene functionalization multivalent glycocluster-oligonucleotide hybrids in which these multivalent sugar-calix[4]arenes
relied on the DNA-based microarray methodology developed by the French group (Figure 1) and (Figure 2).\textsuperscript{11}

![Chemical structures](image)

**Figure 1.** lower rim azido group C-Glycosyl calix[4]arenes.
Dondoni, Marra and co-workers\textsuperscript{12} synthesized sialyl clustering calix[4]arene derivatives \textit{via} C(I)-catalyzed azide-alkyne cycloaddition (\textbf{Table 3}). The higher density of the silyl groups on the calix[4]arene results in higher coupling with hemagglutinin trimers located onto a single virion or to two distinct viral particles.

\textbf{Figure 2.} Multivalent glycocluster-oligonucleotide hybrids.

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<td><img src="image7.png" alt="Diagram" /></td>
<td><img src="image8.png" alt="Diagram" /></td>
<td><img src="image9.png" alt="Diagram" /></td>
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In an interesting approach, Dondoni, Marra and their coworkers used to different click approaches, i.e., thiol-ene coupling and azide-alkyne cycloaddition, to synthesize calix[4]arene glycoside clusters. Tetraalkene on the upper rim and tetraalkyne in the lower rim of the calix[4]arene was treated with peracetylated α-D-linked galactosylmethyl azide and protected β-D-linked galactosymethyl azide (azide-alkyne cycloaddition) (Table 4).

Table 4. tetravalent sugar-calix[4]arene.
Cecioni\textsuperscript{14} et al. used microwave-assisted copper(I)-catalyzed azide-alkyne cycloaddition to synthesize sugar-calix[4]arene hybrid on the lower rim, with a range of substitutions and conformational arrangements (\textbf{Scheme 7 and 8}).

**Scheme 8.** Synthesis of the three conformational isomers of tetrapropargyl calix[4]arenes.

All seven alkyne-calix[4]arene derivatives underwent cycloaddition with extended azido-galactose and only tetravalent alkyne-calix[4]arene was furthermore treated with extended azido-mannose (Scheme 9). Because of the lower steric bulk, the mono- and 1,3-disubstituted calix[4]arene glycoconjugate were synthesized in higher yield than the tetravalent cone calix[4]arene glycoconjugate. From NMR spectroscopic analysis it was confirmed that no ring inversion occurred during the cycloaddition reaction.
1.4.2. **Click chemistry on calix[4]arenes immobilized onto solid surfaces**

In a recent report\(^{15}\) described the synthesis of metal and metal oxide glyconanoparticles coated by monolayer sugar-calix[4]arene via click chemistry (Schemes 10 and 11). With well defined structure and composition of the hybrid
glyconanoparticles the authors expect to constitute a good biometric model of carbohydrate in a globular and polyvalent configuration which due to multivalent interaction can compensate for the low affinity of carbohydrates for their receptors.

A calix[4]arene with tetraazide on the upper rim and tetracarboxyl on the lower rim was first used to form the titanium dioxide nanoparticles followed by a click cycloaddition reaction of the alkynyl carbohydrate to afford the glyconanoparticles.

**Scheme 10.** Synthesis of the nanoparticles.
**Scheme 11.** Synthesis of the glyconanoparticles.


Calix[4]arenes are attractive building blocks in supramolecular chemistry. In particular, water soluble calix[4]arenes due to their well formed hydrophobic cavities make it possible to study molecular recognition in water. Ryu and Zhao used click chemistry which is particularly suitable for attaching water soluble groups. It is modular, tolerant of wide range of solvents and functional groups, simple to proceed and high yielding.

Several water soluble calix[4]arenes have been synthesized via Cu(I) catalysed Huisgen 1,3-dipolar cycloaddition reaction. These compounds were prepared through two complementary pathways (Scheme 12). The first pathway is the synthesis of tetravalent alkynyl calix[4]arene in the lower rim which was then treated with one water soluble
azide. The second pathway is the synthesis of tetravalent azido calix[4]arene in the lower rim which was then treated with three different water soluble alkynes (Scheme 12). It was found that no reaction takes place at room temperature and a complex mixture formed at 60 °C when tetravalent alkynyl calix[4]arene was treated with the water soluble azide. However, when the tetravalent azido calix[4]arene was treated with water soluble alkynes, all reactions proceed very smoothly under similar conditions producing three different polyvalent 1,2,3-triazole calix[4]arenes with different water soluble groups (nonionic, anionic and cationic). Surprising, the resulting nonionic polyvalent 1,2,3-triazole calix[4]arene was insoluble in water. However, both anionic and cationic calix[4]arenes were soluble in water due to the formation of micelle.


Resorcin[4]arenes are interesting macrocyclic compounds and have received considerable attention due to their rigid bowl-shaped cavity that contain multiple of resorcinol rings. These multiple resorcinol rings in the resorcin[4]arene molecules provide π-electrons rich cavity and multiple polar hydroxyl groups in the upper rim of the resorcin[4]arene. These hydroxyl groups support the resorcin[4]arene molecules to form a variety of self assembled supramolecules such as hexamer and dimers. The hexamer form shell-like molecular capsules held by hydrogen bonds in water. The dimers form spherical molecular capsule held by solvent bridges such as alcohol, water, alcohol and water, or alcohol and halide ions.\textsuperscript{18}

Dale and Rebek\textsuperscript{19} reported the synthesis of monoperylene resorcin[4]arene in the lower rim via click chemistry from the reaction of and perylene alkyne. These monoperylene resorcin[4]arene were used for encapsulation in wet chloroform of tetrahexyl ammonium bromide which is known as a guest for hexameric assembly (Scheme 13).

\begin{center}
\includegraphics[width=\textwidth]{Scheme13.png}
\end{center}

Zhan, Tian and Li\textsuperscript{20} have reported a series of calix[4]crowns via click chemistry (\textbf{Scheme 14}) for soft and hard metal binding. The synthesis of these calix[4]crowns have been done by the reaction of a dialkyne-calix[4]arene using DMF at 90 °C with Cu(II)-sulfate/sodium ascorbate with a different diazide bridging reagent.


Calix[4]arene-based supramolecular structure have also been synthesized by Santoyo-Gonzalez\textsuperscript{21} using the click chemistry methodology through Cu(I)-catalyzed reaction of bis-alkyne and bis-azide calix[4]arene and diazide derivatives. Cyclomonomers and cyclodimers were obtained from the reaction of dialkyne-calix[4]arene and 1,2-, 1,3-, and 1,4-Bis-azidomethyl benzene. A calix[4]arene dimer was synthesized in excellent yield (83\%) from the reaction of the dialkyne-calix[4]arene and the diazide-calix[4]arene. (\textbf{Scheme 15, 16}). Furthermore, the dialkyne-calix[4]arene was treated with azidomethyl anthracene and ferrocene derivatives via azide-alkyne
cycloaddition. It was obtained from these studies that CuAAC reaction of the dialkyne and the diazide calix[4]arene derivatives have the propensity leading to describe molecular receptors with only minor formation of the corresponding dimerization compound (Scheme 17).


Li and coworkers\(^{22}\) have reported two triazole-modified calix[4]arene diesters via Huisgen 1,3-dipolar cycloaddition between azide ester and dialkynylcalix[4]arene (Scheme 18).

\[
\begin{align*}
\end{align*}
\]

1.7. **Synthesis Resorcin[4]arene Polymer.**

Click chemistry (CC)\(^1\) reactions are widely used in polymer chemistry due to their quantitative yields and high efficiency that occurs under benign conditions and tolerates a wide range of functional groups.\(^1\) The utility of the Cu(I)-catalyzed azide-alkyne cycloaddition (CuAAC) has been demonstrated in the synthesis of a resorcin[4]arene centered amphiphilic eight-arm star block copolymer (Scheme 19).\(^{23}\)
Present work-

In chapter 2, I will describe our effort on click chemistry (CC)\(^1\) particularly the Cu(I)-catalyzed 1,3-dipolar azide-alkyne cycloaddition (CuAAC). Our aim is to synthesis a resorcin[4]arene dimer via four Cu(I)-catalyzed [3+2] cycloaddition. Two different resorcin[4]arene derivatives were synthesized in which four azide functional groups were introduced on the upper rim of the first resorcin[4]arene and four alkyne functional groups were introduced on the upper rim of the second resorcin[4]arene. The tetraazide and the tetraalkyne resorcin[4]arenes were then used as subjects to the Cu(I)-catalyzed Huisgen 1,3-dipolar cycloaddition reaction to achieve the dimeric resorcin[4]arene capsule. However, no result was obtained and the steric consideration of the resulting dimeric capsules was quite challenging. Therefore each resorcin[4]arene derivative were studied individually via click chemistry in which the tetraazide resorcin[4]arene was undergo cycloaddition with commercially available alkyne reagent and synthesized alkyne reagent, while the tetraalkyne resorcin[4]arene was treated with synthesized azide reagent.

All click results were excellent in the synthesis of the three tetravalent triazole resorcin4[4]arenes in which these result enhanced and support the synthesis of the dimeric resorcin[4]arene using Cu(I)-catalyzed cycloaddition.
2.1. Introduction

In this chapter, I will describe our synthetic strategy using click chemistry (CC)\(^1\) philosophy, specifically the Cu(I)-catalyzed Huisgen 1,3-dipolar cycloaddition method in the synthesis of resorcin[4]arene dimeric capsules (Scheme 20). The starting point was to synthesis two different resorcin[4]arenes by introducing azide and alkyne functional groups on the upper rim of the resorcin[4]arene. The synthesis of the resorcin[4]arene dimeric capsule would then be accomplished by the tandem click coupling of the tetraazide and the tetraalkyne resorcin[4]arenes resulting in triazole linkages. What we looked for is the way that this reaction would take place in which when one cyclization reaction takes place between one azide and one alkyne, the resulting triazole linkage will held these two resorcin[4]arene together making the other azides and alkynes close to each other in proper way that the other cyclization processes take place easily within short period of time.
Continuing the previous work from our research laboratories, we focused on the synthesis of the dimeric capsules of heptyl octahydroxy resorcin[4]arene 3, which was easily synthesized from an ethanolic solution of 2-methyl resorcinol and heptaldehyde in the presence of hydrochloric acid as a catalyst.\textsuperscript{24,25} Each adjacent hydroxyl groups in octahydroxy resorcin[4]arene 3 were bridged with methylene group to make the resorcin[4]arene with no flexibility which is important for the resorcin[4]arene dimeric cage formation.\textsuperscript{24,25} The benzylic carbons on C2 position on the upper rim of the bridged resorcin[4]arene were then brominated by free-radical bromination using NBS.\textsuperscript{25,26,27} Since bromide is a good leaving group, the tetraazide and tetraalkyne resorcin[4]arenes
17 and 19 were synthesized in high yields (90-95%) using nucleophilic substitution by NaN$_3$ and the propargyl alcohol, respectively. The tetraazide and the tetraalkyne resorcin[4]arenes 17 and 19 could now be subjected to the Cu(I)-catalyzed Huisgen 1,3-dipolar cycloaddition reaction conditions to achieve the dimeric resorcin[4]arene capsule. However, the steric consideration of the azide and alkyne functionalized resorcin[4]arene and that of the resulting capsule, as we found out, proved quite challenging. For standardizing the reaction procedure and conditions and establish the synthetic protocol we decided to investigate, separately, the click coupling of the tetraazide and the tetraalkyne with several synthesized and commercially available monomeric azide and alkynes (Figure 3) The results from these reactions were very interesting and different functionalized tetravalent triazole resorcin[4]arenes were thus synthesized successfully in high yields.

![Chemical structures](image)

*Figure 3.* Different synthesized and commercially available azide and alkyne reagents.
2.2. Introduction to Resorcin[4]arenes

Cavitands are open-ended molecules with vase-shape that have restricted structure large enough to host other molecules. They have several properties making them of wide interest and use in which they can be used as a platform for the attachment of ligating groups.\textsuperscript{28}

The first resorcin[4]arene was synthesized by Adolf Von Baeyer in 1872. Baeyer reported a synthesis of a red-colored solution by the addition of concentrated sulfuric acid to an ethanolic solution of benzaldehyde and resorcinol in which a crystalline compound was obtained from the red-colored solution after the solution left for several days.\textsuperscript{29} In 1883, Michael determined that the crystalline compound that was yielded from the red-colored solution was formed from an equal number of benzaldehyde and resorcinol molecules with loss of water molecules.\textsuperscript{30} In 1940, Vogel and Nieder\textsuperscript{31} prepared the crystalline compound that Baeyer described using the same method. They obtained enough data by the molecular weight determination of the crystalline compound and its acetate derivative to establish the ratio between the resorcinol and aldehyde to be 4:4, i.e., a single resorcin[4]arene molecule resulted from four resorcinol and four aldehyde molecules, with the loss of four water molecules.\textsuperscript{32} Lately, in 1968, Erdtman and coworkers obtained the crystal structure of the resorcin[4]arene by x-ray diffraction method (Figure 4).\textsuperscript{33}
Resorcin[4]arenes are known to have five distinct conformational forms (Figure 5). Four of these conformations crown (cone), boat (pinched cone), chair (partial cone) and saddle (1,3-alternative) were introduced by Hogberg.\textsuperscript{28} The additional fifth conformation is the diamond (1,2-alternative) which was observed later by Abis et al.\textsuperscript{34} Hogberg found that only chair and crown conformers are actually formed in which the chair conformation is the kinetic product and the crown conformation is the thermodynamic product depending on the reaction condition and the substituents on the upper and lower rim of the resorcin[4]arene.\textsuperscript{35} If R group is branched or long chain alkane and R\textsubscript{1} group is H or methylene, then the resulting resorcin[4]arene has Crown (C\textsubscript{4v}) as a major conformation because the branched and long chain alkyls prefer to be in the axial position. On the other hand, if R\textsubscript{1} is replaced by methyl group instead of H keeping R group as an aromatic substituent, Chair (C\textsubscript{2v}) conformation will be the major product. Chair (C\textsubscript{2v}) conformation is formed together with Crown (C\textsubscript{4v}) conformation or as a major conformation when the alkyl substituent is replaced by aromatic substituent.
such as phenyl or bromobenzene, this is due to the steric effect which is responsible for yielding Chair ($C_{2v}$) conformation. The conformational changes can be observed using NMR data. Resorcin[4]arenes are interesting macrocyclic compounds and have received considerable attention due to their rigid bowl-shaped cavity that contain multiple of resorcinol rings. These multiple resorcinol rings plays a role in the resorcin[4]arene molecules in which they provide rich π-electrons inside the cavity and multiple polar hydroxyl groups in the upper rim of the resorcin[4]arene. These hydroxyl groups support the resorcin[4]arenes molecules to form a variety of self assemble supramolecules in the solid state such as hexamer and dimers. Different resorcin[4]arene dimers have been reported for encapsulation of organic solvent and other larger molecules and for complexation studies.
Figure 5. Conformations of Resorcin[4]arenes (Top View).
2.3. **Synthesis of Octahydroxy Resorcin[4]arenes**

Several resorcin[4]arenes with substituents on the lower rim were synthesized following a general procedure by acid-catalyzed condensation reaction in ethanol starting from 2-methyl resorcinol and different commercially available aldehydes (Scheme 21). These resorcin[4]arenes were isolated in good yields 68-90% as a yellowish to orange colored solids. All these products were characterized using $^1$H NMR spectral data and by comparison of available data in literature.$^{24,25}$

**Scheme 21.** Condensation reaction of 2-methyl resorcinol with different aldehydes.

Resorcin[4]arene 1 with crown conformation was synthesized by condensation reaction of 2-methyl resorcinol and 37% formaldehyde using hydrochloric acid as an acid catalyst in ethanol. The reaction mixture was refluxed for 12hrs. Resorcin[4]arene 1 was then precipitate out as a yellowish-colored solids and was isolated in 68% yield and characterized using $^1$H NMR spectrum in DMSO d$_6$ (Figure 6). From the $^1$H NMR spectrum we can see the presence of the benzylic proton H$_a$, bridge H$_b$, aromatic benzene H$_d$ and phenolic protons at 2.01, 3.69, 6.77 and 8.60 ppm, respectively, by comparison of available data in literature.\textsuperscript{26}

![Resorcin[4]arene](AH-A-244.001.001.1r.esp)

**Figure 6.** $^1$H NMR spectrum of compound 1.
2.3.2. **Synthesis of Octahydroxy Resorcin[4]arenes with aliphatic substituents (2-4)**

Three different commercially available aliphatic aldehydes (acetaldehyde, heptaldehyde, undecylinic aldehyde) were used for the synthesis of resorcin[4]arenes 2-4, respectively, starting from an ethanolic solution of 2-methyl resorcinol under hydrochloric acid catalyzed condensation. The reaction mixtures were refluxed for 12hrs which led to precipitation of yellow-colored solids. All three aliphatic resorcin[4]arenes 2-4 were isolated and characterized using $^1$H NMR spectra in DMSO d$_6$. The $^1$H NMR spectrum for compound 2 (Figure 7) shows the presence of the methylene $\text{H}_e$, benzylic $\text{H}_a$, bridge $\text{H}_b$, aromatic benzene $\text{H}_d$ and phenolic protons at 1.71, 1.95, 4.44, 7.39 and 8.69 ppm, respectively, by comparison of available data in literature.$^{29}$

![Figure 7. $^1$H NMR spectrum of compound 2.](image)
2.3.3. Synthesis of Octahydroxy Resorcin[4]arenes with aromatic substituents (5-9)

Resorcin[4]arenes 5-9 were prepared under similar reaction conditions used in the synthesis of resorcin[4]arenes 1-4 but using different aromatic aldehydes reagents (benzaldehyde, p-hyroxy benzaldehyde, p-carboxy benzaldehyde, p-bromo benzaldehyde and p-isopropyl benzaldehyde), respectively. Resorcin[4]arenes 5-9 were isolated as yellow to orange colored solids in 80-90% yield. Full NMR characterization was undertaken by $^1$H NMR spectroscopy. The $^1$H NMR spectrum for compound 5 with chair conformation shows the presence of the benzylic H$_a$, aromatic benzene H$_d$ and phenolic protons as two peaks at two different position by comparison of available data in literature (Figure 8).

![Figure 8. $^1$H NMR spectrum of compound 5.](image-url)
Depending on the substituent on the upper and lower rims in the resorcin[4]arene two different conformations, crown and chair conformations, were observed. The Aliphatic substituted resorcin[4]arenes 1-4 prefer the crown conformation while the aromatic substituted resorcin[4]arenes 5-9 prefer the chair conformation. These conformational structures were observed from their $^1$H NMR spectra. For example, In resorcin[4]arenes 2 with crown conformation, the benzylic H$_a$, benzene aromatic H$_d$ and phenolic protons show as singlet at 1.95, 7.39 and 8.69 ppm, respectively. On the other hand, in aromatic substituted resorcin[4]arenes such as resorcin[4]arenes 5 with chair conformation, all benzylic H$_a$, benzene aromatic and phenolic protons appear as two peaks at two different positions in which the benzylic protons H$_a$ appear at 1.91 and 2.11 ppm and the aromatic benzene protons H$_d$ appear at 5.35 and 6.2 ppm, and the phenolic protons show at 7.31 and 7.61 ppm. The difference can be seen by superimpose the $^1$H NMR spectra of compound 2 and 3 (Figure 9).

![Figure 9. Comperresion of $^1$H NMR spectra of compound 2 and 5.](image_url)
All benzylic H, benzene aromatic H and phenolic protons in the chair conformation resorcin[4]arenes show as two peaks at two different positions in the $^1$H NMR spectrum can be explained in (Figure 10). Clearly we can see that when resorcin[4]arenes exist in the chair conformation, two types of equivalent resorcinols will exist; two resorcinols will point out of the plane and two resorcinols will be in the plane. As a result, the equivalent resorcinols will have equivalent protons.

**Figure 10.** Resorcin[4]arene in chair conformation.

The characteristic bowl shape of the resorcin[4]arenes in the crown conformation can be locked into place by bridging the hydroxyl groups on the adjacent ring via covent bonds.\textsuperscript{24,25} Bridged resorcin[4]arenes are necessary for the synthesis of the dimeric capsule. The adjacent hydroxyl groups in compound 1-4 were bridged with methylene groups using dibromomethane and potassium carbonate in DMF at 70 °C for 10 hrs and the progress of the reaction was monitored by TLC. After completion, potassium carbonate was filtered off and the products extracted out from the aqueous phase using chloroform/water or ethyl acetate/water. The crude products 10-13 were purified by column chromatography and isolated in 65-81% yield (Scheme 22).

The bridged resorcin[4]arenes 10-13 were characterized using $^1$H NMR spectrometry in CDCl$_3$. The $^1$H NMR spectrum of bridged resorcin[4]arene 10 shows the disappearance of the singlet peak that represents H$_b$ protons and the appearance of two new doublet peaks at 3.44 and 4.46 ppm (Figure 11). These two doublet peaks represent H$_b$ protons in which one of two H$_b$ protons is pointing inside the cavity, while the other H$_b$ proton is pointing outside the cavity. The $^1$H NMR spectra for all bridged resorcin[4]arene show the disappearance of the phenolic protons and the presence of two new doublets around 4.19 and 5.79 ppm for the inner and outer hydrogen of the newly formed methylene bridge, respectively, such as in $^1$H NMR spectrum of compound 11 (Figure 12). In fact, locking each adjacent hydroxyl groups in the resorcin[4]arene makes the resorcin[4]arene molecule in unchanging structural shape. As a result, the hydrogen in the methylene bridge are in different chemical environment, the H$_{c1}$ protons are inside the resorcin[4]arene cavity and are shielded by the magnetic field of the aromatic cavity and hence appear upfield while the H$_{c2}$ protons are outside the resorcin[4]arene cavity and appear at downfield (Figure 13).
Figure 11. $^1$H NMR spectrum of compound 10.

Figure 12. $^1$H NMR spectrum of compound 11.
Figure 13. Methylene bridged diastereomer protons.
2.5. **Synthesis of tetrabromo resorcin[4]arene (14 and 15)**

Radical bromination on the methyl group at C2 position of the resorcin[4]arene ring was successfully achieved for both compounds 11 and 12 in good yield (Scheme 23).\(^{24,25}\) The bromination reactions for compound 11 and 12 were carried out in benzene in the presence of NBS and AIBN. The reaction mixtures were refluxed for overnight and the reactions were monitored by TLC. Both reactions were worked up by filtering succinimide salt. Benzene was then concentrated and compound 14 was re-crystallized from 1:2 DCM/MeOH to produce the tetrabromo resorcin[4]arene 14 in 82.7% yield while the tetrabromo resorcin[4]arene 15 was re-crystallized out from pure acetone to yield 93%. Both products were characterized by the 250MHz \(^1\)H NMR spectrometry in CDCl\(_3\) (Figure 14 and 15). Both \(^1\)H NMR spectra show the shifting of the benzylic H\(_a\) proton towards upfield from 1.89 to 4.35 ppm.\(^{29,30}\)

![Diagram of the synthesis of tetrabromo resorcin[4]arene](image)

Figure 14. $^1$H NMR spectrum of compound 14.

Figure 15. $^1$H NMR spectrum of compound 15.

Tetrazide resorcin[4]arenes 16 and 17 were synthesized from compounds 14 and 15, respectively, via a nucleophilic substitution by sodium azide (NaN₃) in DMF at room temperature overnight. After completion, the reactions were worked up by filtering NaBr salt and the products were extracted using ethyl acetate/water followed by concentration of ethyl acetate. The products were then re-crystallized out from 2:3 acetone/MeOH to give compound 16 and 17 in 95% yield (**Scheme 24**). Both products were characterized by 250MHz ¹H, ¹³C NMR spectrometry in CDCl₃ (**Figure 16**) and (**Figure 17**). From the ¹H NMR we see that the benzylic proton Hₐ slightly shifted from 4.35 to around 4.2 ppm and from ¹³C NMR (**Figure 18**) and (**Figure 19**) we can see the presence of the benzylic carbon at 45.0 ppm.

Figure 16. $^1$H NMR spectrum of compound 16.

Figure 17. $^1$H NMR spectrum of compound 17.
Figure 18. $^{13}$C NMR spectrum of compound 16.

Figure 19. $^{13}$C NMR spectrum of compound 17.

Resorcin[4]arenes 14 and 15 when subjected to nucleophilic attack by propargyl alcohol underwent substitution reaction in which each bromine group was substituted with propargyl group. The reactions were carried out using freshly available propargyl alcohol and sodium hydride (NaH) in THF at room temperature for 12hrs. The reactions were monitored by TLC and after all tetrabromo-resorcin[4]arene was consumed, the reactions were worked up by quenching the excess NaH using MeOH. THF was concentrated and the products were extracted from the aqueous phase using ethyl acetate/water. Both products were re-crystallized out from 1:2 dichloromethane/hexane to yield compounds 18 and 19 in 90% and 92% yield, respectively, (Scheme 25). Both compounds were characterized by 250MHz $^1$H, $^{13}$C NMR spectrometry in CDCl$_3$. Both $^1$H NMR spectra (Figure 20) and (Figure 21) show the appearance of the alkyne acidic proton H$_m$ as triplet around 2.48 ppm and a new doublet peak which represent H$_k$ around 4.15 ppm. From the $^{13}$C NMR spectra (Figure 22) and (Figure 23) we can see that the alkyne carbons C$_m$ and C$_4$ show at 74.4 and 79.9 ppm, respectively.

Figure 20. $^1$H NMR spectrum of compound 18.

Figure 21. $^1$H NMR spectrum of compound 19.
Figure 22. $^{13}$C NMR spectrum of compound 18.

Figure 23. $^{13}$C NMR spectrum of compound 19.

After successfully synthesizing the tetraazide-resorcin[4]arene 17 and tetraalkyne-resorcin[4]arenes 19, the Cu(I)-catalyzed Husigen 1,3-dipolar cycloaddition reaction was investigated and conditions were optimized. For example, the click coupling of tetraazide 17 with propargyl alcohol was investigated using different reaction conditions listed in *(Table 5)*. It was observed that the temperature plays an important role in this reaction and compound 20 was obtained when the reaction is done irrespective of the solvents used only at elevated temperature.

*Table 5. Different reaction condition for click reaction of compound 17 + propargyl alcohol.*

<table>
<thead>
<tr>
<th>Compound</th>
<th>Reagents</th>
<th>Solvent</th>
<th>Temperature °C</th>
<th>Time</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>17</td>
<td>CuSO₄/sodium ascorbate</td>
<td>THF/H₂O (v:v, 2:1)</td>
<td>25</td>
<td>1 day</td>
<td>no reaction</td>
</tr>
<tr>
<td>17</td>
<td>CuSO₄/sodium ascorbate</td>
<td>THF/H₂O (v:v, 2:1)</td>
<td>80</td>
<td>overnight</td>
<td>20 in 42% yield</td>
</tr>
<tr>
<td>17</td>
<td>CuI, DIPEA</td>
<td>THF</td>
<td>25</td>
<td>1 day</td>
<td>no reaction</td>
</tr>
<tr>
<td>17</td>
<td>CuI, DIPEA</td>
<td>CHCl₃</td>
<td>25</td>
<td>1 day</td>
<td>no reaction</td>
</tr>
<tr>
<td>17</td>
<td>CuI, DIPEA</td>
<td>Toluene</td>
<td>25</td>
<td>1 day</td>
<td>no reaction</td>
</tr>
<tr>
<td>17</td>
<td>CuI, DIPEA</td>
<td>THF</td>
<td>50</td>
<td>overnight</td>
<td>20 in 76% yield</td>
</tr>
<tr>
<td>17</td>
<td>CuI, DIPEA</td>
<td>CHCl₃</td>
<td>60</td>
<td>overnight</td>
<td>20 in 87% yield</td>
</tr>
<tr>
<td>17</td>
<td>CuI, DIPEA</td>
<td>Toluene</td>
<td>80</td>
<td>overnight</td>
<td>20 in 81% yield</td>
</tr>
</tbody>
</table>
From (Table 5) it was inferred that using chloroform as a solvent and CuI/DIPEA as a catalyst at 60 °C is the preferred condition. The poor yield was observed in the the click reaction in the presence of CuSO₄/sodium ascorbate in a mixture of THF/H₂O (v:v, 2:1) was because of the limited solubility of the tetraazide 17 in water. Therefore, other click reactions were carried out using CuI as Cu(I)-catalyst in the presence of N,N-diisopropylethylamine (DIPEA) as a base in CHCl₃. The click coupling of tetraazide-resorcin[4]arenes 17 with commercially available propargyl alcohol was worked up by extraction into the organic phase from the aqueous phase using CHCl₃/ammonium hydroxide solution. The product was then purified by column chromatography using 5% MeOH/DCM to give compound 20 in 87% yield (Scheme 26). Compound 20 was characterized using 250MHz ¹H, ¹³C NMR spectrometry in CDCl₃. It was observed from the ¹H NMR spectrum (Figure 24) that Hₐ proton is shifted downfield from around 4.25 to 5.33 ppm and the presence of two new singlet peaks at 4.67 and 7.47 ppm which represent the methyl alcohol and the triazole protons, respectively. Moreover, it was found from the ¹³C NMR spectrum (Figure 25) that the triazole carbons C₄ and C₅ appear at 120 and 149 ppm, respectively.

Figure 24. $^1$H NMR spectrum of compound 20.

Figure 25. $^{13}$C NMR spectrum of compound 20.
The click coupling of tetraalkyne 19 was carried out with benzyl azide using CuI and DIPEA in CHCl₃. The benzyl azide was prepared in quantitative yield from benzyl chloride by nucleophilic substitution with NaN₃.⁴⁰ Reaction mixture was refluxed for overnight and after completion, the organic phase was extracted from the aqueous phase using CHCl₃/ammonium hydroxide solution. The product was purified by column chromatography using 4:1 ethyl acetate/hexane to give compounds 21 82% yield (Scheme 27). The product was characterized in CDCl₃ using the 250Mz NMR spectrometry. From ¹H NMR spectrum (Figure 26) we can see the appearance of the new benzylic protons Hₙ around 5.49 ppm. It was also observed the presence of the new aromatic protons Hₖ, Hₗ and Hₘ around 7.27 ppm. The new triazole proton Hₚ shows at 7.56 ppm. From ¹³C NMR spectrum (Figure 27) we can see the disappearance of the alkyne carbons and the appearance of four new aromatic carbon peaks at 121.1, 121.8, 129.1 and 134.7 ppm and the appearance of the triazole carbon peaks at 123 and 145 ppm.

![Scheme 27. Synthesis of resorcin[4]arene 21.](image-url)
Figure 26. $^1$H NMR spectrum of compound 21.

Figure 27. $^{13}$C NMR spectrum of compound 21.

We have also successfully synthesized sugar-resorcin[4]arene 25 via click chemistry. The coupling of tetraazide resorcin[4]arene 17 and 1-ethynl-β-D-glucopyranoside-2,3,4,5-tetraacetate was investigated to probe the effect of the steric bulk on the coupling efficiency.

2.9.1. Synthesis of β-D-glycopyronoside pentaacetate and 1-ethynl-β-D-glucopyranoside-2,3,4,5-tetraacetate (22, 23)

β-glucose pentaacetate 22 was prepared from D-glucose using sodium acetate in acetic anhydride at 80 °C. After completion, the reaction mixture was added into ice cold water. The product precipitate was filtered washed with water to give β-glucose pentaacetate 22 in 83% yield. The product was subjected to lewis acid acatlyzed anomeric coupling with propargyl alcohol in the presence of BF₃ etherate in dichloromethane. The reaction mixture was stirred at room temperature for 2h. After completion, potassium carbonate was used for neutralization which was then filtered out. The product was re-crystallized from 1:2 DCM/Hexane to yield compound 23 in 76.8% yield (Scheme 28).

2.9.2. Click coupling of the tetraazide 17 and the 22

Tetraazide resorcin[4]arene 17 was then treated with compound 23 in the presence of CuI and DIPEA in chloroform. The reaction mixture was refluxed overnight. The reaction was worked up by extraction into the organic phase from the aqueous phase using chloroform/ammonium hydroxide solution. The product was then purified by column chromatography using 5% MeOH/DCM to give compound 24 in 79% yield (Scheme 29). The product was characterized using the 250MHz $^1$H, $^{13}$C NMR spectrometry in CDCl$_3$. From $^1$H NMR (Figure 28) we can see the presence of the triazole proton at 7.59 ppm and from the $^{13}$C NMR (Figure 29) we can see the appearance of the triazole carbons at 121.5 and 153.8 ppm.

![Scheme 29](image)

Figure 28. $^1$H NMR spectrum of compound 24.

Figure 29. $^{13}$C NMR spectrum of compound 24.
Conclusion

In conclusion, we successfully synthesized three different functionalized resorcin[4]arenes on the upper rim 20, 21 and 324 via click chemistry using CuI, DIPEA in chloroform in good yields which shows the simple and the powerful of Cu(I)-catalyzed Huisgen 1,3-dipolar cycloaddition reaction. These result serve as important milestones to the synthesis of dimeric resorcin[4]arene capsule via click chemistry in which promising result was obtained which encourage our work in the synthesis of the dimeric cage resorcin[4]arene.
CHAPTER 3
EXPERIMENTAL SECTION

3.1. General experimental procedure

All solvents and reagents were commercially available. Heptanal. THF was dry over sodium metal. Sodium acetate was dried by heating. $^1$H and $^{13}$C NMR spectra were recorded on 250MHz, 400MHz spectrometers.

Synthesis of octahydroxy resorcin[4]arene (1): 2-methyl resorcinol (10g, 0.081mol) was dissolved in (62.7mL, 772mL/mol) ethanol and (14.9mL, 185mL/mol) 37% aqueous HCl. The solution was cooled in ice bath for 5 min and 37% formaldehyde (8.1mL, 0.081mol) was then added slowly in 10 min period of time. The reaction mixture was stirred at 0 $^\circ$C for 5 min which was then refluxed for 12 h. A yellow colored compound was precipitated and filtered out using buchner funnel and washed several times with cooled ethanol and distilled water until turns neutral pH paper yielding 7.4g (68%). The compound was then dried and NMR was taken in DMSO d$_6$. $^1$H NMR $\delta$ 2.01(s, 12H), 3.59(s, 8H), 6.77(s, 4H), 8.61(s, 8H).

Synthesis of octahydroxy resorcin[4]arene (2): 2-methyl resorcinol (10g, 0.081mol) was dissolved in (62.7mL, 772mL/mol) ethanol and (14.9mL, 185mL/mol) 37% aqueous HCl. The solution was cooled in ice bath and acetaldehyde (3.57mL, 0.081mol) was added slowly in 10 min period of time. The reaction mixture was stirred at 0 $^\circ$C for 5 min
which was then refluxed for 12 h. A yellow colored compound was precipitate from the solution and filtered out using buchner funnel and washed several times with cooled ethanol and distilled water until turns neutral pH paper yielding 8.1g (65.3%). The compound was then dried and NMR was taken in DMSO d$_6$. $^1$H NMR $\delta$ 1.71(d, 12H), 1.95(s, 12H), 4.44(q, 4H), 7.39(s, 4H), 8.69(s, 8H).

**Synthesis of octahydroxy resorcin[4]arene (3):** 2-methyl resorcinol (10g, 0.081mol) was dissolved in (62.7mL, 772mL/mol) ethanol and (14.9mL, 185mL/mol) 37% aqueous HCl. The solution was cooled in ice bath and heptaldehyde (11.3mL, 0.081mol) was added slowly in 10 min period of time. The reaction mixture was stirred at 0 °C for 5 min which was then refluxed for 12 h. A yellow colored compound was precipitate and filtered out using buchner funnel and washed several times with cooled ethanol and distilled water until turns neutral pH paper yielding 14.2g (80%). The compound was then dried and NMR was taken in DMSO d$_6$. $^1$H NMR $\delta$ 0.84(t, 12H), 1.23(m, 32H), 1.93(s, 12H), 2.21(m, 8H), 4.18(t, 4H), 7.21 (s, 4H), 8.69(s, 8H).

**Synthesis of octahydroxy resorcin[4]arene (4):** 2-methyl resorcinol (10g, 0.081mol) was dissolved in (62.7mL, 772mL/mol) ethanol and (14.9mL, 185mL/mol) 37% aqueous HCl. The solution was cooled in ice bath and 10-undecenal (16.75mL, 0.081mol) was added slowly in 10 min period of time. The reaction mixture was refluxed for 12 h. A pale yellow colored compound was precipitate and filtered out using buchner funnel and washed several times with cooled distilled water until turns neutral pH paper yielding 17.6g (79.6%). The compound was then dried and NMR was taken in DMSO d$_6$. $^1$H NMR $\delta$ 1.25(m, 56H), 1.95(s, 12H), 2.01(t, 8H), 4.20(t, 4H), 4.95(t, 8H), 5.77(t, 4H), 7.27(s, 4H), 8.69(s, 8H).
Synthesis of octahydroxy resorcin[4]arene (5): 2-methyl resorcinol (10g, 0.081mol) was dissolved in (62.7mL, 772mL/mol) ethanol and (14.9mL, 185mL/mol) 37% aqueous HCl. The solution was cooled in ice bath and benzaldehyde (8.21mL, 0.081mol) was added slowly in 10 min period of time. The reaction mixture was refluxed for 12 h. A pale pink colored compound was precipitate and filtered out using buchner funnel and washed several times with cooled distilled water until turns neutral pH paper yielding 8.1g (83%). The compound was then dried and NMR was taken in DMSO d$_{6}$. $^1$H NMR δ 1.91(s, 6H), 2.11(s, 6H), 5.35(s, 2H), 5.63(s, 4H), 6.20(s, 2H), 6.67(d, 8H), 6.87(m, 12H), 7.32(s, 4H), 7.61(s, 4H).

Synthesis octahydroxy resorcin[4]arene (6): 2-methyl resorcinol (10g, 0.081mol) was dissolved in (62.7mL, 772mL/mol) ethanol and (14.9mL, 185mL/mol) 37% aqueous HCl. 4-hydroxy benzaldehyde (9.84g, 0.081mol) was then added in portions to the solution after it was cooled in ice bath. The reaction mixture was refluxed for 12 h. A yellow colored compound was precipitate and filtered out using buchner funnel and washed several times with cooled distilled water until turns neutral pH paper yielding 15.8g (86%). The compound was then dried and NMR was taken in DMSO d$_{6}$. $^1$H NMR δ 1.89(s, 6H), 2.06(s, 6H), 5.45(s, 4H), 5.73 (s, 2H), 6.13(s, 2H), 6.34(d, 8H), 6.37(d, 8H), 7.11(s, 4H), 7.49(s, 4H), 8.73(s, 4H).

Synthesis of octahydroxy resorcin[4]arene (7): 2-methyl resorcinol (10g, 0.081mol) was dissolved in (62.7mL, 772mL/mol) ethanol and (14.9mL, 185mL/mol) 37% aqueous HCl. 4-carboxy benzaldehyde (12.1g, 0.081mol) was then added in portions to the solution after it was cooled in ice bath. The reaction mixture was refluxed for 12 h. A yellow colored compound was precipitate and filtered out using buchner funnel and
washed several times with cooled distilled water until turns neutral pH paper yielding 14.6g (79.4%). The compound was then dried and NMR was taken in DMSO d$_6$. $^1$H NMR δ 1.90(s, 6H), 2.14(s, 6H), 5.36(s, 2H), 5.72(s, 4H), 6.21(s, 2H), 6.75(d, 8H), 7.46(d, 8H), 7.63(s, 4H), 7.69(s, 4H), 12.3(s, 4H).

**Synthesis of octahydroxy resorcin[4]arene (8):** 2-methyl resorcinol (10g, 0.081mol) was dissolved in (62.7mL, 772mL/mol) ethanol and (14.9mL, 185mL/mol) 37% aqueous HCl. 4-bromo benzaldehyde (14.92g, 0.081mol) was added in portions to the solution after it was cooled in ice bath. The reaction mixture was refluxed for 12 h. A pale pink colored compound was precipitate and filtered out using buchner funnel and washed several times with cooled distilled water until turns neutral pH paper yielding 19.2g (80.4%). The compound was then dried and NMR was taken in DMSO d$_6$. $^1$H NMR δ 1.89(s, 6H), 2.06(s, 6H), 5.25(s, 2H), 5.62(s, 4H), 6.08(s, 2H), 6.57(d, 8H), 7.09(d, 8H), 7.58(s, 4H), 7.68(s, 4H).

**Synthesis of octahydroxy resorcin[4]arene (9):** 2-methyl resorcinol (10g, 0.081mol) was dissolved in (62.7mL, 772mL/mol) ethanol and (14.9mL, 185mL/mol) 37% aqueous HCl. The solution was cooled in ice bath and 4-isopropy benzaldehyde (12.2mL, 0.081mol) was added slowly in 10 min period of time. The reaction mixture was refluxed for 12 h. A pale yellow colored compound was precipitate and filtered out using buchner funnel and washed several times with cooled distilled water until turns neutral pH paper yielding 17.9g (87.4%). The compound was then dried and NMR was taken in CDCl$_3$. $^1$H NMR δ 1.23(d, 24H), 2.06(s, 6H), 2.23(s, 6H), 2.83(m, 4H), 4.69(s, 8H), 5.43(s, 4H), 5.90(d, 2H), 6.23(s, 2H), 6.85(d, 8H), 7.03(d, 8H).
Synthesis of bridged resorcin[4]arene (10): Compound 1 (5g, 9.19mmol) was dissolved in 110mL DMF. Potassium carbonate (10g, 0.07mol) was added into the solution and allowed to stir for 10 min. Dibromomethane (5.3mL, 7.4mmol) was then added and the reaction mixture was heated to 75 °C for 24h. After completion, the reaction mixture was cooled at room temperature and both KBr salt was filtered out by buchner funnel. The organic phase was then extracted from the aqueous phase using (100mL chloroform and 3 X 150mL water). The product was purified by column chromatography as a pale yellow solid compound using 10% chloroform/Hexane yielding 4.3g (79%) yield. The product was then dried and NMR was taken in DMSO d$_6$. $^1$H NMR δ 1.89(s, 12H), 3.19(d, 4H), 4.21(d, 4H), 4.40(d, 4H), 5.86(d, 4H), 6.97(s, 4H).

Synthesis of bridged resorcin[4]arene (11): Compound 2 (5g, 8.33mmol) was dissolved in 110mL DMF. Potassium carbonate (9.2g, 0.067mol) was added into the solution and allowed to stir for 10 min. Dibromomethane (4.76mL, 6.7mmol) was then added and the reaction mixture was heated to 75 °C for 24h. After completion, the reaction mixture was cooled at room temperature and both KBr salt was filtered out. The organic phase was then extracted from the aqueous phase using (100mL chloroform and 3 X 150mL water). The product was purified by column chromatography as a pale yellow solid compound using 10% chloroform/Hexane yielding 4.1g (76%) yield. The product was then dried and NMR was taken in CDCl$_3$. $^1$H NMR δ 1.66(d, 12H), 1.89(s, 12H), 3.19(d, 4H), 4.19(d, 4H), 4.91(q, 4H), 5.79(d, 4H), 7.07(s, 4H).

Synthesis of bridged resorcin[4]arene (12): Compound 3 (5g, 5.67mmol) was dissolved in 110mL DMF. Potassium carbonate (6.26g, 4.5mmol) was added into the solution and allowed to stir for 10 min. Dibromomethane (3.24mL, 4.5mmol) was then added and the
reaction mixture was heated to 75 °C for 24h. After completion, the reaction mixture was cooled at room temperature and KBr salt was filtered out. The organic phase was extracted from the aqueous phase using (100mL ethyl acetate and 3 X 150mL water). The product was purified by column chromatography as a pale yellow solid compound using 10% EA/Hexane yielding 4g (76%) yield. The product was then dried and NMR was taken in CDCl₃. ¹H NMR δ 0.82(t, 12H), 1.23(m, 32H), 1.93(s, 12H), 2.14(m, 8H), 4.19(d, 4H), 4.68(t, 4H), 5.81(d, 4H), 6.90(s, 4H).

**Synthesis of bridged resorcin[4]arene (13):** Compound 4 (5g, 4.56mmol) was dissolved in 110mL DMF. Potassium carbonate (5g, 3.6mmol) was added into the solution and allowed to stir for 10 min. Dibromomethane (2.6mL, 3.6mmol) was then added and the reaction mixture was heated to 75 °C for 24h. After completion, the reaction mixture was cooled at room temperature and KBr salt was filtered out. The organic phase was extracted from the aqueous phase using (100mL ethyl acetate and 3 X 150mL water). The product was purified by column chromatography as a pale yellow solid compound using 10% EA/Hexane yielding 3.9g (75%) yield. The compound was then dried and NMR was taken in CDCl₃. ¹H NMR δ 1.35(m, 56H), 2.01(s, 12H), 2.26(m, 8H), 4.3(d, 4H), 4.79(t, 4H), 5.82(t, 8H), 5.94(d, 4H), 7.02(s, 4H).

**Synthesis of tetrabromo resorcin[4]arene (14):** Compound 11 (10g, 15mmol) and AIBN (0.25g, 1.5mmol) were dissolved in 200mL of a mixture of (1:4) CHCl₃/CCl₄. NBS (12.4g, 0.086mol) was then added and the reaction mixture was refluxed overnight. After completion, the reaction mixture was allowed to cool at room temperature for 10min and then succinimide salt was filtered out using buchner funnel. The solvent mixture was then concentrated over rotovapor and the product was re-crystallized out from 1:2
DCM/MeOH to yield tetrabromo resorcin[4]arene 14 as a pale yellow solid compound in 12.3g (82.7%) yield. The product was then dried and NMR was taken in CDCl₃. ¹H NMR δ 1.79(d, 12H), 4.35(s, 12H), 4.43(d, 4H), 5.55(q, 4H), 5.99(d, 4H), 7.31(s, 4H).

**Synthesis of tetrabromo resorcin[4]arene (15):** Compound 12 (10g, 0.01mol) and AIBN (0.176g, 1mmol) were dissolved in 200mL of a mixture of (1:4) CH₃Cl/CCl₄. NBS (8.7g, 0.048mol) was then added and the reaction mixture was refluxed overnight. After completion, the reaction mixture was allowed to cool at room temperature and then succinimide salt was filtered out using buchner funnel and the solvent mixture was then concentrated over rotovapor. The product was re-crystallized out from pure acetone to give a white solid compound 15 in 12.4g (93%) yield. The product was then dried and NMR was taken in CDCl₃. ¹H NMR δ 0.83(t, 12H), 1.24(m, 32H), 2.14(m, 8H), 4.35(s, 8H), 4.51(d, 4H), 4.73(q, 4H), 5.94(d, 4H), 7.06(s, 4H).

**Synthesis of tetraazide resorcin[4]arene (16):** tetrabromo resorcin[4]arene 14 (5g, 5mmol) was dissolved in 50mL DMF. NaN₃ (2.7g, 0.04mol) was then added and the reaction mixture was allowed to stir at room temperature overnight. After completion, NaBr salt was filtered out using buchner funnel and the organic phase was extracted from the aqueous phase using (50mL ethyl acetate and 3 x 50mL water). The organic phase was dried using NaSO₄ and ethyl acetate was then concentrated over rotovapor. The product was re-crystallized using (2:3) Acetone/MeOH yielding compound 16 as pale yellow solid crystals in 4g (95%) yield. The product was then dried and NMR was taken in CDCl₃. ¹H NMR δ 1.55(d, 12H), 4.12(s, 12H), 4.18(d, 4H), 4.82(q, 4H), 5.74(d, 4H), 7.08(s, 4H). ¹³C NMR δ 16.0, 30.9, 45.0, 99.7, 120.3, 122.2, 139.1, 153.3 ppm.
Synthesis of tetraazide resorcin[4]arene (17): tetrabromo resorcin[4]arene 15 (5g, 4mmol) was dissolved in 50mL DMF. NaN₃ (2g, 0.03mol) was then added and the reaction mixture was allowed to stir at room temperature overnight. After completion, NaBr salt was filtered out using buchner funnel and the organic phase was extracted from the aqueous phase using (50mL ethyl acetate and 3 x 100mL water). The organic phase was dried using Na₂SO₄ and ethyl acetate was then concentrated over rotovapor. The product was re-crystallized using (2:3) Acetone/MeOH yielding compound 17 as pale yellow solid crystals in 4.3g (97.7%) yield. The product was then dried and NMR was taken in CDCl₃. ¹H NMR δ 0.83(t, 12H), 1.23(m, 32H), 2.13(m, 8H), 4.26(s, 8H), 4.31(d, 4H), 4.74(t, 4H), 5.84(d, 4H), 7.08(s, 4H). ¹³C NMR δ 14.1, 22.7, 27.8, 29.5, 30.1, 31.9, 36.9, 45.1, 99.7, 120.8, 122.3, 138.2, 153.7 ppm.

Synthesis of tetraalkyne resorcin[4]arene (18): NaH (60%) (1.7g, 0.04mol) was added slowly to 50mL ice cold THF and allowed to stir for 5min. Propargyl alcohol (2.4mL, 0.04mol) was then added dropwise and the solution was allowed to stir for more 5-10min. A solution of tetrabromo resorcin[4]arene 14 (5g, 5mmol) in 10mL THF was then added dropwise and the reaction mixture was then allowed to stir overnight at room temperature. After completion, the reaction mixture was quenched using MeOH and then both MeOH and THF were concentrated over rotovapor. The organic phase was extracted from the aqueous phase using (50mL ethyl acetate and 2 x 50mL water) and dried using Na₂SO₄ followed by concentration of ethyl acetate. The product was re-crystallized out from (2:3) DCM/hexane yielding compound 18 as white solid crystals in 3.6g (90%) yield. ¹H NMR δ 1.78(d, 12H), 2.48(t, 4H), 4.15(d, 8H), 4.45(d, 4H), 4.47(s, 8H), 5.04(d,
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4H), 5.9(d, 4H), 7.29(s, 4H). \(^{13}\)C NMR \(\delta\) 16.1, 31.1, 57.7, 61.6, 74.4, 79.9, 99.9, 120.1, 123.4, 138.9, 153.8 ppm.

**Synthesis of tetraalkyne resorcin[4]arene (19):** NaH (60%) (1.3g, 0.032mol) was added slowly to 50mL ice cold THF and allowed to stir for 5min. Propargyl alcohol (1.85mL, 0.032mol) was then added dropwise and the solution was allowed to stir for more 5-10min. A solution of tetrabromo resorcin[4]arene 15 (5g, 4mmol) in 10mL THF was then added dropwise and the reaction mixture was then allowed to stir overnight at room temperature. After completion, the reaction mixture was quenched using MeOH and then both MeOH and THF were concentrated over rotovapor. The organic phase was extracted from the aqueous phase using (50mL EA and 2 x 100mL water) and dried using NaSO\(_4\) followed by concentration of ethyl acetate. The product was re-crystallized out from (2:3) DCM/MeOH yielding compound 19 as white solid crystals in 3.9g (92%) yield. The product was then dried and NMR was taken in CDCl\(_3\). \(^1\)H NMR \(\delta\) 0.82(t, 12H), 1.23(m, 32H), 2.15(m, 8H), 2.38(t, 4H), 4.05(d, 8H), 4.35(d, 4H), 4.37(s, 8H) 4.75(t, 4H), 5.79(d, 4H), 7.05(s, 4H). \(^{13}\)C NMR \(\delta\) 14.1, 22.7, 27.9, 29.5, 30.2, 31.9, 36.8, 57.7, 61.7, 99.9, 120.7, 123.5, 137.9, 154.2 ppm.

**Synthesis of tetra (4-methyl alcohol 1,2,3-triazole) resorcin[4]arene (20):** Compound 17 (1g, 0.8mmol) was dissolved in 30mL chloroform. CuI (0.03g, 0.16mmol) and DIPEA (0.95mL, 5.5mmol) were then added to the solution. Propargyl alcohol (0.37mL, 6.45mmol) was then added to the reaction mixture and allowed to reflux overnight. After completion, the reaction was worked up using ammonium hydroxide solution and the organic phase was then extracted and dried using Na\(_2\)SO\(_4\). Chloroform was evaporated and the product was re-crystallized out from a mixture of (1:3) DCM/hex to give
compound 20 as pale yellow solid crystals in 1.09g (85.8%) yield. The product was then dried and NMR was taken in CDCl$_3$. $^1$H NMR δ 0.83(t, 12H), 1.25(m, 32H), 2.12(m, 8H), 4.01(d, 4H), 4.67(s, 8H), 4.71(t, 4H), 5.33(s, 8H), 6.04(d, 4H), 7.03(s, 4H), 7.47(s, 4H). $^{13}$C NMR δ 13.1, 21.6, 26.7, 28.4, 28.6, 29.1, 30.8, 35.8, 42.4, 54.8, 64.8, 100.7, 120.4, 120.6, 120.9, 136.7, 149.1, 153.2 ppm.

**Synthesis of tetra (4-benzyl 1,2,3-triazole) resorcin[4]arene (21):** Compound 19 (1g, 0.87mmol) and benzyl azide (0.87mL, 7mmol) were dissolved in 30mL chloroform. CuI (0.033g, 0.17mmol) and DIPEA (0.9mL, 5.2mmol) were then added to the solution and allowed the reaction mixture to reflux overnight. After completion, the reaction was worked up using ammonium hydroxide solution and the organic phase was extracted and dried using Na$_2$SO$_4$. Chloroform was evaporated and the product was re-crystallized out from (1:3) DCM/hexane to give compound 21 as white solid crystals in 1.19g (81.5%) yield. The product was then dried and NMR was taken in CDCl$_3$. $^1$H NMR δ 0.86(t, 12H), 1.23(m, 32H), 2.12(m, 8H), 4.17(d, 4H), 4.27(s, 8H), 4.55(s, 8H), 4.69(t, 4H), 5.51(d, 4H), 5.53(s, 8H), 7.01(s, 4H), 7.3(m, 20H), 7.6(s, 4H). $^{13}$C NMR δ 13.9, 22.5, 27.8, 29.4, 30.1, 31.7, 54.0, 62.1, 63.8, 99.5, 120.4, 123.2, 123.6, 128.1, 128.6, 129.0, 134.8, 137.7, 145.1, 154.0 ppm.

**Synthesis of (β)-Glucose pentaacetate (22):** D-Glucose (5g, 0.025mol) and sodium acetate (12g, 0.088mol) were added to acetic anhydride (46mL, 0.48mol). The reaction mixture was heated to 80°C overnight. After completion, the reaction mixture was added dropwise in ice cold water and allowed to stir for 10min. The product was then precipitate as a white solid compound and filtered out using buchner funnel to give compound 22 in 9g (83%) yield. The product was then dried and NMR was taken in
CDCl$_3$. $^1$H NMR $\delta$ 2.15(m, 15H), 3.89(dd, 1H), 4.17(d, 1H), 4.31(d, 1H), 5.17(m, 3H), 5.72(d, 1H).

**Synthesis of (β)-Glucose tetraacetate alkyne (23):** (β)-Glucose pentaacetate 22 (5g, 0.013mol) and propargyl alcohol (1.5mL, 0.025mol) were dissolved in 100mL dichloromethane. The solution was cold in ice bath to 0°C and BF$_3$ etherate (48%) (5mL, 0.019mol) was then added dropwise to the solution. The reaction mixture was stirred at room temperature for 2h. After completion, K$_2$CO$_3$ (2.37g, 0.017mol) was added and allowed to stir for 5min then the salt was filtered out using buchner funnel. The reaction mixture was then concentrated and the product was re-crystallized out from (1:3) DCM/hexane to yield compound 23 in 3.8g (76.8%). The product was then dried and NMR was taken in CDCl$_3$. $^1$H NMR $\delta$ 2.15(m, 15H), 2.47(t, 1H), 3.89(dd, 1H), 4.17(d, 1H), 4.31(d, 1H), 4.39(d, 2H), 4.79(d, 1H), 5.12(m, 2H), 5.24(t, 1H).

**Synthesis of tetravalent sugar resorcin[4]arene (24):** Compound 17 (1g, 0.9mmol) was dissolved in 30mL chloroform. CuI (0.035g, 0.18mmol) and DIPEA (0.95mL, 5.5mmol) were added to the solution. Compound 23 (1.4g, 3.65mmol) was then added to the solution and allows the reaction mixture to reflux overnight. After completion, the reaction was worked up using ammonium hydroxide solution and the organic phase was extracted and dried using Na$_2$SO$_4$. Chloroform was evaporated and the product was purified by column chromatography using 5% MeOH/DCM to give compound 24 as a yellow solid compound in 1.9g (79%) yield. The product was then dried and NMR was taken in CDCl$_3$. $^1$H NMR $\delta$ 0.84(t, 12H), 1.25(m, 32H), 1.99(m, 48H), 2.14(m, 8H), 3.71(d, 4H), 4.17(m, 10H), 4.5-5.3(m, 40H), 5.8(d, 4H), 7.11(s, 4H), 7.49(s, 4H). $^{13}$C
NMR δ 14, 20.5, 20.7, 22.8, 29.4, 30.2, 31.7, 36.9, 44.1, 61.7, 62.8, 69.3, 71.1, 71.8, 72.7, 99.4, 99.8, 120.5, 121.4, 123.4, 138.1, 144.0, 153.7, 169.3, 169.4, 170.1, 170.6 ppm
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(c) Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. *Angew Chem. Int. Ed.* **2002**, *41*, 2596-2599.


APPENDIX A

ADDITIONAL FIGURES
Figure 30. $^1$H NMR of compound 1.

Figure 31. $^1$H NMR of compound 2.
Figure 32. $^1$H NMR of compound 3.

Figure 33. $^1$H NMR of compound 4.
Figure 34. $^1$H NMR of compound 5.

Figure 35. $^1$H NMR of compound 6.
Figure 36. $^1$H NMR of compound 7.

Figure 37. $^1$H NMR of compound 8.
Figure 38. $^1$H NMR of compound 9.

Figure 39. $^1$H NMR of compound 10.
Figure 40. $^1$H NMR of compound 11.

Figure 41. $^1$H NMR of compound 12.
Figure 42. $^1$H NMR of compound 13.

Figure 43. $^1$H NMR of compound 14.
Figure 44. $^1$H NMR of compound 15.

Figure 45. $^1$H NMR of compound 16.
Figure 46. $^{13}$C NMR of compound 16.

Figure 47. $^1$H NMR of compound 17.
Figure 48. $^1$H NMR of compound 17.

Figure 49. $^1$H NMR of compound 18.
Figure 50. $^{13}$C NMR of compound 18.

Figure 51. $^1$H NMR of compound 19.
Figure 52. $^{13}\text{C}$ NMR of compound 19.

Figure 53. $^1\text{H}$ NMR of compound 20.
Figure 54. $^{13}$C NMR of compound 20.

Figure 55. $^1$H NMR of compound 21.
Figure 56. $^{13}$C NMR of compound 21.

Figure 57. $^1$H NMR of compound 22.
Figure 58. $^1$H NMR of compound 23.

Figure 59. $^1$H NMR of compound 24.
Figure 60. $^{13}$C NMR of compound 24.